This is to certify that the

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Part I Studies of the Nazarov cyclization coupled with cascade rearrangements.

Part II A study of 4-bromobutyldiphenylphosphine oxide as a synthon for cyclobutylidene derivatives.

presented by

April Gu Gruhn

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Ph.D. degree in Organic Chemistry

William Reusch

Major professor

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PART I

STUDIES OF THE NAZAROV CYCLIZATION COUPLED WITH

CASCADE REARRANGEMENTS

PART II

A STUDY OF 4-BROMOBUTYLDIPHENYLPHOSPHINE OXIDE

AS A SYNTHON FOR CYCLOBUTYLIDENE DERIVATIVES

By

April Gu Gruhn

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ABSTRACT

PART I

STUDIES OF THE NAZAROV CYCLIZATION COUPLED WITH CASCADE REARRANGEMENTS

PART II

A STUDY OF 4-BROMOBUTYLDIPHENYLPHOSPHINE OXIDE AS A SYNTHON FOR CYCLOBUTYLIDENE DERIVATIVES

By

April Gu Gruhn

PART I: The substrate 2-(2'-oxo-(E)-4'-phenyl-3'-butenylidene) spiro[3,5]nonane (**8**) was synthesized in six steps in 51.5% overall yield. Methylenecyclohexane was reacted with dichloroketene via [2+2] cycloaddition to give 1,1-dichlorospiro[3,5]nonan-2-one (**1**). Dichloroketone (**1**) was elaborated to give 1-spiro[3,5]-2'-nonanylidene-2-propanone (**7**), which then underwent aldol condensation with benzaldehyde to give dienone (**8**). Acid-catalyzed reaction and rearrangement of dienone (**8**) was studied by treatment with phosphoric acid, hydrochloric acid, iodotrimethylsilane and tin (IV) chloride. Reaction of (**8**) with phosphoric acid at room temperature gave dispiro[cyclohexane-1,1'-cyclobutane-

3',2"-6"-phenyldihydro-2"*H*-pyran-4"(3"*H*)-one] (**11**) in 31% yield. At 90 °C, this reaction gave 5,7-dimethyltetralin (**12**) in 64% yield and 2-cyclohexenyl-1-methyl-3-phenylbenzene (**13**) in 10% yield, the former by an initial retroaldol reaction and the latter by a series of tautomerizations and electrocyclic reactions following cation induced four-membered-ring cleavage. On treatment with hydrochloric acid, (**8**) gave 2-chloro-2-(2'-oxo-(E)-4'-phenyl-3'-butenyl) spiro[3,5]nonane (**14**) quantitatively. Reflux of (**8**) with iodotrimethylsilane gave compound (**13**) quantitatively. Reflux of (**8**) with one equivalent of tin (IV) chloride in chloroform gave a kinetically controlled mixture of Nazarov rearrangement products: spiro[cyclohexane-1,5'-3'-phenyl-3',4',5',6'-tetrahydropentalen-1'(2'*H*)-one] (**15**), spiro[cyclohexane-1,5'-3'-phenyl-4',5',6',6'a-tetrahydropentalen-1'(3'a*H*)-one] (**16**), and spiro[cyclohexane-1,5'-3'a-phenyl-4',5',6',6'a-tetrahydropentalen-1'(3'a*H*)-one] (**17**) in 20.8%, 16.2% and 34.0% GC yields respectively. This mixture was stable under the reaction conditions, but (**15**) was completely converted to (**16**) on treatment with toluene sulfonic acid. Finally, a discussion of Nazarov cyclization coupled with cascade rearrangements is presented.

PART II: 4-Bromobutyldiphenylphosphine oxide (**1**) was synthesized in 90% yield by aqueous hydrolysis of commercially available 4-bromotriphenyl-phosphonium bromide. Oxide (**1**) was reacted with two equivalents of phenyllithium in tetrahydrofuran, and then with dicyclopropylketone to give (1'-dicyclopropylhydroxymethylcyclobutyl)diphenylphosphinyl oxide (**3**) in 77% overall yield. Oxide (**3**) was then reacted with sodium hydride in dimethyl formamide at room temperature to give cyclobutylidenedicyclopropylmethane (**4**) in 82% yield. Cyclobutylidenedicyclopropylmethane (**4**) was transformed into 2,2-dicyclopropylpentanone (**5**) when it was exposed to air.

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LIST OF ABBREVIATIONS

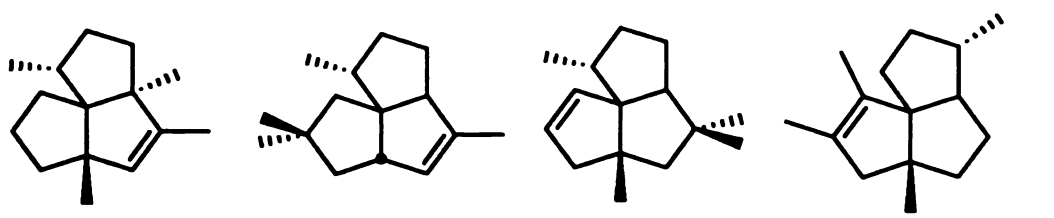
n-BuLi	n-Butyllithium
mCPBA	meta-Chlorperbenzoic acid
DEPT	Distortionless enhancement by polarization tranfer
DMF	N, N-Dimethylformamide
Et	Ethyl
Et_2O	Ether
LDA	Lithium diisopropylamide
MeLi	Methyllithium
Ph	Phenyl
PhLi	Phenyllithium
TEA	Triethylamine
THF	Tetrahydrofuran
TMS	Tetramethylsilane
Ts	Toluenesulfonyl

PART I

STUDIES OF THE NAZAROV CYCLIZATION COUPLED WITH CASCADE REARRANGEMENTS

INTRODUCTION

Largely through the efforts of Bohlman and co-workers, a variety of angular triquinanes has been isolated from natural sources over the past two decades.[1] This class of compounds, having a tricyclo[6.3.0.$0^{1,5}$]undecane ring system, is represented by the hydrocarbons isocomene, pentalenene, silphinene and silphiperfolene (see Figure 1).

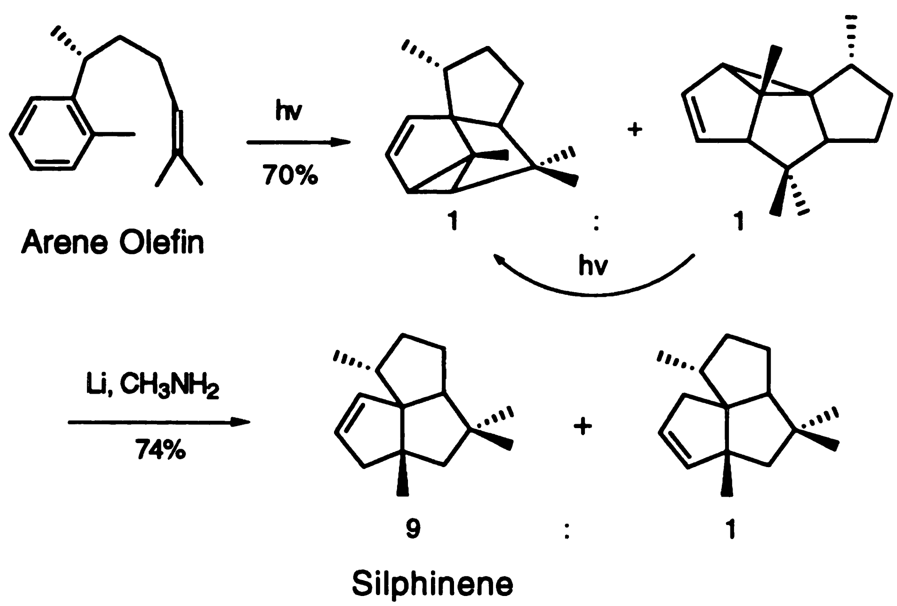


Isocomene Pentalenene Silphinene Silphiperfolene

Figure 1. Angular Triquinanes.

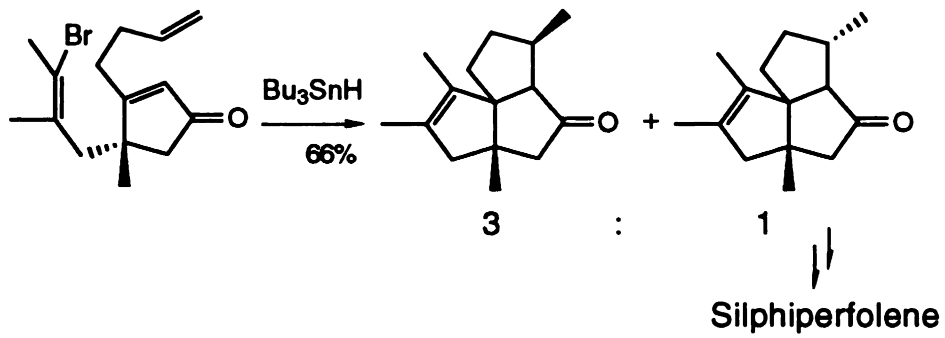
These biologically significant condensed tricyclopentanoids, having contiguous quaternary centers, have awakened a surge of interest in the design and implementation of ingenious routes to their syntheses. These total syntheses can be divided into two categories: the consecutive synthetic approach, and the convergent synthetic approach. The consecutive approach involves stepwise application of classic or recently developed cyclopentannulation reactions to construct the carbon skeleton one ring at a time.[2] Regio- and stereocontrol here are achieved mainly by appropriate chain elongation or functional group elaboration reactions, and in some cases by the cyclopentannulation reactions themselves. The convergent approach is achieved from precursors through a design in which several rings are established simultaneously, with regio- and stereospecificity. For example, arene-olefin meta-photocycloadditions, tandem radical reactions, and cascade rearrangements.

(a) Arene-olefin meta-Photocycloadditions. In one experiment by Wender and co-workers,[3] irradiation of an arene olefin substrate gave a 1:1 mixture of photoadducts in 70% yield. Reductive cleavage of a cyclopropane bond gave silphinene and triquinane in 74% yield in a 9:1 ratio (Scheme 1).



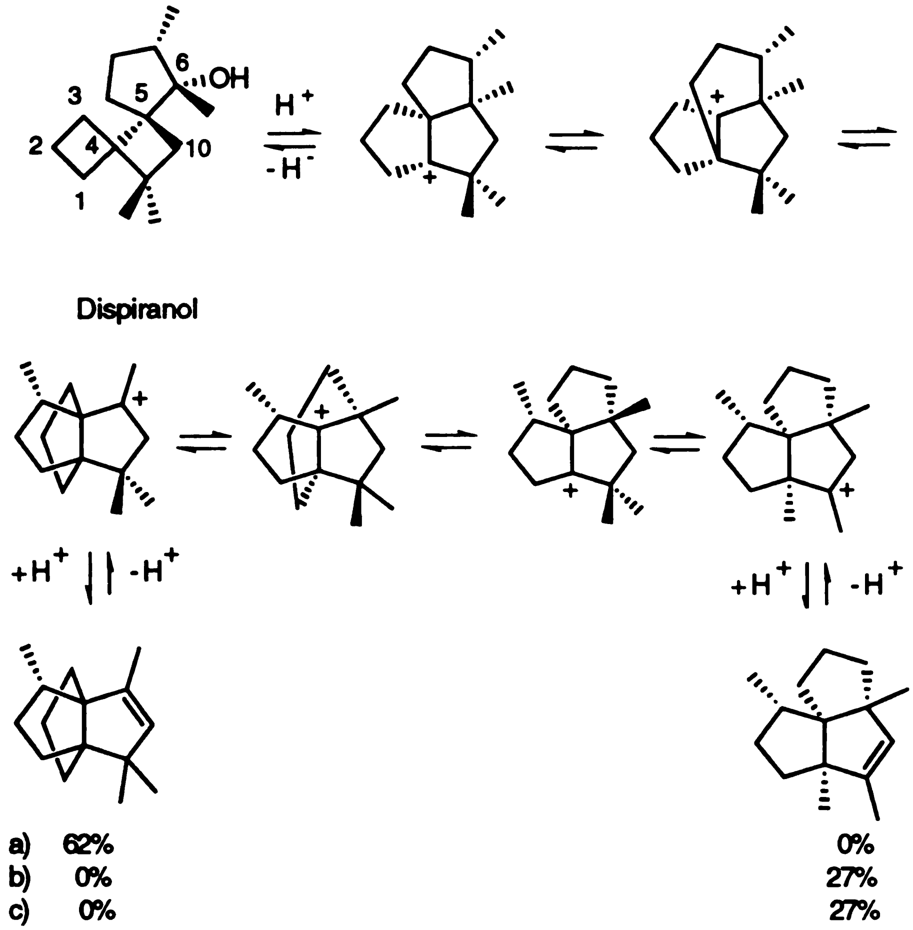
Scheme 1. Arene-olefin meta-Photocycloadditon.

(b) Tandem Radical Reactions. In work by Curran and co-workers,[4] treatment of a substrate with 1.1 equivalents of tri-n-butyltin hydride gave two separable tricyclic products, which are formed in a 3 : 1 ratio (see Scheme 2).



Scheme 2. Tandem Radical Reaction.

(c) Cascade Rearrangements. In a study by Fitjer and co-worker,[5] a dispiranol was heated with an equimolar amount of p-toluenesulfonic acid in benzene to give modehephene and isocomene via initial cyclobutane ring enlargements and subsequent 1,2-shifts (see Scheme 3).



Modehephene

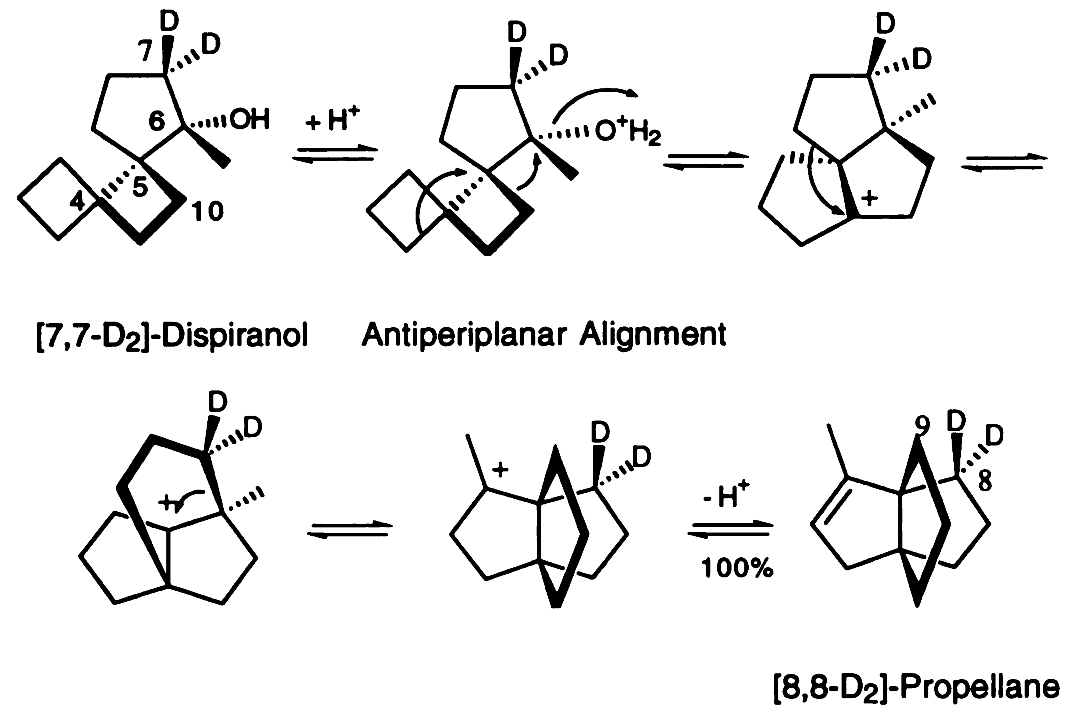
Isocomene

70 °C; a) 10min; b) 22 h; c) 76 h.

Scheme 3. Cascade Rearrangement.

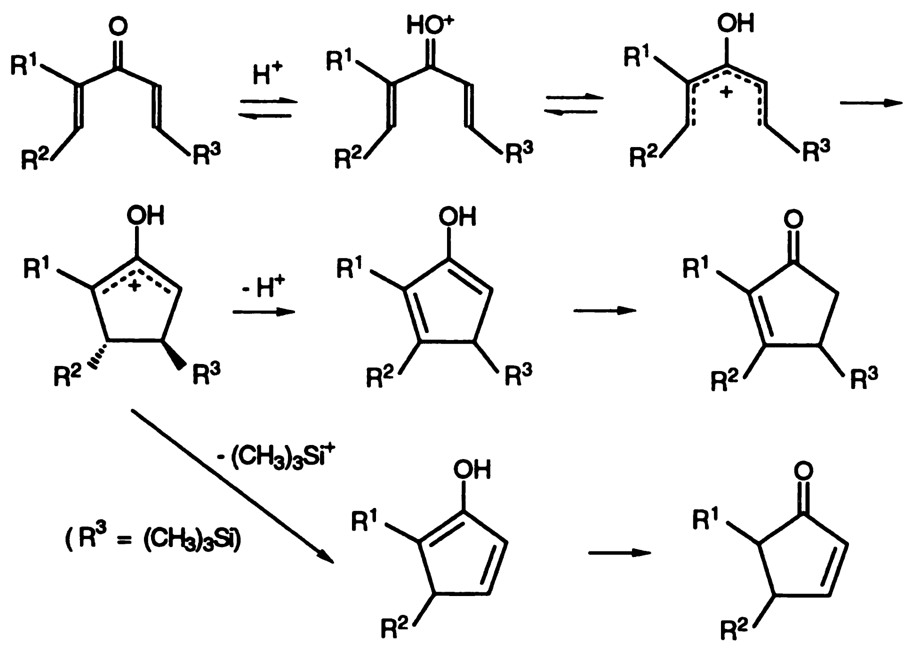
These convergent syntheses built tricyclic skeletons in one fell swoop and demonstrated the relationship between reaction complexity and design brevity.

The chemistry of strained carbon rings has intrigued chemists[6] since Baeyer first speculated about their stabilities over one hundred years ago. Cyclobutanes are known to possess a considerable inherent ring strain energy (about 25 kcal/mole).[7] This angle strain provides a powerful thermodynamic driving force for ring cleavage and ring expansion transformations. Such compounds are often versatile and useful intermediates for organic syntheses; and their applications were reviewed recently,[7,8] with the previously described work of Fitjer being a good example (Scheme 3). In this case, a stereoelectronic effect favors migration of the cyclobutane bond trans to the C-6 hydroxyl group. The favorable alignment of the migrating cyclobutane bond with respect to the leaving group at the developing cationic center, combined with the relief of angle strain, helped facilitate the rearrangements. In Fitjer's model study,[9] [7,7-D_2]-dispiranol gave an [8,8-D_2]-propellane quantitatively. This indicated that the rearrangements of [7,7-D_2]-dispiranol had proceeded regiospecifically, initiated by an exclusive 1,2-shift of that cyclobutane bond having an antiperiplanar alignment with the leaving hydroxyl group (Scheme 4).



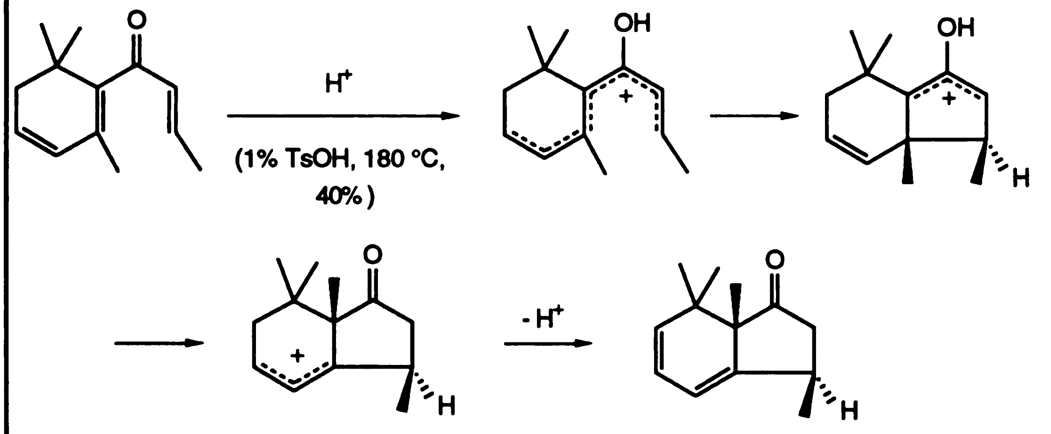
Scheme 4. Rearrangements of [7,7-D_2]-Dispiranol.

During the 1940's and 50's, studies by I. N. Nazarov and coworkers[10] established the Nazarov reaction: a general synthesis of 2-cyclopentenone by acid-induced cyclization of allyl vinyl ketones, divinyl ketones and dienynes. In this dissertation, we propose that Nazarov cyclization can be used to initiate cascade rearrangements of four-membered rings leading to a synthesis of angular triquinanes. The Nazarov cyclization (see Scheme 5) is an intramolecular electrocyclic reaction: the protonated dienone is treated as a hydroxypentadienyl cation having four π-electrons.[11] The thermal electrocyclic reaction should therefore be conrotatory[12] by the Woodward-Hoffmann rules for the conservation of orbital symmetry. The cyclopentenone products of the Nazarov cyclization may include isomers distinguished by different locations of the double bond. Normally, the thermodynamically favored enone will predominate, but appropriately silicone-substituted substrates may be used to direct the initial enone to the less stable location.[13]



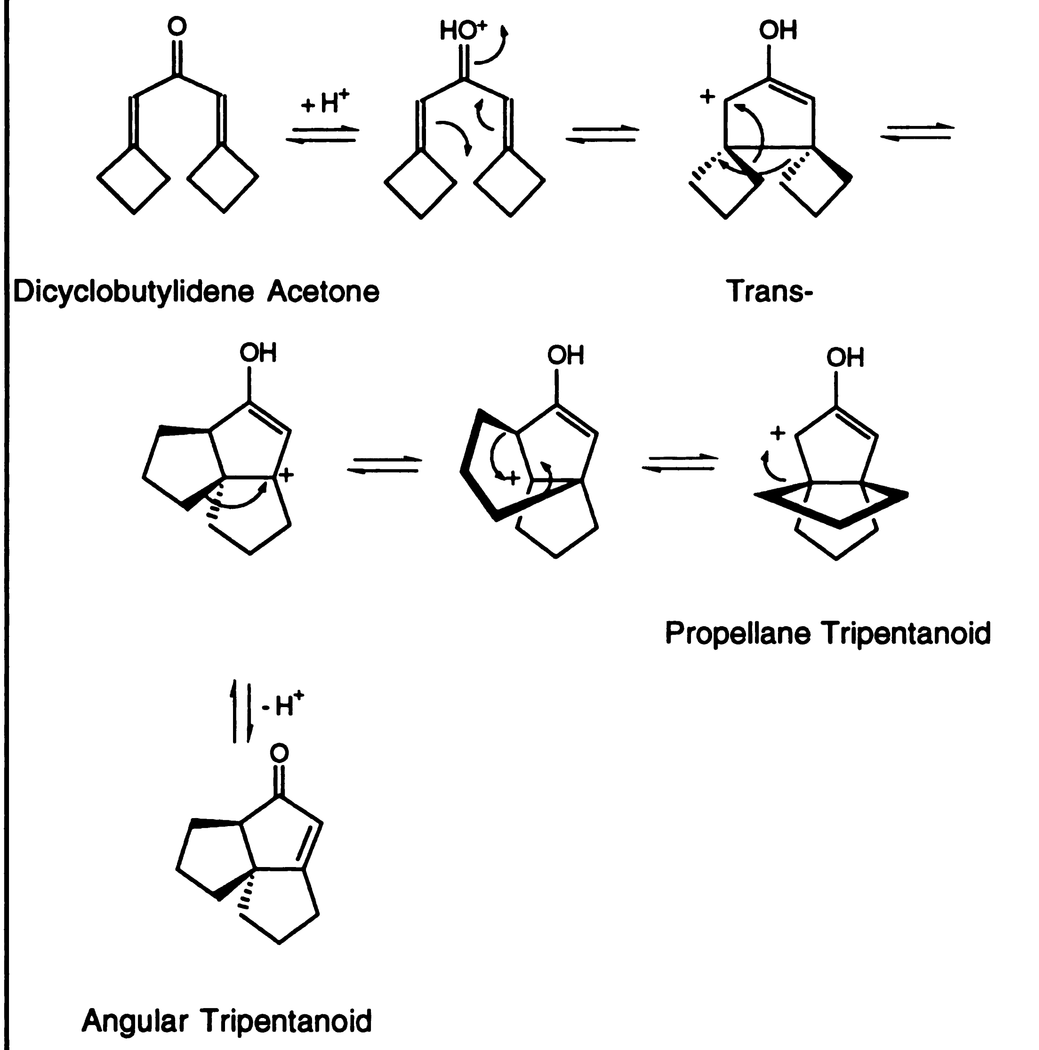
Scheme 5. Nazarov Cyclization Mechanism.

Although Nazarov cyclization is normally followed by proton loss to give a cyclopentenone product, an intervening rearrangement may occur when circumstances are favorable. One example,[14] illustrated in Scheme 6, involves a 1,2-methyl shift facilitated by an adjacent double bond.



Scheme 6. Secondary Cationic Rearrangement.

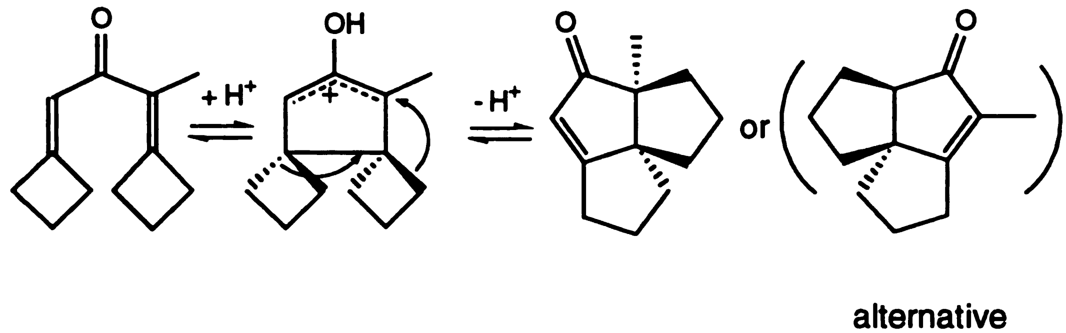
We expect a bis-cyclobutylidene substrate to give an angular tripentanoid via the Nazarov cyclization and subsequent rearrangements (see Scheme 7). In this case, the propellane tripentanoid should not be formed, since the cationic center is destabilized by the adjacent carbonyl group.



Scheme 7. Proposed Rearrangement of Dicyclobutylidene Acetone.

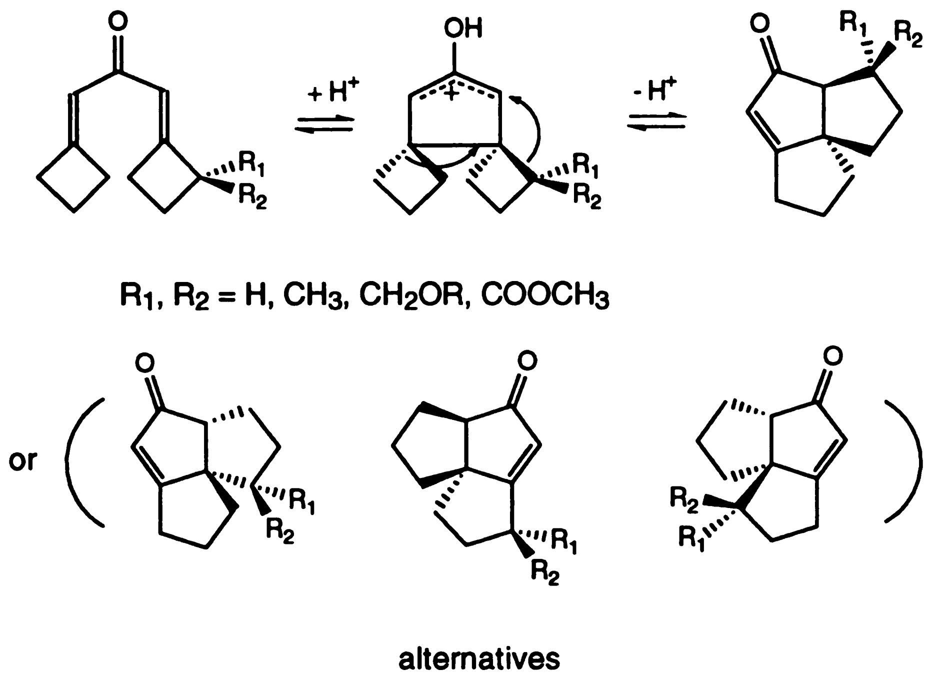
In this sequence of rearrangements, an initial stereochemical factor is absent, but substituent effects may exist. For example, substituents might affect the course of rearrangement in the following ways:

(a) An α-methyl group substituent might direct the initial rearrangement by localization of charge (see Scheme 8).



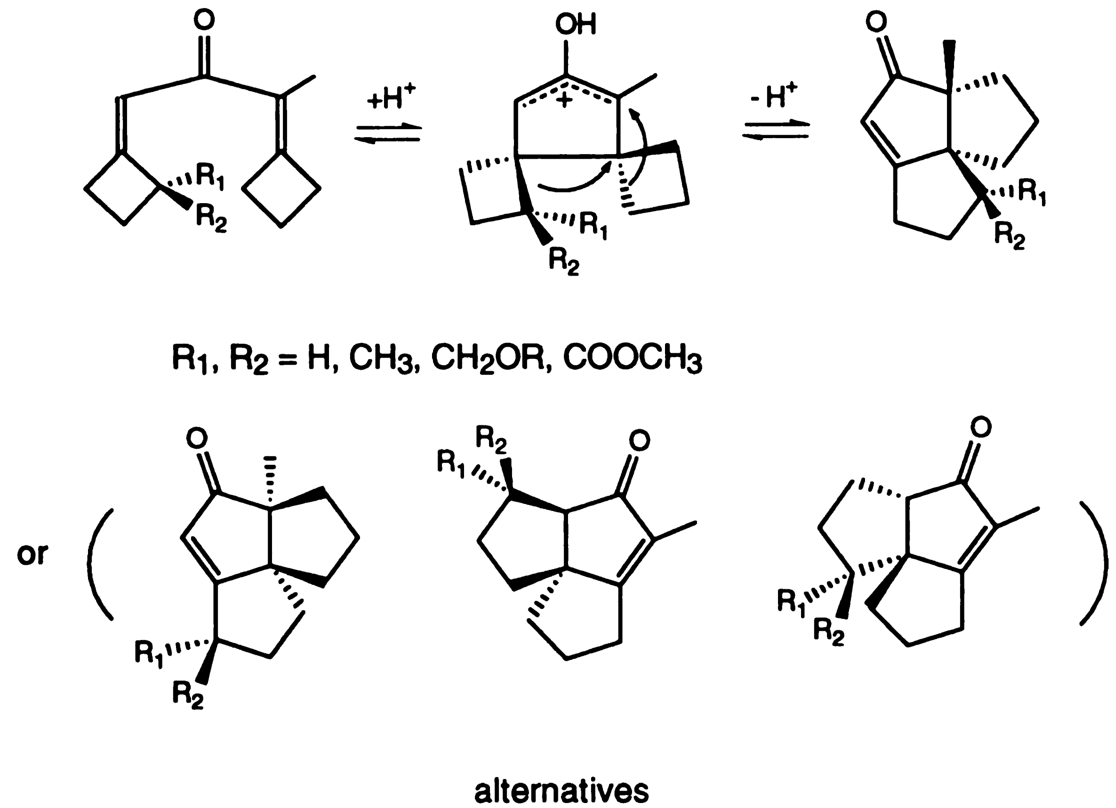
Scheme 8. α-Methyl Group Substituent Effect.

(b) Migratory aptitude might influence the course of rearrangement (see Scheme 9).



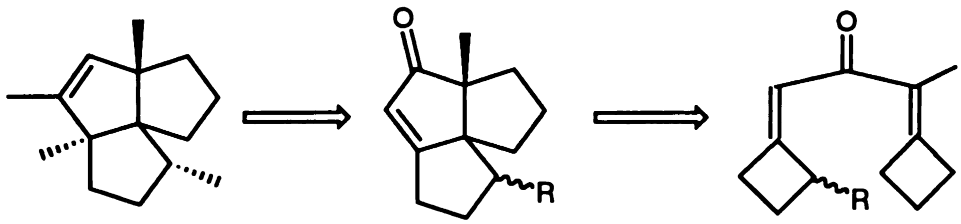
Scheme 9. Migratory Aptitude Effect.

(c) The previous effects might combine in a tandem fashion in a competition substrate (see Scheme 10).



Scheme 10. Substituent Effect.

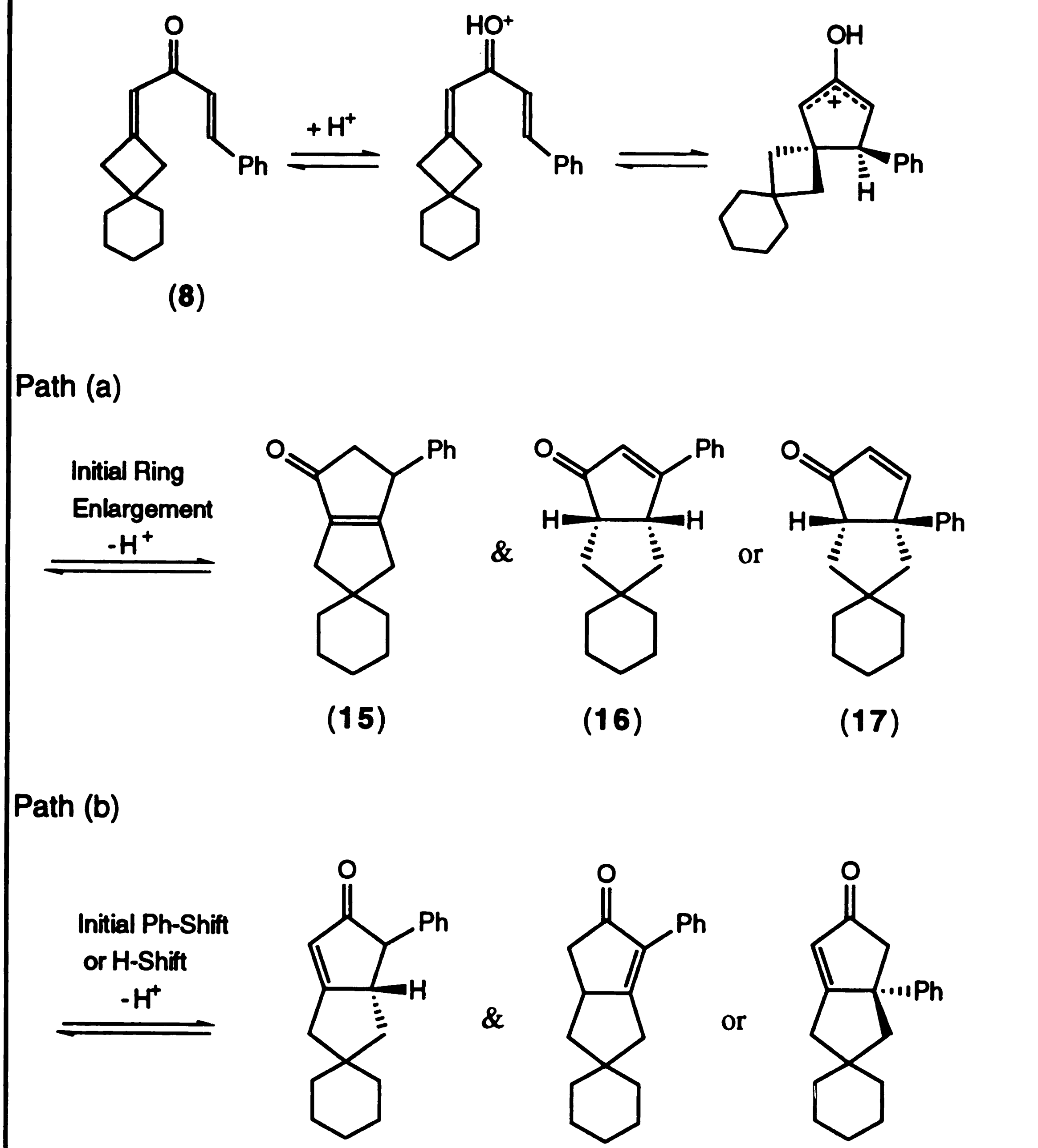
A possible retrosynthesis of isocomene, one of our target molecules, can be formulated according to the proposed rearrangements as shown in Scheme 11.



Isocomene R = CH_3, CH_2OR, $COOCH_3$

Scheme 11. Proposed Retrosynthesis of Isocomene.

Because the bis-cyclobutylidene substrate described in Scheme 7 is not readily available and would pose a challenging synthesis problem, the simpler model, 2-(2'-oxo-(E)-4'-phenyl-3'-butenylidene) spiro[3,5]nonane (**8**), was chosen for the initial study and designed to generate bicyclo[3.3.0]octane products by subsequent ring enlargement of a spirocyclobutane intermediate. This substrate should serve to address questions of whether a Nazarov cyclization can initiate rearrangements of the kind proposed here and the relative facility of ring expansion versus a 1,2-phenyl migration or a 1,2-hydrogen shift (see Scheme 12).



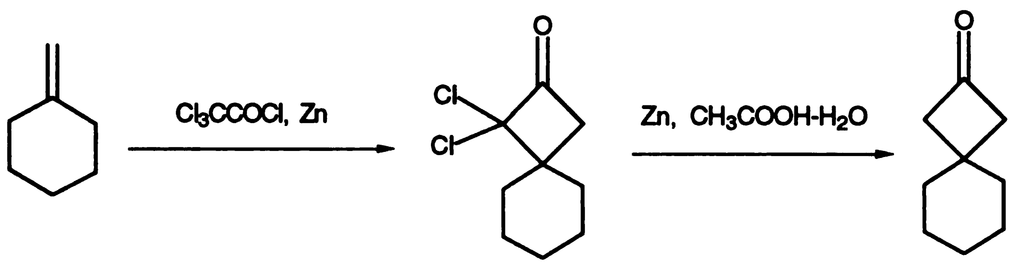
Scheme 12. Proposed Rearrangements of (**8**).

In the course of these studies, products characteristic of initial ring enlargement, as in path (a) in Scheme 12, spiro[cyclohexane-1,5'-3'-phenyl-3',4',5',6'-tetrahydropentalen-1'(2'*H*)-one] (**15**), spiro[cyclohexane-1,5'-3'-phenyl-4',5',6',6'a-tetrahydropentalen-1'(3'a*H*)-one] (**16**), and spiro[cyclohexane-1,5'-3'a-phenyl-4',5',6',6'a-tetrahydropentalen-1'(3'a*H*)-one] (**17**), were indeed isolated. However, elucidation of the various products from dienone (**8**) under different reaction conditions disclosed novel and unexpected transformations. Information obtained during these studies should prove useful in future applications of this synthetic strategy.

SYNTHESIS

Synthesis of the Nazarov cyclization precursor, 2-(2'-oxo-(E)-4'-phenyl-3'-butenylidene) spiro[3,5]nonane (**8**), was accomplished in six steps from methylenecyclohexane. The high yields and the ready availabilities of the starting materials make this an especially attractive method.

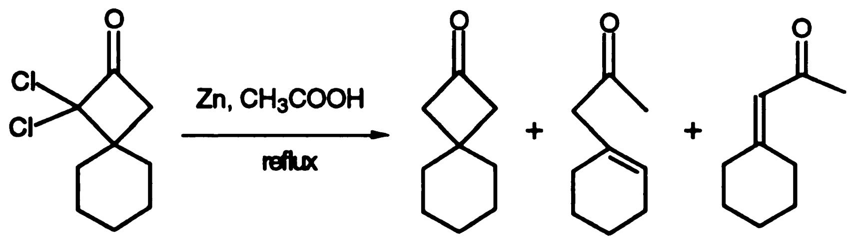
Ultrasound promoted cycloadditon of methylenecyclohexane with in situ-generated dichloroketene gave[15] 1,1-dichlorospiro[3,5]nonan-2-one (**1**) via a $2\pi + 2\pi$ cycloaddition reaction. Reductive removal of the chlorine atoms from dichloroketone (**1**) by treatment with zinc in a mixture of acetic acid and water gave spiro[3,5]nonan-2-one (**2**)[16] in 84.5% overall yield (see Scheme 13).



(**1**) (**2**)

Scheme 13. Preparation of (**2**).

An initial dehalogenation of dichloroketone (**1**) in neat acetic acid[15(a)] generated ketone (**2**) plus 1-cyclohexenyl-2-propanone (**3**) and 1-cyclohexylidene-2-propanone (**4**), two ring cleavage isomers of ketone (**2**), in a 9 : 5 : 1 molar ratio (see Scheme 14). Ketone (**2**), and a mixture of (**3**) and (**4**) were isolated by flash chromatography.

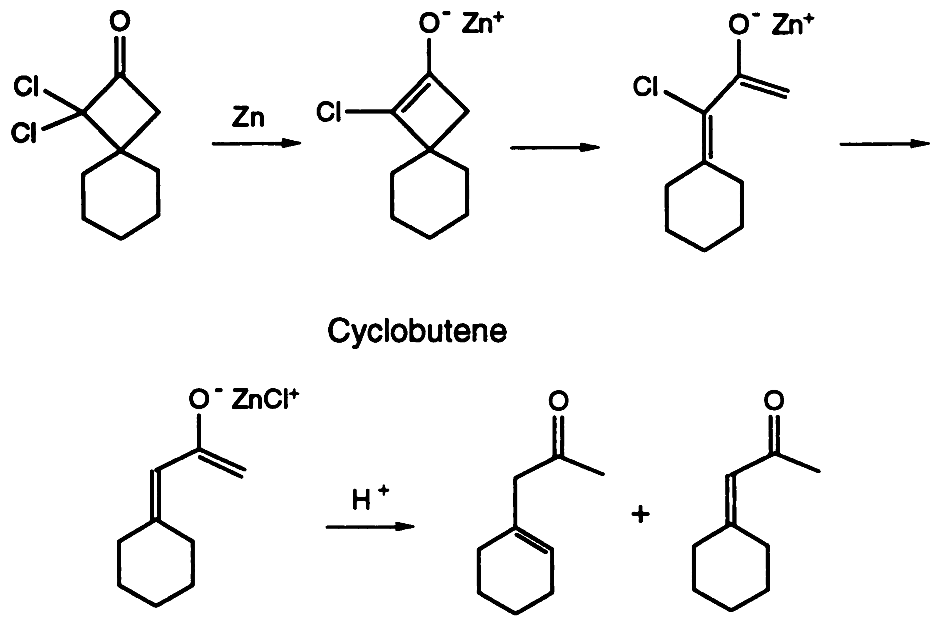


(**1**) (**2**) (**3**) (**4**)

Molar ratio (GC): 9 : 5 : 1

Scheme 14. Dehalogenation of (**1**) in Acetic Acid.

Apparently, isomers (**3**) and (**4**) were formed because the reaction was too acidic and the temperature was too high. The undesirable isomers (**3**) and (**4**) can be avoided by conducting the dehalogenation reaction in a mixture of acetic acid and water at room temperature. In this fashion, ketone (**2**) was obtained exclusively. The mechanism of formation of isomers (**3**) and (**4**) can be rationalized as an electrocyclic opening of an intermediate cyclobutene derivative (see Scheme 15).



Scheme 15. Mechanism of Formations of (**3**) and (**4**).

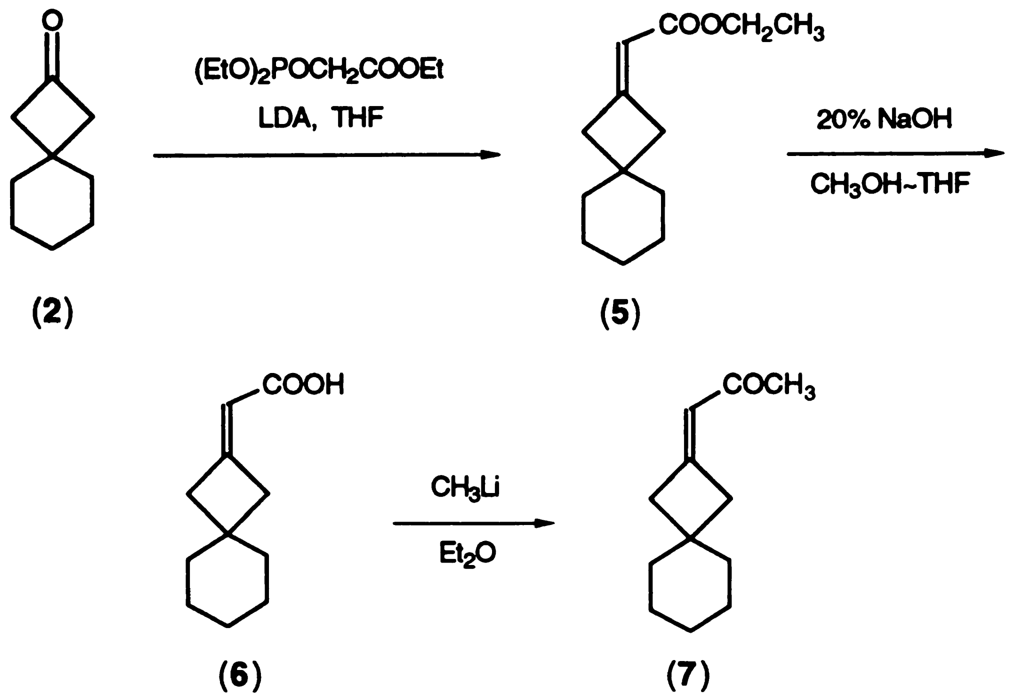
The structure of dichloroketone (**1**) was evident from its spectroscopic characteristics. The mass spectrum showed signals at m/z 210, 208, 206, which were indicative of two chlorine atoms in the molecular ion. A signal at δ 193.1 ppm in the ^{13}C NMR and an infrared absorption at 1809 cm^{-1} reflected the presence of a cyclobutanone carbonyl group.

The structures of ketones (**2**), (**3**) and (**4**) were confirmed by comparing their ^{1}H NMR data with those reported in the literature.[16,17] (see Table 1)

Table 1. ^{1}H NMR Spectra of (**2**), (**3**) and (**4**).

	^{1}H NMR (δ) ppm
(**2**) reported[16]	2.68 (s, 4H), 1.8~1.3 (m, 10H)
(**2**) observed	2.70 (s, 4H), 1.61~1.63 (d, J = 7.0 Hz, 4H), 1.41~1.54 (broad s, 6H)
(**3**) reported[17]	5.55 (m, 1H), 2.94 (broad m, 2H), 2.07 (s, 3H), 1.3~2.2 (8H, broad,)
(**3**) observed	5.56 (m, 1H), 3.00 (m, 2H), 2.13 (m, 3H), 2.03 (m, 2H), 1.88~1.98 (m, 2H), 1.52~1.63 (m, 4H)
(**4**) reported[17]	5.94 (1H, m), 2.1 (3H, s), 1.3~2.2 (broad, 10H)
(**4**) observed	5.99 (m)

Wittig-Horner olefination[18] of ketone (**2**) with the triethylphosphonoacetate derived carbanion proceeded as anticipated; ethyl spiro[3,5]-2-nonanylideneacetate (**5**) was isolated in 91.2% yield. Base hydrolysis of ester (**5**) gave spiro[3,5]-2-nonanylideneacetic acid (**6**) in 84.9% yield. Acid (**6**) then reacted with two equivalents of methyllithium[19] to give 1-spiro[3,5]-2'-nonanylidene-2-propanone (**7**) in 91% yield (see Scheme 16).



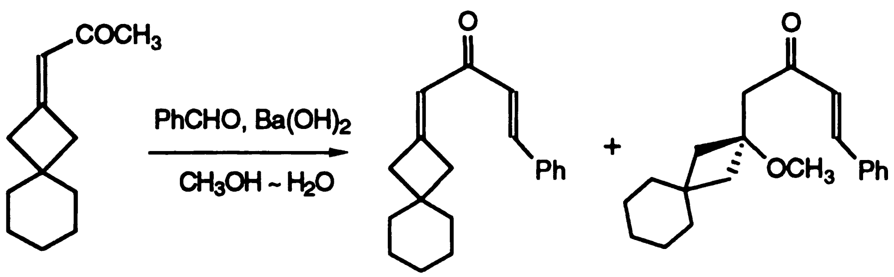
Scheme 16. Preparation of (7).

The spectroscopic characteristics of (5) supported its structure assignment. The molecular ion was found at m/z 208 in the mass spectrum. An infrared absorption at 1716 cm^{-1} and a ^{13}C NMR signal at δ 166.5 ppm were indicative of the carbonyl group. Signals at δ 163.5 and 114.2 ppm in the ^{13}C NMR and a signal at δ 5.68~5.64 (m, 1H) in the ^{1}H NMR were indicative of the double bond. Finally, the ethoxy group was reflected by ^{13}C NMR signals at δ 59.5 and 14.4 ppm, and ^{1}H NMR signals at δ 4.14 (q, J = 7.2 Hz, 2H) and 1.27 (t, J = 7.2 Hz, 3H) ppm.

The molecular ion of acid (**6**) was found at m/z 180 in the mass spectrum. The carboxyl group was characterized by infrared absorptions at 3350~2400 and 1688 cm^{-1}, and a signal at δ 11.5 ppm in the ^1H NMR.

The molecular ion of methyl ketone (**7**) was found at m/z 178 in the mass spectrum. An infrared absorption at 1697 cm^{-1} and a signal at δ 197.8 ppm in the ^{13}C NMR were indicative of the carbonyl group. A signal at δ 2.08 (s, 3H) ppm in the ^1H NMR was indicative of the methyl group.

Aldol condensation of methyl ketone (**7**) with benzaldehyde was more difficult to accomplish than anticipated. Under conventional reaction conditions,[20] with one equivalent of benzaldehyde in a 1:1 mixture of aqueous 20% sodium hydroxide solution and 95% ethanol at room temperature, the reaction gave benzoic acid and benzyl alcohol, products of the Cannizzaro reaction,[21] plus a small amount of starting material and an intractable product mixture. Alternatively, when (**7**) was refluxed with one equivalent of benzaldehyde and 0.43 molar equivalents of barium hydroxide[22] in 95% ethanol overnight, dienone (**8**) was isolated in about 15% yield. The Cannizzaro reaction products of benzaldehyde were not observed, possibly due to fact that the barium hydroxide was poorly soluble in ethanol. Encouraged by this result, we lowered the reflux temperature by using methanol instead of ethanol; thus, methyl ketone (**7**) was reacted with one equivalent of benzaldehyde in methanol to give a mixture of dienone (**8**) (31.8% yield based on ^1H NMR integration) and 2-methoxyl-2-(2'-oxo-(E)-4'-phenyl-3'-butenyl) spiro[3,5]nonane (**9**) (56.5% yield based on ^1H NMR integration) (see Scheme 17). This mixture of (**8**) and (**9**) was refluxed with a catalytic amount of iodine in benzene to give (8) in 86.5% overall yield. 1,4-Addition of methanol to the activated enone double bond of (8) is facilitated by angular strain relief, since the sp^3 β-carbon atom in (9) is less strained than the sp^2 β-carbon in (8).



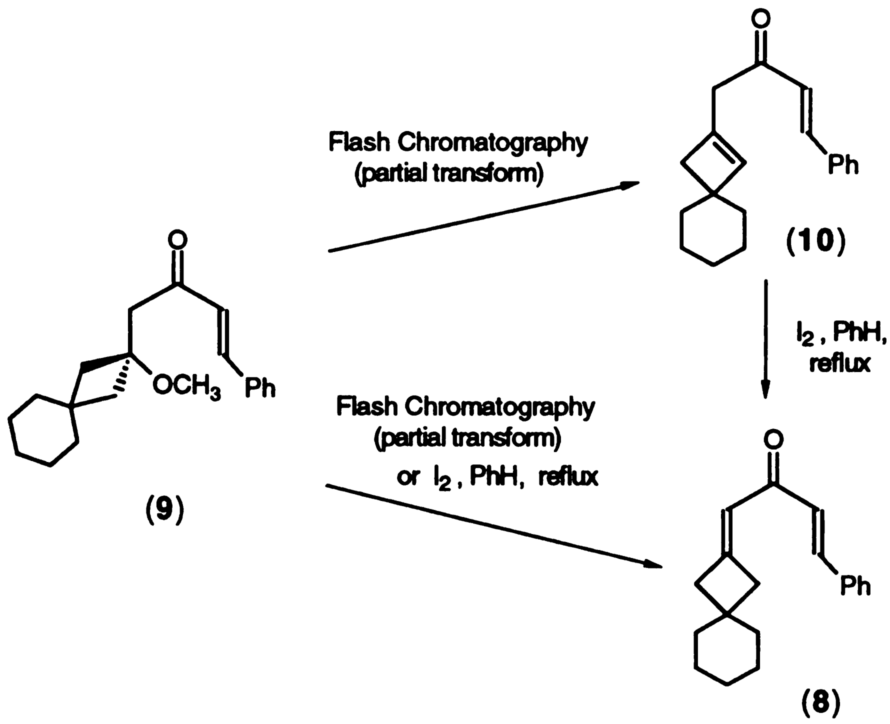
(7) (8) (9)

Scheme 17. Aldol Condensation of (7) with Benzaldehyde.

The structure of (8) was confirmed by spectroscopic evidence. The molecular ion was observed at m/z 266 in the mass spectrum. An infrared absorption band at 1676 cm^{-1} and a signal at δ 189.3 ppm in the ^{13}C NMR indicated the carbonyl group. Infrared absorptions at 3060, 3025 cm^{-1}, together with ^{13}C NMR signals at δ 164.3, 141.9, 135.0 and 130.1 ppm and ^{1}H NMR signals at δ 7.55 (d, J = 16.1Hz, 1H), 6.79 (d, J = 16.1Hz, 1H) and 6.34 (m, 1H) ppm indicated the two double bonds.

The molecular ion of (9) was found at m/z 298 in the mass spectrum. A signal at δ 3.18 (s, 3H) ppm in the ^{1}H NMR was indicative of the methoxy group, and an AB quartet in the ^{1}H NMR at δ 1.94 ppm (J = 12.9 Hz, $\Delta\nu_{AB}$ =19.3 Hz, 4H) was indicative of the two methylene groups on the cyclobutane ring.

About 3~14% compound (**9**) decomposed to 2-(2'-oxo-(E)-4'-phenyl-3'-butenyl) spiro[3,5]nonene (**10**) and dienone (**8**) during flash chromatography. When compound (**9**) or (**10**) was treated with a catalytic iodine[23] in refluxing benzene containing 4A° molecular sieves, it was converted to dienone (**8**) quantitatively (see Scheme 18).



Scheme 18. Transformations of (**9**) and (**10**).

The molecular ion of (**10**) was found at m/z 266 in the mass spectrum. Signals at δ 6.04 (m, 1H) ppm in the ^{1}H NMR indicated a olefinic hydrogen in the endocyclic double bond and signals at δ 2.84 (s, 2H), 2.45 (s, 2H) ppm in the ^{1}H NMR indicated methylene hydrogens adjacent to the carbonyl group and methylene hydrogens in the cyclobutane ring.

The 5 : 1 product ratio of (**3**) and (**4**) (Scheme 14), and the isomerization of (**10**) to (**8**) (Scheme 18) can be analyzed from a thermodynamic standpoint. According to studies of Allinger,[24] the differences of calculated MM2 energies in kcal/mole (heats of formation, gas phase, 25 °C) (experimental values in parentheses) for exo-endo ratios in six- and four-membered rings are, respectively, 3.29 (2.3) and 1.15 (0.9) kcal/mole. In the six-membered ring, torsion strain of the eclipsing unit is greater than angle strain, and the endocyclic double bond is favored. With the four-membered ring, on the other hand, angle strain is greater than torsion, and the endocyclic double bond is disfavored. Thus, dienone (**8**) (exocyclic bond) is more stable than dienone (**10**) (endocyclic bond).

