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PART I
A NOVEL ANNULATION BASED ON SEQUENTIAL
PERICYCLIC REACTIONS
PART II
APPROACHES TO THE SYNTHESIS OF LANOSTEROL

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WILLIAM DANIEL MUNSLOW

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William Reusch
Major professor

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PART I

A NOVEL ANNULATION BASED ON SEQUENTIAL PERICYCLIC REACTIONS

PART II

APPROACHES TO THE SYNTHESIS OF LANOSTEROL

By

William Daniel Munslow

A DISSERTATION

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1981

ABSTRACT

PART I

A NOVEL ANNULATION BASED ON SEQUENTIAL PERICYCLIC REACTIONS

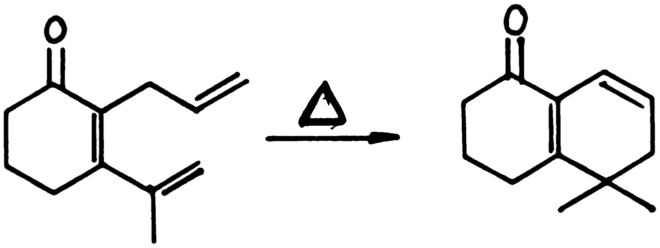
PART II

APPROACHES TO THE SYNTHESIS OF LANOSTEROL

By

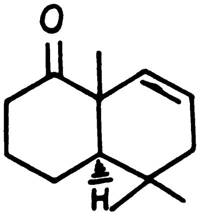
William Daniel Munslow

"Tandem rearrangement" describes a molecular rearrangement of two or more well-known rearrangements occurring in a sequential fashion. For such a transformation to occur, the molecular structure must be favorable for an initial rearrangement, the product from which is susceptible to a subsequent rearrangement. Part I of this dissertation describes the synthesis of compound **36** and its thermolysis to **38** via



36

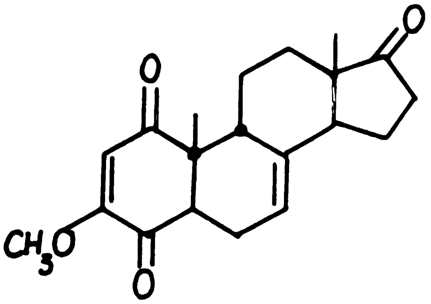
38



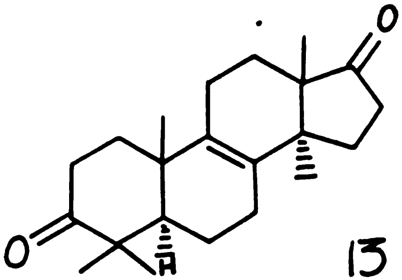
39

sequential pericyclic reactions. Part I also describes the reduction of dienone 38 to its corresponding conjugated enolate, and alkylation of this enolate to the angularly methylated product 39.

Part II of this dissertation describes efforts directed toward converting compound 7,



7



13

a Diels-Alder adduct, into the lanastone skeleton, compound 13.

For those who care most.

ACKNOWLEDGMENTS

I wish to extend my appreciation and gratitude to Professor William H. Reusch who proposed and oversaw this investigation. I would also like to acknowledge the sound technical advice offered by Dr. J. Tou, J. Gibson, J. Dickenson, J. Christensen, B. Chenera, and L. Kolaczkowski.

A special thanks to Mr. Ernst Oliver for his assistance in obtaining mass spectra and an ample supply of Creamora.

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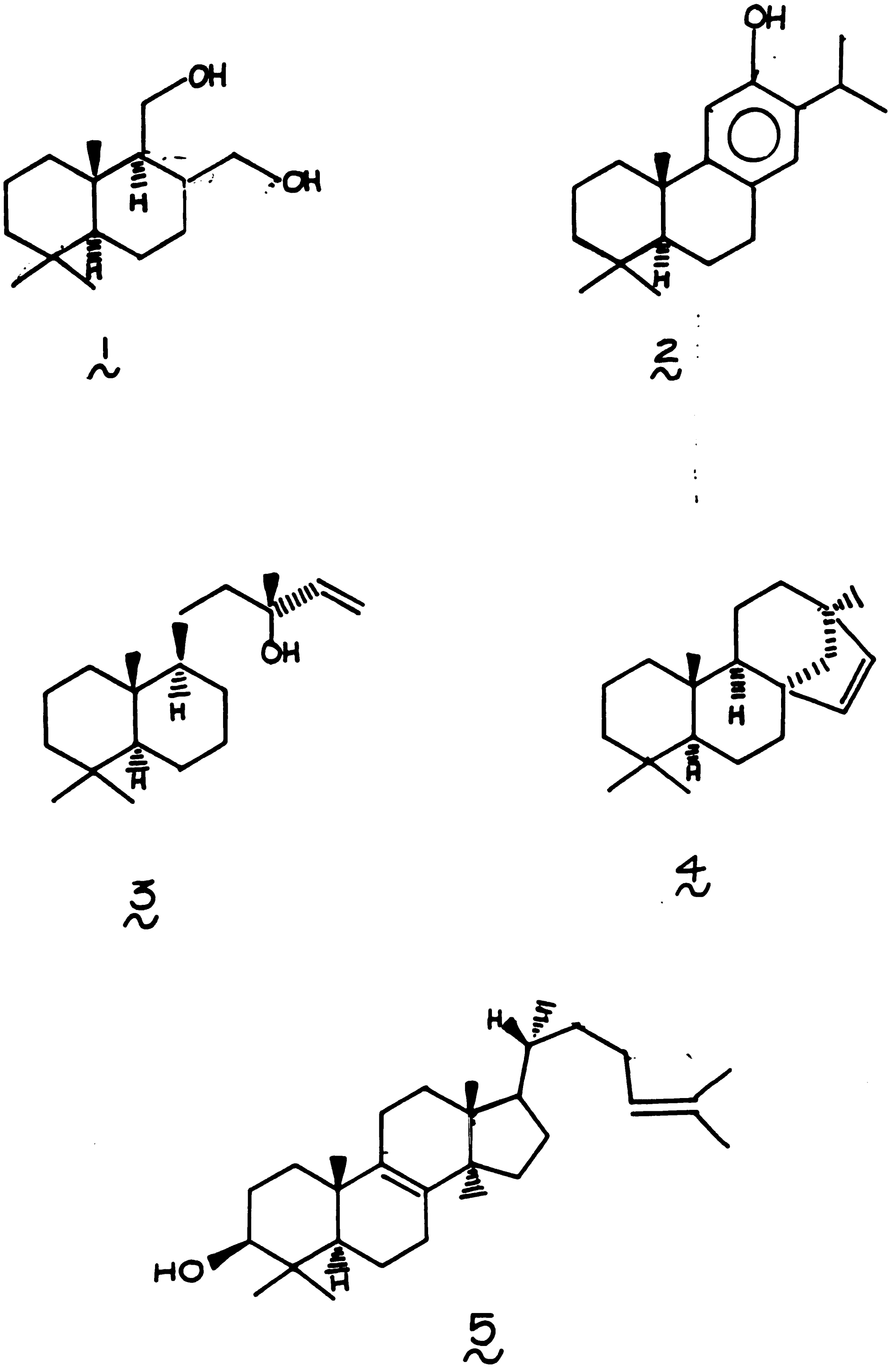
PART I

INTRODUCTION

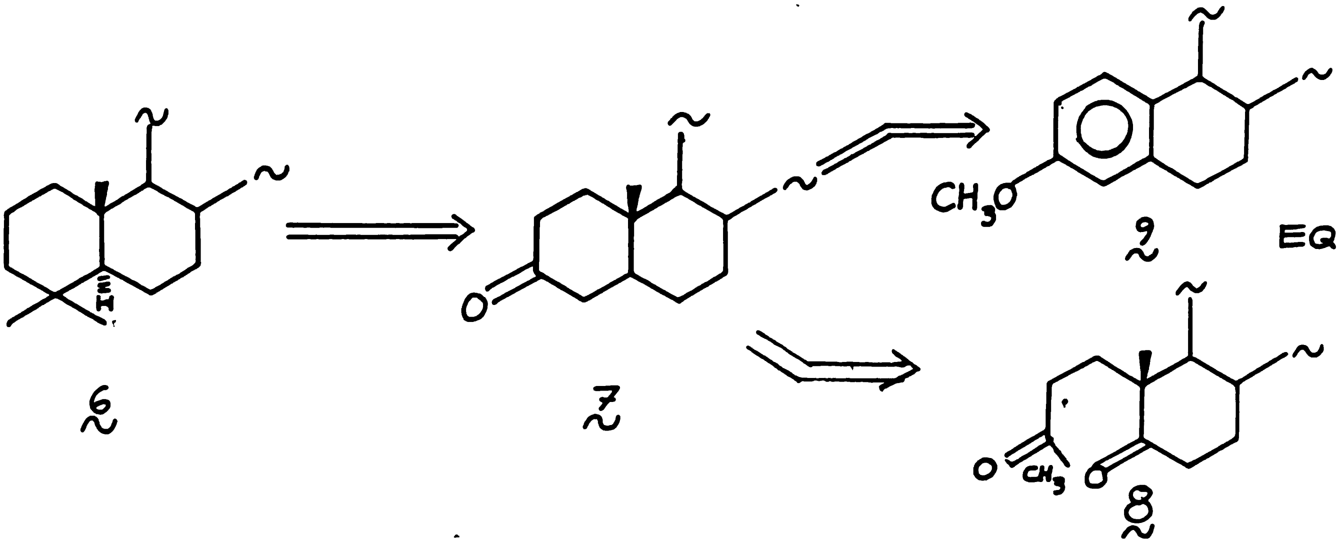
Many terpenoid natural products incorporate fused six-membered rings bearing a gem-dimethyl grouping adjacent to the ring fusion. These include sesquiterpenes of the bicyclofarnesol class (for example, drimenol (**1**)), many diterpenes (for example, ferrunginol (**2**) of the abietane class; mannol (**3**) of the labdane class; and hibaene (4) of the beyerane class), and virtually all the triterpenes having two or more carbocyclic rings (for example, lanosterol (**5**). See Scheme I.

Other features common to these structures are a trans-fused ring geometry and an angular methyl group at the bridgehead carbon remote to the gem-dimethyl moiety.

Synthesis of this structural unit has frequently been accomplished by the alkylation of an appropriate cyclic enone, as shown by the retrograde analysis in Equation 1. Since alkylation of extended metal enolates normally occurs α to the carbonyl, treatment of a species such as **7** with a strong base, followed by reaction with methyl iodide will generally introduce the gem-dimethyl moiety. This procedure is exemplified[1] in Equation 2 for the octalin **10**. This method of introducing methyl groups is also quite common in the construction of the A ring of

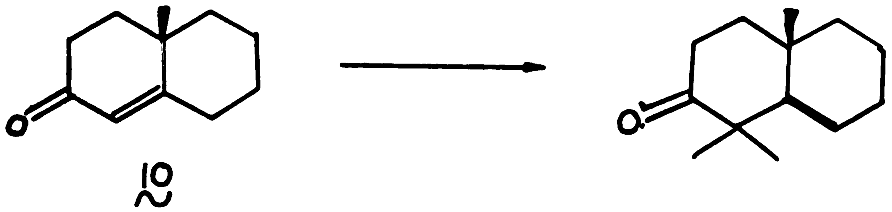


Scheme I



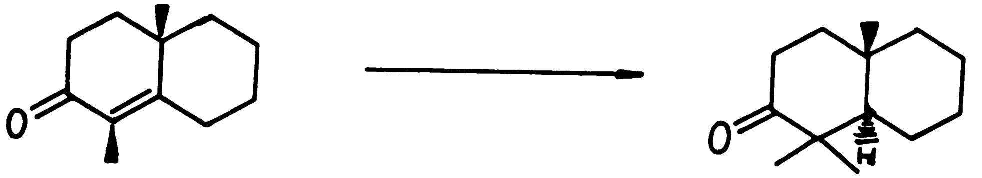
EQ.1

tetracyclic triterpenes and will be discussed in more detail in Part II of this thesis.



EQ.2

By appropriate modification in the synthesis of enones such as 7 it has been possible to prepare precursors of 6 with one of the methyl groups of the gem-dimethyl moiety already in place.[2] With a structure such as **11** in hand, it becomes possible to introduce the second methyl group concurrently with the trans ring fusion by the reductive



11 **12** EQ.3

alkylation procedure developed by Stork[3] (Equation 3).

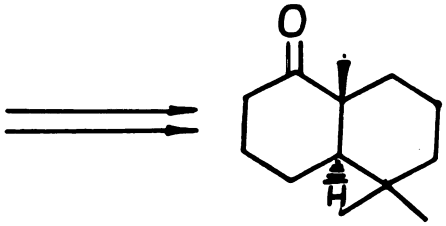
The cyclic enones used in these alkylations are most commonly prepared by an annulation sequence. A great variety of annulations exist,[4] however the Robinson annulation and a modification of it termed the Enol-lactone annulation have found the greatest application in this area. Indeed the Robinson annulation is used to prepare the important bicyclic intermediate known as the Wieland Miescher ketone (**13**) (Equation 4).[5] This versatile intermediate and its methyl analog **11** have been used extensively in the field of natural products synthesis. Compound (**13**) has been converted to **14** in five steps.[6]

A second annulation procedure frequently employed for the construction of these cyclic enones may be considered a modification of the Robinson Annulation. This Enol-lactone-Grignard method (Scheme II) was developed by

13

EQ.4

13

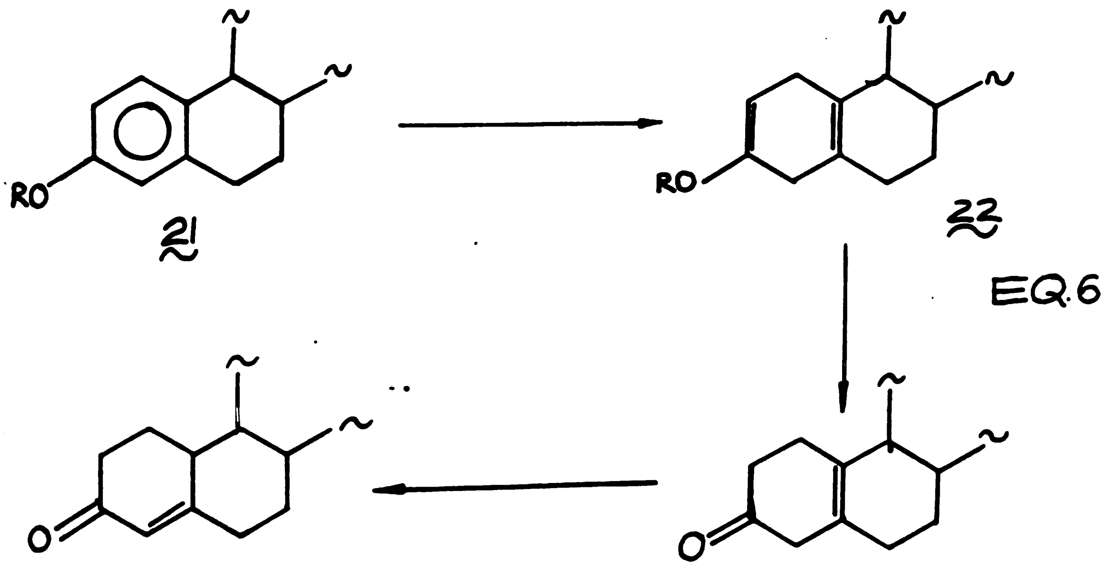


EQ.5

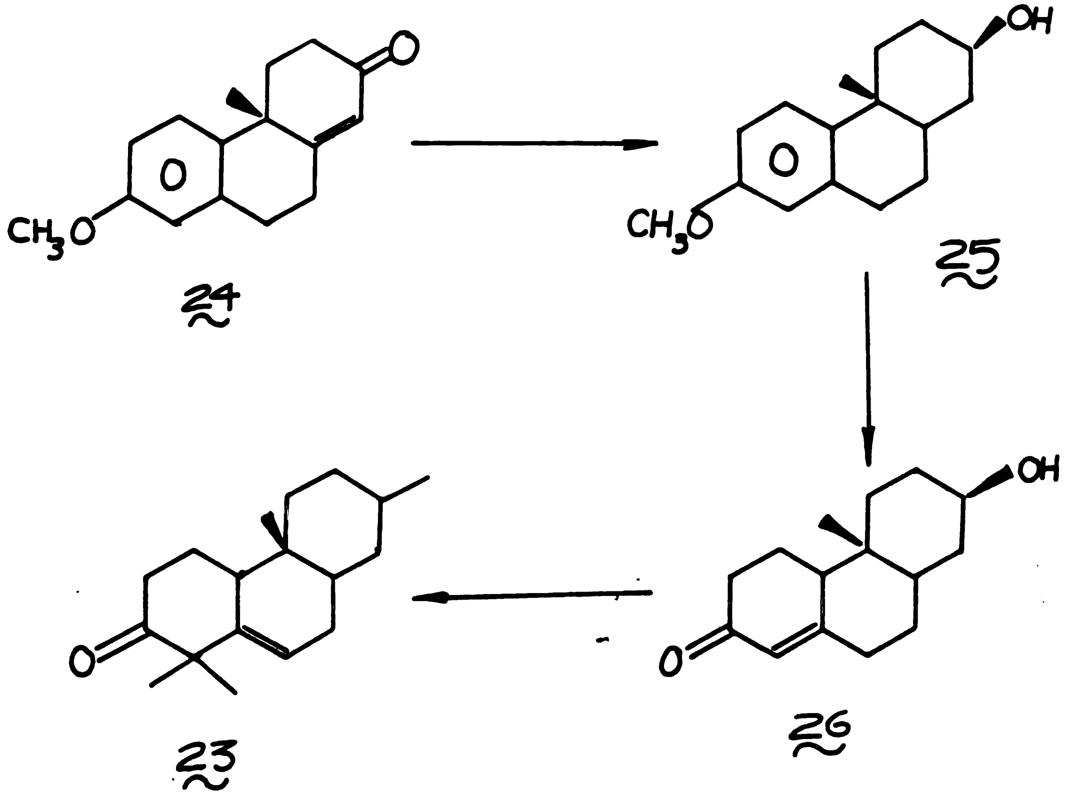
14

Turner and Fujimoto[7] to introduce a labeled carbon at the 4-position of steroid enones. This method involves the addition of a Grignard reagent (**16**) to a six-membered enol lactone (**15**) which rearranges to the ketol salt **18**. The Grignard reaction stops at this stage, since the normally reactive carbonyl function is now so sterically hindered that the Grignard reagent no longer can add to it. The ketal obtained upon hydrolysis then undergoes a base catalyzed reverse aldol condensation to the 1,5-diketone **19**, which is the same intermediate product found in the Robinson annulation, and it then cyclizes to the enone 20.

The cyclic enones 7 needed for alkylation have also been prepared by reduction of an appropriate aromatic precursor. Phenol is only one equivalent of hydrogen away from cyclohexenone hence the dissolving metal reduction developed by Birch^{8} provides the means by which this latent functionality can be realized. In practice, a phenolic ether 21 (Equation 6) is used as the substrate for reduction and the immediate product of that reduction



is the enol ether 22. Mild hydrolysis of 22 affords the unconjugated enone, while treatment under more strenuous conditions gives the conjugated isomer. This procedure has found extensive use in the syntheses of steroids and tri-cyclic terpenes; however, it is not particularly well-suited to the construction of the AB ring moiety in many of these compounds because of an angular methyl group at the AB ring junction. An example in which this scheme has been used to construct the A ring of a naturally occurring tri-cyclic terpene is the synthesis of rimnene (23), which has no angular methyl at the AB ring juncture. Reduction of 24 led to 25 and Birch reduction then gave the enone 26 which was converted to rimnene (23).[9]



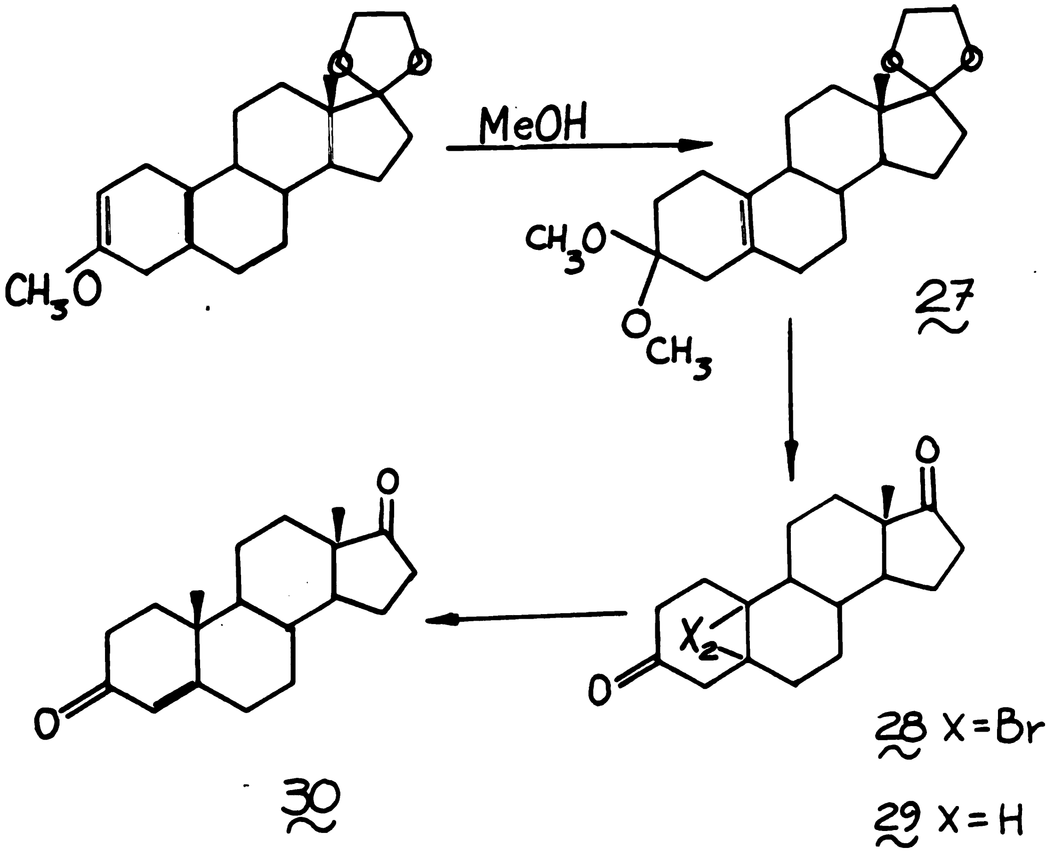
24

25

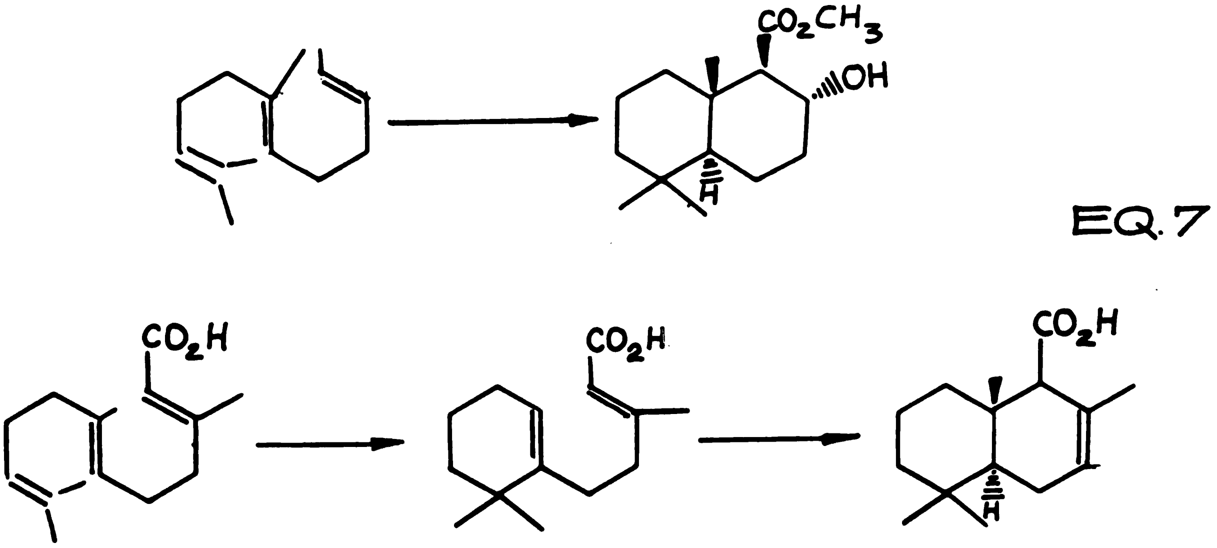
26

23

Since this procedure provides ring fusions in which angular methyl substituents are necessarily missing, work has been directed towards correcting this deficiency. For example, addition of methanol to the enol ether obtained from Birch reduction of estrone-17 ketal gave the mixed ketal 27. This readily added dibromocarbene to afford the cyclopropane 28. The ketones were then reketalized and the halogens removed by treatment with lithium in liquid ammonia. The ketone obtained upon hydrolysis 29, underwent ring-opening with B-elimination upon treatment with acid to give androstenedione (30).[10]



A completely different approach directed towards the synthesis of trans-fused six-membered rings bearing both a gem-dimethyl grouping adjacent to the ring juncture and an angular methyl group is found in polyene cyclizations.[11] Polyene cyclizations have been of interest to workers in the field of natural products because it is known that the biogenesis of triterpenes and steroids proceeds by a cyclization of the open chain polyolefin, squalene.[12] In studies directed toward a better understanding of the chemical and enzymatic processes involved in polyene cyclizations, both Eschemmoser,[13] and Stork[14] have used this technique to prepare decalins similar in structure to compounds prepared in this Thesis (Equation 7).



EQ.7

Polyene cyclizations of appropriate substrates have also been used to prepare a wide variety of tetracyclic structures.

Part I of this thesis will describe a novel synthetic sequence for the preparation of decalins having the substitution pattern described above. The key reaction in this scheme may be described as a tandem, pericyclic thermal rearrangement.

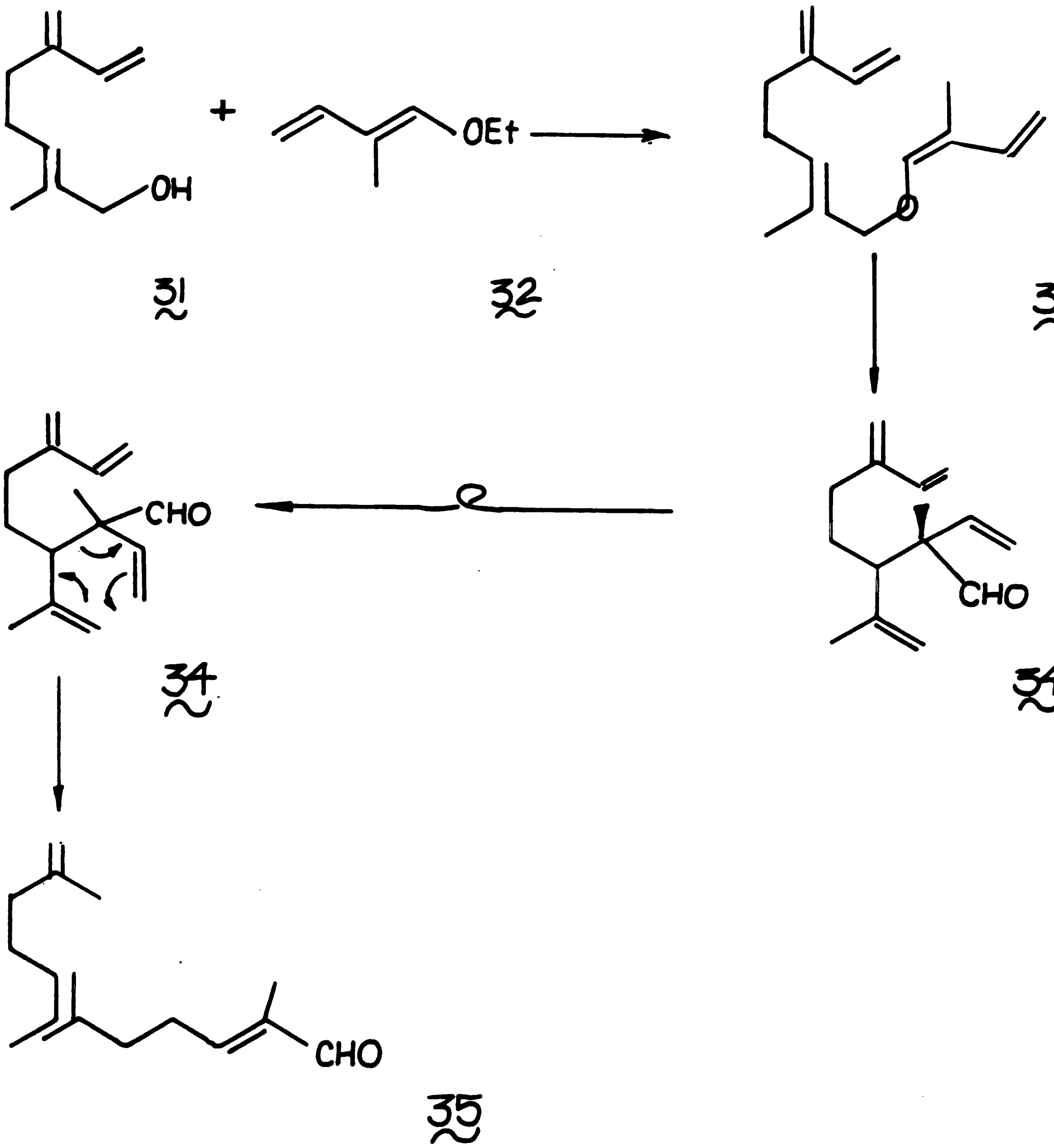
"Tandem rearrangement" describes a molecular rearrangement of two or more well-known rearrangements occurring in a sequential fashion. For such a transformation to occur the molecular structure must be favorable for an initial rearrangement, the product from which is susceptible to a subsequent rearrangement. This requirement limits the generality of the reaction, since rather specific structural conditions must be met; hence examples of these transformation are rare. However, when an appropriate substrate can be designed, tandem rearrangements are often useful because a great deal of structural reorganization takes place in one reaction. This technique therefore provides an efficient synthetic tool.

Of the examples of tandem rearrangements in the literature perhaps the most extensively studied is the tandem Claisen-Cope rearrangement, discovered by Alan F. Thomas and applied by him to the synthesis of long chain aldehydes. The utility of this sequence is demonstrated by the synthesis of the natural product β-Sinensal (**53**),[15] as shown in Scheme III.

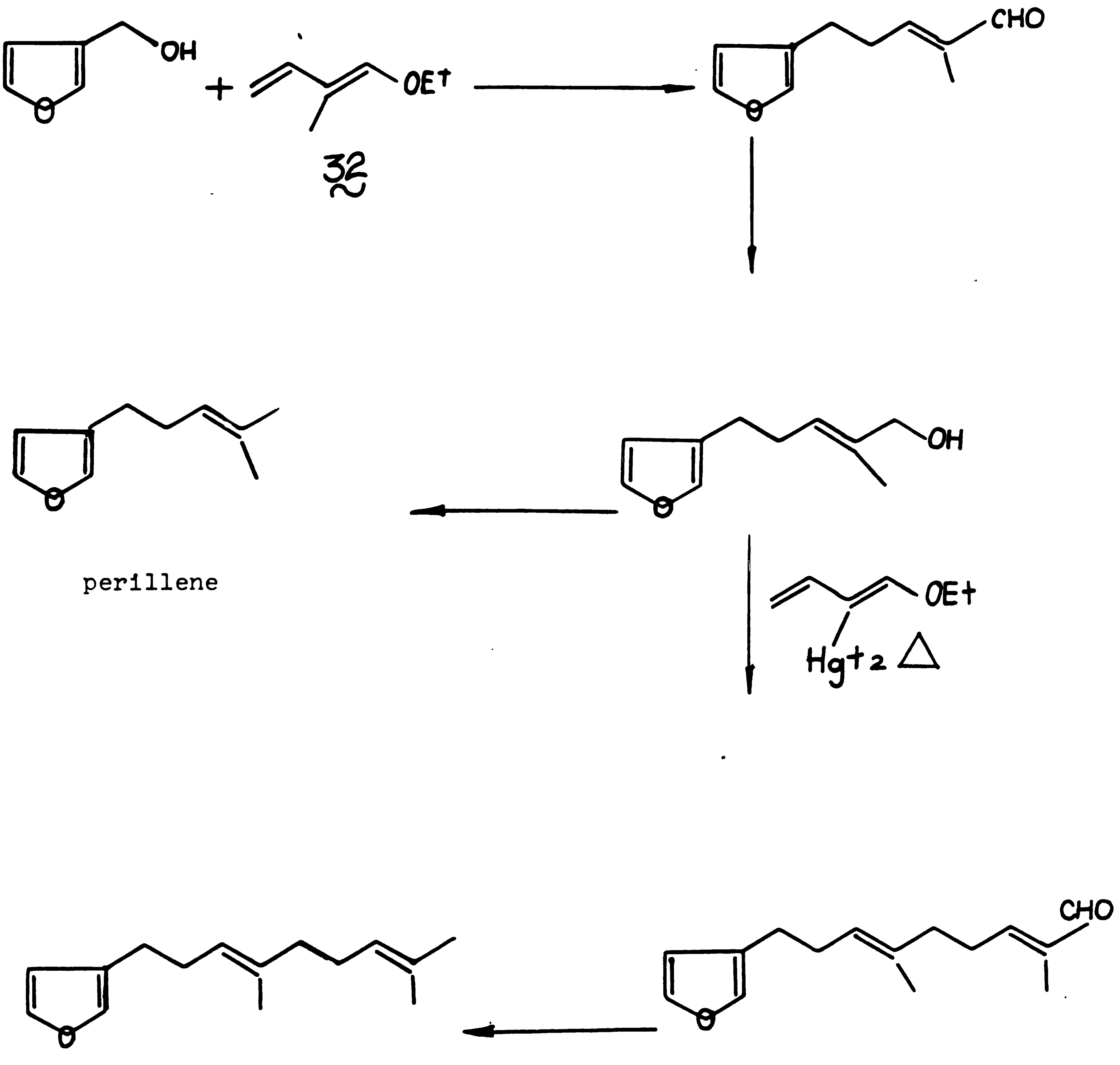
In this synthesis compound **33** is prepared by ether exchange of **31** with **32** in the presence of Hg^{+2}. This product first reacts by a Claisen rearrangement to yield **34**, which then rearranges by a Cope process to yield β-Sinensal (**35**). It is interesting to note that the overall transformation from **31** → **35** takes place in one pot and the net result has been the introduction of a functionalized isoprene unit to the starting allyl alcohol **31**. Furthermore since it is possible to reduce the α,β-unsaturated aldehyde that results from the tandem Claisen-Cope to an α,β-unsaturated alcohol it is possible to repeat the sequence, which therefore provides a means to link isoprene units.

The utility of these procedures was further demonstrated by Thomas in the synthesis of a series of furan ring-containing natural products, as shown in Scheme IV.[16] These transformations illustrate two interesting points: the additions of more than one isoprene unit as discussed above, and the use of an allylic alcohol, the C-C double bond of which is part of an aromatic ring. Thiophene and vinyl ether **32** were also found to undergo the tandem Claisen-Cope sequence in good yield.[16]

In Part I of this dissertation I will describe a novel method for the synthesis of fused six-membered rings bearing a gem-dimethyl grouping adjacent to the ring. The

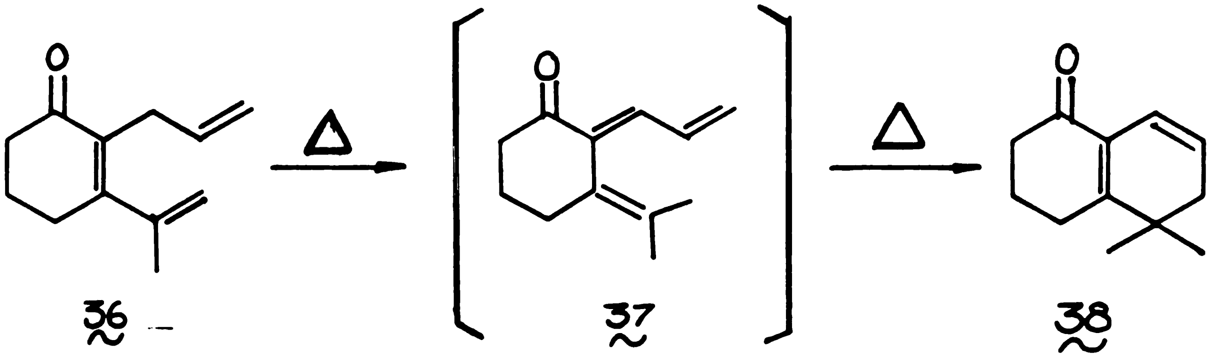


Scheme III



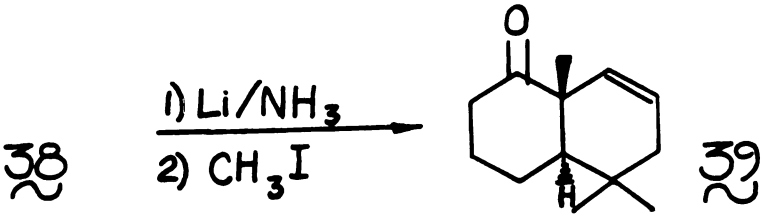
Scheme IV

key reaction in this scheme is a tandem rearrangement of the triene 36, which upon pyrolysis yields dienone 38.



