PART I

PREPARATION AND REACTIONS OF 1-HYDROXY-1,5α-CYCLOCHOLESTAN-7-ONE

PART II

APPROACHES TO THE TOTAL SYNTHESIS OF LACTARORUFIN A

By

Joel Robert Christensen

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ABSTRACT

PART I

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PART I

Cholest-5-ene-1,7-dione, a new polyfunctional steroid, gave 1-hydroxy-1,5α-cyclocholestan-7-one (17) on dissolving metal reduction. Acid and base-catalyzed isomerizations of 17 were studied, and the results compared with corresponding reactions of the parent cyclopropanol 8. The chief arrangement products from 17 were the cis and trans 1,7-diketones 25 and 26, and the ring A spiro epimers 27 and 28. Surprisingly, no B-norsteroid products were obtained despite the isolation of an isomer of 17, 7-hydroxy-5,7β-cyclocholestan-1-one 41, from the base induced reaction of 17. Ring

cleavage reactions of reduced derivatives of 17 and 41 were also examined.

PART II

Hydroazulenone 24 has been prepared in three steps from enedione 21. The possibility of using 24 as a synthon for the total synthesis of Lactarorufin A was explored. A study of the reactivity of 24 found that the enolate derived from 24 (35) was relatively unreactive. However, the silyl enol ether 36 was obtained by reaction of 35 with trimethyl silyl chloride. Enol ether 36 gave the keto-acetal 39 upon alkylation with trimethyl orthoformate in the presence of zinc iodide. Nucleophilic additions to the carbonyl group of 24 were complicated by 1,4 and 1,6-additions to the enone moiety. Oxidation of 24 with singlet oxygen gave endoperoxide 47 and hydroperoxide 48 in nearly a 1:1 ratio. Attempted catalytic reductions of 47 or 54, prepared by the base induced peroxide cleavage of 47, were complicated. Dienone 24 was selectively epoxidized with meta- chloroperoxybenzoic acid.

For my mother, whose love and support

made this possible

ACKNOWLEDGMENTS

The author wishes to express his sincere appreciation to Professor William Reusch for his guidance and encouragement throughout the course of this work.

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PART II

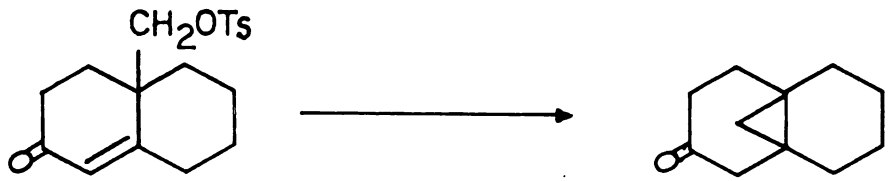
PART I

PREPARATION AND REACTIONS OF

1-HYDROXY-1,5α-CYCLOCHOLESTAN-7-ONE

INTRODUCTION

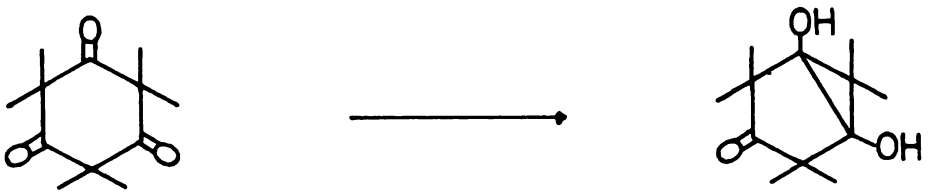
The reduction of α,β-unsaturated carbonyl compounds by solutions of alkali metals in ammonia generates reactive nucleophilic intermediates. These intermediates are presumed to be radical anions or dianions arising from the addition of electrons to the enone moiety.[1-3] Under suitable conditions, the resulting β-carbanion can attack electrophilic centers in either an intra or intermolecular fashion. One of the first examples of intramolecular attack occurred in the reduction of 10-hydroxymethyl $\Delta^{1,9}$-2-octalone tosylate described by Stork and Tsuji[3] (Equation 1)



1 2

Cyclopropane formations of this kind, during alkali metal-ammonia reductions of multifunctional compounds have

been noted in many other systems, as illustrated by Equations 2-4. Thus, even relatively reactive compounds such



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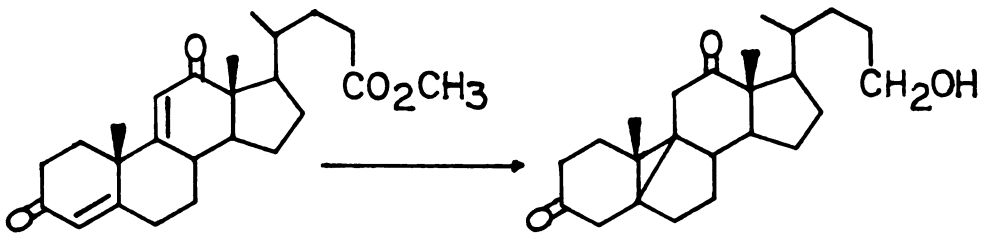

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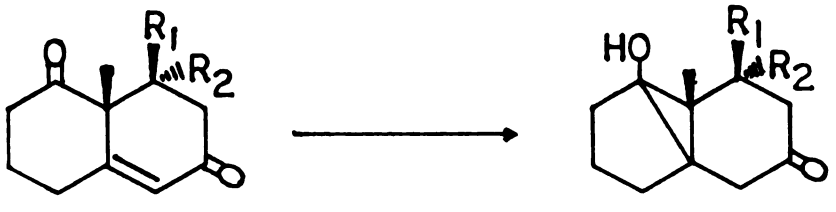


(4)

7 $R_1 = R_2 = H$

8 $R_1 = R_2 = H$

9 $R_1 = CH_3$; $R_2 = H$

10 $R_1 = CH_3$; $R_2 = H$

11 $R_1 = H$; $R_2 = CH_3$

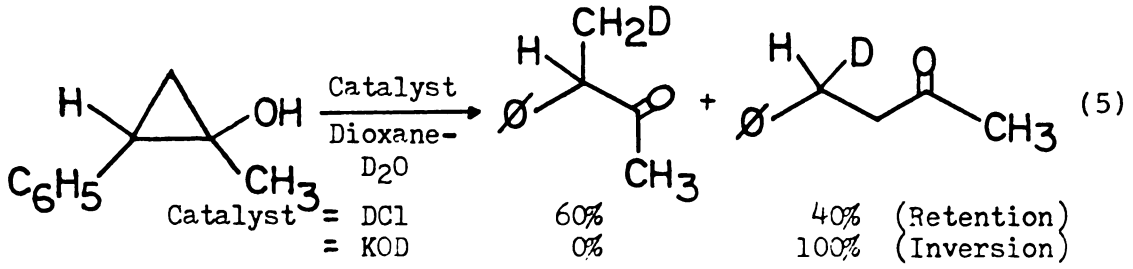
12 $R_1 = H$; $R_2 = CH_3$

as cyclopropanols have been prepared by this method. The Wieland-Miesher ketone 7 and simple alkyl derivatives of 7, such as compounds 9 and 11, have been prepared and

subjected to lithium-ammonia reduction with similar results[6,7]. The ring opening reactions of these cyclopropanols[8,9] have been studied in detail. In fact, oxycyclopropanes, including cyclopropanols have found considerable use in synthetic organic chemistry[10].

Reaction of cyclopropanes with acid may give rise to many ring opened or rearranged products. With cyclopropanols, the hydroxyl group controls and facilitates ring opening by its ability to stabilize an adjacent positive charge. Stereochemical studies of acid-catalyzed cyclopropanol ring openings indicate that they generally proceed with retention of configuration at the protonation site[11b,13]. However, these reactions often do not show high regioselectivity[11,12]. Thus, a mixture of products is usually observed from the acid catalyzed opening of unsymmetrical cyclopropanols, although the product resulting from proton attack at the least substituted carbon generally predominates (Equations 5, 6, and 7). In a few cases cyclopropanol ring opening with inversion has been observed[12,14] (Equation 7).

Base-catalyzed ring opening of cyclopropanols generally proceeds the more stable carbanion[11b,15,16]. Consequently, these reactions often show high regioselectivity[11,15] (Equations 5 and 7). In addition, the C-protonation step is usually characterized by inversion of the β-(carbanionic) carbon[11b,13]



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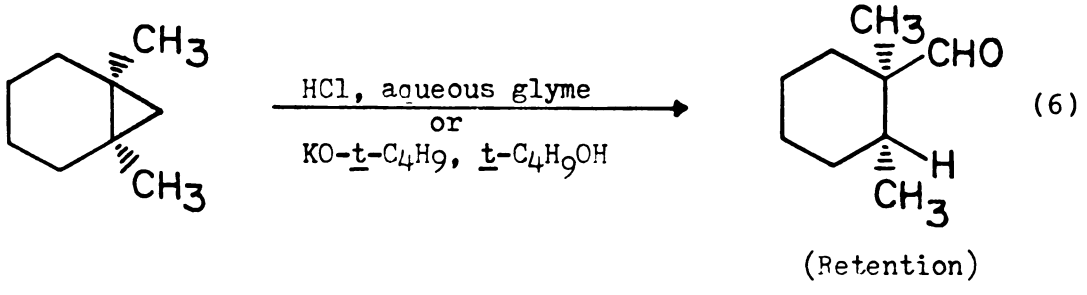

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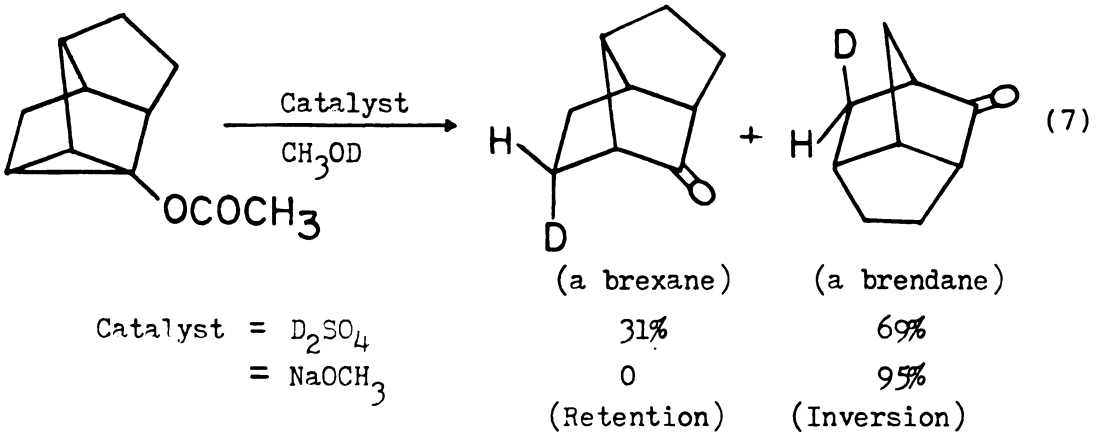
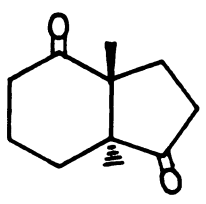


(7)

(Equation 5). However, the stereochemistry of these ring opening reactions appears to depend upon the solvent and the nature of the substrate being studied. In many instances, the stereochemistry of the ring-opened product is consistent

with the observations and interpretations reported by Cram and coworkers for electrophilic substitutions involving carbanionic intermediates[17].

Cyclopropanols such as 8 rearrange under acid- or base-catalysis to the synthetically useful intermediates 13, 14 and 15 in good yield.



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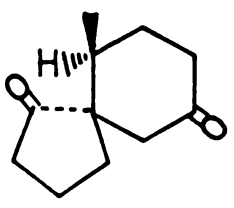

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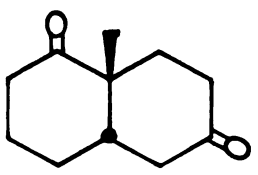
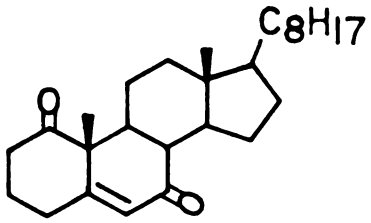


15

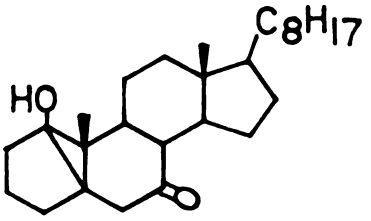
The formation of 13 from 8 has been shown to involve interaction of the cyclopropane moiety with the C(7) carbonyl group, giving an isomeric cyclopropanol which is then cleaved to the hydrindandione (13). Products such as 14 arise from 8 by C(1)-C(10) bond cleavage, occurring with retention of configuration, whereas products 13 and 15 are formed by C(1)-C(5) cleavage which occurs with inversion of configuration.

To extend the cyclopropanol studies of our research group[8,9] to steroids, a preparation of steroid 16 (cholestane series) was needed. Reduction of 16 with lithium in ammonia should yield cyclosterol 17. Since no steroid

having the functionality shown in formula 16 has been reported in the literature, a portion of this thesis is devoted to the synthesis of steroid 16. Subsequent reductive cyclization of 16 to 17 and a study of the acid and base-catalyzed ring opening reactions of 17, with comparisons to the parent system (8, 10 and 12), will also be discussed.



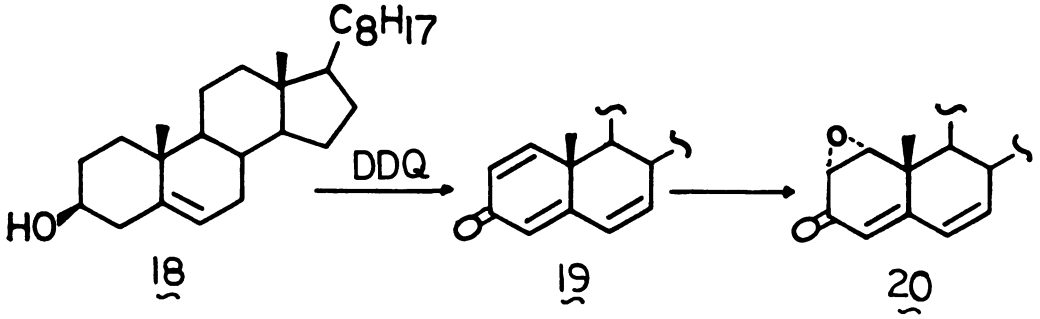
16



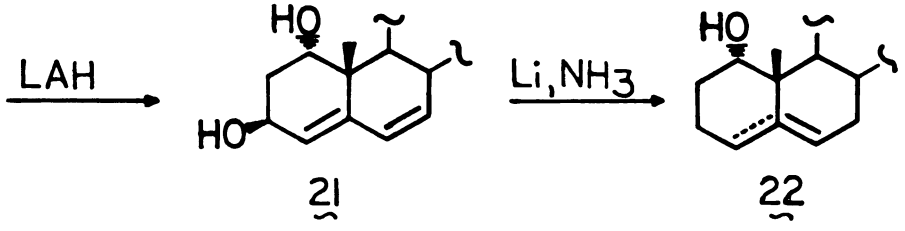
17

RESULTS AND DISCUSSION

Cholesterol 18 is an inexpensive starting material for the synthesis of 16 and was converted to 1α-hydroxy-5-cholestene 22 according to Okamura[18] (Equation 8).

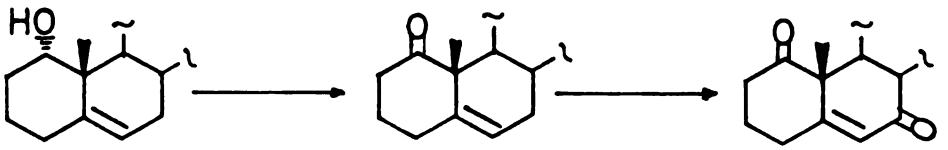


(8)



Samples of 22 prepared in this manner and purified by column chromatography were found to be a mixture of Δ^5 and Δ^4 isomers (roughly 3:1). Oxidation of 22 with pyridinium chlorochromate[19] or pyridinium dichromate[20] gave the

unsaturated ketone 23 as an equivalent mixture of Δ^5 and Δ^4 isomers. Allylic oxidation 22 with Collins reagent, according to Fullerton[21], gave a 25% yield of 16 (Equation 9). Attempted allylic oxidations with sodium



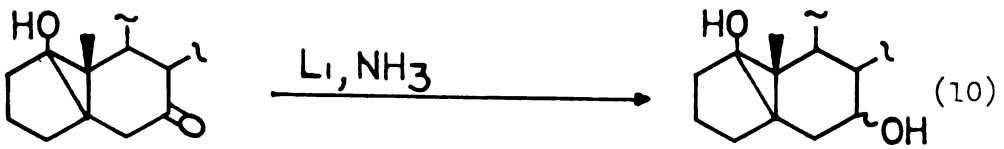
(9)

22 23 16

chromate[22], t-butylchromate[23], 3,5-dimethylpyrazole chromium trioxide complex[24], or N-bromosuccinimide[25] failed to improve this yield. Recycling recovered 23, from the allylic oxidation with Collins, reagent, gave an overall yield of 30% of 16.

Dissolving metal reduction of 16 by lithium in ammonia/THF gave 17 in over 85% yield. Subsequent reduction of 17 by lithium in ammonia yielded diol 24 (Equation 10), which was used without purification in a parallel series of acid and base-catalyzed isomerizations. The only structural characterization for 24 was the absence of carbonyl stretching absorption in its infrared spectrum.

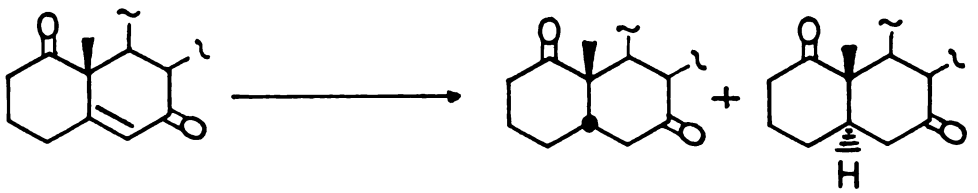
The cis and trans diketones 25 and 26 are potential products from the acid and base-catalyzed reactions of 17,



(10)

17 24

and were prepared independently by catalytic reduction of 16 (Equation 11). The known A/B-trans diketone 26 was separated from its cis isomer (25) by medium pressure liquid chromatography



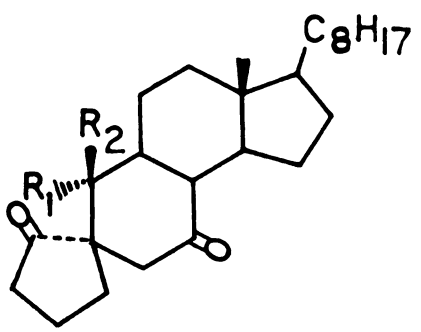
(11)

16 25 26[26]

Compounds 23, 16, 17, and 25 have not been previously described, and their molecular formulae were confirmed by mass spectrometry and elemental analysis. Support for the assigned structures was obtained in part from calculations

of the angular methyl ^{1}H NMR chemical shifts. Bhacca and Williams[27,28] have tabulated the effect of functional substitution at various positions on the chemical shifts of the C(18) and C(19) protons in the 5α,14α-androstane series. From the appropriate functional group increments, the calculated chemical shifts of the C(18) and C(19) protons for compounds 23, 16, 25, and 26 were compared with the observed values (Table 1). Good correlations were found for the assigned structures.

Table 2 lists the chief products from prolonged acid (hydrochloric acid in THF) and base (aqueous potassium hydroxide in THF) treatment of 17 and 24. They include 25, 26 and a difficult to separate mixture of epimeric spiro-diketones 27 and 28. The products from acid and base-catalyzed reactions of 24 were subjected to Jones oxidation prior to chromatography and analysis.



27 $R_1 = H$; $R_2 = CH_3$

28 $R_1 = CH_3$; $R_2 = H$

Table 1. Observed and Calculated C(18) and C(19) Methyl Resonances for Compounds 23, 16, 25, and 26.

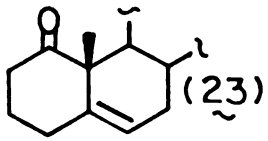
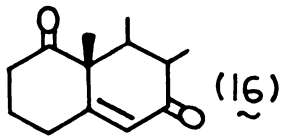
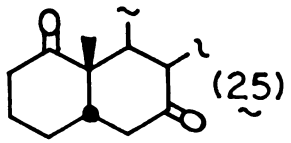
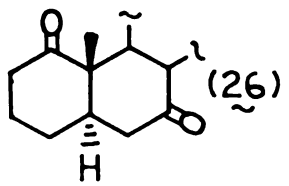
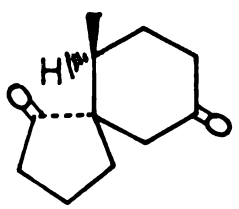
Compound	C(18) Obs (ppm)	C(18) Calcd (ppm)	C(19) Obs (ppm)	C(19) Calcd (ppm)	Steroid Increment Used
 (23)	0.676	0.701	1.266	1.383	5α,14α-androstane 1-oxo, Δ^5, 17β-C_8H_{17}
 (16)	0.689	0.701	1.420	1.542	5α,14α-androstane 1-oxo, Δ^5, 7-oxo, 17β-C_8H_{17}
 (25)	0.645	0.650	1.401	1.400	5β,14α-androstane 1-oxo, 7-oxo, 17β-C_8H_{17}
 (26)	0.650	0.667	1.412	1.425	5α,14α-androstane 1-oxo, 7-oxo, 17β-C_8H_{17}

Table 2. Acid and Base-Catalyzed Reactions of Cyclosterols 17 and 24.

Substrate	Reaction Conditions	Products
17	HCl, THF, 25°, 6 hr.	25 (13%) + 26 (38%) + 27 and 28 (25%) (70:30)
24	1) HCl, THF, 25°, 12 hr 2) Jones oxidation	25 (trace) + 26 (trace) + 27 and 28 (78%) (70:30)
17	KOH, THF/CH_3OH, 25°, 12 hr	25 (66%) + 26 (trace) + 27 and 28 (16%) (70:30)
24	1) KOH, THF/CH_3OH, 25°, 12 hr 2) Jones oxidation	25 (46%) + 26 (trace) + 27 and 28 (30%) (70:30)

The product distributions shown in Table 2 indicate that cyclosterols 17 and 24 undergo acid and base-catalyzed ring opening isomerizations comparable to those reported earlier for 8 and some of its derivatives (Table 3). In particular, removal of the homo-conjugated carbonyl function (as in 24) changes the regioselectivity of these isomerizations in similar ways. For example, both 24 and 30 give a spirodiketone (after Jones oxidation) as the chief product, upon treatment with acid. Two interesting differences between the reactions of 17 and 8 may be noted. First, the stereoselectivity of the C-protonation (leading to 27 and 28) is poorer in the ring opening of 17 than in the equivalent reaction of 8. For example, spiro[5.4]decane products such as 14 are formed from 8 or 30, with exclusive



14

retention of configuration; but 27 and 28 appear to be formed together in roughly 70:30 ratio from both acid and base-catalyzed reactions of 17 and 24. The major epimer, 27, has been assigned the axial methyl configuration

Table 3. Acid and Base-Catalyzed Reactions of 8 and Selected Derivatives.

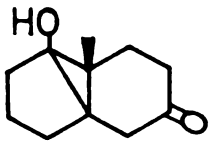
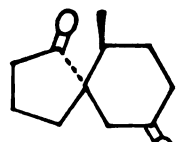
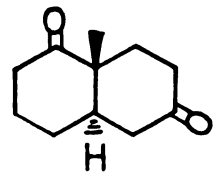
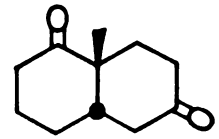
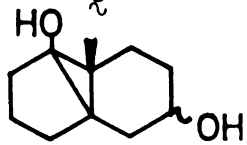
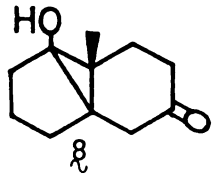
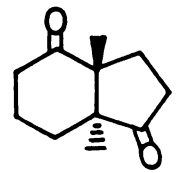
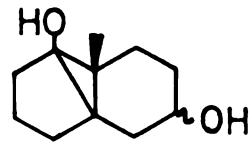
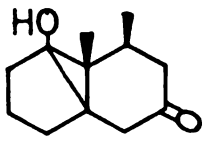
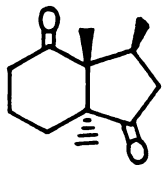
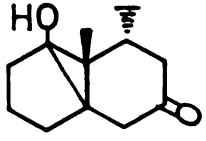
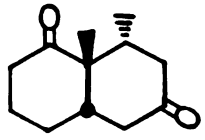
Substrate	Reaction Conditions	Products (Yield)		
 8	HCl in THF, 60°, 2-6 hr	 14 (22)	 29 (19)	 15 (59)
 30	HCl in CH_3OH, 25°, 2-10 hr	14 (90)	29 (trace)	15 (10)
 8	KOH in CH_3OH, 25° 2-10 hr	14 (trace)	 13 (80)	15 (20)
 30	KOH in CH_3OH, 25°, 2-10 hr	14 (60)	------	15 (40)

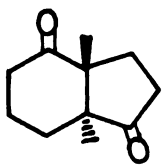
Table 3. Continued.

Substrate	Reaction Conditions	Products (Yield)
 10	KOH, in CH_3OH, 25°, 2-10 hr	 31 (89)
 12	KOH in CH_3OH, 25°C 2-10 hr	 32 (99)[a]

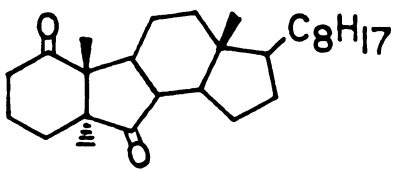
[a]As intramolecular aldol products.

(retention of configuration) on the strength of the chemical shift difference observed for the methyl doublets: 27 (δ1.145 ppm, J = 7.0 Hz), 28 (δ0.935 ppm, J = 6.9 Hz). In this rigid framework an axial methyl group at C(10) (as in 26) is deshielded by the carbonyl function at C(7)[2] (assuming ring B adopts a chair conformation).

A second difference between reactions of 17 and 8 is the absence of a β-norsteroid product 33, equivalent to 13 in the parent system, among the tetracyclic isomers obtained from 17. The formation of 13, by the action of

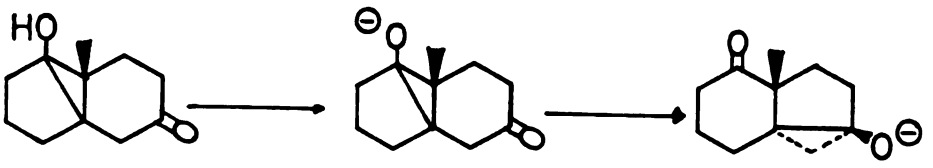


13



33

base on 8, has been proposed to proceed through an isomeric cyclopropoxide 35, which undergoes a regiospecific cleavage of the C(6)-C(7) bond to give 13 (Equation 12). The formation 35 involves an interaction of the carbonyl group with the cyclopropane ring, causing a shift of the C(1)-C(5) bond to the C(5)-C(7) position. A similar β-homoenolate

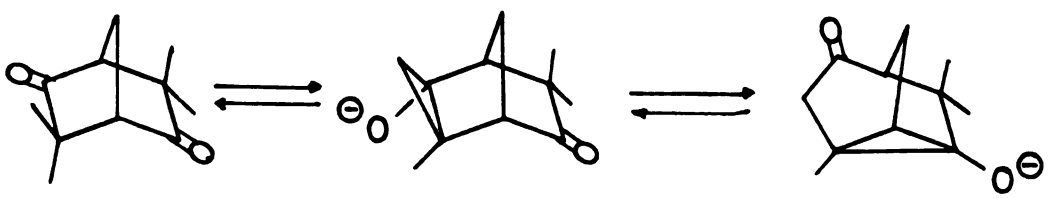


8 34 35

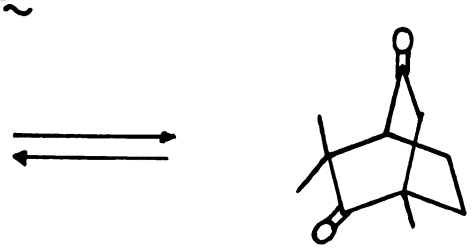
(12)

13

rearrangement has been proposed in the base promoted conversion of diketone 36 to the bicyclooctane 37[29] (Equation 13).



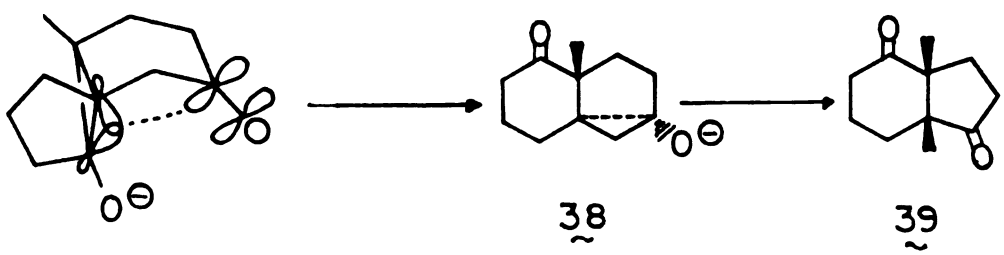
36



37

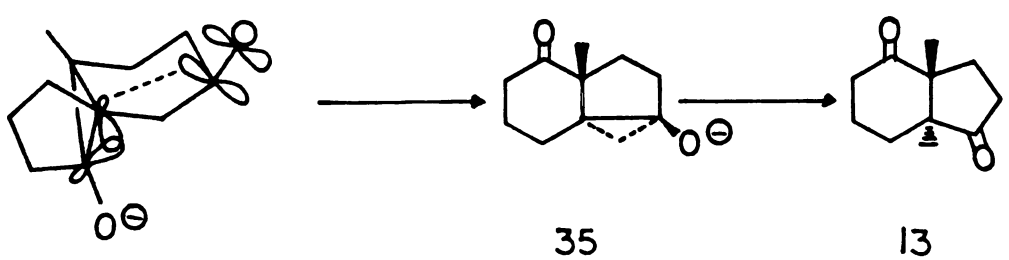
(13)

The six-membered ring of 34 (or 8) can assume one of two possible boat conformations relative to the three membered ring. Thus two kinds of interaction between the cyclopropane ring and the C(7) carbonyl group can be envisioned (Equation 14 and 15).



38 39

(14)

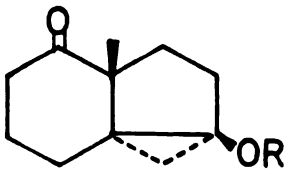


35 13

(15)

Neither the cis-indane 39, nor derivatives of 38, has ever been obtained as a product from 8. Apparently, the interaction leading to 38 does not occur. In fact, it has been noted that cyclopropyl interactions similar to those described here generally proceed with inversion of configuration of the carbon atom common to both three membered

rings[30]. Although the cyclopropanol corresponding to 35 (40a) has never been observed directly, 35 has been trapped as its acetate 40b, which is rapidly converted to 13 on



40a R = H

b R = $OCOCH_3$

treatment with base.[8]

Substituents on 8 which favor conformation B^1 rather than B^2, or which cause subtle changes in the required cyclopropyl-carbonyl orientation and interaction would be expected to hinder formation of the trans-hydrindandione. This hypothesis is supported by the observation that base treatment of 10 gave exclusively the trans-hydrindandione 31, whereas 12 was transformed exclusively to the cis-decalin 32 under similar conditions (Table 3). The more stable conformation of 10,(10b), orients the methyl substituent (R_1 = CH_3) in an equatorial-like position. On the other hand, conformational analysis predicts that the B^1 type conformation, 12a, would be favored in 12 because the methyl substituent (R_2 = CH_3) would occupy an equatorial-like position.

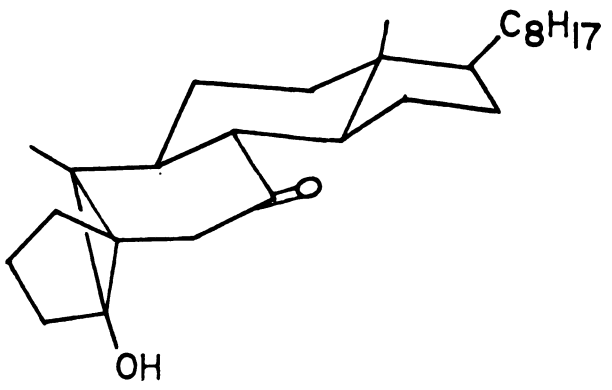
B^1 ..... BOAT CONFORMATION ..... B^2

$\underset{\sim}{8}_a$ ..... $R_1 = H$; $R_2 = H$ ..... $\underset{\sim}{8}_b$

$\underset{\sim}{10}_a$ ..... $R_1 = CH_3$; $R_2 = H$ ..... $\underset{\sim}{10}_b$

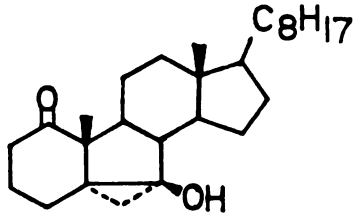
$\underset{\sim}{12}_a$ ..... $R_1 = H$; $R_2 = CH_3$ ..... $\underset{\sim}{12}_b$

This conformational argument cannot be used to explain the absence of norsteroid 33 from reactions of 17. Cyclosterol 17 can adopt only a B^2 type boat conformation, because ring C must necessarily be fused to ring B in a diequatorial fashion. Consequently, the cyclopropyl-carbonyl group orientation necessary for the C(1)-C(5) to C(5)-C(7) bond shift is easily achieved by 17. Indeed,



17 in a B^2 boat conformation

this bond shift is observed. Mild base treatment of 17 gave the isomeric 5,7β cyclosterol 41 in 23% yield, together with 25 (16%), 27 and 28 (8%), and recovered 17 (33%).



41

The configuration of the cyclopropane ring in 41 was assigned by comparing the ^1H NMR signals of the C(19)

methyl and the 6 (α and β) cyclopropyl protons with the corresponding signals reported for known 5,7β-cyclosteroids and their 5,7α isomers[31 (a-c)]. Using the additive approach described by Zurcher[27,28] for calculating the C(19) methyl shifts in steroids, the influence of the 5,7-cyclopropane moiety upon the C(19) methyl shift was determined. Thus, the C(19) methyl shifts for a series of known 5,7β-cyclosteroids were calculated ignoring the effect of the cyclopropane ring. These calculated C(19) methyl shifts were subtracted from the observed C(19) methyl shifts and the resulting shift differences were averaged to obtain a value of 0.09±0.02 ppm (downfield). This value represents the downfield shift of the C(19) methyl resonance induced by the cyclopropane moiety of a 5,7β-cyclosteroid (Table 4). A similar analysis of two 5,7α-cyclosteroids, reported by Joska et al.[31 c], indicates that the configurationally isomeric cyclopropane moiety in these cyclosteroids causes a -0.22±0.03 ppm (upfield) shift of the C(19) methyl signal (Table 5). In both of these computations the 5α-cholestane system was used as a reference, since it more closely approximates the shape of both the 5,7α-and 5,7β-cyclosteroids than does 5β-cholestane. The 5,7-cyclopropyl group increments calculated in this fashion were then used to calculate the C(19) methyl shift in cyclosterol 41 (Table 6). The good correlation between the calculated C(19) methyl shift (δ1.262 ppm) and

Table 4. Observed and Calculated C(19) Shifts for a Series of 5,7β-Cyclosteroids.[a]

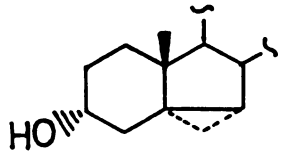
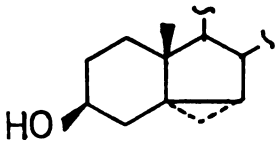
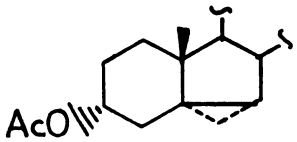
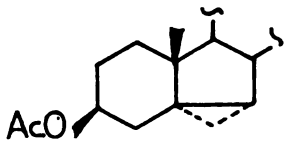
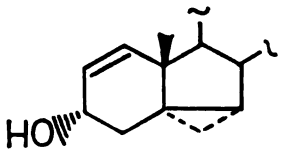
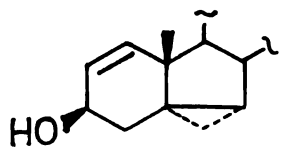
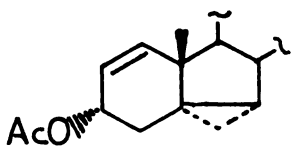
5,7β-Cyclosteroid	C^{19} Obs (ppm)	C^{19} Calcd (ppm)	$\Delta_{Obs-Calcd}$ (ppm)	Steroid Increment Used
	0.88	0.775	0.105	3α-OH
	0.89	0.808	0.082	3β-OH
	0.89	0.800	0.090	3α-OAc
	0.92	0.825	0.0095	3β-OAc

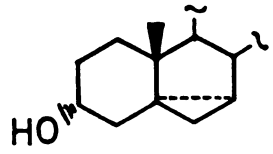
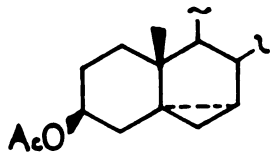
Table 4. Continued.

5,7β-Cyclosteroid	C^{19} Obs (ppm)	C^{19} Calcd (ppm)	ΔObs-Calcd (ppm)	Steroid Increment Used
	0.91	0.825	0.085	3α-OH, Δ^1
	1.00	0.858	0.142	3β-OH Δ^1
	0.92	0.85	0.07	3α-OAc, Δ^1

*ΔObs-calcd. ≈ 0.09±0.2 ppm (average, α-5,7-Cyclopropane ring).

[a]Based on a 0.775 ppm reference value for the 5α-cholestane system.

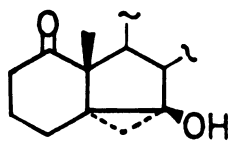
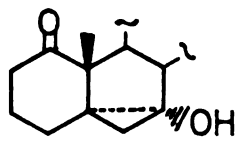
Table 5. Observed and Calculated C(19) Shifts for Two 5,7α-Cyclosteroids.[a]

5,7α-Cyclosteroid	C^{19} Obs (ppm)	C^{19} Calcd (ppm)	$\Delta_{Obs-Calcd}$ (ppm)	Steroid Increment Used
	0.59	0.775	-0.185	3α-OH
	0.57	0.825	-0.255	3β-OAc

*$\Delta_{Obs.-calcd.}$ = -0.22±0.03 ppm (average, β-5,7-cyclopropane ring).

[a]Based on a 0.775 ppm reference value for the 5α-cholestane system.

Table 6. Calculated C(19) Methyl Shifts for 41 and 42.[a]

Cyclosterol	C(19) Calcd. (ppm)	Steroid Increments Used
 41	1.262	1-oxo, α-5,7-cyclopropane (Table 4), 7β-OH
 42	0.992	1-oxo, β-5,7-cyclopropane (Table 5), 7α-OH

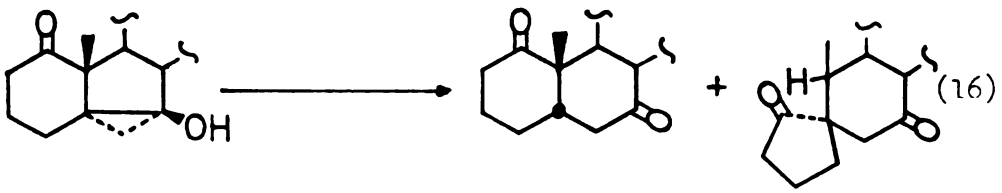
[a]Based on a 0.775 ppm reference value for the 5α-cholestane system.

the observed value of δ1.245 ppm supports 41 as the assigned structure rather than the isomeric 5,7α-cyclosteroid 42.

The geminal cyclopropyl protons in 41 appear as broad doublets at δ0.23 and 1.00 ppm, J = 5.57 Hz, in its ^{1}H NMR spectrum. Some long-range coupling is apparent on close inspection of these signals, and a model suggests that protons at C(8) and C(4)-(β) are ideally oriented for coupling with the 6β and 6α protons respectively. Also note that the relatively small chemical shift (δ0.23 ppm)

associated with one of the cyclopropyl protons, presumably 6β, corresponds to observations made with authentic 5,7β-cyclosteroids[31]. Since the isomeric 5,7α-cyclosteroids[31c] do not exhibit any ^{1}H NMR signals at higher field than the C(18) methyl singlet (@ δ0.70 ppm), this is additional support for the assigned 5,7β-cyclosteroid configuration.

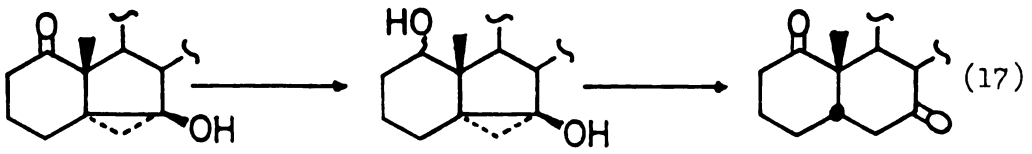
Treatment of 41 with potassium hydroxide in a THF-methanol solution yielded a mixture of 25, 27 and 28 (Equation 16) similar to that obtained from 17 (Table 2). It



41 25(60%) 27 + 28 (10%)

is clear that 17 and 41 must be interconverted under these reaction conditions, but the failure of the latter to isomerize to the β-norsteroid 33 remains unexplained. Such a product would be formed initially in a trans-anti-trans configuration of rings A, B, and C, and this appears to be more strained than the normal steroid ring system. Consequently, it is possible that reaction of 41 by cleavage of the C(6)-C(7) bond is less favorable than the comparable reaction of 40b. When 41 was reduced (Li in NH_3), followed by base treatment and Jones oxidation, 25 was

the only product (Equation 17). Thus, both 41 and 43



(17)

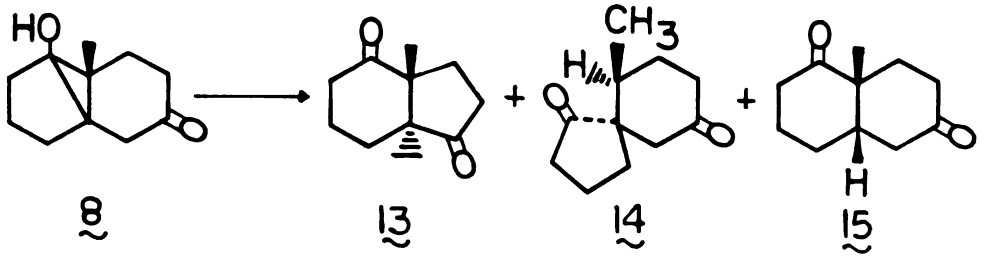
41 43 25

react by cleavage of the C(5)-C(7) bond with retention of configuration. Cyclosterols 17 and 24 react by cleavage of the C(1)-C(10) bond with both retention and inversion of configuration (leading to 27 and 28) or by cleavage of the C(1)-C(5) bond with inversion of configuration.

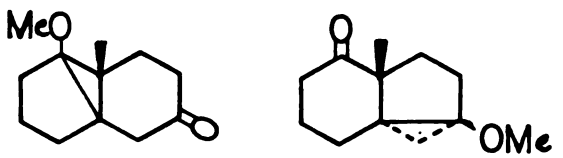
Under basic conditions, it is clear that 17 and 41 are interconverted (Equation 16). This interconversion appears to occur as well during the acid catalysis of 17, since 41 was detected by TLC as a transitory product. This behavior parallels that of the parent system 8, which upon mild treatment with hydrochloric acid in methanol yielded the isomeric 5,7-cyclopropyl-methyl ether 45 as the major product (Equation 18).

One last difference between the reactivity of 17 versus 8 is that the acid catalyzed isomerization of 17 (Table 2) generates a larger amount of the trans decalin 26, than does 8.

Overall, the reactivity of 17 generally parallels that



8 13 14 15 (18)



44 45

of the parent system 8. As with 8, a cyclopropyl-carbonyl group interaction has been demonstrated in 17. As is often observed during acid-catalyzed opening of cyclopropanols, cyclosterol 17 exhibits poor regioselectivity during the ring-opening, however, this reaction is complicated by the cyclopropyl-carbonyl group interaction. Removal of the C(7) carbonyl group, as in 24, followed by acid treatment, yielded (after oxidation) spiro-diketones 27 and 28 as the exclusive product. The absence of the B-norsteroid product 33 may be rationalized in terms of the trans-anti-trans configuration of rings A, B and C which appears to be more strained than the normal steroid system.

EXPERIMENTAL

General

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

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

were obtained with a Finnigan 4000 GC/MS spectrometer.

Preparation of Cholest-5-ene-1-one (23)

To a stirred slurry of 1.05 g (4.9 mmol) of pyridinium chlorochromate in 3 mL of methylene chloride was added a solution of 1.0 g (2.59 mmol) of 1-hydroxycholest-5-ene (22) in 2 mL methylene chloride. This mixture was stirred for 2 hours, diluted with 20 mL of ether and decanted. The black precipitate was washed with ether and the combined ether solutions were filtered through a layer of florisil. Evaporation of the ether gave 0.8 g of a yellow oil which was crystallized from acetone-methanol to afford 0.72 g (72/) of 23, mp 97-101°C. This mixture of Δ^5 and Δ^4 isomers (roughly 70:30) exhibited the following properties: IR ($CHCl_3$) 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ0.677 (s, 3H, C-18), 0.862 (d, 3H, J = 6.55 Hz), 0.865 (d, 3H, J = 6.55 Hz), 0.911 (d, 3H, J = 6.55 Hz, C-21), 1.266 (s, 3H, C-19), 5.50 (br, s, 1H, C-6); ^{13}C NMR ($CDCl_3$) δ195.03, 194.44, 146.57, 141.33, 122.86, 117.51, 56.81, 56.40, 53.76, 51.01, 42.64, 42.46, 39.76, 39.64, 38.11, 36.58, 36.34, 36.17, 35.94, 33.64, 31.99, 31.23, 28.23, 28.05, 27.56, 26.05, 24.34, 24.05, 22.86, 22.64, 19.06, 18.76, 15.12, 12.96, 12.06; MS (70 eV) m/e (rel. intensity) 384 (M^+, 100), 369(15), 27(17), 176(45), 124(47).

Anal. Calcd. for $C_{27}H_{44}O$: C, 84.31; H, 11.53

Found : C, 84.08; H, 11.61.

Preparation of Cholest -5-ene-1,7-dione 16

To a cold (0°) solution of 25.0 g (0.3 mmol) of pyridine in 300 mL of methylene chloride was added with stirring 15.0 g (0.15 mmol) of chromium trioxide. The resulting burgundy colored solution was slowly warmed to room temperature, following which a solution of 4.0 g (0.01 mmol) of 23, dissolved in 3 mL of methylene chloride, was added one portion. An additional portion of the chromium trioxide-pyridine complex (prepared as above) was added after a 24 hr reaction period, and this reaction mixture was stirred for an additional 48 hours. The reaction mixture was decanted, the tarry precipitate was washed three times with 150 mL portions of methylene chloride and the combined solutions were evaporated to afford a dark oil which was then dissolved in 500 mL of ether and filtered. This ether filtrate was washed twice with 150 mL portions of 5% hydrochloric acid, 150 mL of brine, and then dried. Evaporation of the solvent and chromatography of the resulting solid (silica gel, 35% ethyl acetate/hexane) gave 200 mg of recovered 23 and 800 mg (25%) of 16 as a white solid. An analytical sample prepared by recrystallization from methanol, mp 81-82°C, exhibited the following properties: IR ($CHCl_3$) 1715, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ0.689 (s, 3H, J = 6.55 Hz), 0.860 (d, 3H, J = 6.72 Hz), 0.863 (d, 3H, J = 6.55 Hz), 0.915 (d, 3H, J = 6.57 Hz, C-21), 1.419 (s, 3H, C-19), 5.803 (d, 1H, J = 1.37 Hz); ^{13}C NMR ($CDCl_3$)

δ200.38, 196.92, 163.99, 126.10, 54.98, 50.36, 45.12, 43.39, 43.24, 39.49, 38.75, 37.01, 36.21, 35.65, 30.48, 28.46, 27.93, 26.18, 23.87, 23.18, 22.77, 22.53, 18.88, 16.65, 12.12; MS (70 eV) m/e (rel. intensity) 398 (M^+, 2), 380 (22), 342(50), 55(100).

Anal. Calcd. for $C_{27}H_{42}O_2$: C, 81.35; H, 10.62

Found : C, 81.10; H, 10.70

Preparation of 1-hydroxyl-1,5α-cyclocholestan-7-one 17

In a fifty milliliter, three neck, round bottom flask, containing a small piece of sodium metal, was condensed 30 mL of ammonia. The ammonia was then distilled through tygon tubing into a carefully dried fifty milliliter, three neck, round bottom flask containing 30.0 mg (4.2 mmol) of lithium wire. This reaction flask was equipped with a magnetic stir bar, a dry ice condenser, a dry ice-acetone bath, a nitrogen gas inlet, and a septum inlet. By means of a syringe, 5 mL of tetrahydrofuran was added to the ammonia solution, followed by a solution of 300 mg (0.75 mmol) of 16 dissolved in 4 mL of tetrahydrofuran, added dropwise. The reaction mixture was allowed to stir for 0.5 hr and was then quenched with approximately 1 g of solid ammonium chloride. The cooling bath was removed and the ammonia evaporated under a stream of nitrogen. The residue was taken up in an ether and water mixture, and the organic layer was washed with water, brine and finally dried over

sodium sulfate. Evaporation of the solvent gave 267 mg (89%) of 17 as a white foam of purity >90%, which was used without purification for the subsequent ring opening reactions. Thin layer chromatography (silica gel, 35% ethyl acetate/hexane) of the crude cyclopropanol showed it to be homogeneous, R_f = 0.39, except for a small amount of 16. An analytical sample, mp 113-118°C, was prepared by recrystallization from acetone, and exhibited the following properties: IR ($CHCl_3$) 1700, 3350 cm^{-1}; ^1H NMR ($CDCl_3$) δ0.718 (s, 3H, C-18), 0.856 (d, 3H, J = 6.4 Hz), 0.860 (d, 3H, J = 6.75 Hz), 0.915 (d, 3H, J = 6.43 H_2, C-21), 0.928 (s, 3H, C-19); ^{13}C NMR (benzene d-6) δ194.46, 71.28, 55.60, 52.03, 47.36, 43.70, 40.04, 39.87, 39.54, 39.16, 36.60, 36.20, 33.92, 33.44, 32.33, 30.67. 28.56. 28.45, 26.03, 24.74, 24.31, 23.37, 23.02, 22.78, 19.14, 11.97, 8.27; MS (70 eV) m/e (rel. intensity) 400 (M^+, 15), 382 (10), 151(65), 124(100).

Anal. Calcd. for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07
Found : C, 81.23; H, 10.92.

Preparation of 5β-Cholestane-1,7-dione (25) and 5α-Cholestane-1,7-dione (26)

A solution of 50.0 mg (0.13 mmol) of 16 in 3.5 mL of ethyl acetate was hydrogenated over 10% palladium on charcoal for 20 hours (1 atm. H_2). This solution was filtered and evaporated to afford 50 mg of an oil, which on

chromatography (silica gel, 25% ethyl acetate/hexane) yielded 18 mg (36%) of 25 and 28 mg (56%) of 26. Analytical sample of 26, mp 110-111°C (lit. mp 110-111°C)[5], was prepared by recrystallization from 95% ethanol. An analytical sample of 25, mp 148-148.5°C, prepared by recrystallization from 95% ethanol exhibited the following properties: IR ($CHCl_3$) 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ0.645 (s, 3H, C-18), 0.857 (d, 3H, J = 6.55 Hz), 0.862 (d, 3H, J = 6.55 Hz), 0.884 (d, 3H, J = 6.73 Hz, C-21), 1.401 (s, 3H, C-19): MS (70 eV) m/e (rel. intensity) 400 (M^+, 10), 382(2), 111 (30), 43(100).

Anal. Calcd. for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07
Found : C, 81.17; H, 11.08

Acid Catalyzed Opening of Cyclopropanol 17

A solution of 60 mg (0.15 mmol) of 17 in 4 mL of tetrahydrofuran, containing four drops of concentrated hydrochloric acid, was stirred for 6 hours at room temperature. The reaction mixture was diluted with ether, washed with saturated bicarbonate, and dried. Evaporation of the solvent followed by chromatography of the resulting oil (silica gel, 25% ethyl acetate/hexane) gave 8 mg (13%) of 25, 23 mg (38%) of 26, 15 mg (25%) of 27 and 28 (70:30), mp 121-128°C, and 3 mg of 16. Combining the remaining fractions gave 4 mg of an oil containing three unidentified products. The epimeric mixture of 27 and 28 exhibited the following

properties: IR ($CHCl_3$) 1710, 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ0.656 (s, 3H, C-18, 27), 0.664 (s, 3H, C-18, 28), 0.859 (d, 3H, J = 6.55 Hz, 27 and 28), 0.864 (d, 3H, J = 6.7 Hz, 27 and 28), 0.906 (d, 3H, J = 6.55 Hz, C-21 27 and 28), 0.936 (d, 3H, J = 6.85 Hz, equatorial C-19, 28), 1.146 (d, 3H, J = 7.03 Hz, axial C-19, 27); MS (70 eV) m/e (rel. intensity) 400 (M, 10), 382(9), 290(20), 111(30), 55(48), 43(100).

Base Catalyzed Ring Opening of 17

To a solution of 60 mg (0.15 mmol) of 17 in 4 mL of tetrahydrofuran at 0°C was added 0.35 mL (0.45 mmol) of a solution of 0.35 g (6.3 mmol) of potassium hydroxide in 8 mL of a deoxygenated mixture of methanol and water (1:1). This solution was stirred for 2 hours at 0°C and then overnight at room temperature. The reaction mixture was diluted with ether, washed successively with water and brine, and dried. Evaporation of the solvent followed by chromatography of the resulting oil (silica gel, 25% ethyl acetate/hexane) gave 40 mg (66%) of 25, 10 mg (16%) of 27 and 28 (70:30), and 3 mg of 16.

Preparation of 7-hydroxy-5,7β-cyclocholestan-1-one

To a stirred solution of 60 mg (0.15 mmol) of 17 in 4 mL of tetrahydrofuran was added 0.35 mL (0.45 mmol) of

the same KOH solution used in the previous experiment. The progress of this reaction, including the formation of 41, was followed by TLC analysis (silica gel, 35% ethyl acetate/hexane). After 5 hours, the reaction mixture was diluted with ether, washed successively with water and brine, and dried over sodium sulfate. Evaporation of the solvent, followed by chromatography of the resulting oil (silica gel, 25% ethyl acetate/hexane), gave 6 mg (10% of 25, 20 mg of 17, 3 mg of 27 and 28, 3 mg of 16, 3 mg of an oil containing two unidentified components, and 14 mg (23%) of 41, mp 92-94°C. This crystalline solid exhibited the following properties: IR ($CHCl_3$) 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ0.229 (d, 1H, J = 5.57 Hz), 0.673 (s, 3H, C-18), 0.863 (d, 3H, J = 6.53 Hz), 0.879 (d, 3H, J = 6.7 Hz), 0.915 (d, 3H, J = 6.58 Hz, C-21), 0.996 (d, 1H, J = 5.57 Hz), 1.245 (s, 3H, C-19); MS (70 eV) m/e (rel. intensity) 400 (M, 11), 385(8), 151(30), 124(35), 55(60), 43(100).

Base Catalyzed Ring Opening of 41

To a solution of 10 mg (0.025 mmol) of 41 in 1 mL of tetrahydrofuran at 0°C was added 58 μL (0.075 mmol) of the previously described KOH solution. After 2 hours at 0°C and then overnight at room temperature, the reaction mixture was diluted with ether, washed with water and dried. Evaporation of the solvent followed by chromatography of the resulting oil gave 6 mg (60%) of 25 and 1 mg (10%) of 27 and 28 (70:30).

Preparation of 24

A solution of 200 mg (0.5 mmol) of 17 in 15 mL of tetrahydrofuran was added to a cold (-78°C) solution of 28 mg (4.0 mmol) of lithium in 15 mL of freshly distilled ammonia. This solution was refluxed for 2 hours and then quenched with ammonium chloride. Workup as described earlier for the preparation of 17 gave 180 mg (90%) of 24 (epimeric mixture) as a white solid having no carbonyl absorption in the infrared.

Acid Catalyzed Ring Opening of 24

A solution of 60 mg (0.15 mmol) of 24 in 4 mL of tetrahydrofuran containing 4 drops of concentrated hydrochloric acid was stirred overnight. The reaction mixture was diluted with ether, washed with saturated sodium bicarbonate, and dried. Evaporation of the solvent gave 55 mg of isomeric ketols which were oxidized with Jones reagent. Chromatography of the crude oxidation product (silica gel, 25% ethyl acetate/hexane gave 47 mg (78%) of 27 and 28 (70:30). Trace amounts of 25 and 26 could be detected by TLC.

Base Catalyzed Ring Opening of 24

To a solution of 60 mg (0.15 mmol) of 24 in 4 mL of tetrahydrofuran was added 0.35 mL (0.45 mmol) of the usual KOH solution. This solution was stirred overnight, and

workup in the usual manner gave 52 mg of a white solid, which was oxidized with Jones reagent. Chromatography of the crude oxidation product (silica gel, 25% ethyl acetate/hexane) gave 28 mg (46%) of 25 and 18 mg (30%) of 27 and 28 (70:30). A trace of 26 was detected by TLC.

Reduction and Subsequent Reaction of 41

A solution of 4.0 mg (0.01 mmol) of 41 in 1 mL of tetrahydrofuran was added to a solution of 4 mg (0.58 mmol) of lithium in 1 mL of freshly distilled ammonia, cooled to -78°C. This solution was refluxed for 2 hours and then quenched with ammonium chloride. Workup as described for the preparation of 17 gave 3 mg of a white solid, which was immediately dissolved in 1 mL of tetrahydrofuran. To this solution was added 29 μL (0.037 mmol) of the standard base solution and was stirred overnight. Workup in the usual manner followed by Jones oxidation of the residue and chromatography of the crude oxidation product (silica gel, 25% ethyl acetate/hexane) gave 2.0 mg (50%) of 25.

APPENDIX I: SPECTRA PART I

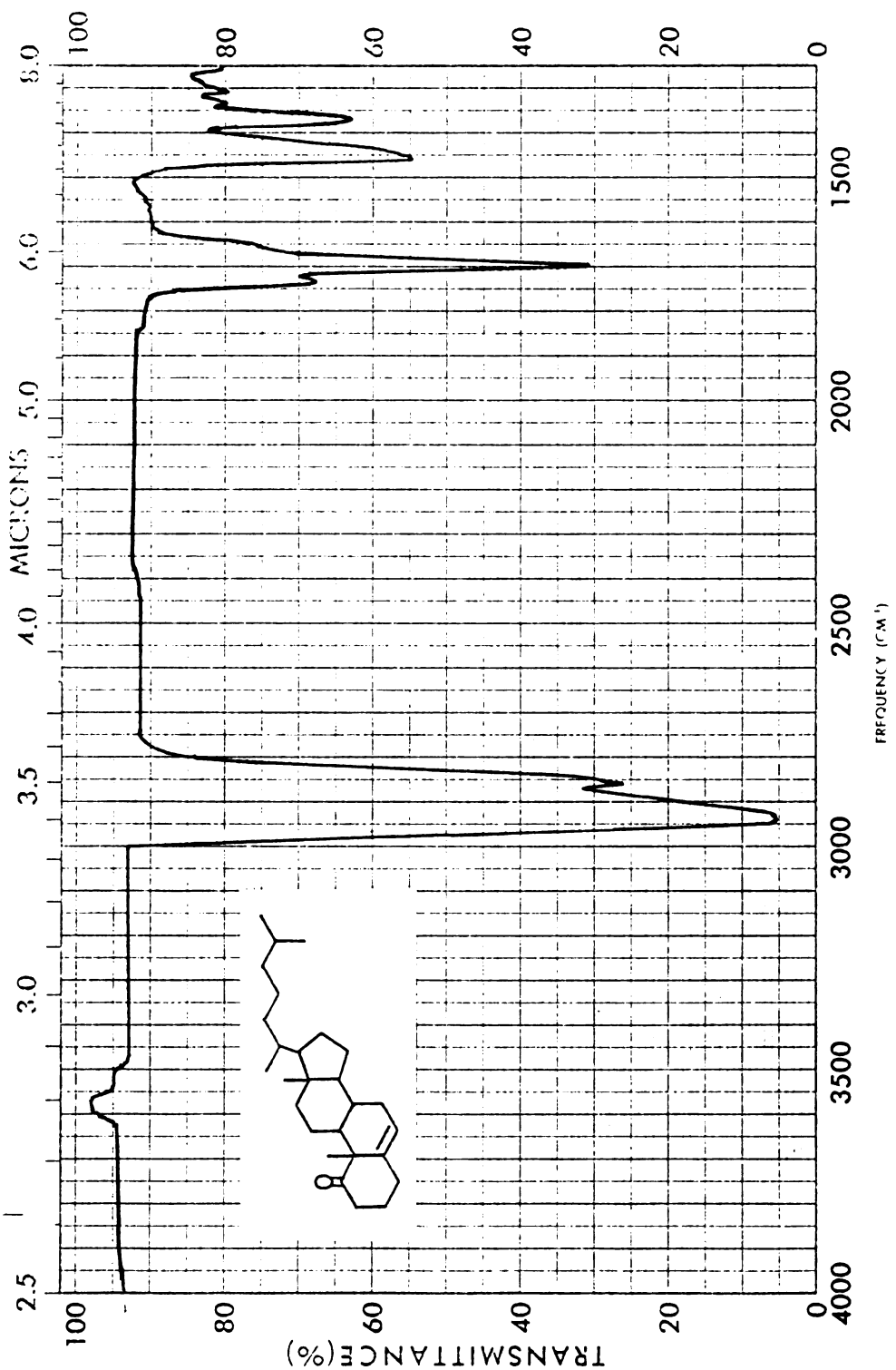


Figure I-1. IR of 23.

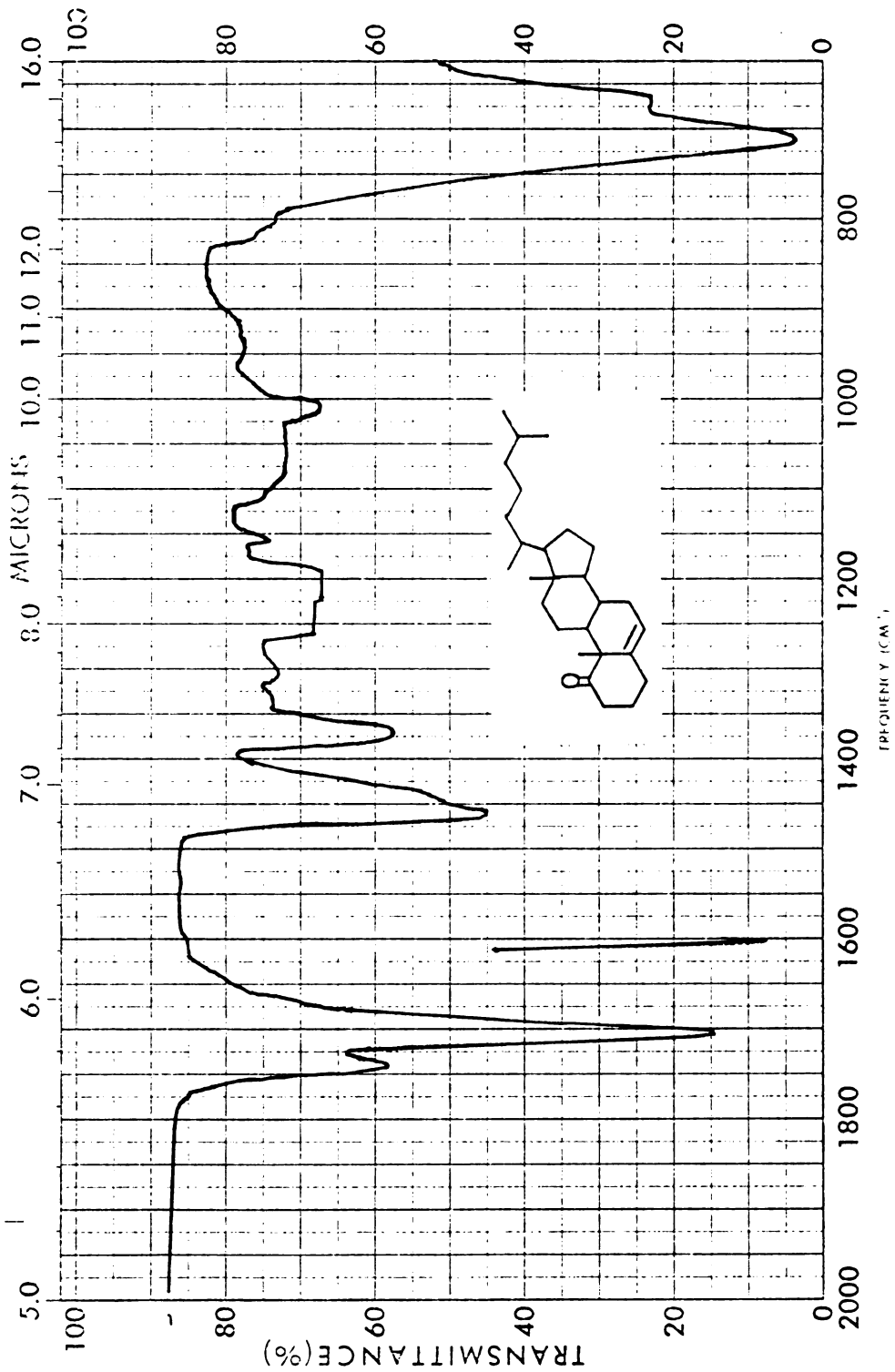


Figure I-2. IR of 23.