With the synthesis of dienone (**8**), we have achieved one of the objectives of this work. We next proceeded to study the Nazarov reactions of this compound.

CYCLIZATION RESULTS AND DISCUSSIONS

The Nazarov cyclization, a thermal conrotatory ring closure of divinyl ketones in acidic medium, generally leads to cyclopentenones in excellent yields.[25] The most useful reagent for this purpose has been reported to be a H_3PO_4/HCOOH mixture.[26] Various other mineral acids or Lewis acids have also been applied.[27] Nazarov cyclization reactions are "temperamental" in that a given set of reaction conditions will often not work as a general method. In this dissertation, after an initial unsuccessful attempt to use ferric chloride, a wide variety of acids and temperatures conducive to the desired cyclizations of dienone (**8**) were screened by ^1H NMR. The Nazarov reactions were then carried out on a preparative scale. Among the reaction conditions investigated for cyclization of dienone (**8**) were: a mixture of phosphoric acid and formic acid; a mixture of phosphoric acid, formic acid and tetrahydrofuran; sulfuric acid; hydrochloric acid; trifluoroacetic acid; iodomethylsilane; boron trifluoride etherate and tin(IV) chloride.

An initial cyclization study of dienone (**8**), using ferric chloride in methylene chloride solution ($FeCl_3/CH_2Cl_2$),[13] gave a pale yellowish solid, insoluble in most organic solvents and water, plus a poor yield of recovered starting material. Broad signals in the ^1H NMR spectrum were not helpful for product identification. Examination of the product mixture suggested that the major loss of dienone was due to polymerization, oxidation or other degradation, and this procedure was not studied further.

A survey of acidic catalyst effectiveness was made by ^1H NMR (Table 2). Solutions of (**8**) in deuterated chloroform were treated with two drops of a catalyst solution. Initial ^1H NMR spectra were taken immediately after mixing (<15 minutes).

Table 2. Reactions of (**8**) Monitored by ^1H NMR.

Entry	Catalysts	<15 minutes, 25 °C	12 hours, 25 °C	12 hours, 40~45 °C
1	conc. HCl	SM[a] + (**14**)[c] (12 : 13)[c]	(**14**)[c]	
2	CF_3COOH	SM[a]	SM[a]	SM[a]
3	BF_3 Ether	SM[a]	SM[a]	SM[a] + (**17**)[d] + Unknown[b] (3 : 1)[d]
4	$SnCl_4$	SM[a]	SM[a] + (**17**)[d] + Unknown[b] (8 : 5)[d]	SM[a] + (**17**)[d] + Unknown[b] (2 : 3)[d]

(a) SM indicated starting material.

(b) Unknown means broad unresolved signals in ^1H NMR spectrum.

(c) Molar ratio was determined by ^1H NMR integration of (**14**) compared to (**8**), compound (**14**) was isolated later.

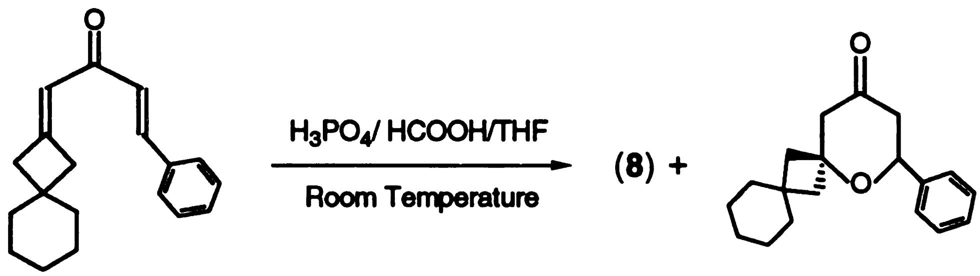
(d) Molar ratios were determined by ^1H NMR integration of the downfield signal of compound (**17**) compared to (**8**), compound (**17**) was isolated later.

Larger scale reactions catalyzed by phosphoric acid, hydrochloric acid, iodotrimethylsilane and tin(IV) chloride were then carried out, as described in the following sections.

1. The Phosphoric Acid Catalyzed Reactions.

(1) Reaction at Room Temperature

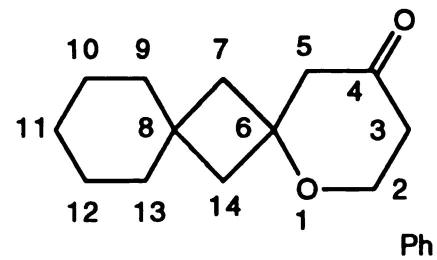
Dienone (**8**) proved to be insoluble in 85% phosphoric acid, or a mixture of 85% phosphoric acid and 88% formic acid; however, it gave a homogeneous solution in a mixture of phosphoric acid, formic acid and tetrahydrofuran. This resulting solution gave recovered starting material and dispiro[cyclohexane-1,1'-cyclobutane-3',2"-6"-phenyldihydro-2"*H*-pyran-4"(3"*H*)-one] (**11**) (see Scheme 19). Compound (**11**) was isolated in 31% yield.



(**8**) (**11**)

Scheme 19. Reaction of (**8**) with Phosphoric Acid at 25 °C.

The structure of (**11**) was assigned with the assistance of ^{1}H NMR decoupling experiments and DEPT in the ^{13}C NMR (see Figure 2).

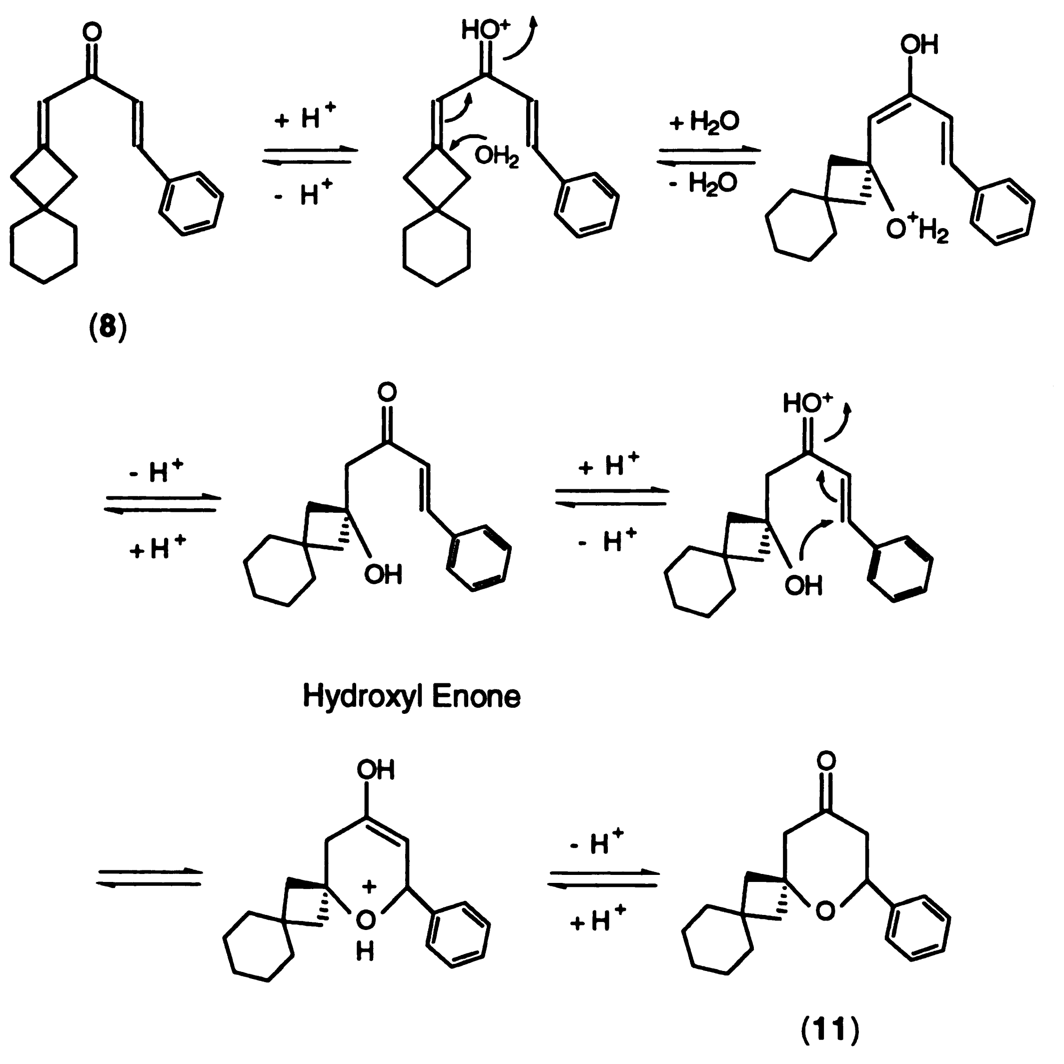


m/z 284 (1) (MS)	molecular ion
1720 cm^{-1} (IR), δ 206.5 ppm (^{13}C NMR)	carbonyl group
δ 4.68(t, J = 7.5 HZ, 1H), 2.52 (d, J = 7.5 Hz, 2H) ppm (^{1}H NMR)	$C^{2}H$-$C^{3}H_2$
δ 1.86 (m, 2H) ppm (^{1}H NMR)	$C^{5}H_2$
δ 2.60 (AB, q, J = 13.8 Hz, $\Delta\nu_{AB}$ = 37.4 Hz, 2H) and	
δ 2.06 (AB, q, J = 12.6 Hz, $\Delta\nu_{AB}$ = 70.6 Hz, 2H) ppm(^{1}H NMR)	$C^{7}H_2$ and $C^{14}H_2$

Figure 2. Spectroscopic Characteristics of (**11**).

The structure of (**11**) was then confirmed by chemical reaction. Thus, reflux of (**11**) with catalytic amounts of iodine and p-toluenesulfonic acid monohydrate in benzene solution gave 58% dienone (**8**) plus recovered (**11**) (determined by ^{1}H NMR). This result leaves no doubt as to the identity of (**11**).

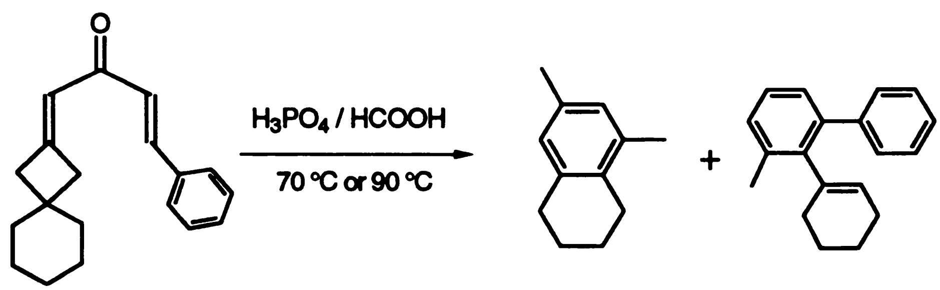
Formation of compound (**11**) can be rationalized (see Scheme 20) as an acid catalyzed 1,4-addition of water to the activated enone double bond to give an hydroxyl enone, which then cyclized by 1,4-addition to the conjugated double bond. This process is, of couse, reversible.



Scheme 20. Mechanism of Formation of (**11**).

(2) Reactions at High Temperature

Reaction of dienone (**8**) with a mixture[26] of 85% phosphoric acid and 88% formic acid at 90 °C gave 5,7-dimethyltetralin (**12**)[28] and 2-cyclohexenyl-1-methyl-3-phenylbenzene (**13**) in 64% and 10% isolated yield (see Scheme 21). No starting material was recovered.



(**8**) (**12**) (**13**)

Scheme 21. Reaction of (**8**) with Phosphoric Acid.

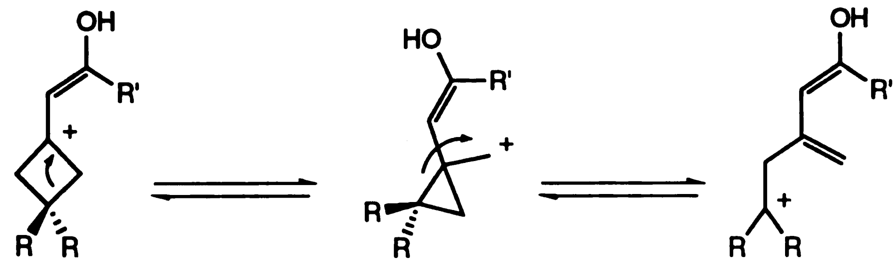
The molar ratios of these products at 70 °C or 90 °C were determined by Gas Chromatography and are given in Table 3. The proportion of (**12**) increased with reaction temperature.

Table 3. Products from Reactions of (**8**) with Phosphoric Acid.

Entries	Reaction Conditions (**8**), 85% H_3PO_4, 88% HCOOH	Molar Ratio (GC) of Products (**12**) : (**13**)
1	0.2 g, 5 mL, 10 mL, 70 °C, 3 h	1 : 5
2	0.49 g, 5 mL, 5 mL, 90 °C, 3 h	6 : 1

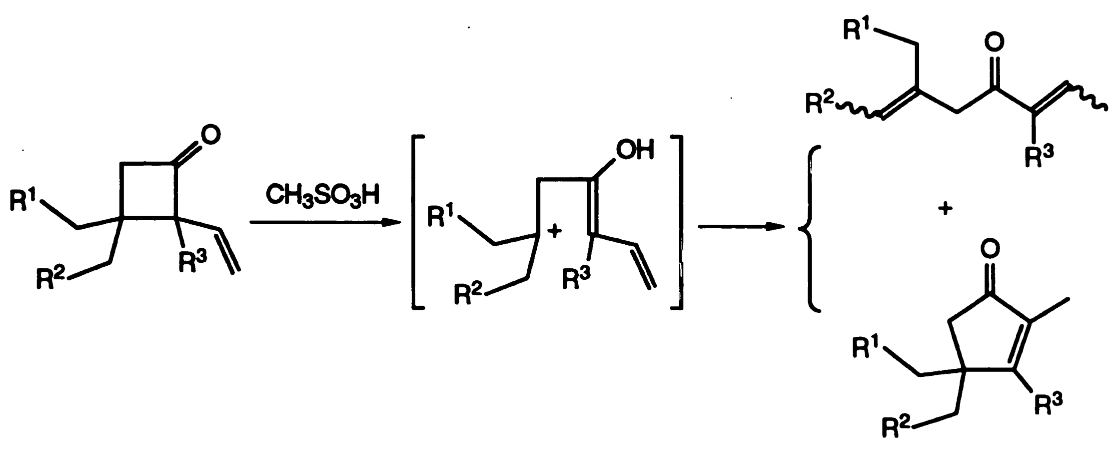
We were initially puzzled by the unanticipated nature of these products and at first assumed they were impurities from solvents. Eventually, the structures of (**12**) and (**13**) were established by spectroscopic methods. The structure of (**12**) was confirmed by comparing its spectra with those reported in the literature.[28] The structure of (**13**) was assigned on the following evidence. A molecular ion at m/z 248 in the mass spectrum was consistent with the $C_{19}H_{20}$ composition. Signals at δ 137.8, 137.4, 136.5, 134.8, 131.8, 129.9, 129.5, 128.7, 127.4, 126.7, 126.5, 123.8 ppm in the ^{13}C NMR indicated twelve distinct sp^2 carbons. A signal at δ 2.42 (s, 3H) ppm in the ^1H NMR was assigned to the aryl methyl group, and signals at δ 2.92~2.82 (m, 4H) and 2.00~1.81 (m, 4H) ppm in the ^1H NMR resulted from the other aliphatic hydrogens.

It is clear that the conversion of (**8**) to (**12**) and (**13**) must involve four-membered ring cleavage at some stage. We attribute this unexpected result to geminal-dialkylation on the distal carbon in the cyclobutylidene, which favors the 3°-homoallyl cation component of the cyclobutyl cation contributor of the conjugated acid of (**8**),[29] as shown in Scheme 22. This, of course, diverts the proposed Nazarov cyclization to other modes of reaction.



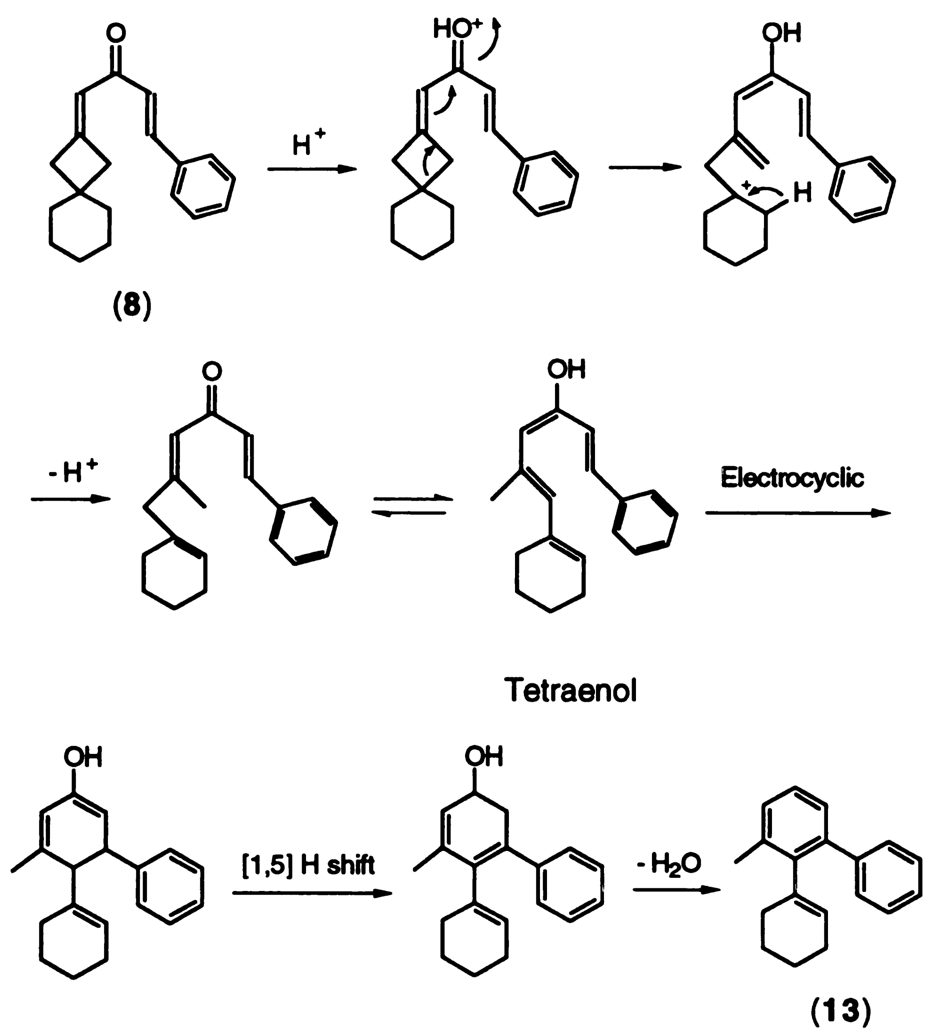
Scheme 22. Cyclobutyl Cation Equilibria.

A similar substitution effect may be operating in the reported acid-catalyzed reactions of 2-vinyl-2,3,3-trialkylcyclobutanone,[30] as shown in Scheme 23.



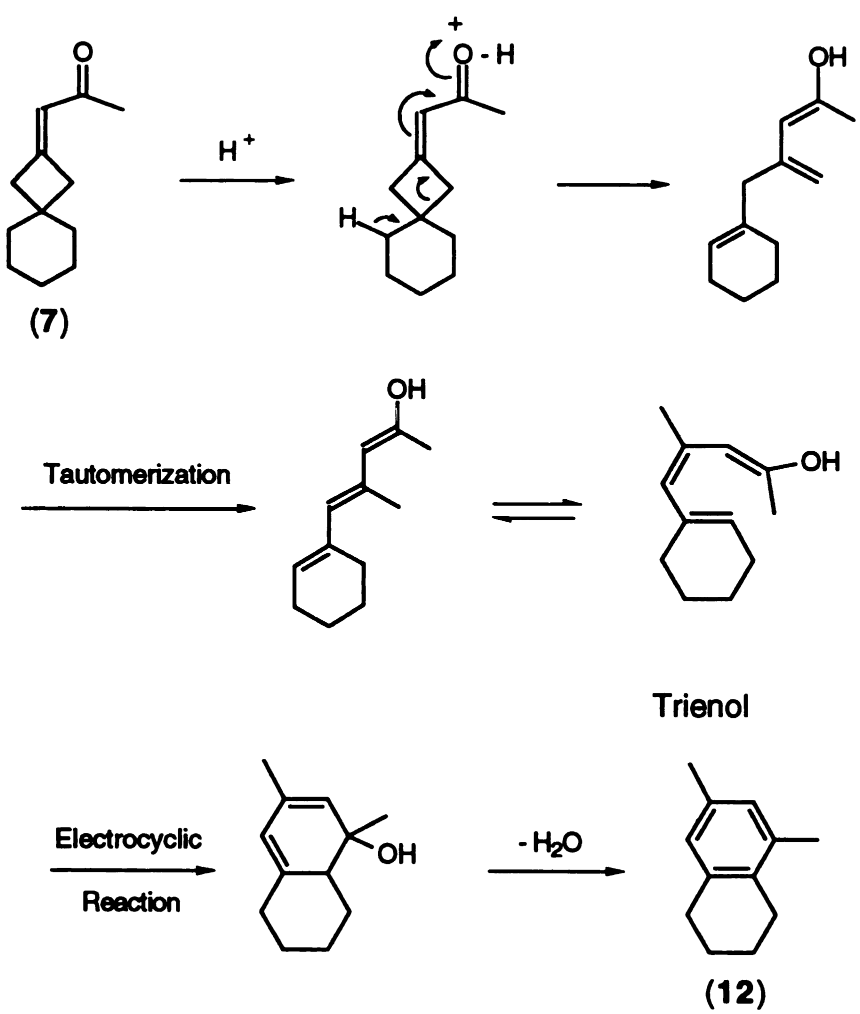
Scheme 23. Reactions of 2-Vinyl-2,3,3-trialkylcyclobutanone

Formation of compound (**13**) can be rationalized as a cyclobutane ring cleavage and tautomerism to a tetraenol, followed by an electrocyclic reaction, [1,5] hydrogen shift, and dehydration to give (**13**) (see Scheme 24) .



Scheme 24. Mechanism of Formation of (**13**).

Formation of compound (**12**) may be rationalized in a similar way, assuming a prior retro-aldol fragmentation of (**8**) to give methyl ketone (**7**). Protonated (**7**) may then experience an initial cyclobutane ring cleavage, followed by tautomerism, electrocyclic closure and dehydration to give compound (**12**) (see Scheme 25).



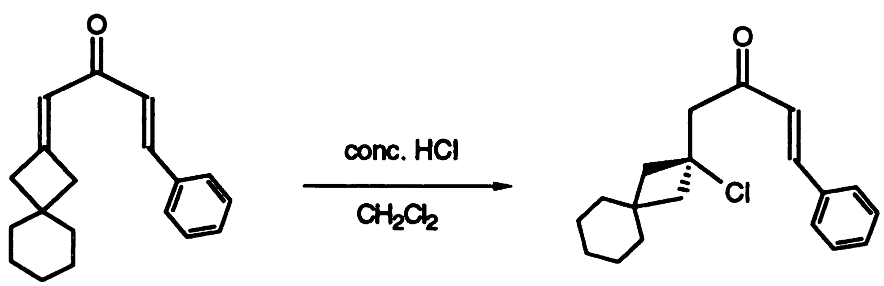
Scheme 25. Mechanism of Formation of (**12**).

The above mechanism was supported by the fact that, under the same reaction conditions, methyl ketone (**7**) gave compound (**12**) quantitatively.

From Table 3, we can see that the retroaldol condensation of dienone (**8**) presumably increases with reaction temperature, as the proportion of product (**12**) increases.

2. The Hydrochloric Acid Catalyzed Reaction.

Dienone (**8**) in methylene chloride solution was reacted with hydrochloric acid[11(d)] at room temperature to give 2-chloro-2-(2'-oxo-(E)-4'-phenyl-3'-butenyl) spiro[3,5]nonane, (**14**), quantitatively (see Scheme 26) via 1,4-addition to the activated enone double bond.



(**8**) (**14**)

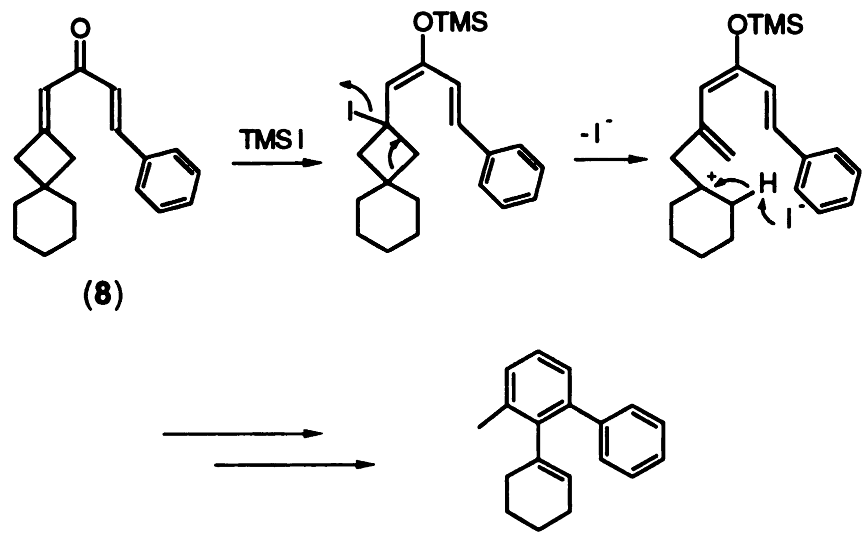
Scheme 26. Hydrochloric Acid Addition to (**8**).

The molecular ion of (**14**) was found at m/z 302 in the mass spectrum. An infrared absorption at 1698 cm^{-1} and a ^{13}C NMR signal at δ 198.1 ppm were indicative of the carbonyl group. A signal at δ 3.02 (s, 2H) ppm in the ^{1}H NMR was generated by the methylene hydrogens adjacent to the carbonyl function. A signal at δ 2.44 (m, 4H) ppm in the ^{1}H NMR reflects the methylene hydrogens on the cyclobutane ring.

3. The Iodotrimethylsilane Catalyzed Reaction.

When dienone (**8**) was reacted with chlorotrimethylsilane and sodium iodide in dimethyl formamide,[31] 2-cyclohexenyl-1-methyl-3-phenylbenzene, (**13**), was obtained in high yield.

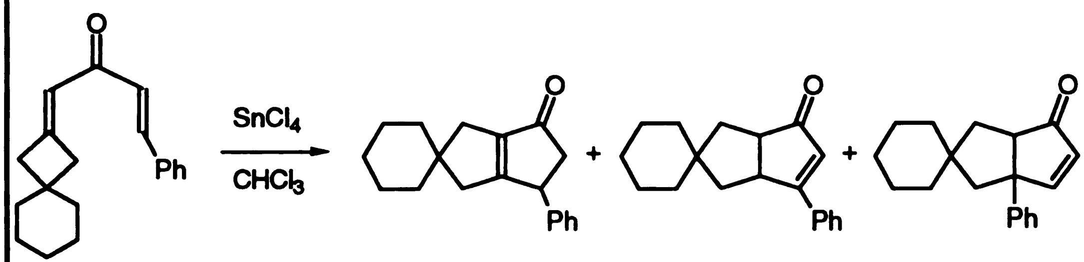
We reasoned that iodotrimethylsilane might form an intermediate silyl enol ether iodide. This very reactive iodide could then initiate a series of tautomerization and hydrogen shifts to give (**13**) (see Scheme 27), which is similar as Scheme 24.



Scheme 27. Mechanism of Formation of (**13**).

4. The Tin (IV) Chloride Catalyzed Reactions.

Refluxing a solution of dienone (**8**) with one equivalent of tin (IV) chloride[27] in chloroform gave dicyclopentanoids (**15**), (**16**) and (**17**) in 20.8%, 16.2% and 34.0% GC yields respectively using phenanthrene as an internal standard (see Scheme 28). The superiority of tin(IV) chloride in effecting the Nazarov cyclization of (**8**) is remarkable.



(8) (15) (16) (17)

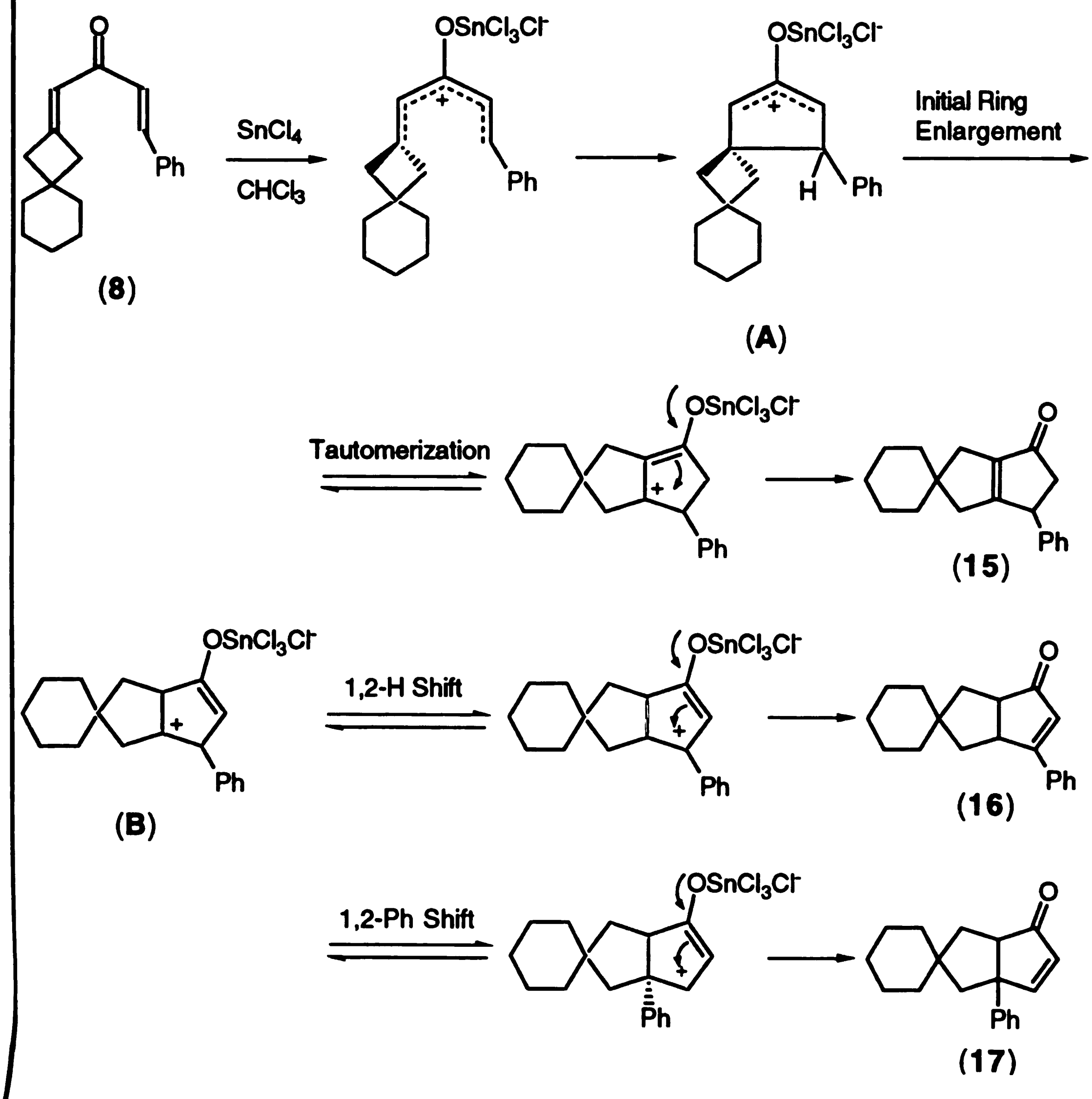
Scheme 28. Reaction of (8) with Tin (IV) Chloride.

GC yields of (**15**), (**16**) and (**17**) are given in Table 4. Combined yields of isolated (**17**) with a isolated mixture of (**15**) and (**16**) averaged 70%. The proportion of (**15**), (**16**) and (**17**) in the product mixture varied slightly with the substrate to catalyst ratio, but in general was nearly equimolar.

Table 4. Products from Reactions of (8) with Tin(IV) Chloride.

Reaction Conditions ((8) : $SnCl_4$)	GC yield (%) (15)	(16)	(17)
1:1, 24 hours, reflux	20.8	16.2	34.0
1:2, 24 hours, reflux	24.8	33.7	26.6

The mechanism may be rationalized (Scheme 29) as Nazarov cyclization of (**8**) initially formed cyclopentenyl cation (**A**), which transformed to (**B**) via enlargement of cyclobutane ring. Cation (**B**) converted subsequently to (**15**), (**16**) via 1,2-hydrogen shift, and (**17**) via a 1,2-phenyl shift.



Scheme 29. Mechanism of Formation of (**15**), (**16**) and (**17**).

Discussions about the mechanism:

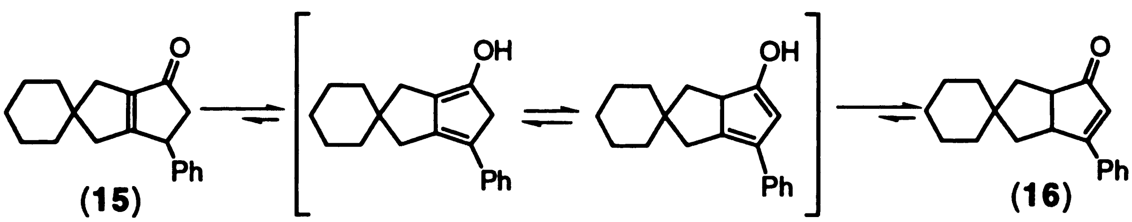
(1) GC analysis indicated that treatment of each of the isomers (**15**), (**16**) and (**17**) in turn under the reaction conditions gave essentially no converision to the other two (< 3%). This suggests that the product mixture obtained from the tin (IV) chloride-induced Nazarov reaction reflects the relative rates at which (**B**) is converted to (**15**), (**16**) and (**17**), i.e. kinetic product control.

(2) When each of the isomers (**15**), (**16**) and (**17**) was refluxed respectively with p-toluene-sulfonic acid monohydrate in chloroform solution, and monitored by GC analysis. Isomer (**15**) was transformed to (**16**) within 24 hours (Table 5). For isomer (**16**), no transformations to either (**15**) or (**17**) were observed during 48 hours period. For isomer (**17**), no transformation to (**15**) and little transformation (< 3% GC yield) to (**16**) were observed during 48 hours period.

Table 5. Acid Catalyzed Isomerizations of (**15**).

	Products: (**15**) : (**16**) : (**17**) (%)	Products: (**15**) : (**16**) : (**17**) (%)	Products: (**15**) : (**16**) : (**17**) (%)	Products: (**15**) : (**16**) : (**17**) (%)
Time (hours)	12	24	36	48
(**15**)	79.6 : 11.2 : 0.0	0.0 : 89.0 : 1.6	0.0 : 75.8 : 1.5	0.0 : 59.3 : 1.2

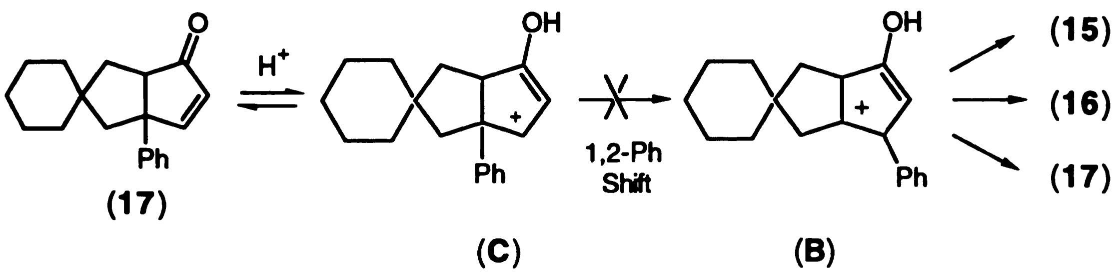
Isomerization of (**15**) to (**16**) indicated interconversion of (**15**) and (**16**) may occur via their common unstable β,γ-unsaturated isomer (Bredt's rule) (see Scheme 30). We expect that the fully conjugated isomer (**16**) is thermodynamically more stable and predominate at equilibrium.



β,γ-unsaturated ketone

Scheme 30. Acid Catalyzed Isomerization of (**15**), and (**16**).

The failure of (**17**) to isomerize indicated that the 1,2-phenyl shift would not occur easily (Scheme 31), and we suggest this reflects a high barrier for the conversion of the oxyallyl conjugate acid cation (**C**) to the isolated cation (**B**), a key species in these reactions (Scheme 29). Apparently, if (**B**) were generated, an equilibrium pathway would exist, and isomer (**16**) would presumably be the favored component.



Scheme 31. Isomerization of **17**).

(3) None of secondary rearrangement products in Scheme 12 (see Figure 3) via an initial 1,2-hydrogen shift or an initial 1,2-phenyl shift were observed. We concluded that the cyclobutane enlargement predominated a 1,2-hydrogen shift or a 1,2-phenyl shift under the Nazarov reaction conditions.

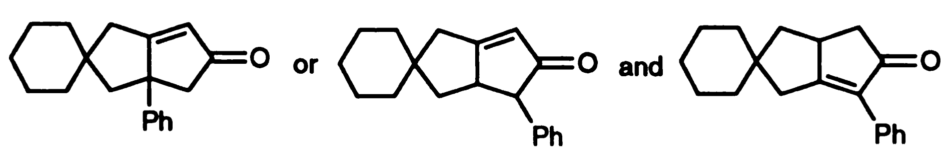
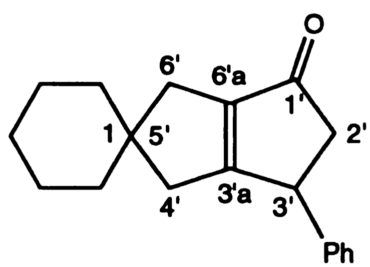


Figure 3. Cyclopentanoids.

It is interesting to note that UV absorption spectroscopy nicely distinguishes these isomers, the $\pi \rightarrow \pi^*$ max being λ_{max} 241 nm for (**15**), 289 nm for (**16**), and 217 nm for (**17**).

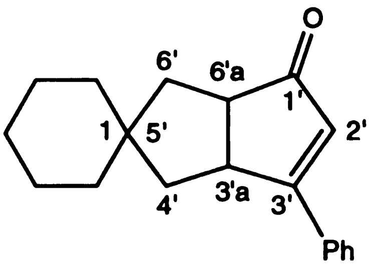
The structure of (**15**), spiro[cyclohexane-1,5'-3'-phenyl-3',4',5',6'-tetrahydropentalen-1'(2'*H*)-one], was assigned on the following evidence (see Figure 4).



m/z 266 (100) (MS)	molecular ion
1699 cm^{-1} (IR), δ 203.7 ppm (^{13}C NMR)	carbonyl group
δ 3.18 (dd, J =18.5, 6.6 Hz, 1H) and 2.65 (dd, J = 18.5, 2.2 Hz, 1H) ppm (^1H NMR)	$C^{2'}H_2$
δ 2.40~2.15 (m, 4H) ppm (^1H NMR)	$C^{4'}H_2$ & $C^{6'}H_2$
δ 3.00 (dd, J = 5.5 Hz, J = 8.9 Hz, 1H) ppm (^1H NMR)	$C^{6'a}H$

Figure 4. Spectroscopic Characteristics of (**15**).

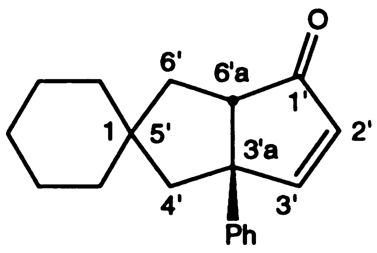
The structure of (**16**), spiro[cyclohexane-1,5'-3'-phenyl-4',5',6',6'a-tetrahydropentalen-1'(3'a*H*)-one], was assigned on the following evidence (see Figure 5).



m/z 266 (39) (MS)	molecular ion
1693 cm^{-1} (IR), δ 212.0 ppm (^{13}C NMR)	carbonyl group
3050 cm^{-1} (IR), δ 7.31 (s, 1H) ppm (^{1}H NMR)	$C^{2'}H$-$C^{3'}$
δ 3.80~3.78 (m, 1H), 3.12~3.03 (m,1H) ppm (^{1}H NMR)	$C^{3'a}H$-$C^{6'a}H$

Figure 5. Spectroscopic Characteristics of (**16**).

The structure of (**17**), spiro[cyclohexane-1,5'-3'a-phenyl-4',5',6',6'a-tetrahydropentalen-1'(3'a*H*)-one] was assigned on the following evidence with assistance of DEPT in the ^{13}C NMR (see Figure 6).



m/z 266 (32) (MS)	molecular ion
1711 cm^{-1} (IR), δ 213.5 ppm (^{13}C NMR)	carbonyl group
3050, 3015 cm^{-1} (IR), δ 7.64 (d, J = 5.5 Hz, 1H) and 6.00 (d, J = 5.5 Hz, 1H) ppm (^{1}H NMR)	$C^{2'}H$-$C^{3'}H$
δ 61.0 ppm (^{13}C NMR)	$C^{3'a}$
δ 2.11 (AB, q, J = 13.7 Hz, $\Delta\nu_{AB}$ = 25.7 Hz, 2H) ppm (^{1}H NMR)	$C^{4'}H_2$
δ 1.98 (m, 2H) ppm (^{1}H NMR)	$C^{6'}H_2$
δ 3.00 (dd, J = 5.5 Hz, J = 8.9 Hz, 1H) ppm (^{1}H NMR) and δ 58.0 ppm (^{13}C NMR)	$C^{6'a}H$

Figure 6. Spectroscopic Characteristics of (**17**).

CONCLUSION

We have learned that additions of the activated double bond of the cyclobutylidene substrate are competitive side reactions for the Nazarov reactions. This complication can be avoided by not using nucleophilic acids, such as: hydrochloric acid, hydrobromic acid or titanium (IV) chloride.[32]

The choice of substrate (**8**) for this study was made for ease of synthesis. However, an unfortunate consequence of this selection was that the geminal-dialkylation at the homoallylic position of the cyclobutylidene moiety served to divert the reaction from the desired Nazarov course. Although our selection of (**8**) as a substrate for this study introduced unnecessary complications, the tin (IV) chloride procedure demonstrates that subsequent ring enlargement rearangements may be effectively coupled to Nazarov ring closure to give fused cyclopentane ring systems.

In summary, we have achieved some success in our strategy of using the Nazarov cyclization coupled with cascade rearrangements to synthsize fused cyclopentane ring systems. The synthesis and rearrangement of a suitably functionalized dienones therefore gains credence as a new pathway to angular triquinanes. And Nazarov reactions need to be studied in much greater detail and their reaction conditions need to be optimized.

EXPERIMENTAL

General. All reactions were conducted under a dry argon or nitrogen atmosphere. All reagents were obtained from commercial suppliers and used without further purification, unless otherwise indicated. Et_2O and THF were freshly distilled under nitrogen from sodium/benzophenone ketyl. Benzene, hexane, methylene chloride, and diisopropylamine were freshly distilled under argon from calcium hydride. Magnetic stirrers were used for small scale reactions, large scale reactions were agitated using paddle stirrers. Organic extracts were dried over anhydrous sodium sulfate or magnesium sulfate. Thin layer chromatography (TLC) analyses were performed using Merck Aluminum-backed F_{254} Silica Gel plates. Ultraviolet light or a 5% sulfuric acid methanol solution with subsequent heating served for visualization. Flash chromatography was performed using Merck Silica Gel 60 (230~400 mesh, ASTM, column diameter 10~50 mm), according to the method of Still.[33] Gas liquid chromatography was performed on a Hewlett Packard 5880A gas chromatograph. Melting points were measured in glass capillaries on a Thomas-Hoover melting point apparatus, or on glass slides using a Reichert hot-stage microscope and are uncorrected. ^1H NMR spectra were obtained using Gemini 300 (300 MHz), Varian VXR 300 (300 MHz) or Varian VXR 500 (500 MHz) spectrometers. Chemical shifts for proton resonances are reported in parts per million (δ) downfield from TMS (δ = 0 ppm) or relative to residual chloroform (δ = 7.24 ppm) as internal standards. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br s, broad singlet;

overlapping m, overlapping multiplet. Coupling constants (J) are given in Hertz. ^{13}C NMR spectra were measured on Gemini 300 (75 MHz) or Varian VXR 300 (75 MHz) spectrometers. Chemical shifts for carbon resonances are reported in parts per million (δ) downfield from TMS (δ = 0 ppm) or deuterated chloroform triplet signal (δ = 77.0 ppm). Infrared (IR) spectra were obtained on a Nicolet PC/IR Fourier Transform spectrometer, equipped with a Nicolet IR/42 optical bench, using sodium chloride salt plates. Ultraviolet spectra were recorded on a Shimadzu UV 160 spectrometer. Mass spectra (MS) were obtained on a Finnigan 4000 GC/MS mass spectrometer equipped with an Incos 4021 data system or a TRIO-1 GC/MS mass spectrometer, both operating at an ionization energy of 70 ev. High resolution mass measurements were determined on a JEOL HX 100 spectrometer at the Michigan State University, Department of Biochemistry, Mass Spectroscopy Facility, East Lansing, Michigan. Microanalyses were conducted by Spang Microanalytical Laboratory, Star Rt. 1, Box 142, Eagle Harbor, Michigan 49951. Ultrasonic activation was accomplished by using a Bransonic Ultrasonic Laboratory cleaner (B-2200R-1, 117 volts, 50/60 Hz), partially filled with water at ambient temperature (15~20 °C).

Registry No. — spiro[3,5]nonan-2-one (**2**), 29800-56-4; 1-cyclohexenyl-2-propanone (**3**), 768-50-3; 1-cyclohexylidene-2-propanone (**4**), 874-68-0; 5,7-dimethyltetralin (**12**), 21693-54-90.

<u>**1,1-Dichlorospiro[3.5]nonan-2-one (1).**</u> To a 250 mL three-neck round bottomed flask fitted with a rubber septum, an addition funnel and a reflux condenser was added 2.00 g (20.8 mmol) methylenecyclohexane, 1.80 g (27.5 mmol) Zn dust and 100 mL of Et_2O. To this suspension, agitated by an ultrasonic bath (Branson 2200) and maintained at 20°C, was added 3.0 mL (4.89 g, 26.9 mmol) of trichloroacetic chloride in 50 mL of Et_2O dropwise over thirty minutes. This mixture was sonicated for three hours. The solid was removed by suction filtration through a Celite pad and washed with Et_2O. The ethereal extract was washed with saturated ammonium chloride, saturated sodium bicarbonate, brine, then dried over anhydrous sodium sulfate. Evaporation of solvent gave pale yellowish liquid 4.08 g (95.0% yield) of dichloroketone (**1**), and was used directly without further purification in the next step. ^1H NMR (300 MHz, $CDCl_3$) δ 3.03 (s, 2H), 1.88~1.62 (m, 7H), 1.38~1.22 (m, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.1, 93.2, 52.0, 46.1, 33.6, 25.0, 23.4 ppm; IR (NaCl) 2936, 2859, 1809, 1452, 990, 750 cm^{-1}; MS (EI) m/z (relative intensity) 210 (0.03), 208 (0.12), 206 (M, 0.19), 171 (5), 164 (34), 93 (29), 81 (73), 68 (100), 55 (35).

<u>**Spiro[3.5]nonan-2-one (2).**</u> A stirred mixture of 3.00 g (14.5 mmol) dichloroketone (**1**), 2.70 g (41.3 mmol) Zn dust, 60 mL of water and 40 mL of acetic acid was reacted overnight at room temperature. Solids were removed by suction filtration through a Celite pad and washed with hexane. The hexane extract was washed with 2 N aqueous sodium hydroxide to pH 10, then washed with brine and dried over anhydrous sodium sulfate. Evaporation of solvent gave a pale yellow liquid 1.78 g (88.9 % yield) of ketone (**2**), and was used directly without further purification in the next step. A small amount was

purified by flash chromatography using a 24:1 mixture of hexane and Et_2O to give a colorless liquid. ^1H NMR (300 MHz, $CDCl_3$) δ 2.70 (s, 4H), 1.63~1.61 (m, 4H), 1.54~1.41 (bs, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.7, 57.1, 37.5, 30.5, 25.6, 24.0 ppm; IR (NaCl) 2934, 2853, 1782 cm^{-1}; MS (EI) m/z (relative intensity) 138 (M, 3), 110 (9), 96 (23), 81 (100), 67 (70), 55 (54).

Dehalogenation of (1) in acetic acid. A stirred mixture of 2.00 g (9.6 mmol) dichloroketone (**1**), 1.6 g (24.5 mmol) Zn dust and 17 mL of acetic acid was reacted at 90 °C overnight. Solids were removed by suction filtration through a Celite pad and washed with hexane. The hexane extract was washed with 2 N aqueous sodium hydroxide to pH 10, then washed with brine and dried over anhydrous sodium sulfate. Evaporation of solvent gave a pale yellow liquid 1.07 g (80.1% yield) mixture of ketone (**2**), 2-cyclohexenyl-2-propanone (**3**) and 1-cyclohexenylidene-2-propanone (**4**) in a 9 : 5 : 1 molar ratio (determined by Gas Chromatography). Ketone (**2**) and a mixture of isomers (**3**) and (**4**) were isolated by flash chromatography using a 9 : 1 mixture of hexane and diethyl ether.

1-Cyclohexenyl-2-propanone (3). ^1H NMR (300 MHz, $CDCl_3$) δ 5.56 (s, 1H), 3.00 (s, 2H), 2.13 (s, 3H), 2.03 (m, 2H), 1.94~1.88 (m, 2H), 1.63~1.52 (m, 4H) ppm. MS (EI) m/z (relative intensity) 139 (1.6), 138 (M, 14), 123 (3), 95 (45), 80 (19), 67 (32).

1-Cyclohexylidene-2-propanone (4). (partial) ^1H NMR (300 MHz, $CDCl_3$) δ 5.99 (s) ppm.

Ethyl spiro[3.5]-2-nonanylideneacetate (5). A solution of LDA was prepared by reacting a cold (-78 °C) solution of 2.5 mL (1.81 g, 17.8 mmol) of diisopropylamine and 20 mL of THF with 6.0 mL 2.5 M (15.0 mmol) of BuLi in a 7 : 3 mixture of hexane and Et_2O (added dropwise over 10 minutes). The this was dropwise added a solution of 3.40 g (15.2 mmol) triethyl phosphonoacetate, followed 10 minutes, later by a solution of 2.00 g (14.5 mmol) ketone (**2**) in 5 mL of THF was added (temperature maintained at - 78 °C throughout). The cooling bath was removed and the resulting mixture was stirred at room temperature for two hours and then poured into water. This mixture was concentrated to a yellow slurry, hexane and brine were added. The hexane extract was washed with brine and dried over anhydrous sodium sulfate. Evaporation of solvent gave pale yellowish liquid 2.75 g (91.2% yield) of ester (**5**), and was used directly without further purification in the next step. A small amount was purified by flash chromatography using a 9 : 1 mixture of hexane and Et_2O to give colorless liquid. ^1H NMR (300 MHz, $CDCl_3$) δ 5.68~5.64 (m, 1H), 4.14 (q, J = 7.2 Hz, 2H), 2.79 (s, 2H), 2.48 (s, 2H), 1.50 (m, 4H), 1.47~1.34 (m, 6H), 1.27 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 163.5, 114.2, 59.5, 44.6, 43.3, 37.7, 36.9, 25.8, 23.3, 14.4 ppm; IR (NaCl) 3050, 2934, 2926, 2853, 1716, 1678, 1199, 1186 cm^{-1}; MS (EI) m/z (relative intensity) 208 (M, 85), 179 (32), 163 (59), 135 (100), 119 (53), 105 (51), 91 (63), 81 (77), 67 (43), 53 (33). High resolution MS, Cal., 208.1463 for formula $C_{13}H_{20}O_2$; Found, 208.1499.

Spiro[3.5]-2-nonanylideneacetic acid (6). 2.00 g (9.6 mmol) ester (**5**) and 50 mL of 20% sodium hydroxide. 20 mL of methanol and 5 mL of THF were mixed. After refluxing for two hours, this mixture was cooled to room temperature, 40 mL of water was added. most of the methanol was evaporated in a rotary evaporator. 15 mL of THF was added, methanol residue and tetrahydrofuran were evaporated in a rotary evaporator. The mixture was neutralized by 2 N hydrochloric acid and extracted with Et_2O. The ethereal extract was combined, washed with brine, then dried over sodium sulfate and evaporated of solvent. The white residue was recrystalized from absolute ethanol, dried in vacuum at 70 °C overnight to give 1.47 (84.9% yield) of acid (**6**), as white square crystals. mp 102 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 11.5 (s, 1H), 5.68 (m, 1H), 2.82 (s, 2H) 2.52 (s, 2H), 1.55~1.48 (m, 4H), 1.48~1.34 (m, 6H) ppm; ^{13}C NMR (75 MHz, CDCl3) δ 172.8, 168.3, 114.2, 45.1, 43.7, 37.7, 36.9, 25.8, 23.3 ppm; IR (NaCl) 3350~2400, 2926, 2849, 2631, 2550, 1688, 1655, 1449, 1433, 1408, 1292, 1259, 1240, 959, 938, 868, 845 cm^{-1}; MS (EI) m/z (relative intensity) 180 (M, 40), 162 (22), 135 (100), 121 (45), 98 (40), 81 (100), 67 (32), 55 (22).

1-Spiro[3.5]-2'-nonanylidene-2-propanone (7). A solution of 1.00 g (5.5 mmol) acid (**6**), 60 mL of Et_2O was cooled to 0 °C. 8.1 mL 1.4 M (11.3 mmol) of MeLi in Et_2O was added dropwise in 10 minutes. The resulting milk-white suspension turned pale yellow and following a 2 h reaction period at 0 °C was neutralized by 1 N hydrochloric acid and extracted with Et_2O. The ethereal extract was washed with brine and dried over sodium sulfate. Evaporation of solvent gave yellow liquid, which was purified by flash chromatography using a 9 : 1 mixture of hexane and Et_2O to give colorless liquid 0.90 g (91.0% yield) of methyl ketone (7). ^1H NMR (300 MHz, $CDCl_3$) δ 5.93 (m, 1H), 2.72 (s, 2H), 2.43 (s, 2H), 2.08 (s, 3H), 1.42 (d, J = 5.7 Hz, 4H), 1.40~1.25 (bs, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.8, 162.2, 124.0, 45.0, 43.5, 37.5, 36.8, 29.9, 25.5, 23.0

ppm; IR (NaCl) 2924, 2852, 1697, 1671, 1637, 1449, 1360, 1254, 1198, 1184 cm^{-1}; MS (EI) m/z (relative intensity) 179 (2), 178 (M, 6), 163 (13), 149 (13), 135 (100), 121 (25), 105 (23), 96 (45), 81 (66), 66 (70), 55 (63). High resolution MS, Cal., 178.1358 for formula $C_{12}H_{18}O$; Found, 178.1340.

