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An approach toward benzo-13-methylphenalene

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AN APPROACH TOWARD BENZO-13-METHYLPHENALENE

by

Carlos W. Alva

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York.

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Abstract

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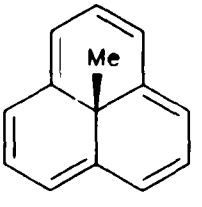
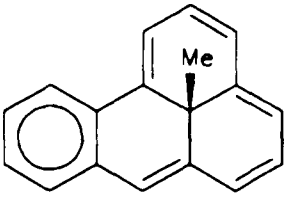
Carlos W. Alva

Advisor: Professor Klaus Grohmann



I



II

Research in the Grohmann group has led to the attempted synthesis of antiaromatic annulenes such as 13-Methylphenalene I and Benzo-13-methylphenalene II. These two compounds present the rigidity that should produce the maximum paratropic effect that is relatively large compared to flexible annulenes. Equally important, they possess a methyl group

located at the center of the polycyclic olefinic chain. This group could be utilized as a marker for observing the expected paramagnetic ring current that is characteristic for antiaromatic systems. The advantage of II over I is the presence of the benzo group as an "electron pool" to stabilize the electron flow around the perimeter; as a result of this effect, II should be relatively more stable than the nonbenzosubstituted counterpart. This thesis covers our approaches toward II beginning with the use of Vanillin as the starting point of this synthetic journey until the final stopping point that is just one double bond away from II itself.

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for his patience, insight, friendliness and willingness to share his scientific knowledge.

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Finally, to Hunter College and specially the Chemistry department.

DEDICATION

I could not have completed this work without the help of those who were always supporting me in one way or another. They shall remain nameless but they should know that this is dedicated to them.

One who has always supported me, through good and bad times is my mother. This is dedicated to her and as well as the others.

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		^1H	^{13}C	IR	UV	MS
Compound	22	219	219	220		
Compound	23	220	221	221		
Compound	31	222	222			
Compound	32	223	223	224		
Compound	35	224		225	225	
Compound	37	226				
Compound	38	226		227		
Compound	39			227		
Compound	46	228				
Compound	74	228	229			
Compound	75	229	230			
Compound	76	230				
Compound	77	231				
Compound	91	231	232			
Compound	92	232				
Compound	95	233	233			
Compound	108	234				
Compound	115	234				
Compound	117	235				
Compound	119	235	236			
Compound	120	236	237			
Compound	121	237				
Compound	124	238		238		
Compound	126	239	239	240		
Compound	130	240		241		
Compound	134	241		242		
Compound	135	242		243		
Compound	140	243	244	244	245	245
Compound	148	246				
Compound	162	246				
Compound	164	247	247	248		
Compound	165	248				
Compound	172	249	249			
Compound	173	250				
Compound	177	250				
Compound	178	251				
Compound	182	251	252	252		
Compound	184	253	253	254		
Compound	185			254		
Compound	186	255				
Compound	191	255				256
Compound	195	257	257 258	259	259	

APPENDIX B

ABBREVIATIONS

Ac	Acetyl
AIBN	2,2'-Azobisisobutyronitrile
DBU	1,8-Diazobicyclo(5.4.0)undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIEA	N,N-Diisopropylethylamine
DIBAL	Diisobutylaluminum hydride
EtOAC	Ethyl acetate
Hex	Hexanes
HOMO	Highest Occupied Molecular Orbital
IMDA	Intramolecular Diels-Alder
IR	Infrared Spectroscopy
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
LUMO	Lowest Unoccupied Molecular Orbital
Ph	Phenyl
PTSA	p-Toluenesulfonic acid
Pyr	Pyridine
MS	Mass Spectroscopy
MsCl	Mesyl chloride
NBS	N-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
TFA	Trifluoroacetic acid
TLC	Thin layer chromatography
TsCl	p-Toluenesulfonyl chloride
UV	Ultraviolet Spectroscopy

CHAPTER 1

1.1.1 INTRODUCTION

The definition of Aromaticity poses a theoretical problem of compelling interest. The electronic structure of benzene presents a puzzle that is still debated. Early stages of valence-bond quantum mechanics, along with modern calculations[1] suggest the Kekulé model as the best description of benzene.[2] That is, the position of the electrons appears to be a blend of two equivalent patterns of alternating double bonds, as proposed by Kekulé in 1872. This is opposed to the picture presenting an entire inmobile π system.[3] These treatments associate the fully occupied π-molecular orbital with the aromatic character. One of these treatments, the Hückel theory has been particularly successful in explaining and predicting the stability of conjugated π systems.

1.1.2 HÜCKEL THEORY

E. Hückel studied the relative stabilities of cyclic conjugated systems and developed what became known as the Hückel molecular orbital (HMO) theory. The principle concept is the approximation that the π electron system can be treated independently from the σ contribution, and is solely responsible for determining the properties of conjugated systems.

Hückel's rule state that cyclic conjugated coplanar polyenes containing (4 n + 2) π electrons are aromatic and those containing (4 n) are antiaromatic.[4] Planar systems possessing 2, 6, 10, 14, 18, . . . π electrons may be expected to be aromatic, bearing a complete paired set of electrons in the degenerate HOMO (closed shell).

When a 4 n π electron system is present, the HOMO is half filled (diradical state, open shell). The degeneracy can be removed by going to a less symmetric structure, where the triplet configuration is no longer a ground state, and as a consequence, the double bonds retain their character presenting no alternation. This is observed for compounds possessing inner bonds which reduce the extent of bond-length alternation or deviation from planarity, i.e. cycloocta[def]fluorene.[5] Another way to distort the molecule

is by the presence of heteroatoms or other functional groups.[6]

Although, it is true that substitution will disturb the symmetry, there is evidence that benzoannelation does not degenerate completely the HOMO, and the Jahn-Teller distortion is minimal. The discussion for benzoannelated annulenes covers this aspect (pages 25-30).

The classical definition of aromaticity states that aromatic compounds possess enhanced thermodynamic stability when compared to the corresponding linear π electron system. By the same definition, antiaromatic compounds are less stable than the linear system. Unfortunately, there is no concrete evidence for conjugated stabilization in aromatic compounds relative to normal or hypothetical substances (i.e. benzene versus cyclohexatriene), the same lack of evidence applies also to the antiaromatic systems. Among the methods for characterizing aromatic and antiaromatic systems, ^{1}H Nuclear Magnetic Resonance (NMR) has been by far the most valuable method.

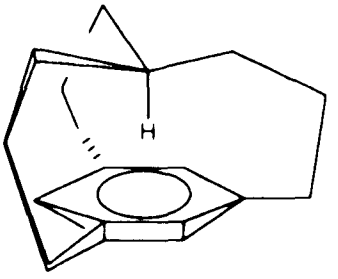
1.1.3 NUCLEAR MAGNETIC RESONANCE

The NMR criterion[7] has been the most accurate and widely used method to characterize a given system as aromatic, non-aromatic or antiaromatic. It is summarized as follows,

An applied perpendicular magnetic field[8] causes the induction of a diamagnetic ring current in a 4 n + 2 system. A consequence of this ring current are strong shielding areas within or above the ring, and strong deshielding areas outside the ring.

A compound which belongs to the group of small strained cyclophanes possessing a methine hydrogen projected toward the center of the aromatic system is now known. The congested in-[$3^{4,10}$][7]metacyclophane <3> has been observed and characterized by Pascal and coworkers.[9]

When <3> is subjected to a magnetic field, the methine hydrogen experiences the diamagnetic anisotropy of the ring. In agreement with the shielding effect, this methine appears at an extremely high field, as a septet at δ -4.03.

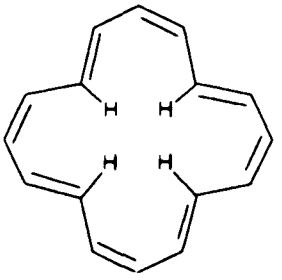


<3>

Figure 1: The diatropic effect of a [6]Annulene

Contrary to the diamagnetic ring current observed and calculated for cyclic 4 n + 2 system, molecules containing 4 n electrons exhibit a magnetic behavior opposite to 4 n + 2 systems: The model of a paramagnetic ring current has been proposed to explain the opposite shielding effects. Protons within a 4 n system will be highly deshielded while protons outside will be shielded.

An example where this deshielding is seen is [16]annulene <18>. The protons located inside the π cavity appear at δ 10.4, a position that indicates deshielding compared to cyclohexadiene (δ 5.8-5.9).



<18>

Figure 2: The paratropic effect of a [16]Annulene

Again, this ring current is just a model, as it is still unclear[10] why 4 n molecules exhibiting low field chemical shifts have strong conjugative stabilization. This NMR analysis is not equivalent to the classical energetic definitions of aromaticity and antiaromaticity.[11]

1.1.4 THE IMPORTANCE OF PLANARITY

According to Hückel's rule, planarity is one of the requirements for either an aromatic or an antiaromatic system. Maximum π overlap is achieved if all π molecular orbitals are coplanar but slight distortion from it still allows conjugation. Sometimes this planarity must be at the expense of other constraints. This is typical behavior observed for small annulenes which present large non-bonded interactions and are prevented from becoming planar. As the size of the annulene increases, the internal steric demands decrease and in certain cases, the rotational barrier is lowered. Larger annulenes are allowed to be planar. As a result of this lowering process, conformational mobility and fast bond shift are observed.[12]

1.1.5 SYMMETRY REQUIREMENT

The symmetry of the molecule is reflected in the degeneracy of the atomic orbitals.[13] For a typical conjugated π system such as benzene, the HOMO is degenerate. In general, a 4 n + 2 arrangement possesses a full set of paired electrons at the HOMO level. For a 4 n, the HOMO accommodates a set of unpaired electrons. If the compound is highly symmetric (i.e. I), this HOMO stays degenerate predicting unlimited paramagnetism. That is, a triplet or diradical configuration for the ground state. If the system is rigid as a result of inner bonding, a substantial decrease in bond-length alternation, and deviation from planarity can be observed as in the pyracylene system.[14] On the other hand, a lack of symmetry (i.e. II) removes the degeneracy of the HOMO. This separation is known as the Jahn-Teller effect which appears to be responsible for the instability of the antiaromatic system. Now the HOMO possesses a paired set of electrons predicting a finite paramagnetism. A consequence of this is a small HOMO-LUMO gap.

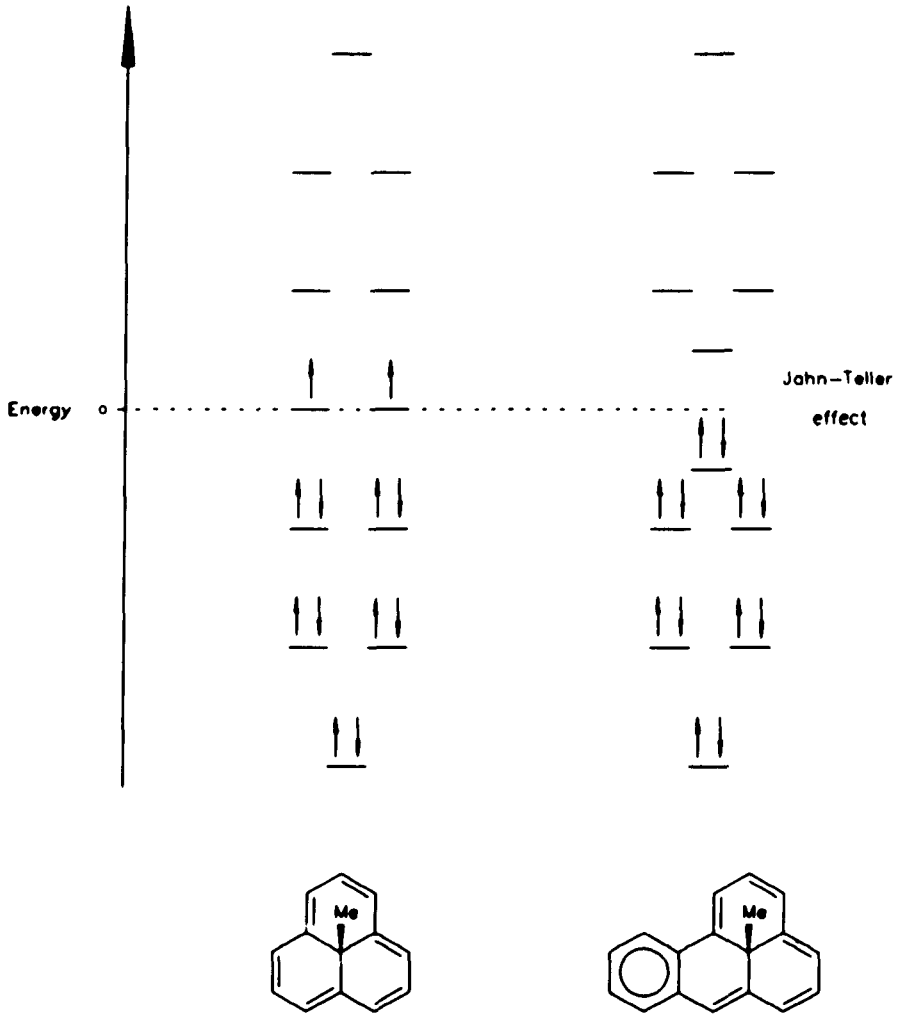
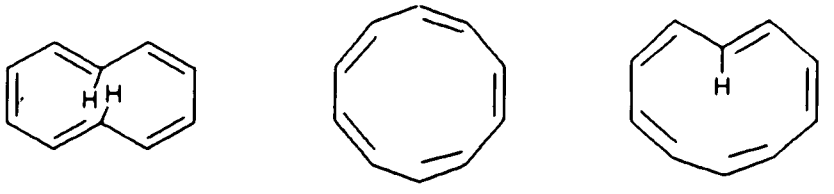


Figure 3: Approximate energy levels for I and II

At this point, it is appropiate to discuss a selected number of annulenes considering only nearly or completely planar and highly symmetric parent systems. Compounds that do not fall into this category are not discussed here.[15]

1.2.1 SELECTED ANNULENES

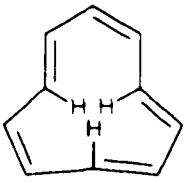
[10]annulene, the next higher homologue of benzene (n 2), can exist as several geometrical isomers. The all-cis <11> and mono-trans <12> isomers have been detected and characterized as non-planar and non-aromatic.[16] 1,5-ditrans[10]annulene <10> having two internal hydrogens has never been observed.



<10> <11> <12>

Figure 4: The [10]Annulenes

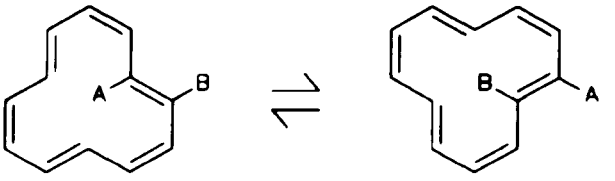
Isomer <13>, 1,3,7-trans[10]annulene, is also unknown apparently for the same reasons as for isomer <10>.



<1.3>

Figure 5: Another [10]Annulene

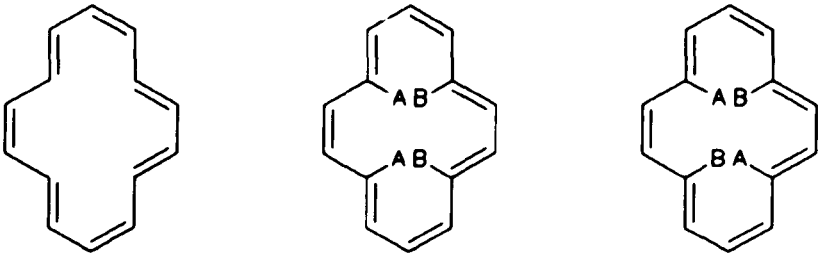
[12]annulene <14> is the smallest 4 n annulene which contains internal hydrogens in a reasonable planar arrangement. <14> has been prepared at -100 °C and is stable at low temperatures only. Due to proton interchange (rotation of the trans-double bonds), its ^1H NMR spectrum at -80 °C consists of two signals of equal intensity at δ 6.9 and 6.0.[17] At -170 °C, the lowest temperature possible, the spectrum now showed a 3 H signal at δ 7.93 ($H_{internal}$) and 9 H signal at δ 5.88 ($H_{external}$). An overcrowding of the inner hydrogens prevent complete planarity lowering the activation energy needed for the interconversion. A non-rigid peripheral allows conformational mobility. The quite large deviation from planarity explains the small NMR shift observed for the inner protons. Nonetheless, it indicates that <14> sustains a paramagnetic ring current.[18]



<14>

Figure 6: The isomerism of <14>

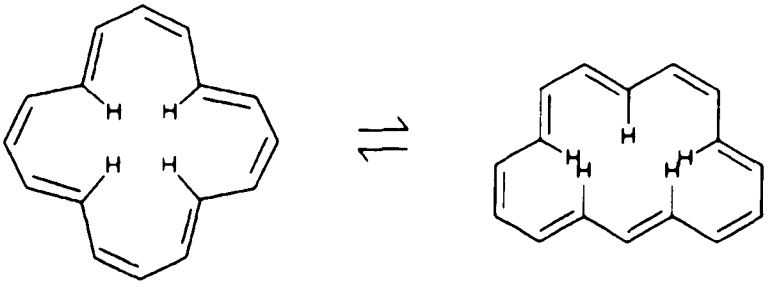
The [14]annulene[19] <15> exists as the two conformational isomers <16> and <17>. Both isomers possess the hydrogens labeled H_A in one plane while H_B are in another plane. At ≈40 °C, they show a singlet at δ 5.58 and 6.07, respectively. At -160 °C, <16> suggest the existence of a ring current which deshields the outer protons (δ 7.6) and shields the inner protons (δ 0) as expected from a 4 n + 2 π system.



<15> <16> <17>

Figure 7: <15> and its two conformers

According to Hückel's rule, [16]annulene[20] is predicted to be antiaromatic. Due to a low barrier of internal rotation, the isomers <18> and <19> are in equilibrium. At ambient temperature, the ^{1}H NMR shows a single peak at δ 6.7. At -120 °C, <18> is present showing the outside protons at high field (12 H, δ 5.4) and the inside protons at low field (4 H, δ 10.4). This is the opposite behavior observed for an aromatic annulene such as <16>.



<18> <19>

Figure 8: A [16]Annulene

The [18]annulene[21] <20> is an example of a system in which the inner protons do not interact with each other. The ^{1}H NMR spectrum of <20> is temperature dependent. At 110 °C, the spectrum shows a single peak (δ ≈5) due to proton interchange caused by rotation. At -60 °C, the spectrum clearly reflects the diamagnetic anisotropy present as two kind of hydrogens are observed: the outer (δ ≈9.5) and the inner (δ -3).

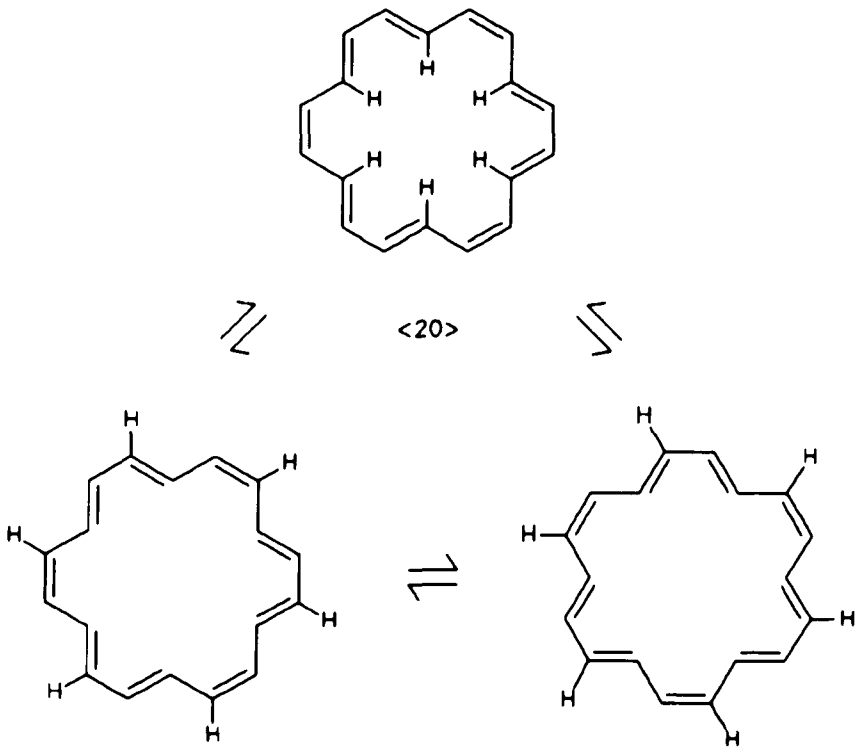


Figure 9: A very flexible [18]Annulene

The preceding annulenes showed the following characteristics:

(a) the smaller the annulene, the greater the interaction between the internal hydrogens;

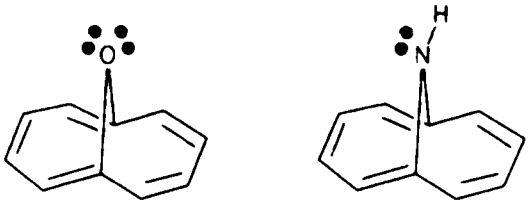
(b) the larger the cyclic polyene, the greater conformational mobility interchanging outer and inner hydrogens;

(c) when the annulene skeleton was not rigid, the ^1H NMR time scale was inadequate to differentiate between internal and external hydrogen atoms. Low temperatures were required to slow down the hydrogen interconversion; and

(d) Hückel's rule is correctly predicting the properties of the annulenes.

One way of removing the van der Waals interaction between the inner protons involves the introduction of carbon or heteroatom bridges. The advantages are the removal of the van der Waals repulsion together with a greater ridigity preventing conformation mobility. On the other hand, the bridge should introduce only a minor perturbation. Good examples[22] are the oxygen and nitrogen bridged annulenes <21> and <22>. They have been isolated and character-

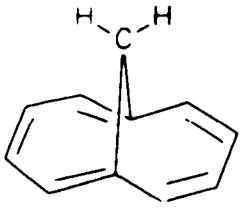
ized as aromatic molecules in both physical and chemical senses.



<21> <22>

Figure 10: Heteroatom bridging

An example of an sp^3 carbon bearing two protons is the annulene <23>. This 1,6-methano[10]annulene has been synthesized[23] by Vogel and Roth. In this compound, the sp^3 carbon takes the place of the former inner protons, and it is the one that feels the electronic effect of the π system. Although the bridge slightly distorts the skeleton from planarity, sufficient π overlap remains to characterize it as an aromatic 10-membered ring. The outer protons appear at δ 6.9-7.3. The hydrogens on the methylene bridge appear as a singlet at δ -0.5.



<23>

Figure 11: Methylene bridging

Annulenes containing the anthracene skeleton and higher annulenes, bridged by methylene, heteroatoms, and other functionalities are known. These latter systems present the possibility of geometrical isomerism, in which the bridges can be syn or anti to each others.[24] This complication is not present in the other examples.

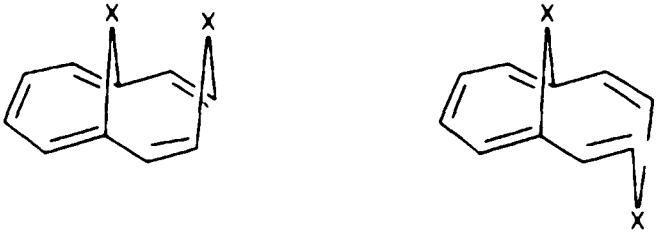
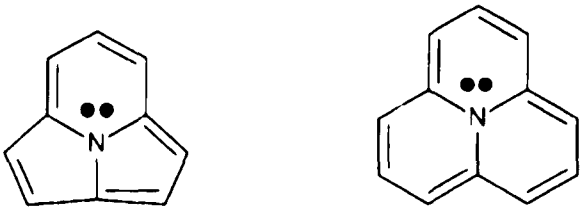


Figure 12: Syn/Anti possibilities

The cycl[3,2,2]azine <24> and the cycl[3,3,3]azine <25> are annulenes[25] consisting of a cyclic π electron system bridged by a nitrogen atom.[26] <24>, a 4 n + 2 π system, is a

stable compound whose ^1H NMR indicates the presence of a diamagnetic ring current (δ ≈7.6). Compound <25>, a 4 n π system, is more reactive possessing a paramagnetic ring current (δ 2-4).



<24> <25>

Figure 13: Bridging by a central nitrogen

However, compounds <24> and <25> show extensive conjugation between the nitrogen lone pair and the π system suggesting that the model of simple N-bridged annulenes is not quite accurate.[27] The lone pair can be delocalized in such a way that several resonance structures are possible. This delocalization is also documented in the inability of the central nitrogen of <24> and <25> to undergo quaternization. Only two of the resonance structures corresponding to compound <25> are shown next,

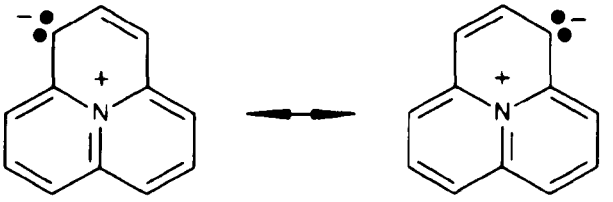
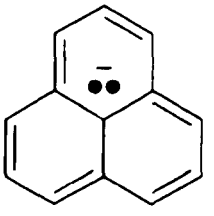


Figure 14: Delocalization of the lone pair of <25>

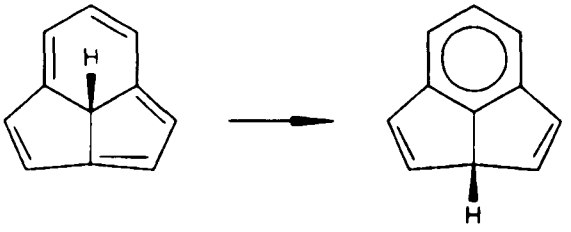
<25> can be considered isoelectronic to the nonalternant phenalenyl anion <26>. The properties of <25> can be rationalized by this anion which is a complete different electronic system.[28] The conjugation of the peripheral chain ring is perturbed and the Hückel approximation can not be applied anymore.



<26>

Figure 15: The isoelectronic <26>

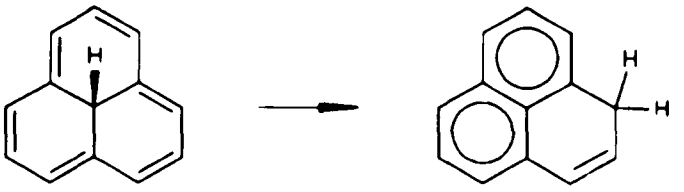
The annulene <27> possesses a carbon bearing a proton instead of the nitrogen whereas compound <27> is the 4 n + 2 analogue of <13>. One of the possible reasons for the failure to isolate compound <27> could be a facile [1,5]-sigmatropic rearrangements leading to the known <28>.



<27> <28>

Figure 16: A Methine bridge

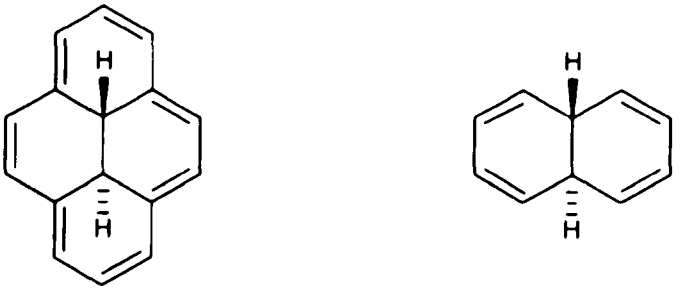
As a result of less angle strain, the phenalene <29> should be relatively more stable than <27>. This compound has not been isolated and attempts to make it resulted in its isomer <30>. Compound <30> seems to be the result of a [1,5] sigmatropic shift that is thermally allowed in <29>. By turning into a naphthalene unit, <29> became a more stable aromatic system.



<29> <30>

Figure 17: A [1,5]sigmatropic shift

The [14]annulene[29] <31> has a geometry similar to <29>. The extra 2 electrons make a major difference, as a 4 n + 2 perimeter is formed. The methine protons are located inside the π cavity, and as predicted by Hückel's rule, this is a stable aromatic annulene. The shielding of the tertiary methine protons (δ -5.49) indicates the presence of a strong diamagnetic ring current, as compared to the tertiary bis-allylic protons[30] in the reference compound <32> (δ 2.8).



<31> <32>

Figure 18: A [14]Annulene and its reference system <32>

One of the problems associated with bridging by heteroatoms, such as in the cyclazines series, is the electronic perturbation imposed by the interaction of the π system with the central nitrogen lone pair. A complication inherent in the bridging by methine is the lability of the methine proton, as observed for systems <27> and <29>.

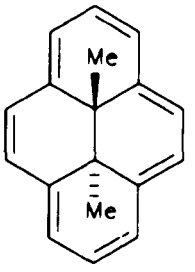
One way of avoiding these problems is bridging by an sp^3 carbon bearing a methyl group. This approach has been taken by several investigators, notably Boekelheide et al.[29,32,33]

Rees et al. have reported the synthesis[31] of <33>, a tricyclic system containing 10 π electrons (4 n + 2). The ^1H NMR spectrum of <33> shows a methyl singlet at δ -1.67, illustrating the presence of a diamagnetic ring current, and aromatic ring protons at δ 7.4-8.2. This annulene also exhibits a [1,5]sigmatropic shift of the methyl group, rearranging to <34> upon heating in solution. The activation energy was found to be 32.7(±1) kcal mol^{-1}. This ease of migration is presumably due to the driving force caused by the formation of a benzene ring. Even so, <33> is an Hückel aromatic system.

<33> <34>

Figure 19: Another [1,5] sigmatropic shift

The bridged [14]Annulene, <35>, synthesized by Boekelheide and coworkers,[32] was the first example of an aromatic molecule having substituents, other than hydrogens, within the cavity of the π electron system. Its methyl groups show an NMR signal at δ -4.23, while the ring protons lie at δ 8-9.7. This clearly demonstrates a strong induced diamagnetic ring current. The X-ray analysis indicated that the maximum deviation of a perimeter atom from a mean plane was no more than 0.027 Å.



<35>

Figure 20: The planar annulene <35>

Moreover, upon 2 electrons reduction[33] of <35>, the system changes from 14 (4 n + 2) to 16 π electrons (4 n). The dianion obtained exhibits a methyl proton signal at δ 21, a downfield shift of 25 ppm, in spite of the negative charges which cause considerable shielding of the protons. The ring protons appear at δ 1-3.6. These results illustrate the importance of planarity and rigidity in achieving antiaromaticity, and an accompanying increase in stability of the system. Similar dianion/dication formation appears to be the most straightforward way of experimentally verifying Hückel's rule.[34]

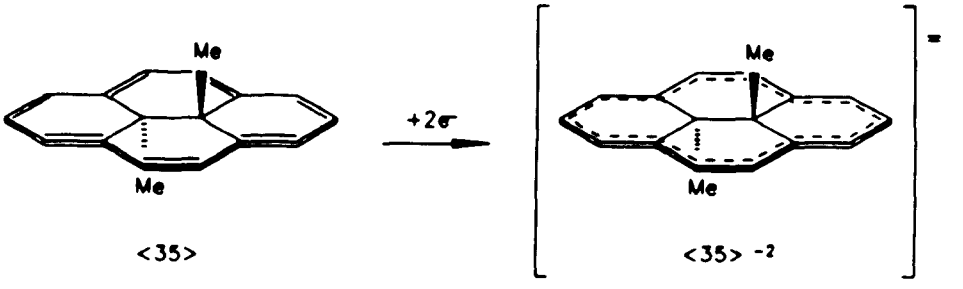
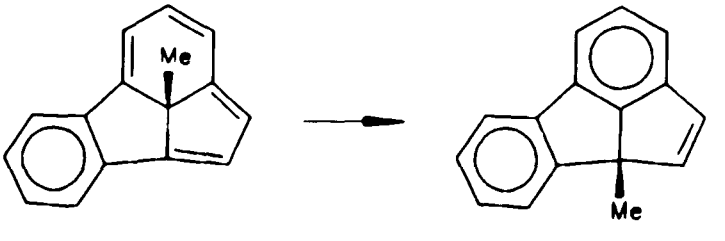


Figure 21: The importance of planarity

Rees has also reported the benzoderivative[35] <36>. The methyl group of <36> appears at δ -0.79, consistent with the existence of a diamagnetic ring current, the peripheral protons appear at δ 7.30-7.58, and the aromatic protons at δ 7.67-8.40. An analysis of <36> indicates that it possesses about 67% of the diamagnetic ring current of the parent compound whose methyl signal appears at δ -1.67. <36> exhibits a [1,5]methyl shift upon heating.

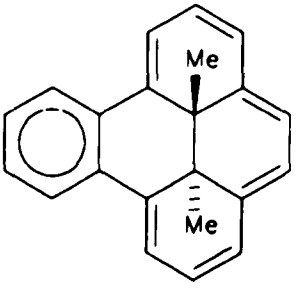


<36> <37>

Figure 22: A Benzannelated <33>

In the search to understand the effect of benzoannelation, Mitchell[36] has studied systems similar to <38>. These compounds have up to two benzo groups attached to the dihydropyrene unit. The following observations[37] have been extracted from his work and applied to the present discussion.

Mitchell and coworkers[38] synthesized the benzoannelated analog of <35>. This molecule, <38>, showed a strong diamagnetic ring current, as implied by an internal methyl signal at δ -1.85, and external proton resonances at δ 6.4-9. The position of the methyl protons indicates that <38> sustains about 54% of the ring current of <35>.



<38>

Figure 23: A Benzannelated <35>

Annulene <35> is known to be planar and fully delocalized, its resonance structures are clear. This compound

possesses two equivalent Kekulé structures. The bridging carbon maintains its sp^3 character and the peripheral bonding changes between a single and double bond.

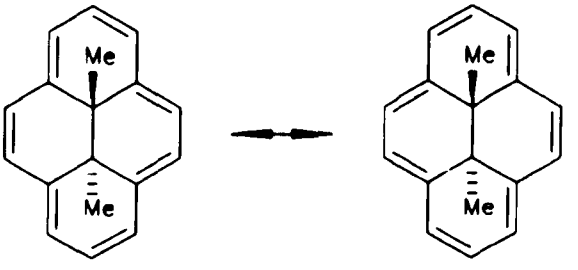
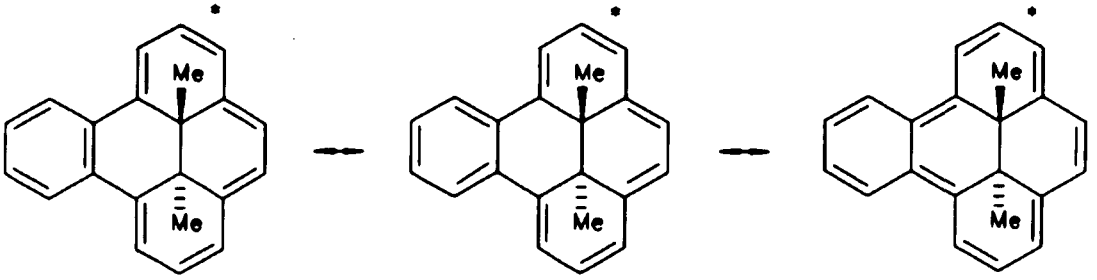


Figure 24: The Kekulé structures of <35>

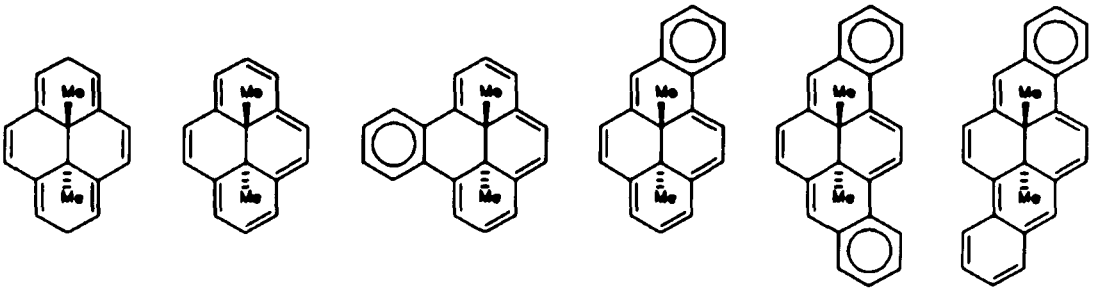
Compound <38> has three non-equivalent Kekulé structures. The bond indicated by the asterisk retains its double bond character in two out of the three structures. In <38c>, the benzene ring becomes a o-quinonoid, increasing the total number of π electrons by four. The overall benzannelation partially localizes the macroring. The geometry of the annulene together with the conjugated system influences the final ring current.



<38a> <38b> <38c>

Figure 25: The Kekulé structures of <38>

Lastly, Mitchell[39] and Thompson et al. performed simple π-SCF bond order calculation and compared them to the NMR results, indicating that these results suggest that the bond delocalization caused by aromatic ring annelation is the principal determinant of the strength of the macrocyclic ring current observed.



<42> <35> <38> <39> <40> <41>

Compound	<35>	<38>	<39>	<40>	<41>
δ (Me)	-4.25	-1.85	-1.60	0.02	-3.58
0.97 - δ (Me)	5.22	2.82	2.57	0.95	4.55
% Ring Current	100	54	49	18	87

Table I: Ring current of selected benzoannulenes The position for the methyl group of <35> has been calculated using the parent compound <42> as the reference (δ 0.97).

The ring current is estimated by

$$\% \text{ Ring Current} = \frac{0.97 - \delta \langle XX \rangle}{5.22}$$

Table I illustrates that the position of the methyl group remains at a higher field than the internal protons of reference compound <42>. This shielding effect is maintained even after up to two benzo groups have been introduced in the molecule. This is an indication that the planarity for conjugation is still maintained even after going to a less symmetric structure. It has been suggested that the Jahn-Teller effect probably forces the ring current to become finite, but does not destroy the anisotropism of the annulenes.

Thus, as the previous discussion has shown, that the benzannelation produces a more stable although less symmetrical system without destroying the anisotropy of the whole, as reflected in the NMR position of the methyl groups.

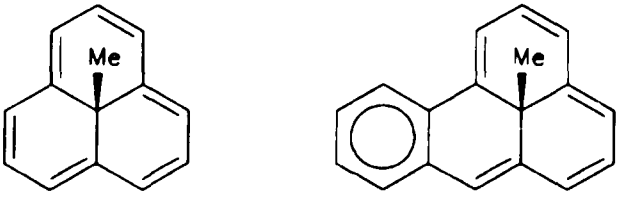
Compound	<33>	<36>	[12]Annulenes	<35>	<38>	$<35>^{-2}$
δ (Me)	-1.67	-0.79		-4.23	-1.85	21
Hückel's type	4 n + 2			4 n + 2		4 n
π electrons	10	10		14	14	16

Table II: The effect of the ring current on the Methyl chemical shift

Table II depicts some of the known annulenes and the NMR position of the methyl group as a result of the ring current. The gap corresponds to the set of unknown [12]annulenes.

1.2.2 THE [12]ANNULENES

One of the goals associated with the Grohmann research group is the synthesis of the two missing 4 n π electrons systems, I and II.



I II

Figure 26: The [12]Annulenes I and II

13-Methylphenalene I is the ideal molecule for the study of a small and highly symmetric planar [12]annulene, a long sought compound.[40] It possesses a rigid structure which should show the maximum ring current effect.[41] The presence of the methyl group attached to the central sp^3 carbon should avoid the problems associated with a highly labile proton or the electronic effects produced by a heteroatom. In addition, it is a sensitive marker for studying the paratropic behavior associated with the 4 n system while introducing only a minor perturbation. I has been observed[42] in our laboratory showing a strong singlet at 35.5 ppm downfield from TMS, but has not been isolated.

The ring current, in the 4 n + 2 π electron systems shown before, is decreased by the attachment of a benzene ring. However, the thermal stability is increased. So far, no observation has been reported for benzo 4 n systems.

The benzannelation of I is only possible at one position.

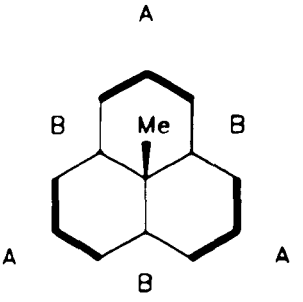
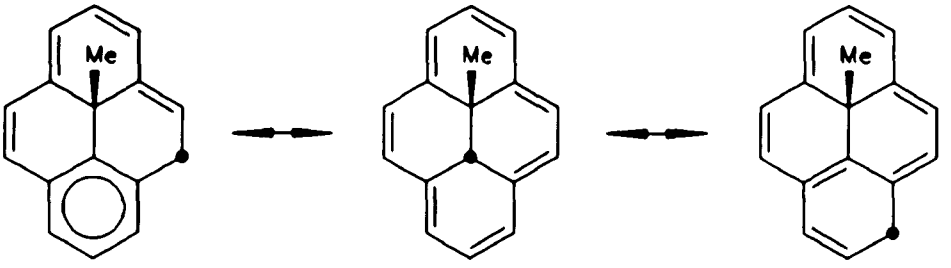


Figure 27: Benzannulation of I

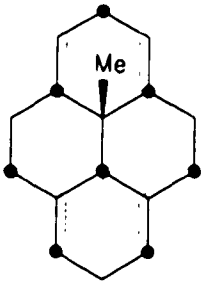
Benzannelation at any bond labeled A produces exclusively II. Substitution at side B gives structures similar to <45>. These structures posses a meta bridged benzene which does not allow throughout conjugation. The carbon marked by the dot indicates the position which can not participate in the π system conjugation. Contributions by the benzene is shown in <46>/<47>.



45 46 47

Figure 28: Improper benzannulation of I

Structure <48> shows a total of eight of these non-participating positions. It is obvious that the only effect obtained from benzannelation at side B is the disruption of the 12 π electron system.



48

Figure 29: Non-participant positions

The resonance of II shows three Kekulé structures. These structures change the peripheral bonds between a single and double bonds. Isomers B and C increase the electrons by four without further perturbation of the system.

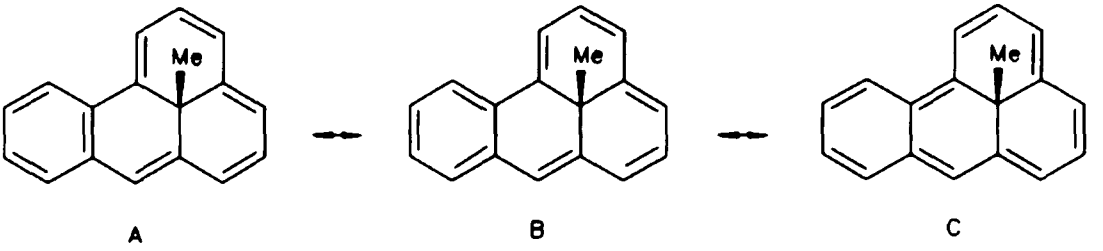


Figure 30: The Kekulé structures of II

The structure assigned to compound II appears to be the molecule of choice to investigate a small rigid [12]annulene along with the effect of benzoannulation in a 4 n π electron system.

1.2.3 THE IMPORTANCE OF II

The synthesis of II will open several areas of theoretical as well as experimental value related to organic, physical and biological sciences.

The organic facet is the potential for synthetic routes for unknown annulenes. This is discussed in section 2.7.0.

The physical aspect corresponds to:

(a) studies of the ^{1}H and ^{13}C NMR will provide information about the planarity and the paramagnetic ring current. Low temperature measurements should reveal possible rapid bond shifts,

(b) Electron Spin Resonance studies,

(c) If crystalline, the X-ray structure should provide the most accurate data about planarity, bond length, etc,

(d) electron transfer and oxidation reactions, as a relatively more stable system will be formed: a 10 or 14 π electrons or aromatic.

Finally, the biological importance of II is still uncertain as little is known yet, but the following discussion should outline the potential behind II.

Several hypotheses try to relate the carcinogenic activity with the aromatic characteristic of known carcinogens.

One of these hypotheses[43] relates the π electron density distribution suggesting the existence of two reactive centers: the K- and the L-regions.

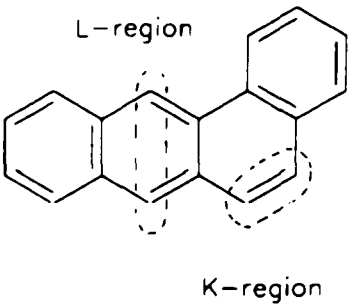


Figure 31: Aromatic reactive centers

The K-region is the bond which has the greatest double bond character, where low bond localization energies appear to be a characteristic for the more active carcinogens. By definition, the L-region is the area which exhibits proper-

ties similar to the 9 and 10 positions of anthracene. A reactive[44] K-region and an unreactive[45] L-region are associated with higher carcinogenic activity.

In an antiaromatic system, the respective K- and L-region should present a complete different picture, as it possesses a paratropic current opposed to the diatropic current associated to aromatic compounds.

Another hypothesis for cancer activity proposes the insertion of the carcinogen between pairs of DNA. This has been derived from studies of acridine dye-DNA complexes.[46] The interaction with DNA is intimately related to the size and substitution of the hydrocarbon. Studies showed that an alkyl group can substantially block ring metabolism redirecting or enhancing the carcinogenic activity.[47]

The possibility of insertion of an antiaromatic compound such as II, between DNA pairs would be interesting. Aromatic systems are known to be planar where insertion appears to be a logical outcome, but nothing is known about a methyl group perpendicular to the plane of the inserting compound.

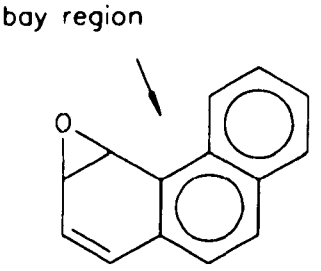


Figure 32: A bay region epoxide

Substitutions on the benzo-rings appear to influence the metabolic formation of "bay region" epoxides of non-K-region dihydrodiols.

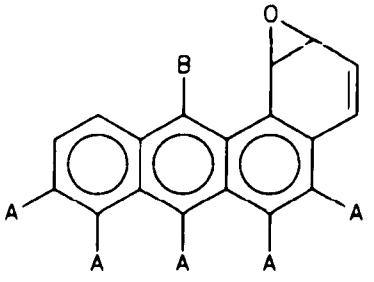


Figure 33: Arene oxides

Studies of arene oxides[48] showed that, when compared to benzo[a]anthracene, substitution at the positions A tend to enhance the epoxide/diol formation, whereas substitution elsewhere in the molecule appear to enhance metabolism through inhibition of other routes of metabolism. Substitution at the position B should block metabolism at the K-

region, distorting the planarity and favoring the formation of a carbonium ion at the benzylic position due to electronic stabilization. This is known for compounds with the substitution coplanar to the system, but nothing is known for compounds with a perpendicular group (i.e. the angular methyl of II).

In general, the biological studies of II and its higher homologues should help toward a better understanding of the relationship of cancer associated to π electron density distribution along with the ring current, DNA insertion, and angular substitution as well.

CHAPTER 2

2.1.0 SYNTHETIC APPROACH

The route to II is based upon an elegant synthesis of the quassinoid[1] skeleton.

D-deoxyquassinoid, a precursor of Klaineone[2], has been extensively studied by Kametani[3] and coworkers. They investigated the thermolysis of benzocyclobutenes[4] and have reported the stereoselective construction of this (d)-deoxyquassinoid, by an intramolecular Diels-Alder (IMDA) cycloaddition of an o-quinodimethane.[5] This is illustrated in figure 1.

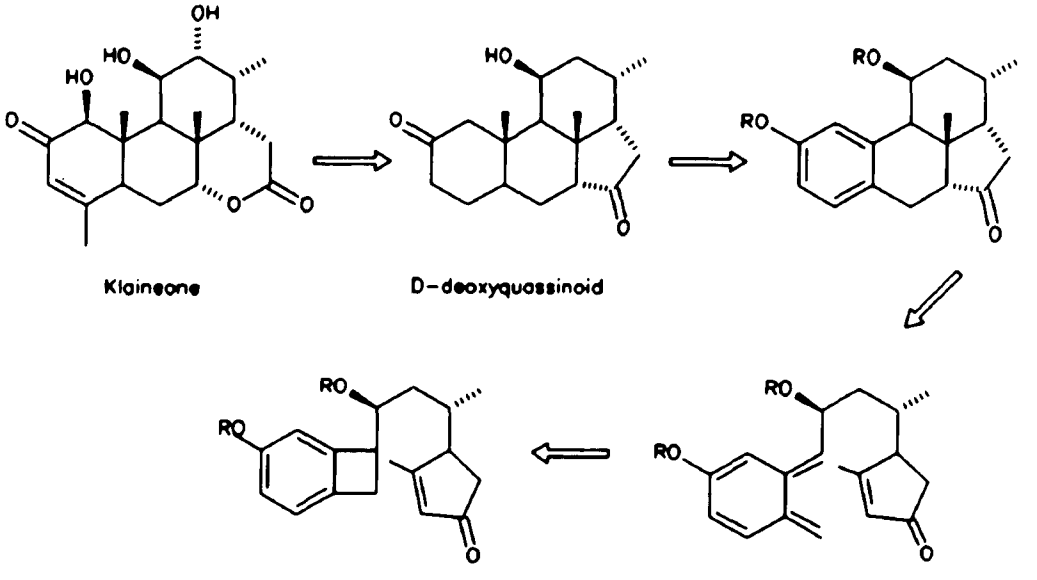


Figure 1: Synthetic Approach to Quassinoids

This synthetic approach incorporates several advantages that were required for building the basic structure needed for II.

These advantages were:

(a) the known high reactivity of the o-quinonedimethane as a diene,

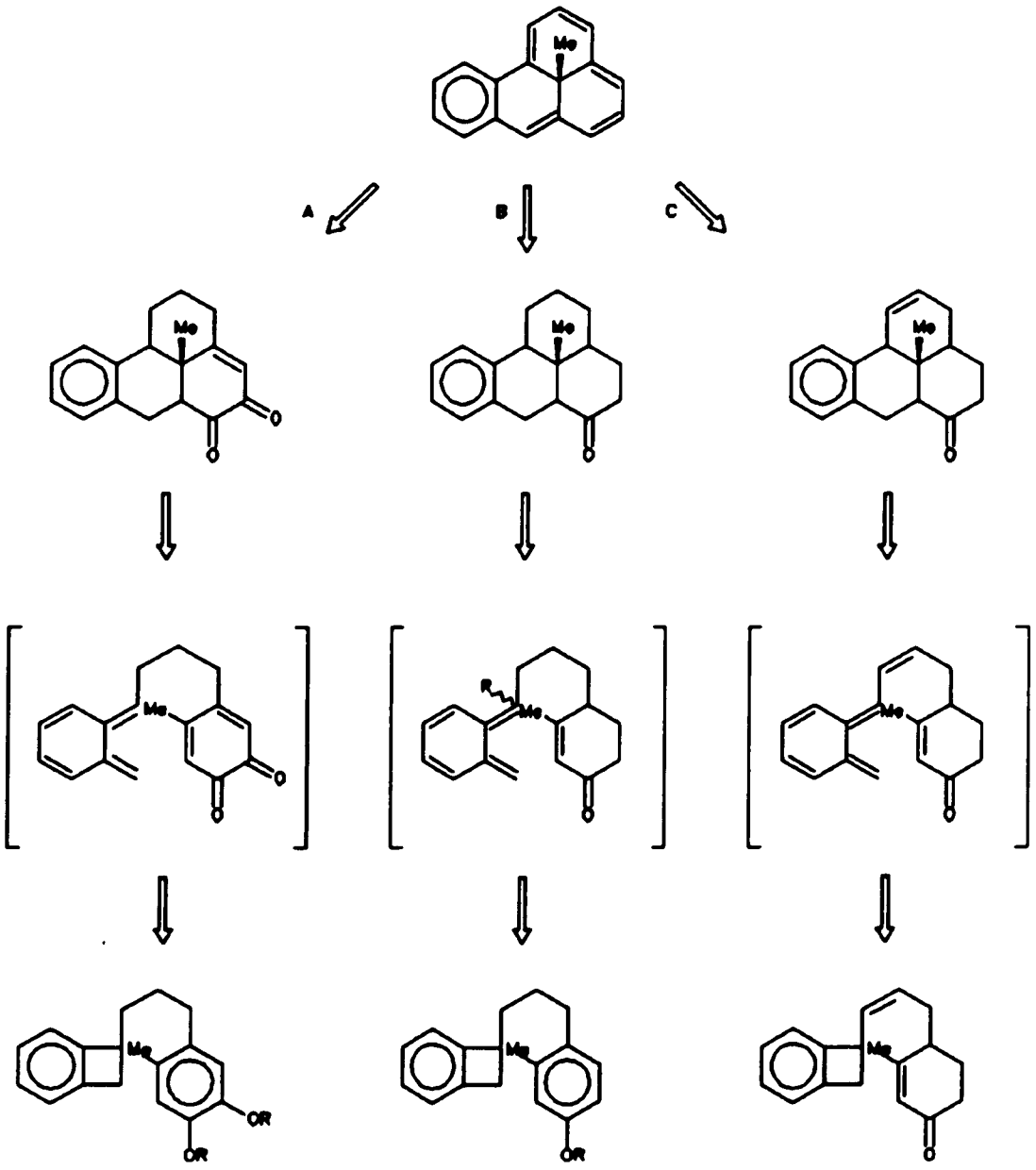
(b) the presence of a carbonyl as a potential double bond, and as a dienophile activator,

(c) the formation of the right peripheral skeleton as a result of high regioselectivity from an intramolecular Diels-Alder, in contrast with low regioselectivity and kinetics from a bimolecular reaction, and

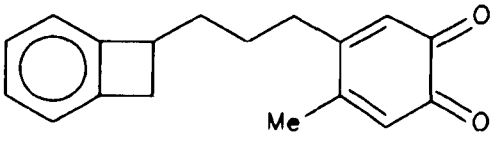
(d) the placement of the methyl group at the center of the polycyclic chain.

