PART I

RING OPENING REACTIONS OF FUSED CYCLOPROPANOL DERIVATIVES

PART II

TOTAL SYNTHESIS OF SPIROVETIVANE SESQUITERPENES

By

K.P. Subrahamanian

A DISSERTATION

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

DOCTOR OF PHILOSOPHY

Department of Chemistry

1978

ABSTRACT

PART I

RING OPENING REACTIONS OF FUSED CYCLOPROPANOL DERIVATIVES

PART II

TOTAL SYNTHESIS OF SPIROVETIVANE SESQUITERPENES

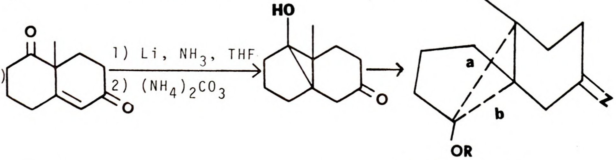
By

K.P. Subrahamanian

PART I

Fused cyclopropanol derivatives 2 - 9 were prepared from the lithium-ammonia reduction of Wieland Mischer ketone 1, followed by simple chemical transformations (equation 1).

(1)



1

2

3=R=H, Z=H, OH

4=R=-Si+, Z=O

5=R=-Si+, Z=H, OH

6=R=-Si+, Z=H, H

7=R=-OAc, Z=O

8=R=-OAc, Z=H, OH

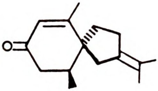
9=R=-OAc, Z=H, H

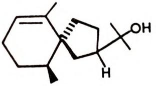
Ring opening reactions of 2 - 9 with electrophiles such as H^+ and Hg^{2+} and bases such as OH^- and guanidine have been studied. A correlation of regioselectivity with stereoselectivity has been noted. Products from 'a' bond cleavage are formed with predominant retention of configuration whereas products obtained from 'b' bond cleavage are formed with inversion of configuration.

Mineral acid catalyzed reactions of cyclopropanol 3, 5, 8, and 9 showed high regioselectivity ('a' bond cleavage) and stereoselectivity (retention of configuration). Compound 6 is somewhat less regioselective possibly due to steric hindrance of the t-butyl dimethyl silyl group. Acid catalyzed cleavage of 2, 4, and 7 proceeded with moderate regioselectivity (bond 'b' repture), the major products forming with inversion of configuration. Although cyclopropanol 3 and 8 showed very poor regioselectivity on reaction with strong bases, very high regioselectivity were observed for comparable reactions of compound 2 and 7 possibly due to carbonyl group participation. Remarkable regioselectivity and stereoselectivity were noted in the reaction of cyclopropanol 2 with guanidine. Cyclopropanols 2 and 3 did not show much stereoselectivity in reaction with Hg^{2+}, even though good regioselective cleavage of bond 'b' was observed for 2.

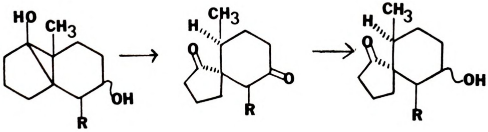
PART II

Two important sesquiterpenes having a spiro[4.5]decane skeleton are β-vetivone **1** and hinesol **2**. The spiroketone **5** and **6** obtained from ring opening reactions of cyclopropanols **3** and **4** respectively have proven to be versatile intermediates in the synthesis of these natural products (equation 1).


1



2

(1)


$\mathbf{3} = R = CH_3$

$\mathbf{4} = R = H$

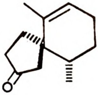
$\mathbf{5} = R = CH_3$

$\mathbf{6} = R = H$

$\mathbf{7} = R = CH_3$

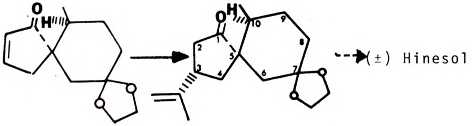
$\mathbf{8} = R = H$

Spiroketone **9**, first prepared by Marshall and Johnson in their synthesis of β-vetivone, has been obtained from ketol **7** in 40-50% yield by a 1,2-carbonyl transposition followed by dehydration.



9

A highly stereoselective synthetic approach to hinesol from enone 10 (obtained from 6) has been studied. Conjugate addition of bisisopropenyl copper lithium to enone 10 proceeded with high stereoselectivity to a single isomer 11. The conversion of 11 to (±) hinesol has been partially completed and follows established chemical transformation.



10

11

DEDICATION

This dissertation is dedicated to the memory of my father.

ACKNOWLEDGEMENT

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

To friends past and present, in the lab and elsewhere, the author extends his gratitude.

Special thanks are also extended to my wife, Indira, and my daughter, Chitra, whose love, encouragement, inspiration, patience, perspiration, and understanding over the years have made this opportunity possible.

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

PART I

PART II

LIST OF FIGURES--Continued

Figure # Page

LIST OF FIGURES--Continued

LIST OF TABLES

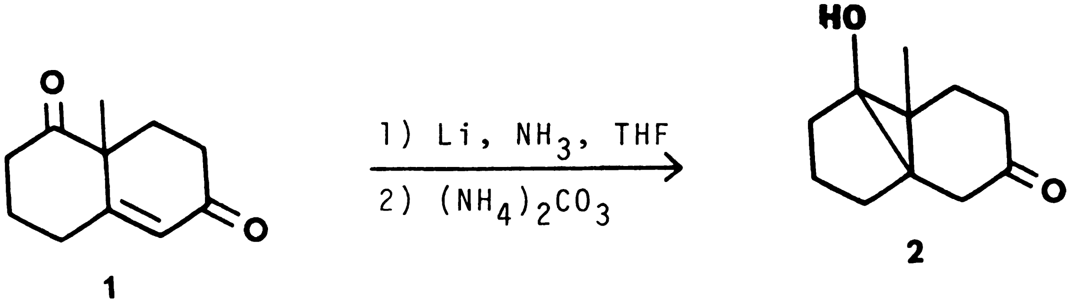
PART I

REACTIONS OF FUSED CYCLOPROPANOL DERIVATIVES

INTRODUCTION

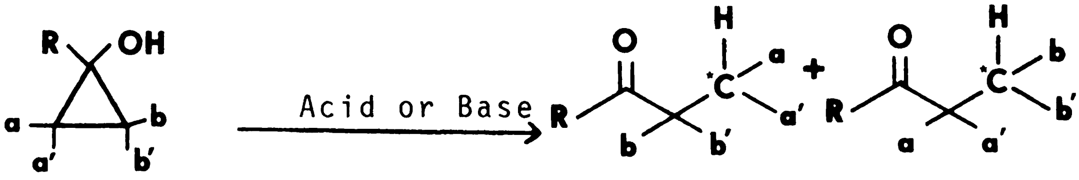
During the past two decades organic chemists have developed an increasing interest in the chemistry of cyclopropanols. Several good methods[1,2,3,4,5] have been developed for the synthesis of cyclopropanols, including an ingenious and potentially very useful synthesis of the tricyclopropanol 2 by reduction of 1-methylbicyclo[4.4.0]dec-6-ene-2,8-dione with lithium and ammonia[6,7,8,9,10,11] (eq. 1).

(1)



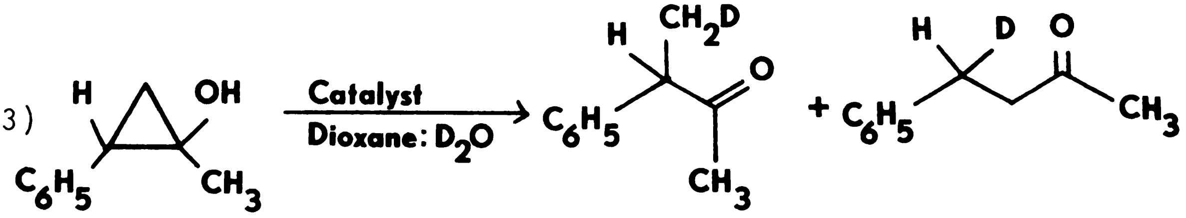
Ring-opening reactions of cyclopropanols and their derivatives may be induced by electrophiles or bases. There are two important aspects of such cyclopropanol ring opening reactions: (1) To what degree is the cleavage of 'α' bond to the 'a' and 'b' side regioselective? (2) What is the degree of stereoselectivity in the protonation stage? (eq. 2)

(2)



Proton induced cyclopropanol ring opening may be regarded as an S_E2 reaction at carbon and often does not show high regioselectivity[11,12] (eq. 3, 4 and 5). Thus a mixture of products is usually obtained from the acid catalyzed opening of unsymmetrical cyclopropanols, although product resulting from proton attack at the least substituted carbon atom generally predominating. Normally these reactions proceed with retention of configuration at the site of electrophilic attack.[11b,13] (eq. 3 and 4)

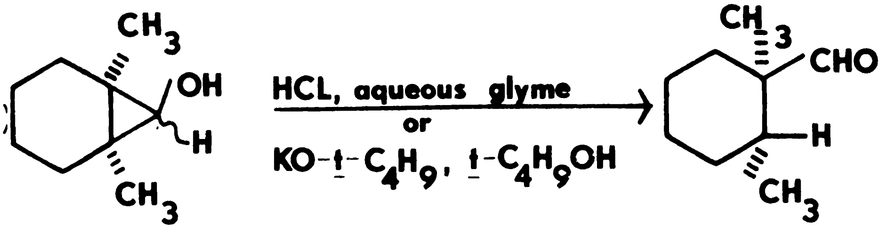
(3)



Catalyst = DCl 60% 40% (Complete Retension)

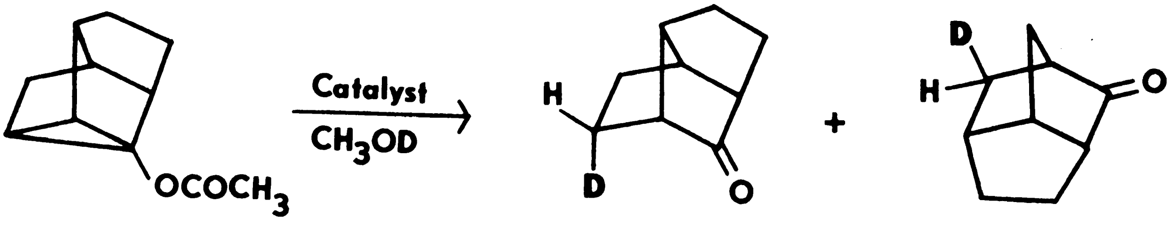
: KOD 0 100% (Complete Inversion)

(4)



(Complete Retention)

(5)



(a brexane) (a brendane)

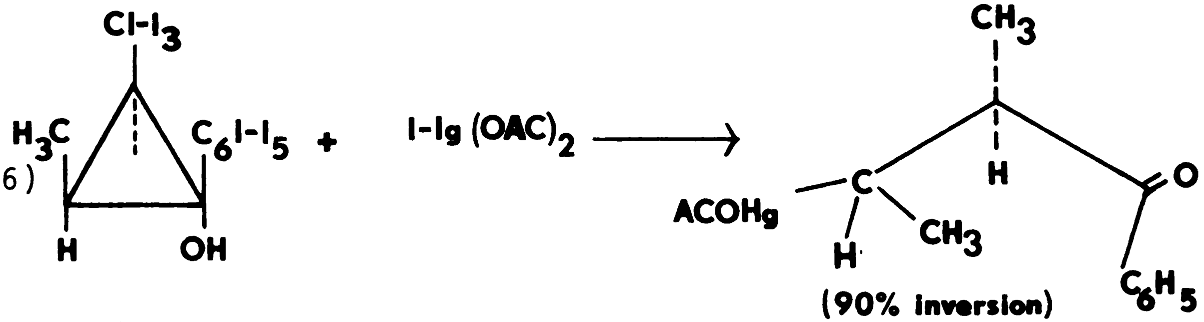
Catalyst = D_2SO_4 31% 69%

= $NaOCH_3$ 0 >95

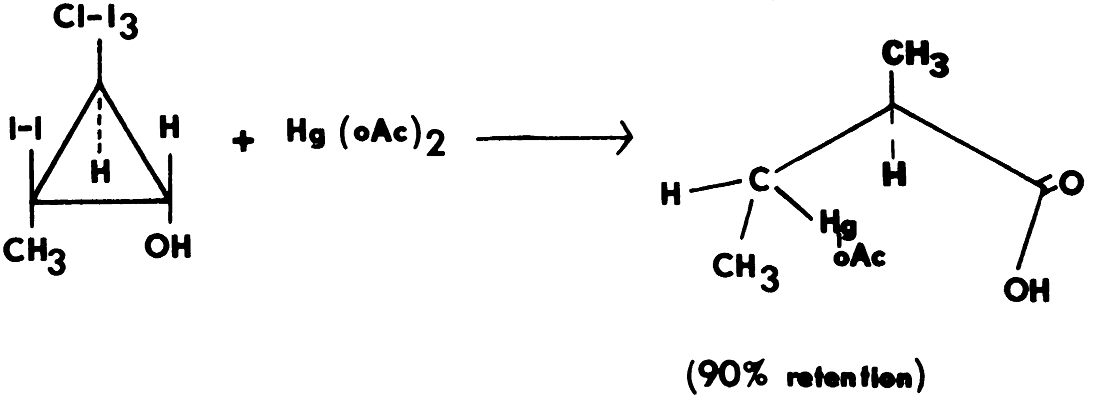
An exceptional case in which inversion at the site of electrophillic attack was observed and could be explained by steric hindrance[12] (eq. 5). Furthermore, an interesting solvent effect on the stereochemistry of protonation has been reported in another case.[13c]

Cyclopropanols and their derivatives react readily with mercuric acetate in either acetic acid or methanol.[11a] The stereochemistry of these reactions depends strongly upon the substitution pattern of the cyclopropanol. Electrophillic attack occurs most readily at the least substituted bond in the molecule to give a β-mercurio aldehyde or ketone. If the α-bonds are equally substituted, attack on a cis substituted bond proceeds more readily than on a trans bond (eq. 6 and 7).

(6)

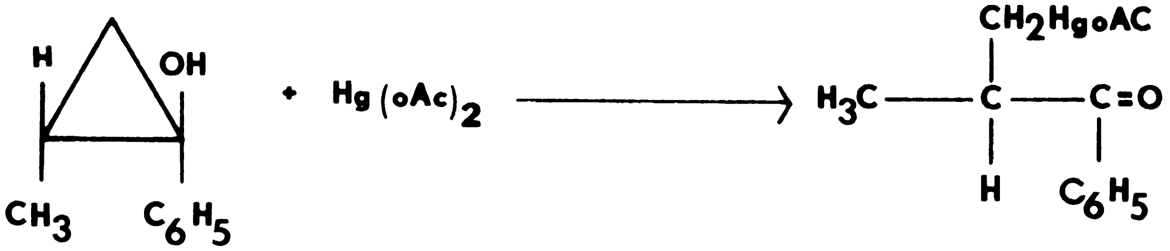


(7)



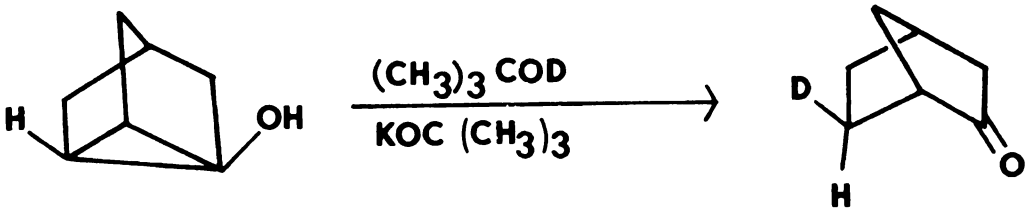
The mercuric acetate ring opening of cyclopropanols is more sensitive to steric hindrance than is proton induced opening[11b] (eq. 8).

(8)

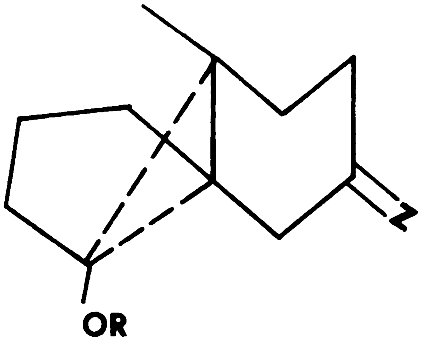


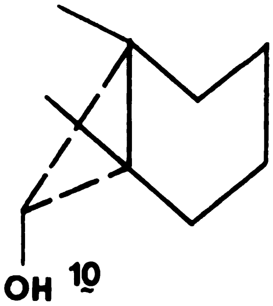
Base catalyzed ring openings of cyclopropanols may be regarded as S_E1 reactions and they generally proceed with high regioselectivity[11,14] (eq. 3 and 5). Furthermore, the c-protonation step is usually characterised by inversion of configuration at the β-carbon atom.[11b,13] However, it is known that the solvent and the nature of the substituents on the ring can alter the stereoselectivity of the reaction.[15] Base catalyzed cleavage of 2-phenyl-1-methyl cyclopropanol in heavy water proceeds with inversion of configuration[11] (eq.3). On the other hand, Wharton and Bair[13a] noted the 7-hydroxy-1,6-dimethylbicyclo[4,4,0] heptane opened with retention of configuration on treatment with potassium *t*-butoxide in *t*-butyl-alcohol. However, the same system reacted with inversion of configuration when an ethylene glycol solvent was used. These results are consistent with the observations and interpretations suggested by Cram,[15] for electrophillic substitution of carbanion intermediates. One exception to the above rule[16] is the ring opening reaction of 1-hydroxynortricyclene with exclusive inversion of configuration in t-butanol solution (eq. 9). This was rationalised as another case of favored exo attack in the norbornyl system.

(9)



In the first part of this dissertation, I will discuss the ring opening reactions of tricyclopropanols 2, 3, 4, 5, 6, 7, 8, and 9 with electrophiles like H^+ and Hg^{2+} and bases like OH^- and guanidine. It is important to recognise that cyclopropanols 2 - 9 are closely related to the compound 10 studied by Wharton and Bair.[13a]





10

2=Z=O, R=H

3=Z=H, OH, R=H

4=Z=O, R=Si

5=Z=H, OH, R=Si

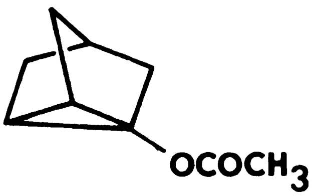
6=Z=H, H, R=Si

7=Z=O, R=Ac

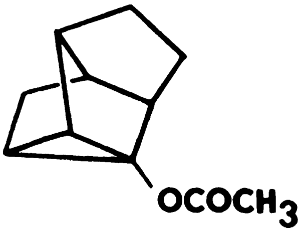
8=Z=H, OH, R=Ac

9=Z=H, H, R=Ac

From the above structures we see that the key difference between our system and that of Wharton is the presence of a two-carbon bridge from one methyl group to the carbinol carbon and a carbonyl function in **2**, **4** and **7**. In compounds **6** and **9** only the two-carbon bridge perturbs the symmetry of **10**, so that the results of ring opening reactions of these cyclopropanols should clearly show the influence of their structural feature. Furthermore, a parallel exists between this study and work of Nickon in which a two-carbon bridge perturbed the symmetry of nor-tricyclic acetate,[11d] **11** and **12**.



11



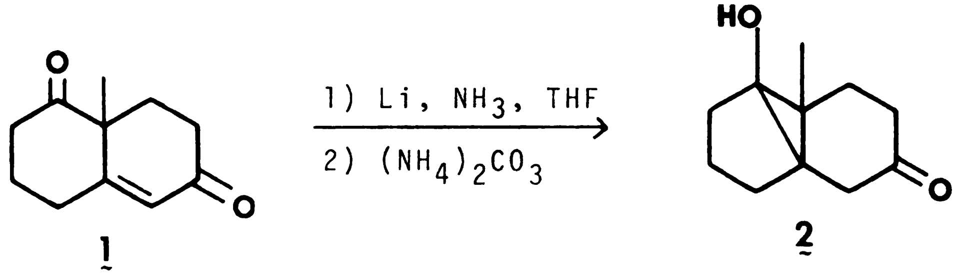
12

RESULTS AND DISCUSSION

RESULTS

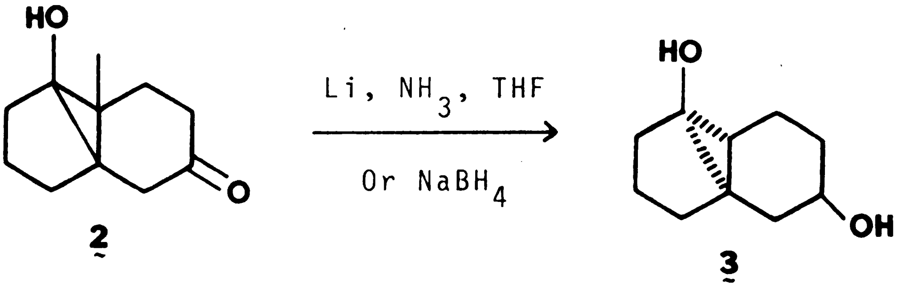
The cyclopropanol, 6-methyl-5-hydroxytricyclo$[4,4,0,0^{1,5}]$-decan-9-one 2, used in this study was prepared by lithium-ammonia reduction of bicyclo dec-6-ene-2,8-dione 1 (equation 1), in 50-90% isolated yield.[6,7,8,9]

(1)



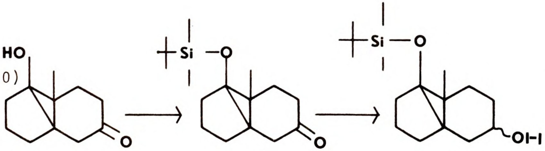
Cyclopropanol derivatives 3 - 9 were obtained from 2 in excellent yields by simple chemical transformations. Thus diol 3 was prepared as an epimeric mixture by reduction of 2 with lithium-ammoniua or sodium borohydride (equation 9).

(9)



Treatment of 2 with tert-butyl dimethylchlorosilane in dimethylformamide containing imidazole as a catalyst proceeded to 4 in 98% yield.[17] Reduction of 4 with sodium borohydride at -78°C (equation 10) was followed by conversion of alcohol 5 into silylether 6 by the excellent procedure

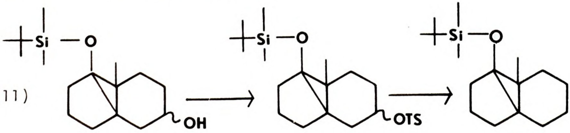
(10)



2 4 5

reported by Y. Fugimoto and T. Tatsuno.[10] Thus, the tosylate of 5 was treated with 5 equivalent of sodium iodide and 10 equivalent of zinc powder in refluxing glyme, and 6 was obtained in 90% yield (equation 11).

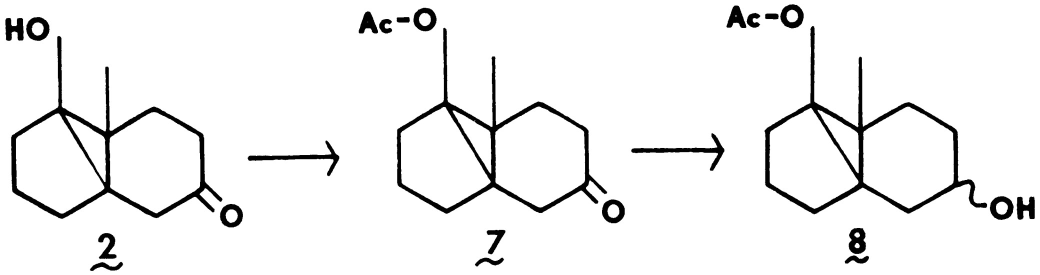
(11)



5 6

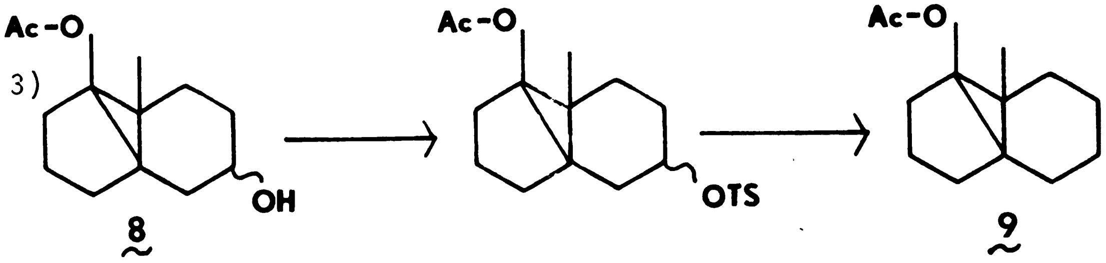
Quantitative conversion of cyclopropanol 2 to the acetate 7 was achieved by stirring 2 with acetic anhydride and pyridine. Reduction of 7 with sodium borohydride then gave an epimeric alcohol mixture 8 in very good yield (equation 12).

(12)



Conversion of this alcohol mixture into the deoxy derivative **9** was accomplished in 80% yield by the same method used in the preparation of **6** (equation 13).

(13)



The products obtained from **2** - **9** on treatment with several different acids and bases are listed in Table I. These reactions were monitored by a combination of TLC (silica gel) and GLC (QF-1), and pure samples of each major component were isolated by preparative GLC and/or crystallization. Identification of these compounds was achieved by a combination of mass spectrometric, infrared and ^{1}H NMR measurements.

Table I. Products derived from the base and acid catalyzed cleavage of cyclopropanol and their derivatives 3 - 9.

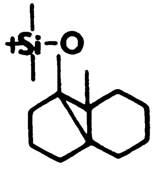
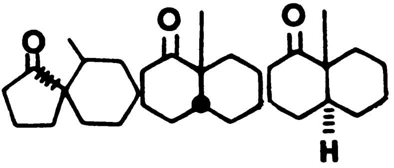
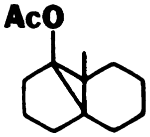
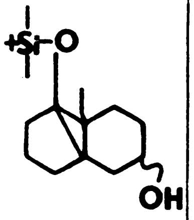
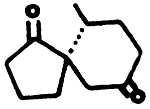
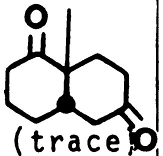
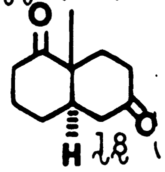
Reactants	Reaction Conditions	Products (% yield)	Stereospecificity		Regioselectivity	
			Retention	Inversion	'a'bond cleavage	'b'bond cleavage
 6	HCl, CH_3OH, 25°C, 3 hrs.	 13 (70) 14 (22) 15 (8)	78	22	70	30
	KOH, CH_3OH	No reaction				
 9	HCl, CH_3OH, 25°C, 40 hrs.	13 (90), 14 (trace), 15 (8)	>98	trace	90	>8
	KOH, CH_3OH, 25°C, 4 hrs.	13 (5), 14 (95), 15 (trace)	5	95	5	95
	KO-t-C_4H_9-t-C_4H_9OH	13 (90), 14 (10), 15 (trace)	90	10	90	10
 5	HCl, CH_3OH, 25°C, 5 hrs.	 16 (99)  17 (trace)	99	trace	99	trace
	OXd^n with Jones Reagent	 18 (trace)				
	KOH, CH_3OH	No reaction				

Table I (cont'd.)

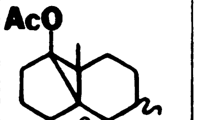
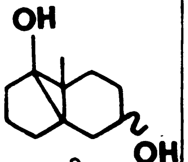
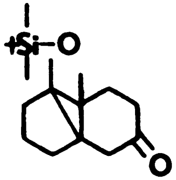
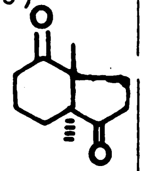
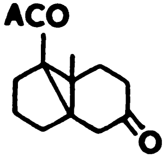
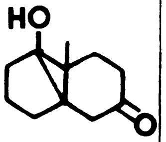
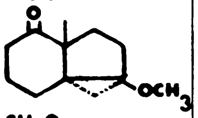
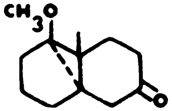
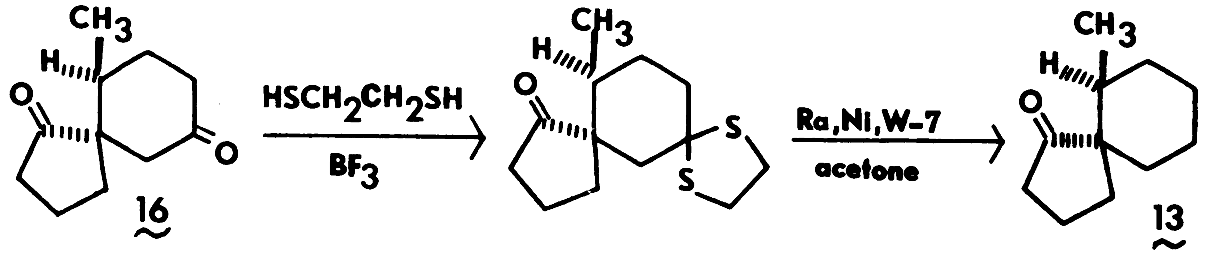
Reactants	Reaction Conditions	Products (% yield)	Stereospecificity		Regioselectivity	
			Retention	Inversion	'a' bond cleavage	'b' bond cleavage
 8	HCl, CH_3OH, 25°C, 40 hrs., OXd[n].	16 (99), 17 (trace), 18 (trace)	99	trace	99	trace
	KOH, CH_3OH, 25°C, 2 hrs., OXd[n].	16 (55), 17 (45)	55	45	55	45
 3	HCl, CH_3OH, 25°C, 10 hrs., OXd[n]	16 (90), 17 (10), 18 (trace)	90	10	90	10
	KOH, CH_3OH, 25°C, 10 hrs., OXd[n].	16 (60), 17 (40)	60	40	60	40
 4	HCl, THF, 25°C, 2 hrs.	16 (21), 17 (55)  19 (24)	21	79	21	79
	KOH, CH_3OH	No reaction				
 7	HCl, THF, 66°C, 6 hrs.	16 (19), 17 (58), 19 (23)	19	81	19	81
	KOH, CH_3OH, 25°C, 2 hrs.	16 (3), 17 (29), 19 (68)	3	97	3	97

Table I (cont'd.)

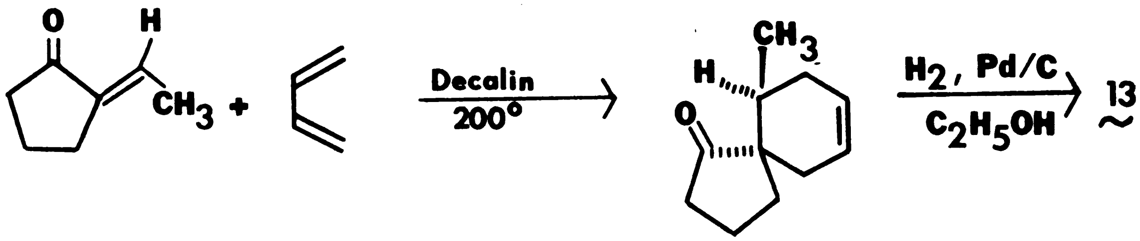
Reactants	Reaction Conditions	Products (% yield)	Stereospecificity		Regioselectivity	
			Retention	Inversion	'a' bond cleavage	'b' bond cleavage
 2	HCl, THF, 66°C, 2 hrs.	16 (22), 17 (59), 19 (19)	22	78	22	78
	HCl, CH_3OH, 25°C, 5 hrs.	16 (trace), 17 (2), 18 (trace), 19 (trace) 20 (64)  21 (32) 	trace	98	trace	98
	HCl, CH_3OH, 25°C, 10 hrs.	16 (trace), 17 (30), 19 (16), 20 (21), 21 (29)	trace	96	trace	96
	KOH, CH_3OH, 25°C, 3 hrs.	16 (0), 17 (20), 19 (80)	0	100	0	100

Authentic samples of cis and trans decalin dione 17 and 18 were prepared by established methods[19] and their configurations were confirmed by the linewidth of their angular methyl ^1H NMR signals.[20] Spirodiketone 16 was identified by its characteristic spectra and its conversion into spiroketone 13 which had been independently synthesized by catalytic reduction of the Diels-Alder adduct from trans-2-ethylidene cyclopentanone and 1,3-butadiene[20,21] (equation 14 and 15).

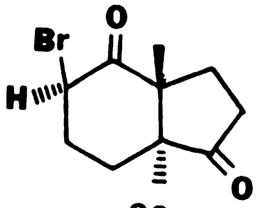
(14)



(15)



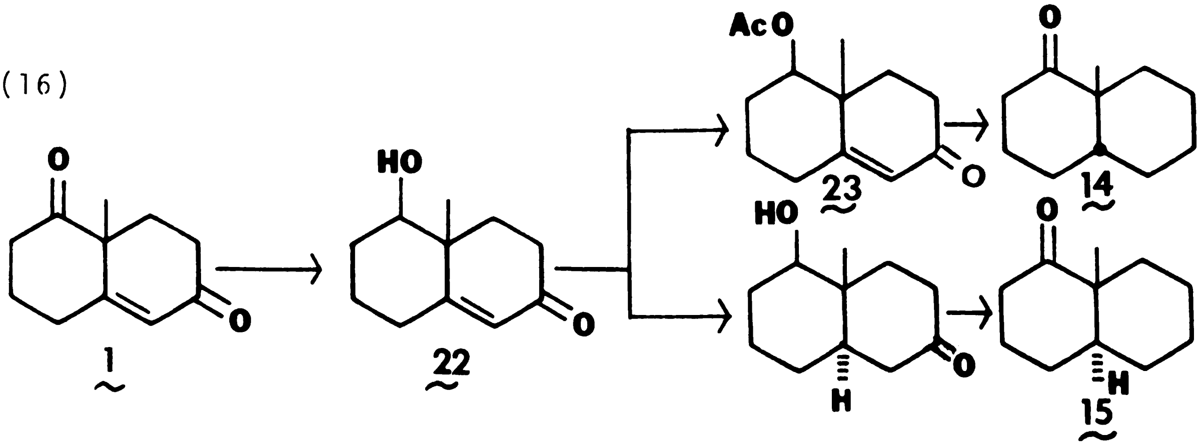
The structure of 19 was unambiguously established by x-ray crystallographic analysis of its bromoderivative[25] 20.



20

Cis and trans-9-methyl decalone-1, 14 and 15 were prepared by roughly the same procedure used for making cis and trans decalin diones 17 and 18[19] (equation 16).

(16)

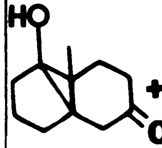
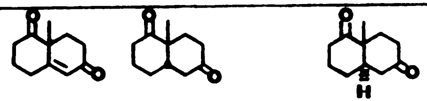
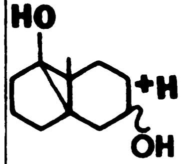
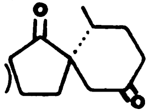


Reduction of 1 with $NaBH_4$ gave very good yield of alcohol 22,[21] which was converted to its acetate derivative 23 on treatment with acetic anhydride and pyridine. Hydrogenation

of the acetate 23 with Pd-$SrCO_3$ followed by Wolf-Kishner reduction and Jones oxidation gave the cis ketone 14 in moderate yield. The trans ketone 15 was prepared by reducing 22 with lithium and ammonia, followed by Wolf-Kishner reduction and oxidation with Jones reagent. The identity of these two isomers was confirmed by the characteristic peak shape of the angular methyl ^{1}H NMR[20] signals and by comparison of their properties with those reported by W.S. Johnson.[22]

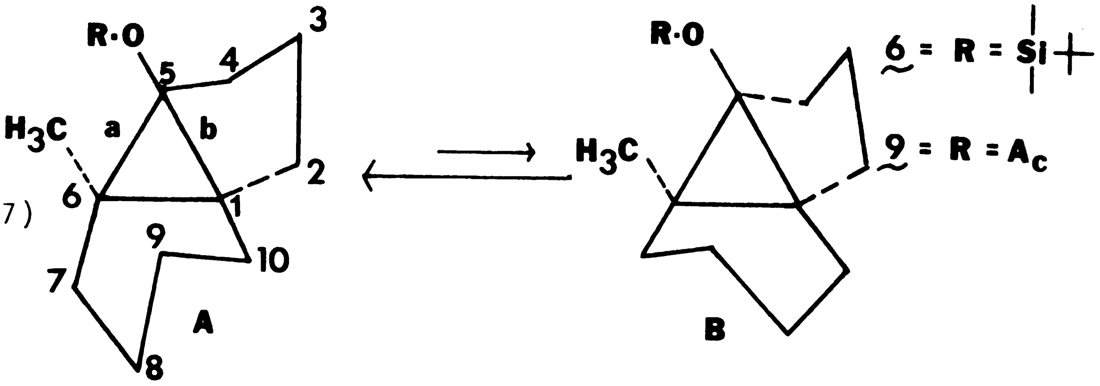
Products derived from reactions of cyclopropanols 2 and 3 with mercuric acetate in acetic acid, followed by demercuration with different reagents are given in Table II.

Table II. Products derived from the reaction of cyclopropanol 2 and 3 with mercuric acetate and acetic acid, followed by demercuration with different reagents.

Reactants	Demercurating agents	Product (% Yield)	Regioselectivity	
			'a' bond cleavage	'b' bond cleavage
 $+Hg(oAc)_2\cdot CH_3COOH$ 2	Heat (steam bath)	 1 (99) 17 (trace) 18 (trace)	0	100
	HCl, CH_3OH, 0°C	1 (95), 17 (1), 18 (4)	0	100
	NaOH, CH_3OH, 0°C	1 (90), 17 (1-2), 18 (8-9)	0	100
	NaOH, $NaBH_4$, CH_3OH Jones oxidation[3]	1 (20-21), 17 (20-21) 18 (53-54)	0	100
	$NaCNBH_4$, HCl, CH_3OH Jones oxidation	1 (10-15), 17 (20-25) 18 (65)	0	100
 $+Hg(oAc)_2\cdot CH_3COOH$ 3	NaOH, $NaBH_4$, CH_3OH Jones oxidation[3]	1 (trace), 16 (30)  17 (46), 18 (23)	30	70

DISCUSSION

The homoketonisation reactions of cyclopropanol derivatives **6** and **9** can be satisfactorily explained by examining plausible conformational interactions in these systems. It can be assumed that an equilibrium exists between two cyclohexane chair forms A and B (equation 17).

(17) 

Approximate measurements made with the aid of Dreiding models suggest that a strong nonbonded interaction between the C-5-OR group and the C-8 axial hydrogen favors conformation A over B. The corresponding OR; C-9-H interaction in A is less severe. If we assume that "A" is the preferred conformation for **6** and **9**, the following arguments can be made.

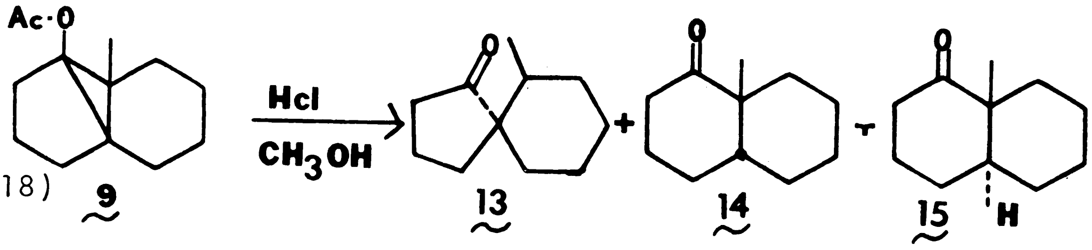
1. The 'b' side of the cyclopropane ring is more hindered than 'a' due to the three carbon bridge from C-1-C-5. Therefore electrophilic cleavage of bond 'b' with retention of configuration is not as favorable as the corresponding cleavage of bond 'a'.

2. Since the 'a' side of the cyclopropane ring is the more

accessible bond for electrophilic attack by "edge cordination", we expect that reaction here will give products having retention of configuration at C-6.

Reaction of cyclopropanol acetate 9 with aqueous hydrochloric acid in methanol gave more than 90% spiroketone 13 along with a small amount of trans ketone 15 (equation 18).

(18)



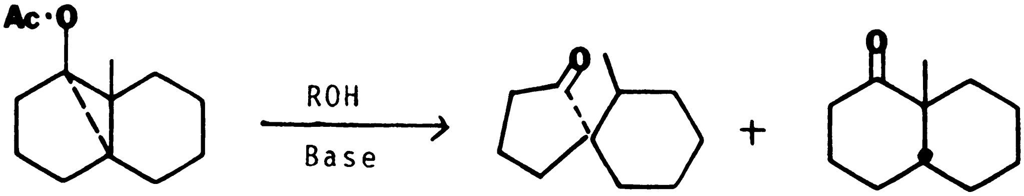
90% (trace) 8%

This result is in agreement with the general principle that "in acid media almost all homoenols and homoenol acetates undergo ketonization with high stereochemical retention (usually 90-100%) irrespective of the substituents or of the solvents".[11b,16,13a]

Silylether 6 underwent acid catalysed ring opening reaction with significantly lower regioselectivity than 9 (equation 19). The formation of cis decalone 14 in 22% with inversion of configuration can be attributed to increased steric hindrance of both the 'a' and 'b' bonds by the bulky t-butyldimethylsilyl group. Since the endo side of the bicyclo [4,1,0]heptane system is blocked, exoprotonation at C-1 begins to compete with the normally facile attack on bond 'a'.

Base catalysed ring opening reactions of these cyclopropanol derivatives have been studied with 9 (6 is not reactive). A dramatic change in the regiospecificity and stereospecificity of these reactions was observed when the reaction condition changed from potassium hydroxide in aqueous methanol to potassium t-butoxide in t-butanol (equation 19).

(19)



9 → 13 + 14

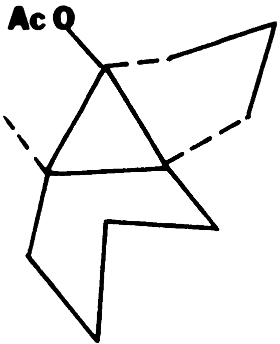
R = CH_3, ∿5% 95%

R = $C(CH_3)_3$, 90% ∿10%

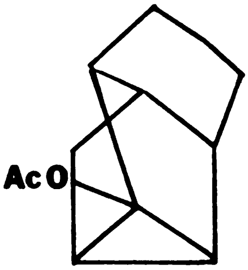
These results are in accordance with Cram's findings in a general study of electrophilic substitution at carbon, namely predominant retention in low dielectric and nondissociating solvents like t-butyl alcohol and inversion in high dielectric and dissociating solvents like water, methanol and ethylene glycol. Even though the stereospecific retention in t-butanol is well documented,[15,13a] the change in regioselectivity (formation of spiroketone 13) with the change of base and solvent requires explanation. The alkoxide base derived from 9 probably exists as a solvated ion pair in nondissociating solvents.[15] Due to steric hindrance from the three carbon bridge, the solvated ion pair will be oriented

over the 'a' side of the cyclopropane ring. This orientation favors collapse to spirocompound with a high degree of retention of configuration.

It will be instructive at this stage to compare and contrast the reactions of 9 with those of Nickon's compound[11d] 12.

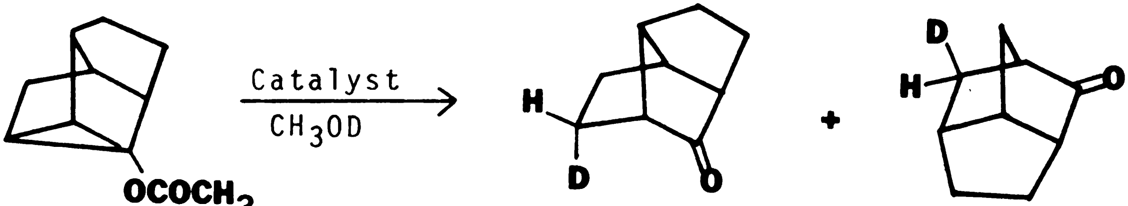


9



12

On treatment with acid, 12 gives 69% of the product resulting from cleavage of bond 'b' with inversion of configuration and 31% of the product from cleavage of bond 'a' with retention of configuration (equation 20). In this case Nickon suggests



(20)

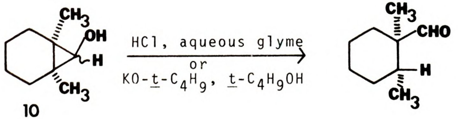
	(a brexane)	(a brendane)
Catalyst= D_2SO_4	31%	69%
= $NaOCH_3$	0	>95%

that the regioselectivity favoring bond breakage is due to the formation of the more stable brendane structure (2.25-3.13 Kcal/mole more stable than brexane). The stereospecificity was attributed to steric hindrance from C-8, C-9 bridge.

This interpretation does not fit the results obtained with 9. Heat of combustion measurements indicates that the spiro[5,4]-decane is less stable than either cis or trans decalin by 4.5-7.0 Kcal/mole, respectively.[23] Nevertheless acid treatment of 9 gives more 90% spiro compound 13 with high stereoselective retention of configuration. Since the 'a' bonds in both 9 and 12 have about the same degree of steric hindrance and since the 'b' bond appeared to be more hindered in 12 than 9, it is difficult to explain the predominance of the brendane product from 12.

Base catalysed reation of 9 and 12 in methanol show a remarkable similarity. High regioselectivity, favoring the thermodynamically more stable bicyclic isomer and high stereoselectivity (inversion of configuration) are found in each case. The acid and base catalysed reactions of 9 agree well with the observation made by Wharton and Bair for the corresponding reactions of compound 10 (equation 21).