36 37 38

Presumably the pyrolysis of 36 first gives 37 via a 1,5 sigmatropic shift of hydrogen, and this is followed by an electrocyclic ring closure of 37 to 38. I will also discuss

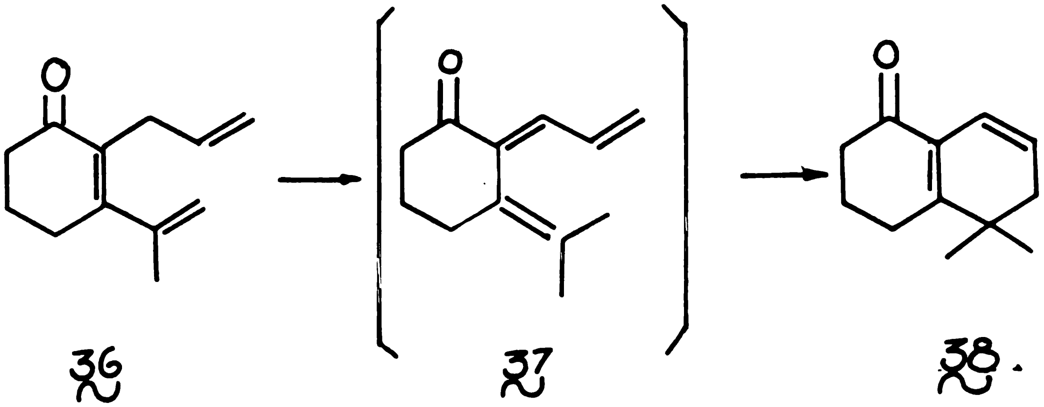


38 39

the reductive alkylation of 38 to the angularly methylated tran-decalin 39.

RESULTS AND DISCUSSION

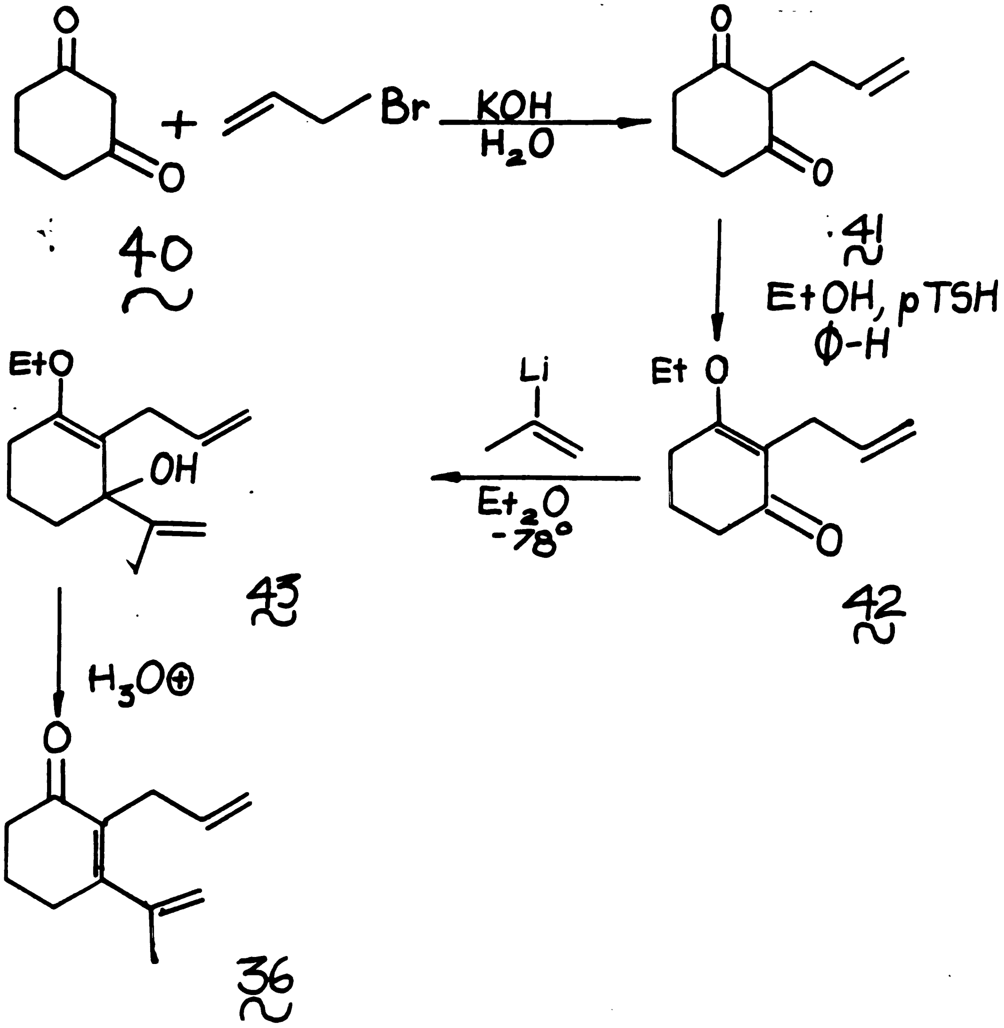
The key transformation in this synthetic sequence is the conversion of triene 36 to the cyclic dienone 38. (Equation 8).



EQ.8

It was proposed that upon pyrolysis, structure 36 would first undergo a 1,5 sigmatropic shift of hydrogen to give 37, which would then react further by an electrocyclic ring closure to yield the desired intermediate 38. Indeed, if triene 36 could be induced to react in this manner then this would constitute the first known example of a tandem rearrangement involving a 1,5 sigmatropic hydrogen shift followed by an electrocyclic ring closure.

In order to investigate the pyrolysis of 36 it was first necessary to prepare it, and this synthesis is described in Scheme V. Reaction of dihydrorescorcinol


O
O
Br
KOH
H2O
40
O
O
41
EtOH, pTSH
ϕ-H
EtO
OH
43
Li
Et2O
-78°
Et O
O
42
H3O⊕
O
36

Scheme V

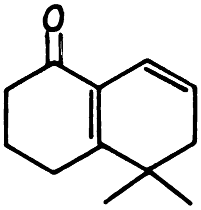
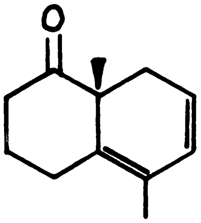
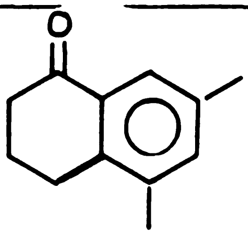
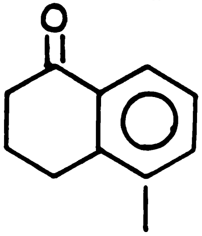
and allylbromide according to a previously described procedure[17] yielded the allylated diketone 41 in good yield. It was then necessary to mask one of the carbonyl groups of the dione and this was accomplished by conversion to the enol ether 42. Although this reaction went in high yield in small scale preparations, conversions were not as high in large scale reactions and unreacted starting material was usually recovered. In the conversion of a ketone to its enol ether an equilibrium is established between the ketone and alcohol reactants and the enol ether and water products. In order to favor the products in reactions in which water is produced, a common procedure is to use a Dean-Stark trap to remove the water as it is produced and thereby shift the equilibrium to the product side. However, this procedure did not work well in this case because it was necessary to conduct the reaction in a large excess of ethanol. The water produced in the conversion of 41 → 42 was missable in the reaction media and the Dean-Stark trap alone was not effective, In small scale reactions the Dean-Stark trap was filled with molecular sieve to remove the water as it was produced. For large scale runs it was more convenient to extract the unreacted starting material with base prior to isolation of the desired enol ether.

The next step in this synthesis was the addition of isopropenyl lithium to the enol ether 42. Isopropenyl lithium was prepared from the corresponding bromide and an alloy containing 97% Li and 3% Na. It is interesting to note that neither alkyl nor alkenyl halides will react with lithium metal unless a small amount (1-5%) sodium is present.[18] The tertiary alcohol **43** obtained from this addition usually was not isolated; instead it was shaken (as an ether solution) with 5% aqueous HCl, which hydrolyzed the enol ether and dehydrated the alcohol, yielding the desired triene **36** in excellent yield.

With triene **36** in hand, its pyrolysis was studied, and the results are summarized in Table 1. Initial efforts involved heating solutions of **36** in solvents of different boiling points. Benzene, toluene, and xylene were tried and, as indicated in Table 1, complex mixtures resulted. Next sealed tube reactions were investigated. Both temperature and reaction time were varied but again only complicated reaction mixtures were obtained. Although these results were discouraging, there was one redeeming feature in most of these experiments. In the ^{1}H NMR spectra of the complex product mixtures frequently there was a strong singlet at δ1.0 ppm. Since this signal was in the range expected for the gem-dimethyl substituent or the desired product **38**, we continued to search for appropriate pyrolysis conditions for this transformation.

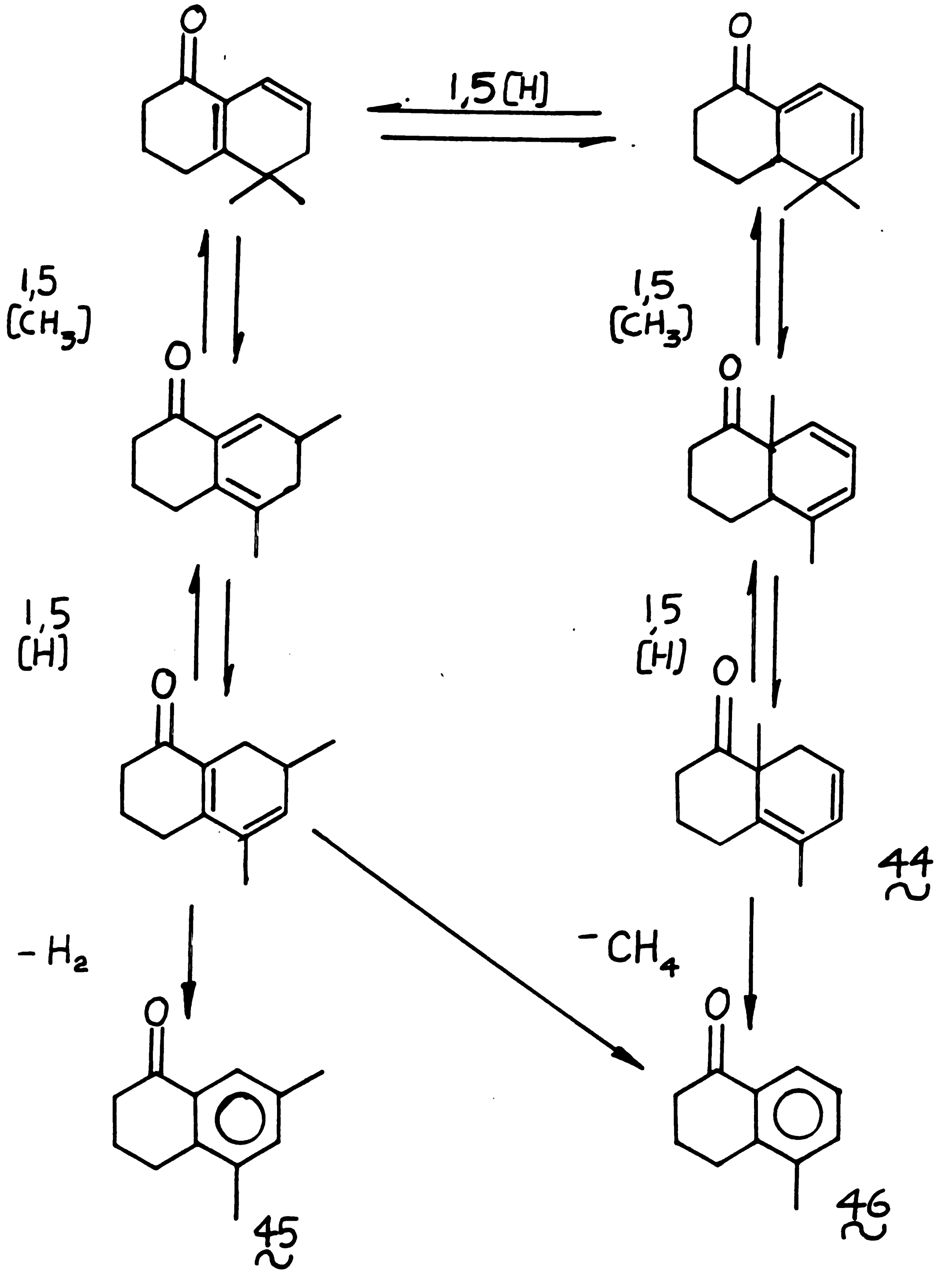
As indicated in Table 1, the pyrolysis of **36** in a flow

Table 1. Pyrolysis of 36.

Pyrolysis Conditions	Products
Triene in solution Benzene (84°C) Toluene (110°C) Xylene (138°)	Complex Product Mixtures
Sealed tube reactions 180°C 200°C 250°C	Complex product mixtures
Flow tube apparatus Contact time <1 min. Temperature <265°	Starting material (36)
Flow tube apparatus Contact time <1 min. Temperature 270<T<280°	 38 (65%) +  44 (8%)
Flow tube apparatus Temperature 320°<T<340°	 45 + tar  46

apparatus with a short contact time and a temperature carefully maintained at 270-280°C gave a reasonable yield (65%) of **38** along with a minor component **44** isolated in 8% yield. No reaction was observed below 265°C and unchanged starting material was recovered. If the temperature was raised above 320°C **38** was not obtained; instead, aromatic structures **45** and **46** were isolated, along with larger amounts of decomposition products. The structure assignment for compounds **38**, **44**, **45**, **46**, rests on their NMR, IR, and mass spectra. (See Experimental.) Additionally, compounds **45**, and **46**, were identified by matching their mass spectra to that contained in the computer library and compound **45** was compared to an authentic sample (Aldrich). At this point in our work we were pleased with the 65% yield of dienone **38**. We were also intrigued by the minor product **44** since at first it appears to result from a 1,3 methyl shift. The Woodward-Hoffman rules[19] require that a 1,3 methyl shift must occur in an antarafacial fashion if it is concerted. In practice this has proved to be a rare event. The products resulting from the pyrolysis at 320-340°C also raise interesting mechanism questions. They are known compounds, but this is not the best way to make them.

In order to determine the origin of structures **44**, **45** and **36**, one can consider the various rearrangement pathways available to both the starting triene **36** (see Scheme VI) and the dienone product **38** (see Scheme VII). As stated previously,



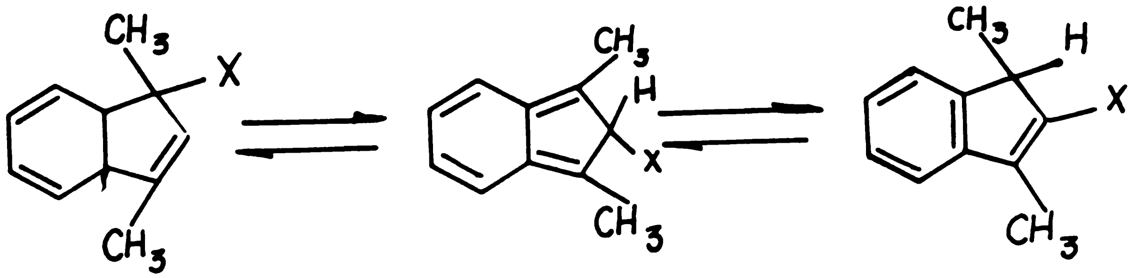
Scheme VII

it was expected that 36 would first react by a 1,5 sigmatropic shift of hydrogen to yield 37. (Scheme VI) It is also possible for a 1,5 shift to yield 47, which differs from 37 in the geometry about the newly formed double bond. Since 1,5 hydrogen shifts are equilibrium reactions, we expected that 47 could rearrange back to 36, and eventually all the material might end up as 38. We also considered the possibility that 38 would react further to give 48 by another 1,5 shift of hydrogen, but felt that this would not present serious problems because both 38 and 48 were expected to give the same enolate anion upon Li/NH_3 reduction (see below). Other possible reaction paths are also shown in Scheme VI. A 1,5 vinyl migration in 36 may lead to the observed minor product 44 via the steps indicated, and it is also possible to account for the over pyrolysis products observed by a series of rearrangements starting with 36 and terminating with an elimination of H_2 or CH_4.

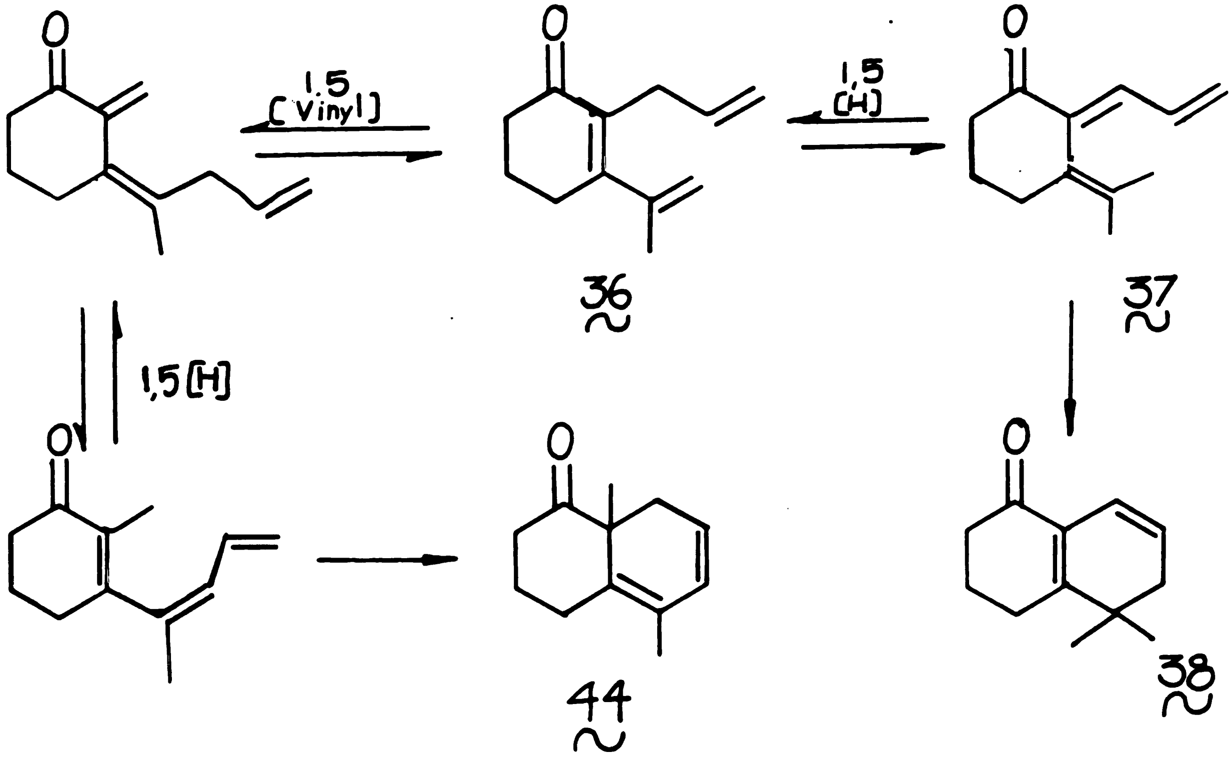
Scheme VII shows some rearrangement pathways that might be followed by the product of the desired tandem rearrangement (38). Note that it is possible to account for both the minor product 44, and the over pyrolysis products 45 and 46 by these pathways. In order to gain some insight regarding the origin of products 44, 45 and 46, two simple experiments were performed: First the purified dienone 38 was pyrolyzed at 275°C. It failed to react and thus it is apparent that compound 44 does not come from further reaction of 38 at

275°C, as suggested in Scheme VII. Next, the purified dienone **38** was pyrolysed at 320°C. Under these conditions the aromatic compounds **45**, and **46** were obtained, and hence the pathway to these structures shown in Scheme VII is at least feasible.

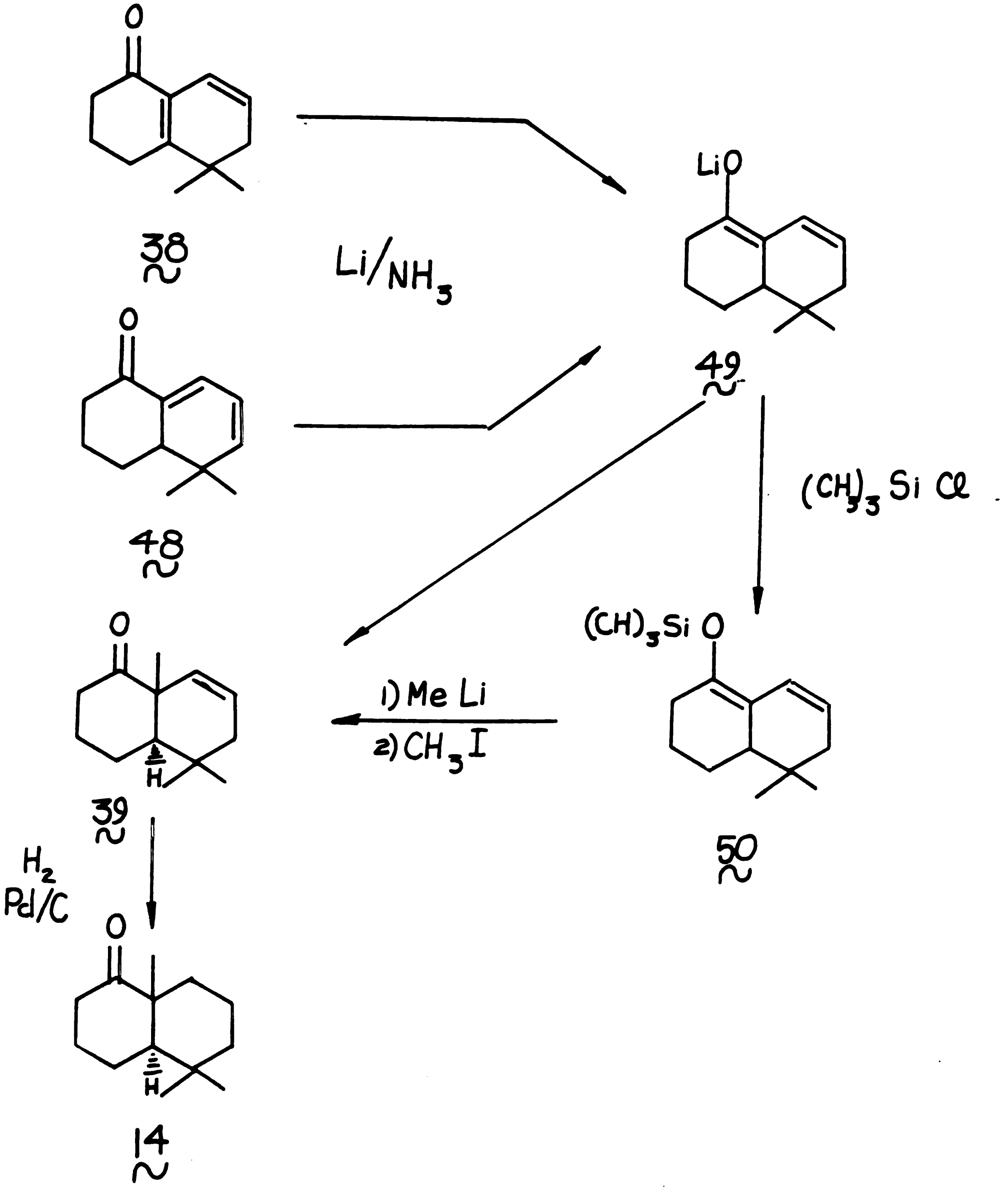
A summary of what is believed to occur upon pyrolysis of **36** at 275°C is given in Scheme VIII. There are two competing 1,5 sigmatropic rearrangements. A 1,5 shift of hydrogen followed by electrocyclic ring closure yields the desired structure **38** while a less favored 1,5 vinyl migration followed by a 1,5 shift of hydrogen and then electrocyclic ring closure gives the minor product **44**. The existence of this minor product is interesting, since sigmatropic vinyl migrations have been known for a relatively short period of time. Work which supports the suggestion that 1,5-hydrogen shifts proceed with greater facility than corresponding vinyl shifts was published by Jones, <u>et</u> <u>al</u>. in 1978.[20] He was able to measure the migratory aptitude for a series of substituents (X) in the reaction shown in Equation 9. The ranking of migratory aptitudes was $CHO>COR>H>CH=CH_2>CONH_2>CO_2Ph>CO_2CH_3>CN>C{\equiv}CH>Alkyl$.



EQ. 9



Scheme VIII


38
Li/NH3
48
LiO
49
(CH3)3 Si Cl
(CH)3Si O
50
O
1) Me Li
2) CH3I
H
39
H2
Pd/C
O
H
14

Scheme IX

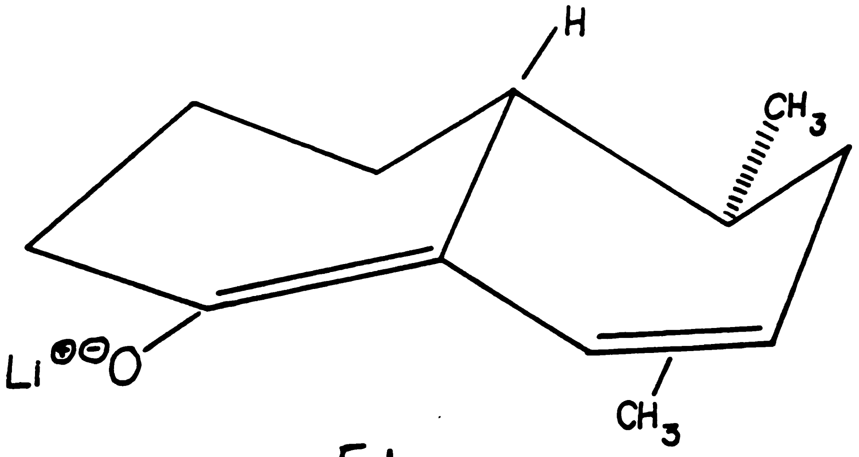
trimethylsilyl chloride, and a good yield of 50 was obtained.

With this knowledge in hand the trapping of enolate 49 with methyl iodide was reinvestigated. Using glyme as a co-solvent, with careful removal of ammonia after the reduction, trapping of 49 with methyl iodide yielded 39 plus two other products. Analysis of the product mixture by GC/MS indicated that the two by-products were formed by over alkylation of 49. To account for this the mechanism of dissolving metal reductions must be considered.[21] The first step is an electron transfer from the metal to

the enone and this is followed by a proton abstraction from the solvent. In a glyme-ammonia mixture the most acidic component is the ammonia, hence proton extraction from ammonia leads to the formation of one equivalent of lithium amide. Since lithium amide is a sufficiently strong base to abstract a proton from ketone 39, and since excess methyl iodide is present, over-alkylation of 39 can occur. To prevent this from happening, one equivalent of a proton donor was added to the system. Water was chosen as the proton donor because the conjugate base, LiOH is not strong enough to abstract protons alpha to carbonyl groups. When the reduction-alkylation was repeated, using glyme as the co-solvent and with one equivalent of water added as a proton donor, we were able to obtain a good yield (65%) of **39** as the sole product.

As part of the structure proof of **39** it was necessary to demonstrate the trans nature of the ring geometry. This was accomplished in two ways. First, catalytic reduction of **39** gave **14** (Scheme IX) and the ^{1}H NMR linewidth of the angular methyl group minus the linewidth of TMS was determined to be 0.8 Hz. Williamson and Spencer[22] measured the ^{1}H NMR linewidths of the angular methyl groups of a large number of *cis* and *trans* decalins, and found that the linewidth relative to TMS for the angular methyl groups for all the *cis* compounds was 0.25±0.11 Hz. The corresponding values for the *trans* compounds was 0.80±0.2 Hz. Since there is no overlap between the *cis* values and the *trans* values this provides an unambiguous method for distinguishing *cis* from *trans* even when one can only measure one of the isomers. A second method for assigning the *trans* ring geometry of **39** is available because **14** is a known compound[23] and its 2,4 DNP has been reported to melt at 168-170°. the 2,4 DNP of **14** melts at 167-170°

The stereoselective alkylation of enolate anion **49** giving only the trans ring fusion of **39**, is one of the more interesting aspects of this work. To understand the preference for this product it is necessary to consider the conformational analysis of enolate 49. From the principle of axial attack one would expect the trans product to be formed by alkylation of conformer 51 while the cis product could result from either 52 or 53. Inspection of 52 leads to the conclusion that it is unfavorable due to the large t-butyl like substituent occupying an axial orientation. To accommodate this large group in an equitorial position, 52 can ring flip to give 53. In 53 however p-orbital overlap is not maintained over the entire conjugated system, and hence 53 is also unfavorable relative to 51. Since conformation 51 maintains good p-orbital overlap and also orients the large t-butyl like substituent in an equitorial position it is the most favored conformation for alkylation.



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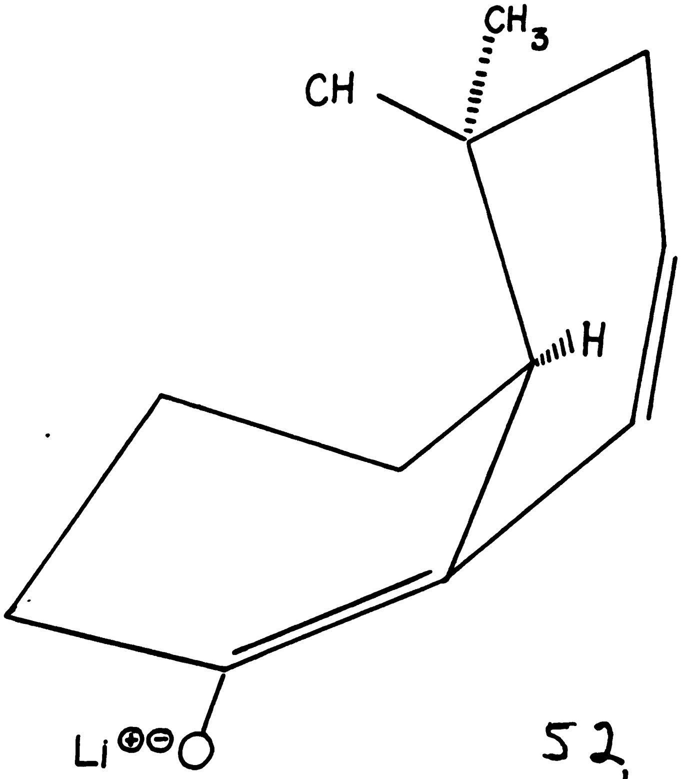

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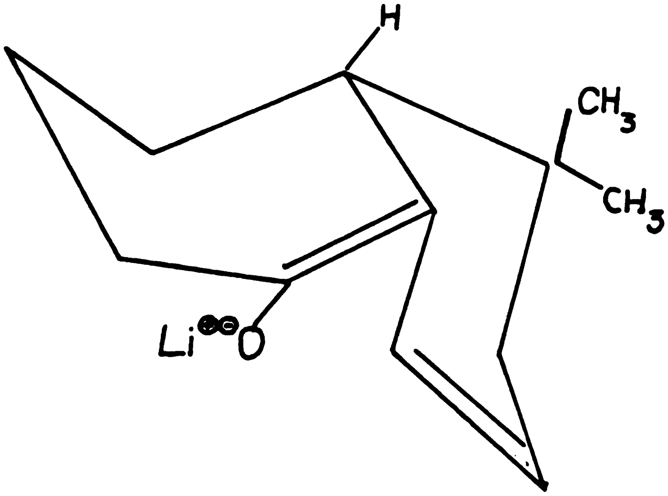

53

EXPERIMENTAL

General

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

Analysis by GLPC was conducted with a Varian 1200 gas chromatograph. Melting points were determined on a Hoover-Thomas apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer. Proton magnetic resonance spectra were taken in deuterochloroform solutions with either a Varian T-60 or a Bruker 250 MHz spectrometer and are calibrated in parts per million downfield from tetramethylsilane as an internal standard. Mass spectra were obtained with a Finnigan 4000 GC/MS spectrometer.

Preparation of Enol Ether 42

For small scale preparations the following procedure was used: 0.5 g (0.003 m) 2-allyldihydroresorcinal was dissolved in a mixture of 3 mL ethanol and 20 mL benzene containing about 21 mg p-toluenesulfonic acid. The reaction flask was fitted with a Dean-Stark trap that had been filled with molecular sieves. The mixture was then heated to reflux under nitrogen for 24 hours, allowed to cool to room temperature and washed twice with 10% NaOH saturated in NaCl. The organic layer was then washed with H_2O to neutral pH, then washed with brine and dried ($MgSO_4$). Removal of the solvent followed by Kugelrohr distillation of the resulting yellowish liquid gave 0.5 g (85%) of product.

For large scale preparations the following procedure was used: 2.4 g (0.013 m) p-toluenesulfonic acid was dissolved in 1 liter benzene and this mixture was heated to reflux with removal of water by a Dean-Stark trap. To this solution was added 40 g (0.26) 2-allyl dihydroresorcinol and 360 mL ethanol. The Dean-Stark trap was replaced with a soxhlet extractor filled with molecular sieves and the whole heated to reflux for 12 hours. The mixture was allowed to cool to room temperature and washed twice with 125 mL 10% NaOH saturated on NaCl. Acidification of the combined base washes gave 11 g starting material. The organic layer was washed with H_2O to neutral pH, brine and dried ($MgSO_4$). Removal of solvent left a yellowish liquid which was distilled through a six inch vigreux column. A small for run was collected 120-147/7 mm, and the product 140-142°/7 mm. Yield 17.4 g (37%), 64% based on recovered starting material.

Preparation of Triene 46

For small scale preparations the following procedure was used: A solution of isopropenyl lithium was prepared by slowly adding a solution of 2.0 g (0.017 m) isopropenyl bromide in 30 mL ether to about 0.5 g of a Li/3% Na alloy suspended in 30 mL ether and maintained at 0°C under Argon. The resulting mixture was allowed to come to room temperature, and was then heated to gentle reflux for a few minutes. During this time LiBr precipitated and was allowed to settle to the bottom of the flask while the unreacted Li alloy floated on top. The ethereal solution of isopropenyl lithium was added dropwise to 1 g (0.005) of the enol ether dissolved in 40 mL ether and maintained at -78°C under argon. The resulting solution was stirred at -78°C for 1 hour then warmed to room temperature and stirred for about 2 hours. After quenching by addition of saturated NH_4Cl, the layers were separated and the organic portion washed twice with 5% HCl, brine and dried over $MgSO_4$. Removal of the solvent left a yellowish liquid which was distilled on the Kugelrohr to yield 0.82 g (85%).

For large scale preparations the following procedure was used: A solution of isopropenyl lithium was prepared by slowly adding a solution of 13.5 g (0.11 m) isopropenyl bromide in 125 mL dry ether to a suspension of about 2.5 g Li/3% Na alloy in 200 mL dry ether; maintained at 0°C under Argon. The resulting mixture was allowed to warm to room temperature and then heated to gentle reflux for a few minutes. During this time LiBr precipitated and settled to the bottom while the unreacted Li/Na alloy floated on top. The ethereal solution of isopropenyl lithium was transferred to an addition funnel under Argon and was added dropwise to 13 g (0.072 m) of the enol ether in 200 mL maintained at -78°. The resulting mixture was allowed to warm to room temperature, stirred for 2-3 hours, then cooled to 0° and quenched by slow addition of 150 mL saturated NH_4Cl. The layers were separated and the ether layer was washed twice with 150 mL 5% HCl, 5% $NaHCO_3$, water, brine, and dried over $MgSO_4$. Removal of solvent gave 12.8 g yellowish liquid which was distilled through an 8 inch virreux column to yield 9.5 g (75%) of the trienone product, bp 96-98°/2.75 mm.

Preparation of Dienone **38**

The trienone **46** (5.9 g, 0.033 m) in 75 mL benzene was pyrolyzed in a flow tube maintained between 270° and 280°C. The product (5.7 g) was collected and chromatographed on 40 g silica gel. Elution with 20% ethylacetate in hexanes gave two products: compounds **44**, (0.47 g, 8%) and **38** (4.8 g, 65%).

Pyrolysis of Triene **46** at 290° to 305°C

The trienone 8.7 g (0.049 m) in 100 mL benzene was pyrolysed in a flow tube maintained between 290-305°C. The product (8.1 g) was collected and passed through a silica column, eluting with ethyl acetate. About 0.2 g of tar was removed and 7.1 g of the collected material was then chromatographed on a High Pressure Liquid Chromatography apparatus. A silica gel column was used and upon elution with 8% ethyl acetate in hexanes, 4.6 g (65%) of the material was found in one fraction with 1.0 g (13%) of the product appearing in three earlier fractions - all complex mixtures. The remaining product proved to be polar tarry material. PMR and GC analysis of the main fraction showed this to be a fairly complex mixture, having ^1H NMR peaks corresponding to the cyclized diene together with significant peaks in the aromatic region. Since aromatic products could result from further pyrolytic reactions of the desired cyclic dienone, this premise was tested by heating 3.0 g of the mixture obtained by HPLC separation in a flow tube at 335°C. The product of this pyrolysis no longer contained any of the cyclic dienone (absence of olefinic protons and gem-dimethyl protons in the NMR). The product of this pyrolysis required extensive purification. It was first subjected to a gravity column (silica gel; 20% ethylacetate in hexanes) from which three fractions were collected. All three fractions were mixtures but the third and major fraction was mainly two compounds. A small portion of this fraction was purified by preparatory gas chromatography and the two major components identified as **45** and **46** from their spectra, comparison with authentic samples and computer search and matching.

Preparation of Silyl Enol Ether **50**

To a solution of Li metal (0.024 g, 3.4×10^{-3} mol) in 50 mL ammonia containing 5 mL dry glyme and maintained at reflux was added over 15 minutes the dienone (0.20 g, 1.14×10^{-3} mol) in 10 mL glyme. The resulting mixture was stirred for 10 minutes then the ammonia was allowed to evaporate through a bubbler and the mixture pumped on at 0.2 torr until it was taken to dryness. The enolate was redissolved in 15 mL fresh glyme, cooled to 0°, and a quenching solution of trimethylsilylchloride added rapidly. The quenching solution was prepared as follows: To a solution of trimethylsilyl chloride (0.21 g, 1.9 x 10^{-3} mol) in 5 mL glyme was added triethylamine (0.08 mL, 5.7 x 10^{-4} mol) and the mixture allowed to stand at room temperature for about 15 minutes until precipitation was complete. The precipitate was filtered and the filtrate used as the quenching solution. After quenching at 0°, the reaction mixture was allowed to come to room temperature and poured into a mixture of 50 mL pentane and 20 mL 5% $NaHCO_3$. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to give 0.2 g product.