Aldol condensation of (7). A 2.00 g (11.22 mmol) sample of methyl ketone (**7**), was mixed with 1.20 g (11.32 mmol) freshly distilled benzaldehyde, 90 mL of methanol, 0.82 g (4.79 mmol) barium hydroxide and 4 drops of water. This mixture was refluxed for two hours. 150 mL of water was added, and most of the methanol was removed by a rotary evaporator. 50 mL of THF was added; residual methanol and THF were removed by a rotary evaporator. The solution was gravity filtered and washed with Et_2O. The ethereal extract was washed with saturated ammonium chloride, brine, then dried over anhydrous sodium sulfate. Evaporation of diethyl ether gave 2.84 g yellow oil mixture of 2-(2'-oxo-(E)-4'-phenyl-3'-butenylidene) spiro[3,5]nonane (**8**) (31.8% yield based on ^1H NMR integration) and 2-methoxyl-2-(2'-oxo-(E)-4'-phenyl-3'-butenyl) spiro[3,5]-nonane (**9**) (56.5% yield based on ^1H NMR integration). The mixture was separated by flash chromatography, using a 9 : 1 mixture of hexane and Et_2O, to give 0.95 g (28.4% yield) of compound (**9**), 0.67 g mixture of dienone (**8**) (19.4% yield based on ^1H NMR integration) and 2-(2'-oxo-(E)-4'-phenyl-3'-butenyl) spiro[3,5]nonene **10**) (3.0% yield based on ^1H NMR integration). The yields changed from 31.8% : 56.5% : 0% to 19.4% : 28.4% : 3% for compounds (**8**), (**9**) and (**10**) indicated that during flash chromatography, (**9**) partially decomposed to (**8**) or (**10**).

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2-(2'-Oxo-(E)-4'-phenyl-3'-butenylidene) spiro[3.5]nonane (8). mp 44 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, J = 16.1 Hz, 1H), 7.51 (m, 2H), 7.36 (m, 3H), 6.79 (d, J = 16.1 Hz, 1H), 6.34 (m, 1H), 2.89 (m, 2H), 2.54 (m, 2H), 1.57~1.48 (m, 4H), 1.47~1.26 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.3, 164.3, 141.9, 135.0, 130.1, 128.8, 128.2, 127.1, 121.6, 45.6, 44.0, 37.6, 37.5, 25.7, 23.2 ppm; IR (NaCl) 3060, 3025, 2922, 2851, 1676, 1638, 1598, 1449, 1202, 694 cm^{-1}; UV (95% ethanol) λ_{max} 308 nm, ε_{max} 2.3x10^4, λ_{max} 227 nm, ε_{max} 6.8x10^3; MS (EI) m/z (relative intensity) 266 (M, 5), 223 (9), 184 (17), 167 (11), 153 (8), 141 (10), 131 (88), 115 (20), 103 (70), 91 (63), 77 (100), 67 (48), 55 (69). Elemental analysis, Cal., C, 85.66%; H, 8.33% for formula $C_{19}H_{22}O$; Found, C, 85.69%; H, 8.47%.

2-Methoxyl-2-(2'-oxo-(E)-4'-phenyl-3'-butenyl) spiro[3.5]nonane (9). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, J = 16.2 Hz, 1H), 7.54~7.50 (m, 2H), 7.35~7.32 (m, 3H), 6.79 (d, J = 16.2 Hz, 1H), 3.18 (s, 3H), 2.89 (s, 2H), 1.94 (AB, q, J = 12.9 Hz, $\Delta\nu_{AB}$ = 19.3 Hz, 4H), 1.49~1.30 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 142.2, 134.5, 130.2, 128.7, 128.2, 126.4, 74.8, 49.7, 49.3, 42.3, 39.2, 38.9, 31.6, 25.6, 23.0, 22.5 ppm; IR (NaCl) 3090, 3060, 3030, 2924, 2851, 1682, 1640, 1607, 1576, 1440, 1332, 1201, 1148, 1064, 978, 743, 693 cm^{-1}; MS (EI) m/z (relative intensity) 298 (M, 2) 266 (5), 238 (2), 202 (22), 174 (100), 128 (12), 103 (100), 91 (16), 77 (90), 67 (28), 55 (28).

2-(2'-Oxo-(E)-4'-phenyl-3'-butenyl) Spiro[3.5]nonene (10). (partial) ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.20 (d, J = 11.9 Hz, 1H), 6.04 (m, 1H), 2.84 (s, 2H), 2.45 (s, 2H) ppm; MS (EI) m/z (relative intensity) 266 (M, 27), 223 (28), 184 (40), 131 (100), 103 (60), 77 (45).

<u>**Conversion of (9) to (8).**</u> A solution of 0.95 g (3.34 mmol) compound (**9**) in 150 mL of benzene containing a catalytic amount iodine, 0.5 g 4A° molecular sieves was refluxed for three hours. The reaction mixture was filtered and washed with benzene. The benzene extract was washed with 20% sodium bisulfite, brine, then dried over anhydrous sodium sulfate. Evaporation of benzene gave 0.84 g (99% yield) of dienone (**8**).

<u>**Isomerization of (10).**</u> A 0.67 g mixture of dienone (**8**) and (**10**) (6 : 1 molar ratio, based on ^{1}H NMR integration) in 150 mL benznene contianing catalytic amount iodine, 0.5 g 4A molecular sieves was refluxed for three hours. The reaction mixture was filtered and washed benzene. The benzene extract was washed with 20% sodium bisulfite, brine, then dried over anhydrous sodium sulfate. Evaporation of benzene gave 0.66 g (98.5% yield) of dienone (**8**).

<u>**Reaction of (8) with phosphoric acid at room temperature.**</u> A solution of 0.300 g (1.13 mmol) dienone (**8**), 15 mL of 85% phosphoric acid, 7.5 mL of 88% formic acid and 7.5 mL of THF was stirred at room temperature for two hours and turned dark red. Benzene and water were added. The benzene extract was washed with saturated sodium bicarbonate, brine, then dried over anhydrous sodium sulfate. Evaporation of solvent gave 0.296 g pale yellowish liquid of product mixture. 0.099 g (31% yield) compound (**11**) was separated by flash chromatography, using a 9 : 1 mixture of hexane and ethyl acetate.

<u>**Dispiro[cyclohexane-1,1'-cyclobutane-3',2"-6"-phenyldihydro-2"*H*-pyran-4"(3"*H*)-one] (11).**</u> ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38~7.29 (m,

5H), 4.68 (t, J = 7.5 Hz, 1H), 2.60 (AB, q, J = 13.8 Hz, $\Delta\nu_{AB}$ = 37.4 Hz, 2H), 2.52 (d, J = 7.5 Hz, 2H), 2.06 (AB, q, J = 12.6 Hz, $\Delta\nu_{AB}$ = 70.6 Hz, 2H), 1.86 (s, 2H), 1.49~1.33 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.5, 140.9, 128.5, 127.8, 125.7, 75.5, 73.0, 53.9, 49.1, 45.7, 42.0, 40.1, 38.4, 31.1, 25.6, 22.9, 22.6 ppm; IR (NaCl) 3090, 3070, 3050, 2924, 2851, 1720, 1450, 1282, 1251, 1056, 989, 742, 698 cm^{-1}; MS (EI) m/z (relative intensity) 284 (M, 1), 266 (1), 131 (100), 104 (82), 94 (13), 81 (17), 67 (19), 56 (20), 41 (12). High resolution MS, Cal., 284.1776 for formula $C_{19}H_{24}O_2$; Found, 284.1723.

Reaction of (11). A 0.100 g (0.352 mmol) sample of compound (**11**) in 100 mL of benzene containing catalytic amounts of iodine and p-toluenesulfonic acid monohydrate was refluxed for four hours. The reaction mixture was filtered and washed with benzene The benzene extract was washed with 20% sodium bisulfite twice, brine, then dried over sodium sulfate. Evaporation of solvent gave a mixture of dienone (**8**) (58% yield, based on ^1H NMR integration) and recovered (**11**).

Reaction of (8) with phosphoric acid at 90 °C. A 0.490 g (1.84 mmol) sample of dienone (**8**) was mixed with 5 mL each of 85% phosphoric acid and 88% formic acid, Then heated at 90 °C for three hours. The dark blue mixture was diluted with 20 mL of water and heated an additional hour. Benzene and water were then added to the cooled reddish brown mixture. The benzene extract was washed with saturated sodium bicarbonate, brine, then dried over anhydrous sodium sulfate. Evaporation of solvent gave 0.38 g pale yellowish liquid of prduct mixture. 0.188 g (64% yield) of 5,7-dimethyltetralin (**12**) and

0.046 g (10% yield) of cyclohexenyl-1-methyl-3-phenylbenzene (**13**) were isolated by flash chromatography using hexane.

5,7-dimethyltetralin (12). ^1H NMR (300 MHz, $CDCl_3$) δ 6.82 (m, 1H), 6.77 (m, 1H), 2.74 (t, J = 6.3 Hz, 2H), 2.59 (t, J = 6.3 Hz, 2H), 2.26 (s, 3H), 2.18 (s, 3H), 1.89~1.71 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.9, 136.5, 134.4, 132.4, 127.9, 127.4, 30.0, 26.3, 23.5, 23.0, 20.8, 19.4 ppm; IR (NaCl) 3004, 2928, 2859, 2838, 1614, 1580, 1481, 1451, 1437, 847, 823, 700 cm^{-1}; MS (EI) m/z (relative intensity) 161 (5), 160 (M, 47), 145 (100), 132 (32), 117 (22), 105 (8), 91 (11), 77 (7), 65 (5).

2-Cyclohexenyl-1-methyl-3-phenylbenzene (13). ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (m, 1H), 7.60 (m, 1H), 7.48~7.32 (m, 5H), 7.07~6.96 (m, 2H), 2.92~2.82 (m, 4H), 2.42 (s, 3H), 2.00~1.81 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 137.4, 136.5, 134.8, 131.8, 129.9, 129.5, 128.7, 127.4, 126.7, 126.5, 123.8, 30.1, 26.5, 23.5, 22.8, 21.0 ppm; IR (NaCl) 3010, 3058, 3025, 3007, 2928, 2856, 2838, 1601, 1576, 1495, 1466, 1448, 1439, 1074, 1028, 960, 862, 752, 692 cm^{-1}; MS (EI) m/z (relative intensity) 250 (2), 249 (16), 248 (M, 100), 233 (67), 220 (25), 205 (50), 191 (16), 170 (18), 155 (35), 141 (22), 128 (34), 115 (33), 108 (27), 91 (46), 89 (17), 77 (16), 65 (7), 55 (1). High resolution MS, Cal., 248.1565 for formula $C_{19}H_{20}$; Found, 248.1563.

Conversion of (7) to (12). A 0.100 g (0.56 mmol) sample of methyl ketone (7) was added to a mixture of 4 mL each of 85% phosphoric acid and 88% formic acid. This mixture was stirred at 85~90 °C for three hours. Benzene and water were added to the dark red solution. The benzene extract was washed with saturated sodium bicarbonate, brine, then dried over anhydrous sodium sulfate. Evaporation of benzene gave 0.86 g (96% yield) of compound (**12**).

Addition of hydrochloric acid to (8). A 100 mL round bottomed flask equipped with a reflux condenser and a magnetic stirrer was alternately evacuated and filled with argon. 0.25 g (0.94 mmol) dienone (**8**), 30 mL of methylene chloride and 30 drops of concentrated hydrochloric acid were added. The mixture was stirred at room temperature for 24 hours and pured to water. Methylene chloride was added. The methylene chloride extract was washed with brine, then dried over sodium sulfate. 0.27 g (yield 95%) liquid of compound (**14**) was isolated.

2-Chloro-2-(2'-oxo-(E)-4'-phenyl-3'-butenyl) spiro[3.5]nonane (14). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59~7.51 (m, 2H), 7.55 (d, J = 16.0 Hz, 1H), 7.41~7.35 (m, 3H), 6.77 (d, J = 16.0 Hz, 2H), 3.02 (s, 2H), 2.44 (s, 4H), 1.74~1.67 (m, 2H), 1.47~1.25 (m, 8H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 196.4, 143.0, 134.3, 130.5, 128.9, 128.3, 126.5, 62.8, 54.6, 49.7, 39.3, 39.1, 33.6, 25.4, 23.1, 22.8, 22.5 ppm; IR (NaCl) 3070, 3040, 3030, 2924, 2851, 1698, 1669, 1638, 1609, 1448, 978, 756, 692 cm^{-1}; MS (EI) m/z (relative intensity) 302 (M, 2), 268 (16), 267 (68), 266 (48), 223 (41), 184 (47), 175 (21), 131 (100), 115 (22), 103 (95), 91 (57), 77 (91), 67 (36), 55 (44).

Reaction of (8) with iodotrimethylsilane. A solution of 0.100 g (0.376 mmol) dienone (**8**) and 0.563 g (3.76 mmol) sodium iodide in 2 mL of DMF was treated with 0.48 mL (0.41 g, 3.77 mmol) of chlorotrimethylsilane. This mixture was then stirred at 60 °C for 10 minutes, then raised to 110~120 °C for five hours. The cooled mixture was diluted with water and Et_2O. The ethereal extract was washed with 20% sodium bisulfite, brine, then dried over sodium sulfate to give 0.88 g (95% yield) of compound (**13**).

Reaction of (8) with tin(IV) chloride. (Table 4, Entry 1) A solution of 0.50 g (1.9 mmol) dienone (**8**) in 100 mL of dry chloroform was treated with 1.9 mL of 1 M (1.9 mmol) of tin(IV) chloride in methylene chloride. This solution was refluxed for twenty-four hours, poured into water, filtered and diluted with methylene chloride. The methylene chloride extract was washed with saturated sodium bicarbonate, water, and then dried over sodium sulfate. The solvent was removed in vacuum. A mixture of (**15**), (**16**) and (**17**) was obtained in 20.8%, 16.2% and 34.0% GC yields. GC yields were determined using phenanthrene as a standard. Some of dicylopentanoid (**15**) and some of (**16**) were isolated by successive flash chromatography using a 35% Et_2O~haxane mixture. Compound (**17**) was isolated by flash chromatography, using a 8% Et_2O~haxane mixture. Combined yields of isolated (**17**) and a isolated mixture of (**15**) and (**16**) over several repetitions of this procedure averaged 70%.

Spiro[cyclohexane-1,5'-3'-phenyl-3',4',5',6'-tetrahydropentalen-1'(2'*H*)-one] (15). ^1H NMR (300 MHz, $CDCl_3$) δ 7.36~7.21 (m, 3H), 7.12~7.08 (m, 2H), 3.96~3.90 (m, 1H), 3.18 (dd, J = 18.5, 6.6 Hz, 1H), 2.62 (dd, J = 18.5, 2.2 Hz, 1H), 2.40~2.15 (m, 4H), 1.60~1.30 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.7, 186.1, 147.2, 141.1, 128.9, 126.1, 50.4, 48.9, 44.1, 43.5, 38.8, 38.5, 37.5, 25.7, 23.1, 22.9 ppm; IR (NaCl) 3050, 2922, 2849, 1699, 1642, 1453, 1223, 762 cm^{-1}; UV (95% ethanol) λ_{max} 241 nm, ε_{max} 7.7×10^3;

MS (EI) m/z (relative intensity) 267 (21), 266 (M, 100), 238 (33), 209 (27), 186 (52), 171 (41), 141 (64), 115 (39), 91 (75), 77 (53). High resolution MS, Cal., 266.1671 for formula $C_{19}H_{22}O$; Found, 266.1632.

Spiro[cyclohexane-1,5'-3'-phenyl-4',5',6',6'a-tetrahydropentalen-1'(3'a*H*)-one] (16). mp 119 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68~7.58 (m, 2H), 7.55~7.40 (m, 3H), 7.31 (s, 1H), 3.80~3.78 (q, m, 1H), 3.12~3.03 (m, 1H), 2.12~1.95 (m, 2H), 1.52~1.15 (m, 12H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.0, 177.1, 133.5, 131.0, 128.8, 127.7, 125.0, 51.1, 47.3, 46.0, 42.7, 38.8, 38.3, 36.3, 26.2, 23.6, 23.0 ppm; IR (NaCl) 3050, 2924, 2853, 1693, 1593, 1570, 1449, 1186, 768 cm^{-1}; UV (95% ethanol) λ_{max} 289 nm, ε_{max} $1.3x10^4$, λ_{max} 220 nm, ε_{max} $6.2x10^3$; MS (EI) m/z (relative intensity) 267 (9), 266 (M, 39), 170 (100), 158 (98), 141 (37), 115 (29), 91 (32), 77 (31). High resolution MS, Cal., 266.1671 for formula $C_{19}H_{22}O$; Found, 266.1646.

Spiro[cyclohexane-1,5'-3'a-phenyl-4',5',6',6'a-tetrahydropentalen-1'(3'a*H*)-one] (17). ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, J = 5.5 Hz, 1H), 7.35~7.18 (m, 5H), 6.00 (d, J = 5.5 Hz, 1H), 3.00 (dd, J = 8.9 Hz, J = 5.5 Hz, 1H), 2.11 (AB, q, J = 13.7 Hz, $\Delta\nu_{AB}$ = 25.7 Hz, 2H), 1.98 (m, 2H), 1.47~1.29 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.5, 171.6, 145.3, 129.9, 128.7, 126.6, 125.9, 61.0, 58.0, 47.8, 46.4, 39.7, 37.3, 26.0, 23.7, 23.0 ppm; IR (NaCl) 3050, 3015, 2926, 2855, 1711, 1495, 1450, 761, 700 cm^{-1}; UV (95% ethanol) λ_{max} 217 nm, ε_{max} $7.1x10^3$; MS(EI) m/z (realative intensity) 267 (6), 266 (M, 32), 238 (7), 224 (23), 170 (100), 158 (51), 141 (35), 128 (37), 115 (31), 91 (35), 77 (28), 67 (35), 55 (31). High resolution MS, Cal., 266.1671 for formula $C_{19}H_{22}O$; Found, 266.1680.

Acid catalyzed isomerisms of (15), (16) and (17). Isomers (**15**), (**16**) and (**17**) were each refluxed in chloroform solution with an equivalent of p-toluenesulfonic acid monohydrate. GC identifications and yields were determined using phenanthrene as an internal standard. Isomer (**15**) was completely converted to (**16**) and a trace of (**17**) within 24 h (see Table 5); however isomers (**16**) and (**17**) remained unchanged, saved for a little decoposition, over a 48h period.

<u>APPENDIX I</u>

SPECTRAL PART I

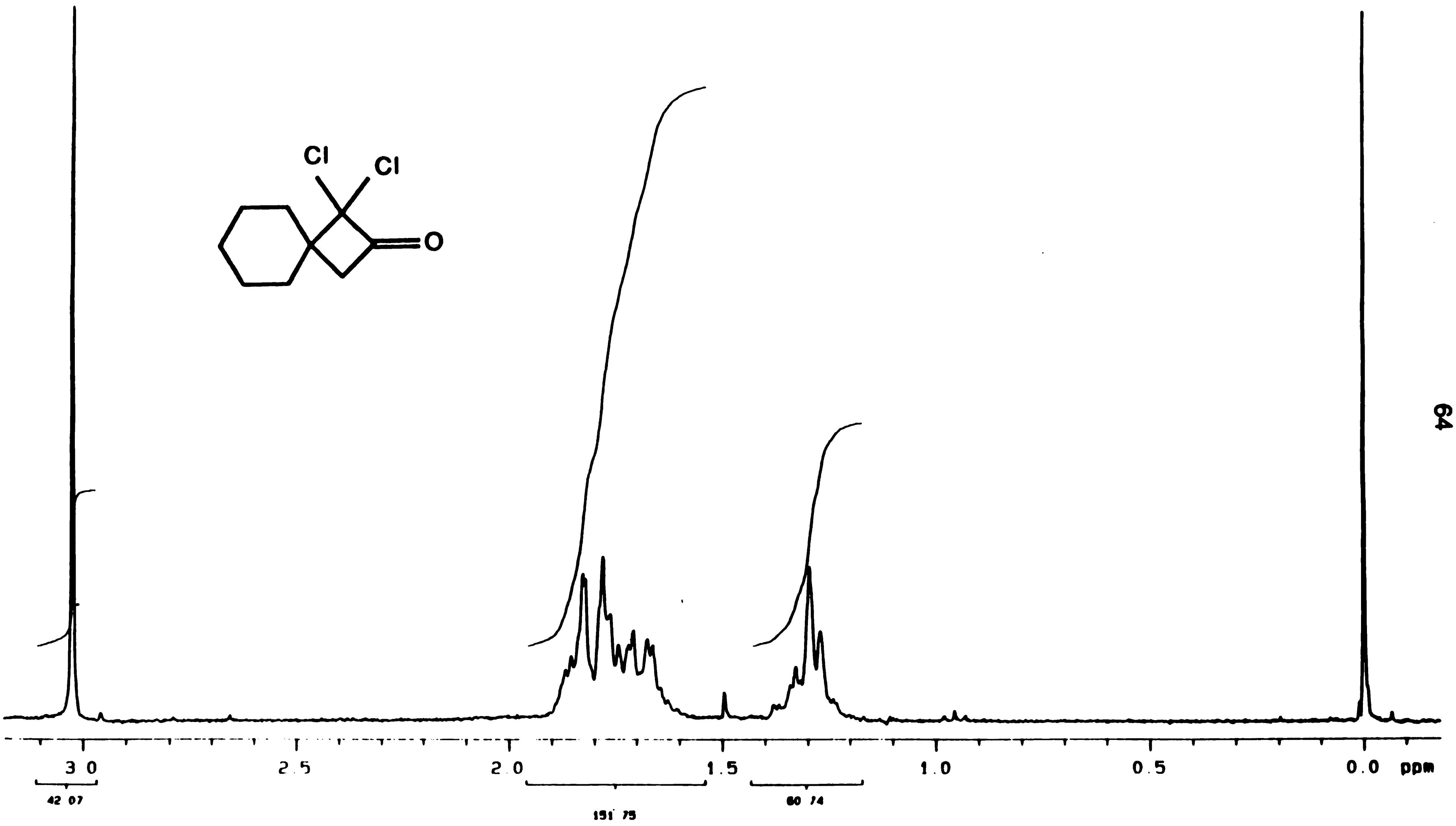


Figure 7. ^{1}H NMR Spectrum of (1).

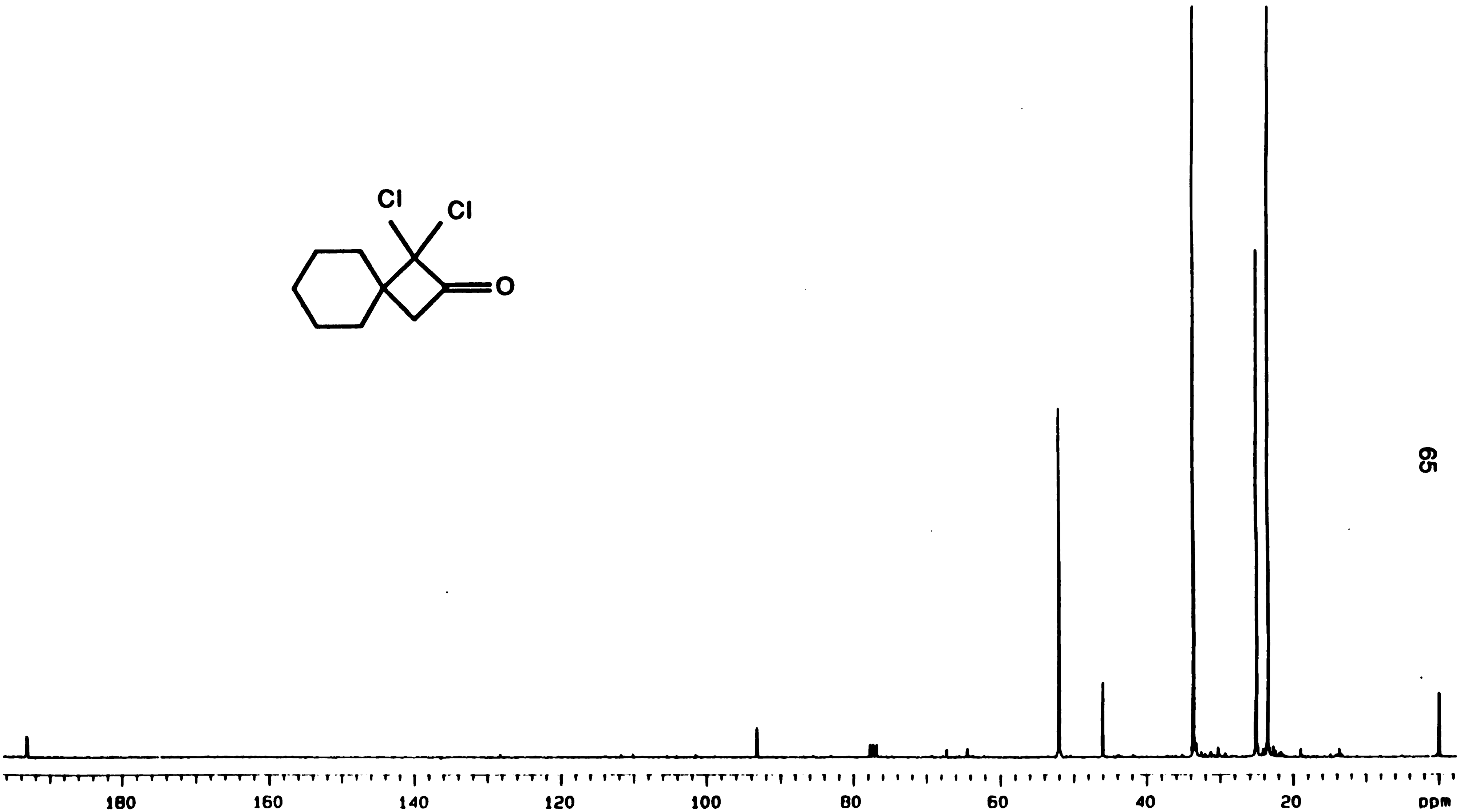


Figure 8. ^{13}C NMR Spectrum of (1).

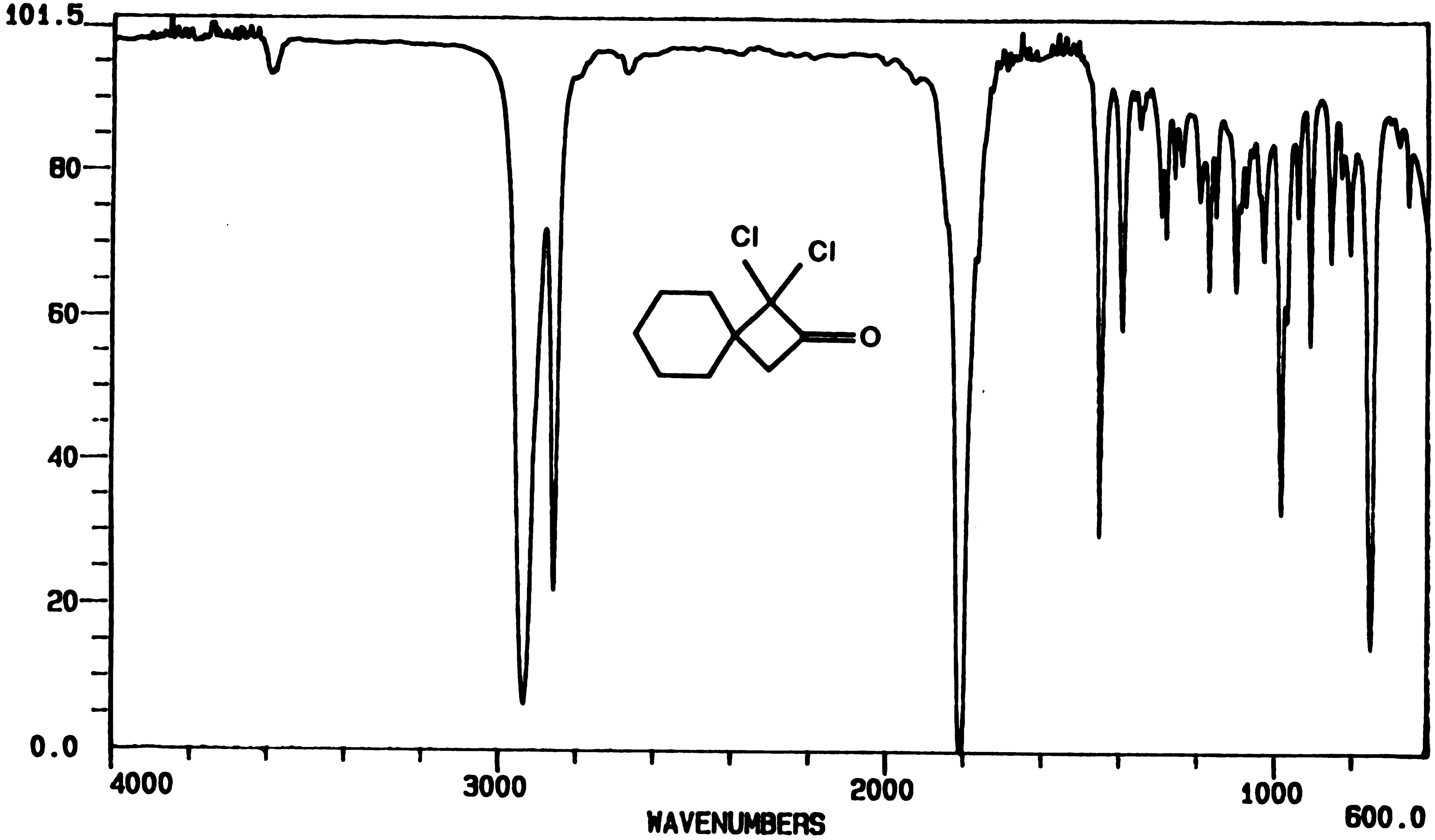


Figure 9. Infrared Spectrum of (1).

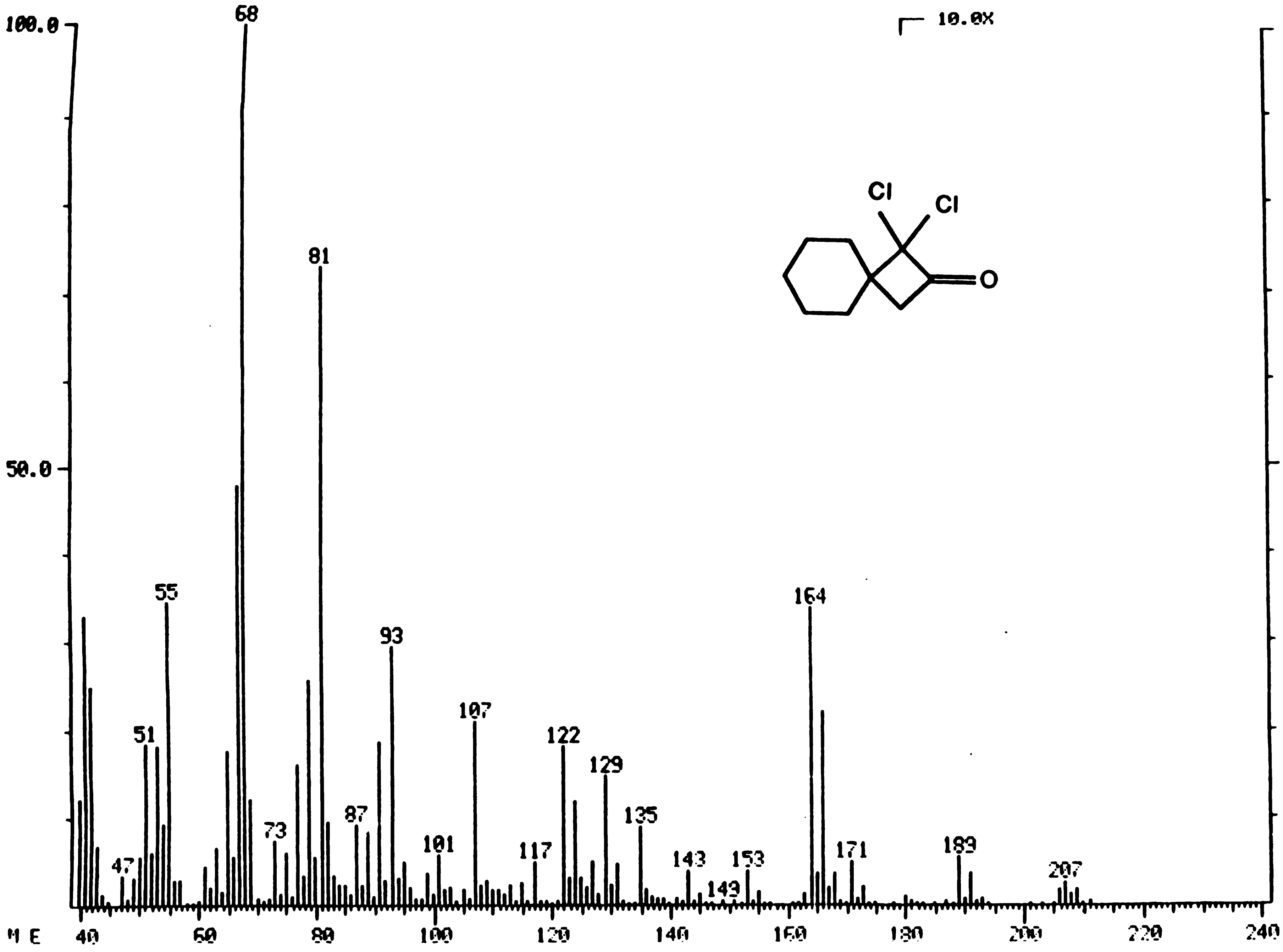


Figure 10. Mass Spectrum of (1).

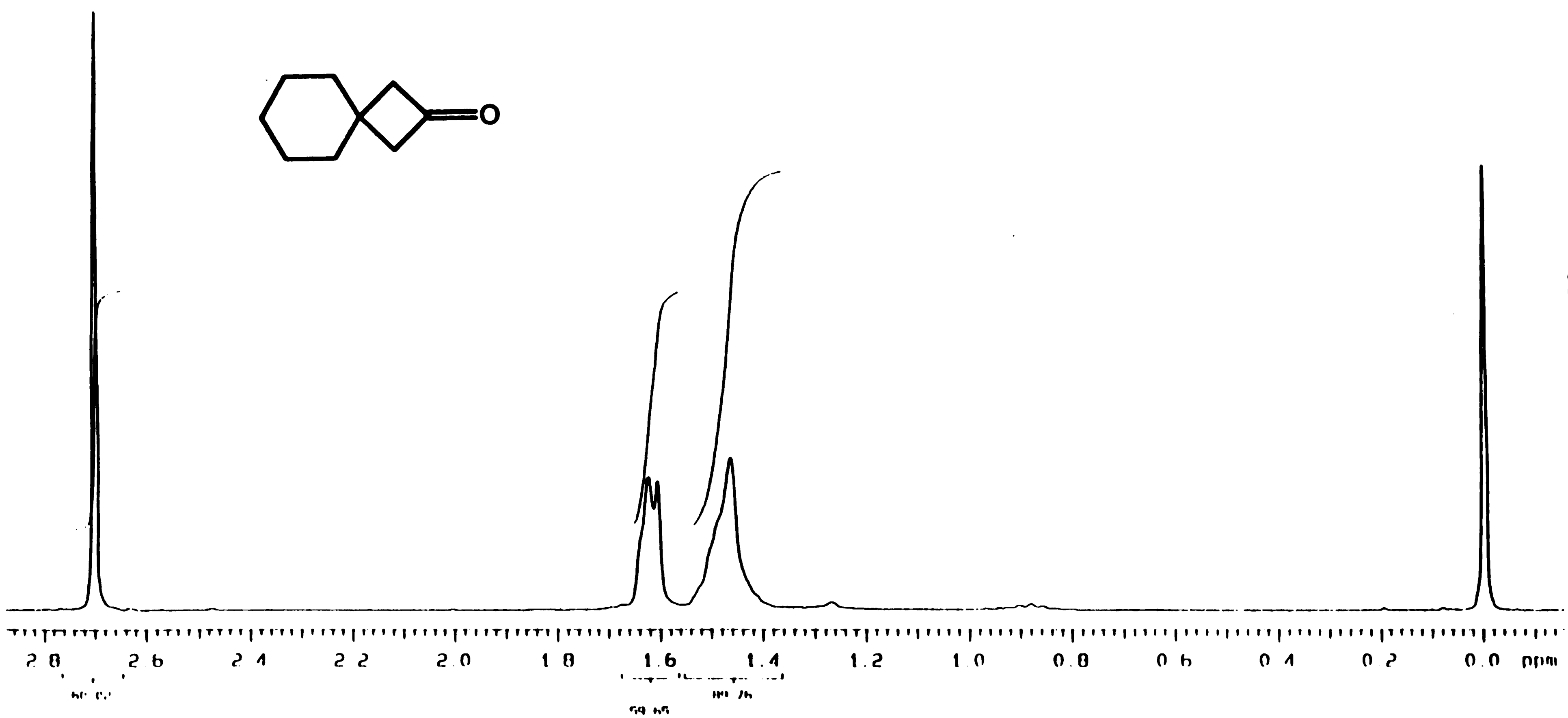


Figure 11. ^{1}H NMR Spectrum of (**2**).

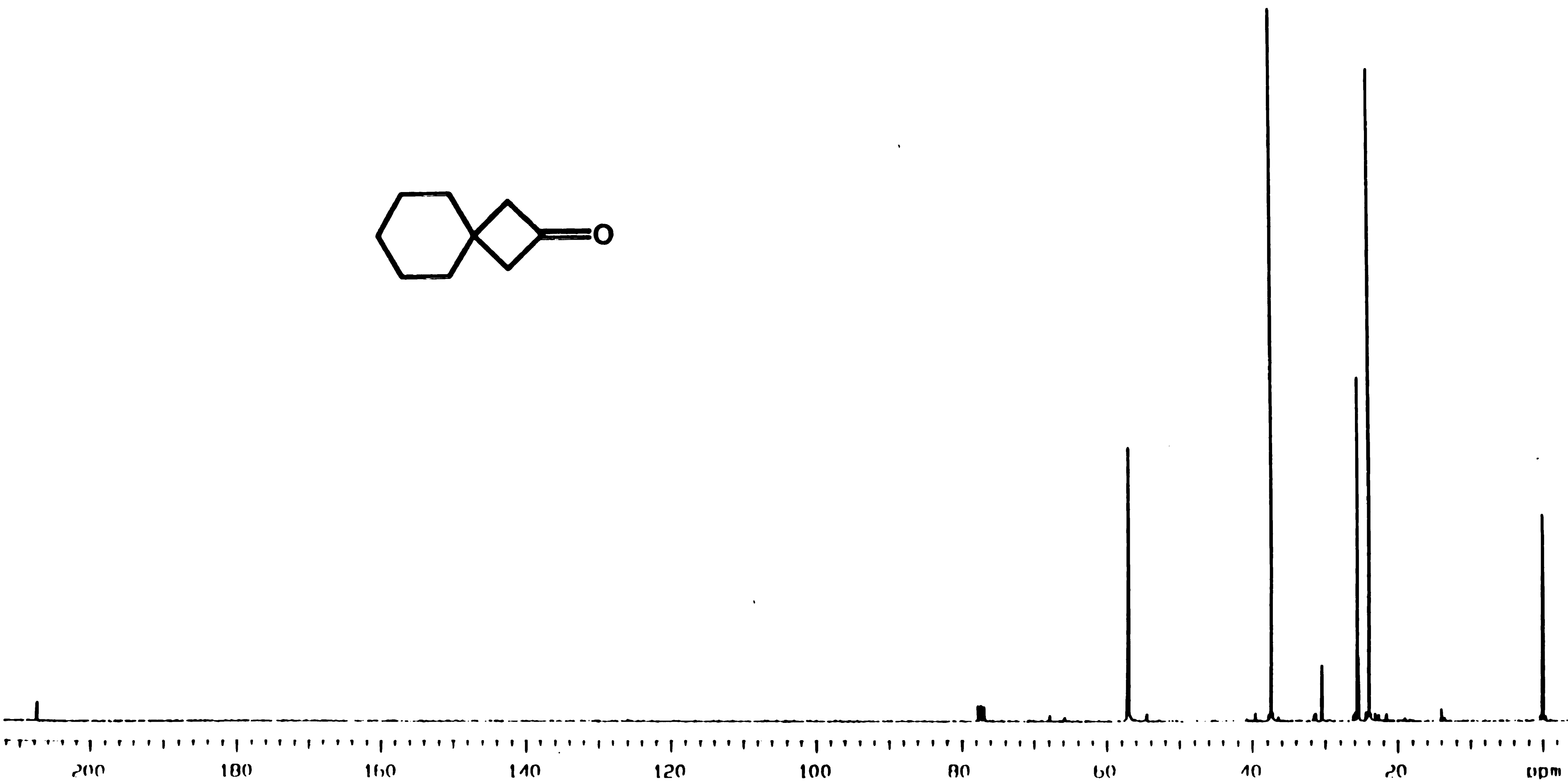


Figure 12. ^{13}C NMR Spectrum of (**2**).

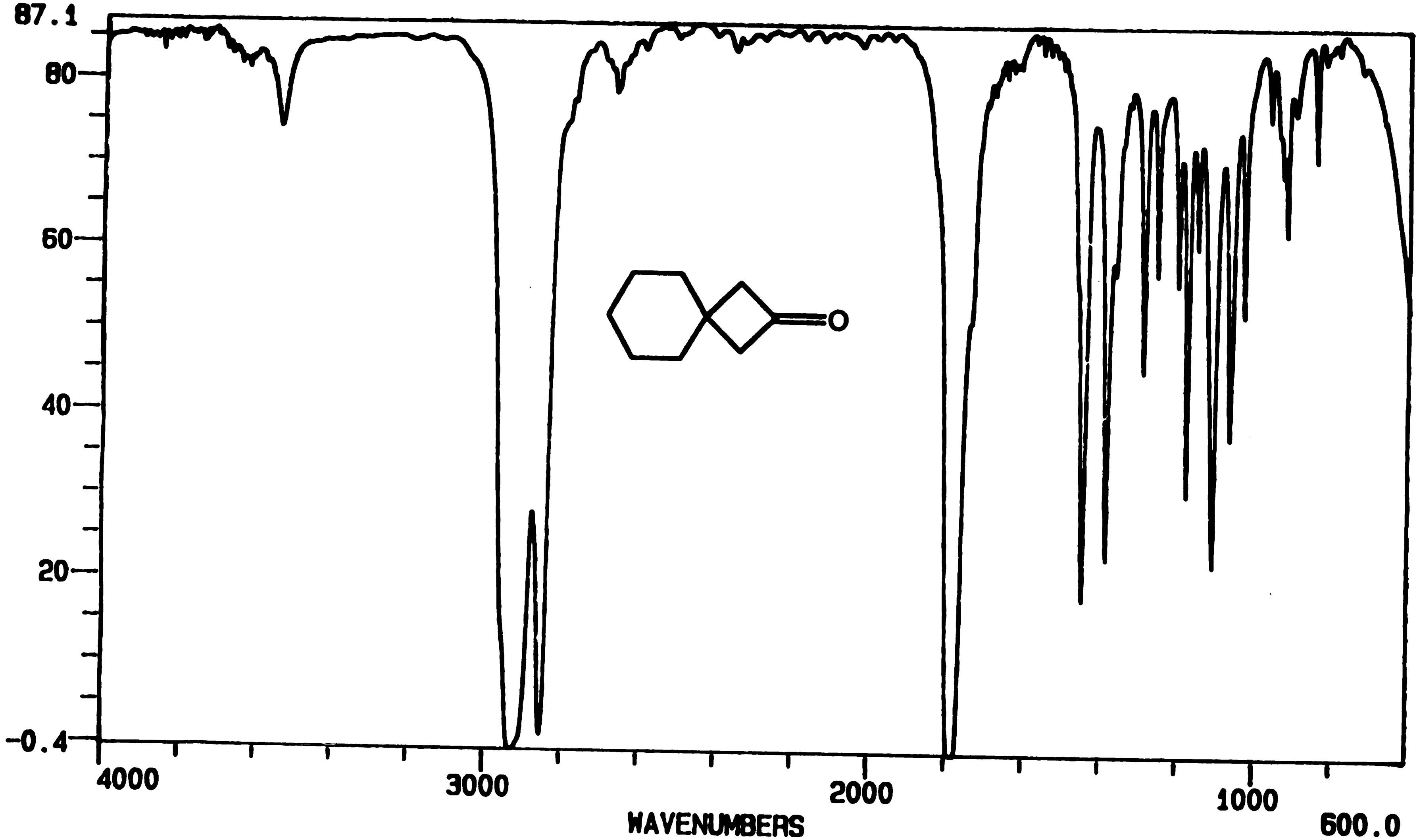


Figure 13. Infrared Spectrum of (2).

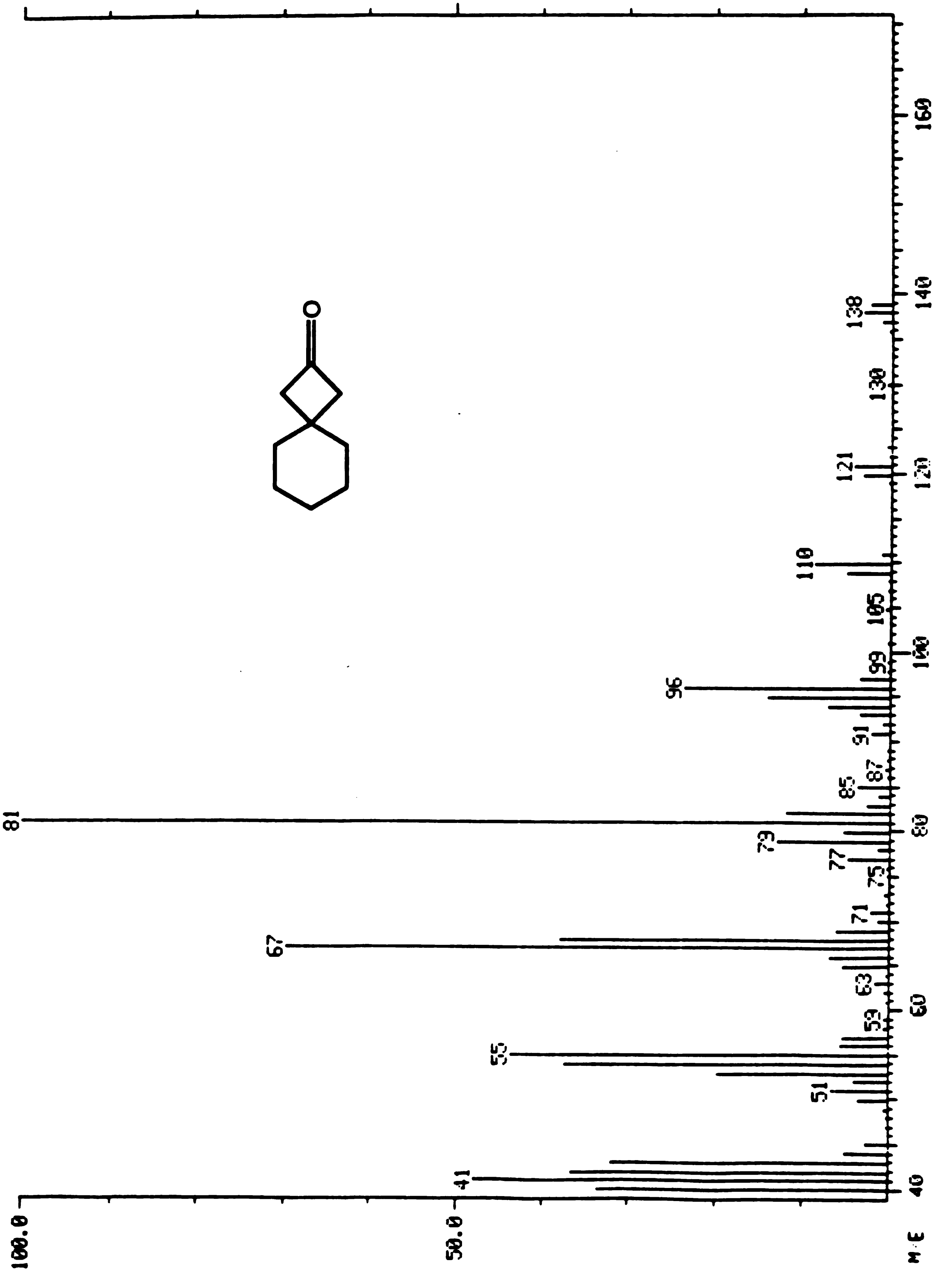


Figure 14. Mass Spectrum of (2).

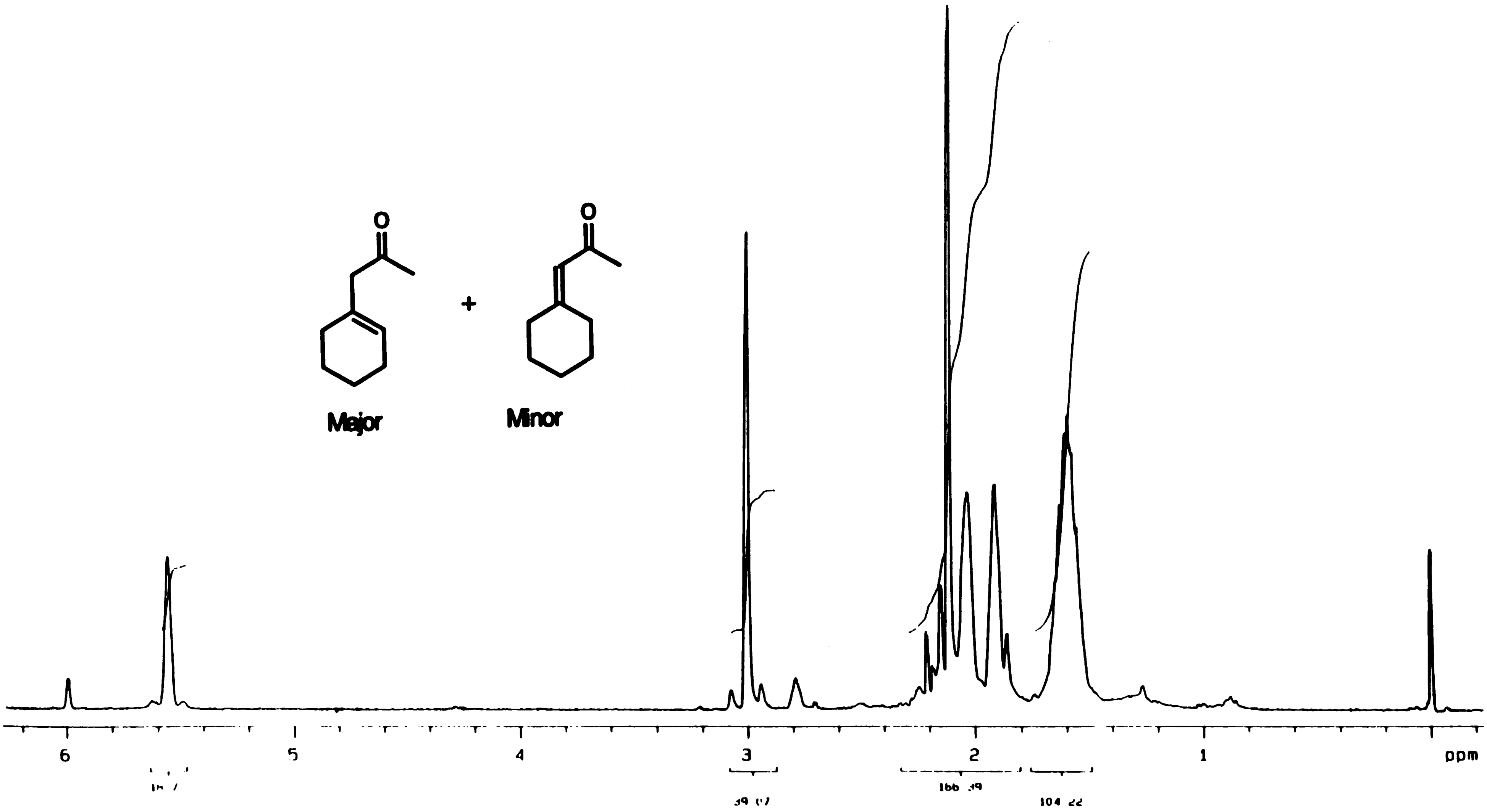


Figure 15. ^{1}H NMR Spectrum of (**3**) and (**4**).

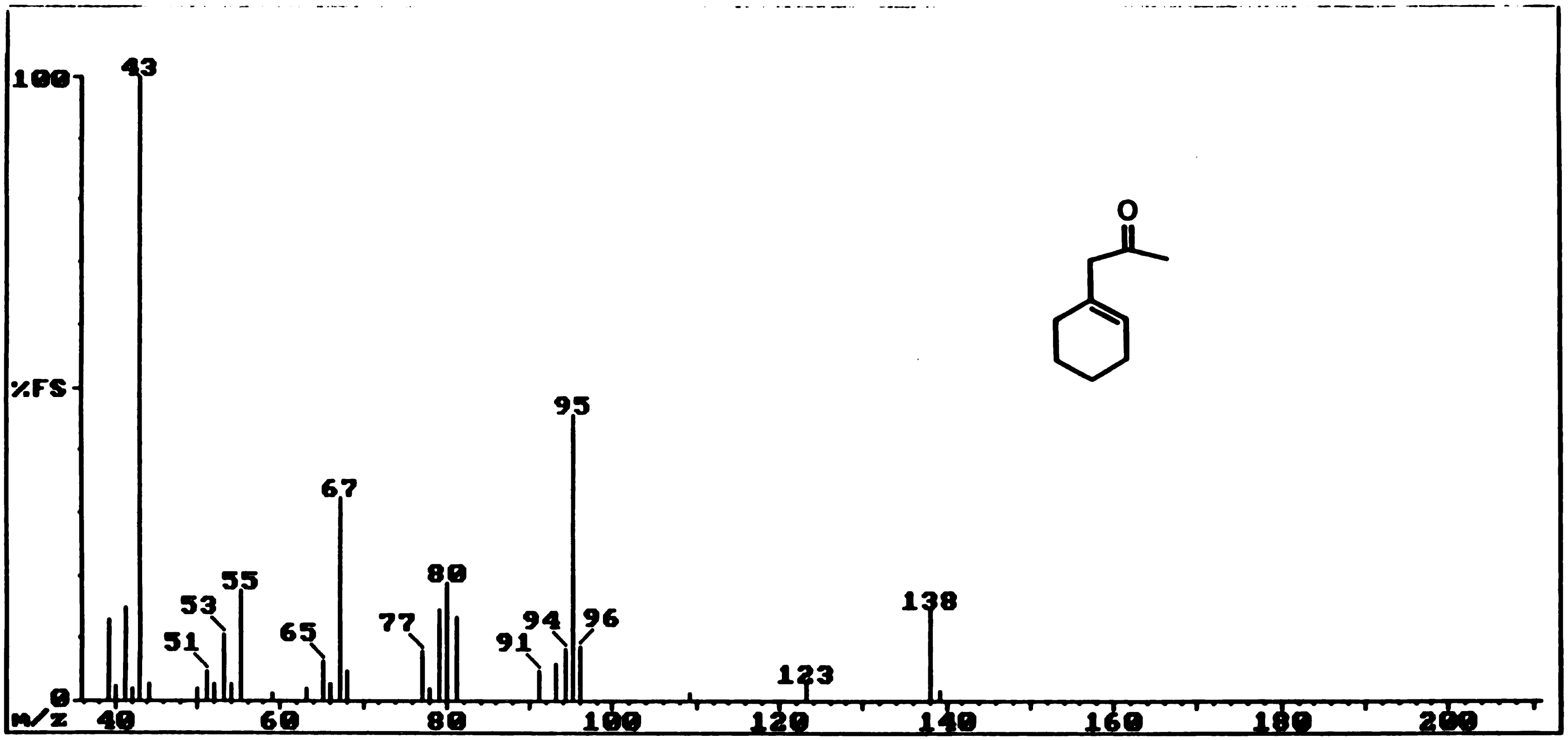


Figure 16. Mass Spectrum of (3).

