This is to certify that the

thesis entitled

Studies directed toward the synthesis of
Tetracyclic triterpenes.

presented by

Jacob S Tou

has been accepted towards fulfillment
of the requirements for

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William H. Reusch
Major professor

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STUDIES DIRECTED TOWARD THE SYNTHESIS OF TETRACYCLIC TRITERPENES

By

Jacob Shya Tou

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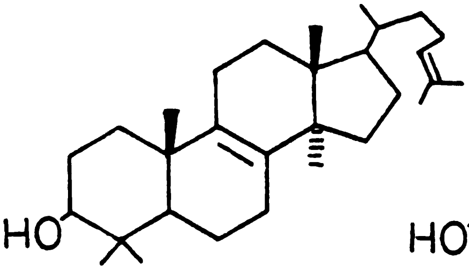
ABSTRACT

STUDIES DIRECTED TOWARD THE SYNTHESIS OF TETRACYCLIC TRITERPENES

By

Jacob Shya Tou

Studies directed toward the synthesis of tetracyclic triterpenes such as lanosterol **1** and euphol **2** from perhydroindanedione **3** are presented.



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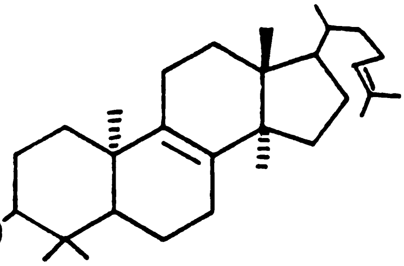

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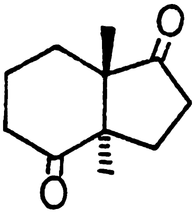

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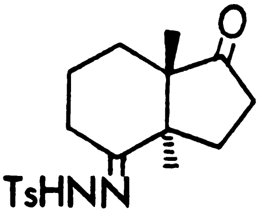
Selective reactivity of the two carbonyl groups in **3** was observed in reactions with tosylhydrazine and with the strong base-lithium diisopropyl amide (LDA). Although **3** was readily converted to the corresponding bis-tosylhydrazone and bis-enolate when two equivalents of these reagents were used, treatment with one equivalent of tosylhydrazine and LDA gave the corresponding mono-tosylhydrazone **4**, and a mono-enolate which was trapped as its silyl enol ether

derivative 5. On the other hand, base-catalyzed condensation of 3 with benzaldehyde occurred preferrentially at the five-membered ring to give 6. Differences in the π-conjugation of the alpha-keto benzylidene moieties may be a major factor in the surprising predominance of this adduct.



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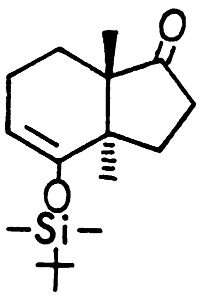

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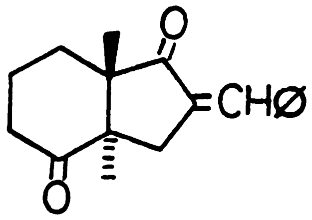

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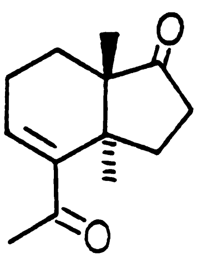
Attempts to fuse six-membered rings to 3, so as to generate the tetracyclic triterpene skeleton, are described in part B of this dissertation. Two potentially useful precursors, 7 and 8, were prepared.



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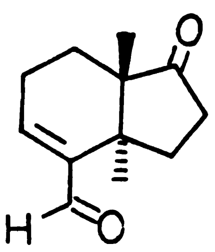

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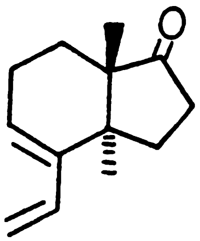
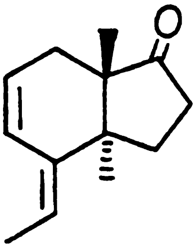


9

The most promising approach was found to be the Diels-Alder reaction of diene 9 with appropriate dienophiles. However, the synthesis of 9 proved more difficult than expected, because it readily isomerized to the transoid isomer 10 on treatment with acid. *In situ* trapping experiments such as dehydration of carbinol 11 in the presence of maleic anhydride (MA), or a thermal reaction between allyl chloride 12 and MA gave modest yields of adduct 13.



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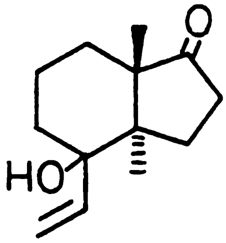

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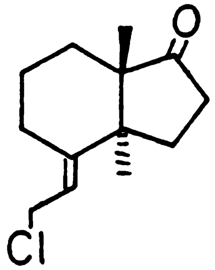

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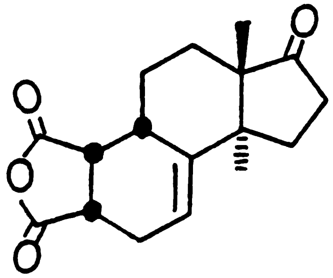
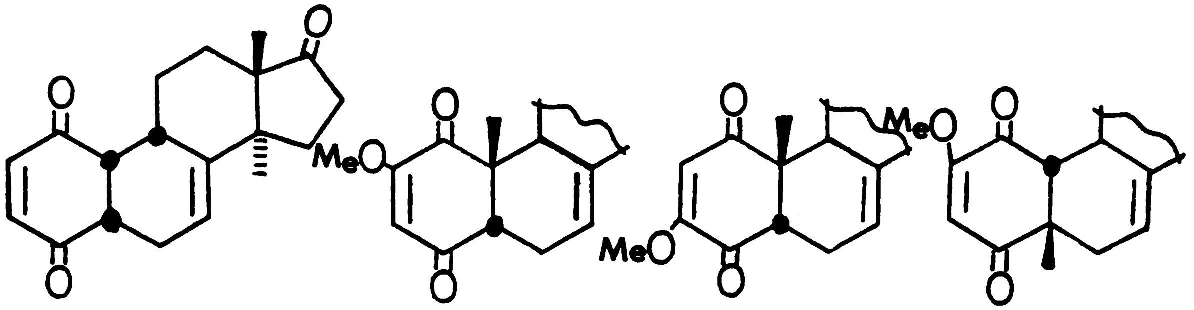


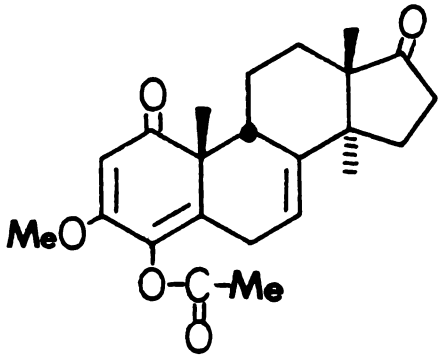
13

A successful preparation of 9 was achieved by treatment of 11 with boron trifluoride etherate in refluxing benzene-THF solution. Diene 9 reacted on heating with a variety of dienophiles to give crystalline alpha-endo adducts, such as 13, 14 and 15. Isomeric adducts 16, and 17 were selectively prepared via Lewis acid-catalyzed Diels-Alder reactions. The configurations of adducts 15-17 have been confirmed by high resolution nmr and X-ray analyses.



14 **15** **16** **17**

Adducts 15 and 16 should be useful precursors for the synthesis of lanostane natural products. Epimerization of C-5 failed in 15 and 16, but epimerization of C-10 in 17 was successful. Synthesis of the mono enol-acetate 18 from 16 not only proved that C-5 is enolizable, but also generates a dienone moiety in ring A, which might be useful in the synthesis of euphane natural products by epimerization of C-10.



18

In the third part of this dissertation, the selective catalysis of Diels-Alder reactions will be discussed. Several important directing effects of normal (thermal) Diels-Alder reactions of substituted quinones are summarized.

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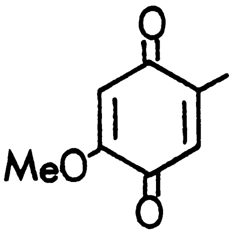
The regioselectivity of Diels-Alder reactions of 2-methoxy-5-methyl benzoquinone 19 with isoprene, piperylene and diene 9 was poor. However, this poor regioselectivity can be directed to favor ortho/para adducts (16, 20 and 21) by using boron trifluoride as the catalyst, or to favor meta adducts (17, 22 and 23) by using stannic chloride as the catalyst:



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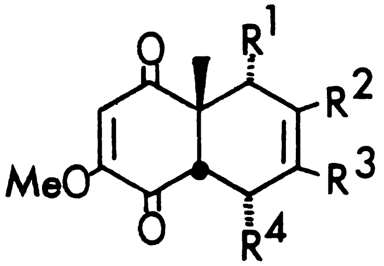
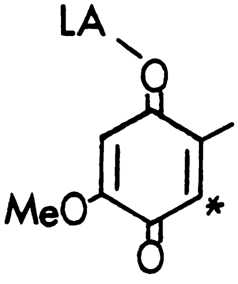


20 R^1=CH_3, R^2,R^3,R^4=H
21 R^3=CH_3, R^1,R^2,R^4=H
22 R^4=CH_3, R^1,R^2,R^3=H
23 R^2=CH_3, R^1,R^3,R^4=H

Two different catalyst-quinone complexes 24 and 25 are proposed to account for this remarkable regioselectivity.



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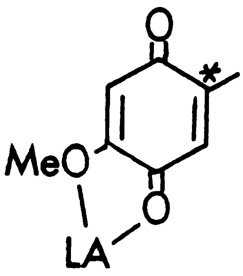

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DEDICATION

This dissertation is dedicated to my mother and to the memory of my father.

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The author wishes to express his sincere appreciation to Professor William H. Reusch for his guidance, conseling and encouragement throughout this study, for his critical reading of this manuscript and for numerous enlightening and informative discussions. Appreciation is extended to Professor E. LeGoff for being second reader and to Professors H. Hart, A. Timnick and M. Rogers for their helpful suggestions.

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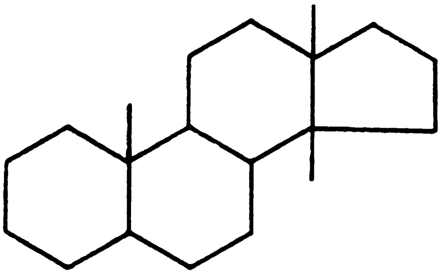
INTRODUCTION

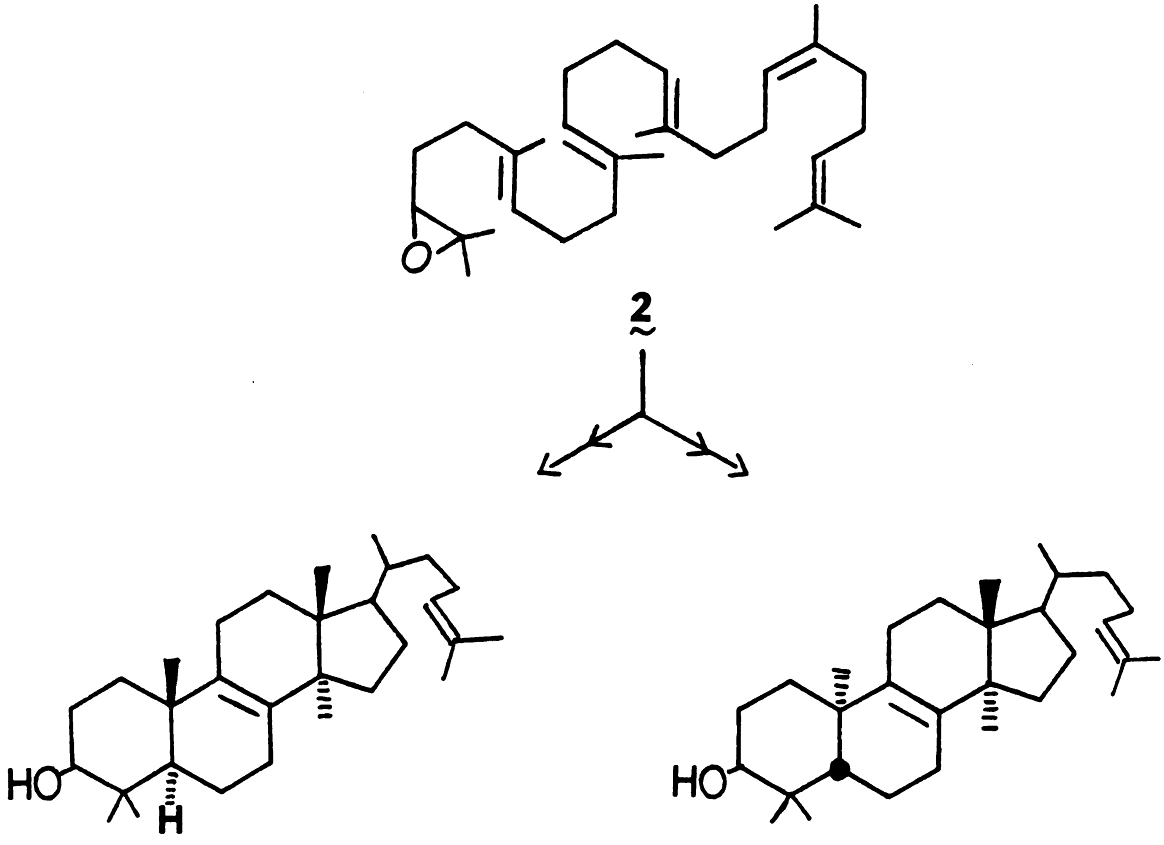
The tetracyclic triterpenes are mostly found in the plant kingdom, and have a common perhydrocyclopentanophenanthrene skeleton **1**:[1,2]



1

Because of their structural resemblance to steroids, the tetracyclic triterpenes are also called methylsteroids or 14-α-methyl analogs of steroids.[3] A number of tetracyclic triterpenes, such as the cucurbitacins, have been shown to have anti-tumor activity and some of their derivatives are also found to be as physiogically active as steroids.[4]

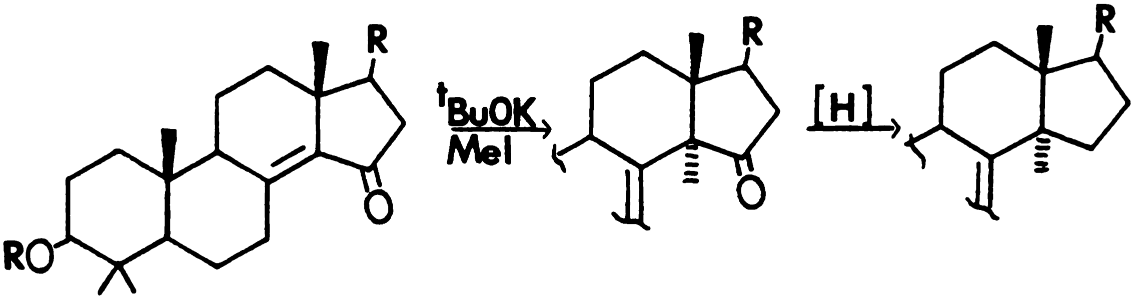
It is now known that the tetracyclic triterpenes and steroids are formed in nature by an enzymatic cyclization of squalene 2,3-oxide **2**.[5] In these biosyntheses, enzymes play an important role in folding the squalene oxide in two different modes: one leads to the lanosterol/steroid system via a chair-boat-chair-boat arrangement, and one to the euphol system via the corresponding chair-chair-chair-boat conformation:



lanosterol **euphol**

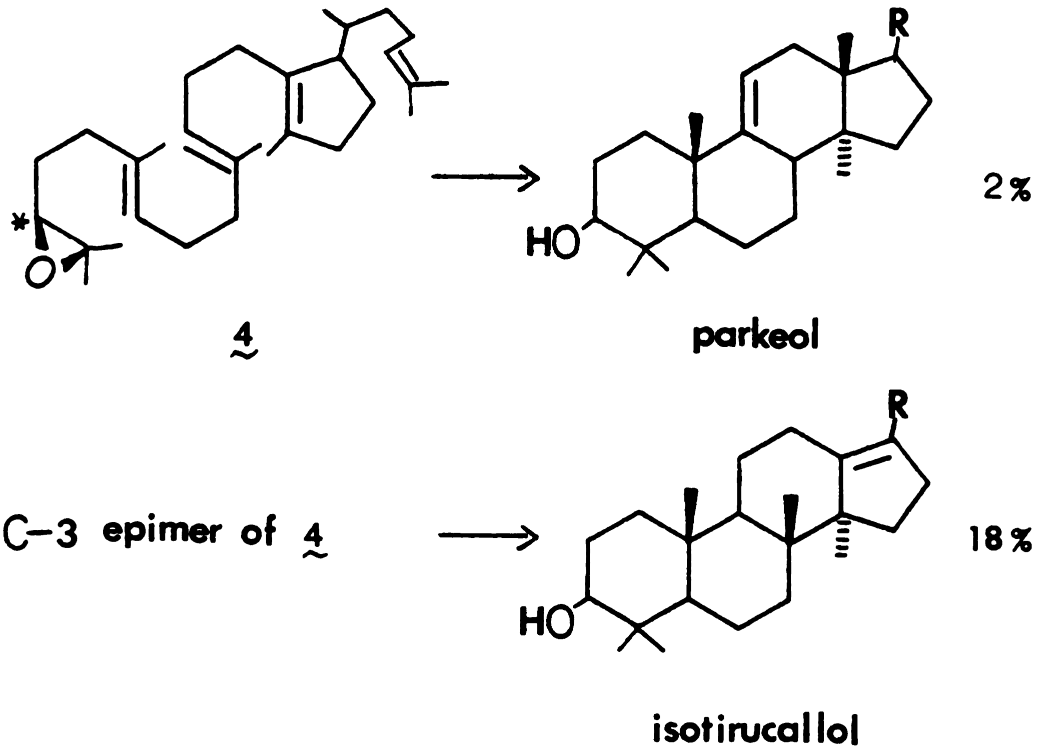
The tetracarbocyclic skeleton and stereochemical complexities of the tetracyclic triterpenes pose a challenge to synthetic organic chemists with many challenges. However, a greater effort has been directed toward the total synthesis of steroids than toward that of the tetracyclic triterpenes. In fact, at the present time, only two distinct approaches have been successful in achieving the total synthesis of a tetracyclic triterpene. The first, developed by Woodward et.al., used cholesterol as the starting meterial for a lanosterol synthesis. The other entirely different approach uses a biogenetically patterned reaction sequence, as effected in van Tamelen's studies.

In Woodward's approach,[6] a key step involved the introduction of a 14-α-methyl group onto a 15-keto-cholestane derivative **3**, as shown below. Lanosterol was thus synthesized in over twenty five steps.

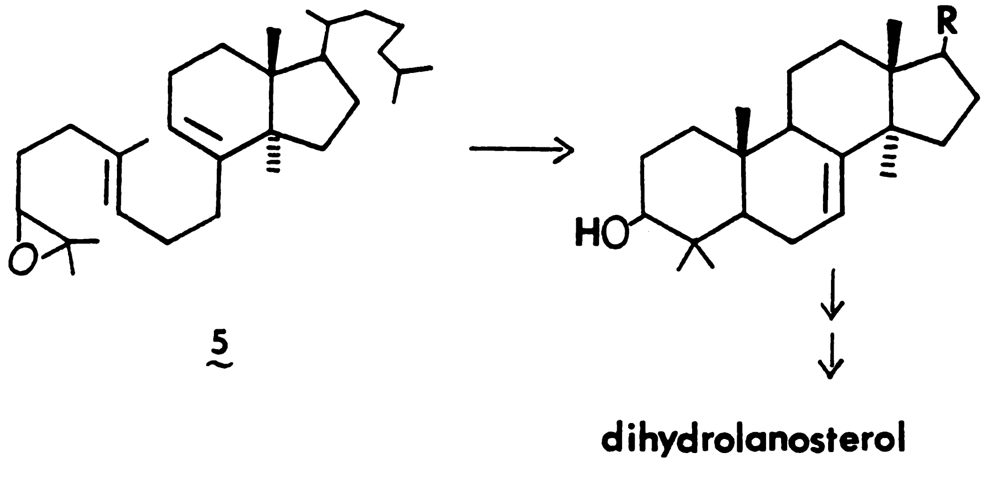


3

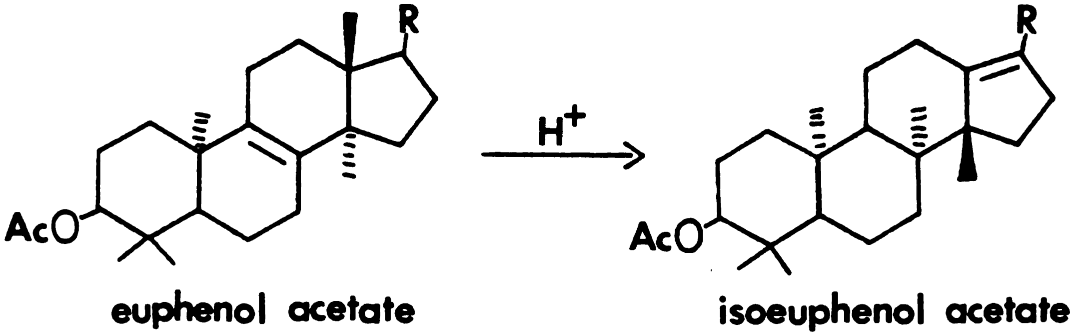
The van Tamelen strategy, on the other hand, involved acid-catalyzed cyclization of a suitable polyene monoepoxide. For example, acid treatment of a mono-carbocyclic derivative of squalene oxide **4** and its C-3 epimer led to the total syntheses of parkeol and isotirucallol, respectively:[7]



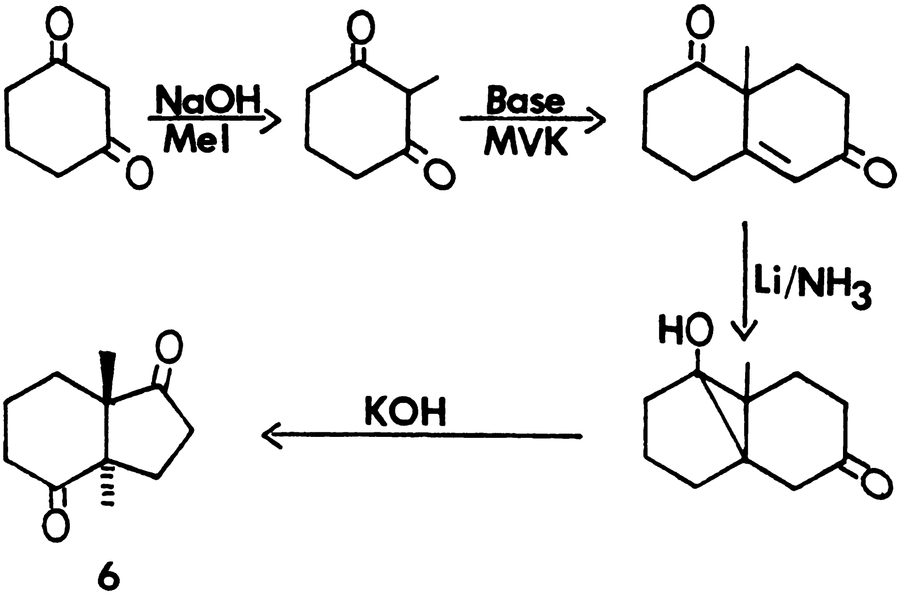
Similarly, when polyene epoxide 5 having a preformed CD ring is used, cyclization to a dihydrolanosterol precursor[8] took place:



Although the lanostane skeleton has been successfully constructed as noted above, a total synthesis of the related euphanes and cucurbitacins has not yet been accomplished. The euphane/tirucallane family will be difficult to prepared by the versatile polyene cyclization approach, because compounds of this kind suffer a facile acid-catalyzed rearrangement to the isoeuphane system:[8,9]

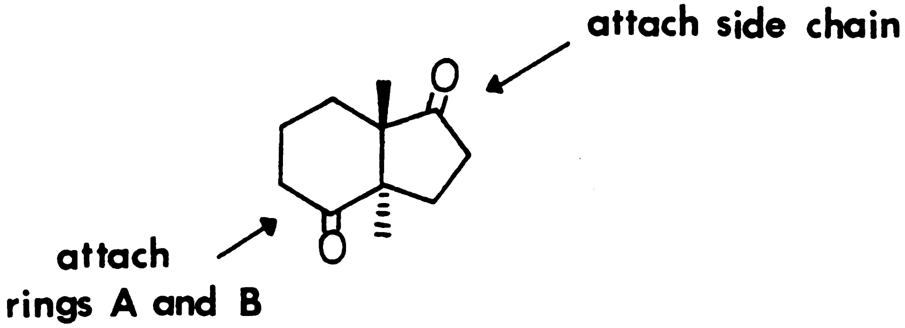


The bicyclic diketone trans-1,6-dimethyl-bicyclo [4,3,0] nonan-2,7-dione 6,[10] has been prepared from cyclohexa-1,3-diketone via the following scheme:



6

This diketone incorporates a common skeletal feature found in the tetracyclic triterpenes. Thus, it should be possible to use compound 6 as a CD synthon in a synthesis of the above natural products. In order to achieve such a total synthesis, two major transformations must be accomplished. First, A and B rings must be attached to the six-membered ring of 6 in a regio- and stereoselective manner. Second, an alkyl side chain must be bonded to the five-membered ring.



6

There are two important advantages to using compound 6 as a starting material in tetracyclic triterpenes synthesis. First, because of the presence of the 14-α-methyl group, the tedious methylation steps in Woodward's synthesis will be eliminated. Secondly, two possible stereo orientations of the methyl group at C-10 are possible, i.e. alpha and beta. Stereochemical control during the introduction of this center would allow synthesis of both important families of these triterpenes. If an alpha configuration is generated, it can be used for the synthesis of euphane natural products. On the other hand, if a beta configuration is obtained, then the resulting product can be used for the synthesis of lanostane natural products.

In developing methods for attaching rings A and B to **6**, it is helpful to examine related systems in which analogous transformations have been achieved. In steroid synthesis, three fundamentally different strategies[11] generally have been used for the fusion of a two-ring fragment to an existing two-ring moiety in order to build up the desired tetracarbocycle:

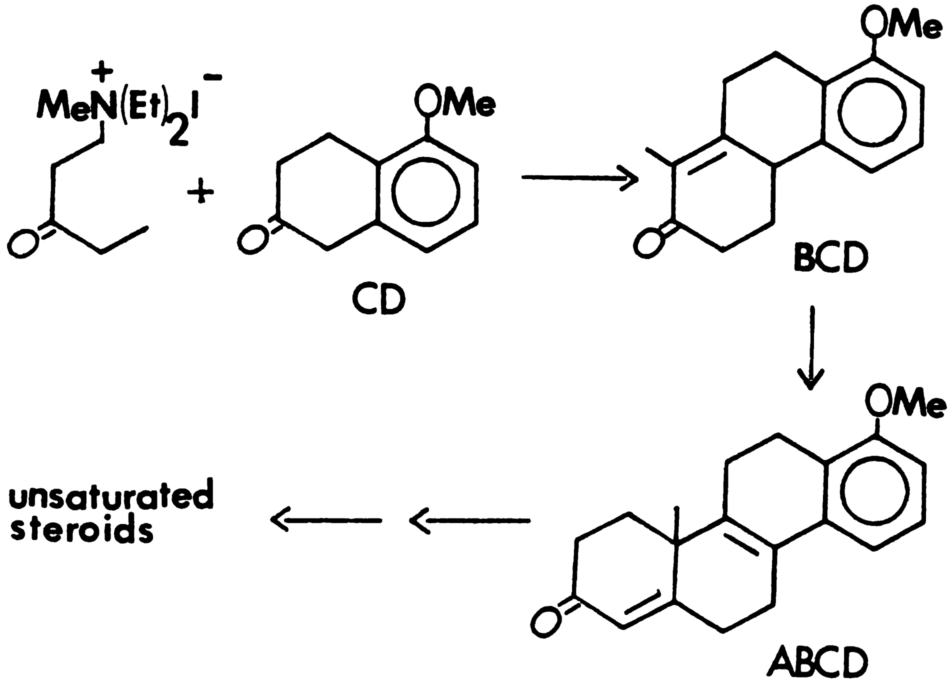
1. CD $\longrightarrow$ BCD $\longrightarrow$ ABCD

   This notation indicates that ring B is first attached to a preformed CD ring system. The ABCD skeleton is then constructed via addition of the A ring to the newly formed BCD unit.

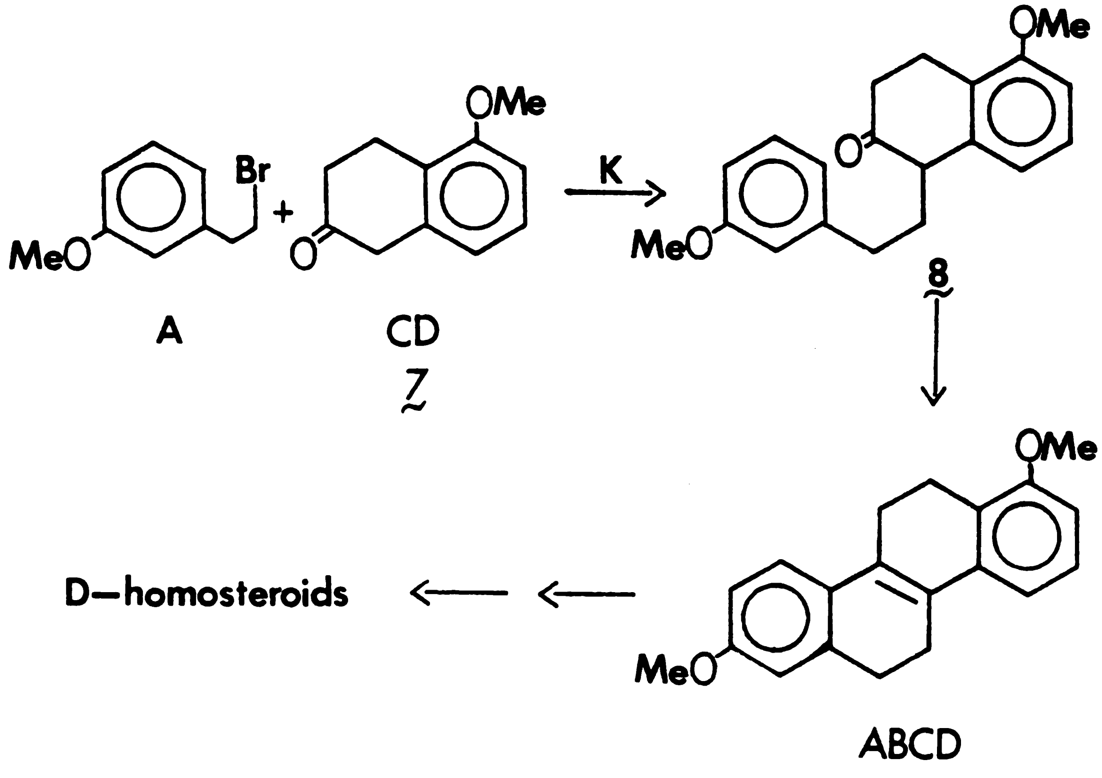
2. CD + A $\longrightarrow$ ACD $\longrightarrow$ ABCD

3. CD + A $\longrightarrow$ ABCD or AB + D $\longrightarrow$ ABCD

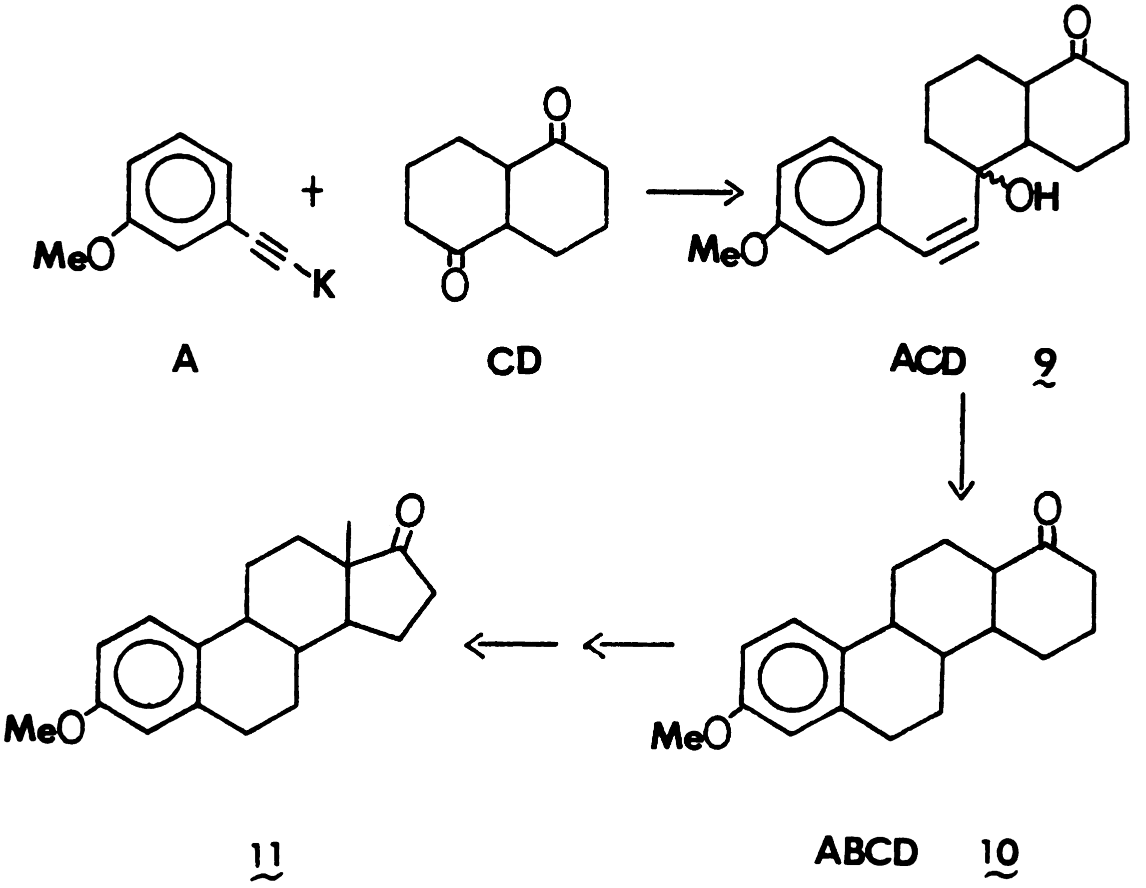
Johnson's steroid synthesis[12,13] is one of the best examples of the first approach. As shown below, the B and A rings were introduced stepwise via a Michael-Aldol reaction sequence.



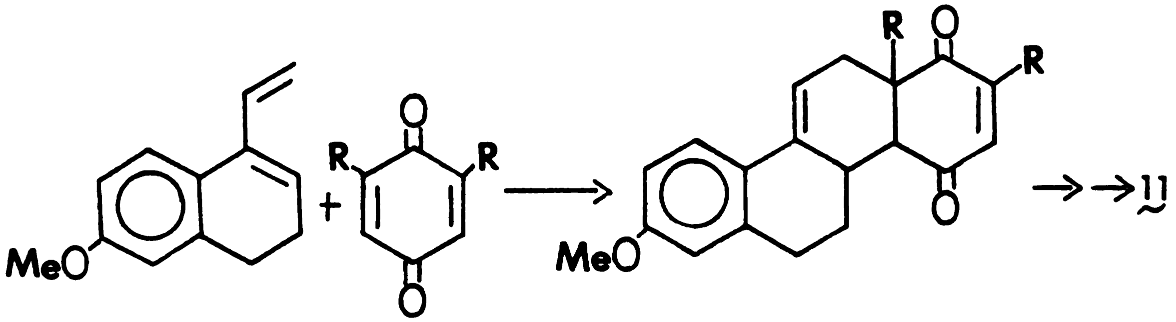
Two examples of the A+CD ⟶ ACD ⟶ ABCD route may be cited. In Birch's preparation of D-homosteroids,[14] an enolate CD fragment was added to a bromide which incorporated the A ring. The resulting ACD intermediate **8** was then cyclized to the desired tetracyclic structure.



Johnson[15] reversed the polarity of this process by having the A ring moiety serve as an anionic species. The alkylation adduct ACD 9 was hydrogenated and then cyclized to yield a tetracyclic compound 10 which eventually led to a total synthesis of estrone methyl ether 11.



The third approach is best accomplished by a Diels-Alder reaction[16] of a bicyclic diene and a monocyclic dienophile. In principle, this type of Diels-Alder reaction can put together all four rings in one step. Surprisingly, the CD + A ⟶ ABCD strategy has not yet been used for a steroid synthesis.[11] However, there are several syntheses which utilize a similar pathway, namely AB + D ⟶ ABCD, for the construction of the tetracyclic system. Johnson's estrone methyl ether synthesis[17] is a notable example. Quinone 13, after condensing with diene 12, gave a cycloadduct 15, which served as a precursor for the total synthesis of estrone methyl ether 11.

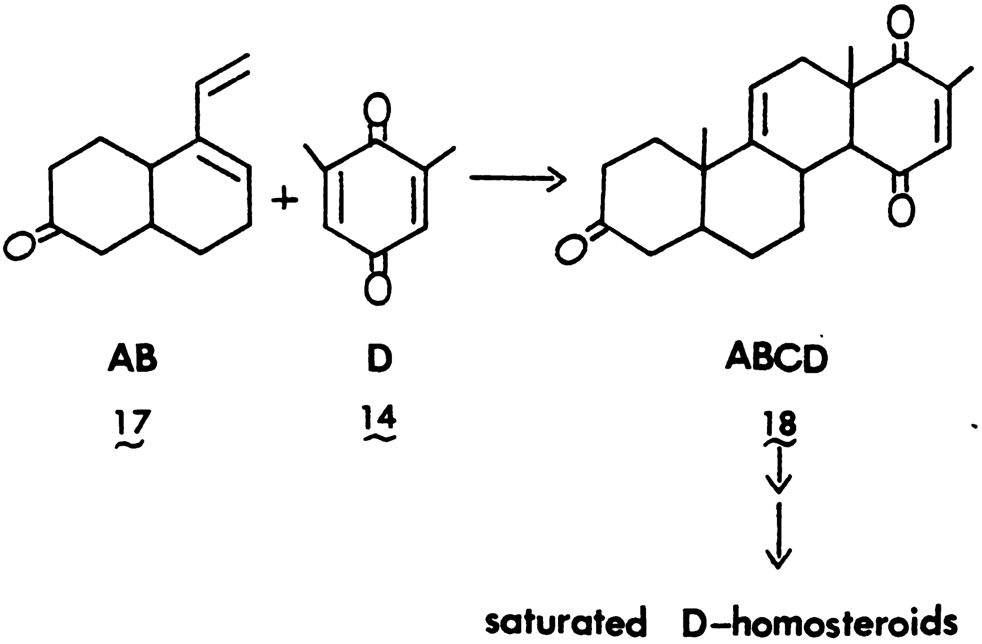


AB D ABCD

12 13 R=H 15 R=H

14 R=Me 16 R=Me

More recently, Valenta and coworkers[18] have achieved a similar steroid synthesis by an elegant Lewis acid-directed Diels-Alder reaction. For example, reaction of diene 12 and substituted quinone 14 in the presence of boron trifluoride etherate gave cycloadduct 16, which was then transformed to 11. Similarly, adduct 18 was obtained from the reaction of diene 17 and quinone 14. This cycloadduct was a key intermediate in a total synthesis of saturated D-homosteroids.[18]

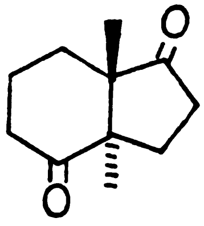


In the first part of this dissertation, the relative reactivities of the carbonyl functions in perhydroindandione 6 will be examined. In the second part, some methods of fusing six-membered rings to 6, so as to generate the tetracyclic skeleton of the lanostane and/or euphane triterpenes, will be tested. Finally, Lewis acid-controlled low-temperature Diels-Alder reactions will be discussed in the third part.

RESULTS AND DISCUSSION

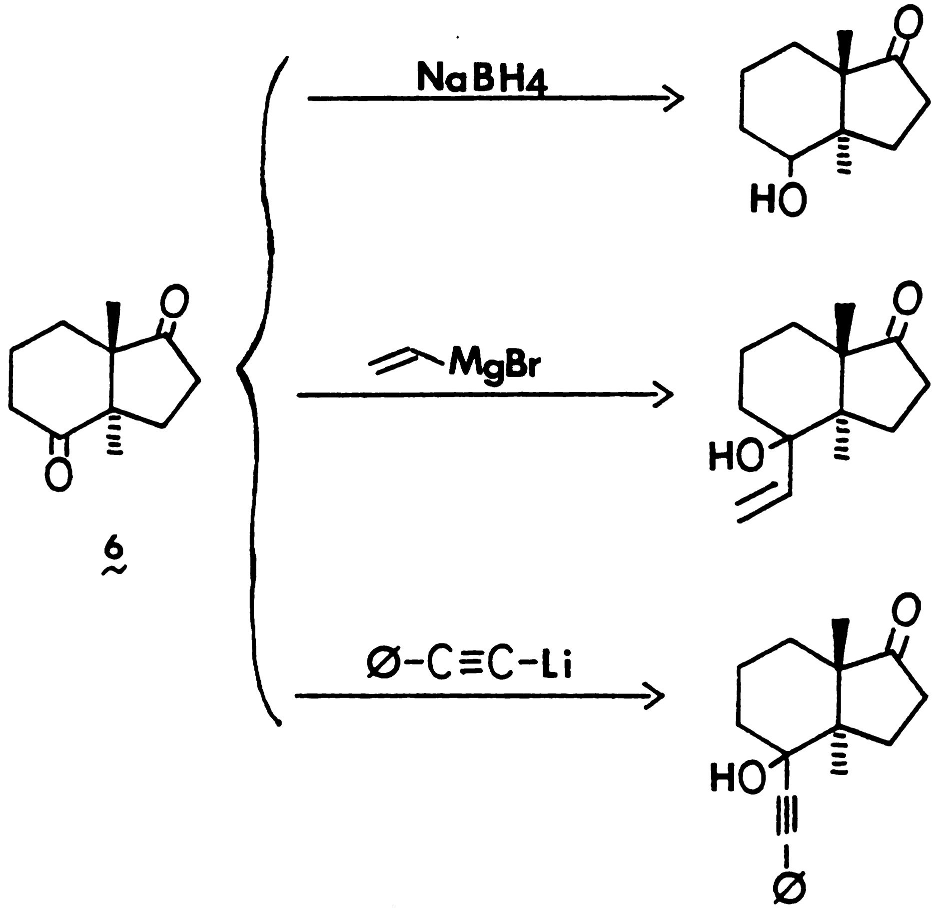
A. Selective Reactions of trans 1,6-Dimethylbicyclo (4,3,0)-nonane-2,7-dione 6[19]

Before undertaking the selective annulation of AB ring fragments to the six-membered moiety of 6, it is necessary to establish the relative reactivities of the two carbonyl groups in the five- and six-membered rings. Indeed, compound 6 is an excellent model compound for studying the chemical behavior of cycloketones with respect to ring size.

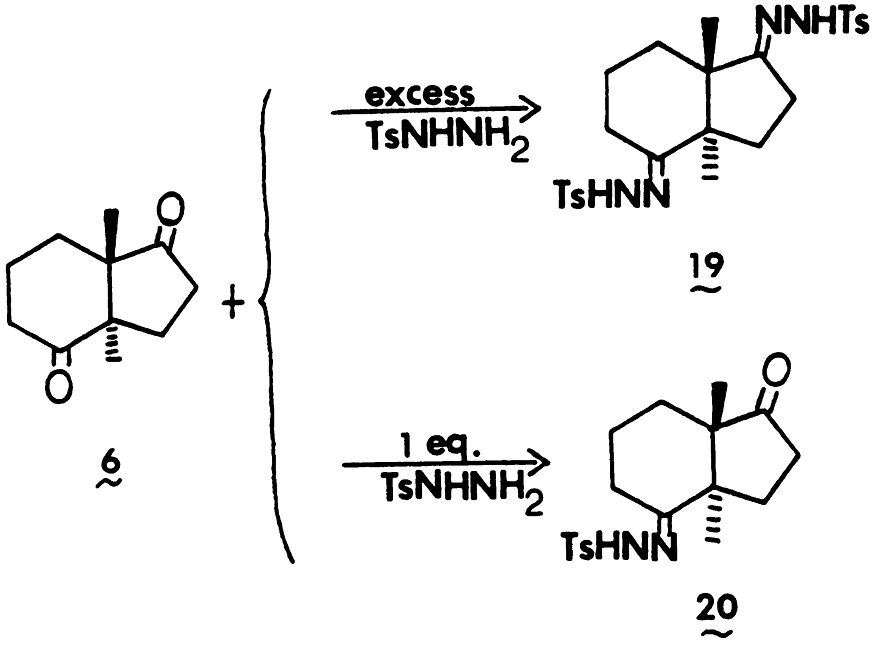


6

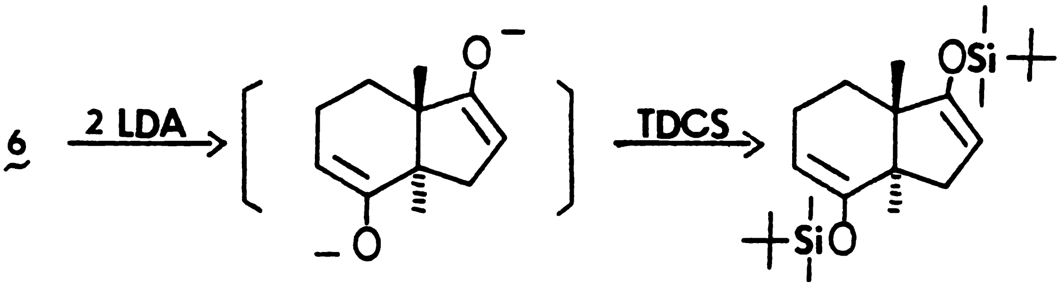
It is well known[20] that the carbonyl group in cyclohexanone is more reactive than that in cyclopentanone. Also previous studies[21] of compound 6 have shown that nucleophilic reagents favor reaction at the six-membered carbonyl site. Examples are sodium borohydride reduction,[21a] lithium phenylacetylide addition[21b] and vinyl magnesium bromide addition[21a]:



All these selective reactions were reported to give good yields without protection of the five-membered carbonyl group. A similar selectivity has now been observed in reactions with tosylhydrazine.[22] Both the carbonyl groups in 6 can undergo condensation reactions with tosylhydrazine ($TsNHNH_2$), and with excess reagent bis-adduct 19 was isolated in 66% yield. When 6 was treated with an equimolar amount of tosylhydrazine, however, the reaction gave a monoadduct (83% yield), which was identified as 20 on the evidence of a strong carbonyl absorption at 1740 cm^{-1} in the infrared.

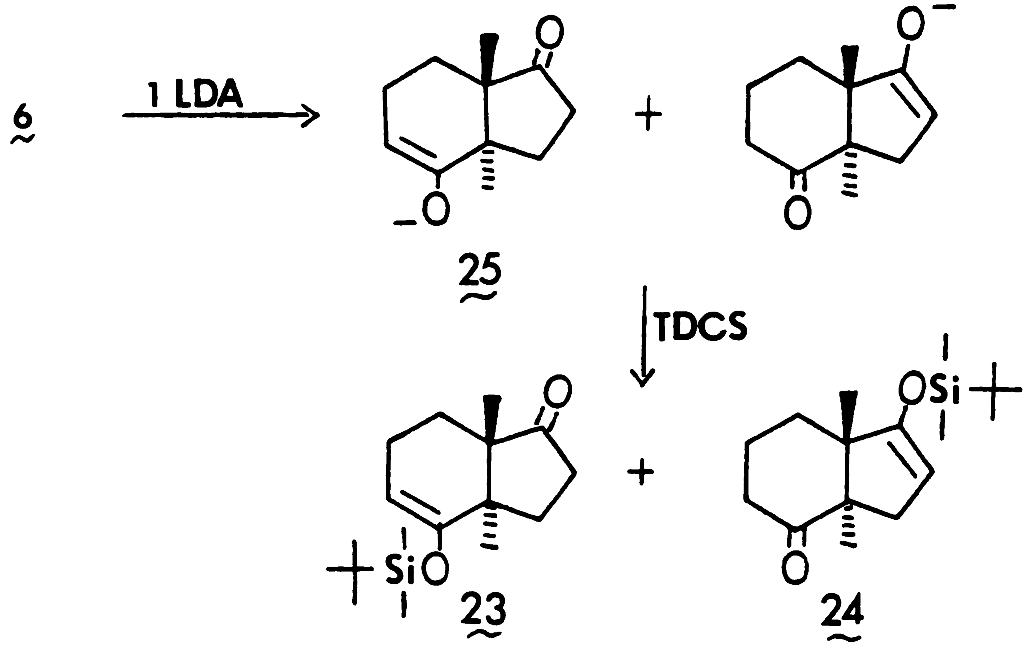


The usefulness of 6 as an intermediate in the total synthesis of natural products would be enhanced if the formation of a selective enolate could be achieved. To this end, reactions involving enolate formation from 6 were investigated. Both the carbonyl functions in 6 proved readily converted to enolate species when excess strong base-lithium diisopropylamide (LDA)-was used. After trapping the bis-enolate species 21 with tert-butyl dimethylchlorosilane (TDCS), the bis-silyl ether 22 was obtained in 85% yield.



21 22

When 6 reacted with an equimolar amount of LDA, two mono enolates were obtained as their silyl enol ether derivatives in roughly quantitative yield. The infrared spectrum of the major product (>95%) indicates the presence of a five-membered ring carbonyl group ($\tilde{\nu}_{max}$=1740 cm^{-1}). This spectral feature strongly supports the assignment of structure 23 to this compound. On the other hand, the infrared spectrum of the minor isomer (ca. 1%) indicates the presence of a six-membered ring carbonyl group, absorption at 1715 cm^{-1}, and clearly suggests structure 24 for this product.

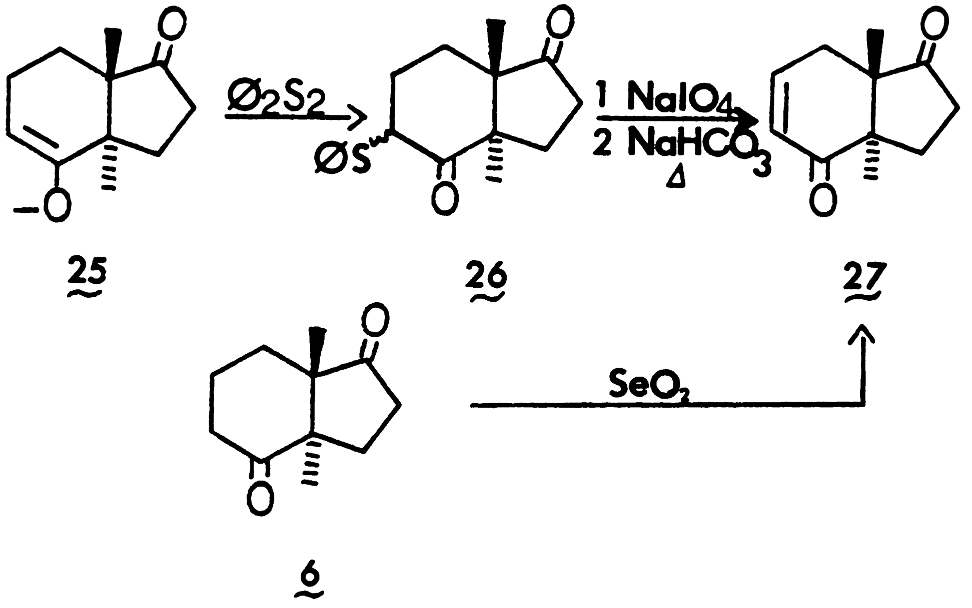


25 23 24

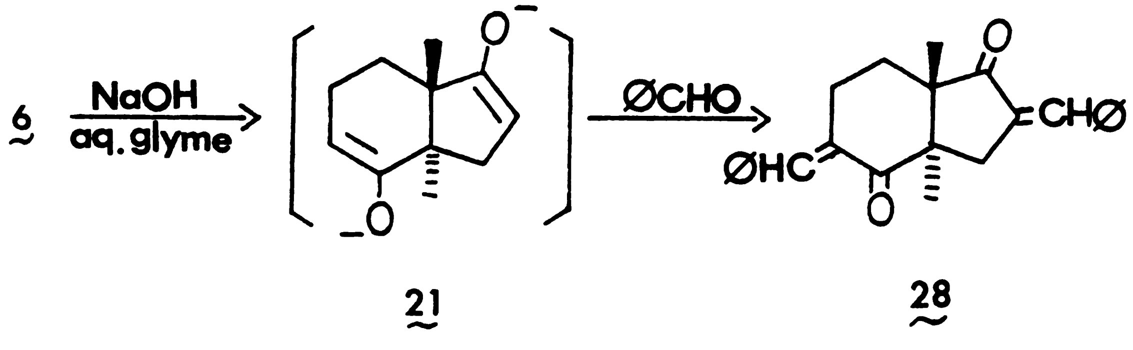
The lithium enolate salts generated as described above were found to be rather insoluble in THF. In order to improve the reactivities of these bases at low temperature, it was necessary to add hexamethylphosphorous triamide (HMPA) to the enolate solution before trapping with TDCS. In fact, in the absence of HMPA the reactions were heterogeneous, and yielded three products: the bis-silyl ether **22** and mono-adducts **23** and **24** in varying proportion.

Since the formation of mono-adduct **23** was independent of either the reaction temperature in the range 0° to 65° or the reaction time, it is assumed that **25** represents the thermodynamically favored mono-enolate species derived from **6**. All attempts to trap a kinetically favored enolate at a lower temperature (∼-16°C) failed because of solubility problems, even though a significant amount of HMPA was added.

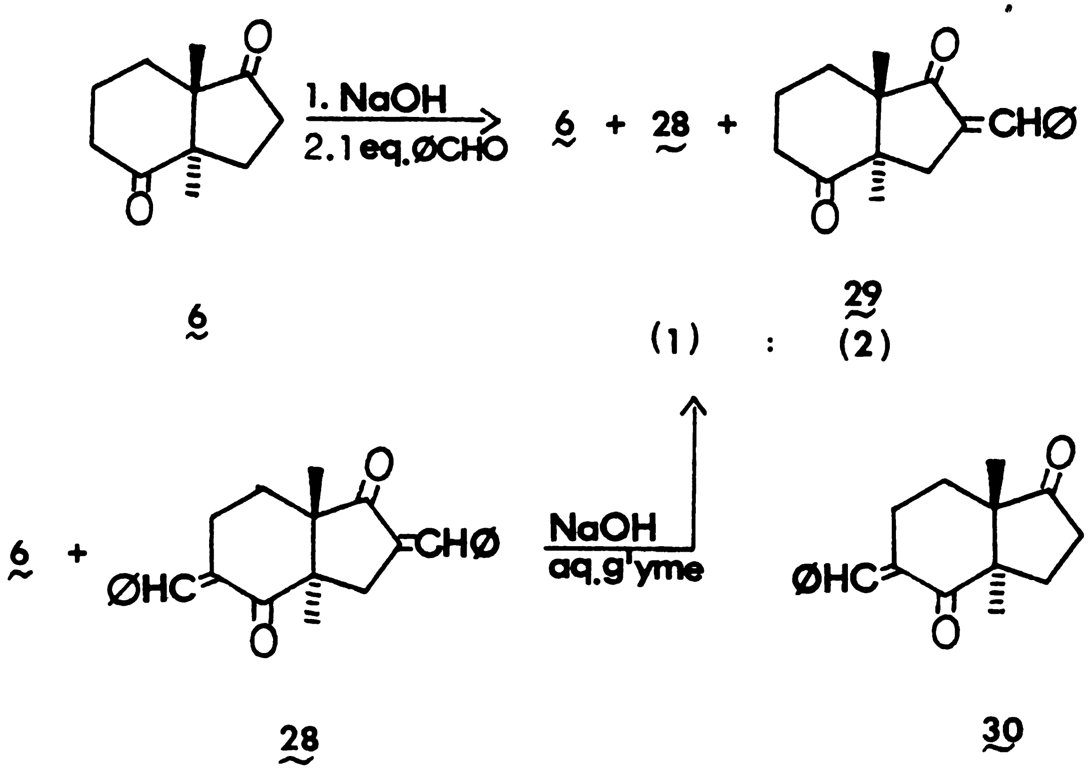
In principle, enolate **25** could be alkylated, acylated or sulfenylated, and would be potentially useful in selective annulation reactions. In practice, it has been found that reaction of diphenyl disulfide with **25** yielded sulfide **26**. Oxidation of **26** followed by elimination of the resulting sulfoxide[23] gave enedione **27**. Alternatively, enedione **27** was also prepared by selenium dioxide oxidation:[24]



An unexpected result was observed in studies of benzaldehyde condensations with 6. Base catalyzed reaction of 6 with excess benzaldehyde gave bisadduct 28.