Direct Methylation of Enolate Anion 49

A solution of H_2O in glyme was prepared by dissolving 0.10 mL H_2O in 50.0 mL dry glyme. The cyclic dienone 0.20 g (1.14 x 10^{-3}) was then dissolved in 10 mL of the above solution and added dropwise to a refluxing solution of 0.024 g (3.4 x 10^{-3}) Li metal in 50 mL ammonia. Stirring was continued for a few minutes after the addition was complete, the ammonia allowed to distill out through a bubbler, and the mixture pumped on at about 0.2 torr until it was taken to dryness. The remaining residue was dissolved in 40 mL glyme, cooled to 0°C and to it was added 2 mL CH_3I in 5 mL glyme. The mixture was allowed to come to room temperature and stirred for about 1 hour, 3 mL H_2O was added, and the mixture taken almost to dryness on the evaporator. The remaining residue was dissolved in CH_2Cl_2, washed with H_2O brine, dried over $MgSO_4$, and evaporated to dryness to yield 0.14 g (64%) product.

Catalytic Reduction of Compound 39

To 0.050 (2.6×10^{-4} m) of the trimethyl decalone in 200 mL ethanol was added a catalytic amount of 10% Pd/C and this mixture shaken under 40 psi H_2 for seven hours. The catalyst was filtered and the solvent removed to give 0.045 g of product.

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REFERENCES

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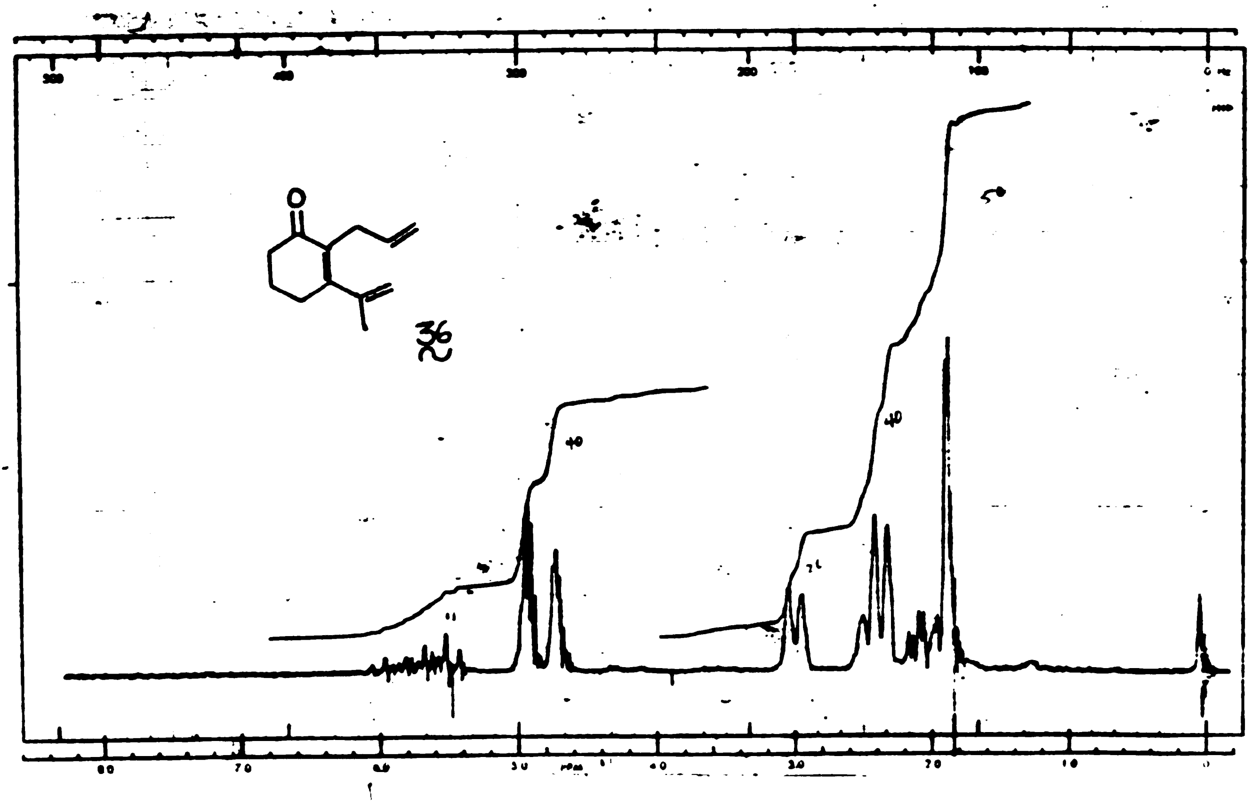

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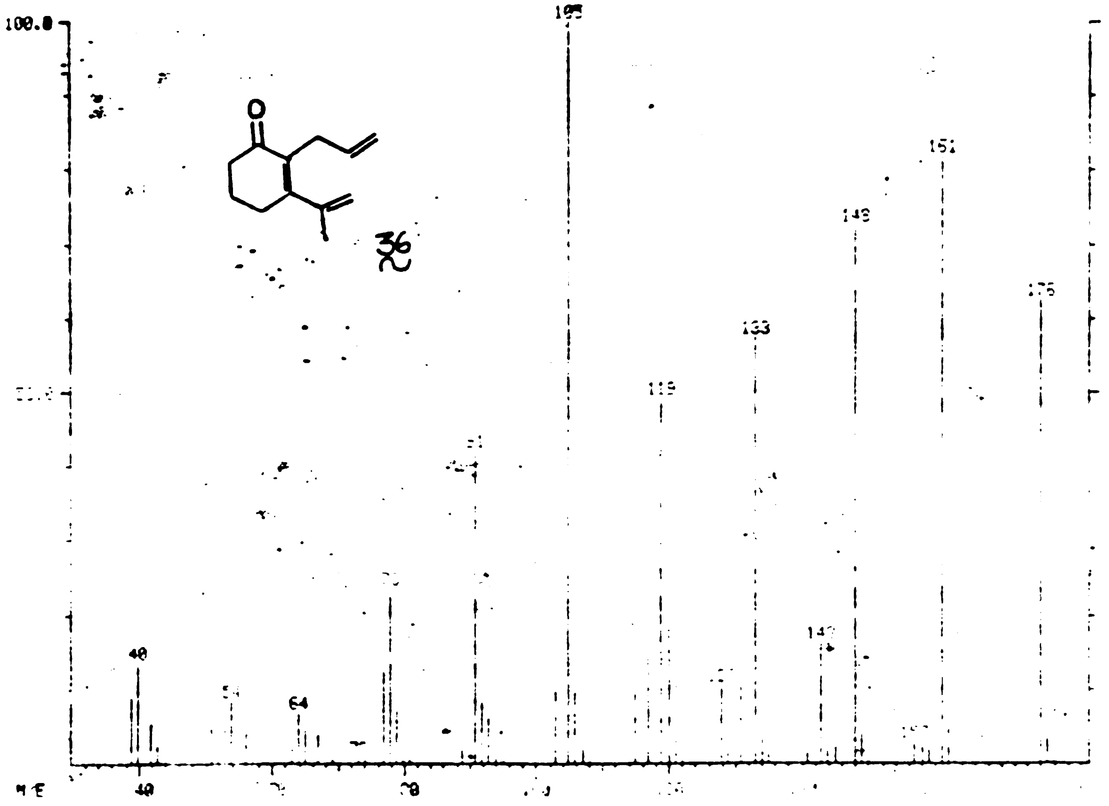

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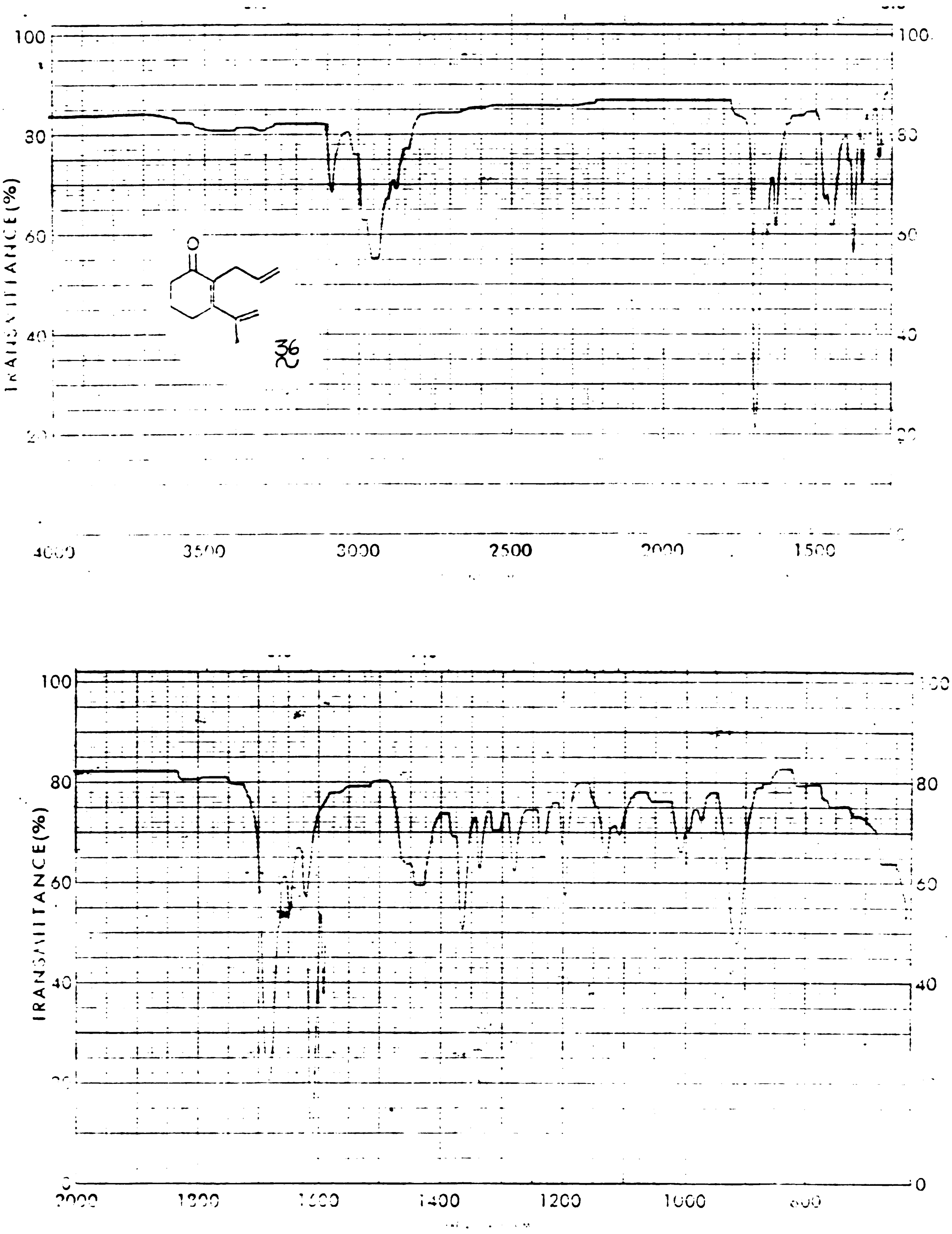

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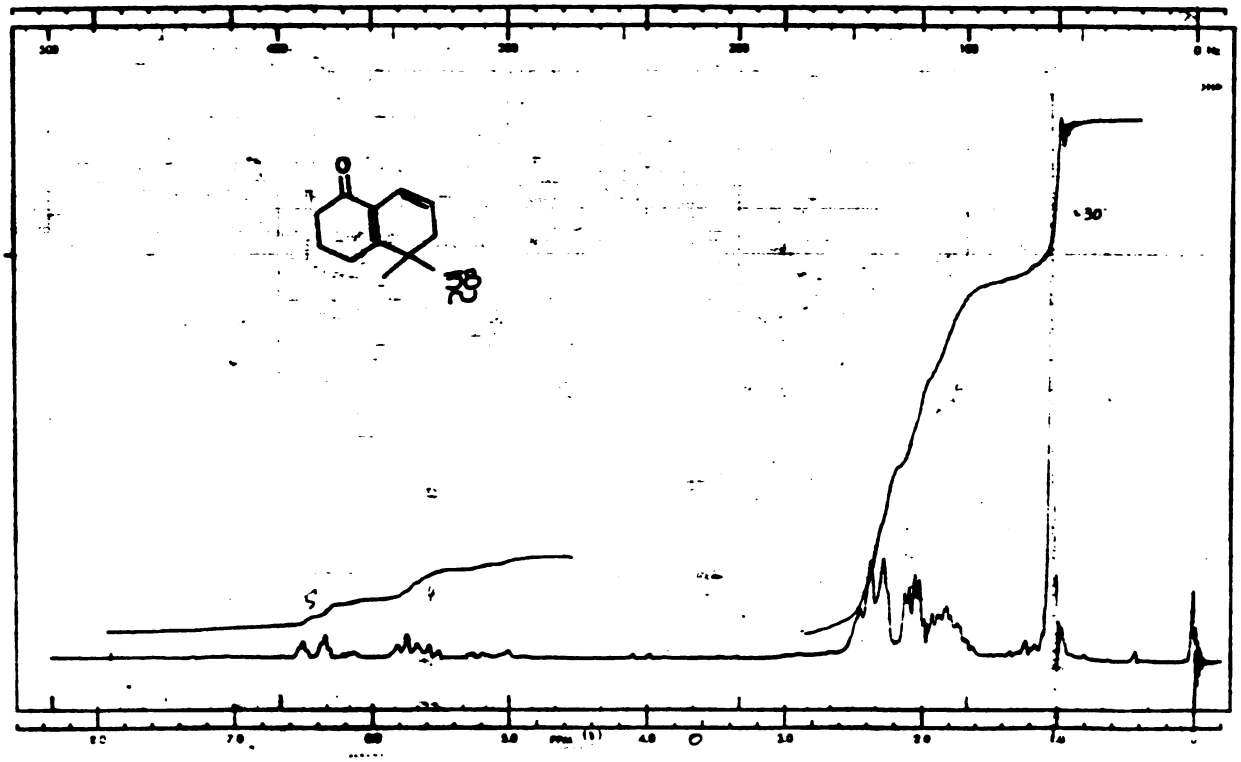

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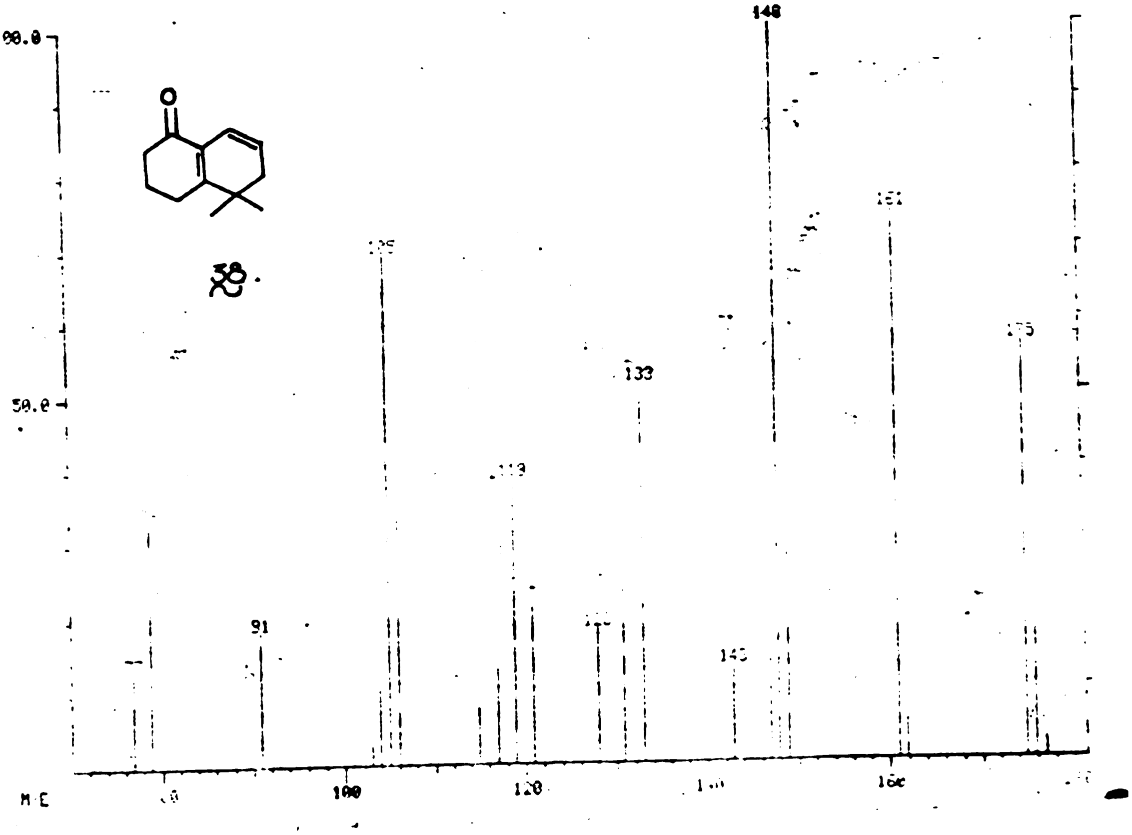

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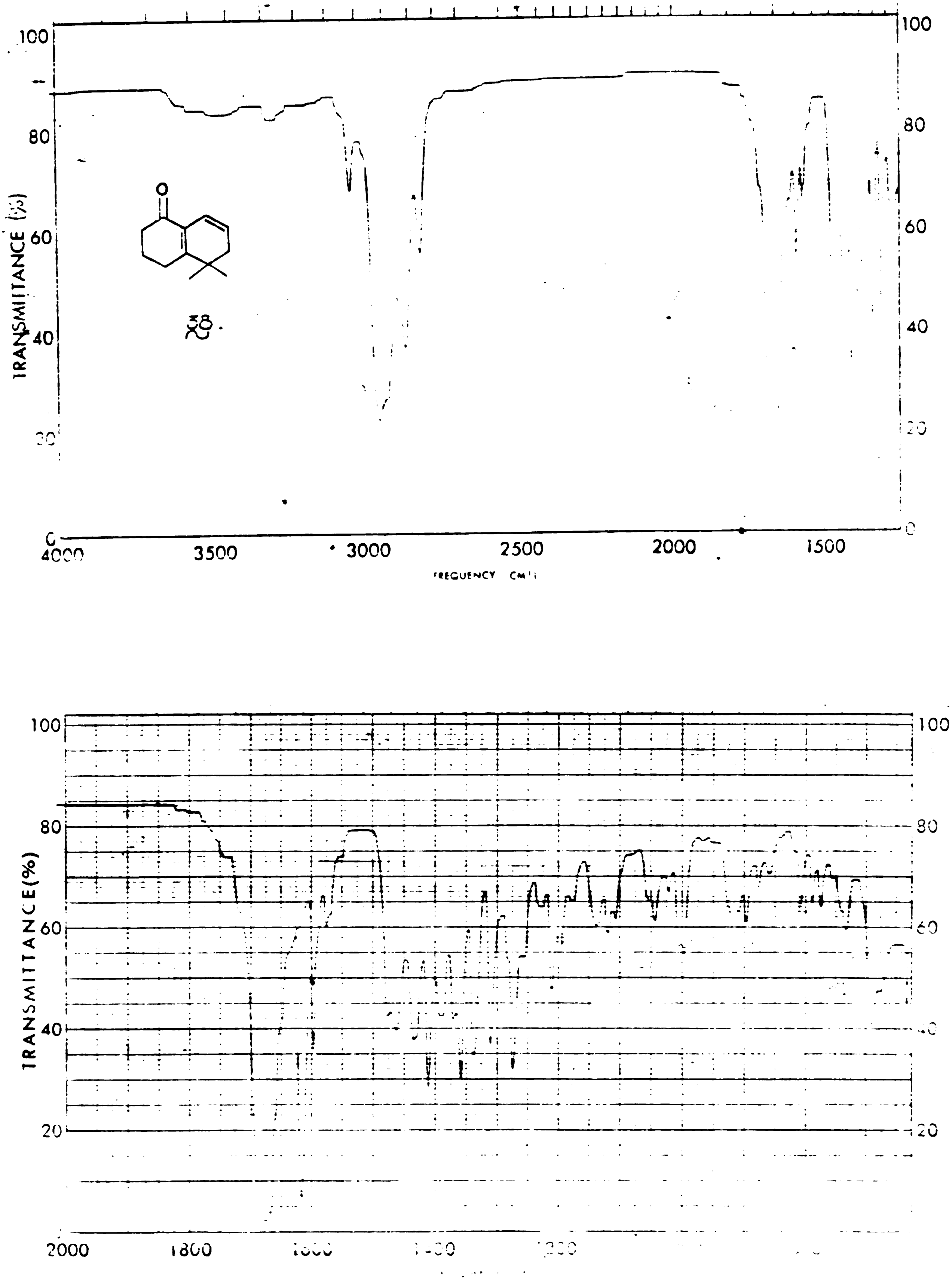

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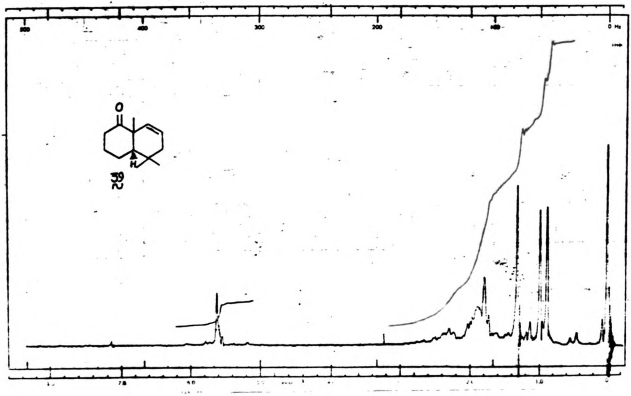

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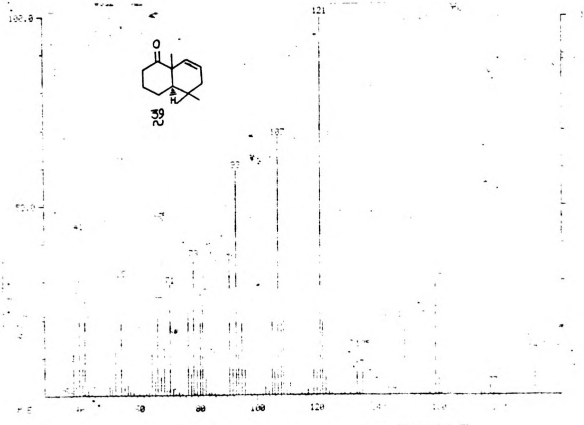

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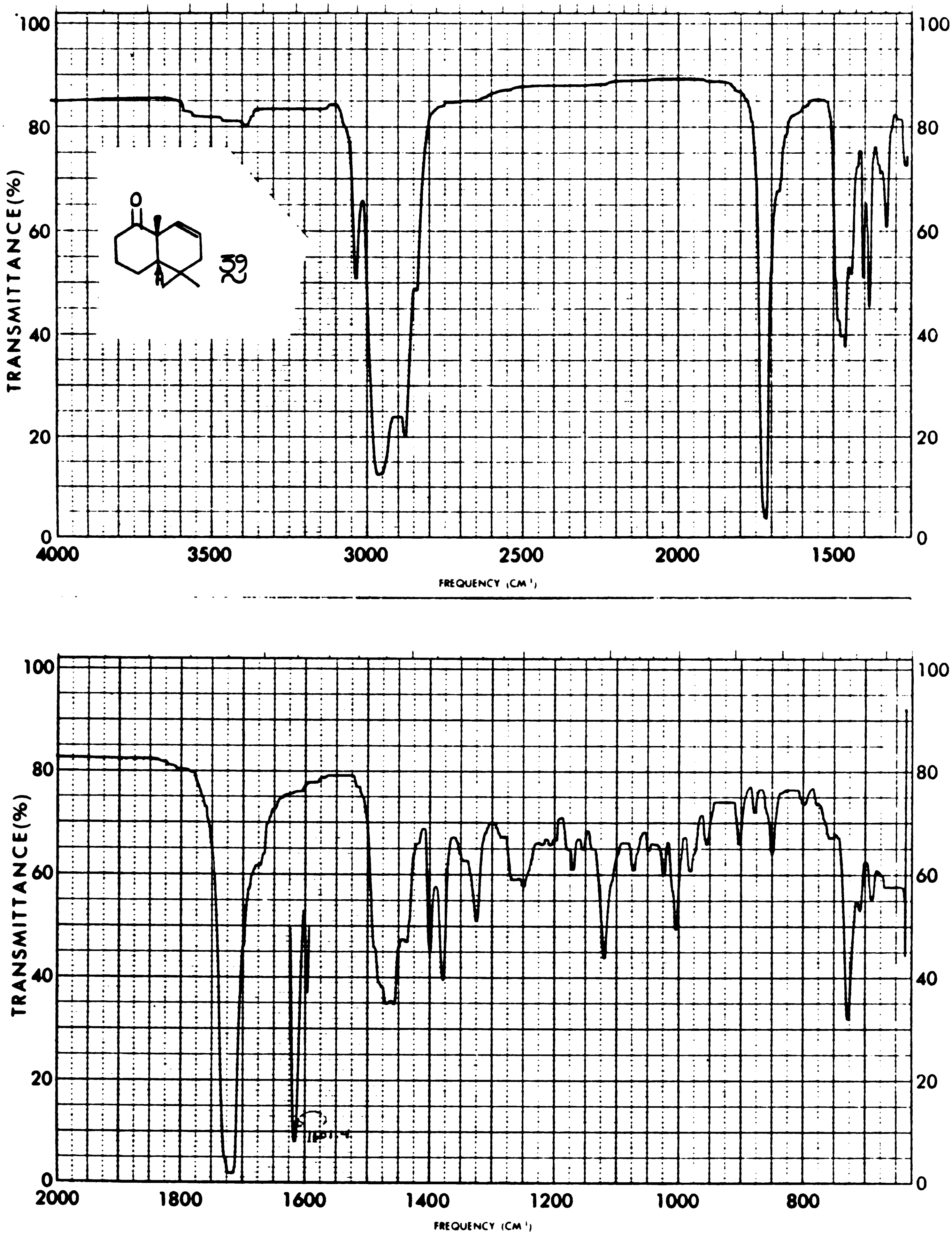

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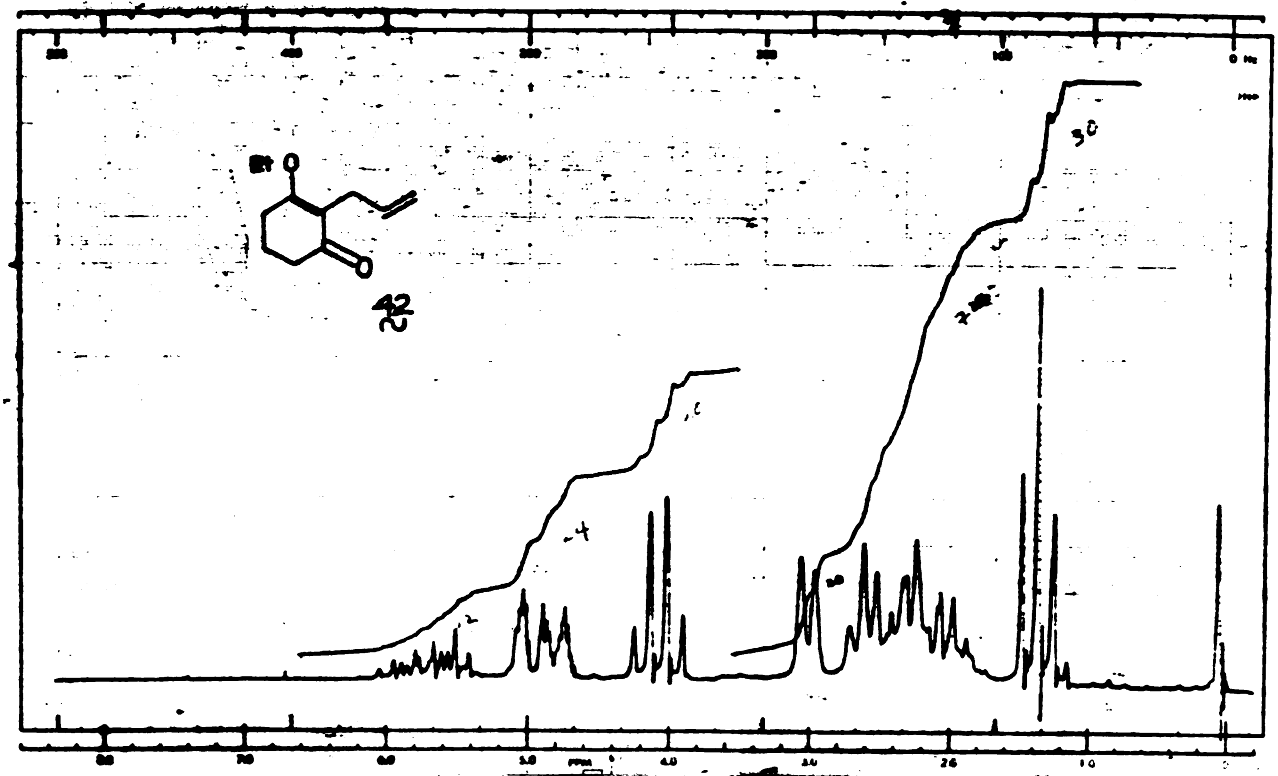

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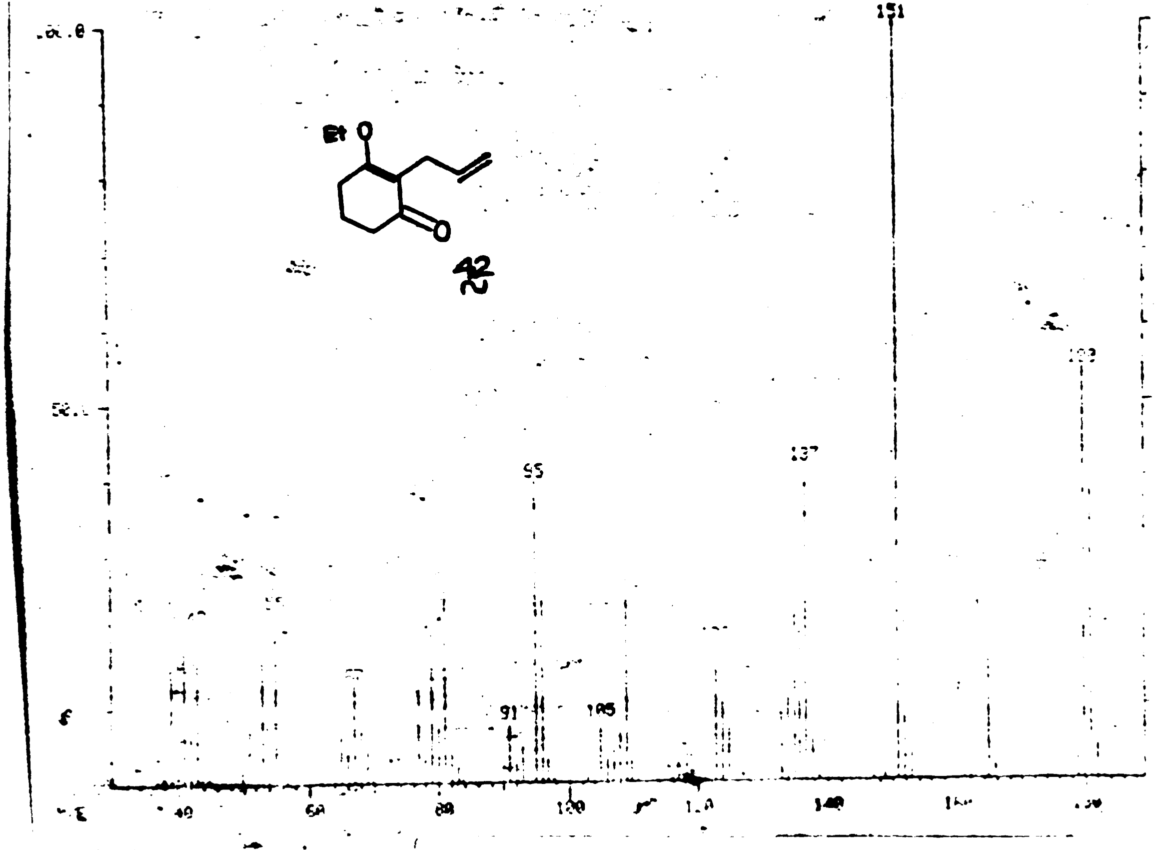

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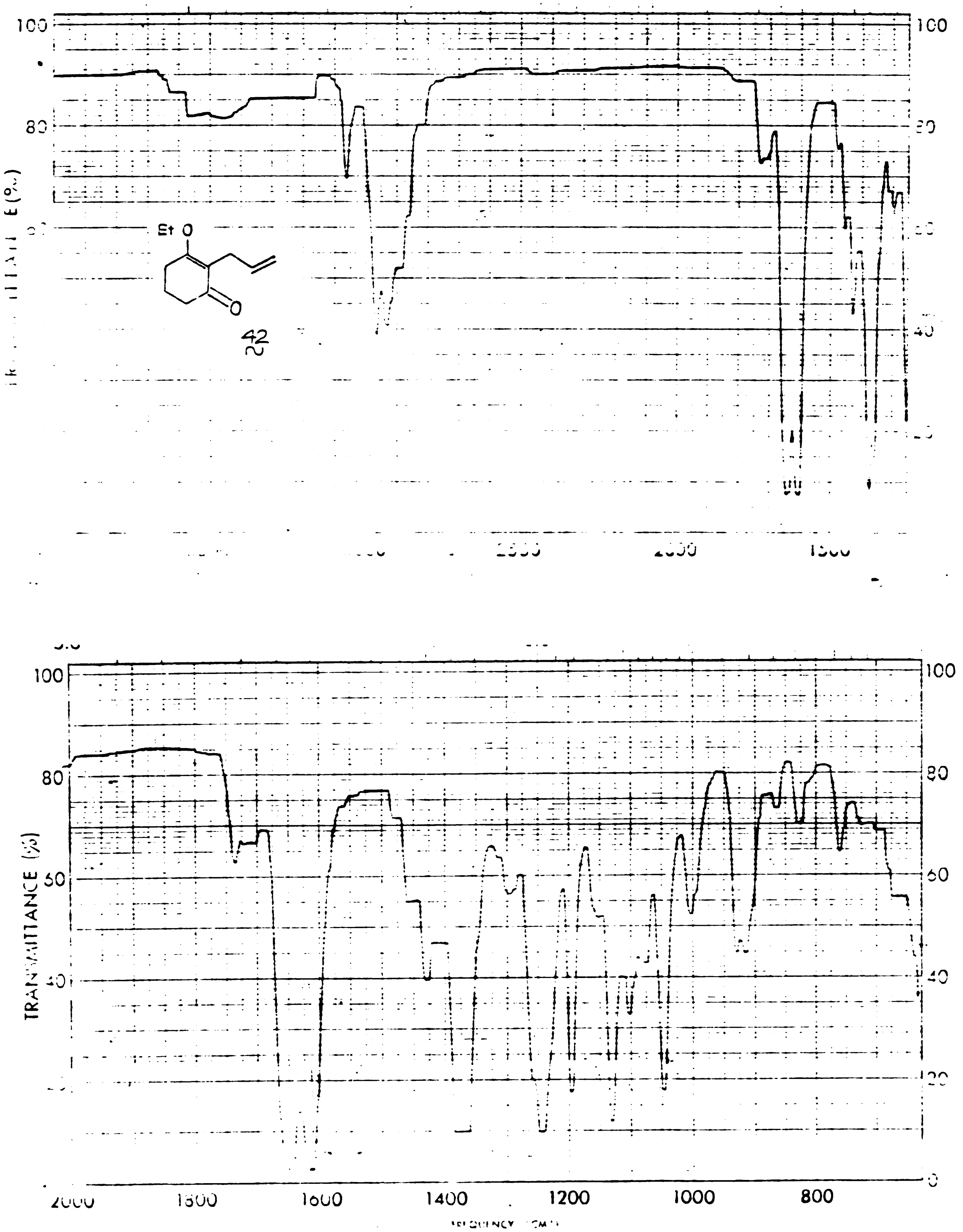

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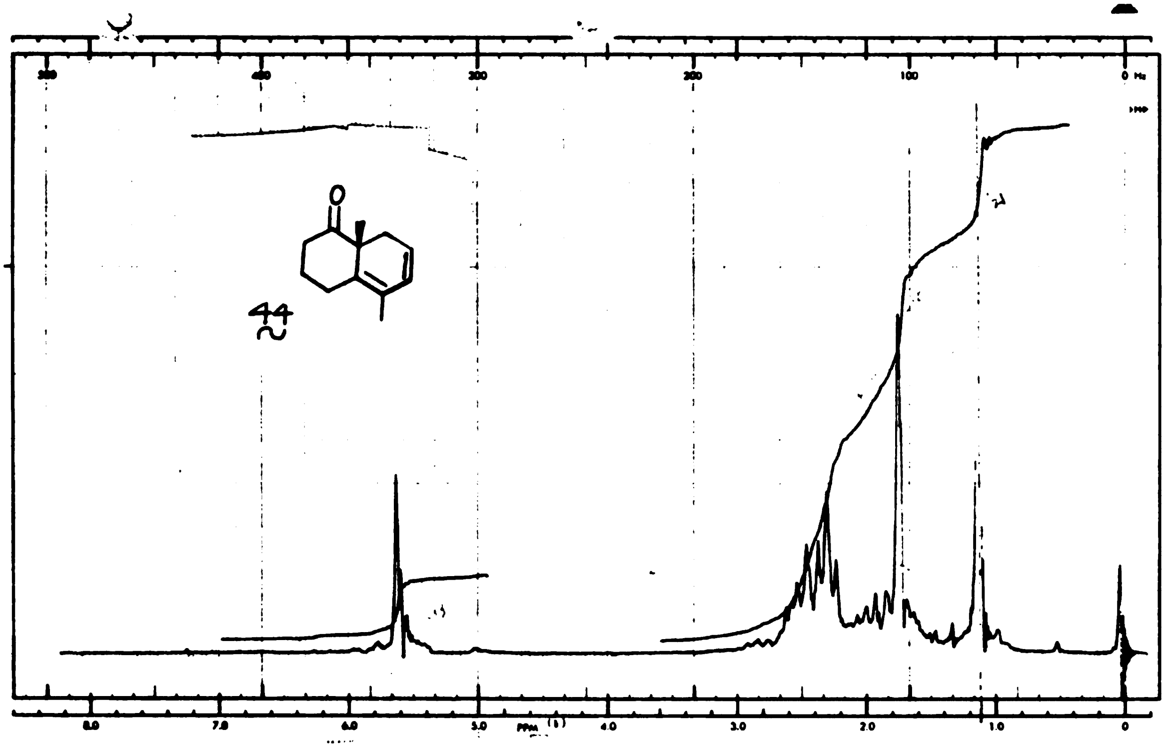