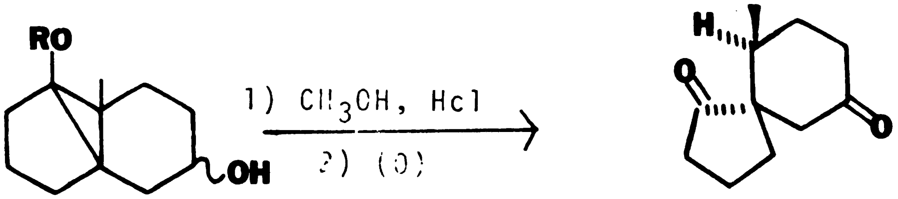
(21)



10

(Complete Retention)

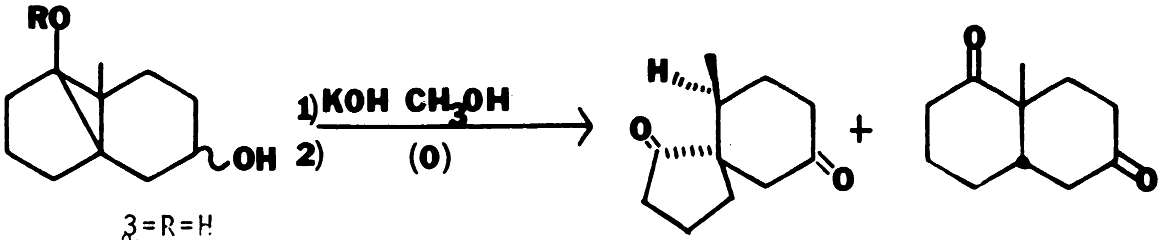
On treatment with acid, cyclopropanols 3, 5, and 8 gave more than 95% spirocompound 16 (equation 22).

(22) 

3 = R = H
5 = R = Si+
8 = R = Ac

16 >(90%)

The high regioselective cleavage of the 'a' bond and stereospecific retention of configuration can be explained in terms of the inductive effect of the C-9-alcoholic group, which inhibits attack of a proton on the nearest cyclopropane bond. Homoketonisation of **3** and **8** with methanolic potassium hydroxide gave about 40% inverted products **17** and 60% spirocompound with retention of configuration (equation 23).



(23) **3**=R=H
8=R=Ac

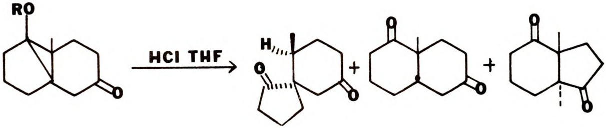
16 (60%)

17 (40%)

The former product is in accordance with Cram's[15] rule, but the latter is difficult to explain.

The products obtained by the treatment of cyclopropanols **2**, **4** and **7** with acid can be explained by the interaction of the cyclopropane 'b' bond and the carbonyl group (equation 24).

(24)

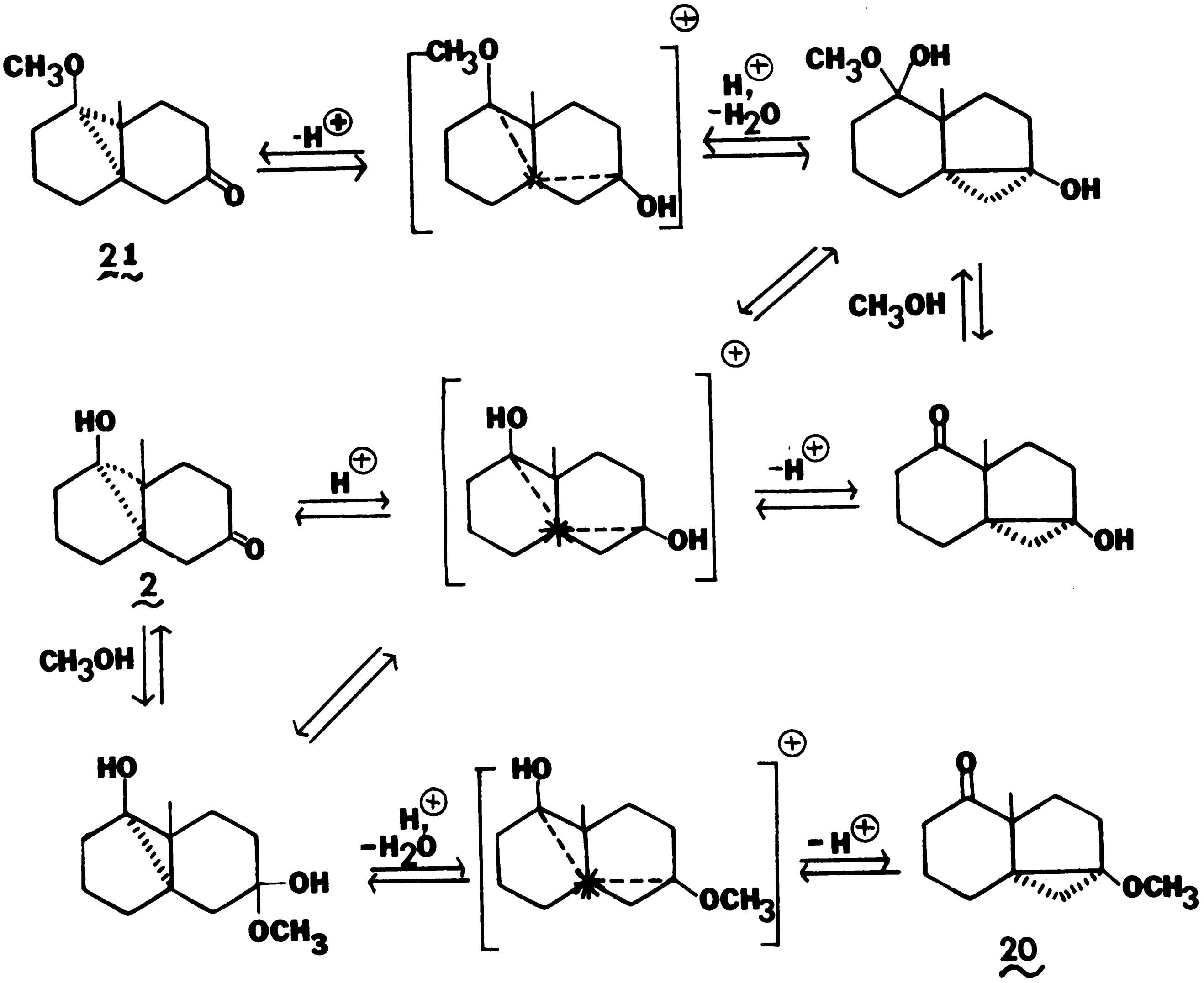


2 = R = H
4 = R = Si+
7 = R = Ac

16 (19-22%) 17 (55-59%) 18 (24%)

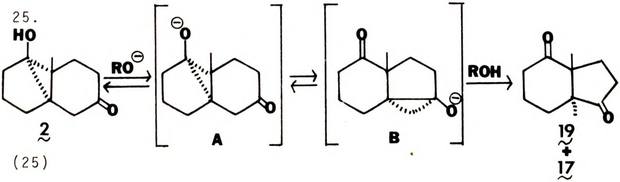
This interaction is evident, for example, in the rapid formation of methoxy ketone 20 on treatment of 2 with methanolic hydrochloric acid. In order to rationalize the results of several related experiments of this kind, it is helpful to consider the equilibrium shown in scheme I. The bracketed cations with the partial bonds are intended to represent either a dynamic bond-switching interconversion of oxycarbonium ions or a nonclassical delocalized cation. In either case the carbon atom designated by an asterisk undergoes on treatment with cold (0°C) methanolic hydrochloric acid for 1 h, 2 was partially converted (ca. 50%) to 20, this being the only significant product other than 2. After 5 h, 2 was still the major product, but substantial amount of the isomer 21 was also obtained. More vigorous conditions

Scheme I



(25°C, longer reaction times) not only gave roughly equivalent amount of 20 and 21, but also yielded products such as 16, 17 and 19. These results point to a very rapid hemiketalization reaction followed by a slower isomerisation of the three-membered ring (via the bracketed cations?) and an even slower ring cleavage of the stable methoxy derivatives 20 and 21. Hence the predominant inversion (80%) and regioselective 'b' bond cleavage of 2, 4, and 7 in acid media appears to be due to facile carbonyl group participation. The formation of 20% spirocompound 16 agrees with the general principle of retention in acid media.

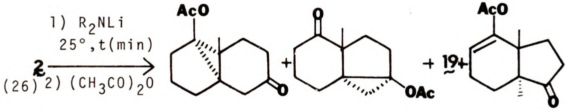
The highly stereospecific and regioselective cleavage of the 'b' bond in 2 and 7 (95%) on treatment with base is also due to carbonyl group interaction as shown in equation 25.



(25)

Since no products incorporating the tricyclic skeleton of B were obtained, J. Yordy[25] trapped the conjugate bases A

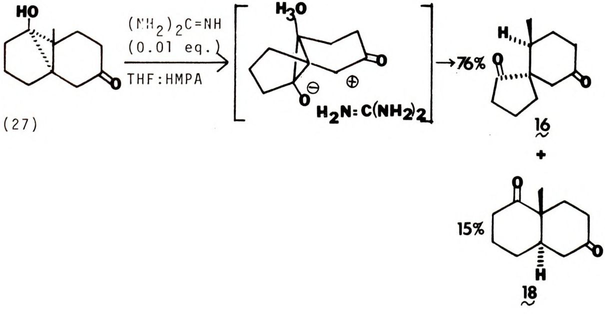
and B in apriotic medium by acetic anhydride and lithium di-isopropyl amide base (equation 26).



(26)

t = 45:	72%	18%	8%	trace
90:	40%	30%	16%	11%

A remarkable change in stereospecificity and regioselectivity can be observed in cyclopropane ring opening reaction of 2 with guanidine as a base (equation 27). A catalytic amount of guanidine in hexamethyl phosphoamide gave the spirocompound (76%) and trans-decalindione 18 (51%), both with retention of configuration, in contrast to the inversion normally observed with base.

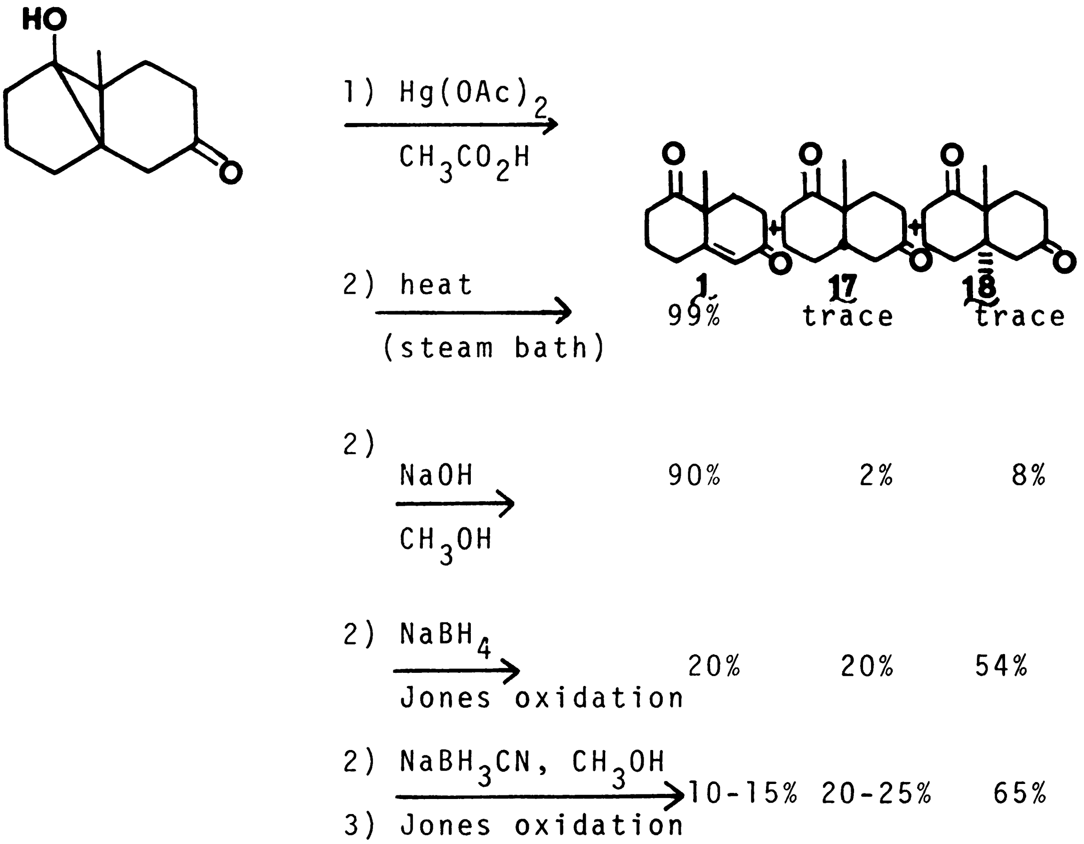


(27)

This stereochemistry undoubtedly reflects the fact that guanidinium cation, formed as a result of proton abstraction from the cyclopropanol, is the only proton source for the ring opening step and is necessarily oriented beneath the six membered ring. Treatment of **2** with a large excess of guanidine gave a product mixture similar to that obtained from methanolic potassium hydroxide.

De Puy and co-workers have noted that mercury (II) acetate cleavage reactions of cyclopropanols proceed with variable stereoselectivity,[11a,b] sometimes giving inversion and other times retention of configuration. Steric hindrance seems to be an important controlling factor. Cyclopropanol **2** is cleaved by mercury (II) acetate with high regioselectivity (equation 28).

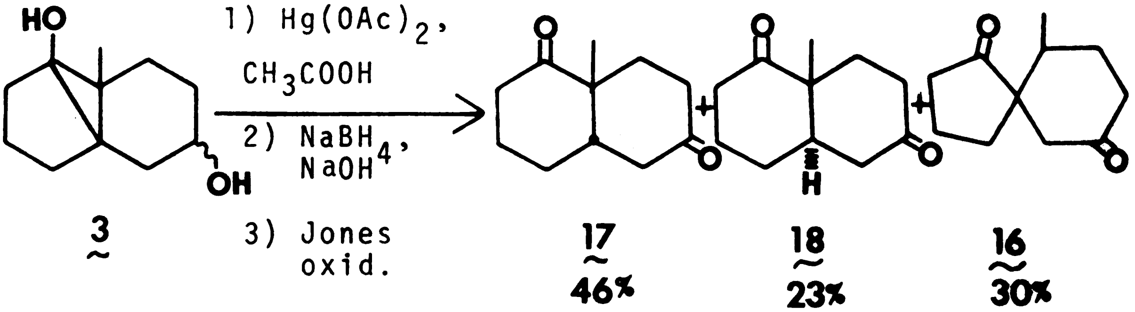
(28)



The fate of the mercury containing group depends on the method of work-up. Thermal decomposition gives elimination, and reductive C-Hg cleavage gives a mixture of cis and trans-decalin derivatives, the latter predominating. It is not possible from this data to determine the stereoselectivity of mercury attack on the three membered ring, because the demercuration step may not be stereoselective.[26,27]

Cyclopropanol **3** shows low regioselectivity in mercury (II) induced ring opening (equation 29). This probably reflects the low of homoconjugation of the three-membered ring with the carbonyl function.

(29)



EXPERIMENTAL

GENERAL

Except as indicated, all reactions were conducted under dry nitrogen or argon, using solvents purified by distillation from suitable drying agents. Magnetic stirring devices were used for most small scale reactions; larger reactions were agitated by paddle stirrers. Organic extracts were always washed with water and brine and dried over anhydrous sodium sulfate or anhydrous magnesium sulphate 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 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 CCl_4 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 Labs, Ann Arbor, Michigan.

Preparation of (IR*,5,6)-5-Hydroxy-6-Methyl-Tricyclo-[4.4.0.0^{1,5}]decan-9-One, 2

In a one liter, three neck, round bottom flask containing a small lump of sodium metal, was condensed 500 ml of ammonia. The ammonia was then distilled through Tygon tubing into a carefully dried two liter, three neck, round bottom flask containing 1.78 g (0.25 M) of lithium ribbon. The reaction flask was equipped with a paddle stirrer, a dry ice condenser, a dry ice-acetone bath, and an addition funnel to which a nitrogen gas line was attached. A solution of 17.8 g (0.1 M) of the enone 2 dissolved in 250 ml of THF was placed in the addition funnel and added dropwise over a one hour period. The blue color of the reaction was discharged by dropwise addition of ethylene dibromide, following which 10 g of finely ground ammonium carbonate was added in one portion.

The cooling bath was removed and the ammonia was evaporated into the hood under a stream of nitrogen by hot water bath. The residue was taken up in 300 ml of water and this mixture was extracted four times with 200 ml of ether. The extracts were washed sequentially with water and brine, and then dried. After removal of the solvent, 18.00 g of light yellow oil was obtained, which was triturated with 10 ml of ether and placed in the refrigerator. Crystallization yielded 12.00 g (66%) of the white, crystalline cyclopropanol. An analytical sample had mp 98-100° (ether).

Preparation of cyclopropyl silyl ether **4**

To a solution of 2.7 g (0.015 mol) of **2** in 150 ml of dimethylformamide was added 4.5 g (0.030 mol) of dimethyl tert-butyl silylchloride and 2.5 g (0.0375 mol) of imidazole and the solution was stirred at 45°C for 7 h. The reaction mixture was diluted with ether and washed with water and brine and dried by anhydrous magnesium sulphate. The oil, after evaporation of the solvent, on bulb to bulb distillation at 109°C in 0.0025 mm Hg gave 4.33 g of pure **4** (98%). IR (neat) 1710 cm^{-1}; ^{1}H NMR (CCl$_4$) δ0.06 (s, 3H), 0.15 (s, 3H), 0.9 (s, 9H), 1.06 (s, 3H), 1.2-2.4 (m, 12H); and mass spectrum (70 ev) m/e (relative intensity) 294 (20), 279 (100), 237 (99), 181 (52), 145 (60), 58 (99).

Anal. calcd. for $C_{17}H_{30}O_2Si$: C, 69.33; H, 10.26

Found: C, 69.35; H, 10.27

Preparation of silyl ether 6

A solution containing 2.303 g (0.0078 mol) of 4 in 25 mL ethanol was treated with 227 mg (0.006 mol) of sodium borohydride at 0°C. The reaction was quenched after 2 hours at room temperature by the addition of water/ethyl acetate mixture, and extracted with methylene chloride. The combined methylene chloride extract was washed with water and brine and dried by anhydrous magnesium sulphate. Removal of the solvent gave 2.384 g of an oil which was found to be an epimeric mixture of two isomeric alcohol 5 in the ratio 65:35. IR (CCl_4) (3600-3100) cm^{-1}; ^1H NMR (CCl_4) δ0.2 (bs, 6H), 0.9 (s, 9H), 1.0 (s, 3H), 2.2-1.2 (m, 12H), 3.2 (bs, 1H), 3.6 (bs, 1H).

The crude product from above (2.384 g = 0.0078 mol) was treated with 2.23 g (0.0117 mol) of p-toluene sulphonyl chloride in 25 mL of pyridine for 10 h at room temperature. The reaction mixture was poured into water and extracted with ether. After the usual work-up, these extracts yielded 3.619 g of white crystals having a very broad melting point (61-83°C). IR ($CDCl_3$) 1175 cm^{-1}; ^1H NMR ($CDCl_3$) δ0.15 (s, 3H), 0.2 (s, 3H), 0.9 (s, 12H), 2.2-1.4 (m, 12H), 2.5 (s, 3H), 4.6 (m, 1H), 7.5 (d, J=8 Hz, 1H), 7.8 (d, J=8 Hz, 1H).

A mixture of 3.6 g (0.0078 mol) of the tosylate from above, 7.5 g (0.05 mol) of sodium iodide and 6.5 g (0.01 mol) of zinc powder in 100 mL of glyme was heated at 85°C for 2 h. On cooling, the mixture was filtered, diluted with water and extracted with ether. The ether extract, after washing and

drying, yielded an oil which was distilled at 65°C (0.0025 mm of Hg), yielding 2.09 g (93%) of **6**.

IR (CCl_4) 2900, 1245, 1120 cm^{-1}; ^1H NMR (CCl_4) δ0.15 (bs, 6H), 0.9 (s, 9H), 1.0 (s, 3H), 2.2-1.2 (m, 14H); mass spectrum (70 ev) m/e (rel aboundance) 280 (6), 265 (51), 251 (11), 238 (12), 220 (34), 147 (100), 76 (99).

Anal. calcd. for $C_{17}H_{32}OSi$: C, 72.78; H, 11.49

Found: C, 72.86; H, 11.46

Preparation of cyclopropanol acetate **7**

A solution containing 3.6 g (0.02 mol) of **2** and 10 mL of freshly purified acetic anhydride in 50 mL of pyridine was stirred for 10 h at room temperature. This reaction mixture was diluted with water and extracted with ether. After the ether extract was washed and dried, it yielded 4.1 g (92.3%) of **7** as pale yellow crystals. An analytical sample was obtained by crystallization from ether-pet. ether mixture; mp 53-54°C.

IR (CCl_4) 1745, 1710 cm^{-1}; ^1H NMR (CCl_4) δ1.2 (s, 3H), 1.9 (s, 3H), 1.9 (s, 3H), 2.6-1.4 (m, 12H); mass spectra (70 ev) m/e (relative intensity) 222 (10), 214 (15), 181 (96), 179 (34), 166 (92), 152 (100).

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

Found: C, 70.27; H, 8.07

Preparation of cyclopropylacetate **9**

A solution containing 4.0 g (0.018 mol) of **7** in 50 mL of absolute ethanol was treated with 740 mg (0.02 mol) of sodium

borohydride at -78°C. After 3 hr, the reaction was quenched with a water ethyl acetate mixture and extracted with ether. The ether extract yielded 4.086 g of an oil (98%), assigned structure **8** on the basis of the following spectroscopic evidence:

IR (neat) (3600-3200), 1750 cm^{-1}; ^{1}H NMR (CCl_4) δ1.0 (s, 3H), 2.4-1.2 (m, 15H), 2.6 (bs, 1H), 3.6 (m, 1H).

This epimeric alcohol mixture was converted to a tosylate derivative by treatment with 5.7 g (0.03 mol) of p-toluene sulphonyl chloride in 50 mL of pyridine for 10 h at room temperature. The reaction mixture was poured into water and extracted with ether. The ether layer was washed with water, dilute hydrochloric acid and brine and dried by anhydrous magnesium sulphate. The ether layer gave 5.642 g of an oil which was used for the subsequent step without further purification.

IR (CCl_4) 1745 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ1.0 (s, 3H), 2.2-1.4 (m, 15H), 2.4 (s, 3H), 4.4 (m, 1H), 7.2 (d, J=8 Hz, 1H), 7.8 (d, J=8 Hz, 1H).

Reduction of the crude tosylate to **9** was effected by the procedure of Y. Fugimoto and T. Tatsuno.[18] A mixture of 5.642 g (0.0149 mL) of tosylate, 9.75 g (0.15 mol) of zinc dust and 11.25 g (0.075 mol) of sodium iodide in 100 mL of glyme was heated at 85° for 3 h. This mixture was cooled, filtered, diluted with water and extracted with ether. The ether layer was washed with water and brine and dried over anhydrous magnesium sulphate. The oil obtained after evaporation of the

ether layer was distilled at 75°C in 0.0025 mm of Hg. Yield: 2.6 g (84%). An analytical sample was prepared by preparative TLC (SiO_2 eluted by 10% ethylacetate and hexane).

IR (neat) 1745 cm^{-1}; ^1H NMR δ1.1 (s, 3H), 2.4-1.2 (m, 17H); mass spectrum (70 ev) (relative intensity) 166 (8) (M^+-42), 151 (60), 148 (100), 133 (50), 119 (37), 105 (45), 91 (50).

Anal. calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68

Found: C, 74.86; H, 9.68

Preparation of trans-9-methyldecalene-1 **15**

A solution of 1.1 g (0.006 mol) of hydroxyenone **22**[19] in 20 mL of tetrahydrofuran was added dropwise (30 minutes) to a stirred solution of 0.445 g of lithium in redistilled liquid ammonia (100 mL). After the blue color was discharged by the addition of ammonium carbonate, the ammonia was evaporated and the residue was dissolved in water and extracted with ether. The ether extracts yielded 0.94 g of a colorless oil, which was deoxygenated by heating with 22.4 mL (0.462 mol) of hydrazine hydrate (99%) and 5.8 g (0.056 mol) of hydrazine hydrochloride in 126 mL of triethylene glycol at 110°C for 3 h, followed by the addition of 7.84 g (0.14 mol) of potassium hydroxide and additional heating at 210°C for 6 h. This reaction mixture was poured into ice cold water and extracted with methylene chloride. The oil obtained from the methylene chloride layer was oxidised by Jones' reagent to give 465 mg (47%) of **15**. The properties of a sample purified by preparative GLPC (4% QFI, 160°C) were:

IR ($CDCl_3$) 1700 cm^{-1}; ^1H NMR ($CDCl_3$) $\delta 1.0$ (s, 3H), 2.6-1.2 (m, 15 H); mass spectrum (70 ev) (relative intensity) 166 (61), 151 (18), 148 (51), 133 (20), 122 (100).

A 2,4-DNP derivative of this compound was prepared and recrystallized from ethyl acetate methanol mixture, mp: 170-171°C (171.5-172°C reported by W.S. Thomson).[22]

Preparation of cis-9-methyldecalene-1 14

A mixture of 1.7 g (0.009 mol) of the enone alcohol 22,[19] 6 mL of freshly distilled acetic anhydride and catalytic amount (170 mg) p-toluene sulphonic acid in 25 mL carbon tetrachloride was stirred for 10 h at room temperature. The solution was diluted with water, washed with dil. hydrochloric acid and brine and dried over anhydrous magnesium sulphate. Removal of the solvent gave 1.8 g of crude product as an oil. Chromatography of the oil on 200 g silica (eluted with ether) provided 920 mg of pure crystals. An analytical sample had mp 83-85°C (87-89°C lit.[19]).

To a solution of 100 mg (0.45 mmol) of the above acetate in 10 mL ethanol, was added 50 mg of 2% palladium on strontium carbonate and the resulting solution was hydrogenated at room temperature and atmospheric pressure. Hydrogen uptake ceased after 2 h and the catalyst was then removed by filtration. Removal of the solvent gave 100 mg of pure *cis* acetate. Analytical sample obtained by recrystallisation from pentane had mp 48-50°C (50-51°C[19]).

A 125 mg (0.5 mmol) sample of the acetate was heated at 110°C with 3.2 mL (66 mmol) of 99% hydrazine hydrate and 840 mg (8 mmol) of hydrazine hydrochloride in 18 mL of triethylene glycol for 2 h, followed by the addition of 1.12 g (20 mmol) potassium hydroxide and further heating (6 h, 210° C). This reaction mixture was poured into ice water and extracted with methylene chloride. The oil obtained from methylene chloride after the usual work up was oxidized by Jones reagent to give 70 mg of pure **14**. An analytical sample collected by preparative GLPC (4% QF-1, 160°C) displayed the following properties.

IR ($CDCl_3$) 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ1.1 (s, 3H), 2.4-1.2 (m, 15H); mass spectrum (70 ev) (relative intensity) 166 (24), 15 (18), 148 (9), 124 (58), 111 (100).

A 2,4-DNP of the above compound was prepared and recrystallised from ethyl acetate and methanol, mp: 158-160°C (lit. 164-165°C,[19] 159-160°C[26]).

Acid treatment of cyclopropanols and their derivatives

A general procedure for acid catalysed ring opening of cyclopropanols and their derivatives is illustrated by the reaction of cyclopropanol silylether **6** with hydrochloric acid and aqueous methanol.

(a) Reaction of cyclopropanol silylether **6** with hydrochloric acid.

To a solution of cyclopropanol silylether **6** (100 mg,

0.35 mmol) in 5 mL of aqueous methanol (1:1) was added six drops of concentrated hydrochloric acid at room temperature. The reaction mixture was stirred for 3 h under nitrogen, while being monitored by TLC. After quenching the reaction mixture with aqueous sodium bicarbonate, the methanol was evaporated at reduced pressure, and the aqueous suspension was extracted with ether. The washed and dried ether extracts yielded 60 mg of an oil, which proved to be a mixture of **13** (70%), **14** (22%) and **15** (8%). This product identification was made by comparing the GLPC retention times (4% QF-1, 100°C), infrared and ^{1}H NMR spectra with authentic samples of **13**, **14** and **15**. Spiroketone **13** was prepared by the procedure reported by Kurt Girm[21] and the preparations of **14** and **15** are given earlier in this thesis.

(b) Reaction of cyclopropanol acetate **9** with hydrochloric acid.

Acid treatment of 22 mg (0.1 mmol) cyclopropanol acetate **9** with two drops of concentrated hydrochloric acid in 1 mL of methanol/water (1:1) gave, after 40 h at room temperature, 12 mg of an oil which proved to be a mixture of **13** (90%), **14** (trace) and **15** (8%) (GLPC analysis, 4% QF-1, 100°C).

(c) Preparation of cyclopropanol silylether **5** and reaction with hydrochloric acid.

A solution of 200 mg (0.68 mmol) of cyclopropyl silylether **4** in 10 mL of ethanol was reduced by 37 mg (1 mmol) of sodium borohydrode at -78°C. To this was added 5 mL of

concentrated hydrochloric acid and was stirred for 5 h at 25°C. The usual work-up followed by Jones oxidation gave 68 mg of an oil, which proved to be 99% spiro diketone **16** containing traces of cis and trans decaline diones **17** and **18** (GLPC analysis and infrared spectroscopy).

(d) Preparation of cyclopropyl acetate **8** and reaction with hydrochloric acid.

A solution of 79 mg (0.35 mmol) cyclopropyl acetate **7** in 10 mL of ethanol was reduced by 37 mg (1 mmol) of sodium borohydride at -78°C. After 4 h the reaction mixture was treated with 5 mL of concentrated hydrochloric acid and stirred for 40 h at room temperature. The usual work-up followed by oxidation with Jones reagent gave 40 mg of an oil. Analysis by GLPC indicated this material to be chiefly 99% spiro diketone **16**.

(e) Preparation of cyclopropanol **3** and reaction with hydrochloric acid.

i) A solution of cyclopropanol **2** (180 mg, 1 mmol) in 10 mL of methanol was treated with 32.6 mg (16 meq) of sodium borohydride at -78°C. After 3.5 h the reaction was quenched with a few drops of acetic acid and permitted to warm to room temperature. This solution of 3 epimers was then treated with aqueous hydrochloric acid (0.5 mL conc. HCl in 4 mL water) overnight. Extraction with ether yielded after appropriate washing, ca. 145 mg of an oil which GLPC analysis (QF-1, 185°C) indicated to be a 85:15 mixture of two components.

Jones oxidation of this mixture gave spiro diketone **16** in 90% yield. Less than 10% **17** and **18** were present in the oxidation mixture. Identification of **16** as the major product was achieved by a comparison of chromatographic retention times and infrared spectrum with an authentic sample.

ii) A solution of cyclopropanol **2** (360 mg, 2 mmol) in 50 mL of THF was added to a solution of lithium (ca. 3 mmol) in 50 mL of freshly distilled ammonia cooled to -78°C. Following a 2 h period, during which the temperature of the reaction mixture increased to the point of reflux, the remaining lithium was quenched by a few drops of ethylene dibromide (blue color is discharged). Work-up in the usual fashion yielded 350 mg of **3** epimers, portions of which were subjected to acid and base-catalyzed ring-cleavage. Thus, a 170 mg portion, on treatment overnight with methanolic hydrochloric acid, gave a 65:35 mixture of isomeric ketols. Oxidation of this mixture with Jones reagent yielded 160 mg of spiro diketone 16 containing no discernible amounts of **17** and **18** (GLPC analysis).

(f) Reactions of cyclopropyl silylether **4** with hydrochloric acid.

A solution of 294 mg (1 mmol) of silylether **4** in 10 mL THF/water (1:1) was treated with 5 mL of 6 N hydrochloric acid for 2 h at room temperature. On work-up, this mixture gave 165 mg of an oil, which by GLPC analysis proved to be a mixture of **16** (25%), **17** (55%) and **19** (24%).

(g) Reaction of cyclopropyl acetate **7** with hydrochloric acid.

A solution of 46 mg (0.2 mmol) of acetate **7** in 2.5 mL of THF/water (1:1) was treated with 10 drops of concentrated hydrochloric acid at 66°C for 6 h. The usual work-up yielded 30 mg of an oil, which by GLPC analysis was found to be a mixture of **16** (19%), **17** (58%) and **19** (23%).

(h) Reactions of cyclopropanol **2** with hydrochloric acid.

i) In aqueous THF solution

Treatment of 100 mg (0.55 mmol) of **2** in 7 mL of THF/water (1:1) with 10 drops of concentrated hydrochloric acid gave, after 2 h at 66°C, 80 mg of an oil. This oil proved to be a mixture of **16** (22%), **17** (54%) and **19** (24%) by GLPC analysis.

ii) In aqueous methanol solution

A solution of cyclopropanol **2** (60 mg, 0.33 mmol) in 10 mL of methanol was cooled to 0°C and treated with six drops of conc. hydrochloric acid. The reaction mixture was permitted to warm to room temperature, while being monitored by TLC. After 4 h at room temperature, the starting material was consumed and the reaction was quenched in aqueous bicarbonate solution. Removal of the methanol at reduced pressure followed by extraction with ether yielded 50 mg of an oil, which proved to be a mixture of **20** (64%) and **21** (32%) along with traces of **16**, **17**, **18** and **19** (GLPC analysis, 4% QF-1, 160°C). Analytical samples of **20** and **21** were obtained by

preparative GLPC and characterized by the following measurements:[25]

20, (1S*, 3, 6)-3-Methoxy-6-methyltricyclo[4.4.0.0^{1,3}]-decan-7-one; ir (film) 1705, 1439, 1234, 1045 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ0.34 (d, J=5.5 Hz, 1H), 0.74 (d, J=5.5 Hz, 1H), 1.32 (s, 3H), 1.36-2.80 (m, 10H), 3.37 (s, 3H); mass spectrum (70 ev) m/e (rel. intensity) 194 (14), 179 (100), 151 (26), 138 (27), 123 (80), 110 (35), 91 (36).

Anal. calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34

Found: C, 73.92; H, 9.45

21, (1R*, 5, 6)-5-Methoxy-6-methyltricyclo[4.4.0.0^{1,5}]-decan-9-one; ir (film) 1710 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ1.12 (s, 3H), 1.2-2.80 (m, 12H), 3.37 (s, 3H); mass spectrum (70 ev) m/e (rel. intensity) 194 (12), 179 (100), 151 (15), 137 (88), 123 (31), 105 (34), 93 (38), 91 (50).

Anal. calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34

Found: C, 74.00; H, 9.41

Compound 20 was also prepared[25] by methylation of the conjugate base of 2. Reaction of 1.0 g (5.6 mmol) of 1 with a suspension of 0.24 g of sodium hydride in a 1:1 mixture of benzene and DMF (940 mL total volume) gave, after quenching with 3 g (21 mmol) of methyl iodide and conventional work-up, 0.6 g of an oil. Analysis by GLPC indicated this material to be chiefly compound 20 and the pmr spectrum supported this conclusion. A semicarbazone derivative was prepared, mp 212-213°C.

A similar reaction of 90 mg (0.5 mmol) of 2 in 10 mL of methanol/water (1:1) containing six drops of conc. hydrochloric acid for 10 h at room temperature yielded 87 mg of an oil, which proved to be a mixture of 16 (10%), 17 (20%), 18 (4%), 19 (16%), 20 (21%) and 21 (29%) by GLPC analysis.

Base catalysed reactions of cyclopropanols and their derivatives

(a) Reaction of 9 with methanolic potassium hydroxide

A solution of 41 mg (0.19 mmol) of cyclopropyl acetate 9 in 5 mL methanol/water (1:1) was treated with excess of potassium hydroxide (70 mg) for 4 h at room temperature. The reaction mixture was quenched with dilute hydrochloric acid and extracted with methylene chloride. The methylene chloride extracts were then washed with water and brine and dried by anhydrous magnesium sulphate. Evaporation of the solvent gave 28 mg of an oil, which was found to be a mixture of 13 (5%), 14 (95%) and 15 (trace) by GLPC analysis.

(b) Reaction of 9 with potassium tert. butoxide in t-butanol

Treatment of 20 mg (0.096 mmol) of 9 with 112 mg (1 mmol) of potassium tert. butoxide in 5 mL of tert. butanol for 12 h at 25°C gave, after the usual work-up, 15 mg of an oil which proved to be a mixture of 13 (90%), 14 (10%) and 15 (trace) by GLPC analysis.

(c) Reaction of cyclopropyl acetate 8 with potassium hydroxide

A solution of 90 mg (0.4 mmol) of cyclopropyl acetate 7

in 1 mL of ethanol was reduced by 37 mg (1 mmol) of sodium borohydride for 4 h at -78°C. This reaction mixture was then treated with 70 mg (excess) of potassium hydroxide and stirred at room temperature for 4 h. After the usual work-up followed by oxidation with Jones reagent, this reaction gave 50 mg of an oil, which proved to be a mixture of **16** (85%) and **17** (45%) by GLPC analysis.

(d) Base-catalysed reaction of epimeric diols **3**

A 300 mg sample of **3** (1.6 mmol), prepared by sodium borohydride reduction of **2** was dissolved in 15 mL of methanol containing sufficient potassium hydroxide to raise the pH 13. After an overnight reaction period at room temperature, the mixture was diluted with water and extracted with ether. The residue from the ether extracts was oxidized by Jones reagent and worked up in the usual fashion. Analysis of the crude product by GLPC (QF-1, 185°C) showed it to be a 58:42 mixture of spirodiketone **16** and cis-decalin **17**. These products were separated and identified by their characteristic spectra and appropriate mixed mp measurements.

(e) Reaction of acetate **7** with potassium hydroxide

A solution of 41 mg (0.18 mmol) of cyclopropyl acetate **7** and 70 mg (excess) of potassium hydroxide in 5 mL methanol/water (1:1) was stirred for 4 h at 25°C. The usual work-up gave 28 mg of an oil which proved to be **16** (13%), **17** (29%) and **19** (68%) by GLPC analysis.

Reaction of **2** with guanidine

Treatment of a suspension of guanidine carbonate in ethanol with an equivalent amount of sodium ethoxide, followed by filtration of the insoluble sodium carbonate and evaporation of the solvent, gave crude guanidine. Residual ethanol was removed by repetitive shaking with anhydrous THF, in which guanidine is relatively insoluble. The resulting anhydrous guanidine was a colorless solid, mp ca. 50°. A stock solution of 0.01 M guanidine in 1:1 THF:HMPA was prepared, and 0.5 mL of this solution was added to a solution of **2** (90 mg, 0.5 mmol) in 10 mL of THF:HMPA. After 10 h at room temperature, the reaction mixture was quenched in ice water, acidified with dilute HCl and extracted with ether. The ether extracts yielded 90 mg of an oil, which proved to be a mixture of **16** (76%), **17** (8%) and **18** (15%) by GLPC analysis (4% QF-1, 160°C). The major product **16** was isolated by preparative GLPC, and proved to be identical (mp, ir, pmr) with the major product from heterogeneous protonation of the sodium salt of **2**.[25] Compounds **17** and **18** were identified by spiking the GLPC analysis with authentic samples.

When the guanidine:cyclopropanol molar ratio was increased to 20:1, the above reaction yielded a mixture of **17** (20%), **18** (trace) and **19** (79%) in good yield. Only a trace of **17** was observed.

Reaction of **2** with mercuric acetate

To a suspension of 330 mg (1.1 mmol) mercuric acetate in 2 mL of acetic acid was added dropwise a solution of 180 mg

(1 mmol) of cyclopropanol **2** in 3 mL of acetic acid. After stirring overnight at room temperature, the reaction mixture was neutralized by bicarbonate at 0°C. The resulting solution was extracted with methylene chloride, washed with water and brine and dried over anhydrous magnesium sulphate. Evaporation of the solvent gave 430 mg of a white solid which was found to be very unstable (even at room temperature). This solid was completely decomposed by heating on steam bath, and the residue, on extraction with methylene chloride, gave 99% Wieland Mischer ketone. Subsequent demercuration reactions were effected without isolating the intermediate organomercurial species.

(a) Demercuration reaction with acid

The mercury compound prepared by the above procedure from 180 mg (1 mmol) of cyclopropanol **2** in 10 mL of methanol was treated with 0.8 mL of concentrated hydrochloric acid at 0°C. The reaction was quenched with bicarbonate after 4 h, and the methanol was removed under reduced pressure. The residue was extracted with methylene chloride, and the usual work-up gave 180 mg of an oil which was proved to be a mixture of Wieland Mischer ketone 95%, **17** (1%) and **18** (4%) by GLPC analysis (4% QF-1, 180°C).

(b) Demercuration with sodium hydroxide

The mercury compound prepared from 180 mg (1 mmol) of cyclopropanol **2** in 10 mL of methanol was treated with an excess of sodium hydroxide until the solution became strongly

alkaline. After 4 h stirring, the methanol was removed under reduced pressure and extracted with methylene chloride and the usual work-up gave 170 mg of an oil which was a mixture of **1** (90%), **17** (1-2%) and **18** (8-9%) by GLPC analysis.

(c) Demercuration with alkaline sodium borohydride

The mercury compound from 180 mg (1 mmol) of cyclopropanol **2** was treated with 2 mL of 4 M sodium borohydride solution (sodium borohydride 4 molar in 14 molar sodium hydroxide, Alfa product). After 4 h at 25°, the reaction was quenched with acetic acid and the solvent was removed under reduced pressure. The residue was dissolved in water, extracted with methylene chloride, and the oil obtained from the extracts after removal of the solvent was oxidized by Jones reagent. Work-up gave 144 mg of an oil which proved to be a mixture of **2** (20-21%), **17** (20-21%) and **18** (53-54%) by GLPC analysis.

(d) Demercuration with sodium cyanoborohydride

The mercury compound from 180 mg (1 mmol) of cyclopropanol **2** was treated with 200 mg of sodium cyanoborohydride in 10 mL of methanol at 0°C (pH 5-6). After stirring overnight, the solvent was removed under reduced pressure, and the residue was extracted with methylene chloride. The oil obtained from the extracts was oxidized by Jones reagent to give 140 mg of an oil which was found to be a mixture of **1** (10-15%), **17** (20-25%) and **18** (65%) by GLPC analysis.

Reaction of 3 with mercuric acetate, followed by demercuration with sodium borohydride

Cyclopropanol 3 was prepared from 180 mg (1 mmol) of cyclopropanol 2 by sodium borohydride (37 mg, 4 mmol) reduction at -78°C. Mercuration of 3 was effected by the same procedure given earlier for 2, using 396 mg (1 mmol) of mercuric acetate in 10 mL acetic acid. The crude mercury compound was demercurated by treatment with 2 mL of 4 M sodium borohydride solution (4 M sodium borohydride in 14 M sodium hydroxide solution) in 10 mL of methanol. An overnight reaction period was followed by an acetic acid quench, and the solvent was removed under reduced pressure. The oil obtained after extraction of the residue with methylene chloride was oxidized by Jones reagent to give 100 mg of an oil which was proved to be a mixture containing 16 (30%), 17 (46%) and 18 (23%) by GLPC analysis.