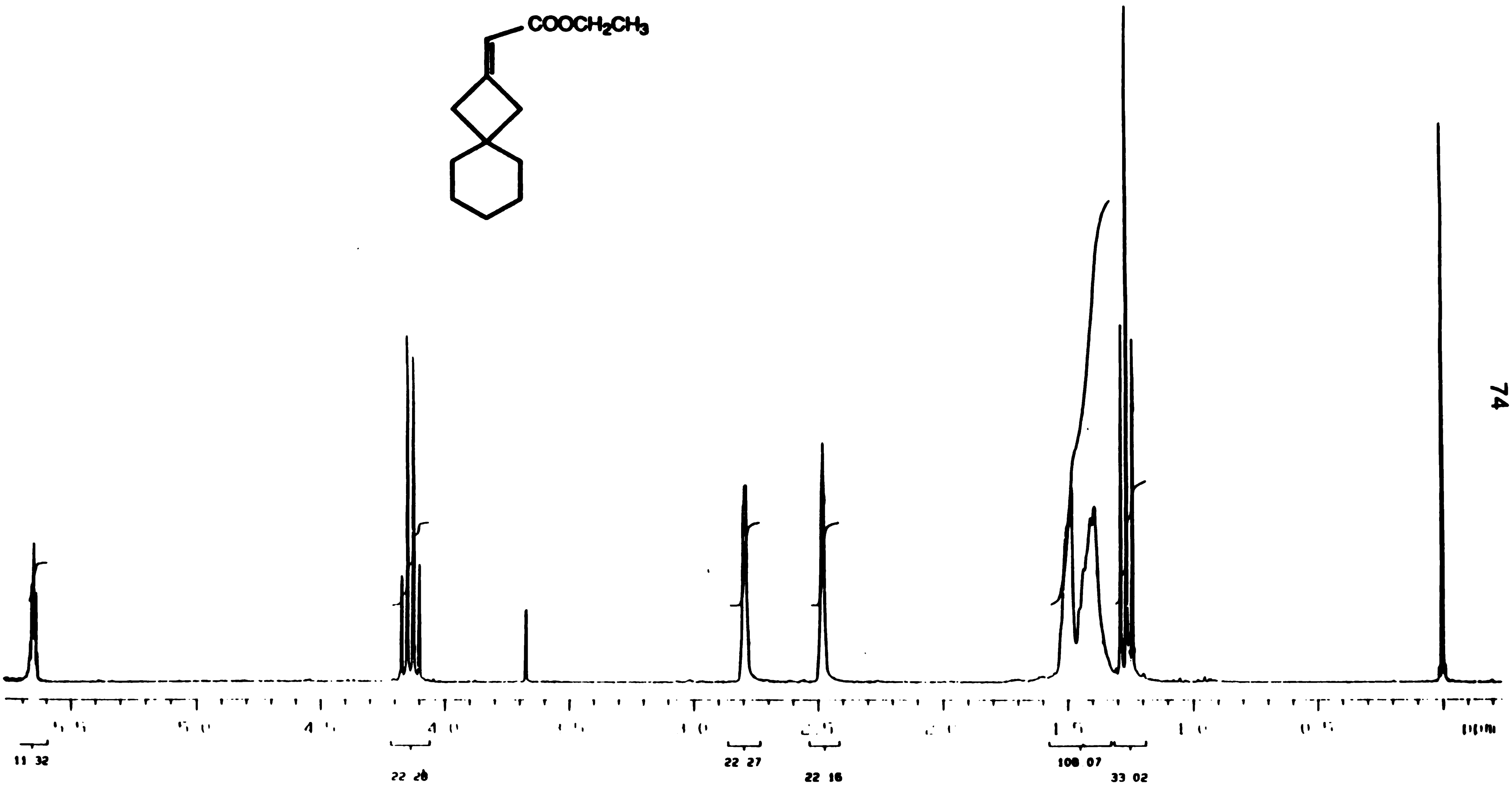


Figure 17. ^{1}H NMR Spectrum of (5).

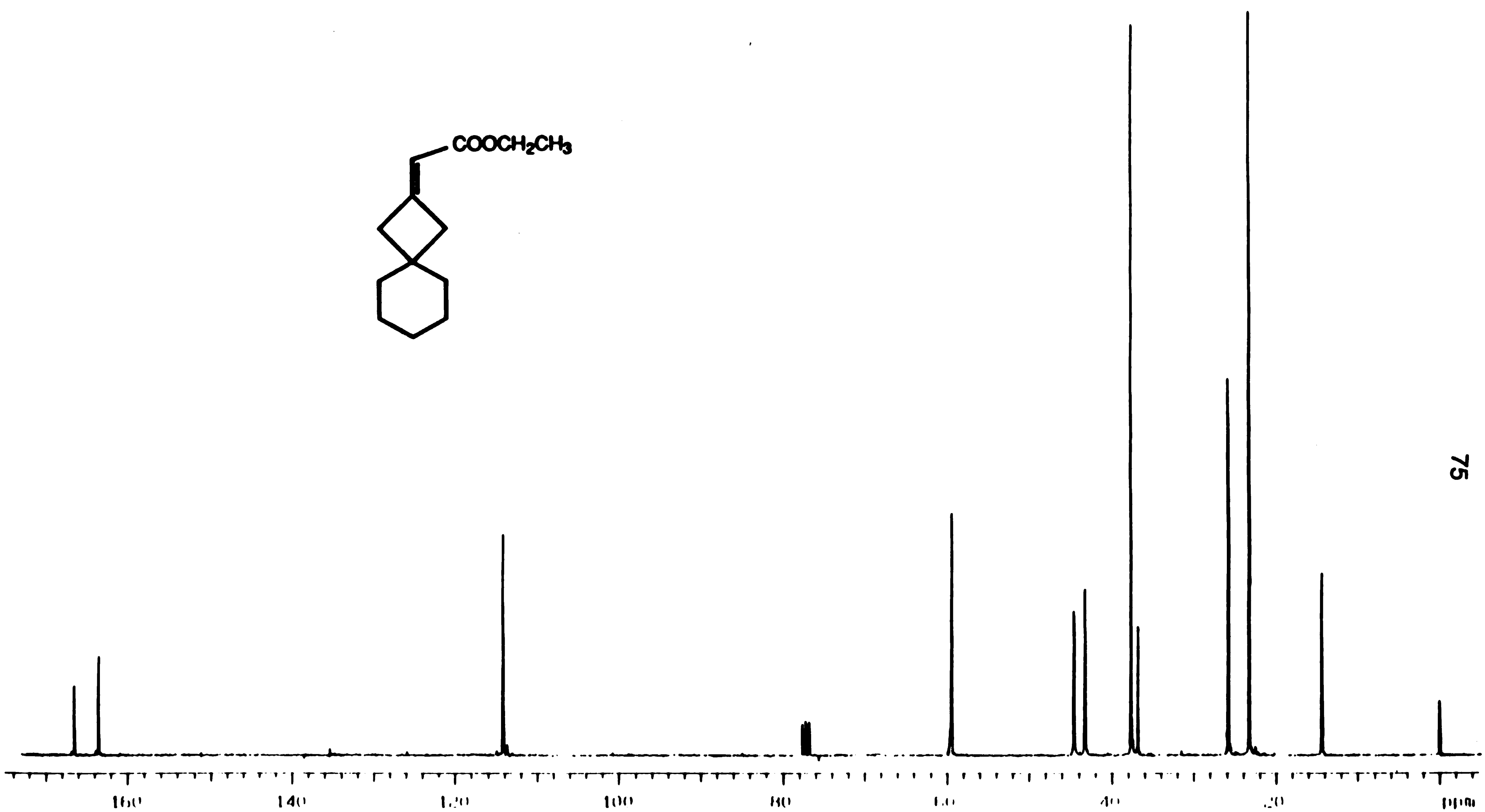


Figure 18. ^{13}C NMR Spectrum of (5).

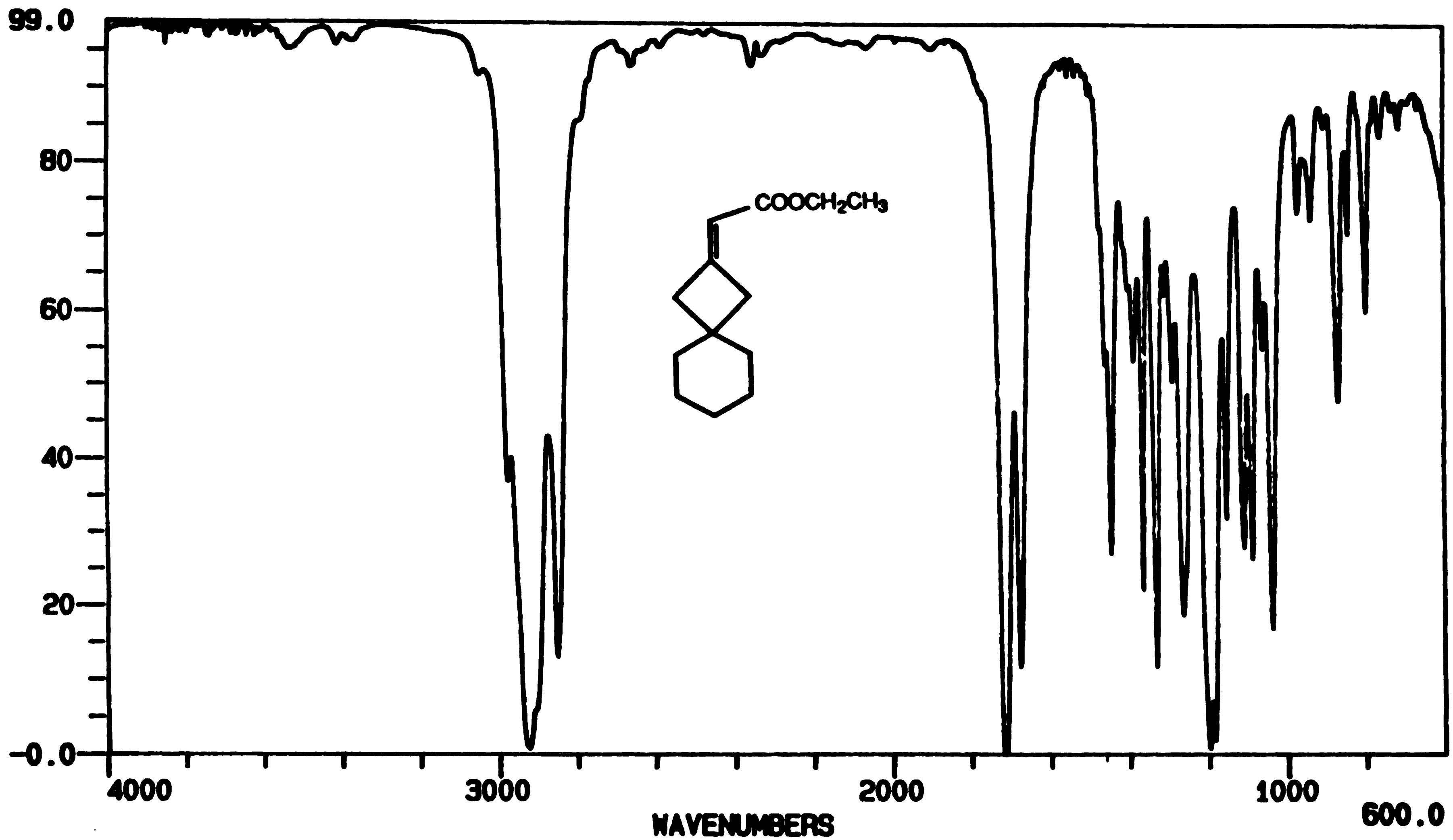


Figure 19. Infrared Spectrum of (5).

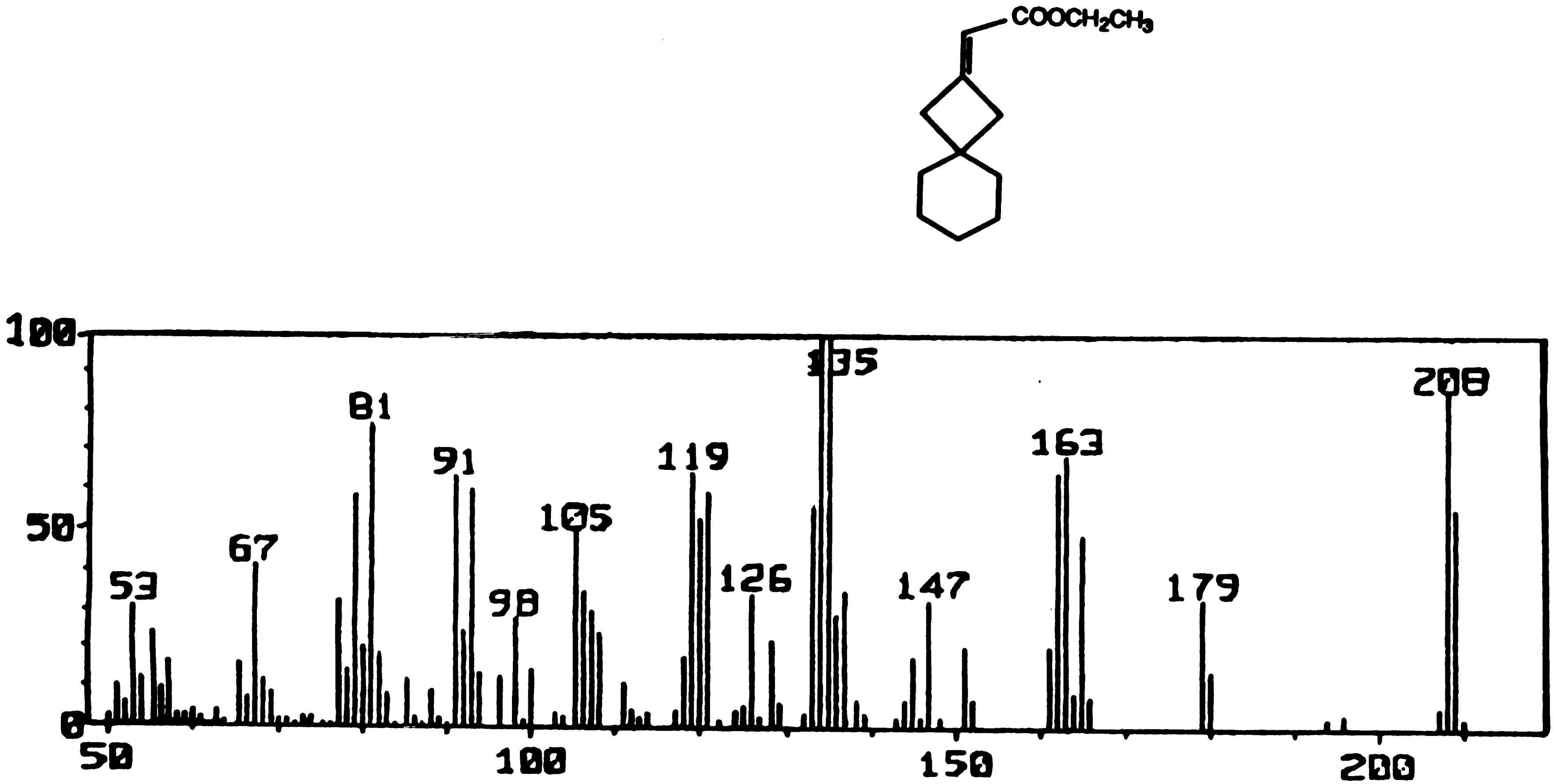


Figure 20. Mass Spectrum of (5).

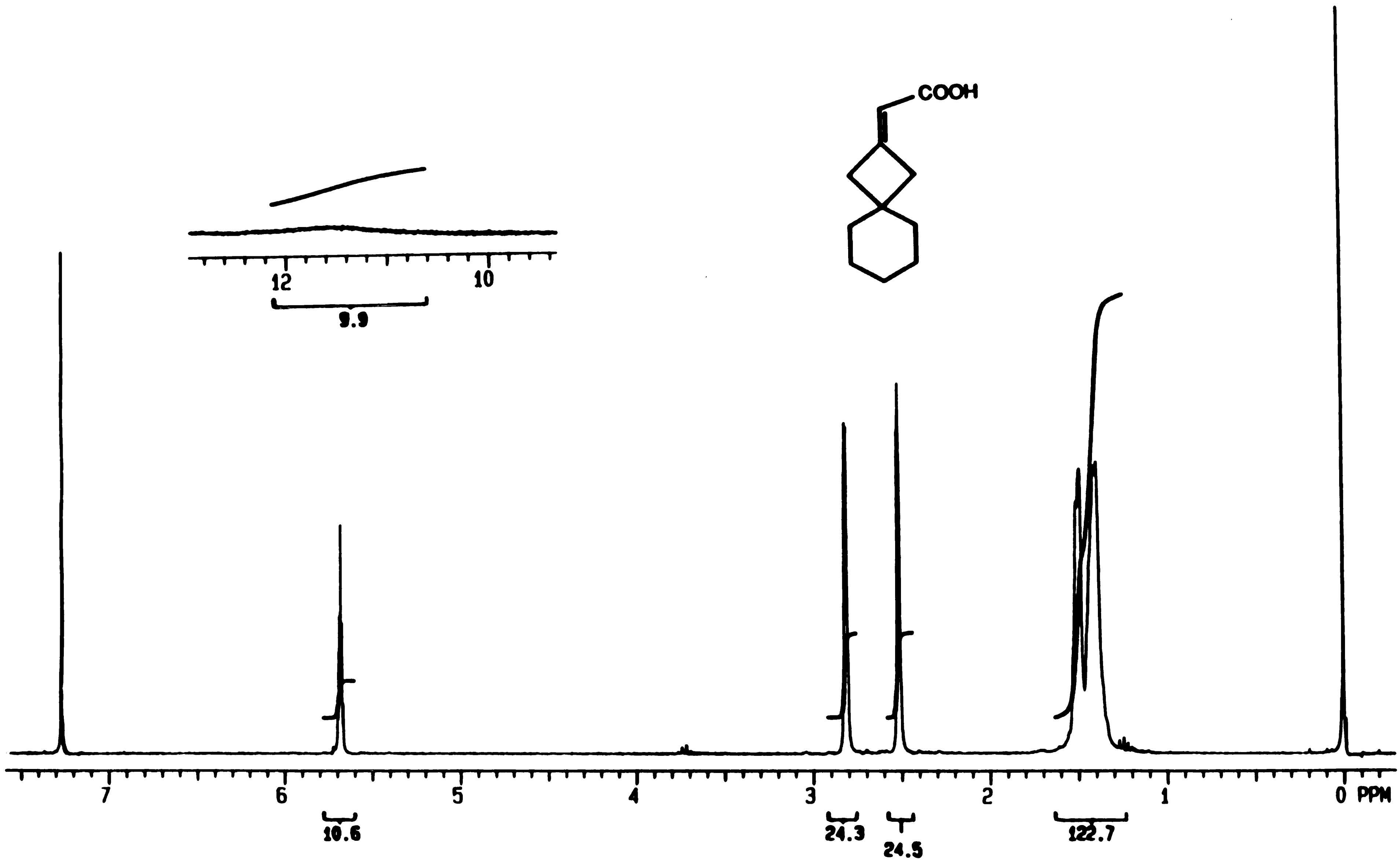


Figure 21. ^1H NMR Spectrum of (6).

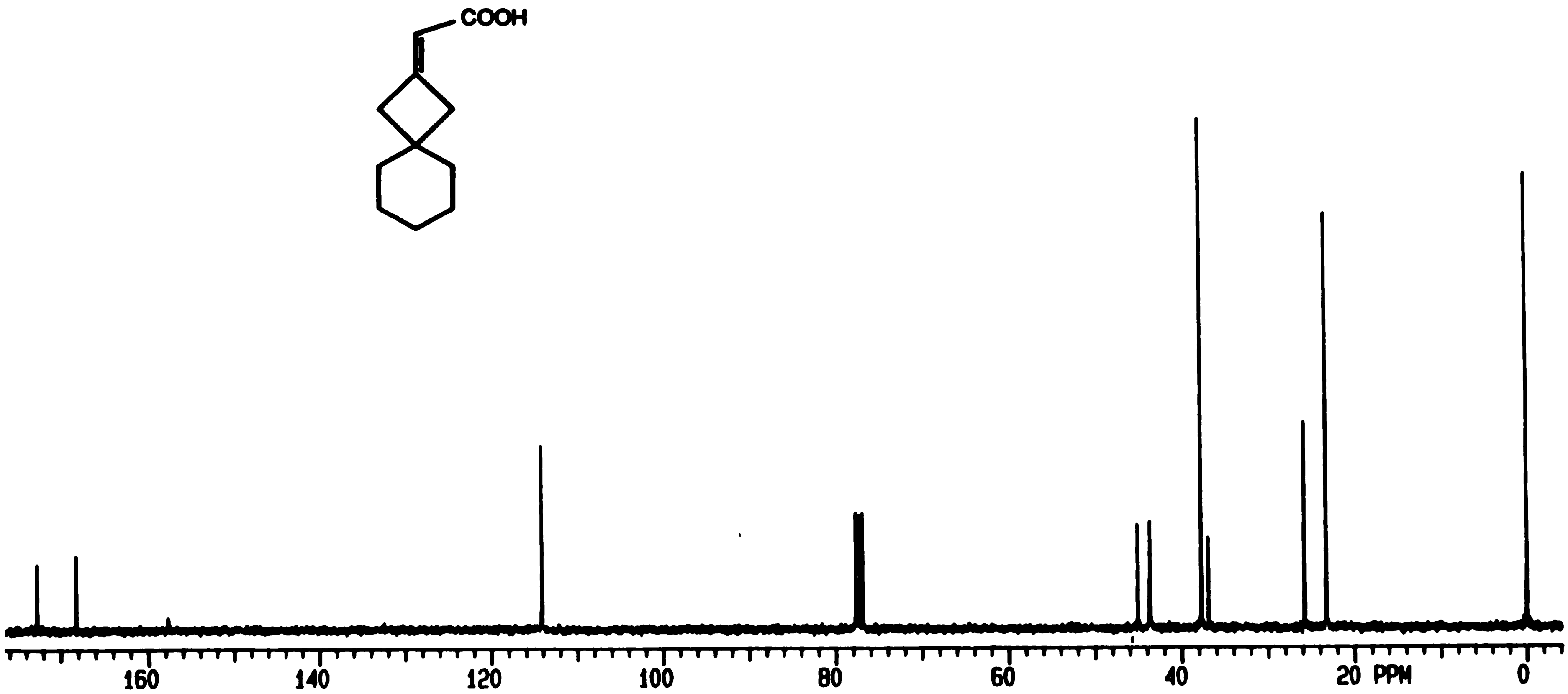


Figure 22. ^{13}C NMR Spectrum of (**6**).

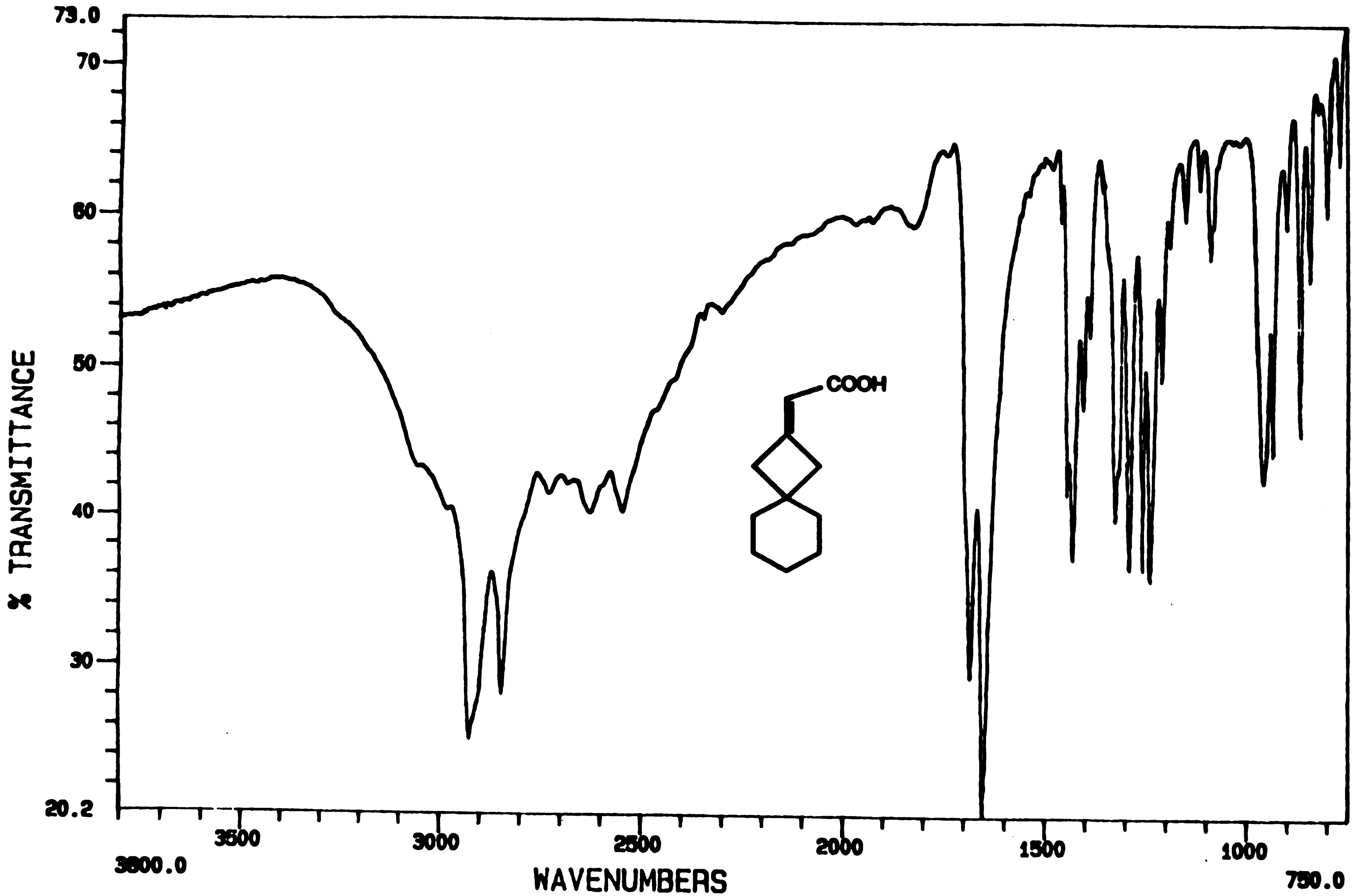
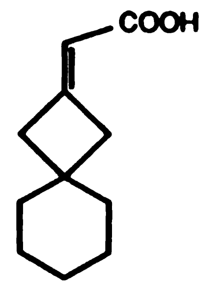


Figure 23. Infrared Spectrum of (6).



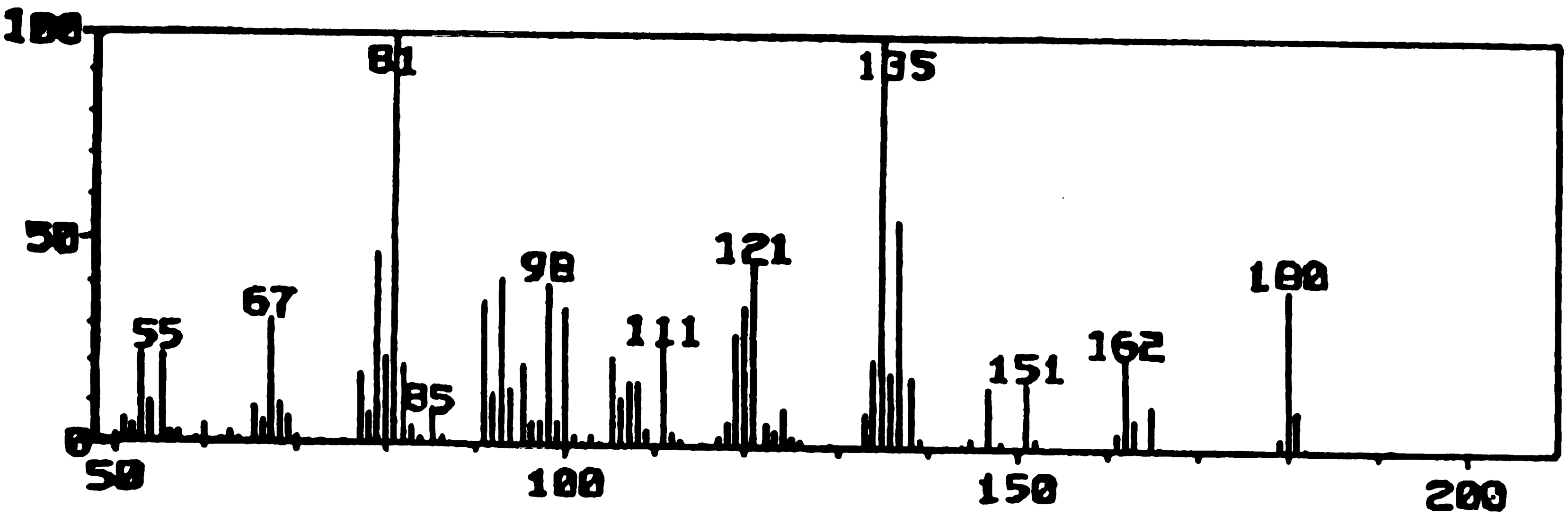


Figure 24. Mass Spectrum of (6).

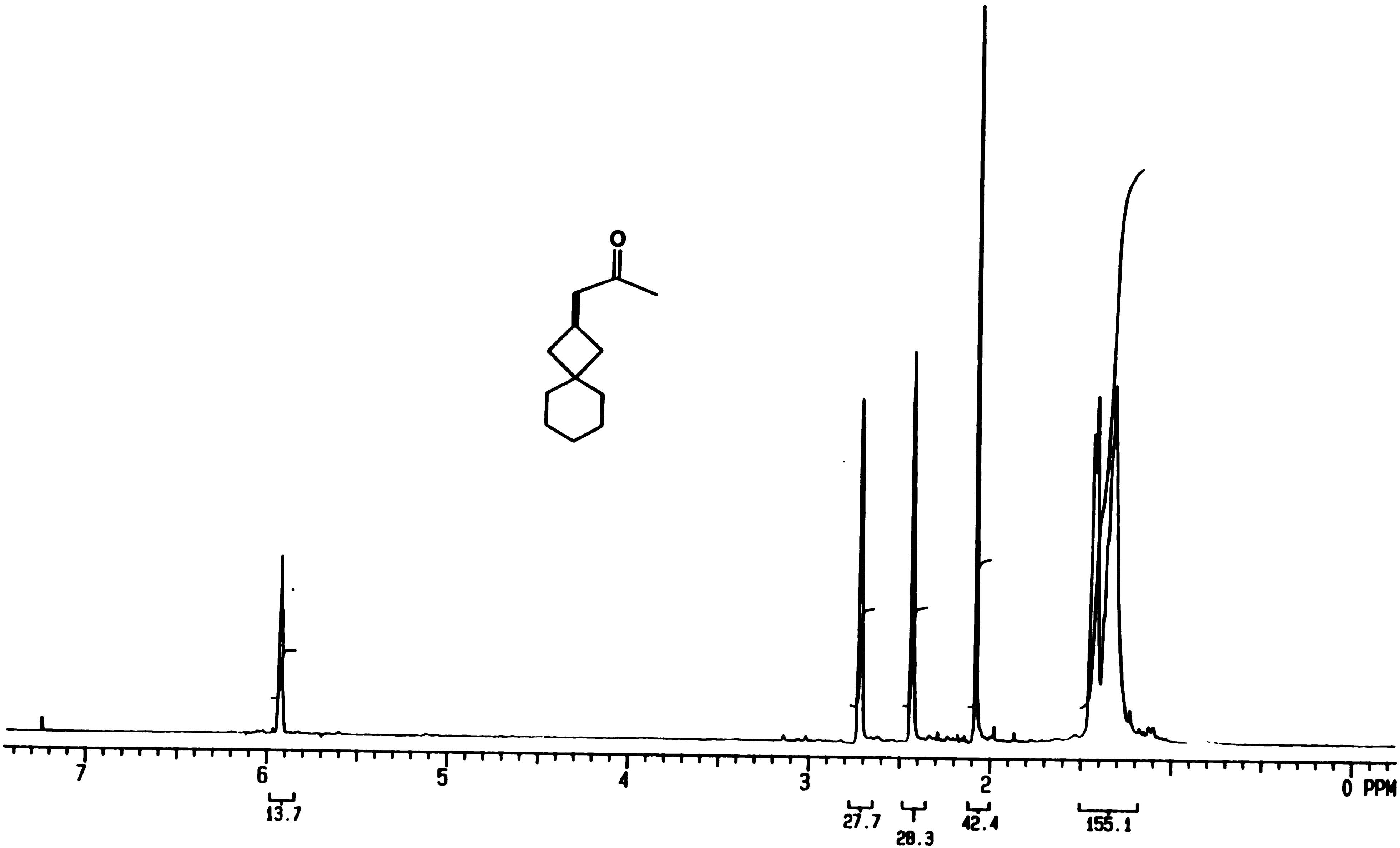


Figure 25. ^{1}H NMR Spectrum of (**7**).

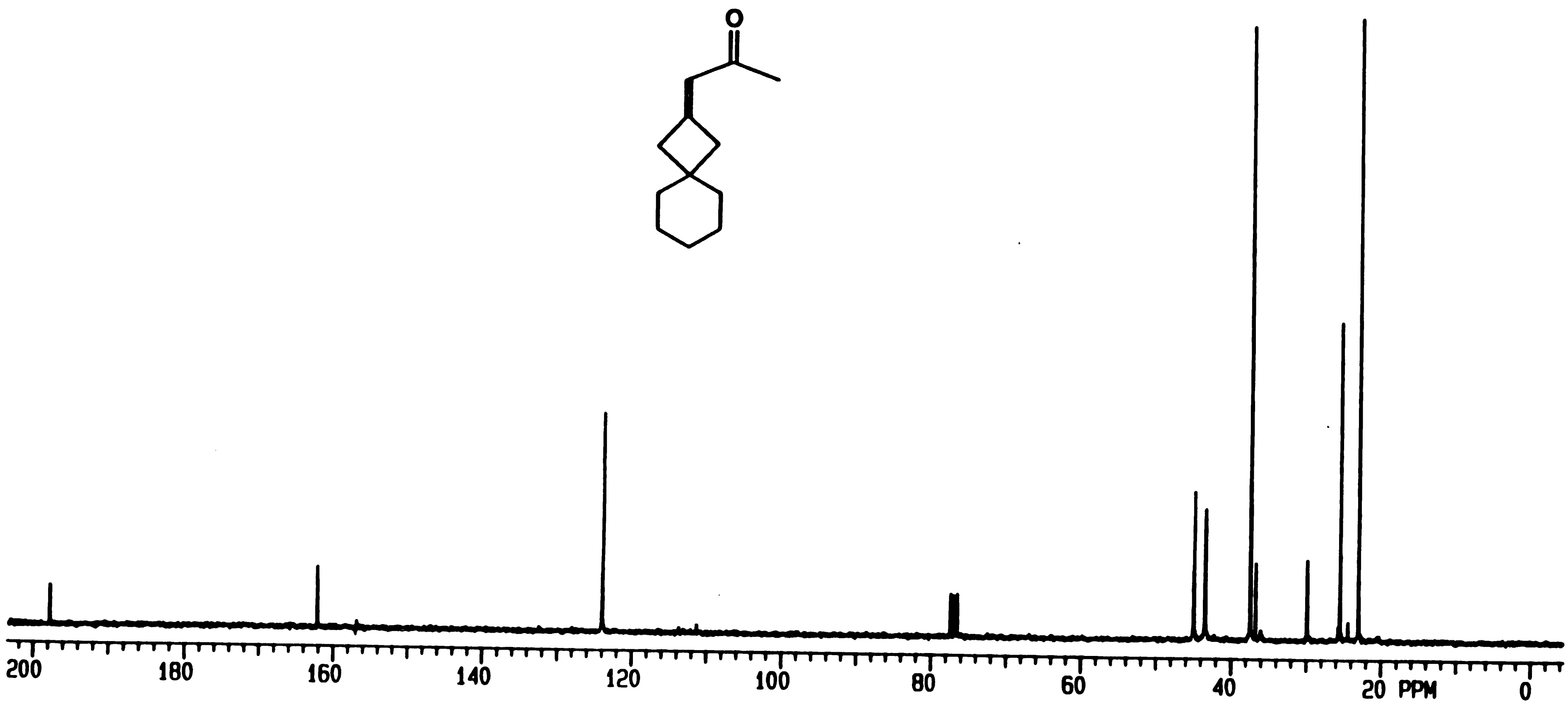


Figure 26. ^{13}C NMR Spectrum of (7).

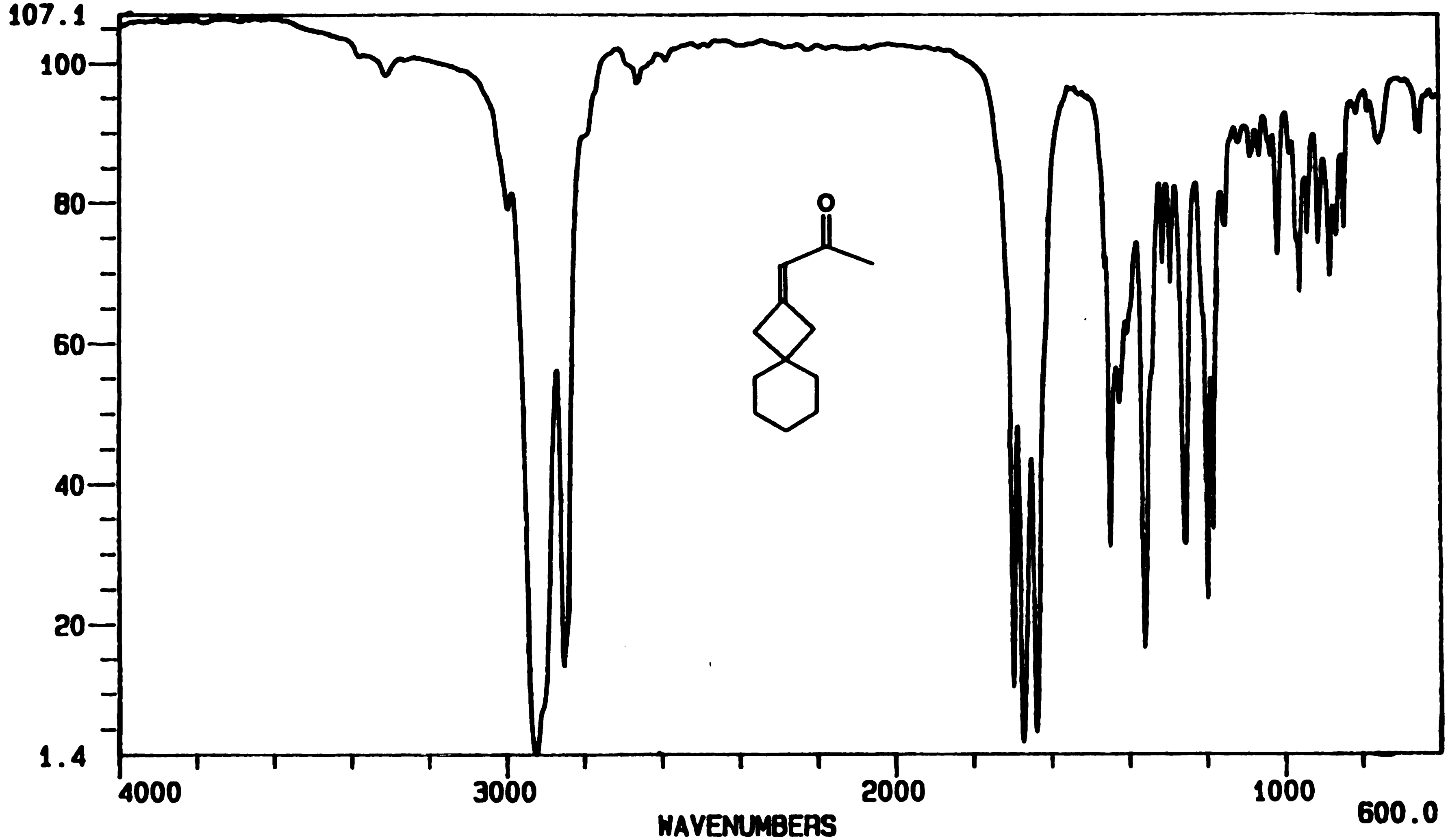


Figure 27. Infrared Spectrum of (7).

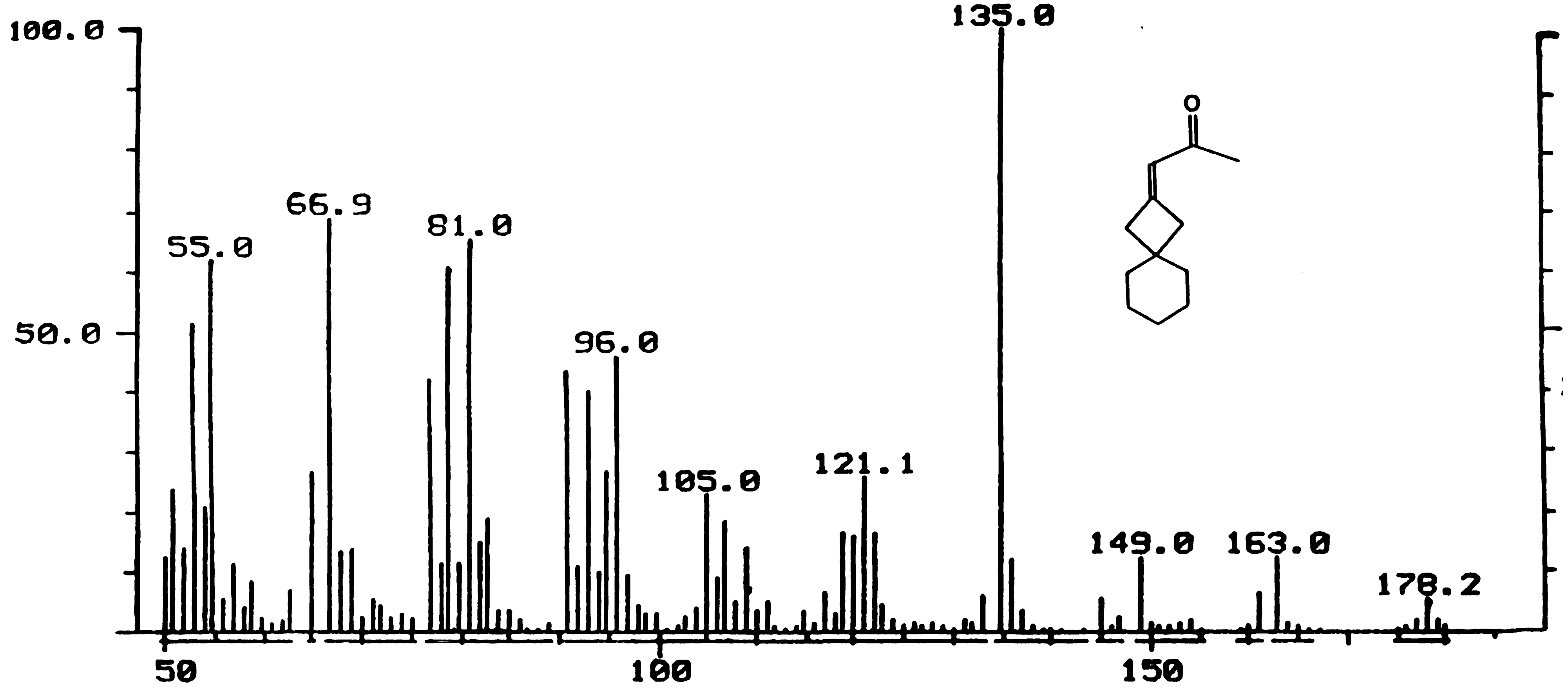


Figure 28. Mass Spectrum of (7).

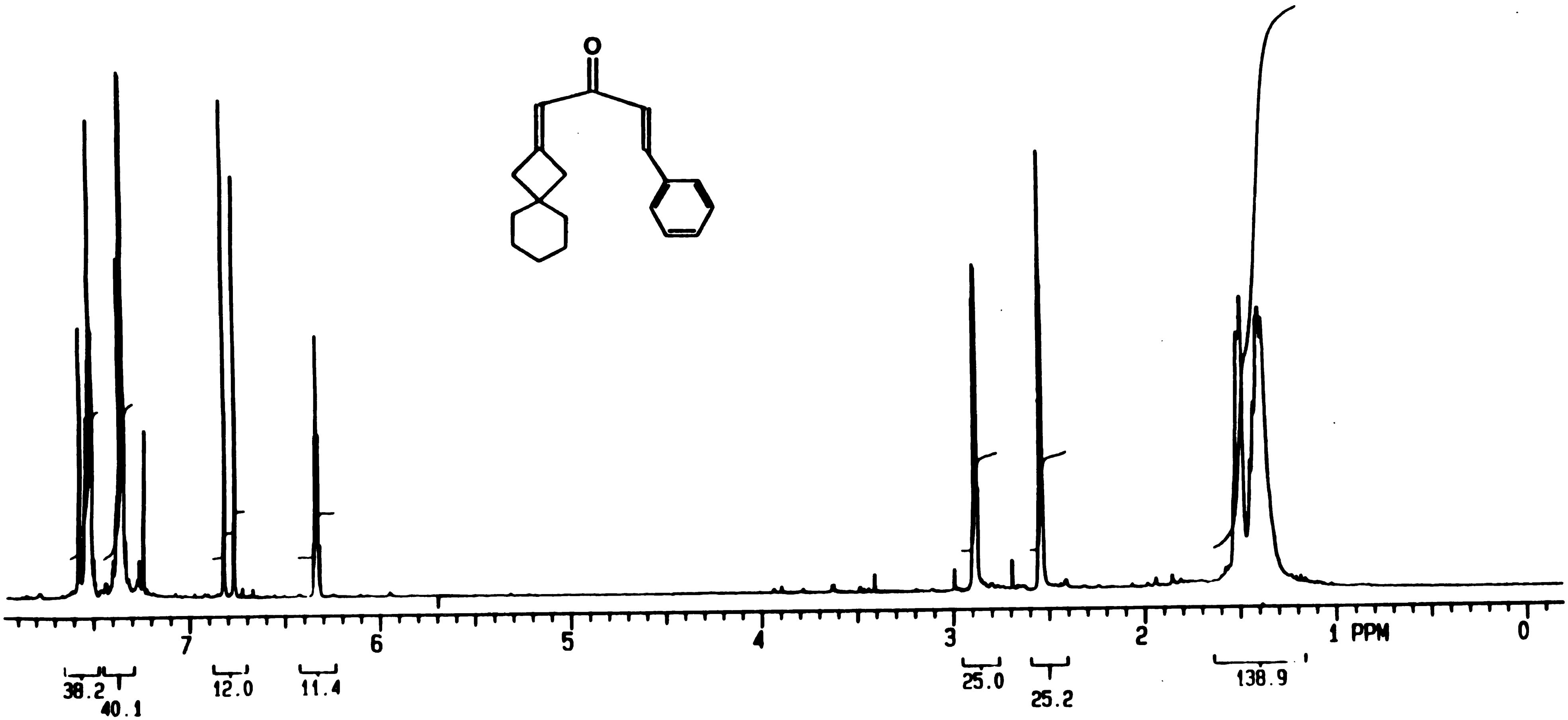


Figure 29. ^1H NMR Spectrum of (8).

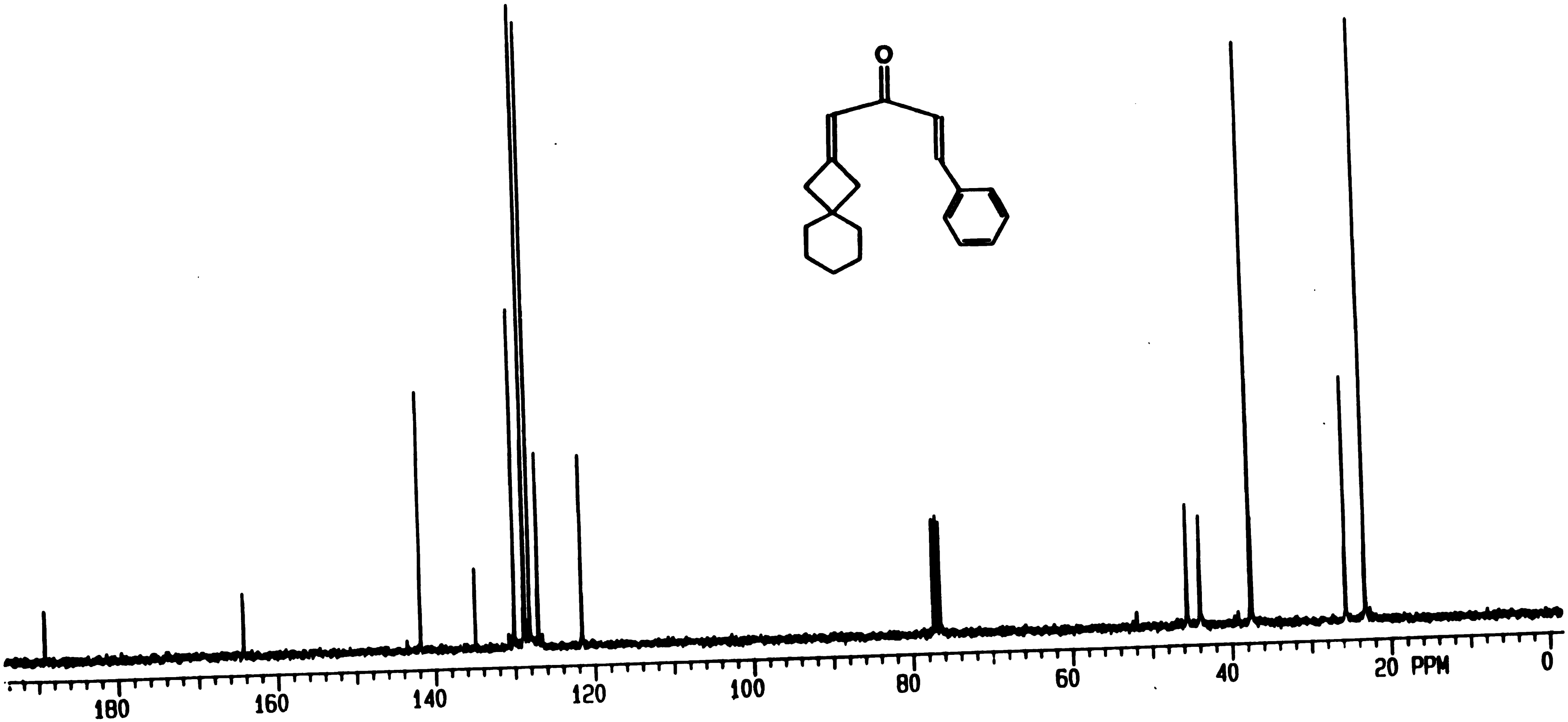


Figure 30. ^{13}C NMR Spectrum of (8).

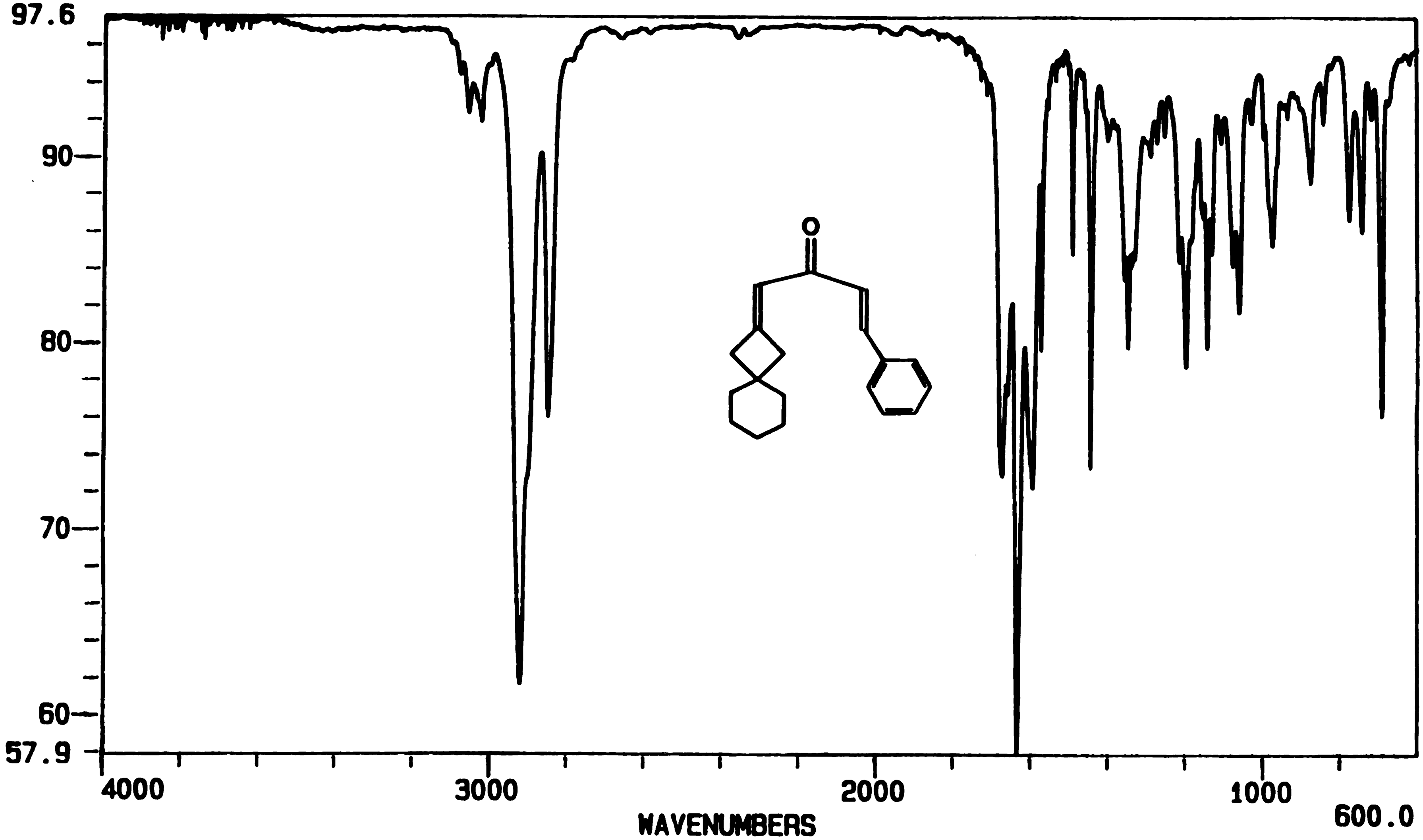


Figure 31. Infrared Spectrum of (8).