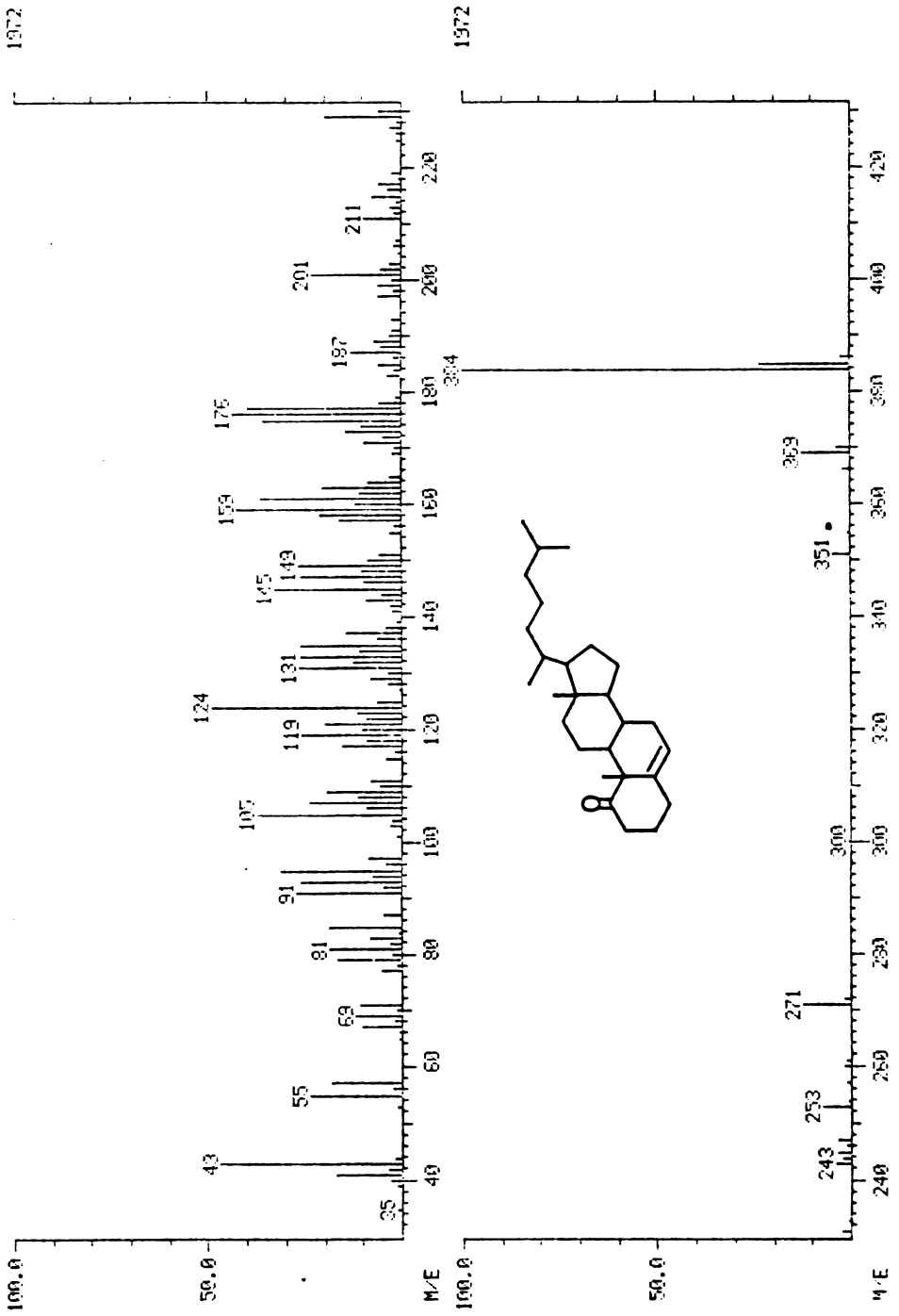


Figure I-3. Mass spectrum of 23.

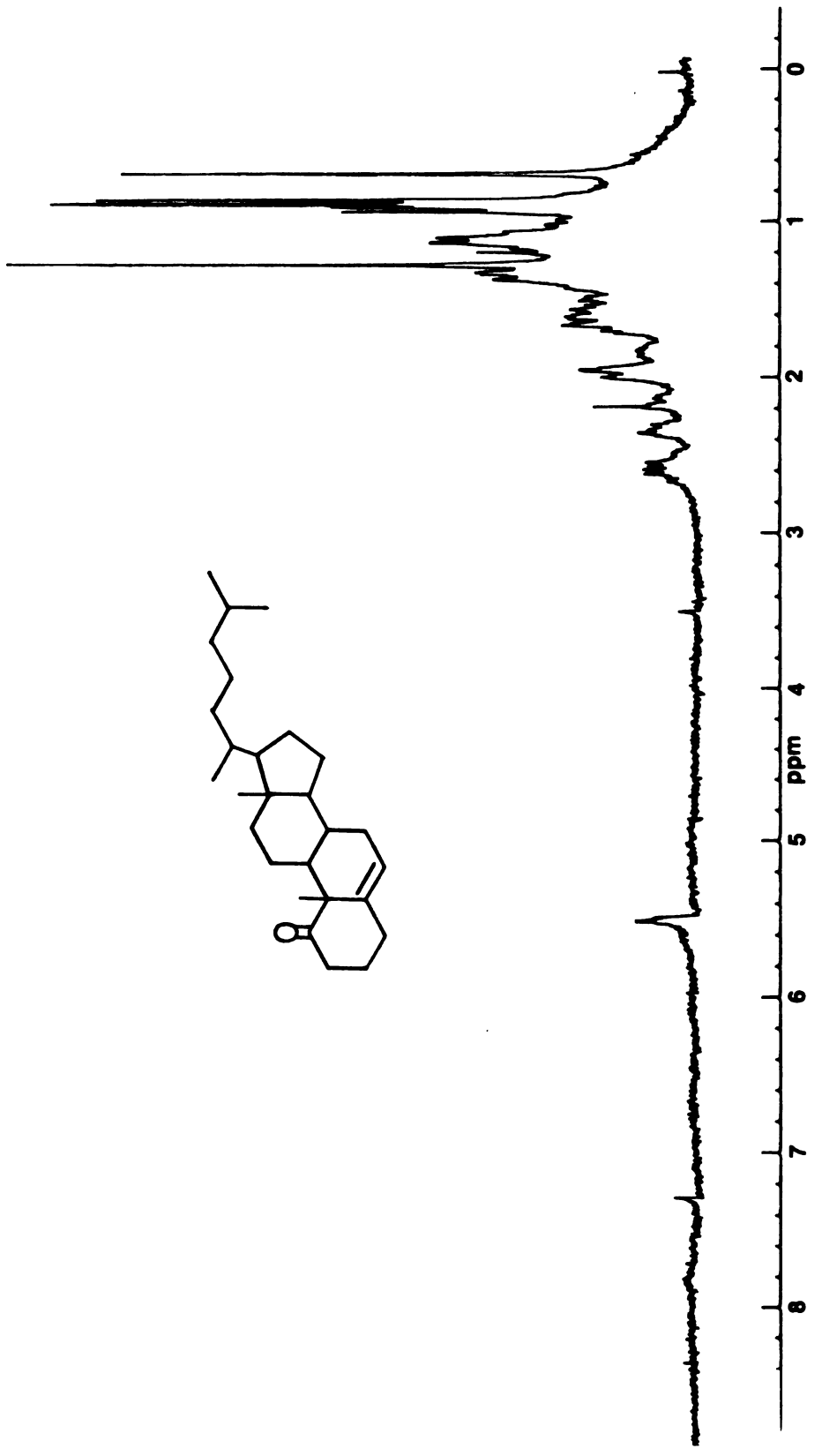


Figure I-4. Proton NMR of 23.

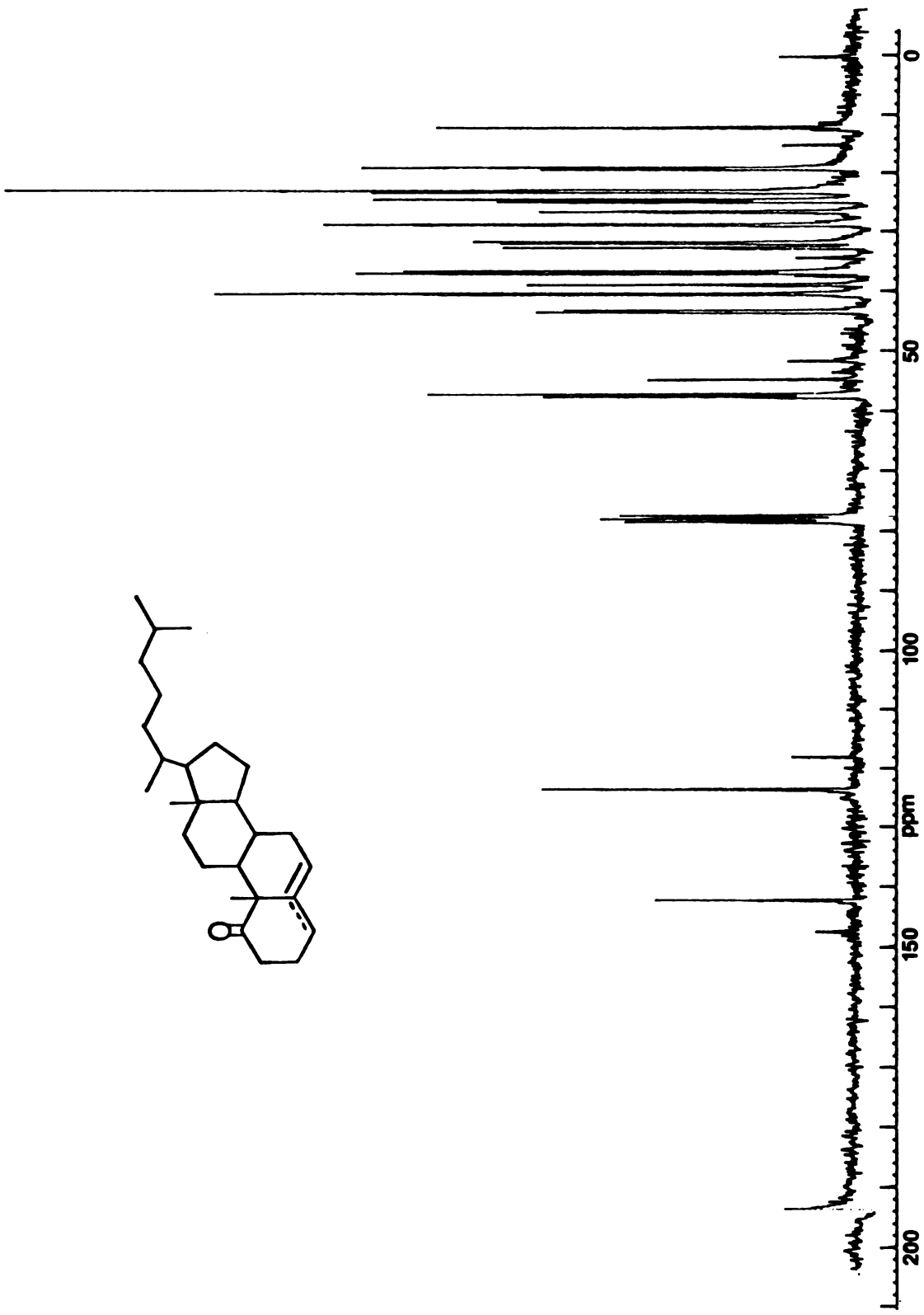


Figure I-5. Carbon-13 NMR of 23.

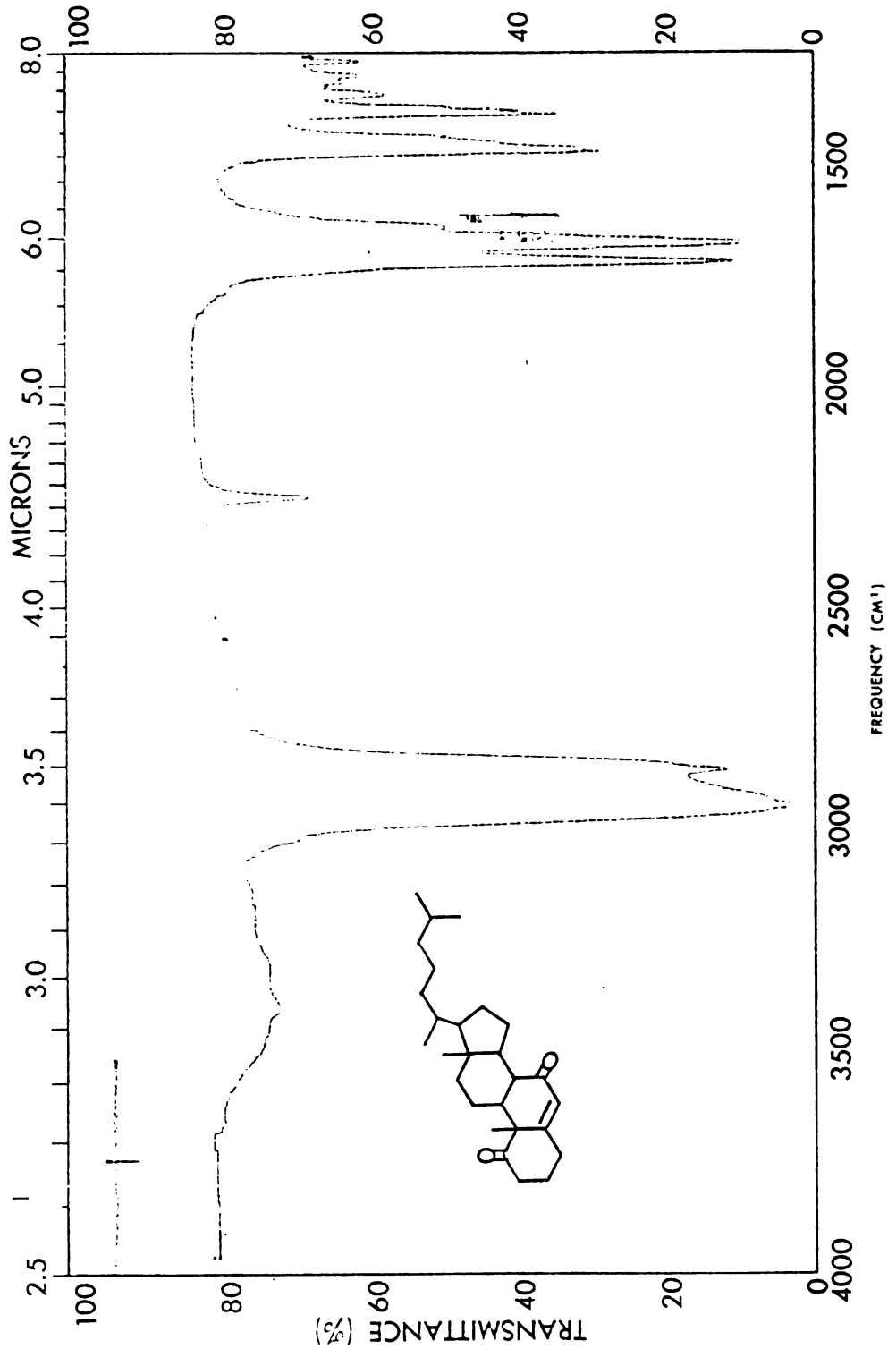


Figure I-6. IR of 16.

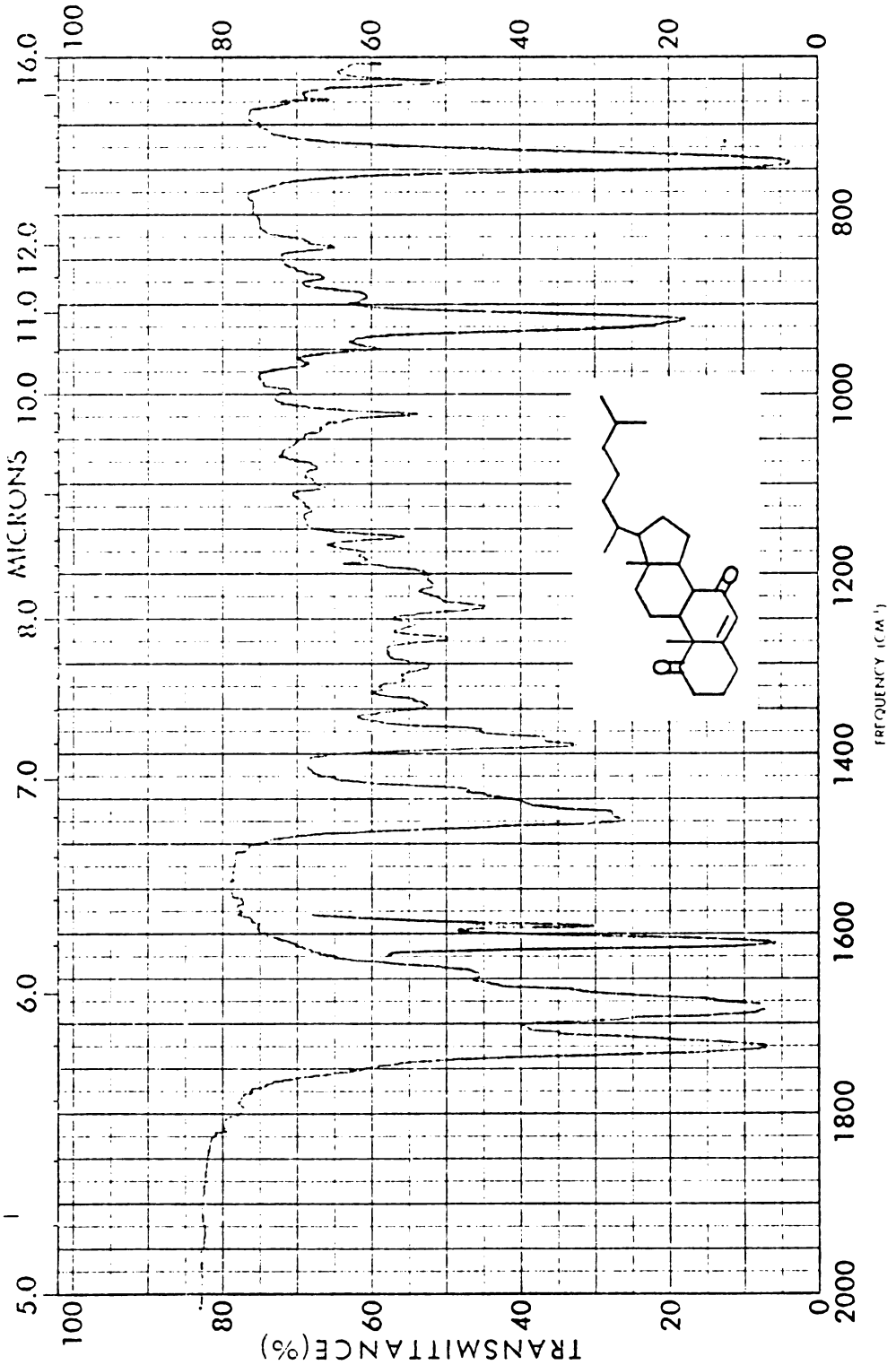


Figure I-7. IR of 16.

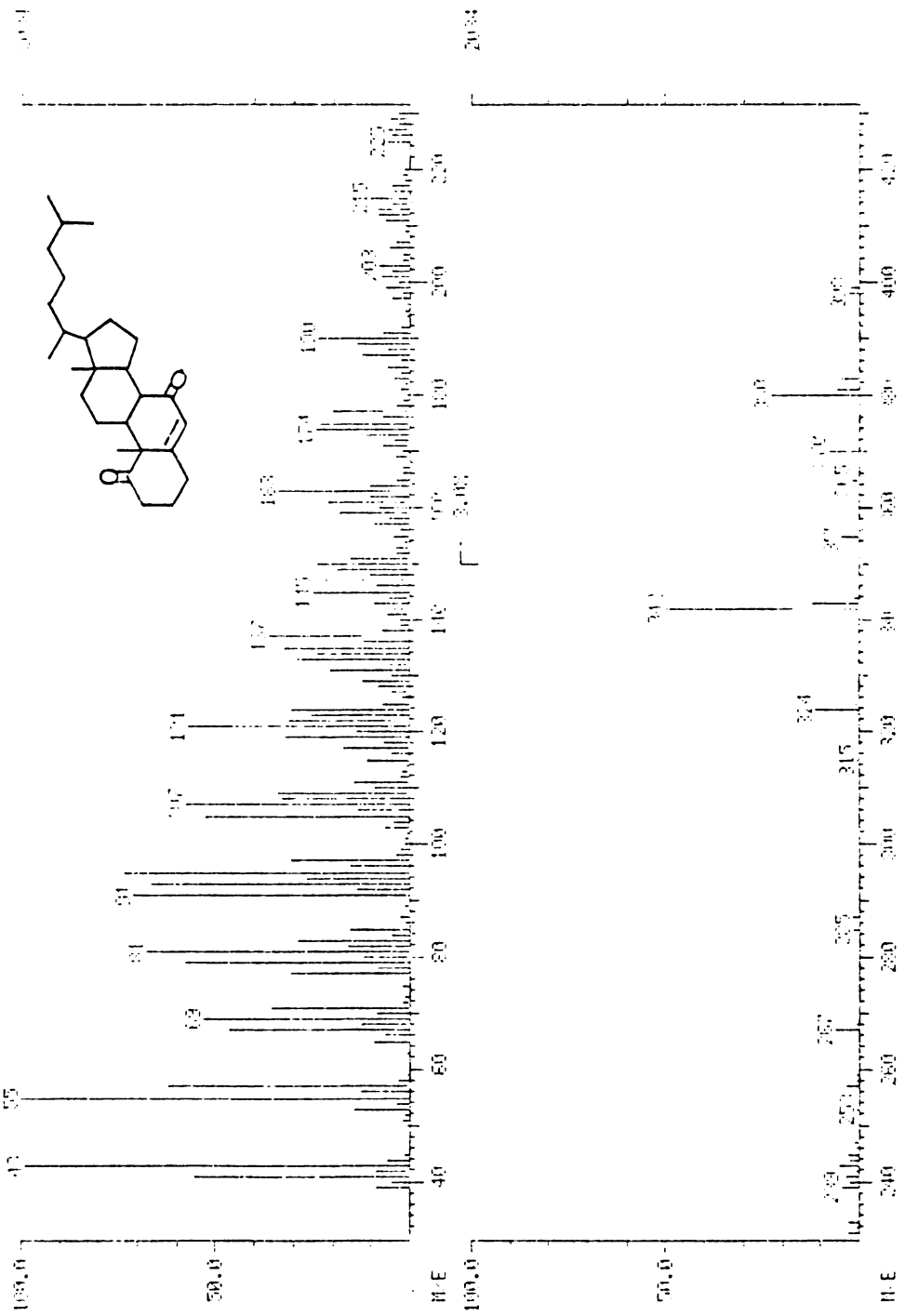


Figure I-8. Mass spectrum of 16.

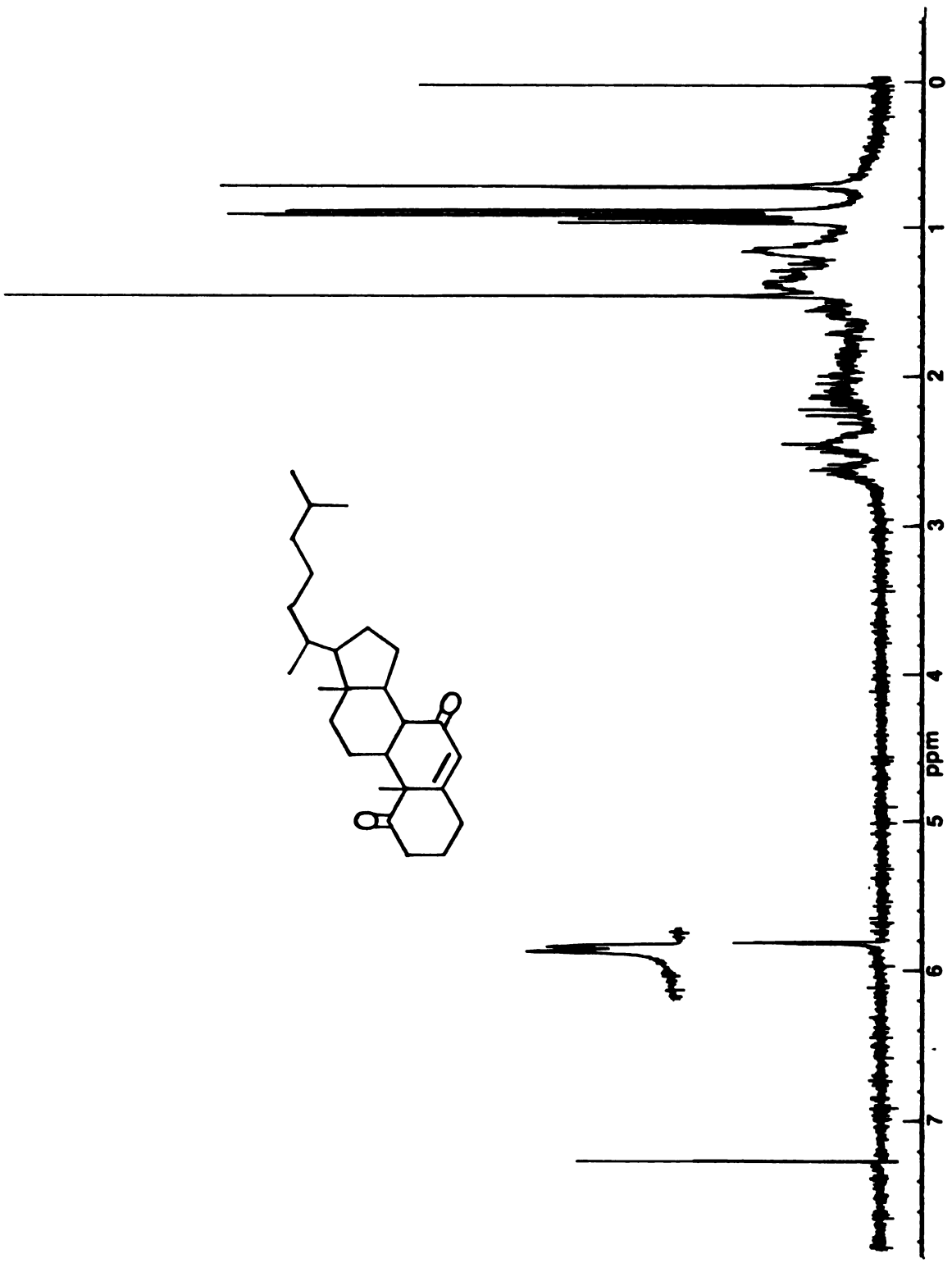


Figure I-9. Proton NMR of 16.

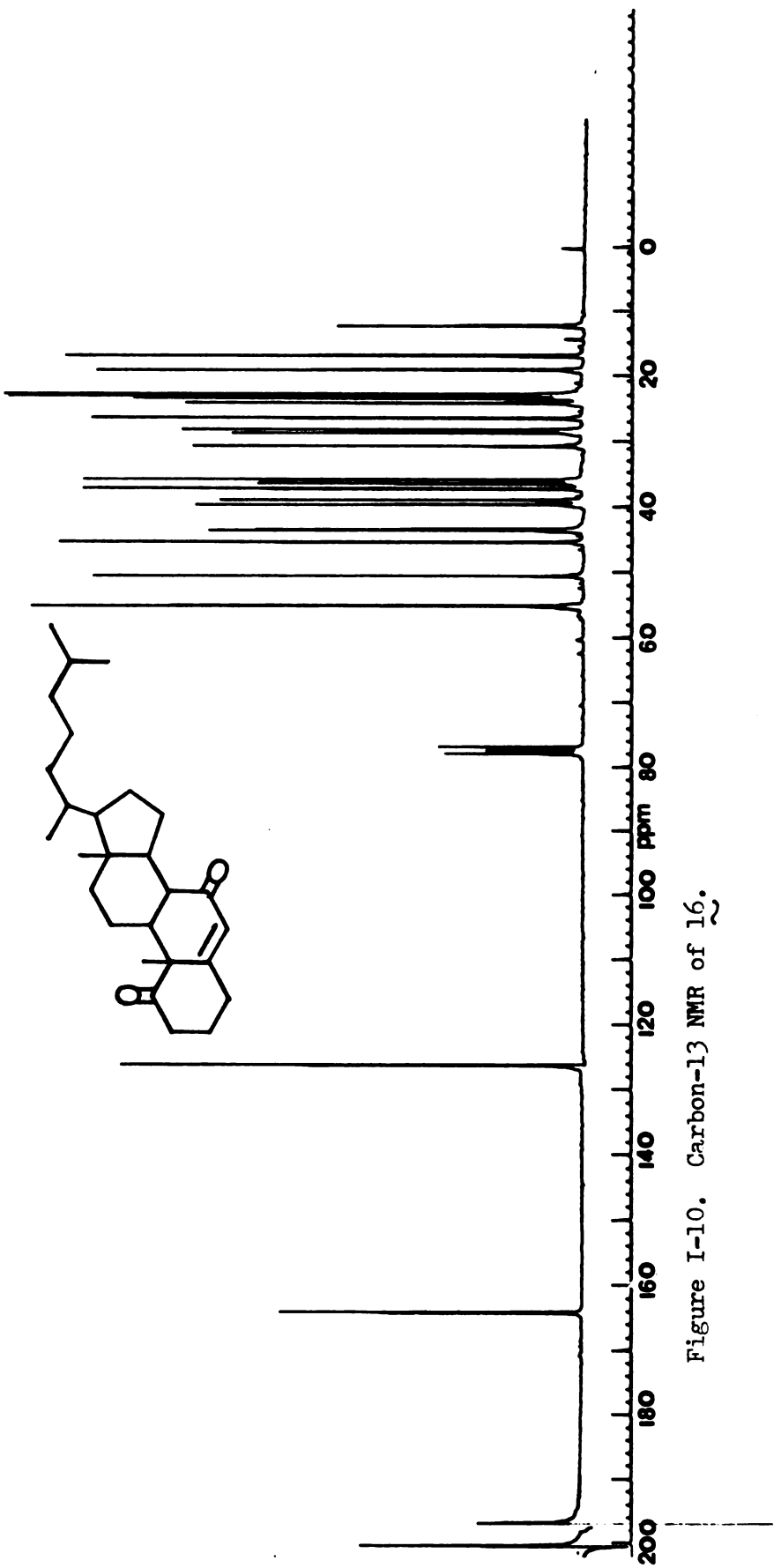


Figure I-10. Carbon-13 NMR of 16.

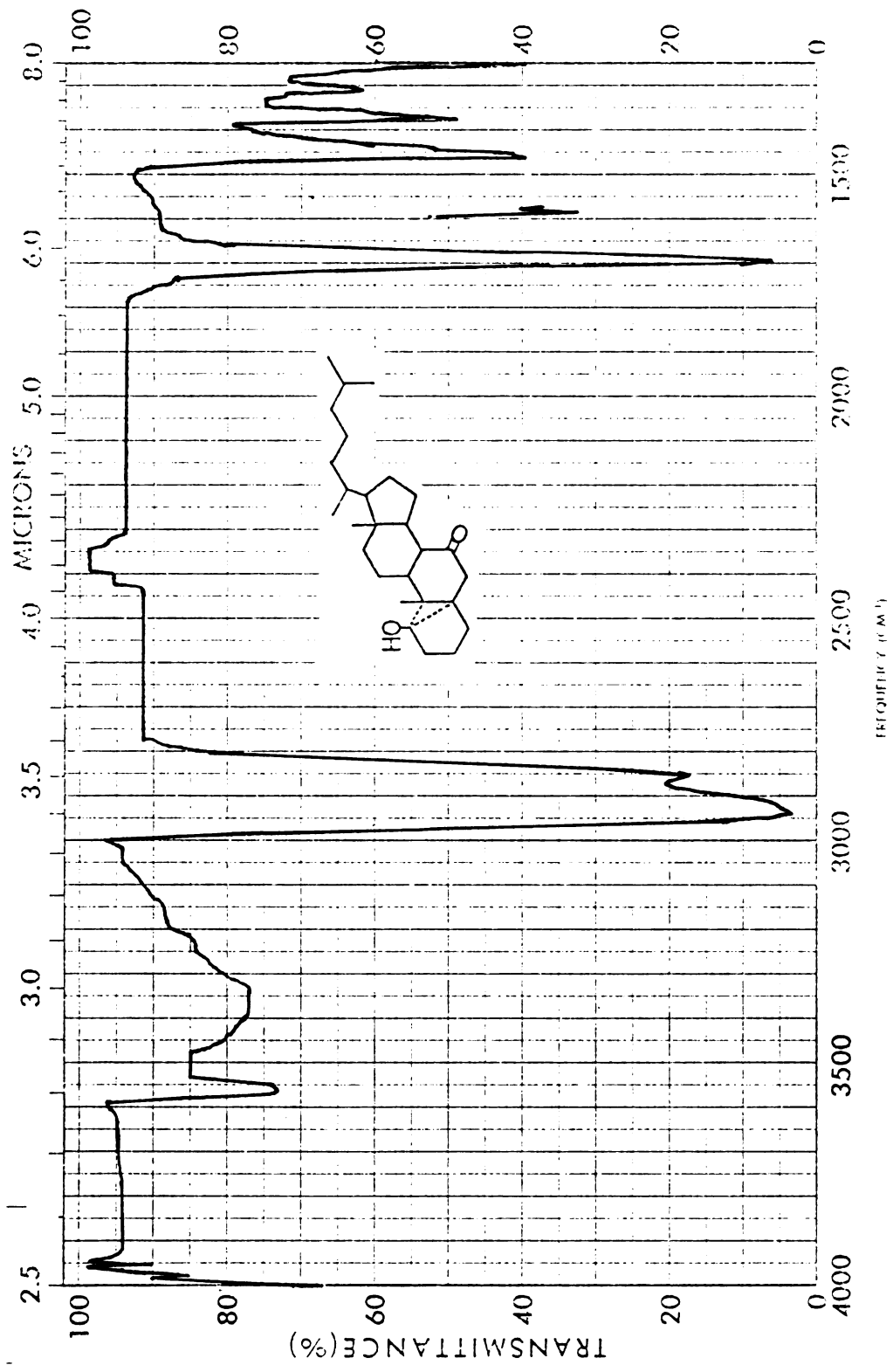


Figure I-11. IR of 17.

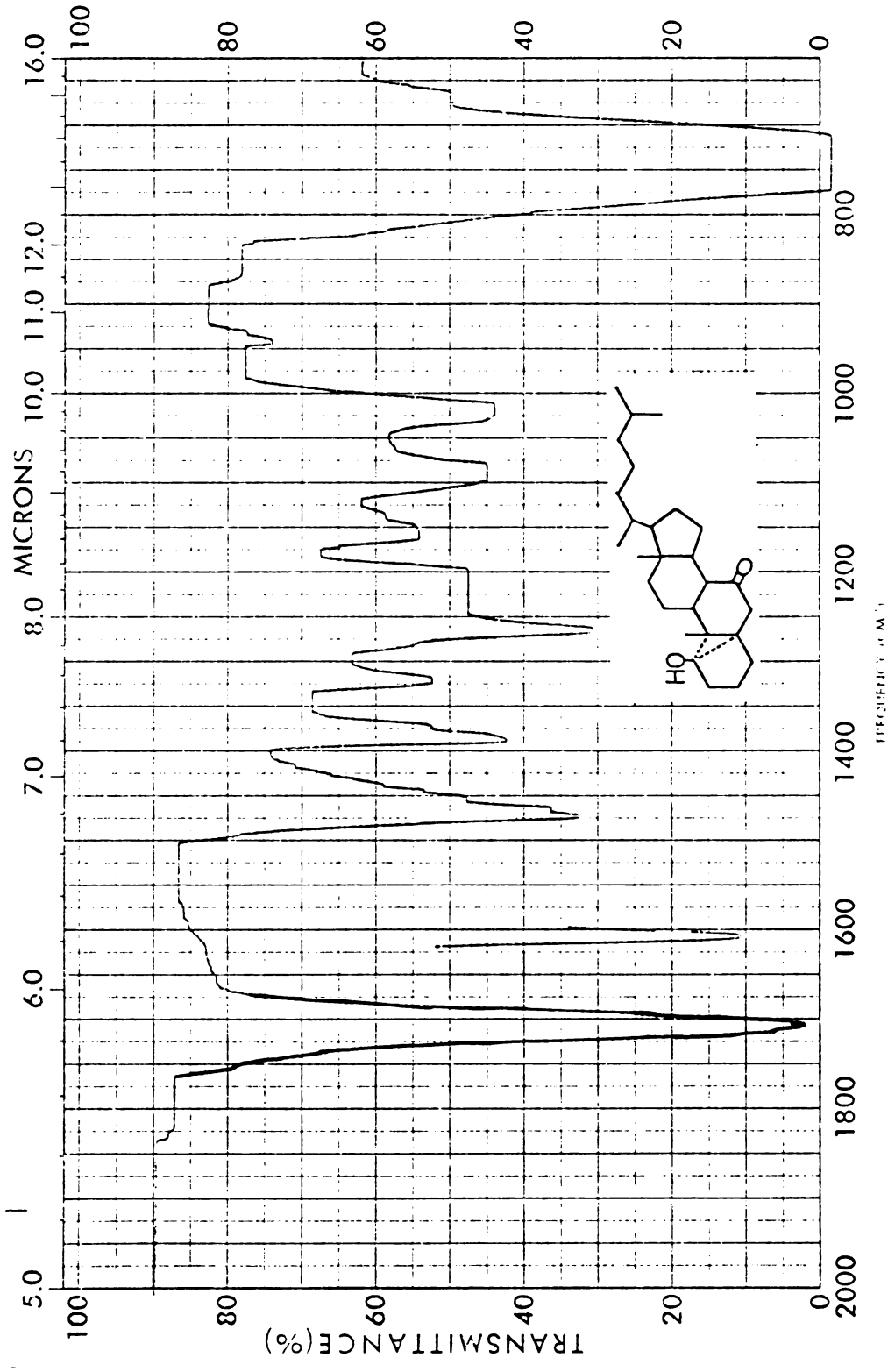


Figure I-12. IR of 17.

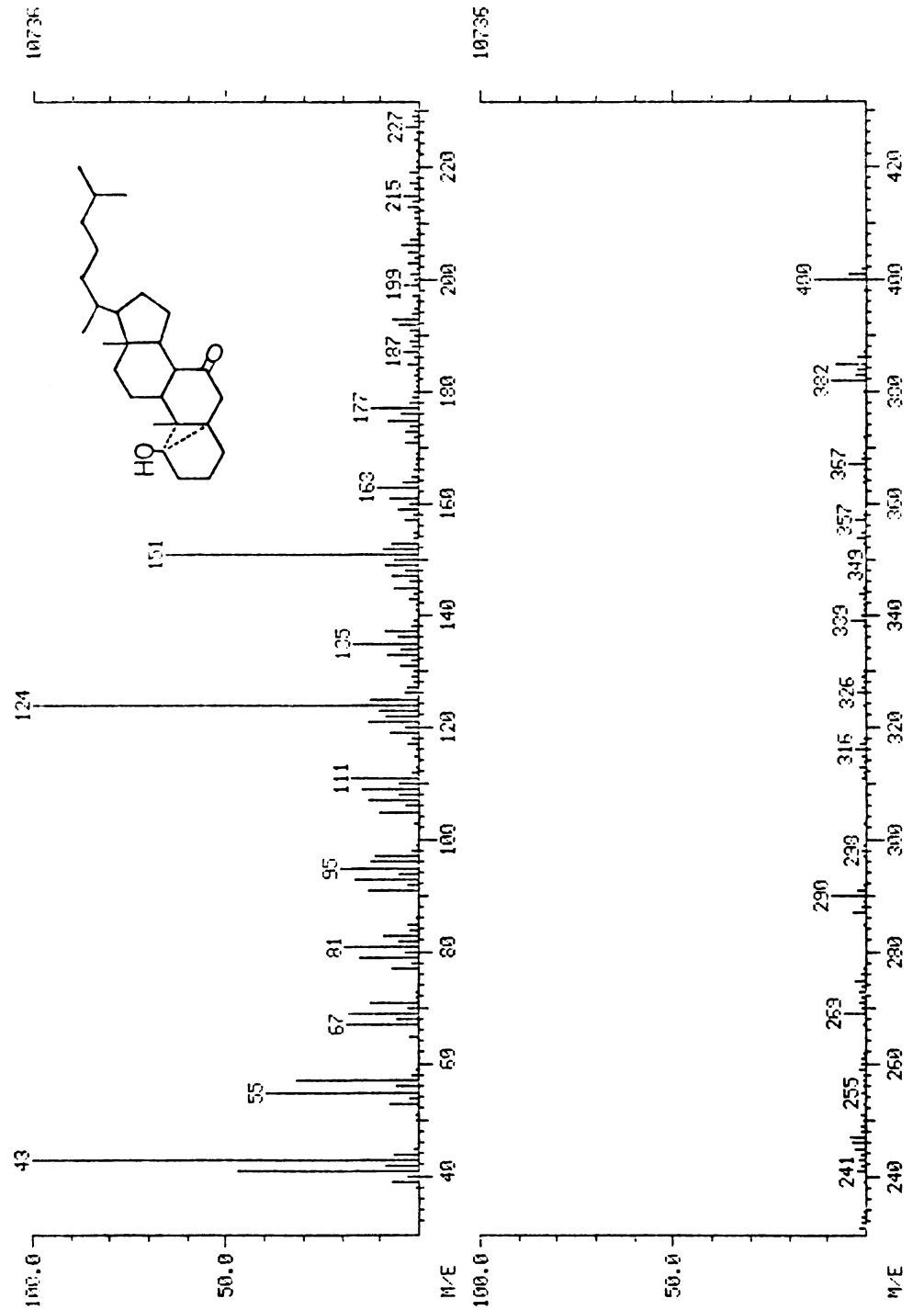


Figure I-13. Mass spectrum of 17.

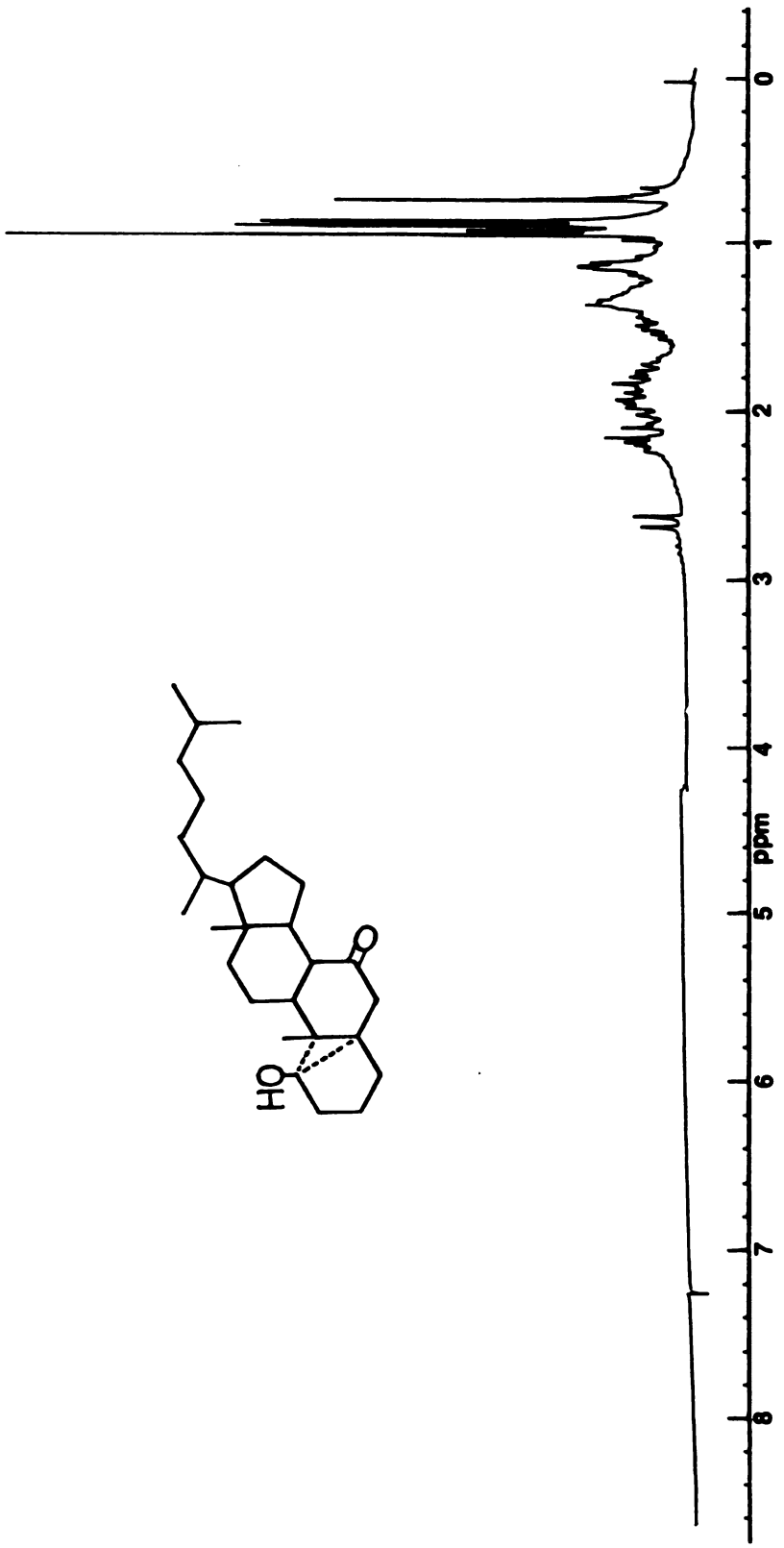


Figure I-14. Proton NMR of 17.

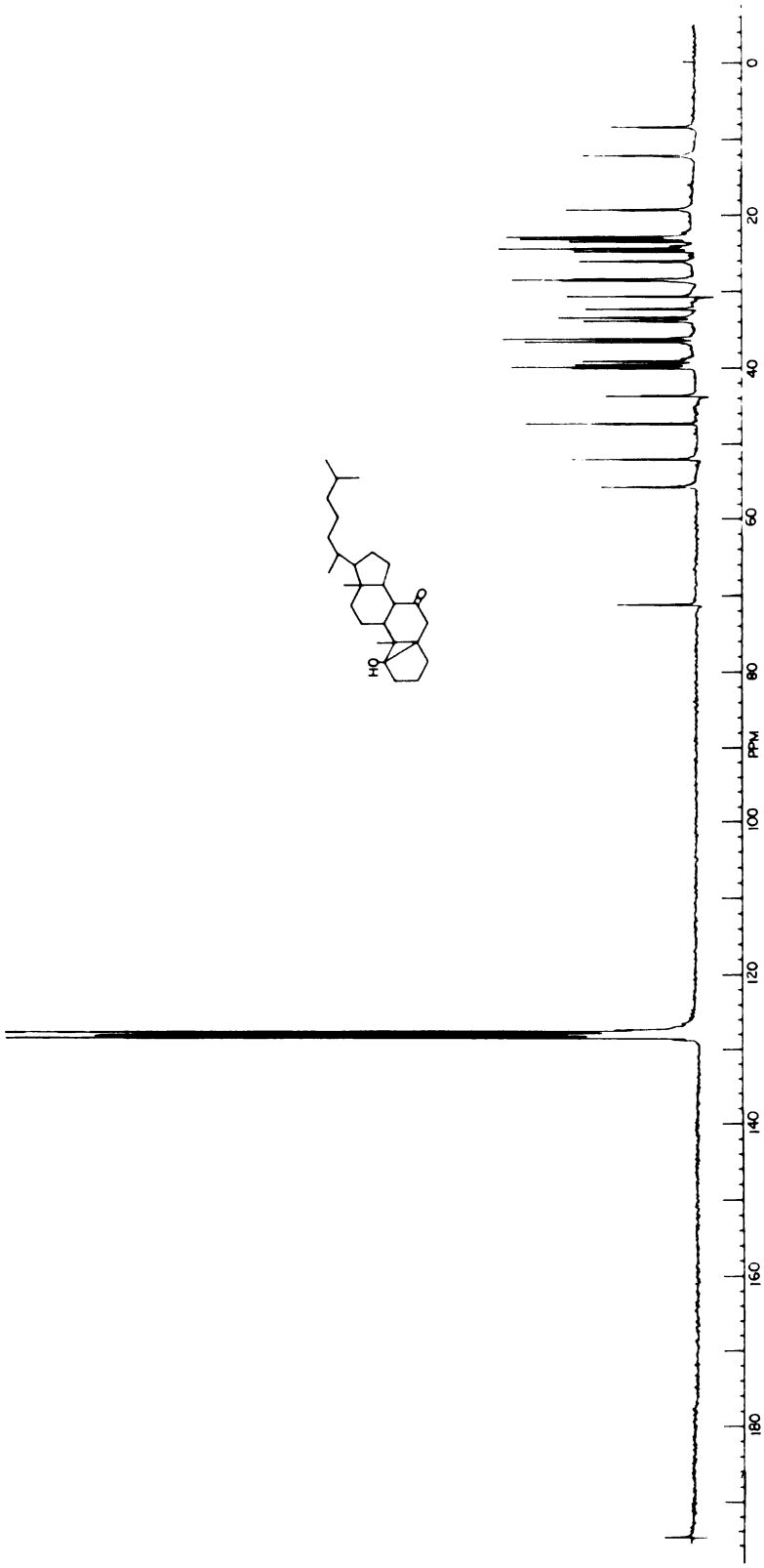


Figure I-15. Carbon-13 NMR of 17.

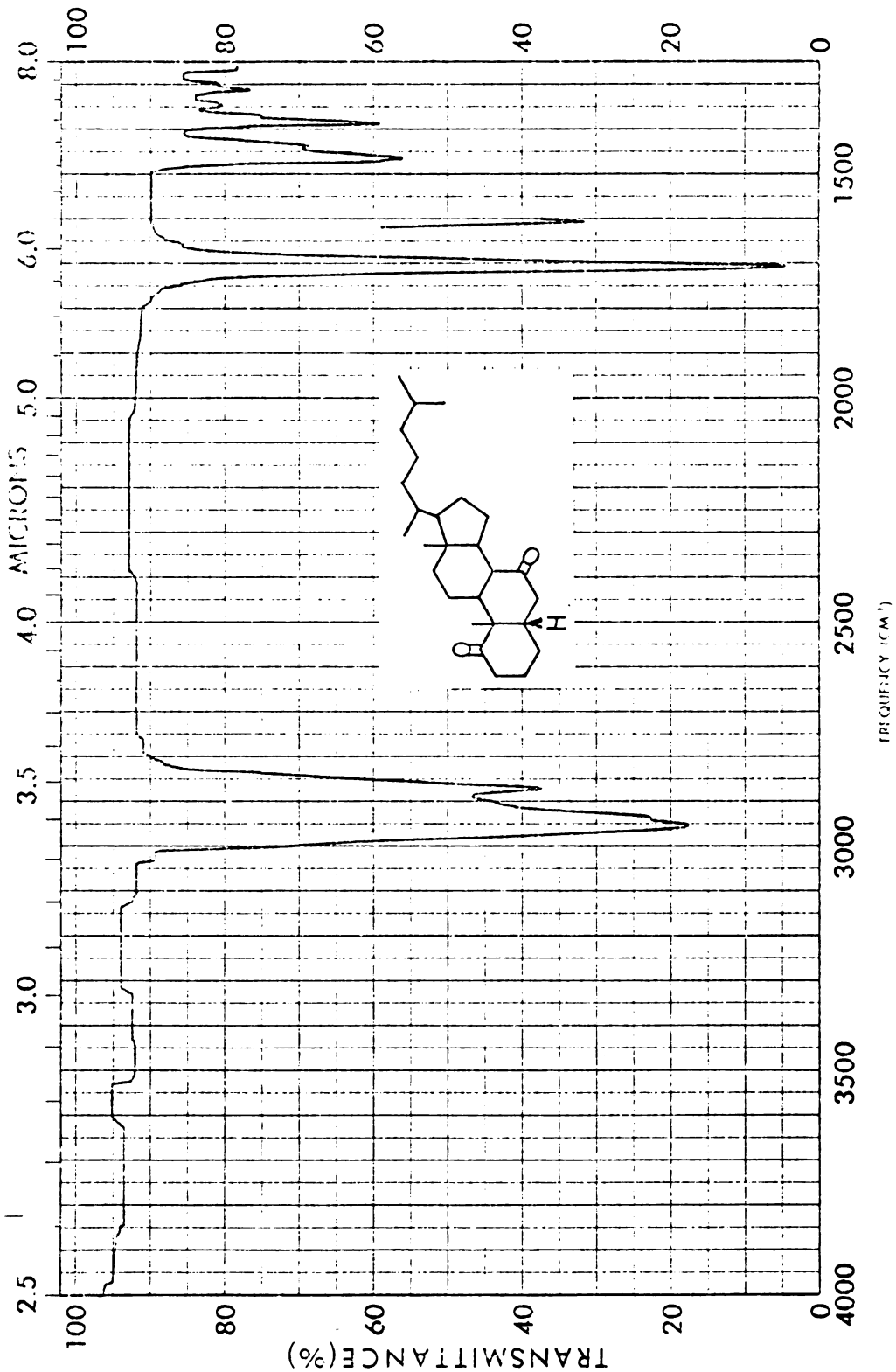


Figure I-16. IR of 25.

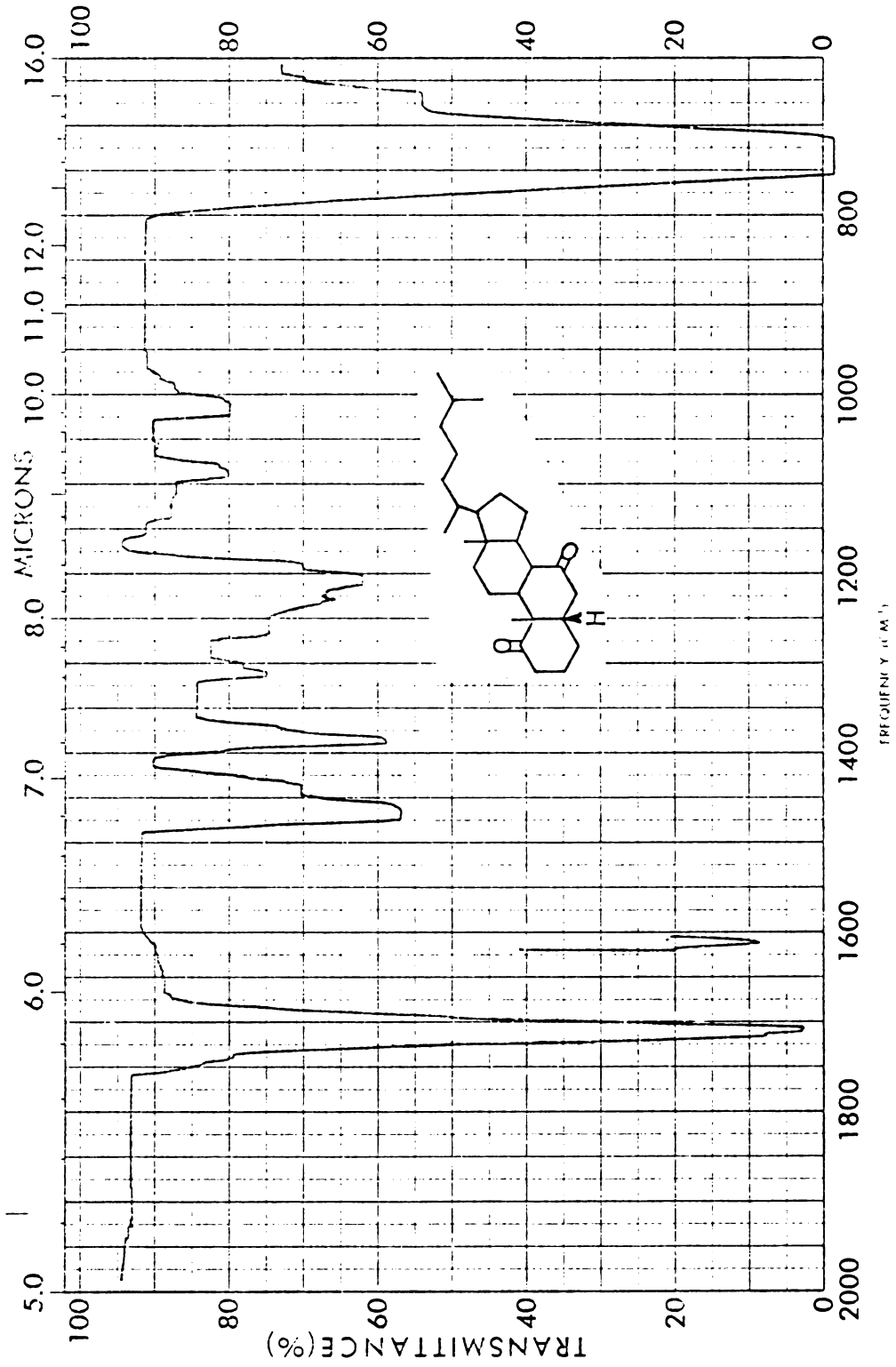


Figure I-17. IR of 25.

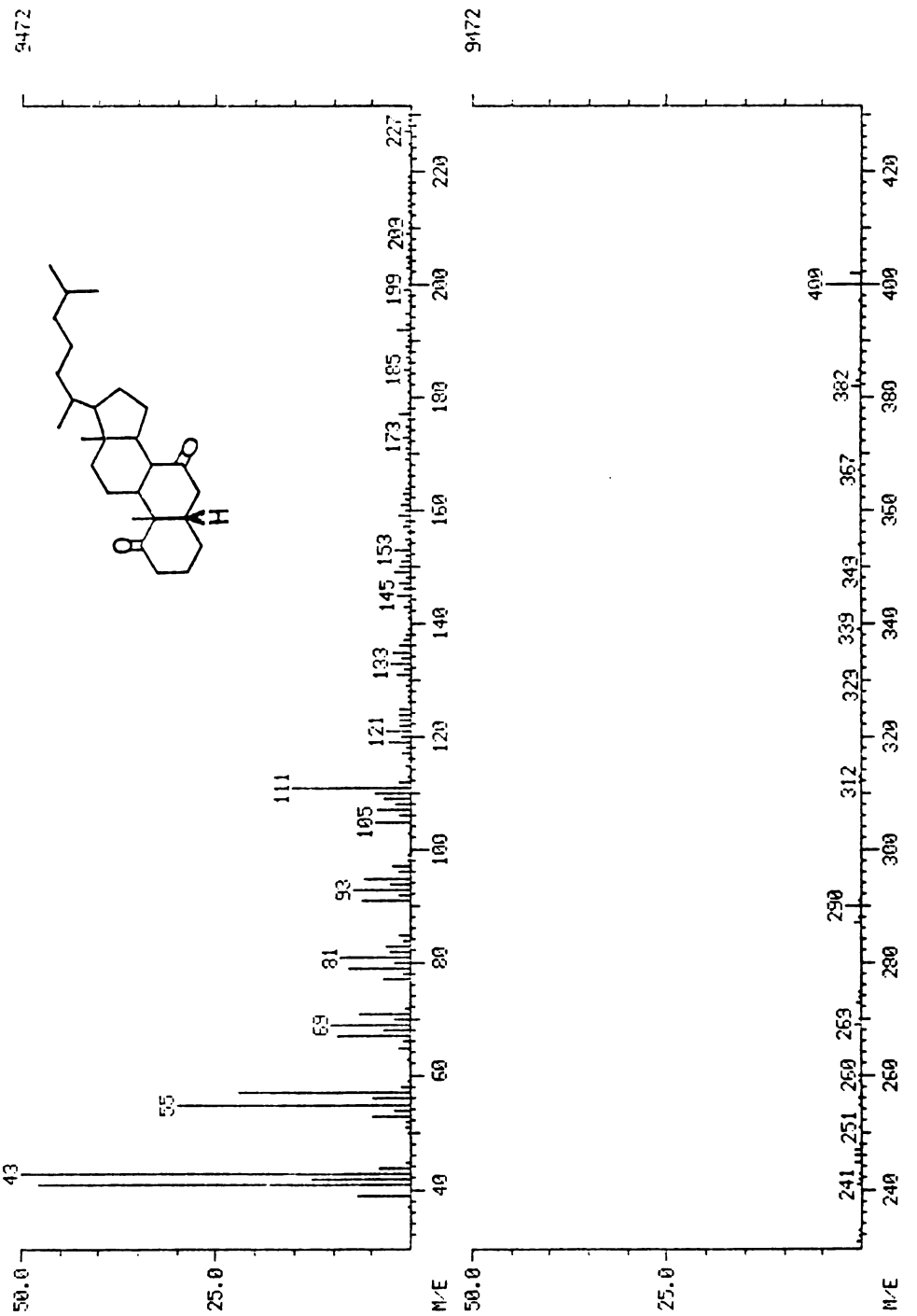


Figure I-18. Mass spectrum of 25.

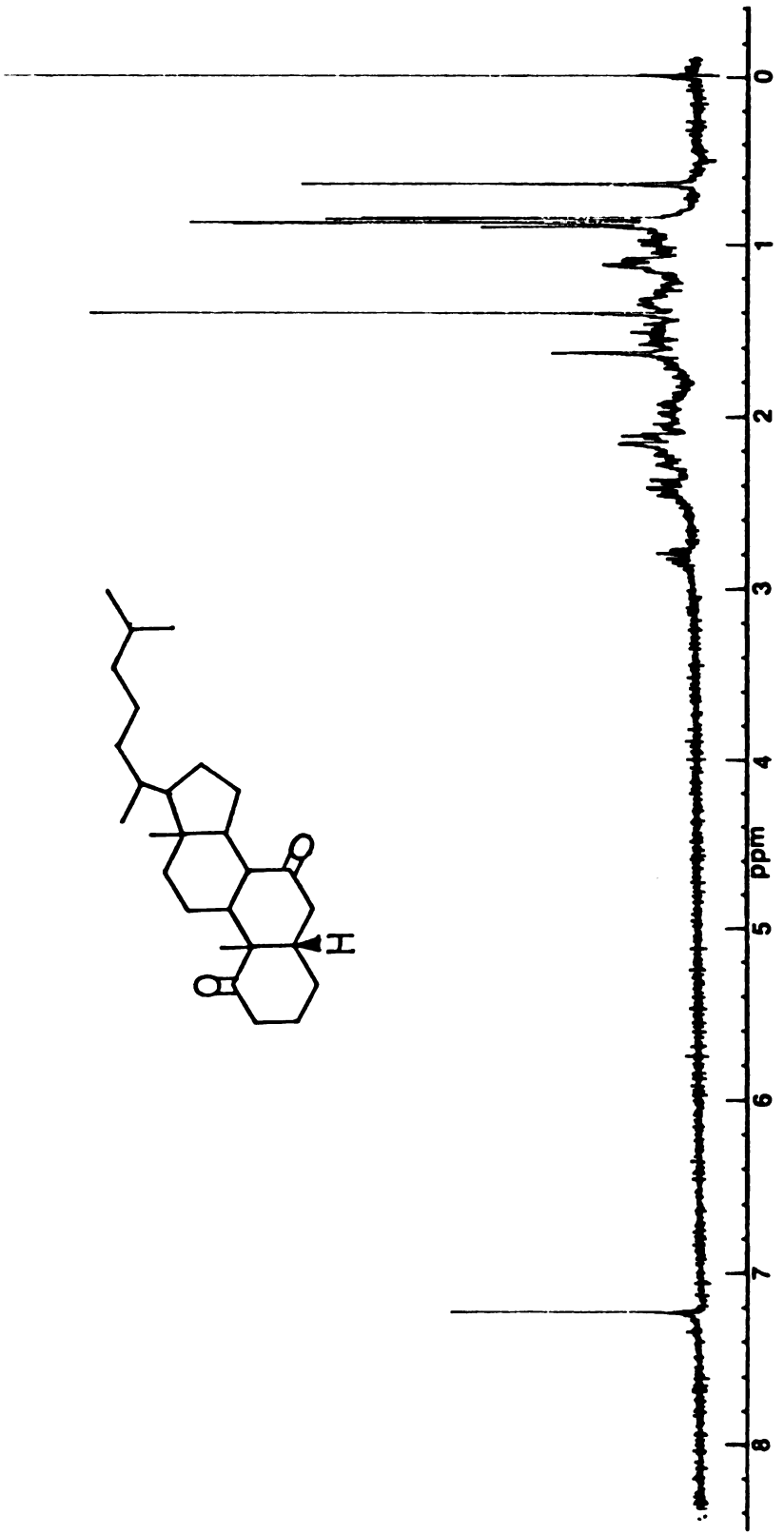


Figure I-19. Proton NMR of 25.

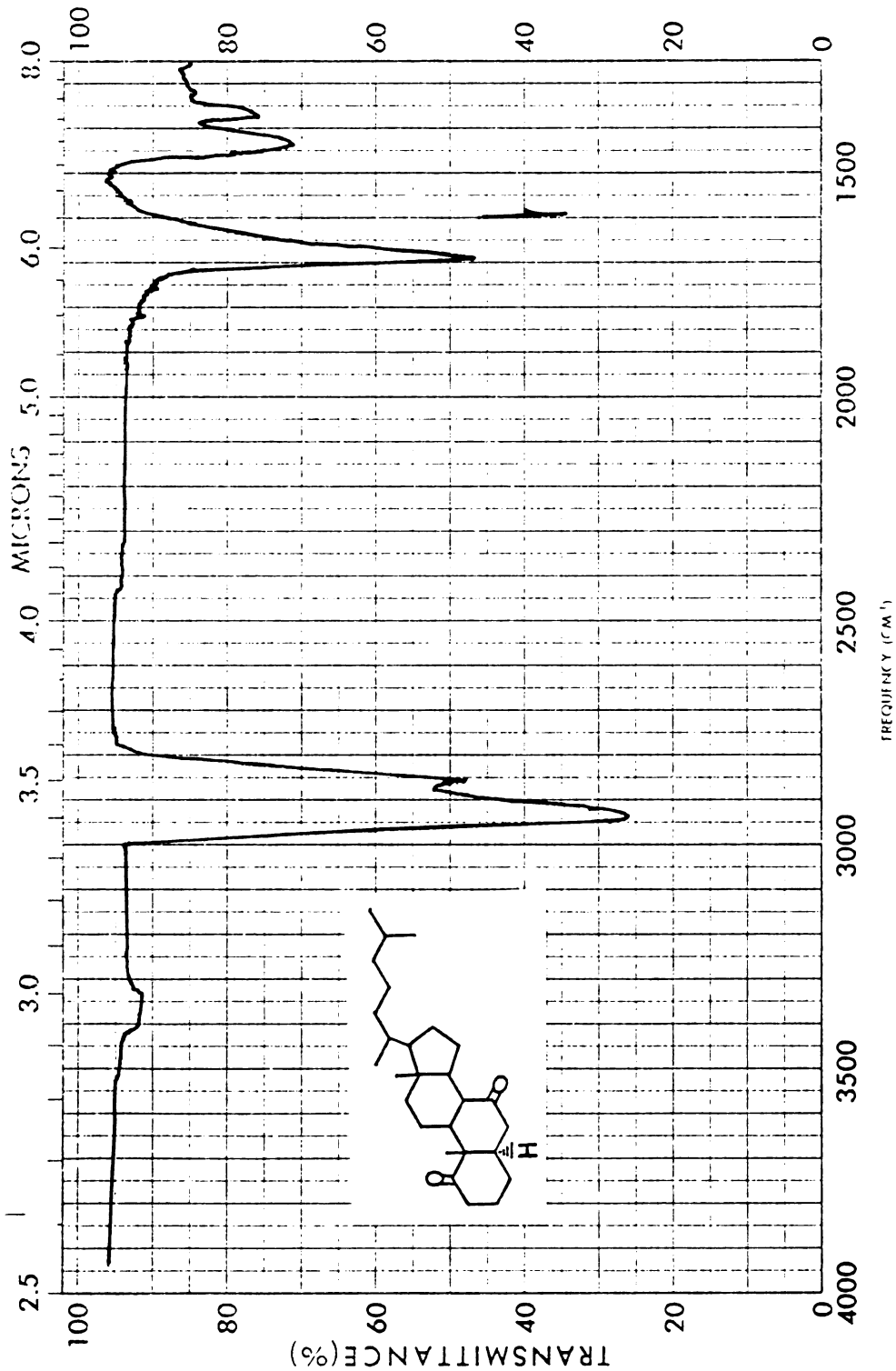


Figure I-20. IR of 26.