APPENDIX: SPECTRA

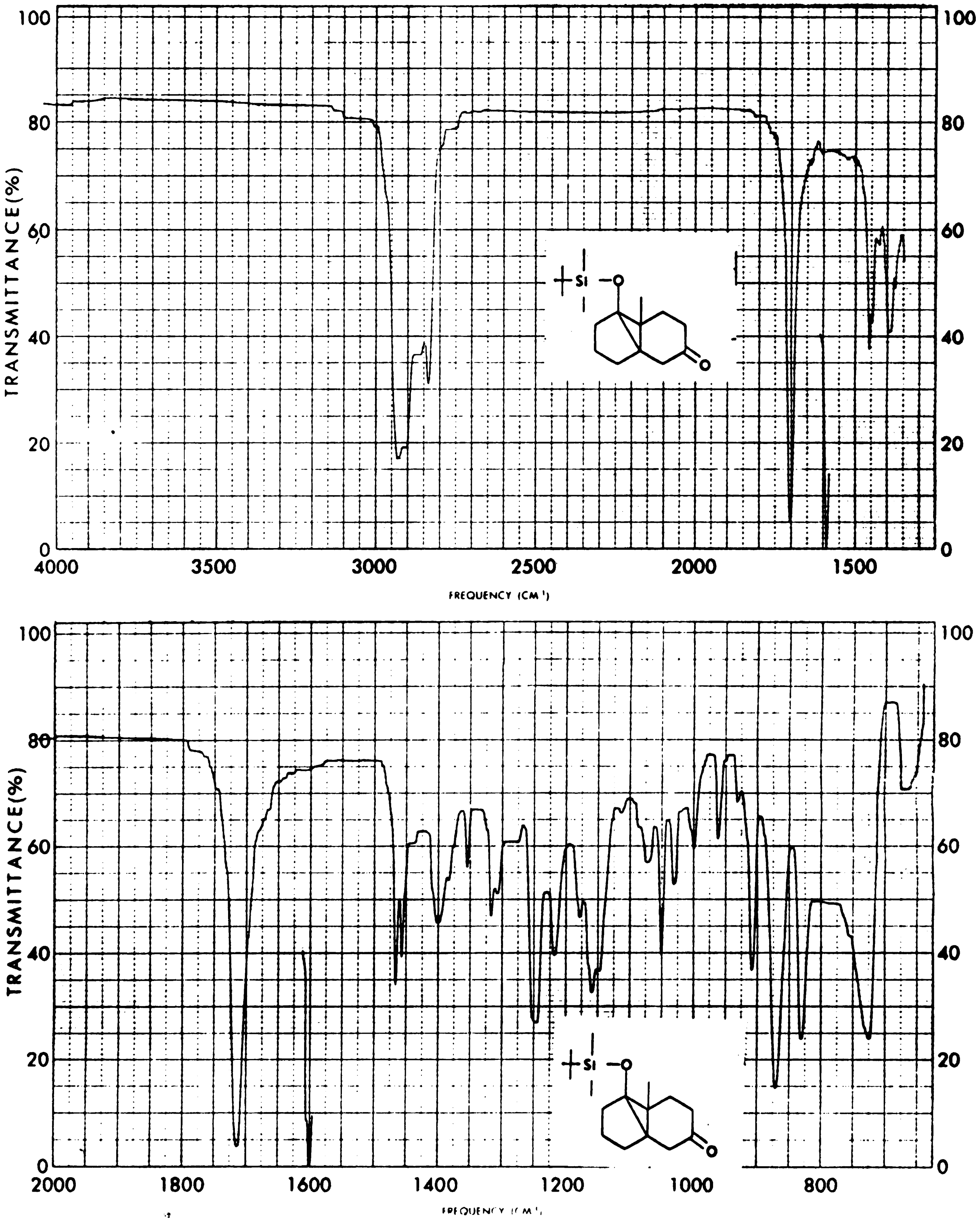


Figure 1. Infrared spectrum of **4**

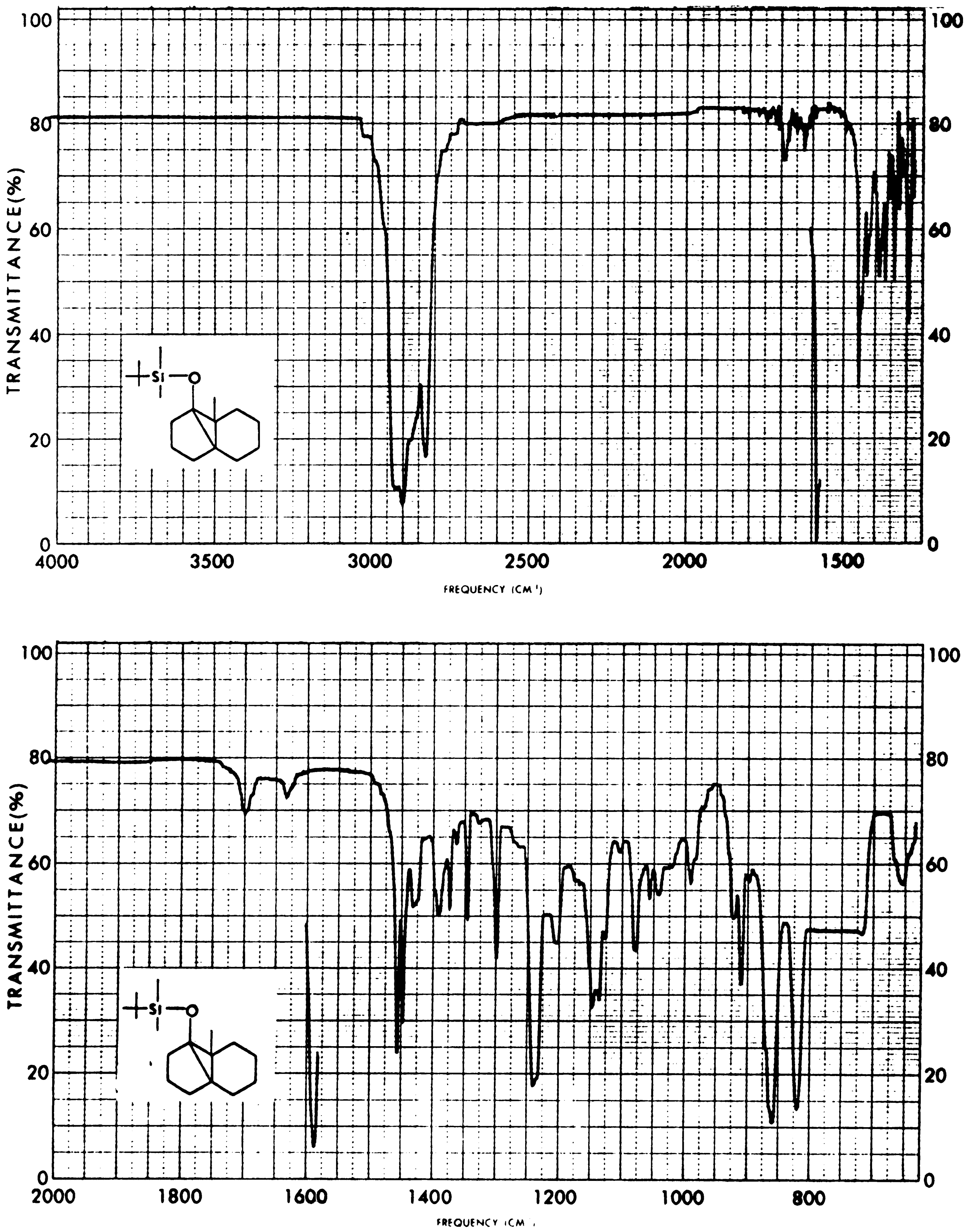


Figure 2. Infrared spectrum of 6

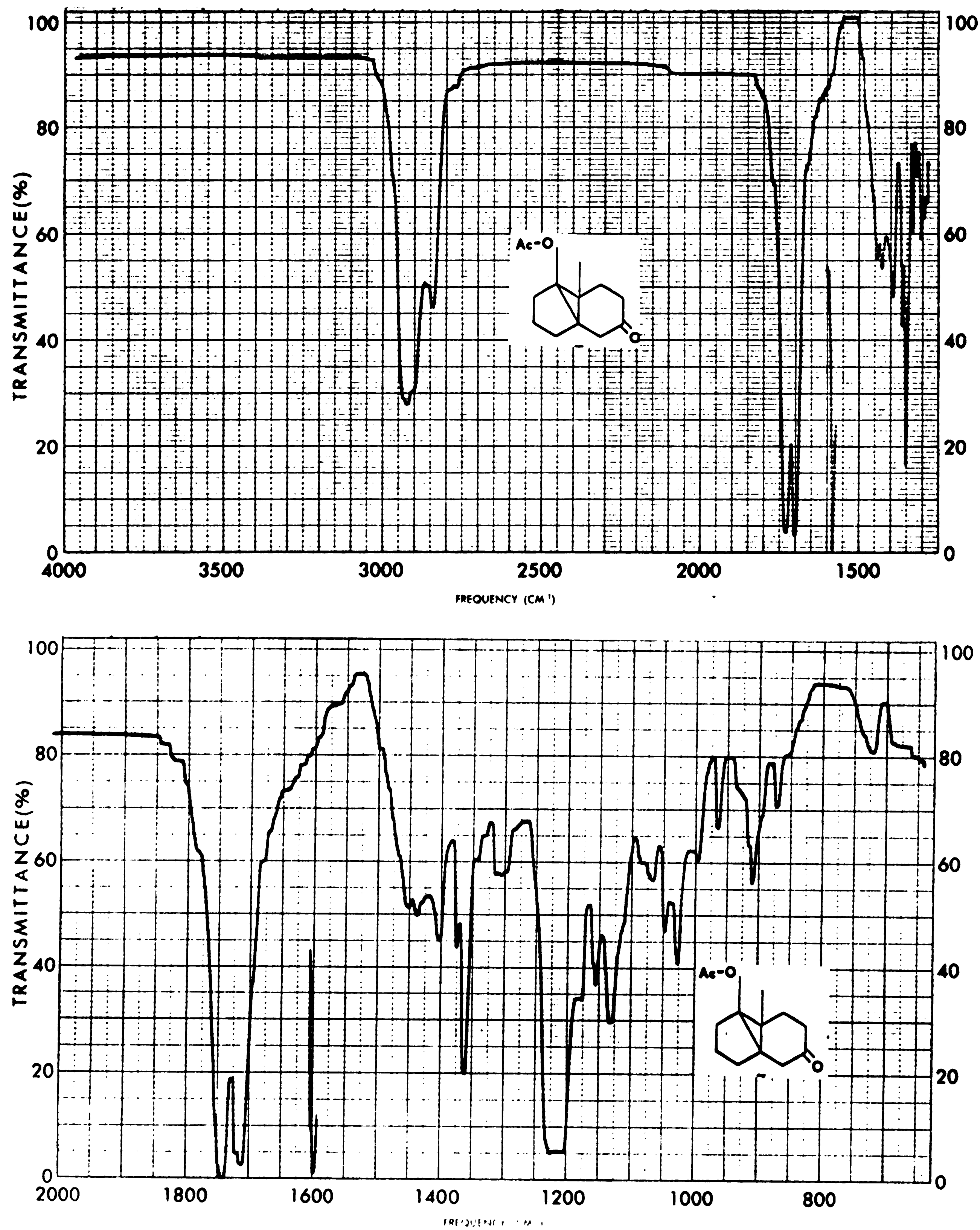


Figure 3. Infrared spectrum of 7

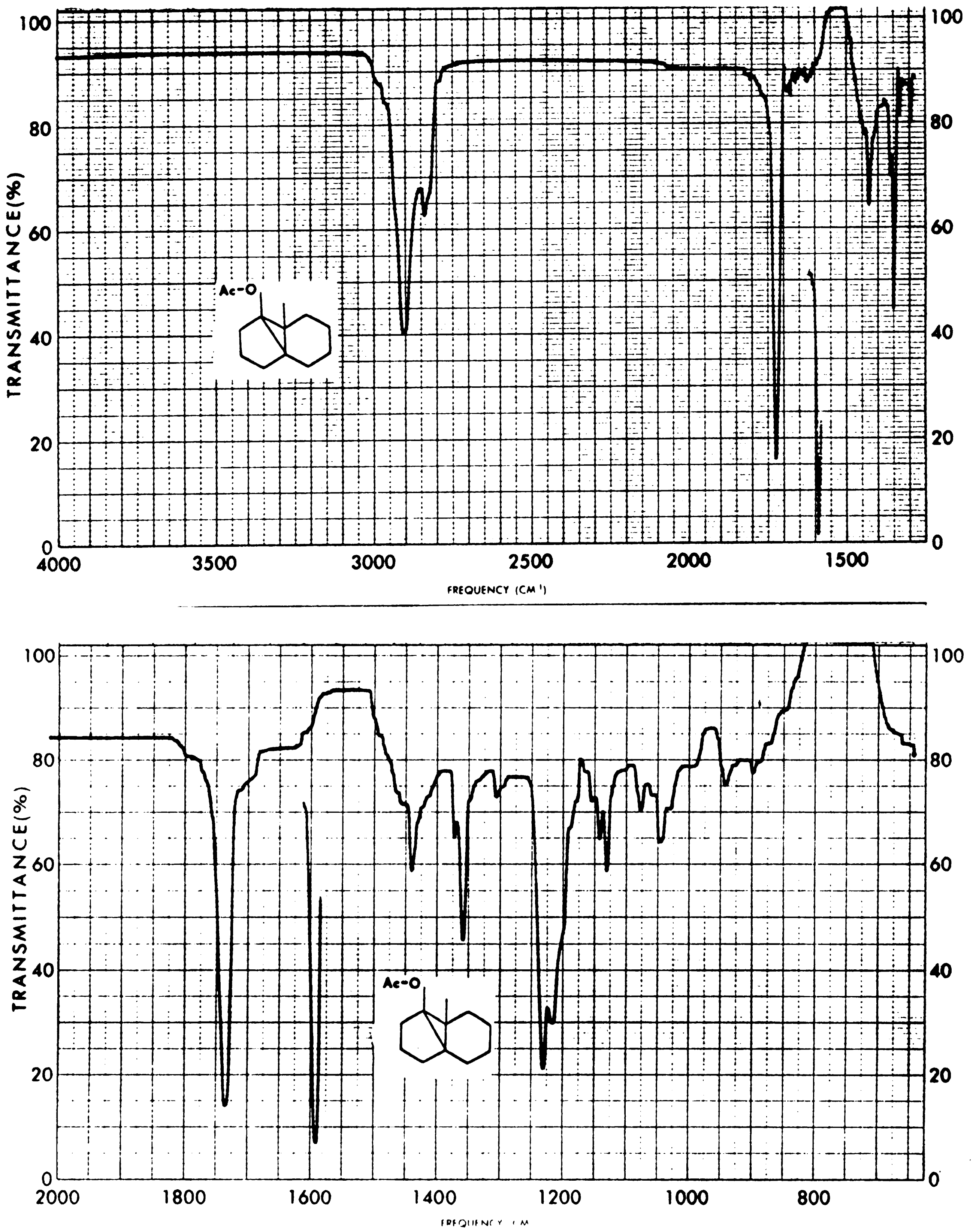


Figure 4. Infrared spectrum of 9

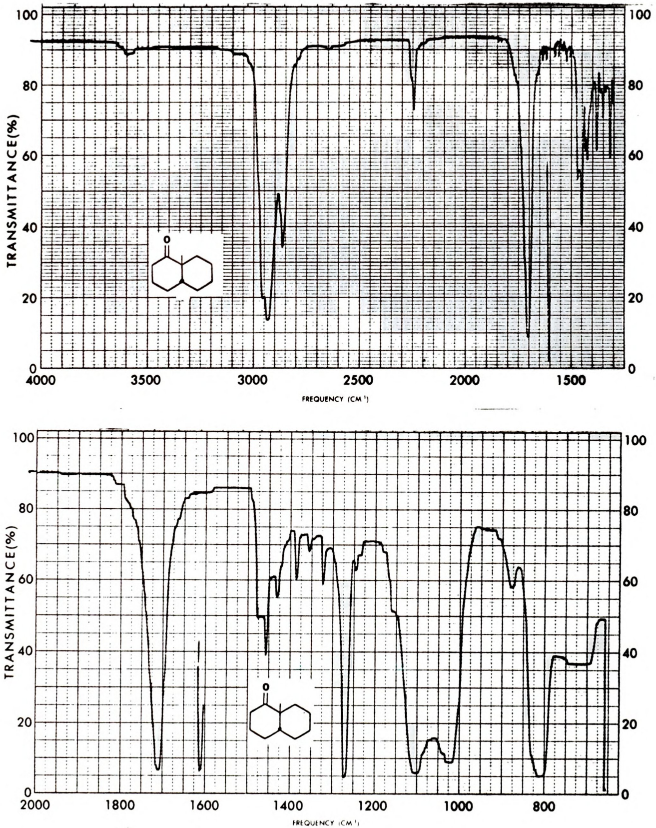


Figure 5. Infrared spectrum of 14

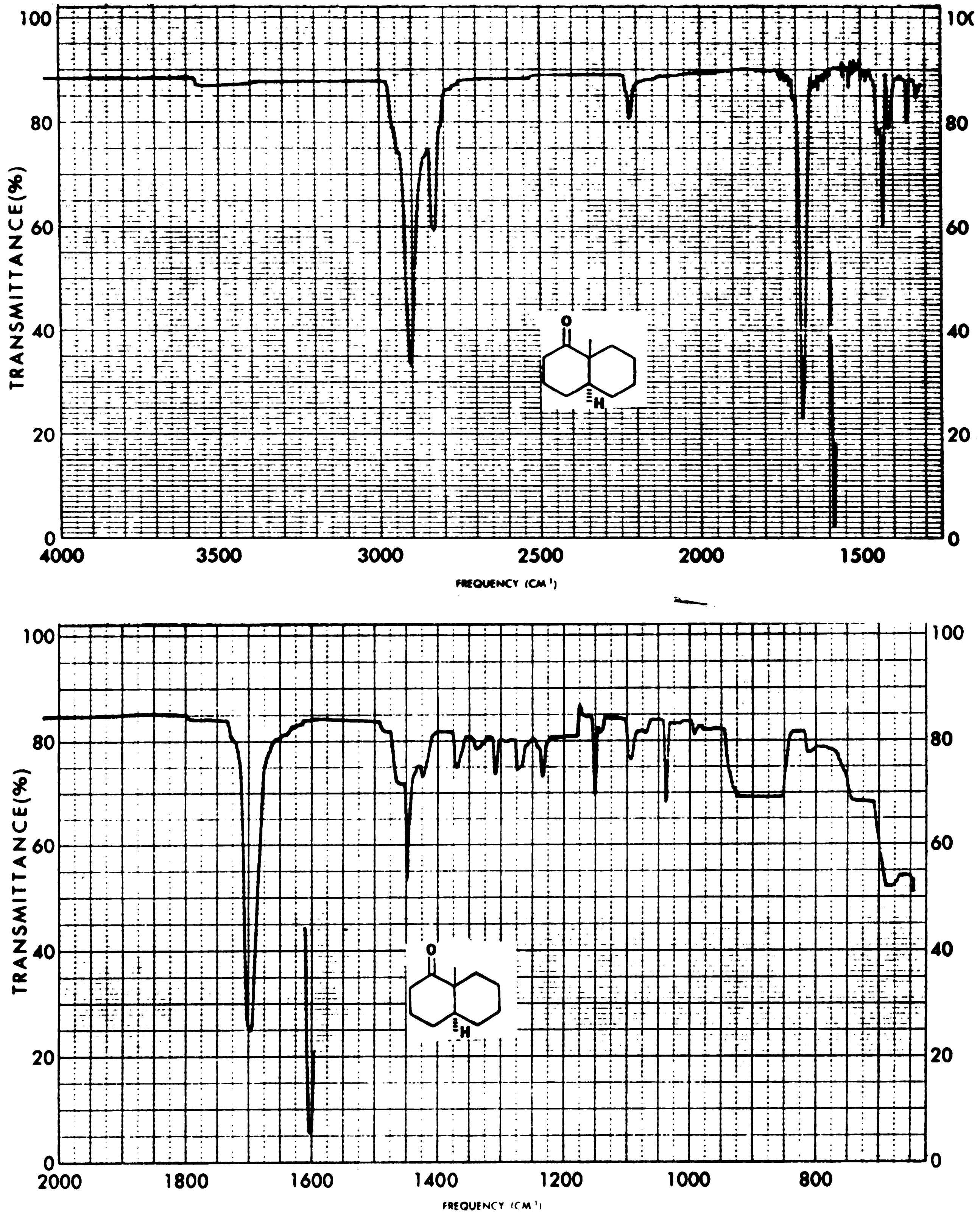


Figure 6. Infrared spectrum of 15

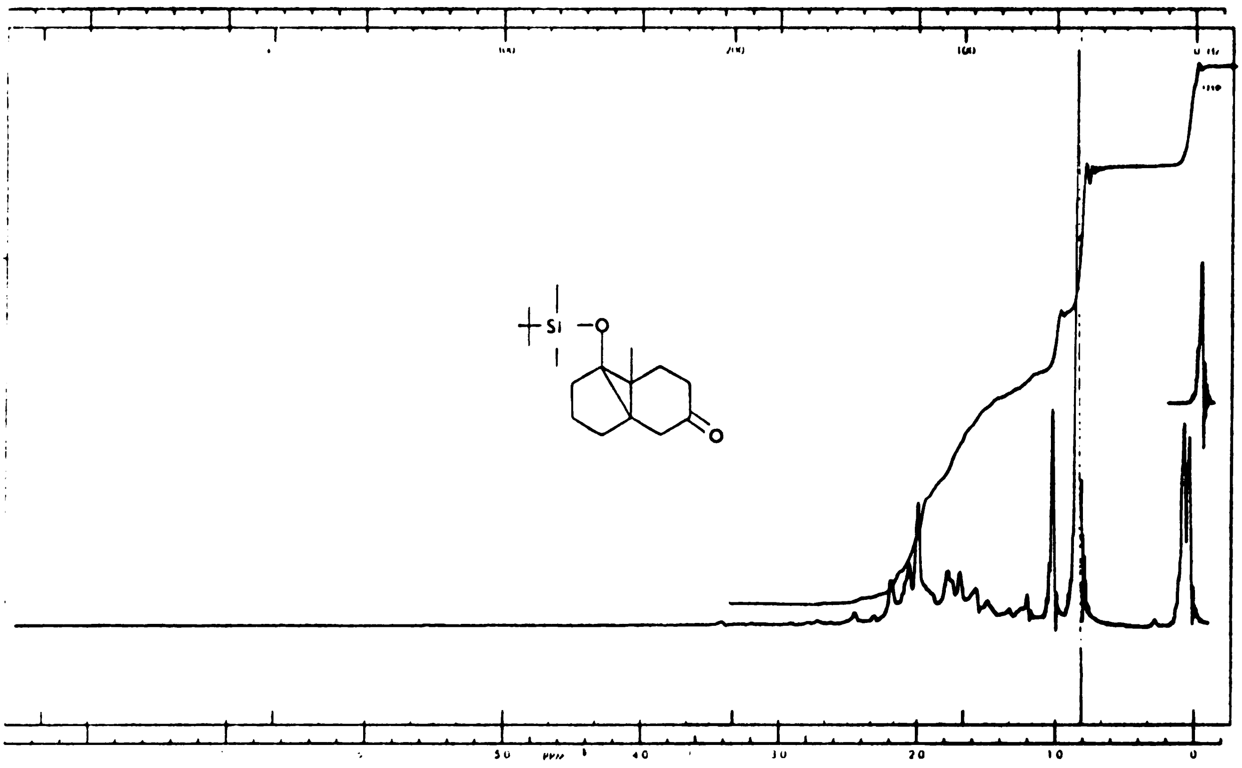


Figure 7a. ^{1}H NMR spectrum of 4

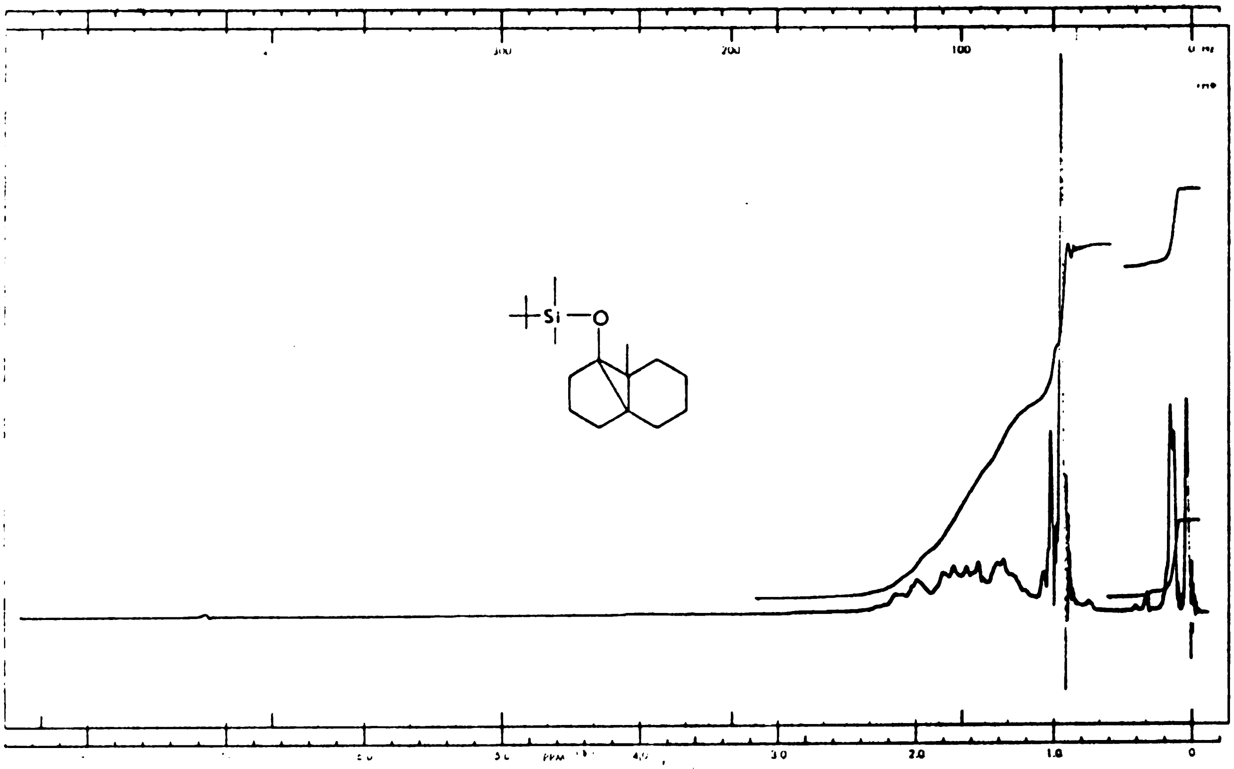


Figure 7b. ^{1}H NMR spectrum of 6

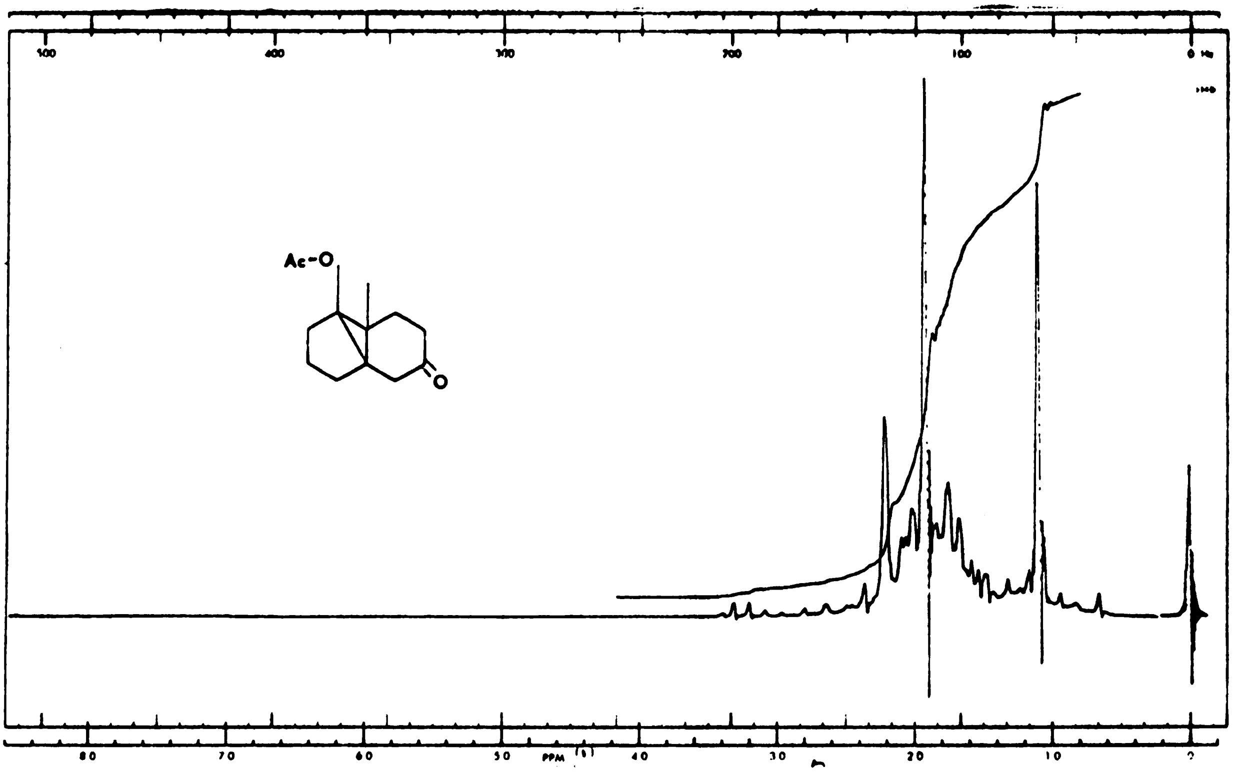


Figure 8a. ^{1}H NMR spectrum of 7

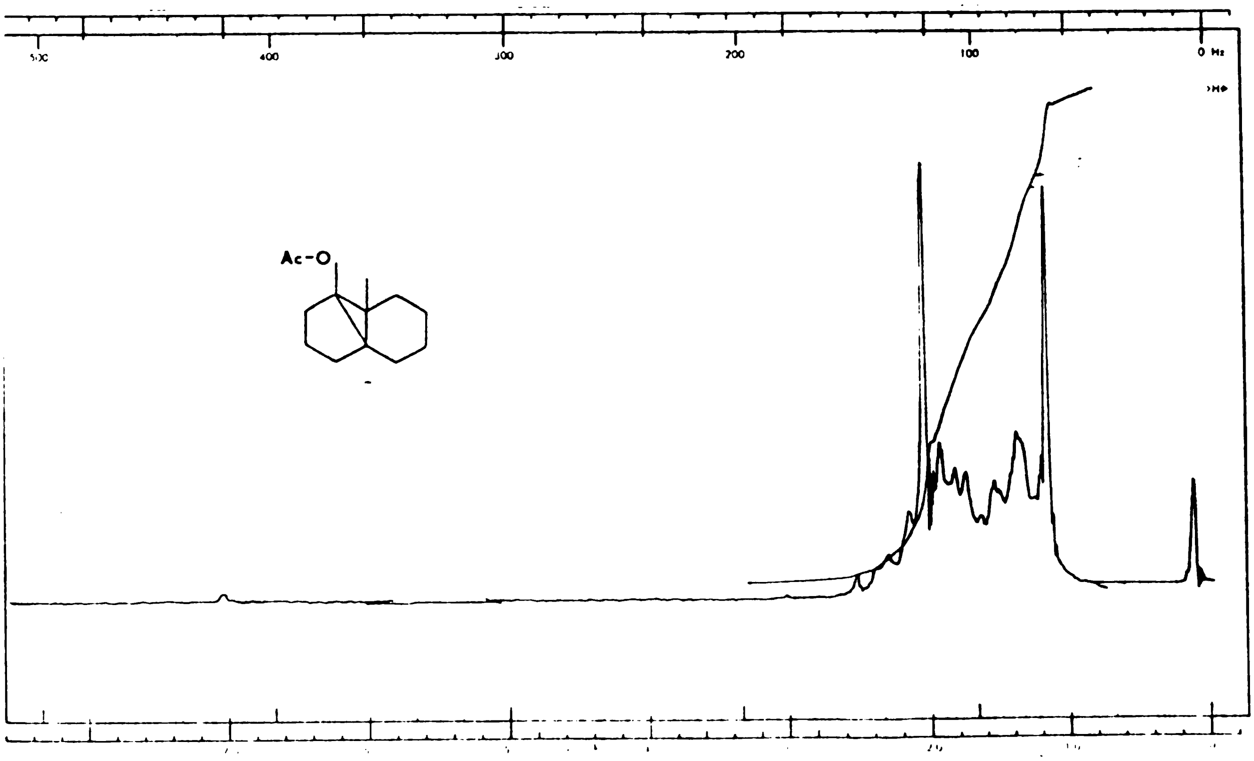


Figure 8b. ^{1}H NMR spectrum of 9

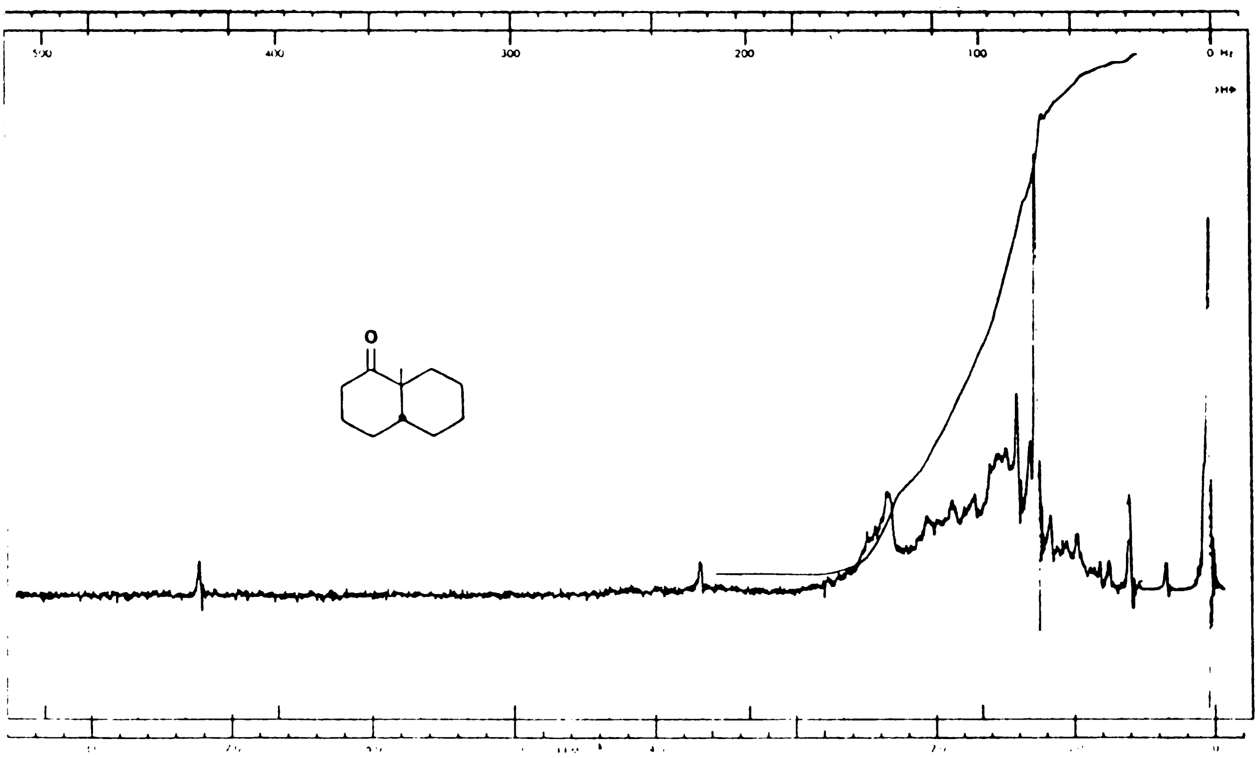


Figure 9a. ^{1}H NMR spectrum of 14

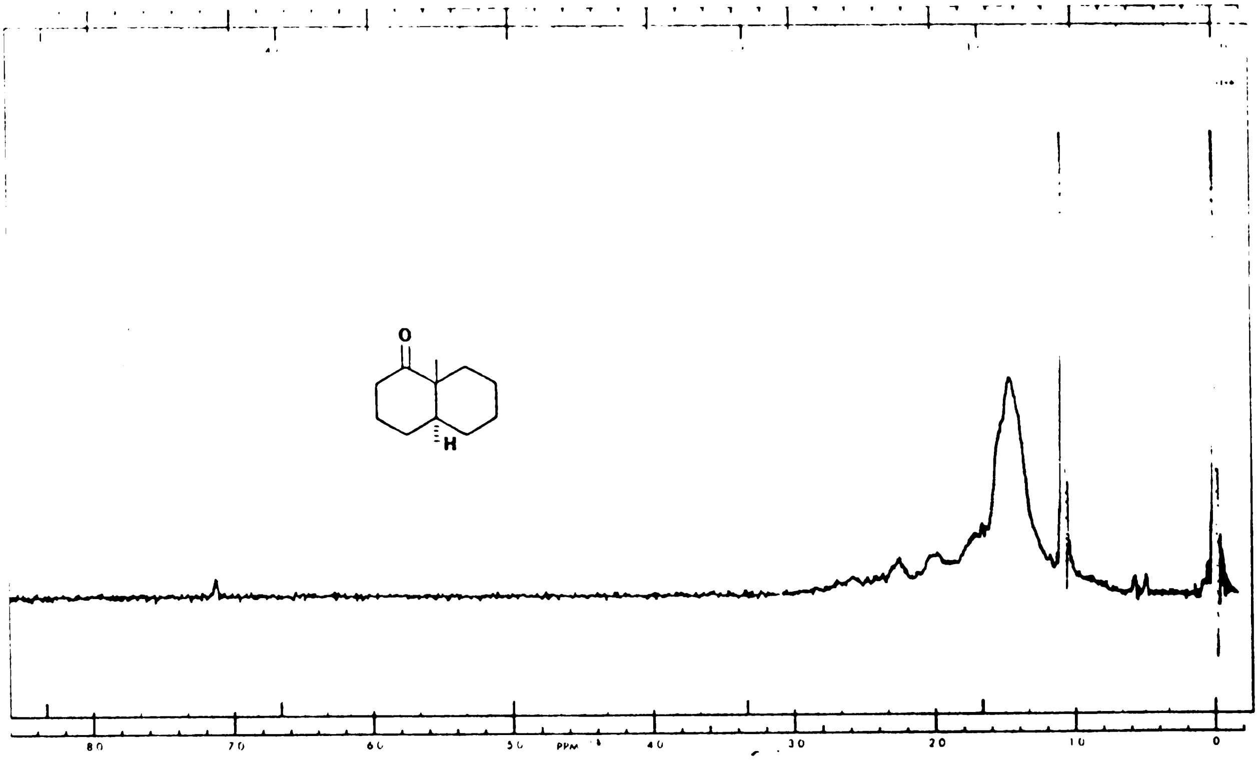


Figure 9b. ^{1}H NMR spectrum of 15

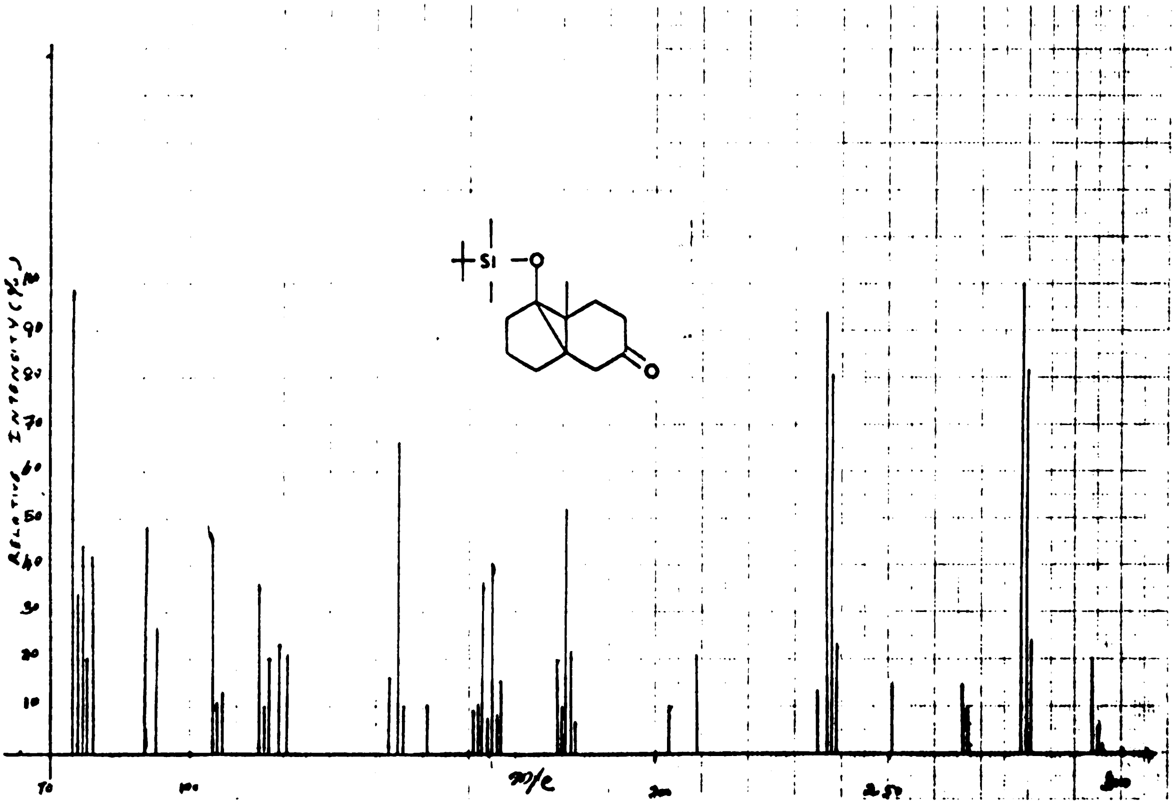


Figure 10a. Mass spectrum of 4

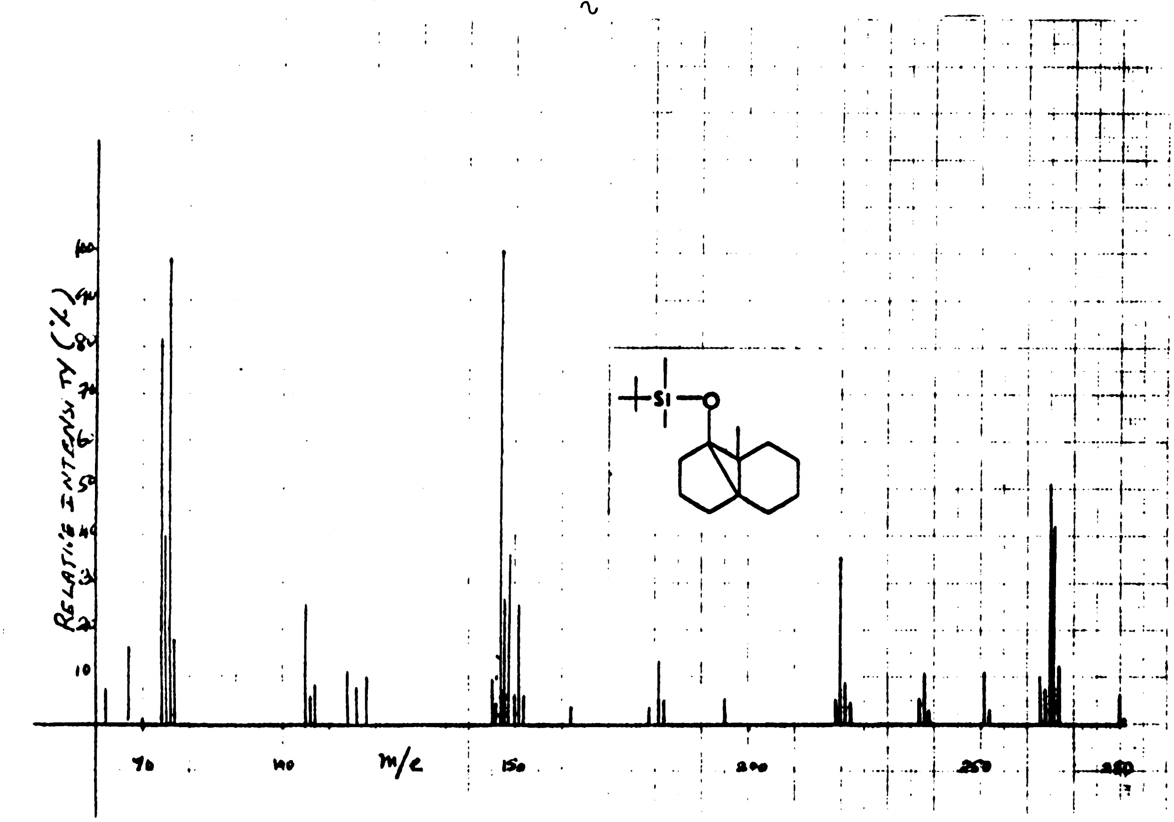


Figure 10b. Mass spectrum of 6

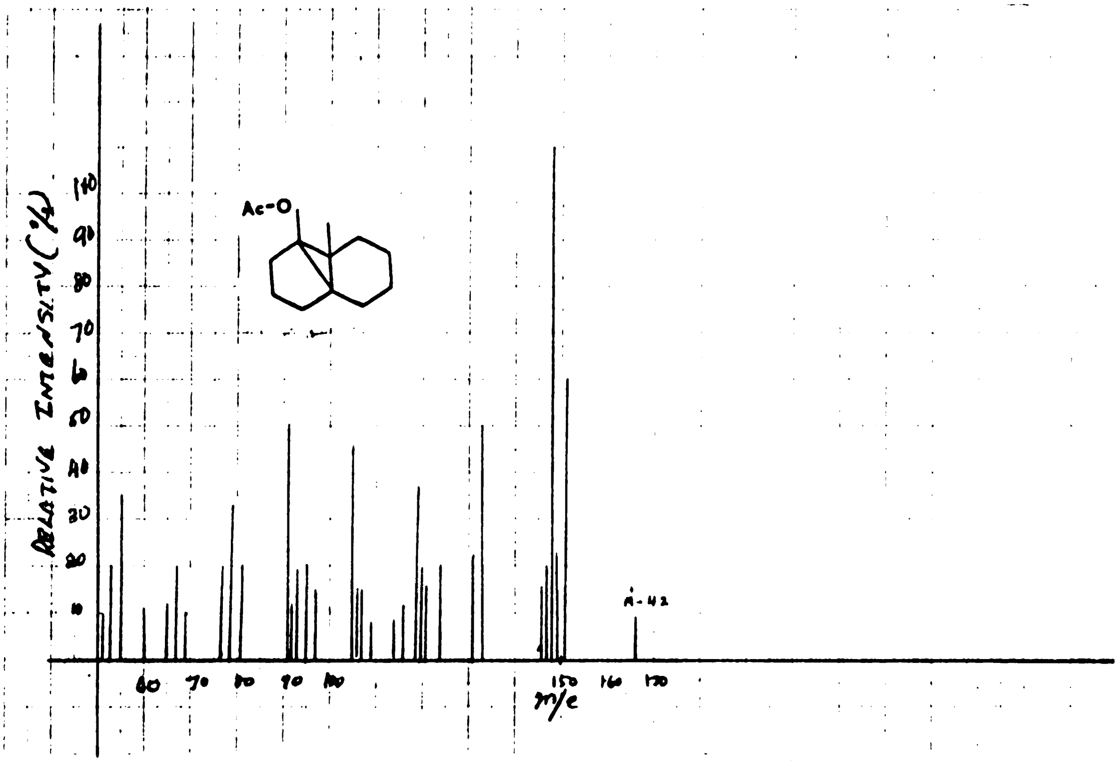


Figure 11a. Mass spectrum of 7

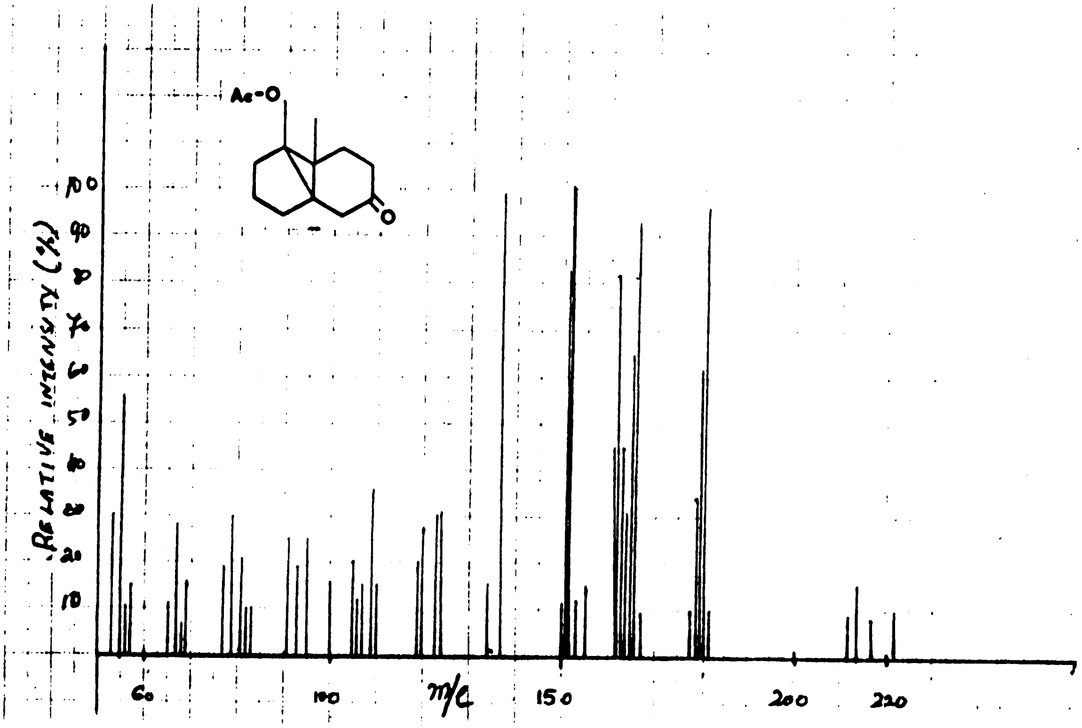


Figure 11b. Mass spectrum of 9

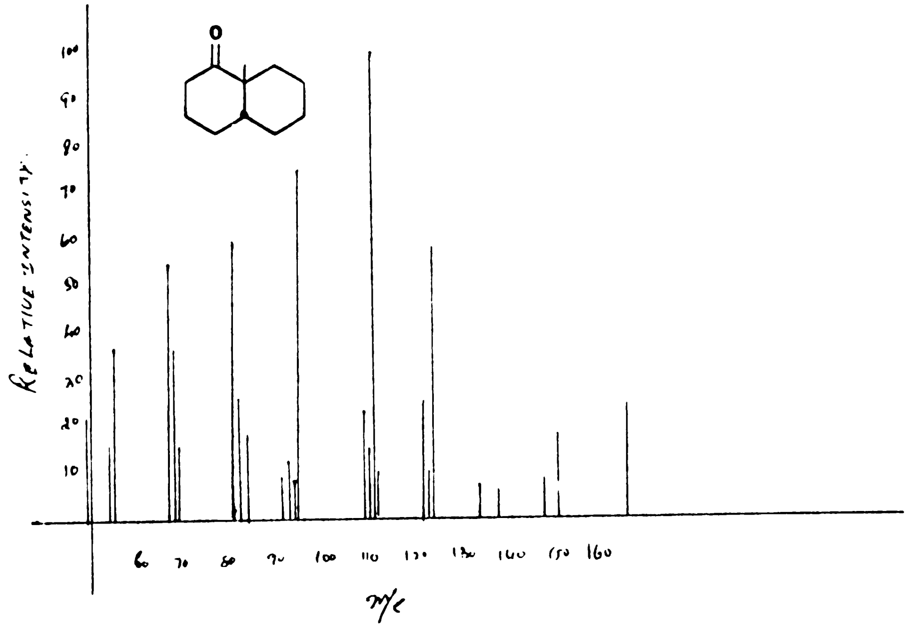


Figure 12a. Mass spectrum of **14**

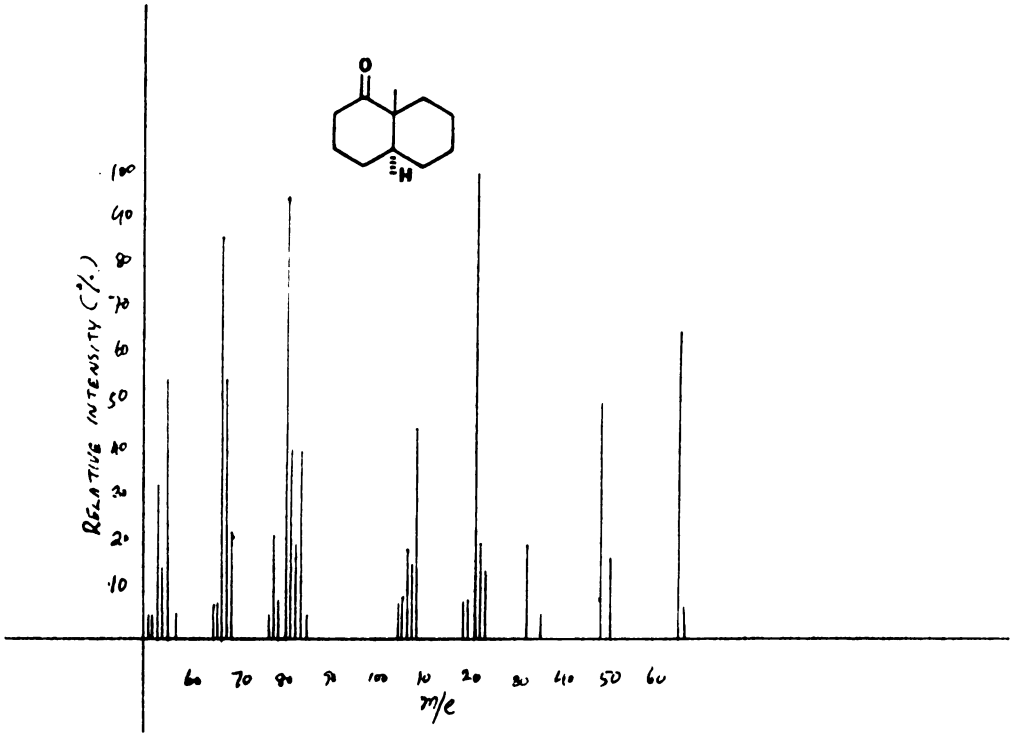


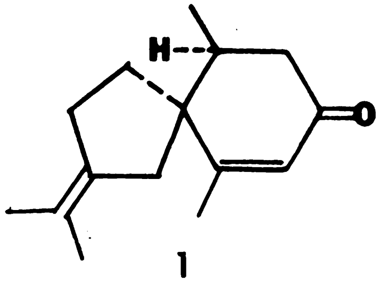
Figure 12b. Mass spectrum of **15**

PART II

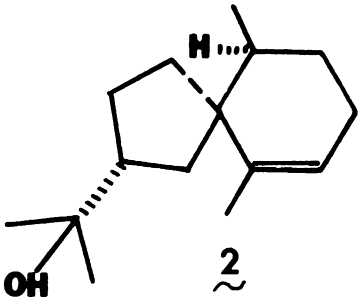
TOTAL SYNTHESIS OF SPIROVETIVANES

INTRODUCTION

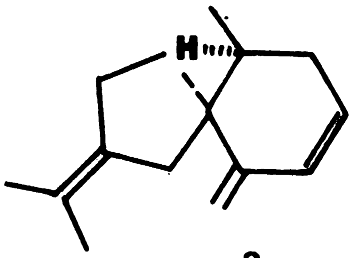
The sesquiterpenes provide a rich storehouse of diverse carbocyclic-structural types whose complexity has challenged the talent and imagination of synthetic chemists since the beginning of this century. In recent years, much attention has been directed toward the total synthesis of members of a rapidly expanding class of sesquiterpenes known as the spirovetivanes. This class is characterized by the spiro-[4.5]decane skeleton, seen in such representative members as β-vetivone **1**,[28] hinesol **2**,[29] β-vetispirene **3**,[30], α-vetispirene **4**,[31,30a] anhydro-β-rotunol **5**[32] and agrospirol **6**.[33,34]



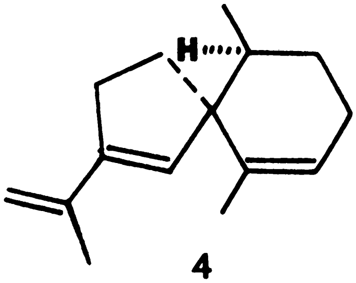
1



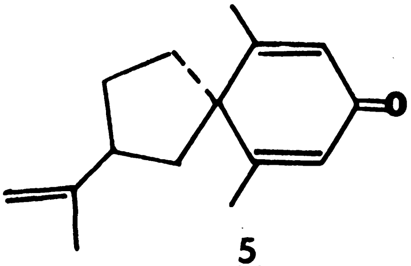
2



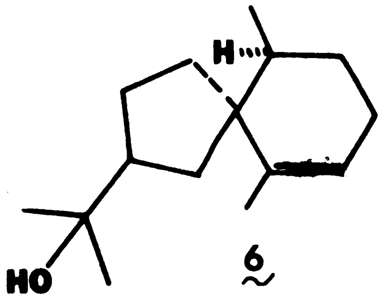
3



4

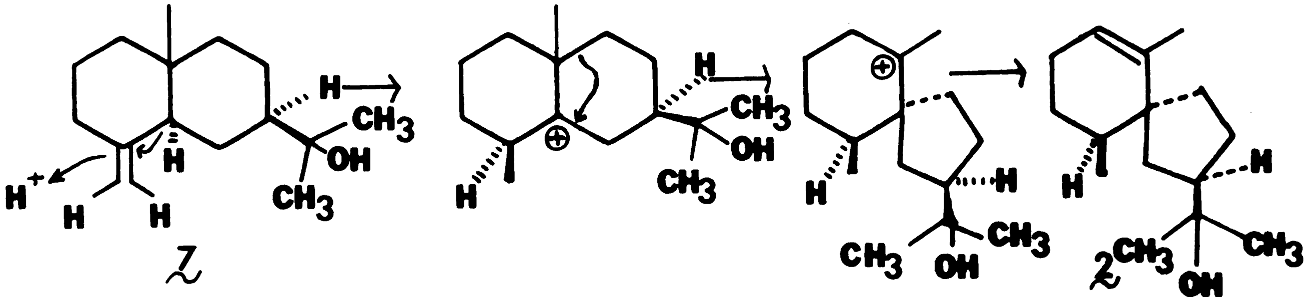


5



6

All the above spirovetivanes can be envisioned as originating from a eudesmane intermediate. This is illustrated for hinesol 2 by the following idealized carbonium ion rearrangement^{30a} (eq. 1). (Natural sources of hinesol usually contain β-eudesmol as well.^{35})

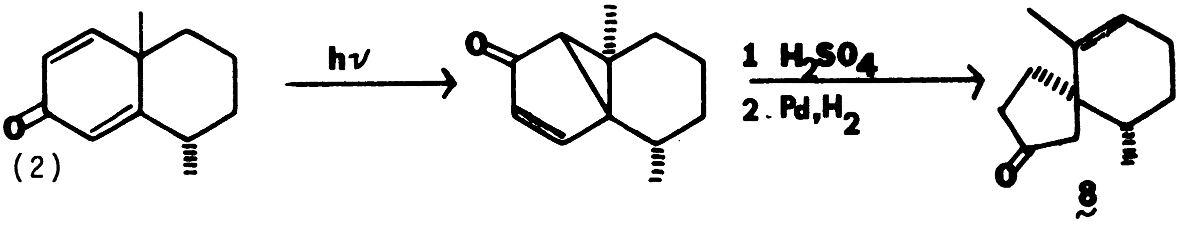


Although agarospirol 6 was the first sesquiterpene to be recognized as a spiro[4.5]decane derivative, β-vetivone 1 and hinesol 2 have received most of the attention of chemists over the past ten years. Marshall and co-workers^{28} conclusively proved that β-vetivone 1, obtained from the essential oil of vetiver, and hinesol 2 obtained from 'atractylis'^{36} oil of Chinese origin, possess the spiro[4.5]decane skeleton rather than the previously assigned hydrazulenic structure.^{37}

Many syntheses of spirovetivane sesquiterpenes have been reported over the past eight years. Most of these efforts have been directed at β-vetivone^{28,30b,31a,b,32c,38} and hinesol.^{30b,33b,38a,c,d,39} In the landmark synthesis of β-vetivone by Marshall and Johnson,^{28} the intermediate

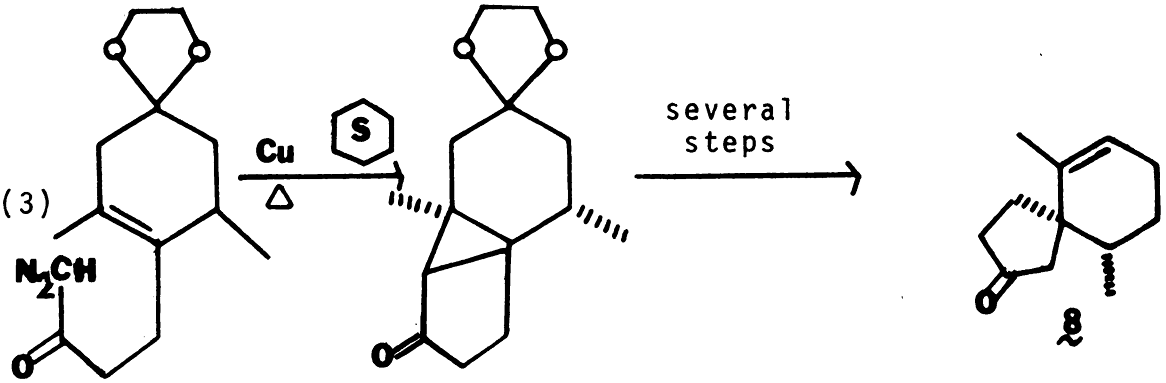
enone 8 was prepared in 36% overall yield from a decalin starting material (eq. 2). Other preparations of intermediate

(2)

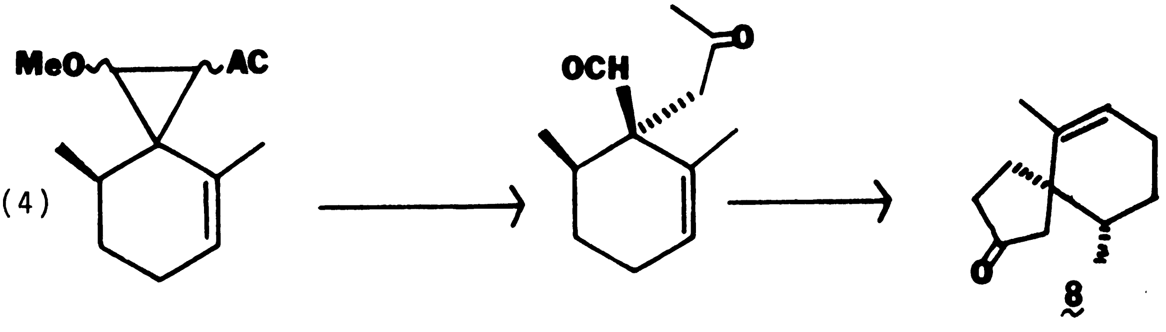


8 have been reported,[40,41] but they do not match the original in either convenience or yield. It is interesting to note that all these approaches to 8 involve a cyclopropanone precursor (eq. 3 and 4).

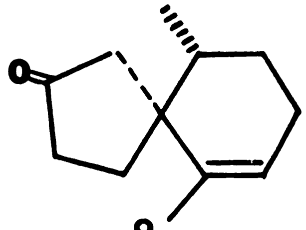
(3)



(4)



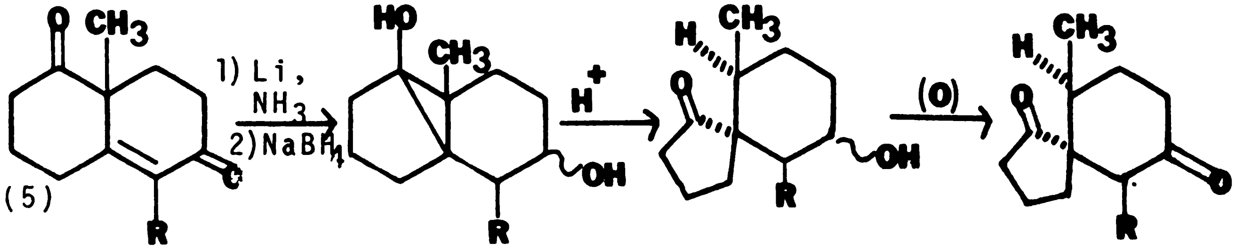
Enone 9, an isomer of 8, has also served as an intermediate in spirovetivane synthesis.



9

Many of the spirovetivane syntheses reported to date suffer from poor overall yield and/or lack of stereospecificity. The approach of Stork et al.,[38a] Yamada et al.,[31a] and Dauben and Hart[38c] are among the best.

In this part of my dissertation, I will describe an efficient synthesis of spirovetivanes precursor 8 from the versatile cyclopropanol intermediate 10 (eq. 5). I will



(5)

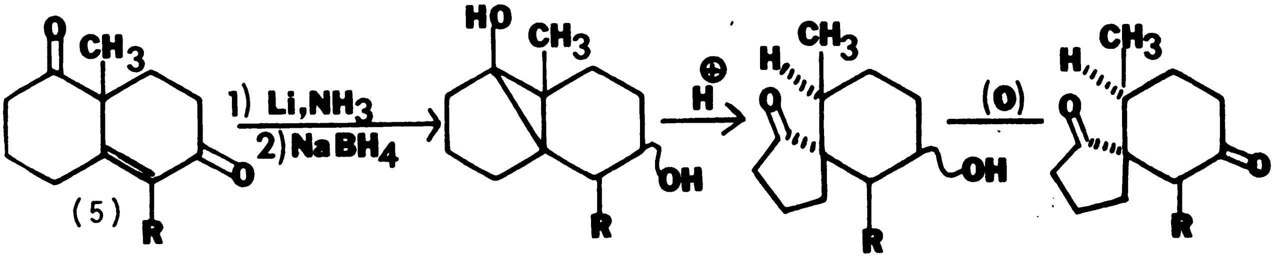
10' $R=CH_3$ 10 $R=CH_3$ 12 $R=CH_3$ 14 $R=CH_3$

11' $R=H$ 11 $R=H$ 13 $R=H$ 15 $R=H$

also describe a highly stereospecific approach to the synthesis of hinesol 2 by an independent route.

RESULTS AND DISCUSSION

Spiro[4.5]decane intermediates that might serve as precursor to the spirovetivanes are readily prepared by acid catalysed ring opening of cyclopropanols **10** and **11** (eq. 5). The predominantly equatorial hydroxyl function in ketol **12** and **13** may be oxidised to spirodiketone **14** and **15**, and also obtained directly from the corresponding ketocyclopropanols.[10]

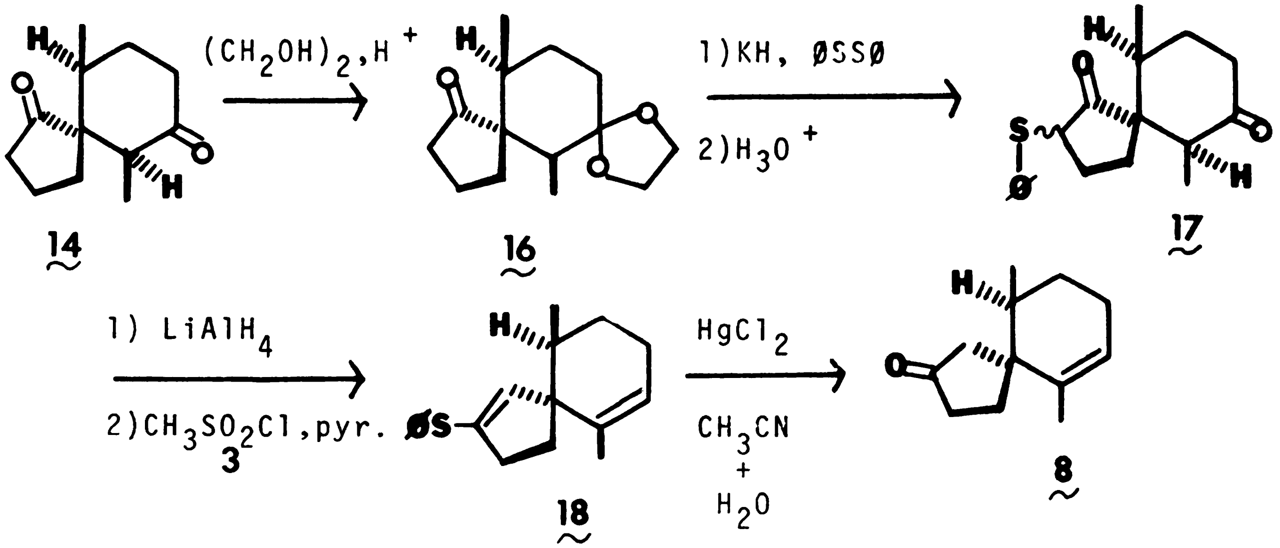


(5)

10' R=CH$_3$	**10** R=CH$_3$	**12** R=CH$_3$	**14** R=CH$_3$
11' R=H	**11** R=H	**13** R=H	**15** R=H

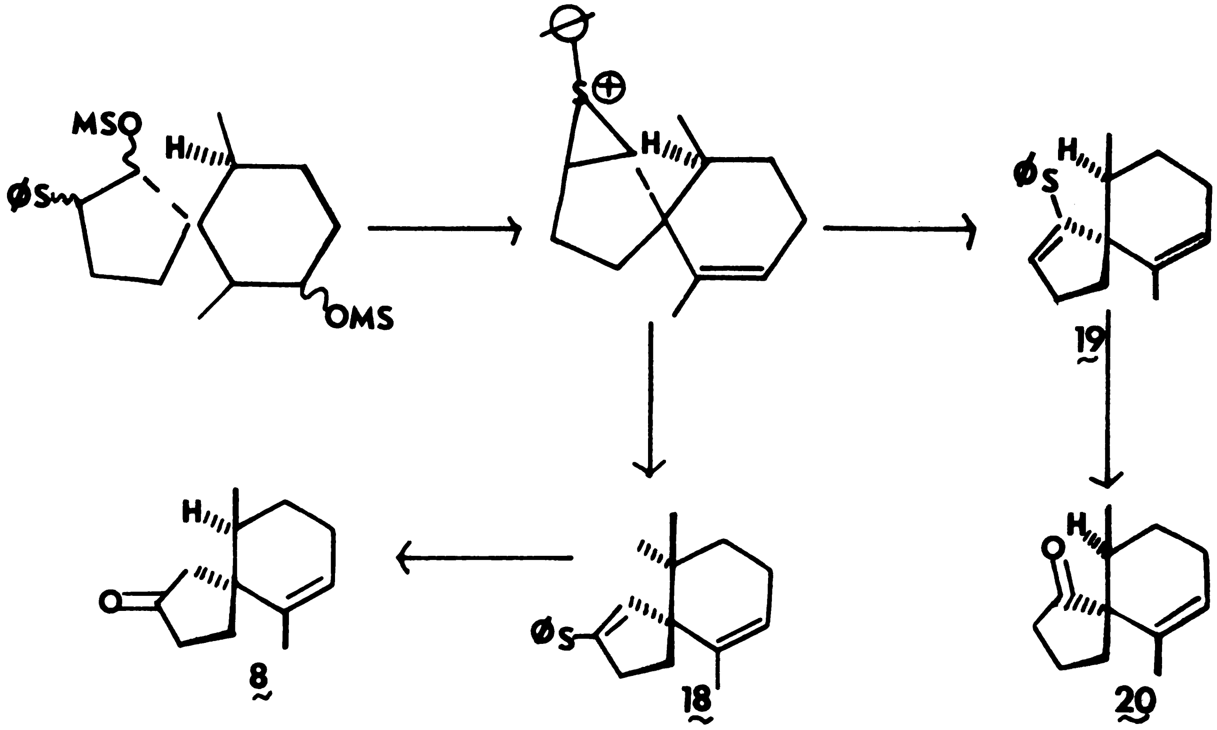
A. Synthesis of a β-Vetivane Precursor

Spiroenone **8** was a key intermediate in Marshall's synthesis of β-vetivone. Methods for transforming dione **14** into **8** were explored, in part to demonstrate the potential usefulness of **14** as a synthetic intermediate, and also to confirm its configuration. The first approach to this transformation is outlined in Scheme I. A key feature of this synthesis is an application of the 1,2-carbonyl transportation procedure devised by Trost.[42]



Sulfenylation of ketal 16 with diphenyl disulphide and potassium hydride proceeded in quantitative yield. Subsequent hydrolysis with dil. hydrochloric acid gave the diketone 17, which was then reduced by lithium aluminum hydride. Since five membered ketone was very resistant to reduction (steric hindrance), the hydride reaction required 48 h. The diol thus obtained was converted into a dimeysalate derivative by reaction with methane sulphanylchloride and pyridine. Bis-elimination was then effected, either by treatment with potassium t-butoxide or better by heating in pyridine solution. Instead of a single isomer (18), as suggested by Trost, the elimination product was found to consist of two isomers, 18 and 19 (^{1}H NMR analysis and subsequent chemical reaction). This can be explained by a neighboring group participation by sulfur, as shown in the equation 6.

(6)

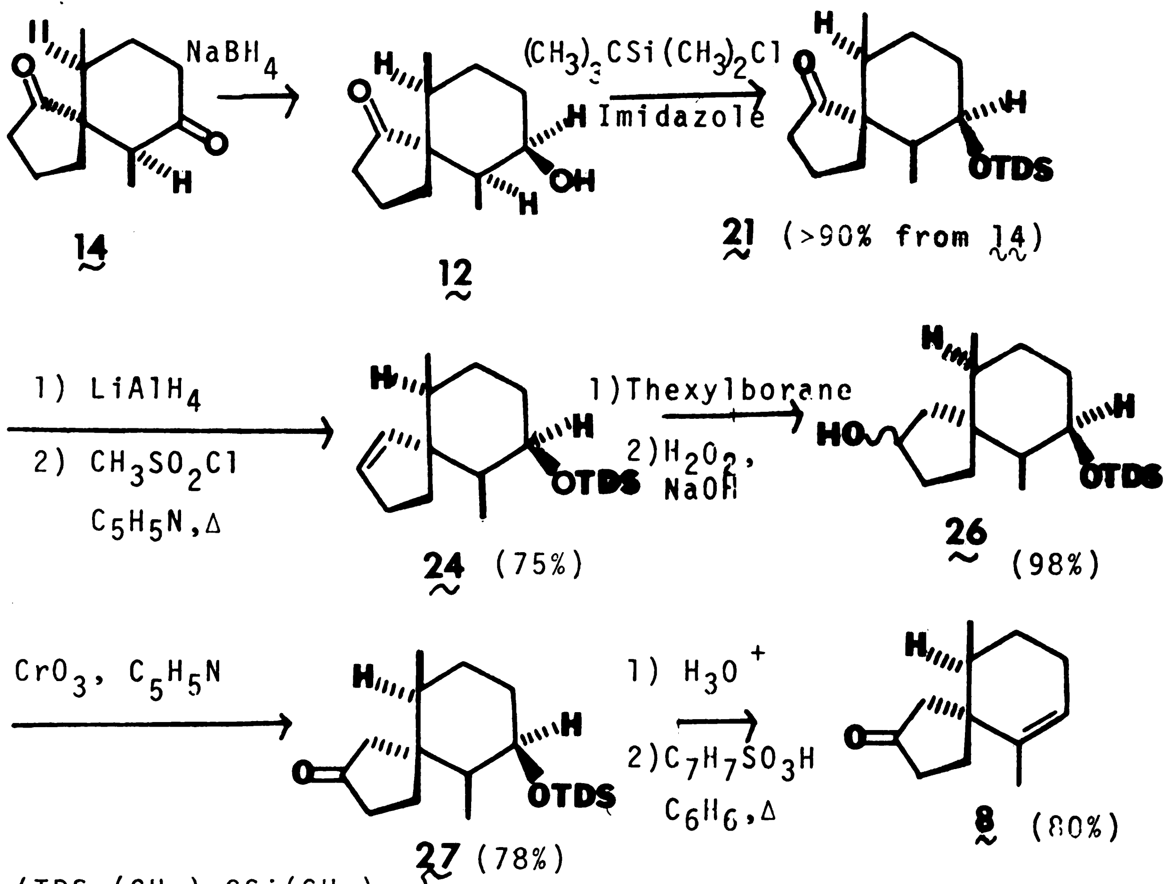


This type of aryl sulphide participation with interconversion of isomeric vinyl sulphides has been well documented in the literature.[43,44] Hydrolysis of the isomeric vinyl sulphides by a refluxing soltuion of mercuric chloride in aqueous acetonitrile gave a 60% yield of the target molecule 8 and its isomer 20 in approximately a 1:1 ratio. This isomeric mixture was difficult to separate by the usual analytical methods, but the 2,4-DNP derivatives of these ketones were separated by column chromatography (SiO_2 and 10% ethylacetate/hexane). The melting point of an isomer was found to be 105-107°C which is in agreement with the melting point reported for this compound 8 by Marshall and Wenkert.[28] An authentic sample of 20 was prepared by dehydration of 12 and its 2,4-DNP derivative proved identical to that of the