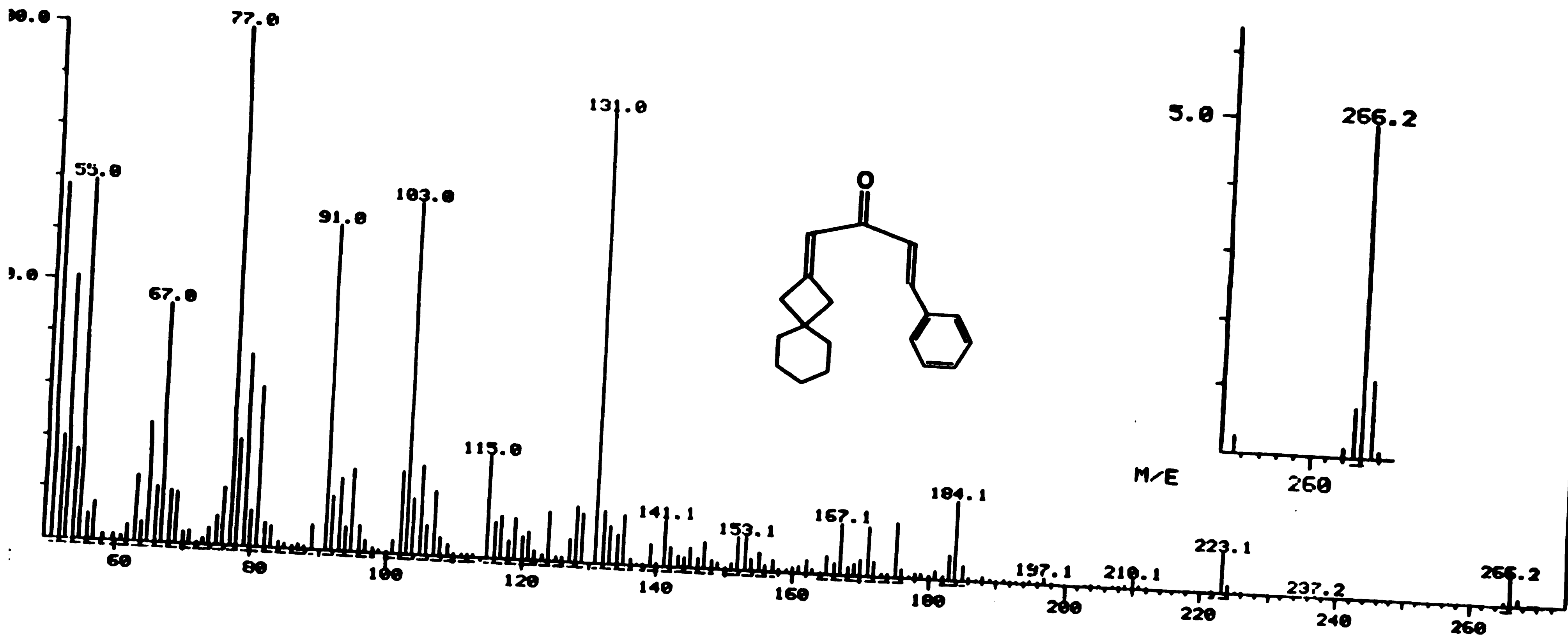


Figure 32. Mass Spectrum of (8).

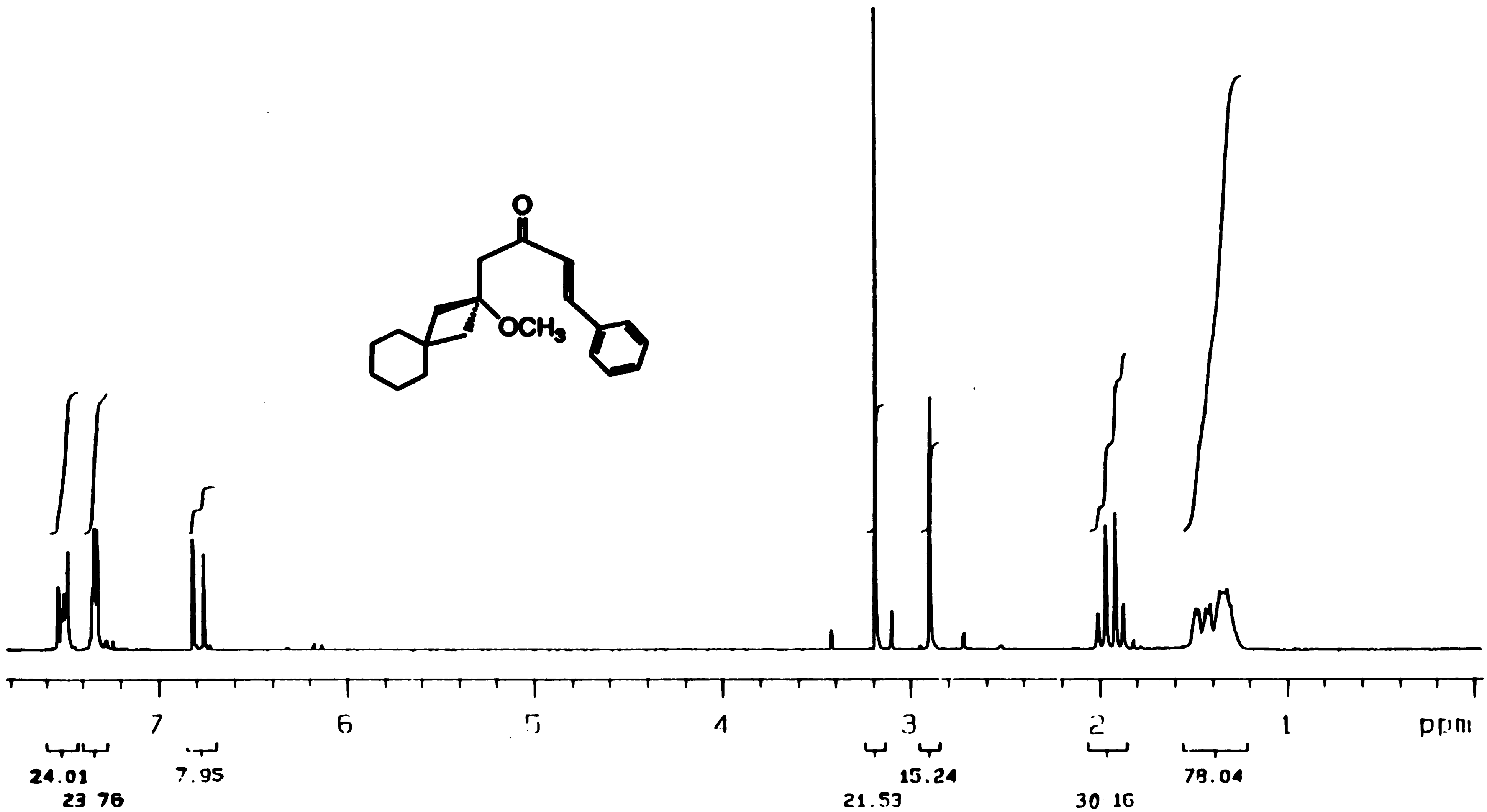


Figure 33. ^{1}H NMR Spectrum of (**9**).

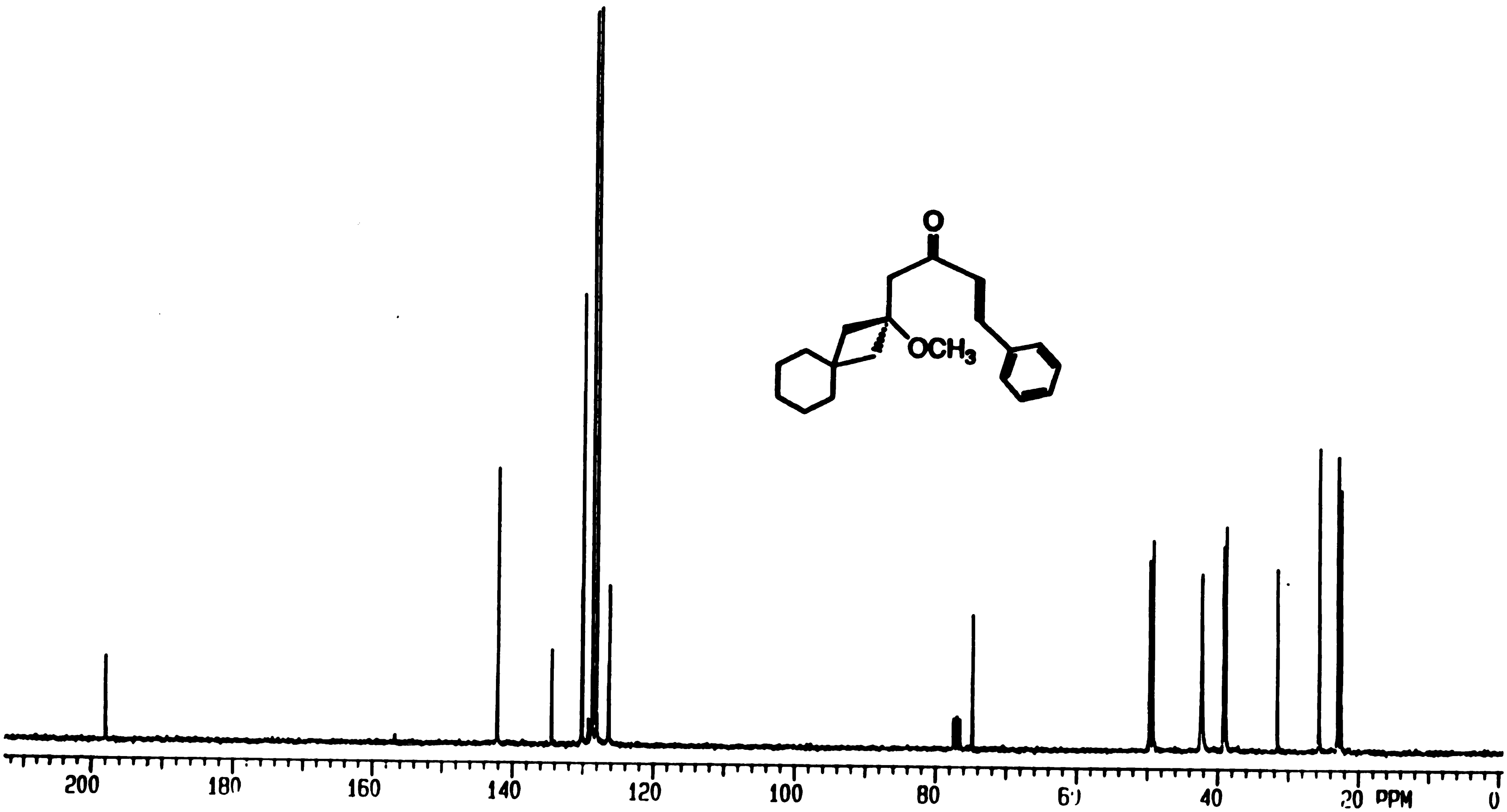


Figure 34. ^{13}C NMR Spectrum of (**9**).

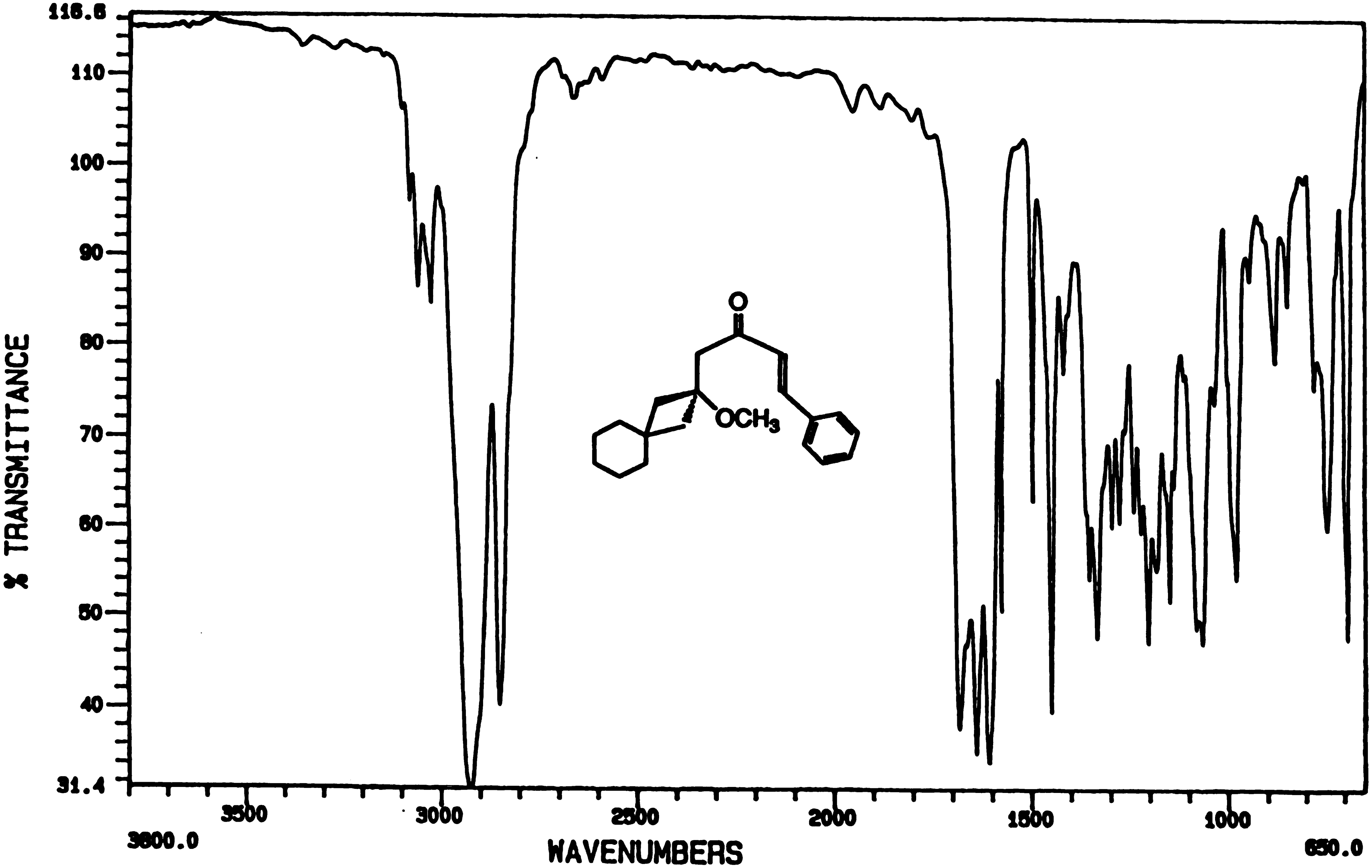


Figure 35. Infrared Spectrum of (9).

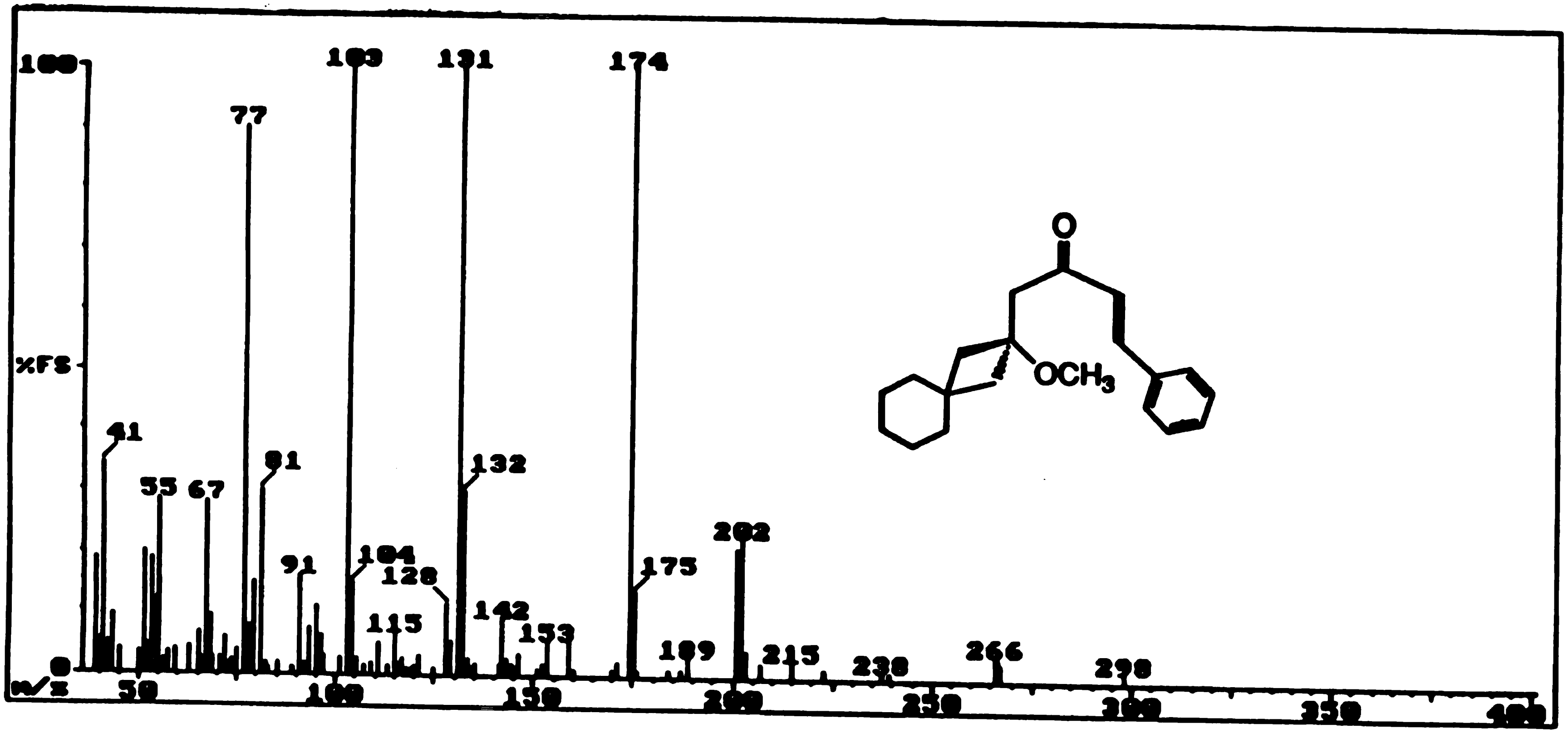


Figure 36. Mass Spectrum of (9).

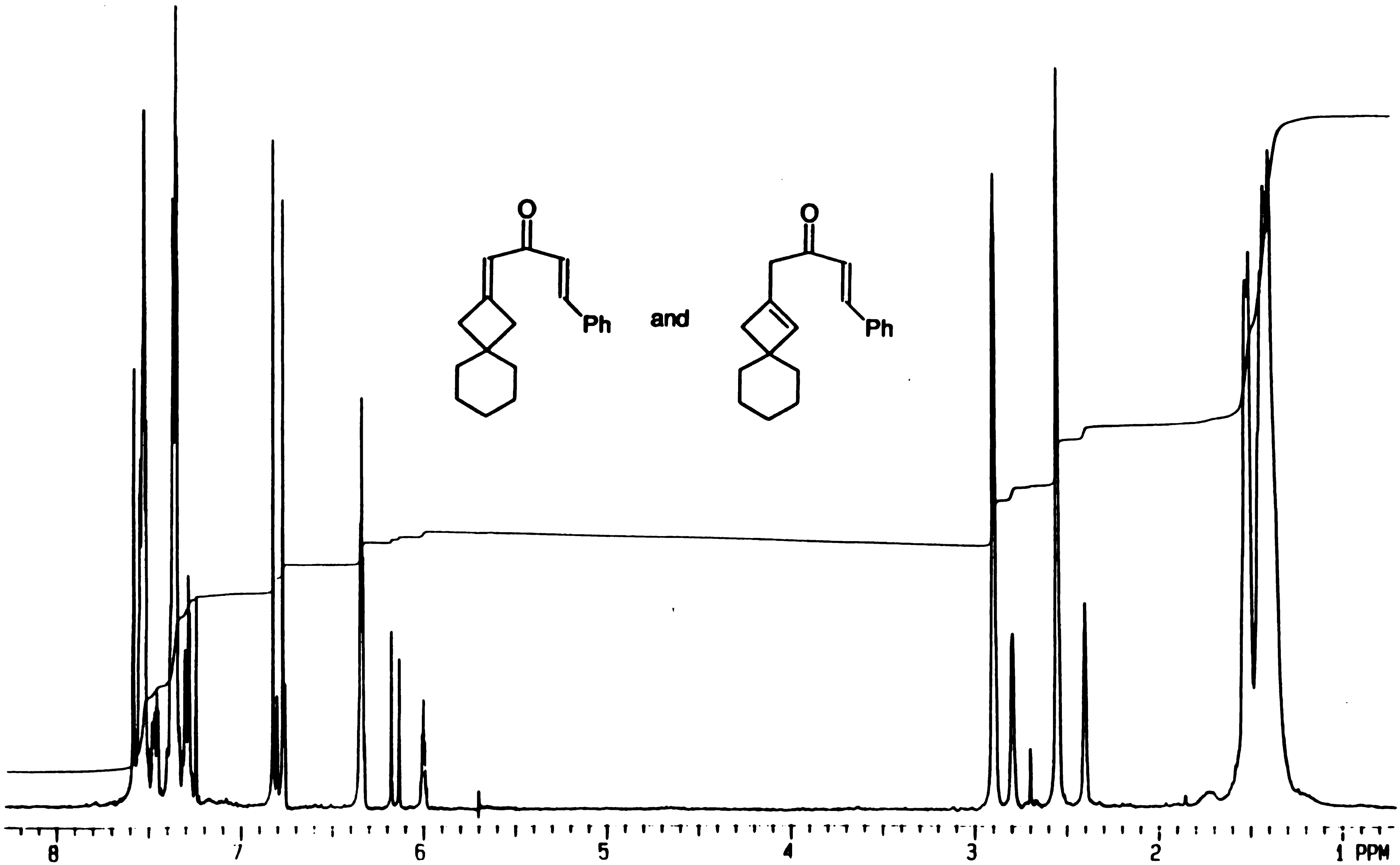


Figure 37. ^{1}H NMR Spectrum of (**8**) and (**10**).

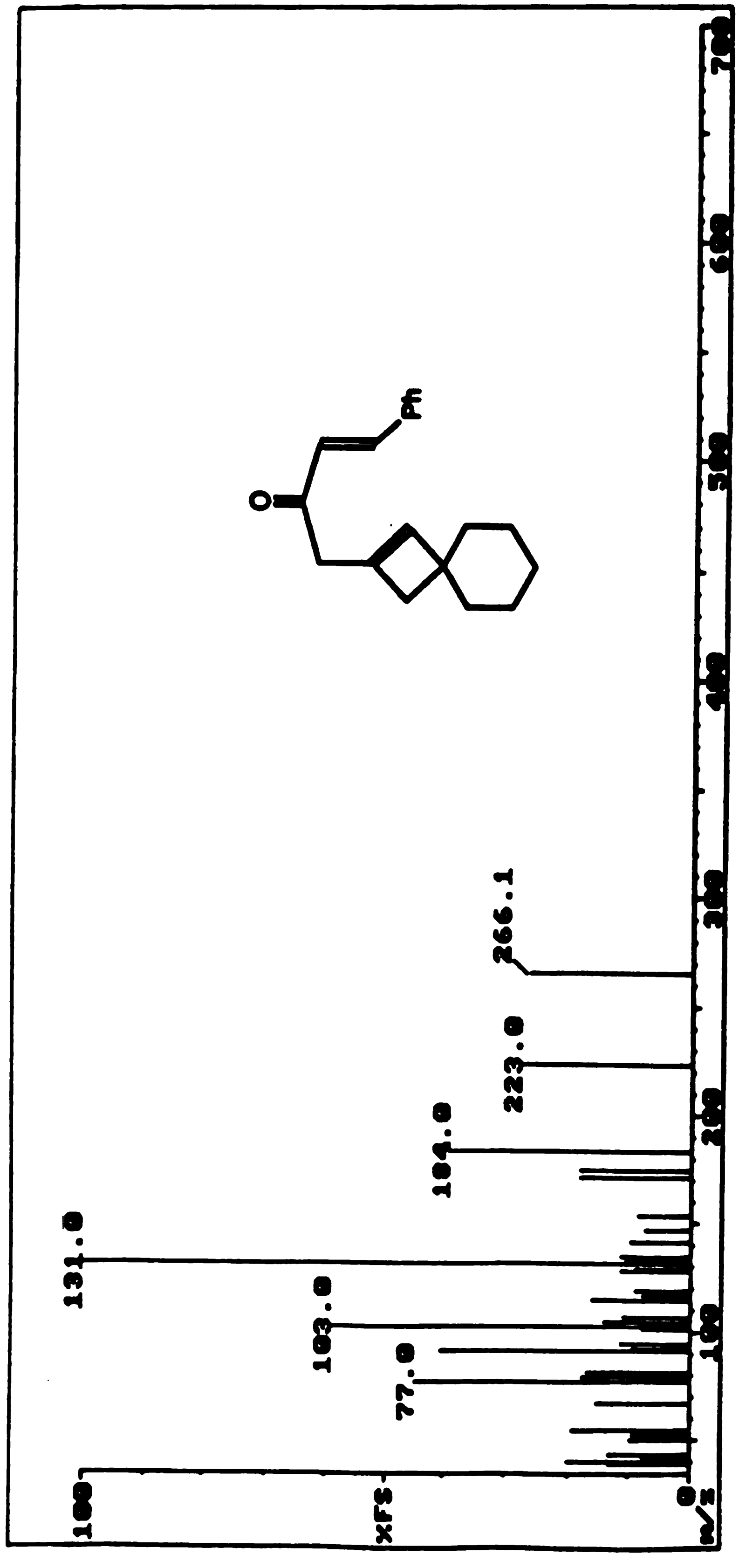


Figure 38. Mass Spectrum of (10).

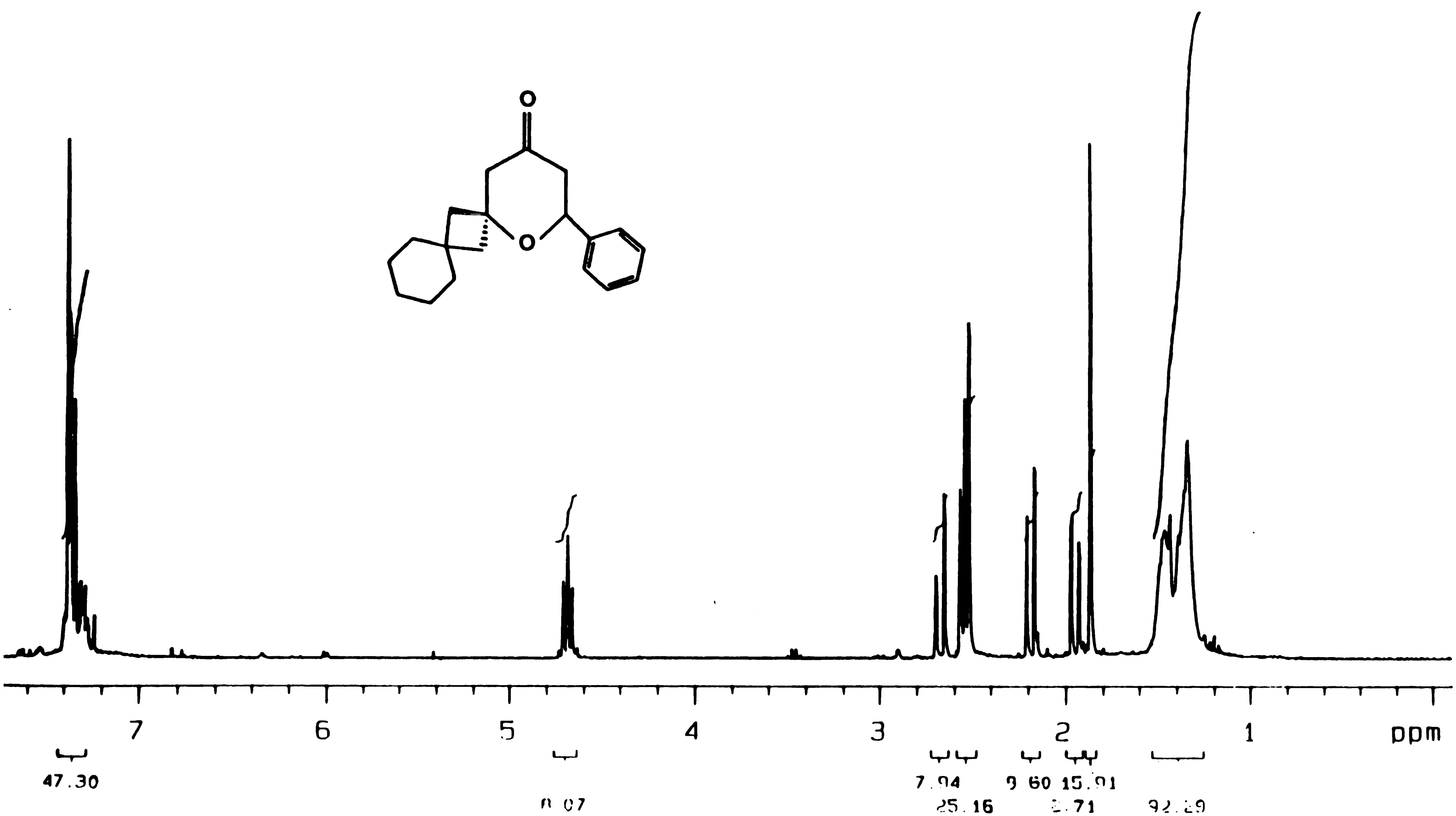


Figure 39. ^{1}H NMR Spectrum of (11).

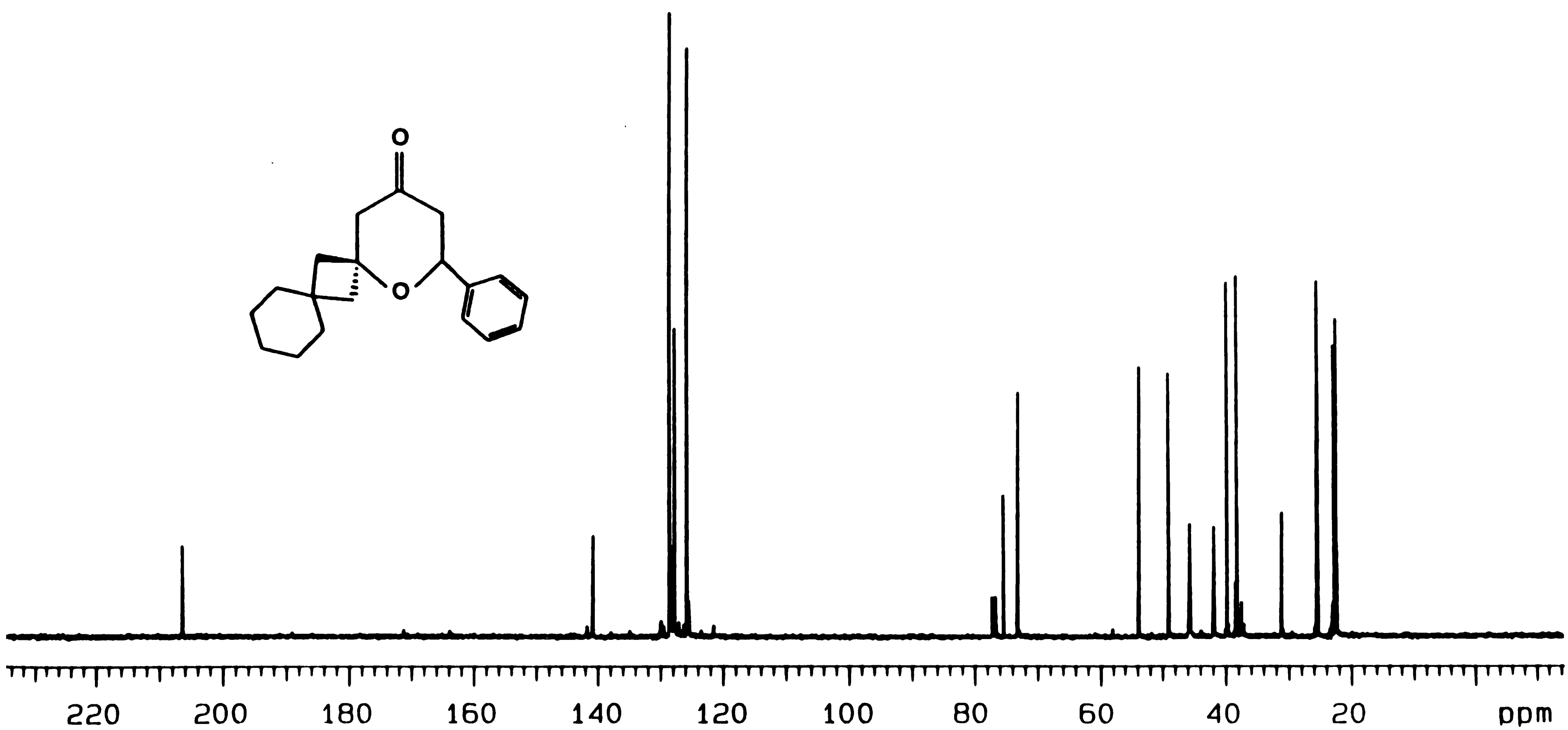


Figure 40. ^{13}C NMR Spectrum of (**11**).

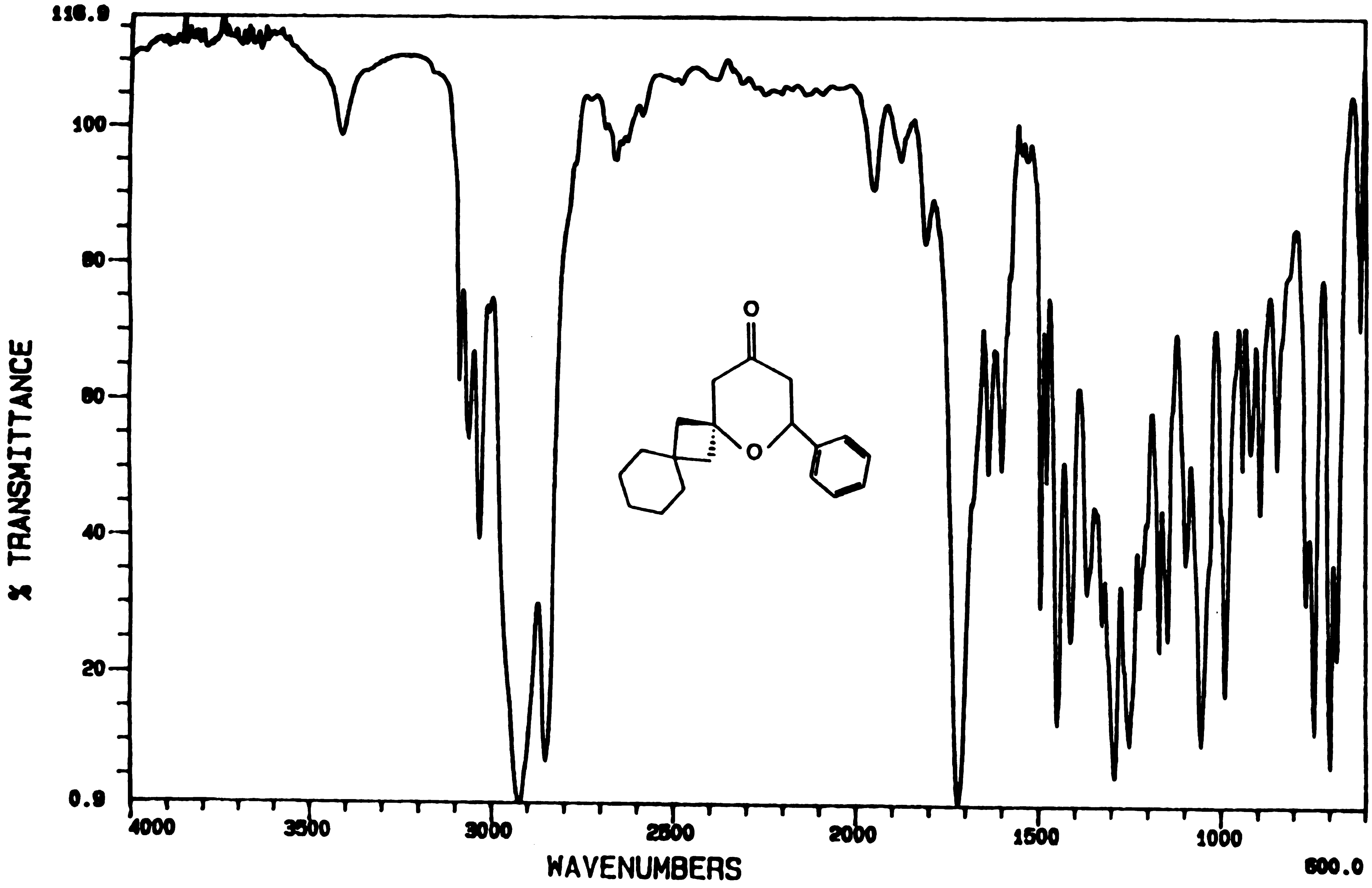


Figure 41. Infrared Spectrum of (11).

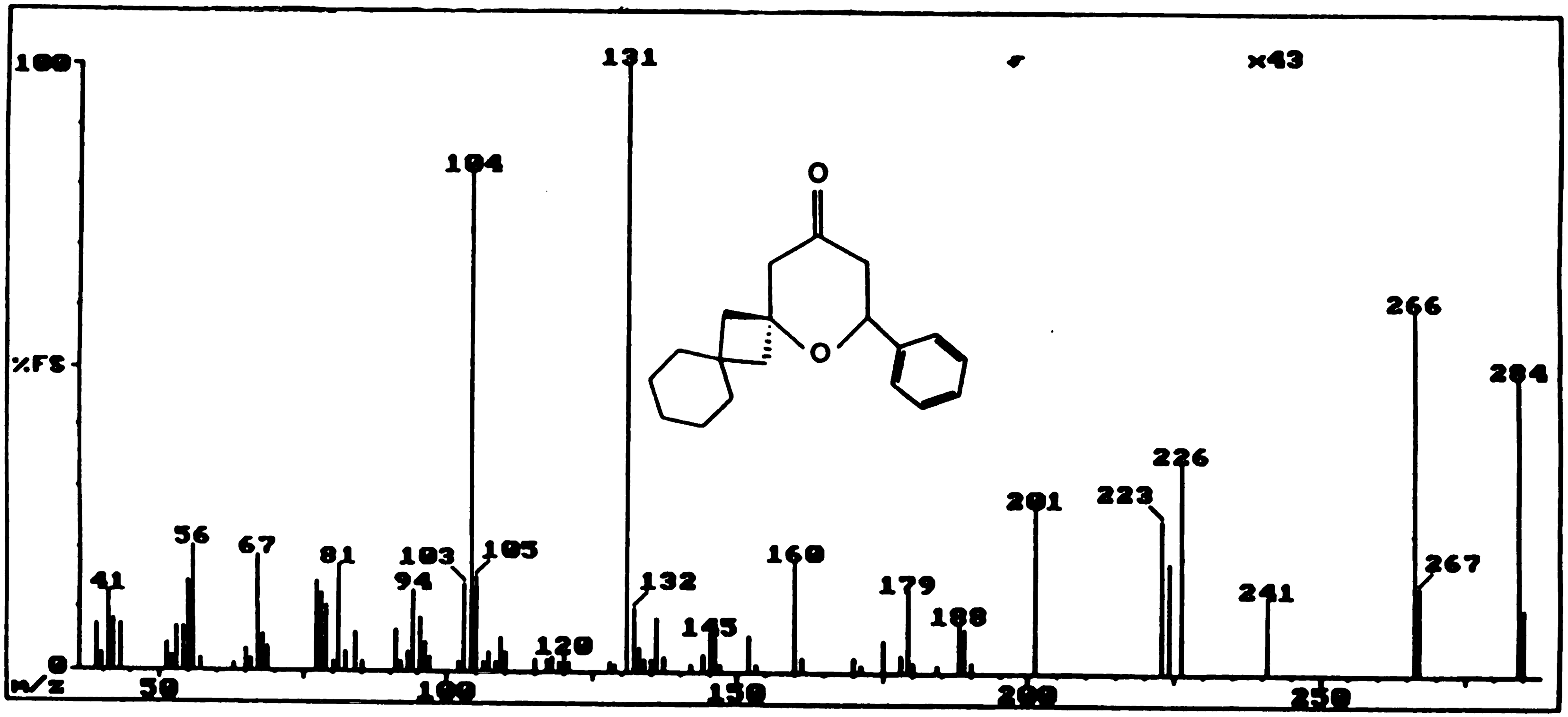


Figure 42. Mass Spectrum of (11).

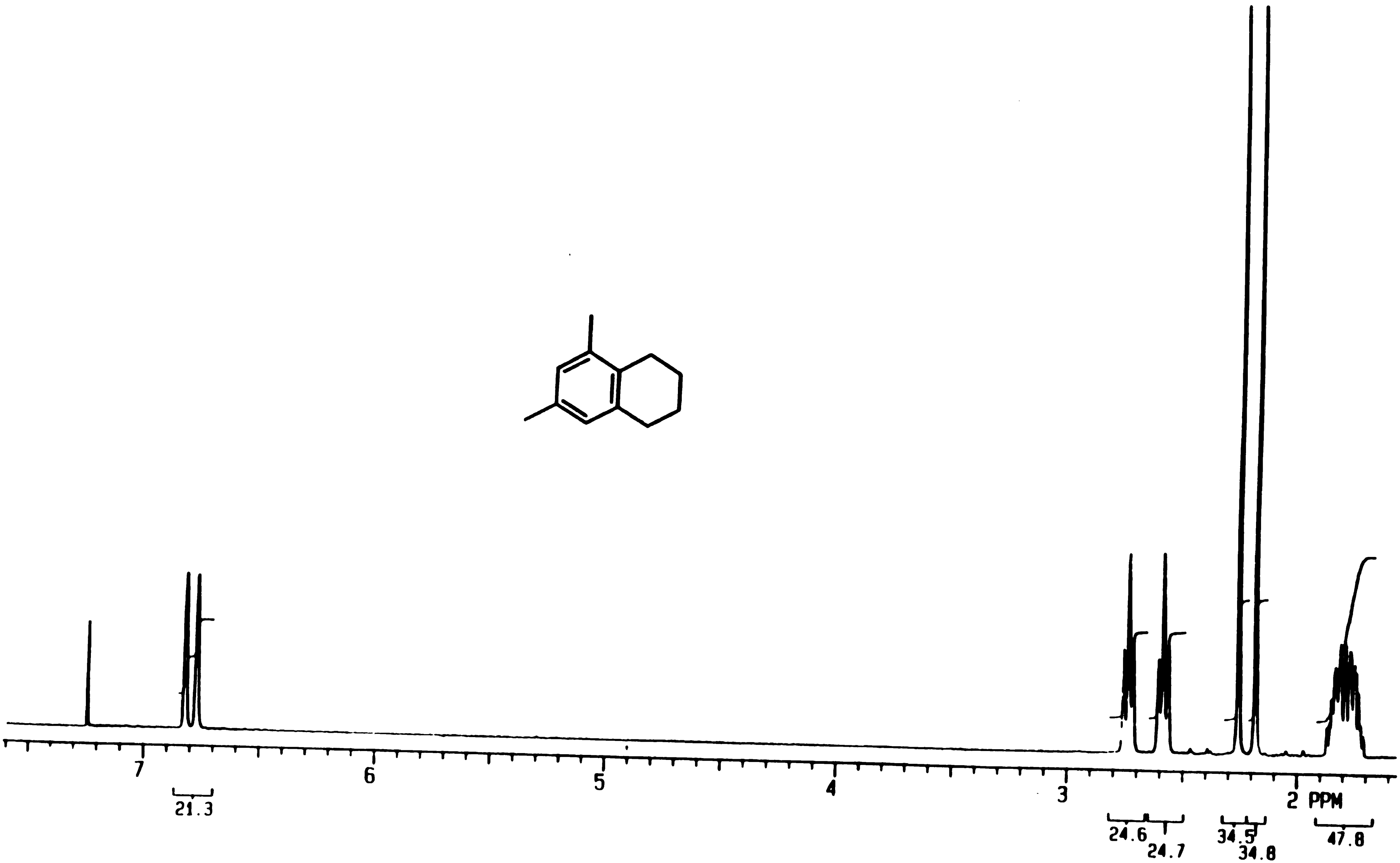


Figure 43. ^1H NMR Spectrum of (**12**).

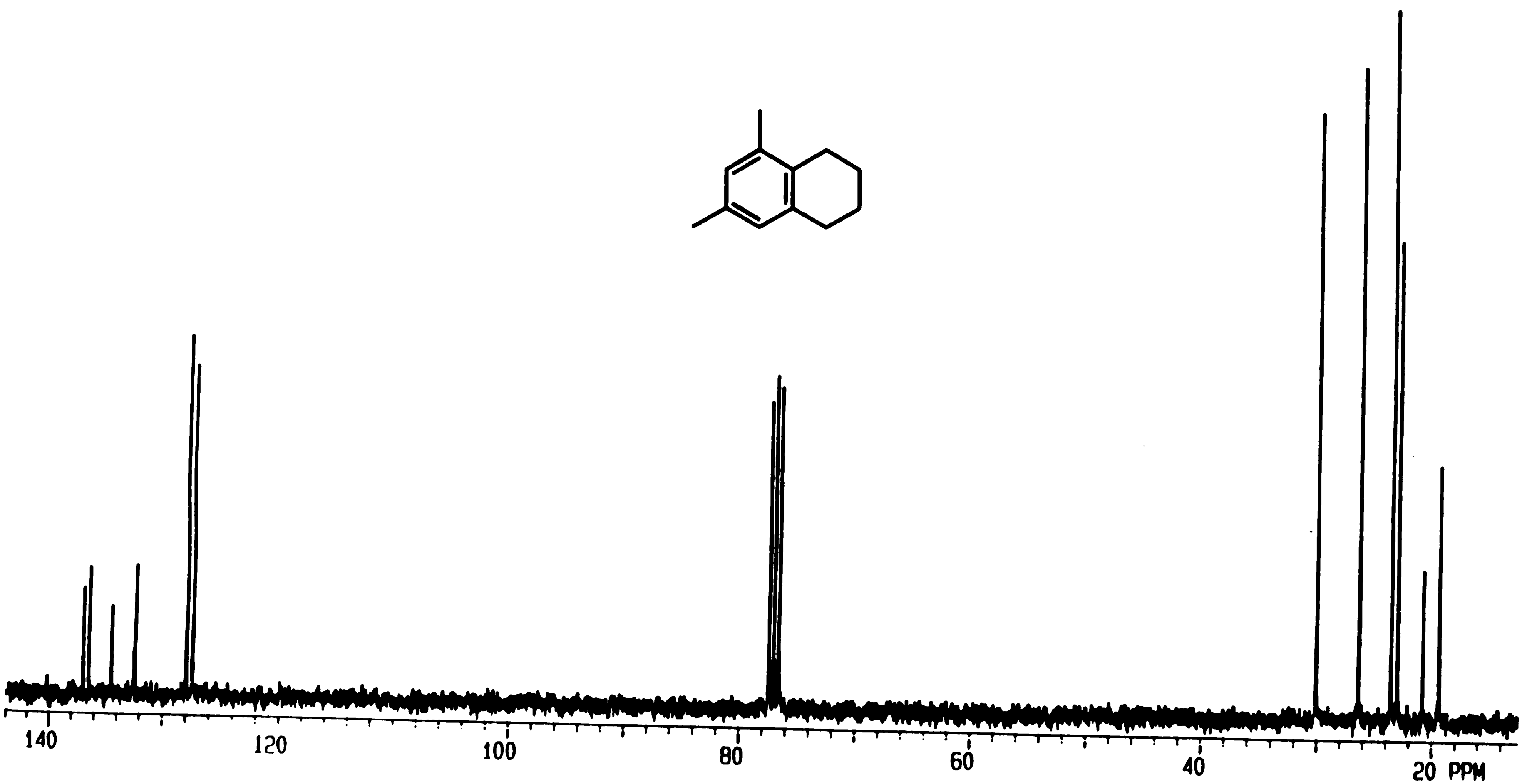


Figure 44. ^{13}C NMR Spectrum of (**12**).

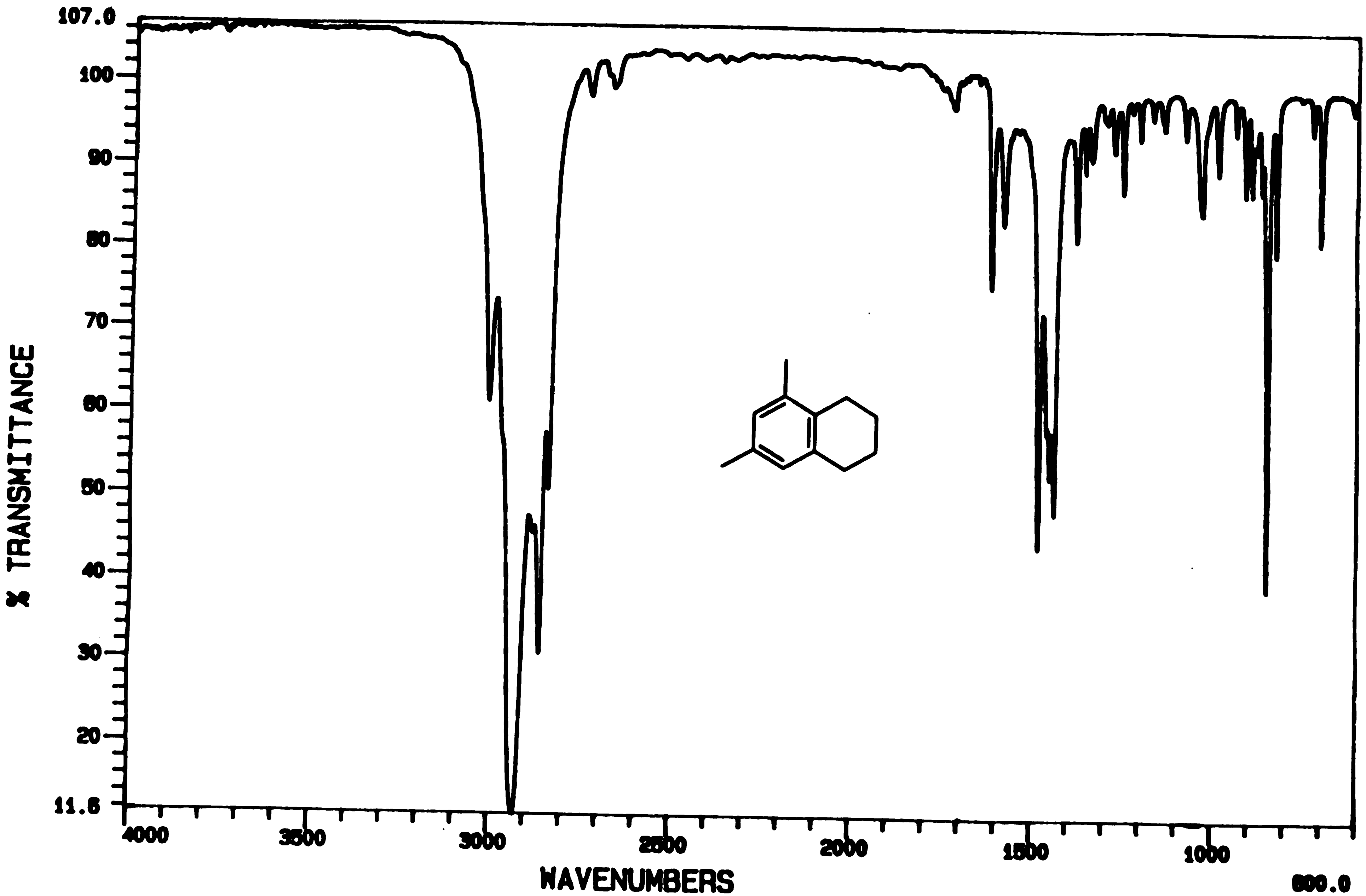


Figure 45. Infrared Spectrum of (12).

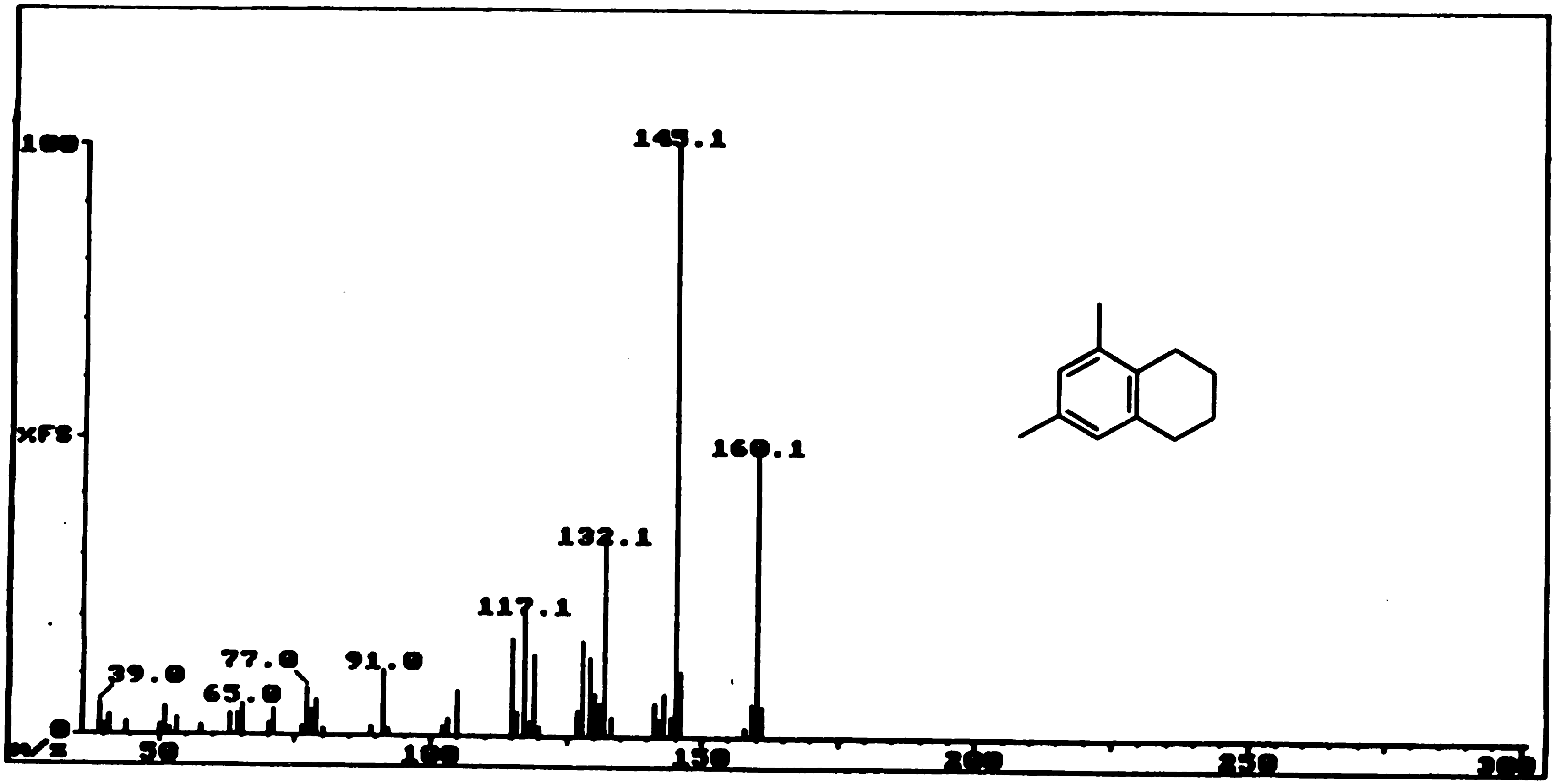


Figure 46. Mass Spectrum of (12).