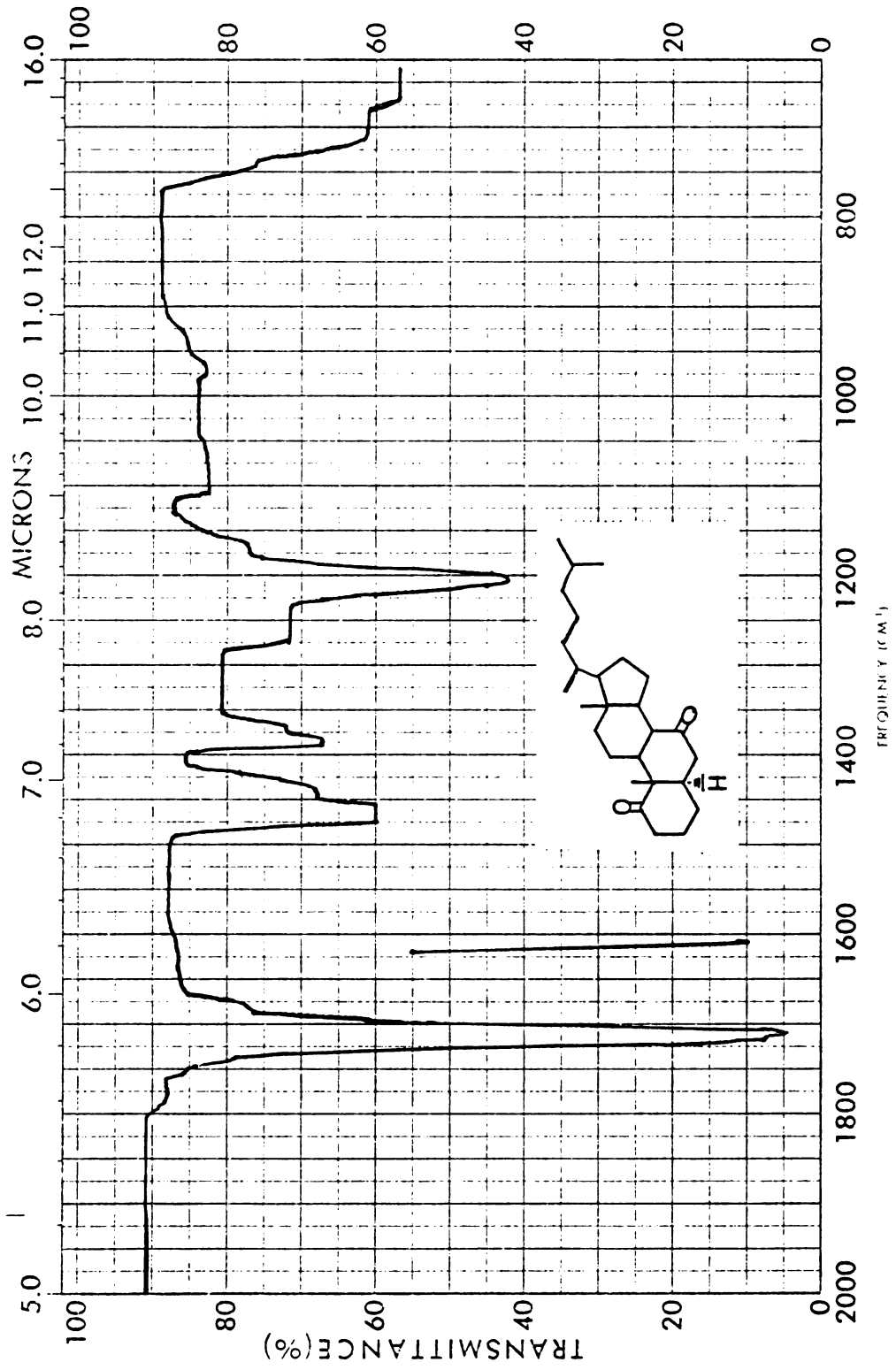


Figure I-21. IR of 26.

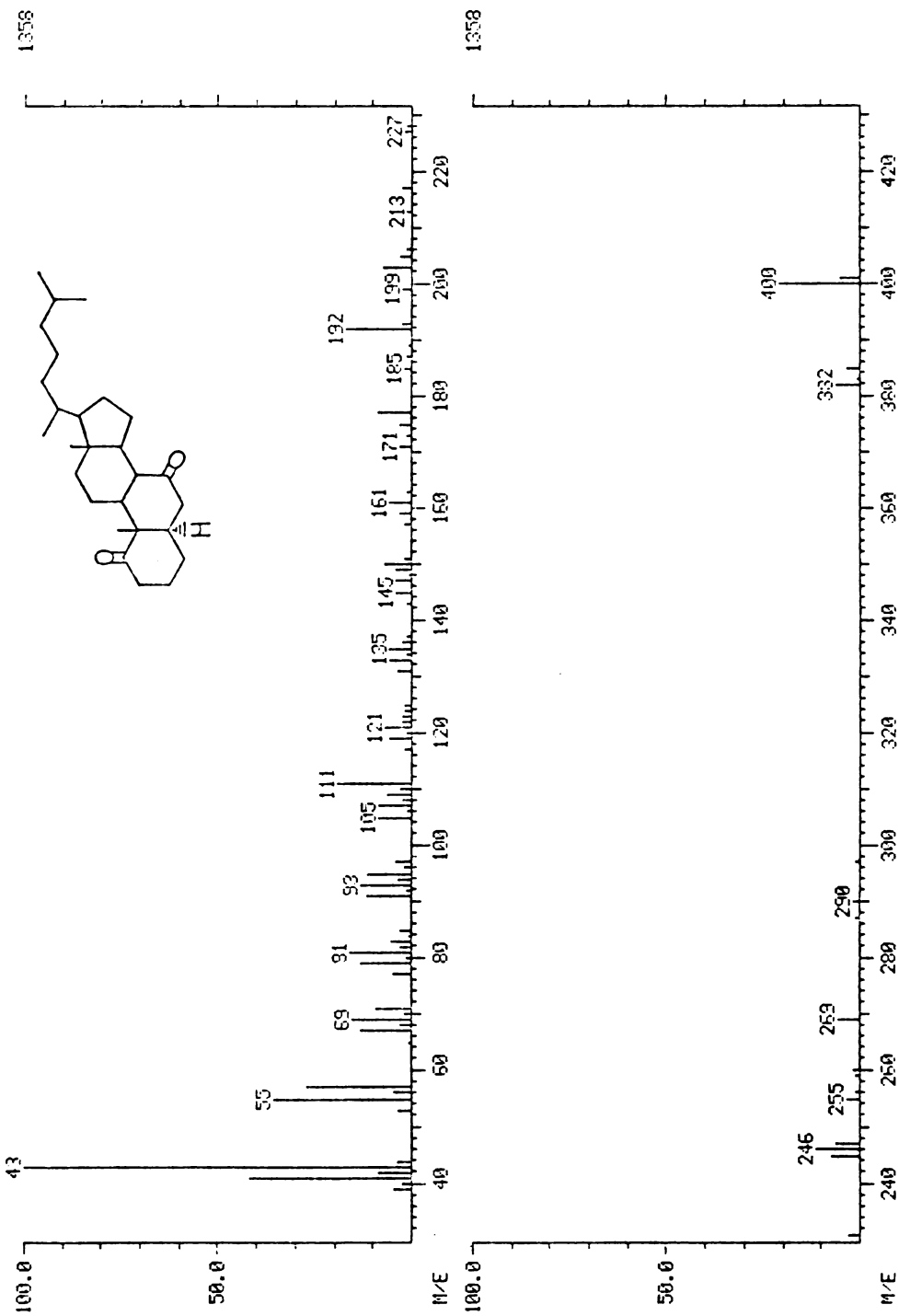


Figure I-22. Mass spectrum of 26.

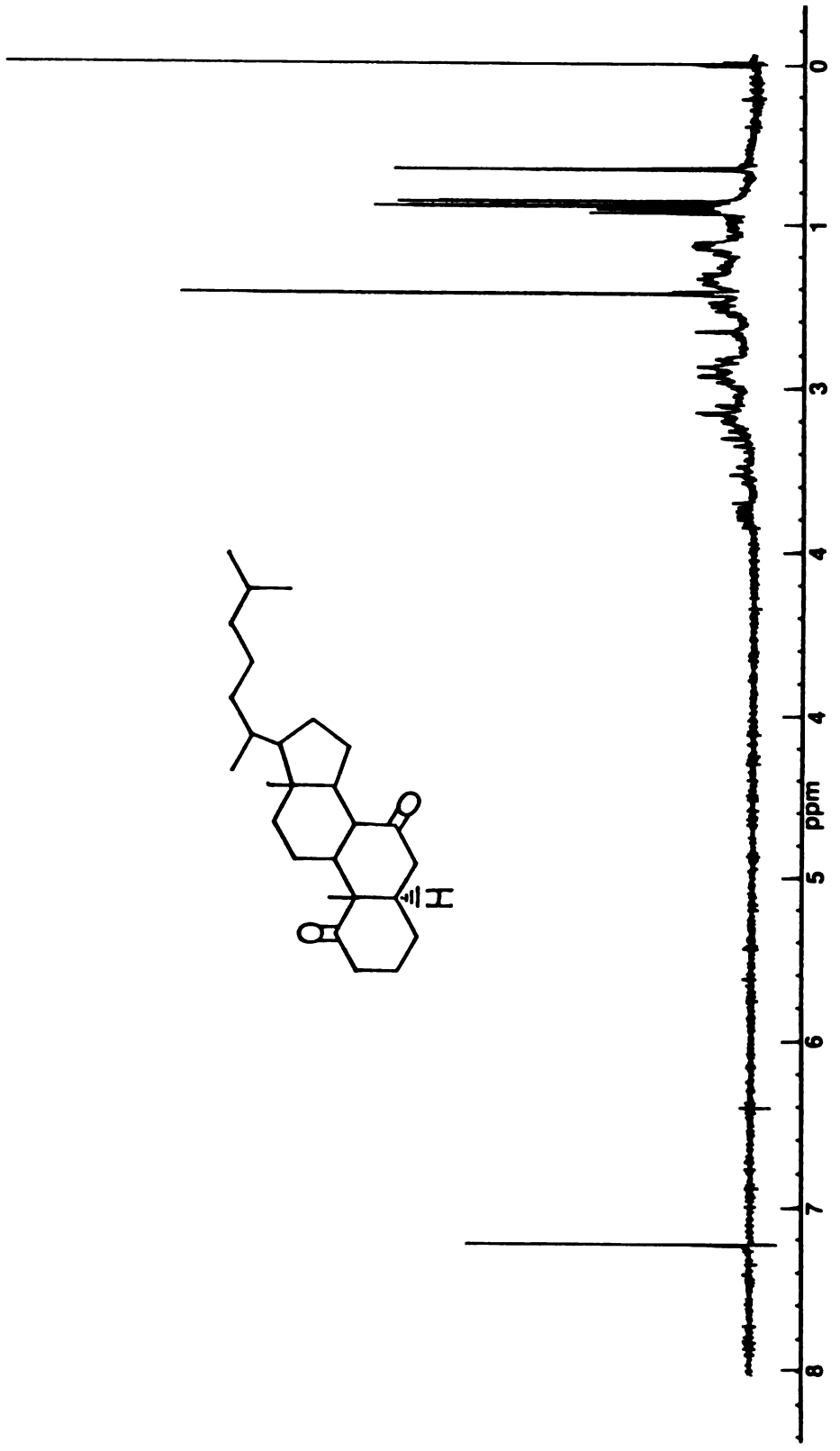


Figure I-23. Proton NMR of 26.

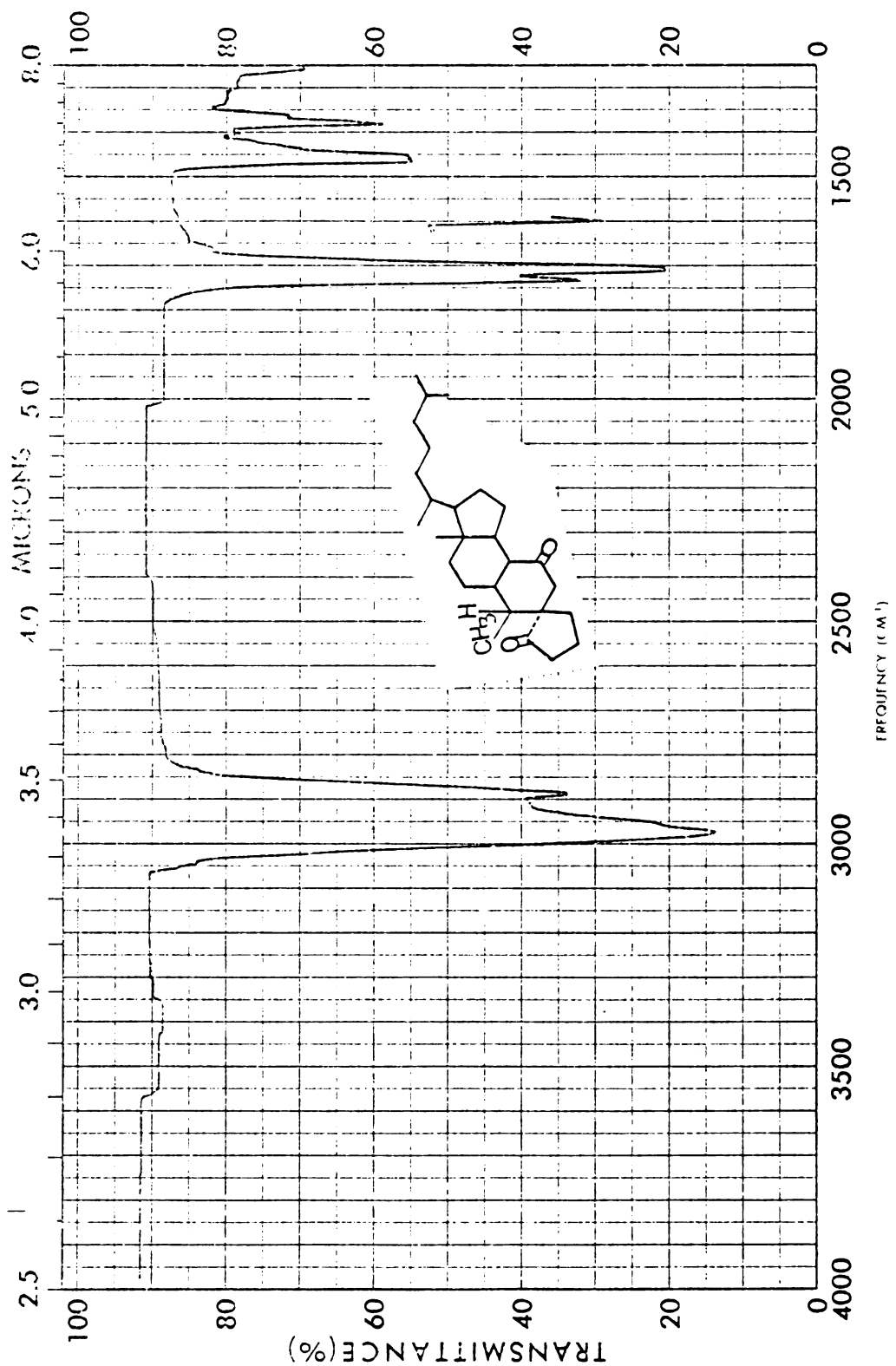


Figure I-24. IR of 27 + 28.

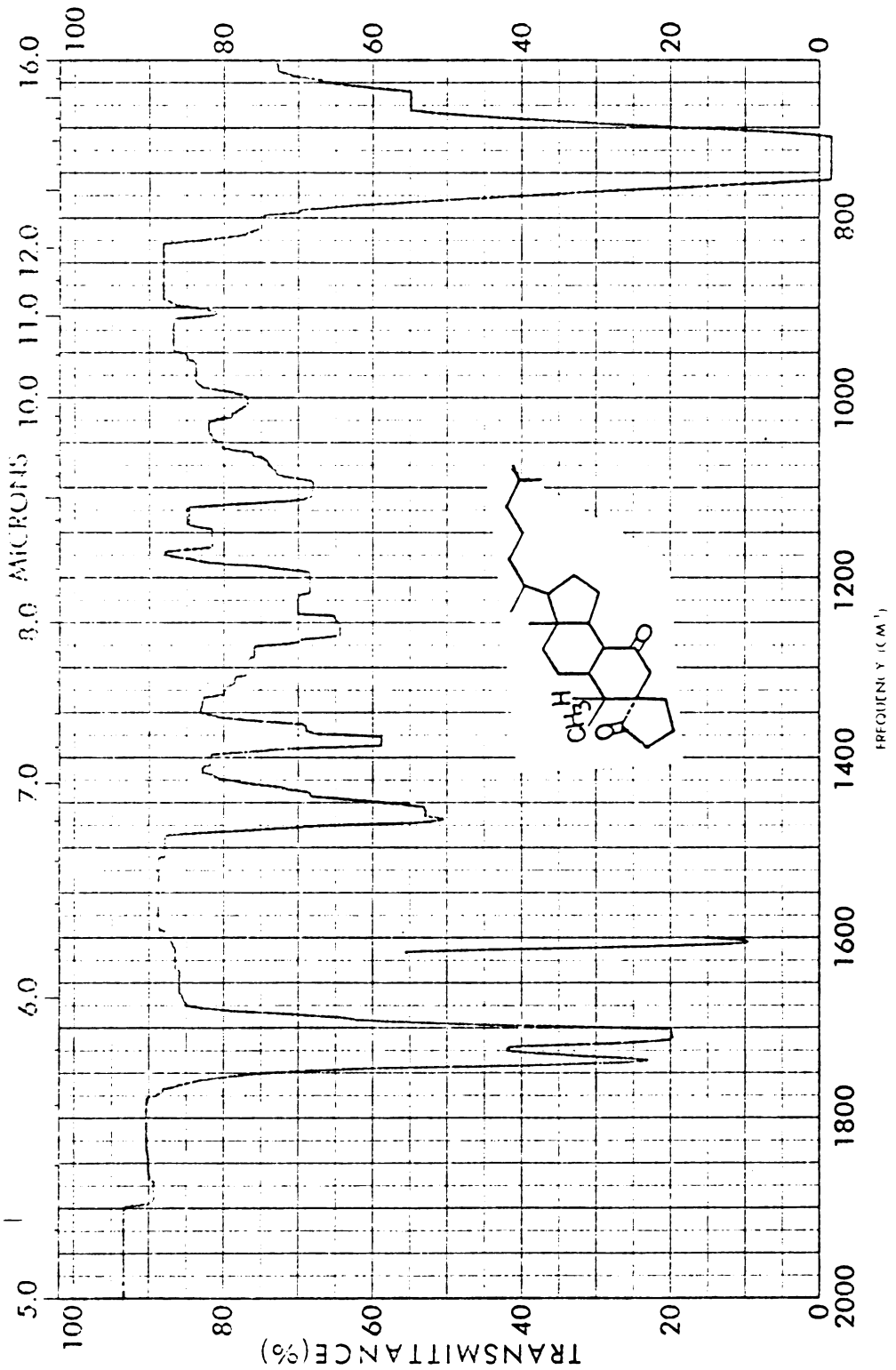


Figure I-25. IR of 27 + 28.

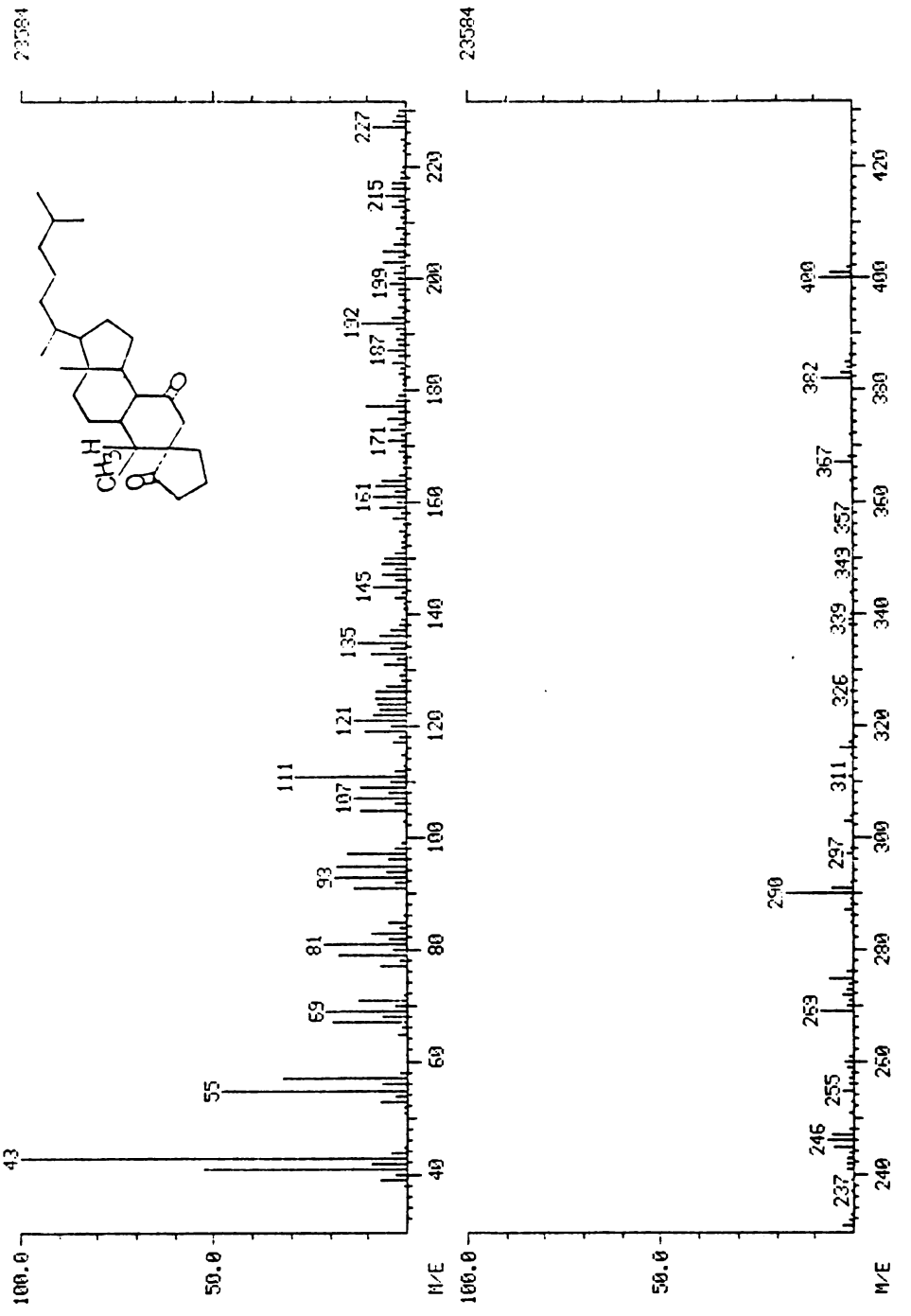


Figure I-26. Mass spectrum of 27 + 28.

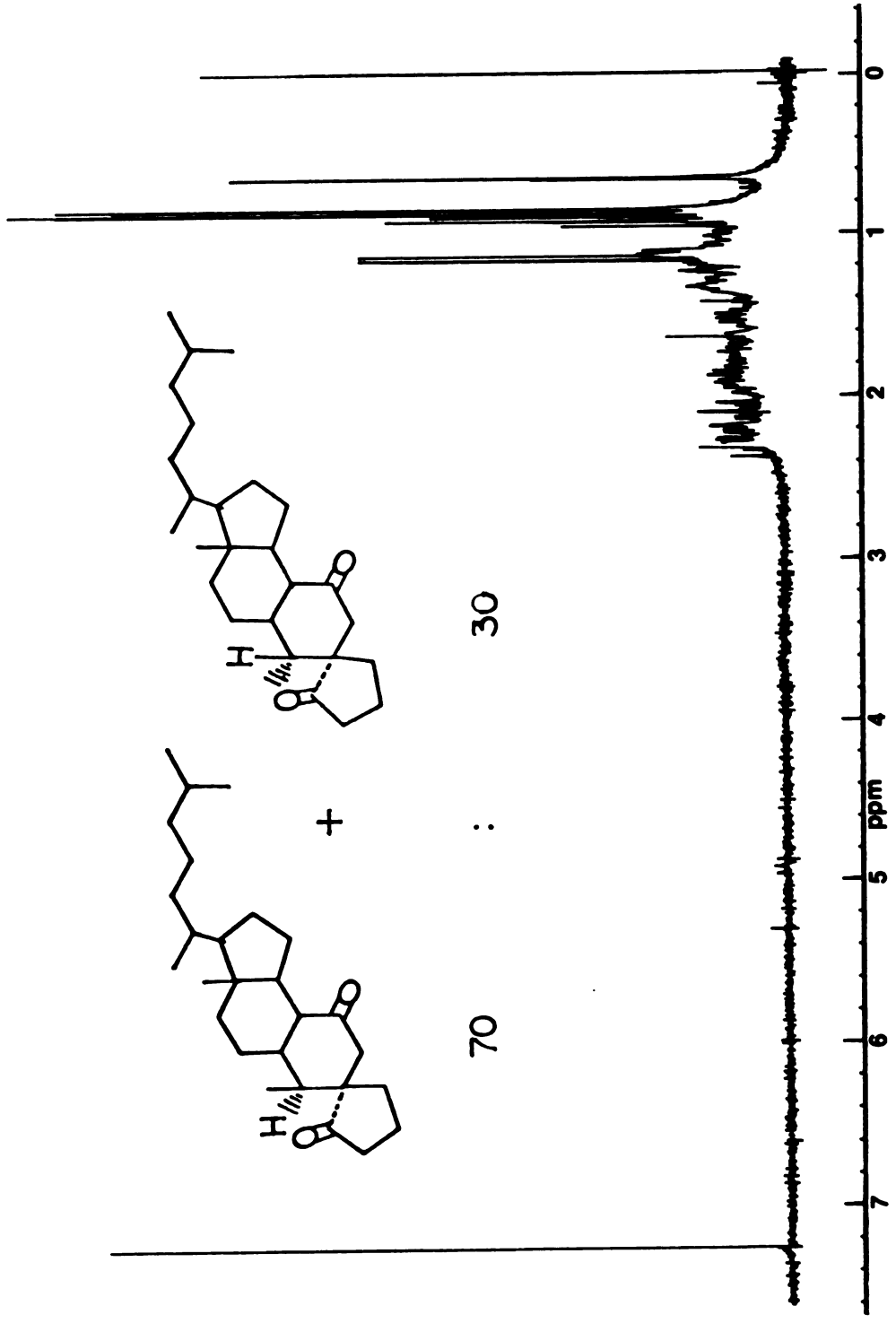


Figure I-27. Proton NMR of 27 + 28.

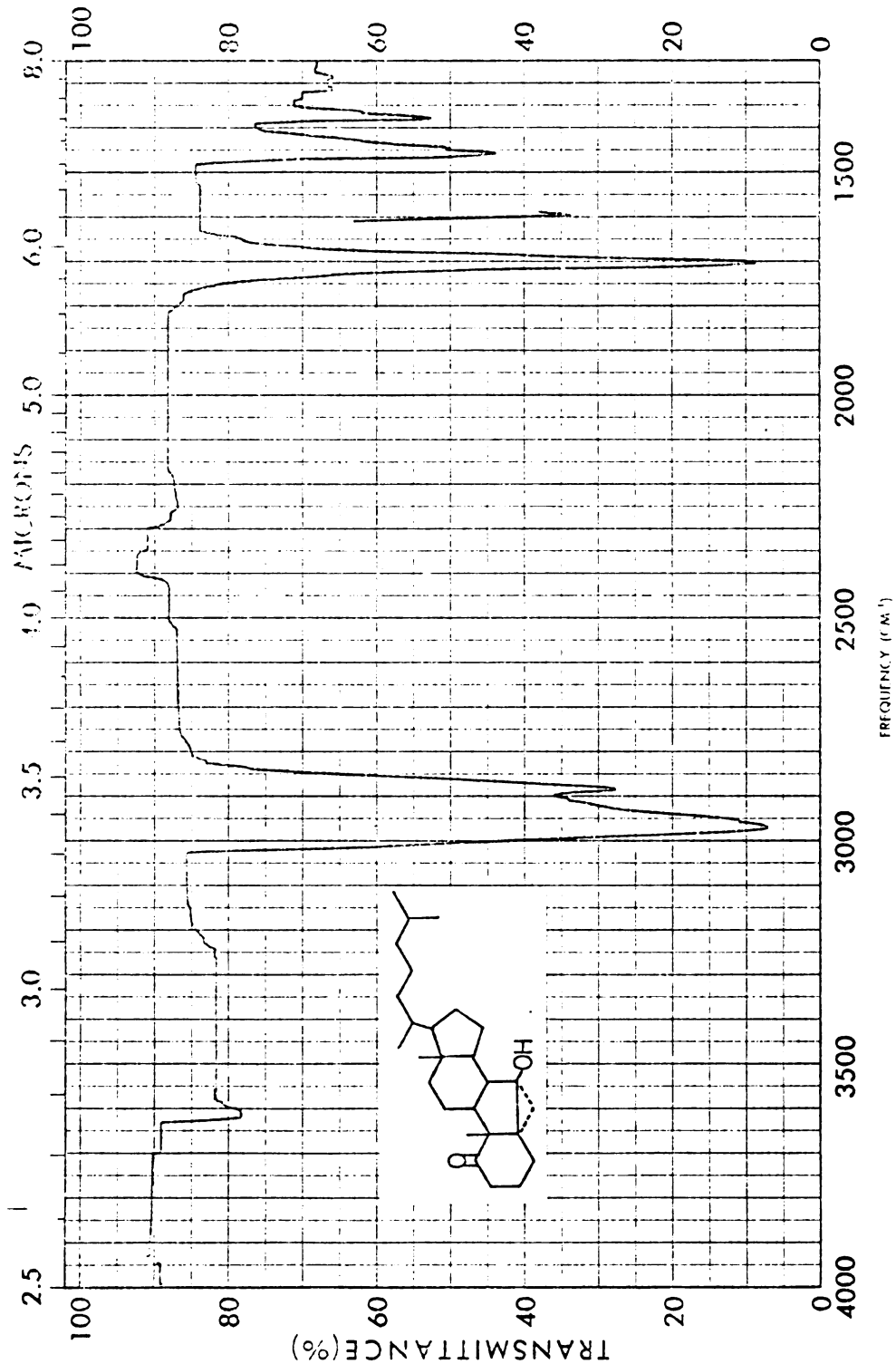


Figure I-28. IR of 41.

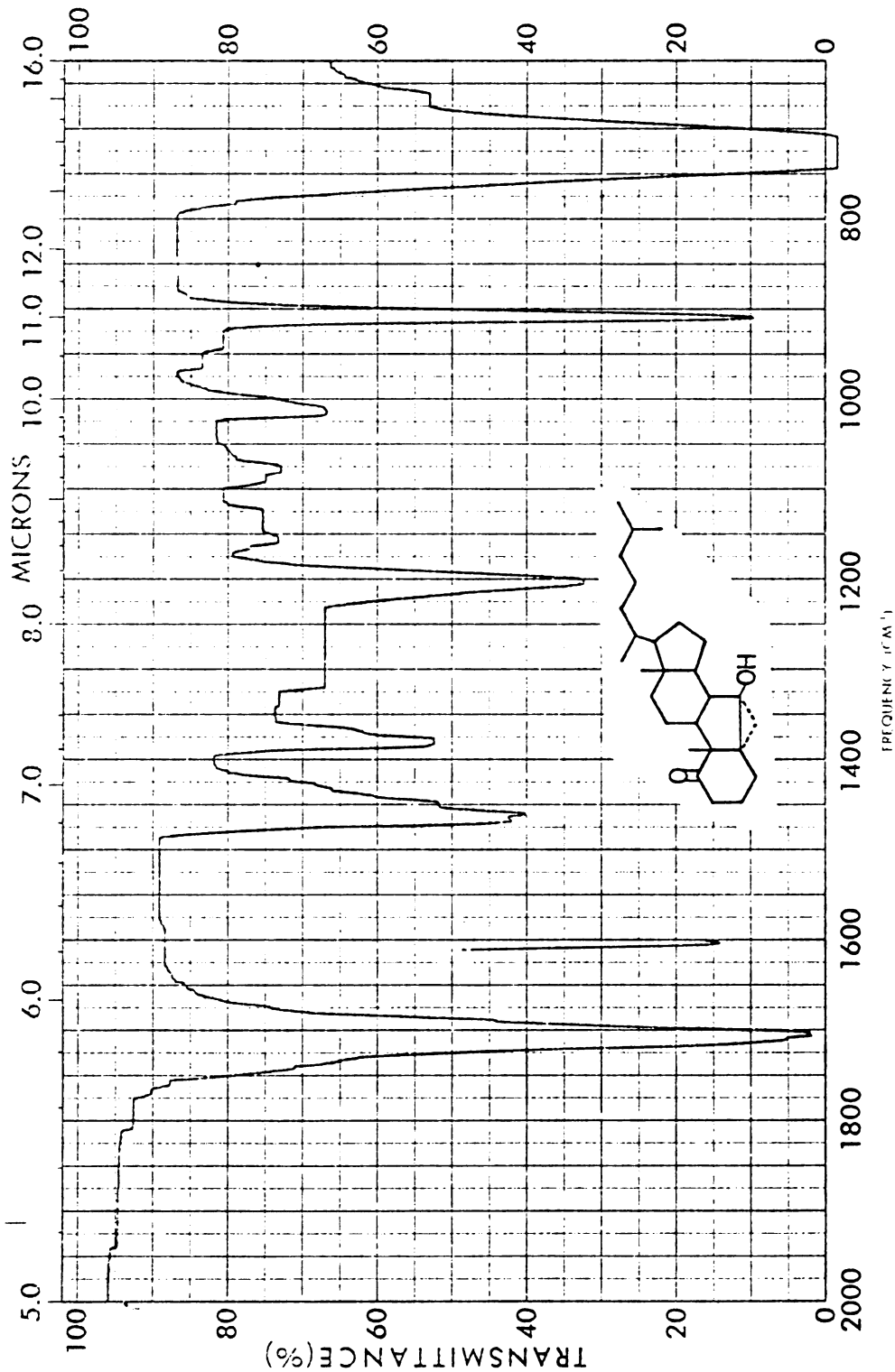


Figure I-29. IR of 41.

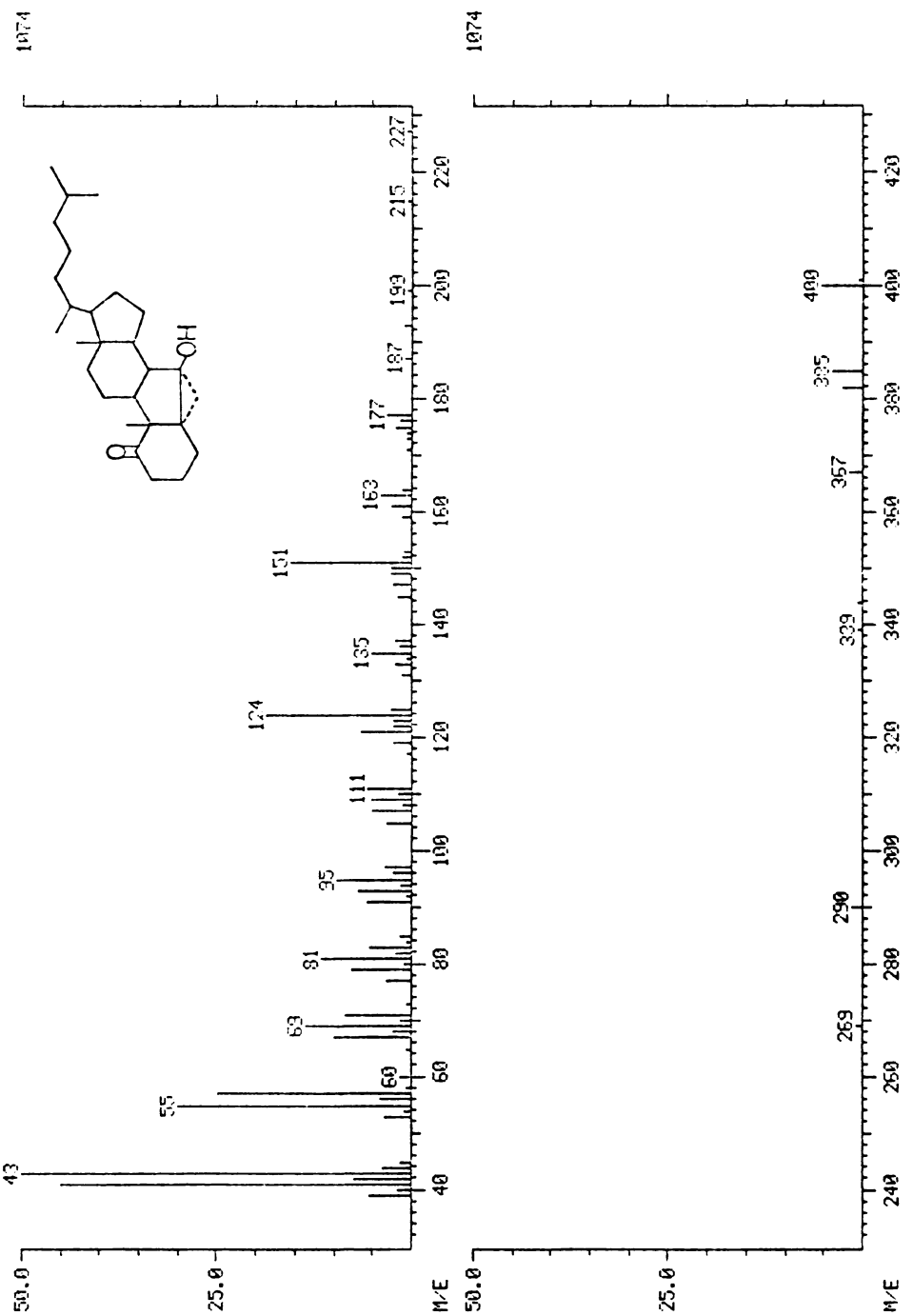


Figure I-30. Mass spectrum of 41.

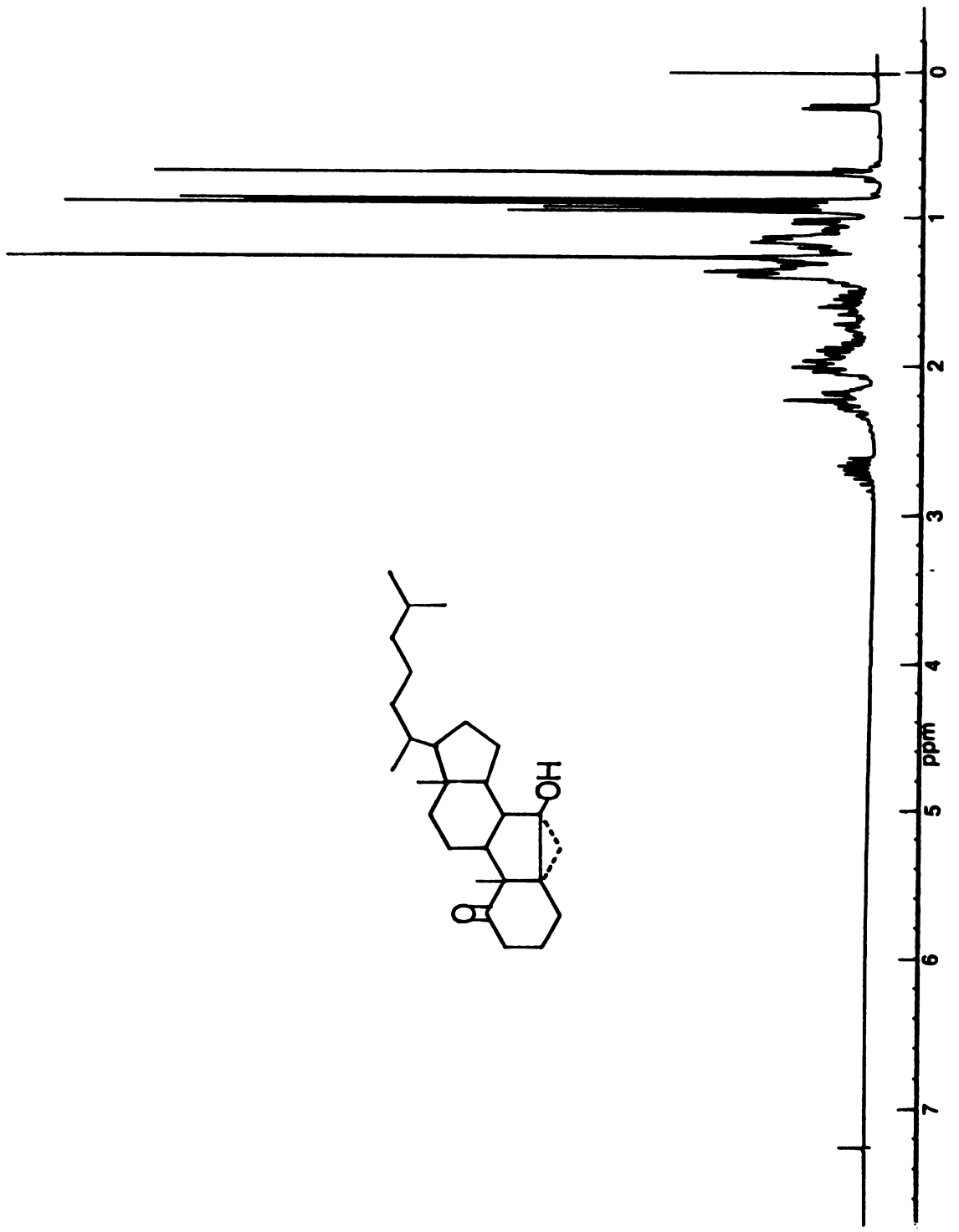


Figure I-31. Proton NMR of 41.

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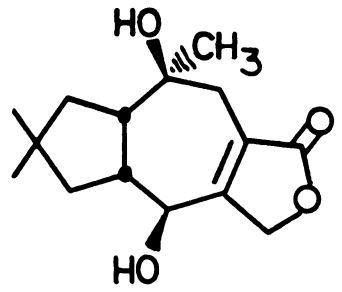
PART II

APPROACHES TO THE TOTAL SYNTHESIS OF LACTARANE SESQUITERPENES

INTRODUCTION

Nature provides a variety of terpenoid compounds, whose carbocyclic structures have challenged the skill and imagination of synthetic chemists. One rich and diverse source of such substances is a rather highly specialized and advanced fungi known as Basidiomycetes, a class to which "mushrooms" and "toadstools" belong. A number of sesquiterpenes isolated from Basidiomycetes[1], such as those belonging to the marasmane[2a-f] and hirsutane[3a-n] classes, have received widespread attention due in part to their biological activity. In the last few years, eleven new members of a class of sesquiterpenes known as the lactaranes[1] (from Basidiomycete "lactarius") have been isolated and identified. This class is characterized by a hydroazulenic skeleton containing a geminally substituted dimethyl cyclopentane ring, representative members being lactarorufin A $\underset{\sim}{1}$[4a-e], furoscrobiculide B $\underset{\sim}{2}$[5], lactarolide A $\underset{\sim}{3}$[6], furan ether A $\underset{\sim}{4}$[5,7], vellerolactone $\underset{\sim}{5}$[8a,b], and pyrovellerolactone $\underset{\sim}{6}$[8a,b], Figure II-1.

The biogenesis of these humulene derived sesquiterpenes is depicted in Figure II-2. Humulene, which arises by the cyclization of farnesyl pyrophosphate ($\underset{\sim}{7}$), can undergo further cyclization to a variety of carbocyclic structures



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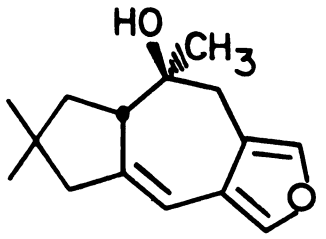

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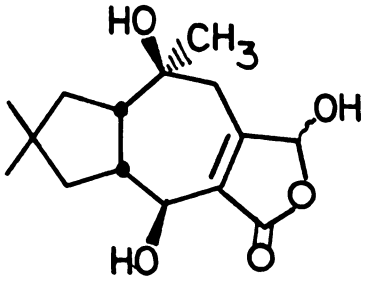

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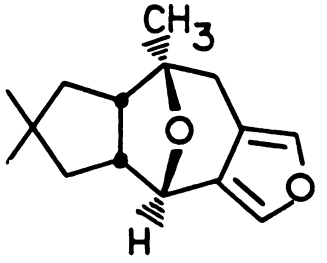

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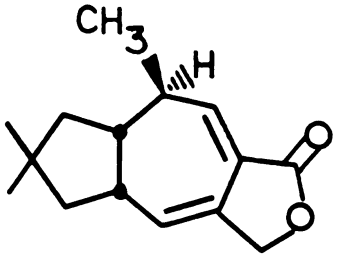

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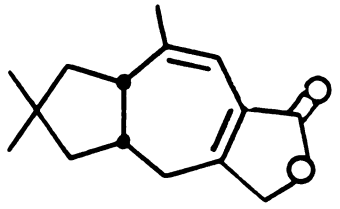

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Figure II-1. Representative lactarane sesquiterpenes.

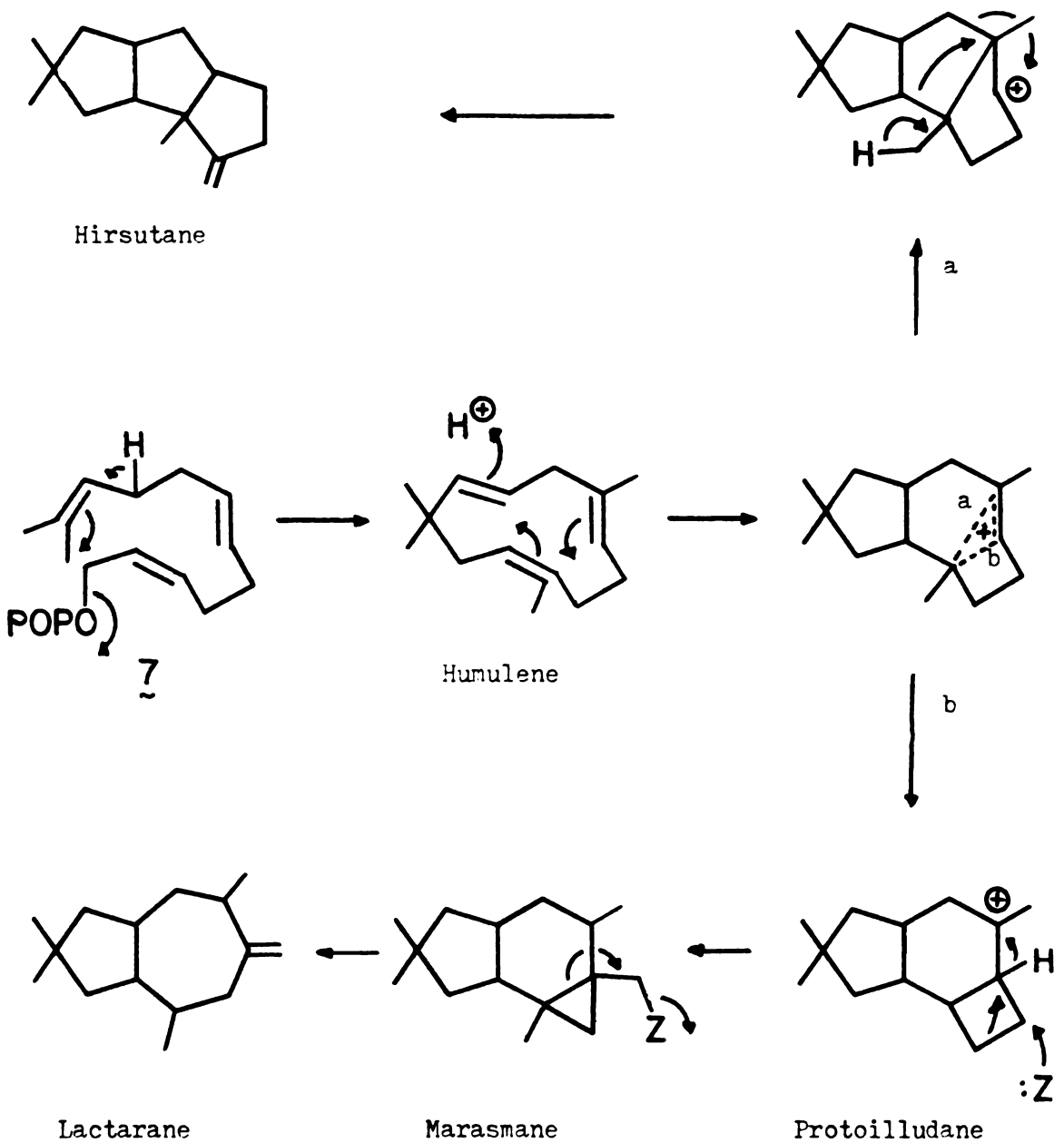
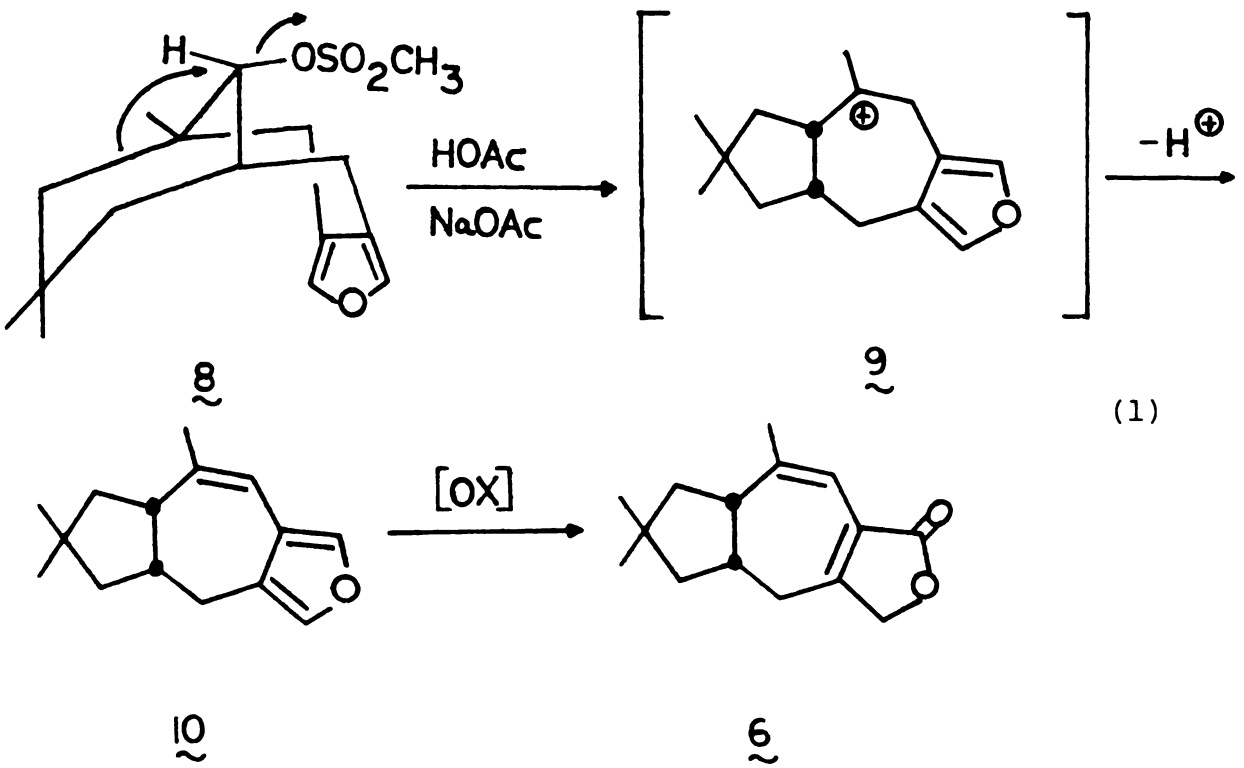


Figure II-2. Biogenesis of selected humulene derived sesquiterpenes.

ultimately leading to the lactarane, marasmane, hirsutane and other classes of sesquiterpenes. Several biosynthetic investigations support this scheme[3c-e,9a-b,10].

Syntheses of hydroazulenic sesquiterpenes have been directed mainly at compounds of the guaine class[11]. Although there are approximately thirty members of the lactarane sesquiterpenes, only two syntheses of compounds in this class have been reported. Pyrovellerolactone 6 was synthesized in 1975 by Magnusson and coworkers[12]. The key step in this synthesis involved a ring contraction initiated during the acetolysis of 8, which presumably proceeds via carbocation 9. Loss of a proton from 9 afforded a mixture of products, from which olefin 10 was isolated and oxidized to pyrovellerolactone 6 in poor overall yield (Equation 1). The solvolysis of appropriately function-



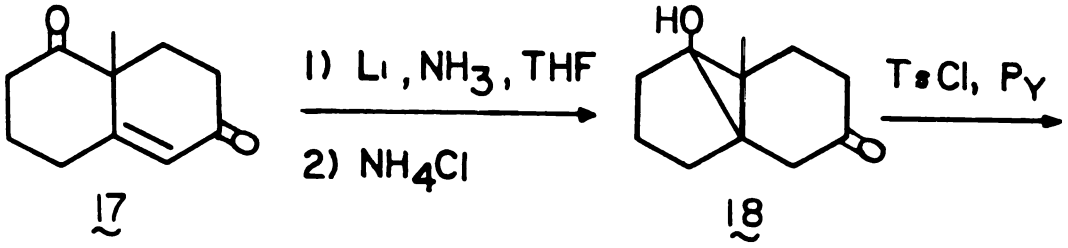
8 9 (1)

10 6

alized bicyclo-[4.3.1]-decanes such as 8 to form hydroazulenes was first demonstrated by Marshall[13].

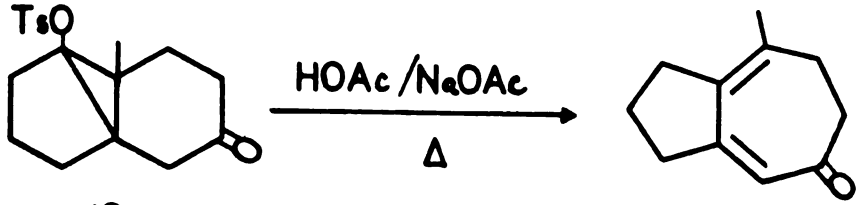
In 1978, Magnusson and Froborg reported a vastly improved synthesis of the lactaranes velleral and vellerolactone[14]. Cycloaddition of a functionalized acetylene with enamine 12 provided cyclobutene 13 which, without purification, underwent a clean thermal electrocyclic ring opening to afford 14. Deamination of 14 gave 15 which was converted to velleral 16[15] and vellerolactone 5 (Figure II-3).

In 1971, Reusch and co-workers reported the conversion of the Wieland-Miescher ketone 17 to the hydroazulene 20 by way of cyclopropanol 18[16] (Equation 2). Since then it



17 18

(2)



19 20

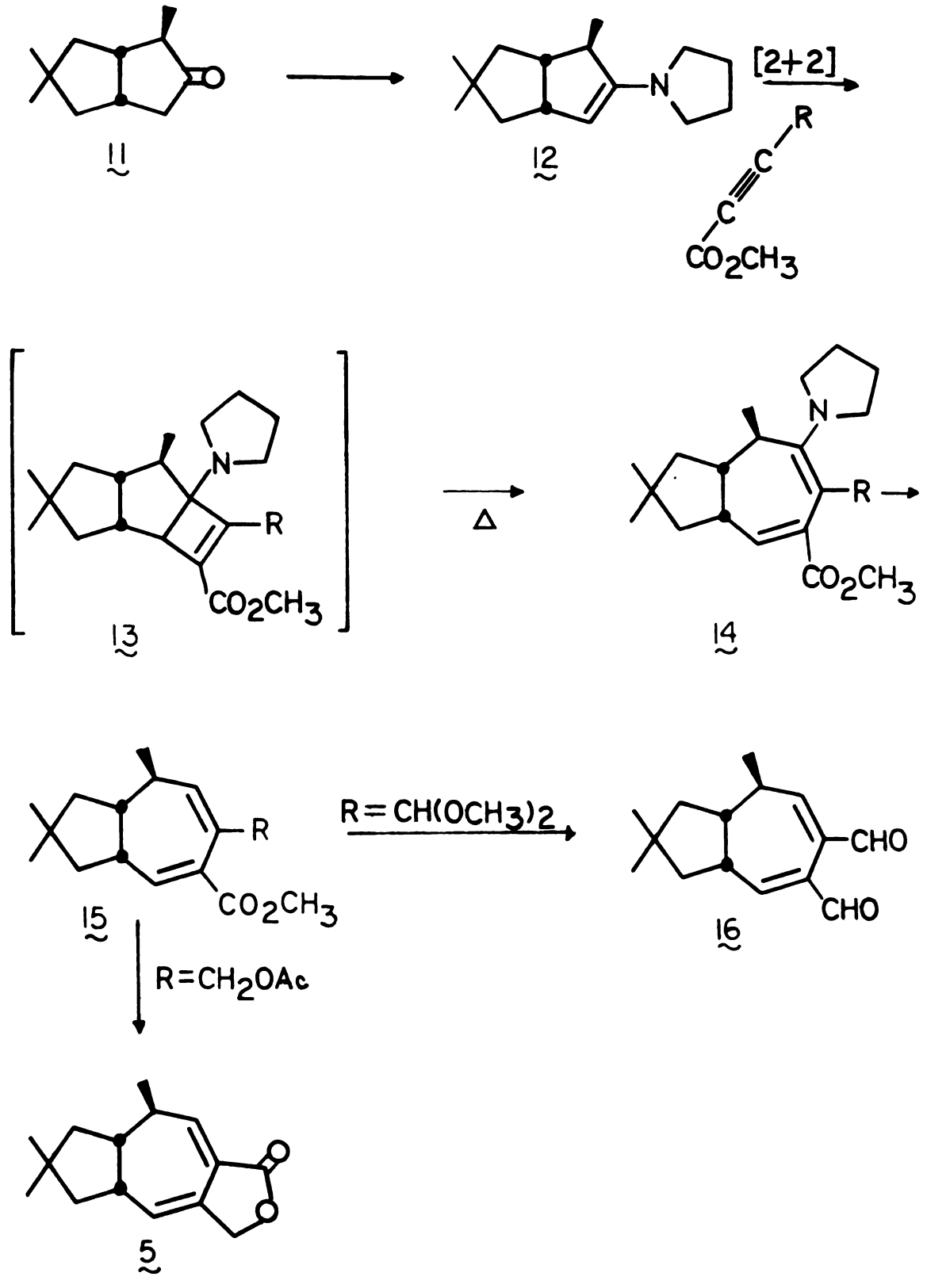
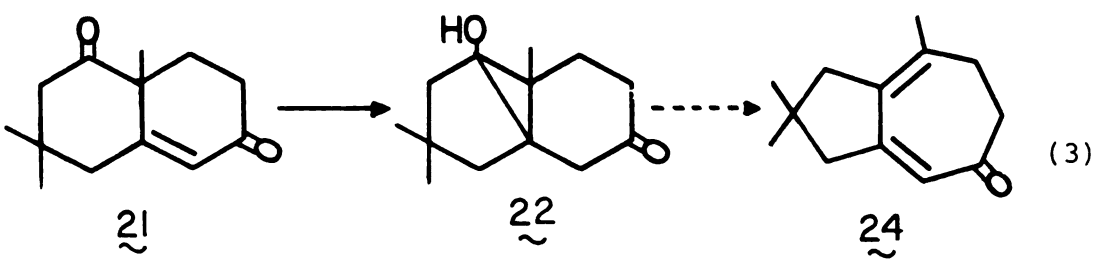


Figure II-3. Synthesis of velleral 16 and vellerolactone 5.

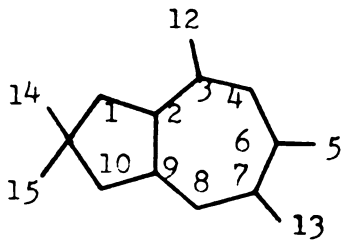
has been found that simple alkyl derivatives of 17 also undergo analogous cyclopropanol formation during reduction with lithium in ammonia[17]. For example, lithium-ammonia reduction of 21 proceeded smoothly to give cyclopropanol 22. Using the methodology employed for the conversion of 18 to 20 it should be possible to convert 22 to the gem-dimethyl hydrazulene 24 (Equation 3).



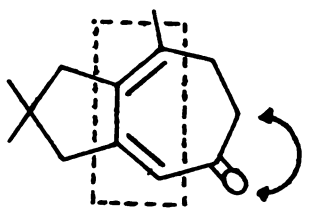
21 22 24 (3)

Even a cursory examination of dienone 24 suggests that it could serve as a valuable synthon for the total synthesis of lactarane sesquiterpenes. Thus the requisite gem-dimethyl cyclopentane ring is present, and the diene portion incorporating carbons 3-2-9-8 (lactarane numbering, Scheme 1) provides suitable functionality for the introduction of the oxygen functional groups present at one or more of these carbon atoms in the majority of the lactaranes. The C-12 methyl group is present and the carbonyl function

activates carbons 6 and 7, providing a potential for furan, lactone or lactol annulation (Scheme 1).



Lactarane



24

Attach carbons 5 and 13 which make up furan, lactone, or lactol ring.

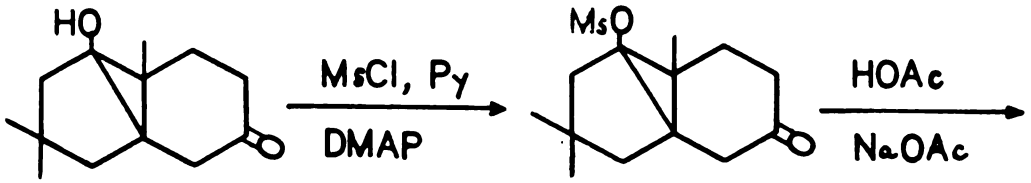
Oxidize diene moiety to provide requisite oxygen functionality and in addition establish the proper ring fusion stereochemistry

Scheme I

A study of compound 24 as an intermediate for the synthesis of lactarorufin A was set as the initial goal of this project, and most of the chemistry described here was carried out with this goal in mind. This portion of the thesis describes an efficient synthesis of 24, and the results of several studies designed to convert it to lactarorufin A.

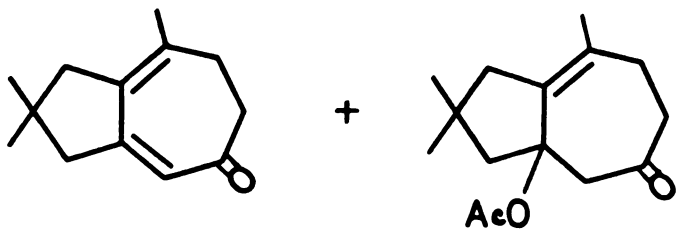
RESULTS AND DISCUSSION

Cyclopropanol 22 was prepared by lithium in ammonia reduction of enedione 21[17], which had been synthesized according to the procedure of Heathcock[18]. Reaction of 22 with methanesulfonyl chloride in pyridine containing a catalytic amount of dimethylaminopyridine[19] gave the corresponding mesylate ester 23. Acetolysis of 23 yielded dienone 24, accompanied by a higher molecular weight product believed to have structure 25 (Equation 4)[20].