The general retrosynthetic approach to II is shown in scheme <1>. This scheme utilizes the intramolecular Diels-Alder for the cycloaddition leading to the tricyclic system.

SCHEME <1>



Our initial tentative required the synthesis of the o-quinone 39 and has been labeled as pathway A.

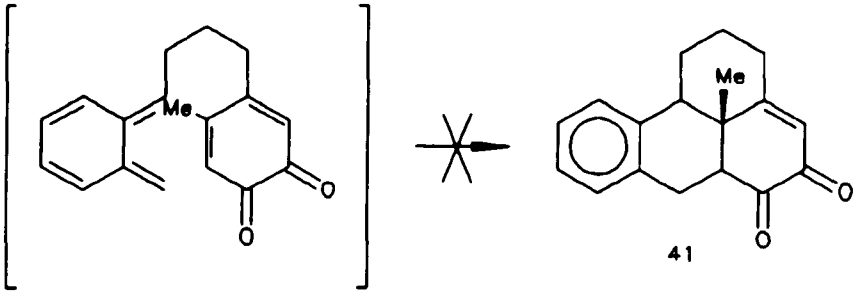


39

Figure 2: The reagent for pathway A

This pathway utilizes an approach similar to the synthesis of Quassin[6] and Lachnanthocarpone[7], by Mandell and Edwards, respectively. Both approaches employed an o-quinone as the dienophile.

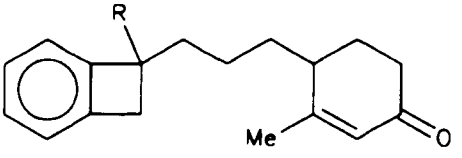
During the thermolysis of o-quinone 39, it became odvious that its dienophilic behavior was not well defined as the Diels-Alder product 41 could not be identified.



41

Figure 3: The IMDA for pathway A

Although 126 and 135 possessed less functionality than 39, it appeared that both ketones could avoid the difficulties experienced by the o-quinone. One of the reasons favoring 126 was the presence of the cyano group. This group lowers the cyclobutene opening[8] temperature to ≈110 °C. Moreover, the α,β-unsaturated ketone, used instead of the o-quinone, is well documented to be dienophilic in nature.



126,R=NC 135,R=H

Figure 4: The alternative to the o-quinone approach

Only 135 lead to a successful intramolecular cycloaddition giving the tricyclic ketone 140. This approach became the pathway B. Functionalization of 140 was not straightforward as both benzylic positions were not equally reactive, and the tertiary benzylic carbon would not be activated.

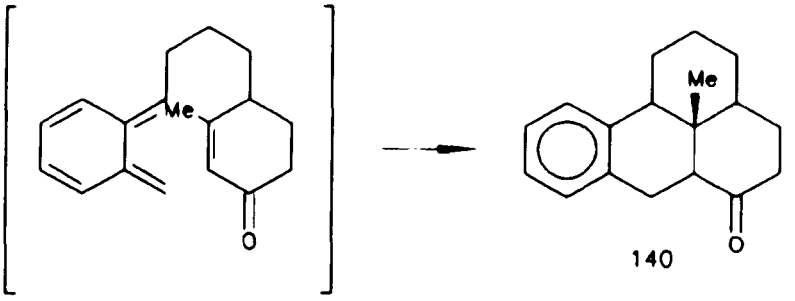


Figure 5: The IMDA for pathway B

Rethinking of our way to access a conjugated system, with better control of the tertiary benzylic position, parallel with higher isolated yields, led us to try an IMDA using a double bond adjacent to the o-quinonedimethane system. This became the pathway C.

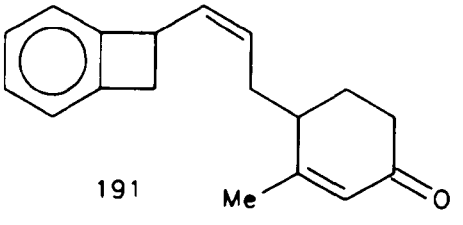


Figure 6: The key intermediate for pathway C

This route allowed the functionalization of the tricyclic 195 up to the conjugated pentaene, possibly II, and beyond.

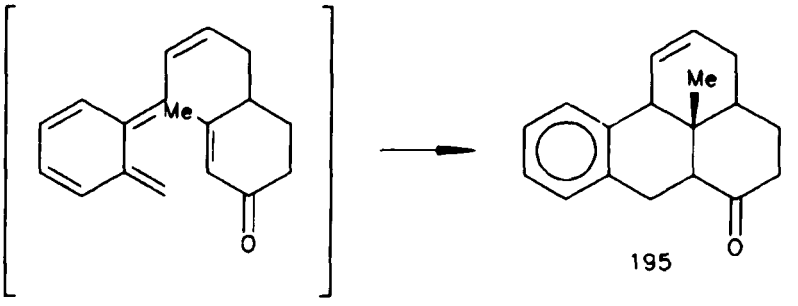
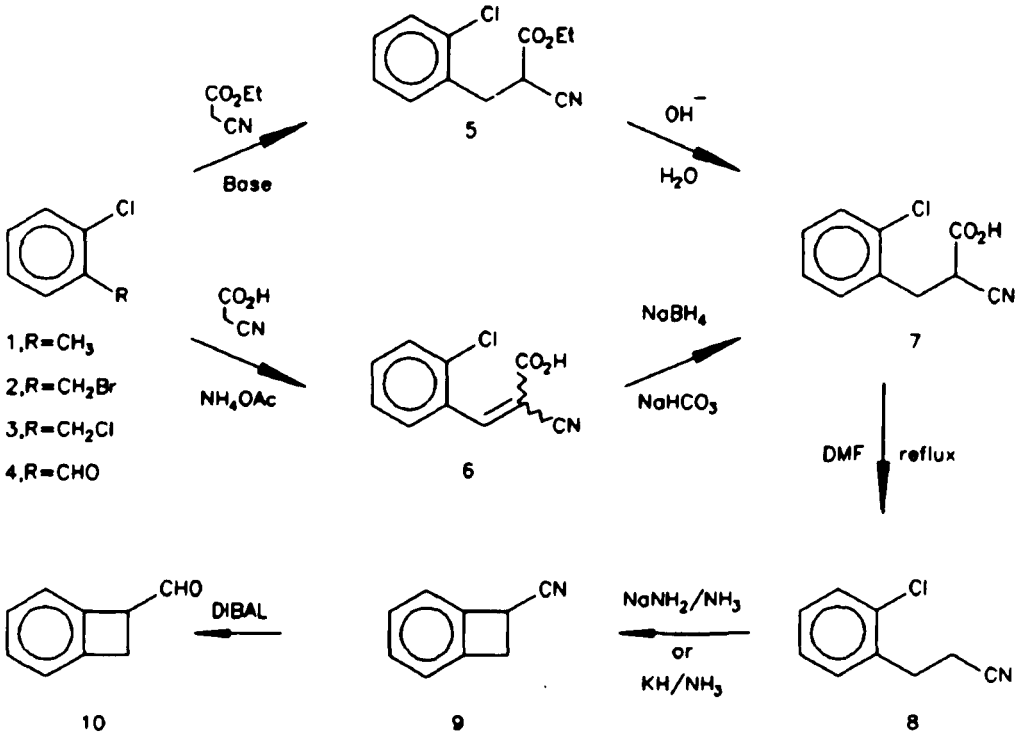


Figure 7: The IMDA for pathway C

2.2.0 THE SYNTHESIS OF THE BENZOCYCLOBUTENE UNIT

SCHEME <2>



The top portion of scheme <2> depicts the known synthesis[9] of 1-cyano-benzocyclobutene 9. That is, the conversion of the dichlorinated toluene 3 to the ethyl cyanoacetate derivative 5 to the carboxylic acid 7.

We improved the yield from 3 to 5, by 10%, by using α-bromo-2-chlorotoluene 2 instead of 3. The bromination of 1 to 2 was straightforward using N-bromosuccinimide as the halogenating agent.[10] Compound 2 was a strong lachrymator and we had to discontinue its use. The other route was developed by Jung.

Using the benzocyclobutene system, Jung and coworkers have proposed a synthesis[11] of analogues of Podophyllotoxin. They reported a modified approach toward 9, using 6-bromo-piperonal as the starting material; our procedure used commercially available 2-chlorobenzyl chloride 3 instead. The most important part of this work is the use of potassium hydride for the formation of potassium amide. The ring closure of 8 to 9 was more consistent with this procedure, produced better yields of product which was also easier to purify. Further transformation to the benzocyclobutene aldehyde 10 was achieved by reduction of 9 with DIBAL[12] followed by acidic work-up.

2.3.0 THE PATHWAY A TOWARD II

This approach required the o-quinone as the dienophile in the IMDA reaction.

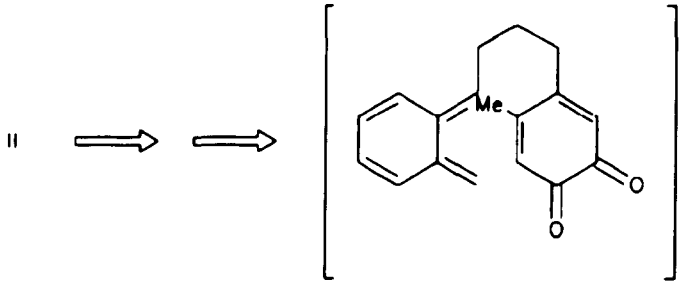


Figure 8: The pathway A toward II

2.3.1 RETROSYNTHETIC ANALYSIS FOR PATHWAY A

Figure 9 illustrates the retrosynthetic pathway toward the o-quinone masked as a dimethoxy derivative, using a Wittig coupling to the corresponding aldehyde.

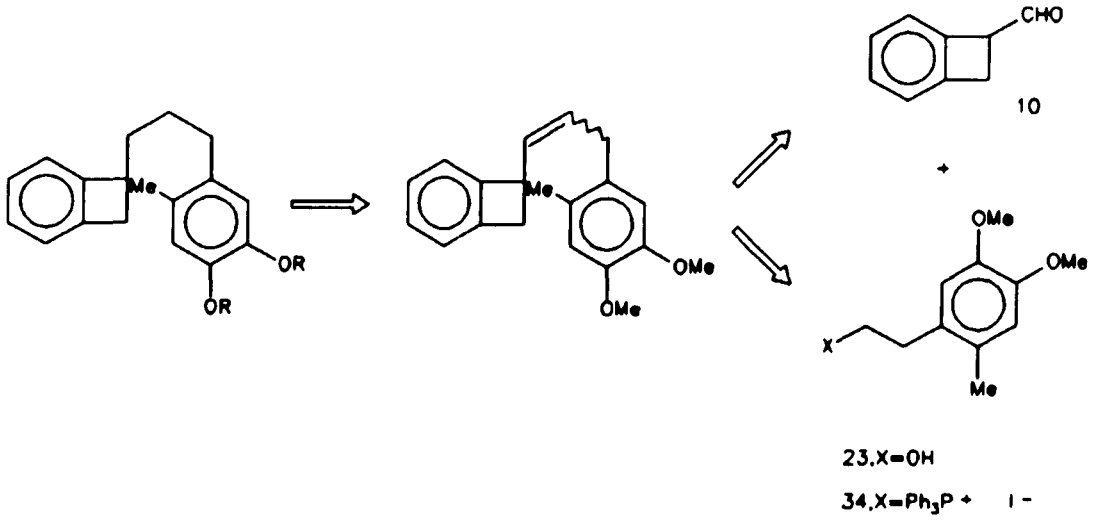
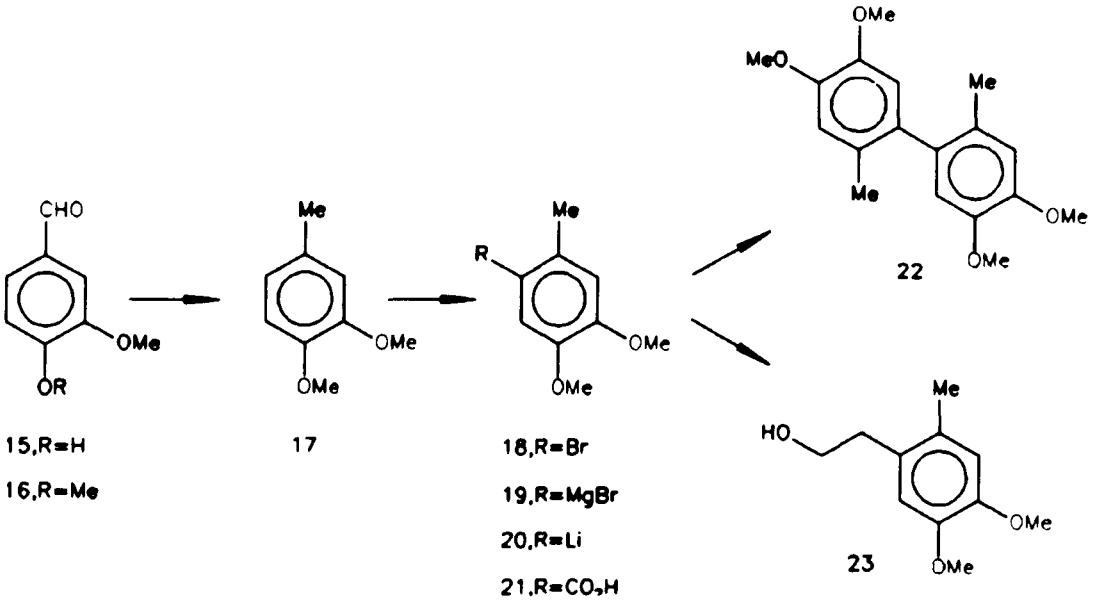


Figure 9: Retrosynthetic analysis for pathway A

2.3.2 THE SYNTHESIS OF ALCOHOL 23

SCHEME <3>



The starting material used in scheme <3> was prepared from readily available Vanillin 15 which was converted to Veratraldehyde 16 by a reported procedure.[13] This aldehyde was changed to the toluene 17 by a modified Wolff-Kishner reduction,[14] then brominated to 18 in quantitative yields.[15]

Once 18 was available, several attempts were made to convert it to alcohol 23. Preparation of the Grignard reagent[16] of 18 with several kinds of magnesium,[17] followed by reaction with ethylene oxide,[18] led mainly to the biphenyl 22. To test the reactivity at the halogenated position, metal halogen exchange using lithium metal, followed by carbon dioxide, was tried. This latter procedure did not give the respective benzoic acid derivative 21. n-Butyllithium was used instead of magnesium. It gave 22 as the major product, and the alcohol 23 in 16% yield. Model studies using p-bromoanisole 24 led to a successful synthesis of 26 which is discussed in the next section.

2.3.3 MODEL STUDIES OF p-BROMOANISOLE 24

The commercially available 4-bromoanisole 24 was tested with plain and activated[19] magnesium followed by ethylene oxide, under several conditions, all leading to the biphenyl 25. An attempt using n-butyllithium followed by the oxide, led to identifiable products.

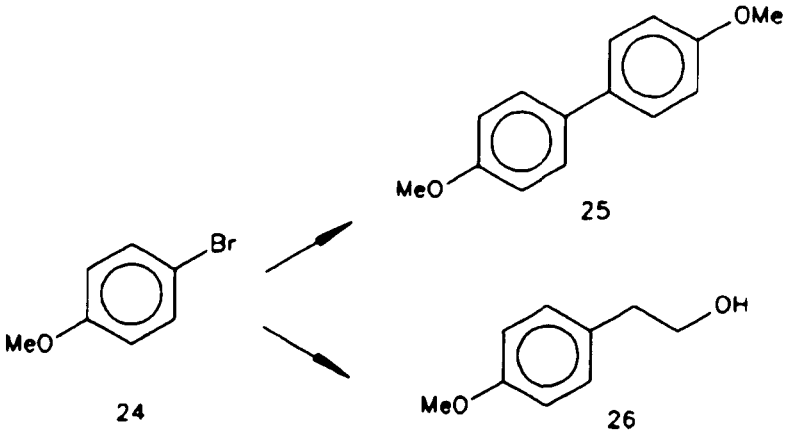
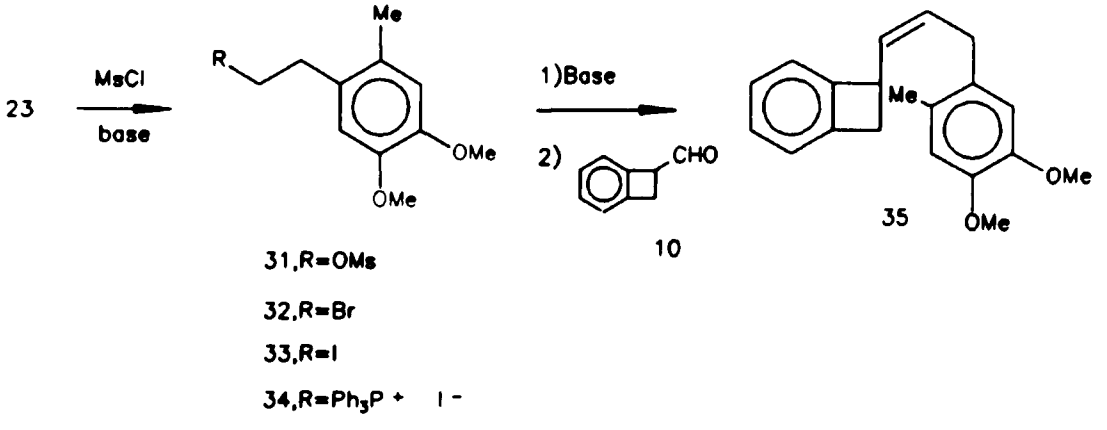


Figure 10: Model Studies of p-Bromoanisole

It has been shown that the halogen of 4-bromoanisole undergoes rapid metal-halogen exchange with n-butyllithium. If long reaction times or high temperatures are used, the metallation undergoes thermodynamic[20] proton exchange with the hydrogen located ortho to the methoxy, leading to other products. This equilibrium has been studied extensively.[21] It appeared that our conditions were thermodynamic. We

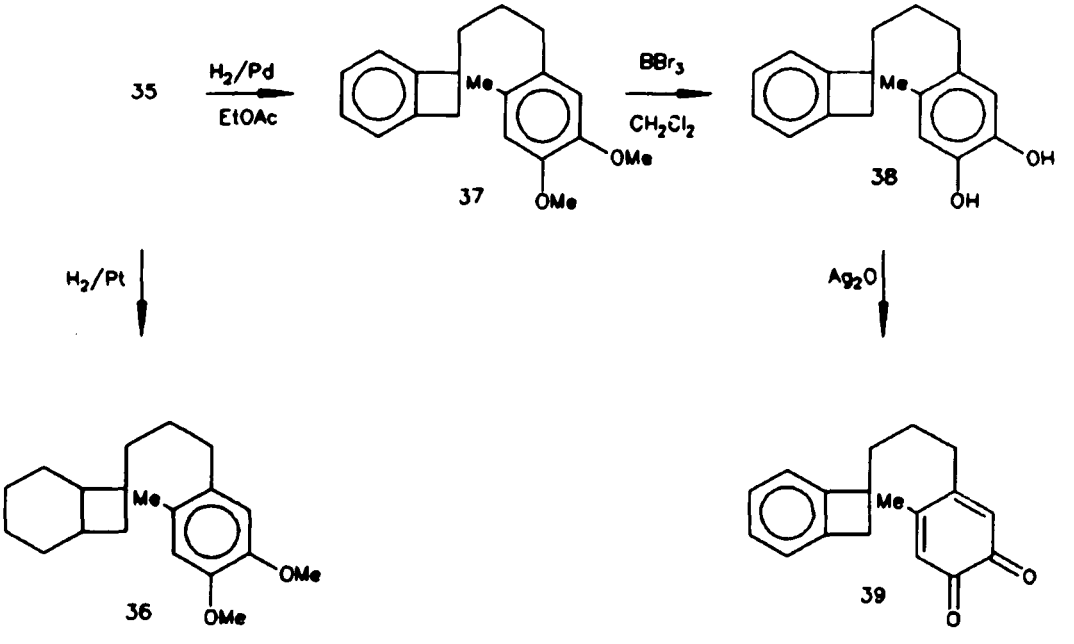
modified our procedure to the kinetic conditions[22] of low temperature and short times. The 4-bromoanisole 24 was cooled to -78 °C before the base was introduced, and after exactly 10 minutes, liquid ethylene oxide[23] was poured into the reaction mixture. Upon work-up, the alcohol 26 was obtained in 86% yield. This procedure was repeated on 18 giving the alcohol 23 in 68% isolated yield.

SCHEME <4>



The conversion of 23 to the halogen derivatives 32 and 33 was quantitative thanks to a procedure used by Danishefsky et al. in the total synthesis of dl-Quadrone.[24] The phosphonium salt 32 gave a messy oil that could not be crystallized. The iodo salt[25] 34 was better behaved. Wittig coupling of 34 to the aldehyde 10 was performed with a variety of bases and reaction conditions. The use of potassium t-butoxide gave the most satisfactory results. The olefin 35 was characterized* by its ^1H NMR (71% yield).

SCHEME <5>



*. For a discussion on the stereochemistry of the olefin refer to section 2.5.0.

The reduction of 35, using 10% platinum on activated charcoal, resulted in overreduction of the aromatic ring system attached to the cyclobutene unit. Reduction using 5% palladium gave the saturated 37 in quantitative yields. Demethylation[26] of 37 using boron tribromide gave the hydroquinone 38. This compound was identified by a broad IR band at 3330 cm^{-1}. Treatment of 38 with freshly prepared[27] silver(II)oxide and 6 N nitric acid[28] led to the quantitative formation of the deep red and unstable o-quinone 39. This quinone showed strong IR bands at 1720 and 1680 cm^{-1}; the band at 3330 cm^{-1} was no longer present.

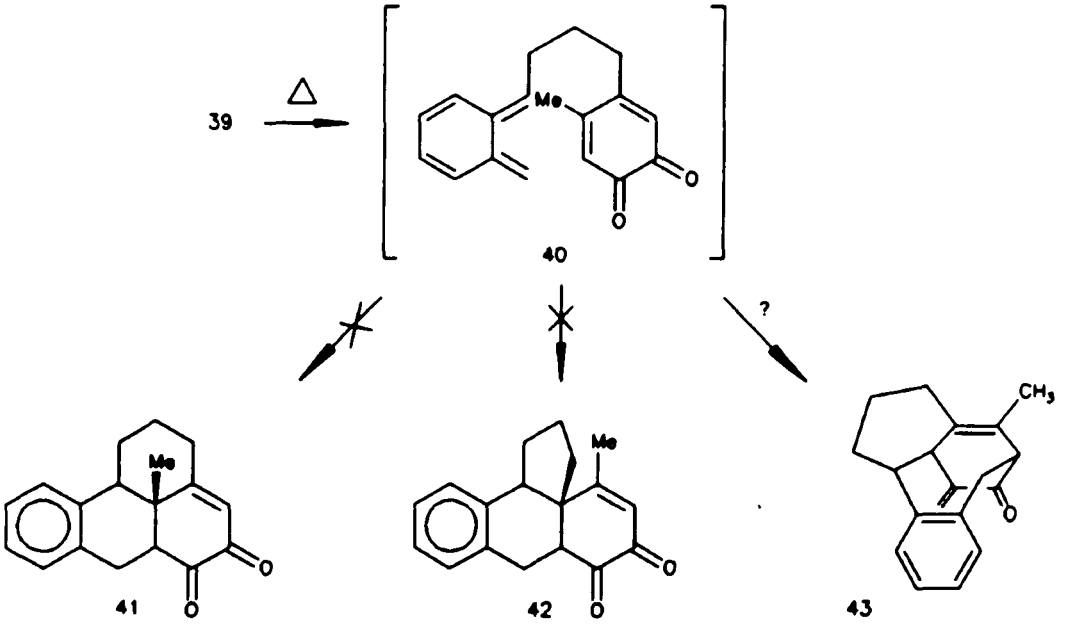


Figure 11: The thermolysis of the o-quinone 39

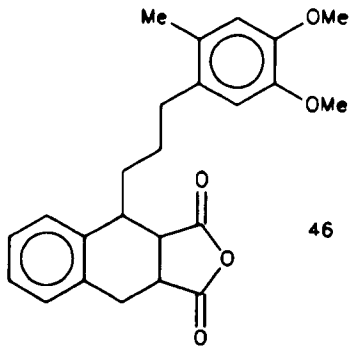
The thermolysis of 39 was carried out in several ways, but the final adducts 41 and 42 were not obtained. The hydroquinone 38 was obtained in small amounts. In one case, a new compound was isolated. Spectroscopic data suggest 43 as its structure.

We therefore discontinued this route and turned to pathway B (section 2.4).

2.3.4 THE TESTING OF THE DIENE

In order to test the Diels-Alder reactivity of 39, the following was carried out:

The thermolysis of compound 37 was done in the presence of maleic anhydride in m-dichlorobenzene. The reaction was followed by observation of the ^1H NMR spectrum (DMSO-d_6) after every 10 °C increase.* This procedure indicated that the cyclobutene opened around 180 °C, proving without any doubts the reactivity of this o-quinodimethane. The Diels-Alder adduct 46 was isolated in 66% yield (mp 149.8-151 °C).



46

Figure 12: The Diels-Alder adduct from 37

*. The solution was kept at the required temperature for 15 minutes before the ^1H NMR analysis.

2.3.5 THE TESTING OF THE DIENOPHILE

Testing of the dienophilic character of an o-quinone required the synthesis of 51. This o-quinone was going to be made from the dimethoxy derivative 49 and transformed in a similar way as 37 to 38 and 39. The highly symmetric 1,2-dimethoxy-4,5-dimethylbenzene 49 was made from butyllithium and methyl iodide treatment of 18, and it was the last compound made using the pathway A. We did not pursue this approach to 52 as there was evidence that an o-quinone was not a dienophile but a diene. This is explained in the following section.

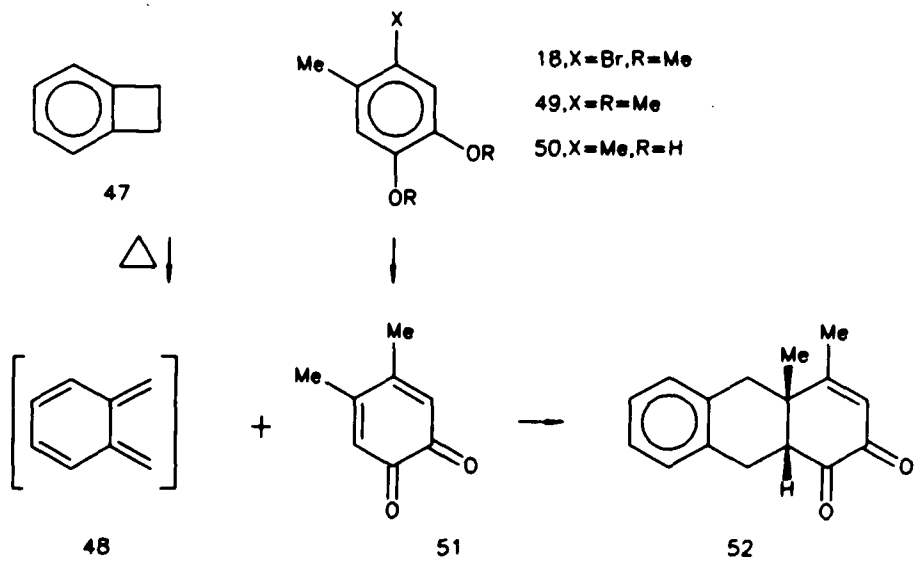


Figure 13: Unfinished route toward 52

2.3.6 THE o-QUINONE 39: DIENE or DIENOPHILE?

During the course of a synthesis toward quassin, Mandell and coworkers reported[29] their attempt to cyclize their o-quinone which did not succeed. They summarize possible reasons for the failure of the IMDA using the o-quinone 39 as follows:

(a) Substitution at the 4,5-positions of the o-quinone reduces the dienophilic behavior due to steric hindrance while increasing the diene character. This is known from studies[30] of bicyclic o-quinones, which indicated that the steric effects are of much greater significance than the electronic effects. The o-quinone behaves as a diene.

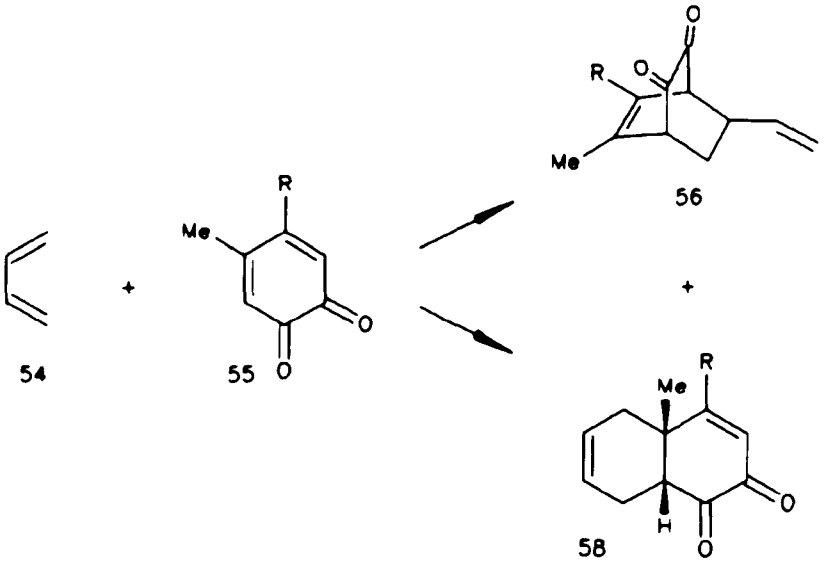


Figure 14: The reaction of 54 and 55

(b) Results from Veliev[31] et al. showed that drastic condition had to be used for the reaction of tetrachloro-1,2-benzoquinone with allylacetylene, requiring heating without solvents at temperatures of 160-180 °C. Again, the o-quinone behaved as a diene.

(c) The possibility of a bis product.

Figure 15: A double Diels-Alder reaction

(d) Possible dehydrogenation of the final product causing aromatization of the molecule.[32] This could be the rationale why traces of hydroquinone 38 were isolated after the thermolysis of 39.

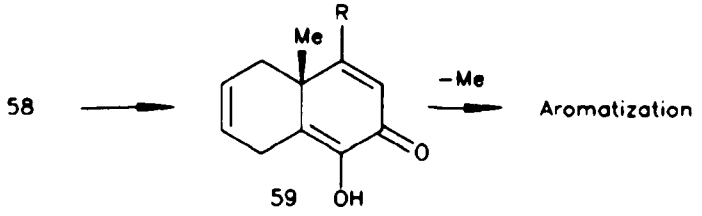


Figure 16: Aromatization

(d) Tautomerization of 4-methyl-o-quinones could lead to the 2-hydroxycyclohexadienone.

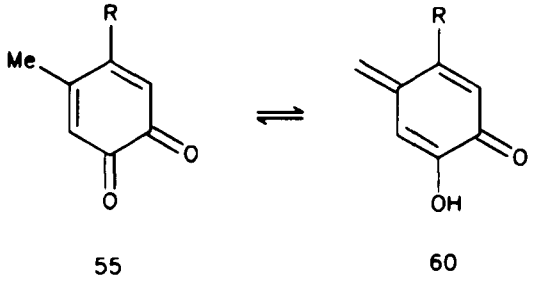


Figure 17: Tautomerism

Tautomer 60 could undergo cycloaddition at the exocyclic methylene group, as a spiro system has been reported.[33]

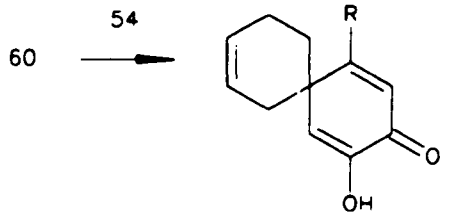


Figure 18: An unusual Diels-Alder adduct

(e) Instability of the o-quinone at high temperatures, as the opening of the unsubstituted cyclobutene moiety requires temperatures higher than 170 °C.

2.4.0 THE PATHWAY B TOWARD II

This approach required the 3-methyl-cyclohexene-1-one as the dienophile in the IMDA reaction.

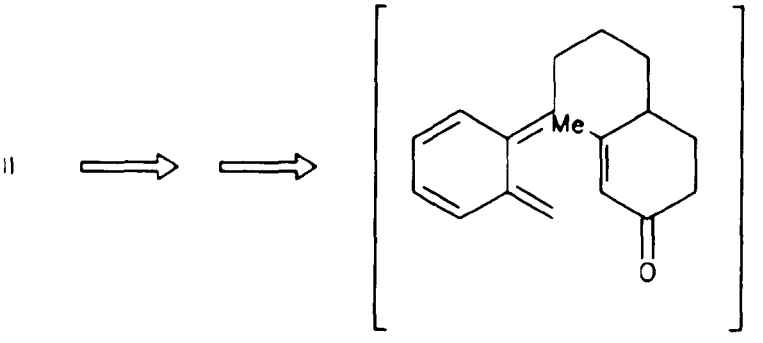


Figure 19: The pathway B toward II

2.4.1 RETROSYNTHETIC ANALYSIS FOR PATHWAY B

Figure 20 shows the 1-cyanobenzocyclobutene 9 and the ketone or the ketal as the units needed for the formation of 126/135. Retrosynthetic analysis of the ketone suggested that it could be made through a Birch reduction of the respective anisole or the known Hagemann's ester 85.

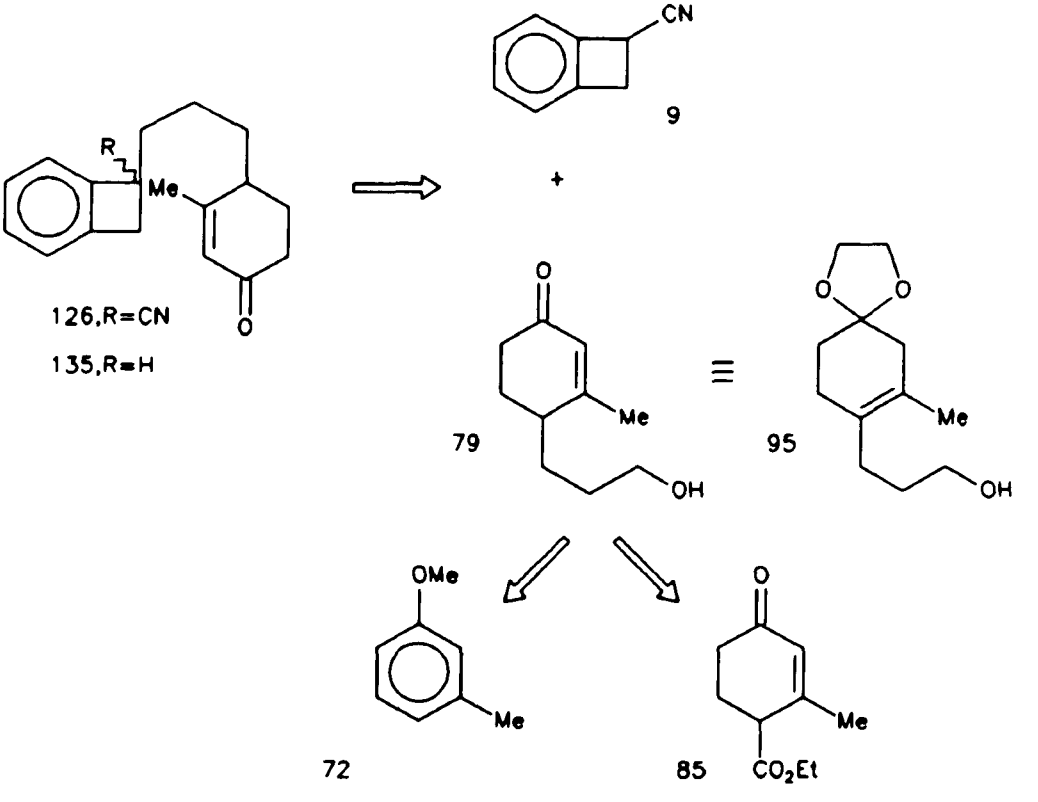


Figure 20: Retrosynthetic analysis for pathway B

Our early approach toward 79 was through the useful and versatile 4-bromo-3-methylanisole 73. This compound was made by halogenation[34] of 3-methylanisole. The bromide 73 was treated with n-butyllithium followed by allyl bromide, but the olefin 63 was not produced. Treatment of 73 with magnesium and copper bromide[35] followed by acrolein did not give the expected aldehyde 64.

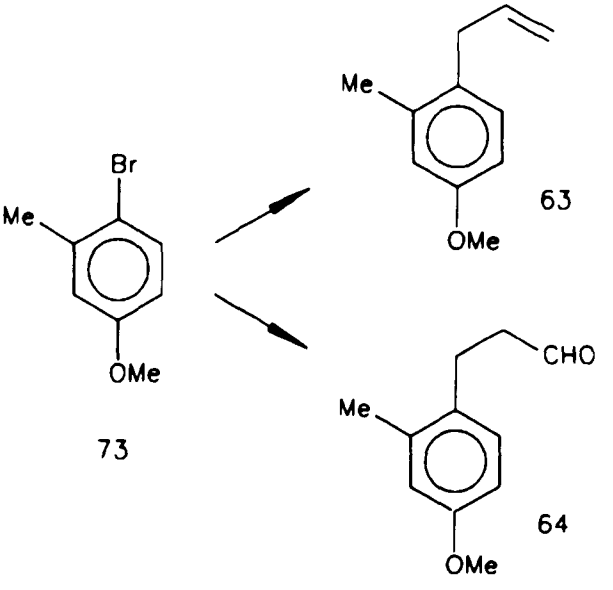
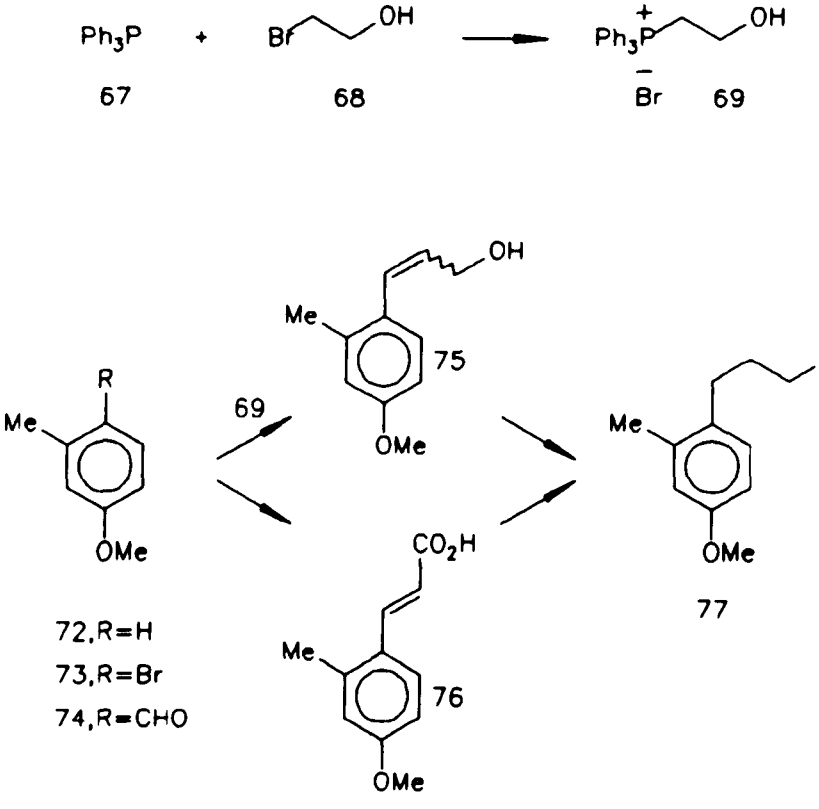


Figure 21: Early attempts using 73

2.4.2 THE ATTEMPTED BIRCH APPROACH TOWARD 79

Our second approach was based on known methodology and is shown in scheme 6. The 4-methoxy-2-methybenzaldehyde 74 was made in two steps from 72, according to a procedure[36] reported by Quinkert and coworkers in their total synthesis of 19-Nor-Steroids. The Wittig reaction of compounds similar to 74 has been investigated by Maryanoff and coworkers, who studied[37] the stereochemistry of the Wittig reaction of oxido ylides and benzaldehyde. Using Maryanoff procedure, we tried the coupling of the salt[38] 69 and 74 to the corresponding allylic alcohol 75, obtaining only 29% as our best isolated yield under improved conditions. Here, the Perkin reaction[39] of 74 with malonic acid in the presence of piperonal, gave the trans-cinnamic acid derivative 76, in 69% yields, without problems. LAH reduction[40] of either the cinnamic alcohol 75 or the acid 76 gave quantitative yields of 77.

SCHEME <6>



Birch reduction[41] of 77, using alkali metals, and several alcohols, in different combinations, did not produce any changes in the compound. The modified[42] Birch reduction conditions developed by Wilds and Nelson, for the reduction of 4-cyclohexylanisole and similar compounds, indicated that these reductions were difficult with sodium, but easy with

lithium, producing polycyclic tetrasubstituted reduced anisole derivatives. This method, when applied to our system, failed. It has been proposed that the nonrigid substitution of 77 as well as the presence of several electron donating groups could be responsible for this lack of reactivity. The most severe of the Birch conditions used led to the replacement of the methoxy by a phenolic group.

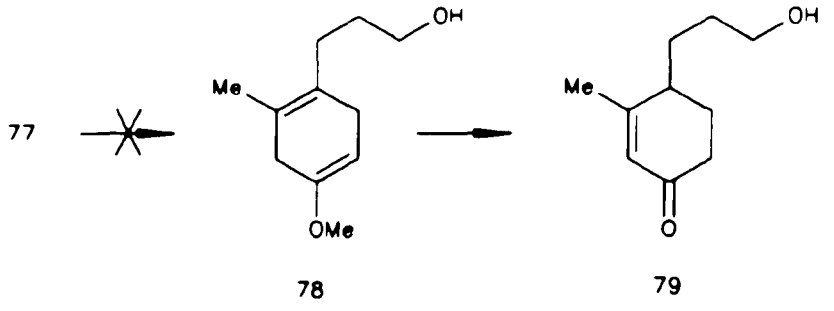
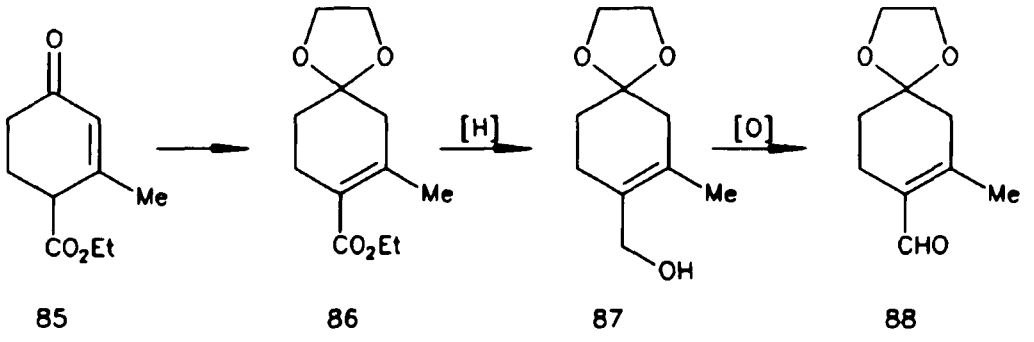


Figure 22: The proposed Birch reduction of 77

2.4.3 THE HAGEMANN'S ESTER APPROACH TOWARD 79.

The commercially available ester 85 can easily be protected, reduced, and oxidized by well known methods.[43] All these derivatives are shown below,



85 86 87 88

Hagemann's Ester

Figure 23: The Hagemann's Ester Approach

The α,β-unsaturated aldehyde 88 was the starting material, as shown in figure 24. This figure shows the Wittig reaction of 88 to the α,β,γ,δ-unsaturated ester 91. Reduction of the α,β-position of 91 was attempted with several concentrations of palladium metal on activated charcoal. Platinum(IV) oxide and rhodium on alumina were also unsuccessful. The alcohol 92 behaved in a similar manner.[44] Reduction of the disubstituted double bond led to overreduction at the tetrasubstituted part. Known 1,2-addition of sodium thiophenoxide to the ester also failed.[45]

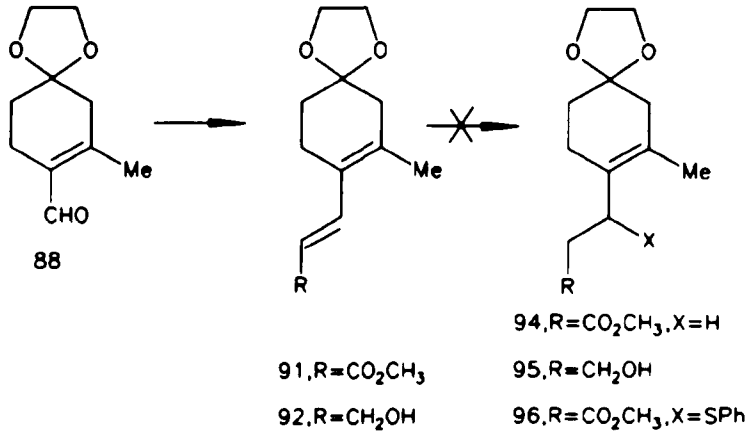


Figure 24: The Wittig reaction of 88

The Grignard reaction that led to the double allylic alcohol 101 proceeded in high yields, but subsequent hydrogenolysis[46] using pyridine-sulfur trioxide gave a 1:1 mixture of the isomers 102 and 103. Low yields and the problem of separation of these isomers forced us to change tactics.

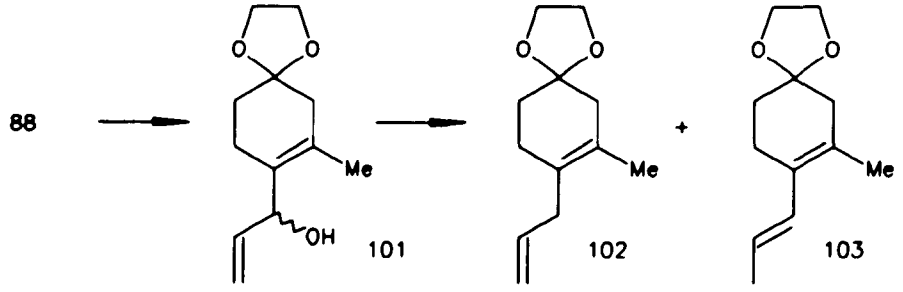


Figure 25: The Grignard reaction of 88

The major problem related to figures 24 and 25 was to try to avoid conjugation to the tetrasubstituted double bond. Conversion of 87 into the allylic halogenated derivative 106 was our next approach.

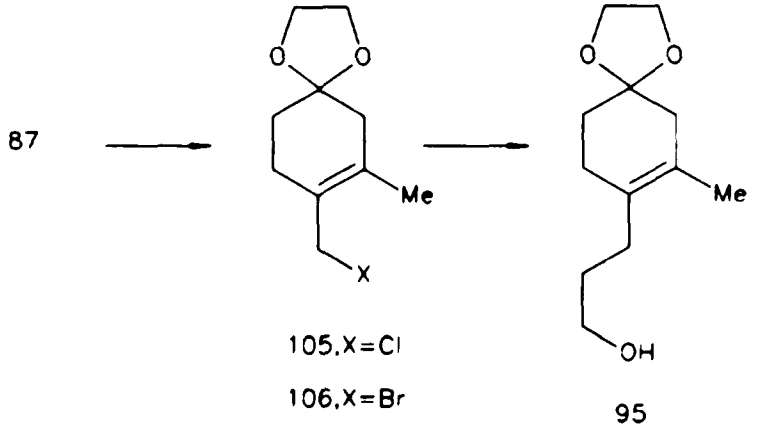


Figure 26: An attempted short route toward 95

Harding and Parker had reported the transformation of Hagemann's ester to the chlorinated[47] compound 105 and indicated its instability upon exposure to air. Stork has also described a similar conversion.[48] An attempt was made to synthesize the allylic bromide 106. We followed a methodology[49] described by Corey et al. in the total synthesis of α- and ß-trans-Bergamotene. This technique required the use of phosphorus tribromide in the presence of calcium hydride and the respective allylic alcohol 87. Without purification

of 106, we attempted the metal-halogen exchange of the bromine by lithium, followed by ethylene oxide.

The proposed transformation of 87 should have given 95 in fewer steps. To our surprise, the ether 108 was obtained. The ^{1}H NMR spectrum contained the aromatic/methylene/methyl protons in a 3:2:6 ratio. Coupled ^{13}C NMR showed the presence of a methylene unit at δ 66.7. All this data was consistent with structure 108. Moreover, mild acidic treatment of 87 gave the dienone 109, but more acidic conditions lead to the phenol 110.

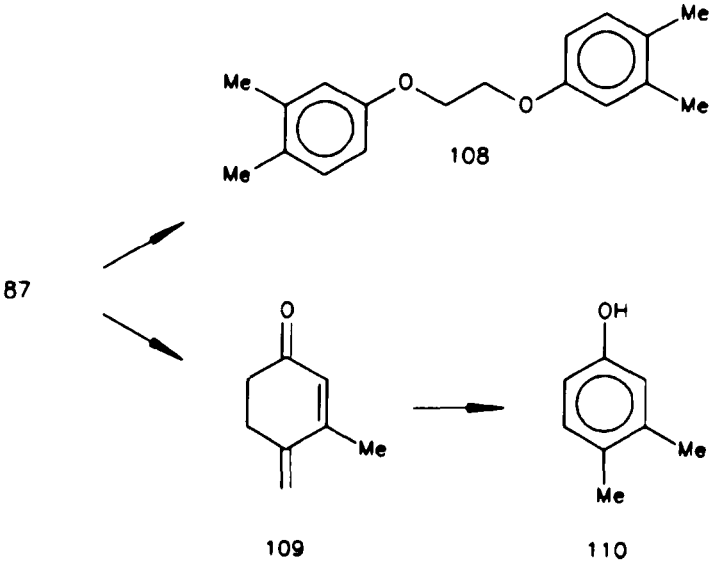


Figure 27: The hydrolysis of 87 and 109

2.4.4 JOHNSON'S MODIFICATION OF THE HAGEMANN ESTER APPROACH

A compound similar to the precursor of our target 95 is the thioketal-ester 116. This 116 has been synthesized[50] by Johnson and coworkers. Analysis of 116 and its precursor, leads back to Hagemann's ester. Minor modifications of Johnson's work lead to a successful synthesis of 117. This is outlined in figure 28.