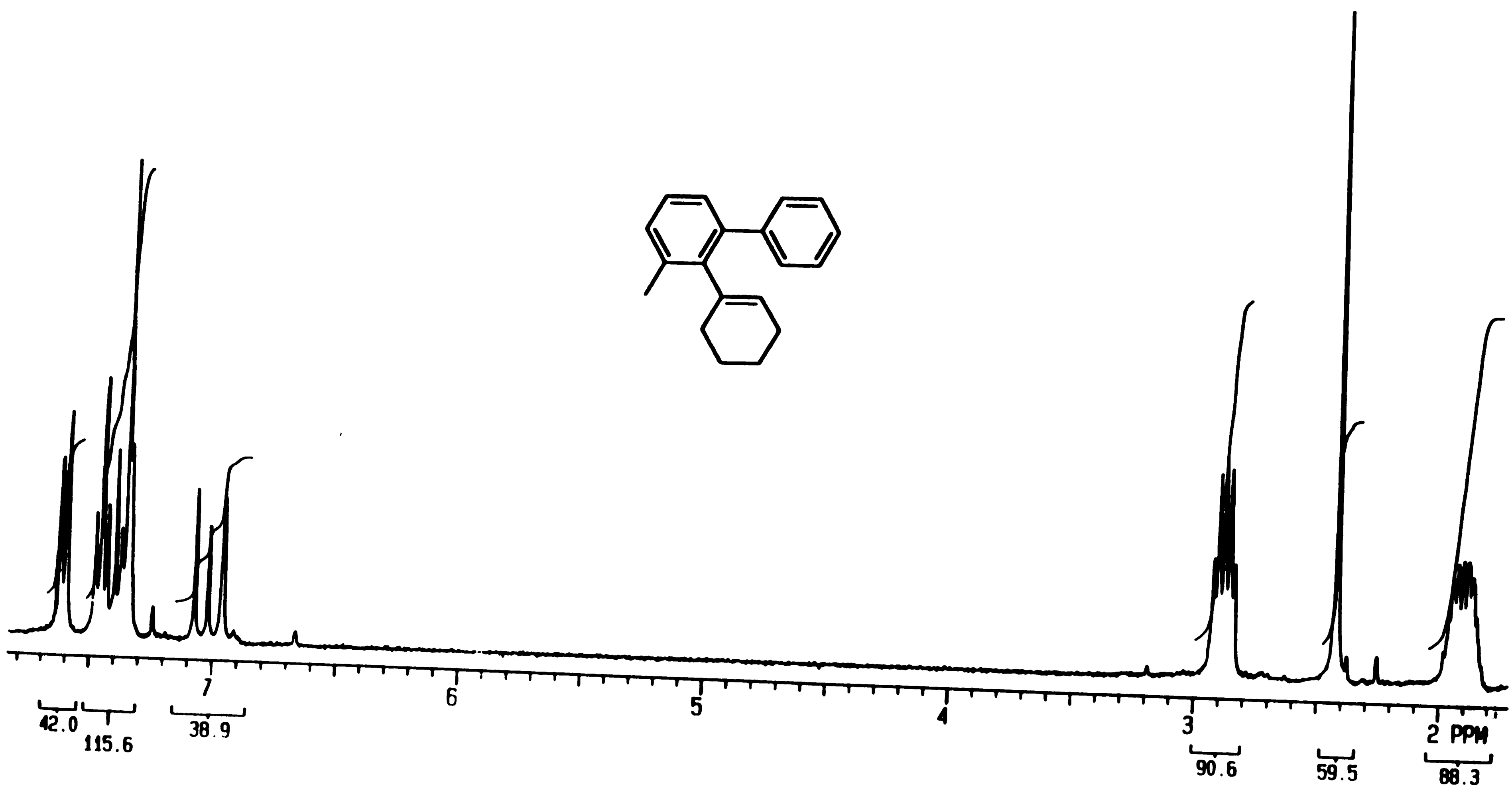


Figure 47. ^{1}H NMR Spectrum of (**13**).

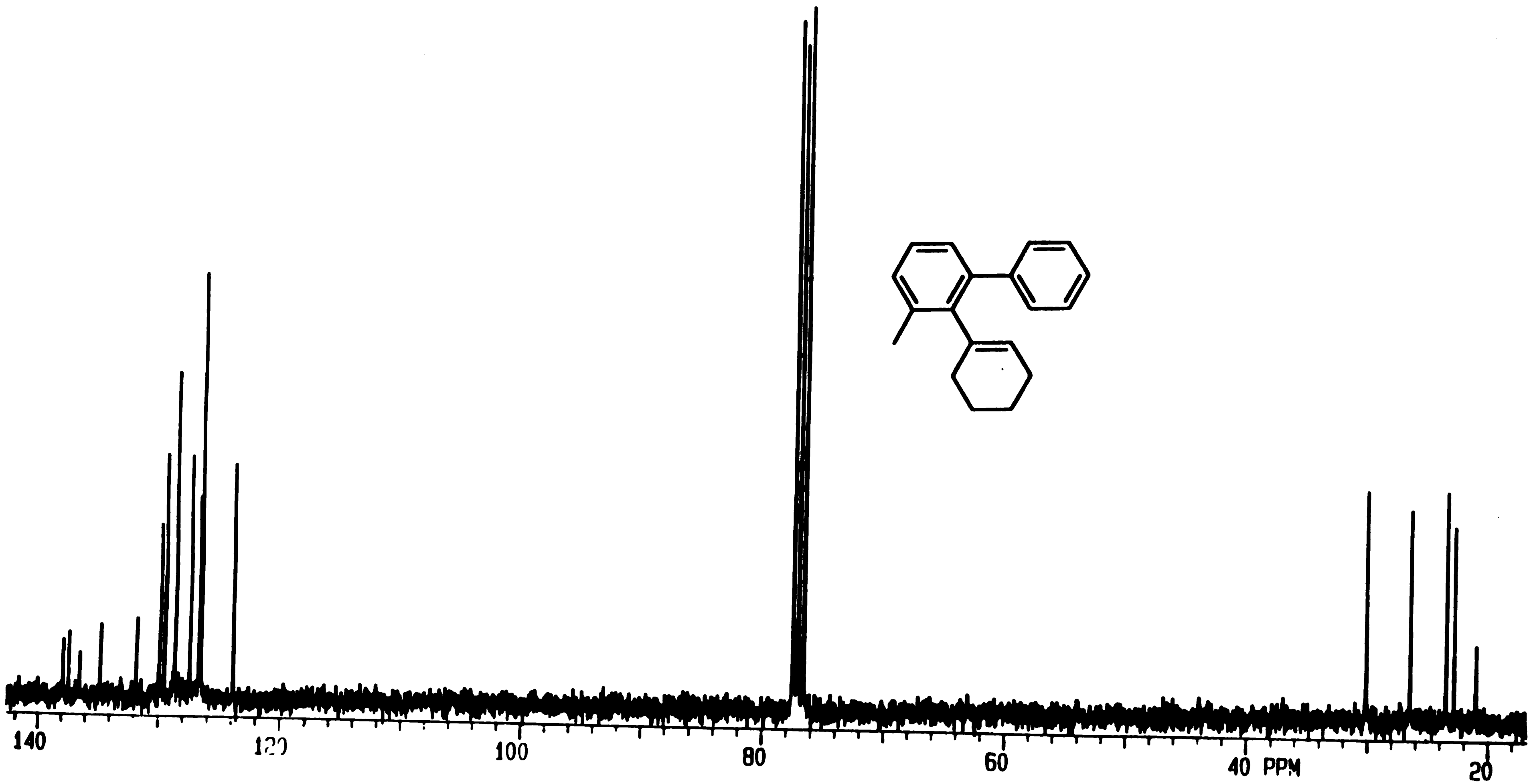


Figure 48. ^{13}C NMR Spectrum of (**13**).

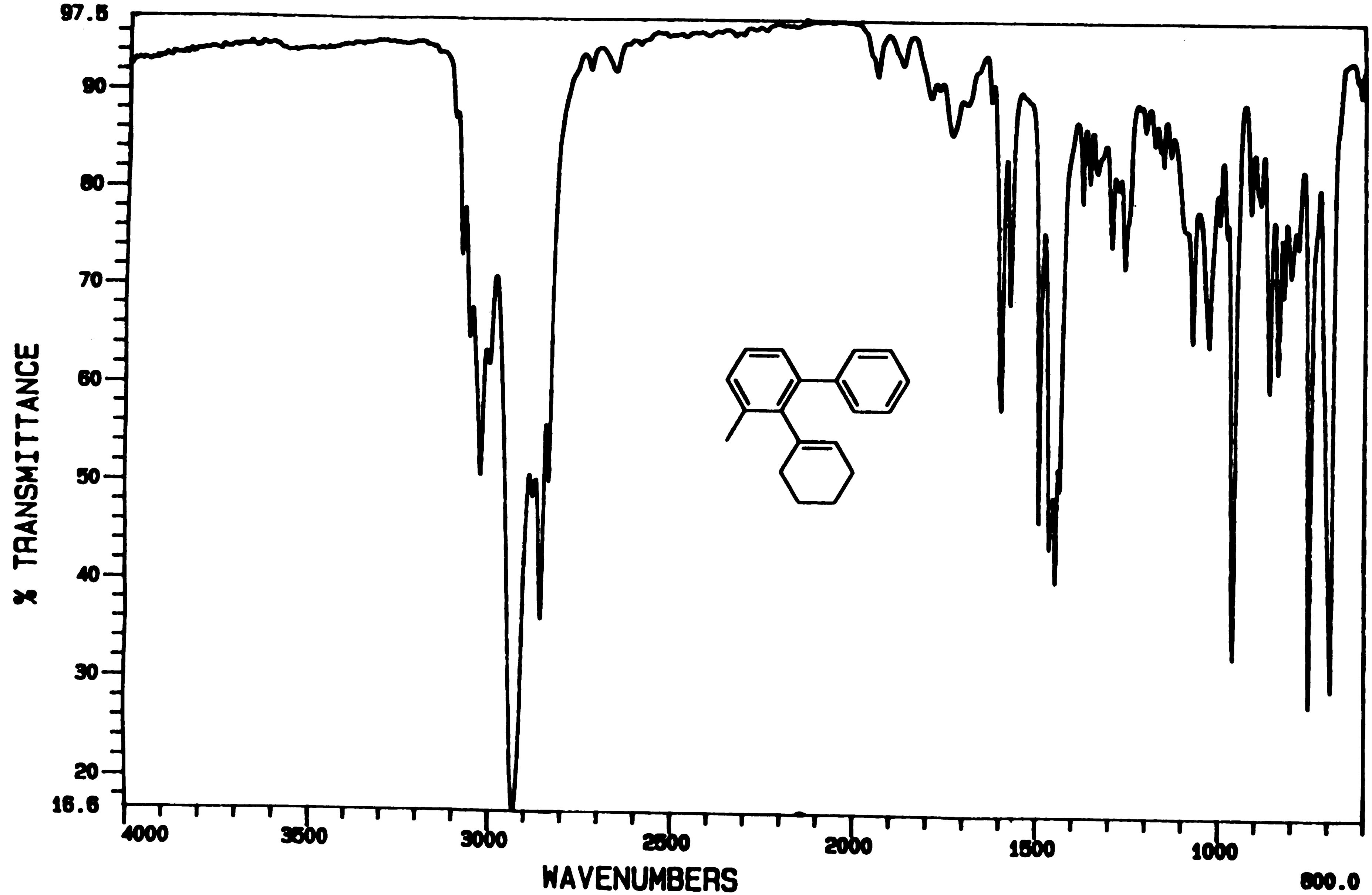


Figure 49. Infrared Spectrum of (13).

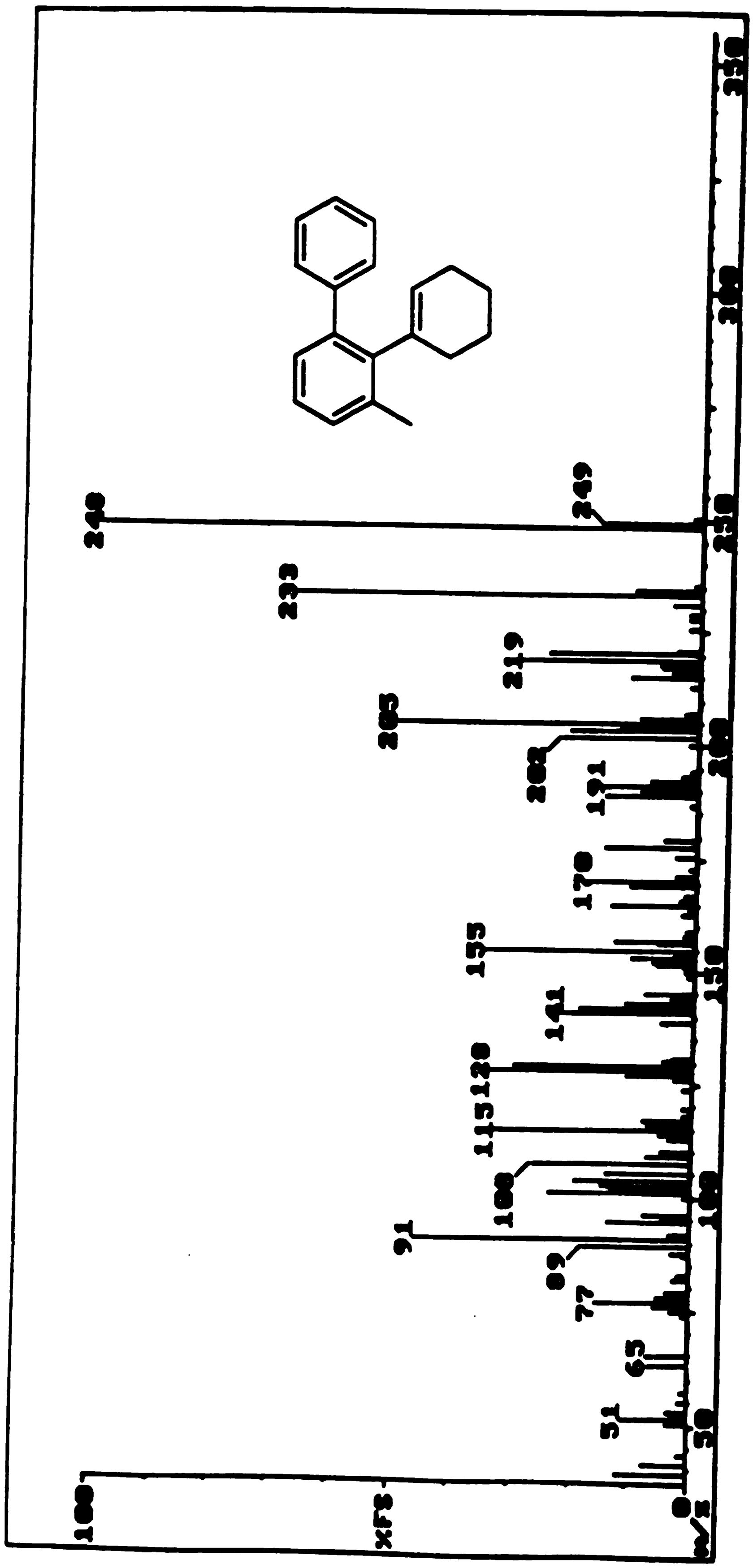


Figure 50. Mass Spectrum of (13).

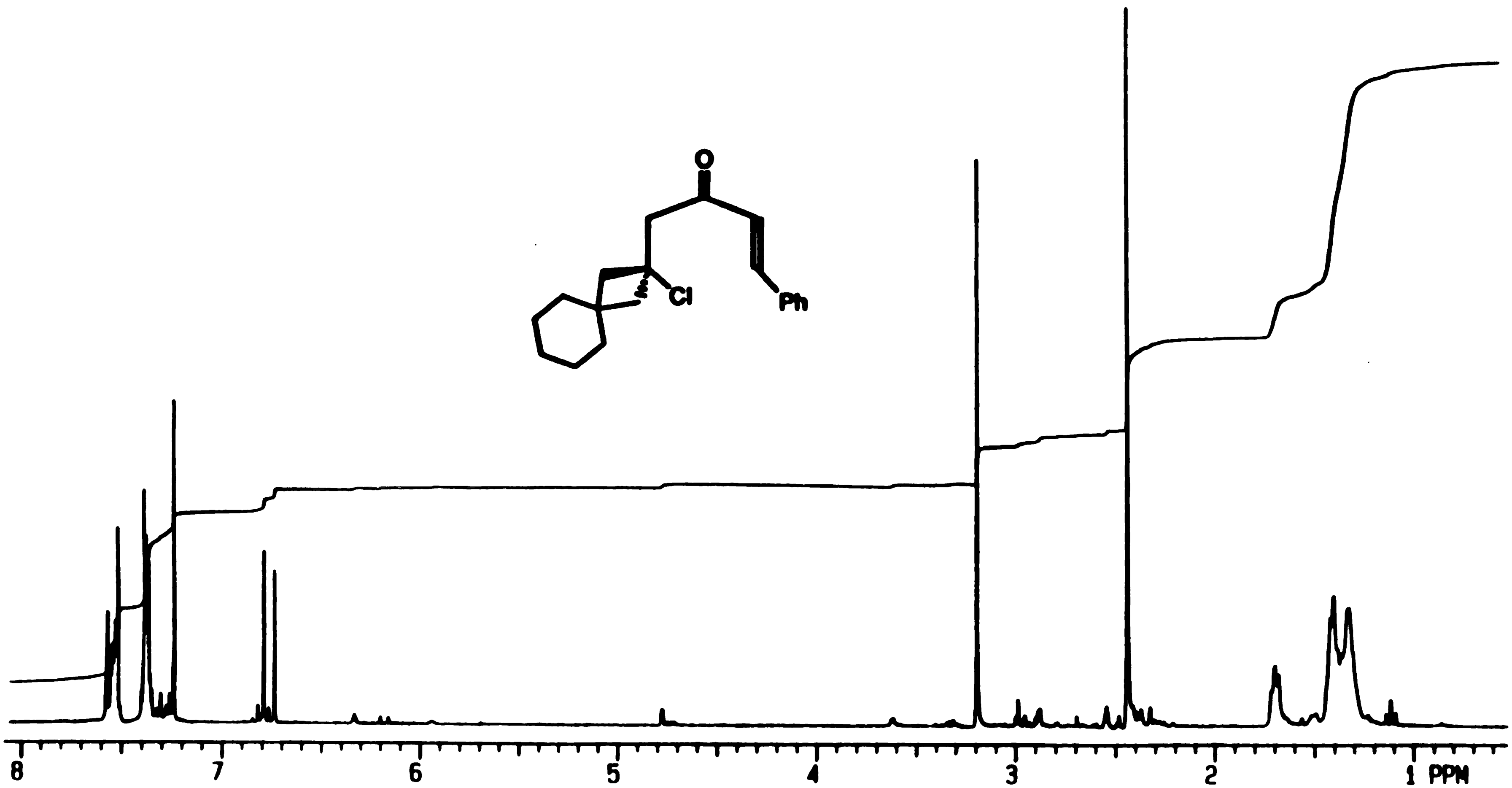


Figure 51. ^{1}H NMR Spectrum of (14).

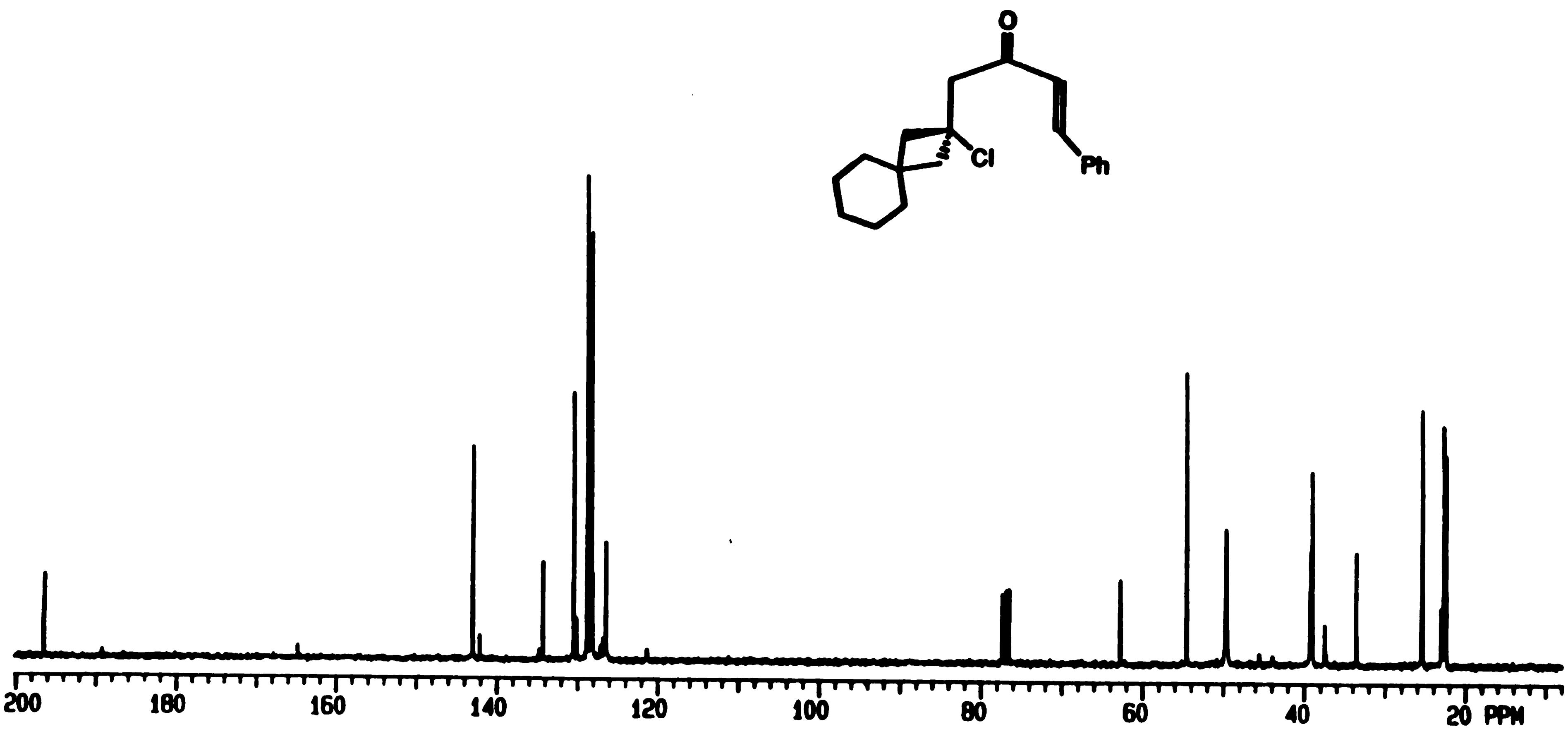


Figure 52. ^{13}C NMR Spectrum of (14).

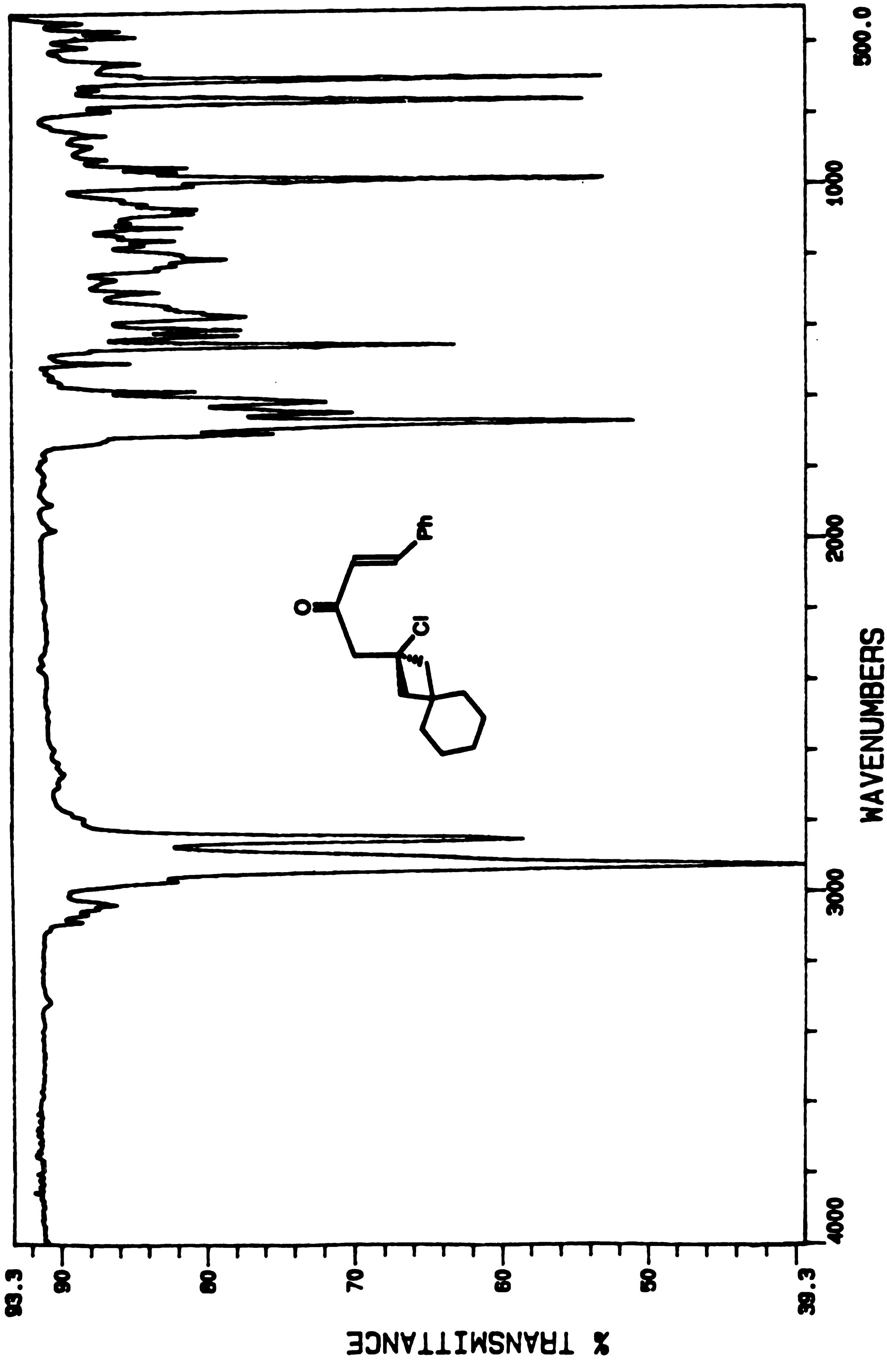


Figure 53. Infrared Spectrum of (14).

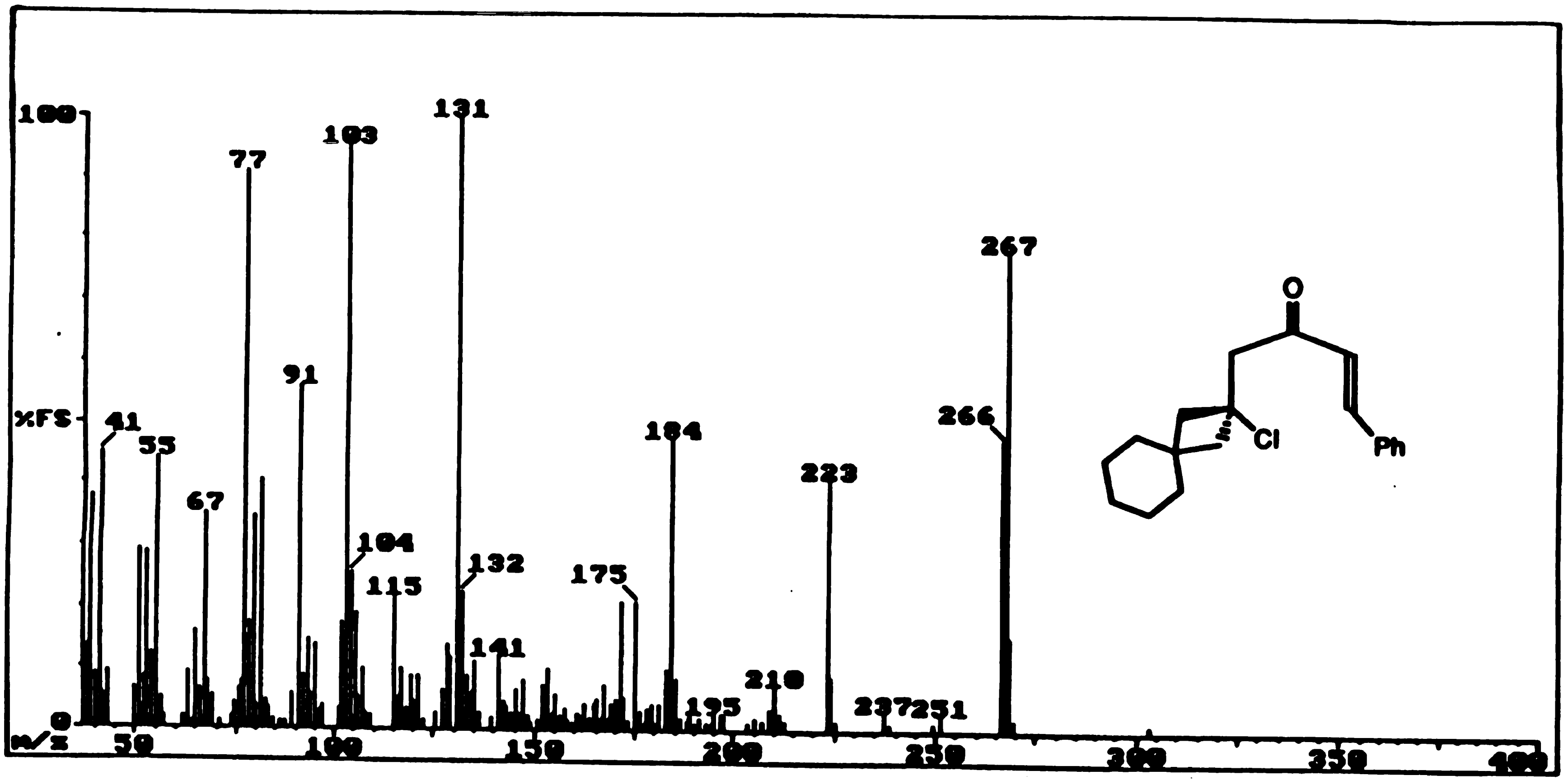


Figure 54. Mass Spectrum of (14).

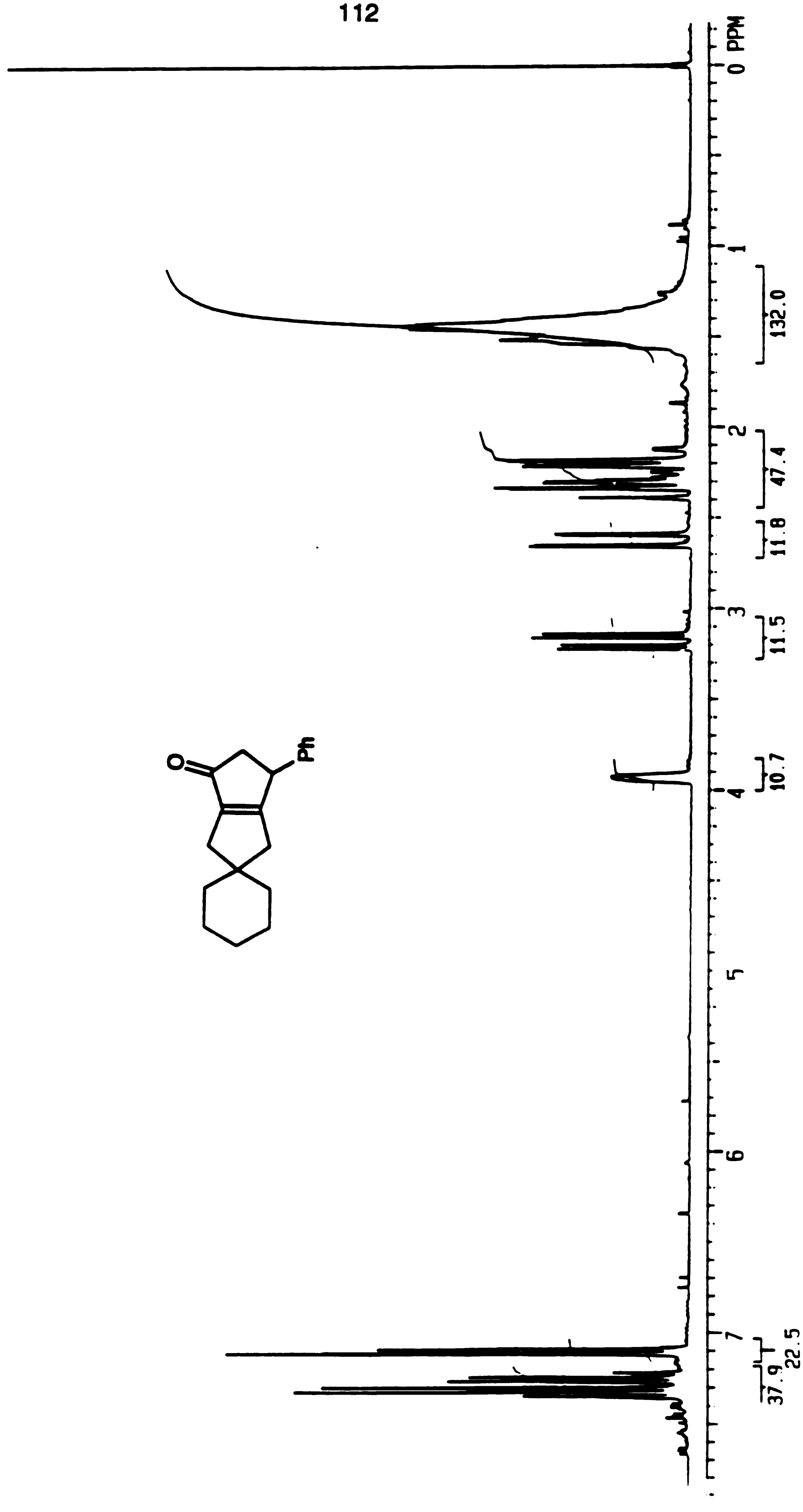


Figure 55. ^{1}H NMR Spectrum of (15).

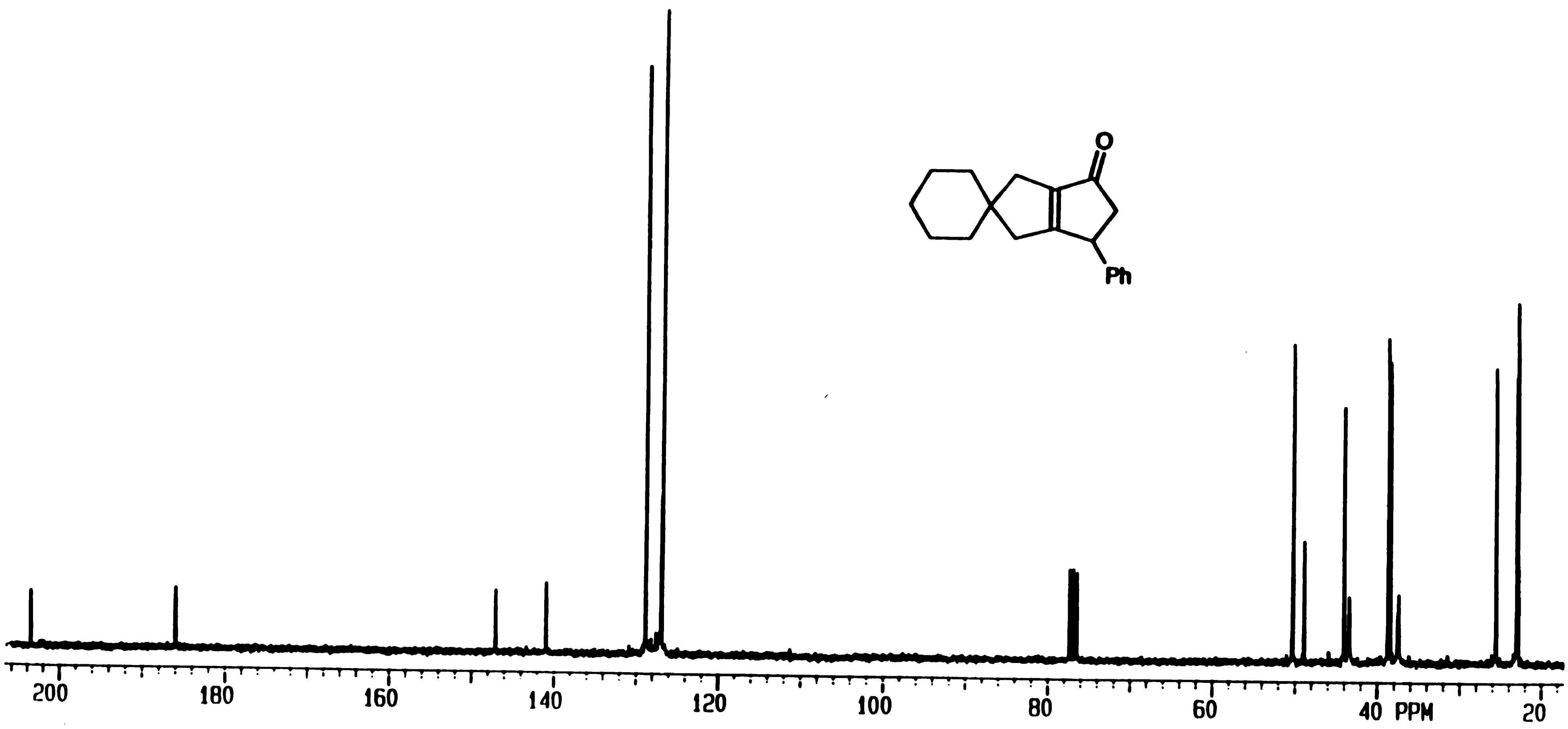


Figure 56. ^{13}C NMR Spectrum of (**15**).

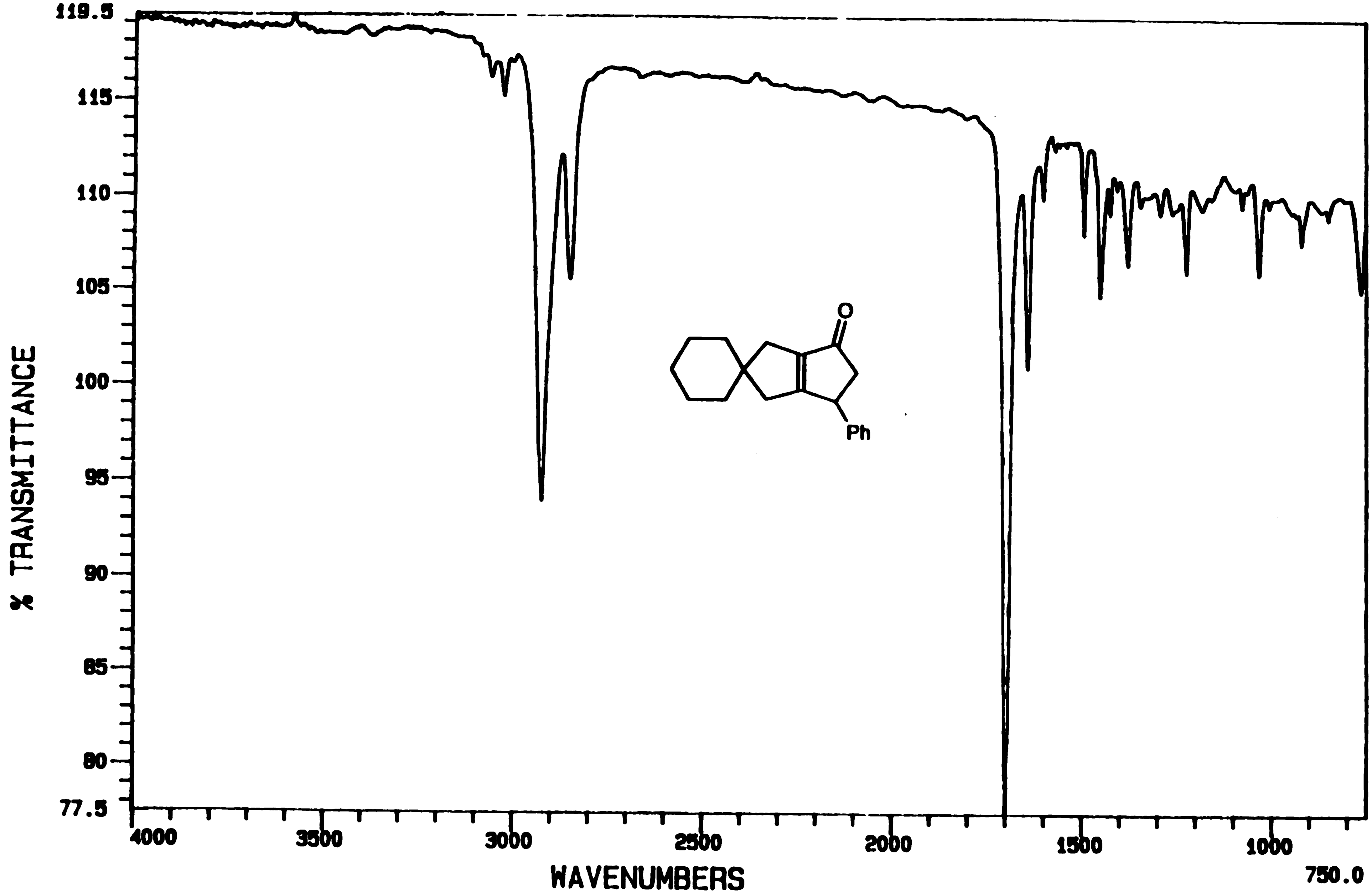


Figure 57. Infrared Spectrum of (15).

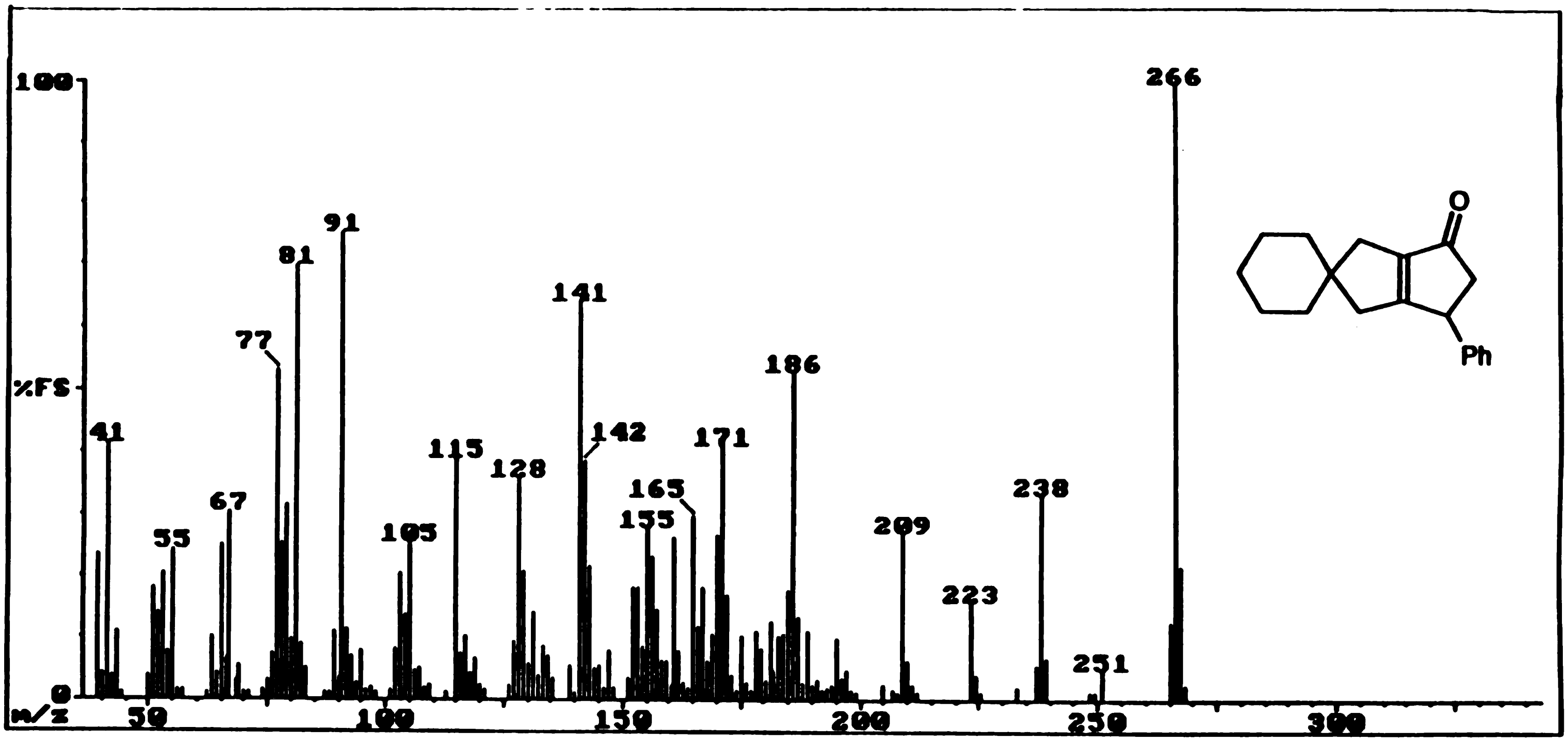


Figure 58. Mass Spectrum of (15).

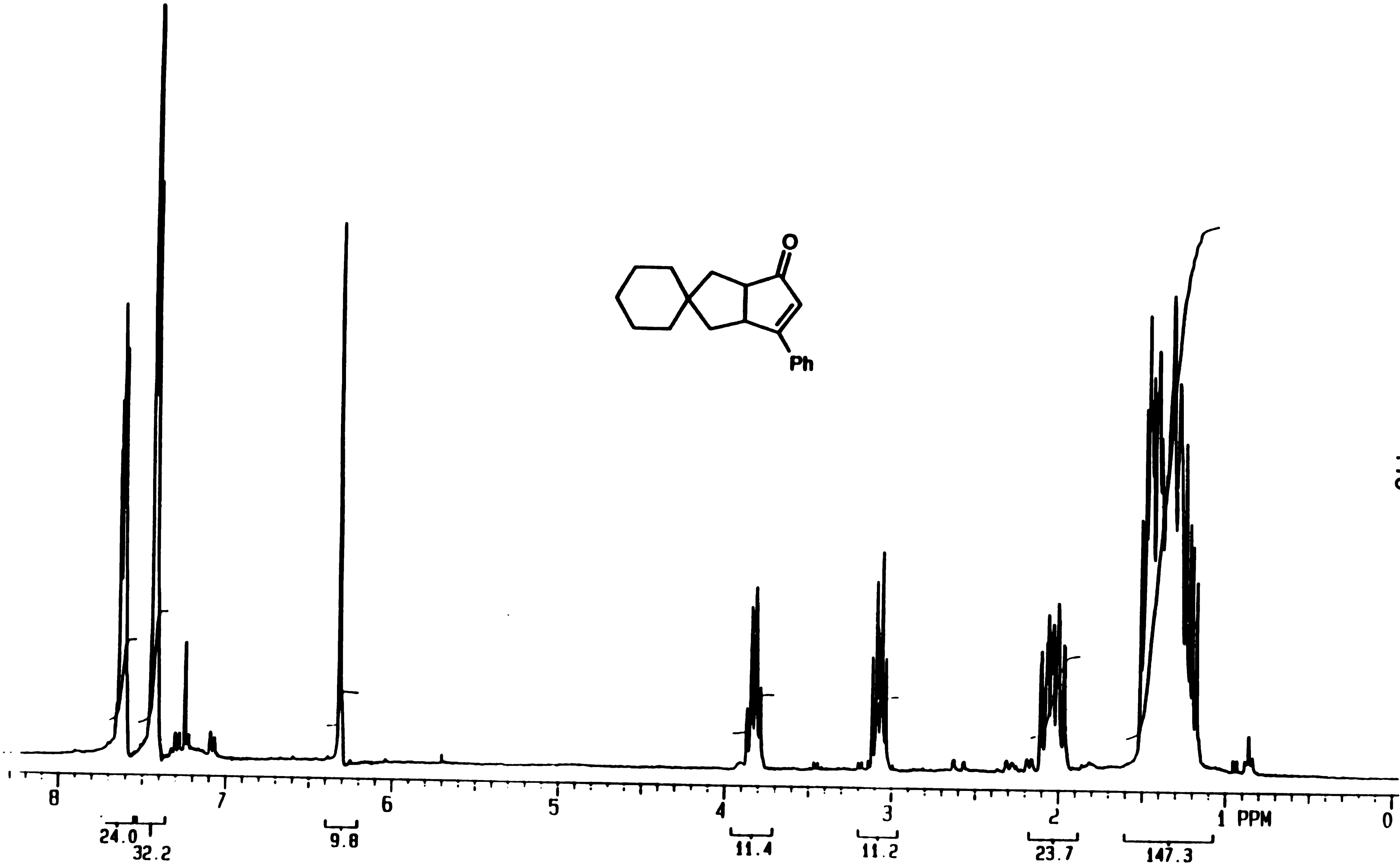


Figure 59. ^{1}H NMR Spectrum of (**16**).

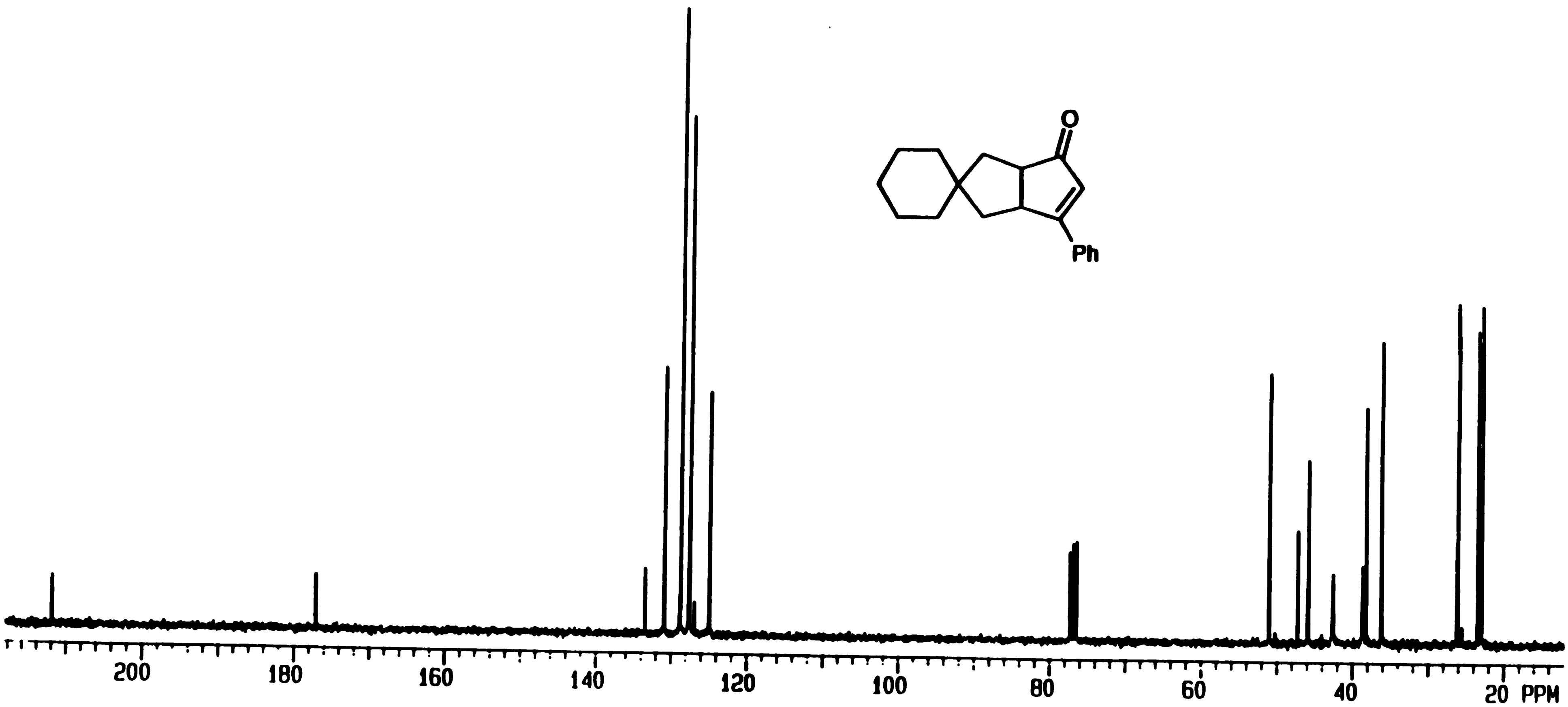


Figure 60. ^{13}C NMR Spectrum of (**16**).

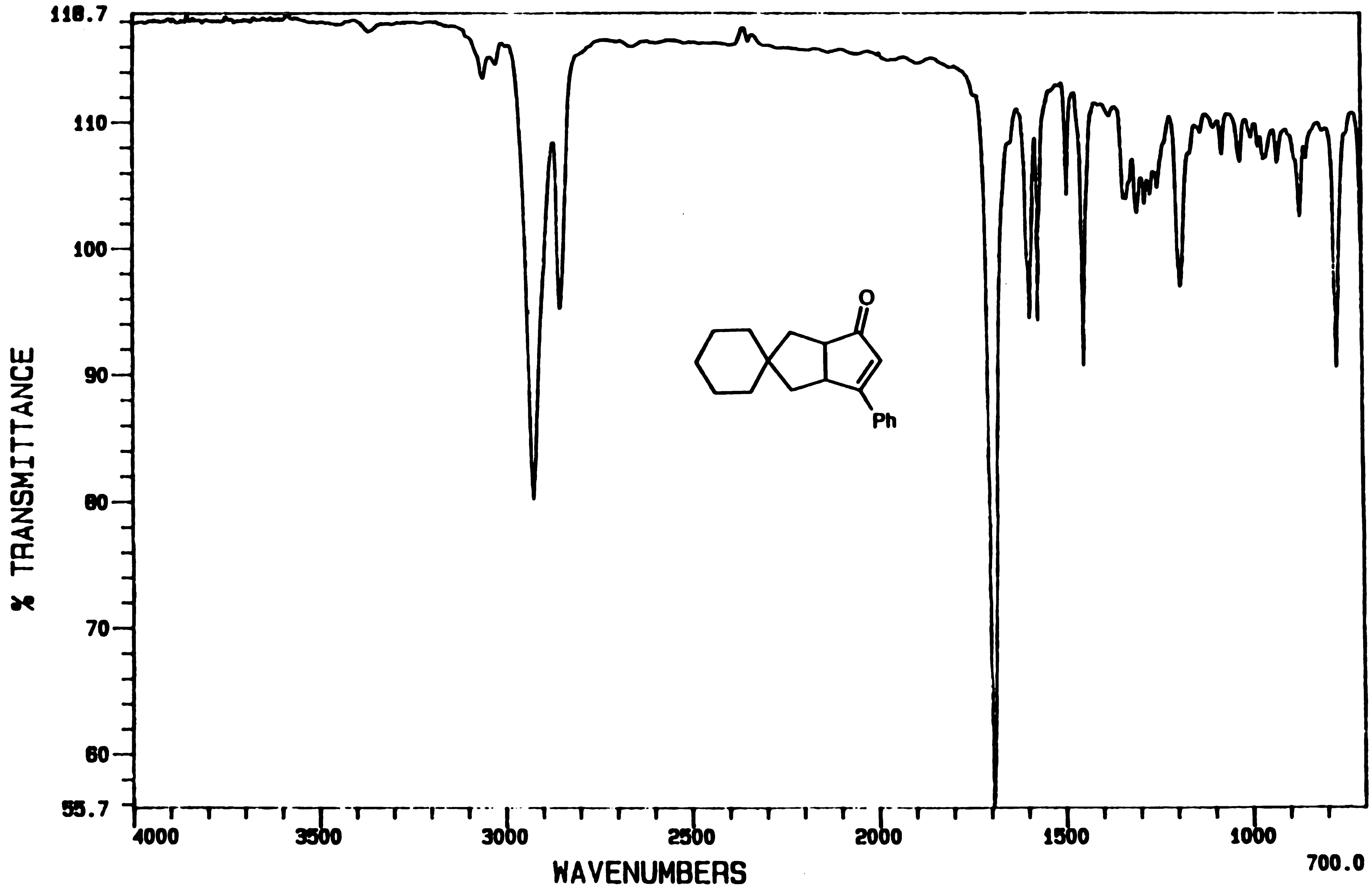


Figure 61. Infrared Spectrum of (16).

