This is to certify that the

thesis entitled
PART I
STUDIES TOWARD THE TOTAL SYNTHESIS OF
A 14_a-METHYL ANALOG OF VITAMIN D
PART II
TYPE I PHOTO-REACTIONS OF BICYCLIC KETONES
presented by

JUNG-HWA SHAU

has been accepted towards fulfillment
of the requirements for

Ph.D. degree in Chemistry

William H. Reusch
Major professor

Date 9/7/'79

O-7639


MICHIGAN STATE UNIVERSITY

PART I

STUDIES TOWARD THE TOTAL SYNTHESIS OF A 14α-METHYL ANALOG OF VITAMIN D

PART II

TYPE I PHOTO-REACTIONS OF BICYCLIC KETONES

By

Jung-Hwa Shau

A DISSERTATION

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

DOCTOR OF PHILOSOPHY

Department of Chemistry

1979

ABSTRACT

PART I

STUDIES TOWARD THE TOTAL SYNTHESIS OF A 14α-METHYL ANALOG OF VITAMIN D

PART II

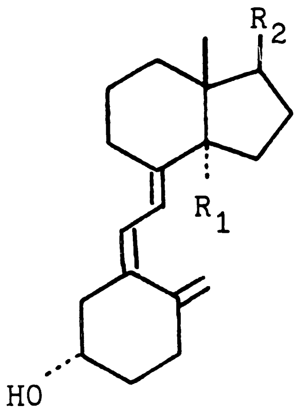
TYPE I PHOTO-REACTIONS OF BICYCLIC KETONES

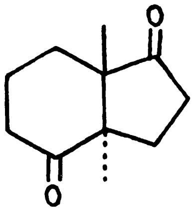
By

Jung-Hwa Shau

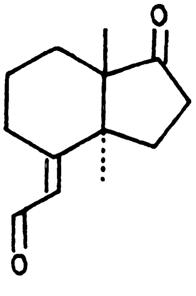
PART I

Two strategies have been tried to synthesize the 14α-methyl analog **1** of vitamin D, **2**. In the first approach, reaction between perhydroindene-dione **3** and trimethylsilylated aldimine **4** followed by acid hydrolysis gave α,β-unsaturated aldehyde **5**.





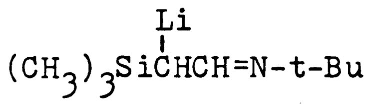
3



5

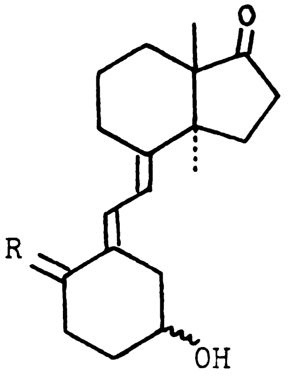
1 $R_1 = CH_3$, $R_2 = O$

2 $R_1 = H$, $R_2 = C_9H_{17}$
or C_8H_{17}



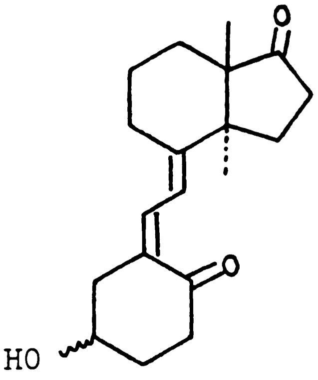
$(CH_3)_3Si\overset{Li}{\overset{|}{C}}HCH{=}N\text{-}t\text{-}Bu$

4



6 R = O

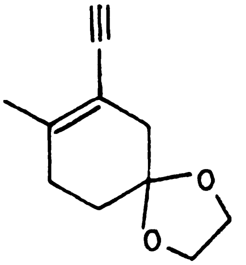
8 R = CH_2



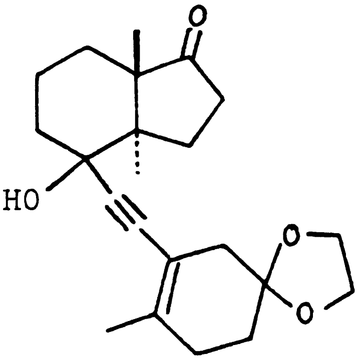
7

Aldol condensation of **5** with 4-hydroxycyclohexanone provided dienone **6** and a small amount of bis-condensation product. Photoisomerization of the central double bond ended up with a 1:1 mixture of **6** and **7**. Treatment of **6** with triphenylphosphonium methylide gave olefin **8**, which is a 14α-methyl analog of 5,6-trans-vitamin D.

In the second approach, acetylenic ketal **9** was prepared from 1,3-cyclohexanedione by four steps. There was no significant reaction between dione **3** and anion of **9** under conditions established by model studies. This problem has finally been solved by complexation of the carbonyl function in **3** with lithium iodide prior to the addition of nucleophile. Adduct **10** obtained from this reaction was a precursor of **1**.



9



10

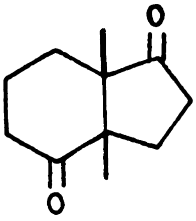
Jung-Hwa Shau

PART II

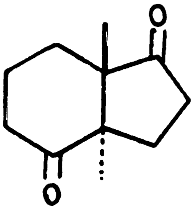
In order to synthesize cis-1,6-dimethyl[4·3·0]nonane-2,7-dione 1, Norrish type I reactions of diketone 2, alcohol 3 and acetate 4 have been studied.

Photolyses of these compounds in various solvents yielded the corresponding cis-isomers and products via ketene intermediates, such as ester 5, lactone 6, amide 7, etc.

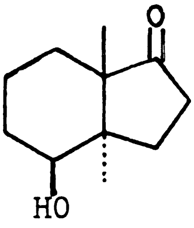
It was surprising to find out that α-cleavage of the six-membered ketone is favored in the photolysis of 2. Since the cis-isomer of acetate 4 was obtained in highest yield, it was hydrolyzed, and then oxidized to give the desired compound 1. The chromatographic and spectroscopic properties of these epimers were compared.



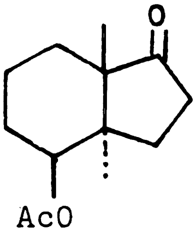
1



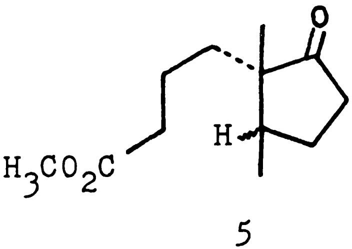
2



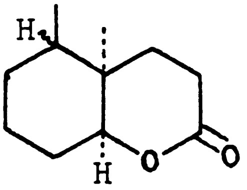
3



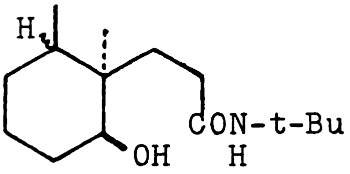
4



5



6



7

DEDICATION

This dissertation is dedicated to my parents.

ACKNOWLEDGMENTS

The author is deeply grateful to Professor William H. Reusch for his guidance, enthusiasm and encouragement during the course of this work.

Appreciation is extended to my colleagues for their friendship and discussion. Special thanks are also extended to my sisters and other friends for their love and concern.

The author acknowledges the financial support from the National Institutes of Health and the Department of Chemistry at Michigan State University.

TABLE OF CONTENTS

Page

PART I

TABLE OF CONTENTS --continued

Page

PART II

LIST OF FIGURES

Figure # Page

PART I

LIST OF FIGURES--continued

PART II

LIST OF FIGURES--continued

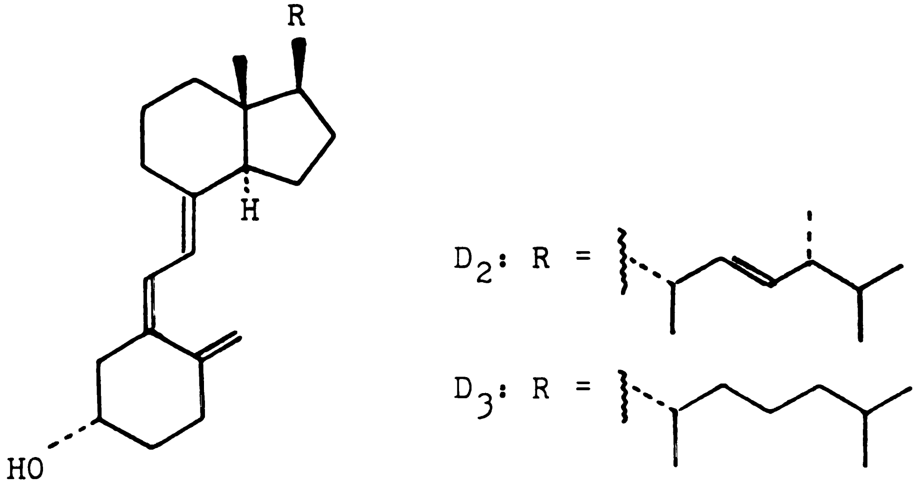
LIST OF TABLES

PART I

STUDIES TOWARD THE TOTAL SYNTHESIS OF A 14α-METHYL ANALOG OF VITAMIN D

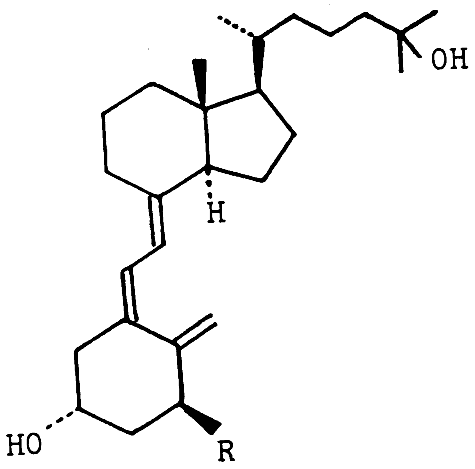
INTRODUCTION

Vitamins are essential dietary factors required by an organism in small amounts and whose absence results in deficiency diseases. Among them, vitamin D is the only one derived from steroids. Vitamin D promotes the absorption of calcium and phosphorous from the intestine into the bloodstream, so that it reaches a level high enough to permit proper bone mineralization.



Vitamin D

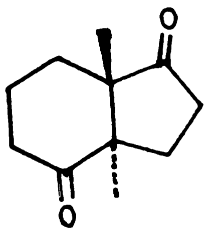
It has been found that vitamin D$_3$(cholecalciferol) is metabolized to 25-hydroxycholecalciferol **1**[1] in the liver and then to 1(S),25-dihydroxycholecalciferol **2**[2,3] in the kidney. Both metabolites exhibit much greater physiological activity than the vitamin itself.



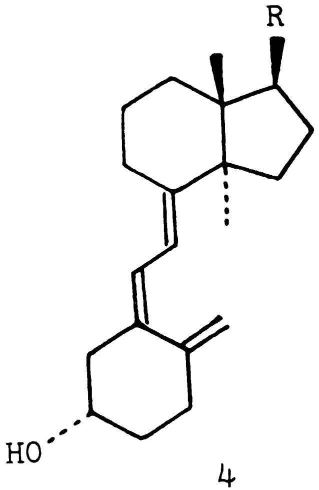
1 R = H

2 R = OH

In order to study the relationship between structure and reactivity in vitamins, much effort has been directed to the synthesis of structural analogs. To this end, the availability of perhydroindene-dione **3** has prompted us to explore the synthesis of a 14α-methyl analog **4** of vitamin D. This dissertation describes our efforts to join ring A and two bridging carbon atoms onto **3**.

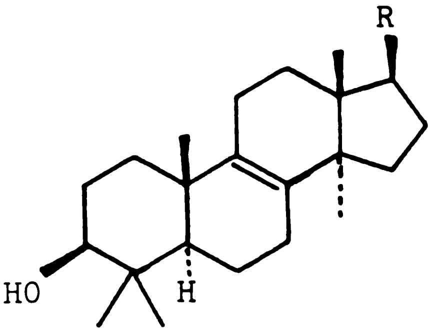


3

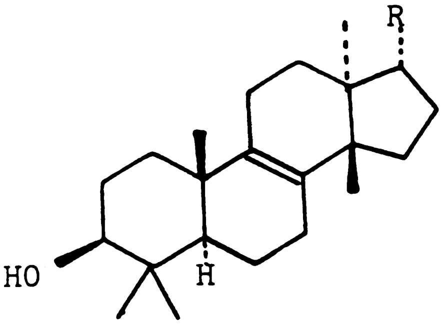


4

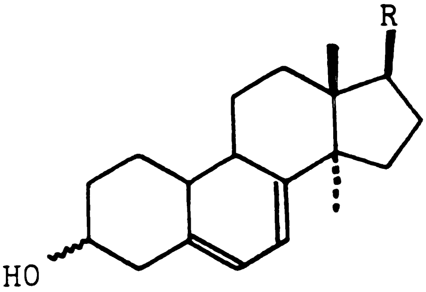
Triene 4 is interesting for at least two independent reasons. First, the possibility of a [1,7] sigmatropic hydrogen shift followed by an electrocyclic ring closure would, if realized, generate tetracyclic intermediates 5 related to lanostane and euphane triterpenes. This would provide an alternative synthetic route to such compounds[5, 19] which has precedent in vitamin D chemistry[6].



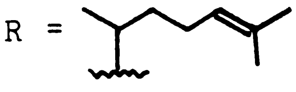
lanosterol



euphol



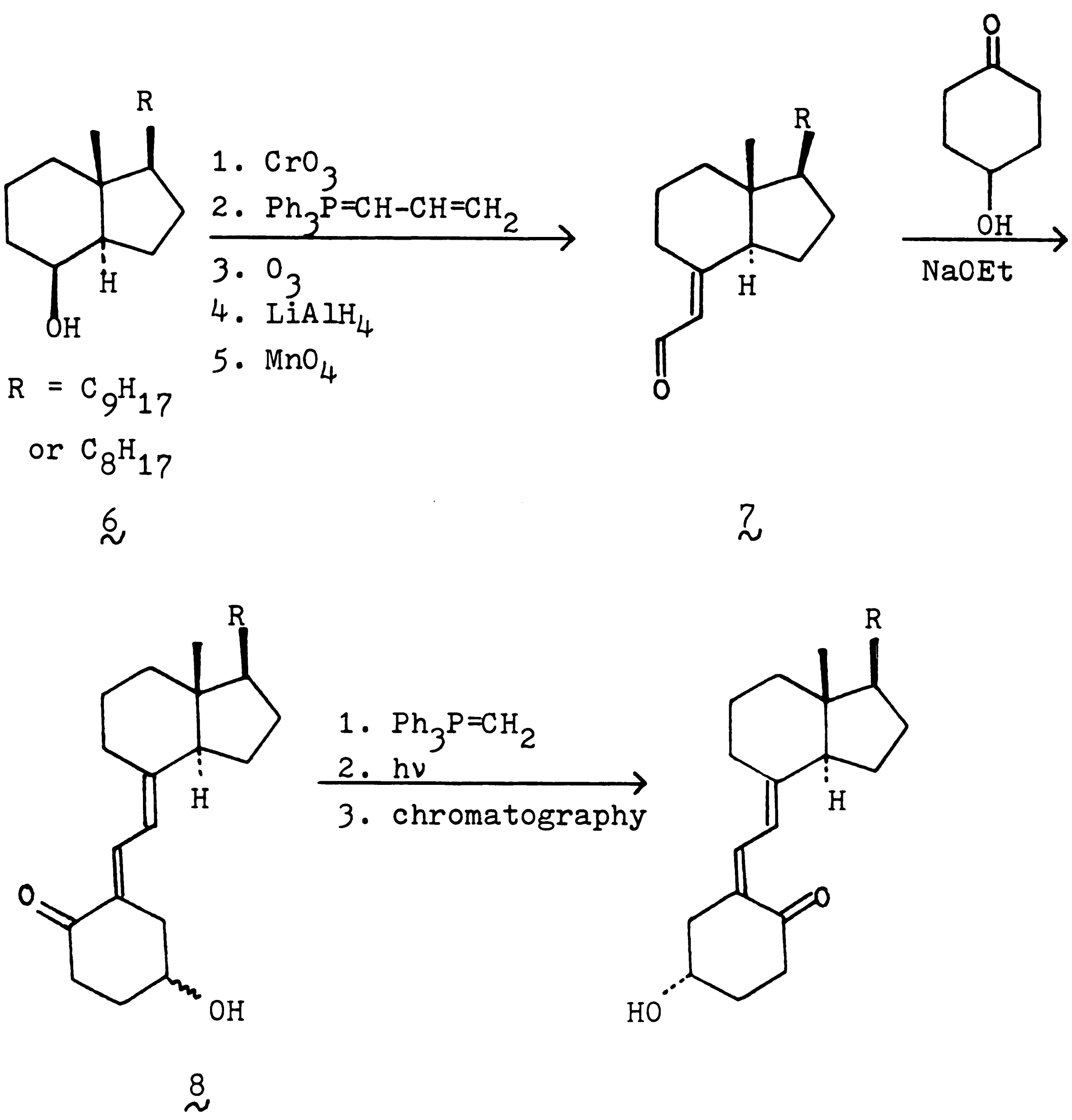
5



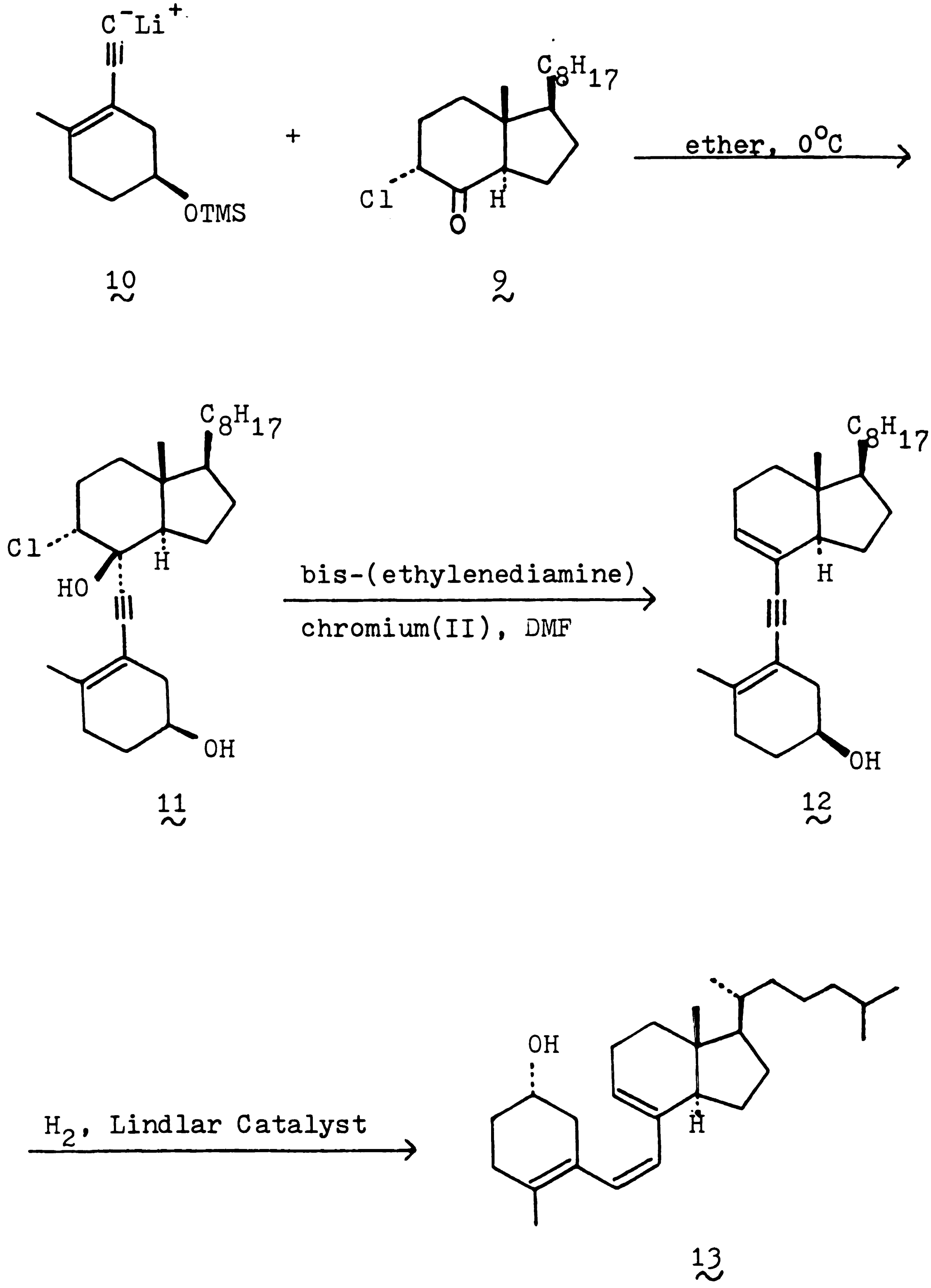
Second, the precursor of vitamin D has the 14α-methyl group. In the biosynthesis of steroids from squalene via lanosterol, the 14α-methyl group appears to be removed before the C-4 methyl groups and before the appearance of a Δ^5-double bond[7]. Indeed, no sterol having a 14α-methyl group in the absence of a gem-dimethyl unit at C-4 has ever been found in mammalian tissues. Compound 4 therefore is a vitamin D analog that nature either chose to by-pass entirely, or may have abandoned in as yet undiscovered earlier organisms.

Five pathways have been employed in the total synthesis of vitamin D. Inhoffen[8] used a Wittig reaction to introduce the sensitive triene system in the last step. In this synthesis alcohol 6 was converted to α,β-unsaturated aldehyde 7 by a bis-homologation requiring five steps. Aldol condensation between 7 and 4-hydroxycyclohexanone gave trans-dienone 8 as a mixture of C_3-epimers. A Wittig reaction followed by photochemical isomerization then led to vitamin D (Scheme I).

Lythgoe used an acetylene unit as a precursor of the two bridging carbon atoms between ring A and C[9]. Chloroketone 9 and the lithium derivative of enyne 10 were combined to give chlorohydrin 11. Reductive elimination of 11 generated dienyne 12, which on controlled hydrogenation of the acetylene link gave precalciferol 13 (Scheme II).


R
H
OH
R = C_9H_{17}
or C_8H_{17}
6
1. CrO_3
2. $Ph_3P{=}CH{-}CH{=}CH_2$
3. O_3
4. $LiAlH_4$
5. MnO_4
R
H
O
7
O
OH
NaOEt
R
H
O
OH
8
1. $Ph_3P{=}CH_2$
2. hν
3. chromatography
R
H
O
HO

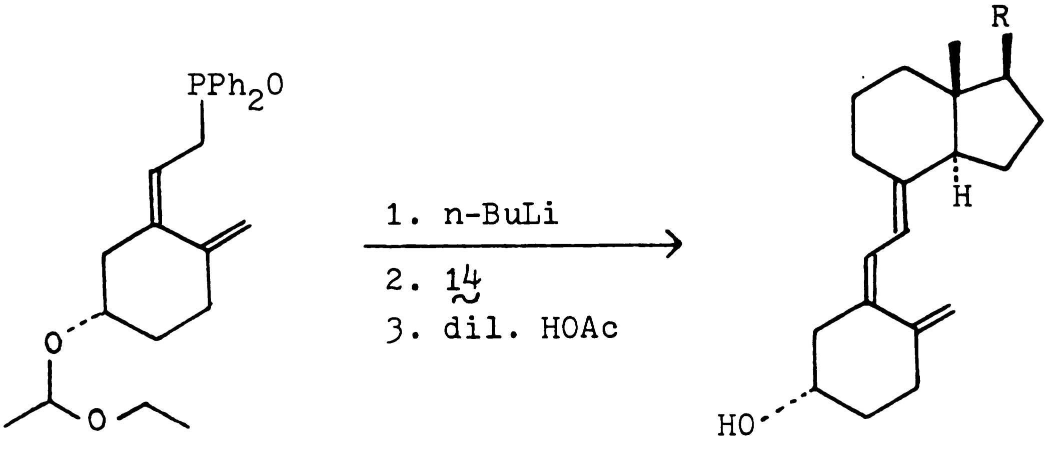
Scheme I


C⁻Li⁺
OTMS
+
C8H17
Cl
H
O
ether, 0°C
10
9
C8H17
Cl
HO
H
OH
bis-(ethylenediamine)
chromium(II), DMF
C8H17
H
OH
11
12
H2, Lindlar Catalyst
OH
H
13

Scheme II

In Okamura's approach[10], 3-deoxy-1-hydroxyvitamin D_3 18 was synthesized via a vinylallene intermediate. The key step involved coupling of the cuprate complex 16 with the ethynyl acetate 15. This coupling followed by deprotection afforded vinylallene 17 as a mixture of C_1-epimers, which were converted to 18 by a thermal sigmatropic rearrangement (Scheme III).

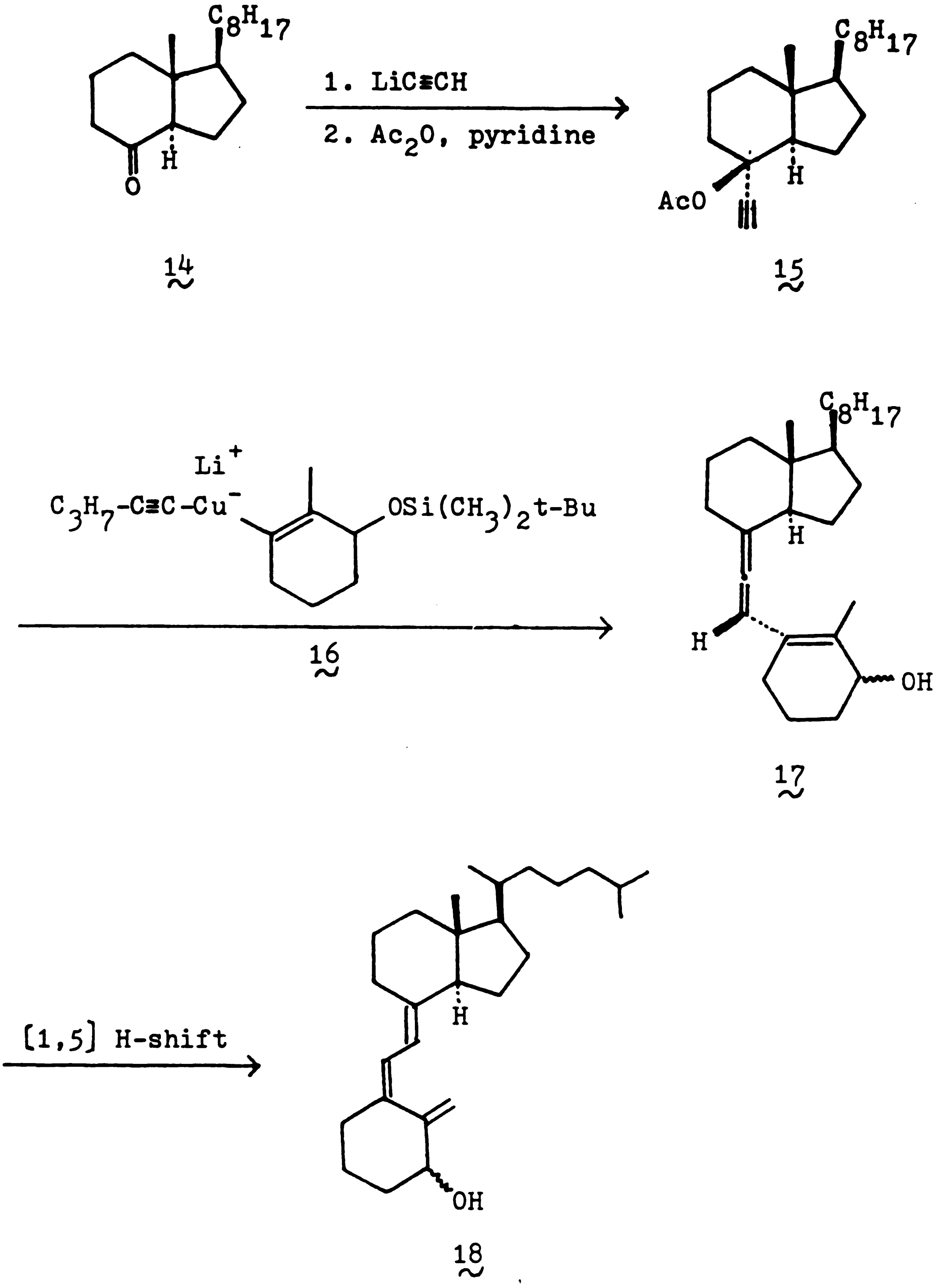
In the above methods, the triene system of vitamin D has been established by photochemical or thermal isomerization processes. Recently, Lythgoe reported a direct total synthesis of vitamin D[11] by adding the optically active phosphine oxide 19 to the Widaus-Grundmann ketone 14.



19

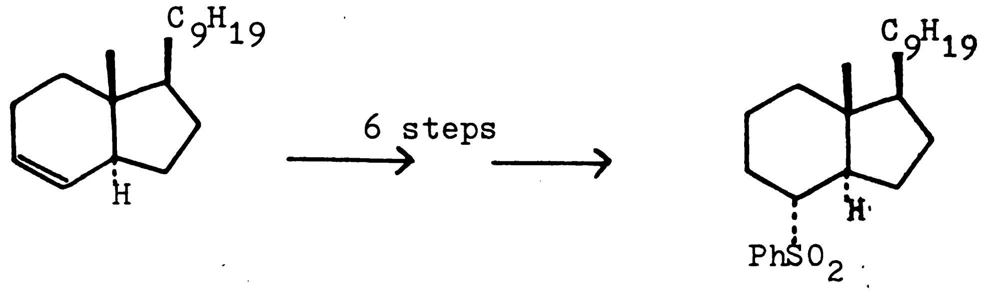
R = C_9H_{17} or C_8H_{17}

In this reaction, the original Z-allyl geometry of the phosphine oxide was completely preserved in the 5,6-double bond of the product, and the new 7,8-double bond was formed with exclusive E-geometry.


C_8H_{17}
1. LiC≡CH
2. Ac_2O, pyridine
C_8H_{17}
H
O
AcO
H
14
15
Li$^+$
C_3H_7-C≡C-Cu$^-$
OSi$(CH_3)_2$t-Bu
16
C_8H_{17}
H
H
OH
17
[1,5] H-shift
H
OH
18

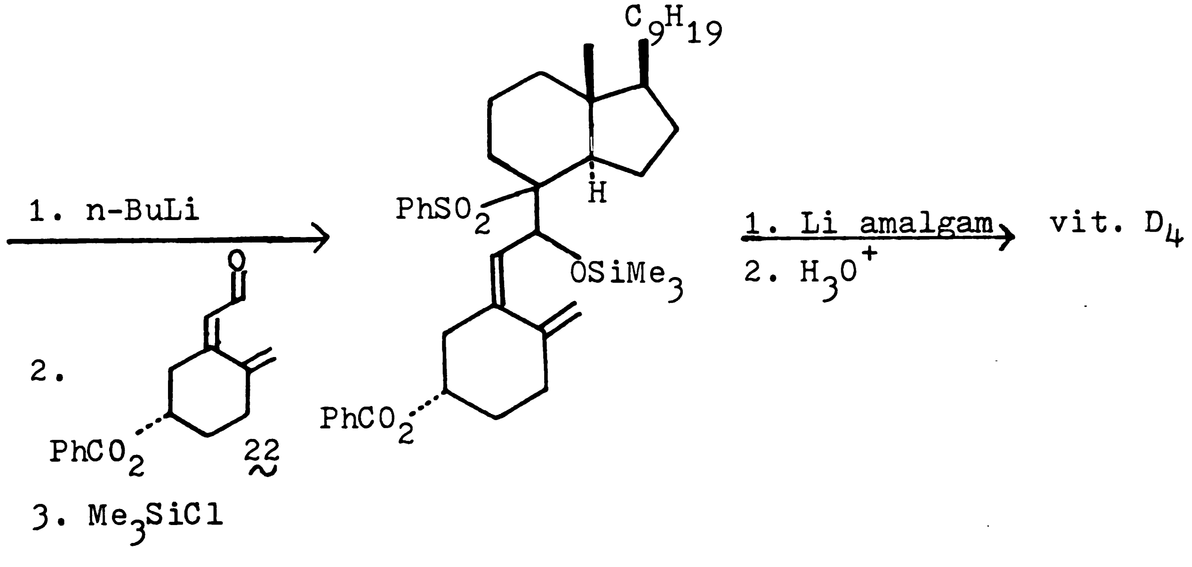
Scheme III

Lythgoe has also developed a modification of this synthesis, in which the reactivities of the intermediates are reversed[12]. Thus 8α-phenylsulfonyl-des-AB-ergostane 21, prepared from 20, formed a lithium derivative which reacted with the benzoyloxy-aldehyde 22 to give, after treatment with trimethylchlorosilane, a mixture of β-silyloxy-sulfones 23. Reduction with lithium amalgam, followed by removal of the benzoyl group, gave vitamin D_4.



20

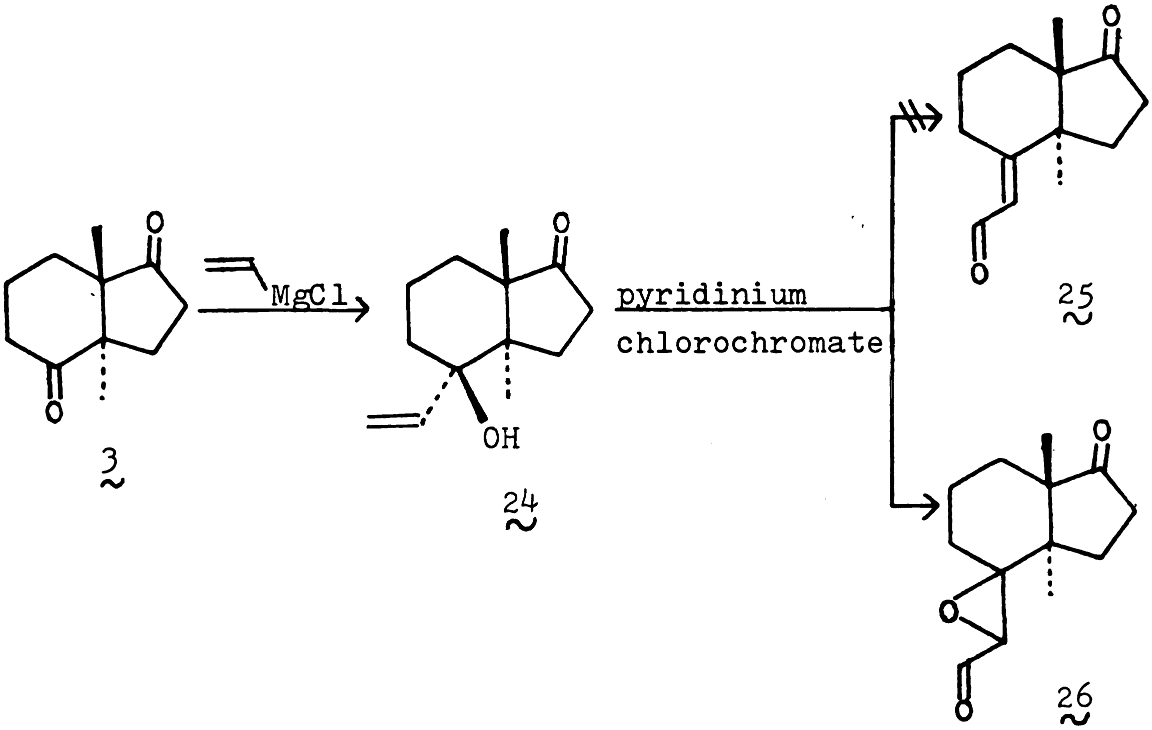
21



The approaches to the synthesis of a 14α-methyl analog of vitamin D described in this thesis are based on the first two strategies noted here.

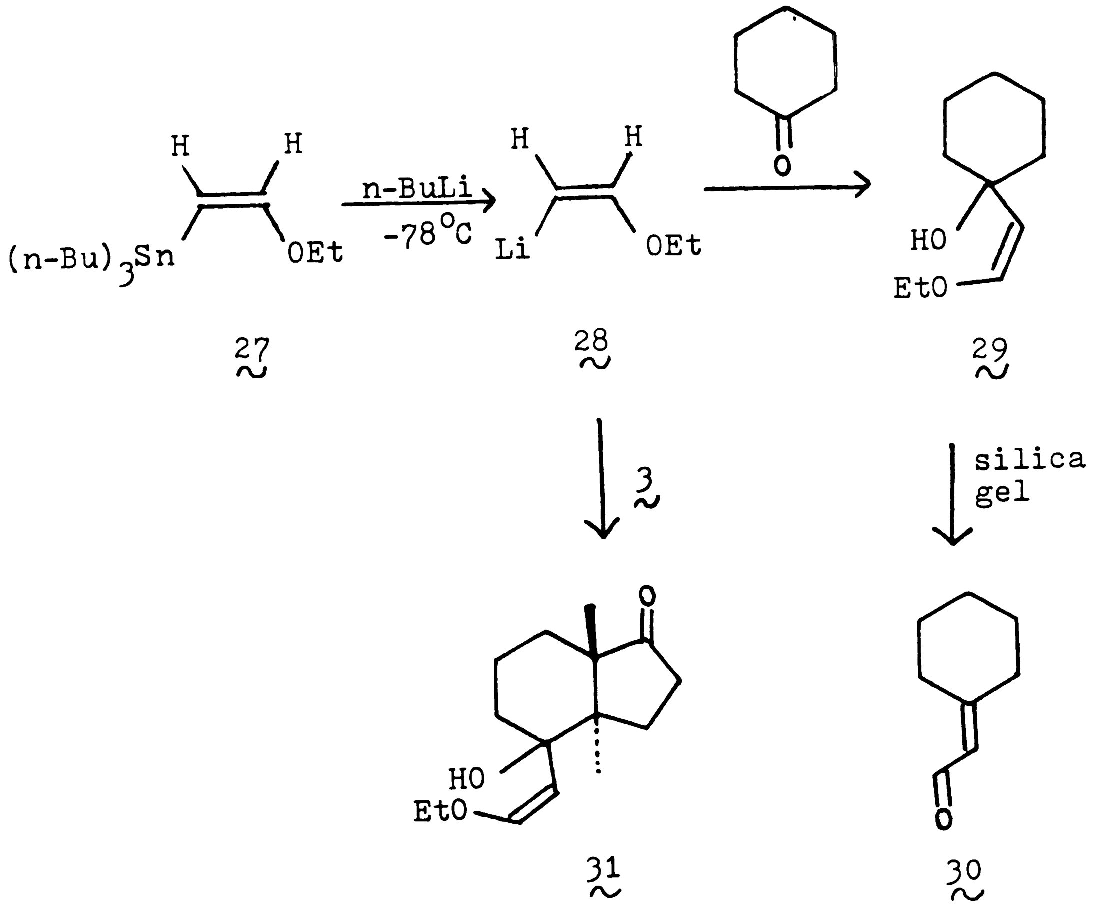
RESULTS AND DISCUSSION

The bicyclic α,β-unsaturated aldehyde **7** served as a key intermediate in Inhoffen's vitamin D synthesis, and the corresponding methyl homolog **25** is a necessary intermediate in a parallel route to 14α-methyl vitamin D derivatives. Recently, several facile new methods for converting aldehydes or ketones to α,β-unsaturated aldehydes with simultaneous chain extension have been reported. However, not all of these proved effective with perhydroindene-dione **3**. For example, addition of vinyl magnesium chloride to **3** followed by oxidative



rearrangement with pyridinium chlorochromate[13] gave α,β-epoxyaldehyde **26** instead of **25**. This deviation from the expected reaction has been noted previously[13c] for hindered allylic alcohols. Attempts to convert **26** to **25** by heating with triphenylphosphine[14] or zinc dust in acetic acid[15] failed.