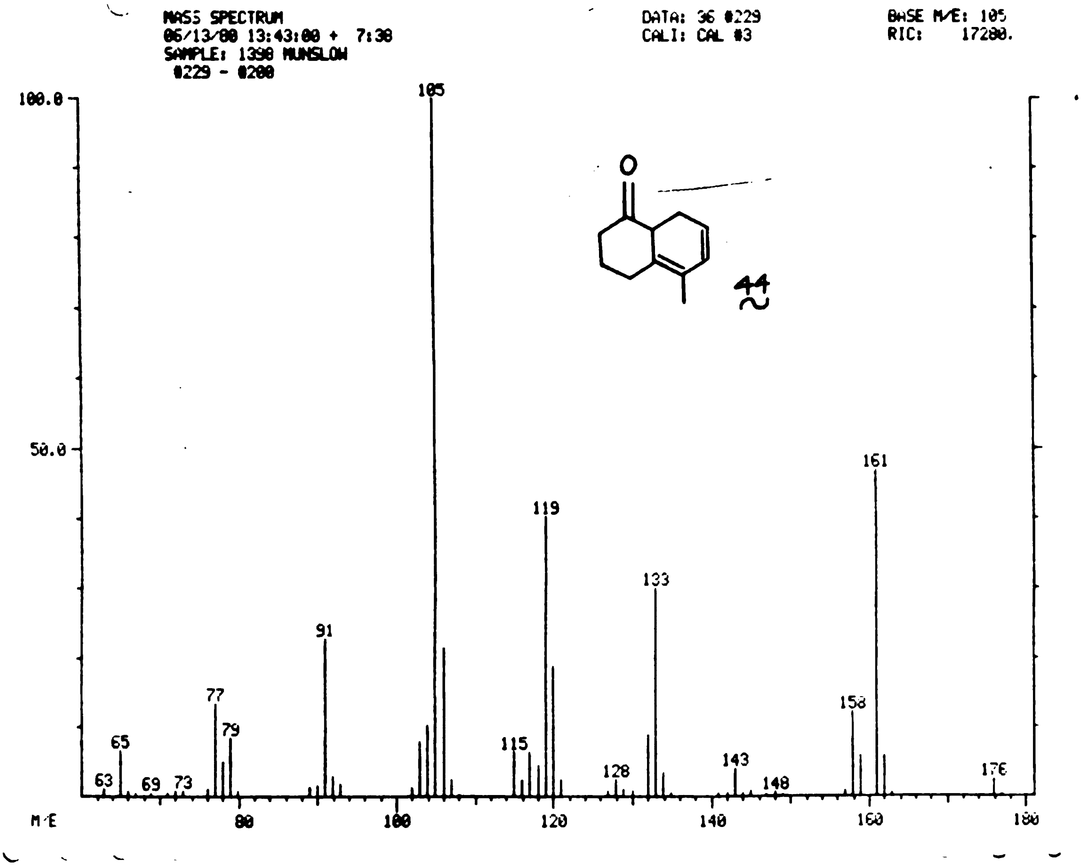

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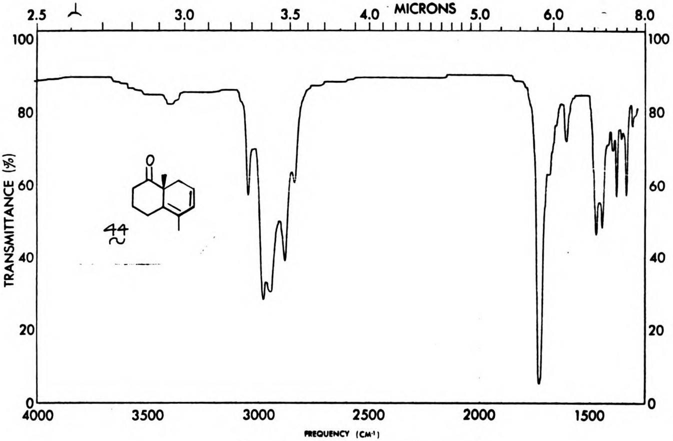

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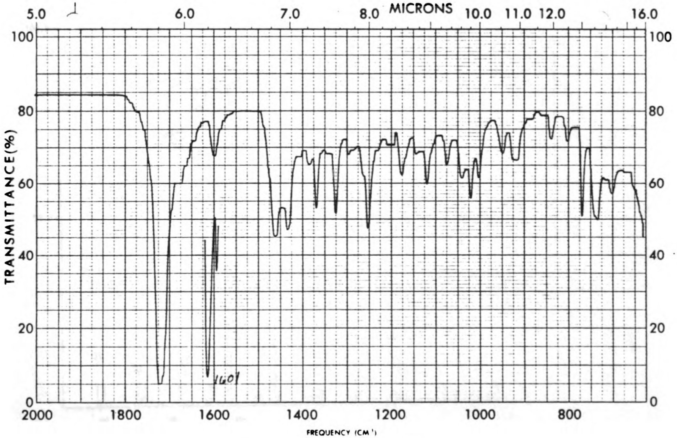

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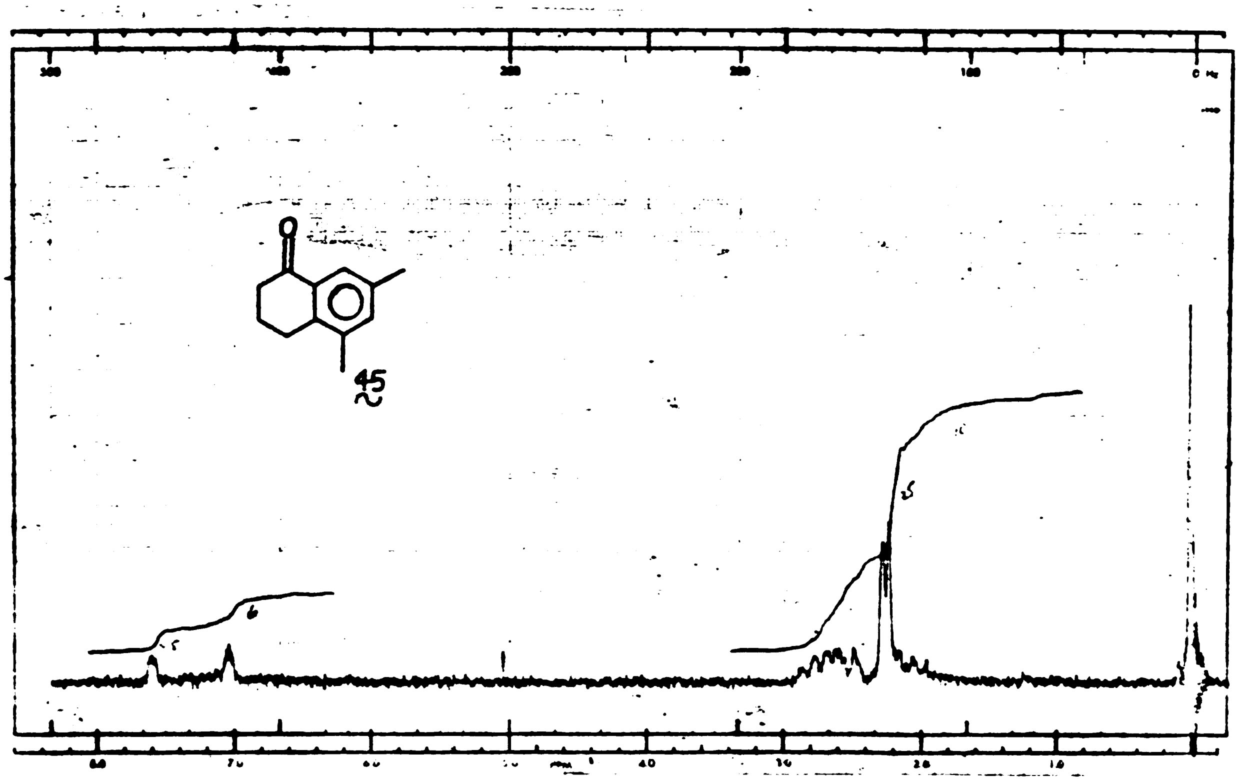

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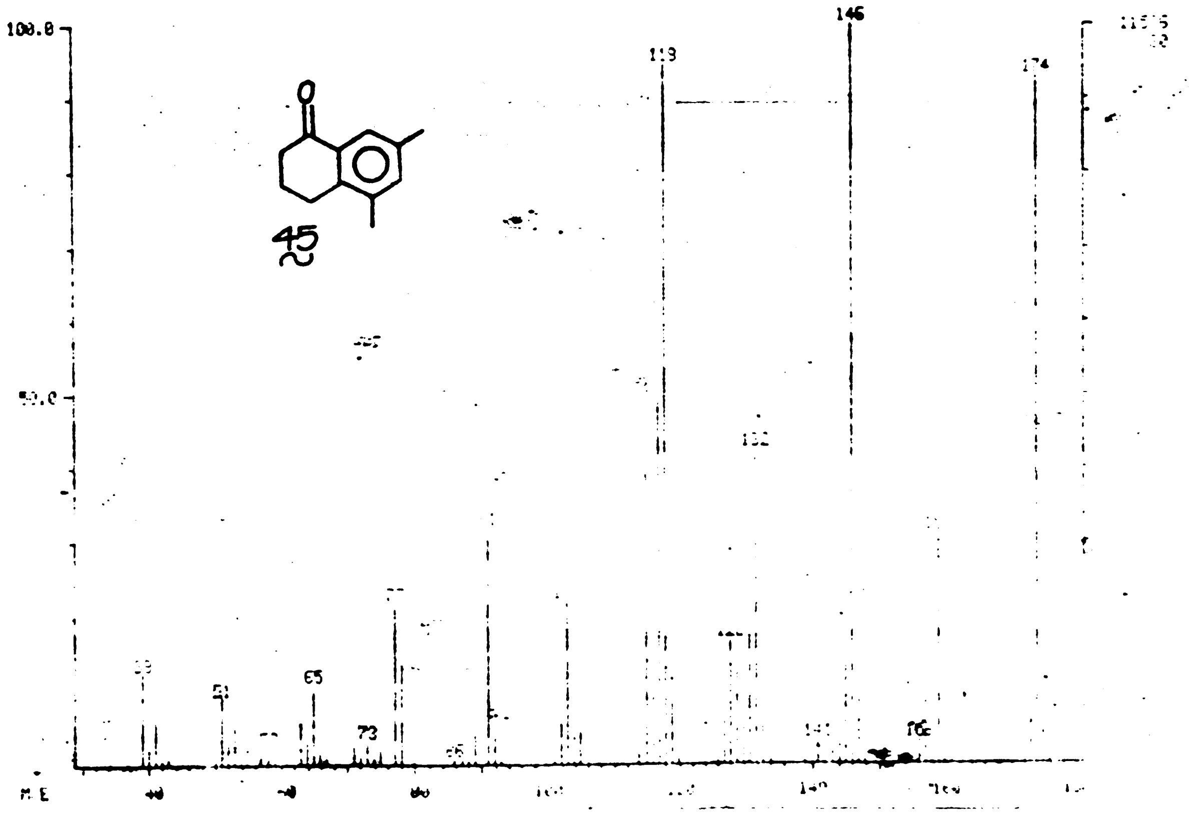

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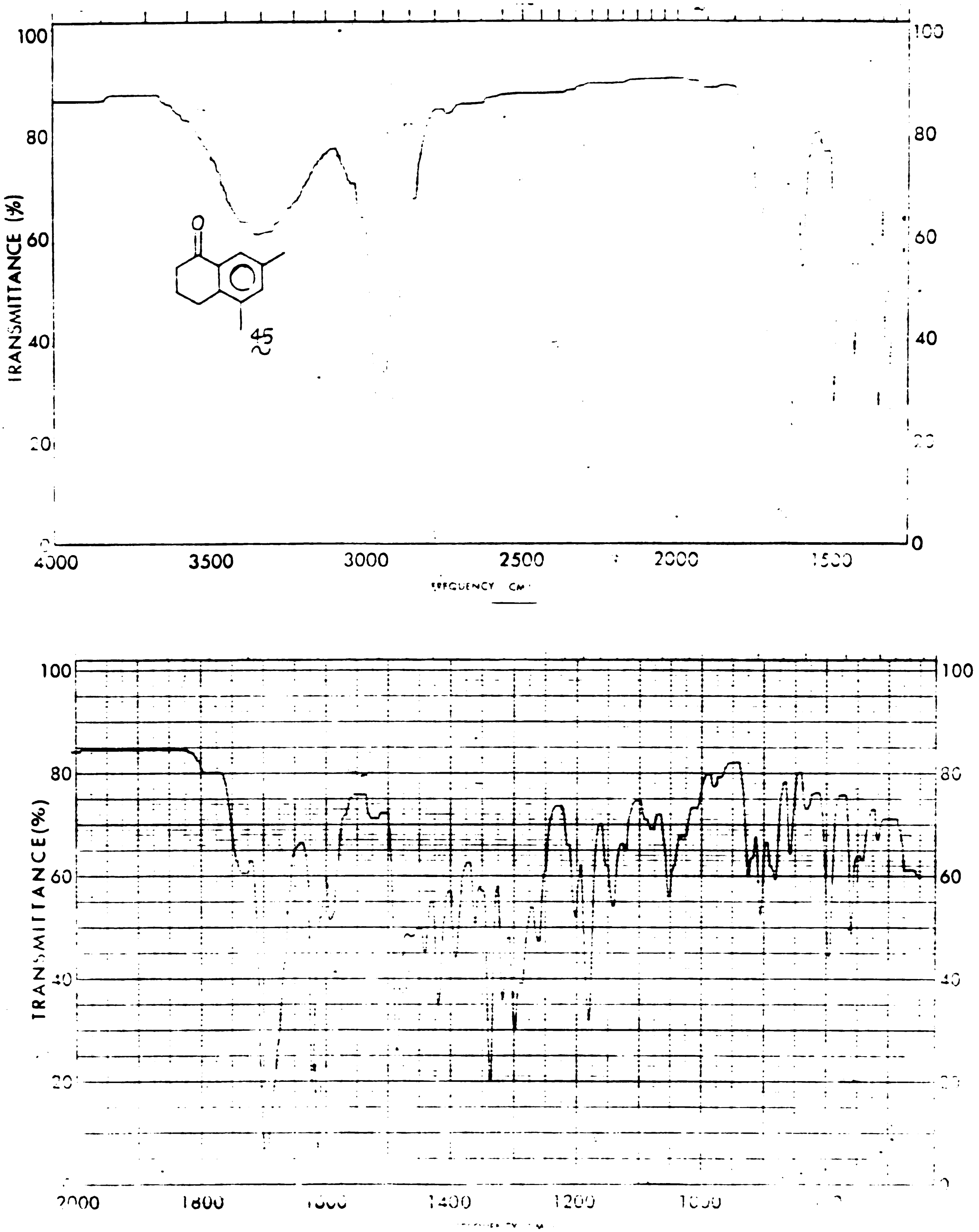

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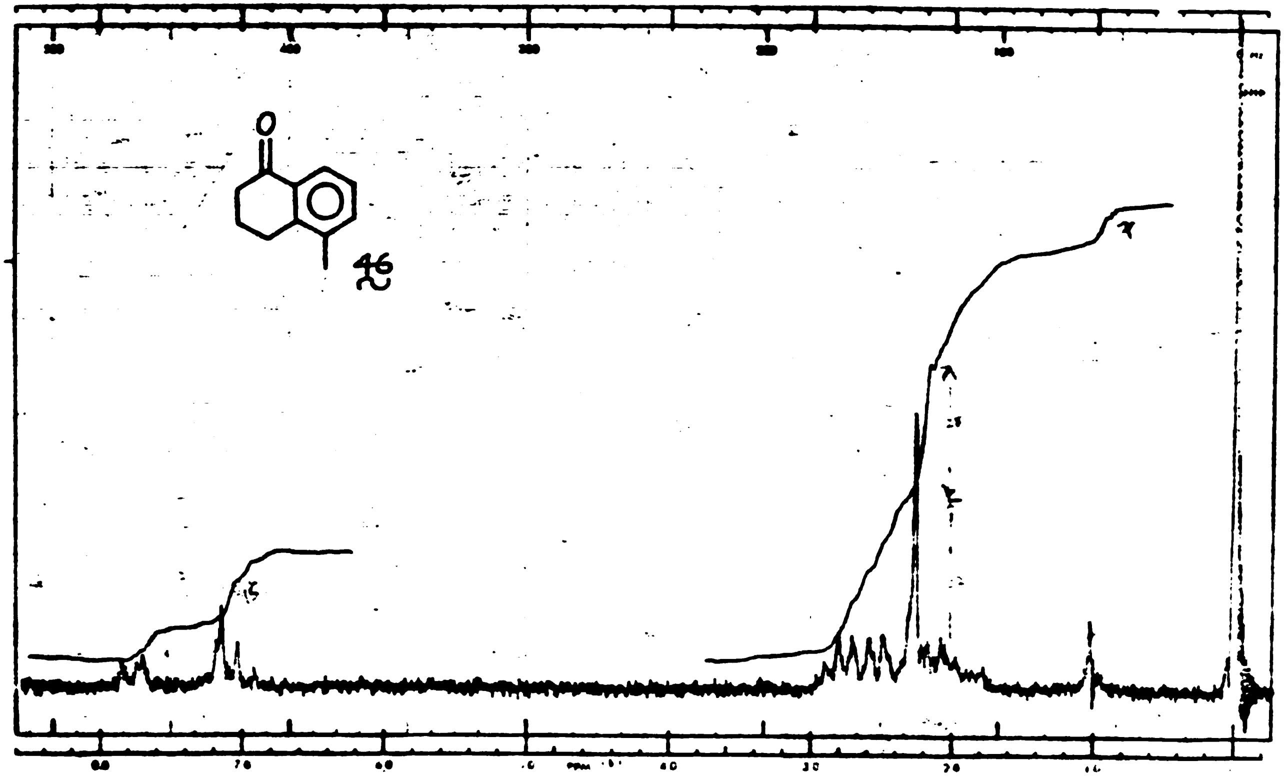

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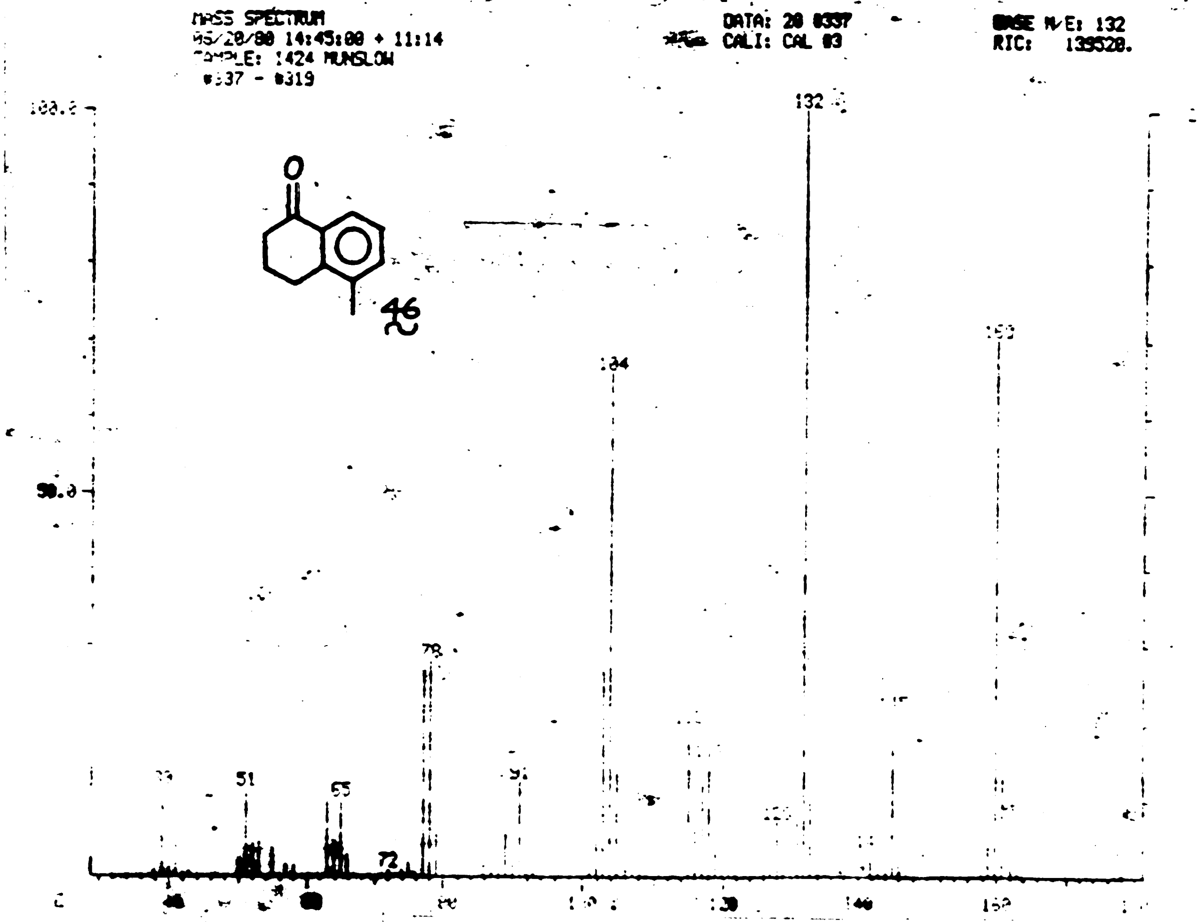

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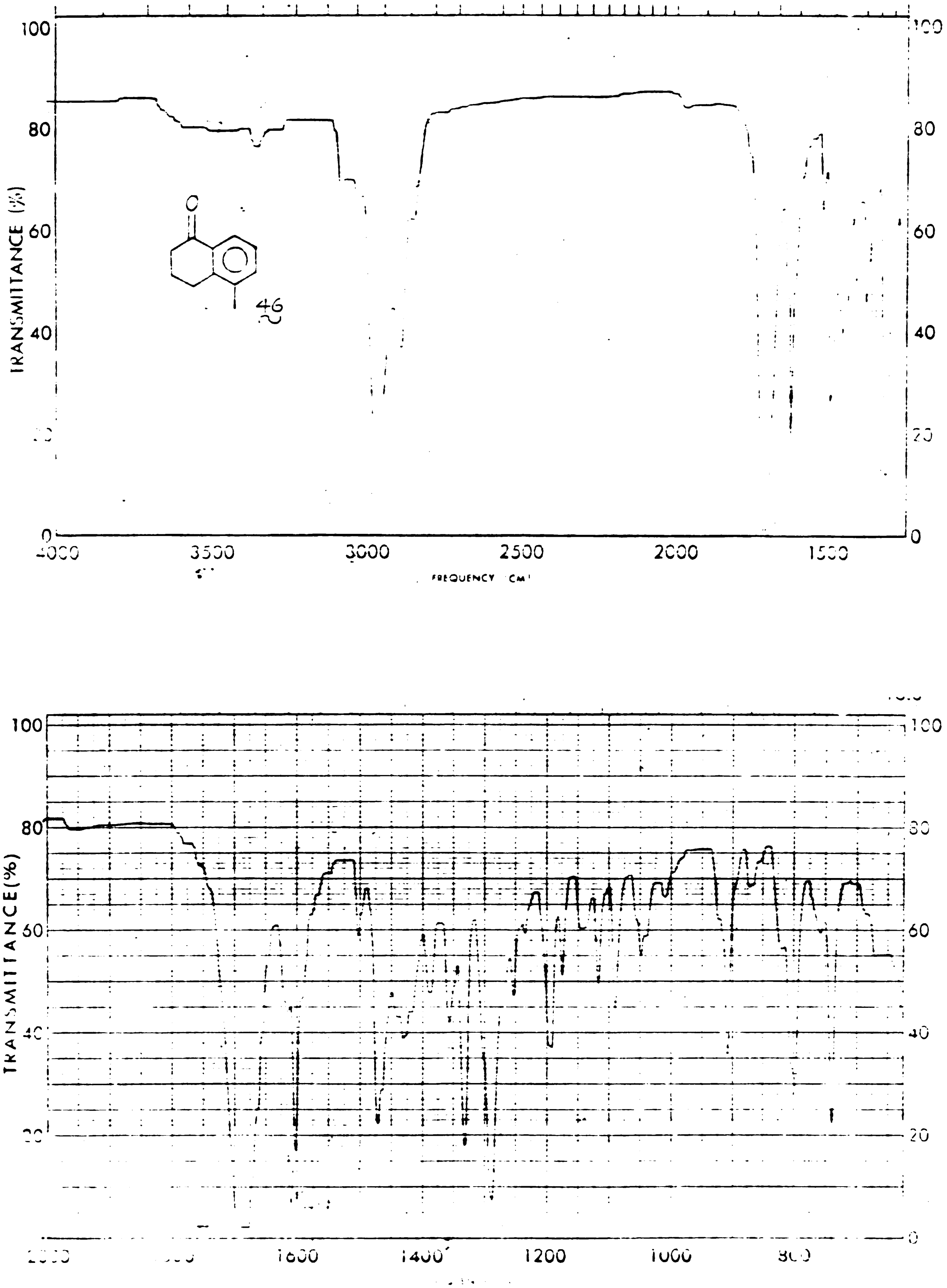

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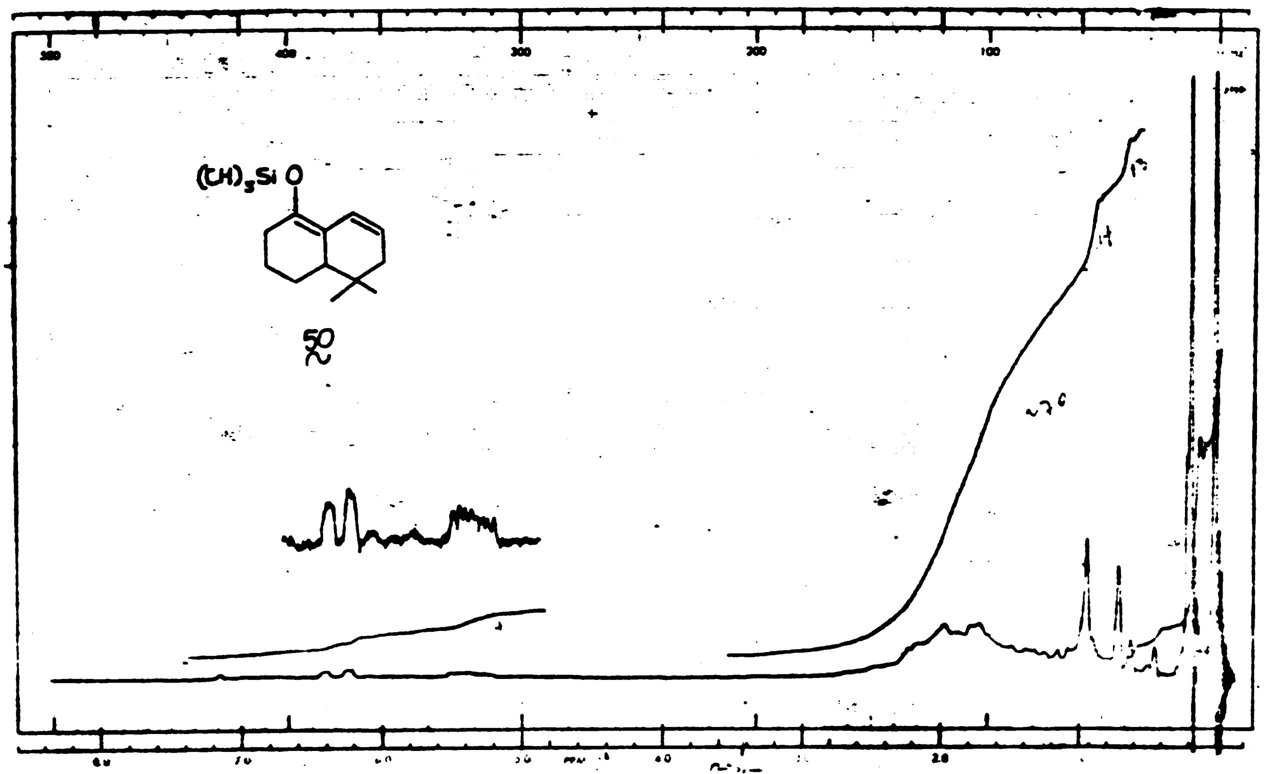

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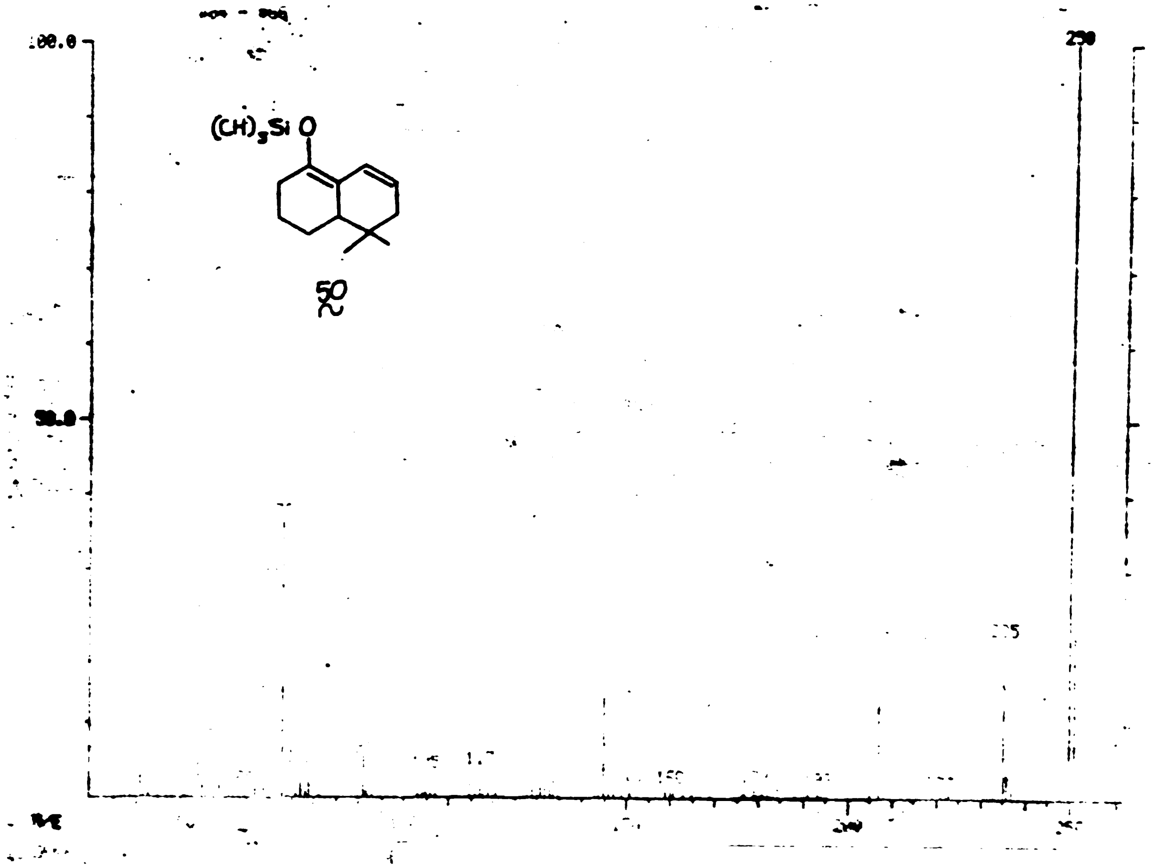

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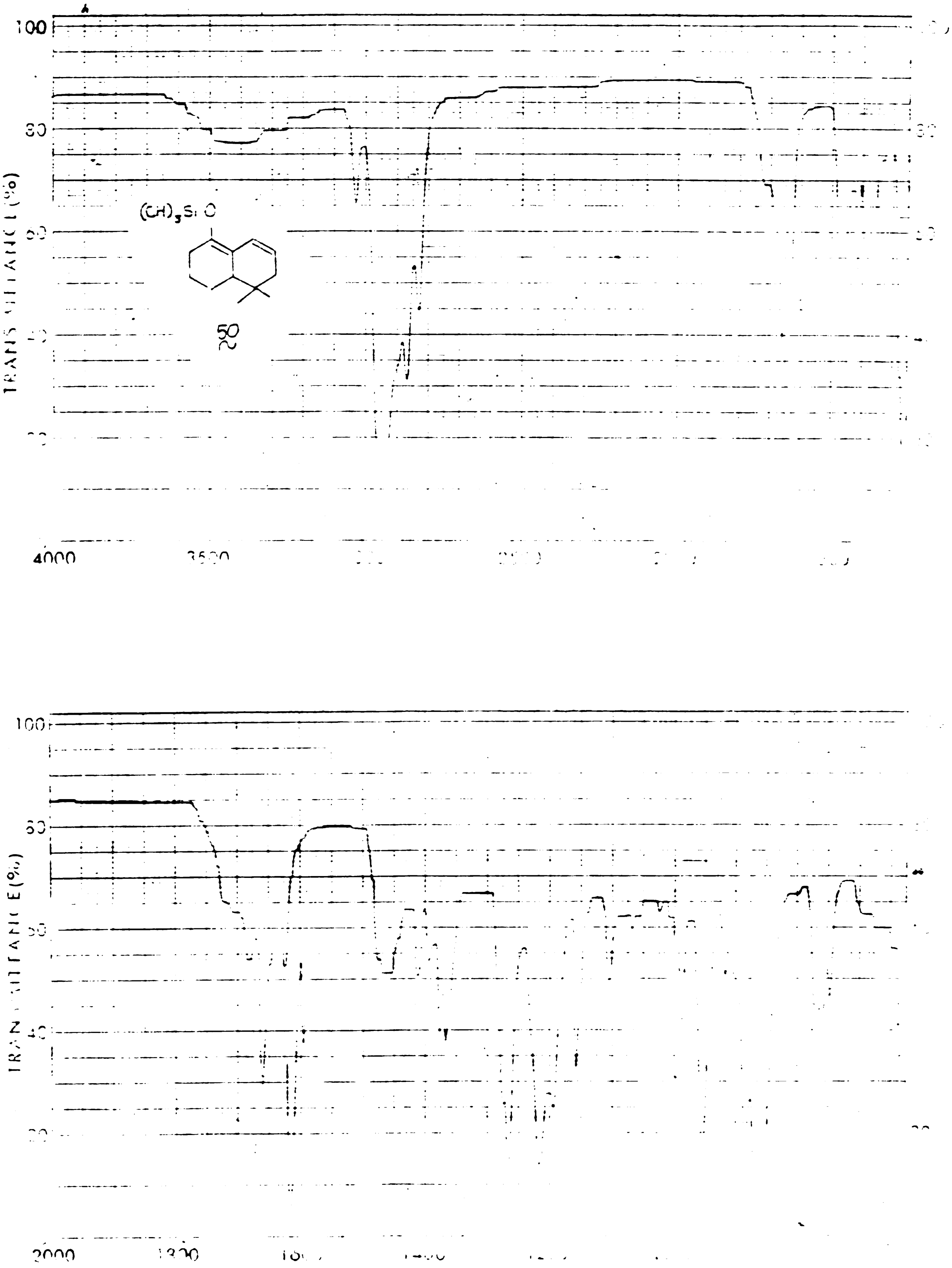
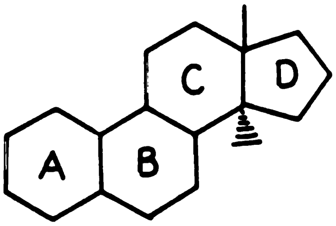


Infrared spectrum of 50

PART II

INTRODUCTION

The tetracyclic triterpenes are a group of thirty-carbon natural products having a common perhydrocyclopentanthrene skeleton 1.[1,2]



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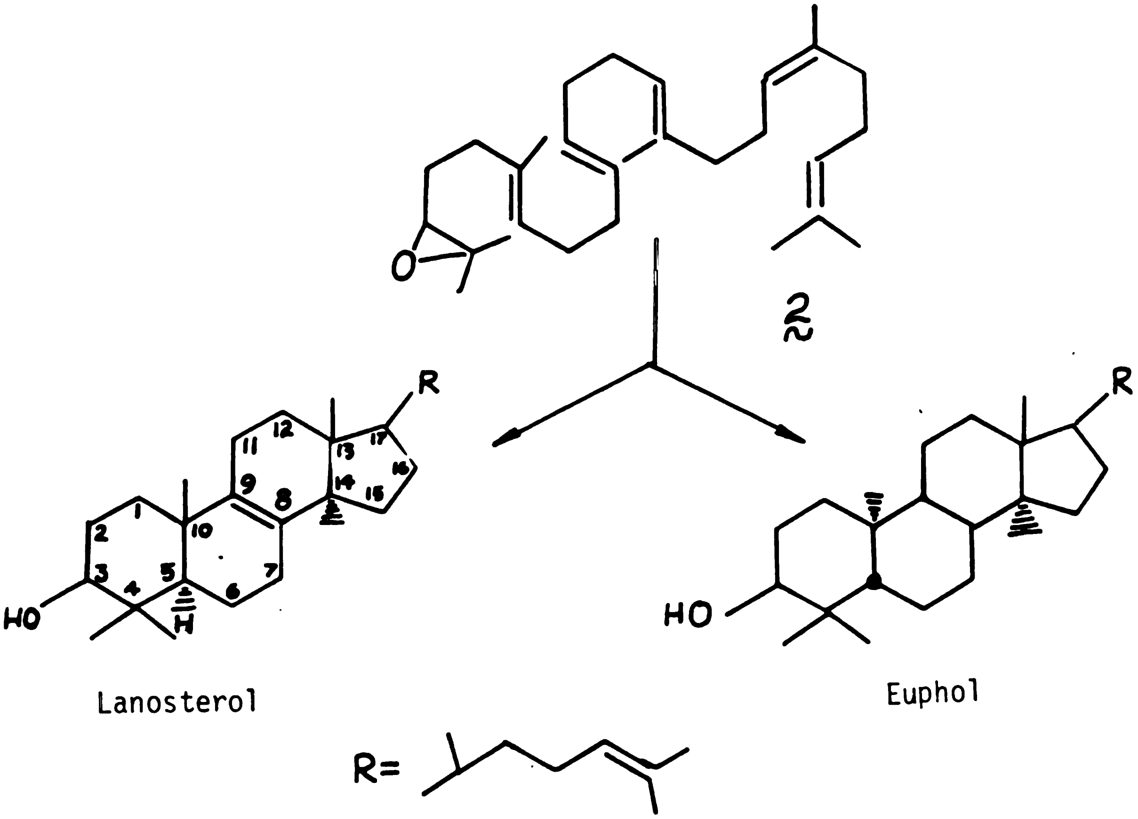
Because of their structural resemblance to steroids, the tetracyclic triterpenes are also called methyl steroids or 14-alpha analogs of steroids. A number of tetracyclic triterpenes such as the curcurbitacins have been shown to have anti-tumor activity and some of their derivatives are also found to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

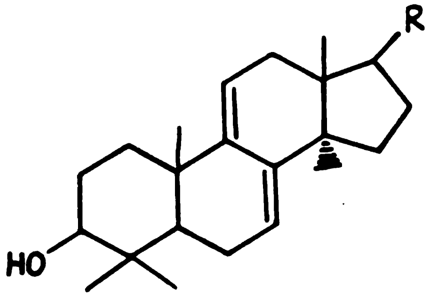
It is known that the tetracyclic triterpenes are formed in nature by an enzymatic cyclization of squalene 2,3-oxide 2.[4] In these biosynthesis, enzymes play an important role in folding the squalene oxide in two different modes: one leads to the lanosterol system via a chair-boat-chair-boat folding and one to the euphol system via the corresponding chair-chair-chair-boat conformation. Steroids are formed by enzymatic demethylation of lanostane intermediates.