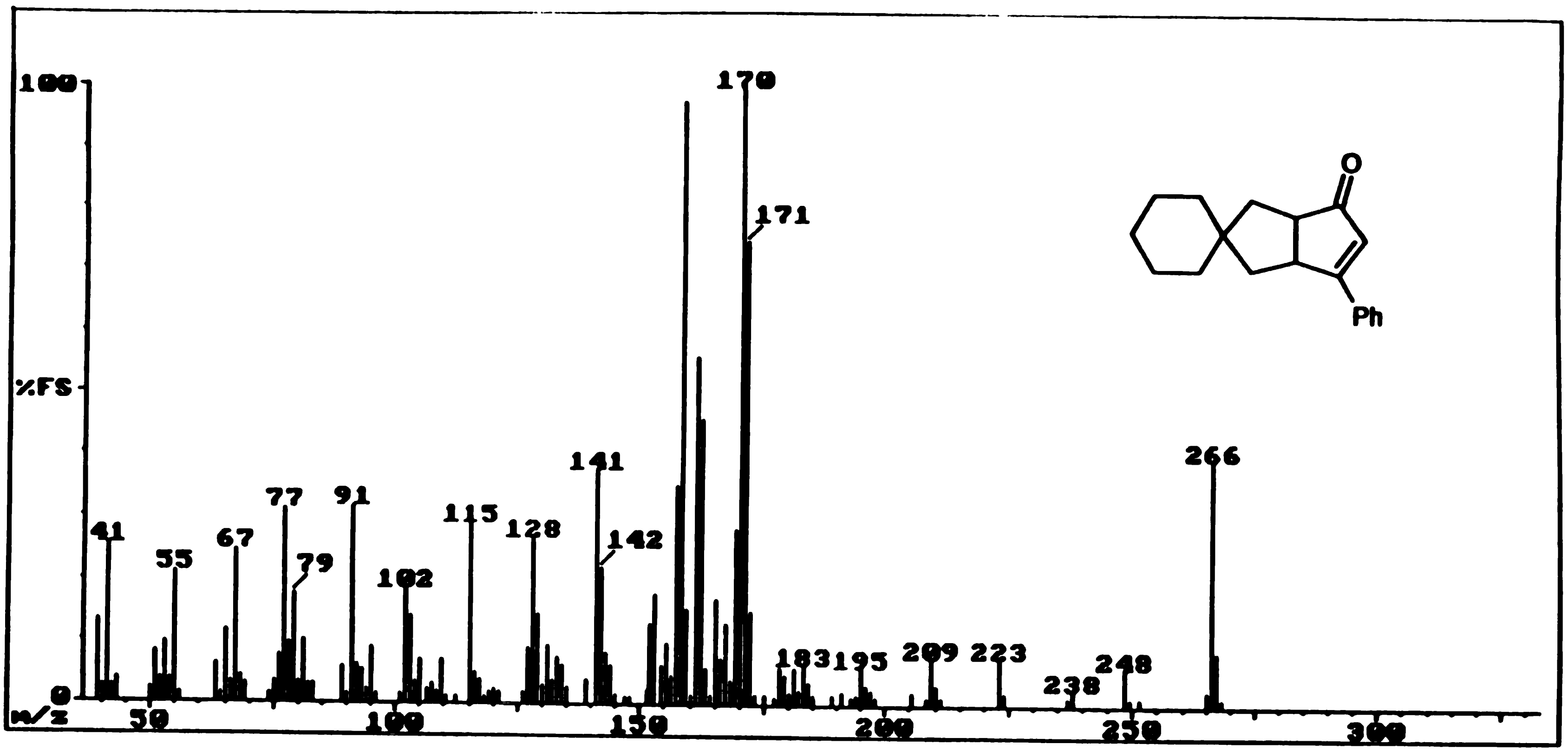


Figure 62. Mass Spectrum of (16).

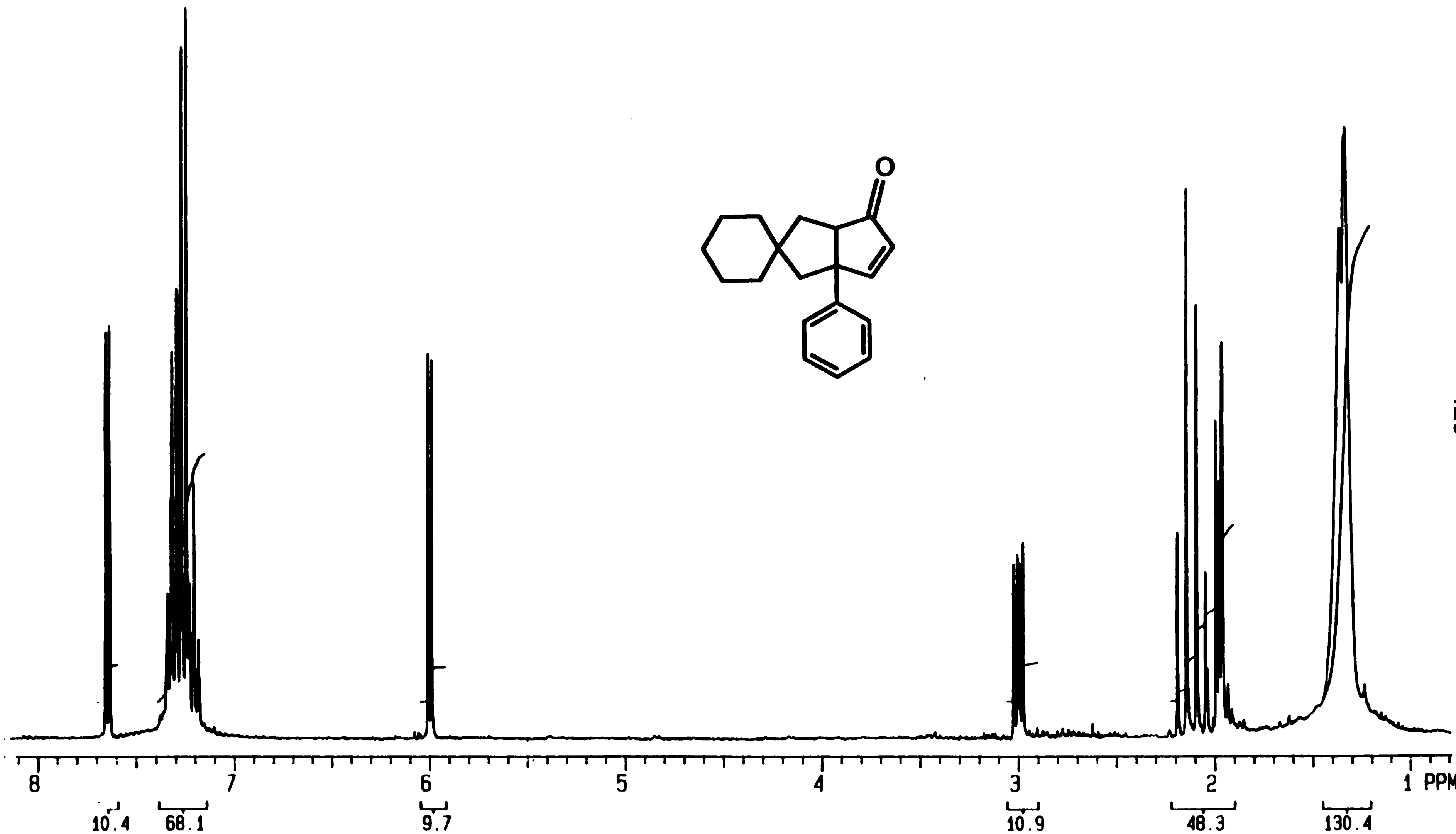


Figure 63. ^{1}H NMR Spectrum of (**17**).

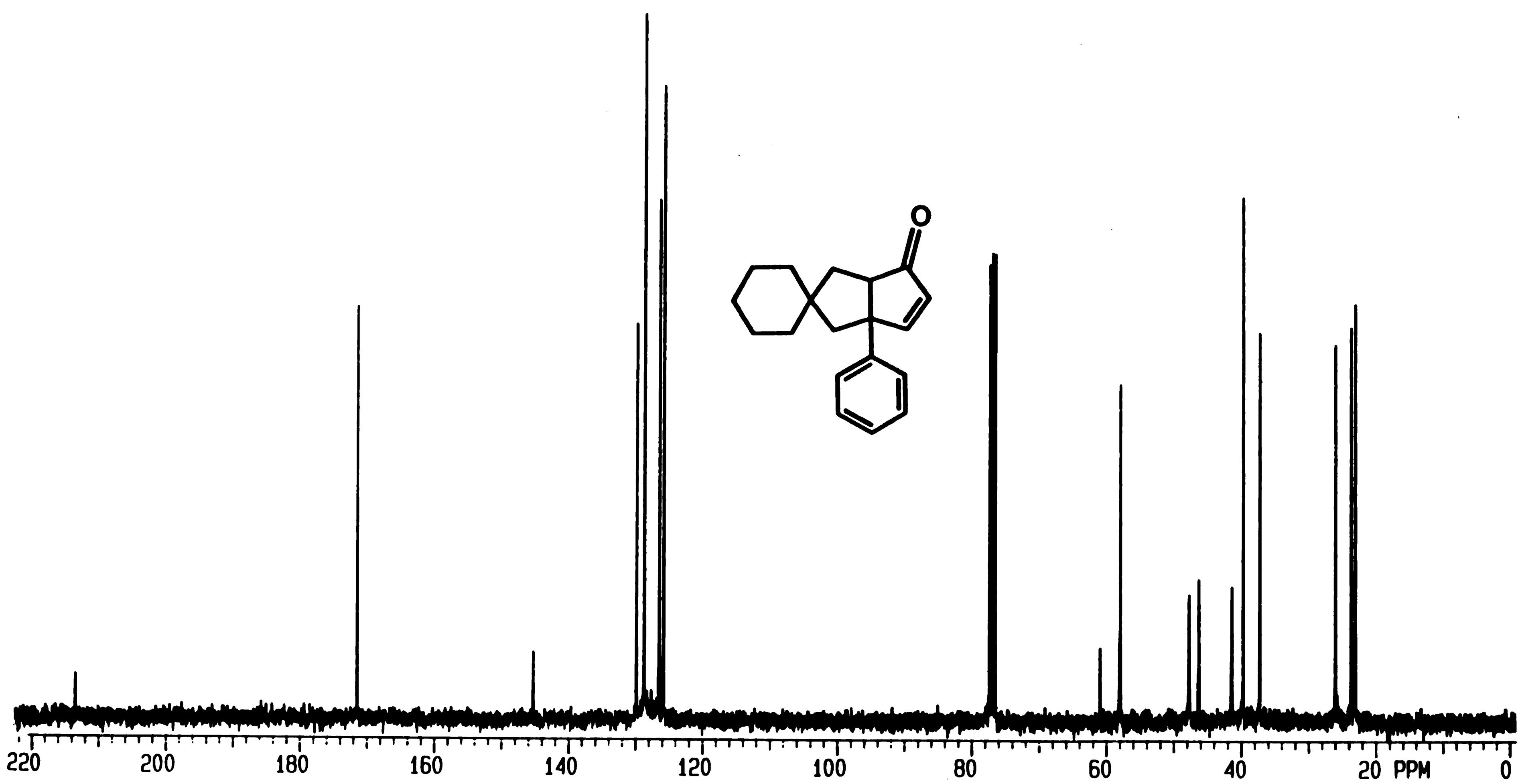


Figure 64. ^{13}C NMR Spectrum of (17).

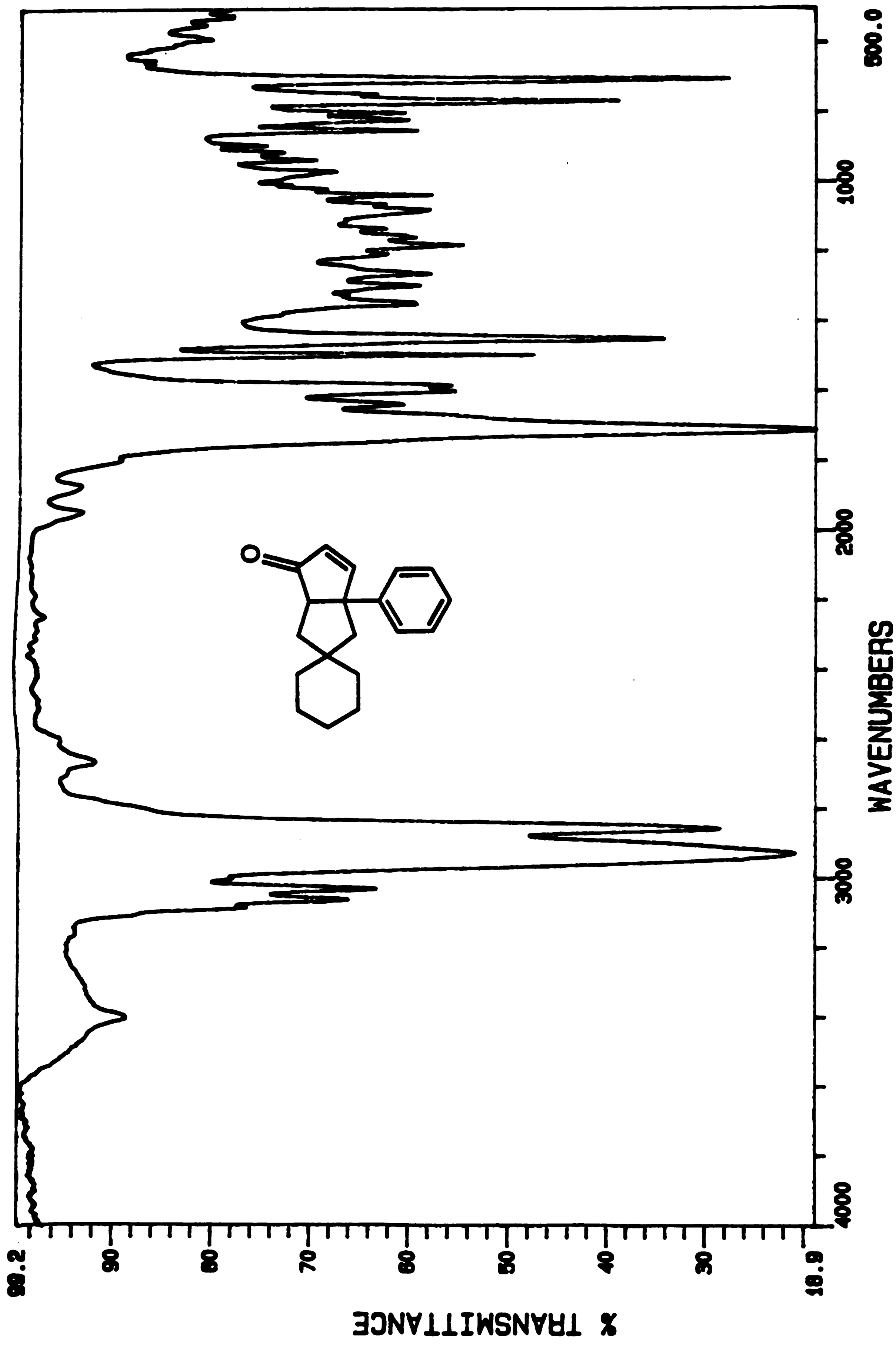


Figure 65. Infrared Spectrum of (17).

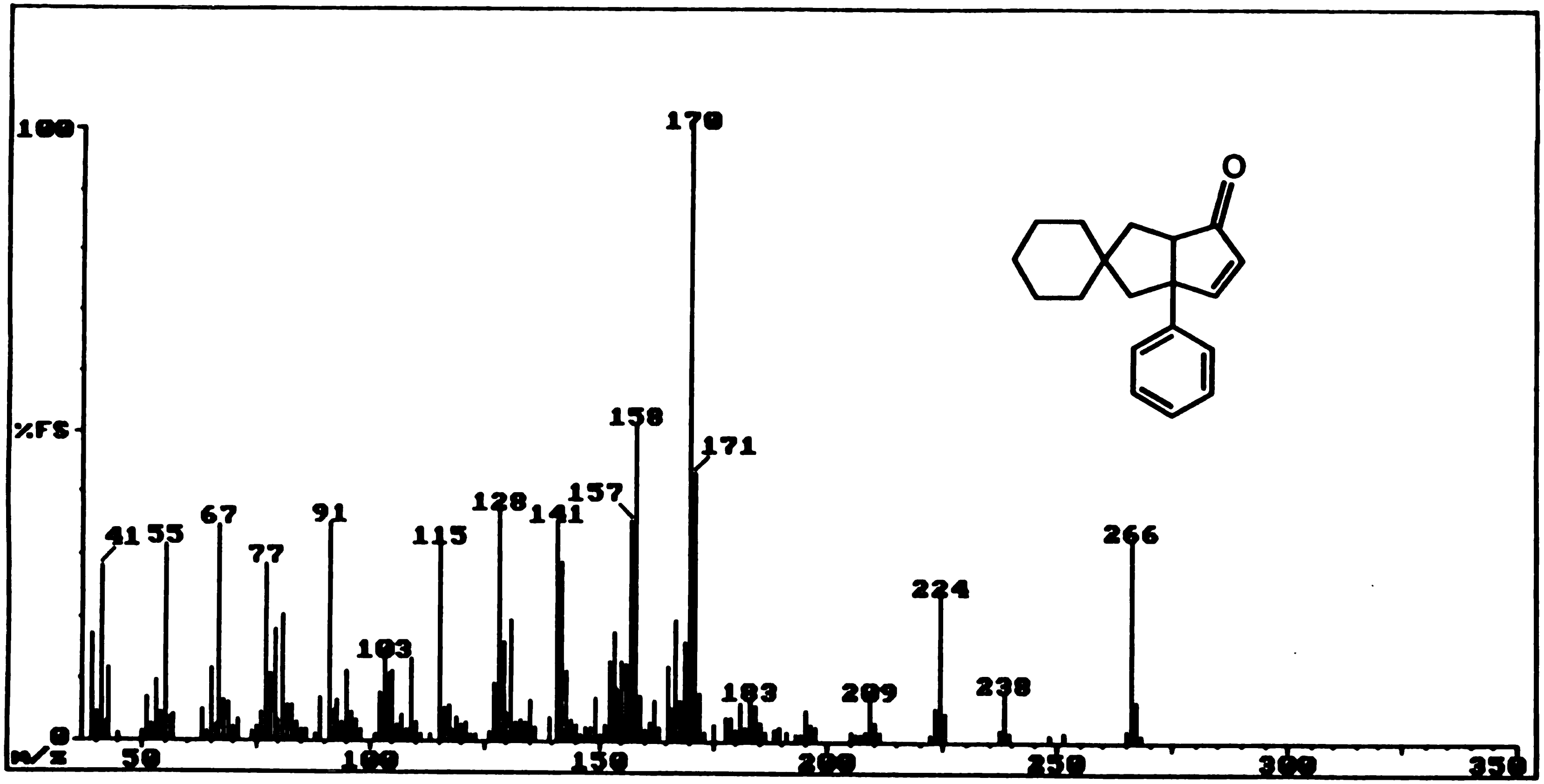


Figure 66. Mass Spectrum of (17).

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PART II

A STUDY OF 4-BROMOBUTYLDIPHENYLPHOSPHINE OXIDE

AS A SYNTHON FOR CYCLOBUTYLIDENE DERIVATIVES

INTRODUCTION

Cyclobutanone is a potentially valuable building block in the synthesis of cyclobutylidene substrates, but its use is hampered by its relatively high cost and its low availability.[1] A possible precursor of a cyclobutylidene ylide, cyclobutyltriphenylphosphonium bromide, gave intractable mixtures of crude products when it reacted with one equivalent of phenyllithium.[2] This difficulty was overcome by using 4-bromobutyldiphenylphosphine oxide (**1**), as a precursor to an equivalent ylide reagent, cyclobutyldiphenylphosphine oxide (**2**). Alternatively (**2**) may be prepared by aqueous alkaline hydrolysis[3] of cyclobutyltriphenylphosphonium bromide. The usefulness of reagent (**1**) was demonstrated by its reaction with dicyclopropylketone to give cyclobutylidene-dicyclopropylmethane, an interesting substrate for vinylcyclopropanecyclopentene rearrangements (VCR)[4] or singlet oxygen ($O^1{}_2$) reactions.[5]

RESULTS AND DISCUSSIONS

A new synthon, 4-bromobutyldiphenylphosphine oxide (**1**), was obtained in 90% yield by aqueous alkaline hydrolysis of commercially available 4-bromobutyltriphenylphosphonium bromide (see Scheme 1).

$$\overset{Br^-}{Ph_3P^+}\,CH_2CH_2CH_2CH_2Br \xrightarrow{\text{20\% NaOH}} \underset{(\mathbf{1})}{Ph_2POCH_2CH_2CH_2CH_2Br}$$

Scheme 1. Preparation of (**1**).

The molecular ion of (**1**) was found at m/z 336 in the mass spectrum, and an infrared absorption at 1184 cm^{-1} was indicative of the P=O group. The ^1H NMR and ^{13}C NMR spectra were also consistent with the assigned structure.

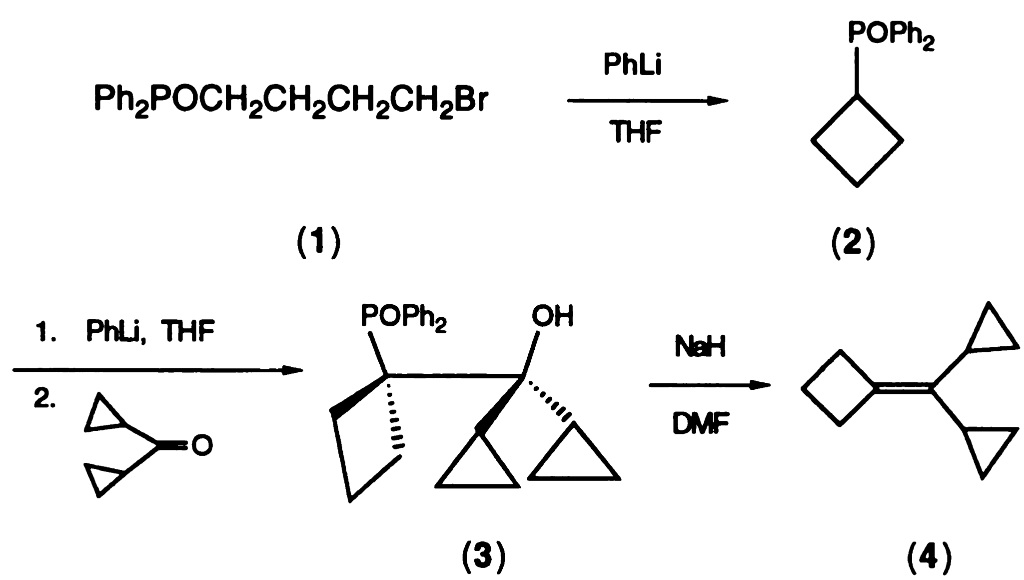
Oxide (**1**) possesses the following advantages:

(a) Unlike the precursor phosphonium salt, it is soluble in tetrahydrofuran. Reactions of oxide (**1**) can therefore proceed in homogeneous solutions.

(b) Hydroxyphosphine oxide adducts are normally crystalline and readily purified. The by-product, sodium diphenylphosphinate, can be easily removed by water.

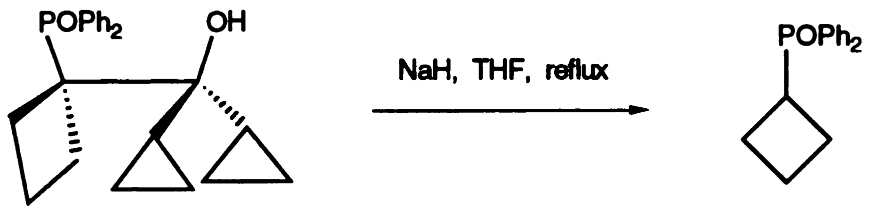
Cyclobutylidene products were synthesized from (**1**) by reaction of the cyclized ylide with an aldehyde or a ketone in a Wittig-Horner like reaction.

For example, oxide (**1**), on treatment with one equivalent of phenyllithium in tetrahydrofuran at - 78 °C, gave cyclobutyldiphenylphosphine oxide (**2**)[3] in 92% yield. Reaction with a second equivalent of phenyllithium followed by dicyclopropylketone gave (1'-dicyclopropylhydroxymethyl-cyclobutyl)-diphenylphosphinyl oxide (**3**) in 84% yield. Finally oxide (**3**) was reacted with sodium hydride in dimethyl formamide at room temperature[6] to give cyclobutylidenedicyclopropylmethane (**4**) in 82% yield (see Scheme 2).



Scheme 2. Preparation of (**4**).

The solvent and temperature employed in the final condensation step are critical. When (**3**) was refluxed[7] with sodium hydride in tetrahydrofuran, it decomposed to (**2**) quantitatively (see Scheme 3).



(**3**) (**2**)

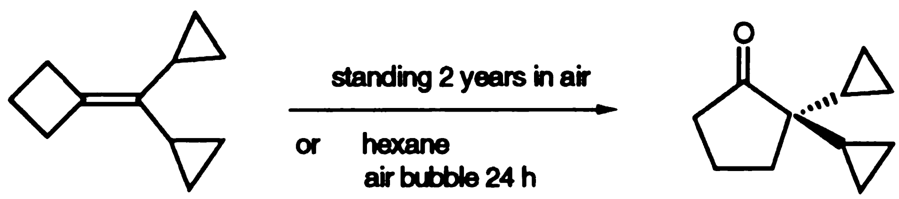
Scheme 3. Retroalkylation of (**3**).

The structure of (**2**) was confirmed by comparing its ^{1}H NMR data with those in the literature.[5]

The molecular ion of (**3**) was found at m/z 366 in the mass spectrum. An infrared signal at 3450~3150 cm^{-1}, a signal at δ 73.9 ppm in the ^{13}C NMR and a signal at δ 4.68 (s, 1H) ppm in the ^{1}H NMR were indicative of the hydroxyl group.

The molecular ion of (**4**) was found at m/z 144 in the mass spectrum. Signals at δ 134.9, 129.0 ppm in the ^{13}C NMR were indicative of the double bond.

On standing for a prolonged time exposed to air, alkene (**4**) underwent a novel oxidative rearrangement to give 2,2-dicyclopropylpentanone (**5**). In hexane solution, alkene (**4**) was transformed to (**5**) within 24 hours on treatment with a stream of air (see Scheme 4).

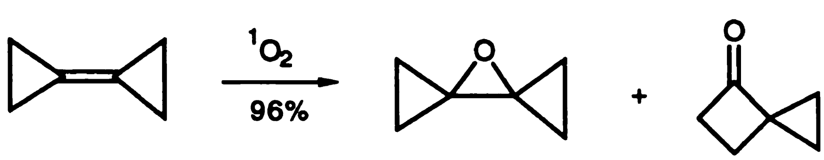


(**4**) (**5**)

Scheme 4. Reaction of (**4**).

The molecular ion of (**5**) was found at m/z 164 in the mass spectrum. An infrared absorption at 1734 cm^{-1} and a signal at δ 221.6 ppm in the ^{13}C NMR were indicative of the carbonyl group.

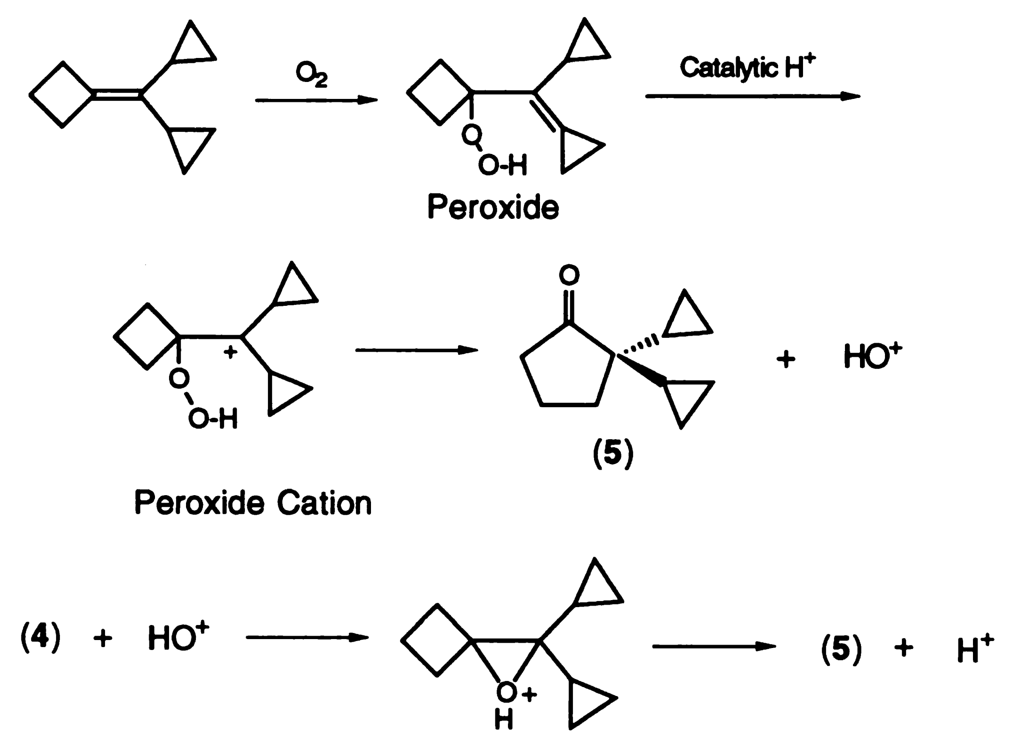
This reaction of (**4**) is similar to the reported reaction[8] of bicyclopropylidene with singlet oxygen (see Scheme 5). However, only triplet oxygen was involved in the reaction of (**4**).



3 : 5

Scheme 5. Reaction of Bicyclopropylidene

A tentative mechanism for the conversion of (4) to (5) is proposed in Scheme 6. Auto-oxidation[9] of (4) should generate a peroxide, which may react with catalytic acid to give a peroxide cation. This cation should then rearrange to (5) with loss of HO^+ cation. The HO^+ would cause rearrangement of another molecule of (4) and provide a proton for the acid-catalyzed conversion of another peroxide.



Scheme 6. Mechanism of Formation of (5).

The reactivity of (4) possibly results from a combination of cyclobutane ring strain and cyclopropyl radical or charge delocalization.[10] The cyclobutane ring strain is relieved to some extent (sp^2 carbon to sp^3 carbon) when addition of oxygen occurs. Regioselectivity is provided by the cyclopropyl substituents. In the bisected cyclopropylcarbinyl cation,[10(b)] the carbonyl carbon (C_4) and its substituents lie in a plane that is perpendicular to the plane of the cyclopropane ring and bisects C_1 and the C_2 - C_3 bond (see Figure 1). The vacant p orbital at C_4 is parallel to the plane of the ring and to the C_2 - C_3 bond. By π overlap with the C - C bonding orbitals of the cyclopropane rings, which, because of angle strain, have an abnormal amount of p character, the positive charge at C_4 is delocalized to all three ring carbons.

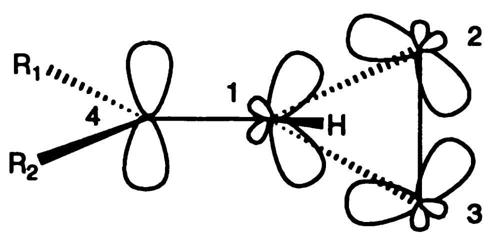
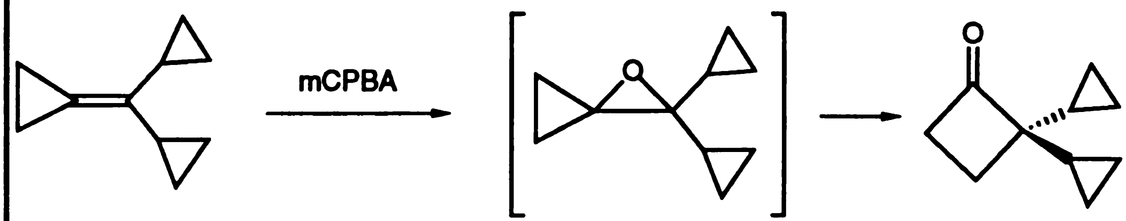


Figure 1. Bisected Cyclopropylcarbinyl Cation.

Frimer and co-worker[5] attempted to prepare the epoxide derivative of cyclopropylidenedicyclopropylmethane by reacting it with a peracid. Under this condition the epoxide rearranged rapidly to an isomeric 2,2-dicyclopropyl-cyclobutanone (see Scheme 7), consistent with our speculation that an intermediate in the transformation from (**4**) to (**5**) may be an epoxide like species.



Scheme 7. Reaction of Cyclopropylidenedicyclopropylmethane.

In summary, oxide (**1**) can be used as a precursor of cyclobutylidene derivatives.

EXPERIMENTAL

Registry No. — cyclobutyldiphenylphosphine oxide (**2**), 16958-47-7.

4-Bromobutyldiphenylphosphine Oxide (1). To 20.00 g (41.8 mmol) of 4-bromobutyltriphenylphosphonium bromide in a 500 mL round bottom flask was added 200 mL of a 20% aqueous solution of sodium hydroxide. This mixture was refluxed for fifteen minutes, allowed to cool to room temperature, and the oily globules of product were extracted with methylene chloride. The methylene chloride extracts were combined, washed with water, dried over anhydrous sodium sulfate, and evaporated to near dryness in a rotary evaporator. The gummy residue was recrystallized from a 1:1 mixture of ethyl acetate and hexane and dried overnight in vacuum at 56 °C to give 12.8 g (90.1% yield) of oxide (**1**), as white needle crystals. mp 84 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79~7.71 (m, 4H), 7.54~7.46 (m, 6H), 3.38 (t, J = 6.6 Hz, 2H), 2.33~2.24 (m, 2H), 2.02~1.94 (m, 2H), 1.93~1.78 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.5 (d, J = 95 Hz), 132.3, 131.2 (d, J = 9 Hz), 129.2 (d, J = 12 Hz), 33.6 (d, J = 14 Hz), 32.7, 28.9 (d, J = 72 Hz), 20.4 (d, J = 4 Hz) ppm; IR (NaCl) 3300, 3060, 2960, 1437, 1184, 1120, 718, 696 cm^{-1}; MS (EI) m/z (relative intensity) 336 (M, 7), 257 (100), 229 (45), 215 (16), 201 (100), 155 (16), 91 (7), 77 (44). Elemental analysis, Cal., C, 56.97%; H, 5.38% for formula $C_{16}H_{18}BrOP$; Found, C, 56.85%; H, 5.51%.

Cyclobutyldiphenylphosphine Oxide (2). A 5.00 g (14.8 mmol) sample of oxide (**1**) was dissolved in 50 mL of THF in a 250 mL three-neck round bottomed flask and then the flask was immersed in a -78 °C isopropyl alcohol-dry ice bath. The mixture was stirred for 20 minutes and 8.6 mL (15.5 mmol) 1.8 M of PhLi in a 7 : 3 mixture of cyclohexane and Et_2O was added dropwise over 20 minutes. The reaction mixture turned pale yellowish orange and was stirred for an additional two hours at - 78°C. The dry ice bath was removed, and the reaction mixture was allowed to warm to room temperature. The mixture was then poured into water, neutralized by dilute hydrochloric acid and extracted with Et_2O. The extracts were combined, washed with brine and dried over anhydrous sodium sulfate. Evaporation of the solvent and recrystallization from a 1 : 1 mixture of methylene chloride and diethyl ether and dried overnight in vacuum gave 3.5 g (92.1% yield) of oxide (**2**), as white needle crystals. mp 162 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75~7.65 (m, 4H), 7.58~7.40 (m, 6H), 3.40~3.25 (m, 1H), 2.63~2.45 (m, 2H), 2.24~1.98 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.0 (d, J = 96 Hz), 132.1 (d, J = 3 Hz), 131.5 (d, J = 9 Hz), 129.0 (d, J = 11 Hz), 32.7 (d, J = 73 Hz), 21.4 (d, J = 5 Hz), 20.3 (d, J = 16 Hz) ppm; IR (NaCl) 3052, 2951, 2936, 2855, 1437, 1183, 1117, 748, 719, 702 cm^{-1}; MS (EI) m/z (relative intensity) 256 (M, 73), 227 (12), 202 (100), 183 (26), 155 (31), 77 (32).

(1'-Dicyclopropylhydroxymethyl-cyclobutyl)-diphenylphosphinyl oxide (3). A 250 mL three-neck round bottomed flask equipped with a rubber septum, an addition funnel, an argon inlet and a magnetic stirrer was alternately evacuated and filled with argon. 3.00 g (11.7 mmol) oxide (**2**) and 50 mL of THF were added. Oxide (**2**) was dissolved, the flask was immersed in a - 78 °C isopropyl alcohol-dry ice bath and the mixture was stirred for 20 minutes. 7.0 mL 1.8 M (12.6 mmol) of PhLi in a 7 : 3 mixture of cyclohexane and Et_2O was added dropwise at - 78 °C over 15 minutes. The reaction mixture turned dark red and was stirred for an additional 10 minutes, following which 1.5 mL (1.47 g, 13.3 mmol) of dicyclopropylketone was added at - 78 °C. The resulting mixture was stirred at - 78 °C for two hours; The dry ice bath was removed, and the reaction mixture was allowed to warm to room temperature. The mixture was then poured into water and neutralized by dilute hydrochloric acid. THF was removed on a rotary evaporator, and excess dicyclopropylketone was removed by steam distillation. The aqueous residue was extracted with methylene chloride. The methylene chloride extract was washed with water and dried over anhydrous sodium sulfate. Evaporation of solvent and recrystallization from a 1 : 1 mixture of methylene chloride and Et_2O gave 3.6 g (84.0% yield) of oxide (**3**), as white square crystals. mp 151 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.94~7.84 (m, 4H), 7.52~7.40 (m, 6H), 4.68 (s, 1H), 2.88~2.72 (m, 2H), 2.70~2.52 (m, 2H), 2.19~2.02 (m, 1H), 1.50~1.35 (m, 1H), 1.17~1.06 (m, 2H), 0.77~0.65 (m, 2H), 0.62~0.52 (m, 2H), 0.38~0.27 (m, 2H), -0.18 ~ - 0.30 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.9 (d, J = 94 Hz), 132.1 (d, J = 8 Hz), 131.6, 128.7 (d, J = 11 Hz), 73.9, 50.7 (d, J = 63 Hz), 25.4, 18.7 (d, J = 7 Hz), 17.8 (d, J = 11 Hz), 2.4, 1.5 ppm; IR (NaCl) 3450~3150, 3050, 3009, 2980, 1437, 1152, 1111, 713, 697 cm^{-1}; MS (EI) m/z (relative intensity) 368 (14), 367 (52), 366 (M, 3), 349 (100), 255 (34), 201 (100), 147 (32), 91(57), 77 (46); Elemental analysis, Cal., C, 75.37%; H, 7.43% for formula $C_{23}H_{27}O_2P$; Found, C, 75.36%; H, 7.38%.

Cyclobutylidenedicyclopropylmethane (4). A 250 mL three-neck round bottomed flask equipped with an argon inlet and a magnetic stirrer was alternately evacuated and filled with argon. 0.20 g (8.3 mmol) sodium hydride, 60 mL of DMF and 3.00 g (8.2 mmol) oxide (**3**) were added. The resulting brownish foamy suspension was stirred at room temperature for 30 minutes. The mixture was then poured over water. THF was removed and the residue was extracted with hexane. The hexane extract was washed with water and dried over anhydrous sodium sulfate. Evaporation of solvent gave 1.05 g (86.0% yield) pale yellowish oil of compound (**4**). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.74 (t, J = 7.6 Hz, 4H), 1.89 (quintet, J = 7.6 Hz, 2H), 1.06 (quintet, J = 6.8 Hz, 2H), 0.50~0.43 (m, 8H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.9, 129.0, 30.7, 16.9, 10.9, 3.6 ppm; IR (NaCl) 3088, 3011, 2959, 2928, 2874, 2856, 1458, 1427, 1379, 1018 cm^{-1}; MS (EI) m/z (relative intensity) 148 (M, 90), 133 (27), 119 (39), 105 (94), 91 (100), 79 (55), 77 (35), 65 (13); High resolution MS, Cal., 148.1252 for formula $C_{11}H_{16}$; found, 148.1265.

Retroalkylation of (3). A 100 mL three-neck round bottomed flask equipped with an argon inlet and a magnetic stirrer was alternately evacuated and filled with argon. 0.50 g (20.8 mmol) sodium hydride, 0.54 g (1.5 mmol) oxide (**3**) and 40 mL of THF were added. The resulting suspension was stirred at room temperature overnight and refluxed for 10 minutes. The mixture was poured over water. Evaporation of THF gave yellowish slurry, which was extracted with methylene chloride. The extracts were washed with water and

dried over anhydrous sodium sulfate. Evaporation of solvent gave 0.37 g (98.0% yield) white solid oxide (**2**).

2,2-Dicyclopropylcyclopentanone (5). Compound (**4**) was stored without argon for two years to give compound (**5**) quantitatively. Compound (**4**) was bubbled with air for 24 hours in hexane to give compound (**5**) quantitatively. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.14 (t, J = 7.0 Hz, 2H), 1.84 (quintet, J = 7.0 Hz, 2H), 1.47 (t, J = 7.0 Hz, 2H), 0.94~0.83 (m, 2H), 0.45~0.23 (m, 6H), 0.19~0.09 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 221.6, 49.7, 39.1, 31.2, 19.0, 16.1, 1.0, 0.4 ppm; IR (NaCl) 3081, 3007, 2961, 2888, 1734, 1464, 1406, 1149, 1018, 818 cm^{-1}; MS (EI) m/z (relative intensity) 164 (M, 1), 136 (70), 121 (45), 108 (83), 93 (77), 79 (100), 67 (34), 55 (16); High resolution MS, Cal., 164.1201 for formula $C_{11}H_{16}O$; Found, 164.1203.

APPENDIX II

SPECTRAL PART II

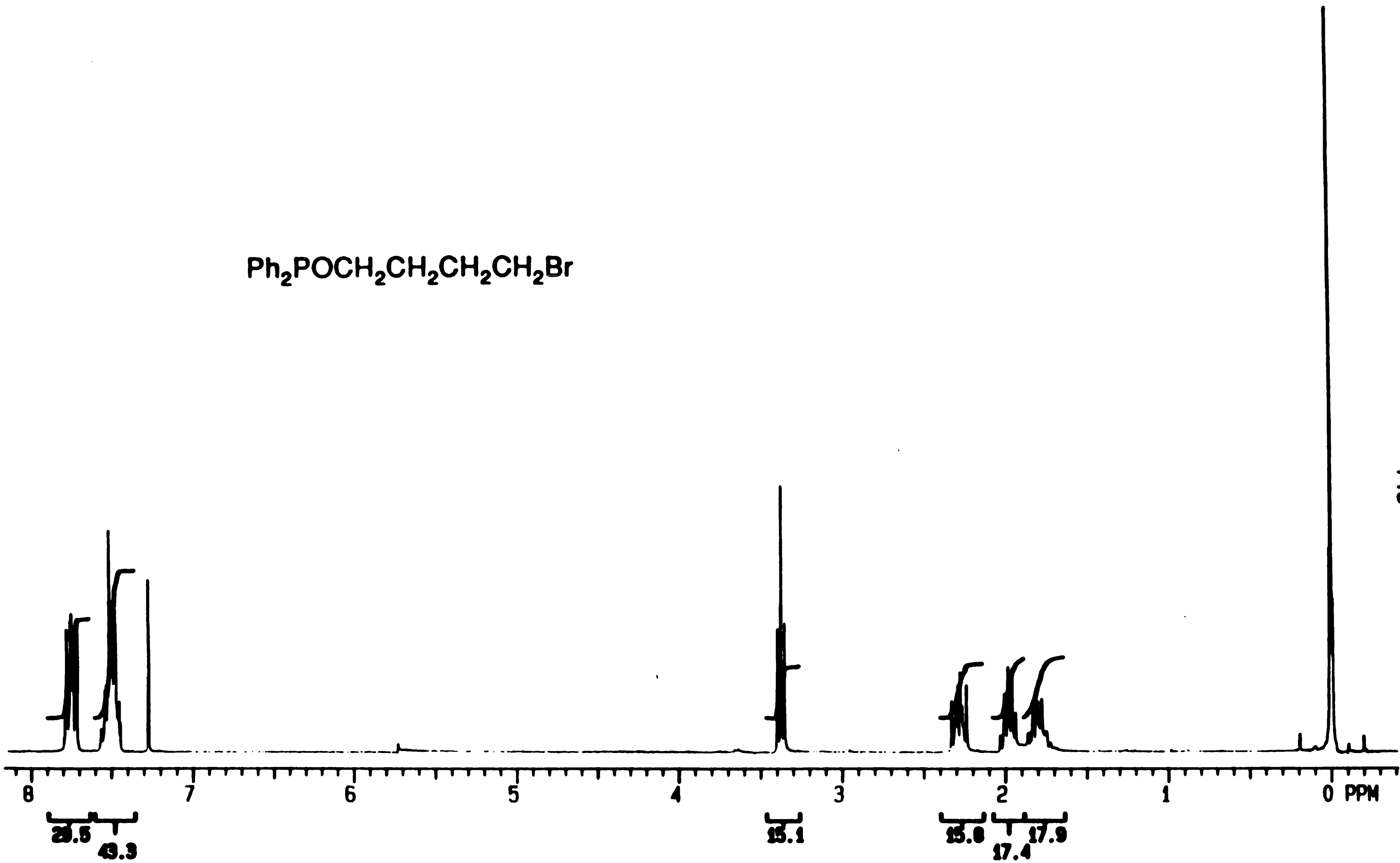


Figure 2. ^{1}H NMR Spectrum of (1).

Figure 3. ^{13}C NMR Spectrum of (1).

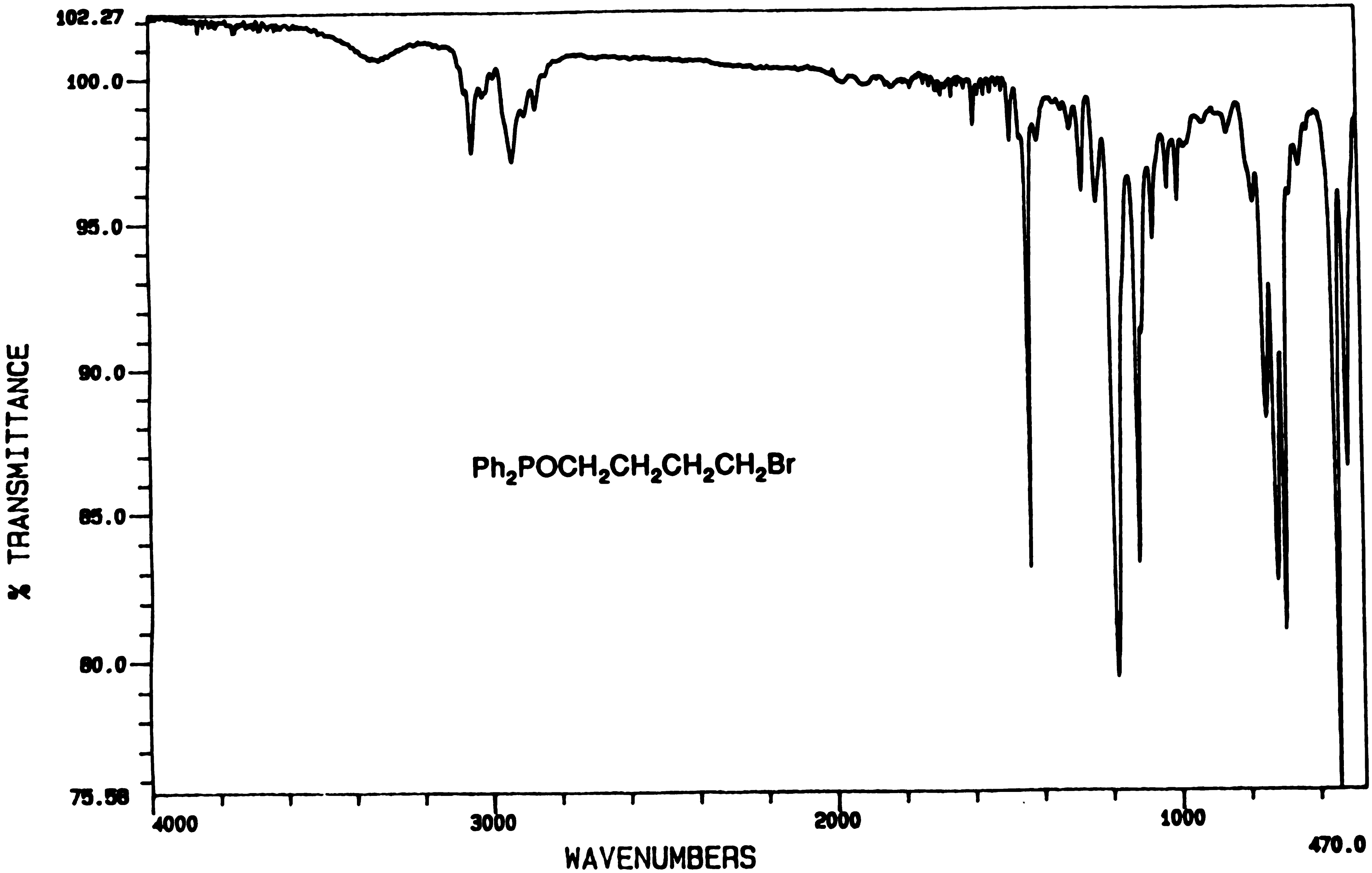


Figure 4. Infrared Spectrum of (1).

$Ph_2POCH_2CH_2CH_2CH_2Br$

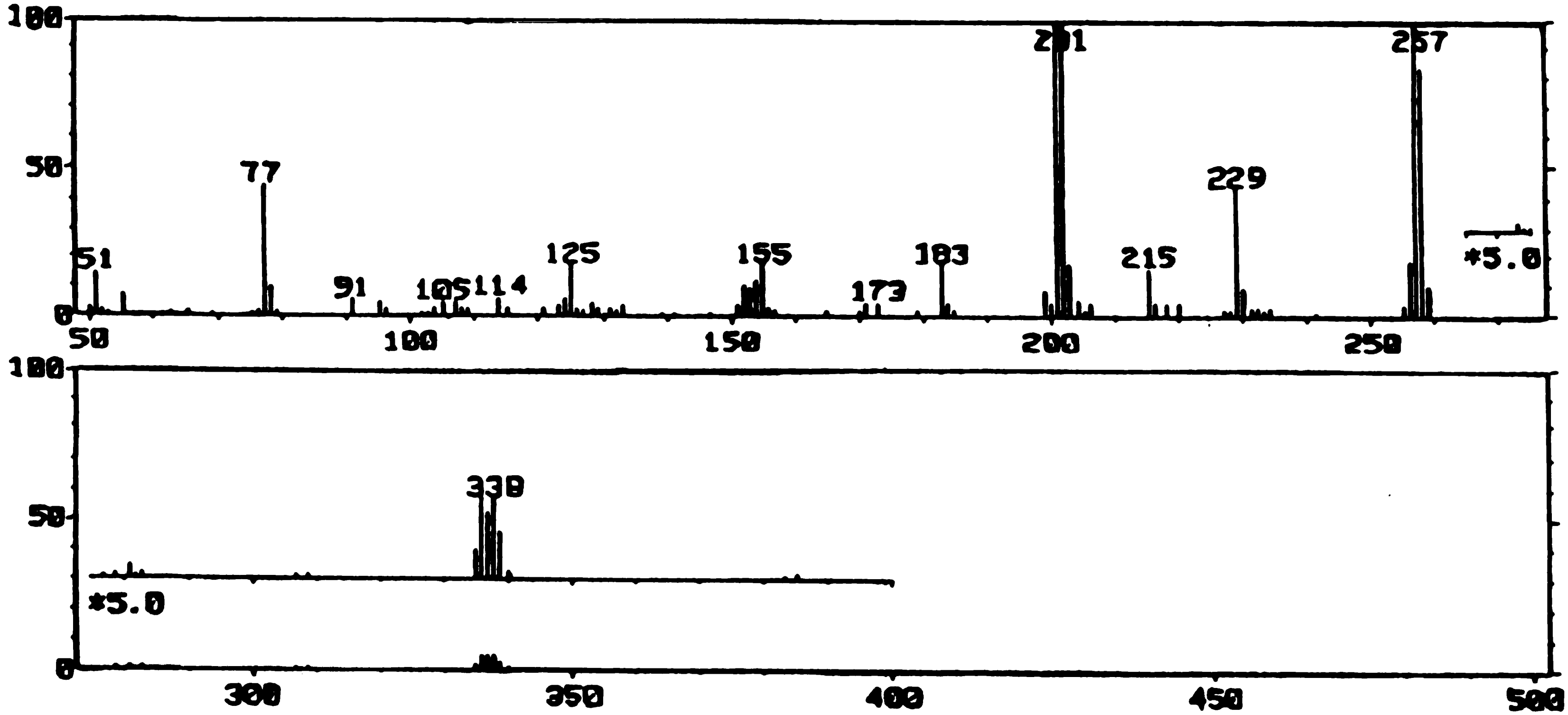


Figure 5. Mass Spectrum of (1).

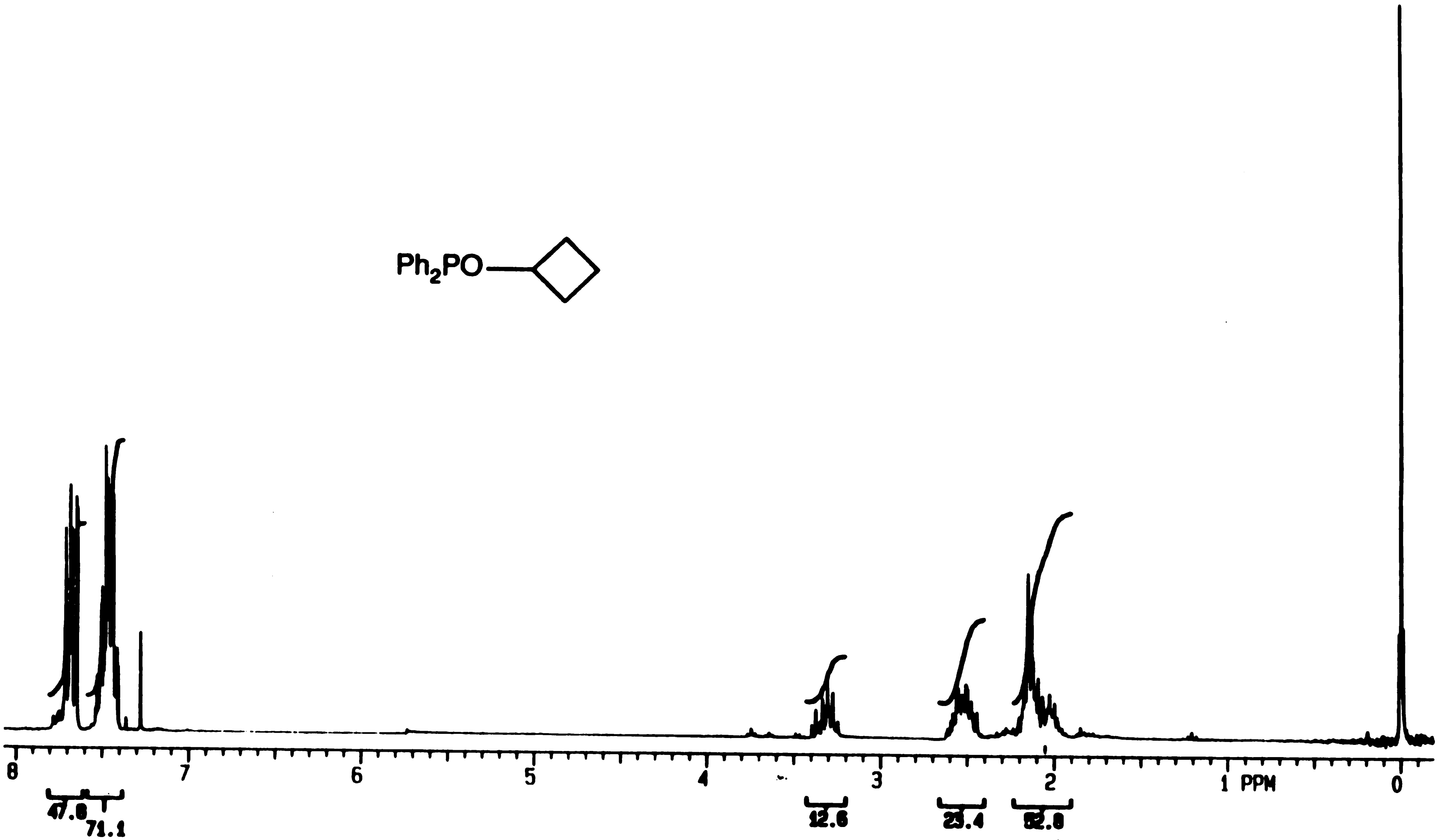


Figure 6. ^{1}H NMR Spectrum of (2).