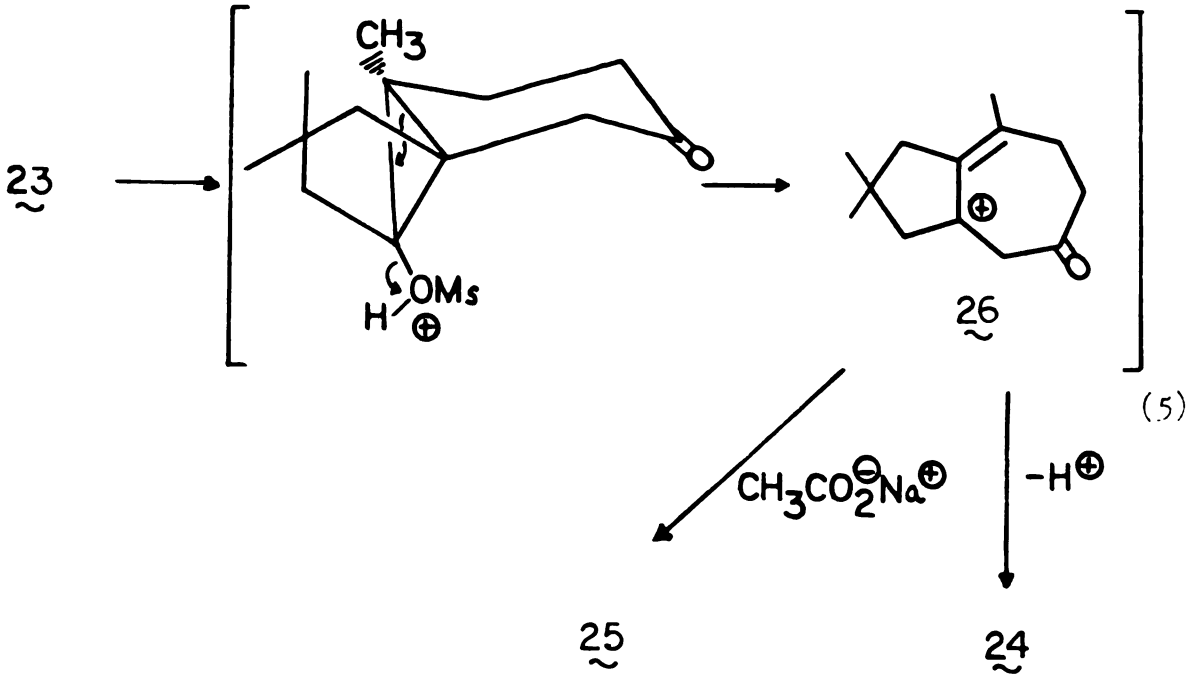
22 23

(4)



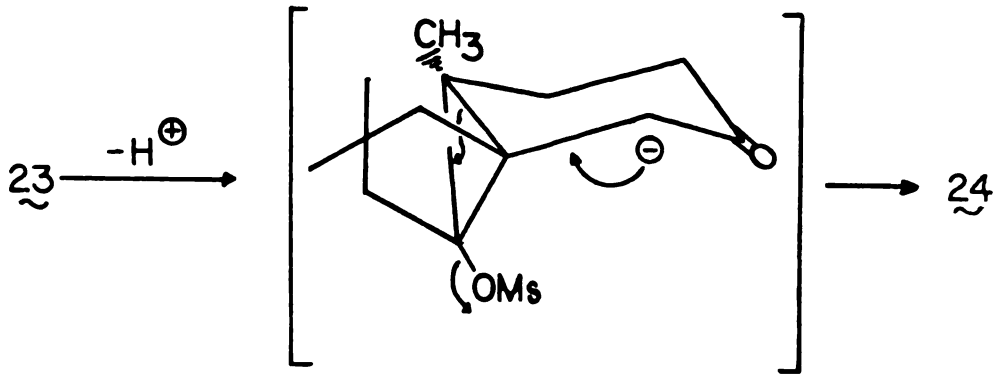
24 25

The observance of 25 in roughly a 2:3 ratio with 24 supports a solvolysis mechanism in which carbonium ion 26 is formed as the key intermediate (Equation 5). Thus 26 may lose a proton to generate 24, or suffer nucleophilic attack



(5)

by sodium acetate to give 25. Varying the amount of sodium acetate used in the solvolysis or increasing the reaction temperature failed to effect a cleaner conversion. To circumvent this problem, the possibility that 23 might undergo ring expansion under basic conditions was studied (Equation 6). Although amine bases had no effect on 23, stronger bases such as alkali metal alkoxides, sodium



(6)

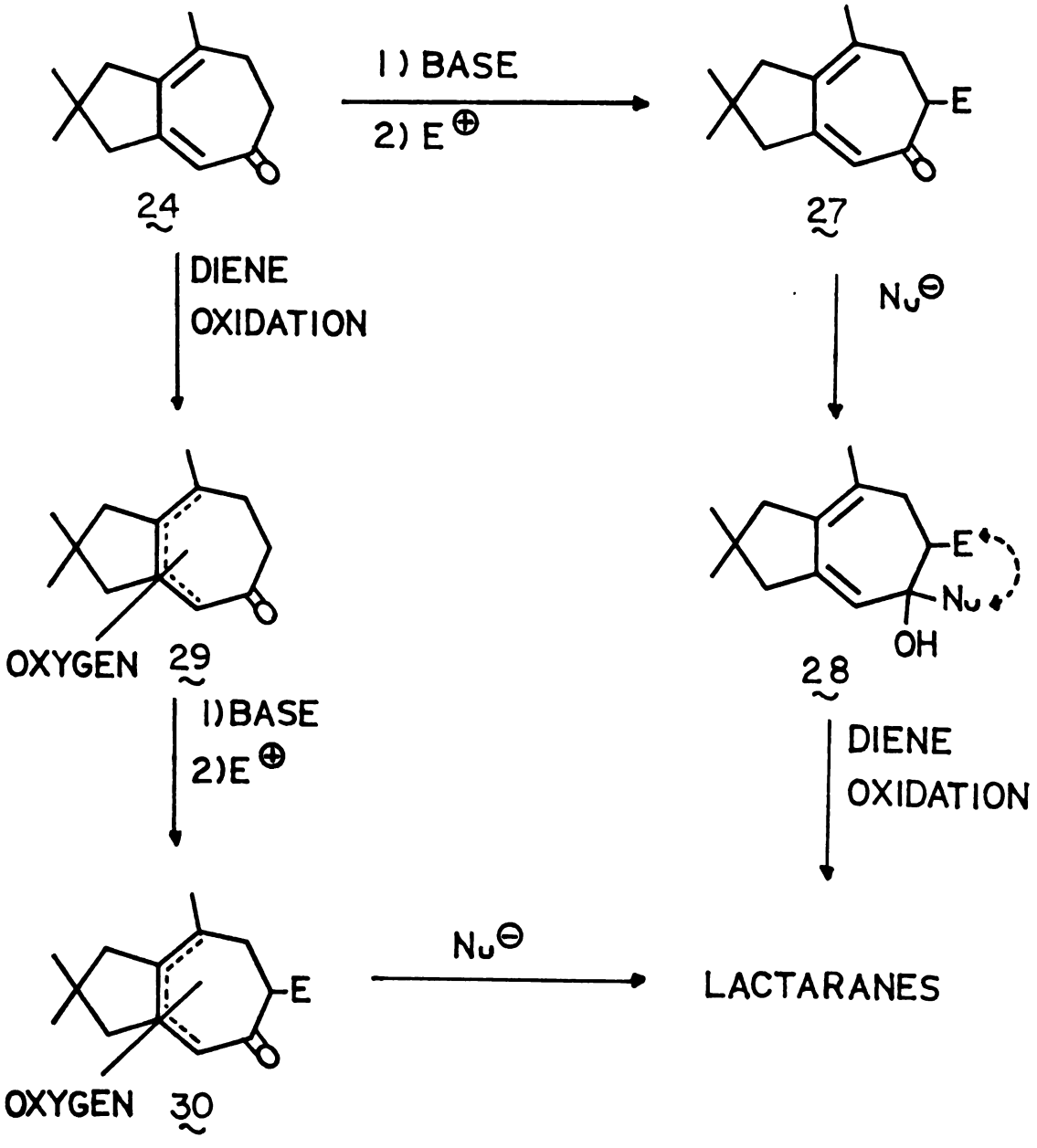
hydride, lithium diisopropyl amide and dimsylsodium were effective in promoting the conversion of 23 to 24. Unfortunately the yield was poor and the occurrence of side products complicated the reaction.

Since neat acetic acid proved ineffective for the conversion of 23 to 24, it was proposed that a stronger acid, with a less nucleophilic conjugate base would be an ideal solvent for this reaction. Trifluoroacetic acid fits this requirement, and a solution of 23 in neat trifluoroacetic acid yielded 24 in nearly quantitative yield.

With an efficient synthesis of 24 established, it became necessary to investigate the viability of 24 as a lactarane synthon. Two basic strategies were explored and are illustrated in Scheme 2. One approach, A, involves the introduction of missing carbons 5 and 13 (Scheme I) to obtain an intermediate of structure 28. The notation

"E" represents a one-carbon moiety added to 24 by reaction of a suitable electrophile (E^+) with an enolate species derived from 24. The notation "Nu" represents a one-carbon moiety appended to the dienone skeleton by 1,2-addition of an appropriate nucleophile (Nu^-) to the carbonyl function of 27. These one carbon units must be suitable functionalized so that cyclization to the lactone, furan or lactol ring may be effected at a later stage. Oxidation of the diene system of 28 should then provide a lactarane sesquiterpene. Conversely, as in approach B, diene oxidation could be effected first, leading to intermediate 29. Lactone, furan, or lactol annulation would then proceed as in the case of 28. This is of course a simplified picture but it serves to illustrate three objectives which must be undertaken concerning the use of 24 as a functional lactarane synthon.

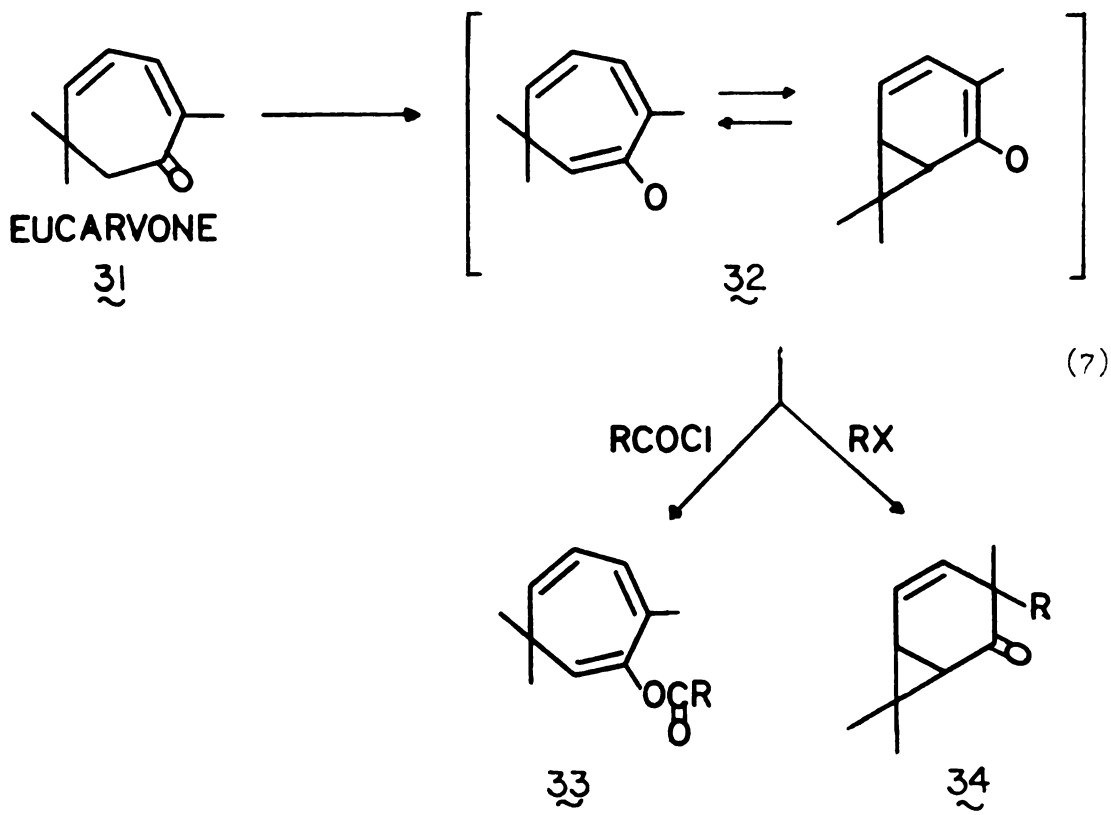
1. Reactions of the cycloheptatrienylate conjugate base of 24 must be studied.
2. The reactivity of theketone carbonyl present in 27 or 30 towards nucleophilic 1,2-addition must be examined.
3. Methods of oxidizing the diene moiety in 24 need to be studied, keeping in mind the stereoselectivity needed in these transformations.


1) BASE
2) E⊕
24
27
E
DIENE
OXIDATION
Nu⊖
E
Nu
OH
OXYGEN 29
28
1)BASE
2)E⊕
DIENE
OXIDATION
E
Nu⊖
LACTARANES
OXYGEN 30

Scheme II

1. Reactivity of the Cycloheptatrienylate Conjugate Base (35) of Dienone 24

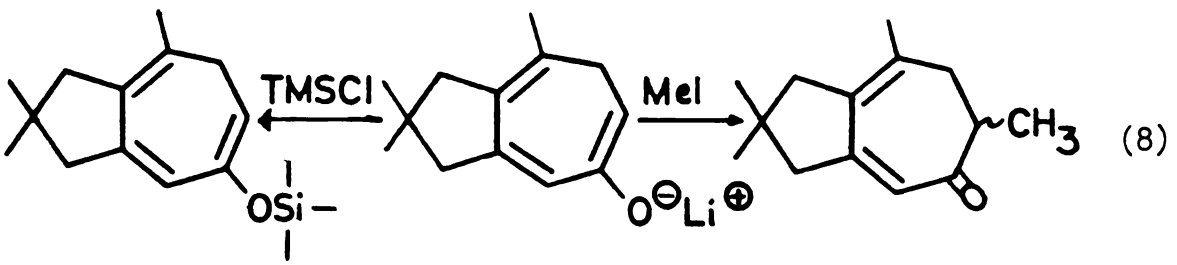
The success of the lactone annulation will depend in part on how 35, the cycloheptatrienylate conjugate base of 24, reacts with electrophilic reagents. The possibility that the bicyclic enolate ion will exist in equilibrium with a tricyclic enolate ion may pose a problem. This cycloheptatrienylate-norcaradienylate equilibrium was first studied by Corey[21] (Equation 7).



(7)

Corey observed that when reactive electrophiles, such as acid chlorides, were added to the conjugate base derived

from eucarvone 31, a cycloheptatriene product such as 33 was obtained. However, reaction of 32 with less reactive electrophiles, alkyl halides for example, gave the norcarene product 34. In the present study, when 24 was treated with lithium diisopropyl amide followed by addition of trimethylsilyl chloride the expected cycloheptatrienol silyl ether 36 was isolated. Similarly, reaction of 35 with methyliodide gave exclusively the alkylated hydroazulenic dienone 37 (Equation 8).

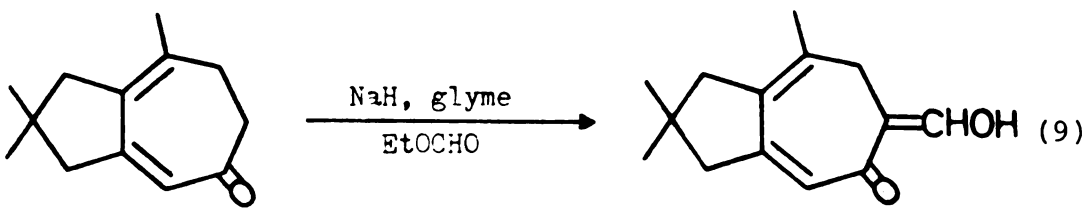


(8)

36 35 37

Although it is not possible to rule out a cycloheptatrienylate-norcaradienylate equilibrium here, product analysis of 36 and 37 indicates that 35 reacts exclusively as the cycloheptatrienylate form at room temperature. The fusion of the geminally substituted dimethyl cyclopentane ring may impart sufficient rigidity or steric constraint so as to shift the proposed equilibrium to favor the cycloheptatrienylate isomer.

The reaction of 35 with trimethylsilyl chloride was rapid at 0°, but to achieve reaction with methyliodide it was necessary to reflux the reaction mixture for 0.5 hr. The lithium enolate 35, proved to be relatively unreactive with certain other electrophiles, failing to react with carbon dioxide, diethyl carbonate, ethylformate, and carbon disulfide. However, the sodium enolate, prepared by reaction of sodium hydride with 24, in glyme containing ethyl formate yielded the α-hydroxymethylene product 38 (Equation 9). The formation of unidentified side products,



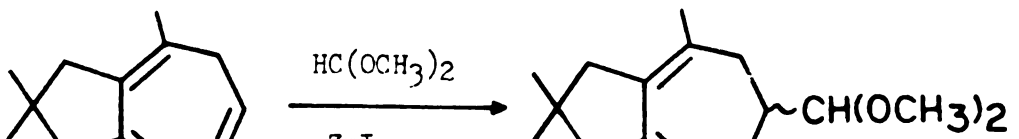
(9)

24 38

lack of reproducibility, and difficulties in product purification complicated this reaction.

Owing to the limited reactivity exhibited by 35, alkylation reactions of the silyl enol ether 36 were also studied. Alkylations of silyl enol ethers with trimethyl orthoformate in the presence of Lewis acids have been reported by numerous groups[22a-c]. In applying this method to the

present study, it was found that 36 reacts with trimethyl orthoformate in the presence of zinc iodide to give the β-ketoacetal 39 (Equation 10). Thus, in contrast to the



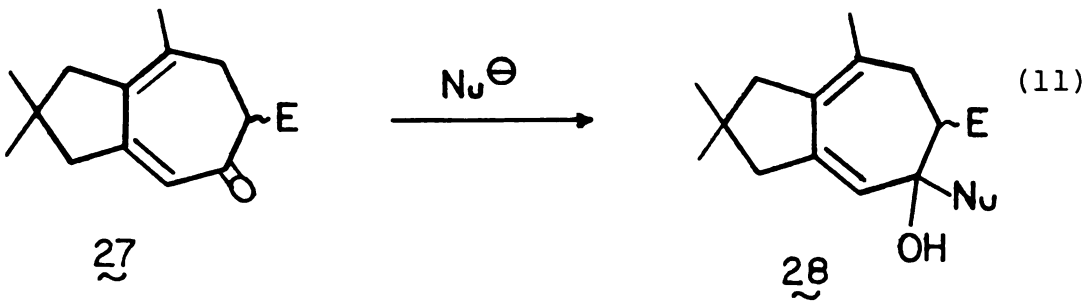
(10)

36 39

direct use of the enolate 35 as a nucleophile in reactions with a number of simple electrophiles, the alkylation of the silyl enol ether 36 was an encouraging result. The synthesis of an intermediate of type 27, specifically product 39, completed the first stage of this investigation.

2. Reactivity of the Unsaturated Ketone 24 with Nucleophiles

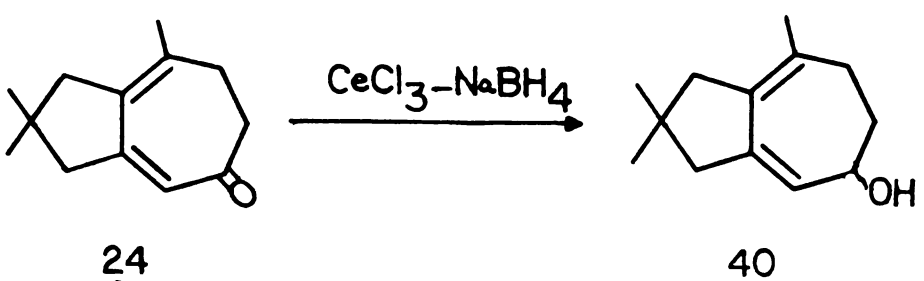
Following the introduction of carbon number 5 ("E" in Scheme II) by electrophilic attack on enolate 35 or enol ether 36, the construction of the fused lactone or furan ring of the lactaranes requires a 1,2-addition of a suitably functionalized carbon nucleophile (Nu^-) to 27, as shown in Equation 11.



27 28 (11)

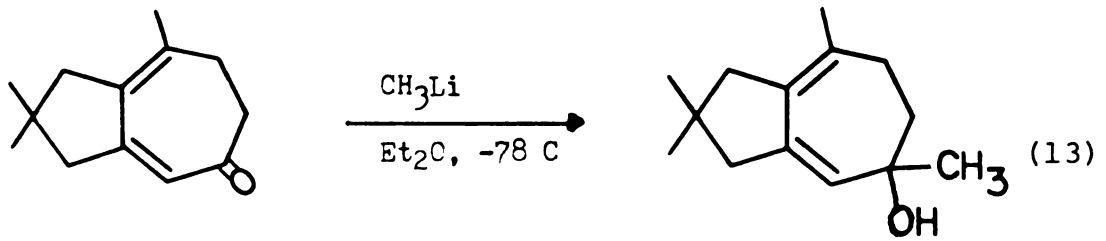
Cyclization of the appropriately functionalized one carbon appendages "E" and "Nu" at some later stage of the synthesis completes the annulation.

In order to examine the reactivity of this dienone system (27) towards nucleophiles, the unsubstituted dienone 24 was used as a model. It was found that 24 could be selectively reduced to allylic alcohol 40 by the sodium borohydride-cerium trichloride reagent[23] (Equation 12)



24 40 (12)

Addition of methyllithium to 24 also gave the 1,2-addition adduct 41 (Equation 13).



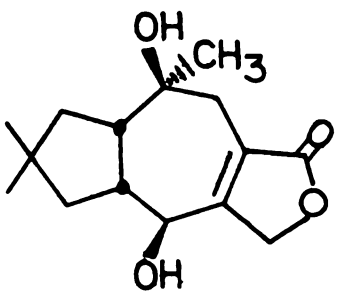
24 41 (13)

Unfortunately, stabilized nucleophiles, bearing sufficient functionality so as to be useful in the later planned cyclization, failed to add cleanly to 24. Thus, addition of anions derived from phenyl chloromethyl sulfoxide[24a-c], thioanisole[25], and dimethylsulfide[26] to 24 gave only complex mixtures. The possibility of nucleophilic 1,4- or 1,6-addition and enolization most likely complicate these reactions.

Although dimethylsulfonium ylide[27] is known to undergo exclusive 1,2-addition to unsaturated ketones, its reaction with 24 also proved complicated, perhaps due to instability of the resulting allylic epoxide. The reaction of trimethylsilyl cyanide with 39 was equally disappointing. This reagent normally reacts with unsaturated ketones to give the corresponding unsaturated cyanohydrin TMS

derivatives[28]. However, no reaction was observed with 39 in the presence of a zinc iodide catalyst.

These findings appear to limit the usefulness of approach A (Scheme II). Approach B, in which the diene system of 24 is modified prior to lactone annulation, was therefore investigated. Indeed, there is reason to believe that early transformation of the diene moiety in 24 may be advantageous. For example, by establishing the proper oxidation state and stereochemistry of contiguous carbons 3-2-9-8 (Scheme I) as in lactarorufin A (1),



1

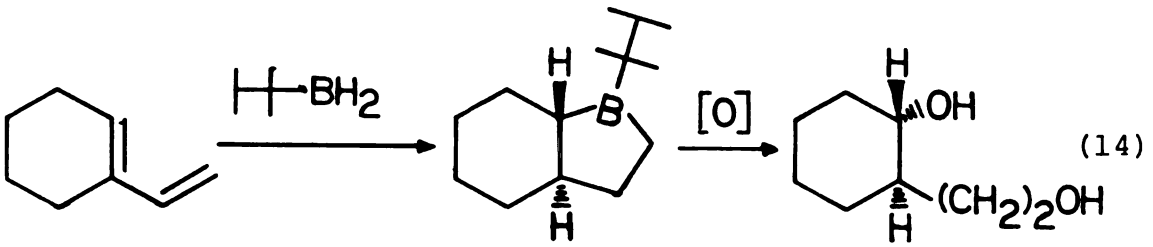
the olefinic conjugation with the carbonyl group in 24 is removed, and nucleophilic additions to this function may be rendered less complicated.

3. Oxidations of the Diene Moiety of 24 and Attempts at Establishing the Ring Fusion Stereochemistry

Three approaches for effecting oxidation of the diene system of 24 were investigated with varying degrees of

success: hydroboration with thexylborane, cycloaddition with singlet oxygen, and epoxidation with meta-chloroperoxybenzoic acid.

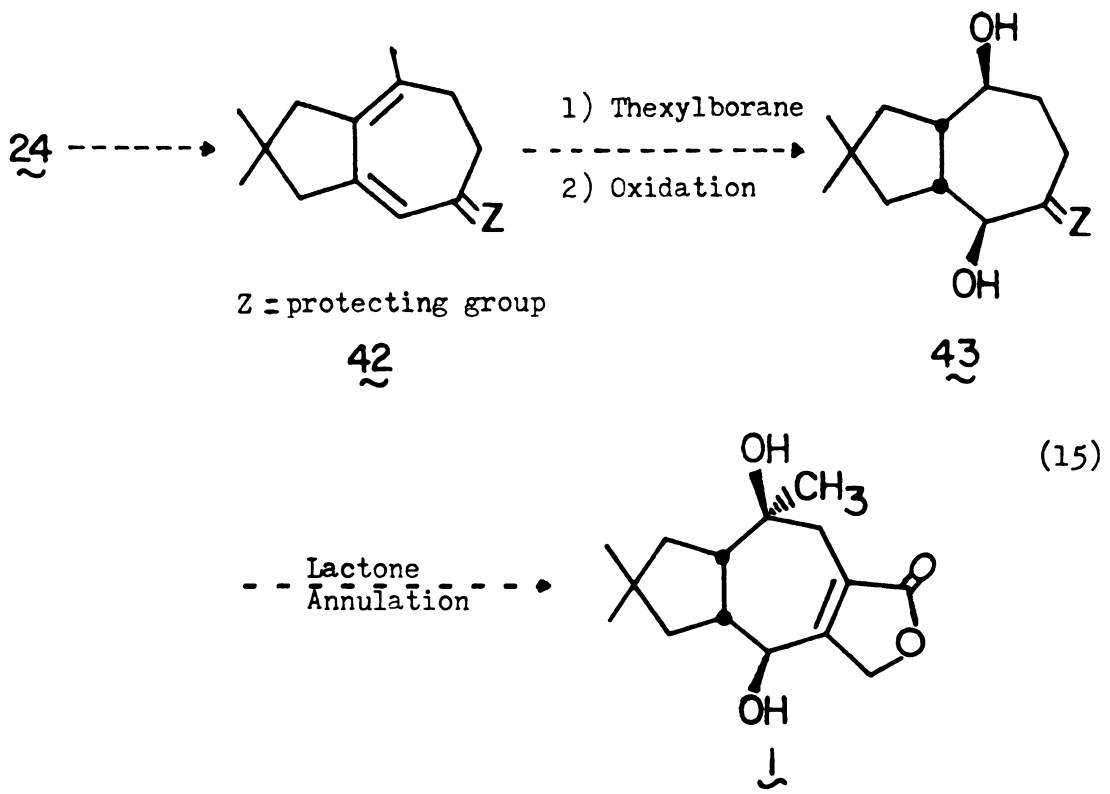
Cyclic hydroboration of 24 with thexylborane appeared to be an attractive method for converting the diene moiety into a cis 1,4-diol, with concommitant fixing of the ring fusion stereochemistry in the desired cis conformation. It has been shown that certain dienes react with thexylborane to yield cyclic boranes which can be oxidized to 1,4-diols, as shown in Equation 14[29].



(14)

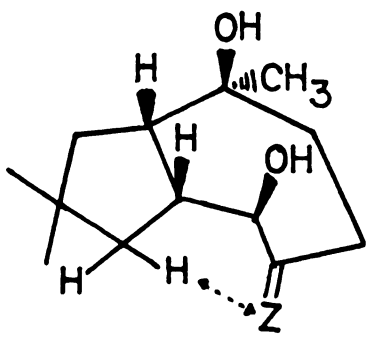
An equivalent cyclic hydroboration of 24, after protection of the carbonyl function, would provide an especially short and stereospecific procedure for establishing the desired configuration at four contiguous asymmetric carbons (Equation 15).

In principle the protecting group in 42 (Z) should be as small as possible since models indicate that the cis ring fusion forces the hydroazulenic skeleton to adopt a folded structure. Severe non-bonded interactions exist



(15)

between the methylene group of the cyclopentane ring and the protective group Z in such a compound (43).



43

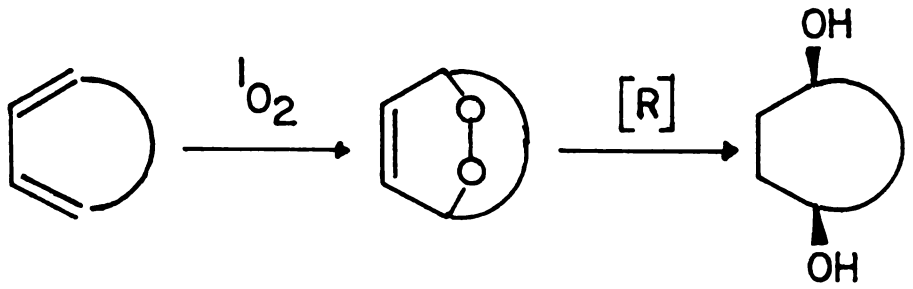
Ketalization of 24 with ethylene glycol proceeded in an unsatisfactory fashion. The reaction of 24 in refluxing

benzene containing ethylene glycol and a catalytic amount of para-toluenesulfonic acid gave a mixture (>3) of ketals. Double bond migration is often observed during the ketalization of unsaturated ketones, and is most likely occurring in this reaction. It has been reported that the use of weaker acid catalysts avoids this double bond migration. However, ketalization using fumaric acid[30] as a catalyst also gave an unresolvable mixture of ketals.

Since the carbonyl group of 24 could not be suitable protected, as in 42, the cyclic hydroboration of the unprotected ketone 24 was attempted. Thexylborane is known to react with ketones although at a rate slower than with olefins. However, reaction of 24 with thexylborane gave a complex mixture of products. Reaction of 41 with thexylborane was equally disappointing, again, a complex mixture of products was obtained. It has been reported that conjugated dienes are less reactive towards cyclic addition of thexylborane. In addition, the cyclic borane expected from reaction of thexylborane with a diene such as 42 results in the formation of a relatively strained intermediate. These two facts may account for the observed results with substrates 24 and 41.

A promising alternative for the synthesis of cis 1,4-diols is the photo-sensitized oxidation of conjugated dienes with singlet oxygen, first observed by Windaus[31]. These reactions have been shown to proceed by 1,4-cyclo-

addition of singlet oxygen to give an endoperoxide intermediate (Equation 16). Subsequent reduction of this

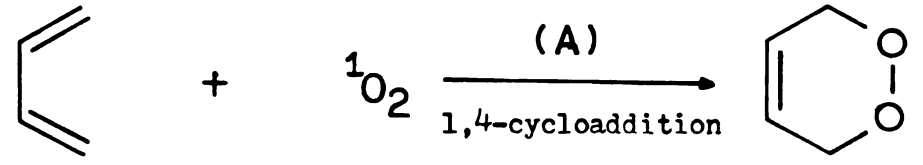


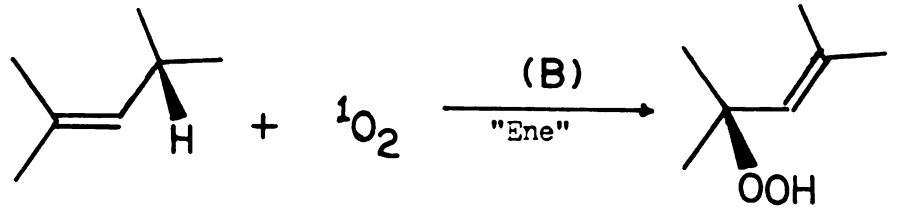
(16)

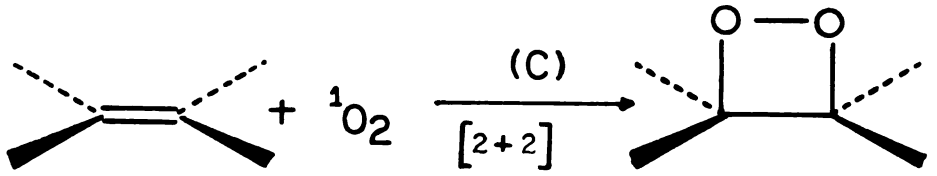
intermediate provides a good general method for the introduction of cis hydroxyl groups at the terminal carbon atoms of a conjugated diene. Indeed, the role of endoperoxides in synthetic chemistry has increased dramatically in the last few decades[32].

Reactions of singlet oxygen with olefinic substrates often are complicated by alternative modes of reactivity. The three most common modes of reaction of singlet oxygen with olefins are: 1,4-cycloaddition (A) forming endoperoxides, the ene reaction (B) leading to hydroperoxides, and [2+2] cycloaddition to activated olefins (C) resulting in the formation of 1,2-dioxetanes (Scheme III).

In practice, competition among these three kinds of reactions is often observed, the structure of the substrate being an important factor in determining the product

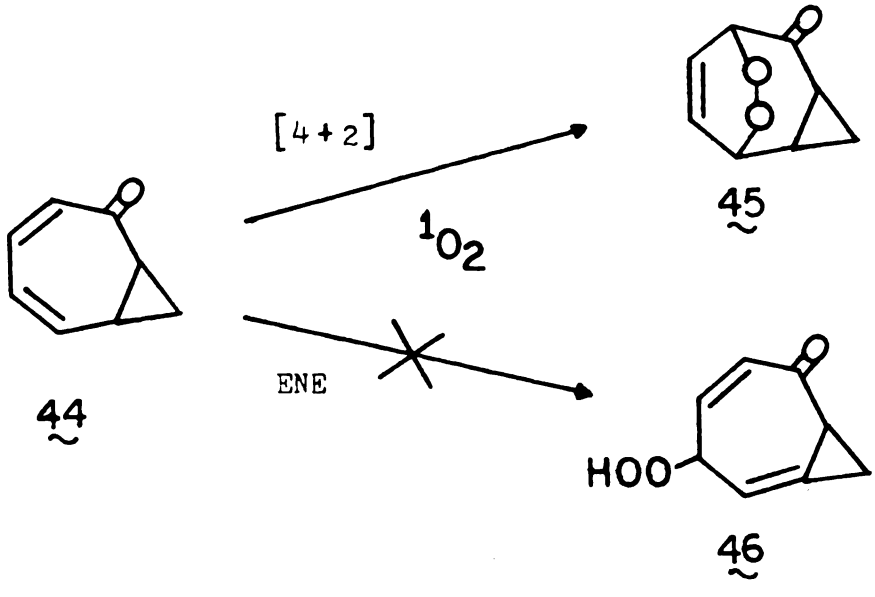






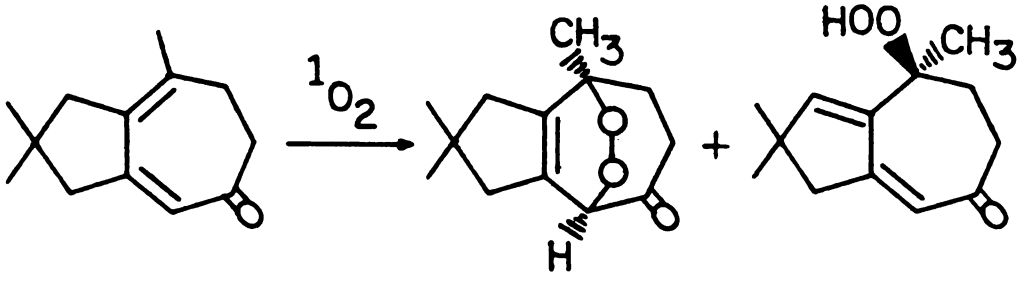
Scheme III

distribution. It is generally accepted that for a conjugated diene fixed in a cisoid fashion, the energy of activation for 1,4-cycloaddition is near zero. The ene reaction appears to be electrophilic in nature, and as a rule, tetrasubstituted double bonds react nearly as rapidly as 1,3-cyclohexadienes, whereas tri-, di-, and monosubstituted double bonds react more slowly. Consequently, if a substrate incorporates both a conjugated diene and a tetrasubstituted double bond, a mixture of hydroperoxide and endoperoxide products may be obtained. This situation is realized in the reaction of singlet oxygen with dienone 24. Cycloaddition to the diene moiety is desired in order to effect the cis hydroxylation needed for a synthesis of lactarorufin A. Such a reaction has in fact been observed for the similar cycloheptadienone 44[33] (Equation 17).



(17)

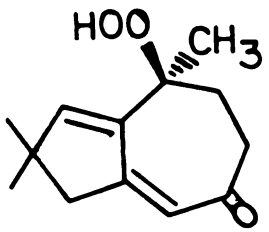
The exclusive formation of the endoperoxide 45 is readily rationalized. The double bonds of the diene system in 44 are disubstituted and thus less likely to participate in an ene reaction. Furthermore, the only possible ene product, 46, has a strained double bond. Both 24 and 44 have an electron withdrawing carbonyl function conjugated with the diene system. This conjugation should in principle deactivate the diene systems in reactions with electrophilic reagents. In the present study, photooxidation of 24 in acetone, with hematophorphyrin as a sensitizer yielded two crystalline products, as shown in Equation 18.



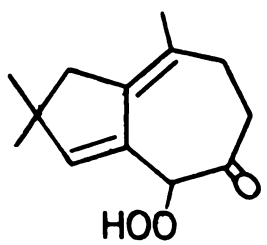
24 47 (49%) 48 (42%) (18)

Although endoperoxide 47 is the major product, the isomeric hydroperoxide 48 is formed in only slightly lower yield. Interestingly, 48 is only one of four possible

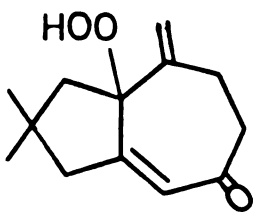
"ene" products derived from reaction at the four different allylic sites available in 24 (48-51).



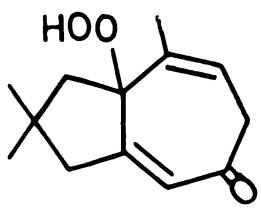
48



49

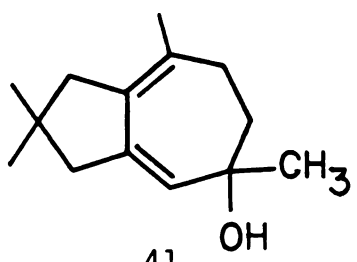


50



51

Hydroperoxide 48 comes from an ene reaction at the most electron rich double bond in 24 (i.e., the most substituted and most removed from the carbonyl function). In addition, this hydroperoxide product (48) maintains a fully conjugated dienone system unlike 49, 50 or 51. Thus, product stability helps to lower the energy of activation for the reaction leading to 48. This conclusion is supported by the observation that photo-sensitized oxidation of alcohol 41 yielded only a mixture of ene products. Clearly, the



41

the carbonyl function in 24 has a dramatic effect upon the reactivity of the diene system with singlet oxygen. The hypothesis that the carbonyl function would deactivate 24 towards participation in an ene reaction appears to be true to an extent. However, the established reactivity of tetrasubstituted double bonds in "ene" reactions continues to be a significant factor, as the formation of 48 demonstrates.

In 1981 Matsumoto[34] reported an interesting solvent effect in reactions of acyclic conjugated dienes with singlet oxygen. Prior to this report, no study involving the solvent dependency of the ene reaction versus the cycloaddition reaction had been published. For a number of simple acyclic dienes, Matsumoto found that carbon tetrachloride was the best solvent for the 1,4-cycloaddition reaction. It appears that the cycloaddition process is more sensitive to the lifetime of singlet oxygen than the ene reaction, since singlet oxygen is known to have a considerably longer lifetime in carbon tetrachloride than in other solvents such as simple alcohols or ketones.

In an effort to maximize the yield of endoperoxide 47, a study of the solvent dependency of the photo-sensitized oxidation of 24 was carried out (Table 1). Surprisingly, carbon tetrachloride favored the ene reaction. Overall, the photo-sensitized oxidation appeared to exhibit little dependency on the solvent or the sensitizer.

Table 1. Solvent Effect in the Reaction of Singlet Oxygen With 24.

Solvent	Sensitizer	Relative Ratio:[a] 47	48
Acetone	None	NR[b]	
Acetone	Hematophorphine (HP)	1.16	1
Acetone	Rose bengal (RB)[c]	1	1
Carbon Tetrachloride	HP	1	1.5
Carbon Tetrachloride	HP[d]	1	2.3
Carbon Tetrachloride	Tetraphenylphorphine	1	1.5
Ether	HP	NR	
Ethyl Acetate	HP	1	1.08
Methanol	RB	1	1
Methanol	HP	1	1

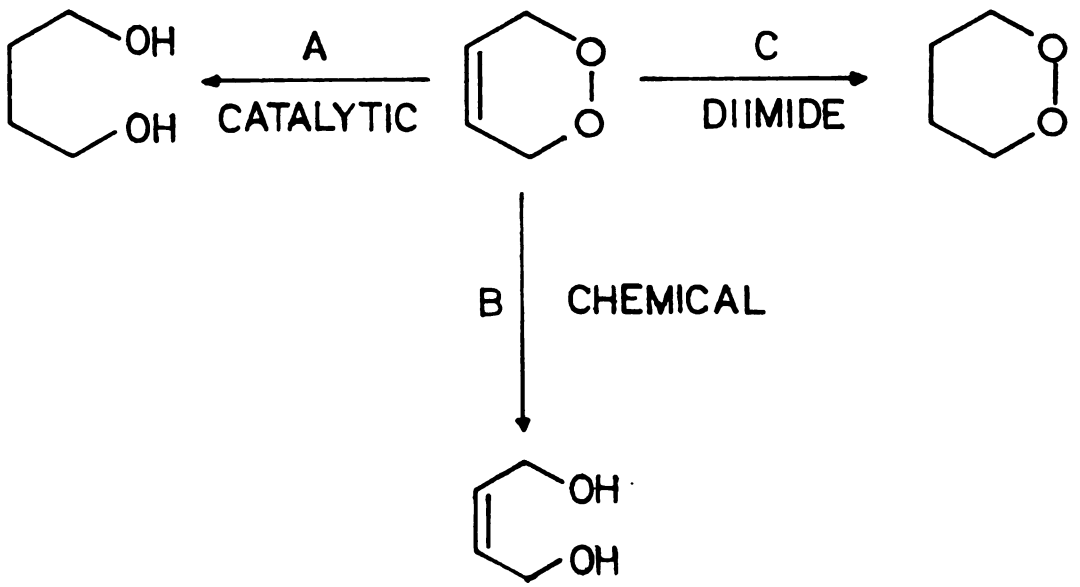
[a]Reaction times varied from 2-12 hours for completion.

[b]After extended periods >24 hrs a small amount (<10%) of 48 was detected.

[c]An unidentified product (10%) was isolated.

[d]Reaction performed at 0°.

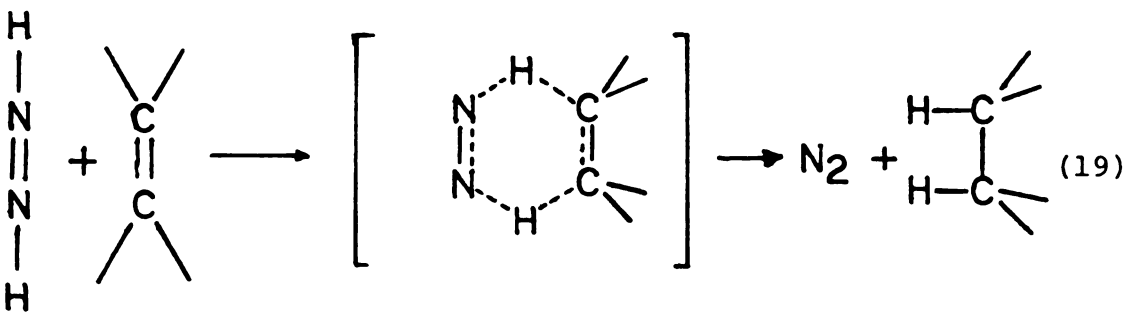
The yield of endoperoxide 47 is moderate but acceptable, considering that the terminal carbon atoms of the diene system have undergone the cis-oxidations. Unfortunately, efforts to reduce 47 to the corresponding diol proved unsatisfactory. Various methods exist for the reduction of endoperoxides and these can be classified into three types (Scheme IV).



Scheme IV

Thus an unsaturated endoperoxide can be converted to the saturated 1,4-diol (A) by catalytic reduction, or to the unsaturated allylic 1,4-diol (B) by chemical reduction of the peroxide bond, or to the saturated endoperoxide (C) by selective reduction of the carbon-carbon π bond with diimide[35]. In particular, the latter reaction seemed to offer an ideal first step in transforming 47 for a lactarane synthesis.

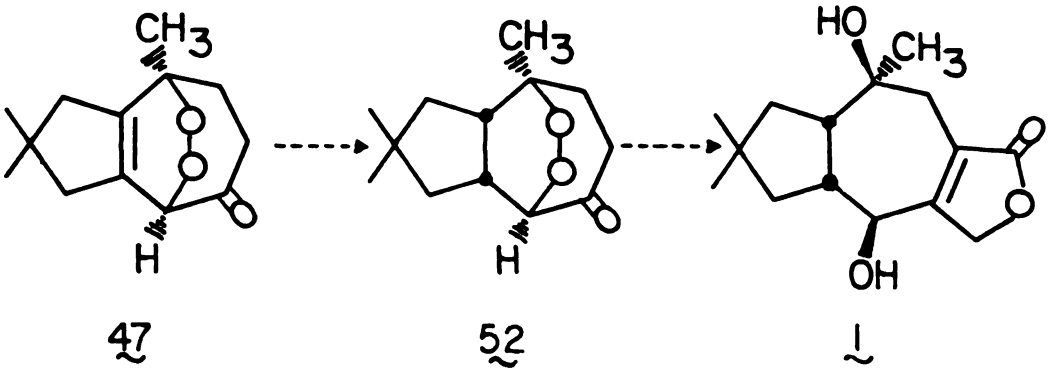
Reduction of olefinic bonds with diimide, generated by the acid decomposition of potassium azodicarboxylate, has been extensively studied[36]. These reductions are presumed to proceed by a "synchronous transport" of hydrogen through a cyclic transition state[37a-c] (Equation 19).



(19)

Not surprisingly, the reduction with diimide is quite sensitive to steric factors. Models indicate that the oxygen bridged side of 47 is considerably less hindered than the carbon bridged side. Consequently, reduction from the

peroxide bridge side should establish the desired stereochemistry at the ring junction, leading eventually to a synthesis of lactarorufin A or another of the lactaranes (Equation 20).



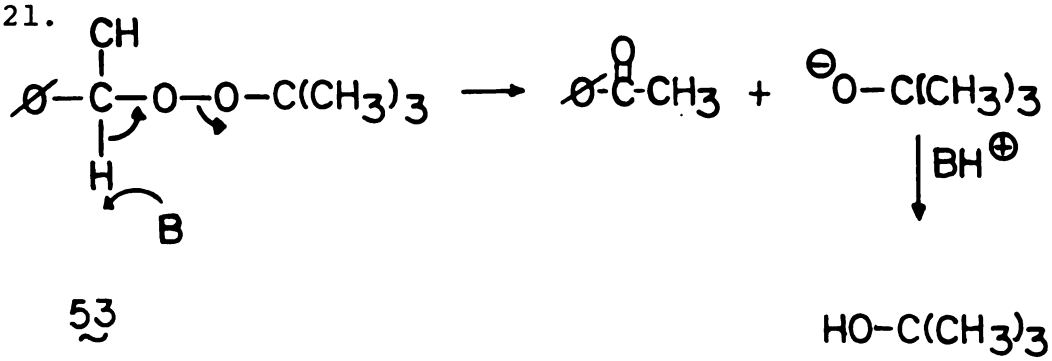
47 52 1 (20)

Diimide reductions are normally observed to be smooth and selective reactions. The presence of other functional groups, such as halogens, carbonyls, and esters do not normally interfere with olefin reductions. Unexpectedly, the endoperoxide 47 proved to be very sensitive to the conditions of diimide reduction, yielding only a complex mixture of products in methanol, dioxane, pyridine, or dimethylsulfoxide solutions.[36]

Owing to the reactive nature of 47, initial reduction of the peroxide linkage, as in approaches (A) and (B), was next explored in the hope of achieving an intermediate more amenable to subsequent manipulation. Catalytic reduction of 47 over 10% palladium on charcoal in ethyl acetate

gave only an unresolvable mixture of compounds. This result was not altogether unexpected since the peroxide linkage in 47 would certainly undergo reductive cleavage before olefin reduction, and without an intact peroxide bridge both faces of the double bond will be accessible to the addition of hydrogen. Hydrogenolysis of the initially formed allylic 1,4-diol and hemiketal formation may also be complicating factors in this reaction. Chemical reduction of the peroxide bridge with triphenyl phosphine[38] or thiourea was expected to give the unsaturated allylic 1,4-diol, but this also proved unexpectedly complicated.

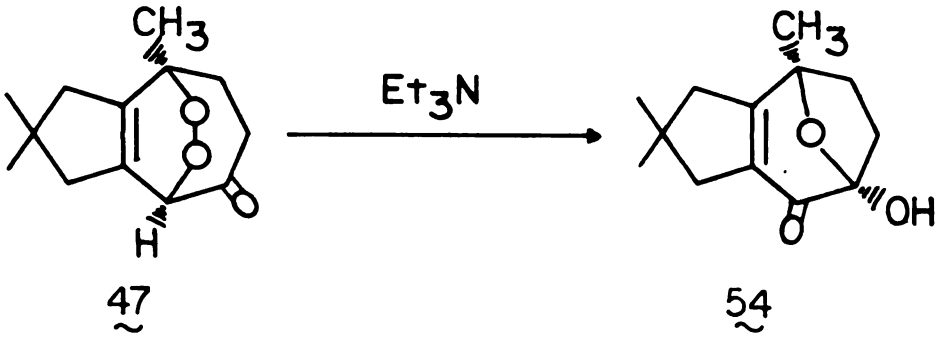
It has been observed that peroxides are sensitive to base. Kornblum and de-la Mare first reported a base-catalyzed decomposition of a dialkyl peroxide in 1951[39]. Bases such as potassium hydroxide, alkali metal alkoxides, or piperidine were found to catalyze the decomposition of 1-phenylethyl-tert-butyl peroxide 53 as shown in Equation 21.



(21)

Application of this mechanism to unsaturated endoperoxides would predict the formation of hydroxy-enones. This

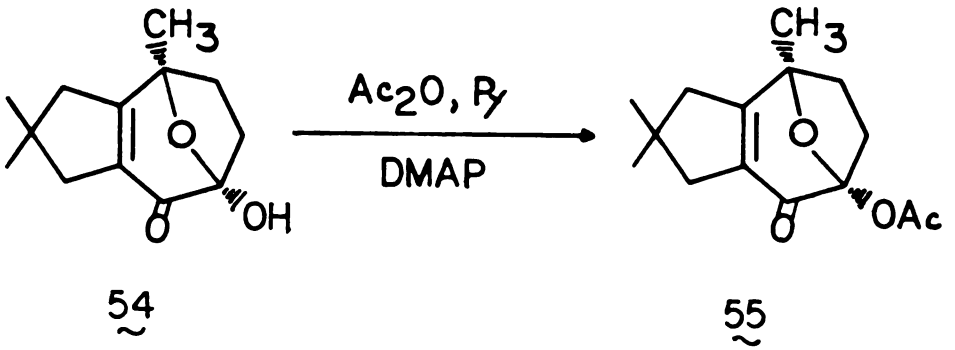
potentially useful synthetic pathway has been confirmed for a variety of endoperoxides[40a-c]. In the present case, treatment of endoperoxide 47 with triethylamine gave the bridged hemiketal 54 as a stable crystalline substance (Equation 22).



47 54 (22)

It was hoped that this hemiketal (54) would lend itself to stereoselective double bond reduction more readily than the isomeric endoperoxide (47).

Methods for the reduction of α,β-unsaturated ketones to saturated ketones are well documented[41a,b]. In the present case it was assumed that reduction of the double bond by diimide or the catalytic addition of hydrogen would proceed from the least hindered oxygen bridged side. Such reductions were carried out, either with the free hemiketal (54) or the acetate derivative (55). The latter was prepared by the reaction of 54 with acetic anhydride in pyridine containing a catalytic amount of 4-dimethylaminopyridine (Equation 23).



54 55 (23)

Attempted diimide reductions of 54 or 55 in methanol or pyridine solution were ineffective, with only starting material being recovered. Likewise, numerous efforts to effect catalytic reduction of these compounds (Table 2) failed to give the desired dihydro cis-fused products.

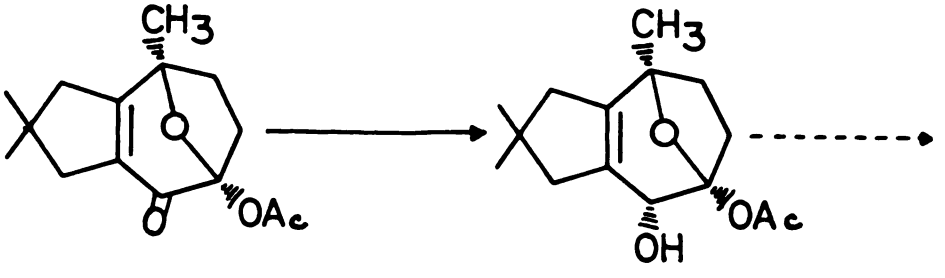
At some stage in any proposed lactarane synthesis proceeding from intermediate 55, it would be necessary to reduce the carbonyl group. Reduction of 55 with sodium borohydride-cerium trichloride reagent[23] gave a single product 56, in which the hydroxyl group was assigned the α-configuration on the assumption that reduction took place from the less hindered oxygen bridged side of the carbonyl group. Although this is the wrong

Table 2. Results of Attempted Catalytic Reductions of 54, 55 and 56.

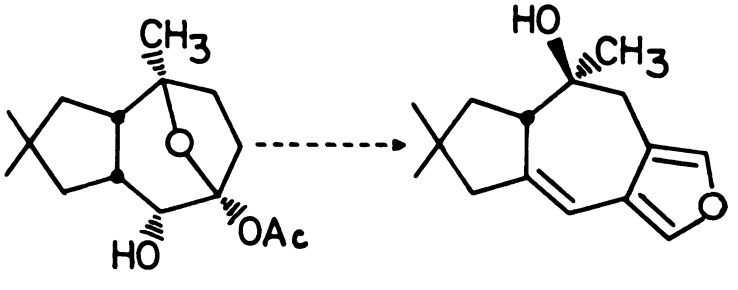
Substrate	Catalyst	Solvent	Temp.	Pressure	Reaction Time	Result
54	PtO_2	EtOH	RT	1 atm.	2 hrs.	NR[a]
54	PtO_2	AcOH	RT	"	"	NR
54	10% Pd/C	EtOAc	RT	"	"	Isomers[b]
54	2% $Pd/CaCO_3$	EtOH	RT	"	"	NR
55	10% Pd/C	EtOAc	RT -45°C	"	3	NR
55	5%/Pd-C	MeOH	RT	"	3	NR
55	Rh/Al	MeOH[c]	RT	"	4	NR
55	10% Pd/C	EtOAc	RT	30 psi	3	NR
56	10% Pd/C	EtOAc	RT	1 atm	2	complex mixture
56	Rh/Al	MeOH	RT	"	2	NR

[a]NR = no reaction. [b]Mixture of two unidentified isomers (80%). [c]1 drop of acetic acid was added.

configuration for lactarorufin A, it was proposed that 56 might be useful as an intermediate in a synthesis of Furoscrobiculide B, 2 (Equation 24). Unfortunately, the



55 56 (24)

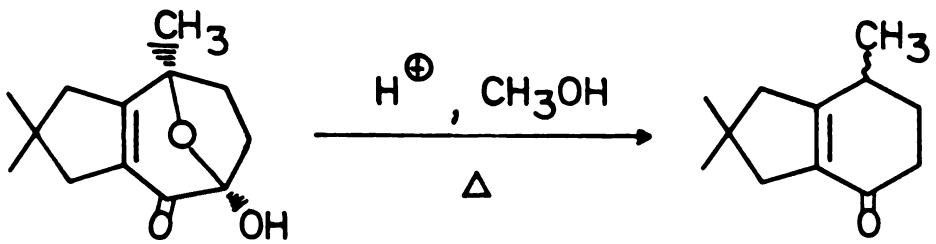


2

catalytic reduction of 56 proved to be exceedingly complex with 10% palladium on charcoal and ineffective with rhodium on alumina (Table 2).

Before the preparation of 55 had been achieved, efforts were made to convert 54 to a methyl ketal derivative. In refluxing methanol containing a little p-toluenesulfonic acid, 54 did not undergo any significant reaction. However 54 did react in refluxing methanol containing one drop of sulfuric acid and yielded a single product having a

molecular weight of 178. The presence of a methyl doublet centered at δ = 1.12 ppm (J = 7.2 Hz) and two singlets at δ = 1.09 and δ = 1.10 ppm, and in addition, a strong carbonyl absorption at 1650 cm^{-1} observed in the infrared spectrum supports the assignment of structure 57 for this product (Equation 25).

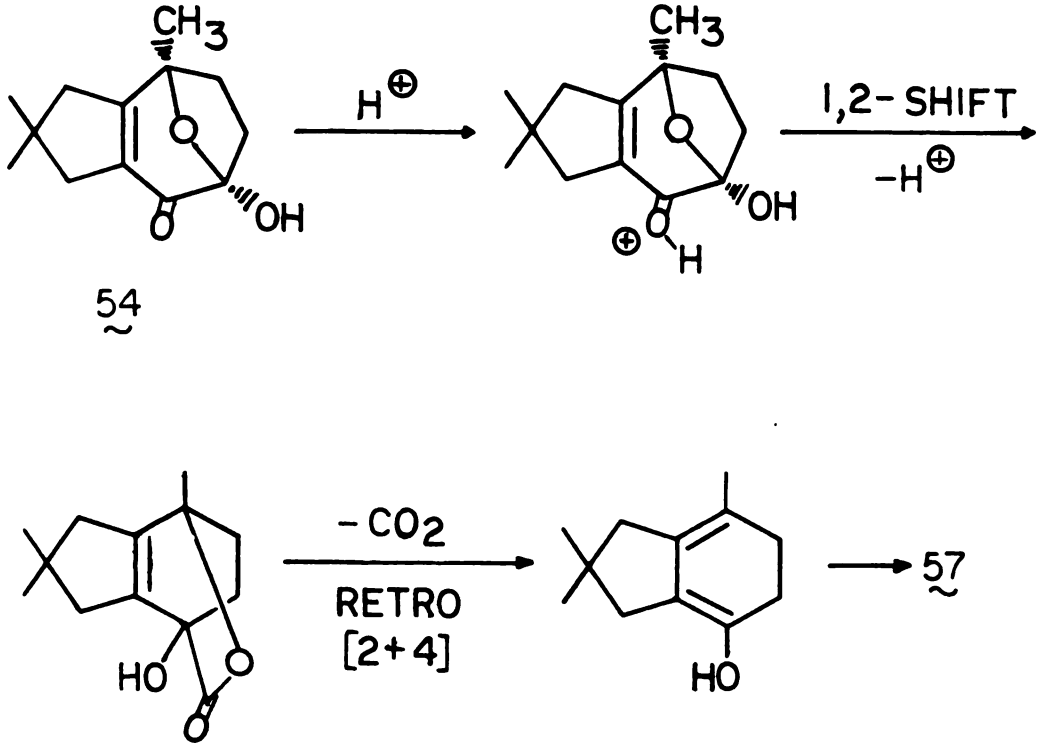


54 57 (25)

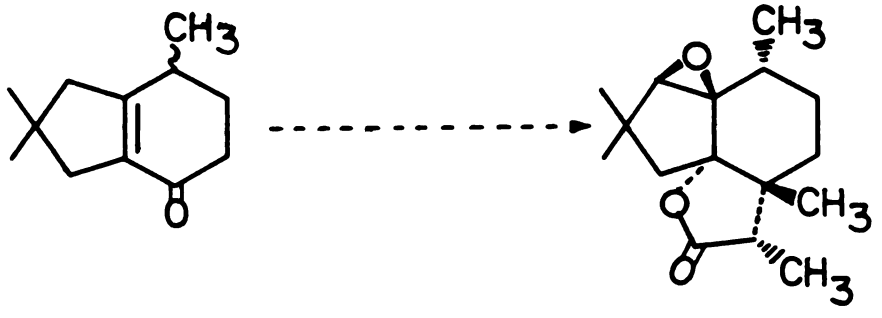
In the presence of strong acid 54 appears to suffer the loss of carbon dioxide. A plausible mechanism for this novel transformation is illustrated in Scheme V.

It is interesting to conjecture, based on the structural similarity of 57 with the recently discovered class of sesquiterpenes known as the alliacanes, the possibility of using 57 as an intermediate for the synthesis of a natural product such as alliacolide 58[42] (Equation 26).

Alliacolide 58 was isolated from the Basidiomycete Marasmium Alliaceus. The biogenesis of the alliacane skeleton has yet to be established but it is significant



Scheme V

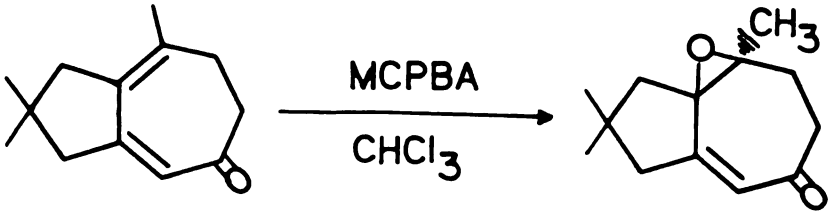


(26)

ALLIACOLIDE 58

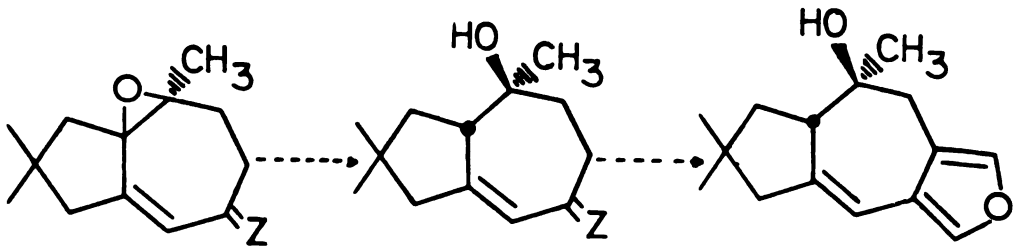
that the alliacanes contain the same geminally substituted dimethyl cyclopentane ring commonly found in the sesquiterpenes isolated from Basidiomycetes. As with the lactaranes, evidence has been obtained which indicates that the alliacanes could arise from farnesyl pyrophosphate via a humulene intermediate[43].

The last oxidation method explored in this study was the selective epoxidation of the tetrasubstituted double bond of 24 with m-chloroperoxybenzoic acid to give 59 (Equation 27).



24 59 (27)

Time permitted only a preliminary investigation involving the use of 59. It was proposed that 59 may be a useful intermediate for the synthesis of furoscrobiculide B (Equation 28). A crucial step would invole the regio- and stereospecific reduction of 59 to the homoallylic alcohol 60. Attempted catalytic reductions with palladium on calcium carbonate or palladium on charcoal were complicated.



(28)

Z = O, protective group

59 60 1

EXPERIMENTAL

General

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

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

were obtained with a Finnigan 4000 GC/MS spectrometer.

Preparation of 23

One liter of ammonia was condensed in a carefully dried two-liter, three-neck, round bottom flask containing 75 mL of tetrahydrofuran, one-tenth gram of lithium wire, and equipped with a mechanical stirrer, an addition funnel, a dry ice condenser, and cooled by a dry ice-acetone bath. An additional 1.02 g (147 mmol) of lithium wire was added to the stirred blue solution, followed by dropwise addition of a solution of 12.0 g (59.3 mmol) of 21 dissolved in 150 mL of tetrahydrofuran. This reaction mixture was stirred an additional 0.5 hr and was then quenched by careful addition of approximately 3 g of solid ammonium chloride. The cooling bath was removed and the ammonia was evaporated under a stream of nitrogen. The residue was diluted with 500 mL of ether and washed with water, saturated brine, and dried over sodium sulfate. Evaporation of the ether gave 11.9 g of a yellow oil which was judged by ^{1}H NMR to be 90% pure, containing approximately 10% of enedione 21. This crude cyclopropanol was immediately dissolved in 35 mL of cold pyridine (0°C) and added to a solution of 7.0 mL (90 mmol) of freshly distilled methanesulfonyl chloride dissolved in 35 mL of cold pyridine, containing 0.5 g (4.0 mmol) of 4-dimethylaminopyridine. This mixture was stirred overnight at 0°C, poured into 400 mL of ice water,

and extracted twice with 500 mL portions of ether. The organic layer was washed successively with 2% hydrochloric acid and saturated sodium bicarbonate solution, and dried. Evaporation of the solvent gave a crude solid which was triturated with cold ether and filtered to give 11.0 g (65% from 21) of 23 as a white powder, mp 101-103 with decomposition (ether).

Anal. Calcd. for $C_{14}H_{22}O_4S$: C, 58.71; H, 7.74;
Found : C, 58.54; H, 7.75.

Preparation of 24

To 20 mL of trifluoroacetic acid was added 2.0 g (7.0 mmol) of 23. This solution was stirred for 0.5 hr at room temperature, poured into 100 mL of water and extracted with 100 mL of ether. The ethereal layer was washed with 100 mL portions of saturated sodium bicarbonate solution until carbon dioxide evolution ceased, and dried. Evaporation of the solvent followed by column chromatography (silica gel, 25% ethyl acetate/hexane) gave 1.18 g (91%) of 24 as a light yellow oil, (λ_{max} 95% EtOH = 315, ε = 6250).

Anal. Calcd. for $C_{13}H_{18}O$: C, 82.13; H, 9.53;
Found : C, 81.92; H, 9.47.

Preparation of 36

A solution of 2.4 mmol of lithium diisopropyl amide was prepared by addition of 0.26 mg (2.6 mmol) of diisopropyl

amine to a cold (0°C) solution of 1.6 mL (2.4 mmol) of 1.5 M n-butyllithium in 5 mL of hexane. This mixture was stirred at 0°C for 10 minutes, the ice-bath was removed, and the solvents and excess amine were evaporated under reduced pressure, leaving a white solid. After purging the product with argon and recooling to 0°C, the amide was dissolved in 2.5 mL of tetrahydrofuran, following which a solution of 418 mg (2.2 mmol) of 24 in 1 mL of tetrahydrofuran was added. After a ten minute reaction period, 0.32 mL (2.4 mmol) of trimethylsilyl chloride was added, the mixture was stirred 5 minutes and the solvent was removed under vacuum. The residue was dissolved in 20 mL of pentane, filtered, and evaporated to yield 536 mg (93%) of 36 as a yellow oil.

Methylation of 24

To 2.2 mL (0.88 mmol) of a 0.4 M solution of lithium diisopropyl amide in tetrahydrofuran cooled to 0°C was added a solution of 0.13 g (0.7 mmol) of 24 dissolved in 1 mL of tetrahydrofuran. After stirring 10 minutes, 140 mg (1.0 mmol) of methyliodide was added and the reaction mixture was warmed to room temperature and then refluxed for 30 minutes. After cooling, the reaction mixture was diluted with 30 mL of ether, washed successively with water and saturated brine, and dried. Evaporation of the solvent and column chromatography of the residue (silica gel, 20% ethyl acetate/hexane) gave 0.12 g (82%) of 37 as a yellow oil.

Formylation of 24

To a slurry of 51 mg (2.12 mmol) of sodium hydride in 2 mL of ethyl formate was added a solution of 100 mg (0.53 mmol) of 24 dissolved in 1 mL of dimethoxyethane. This reaction mixture was stirred for 1.5 hrs, poured into ammonium chloride solution, extracted with ether, and dried. Evaporation of the solvent gave a dark-red oil which was distilled (kugelrohr $Bp_{.05mm}$ = 150-160°C) to obtain 35 mg (30%) of 38 as a red oil. Proton NMR indicates 38 exists as a mixture of Z and E isomers in a 2:1 ratio.