other isomer (85-87°C). ^{1}H NMR also showed that the epimeric mixture is in the ratio of 1:1 by the approximate measurement of the peak at δ0.8-0 region

Since the first approach was not satisfactory, another attempt was made, following Scheme II.

Scheme II



(TDS=$(CH_3)_3CSi(CH_3)_2$-)

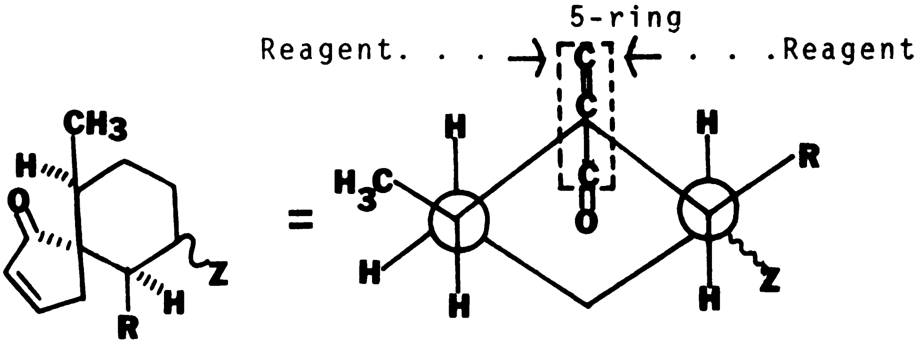
The axial epimer of ketol 12 was used for this synthesis, since it undergoes the final elimination much more effectively than the equatorial isomer. Preparation of the axial alcohol (12) was readily achieved in 92% yield by sodium borohydride reduction of the diketone 14.[21] The stereoselectivity of this reduction contrasts with the alternative preparation of 12 from hydroxycyclopropanol 10 (equation 5). The equatorial epimer is favored by a 4:1 ratio in this latter synthesis. Conversion of spiro alcohol 12 into its silylether 21 was effected in quantitative yield by treatment with tert-butyl dimethyl chlorosilane in dimethyl formamide containing imidazole. Silylation of the axial epimer was found to be very slow (48 h at 60°C), but the product was stable to subsequent reactions (unlike the equatorial analog). Conversion of silylether 21 into the olefin 24 was achieved (80%) by reducing the ketone with lithium aluminum hydride, followed by dehydration with methanesulphenyl chloride and pyridine. Hydroboration of 24 with thexylborane[45] followed by oxidation with hydrogen peroxide gave alcohol 26 in excellent yield (quantitative). Alcohol 26 was then oxidized to the corresponding ketone (27) in 75% yield by the action of Sarett's reagent. Hydrolysis of the silyl ether function followed by acid-catalyzed dehydration gave enone 8 in 80% yield. The spectroscopic properties of 8 (^{1}H NMR, IR and mass spec) together with the 2,4-DNP melting point were in agreement with the data reported for this compound by Marshall (lit[28] DNP 107-109°C, observed 105-107°C).

B. Studies Toward Total Synthesis of Hinesol

The synthesis of β-vetivone precursor **8** reported here not only proved that compound **14** is a useful intermediate in the total synthesis of spirovetivane sesquiterpenes, but also established the stereochemistry at C-10 during the ring opening reaction of cyclopropanol **10** (equation 5). In this reaction the potential usefulness of intermediates **12** through **15** in a synthesis of hinesol will be explored.

The most important step in such a synthesis is the stereoselective introduction of a three carbon side chain at C-3. It is known from earlier studies that even though the spiro alcohol **12** appears to be an ideal intermediate for a hinesol synthesis, very poor selectivity is achieved during the introduction of a side chain at C-3.[21]

The two methyl groups on the six-membered ring bracket the five-membered ring, making the steric hindrance to approach from either side about the same. Intermediates lacking one of these methyl groups (e.g., **22** and **29**) would strongly favor approach of a reagent from the unsubstituted side.

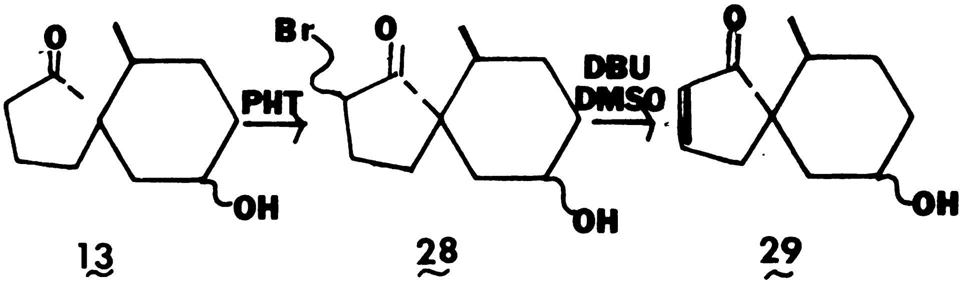


22 R=CH_3, Z=OH, **29** R=H, Z=OH

In order to attach a side chain at C-3 in compound 13 it is necessary to introduce a conjugated double bond, so that a 1,4-addition can be effected. Several well-documented methods are known by which a double bond may be introduced α,β to a ketone.

One straightforward method involves a α-bromination followed by dehydrobromination (equation 7). Direct bromination of 13 by the recently reported reagent 2-pyrrolidone hydrotribromide (PHT) was tried but gave limited success. The main problem seemed to be dihalogenation at the α-position of the ketone in large scale reactions (2g). The monobrominated compound 28 was prepared in 80% yield in small scale reactions run at 0°C. Subsequent dehydrobromination of 28 under different conditions (lithium carbonate-toluene, diazobicyclo undecane (DBU)-toluene or DMSO, or lithium chloride-lithium carbonate-DMF) gave only moderate yields of 29 on a small scale. Very poor yields were obtained in larger scale reactions.

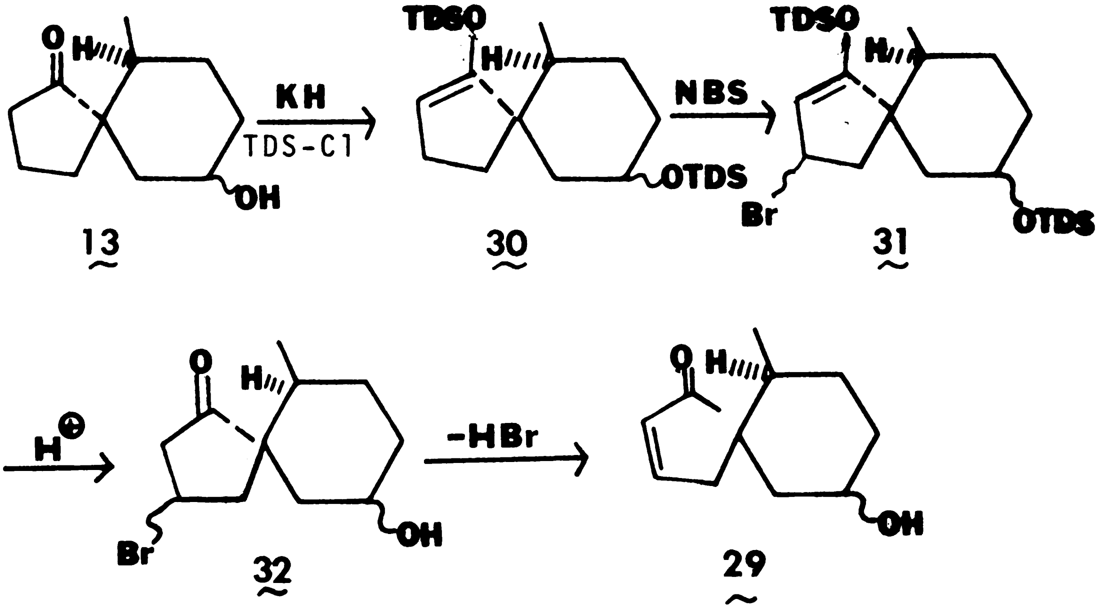
(7)



Another approach to double bond insertion would be to prepare a β-halo ketone. Such compounds undergo facile

dehydrobromination. The reaction sequence outlined in Scheme II was therefore examined.

Scheme II

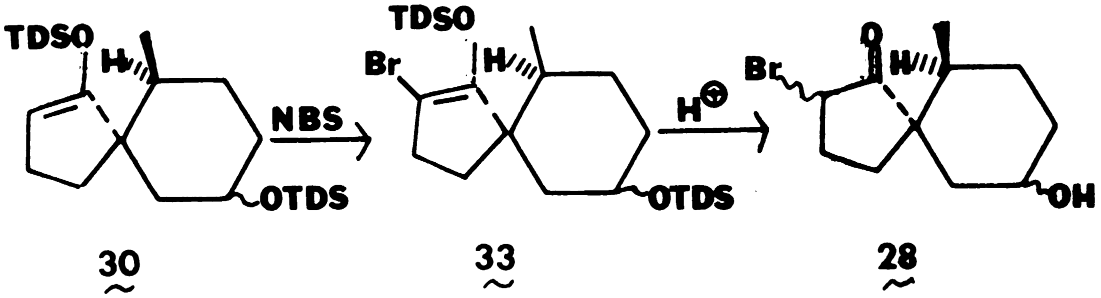


$(TDS=(CH_3)_3CSi(CH_3)_2-)$

Compound 30 was prepared in quantitative yield from potassium hydride and tert-butyl dimethyl chlorosilane. However, allylic bromination with N-bromosuccinamide gave the vinylic bromide 33 instead of the expected allylic bromide 31. This may be due to the addition of bromine from NBS to the electron-rich vinyl silyl[53] ether double bond. Hydrolysis of 33 was difficult, but gave a very good yield

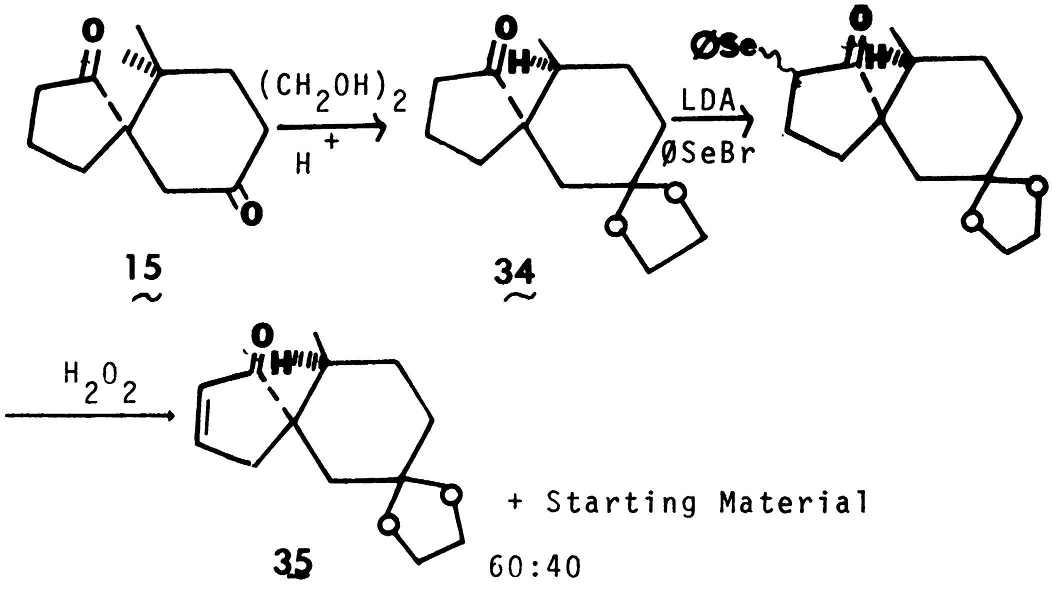
of the α-bromide 28. Unfortunately, this improvement in the α-bromination step could not be matched by an improvement in the dehydrobromination step (equation 8).

(8)



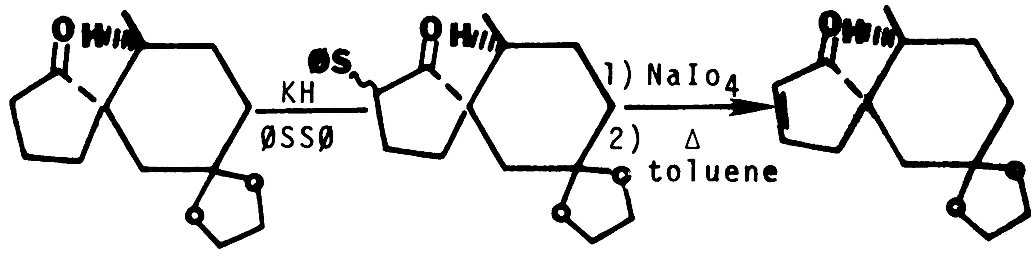
A third approach to the introduction of a conjugated double bond involved β-seleneylation^{48} followed by oxidative elimination to the α,β-unsaturated ketone. For this study ketone 15 was used as the starting material, as outlined in equation 9.

(9)



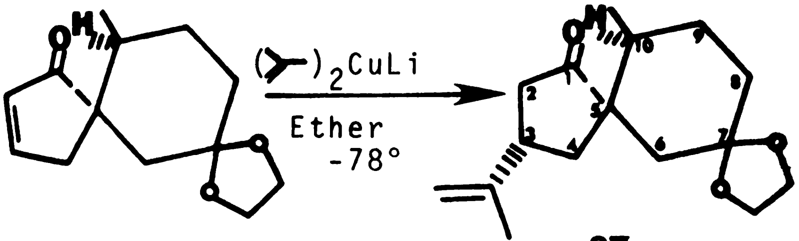
Conversion of diketone **15** to ketal **34** took place in quantitative yield. Transformation of **34** to enone **35** in 60% overall yield was then effected by treatment with lithium diisopropyl amide and various seleneylating agents (diphenyl diselenide, phenyl selenium bromide and phenyl selenium chloride), followed by oxidative elimination with 30% hydrogen peroxide. The main problem associated with this approach was the separation of the 30% starting material along with the product.

From the above results it appeared that a very strong base was required to convert the five-membered ketone completely into its enolate salt possible due to steric hindrance and the strain of a double bond in the five-membered ring. The best reagent for this purpose proved to be potassium hydride, which is known to be useful in the formation of strained enolates.[49] Indeed, enol silyl ether **30** was formed in quantitative yield after reaction of **13** with KH. A fourth method of double bond insertion, developed by Trost et al.,[50] was then applied to **34**. The potassium enolate salt from **34** was treated with diphenyldisulfide followed by oxidative elimination with sodium periodate. This reaction sequence (equation 10) was found to form the enone **35** in quantitative yield. In this system it appears that phenylsulfide elimination is more effective than the corresponding selenide reactions.