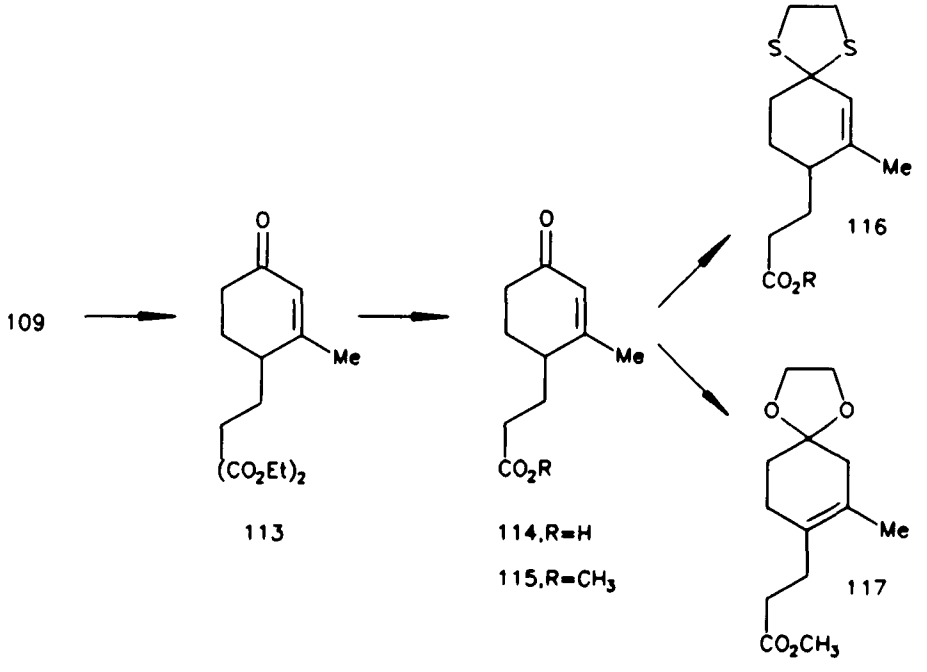


Figure 28: Johnson's approach toward 116

The synthesis started with the ketal-allylic alcohol 87 which upon deprotection/dehydration afforded the dienone 109 in 74% isolated yield. The ketone 109 was subjected to a 1,6 Michael addition with sodium ethoxide and excess malonic ester to give 113 in 65% yield. The diester 113 was hydrolized and decarboxylated to the free acid in 63% crude overall yield from 109. Esterification with absolute methanol and catalytic amounts of PTSA followed by ketalization afforted 117 in 88% yield.

The methyl ester 117 was reduced with LAH. The conversion of the alcohol 95, to the mesylate 119, gave the aromatic dimer 121 when the corresponding mesylation reaction was left stirring overnight. Otherwise, the reaction presented no problems. The iodide 120 was obtained in a way similar to that which gave 33. In a few intances, the iodoketone 122 was isolated,* which had to be reprotected to 120. The overall transformation of 117 to 120 was in very high yields.

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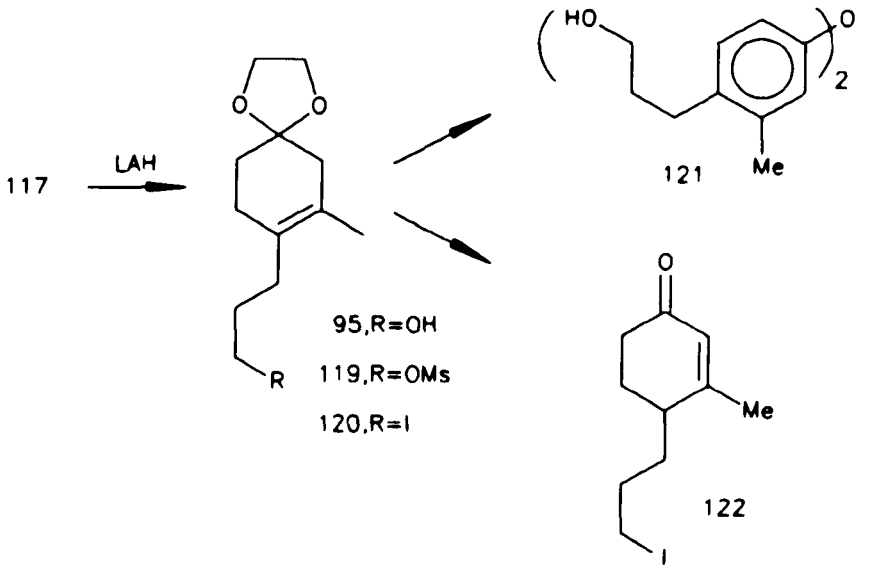
*. Even in the presence of solid sodium bicarbonate.

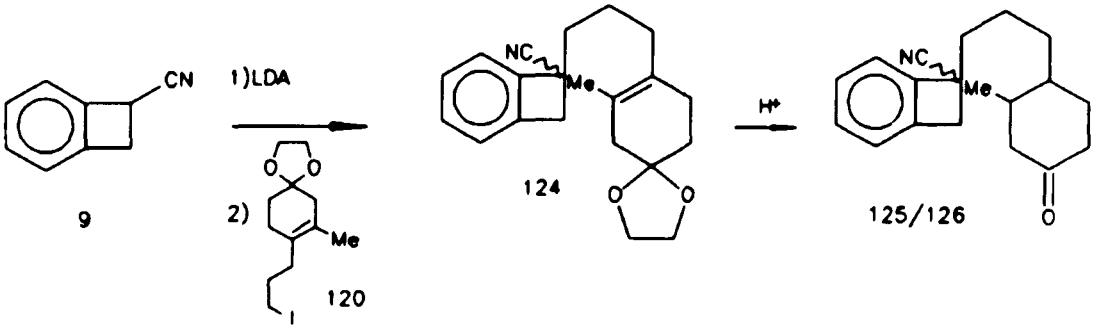
SCHEME <7>



Coupling of the ketal 120 to 9 was performed using LDA as the base.[51] The ketone 125 was well characterized by its ^{1}H NMR spectrum which showed a singlet at δ 1.61 (vinylic methyl), a set of two doublets at 3.27 and 3.72 (benzylic protons, $J_{doublet}$ 14.1 Hz), and a singlet for the acetal at δ 3.97. The IR analysis showed a nitrile band at 2240 cm^{-1}.

Regeneration of the ketone 126 was the next step, as shown in scheme <8>.

SCHEME <8>



The ketal 124 was hydrolyzed to the unsaturated ketones 125 and 126 in THF/10% HCl.

2.4.5 THE ISOMERIZATION OF 125

Isomerization of the ß,γ-unsaturated ketone 125 to the α,ß-unsaturated ketone 126 was attempted under acidic as well as alkaline conditions.

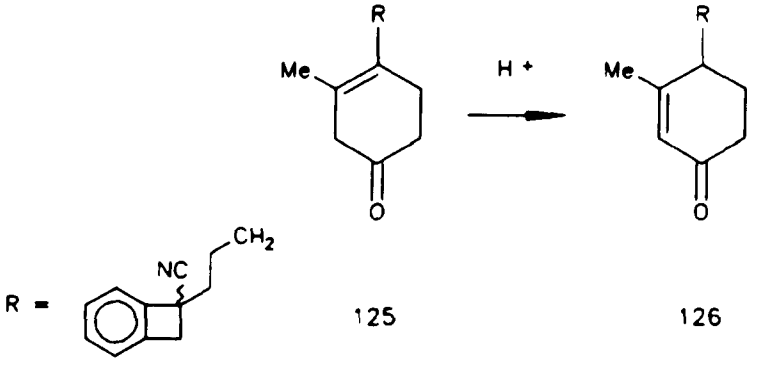


Figure 29: The isomerization of 125

The ketal 124 was deprotected with dilute acid solution, during a two hour period, as described in the experimental section. ^{1}H NMR analysis showed a mixture of unsaturated ketones 125 and 126, in a 1:1 ratio, as demonstrated by the vinylic methyls (δ 1.65 and 2, respectively). The sets of doublets corresponding to the benzylic protons showed the same ratio. In addition, the TLC analysis showed two spots (Hex/ETOAc, 2:1, R_f 0.14 and 0.51).

The yellowish oily residue was treated as follows: 0.10 g of the crude residue was dissolved in 40 mL portions of THF and 10% HCl (v/v). A similar amount was dissolved in THF and 2 N NaOH. Both solutions were stirred at room temperature for two hours. After work-up, the spectrum corresponding to the sample treated under basic conditions, showed no apparent change in the region of the benzylic protons. The four sets of doublets were still present, but integration of these protons was not too clear. The residue obtained from the acidic conditions showed only two sets of benzylic doublets, and a single methyl peak. These latter results were consistent with the structure assigned to the α,ß-unsaturated ketone 126.

2.4.6 THE INTRAMOLECULAR DIELS-ALDER of 126 and 135

The thermolysis of 126 was attempted at several temperatures and in different solvents. The only procedure that led to identifiable compounds used o-dichlorobenzene. Ketone 126 was refluxed in this solvent and gave a mixture of dimers and monomers.

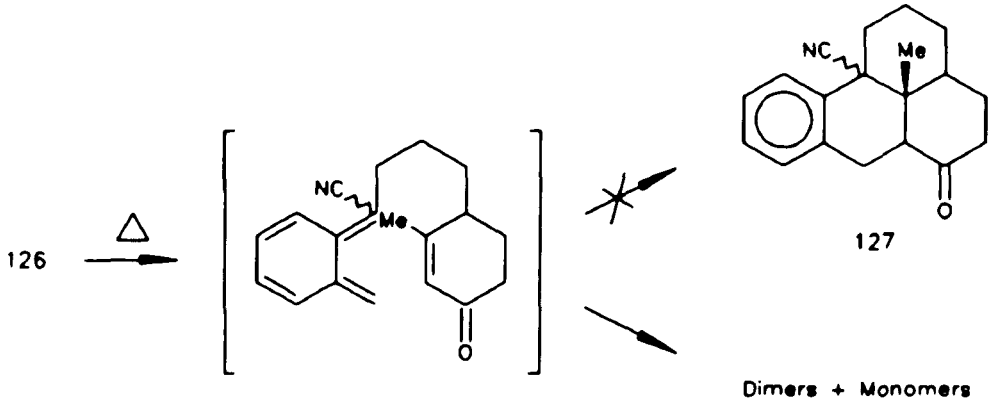
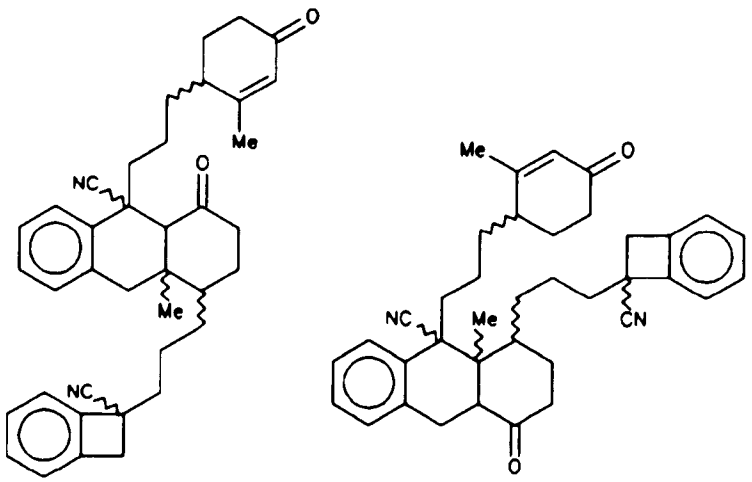


Figure 30: The thermolysis of 126

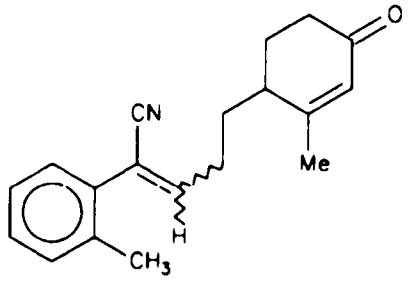
The dimers purified by chromatography and identified by their IR spectra as the 2240 cm^{-1} region showed two bands corresponding to two different nitriles present in the same molecule. The ^1H NMR spectrum showed an α-proton and two α-methyls. These dimers were produced by a bimolecular Diels-Alder reaction.



128 129

Figure 31: Possible structures from the dimeric products

The opening of the benzocyclobutene is known to be conrotatory[52] favoring the Z-type intermediate, but only the E-type possesses the right geometry for a 1,5-hydrogen shift.



130

Figure 32: The [1,5]shift product

Studies by Kametani[53] indicate that the competitive sigmatropic and cycloaddition reactions depend on the geometry of o-quinodimethanes, and the size of substituents controlling the direction of the ring opening. The intermediate formed from 126 seemed to be the E-type producing 130. The stereochemistry at the double bond was not determined.

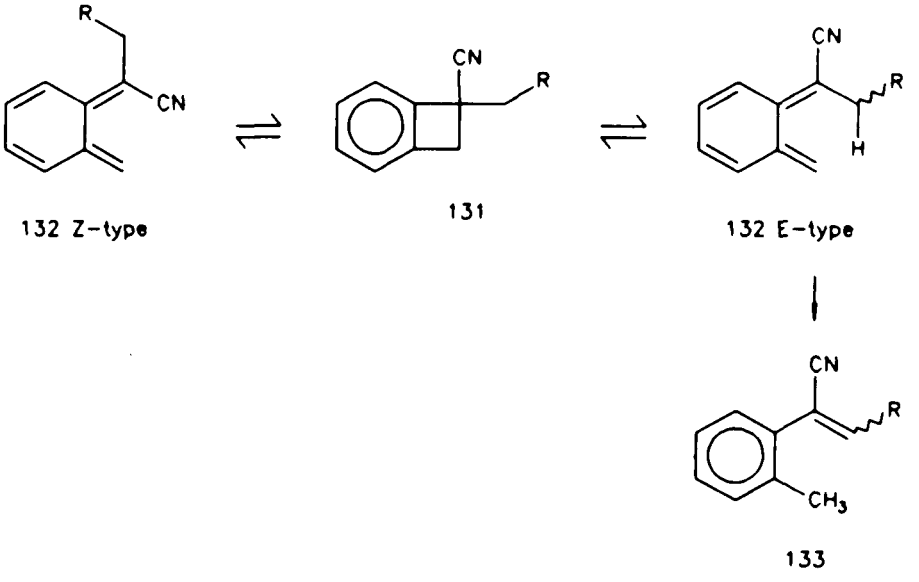


Figure 33: The opening of the benzocyclobutene

The $^{13}C/^{1}H$ NMR and IR analysis suggesting structure 130 to be correct are the following:

(a) no cyclobutene protons present,

(b) a vinylic nitrile (2230 cm^{-1}),

(c) a triplet integrating for one proton at δ 6.43 (vinylic proton), and

(d) a singlet methyl at δ 2.4 (benzylic protons).

The other isomer showed a vinylic proton at δ 6.7. Likewise, the nitrile IR band appeared at 2260 cm^{-1}.

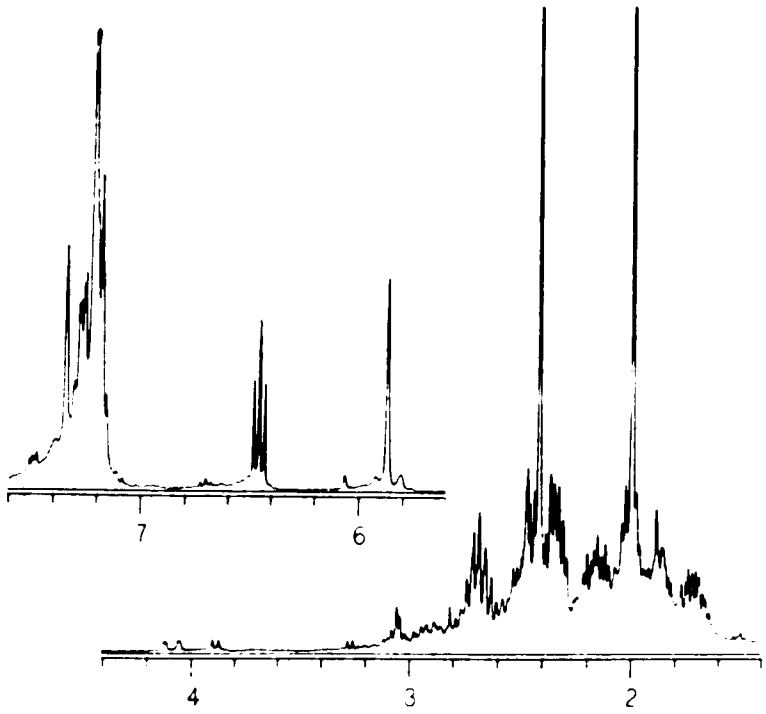


Figure 34: 1-D ^{1}H NMR Spectrum of 130

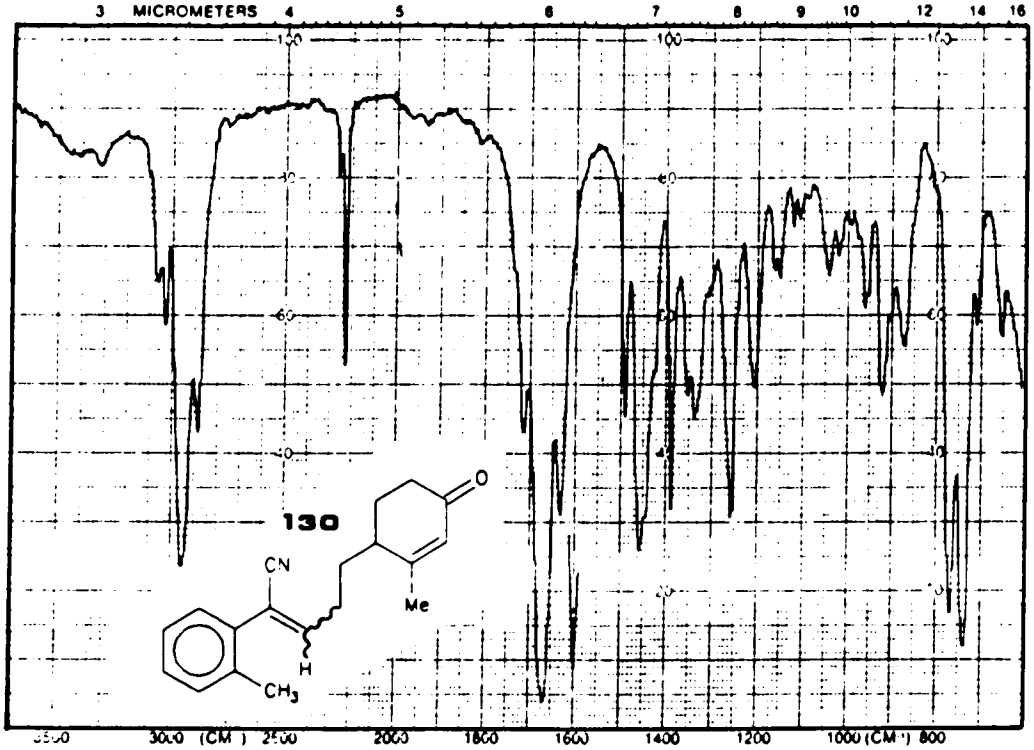


Figure 35: Infrared Spectrum of 130

Since it appeared that the nitrile group interfered in the IMDA favoring sigmatropic rearragements, this nitrile was removed by a standard method[54] which required treatment of 124, in liquid ammonia and absolute ethanol, with excess sodium metal. The decyanated compound was isolated, deprotected and isomerized to the ketone 135 in 56% overall yield from 124.

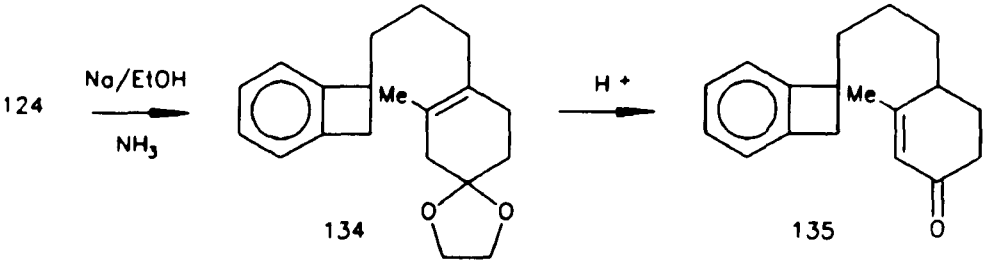


Figure 36: Decyanation/deprotection of 124

The thermolysis of 135, in refluxing o-dichlorobenzene, proceeded without any complication as the tricyclic compound 140 was detected upon removal of the solvent.

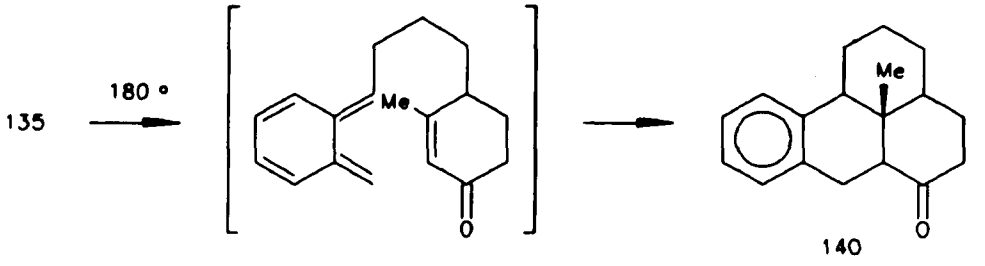


Figure 37: The thermolysis of 135

Examination of the stereochemistry of the transition state intermediate, by means of molecular models, indicated that there were four possible diene-dienophile interactions.

Among the four transition states: 136^{TS}, 137^{TS}, 138^{TS} and 139^{TS}, two were ruled out since the enantiotopic proton should point away from the interaction center. This eliminated compounds 141 and 143. Secondary orbital effects were also expected from the cyclohexenone favoring the endo over the exo approach of the dienophile. Thus a cis* ring juncture was expected at the tertiary benzylic proton. This left one possibility: 142. The X-rays results indicated that this analysis was incorrect as the Diels-Alder adduct was 140 and is discussed in the next section.

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*. Cis to $C_{(14)}$.

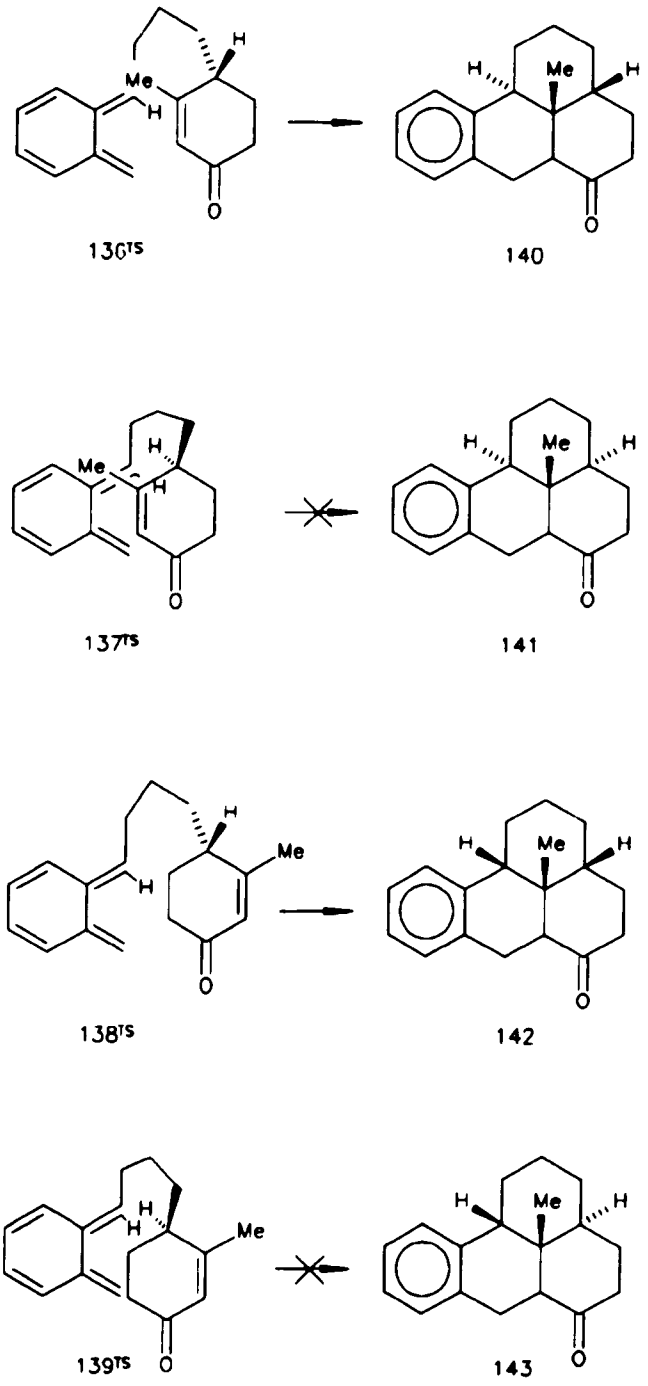


Figure 38: The isomers from the thermolysis of 135

2.4.7 CHARACTERIZATION OF THE DIELS-ALDER ADDUCT 140

The ketone was characterized by the following NMR/IR results,

(a) The absence of a vinylic methyl group and the appearance of a methyl singlet at δ ≈1.1;

(b) The absence of the vinylic proton of 135;

(c) The presence of a double doublet from the coupling of the axial ($C_{(3)}$-H) to the geminal proton (J 17.6 Hz) and to $C_{(4)}$-H (J 7.4 Hz); the presence of the corresponding doublet for $C_{(4)}$-H (J 7.5 Hz); and a doublet for the equatorial $C_{(3)}$-H;

(d) The IR shift of the α,δ-unsaturated cyclohexenone (1660 cm^{-1}) to the cyclohexanone (1720 cm^{-1}); and

(e) The ^{13}C NMR peaks corresponding to the right number of carbons: methyl (1), methylenes (6), methines (3), quaternary aliphatic (1), aromatic carbons (6), and a carbonyl (1).

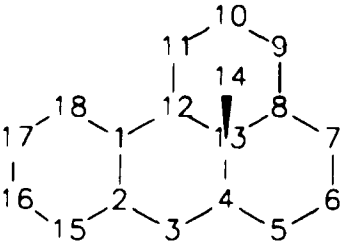


Figure 39: The numbering of 140

The X-rays analysis proved the structure of **140**, as it indicated that the $C_{(12)}$-H was trans to the methyl ($C_{(14)}$). Figure 40 shows the correct stereochemistry of **140**. This hydrogen was perpendicular to the benzene ring, and embedded in the molecule. Moreover, the lone pairs from the carbonyl group appeared to be in the right position for intramolecular bonding with the secondary benzylic protons blocking any attack toward $C_{(12)}$-H. All these factors could have contributed to the unreactivity of the $C_{(12)}$, as it would not be transformed into a sp^2 center. It was suggested that a reduction of the ketone to an axial alcohol could help activate the $C_{(12)}$-H.

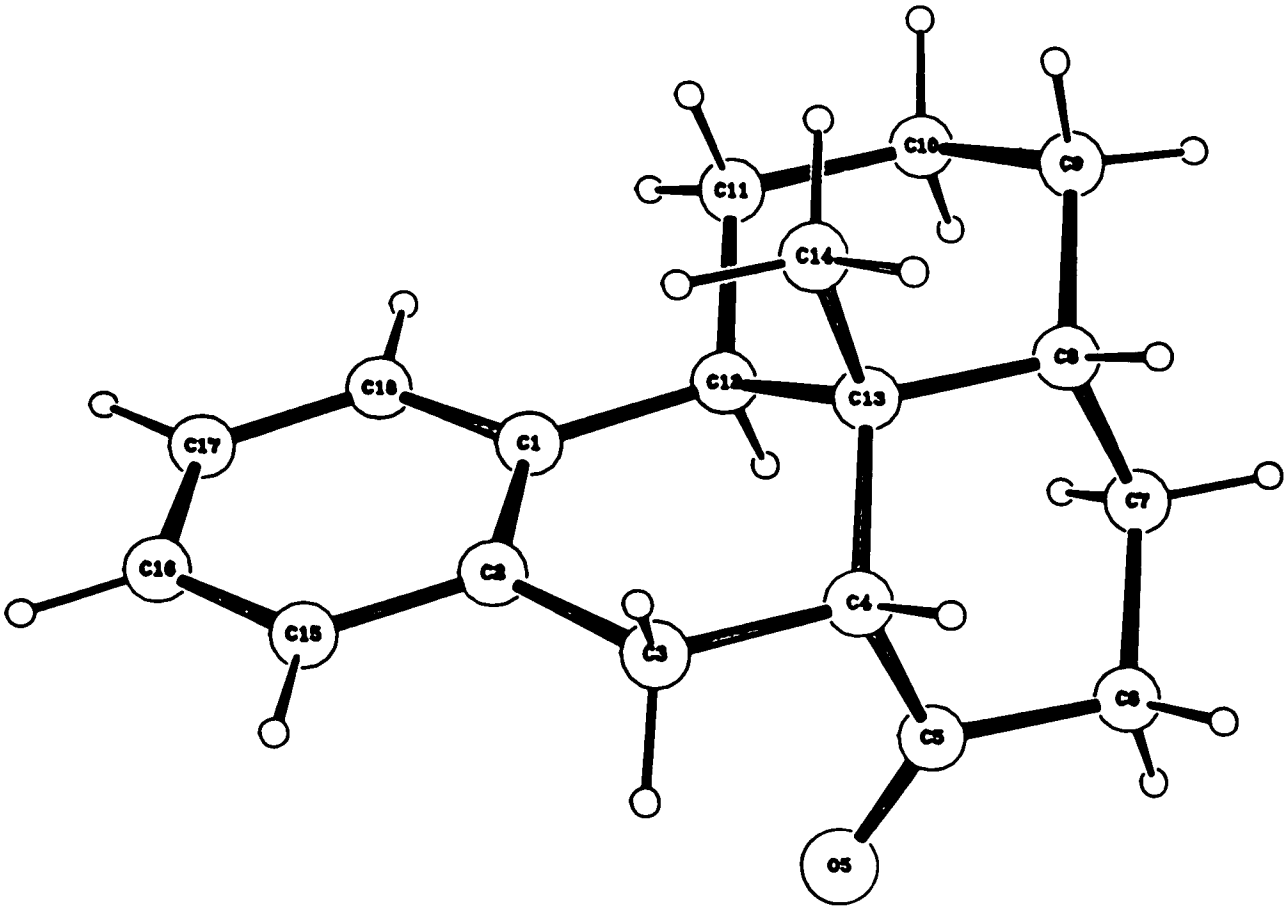


Figure 40: A perspective drawing of 140

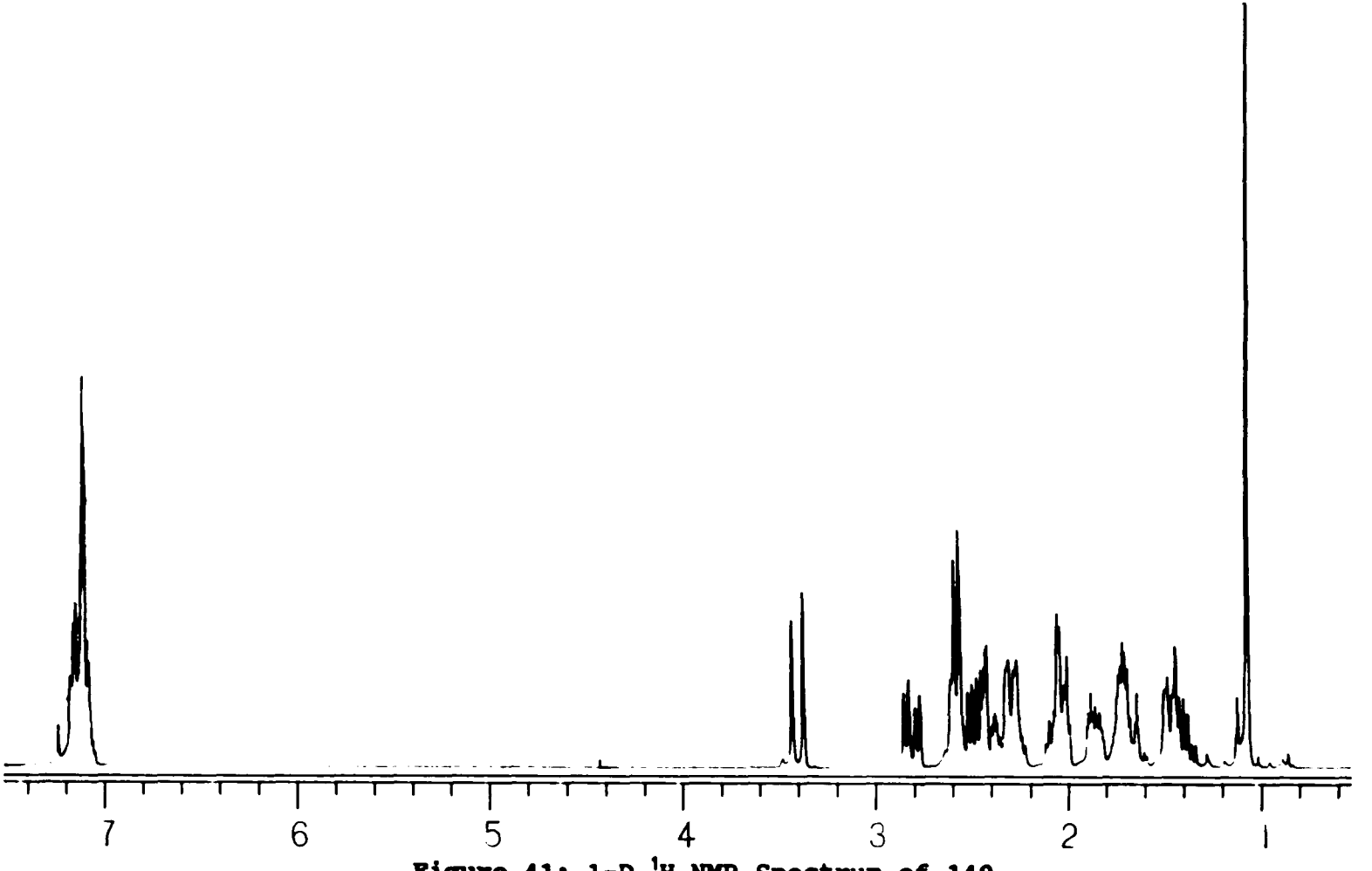
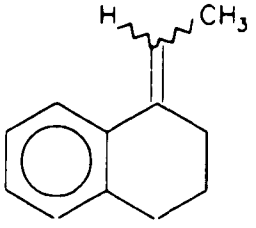


Figure 41: 1-D ^{1}H NMR Spectrum of 140

2.4.8 THE CONVERSION OF 140 INTO THE KETONE 151

One of our first attempts to introduce two conjugated double bonds, was by bromination of the benzylic positions $C_{(3)}$-H_2 and $C_{(12)}$-H, by NBS, followed by dehydrobromination with several bases. The ^1H NMR signal corresponding to the double bond produced between $C_{(3)}$-$C_{(4)}$ was a sharp singlet at δ 7. The double bond protons between $C_{(11)}$-$C_{(12)}$ were expected to be in the vicinity of 5.6-6.1, as seen from model studies of compound 148. The conjugated alkene 148 was prepared from a Wittig reaction between α-Tetralone and (ethyl)triphenyl-phosphonium bromide, and isolated as an inseparable E/Z mixture. The vinylic protons appeared as quartets at δ 5.6 (Z) and 6.1 (E), with vicinal coupling constants of 6.3 and 6.9 Hertz respectively.



148

Figure 42: Structure of 148

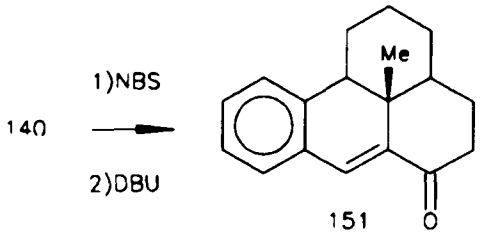


Figure 43: Bromination/dehydrobromination of 140

Not surprisingly, only the secondary benzylic position of 140 was brominated. Dehydrobromination using triethylamine failed. DBU[55] gave the conjugated ketone 151, together with an impurity that could not be separated. This impurity gave a dark brown color to the reaction residue, and was partially removed using the Chromatotron. The α,β-unsaturated ketone 151 was obtained in 10-20% isolated yield.

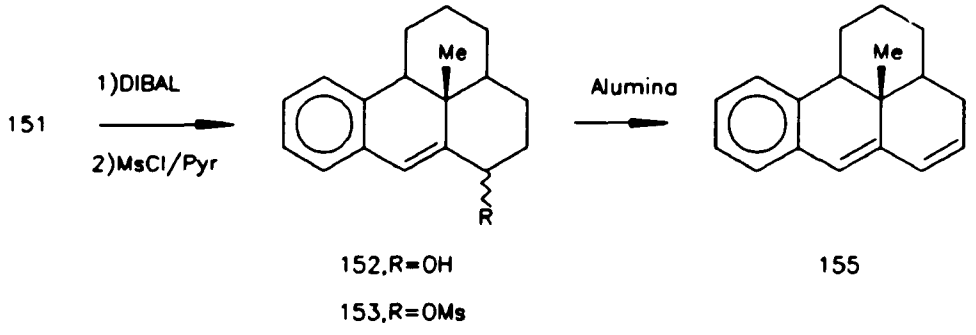


Figure 44: Formation of the triene 155

The reduction of ketone 151 using DIBAL-H gave an alcohol which could not be purified for characterization. It appeared that the alcohol obtained was cis to the central methyl, but we could not be sure. This alcohol was mesylated, then dehydromesylated[56] by stirring with neutral Alumina activity 1. The mesylate was absorbed on dry Al_2O_3 and left undisturbed for one hour. Then the treated alumina was covered with methylene chloride and stirred overnight. After filtration and removal of the solvent, compound 155 was isolated in ≈60% yield.

The spectrum corresponding to the triene 155 showed the following resonance in its ^1H NMR: (a) a multiplet splitting for $C_{(6)}$-H (δ 6.07), (b) a singlet for $C_{(3)}$-H (δ 6.17), and (c) double doublet for $C_{(5)}$-H (δ 6.39, J_{57} 2.47 and J_{56} 9.52 Hz).

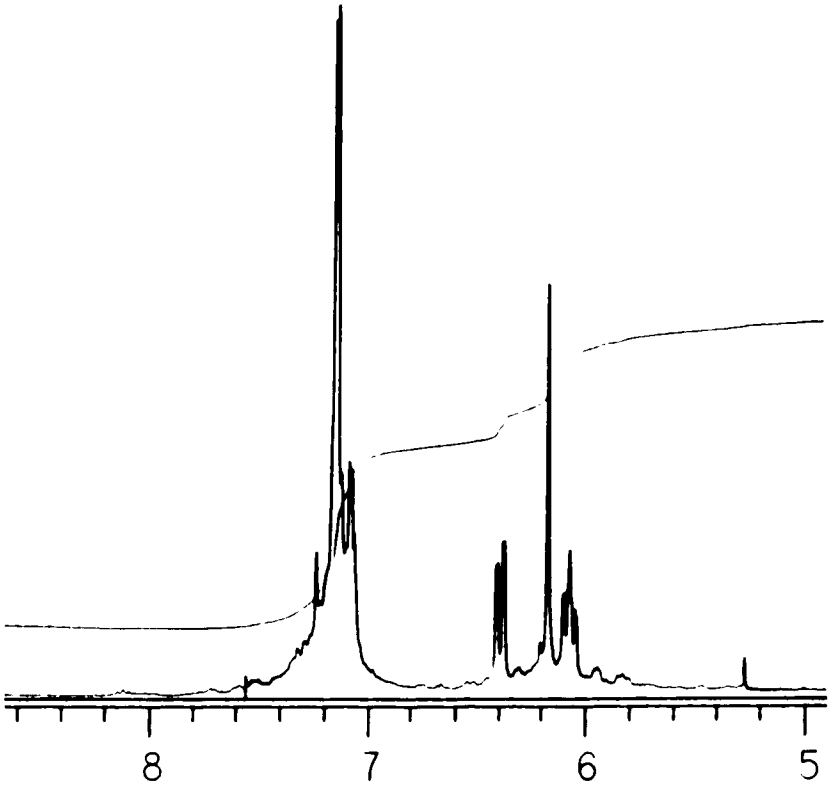


Figure 45: 1-D ^{1}H NMR Spectrum of 155

Addition of an equimolar amount of bromine, to 155, followed by dehydrobromination gave a low yield mixture of unidentifiable compounds.

2.4.9 THE OXIDATION of 140 by DDQ

Several ways[57] to form the conjugated system were attempted. Turner and Brown have used DDQ in their work to oxidize Neoergosterol.[58] Although, they observed that among several possible sites for attack by oxidizing agents, experimentally, the attack involved only the axial α-hydrogen atoms (tertiary and benzylic). An added example comes from Mechoulam et al.. This latter group worked[59] on the synthesis of dl-Cannabichromene. They studied the oxidation of both cis and trans precursors of Cannabinol, in which the α-hydrogen was benzylic as well as allylic. Only the trans hydrogen was nearly perpendicular to both unsaturated systems. The cis isomer was perpendicular to the double bond but parallel to the plane of the aromatic ring. During the abstraction of this α-hydrogen, by chloranil, the trans elimination was favored over the cis elimination. The observation obtained from both works, was that the reactive α-hydrogen was orthogonal to the plane of the aromatic ring. This orthogonality appeared to allow a σ-π overlap necessary for the hydrogen abstraction. None of the other benzylic positions were favored for similar interactions. It can be concluded that stereoelectronic factors influence the course of the reaction sites of apparent similar reactivity.

Considering the perpendicularity of $C_{(12)}$-H to the benzo group, the oxidation[60] of 140 by DDQ was tried. The crude NMR showed the presence of an all conjugated double bond system. All the data fitted for the expected and final compound II, except for one odd and very important observation: the singlet peak corresponding to the $-C_{(14)}H_3$ (methyl) was absent. Using a similar procedure, W. Huang has observed[61] the transformation of the pentaene 159 into the known ketone 160.

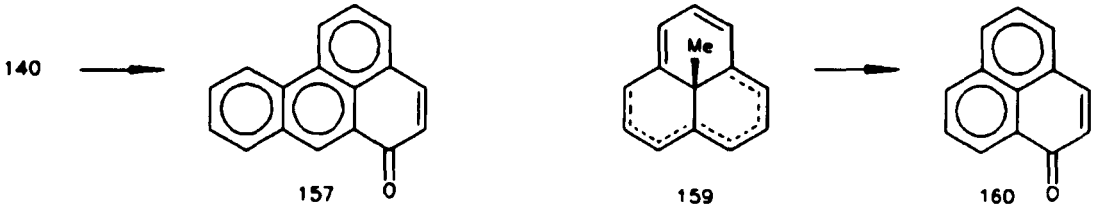


Figure 46: The aromatization by DDQ

The isolation of the aromatic ketone[62] 157 has been described by R. Harvey and coworkers. They have studied benzylic oxidation with DDQ in aqueous media, and have concluded that when a benzylic site was present, the reaction took place on the carbon which afforded the most stable carbocation intermediate.[63] This seemed to be the case for $C_{(13)}$. It became clear, that DDQ was too strong for our purposes.

Harvey[64] provided us with an authentic sample of ketone 157. Comparison of the 300 MHz spectrum of Harvey's and our ketone proved without doubt that both compounds were identical.

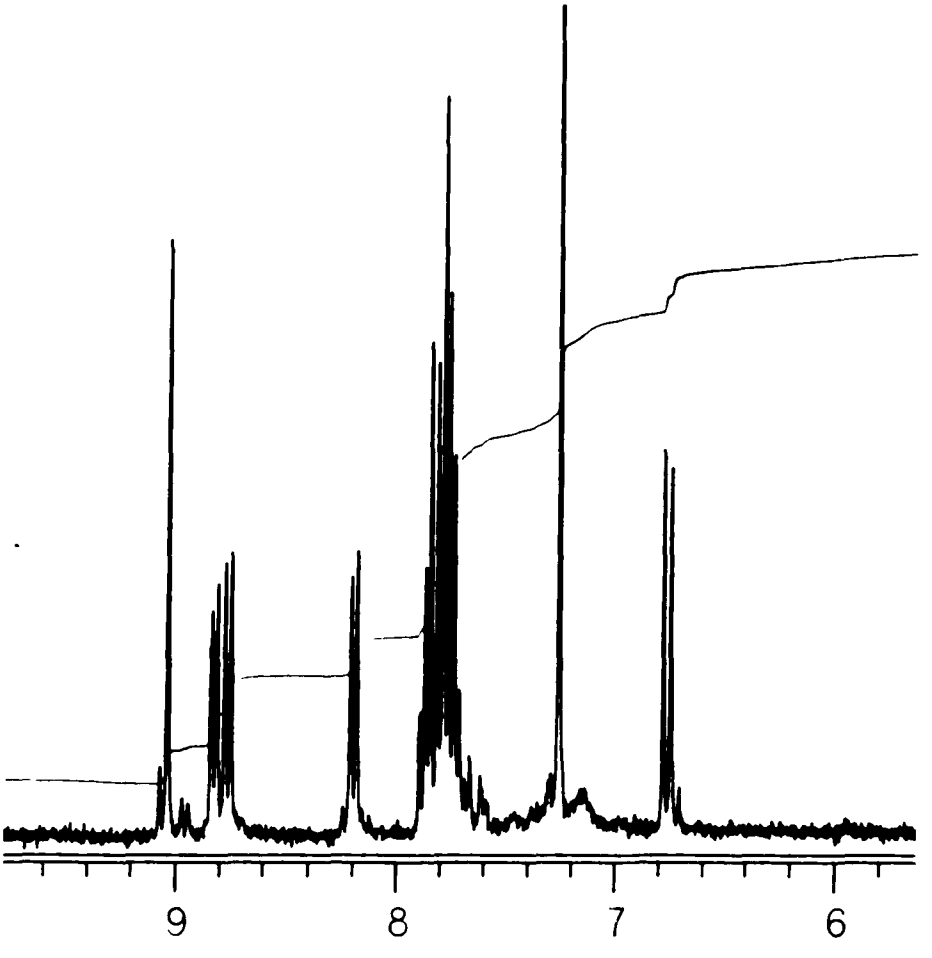


Figure 47: 1-D ^{1}H NMR Spectrum of 157

2.5.0 THE PATHWAY C TOWARD II

One of the problems associated with pathway B was the lack of proper functionality in the top ring, as well as the difficulty in introducing it, for the formation of the peripheral conjugated π system. We therefore considered the introduction of a "handle" for one double bond masked as a protected alcohol, as reported by Kametani during one of his syntheses of steroids.[65] A more direct approach involves the synthesis of 191 (figure 50) and its subsequent IMDA to 195 via the conjugated o-quinodimethane shown in figure 48. We looked into the unstabilized Wittig reaction between 10 and 168 (figure 51), as the source of the cis olefin 191, followed by the IMDA cycloaddition.

This is illustrated as the pathway C from scheme 1.

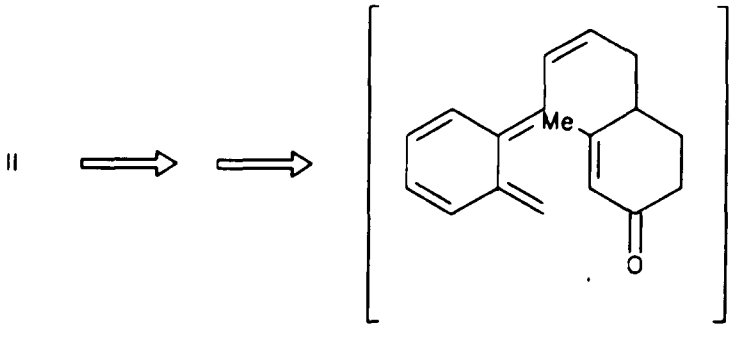


Figure 48: The pathway C toward II

To the best of our knowledge, there is no report of any Diels-Alder of an o-quinodimethane with an adjacent double bond. The presence of a double bond presented several[66] drawbacks:

(a) the possibility of a known 3,3-sigmatropic Cope rearrangement,[67] or

(b) a 1,7-hydrogen shift,[68] and

(c) a possible cis/trans isomerization during the required thermolysis.

To test the possible outcome, the Diels-Alder cycloaddition of 35, an structurally related system, and maleic anhydride, was examined. The ^{1}H NMR spectrum of the reaction mixture indicated that the double bond was unchanged, and retained its stereochemistry. The Diels-Alder adduct 162 was isolated pure in 50% yield.

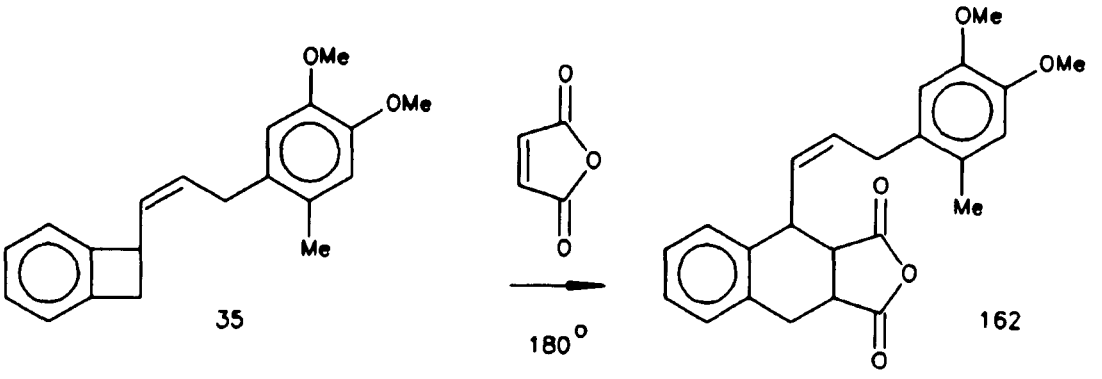


Figure 49: Model studies of 35

The synthesis of 162 appeared to be the first case where none of the expected rearrangements were observed. This opened new possibilities with only one restriction: the double bond had to be cis to allow diene-dienophile interaction. The J coupling constant between the two vinylic protons of either 35 or 162 was 10.5-11 Hertz, a borderline value that could be either cis or trans.

The synthesis of the required α,ß-unsaturated ketone 191 is discussed in the next section.

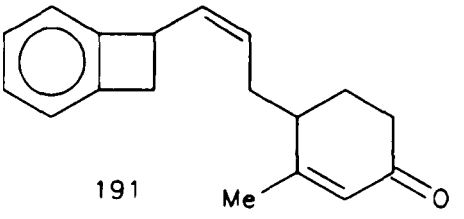


Figure 50: The Diels-Alder precursor for pathway C

2.5.1 RETROSYNTHETIC ANALYSIS FOR PATHWAY C

The retrosynthetic analysis for compound 191 is a combination of the other pathways. That is, it combines the Wittig coupling used in pathway A, and the 3-methylcyclohex-2-ene-1-one dienophile used in pathway B.