Reduction of 24

To 4.6 mL (1.84 mmol) of a 0.4 M solution of cerium(III) chloride in methanol was added 0.35 g (1.84 mmol) of 24. To this stirred solution was slowly added 69.3 mg (1.8 mmol) of sodium borohydride, and after stirring for 5 minutes, the reaction mixture was hydrolyzed, extracted with ether, and the ethereal layer washed with saturated brine and dried. Evaporation of the solvent followed by column chromatography of the residue (silica gel, 40% ethyl acetate/ hexane) gave 0.28 g (80%) of 40 as a colorless oil.

Preparation of 39

To a solution of 0.97 g (3.67 mmol) of 36 dissolved in 20 mL of dry trimethyl orthoformate was added 1.28 g (4.0 mmol)

of zinc iodide. This mixture was stirred for 1 hr, diluted with 100 mL of ether, washed with 100 mL portions of water and brine, and dried. Evaporation of the solvent followed by chromatography (MPLC, silica gel, 25% ethyl acetate/hexane) gave 0.86 g (85%) of 39 as a yellow oil.

Anal. Calcd. for $C_{15}H_{24}O_3$: C, 72.69; H, 9.15;
Found : C, 72.31; H, 9.09.

Preparation of 41

To a stirred solution of 90 mg (0.47 mmol) of 24 dissolved in 1.5 mL of ether and cooled to -78°C was added 0.34 mL (0.51 mmol) of a 1.5 M solution of methyllithium in ether. The reaction mixture was warmed to room temperature, stirred an additional one hour, and quenched with saturated ammonium chloride. The ethereal layer was washed with water and brine, and dried over sodium sulfate. Evaporation of the solvent followed by chromatography (MPLC, silica gel, 25% ethyl acetate/hexane) gave 75 mg (77%) of 41 as a pale yellow oil.

Photo-Oxidation of 24

To a solution of 190 mg (1.0 mmol) of 24 in 15 mL of acetone was added 10 mg of hematoporphyrin. This solution was irradiated with visible light (200 watt bulb), while oxygen was slowly bubbled through the solution. The reaction vessel consisted of a 25 mL side-arm test tube

fitted with two septa. Oxygen was introduced into this system through a syringe needle fitted through the top septum and bubbled directly into the acetone solution. An additional fine bore needle fitted through the side arm septum provided a vent for the escape of oxygen. Occasionally, acetone was added to the reaction mixture to replace that which had been lost to evaporation. After approximately 10 hrs, the reaction mixture was evaporated under reduced pressure to yield 230 mg of a semisolid residue, which was chromatographed (silica gel, 50% ethyl acetate/hexane) to give 110 mg (49%) of 47 as white solid, mp, 67.5-68°C (hexane), and 93 mg (42%) of 48 as a white crystalline solid, mp, 133.5-134.5°C.

48 Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16;
Found : C, 70.34; H, 8.21.

Base Treatment of 47

To a solution of 100 mg (0.45 mmol) of 47 dissolved in 5 mL of methylene chloride was added 4.5 mg (0.45 mmol) of triethylamine. This solution was stirred at room temperature for 1 hr, following which the solvent and amine were removed under reduced pressure, yielding 100 mg (100%) of 54 as a white solid, mp 106-108° (hexane-ethyl acetate).

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16;
Found : C, 69.92; H, 8.16.

Acetalization of 54

To a solution of 1.5 mL of acetic anhydride in 1.5 mL of pyridine, containing 5.0 mg of 4-dimethylaminopyridine, was added 100 mg (0.45 mmol) of 54. This mixture was stirred for one hour at room temperature, poured into 20 mL of water and extracted with ether. The ethereal layer was washed successively with 2% hydrochloric acid and saturated sodium bicarbonate solutions, and dried. Evaporation of the solvent gave 105 mg (88%) of 55 as a white solid. Recrystallization from hexane gave pure 55, mp 112-113°C.

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.62;
Found : C, 68.23; H, 7.66.

Reduction of 55

To 5.6 mL (2.28 mmol) of a 0.4 M solution of cerium(III) chloride dissolved in methanol was added 200 mg (0.76 mmol) of 55. To this stirred solution was added 86.0 mg (2.28 mmol) of sodium borohydride over a 2 minute period. After stirring 5 minutes, the reaction mixture was hydrolyzed, extracted with ether, and the ethereal layer was washed with brine, and dried. Evaporation of the solvent gave 198 mg (99%) of 56 as a colorless oil.

Acid Treatment of 54

A solution of 10.0 mg (0.045 mmol) of 54 dissolved in 20 mL of methanol containing one drop of concentrated

sulfuric acid was refluxed for five hours. The reaction mixture was cooled, diluted with ether, washed with saturated sodium bicarbonate solution, and dried. Evaporation of the solvent and chromatography of the residue (MPLC, silica gel, 25% ethyl acetate/hexane) gave 7.0 mg (87%) of 57 as a clear oil.

Epoxidation of 24

To a solution of 4.8 g (25 mmol) of 24 dissolved in 100 mL chloroform was added 10.1 g (50 mmol) of m-chloroperoxybenzoic acid (85%). This solution was stirred for one hour at room temperature, washed successively with water, 10% sodium sulfite and saturated sodium bicarbonate, and dried. Evaporation of the solvent followed by column chromatography of the residue (silica gel, 25% ethyl acetate/hexane) gave 4.1 g (80%) of 59 as a clear oil.

Anal. Calcd. $C_{13}H_{18}O_2$: C, 75.69; H, 8.79;

Found : C, 75.51; H, 8.74.

APPENDIX II: SPECTRA PART II

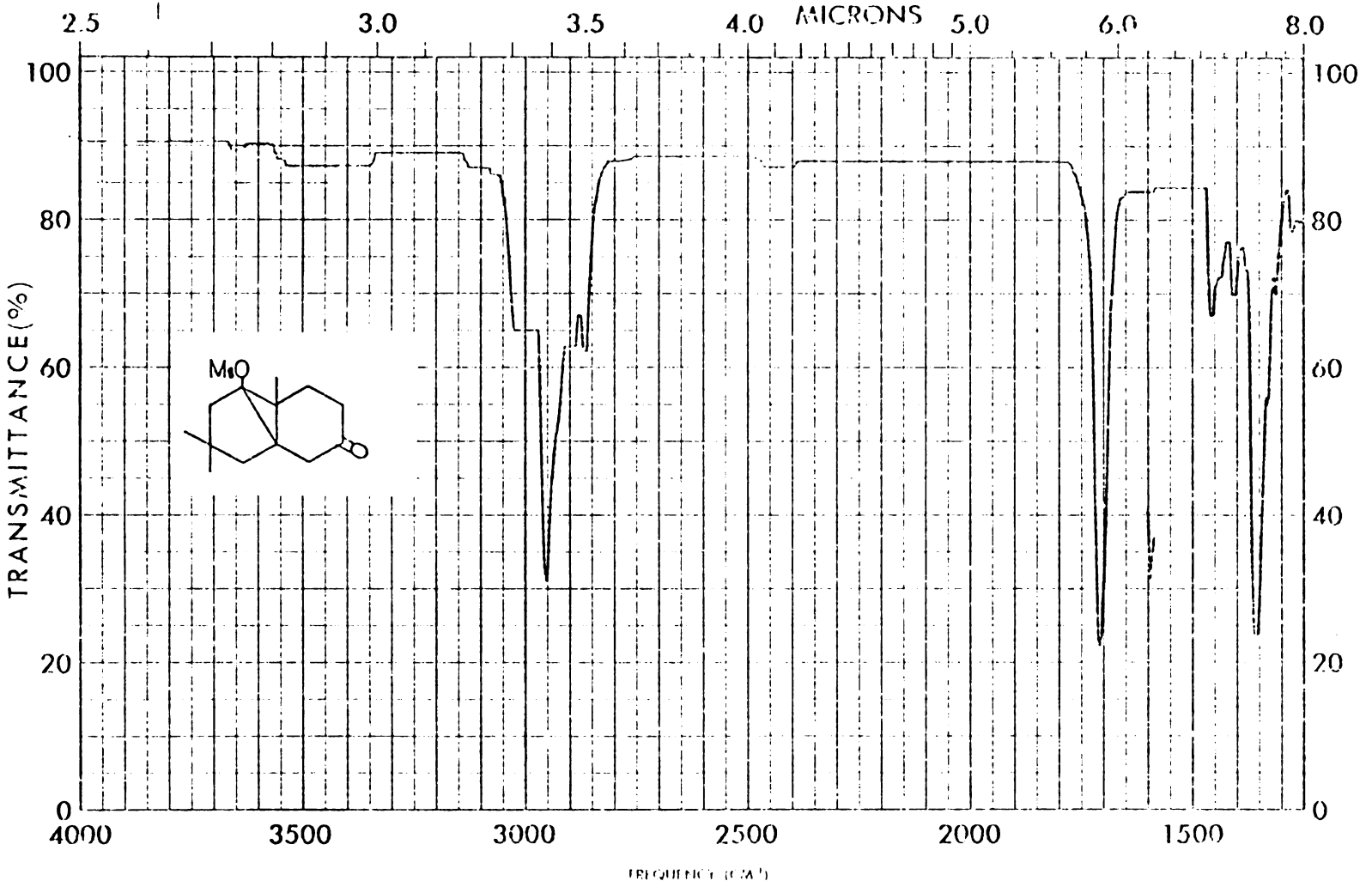


Figure II-4. IR of 23.

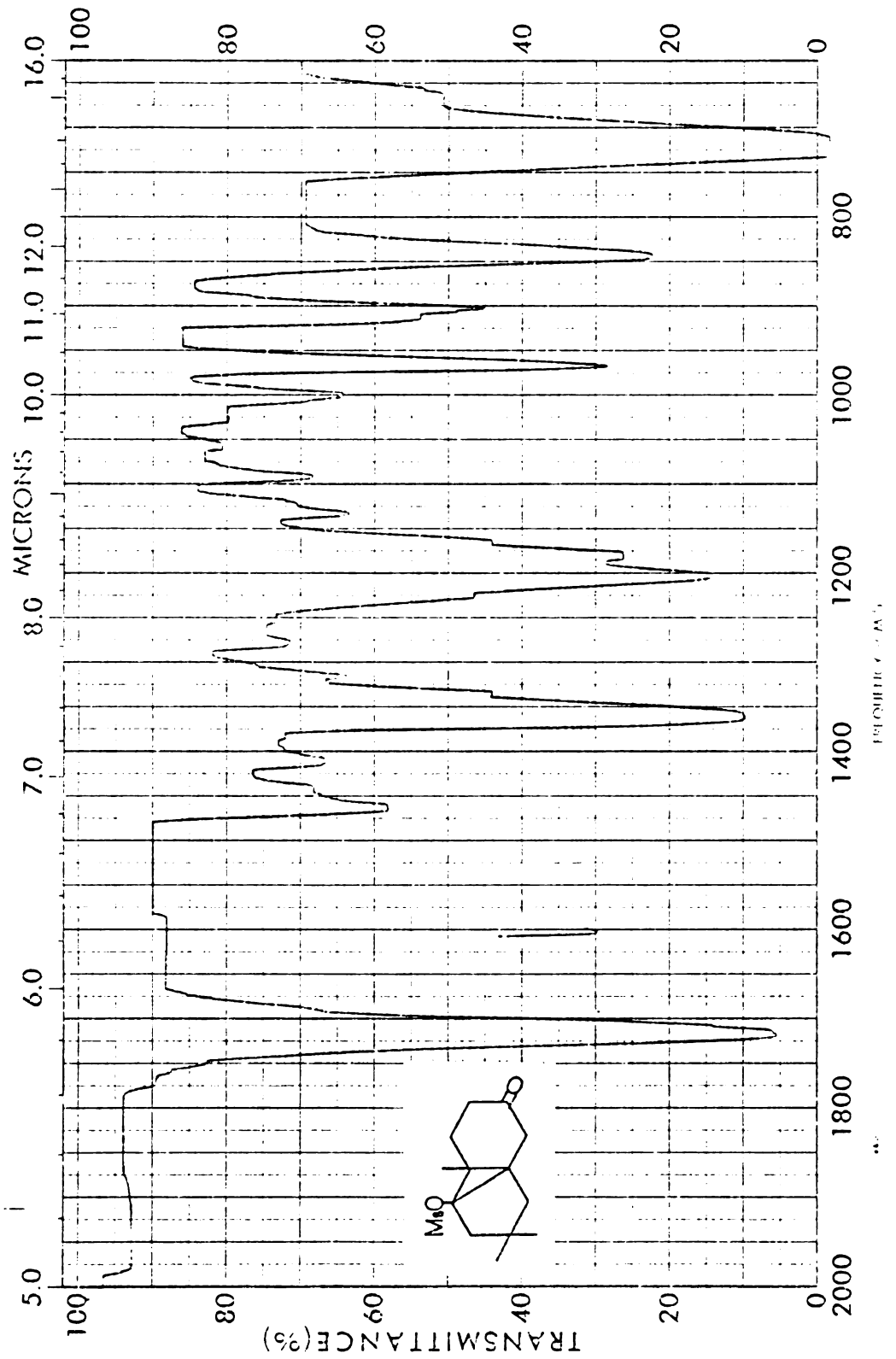


Figure II-5. IR of 23.

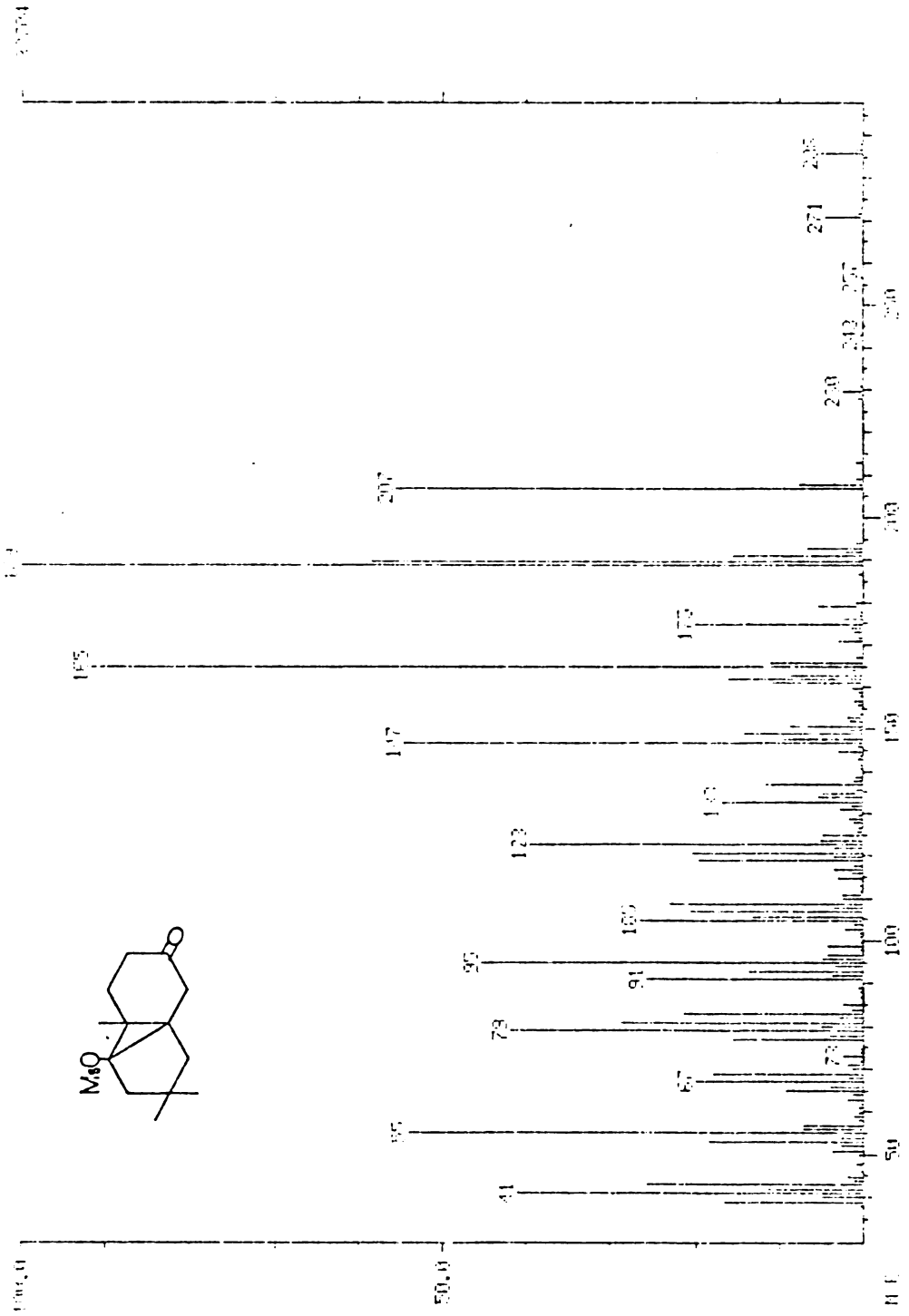


Figure II-6. Mass spectrum of 23.

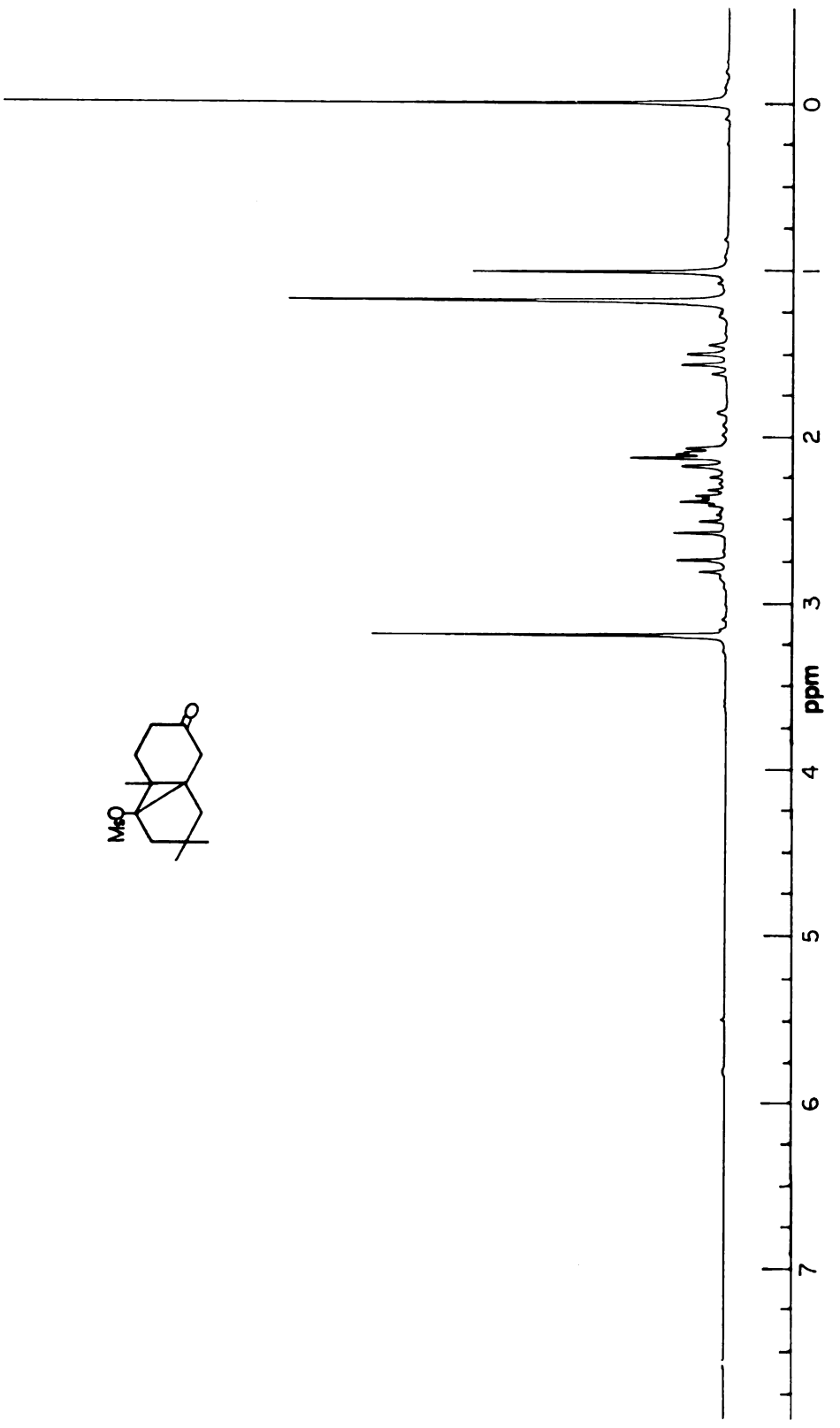


Figure II-7. Proton NMR of 23.

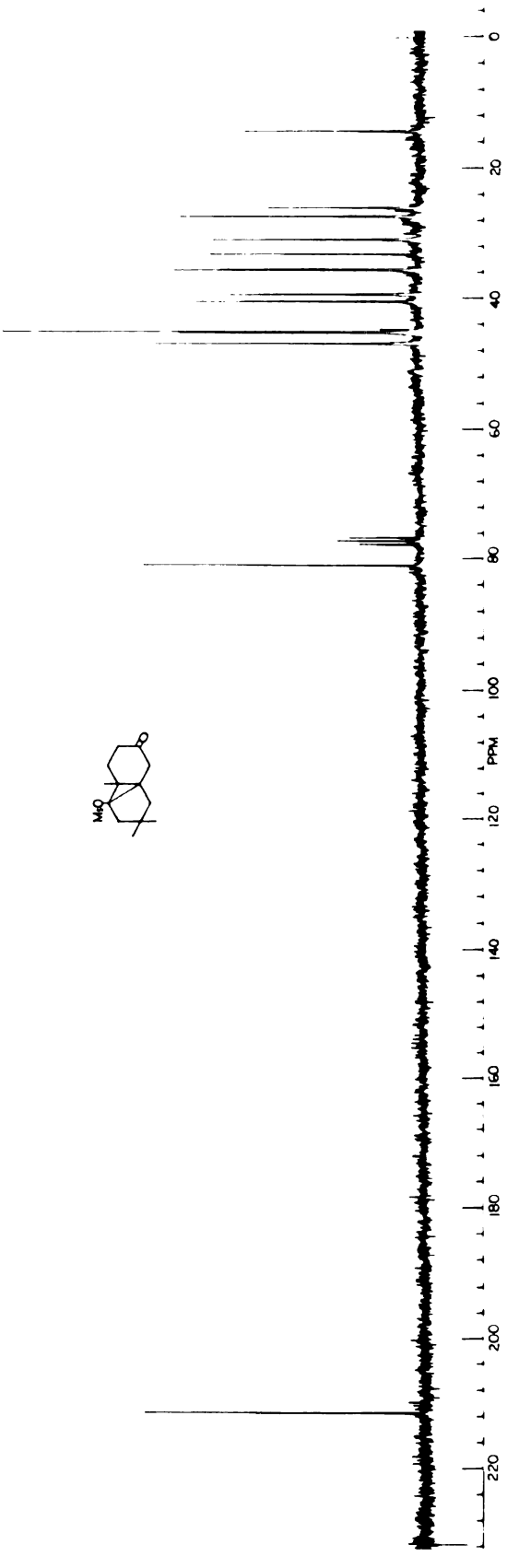


Figure II-8. Carbon-13 NMR of 23.

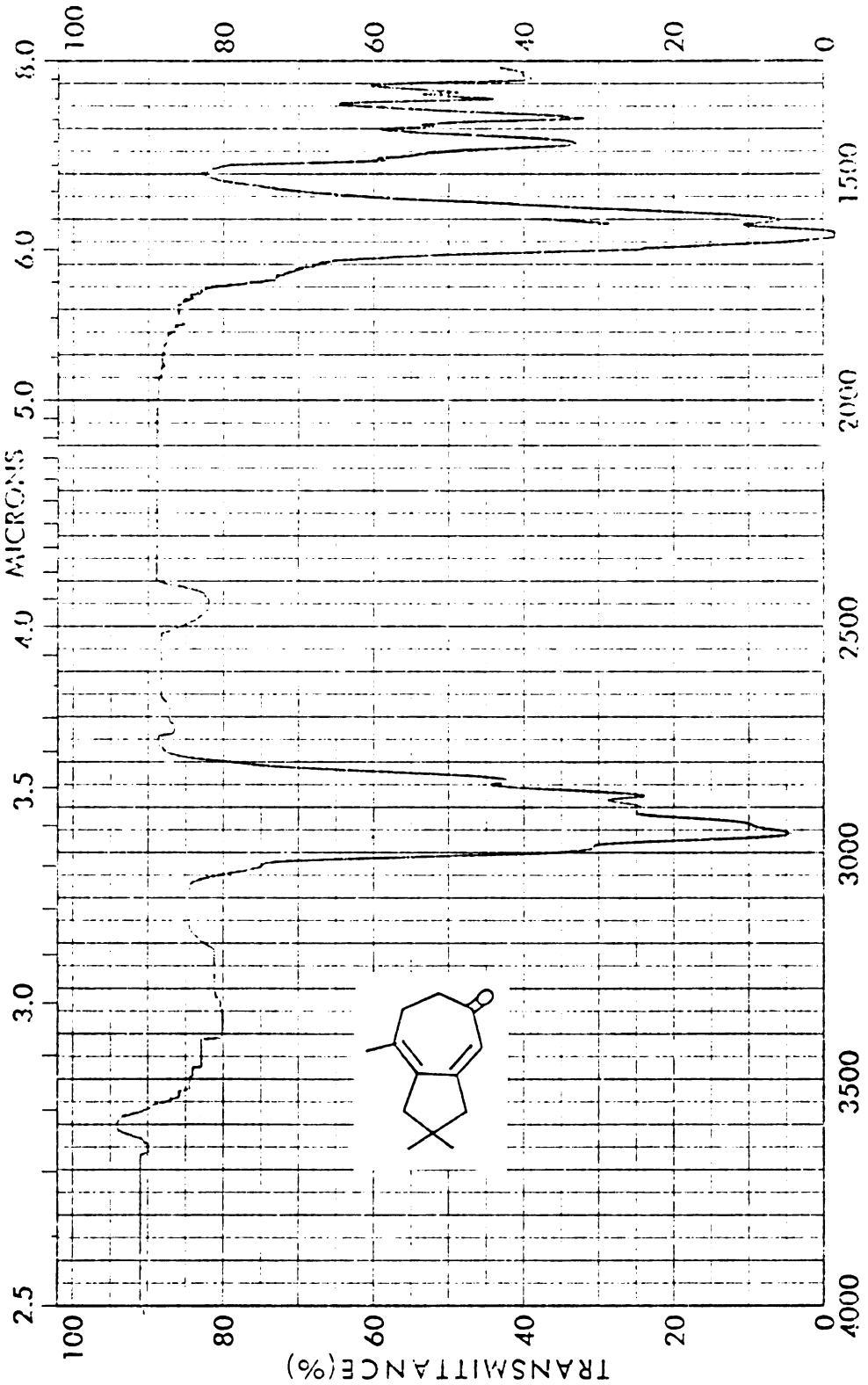


Figure II-9. IR of 24.

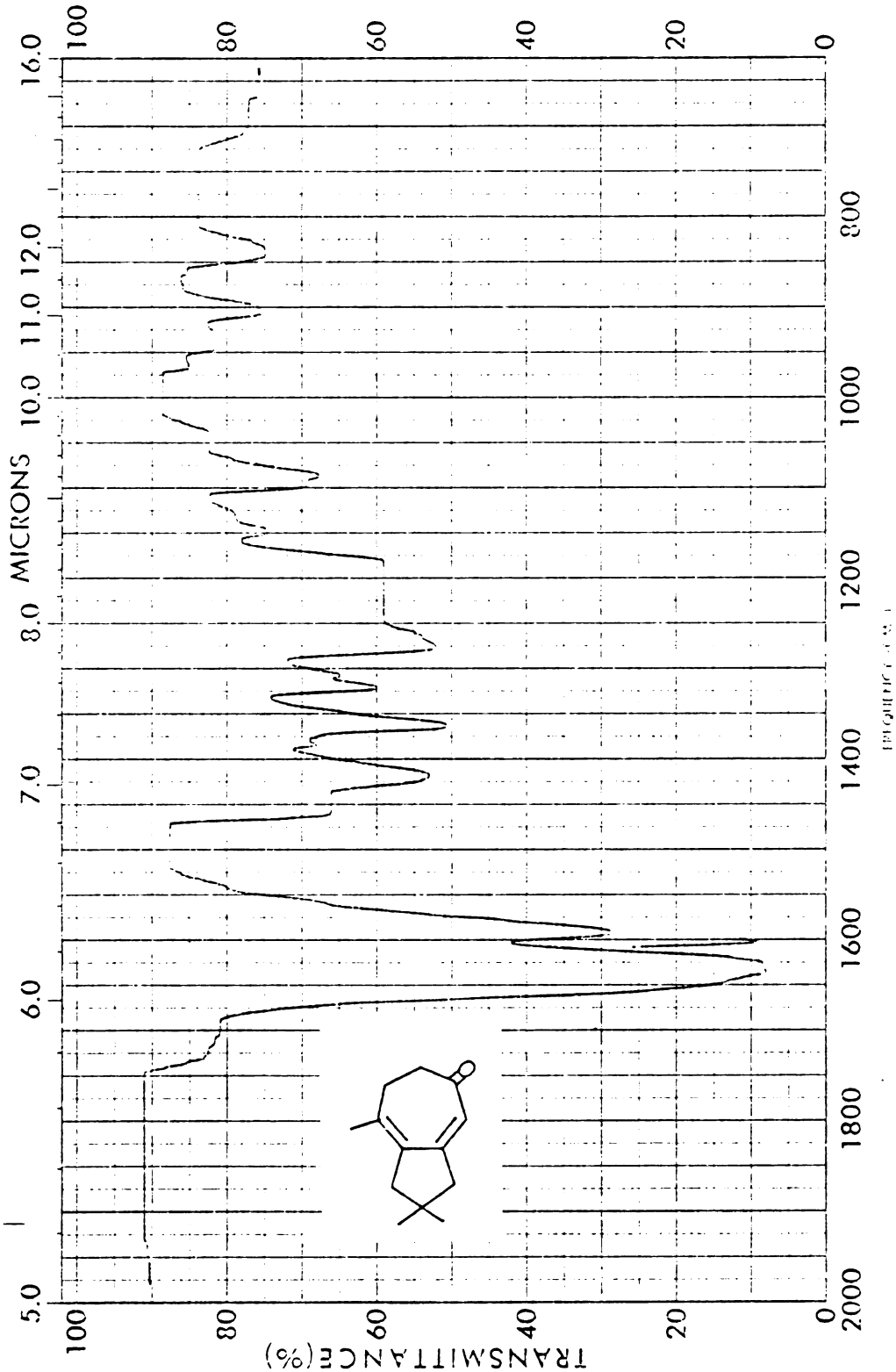


Figure II-10. IR of 24.

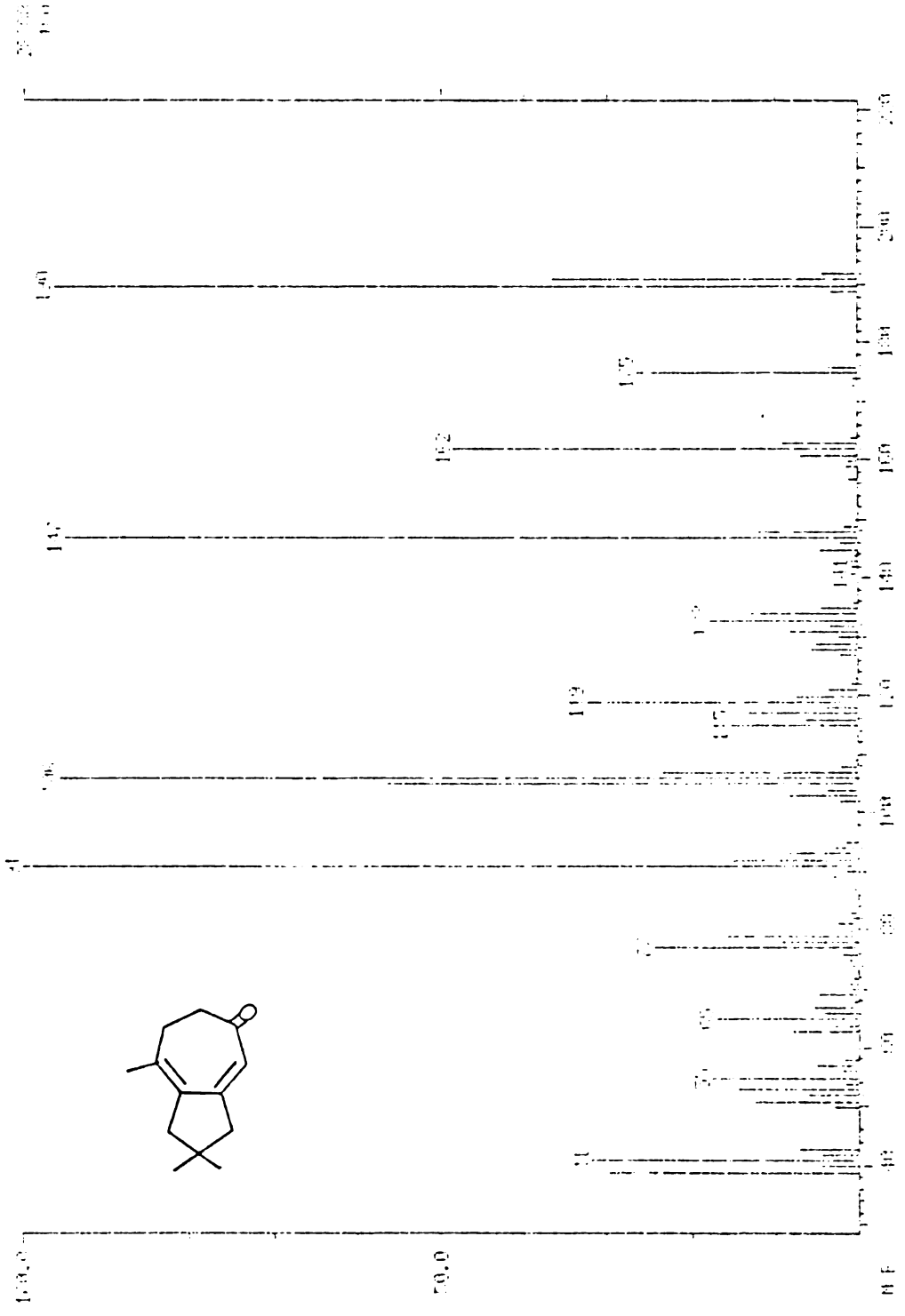


Figure II-11. Mass spectrum of 24.

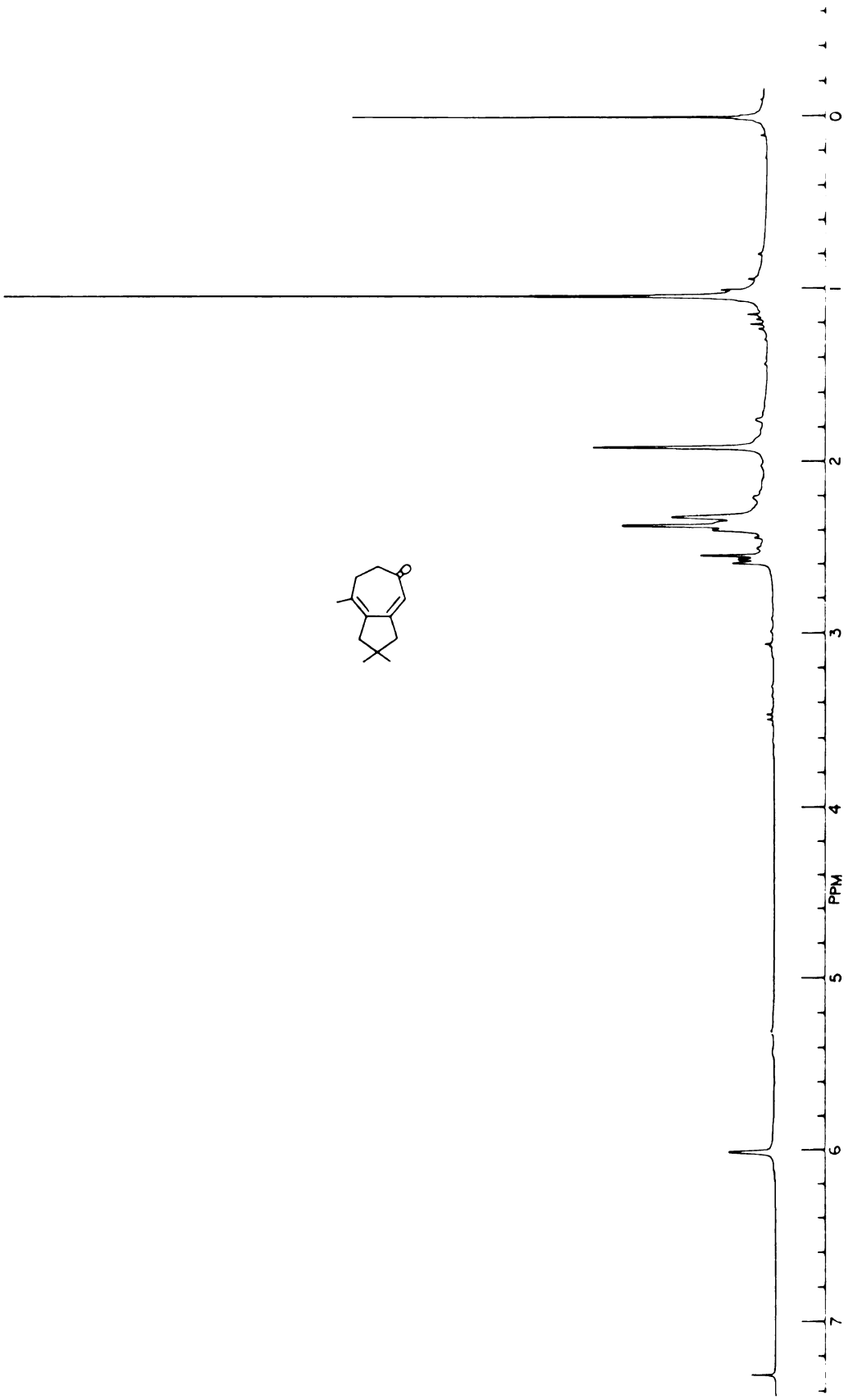


Figure II-12. Proton NMR of 24.

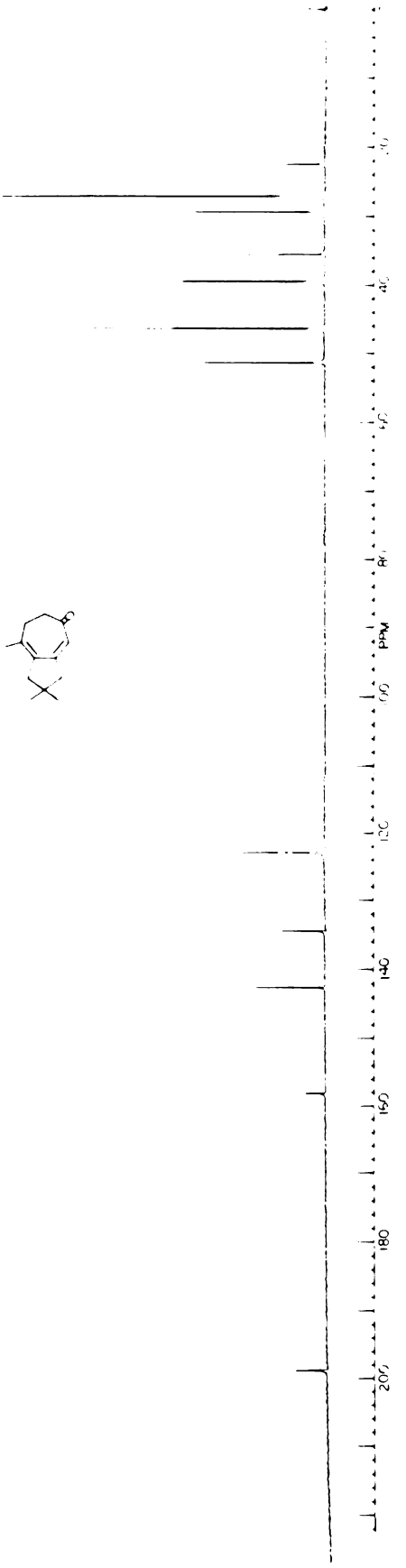


Figure II-13. Carbon-13 NMR of 24.

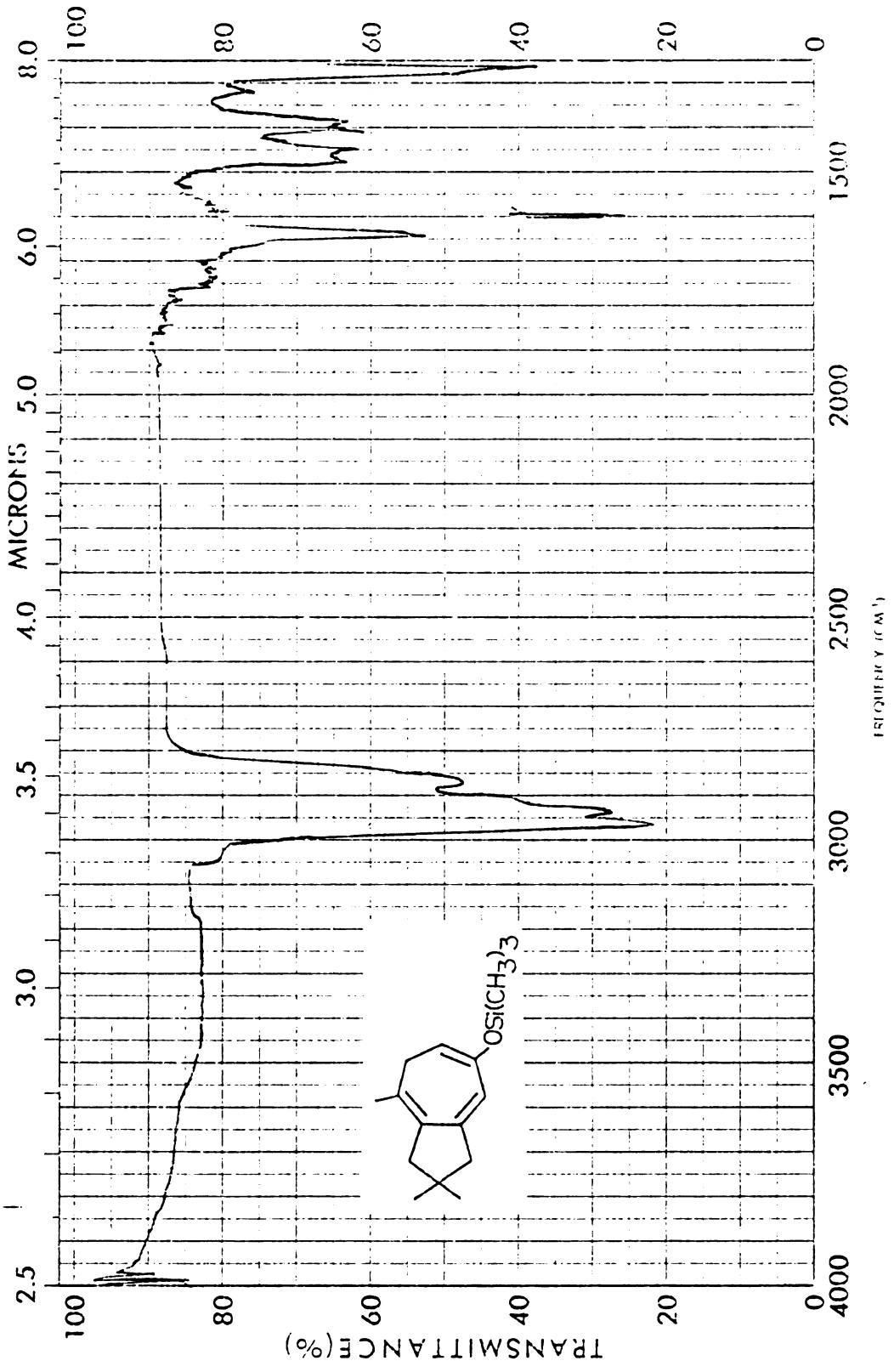


Figure II-14. IR of 36.

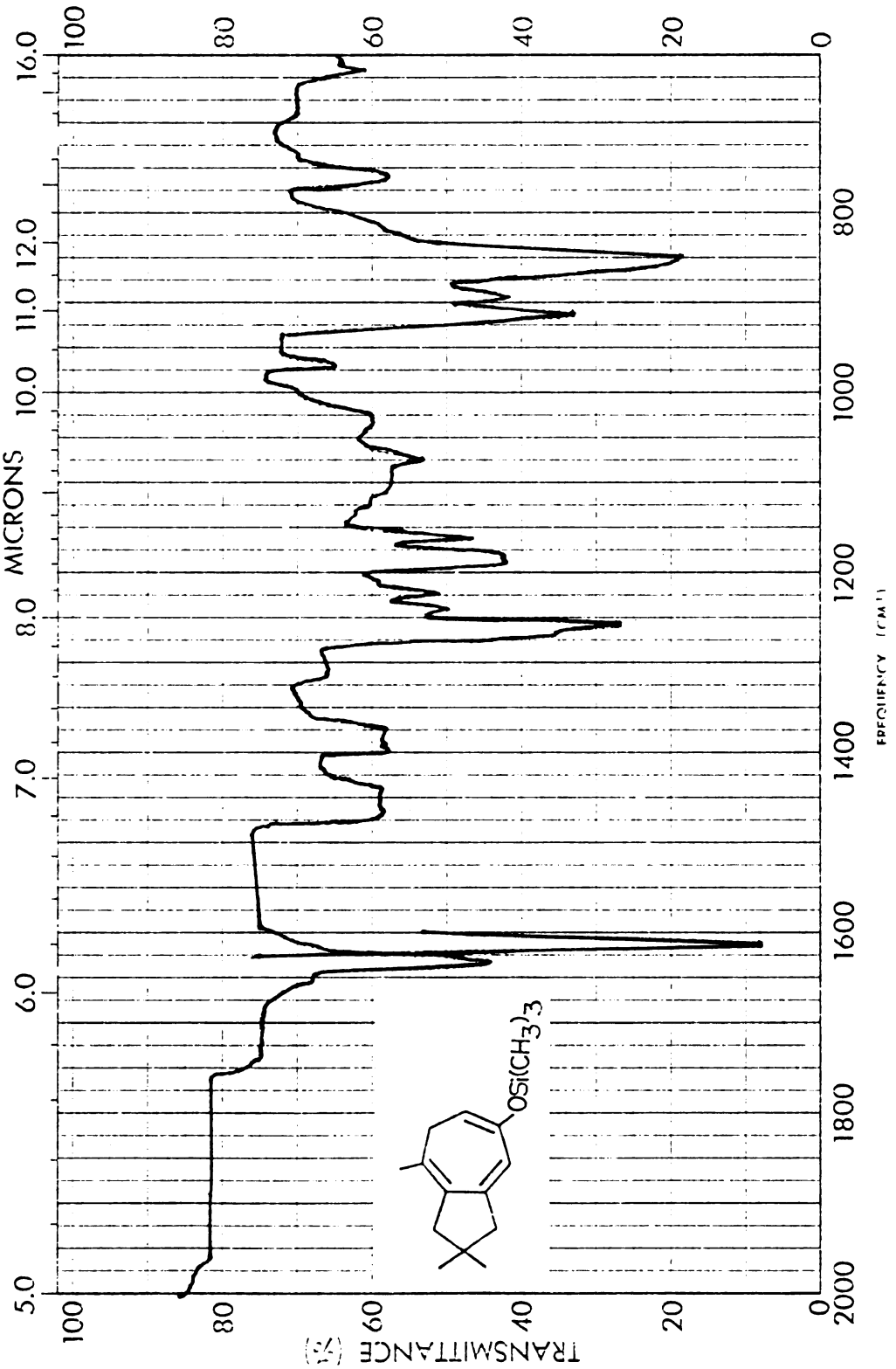


Figure II-15. IR of 36.

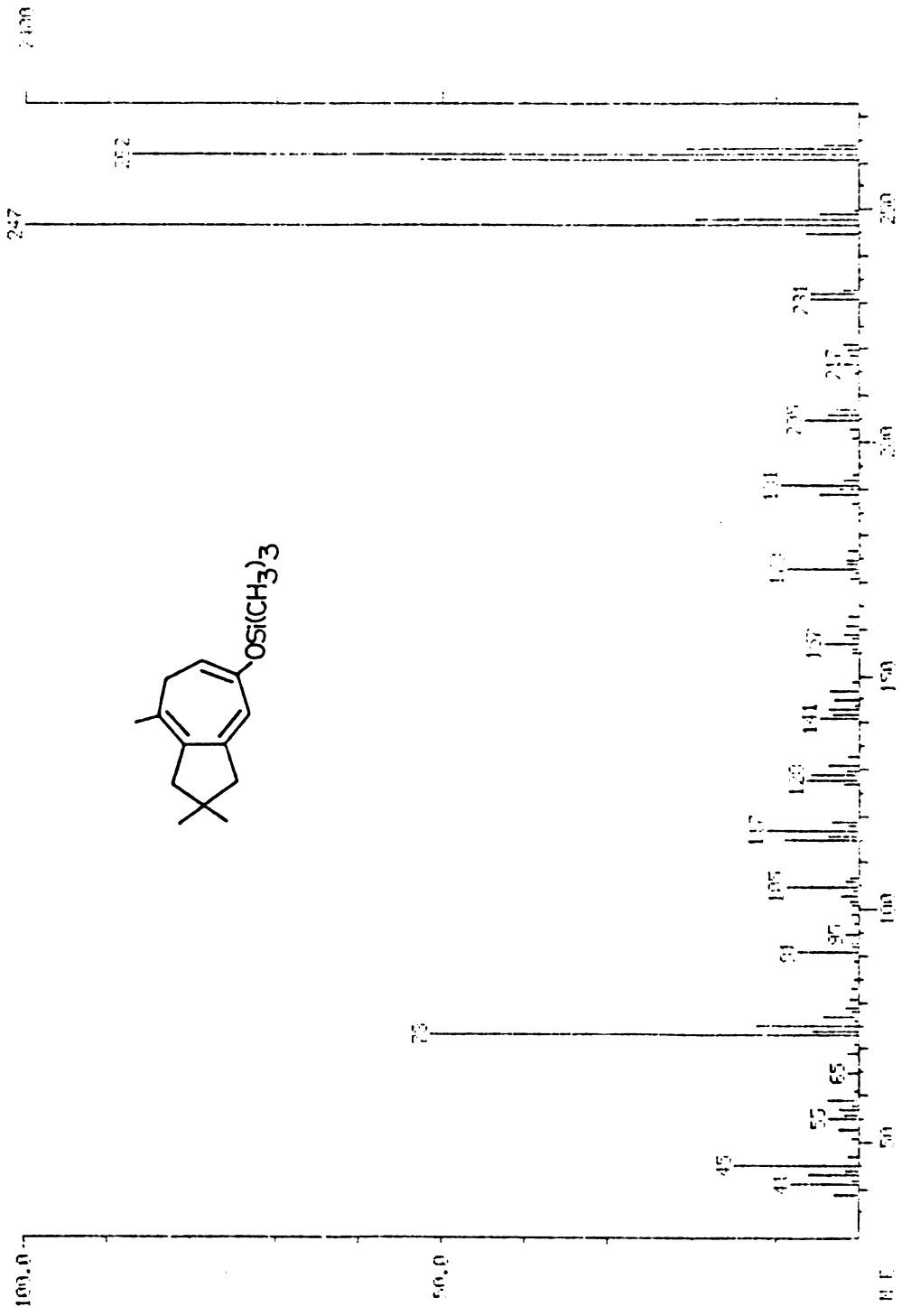


Figure II-16. Mass spectrum of 36.

Figure II-17. Proton NMR of 36.

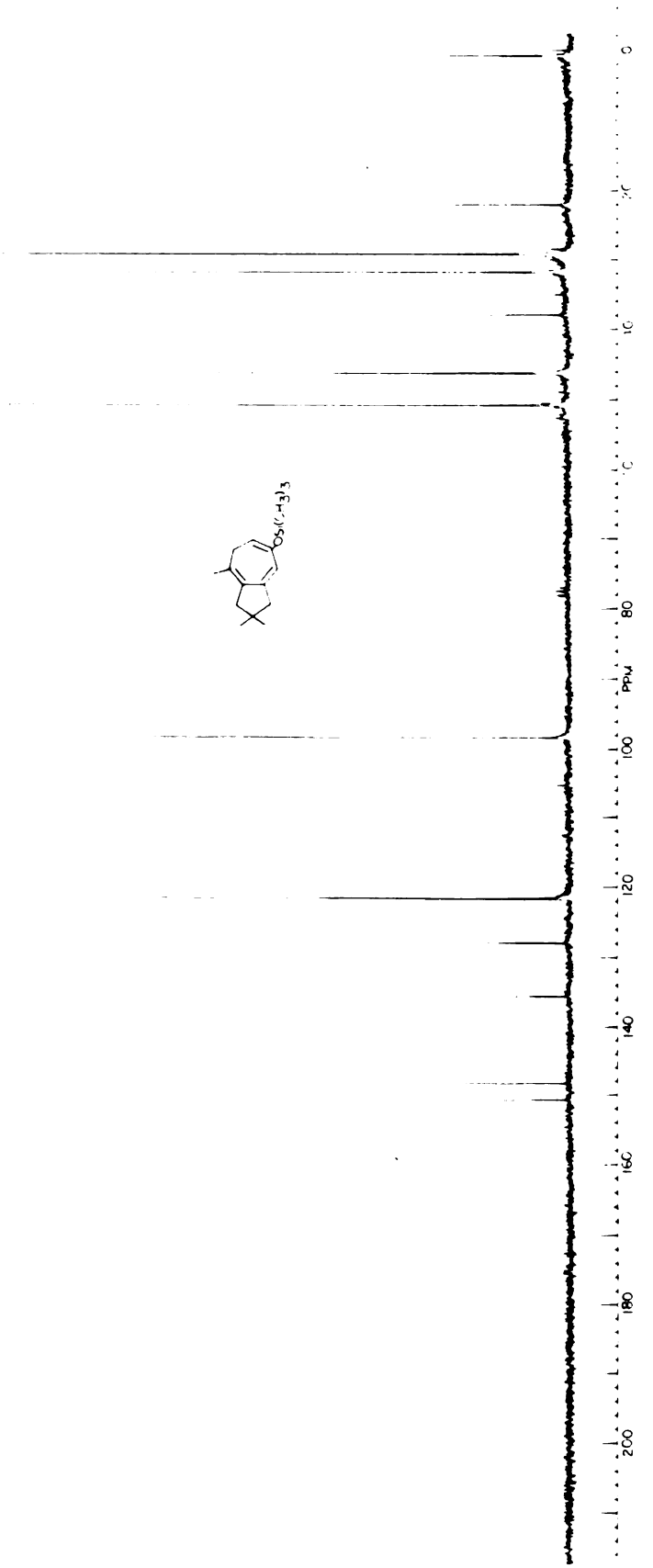


Figure II-18. Carbon-13 NMR of 36.

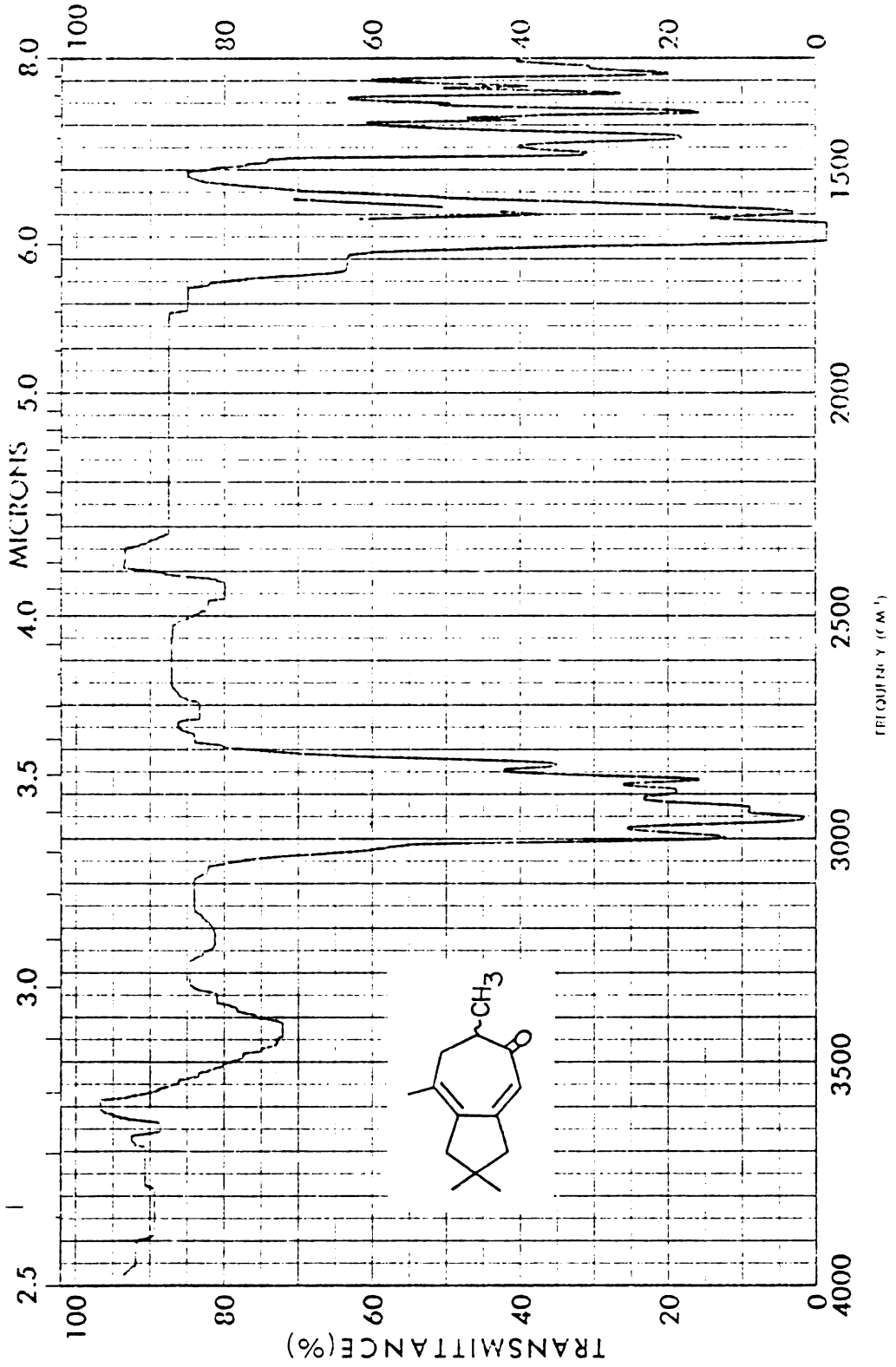


Figure II-19. IR of 37.

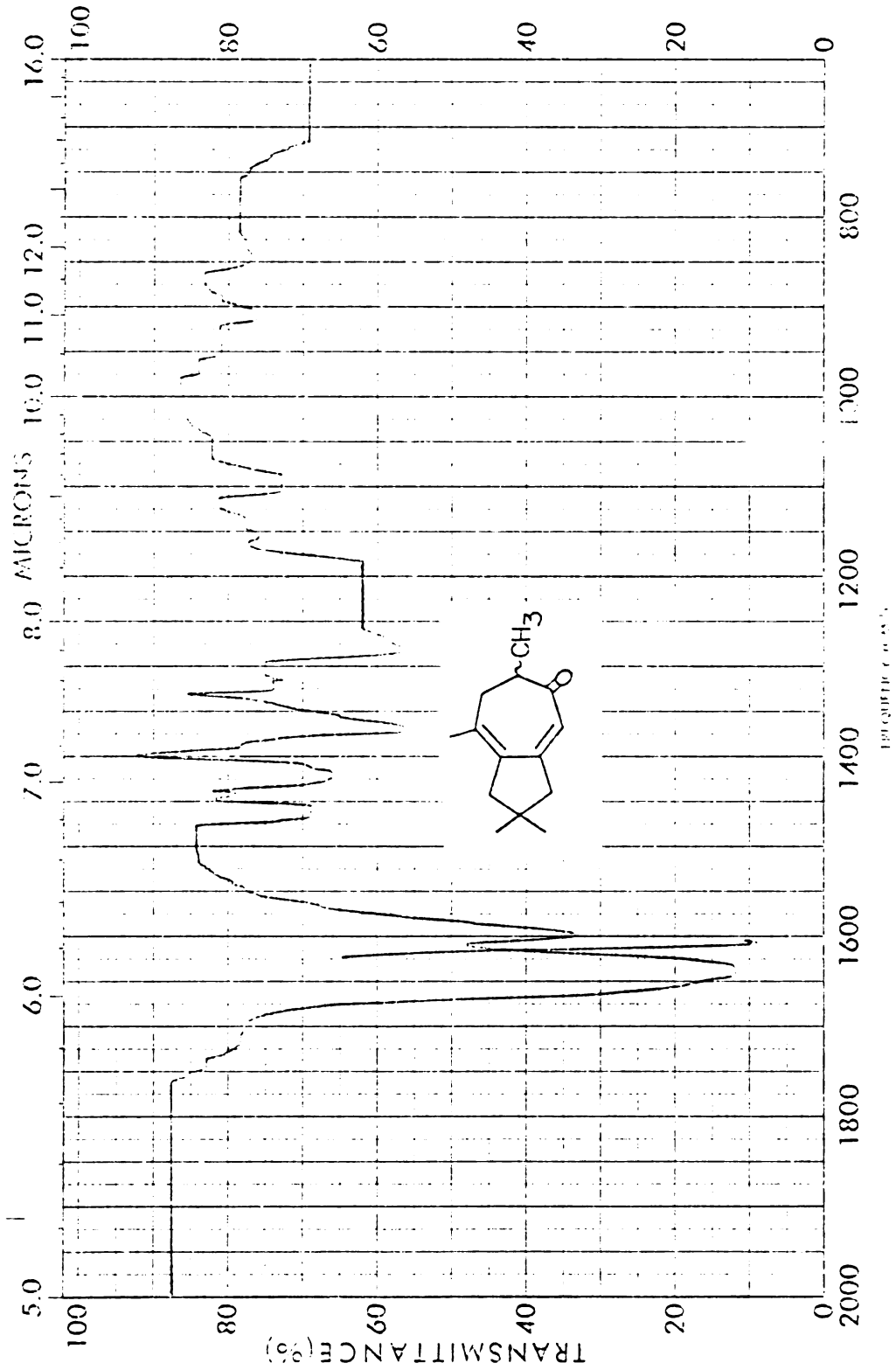


Figure II-20. IR of 37.

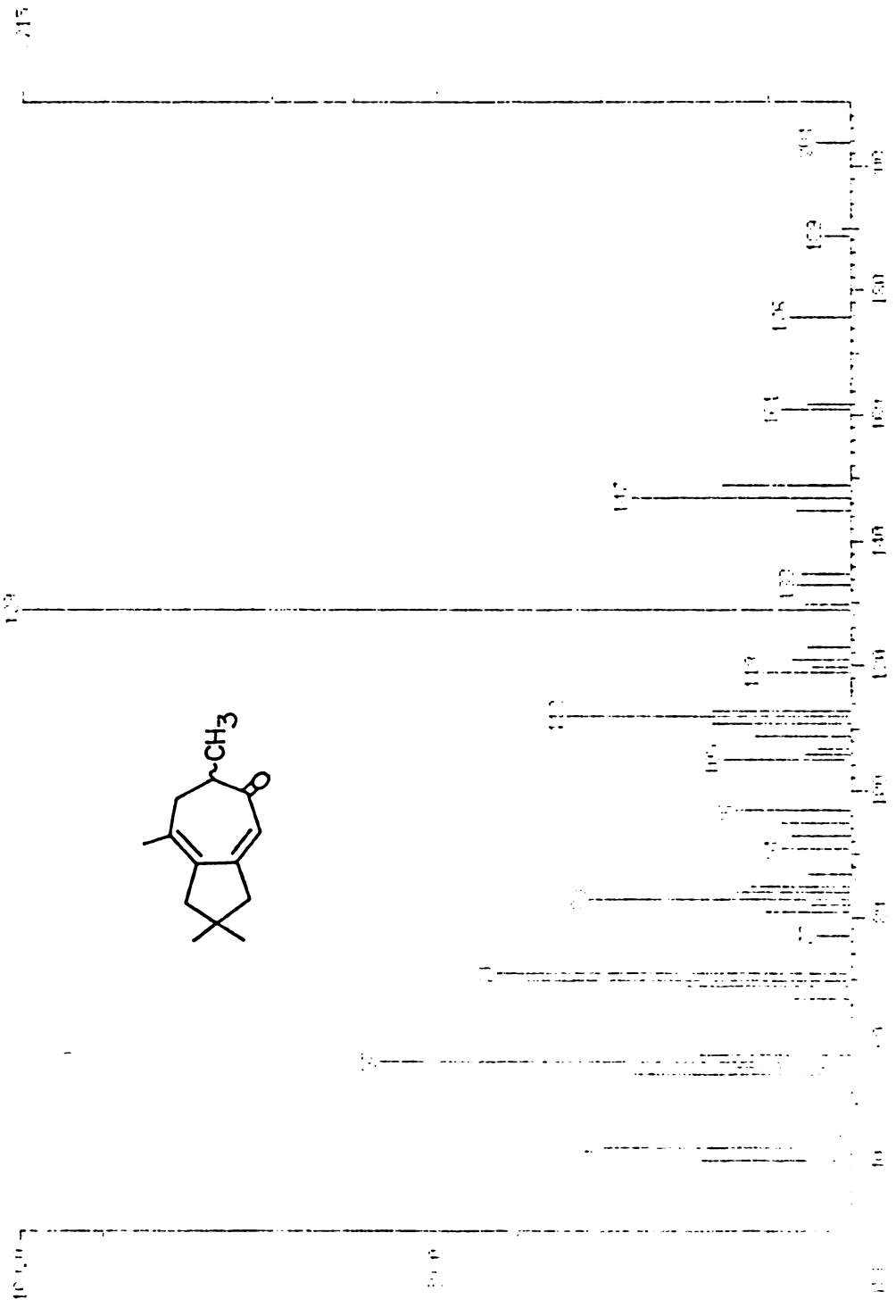


Figure II-21. Mass spectrum of 37.