This demonstrates that both the alpha methylene groups in the five- and six-membered rings can serve as enolate donors. When one equilvalent of benzaldehyde was used, however, two condensation adducts were isolated in a 1:2 ratio. One of the products was the bis-adduct 28 and the other was a mono-adduct which, surprisingly, was identified as five-membered ring adduct **29**. It should be noted that none of the mono-adduct **30** was detected in this reaction. Further studies showed that when the bis-adduct **28** was treated with one equivalent of **6** under similar reaction conditions, the same mixture of **28** and **29** was obtained.

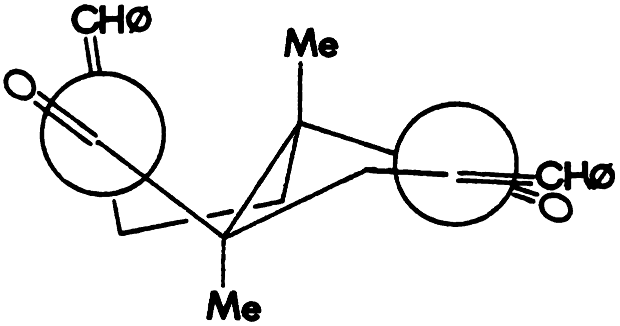


As expected, mono-adduct **29** was the chief condensation product when **6** reacted with half an equivalent of benzaldehyde:

$$\mathbf{6} + 0.5\ \text{equiv.}\ \text{ØCHO} \xrightarrow[\text{aq.glyme}]{\text{NaOH}} \mathbf{6} + \mathbf{28} + \mathbf{29}$$

ratio (52) : (7) : (57)

At first glance, the above condensation reactions seem to conflict with the silyl enol ether trapping experiments described above. However, this inconsistency may be rationalized by the difference in π-conjugation of the α-keto benzylidene groupings in the five- and six-membered rings. According to Dreiding molecular models, there is a substantial dihedral angle (ca. 35°) between the six-membered carbonyl group and its alpha benzylidene grouping, whereas the two functions are essentially coplanar when on a five-membered ring. (see 28')



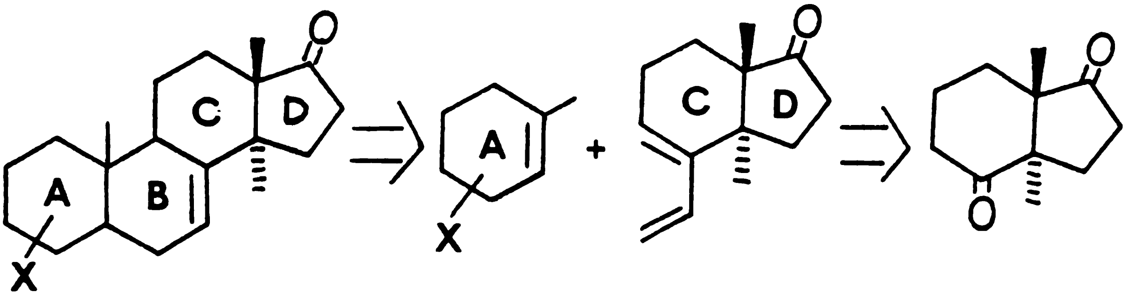
28'

This suggests that a benzylidene group alpha to a five-membered ring ketone has greater π-conjugation than the six-membered analog. Furthermore, the relatively higher molar extinction coefficient (ϵ=25,000) of the adduct 29 also implies greater coplanarity between carbonyl and the α-benzylidene groups. For example, α-benzylidenecyclohexanones have molar extinction coefficients (ϵ=16,000) roughly 70% that of acyclic or five-membered analogues (ϵ=24,000).[37]

Since these condensations are reversible, the product distribution should reflect the thermodynamic equilibrium of the two adducts. If the greater conjugation in **29** makes it more stable than **30**, the predominance of the former mono adduct in these product mixtures is reasonable.

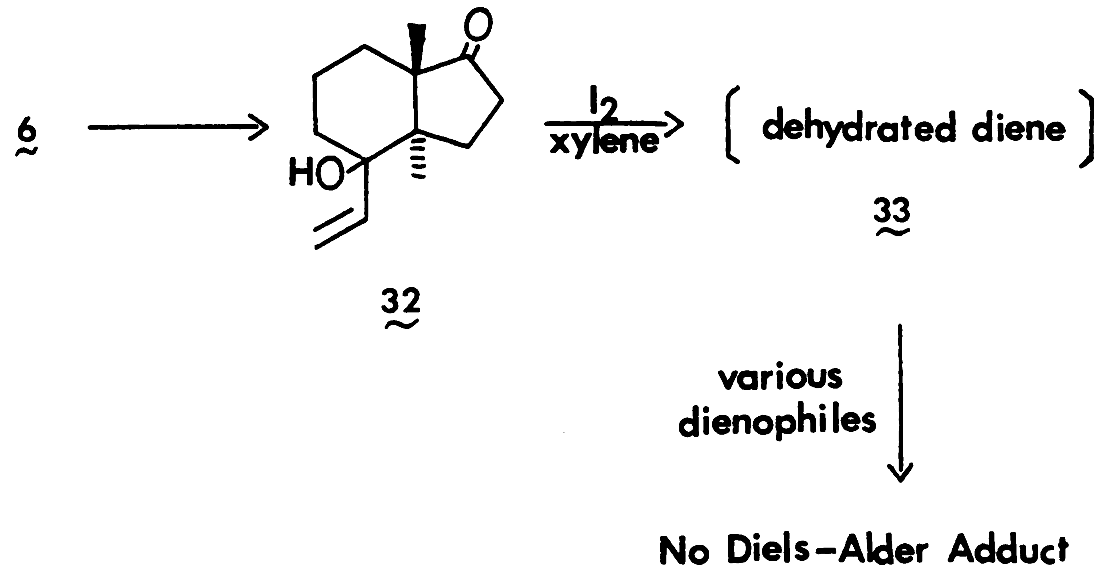
B. Approaches to AB ring Synthesis

From the beginning, a Diels-Alder reaction between diene 31 and a suitable dienophile appeared to be the most direct means of fusing an AB ring unit to intermediate 6:

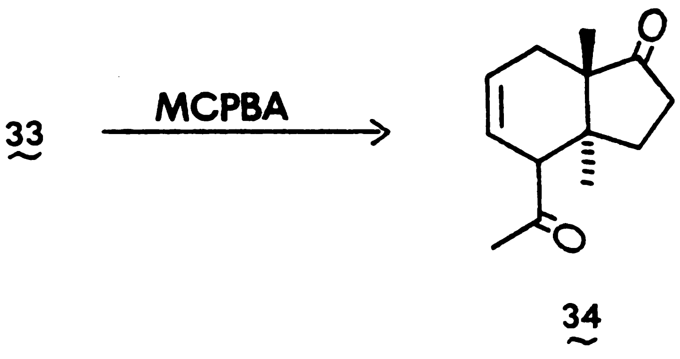


31 6

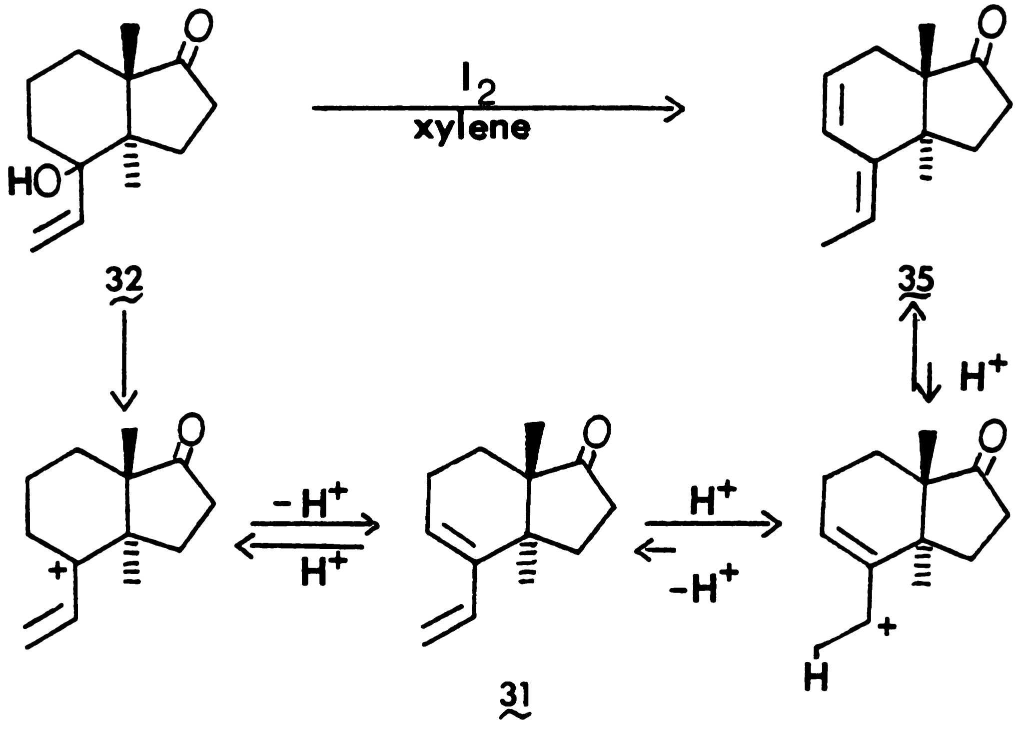
In order to put this A + CD ⟶ ABCD approach into practice it was first necessary to develop an efficient synthesis of diene 31 from 6. In initial studies by J. Martin,[21a] vinyl carbinol 32 was prepared in moderate yield by treatment of dione 6 with vinyl Grignard reagent. Dehydration of 32 in refluxing xylene containing a little iodine gave a product initially believed to be the desired diene 31.[21a] However, no Diels-Alder adducts were obtained from reactions of this product (33) with maleic anhydride, tetracyanoethylene, p-benzoquinone and dimethyl acetylene dicarboxylate under varying reaction conditions:[21a]



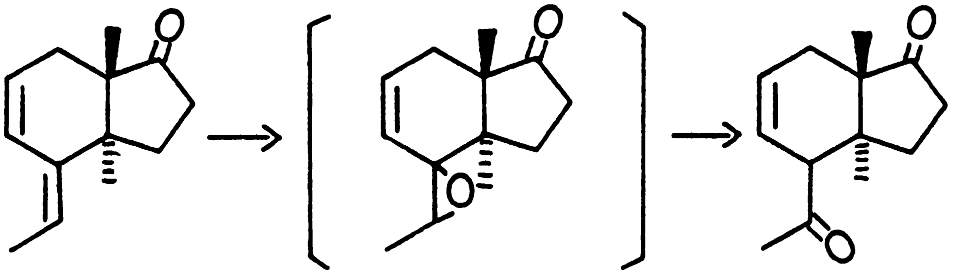
Epoxidation of diene 33 by m-chloroperbenzoic acid has now been shown to yield enedione 34. This unexpected product is not easily rationalized starting from diene 31, suggesting that a reexamination of 33 be made.



A careful review of the pmr spectrum of diene 33 now shows it to be the rearranged transoid isomer 35, resulting from an acid-catalyzed rearrangement[25] of cisoid diene 31 under the dehydration condition:



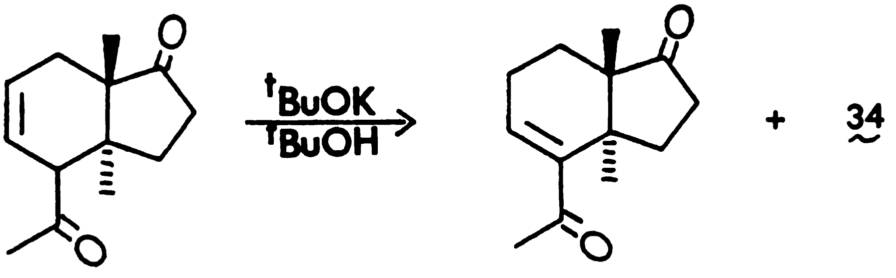
The correct structural assignment of diene 35 not only explains the failure of attempted Diels-Alder reactions, but also is consistent with the formation of the unexpected enone 34. It is believed that epoxide 36 undergoes a facile 1,2-hydride shift[26] under the reaction conditions to yield enone 34. In fact, this reaction is best carried out by introducing a catalytic amount of boron trifluoride etherate, which acts to catalyze the rearrangement of intermediate epoxide 36. By this means, enone 34 was obtained in 65% yield.



35 **36** **34**

The above findings led to two interesting follow-up studies. First, although carbinol **32** did dehydrate under the iodine-catalyzed treatment, the resulting transoid diene **35** was not suitable for the Diels-Alder approach; consequently, it was necessary to find suitable conditions for generating cisoid diene **31**. A variety of dehydration reactions of **32** were investigated and will be discussed later in this dissertation. Second, since β,γ-unsaturated ketone **34** could be obtained from **35** in good yield, it was considered as a possible alternative in the AB ring annulation.

Treatment of **34** with potassium t-butoxide in t-butanol solution partially isomerized the double bond to give conjugated enone **37**. The product mixture from this treatment proved to be 87% **37** and 13% **34**, as evidenced from pmr spectroscopy.

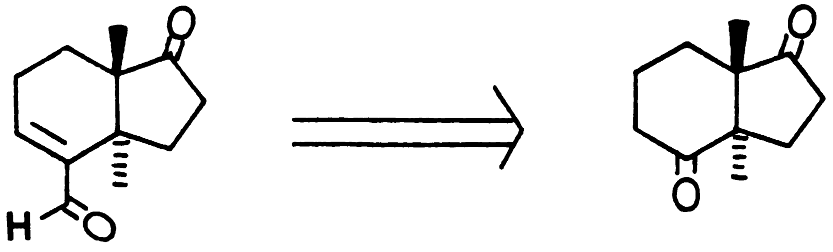


34 37

(87) : (13)

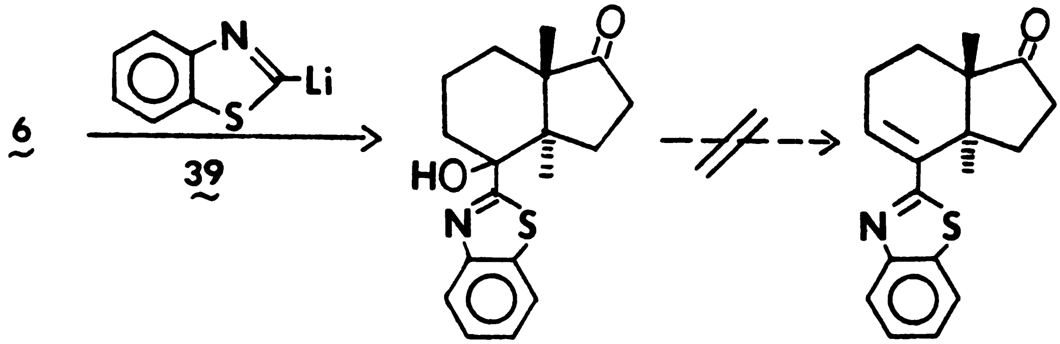
That enone 37 is a potentially useful synthon for subsequent annulation via the well-known Michael-Aldol reaction sequence is clear from the reported studies of Robinson and others on simpler systems.[27] Unfortunately, all attempts to effect the Michael addition of diethyl malonate and 2-methyl-1,3-cyclohexadione to 37 failed.

In a related study, methods of preparing the equivalent unsaturated aldehyde 38 from 6 were also explored. Two potentially useful precursors to 38 were prepared by taking advantage of the different reactivities



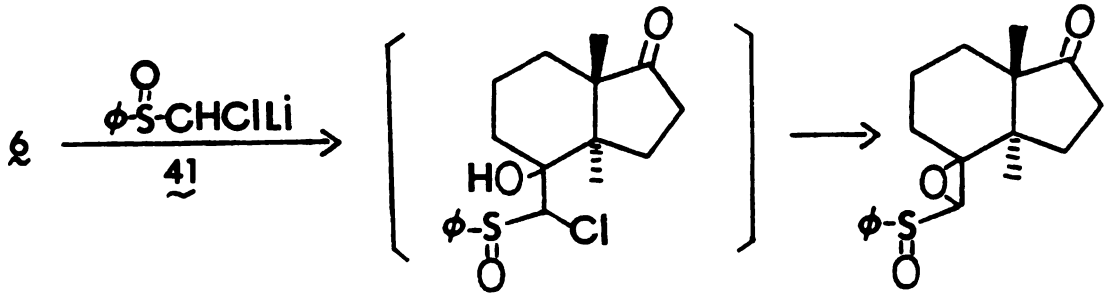
38 6

of the two carbonyl functions in 6. When compound 6 was treated with the lithium derivative of benzothiazole 39[28] in THF, a single adduct, 40, was obtained in 70% yield. However, efforts to effect dehydration of 40 under a variety of conditions failed. These included treatment with phosphorous pentoxide in methane sulfonic acid,[28] iodine in refluxing xylene, boron trifluoride in benzene/THF and p-toluenesulfonic acid in benzene.



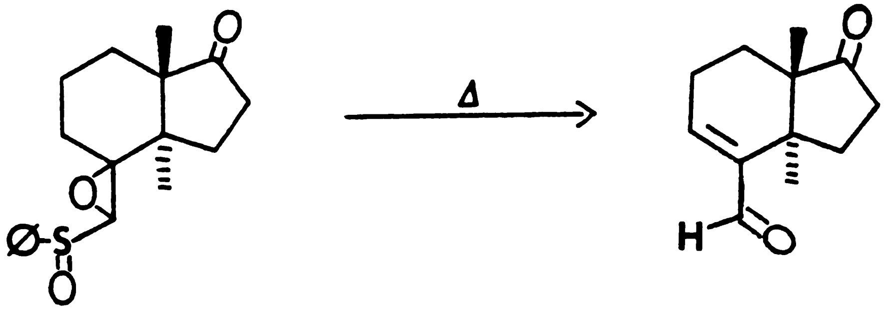
40

A second approach to the synthesis of 38 proved successful. The lithium reagent 41, derived from chloromethyl phenyl sulfoxide,[29] was added to 6 and yielded ketoepoxide 42. This reaction apparently proceeds via an addition to give 43, followed by dehydrochlorination to 42.



43 42

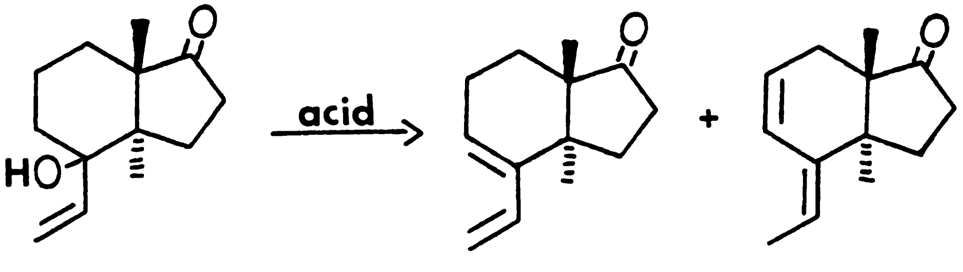
Compound 42 underwent a facile thermal decomposition reaction to yield the desired aldehyde 38,[29b] which exhibited a one proton triplet at δ6.4 and a one proton singlet at δ9.2 in the pmr spectrum.



42 38

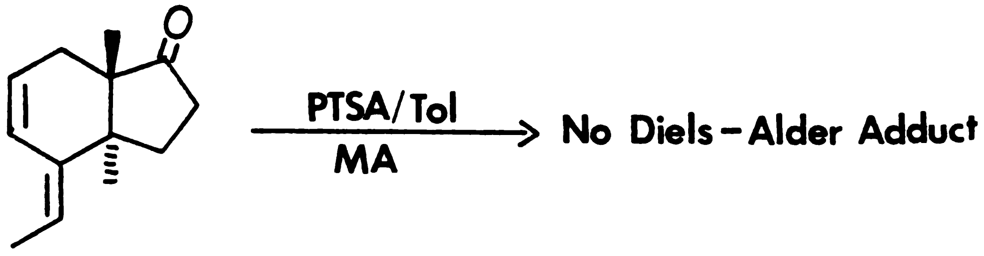
Although 38 is a potentially useful synthon for subsequent annulation, the failure of Michael addition reactions to the similar unsaturated ketone 37 together with the success of the Diels-Alder approach discouraged further investigations with this intermediate.

Because of the superiority of the Diels-Alder approach, the preparation of diene 31 by dehydration of 32 became the subject of an extensive investigation. Unfortunately, this transformation proved very sensitive to acid-catalyzed isomerization of 31 to the undesired isomer 35. Typical examples were found in the iodine and ferric chloride/silica gel catalyzed dehydrations which gave the rearranged diene 35 exclusively. Treatment of 32 with p-toluenesulfonic acid in refluxing toluene gave a 50:50 mixture of 31 and 35. Diene 31 is apparently the initial product of this dehydration, since 35 is not isomerized to 31 under equivalent conditions.



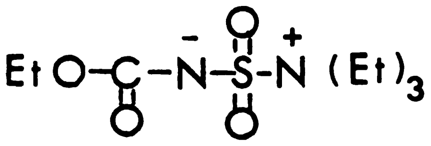
32 31 35

Studies also showed that transoid diene 35 was resistant to <u>in situ</u> isomerization to cisoid diene 31. No Diels-Alder adduct was obtained when the reaction was carried out in the presence of maleic anhydride (MA), which served as a trapping reagent.



31

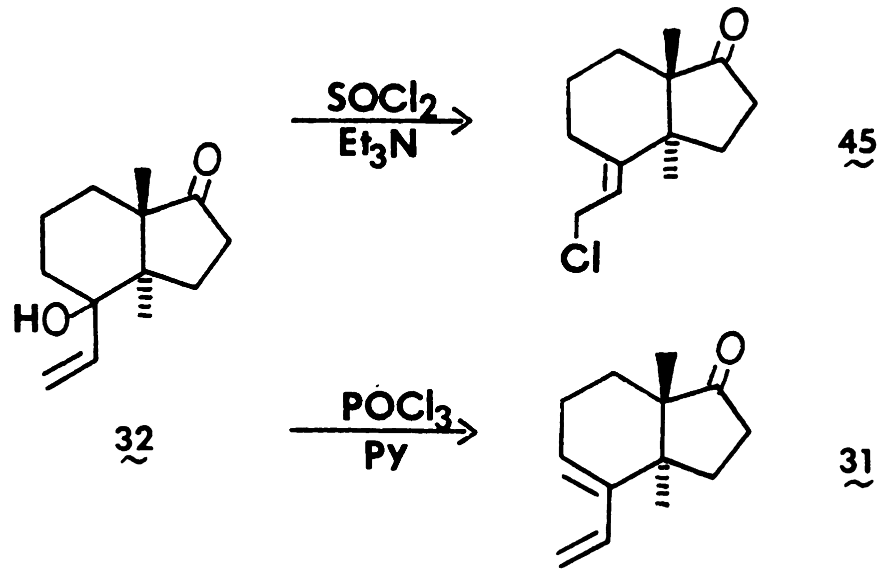
The Burgess reagent **44**, a zwitterionic salt which has been shown to be useful for effecting acid-sensitive dehydration reactions,[33] gave a complicated mixture of products when used for the dehydration of **32**.



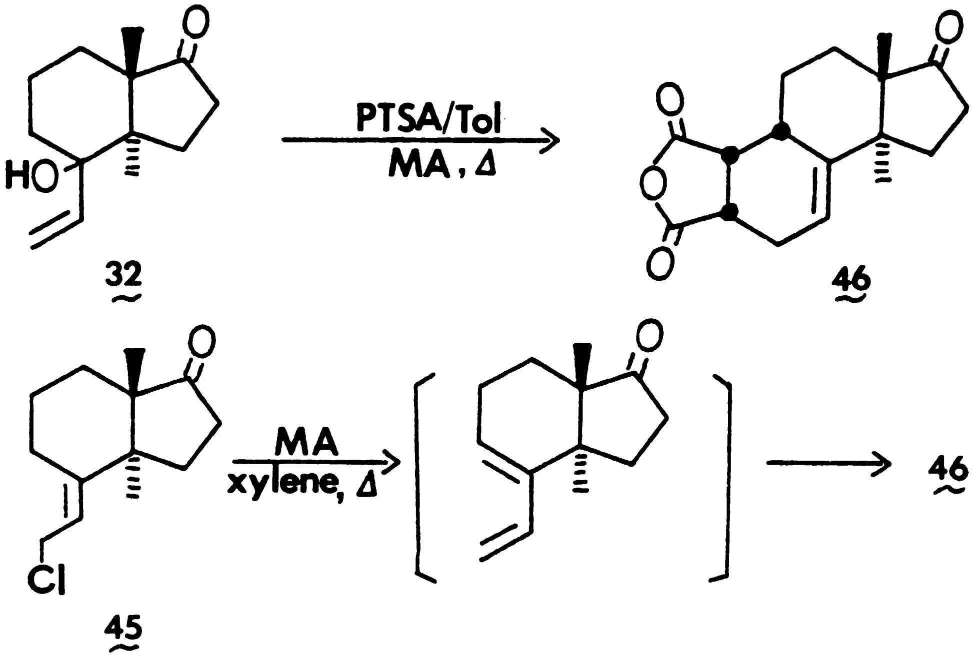
$$\mathrm{EtO{-}\underset{\underset{O}{\|}}{C}{-}\overset{-}{N}{-}\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}{-}\overset{+}{N}(Et)_3}$$

44

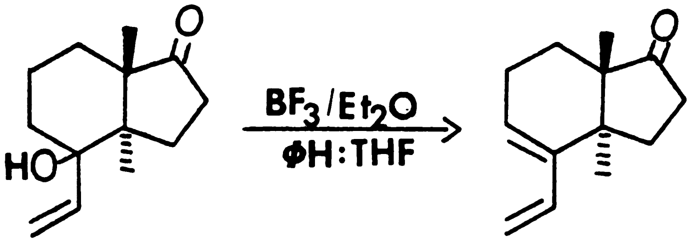
The possibility of effecting dehydration of **32** under basic conditions was next explored. Treatment of carbinol **32** with thionyl chloride in triethylamine,[34] gave allyl chloride **45** as a S_N2' rearranged product. Moreover, with phosphorous oxychloride in refluxing pyridine,[35] carbinol **32** produced the desired cisoid diene **31** as the only volatile product. Unfortunately, the recovered yield of **31** was quite low (ca. 20%), possibly because its volatility resulted in loss during the removal of pyridine.



The prospect for the Diels-Alder approach was improved by successful trapping experiments. When carbinol 32 was treated with an excess of maleic anhydride in refluxing toluene containing a catalytic amount of PTSA, a crystalline Diels-Alder adduct 46 was obtained in 30-40% yield. The same product also resulted from a reaction between allyl chloride 45 and maleic anhydride in refluxing xylene solution.

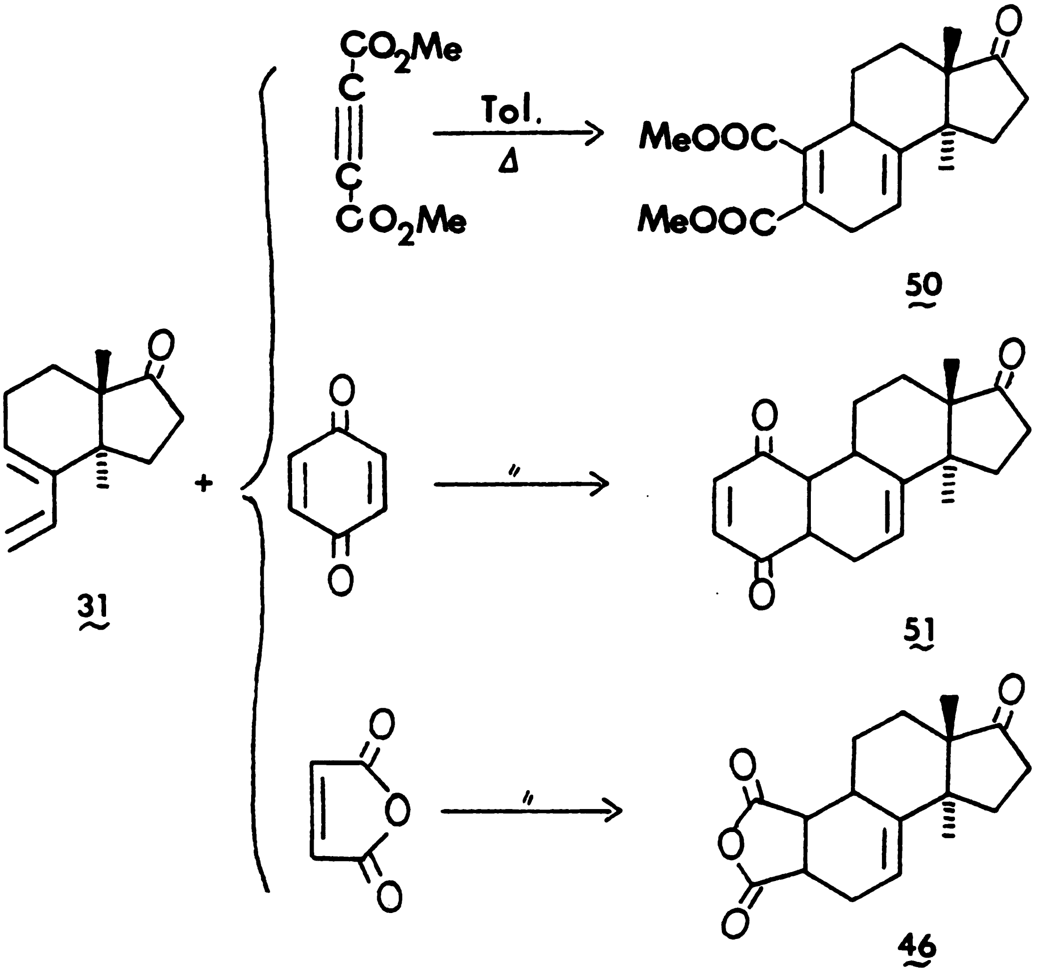


After considerable effort, a satisfactory procedure for preparing 31 from 32 was finally discovered. This involved treatment of 32 with boron trifluoride etherate in refluxing benzene-THF solution,[18b] followed by Kugelrohr distillation of the crude product to yield essentially pure cisoid diene 31 as a colorless low melting solid in 75-80% yield.

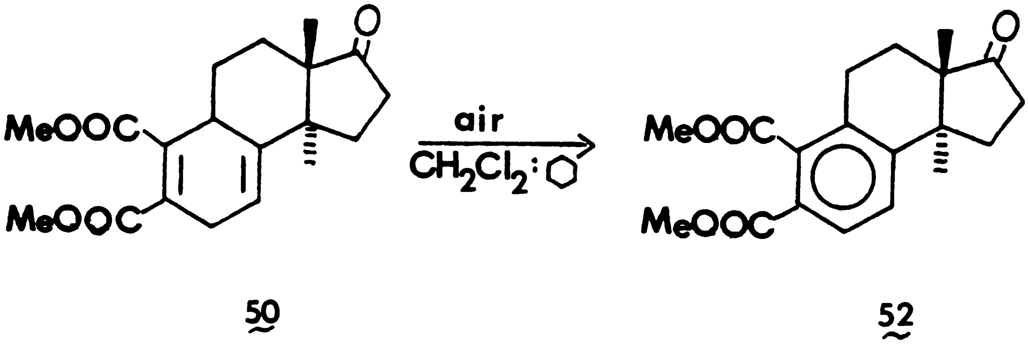


32 31

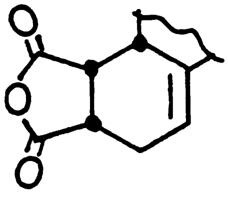
With the availability of cisoid diene 31 assured, a series of Diels-Alder reactions became the subject of study. Reactions of 31 with dienophiles, such as dimethyl acetylene dicarboxylate, p-benzoquinone and maleic anhydride, yielded cycloaddition adducts 50, 51 and 46.



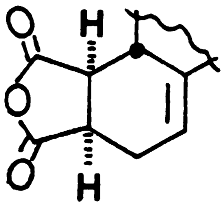
These crystalline adducts were obtained in about 45-65% yield as the only condensation products from the reactions. The diester adduct 50 was found to undergo facile air oxidation to the corresponding aromatized product 52.



Four diastereomeric structures are possible for the Diels-Alder adducts derived from the symmetrical dienephiles p-benzoquinone and maleic anhydride. These are α-endo **46**, α-exo **47**, β-endo **48**, and β-exo **49**, where α and β refer to the bottom and top side of the diene.



46



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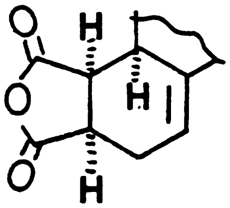
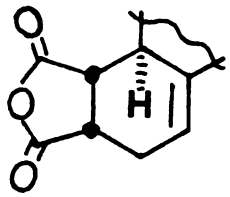


48



49

It is imperative to know which isomer if any is favored in the 4+2 cycloaddition reactions reported here. Accordingly, high-resolution pmr and ^{13}C nmr spectroscopic analyses were conducted for each adduct. In particular, adduct **46** has unique pmr spectroscopic characteristics (Figure 1) which provide key evidence for the assigned structure.

The spin-spin couplings of protons A through F with each other have been elucidated by inspection and decoupling measurements (Figure 2). Dreiding models of the four diastereomers of the maleic anhydride adduct were then examined to determine how well each fit with established geometrical relationships for these coupling constants.[36] The α-endo configuration shown in Figure 1 proved to have

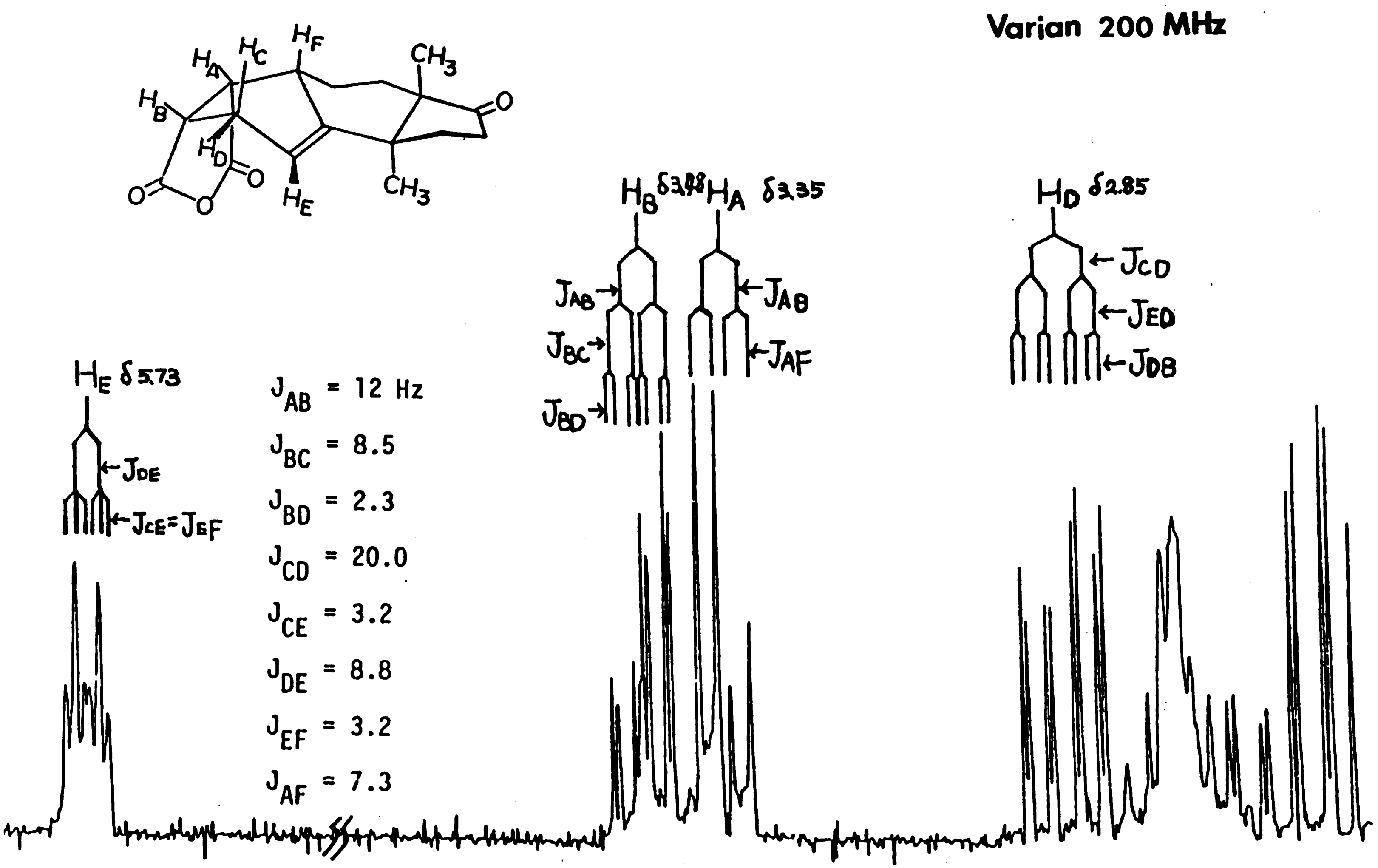


Figure 1. Conformational drawing and part of the pmr spectrum of adduct 46.

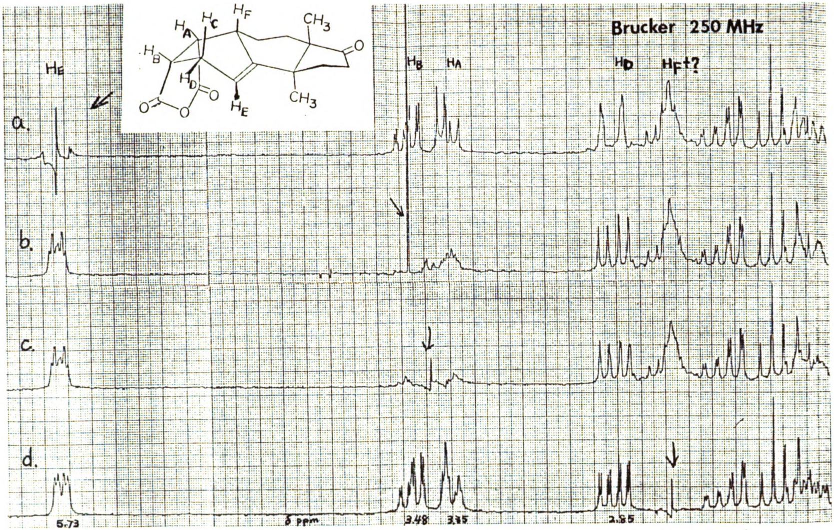
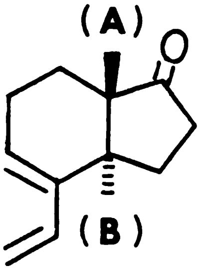


Figure 2. Spin-spin decoupling spectrum of 46.
a). Irradiation at H_E. b). Irradiation at H_B. c). Irradiation at H_B and H_A. d). Irradiation at H_F.

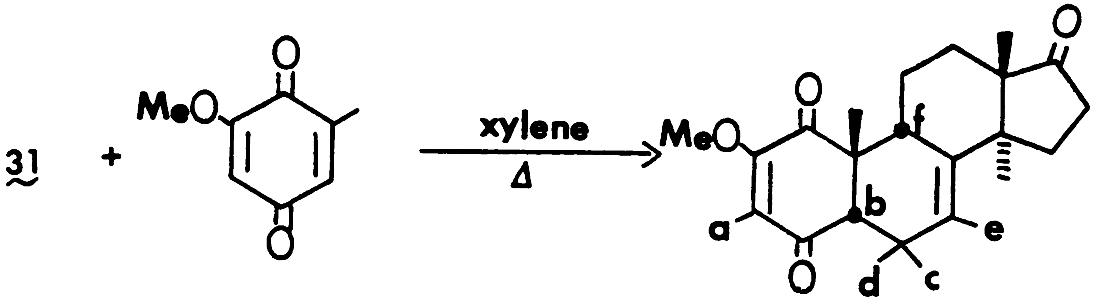
the best fit. Although quinone adduct 51 displayed fewer well-defined coupling patterns in its pmr spectrum, those that could be unambiguously assigned were also consistent with an α-endo configuration. Furthermore, X-ray diffraction studies of substituted quinone adducts (see below) confirm this assignment.

The α-endo configurations established for adducts 46, 51 and 54 raise a subtle but interesting paradox. According to Dreiding molecular models, the C ring of all α-endo adducts is constrained in a twist-boat conformation whereas that of the β-endo or exo adducts can have a more stable chair conformation. Therefore, α-adduct 46 should be thermodynamically unstable compared to the corresponding β-adduct 48. On the other hand, molecular models of diene 31 show that methyl (A) is tilted over the endocyclic double bond while methyl (B) is tilted back-away from it. This implies that the bottom (or α side) of the diene is less hindered than the top side, and that α addition should be favored. The exclusive formation of α-adducts from diene 31 suggests that "steric approach control" is a stronger factor in the course of these cycloaddition reactions than is product stability. However, Diels-Alder reactions of simpler, less polar reactants are known to have product-like transition states,[16] which favor the more stable cycloadducts. These conflicting results are probably due to a wide "spectrum" of Diels-Alder transition states.



31

When an unsymmetrical dienophile reacts with 31 the question of regioselectivity must be considered. Treatment of quinone 53[38] with 31 in refluxing xylene solution gave adduct 54 in 58% yield. The 250 MHz pmr spectrum of this sharp-melting compound suggested high regio- and stereoselectivity in this Diels-Alder reaction.

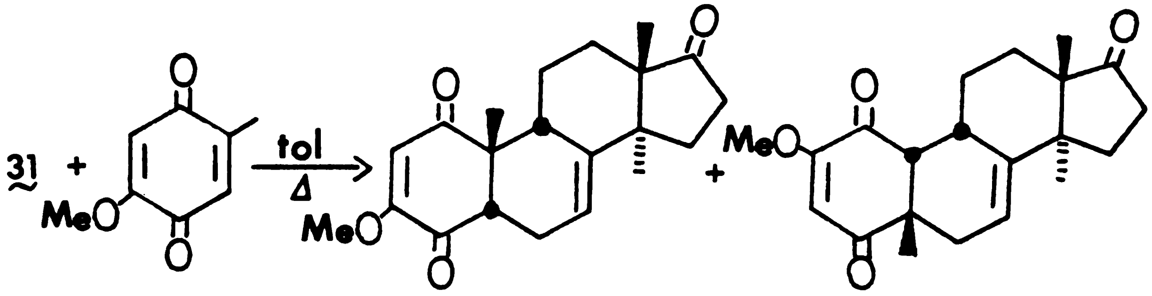


53 54

As expected from other cycloaddition reactions of 53, the angular methyl group and the terminal diene substituent were ortho to each other in the newly formed B ring. In the pmr spectrum of 54 a long range coupling between H_A

and H_B shows up as a δ 5.58 doublet (J=1.5 Hz) for the vinyl hydrogen H_A. A one proton quartet at δ 6.21 accounts for H_E, which is coupled with H_C, H_D and H_F ($J_{EC} \sim J_{ED} \sim J_{EF} \sim 2.7$ Hz). The similar magnitude of the coupling constants between J_{EC} and J_{ED} implies that the C-H_E bond bisects the dihedral angle of H_B-C-H_C. The structure of adduct 54 was firmly established by an X-ray diffraction analysis[39] which is summerized by the stereoscopic view shown in Figure 3.

Unlike the regioselective thermal cycloaddition of quinone 53 with 31, the isomeric quinone 55 showed poor selectivity in refluxing toluene solution. This reaction gave two isolable cycloadducts in a 2:1 ratio. The major adduct was identified as 56, and the minor adduct was its regioisomer 57.



55 56 57

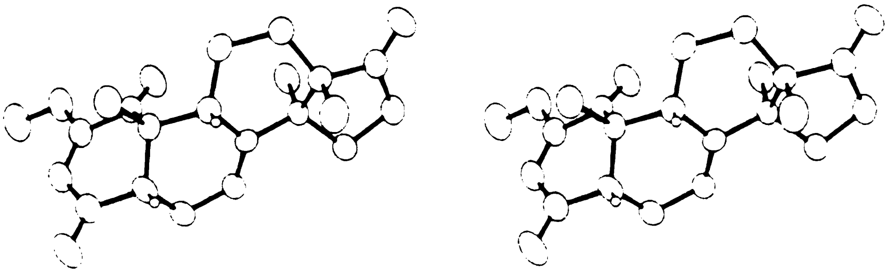
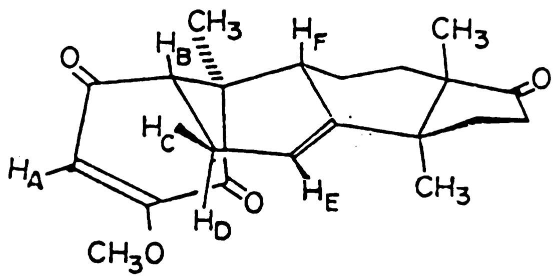


Figure 3. Stereodrawings illustrating adduct 54 as determined by X-ray analysis.

Except for the position of the methoxyl group, 56 is structurally very similar to 54. The pmr spectra of these two compounds reflect this similarity, the chief difference being that the long range coupling between H_A and H_B observed in 54 is no longer present in 56. The splitting patterns of H_B in adducts 54 and 56, as well as one of the decoupling experiments are shown in Figure 4. An X-ray diffraction study[39] of 56 confirms the assigned structure, a stereoscopic view of which is shown in Figure 5.

Adduct 57 displays a similar pmr signal for vinyl hydrogen H_E as do the isomeric adducts 54 and 56. Unfortunately, the bridgehead C-10 hydrogen and the C-6 methylene hydrogens in 57 are not well resolved. However, this structure was also established by an X-ray diffraction analysis,[39] and a stereoscopic view of the molecule is shown in Figure 6.

Both adducts 54 and 56 are potentially useful precursors for a total synthesis of tetracyclic triterpenes. In fact, adduct 56 is probably the better of the two for this purpose, but its usefulness is limited by the poor selectivity of the thermal cycloaddition of 55 and 31. It was thus necessary to develop reaction conditions which favor the selective formation of 56. To this end, Lewis acid-catalyzed low-temperature Diels-Alder reactions were explored. Most of the important selective catalytic effects that were discovered in this study will be described in part C of this dissertation, but two results



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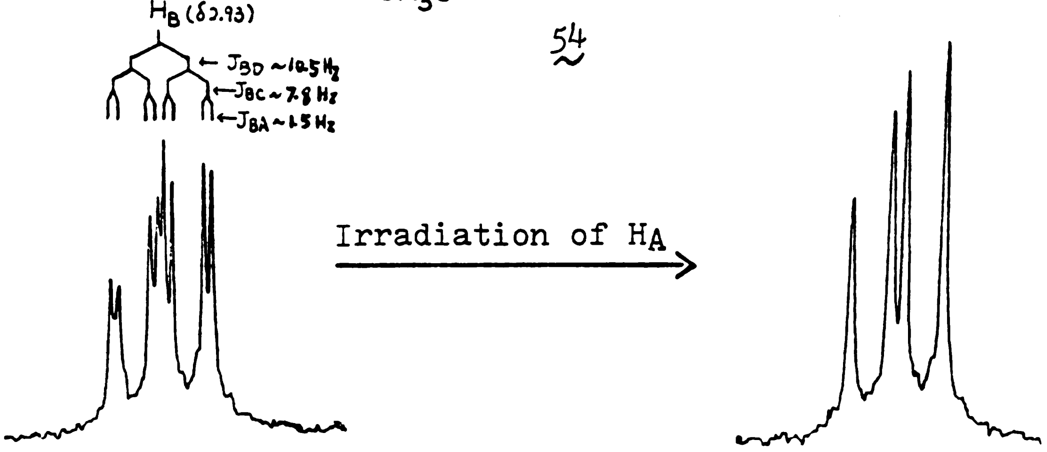

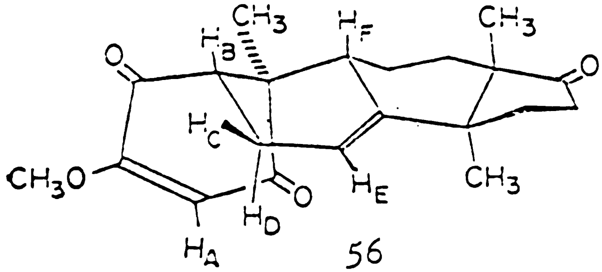

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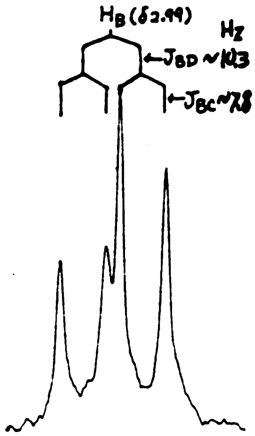


Figure 4. Coupling constants of H_B in the isomeric adducts 54 and 56.

a). Irradiation of H_A in 54 resulted in the collapse of the multiplet to a doublet of doublets.

b). A similar doublet of doublets is observed in 56, in which the long range coupling between H_A and H_B is not significant.

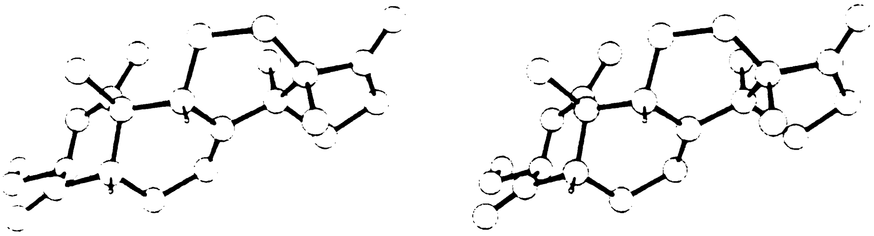


Figure 5. Stereodrawings illustrating adduct $\underset{\sim}{56}$ as determined by X-ray analysis.

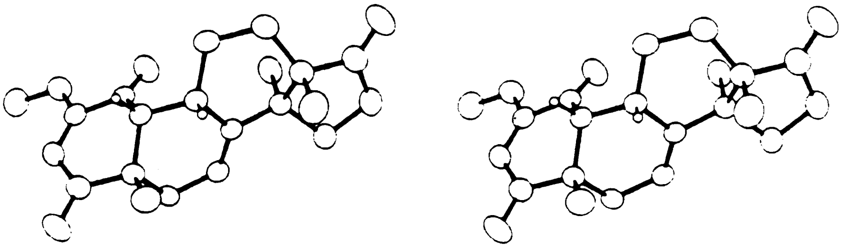
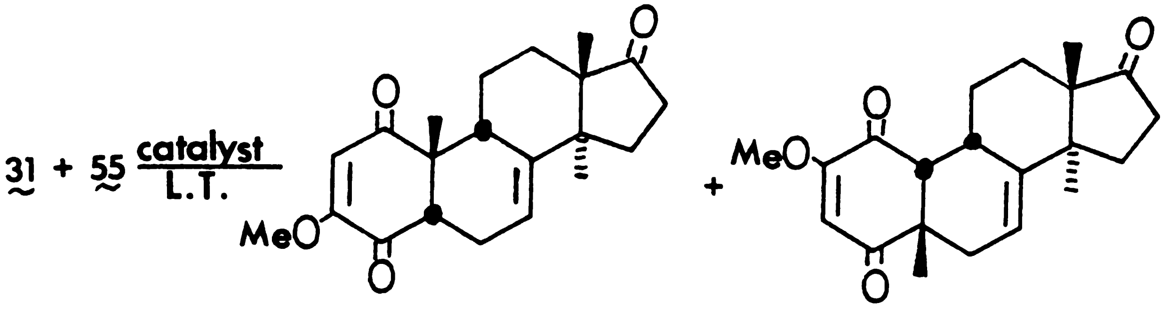


Figure 6. Stereodrawings illustrating adduct 57 as determined by X-ray analysis.

are of special interest.

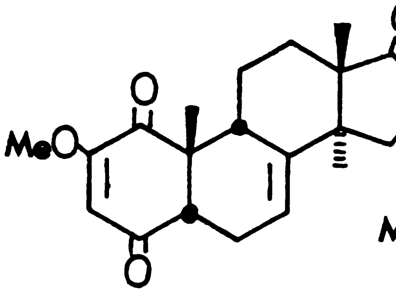
Addition of 55 to diene 31 in the presence of stannic chloride gave 57 as the only significant cycloadduct, based on high-resolution pmr and ^{13}C nmr analyses. Remarkably, the corresponding boron trifluoride catalyzed reaction gave a mixture of 56 and 57, in which the former predominated by 10:1. The minor isomer 57 can be easily removed by slow crystallization from methylene chloride-cyclohexane solution.



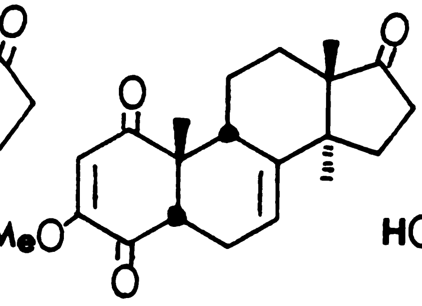
56 57

catalyst used:		56		57	
	$SnCl_4$,	<1	:	>99	74%
	BF_3/Et_2O,	10	:	1	55%

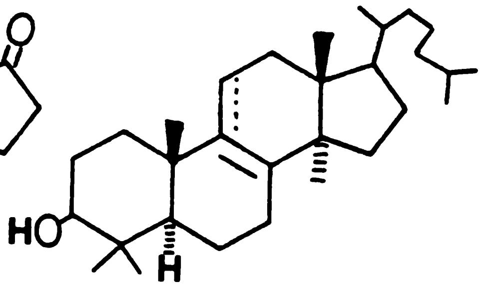
Thus, successful selective additions of quinones 53 and 55 with diene 31 not only produce the desired tetracyclic skeleton of the target molecule, but also introduce the necessary C-19 methyl group. The remaining stages of a triterpene synthesis can now be outlined. The configuration of 54 and 56 are clearly best suited to a synthesis of lanosterol or one of its olefinic isomers such as parkeol. The transformations required to accomplish this can be grouped into three operational categories. First, the isolated double bond must be shifted to the tetrasubstituted $\Delta^{8(9)}$ position so that the unnatural configuration at C-9 is eliminated. A necessary epimerization at C-5 might be effected at the same time. Second, the functionality in ring A must be changed to match that of lanosterol, and the gem-dimethyl groups at C-4 introduced. The well known Woodward[6] dimethylation procedure gives a Δ^{5}-unsaturated derivative that can be hydrogenated to the desired AB-trans system. Finally, the terpene side chain must be attached at C-17 in a stereospecific fashion.