A second approach involved the addition of a nucleophilic acetaldehyde equivalent, (Z)-2-ethoxyvinyl lithium **28**[16], to **3**. Although **28** reacted with cyclohexanone to produce enol ether **29** in excellent yield, there was only modest reaction between **28** and **3** below the decomposition temperature of **28** (ca. -40°C). Compound **31** was stable to



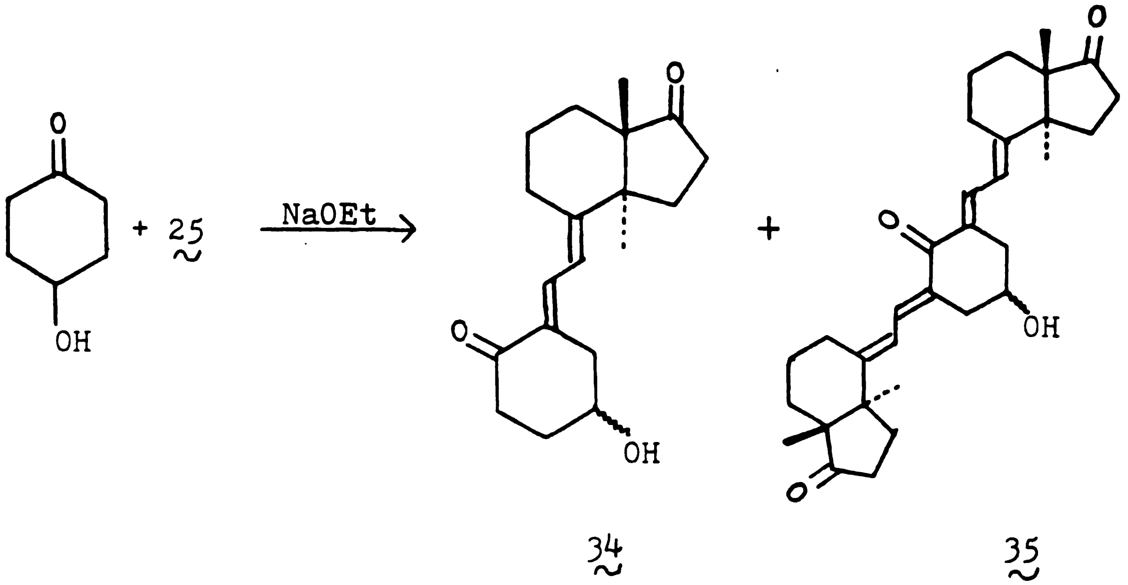
chromatographic purification on silica gel while 29 was completely converted into 30 under the same conditions. The acid hydrolysis of enol ether 31 was not tried because a better method of preparation of aldehyde 25 was found.

By using the lithium derivative of trimethylsilylated aldimine 33[17] as a nucleophile, aldehyde 25 was prepared in 66% yield (based on recovered starting material):

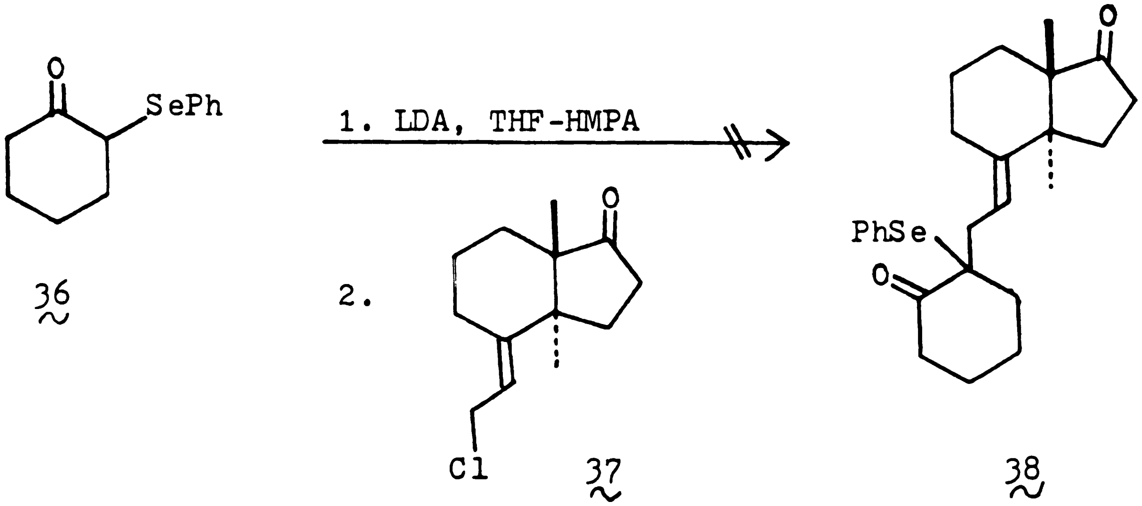
$$\underset{32}{\mathrm{CH_3CH{=}N\text{-}t\text{-}Bu}} \xrightarrow[\text{2. }(\mathrm{CH_3})_3\mathrm{SiCl}]{\text{1. LDA}} \underset{33}{(\mathrm{CH_3})_3\mathrm{SiCH_2CH{=}N\text{-}t\text{-}Bu}}$$

$$\xrightarrow[\substack{\text{2. } 3 \\ \text{3. } (\mathrm{COOH})_2,\ \mathrm{H_2O}}]{\text{1. LDA}} 25$$

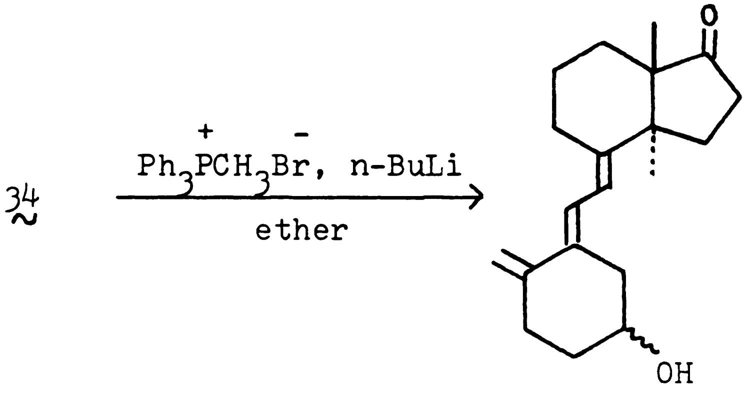
The next few steps in this synthesis followed Inhoffen's procedure[8]. Thus aldol condensation of 25 with 4-hydroxycyclohexanone in the presence of sodium ethoxide gave the desired adduct 34 along with a small amount of bis-condensation product 35 (5.8:1). Since formation of 35 consumed two equivalents of 25 and caused problems in the purification of 34, an effort was made to minimize this product. Unfortunately, the use of excess 4-hydroxycyclohexanone did not prevent the formation of 35 under conditions that still yield 34.



An alternative approach involving coupling[18] between keto selenide 36 and allylic chloride 37[19] was considered as a model for vitamin D synthesis; however, no alkylation products were obtained in these experiments.



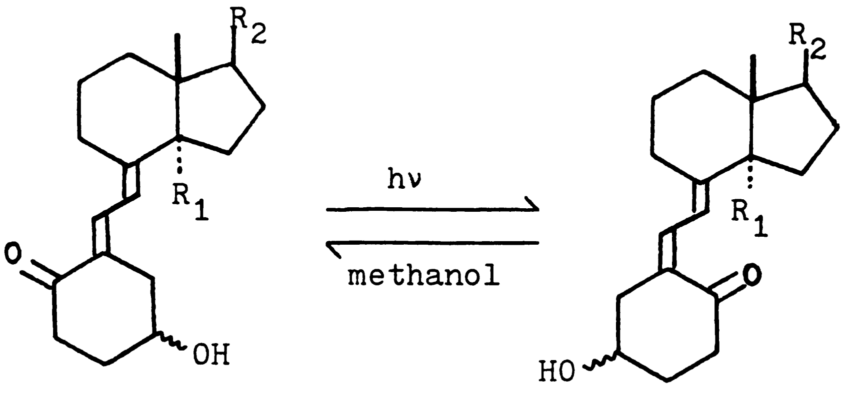
Reaction of 34 with triphenylphosphonium methylide gave olefin 39, which exhibited UV absorption



39

(λ_{max} = 270 nm, ϵ = 22000) very close to that reported for 5,6-trans-vitamin D_2 (λ_{max} = 272-273 nm, ϵ = 22700)[8]. In order to improve the yield of the above Wittig reaction, a modification using a stronger base and different solvent was studied. Although Corey and Chaykovsky reported that Wittig reactions proceeded more rapidly and gave better yields with dimsyl sodium in dimethylsulfoxide[20], none of olefin 39 was obtained under these conditions.

Since vitamin D has a cis configuration at the 5,6-position, 34 had to be isomerized through irradiation. When a methanol solution of dienone 8 was irradiated with light filtered to give 365 nm[21], the photoequilibrium favored 40 by at least 4:1. The same conditions were applied to 34, but the photoequilibrium was only 1:1, 34:41. Apparently the 14α-methyl group has an effect on the photoisomerization equilibrium.



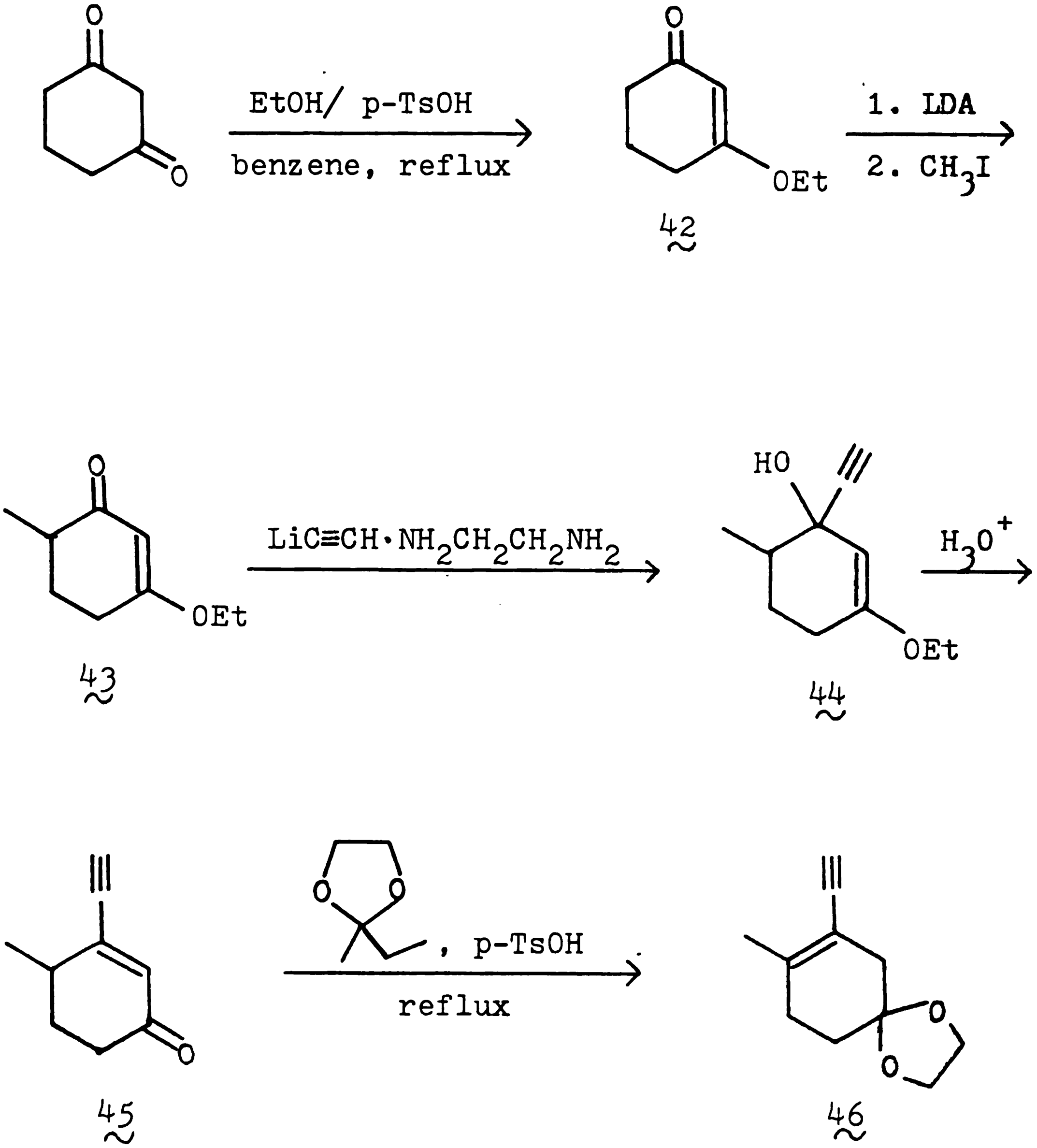
8 $R_1 = H$, $R_2 = C_9H_{17}$ or C_8H_{17}

34 $R_1 = CH_3$, $R_2 = O$

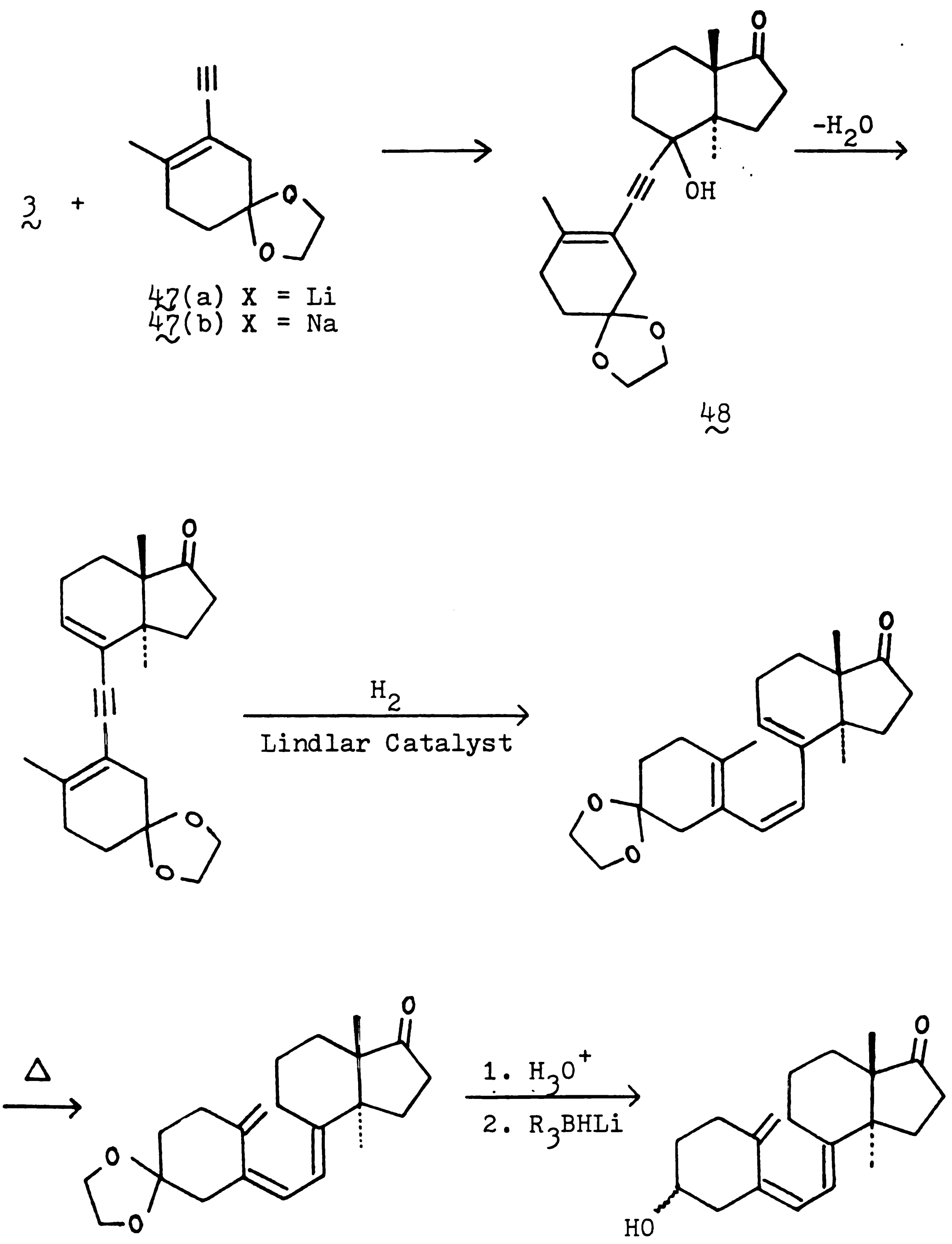
40 $R_1 = H$, $R_2 = C_9H_{17}$ or C_8H_{17}

41 $R_1 = CH_3$, $R_2 = O$

A second approach to 14α-methyl vitamin D analog was patterned after Lythgoe's synthesis of precalciferol[9]. This synthesis required the preparation of acetylenic ketal 46 as a key intermediate. Scheme IV shows the way in which this was accomplished. Thus the enol ether[22] of 1,3-cyclohexanedione was alkylated regiospecifically[23] to give 43 by treatment with lithium diisopropylamide and methyl iodide. Reaction of 43 with lithium acetylide· ethylenediamine[24] gave ethyl carbinol 44, which proved unstable and easily lost ethanol giving conjugated ketone 45. Direct ketalization[25] of 45 by ethylene glycol led to many undesired products, so exchange ketalization[26] was used instead. The acetylene intermediate 46 is especially attractive because it does not have any asymmetric carbon atoms. Thus addition of anion 47 to 3 should not generate


EtOH/ p-TsOH
benzene, reflux
OEt
42
1. LDA
2. CH₃I
OEt
43
LiC≡CH·NH₂CH₂CH₂NH₂
HO
OEt
44
H₃O⁺
45
, p-TsOH
reflux
46

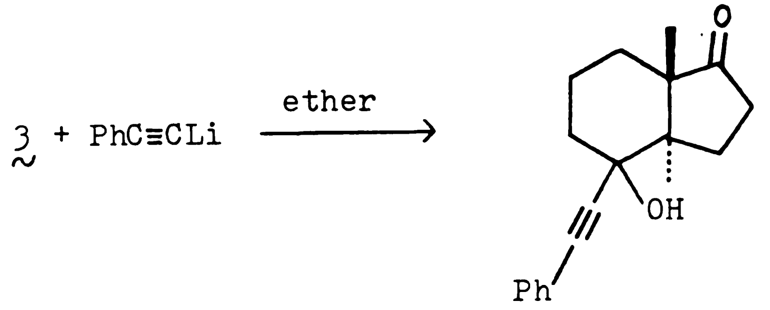
Scheme IV


3
+
47(a) X = Li
47(b) X = Na
48
$-H_2O$
H_2
Lindlar Catalyst
Δ
1. H_3O^+
2. R_3BHLi
OH
HO

Scheme V

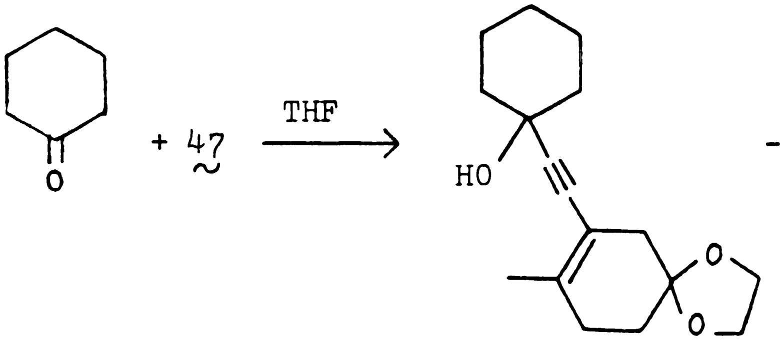
diastereoisomeric mixtures as was the case in 34. The hydroxyl group at the C-3 position would then be introduced at a later stage in the synthesis. The approach is outlined in Scheme V.

To establish conditions for the reaction between 3 and 47, the following two model systems were studied:



49

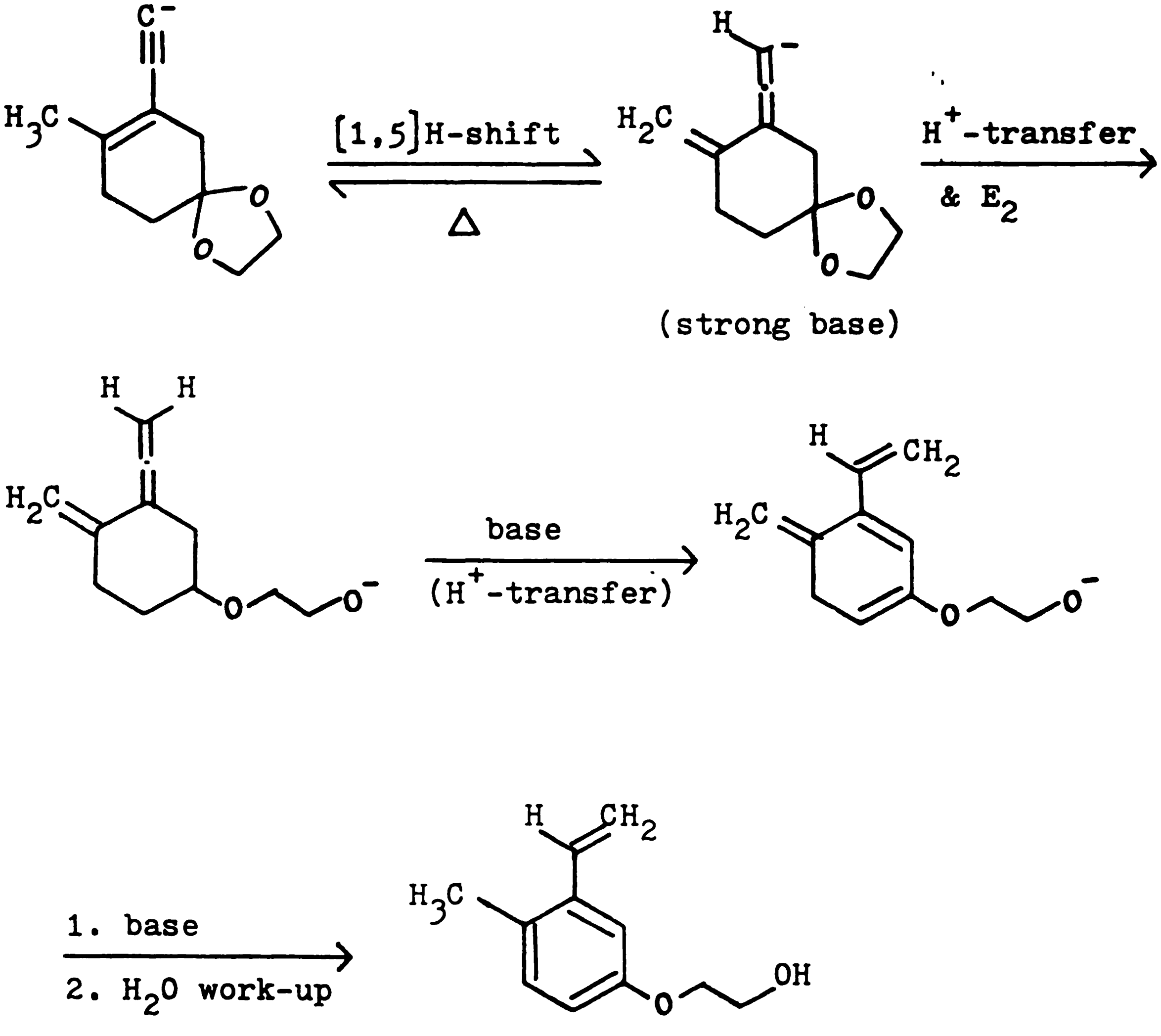
------- (1)



50

------- (2)

Although reactions (1) and (2) proceeded smoothly to give adducts 49 and 50, respectively[9], no product was obtained from 47 and 3 under the same conditions. Various bases and solvents, such as NaH/DMSO, NaH/ether, CH_3MgBr/ether, were tried without success. Indeed, forcing conditions led to the transformation of 47(b) to 51, which may proceed via sigmatropic rearrangement and proton transfer as illustrated in Scheme VI.

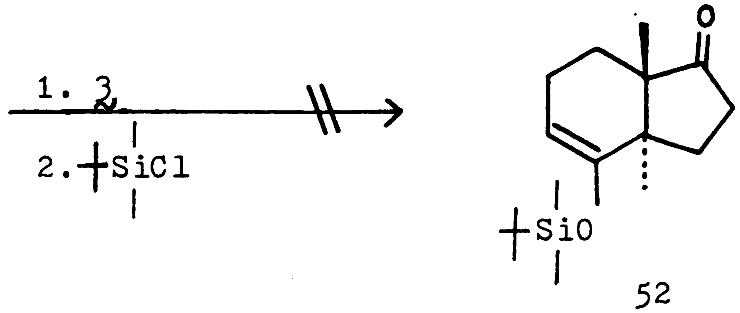


51

Scheme VI

A possible reason for the failure of addition may be competitive enolate anion formation on the six-membered ring. This has been ruled out by trapping experiments with t-butyldimethylsilyl chloride, which are known[27] to give O-silylated derivatives on reaction with ketone enolates. No silyl ether **52** was obtained in the following reaction:

47(b)



52

Complexation of the carbonyl function in **3** with certain electrophiles overcomes the sluggishness of this reaction. When **3** was treated wtih lithium iodide prior to reaction with **47**(a), a 12% of adduct **48** was obtained.

EXPERIMENTAL

GENERAL

All reactions in which strongly basic reagents were used were conducted under nitrogen or argon, using solvents purified by distillation from suitable drying agents. Magnetic stirring devices were used for most small scale reactions; larger reactions were agitated by paddle stirrers. Organic extracts were always washed with water and brine and dried over anhydrous sodium sulfate or anhydrous magnesium sulfate before being concentrated or distilled under reduced pressure. The progress of most reactions was followed by thin layer chromatography (TLC) and/or gas liquid phase chromatography (GLPC). Visualization of the thin layer chromatograms was effected by spray reagents such as 5% p-anisaldehyde in ethanol and 30% sulfuric acid with subsequent heating.

Analysis by GLPC was conducted with A-90-P3 or 1200 Varian-Aerograph instruments. Preparative layer chromatography was carried out on 2 mm silica gel or 1.5 mm alumina F-254 adsorbent on 20 x 20 cm glass plates. Visualization of the preparative plates was effected by ultraviolet light and/ or charring with a hot wire. Melting points were determined on either a Hoover-Thomas apparatus (capillary tube) or on a Reichert hot-stage microscope and are uncorrected. Infrared spectra (IR) were recorded on a Perkin-Elmer 237B grating spectrophotometer. Proton magnetic resonance spectra (PMR) were taken in deuterochloroform or carbon tetrachloride solutions with a Varian T-60 spectrometer and are calibrated in parts per million (δ) downfield from tetramethylsilane as an internal standard. Ultraviolet spectra (UV) were recorded on a Unicam SP-800 spectrophotometer. Mass spectra (MS) were obtained with a Hitachi RMU 6 mass spectrometer. Carbon magnetic resonance spectra (CMR) were taken in deuterochloroform solution with a Varian CFT-20 spectrometer and are calibrated in parts per million (δ) downfield from tetramethylsilane as an internal standard.

Microanalyses were performed by Spang Microanalytical Laboratories, Eagle Harbor, Michigan.

Preparation of epoxyaldehyde 26.

A solution of 816.7 mg (3.9 mmole) of alcohol 24[27a] in 14 ml of methylene chloride was added to a suspension of 3.2 g (15.6 mmole) pyridinium chlorochromate in 10 ml of methylene chloride. The mixture was stirred at room temperature under nitrogen overnight, diluted with 80 ml of ether and filtered through Florisil. After removal of solvent, 790 mg of yellow oil was obtained. Crystallization in ether gave 274 mg of 26 (34%), which displayed the following properties: mp 95.5-96.5°; IR ($CDCl_3$) 1735, sh 1715, 1256 cm^{-1}; PMR ($CDCl_3$) δ 1.05 (s, 3H), 1.17 (s, 3H), 1.4-2.6 (m, 10H), 3.07 (d, 1H, J=5 Hz), 9.37 (d, 1H, J=5 Hz); MS (70 eV) m/e (rel intensity) 222(4), 207(8), 121(25.5), 110(100), 84(67.5).

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.27; H, 8.17

Found: C, 70.25, H, 8.16

Reaction of epoxyaldehyde 26 with triphenylphosphine.

A solution of epoxyaldehyde 26 (97 mg, 0.44 mmole), triphenylphosphine (119 mg, 0.45 mmole) and hydroquinone (19 mg, 0.17 mmole) in 10 ml of triethyleneglycol was heated at 160°C for 5 hr and 190°C for 2 hr. The tarry residue showed the same chromatographic properties as the starting materials.

Reaction of epoxyaldehyde 26 with zinc dust in acetic acid.

To a stirred solution of 26 (25 mg, 0.11 mmole) in 10 ml of THF was added zinc dust, followed by dropwise addition of 2 ml (30 mmole) of acetic acid. After refluxing for 6 hr, the solution was filtered, and the filtrate was extracted by ether and water, washed with sat. sodium bicarbonate, water, brine and dried. Removal of solvent gave 23.4 mg crude product which proved to be a mixture of 26(30%) and 3 (70%) by GLPC analysis. The latter was collected by GLPC (4% QF-1, $180^{\circ}C$) and exhibited an infrared spectrum identical to that of an authentic sample of 3.

Preparation of enol ether 31.

To a solution of cis-1-ethoxy-2-tri-n-butylstannylethylene 27[16] (410.8 mg, 1.14 mmole) in 6 ml of THF was added 2.42M n-BuLi (0.46 ml, 1.11 mmole) at $-78^{\circ}C$. After 1 hr, the solution was treated with a solution of ketone 3 (90 mg, 0.5 mmole) in THF. The mixture was stirred at this temperature for 2 hr, warmed up to room temperature, and quenched by sat. sodium bicarbonate solution. Work-up of the reaction mixture by the previously described procedure gave 421 mg of crude product, which was chromatographed on HPLC (silica gel) with 20% ethyl acetate-hexane to afford 47.1 mg (41% based on the recovered 3) of 31: IR ($CDCl_3$) 3520, 1733, 1667 cm^{-1}; PMR ($CDCl_3$) δ 0.85 (s, 3H), 1.30 (s, 3H and t, 3H, J=7 Hz), 1.4-2.4 (m, 10H), 3.77 (q, 2H, J=7 Hz), 4.07 (s, 1H), 4.37 (d, 1H, J=7 Hz), 5.87 (d, 1H, J=7 Hz); MS (70 eV) m/e (rel intensity) 252(0.30), 237 (1.35), 235(1.61), 206(1.65), 165(11.94), 140(76.78), 71 (100). An analytical sample was crystallized from ether, mp 52-55°.

Preparation of imine **32**[28].

A three neck, round bottom flask, fitted with a reflux condenser and a dropping funnel, was packed in an ice bath and charged with 41 ml (0.39 mole) of t-butylamine and 22 ml (0.39 mole) of acetaldehyde. The mixture was stirred for 20 min., 2 g of potassium hydroxide was added, and the reaction mixture was allowed to stand until separation into two layers appeared complete. The organic layer was dried over crushed potassium hydroxide in the refrigerator overnight, and then distilled from fresh potassium hydroxide at 70-74°C to afford 29.88 g (77%) of acetaldehyde t-butylimine **32**.

Preparation of trimethylsilylated aldimine **33**.

To a stirred solution of n-butyllithium (55 ml, 0.12 mole) in 80 ml of THF at -78°C was added dropwise **32** (14 ml, 0.11 mole). This solution was stirred for 20 min. and then treated with trimethylchlorosilane (15.2 ml, 0.12 mole). After the reaction mixture had warmed to 0°C, it was poured into 250 ml of water and extracted with ether. The combined organic extracts were washed with brine, dried over potassium carbonate and concentrated. The residual liquid was distilled at 69-71°C (9 mm) to afford 12.9 g (69%) of 33: MS (70 eV) m/e (rel intensity) 171(9.5), 156(21.5), 147(100), 100(37).

Preparation of unsaturated aldehyde 25.

To a stirred solution of LDA (made in situ from 8 ml of 2.42 M n-BuLi and 3 ml of diisopropylamine) in 40 ml of THF at 0°C was added imine 33 (3.24 g, 18.9 mmole) over a 5 min. period. This reaction mixture was stirred for 15 min., cooled to -78°C and treated with a solution of 3 (1.5 g, 8.3 mmole) in 10 ml of THF. The resulting mixture was stirred at -78°C for 2 hr, -20°C for 0.5 hr, and then quenched with aqueous oxalic acid to bring the pH of the solution to 4.5. After another 2 hr at room temperature, the mixture was poured into brine and extracted with ether and ethyl acetate. The organic layer was washed with sat. sodium bicarbonate, water and brine. After dring and removal of the solvent, 2 g of yellow oil was obtained. Crystallization from ether gave 493 mg of 25, mp 72.5-74°. The mother liquid was chromatographed on HPLC (silica gel) with 20% EtOAc-hexane to afford 198.6 mg of 3 and 806 mg of 25, from which 488 mg of 25 was crystallized from ether. Aldehyde 25, obtained in 66% yield (based on the recovered starting material), had the following properties: IR ($CDCl_3$) 1729, 1657 cm^{-1}; Pmr ($CDCl_3$) δ 0.99 (s, 3H), 1.13 (s, 3H), 1.33-2.07 (m, 6H), 2.33 (m, 4H), 5.83 (dd, 1H, J=8, 2 Hz), 9.67 (d, 1H, J=8 Hz); CMR ($CDCl_3$) 18.03, 21.06, 23.08, 23.81, 25.24, 28.43, 33.21, 48.78, 53.56, 125.2, 169.0, 190.4, 217.5; MS (70 eV) m/e (rel intensity) 206(65), 191 (11), 177(10), 163(56), 149(26), 135(49), 121(40), 107(42), 41(100).

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80
Found: C, 75.77; H, 8.85

Preparation of dienone **34**.

To a solution of sodium (0.23 g, 0.01 mole) in 14 ml of absolute ethanol was added dropwise a solution of 4-hydroxycyclohexanone[29] (2.97 g, 0.026 mole) in 7 ml of ethanol. This mixture was stirred for 5 min. and then treated with a solution of **25** (537 mg, 2.6 mmole) in 7 ml of ethanol. The resulting mixture was stirred for 30 min. and then neutralized with 10% HOAc-EtOH. After removal of ethanol, the residue was worked up and the excess 4-hydroxycyclohexanone was removed by Kugelrohr distillation (5×10^{-4} mm, 110°C, 40 min.). The residual dark red oil (0.99 g) was chromatographed on alumina (50 g, neutral, activity grade I); eluting with $CHCl_3$ gave 148 mg of **35** and then 525 mg (67%) of **34**. Analytical samples of **34** and **35** were crystallized from ether-ethyl acetate: **34**; mp 145-147°; IR ($CDCl_3$) 3601, 1733, 1673, 1612, 1573 cm^{-1}; PMR ($CDCl_3$) δ 0.94 (s, 3H), 1.17 (s, 3H), 1.41-3.75 (m, 17H), 4.24 (m, 1H), 5.97 (d, 1H, J=12 Hz), 7.45 (d, 1H, J=12 Hz); UV (CH_3OH) λ_{max}= 312 nm, ϵ= 29000; MS (70 eV) m/e (rel

intensity) 302(37), 287(37), 190(34.5), 178(30), 164(100).
Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67
Found: C, 75.55; H, 8.76

35; mp 214-217°; IR ($CDCl_3$) 3583, 1734, 1651, 1618, 1591 cm^{-1}; PMR ($CDCl_3$) δ 0.99 (s, 6H), 1.23 (s, 6H), 1.45-3.45 (m, 25H), 4.28 (m, 1H), 6.08 (d, 2H, J=12 Hz), 7.74 (d, 2H, J=12 Hz); MS (70 eV) m/e (rel intensity) 490(58), 475(51), 378(25), 352(100); UV (CH_3OH) λ_{max}= 360 nm, ϵ= 29000.

Preparation of keto selenide **36**.

A three neck, round bottom flask, equipped with addition funnel, was cooled to -78°C and charged with diisopropylamine (1.8 ml, 12.8 mmole), 2.3M of n-BuLi (5.2 ml, 12 mmole) and 20 ml of THF. The mixture was stirred for 15 min. and treated with a solution of cyclohexanone (1 ml, 9.7 mmole) in 8 ml of THF. Into the funnel was added Ph_2Se_2 (1.8 g, 5.8 mmole) and 10 ml of THF. Bromine (0.3 ml, 5.5 mmole) was then added dropwise to the solution. After 10 min. the PhSeBr solution was added to the enolate solution in one portion. The resulting mixture was stirred for 15 min., poured into 50 ml of 0.5 N HCl and extracted with 50% ether-pentane. The organic layer was washed with sat. $NaHCO_3$, water and brine. After dring and removal of solvent, 3 g of crude product was obtained. An analytical sample of **36** was crystallized from ether-pentane: mp 57-58°; PMR (CCl_4): δ 1.4-3.1 (m, 8H), 3.7 (br t, 1H, J=5 Hz), 6.85-7.48 (m, 5H).

Reaction between keto selenide 36 and allylic chloride 37.

To a solution of 1 equiv. LDA (made in situ from 0.6 ml of 2.42M n-BuLi and 0.22 ml of diisopropylamine) at 0°C, was added 0.3 ml of HMPA followed by dropwise addition of keto selenide 36 (360 mg, 1.42 mmole). The mixture was stirred for 5 min. and allylic chloride 37[19] (280.5 mg, 1.24 mmole) was added in one portion. After stirring at room temperature for 3 hr, this reaction mixture was quenched with water and worked-up to give 613.8 mg of a brown oil. However, the PMR and MS showed that this oil was a mixture of starting materials, and no 38 could be detected.

Preparation of olefin 39.

To a 10 ml, three neck, round bottom flask equipped with a condenser and argon inlet was added 4 ml of ether and 0.2 ml of 2.42M n-BuLi (0.48 mmole) followed by methyltriphenylphosphonium bromide (239 mg, 0.67 mmole) in two portions. After 2.5 hr, a solution of 34 (30.2 mg, 0.1 mmole) in 2 ml of THF was added and the mixture was heated to 50°C for 1.5 hr. After cooling to room temperature, the precipitate was removed by suction filtration and washed with ether and ethyl acetate. The combined filtrates were washed with water and brine, dried and stripped of solvent. The residue (150 mg) was chromatographed on a preparative alumina plate, elution with 45% ethyl acetate-hexane giving 5 bands. The first band gave 4 mg of 25 and the second band gave 5 mg of 30. The latter material had the following properties: UV (ethanol) λ_{max}=270 nm, ϵ=22000; MS (70 eV) m/e (rel intensity) 300(21), 267(95), 149(100).