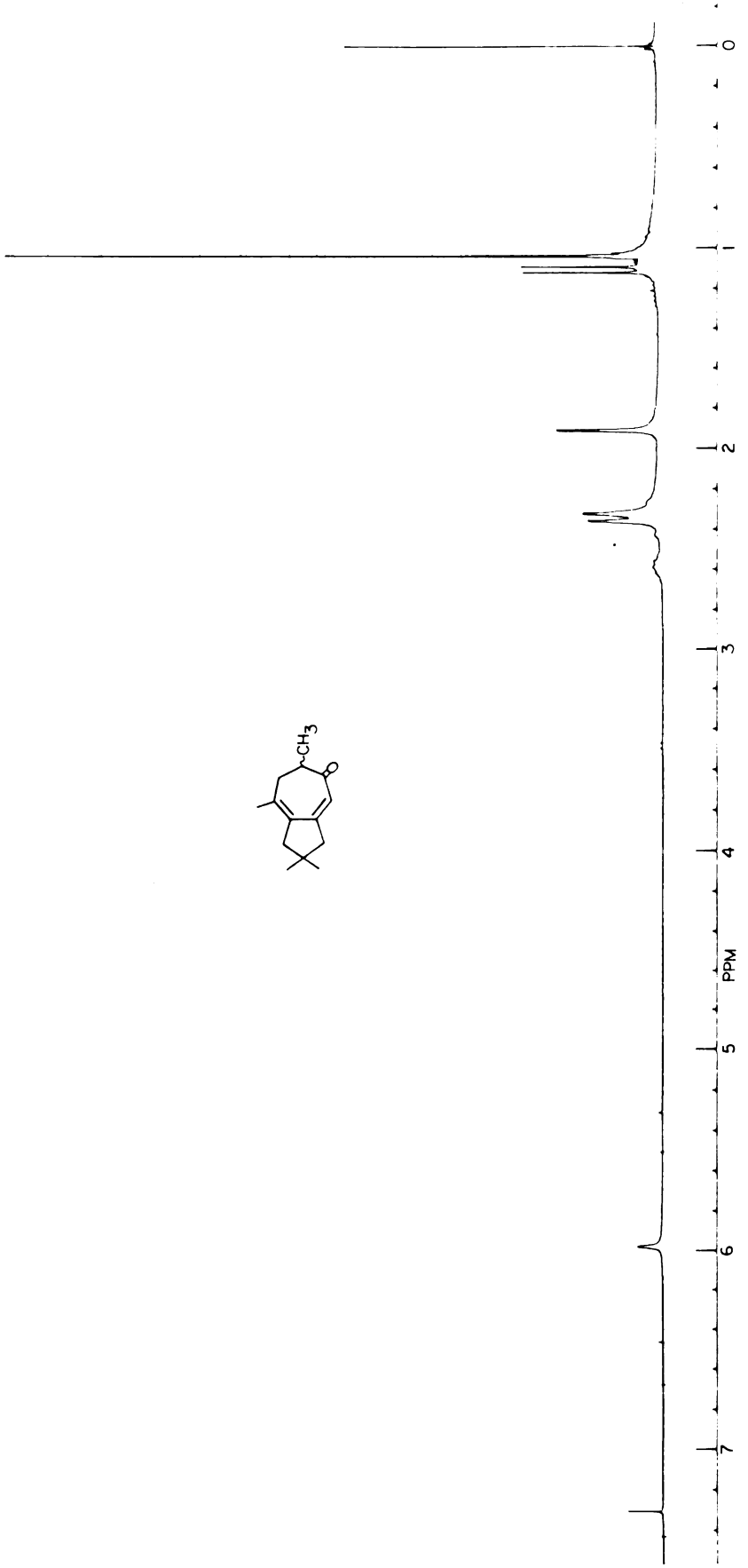


Figure II-22. Proton NMR of 37.

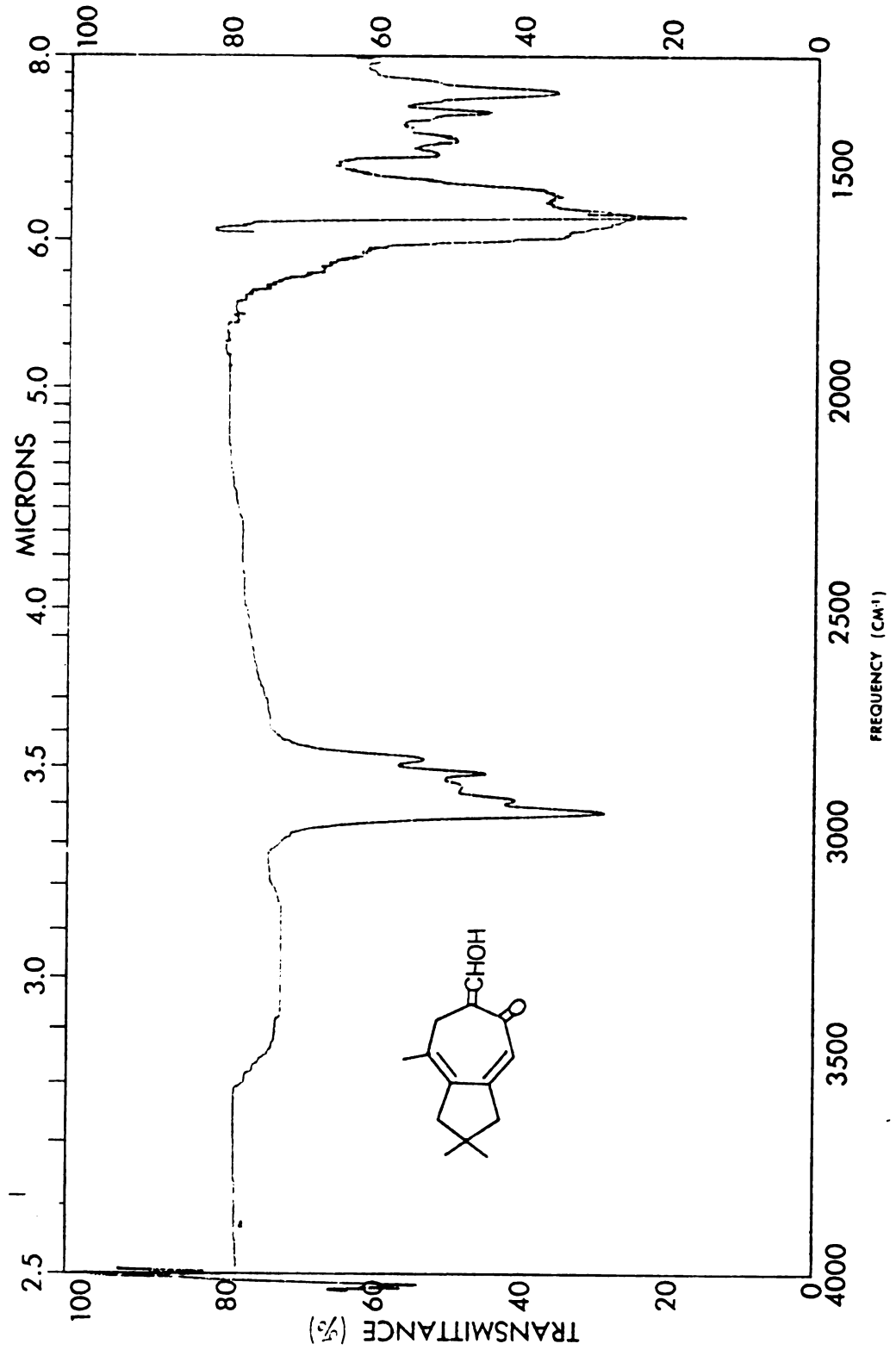


Figure II-23. IR of 38.

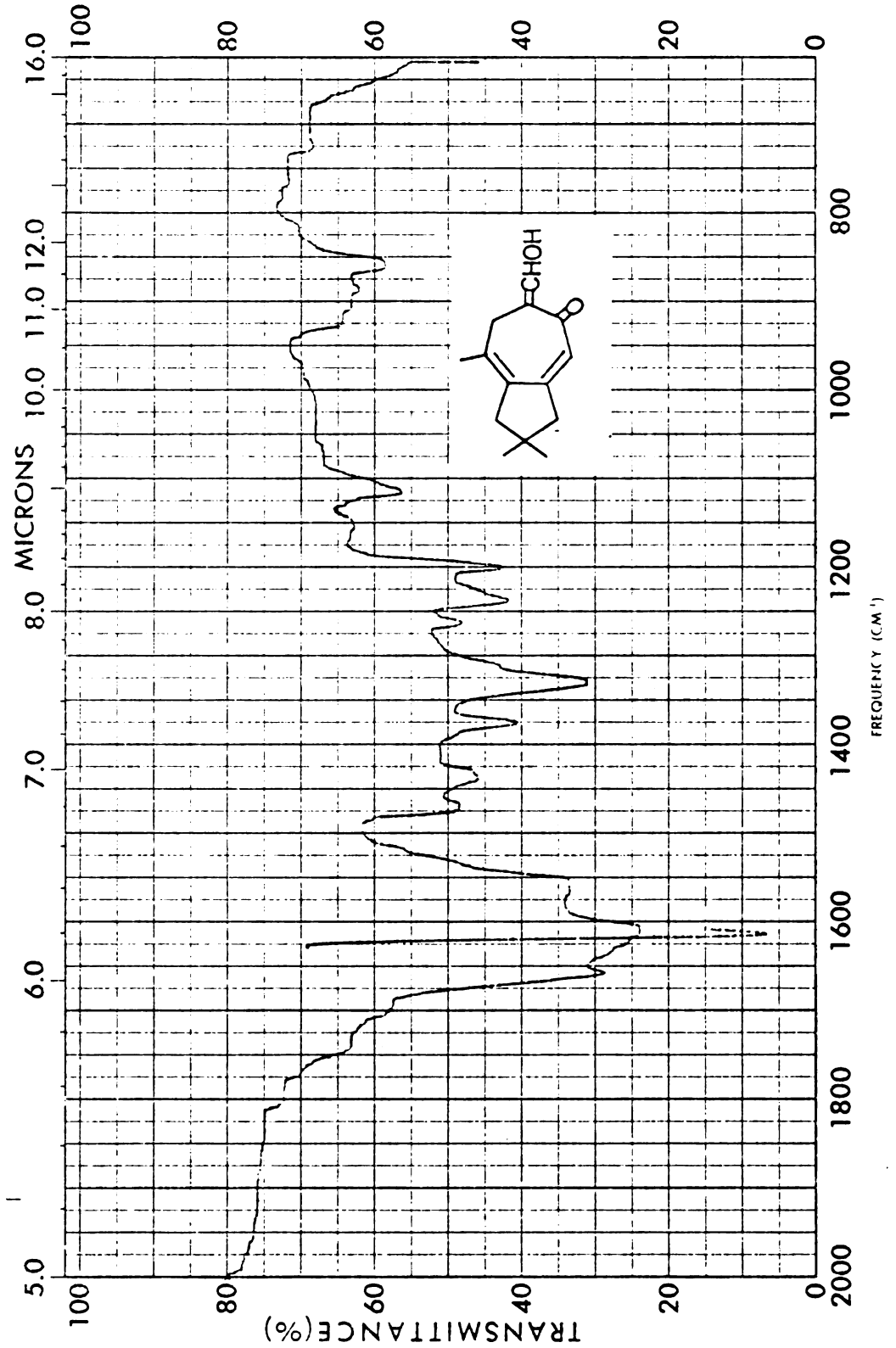


Figure II-24. IR of 38

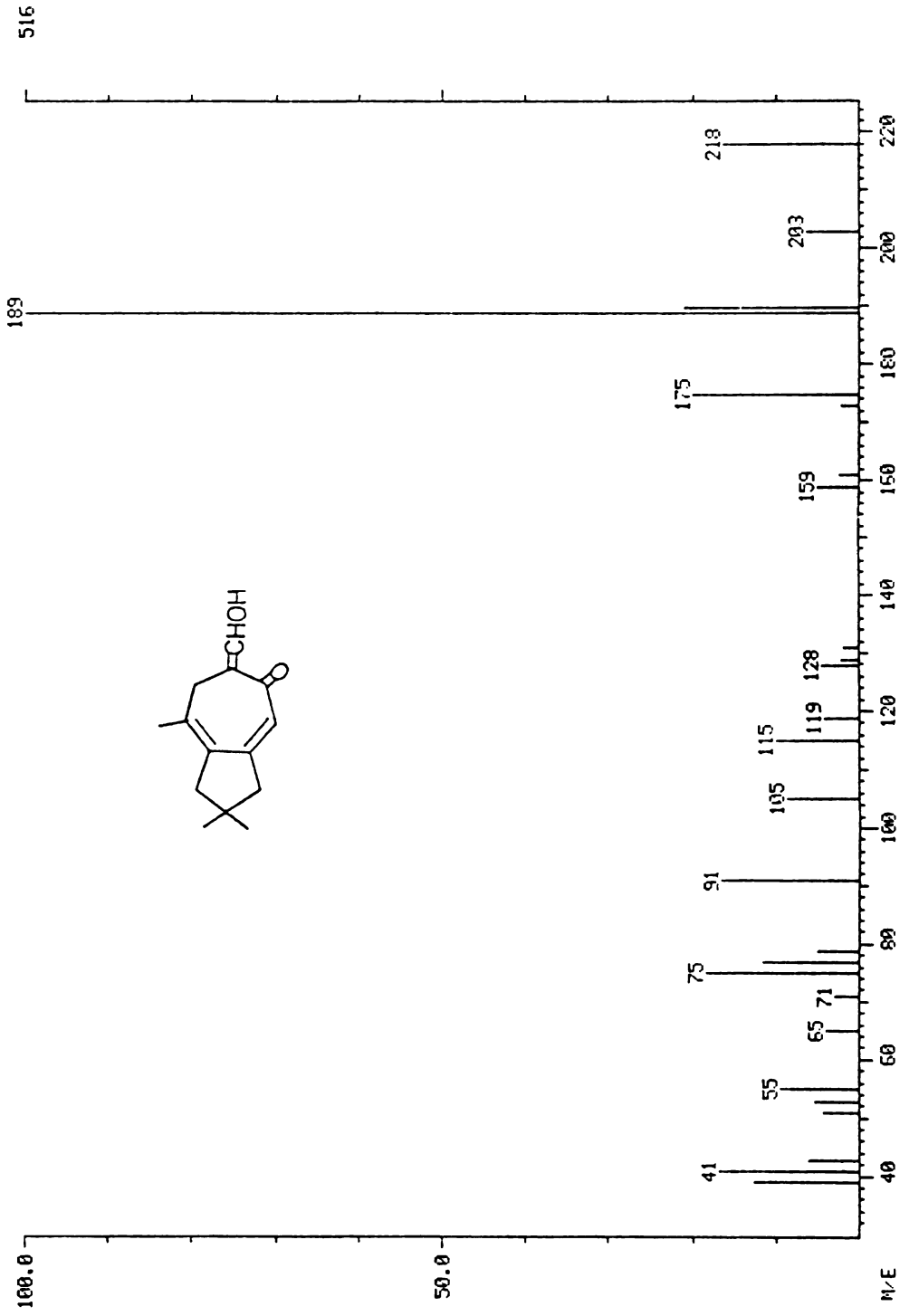


Figure II-25. Mass spectrum of 38.

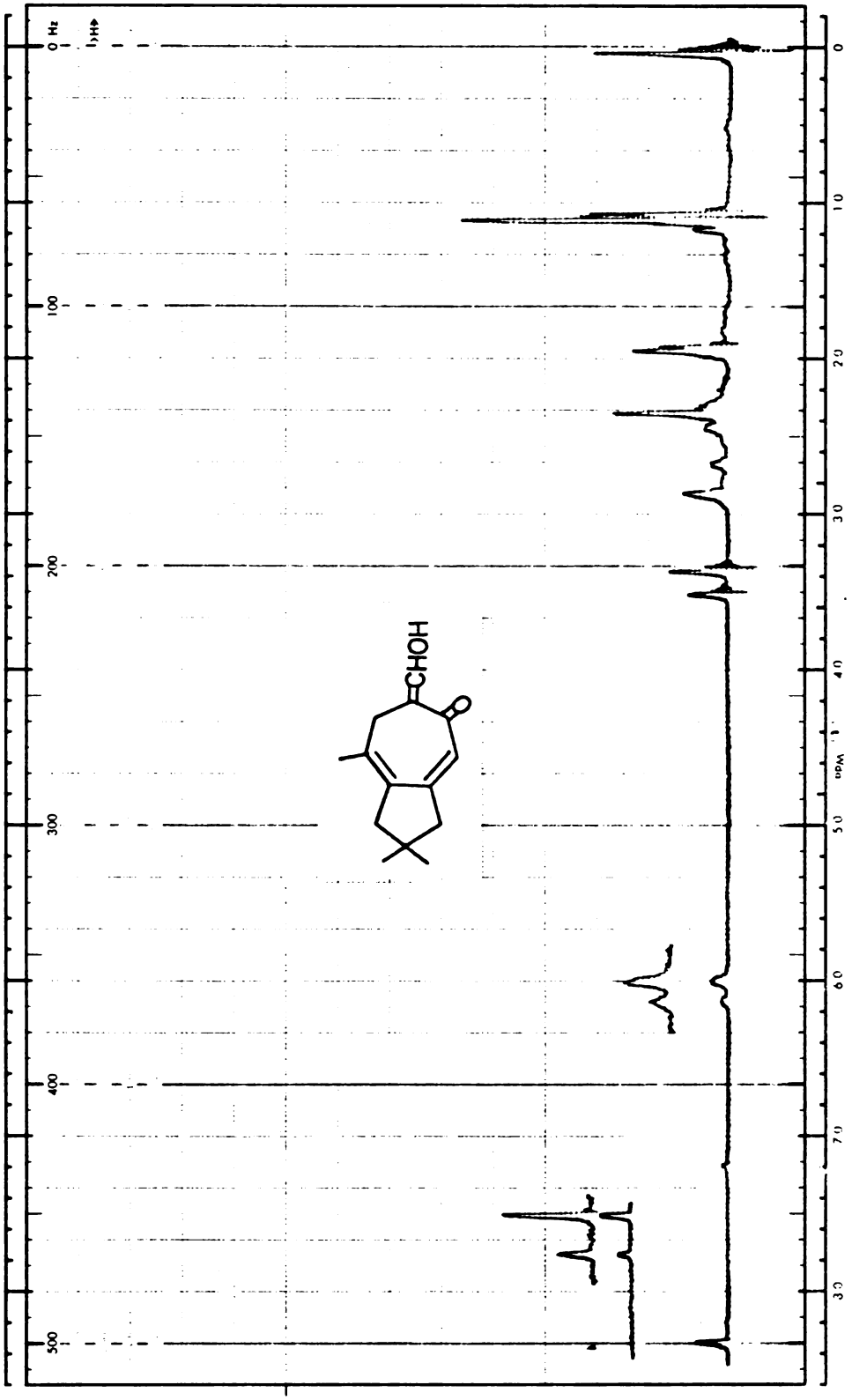


Figure II-26. Proton NMR of 38.

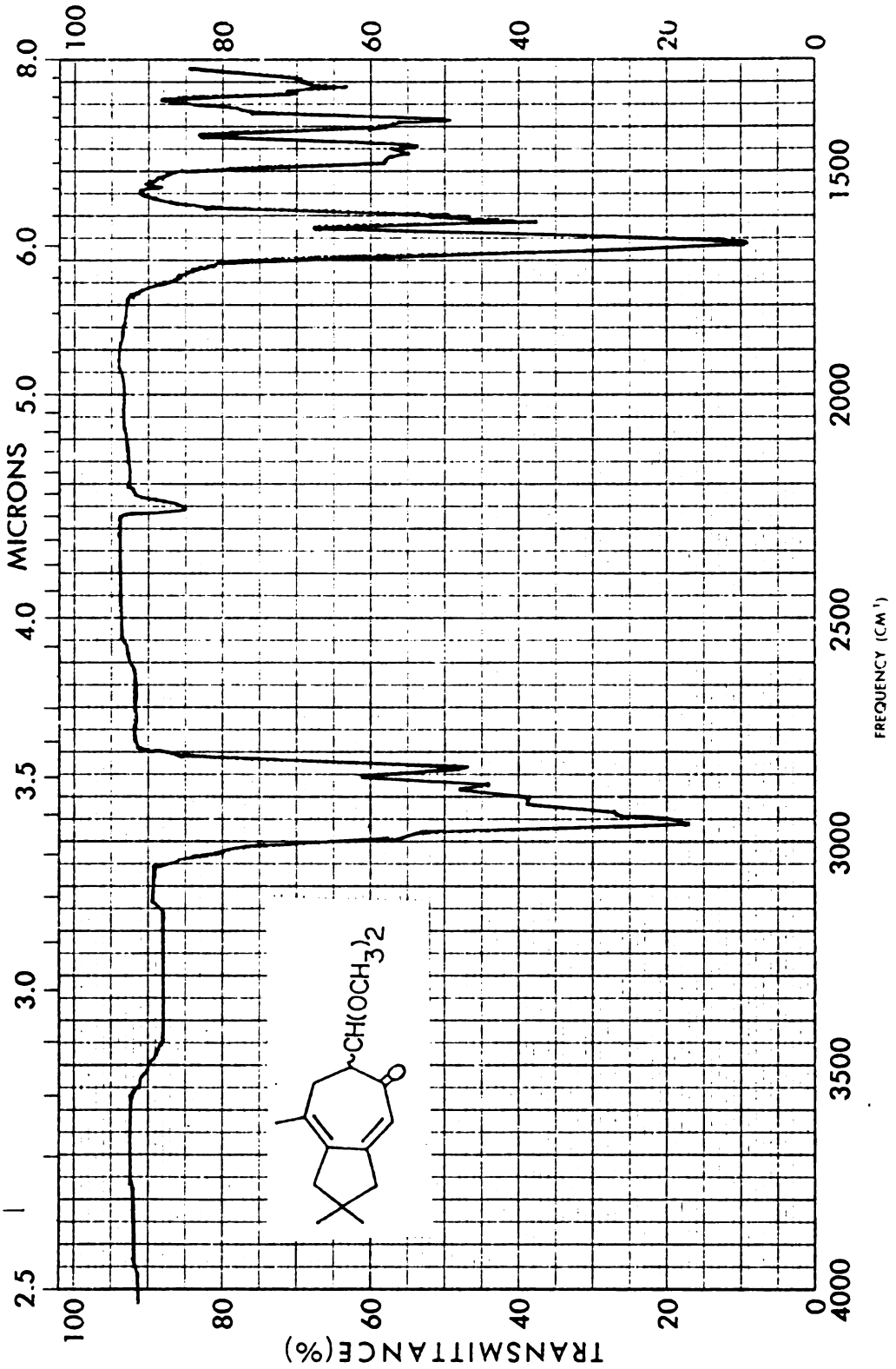


Figure II-27. IR of 39.

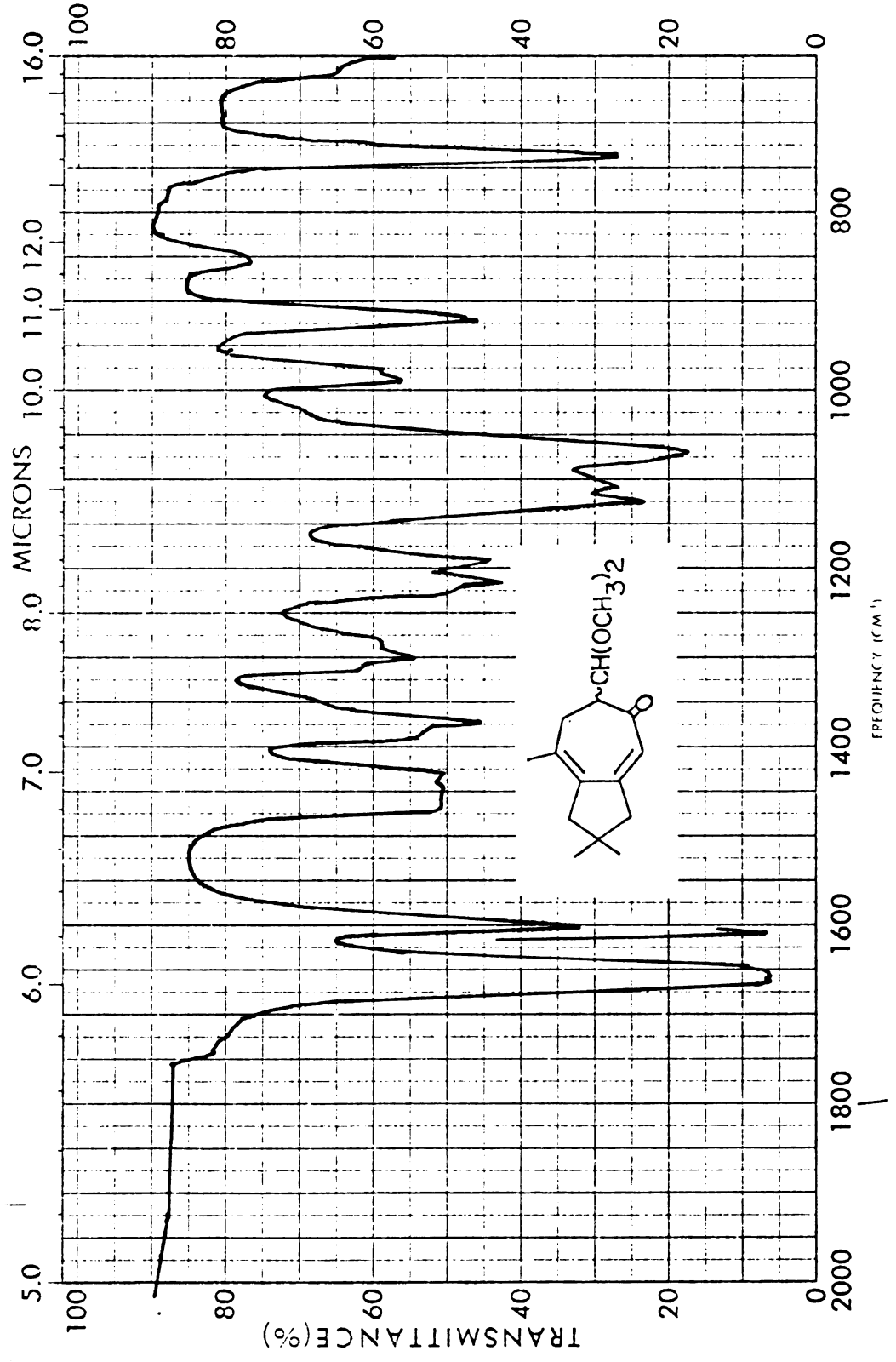


Figure II-28. IR of 39.

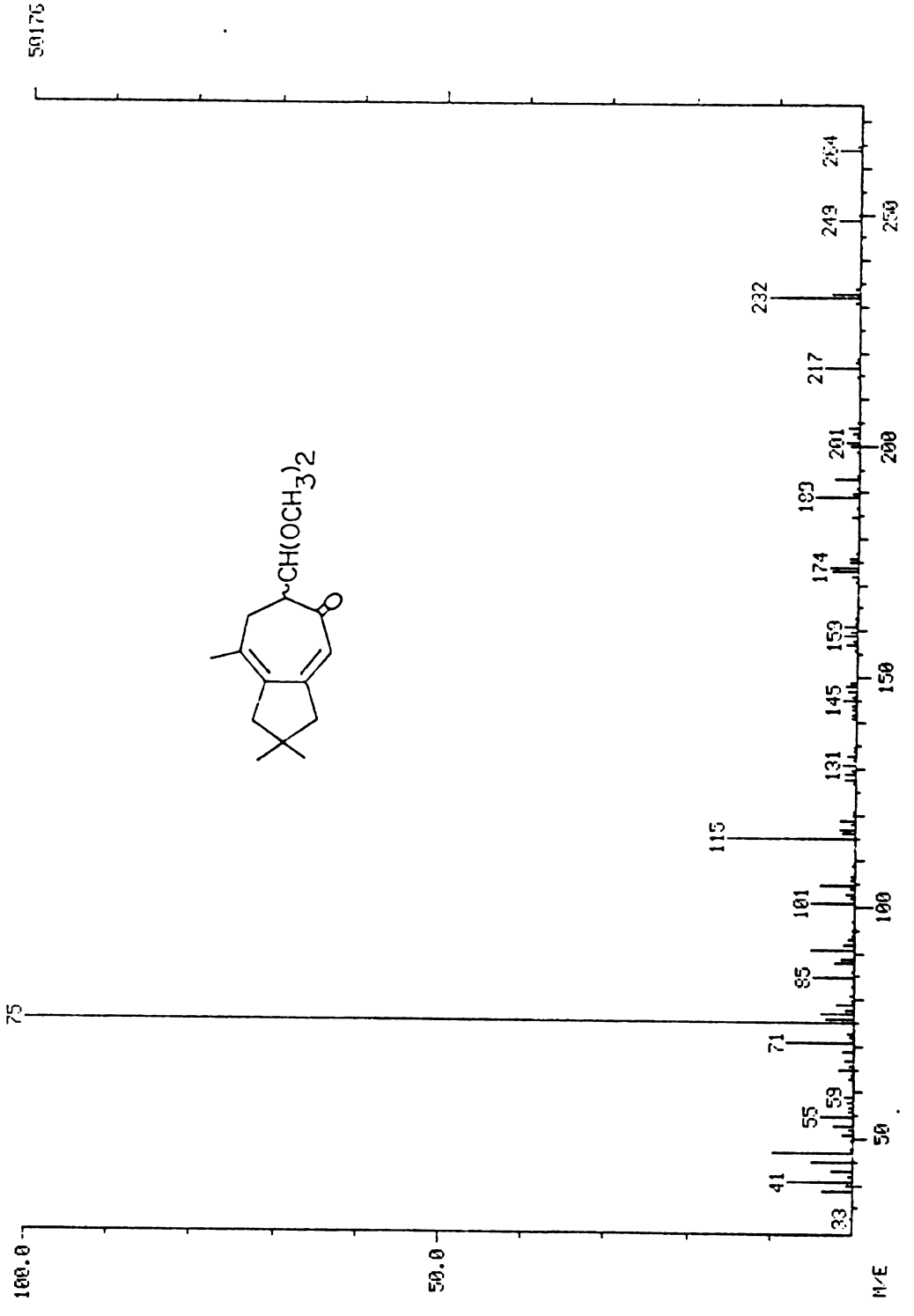


Figure II-29. Mass spectrum of 39.

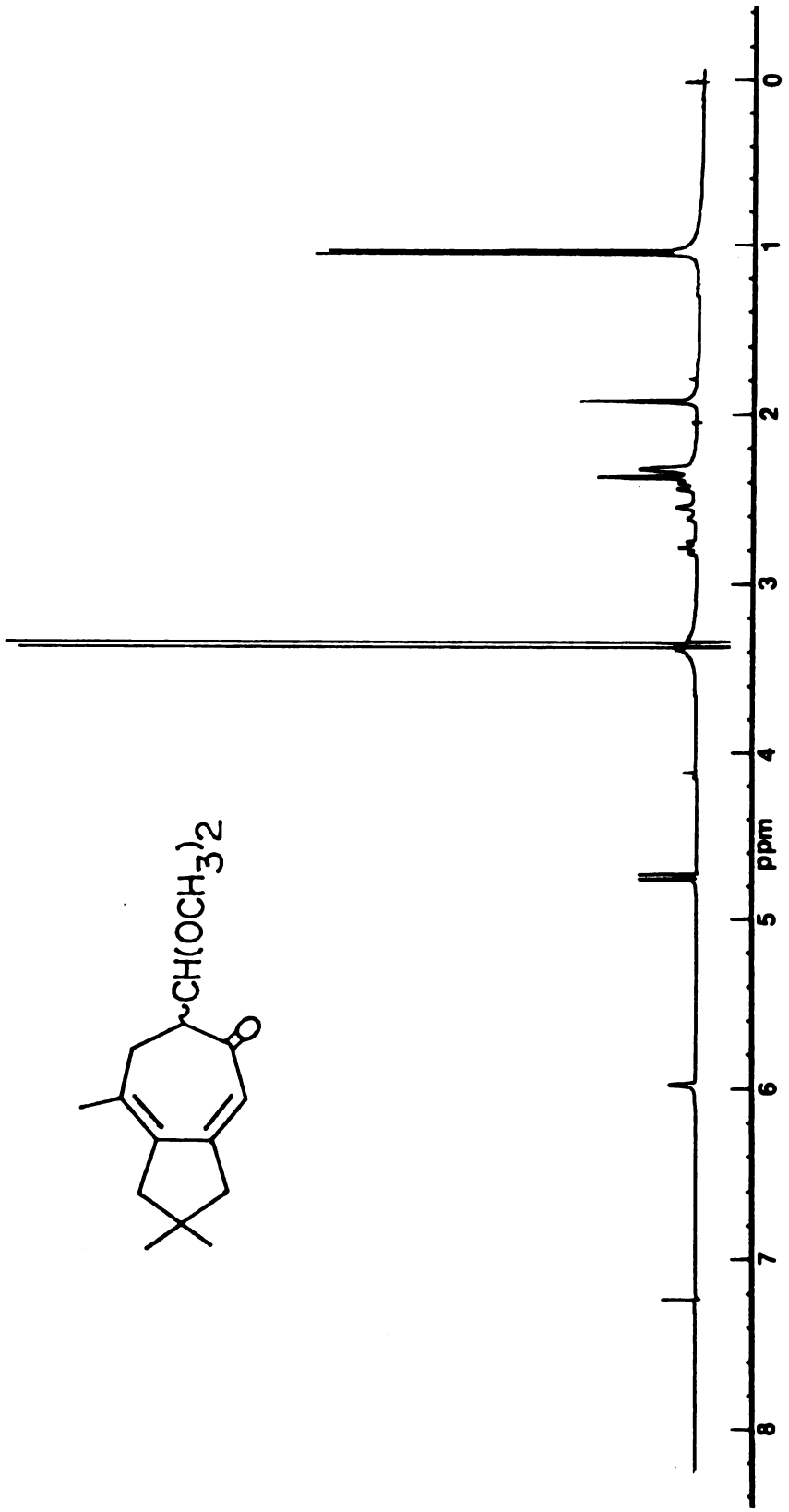


Figure II-30. Proton NMR of 39.

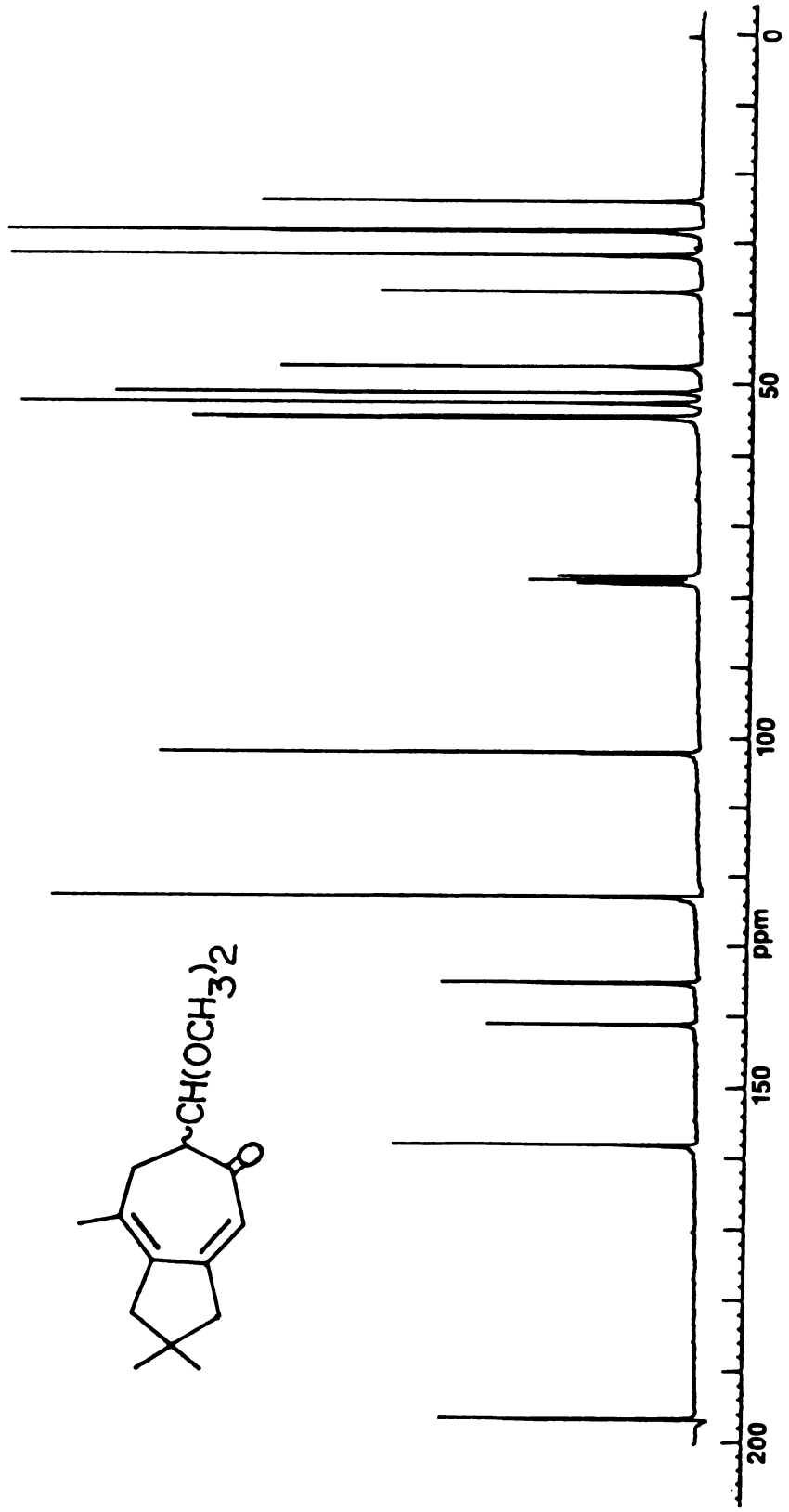


Figure II-31. Carbon-13 NMR of 39.

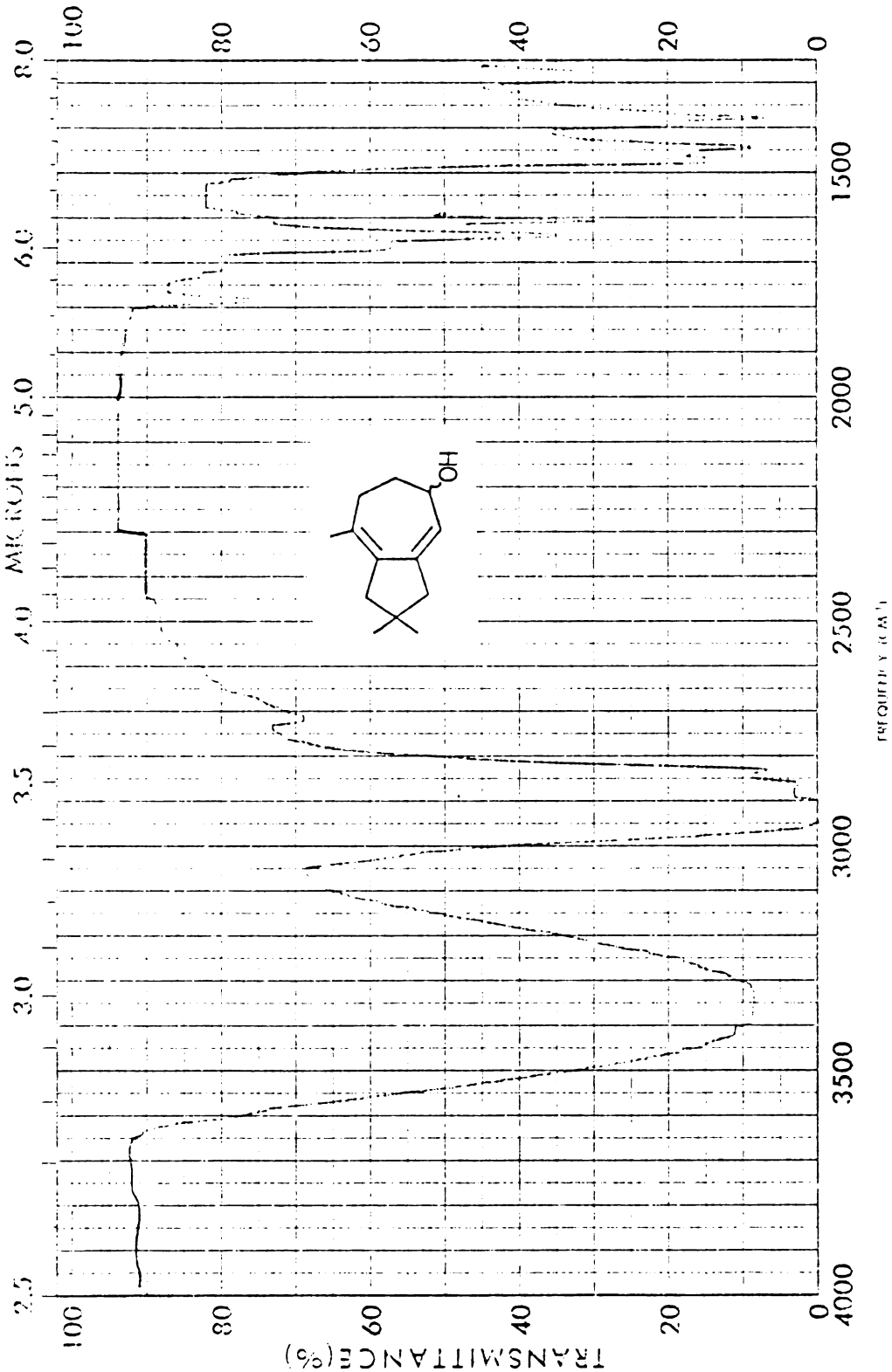


Figure II-32. IR of 40.

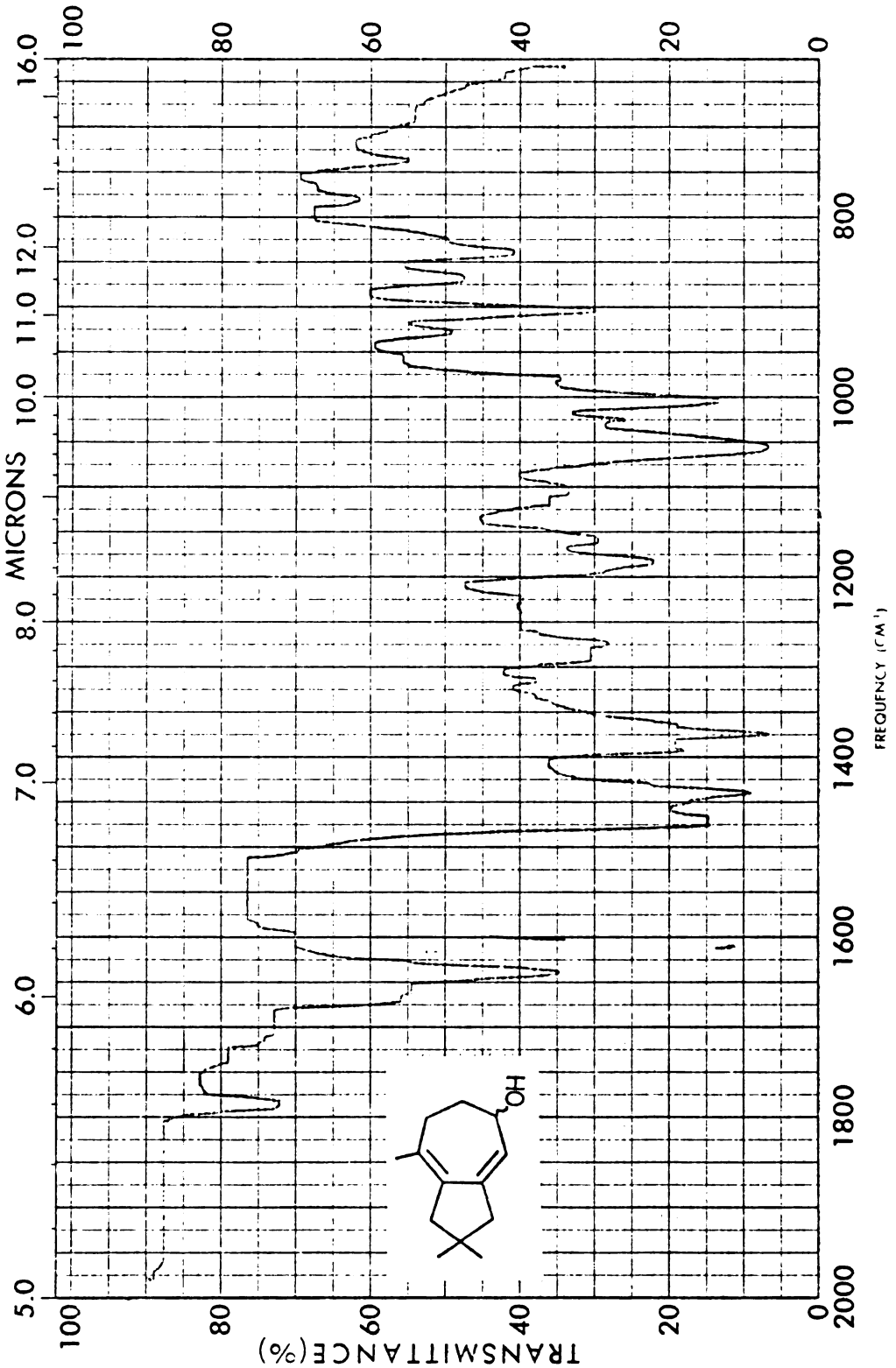


Figure II-33. IR of 40.

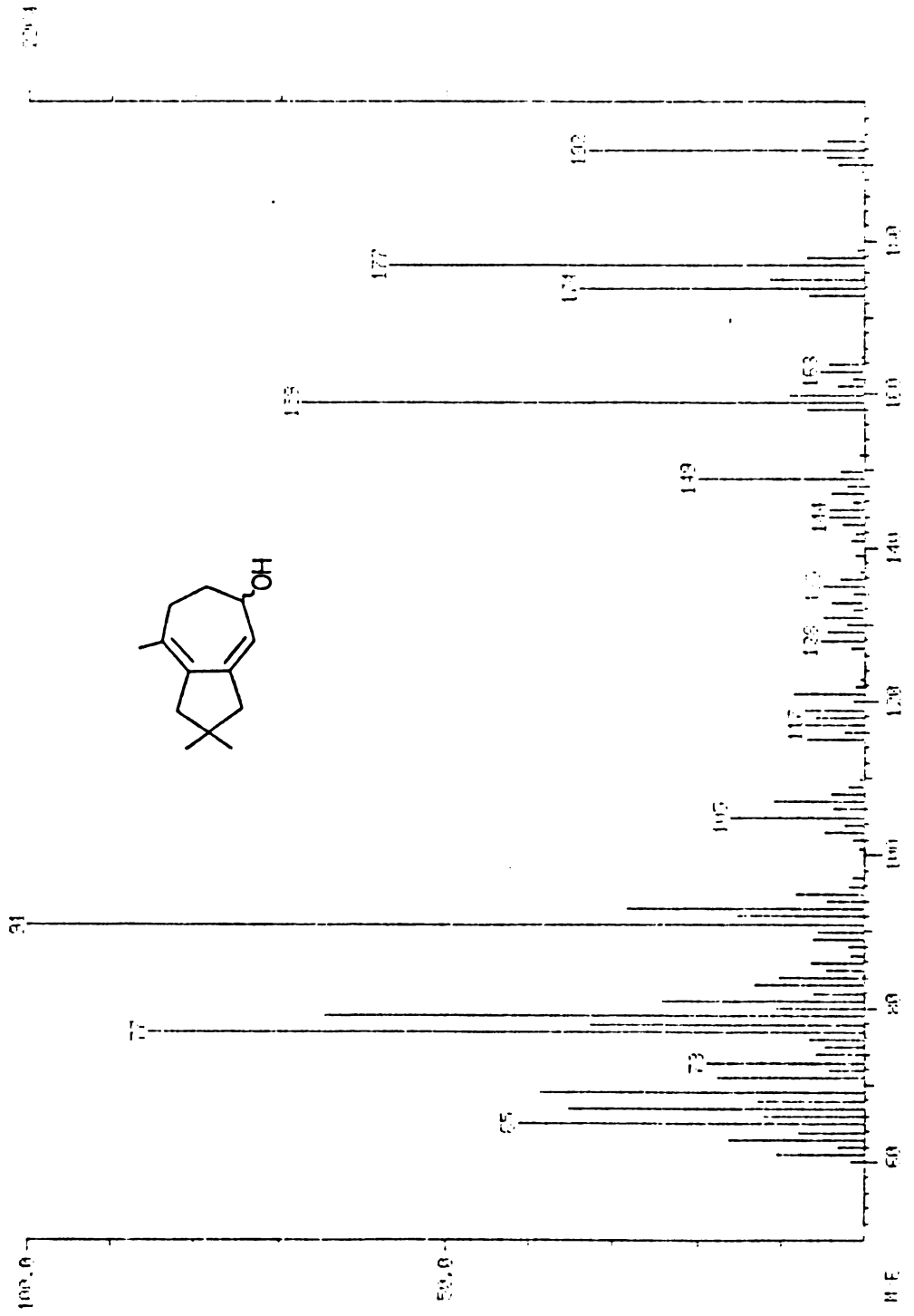


Figure II-34. Mass spectrum of 40.

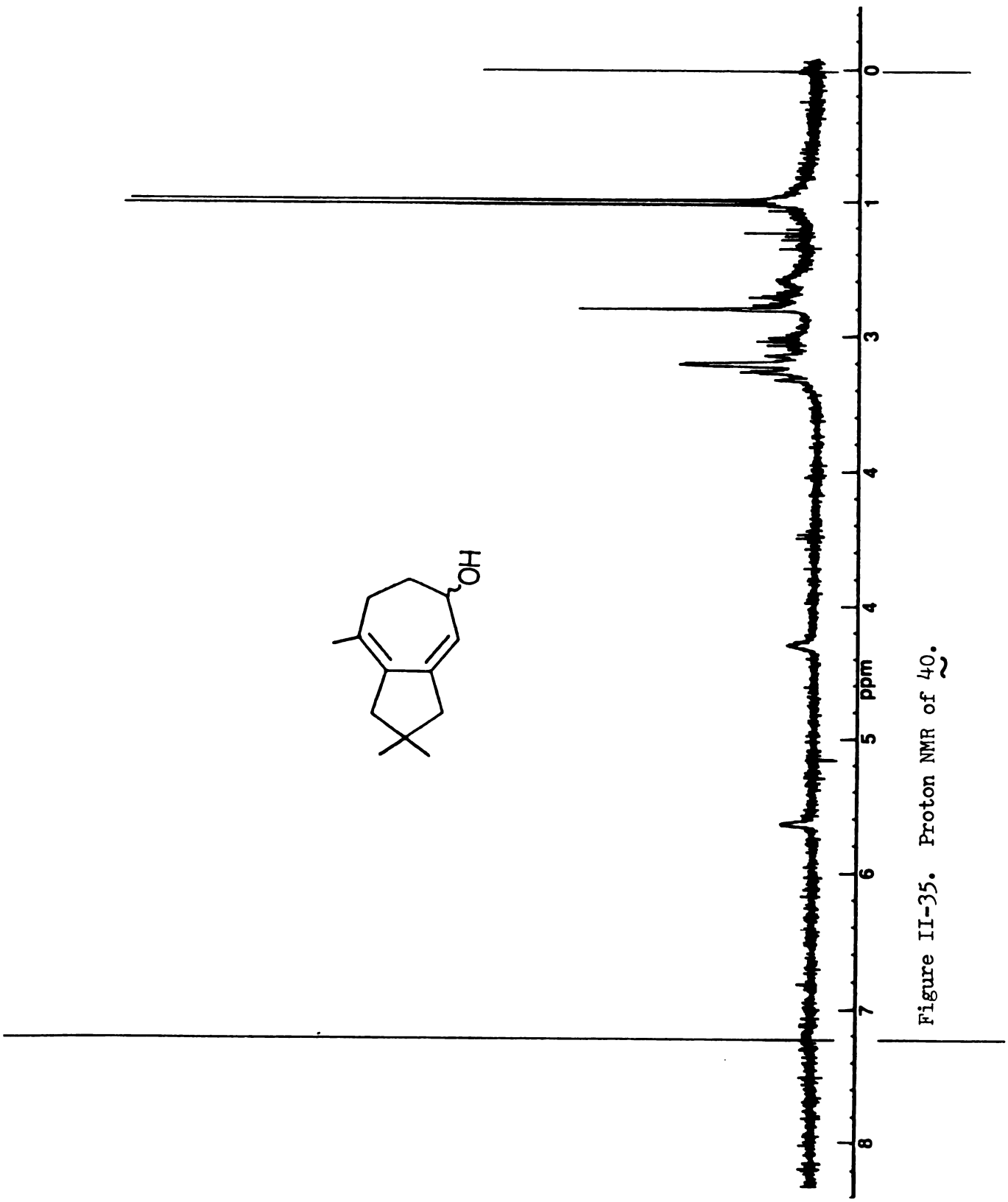


Figure II-35. Proton NMR of ~~40~~.

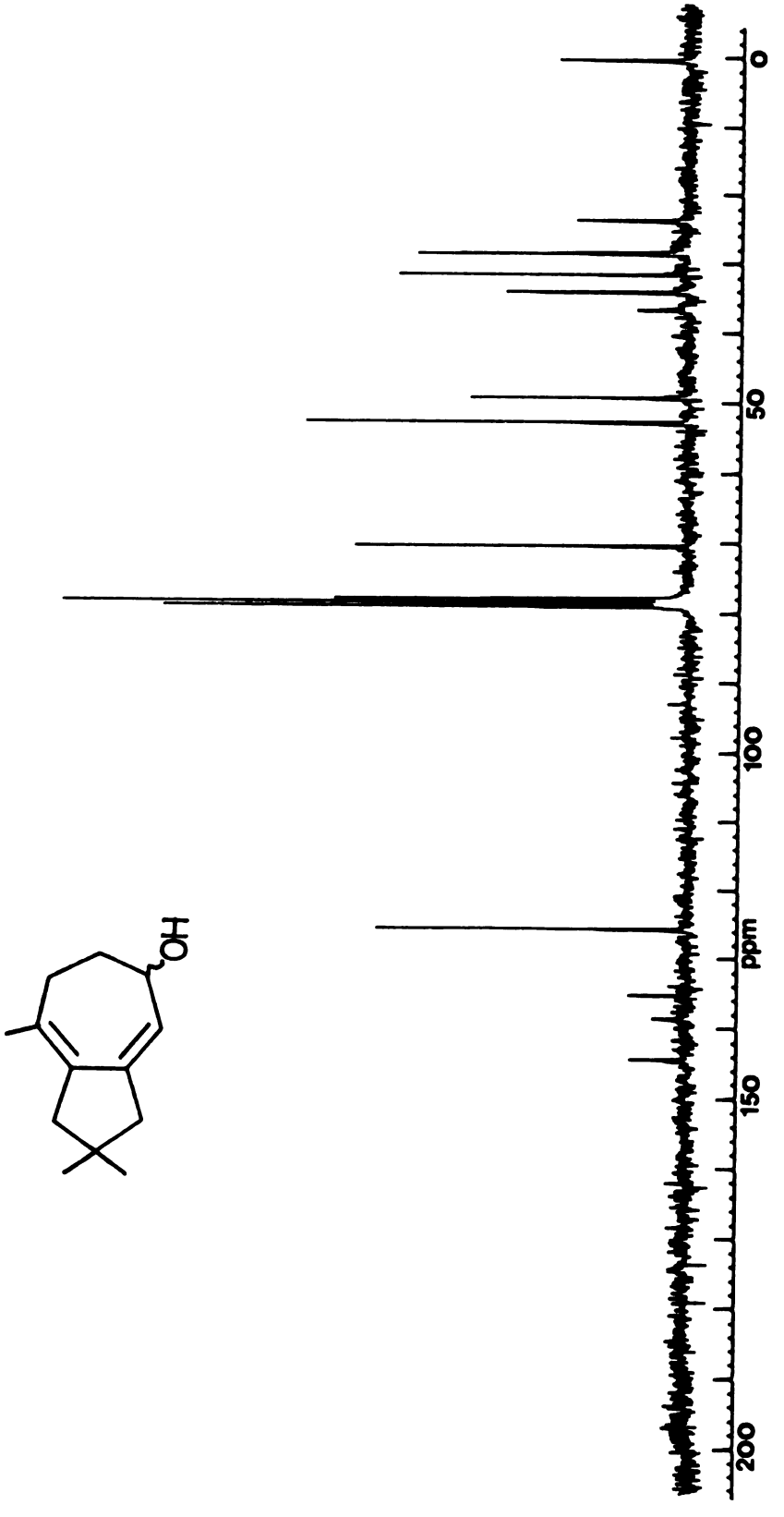


Figure II-36. Carbon-13 NMR of 40.

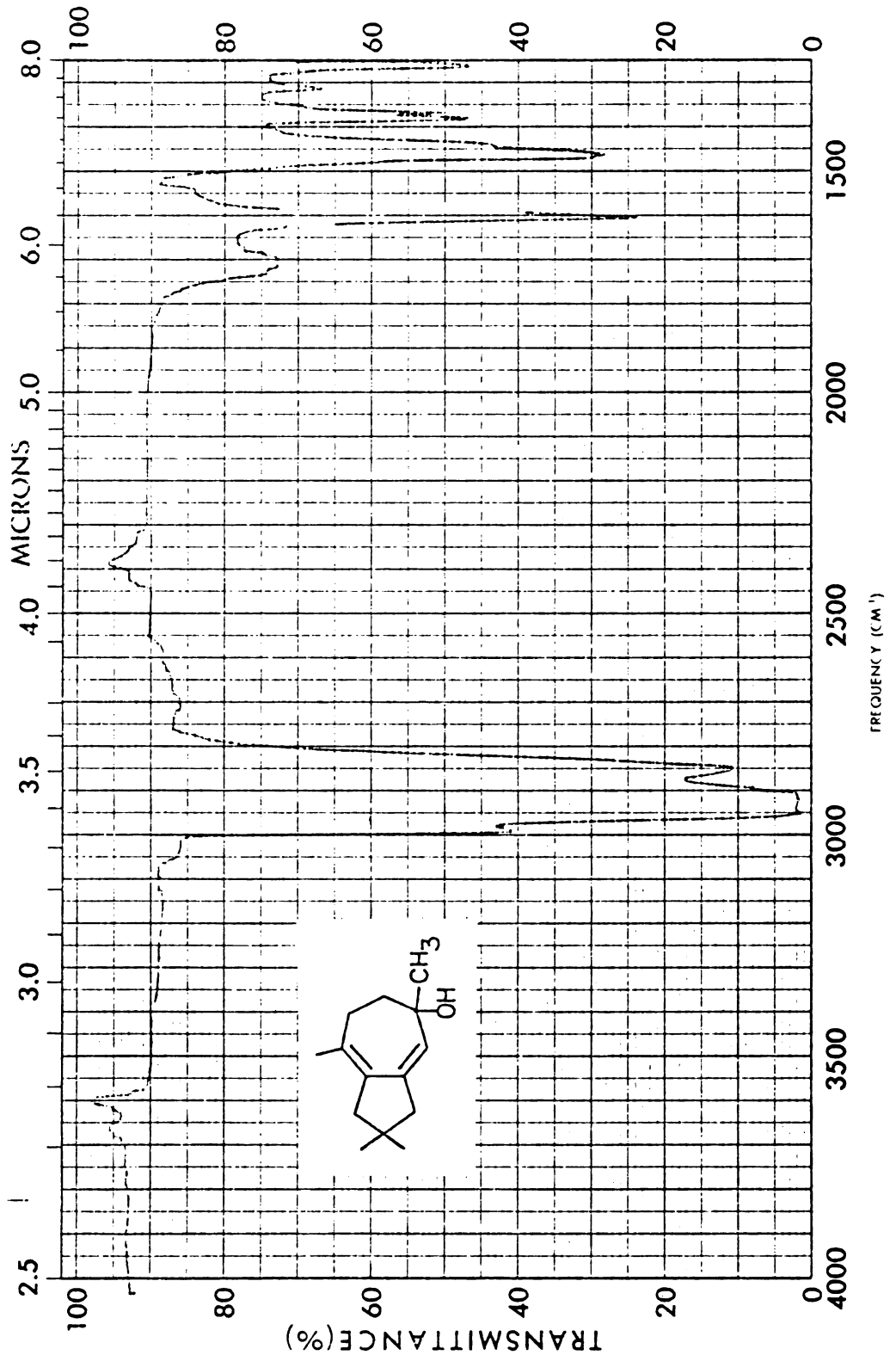


Figure II-37. IR of 41.

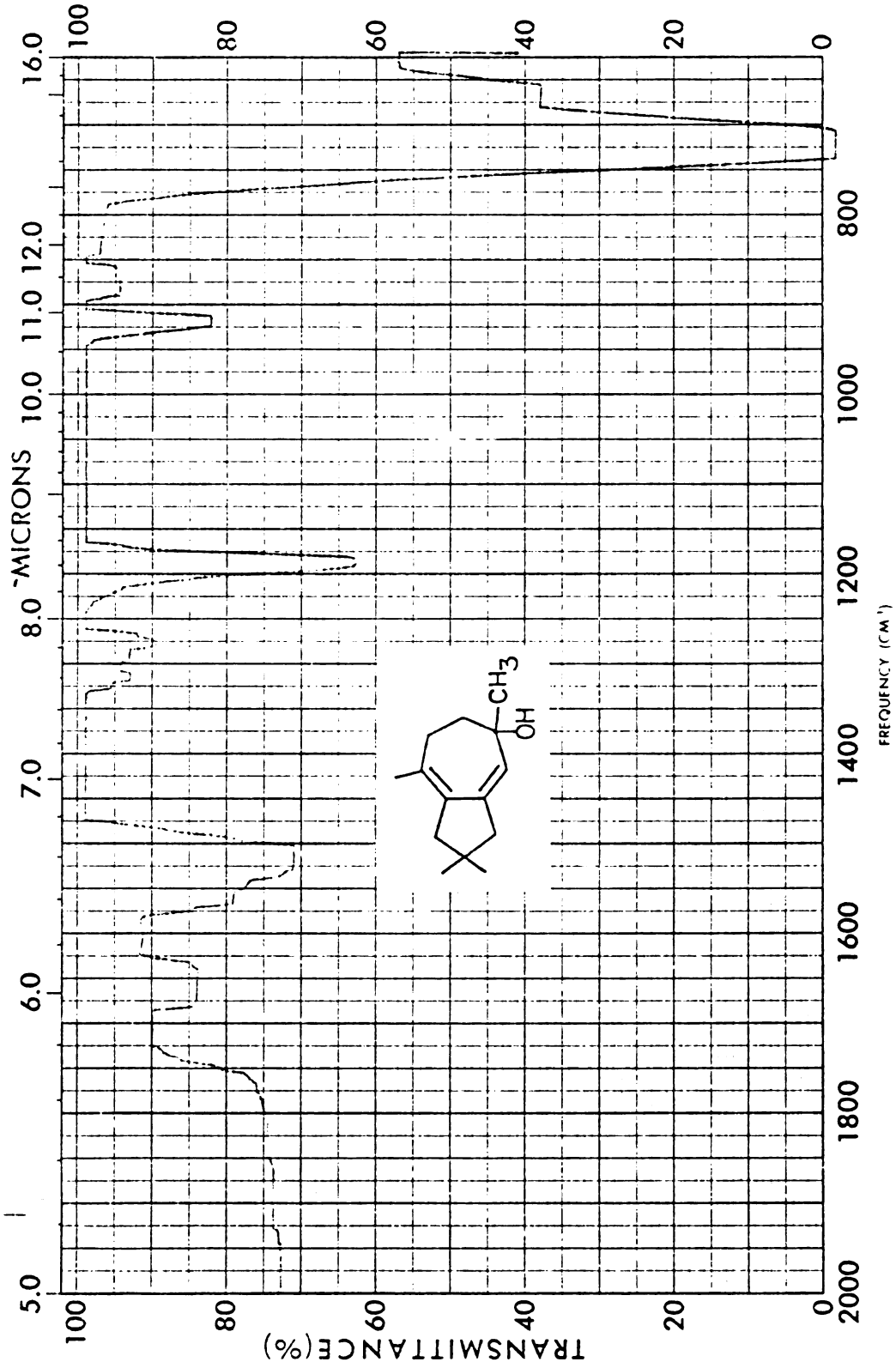


Figure II-38. IR of 41.

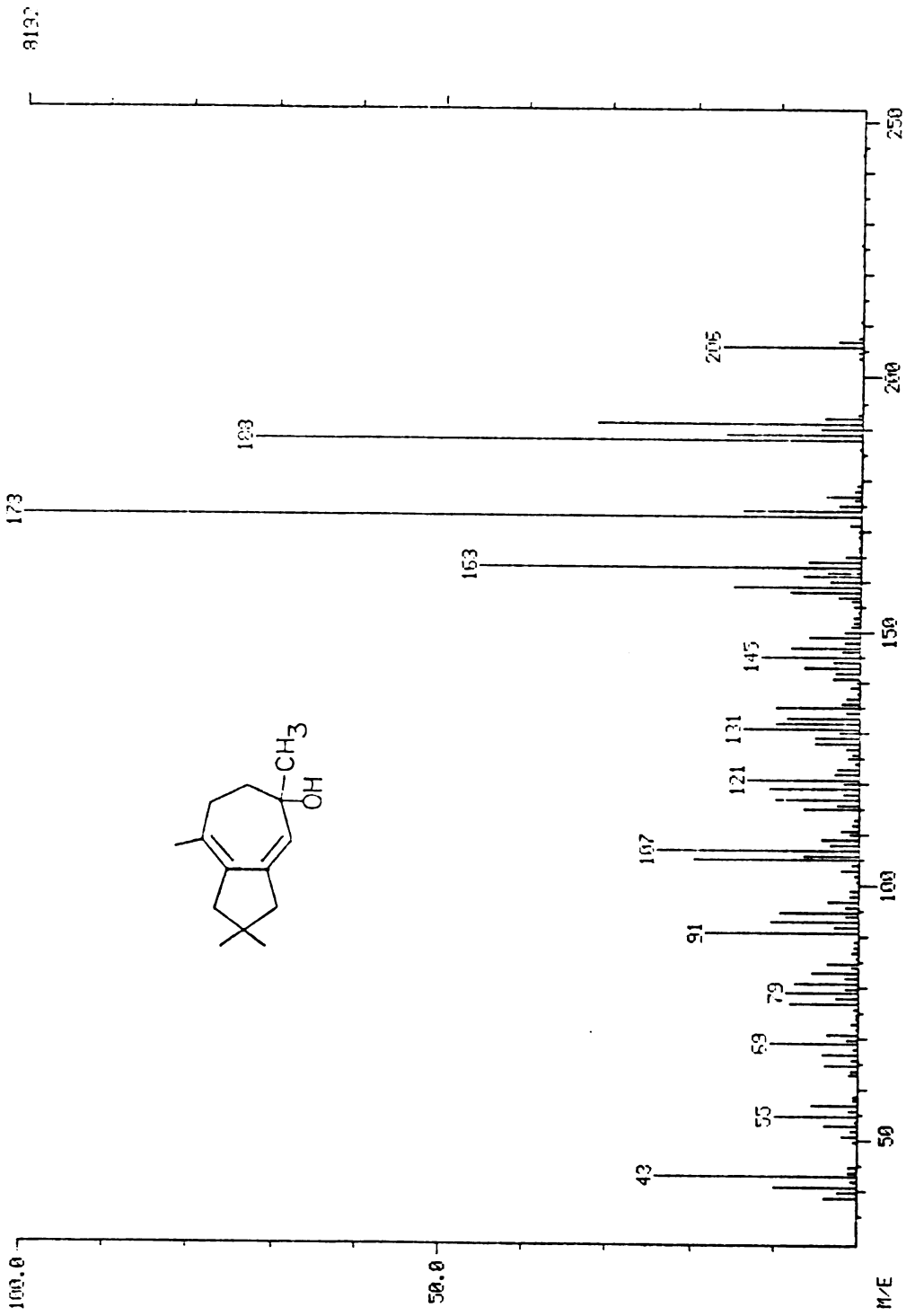


Figure II-39. Mass spectrum of 41.