54

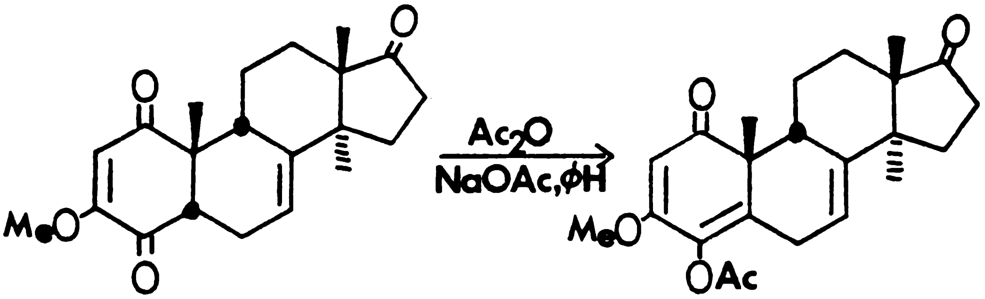


56



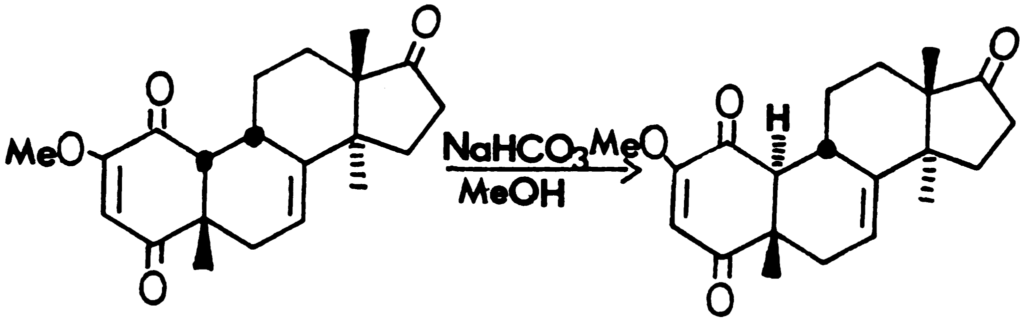
lanosterol
parkeol = $\Delta^{9(11)}$

Surprisingly, compound **56** was found to be resistant to either C-5 epimerization or double bond migration under both acidic and basic conditions, such as PTSA/benzene, Dowex 50-8/methanol,[40] sodium bicarbonate/methanol and sodium hydroxide/methanol. It should be noted that the C-4 carbonyl group of **56** is enolizable as evidenced from a trapping experiment which gave a selective monoacetate **58** in 71% yield.



56 **58**

Thus the reluctance of **56** to epimerize clearly indicates that a trans-fused AB ring junction is not favored compared to the cis-fused **56**. In contrast to this, regio isomer **57** was epimerized quite readily in sodium bicarbonate/methanol solution to yield **59**.



57 59

An examination of Dreiding molecular models of 56, 57 and their isomers 59, 60, 61 and 62 is helpful in explaining the difficulty encountered here (Figure 7). In all cases having a 9-β-hydrogen configuration, the C ring is always forced to be in a twist-boat conformation. The cis-syn conformation of 56 gives it a chair-like B ring. On the other hand, its C-5 epimer, 60, would be forced to have a boat-like B ring with H-9 and C-19 eclipsed. Therefore, compared to 56, structure 60 should be less stable, and the failure of 56 to epimerize is understandable. Both compound 57 and its C-10 epimer 59 have chair-like conformations of the B ring; however, the A ring is fused in a diequatorial fashion in 59 instead of the equatorial-axial fashion found in 57. This accounts for the successful transformation of 57 to 59. It is also expected from conformational analysis that structure 62 would be more stable than 61 for similar reasons.

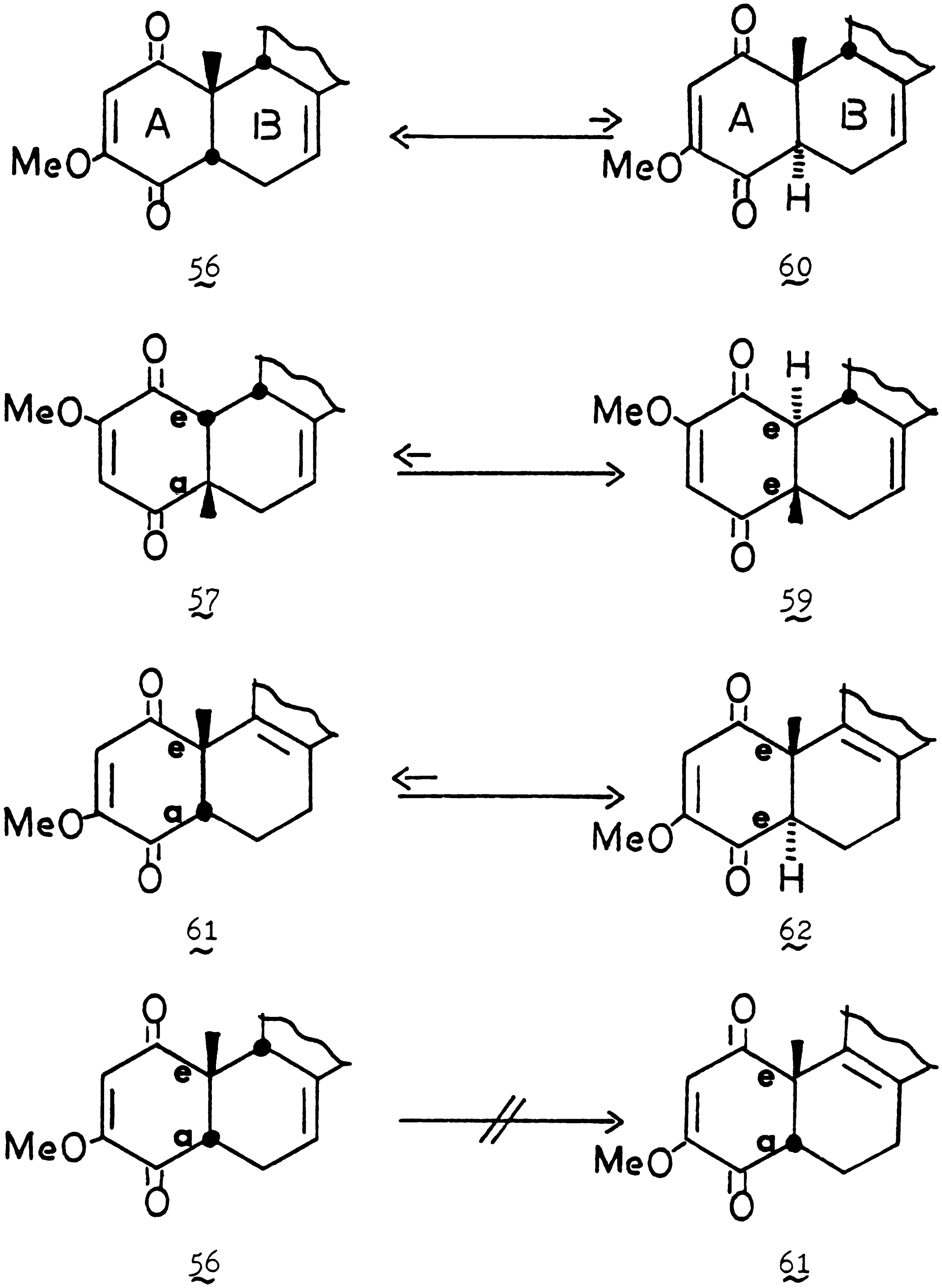
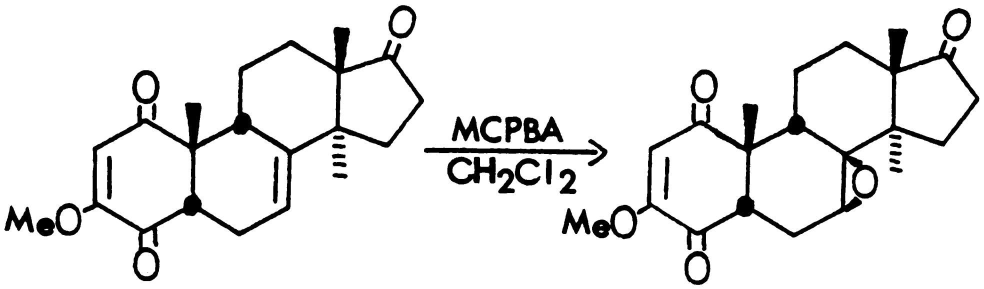


Figure 7. The stabilities between the two Diels-Alder adducts 56/57 and the corresponding isomers 60, 61, 59 and 62, as predicted by Dreiding molecular models.

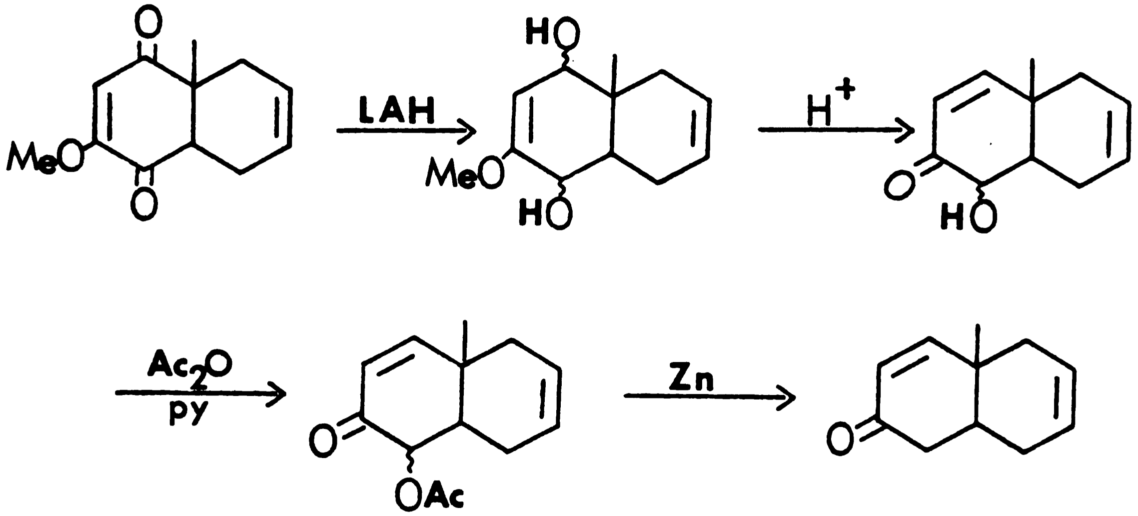
This conformational analysis suggests that a shift of the Δ^7 double bond to Δ^8 should facilitate subsequent epimerization at C-5 to give compound 62. Since the Δ^7 double bond in 56 proved to be stable under both acidic and basic conditions, an alternative means of transforming this function was examined. Treatment of 56 with m-chloroperbenzoic acid in methylene chloride yielded a homogeneous product in quantitative yield. A rigorous assignment of the stereochemistry of the epoxide ring is not possible from the high-resolution nmr; however, a doublet of doublets (J=11.9 and 5.2 Hz) at δ 2.83 suggests a beta-epoxide orientation, as in 63. Compound 63 is a potentially useful intermediate which may lead both to the formation of a Δ^8 double bond and epimerization at C-5.



56

63

In subsequent elaboration of ring A functionality, a conversion of the enedione moiety to a 3β-OH and introduction of a C-4 gem-dimethyl system are necessary. There are similar transformations of this type in the literature,[41,42,43] and the most attractive of these is that used by Woodward in his cholesterol synthesis, illustrated below:

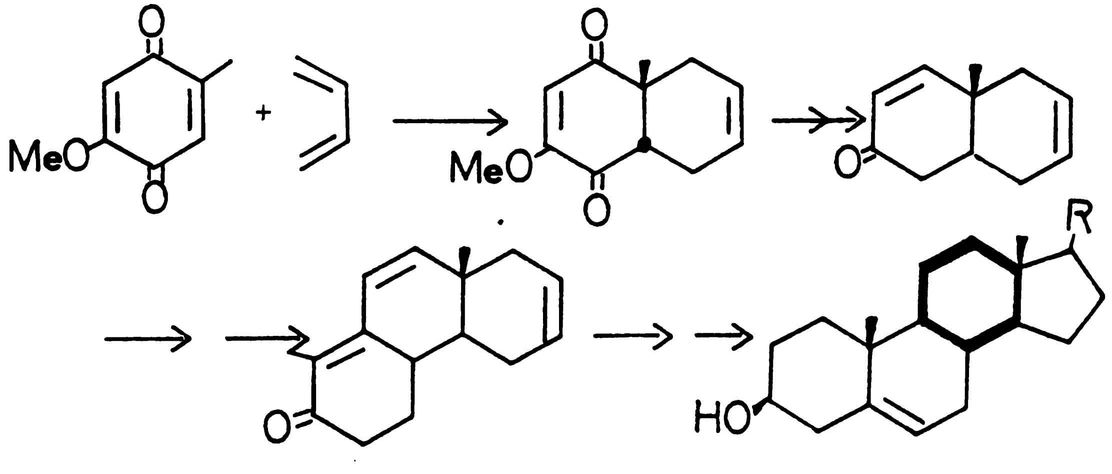


C. Selective Catalysis of Diels-Alder Reactions of 2-methoxy-5-methyl-1,4-benzoquinone[44]

The Diels-Alder reaction has been used extensively for the formation of six-membered rings.[16] Because of its directness, it is frequently one of the most important steps in the synthesis of fused ring structures, including many natural products. Many dienophiles have been used effectively in these reactions, but derivatives of p-benzoquinone offer special interest and advantage because of their high degree of functionalization. This is convincingly demonstrated by reported syntheses of steroids,[18,41] gibberellic acid,[43] dendrobine,[45] reserpine[46] and trichodermol,[47] excerpts from which are shown in schemes I-VI.

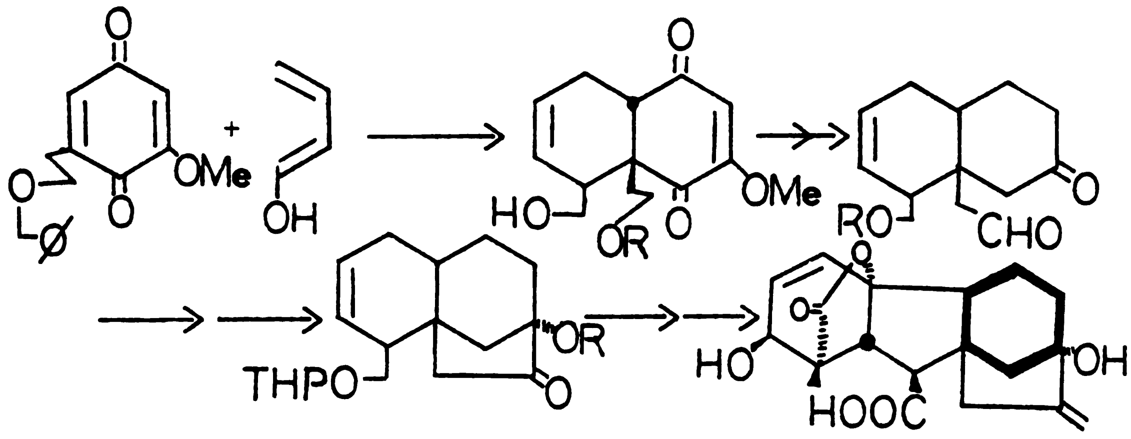
One advantage to using quinone dienophiles in total synthesis is the stereospecific construction of a cis configuration in the newly formed ring junction. When a trans ring-fusion is required, a subsequent epimerization can be carried out because of the adjacent carbonyl functions (Schemes I and V). Furthermore, the quinone moiety is highly functionalized and can be elaborated in

Scheme I.[41]



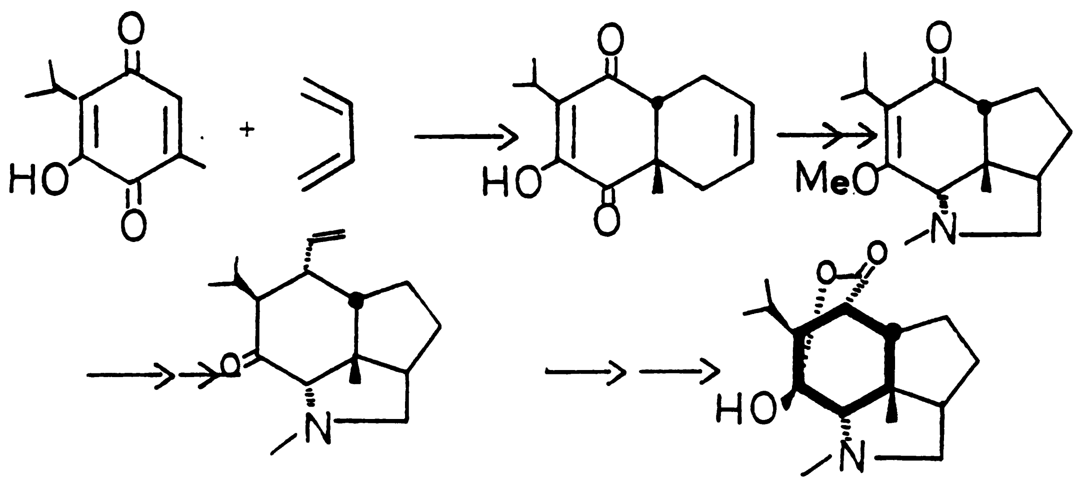
Cholesterol (1953)

Scheme II.[43]



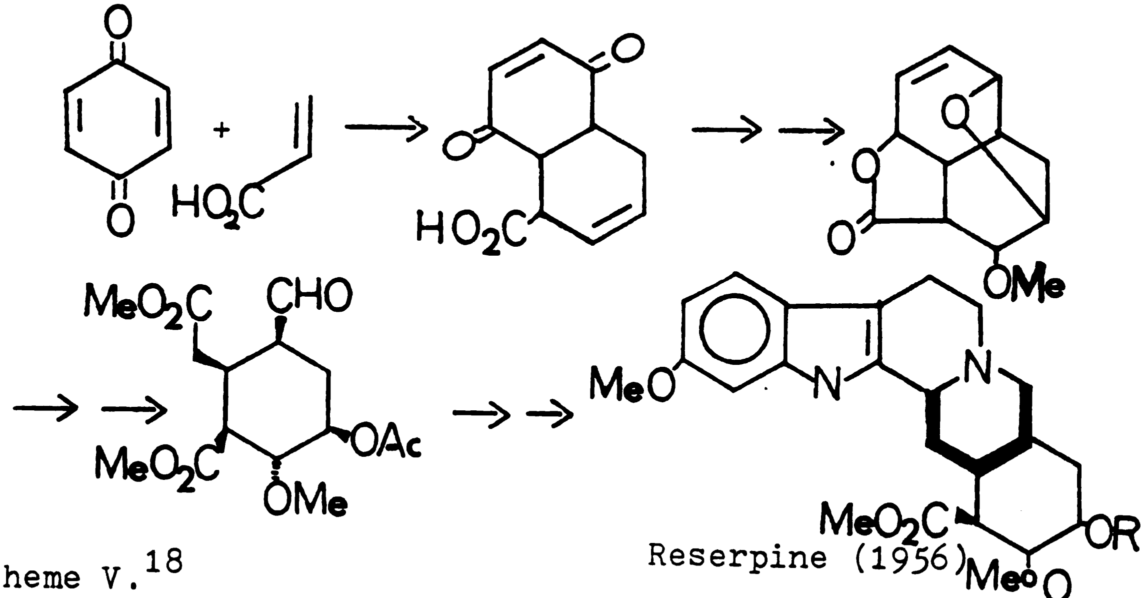
Gibberellic acid (1978)

Scheme III.[45]



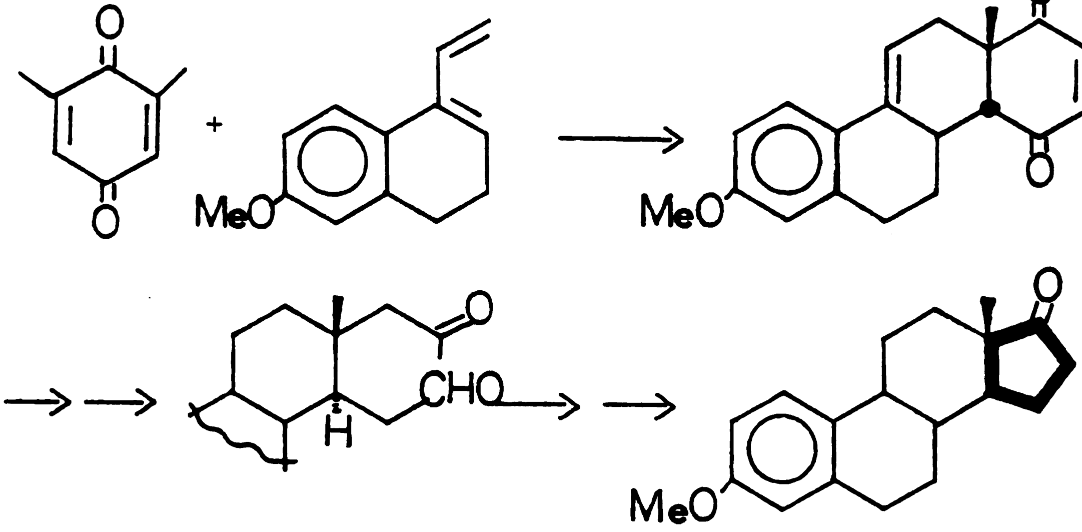
Dendrobium (1974)

Scheme IV.[46]



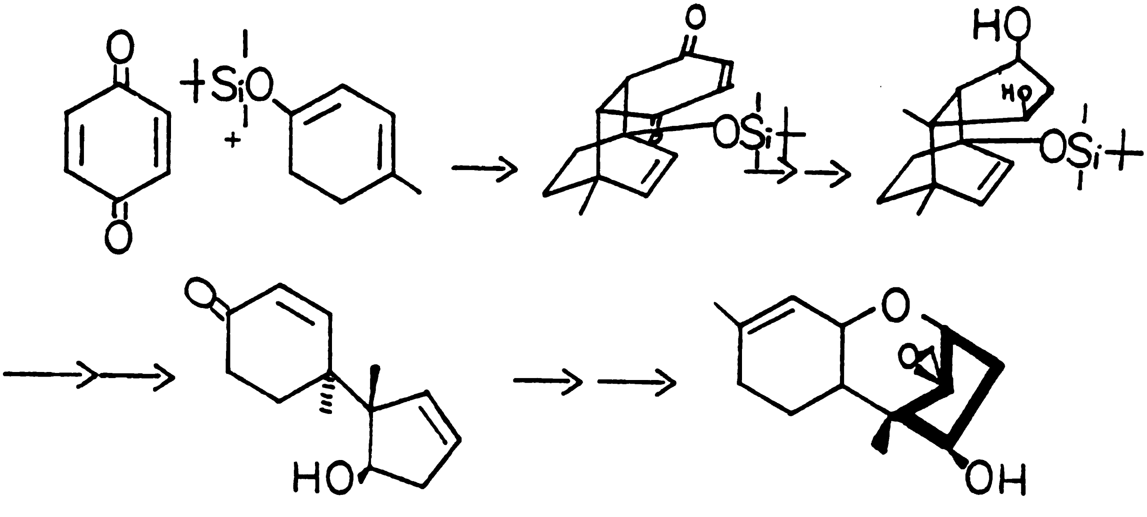
Reserpine (1956)

Scheme V.[18]



Estrone methylether (1972)

Scheme VI.[47]



Trichodermol (1980)

many ways (Schemes I-VI). In Schemes I, II and III, the quinone ring remains intact throughout the entire reaction sequence and becomes part of the target molecule. Woodward's reserpine synthesis (Scheme IV) provides an interesting example in which the quinone ring first served as a handle for stereochemical control of sites on the neighboring cyclohexane ring, following which it was cleaved and eventually became part of a piperidine ring. The formation of a five-membered carbocyclic system from the quinone ring can be effected by the strategies shown in Valenta's steroid (Scheme V) and Still's trichodermol (Scheme VI) syntheses. It is also interesting to note that in Kende's dendrobine synthesis (Scheme III), six of the seven asymmetric centers are precisely created on a cyclohexane ring which is derived from the starting quinone.

When substituted p-benzoquinones serve as dienophilies with unsymmetrical dienes, four regio-isomers are possible. As shown in Figure 8a, the diene can approach from side A or B to give two isomeric adducts. Furthermore, two different diene orientations, C and D, are possible at each side as shown in Figure 8b.

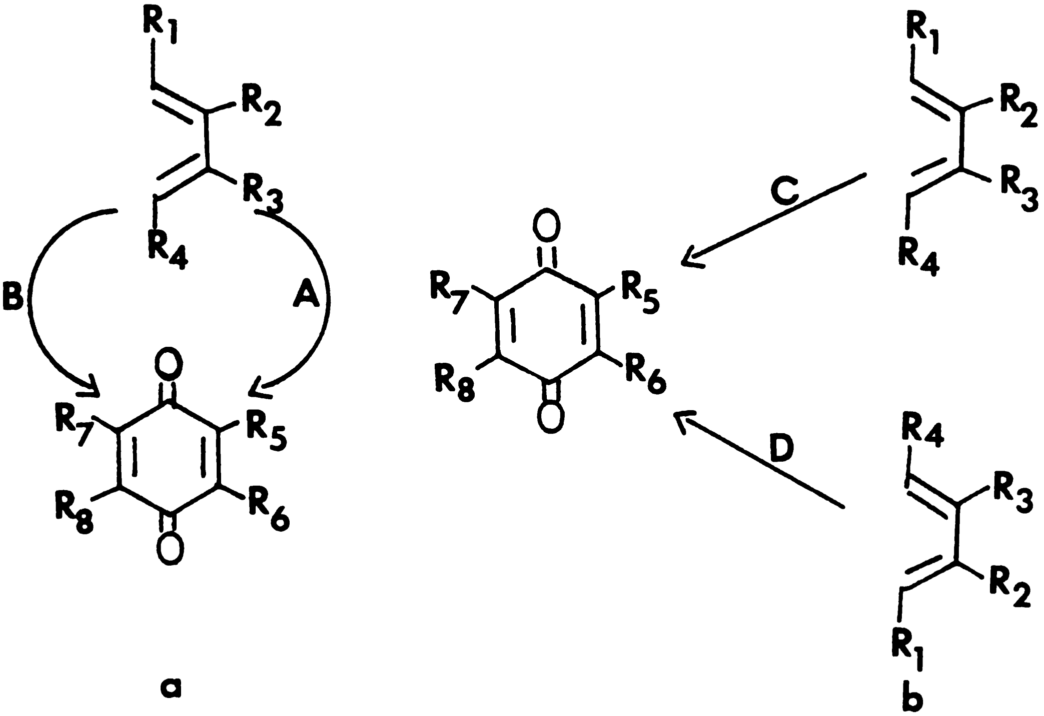


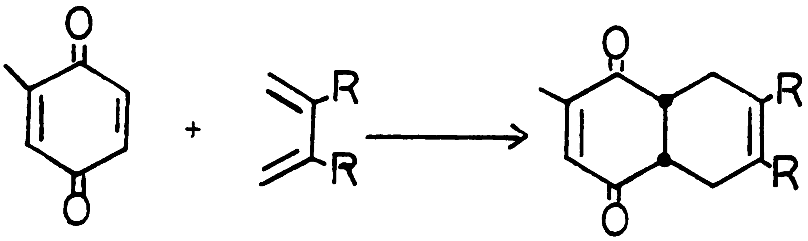
Figure 8. Different approaches of diene to a p-benzoquinone.

Several important directing effects concerning p-benzoquinone Diels-Alder reactions have been noted in the literature:

a) Electron donating substituents on the quinone deactivate the double bond to which they are attached ($OCH_3 > CH_3 > H > COOR$). Examples are shown in equations 1, 2 and 5-7.

b) Substituents on the dienophilic double bond usually direct addition reactions with

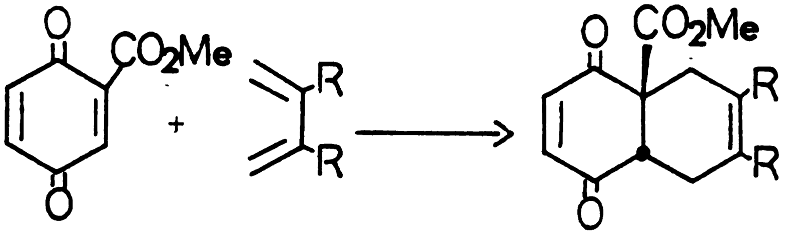
1[48]



R=H 65%

R=CH_3 61%

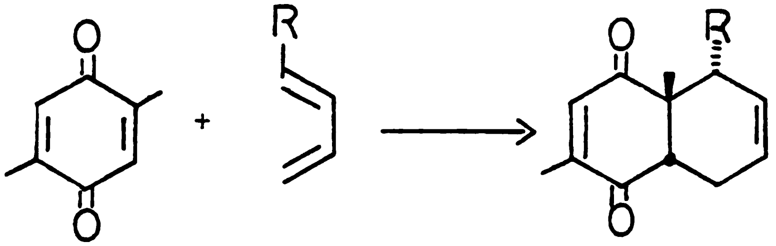
2[48]



R=H 60%

R=CH_3 95%

3[49]

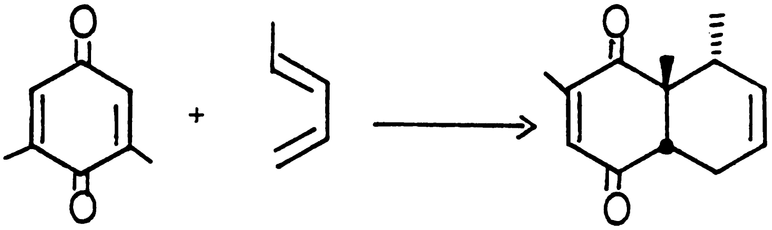


R=H (major)

R=CH_2OAc 80%

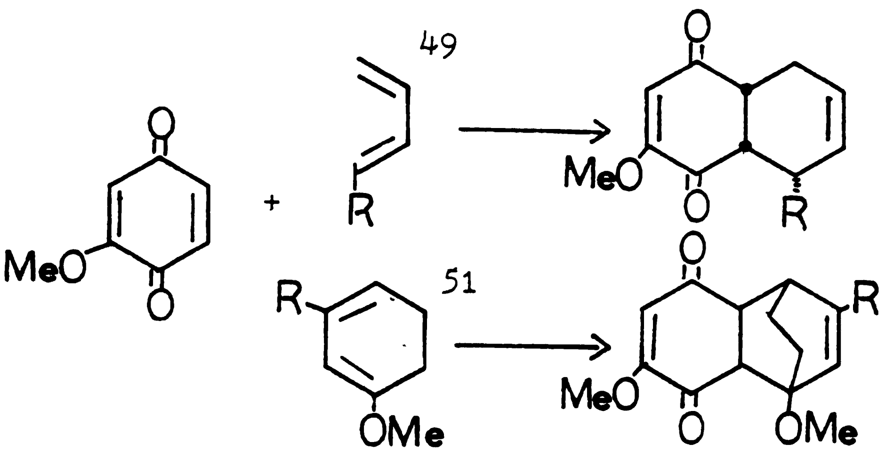
R=$COOCH_3$ 55%

4[50]



85%

5



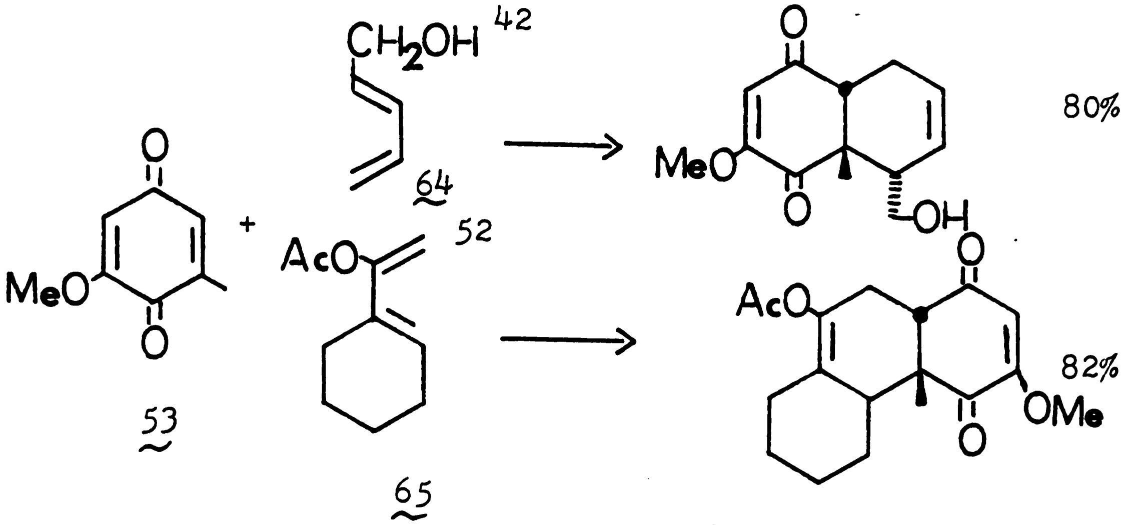
R=CH_3 85%

R=CH_2OAc 85%

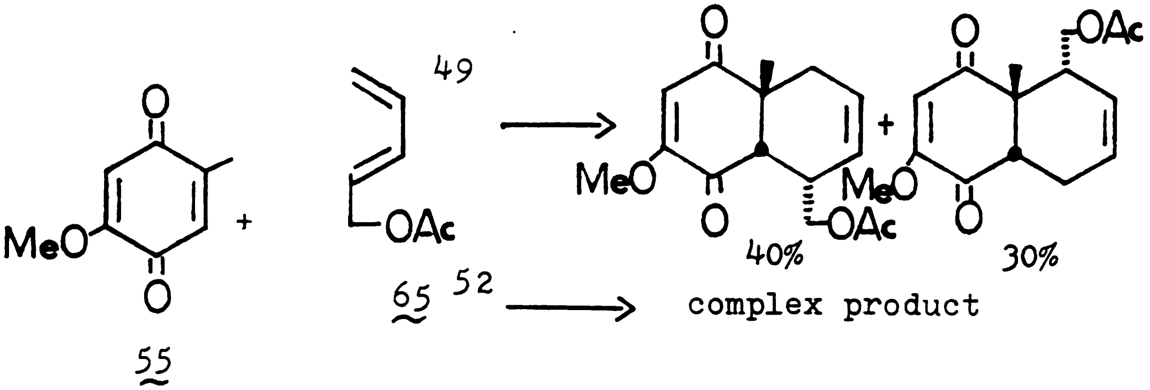
R=H, CH_3 60%

(no isomer)

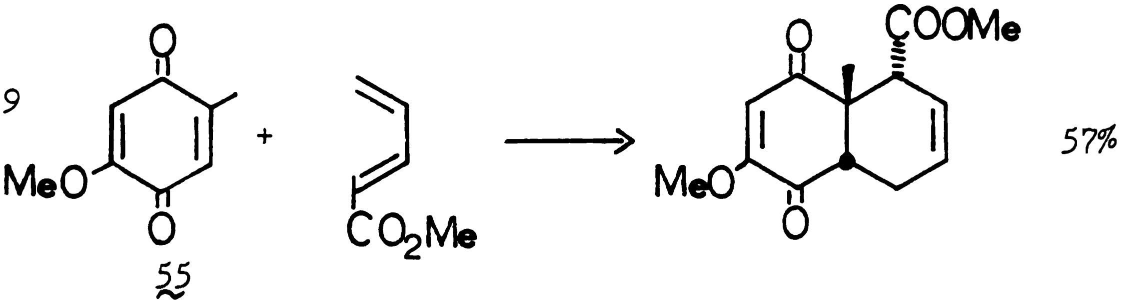
6



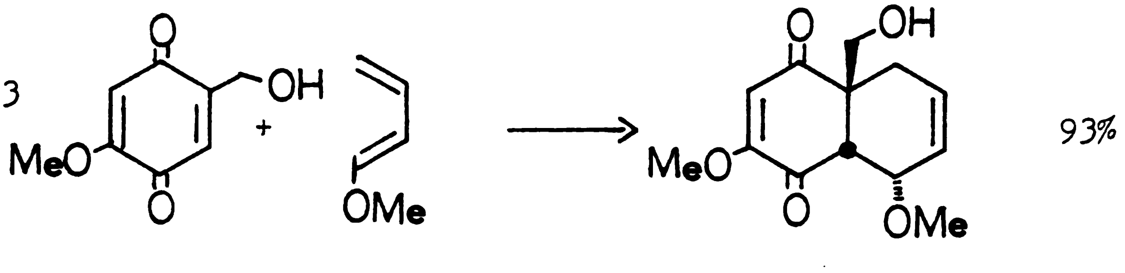
7



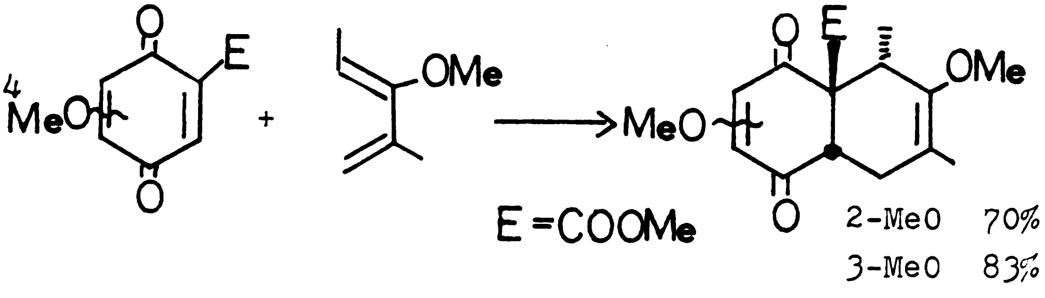
8[49]



9[53]



10[54]



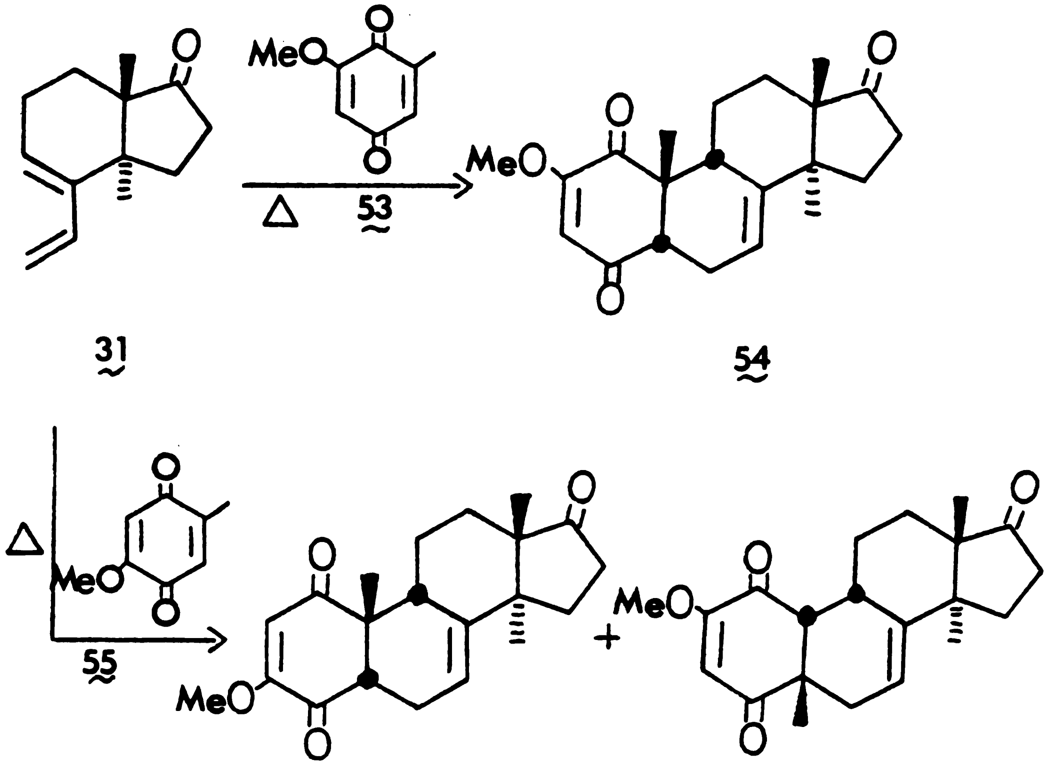
1-substituted dienes to give ortho adducts (Equations 3 and 4) and additions with 2-substituted dienes to the para adducts.[55]

c) A remote methoxy substituent exerts a strong influence on the orientation of addition reactions at the double bond on the other side of the quinone (Equation 5).

As shown in equation 5, the predominate adduct from reaction of methoxy 1,4-benzoquinone with 1-substituted dienes is that in which the diene substituent is adjacent to the ketone-like carbonyl group. The same orientation was observed in the reaction of 2-methoxy-6-methyl-p-benzoquinone 53 with dienes 64 and 65 (Equation 6). It should be noted that in these cases directing effect (b) acts in concert with effect (c) to give the observed ortho adduct. However in 2-methoxy-5-methyl-p-benzoquinone 55, directing effects (b) and (c) are opposed to each other, and the observed selectivities in these reactions are found to be very poor (Equation 7). This lack of specificity can be tipped in favor of the ortho adduct by replacing the 1-alkyl substituent on the diene with an electron withdrawing group (e.g. $COOCH_3$), as shown in Equation 8, or in favor of the meta adduct by replacement with an electron donating group (e.g. OCH_3 in Equation 9). In fact, the influence of the methoxy substituent on the orientation of cycloaddition reactions seems to be negligable if a strong electron withdrawing group (e.g.

$COOCH_3$) is located on the reactive double bond of the quinone. Examples are shown in Equation 10.

In the course of studies toward a total synthesis of tetracyclic triterpenes, efforts were made to attach a potential AB ring fragment to CD moiety 31 via a Diels-Alder reaction (see Part B in this dissertation). As suggested by the previous work, quinone 55 was observed to undergo thermal cycloaddition with the bicyclic diene 31 to give a 2:1 mixture of adducts 56 and 57 in approximately a 34% isolated yield. In contrast, 31 reacted with quinone 53 under similar conditions to afford 54 as the only detectable adduct in over 55% yield.



31

54

56

57

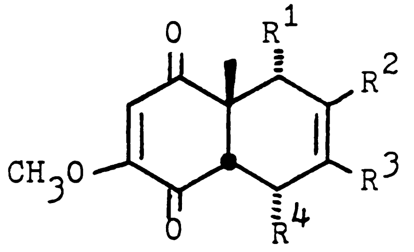
The poor regioselectivity of Diels-Alder reactions of **55** with diene **31** can be changed to favor either isomeric adduct by using appropriate Lewis acid catalysts. Thus mixtures of the two regioisomers **56** and **57** were obtained from aluminum chloride catalyzed reactions of **31** and **55** at -78°C. The composition of these mixtures varied as the amount of aluminum chloride catalyst was changed. In general, when a 1:2 ratio of $AlCl_3$: quinone was used, **56** was the favored adduct. As the amount of catalyst increased, adduct **57** was found to be enriched. In the case of a 2:1 ratio of catalyst: quinone, adduct **57** was the major component in a 5:1 mixture with the other isomer (Table 1).

Table 1. Aluminum chloride catalyzed Diels-Alder reactionsof **55** with **31**.

$AlCl_3$	Quinone **55**	product ratio **56**:**57**
0.4	1	2:1
0.8	1	3:2
1.2	1	1:2
2.0	1	1:5

A dramatic improvement in selectivity was observed when stannic chloride and boron trifluoride were used as catalysts. For example, reaction of 31 and 55 in methylene chloride solution at $0^{o}C$ with stannic chloride as a catalyst (1:1 catalyst:quinone), yielded adduct 57 in over 75% yield. None of the known regio- or stereo-isomers of 57 was detected in this reaction by pmr analysis. On the other hand, the corresponding boron trifluoride catalyzed reaction at $-16^{o}C$ gave a 50-55% isolated yield of 56, contaminated by no more than 10% of 57.

These studies were then extended to similar reactions of 55 with piperylene and isoprene. Thermal cycloaddition reactions of quinone 55 to piperylene and isoprene were generally found to give a mixture of two regioisomeric adducts in about 1:1 ratio. In contrast, stannic chloride catalysis of reactions of 55 with piperylene and isoprene gave mainly the meta adducts (66 and 69 respectively), while the boron trifluoride catalyzed reactions favored the ortho/para adducts (67 and 68). The results are shown in Tables 2 and 3.



66, $R^4=CH_3$; $R^{2,3,1}=H$
67, $R^1=CH_3$; $R^{4,2,3}=H$
68, $R^3=CH_3$; $R^{1,2,4}=H$
69, $R^2=CH_3$; $R^{1,3,4}=H$

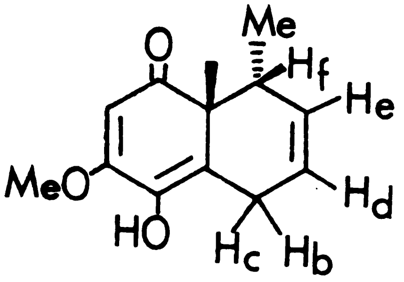
Table 2. Diels-Alder Reactions of **55** with Piperylene

	Thermal(100°)	$SnCl_4$(-16°)	BF_3(-16°)
Ratio **67**:**66**	1:1	1:20	4:1
Yield (%)	80	85	85

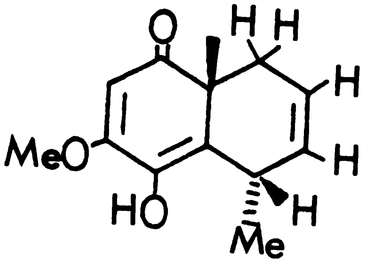
Table 3. Diels-Alder Reactions of **55** with Isoprene

	Thermal(100°)	$SnCl_4$(-16°)	BF_3(0°)
Ratio **68**:**69**	1:1	1:20	2.4:1
Yield (%)	70	80	70

In the stannic chloride catalyzed piperylene Diels-Alder reaction, the meta adduct **66** was isolated as a solid (mp 70-73°) with a pmr spectrum identical to that reported by Bohlmann and coworkers.[49] The meta orientation was clearly indicated by the presence of a one proton doublet at δ 2.99 (J=5.5 Hz) in the pmr spectrum. This doublet is assigned to the bridgehead hydrogen which is split by the adjacent methine hydrogen. Mixtures of isomers **66** and **67** are difficult to separate, and are best analyzed by a combination of gas chromatogrophy, ^{1}H pmr and ^{13}C nmr. A pure sample of **67** was not obtained. However, when the mixture of **66** and **67** was left standing at room temperature for several days, a new compound slowly crystallized. This isomeric material was then identified as **70**, an enol form of **67**. A possible regio isomer **71** was excluded, based on the pmr signals of the double-allylic protons H_c and H_b at δ2.76 and δ3.40 respectively, and a quintet from the allylic proton H_f, appearing at higher field (δ2.59). The presence of a hydroxyl group was clearly indicated by its facile exchange with D_2O, and infrared spectroscopy ($\tilde{\nu}_{OH}$ 3300 cm^{-1}). An absorption at λ_{max}340 nm (ethanol) (ϵ=3300) in the UV is consistent with the presence of a dienone moiety. The assignment of structure **70** was confirmed by a series of decoupling experiments. This unusual tautomerization, **67**→**70**, which has not been observed in any of the other similar cases, may be due to interaction between the methyl groups.



70

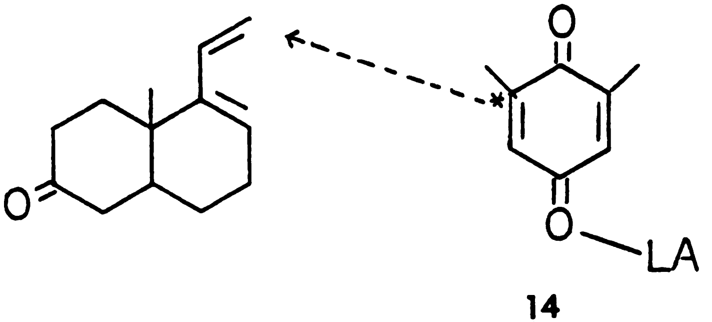


71

Our assignment of 67 as the major component of the boron trifluoride catalyzed piperylene Diels-Alder reaction is based primarily on its conversion to enol 70.

The assignments of the isoprene Diels-Alder adducts 68 and 69 are not obvious from spectroscopy, because of their structural similarity. However, 69 isolated from the stannic chloride catalyzed reaction proved to be a solid having an identical melting point (116-118°) to that reported by Ayer and coworkers.[56] These workers claim that the thermal cycloaddition of isoprene with 55 gives pure 69, in contradiction to the findings reported here, as well as an unpublished study by W. S. Knowles.[57a] The product obtained by Ayer et. al. was well-characterized by their degradative work, and this is the basis for our structure assignment. A possible explaination for their contradictory result is that a metal ion catalyst may inadvertently have been incorporated in their experiments. In such an event 69 might well be the only product isolated, as in the stannic chloride catalyzed reaction reported here. One possible source for such metal ion contamination may be the preparation of quinone 55 by the method of Ashley,[38] which gives a product containing zinc salts that are difficult to remove.[41] The major component 68 from the boron trifluoride catalyzed reaction of 55 and isoprene was isolated via recrystallization from an ethyl acetate: pet ether solution. The melting point of 68 (87-89°) agrees well with that reported by Woodward.[57b]

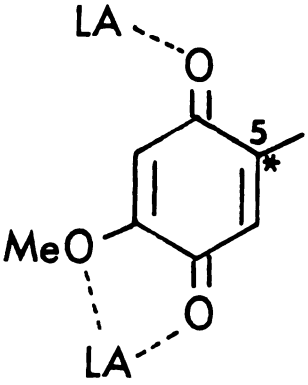
It is well known that Lewis acid catalysts have a profound influence on the rate of Diels-Alder reactions.[58] However, the fact that they can change the regio chemistry of these reactions was not known until the work of E. Valenta and coworkers[18] appreared in 1972. Valenta reported an efficient regio-reversal in reactions of 2,6-dimethyl-p-benzoquinone 14 with various dienes in the presence of Lewis acid catalysts. The exclusive formation of the "abnormal" (non-thermal) isomer was rationalized by a specific coordination of the Lewis acid with one of the carbonyl groups of 14 to give a reactive quinone-Lewis acid complex. The complexed quinone is assumed to have a different electronic distribution than the uncomplexed quinone, and this is believed to be responsible for the orientation reversal effect (Figure 9).[59]



14

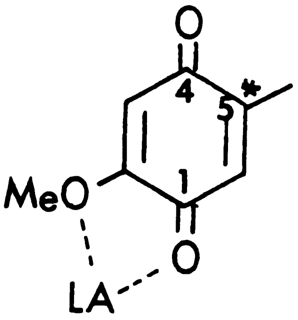
Figure 9. The proposed quinone-Lewis acid complex and its regio-reversal addition to a substituted diene.

The present studies of 2-methoxy-5-methyl-p-benzoquinone **55** provide more evidence for a selective complexation of Lewis acids with unsymmetrical quinones. The aluminum chloride-catalyzed experiments show that the regioselectivity is dependent upon the amount of Lewis acid used. A possible explaination assumes that both bis- and mono-complexs were formed between **55** and aluminum chloride. When two equivalents of aluminum chloride were used, the bis-complexed species I predominates and the activation at C-5 dominates the directing effects, thus giving the meta-oriented adduct.

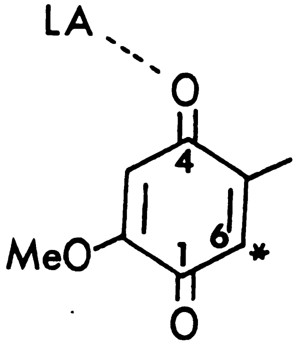


I

When a 1:1 ratio of quinone: Lewis acid was used, selective complexation may occur. There are two types of mono-complexation that should enhance Diels-Alder reactions. First, the Lewis acid may complex at the C-1 carbonyl group, in which case stabilization by chelation would be possible, as shown in II. Second, the Lewis acid may complex to the more basic ester-like C-4 carbonyl group as in III. Complexes in which the Lewis acid moiety is syn to the dienophilic double bond are not considered because of their steric hinderance to the Diels-Alder reaction.



II



III

In those reactions using one equivalent of boron trifluoride or aluminum chloride catalysts, the type III complex will be favored because of the poor chelating ability of boron and aluminum. The activation of C-6 in these complexes accounts for the formation of ortho- or para- cycloadducts in the Diels-Alder reactions. On the other hand, catalysts that have strong chelating tendencies (e.g., stannic chloride and titanium chloride[60]) tend to form type II complexes, which activate C-5. Consequently, the meta-oriented cycloadducts will be favored.

EXPERIMENTAL

General

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

Analysis by GLPC was conducted with A-90-P3 or 1200 Varian-Aerograph instruments. Preparative layer chromatography was carried out on 2 mm silica gel F-254 adsorbent on 20 X 20 cm glass plates. Visualization of the preparative plates was effected by ultraviolet light and/or charring with a hot wire. Melting points were determined on either a Hoover-Thomas apparatus (capillary tube) or on a Reichert hot-stage microscope and are uncorrected. Infrared spectra (IR) were recorded on a Perkin-Elmer 237B grating spectrophotometer. Proton magnetic resonance spectra (PMR) were taken in deuterochloroform or CCl_4 solutions with either a Varian T-60, a Bruker 180 MHz or a Bruker 250 MHz spectrometer and are calibrated in parts per million (δ) downfield from tetramethylsilane as an internal standard. Ultraviolet spectra (UV) were recorded on a Unicam SP-800 spectrophotometer. Mass spectra (MS) were obtained with either a Hitachi RMU 6 mass spectrometer or a Finnigan 4,000 GC/MS spectrometer. Carbon magnetic resonance spectra (CMR) were taken in deuterochloroform solution with a Varian CFT-20 spectrometer and are calibrated in parts per million (δ) downfield from tetramethylsilane as an internal standard.

Microanalyses were performed by Spang Microanalytical Labs, Ann Arbor, Michigan, and Guelph Chemical Laboratories Ltd., Guelph, Ontario, Canada.

Preparation of Bis-tosylhydrazone **19** and mono-tosylhydrazone **20**.

In a 50-mL flask, tosylhydrazine, 0.744 g (0.004 mol), was dissolved in a minimum amount of ethanol containing 2 drops of concentrated HCl on steam bath. After the mixture was cooled to room temperature, the diketone **6** (0.18 g, 0.001 mol) was added in one portion. The reaction mixture was then refluxed for 3 h. After cooling in the refrigerator, the white fine precipitate was filtered, giving 0.34 g (66%) of the bis-adduct **19**, which displayed the following properties: mp 233-235°C (dec); IR (Nujol) 3200, 1590, 1160 cm^{-1}; PMR (CF_3COOH) δ 0.85-0.9 (2s, 6H), 2.02 (s, 6H) 1.2-3.2 (m, 12H), 6.8-7.4 (q, 8H); MS (70 eV) (rel intensity) m/e CI, 517 (M+1) (3), 361 (9), 343 (8), 173 (14), 157 (100), 139 (36), 93 (25).

If 1.2 equiv of tosylhydrazine was used, the mono-adduct **20** was obtained in 78% yield: mp 180-182°C; IR (Nujol) 3180, 1730, 1610, 1590, 1160 cm^{-1}; PMR ($CDCl_3$) 180 MHz, δ 0.7 (s, 3H), 1.0 (s, 3H), 2.4 (s, 3H), 1.3-2.4 (m, 10H), 6.8-7.9 (m, 5H); MS (70 eV) (rel intensity) m/e 348 (3), 193 (46), 163 (25), 135 (20), 122 (100), 107 (25), 93 (9).

Preparation of bissilyl ether **22** and monosilyl ether **24**.

A solution of LDA was prepared by reacting 0.61 mL (4.4 mmol) of diisopropylamine in 10 mL of dry THF with 1.74 mL of 2.42 M n-butyllithium in hexane for 20 min at

-78°C. To this was added a solution of 0.36 g (2 mmol) of dione **6** in 10 mL of THF, and the resulting cloudy mixture was warmed to 0°C following the addition of 0.5 mL of HMPA (hexamethylphosphoric triamide). After this enolate solution was quenched with tert-butyldimethylchlorosilane (0.63 g in 5 mL of THF), the resulting mixture was warmed to room temperature and worked up by addition to ice water and extraction with ether. The combined ether extracts were washed and dried before removal of the solvent. The resulting yellow oil was purified by distillation (110°C, 10^{-3} torr), yielding 0.69 g (85%) of a low-melting solid. Analysis of this product by GLC (4% QF-1, 180°C) and TLC showed it to be chiefly the bis adduct **22**, containing ca. 2% of the mono adduct **24**. A sample of **22** obtained by GLC (5% PDEAS, 160°C) had the following properties: mp 57-59°C; IR (CCl_4) 1645 and 1620 cm^{-1}; PMR (CCl_4) δ 0.15 (s, 12H), 0.9 (br s, 21H), 1.15 (s, 3H), 1.2-2.6 (m, 6H), 4.2 (m, 2H); MS (70 eV), m/e (rel intensity) 408 (12), 393 (11), 351 (6), 277 (11), 75 (35), 73 (100), 69 (30), 61 (34).