Reaction of dienone 34 with Wittig reagent in DMSO.

Sodium hydride (40 mg as a 57% dispersion in mineral oil, 0.95 mmole) in a 25 ml three neck flask was washed with several portions of pentane to remove the oil. The system was alternatively evacuated and filled with argon; 3.5 ml of DMSO was added, and the mixture was heated to 75°C until the evolution of hydrogen ceased (about 45 min.). The resulting solution of dimsyl sodium was cooled to room temperature and treated with methyltriphenylphosphonium bromide (317 mg, 0.89 mmole) in 3 ml of DMSO. The resulting yellow solution was stirred at room temperature for 15 min. and then mixed with 34 (45 mg, 0.15 mmole) in 2 ml of DMSO. This mixture was heated at 50°C overnight, cooled to room temperature and poured into water. The usual work-up followed by chromatography on a preparative alumina plate with 45% ethyl acetate-hexane gave 18 mg of 34 and 9 mg of side products. No olefin 39 could be detected.

Isomerization of 34 to 41.

A solution of 34 (8.4 mg, 0.028 mmole) in 22 ml of methanol was irradiated at 0°C with a medium pressure mercury lamp, the light from which was filtered through aqueous 15% copper sulfate. The reaction was followed by reverse phase analytical HPLC; eluting with 45% MeOH-H_2O. After irradiation for 20 min., the solution changed to a 1:1 mixture of 34 and 41. Longer reaction times did not change the equilibrium concentration, but caused decomposition of both isomers. The UV absorption of the reaction mixture did not shift to shorter wavelength as reported in vitamin D chemistry[21], but the extinction measured at 305 nm had decreased by 17% after 3.3 hr.

Preparation of enol ether 43.

To a solution of 2.42M n-BuLi (10 ml, 24.2 mmole) in hexane at 0°C was added dropwise 3.65 ml of TMEDA (24.2 mmole), followed by 3.6 ml of diisopropylamine (25.8 mmole). After 10 min. this solution was cooled to -78°C and formed some precipitate which was dissolved by adding 5 ml of THF. A solution of 42 (3.3 g, 23.8 mmole) in 3 ml of THF was added over a 5 min. period. After stirring for 40 min., 1.56 ml of methyl iodide (25 mmole) was added and the resulting turbid solution was stirred overnight, quenched by water and extracted with ether. The organic layer was washed with 2N HCl, water and brine. Drying and removal of solvent gave 3.21 g (88%) of 43, which had the following properties: PMR (CCl_4) δ 1.05 (d, 3H, J=6 Hz), 1.33 (t, 3H, J=7 Hz), 1.5-2.5 (m, 4H), 3.81 (q, 2H, J=7 Hz), 5.1 (s, 1H); MS (70 eV) m/e (rel intensity) 154(36), 112(68), 84(100), 68(76).

Preparation of unsaturated ketone 45.

To a suspension of lithium acetylide•ethylenediamine complex (400 mg, 4.35 mmole) in 5 ml of THF at 38°C was added dropwise a solution of 43(643 mg, 4.17 mmole) in THF. The mixture was stirred at room temperature overnight and TLC indicated there was still some starting material left. However, addition of more lithium acetylide and a longer heating period did not complete the reaction. After cooling to room temperature, water was added slowly to quench the reaction, and the usual work-up gave 640.8 mg crude product which showed 70% addition from PMR (80% addition can be obtained by using 1.7 equiv. of lithium acetylide in 50% benzene-THF). During separation by HPLC (25% ethyl acetate -hexane, silica gel) the acetylenic alcohol 44 lost ethanol giving 305 mg (55%) of 45 along with 160 mg of 43. Ketone 45 had the following properties: IR (neat) 3234, 2084, 1673, 1575 cm^{-1}; PMR ($CDCl_3$) δ 1.38 (d, 3H, J=6.8 Hz), 1.59-2.95 (m, 5H), 3.59 (s, 1H), 6.24(d, 1H, J=2 Hz); MS (70 eV) m/e (rel intensity) 134(53), 119(46), 117(48), 106(100), 78(56). A 2,4-DNP derivative of 45 was prepared and crystallized from ethanol: mp 147-148°.

Anal. Calcd. for $C_{15}H_{14}N_4O_4$: C, 57.32; H, 4.49; N, 17.83

Found: C, 57.44; H, 4.51; N, 17.89

Preparation of ketal 46.

A mixture of ketone 45 (1.1 g, 8.2 mmole), p-toluenesulfonic acid monohydrate (82 mg, catalytic amount) and

2-methyl-2-ethyl-1,3-dioxolane (18 ml, excess) was heated and the liberated butanone distilled slowly. The mixture was stirred at 100°C overnight in order to get the thermodynamically more stable isomer 46. The cooled reaction mixture was diluted with ether, washed successively with 5% aqueous sodium bicarbonate and water. Drying and removal of solvent gave 1.34 g crude product, which was chromatographed on HPLC (silica gel) with 17% ethyl acetate-hexane to afford 0.71 g of 46 (49%): IR (neat) 3218, 2084, 1089, 1067 cm^{-1}; PMR (CCl_4) δ 1.5-1.8 (m, 4H), 1.88 (br s, 3H), 2.23 (m, 4H), 2.83 (s, 1H), 3.84 (s, 4H); MS (70 eV) m/e (rel intensity) 178(63), 163(13), 86(100).

Preparation of alcohol 49.

A solution of phenyl acetylene (0.26 ml, 2.4 mmole) in 8 ml of ether was treated with 2.42M n-BuLi (0.84 ml, 2 mmole). This mixture was stirred at room temperature for 1 hr, cooled to 0°C, and a solution of 3 (180 mg, 1 mmole) in 5 ml of ether was then added. After stirring for 2.5 hr at 0°C followed by overnight at room temperature, the reaction was quenched with water and worked up as usual. The residue was chromatographed on HPLC (silica gel) with 25% ether-hexane to give 177.6 mg (63%) of 49. Crystallization from ether afforded 80 mg of analytical sample: IR (CCl_4) 3630, 1735, 863 cm^{-1}; PMR (CCl_4) δ 1.03 (s, 3H), 1.2 (s, 3H), 1.3-2.5 (m, 11H), 7.15 (s, 5H); MS (70 eV) m/e (rel intensity) 282(2), 281(12), 267(7.5), 264(1.5), 239(7), 170(100), 169(100).

Preparation of alcohol 50.

Sodium hydride (65 mg, 57%, 1.54 mmole) was washed with pentane to remove the mineral oil and heated with 3 ml of DMSO at 50°C until hydrogen evolution was complete. After cooling, a solution of 46 (230 mg, 1.29 mmole) in 1 ml of DMSO was added dropwise. The resulting deep blue mixture was stirred for 0.5 hr and then treated with cyclohexanone (0.13 ml, 1.25 mmole). This reaction mixture was stirred at room temperature overnight and quenched with water. The usual work-up gave 230.8 mg of a red oil, which was chromatographed on HPLC (silica gel) with 20% ethyl acetate-hexane to give 160.6 mg (47%) of 50. An analytical sample was crystallized from ether and displayed the following properties: mp 79.5-80.5°; IR ($CDCl_3$) 3608, 3485, 1070 cm^{-1}; PMR ($CDCl_3$) δ 1.0-1.8 (m, 10H), 1.87 (br s, 3H), 2.07-2.47 (m, 4H), 3.75 (s, 4H); MS (70 eV) m/e (rel intensity) 276(4.6), 261(2.1), 86(100).

Anal. Calcd. for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75

Found: C, 73.86; H, 8.72

Reaction of ketone 3 with acetylide 47(a).

To a solution of 2.42M n-BuLi (0.39 ml, 0.94 mmole) and TMEDA (0.15 ml, 1 mmole) in THF at 10°C was added dropwise a solution of 46 (184 mg, 1.03 mmole) in THF. The resulting brown solution was stirred for 25 min., then cooled to -78°C and treated with a solution of ketone **3** (81 mg, 0.45 mmole) in THF. After stirring for 1 hr at -78°C, followed 1.5 hr at 0°C, the reaction mixture was worked up in the usual way. The crude product (0.23 g) was chromatographed on HPLC (silica gel) with 25% ethyl acetate -hexane to afford 88.1 mg of **46** and 60 mg of **3**.

Transformation of ketal **46** to alcohol **51**.

To 3 ml of a dimethyl sulfoxide solution of dimsylsodium (1.28 mmole) was added a solution of **46** (192 mg, 1.08 mmole) in 2 ml of DMSO. This solution was then treated with ketone **3** (82 mg, 0.46 mmole) in DMSO and the mixture was heated at 50°C for two days. After cooling, the usual work-up gave 110 mg of crude product. This oil was spread on a preparative silica gel plate; eluting with 20% ethyl acetate-hexane gave four bands. The third band yielded 15.2 mg of **51**: IR ($CDCl_3$) 3590, 1601, 1567, 1490, 1283, 1243, 1071, 1037 cm^{-1};PMR (CCl_4) δ 1.85 (s, 1H), 2.24 (s, 3H), 3.6-4.2 (m, 4H), 5.17 (dd, 1H, J=10.4, 2 Hz), 5.47 (dd, 1H, J=17.6, 2 Hz); MS (70 eV) m/e (rel intensity) 178(66.5), 134(100), 133(88.5).

Reaction of ketone **3** with Grignard reagent from **46**.

To a three-neck, round bottom flask containing magnesium turnings (24 mg, 1mmole) and ether was added dropwise an ether solution of methyl iodide (0.036 ml, 0.58 mmole). After this mixture became turbid, it was stirred for

30 min. to complete the methyl magnisium iodide formation and then a solution of 46 (104 mg, 0.58 mmole) in ether was added dropwise. The reaction mixture was stirred for 1 hr and then treated with a solution of 3 (47 mg, 0.26 mmole) in ether. After stirring at room temperature overnight, this solution was quenched with sat. ammonium chloride and worked up in the usual way. The crude product (147.5mg) displayed spectral and chromatographic properties identical with a mixture of 46 and 3.

Attempt to trap enolate from 3 with t-butyldimethylchlorosilane.

To a solution of dimsylsodium (0.57 mmole) in 3 ml of DMSO was added dropwise a solution of 46 (100.7 mg, 0.56 mmole) in DMSO. The mixture was stirred for 30 min. and combined with a solution of 3 (47 mg, 0.26 mmole) in DMSO. After 3.5 hr, this solution was mixed with a solution of t-butyldimethylchlorosilane (135 mg, 0.90 mmole) in THF. The resulting mixture was stirred overnight, quenched with water and extracted with ether. The usual work-up yielded 199 mg of crude product which proved to be a mixture of 3 and some unidentified isomers of 46. The GLPC analysis and mass spectrum of the crude product showed that no silyl ether 52 was formed.

Preparation of alcohol 48.

To a solution of 46 (200mg, 1.12 mmole) in THF was added dropwise 2.42M n-BuLi (0.42 ml, 1.02 mmole) at room temperature. This mixture was stirred for 1 hr, cooled to 0°, and then treated with a solution of 3 (90 mg, 0.5 mmole) and lithium iodide (160 mg, 1.20 mmole) in THF. After stirring for 2.5 hr at 0°C, followed by overnight at room temperature, the reaction was quenched with water and extracted with ether and ethyl acetate. This extract gave 250 mg of crude product, and 205.7 mg of the residual oil was chromatographed on two preparative silica gel plates. Elution with 25% ethyl acetate-hexane gave 18 mg (12%) of 48: IR (CCl_4) 3605, 1738, 1065 cm^{-1}; PMR (CCl_4) δ 0.92 (s, 3H), 1.12 (s, 3H), 1.28-2.45 (m, 20H), 3.75 (s, 4H); MS (70 eV) m/e (rel intensity) 358(3.5), 340(2.5), 246(12), 180(21), 110(31), 88(67), 86(70), 70(100). An analytical sample of 48 was crystallized from ether-ethyl acetate, mp 134.5-135°.

APPENDIX

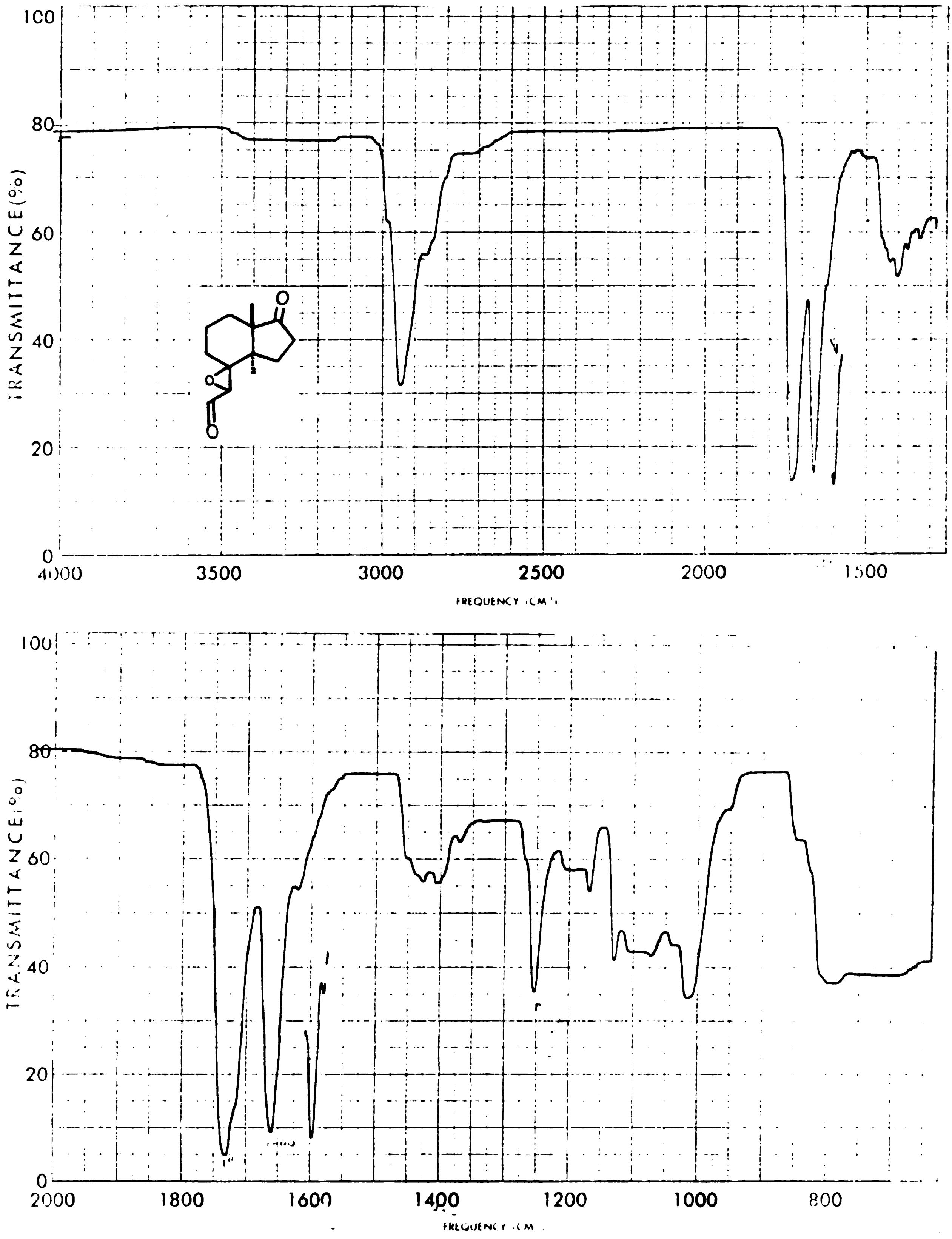


Figure 1. Infrared spectrum of $\underset{\sim}{26}$.

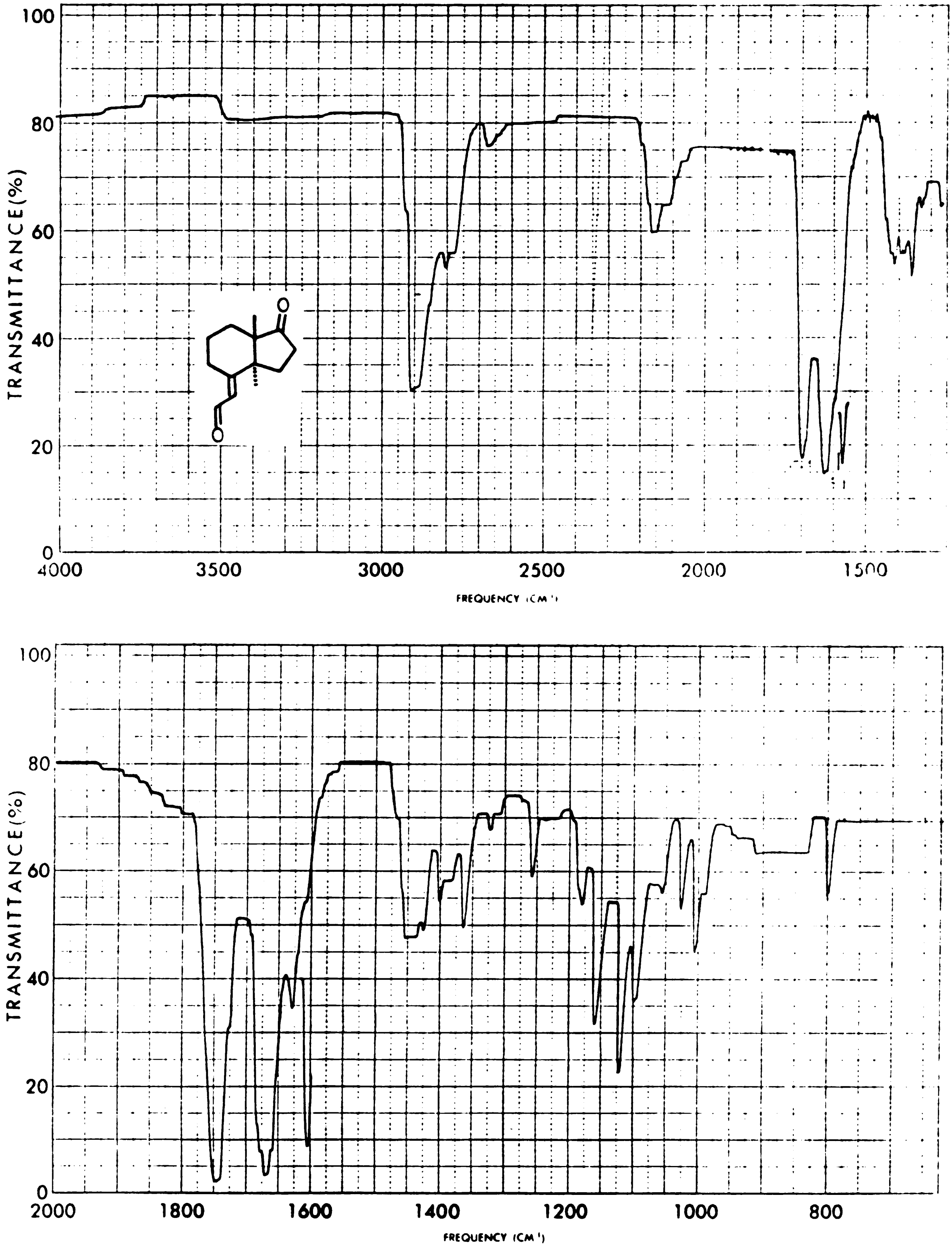


Figure 2. Infrared spectrum of 25 (in $CDCl_3$).

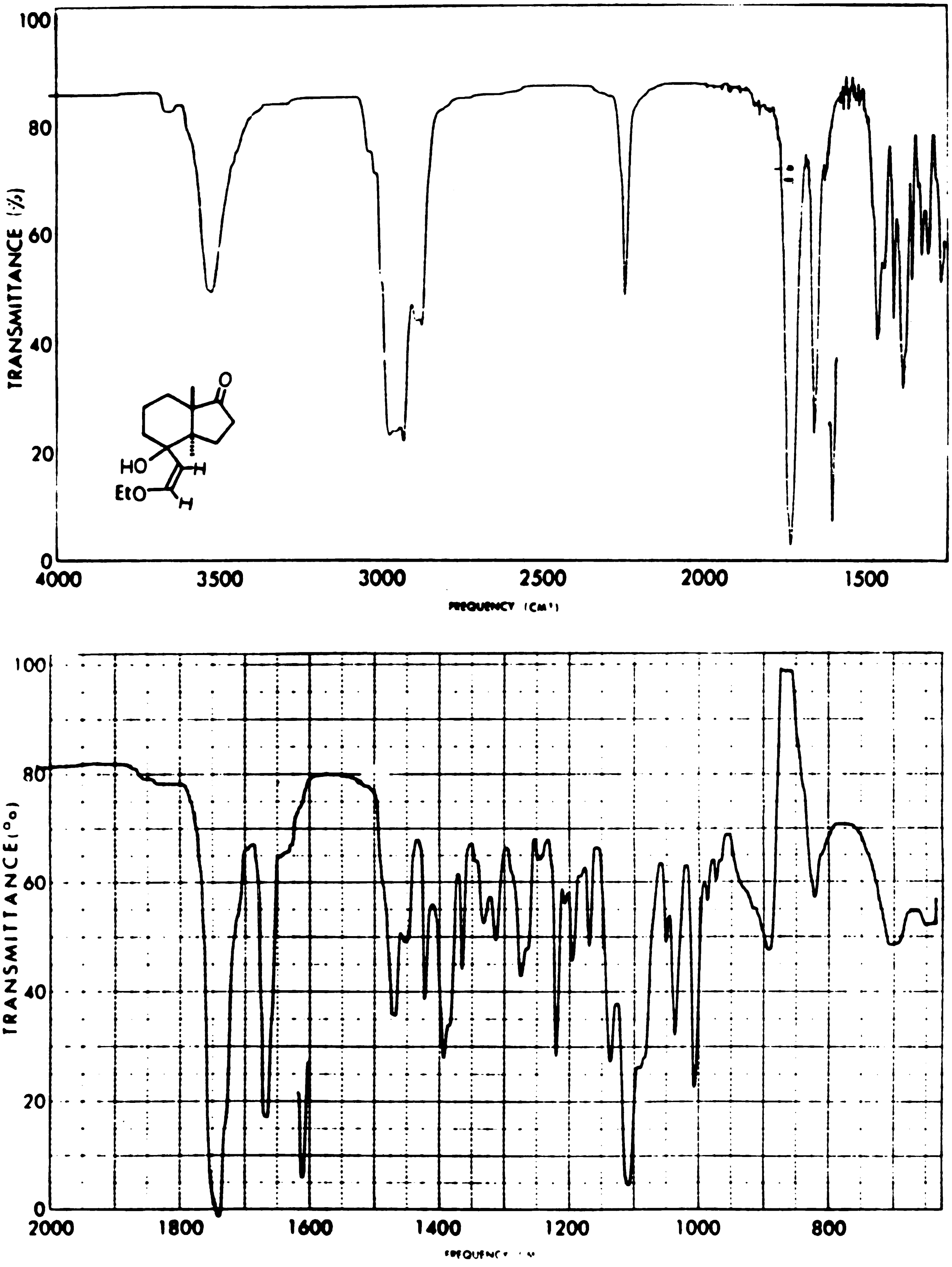


Figure 3. Infrared spectrum of $\underset{\sim}{31}$ (in $CDCl_3$).

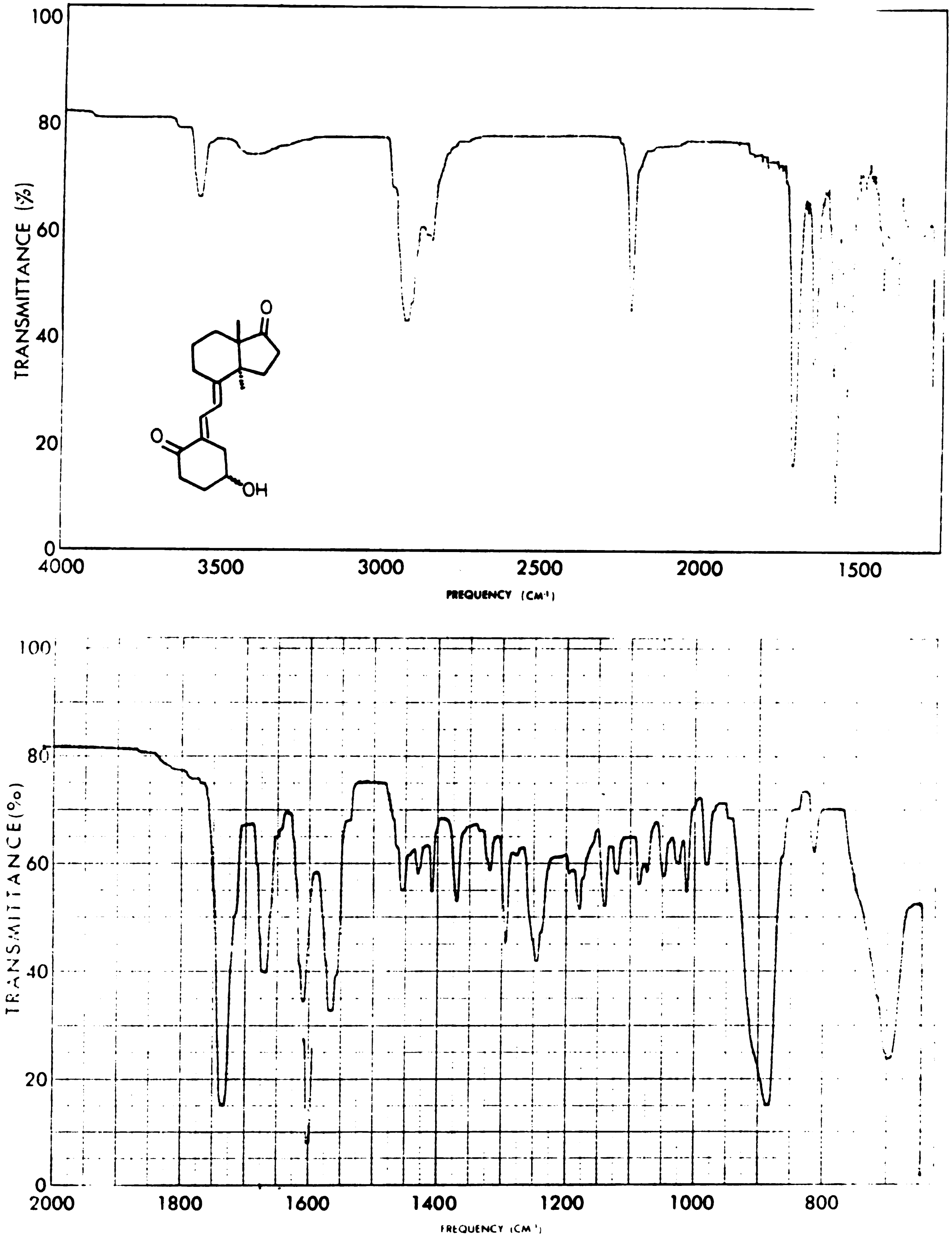


Figure 4. Infrared spectrum of 34 (in $CDCl_3$).

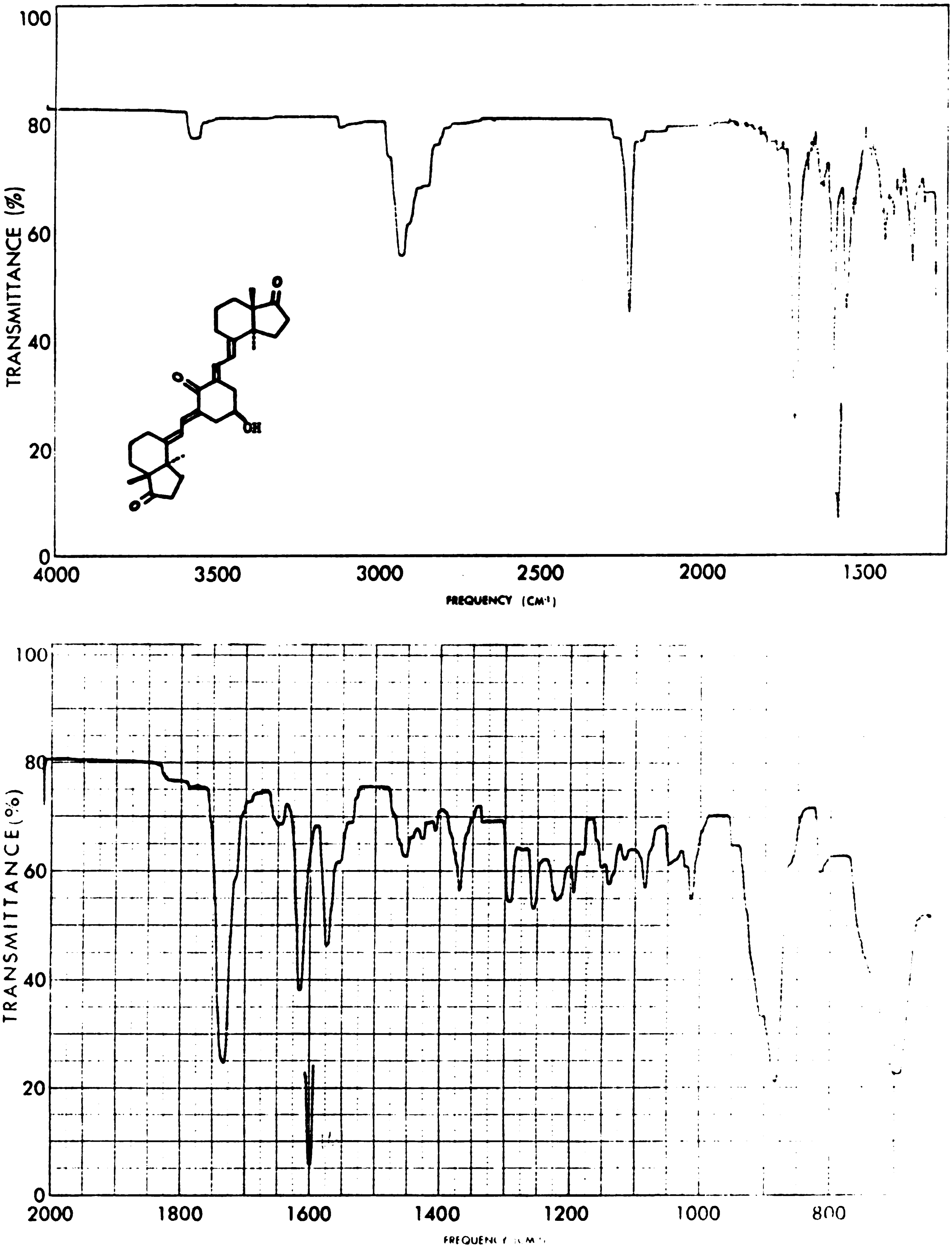


Figure 5. Infrared spectrum of 35 (in $CDCl_3$).

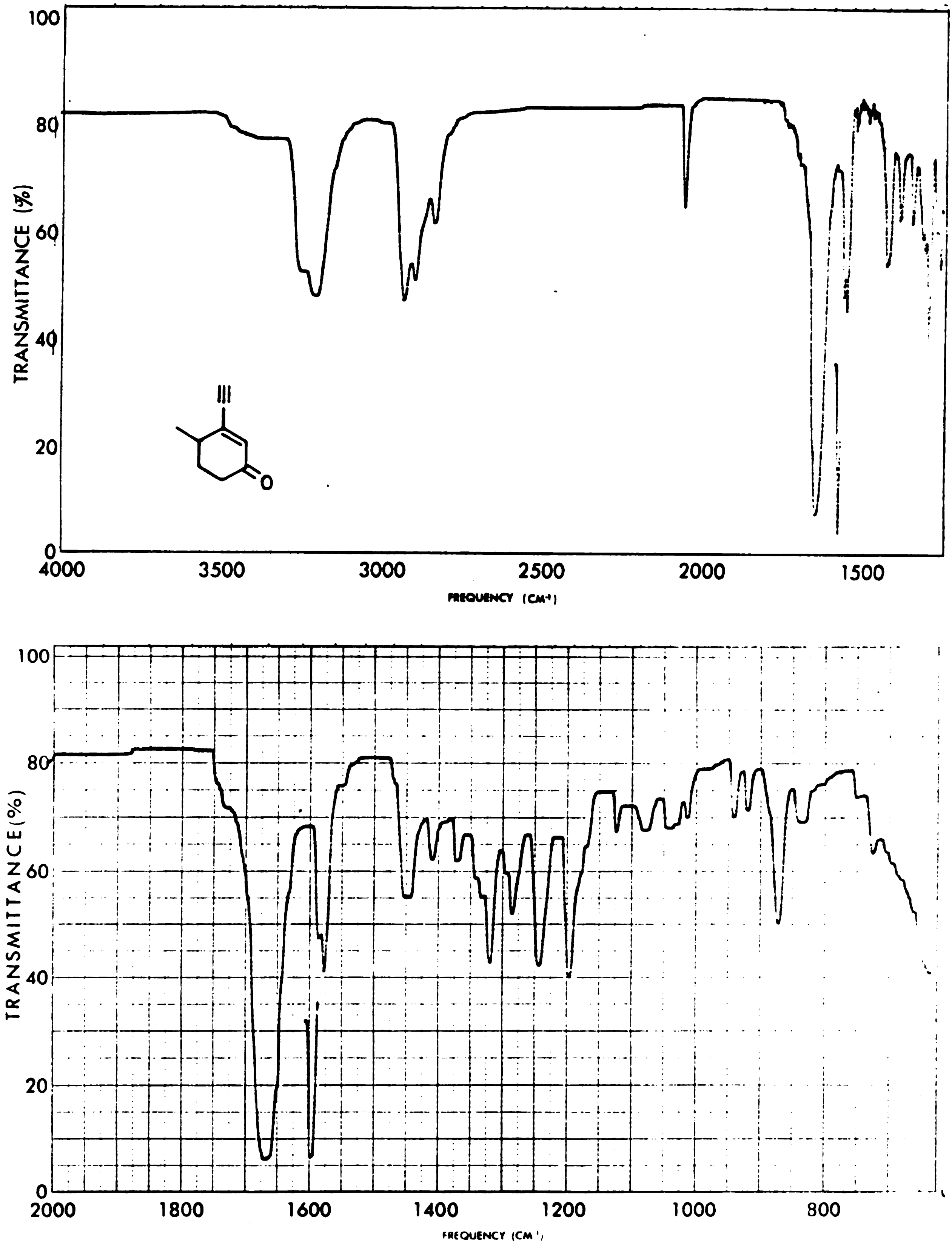


Figure 6. Infrared spectrum of 45.

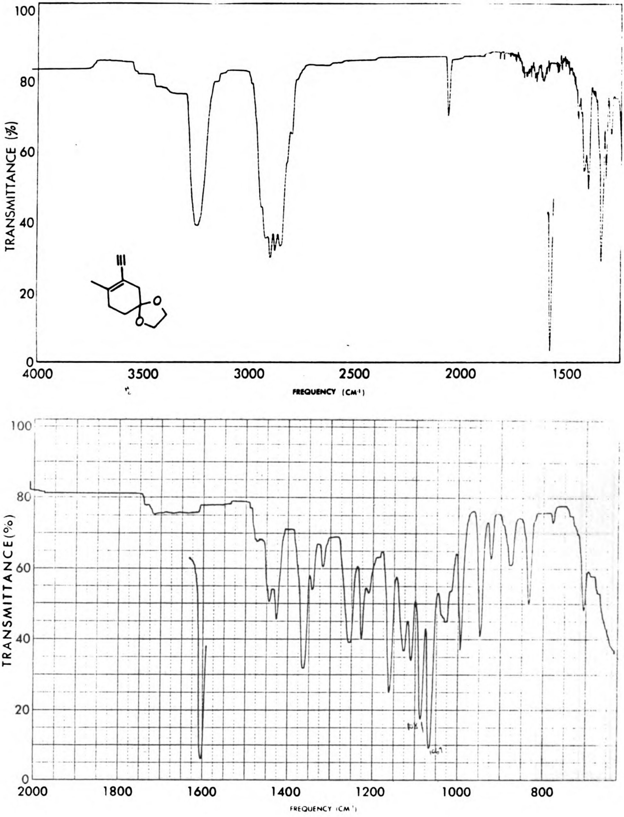


Figure 7. Infrared spectrum of 46.

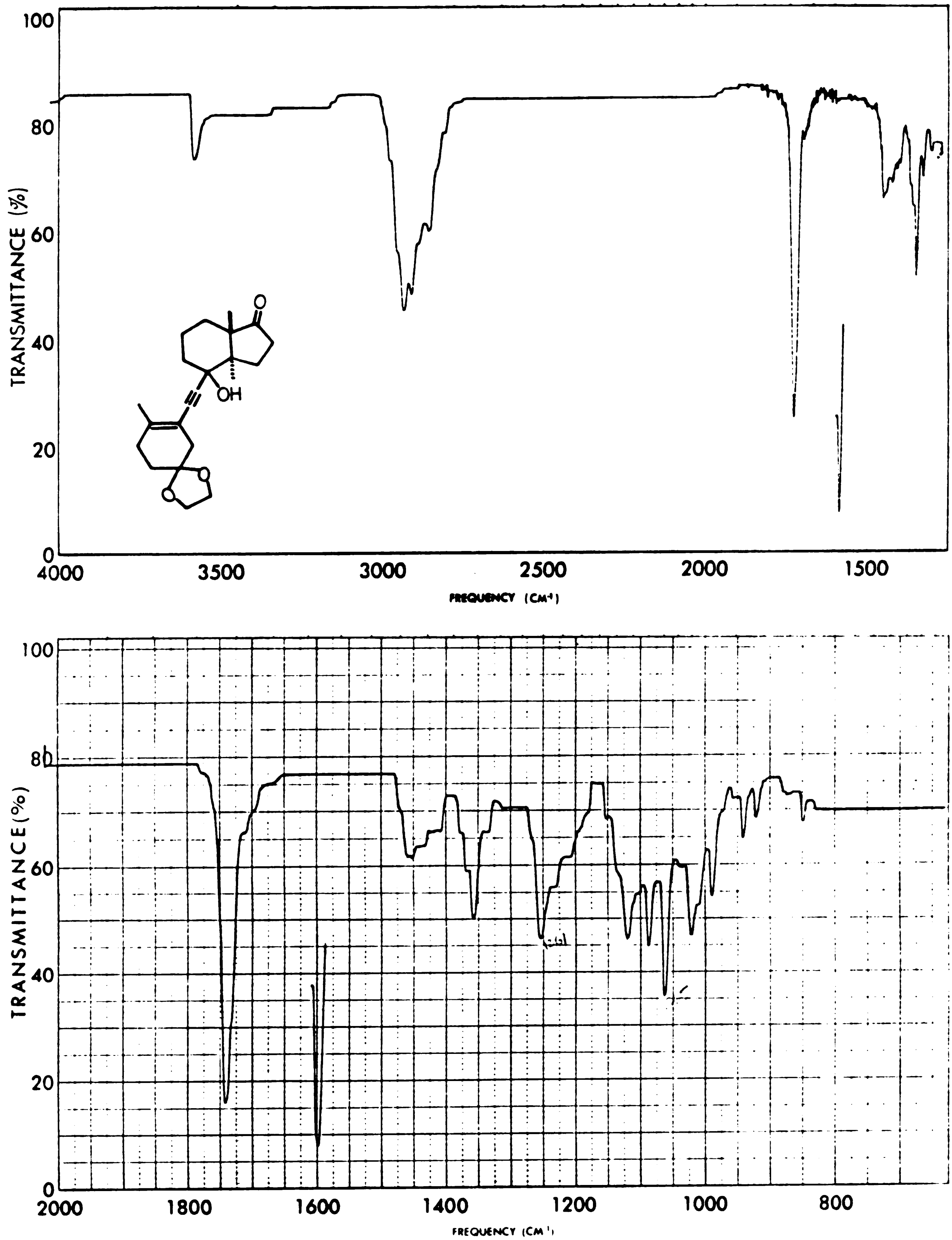


Figure 8. Infrared spectrum of 48.