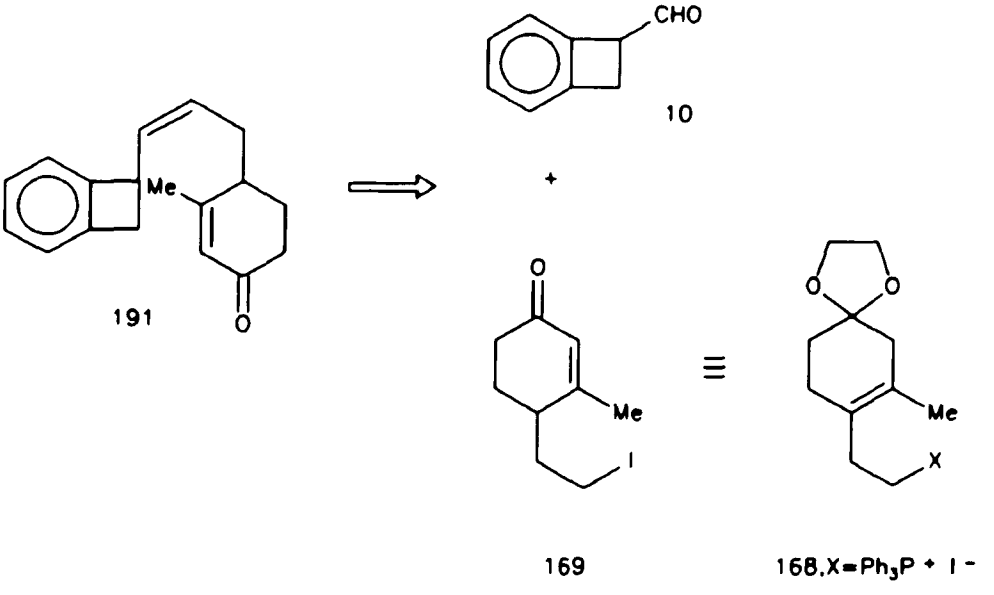


Figure 51: Retrosynthetic analysis for pathway C

2.5.2 THE SYNTHESIS OF THE 3-METHYL-KETONE

A variation of our early Hagemann's ester approach became necessary, as the group attached to $C_{(4)}$ needed to be only two carbons long. The other connecting carbon was supplied by the aldehyde from the benzocyclobutene moiety.

Initially, we tried the Wittig reaction of the aldehyde 88. We succeeded in the synthesis of the conjugated diene 164 in 68% yield. Looking into the conversion of 164 to terminal alcohol 165, we came across Brown's report about the hydroboration of Myrcene[69] with disiamylborane. The direct conversion of several olefins to primary iodides via hydroboration-iodination is also known.[70] Attempts using either diborane, disiamylborane, or 9-BBN, followed by sodium hydroxide and iodine did not give the halogenated compound 167. The hydroboration to the alcohol 165 was also tried and was only successful with 9-BBN, but purification of the alcohol presented problems causing us to attempt a different approach. The unsaturated system 164 was very similar to 91/92, and showed a comparable unreactivity toward known procedures. It seemed that the highly conjugated and unsaturated system either hindered any further reactivity or enhanced it in an uncontrollable manner, such as overreduction of 91.

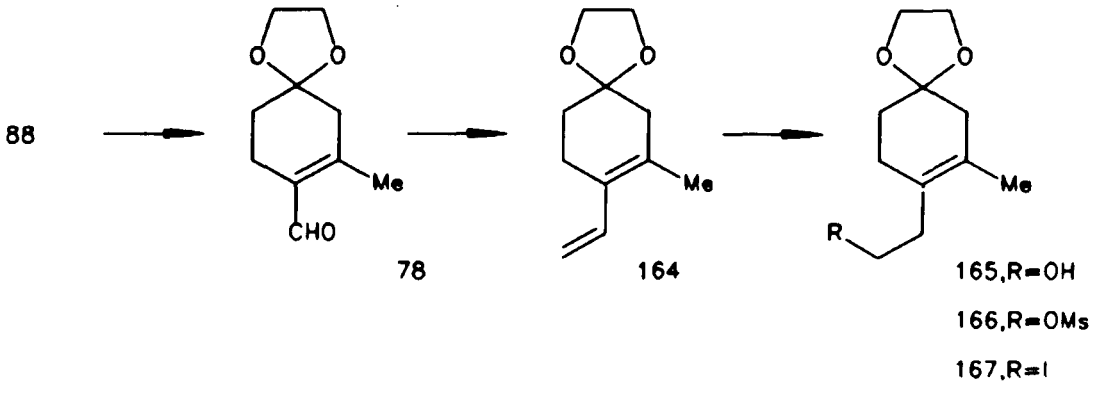
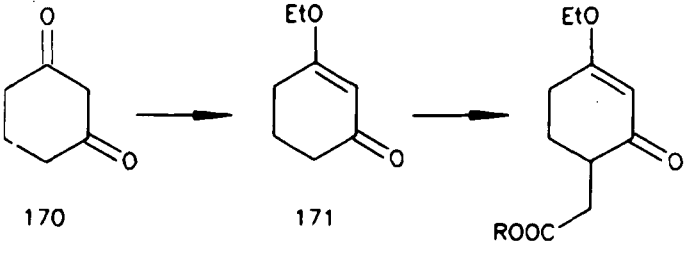


Figure 52: An attempt toward 165

2.5.3 THE STORK ENOLATE APPROACH TOWARD 99

Our last alternative examined Stork's procedure for regiospecific alkylation of cyclic ß diketone enol ethers,[71] such as 171. The diketone 170 was easily converted to 171 by a known procedure[72] in 91% yield. Hydrogen abstraction was affected regiospecifically, under kinetic conditions with n-butyllithium at -78 °C, followed by alkylation to the t-butylester derivative[73] 172 as the only product, although it was converted to carboxylic acid 173 during distillation when the temperature or pressure were too high (73% combined yield).



170 171

172,R=t-Bu

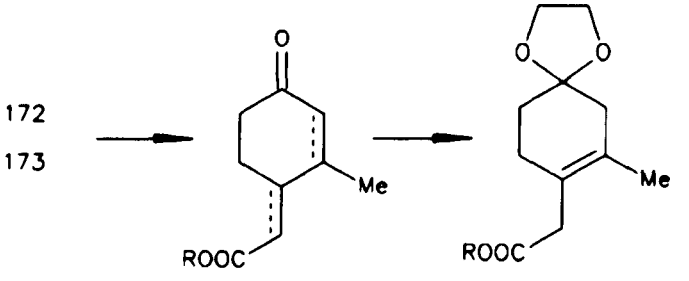
173,R=H

Figure 53: The enolate approach

Treatment of the ester 172 with methylmagnesium bromide, followed by acidic workup, produced a 1:1 mixture of two isomers: the α,ß-unsaturated ketone and what seemed to

be the α,ß-unsaturated ester. Rinehart and Dolby studied[74] the equilibria of systems similar to 176, and indicated that if the group at the ester position was replaced by larger or more branched groups, the proportion of the conjugated ester increased. This appeared to be the case for 176.

On the other hand, 173 was treated with two equivalents of methylmagnesium bromide yielding the α,ß-unsaturated ketone 177 as the exclusive isomer.



176,R=t-Bu
177,R=H
178,R=Et

180,R=t-Bu
181,R=Et

Figure 54: Alkylation and protection to the ketal

Conversion of both t-butyl ester and free acid to the ethyl ester 178 was accomplished by refluxing them in absolute ethanol using catalytic amounts of PTSA (58% conversion for 176 and quantitative for 177).

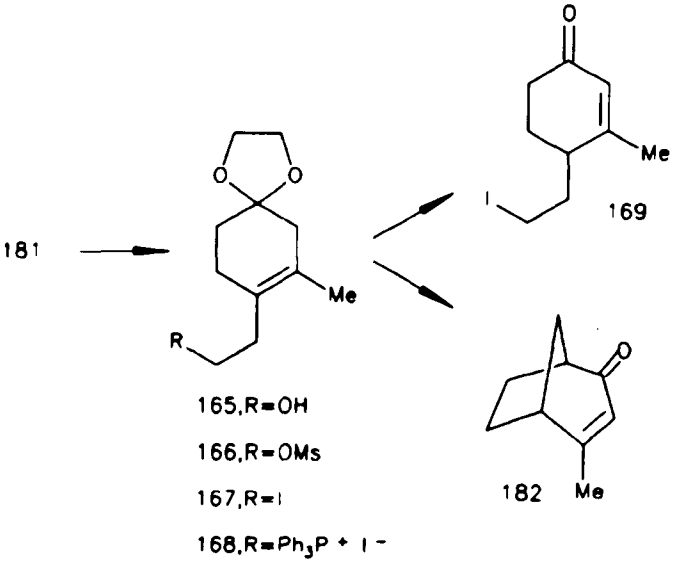


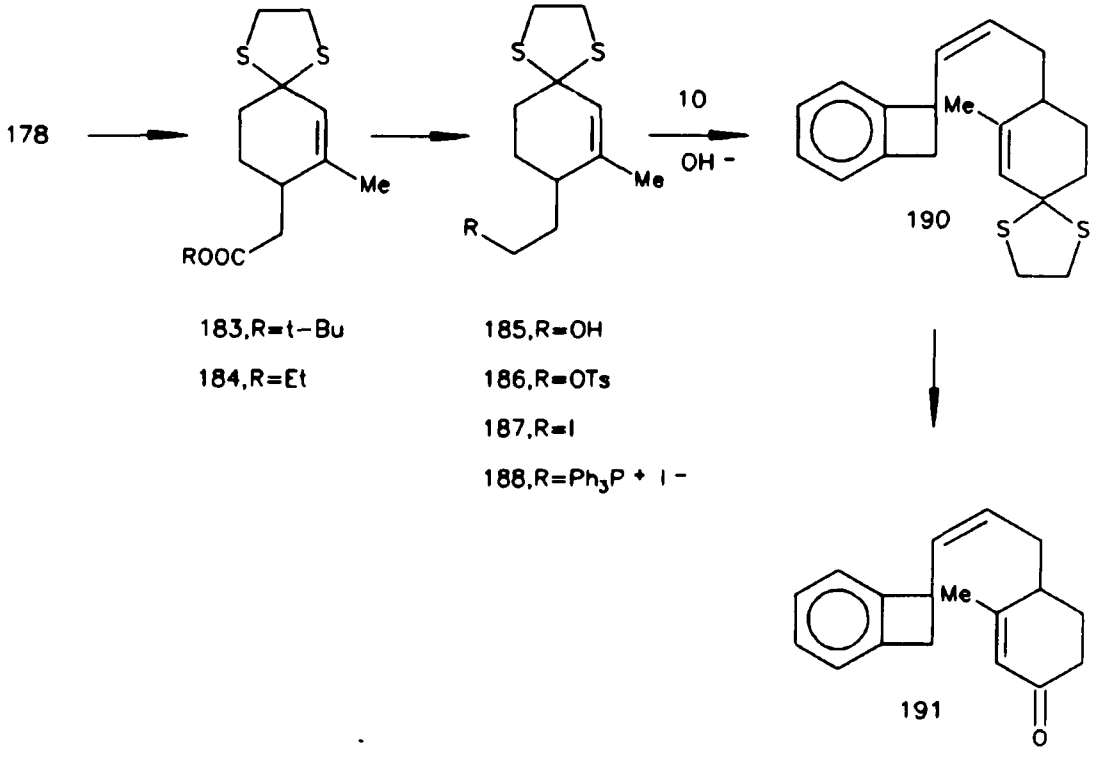
Figure 55: The transformation of 181 and its sideproducts

Protection of the ketone 178, to the ketal 181, reduction to the alcohol 165, and its transformation to the mesylate derivative 166 proceeded in very high yields. The mesylate-halide exchange of 166 gave the ketone 169 which had to be reprotected to 167 (88% yield). During the formation of the phosphonium salt 168, the bicyclic ketone[75] 182 was isolated instead. It appeared that traces of hydrogen iodide, formed in the preparation of the salt, deprotected

and rearranged the ketal 167. This acid catalyzed isomerization could be avoided by changing protecting groups: a thioketal instead of the ketal, with small amounts of diisopropylethylamine (DIEA) as an acid scavenger, as reported by McCarry in his work[76] on this system, prove effective.

One advantage of the thioketals series was that the double bond did not migrate to give the tetrasubstituted alkene. Regeneration to the α,β-unsaturated ketone 191, from the ketal, would have required catalytic amounts of PTSA, which could have affected the cis double bond formed from the Wittig reaction in the synthesis of 190. Rearrangement of the olefin could have changed the stereochemistry required for the intramolecular Diels-Alder cycloaddition, hindering and possibly preventing it.

SCHEME <9>



The ketone 178 was protected to the thioketal[77] 184 by treatment with ethane dithiol/BF_3 etherate in 84% yield. The standard LAH reduction of the ester 184 gave quantitative amounts of the alcohol 185 as a white cloudy oil. This alcohol was treated with p-toluenesulfonyl chloride in pyridine, followed by sodium iodide in acetone with traces of DIEA, affording the iodo derivative 187. This 187 was heated in acetonitrile, in the presence of triphenylphos-

phine and DIEA, giving the salt 188 in ≈80% yield from 185. The Wittig coupling of the thioketal-phosphonium[78] salt 188 with 10 gave the oil 190 in 85% isolated yield. The ^{1}H NMR of 190 presented a quartet overlapping with a singlet in the region around δ 5.7. The $J_{quartet}$ coupling constant appeared to be around 9 Hertz but it could not be determined properly. The deprotection to 191 was performed by heating 190 in a solution of MeI/H_2O/acetonitrile (89% yield).

2.5.4 CHARACTERIZATION OF 191

The ketone 191 was characterized by its ^1H NMR spectrum showing the following:

(a) a singlet methyl peak (δ 2.02),

(b) two sets with double doublet splitting corresponding to the secondary benzylic protons, (δ 2.91, 2.41 and 14.1 Hz; and δ 3.52, 5.4 and 14.1 Hz),

(c) a broad multiplet for the tertiary benzylic proton (δ 4.35),

(d) a vinylic multiplet (δ 5.46, 1H), a triplet-doublet (δ 5.74, 1H, 1.3 and 9.6 Hz),

(e) a vinylic singlet (δ 5.59, 1H)

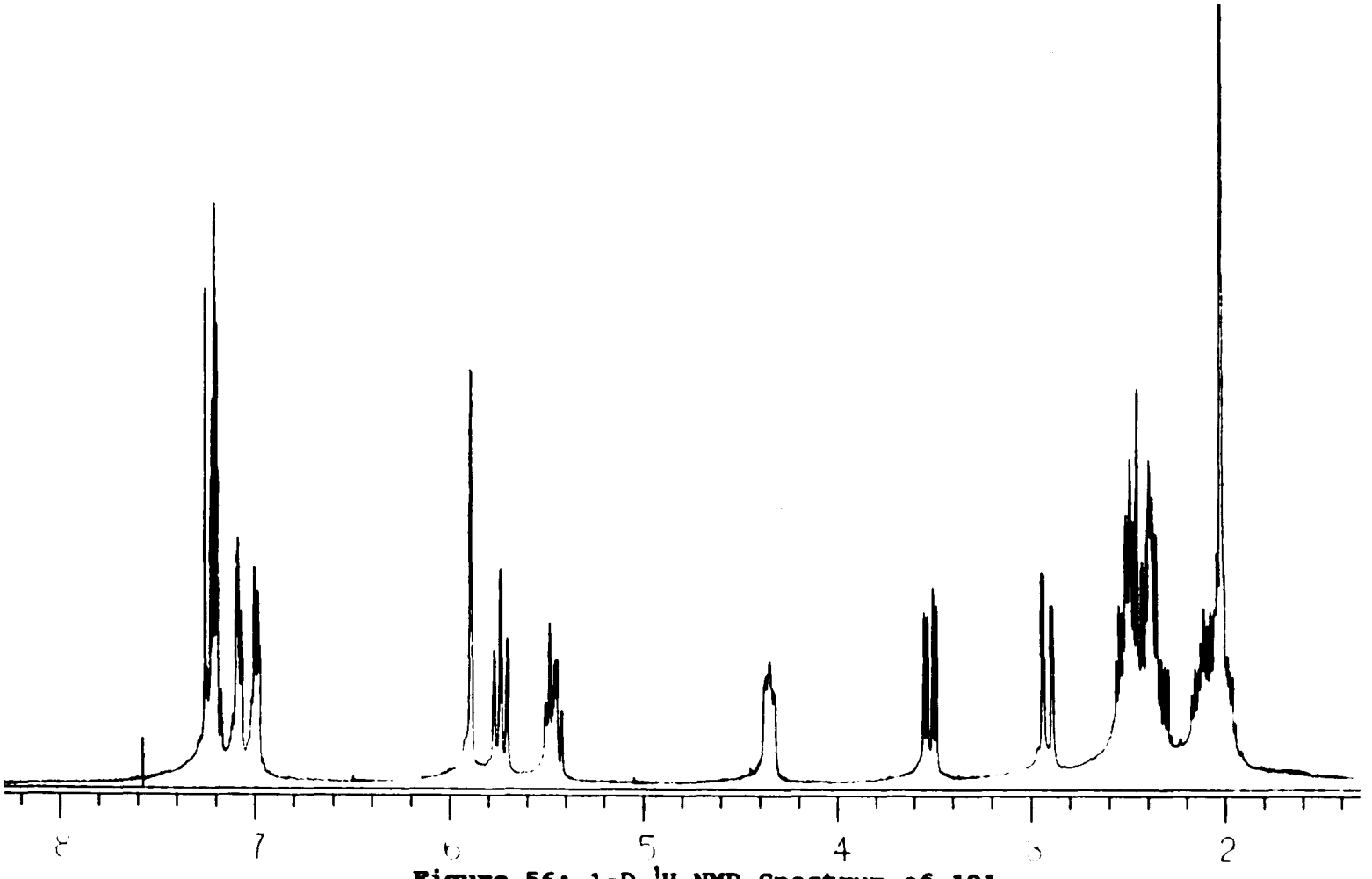


Figure 56: 1-D ^{1}H NMR Spectrum of 191

2.5.5 THE INTRAMOLECULAR DIELS-ALDER REACTION of 191

The thermolysis of 191 was tried in refluxing o-dichlorobenzene, and followed by TLC. After 1.5 hours, the ketone had disappeared, and a spot* with a higher R_f appeared instead.

The crude NMR analysis of the reaction mixture showed:

(a) the presence of a singlet methyl at δ 0.92,

(b) both a vinylic doublet and a multiplet, and

(c) a pattern similar to the one obtained for the secondary benzylic hydrogen and the $C_{(4)}$-H of 140.

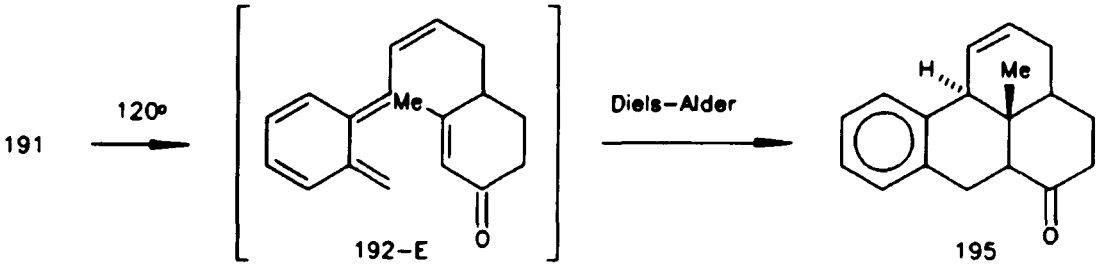


Figure 57: The intramolecular cycloaddition of 191

*. This spot is not UV active.

Moreover, this thermolysis was repeated at several temperatures. We started monitoring this cyclization at 100 °C, and took samples for analysis after raising the temperature in increments of 10 °C, followed by equilibration for 15 minutes. This TLC analysis showed the presence of the Diels-Alder adduct 195 at ≈110 °C. This indicated that the isolated double bond produced a stabilization similar to the nitrile moiety, helping to lower the cyclobutene opening temperature. Based on this result, 191 was refluxed for 10 hours in toluene.* The ^{1}H NMR spectrum showed 195 as the major product. Purification by column chromatography separated an interesting set of isomeric compounds.

The tricyclic 195 was isolated in 42% yield. It was characterized by its 2-D ^{1}H NMR spectrum. This spectrum indicated that $C_{(7)}$ has two nonequivalent geminal protons. Molecular models suggested that the axial proton was under the electronic influence of the isolated double bond, as it appeared 0.2 ppm downfield from the equatorial proton.

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*. Oil bath at 120 ± 2°C.

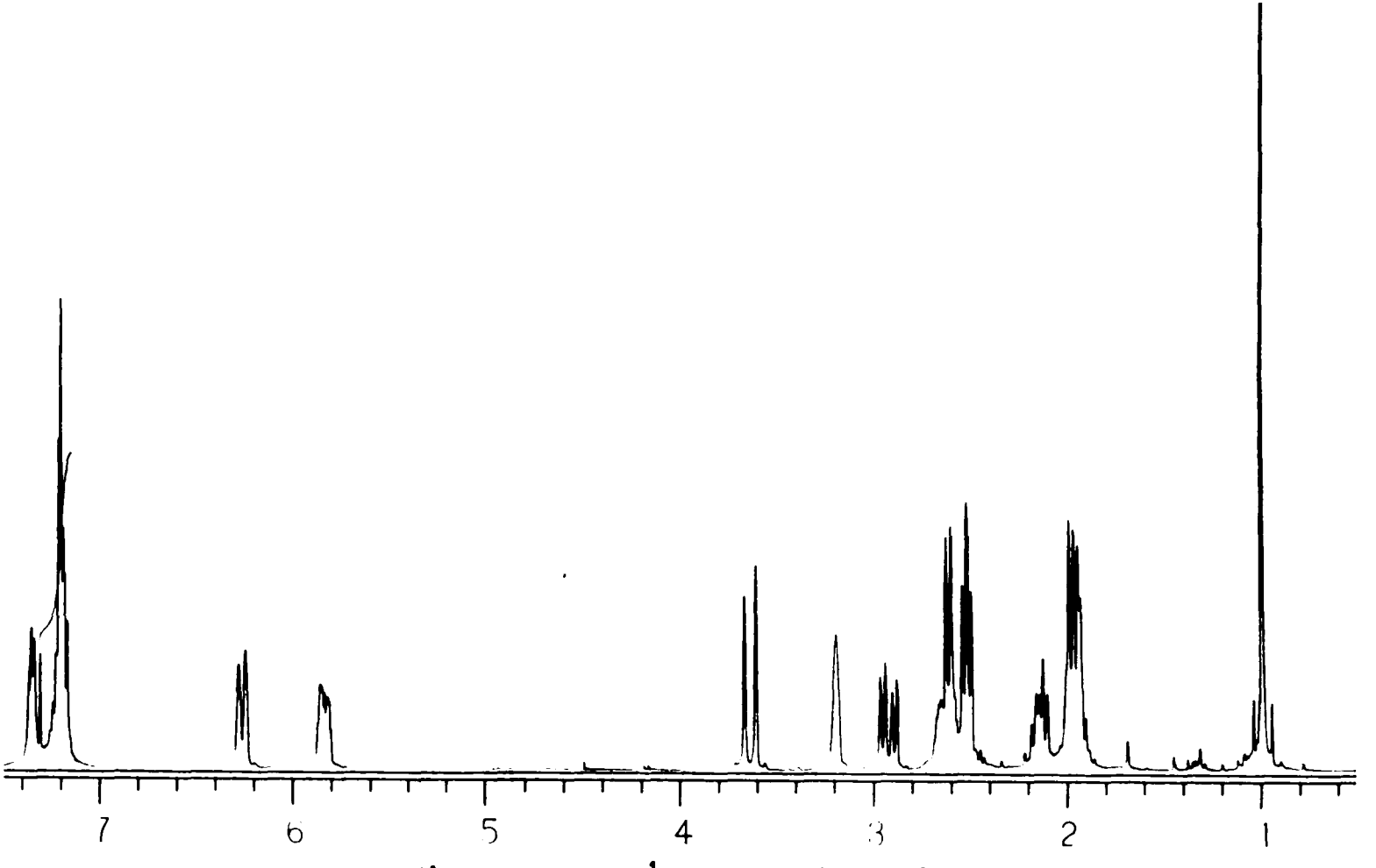


Figure 58: 1-D ^{1}H NMR Spectrum of 195

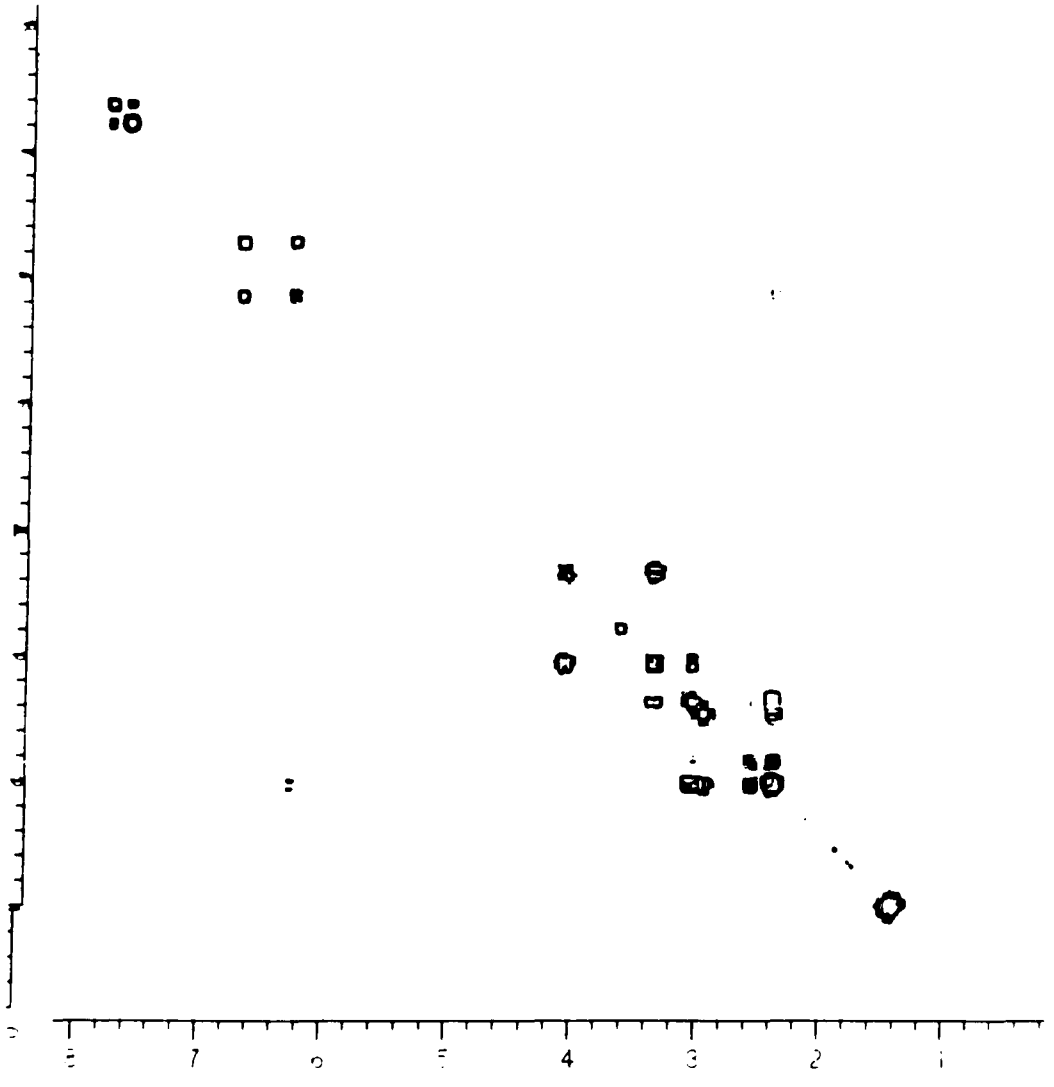


Figure 59: 2-D ^{1}H NMR Spectrum of 195

The 1,7 sigmatropic shift product 196 was present in ≈7%. The isomer 197, the result from the Cope rearrangement of 192, accounted for ≈9%. The ketone 197 was characterized by its vinylic protons, but could not be isolated pure.

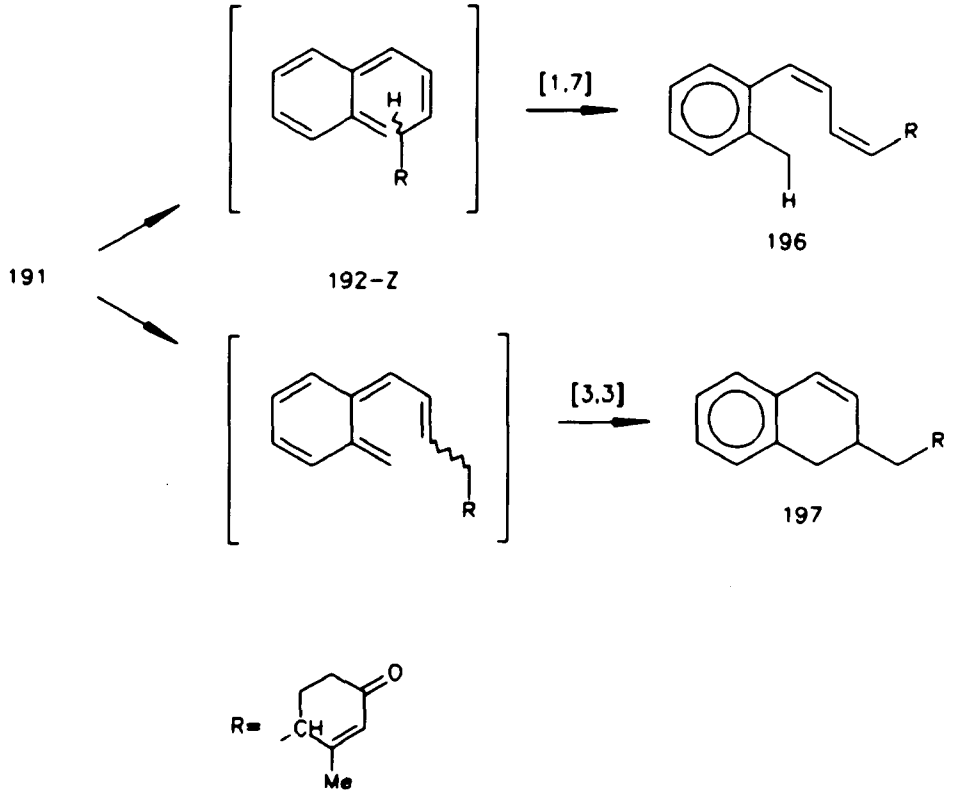


Figure 60: The isomers of 195

Furthermore, 197 could not be oxidized, by DDQ, to the respective naphthalene derivative.

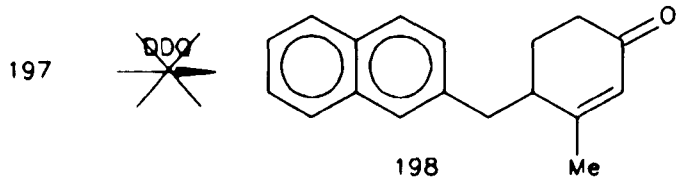


Figure 61: Attempted oxidation of 197

The reduction of 195, to the alcohol, using sodium borohydride in refluxing ethanol, gave the axial and the equatorial epimers in a ratio of 3:1. Mesylation of the alcohol mixture was quantitative. The ^1H NMR spectrum corresponding to 200 showed two different methyl mesylates (δ 2.4 and 3) but one single methyl peak (δ 0.9).

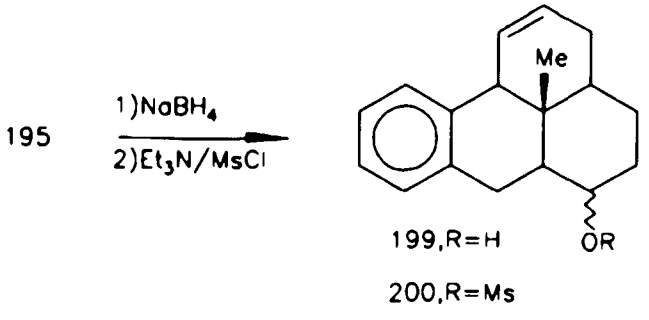


Figure 62: The reduction/mesylation of 195

Dehydromesylation on alumina gel gave only the most substituted triene 201 in 66% isolated yield. The unreacted equatorial mesylate was recovered in ≈17%. The axial mesylate was the isomer possessing the right stereochemistry required for the dehydromesylation, as it was antiperiplanar to the $C_{(4)}$-H. The recovered equatorial mesylate 200 might be transformed to the axial alcohol according to known procedures.[79] In this way, both mesylates could be used for improving the yields of 201.

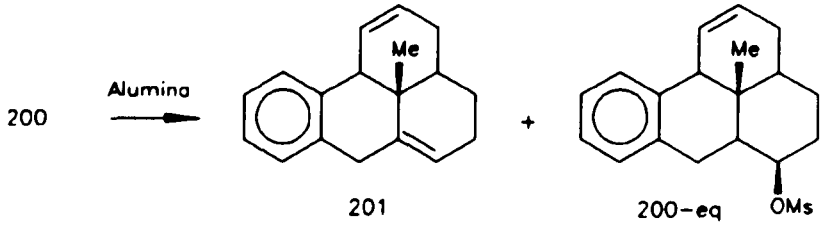
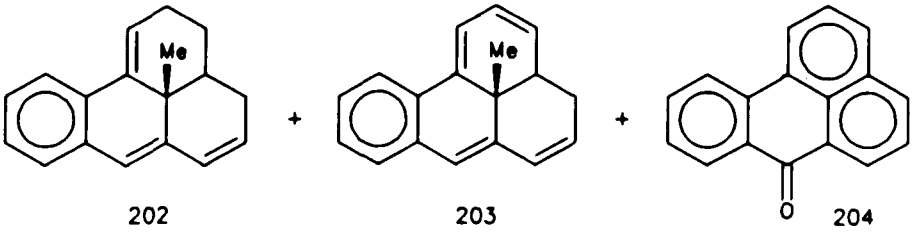


Figure 63: The dehydromesylation of 200

Further functionalization of the triene was tried in several ways. Bromination by NBS, followed by treatment with potassium t-butoxide gave a dark residue from which traces of the desired cyclic pentaene 203 were observed. Next, the oxidation by DDQ was tried under different mild conditions and ratios, giving the tetraene 202, the pentaene 203, and the known aromatic ketone[80] 204 as the products.



202 203 204

Figure 64: The oxidation of 201

The olefins 202 and 203 showed very similar R_f values even under chromatotron conditions, but they might be separated using HPLC.

A tentative assignment for the ^1H NMR spectrum of 202 and 203 appears on table I. This assignment has been possible by the combination of the 1-D and 2-D spectra.

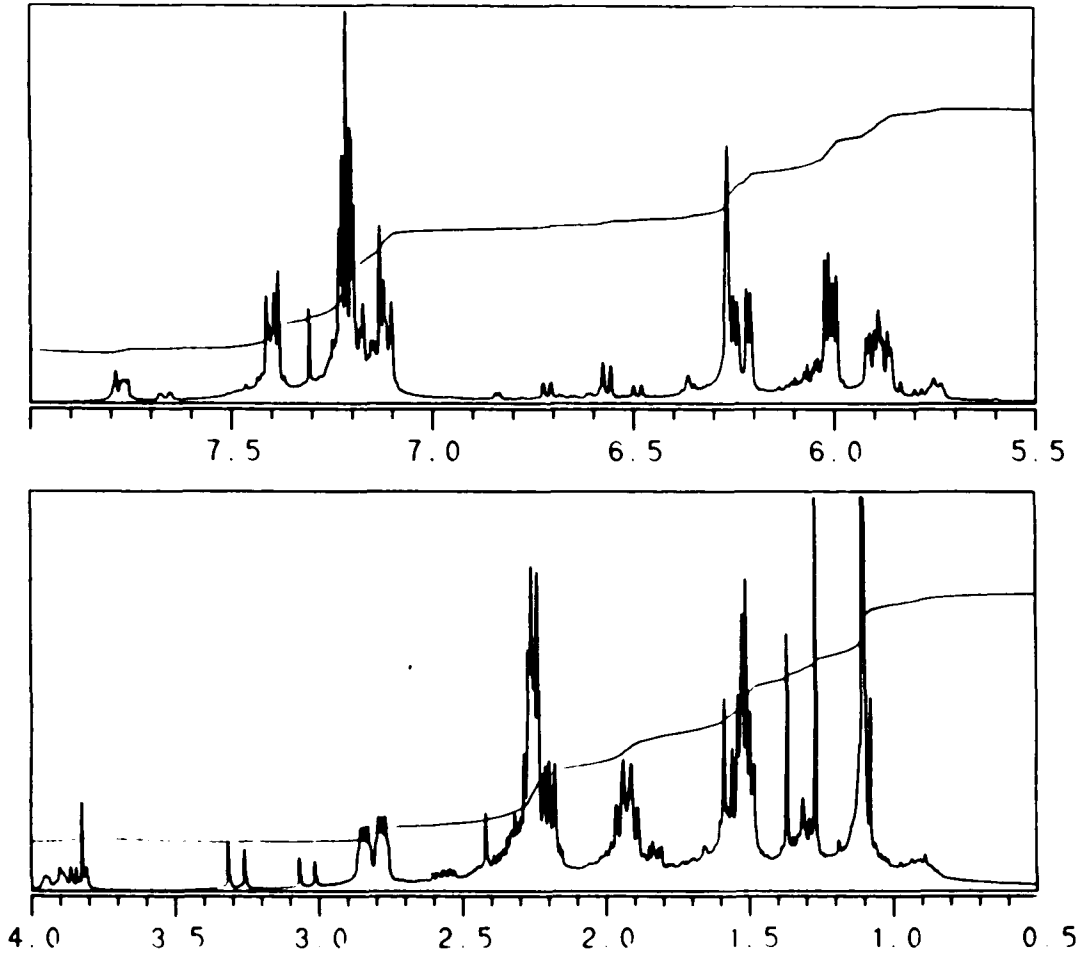


Figure 65: 1-D ^{1}H NMR Spectrum of 202

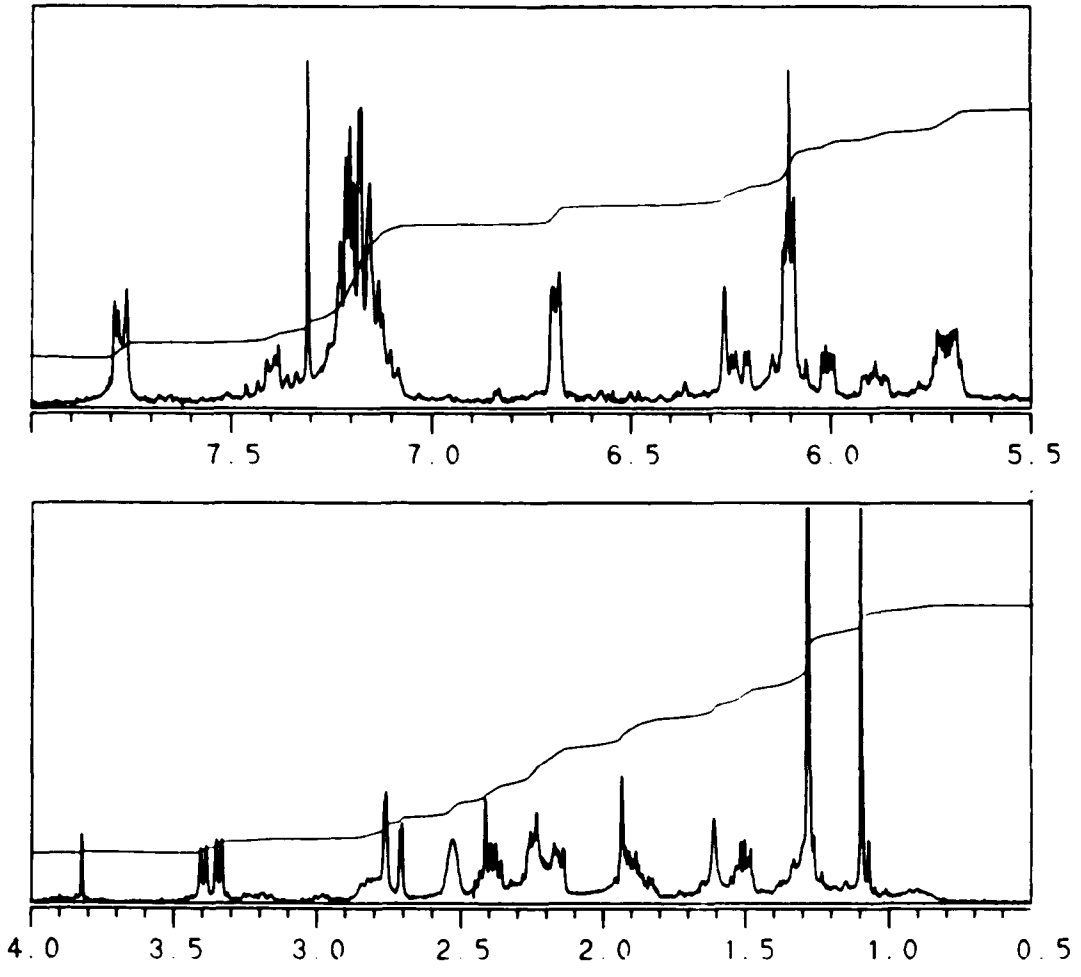


Figure 66: 1-D ^{1}H NMR Spectrum of 203

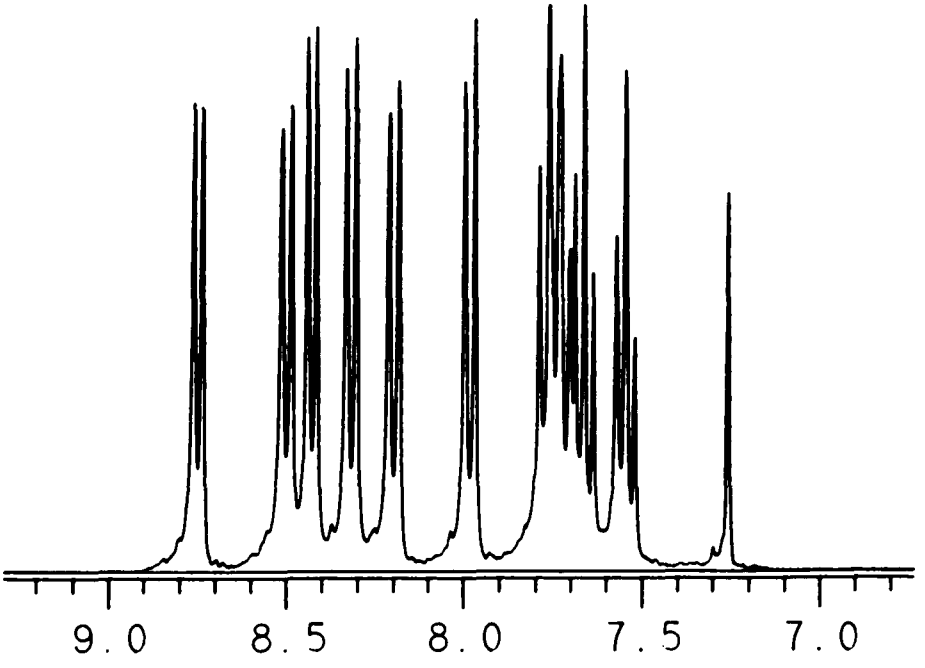
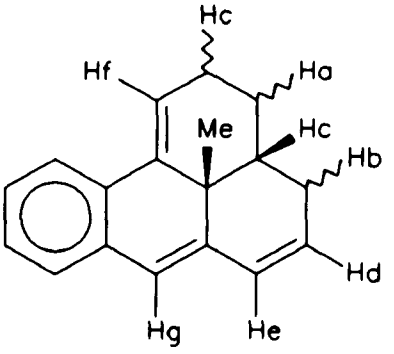
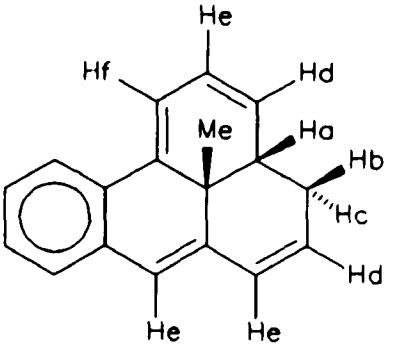


Figure 67: 1-D ^{1}H NMR Spectrum of 204



202



203

	-Me	-Ha	-Hb	-Hc	-Hd	-He	-Hf	-Hg
202	1.1	1.4 1.8	2.2	2.8	5.9	6.0	6.2	6.3
203	1.3	2.4	2.8	3.4	5.7	6.1	6.7	

Table I. ^{1}H NMR assignment for compounds 202 and 203. All the values are in ppm or δ units.

The 2-D NMR shows that there is no vinylic proton present in the aromatic region.

Although, the ^{1}H NMR spectrum of commercially available Benzanthrone, and the one corresponding to the reaction mixture appeared to be different, the identity of the ketone 204 was proven to be correct. Addition of small amounts of benzanthrone, into the mixture, did not introduce additional

peaks on the spectrum but only increased the ratio of the aromatic protons versus the non-aromatic region.

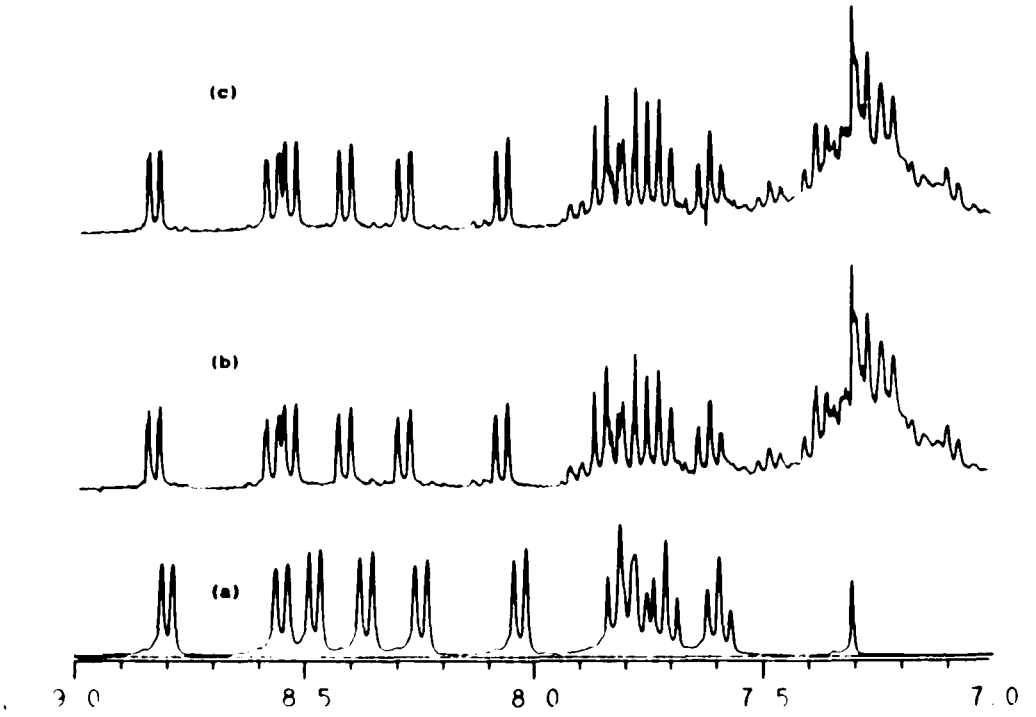


Figure 68: ^{1}H NMR spectrum of (a) Benzanthrone, (b) the reaction mixture, and (c) the benzanthrone and the reaction mixture

The splitting and shifting of the peaks at δ 7.4-8.8 appear to be due to the presence of traces of acid from the solvent. This conclusion comes from the ^{1}H NMR analysis of the benzanthrone in chloroform-d followed by the addition of a drop of trifluoroacetic acid. These results are consistent with a similar analysis of Perinaphthenone as reported[61] by H. Prinzbach et al.

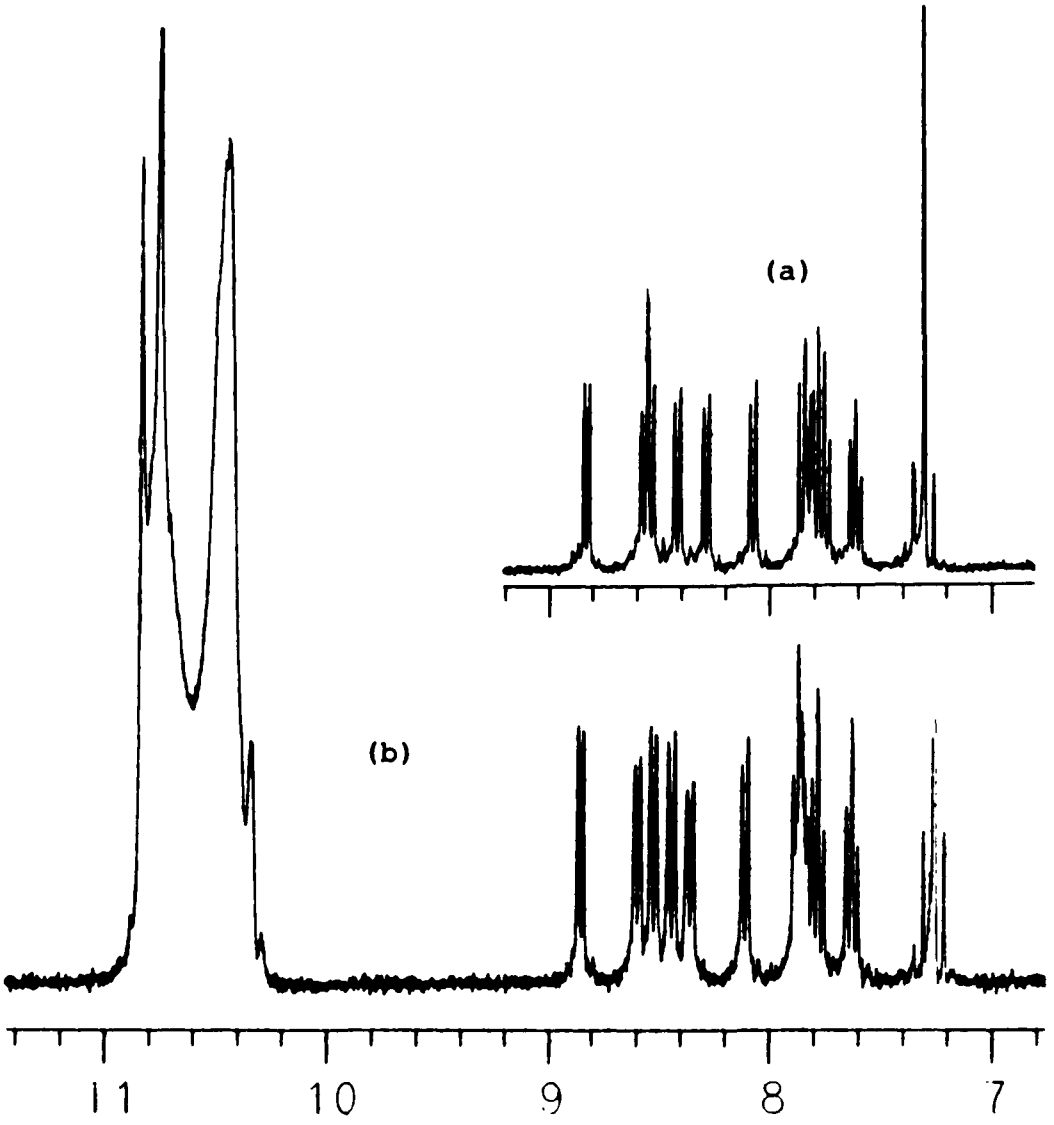
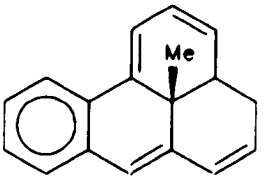


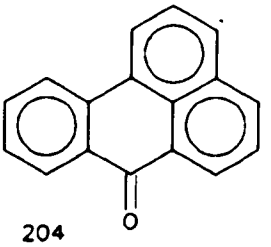
Figure 69: (a) Benzanthrone, (b) benzanthrone and TFA

2.6.0 CONCLUSION

The search for II has come a long way since its first approach through the o-quinone intermediate. The presence of the pentaene 203 and the benzanthrone 204 seem to indicate that milder reaction conditions (temperatures lower than ambient temperature) or a different approach have to be tried. The main question remains: was II present after the formation of 203 and before the benzanthrone?. It is most likely that II has been synthesized but was not detected because it decomposed or the right conditions were not present. Maybe DDQ is too reactive for our case. Chloranil could be a better oxidizing agent.