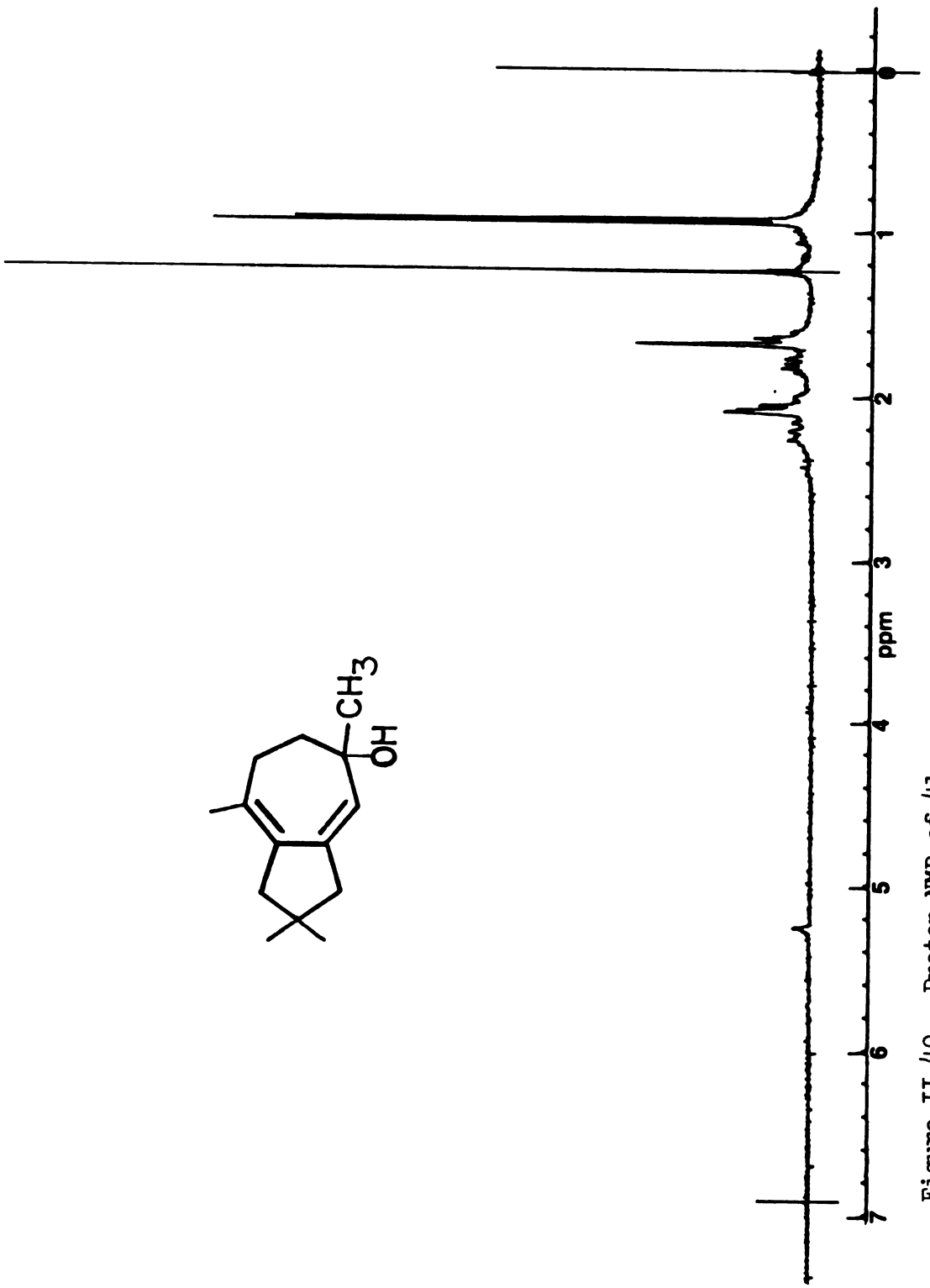


Figure II-40. Proton NMR of 41.

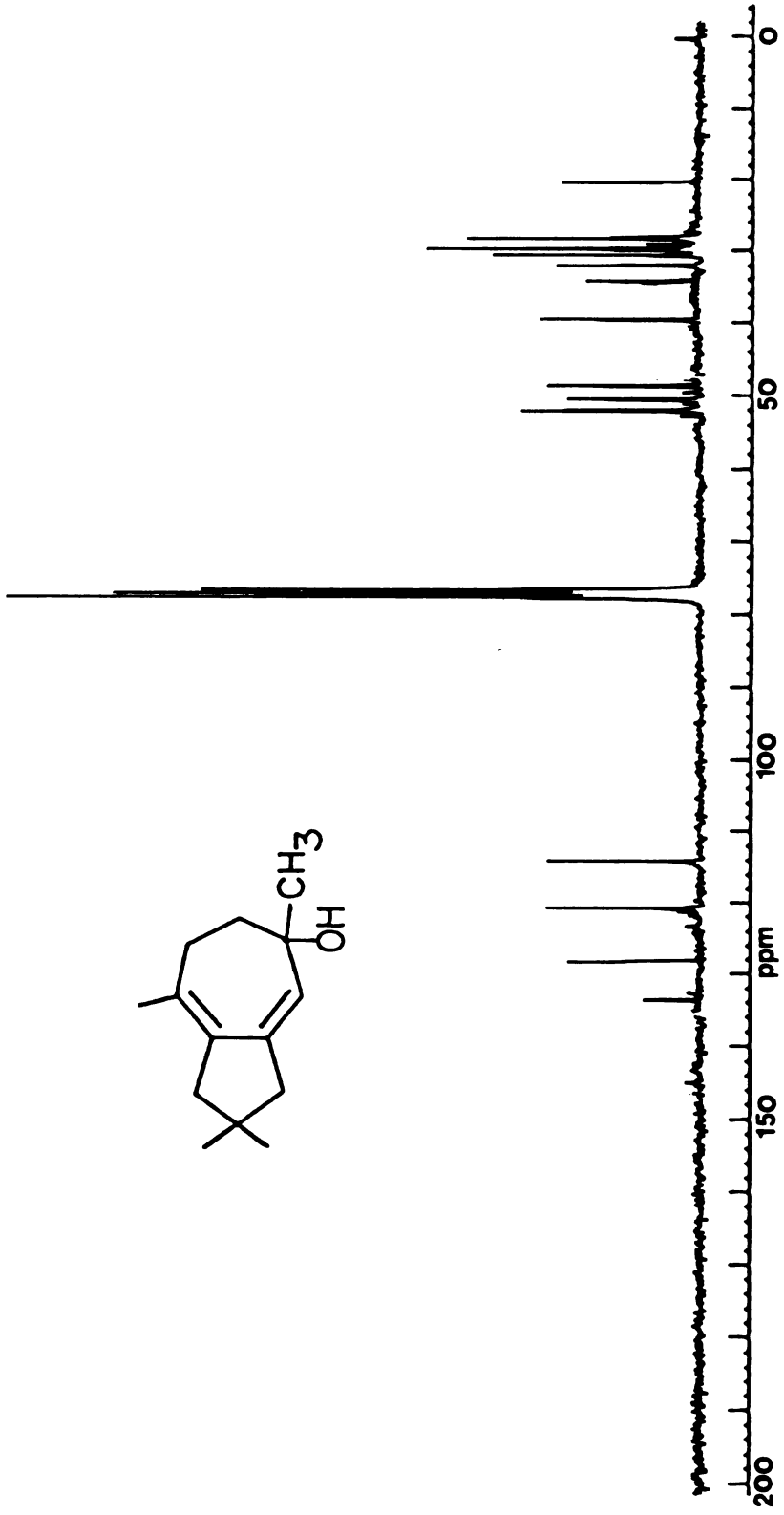


Figure II-41. Carbon-13 NMR of 41.

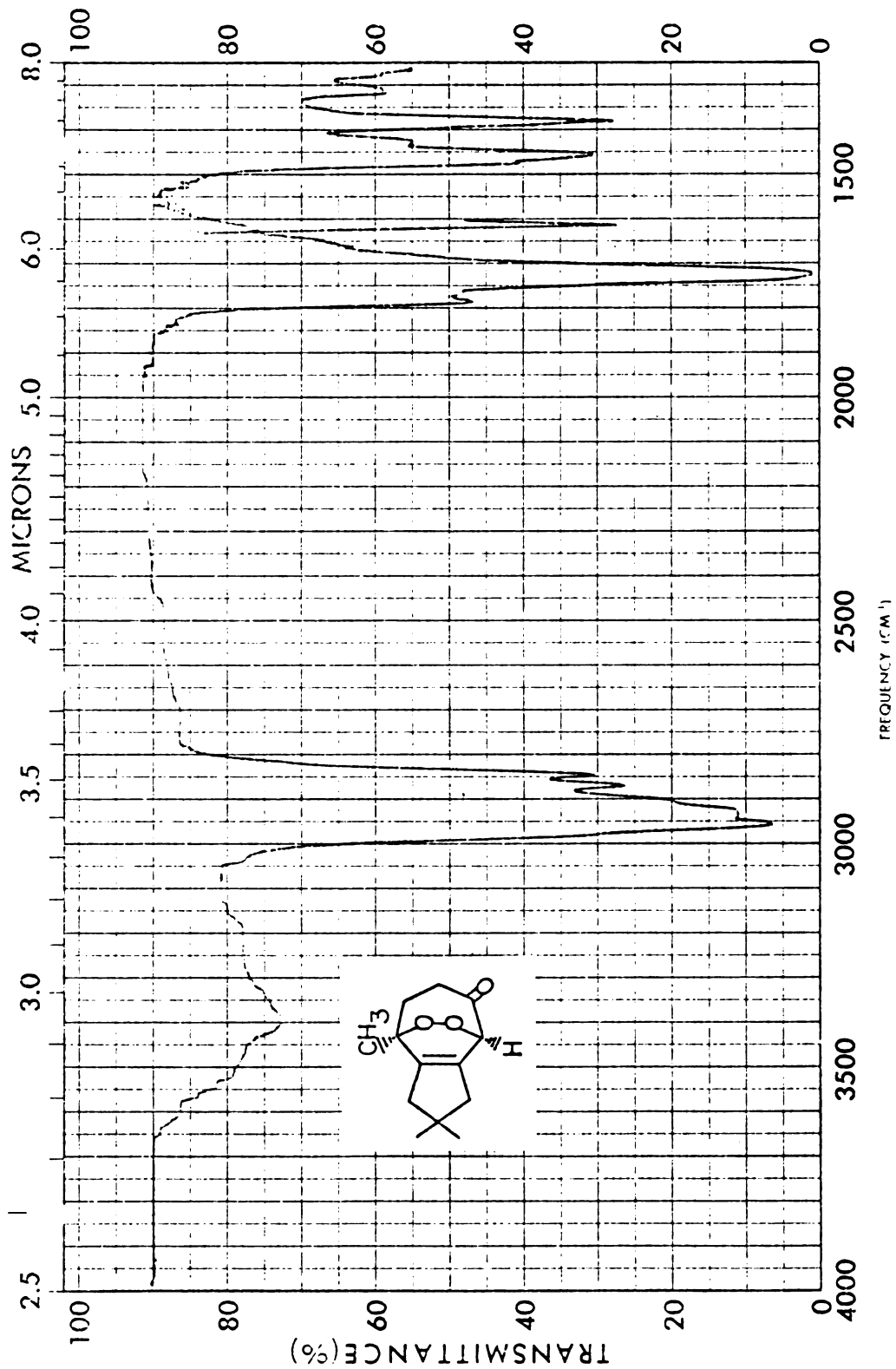


Figure II-42. IR of 47.

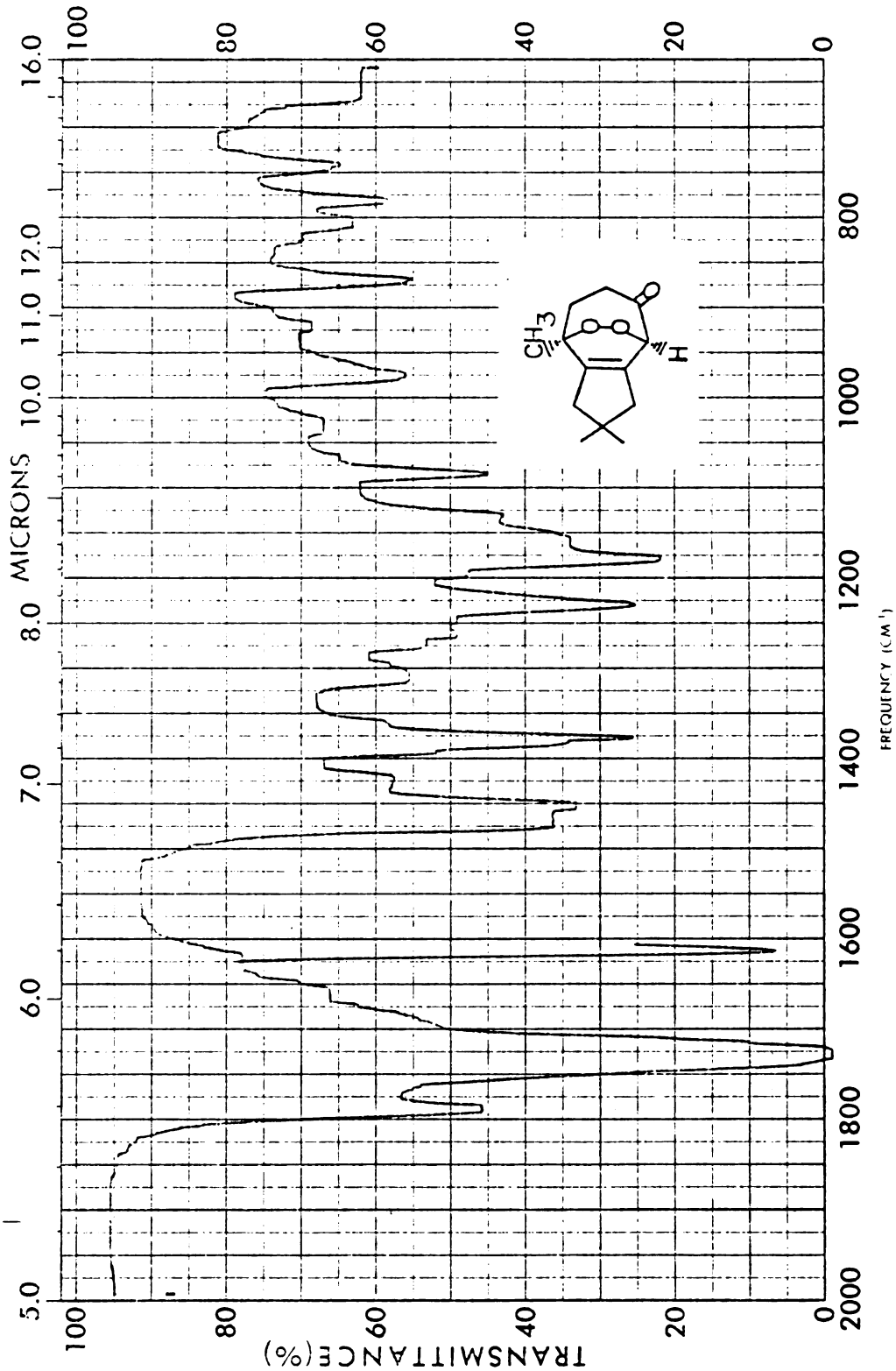


Figure II-43. IR of 47.

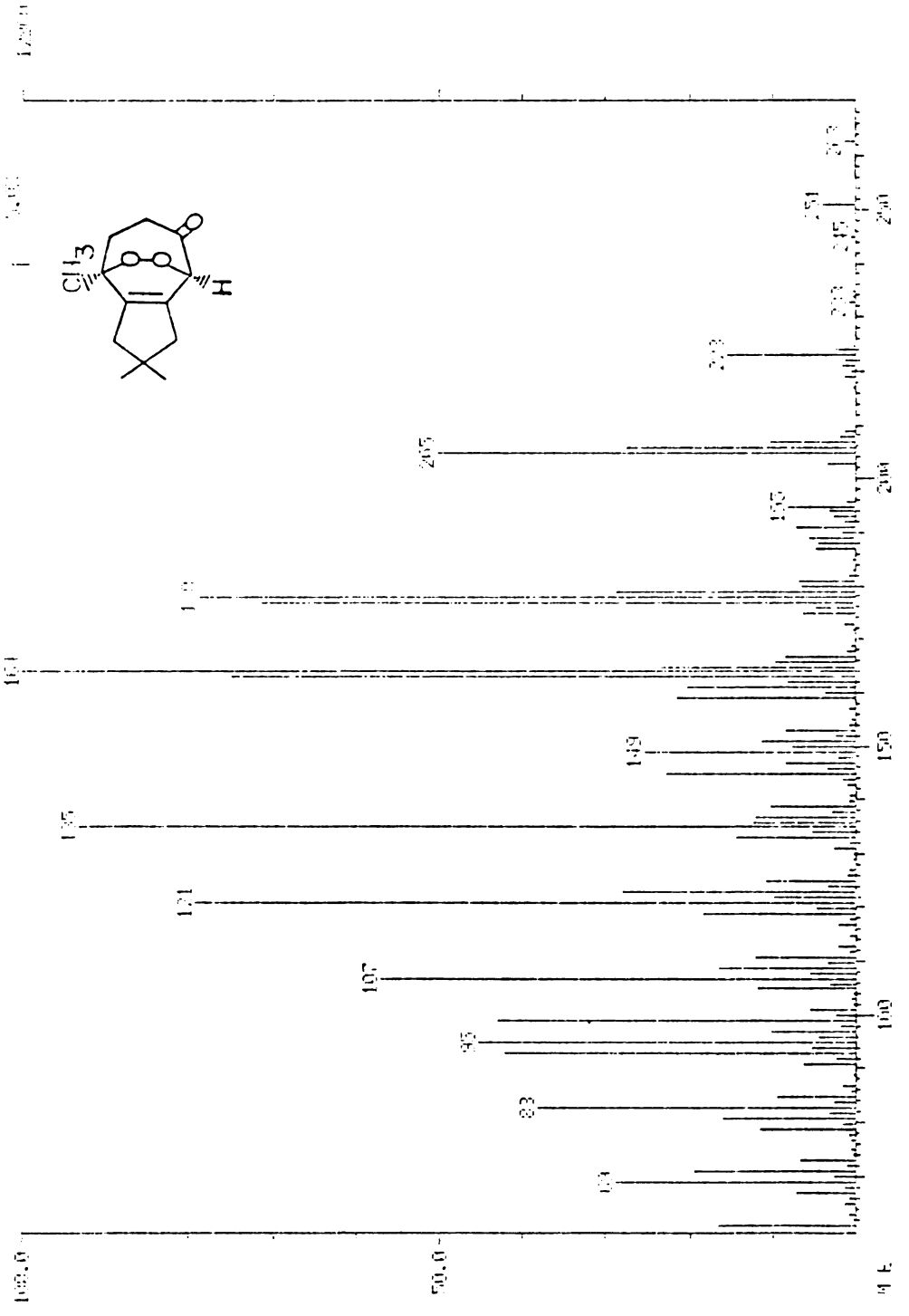


Figure II-44. Mass spectrum of 47.

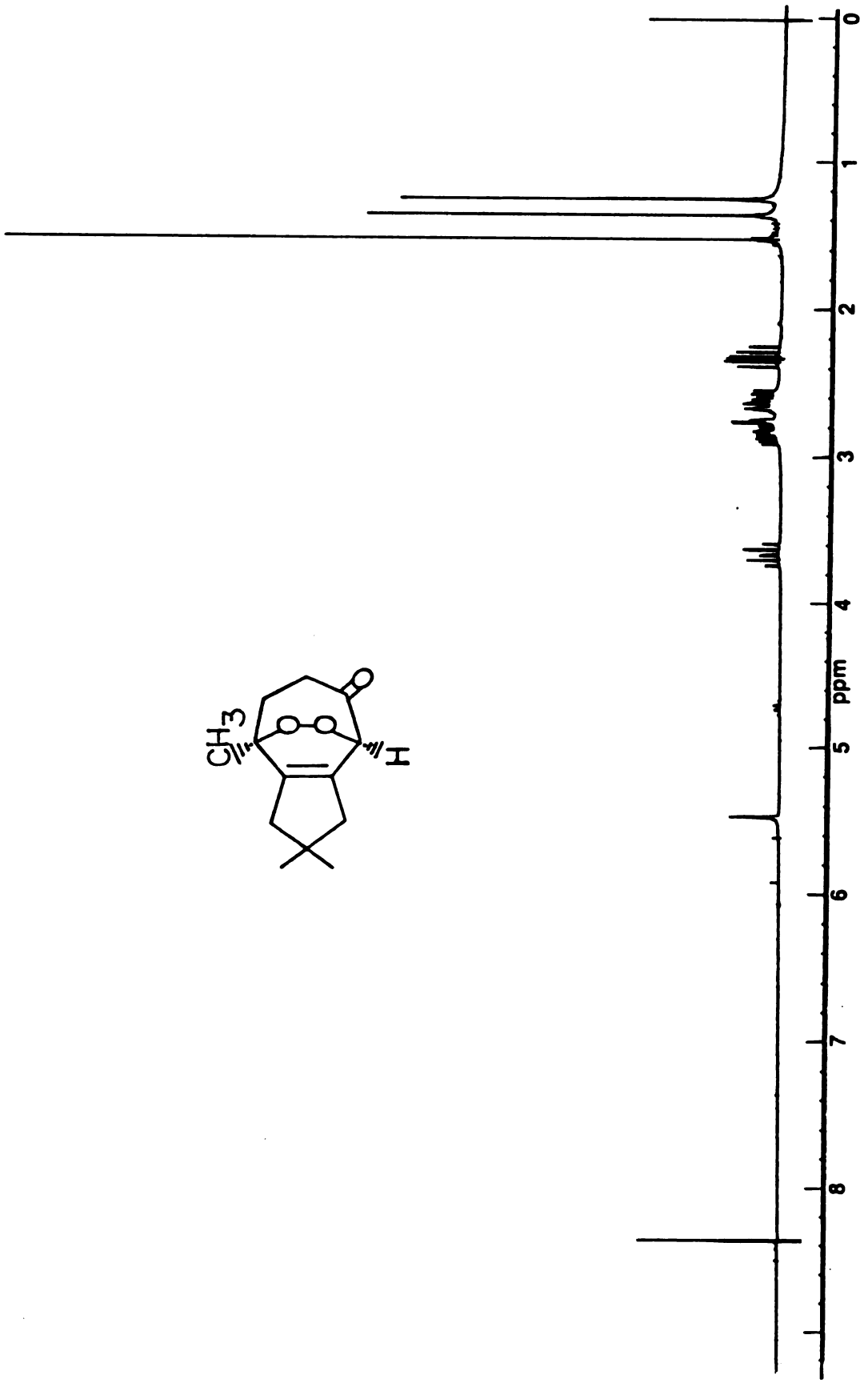


Figure II-45. Proton NMR of 47.

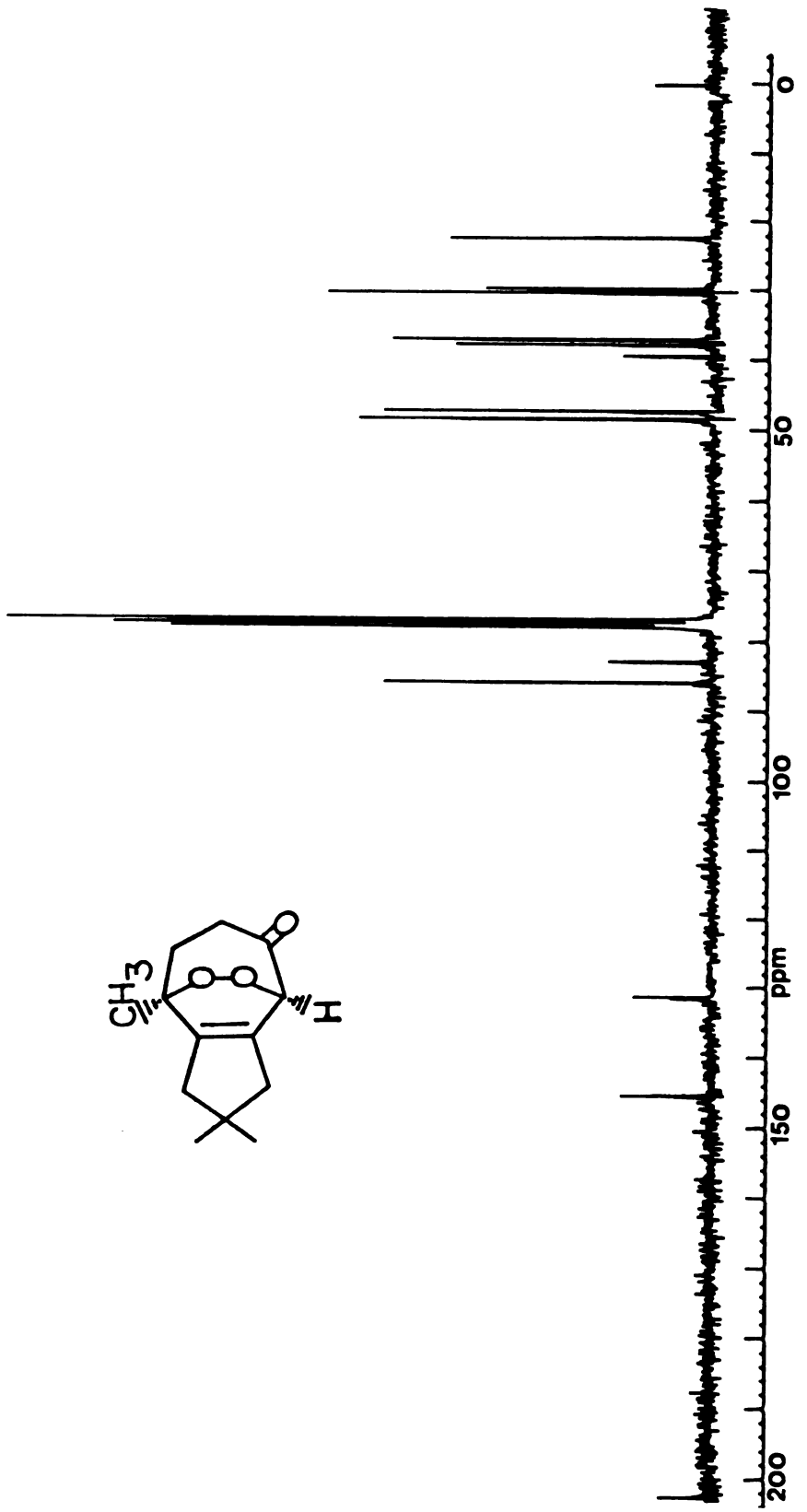


Figure II-46. Carbon-13 NMR of 47.

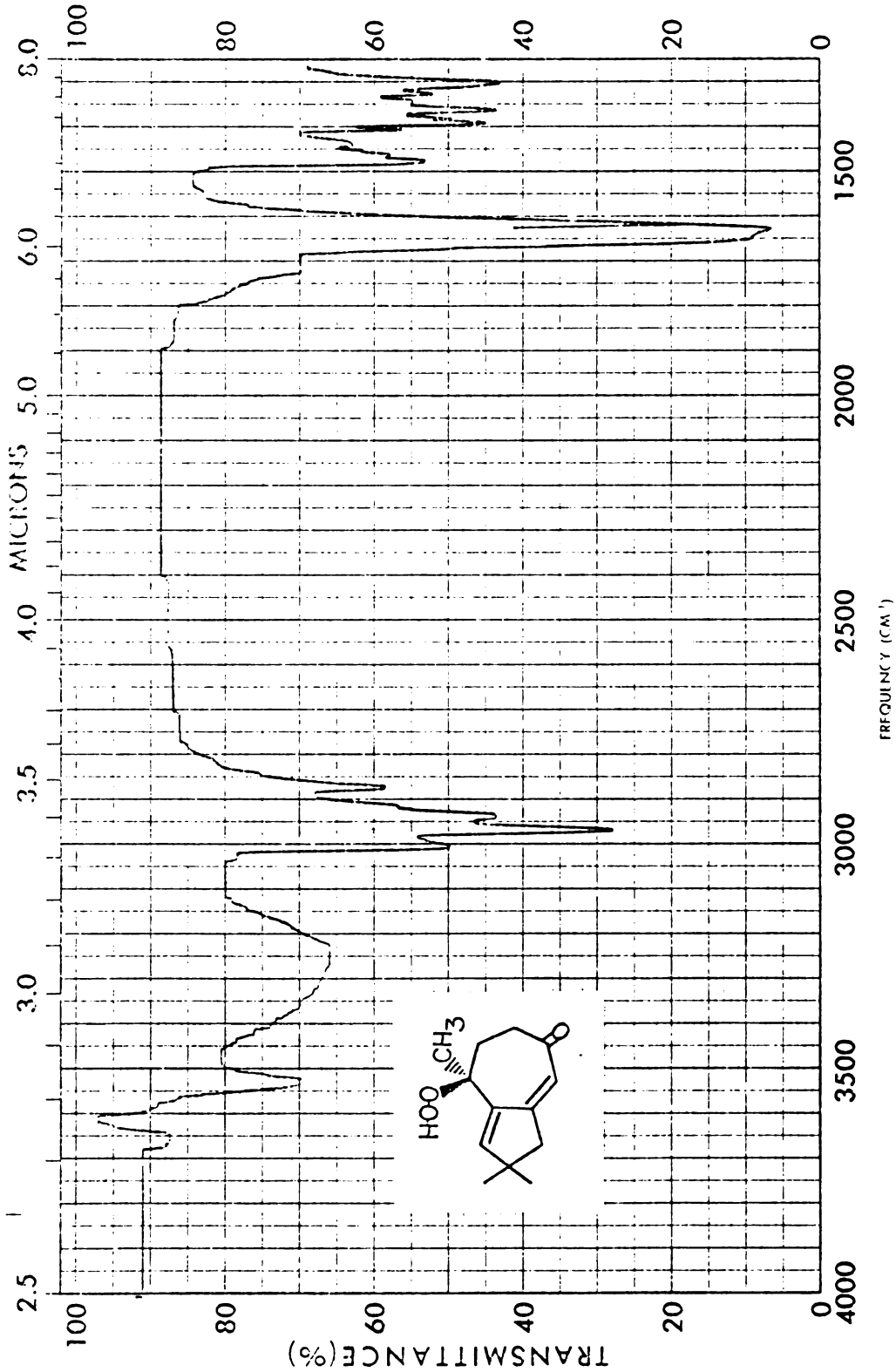


Figure II-47. IR of 48.

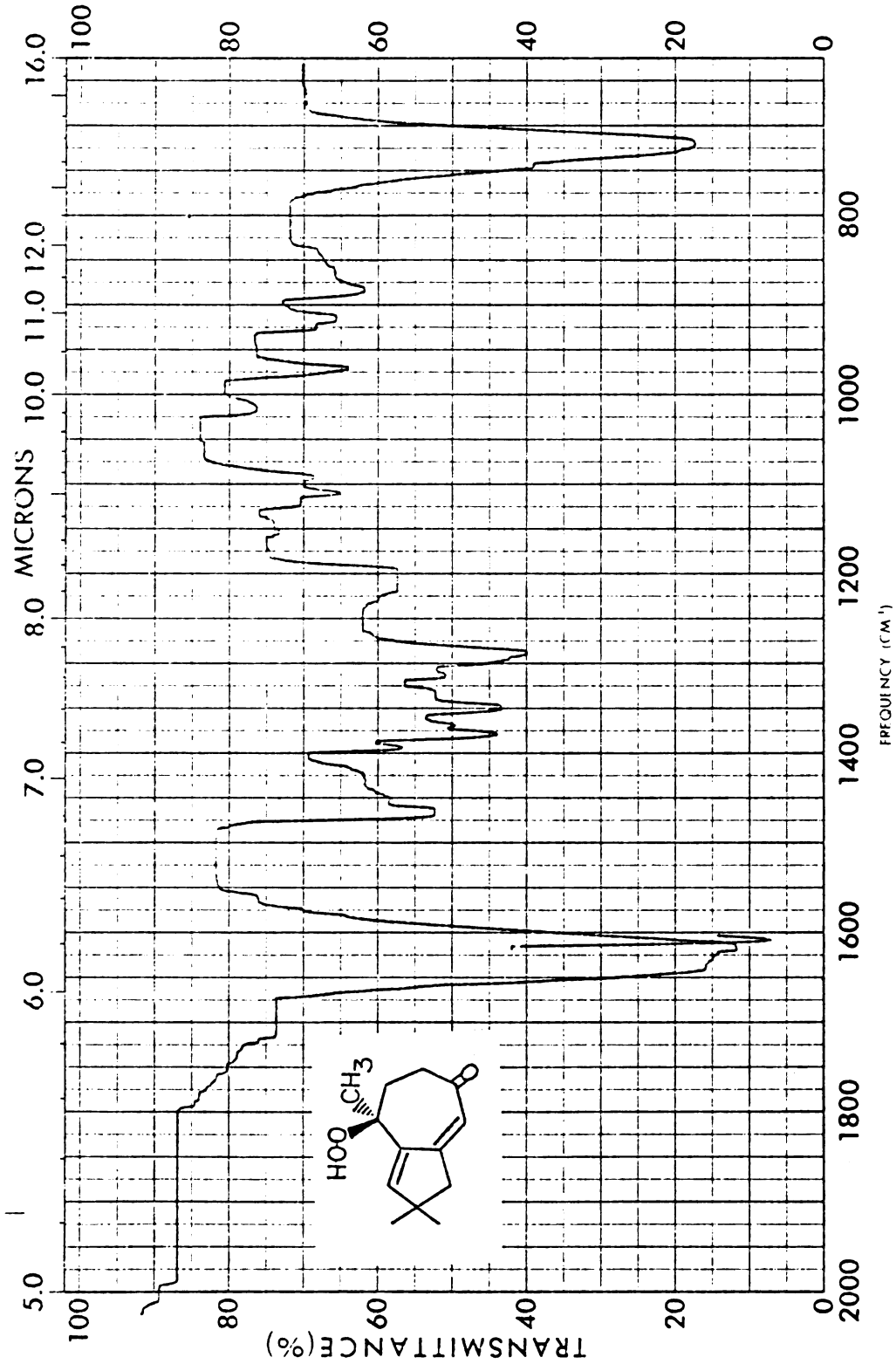


Figure II-48. IR of 48.

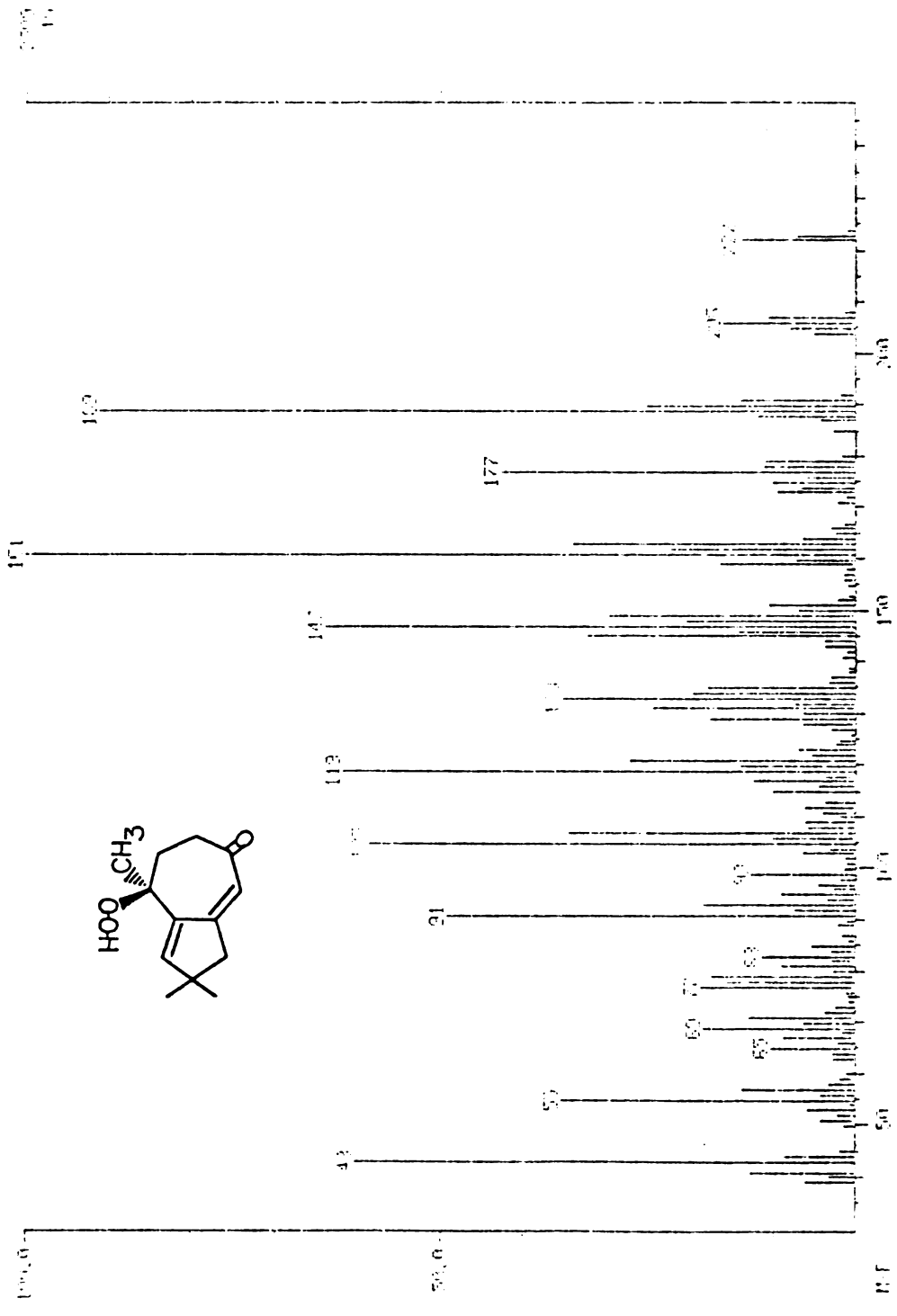


Figure II-49. Mass spectrum of 48.

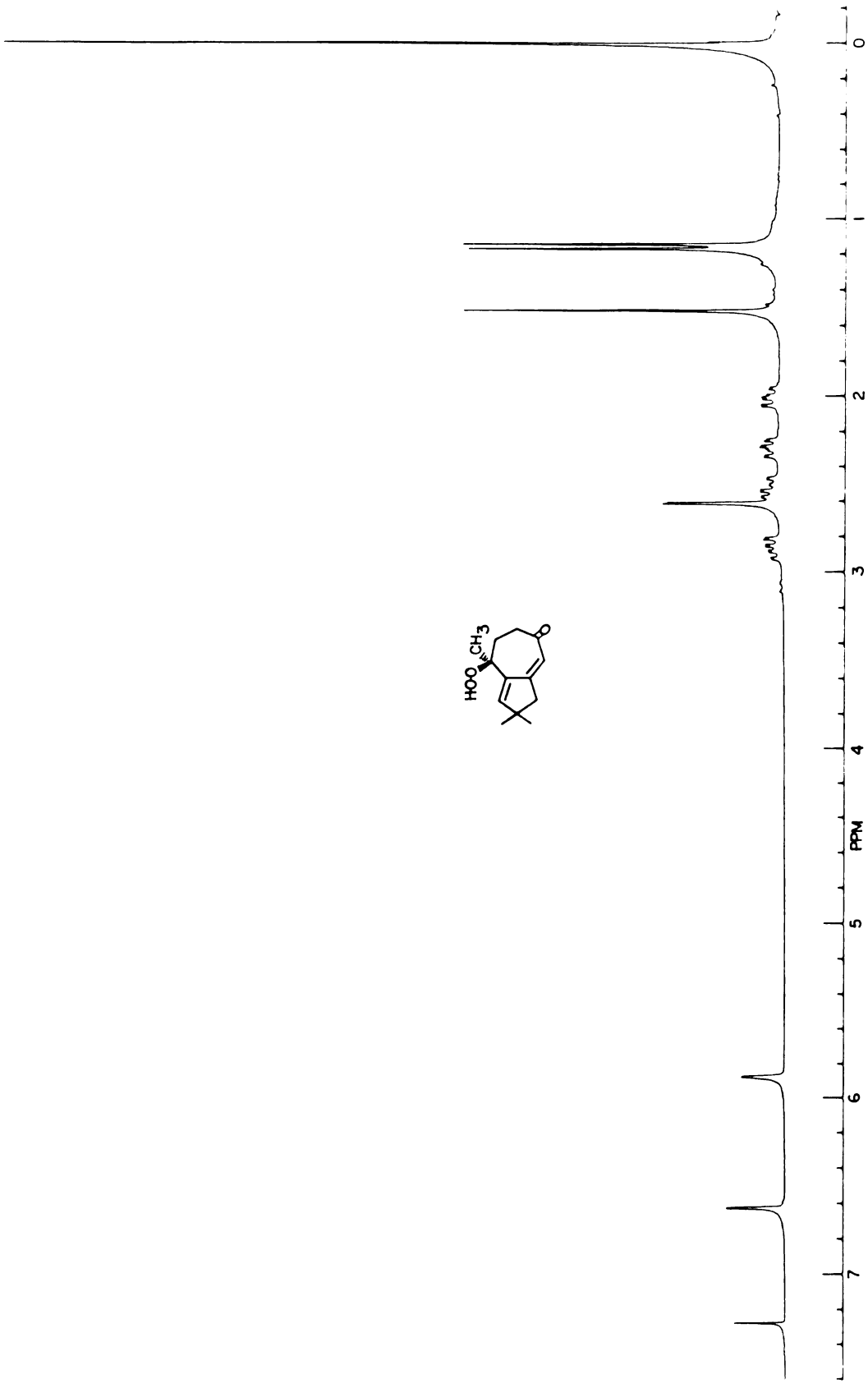


Figure II-50. Proton NMR of 48.

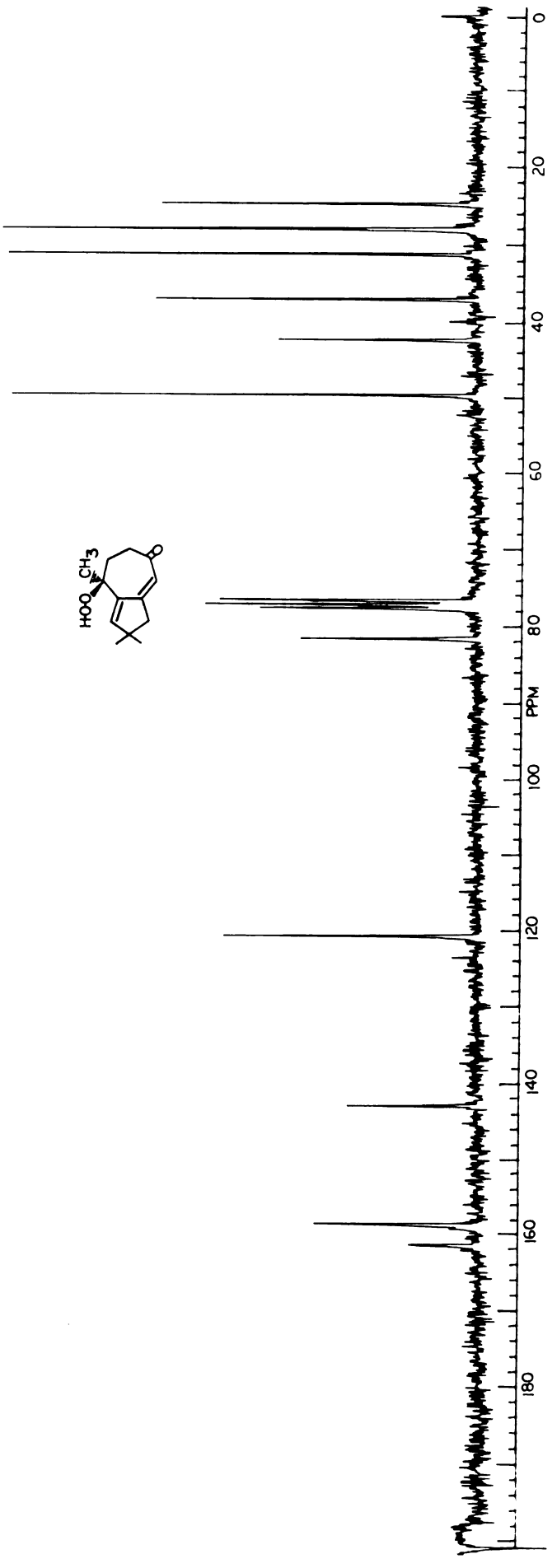


Figure II-51. Carbon-13 NMR of 48.

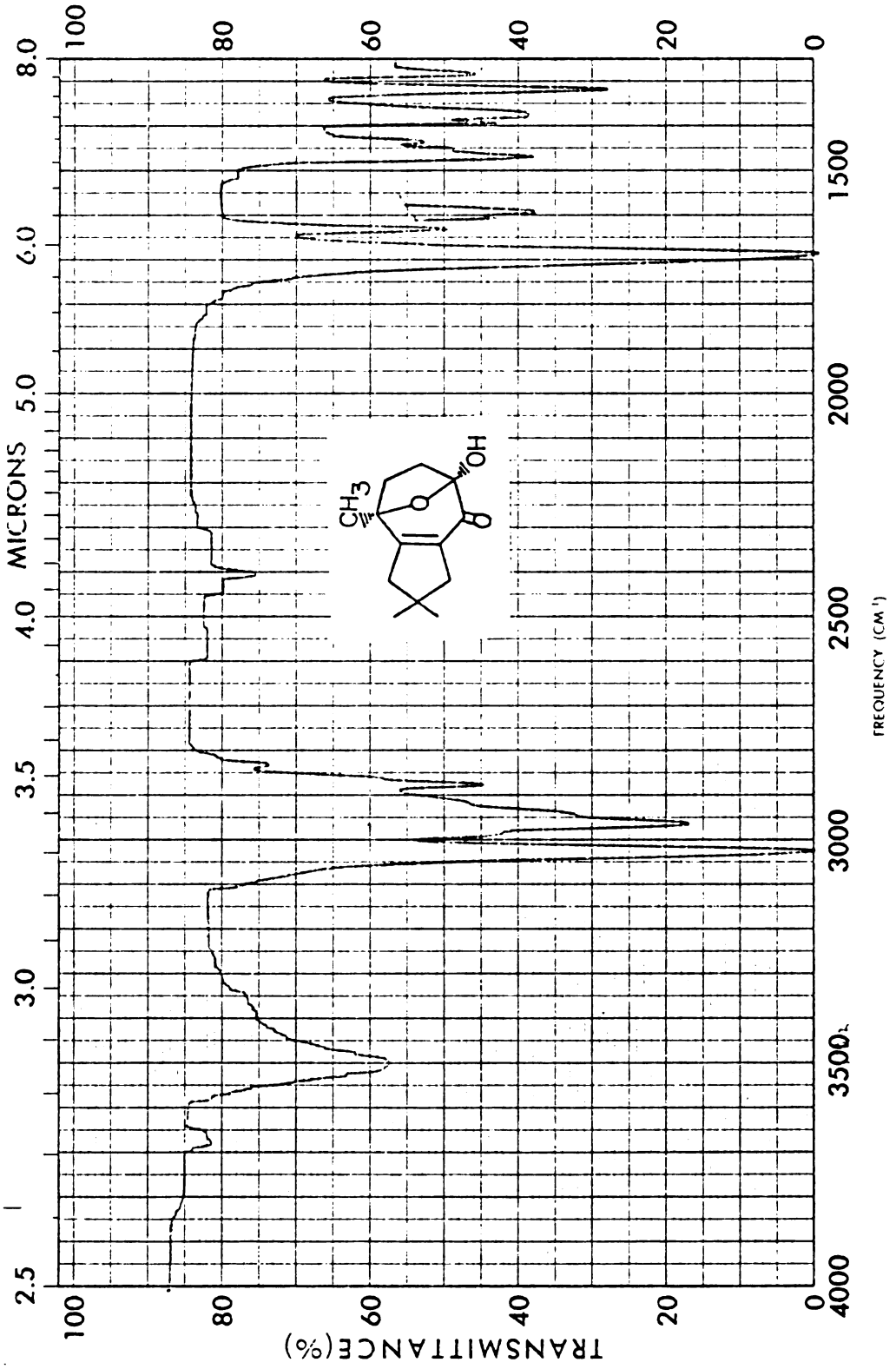


Figure II-52. IR of 54.

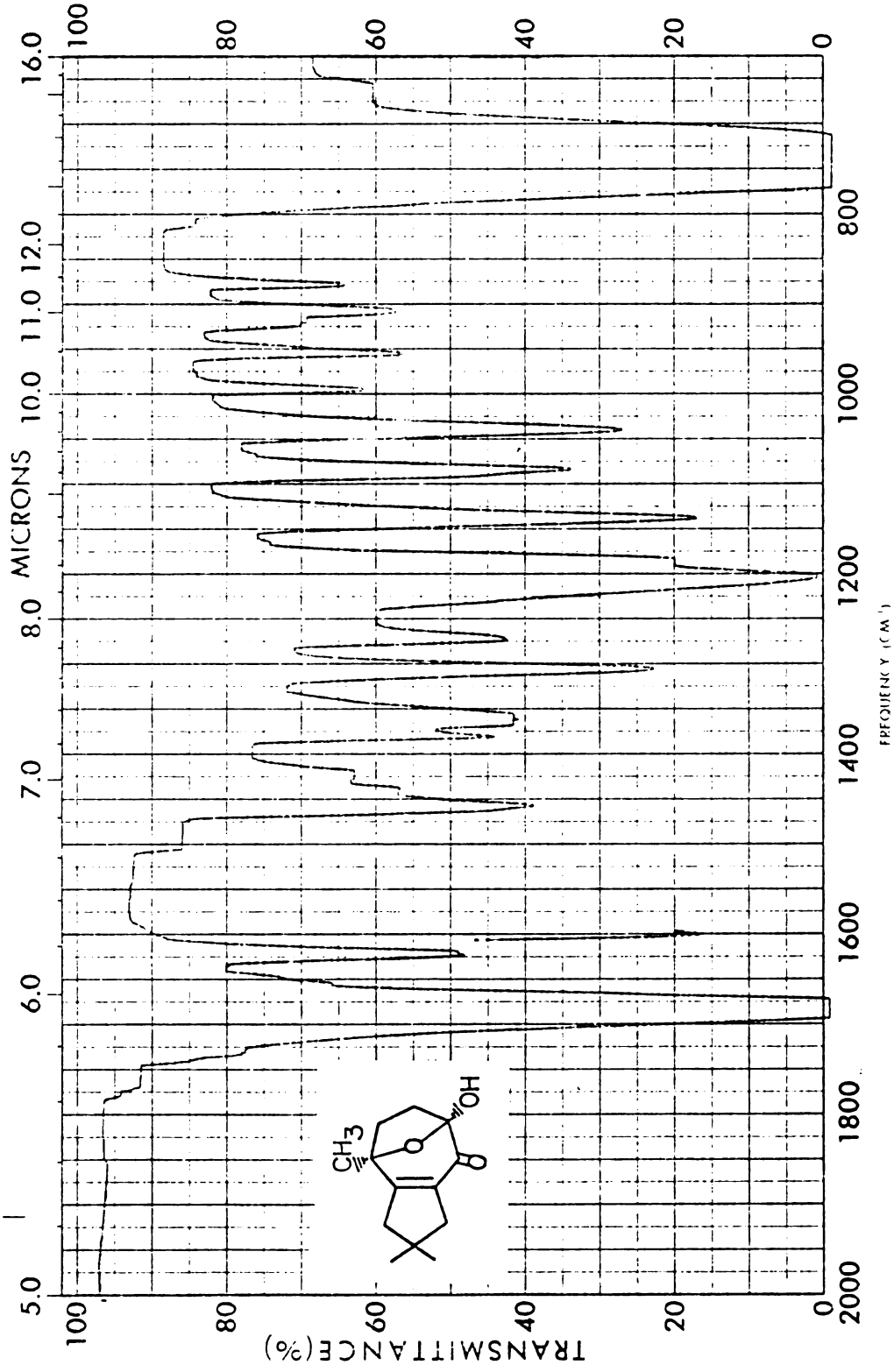


Figure II-53. IR of 54.

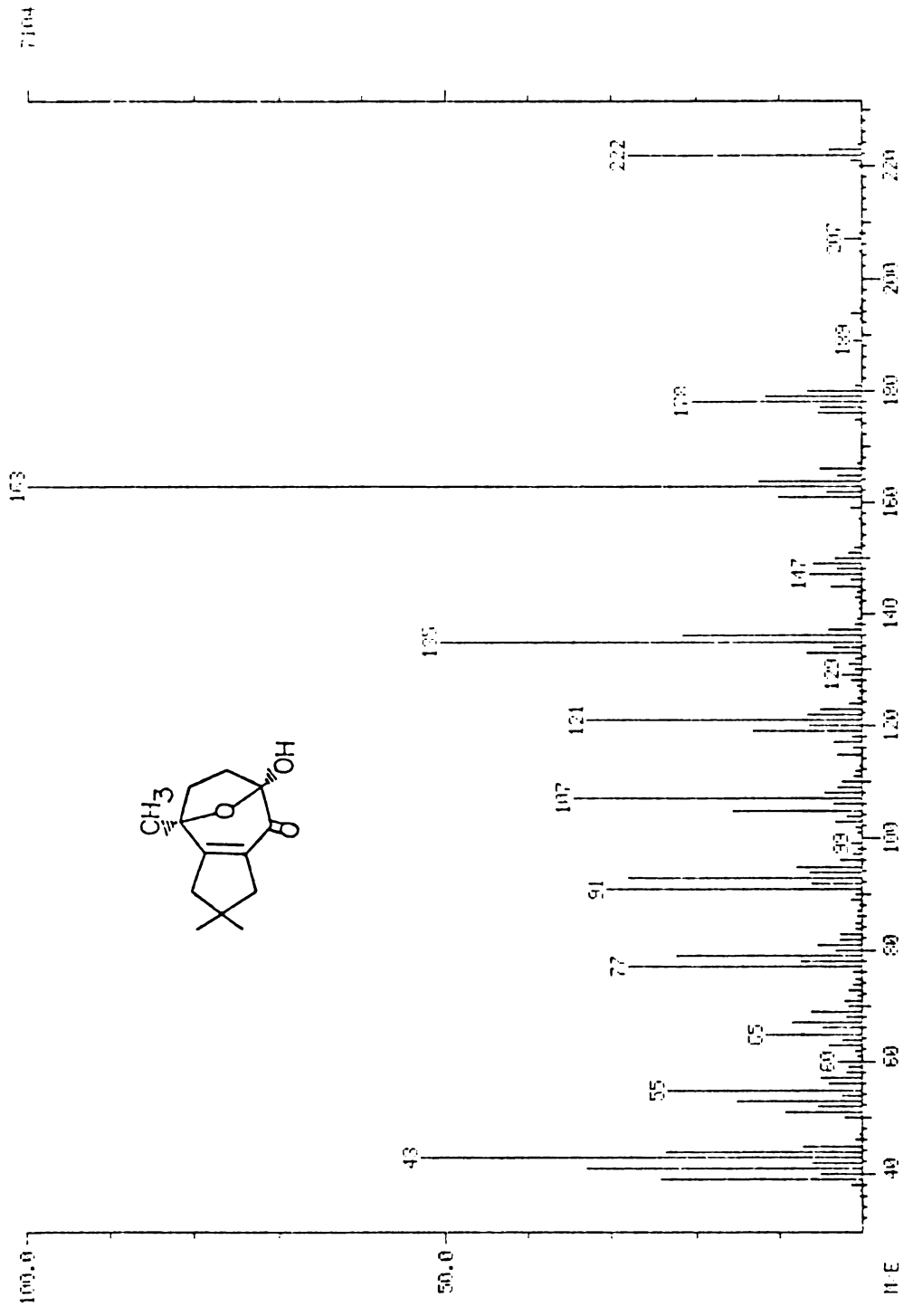


Figure II-54. Mass spectrum of 54.

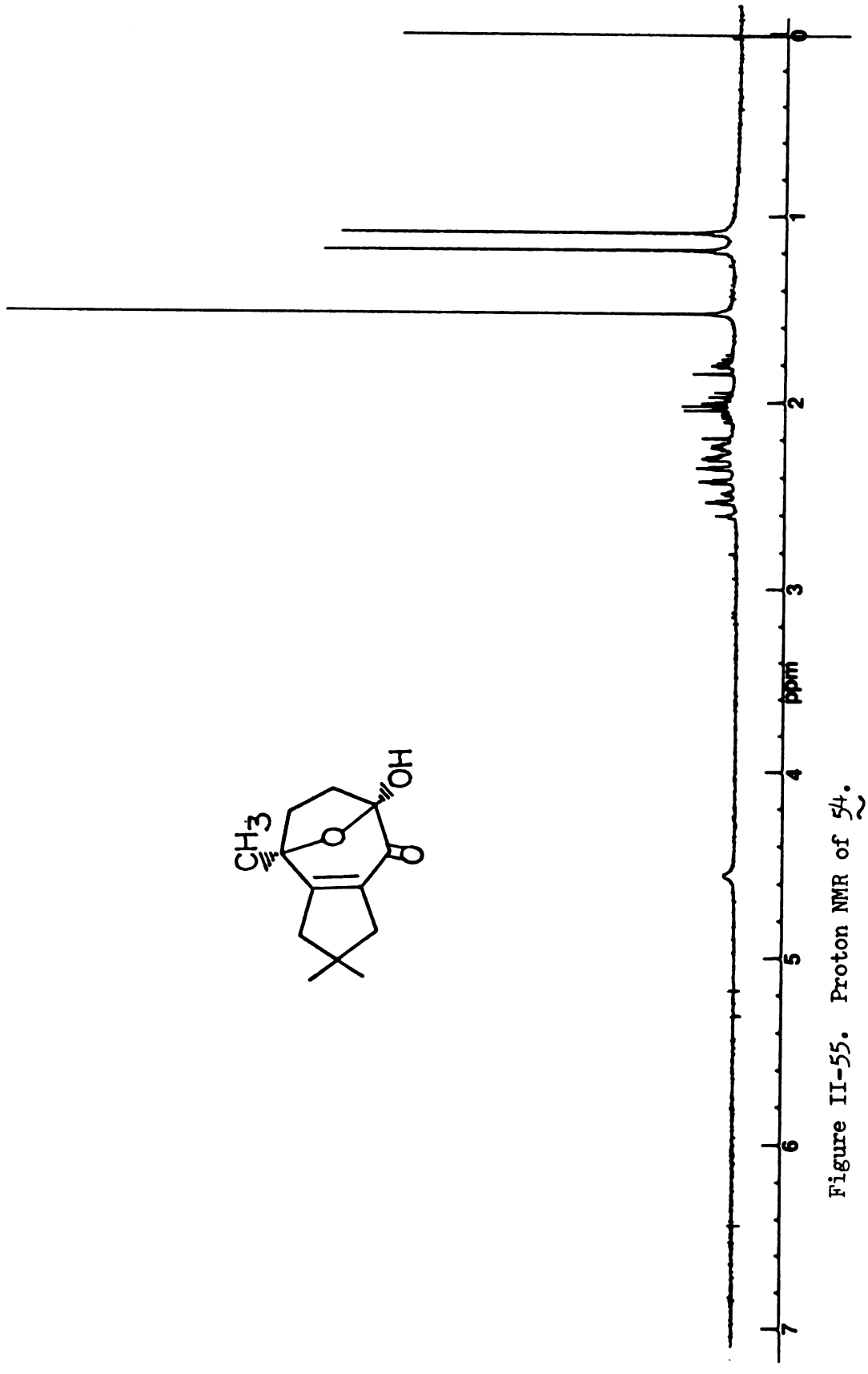


Figure II-55. Proton NMR of 54.

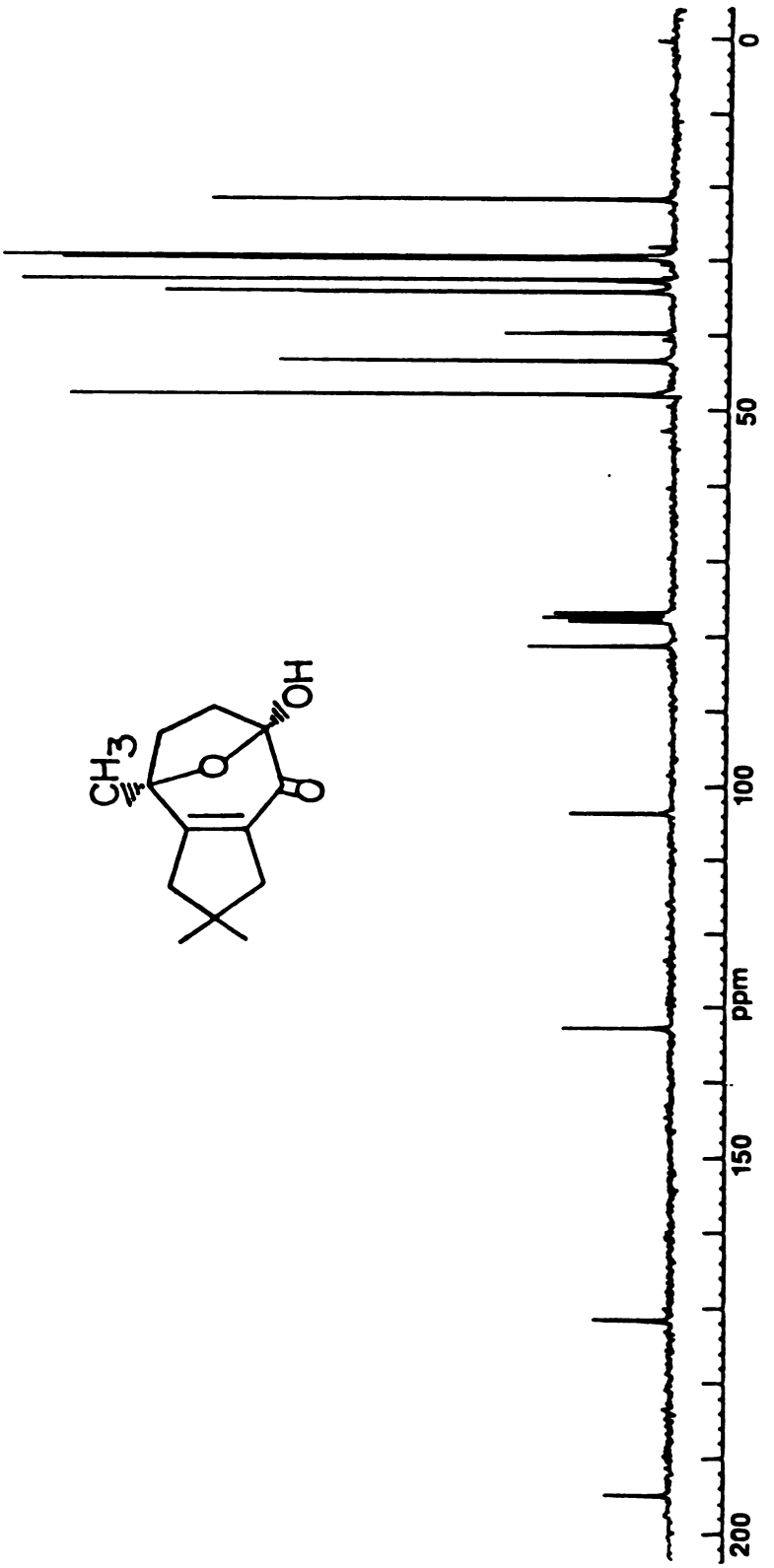


Figure II-56. Carbon-13 NMR of 54.