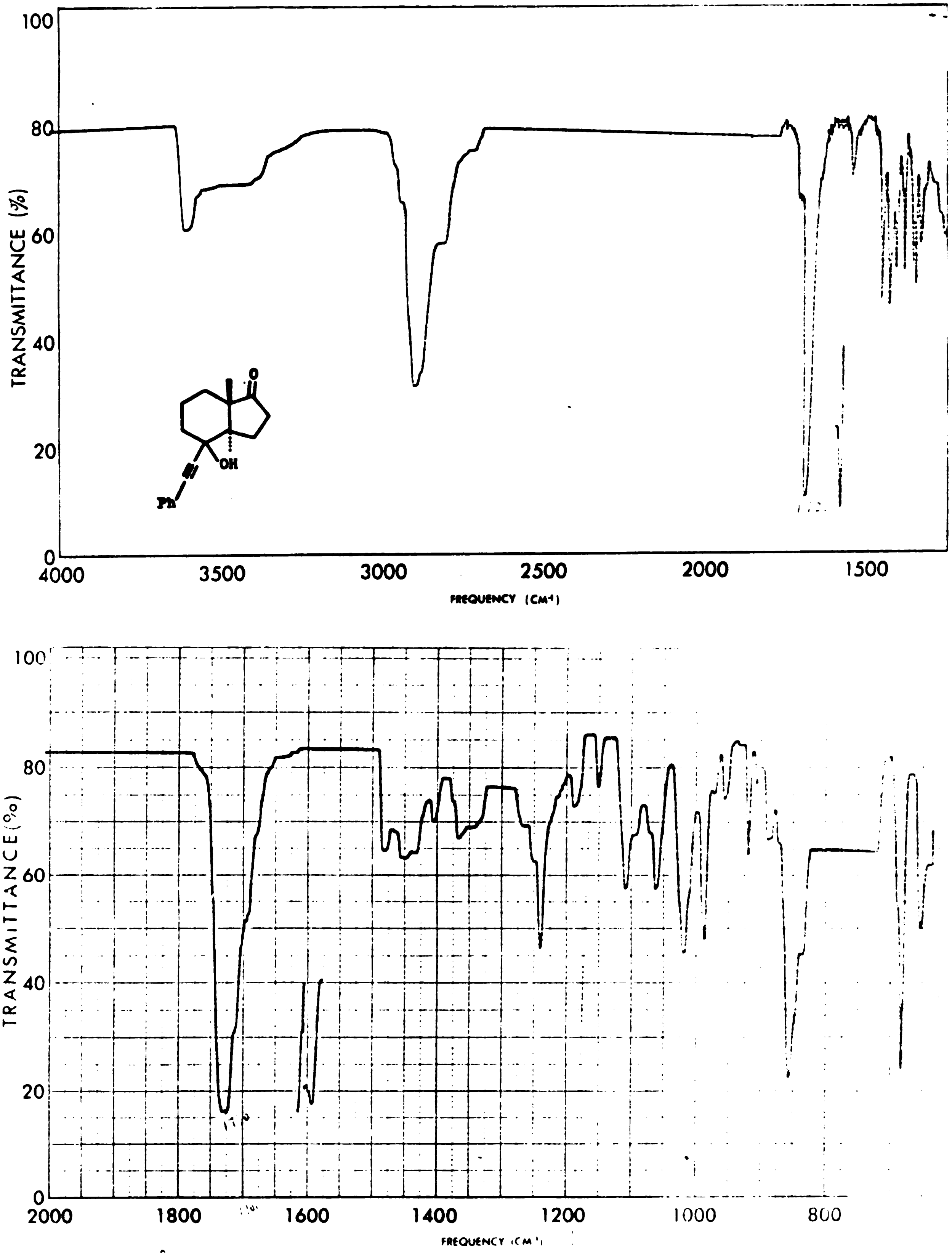


Figure 9. Infrared spectrum of 49.

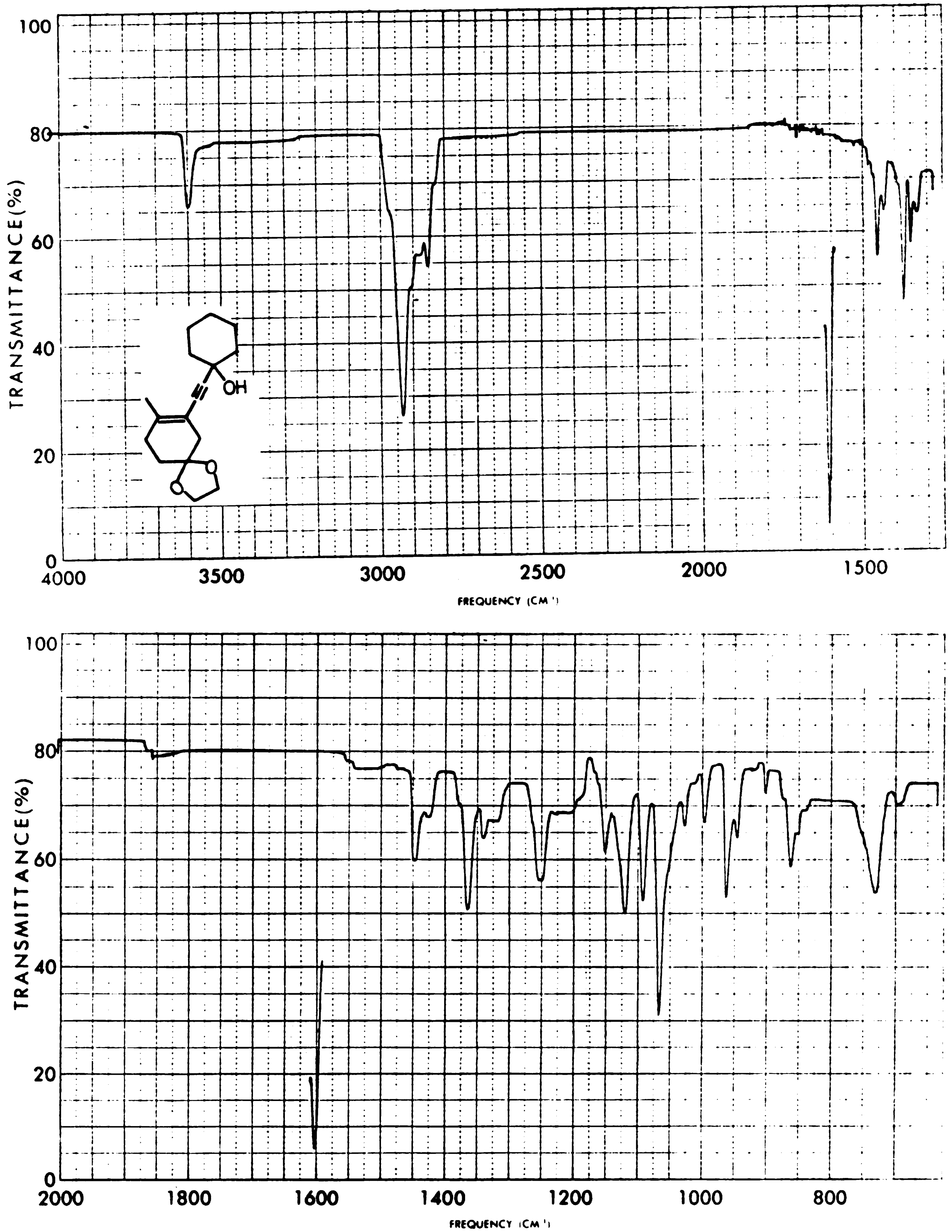


Figure 10. Infrared spectrum of 50.

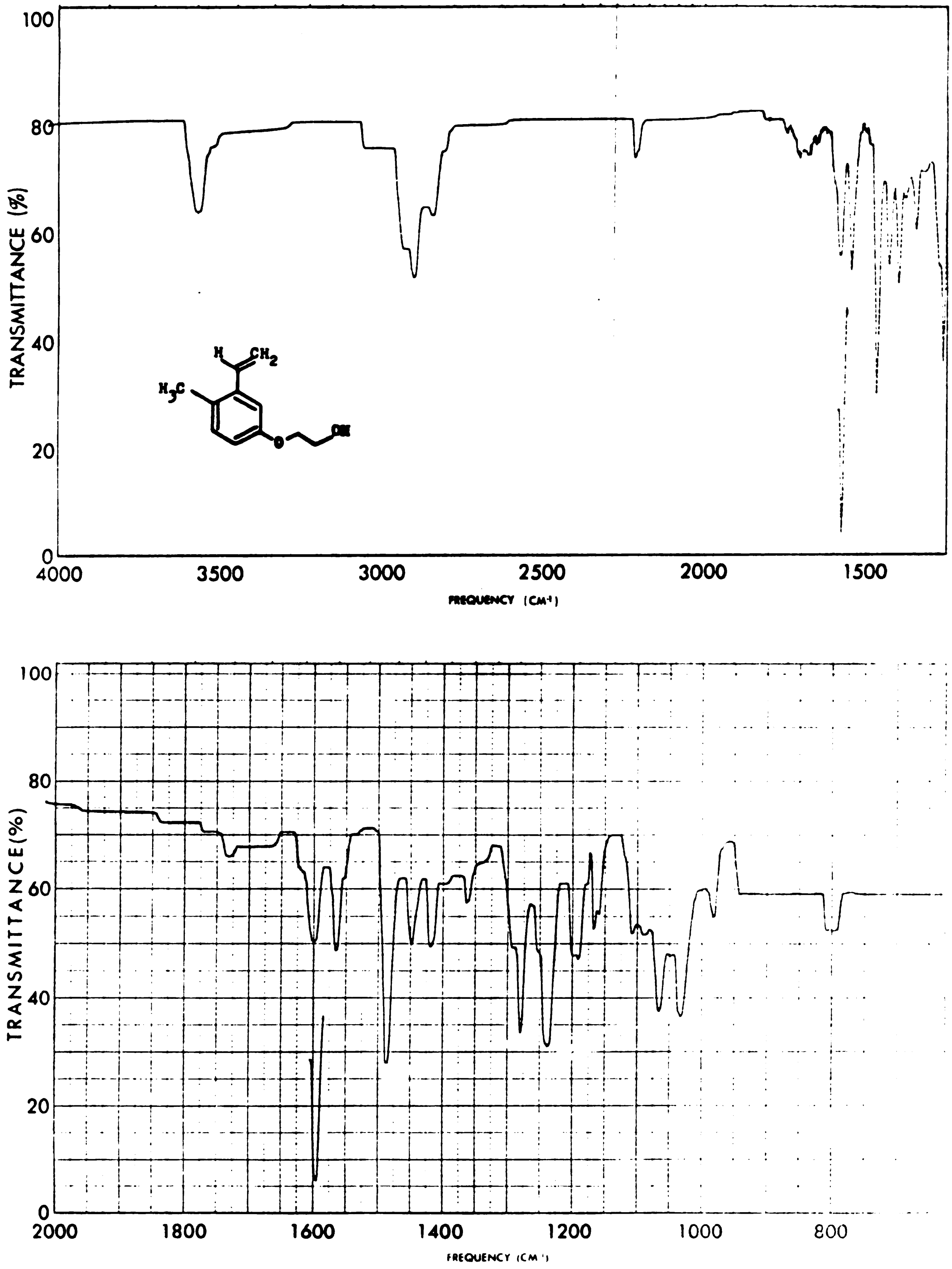


Figure 11. Infrared spectrum of 51 (in CDCl$_3$).

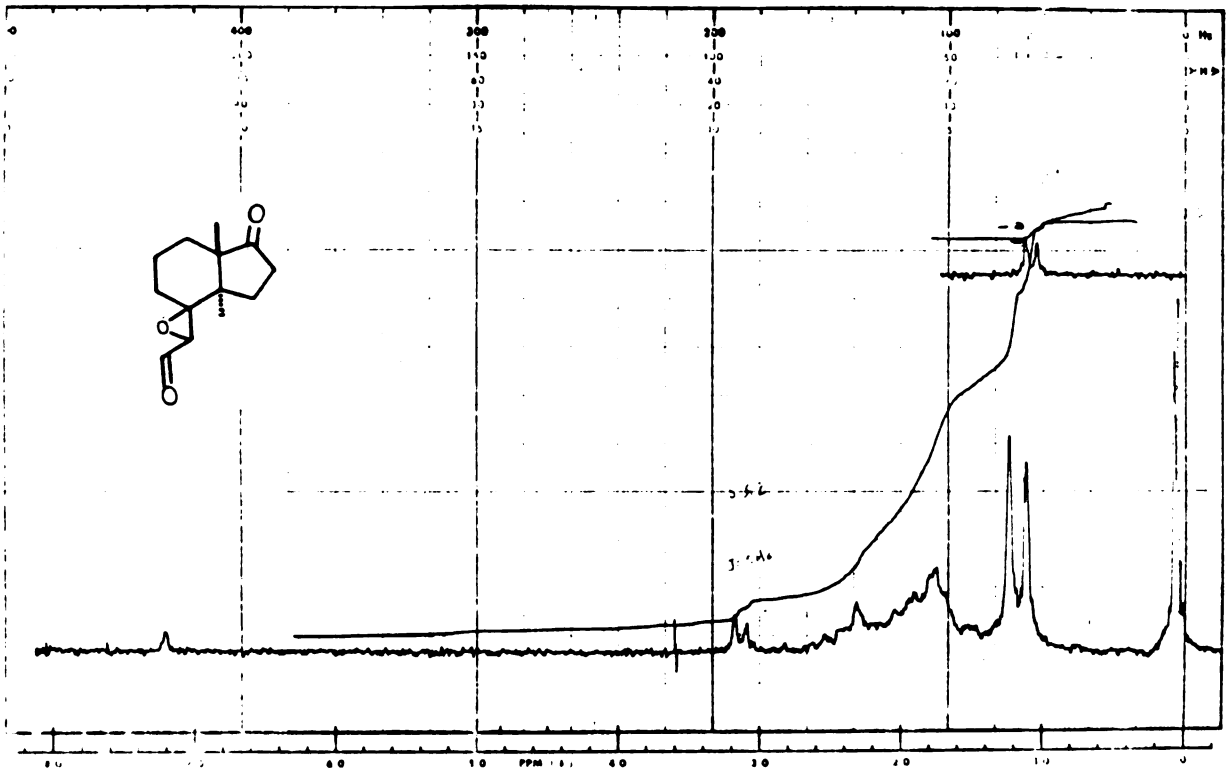


Figure 12. PMR spectrum of 26.

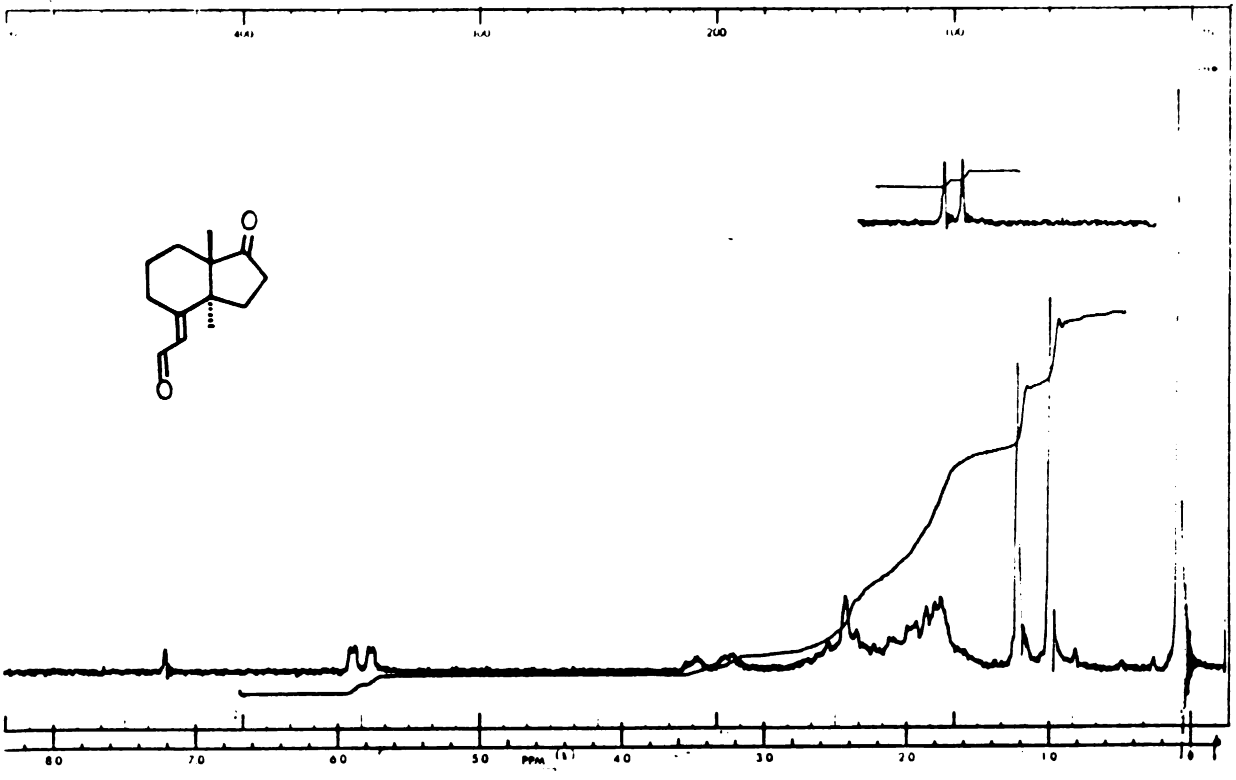


Figure 13. PMR spectrum of 25.

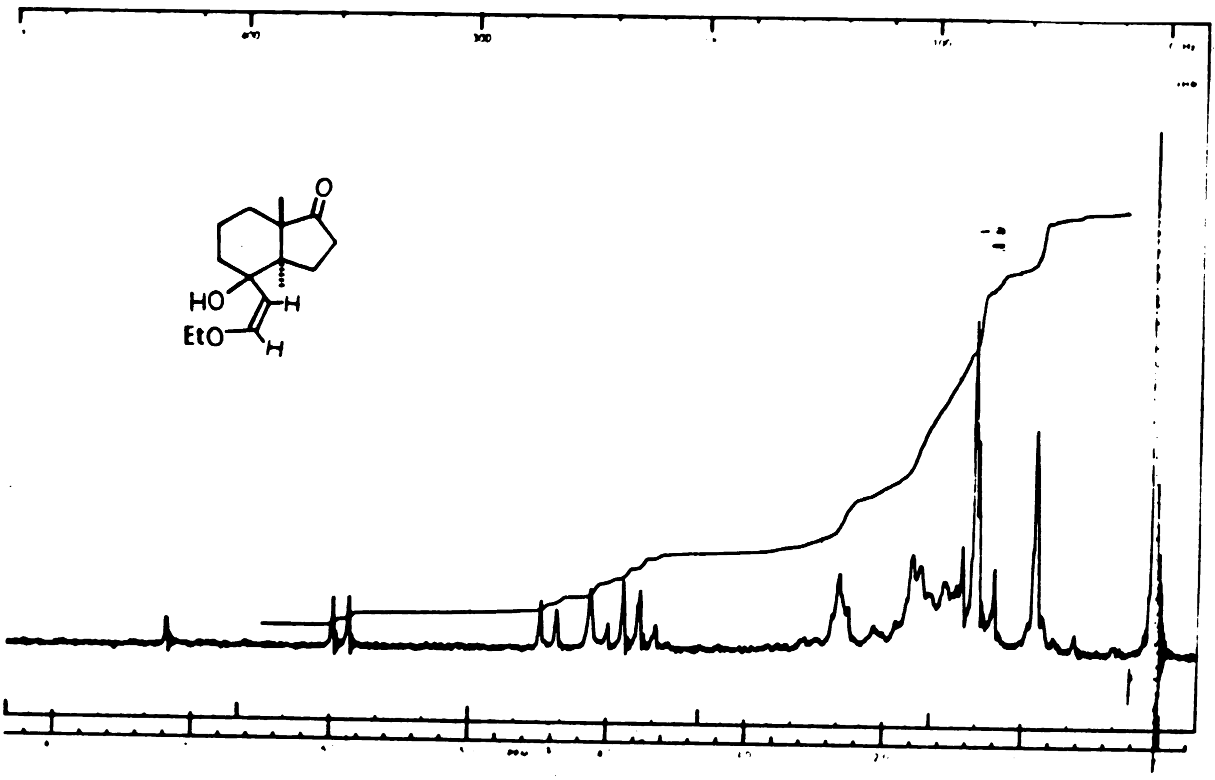


Figure 14. PMR spectrum of $\underset{\sim}{31}$.

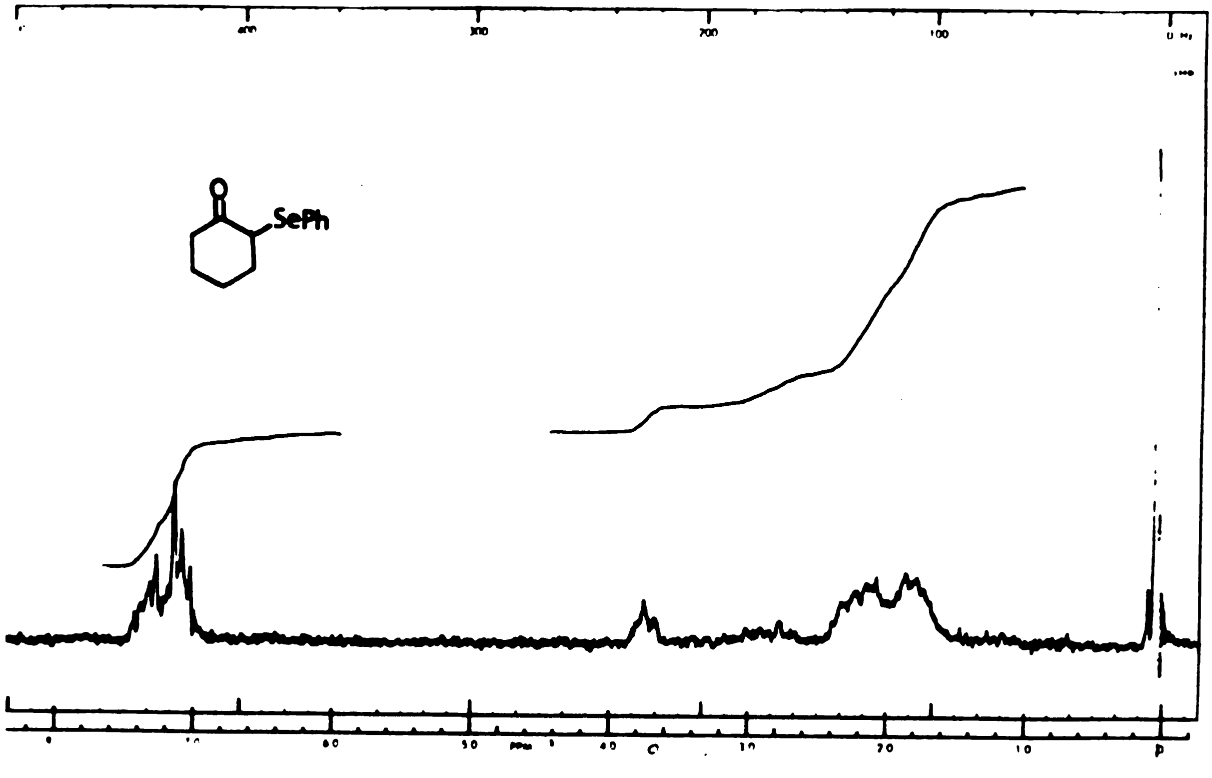


Figure 15. PMR spectrum of $\underset{\sim}{36}$.

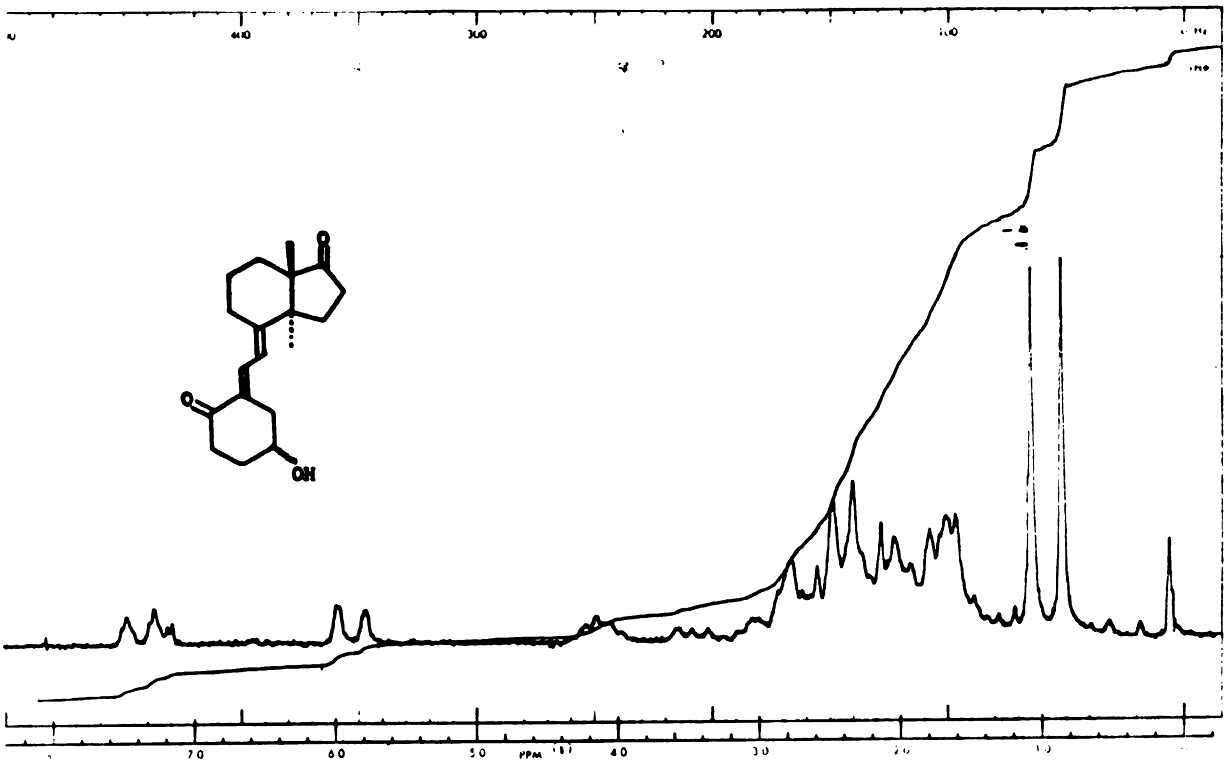


Figure 16. PMR spectrum of 34.

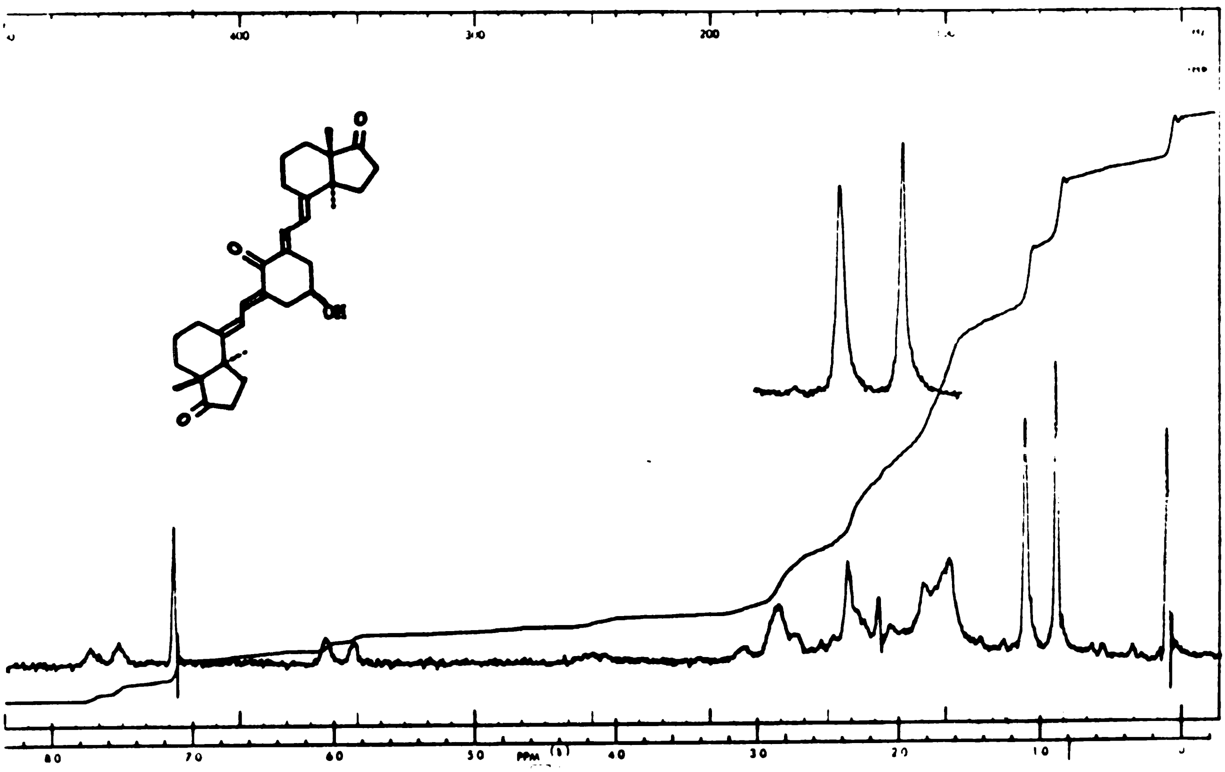


Figure 17. PMR spectrum of 35.

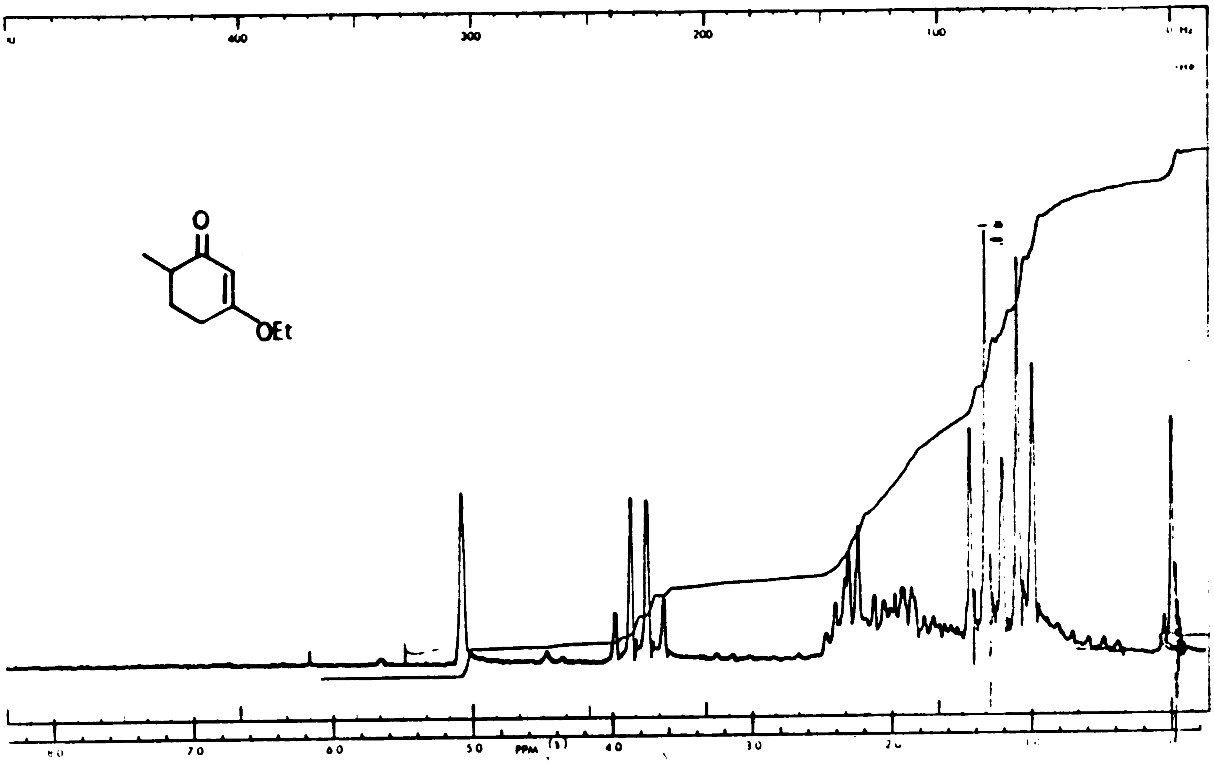


Figure 18. PMR spectrum of 43.

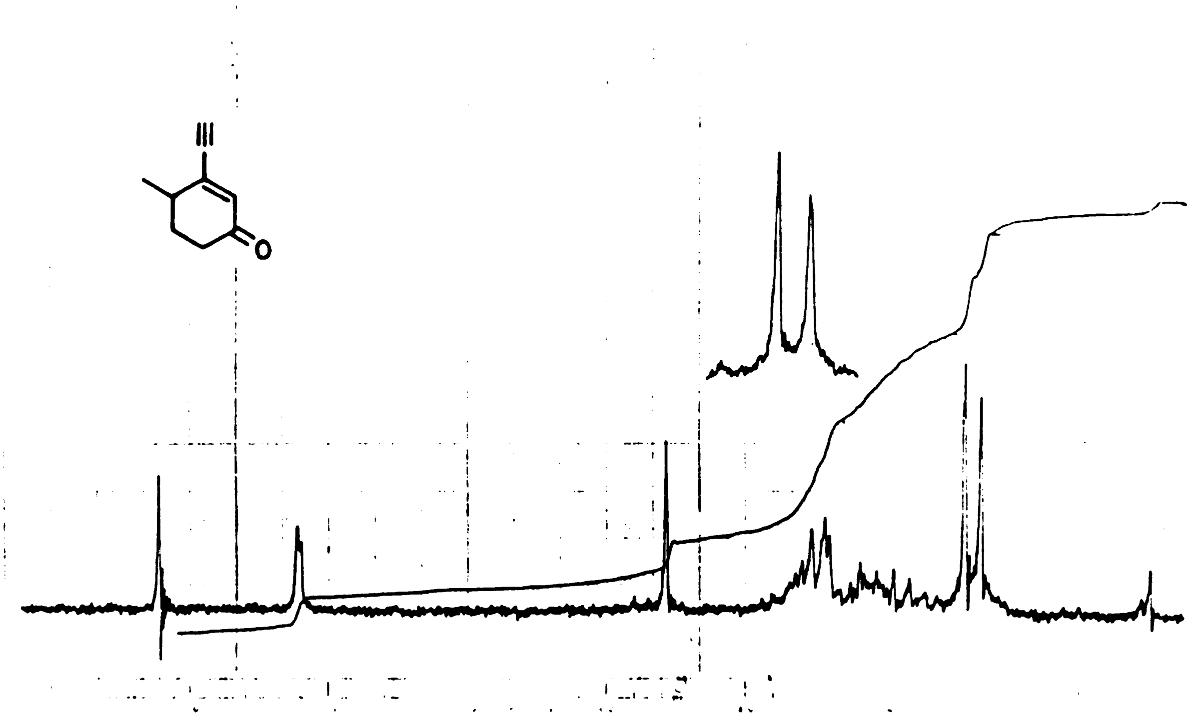


Figure 19. PMR spectrum of 45.

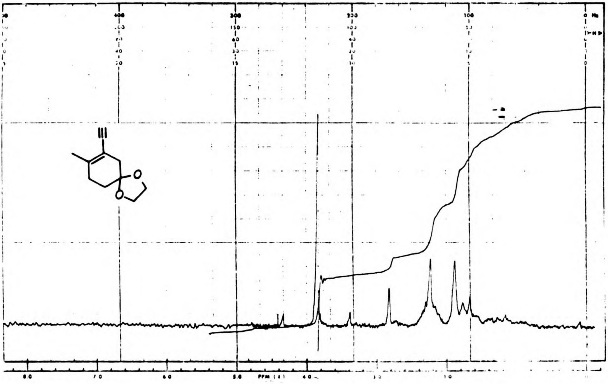


Figure 20. PMR spectrum of 46.

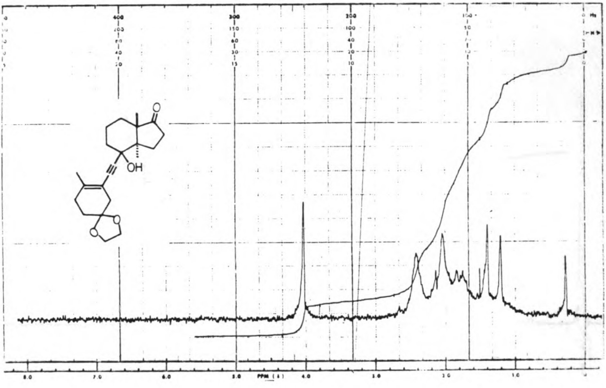


Figure 21. PMR spectrum of 48.