203



204

Figure 70: The pentaene 203 and the ketone 204

A speculative mechanism for the formation of 204 is derived from the weakness of the $C_{(13)}$-Me bond, as the ketones 157 and 160 (section 2.4.9) have been observed, but before any speculations, a brief introduction of the known chemistry of the phenalenes and a discussion of DDQ oxidation is in order.

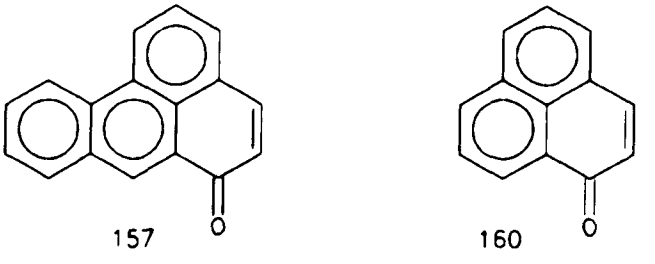


Figure 71: Products from DDQ oxidation in the 13-Methylphenalene system

Several features of the chemistry of phenalenes[82] are known. Phenalene forms remarkably stable anion, cation, and radical species, generated by the loss of a proton, hydride, or hydrogen atom, respectively. Quantum chemical studies as well as Hückel molecular orbital calculations predict that anion, cation, and radical possess the same π-electron delocalization energy.[83] The electron density distribution (HMO) of the phenalenium cation at positions 1,3,4,6,7, and 9 are +0.167, and zero at positions 2,5,8, and 13. Phenalenium perchlorate, as well as other salts, are known to be attacked irreversibly by moist air producing phenalenone and phenalene. The phenelenyl radical has been made by shaking a solution of the phenalene anion in an atmosphere of oxygen, forming phenalenone and a higher polymer.[84] In the absence of oxidizing agents the radical is stable for indefinitely long periods.[85] The reactivity of any of the phenalene ionic species produces a common compound as represented by the phenalenone.

Mechoulam[86] has pointed out that quinone dehydrogenation of hydroaromatic compounds has been shown to be a two step reaction proceeding through a cationic intermediate. Müller, Joly, and Mermoud[87] studied the mechanistic hypothesis of cis over trans abstraction of two hydrogen atoms by DDQ and have concluded that both mechanisms are consistent with their experimental results, that is, that there is no stereochemical requirement for removal of the hydrogens.

The reaction of pentaene 203 with DDQ present the possibility of forming carbonium centers at either $C_{(7)}$ or $C_{(8)}$.

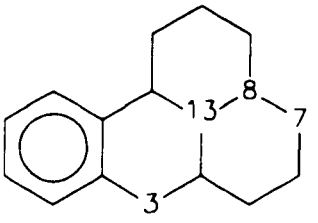


Figure 72: Numbering of 203

Abstraction of the axial $C_{(7)}$-H hydride should be favored over the other two allylic hydrogens, as $C_{(8)}$-H is partially blocked by the central methyl group. The resulting vacant p orbital at $C_{(7)}$ becomes coplanar to the sp^3 $C_{(8)}$-H bond, constituting the ideal condition for the $C_{(8)}$-H 1,2-hydrogen shift as,

(a) the thermodynamic driving force in the direction of forming a more stable carbonium ion such as a tertiary center at $C_{(8)}$ is available, and

(b) the stability gained by the decrease in the molecular strain imposed by the steric interaction between $C_{(13)}$-Me and $C_{(8)}$-H.

Once the hydride is removed and the rearrangement has taken place, another driving force appearing to contribute to the loss of the methyl group is the formation of a benzene system. This could lead to compound 205.

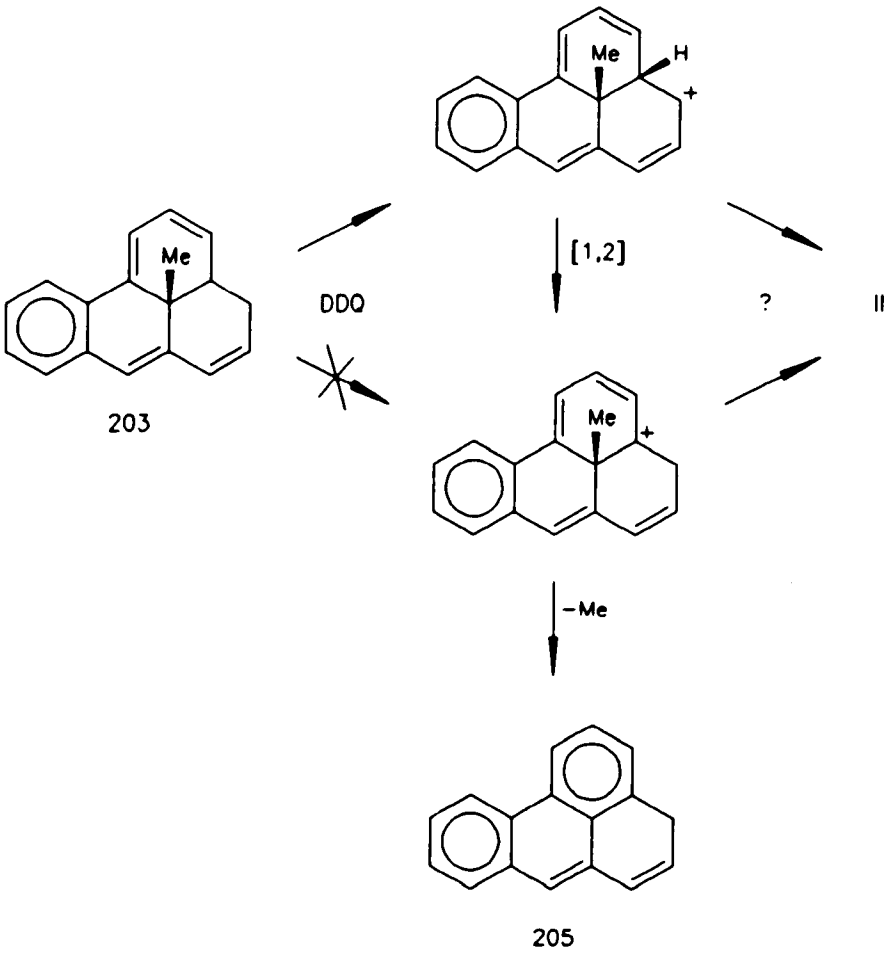


Figure 73: Speculative pathway toward 205

A possibility that should not be excluded is an S_N2 attack, on the methyl, by the phenolate ion, producing a methoxyphenol derivative as well as 205. The NMR spectrum of the reaction mixture shows a singlet at δ ≈3.8 that could well be the methoxy group.

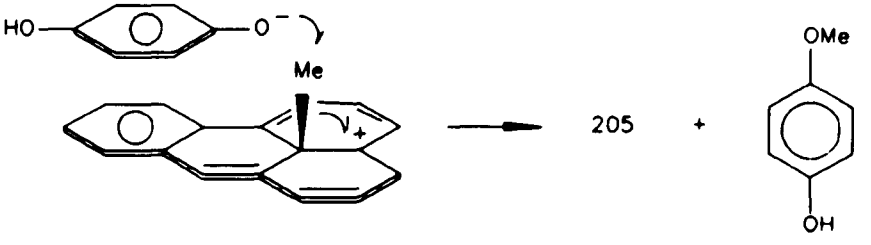
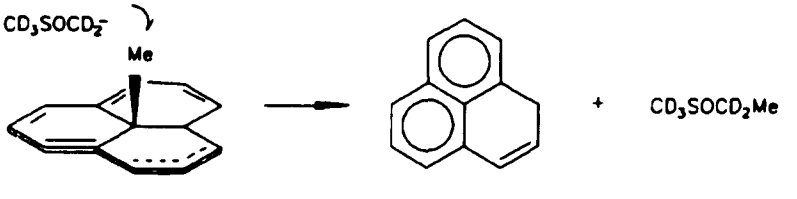


Figure 74: Speculative S_N2 toward 205

Moreover, there is supporting evidence that a similar reaction has been observed by Huang.[88] Treatment of the pentaene 159 and methylsulfinyl carbanion-d_5 indicated the presence of phenalene anion and the respective sulfoxide.



159

Figure 75: Speculative S_N2 toward Phenalene

A hydride abstraction of 205, further delocalization of the cation at $C_{(7)}$ to the more stable isomer containing a naphthalene unit and the double resonance stabilized charge at $C_{(3)}$, with a subsequent attack by moist air is proposed for the function of the analogue of the phenalenone, that is, the benzanthrone 204, and the benzophenalene 206.

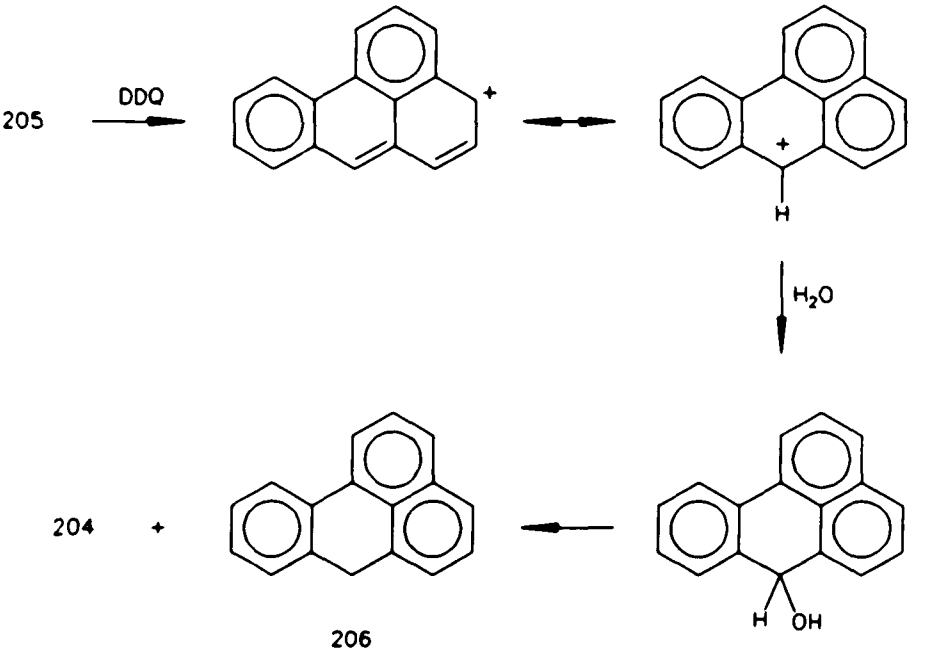


Figure 76: Speculative oxidation toward 204 and 206

Another possible mechanism that accounts for the formation of 204 comes from the interaction of molecular oxygen and II. That is, the attack at $C_{(3)}$ followed by delocalization of the electron density, and cleavage of a methyl radical.

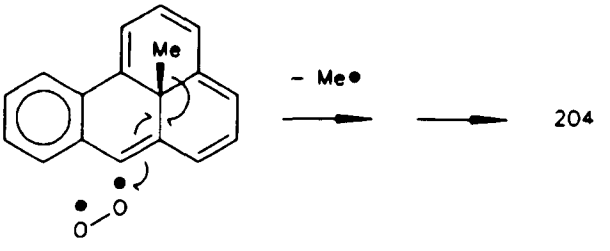


Figure 77: Another speculative formation of 204

If these speculations are true, DDQ is ideal for the synthesis of 203 and no further. The last double bond needed for the formation of II should be made by some other synthetic method; maybe the bromination/dehydrobromination of 203, at low temperatures, or the generation[89] of the dianion, an aromatic 14 π ionic species, followed by its oxidation would give the desired 12 π electron system.

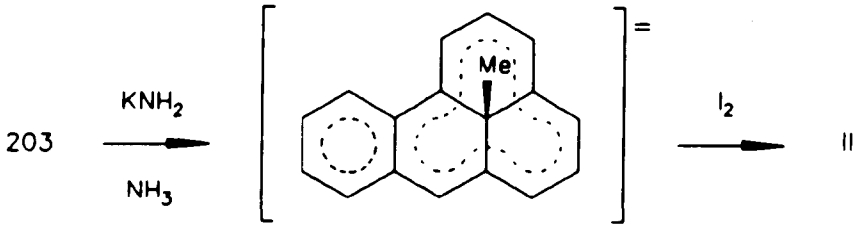
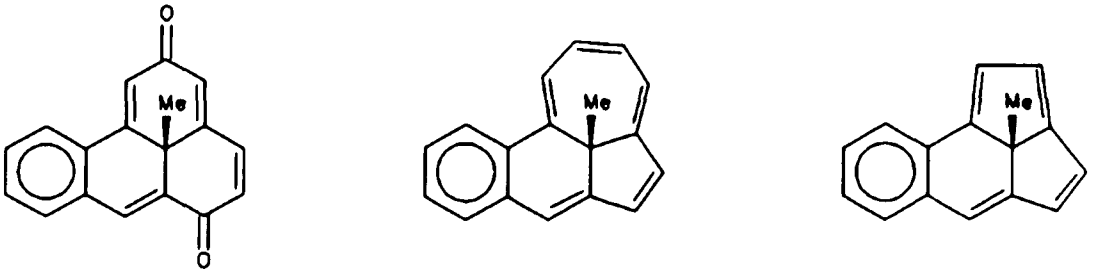


Figure 78: Possible synthesis of II

2.7.0 OUTLINE OF FURTHER STUDIES

As it is apparent from the foregoing discussion, the general new approach toward functionalized polycyclic precursors for II can be modified and extended providing synthetic access to the theoretically significant related molecules 220, 221, and 222.



220 221 222

Figure 79: Synthetic Possibilities

The quinone 220, an expectedly stable precursor to II is similar to the key intermediate used in the synthesis of the trans-15,16-dimethyldihydropyrene 227.

Boekelheide and Phillips have reported the treatment of the quinone 224 with zinc dust in acetic anhydride to the hydroquinone diacetate 225. This diacetate possessed a strong diatropic ring current as the internal methyls appeared at δ -4. Treatment of 224 with aluminum hydride-aluminum chloride gave the bistriene 226. Further treatment with palladium on charcoal in boiling solvent (benzene or cyclohexene) gave 227 in 75% yield from 224.

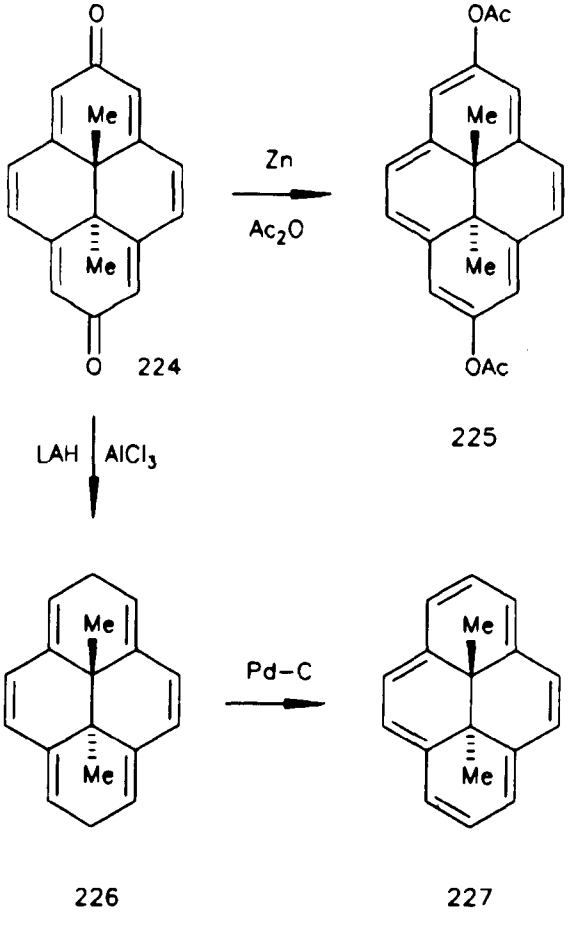
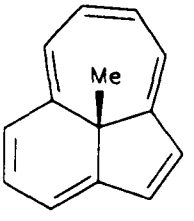


Figure 80: Boekelheide approach toward 227

While II is antiaromatic and, according to our findings, very unstable, 220 has the additional advantage as it is a 10 π diketone system; therefore, it should be stable and its conversion into II might proceed under very mild conditions as found by Boekelheide for the related compound 227.

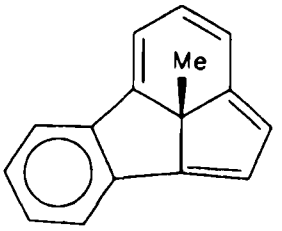
Compounds 221 and 222 are of interest as structural analogues, where 221 being the benzo-analogue of the isoelectronic [5.6.7] system 228.



228

Figure 81: A [12]annulene 228

While 222 is the benzo-analogue of the 10 π system, the isomer 229 has been prepared by the route developed by Rees.[31,35]



229

Figure 82: The known [10]annulene 229

Our route will allow to prepare the isomeric benzoderivative 222 and thus allow its comparison with 229 and the parent system. The annulene 221 will allow its comparison with II as well as the parent [5.6.7] system 228 reported by Hafner.[90]

2.7.1 RETROSYNTHETIC ANALYSIS of 220, 221, and 222

The retrosynthetic analysis of 220 indicates that this quinone could be made from the diketone 230, which in turn comes from the IMDA of 231.

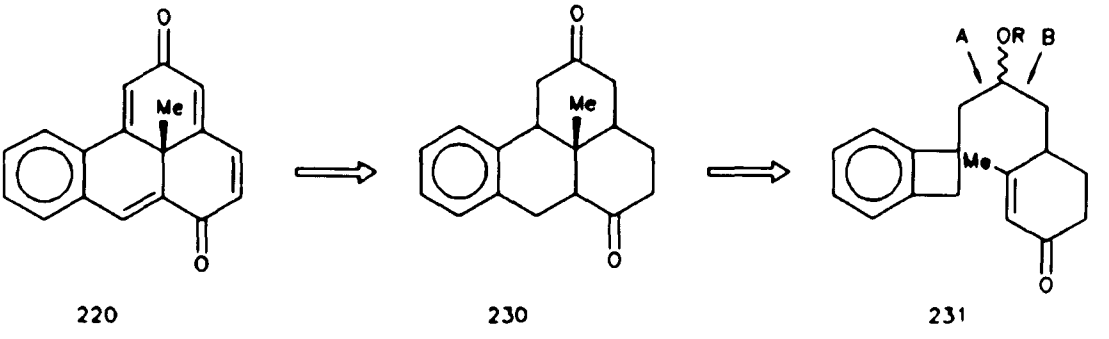


Figure 83: Retrosynthetic analysis for 220

In addition to 231, the ready availability of the ketone 232 and the ketal 233 makes this approach promising.

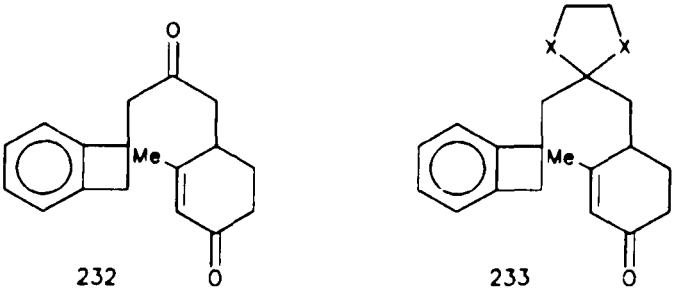


Figure 84: Potential IMDA adducts

The following sequence illustrates two proposed routes using a Grignard approach. The connection could be made through either bond A or B. This is shown as disconnections A and B respectively.

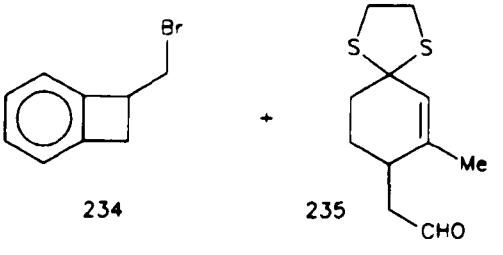
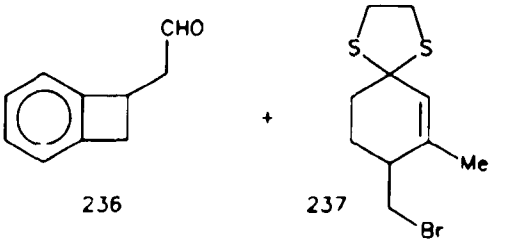


Figure 85: Disconnection A toward 231



236 237

Figure 86: Disconnection B toward 231

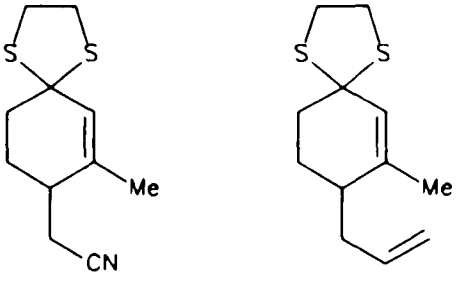
A synthesis providing all the benzocyclobutene units needed for the formation of 220, 221, and 222 could begin with the known 1-cyanobenzocyclobutene 9 and the aldehyde 10 to the aldehyde 236.

9,R=CN
10,R=CHO

236

Figure 87: The diene synthesis

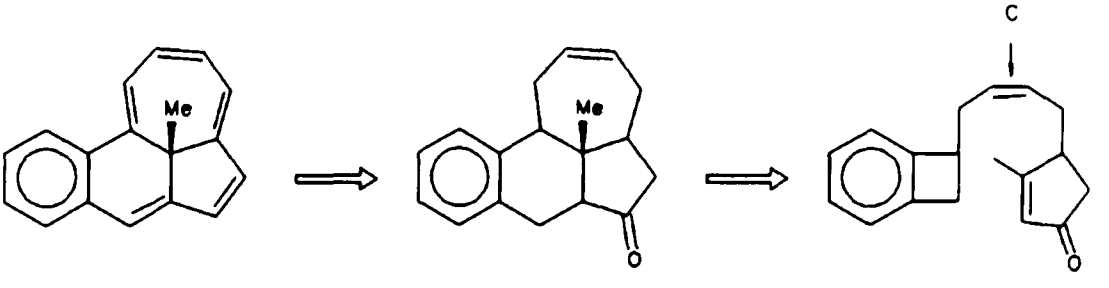
The cyclohexenone unit can be made by the homologation of Hagemann's ester as reported by Schuber[78a] or Johnson[78b] in the synthesis of the nitrile 238, or the alkene 239, respectively.



238 239

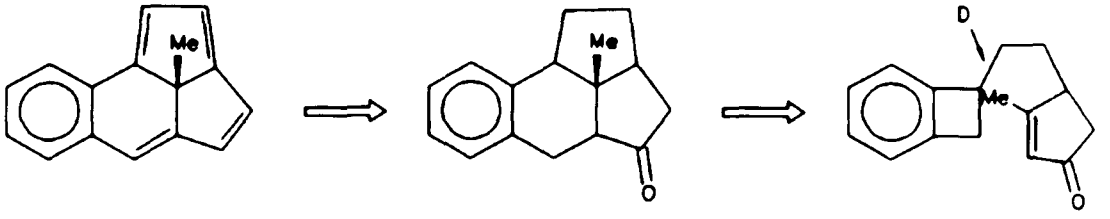
Figure 88: Dienophile precursors

Likewise, the synthesis of compound 221 can be envisioned in a similar fashion. Disconnection C suggests a facile Wittig coupling.



221 241 242

Figure 89: Disconnection approach toward 221



222 243 244

Figure 90: Disconnection approach toward 222

Analogously, the synthesis of 222 can be envisioned from the IMDA of 244.

Thus, the methodology developed in this thesis is not only directed toward the synthesis of II but also to compounds which will lead to better understanding in the comparison of structurally related aromatic versus antiaromatic systems.

CHAPTER 3

3.1 EXPERIMENTAL SECTION

SPECTROSCOPY

^{1}H and ^{13}C Nuclear Magnetic Resonance spectra were recorded with a 300-MHz General Electric QE-300 spectrometer for solutions in chloroform-d (99.8% D, 0.03% v/v TMS, Aldrich). Early proton measurements were done on a 60-MHz Varian EM-360A spectrometer. Chemical shifts are expressed in δ or ppm units downfield from internal Me_4Si. Resonance splitting are described as s=singlet, d=doublet, t=triplet, m=multiplet, fs=fine splitting, and b=broad. Coupling constants are reported in Hertz units (J value). Labile protons were exchanged using deuterium oxide (99.8% D, Aldrich, Gold Label) and are represented by l=labile.

Infrared spectra were measured with a Perkin-Elmer 1310 IR spectrophotometer, during 12 minutes scans, and calibrated with a polystyrene film. Bands are reported in wavenumbers using the 1601 cm^{-1} band from the calibration film, and described as s=sharp, m=medium, w=weak, and b=broad. Liquid samples were prepared as thin films deposited between sodium chloride cells (23 x 4 mm). Solid samples were prepared as either melts or in solutions using sodium chloride cells and carbon tetrachloride as the solvent.

Ultraviolet spectra were measured with a Beckman DU-8 spectrophotometer, between 400 and 250 nm using either methylene chloride or carbon tetrachloride as the solvent. UV bands are reported by the maximum wavelength and the absorbance intensity.

CHROMATOGRAPHY

Column Chromatography. All regular and flash[1] column chromatography separations were performed using grade 60 silica gel available from Aldrich Chem. Co.. A separation by a R_f difference of ≈0.1 units required 40-55 g of gel per gram of residue to be purified. A bigger difference usually required ≈30 g of gel.

Radial Thin-layer Chromatography. A mixture of compounds, with a mass of 0.5 g or less, was purified on a chromatotron model 7924T made by Harrison Research. The chromatotron plates were coated with Silica gel 60 PF-254 containing calcium sulfate, available from EM Science or VWR Scientific, according to a recipe supplied by Harrison.[2] The sample was introduced using the minimum amount of a good solvent (i.e. methylene chloride), dried, and eluted with hexanes. The polarity of the eluent was increased only after a good separation was observed. This polarity change was accomplished by 2.5% increments of ethyl acetate (v/v). The

plates were observed using the UV light described for TLC.

Thin layer chromatography. TLC analysis were done on Polygram Sil G/UV plates available from Macherey-Nagel, and visualized using (a) a UVS-54 short wave ultraviolet lamp from Ultraviolet Products Inc., and (b) by exposure to iodine. Ratio to front values (R_f) were measured from the center of the respective spot to its initial position divided by the distance traveled by the solvent front.

ELUENTS

Hexanes and ethyl acetate were distilled prior to use.

MELTING POINTS

The melting points were determined in capillary tubes (1.5 x 90 mm, Kimax) using a Dr. Tottoli melting point apparatus made by Büchi and were uncorrected.

SOLVENTS AND REAGENTS

Solvents were available from either Fischer or Aldrich Chemicals. Commercially available reagents were obtained from Aldrich Chemicals Co.

Anhydrous diethyl ether and ethanol were used as obtained from the suppliers.

All solvents and bases listed below were refluxed until dried[3] prior to distillation under a blanket of either anhydrous nitrogen or argon.

SOLVENT	DRIED OVER
Acetone	Potassium carbonate.
Acetonitrile	Calcium hydride.
Benzene	" "
Liquid ammonia[4]	Sodium metal.
Diisopropylethylamine	" "
Dimethylformamide	Potassium hydroxide (solid), then with calcium carbonate.
1,4-Dioxane	Sodium metal.
Ethyl acetate	Calcium hydride.
Methanol	Magnesium metal.
Methylene chloride	Calcium hydride.
Piperidine	" "
Pyridine	" "
Triethylamine	" "
Tetrahydrofuran	Potassium metal.

Ethylene glycol was dried by azeotropic removal of water using benzene (thiophene free) and a Dean-Stark apparatus.

Potassium tert-butoxide was sublimed prior to use.

Solutions of n-butyllithium were estimated using either one of the following procedures (a) Gilman's double titration method,[5] (b) titration using 1,3-diphenylacetone p-

tosylhydrazone[6] or (c) 2,5-dimethoxybenzyl alcohol[7] as indicators. The end point found by means of the hydrazone was not always sharp[8] as compared to the alcohol. The reagents supplied in a septum bottle, as n-butyllithium, were transferred by syringe techniques.[9]

All other solvents and reagents were distilled prior to use. Sodium iodide, lithium bromide and lithium iodide were kept in an oven (125 °C) until needed. Phosphonium salts were dried by heating at ≈60°C while under reduced pressure (vacuum pump) for 4 hours minimum. Tosyl chloride was recrystallized from chloroform as described by Pelletier.[10]

MASS AND YIELDS

All masses were determined in a model 300 OHAUS balance (readings accurate to 1/100th of a gram). All final yields were calculated based on the theoretical limiting reagent and appear, between parenthesis, in the following order: (x grams, y millimoles, z% yield).

REACTION CONDITIONS

All nonaqueous reactions were run under a blanket of either anhydrous nitrogen or argon. Glassware was either oven-dried overnight or flame dried under vacuum and flushed with a stream of anhydrous nitrogen. Usually, a three-necked

round-bottomed flask equipped with a pressure-equalizing dropping funnel, a magnetic stirrer, a rubber septum, and a reflux condenser was used. The top of the condenser was connected to a three-way stopcock with one branch connected to the nitrogen source and the other to a drying tube. Drying tubes were filled with anhydrous calcium chloride or potassium hydroxide as required. Reactions were followed by TLC whenever possible. A mechanical stirrer with a ground-glass shaft bearing lubricated with mineral oil was used for reactions which required volumes larger than 500 mL.

GENERAL WORK-UP PROCEDURE

After quenching the reaction, usually by addition of distilled water, the reaction solvent was removed (if THF), and the residue was dissolved in either ether or methylene chloride.[11] If neutralization of an acidic solution was required, the excess acid was extracted with a saturated solution of sodium chloride until the pH was close to 7, then followed by a washing with a saturated solution of sodium bicarbonate. If slightly acidic conditions were required, the washing was done with a saturated ammonium chloride solution. The organic layer was dried with either anhydrous Na_2SO_4 or $MgSO_4$. If the final organic layer was basic (i.e. did not contained an alcohol group), then the drying agent of choice was anhydrous K_2CO_3. The drying agent was removed by gravity filtration. Low boiling point solvents and bases were removed by gentle heating,[12] under reduced pressure provided by a water aspirator and a Büchler flash-evaporator. In order to remove traces[13] of solvent, the final residue was dissolved in CCl_4, and flash-evaporated several times. Finally, a vacuum pump was used to remove the last traces of solvent. This crude residue was used for the initial ^1H NMR analysis.

GENERAL PROCEDURE FOR REDUCTIONS WITH LAH

To a 0 °C anhydrous ether solution, 4 equivalents[14] of LAH were carefully delivered, followed by 1 equivalent of the compound[15] to be reduced. The solution was stirred overnight and cooled to 0 °C before quenching. To destroy excess hydride, a saturated solution of Na_2SO_4 was added in a very slow manner[16] to allow the formation of a gray/white inorganic salt. The solution was filtered to remove the inorganic material which was rinsed with more ether. The combined organic solution was dried (Na_2SO_4). After removal of the solvent in vacuo, quantitative amounts of the reduced product was obtained in a very high degree of purity.

GENERAL PROCEDURE FOR WITTIG REACTIONS

Most of the by-product triphenylphosphine oxide was removed by either:

(a) dissolving the reaction residue in anhydrous ether to precipitate the Ph_3PO, filtered, and washed, or

(b) filtered thru a short column packed with either silica or alumina gel[17] using ether as the eluent.

3.2 SPECIFIC EXPERIMENTALS

Compound 2

o-Chlorotoluene 1 to α-bromo-o-chlorotoluene 2

In a 2 L flask containing a a solution of the substituted toluene (140.18 g, 1.11 mol), N-bromosuccinimide (199.56 g, 1.11 mol), in carbon tetrachloride (1200 mL) was refluxed until the NBS was no longer present.* The refluxing was continued for 30 minutes longer. The solvent was removed in vacuo and the residue neutralized with saturated sodium bicarbonate. The product was extracted with methylene chloride and dried ($CaCl_2$). Vacuum distillation (bp 140 °C, ≈25 mm Hg) gave a pale yellow oily 2 (161.56 g, 0.79 mol, 75% yield).

^1H NMR (60 MHz); δ 4.4 (s, 2H) and 6.8 (m, 4H).

Compound 5

α-Bromo-o-chlorotoluene 2 to ethyl-2-(o-chlorobenzyl) cyanoacetate 5

In a 2 L three-neck flask equipped with a mechanical stirrer, condenser, and dropping funnel, sodium metal (18.43 g, 0.8 g atom) was reacted with absolute ethanol (525 mL). Ethyl cyanoacetate (395 mL, 3.7 mol) was added to the

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*. A 100% syspension indicated the completion of the reaction.

sodium ethoxide solution, followed by the addition of the α-chloro-o-chlorotoluene 3 (161.56 g, 0.79 mol) over two hours period. After stirring for 3.5 hours, the solution was filtered to remove the sodium chloride formed as a by-product. The excess ethanol was removed in vacuo. The product was worked-up by addition of 0 °C water (150 mL) and extracted with ethyl acetate (3 X 100 ml), and dried (sodium sulfate). Careful fractional vacuum distillation (bp 100-105 °C, 0.1 mm Hg) separated the unreacted ethyl cyanoacetate from 5 (111.48 g, 0.47 mol, 59% yield).

^{1}H NMR; δ 1.29 (t, 3H, 7.16 Hz), 3.21 (dd, 1H, 9.45 and 13.79 Hz), 3.51 (dd, 1H, 6.25 and 13.78 Hz), 3.91 (dd, 1H, 6.25 and 9.44 Hz), 4.26 (q, 2H, 7.11 Hz), and 7.32 (m, 4H).

Compound 6

A solution of the 2-chlorobenzaldehyde 4 (166.67 g, 1.15 mol, 97%), cyanoacetic acid (94.83 g, 1.07 mol, 99%), ammonium acetate (10.48 g, 0.14 mol), pyridine (230 mL), and benzene (1045 mL) was refluxed using a Dean-Stark apparatus until the required amount of water was collected. After cooling, the pyridine salt of 6 precipitated out of the solution. This 6 was used without purification.

Compound 7

The reduction of 5/6 to the carboxylic acid 7

Method A. A solution of the ester 5 (111.48 g, 0.47 mol) and 10% sodium hydroxide (300 mL) was stirred for 15 minutes before cooling (0 °C) and acidification with 6 N hydrochloric acid (150 mL). Upon formation of the acid 7, it precipitated from the solution. The solid 7 was filtered and washed with cold water. Excess water was removed in vacuo before decarboxylation to 8.

Method B. The pyridine salt of 6 (1.15 mol) was place in a saturated solution of sodium bicarbonate (≈2 L) and heated (≈90 °C) until most of the salt had dissolved. Sodium borohydride (≈110 g) was added in small portions. This final solution was left refluxing overnight (≈110 °C). Upon cooling, the solution was acidified until a pH of ≈2 was obtained. The water was removed and the residue decarboxylated as described for compound 8. This procedure gave 8 in 47% isolated yield from the 2-chlorobenzaldehyde.

^{1}H NMR; δ 3.20 (dd, 1H, 9.95 and 13.78 Hz), 3.55 (dd, 1H, 5.75 and 13.81 Hz), 3.95 (dd, 1H, 5.75 and 9.92 Hz), ≈6-7 (bsl, 1H), and ≈7.4 (m, 4H).

Compound 8

The decarboxylation of the acid 7 to 2-chlorobenzo-1-propanonitrile 8

The acid 7 (0.47 mol) was refluxed in dimethylformamide (250 mL) for two days. Vacuum distillation* (bp 65-67 °C, 0.01 mm Hg) afforded pure 8 (68.46 g, 0.41 mol, 88% yield from 5).

Compound 9

Method A. The sodium amide procedure.

Powder sodium amide (16.43 g, 0.40 mol, 95%) was placed in a flask containing ≈250 mL of dry ammonia. The 2-chlorohydrocinnamonitrile 8 (16.56 g, 0.1 mol) was added next. The solution was stirred for 3 hours at -78 °C. The reaction was quenched with solid ammonium nitrate (24 g). The ammonia was allowed to evaporate overnight. Water (≈80 mL) was added to the reaction residue. The work-up was performed with chloroform (3 X 50 mL), 5% HCl (2 X 50 mL), and water (2 X 50 mL). After drying with anhydrous magnesium sulfate, the final dark residue was distilled (bp 52-54 °C, 0.1 mm Hg) using a 10 cm Vigreux column affording colorless 9 (7.36 g, 0.057 mol, 57% yield).

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*. The DMF must be removed completely before proceeding to the cyclization to 9.

Method B. The potassium hydride procedure.

Potassium hydride (≈80 g, 0.7 mol, 35% dispersion in mineral oil) was added to a flask containing dry liquid ammonia (1 L). The solution was stirred until most of the hydride had reacted. Compound 8 (29.81 g, 0.18 mol) was added dropwise over a one hour period. The reaction mixture was stirred for two hours before quenching with excess solid ammonium chloride. The ammonia was allowed to evaporate overnight. The residue was worked-up with water (50 mL) followed by chloroform (3 X 40 mL) and drying with sodium sulfate. Distillation gave ≈90% yield of the desired 9 (20.9 g, 0.16 mol).

Compound 10

1-Cyano benzocyclobutene 9 to 1-formyl benzocyclobutene 10

In a 500 mL two-neck flask equipped with a condenser, a mechanical stirrer, a nitrogen inlet and a rubber septum, containing a solution of the cyano 9 (6.46 g, 50 mmol) in methylene chloride (200 mL) was injected DIBAL-H (50 mL, 50 mmol, 1.0 M solution in methylene chloride) at 0 °C. The solution was refluxed gently (≈50 °C) for 2 hours. After cooling to 0 °C, 10% sulfuric acid (90 mL) was added dropwise* until the resulting solution turned cloudy and thick, and a little faster until clear, then stirred overnight.

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*. The addition of the acid must be in portions of no more than one mL at any time. Magnetic stirring is not recommended.

The final solution containing the organic and aqueous layers was transferred to a continuous extraction apparatus. After saturation with sodium chloride and 6 hours extraction* with ether, the organic layer was washed with saturated $NaHCO_3$ and NaCl. Distillation (bp 44 °C, 0.01 mm Hg) gave a colorless 10 (5.66 g, 43 mmol, 86% yield).

^1H NMR; δ 3.44 (d, 2H, 3.72 Hz), 4.25 (ddd, 1H, ≈3.44 Hz), ≈7.2 (m, 4H), and 9.76 (d, 1H, 3.75 Hz).

Compound 17

Reduction of 3,4-dimethoxybenzaldehyde 16 to 3,4-dimethoxytoluene 17

In a 500 mL flask, a solution of the veratraldehyde 16 (49.86 g, 0.3 mol) in triethylene glycol (150 mL), sodium hydroxide (13.14 g) and hydrazine (70.41 g, 65% in water), was refluxed until the solution turned homogeneous (≈1 hour). After removing the condenser, it was heated slowly to 150 °C and kept at this temperature for two hours (nitrogen evolution). The product was removed by steam distillation (bp 116-117 °C), extracted with ether, and dried. The toluene (40.25 g, 0.26 mol, 88.2% yield) was obtained in a high degree of purity. The extraction was not essential as the azeotrope could be cooled (0 °C), forcing the product to separate and freeze. Pure 17 can be obtained by distillation

*. The yield drops if stirring is done for shorter times (i.e. 66% for 1 hour).

(bp 60-62 °C, 0.1 mm Hg).

Compound 18

3,4-dimethoxytoluene 17 to 6-Bromo-3,4-dimethoxytoluene 18

In a 50 mL three-necked flask containing the toluene 17 (10.08 g, 66 mmol) in carbon tetrachloride (6.5 mL) at 0 °C, a solution of liquid bromine* (3.4 mL, 66 mmol) diluted with the same solvent (7 mL) was added dropwise while stirring. After additional stirring of 10 minutes, the solvent was removed in vacuo and the residue was extracted with ether, washed with sat. sodium bicarbonate, followed by sat. sodium chloride, and dried. The final residue was distilled (bp 100-106 °C, 0.225 mm Hg) giving an oily 18 (13.82 g, 0.060 mol, 91% yield).

^{1}H NMR; δ 2.31 (s, 3H), 3.81 (s, 6H), 6.70 (s, 1H), and 6.97 (s, 1H).

Compound 22

The Grignard reaction described for compounds 25/26 was applied to compound 18 giving the biphenyl 22. No yields were recorded. Mp 119.0-120.2 °C.

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*. If the ratio of the bromine was higher than 1:1, over-bromination was observed at the benzylic position (?).

^{1}H NMR; δ 2.03 (s, 3H), 3.84 (s, 3H), 3.92 (s, 3H), 6.65 (s, 1H), and 6.77 (s, 1H).

^{13}C NMR; δ 19.35, 55.89, 56.01, 112.70, 112.89, 128.20, 133.35, 146.47, and 147.71.

IR (KBr); 3050, 3020, 2940, 2900, 2840, 2820, 1700 (w), 1600 (ms), 1500, 1450, 1460, 1370, 1320, 1240, 1210, 1200, 1180 1150, 1110, 1035, 985, 860, 820, 780, and 610 cm^{-1}.

Compound 23

6-Bromo-3,4-dimethoxytoluene 18 to 6-(2-hydroxyethyl)-3,4-dimethoxytoluene 23

In a 500 mL three-neck flask equipped with a nitrogen inlet, dropping funnel, and a rubber septum, containing a cooled (-78 °C) solution of the bromotoluene 18 (8.39 g, 36.3 mmol) and anhydrous ether (250 mL), n-butyllithium (22.5 mL, 36 mmol, 1.6 M) was injected. The solution was stirred for exactly 10 minutes, then the ethylene oxide (≈25 mL) was delivered in one lot. After removing the bath, the solution was stirred to ambient temperature followed by acidification with 10% hydrochloric acid. The aqueous layer was extracted with ether (2 X 30 mL). The combined organic layer was washed with saturated NaCl and dried. Distillation (bp 110-118 °C, ≈0.001 mm Hg) gave the colorless 23 (4.81 g, 24.5 mmol, 68% yield).

^{1}H NMR; δ 2.25 (s, 3H), 2.72 (sl, 1H), 2.79 (t, 2H, 7.09 Hz), 3.74 (t, 2H, 7.09 Hz), 3.82 (s, 6H), 6.66 (s, 1H), and 6.68 (s, 1H).

^{13}C NMR; δ 18.87, 36.18, 55.90, 56.01, 62.73, 113.38, 113.84, 128.42, 128.52, 146.93, and 147.25.

IR (melt); 3500 (bs), 3000, 2950, 2870, 1610 (s), 1580 (w), 1505, 1455, 1400, 1340, 1260, 1220, 1200, and 1100 cm^{-1}.

Compounds 25/26

p-Bromo anisole 24 to 4,4'-dimethoxy biphenyl 25 and the alcohol 26

In a 20 mL flask containing a suspension of magnesium turnings (1.48 g, 60.9 mmol or g atom) in dry THF (12 mL), was refluxed gently. A solution of p-bromo anisole (5.61 g, 30 mmol), and freshly distilled 1,2-dibromoethane (5.60 g, 29.8 mmol), was delivered dropwise over a 1.5 hours period. The refluxing was continued for one more hour, and then the solution was cooled to -78 °C. Ethylene oxide* (5 mL) was distilled into the solution. The stirring was continued for one more hour at 30 °C. The volume was reduced to half of the original, and left refluxing overnight. The resulting brown solution was cooled and quenched with water (25 mL),

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*. This reagent was distilled into a flask containing soda lime before redistilling into the reaction flask.

acidified using a 10% hydrochloric acid solution, extracted with ether, and dried. Removal of the solvent left a solid residue. This solid (4.18 g) was prepurified (abs. ethanol/norite) before column chromatography using silica gel (80 g) and hexanes/EtOH (9:1) as eluent. A solid (mp 178.5-180.4 °C) biphenyl 25 (1.00 g, 4 mmol, R_f 0.42, 27% yield) was collected along with an oil (bp 97 °C, 0.55 mm Hg), which was identified as the alcohol 26 (0.74 g, 4.9 mmol, R_f 0.06, 16% yield).

Compound 25

^{1}H NMR; δ 3.84 (s, 3H), 6.96 (dd, 2H, 1.26 and 8.50 Hz), and 7.48 (dd, 2H, 1.22 and 8.79 Hz).

^{13}C NMR; δ 55.37, 114.16, and 127.76.

Compound 26

p-Bromo anisole 24 to 4-(2-hydroethyl)-anisole 26

Ethylene oxide (10 mL) was collected in a three-neck flask connected to the reaction vessel and diluted with anhydrous ether (10 mL). In the -78 °C reaction flask containing a solution of the p-bromoanisole (1.83 g, 10 mmol) in anhydrous ether (20 mL), the n-butyllithium (6.4 mL, 10 mmol, 1.6 M) was injected and the solution stirred for exactly 12 minutes before pouring the ethylene oxide solution at once. The dry ice/acetone bath was removed and the solution stirred until ambient temperature (1 hour) was

reached. A solution of 1 N hydrochloric acid was delivered dropwise (10.5 mL). The organic layer was separated. The aqueous layer was extracted with ether (3 X 30 mL). The combined organic layer was dried (potassium carbonate), filtered and the solvent removed in vacuo. Distillation (bp 72-78 °C, 1.1 mm Hg) gave pure 26 (1.31 g, 8.6 mmol, 86% yield).

^{1}H NMR (60 MHz); δ 1.94 (bsl, 1H), 2.69 (t, 2H, 6.5 Hz), 3.7 (s, 3H), 3.8 (t, 2H, 6.5 Hz), and 6.8 (m, 4H).

Compound 31

6-(2-hydroxyethyl)-3,4-dimethoxytoluene 23 to 6-(2-mesyl ethyl)3,4-dimethoxytoluene 31

The alcohol 23 (61.61 g, 0.314 mol) was transferred to a 2 L two-neck flask equipped with a condenser, a nitrogen inlet, and a mechanical stirrer, using anhydrous ether (700 mL). Freshly distilled Et_3N (≈219 mL,?1.571 mol, 5 eq) was added dropwise to the cooled solution (0 °C) containing the alcohol, followed by slow addition of mesyl chloride (≈73 mL, 0.942 mol, 3 eq). The solution was left stirring for 3 hours, then worked-up with ether and sat. sodium chloride, and dried. The final residue was used without further purification (mp 90.4-92.6 °C).

^{1}H NMR; δ 2.27 (s, 3H), 2.87 (s, 3H), 3.00 (t, 2H, 7.25 Hz), 3.84 (s, 6H), 4.34 (t, 2H, 7.24 Hz), 6.68 (s, 1H), and 6.69 (s, 1H).

^{13}C NMR; δ 18.81, 32.72, 37.30, 55.88, 56.09, 69.65, 113.25, 113.80, 126.03, 128.55, 147.15, and 147.83.

Compound 32

6-(2-hydroxyethyl)-3,4-dimethoxytoluene 23 to 6-(2-bromoethyl)-3,4-dimethoxytoluene 32

The procedure used for 33 was repeated here to convert the mesyl group to the bromo, using lithium bromide instead of sodium iodide.

^{1}H NMR; δ 2.30 (s, 3H), 3.13 (t, 2H, 8.01 Hz), 3.51 (t, 2H, 8.00 Hz), 3.88 (s, 3H), 3.89 (s, 3H), and 6.71 (s, 2H).

^{13}C NMR; δ 18.76, 32.04, 36.82, 55.91, 56.08, 112.96, 115.03, 128.17, 129.01, 147.09, and 147.73.

IR (neat); 3000, 2960, 2940, 2860 (b), 1605 (s), 1510, 1470, 1400 (s), 1350, 1290, 1275, 1260, 1225, 1200, 1120, and 1100 cm^{-1}.

Compound 33

6-(2-mesylethyl)-3,4-dimethoxytoluene 31 to 6-(2-iodoethyl)-3,4-dimethoxytoluene 33

To an ice cooled solution of the mesylate 31, in reagent grade acetone (500 mL), sodium iodide* (141.2 g, 0.942 mol) was added slowly. The solution was refluxed for 6 hours turning cloudy-yellowish. Once the stirring was stopped, a milky layer formed. After work-up and continuous extraction of the aqueous residue**, TLC showed a single spot (R_f 0.40, hexanes/EtOAc, 13:7). Distillation (bp 128-138 °C, 0.01 mm Hg) gave a light yellow liquid 33 (88.51 g, 0.289 mol, 92% yield from the alcohol) which solidified upon standing. Compound 33 did not have to be purified for conversion to the phosphonium salt.

^{1}H NMR; δ 1.92 (s, 3H), 2.97 (m, 2H), 3.80 (s, 3H), 3.91 (s, 3H), ≈3.9 (m, 2H), 6.54 (s, 1H), 7.12 (s, 1H), and 7.82 (m, 15H).

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*. Lithium iodide could also be used.

**. If the continuous extraction is omitted, the yield drops to 70%.

Compound 34

6-(2-iodoethyl)-3,4-dimethoxytoluene 33 to 6-(2-triphenylphosphonium iodo ethyl)-3,4-dimethoxytoluene 34

The iodo 33 (10 mmol) was mixed with an equimolar amount of triphenylphosphine in toluene (25 mL), and refluxed for 10 hours. After removal of the solvent, the oily residue was recrystallized (mp 181.3-183.6 °C) from CH_2Cl_2/EtOAc (3.30 g, 5.8 mmol, 58% yield).

^1H NMR; δ 1.92 (s, 3H), 2.97 (m, 2H), 3.80 (s, 3H), 3.91 (s, 3H), 6.54 (s, 1H), 7.12 (s, 1H), and 7.82 (m, 16H).

Compound 35

The Wittig adduct 35 from the reaction of 10 and the phosphonium salt 34

In a 1 L flask, a solution of dry THF (700 mL) containing the phosphonium salt 34 (42.00 g, 0.074 mol) and potassium tert-butoxide (8.29 g, 0.074 mol), was stirred for 2 hours at room temperature. To the red solution containing the ylide, a solution of 10 (9.76 g, 0.074 mol) diluted with THF (50 mL), was delivered dropwise over a 30 minutes period. The resulting mixture was stirred for an additional 12 hours, and then quenched with water (50 mL). The THF was removed under reduced pressure. The aqueous layer was extracted with ether and dried over anhydrous magnesium sulfate. The Ph_3PO-free residue was chromatographed using silica gel (35 g gel/residue) and eluted with hexanes/EtOAc

(4:1, R_f 0.33). A white solid (mp 59.6-60.4 °C) identified as 35 (15.42 g, 52 mmol) was isolated in 70.3% yield.

^{1}H NMR; δ 2.30 (s, 3H), 2.96 (dd, 1H, 2.34 and 14.04 Hz), 3.48 (m, 2H), 3.55 (dd, 1H, 5.35 and 14.07 Hz), 3.87 (s, 6H), 4.52 (m, 1H), 5.58 (m, 1H), 5.72 (m, 1H), 6.70 (s, 1H), 6.75 (s, 1H), and 7.14 (m, 4H).

IR (melt); 3060, 3000, 2950, 2915, 2905, 2840, 2820, 1600, 1510, 1450 (b), 1390, 1330, 1290, 1265, 1245, 1220, 1195, 1180, 1040, 1030, 1000, 950, 915, 880, 855, 835, 815, 800, 750, 720, 705, and 690 cm^{-1}.

UV; 266.42 (1.4664 A), 272.25 (1.6921 A), and 285.58 nm (1.6759 A).

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.53, H, 7.60.