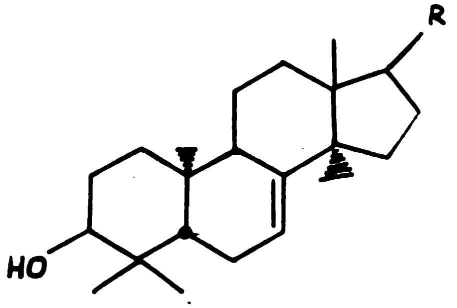
Lanosterol

Euphol

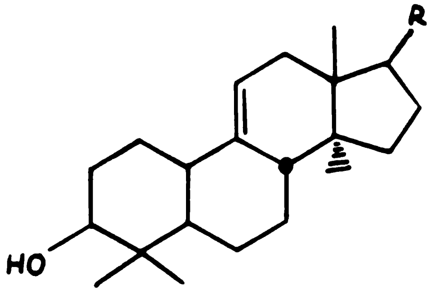
Other examples of lanostanes and euphanes which occur in nature are the following:



Agnosterol



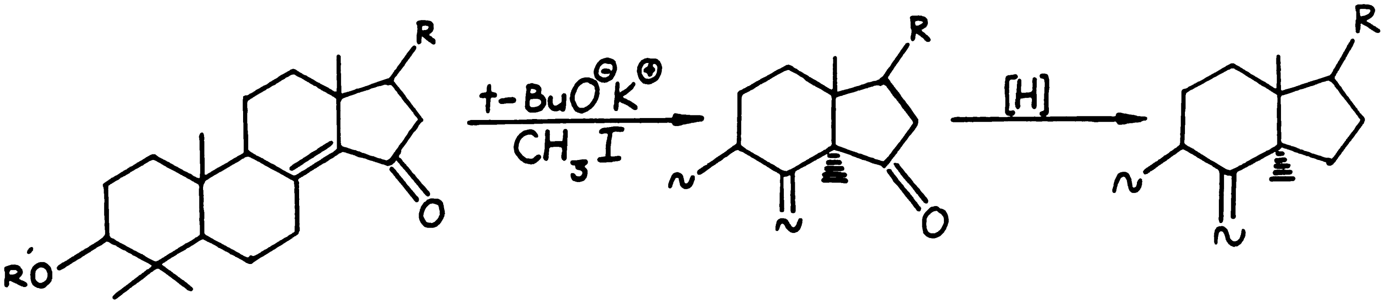
Butyrospermol



Parkeol

The tetracarbocyclic skeleton and stereochemical complexities of these triterpenes poses a considerable synthetic challange to the organic chemist. 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 material for a lanosterol synthesis. The other entirely different approach, pioneered by van Tamelen, uses a biogenetically patterned polyene cyclization.

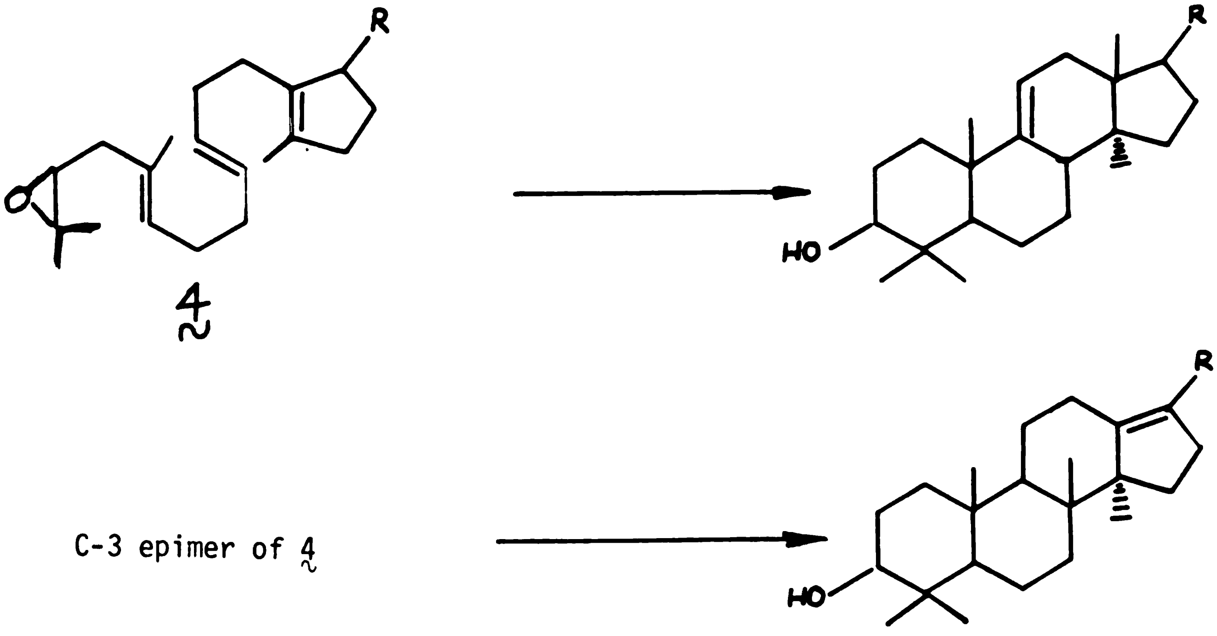
In Woodward's approach,[5] a key step involved the introduction of a 14-alpha methyl group onto a 15-keto cholestane derivative **3** as shown in Equation 1. The entire sequence of reactions for the lanosterol synthesis required over 25 steps.



3

EQ. 1

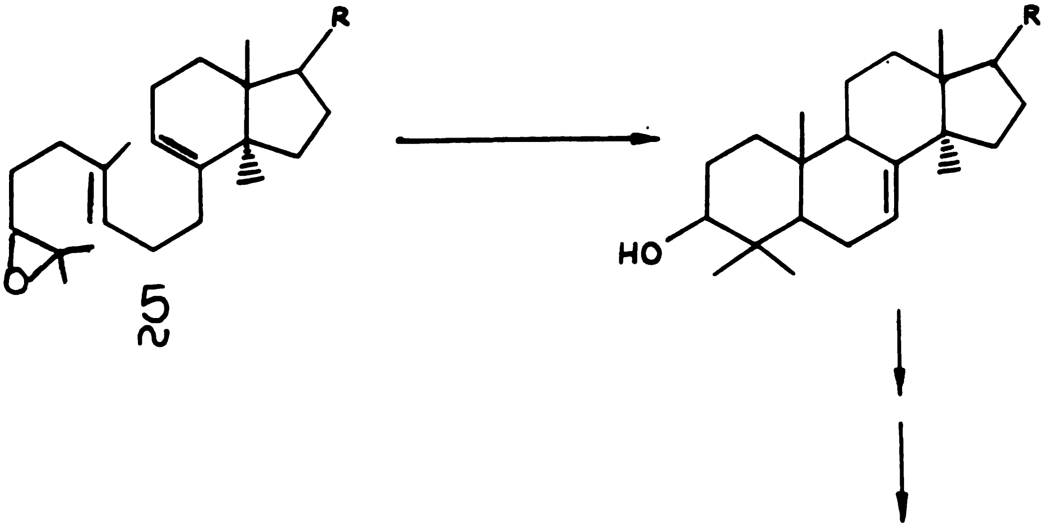
The van Tamelen strategy involved acid catalyzed cyclization of a suitable polyene monoepoxide. For example, acid treatment of a mono-carbocyclic derivative of squalene oxide **4**, and its 3-epimer led to the total synthesis of Parkeol and Isotirucallol, respectively.[6]



4

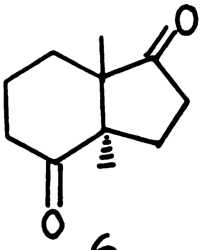
C-3 epimer of **4**

Similarly, when bicyclic epoxide 5 is used, cyclization to a dihydrolanosterol precursor took place.[7]



5

Recently, work in our laboratory has been directed toward the total synthesis of several classes of triterpenes. Impetus for this goal came from the discovery of an efficient way to make the bicyclic diketone, trans-1,6-dimethyl-bicyclo(4.3.0)nonan-2,7 dione (6).[8]



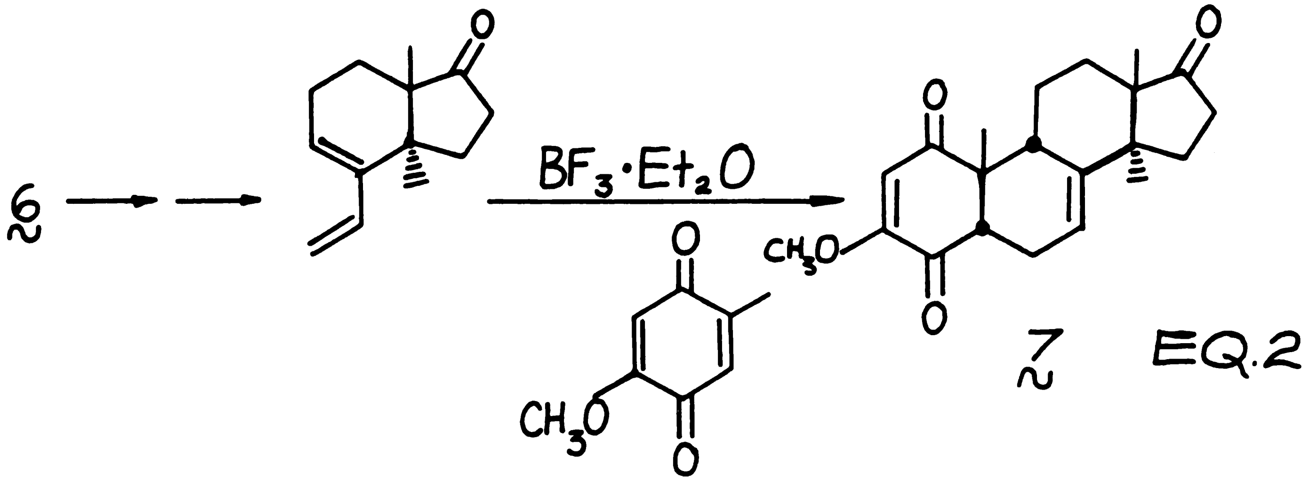
6

This diketone incorporates a common skeletal feature found in all the previously described triterpenes. Thus compound

6 could be used as a CD synthon in the synthesis of these natural products. In order to achieve such a total synthesis two major transformations must be accomplished. The alkyl side chain must be attached to the five membered ring and rings A and B of the tetracyclic triterpene must be attached to the six membered ring of **6** in a stereoselective manner.

There are three important advantages to using compound **6** as a starting material in tetracyclic triterpene synthesis. First, because of the presence of the 14-alpha methyl group, some of the tedious methylation steps in Woodward's synthesis[5] will be eliminated. Secondly, stereochemical control during the introduction of the methyl group at C-10 would allow synthesis of both important families of triterpenes. If the alpha configuration is generated at C-10, the euphane class results; if the beta configuration is obtained, then the lanostane ring structure results. A third advantage of compound **6** is that it can be prepared enantiomerically pure in either configuration. Synthesis of **6** begins with Wieland-Miescher ketone, a versatile bicyclic intermediate, which can be prepared optically active in either enantiomeric form by using (+) or (-) proline as a condensation catalyst.[9]

Jacob Tou of this laboratory was able to attach rings A and B onto **6** by way of an acid-catalyzed Diels-Alder reaction as shown in Equation 2.[10]

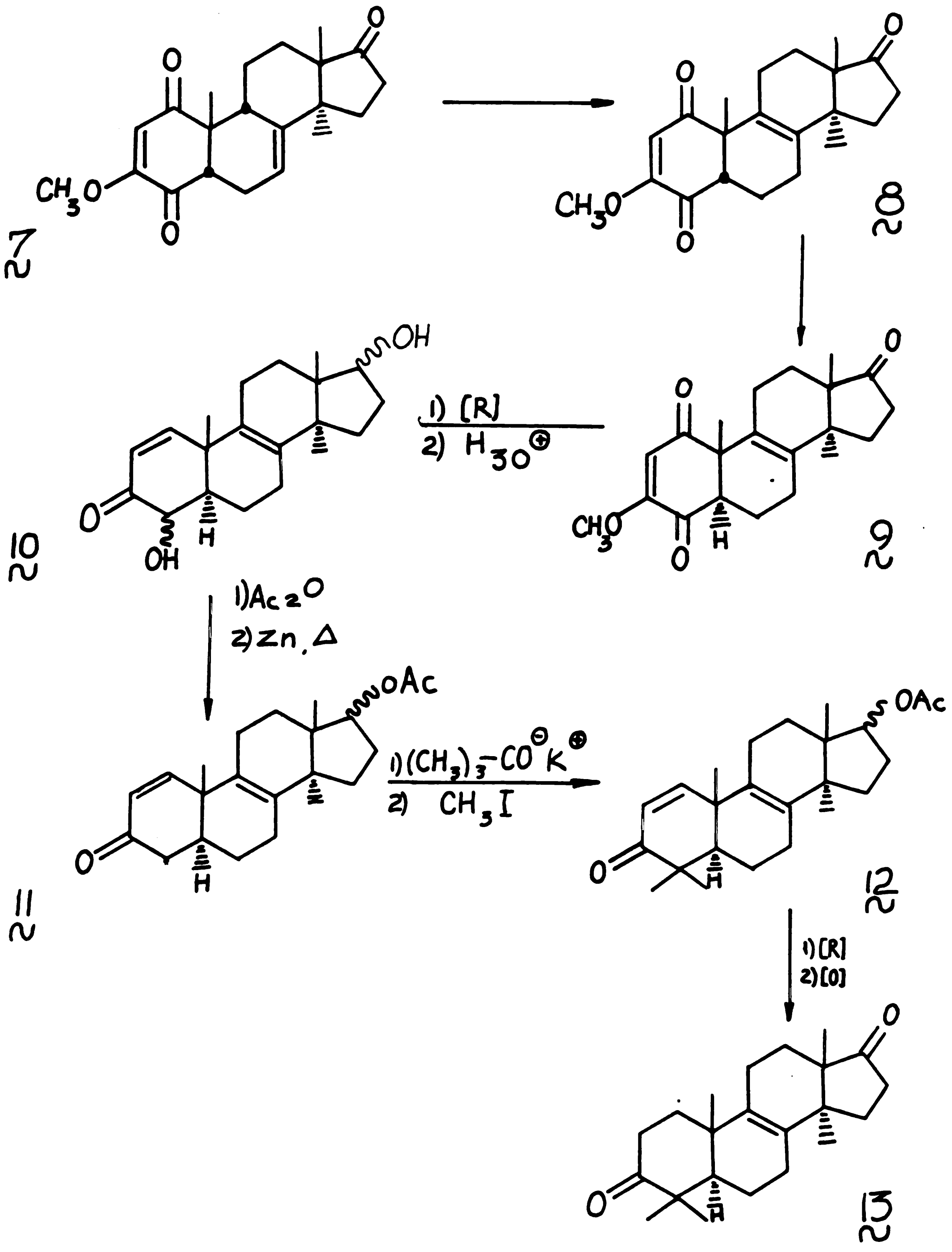


EQ.2

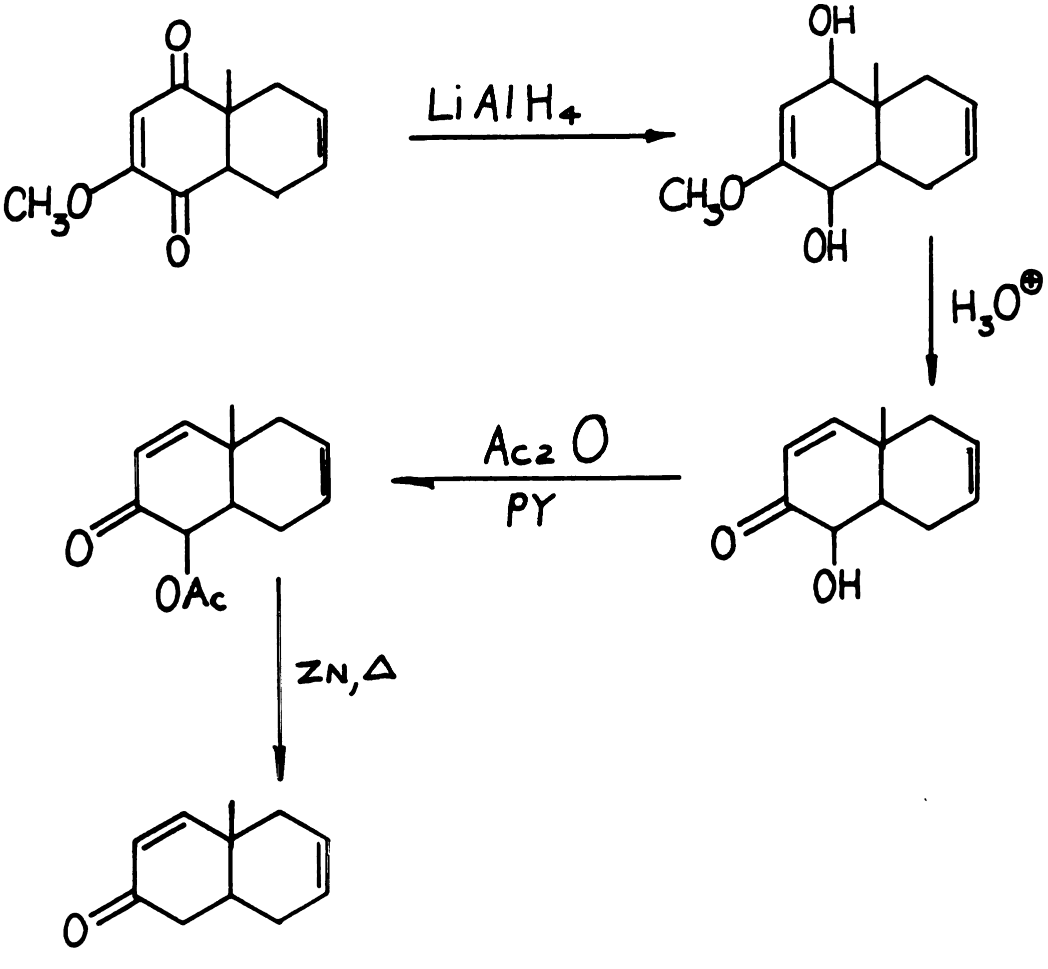
Although structure 7 is tetracyclic, with all the ring-carbons and angular methyl groups in place, a number of transformations remain to convert 7 into a lanostane natural product. For example, the stereochemistry at C-5 and C-9 needs to be changed, the $\Delta^{7,8}$ double bond should be moved, the functionality of ring A needs to be altered drastically and a gem-dimethyl group must be introduced at C-4. Part II of this thesis describes efforts directed toward these goals.

RESULTS AND DISCUSSION

Our initial strategy for the conversion of 7 into the lanostane skeleton is outlined in Scheme I. The first step is the isomerization of the $\Delta^{7,8}$ double bond to the $\Delta^{8,9}$ position, where it would be tetra-substituted and presumably thermodynamically favored. If this reaction were successful the double bond would be in the correct position for lanosterol and obviously would remove the unnatural configuration at C-9. Next our plan called for epimerization at C-5 to yield compound 9 which has the desired trans AB ring junction. With these isomerizations accomplished the functionality of ring A must be manipulated to convert it to the substitution pattern observed in the triterpenes. In order to achieve this functional group manipulation, we anticipated following a scheme developed by Woodward and applied by him to a decalin system (Scheme II) which contained an enedione substitution pattern similar to that of intermediate 9.[11] In this manner compound 9 would be converted to 11, which on treatment with t-butoxide and methyl iodede should give the gem-dimethylated derivative 12. Lithium/ammonia reduction, followed by an oxidation would then yield a dione suitable for subsequent conversion to lanosterol.

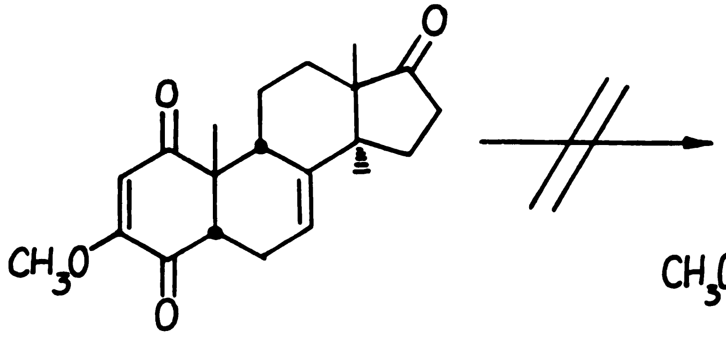

CH3O
7
8
1) [R]
2) H3O⊕
9
10
1)Ac2O
2)Zn, Δ
11
1)(CH3)3-CO⊖ K⊕
2) CH3I
12
1)[R]
2)[O]
13
OH
OAc
H

Scheme I



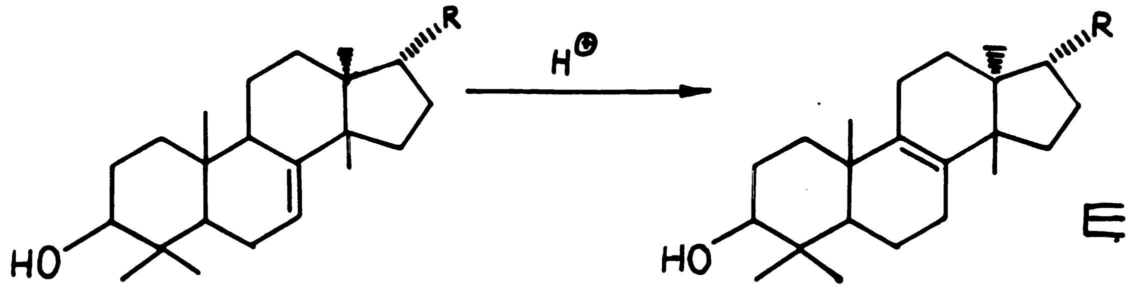
Scheme II

Our efforts to convert Diels-Alder adduct 7 into the lanostane ring system began with attempts to epimerize C-5 and/or move the $\Delta^{7,8}$ double bond to the tetrasubstituted $\Delta^{8,9}$ position. This double bond migration has been observed in both the lanostane and euphane series (Equation 3) under the influence of dry HCl gas.[12] We had expected epimerization of 7 to proceed easily, because trans-fused six-membered rings are usually more stable than the corresponding <u>cis</u> fused system. Since C-5 is alpha to a carbonyl group in 7, treatment with acid or base should allow equilibration to the thermodynamically favored epimer.



7

9



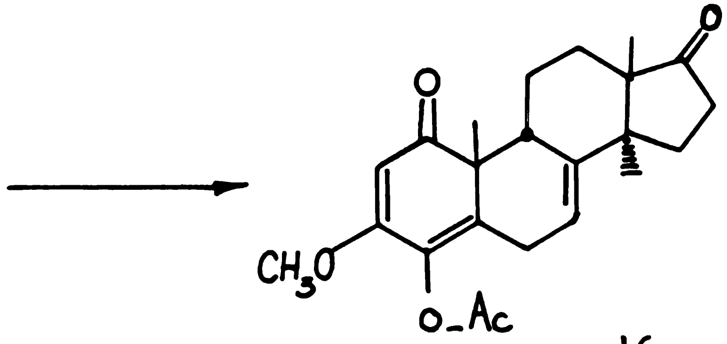
EQ.3

14

15

Surprisingly, adduct 7 was found to be resistant to either C-5 epimerization or double bond migration under both acidic and basic conditions. Jacob Tou[13] reported that 7 was recovered unchanged from treatment with p-TSA/benzene, Dowex 50-8/methanol, sodium bicarbonate/methanol or sodium hydroxide/methanol. He showed however that the enolate at C-5 was formed by isolating enol acetate 16 in good yield.

7



16

Additional efforts to isomerize 7 have also proven unsuccessful. For example, the work of Irving _et_ _al_. showed that dry HCl has effected the isomerization of 14 to 15 in chloroform solution.[12] However, under these conditions 7 was recovered unchanged, except for some tarry material which did not move on a tlc plate. Possibly the HCl reacted preferentially with the enedione portion of ring A, causing slow decomposition rather than double bond isomerization. We therefore attempted to protect the enedione functionality through complexation with titanium tetrachloride prior to treatment with HCl gas. In this experiment no decomposition was observed, hence it appears that complexation does protect the ring A functions; however, no isomerization was observed and starting material was recovered unchanged. Since rhodium trichloride is known to catalyze double bond isomerization[14] the possibility of isomerizing **7** to **8** with this reagent was also studied. Unfortunately, no reaction of any kind could be effected.

The resistance of **7** to epimerization under a variety of conditions, including some that are known to effect enolization, can only be interpreted to mean that this A/B *cis* compound is more stable than its *trans* isomer. This contrasts strikingly with the facile epimerization of **18** to **19** accomplished by Jacob Tou[13] (Figure 1).

An examination of Drieding molecular models of **7**, **8** and **18** and their *trans* isomers **17**, **9** and **19**, is helpful in explaining the difficulty encountered here (Figure 1). In all cases having a 9-beta hydrogen configuration, the C ring is forced to assume a twist boat conformation. The *cis*-*syn* configuration of **7** allows a chair-like B ring; however, the *trans*-*syn* configuration of **17** would require a half-boat conformation of B, with H-9 and C-19 eclipsed. Therefore, **17** should be less stable than **7**, and the failure of **7** to epimerize is understandable. Both compound **18** and its C-10 epimer **19** have chair-like conformations of the B ring; however, the A ring is fused in a diequatorial

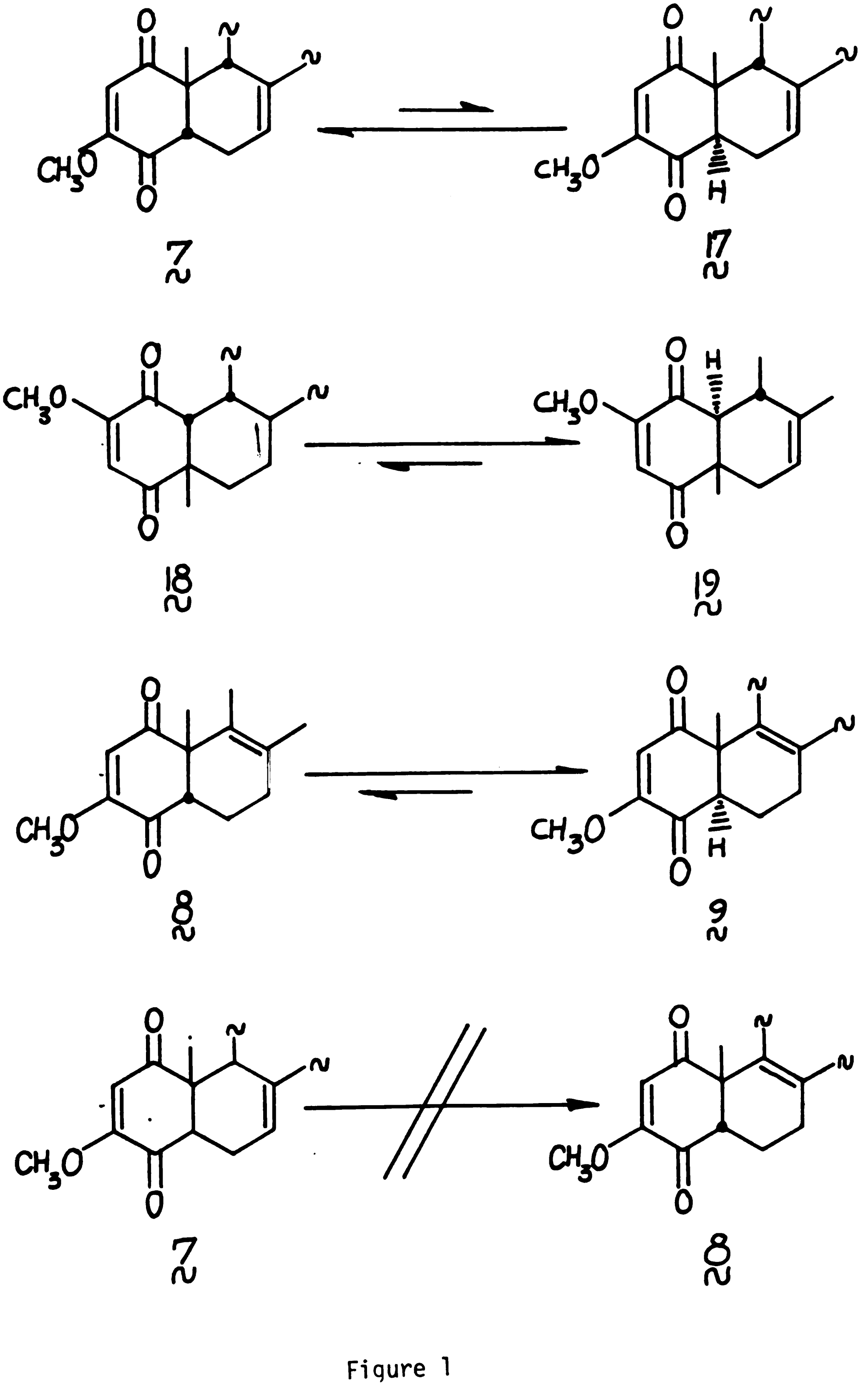
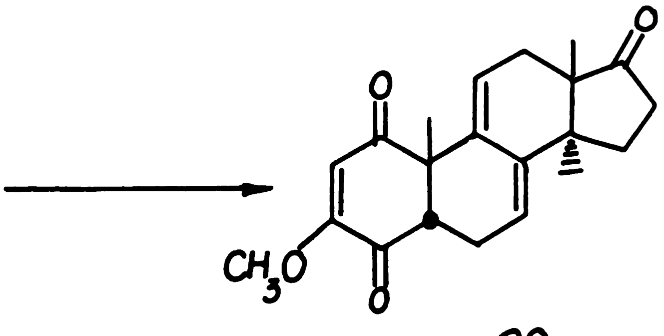


Figure 1

fashion in 19 instead of the less stable equatorial-axial fashion found in 18. This accounts for the successful isomerization of 18 to 19. A similar conformational analysis also suggests structure 9 would be more stable than 8. Therefore, a shift of the Δ^7 double bond to Δ^8 should facilitate epimerization at C-5 to give compound 9. Since the Δ^7 double bond proved to be stable under all the conditions studied, this attractive solution to the epimerization problem has not yet been realized.

An alternative way to introduce the Δ^8 double bond is by dissolving metal reduction of the corresponding $\Delta^{7,9(11)}$ diene. Brewis[15] studied the reduction of the $\Delta^{7,9(11)}$ diene system in several tetracyclic triterpenes and found both 1,2 and 1,4 addition of hydrogen, leading to Δ^7 and Δ^8 double bonds in the products. In several instances only the Δ^8 unsaturated product was formed, and we hoped this would be the case in our system. Another reason for introducing a $\Delta^{9(11)}$ double bond is that this would remove the 9-beta configuration, which is apparently responsible for earlier difficulty in the epimerization of C-5. Hence, we began to look for an efficient way to introduce the $\Delta^{9(11)}$ double bond (Equation 4).

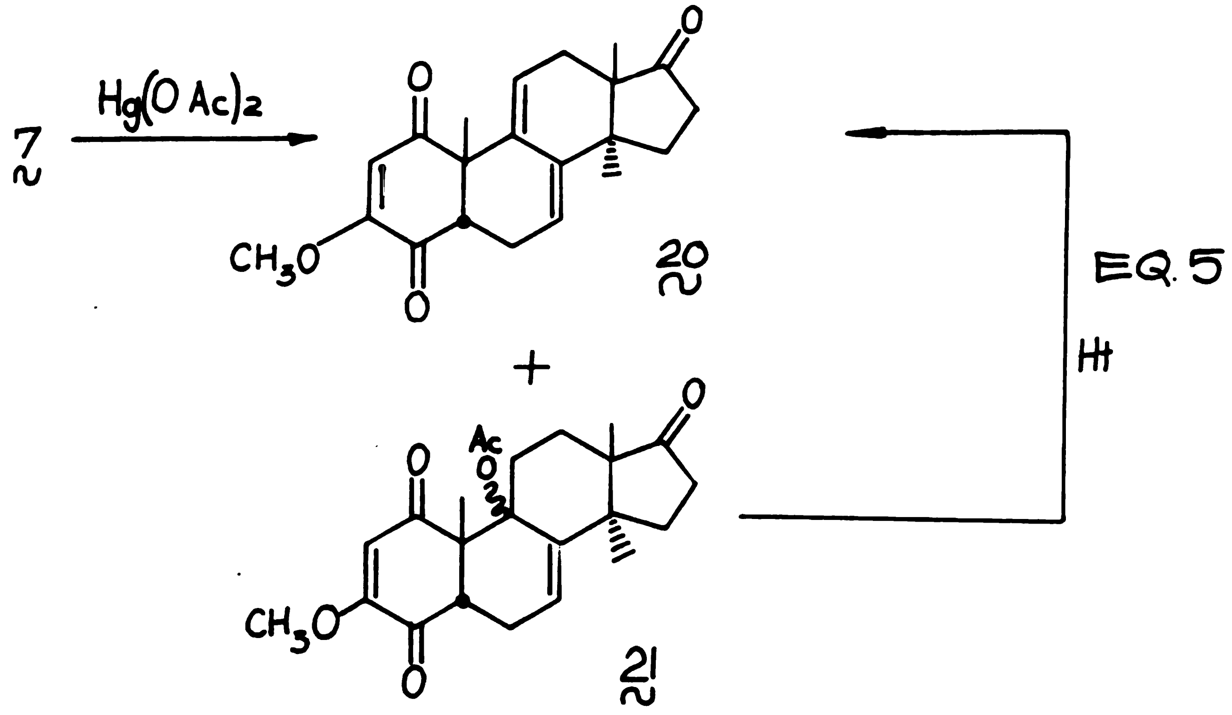
7



EQ.4

20

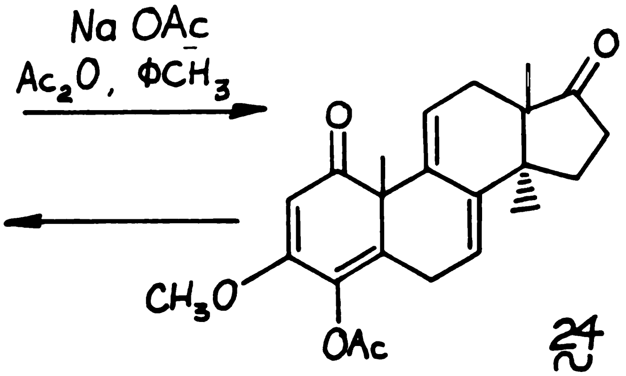
Transformations similar to this have been accomplished in other systems by the action of SeO_2, N-Bromosuccinimide or $Hg(OAc)_2$.[16] We found that reaction of 7 with SeO_2 and N-Bromosuccinimide gave intractable mixtures; however, $Hg(OAc)_2$ gave a mixture of two major components, which were separable by chromatography. The first fraction to elute gave a 20% yield of the desired diene 20 and the second a 50% yield of what appeared to be a mixture of acetates 21. Since 21 could be treated with p-TSA and converted to diene 20, conditions were worked out whereby the reaction mixture from the $Hg(OAc)_2$ oxidation was treated with p-TSA without isolation of 21. However, the overall yield of 20 from 7 was only 30-40% (Equation 5).



An understanding of how acetate is incorporated into the substrate was an important first step to improving the synthesis of **20**. In Scheme III diene **20** is formed by loss of the C-11 proton from the allylic cation **22**. However, intermediate **23** or cation **22** may react with acetate anion to give **21**. If this is true, it argues that oxidation with a mercury II salt having a less nucleophilic counterion should lead to a higher proportion of diene product. Indeed when Hg(CF_3CO_2)$_2$ was used as the oxidizing agent, diene **20** was obtained as the sole product in 90% yield.