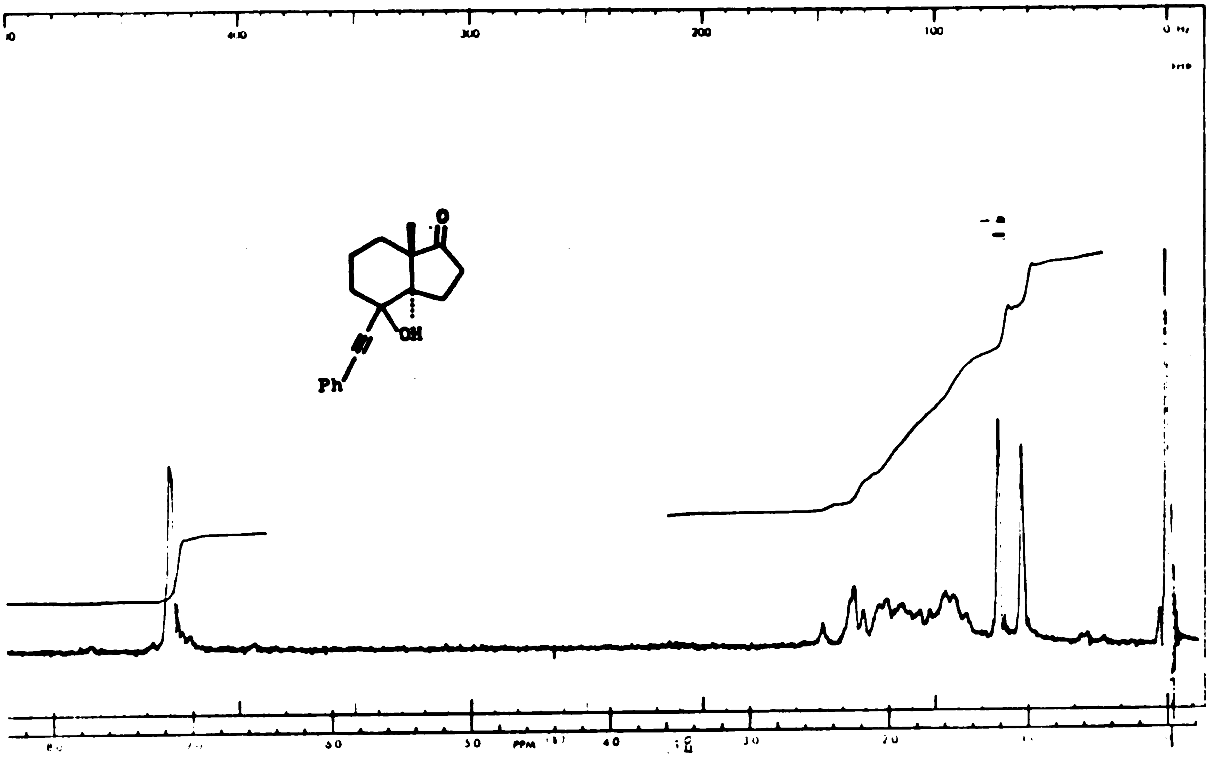


Figure 22. PMR spectrum of $\underset{\sim}{49}$.

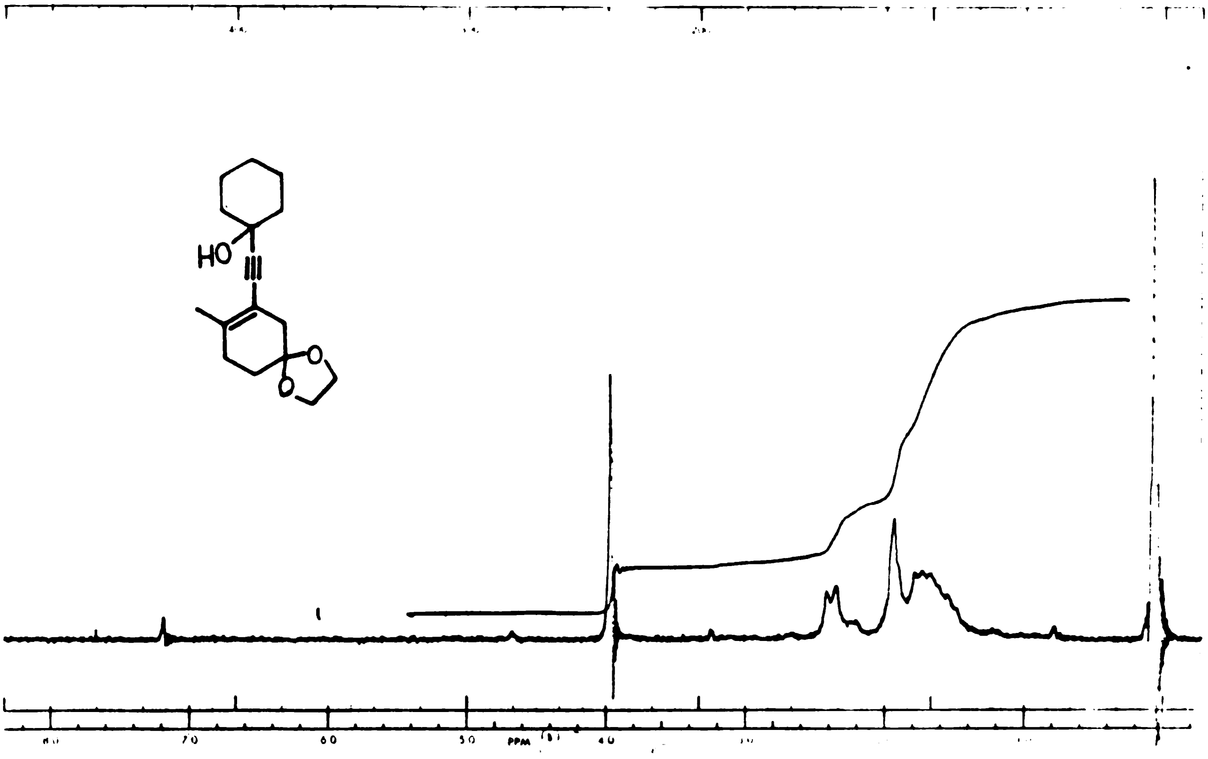


Figure 23. PMR spectrum of $\underset{\sim}{50}$.

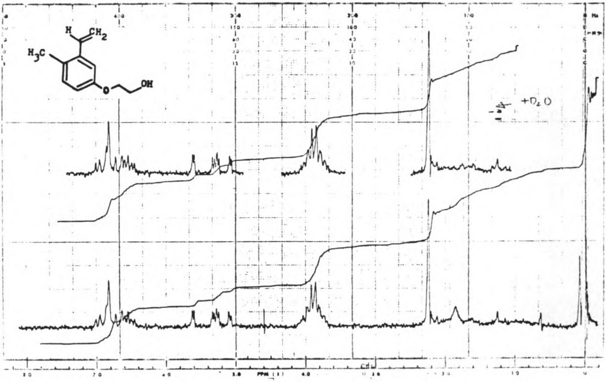


Figure 24. PMR spectrum of 51.

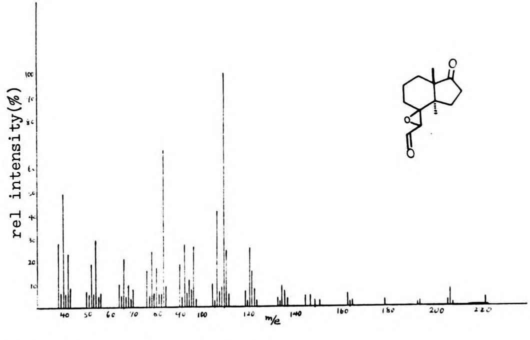


Figure 25. Mass spectrum of 26.

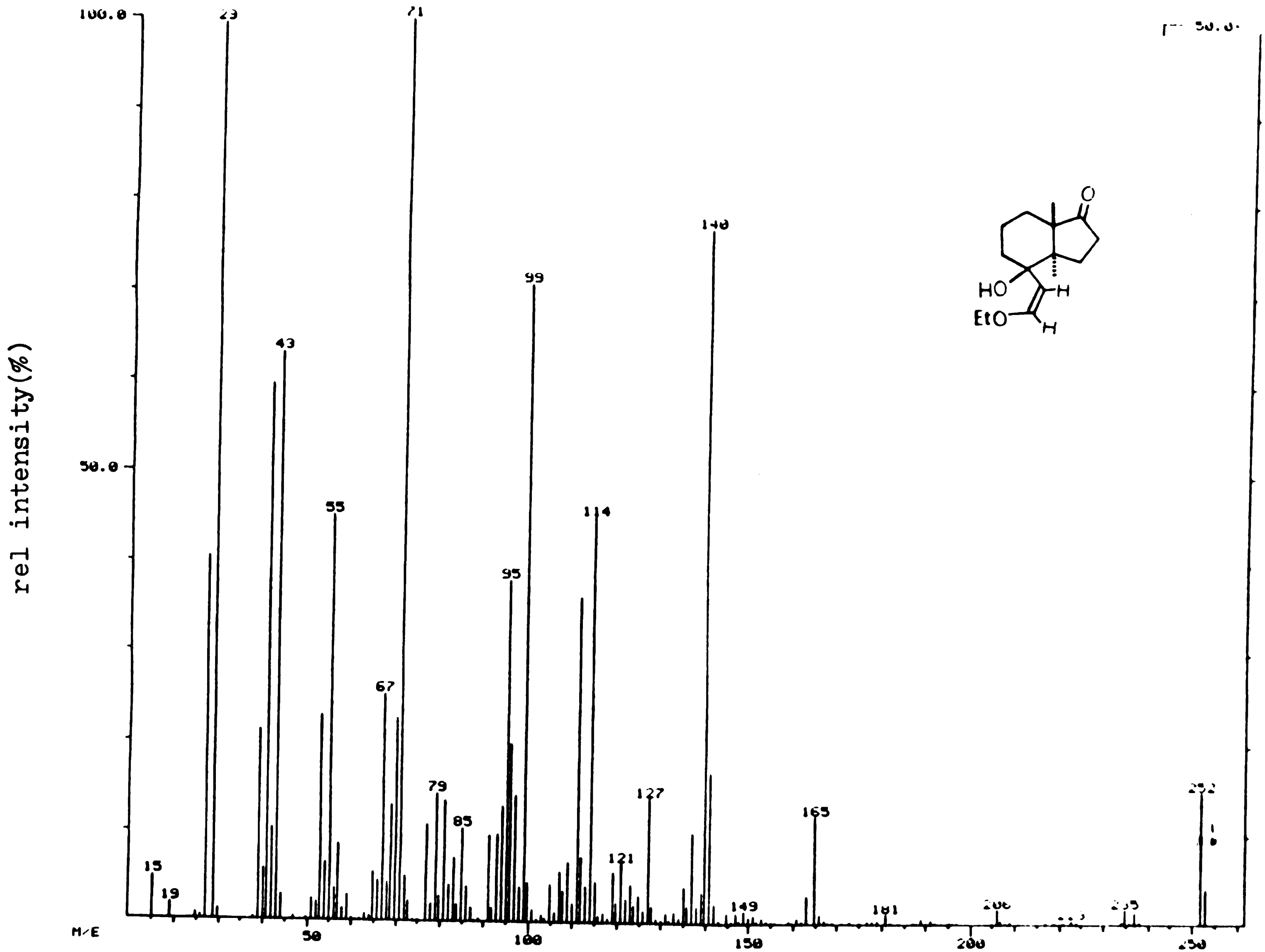


Figure 26. Mass spectrum of 31.

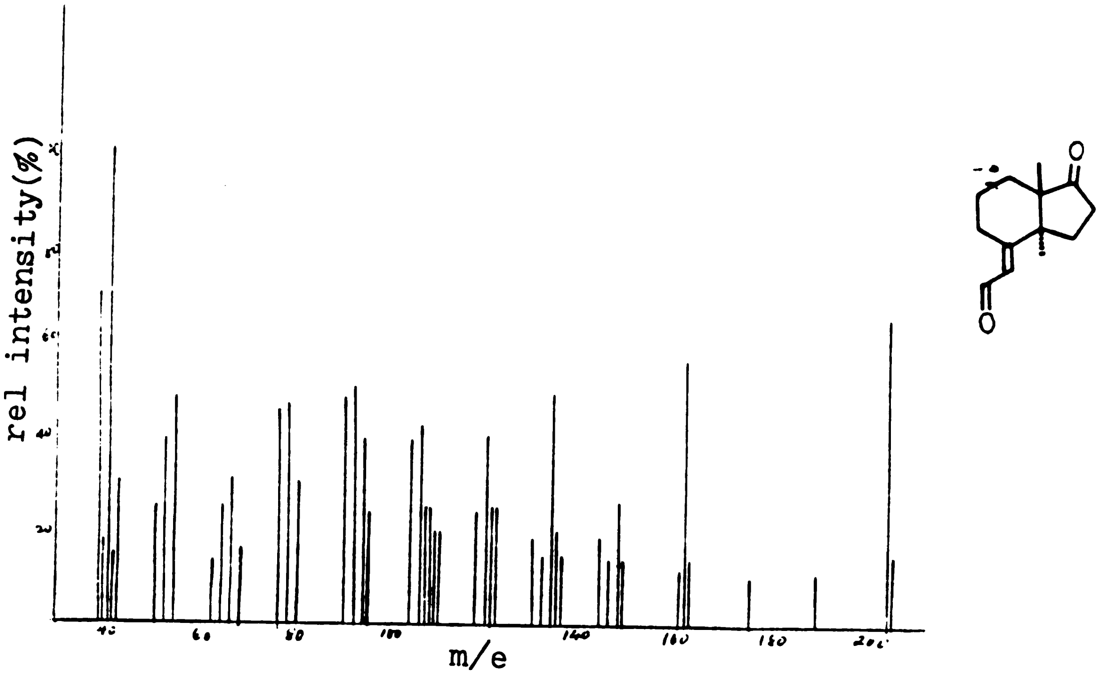


Figure 28. Mass spectrum of $\underset{\sim}{34}$.

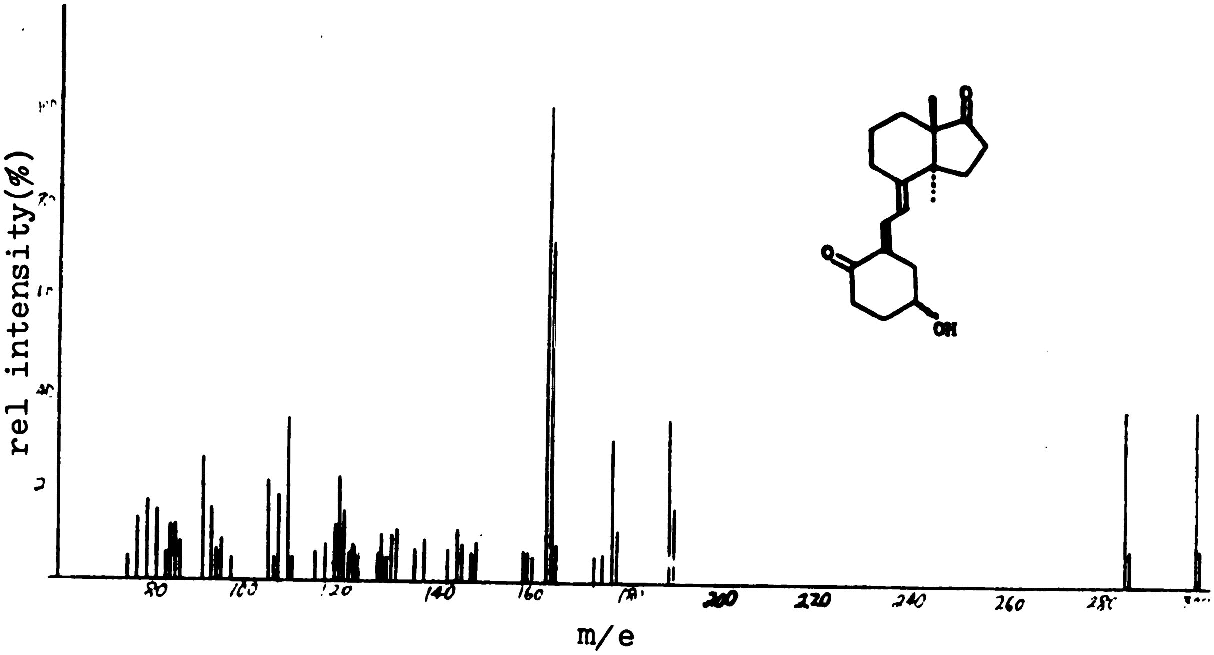


Figure 27. Mass spectrum of $\underset{\sim}{25}$.

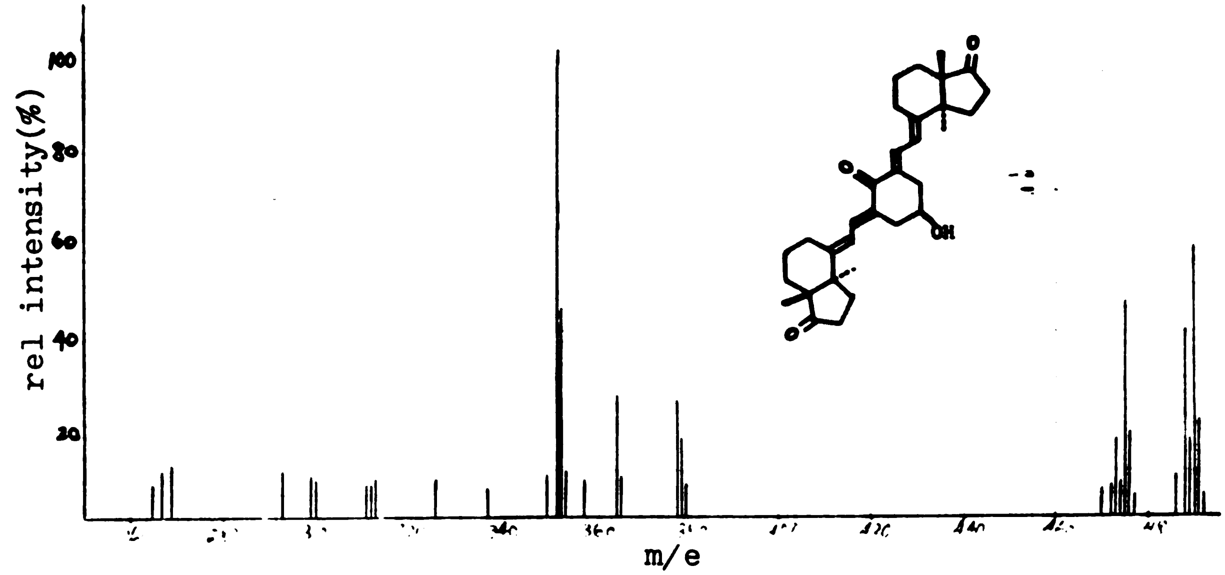


Figure 29. Mass spectrum of $\underset{\sim}{35}$.

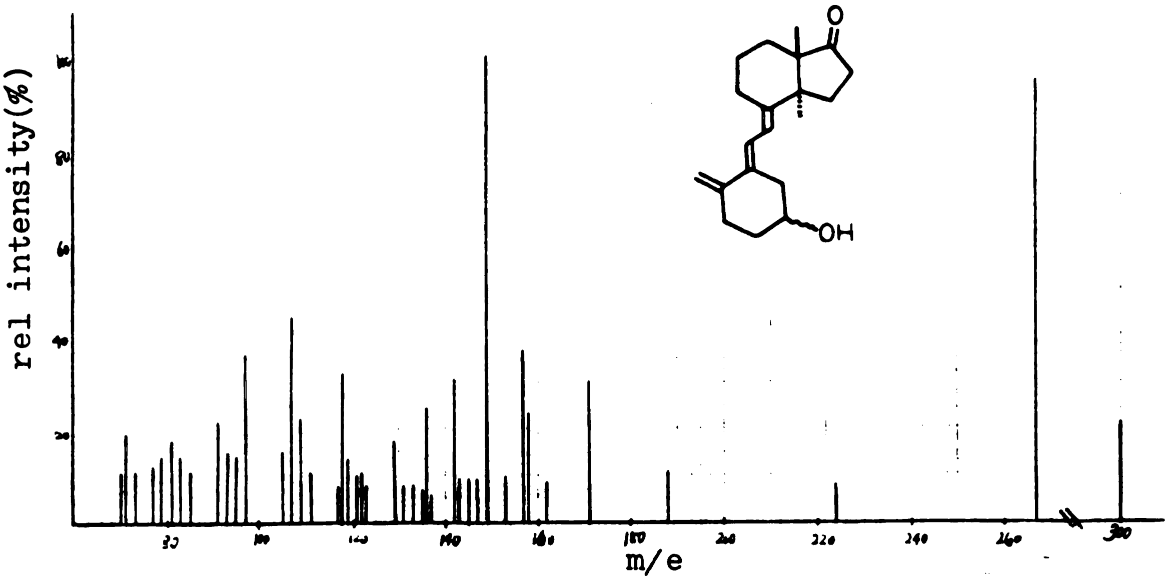


Figure 30. Mass spectrum of $\underset{\sim}{39}$.

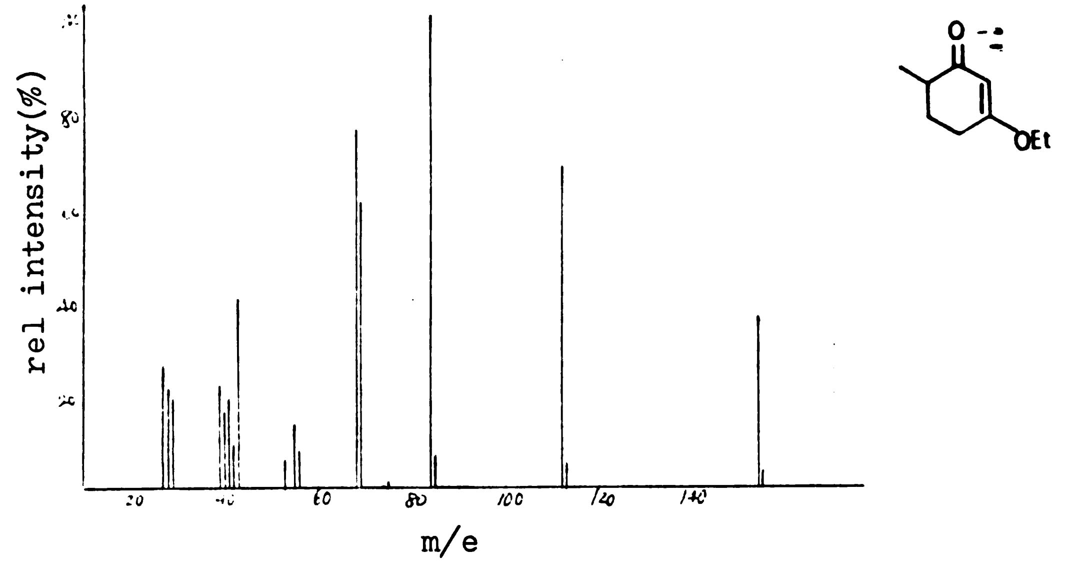


Figure 31. Mass spectrum of 43.

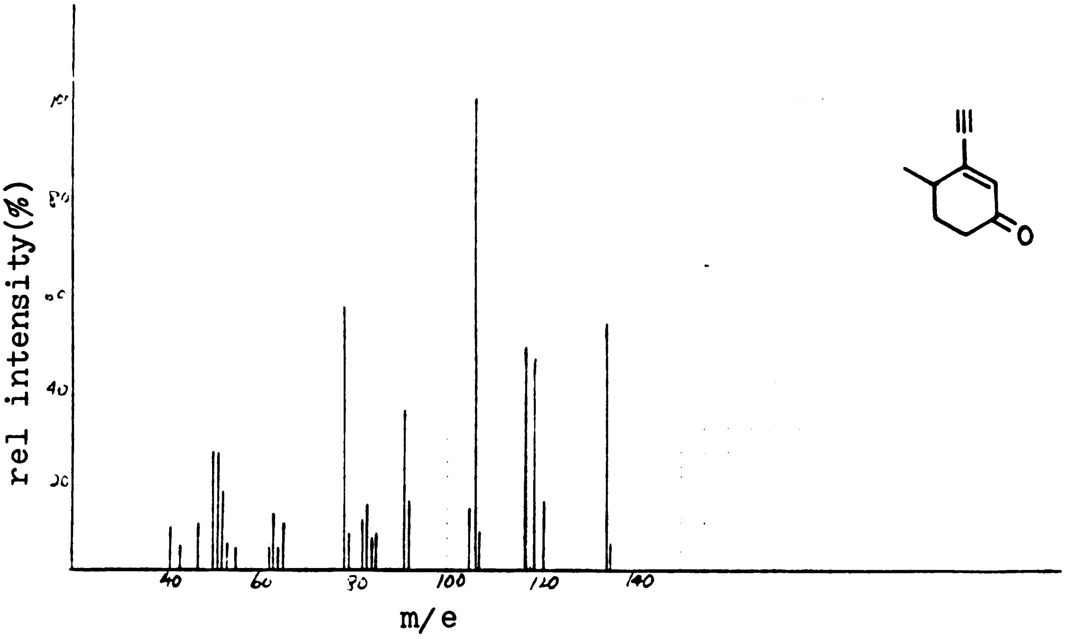


Figure 32. Mass spectrum of 45.

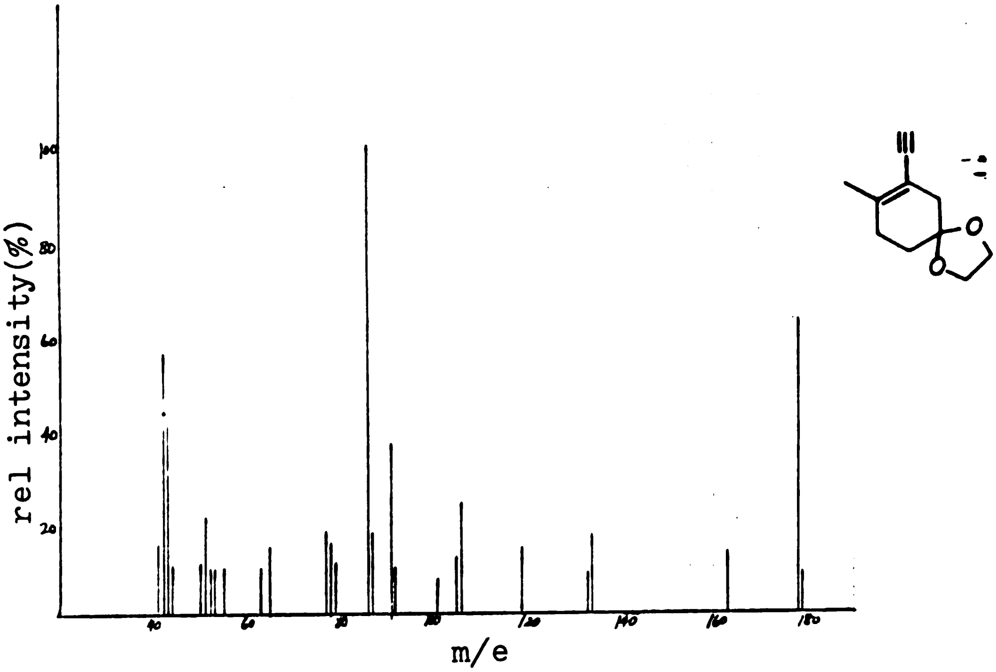


Figure 33. Mass spectrum of 46.

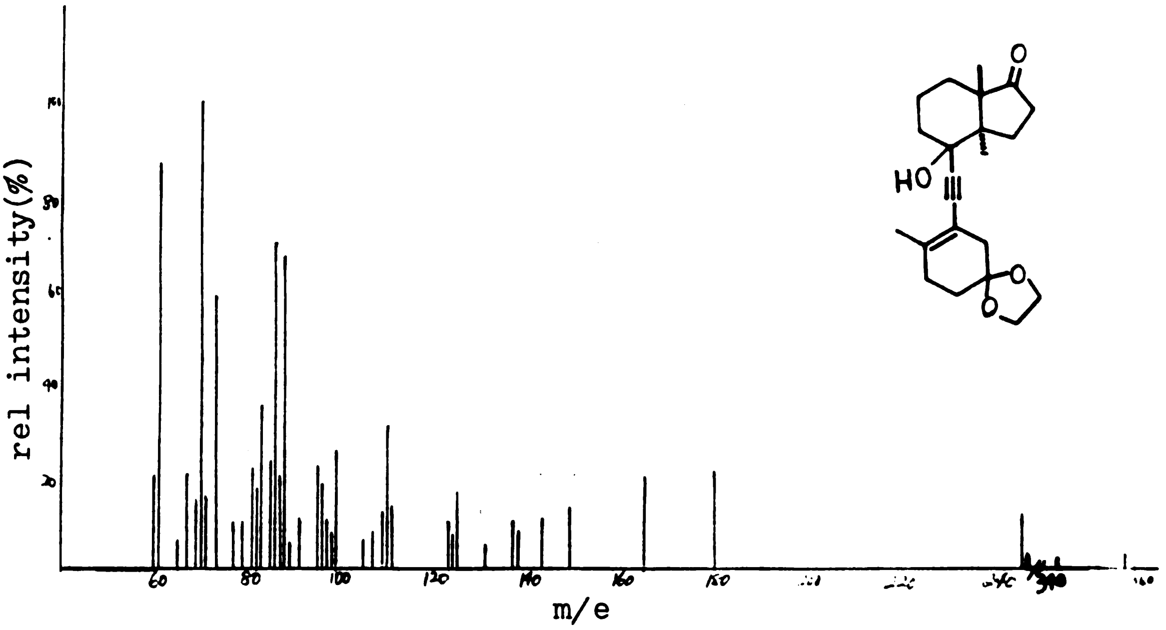


Figure 34. Mass spectrum of 48.

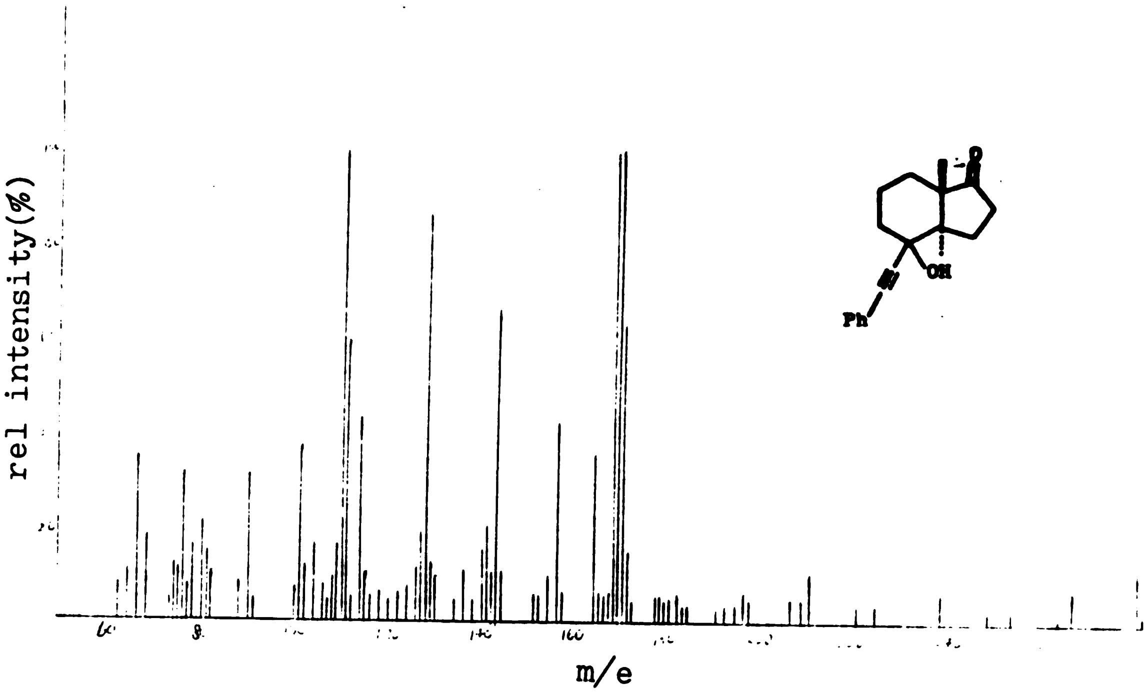


Figure 35. Mass spectrum of 49.

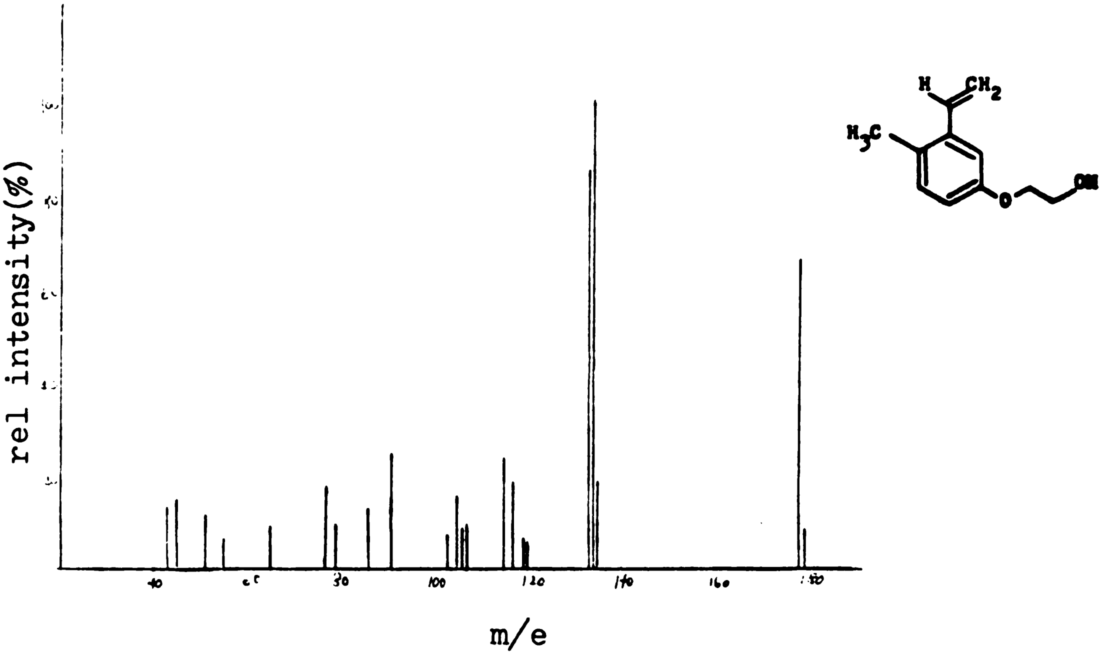


Figure 36. Mass spectrum of 51.

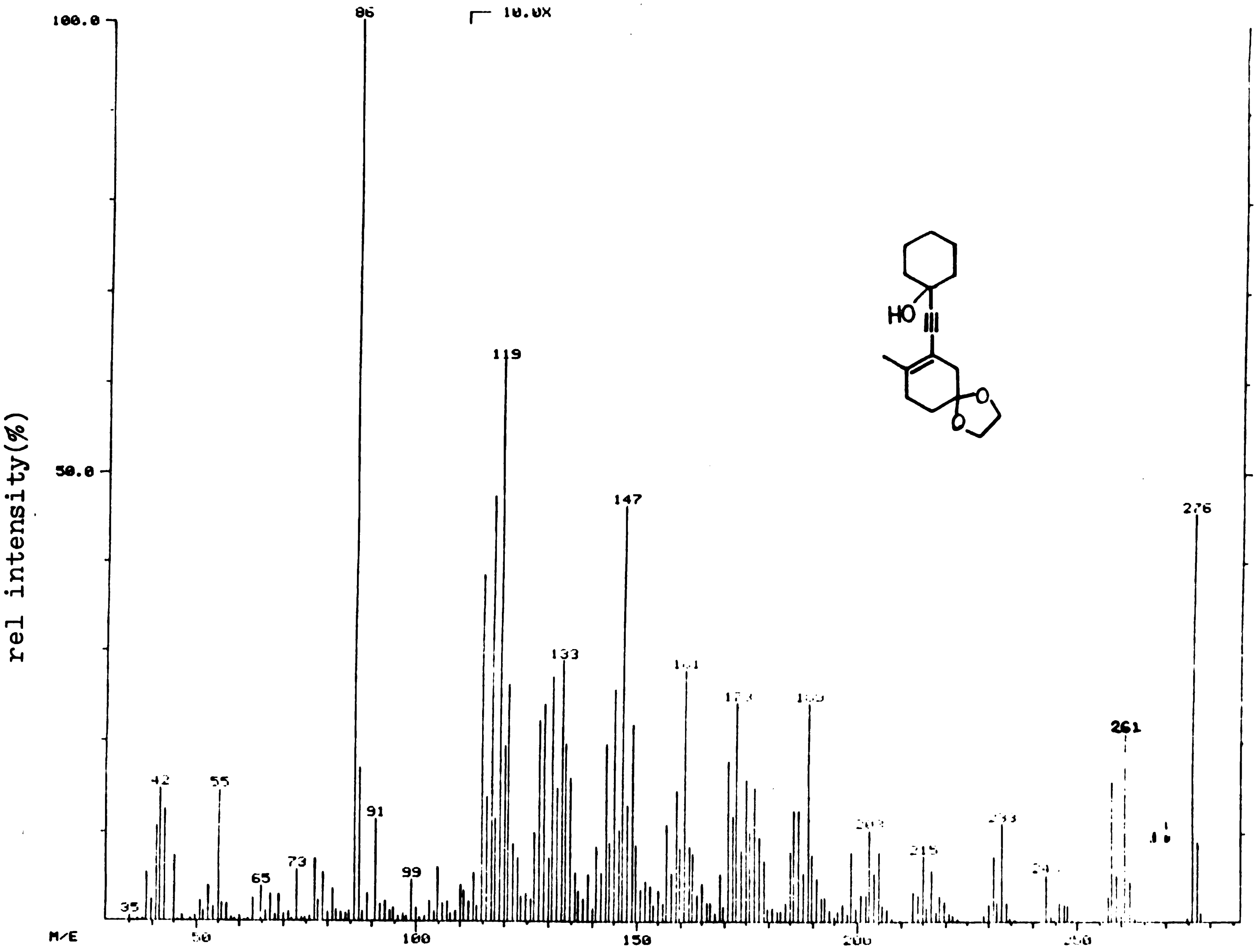


Figure 37. Mass spectrum of 50.