Compound 36

The procedure used for the reduction of compound 35 to 37 was attempted using 5% platinum on activated carbon as the catalyst but compound 36 was isolated instead. No yields were recorded.

^{1}H NMR; δ 1.2-2 (m, ≈17H), 2.29 (s, 3H), 2.55 (m, 2H), 3.92 (s, 6H), and 6.71 (s, 2H).

Compound 37

Reduction of 35 to 37

The Wittig product 35 (0.29 g, 1 mmol) was dissolved in ethyl acetate (15 mL) containing pretreated* palladium (≈0.02 g, 10% in charcoal), and exposed to hydrogen gas (balloon), and stirred for one hour. The solution was filtered using a Büchner funnel containing a layer of Celite. The solvent was removed in vacuo and the product used without purification.

^{1}H NMR; δ 1.72 (m, 4H), 2.25 (s, 3H), 2.59 (m, 2H), 2.75 (dd, 1H, 2.23 and 13.99 Hz), 3.32 (dd, 1H, 5.17 and 13.95 Hz), 3.48 (m, 1H), 3.85 (s, 6H), 6.66 (s, 2H, and 7.15 (m, 4H).

Compound 38

Conversion of 37 to the hydroquinone 38

The dimethoxy 37 (0.29 g, 1 mmol) was dissolved in methylene chloride (5 mL), followed by the addition of boron tribromide (5 mL, 1 M in methylene chloride). The red solution was stirred for one hour, cooled to 0 °C, and

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*. The catalyst was pretreated using vacuum followed by saturation with hydrogen gas.

quenched with water (10 mL). The organic phase was extracted with 1 N NaOH (5 X 10 mL). This aqueous layer was acidified with conc. HCl, and reextracted with ether until the aqueous layer became clear. After drying with anhydrous sodium sulfate, and removal of the organic solvent, the quantitative amount of residue was used without further purification.

^{1}H NMR; δ 1.71 (m, 4H), 2.14 (s, 3H), 2.45 (m, 2H), 2.72 (dd, 1H, 2.28 and 13.99 Hz), 3.29 (dd, 1H, 5.22 and 13.92 Hz), 3.44 (bs, 1H), 5.64 (bsl, 2H), 6.63 (s, 1H), 6.65 (s, 1H), and 7.15 (m, 4H).

^{13}C NMR; δ 19.27, 29.23, 32.84, 34.45, 36.00, 45.55, 116.39, 116.52, 117.61, 117.73, 122.05, 123.15, 126.70, 127.19, 128.56, 133.70, 141.17, 141.31, and 149.94.

IR (neat); 3280 (b), 3060, 3020, 2920, 2960, 1601, 1610, 1450, 1280, 1170, 1080, 990, 870, 740, and 700 cm^{-1}.

Compound 39

Oxidation of the hydroquinone 38 to the o-quinone 39

A red solution of the hydroquinone 38 (0.26g, 1 mmol), silver(II)oxide (0.46 g, 2 mmol), dry THF (10 mL), and 6 N nitric acid (0.33 mL) was stirred for 30 minutes at room temperature. Saturated sodium chloride (20 mL) was added to quench the reaction. The product was extracted with methyl-

ene chloride, and dried with sodium sulfate. The final residue was deep red and unstable decomposing overnight upon standing.

^{1}H NMR; δ 1.40 (m, 2H), 1.79 (m, 2H), 2.16 (sfs, 3H), 2.46 (m, 2H), 2.77 (dd, 1H, 2.10 and 14.10 Hz), 3.36 (dd, 1H, 5.41 and 14.11 Hz), 3.51 (m, 1H), 6.18 (s, 1H), 6.24 (sfs, 1H), and 7.19 (m, 4H).

IR (neat); 3090, 3040, 2940, 2880, 1740, 1680, 1670, 1575, 1455, 1385, 1280, 790, 760, and 710 cm^{-1}.

Compound 46

Diels-Alder adduct 46 from the reaction between 37 and maleic anhydride

A solution of 37 (0.15 g, 0.5 mmol), maleic anhydride (1 mmol), in m-dichlorobenzene (80 mL), was refluxed overnight. The solvent was removed in vacuo, and the residue recrystallized from absolute ethanol, giving 46 (0.13 g, 0.33 mmol, 66% yield) as a white solid (mp 149.8-151 °C).

^{1}H NMR; δ 1.71 (m, 1H), 1.90 (m, 1H), 2.15 (m, 2H), 2.26 (s, 3H), 2.68 (m, 2H), 2.89 (m, 1H), 2.96 (m, 1H), 3.09 (m, 1H), 3.59 (m, 2H), 3.85 (s, 6H), 6.67 (s, 1H), 6.68 (s, 1H), and 7.22 (m, 4H).

Compound 49

6-bromo-3,4-dimethoxytoluene 18 to 1,2-dimethoxy-3,4-dimethylbenzene 49

n-Butyllithium (4.38 mL, 7 mmol, 1.6 M) was added to a -78 °C solution of 17 (1.16 g, 5 mmol) in anhydrous ether (25 mL) producing a milky solution. After stirring for 8 minutes, methyl iodide (2 mL) was added in one shot. After additional stirring for 30 minutes and warming up to 0 °C, water (10 mL) was added, followed by 2 N HCl (5 mL). After extracting with ether and drying, the residue was chromatographed (silica gel, hexanes/EtOAc 2:1, R_f 0.51) giving pure 49 (0.74 g, 4.45 mmol, 89% yield).

^{1}H NMR ; δ 2.19 (s, 6H), 3.82 (s, 6H), and 6.65, (s, 2H).

^{13}C NMR; δ 19.22, 55.97, 113.44, 128.14, and 146.73.

Compound 69

Preparation of the phosphonium salt 69

A solution of 2-bromoethanol 68 (99.16 g, 0.75 mol, 95%), triphenylphosphine 67 (181.55 g, 0.685 mol, 99%), in dry acetonitrile (500 mL), was refluxed for 48 hours. The solution was cooled to ambient temperature. Anhydrous ether (150 mL) was added dropwise to precipitate the phosphonium salt. The crystals were filtered and rinsed with anhydrous ether giving good quality salt (247.44 g, mp 218.8-219.9 °C, 93% yield).

^{1}H NMR; δ 3.82 (q, ?H, 6.00 Hz), 4.06 (t, ?H, 6.01 Hz), 4.12 (t, ?H, 6.04 Hz), and 7.76 (m, 15H).

Compound 73

3-methyl anisole 72 to the 4-bromo-3-methyl anisole 73

The procedure used for bromination of 17 was repeated here. Reagents: 3-methylanisole (30.85 g, 0.25 mol, 99%) diluted with carbon tetrachloride (40 mL), liquid bromine (12.81 mL, 0.25 mol) diluted to 25 mL with the same solvent. Distillation (bp 100-102 °C, ≈10 mm Hg) gave a slightly yellow liquid 73 (45.51 g, 0.227 mol, 91% yield).

^{1}H NMR; δ 2.35 (s, 3H), 3.86 (s, 3H), 6.54 (dd, 1H, 3.12 and 8.72 Hz), 6.71 (d, 1H, 3.04 Hz), and 7.33 (d, 1H, 8.74 Hz).

Compound 74

4-bromo-3-methylanisole 73 to 4-methoxy-2-methylbenzaldehyde 74

A mixture of magnesium metal (0.52 g, 21.2 g atoms), 73 (4.00 g, 20 mmol), in dry THF (30 mL) was heated at 55 °C for 2 hours.* After cooling to -40 °C, dry DMF (1.55 mL, 20 mmol) in THF (10 mL) was added to the solution containing the magnesium complex, and stirred one hour, then warmed up to ambient temperature for another hour period. This solu-

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*. In some cases, the reaction did not proceed as expected. 0.5 mL of 1,2-dibromoethane was used as intrainer with additional magnesium.

tion was poured into a solution of saturated ammonium chloride (70 mL), filtered and extracted with ether. The organic layer was washed with 10% sulfuric acid (3 X 25 mL), then with sat. $NaHCO_3$, and dried (Na_2SO_4). Distillation (bp 66-70 °C, 0.01 mm Hg) gave the aldehyde 74 (2.24 g, 15 mmol, 75% yield) as a colorless liquid. R_f 0.32, hexanes/EtOAc, 4:1.

^1H NMR; δ 2.65 (s, 3H), 3.87 (s, 3H), 6.74 (d, 1H, 2.44 Hz), 6.84 (dd, 1H, 8.56 and 2.54 Hz), 7.75 (d, 1H, 8.56 Hz), and 10.11 (s, 1H).

^{13}C NMR; δ 19.77, 55.37, 111.46, 116.96, 127.94, 134.66, 143.18, 163.61, and 191.02.

Compound 75

The Wittig reaction of 4-methoxy-2-methylbenzaldehyde 74 to the 4-methoxy-2-methylcinnamyl alcohol 75

To a cooled solution (-78 °C) of (2-hydroxyethyl)triphenylphosphonium bromide 69 (2.03 g, 5.25 mmol) in dry THF (125 mL), n-butyllithium (10 mmol) was injected. The solution was allowed to warm up overnight. A solution of 74 (0.75 g, 5 mmol) diluted with THF (10 mL) was added followed by additional stirring for 24 hours. Distilled water (10 mL) was used to quench the reaction. The THF was removed in vacuo followed by the addition of 10% hydrochloric acid (50 mL), and extraction with methylene chloride. The organic layer was washed with sat. sodium bicarbonate, sodium chlo-

ride and dried with anhydrous sodium sulfate. The final residue (1.93 g) was chromatographed using silica gel (90 g) and eluted with hexanes/EtOAc (2:1, R_f 0.23). Pure alcohol (0.26 g, 1.5 mmol, 29% yield) was obtained as an oil.

^{1}H NMR; δ 2.05 (bs, 1H), 2.31 (s, 3H), 3.77 (s, 3H), 4.28 (dd, 1.43 and 5.92 Hz), 6.13 (ddd, 1H, 15.64 and 5.92 Hz), 6.72 (m, 3H), and 7.36 (d, 1H, 8.23 Hz).

Compound 76

Perkin reaction of 4-methoxy-2-methylbenzaldehyde 74 to 4-methoxy-2-methylcinnamic acid 76

A solution of the aldehyde 74 (15.02 g, 0.1 mol), malonic acid (19.97 g, 0.19 mol, 99%), dry pyridine (60 mL), and dry piperidine (1 mL, 10 mmol), was heated at 100 °C for 16 hours. The cooled solution (0 °C) was poured into a beaker containing conc. hydrochloric acid (90 mL) and ice (200 g), and stirred for one hour. The precipitate was filtered, washed with 10% HCl, water, and recrystallized from abs. ethanol, giving 76 (9.31 g, 0.062 mol, 69% yield) as a white solid (mp 178.8-184.2 °C).

^{1}H NMR; δ 2.45 (s, 3H), 3.83 (s, 6H), 6.29 (d, 1H, 15.79 Hz), 6.76 (m, 2H), 7.57 (d, 1H, 8.51 Hz), and 8.03 (d, 1H, 15.81 Hz).

Compound 77

LAH reduction of 4-methoxy-2-methylcinnamic alcohol/acid 75/76 to 3-(4-methoxy-2-methylphenyl)-1-propanol 77

The general procedure* for reduction with LAH was followed here. The alcohol 77 was purified by distillation (bp 91-93 °C, 0.01 mm Hg) giving quantitative yield.

^{1}H NMR; δ 1.64 (bsl, 1H), 1.83 (m, 2H), 2.29 (s, 3H), 2.63 (dd, 2H, 7.78 Hz), 3.70 (dd, 2H, 6.44 Hz), 3.78 (s, 3H), 6.69 (m, 2H), and 7.05 (d, 1H, 8.13 Hz).

Compound 86

Hagemann's ester to the protected ketone 86

In a 1 L flask equipped with Dean-Stark collector, condenser, magnetic stirrer and heating mantle, a solution of commercially available Hagemann's ester (100.00 g, 0.50 mol, 90%), p-toluenesulfonic acid (0.84 g), ethylene glycol (85 mL) and benzene (700 mL), was refluxed for 24 hours. After removing the benzene, the organic residue was dissolved in ether, and washed with saturated sodium chloride followed by sodium bicarbonate. The final residue was distilled (bp 94-96 °C, 0.1 mm Hg) as a yellow liquid (99.53 g, 0.44 mol, 88% yield).

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*. Refer to the reduction of compound 52.

^{1}NMR; δ 1.28 (t, 3H, 7.13 Hz), 1.75 (m, 2H), 2.01 (fs, 3H), 2.37 (fs, 2H, 0.78 Hz), 2.53 (m, 2H), 3.98 (s, 4H), and 4.18 (q, 4H, 7.16 Hz)

^{13}C NMR; δ 14.19 (CH_3), 21.53 (CH_3), 25.47 (CH_2), 30.65 (CH_2), 43.33 (CH_2), 59.92 (CH_2), 64.34 (OCH_2), 107.24 (C), 123.58 (C), 143.07 (C), and 168.20 (CO).

Compound 87

The ketal 86 to the allylic alcohol 87

The ketal 86 (99.53 g, 0.44 mol) was transferred to a dropping funnel and diluted with anhydrous ether (200 mL). In a 3 L, three-neck round bottomed flask equipped with a mechanical stirrer, a nitrogen inlet, the dropping funnel containing the ketal, in anhydrous ether (1.3 L) at 0 °C, LAH (40.42 g, 95%) was carefully added. The acetal was added dropwise at a rate of 1 drop/second while stirred vigorously. The solution was left stirring for 20 hours at room temperature. Then after cooling to 0 °C, saturated sodium sulfate (200 mL) was added carefully. Upon addition of this aqueous solution, a gray salt formed. After separation of the organic layer, the inorganic residue was washed with concentrated ether (1 L). The solvent was removed in vacuo. Distillation of the final residue (bp 94-96 °C, 0.1 mm Hg) gave 87 as a yellow liquid (79.22 g, 0.43 mol, 98% yield).

^{1}NMR; δ 1.27 (bsl, 1H), 1.71 (s, 3H), 1.77 (t, 2H, 6.56 Hz), 2.24 (s, 2H), 2.36 (m, 2H), 3.98 (s, 4H), and 4.15 (d, 2H, 4.15 Hz)

Compound 91

Wittig reaction of 109 to Trans-(2-methyl-4,4-ethylenedioxy-cyclohex-1-enyl)propanoic acid methyl ester 91

Methyl(triphenyl phosphoranylidene) acetate (32.49 g, 97 mmol) was mixed with the aldehyde 109 (14.17 g, 78 mmol) in dry toluene (200 mL). The solution was refluxed for 3 days or until the TLC analysis showed the absence of the aldehyde. After the toluene was removed in vacuo, the residue was filtered thru a silica gel column to remove the Ph_3PO, and giving 24.16 g of impure residue. Column chromatography using silica gel (hexanes/EtOAc, 2:1; R_f 0.21), gave the ester 91 (13.81 g, 58 mmol, 74% yield).

^{1}H NMR; δ 1.81 (t, 2H, 6.6 Hz), 1.92 (s, 3H), 2.41 (bs, 4H), 3.75 (s, 3H), 3.99 (s, 4H), 5.83 (d, 1H, 15.63 Hz), and 7.82 (d, 1H, 15.68 Hz).

^{13}C NMR; δ 19.57, 24.46, 30.74, 43.15, 51.34, 64.44, 107.40, 115.50, 126.47, 140.11, 141.85, and 168.10.

Compound 92

LAH reduction of 91 to the unsaturated alcohol 92

^{1}H NMR; δ 0.87 (m, 1H), 1.30 (m, 2H), 1.79 (s, 3H), 2.33 (s, 3H), 2.39 (br, 2H), 3.98 (s, 3H), 4.20 (m, 2H), 5.79 (m, 1H), and 6.68 (d, 1H, 15.66 Hz).

Compound 95

LAH reduction of the Ketal methyl ester 117 to the ketal-alcohol 95

^{1}H NMR; δ 1.44 (tl, 1H, 5.56 Hz), 1.66 (s, 3H), 1.67 (m, 2H), 1.73 (t, 2H, 6.37 Hz), 2.12 (t, 2H, 7.63 Hz), 2.19 (bs, 4H), 3.64 (dd, 2H, 6.16 and 12.05 Hz), and 3.97 (s, 4H).

^{13}C NMR; δ 18.88, 28.45, 28.94, 31.02, 31.39, 41.54, 62.44, 64.21, 108.35, 123.95, and 128.93.

Compound 101

Grignard reaction of the aldehyde 88 to 1,1-ethylenedioxy-3-methyl-4(1-hydroxy-2-propenyl)cyclohex-3-ene 101

An ice cooled solution of magnesium metal (0.17 g, 7.2 g atoms), dry THF (2 mL), and vinyl bromide (≈1 mL) was stirred for one hour. Followed by the addition of the aldehyde 88 (0.91 g, 5 mmol) diluted with THF (3 mL). The solution was stirred for 24 hours before quenching with sat. NH_4Cl (10 mL). The product was extracted with ether and dried with anhydrous sodium sulfate. TLC showed 2 spots, R_f 0.38 (alcohol, major) and 0.52; hexanes/EtOAc 1:2. No purification was attempted.

^1H NMR; δ 1.77 (s, 3H), 1.85 (m, 2H), 2.32 (s, 2H), 2.42 (m, 2H), 4.00 (s, 4H), 4.17 (s, 1H), 5.18 (m, 1H), 5.20 (s, 1H), 5.33 (m, 1H), and 5.95 (m, 1H).

Compound 102 and 103

Hydrogenolysis of 101 to 102 and 103

A solution of the alcohol 101 (5 mmol) and SO_3.Pyr (1.19 g, 7.5 mmol) in dry THF (50 mL) was stirred at room temperature. A TLC was taken every hour but there was no change observed. LAH (0.80 g, 20 mmol, 95%) was added to the cooled solution (0 °C) and left stirring overnight. Finally, 1 M NaOH (20 mL) was added to quench the reaction. The THF was removed and the aqueous layer extracted with diethyl

ether and dried with anhydrous potassium carbonate. The crude residue (0.59 g) was chromatographed (silica gel, 20 g) eluting with hexanes/EtOAc (2:1). TLC (before separation) 5 spots, R_f 0, 0.11, 0.18, 0.31, and 0.43.

Compound 102

1,1-ethylenedioxy-3-methyl-4-allyl-cyclohex-3-ene 102

TLC, 3 spots, R_f 0.45, 0.51, and 0.66.

^{1}H NMR; δ 1.85 (s, 3H), ≈1.85 (m, 2H), 2.35 (s, 2H), 2.40 (m, 2H), 4.00 (s, 4H), 4.22 (d, 2H, ≈5 Hz), 5.20 (m, 1H), 5.80 (m, 1H), and 6.71 (m, 1H).

Compound 103

1,1-ethylenedioxy-3-methyl-4(1-propenyl)cyclohex-3-ene 103

TLC, 2 spots, R_f 0.45 and 0.51.

^{1}H NMR; δ 1.58 (s, 3H), 1.65 (d, 3H, ≈10 Hz), 1.76 (m, 4H), 2.18 (bs, 2H), 4.00 (s, 4H), 5.64 (m, 1H), and 6.46 (m, 1H).

Compound 108

Reaction of 87 to 1,2-bis(3,4-dimethylphenoxy)ethane 108

To a 0 °C equimolar mixture of the alcohol 87 and calcium hydride, all in methylene chloride, one equivalent of phosphorus tribromide was added. The solution was stirred overnight. The reaction was quenched by adding water at 0 °C. After filtration, drying, and removal of the

organic solvent, a colorless oil was obtained.

^{1}H NMR; δ 2.19 (s, 3H), 2.23 (s, 3H), 4.27 (s, 2H), 6.69 (dd, 1H, 2.60 and 8.24 Hz), 6.76 (d, 1H, 2.48 Hz), and 7.03 (d, 1H, 8.23 Hz).

^{13}C NMR; δ 18.84, 20.06, 66.69, 111.71, 116.46, 129.01, 130.35, 137.75, and 156.89.

Compound 109

The allylic alcohol 87 to the dienone 109

A solution of the alcohol 87 (9.21 g, 50 mmol), THF (170 mL), and 10% HCl (170 mL), was stirred for 4 hours. The aqueous layer was salted out with sodium chloride. The THF was removed in vacuo. The remaining aqueous layer was extracted with methylene chloride (3 X 100 mL). The combined organic layer was washed with sat. sodium chloride (2 X 100 mL), with sat. sodium bicarbonate (100 mL), and dried with anhydrous sodium sulfate. The oily residue was distilled (bp 34-36 °C, 0.01 mm Hg; and 120-122 °C, 30 mm Hg), giving a colorless 109 (4.58 g, 37 mmol, 74% yield).

^{1}NMR; δ 2.07 (s, 3H), 2.49 (t, 2H, 7.04 Hz), 2.74 (t, 2H, 6.92 Hz), 5.35 (d, 2H, 7.03 Hz), and 5.92 (s, 1H).

^{13}C NMR; δ 19.99, 31.26, 37.59, 115.48, 127.71, 142.13, and 154.34.

Compound 110

Conversion of 4-methylene-3-methyl-2-ene-1-one 109 to 3,4-dimethylphenol 110

The dienone 109 (50 mmol) was refluxed for 12 hours using a solution of HOAc/H_2O/HCl (100 mL, 5:5:1). The organic material was extracted with ether, washed with water to remove excess acid, and dried with Na_2SO_4. The crude residue showed the presence of 110. No yields were recorded.

^{1}H NMR; δ 2.18 (s, 3H), 2.21 (s, 3H), ≈4.62 (bsl, 1H), 6.57 (dd, 1H, 2.53 and 8.10 Hz), 6.64 (d, 1H, 2.61 Hz), and 6.98 (d, 1H, 8.11 Hz)

Compound 113

The dienone 109 to the Michael adduct 113

In a three neck flask equipped with a condenser, a nitrogen inlet, a magnetic stirrer, and containing freshly prepared sodium ethoxide (0.30 g of sodium metal and 400 mL of absolute ethanol), diethylmalonate (75 mL, 0.495 mol, 4.5 eq) was added, followed by the addition of the dienone (13.44 g, 110 mmol) diluted with ethanol (75 mL). This solution was refluxed for two days. Water (100 mL) was added to quench the reaction. The ethanol was removed in vacuo. The residue was extracted with ether, and dried with sodium sulfate. The unreacted diethylmalonate was removed by fractional distillation with a 20 cm long Vigreux column (bp 30-35 °C, 0.01 mm Hg, water bath at ≈65 °C). The final residue

was distilled (bp 130-136 °C. 0.01 mm Hg) as a thick oil (20.18 g, 71 mmol, 65% yield). R_f 0.19, hexanes/EtOAc, 2:1.

^{1}NMR; δ 1.28 (m, 6H), 1.96 (m, 2H), 2.02 (s, 3H), 2.32 (m, 2H), 2.46 (m, 2H), 2.77 (m, 1H), 3.50 (m, 1H), 4.23 (m, 8H), and 5.85 (s, 1H).

Compound 114

Michael adduct 113 to the keto-acid 114

The keto-diethyl ester 113 (20.18 g, 71 mmol) was dissolved in a solution of HOAc/H_2O/HCl (5:5:1, 150 mL) solution, and refluxed for 16 hours. The cooled solution was saturated with NaCl and extracted with methylene chloride (3 X 100 mL). The organic layer was washed with sat. sodium chloride (3 X 100 mL) and dried. The solvent was removed in vacuo leaving a dark brown syrup as the product. The residue (8.20 g, 45 mmol, 63% yield) was used without further purification.

^{1}NMR; δ 1.6-2.6 (m, ≈9H), 2 (s, 3H), and 5.87 (s, 1H).

Compound 115

The keto-acid 114 to the keto-methyl ester 115

The impure keto-acid 114 (≈45 mmol) prepared in the preceding step was dissolved in methylene chloride (≈110 mL) containing p-toluenesulfonic acid monohydrate (0.05 g), and absolute methanol (7 mL, ≈180 mol). This solution was heated to 60 °C and stirred for 16 hours. The water was removed by azeotropic distillation (Dean-Stark apparatus) with benzene. After cooling to ≈55 °C, additional absolute methanol (≈7 mL) was added and refluxed for two more hours. The solvents were removed in vacuo. The residue was dissolved in ether, washed with sat. $NaHCO_3$, and dried (Na_2SO_4). The final residue was used without purification. A small amount was distilled for ^1H NMR analysis (bp 100-110 °C, 0.01 mm Hg).

^1H NMR; δ 1.83 (m, 2H), 2.00 (s, 3H), 2.08 (m, 3H), 2.28 (m, 2H), 2.43 (m, 2H), 3.70 (s, 3H), and 5.85 (s, 1H).

Compound 117

The keto-methyl ester 115 to the protected methyl ester 117

Using a Dean-Stark apparatus, the impure keto-methyl ester 115 (≈45 mmol) was refluxed overnight in benzene (100 mL), containing p-toluenesulfonic acid (0.1 g), and ethylene glycol (10 mL). The benzene was removed in vacuo. The residue was worked-up with ether, and then washed with sat. $NaHCO_3$, and dried (Na_2SO_4). Distillation (bp 85-89 °C, 0.01 mm Hg) afforded the pale yellow oil 117 (9.62 g, 40 mmol,

88% yield from 114). TLC: hexanes/EtOAc, 1:2, R_f .0.51, Iodine chamber.

^{1}NMR; δ 1.63 (s, 3H), 1.72 (t, 2H, 6.52 Hz), 2.19 (bs, 4H), 2.36 (s, 4H), 3.67 (s, 3H), and 3.97 (s, 4H).

Compound 119

Ketal-alcohol 95 to the mesylate 119

The procedure used for compound 31 was repeated here.

^{1}H NMR; δ 1.63 (s, 3H), 1.73 (t, 2H, 6.44 Hz), 1.85 (dd, 2H, 6.56 and 15.00 Hz), 2.16 (m, 2H), 2.20 (bs, 2H), 2.26 (m, 2H), 3.01 (s, 3H), 3.97 (s, 4H), and 4.21 (t, 2H, 6.45 Hz)

^{13}C NMR; δ 18.98, 27.53, 28.32, 28.38, 31.40, 37.25, 41.64, 64.30, 69.84, 108.14, 125.30, and 127.46.

Compound 120

The ketal- mesylate 119 to the protected iodo 120

The procedure used for compound 33 was repeated here.

^{1}H NMR; δ 1.65 (s, 3H), 1.72 (t, 2H, 6.46 Hz), 1.93 (m, 2H), 2.13 (m, 2H), 2.19 (s, 2H), 2.26 (m, 2H), 3.17 (t, 2H, 6.94 Hz), and 3.97 (s, 4H).

^{13}C NMR; δ 6.85, 19.19, 28.64, 31.49, 32.27, 33.44, 41.69, 64.34, 108.20, 125.10, and 127.65.

Compound 121

^{1}H NMR; δ 2.04 (q, 2H, 7.15 Hz), 2.27 (s, 3H), 2.65 (t, 2H, 7.55 Hz), 3.21 (t, 2H, 6.83 Hz), 4.59 (sl, 1H), 6.60 (dd, 1H, 2.28 and 8.16 Hz), 6.64 (bs, 1H), and 7.00 (d, 1H, 8.16 Hz).

Compound 122

The unexpected deprotection of the ketal-iodo 120 to the unsaturated ketone-iodo 122

The procedure used for compound 33 was repeated here. The reaction solution was stirred for 16 hours instead of the required 6. Upon work-up, the ketone 122 was isolated in quantitative amounts.

^{13}C NMR; δ 6.52, 22.98, 26.11, 31.28, 31.51, 33.73, 38.44, 126.87, 165.07, and 198.84.

Compound 124

The coupling of 1-cyanobenzocyclobutene 9 with the iodo 120 resulting in 124

Two dropping funnels were prepared as follows, one containing the 1-cyano benzocyclobutene (2.58 g, 20 mmol), and the second the impure iodo ketal (6.64 g, 20 mmol). Both reagents were diluted with dry THF (25 mL).

A 500 mL four-neck round bottom flask was equipped with the two dropping funnels, a condenser with a nitrogen inlet, a septum, and a magnetic stirrer. The flask contained dry THF (200 mL) and diisopropylamine (2.80 mL, 20 mmol). The solution was cooled to 0 °C and n-butyllithium (8.70 mL, 20 mmol, 2.3 M solution) was injected. The reaction mixture was stirred for 10 minutes, then cooled to -78 °C and stirred for 10 more. The solution containing the 1-cyano benzocyclobutene was delivered over a 5 minute period, and stirred for 20 minutes before the iodo compound was introduced (1 drop/second). The final solution was left stirring for one hour before quenching with water (50 mL). The THF was removed in vacuo. The organic residue was extracted with ether, washed with sat. NaCl, sat. $NaHCO_3$, and dried (Na_2SO_4).

^1H NMR; δ 1.61 (s, 3H), 1.72 (m, 4H), 1.94 (m, 2H), 2.10 (t, 2H, 7.68 Hz), 2.19 (bs, 2H), 3.26 (d, 1H, 14.10 Hz), 3.71 (d, 1H, 14.16 Hz), 3.96 (s, 4H), 7.14 (d, 1H, 6.50 Hz), 7.20 (d, 1H, 6.47 Hz), and 7.30 (m, 2H).

^{13}C NMR; δ 22.90, 24.60, 26.01, 30.35, 33.73, 37.20, 39.11, 42.77, 42.88, 121.48, 121.56, 124.00, 126.74, 128.14, 129.59, 141.31, 143.65, 165.37, and 198.89.

IR (neat); 3080, 2940 (b), 2245 (s), 1465, 1435, 1375, 1325, 1260, 1215, 1170, 1140, 1105, 1070, 1050, 1000, 950, 935, 845, 790 (b), 760, 720, and 700 cm^{-1}.

Compound 126

A solution of the ketal 124 (6.15 g, 20 mmol), THF (100 mL), and 10% HCl (100 mL), was stirred for four hours at room temperature. After saturation with sodium chloride. The solution was worked-up with ether and dried with Na_2SO_4. TLC (hexanes/EtOAc, 2:1) showed two spots: R_f 0.14, and 0.51 (trace). Purification by column chromatography (silica gel, 210 g) using hexanes/EtOAc (1:1, R_f 0.34 and 0.63 respectively), gave pure colorless oil 126 (4.82 g, 17 mmol, 85% yield).

^1H NMR; δ 1.45 (m, 2H), 1.60 (m, 2H), 1.78 (m, 2H), 1.88 (s, 3H), 1.99 (m, 2H), 2.17 (m, 2H), 2.33 (m, 1H), 3.24 (d, 1H, 14.18 Hz), 3.65 (d, 1H, 14.20 Hz), 5.75 (s, 1H), and 7.17 (m, 4H).

^{13}C NMR; δ 22.90, 24.60, 26.01, 30.35, 33.73, 37.20, 39.11, 42.77, 42.88, 121.48, 121.56, 124.00, 126.74, 128.14, 129.59, 141.31, 143.65, 165.37, and 198.89.

IR (neat); 3080, 3030, 2940, 2870, 2240 (s), 1665 (b), 1630, 1460, 1440, 1380, 1330, 1250, 1200, 1150, 1020, 1000, 965, 950, 865, 850, 775, 760, 720 (s), and 700 cm^{-1}.

Compound 130

^{1}H NMR; δ 2 (s, 3H), 2.44 (s, 3H), 5.87 (s, 1H), and 6.45 (t, 1H, ? Hz).

IR (neat); 3065, 3015, 2950, 2880, 2260 (w), 2230 (s), 1715 (w), 1670, 1630, 1490, 1460, 1385, 1355, 1340, 1260, 1200, 1160, 1150, 960, 920, 870, 770, 735, 710, and 750 cm^{-1}.

Compound 134

The removal of the nitrile from 124 into 134

In a 250 mL three-neck round bottom flask equipped with a dry ice condenser, a mechanical stirrer, a gas inlet, and a drying tube filled with potassium hydroxide, containing a -78 °C solution of the nitrile (2.15 g, 7 mmol), dry THF (8 mL), absolute ethanol (0.32 mL), and dry ammonia liquid (≈80 mL), sodium metal (5 eq) was added in small pieces while stirring vigorously, turning the solution blue, then colorless. The solution was stirred for an additional hour before quenching with sat. ammonium chloride. The product was extracted with ether, dried (Na_2SO_4). The crude residue was analyzed by IR, showing the absence of the nitrile band. Ketal 134 was purified by column chromatography (silica gel, hexanes/EtOAc, 3:1) containing 3 spots close together: R_f 0.3, 0.25 (major), and 0.2, in 69-95% yields.

^{1}H NMR; δ 1.63 (s, 3H), 2.21 (bs, 2H), 2.73 (dd, 1H, ?Hz), 3.32 (dd, 1H, ?Hz), 3.45 (m, 1H), 3.97 (s, 4H), and 7.13 (m, 4H).

IR (neat); 3080, 2920 (b), 1460, 1375, 1350, 1325, 1260, 1140, 1110, 1070, 1050, 950, 940, 900, 845, 790, 770, 750, and 715 cm^{-1}.

Compound 135

The deprotection of the ketal 134 into the unsaturated ketone 135

A solution of the impure ketal 124 (≈7 mmol) in THF (100 mL) and 10% HCl (100 mL) was stirred for 5 hours at ambient temperature. After saturation with sodium chloride, the two layers solution was extracted with ether. The combined organic layers were washed with sat. sodium chloride followed by sodium bicarbonate solution. After removal of all the solvent in vacuo, the residue was redissolved in ether and dried (Na_2SO_4). The final residue was purified by column chromatography (silica gel, 75 g) using hexanes/EtOAc (3:1) giving (0.96 g, 4 mmol, ≈57% yield from 134). TLC indicated that the final product was a mixture as indicated by two spots close together: R_f 0.25 (major) and 0.31.

^{1}H NMR; δ 1.53 (m, 2H), 1.70 (m, 2H), 1.96 (s, 3 H), 2.09 (m, 2H), 2.29 (m, 3H), 2.43 (m, 2H), 2.75 (dd, 1H, 2.22 and 13.97 Hz), 3.34 (dd, 1H, 4.15 and 13.97 Hz), 3.46 (m, 1H), 5.84 (s, 1H), and 7.13 (m, 4H).

IR (neat); 3070, 3020, 2920 (b), 2860, 1660 (b), 1625, 1510 (w), 1450, 1440, 1380, 1330, 1250, 1200, 1150, 1130, 1050, 1025, 1000, 970, 950, 865, 850, 740 (s), and 710 cm^{-1}.

Compound 140

The intramolecular Diels-Alder reaction of 135 into the tricyclic ketone 140

The total amount of 135 (9.57 g, 38 mmol) was divided into small portions. A typical thermolysis can be described as follows,

A solution of 135 (2.60 g, 10 mmol) in m-dichlorobenzene (800 mL) was refluxed for 16 hours turning from a pale yellow to a dark brown solution. The solvent was removed in vacuo leaving a dark solid. The combined residue was partially purified by column chromatography (silica gel, hexanes/EtOAc, 3:1). The main fraction collected (R_f 0.20-0.34) was recrystallized from hexanes giving the ketone 140 (1.26 g, ≈5 mmol, 48% yield) as a white solid (mp 112.2-114.2 °C). The remaining material could not be identified as it was mixed with decomposed material.

^{1}H NMR; δ 1.07 (s, 3H), 1.43 (m, 2H), 1.69 (m, 2H), 1.85 (m, 1H), 2.04 (m, 2H), 2.32 (m, 2H), 2.48 (m, 2H), 2.57 (d, 1H, 7.52 Hz), 2.81 (dd, 1H, 7.37 and 17.57 Hz), 3.40 (d, 1H, 17.70 Hz), and 7.12 (m, 4H).

^{13}C NMR; δ 20.76 (CH_3), 20.80 (CH_2), 24.55 (CH_2), 24.86 (CH_2), 25.88 (CH_2), 28.25 (CH_2), 35.30 (CH), 40.95 (CH_2), 41.32 (CH), 54.50 (CH), 125.17 (CH), 125.54 (CH), 125.75 (CH), 128.81 (CH), 134.13 (C), 137.73 (C), and 211.73 (CO).

IR (CCl_4); 3080 (w), 3015 (w), 2940 (b), 2880, 1710, 1490, 1380, 1350, 1330, 1300, 1230, 1180, 1050, 1000, 960, 930, 870, and 650 cm^{-1}.

UV; 266.42 (1.3648 A) and 273.08 nm (1.2960 A).

MS (CI) MH^+ at m/e 255 (10), 254 (54), 239 (43), 236 (5), 222 (18), 221 (100), 195 (23), 179 (13), 155 (17), 141 (43), 128 (18), 115 (16).

Anal. Calcd. for $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found: C, 84.86, H, 8.68.

Compound 148

Model studies of α-tetralone: the Wittig adduct 148

To a -78 °C solution of (ethyl)triphenylphosphonium iodide (1.84 g, 4.40 mmol) in dry THF (50 mL) was introduced n-butyllithium (0.70 mL, 4.4 mmol, 2.5 M) turning the solution bright orange. After stirring for 30 minutes, α-tetralone (0.60 g, 4 mmol) in THF (10 mL) was delivered. The reaction was quenched after 16 hours of stirring (water, 1 mL). After the usual worked-up, the TLC analysis (hexanes/EtOAc, 3:1) showed unreacted α-tetralone (R_f 0.37) and two spots very close together (R_f ≈0.62) which could not be separated in the chromatotron. The ^1H NMR spectrum indicated that the product was a mixture of the expected E/Z isomers. No yields were recorded.

^1H NMR; δ 0.86 (m, ?H), 1.85 (m, ?H), 2.40 (m, ?H), 2.49 (t, ?H, 6.17 Hz), 2.74 (t, ?H, 6.13 Hz), 2.81 (t, ?H, 6.65 Hz), 5.55 (t, ?H, ≈7.24 Hz), 6.10 (q, 3H, 6.92 Hz), and 7.30 (m, ?H).

Compound 151

The bromination of 140 followed by dehydrobromination into the unsaturated ketone 151

Under a dry nitrogen atmosphere, the solution of the tricyclic 140 (≈1.52 g, 6 mmol), NBS (2.35 g, 13 mmol), in carbon tetrachloride (80 mL), and a trace of AIBN, was refluxed for 2 hours. The solution was worked-up with sat.

sodium chloride, sodium bicarbonate, and dried with anhydrous magnesium sulfate. This brominated compound showed a single spot on the TLC plate (R_f 0.48, hexanes/EtOAc, 3:1). A ^1H NMR analysis showed a complicated spectrum. The residue was dissolved in dry dioxane (80 mL), followed by the addition of DBU (1.4 mL, 10 mmol), and refluxed. The reaction was followed by TLC, and it showed additional spots at the end of one hour (R_f 0.34 and 0.38) plus a long yellow streak. The reaction was refluxed until the reagent was no longer present (24 hours). The solution turned from a light brown to dark brown/black. A coating, of a dark solid, was observed. After quenching with water, it was extracted with ether. The dark coating was insoluble in the aqueous and organic layers. The combined organic layer was dried (Na_2SO_4) and the solvent was removed in vacuo. A small amount (0.15 g) of the total residue (1.07 g) was purified using the chromatotron, and only one band (R_f 0.38, hexanes/EtOAc, 3:1) was consistent with the ^1H NMR analysis (vinylic singlet at 7.08 ppm). This pure brown residue could not be weight out in the regular balance. The remaining brown-orange 0.92 g was used without purification.

^1H NMR; δ 0.88 (s, 3H), 1.20 (m, ?H), 1.61 (m, ?H), 1.87 (m, ?H), 2.35 (m, ?H), 3.13 (m, 1H), 7.08 (s, 1H), and 7.26 (m, 4H).

^{13}C NMR; δ 19.39 (CH_3), 21.95 (CH_2), 23.56 (CH_2), 25.52 (CH_2), 27.85 (CH_2), 35.86 (CH_2), 39.61 (C), 40.89 (CH), 41.90 (CH), 124.43 (CH), 126.33 (CH), 128.49 (CH), 129.51 (CH), 131.72 (CH), 132.51 (C), 140.10 (C), 146.12 (C), and 203.55 (CO).

Compound 152

The reduction of the conjugated ketone 151 into the allylic alcohol 152

In a 500 mL three-neck round bottom flask equipped with a nitrogen inlet, a condenser, a mechanical stirrer, and a rubber septum, an orange solution of the crude 151 (0.92 g, ≈3.7 mmol) in methylene chloride (150 mL) was cooled to 0 °C. DIBAL-H (5.5 mL, 5.5 mmol, 1 M solution in methylene chloride) was added dropwise while stirring vigorously. The solution was stirred for one hour followed by the addition of methanol (5 mL) and water (50 mL). The thick solution was extracted with ether. The remaining inorganic salt was washed with methylene chloride. The combined organic layers was dried with $MgSO_4$. The crude alcohol 152 was used without purification.

^1H NMR; δ 0.8 (s, 3H), 0.8-2.4 (m, 12H), 3 (m, 1H), 4.6 (m, 1H), 6.4 (s, 1H), and ≈7.1 (m, 4H).

Compound 155

The mesylation and dehydromesylation of the alcohol 152 into the conjugated triene 155

A solution of the crude alcohol 152 (≈3.7 mmol), anhydrous ether (120 mL), triethylamine (≈3.6 mL), and mesyl chloride (≈1.2 mL) was stirred for two hours at room temperature. The reaction was quenched with water (10 mL), and extracted with ether. The combined organic layer was washed with sat. sodium chloride, and dried (Na_2SO_4). TLC showed a major spot at R_f 0.25 (hexanes/EtOAc, 3:1). After removal of the solvent, the residue was thoroughly mixed with neutral alumina (20 g, activity 1), and left undisturbed for one hour. Methylene chloride (60 mL) was poured into the flask containing the alumina; the solution was left stirring overnight. The alumina was filtered and washed with methylene chloride. The final residue (0.54 g) was purified by radial chromatography and it gave a red-orange oil 155 (0.42 g, 1.7 mmol, 46% yield) (R_f 0.62, hexanes/EtOAc, 3:1). The brown-orange impurity could not be separated from the triene.

^{1}H NMR; δ 0.84 (s, 3H), ≈2.86 (m, 1H), 6.07 (m, 1H), 6.17 (s, 1H), 6.39 (dd, 1H, 2.47 and 9.52 Hz), and 7.16 (m, 4H).

Compound 157

The DDQ oxidation of 140 into the aromatic ketone 157

A solution of the tricyclic 140 (0.05g, 0.2 mmol) in dry dioxane (20 mL), DDQ (3.3 eq), a trace of p-toluenesulfonic acid monohydrate (0.03 g) was refluxed (oil bath at 125 °C) for 10 hours. As the solution was cooling to room temperature, a precipitated formed. The solution was filtered and the dioxane removed in vacuo. The residue was extracted with ether, washed with sat. Na_2SO_4, 5% NaOH, NaCl, and dried with K_2CO_3. TLC showed two yellow spots (R_f 0.22 and 0.34, Hex/EtOAc, 3:1) and a long streak. This mixture was purified using the chromatotron (hexanes/EtOAc, 9:1). The first fraction was discarded as it could not be identified.

^{1}H NMR; δ 6.77 (d, 1H, 9.76 Hz), 7.81 (m, 5H), 8.20 (dfs, 8.02 Hz), 8.77 (d, 1H, 8.35 Hz), 8.83 (dd, 1H, 1.84 and 7.42 Hz), and 9.04 (s, 1H).

Compound 162

The Diels-Alder reaction between 35 and maleic anhydride

A solution of the olefin 35 (0.15 g, 0.5 mmol) in m-dichlobenzene, and maleic anhydride (0.25 g, 2.5 mmol) was refluxed for 10 hours. After removal of the solvent, the residue was recrystallized from absolute ethanol (0.10 g, 0.25 mmol, 50% yield) as a white solid (mp 158.4-160.6 °C).

^{1}H NMR; δ 2.01 (dd, 1H, 7.56 and 15.18 Hz), 3.36 (dd, 1H, 3.36 and 15.14 Hz), 3.37 (dd, 2H, 1.52 and 7.21 Hz), 3.50 (dd, 1H, 5.85 and 10.19 Hz), 3.67 (m, 1H), 3.76 (s, 3H), 3.85 (s, 3H), 4.07 (bdd, 1H, 5.87 and 10.03 Hz), 5.99 (dtt, 1H, 0.68, 7.02, and 7.12 Hz), 6.21 (m, 1H), 6.62 (s, 1H), 6.68 (s, 1H), and 7.26 (m, 4H).

Compound 164

The Wittig reaction of the aldehyde 88 into the conjugated diene 164

To a 0 °C solution of methyltriphenylphosphonium iodide (30.10 g, 75 mmol) in dry THF (300 mL), was injected n-butyllithium (30 mL, 72 mmol, 2.43 M), and stirred for 30 minutes. To a now red solution containing the ylide, the aldehyde 88 (4.56 g, 25 mmol) was added dropwise. The solution was left stirring overnight. The reaction was quenched with water (2 mL). The diene was extracted with ether, and dried with $MgSO_4$. Purification by column chromatography (R_f 0.32, hexanes/EtOAc, 3:1) gave pure liquid 164 (3.06 g, 17 mmol, 68% yield, bp 56-60 °C, 0.1 mm Hg).

^{1}H NMR; δ 1.78 (s, 3H), 1.76 (m, 2H), 2.31 (bs, 2H), 2.36 (m, 2H), 3.96 (s, 4H), 4.98 (d, 1H, 10.99 Hz), 5.12 (d, 1H, 17.23 Hz), and 6.79 (dd, 1H, 11.00 and 17.31 Hz).

^{13}C NMR; δ 18.90 (CH_3), 24.05 (CH_2), 30.90 (CH_2), 42.49 (CH_2), 64.34 (OCH_2), 107.89 (C), 111.28 (CH_2), 127.41 (C), 130.34 (C), and 134.10 (CH).

IR (neat); 3100, 3020, 2920 (b), 1730 (w), 1640 (s), 1600, 1450, 1420, 1370, 1350, 1325, 1260, 1220, 1160, 1130, 1085, 1060, 1050, 1015, 990, 950, 935, 900, 840, 785, 740, 720, 700, and 680 cm^{-1}.

Compound 165

Method A

The hydroboration of the diene 164 into the alcohol 165

To a solution of the diene 164 (0.38 g, 2.1 mmol) in dry THF (30 mmol) was injected 9-BBN (6.3 mL, 3.15 mmol, 0.5 M in hexanes). This solution was stirred for one hour at room temperature, then cooled to 0 °C for the addition of water (1 mL), 1 N sodium hydroxide (2.1 mmol), and finally 30% hydrogen peroxide (0.7 mL). The product was extracted with diethyl ether and dried with sodium sulfate. A fractional vacuum distillation was attempted to purify the alcohol but other compounds were still present.

Method B

LAH reduction of the ketal-ester 180 into the alcohol 165

^1H NMR; δ 1.57 (bs, 2H), 1.67 (s, 3H), 1.74 (m, 2H), 2.22 (bs, 3H, -OH), 2.35 (t, 2H, 6.81 Hz), 3.67 (t, 2H, 6.83 Hz), and 3.98 (s, 4H).

Compound 166

The mesylation of the alcohol 165

To an ice cold solution of triethylamine (58.5 mL, 0.42 mol) in anhydrous ether (700 mL), was added the alcohol 165 (17.73 g, 84 mmol) followed by dropwise addition of mesyl chloride (19.5 mL, 0.25 mol). The solution was stirred for one hour at 0 °C and one more at ambient temperature. The reaction was worked-up with water/ether. The organic layer was dried (Na_2SO_4). After removal of the solvent, the mesylate 166 was used without purification.

^{1}H NMR; δ 1.66 (s, 3H), 1.73 (bt, 2H, 6.63 Hz), 2.22 (bs, 2H), 2.51 (t, 2H, 7.35 Hz), 2.99 (s, 3H), 3.97 (s, 4H), and 4.22 (t, 2H, 7.37 Hz).

Compound 167

The ketone 170 was protected to the ketal 167 in a similar fashion as Hagemann's ester in ≈88% crude yield.

^{1}H NMR; δ 1.63 (s, 3H), 1.73 (t, 2H, 6.39 Hz), 2.29 (s, 2H), 2.21 (b, 2H), 2.63 (t, 2H, 8.18 Hz), 3.14 (t, 2H, 8.26 Hz), and 3.97 (s, 4H).

Compound 169

The transformation of the mesylate 166 into the iodo 167 was according to the method for compound 33. The deprotected ketone 169 was isolated instead. No yields were recorded.

^{1}H NMR; δ 1.27 (m, 3H), 1.6-1.9 (m, 3H), 1.71 (sfs, 3H, 1.22 Hz), 2.42 (t, 1H, 4.77 Hz), 2.54 (t, 1H, 5.57 Hz), and 5.30 (sfs, 1H, 0.49 Hz).

^{13}C NMR; δ 22.77 (CH_3), 25.38 (CH_2), 29.01 (CH_2), 39.09 (CH_2), 42.80 (CH), 49.11 (CH), 122.99 (CH), 169.61 (C), and 203.15 (CO).

Compound 171

Dihydroresorcinol 170 to 3-ethoxy-2-cyclohexenone 171

A solution of dihydroresorcinol (97 g, 0.87 mol), p-toluenesulfonic acid monohydrate (3.80 g), absolute ethanol (350 mL), and benzene (1300 mL) was distilled until the fraction distilling at 78 °C was reached. The solution was washed with NaOH (10%, 4 X 100 mL) solution.* The organic layer was washed with sat. sodium bicarbonate (100 mL) and dried ($NaHCO_3$). The concentrated residue was distilled (bp 62-70, 0.1 mm Hg) to give pure 171 (110.74 g, 0.79 mol, 91%

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*. The alkaline solution was saturated with sodium chloride.

yield).

^{1}H NMR; δ 1.28 (tfs, 3H, 0.67 and 7.05 Hz), 1.90 (q, 2H, ≈6.44 Hz), 2.26 (t, 2H, 6.55 Hz), 2.33 (t, 2H, 6.25 Hz), 3.83 (q, 2H, 7.03 Hz), and 5.26 (s, 1H).

Compound 172

To a 0 °C solution of 3-ethoxy-2-cyclohexenone 171 (65.13 g, 0.46 mol) in THF (200 mL) was added a freshly prepared solution of LDA (0.5 mol, diluted in 200 mL THF) and stirred for 0.5 hour before cooling to -78 °C. tert-Butyl bromo acetate (99 g, 0.51 mol, diluted to 150 mL in THF) was added dropwise and stirred for 2.5 hours before warming up to room temperature (0.5 h). Sat. sodium chloride (200 mL) was added to quench the reaction. The THF was removed in vacuo before extraction with ether (4 X 100 mL). The organic layer was washed with sat. sodium chloride (2 X 100 mL), sat. ammonium chloride (2 X 50 mL), and dried ($MgSO_4$). The distillation* gave the t-butyl ester 172 (64.41 g, 0.25 mol, 29%) as well as the acid 173 (76.21 g, 0.38 mol, 44%).

^{1}H NMR; δ 1.36 (t, 3H, 7.02 Hz), 1.46 (s, 3H), 1.77 (dq, 1H, 5.04 and 12.50 Hz), 2.09 (m, 1H), 2.19 (dd, 1H, 7.91 and 16.16 Hz), 2.38 (ddd, 1H, 3.07, 5.01 and 17.58 Hz), 2.61 (m, 2H), 2.84 (dd, 1H, 5.03 and 16.15 Hz), 3.89 (m, 2H), and

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*. Refer to section 2.5.3

5.34 (sfs, 1H, 1.40 Hz).

^{13}C NMR; δ 14.12, 27.02, 28.08, 28.95, 35.89, 42.38, 64.28, 80.39, 102.02, 172.02, 177.04, and 199.23.

Compound 173

The free acid 173 was obtained in 44% yield from the distillation of the t-butyl ester 172 (mp 117.1-117.6 °C)

^{1}H NMR; δ 1.38 (t, 2H, 7.06 Hz), 1.81 (dq, 1H, 5.05 and 12.81 Hz), 2.13 (m, 1H), 2.34 (dd, 1H, 6.06 and 16.06 Hz), 2.39 (ddd, 1H, 2.76, 5.07, and 17.74 Hz), 2.45 (dd, 1H, 2.75 and 4.99 Hz), 2.59 (m, 1H), 2.73 (m, 1H), 2.95 (dd, 1H, 6.63 and 16.07), 3.93 (m, 2H), and 5.40 (sfs, 1H, 1.18 Hz).