(10) 

34 **36** **35** **(100%)**

With the enone **35** in hand, it was decided to introduce a three-carbon unit at C-3, by 1,4-addition. The 1,4-addition of lithium dialkylcuprate reagents to α,β-unsaturated ketones has been extensively studied by House and co-workers,[51] and this useful reaction has proven to be effective in this synthesis. Thus, enone **35** underwent a 1,4-addition with lithium diisopropenyl cuprate (ether solution at -78°C) giving an excellent yield of **37** as a single isomer (equation 11).

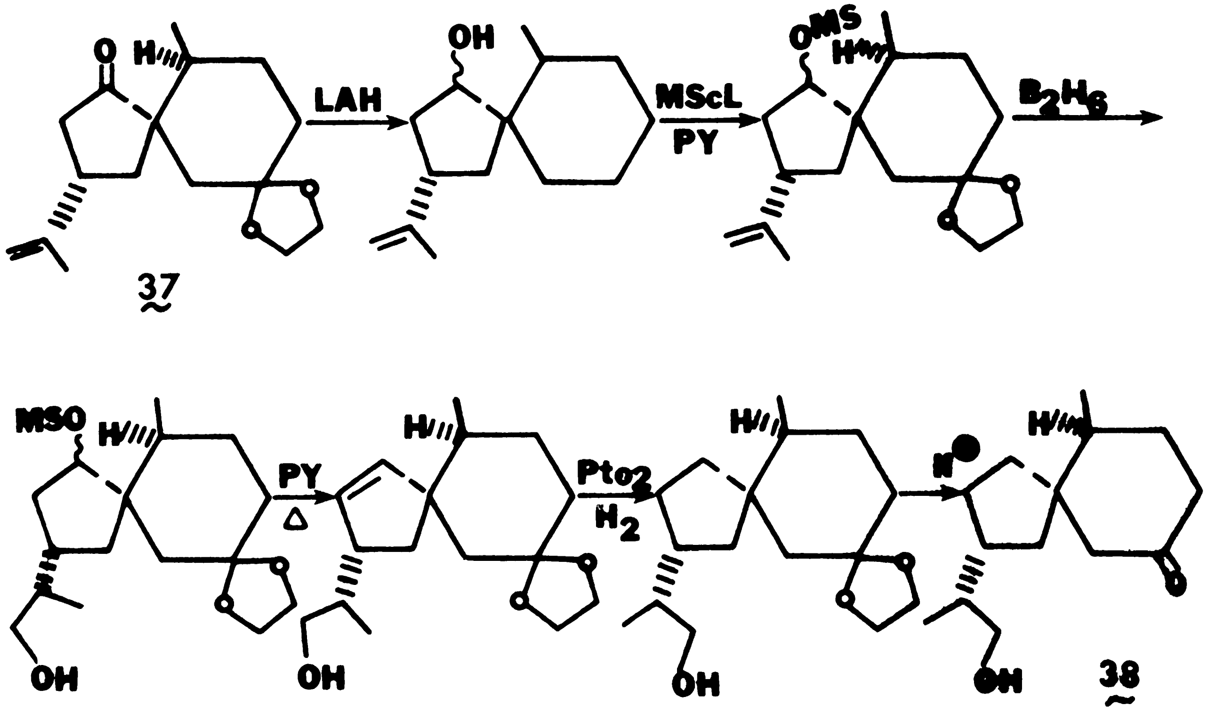
(11) 

35 **37**

The penultimate stage in this synthesis of hinesol requires the removal of the carbonyl group at C-1 and the introduction of a methyl group at C-6. From previous work with ketones **14** and **15** it was known that this carbonyl function

is badly hindered, and its removal is not as easy as Trost suggests in one of his papers.[52] Various modifications of the Wolff-Kishner reduction were studied; however, starting material 37 was recovered in poor yield. A stepwise reduction of the carbonyl function was therefore undertaken, as described in Scheme III. Elimination of the corresponding alcohol with methanesulphenyl chloride and pyridine was effected as before, the isopropenyl side chain being protected as a primary alcohol. In the first application of this reaction sequence, a modest yield of compound 38 was obtained. Further study is needed to optimize this yield.

Scheme III



The final stage of this hinesol synthesis requires methylation of the six-membered ketone at C-6, followed by conversion of the ketone to a Δ^6 double bond. Concurrent or subsequent reformation of the isopropenyl group should give hinesol.

EXPERIMENTAL

GENERAL

In addition to the general described in Part I, ^{1}H NMR spectra were taken on Bruker WH -180 and high resolution mass spectra were taken on Varian, MAT, CH-5 mass spectrometer.

<u>Preparation of cyclopropanol **10**</u>. In a one liter, three neck, round bottomed flask containing a small amount of sodium metal, was condensed 500 mL of ammonia. The ammonia was then distilled through Tygon tubing into a carefully dried two liter three neck flask containing 1.78 g (0.25 mol) of lithium ribbon. The reaction flask was equipped with a paddle stirrer, a dry ice condenser, a dry ice, actone bath and an additional funnel to which a nitrogen gas line was attached. A solution of 13.0 g (0.067 mol) of the enone (**10**[1]) dissolved in 250 mL of THF was added dropwise over a one hour period. The blue color of the reaction was discharged by dropwise addition of ethylene dibromide, following which 10 g of finely ground ammonium carbonate was added in one portion. The cooling bath was removed and the ammonia was evaporated into the hood under a steam of nitrogen. The residue was taken up in 300 mL of water and the mixture was extracted three times with 200 mL of ether. The ether extracts were combined, washed sequentially with

water and brine, and then dried by anhydrous magnesium sulphate. After removal of the solvent 13 g of an oil was obtained which gave 7.3 g (60%) crystals from ether/pentane, mp = 96-98°C.

Preparation of spiroalcohol 12 and subsequent oxidation to spiroketone 14. To a solution of 6 g (0.03 mol) of cyclopropanol (10) in 50 mL of absolute ethanol at -18°C was added a solution of 6 g (excess) of sodium borohydride in absolute ethanol. The reaction mixture was stirred at 0°C for 4 h while monitoring the reaction by TLC. The reaction was quenched by dropwise addition of 20 mL of concentrated hydrochloric acid in 20 mL ethanol, and the reaction mixture was stirred at room temperature for 10 h (overnight). Precipitated salt was filtered and ethanol was removed from the filtrate under reduced pressure. The residue was dissolved in ether, washed sequentially with sodium bicarbonate, water and brine, and dried over anhydrous magnesium-sulphate. Removal of the solvent gave 5.98 g of epimeric alcohols in the ratio 1:4. This mixture was separated by column chromatography (silica eluted with ether) to give 3.1 g of pure equatorial alcohol mp 76-77° and 1 g of axial alcohol mp 78-79°C (IR and ^{1}H NMR were in agreement with Kurt Grim's description of these compounds). The epimeric alcohol was oxidized quantitatively into the diketone 14 mp = 64-66°C (lit.[21] 64-66°C).

Preparation of ketal 16. A solution of 2.0 g (0.0103 mol) of the diketone 14 in 150 mL dry benzene containing 20 mL ethylene glycol and 100 mg of p-toluene sulphonic acid was refluxed through a Dean Stork trap. The reaction appeared to be finished after a half hour period (GLPC 4% QF-1, 160°C), and the benzene solution was washed with sodium bicarbonate water and brine and dried over anhydrous magnesium sulphate. This solution yielded 2.367 g (97%) of pure ketal 16. IR (neat) 1735 cm^{-1}; ^1H NMR (CCl_4) $\delta 0.7$ (d, J=4.5 Hz, 3H), 0.8 (d, J=4.5 Hz, 3H) 1-2.4 (m, 12H), 3.8 (m, 4H); mass spectrum (70 eV) m/e (relative intensity) 238 (8), 210 (2), 182 (3), 126 (53), 99 (100), 86 (77), 55 (38).

Anal. calcd. for $C_{14}H_{22}O_3$: m/e 238.15636.

Found: m/e 238.15688.

Preparation of the α-phenyl sulphide 17. A solution of 2.6 g (0.0109 mol) of the ketal 16 and 10 g (excess of potassium hydride in 100 mL of glyme was refluxed under argon for two h. The mixture was cooled to room temperature followed by the sequential addition of 8 mL of HMPA and 2.6 g (0.012 mol) of diphenyl disulphide in 10 mL of glyme. After 3 h, the excess potassium hydride was quenched by dropwise addition of water at 0°C and the mixture was then treated overnight with 30 mL of concentrated hydrochloric acid. The reaction mixture was neutralized with sodium bicarbonate

and extracted with ether. The combined ether layers gave an oil which was percolated through 50 gm of silica to remove the mineral oil and other non-polar materials. The pure sulphide was eluted by ether as an oil (3.3 g, <95%) which solidified on cooling. An analytical sample was obtained by crystalization from ether/pentane, mp = 75-78°C; IR (neat) 1700, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ0.8-9 (m, 6H) 1.2-2.8 (m, 10H), 3-6 (m, 1H), 7.3 (m, 5H) and mass spectrum (70 eV) *m/e* relative intensity 304 (5), 303 (14), 302 (65), 193 (9), 136 (100), 110 (12), 91 (11), 77 (8).
Anal. calcd for $C_{18}H_{22}O_2S$: m/e 302.13571.
Found: m/e 302.13403.

Preparation of isomeric vinyl sulphides **18** *and* **19**. A solution of 100 mg (0.32 mmol) of the diketone **17** in 10 ml of ether was reduced with 37 mg (1 mmol) of lithium aluminum hydride over a period of 48 h at room temperature. The reaction mixture was quenched by dropwise addition of sodium hydroxide solution and then extracted with ether. The ether extract, after the usual work up, gave 98 mg of the diol (checked by IR).

The diol was dehydrated by treatment with a solution of 1 mL of methyl sulphonyl chloride in 10 mL pyridine for 6 h at room temperature (bis-mesylate formation), followed by refluxing for 9 h. Removal of the pyridine left a residue which was extracted with methylene chloride. Purification

by preparative TLC (SiO_2, 10% EtOAC/Hexane) yielded 53 mg of an oil (60%). IR (neat) 1600, 1625 cm^{-1}; ^1H NMR (CCl_4) δ0.8-0.95 (m, 3H) 1.2-2.4 (m, 12H), 5.1-5.4 (m, 2H), 7.25 (m, 5H) and mass spectrum (70 eV) m/e (relative intensity) 272 (3), 271 (5), 270 (22), 228 (90), 218 (77), 202 (100), 109 (98), 91 (58), 77 (97).

Preparation of isomeric ketones 8 and 20. To a solution of 108 mg (0.4 mmol) of the vinyl sulphide in 4 mL of aqueous acetonotrile (13) was added 300 mg (1 mmol) mercuric chloride, and this mixture was refluxed for 78 h (the reaction was monitored by GLPC, 4% QF-180°C). The solvent was removed under reduced pressure and a pet ether solution of the residue was filtered through silica using petroleum ether as elutent. Removal of the solvent gave 40 mg of an oil (56%). IR (CCl_4) 1750 cm^{-1}; ^1H NMR (CCl_4) δ0.8-1 (m, 6H), 1.4-2.8 (m, 1H), 5.4 (m, 1H) and mass spectrum (70 eV) m/e (relative intensity) 179 (8), 178 (51), 163 (14), 150 (8), 145 (11), 136 (18), 122 (50), 110 (33), 107 (100). A 2,4-DNP derivative of this mixture was prepared and purified by column chromatography (SIO_2 and 10% EtoAC/Hexane as elutent). The first fraction was recrystalized from ethanol, mp 85-87°C (85-86°C observed in DNP of authentic sample of 20). The second fraction was recrystalized from ethanol, mp 105-107°C (lit[28]= 107-109°C).

Preparation of silyl ether 21. To a solution of 1.1 g (0.0056 mol) of the axial alcohol 12 in 50 mL of dimethyl formamide was added 1.26 g (0.0084 mol) of dimethyl tert butyl silyl chloride and 952 mg (0.014 mol) of imidazole, and the soltuion was stirred at 45°C for 48 h. The reaction mixture was diluted with ether, washed with water and brine and dried by anhydrous magnesium sulphate. Removal of the solvent gave 1.8 g of pure silyl ether 21 (99%). IR ($CDCl_3$) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ0.034 (s, 6H), 0.8-1 (m, 6H), 0.9 (s, 9H), 1.2-2.4 (m, 12H) 3.8 (m, 1H); and mass spectrum (70 eV) m/e (relative intensity) 310 (6), 295 (5), 253 (97), 200 (12), 199 (10), 185 (18), 161 (43), 75 (100). Anal. calcd for $C_{18}H_{34}O_2Se$: m/e 310.23514.
Found: m/e 310.23279.

Preparation of spiro alcohol 22. A solution of 1.54 g (0.00496 mol) of silyl ether 21 in 100 mL of ether was treated with 500 mg (excess) of lithium aluminum hydride at room temperature. The reaction was quenched after 6 h by dropwise addition of sodium hydroxide solution, and the precipitate was filtered and washed several times with ether. The organic layer after the usual work up gave 1.43 g pure alcohol 22 (92%). IR (CCl_4) 3500-3200 cm^{-1}; ^1H NMR (CCl_4) δ0.034 (s, 6H), 0.9 (m, 15H), 1.2-2.4 (m, 13H), 3.7 (m, 1H) 4.0 (m, 1H)

Preparation of olefin 24. A solution of 1.43 g (0.0045 mol) of the alcohol 22 and 1.7 g (1 mL, excess) of methyl sulphonyl chloride in 10 mL of pyridine was stirred for 10 h and then refluxed for another 8 h. The pyridine was removed under reduced pressure and the residue was dissolved in ether, washed with water and brine and dried. Removal of the solvent gave 1.075 g of a single product 24 (80%). IR (CCl_4) 1480 cm^{-1}; ^1H NMR (CCl_4) δ0.034 (s, 6H) 0.8-1 (m, 15H), 1.2-2.4 (m, 10H), 3.8 (m, 1H), 5.1 (m, 1H), 5.6 (m, 1H), and mass spectrum (70 eV) m/e (relative intensity) 294 (4), 279 (3), 237 (45), 161 (24), 107 (22), 75 (100).
Anal. calcd for $C_{18}H_{34}OSe$: m/e 294.23932.
Found: m/e 294.23788.

Preparation of spiro alcohol 26. To a solution of 0.72 mL (6 mmol) of 2,3-dimethyl-2-butene in 10 mL of THF at 0°C was added 3 mL (3 mmol) of 1 molar solution of diborane in THF. The solution was stirred at this temperature for 2 h. To this mixture was added dropwise 800 mg (2.72 mmol) of olefin 24 in 10 mL of THF and the reaction mixture was stirred at 0°C for 6 h followed by 5 h at room temperature. Oxidation of this borane mixture was effected by adding 12 mL of 10% sodium hydroxide followed by 12 mL of 15% hydrogen peroxide. After 3 h stirring, the aeuqous layer was saturated with sodium chloride and the THF layer was separated. After working up the THF layer, 0.84 gm of an

oil (98%) was obtained. IR (CCl_4) 3100-3600 cm^{-1}; ^1H NMR (CCl_4) δ0.034 (s, 6H), 0.8-1 (m, 15H), 1.1 (s, 1H exchangeable), 1.2-2.4 (m, 12H), 3.8-4.2 (m, 2H).

Preparation of spiroketone 27. Pyridine chromium trioxide compound was prepared by adding 1.2 g (4 mmol) of chromium trioxide to 30 mL of ice cold pyridine and the mixture was stirred for half an hour. To this solution was added 800 mg (2.56 mmol) of alcohol 26 in 10 mL of pyridine and was stirred at room temperature overnight. The brown solution was diluted with excess of water and neutralized by dilute hydrochloric acid and extracted several times with methelene chloride. The organic layer after the usual work up gave 600 mg of a simgle compound 27 (76%). IR (CCl_4) 1735 cm^{-1}; ^1H NMR (CCl_4) δ0.034 (s, 6H) 0.9-1.1 (m, 15H), 1.2-2.2 (m, 8H), 2.2-2.7 (m, 4H) 3.8 (m, 1H) and mass spectrum (70 eV) m/e (relative intensity) 310 (3), 295 (2), 253 (34), 195 (12), 161 (42), 75 (100).

Anal. calcd for $C_{18}H_{34}O_2Si$: m/e 310.23422.

Found: m/e 310.23279.

Preparation of unsaturated ketone 8. The silylether 27 was hydrolysed by stirring 181 mg (0.58 mmol) of it with 5 mL 6 N hydrochloric acid in 10 mL of THF. After overnight stirring the alcohol was dehydrated by refluxing in benzene solution containing a little p-toluene sulphonic acid. After

the usual work up the benzene layer gave 65 mg of unsaturated ketone 8 (80%). IR (CCl_4) 1735 cm^{-1}, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ0.92 (3H, d, J=7.2 Hz), 1.65 (3H, d, J=3.2 Hz), 1.7-2.2 (m, 9H) 2.03 (d, J=18 Hz, 1H), 2.32 (d, J=18 Hz, 1H), 5.3 (m, 1H); mass spectrum (70 eV) m/e (relative intensity) 178 (53), 163 (15), 150 (13), 149 (10), 137 (12), 136 (24), 123 (15), 108 (22), 107 (100), 93 (85), 68 (40), 55 (25).

Preparation of α-bromoketone 28 with PHT and dehydrobromination to prepare enone 29. To a solution of 4.6 g (0.025 ml) of ketoalcohol 13 in 200 mL dry tetrahydrofuran was added 15.19 g (0.3 ml) of 2-pyrrolidone hydrotribromide, PHT. The resulting organic solution was stirred at room temperature for 12 h in complete darkness, during which time a white crystalline solide precipitated. Following filtration, 100 mL of ether was added to the filtrate and the organic solution was washed with aqueous sodium bicarbonate, water and brine. Removal of the solvent gave an oil which proved to be a mixture. An analytical sample of the major component was isolated by GLPC (4% QF-180°C) and displayed the following properties. IR (CCl_4) 3200-3500, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ0.8 (3H, d, J=6Hz) 1.2-2.6 (m, 12H) 3.4-3.8 (m, 1H), 4-4.4 (m, 1H) and mass spectrum (70 eV) m/e (relative intensity) 262 (10), 260 (10), 163 (70), 93 (100).

Anal. calcd for $C_{11}H_{17}O_2Br$: C, 50.59; H, 6.56.
Found: C, 50.58; H, 6.52.

A solution of crude bromoketone 28 in 20 mL of dry DMSO containing 20 mL of 1,5-diazobicyclo[5.4.0]undec-5-ene was heated overnight under nitrogen. The resulting dark solution was diluted with 300 mL of ice water and extracted several times with ether. The ether extract was washed with 10% hydrochloric acid, water and dried over anhydrous magnesium sulphate. Removal of the solvent gave 2.5 g of an oil which on distillation at 125°C (0.0025 torr) gave 1 g oil that crystallised from ether and pentane. The enone alcohol 29 displayed the following properties, mp 90-91°C, IR ($CDCl_3$) 3600, 1690, 1603 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ0.68 (3H, d, J=6.8 Hz), 1.2-2.1 (m, 7H), 2.6 (1H, ddd, J=20, 3, 2 Hz), 3.0 (1 H, ddd, J=20, 3, 2 Hz), 4.2 (bs, 1H), 6.1 (1H, dt, J=6, 2 Hz), 7.6 (1H, dt, J=6, 3 Hz) and mass spectrum (70 eV) m/e (relative intensity) 180 (22), 162 (45), 147 (30), 133 (26), 95 (100).

Anal. calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.9.
Found: C, 73.35; H, 9.08.

Preparation of α-bromoketone 28. To a suspension of 6 g (0.033 mol) of 22.1% potassium hydride in 50 mL glyme was added 1.82 g (0.01 M) of ketoalcohol 13 in 10 mL of glyme, and this mixture was refluxed for 90 min under argon. This mixture was cooled and then treated with 4 mL of triethylamine and 4 g (0.026 mol) of tert-butyl dimethyl chlorosilane in 5 mL of glyme. After 15 min the excess potassium hydride was quenched by adding water dropwise (0°C) under

an argon atmosphere. The aqueous layer was extracted three times with ether, and the ether extracts, after washing with water and brine and drying with anhydrous magnesium sulphate, gave a colorless oil which was used for the subsequent step without further purification. An analytical sample, collected by GLPC (4% QF1-180°C) showed the following properties. IR (CCl_4) 1675 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ0.0 (s,6H) 0.2 (s, 6H), 0.8 (s, 9H), 0.9 (s, 9H), 1.2-2.3 (m, 11H), 3.2-3.8 (m, 1H), 4.4 (1H, t, J=2, 1 Hz) and mass spectrum (70 eV) m/e (relative intensity) 410 (23), 353 (74), 237 (77), 149 (100).

To a refluxing solution of the above oil in 100 ml of carbon tetrachloride was added 1.8 g (0.01 M of N-bromosuccinamide. Analysis by GLPC (4% QF-1, 160°C) showed the occurance of a very rapid reaction. The succinamide was filtered from the cooled (0°) mixture, and the carbon tetrachloride layer was washed with sodium bicarbonate solution, water and brine and dried by anhydrous magnesium sulphate. Removal of the solvent gave light yellow oil which was utilized for the subsequent step without further purification. An analytical sample collected by GLPC (4% QF1-200°C) exhibited the following properties: IR (CCl_4) 1675 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ0.0 (s, 6H), 0.3 (s, 6H), 0.8 (s, 9H), 0.95 (s, 9H), 1.2-2.4 (m, 11H) 3.2-3.8 (m, 1H) and mass spectrum (70 eV) m/e (relative intensity) 490 (12), 488 (12), 433 (39), 431 (39), 147 (100).

The crude product from above was hydrolysed by refluxing

in a solution of 20 mL of 4N hydrochloric acid and 50 mL of methanol overnight. After removing the solvent, the residue was dissolved in water and neutralized with aqueous soidum bicarbonate. The aqueous layer was extracted several times with methylene chloride, and washed with water and brine and dired by anhydrous magnesium sulphate. Removal of the solvent and residual oil (from KH) by pentane gave 2.03 g (80%) of a α-bromoketone 28. The GLPC retention time, IR and ^{1}H NMR were identical to those reported earlier for 28 prepared from spiroalcohol 13 and PHT: IR (CCl$_4$) 3200-3500, 1750 cm^{-1}, ^{1}H NMR (CDCl$_3$) δ0.8 (d, J=6 Hz, 3H), 1.2-2.6 (m, 12H), 3.4-3.8 (m, 1H), 4-4.4 (m, 1H) and mass spectrum (70 eV) m/e (relative intensity), 262 (10), 260 (10), 163 (70), 93 (100).

Preparation of spiroketal 34. A solution of 0.48 g (0.0026 mol) of diketone 15 in 100 mL of dry benzene and 20 mL of dry ethylene glycol, together with 20 mg of p-toluene sulphonic acid, was refluxed through a Dean Stork trap. The reaction appeared to be finished after a half hour period (GLPC analysis, 4% QF-1, 160°C), and the benzene solution was then washed with sodium bicarbonate, water and brine, and then dried over anhydrous magnesium sulphate. This solution yielded 600 mg (100%) of a colorless oil which displayed the following properties. IR (CCl$_4$), 1730, 1150, 1100 cm^{-1}; ^{1}H NMR (CCl$_4$) δ0.8-0.9 (3H, d, J=8 Hz), 2.5-1.2

(m, 13H), 3.9 (bs, 4H), and mass spectrum (70 eV) m/e (relative intensity) 224 (6), 196 (3), 150 (2), 126 (45), 99 (100).

Anal. calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99.
Found: C, 69.62; H, 8.93.

Preparation of enone **35** via α-selenation. A solution of 1.1 mmol of lithium diisopropyl amide was prepared under an argon atmosphere by adding 0.45 mL (1.1 mmol) of a 2.4 molar solution of n-butyllithium in 10 mL of THF to a solution of 0.175 mL (1.2 mmol) of freshly distilled diisopropyl amine in 10 mL of THF at -78°C. After 15 min, a solution of 224 mg (1 mmol) of ketal **34** in 10 mL of THF was added dropwise and was stirred for 1 h at room temperature. To this was added a solution of 1.2 mmol phenyl selenium bromide, prepared by mixing 197 mg (0.6 mmol) of diphenyl diselinide and 0.02 mL (0.6 mmol) of bromine in 5 mL THF. After stirring for 8 h, the reaction was quenched by the addition of ammonium chloride, and the aqueous layer was extracted with ether. The ether layer, after the usual work up, gave a yellow oil which was oxidized by 2 mL of 15% H_2O_2 in 5 mL of methylene chloride and 0.2 mL of pyridine at room temperature. After one hour the reaction mixture was diluted with sodium bicarbonate solution and extracted with methylene chloride. The methylene chloride layer, after the usual work up, gave 145 mg of an oil which was found to be a mixture of enone **35** and

starting material in the ratio 60:40 by GLPC analysis and IR and ^{1}H NMR spectra.

*Preparation of spiroalcohol **13** and subsequent oxidation to the spirodiketone **15**.* To a solution of 9.0 g (0.05 mol) of cyclopropanol **11** in 100 mL of absolute ethanol at -78°C was added 6.25 g (0.17 mol) of sodium borohydride, and this mixture was stirred under nitrogen for 5 h at 0°C. The resulting solution at -78° was treated with a solution of 30 mL of concentrated hydrochloric acid in 30 mL of ethanol, added dropwise, followed by an overnight reaction period. Precipitated salts were filtered and the solvents were removed under reduced pressure. The residue was dissolved in water and neutralized with sodium bicarbonate, following which the aqueous layer was extracted several times with ether. The combined ether layers were washed with water and brine and dried over anhydrous magnesium sulphate. Removal of the solvent gave 9.047 g of an oil, which was found to be an epimeric mixture of axial and equatorial alcohol in the ratio 14:85. The major isomer was crystallised from ether and pentane, 7.3 g (81%). The major alcohol in this case was identical with the minor alcohol obtained from lithium/ammonia reduction of cyclopropanol followed by acid treatment (60:40). The equatorial alcohol **13** displayed the following properties: mp, 76-78°C, IR (CCl_4) 3600 (sharp), 3200-3500, 1725 cm^{-1}; ^{1}H NMR (CCl_4) δ0.8 (3H, d, J=8 Hz),

1.1-2.3 (m, 13H), 2.8 (s, 1H, exchanged), 3.3 - 3.8 (m, 1H) and mass spectrum (70 eV) m/e (relative intensity) 183 (5), 182 (40), 164 (56), 93 (100), 81 (37), 74 (56).
Anal. calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95.
Found: C, 72.56; H, 9.93.

The minor (axial) alcohol showed the following properties: mp, 81-83.5°C, IR (CCl_4) 3600 (sharp), 3200-3600, 1730 cm^{-1}; ^1H NMR (CCl_4), δ0.8 (3H, d, J=8 Hz), 1.2-2-2 (m, 13H), 2.4-2.6 (bs, 1H, exchanged), 3.8-4.0 (m, 1H) and mass spectrum (70 eV) m/e (relative intensity) 182 (10), 164 (5), 137 (8), 124 (70), 111 (100), 93 (25), 79 (20).

A 6.8 g (0.037 mol) sample of alcohol **13** was oxidized by Jone's reagent in acetone to give 6.5 g (98%) of an oil, from which 4.01 g of crystalline **15** was isolated (crystallization from ether:pentane). The mp (60-62°C), IR and ^1H NMR of this compound agreed with the corresponding properties for **15** reported by Kurt Grimms.[21]

*Preparation of enone **35** by α-sulfoxide elimination.* To a suspension of 20.0 g (0.12 mol) of 24% potassium hydride in 100 mL of glyme was added 4.942 g (0.0022 mol) of ketal **34** in 20 mL of glyme, and this mixture was refluxed for 90 min under argon. After this reaction mixture was cooled to room temperature, it was treated with 1.6 mL hexamethyl phosphoamide followed by 5.45 g (0.025 mol) of diphenyl disulphide in 10 mL of glyme, and allowed to react for 1 h. Excess

potassium hydride was quenched by adding water dropwise at 0°C, and the aqueous layer was extracted several times with ether. The combined ether layers, after washing with water and brine, were dried by anhydrous magnesium sulphate. The crude product, contaminated with oil from the potassium hydride, was found to contain no starting material by GLPC analysis (4% QF-1, 180°C).

The product from the above step was oxidized overnight by 5.35 g (0.0025 mol) sodium periodate in 100 mL aqueous methanol. A precipitate which formed was filtered and washed with ether. Solvents in the combined filtrate and wash were removed under reduced pressure and the resulting oil was dissolved in ether and washed with water and brine and dried by anhydrous magnesium sulphate. The crude product (sulfoxide) obtained by removal of the solvent was refluxed for 2 h in 100 mL toluene containing 2.1 g (0.0025 mol) of anhydrous solid sodium bicarbonate. The organic layer was washed with water and brine and dried by anhydrous magnesium sulphate. Removal of the solvent gave an oil which was purified by percolation through 50 g of silica. An initial pet ether eluted fraction contains the oil from potassium hydride and other products from diphenyl disulphide. Enone 35 was eluted with ether, as an oil (8 g) which exhibited the following properties: IR (neat) 1710, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ0.68 (3H, d, J=6, 8 Hz), 1.35-1.94 (m = 7H), 2.57 (1H, ddd, J=19.8, 3, 2 Hz), 2.91 (1H,

ddd, J=19.8, 3, 2 Hz), 3.93 (m, 4H), 6.18 (1H, dt, J=6, 2Hz), 7.7 (1H, dt, J=6, 3 Hz) and mass spectrum (70 eV) m/e (relative intensity) 222 (61), 207 (5), 194 (5), 193 (11), 166 (83), 126 (100), 99 (75), 77 (90), 66 (20).
Anal. calcd for $C_{13}H_{18}O_3$: m/e 222.12675.
Found: 222.12558.

*Preparation of ketal **37**.* To a suspension of 1.0 g (0.071 mol) of 50% lithium sand (washed three times with pentane) in 20 mL of ether was added 1.6 g (0.013 mol) of freshly distilled isopropenyl bromide under argon. Vigorous reaction was observed in a few minutes and external heat was applied to induce reflux for 20 min after the initial reaction subsided. To the above solution at -78°C was added 1.14 g (0.006 mol) of copper (I) iodide, and this mixture was allowed to warm until a yellow color was observed (*ca.* -40°C). This solution was cooled to -78°C, following which 630 mg (0.0028 mol) of enone **35** in 10 mL of ether was added dropwise. After an hour at -78°C, the reaction mixture was warmed to 0°C and quenched by dropwise addition of saturated ammonium chloride solution. Solids which formed were filtered and washed several times with ether. The combined ether layers were washed with 10% solution of ammonium hydroxide, water and brine, and dried over anhydrous magnesium sulphate. Removal of the solvent gave 732 mg (100%) of **31** which showed the following properties: IR (neat) 1750, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ0.79 (3H, d, J=8 Hz), 1.8 (s, 3H), 1.2-2.8 (m, 12H),

3.79 (m, 4H), 4.63 (2H, d, J=4 Hz) and mass spectrum (70 eV) m/e (relative intensity) 264 (8), 208 (2), 207 (6), 126 (52), 119 (6), 99 (100).

Anal. calcd for $C_{16}H_{24}O_3$: m/e 264.17471.

Found: m/e 264.17255.