<u>Anal</u>. Calcd for $C_{23}H_{44}O_2Si_2$: C, 67.56; H, 10.87
Found: C, 67.58; H, 10.74

A sample of **24** was also obtained by GLC and displayed the following properties: IR (CCl_4) 1720, 1620 cm^{-1}; PMR (CCl_4) δ 0.15 (s, 6H), 0.9 (s, 12H), 1.3 (s, 3H), 1.4-2.8 (m, 8H), 4.2-4.3 (m, 1H); MS (70 eV), m/e (rel intensity) 294 (30), 279 (15), 251 (5), 237 (12), 223 (16), 75 (100), 73 (90).

Preparation of monosilyl ether **23**.

To a solution of LDA (1.1 mmol) in 10 mL of THF at -78°C was added a solution of 180 mg of **6** (1.0 mmol) in 10 mL of THF. The resulting mixture was stirred for 20 min, warmed to 0°C (the enolate salt precipitates), and then combined with 4 mL of HMPA to give a clear light-yellow solution. This enolate solution was quenched at 0°C by addition of 0.243 g of tert-butyldimethylchlorosilane (1.5 mmol) in 5 mL of THF. In a second experiment, the enolate solution was refluxed for 4 h prior to quenching, and the results were the same. Workup of the reaction mixture by the previously described procedure gave, after distillation (100°C, 10^{-3} torr), 0.278 g of a colorless solid (95%) which proved to be **23** contaminated with ca. 1% **24**. A sample of **23** obtained by GLC (5% PDEAS, 160°C) had the following properties: mp 58-60°C; IR (CCl_4) 1740, 1645 cm^{-1}; PMR (CCl_4) δ 0.15 (s, 6H), 0.9-1.1 (overlapping s, 15H), 1.2-1.5 (m, 8H), 4.3 (t, 1H); MS (70 eV), m/e (rel intensity) 294 (26), 270 (20), 237 (38), 145 (37), 75 (100), 73 (78), 60 (53).

Anal. Calcd for $C_{17}H_{30}O_2Si$: C, 69.32; H, 10.29

Found: C, 69.28; H, 10.27

Preparation of enedione 27.

(a) via SeO_2 reaction:

A solution of 0.18 g (0.001 m) of dione 6, 0.44 g (4 mmol) of selenium dioxide in 15 mL of t-BuOH and 1 mL of glacial acetic acid was heated under reflux in an atomosphere of nitrogen for about 20 h. The resulting mixture was then cooled, diluted with ether which was then washed with water, brine and dried. Removal of the solvent gave a yellowish oil which was distilled by Kugelrohr (50°C, 5 microns) afforded the enedione 27 (32 mg, 18%) as a yellowish solid; mp 101-102°C; IR ($CDCl_3$) 3120, 2950, 1745, 1680, 1605 cm^{-1}; PMR ($CDCl_3$) δ 1.1 (s, 3H), 1.2 (s, 3H), 1.4-2.7 (m, 6H), 5.7-6.1 (m, 1H), 6.5-6.9 (m, 1H); MS (70 eV) m/e (rel intensity) 178 (54), 163 (18), 150 (30), 123 (56), 68 (100).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92
Found: C, 74.02; H, 7.86

(b) via enolate reaction:

To a monoenolate solution of the diketone 6 (0.18 g, 1 mmol) prepared as described before, was added a solution of 0.327 g (1.5 mmol) of diphenyl disulfide in 5 mL of THF at 0°C. The reaction mixture was stirred 30 min at this temperature, followed by 4 h at room temperature. The reaction was quenched by adding water dropwise at 0°C, and the aqueous layer was extracted with ether. The combined ether layer was washed with water, brine, and dried. The crude product from the above step was oxidized overnight by 0.53 g (1.5 mmol) of sodium periodate in 15 mL aqueous methanol. The precipitate formed was filtered and washed with ether. Solvents in the combined filtrate and washes were removed under reduced pressure and the resulting oil was dissolved in ether and washed with water, brine and dried. The crude product obtained by removal of the solvent was refluxed for 4 h in 25 mL toluene containing 0.11 g (1.3 mmol) of anhydrous sodium bicarbonate. The oil obtained in usual was purified percolation through 25 g of silica (first eluted with pet ether, followed by ether). Removal of the solvent, gave 0.15 g of a residue which contained both the starting diketone 6 and the desired unsaturated ketone 27 with a ratio of 2:3 based on GLC and NMR spectral analyses. The yield of the unsaturated ketone 27 was not optimized.

Preparation of benzylidene adduct 28.

A mixture of 0.18 g 6 (1 mmol), 0.4 g of benzaldehyde (2.5 mmol), and 40 mg of sodium hydroxide in 20 mL of 1:1 water-ethanol was refluxed for 40 h. The cooled reaction mixture was filtered and the solid product washed with aqueous ethanol. Recrystallization of the crude product from ethyl acetate/pet ether gave 0.3 g (85%) of 28: mp 163-166°C; IR (CCl_4) 1720, 1695, 1630, and 1595 cm^{-1}; PMR ($CDCl_3$) δ 1.2 (br s, 6H), 1.4-3.6 (m, 6H), 7.2-7.5 (m, 12H); MS (70 eV), m/e (rel intensity) 356 (40), 341 (31), 313

(36), 226 (70), 199 (100), 116 (97).

Anal. Calcd for $C_{25}H_{24}O_2$: C, 84.24; H, 6.79
Found: C, 84.33; H, 6.87

Preparation of benzylidene adducts **28** and **29**.

A mixture of 0.144 g of **6** (0.8 mmol), 96 mg of benzaldehyde (0.9 mmol), and 36 mg of sodium hydroxide in 25 mL of 2:3 water-glyme was refluxed for 45 h (the reaction mixture remains homogeneous throughout). After it was cooled, the reaction mixture was neutralized with aqueous hydrochloric acid and concentrated under reduced pressure. This concentrate was dissolved in a mixture of water and ether, and the aqueous portion was extracted with additional ether. The combined organic extracts were washed and dried in the usual fashion. Evaporation of the solvent gave a product mixture which was separated by preparative TLC (silica gel, 40% ethyl acetate/cyclohexane). The R_f=0.4 band yielded 58 mg (36% based on benzaldehyde) of **28**. A band at R_f=0.28 yielded 87 mg (36%) of mono adduct **29**, and a weak band at R_f=0.17 proved to be 26 mg of recovered **6**. Compound **29** exhibited the following properties: mp 126-129°C; IR ($CDCl_3$) 1715 and 1630 cm^{-1}: PMR ($CDCl_3$) δ 0.95 (s, 3H), 1.15 (s, 3H), 1.4-3.4 (m, 8H), 7.0-7.5 (m, 6H); MS (70 eV), m/e (rel intensity) 268 (35), 253 (12), 116 (100), 115 (35); $\tilde{\nu}_{max}$(EtOH) 294 nm (ϵ = 25,000).

Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51
Found: C, 80.64; H, 7.54

In a parallel experiment, a mixture of 90 mg of **6** (0.5 mmol), 214 mg of **28** (0.6 mmol), and 36 mg of sodium hydroxide in 25 mL of 2:3 water-glyme was refluxed for 42 h. Workup and separation as before gave 110 mg of **28** (0.3 mmol), 101 mg of **29** (0.4 mmol), and 20 mg of **6**.

Preparation of cisoid diene **31**.

The alcohol **32**, 1.25 g (6 mmol), was dissolved in a solution of 12 mL of dry THF and 48 mL of benzene in room temperature. While stirring, 1 mL of boron trifluoride etherate was added via syringe. The solution was stirred and heated at reflux (bath temperature 90-95°C) for about 20 h. The solution was then cooled and diluted with ether and ice-cold water. The ether layer was washed sequentially with 10% NaOH solution, water, and brine, and then dried. Removal of the solvent, gave an oil residue which was purified by Kugelrohr distillation (120°C, 35 microns, the receiver was cooled at ice bath during distillation). The colorless low melting solid **31** (0.86-0.97 g) was obtained in 75-80% yield. This material showed the following properties: IR (CCl_4) 2950, 1750, 1665, 1625 cm^{-1}; $\bar{\nu}_{max}$ (EtOH) 235 nm (ϵ=11,900) (Calcd. 224 nm); PMR (CCl_4) δ 0.9 (s, 3H), 1.0 (s, 3H), 1.1-2.6 (m, 8H), 4.6-4.8 (d, 1H, J=11 Hz), 4.9-5.2 (d, 1H, J=17 Hz), 5.4 (t, 1H, J=3 Hz), 5.7-6.3 (dd, 1H, J=17, 11 Hz); MS (70 eV) m/e (rel intensity) 190 (79), 175 (38), 133 (100), 119 (85), 105 (62), 91 (73), 79 (39).

Anal. Calcd for $C_{13}H_{18}O$: m/e 190.1358
Found: m/e 190.1345

Preparation of transoid diene 35.

A catalytic amount of iodine was added to a solution of 1.04 g (5 mmol) of the enol 32 in 50 mL of p-xylene, and this solution was refluxed for 3-4 days. The reaction mixture was cooled to room temperature and washed sequentially with 0.5 M sodium thiosulfate, water brine and then dried. Evaporation of the solvent gave a colored oily residue which was then eluted with ether through a short column of silica gel and charcoal. The solvent was again removed and the residue purified by Kugelrohr distillation (60°C, 10 microns). The distillate crystallized as a white solid, 0.89 g (94%), which displayed the following properties: mp 67-71°C; UV (95% ethanol) 235 nm (calcd. 235 nm); IR (CCl_4) 3010, 1730, 1675 cm^{-1}; PMR ($CDCl_3$) δ 0.75 (s, 3H), 0.85 (s, 3H), 1.6-1.8 (d, 3H, J=5.88 Hz) 1.8-2.5 (m, 6H), 5.0-5.4 (q, 1H, J=5.88 Hz), 5.5-5.7 (m, 1H), 6.0-6.4 (m, 1H); MS m/e (rel intensity), 190 (43), 175 (16), 157 (8), 147 (10), 133 (37), 119 (100), 105 (28).

Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53
Found: C, 82.22; H, 9.70

Preparation of nonconjugated diketone 34.

A solution of 75.94% m-chloroperbenzoic acid (1.05 g, 4.6 mmol) in methylene chloride (30 mL) was slowly added to a solution of diene 31 (0.865 g, 4.5 mmol) in methylene chloride (10 mL). The addition was carried out at room temperature with constant stirring for about 24 h. Boron trifluoride etherate (about 1 mL) was added and the reaction mixture was then stirred for another two h. The reaction mixture was diluted with methylene chloride, and then washed with 20% sodium bisulfite solution, 10% sodium bicarbonate solution and brine. After removal of the solvent from the dried organic layer, 0.885 g (94%) of crude reaction adduct was obtained. The crude material was purified by preparative TLC (20 % ethyl acetate/ cyclohexane) to give 34 which displayed the following properties: mp 75-77°C; IR (CCl_4) 2950, 1745, 1700, 1680 cm^{-1}; PMR ($CDCl_3$) δ 0.8 (s, 3H), 1.1 (s, 3H), 2.3 (s, 3H), 1.0-2.8 (m, 6H), 3.2-3.3 (m, 1H), 5.7-5.8 (s, 2H); MS (70 eV) m/e (rel intensity) 206 (32), 164 (30), 163 (45), 149 (47), 146 (73), 131 (100), 119 (71), 93 (52), 91 (88).

<u>Anal</u>. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80
Found: C, 75.78; H, 8.78

Isomerization of 34 to conjugated diketone 37.

The above crude nonconjugated ketone 34 was dissolved in 20 mL of methanol in presence of 2 g of sodium hydroxide. The reaction mixture was stirred at room temperature for about 24 h. After neutralized with dil aqueous HCl solution, methanol was removed in vacuo and the residue was diluted with methylene chloride. The organic layer was washed with dil sodium bicarbonate, water, brine and dried. After removal of solvent, the oily residue was found containing the isomerized conjugated ketone **37** (δ=6.5 ppm, t, 1H) and some unreacted material **34** in a 82:18 ratio as evidenced from pmr spectroscopy.

Preparation of benzothiazole adduct **40**.

To a cold (-78°C) solution of 0.5 mL (1.2 mmol) of 2.42 M n-butyllithium (hexane solution) in 15 mL of dry ether was added 0.135 g (1.2 mmol) of benzothiazole. After 20 min, a solution of 0.18 g (1.0 mmol) of **6** in 15 mL of ether was added dropwise with stirring, and the reaction mixture was then warmed to room temperature. Following a 1-h reaction period, the mixture was quenched with water and extracted with ether. The combined ether extracts were washed, dried, and condensed, yielding 0.22 g (70%) of the adduct **40**. Recrystallization from ether gave a pure sample: mp 193-194.5°C; IR ($CHCl_3$) 3555, 3400, 2925 and 1725 cm^{-1}; PMR ($CDCl_3$) δ 0.90 (s, 3H), 1.4 (s, 3H), 1.5-2.8 (m, 11H), 3.2 (s, 1H), 7.0-7.4 (m, 2H), 7.5-8.0 (m, 2H); MS (70 eV), m/e (rel intensity) 315 (50), 300 (17), 204 (37), 178 (64), 149 (100), 136 (45).

<u>Anal</u>. Calcd for $C_{18}H_{21}NSO_2$: C, 68.53; H, 6.72; N, 4.44

Found: C, 68.67; H, 6.68; N, 4.44

Preparation of epoxide adduct $\utilde{42}$.

To a solution of 0.36 g (2 mmol) of chloromethyl phenyl sulfoxide in 15 mL of dry THF at -78°C was added 1.0 mL (2.4 mmol) of 2.42 M n-BuLi. After stirring for 45 min, the diketone $\utilde{6}$, 0.72 g (4 mmol) in 12 mL of THF, was added via syringe, and the reaction mixture was allowed to stir at this temperature for 30 min, then 1 h at -20°C. After warming to room temperature, the reaction mixture was quenched by adding saturated ammonium chloride solution. The solution was extracted several times with ether. The combined organic solution was washed with water, brine, and dried. After removal of solvent, the residue was treated with ether and placed in refrigerator. The colorless epoxide $\utilde{42}$ was then filtered off to give 0.445 g in 70% yield: mp 141-143°C; IR ($CDCl_3$) 3050, 3000, 2950, 1740, 1580 cm^{-1}; PMR ($CDCl_3$) 180 MHz δ 1.09 (s, 3H), 1.11 (s, 3H), 1.4-2.6 (m, 10H), 3.58 (s, 1H), 7.4-7.7 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 216.7, 141.9, 131.6, 129.5, 124.4, 72.9, 69.8, 52.9, 44.2, 32.6, 25.7, 24.9, 24.3, 22.0, 18.3, 17.7; MS (70 eV) (rel intensity) m/e CI, 319 (M+1) (4), 193 (100), 175 (40), 165 (25), 147 (40), 133 (15).

Anal. Calcd for $C_{18}H_{22}O_3S$: C, 67.88; H, 6.98
Found: C, 67.87; H, 6.97

Preparation of α,β-unsaturated aldehyde $\utilde{38}$.

A solution of epoxide $\utilde{42}$ (0.318 g, 1 mmol) in 5 mL of methylene chloride was evaporated onto 0.5 g of calcium carbonate and the mixture was distilled by Kugelrohr apparatus (150-160°C, 50 microns) to give 0.216 g of crude distillate which was chromatographed on silica gel. The crude material was eluted with pentane followed by 30% ethyl acetate in hexane to furnish 0.132 g (69%) of α,β-unsaturated aldehyde **42**: IR (CCl_4) 2950, 1750, 1695, 1625 cm^{-1}; PMR (CCl_4) δ 0.84 (s, 3H), 0.88 (s, 3H), 1.0-2.7 (m, 8H), 6.4 (t, 1H), 8.9 (s, 1H); MS (70 eV) (rel intensity) m/e 193 (15), 192 (100), 177 (25), 165 (10), 163 (18), 149 (22), 136 (30), 135 (60), 131 (45), 121 (70), 109 (75), 107 (83), 105 (40), 93 (68), 91 (70), 79 (63), 55 (50).

Preparation of allyl chloride **45**.

A solution of 0.238 g (2 mmol) of thionyl chloride in 5 mL of carbon tetrachloride was added to a stirred solution of 0.208 g (1 mmol) of the allyl alcohol **32** and 0.97 mL of triethylamine in 10 mL of carbon tetrachloride at 0°C under nitrogen. After refluxing for 3 h, the reaction mixture was then cooled, diluted with water, and neutralized with dilute hydrochloric acid. The neutral solution was extracted twice with ether. The combined ether extracts were washed with sodium bicarbonate solution, water and brine. The dried solution was eluted through a short column which was packed with charcoal and silica gel to remove the impure colored materials. Evaporation of the solvent gave 0.193 g (86%) of the rearranged product **45** as a yellow-brown oil, which displayed the following spectral data: IR (CCl_4) 2955, 1750, 1665 cm^{-1}; PMR (CCl_4) δ 0.8 (s, 3H), 1.0 (s, 3H), 1.0-2.8 (m, 10H), 3.8-4.1 (d, 2H), 5.1-5.5 (t, 1H); MS (70 eV, direct probe) m/e (rel intensity) 228 (10), 226 (28), 213 (9), 211 (23), 191 (50), 190 (54), 175 (32), 135 (88), 133 (81), 41 (100).

Preparation of maleic anhydride Diels-Alder adduct **46**.

A solution consisting of 0.19 g (1 mmol) of diene **31**, 0.185 g (2.5 mmol) of maleic anhydride and 10 mL of xylene was refluxed for 24 h. The reaction mixture was then concentrated, diluted with water, and extracted several times with methylene chloride. The organic layer was then washed with water, brine, and dried. It gave 0.3 g of crude product on evaporation of the solvent. This crude material was treated with ether to give 0.16 g (56-60%) colorless solid which was further recrystallized from ethyl acetate/petroleum ether to give colorless crystals **46**; mp 221-222.5°C; IR ($CDCl_3$) 2950, 1850, 1780, 1740, 1625 cm^{-1}; PMR ($CDCl_3$) 250 MHz, δ 0.88 (s, 3H), 0.95 (s, 3H), 1.4-1.82 (m, 10H), 2.80-2.90 (ddd, 1H, J=2.3, 8.8, 20 Hz), 3.32-3.38 (dd, 1H, J=12.5, 7.3 Hz), 3.43-3.52 (ddd, 1H, J=2.3, 8.5, 12.5 Hz), 5.70-5.76 (dt, 1H, J=3.2, 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 218.8, 174.2, 172.1, 148.9, 118.3, 51.5, 46.3, 44.5, 40.9, 34.0, 29.4, 23.9, 23.8, 23.7, 22.4, 18.7; MS (70 eV) m/e (rel intensity) 288 (10), 273 (19), 218 (8), 189 (8), 181 (18), 173 (11), 160 (9), 157 (25), 143 (20), 131 (37), 117 (35), 91 (100), 77 (44).

Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99
Found: C, 70.57; H, 7.12

In a trapping experiment, a solution of allyl alcohol **32** (0.208 g, 1 mmol), p-toluenesulfonic acid (28 mg, 1.5 mmol) and excess of maleic anhydride (0.3 g, 3 mmol) in 30 mL of toluene was refluxed under nitrogen atomosphere. Work-up as usual gave 0.12 g (45%) colorless solid **46** which showed the same properties as above.

Similar result was obtained from a reaction of allyl chloride **45** and maleic anhydride in refluxing xylene solution.

Preparation of diester adducts **50** and **52**.

A solution of 0.323 g (0.0017 mmol) of diene **31** and 0.4 mL (3.1 mmol) of dimethyl acetylenedicarboxylate in 10 mL of benzene was refluxed under N_2 for about 10 h. After cooling to room temperature, the mixture was diluted with ether and then washed with water, brine and dried. After evaporation of the solvent, the resulting residue was crystallized from ether/hexane to give 0.316 g (56%) as an off-white solid **50** which gave the following properties; IR (CCl_4) 2920, 1760 (broad), 1660 cm^{-1}; PMR ($CDCl_3$) δ 1.0 (s, 3H), 1.1 (s, 3H), 1.3-3.2 (m, 11H), 3.6-3.7 (2s, 6H), 5.5 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 218.2, 169.6, 166.1, 144.1, 142.6, 127.3, 118.1, 52.2, 51.0, 46.5, 35.5, 34.1, 30.7, 28.0, 27.1, 24.4, 23.7, 22.1; MS (70 eV) m/e (rel intensity) 332 (3), 300 (67), 285 (47), 273 (36), 241 (50), 105 (82), 84 (100).

The above material was air oxidized to **52** during a slow recrystallization from methylene chloride/cyclohexane solution. Compound **52** displayed the following properties; mp 124-5°C; IR ($CDCl_3$) 2950, 1740 (broad), 1595 cm^{-1}; PMR ($CDCl_3$) 250 MHz, δ 0.83 (s, 3H), 1.08 (s, 3H), 1.1-3.0 (m, 8H), 3.89 (s, 3H), 3.95 (s, 3H), 7.23-7.89 (AB quartet, 2H); MS (70 eV) m/e (rel intensity) 330 (1), 315 (2), 299 (26), 298 (100), 241 (38).

Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.08; H, 6.71
Found: C, 69.01; H, 6.75

Preparation of p-benzoquinone Diels-Alder adduct **51**.

A solution of 0.216 g (2 mmol) of p-benzoquinone and 0.19 g (1 mmol) of diene **31** in 10 mL of xylene was refluxed for about 20 h. The reaction mixture was added water and then extracted with methylene chloride. The organic layer was sequentially washed with water and brine and then dried. After removal of the solvent, the residue was crystallized from ethanol/pet ether to yield 0.132 g (44%) of light yellow, crystalline **51**. An analytical sample of **51** displayed the following properties; mp 170-3°C; IR ($CHCl_3$) 1740, 1690, 1600 cm^{-1}; PMR 180 MHz ($CDCl_3$) δ 1.05 (s, 3H), 1.2 (s, 3H), 2.4-3.4 (m, 13H), 5.2 (q, 1H , J=2.93 Hz), 6.49-6.56 (d of half of a AB quartet, 1H, J=1.22 Hz, 10.3 Hz), 6.59-6.65 (half of a AB quartet, 1H, J=10.3 Hz); ^{13}C NMR ($CDCl_3$) δ 219.2, 201.0, 198.9, 144.8, 141.0, 137.0, 115.6, 51.0, 50.3, 46.7, 35.3, 34.1, 30.6, 27.2, 26.3, 24.7, 23.7, 20.7; MS (70 eV) m/e (rel intensity) 298 (14), 282 (2), 265 (2), 255 (5), 189 (27), 161 (10), 145 (25), 131 (27), 123 (100), 105 (32), 91 (65), 77 (30).

Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.49; H, 7.43
Found: C, 76.58, H, 7.44

Preparation of Diels-Alder adduct 54.

A solution of 0.57 g (3 mmol) of diene 31 and 0.912 g (6 mmol) of 6-methoxy-2-methyl-benzoquinone 53 in 15 mL of p-xylene was refluxed for 25 h. The solvent was then removed in vacuo, and the crude yellow residue was stirred in aqueous sodium bisulfite/methylene chloride solution. The organic layer was then separated and the aqueous layer was extracted with methylene chloride. The combined organic layers were washed with water, brine and dried. Removal of the solvent, gave a crude mixture which was found to be mainly the adduct 54, with a small amount of 56 which was formed by the contaimination of quinone 55 in the starting dienophilic material. Pure sample of adduct 54 was obtained by the flash chromatographic column separation (50 mm column diameter, packed with 40-63 um silica gel, using 50% ethyl acetate/pet ether as eluting solvent). The fractions with R_f=0.20 were combined and concentrated, giving 0.596 g (58%) of slight yellow solid which was washed with ether to give 0.472 g (46%) of colorless crystals; mp 227.5-230°C; IR ($CDCl_3$) 2950, 2875, 1735, 1715, 1670, 1650, 1601 cm^{-1}; PMR ($CDCl_3$) 180 MHz δ 1.0 (s, 3H), 1.15 (s, 3H), 1.4 (s, 3H), 1.42-2.85 (m, 11H), 2.87-2.98 (ddd, 1H, J=10.5, 7.83, 1.47 Hz), 3.65 (s, 3H), 5.1 (q, 1H, J=2.93 Hz), 5.58 (d, 1H, J=1.47 Hz); ^{13}C NMR ($CDCl_3$) δ 219.4, 200.6, 196.5, 160.2, 144.4, 116.1, 107.2, 56.9, 56.5, 50.8, 50.7, 46.8, 42.1, 34.2, 30.8, 28.4, 25.6, 25.1, 24.6, 23.4, 17.8; MS (70 eV) m/e (rel intensity) CI 343 (M+1, 100), 325 (95), 315 (27), 307 (31); stereoscopic views of 54 from X-ray crystallographic studies are shown in page 38.

Preparation of Diels-Alder adduct 56.

Quinone 55 (0.76 g, 5 mmol) was dissolved in 15 mL of methylene chloride at 0°C. To this solution, 0.5 mL (4.5 mmol) of boron trifluoride etherate was added via syringe. After stirring at this temperature for one h, the colored solution was cooled to -16°C, and a solution of 0.57 g (3 mmol) of diene 31 in 15 mL of methylene chloride was slowly introduced. After about four h stirring, water and methylene chloride was added. The organic layer was washed with saturated sodium bicarbonate solution, and then condensed. The residue was stirred with aqueous sodium bisulfite solution for one h. Methylene chloride was added and the organic layer was then washed with water, brine, and dried. Evaporation of the solvent in vacuo gave an off-white solid which was triturated with ether and placed in refrigerator. The white solid (562 mg, 55%) was filtered and was identified to be mainly adduct 56 with small amount of its isomer 57 (about 10:1 ratio). The minor adduct 57 can be removed by recrystallization from cyclohexane/methylene chloride solution to furnish pure 56 which displayed the following properties: mp 260-1°C: IR ($CHCl_3$) 2950, 1740, 1710, 1675, 1605 cm^{-1}; PMR ($CDCl_3$) 180 MHz, δ 1.01 (s, 3H), 1.15 (s, 3H), 1.39 (s, 3H), 1.40-2.8 (m, 11H), 2.94-3.04 (dd, 1H), 3.76 (s, 3H), 5.28-5.31 (q, 1H), 5.67 (s, 1H); MS (70 eV) m/e (rel intensity) CI 343 (M+1, 100), 325 (26), 315 (14), 285 (25), 189 (25), 181 (44), 171 (56), 167 (81), 153 (65); stereoscopic views of 56 from X-ray crystallographic studies are shown in page 41.

<u>Anal</u>. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65
Found: C, 73.37; H, 7.70

Preparation of Diels-Alder adduct 57.

To a solution of 0.152 g (1 mmol) of quinone 55 in 8 mL of methylene chloride at 0°C was added 0.8 mL (0.8 mmol, 1 M solution in methylene chloride) of stannic chloride, and this mixture was stirred for 1 h. A solution of 0.114 g (0.6 mmol) of diene 31 in 9 mL of methylene chloride was then added at 0°C. After stirring at this temperature for about 1.5 h, the reaction mixture was decomposed by the addition of 10 mL of water. After the solution warmed up to room temperature, the organic layer was separated and the aqueous layer was extracted with methylene chloride. The combined organic extracts were processed in the same manner as in the corresponding boron trifluoride-catalyzed reaction giving 0.193 g of solid which contained adduct **57** as the only detected Diels-Alder adduct. This material was triturated in ether and the resulting colorless solid was filtered. Recrystallization from methylene chloride/ether gave 0.152 g (74%) of **57** which displayed the following properties; mp 239.5-241.0°C; IR (KBr) 2950, 1740, 1710, 1665, 1610 cm^{-1}; PMR ($CDCl_3$) δ 1.05 (s, 3H), 1.2 (s, 3H), 1.5 (s, 3H), 1.6-3.0 (m, 13H), 3.7 (s, 3H), 5.2 (dd, 1H), 5.65 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 217.8, 201.4, 194.1, 161.8, 143.8, 115.5, 108.3, 56.3, 55.8, 51.0, 50.3, 46.8, 34.9, 34.2, 31.7, 30.6, 26.5, 25.0, 23.8, 21.3, 20.9; UV $\tilde{\nu}_{max}$(EtOH) 268 nm, $\epsilon = 1.5 \times 10^4$; MS (70 eV) (rel intensity) m/e 342 (1), 327 (4), 314 (100), 299 (69), 281 (14), 105 (33), 91 (33), 69 (56).

Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65
Found: C, 73.75; H, 7.75

Thermal reaction of quinone **55** and diene **31**.

A solution of 1.026 g (3 mmol) of diene **31** and 0.912 g (6 mmol) of quinone **55** in 15 mL of xylene was refluxed for 26 h. The xylene was removed under reduced pressure and the residue was treated with saturated aqueous sodium bisulfite solution. The organic solution was then washed with water, brine and dried. After removal of the solvent, the residue was treated with ether. The resulting solid was filtered to yield 0.35 g (34%) of two isomers 56 and 57 in a ratio of 2:1 as evidenced by pmr spectroscopy.

Preparation of monoacetate 58.

A mixture of 0.1 g (0.29 mmol) of 56, 0.04 g (0.49 mmol) of sodium acetate, 5 mL of acetic anhydride, and 4 mL of benzene was refluxed for about 60 h. The solvent was removed in vacuo, the residue was treated with methylene chloride and was filtered. The filtrate was washed with water, brine and dried. After removal of the solvent, a brown oil was recovered which contained a mono acetate 58 and trace amount of starting material 56 as evidenced from pmr spectroscopy. This material was treated with ether and the resulting white precipitate was filtered to give 80 mg (71%) of 58. An analytical sample of 58 (recrystallized from ethyl acetate/pet ether) displayed the following properties: mp 195-197°C; IR ($CDCl_3$) 2950, 1760, 1740, 1675, 1605 cm^{-1}; PMR ($CDCl_3$) 250 MHz, δ 0.97 (s, 3H), 1.26 (s, 3H), 1.50 (s, 3H), 2.26 (s, 3H), 1.6-3.1 (m, 11H), 3.75 (s, 3H), 5.43 (s, 1H), 5.56 (m, 1H); MS (70 eV) (rel intensity) m/e 385 (3), 384 (10), 343 (23), 342 (100), 327 (33), 309 (10), 207 (20), 181 (11), 167 (13), 166 (34).

<u>Anal</u>. Calcd for $C_{23}H_{28}O_5$: m/e 384.1937

Found: m/e 384.1950

Epimerization of adduct **57** to **59**.

A solution of 0.1 g (0.29 mmol) of **57** and 0.025 g (0.25 mmol) of sodium bicarbonate in 7 mL of absolute methanol was refluxed for 40 h. The solution was cooled to room temperature and filtered. The filtrate was then diluted with methylene chloride and washed with water, brine and dried. After removal of the solvent, 0.08 g (80%) of off-white solid was recovered. This material contained a trace amount of starting material **57** and a major product which is believed to be its epimer **59** as evidenced from pmr spectroscopy: (in $CDCl_3$) δ 1.0 (s, 3H), 1.2 (s, 6H), 1.5-2.9 (m, 12H), 3.8 (s, 3H), 5.4 (m, 1H), 5.6 (s, 1H).

Epoxidation of adduct **56** to **63**.

To a solution of 0.12 g (0.35 mmol) of **56** in 5 mL of methylene chloride at room temperature was added 0.092 g (0.4 mmol, 75.52%) m-chloroperbenzoic acid in 5 mL of methylene chloride. The reaction mixture was stirred for 24 h, and then sequentially washed with 10% sodium bisulfite, dilute sodium bicarbonate, water and brine. The organic layer was dried and the solvent was evaporated to give an essentially pure solid in quantitative yield. An analytical sample of **63** (recrystallized from methylene chloride/cyclohexane) displayed the following properties: mp 206-209^{o}; IR ($CDCl_3$) 2950, 1740, 1720, 1675, 1605, and 1175 cm^{-1}; PMR ($CDCl_3$) 250 MHz, δ 1.04 (s, 3H), 1.07 (s, 3H), 1.35 (s, 3H), 1.4-2.8 (m, 13H), 3.65 (s, 3H), 5.6

(s, 1H); MS (70 eV) (rel intensity) m/e 358 (2), 340 (2), 325 (1), 167 (23), 84 (41), 69 (100), 55 (44).

Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.36; H, 7.32
Found: C, 70.22; H, 7.32

Thermal reaction of quinone 55 and isoprene.

A solution of 0.56 g (3.7 mmol) of quinone 55 and 6.2 mL (62 mmol) of isoprene in 10 mL of benzene was heated at 90-100° in a sealed tube for six days. The solution was then cooled to room temperature and the solvent was evaporated in vacuo. Addition of pet ether to the resulting oil gave 0.58 g (72%) of crude solid. This material was found to be a mixture of adducts 68 and 69 (~1:1 ratio) as analyzed by high resolution pmr and ^{13}C nmr.

Thermal reaction of quinone 55 and piperylene.

Quinone 55 (0.46 g, 3 mmol), piperylene (1 mL, mixture of 50:50 cis:trans) and benzene (5 mL) were heated at 90-100° in a sealed tube for six days. Work-up as usual gave 0.532 g (81% yield) of mixed product 66 and 67 as evidenced by high resolution pmr, ^{13}C nmr and GLPC (4% SE-30 column).

Stannic chloride-catalyzed reaction of quinone 55 and isoprene.

A solution 0.228 g (1.5 mm) of quinone 55 in 8 mL of methylene chloride was stirred at 0° while 1.5 mL (1.5 mm) of 1 M stannic chloride solution was added. The resulting mixture was stirred for one h then cooled to -16° whereupon a solution of isoprene (0.5 mL, 5mm) in 8 mL of methylene chloride was added. After stirring at -16° for four h, the reaction mixture was decompored by the addition of water. The organic layer was washed with dilute sodium bicarbonate, sodium bisulfite solution, water and brine. Crystallization of the condensed residue from pet ether gave adduct **69** (0.205 g, 62%): mp (recrystallized from ether/pet ether) 116-118° (lit. mp 115-118°).[56]

Stannic chloride-catalyzed reaction of quinone **55** and piperylene.

Following the same reaction procedure as the corresponding isoprene Diels-Alder reaction, the reaction of piperylene (0.4 mL, excess, mixture of 50:50 cis:trans), quinone **55** (0.228 g, 1.5 mmol) and stannic chloride (1.4 mL, 1 M) in methylene chloride solution gave 0.381 g of crude oil. Recrystallization from ether/pet ether afforded 0.195 g of pure adduct **66** which displayed the following properties: mp 70-73°; IR, NMR, MS agree with literature data.[49]

Boron trifluoride-catalyzed reaction of quinone **55** and isoprene.

A solution of 0.456 g (3 mmol) of quinone **55** in 12 mL of methylene chloride was stirred at 0° while 0.35 mL of boron trifluoride etherate solution was added. The resulting mixture was stirred at this temperature for one h then a solution of isoprene (0.6 mL, 6 mm) in 6 mL of methylene chloride was added slowly. After stirring at 0°

for three hour, the reaction mixture was decomposed by the addition of water. The organic layer was washed sequentially with dilute sodium bicarbonate solution, sodium bisulfite solution, water and brine. After drying, the solvent was removed in vacuo to give quantitative amount of oil which contained adduct **68** and **69** in approximately 2.4:1 ratio based on 250 MHz nmr. This crude oil solidified on standing at room temperature. The seperation of **68** and **69** was achieved by recrystallization methods. The major adduct **68** was obtained by recrystallization from ether/pet ether solution as a pure colorless solid which displayed the following properties: mp 86-88°; IR ($CDCl_3$) 1720, 1660 and 1610 cm^{-1}, PMR ($CDCl_3$) 250 MHz, δ 1.31 (s, 3H), 2.0 (s, 3H), 2.1-2.8 (m, 4H), 2.93 (t, 1H), 3.79 (s, 3H), 5.31 (m, 1H), 5.83 (s, 1H); MS (70 eV) (rel intensity) m/e 220 (5), 205 (6), 192 (72), 177 (100), 173 (19), 161 (8), 145 (20), 91 (37), 77 (21), 69 (72).

<u>Anal</u>. Calcd for $C_{17}H_{16}O_3$: m/e 220.1099
Found: m/e 220.1090

The minor component, **69**, was selectively crystallized in pure from (mp 116-118°) in methylene chloride/cyclohexane.

Boron trifluoride-catalyzed reaction of quinone **55** and piperylene.

Quinone **55** (1.52 g, 0.01 mol, in 30 mL of methylene chloride) and boron trifluoride etherate (1.2 mL, 10 mmol) was complexed as described before. The reaction solution was then cooled to -16° and a solution of piperylene (5 ml, 50 mmol, mixture of 50:50 cis:trans) in 10 mL of methylene chloride was added. After stirring at -16° for 4 h, the reaction was quenched by the addition of water. Work-up as usual gave an orange colored oil which was purified via Kugelrohr distillation (50 microns, 120°). The yellow oil (1,982 g, 90%) obtained was found to be a mixture of products **67** and **66** in a 4:1 ratio as evidenced by GLPC (4% SE-30 column, 200°), GC/MS and high resolution pmr. Attempts to separate the two isomers by preparative GLPC (15% SE-30 column, 220°) and HPLC (neutral aluminum) failed. However, when the mixture of **66** and **67** was left standing at room temperature for several days, a new compound slowly crystallized. This material, **70**, was then isolated and displayed the following properties: mp 120-123°C; IR (KBr) 3300, 1675, 1601 cm^{-1}; PMR ($CDCl_3$) 250 MHz, δ 0.71 (d, 3H), 1.30 (s, 3H), 2.59 (quintet, 1H), 2.76 (dt, 1H), 3.40 (ddd, 1H), 3.88 (s, 3H), 5.35 (s, 1H), 5.47 (s, 1H), 5.60 (dt, 1H), 5.65 (m, 1H); MS (70 eV) (rel intensity) m/e 220 (100), 205 (38), 192 (29), 191 (28), 177 (43), 173 (32), 159 (26), 153 (38), 145 (36), 91 (79), 69 (90); UV $\tilde{\nu}_{max}$(EtOH) 340 nm (ϵ =3300) (Calcd. ~ 350 nm).

APPENDIX

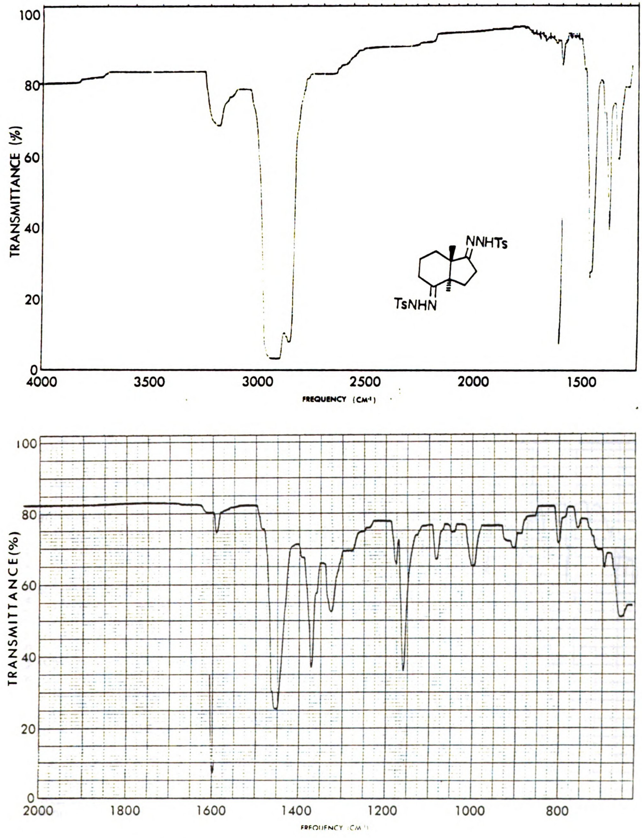


Figure 10. Infrared spectrum of 19.

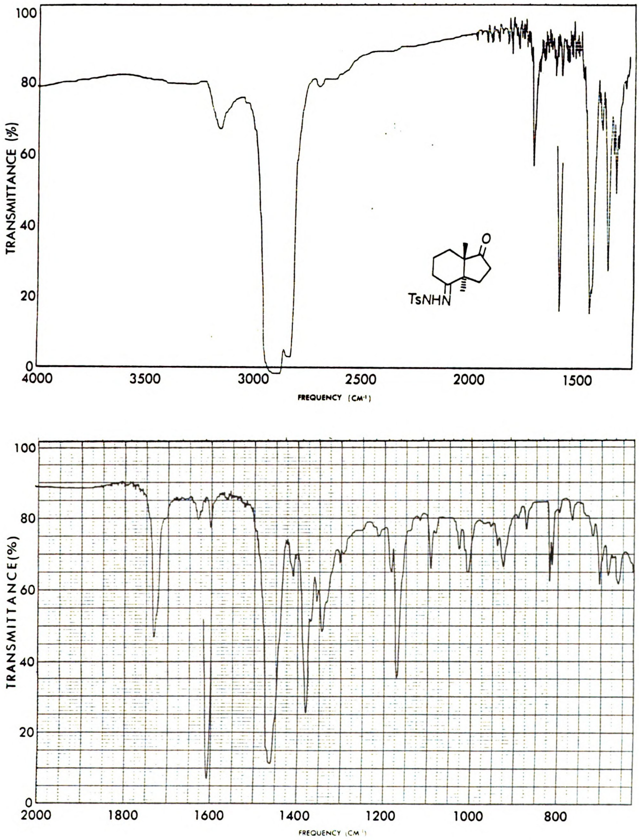


Figure 11. Infrared spectrum of 20.

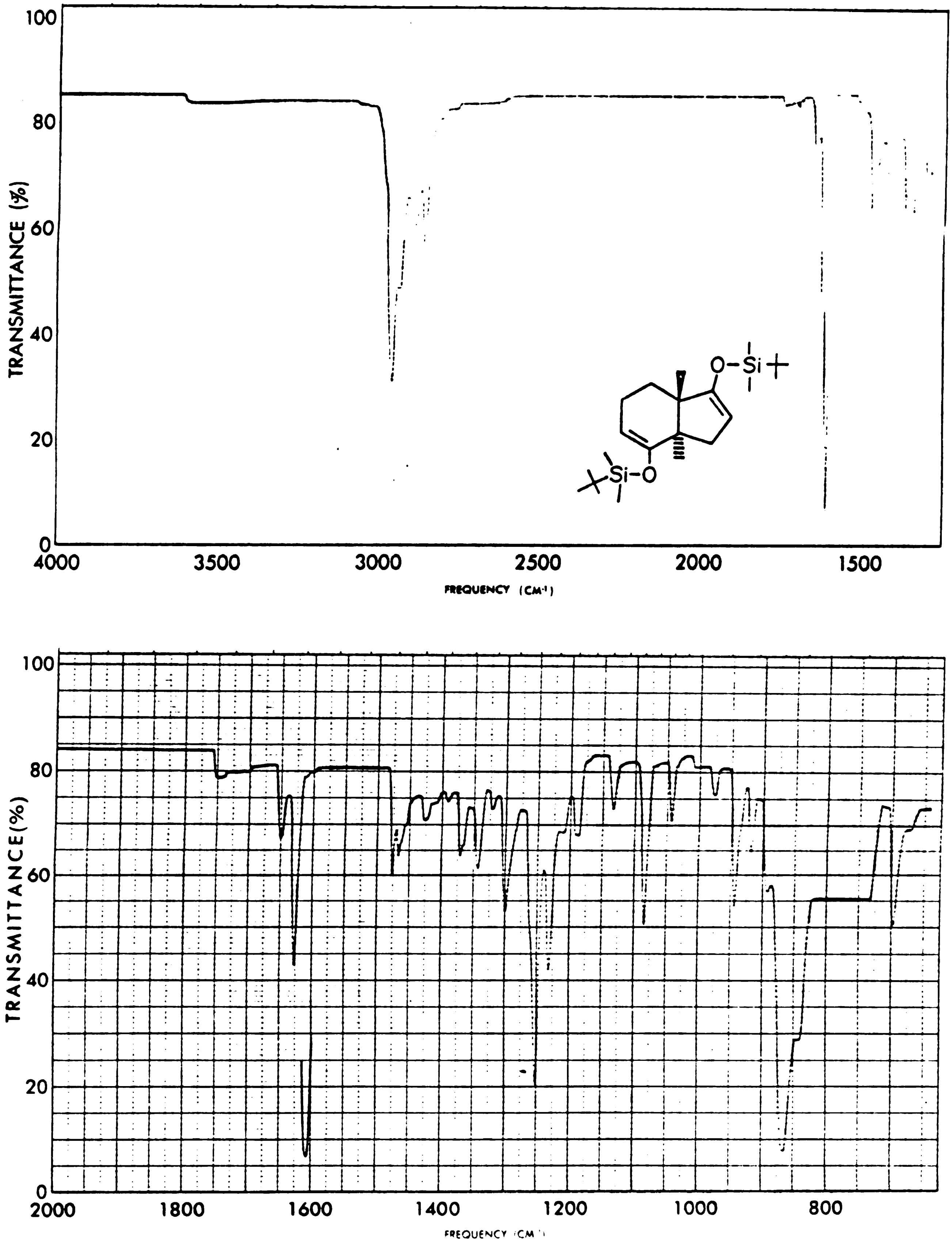


Figure 12. Infrared spectrum of 22.

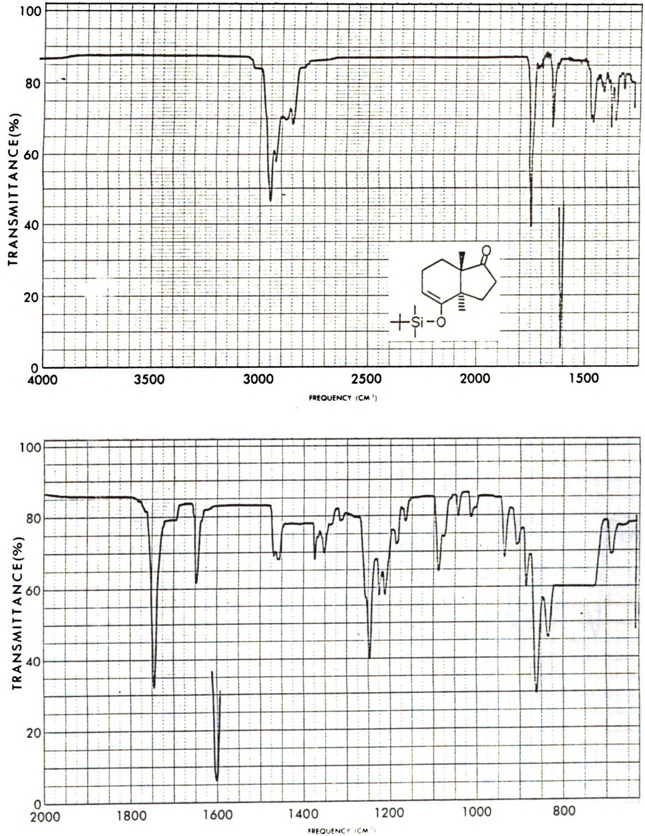
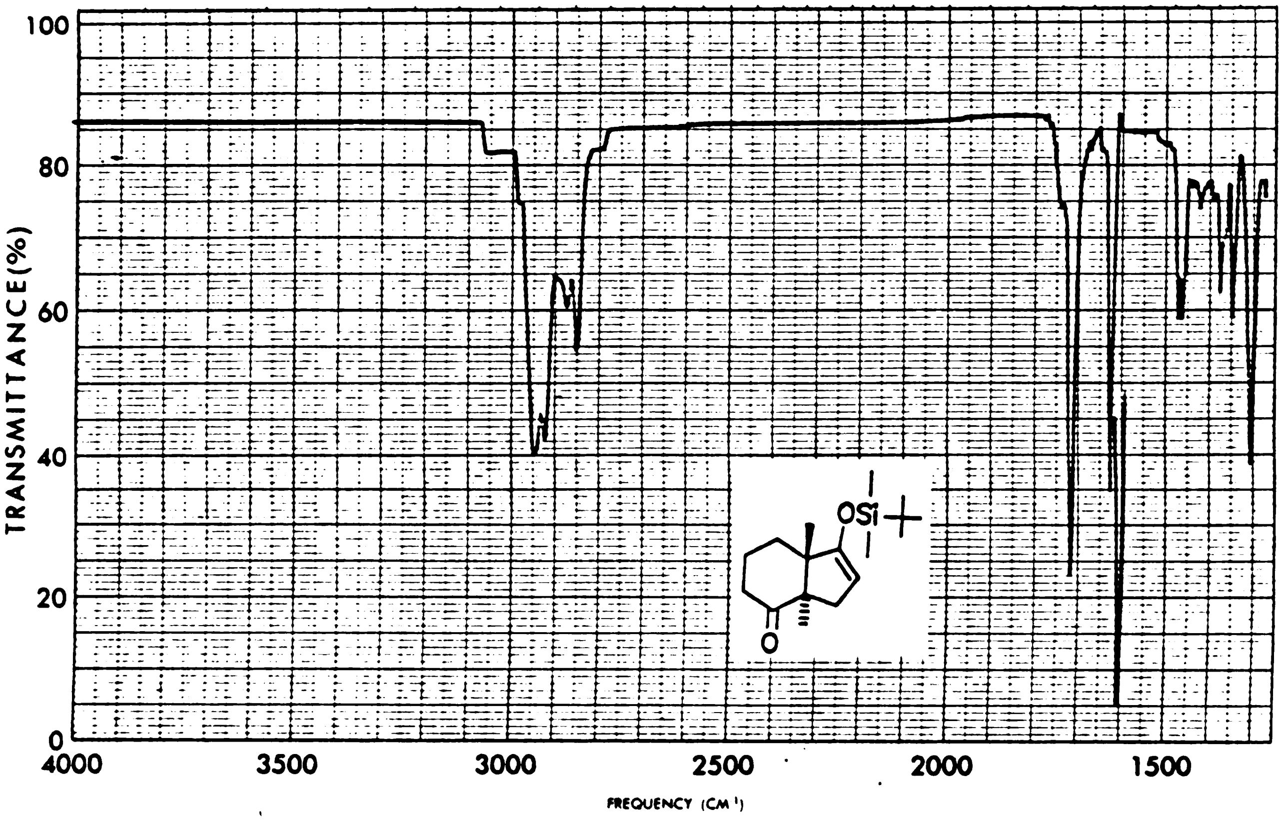


Figure 13. Infrared spectrum of 23.



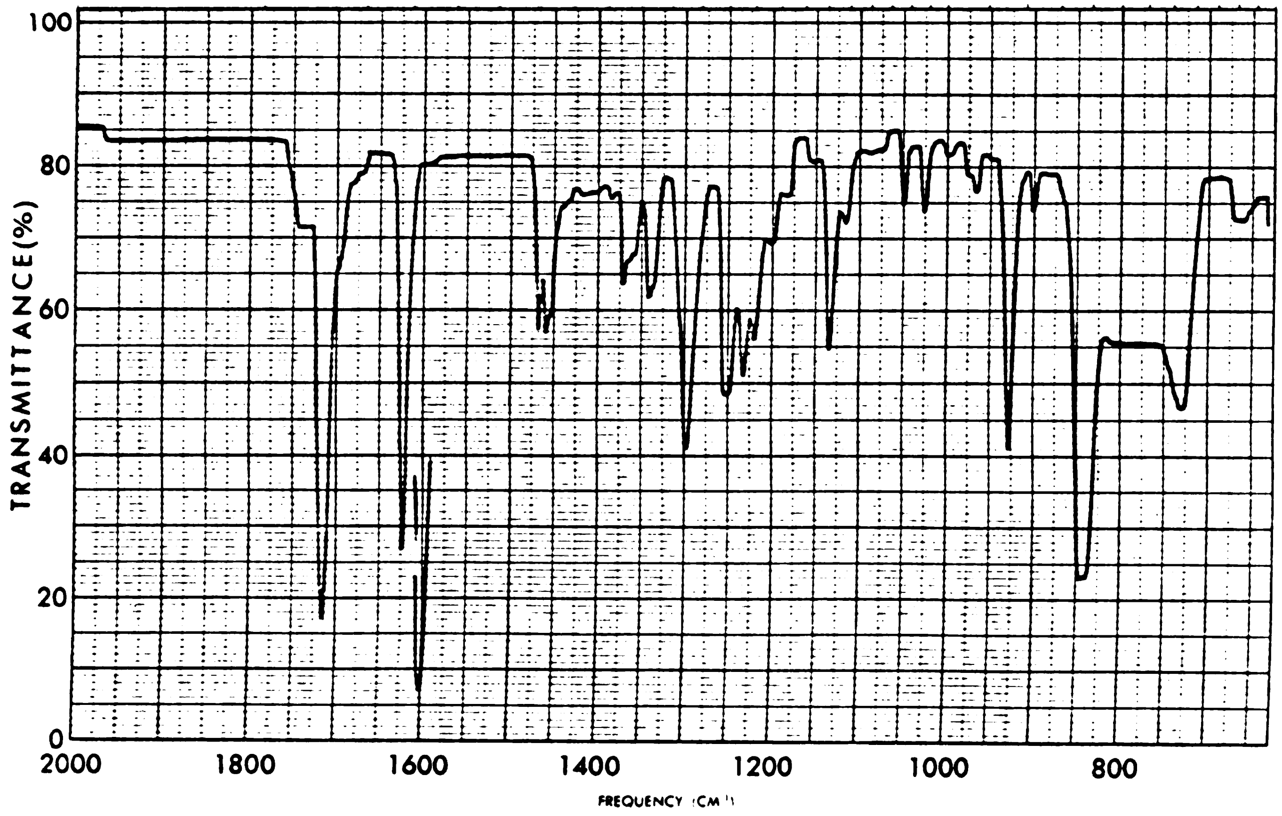


Figure 14. Infrared spectrum of 24.