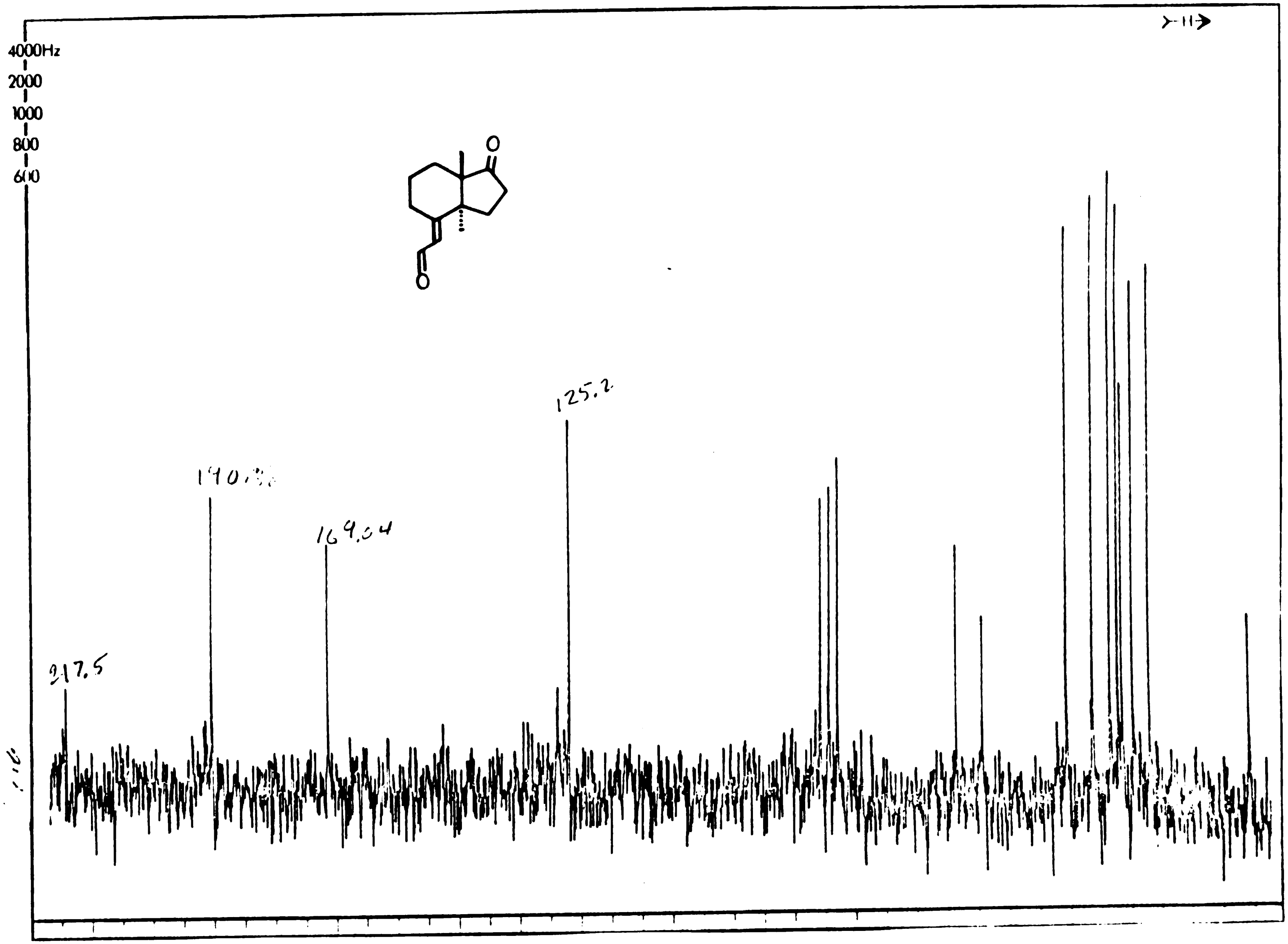


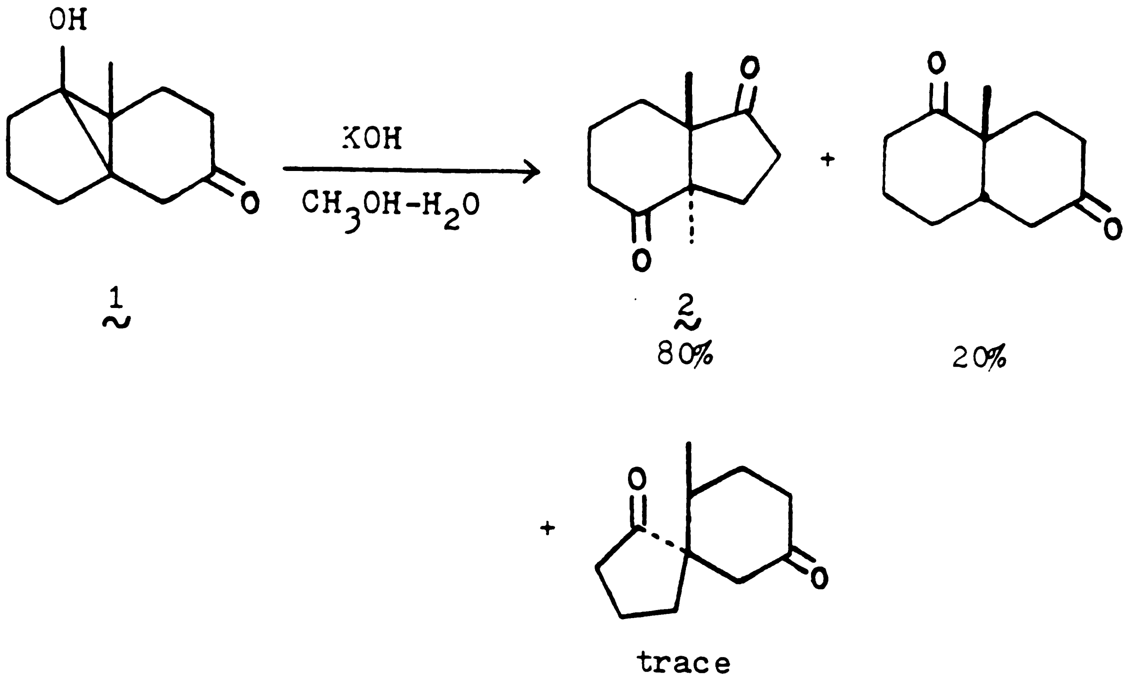
Figure 38. CMR spectrum of 25.

PART II

TYPE I PHOTO-REACTIONS OF BICYCLIC KETONES

INTRODUCTION

Ring opening reactions of 6-methyl-5-hydroxy-tricyclo[4·4·0·0]decane-9-one 1 have been studied in our laboratory[4]. The formation of trans-1,6-dimethylbicyclo[4·3·0]nonane-2,7-dione 2, a versatile intermediate in synthesis, from reaction of 1 with methanolic base[4] was particularly interesting.



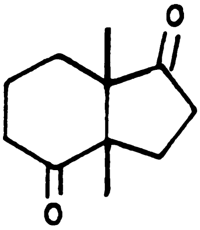
1

2
80%

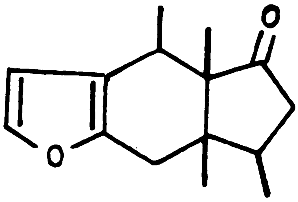
20%

trace

In connection with our published study of this reaction, it was important to find out whether the cis-isomer **3** was also present among the products. To this end an independent synthesis of **3** from **2** was developed, and the chromatographic and spectroscopic properties of these isomers were compared. Compound **3** held additional interest as a potential intermediate for a synthesis of pinguisone[31].

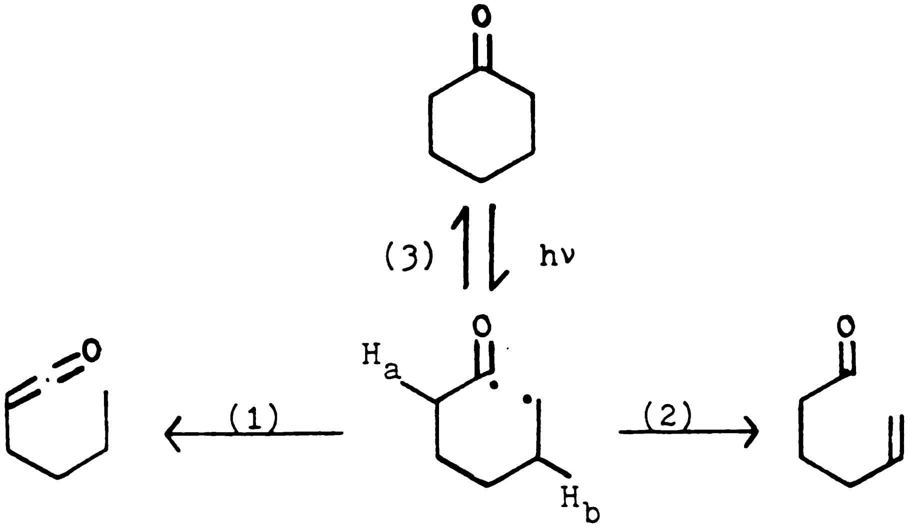


3



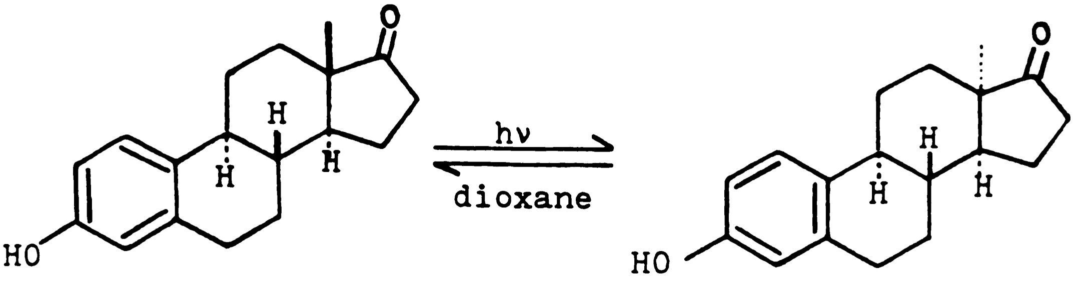
pinguisone

It is known that $n \rightarrow \pi^*$ photoexcitation of saturated ketones causes homolytic cleavage of a bond α to the excited carbonyl function (Norrish type I process)[37]. The biradicals derived from cyclopentanones and cyclohexanones then undergo subsequent reaction to: (1) form ketenes through transfer of H_a; (2) form unsaturated aldehydes through transfer of H_b; and (3) recyclize to the starting ketone or a stereoisomer thereof (Scheme I).



Scheme I

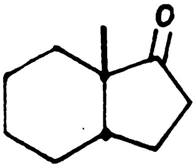
The third process has been used to epimerize 17-keto steroids to analogs having an unnatural configuration. For example[32]:

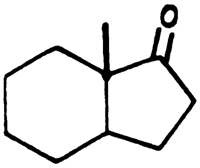


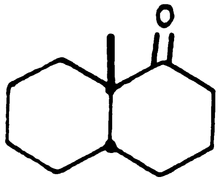
estrone

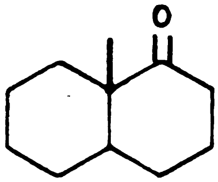
1 : 5.5

In 1971 N. C. Yang[33] reported a study of the photochemistry of 8-methyl-1-hydrindanones (4a and 4b) and 9-methyl-1-decalones (5a and 5b).

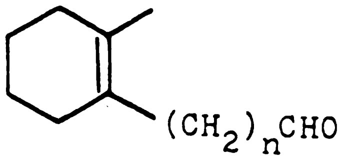

4a


4b


5a

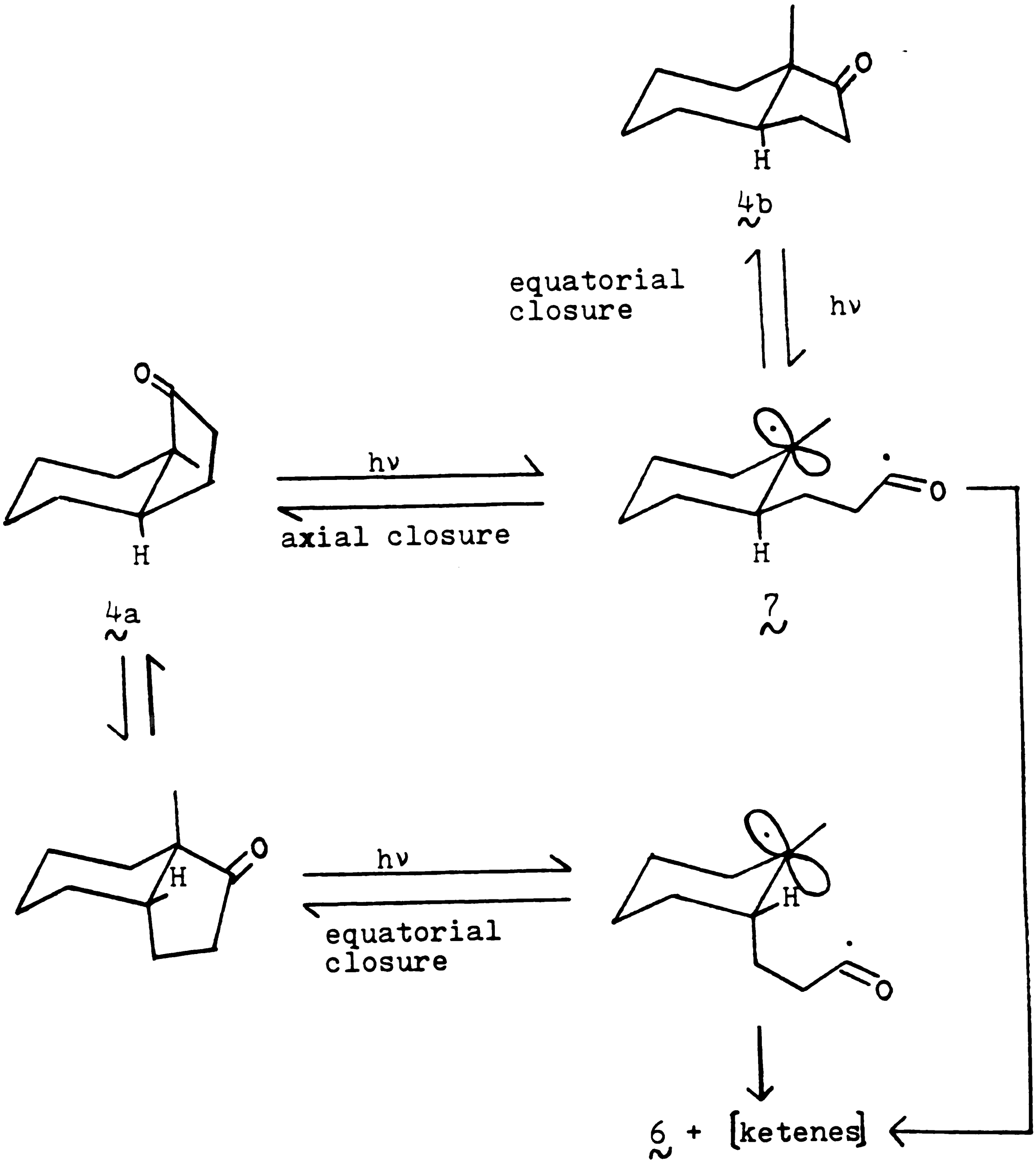

5b

Irradiation of these compounds in hexane yielded the corresponding configurational isomers and an unsaturated aldehyde 6 as the only products detectable by GLPC. The


6

following conclusions were drawn:

1. The rate of α-cleavage decreased as the internal strain of these molecules decreased.
2. The quantum efficiencies of isomerization depended on the stereochemistry of ring closure of the biradical intermediate 7 (Scheme II). Thus photoisomerization occurred much more efficiently from trans-ketones than cis-ketones (e.g., $\phi_{4b\rightarrow4a}=0.46$, $\phi_{4a\rightarrow4b}=0.02$). This suggests preferential ring closure of the biradical intermediate from the axial side.

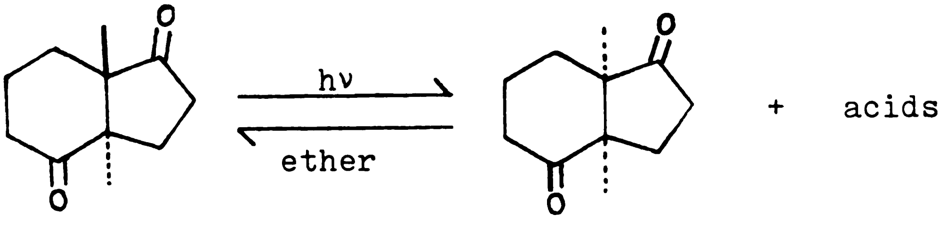

O
H
4b
equatorial closure
hν
O
H
4a
hν
axial closure
O
H
7
O
H
hν
equatorial closure
H
O
6 + [ketenes]

Scheme II

In this dissertation, type I reactions of diketone $\underset{\sim}{2}$ and some derivatives have been studied.

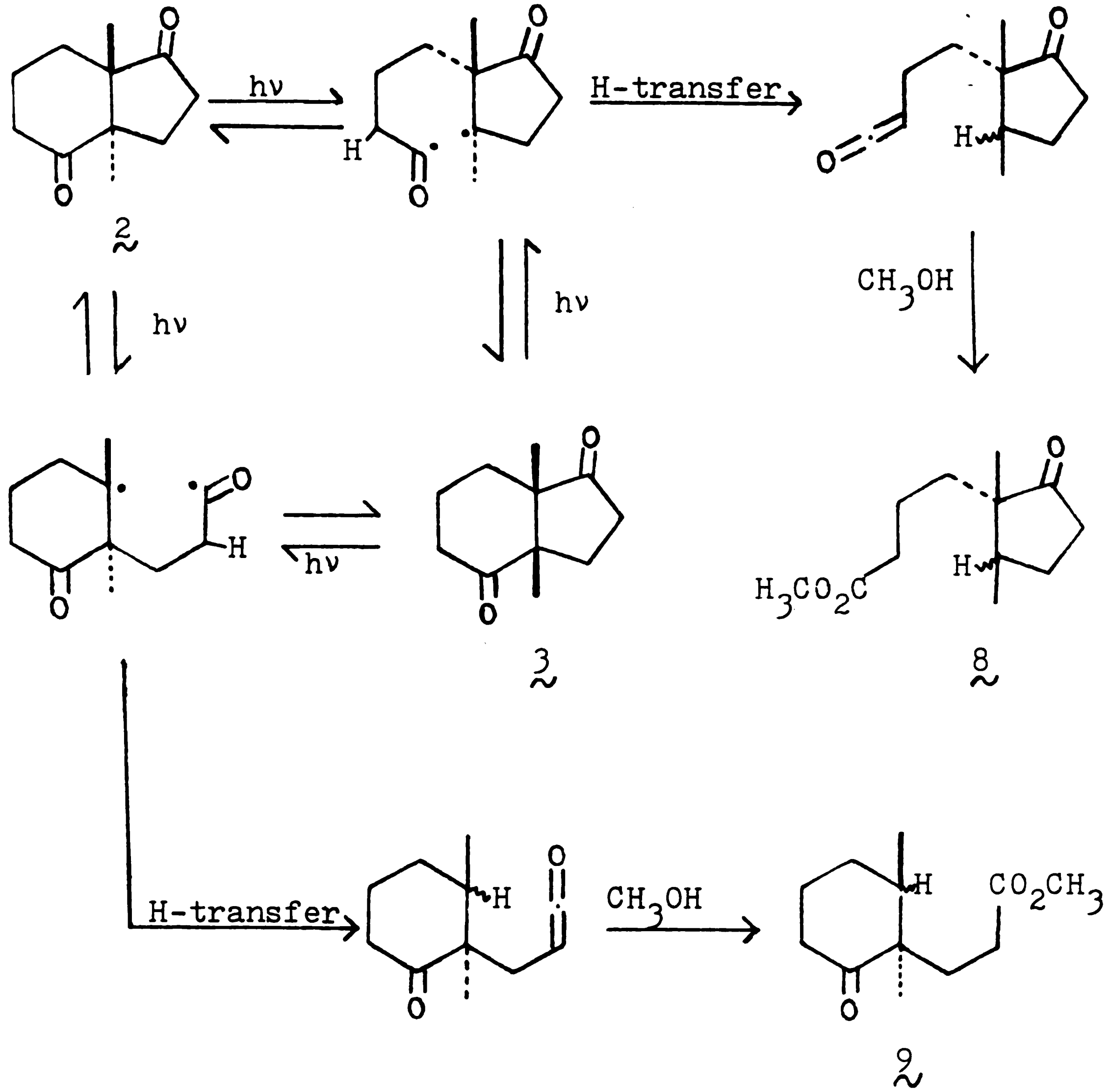
RESULTS AND DISCUSSION

Irradiation of dione 2 in ether gave the cis-isomer 3 as the major product detectable (>90%) by GLPC, but the actual yield of 3 was only 16% when compared to an internal standard. When this reaction mixture was washed with 5% aqueous sodium hydroxide, only 53% of neutral product was obtained from the organic layer. This result suggested that the poor yield of epimerization was due to formation of a carboxylic acid via a ketene intermediate.



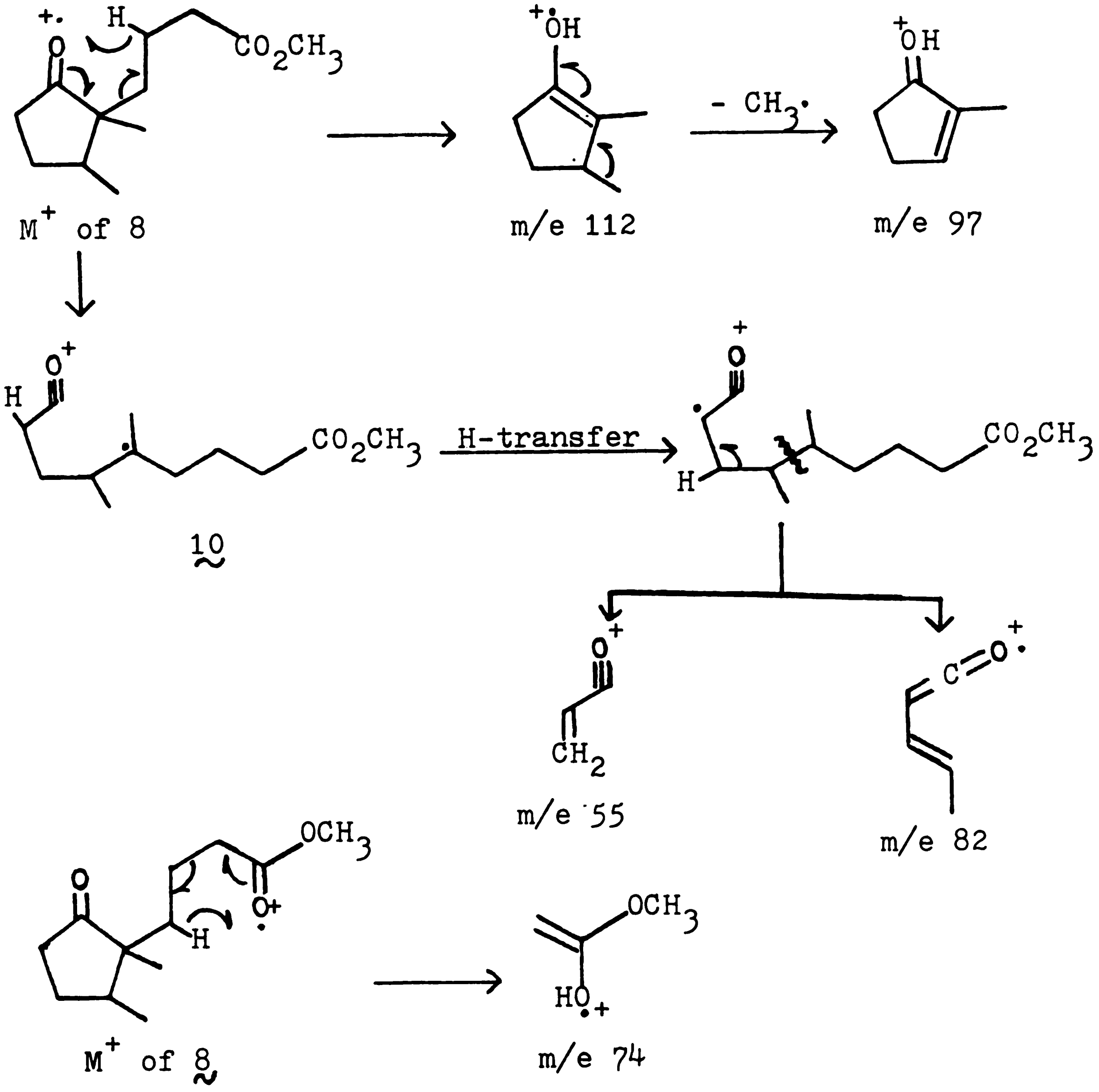
2 3

This ketene intermediate was trapped as a methyl ester by irradiation of 2 in methanol. Two pathways of this kind can be envisaged, as illustrated in Scheme III. The isolated ester is assigned as 8 rather than 9 because of the absence of a 1710 cm^{-1} absorption band in its IR spectrum. Additional support for this assigned structure was provided by its mass spectrum. The m/e 112 and m/e 74

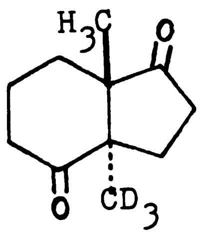

hν
H-transfer
hν
hν
CH$_3$OH
hν
H-transfer
CH$_3$OH
2
3
8
9
H$_3$CO$_2$C
CO$_2$CH$_3$

Scheme III

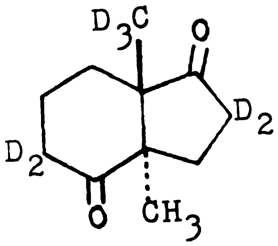
fragments were formed by McLafferty rearrangements involving ketone and ester groups of 8. Hydrogen transfer and bond rupture from the initial α-cleavage product 10 generated the m/e 82 and m/e 55 fragments.



The formation of ester 8 indicates a preferential α-cleavage of the six-membered ketone 2. This is a surprising result since it is not consistent with the strain effect noted earlier by N. C. Yang^{33}. Furthermore, mass spectral studies of specifically labeled analogs (**11a** and **11b**) of **2** indicate that fragmentation of the methyl group adjacent to the six-membered ketone function is six times more facile than fragmentation of the other methyl group$^{5b, 38}$.

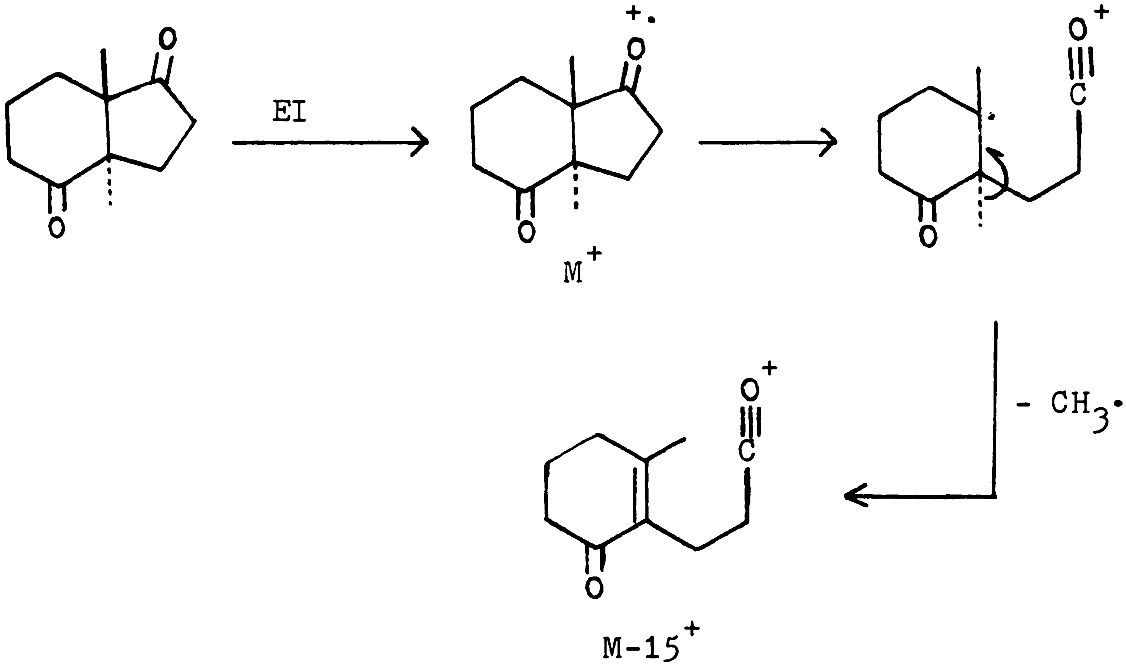


11a

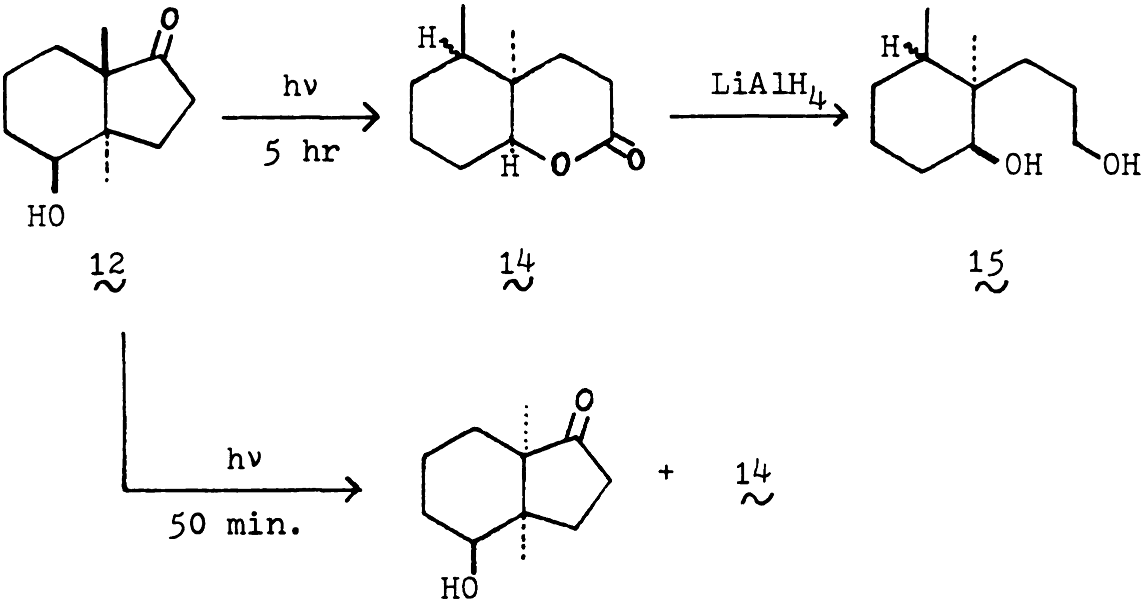


11b

The most straightforward rationalization of this fragmentation selectivity assumes that opening of the strained five-membered ring is faster than the corresponding opening of the six-membered ring.



In order to exclude the influence of the carbonyl group on the six-membered ring, dione **2** was reduced selectively to alcohol **12** by the action of sodium borohydride[27a]. When a solution of alcohol **12** in ether was irradiated until all the starting material was consumed, the product proved to be lactone **14** rather than cis-isomer **13**. Reduction of **14** with lithium aluminum hydride gave diol **15** providing additional support for the assigned structure.



12 **14** **15**

13

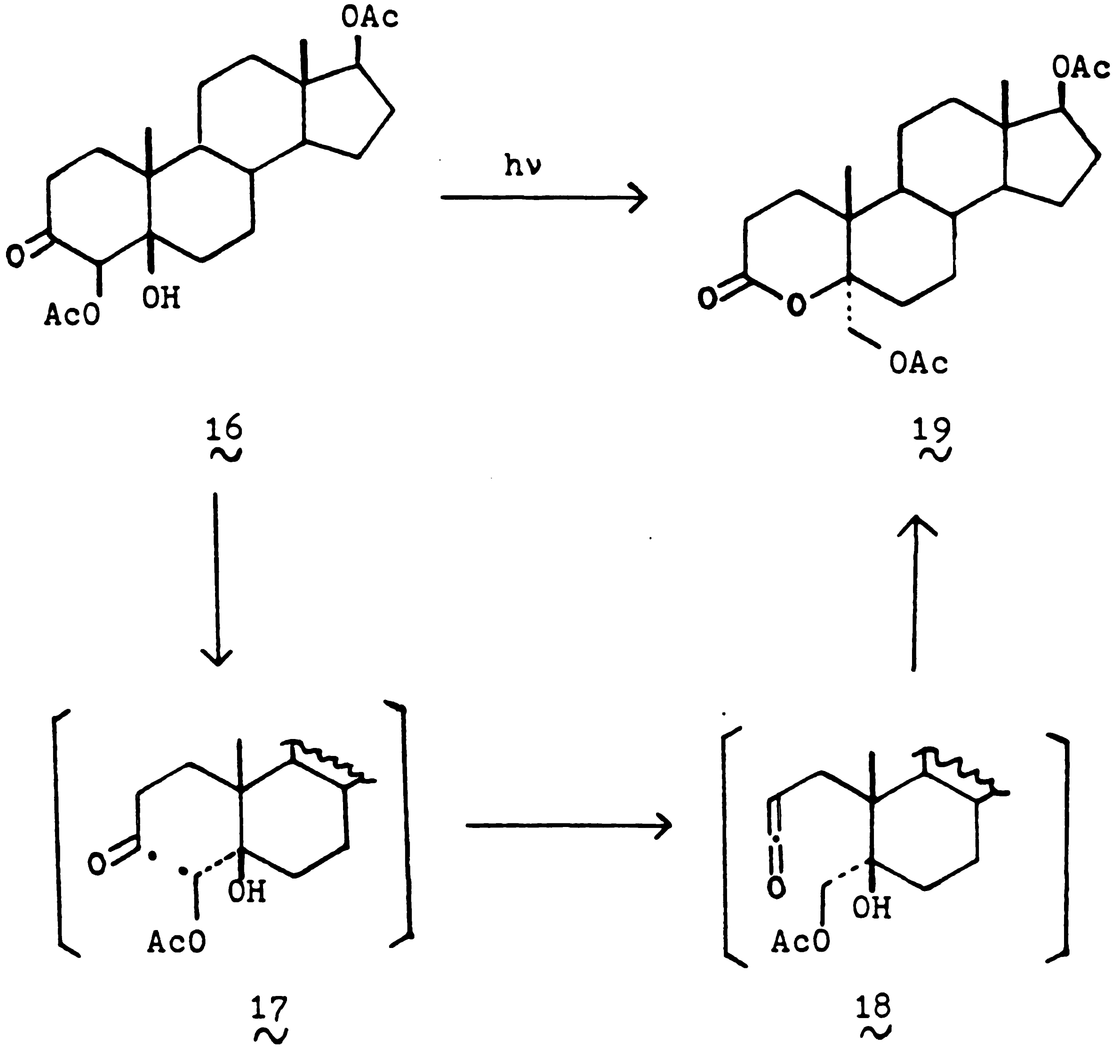
In a second study of **12**, it was found that both **13** and **14** were formed in the early stages of photolysis, and that **13** was consumed during a longer irradiation (Table I).

Table I. Irradiation of 12 in benzene, using phenyl ether as internal standard.

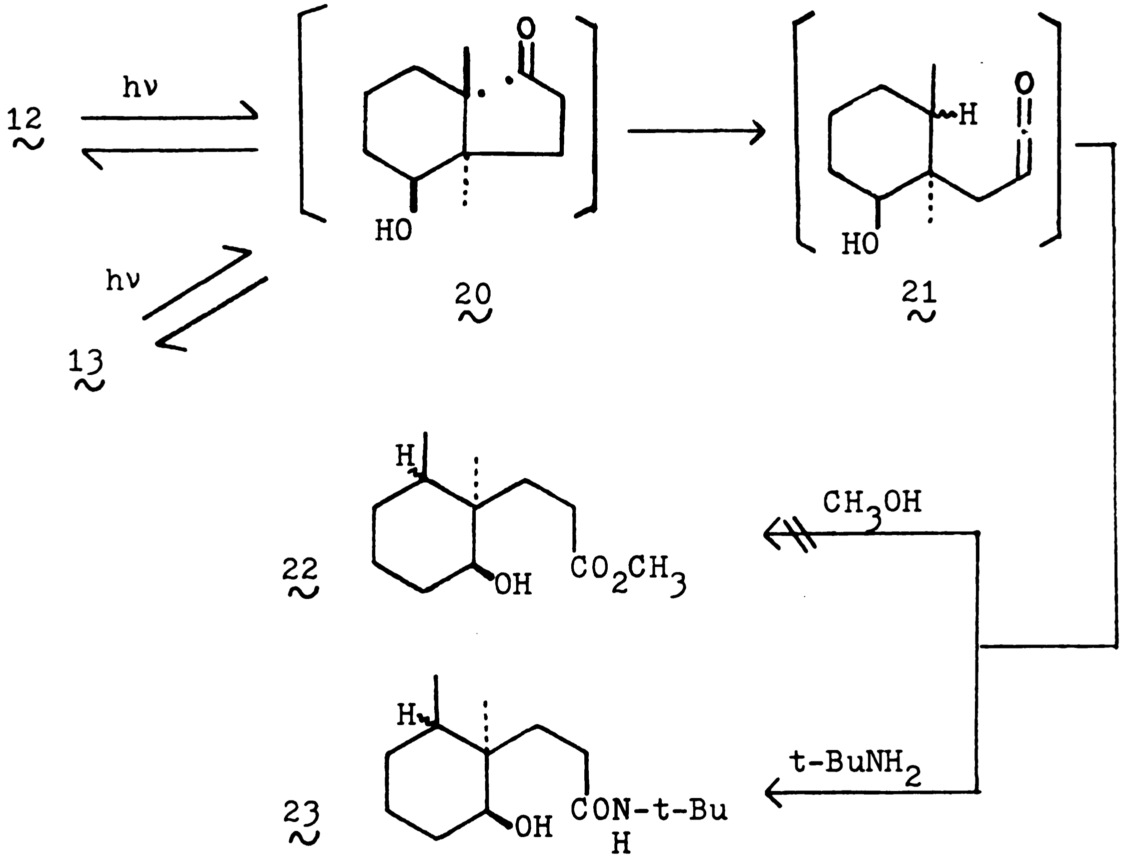
time/percentage(%)	12	13	14	total
0 min.	100	0	0	100
25 min.	28	34	16	78
50 min.	5	38	28	71
85 min.	2	25	42	69
120 min.	0	18	43	61

A similar result has been reported by Hüppi and coworkers[34] (Scheme IV). In their study, α-acetoxy-β-hydroxyketone 16 was isomerized to acetoxylactone 19 in 88% yield on irradiation in benzene. The mechanism was presumed to involve α-cleavage to biradical 17, followed by an intramolecular hydrogen transfer and subsequent lactonization of ketene 18.

In order to show whether lactone 14 was formed by a similar pathway, alcohol 12 was irradiated in methanol[35]; however, none of the expected ester 22 could be detected. Ketene 21 was subsquently trapped by adding t-butylamine (Scheme V and Table II).