Surprisingly diene **20** also failed to epimerize at C-5. That the enol does form was again shown by conversion of **20** to its enol acetate. Hydrolysis of the enol acetate back to the starting ketone indicates that here too the AB

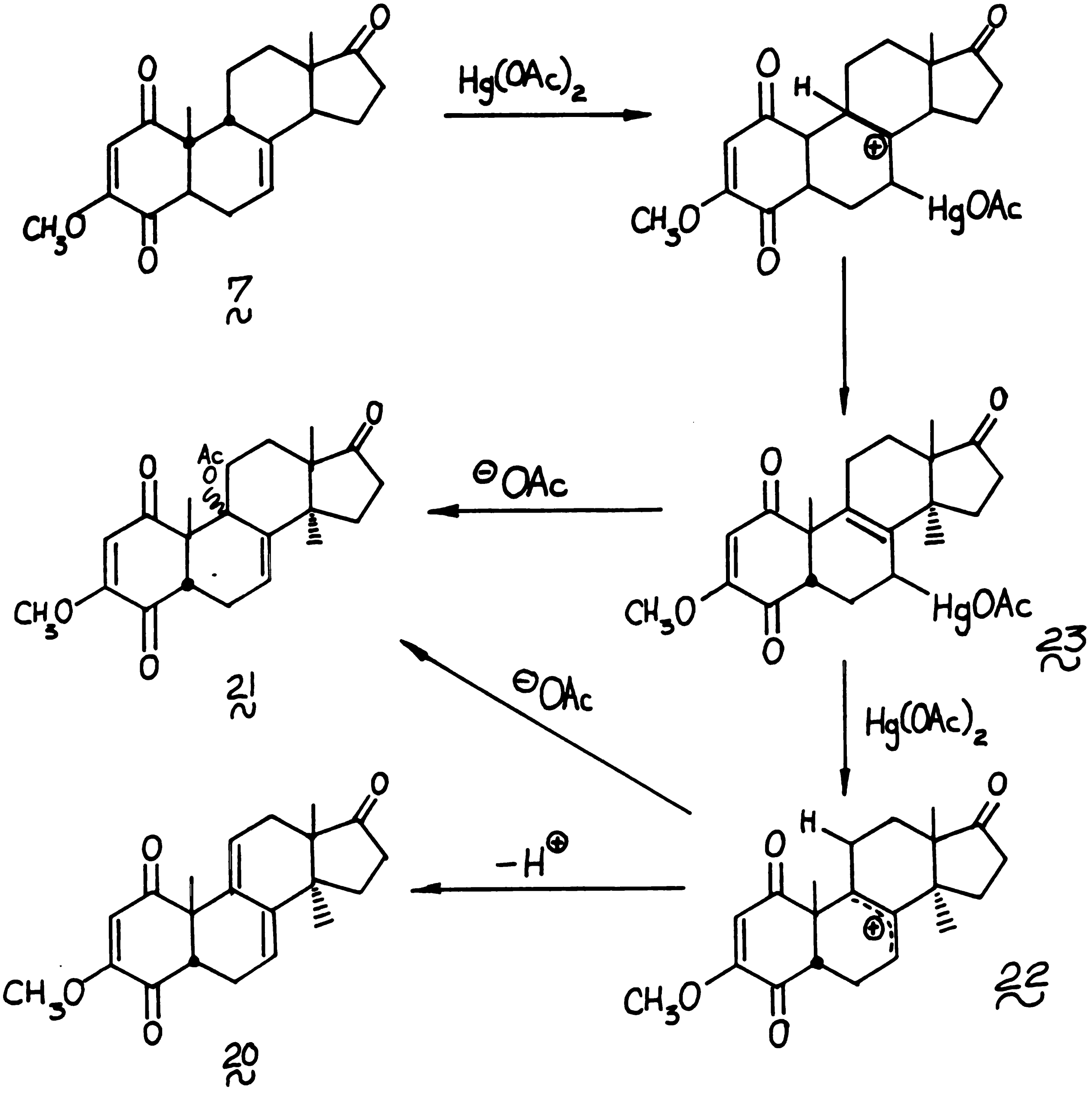
20



24

cis juncture is favored relative to the trans.

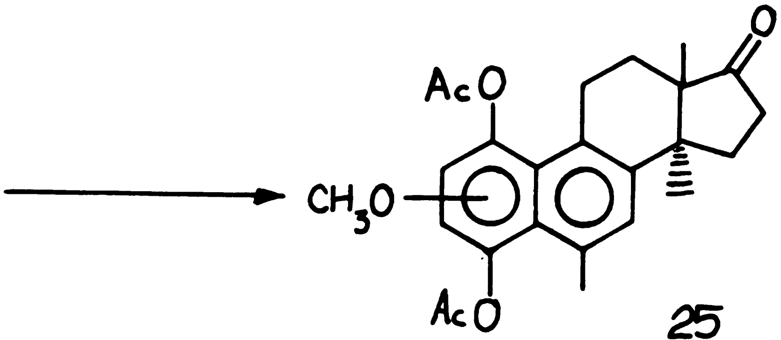
In the course of studying the formation of enolacetate **24** an interesting rearrangement was discovered. When diene **20** was refluxed in acetic anhydride containing excess sodium acetate (no co-solvent) the aromatic compound **25** was



Scheme III

obtained. Apparently the enol acetate is formed first and this is followed by acylation of the ester like carbonyl.

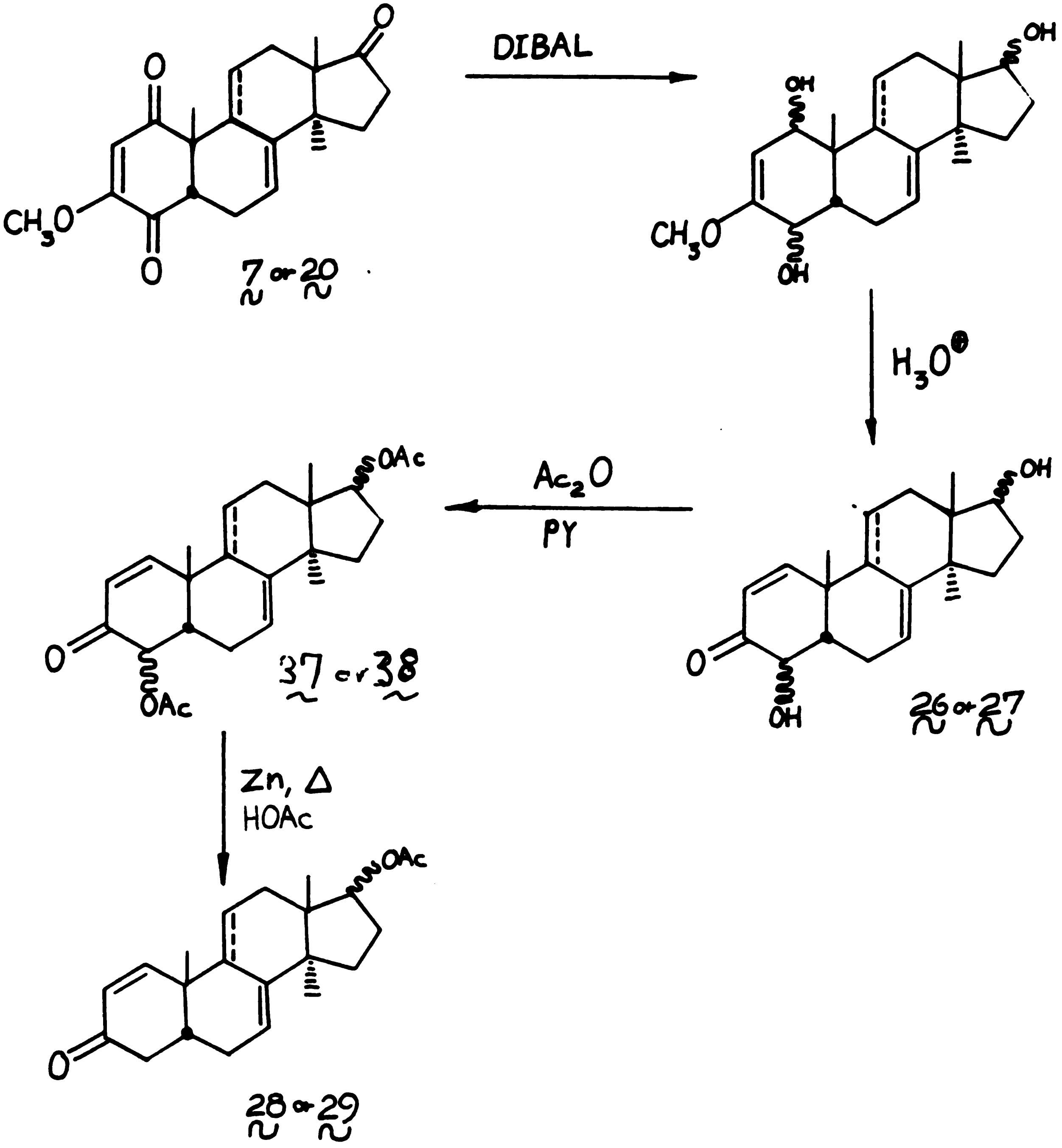
20



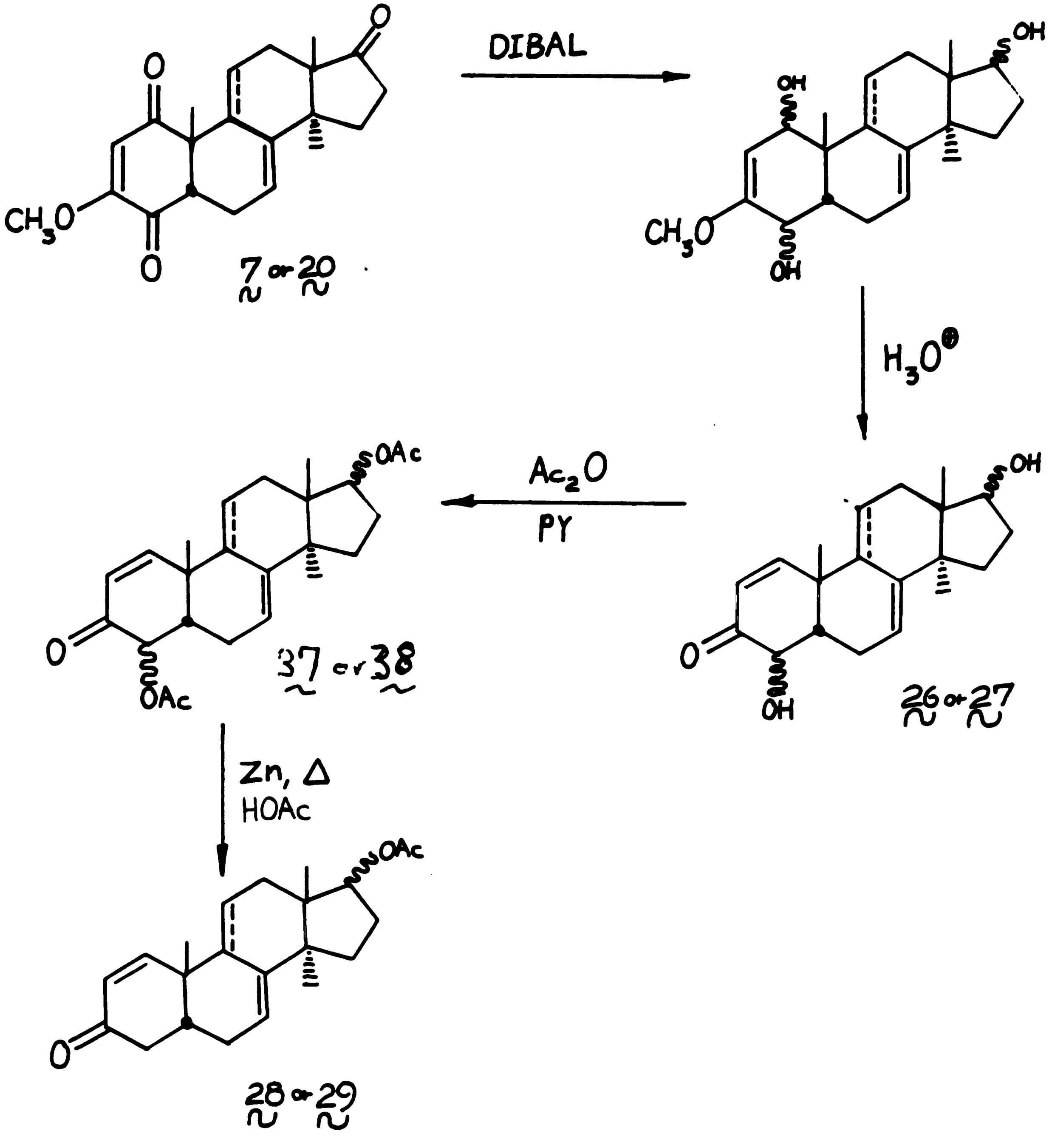
25

Subsequent methyl migration and aromatization then yields 25. It is not possible to unambiguously determine the position of the methoxy substituent in ring A from spectroscopic or analytical data.

Because of the difficulties encountered in epimerization of C-5, we decided to investigate some transformations of ring A functionality and return to the question of C-5 stereochemistry at a later stage. Therefore the Diels-Alder adduct 7 and its dehydro derivative 20 were carried through the sequence of reactions shown in Scheme IV. Reduction of all the carbonyl groups with diisobutylaluminum hydride followed by acid catalyzed hydrolysis and dehydration led to a mixture of epimeric diols 26 or 27. Diacetylation followed by reductive removal of acetate gave a mixture of epimeric acetates 28 or 29. At each stage of this sequence a mixture of at least two components is


CH3O
7 or 20
DIBAL
OH
OH
OH
CH3O
H3O⊕
OH
OH
26 or 27
Ac2O
PY
OAc
OAc
37 or 38
Zn, Δ
HOAc
OAc
28 or 29

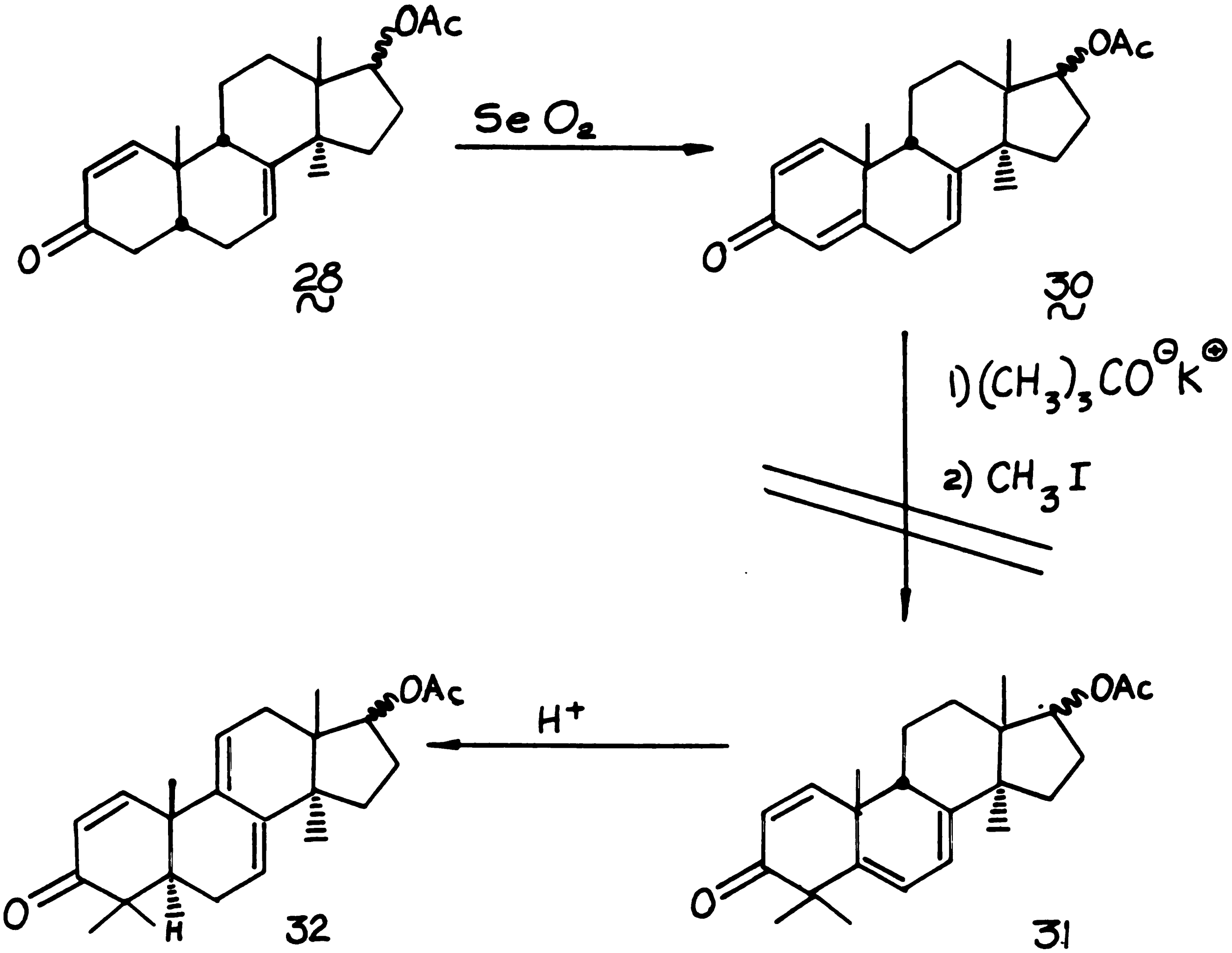
Scheme IV


CH3O
O
O
7 or 20
DIBAL
OH
OH
OH
CH3O
H3O⊕
OH
O
OH
26 or 27
Ac2O
PY
OAc
O
OAc
37 or 38
Zn, Δ
HOAc
OAc
O
28 or 29

Scheme IV

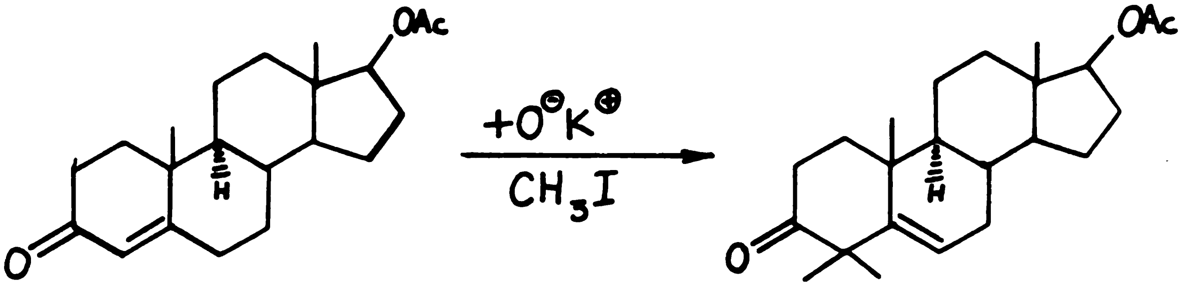
present because of the hydroxyl epimers in the five membered ring. Since this function will eventually be reoxidized to a ketone prior to introduction of the side chain, both epimers are useful in this synthesis and are therefore carried along. Although the presence of these epimers shouldn't matter chemically, it makes crystallization of the product unlikely and at times complicates the spectral data. In the sequence in Scheme IV for both substrates, purification was not attempted until after the zinc reduction. HPLC purification at this stage yields the indicated products in about 40% overall yield.

Having obtained **28**, we felt we had another handle to control the stereochemistry of C-5. Although DDQ failed to react with **28**, it was possible to introduce a Δ^4 double bond in 70% yield by oxidation with selenium dioxide. Our plan at this stage was to introduce the gem-dimethyl moiety at C-4, and to then isomerize to the transoid diene **32**. Unfortunately **30** proved unreactive when treated with t-butoxide and methyl iodide. To confirm this surprising inertness some work with model compounds was conducted. In this study steroidal enone **33** was gem-dimethylated in good yield by the classical procedure developed by Woodward.[17] The cross-conjugated dienone **34**, however, proved completely unreactive to equivalent reaction conditions. The reluctance of a $\Delta^{1,4}$-3-ketosteroid to methylate has also been reported in the literature for compound **35**.[18]

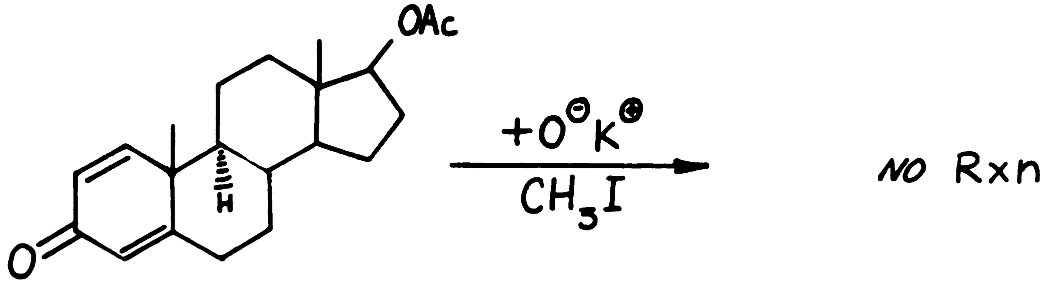


The reason for this surprising behavior is unknown.

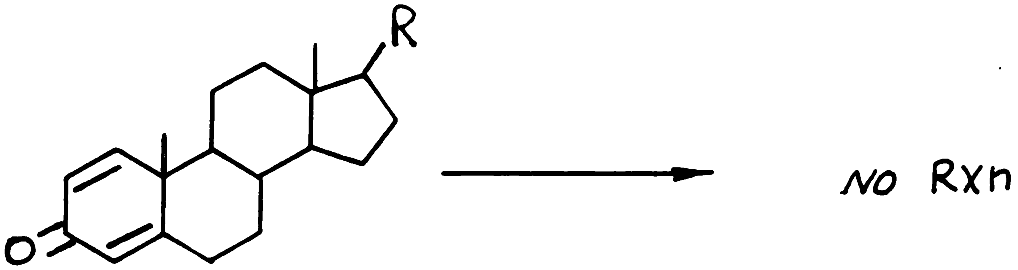
Since the Δ^1 double bond seems to interfere with the methylation of 30, the Δ^1 double bond of 30 was selectively reduced over Wilkenson's catalyst[17] to give 36. Methylation of 36 was then investigated using *t*-butoxide/CH_3I in *t*-butanol and LDA in THF but again no satisfactory method was found for the introduction of the gem-dimethyl moiety. A summary of these methylation



33



34



35

attempts is presented in Table 2.

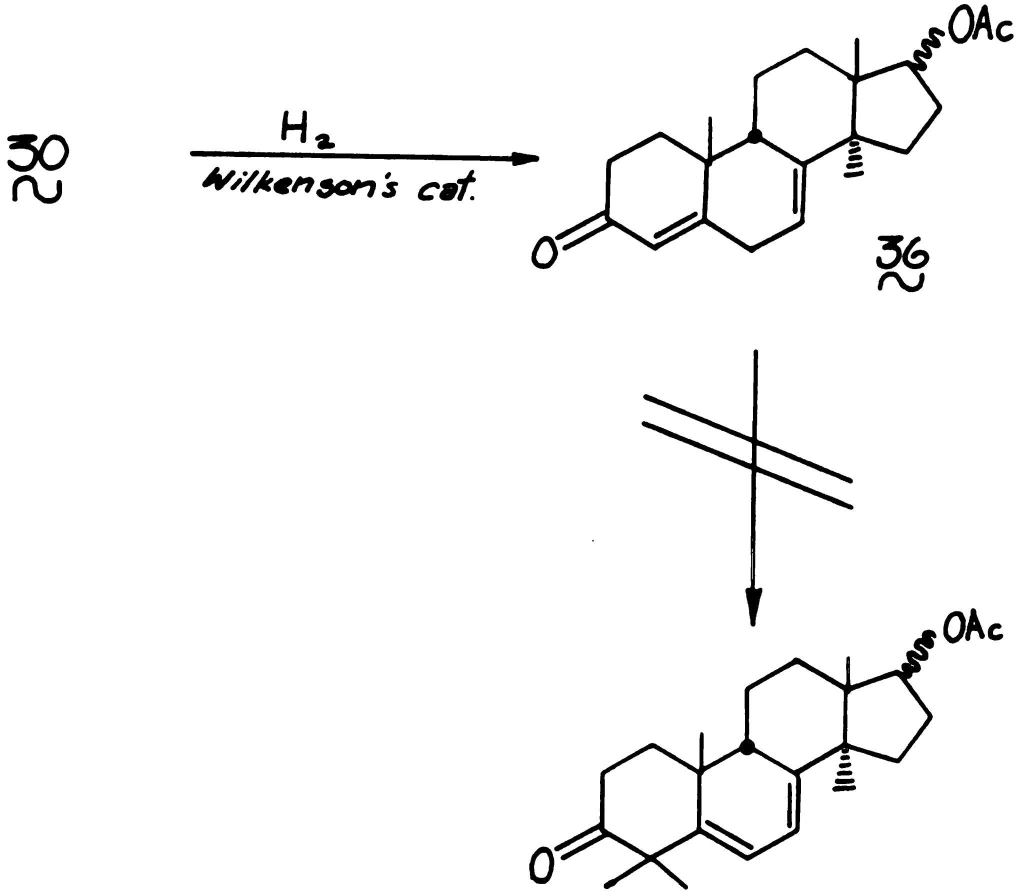
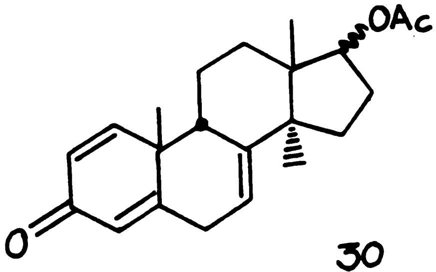
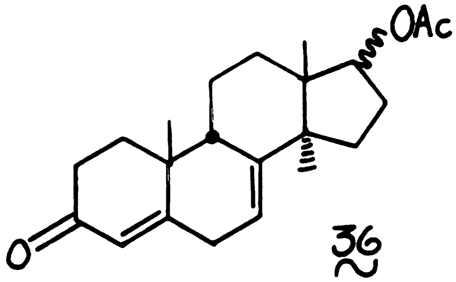
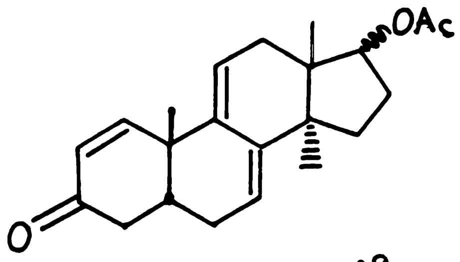

30
H₂
Wilkenson's cat.
OAc
O
36
OAc
O

Table 2. Attempted Methylations.

Compound	Condition	Results
 30	t-butoxide, CH_3I/ t-butanol	No RXN
	t-butoxide, CH_3I/ DMSO	No RXN
 36	t-butoxide, CH_3I/ t-butanol	Complicated mixtures
	LDA CH_3I/THAF	
 29	t-butoxide CH_3I/ t-butanol	No RXN
	t-butoxide CH_3I/DMSO	Complicated mixture
	t-butoxide CH_3I/THF	complicated mixture
	LDA CH_3I/THF	No RXN

EXPERIMENTAL

General

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

Analysis by GLPC was conducted with a Varian 1200 gas chromatograph. Melting points were determined on a Hoover-Thomas apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer. Proton magnetic resonance spectra were taken in deuterochloroform solutions with either a Varian T-60 or a Bruker 250 MHz spectrometer and are calibrated in parts per million downfield from tetramethylsilane as an internal standard. Mass spectra were obtained with a Finnigan 4000 GC/MS spectrometer.

Preparation of **20**

A solution of the tetracyclic adduct(**7**) (1.5 g, 4.38 x 10^{-2} mol) in 250 ml dry THF was stirred at room temperature under a blanket of nitrogen until the solid completely dissolved. Mercury trifluoroacetate (4.8 g, 1.1 x 10^{-2} mol) was then added in one portion and the mixture was stirred for eleven hours while the progress of the reaction was monitored by tlc (silica gel, 50/50 Hexanes/Ethylacetate). The reaction mixture was then evaporated to dryness and chromatographed on a silica column (30% Ethylacetate on Hexanes) to remove the mercury salts. The fractions containing the desired product were combined, evaporated to dryness and the solid product was crystallized from ethanol to give 1.3 g (87%) **20** mp 191-192.

Preparation of **27**

The dehydro adduct **20** (1 g, 2.9 x 10^{-3} mol) was dissolved in 100 ml CH_2Cl_2 and cooled to 0° under a blanket of nitrogen. To this was added slowly, via a syringe, 11 ml of a 1 molar solution of diisobutylaluminum hydride in hexane. The resulting mixture was stirred at 0° for two hours, then quenched by slow addition of a saturated sodium sulfate solution until the evolution of gas ceased. The cooling bath was removed, and methanol added slowly until the solution became less viscous. On standing this solution deposited a precipitate. The solid was filtered and washed twice with boiling methanol; and the combined filtrate and washings were refiltered, evaporated almost to dryness, redissolved in a mixture of 50 ml dioxane plus 50 ml 10% H_2SO_4 and held at room temperature for 6-12 hours. The volume of this mixture was reduced to half by evaporation and the resulting solution was extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated to dryness to give 0.9 g **27** as an oil. Thin layer chromatography of this product showed the absence of starting material and two new spots with Rf lower than that for starting material. (Silica, 50/50 Hexanes/Ethylacetate.)

Preparation of **38**

Diol **27** (0.6, 1.95 x 10^{-3} mol) was dissolved in 50 ml pyridine and then treated with 20 ml acetic anhydride. The resulting mixture was kept at room temperature for 18 hrs. and then evaporated almost to dryness. The residue was dissolved in CH_2Cl_2, washed with 10% H_2SO_4, sat. $NaHCO_3$ and brine and then dried ($MgSO_4$). Evaporation gave 0.7 g (90%) **38** as an oil.

Preparation of **29**

To a solution of the diacetate **38** (0.60 g, 1.51 x 10^{-3} mol) in 25 ml glacial acetic acid was added 0.60 g of washed Zn dust and two drops of concentrated HCl. This mixture was heated to reflux for 1.25 hours, allowed to cool to room temperature, filtered by gravity and evaporated to dryness. The residue was then chromatographed by HPLC (silica, 35% ethylacetate in Hexanes). The main fraction contained the desired product **29**, 0.21 g. The ultraviolet spectrum of B (λ_{max} = 235, 240 nm e = 12,690) is consistent with the enone and diene chromophores designated in the formula.

Preparation of **24**

The dehydro adduct **20** (0.10 g, 2.9 x 10^{-4} mol) was dissolved in 10 ml benzene containing 5 ml acetic anhydride and 0.05 g sodium acetate. This mixture was heated to reflux for 24 hours, cooled and then evaporated to dryness. A solution of the residue in CH_2Cl_2 was washed with sat. $NaHCO_3$, H_2O and brine, dried ($MgSO_4$) and evaporated. The resulting oil solidified upon standing, and crystallization from acetone/water gave **24**, mp 205-207°.

Preparation of **25**

A solution of dehydro adduct **20** (0.10 g, 2.9 x 10^{-4} mol) in 10 ml acetic anhydride containing sodium acetate (0.05 g, 6.1 x 10^{-4} mol) was heated to reflux for four hours. Most of the acetic anhydride was removed by evaporation at reduced pressure and the residue was dissolved in CH_2Cl_2, filtered and evaporated to dryness. The resulting dark oil solidified and was crystallized from acetone/water, to give 0.05 g of an off-white solid, mp 215-217.

Preparation of **26**

A solution of the Diels-Alder adduct **7** (5.0 g, 1.46 x 10^{-2} mol) in 500 ml CH_2Cl_2 was cooled to 0°, and maintained under nitrogen as 66 ml of a 1 molar solution of diisobutylaluminum hydride in hexane was added dropwise. During this addition a precipitate formed, which redissolved as the addition was completed. The resulting mixture was stirred at 0° for two hours, then quenched by slow addition of saturated Na_2SO_4, until the evolution of gas ceased. The cooling bath was removed and methanol was added dropwise slowly until the solution became less viscous. On standing at room temperature a precipitate formed. This solid was filtered and washed twice with boiling methanol. The filtrate and washings were combined, refiltered and evaporated almost to dryness. The residue was dissolved in a mixture of 250 ml dioxane plus 250 ml 10% H_2SO_4 and stirred at room temperature for 6-24 hours. The volume of this mixture was reduced to half by evaporation at reduced pressure then extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated to give 4.6 g (100%) of an oil.

Preparation of 37

Diol 26 (4.7 g, 0.0149 mol) was dissolved in 100 mL dry pyridine and treated with 75 mL acetic anhydride. The resulting mixture was kept at room temperature for six hours, during which time the solution darkened. This mixture was evaporated and the residue was dissolved in CH_2Cl_2, washed with 10% H_2SO_4 sat. $NaHCO_3$, H_2O, brine and dried over $MgSO_4$. Thin layer chromatography (silica, ethylacetate/hexanes 1/1) showed the starting material had been consumed and displayed two new spots of higher Rf. Evaporation to dryness gave 5.6 g of an oil (95%).

Preparation of 28

Diacetate 37, (5 g, 1.25×10^{-2} mol) was dissolved in 225 mL glacial acetic acid. To this was added 5 g freshly washed Zn dust, and this mixture was heated to reflux for one hour, allowed to cool to room temperature, filtered and evaporated to dryness. The residue was dissolved in a mixture of 50/50 Hexanes/Ethylacetate, and on standing at room temperature for about one hour deposited a gummy solid. This solid was filtered and the filtrate evaporated to give 4.1 g of a dark yellow oil, which was chromatographed on silica (20% ethylacetate in hexanes). Two small fractions 0.17 g and 0.33 g were first collected followed by one major fraction, 1.5 g, which contained the desired product.

Preparation of 30

Enone 28 (1.2 g, 3.5×10^{-3} mol) was dissolved in 50 mL dry t-butanol containing 2 drops pyridine and 1.0 g SeO_2. This mixture was heated to reflux under N_2 for one hour, cooled to room temperature, diluted with CH_2Cl_2 and filtered. The filtrate was evaporated to dryness, dissolved in 34% ethylacetate in hexanes and chromatographed on 60 g silica. The product eluted in an 80 mL portion of the first 300 mL of eluent, to give 0.9 g of the desired product (75%).

Preparation of 36

A 100 mL flask was evacuated and filled with hydrogen three times and then charged with 0.38 g (1.1×10^{-3} mol) of the trienone 30, in 50 mL absolute ethanol. To this solution was added 0.35 g of freshly prepared Wilenson's catalyst, and the mixture was stirred at room temperature, under a positive pressure of hydrogen for four hours. The reaction mixture was evaporated to dryness, dissolved in 50/50 hexane/ethylacetate, and filtered through a short column of silica, using 50/50 hexanes/ethylacetate as the eluent solvent. The product was eluted along with some colored impurities but is reasonably pure. Evaporation of the solvent gave 0.28 g (74%).