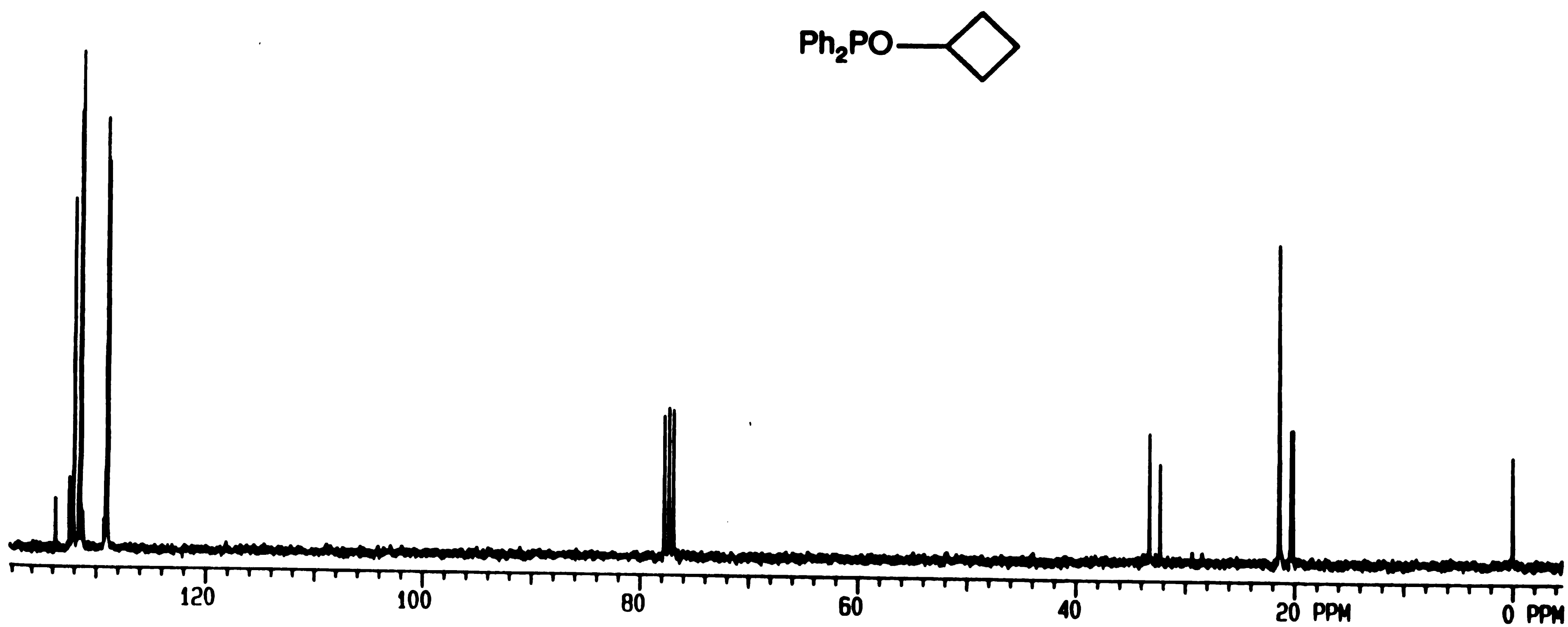


Figure 7. ^{13}C NMR Spectrum of (**2**).

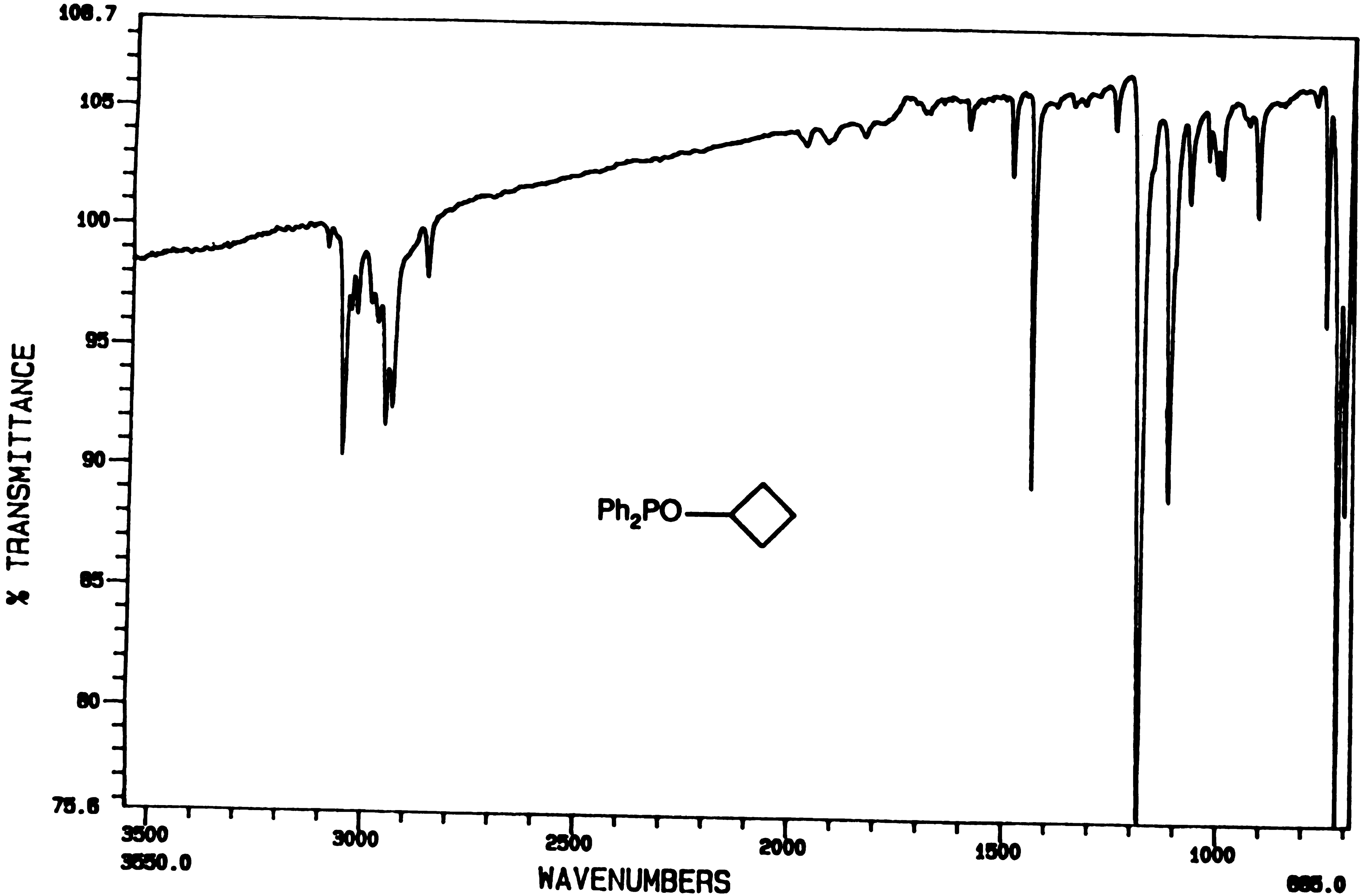


Figure 8. Infrared Spectrum of (2).

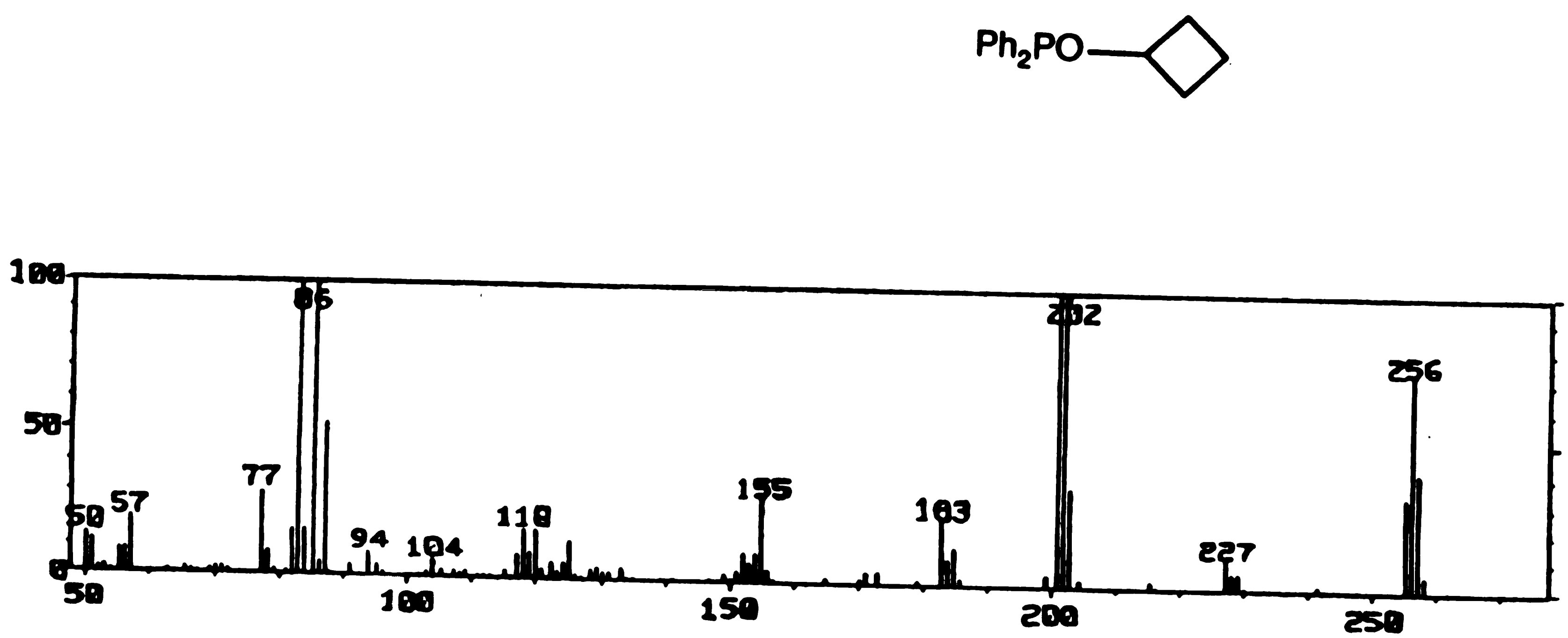


Figure 9. Mass Spectrum of (2).

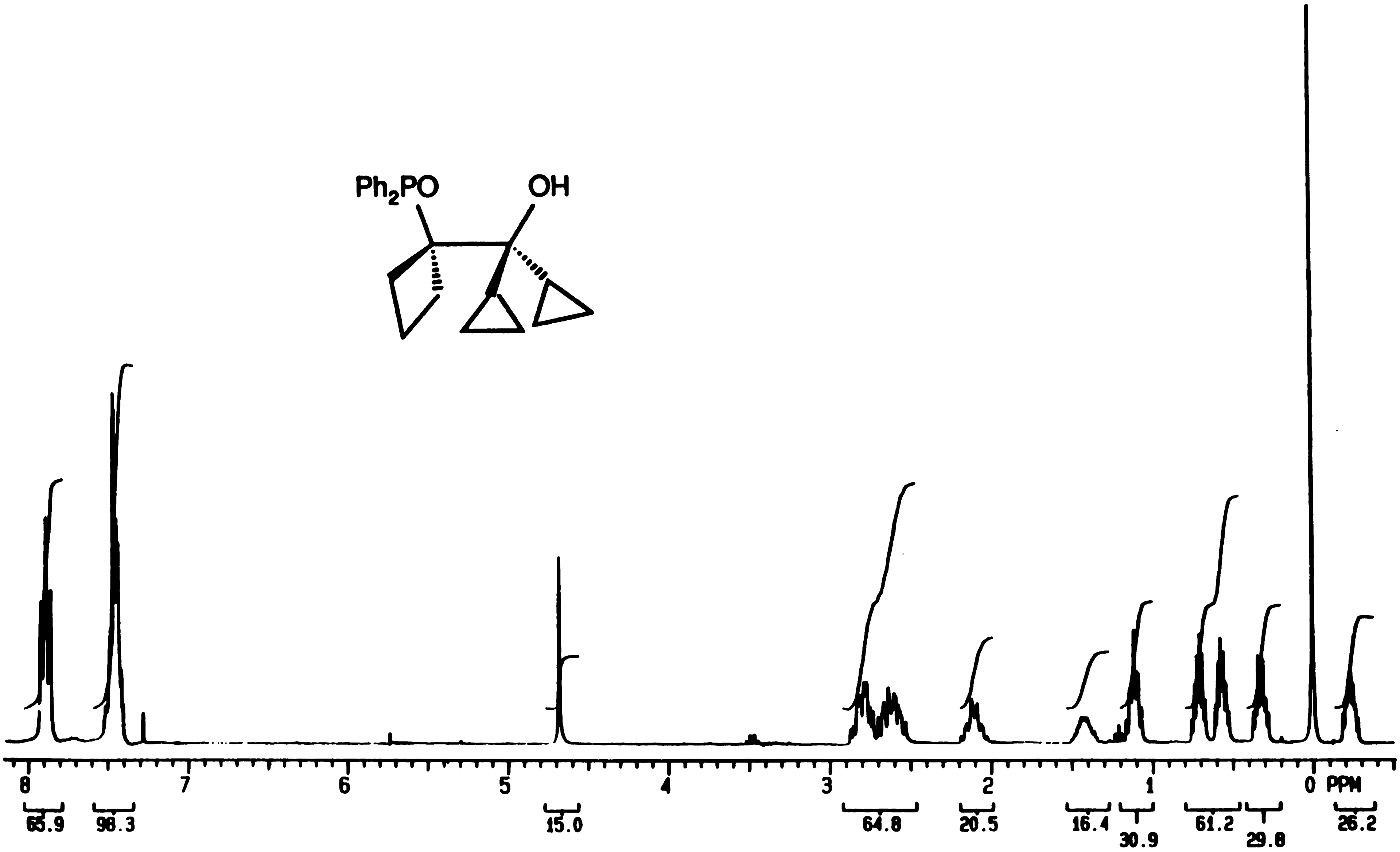


Figure 10. ^{1}H NMR Spectrum of (3).

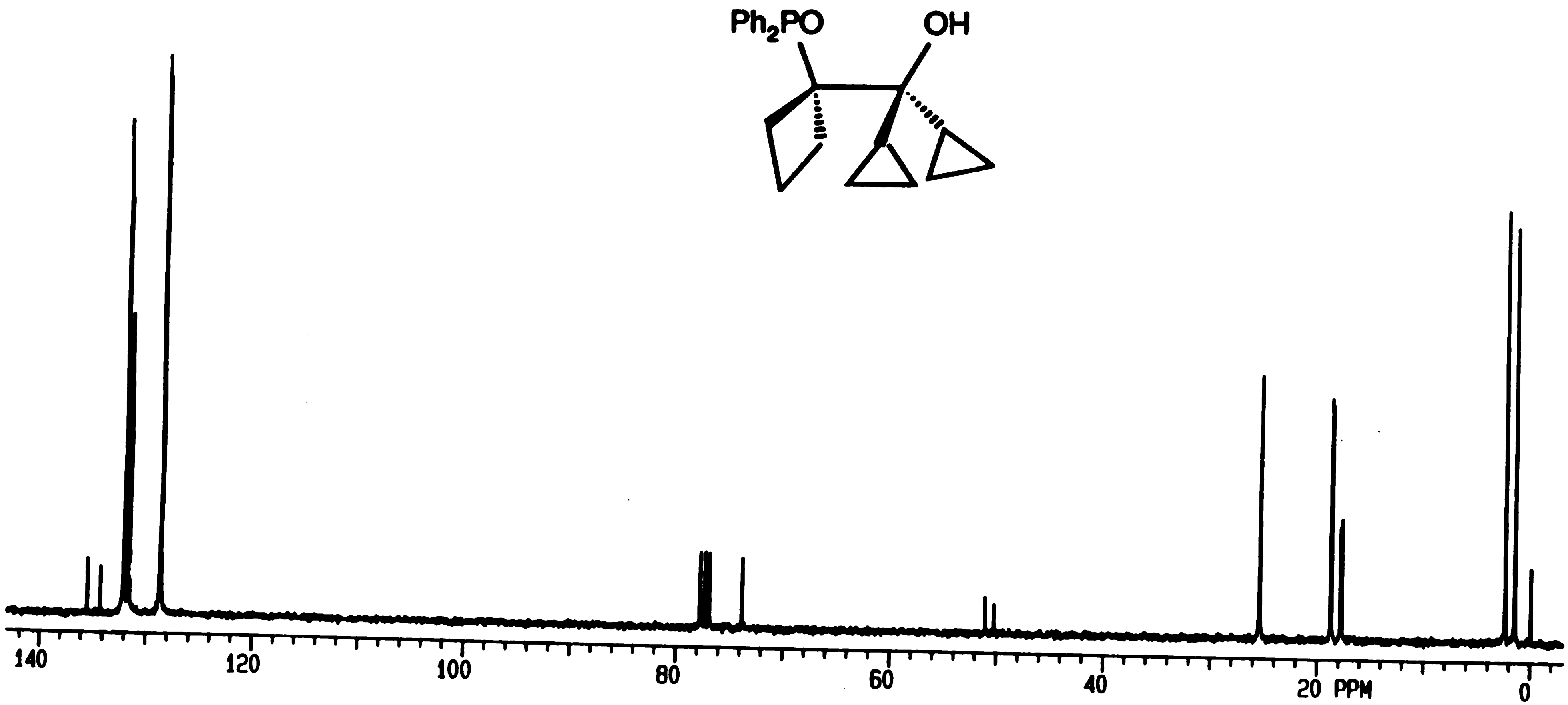


Figure 11. ^{13}C NMR Spectrum of (3).

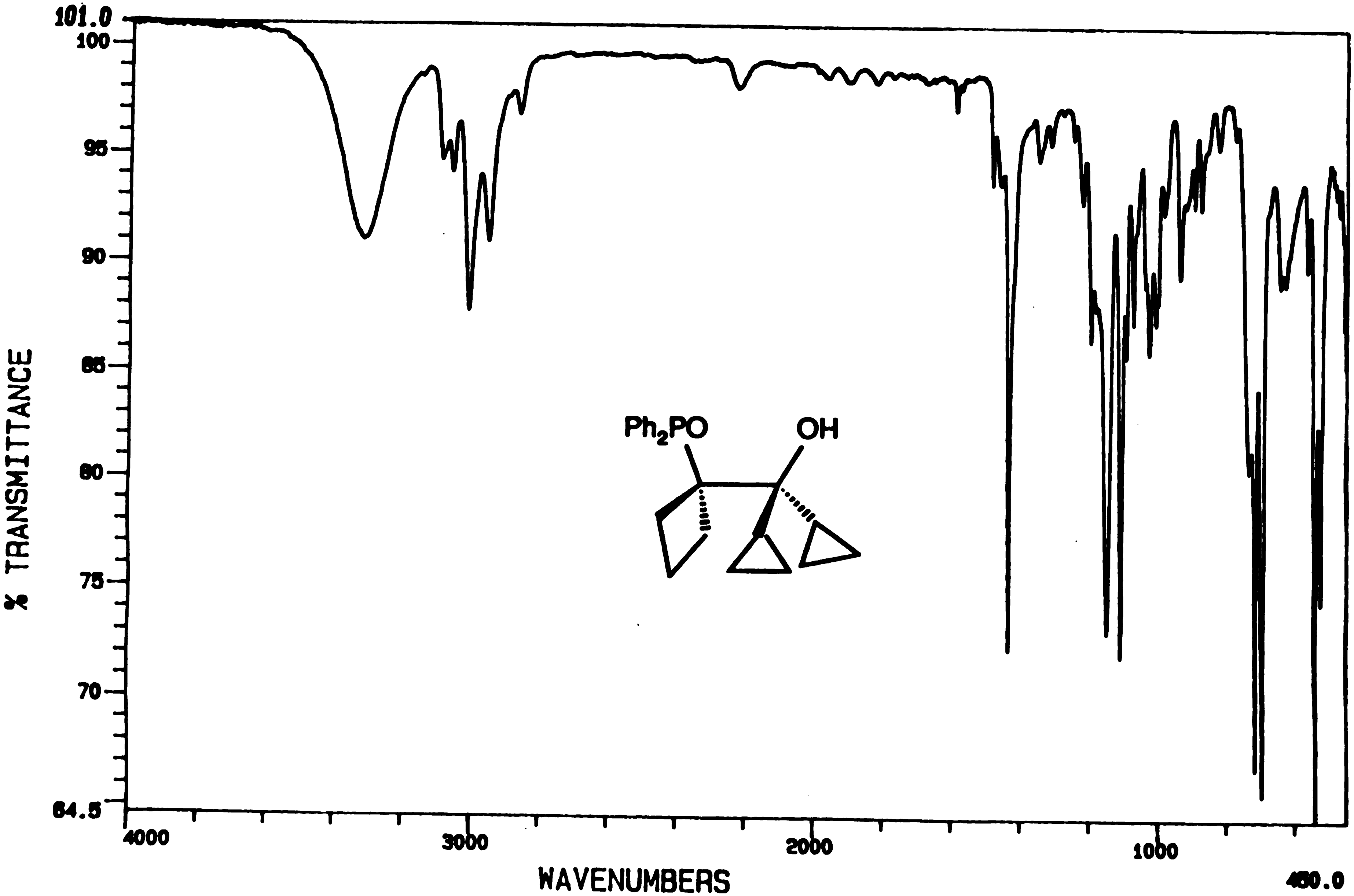


Figure 12. Infrared Spectrum of (3).

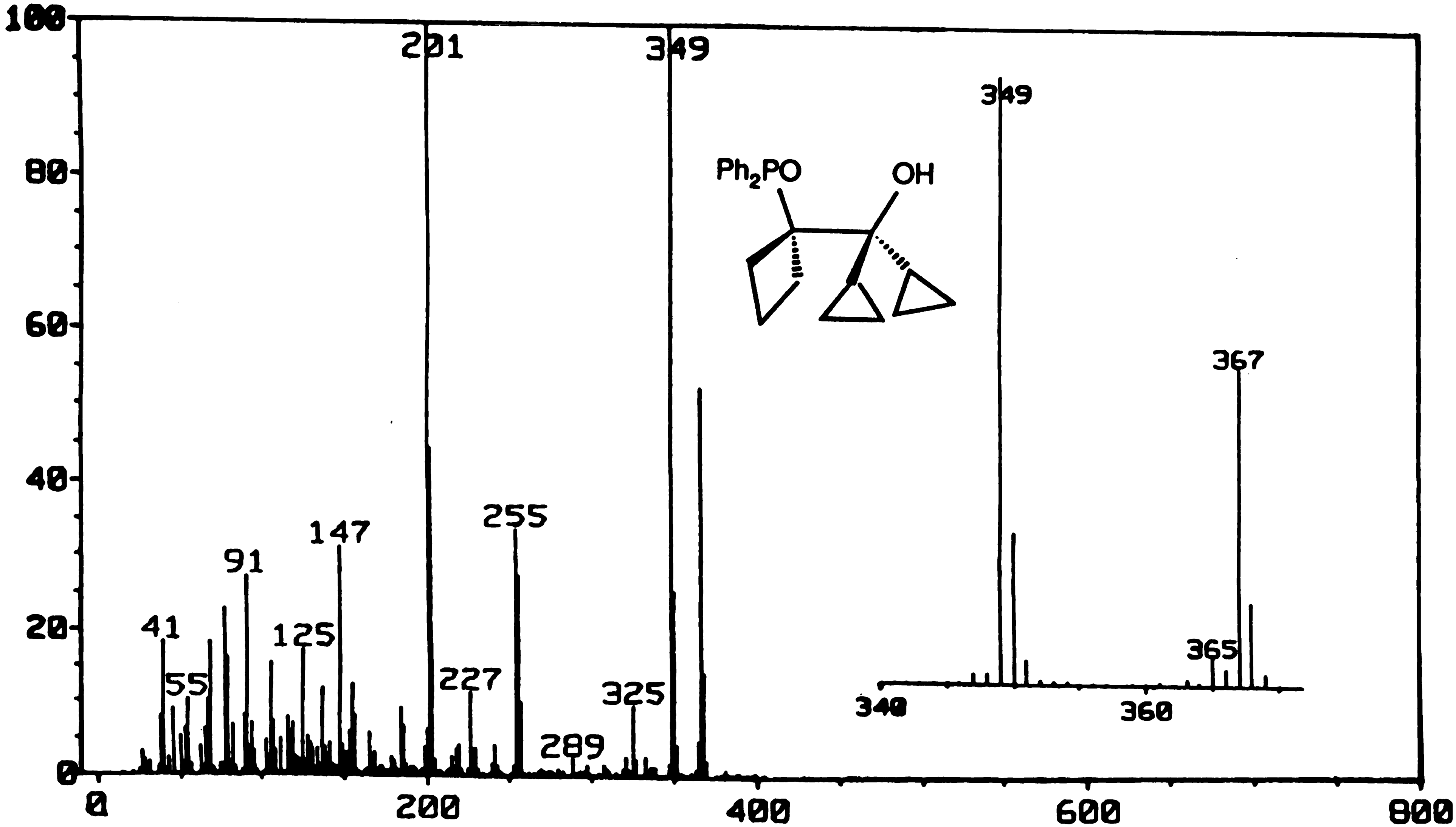


Figure 13. Mass Spectrum of (3).

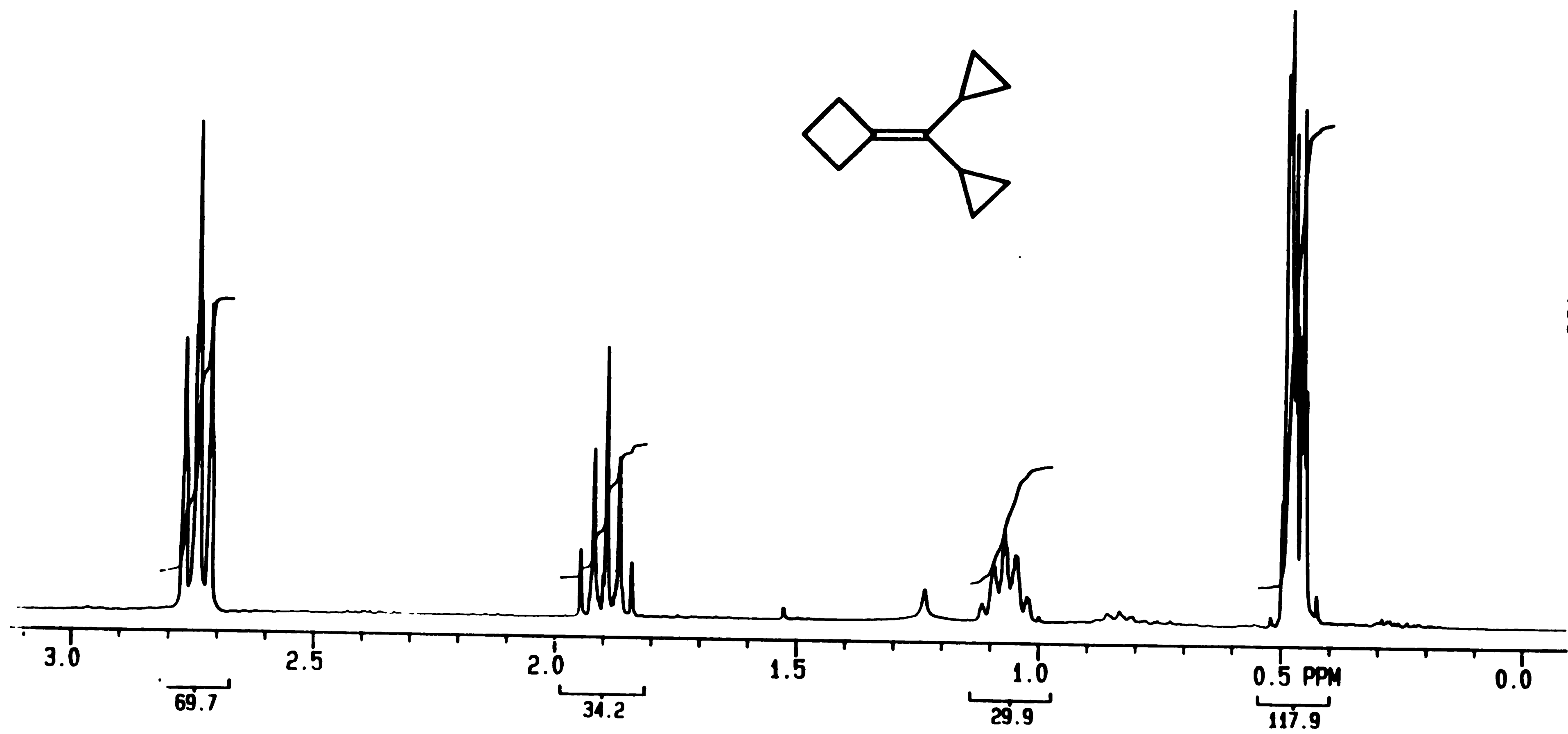


Figure 14. ^{1}H NMR Spectrum of (**4**).

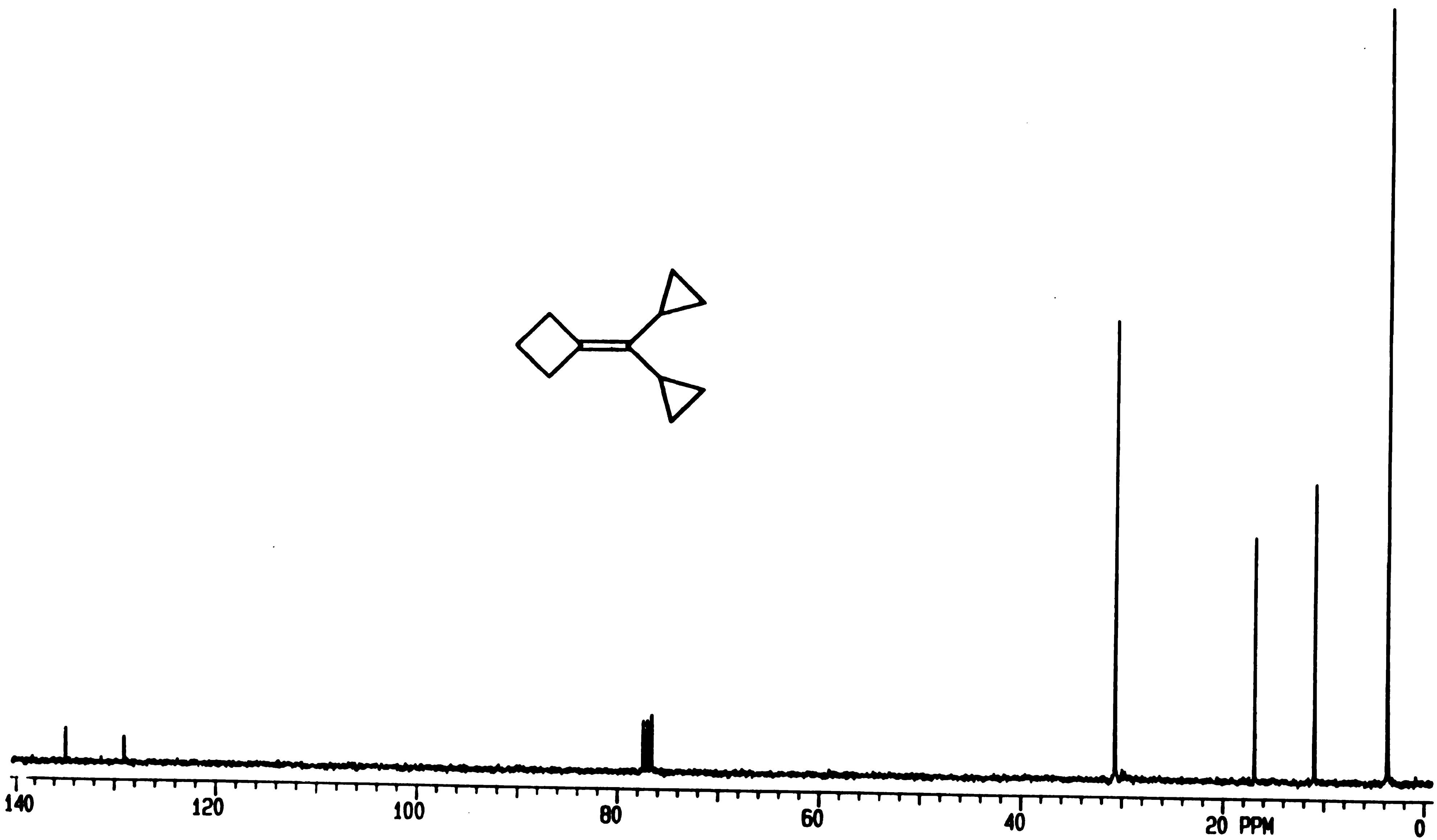


Figure 15. ^{13}C NMR Spectrum of (**4**).

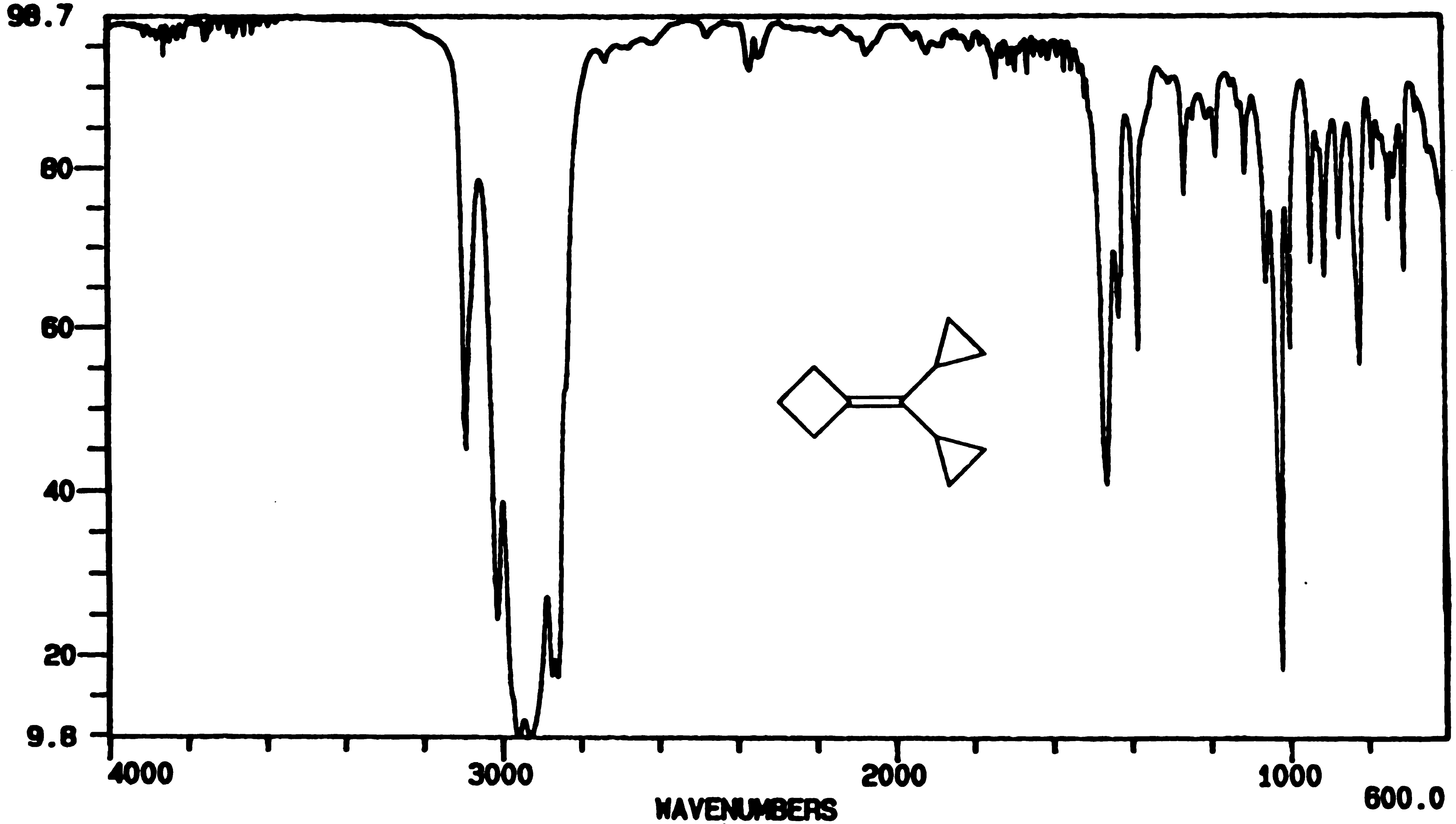


Figure 16. Infrared Spectrum of (4).

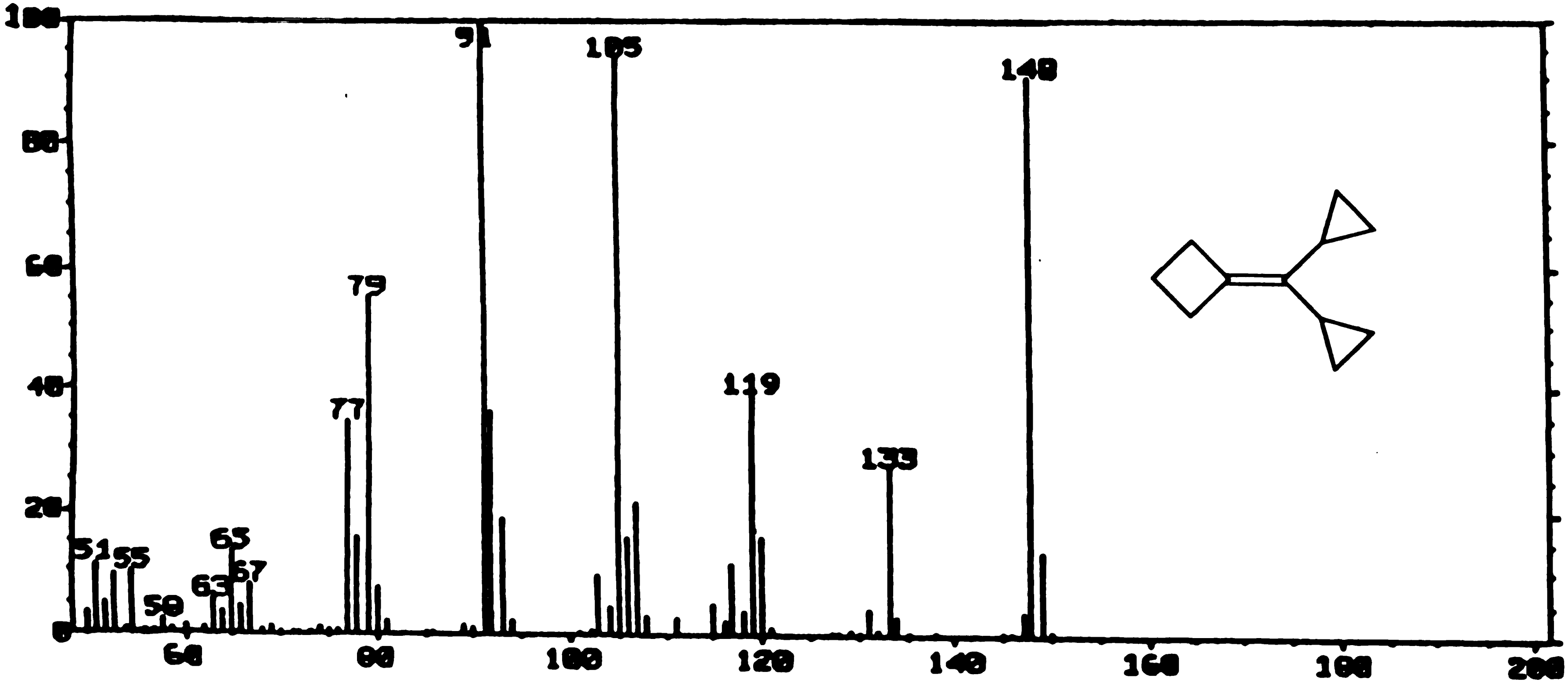


Figure 17. Mass Spectrum of (4).

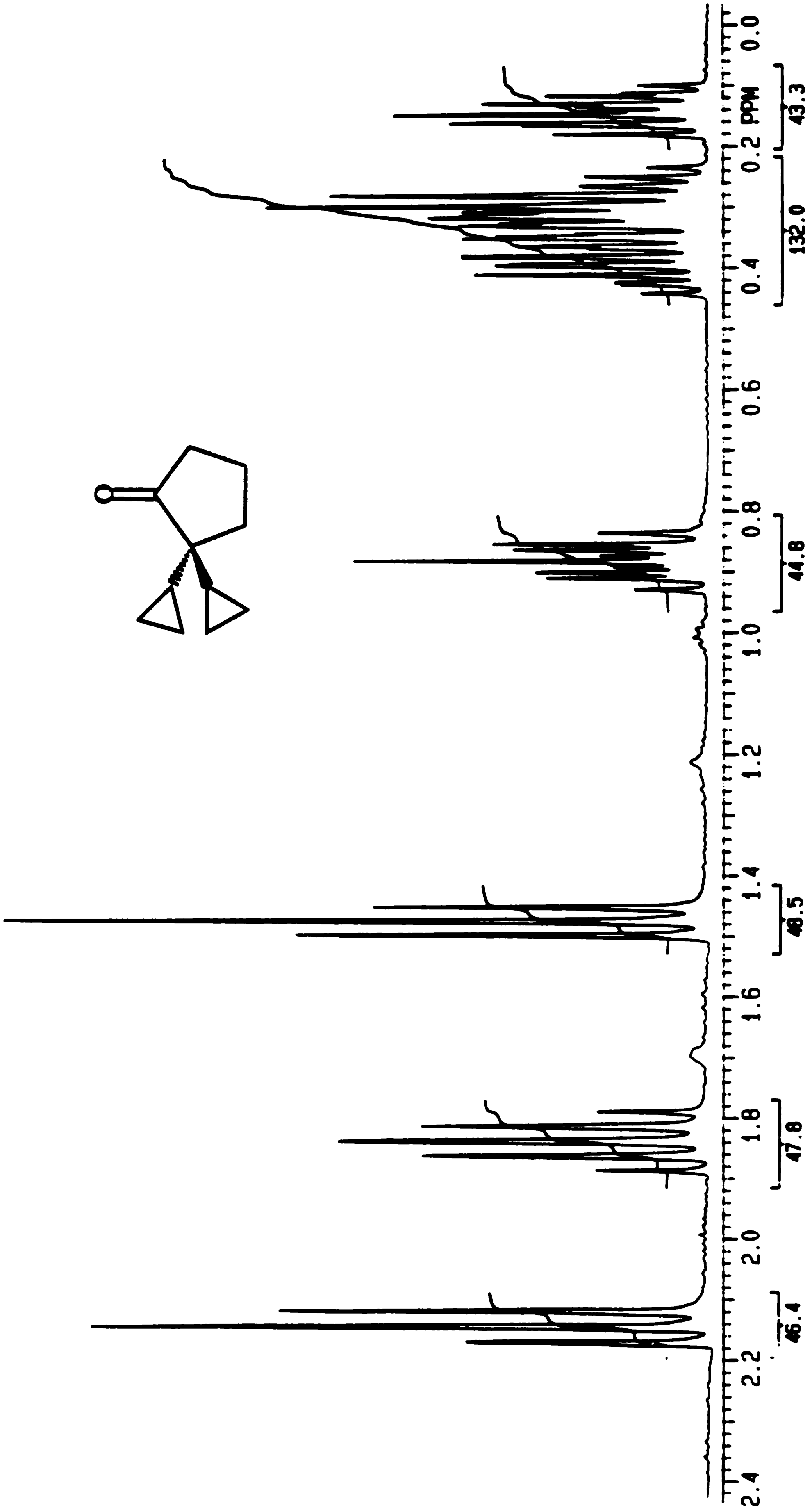


Figure 18. ^{1}H NMR Spectrum of (5).

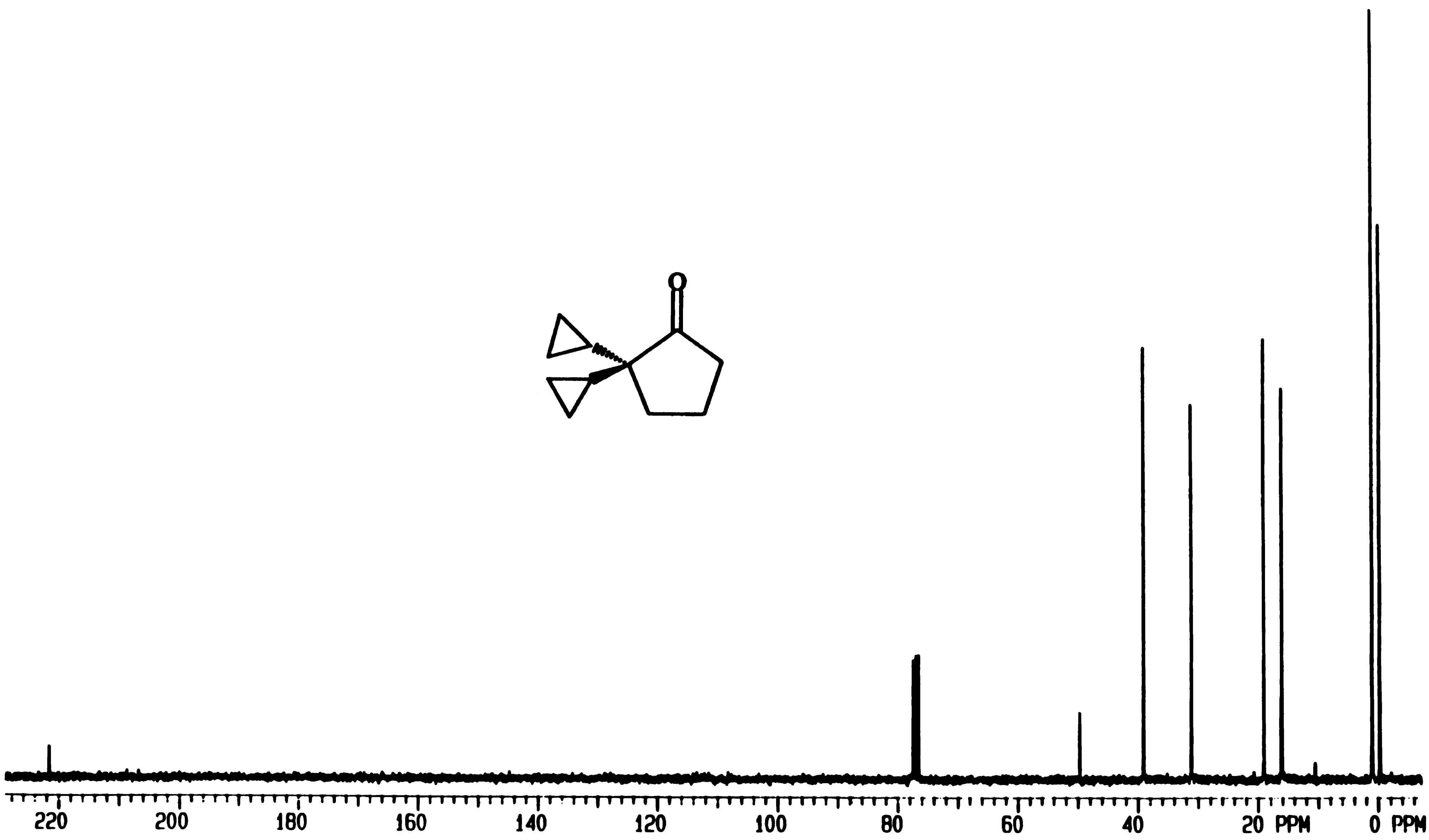


Figure 19. ^{13}C NMR Spectrum of (**5**).

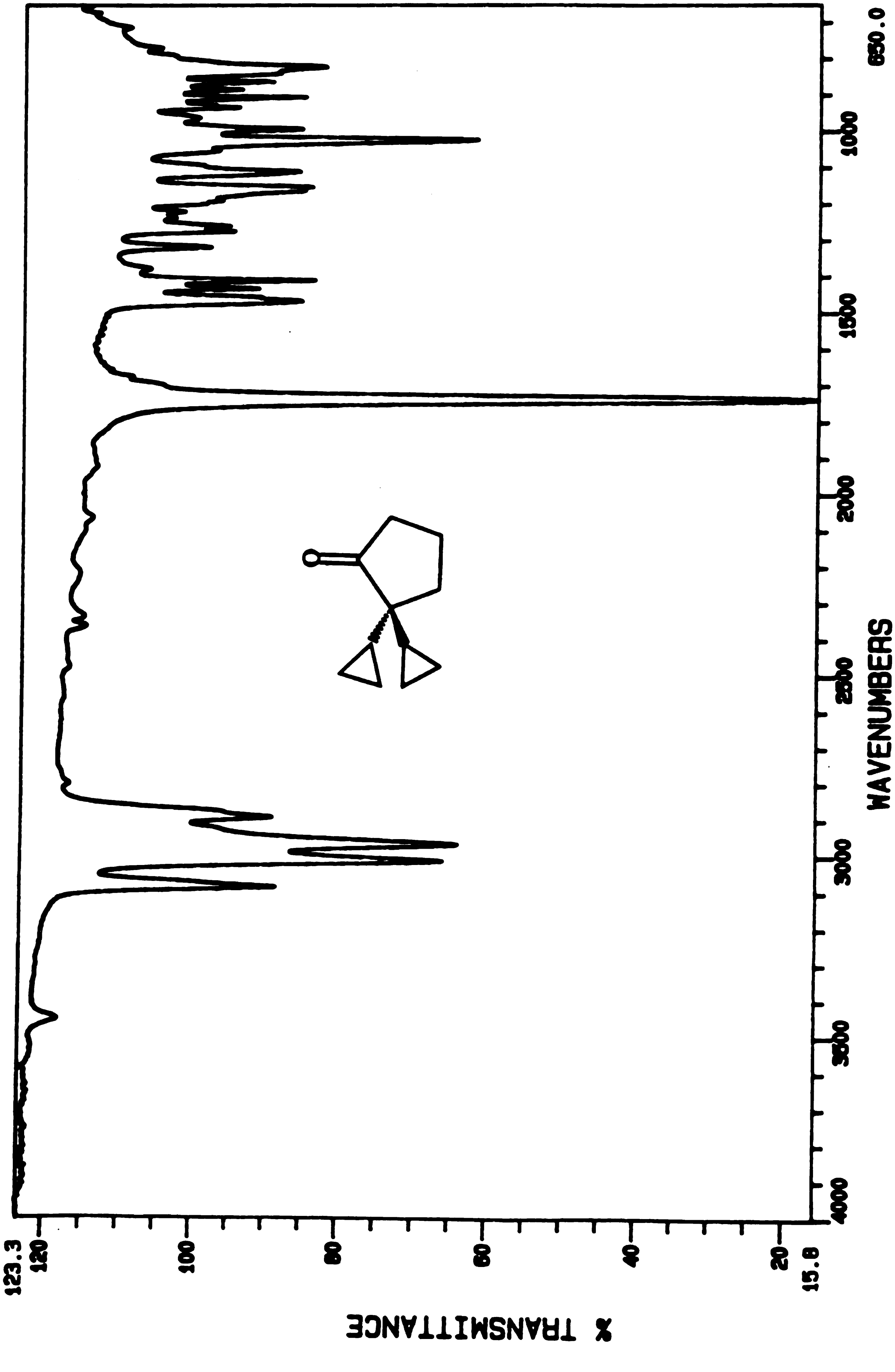


Figure 20. Infrared Spectrum of (5).

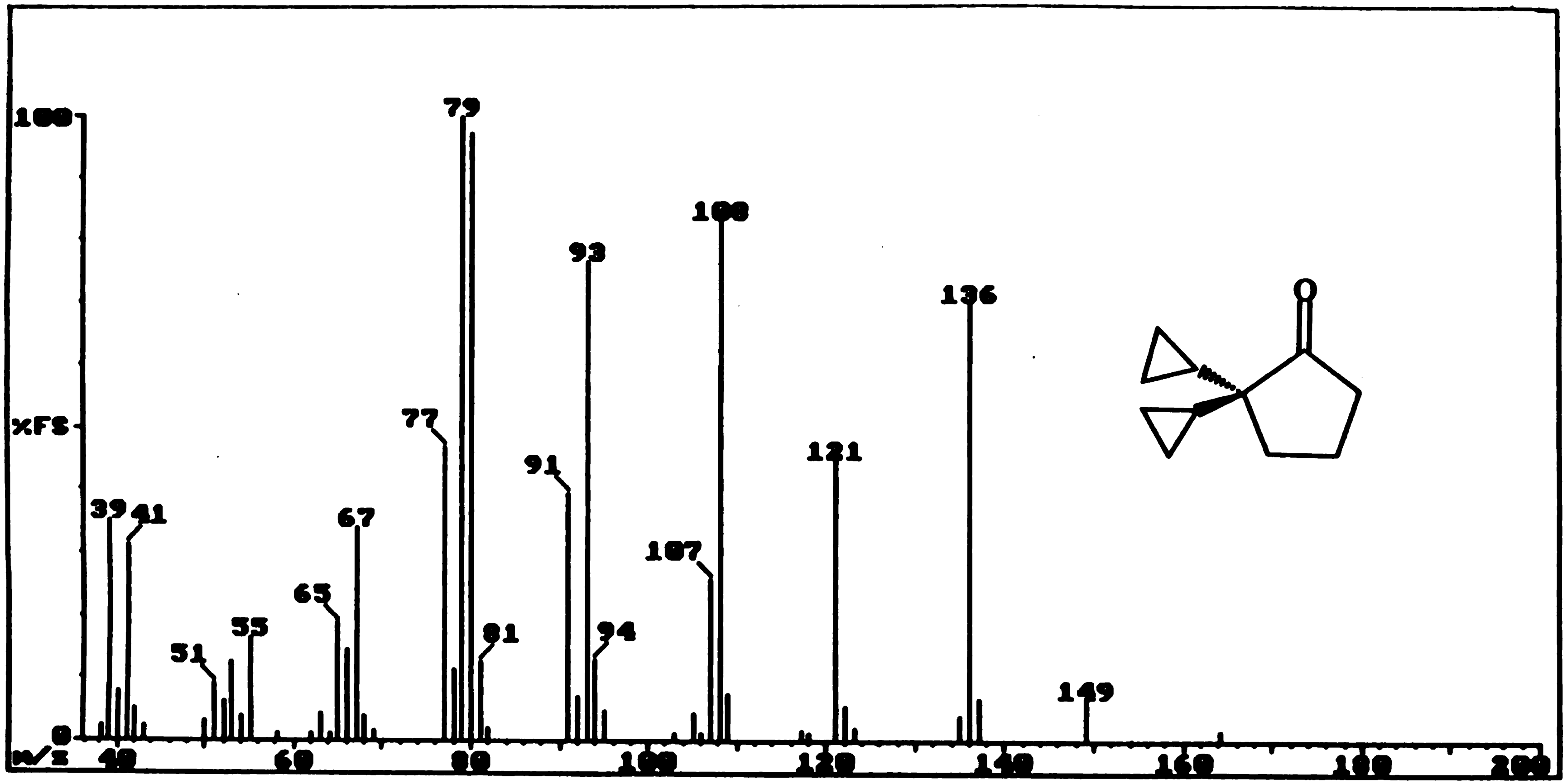


Figure 21. Mass Spectrum of (5).

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