Scheme IV



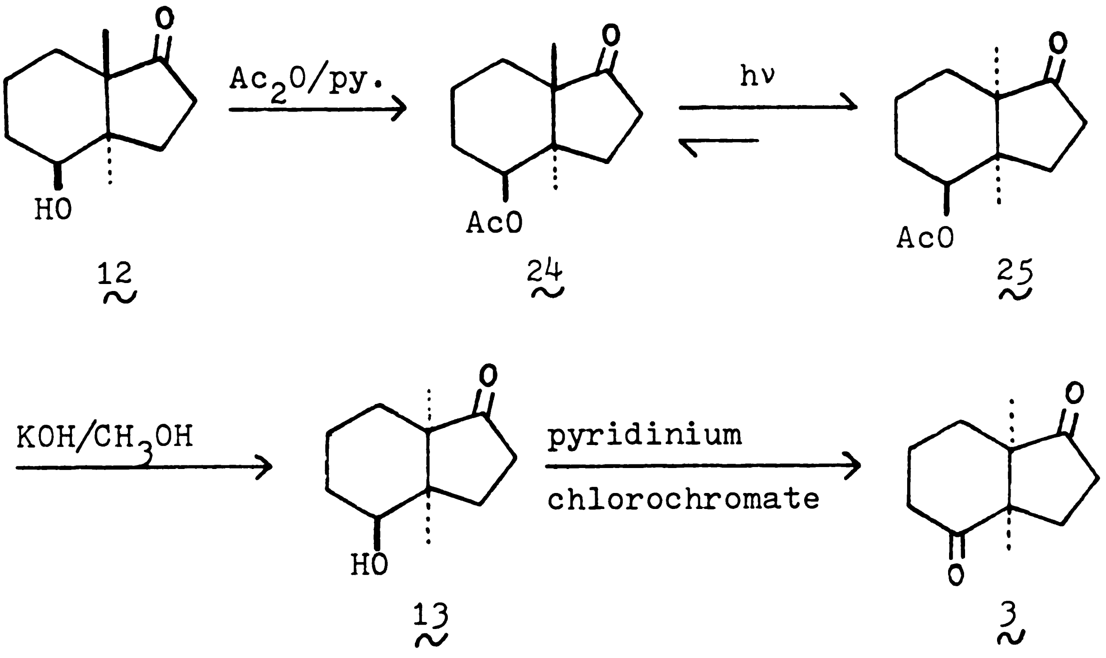
Scheme V

Table II. Irradiation of 12 and 10 equiv. of t-BuNH$_2$ in ether

time/percentage(%)	12	13	14	23
0 hr	100	0	0	0
1 hr	21.1	38.7	2.9	3.4
2 hr	4.2	44.2	7.1	8.4
3 hr	0	33.7	8.7	10.3

The experimental data showed that amide 23 was formed along with lactone 14. Addition of more t-butylamine only slowed down the reaction, perhaps by forming a charge-transfer complex with biradical 20[36].

Since the isolated yield of epimerized alcohol 13 was low, the photo-epimerization of a derivative of 12 was examined. Irradiation of acetate 24, prepared from 12 by reaction with acetic anhydride in pyridine, gave cis-isomer 25 in 45% yield. Alkaline hydrolysis of 25 followed by oxidation with pyridinium chlorochromate provided the desired cis-diketone 3 (Scheme VI).



Scheme VI

The three cis-isomers obtained from these photo-epimerizations, dione **3**, alcohol **13** and acetate **25**, were easily distinguished from the correponding trans-isomers by PMR spectra and GLPC analyses. The two angular methyl groups of the trans-isomers are separated by a larger chemical shift than those of cis-isomers. The C-5 proton of acetate **24** showed a broader PMR signal than that from acetate **25**. This suggests that the former is axial and the latter equatorial. The same difference existed between **12** and **13**. Compound **3**, **13** and **25** have shorter retention time on GLPC (4% QF-1) than their trans-isomers. From these results, we can show that **3** is not formed in the ring opening reaction of **1**.

EXPERIMENTAL

GENERAL

In addition to the general described in Part I, all the irradiations were carried out under nitrogen at 0^oC with light from an ACE-Hanovia 450 W. medium-pressure mercury lamp. The reactions were followed by GLPC (4% QF-1, 160^oC).

Irradiation of dione **2** in ether.

A solution of dione **2** (617.3 mg, 3.43 mmole) in 300 ml ether was irradiated through a corex filter until the ratio of cis-isomer **3** to **2** was 30:1 (2hr). Removal of the solvent gave 701 mg crude product. The internal standard analysis indicated that the yield of **3** was 16% (Table III).

Table III. Comparison of **3** and crude product with trimethyl-1,3,5-benzenetricarboxylate **26** by GLPC.

run	sample	weight	integration ratio
1	**3** (authentic)	4.5 mg	40.8
	26	4.9 mg	28.0
2	crude product	10.8 mg	42.5
	26	4.2 mg	73.5

The ether solution of 649 mg of crude product was washed with 5% NaOH. The organic layer was concentrated to 349 mg of oil, which was chromatographed on HPLC (silica gel) with 0.5% CH_3OH-CH_2Cl_2 to afford 90.2 mg (15%) of **3**. The aqueous layer was neutralized and then extracted with chloroform. Removal of solvent gave 198 mg of unidentified residue.

Irradiation of dione **2** in methanol.

A solution of **2** (115.5 mg, 0.64 mmole) in 75 ml of methanol was irradiated for 50 min. through a corex filter. Removal of the solvent gave 140 mg of crude product which proved to be a mixture of **8** (70%), **3** (15%) and side products (15%). An analytical sample of ester **8**, collected by GLPC (4% QF-1, 175°C), showed the following properties: IR (neat) 1736, 1200 cm^{-1}; MS (70 eV) m/e (rel intensity) 212(0.39), 181(2.27), 97(58.94), 82(38.89), 74(27.25), 55(71.40), 41(100).

Preparation of lactone **14** by irradiation of alcohol **12**.

A solution of alcohol **12** (801.8 mg, 4.4 mmole) in 74 ml of ether was irradiated for 5 hr through a corex filter. The solvent was removed with the aid of a rotoevaporator. Recrystallization of the residue from ether-pentane gave 129.8 mg (16%) of lactone **14**. The mother liquid contained lactone **14** and some unidentified high molecular weight compounds. Lactone **14** displayed the following properties: mp 73-73.5°; IR (CCl_4) 1741, 1250, 1205, 1138 cm^{-1}; PMR ($CDCl_3$) δ 0.83 (d, 3H, J=8 Hz), 0.9 (s, 3H), 1.1-2.1 (m, 9H), 2.38 (d, 1H, J=6 Hz), 2.55 (dd, 1H, J=6, 2 Hz), 4.1 (t, 1H, J=3 Hz); MS (70 eV) m/e (rel intensity) 182(34), 164(7), 122(22), 110(44), 96(100).

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.36; H, 9.88

Found: C, 72.49; H, 9.96

Reduction of lactone 14 to diol 15.

To a refluxing suspension of lithium aluminum hydride (50 mg, 1.3 mmole) in 20 ml of ether was added dropwise a solution of lactone **14** (130 mg, 0.71 mmole) in 10 ml of ether. The reduction was followed by GLPC, and the reaction mixture was quenched by careful addition of 1.5 ml of water and 1 ml of 10% aqueous NaOH when **14** was consumed. The precipitated solids were filtered and washed with methanol. The combined filtrate and wash were evaporated at reduced pressure, and the resulting residue was extracted with ether. After the ether extracts were washed with brine and dried, removal of the solvent and crystallization from acetone-hexane gave 89.2 mg (68%) of **15**: mp 109.5-111°; IR ($CDCl_3$) 3613, 1451, 1376 cm^{-1}; PMR ($CDCl_3$) δ 0.77 (s, 3H), 0.8 (d, 3H, J=5 Hz), 1.1-1.8 (m, 11H), 1.84 (s, 2H), 3.4-3.7 (m, 3H); MS (70 eV) m/e (rel intensity) 186(4), 168(15), 156(21.5), 109(92), 41(100).

Short irradiation of alcohol **12**.

A solution of alcohol **12** (240 mg, 1.32 mmole) in 250 ml ether was irradiated for 50 min. through a corex filter. The concentrated residue was dissolved in 5% methanolic sodium hydroxide and stirred for 1 hr. After the methanol was removed under reduced pressure, the residue was extracted with ether and the combined extracts were washed and dried. Removal of the solvent gave 167.5 mg of crude product from which 143.3 mg (60%) of **12** and **13** in 1:4 ratio was obtained as white solid by Kuglerohr distillation. The aqueous layer was acidified and extracted by chloroform to give 73 mg (30%) of lactone **14**.

Irradiation of alcohol **12** with added t-butylamine.

A solution of alcohol **12** (25.8 mg, 0.14 mmole), t-butylamine (0.146 ml, 1.4 mmole) and tetracosane (13.9 mg, 0.042 mmole) in 5.5 ml ether was irradiated through a corex filter. The results are listed in Table II. An analytical sample of amide **23** had the following properties: mp 108.5-110.5^{o}; IR ($CDCl_3$) 3600, 3419, 1650 cm^{-1}; PMR ($CDCl_3$) δ 0.72 (s, 3H), 0.77 (d, 3H, J=7 Hz), 1.3 (s, 9H), 1.4-2.0 (m, 9H), 2.07 (d, 2H, J=6 Hz), 3.42 (br s, 2H), 5.5 (br s, 1H); MS (70 eV) m/e (rel intensity) 255(1.05), 237(0.36), 227(0.52), 222(0.37), 128(24.38), 115(94.42), 58(100).

Preparation of acetate 24.

To a solution of alcohol 12 (297.5 mg, 1.63 mmole) in 25 ml of pyridine was added 5 ml of acetic anhydride (excess). This solution was stirred for two days and quenched with ice water. Most of the pyridine was removed at reduced pressure and the residue was extracted with ether, washed with 5% HCl, 10% $NaHCO_3$, water, brine and dried. Removal of the solvent gave 246.6 mg (67%) of 24 which was crystallized from petroleum ether to give pure 24 (66%): mp 49.5-51.5°; IR (CCl_4) 1738, 1238 cm^{-1}; PMR ($CDCl_3$) δ 0.94 (s, 3H), 1.22 (s, 3H), 1.33-1.95 (m, 8H), 2.07 (s, 3H), 2.25 (m, 2H), 4.93 (br t, 1H, J=2 Hz); MS (70 eV) m/e (rel intensity) 224(2), 182(1.06), 181(1.27), 164(1.62), 136(5.68), 122(10.11), 108(10.49), 43(100).

Preparation of acetate 25.

A solution of acetate 24 (128 mg, 0.57 mmole) in 75 ml of ether was irradiated for 9 hr through a pyrex filter. Removal of the solvent gave 140 mg of crude products giving four components on GLPC, of which acetate 25 proved to be the major product (65%). Recrystallization from petroleum ether gave 32.8 mg of 25. The residue was purified by HPLC (silica gel), eluting with 15% HOAchexane to give 29.3 mg of acetate (**25**:**24**=4.6:1). Acetate **25**, obtained in 45% yield, had the following properties: mp 75-76°; IR (CCl_4) 1741, 1236 cm^{-1}; PMR ($CDCl_3$) δ 0.92 (s, 3H), 0.99 (s, 3H), 1.2-1.9 (m, 8H), 2.0 (s, 3H), 4.8 (broad, 1H); MS (70 eV) m/e (rel intensity) 224(5), 182(9), 164(14), 145(19), 122(21), 111(32), 109(38), 44(100).

Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99 (C:H=7.74)
Found: C, 68.17; H, 8.86 (C:H=7.69)
or C, 68.33; H, 8.87 (C:H=7.70)

Acetate **25** is easy to sublimate, so that the found percentage of C and H is lower than the calculated value. However, the ratios of C to H are consistent.

Hydrolysis of acetate **25**.

To a solution of KOH (0.4 g, excess) in 4 ml of methanol was added acetate **25** (202 mg, 0.90 mmole). This mixture was stirred for 30 min., following which the solvent was removed at reduced pressure. The residue was extracted with ether and water, washed with brine and dried. Evaporation of the ether yield 145 mg (89%) of alcohol **13**: IR ($CDCl_3$) 3600, 1720, 1450, 1380, 1090 cm^{-1}; PMR ($CDCl_3$) δ 0.96 (s, 3H), 1.0 (s, 3H), 1.2-1.8 (m, 9H), 2.3 (br s, 2H), 3.58 (broad, 1H); MS (70 eV) m/e (rel intensity) 182(32.5), 167(36), 149(30), 122(42), 111(92), 109(100).

Oxidation of alcohol **13**.

A solution of alcohol **13** (245 mg, 1.35 mmole, crude product) in CH_2Cl_2 was added to a suspension of pyridinium chlorochromate (232.6 mg, 1.13 mmole) in 20 ml of CH_2Cl_2. The reaction mixture was stirred vigorously for 24 hr, diluted with ether and filtered through Florisil. The filtrate was washed with water, brine and dried. Removal of the solvent followed by recrystallization from ether-pentane gave 74 mg (31%) of dione **3**: mp $147-150^{\circ}$, IR (CCl_4) 1740, 1710 cm^{-1}; PMR ($CDCl_3$) δ 1.0 (s, 3H), 1.17 (s, 3H) 1.3-2.9 (m, 10H); MS (70 eV) m/e (rel intensity) 180(2.78), 165(7.48), 137(7.00), 125(6.98), 110(8.93), 42(100).

APPENDIX

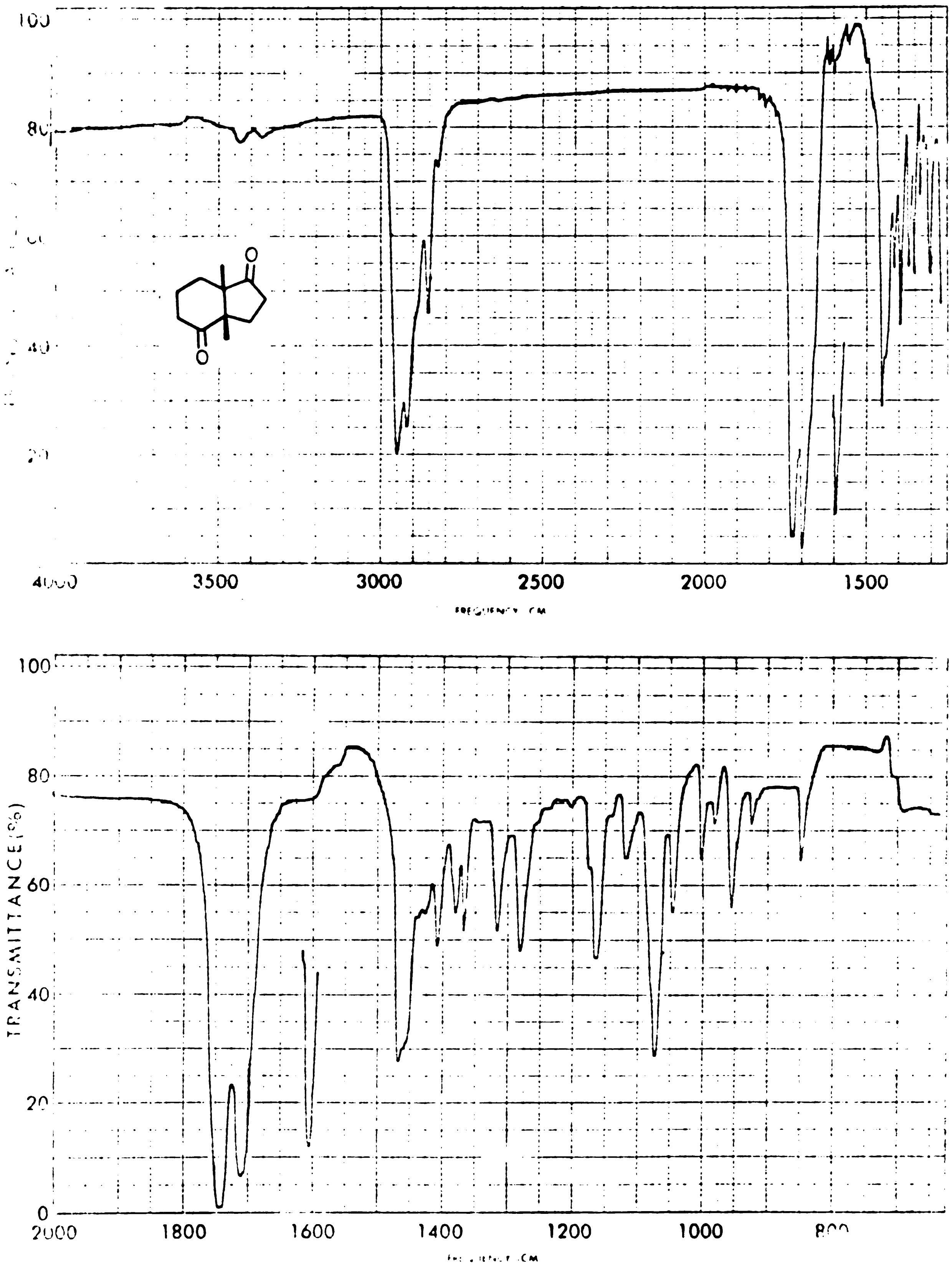


Figure 39. Infrared spectrum of **3**.

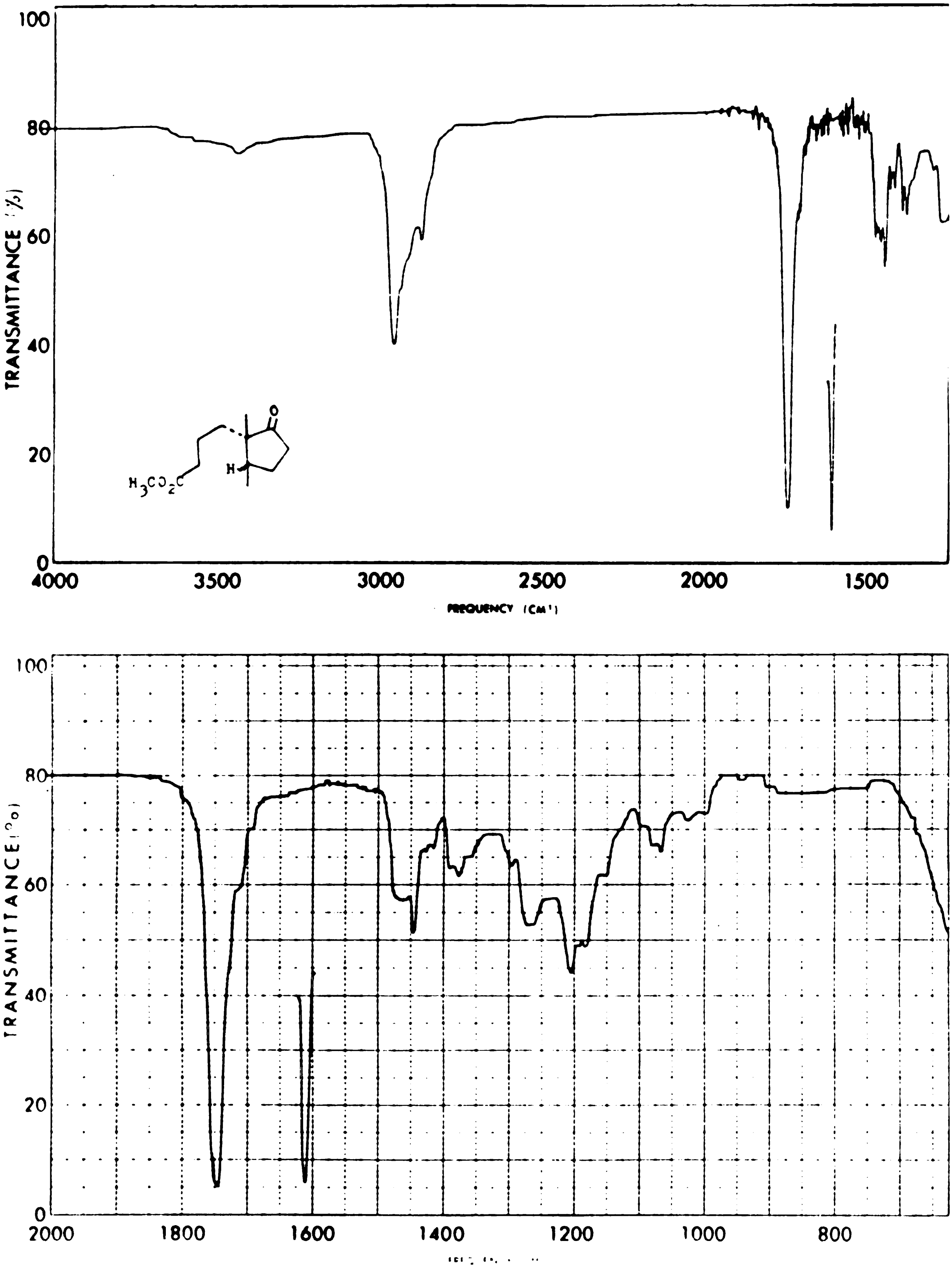


Figure 40. Infrared spectrum of 8.

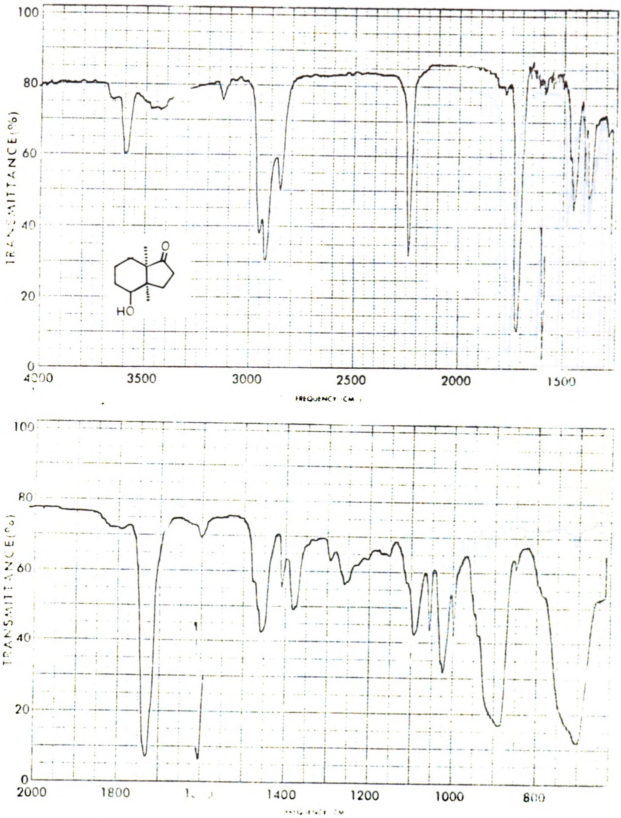


Figure 41. Infrared spectrum of 13 (in $CDCl_3$).

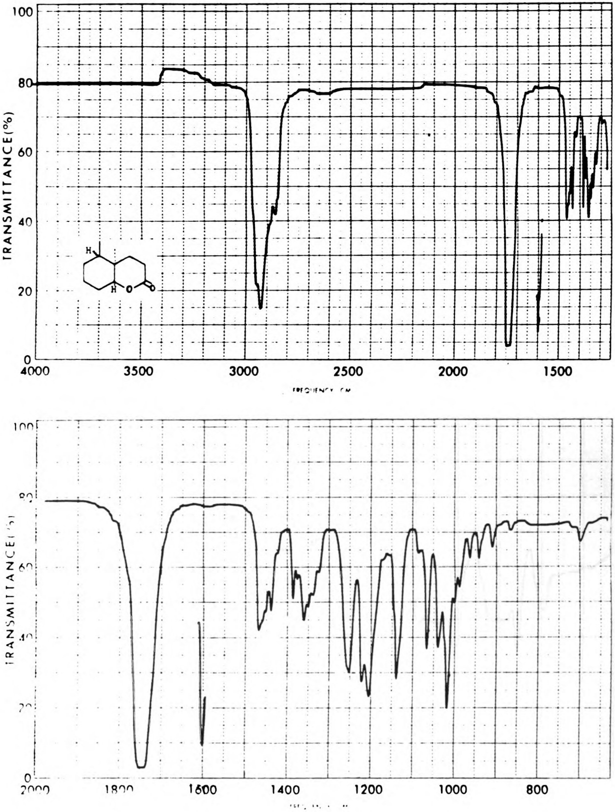


Figure 42. Infrared spectrum of $\underset{\sim}{14}$.

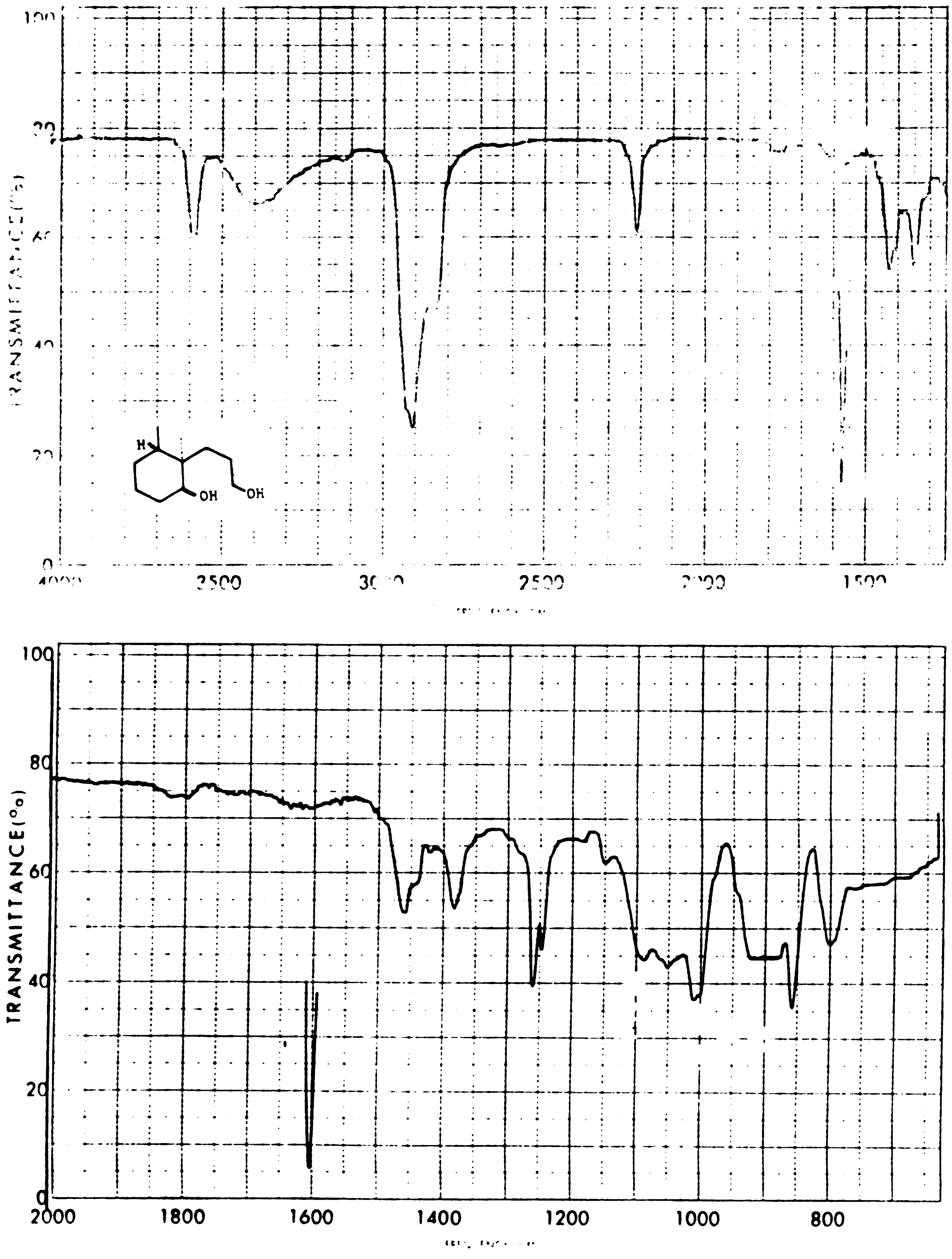


Figure 43. Infrared spectrum of 15 (in $CDCl_3$).

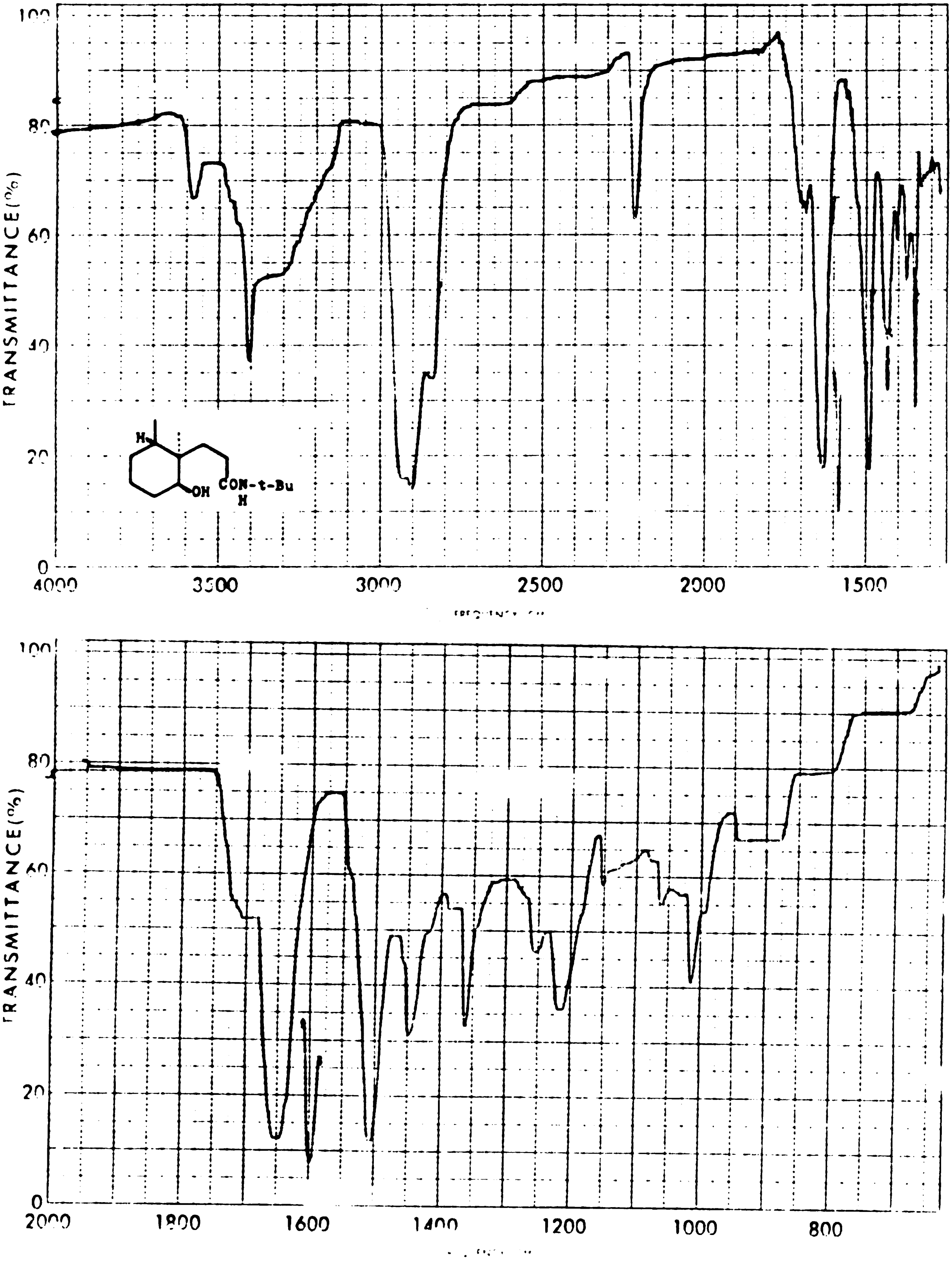


Figure 44. Infrared spectrum of 23 (in $CDCl_3$).

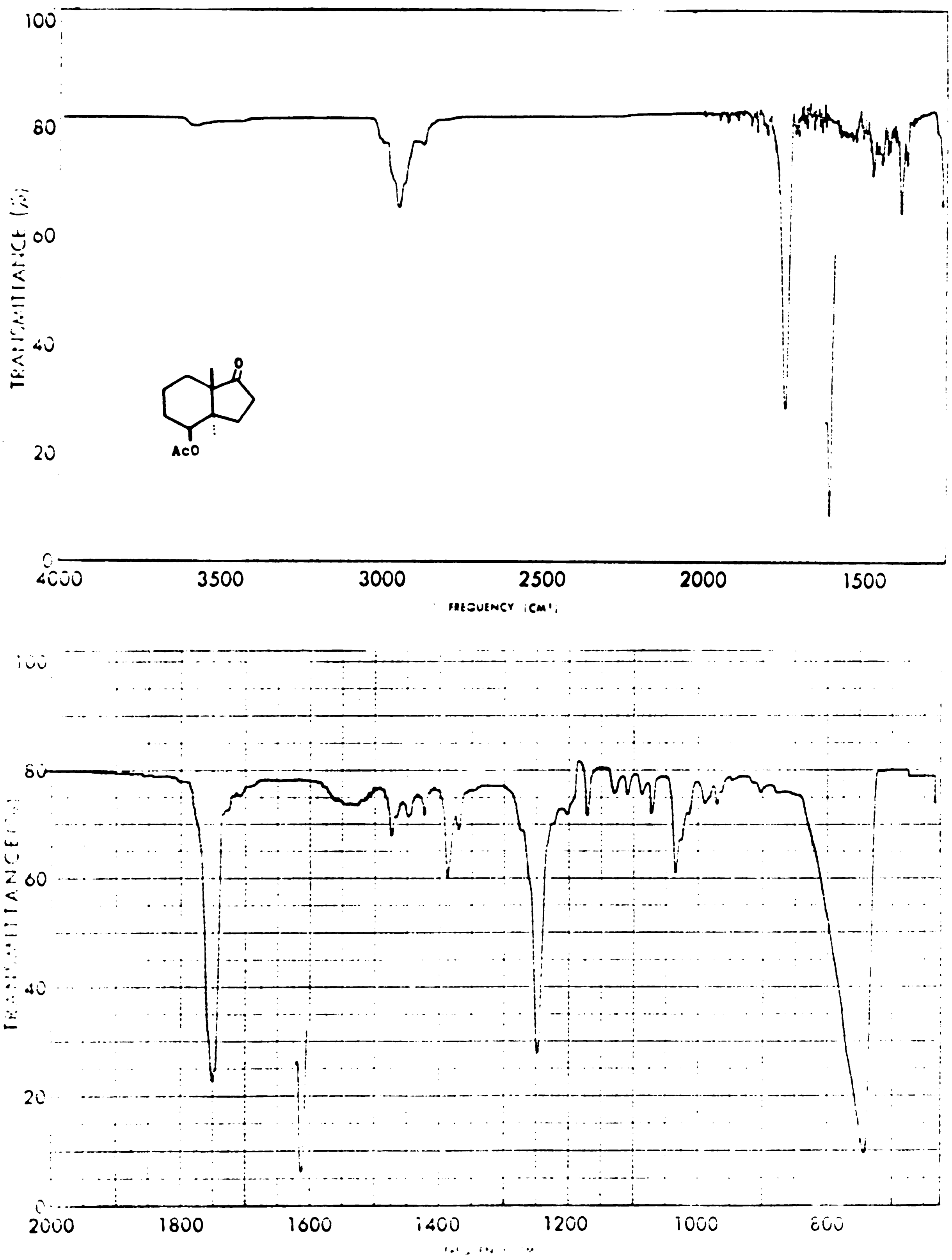


Figure 45. Infrared spectrum of 24.

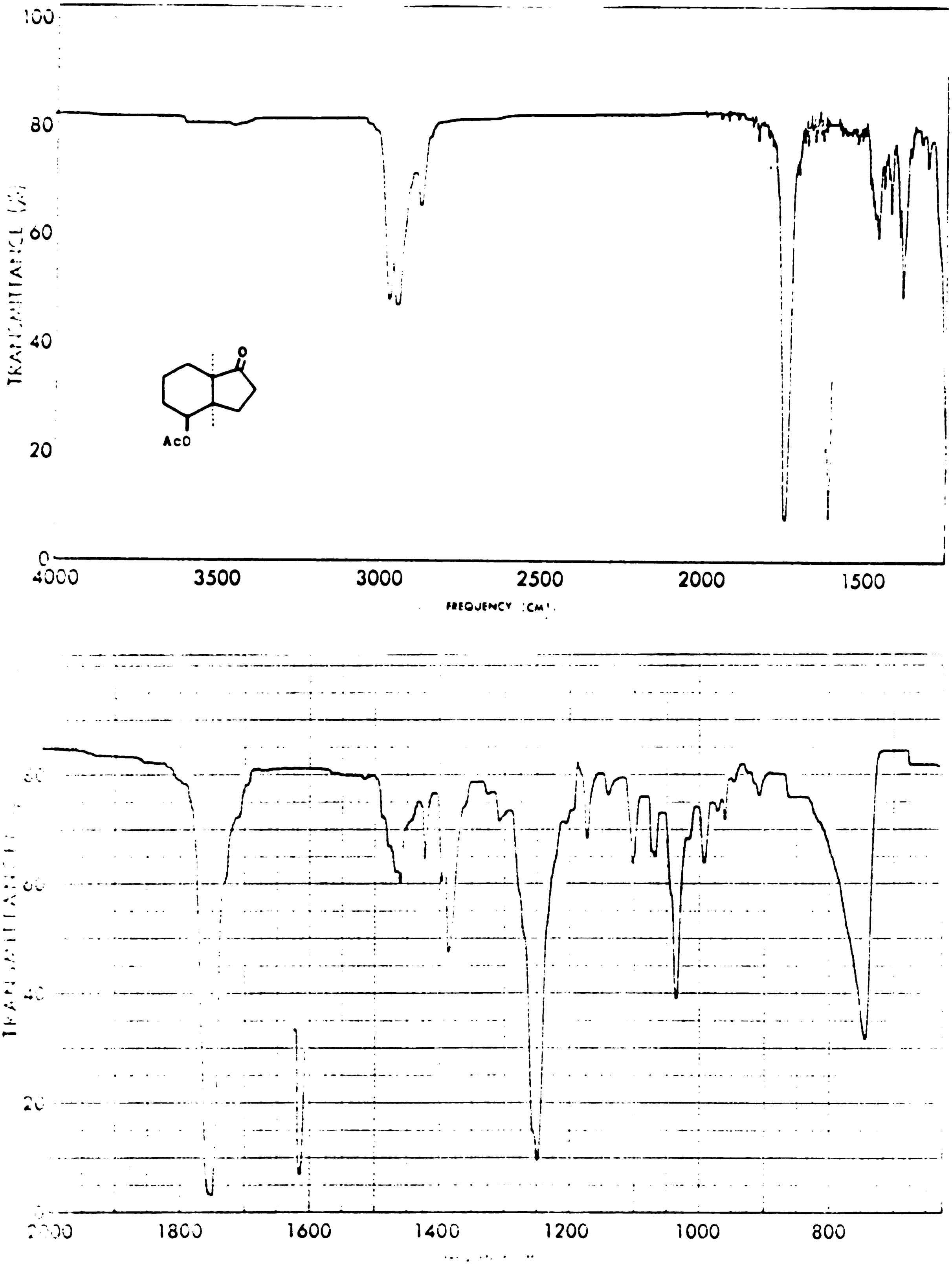


Figure 46. Infrared spectrum of 25.

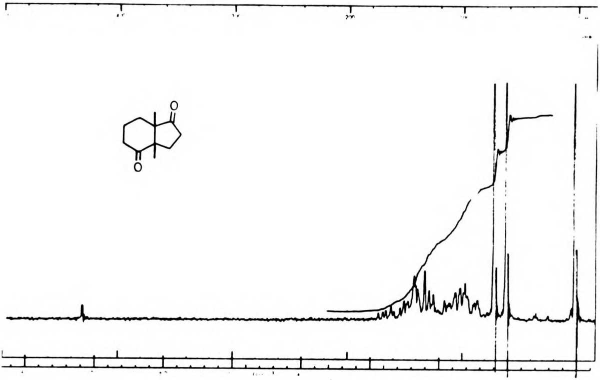


Figure 47. PMR spectrum of 3.