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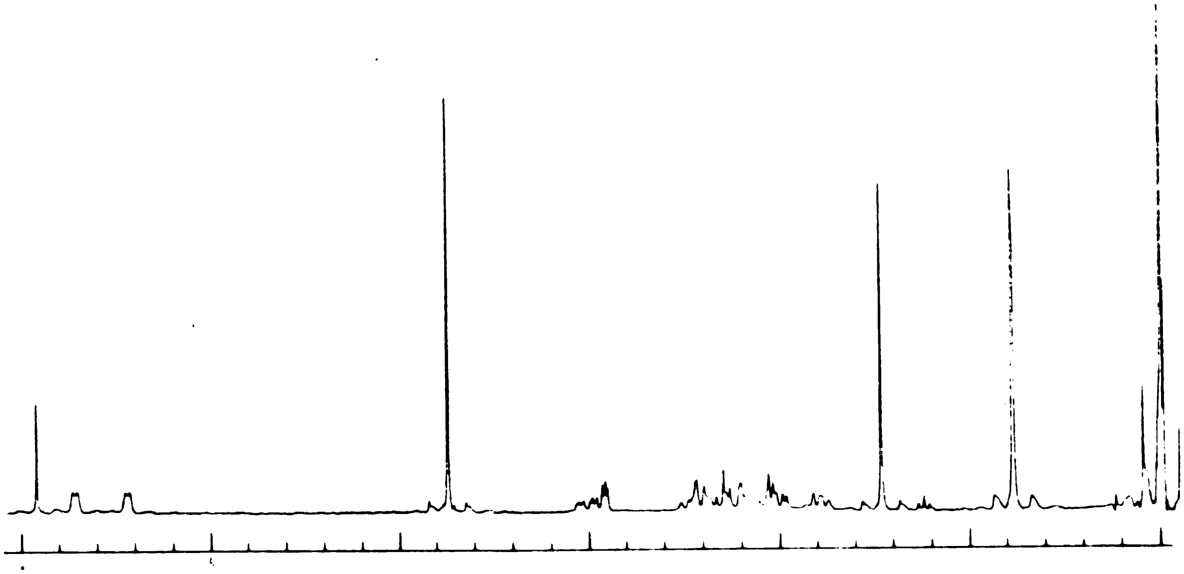
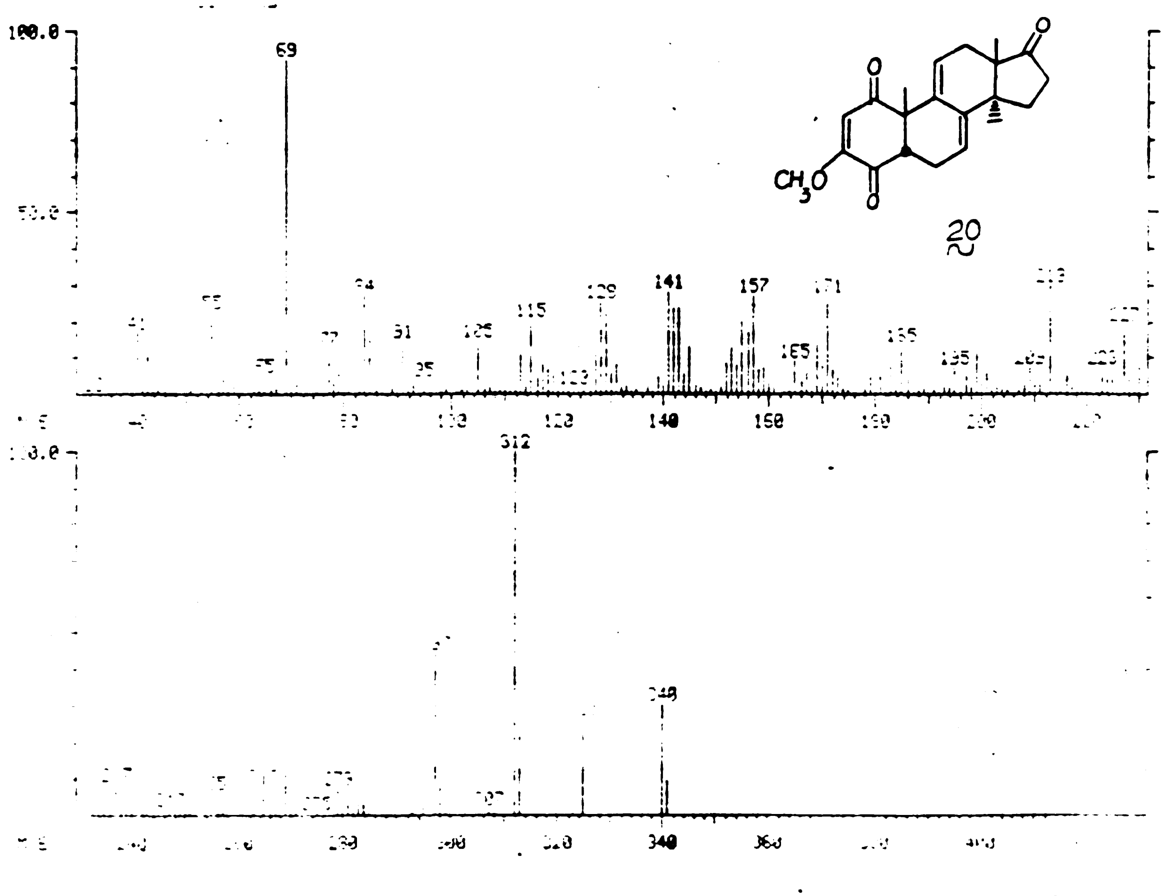
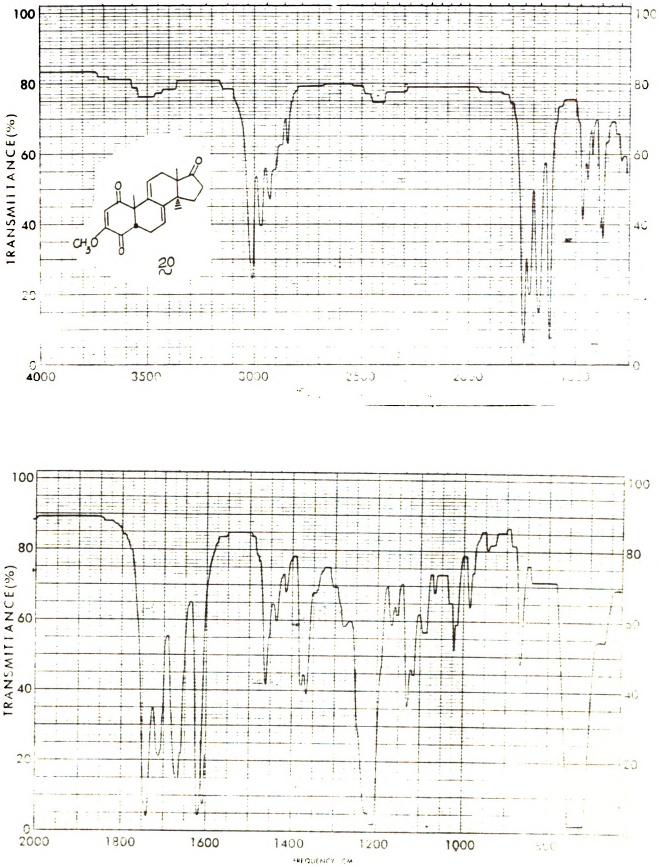


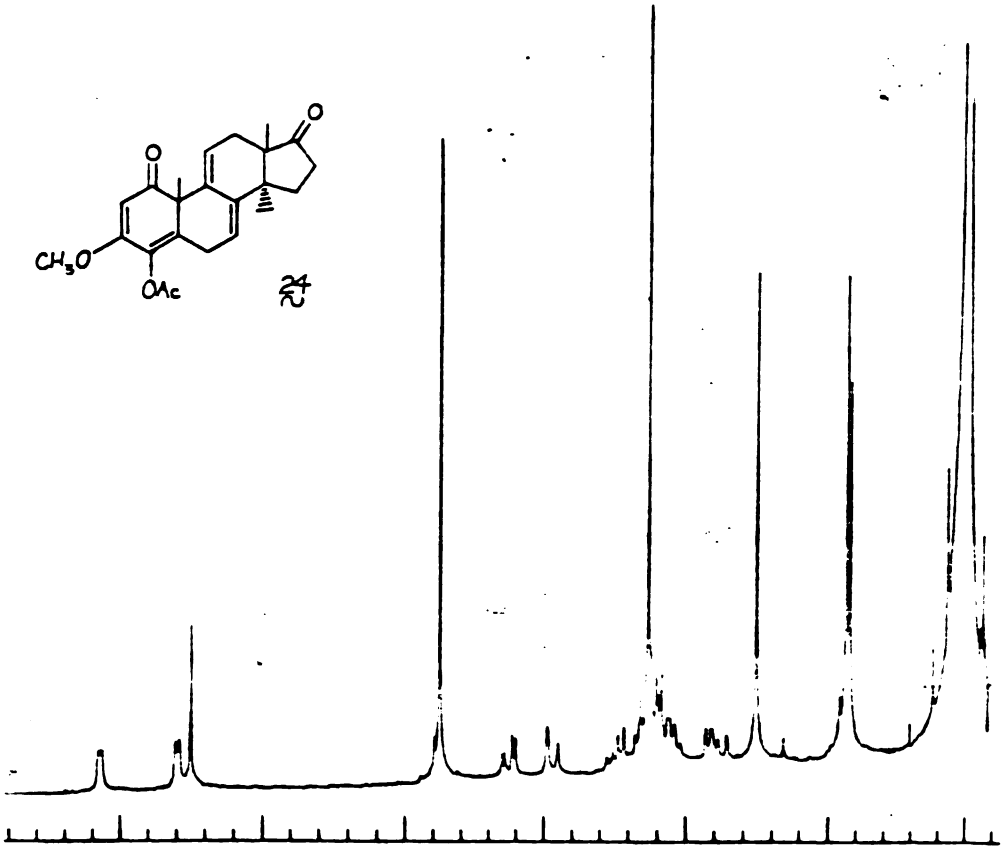
250 NMR spectrum of **20**



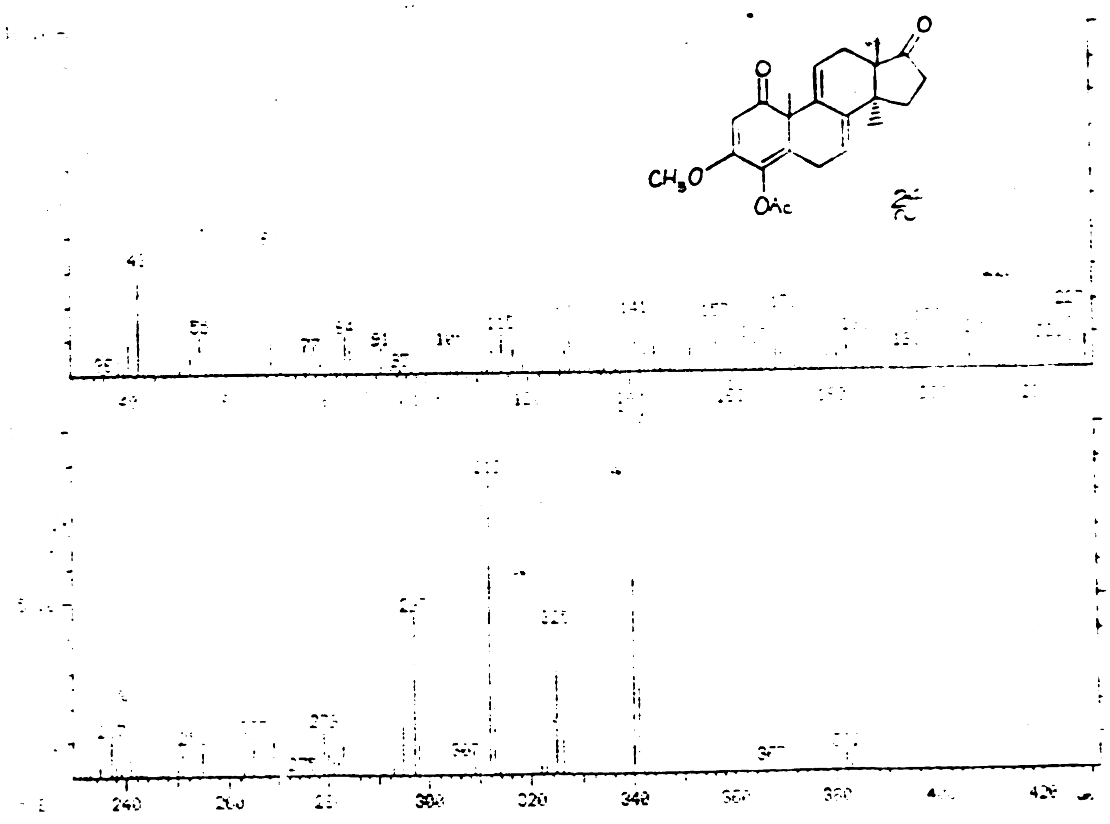
Mass spectrum of **20**



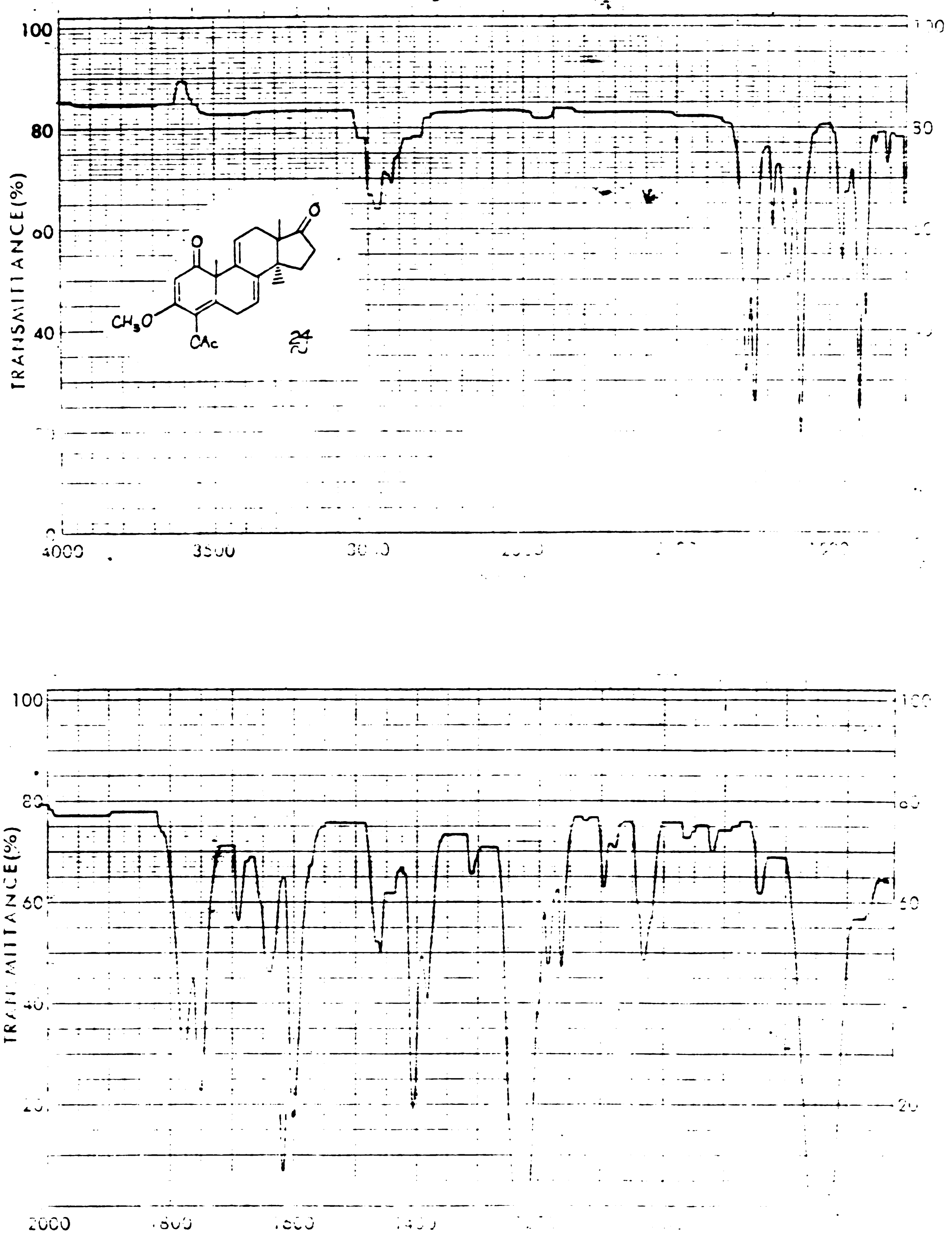
Infrared spectrum of 20



250 NMR spectrum of 24



Mass spectrum of 24



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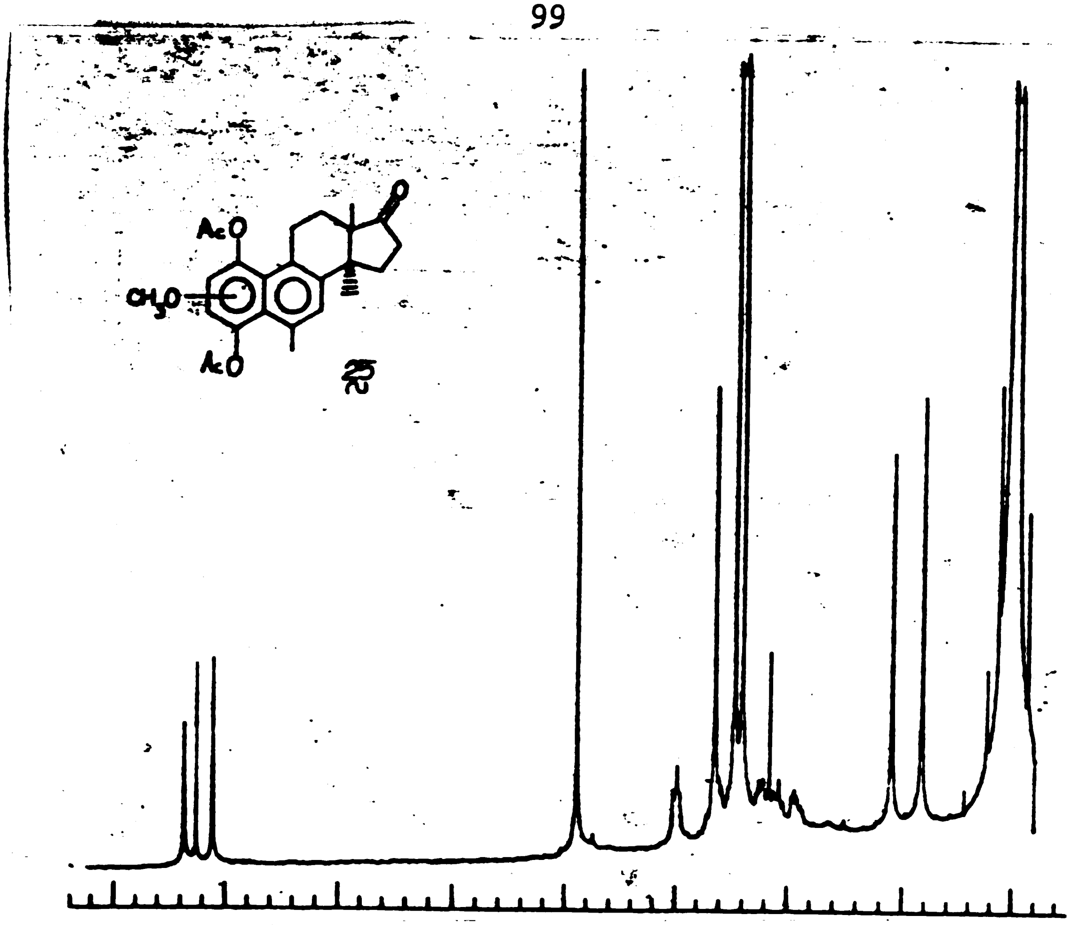
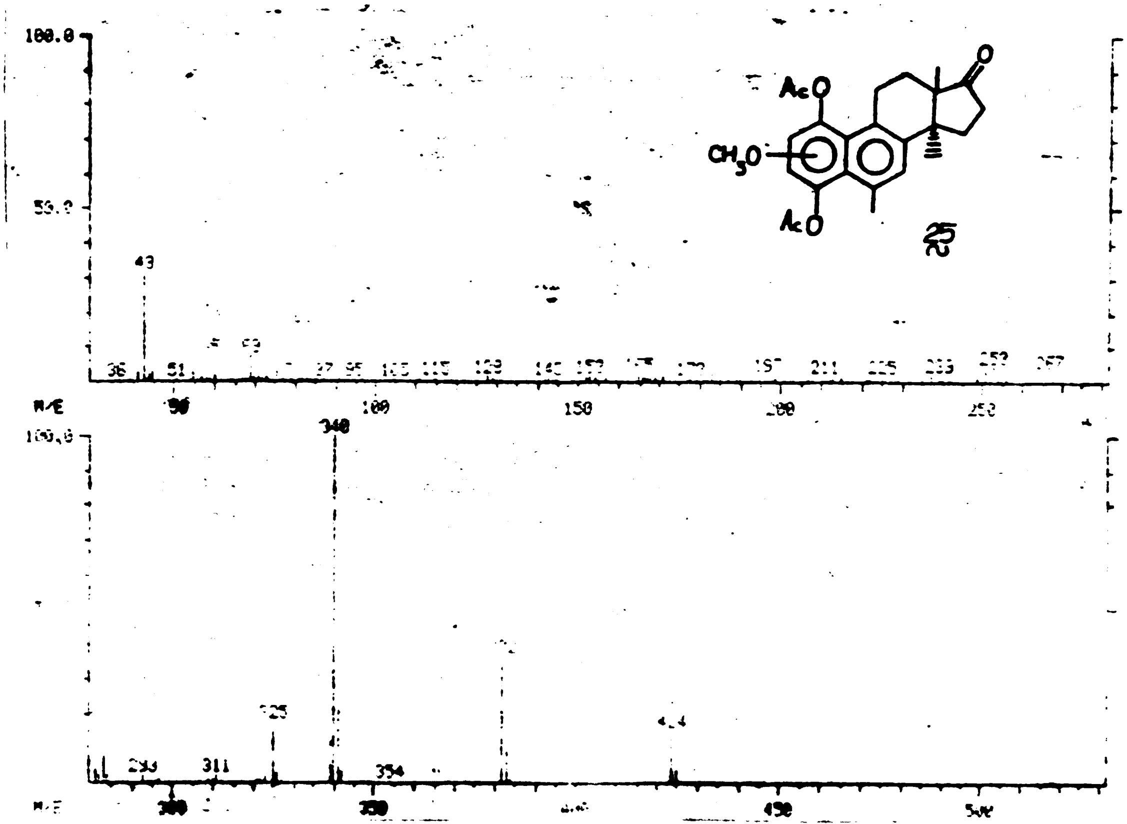
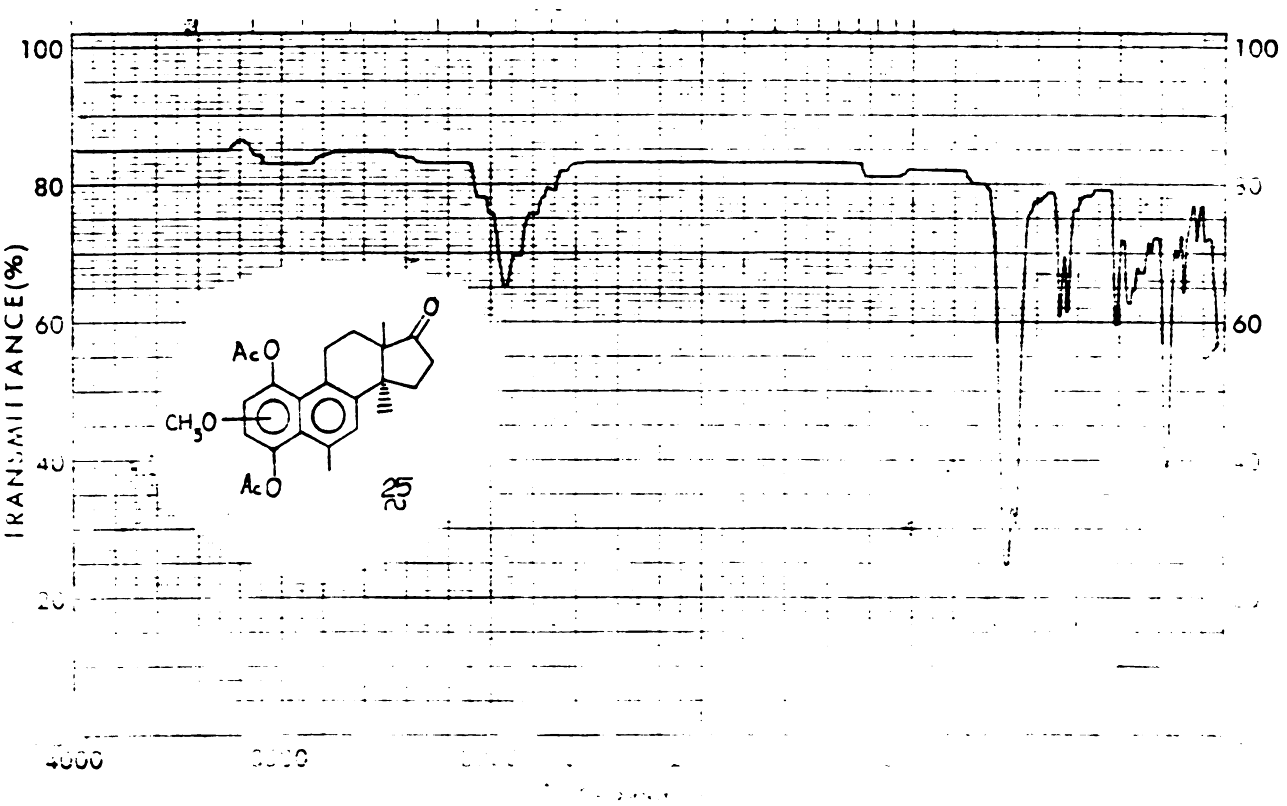
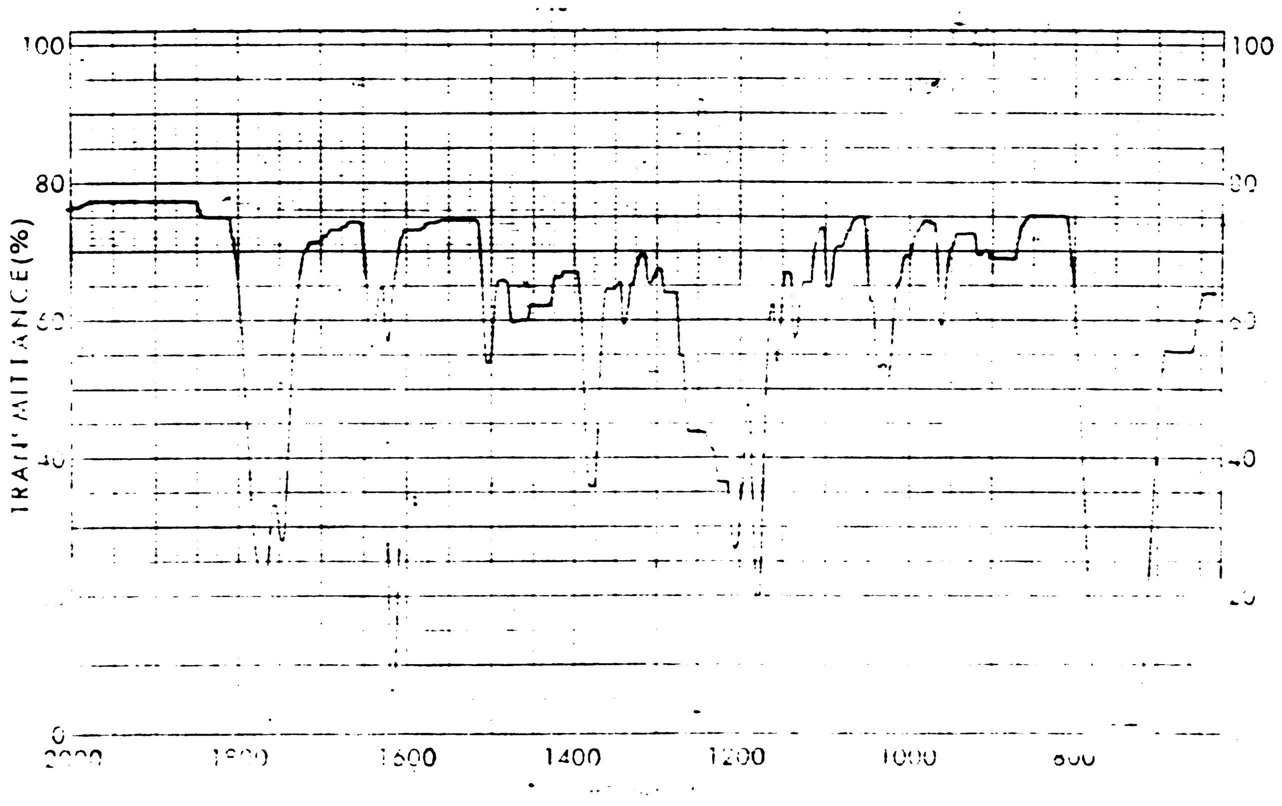