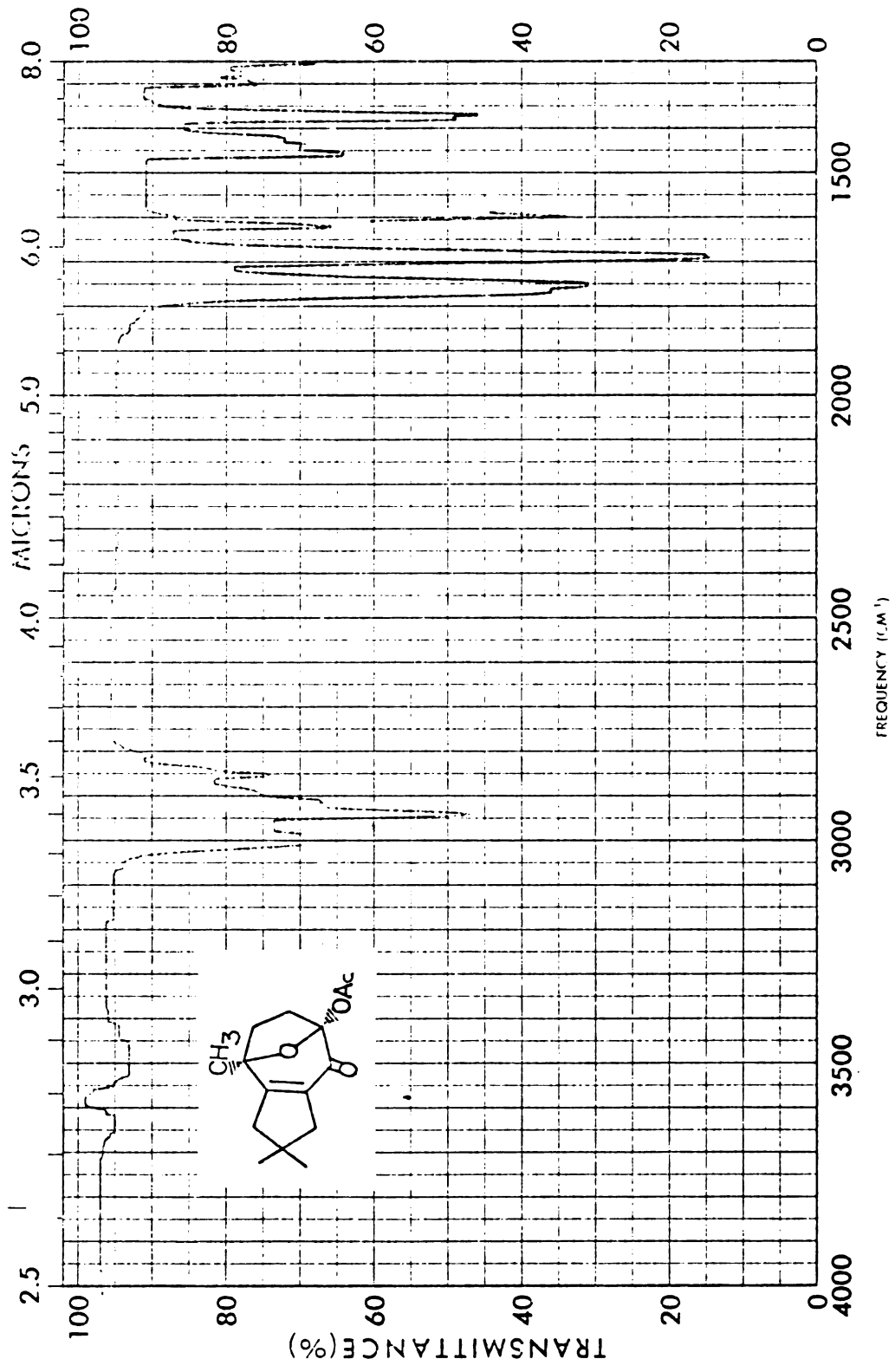


Figure II-57. IR of 55.

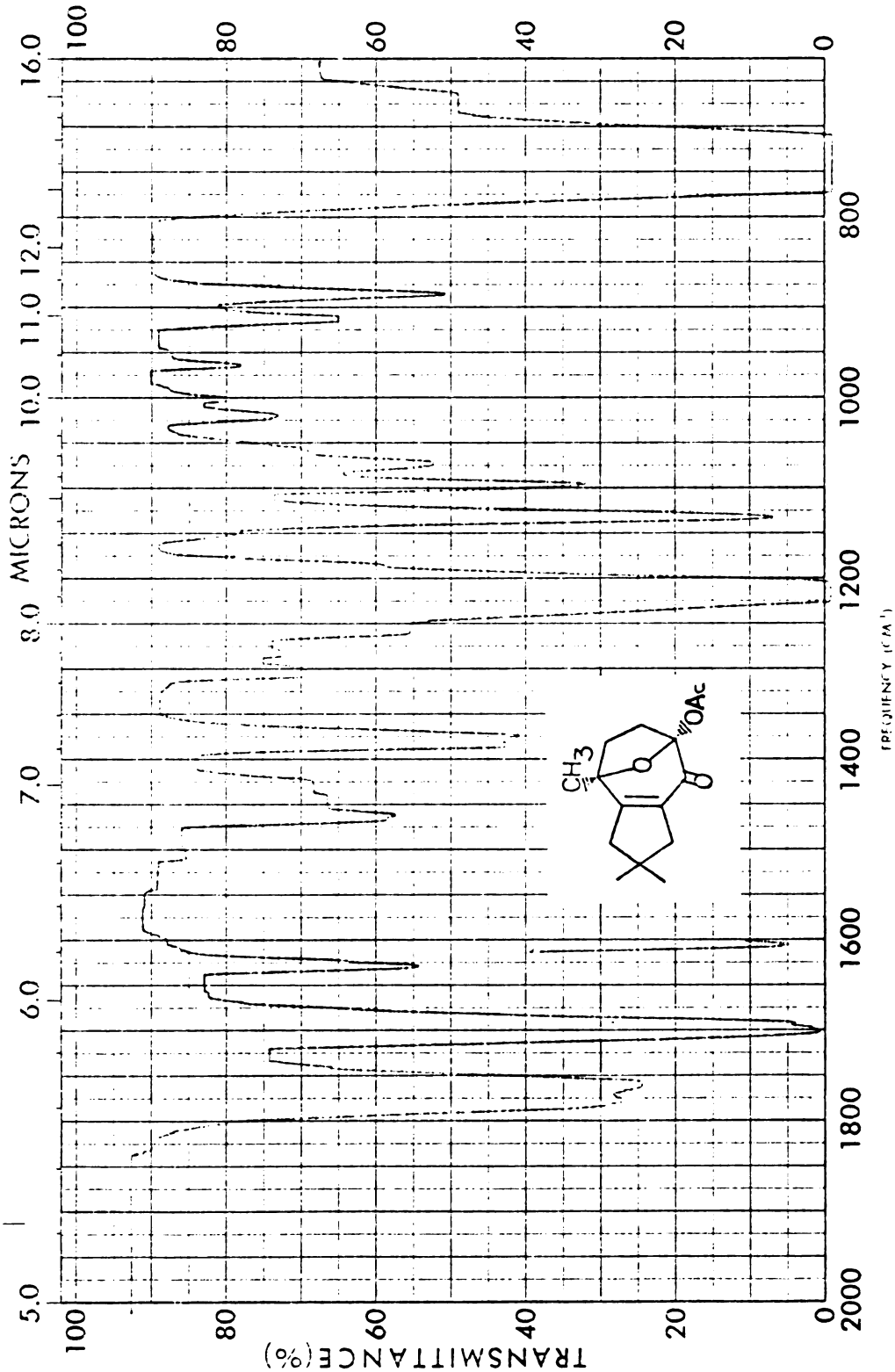


Figure II-58. IR of 55.

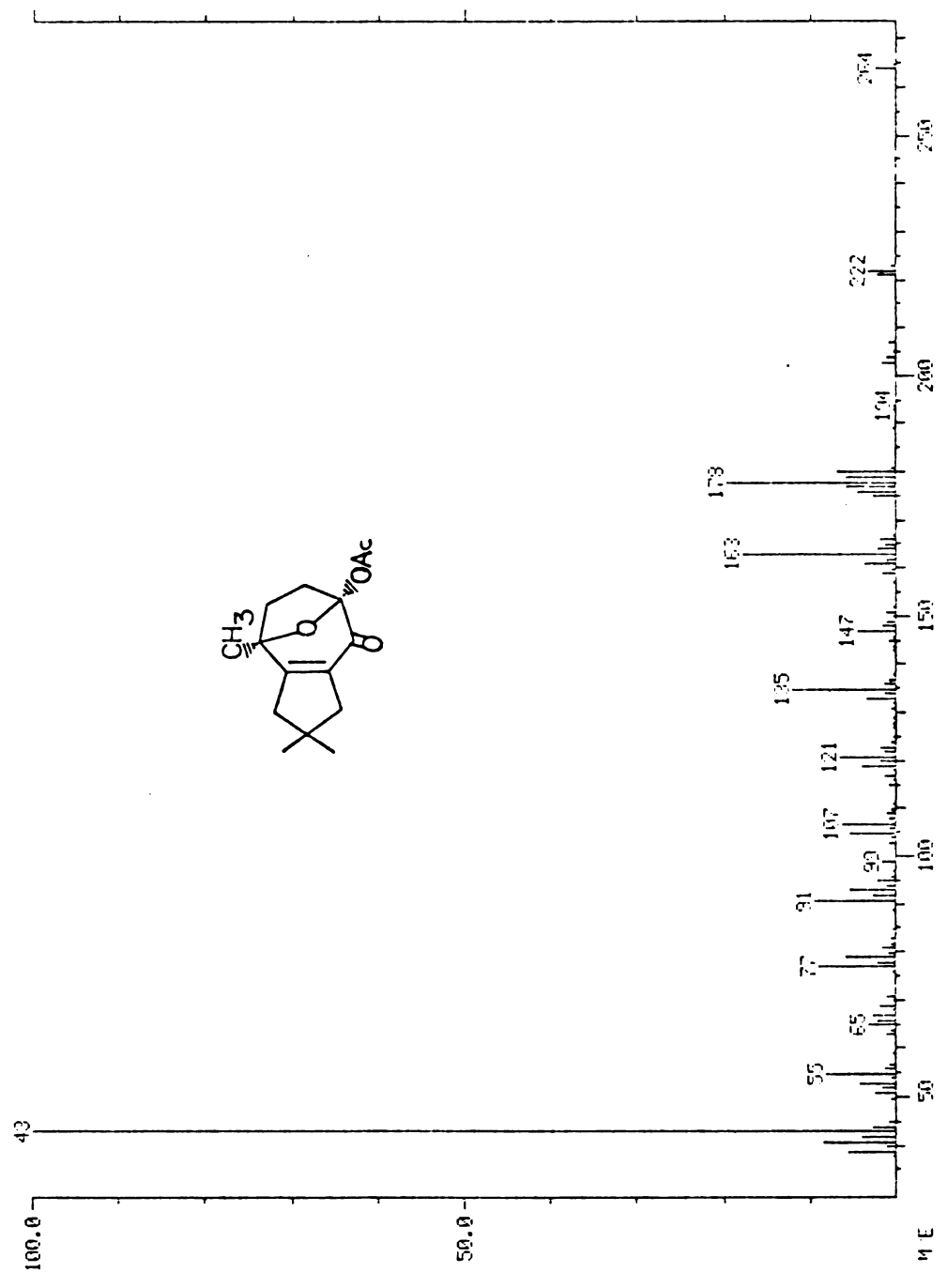


Figure II-59. Mass spectrum of 55.

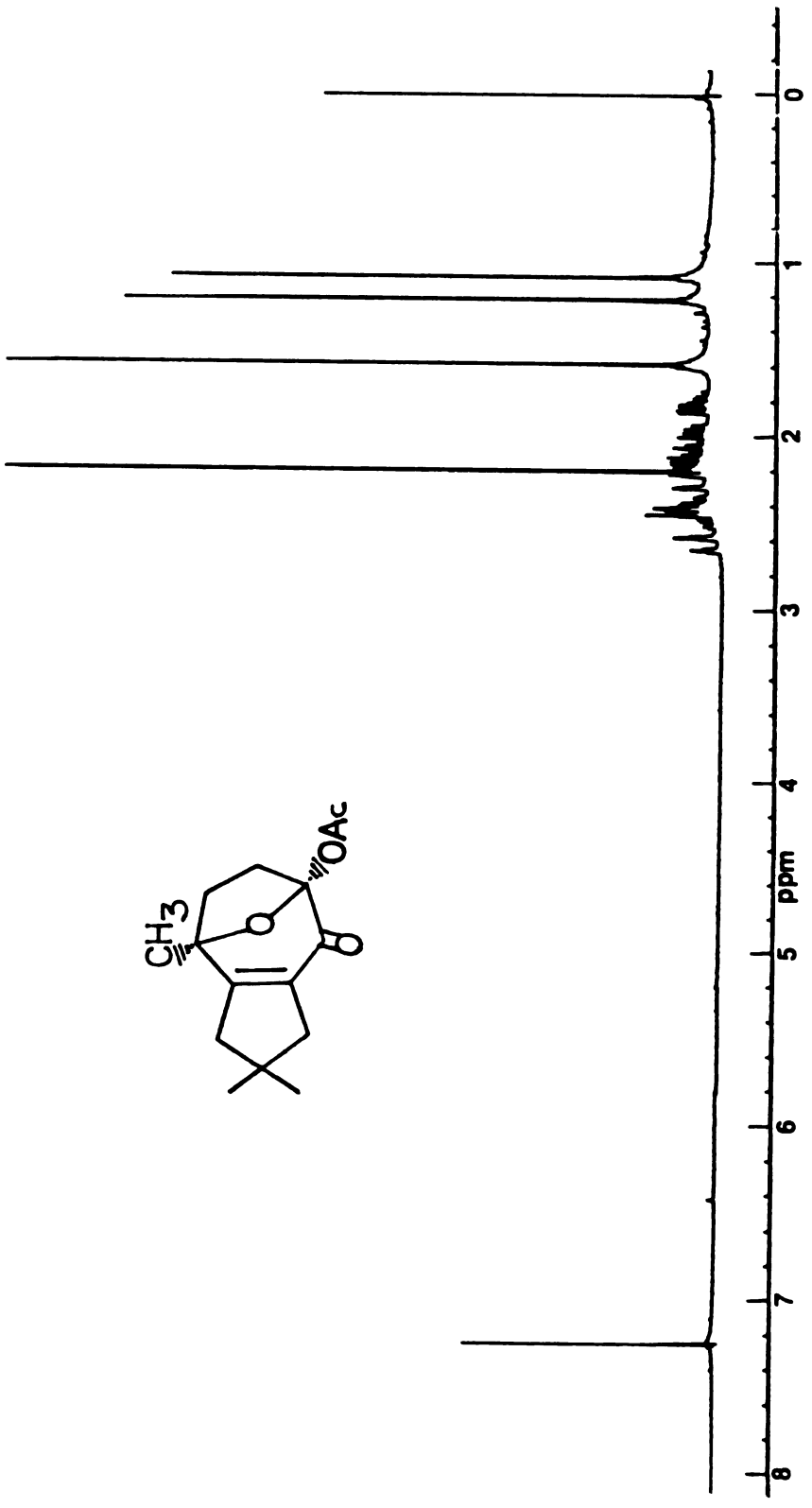


Figure II-60. Proton NMR of 55.

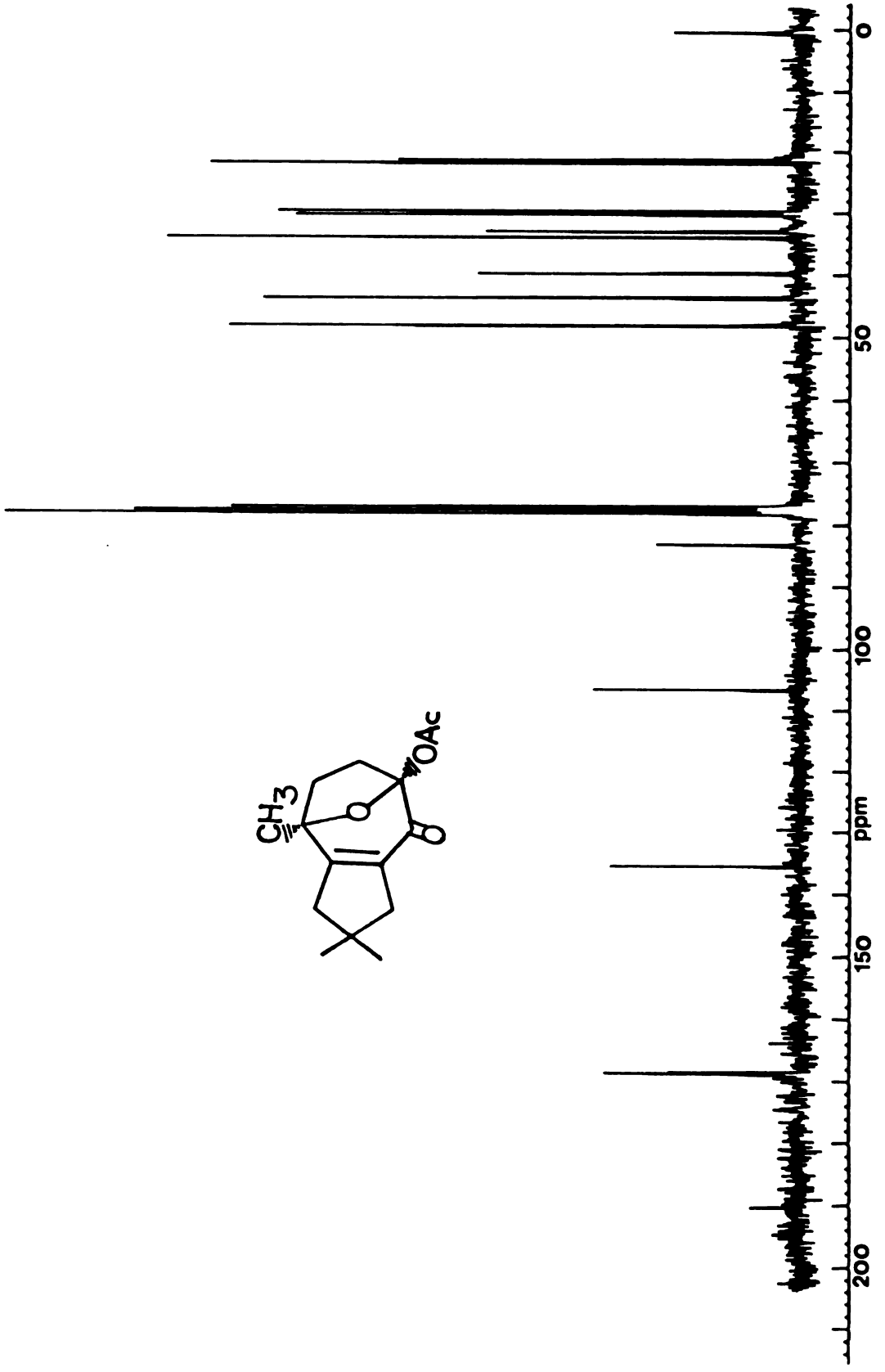


Figure II-61. Carbon-13 NMR of 55.

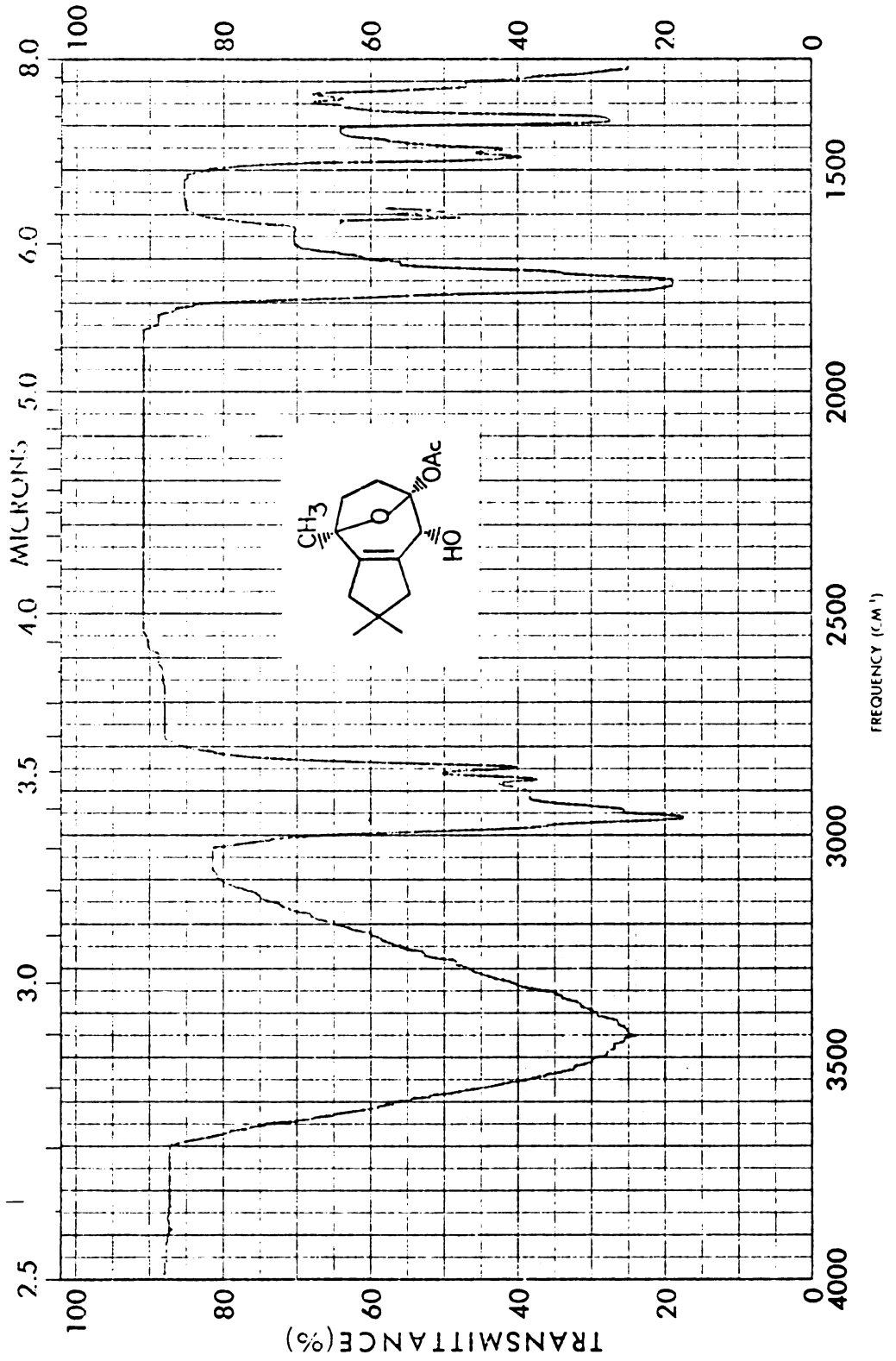


Figure II-62. IR of 56.

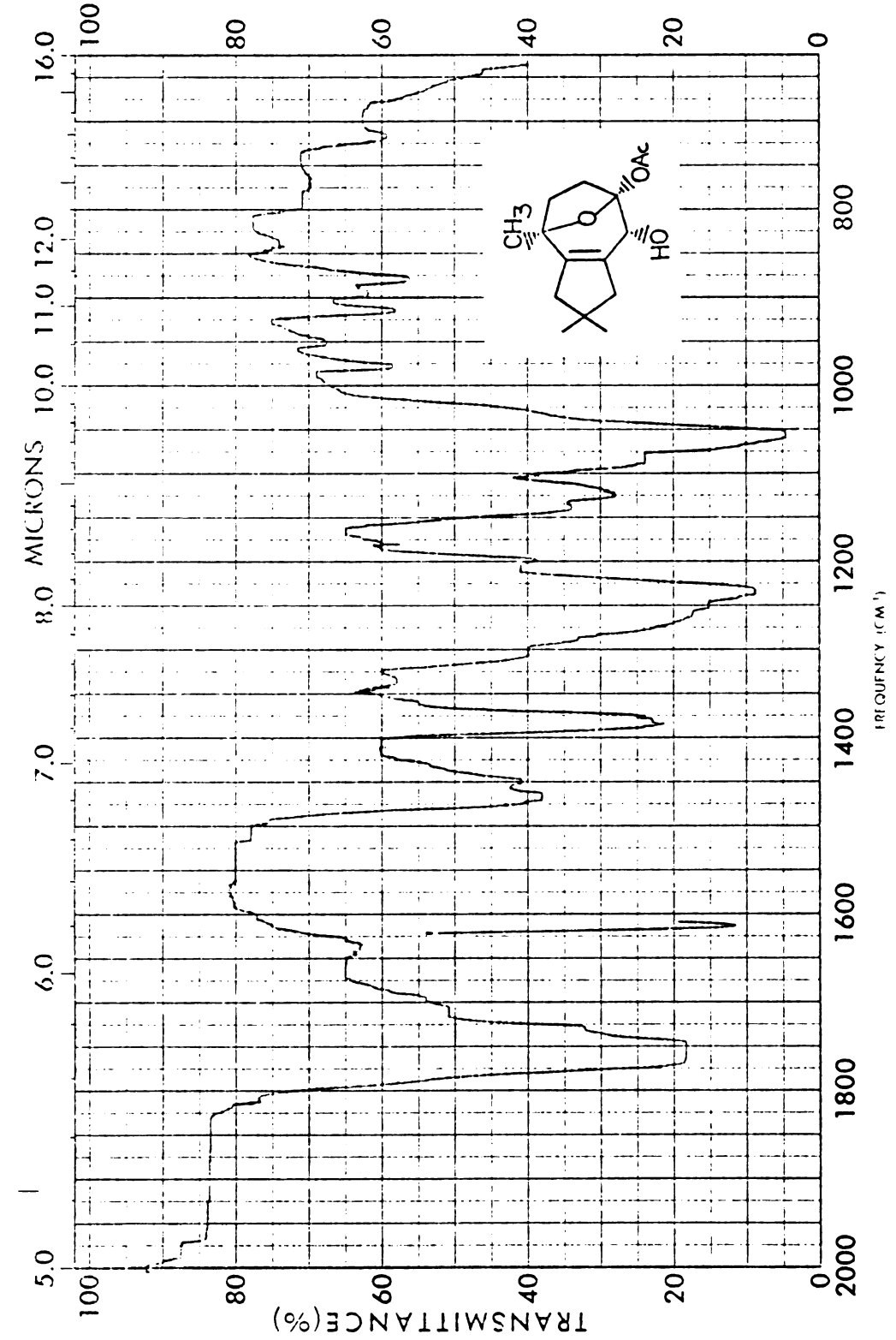


Figure II-63. IR of 56.

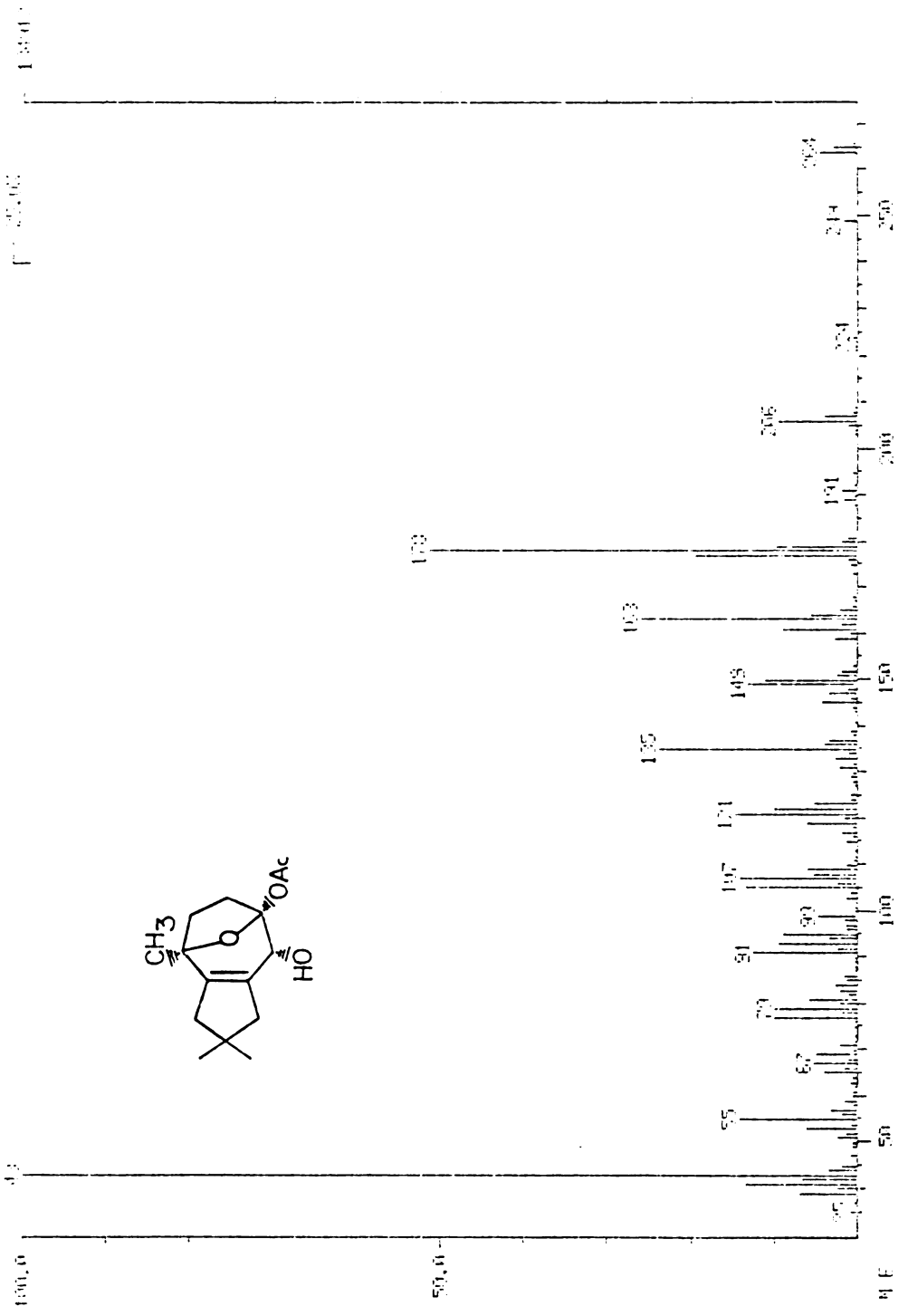


Figure II-64. Mass spectrum of 56.

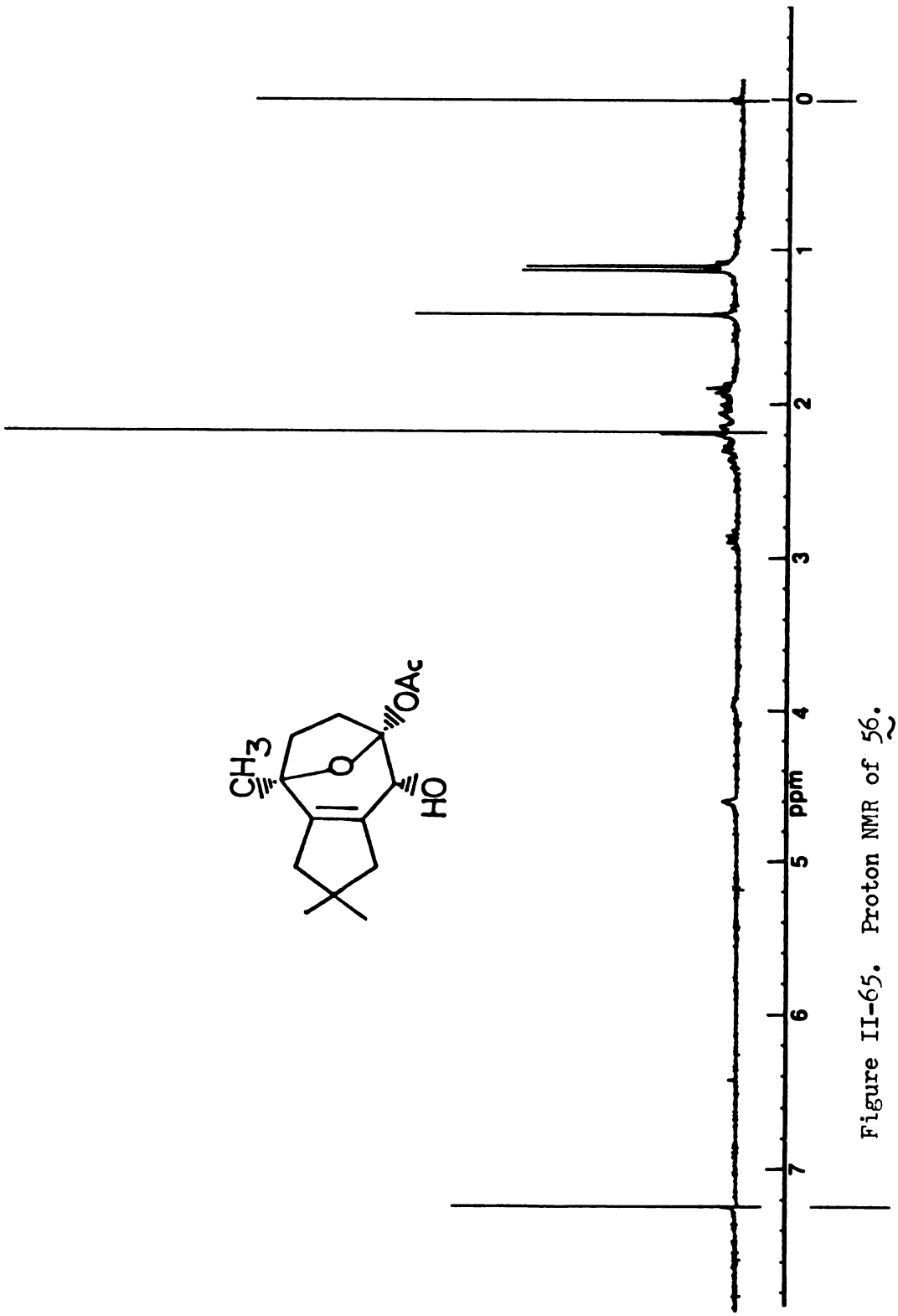


Figure II-65. Proton NMR of 56.

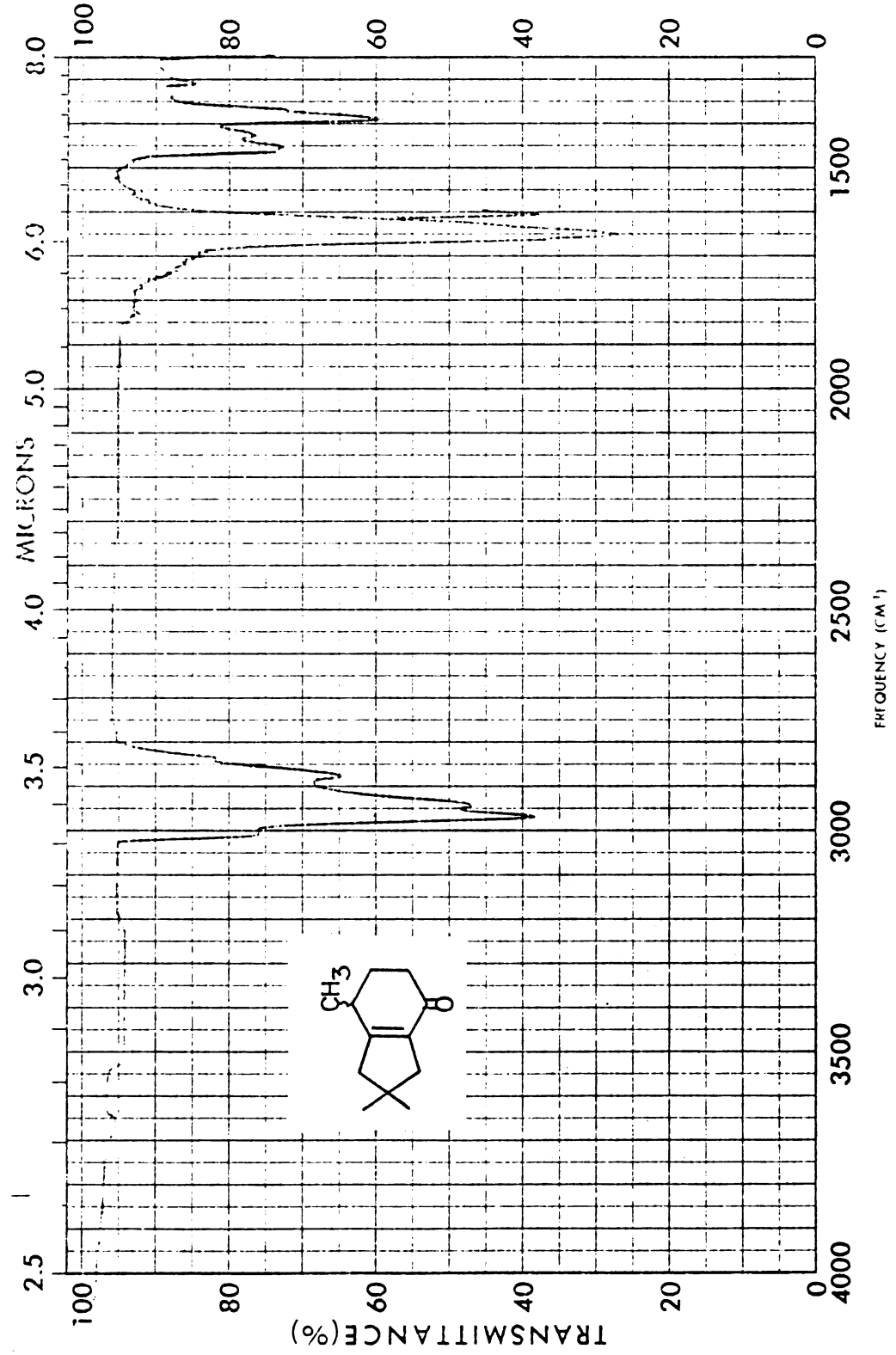


Figure II-66. IR of 57.

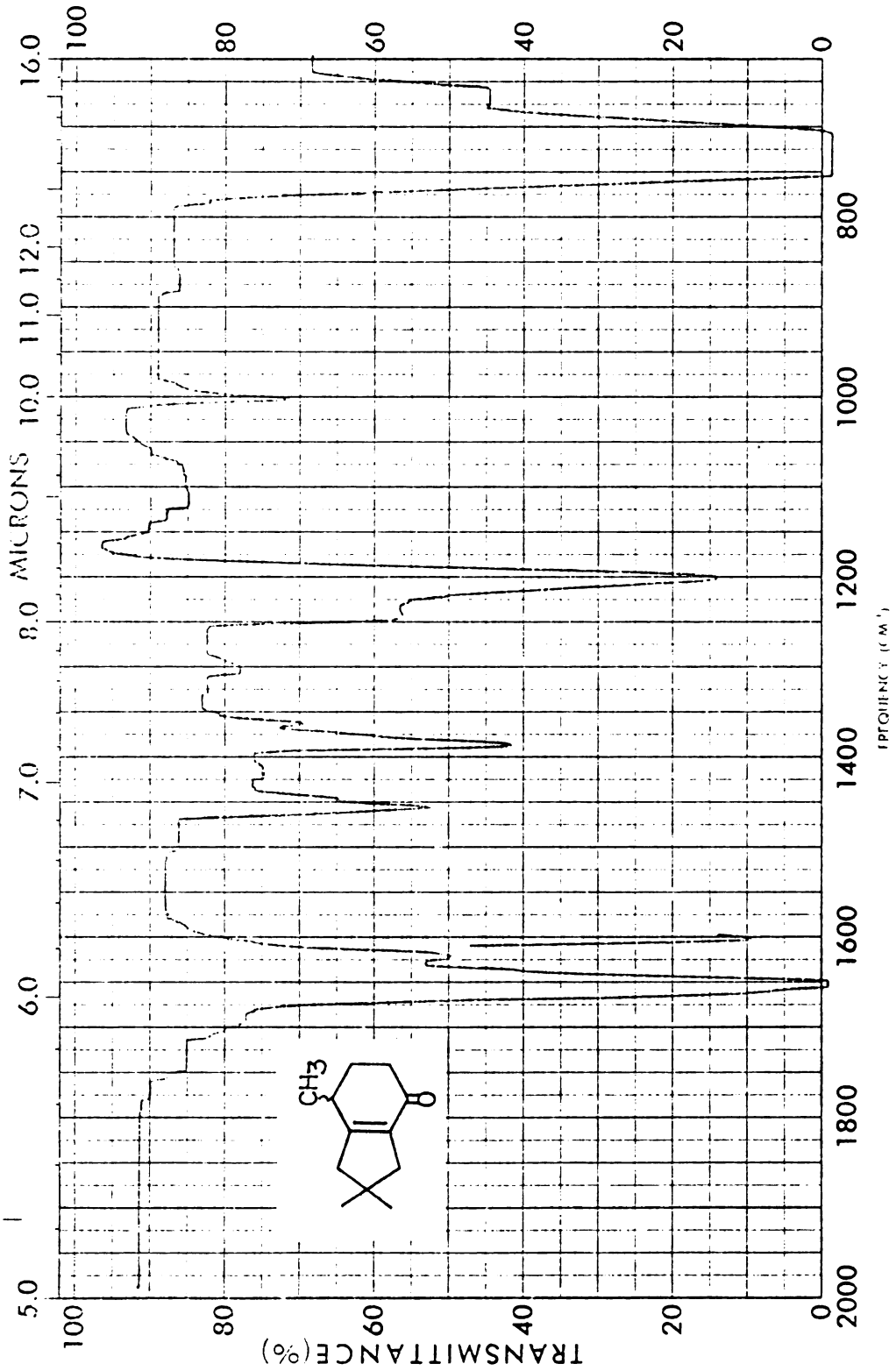


Figure II-67. IR of 57.

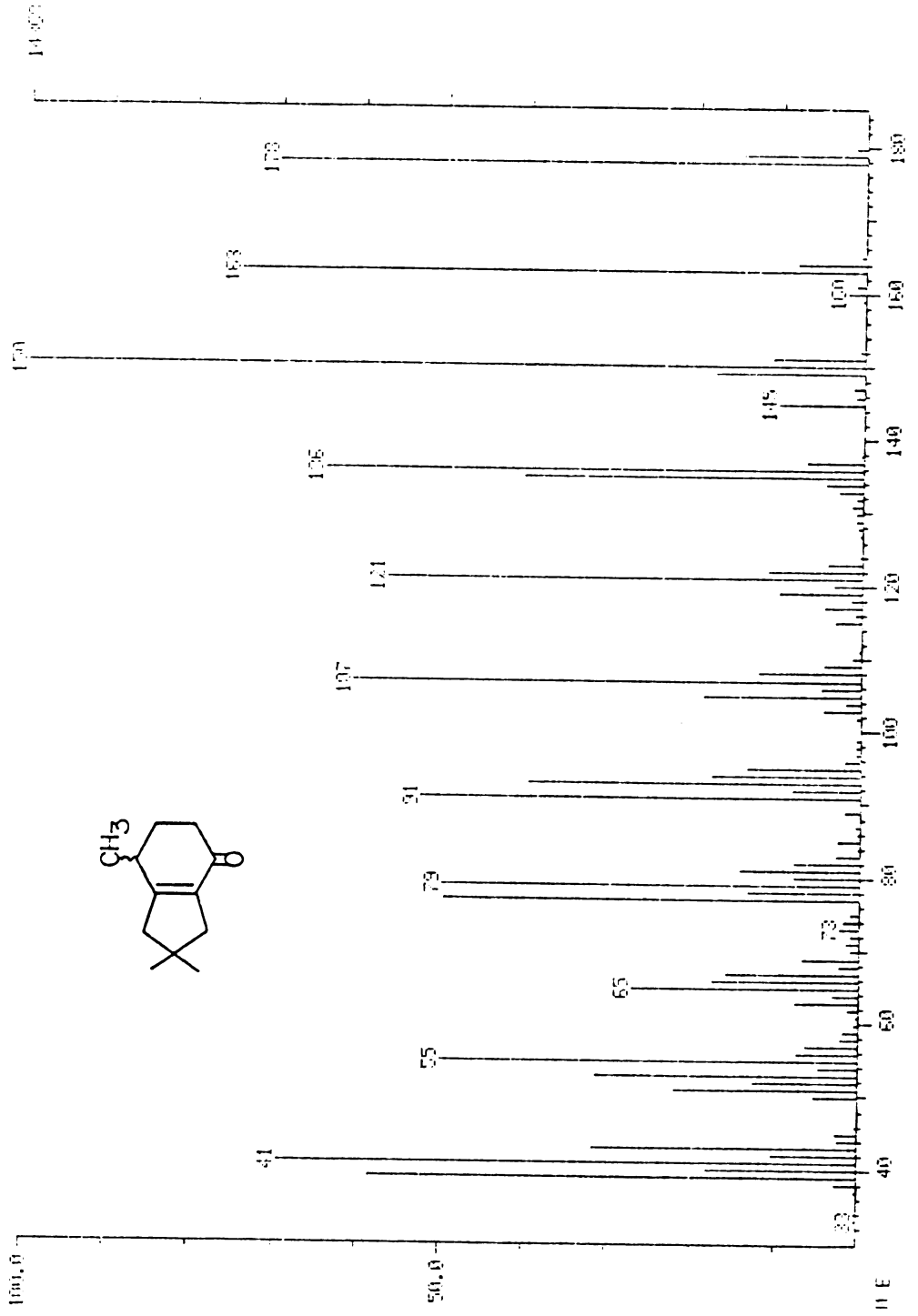


Figure II-68. Mass spectrum of 57.

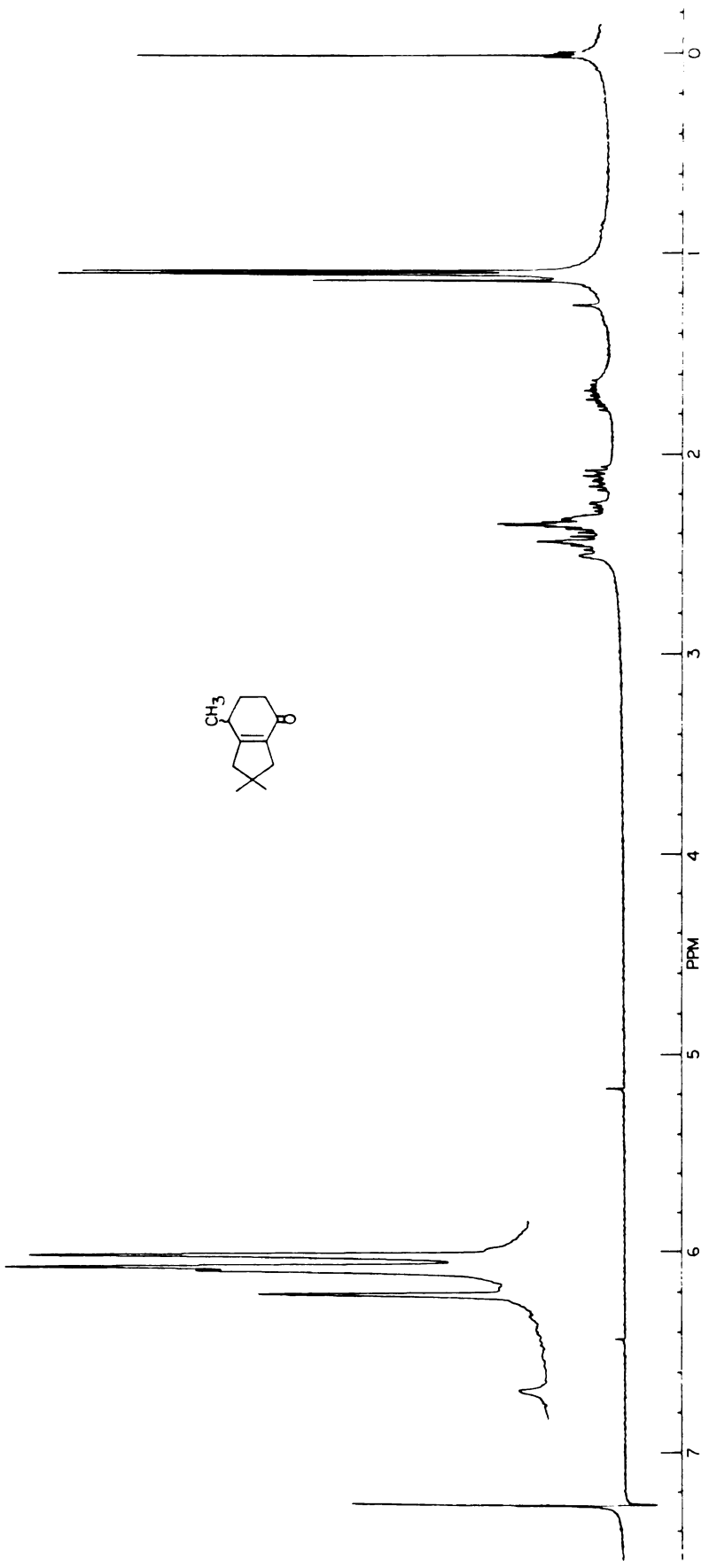


Figure II-69. Proton NMR of 57.

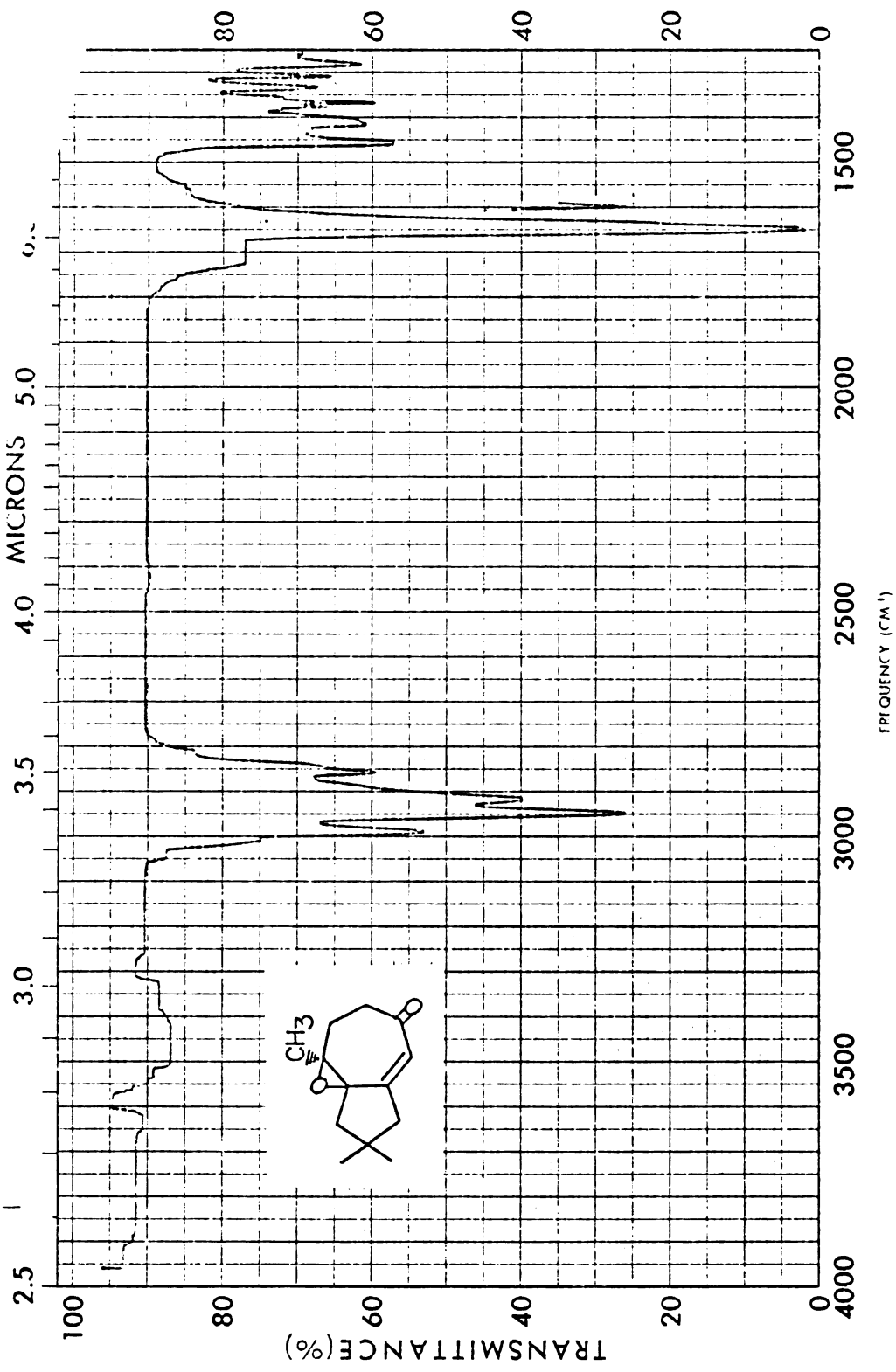


Figure II-70. IR of 59.

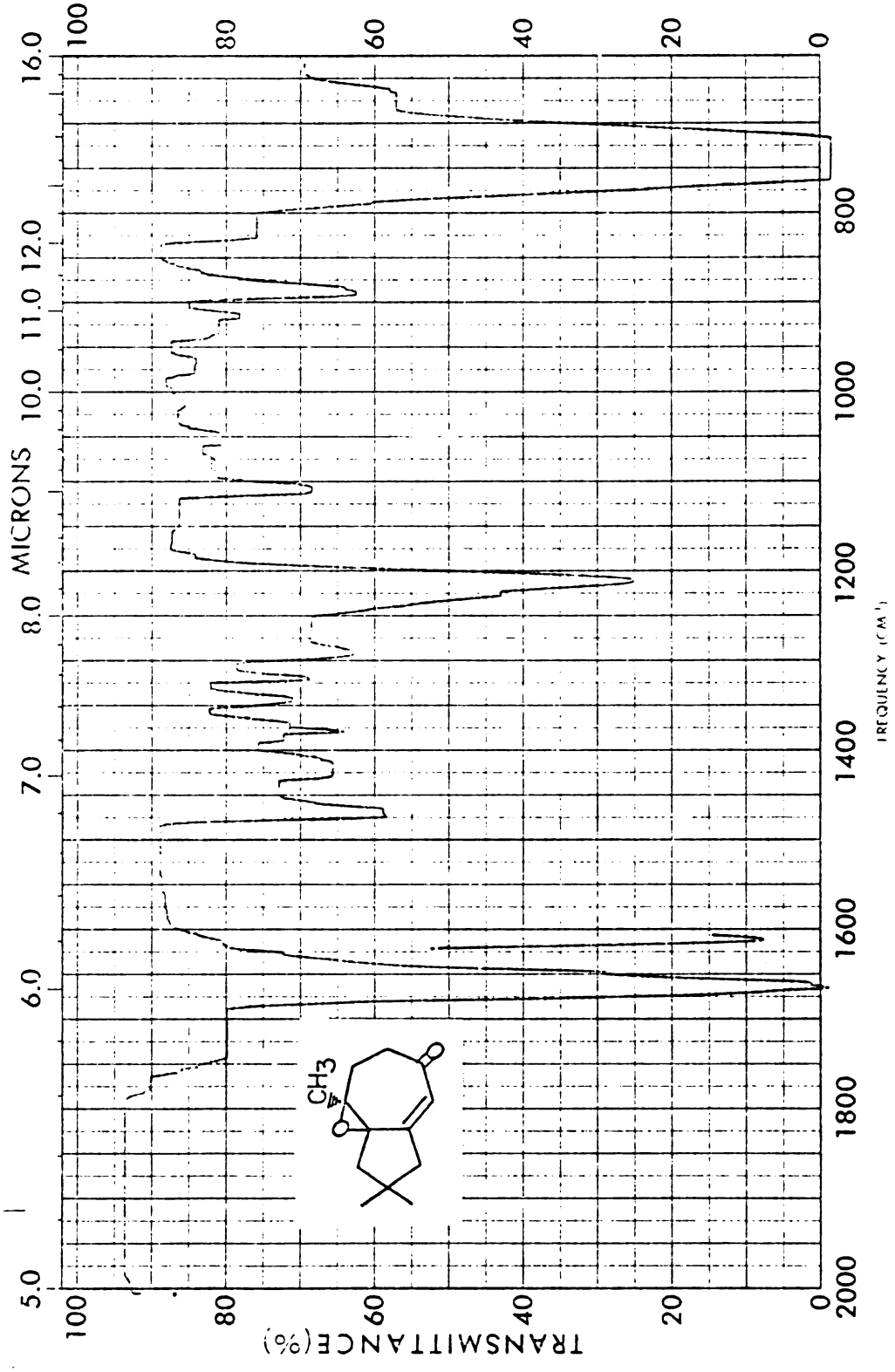


Figure II-71. IR of 59.

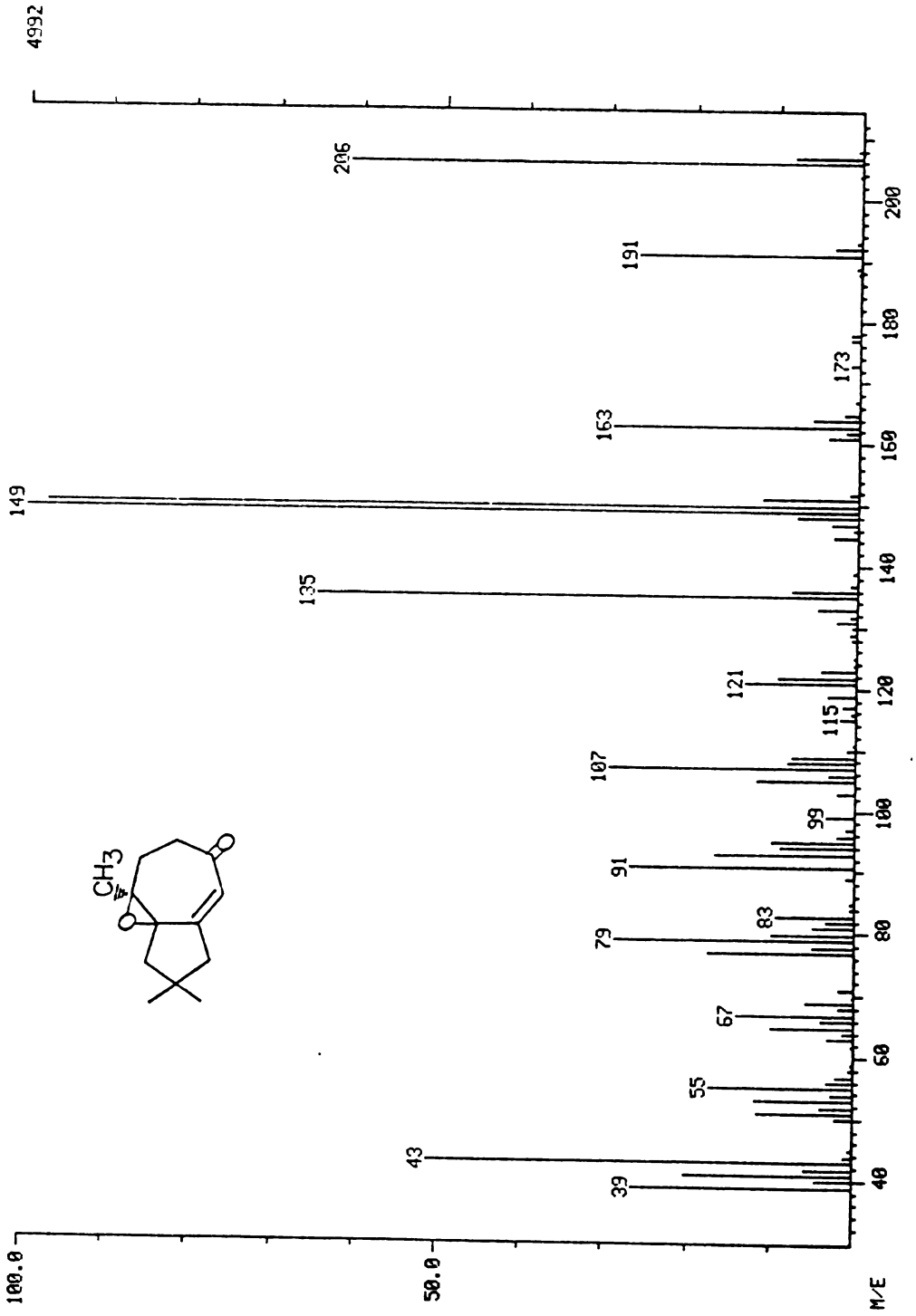


Figure II-72. Mass spectrum of 59.

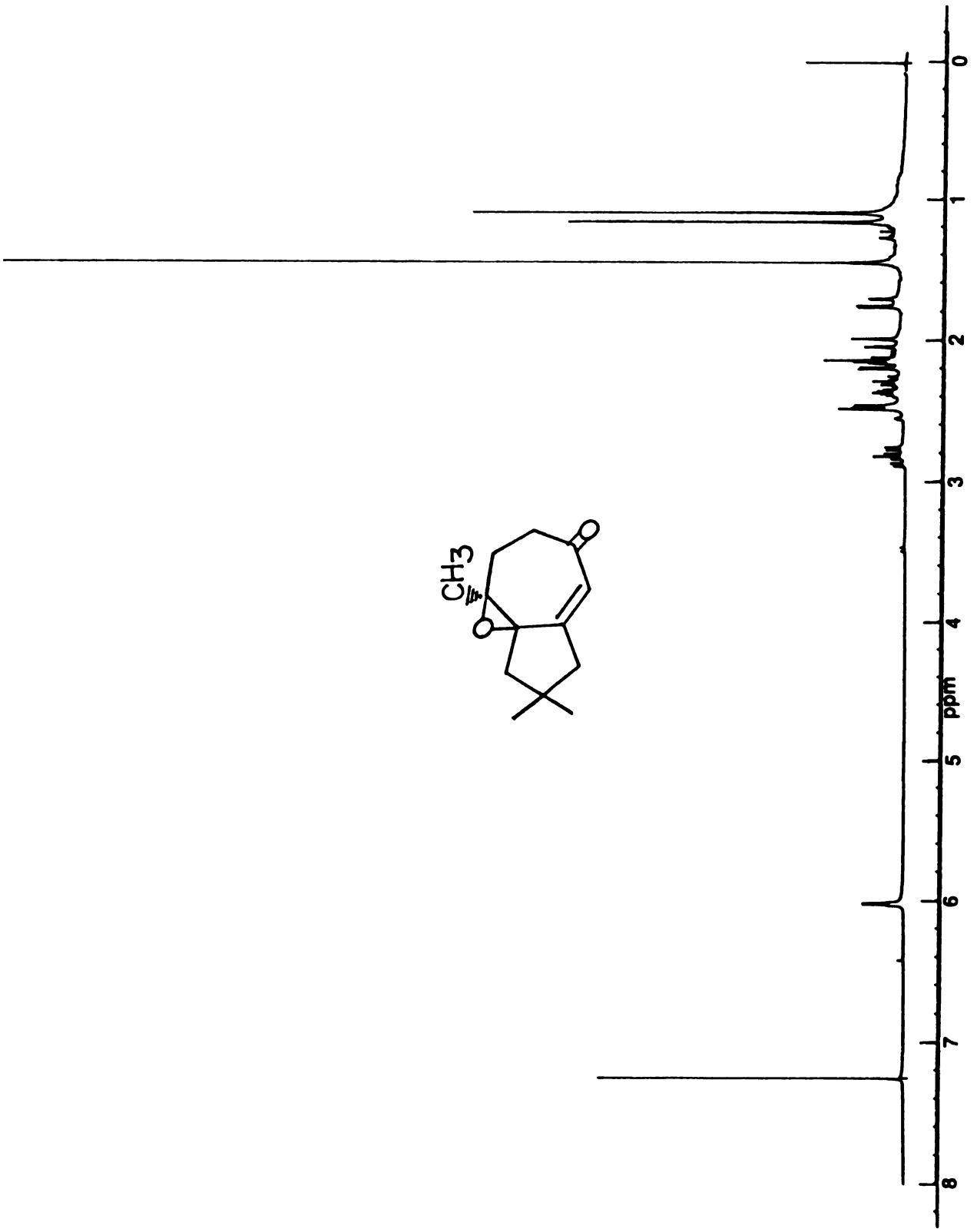


Figure II-73. Proton NMR of 59.

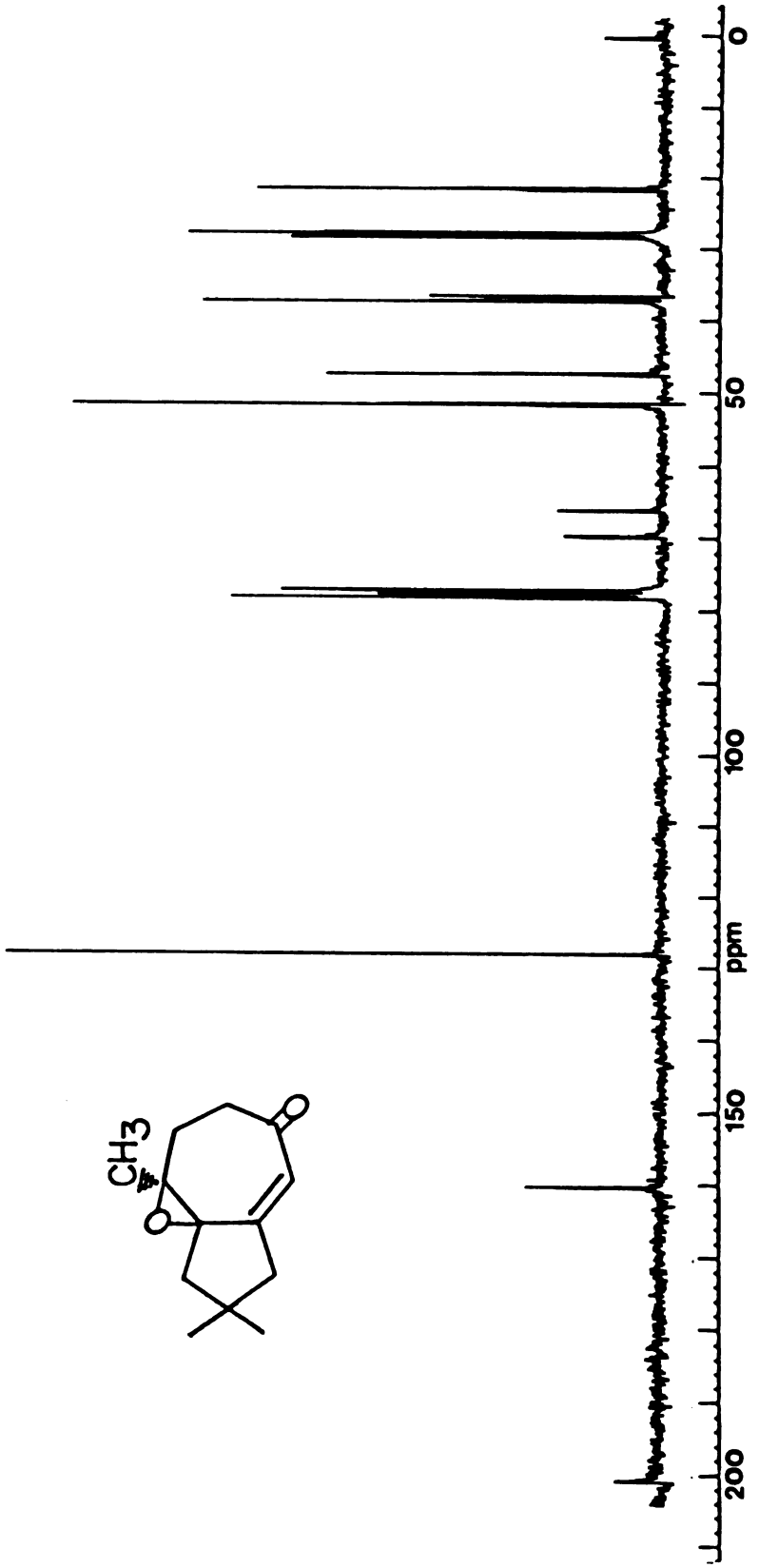


Figure II-74. Carbon-13 NMR of 59.

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