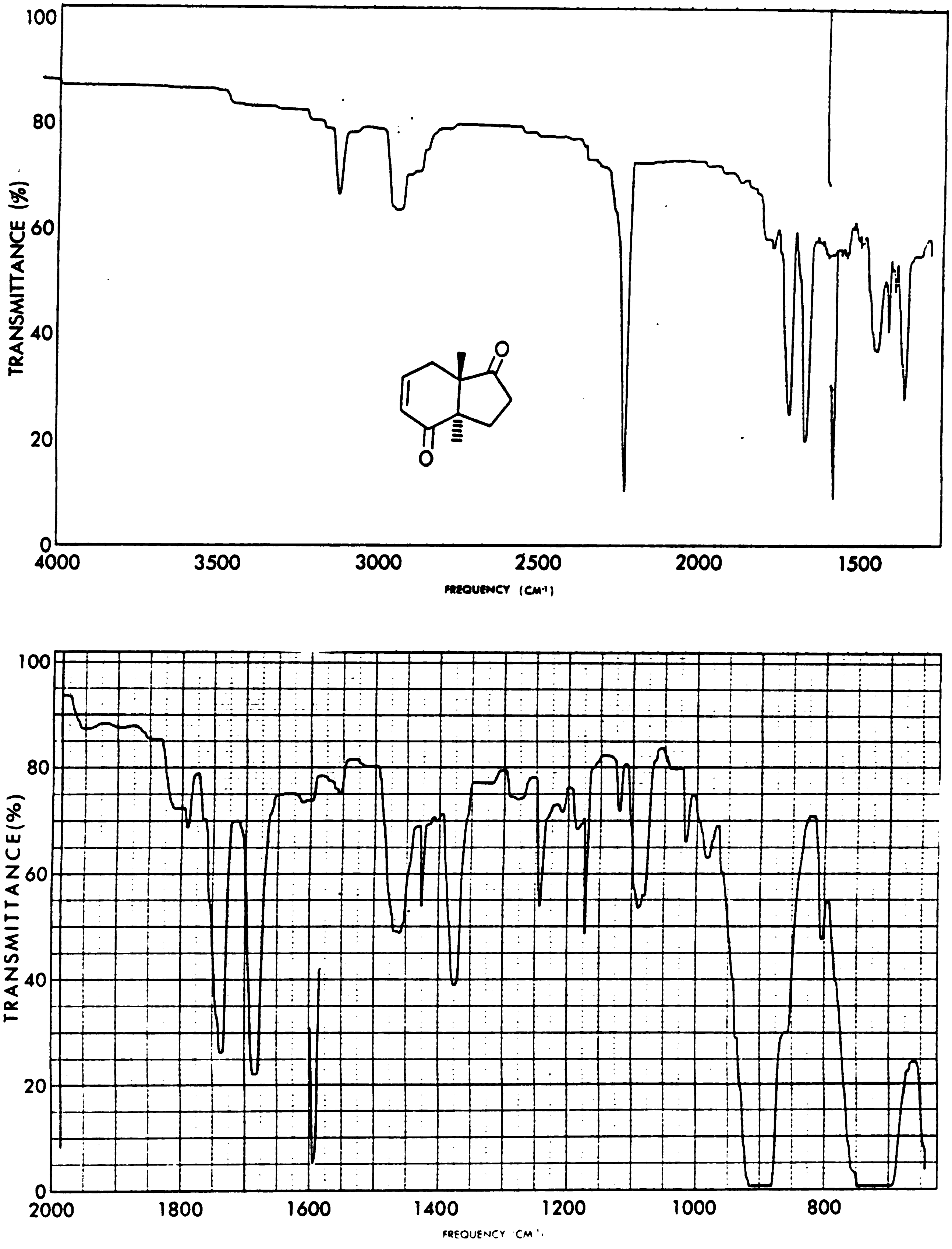


Figure 15. Infrared spectrum of 27.

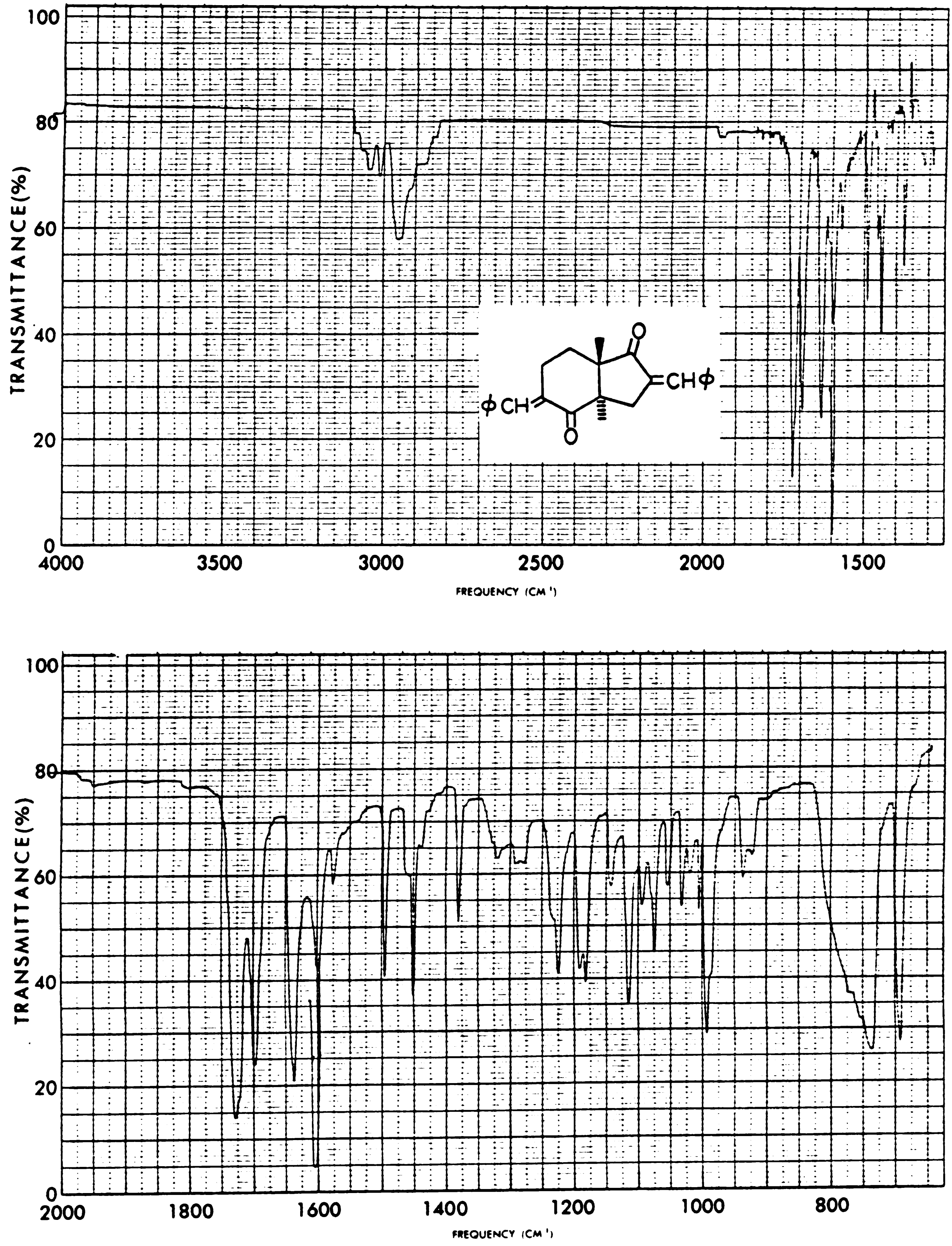


Figure 16. Infrared spectrum of 28.

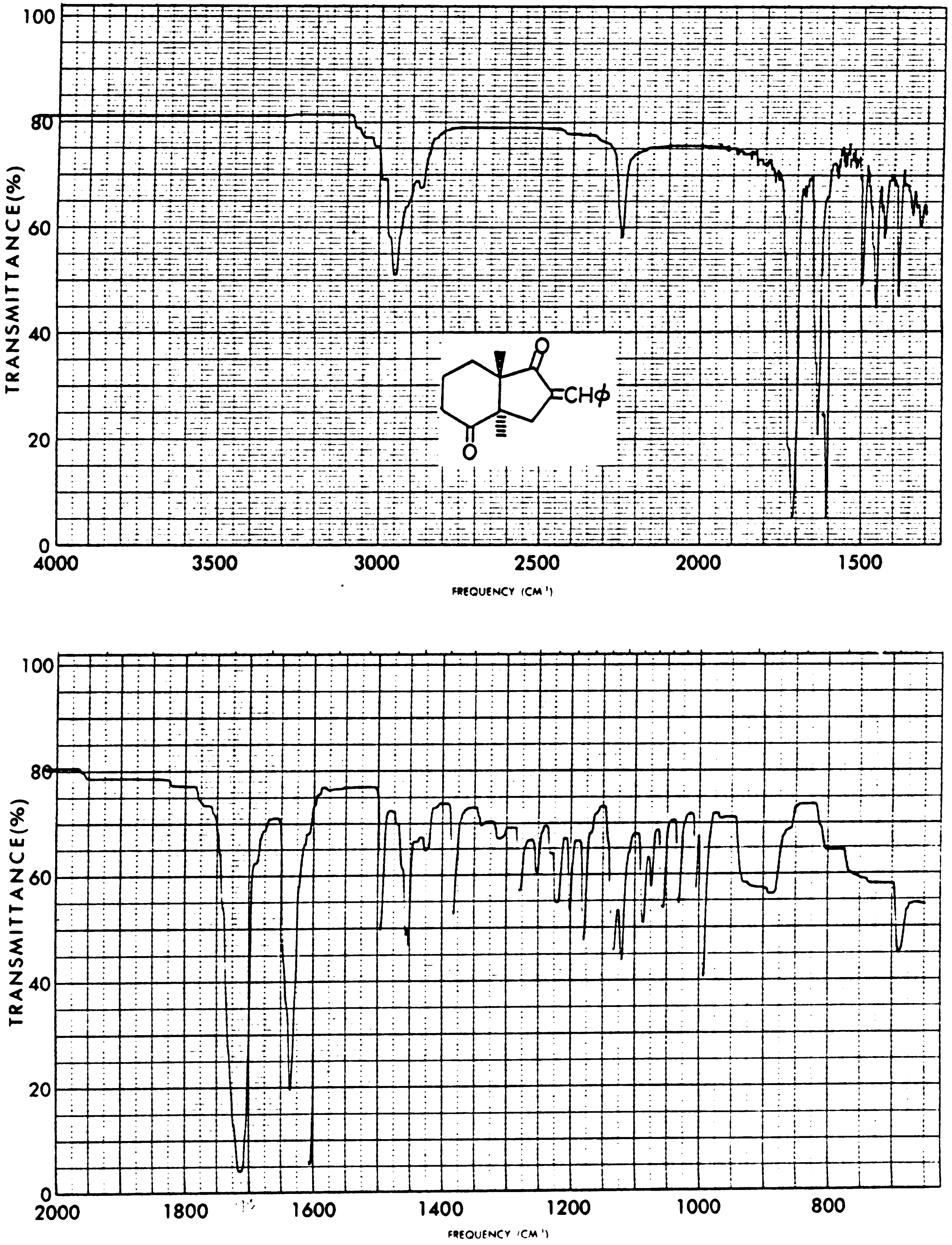


Figure 17. Infrared spectrum of 29.

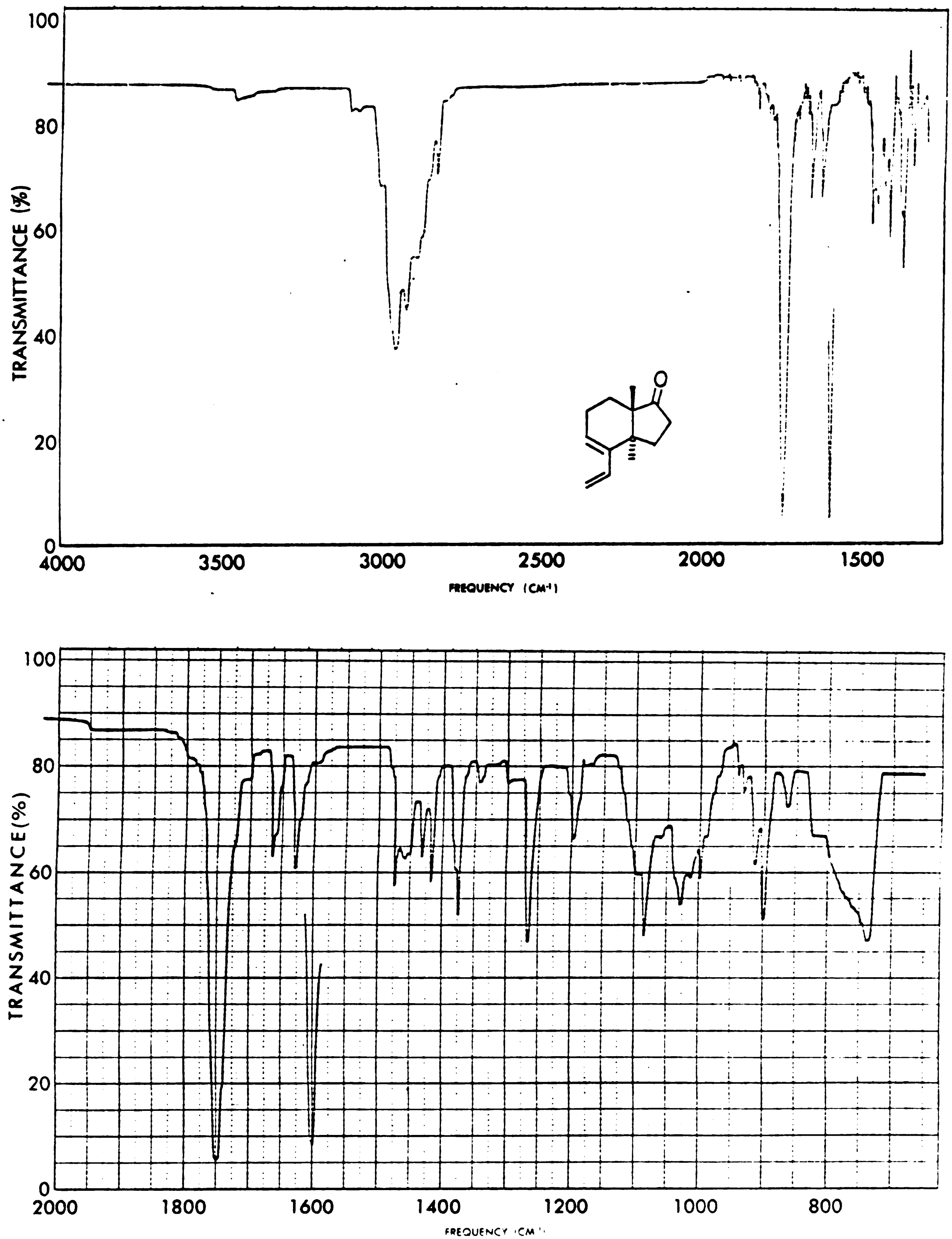


Figure 18. Infrared spectrum of 31.

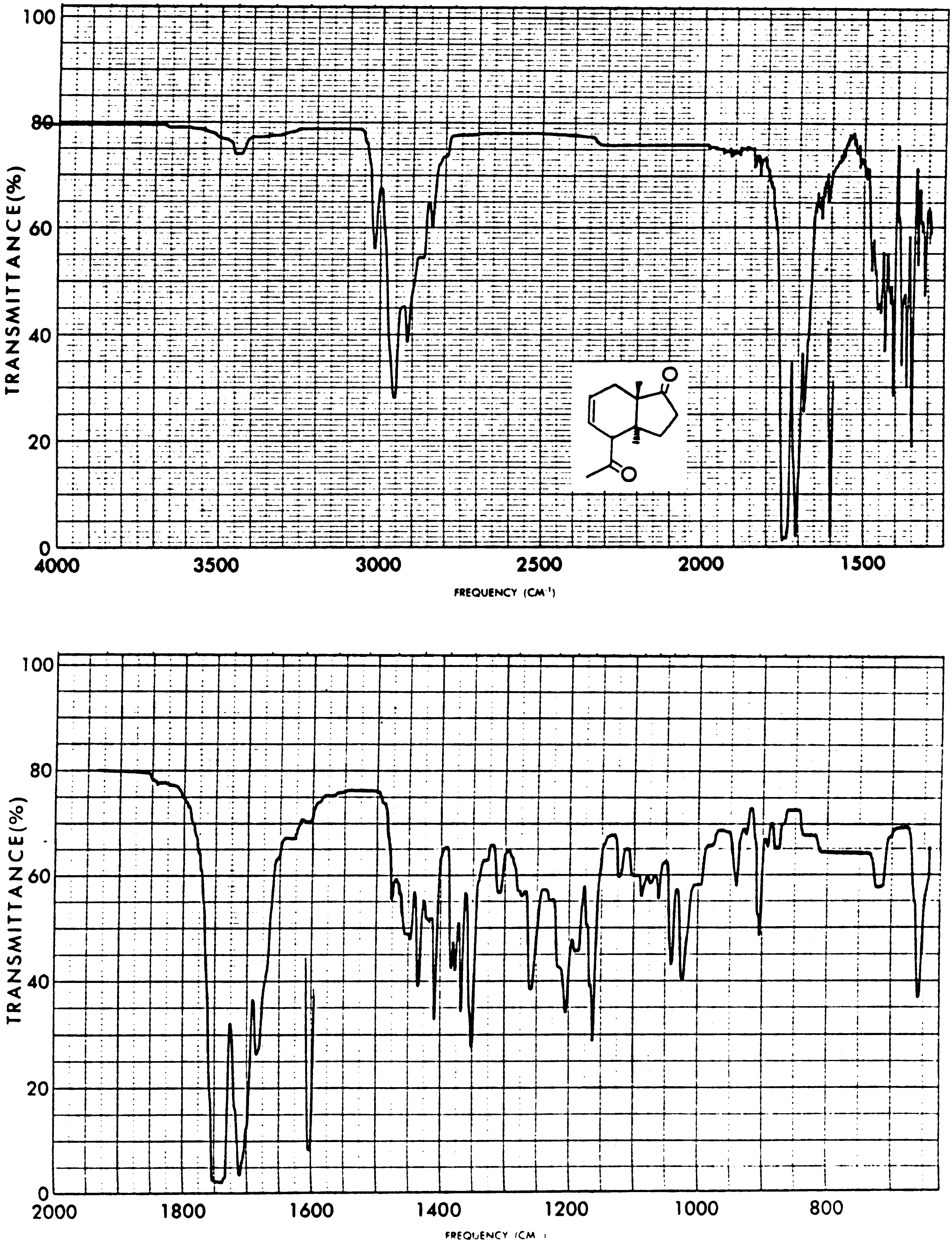


Figure 19. Infrared spectrum of 34.

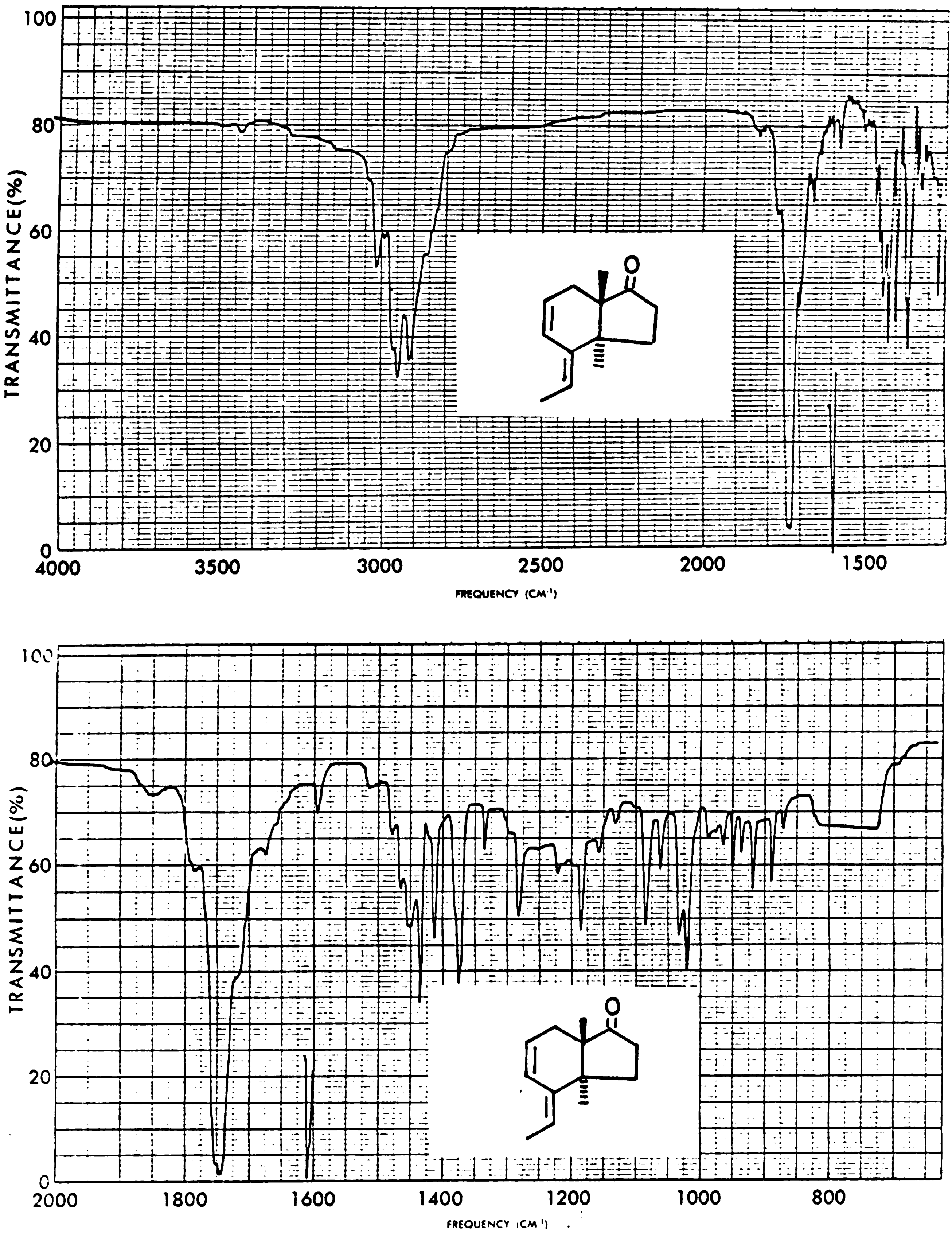


Figure 20. Infrared spectrum of 35.

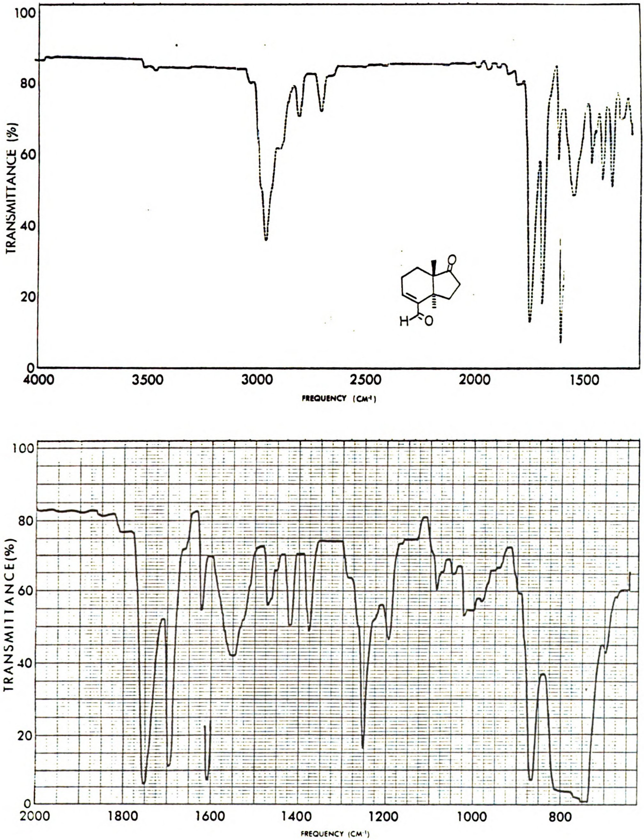


Figure 21. Infrared spectrum of 38.

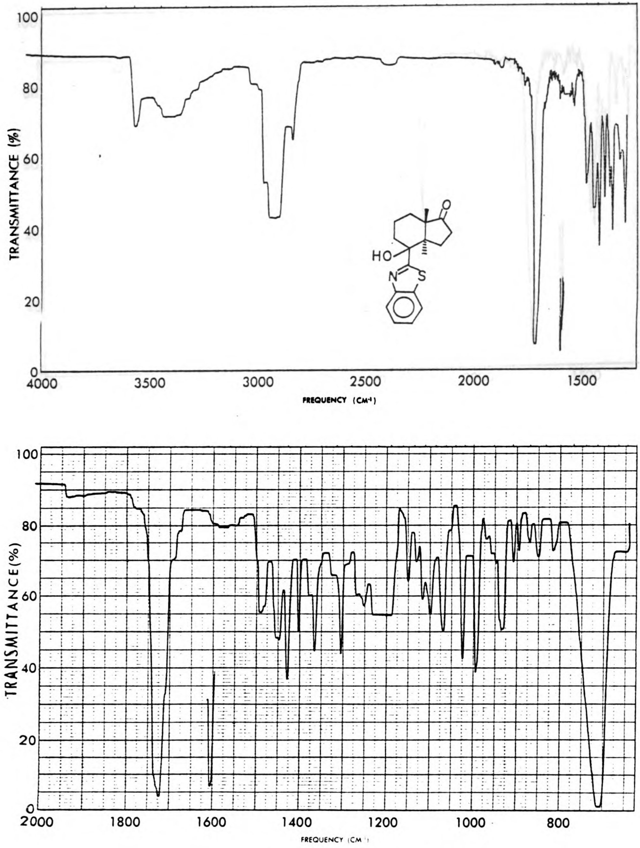


Figure 22. Infrared spectrum of 40.

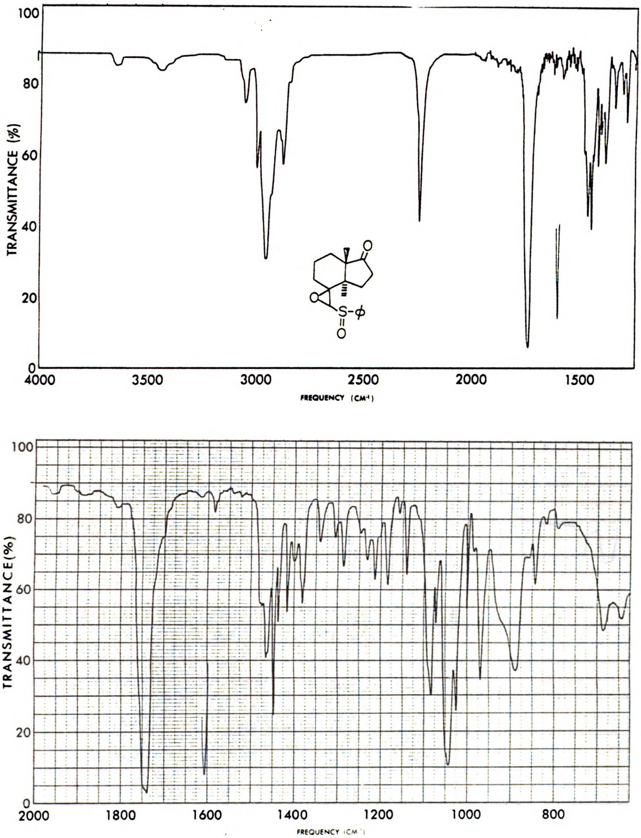


Figure 23. Infrared spectrum of 42.

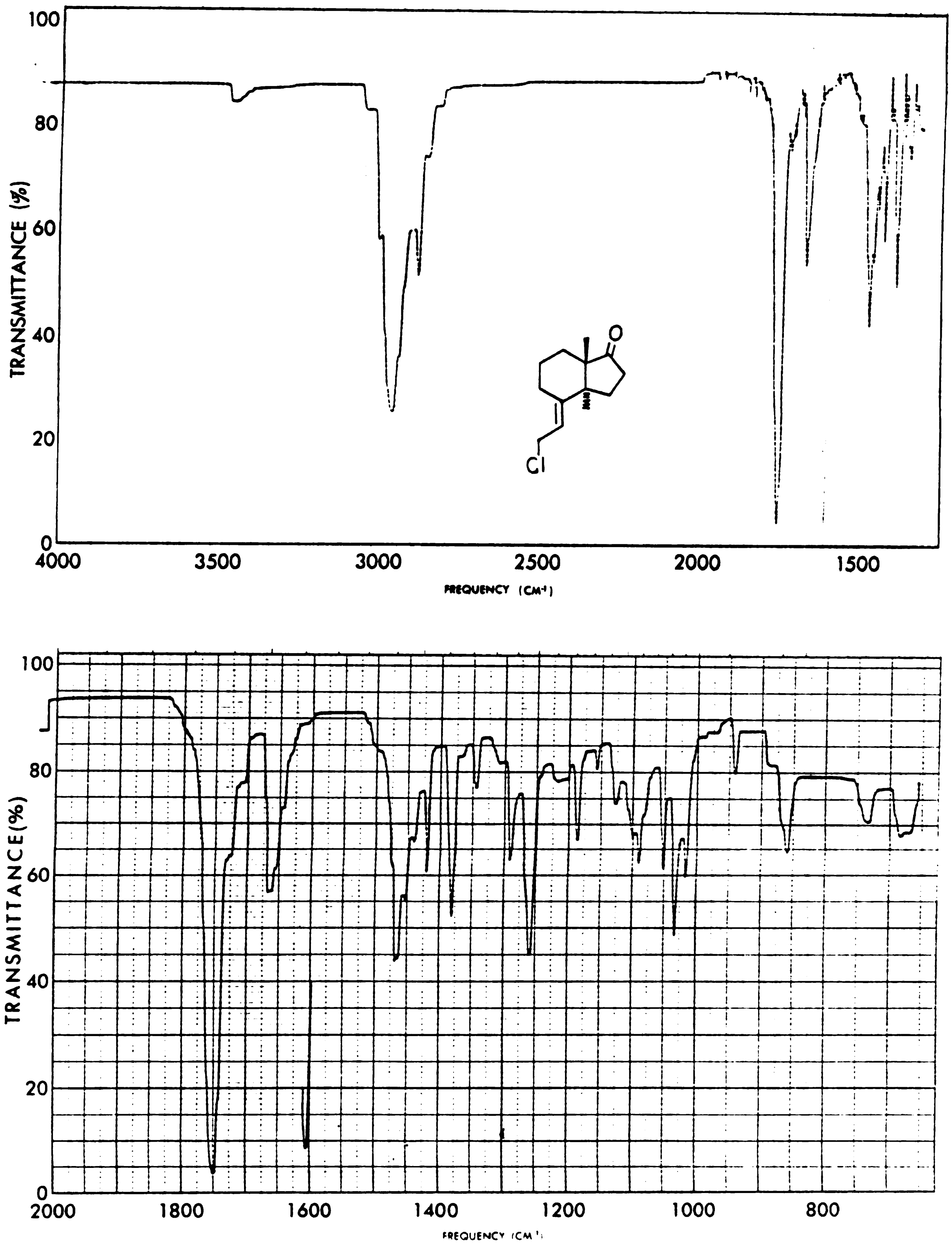


Figure 24. Infrared spectrum of 45.

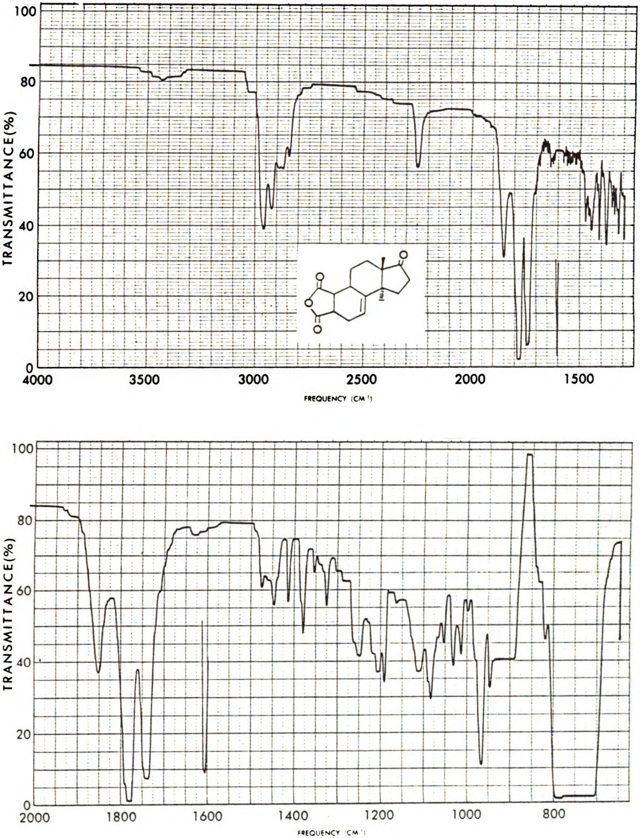


Figure 25. Infrared spectrum of **46**.

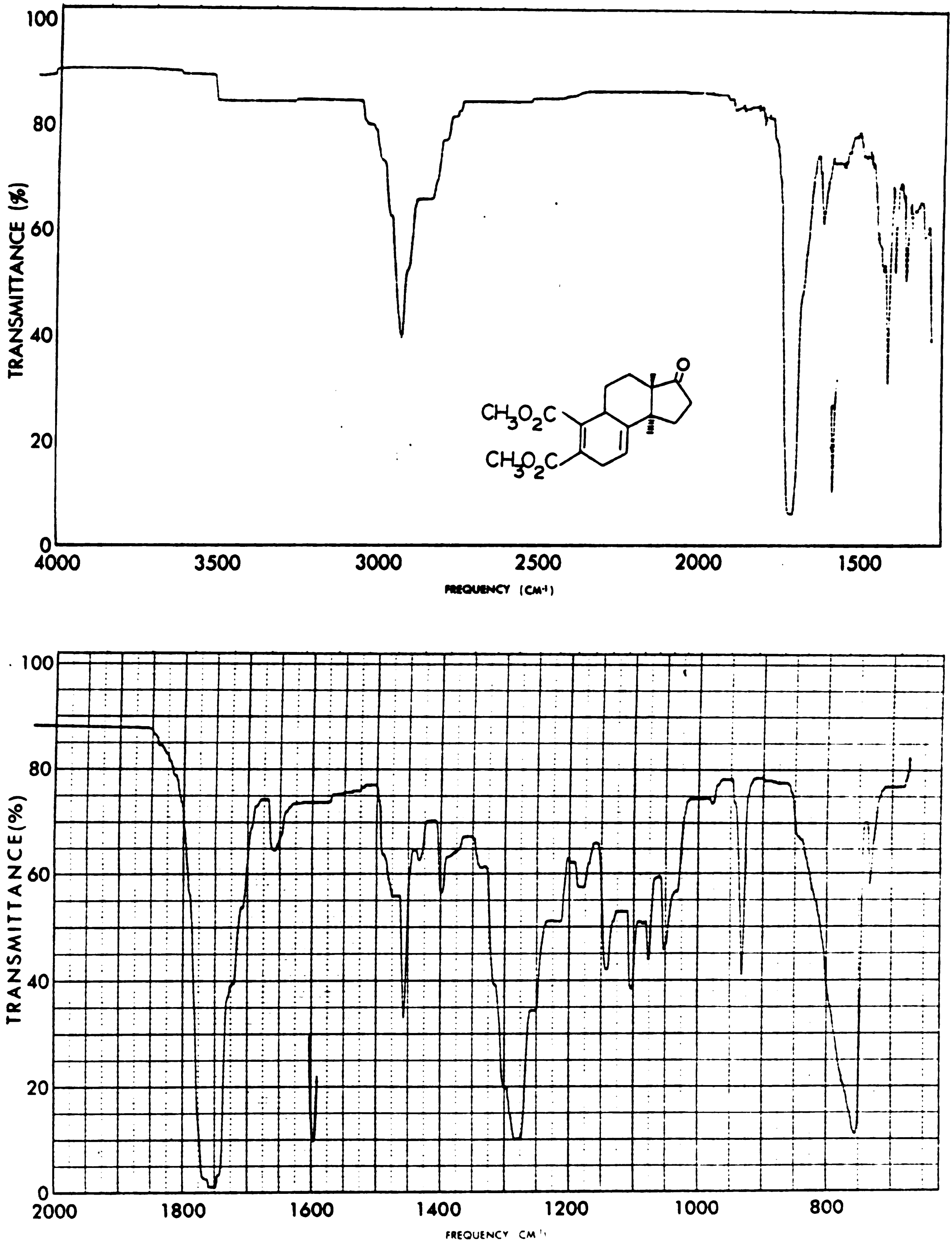


Figure 26. Infrared spectrum of 50.

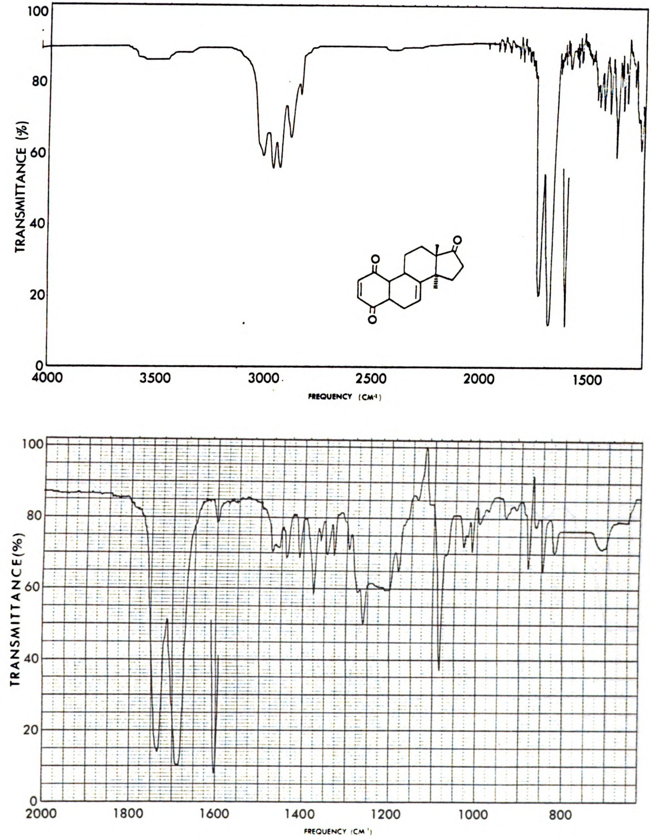


Figure 27. Infrared spectrum of 51.

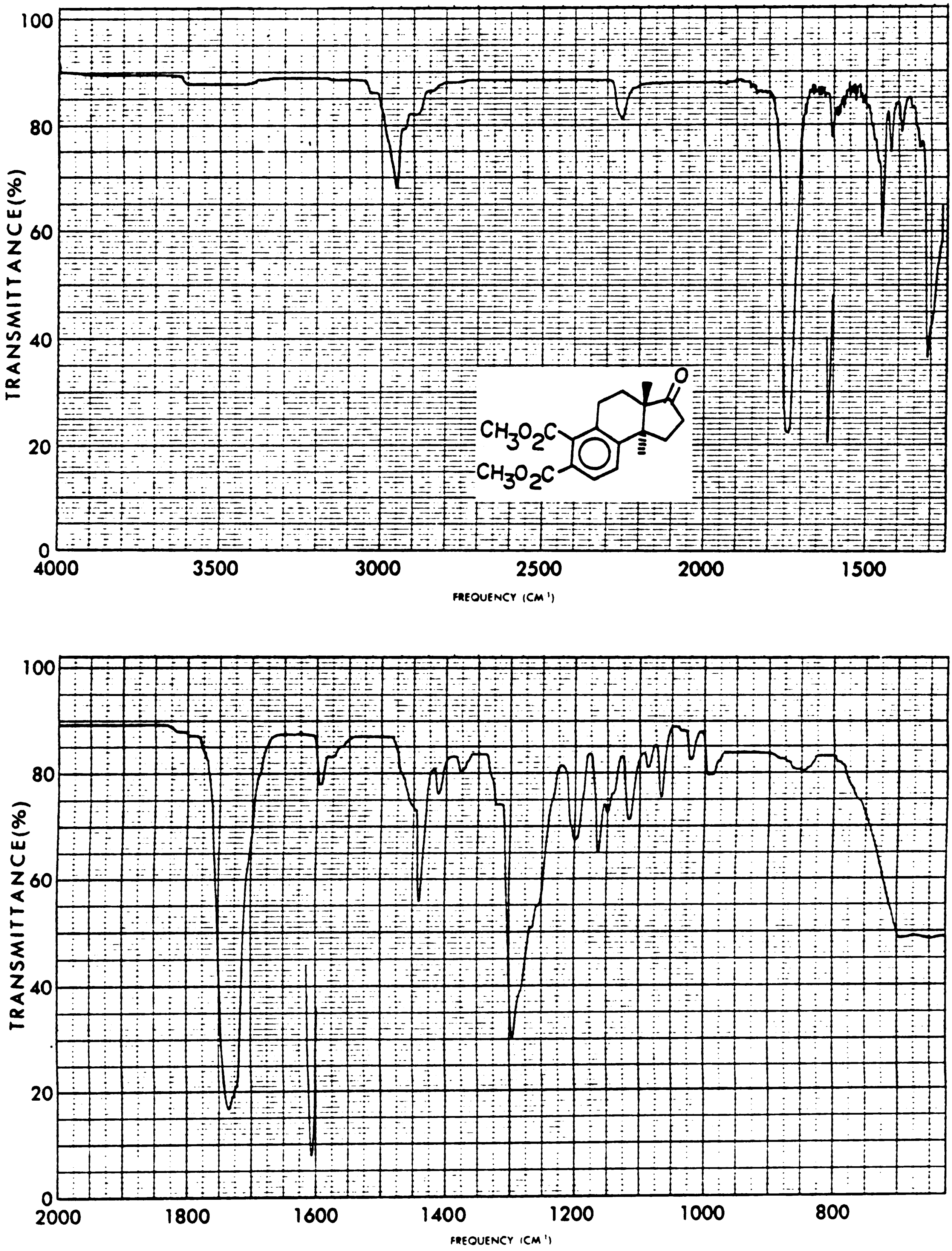


Figure 28. Infrared spectrum of 52.

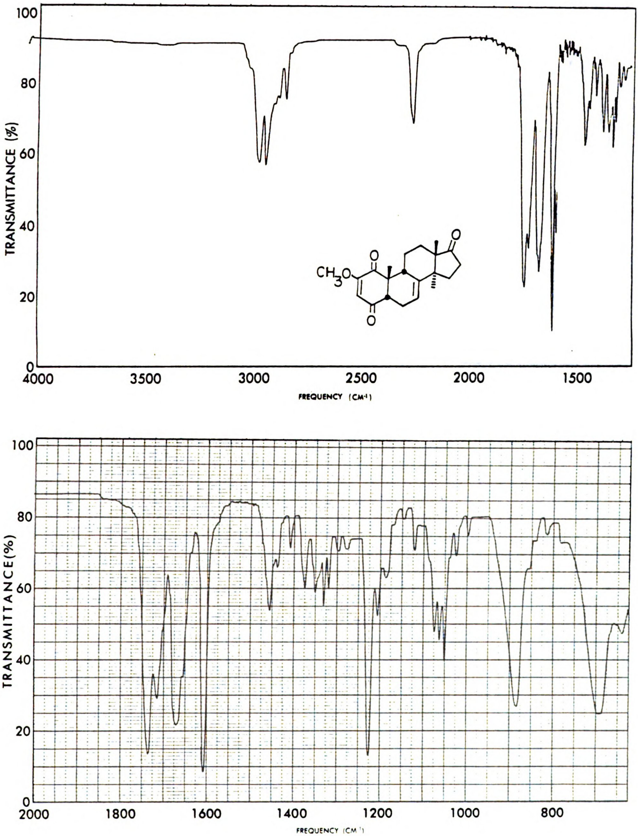


Figure 29. Infrared spectrum of 54.

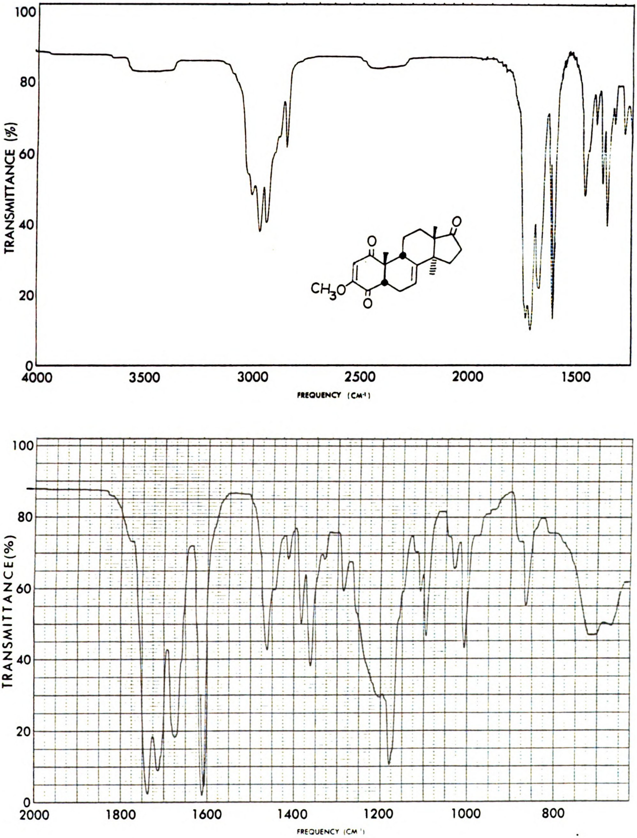


Figure 30. Infrared spectrum of 56.

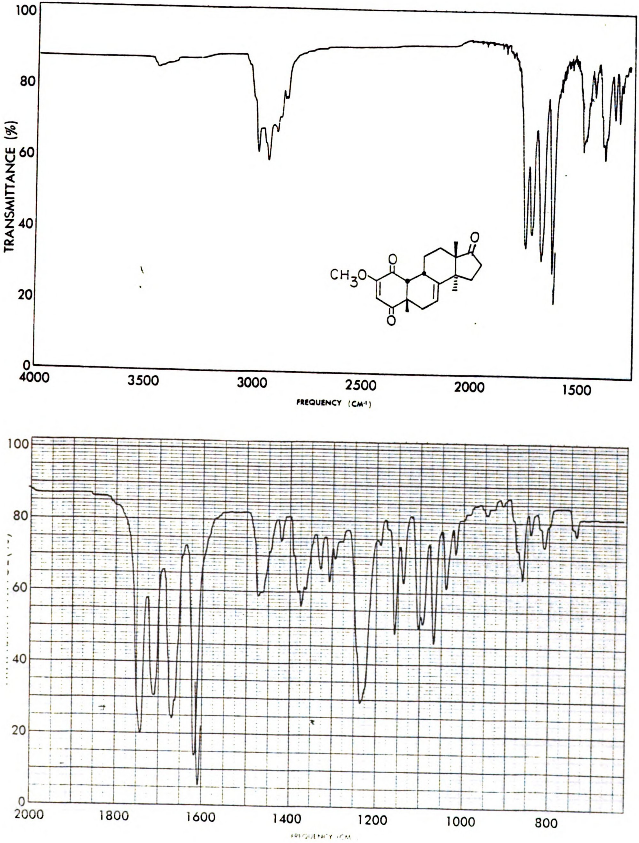


Figure 31. Infrared spectrum of 57.

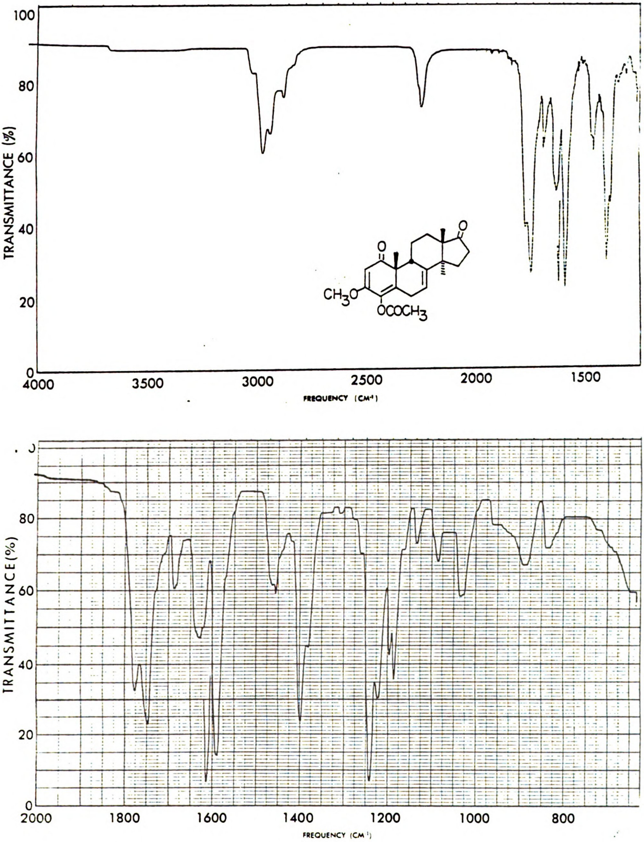


Figure 32. Infrared spectrum of 58.

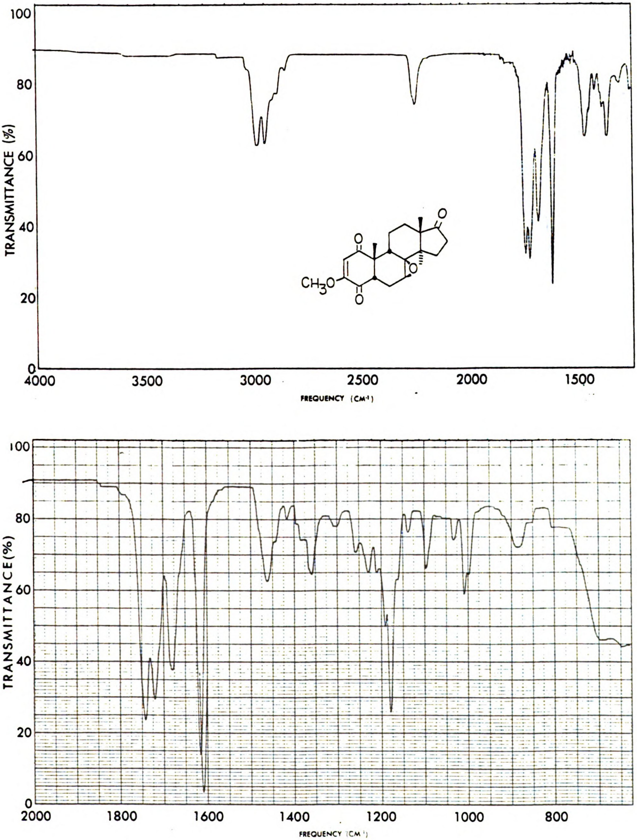


Figure 33. Infrared spectrum of 63.

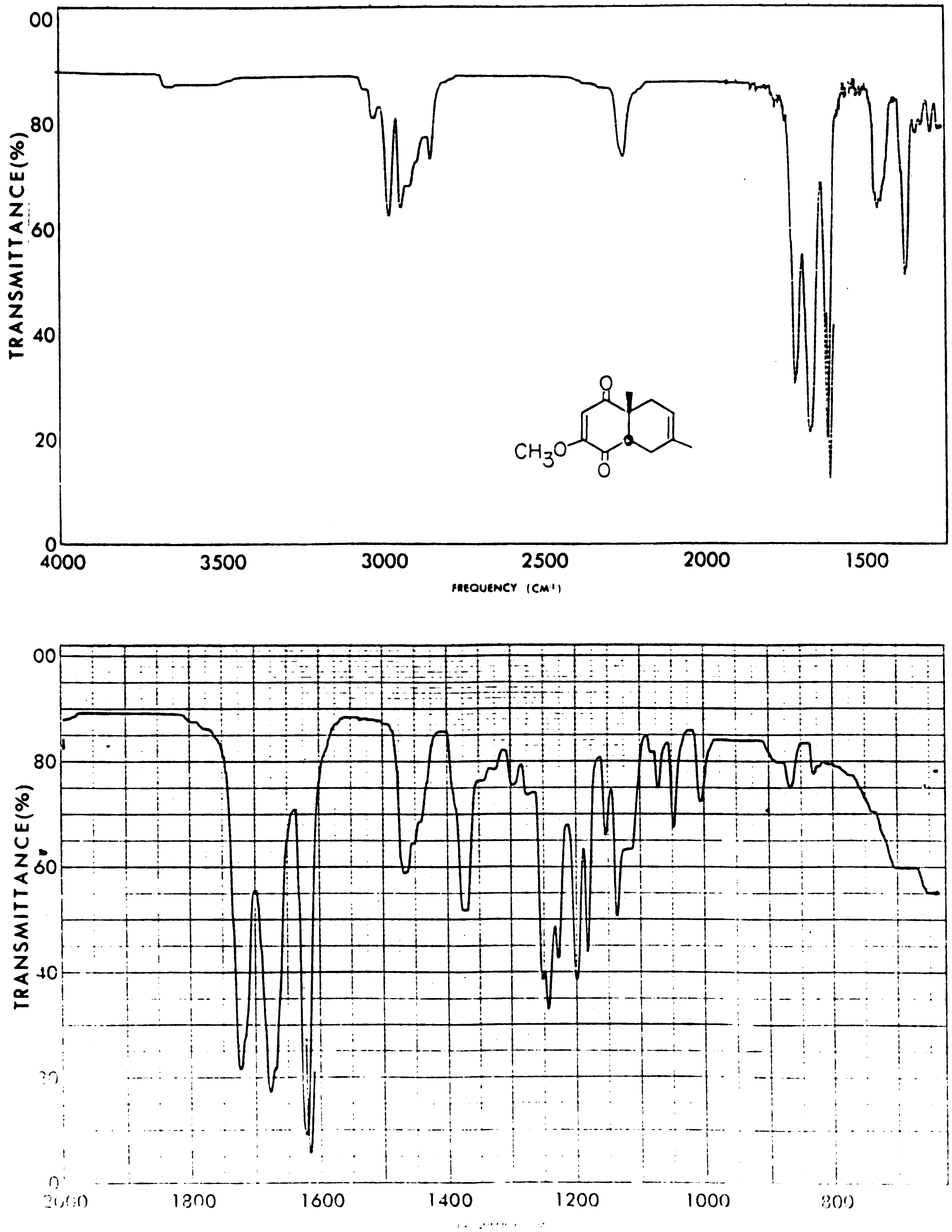


Figure 34. Infrared spectrum of 68.

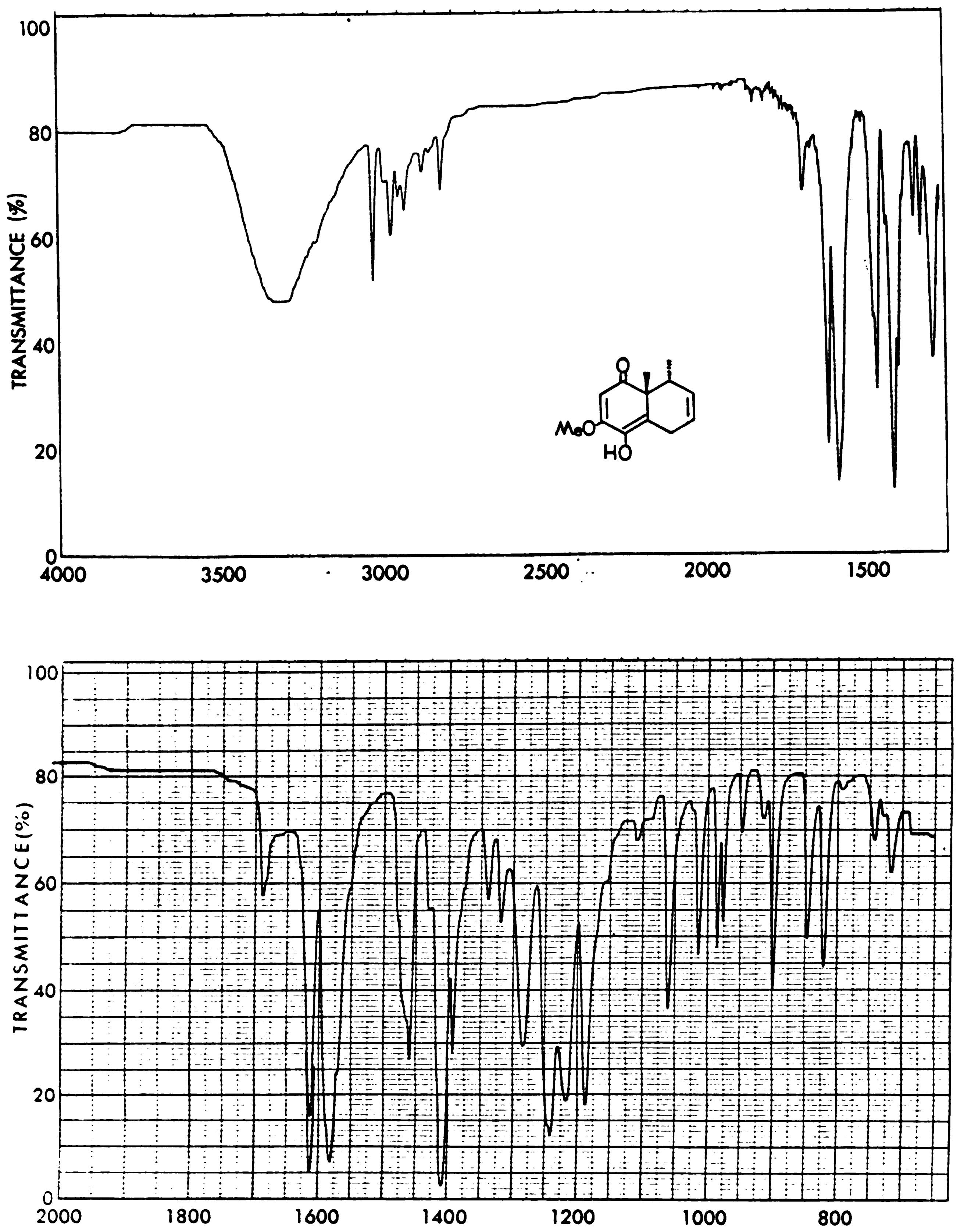


Figure 35. Infrared spectrum of 70.