APPENDIX: SPECTRA

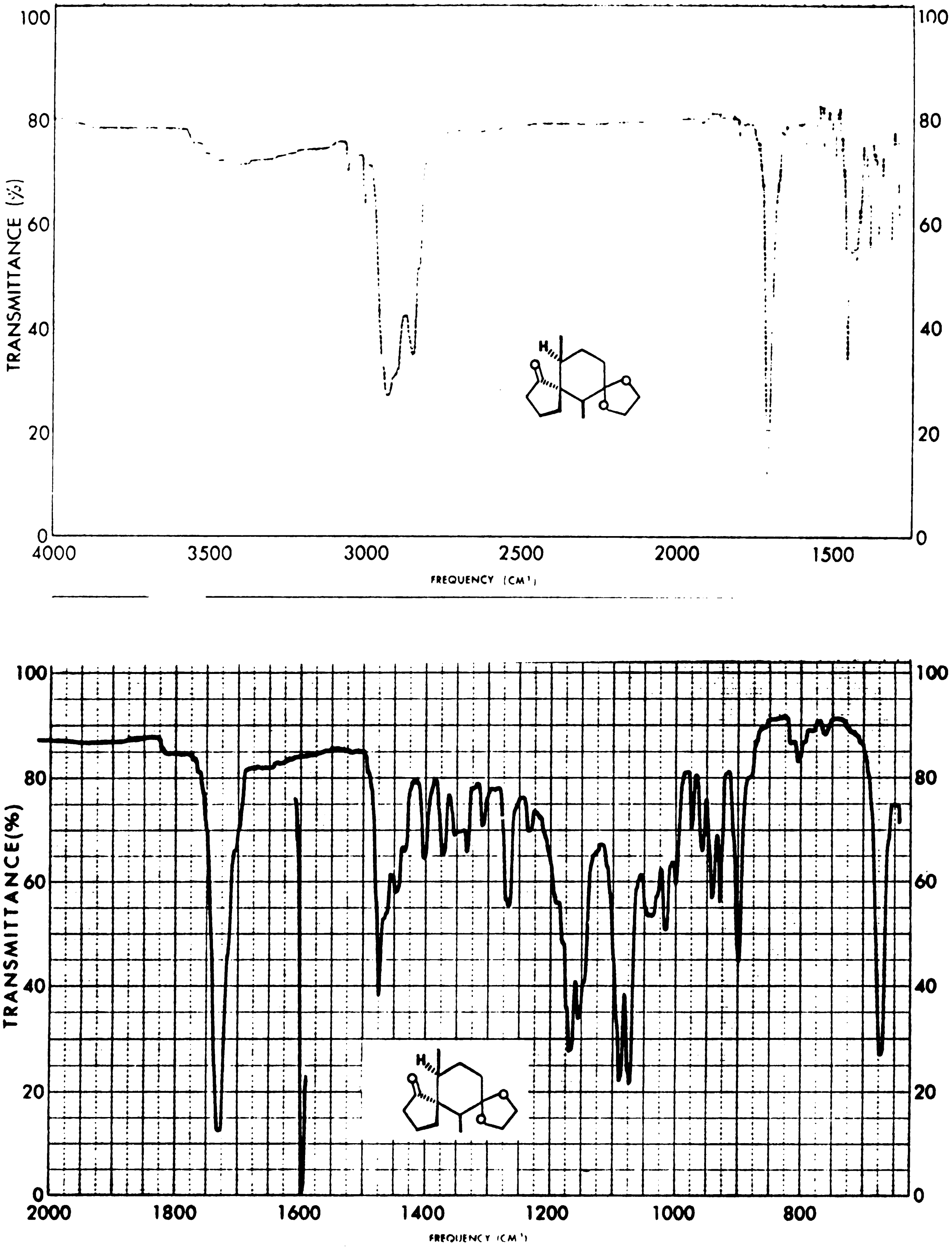


Figure 13. Infrared spectrum of 16

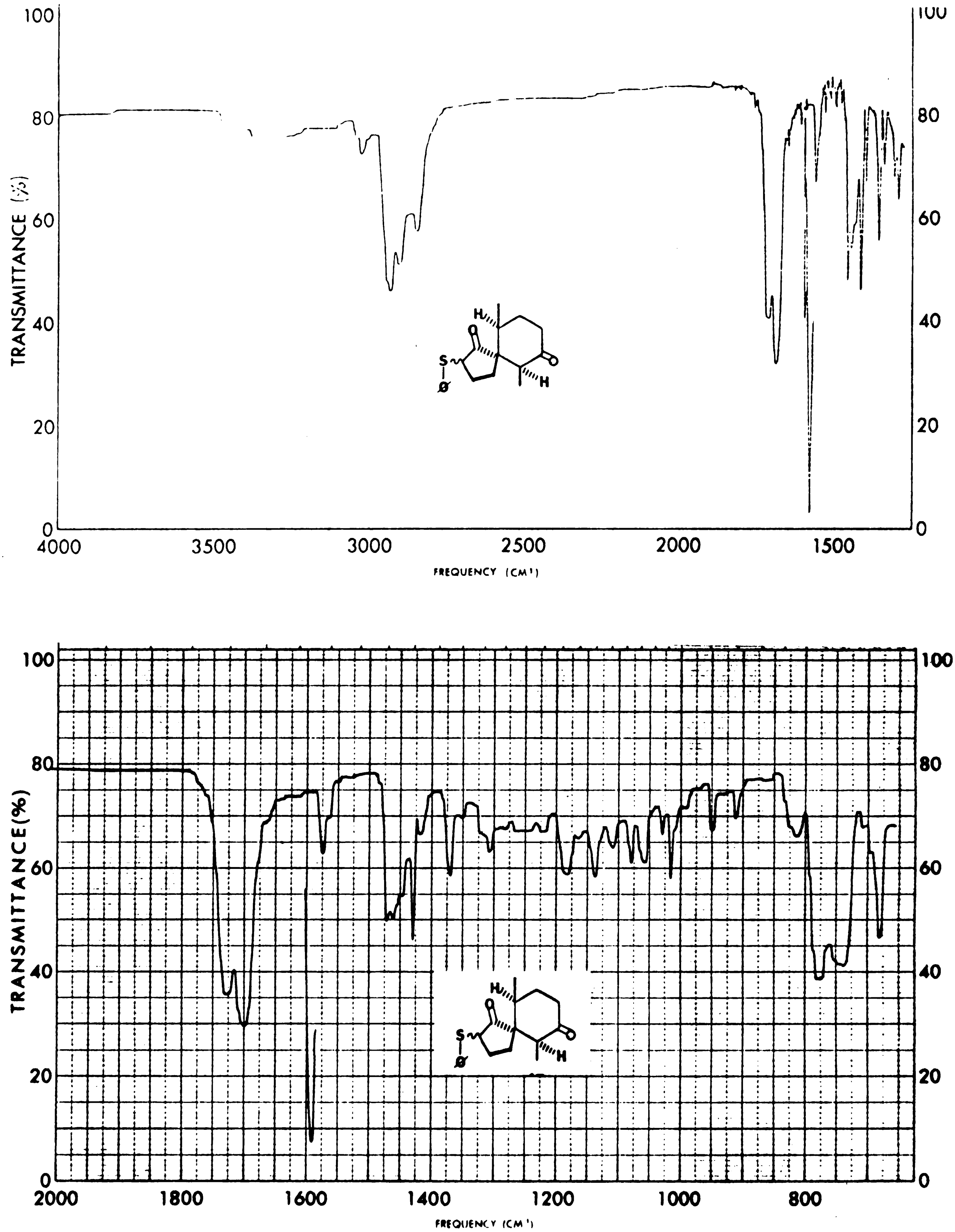


Figure 14. Infrared spectrum of 17

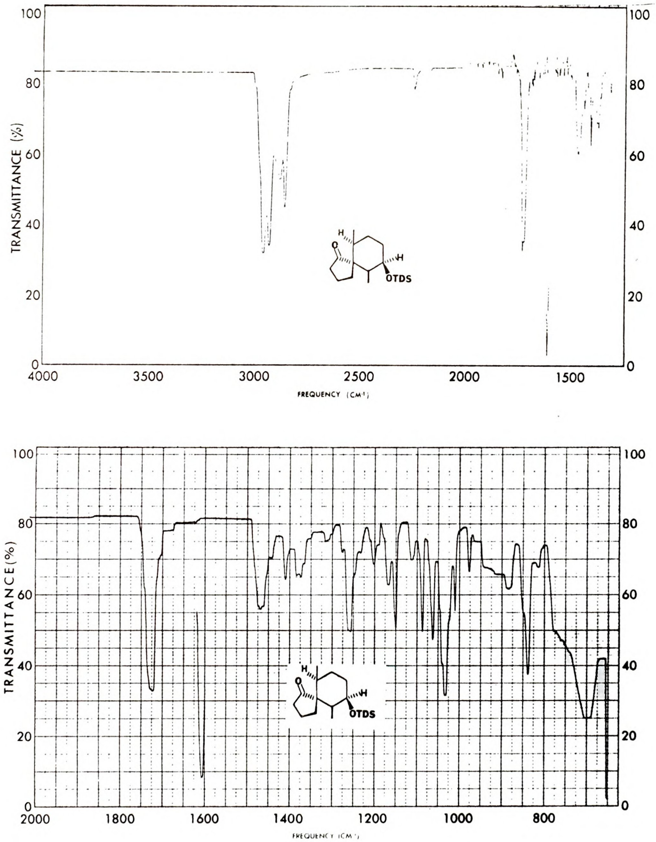


Figure 15. Infrared spectrum of 21

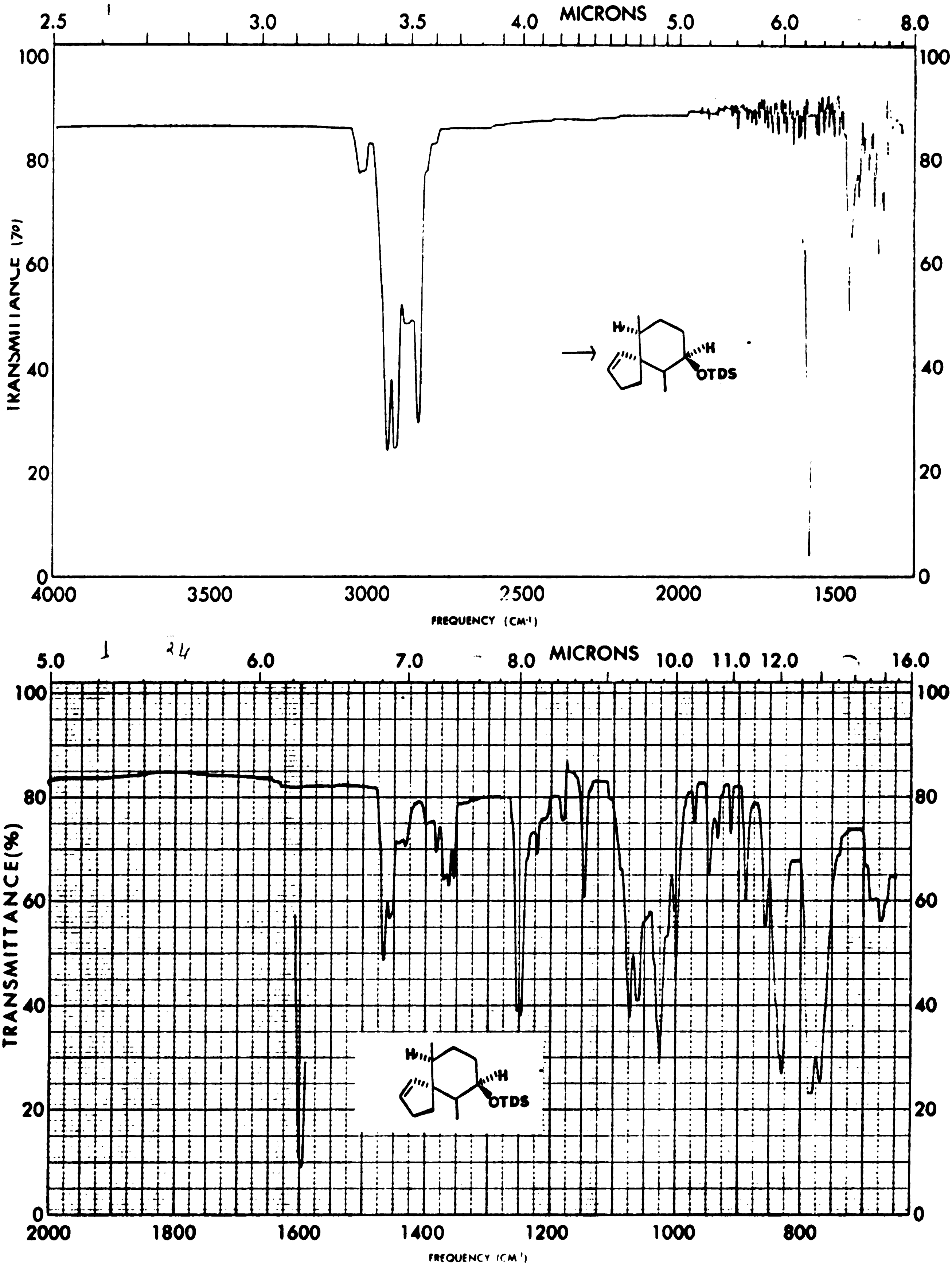


Figure 16. Infrared spectrum of 24

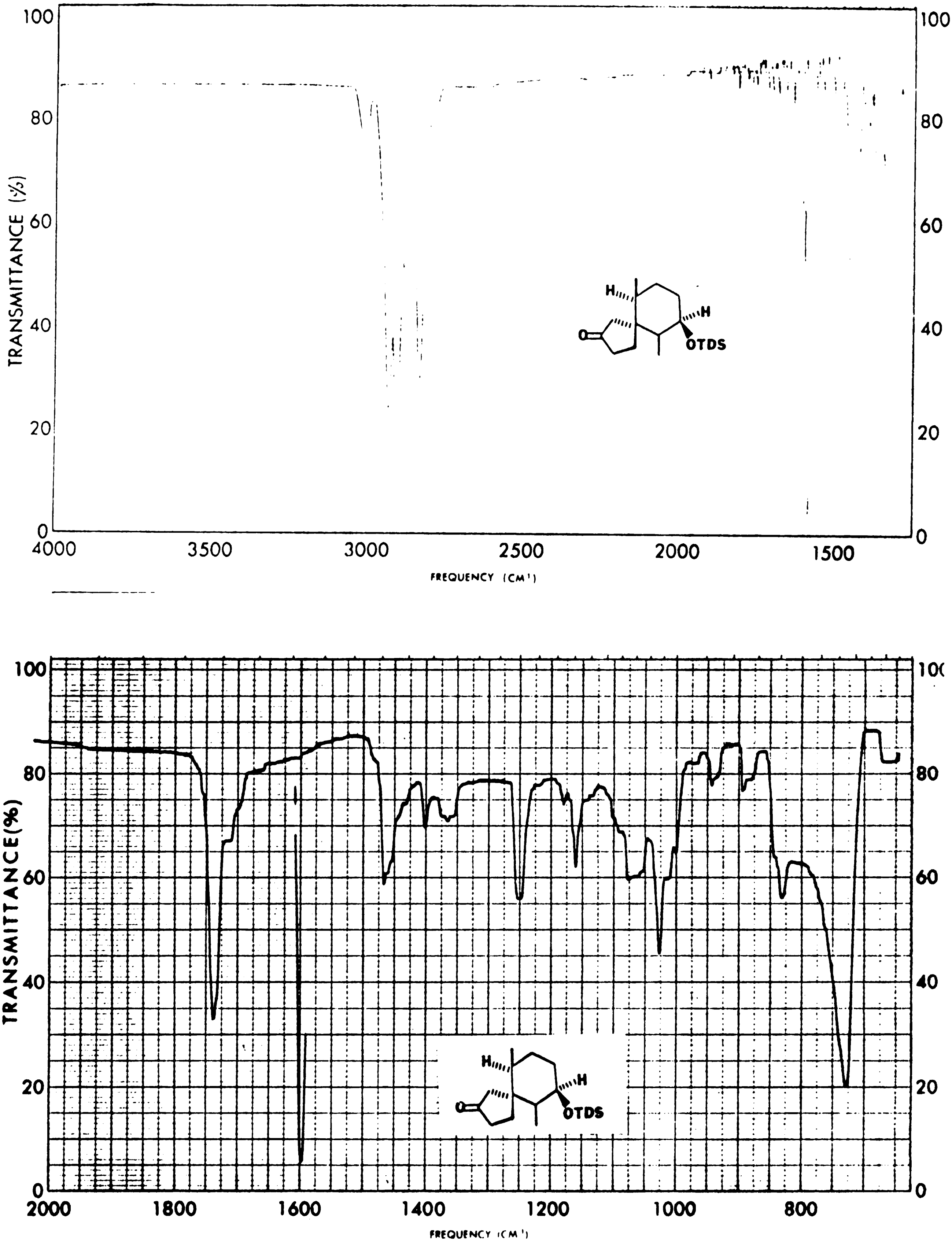


Figure 17. Infrared spectrum of 27

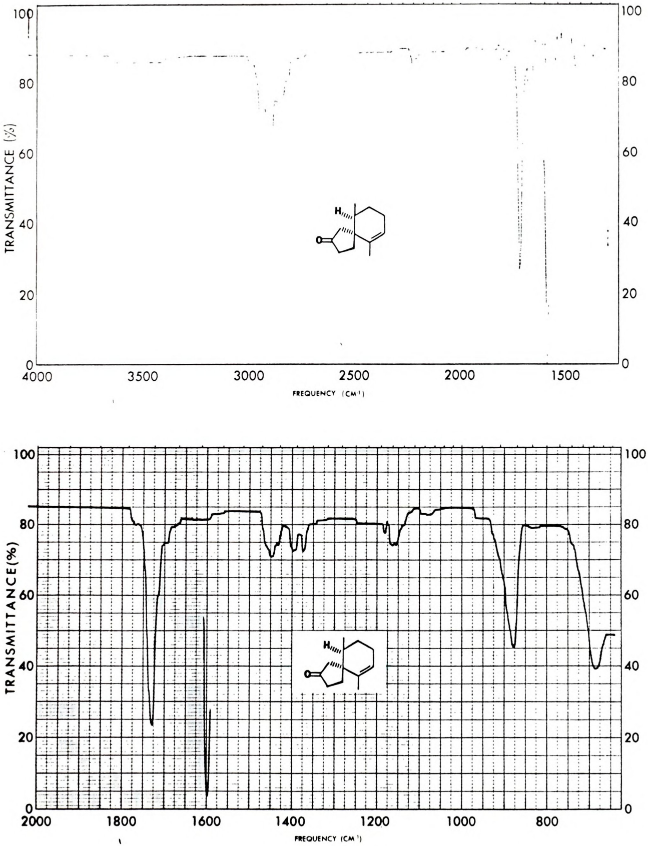


Figure 18. Infrared spectrum of **8**

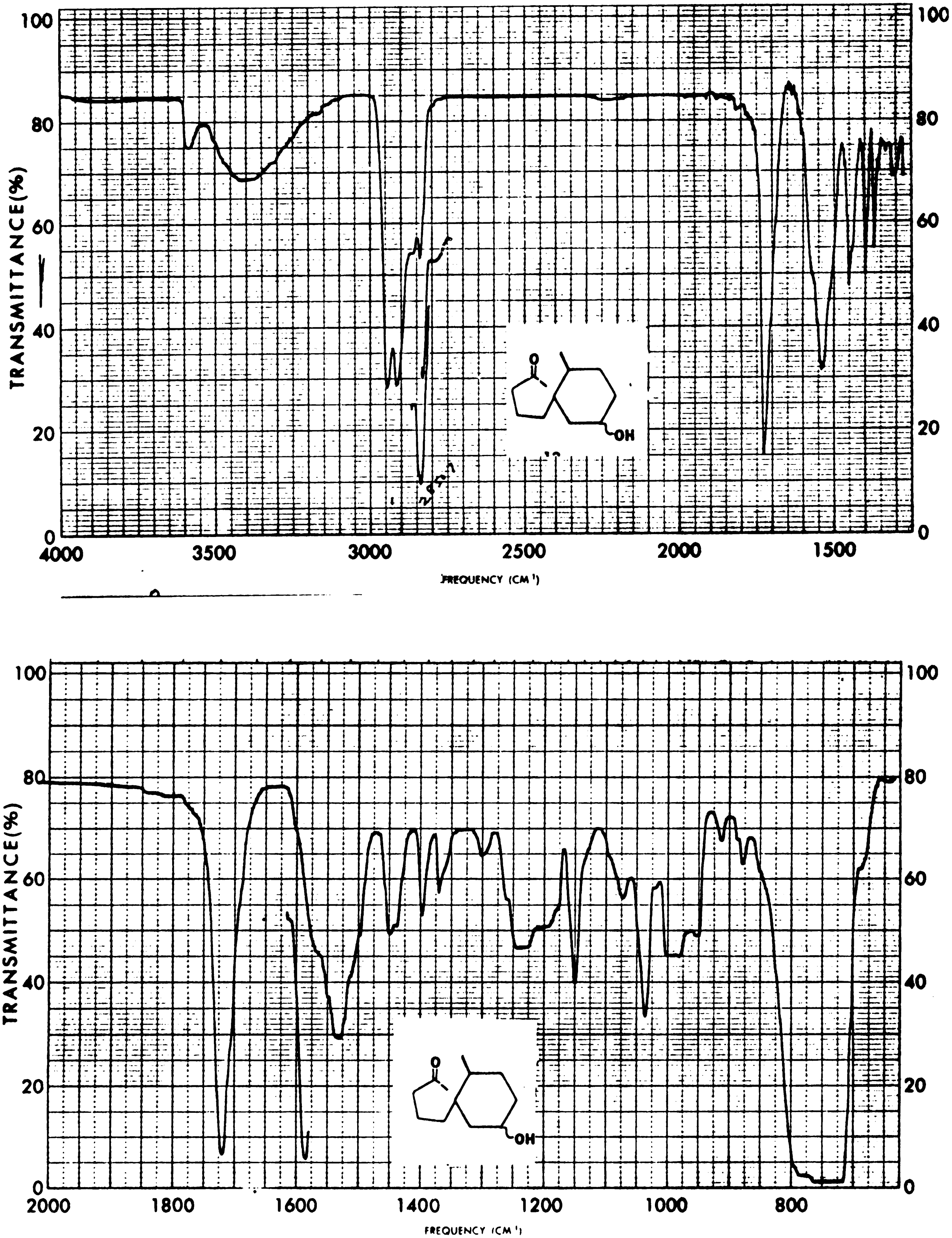


Figure 19. Infrared spectrum of equatorial alcohol 13

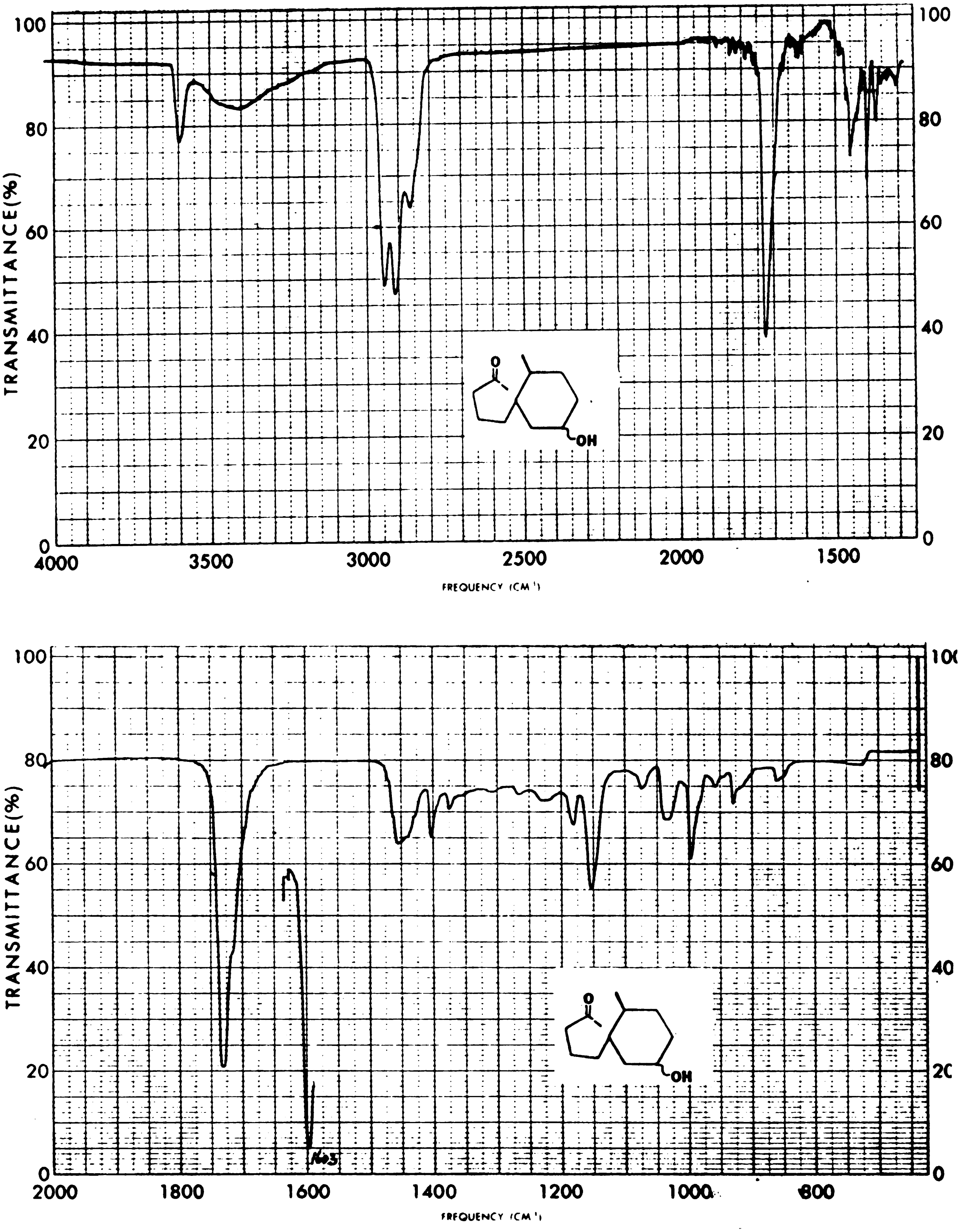
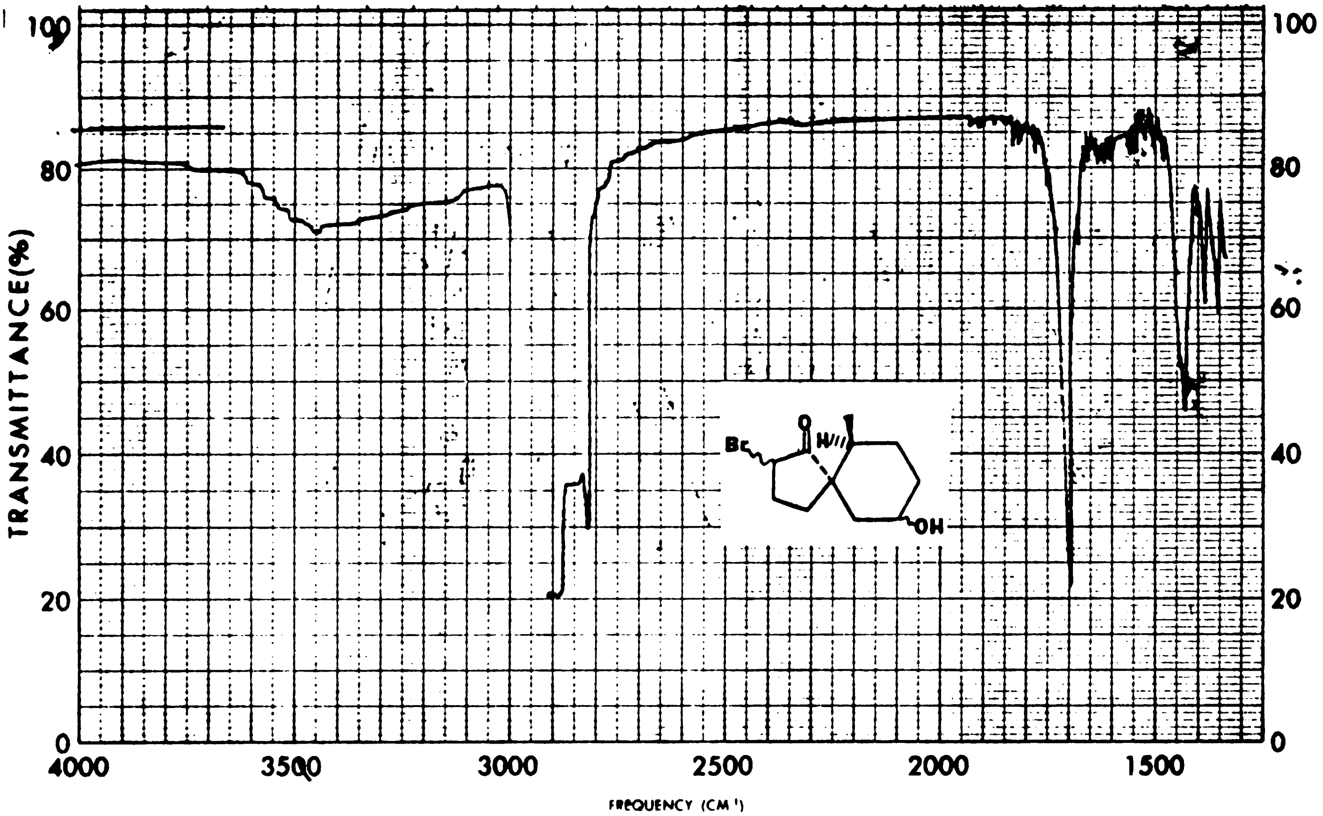


Figure 20. Infrared spectrum of axial alcohol **13**



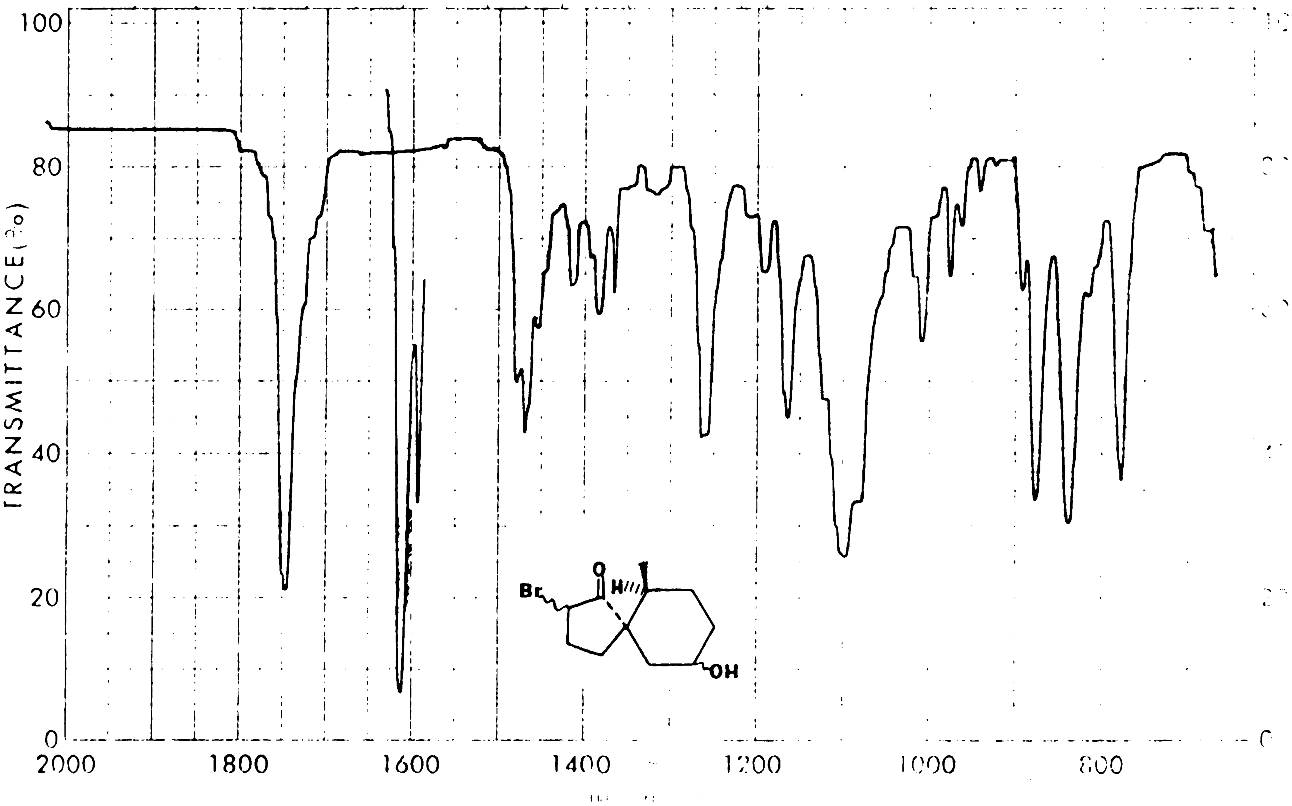


Figure 21. Infrared spectrum of 28

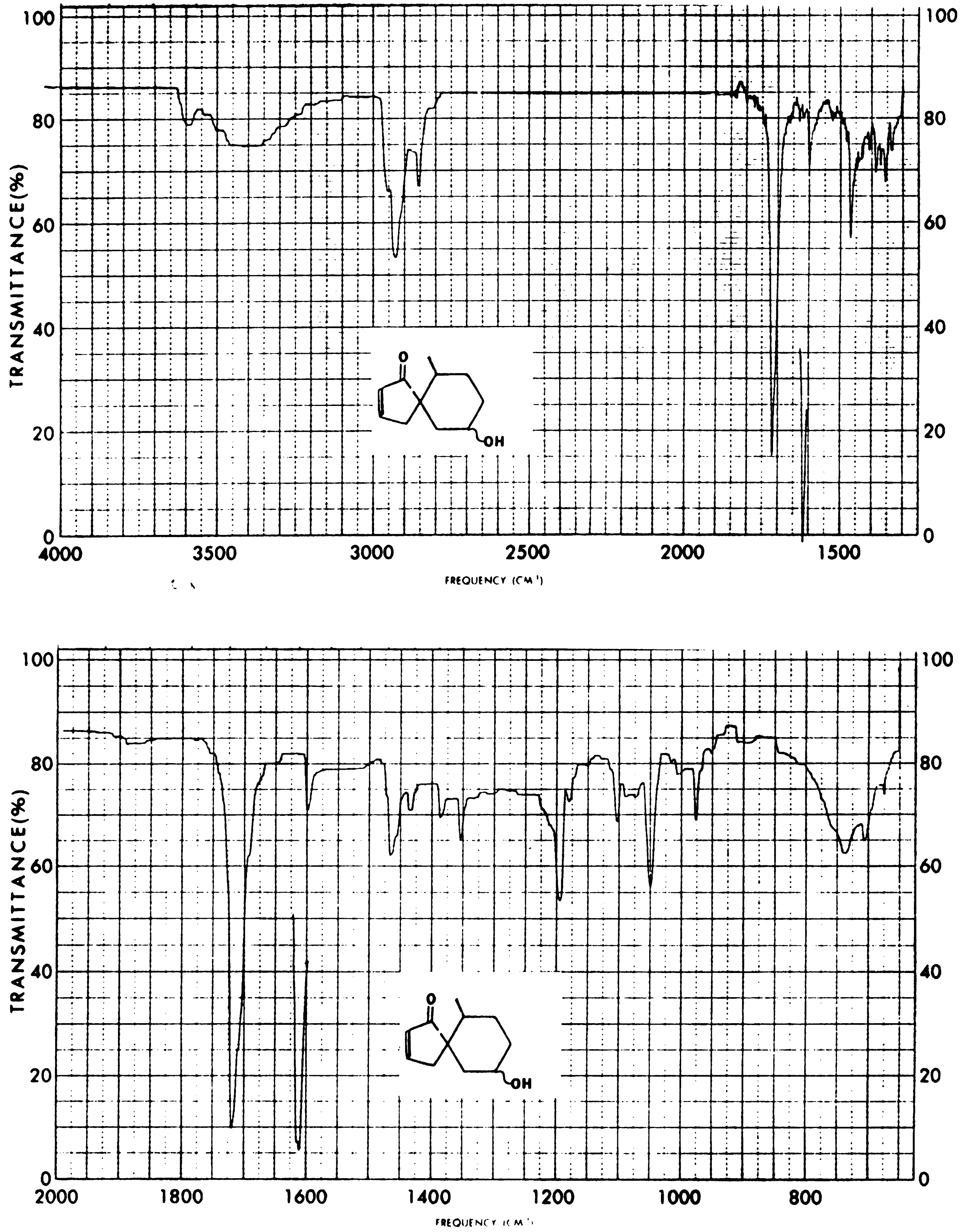


Figure 22. Infrared spectrum of 29

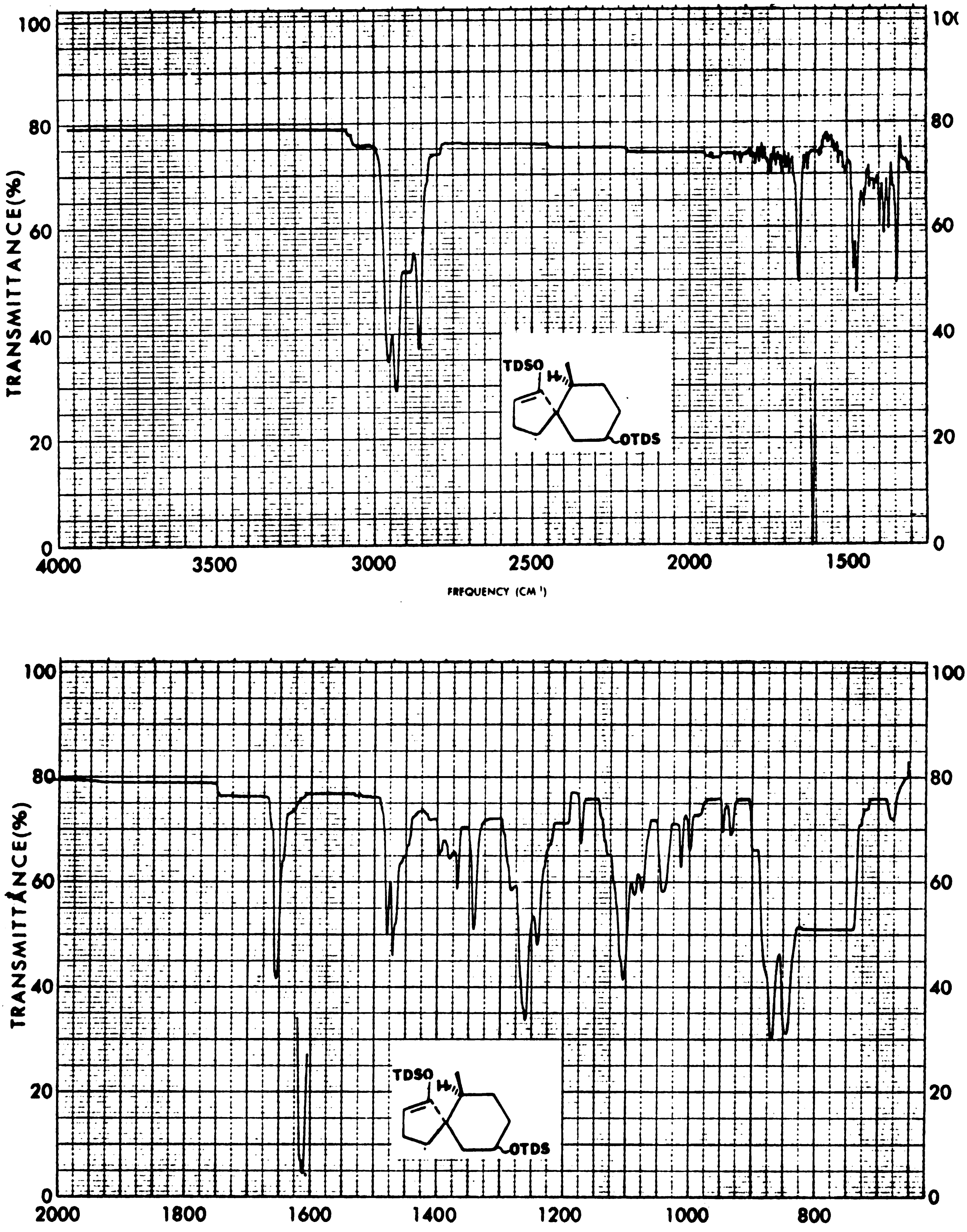


Figure 23. Infrared spectrum of 30

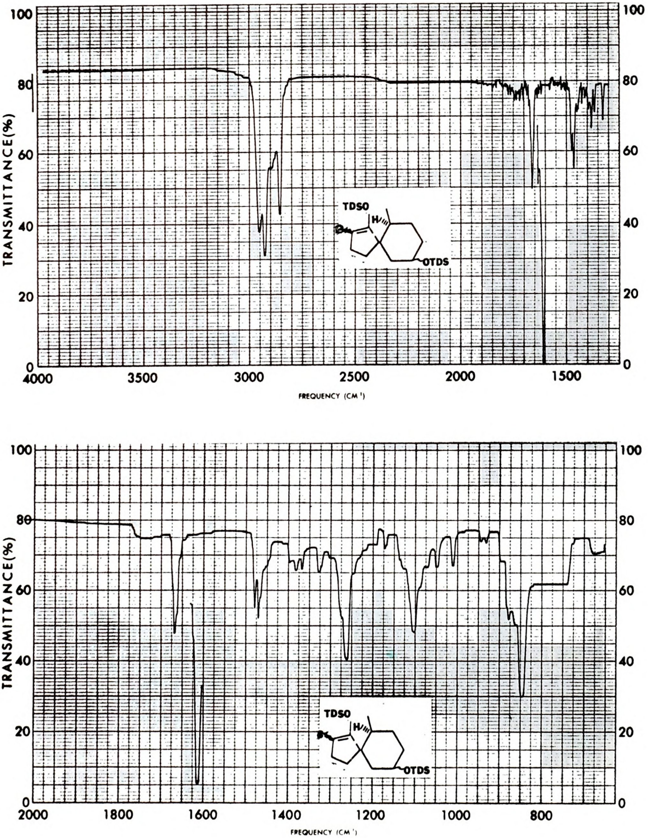
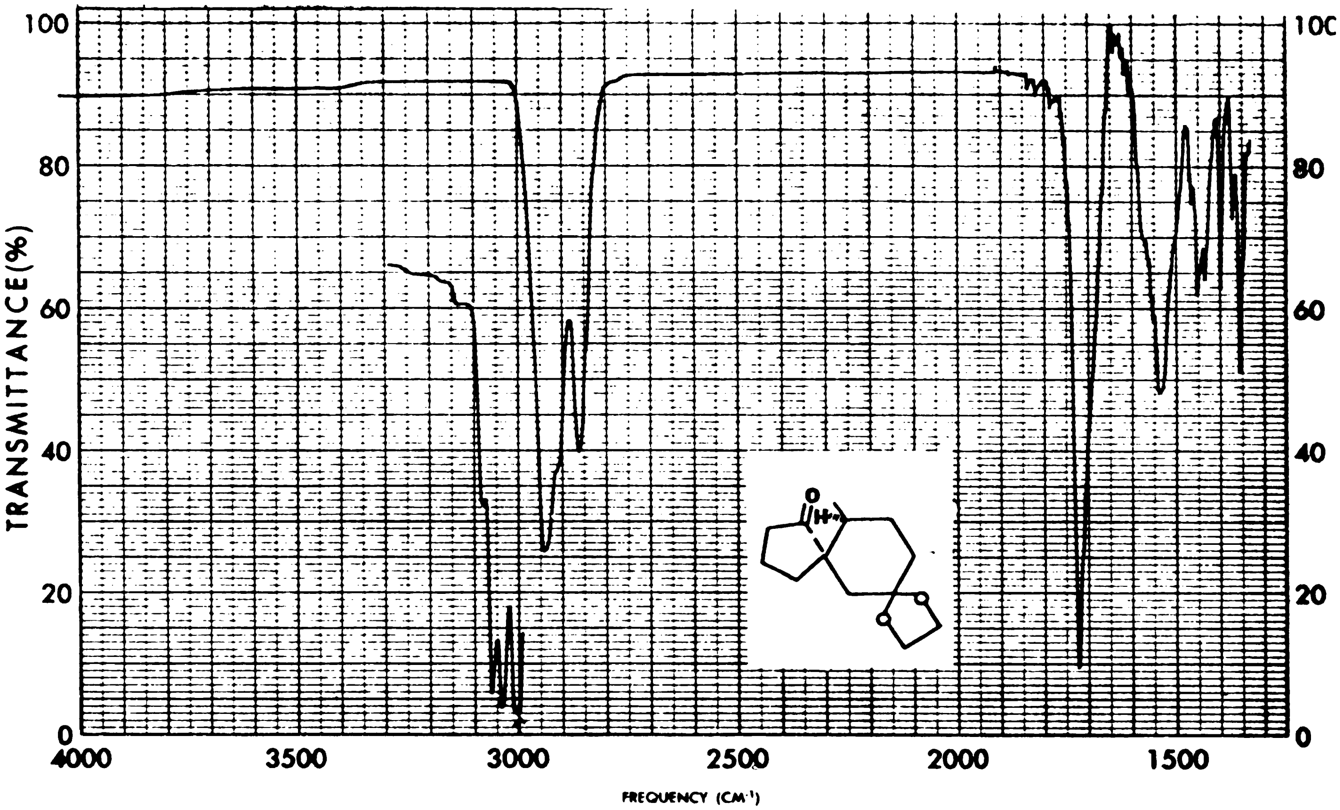