Compound 176

To 0 °C solution of 172 (64.41 g, 0.25 mol) in dry THF (500 mL) was introduced methylmagnesium bromide (125 mL, 0.375 mol, 3 M solution in diethyl ether). The solution was stirred for 2 hours before quenching with water (50 mL) followed by acidic work-up with 1 N HCl and drying ($MgSO_4$). The crude residue (21.76 g, ≈0.11 mol, 44% yield) was analyzed by ^{1}H NMR showing the presence of two vinyllic protons in a 1:1 ratio. This analysis suggested the presence of the α,β-unsaturated ketone and the α,β-unsaturated t-butyl

ester.*

^{1}H NMR; δ 1.47 (s, CH_3), 1.48 (s, t-butyl), 1.72 (s, ?H), 1.97 (s, ?H), 5.45 (s, ?H), and 5.87 (s, ?H).

Compound 177

The alkylation of the free acid 173

To a 0 °C solution of the free acid 173 (31.56 g, 0.16 mol) in dry THF (600 mL), was added methylmagnesium bromide (181 ml, 0.54 mol, 3 M solution in diethyl ether), and stirred for 2 hours. The reaction was quenched with water (50 mL) followed by an acidic work-up with 1 N HCl (3 X 150 mL). The organic layer was washed with sat. sodium chloride and dried (Na_2SO_4). The NMR analysis of the crude residue indicated traces of unreacted material. The free acid 177 was converted to the ethyl ester 178 without purification.

Compound 178

Method A.

The esterification of the acid 177 into the ethyl ester 178

A solution of the crude acid 177 (≈0.16 mol), p-toluenesulfonic acid monohydrate (0.70 g), absolute ethanol (61 mL) and benzene (240 mL) was distilled until the distilling fraction reached 78 °C. The solvents were removed in vacuo, and the residue worked-up with ether, sat. sodium bicarbon-

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*. Refer to section 2.5.3.

ate, and dried (Na_2SO_4). This procedure gave a crude residue of the ethyl ester 178 (21.76 g, 0.11 mol, ≈69% from 173). The ester 178 was protected to either the ketal 181 or the thioketal 184 without purification (R_f 0.14, hexanes/EtOAc, 3:1).

^1H NMR; δ 1.29 (t, 2H, 7.15 Hz), 1.90 (m, 1H), 1.97 (sfs, 3H, 0.54 Hz), 2.12 (m, 1H), 2.39 (m, 3H), 2.62 (m, 1H), 2.82 (m,1H), 4.19 (q, 2H, 7.14 Hz), and 5.88 (sfs, 1H, 1.17 Hz).

Method B

The transformation of the α,ß-unsaturated ketone/t-butyl ester into the α,ß-unsaturated ketone 178

A solution of 176 (22.43 g, 0.1 mol), p-toluenesulfonic acid monohydrate (1.90 g, 10 mmol), in absolute ethanol (400 mL) was refluxed for 48 hours. The ethanol was removed in vacuo before extraction with ether. The organic layer was washed with sat. sodium bicarbonate, sat. sodium chloride, and dried ($MgSO_4$). Distillation (bp ≈100 °C, 0.025 mm Hg) using a Vigreux column gave 178 (11.34 g, 0.058 mol, 58%).

Compound 180

The protection of the α,ß-unsaturated ketone/α,ß-unsaturated t-butyl ester 176 was attempted in a similar way as compound 181 but the distilled residue (bp 110-112 °C, 0.025 mm. Hg) appeared to be a mixture inseparable of isomers as indicated by the ^1H NMR spectrum (several peaks in the

olefinic region).*

^{1}H NMR; δ 1.5 (s, t-butyl), 1.97 (s, ?), 2.94 (s, ?), 4.71 (s, ?), 5.53 (s, ?), and 5.87 (s, ?).

Compound 181

A solution of the crude ethyl ester 178 (≈0.11 mol), p-toluenesulfonic acid monohydrate (0.18 g), ethylene glycol (18.6 mL, 0.33 mol) and benzene (186 mL) was refluxed using a Dean-Stark collector. After work-up with sat. sodium bicarbonate and drying, the residue was distilled giving the ketal 181 in ≈98% yield (bp 110-112 °C, 0.025 mm Hg).

^{1}H NMR; δ 1.26 (t, 3H, 7.14), 1.67 (sfs, 3H, 0.21 Hz), 1.75 (m, 2H), 2.26 (bs, 2H), 3.05 (s, 2H), 3.92 (s?, 1H), 3.98 (s?, 4H), and 4.14 (q, 2H, 7.13 Hz).

Compound 182

The bicyclic ketone 182 was collected during the formation of the phosphonium salt 168. No yields were recorded.

^{1}H NMR; δ 1.27 (m, 3H), ≈1.67 (bs, 1H), 1.71 (sfs, 3H, 1.22 Hz), 1.80 (m, 2H), 2.42 (bt, 1H, 4.77 Hz), 2.54 (t, 1H, 5.57 Hz), and 5.30 (sfs, 1H, 0.49 Hz).

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*. Refer to section 2.5.3.

^{13}C NMR; δ 22.77 (CH_3), 25.38 (CH_2), 29.01 (CH_2), 39.09 (CH_2), 42.80 (CH), 49.11 (CH), 122.99 (CH), 169.61 (C), and 203.15 (CO).

IR (neat); 3300 (CO overtone), 3030, 2940 (b), 2870, 1620 (b), 1625, 1435, 1330, 1310, 1290, 1275, 1250, 1220, 1180, 1150, 1120, 1050, 1040, 1020, 980, 970, 930, 915, 870 (s), 810, 790, 715, and 775 cm^{-1}.

Compound 184

The protection of the ketone 178 to the thioketal 184

The keto-ester 178 (5.88 g, 30 mmol) was dissolved in methylene chloride (≈250 mL) followed by the addition of 1,2-ethanedithiol (3.77 mL, 45 mmol), and boron trifluoride etherate (1 mL). The solution was stirred for 16 hours at ambient temperature before washing with 5% sodium hydroxide (50 mL). The organic layer was separated, washed with sat. sodium chloride, and dried ($MgSO_4$). Purification by column chromatography (silica gel, hexanes/EtOAc 3:1, R_f 0.55) gave the thioketal 184 (6.90 g, 25 mmol) in 83% yield.

^1H NMR; δ 1.26 (t, 3H, 7.13 Hz), 1.68 (s, 3H), 1.94 (m, 1H), 2.18 (m, 4H), 2.51 (m, 2H), 3.33 (m, 4H), 4.14 (q, 2H, 7.12 Hz), and 5.62 (s, 1H).

^{13}C NMR; δ 14.27 (CH_3), 21.62, 28.07, 34.79, 37.33, 38.38, 39.76 (SCH_2), 39.92 (SCH_2), 60.41, 65.40, 128.59, 136.94, and 172.68 (CO).

IR (neat); 3000, 2980, 2920, 2870, 1725 (s), 1450, 1370-1030, 850 cm^{-1}.

Compound 185

The reduction of the thioketal 184 to the alcohol 185

The standard LAH reduction of the ester gave quantitative amounts of the alcohol 185 as a white cloudy oil.

^1H NMR; δ 1.4-2.4 (m, 10H), 1.72 (s, 3H), 3.35 (m, 4H), 3.71 (m, 2H), and 5.61 (s, 1H).

IR (neat); 3360 (b), 3015 (w), 2940, 2870, 1650 (w), 1600, 1450, 1380, 1280, 1255, 1245, 1170, 1100, 1065, 1035, 980, 850, 790, and 765 cm^{-1}.

Compound 186

The tosylation of the alcohol 185 to 186

A solution of the alcohol 186 (1.15 g, 5 mmol) in dry pyridine (10 mL) was added to a 0 °C solution of p-toluenesulfonyl chloride in pyridine (10 mL), and stirred for two hours. Aqueous lactic acid (≈30 mmol, 85%) was added dropwise to the solution with additional stirring (30 minutes, 0 °C) before pouring into a beaker containing 10% hydrochloric

acid (38 mL) and ether (≈50 mL). The organic layer was washed with 10% HCl followed by sat. sodium bicarbonate and drying ($MgSO_4$). The tosylate 186 was converted to the iodo derivative 187 without further purification.

^1H NMR; δ 1.3-1.85 (m, 3H), 1.61 (s, 3H), 1.9-2.2 (m, 5H), 2.46 (s, 3H), 3.32 (m, 4H), 4.08 (m, 2H), 5.59 (s, 1H), 7.35 (d, 2H, 8 Hz), and 7.80 (d, 2H, 8.30 Hz).

Compound 187

The conversion of the tosylate 186 to the iodo derivative 187

A solution of DIEA (0.02 mL), sodium iodide (1.5 g, 10 mmol) in reagent grade acetone (10 mL) was added to a tosylate 186 solution in acetone (≈10 mL) and stirred for 2.5 hours at ambient temperature. After removal of the acetone, 187 was extracted with ether, washed with sat. sodium bicarbonate, and dried ($MgSO_4$). The iodo 187 was converted to the phosphonium salt without further purification (R_f 0.64, hexanes/EtOAc, 3:1).

Compound 188

The phosphonium salt 188 from the iodo 187

A mixture of the iodo 187 (≈5 mmol), DIEA (0.14 ml), triphenylphosphine (1.84 g, 5 mmol), and dry acetonitrile (15 mL), was heated (50 °C) for 24 hours. The mixture was poured into hexanes (150 mL). The resulting oily salt was

washed with hexanes and dried under vacuum giving ≈80% yield from the thioketal 184 (R_f 0.64, hexanes/EtOAc, 3:1).

Compound 190

The Wittig coupling between the aldehyde 10 and the salt 188

Freshly sublimed potassium tert-butoxide (0.56 g, 5 mmol) in THF (30 mL) was added dropwise to a 0 °C solution of the phosphonium salt 188 (2.80 g, 4.6 mmol) and the aldehyde 10 (1.10g, 8.3 mmol) in THF (30 mL). The reaction mixture was stirred for 16 hours before quenching, at 0 °C, with water (2 mL). The THF was removed and the residue extracted with ether. The organic layer was washed with sat. sodium chloride and dried (K_2CO_3). The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 4:1) giving an oily 190 (1.28 g, 3.9 mmol) in 85% yield (R_f 0.59, hexanes/EtOAc, 3:1).

^{1}H NMR; δ 1.7 (s, 3H), 2.9 (d, 1H, ?Hz), 3.3 (m, 4H), 3.5 (dd, 1H, ? Hz), 4.35 (m, 1H), 5.4 (m, 1H), 5.64 (s, 1H), and 5.65 (m, 1H).

Compound 191

The deprotection of the Wittig adduct 190 to the unsaturated ketone 191

A mixture of the thioketal 190 (1.28 g, 3.9 mmol), acetonitrile (49 mL), water (9.8 mL), and methyl iodide (5.5 mL) was stirred at 45 °C for 16 hours. The solvents were

removed in vacuo before extraction with ether. The ether layer was washed with aqueous sodium thiosulfate followed by sat. sodium bicarbonate and drying (K_2CO_3). The final crude residue (R_f 0.21, hexanes/EtOAc, 3:1) was used in the thermolysis without purification.

^1H NMR; δ 2.02 (sfs, 3H, 0.93 Hz), 2.07 (m, 2H), 2.43 (m, 5H), 2.91 (dd, 1H, 2.41 and 14.09 Hz), 3.52 (dd, 1H, 5.40 and 14.06 Hz), 4.35 (m, 1H), 5.46 (m, 1H), 5.74 (dt, 1H, 1.31 and 9.62 Hz), 5.89 (s, 1H), and 7.11 (m, 4H)

^{13}C NMR; δ 23.04, 26.63, 29.35, 29.47, 34.06, 37.69, 37.74, 39.77, 40.77, 121.94, 122.90, 122.98, 127.01, 127.13, 127.22, 127.31, 127.47, 127.55, 133.74, and 209.97(?).

MS (GC NEG ION W/METHANE) MH^+ at m/e 252.9 (100), 235 (30), 143 (64), 117 (35).

The thermolysis of 191 into the different isomers 195, 196, and 197

A solution of the ketone 191 (1.48 g, 6 mmol) in toluene (600 mL) was heated for 16 hours (oil bath at 120 ± 2 °C). Column chromatography of the reaction residue (silica gel, hexanes/EtOAc, 3:1) gave pure tricyclic 195 (0.62 g, 2.5 mmol, R_f 0.42, 42% isolated yield), the diene 196 (0.10 g, impure, R_f 0.3, ≈7%), and 197 (0.14 g, impure, R_f ≈0.3, ≈9%).

Compound 195

^{1}H NMR; δ 0.99 (s, 3H), 1.94 (m, 3H), 2.14 (m, 1H), 2.52 (m, 2H), 2.61 (d, 1H, 7.55 Hz), 2.66 (m, 1H), 2.92, (dd, 1H, 7.77 and 17.89 Hz), 3.19 (bs, 1H), 3.63 (d, 1H, 17.81 Hz), 5.83 (m, 1H), 6.25 (d, 1H, 10.24 Hz), and 7.26 (m, 4H).

^{13}C NMR; δ 20.36 (CH_3), 24.45 (CH_2), 29.20 (CH_2), 29.63 (CH_2), 35.86 (CH), 39.55 (C), 39.90 (CH), 40.69 (CH_2), 53.76 (CH), 123.77 (CH), 124.43 (CH), 125.54 (CH), 125.84 (CH), 129.13 (CH), 134.53 (C), 135.56 (C), and 210.94 (CO).

UV; 268.08 (1.4419 A), 274.75 (1.4998 A), and 303.08 (1.8362 A).

Compound 196

The [1,7] sigmatropic shift of 191 to 196

^{1}H NMR; δ 1.89 (sfs, 3H, 0.66 Hz), 2.08 (m, 2H), 2.27 (s, 3H), 2.41 (m, 2H), 2.96 (m, 1H), 5.79 (dd, 1H, 8.47 and 15.55 Hz), 5.88 (sfs, 1H), 6.29 (t, 1H, 11.11 Hz), 6.45 (m, 2H), and 7.22 (m, 4H).

Compound 199

The reduction of the ketone 195 into the alcohols 199

A solution of the ketone 195 (0.52 g, 2 mmol), excess $NaBH_4$, in absolute ethanol (50 mL) was refluxed for 2 days. After removal of the ethanol, water was added (20 mL) followed by 10% HCl (20 mL). The alcohol was extracted with ether and dried ($MgSO_4$). The residue was converted to the mesylate without further purification.

^1H NMR; δ 0.81 and 0.84 (2s, 3H), 5.77 (m, 1H), 6.2 (d?, 1H), and 7.1-7.4 (m, 4H).

Compound 200

The mesylation of alcohols 199 into the isomeric mixtures of 200

A solution of the alcohols 199 (≈2 mmol), triethylamine (1.4 mL, 10 mmol), mesyl chloride (0.46 mL, 6 mmol), in anhydrous ester (25 mL) was stirred for one hour at room temperature. The solution was washed with sat. sodium chloride followed by sat. sodium bicarbonate, and dried ($MgSO_4$). The ^1H NMR spectrum of the crude residue indicated the presence of the axial/equatorial mesylate in ≈2:1 ratio.

^1H NMR; δ 0.89 (s, 3H), 2.34 (s, axial OMs), 2.95 (s, equatorial OMs), 3.9 (bs, 1H), 1.92 (m, 1H), 5.7 (m, 1H), 6.2 (m, 1H), and 7.1-7.7 (m, 4H).

Compound 200 (equatorial mesylate)

^{1}H NMR; δ 0.88 (s, 3H), 1.62 (m, 4H), 1.76 (dd, 1H, 6.75 and 10.68 Hz), 1.84 (m, 1H), 2.40 (m, 1H), 2.50 (m, 1H), 2.95 (s, 3H), 3.00 (d, 1H, 18.25 Hz), 3.15 (dd, 1H, 6.89 and 18.59 Hz), 3.46 (bs, 1H), 4.63 (dt, 1H, 5.12 and 10.55 Hz), 5.74 (m, 1H), 6.21 (bd, 1H, 10.39 Hz), and 7.23 (m, 4H).

^{13}C NMR; δ 20.27, 27.60, 27.89, 29.44, 33.26, 34.62, 36.96, 38.65, 39.85, 45.57, 82.79, 126.89, 124.89, 125.83, 125.87, 125.98, and 129.51.

Anal. Calcd. for $C_{19}H_{24}O_3S$: C, 68.64; H, 7.28. Found: C, 68.71; H, 7.34.

Compound 201

The dehydromesylation of the mesylate 106b-axial into the unconjugated triene 201

The mixture of mesylates (≈2 mmol) was treated with neutral alumina gel (10 g, activity 1) and left undisturbed for 1 hour. Methylene chloride (25 mL) was added to the alumina gel followed by stirring for 24 hours. The alumina gel was filtered and washed with methylene chloride. After removal of the solvent, the residue (≈0.56 g) was purified in the chromatotron giving 201 (0.31 g, 1.3 mmol, R_f 0.65, hexanes/EtOAc, iodine chamber, 65% from 195), the equatorial mesylate 200 (0.11g, 0.33, R_f 0.33, ≈17%), and a mixture of 200 with an unidentified compound (0.24 g, R_f 0.29).

^{1}H NMR; δ 0.92 (s, 3H), 3.61 (bs, 1H), 5.47 (t?, 1H, ≈2.77 Hz), 5.81 (m, 1H), 6.18 (bdd, 1H, 2.03 and 10.35 Hz), 7.12 (m, 3H), and 7.37 (d, 1H, 6.68 Hz).

Compounds 202, 203 and 204

The oxidation of the triene 201 by DDQ

A solution of the triene 201 (≈0.11 g, 0.5 mmol), DDQ (0.23 g, 1 mmol), in benzene (≈40 mL) was stirred for 16 hours at room temperature. The solution was worked-up with sat. sodium bisulfite, ether, and dried (Na_2SO_4). The crude residue (3 spots, R_f 0, 0.2, and 0.24, hexanes) was filtered through a short column filled with silica gel before separation in the chromatotron. The isomers 202, 203, and the ketone 204 were isolated. No yields were recorded.

Compound 202

^{1}H NMR; δ 1.10 (s, 3H), 1.9 (m, 1H), 2.2 (m, ?H), 2.81 (m, 1H), 5.9 (m, 1H), 6.00 (dd, 1H, 2.73 and 5.99 Hz), 6.22 (dd, 1H, 2.81 and 9.68 Hz), 6.26 (s, 1H), and 7.2 (m, ?H).

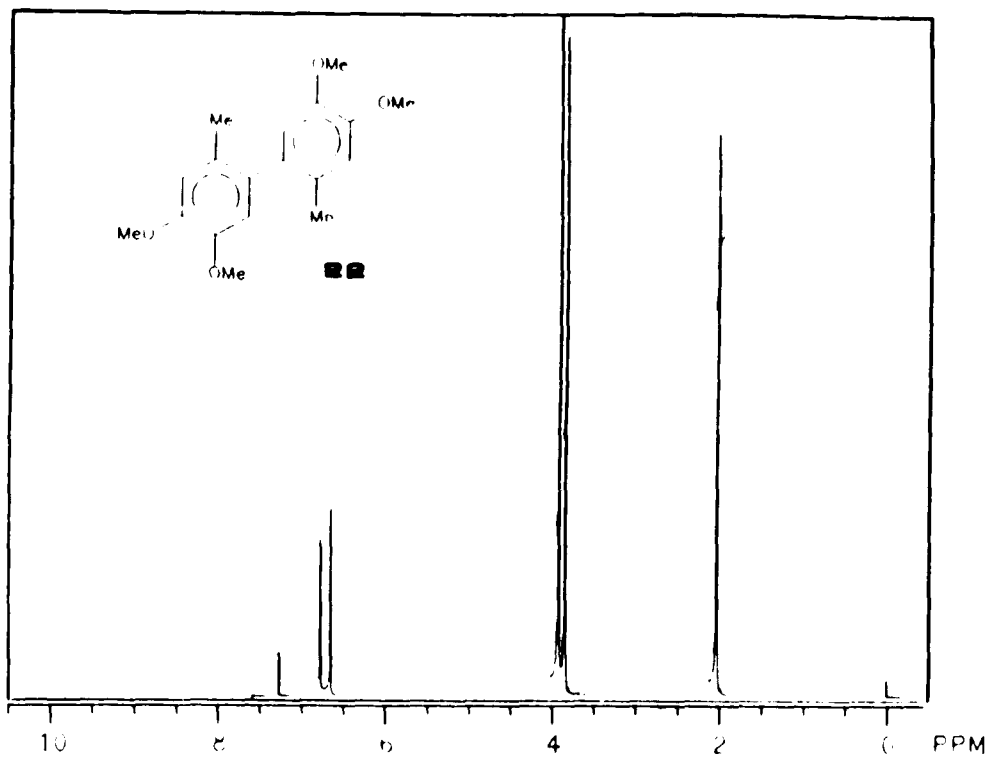
UV; 259.75 (1.9070 A), 268.08 (1.8092 A), and 318.92 nm (1.3464 A).

Compound 203

^{1}H NMR; δ 1.28 (s, 3H), 2.53 (m, 1H), 2.73 (dd, 1H, 1.99 and 16.22 Hz), 3.37 (dd, 1H, 5.69 and 16.29 Hz), 5.36 (m, 1H), 5.71 (m, 1H), 5.9-6.2 (m, 2H), 6.10 (s, 1H), 6.69 (d, 1H, 4.94 Hz), 7.2 (m, ?H).

UV; 256.42 (0.8905 A), 320.58 (0.8195 A), and 332.25 nm (0.8053 A).