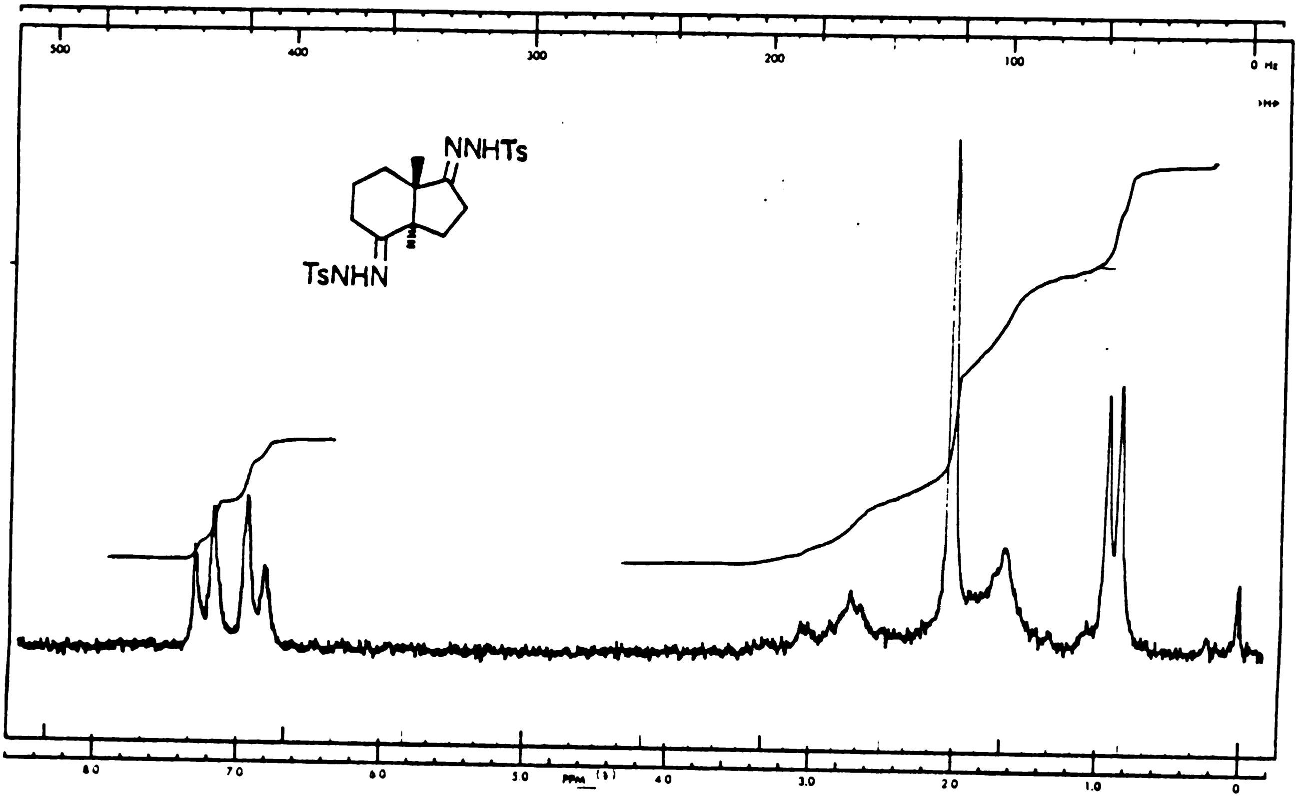
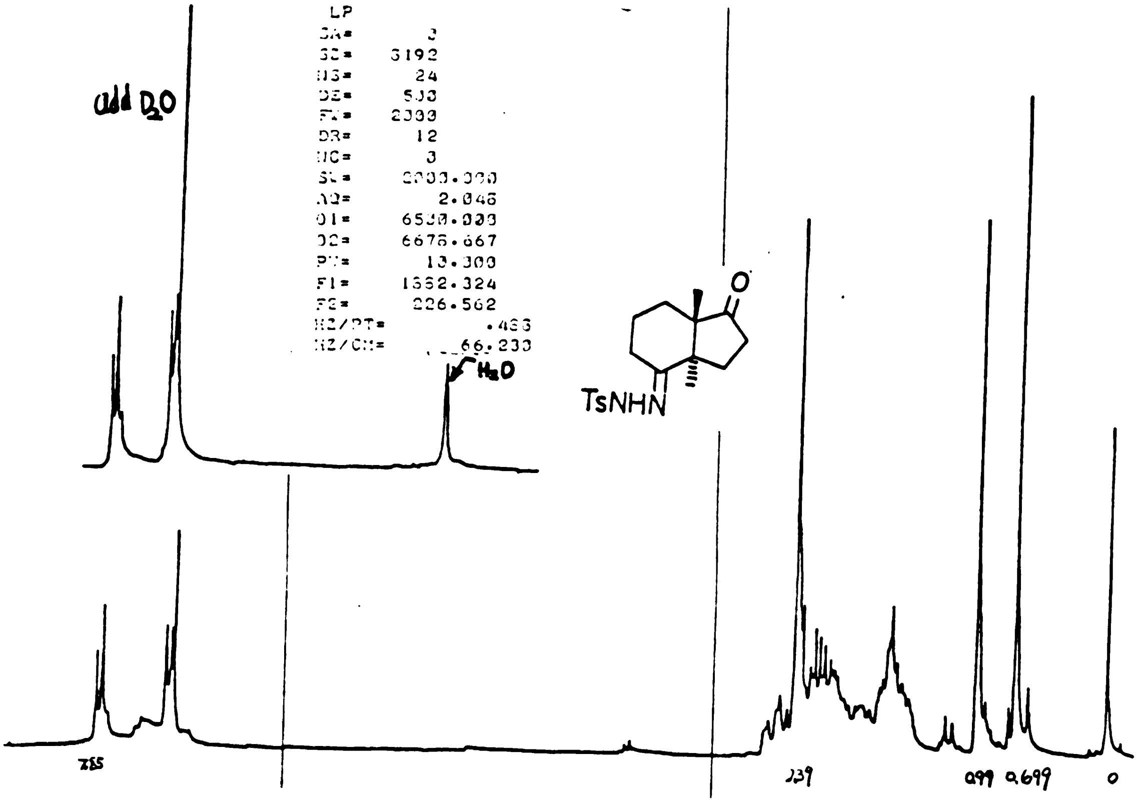


Figure 36. Pmr spectrum of 19.



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FW=     2000
DR=       12
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PW=        13.000
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F2=       226.562
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HZ/CM=       66.233
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Figure 37. Pmr spectrum of 20.

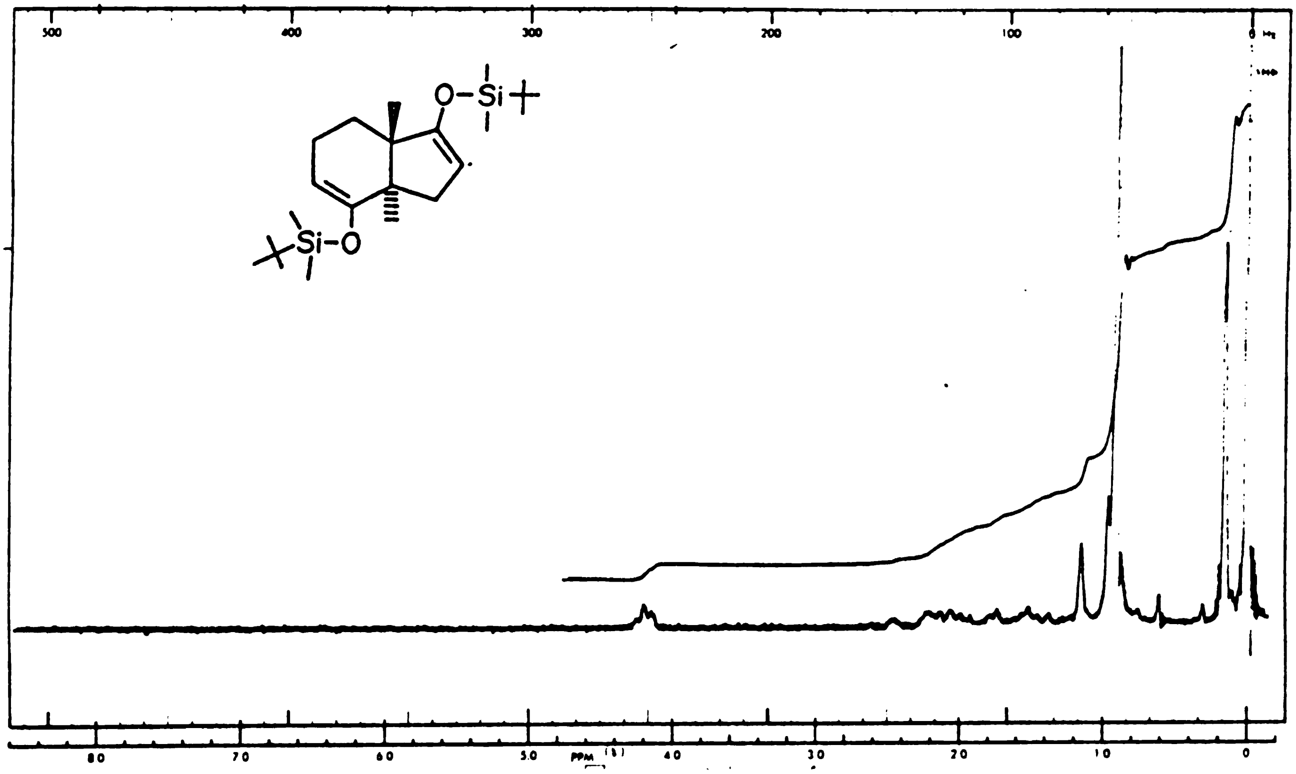


Figure 38. Pmr spectrum of 22.

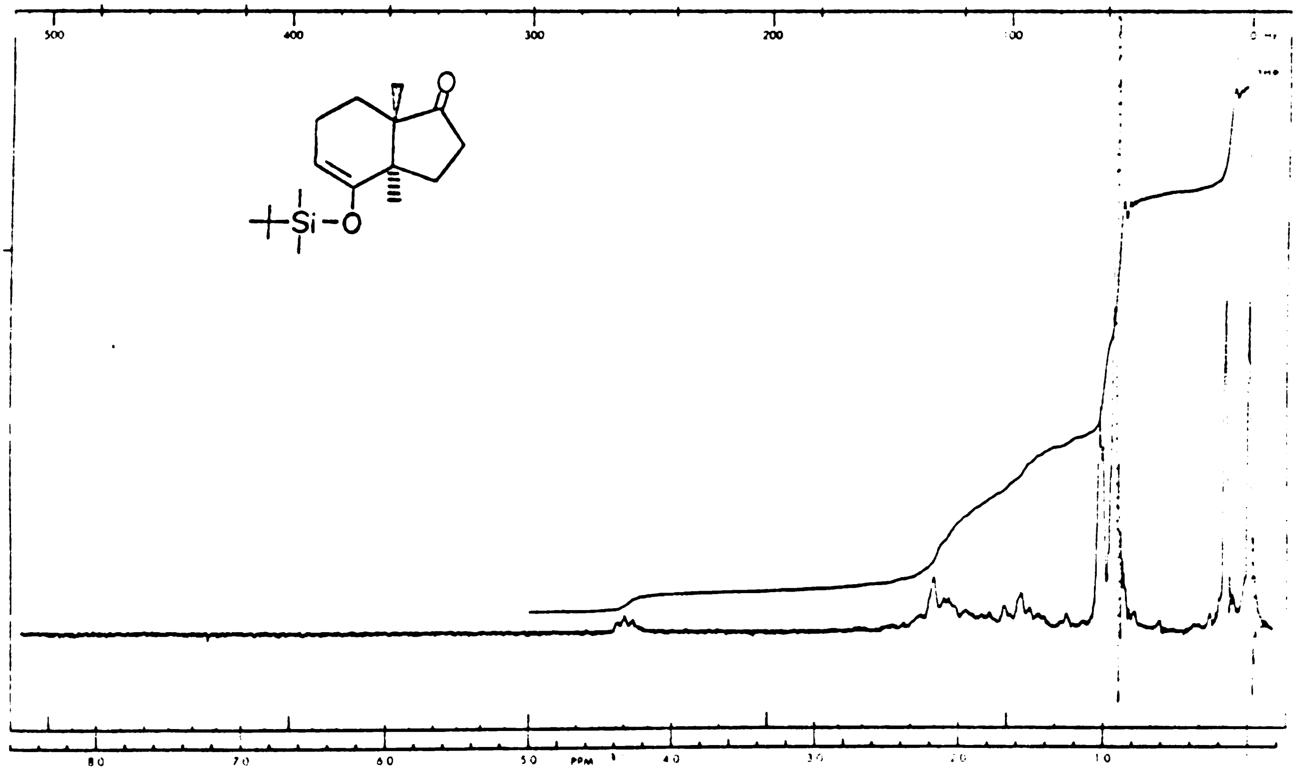


Figure 39. Pmr spectrum of 23.

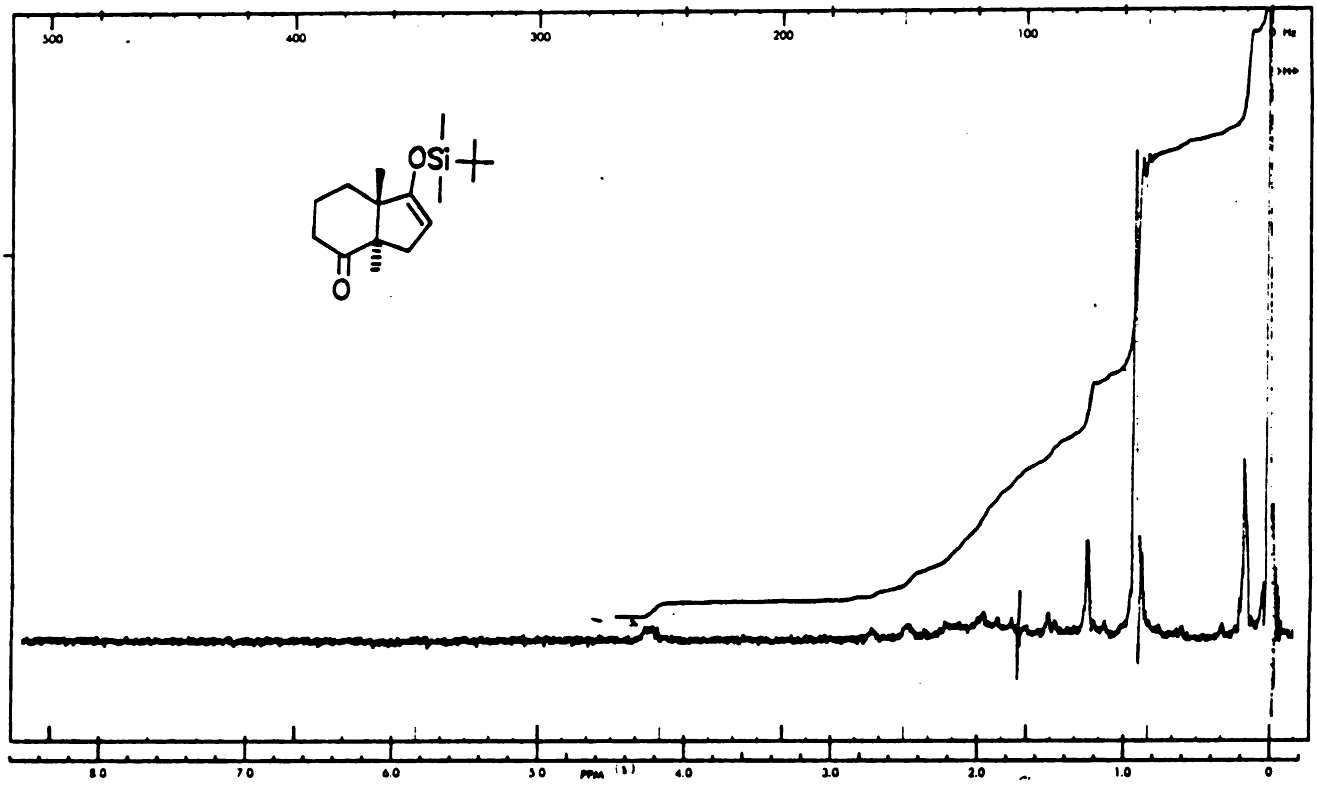


Figure 40. Pmr spectrum of $\underset{\sim}{24}$.

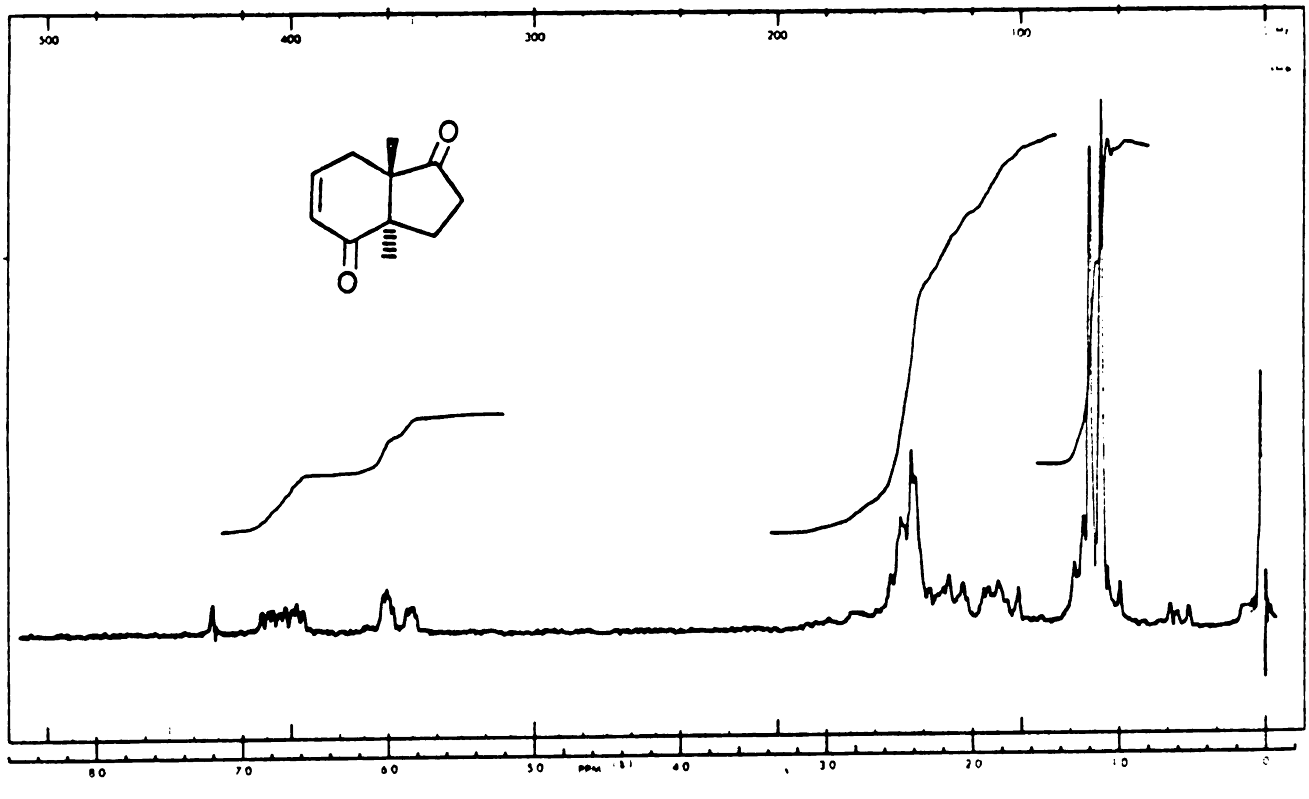


Figure 41. Pmr spectrum of $\underset{\sim}{27}$.

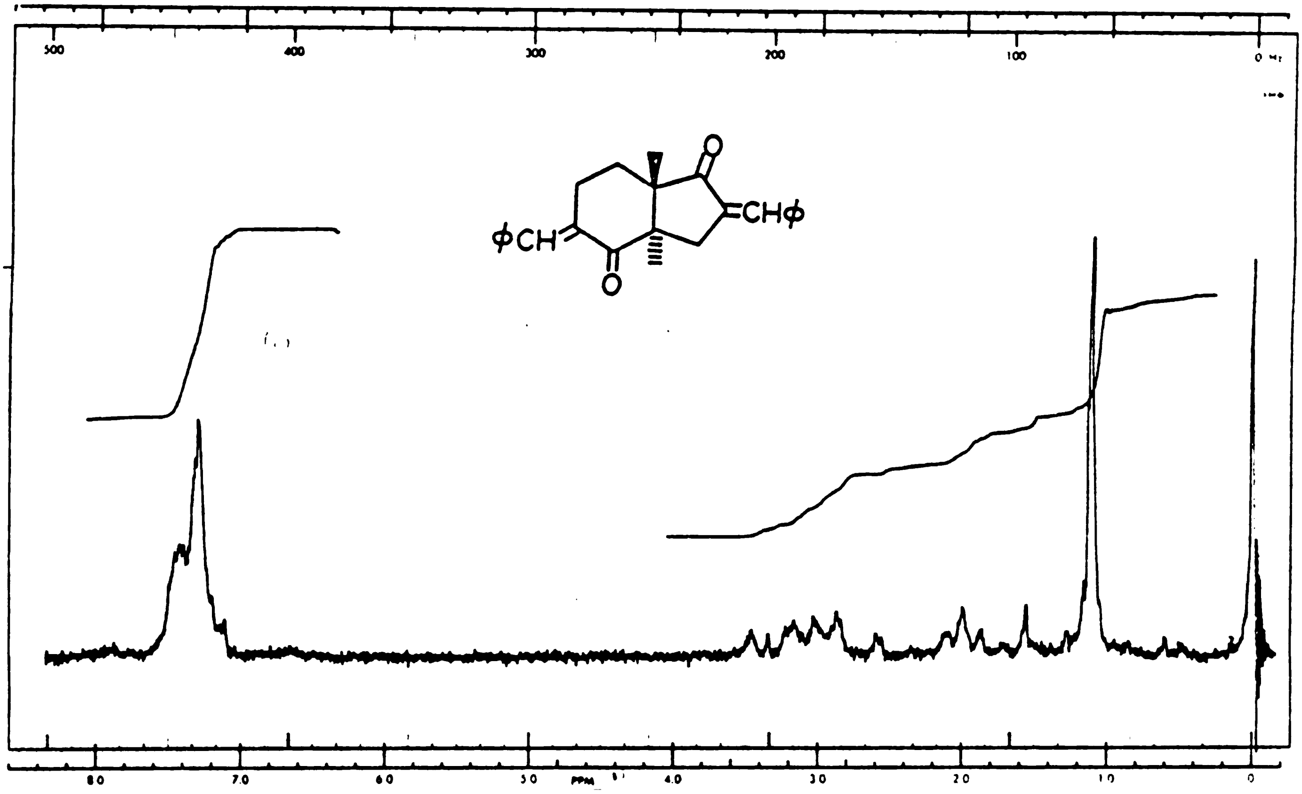


Figure 42. Pmr spectrum of 28.

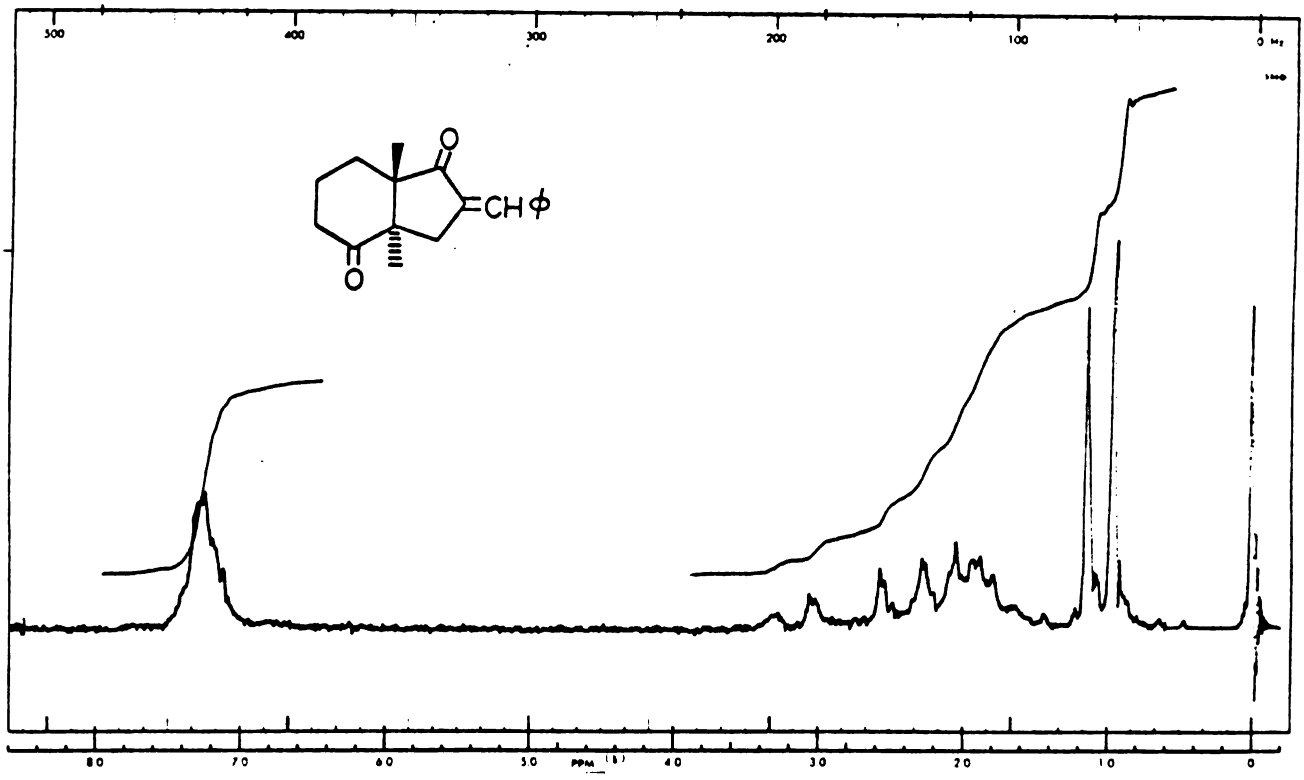


Figure 43. Pmr spectrum of 29.

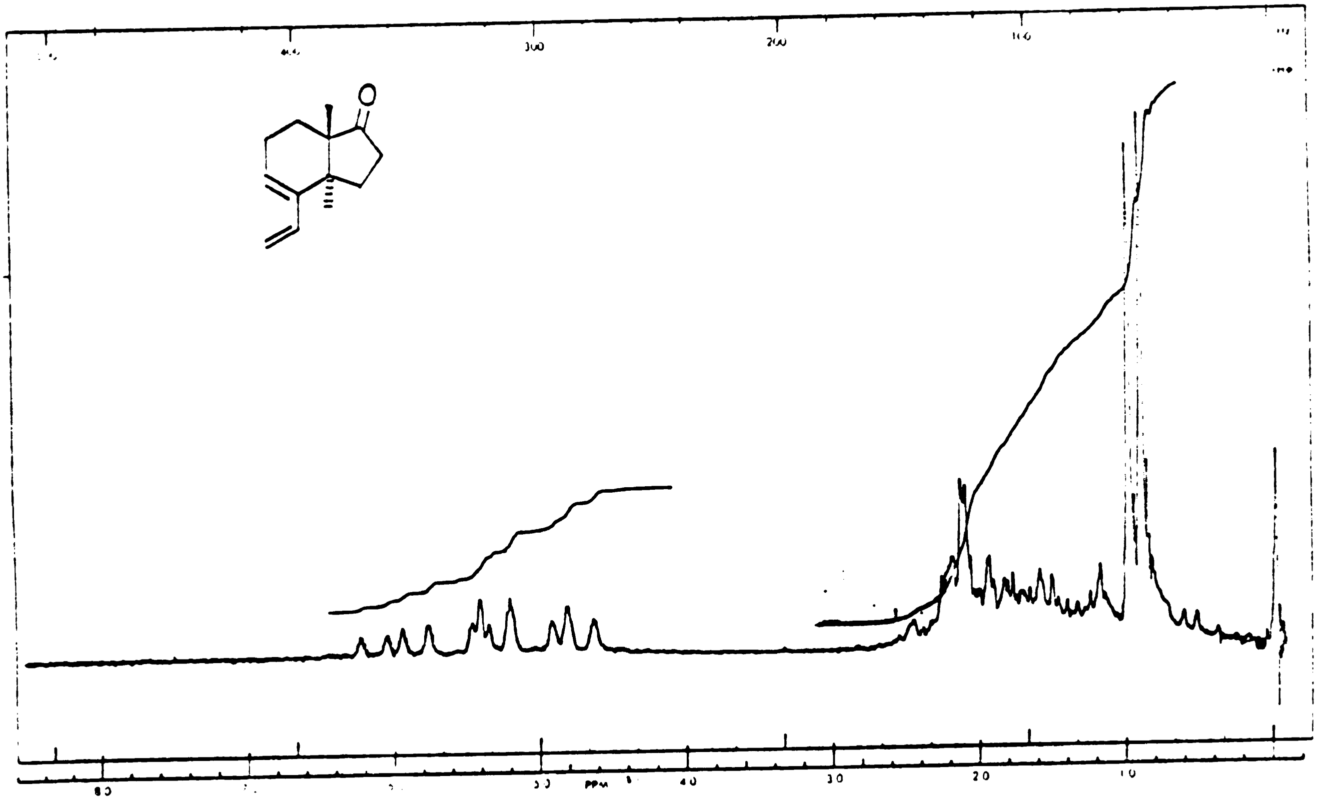


Figure 44. Pmr spectrum of 31.

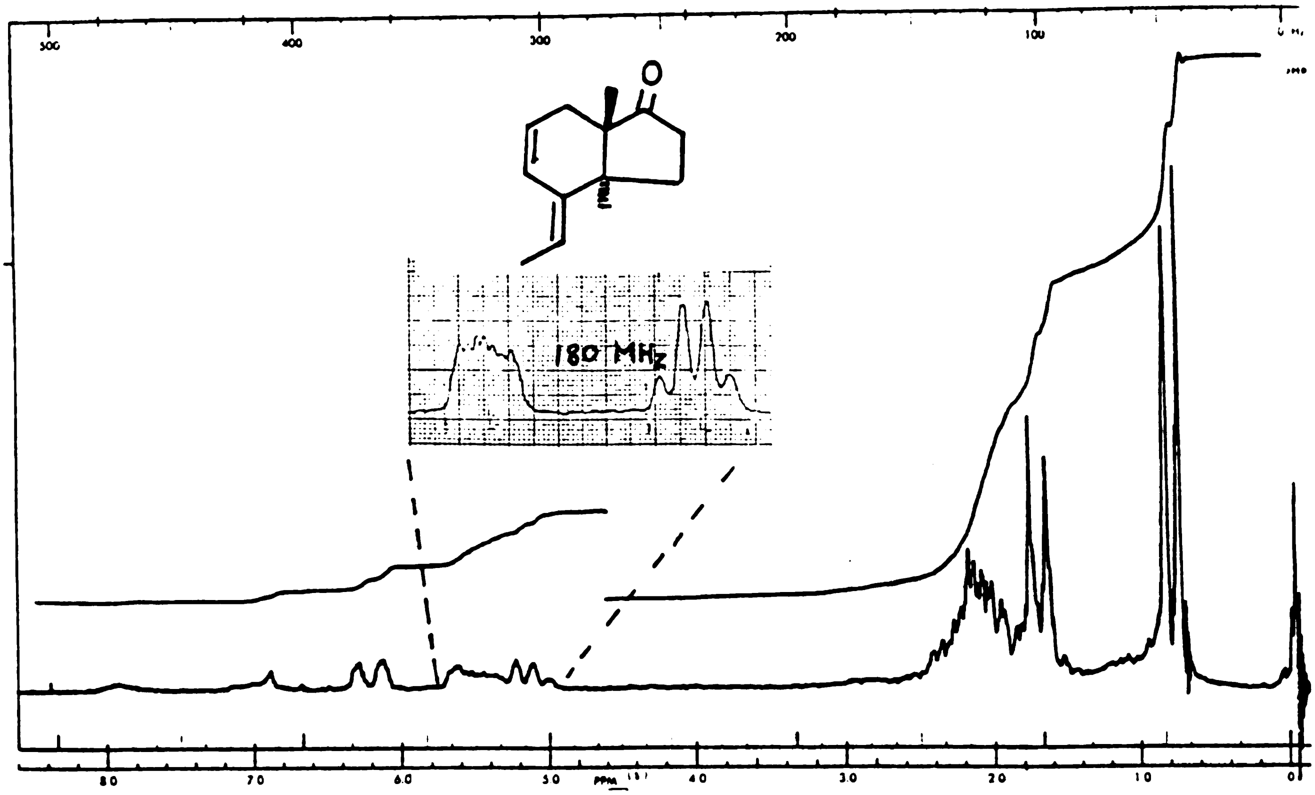


Figure 45. Pmr spectrum of 35.

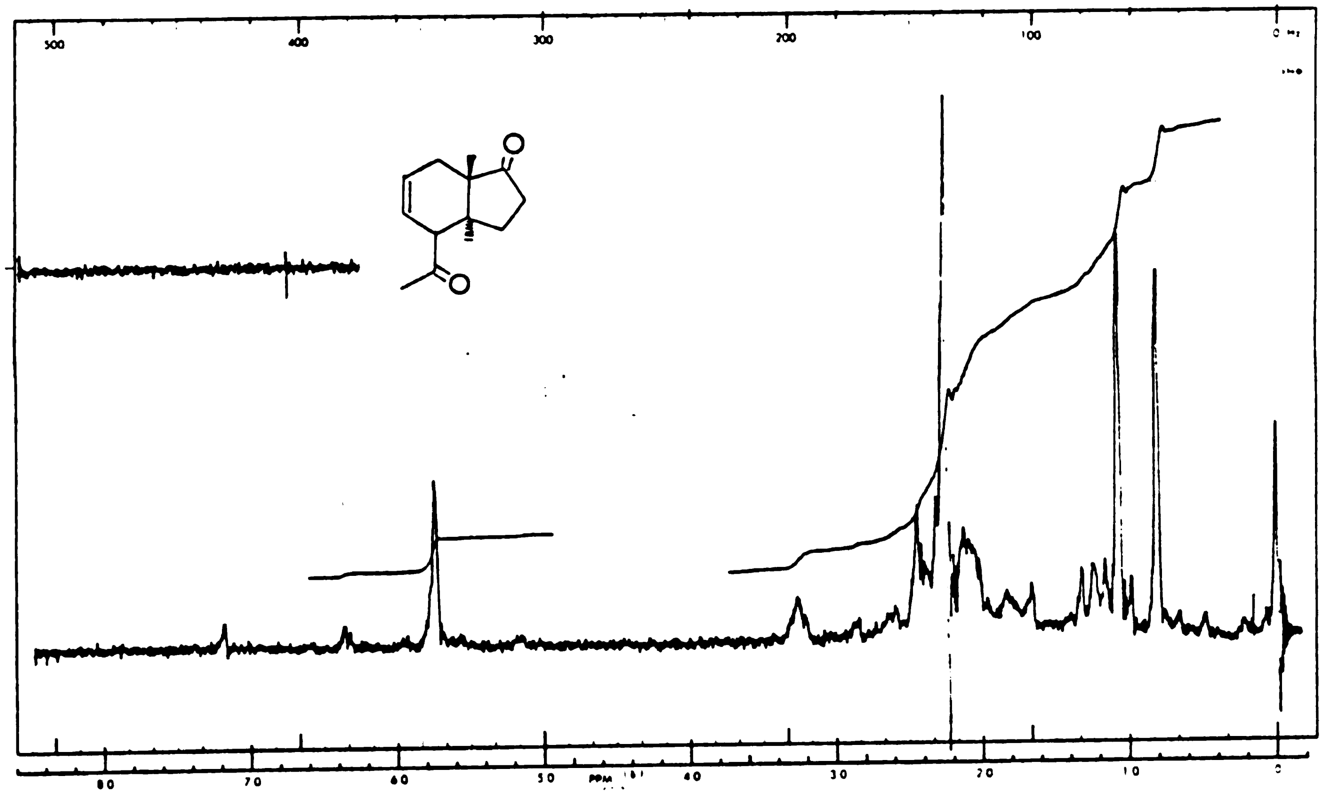


Figure 46. Pmr spectrum of 34.

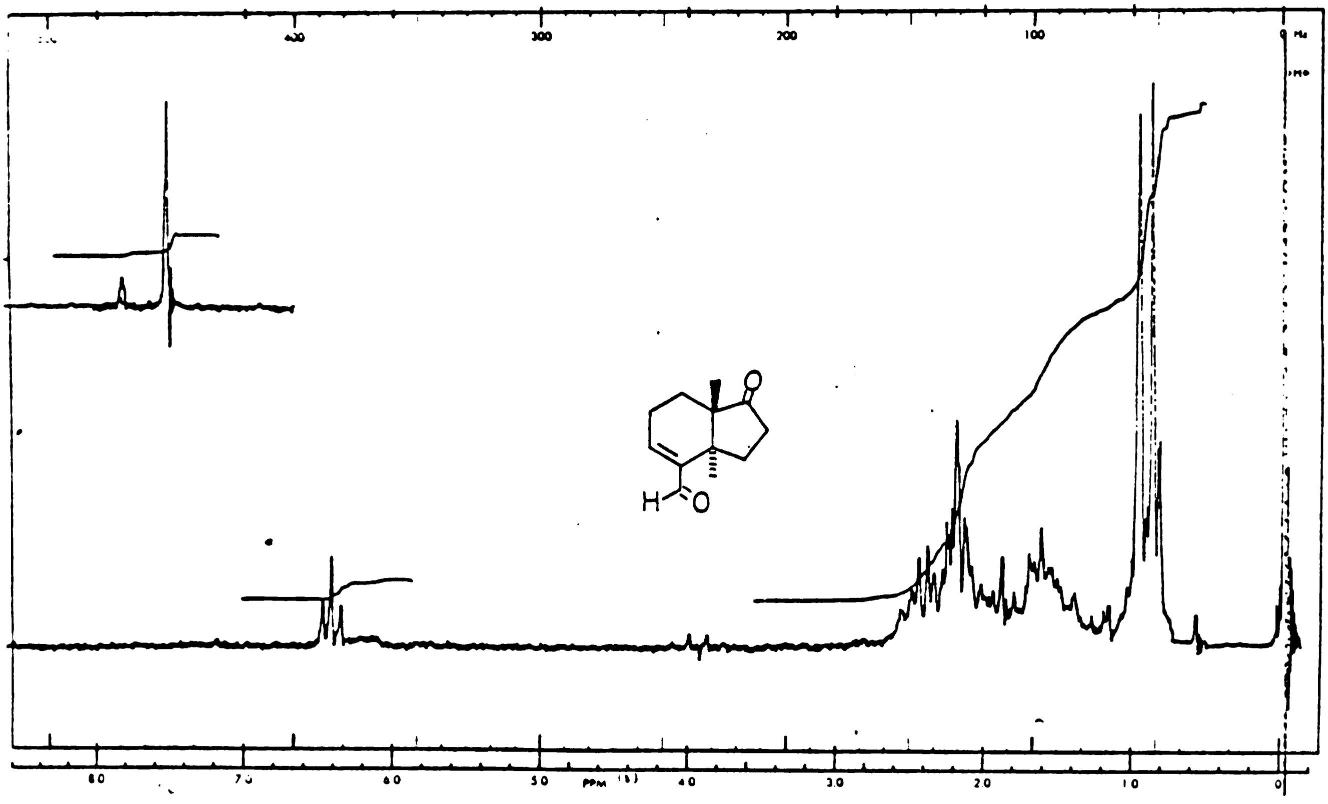


Figure 47. Pmr spectrum of 38.

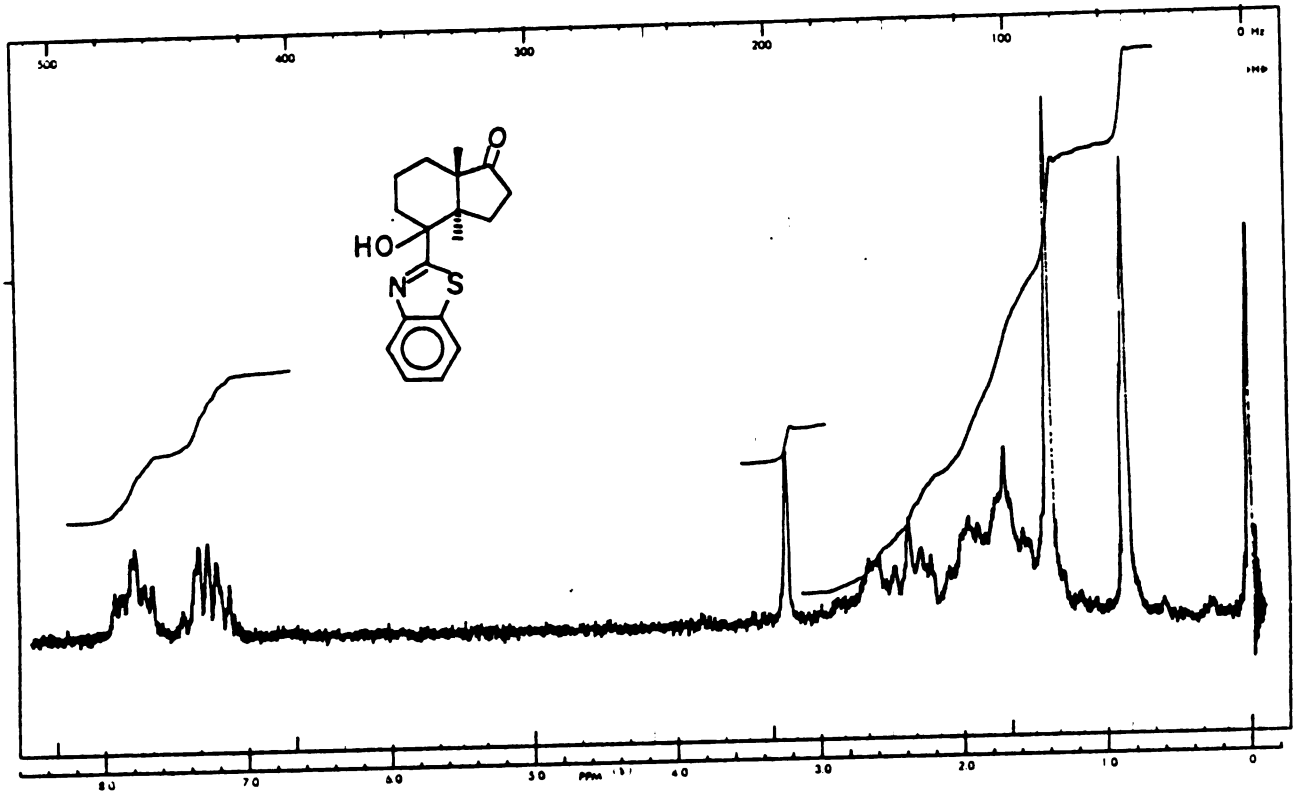
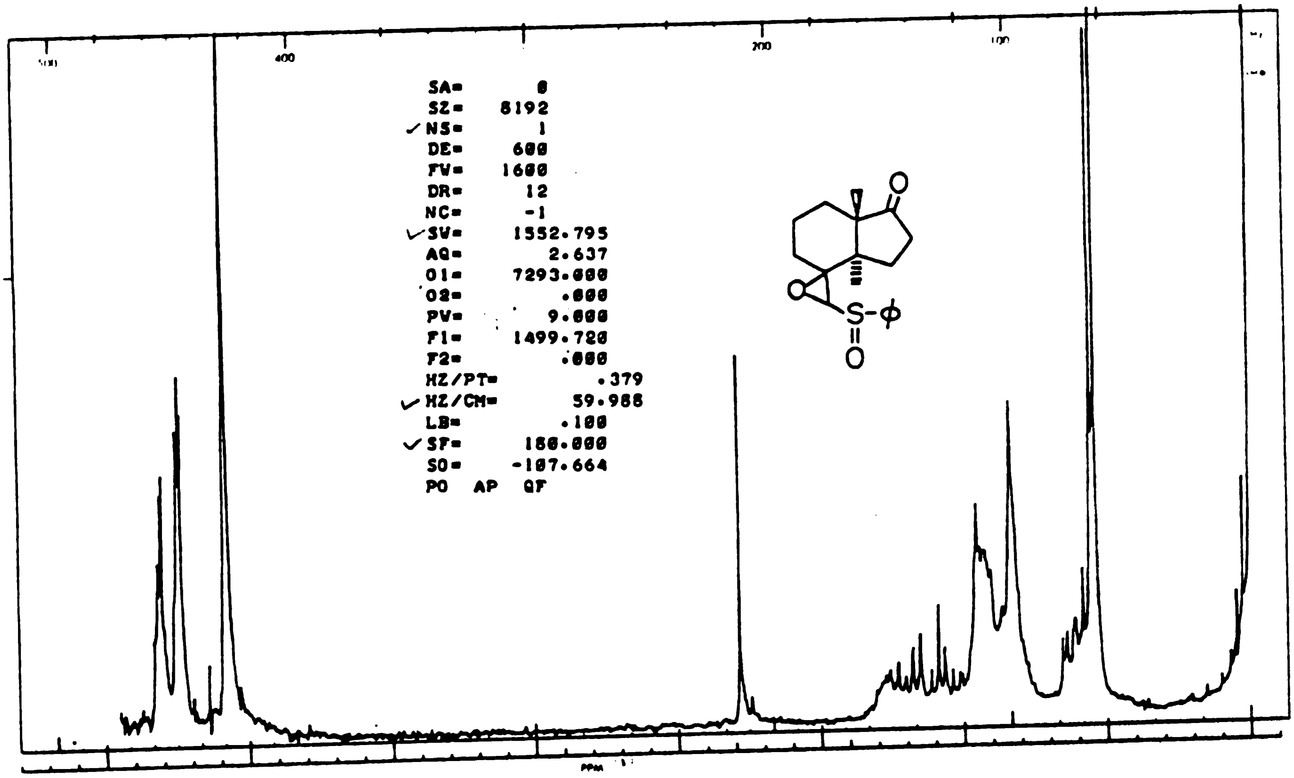


Figure 48. Pmr spectrum 40.



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  O1=     7293.000
  O2=         .000
  PV=        9.000
  F1=     1499.720
  F2=         .000
  HZ/PT=        .379
✓ HZ/CM=      59.988
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✓ SF=      100.000
  SO=     -107.664
  PO   AP   QF
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Figure 49. Pmr spectrum 42.

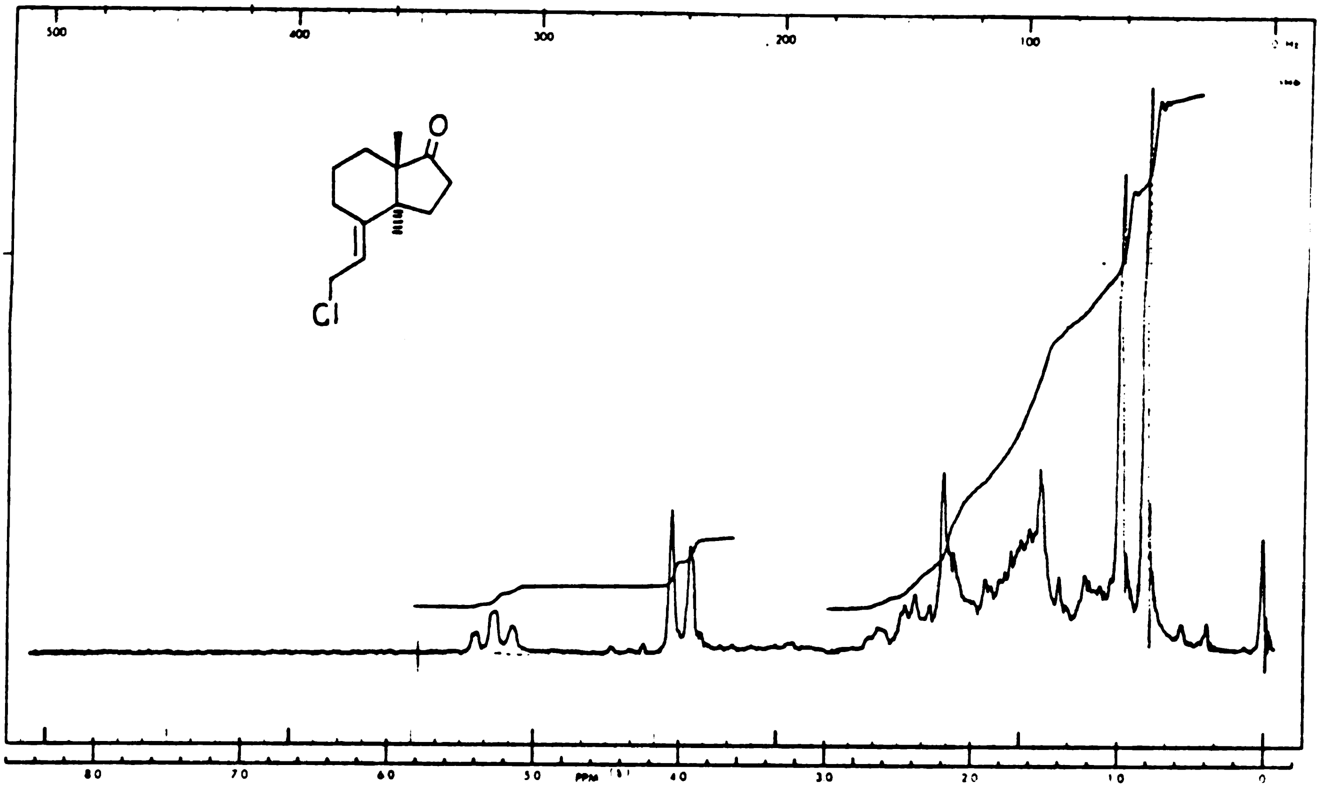


Figure 50. Pmr spectrum of $\underset{\sim}{45}$.

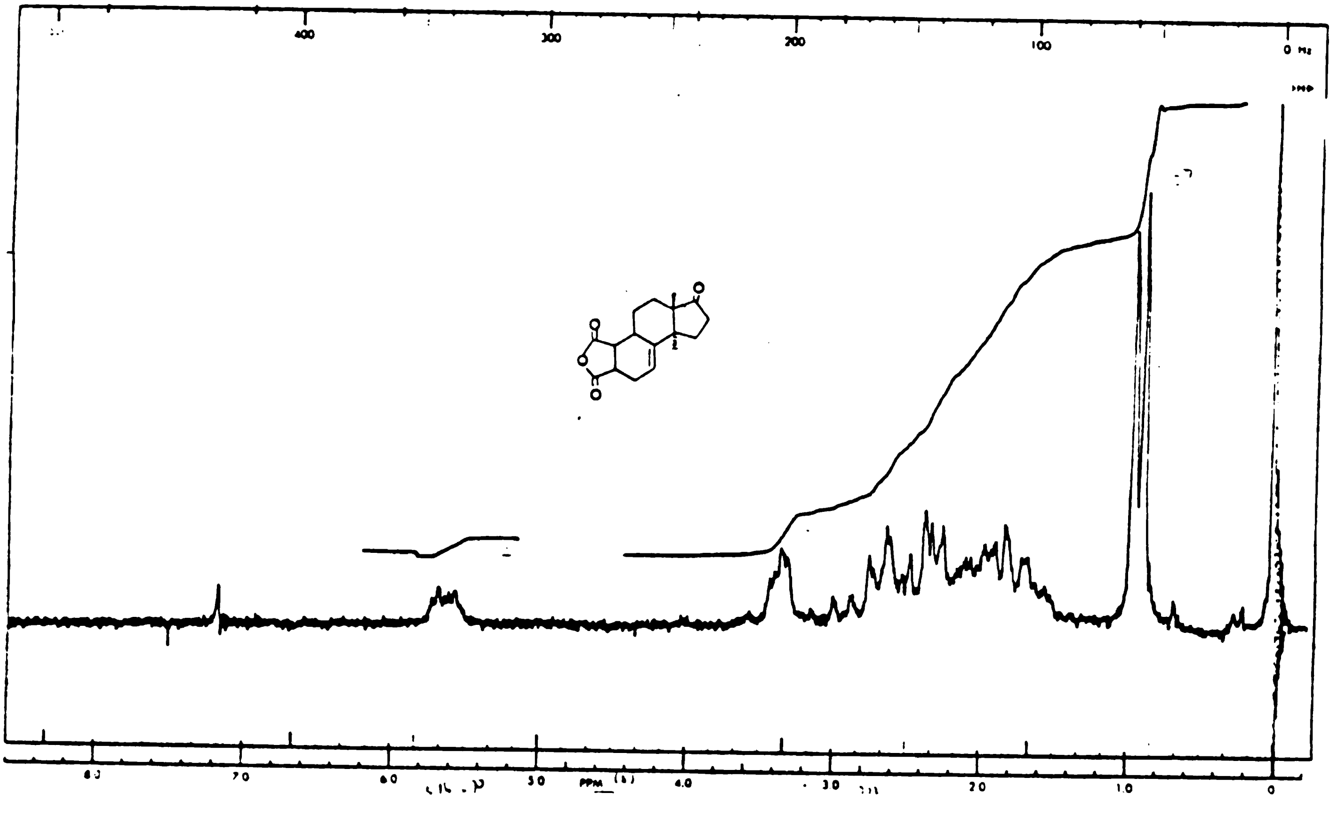


Figure 51. Pmr spectrum of $\underset{\sim}{46}$.