Figure 24. Infrared spectrum of 33



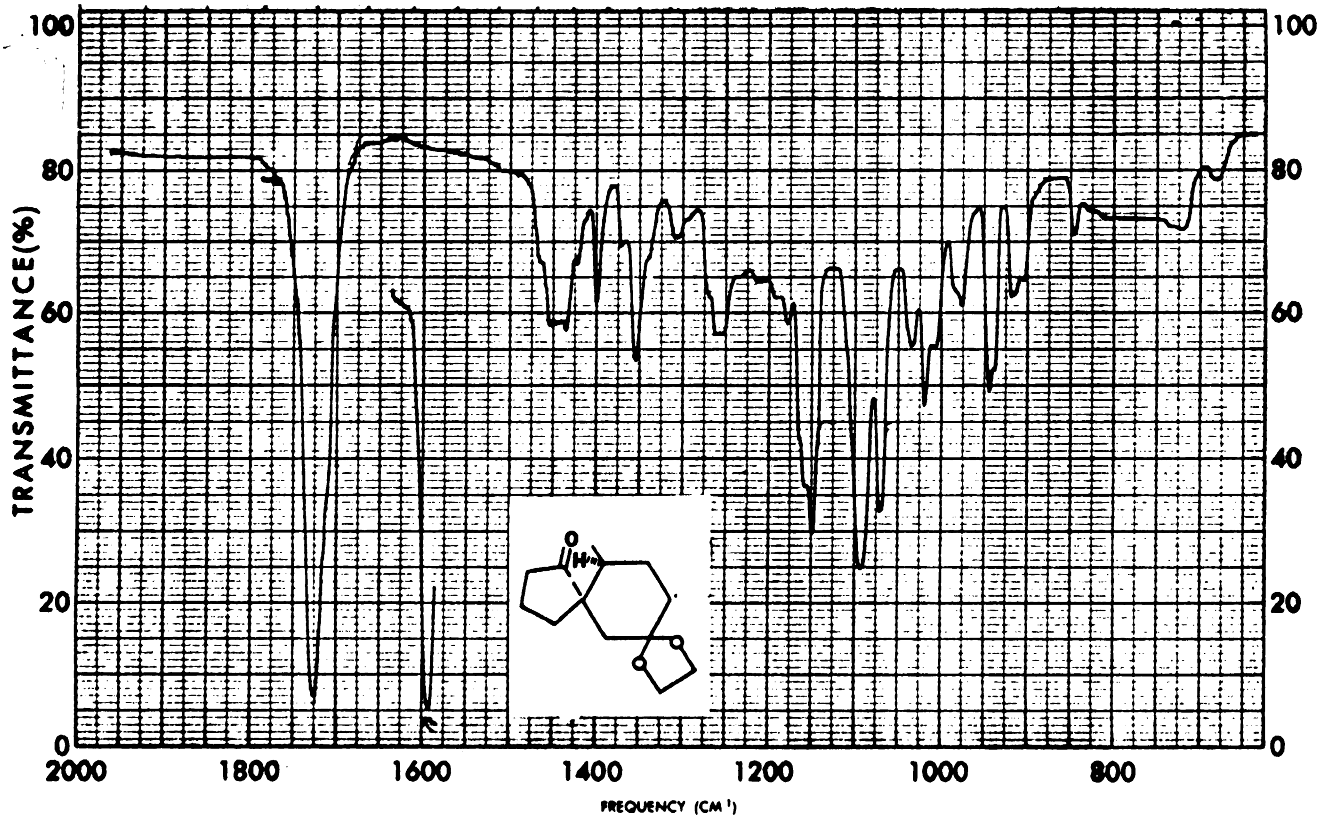


Figure 25. Infrared spectrum of 34

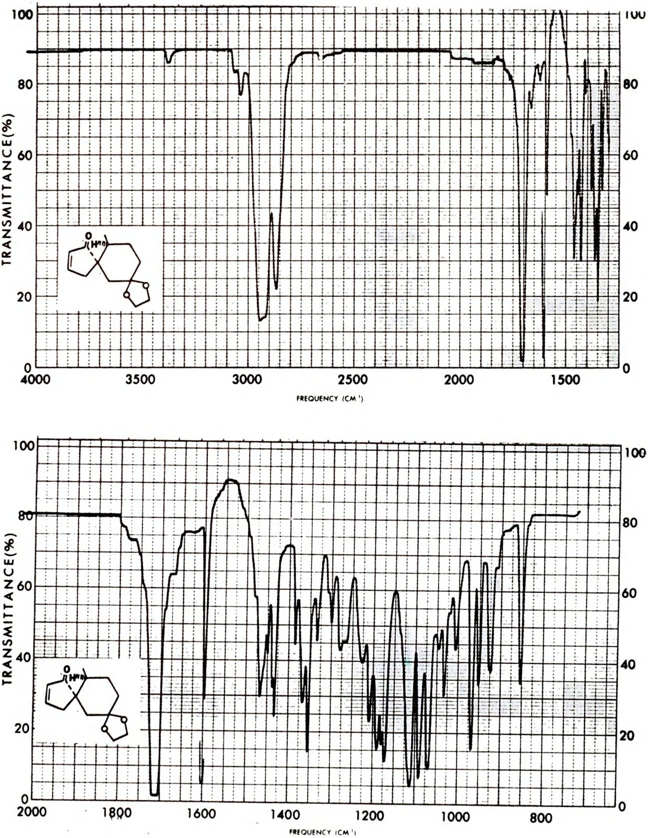


Figure 26. Infrared spectrum of 35

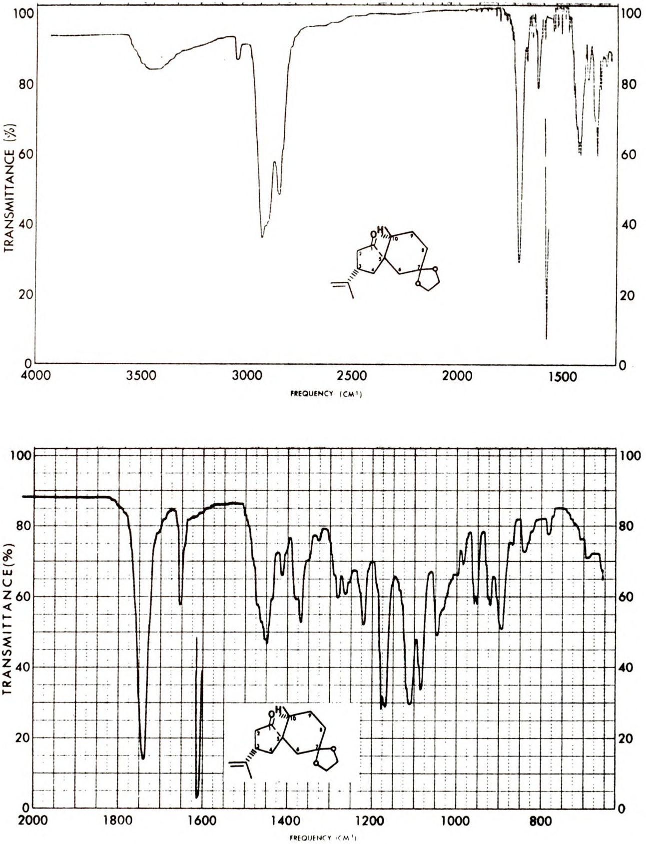


Figure 27. Infrared spectrum of 37

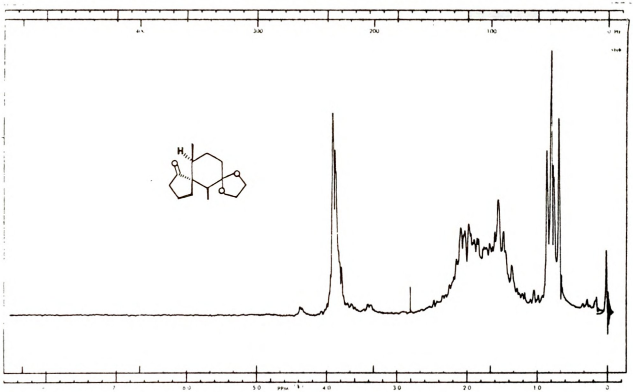


Figure 28a. ^{1}H NMR spectrum of 16

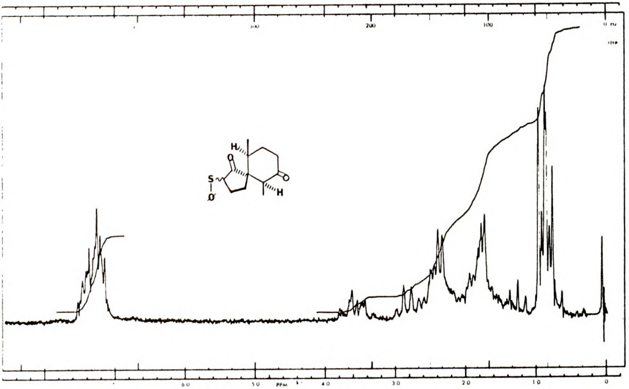


Figure 28b. ^{1}H NMR spectrum of 17

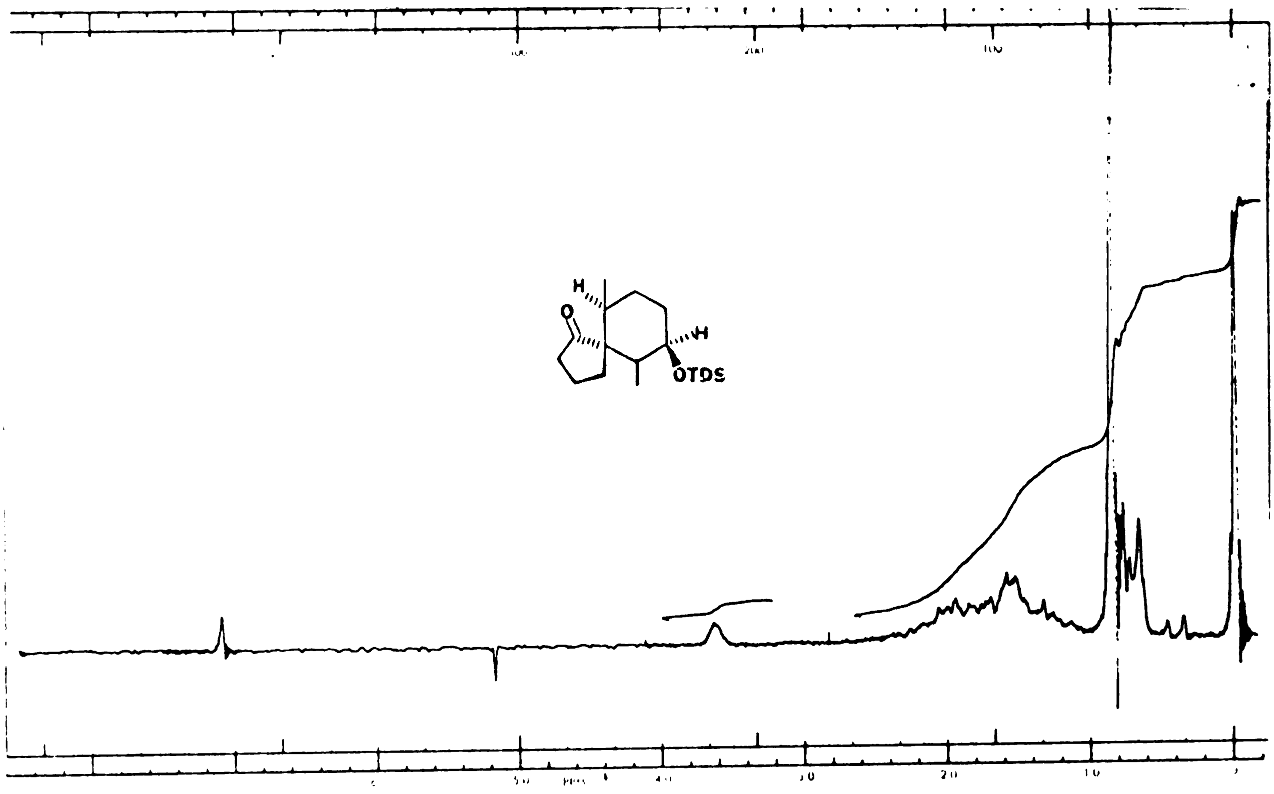


Figure 29a. ^{1}H NMR spectrum of 21

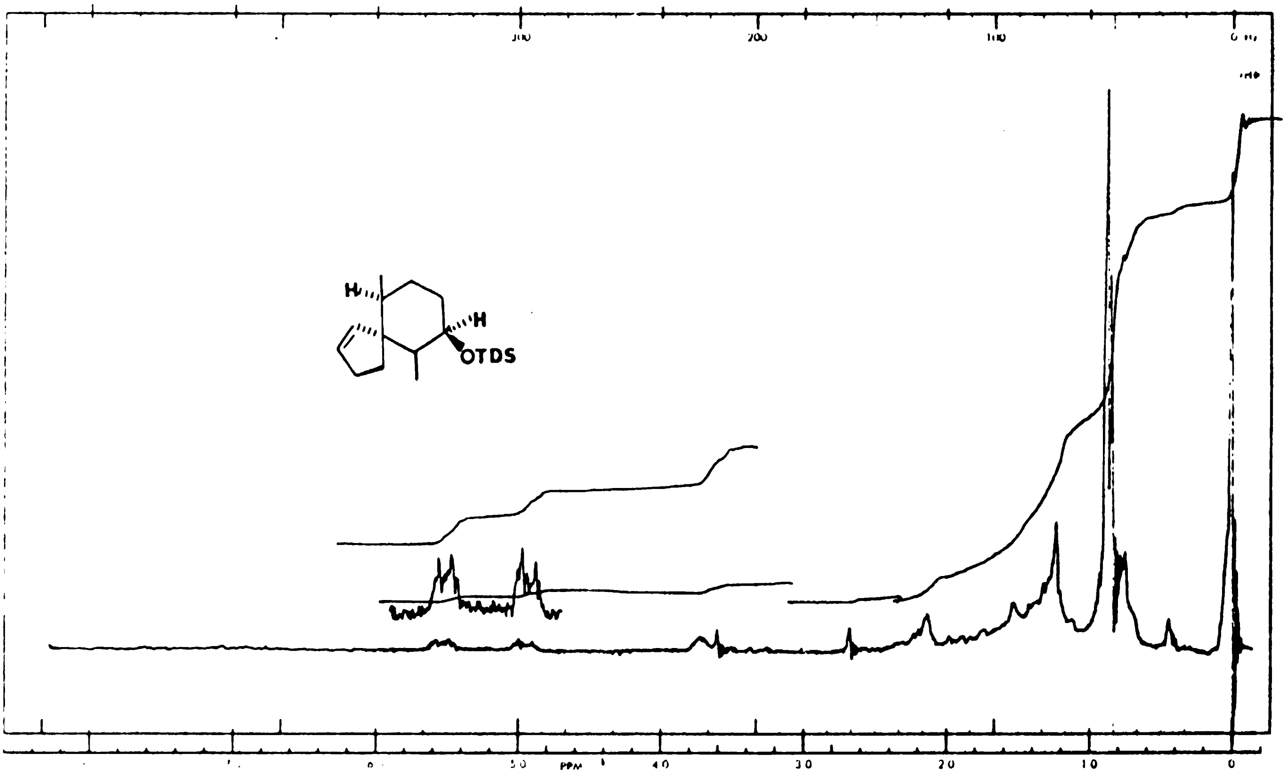


Figure 29b. ^{1}H NMR spectrum of 24

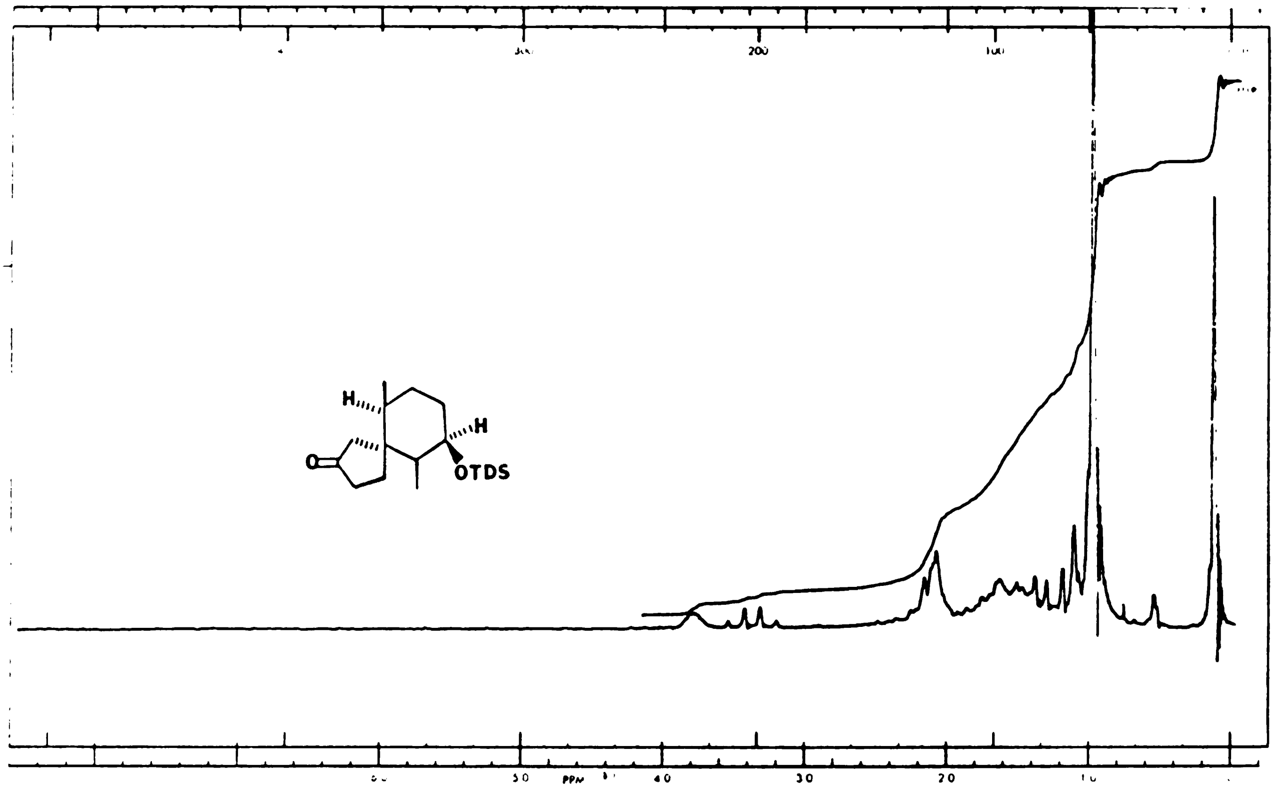


Figure 30a. ^{1}H NMR spectrum of 27

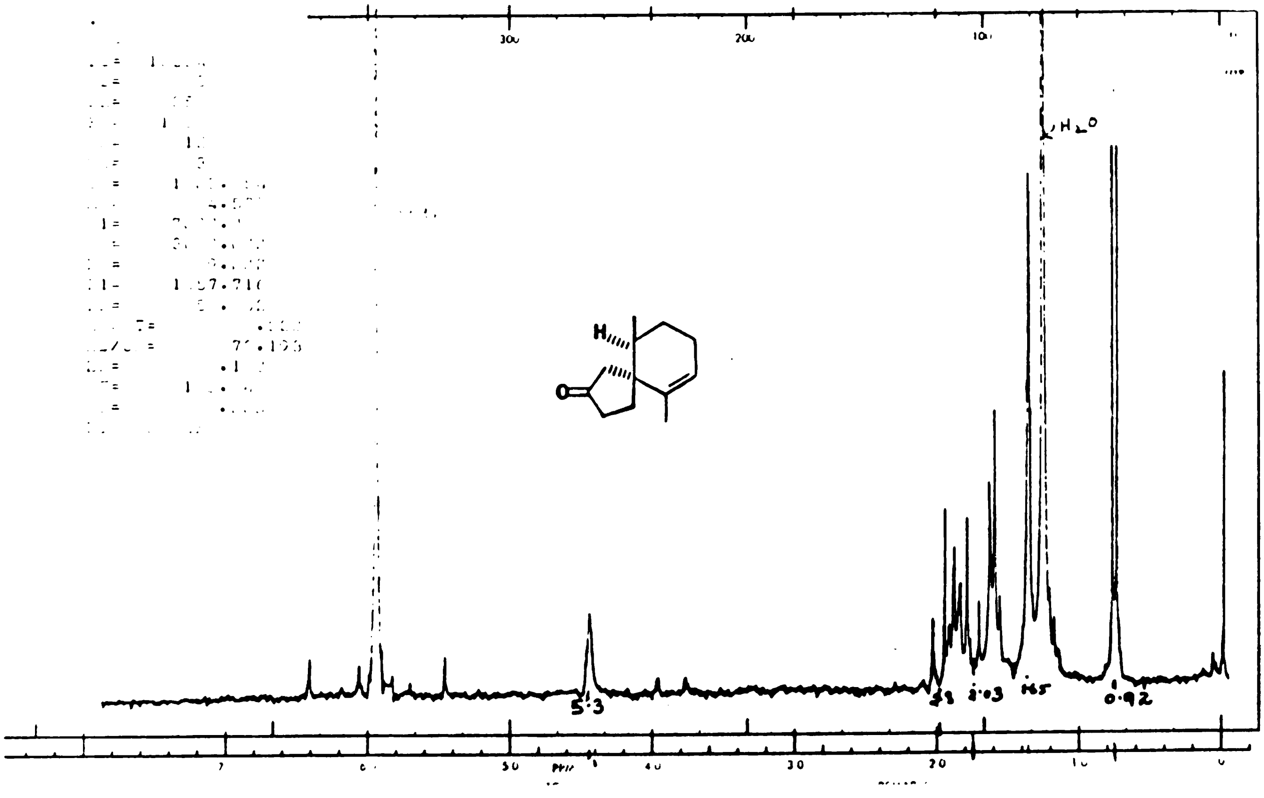


Figure 30b. ^{1}H NMR (180 MHz) spectrum of 8

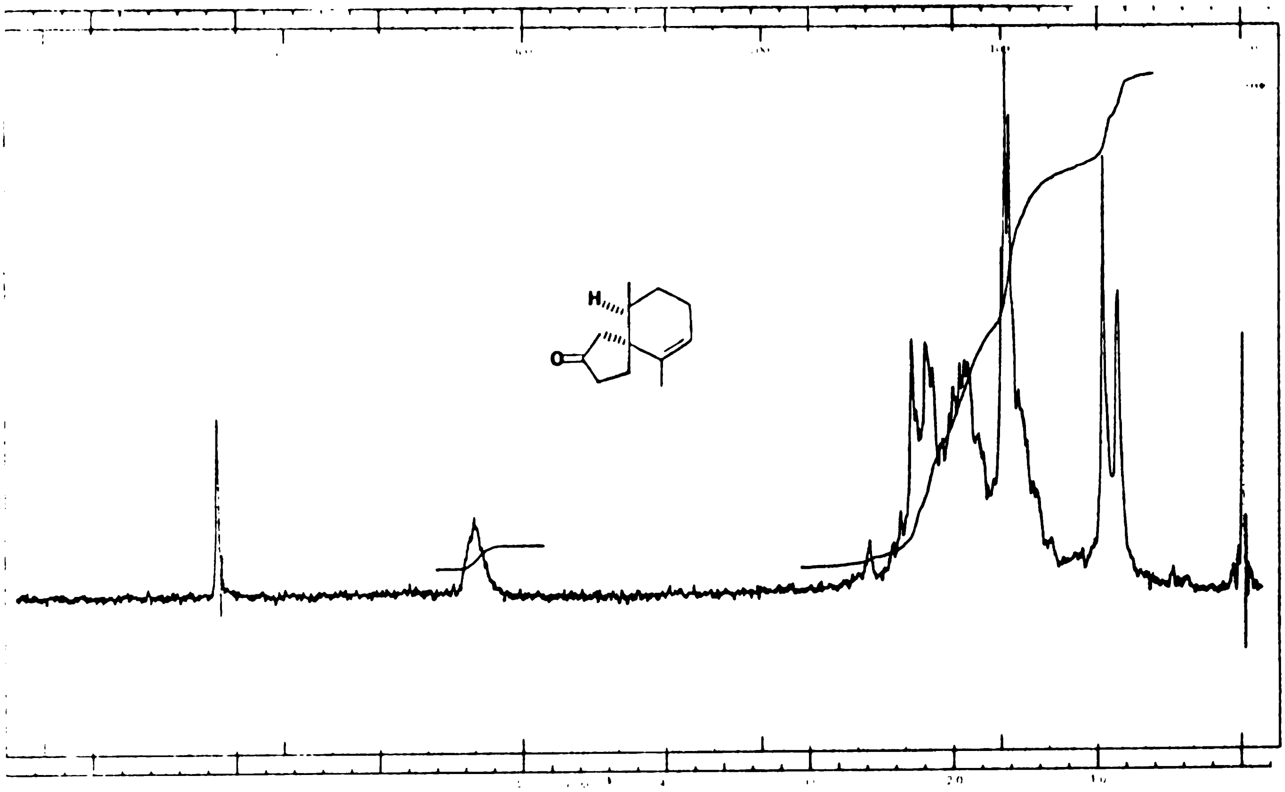


Figure 31a. ^{1}H NMR spectrum of 8

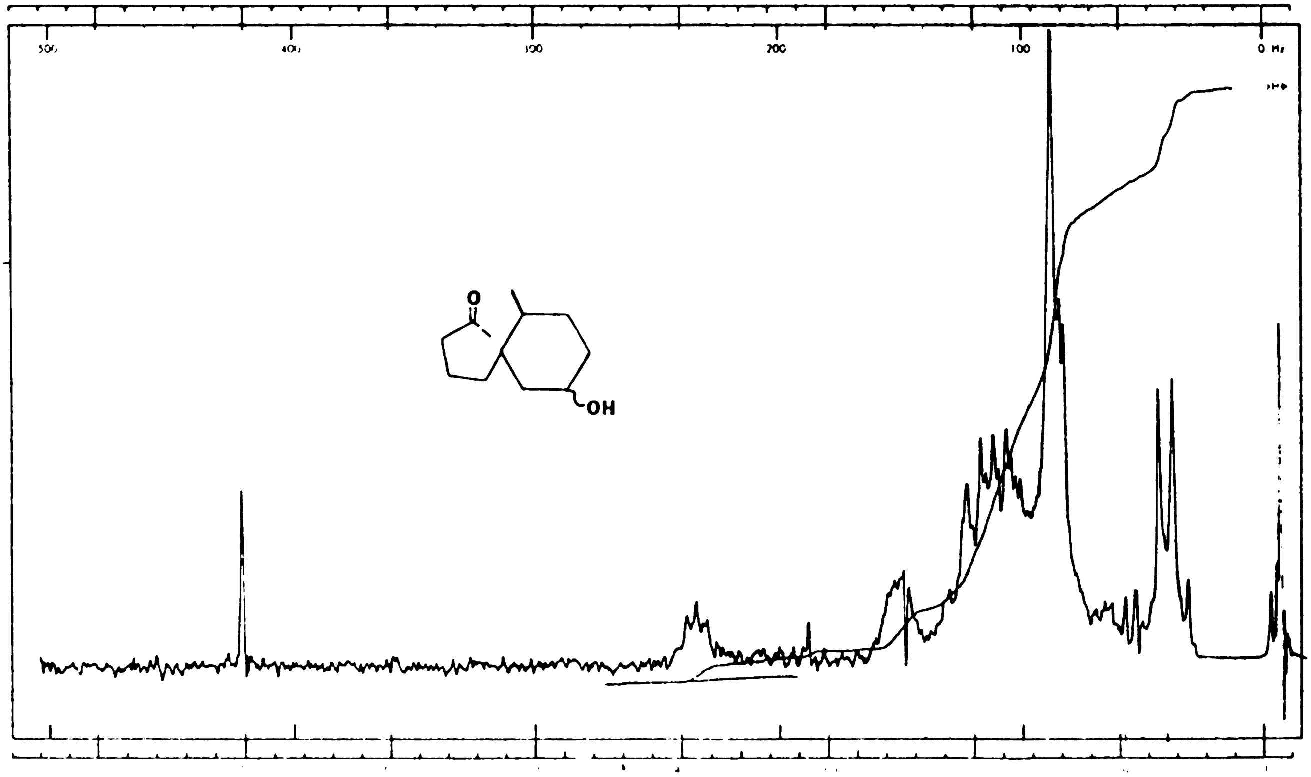


Figure 31b. ^{1}H NMR spectrum of axial alcohol 13

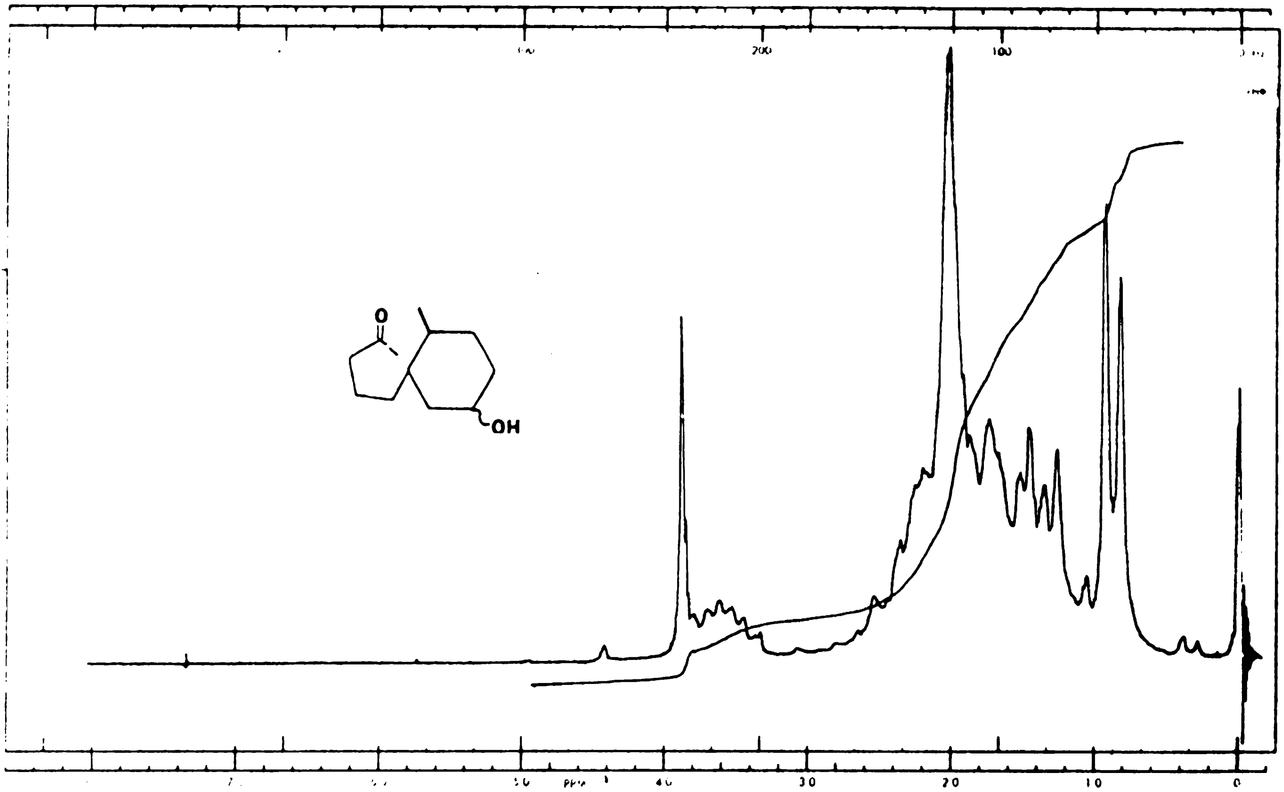


Figure 32a. ^{1}H NMR spectrum of equatorial alcohol 13

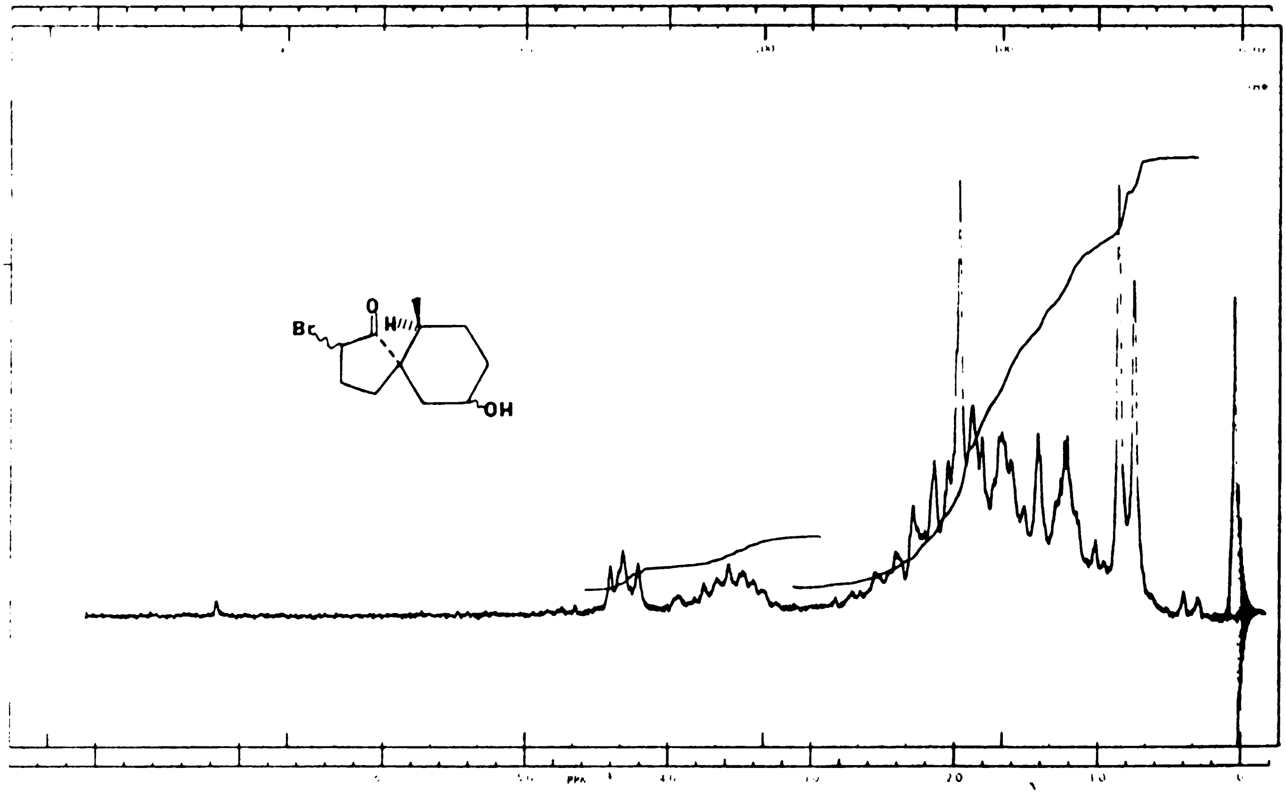


Figure 32b. ^{1}H NMR spectrum of 28

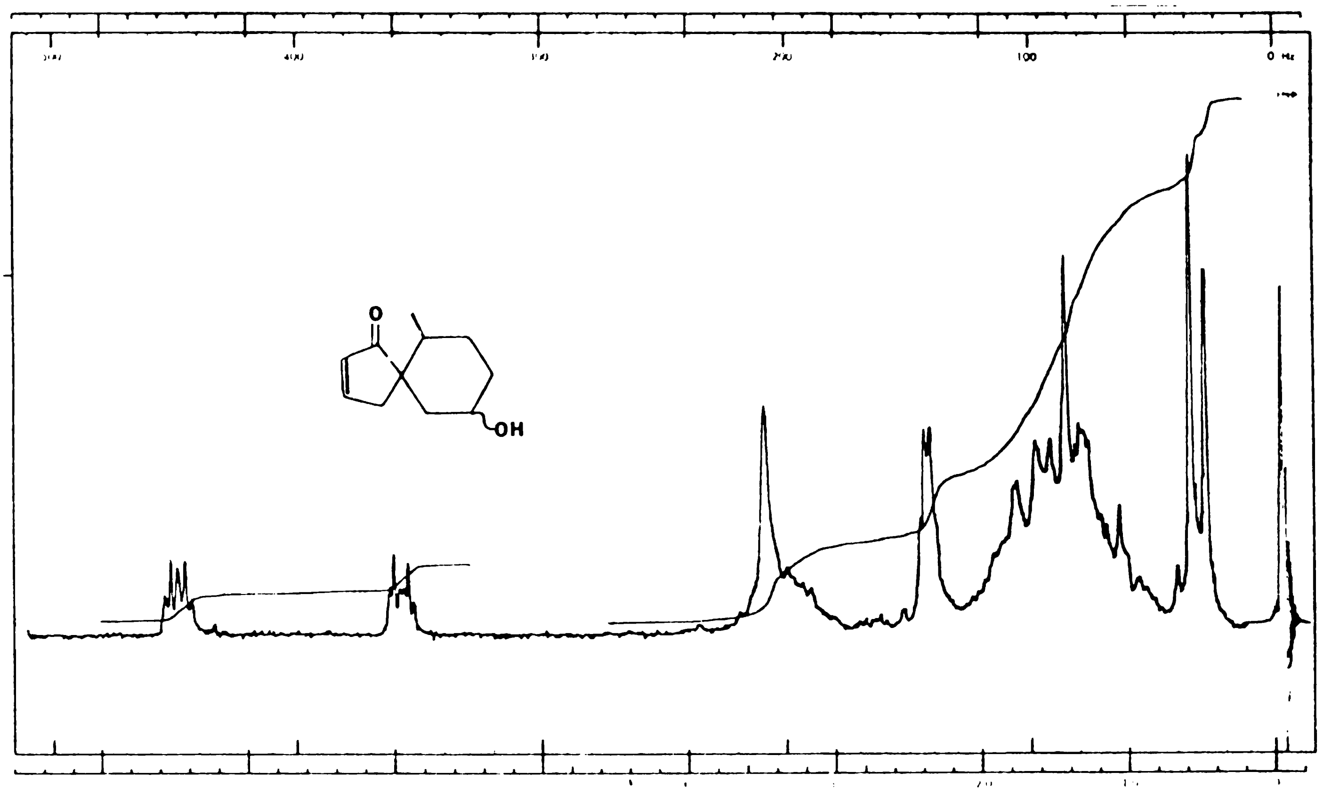


Figure 33a. ^{1}H NMR spectrum of 29

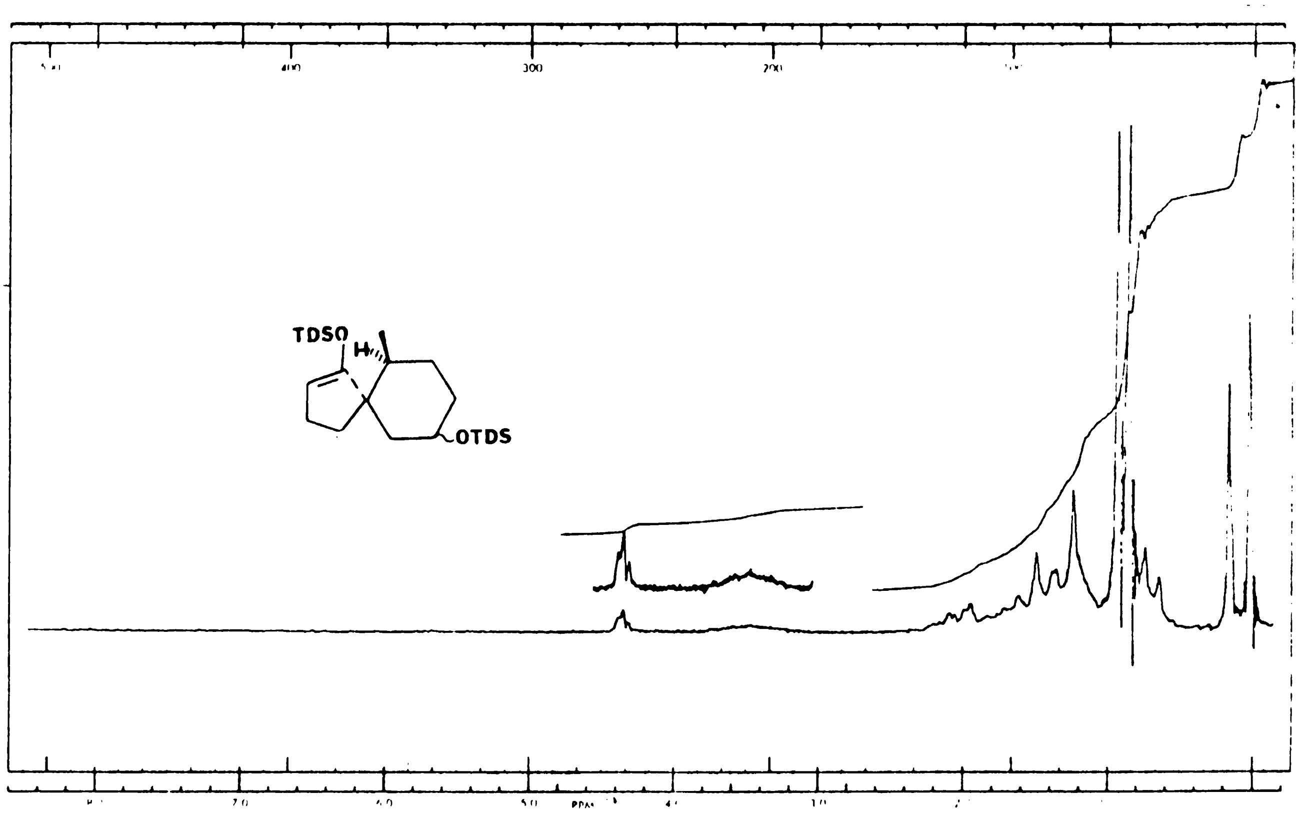


Figure 33b. ^{1}H NMR spectrum of 30

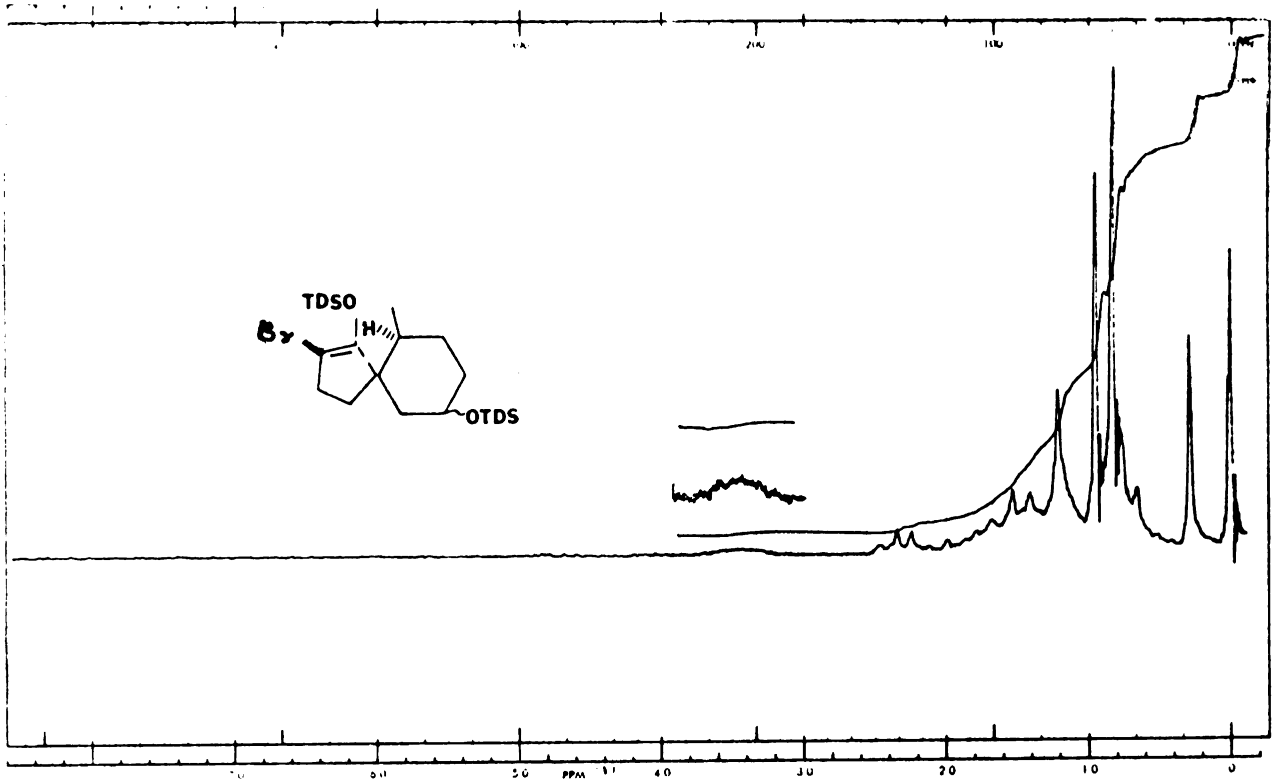


Figure 34a. ^{1}H NMR spectrum of 33

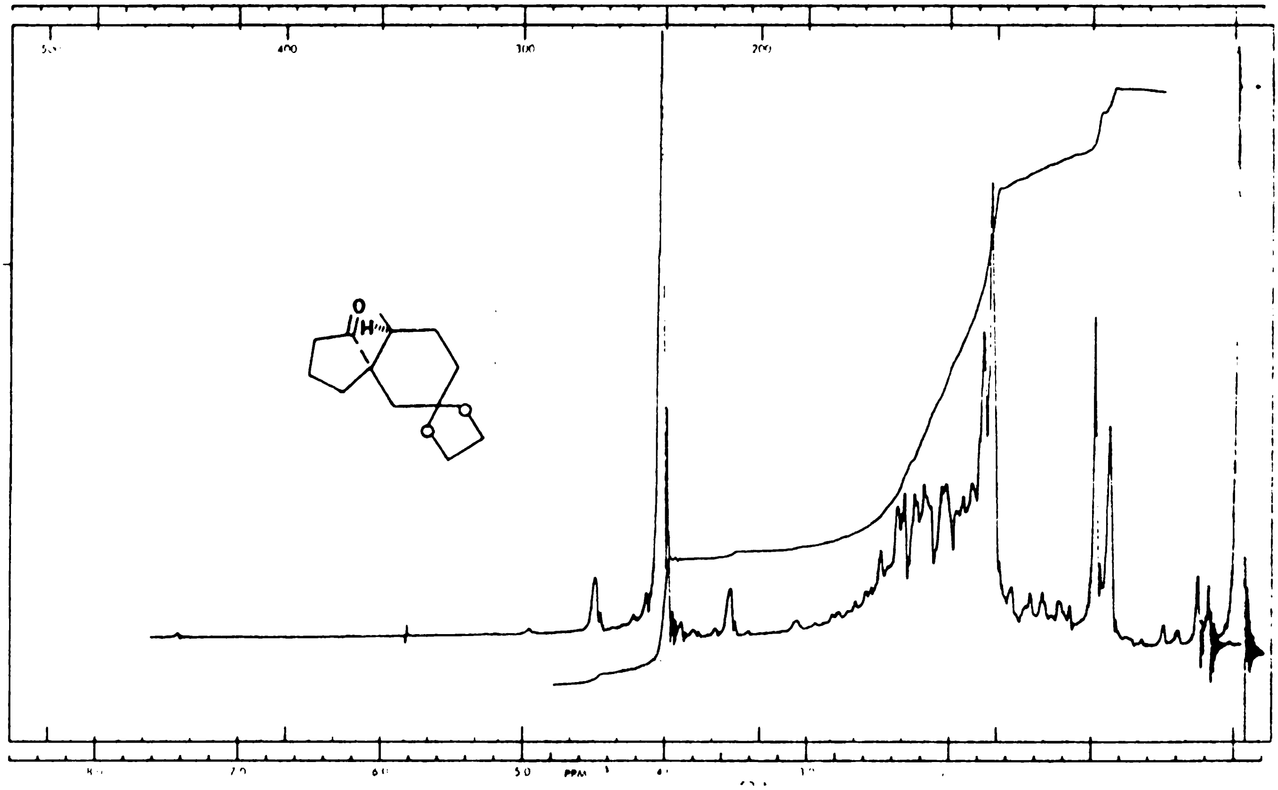


Figure 34b. ^{1}H NMR spectrum of 34

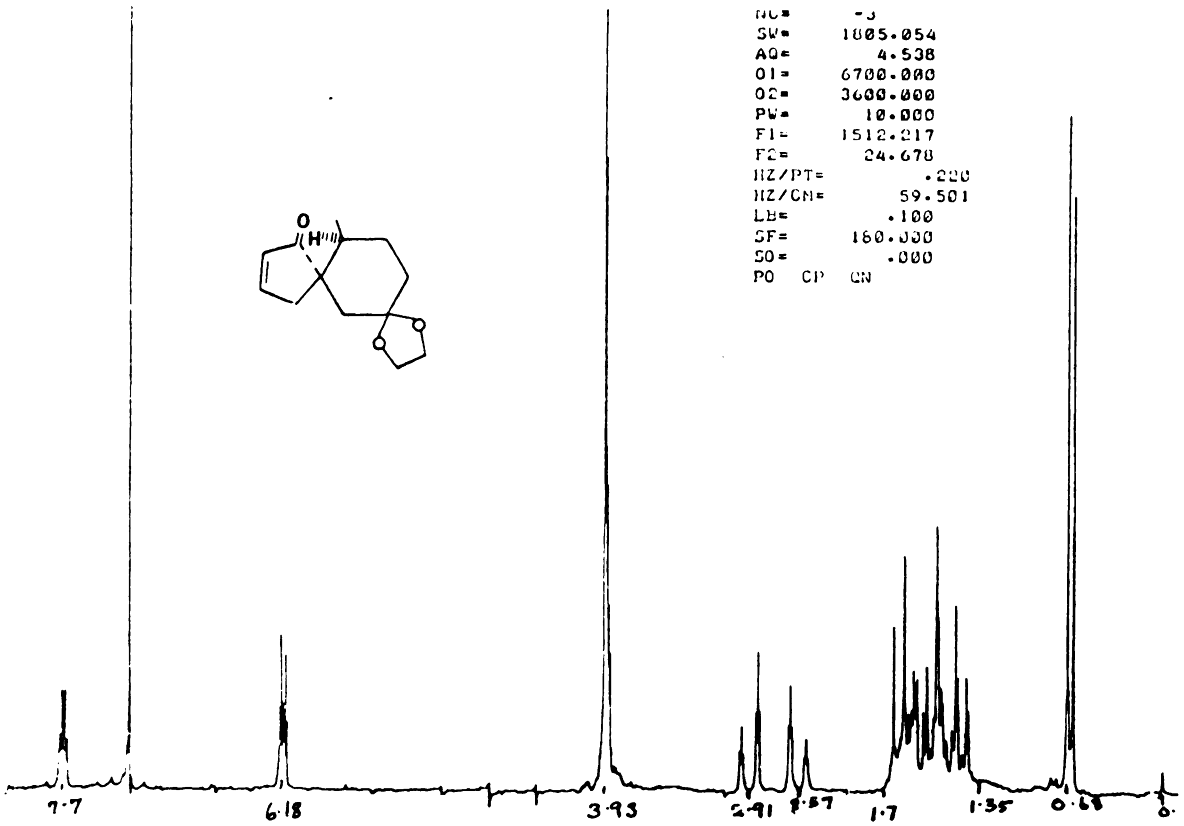


Figure 35a. ^{1}H NMR (180 MHz) spectrum of 35

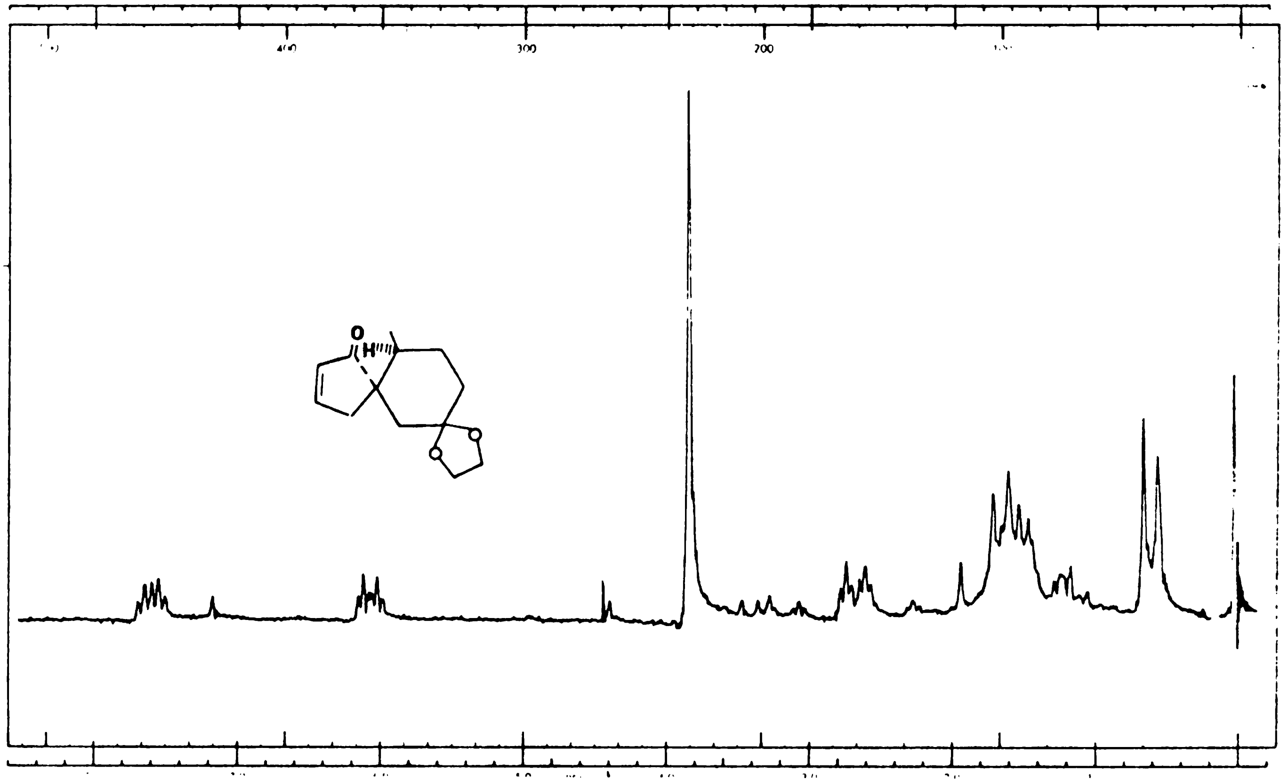


Figure 35b. ^{1}H NMR spectrum of 35

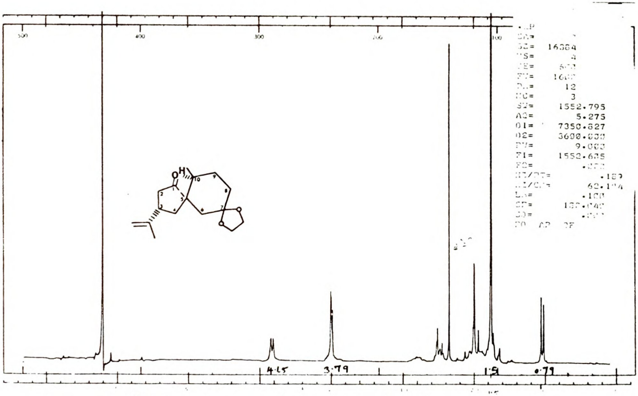


Figure 36a. ¹H NMR (180 MHz) spectrum of 37

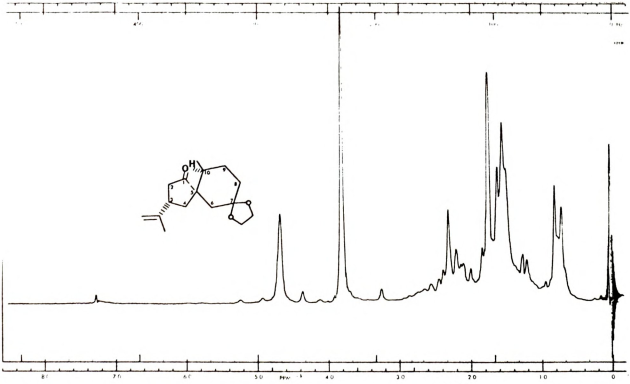


Figure 36b. ¹H NMR spectrum of 37

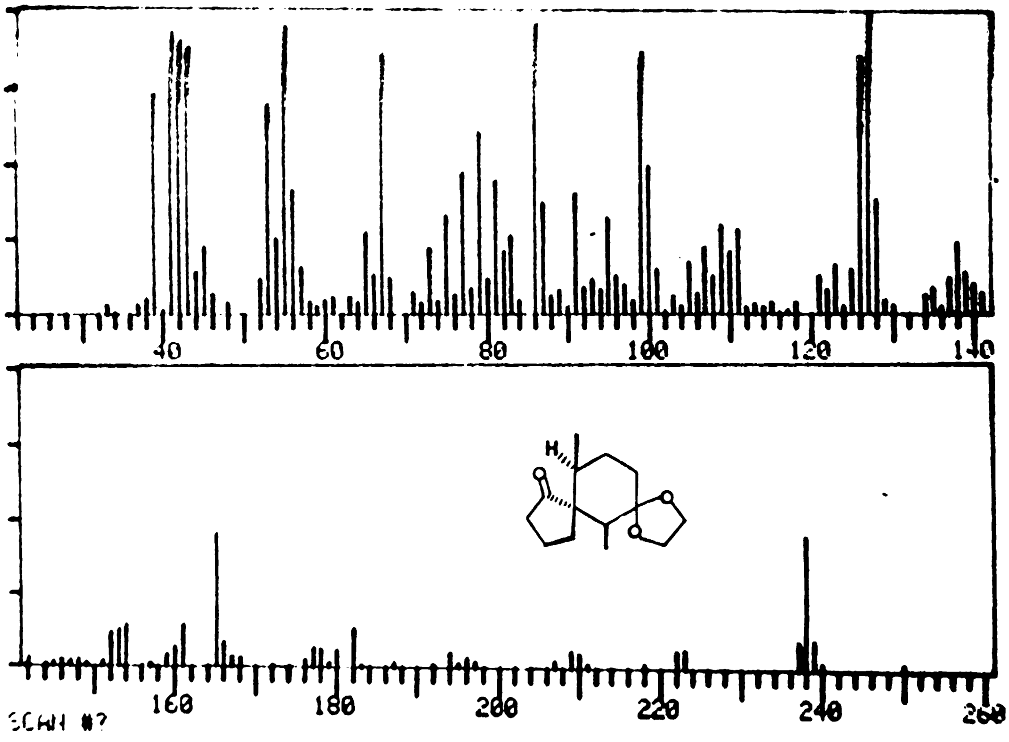


Figure 37a. Mass spectrum of 16

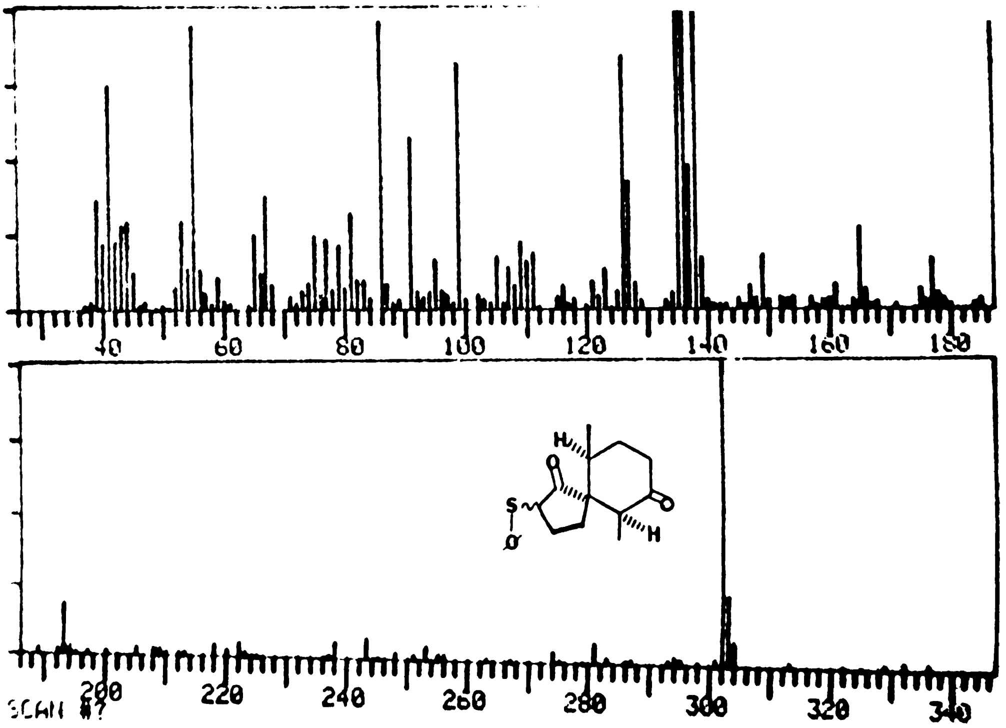


Figure 37b. Mass spectrum of 17

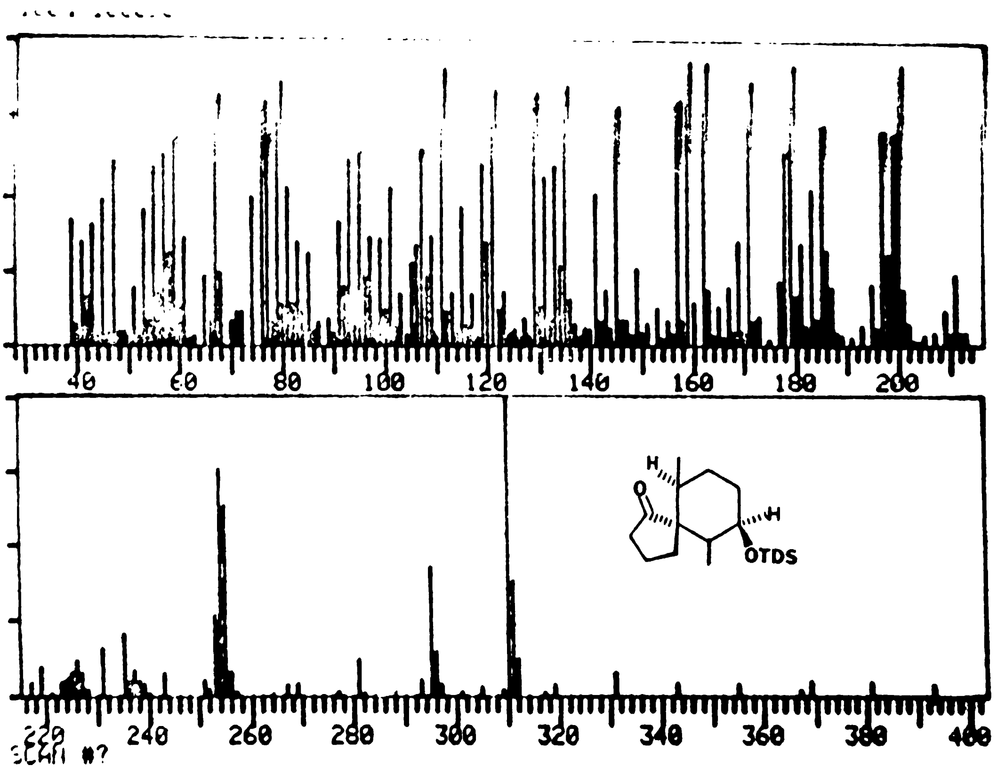


Figure 38a. Mass spectrum of 21

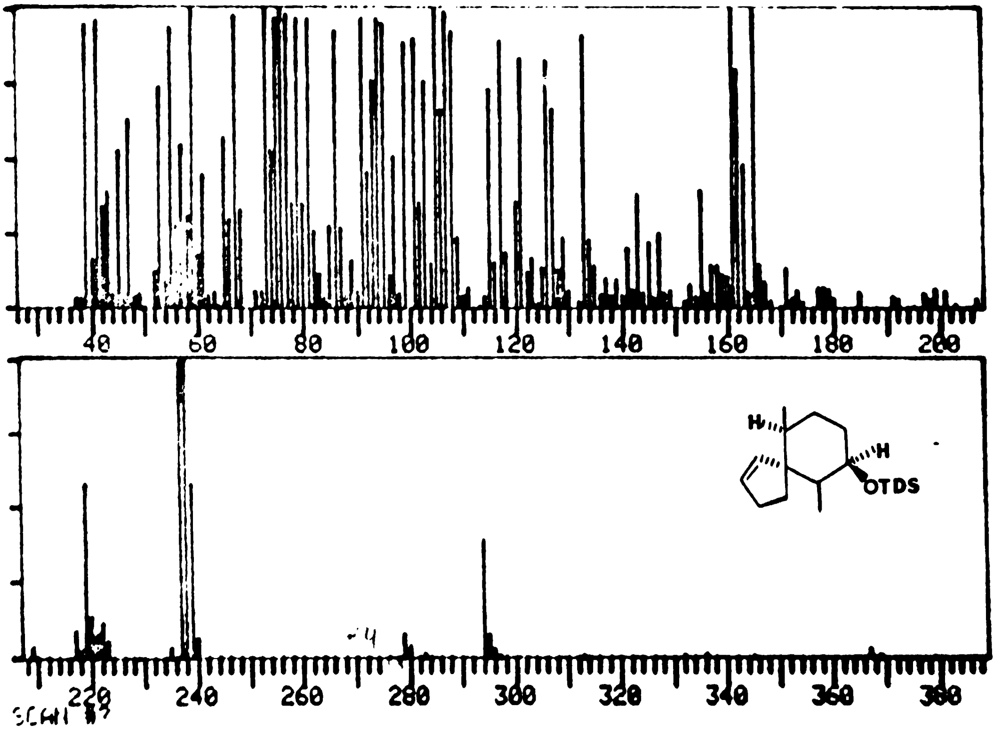


Figure 38b. Mass spectrum of 24

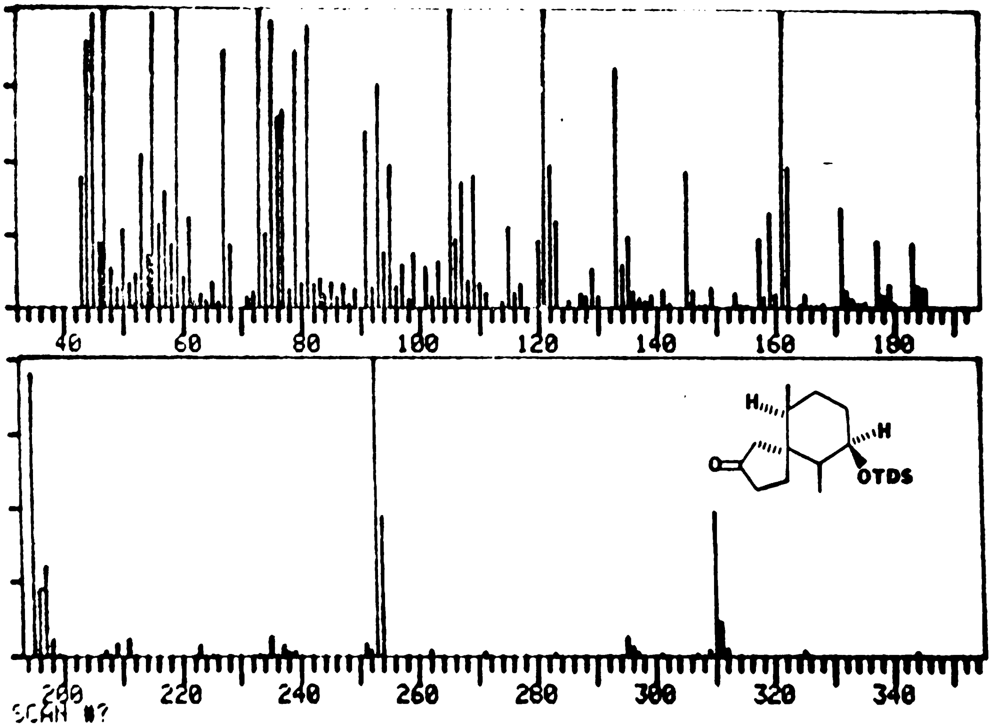


Figure 39a. Mass spectrum of 27

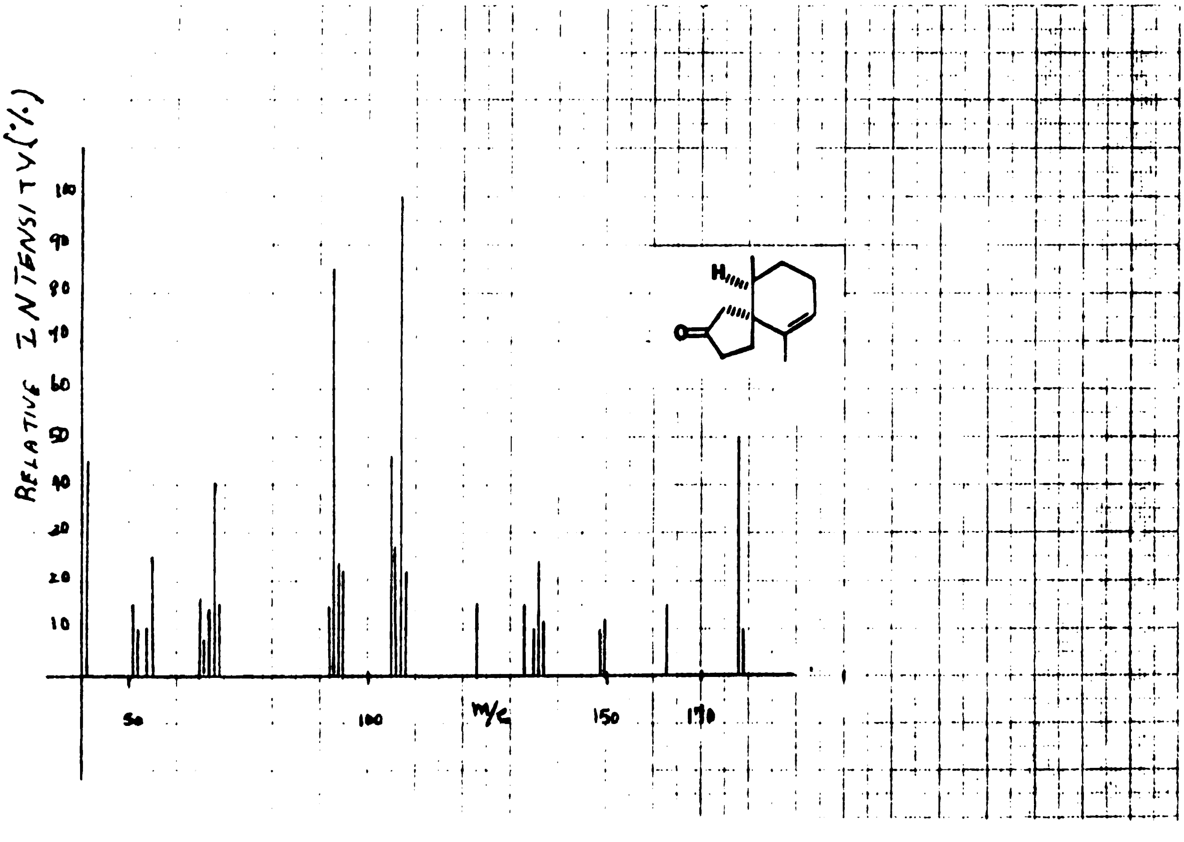


Figure 39b. Mass spectrum of 8

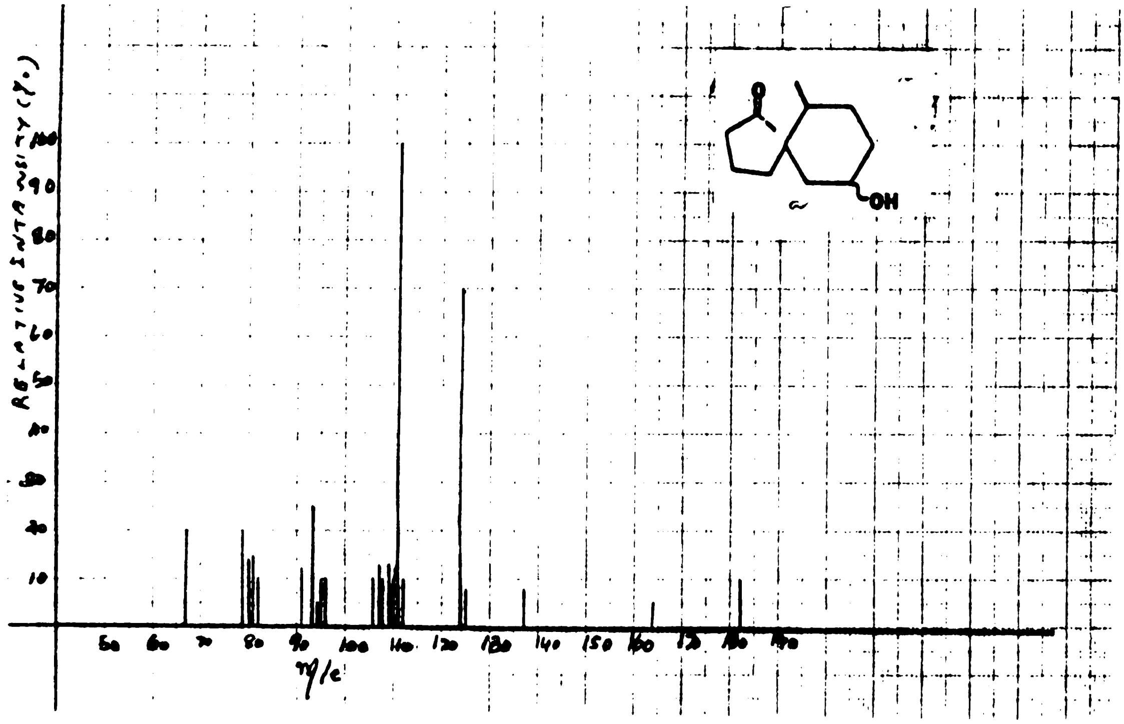


Figure 40a. Mass spectrum of axial alcohol 13

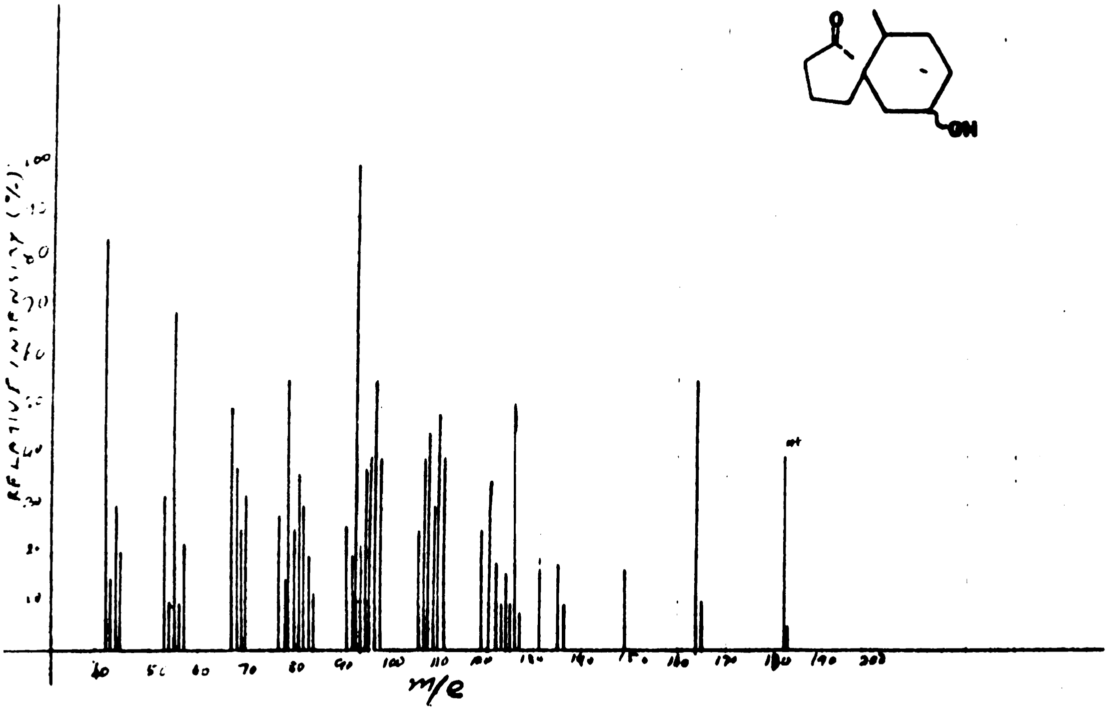


Figure 40b. Mass spectrum of equatorial alcohol 13

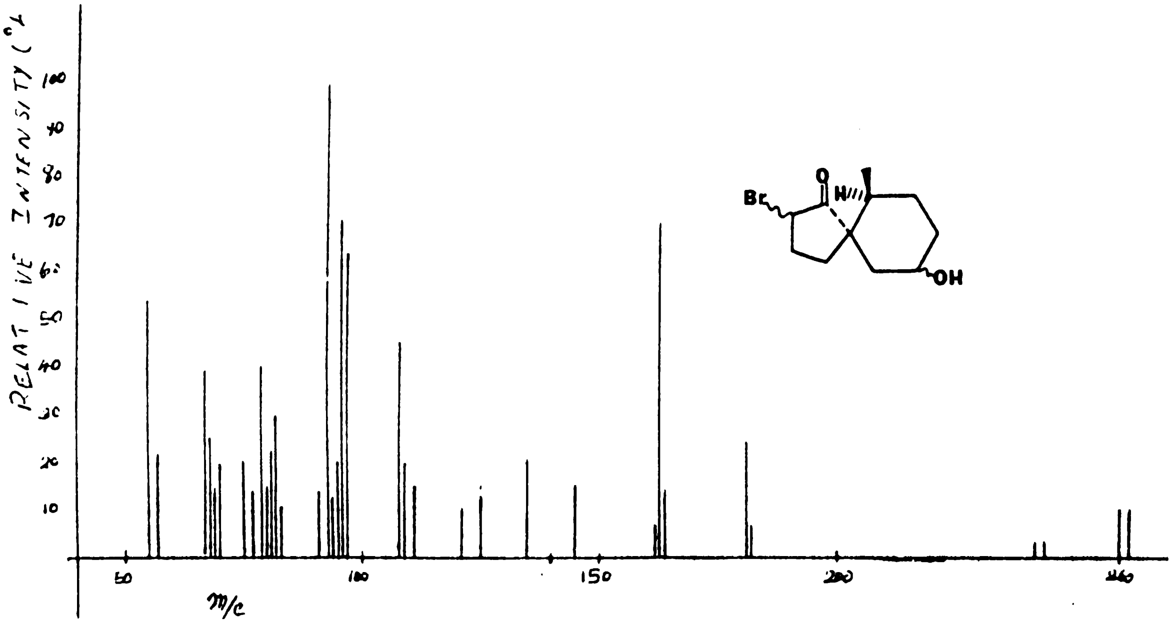


Figure 41a. Mass spectrum of 28

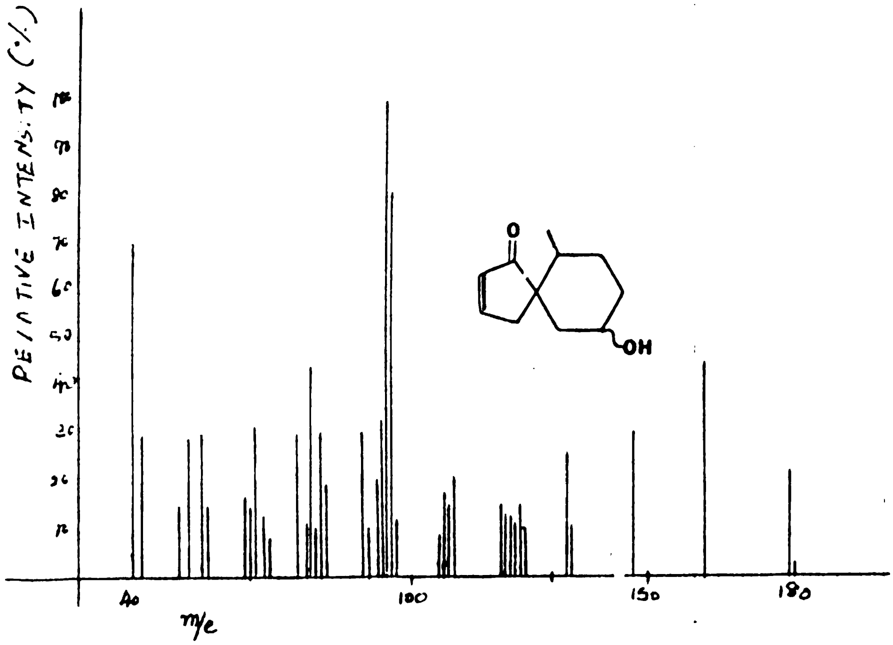


Figure 41b. Mass spectrum of 29

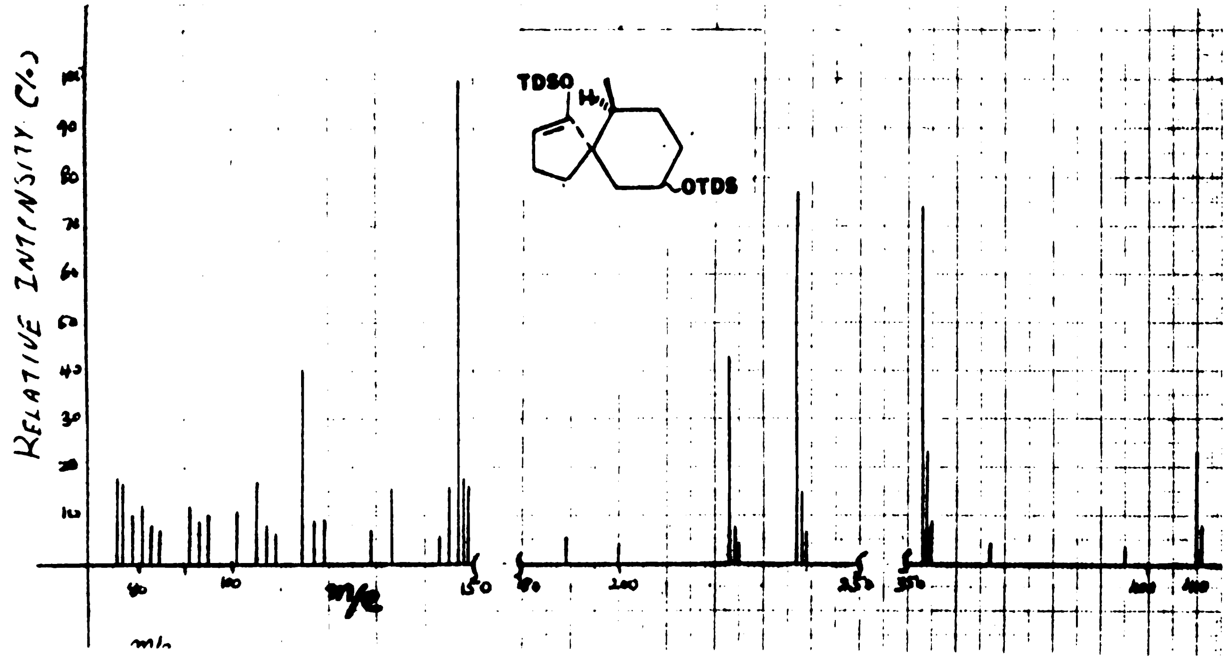


Figure 42a. Mass spectrum of 30

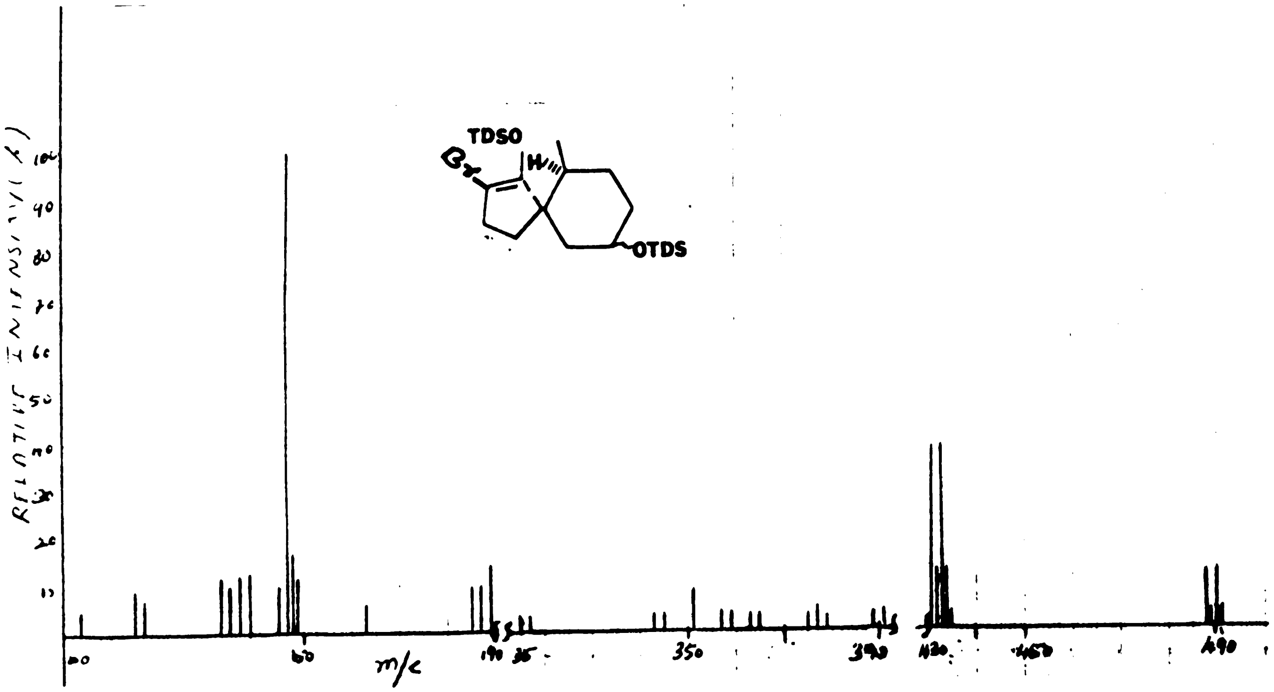


Figure 42b. Mass spectrum of 33

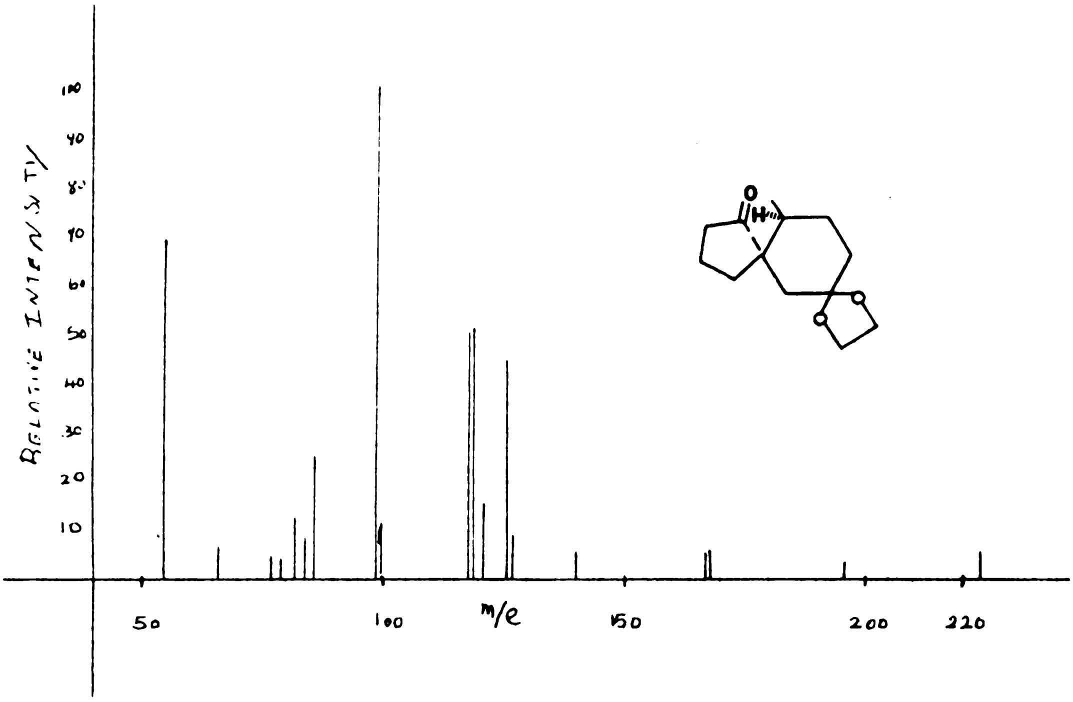


Figure 43a. Mass spectrum of 34

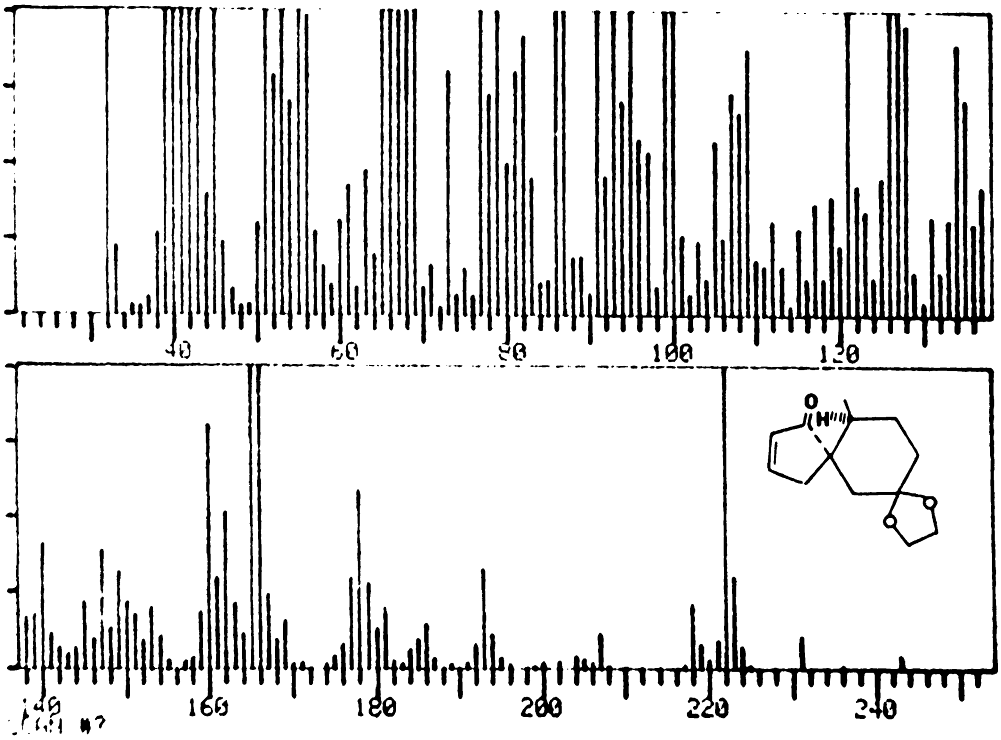


Figure 43b. Mass spectrum of 35

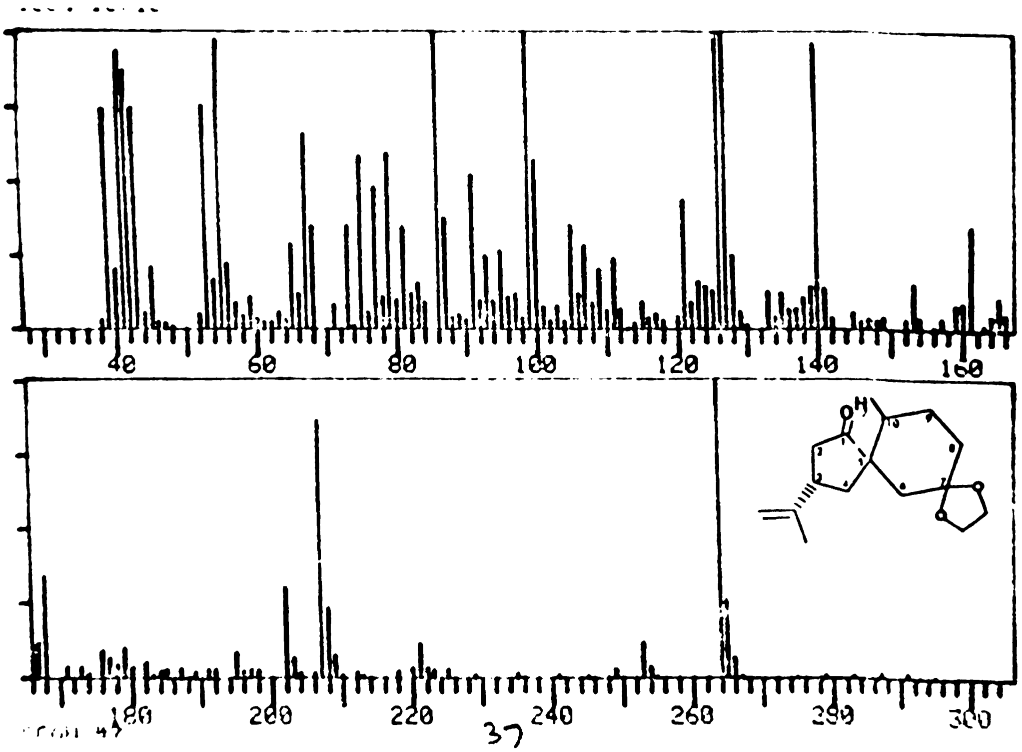


Figure 44. Mass spectrum of 37

APPENDIX: ABBREVIATIONS

ABBREVIATIONS

Ac	Acetyl
DBU	Diazobicyclo undecane
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
DNP	2,4,Dinitrophenylhydrazone
Et	Ethyl
GLPC, GLC	Gas liquid chromatography
h, hr	Hour
H_3O^+	Aqueous acid
HMPA	Hexamethylphosphoramide
LAH	Lithium aluminum hydride
Me	Methyl
Ms	Methanesulfonyl
NBS	N-Bromosuccinimide
(O)	Oxidation
Ph, Ø	Phenyl
Pet ether	Petroleum ether
Py	Pyridine
PHT	2-pyrrolidone hydrotribromide
t, tert	Tertiary
TDS	Tertiary Butyldimethylsilyl
THF	Tetrahydrofuran
Ts	p-toluenesulphonyl
TLC	Thin layer chromatography

LIST OF REFERENCES

LIST OF REFERENCES

1. J.K. Magrave and D.L. Cottle, *J. Am. Chem. Soc.*, **64**, 484 (1942).

2. R. Gerdil, *Helv. Chim. Acta*, **53**, 2100 (1970).

3. D.T. Longone and W.D. Wright, *Tetrahedron Lett.*, 2859 (1969).

4. R. Koster, S. Arora and P. Binger, *Angew. Chem. Int. Ed.*, **8**, 205 (1969).

5. H.H. Wasserman, R.E. Cochoy, and M.S. Baird, *J. Am. Chem. Soc.*, **91**, 2375 (1969).

6. P.S. Venkataramani and W.H. Reusch, *Tetrahedron Lett.*, 4283 (1968).

7. P.S. Venkataramani, J.E. Karoglan and W.H. Reusch, *J. Am. Chem. Soc.*, **93**, 269 (1971).

8. K. Grim, P.S. Venkataramani, and W.H. Reusch, *J. Am. Chem. Soc.*, **93**, 270 (1971).

9. W.H. Reusch, K. Grim, J.E. Karoglan, J. Martin, K.P. Subrahamanian, Y.C. Toong, P.S. Venkataramani, John D. Yordy, and Paul Zoutendam, *J. Am. Chem. Soc.*, **99**, 1953 (1977).

10. (a) W.H. Reusch, Kurt Grim, J.E. Karoglan, J. Martin, K.P. Subrahamanian, Y.C. Toong, P.S. Venkataramani, John D. Yordy, and Paul Zoutendam, *J. Am. Chem. Soc.*, **99**, 1958 (1977); (b) W.H. Reusch, Kurt Grim, J.E. Karoglan, J. Martin, K.P. Subrahamanian, Y.C. Toong, P.S. Venkataramani, John D. Yordy, and Paul Zoutendam, *J. Am. Chem. Soc.*, **99** 1965 (1977).

11. (a) A. Deboer and C.H. Depuy, *J. Am. Chem. Soc.*, **92**, 4008 (1970); (b) C.H. Depuy, F.W. Breitbell, and K. Debruin, *ibid.*, **88**, 3347 (1966); (c) C.H. Depuy and R. Vanlener, *J. Org. Chem.*, **39**, 3360 (1974); (d) Nickon, D.F. Covey, G.D. Pandit and J.J. Frank, *Tetrahedron Lett.*, 3681 (1975).