250 NMR spectrum of 25

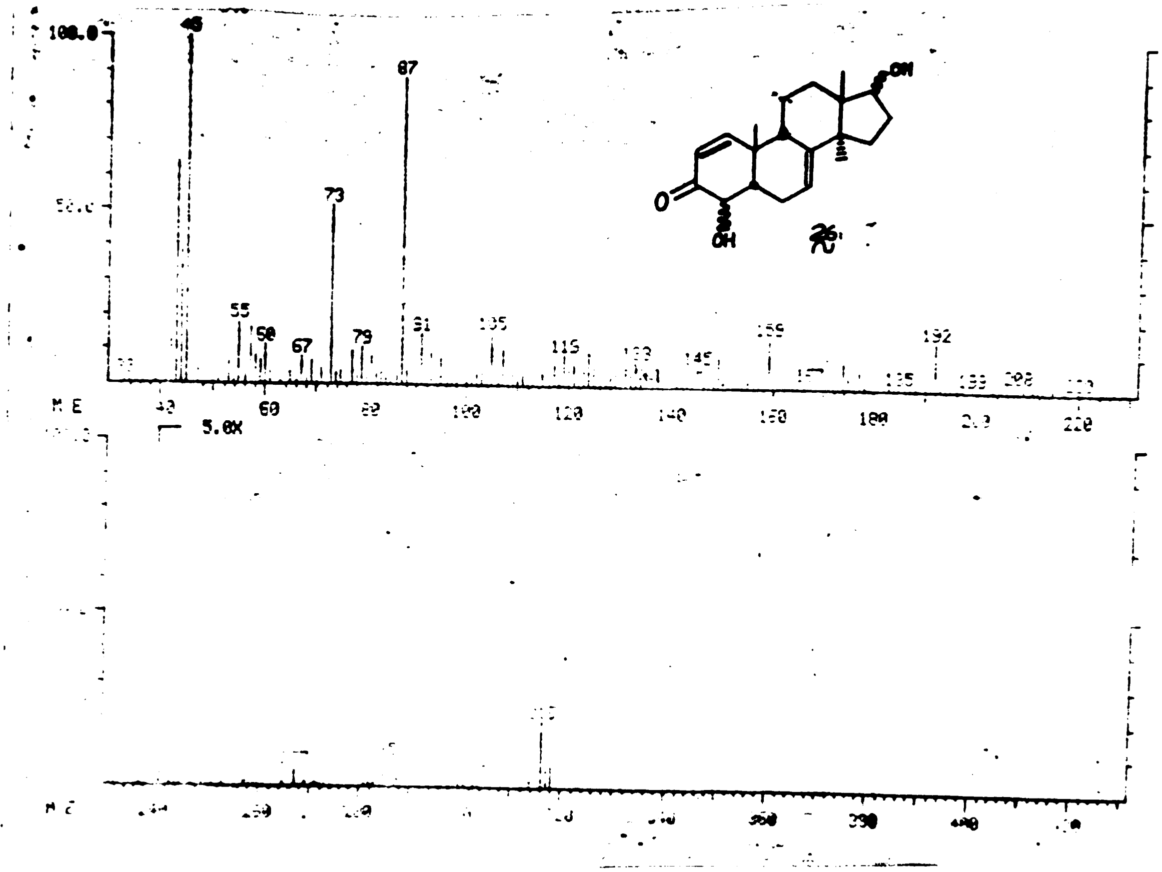


Mass spectrum of 25

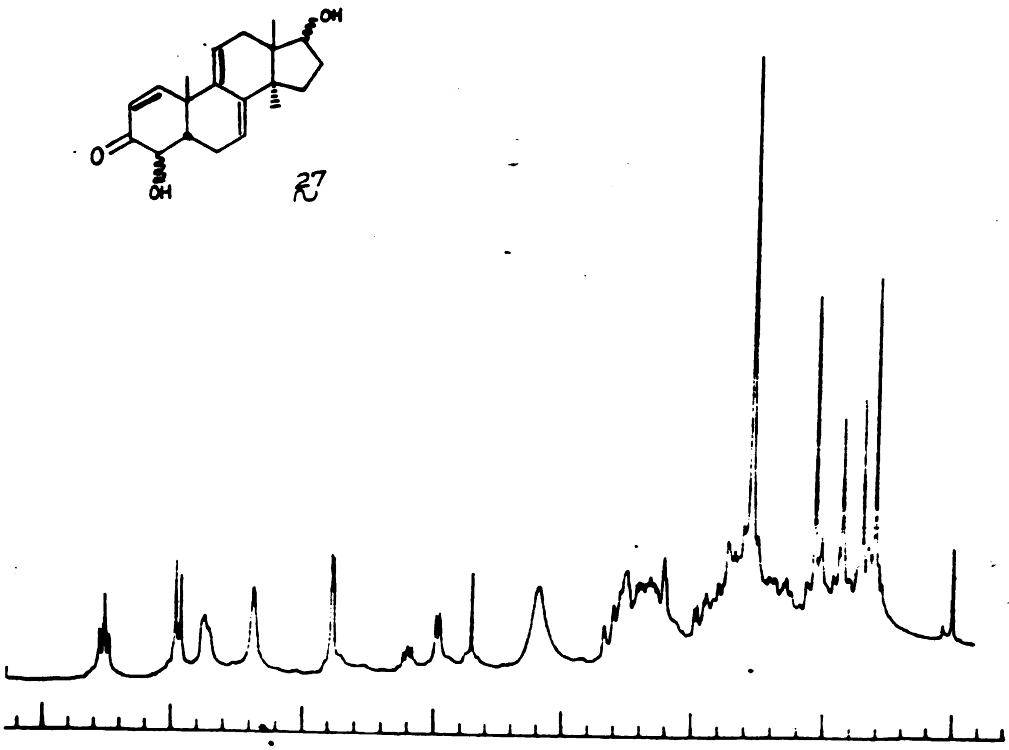




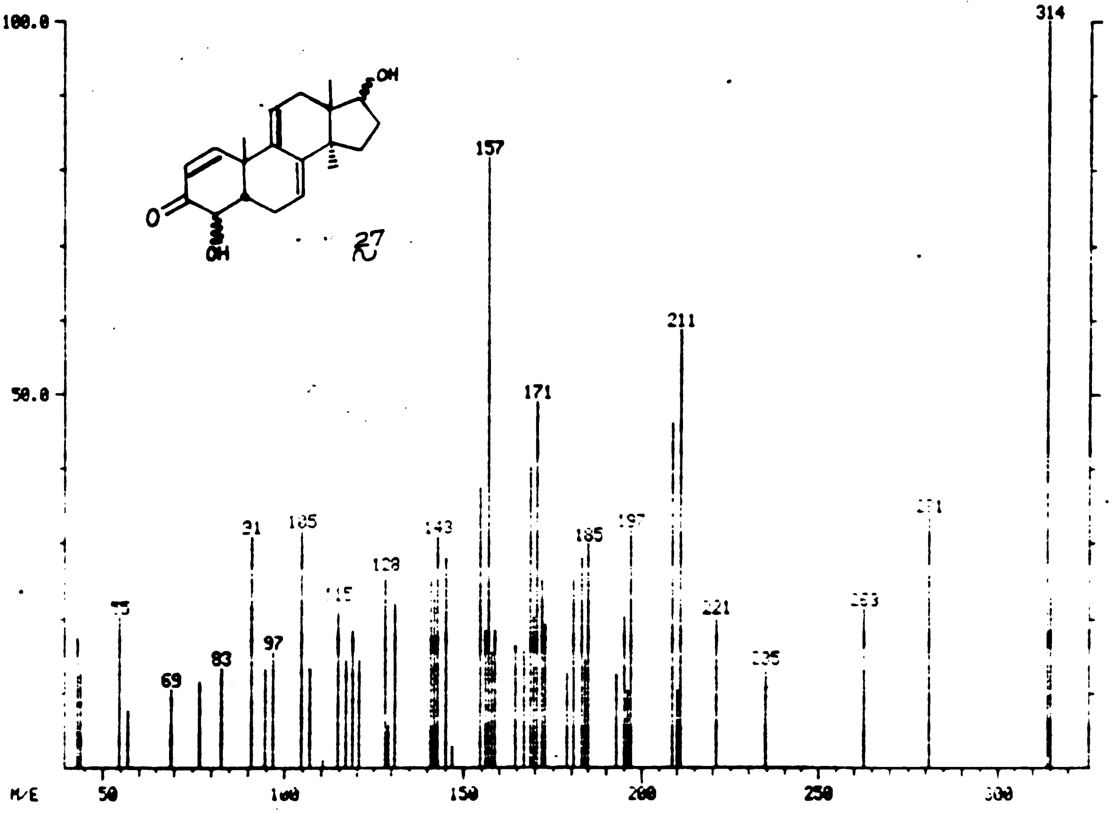
Infrared red spectrum of 25



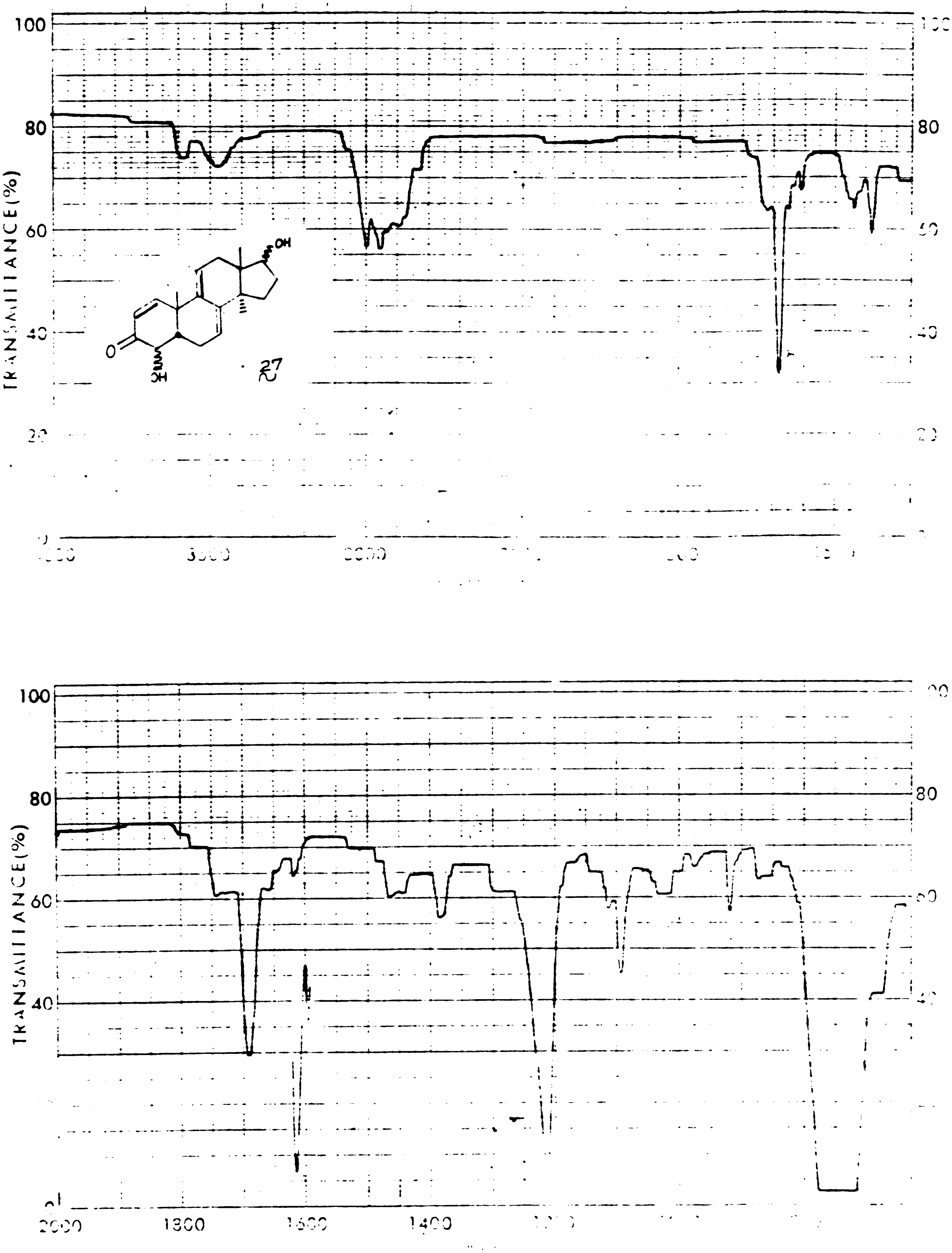
Mass spectrum of 26



250 NMR spectrum of 27



Mass spectrum of 27



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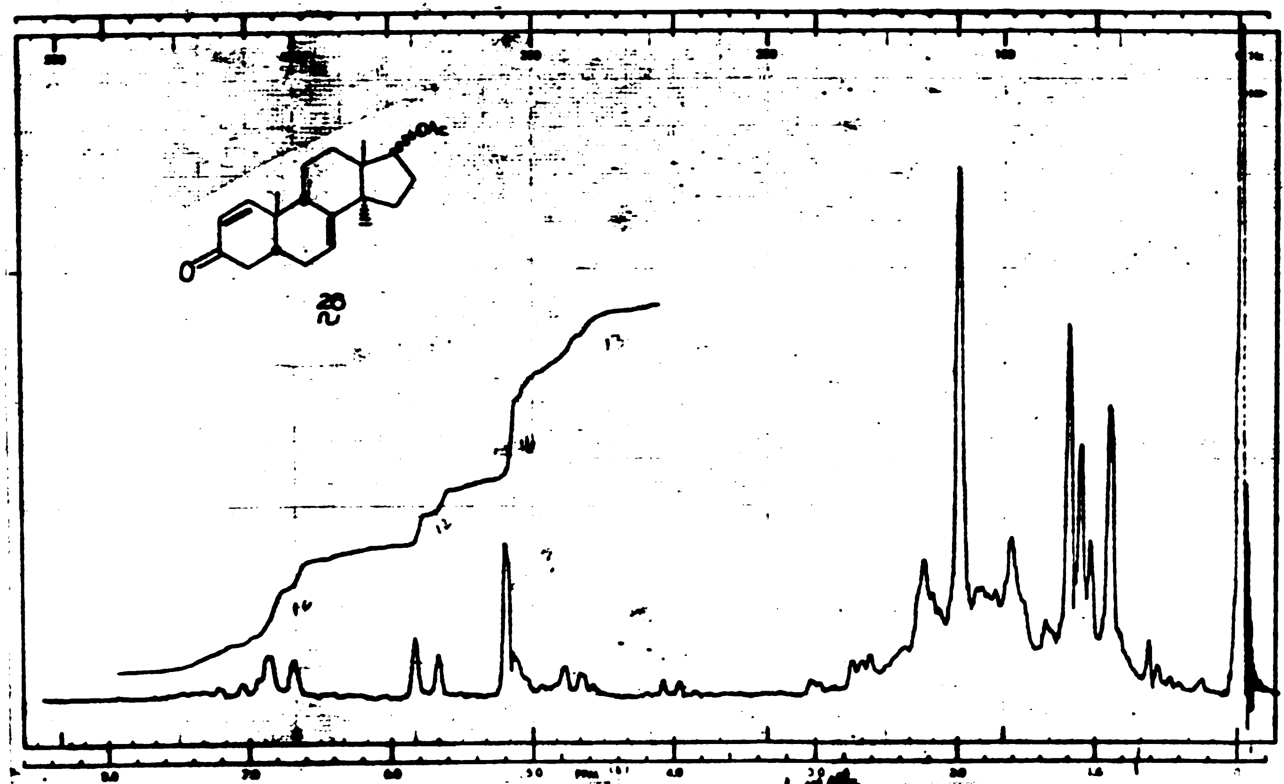
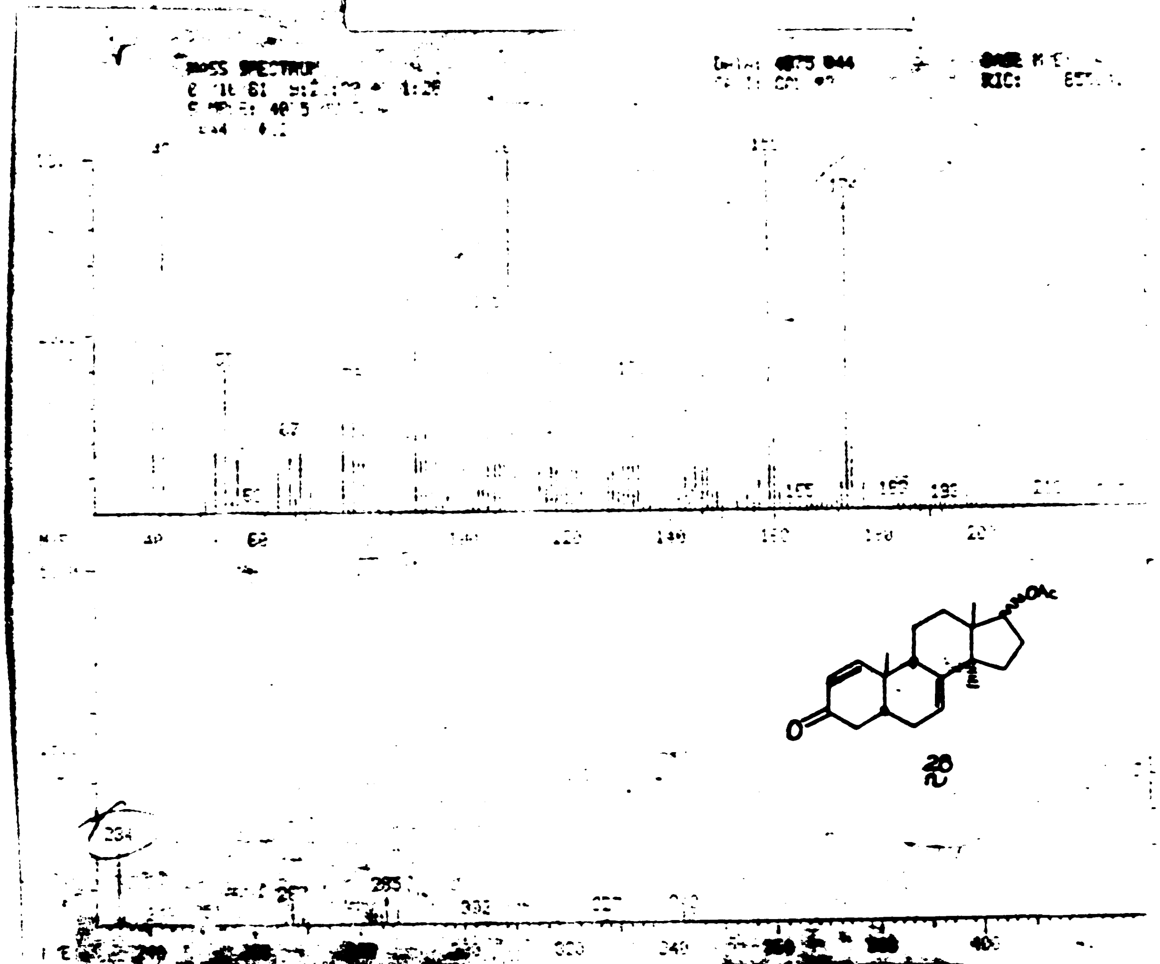
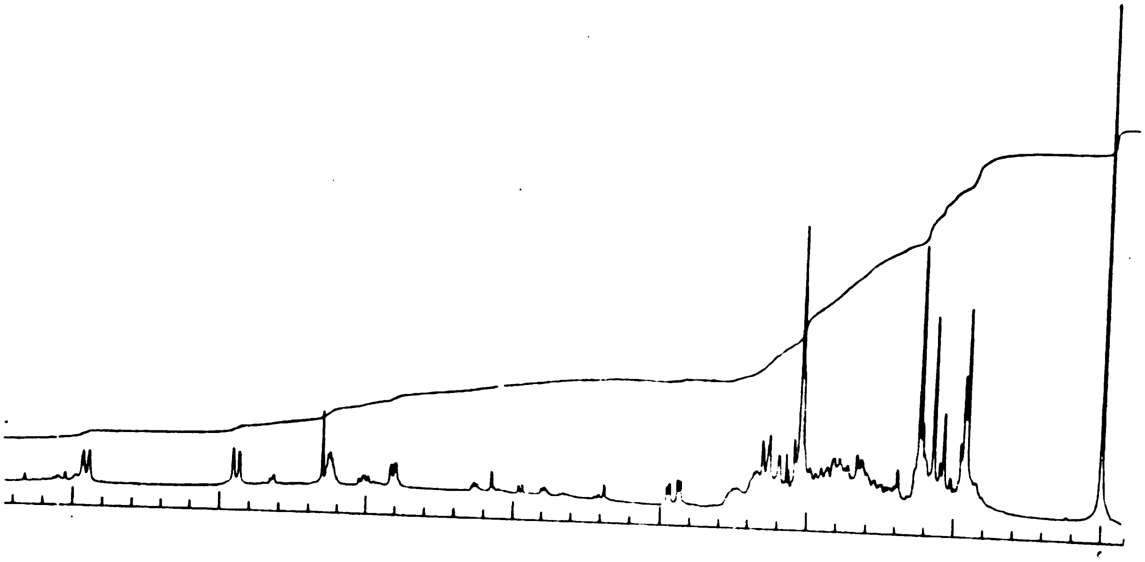


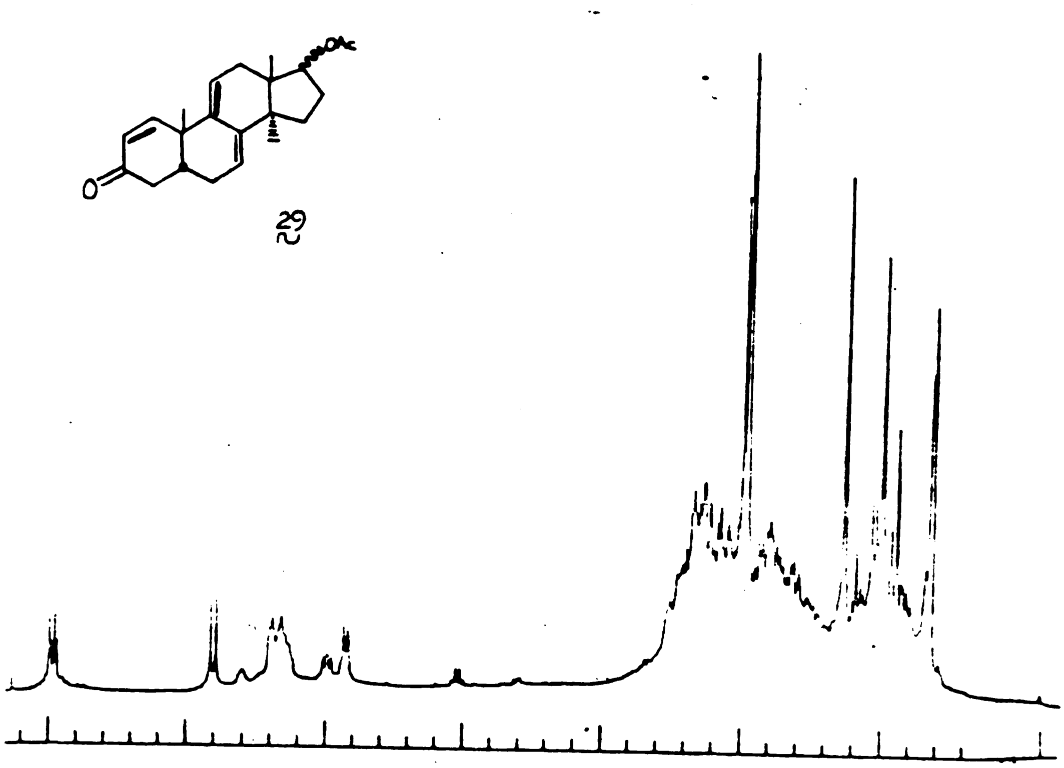
NMR spectrum of 28



Mass spectrum of 28



250 NMR (^1H) of 28



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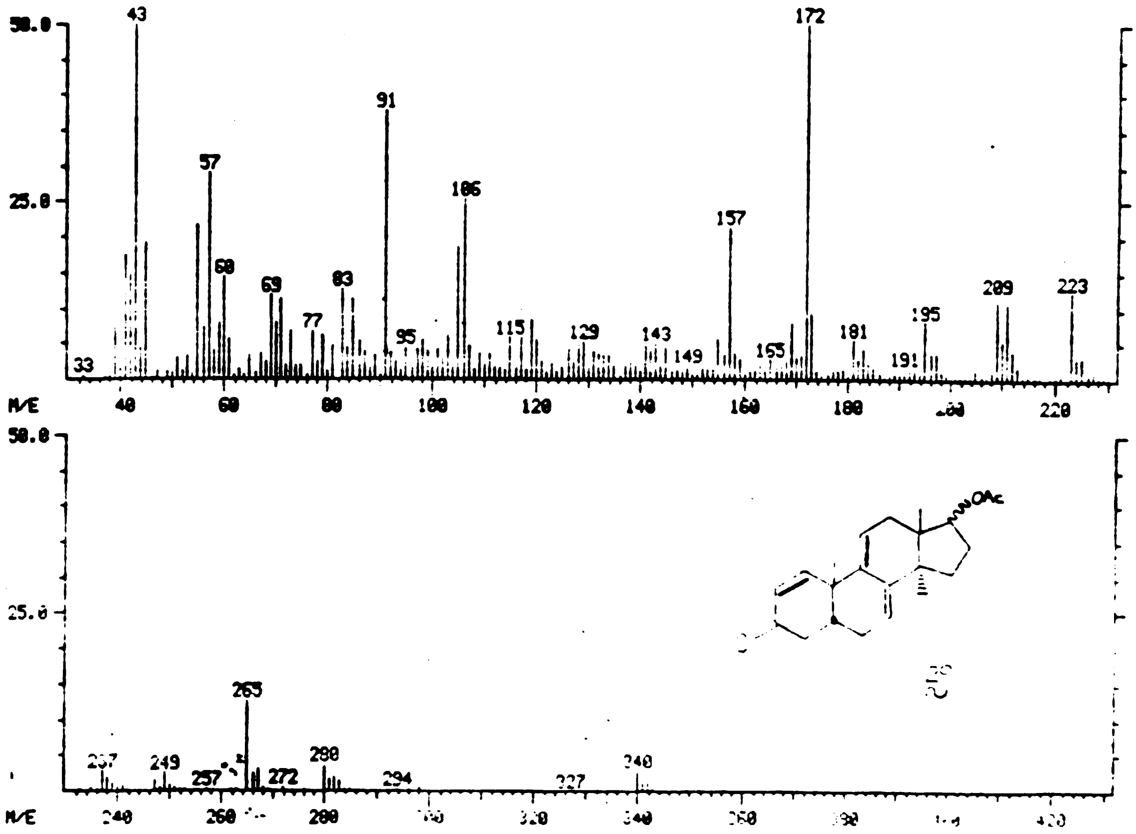
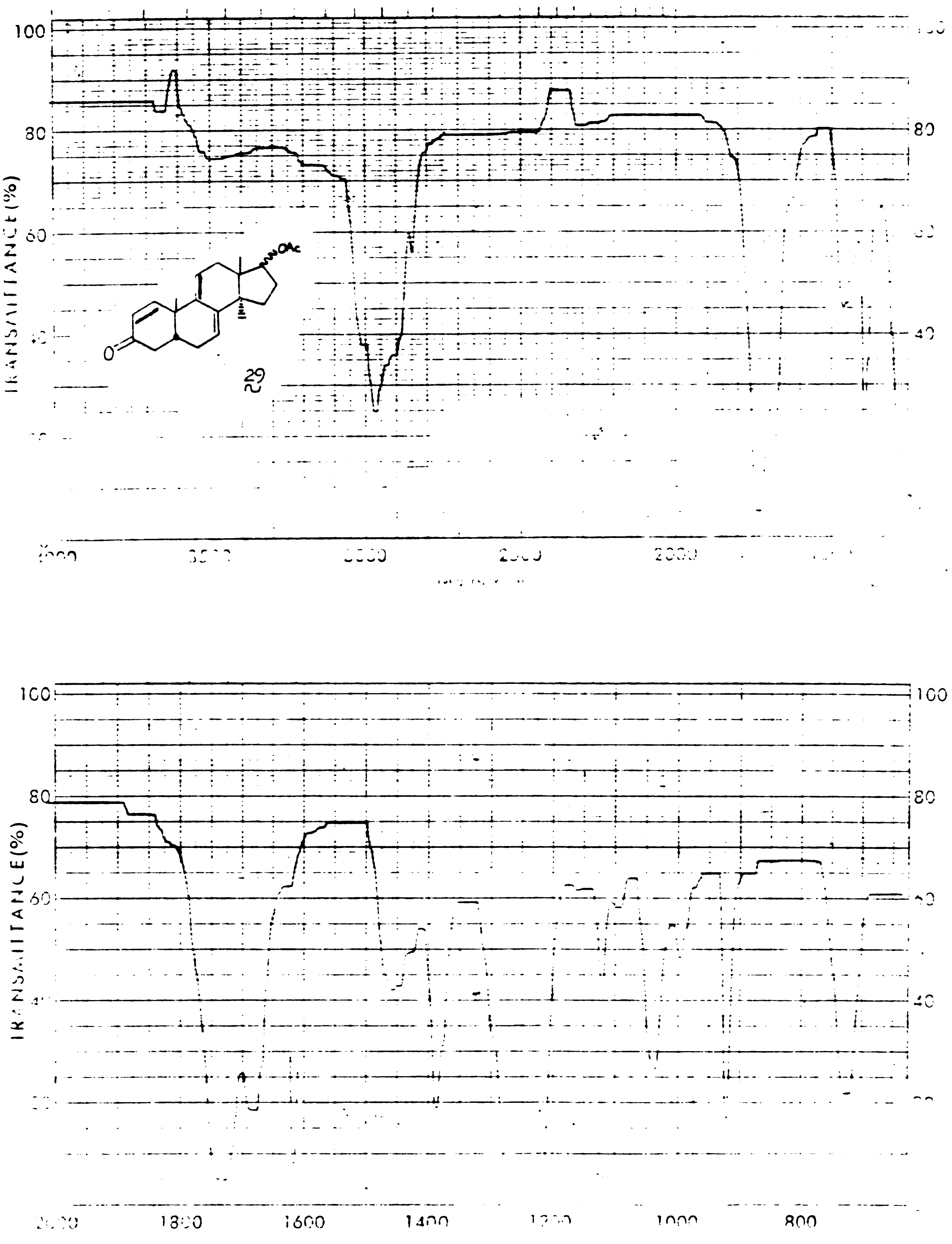


Mass spectrum of 29



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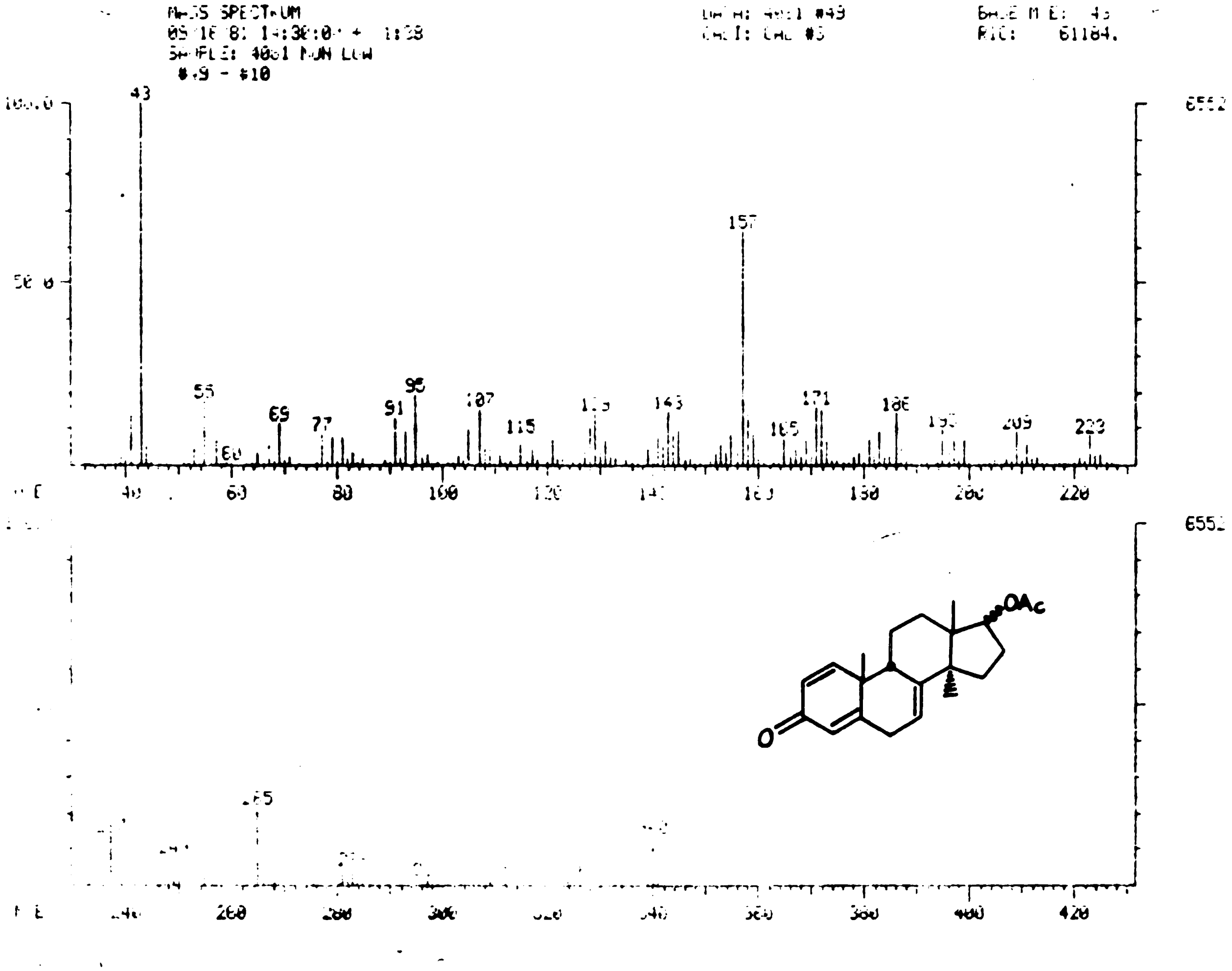

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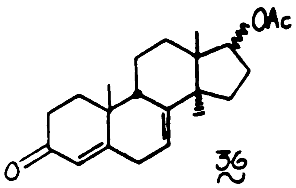

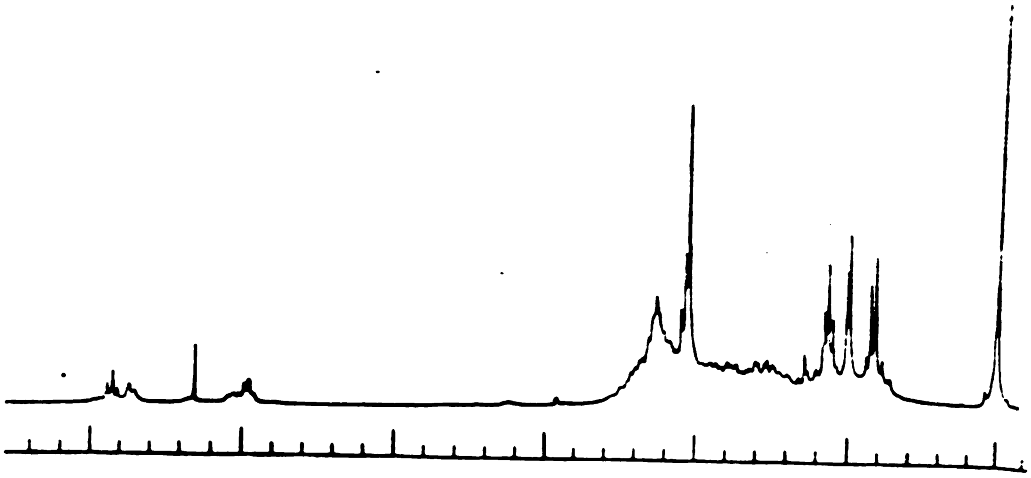

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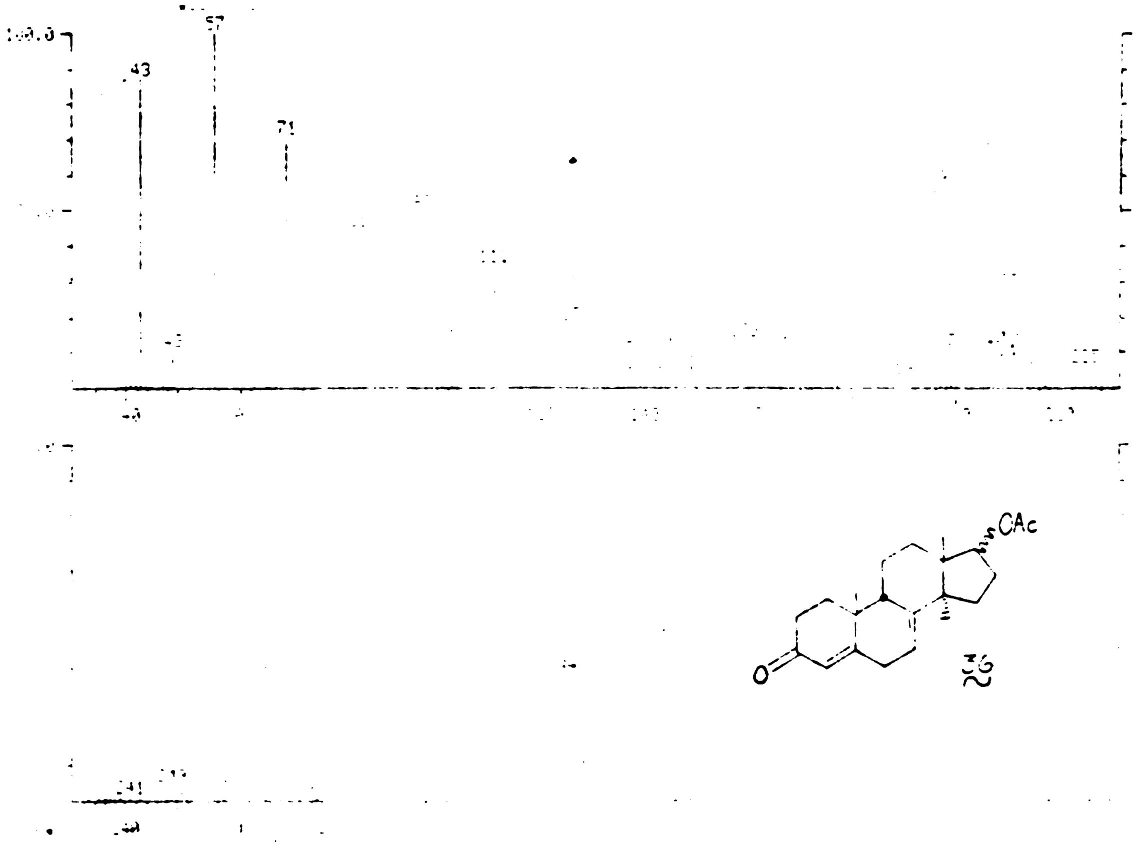

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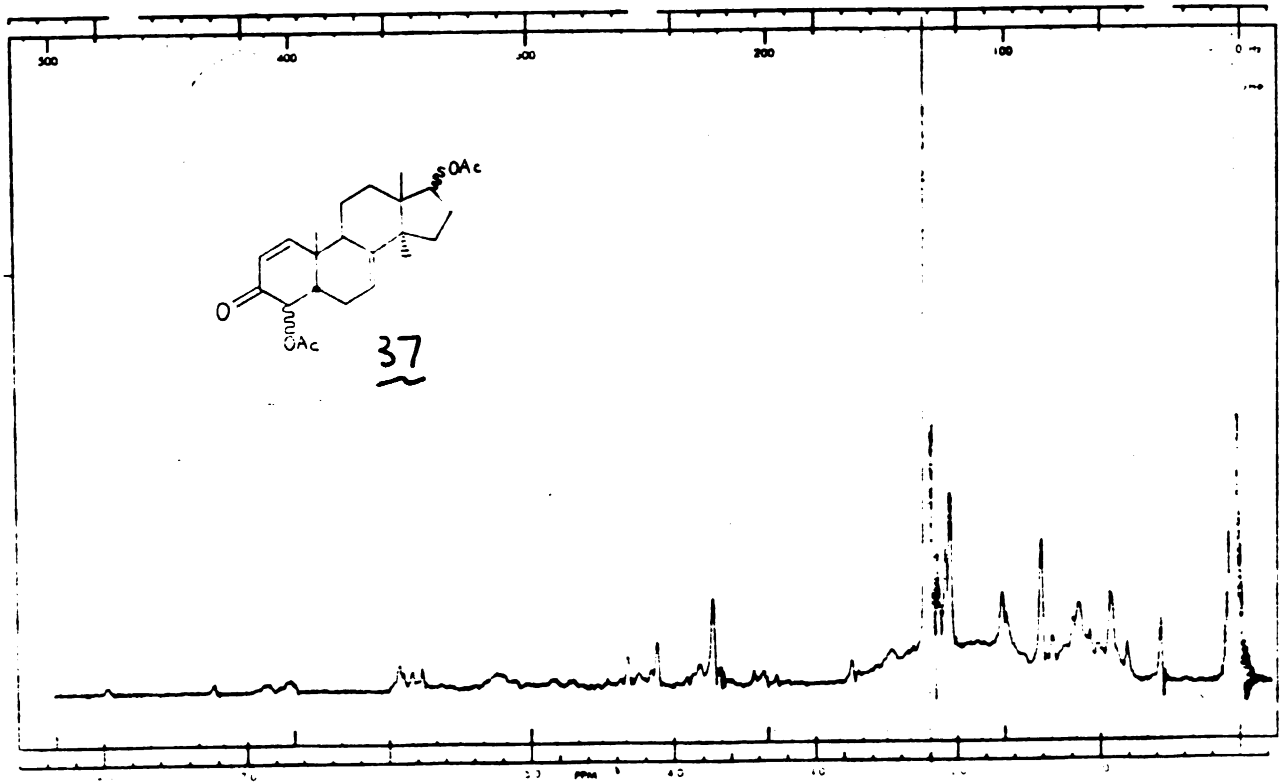

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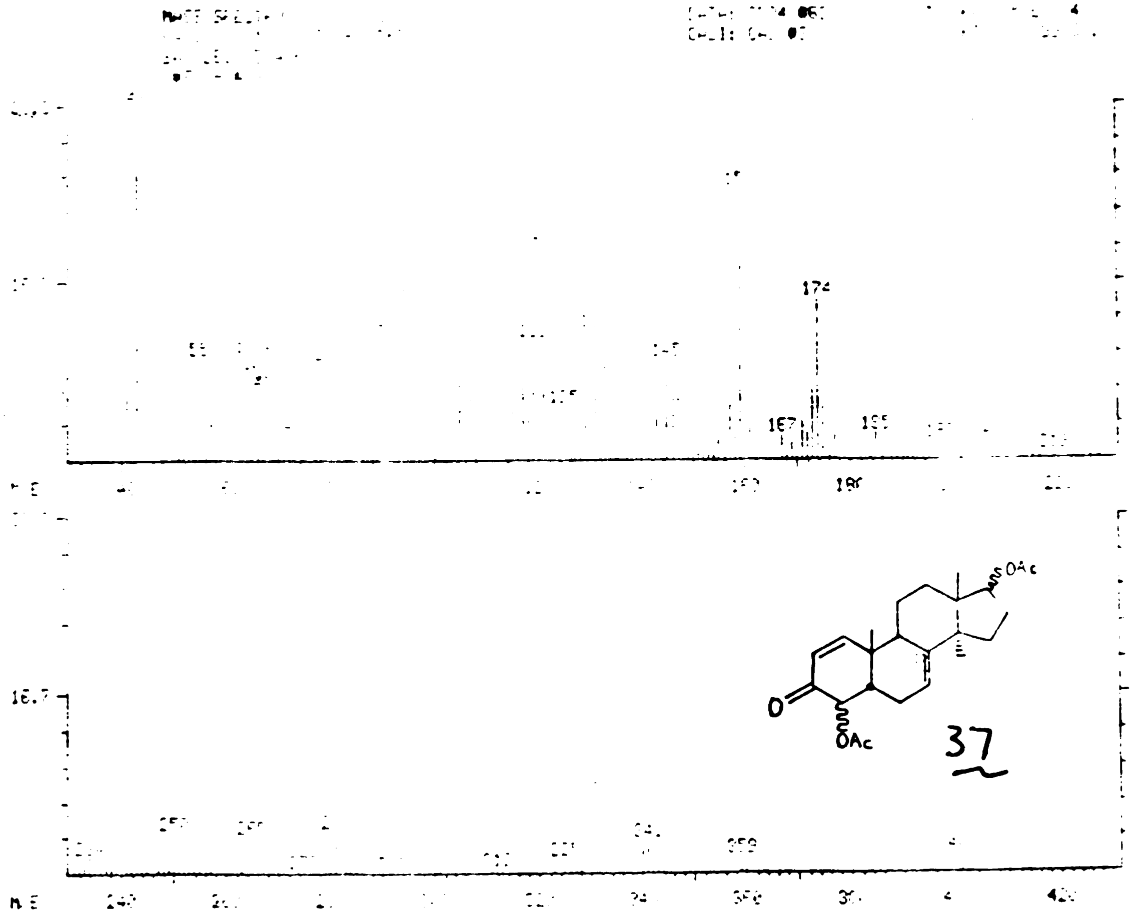

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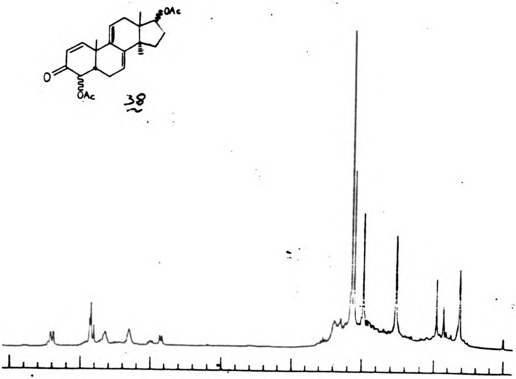

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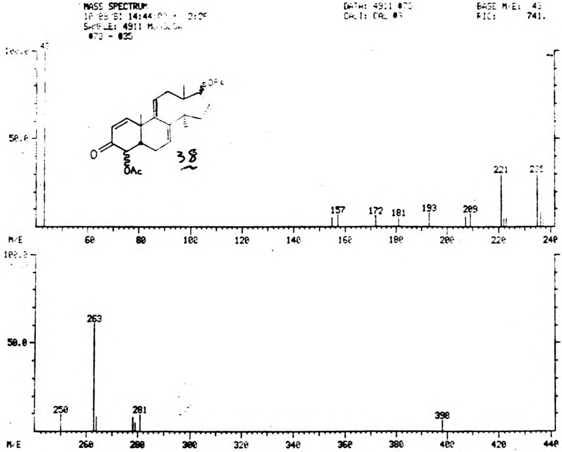

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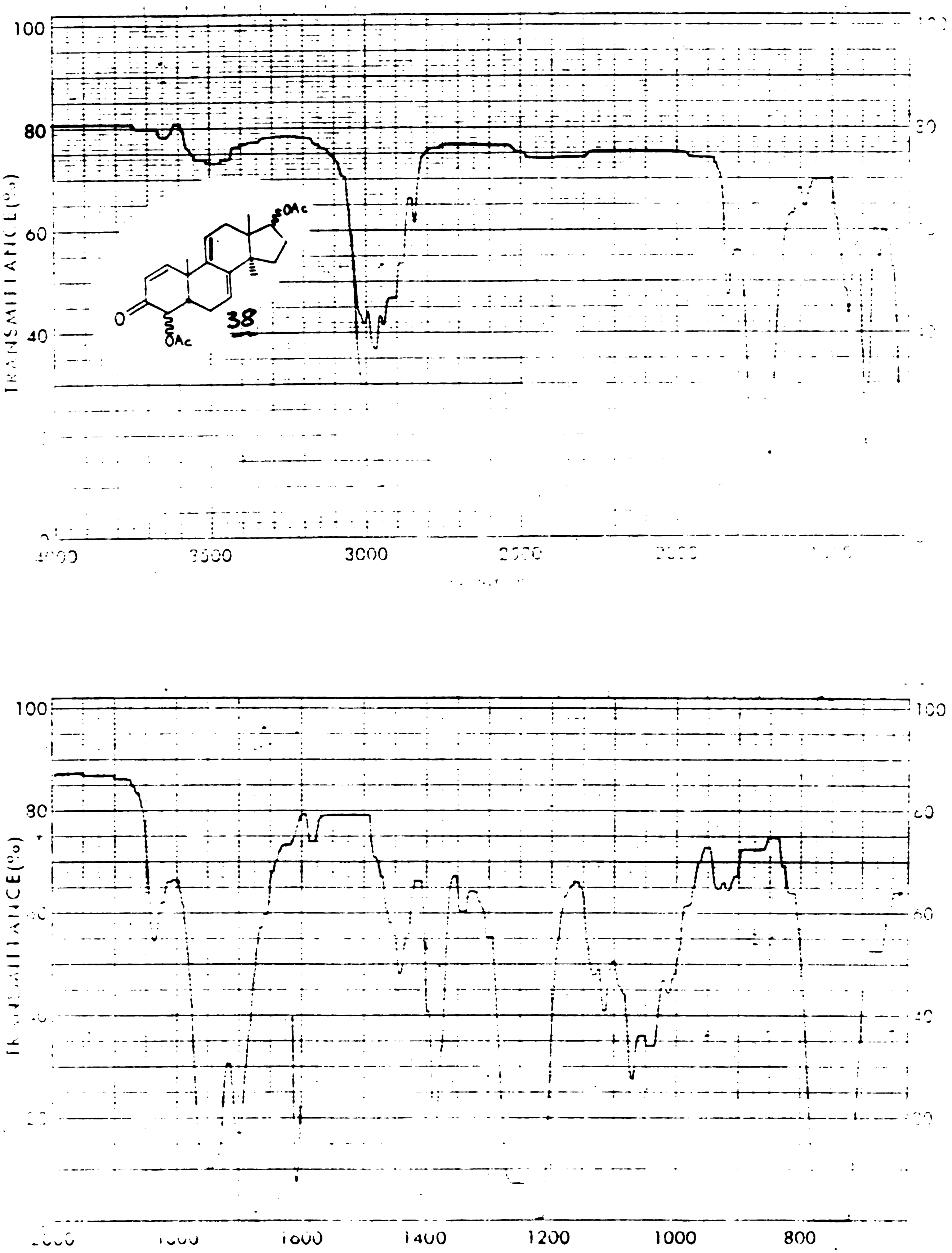

Infrared spectrum of 38