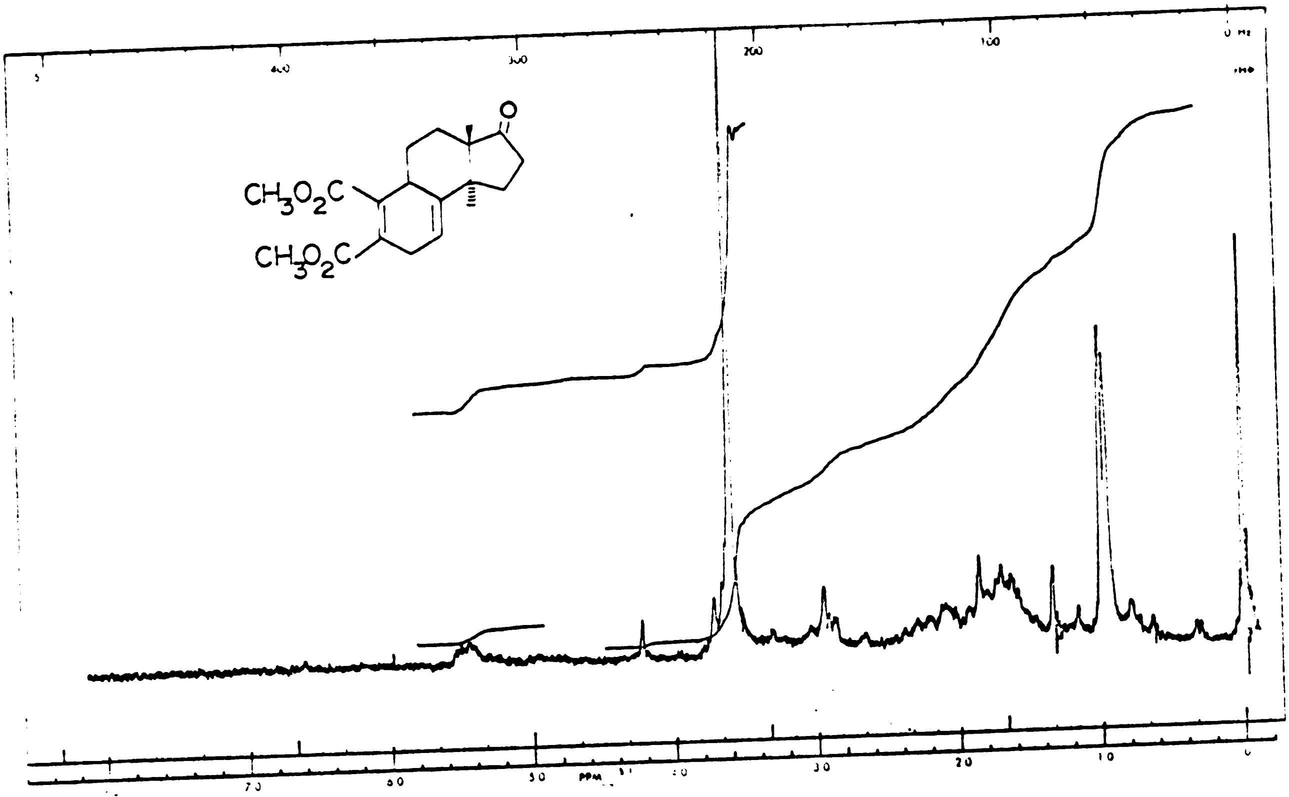
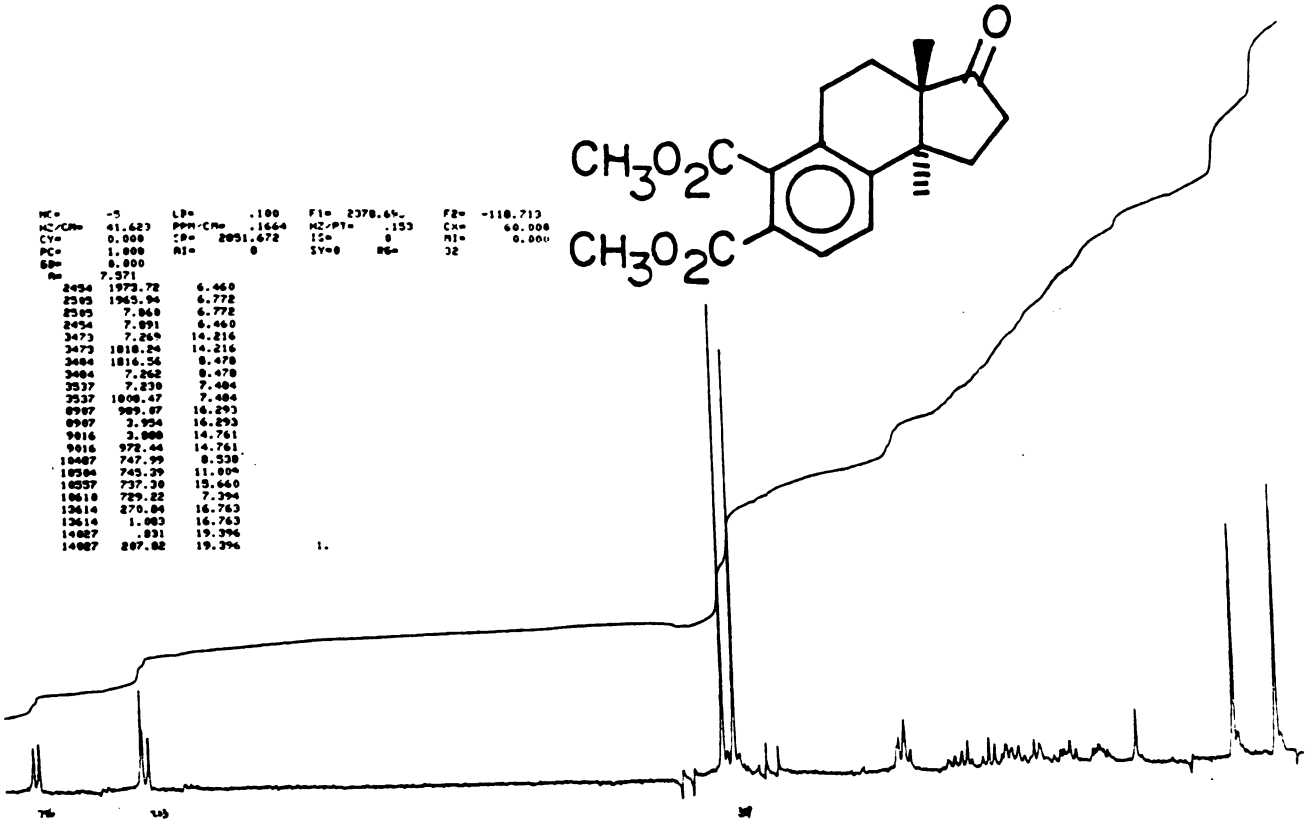


Figure 52. Pmr spectrum of 50.



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PC=      1.000   AI=         0     SY=0     RG=     32
GD=      0.000
 A=     7.571
   2454  1973.72     6.460
   2505  1965.94     6.772
   2505     7.060    6.772
   2454     7.091    6.460
   3473     7.269   14.216
   3473  1010.24    14.216
   3404  1016.56     0.470
   3404     7.262    0.470
   3537     7.230    7.404
   3537  1000.47     7.404
   0907   909.07    16.293
   0907     3.954   16.293
   9016     3.000   14.761
   9016   972.44    14.761
  10407   747.99     0.530
  10504   745.39    11.004
  10557   737.30    15.660
  10610   729.22     7.394
  13614   270.04    16.763
  13614     1.003   16.763
  14027      .031   19.396
  14027   207.02    19.396          1.
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Figure 53. Pmr spectrum of 52.

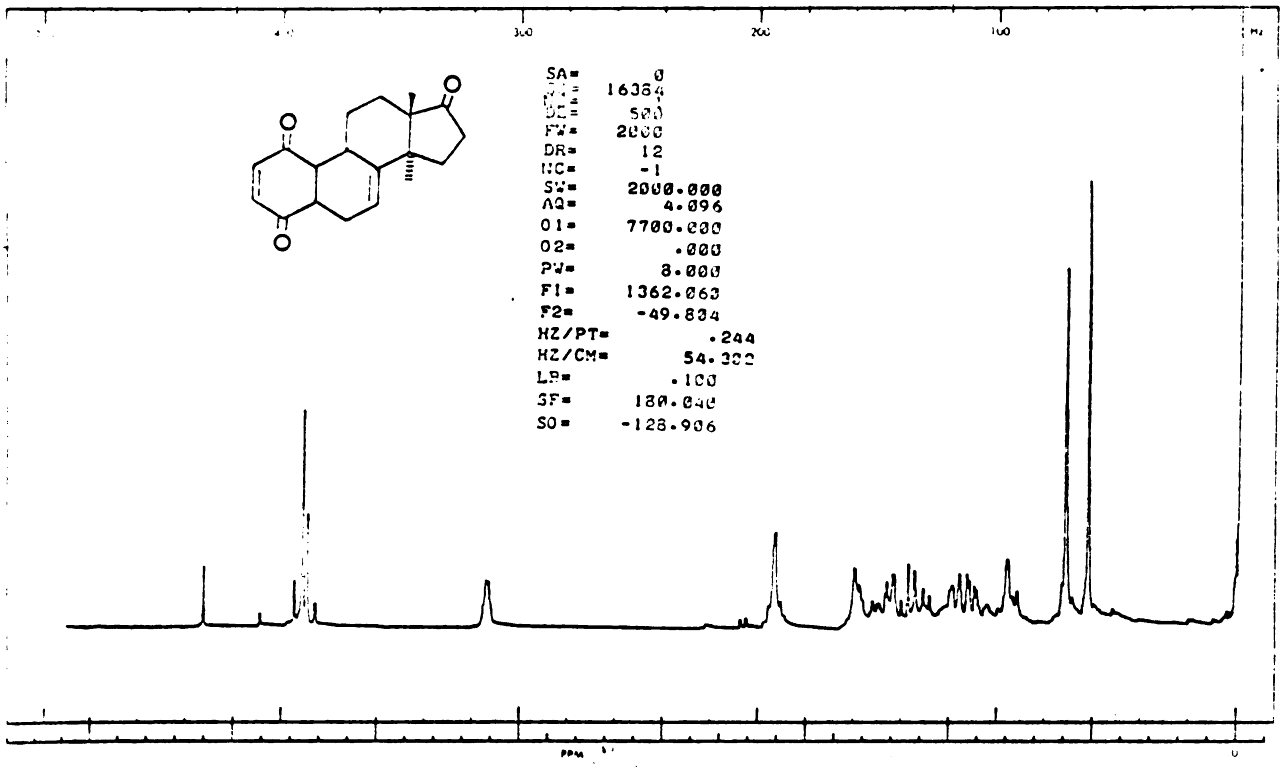


Figure 54. Pmr spectrum of 51.

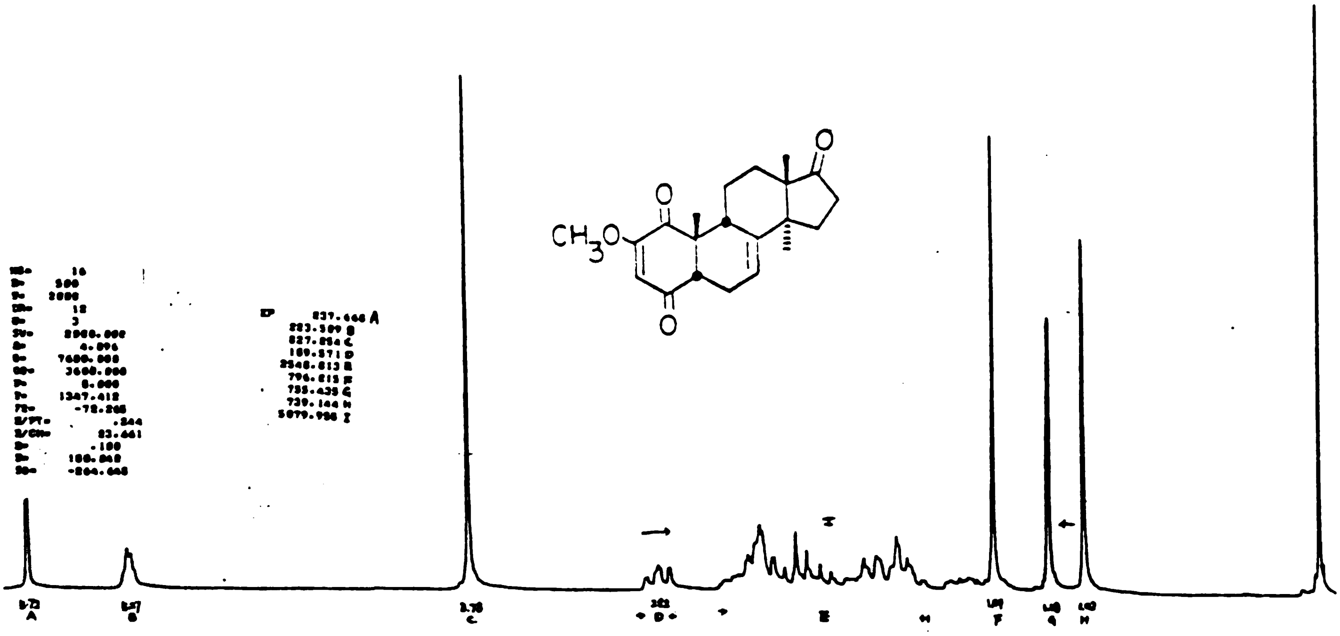


Figure 55. Pmr spectrum of 54.

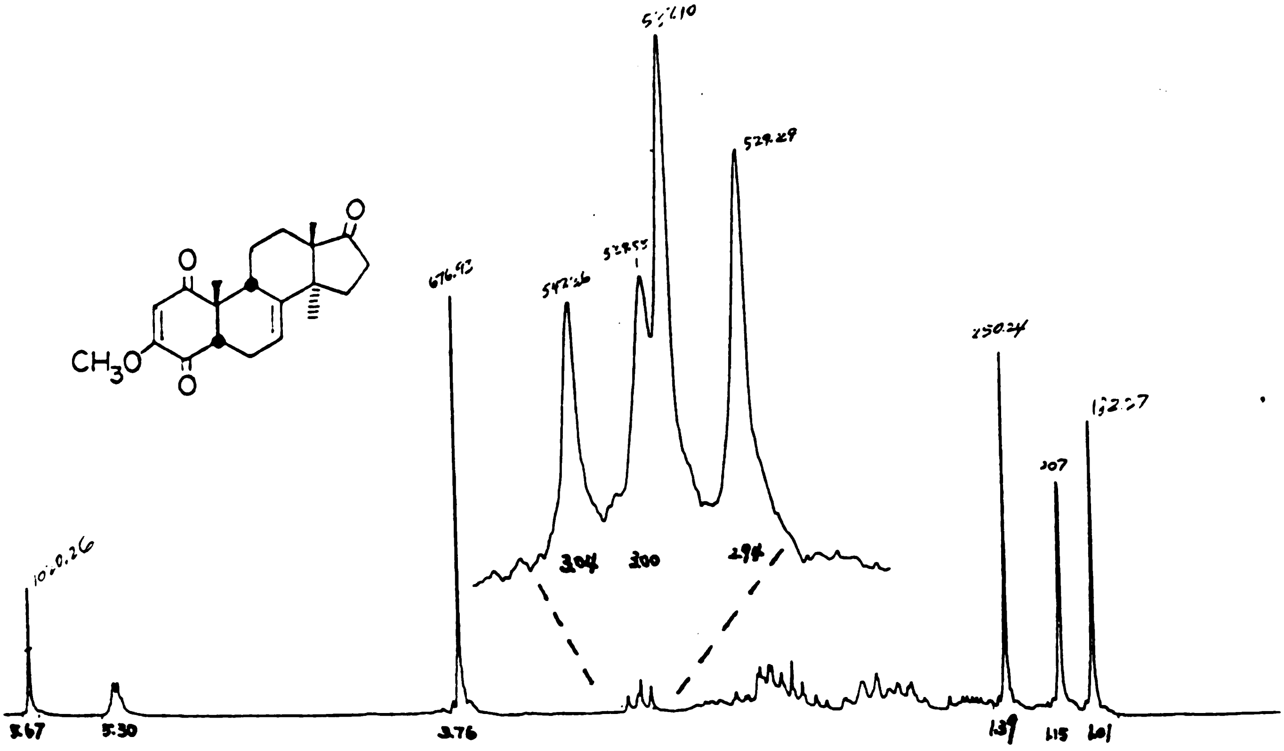


Figure 56. Pmr spectrum of 56.

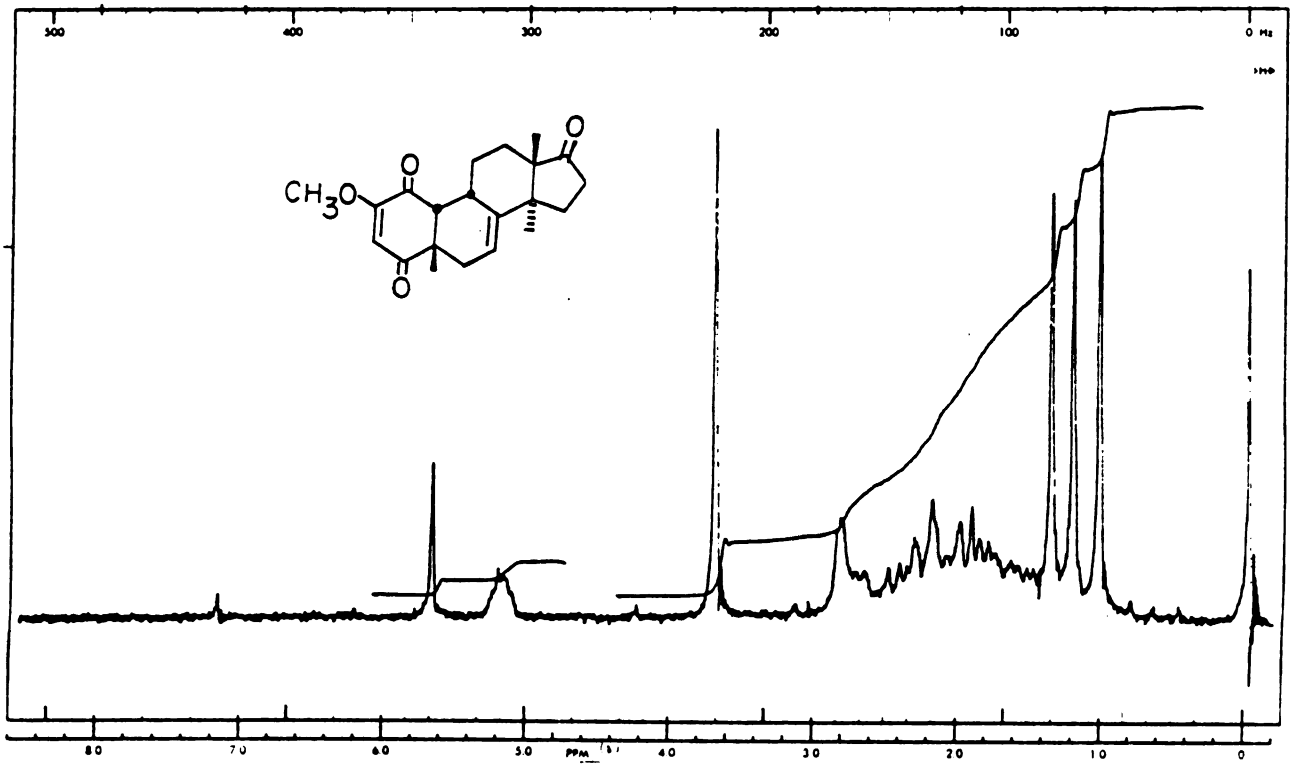
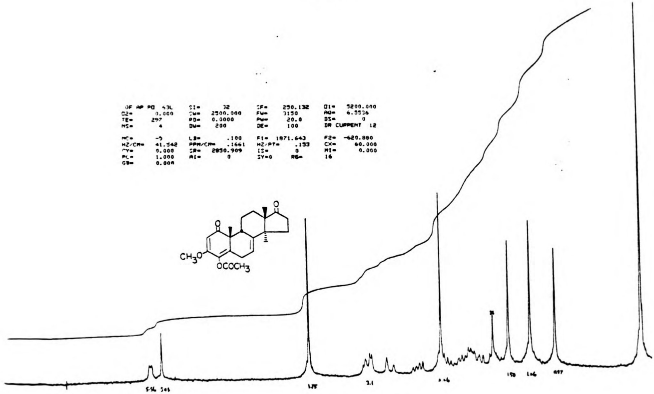


Figure 57. Pmr spectrum of 57.



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NS=      4       DW=    200       DE=     100      DR CUPPENT  12

NC=     -5       LB=       .100   F1=  1871.643    F2=  -620.880
HZ/CM=  41.542   PPM/CM=  .1661   HZ/PT=    .153   CX=    60.000
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PC=     1.000    AI=        0     SY=0      RG=    16
GB=     0.000
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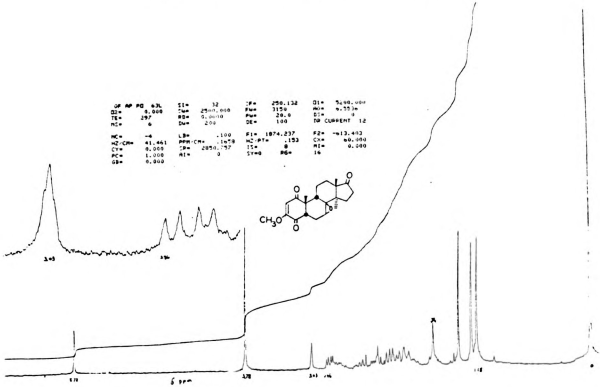
Figure 58. Pmr spectrum of 58.



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NS=      6       DW=    200       DE=     100      DR CURRENT  12

NC=     -4       LB=       .100   F1=  1874.237    F2=  -613.403
HZ/CM=  41.461   PPM/CM=  .1658   HZ/PT=    .153   CX=    60.000
CY=     0.000    SR=  2850.757    IS=       8      MI=     0.000
PC=     1.000    AI=        0     SY=0      RG=    16
GB=     0.000
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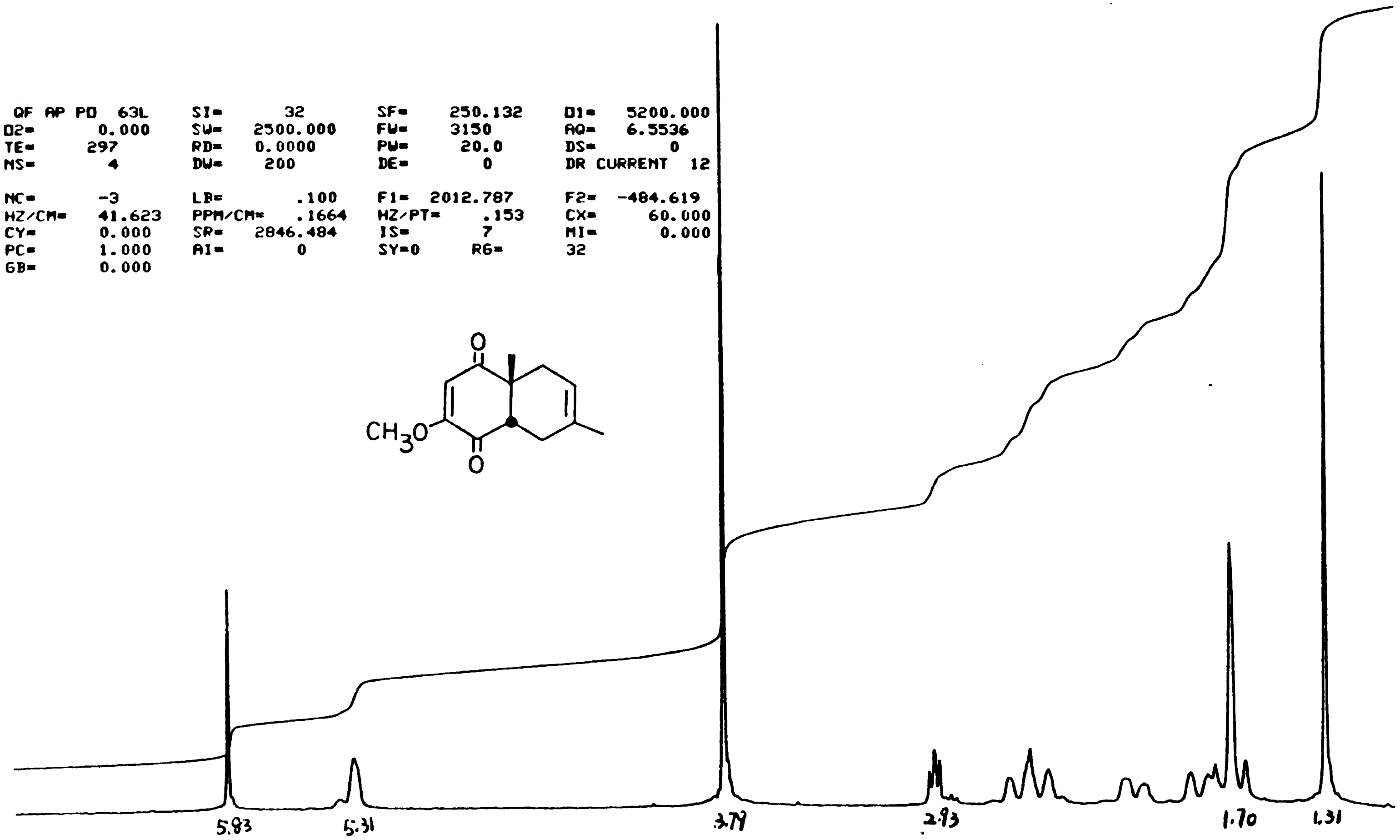
Figure 59. Pmr spectrum of 63.



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NS=        4       DW=    200        DE=         0      DR CURRENT  12

NC=       -3       LB=        .100   F1=  2012.787      F2=  -484.619
HZ/CM=    41.623   PPM/CM=   .1664   HZ/PT=     .153    CX=     60.000
CY=       0.000    SR=  2846.484     IS=         7      MI=      0.000
PC=       1.000    AI=        0      SY=0      RG=      32
GB=       0.000
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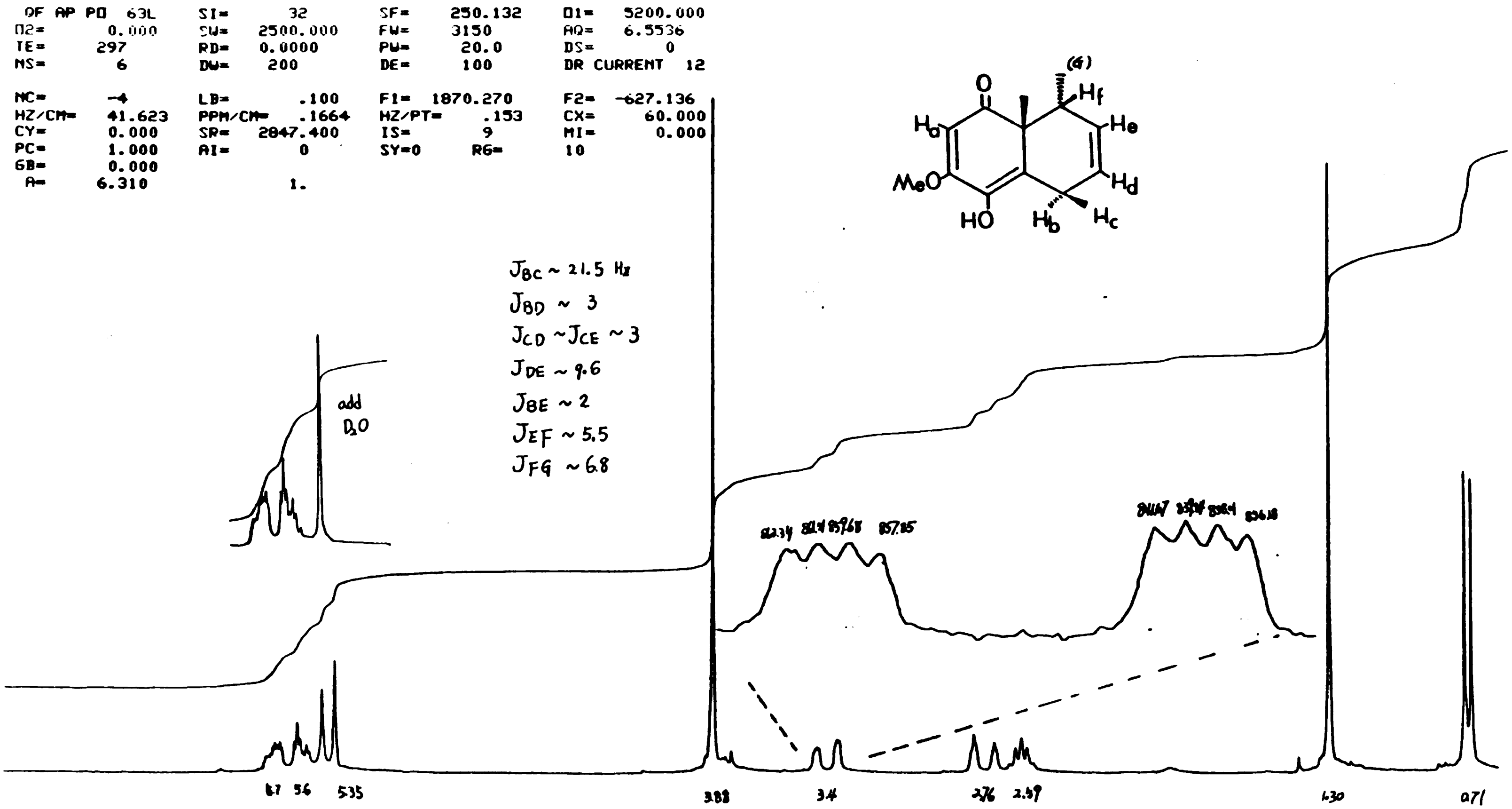
Figure 60. Pmr spectrum of 68.



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O2=       0.000     SW=   2500.000      FW=     3150        AQ=    6.5536
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NS=        6        DW=    200          DE=      100        DR CURRENT  12

NC=       -4        LB=          .100   FI=  1870.270       F2=  -627.136
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CY=       0.000     SR=   2847.400      IS=         9       MI=     0.000
PC=       1.000     AI=         0       SY=0       RG=      10
GB=       0.000
 A=      6.310                1.
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$J_{BC} \sim 21.5$ Hz

$J_{BD} \sim 3$

$J_{CD} \sim J_{CE} \sim 3$

$J_{DE} \sim 9.6$

$J_{BE} \sim 2$

$J_{EF} \sim 5.5$

$J_{FG} \sim 6.8$

Figure 61. Pmr spectrum of 70.

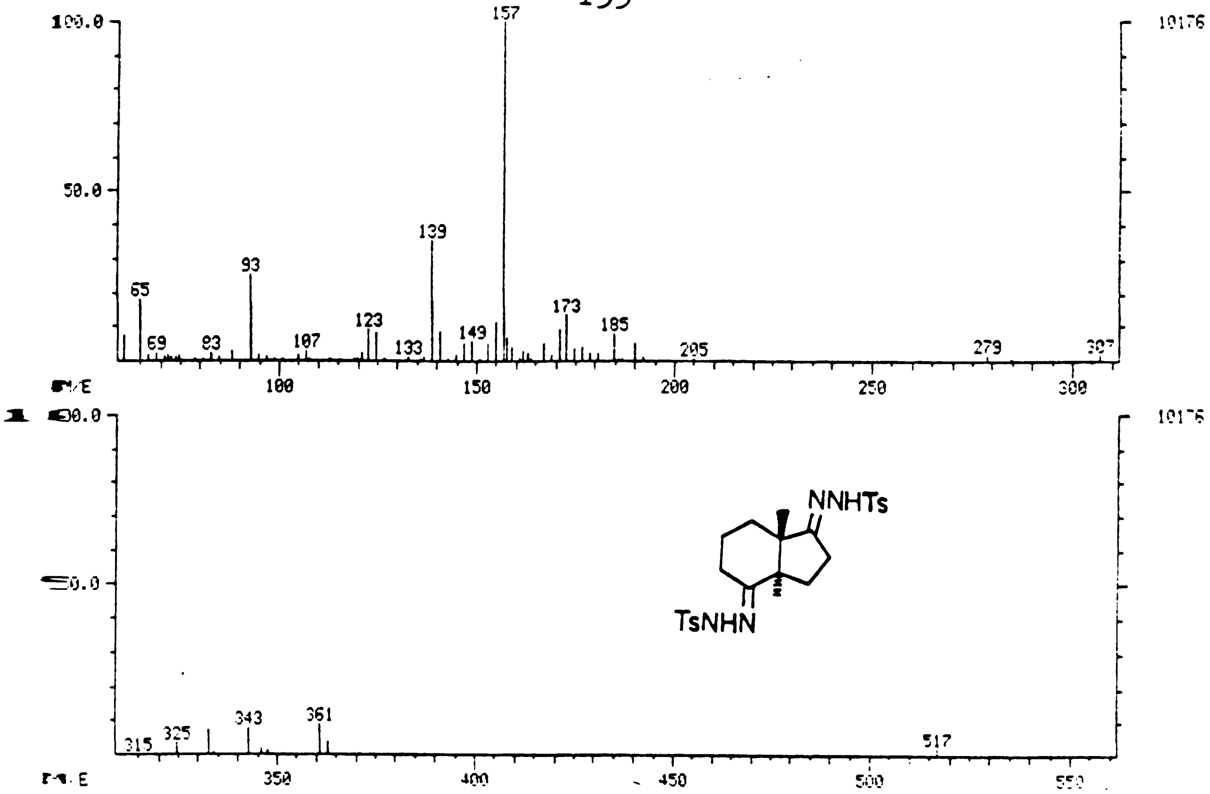

Figure 62. Mass spectrum of 19.

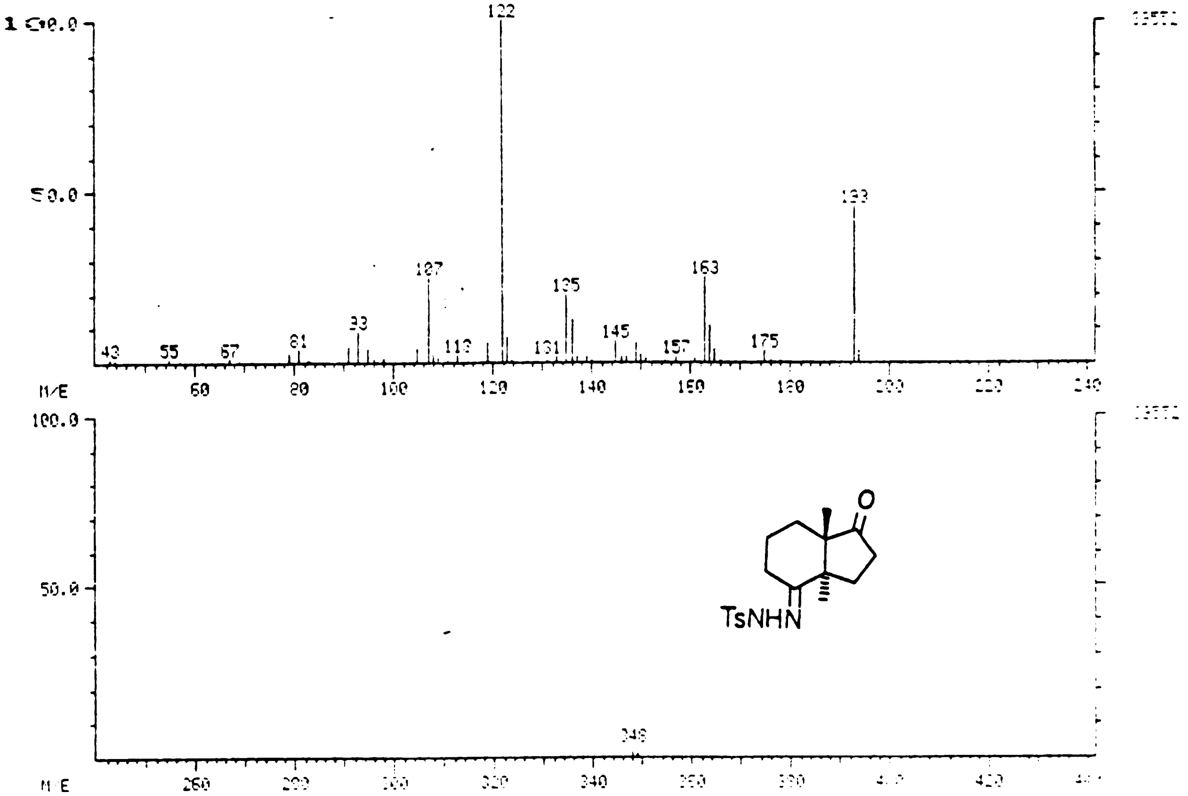

Figure 63. Mass spectrum of 20.

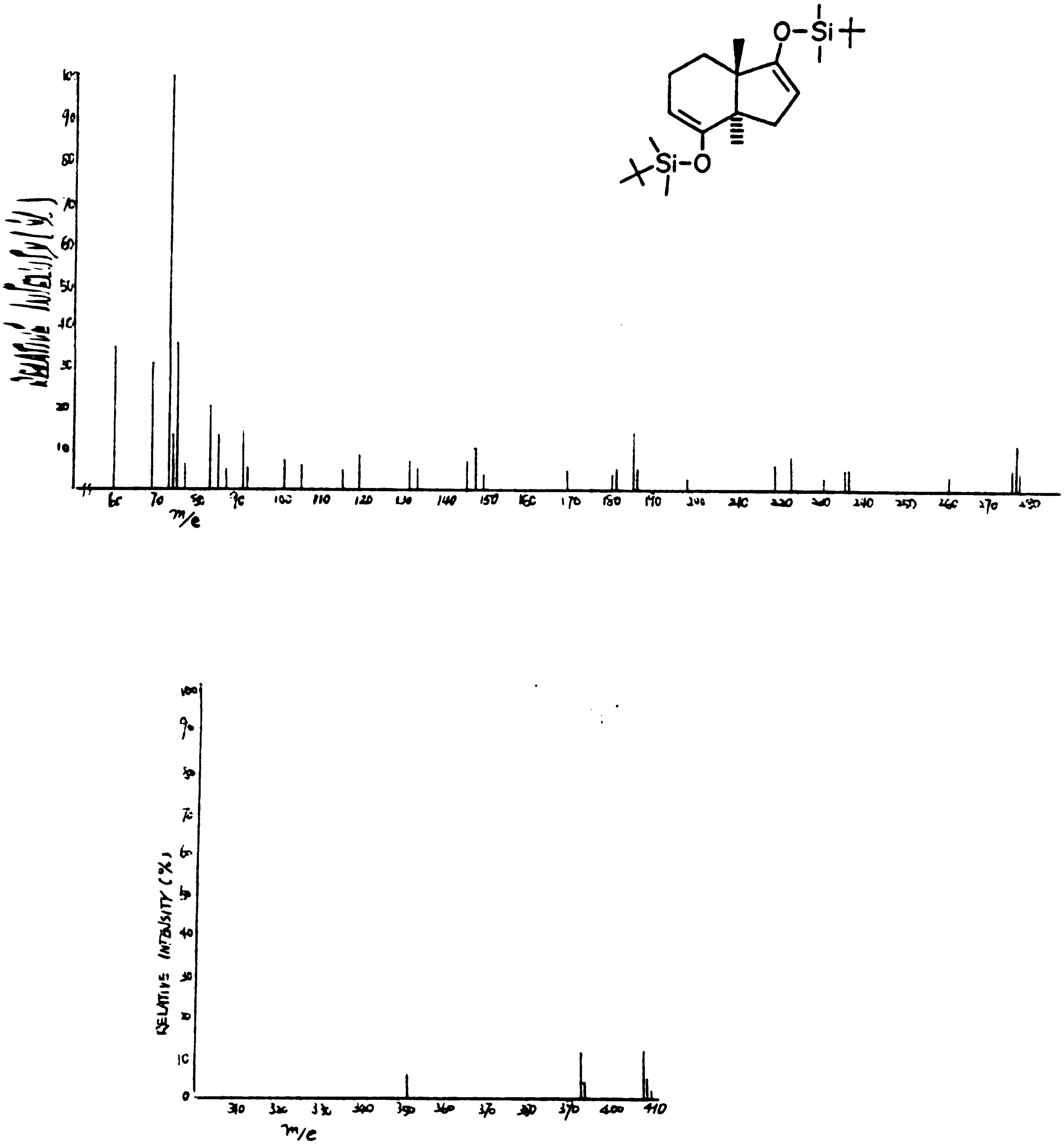

Figure 64. Mass spectrum of 22.

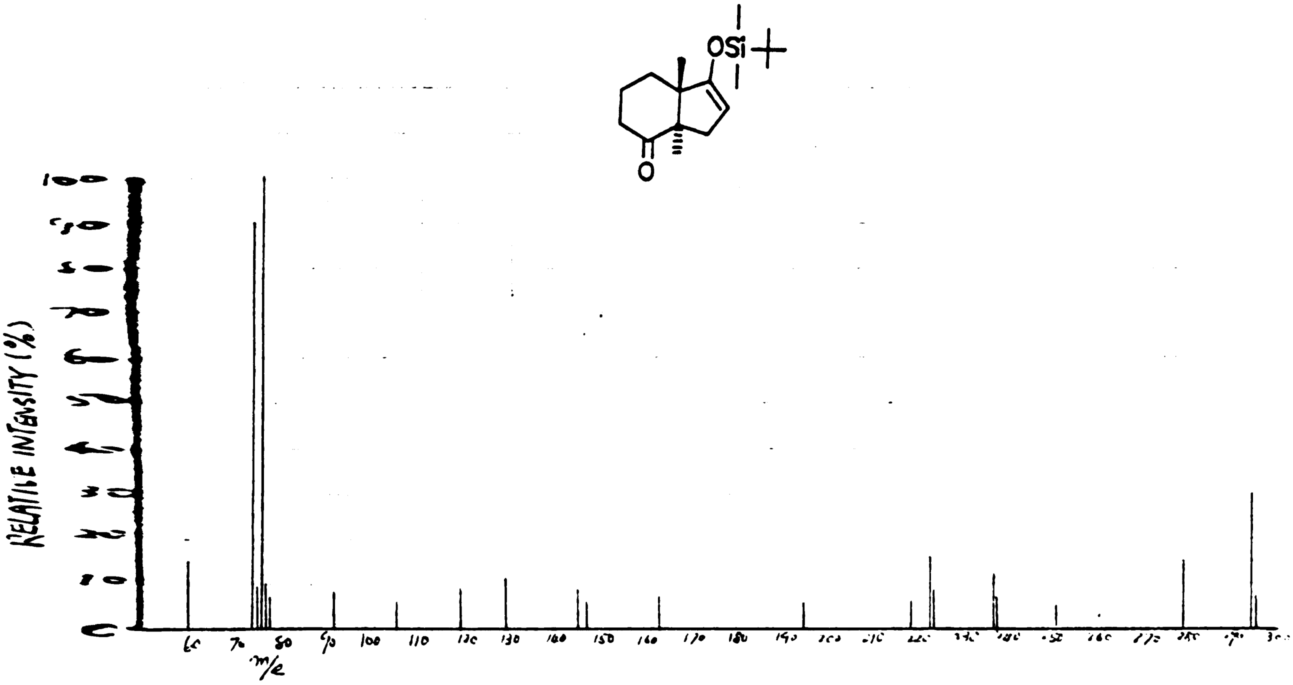

Figure 65. Mass spectrum of 24.

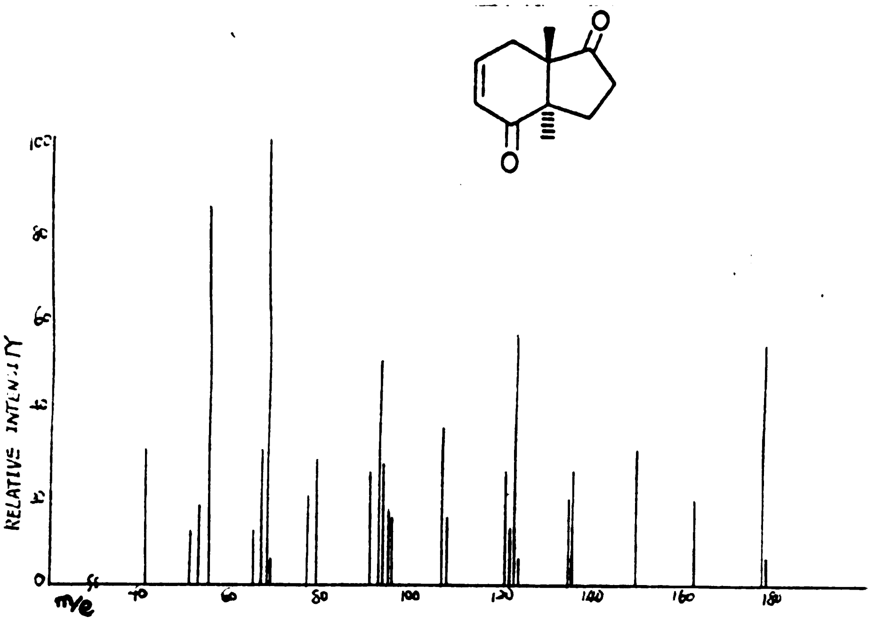

Figure 66. Mass spectrum of 27.

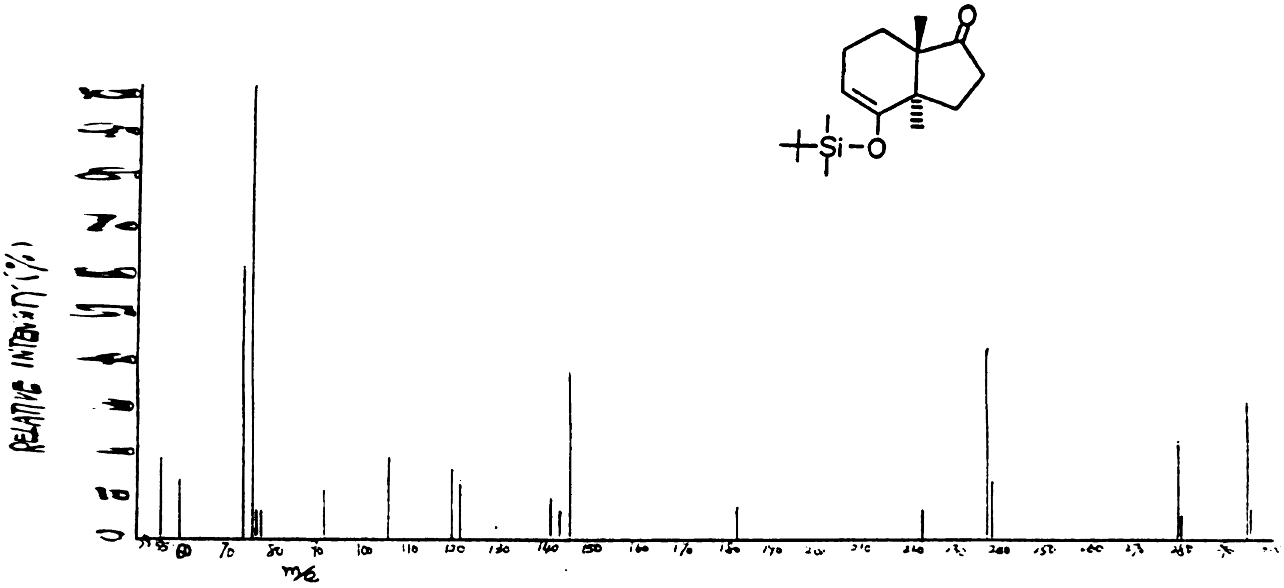

Figure 67. Mass spectrum of 23.

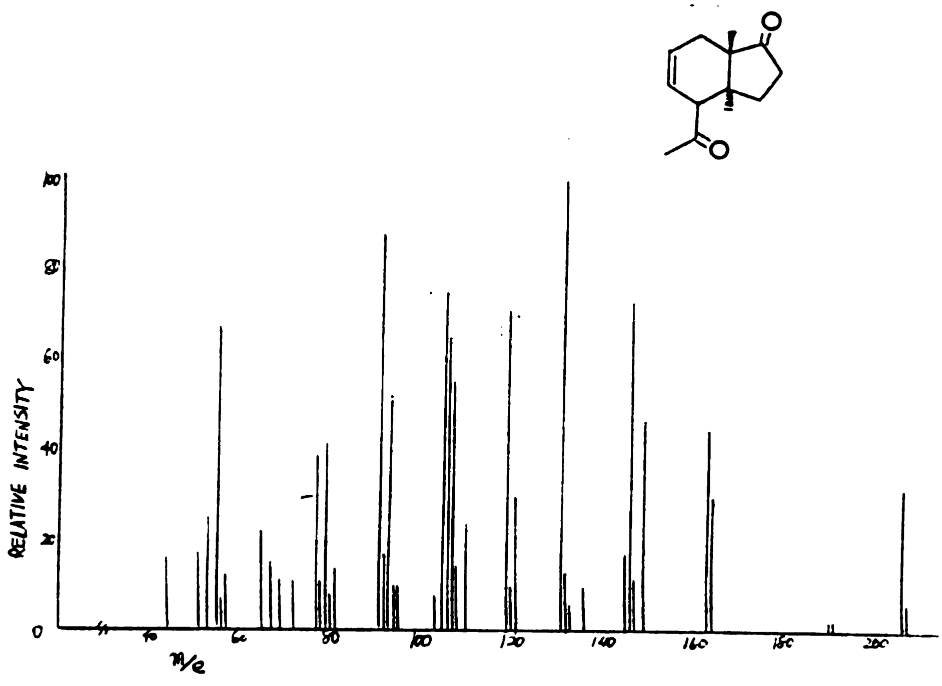

Figure 68. Mass spectrum of 34.

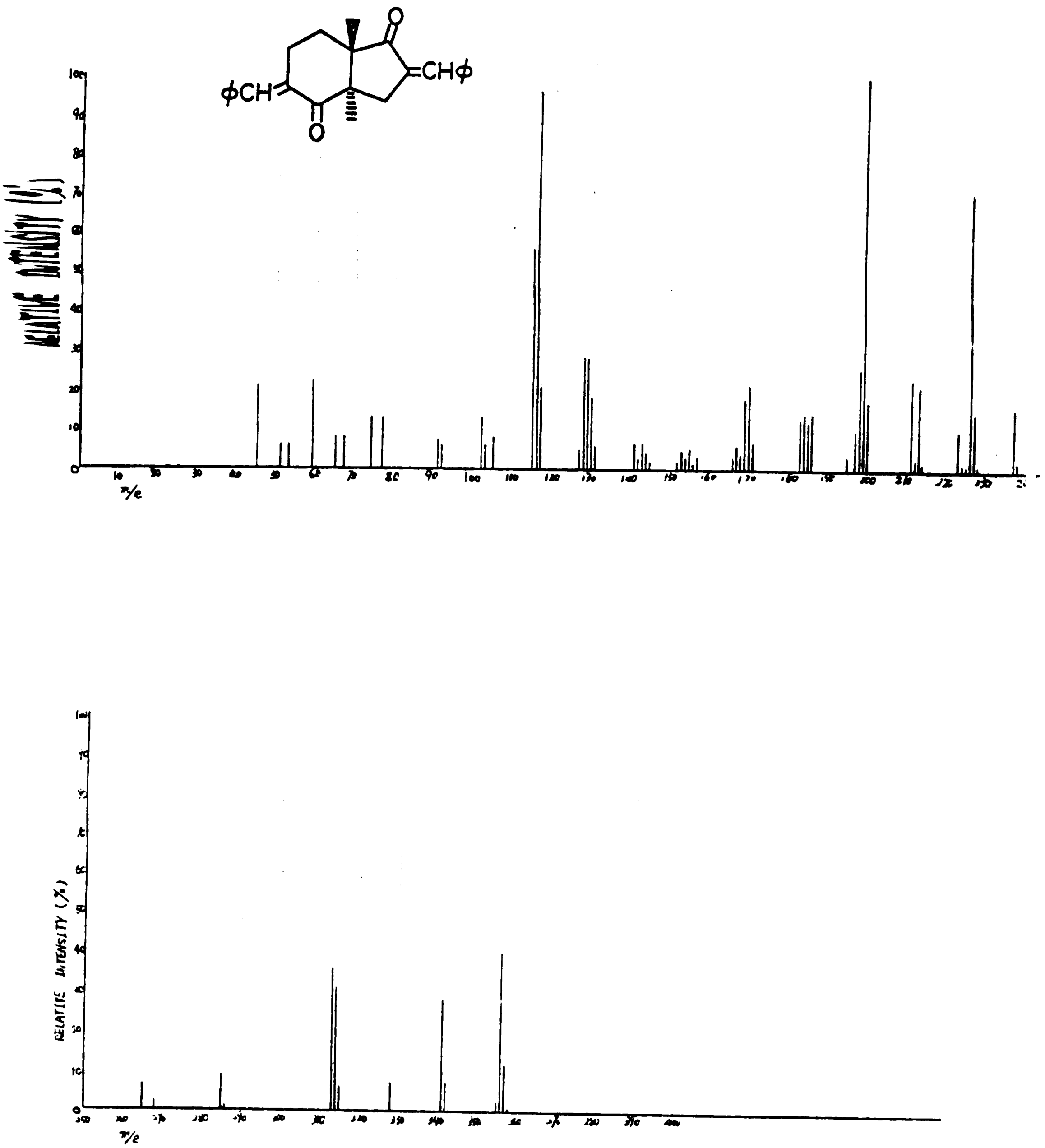

Figure 69. Mass spectrum of **28**.

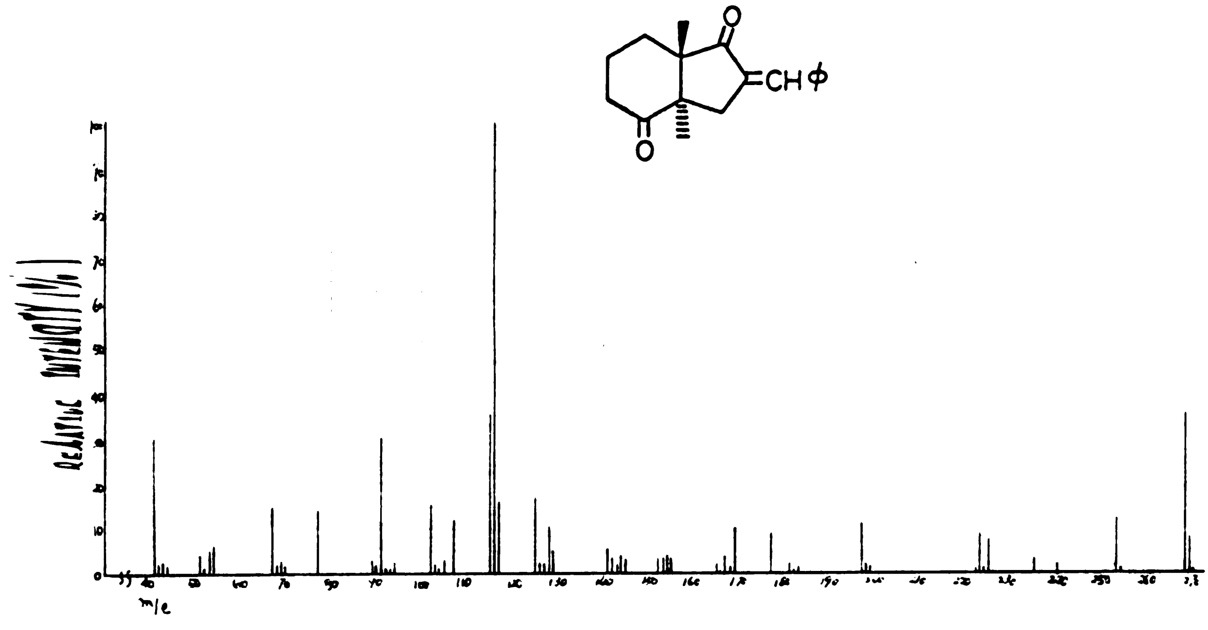

Figure 70. Mass spectrum of 29.

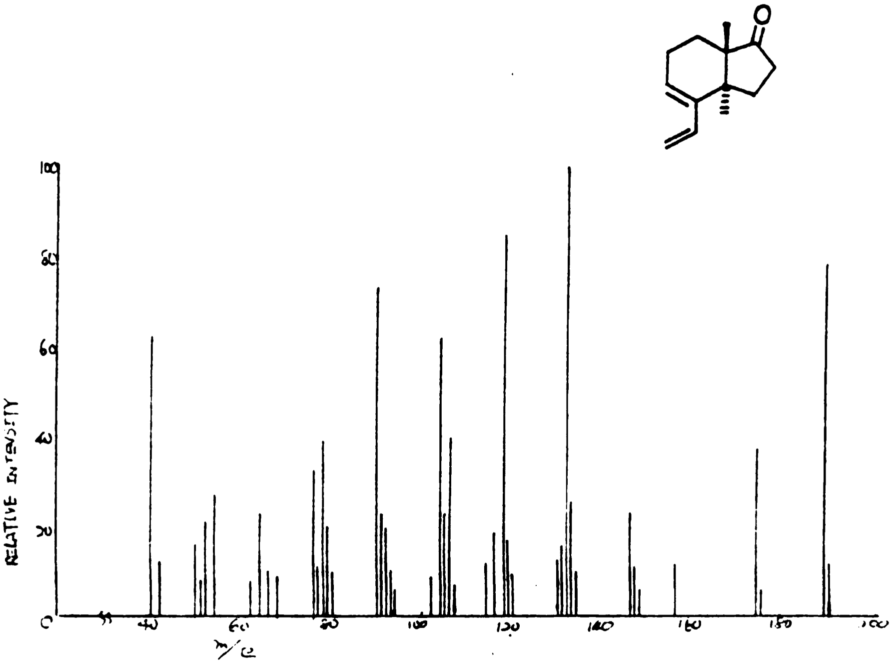

Figure 71. Mass spectrum of 31.