12. Z.J. Barneis, R.J. Warnet, D.M.S. Wheeler, M.G. Waite, and G.A. Sim, *Tetrahedron*, **28**, 4683 (1972).

13. (a) P.S. Wharton and I.I. Bair, *J. Org. Chem.*, **31**, 2480 (1966); (b) A. Nickon, J.J. Frank, D.F. Covey and Yun, *J. Am. Chem. Soc.*, **96**, 7574 (1974); (c) A. Nickon and J.J. Frank, *Tetrahedron Lett.*, 4335 (1975).

14. C.H. Depuy, N.C. Arney, Jr., and D.H. Gibson, *J. Am. Chem. Soc.*, **90**, 1830 (1968).

15. D.J. Cram, "Fundamentals of Carbanion Chemistry", Academic Press, New York.

16. A. Nickon, J.L. Lambert, R.O. Williams and M.H. Westissky, *J. Am. Chem. Soc.*, **88**, 3354 (1966).

17. E.J. Corey and Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).

18. Y. Fujimoto and T. Tatsuno, *Tetrahedron Lett.*, **37**, 3325 (1976).

19. C.B.C. Boyce and J.S. Whitehurst, *J. Chem. Soc.*, 2680 (1960).

20. (a) K.L. Williamson, T. Howell and T.A. Spencer, *J. Am. Chem. Soc.*, **88**, 325 (1966); (b) L. Birkofer, S.M. Kim and H.D. Engles, *Chem. Ber.*, **95**, 1495 (1962).

21. K. Grim, Ph.D. Thesis, Michigan State University, 1971.

22. W.S. Johnson, *J. Am. Chem. Soc.*, **65**, 1317 (1943).

23. (a) M.P. Kozina, A.K. Mirzawa, I.E. Sosnina, N.V. Elagina, and S.M. Skuraton, *Dokl. Akad. Nauk.*, SSSR, 155, 1123 (1964), *Chem. Abst.*, **61**, 2540d (1964); (b) D.M. Speros and F.D. Rossini, *J. Phy. Chem.*, **64**, 1723 (1966).

24. M.B. Turova-Pollack, et al., *Obschch. Khim.*, **27**, 586 (1966).

25. John D. Yordy, Ph.D. Thesis, Michigan State University, 1974.

26. F. Jensen and B. Rickborn, "Electrophilic Substitution of Organo Mercurials", p. 4666.

27. G.M. Whitesides and J.S. Filipo, *J. Am. Chem. Soc.*, **92**, 6611 (1970).

28. J.A. Marshall and P.C. Johnson, *J. Org. Chem.*, **35**, 192 (1970).

29. F. Sorm and V. Herout, *Coll. Czech. Chem. Comm.*, **13**, 177 (1948).

30. (a) For the structure of this substance, see N.H. Anderson, M.S. Falcone, and D.D. Syrdal, *Tetrahedron Lett.*, 1759 (1970); (b) For the first total synthesis, see P.M. McCurry and R.K. Singh, *ibid*., 3325 (1973).

31. (a) K. Yamada, H. Nagase, Y. Hayakawa, K. Aoki and Y. Hirata, *Tetrahedron Lett.*, 4963, 4967 (1973); (b) Drurycaine, *et al.*, *J. Org. Chem.*, **41**, 1539 (1976).

32. (a) D.T. Coxon, K.R. Price, and B. Howard, *Tetrahedron Lett.*, 2921 (1974) (for the structure); (b) H. Hikino, K. Aota, D. Kuwano, and T. Takemoto, *Tetrahedron*, **27**, 4831 (1971) (synthesis); (c) D. Caine and C. Chu, *Tetrahedron Lett.*, 703 (1974).

33. (a) K.R. Varma, M.L. Maheshwari, and S.C. Bhattachryya, *Tetrahedron*, **21**, 115 (1965); (b) M. Mongrain, J. Lafontaine, A. Belanger and P. Deslongchamps, *Canad. J. Chem.*, **48**, 3273 (1970); (c) M. Deighton, C.R. Hugher, and R. Ramage, *J.C.S. Chem. Comm.*, 662 (1975).

34. For a review on the spirovetivanes, see J.A. Marshall, S.F. Brady and N.H. Anderson, *Fortschr. Chem. Org. Naturst.*, **31**, 283 (1974).

35. I. Yoshioka, S. Takahashi, H. Hikino and Y. Sasaki, *Chem. Pharm. Bull. (Tokyo)*, **7**, 319 (1959).

36. O. Motl, W.Z. Chow, and F. Sorm, *Chem. Ind.*, 207 (1961).

37. A.S. Pfau and P.A. Plattner, *Helv. Chim. Acta.*, **22**, 202 (1939).

38. (a) G. Stork, R.L. Danheiser, and B. Ganem, *J. Am. Chem. Soc.*, **95**, 414 (1973); (b) G. Bozzato, J.P. Bachmann, and M. Pesaro, *J. Chem. Soc., Chem. Commun.*, 1005 (1974); (c) W.G. Dauben and D.J. Hart, *J. Am. Chem. Soc.*, **97**, 1622 (1975); (d) G. Buchi, D. Berthet, R. Decorzant, A. Grieder, and A. Hauser, *J. Org. Chem.*, **41**, 3208 (1976).

39. (a) J.A. Marshall and S.F. Brady, *J. Org. Chem.*, **35**, 4068 (1970); *Tetrahedron Lett.*, 1387 (1969); (b) B.M. Trost, M. Preckel and L.M. Leichter, *J. Am. Chem. Soc.*, **97**, 2224 (1975).

40. P.M. McCurry, Jr., *Tetrahedron Lett.*, **21**, 1845 (1971).

41. E. Wenkert, *et al.*, *J. Am. Chem. Soc.*, **100**, 1267 (1978).

42. B.M. Trost, K. Hiroi, S. Kurozumi, *J. Am. Chem. Soc.*, **97**, 438 (1975).

43. K. Gunderman, *Angew. Chem. Internat. Edit.*, **2**, 674 (1963).

44. B. Capon, *Quart. Rev.*, **18**, 45 (1964).

45. H.C. Brown, G. Zweifel, *J. Am. Chem. Soc.*, **85**, 2066 (1963).

46. W.E. Daniels, M.E. Chiddix, and S.A. Glickman, *J. Org. Chem.*, **28**, 573 (1963).

47. D.V.C. Awang and S. Wolfe, *Can. J. Chem.*, **47**, 706 (1969).

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

49. C.A. Brown, *J. Org. Chem.*, **39**, 1324 (1974).

50. B.M. Trost, T.N. Salzman, Kunio Hiroi., *J. Am. Chem.* Soc., **98**, 4887 (1976).

51. H.O. House and J.M. Wilkins, *J. Org. Chem.*, **43**, 2443 (1978) and references therein.

52. B.M. Trost, M. Preckel, and L.M. Leichter, *J. Am. Chem. Soc.*, **97**, 2224 (1975).

53. (a) J.K. Rasmussen, *Synthesis*, **91** (1977); (b) M. Zembayashi, K. Tamao, and Kumada, *Synthesis*, 422 (1977).