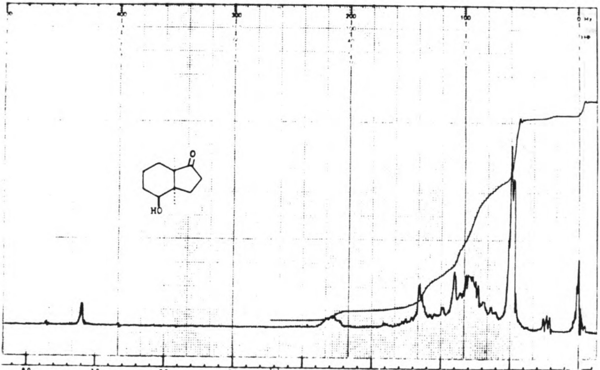


Figure 48. PMR spectrum of 13.

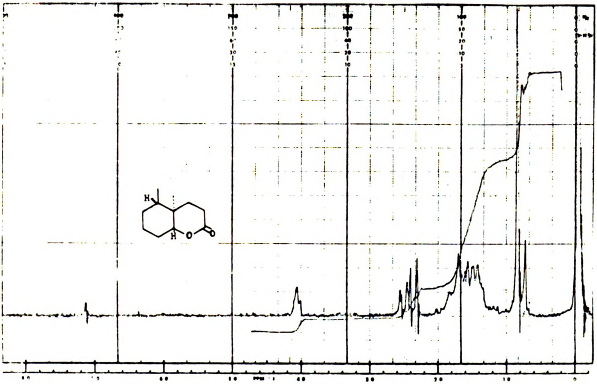


Figure 49. PMR spectrum of 14.

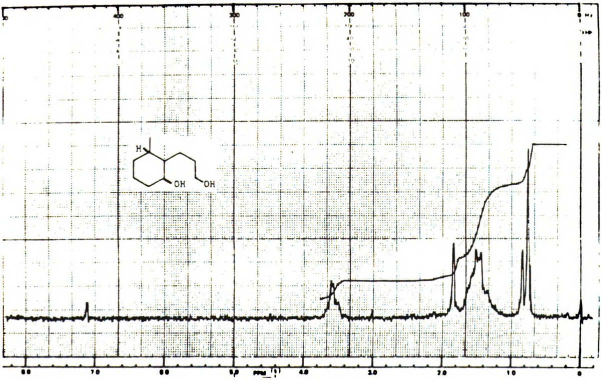


Figure 50. PMR spectrum of 15.

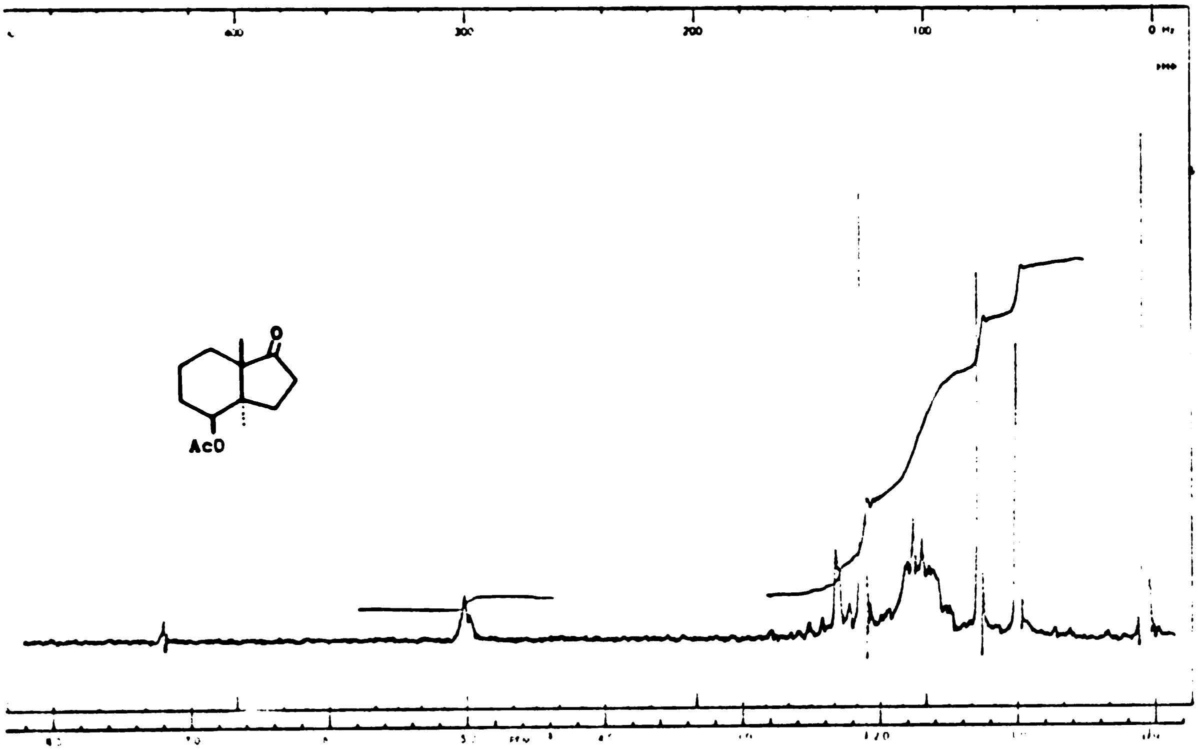


Figure 51. PMR spectrum of 24.

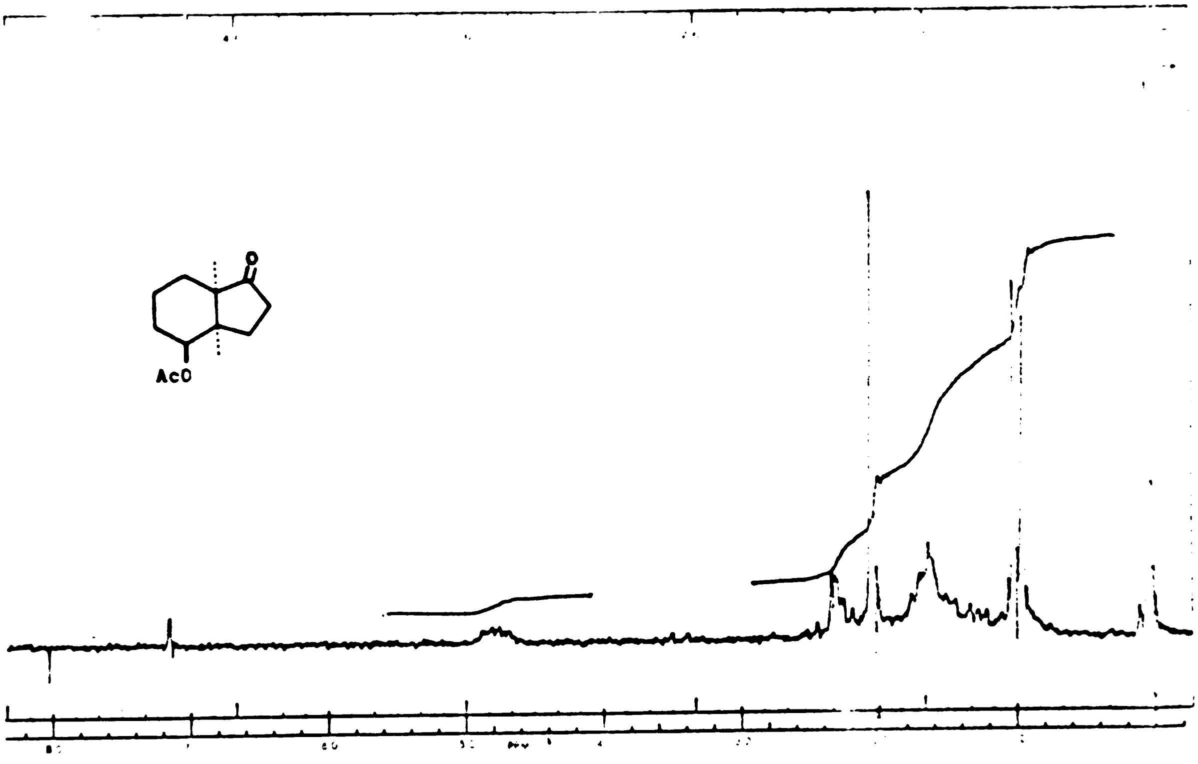


Figure 52. PMR spectrum of 25.

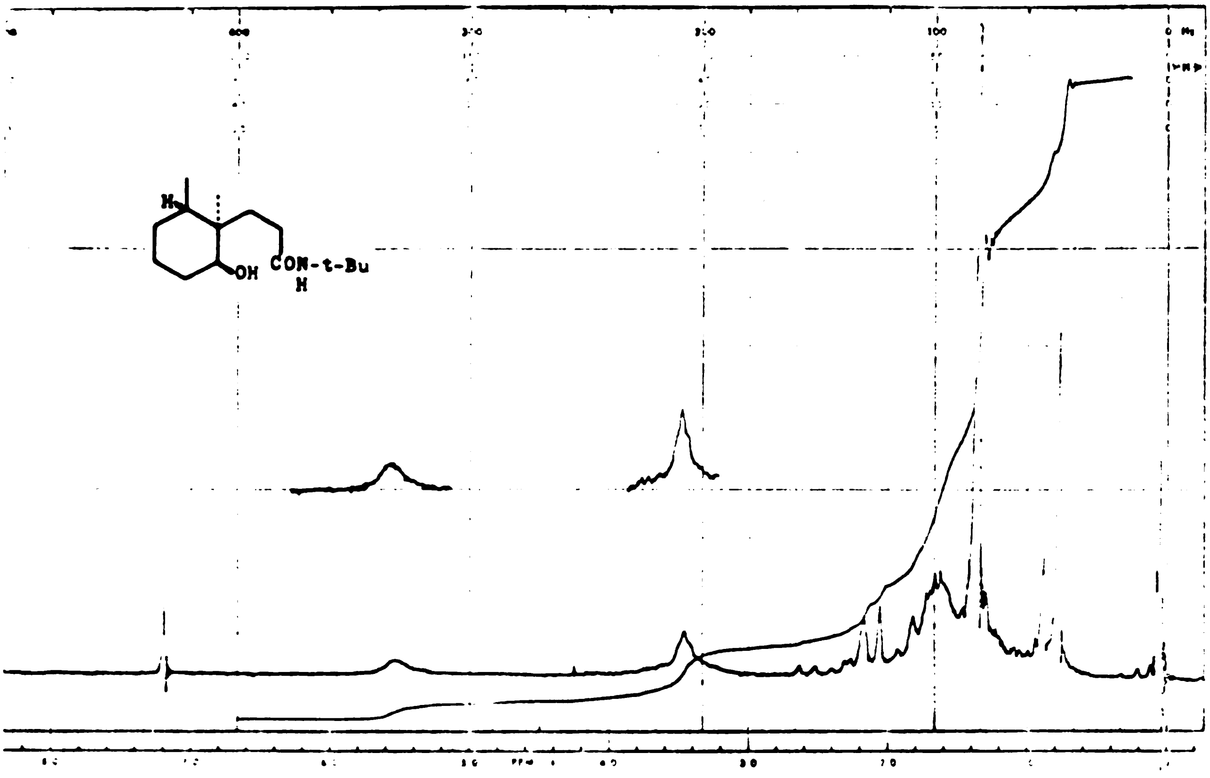


Figure 53. PMR spectrum of 23.

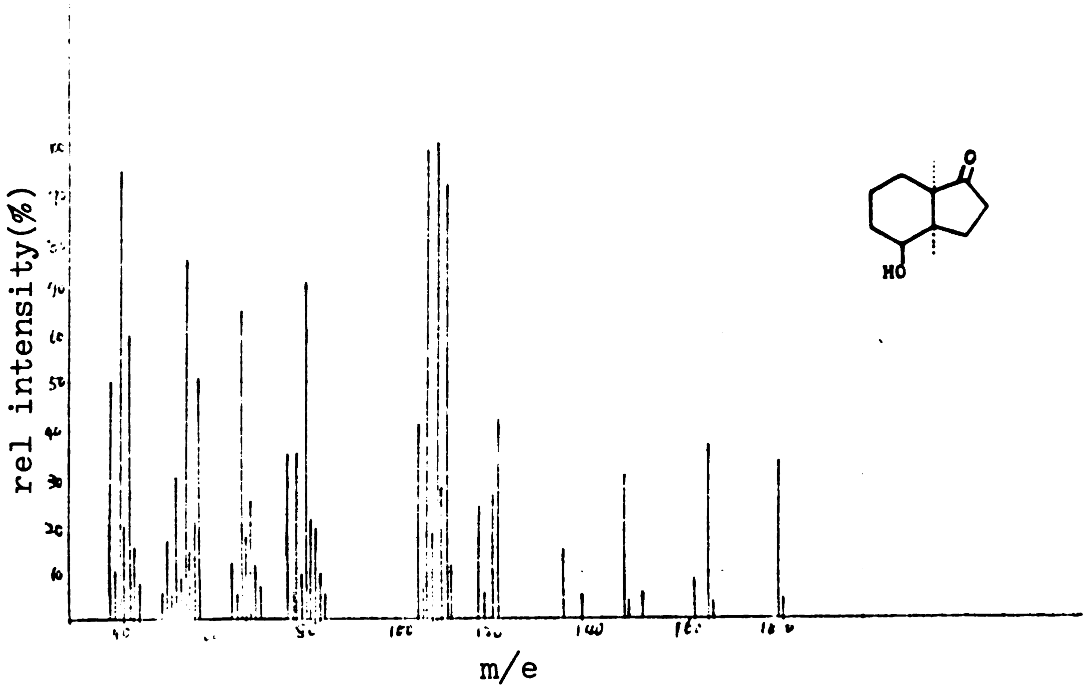


Figure 54. Mass spectrum of 13.

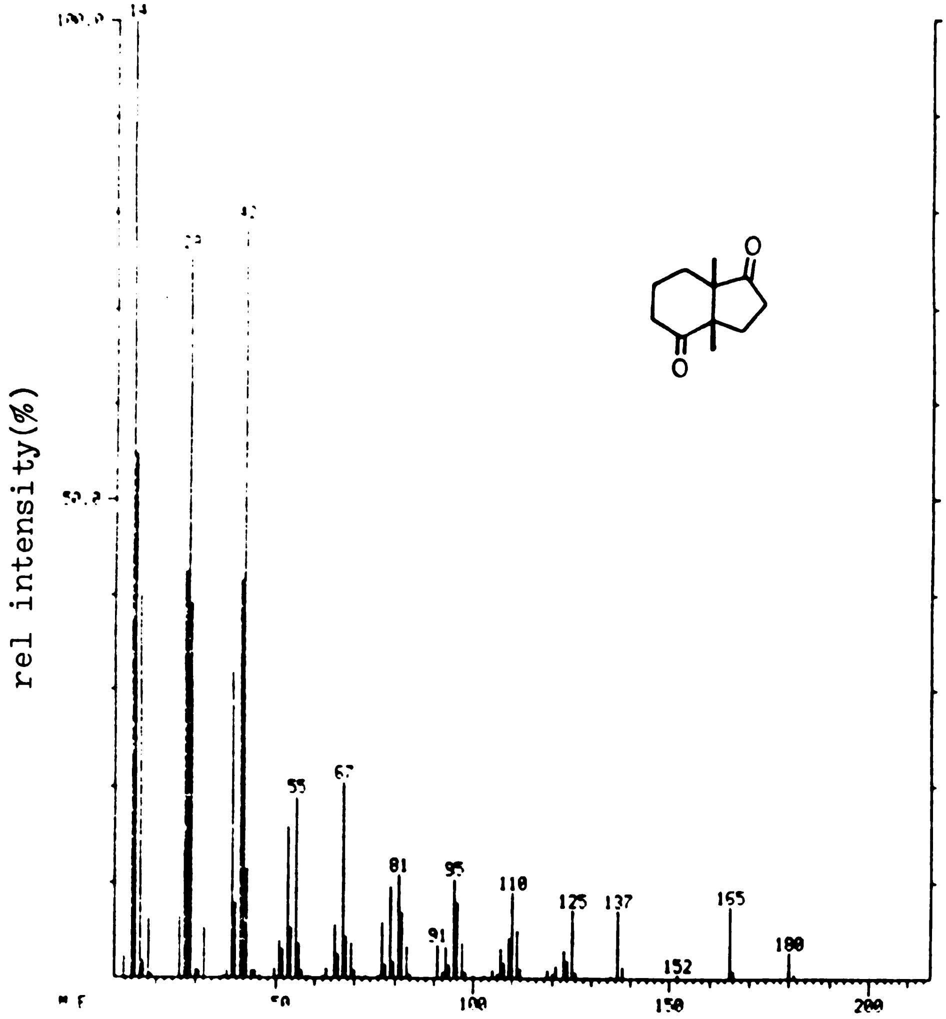


Figure 55. Mass spectrum of 3.

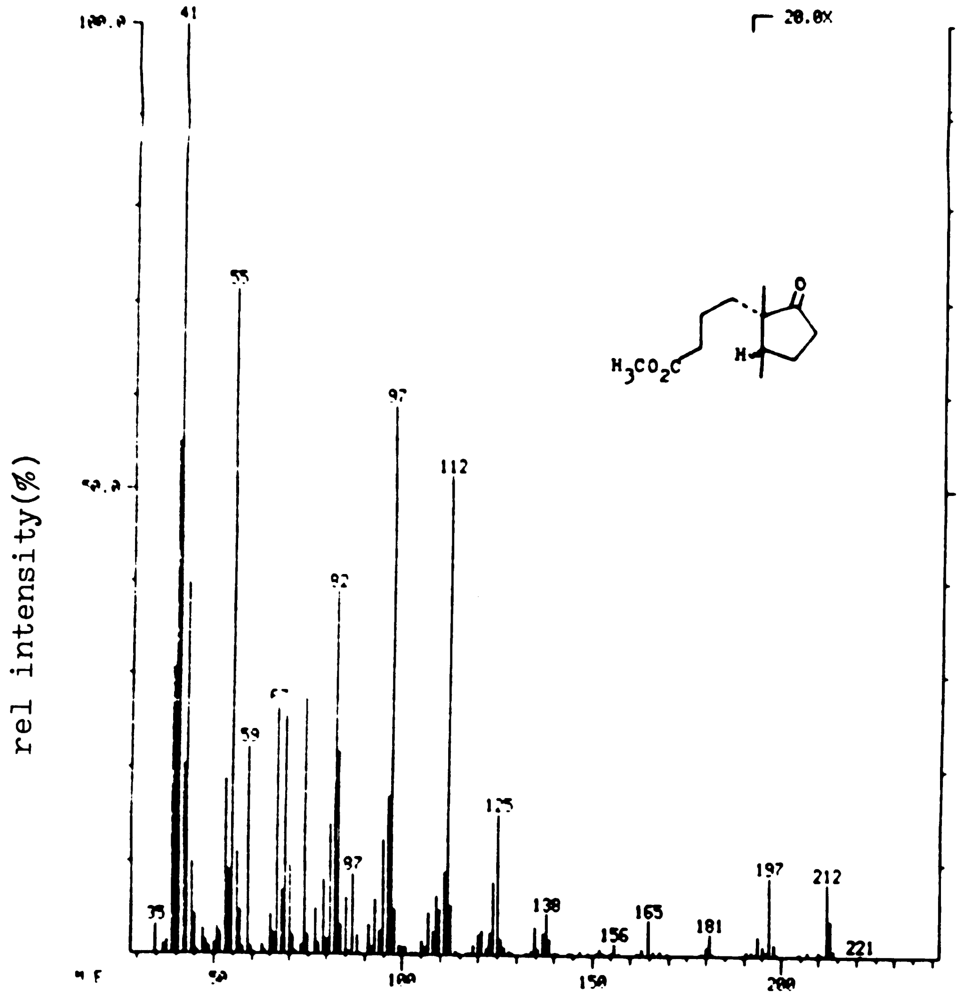


Figure 56. Mass spectrum of 8.

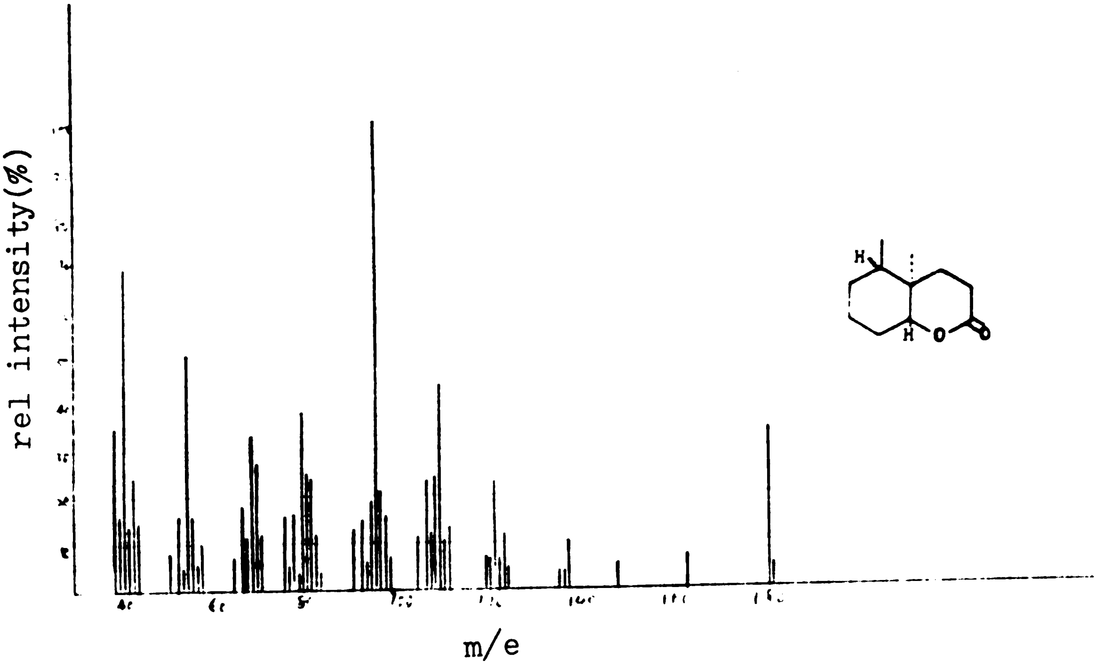


Figure 57. Mass spectrum of 14.

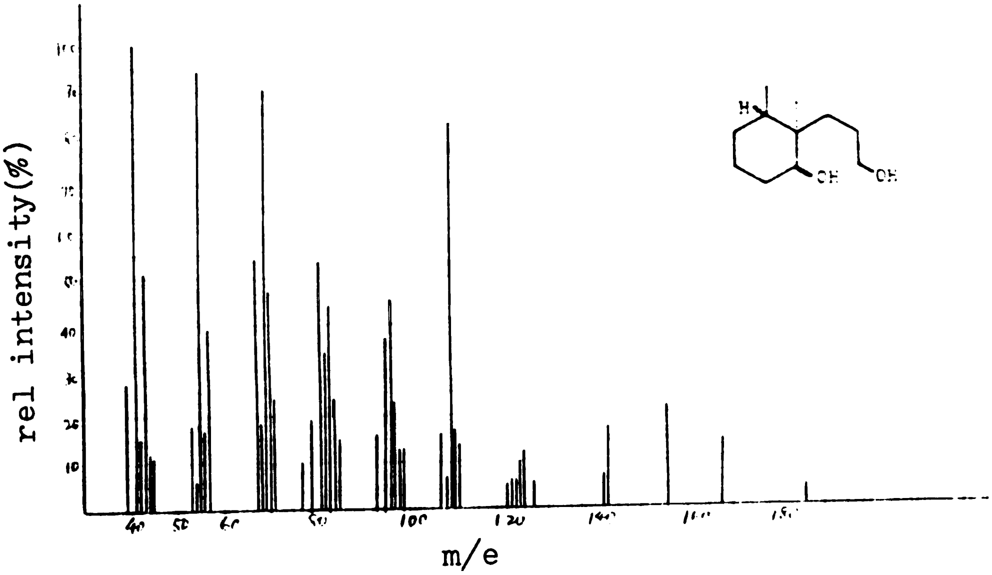


Figure 58. Mass spectrum of 15.

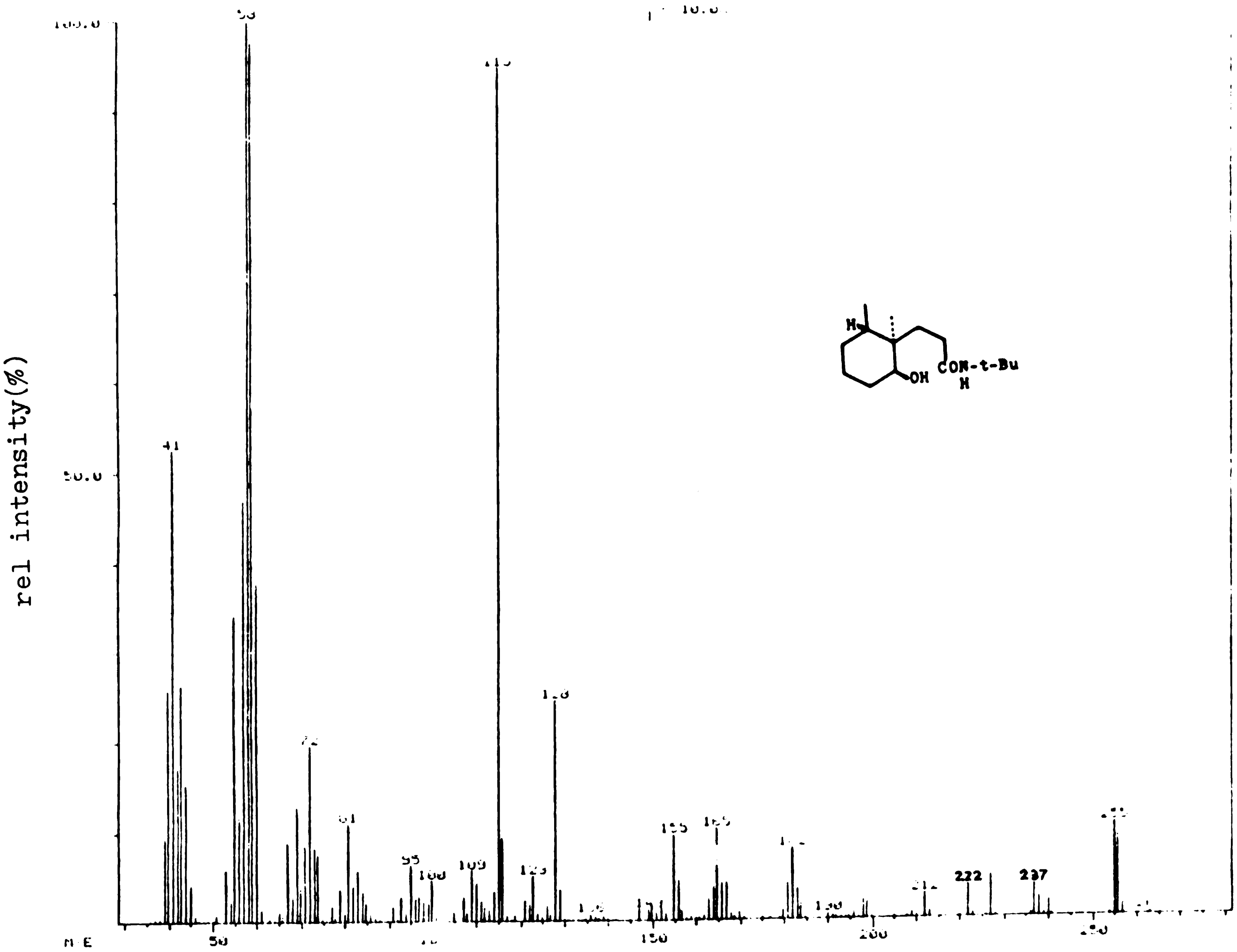


Figure 59. Mass spectrum of 23.

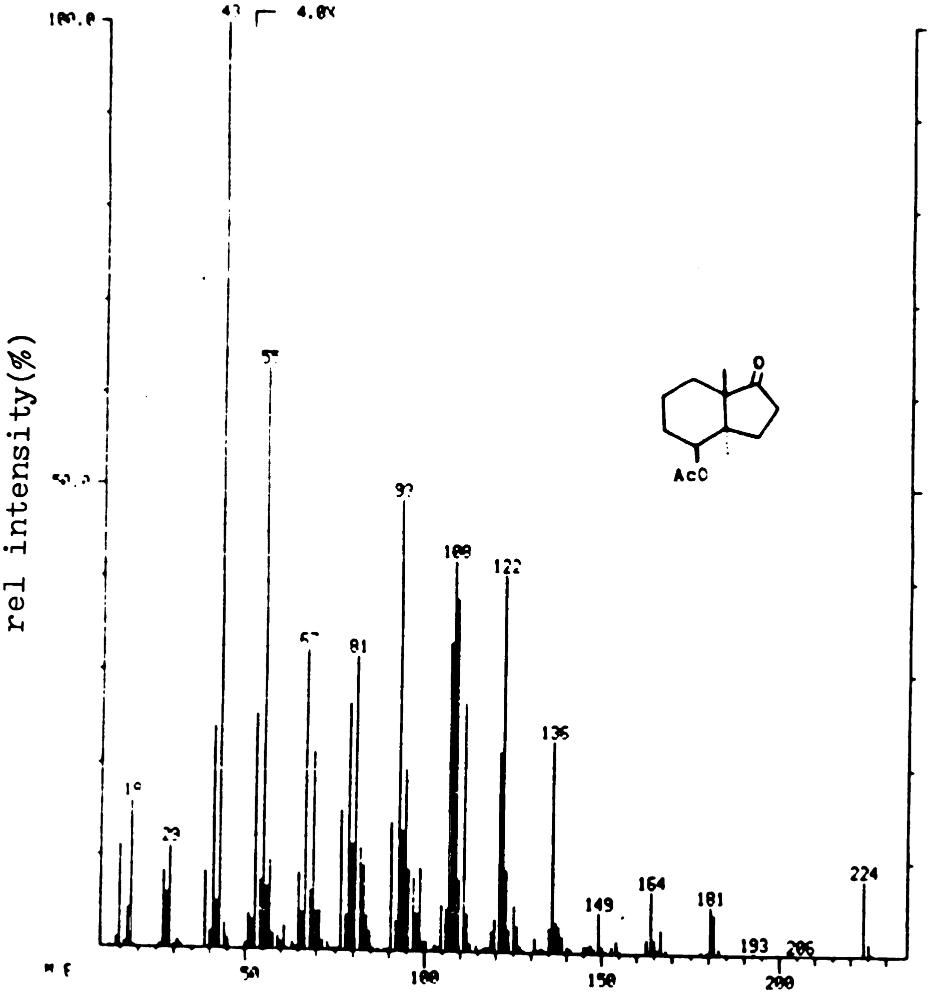


Figure 60. Mass spectrum of **24**.

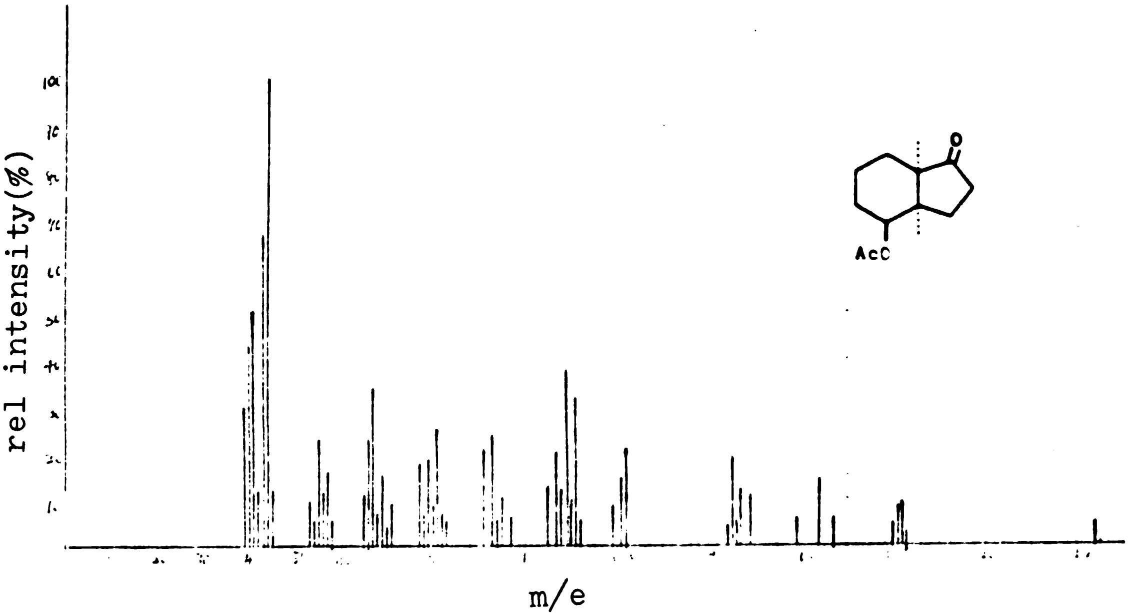


Figure 61. Mass spectrum of 25.

LIST OF REFERENCES

LIST OF REFERENCES

1. J. W. Blunt, H. F. DeLuca and H. K. Schnoes, *Biochemistry*, **7**, 3317 (1968).

2. D. R. Fraser and E. Kodicek, *Nature*, **228**, 764 (1970).

3. A. W. Norman, R. J. Midgett, J. F. Myrtle and H. G. Nowicki, *Biochem. Biophys. Res. Comm.*, **42**, 1082 (1971).

4. W. Reusch, K. Grimm, J. Karoglan, J. Martin, K. P. Subrahamanian, and P. S. Venkataramani, *J. Am. Chem. Soc.*, **99**, 1958 (1977).

5. (a) R. B. Woodward, A. A. Patchett, D. H. R. Barton and R. B. Kelly, *J. Chem. Soc.*, 1131 (1957); (b) J. Martin, Ph.D. Thesis, Michigan State University, 1976.

6. (a) E. Havinga, *Experientia*, **29**, 1181 (1973); (b) L. F. Fieser and M. Fieser, "Steroids", Reinhold Publishing Corporation, New York, 1959, pp. 146-150.

7. (a) F. Gautschi and K. Bloch, *J. Am. Chem. Soc.*, **79**, 684 (1957); (b) M. Akhtar, K. Alexander, R. B. Boar, J. F. McGhie and D. H. R. Barton, *Chem. Comm.*, 383 (1972).

8. (a) H. H. Inhoffen, *Angew. Chem.*, **72**, 875 (1960); (b) H. H. Inhoffen, K. Irmscher, H. Hirschfeld, U. Stache and A. Kreutzer, *Ber.*, **91**, 2309 (1958).

9. B. Lythgoe, T. M. Dawson, J. Dixson, P. S. Littlewood and A. K. Saksena, *J. Chem. Soc. (c)*, 2920 (1971).

10. W. H. Okamura, M. L. Hammond and A. Mouriño, *J. Am. Chem. Soc.*, **100**, 4907 (1978)

11. B. Lythgoe, T. A. Moran, M. E. N. Nambudiry, J. Tideswell and P. W. Wright, *J. C. S. Perkin I*, 590 (1978).

12. B. Lythgoe, P. J. Kocienski and S. Ruston, *J. C. S. Perkin I*, 1290 (1979).

13. (a) J. H. Babler and M. J. Coghlan, *Syn. Comm.*, **6**(7), 469 (1976); (b) W. G. Dauben and D. M. Michno, *J. Org. Chem.*, **42**, 682 (1977); (c) W. Herz and P. Sundararaman, *J. Org. Chem.*, **42**, 813 (1977).

14. G. Wittig and W. Haag, *Ber.*, **88**, 1654 (1955).

15. L. F. Fieser, *Am. Soc.*, **75**, 4395 (1953).

16. (a) R. H. Wollenberg, K. F. Albizabi and R. Peries, *J. Am. Chem. Soc.*, **99**, 7365 (1977); (b) K. S. Y. Lau and M. Schlosser, *J. Org. Chem.*, **43**, 1595 (1978).

17. E. J. Corey, D. Enders and M. G. Bock, *Tet. Lett.*, **7** (1976).

18. P. A. Grieco, M. Nishizawa, T. Oguri, S. D. Burke and N. Marinovic, *J. Am. Chem. Soc.*, **99**, 5777 (1977).

19. J. S. Tou, unpublished work in our laboratory.

20. E. J. Corey, M. Chaykovsky and R. Greenwald, *J. Org. Chem.*, **28**, 1128 (1963).

21. B. Lythgoe and I. T. Harrison, *J. Chem. Soc.*, 837 (1958).

22. H. O. House and W. F. Gannon, *Org. Syn.*, **40**, 41.

23. G. B. Stork and R. L. Danheiser, *J. Org. Chem.*, **38**, 1775 (1973).

24. O. F. Beumel, Jr. and R. F. Harris, *J. Org. Chem.*, **29**, 1872 (1964).

25. O. R. Peterson and E. E. Sowers, *J. Org. Chem.*, **29**, 1627 (1964)

26. H. J. Dauben, Jr., B. Löken and H. J. Ringold, *Am. Soc.*, **76**, 1359 (1954).

27. (a) W. Reusch, J. L. Martin and J. S. Tou, *J. Org. Chem.*, in press; (b) H. O. House, L. J. Czuba, M. Gall and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).

28. K. Campbell, A. Sommers and B. Campbell, *J. Am. Chem. Soc.*, **66**, 82 (1944).

29. M. Haslanger and R. G. Lawton, *Syn. Comm.*, **4**(3), 155 (1974).

30. H. J. Reich, J. M. Renga and I. L. Reich, *J. Am. Chem. Soc.*, **97**, 5434 (1975).

31. (a) V. Benesova, Z. Samek, V. Herout and F. Sorm, Coll. Czech. Chem. Comm. , 34, 582 (1969); (b) A. Corbella, P. Garibaldi, G. Jommi, F. Orsini, A. DeMarco and A. Immirzi, J.C.S. Perkin I, 1875 (1974).

32. H. Wehrli and K. Schaffner, Helv. Chim. Acta, 385 (1962).

33. N. C. Yang and R. H. K. Chen, J. Am. Chem. Soc., 93, 530 (1971).

34. G. Hüppi, F. G. Eggart, S. Iwasaki, H. Wehrli, K. Schaffner and O. Jeger, Helv. Chim. Acta, 49, 1986 (1966).

35. C. Ouannes and R. Beugelmans, Bull. Soc. Chim. Fr., 4275 (1972).

36. S. G. Cohen, A. Parola and G. H. Parson, Chem. Rev., 141 (1973).

37. N. J. Turro, J. C. Dalton, K. Dowes, G. Forrington, R. Hautala, D. Morton, M. Nifmczyk and N. Schore, Acc. Chem. Res., 5, 92 (1972).

38. J. Karoglan, unpublished work in our laboratory.