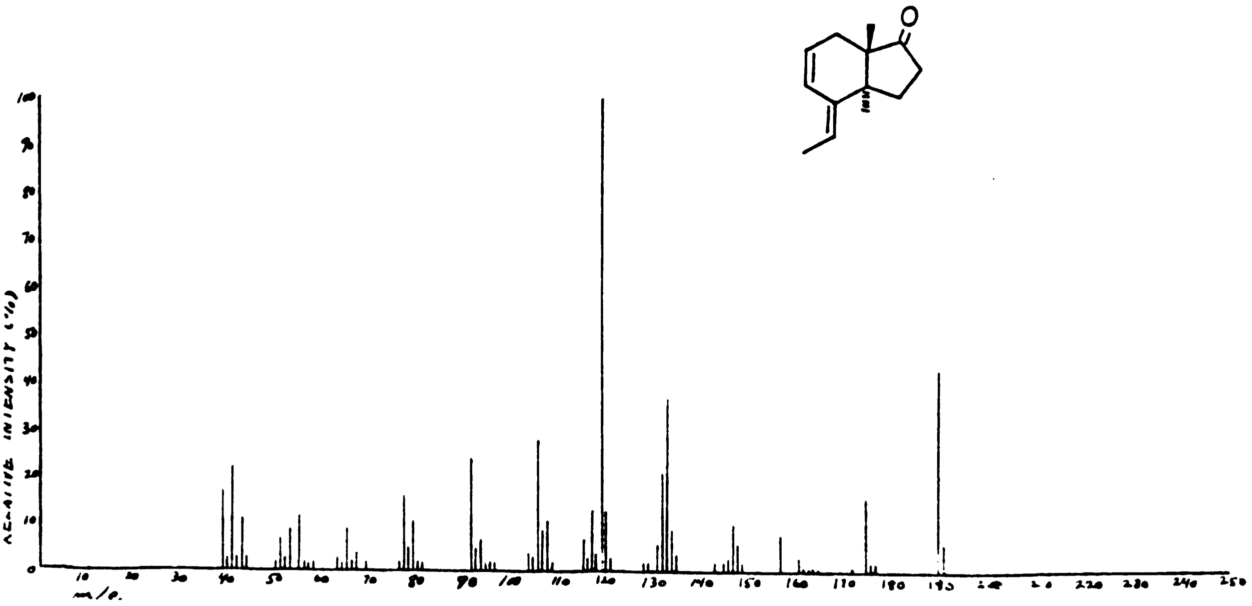

Figure 72. Mass spectrum of 35.

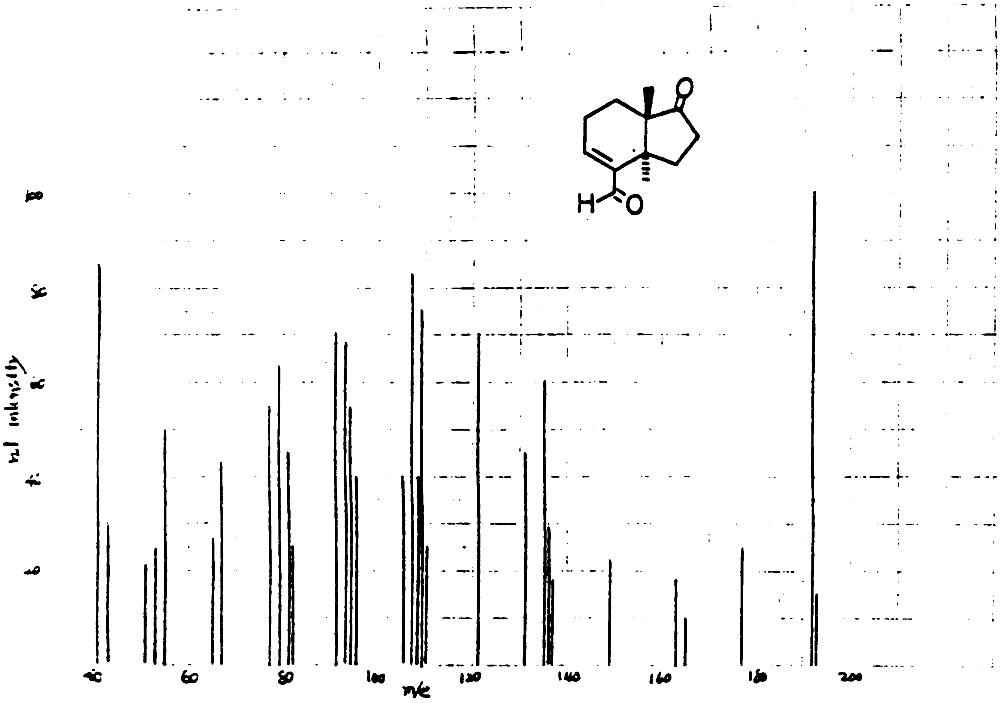

Figure 73. Mass spectrum of 38.

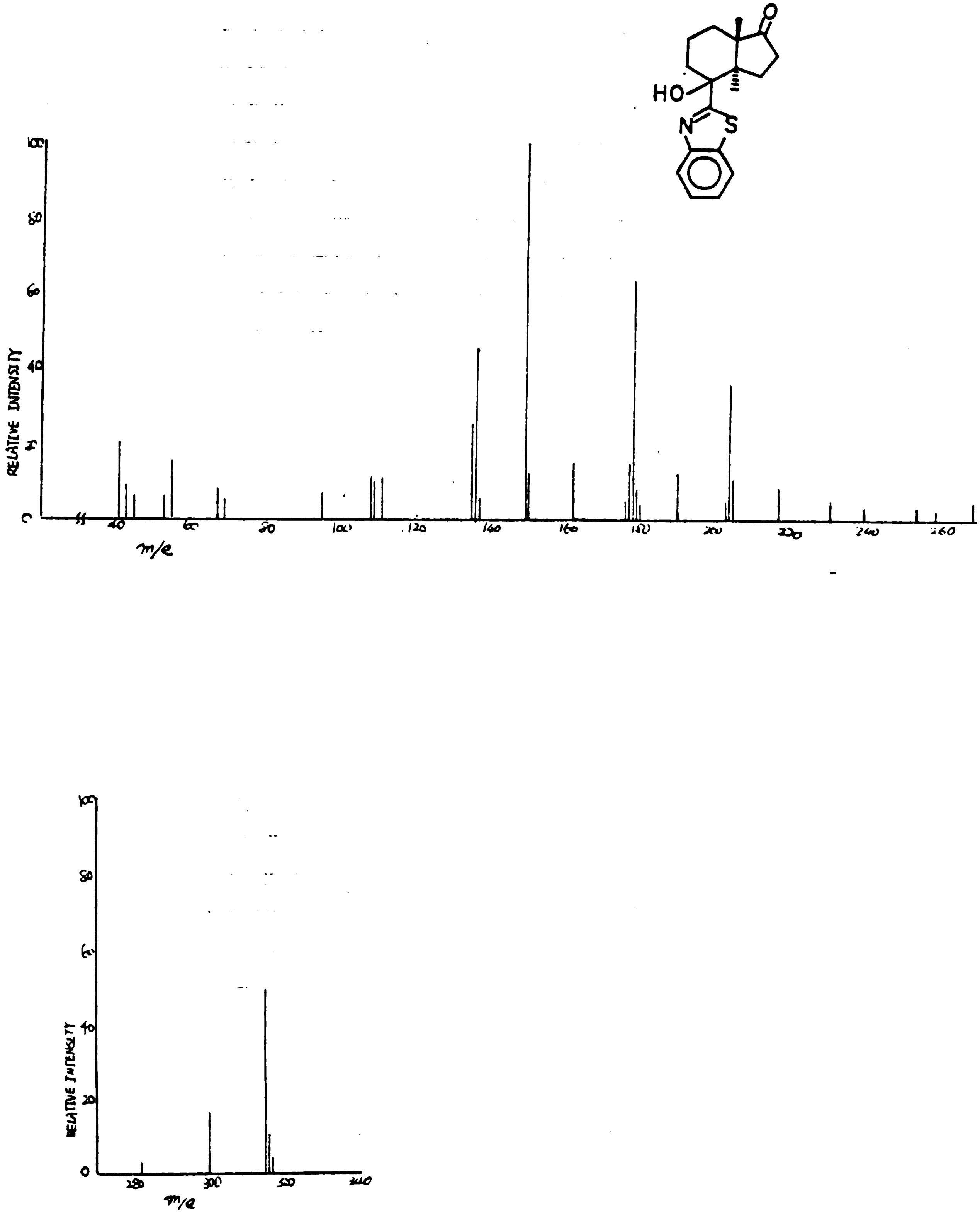

Figure 74. Mass spectrum of 40.

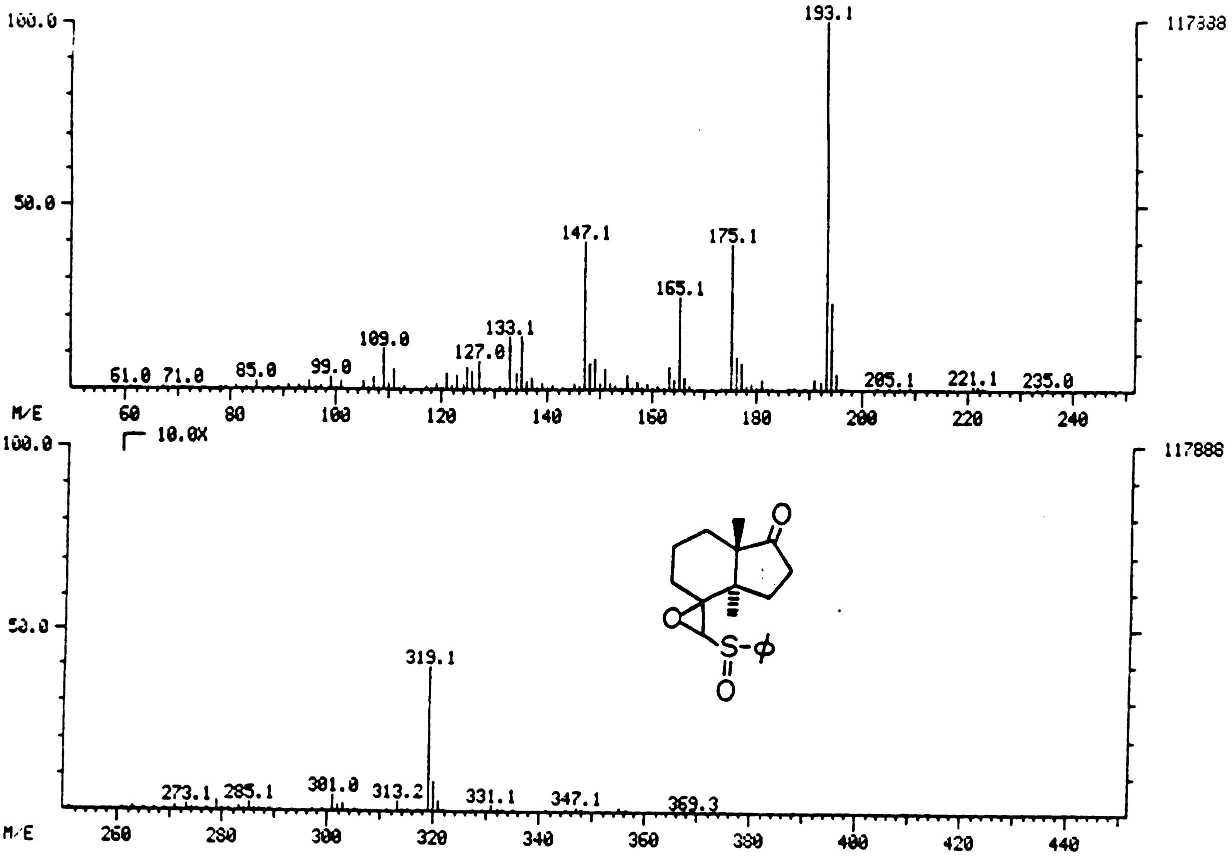

Figure 75. Mass spectrum of 42.

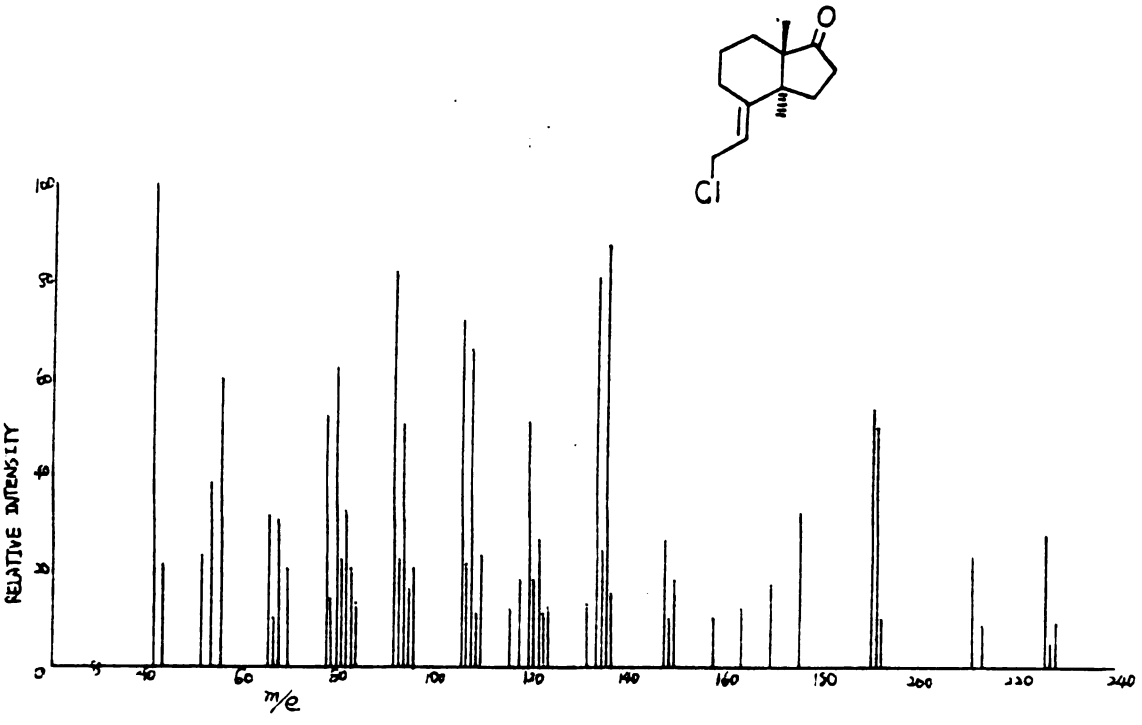

Figure 76. Mass spectrum of 45.

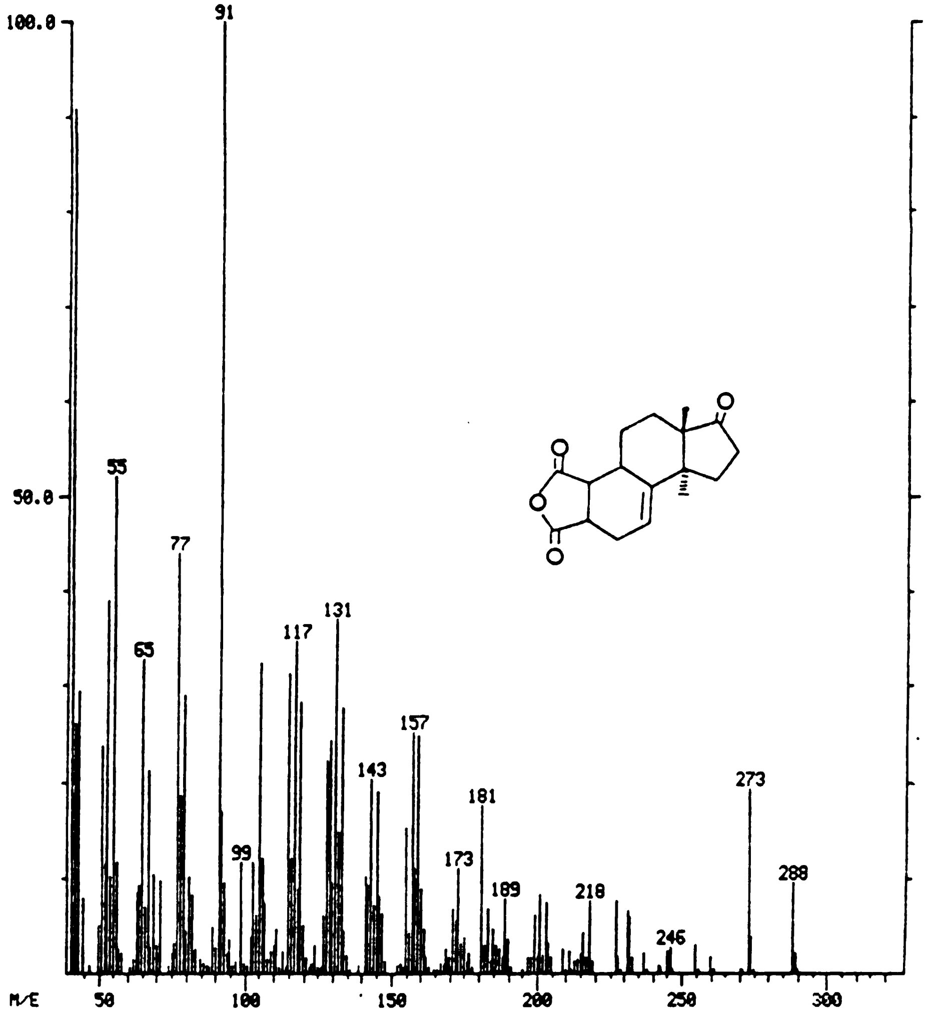

Figure 77. Mass spectrum of 46.

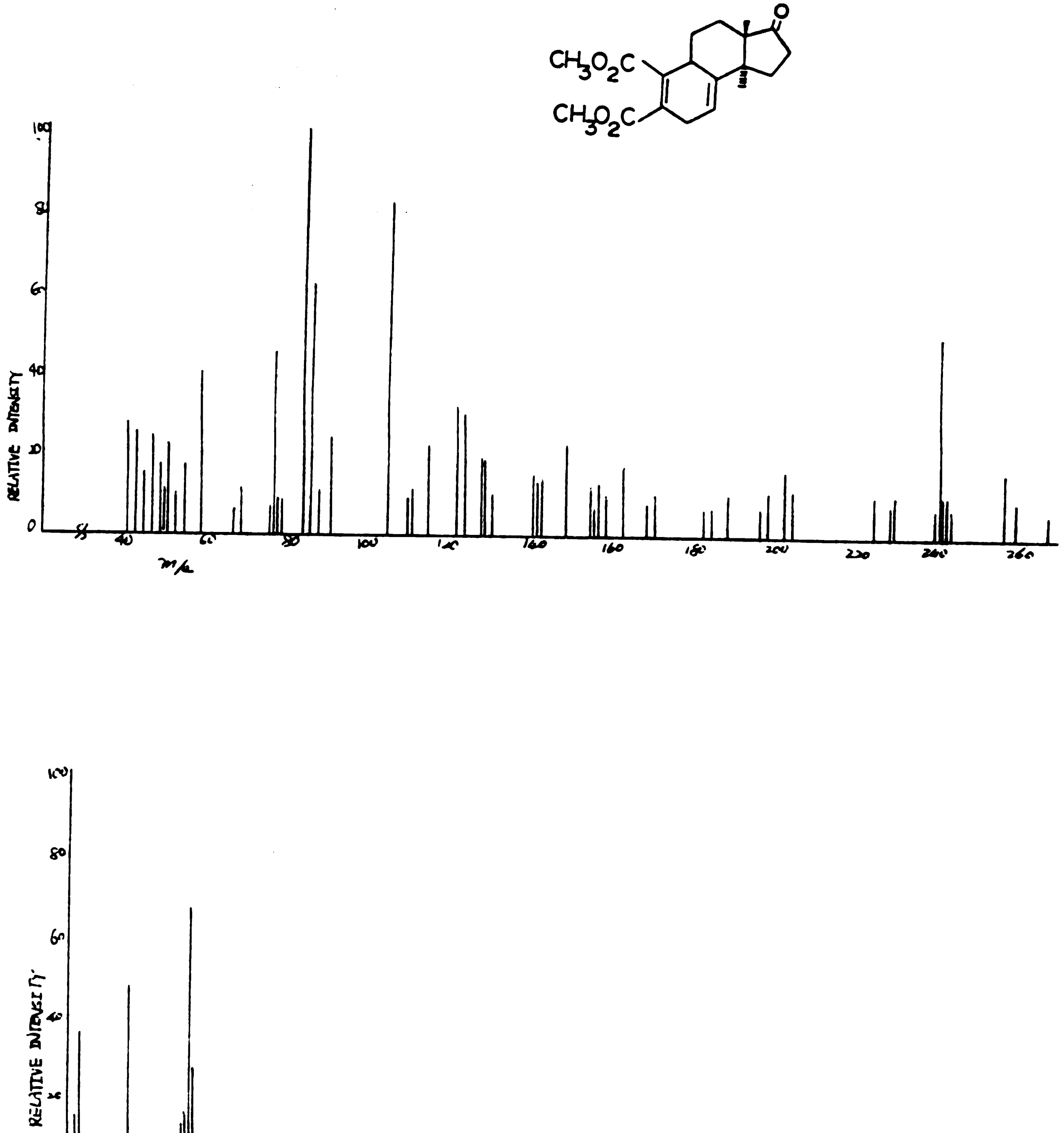

Figure 78. Mass spectrum of 50.

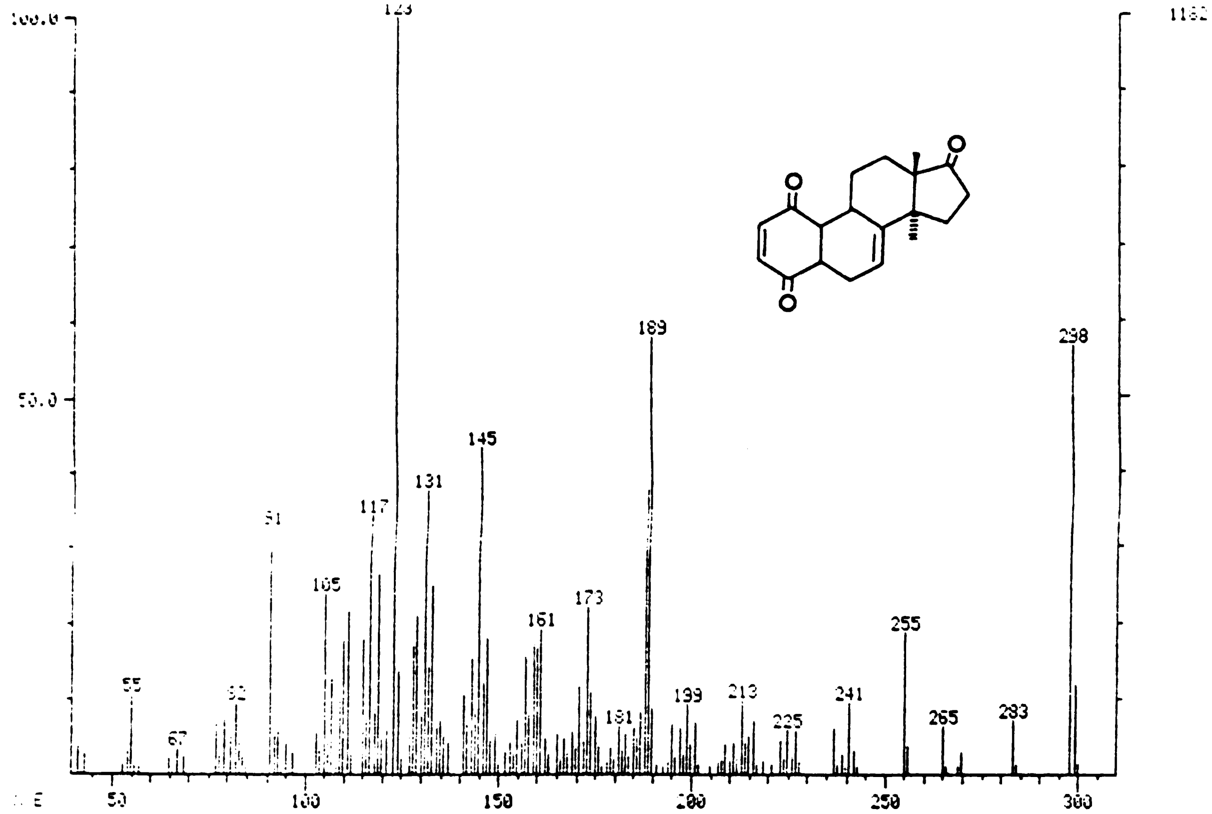

Figure 79. Mass spectrum of 51.

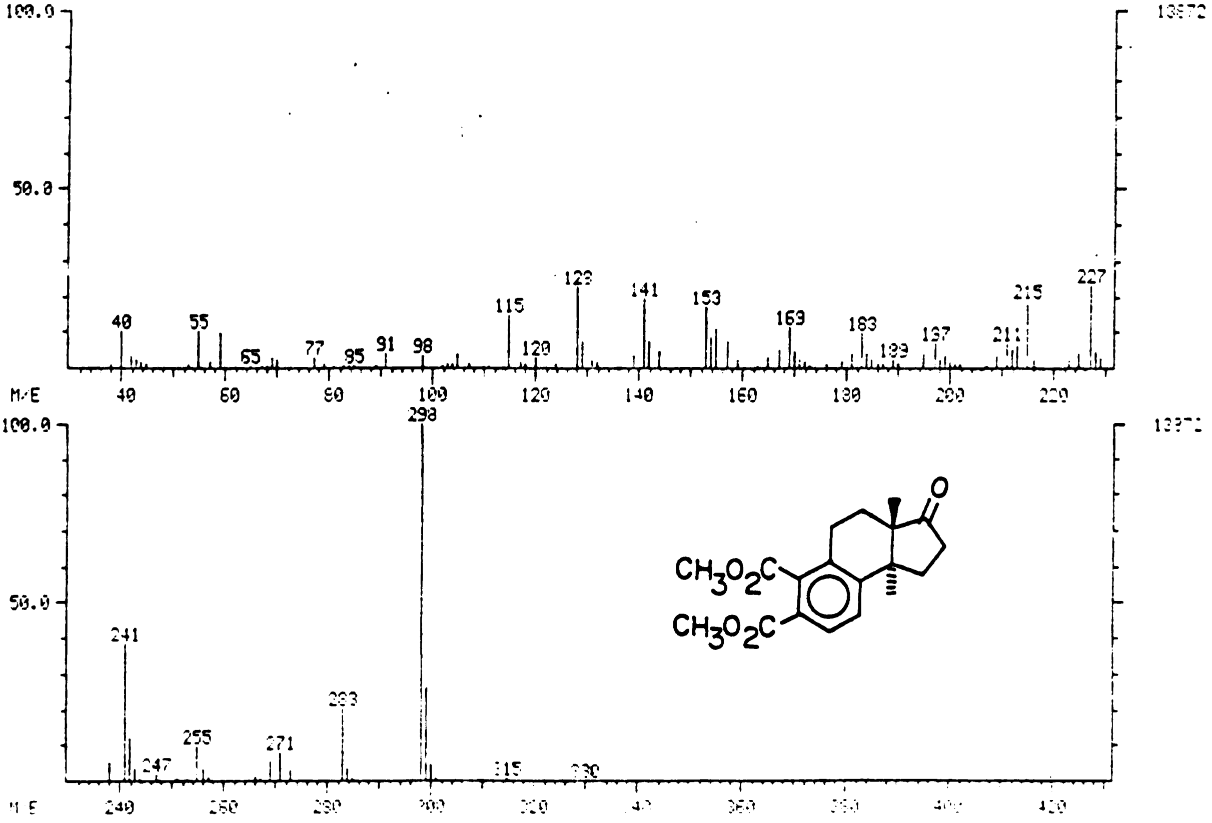

Figure 80. Mass spectrum of 52.

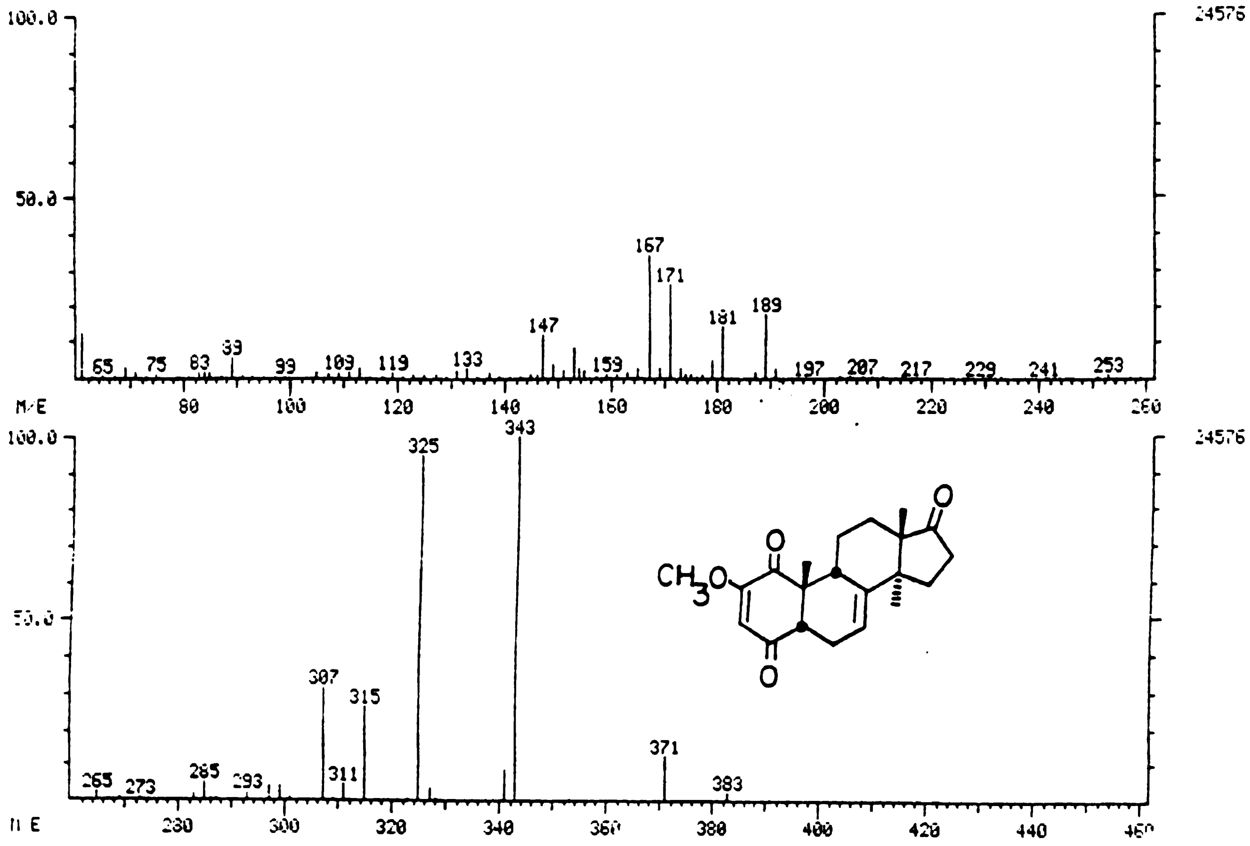

Figure 81. Mass spectrum of 54.

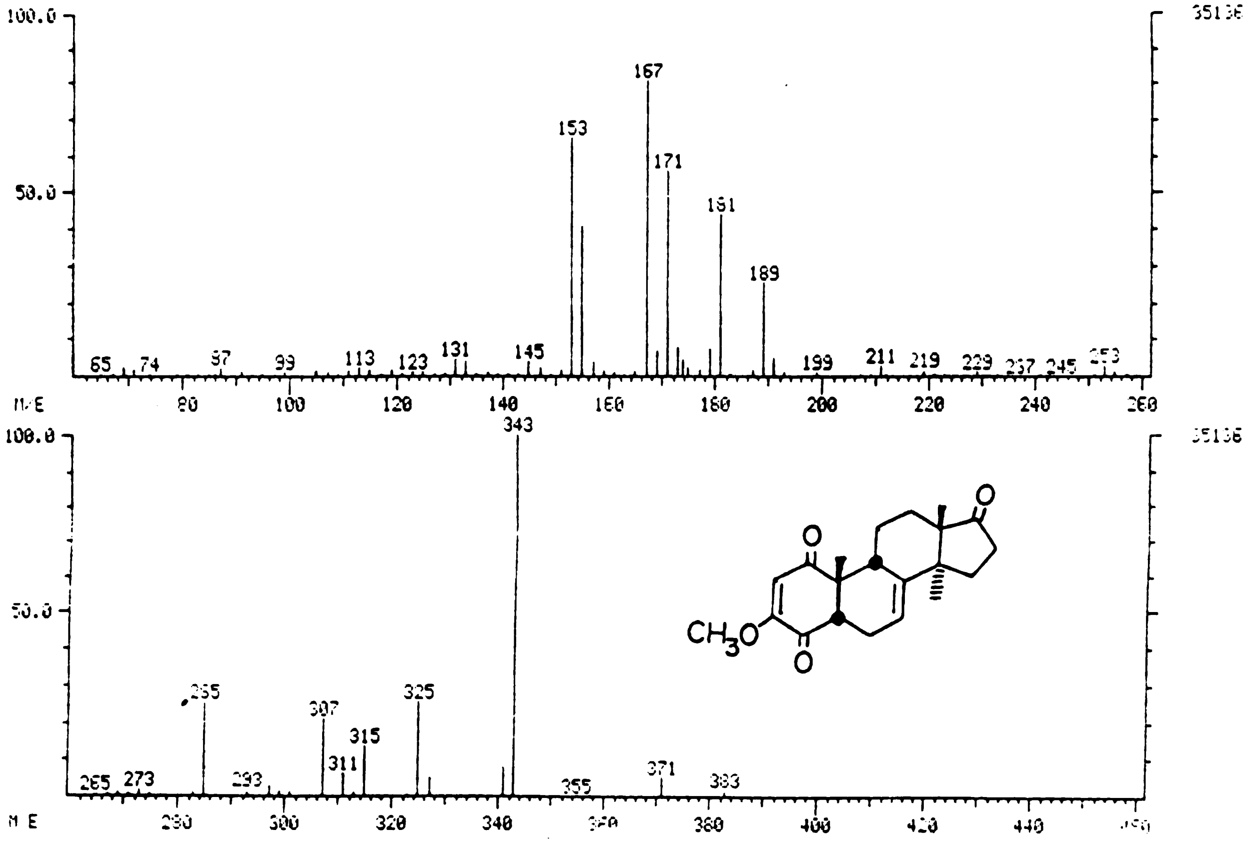

Figure 82. Mass spectrum of 56.

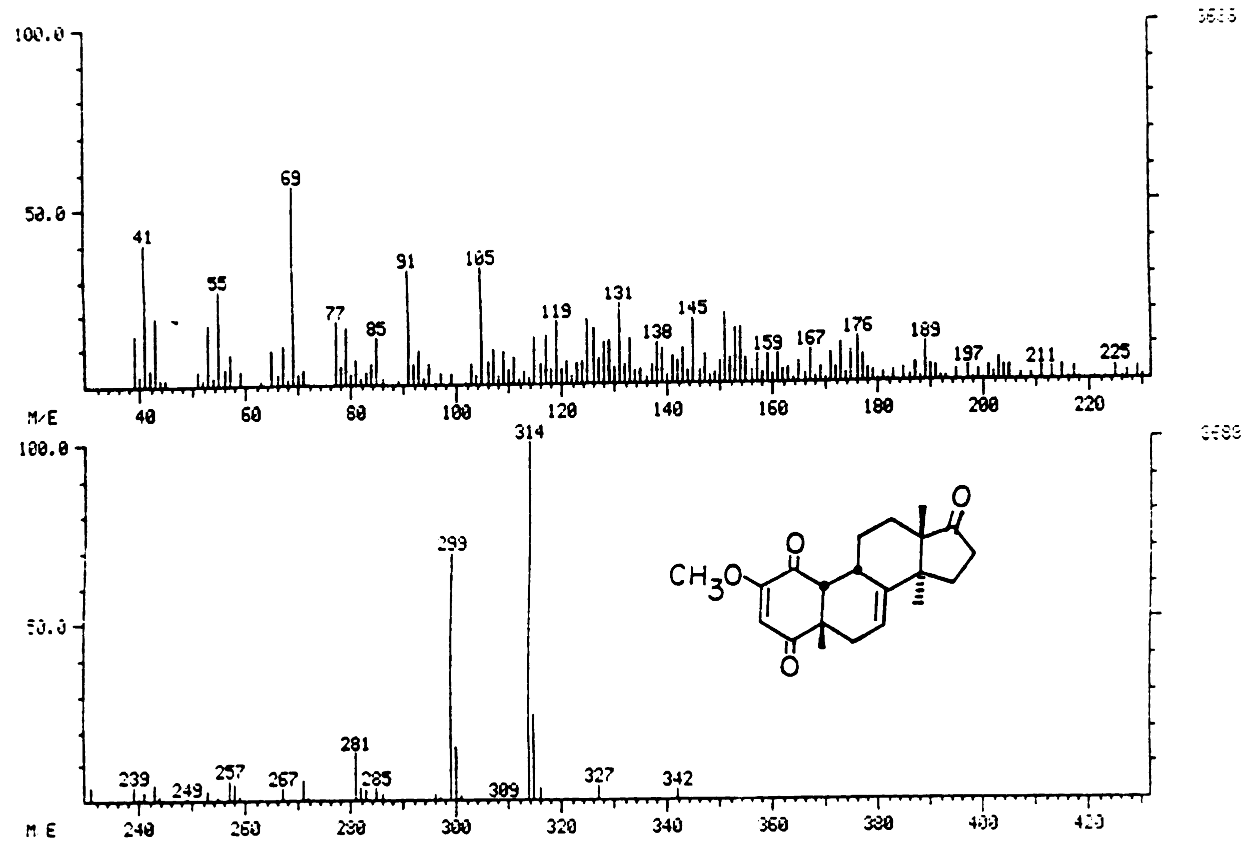

Figure 83. Mass spectrum of 57.

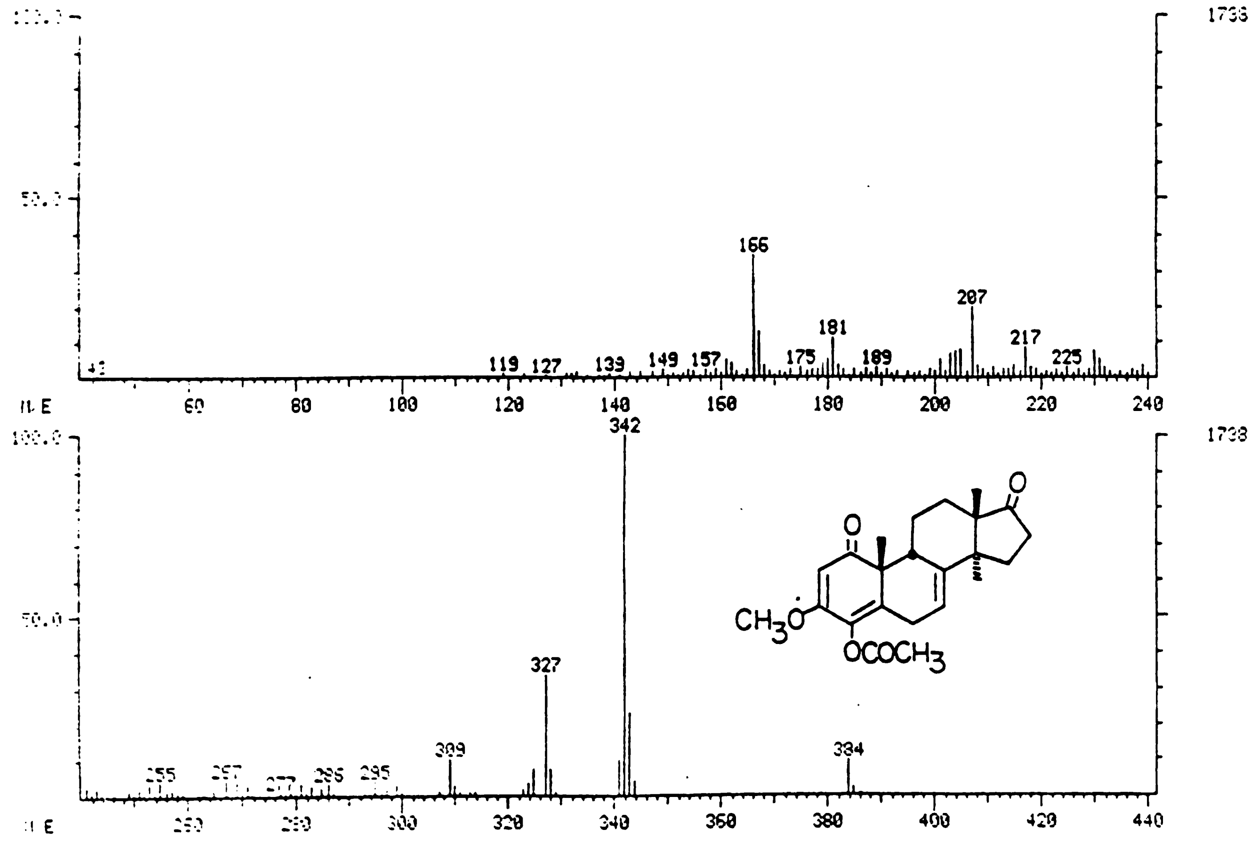

Figure 84. Mass spectrum of 58.

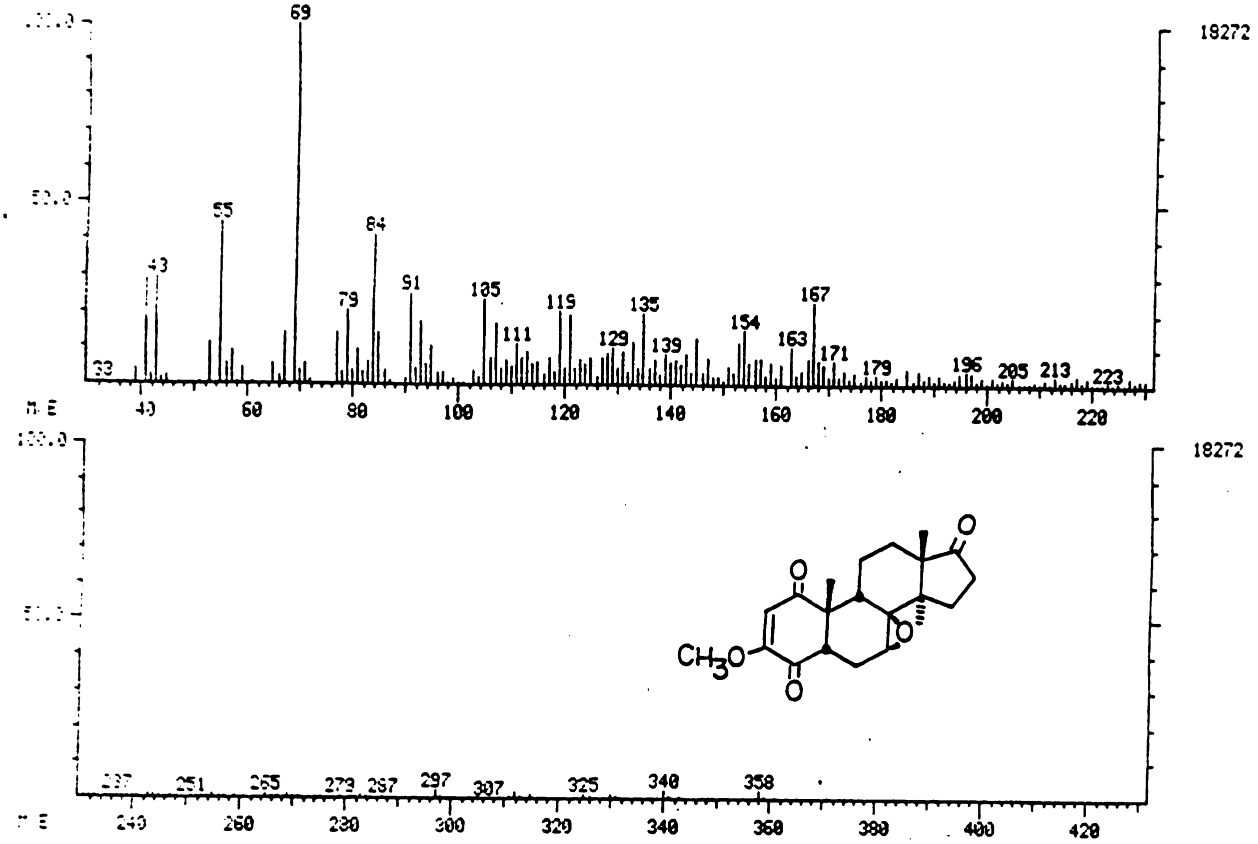

Figure 85. Mass spectrum of 63.

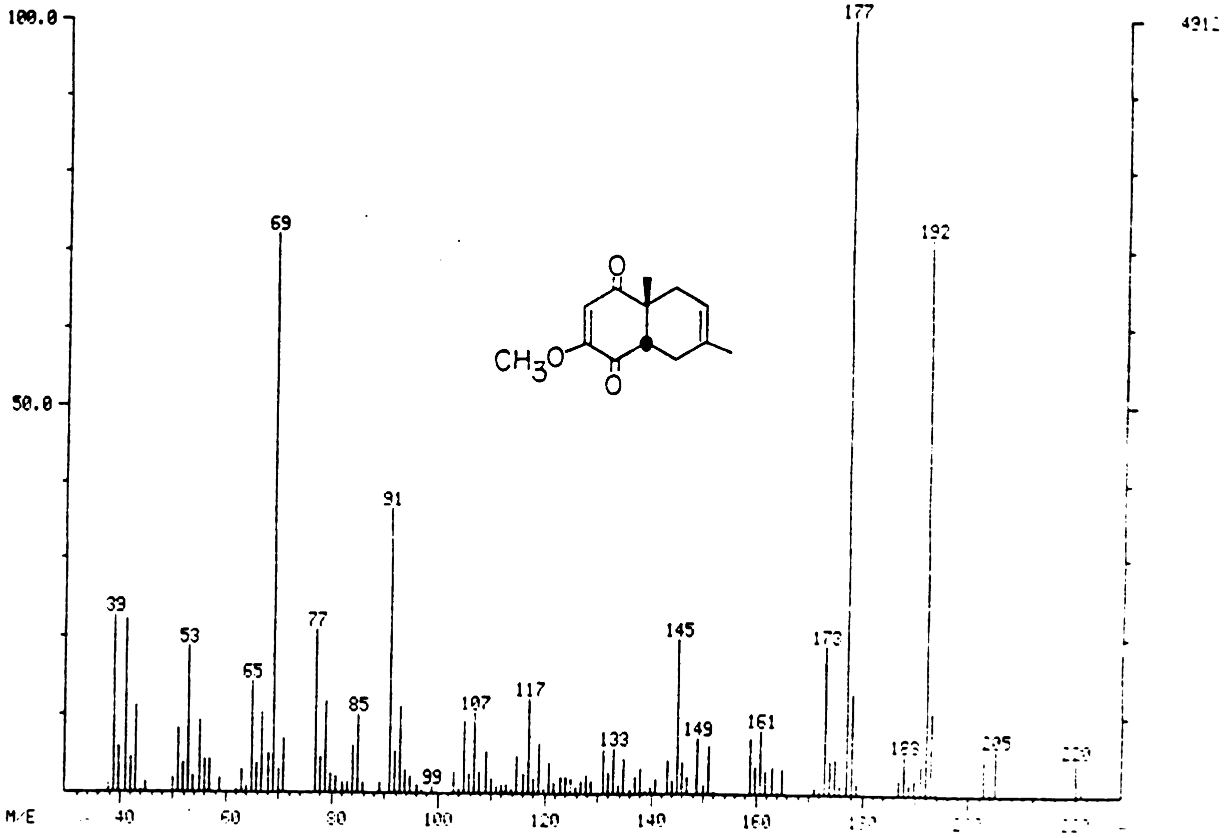

Figure 86. Mass spectrum of 68.

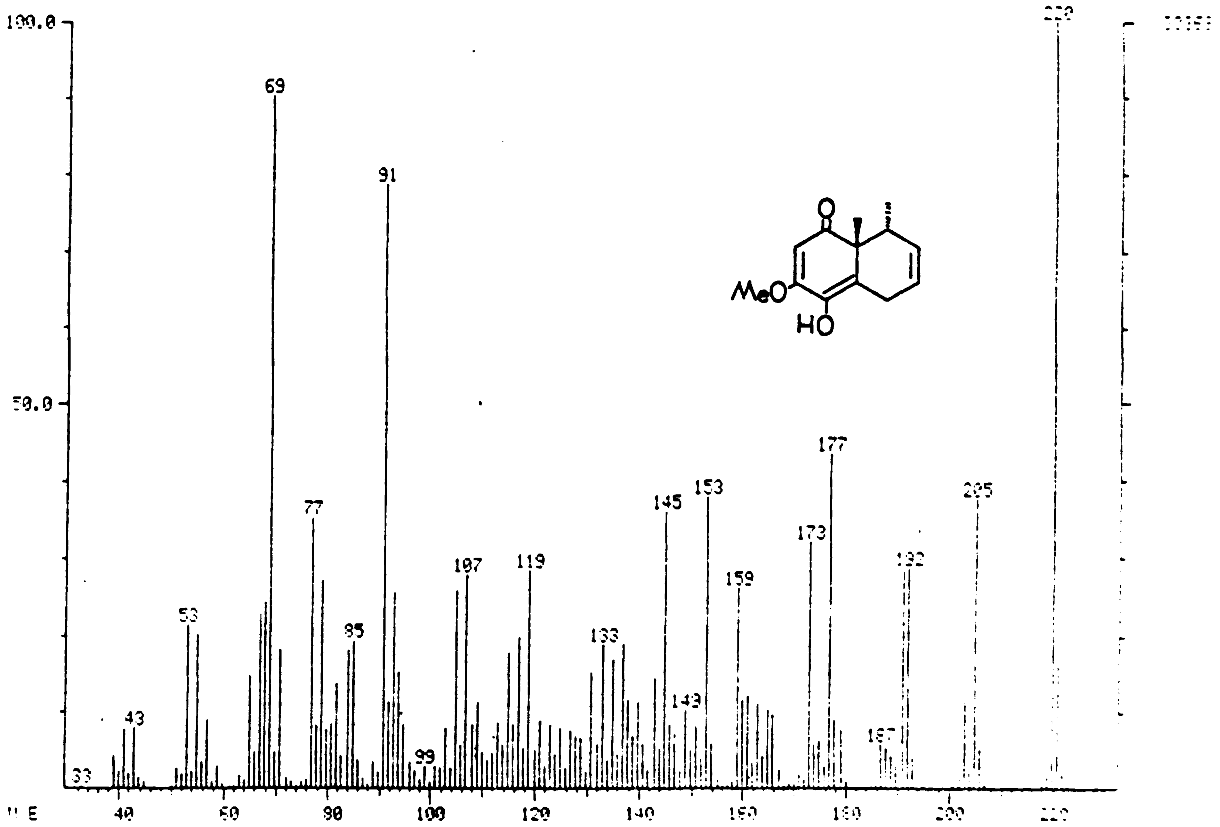

Figure 87. Mass spectrum of 70.

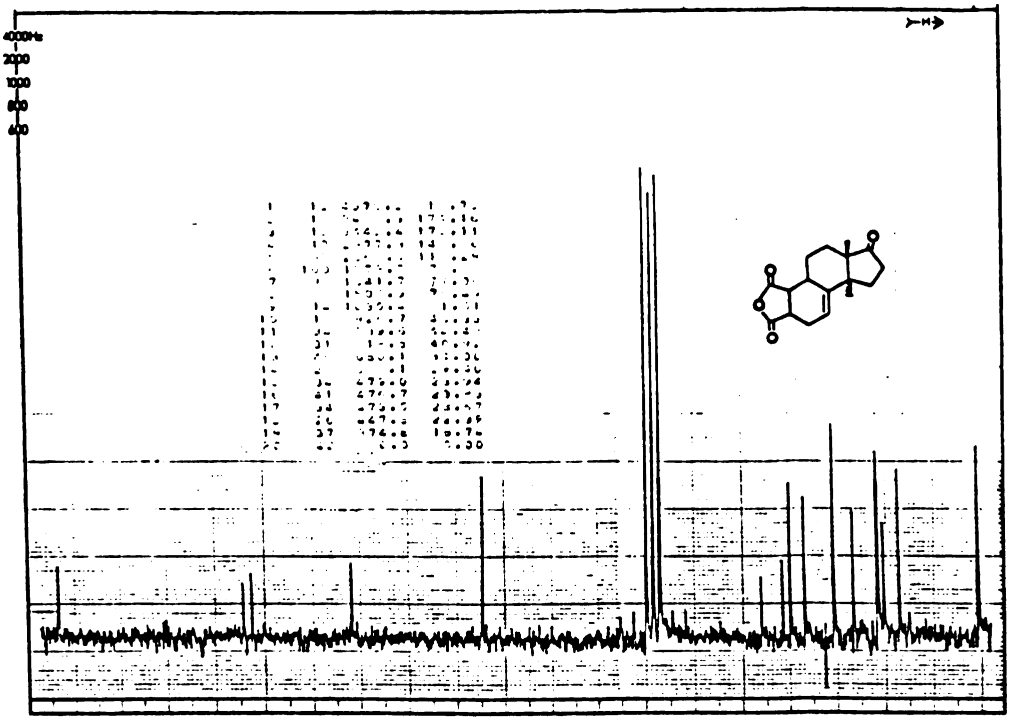

Figure 88. ^{13}C NMR spectrum of 46.

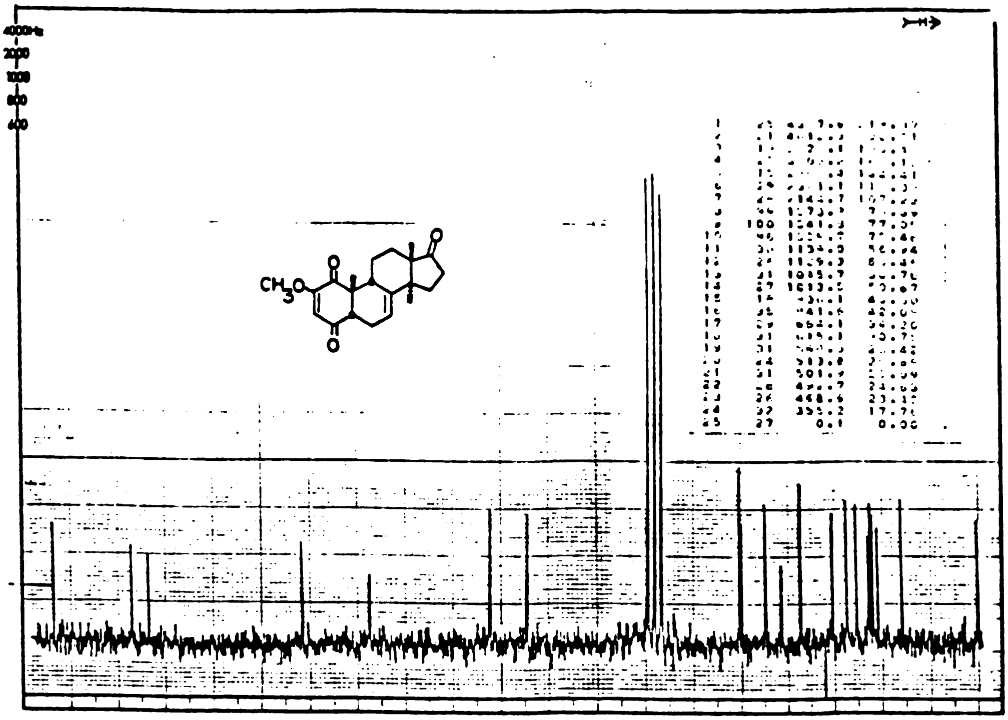

Figure 89. ^{13}C NMR spectrum of 54.

BIBLIOGRAPHY

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