APPENDIX A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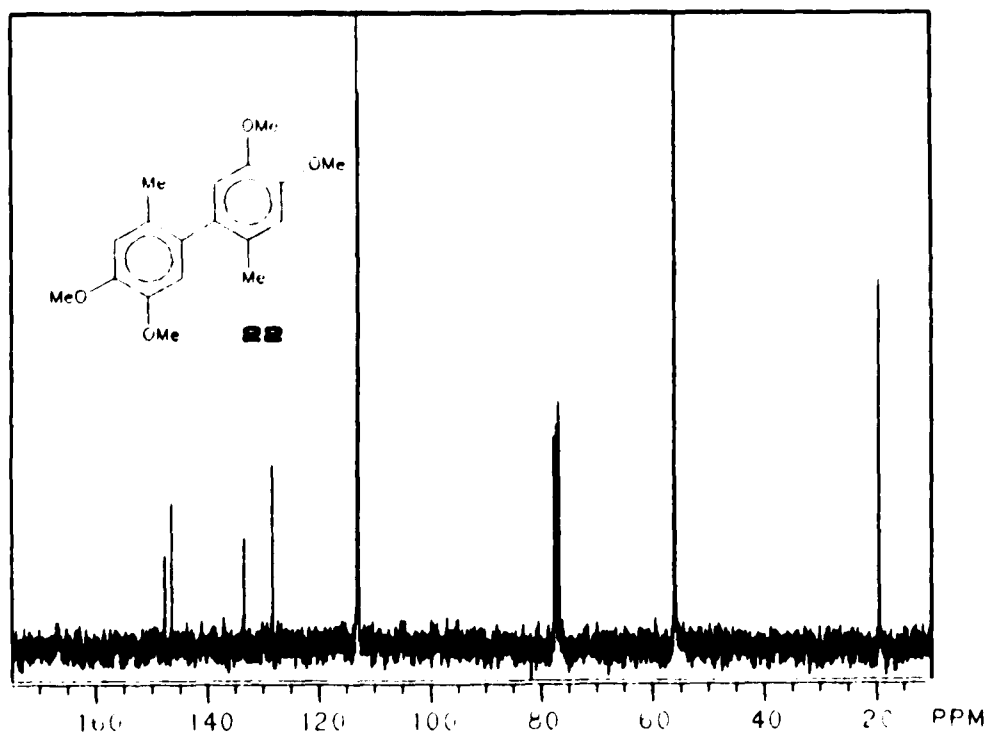
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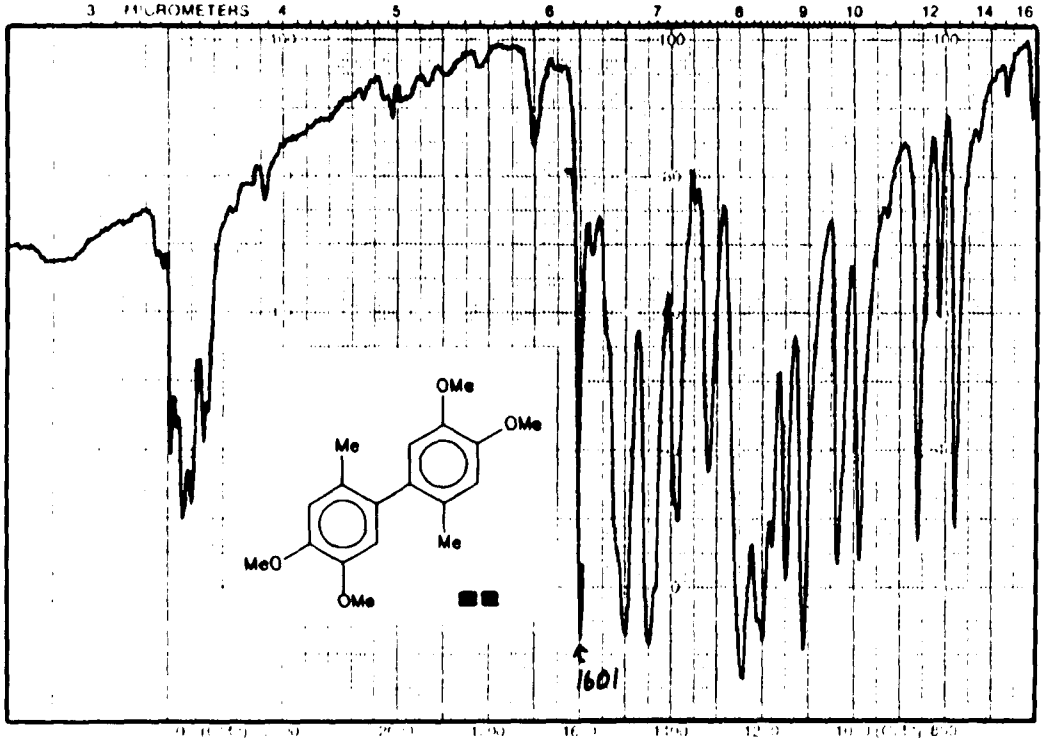
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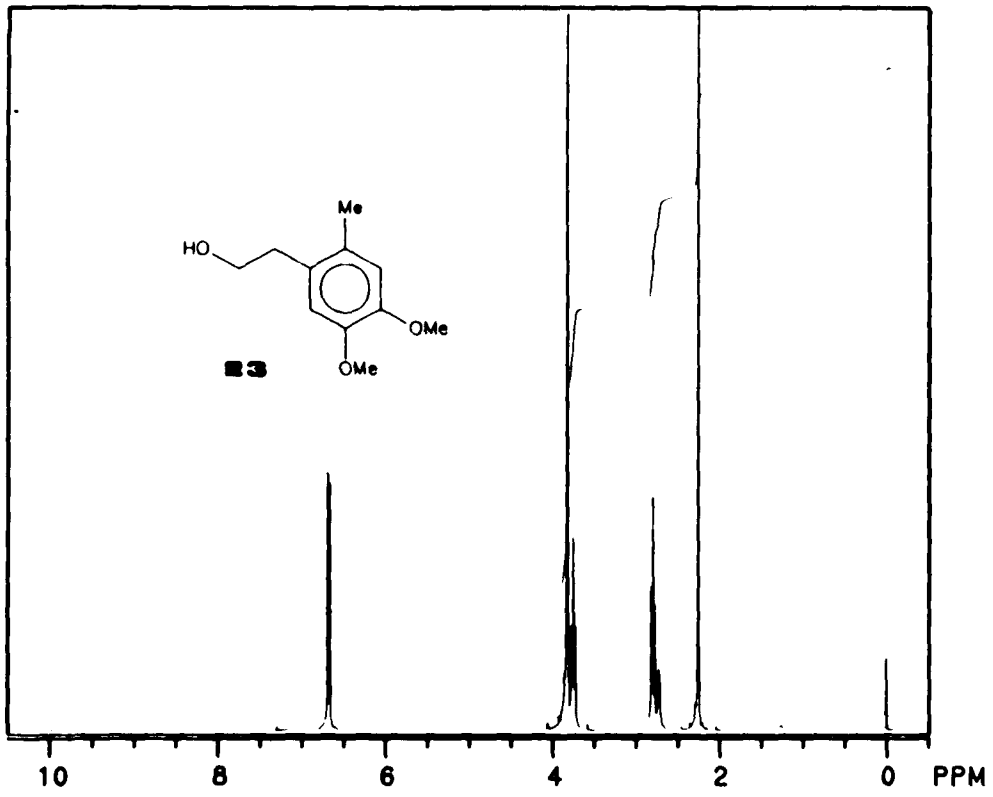
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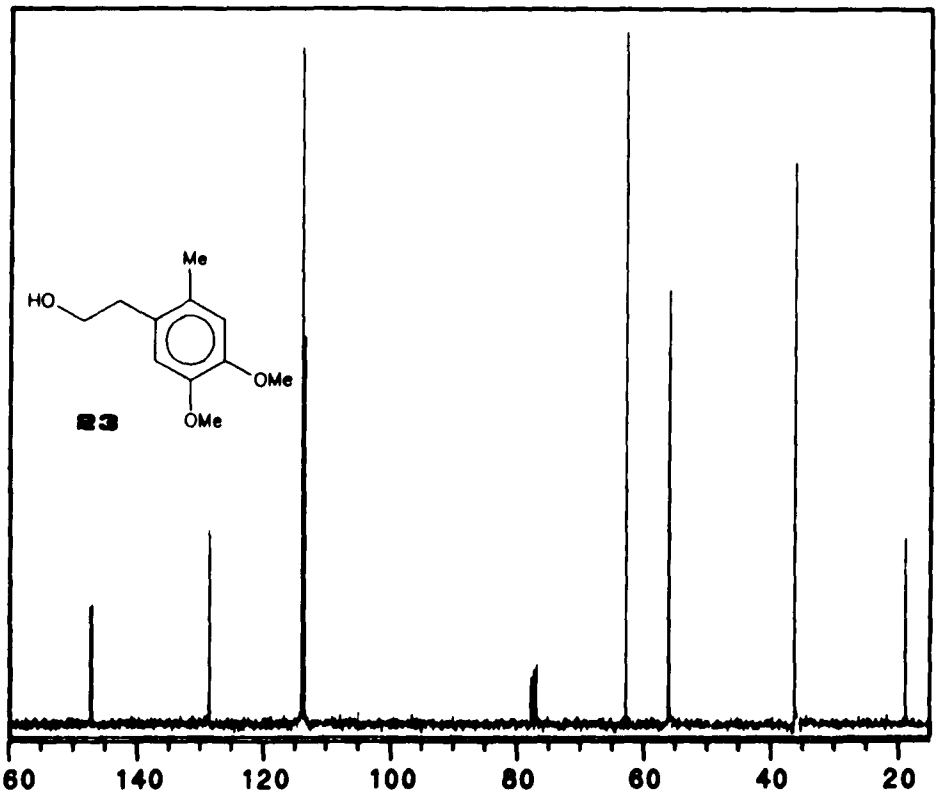
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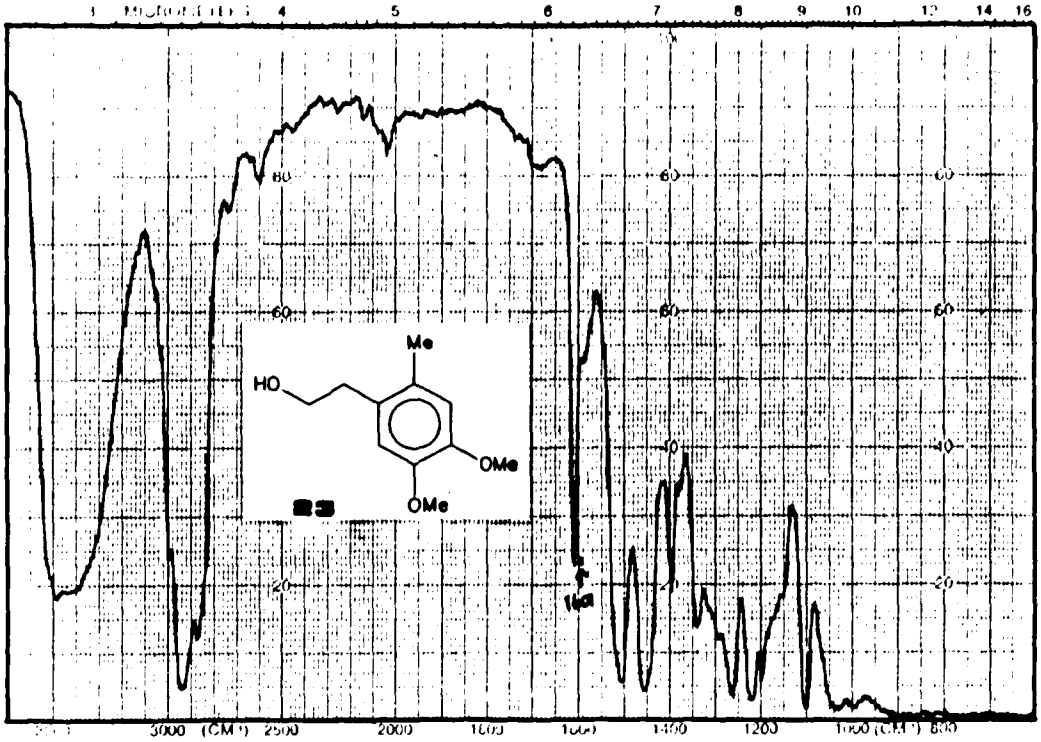
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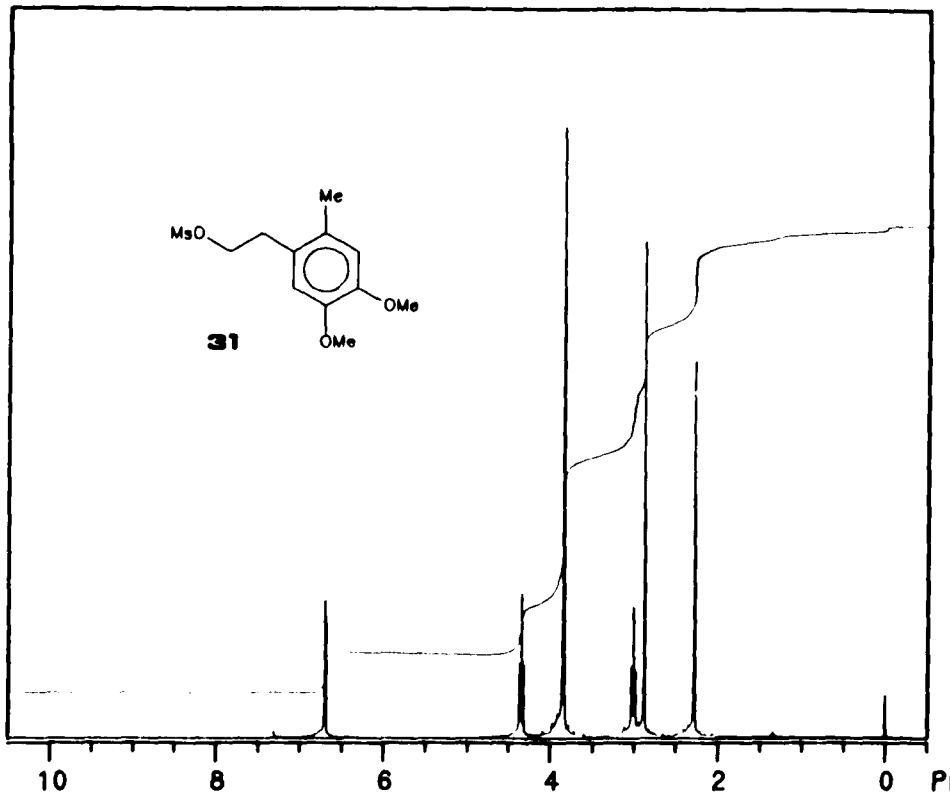
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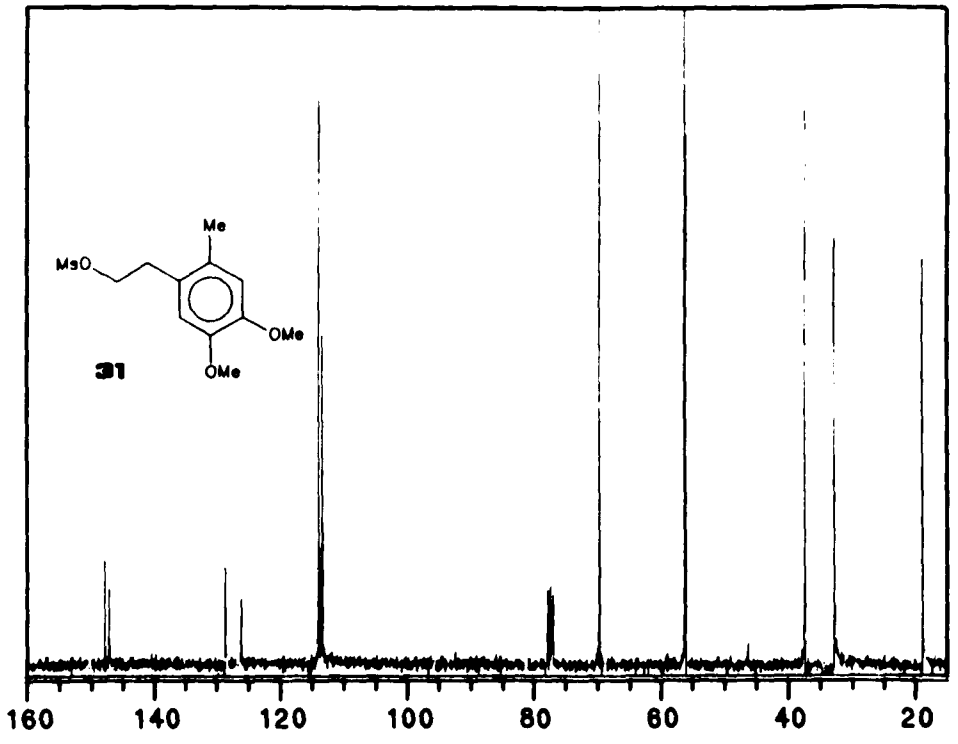
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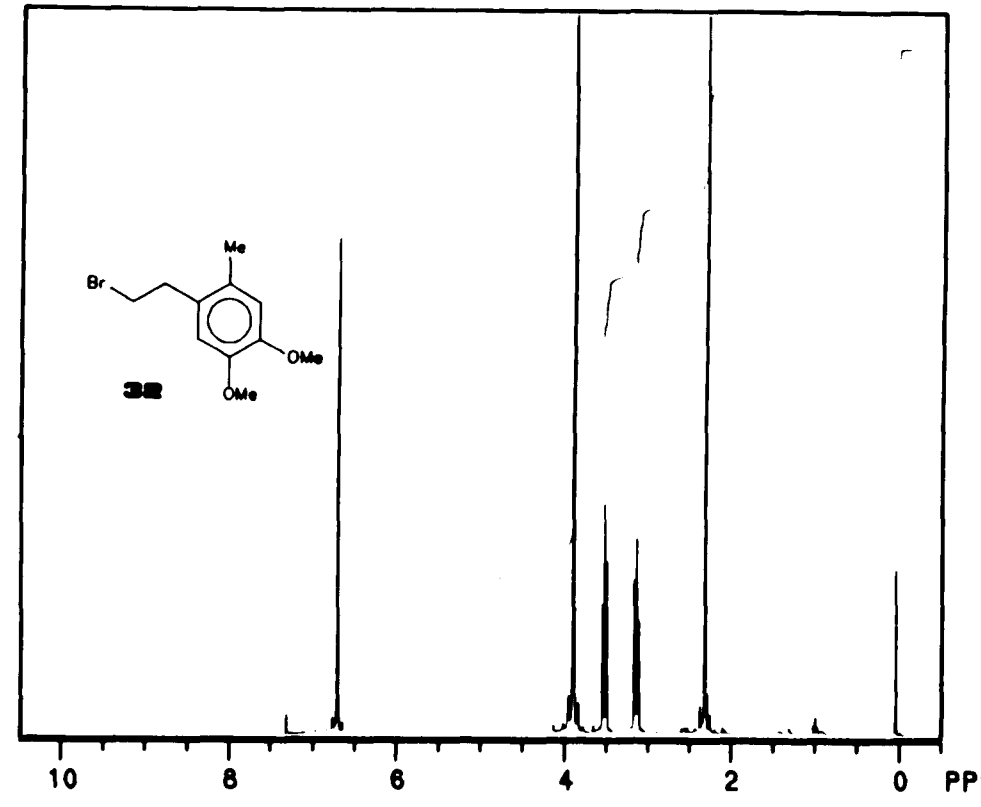
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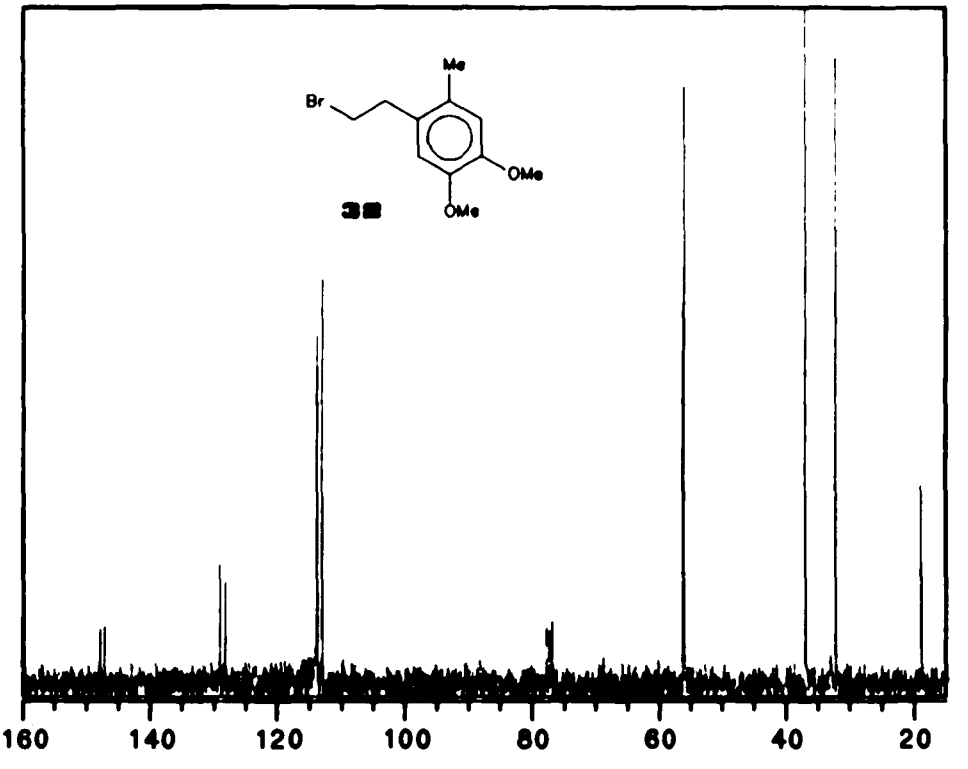
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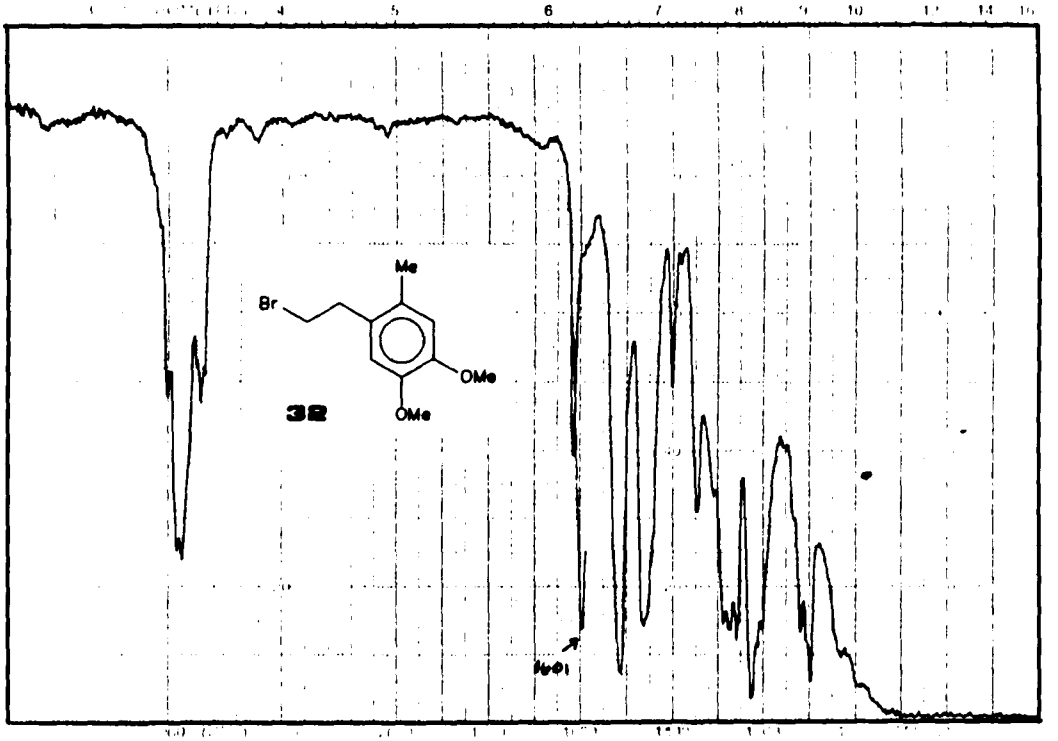
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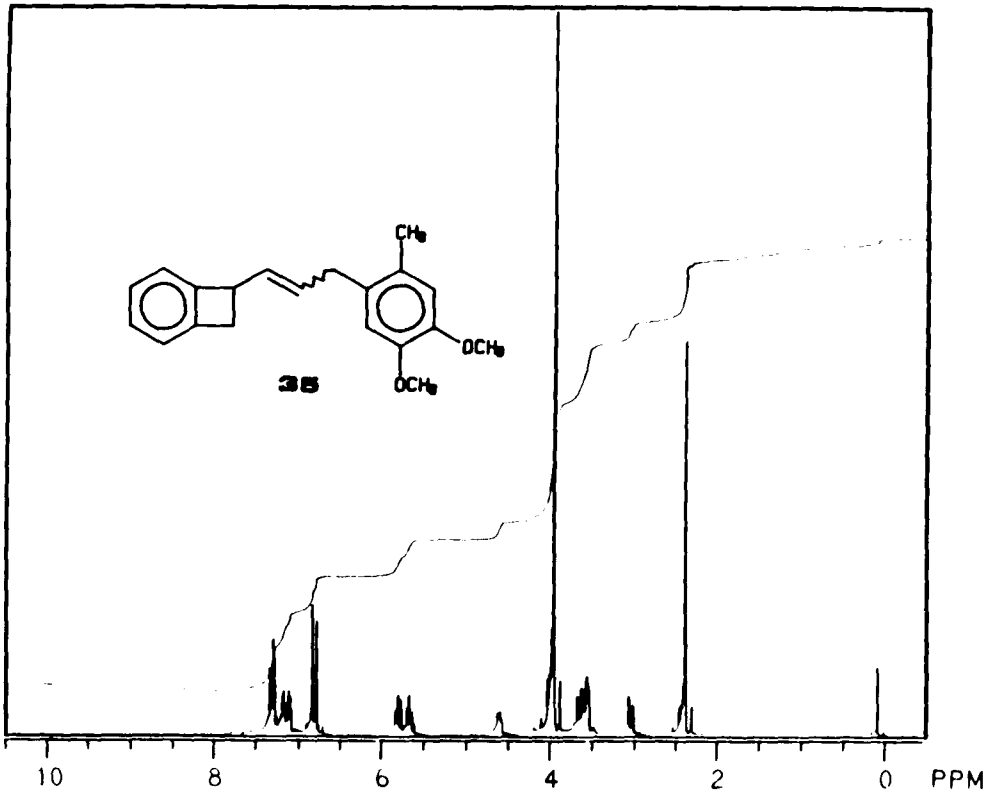
Br
OMe
OMe
32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OCH3
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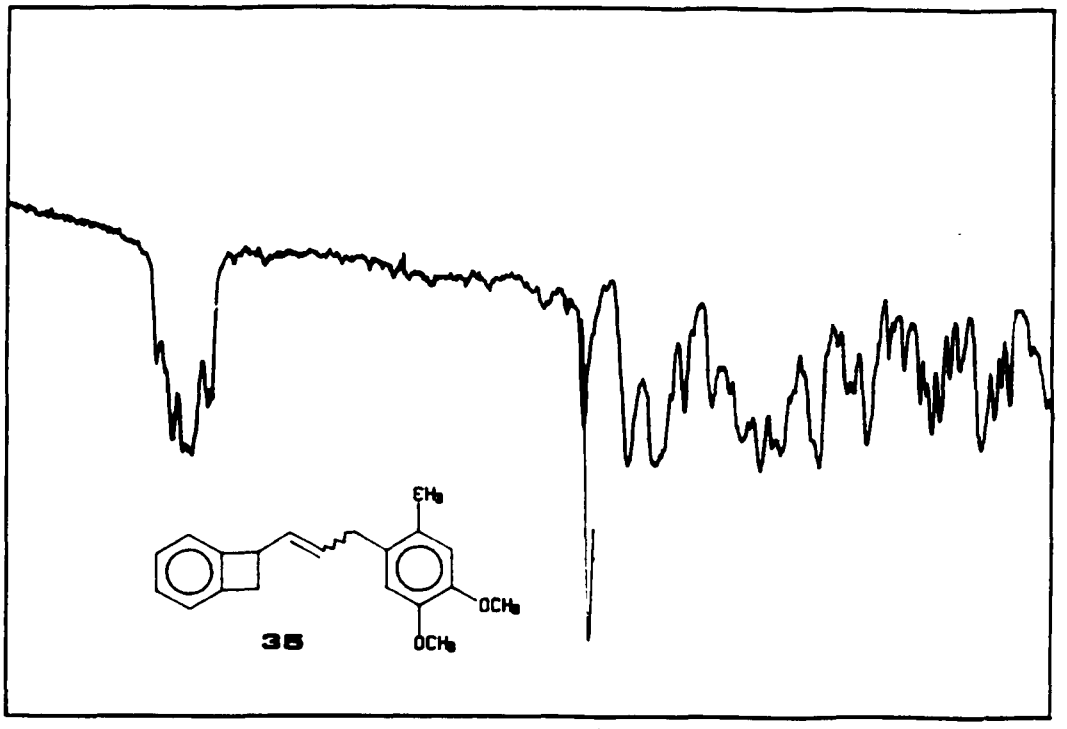
PPM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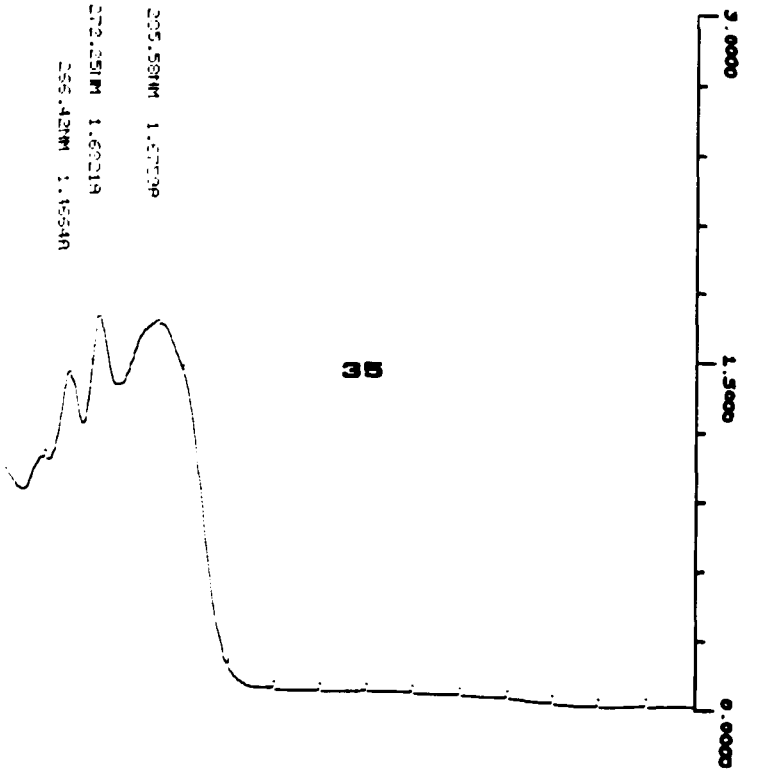
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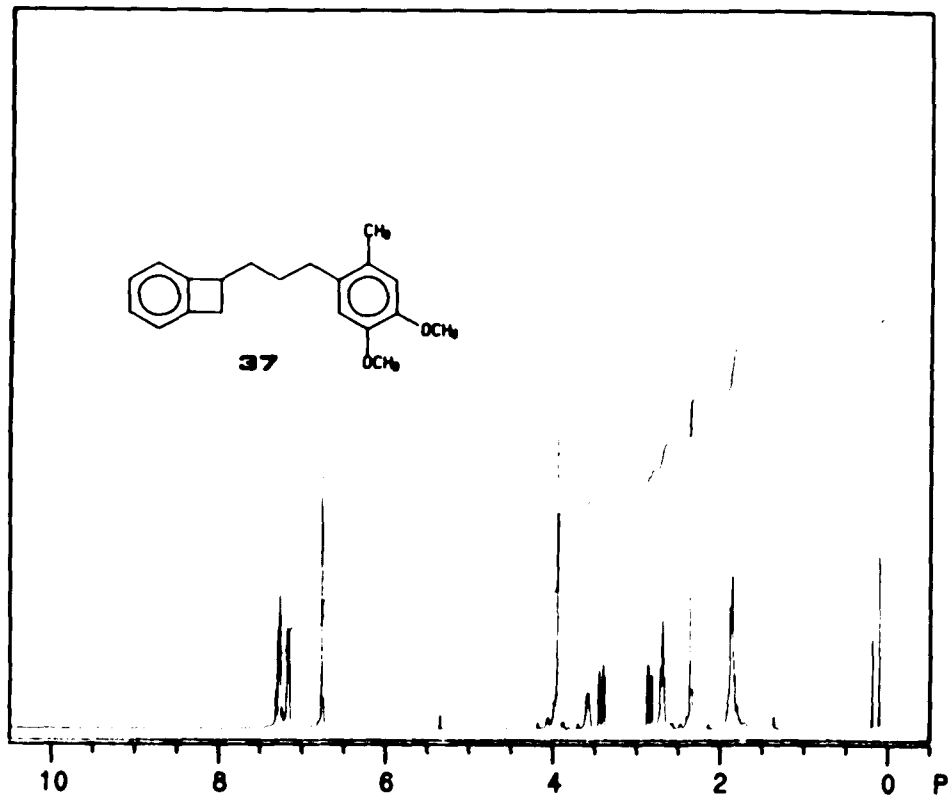
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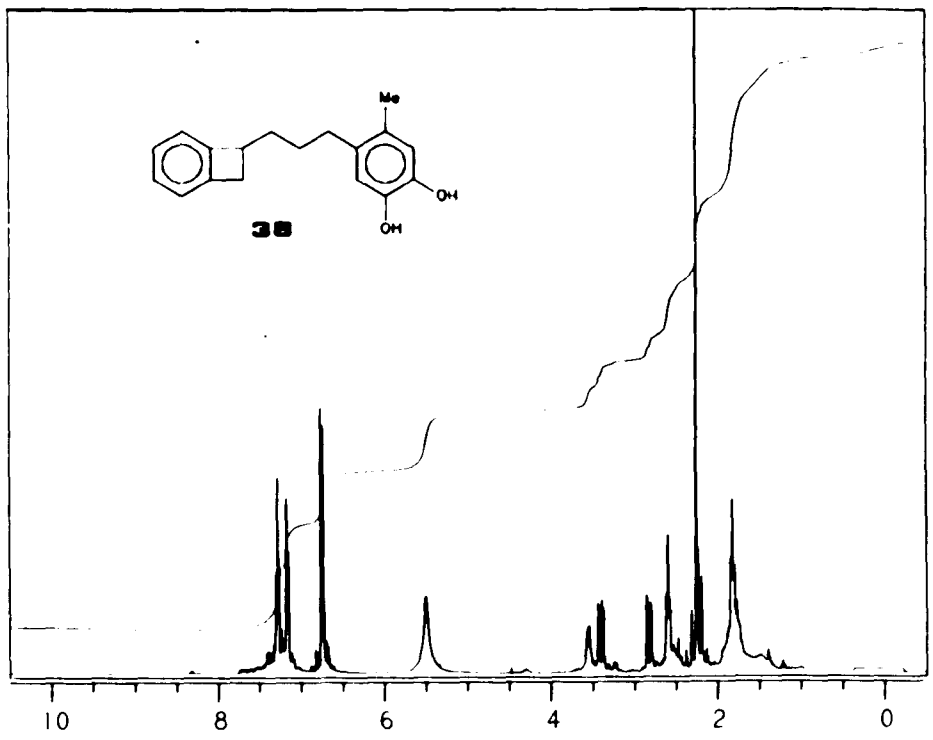
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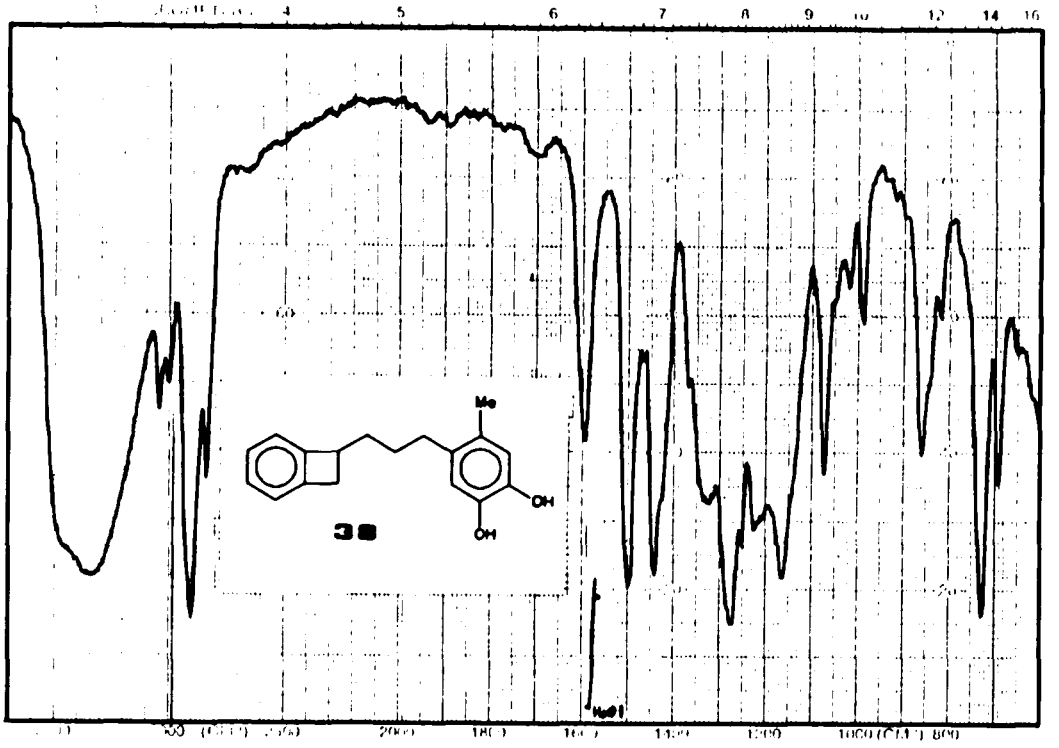
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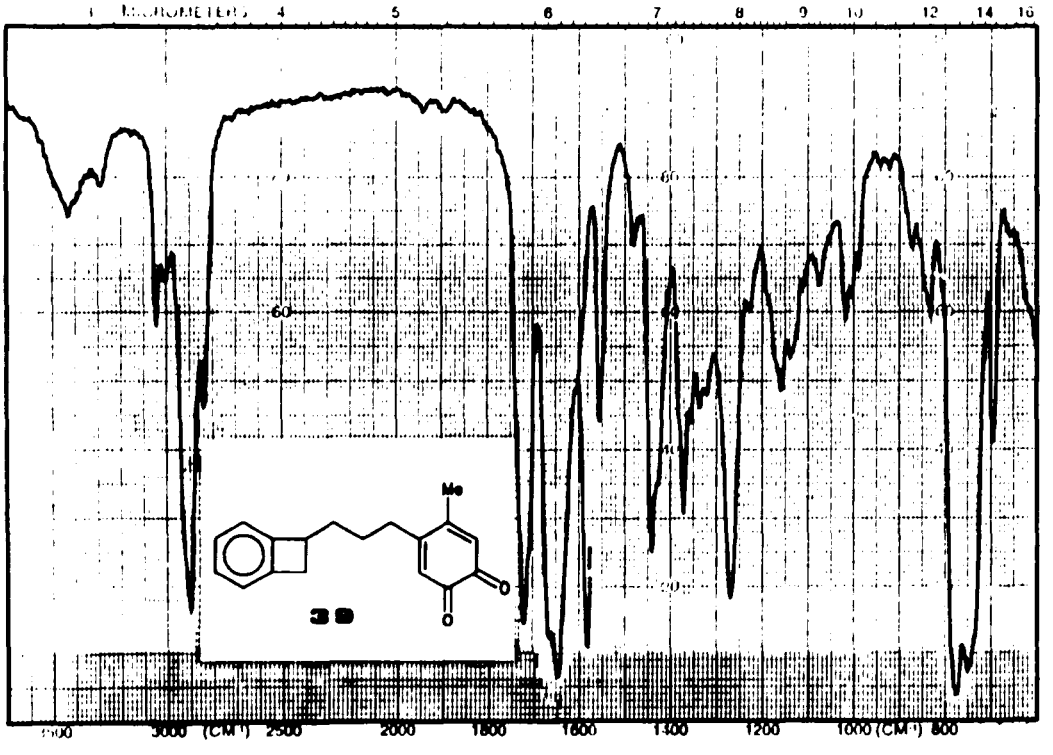
OH
38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O
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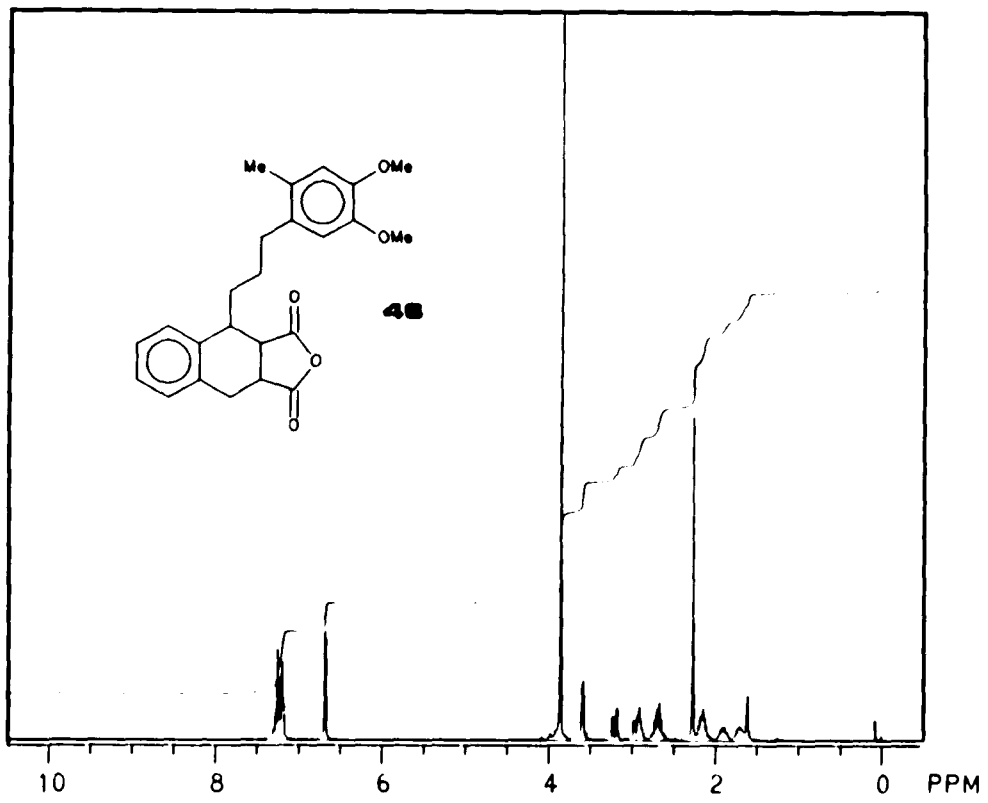
3000 (CM⁻¹) 2500
2000
1800
1600
1400
1200
1000 (CM⁻¹) 800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OMe
OMe
O
O
O
10
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2
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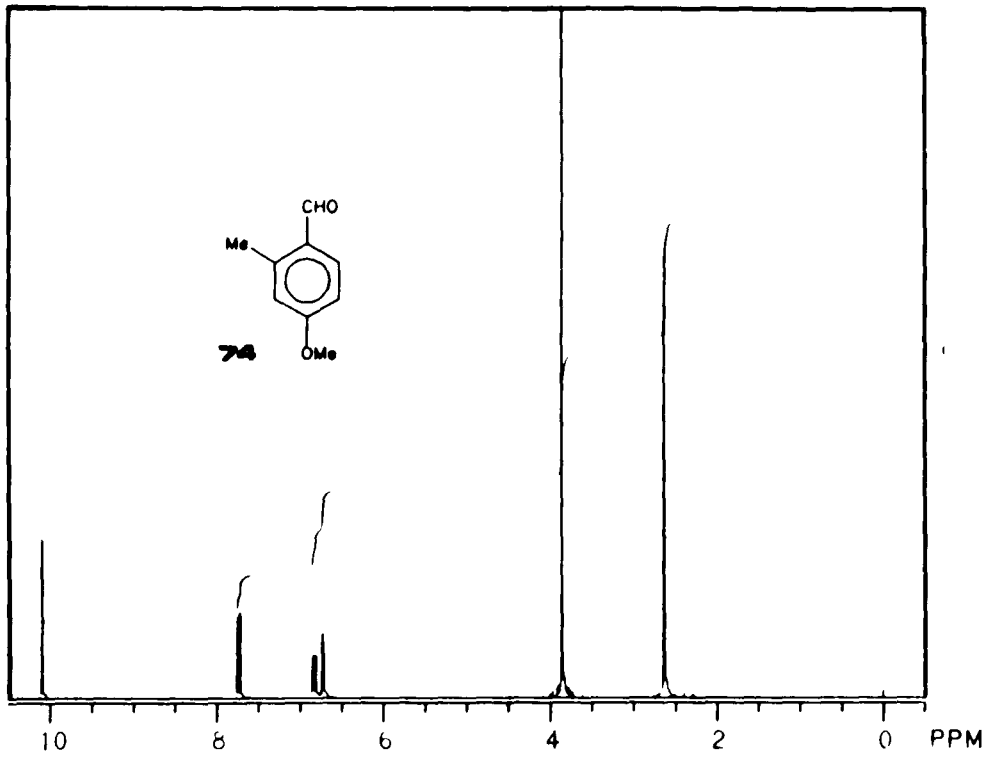
PPM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OMe
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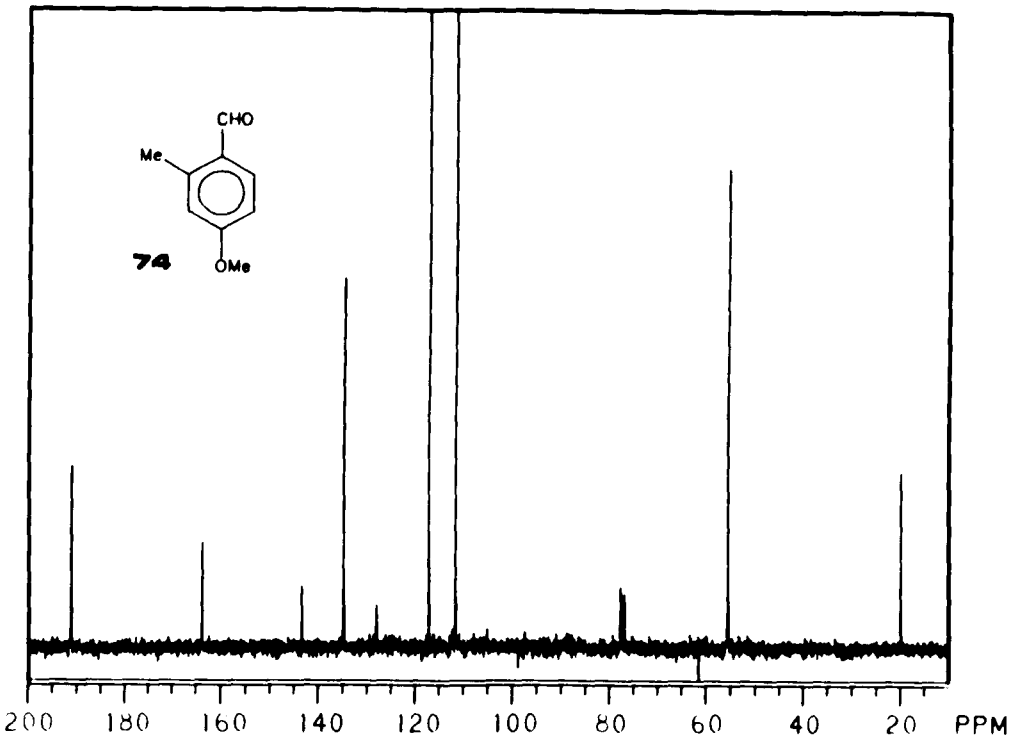
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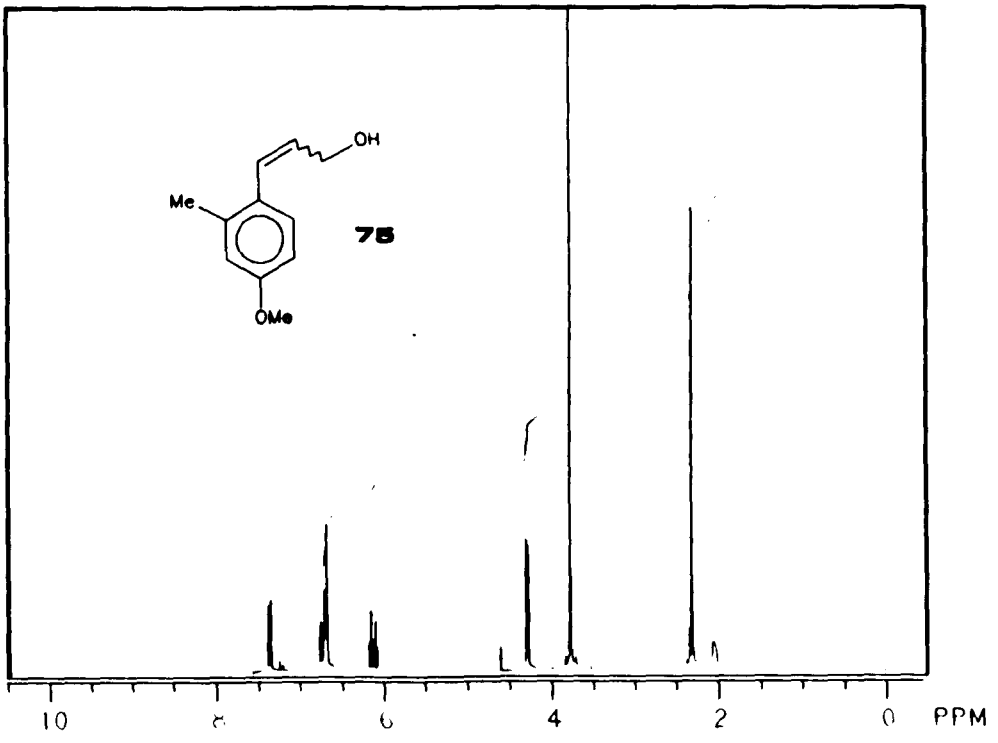
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OMe
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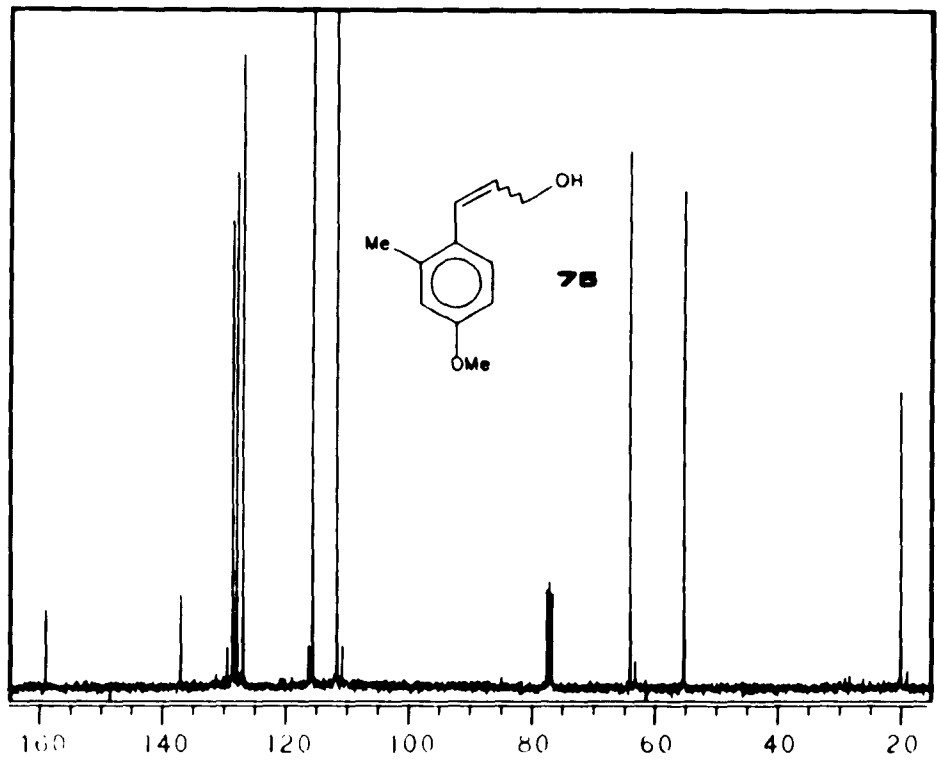
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OMe
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20
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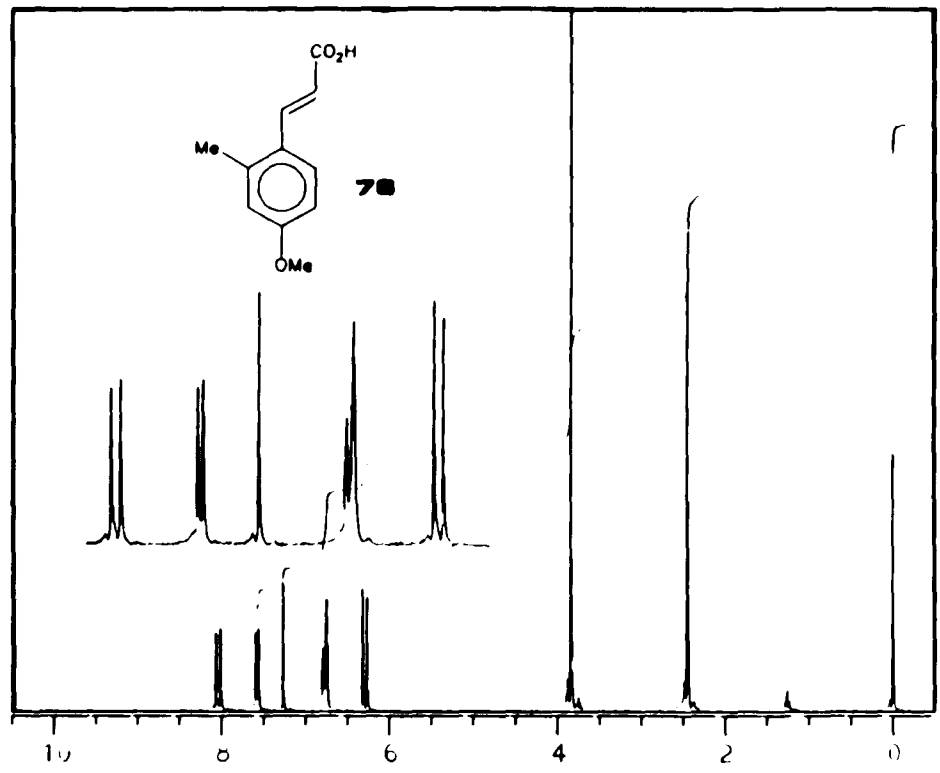
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Me
OMe
76
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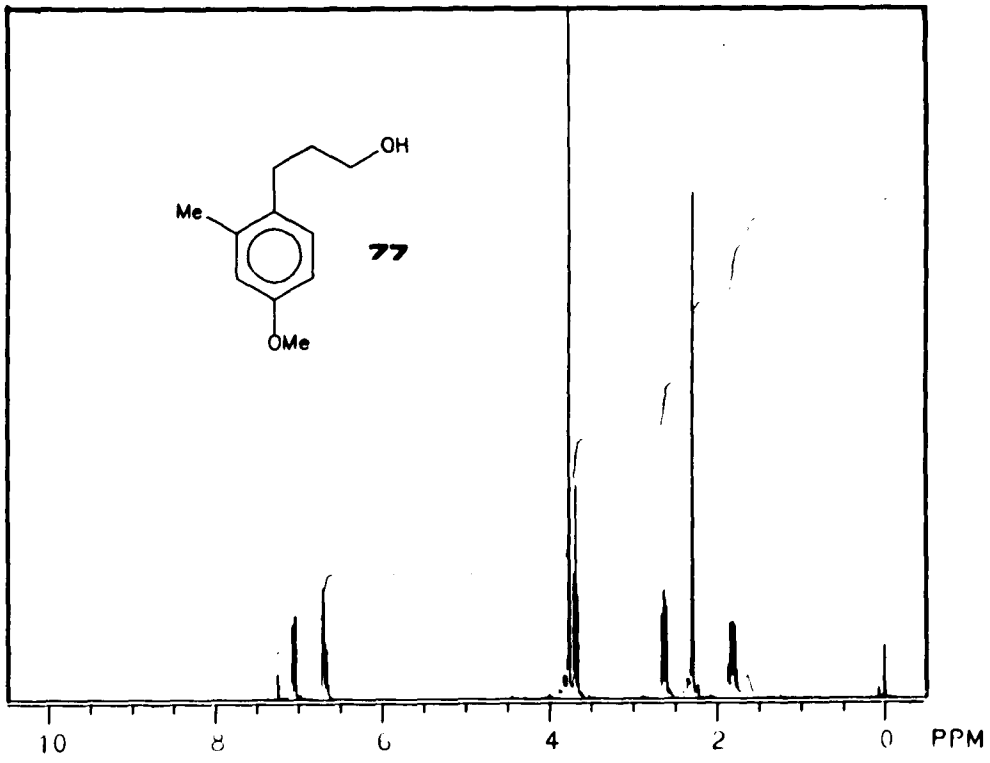
2
0
PPM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77
OMe
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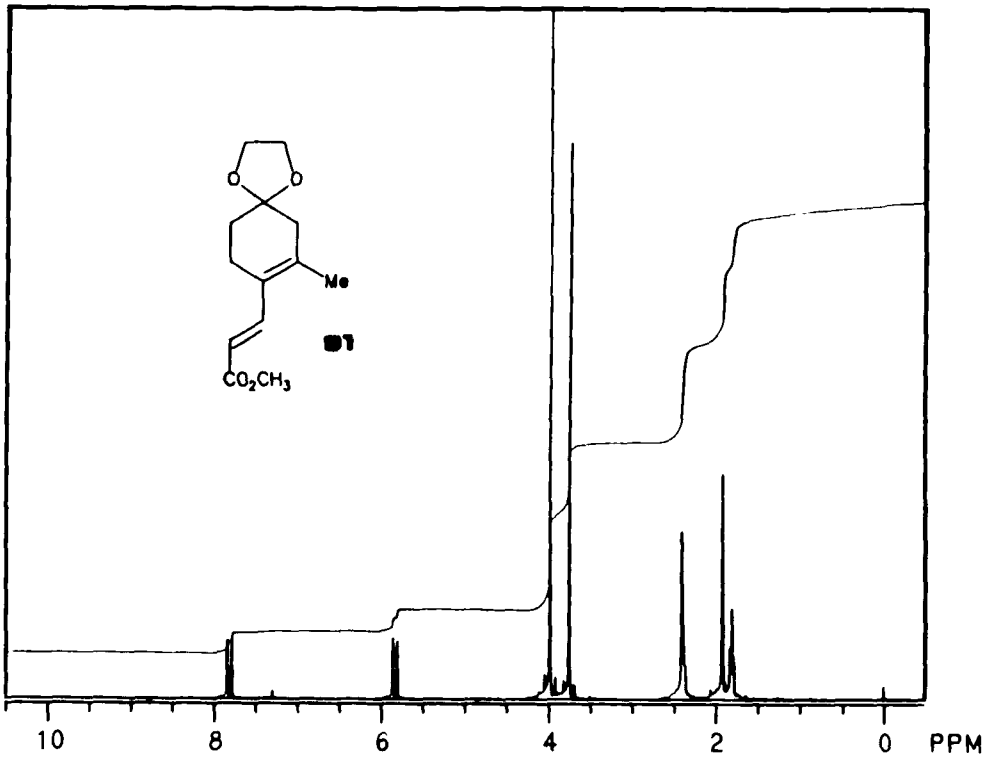
PPM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8
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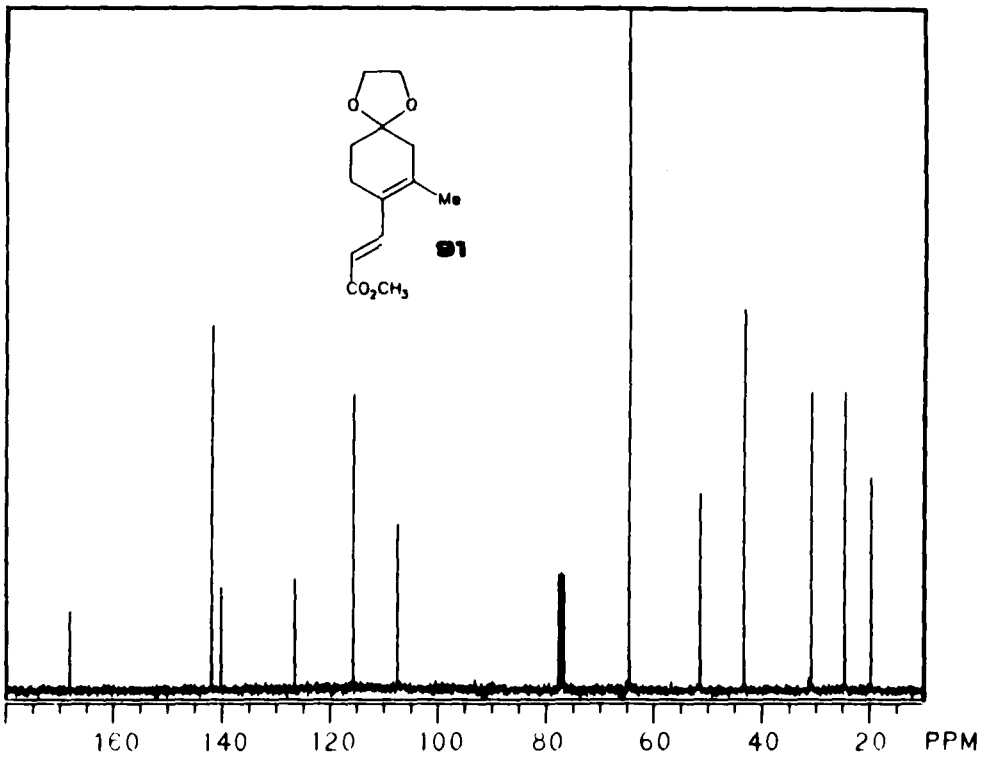
PPM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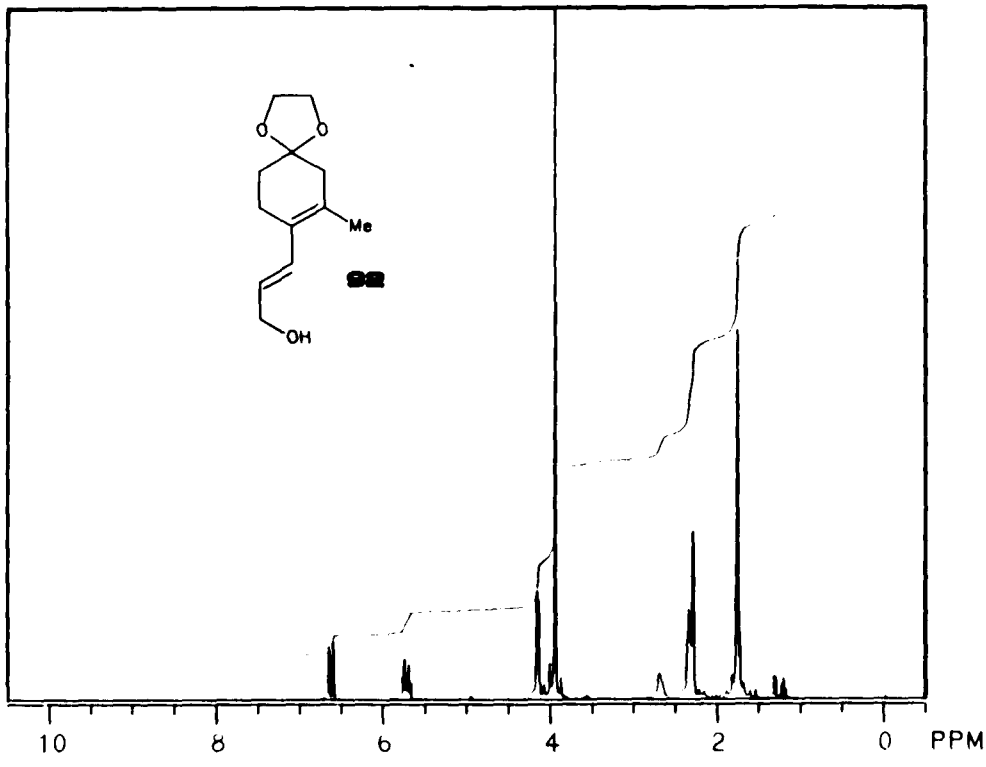
PPM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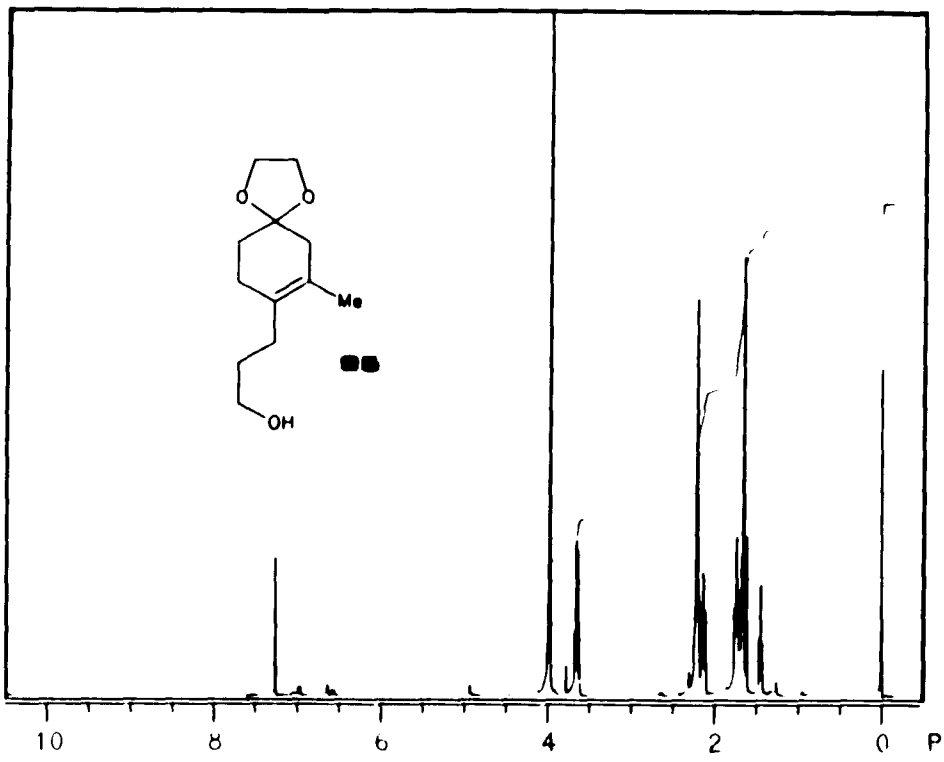
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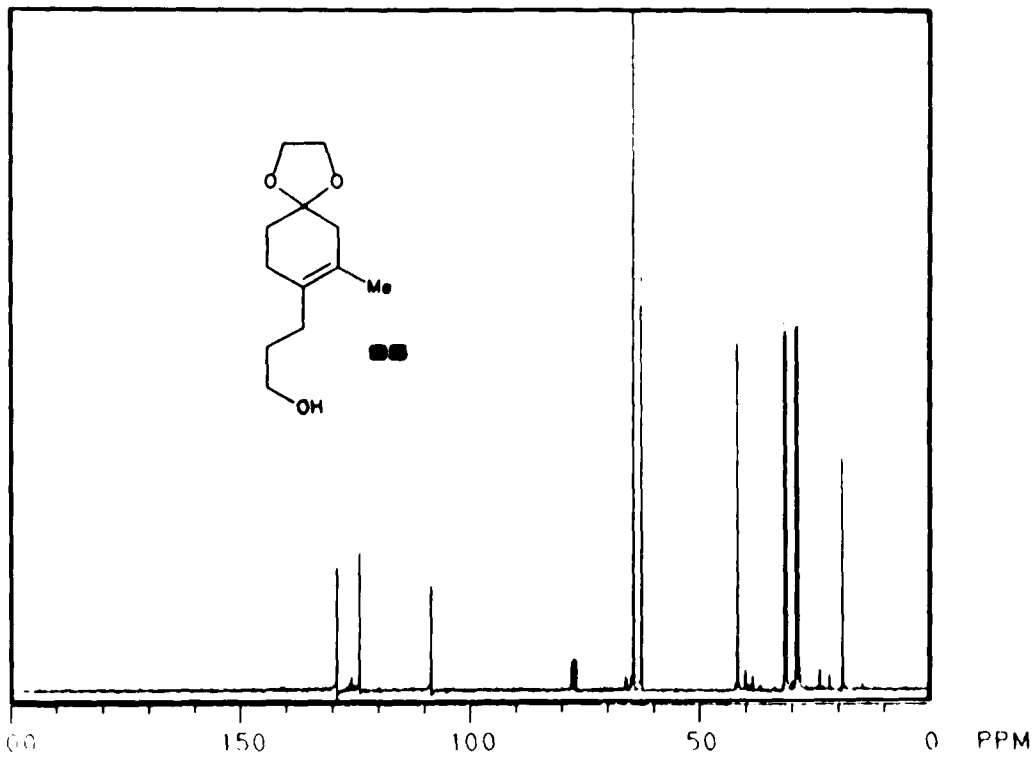
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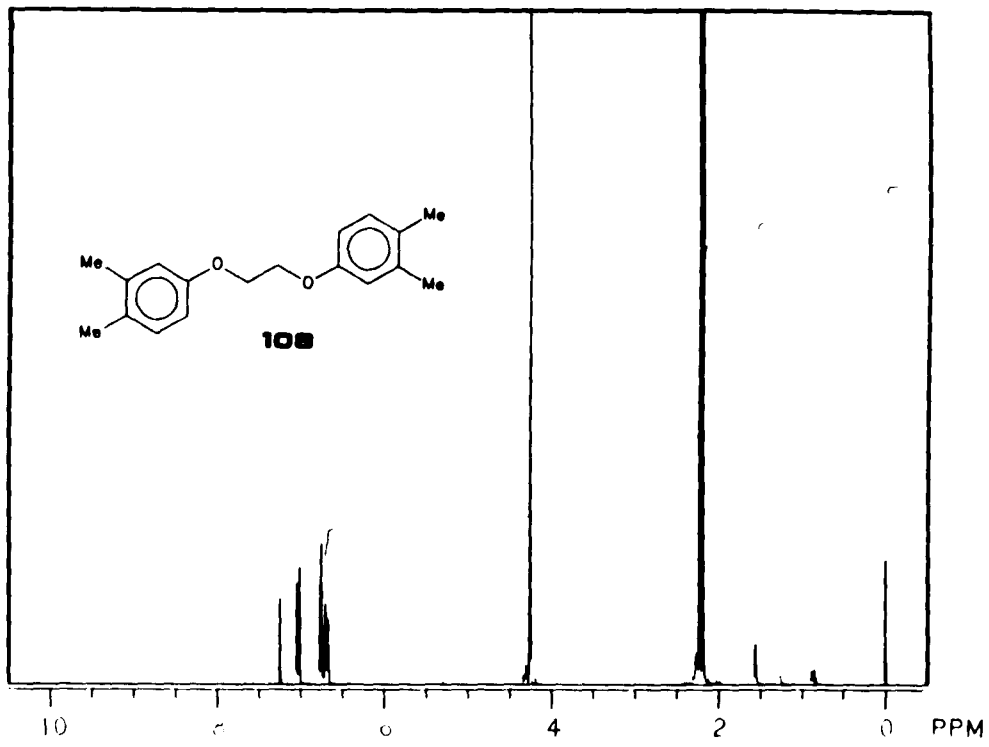
PPM



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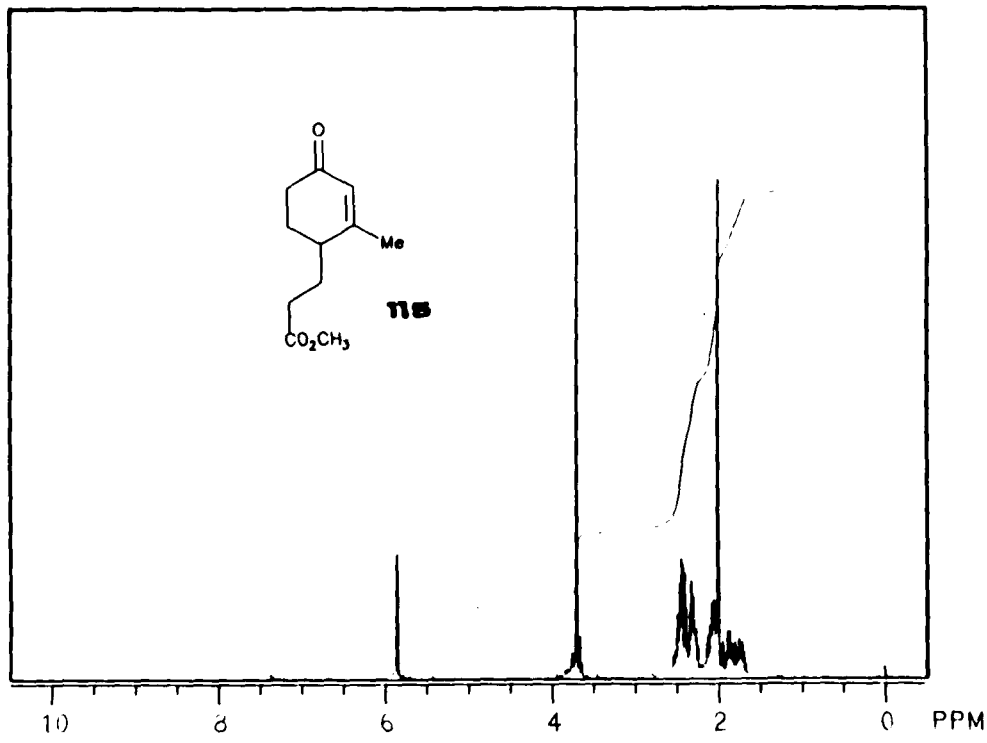

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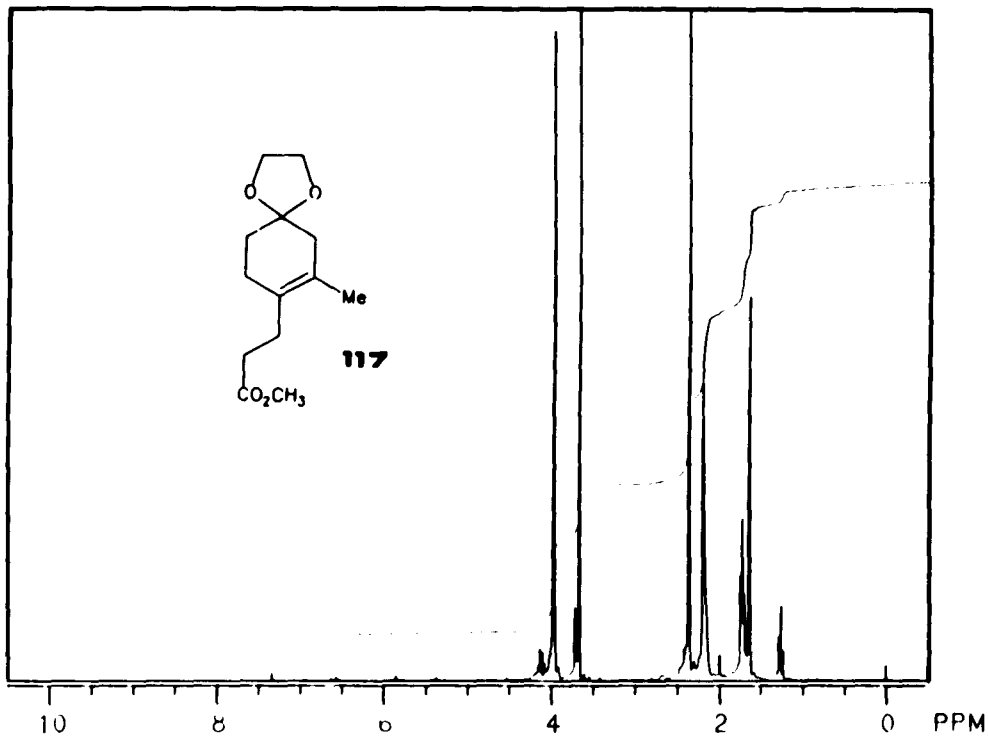
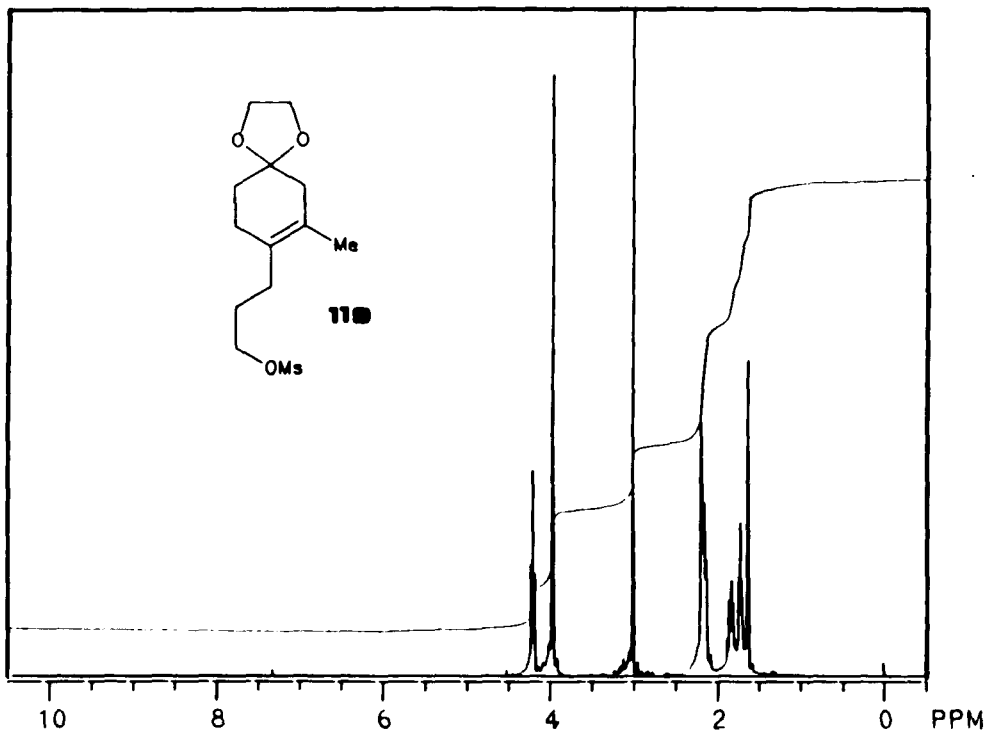

Me
117
CO_2CH_3
10
8
6
4
2
0
PPM


Me
118
OMs
10
8
6
4
2
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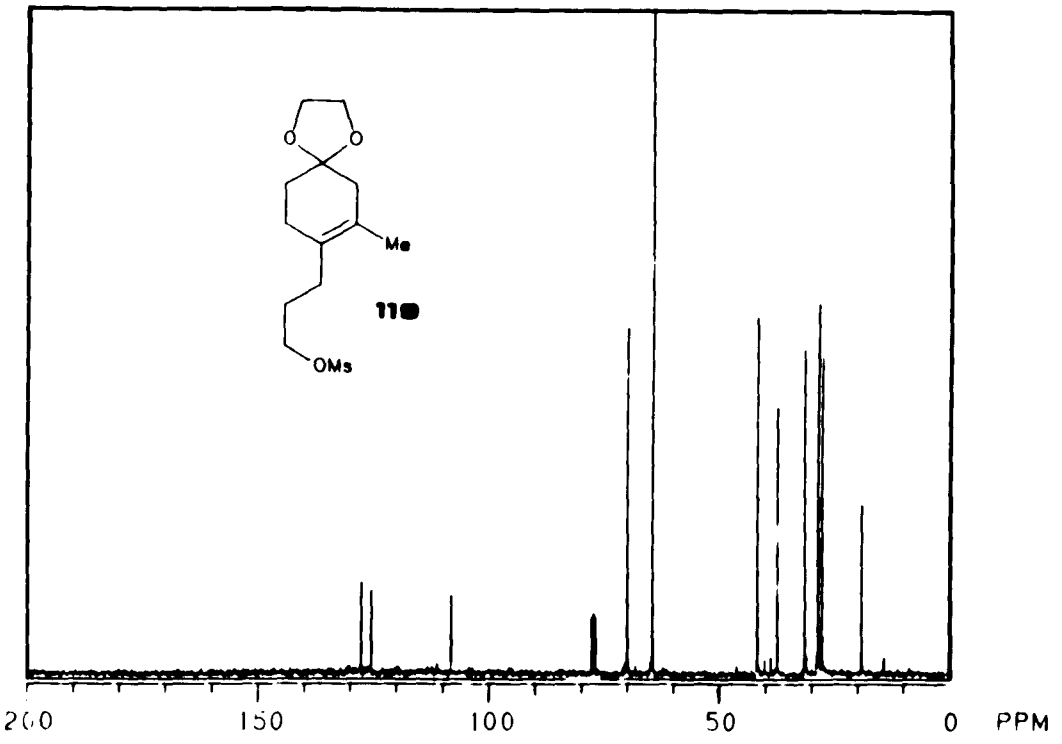
PPM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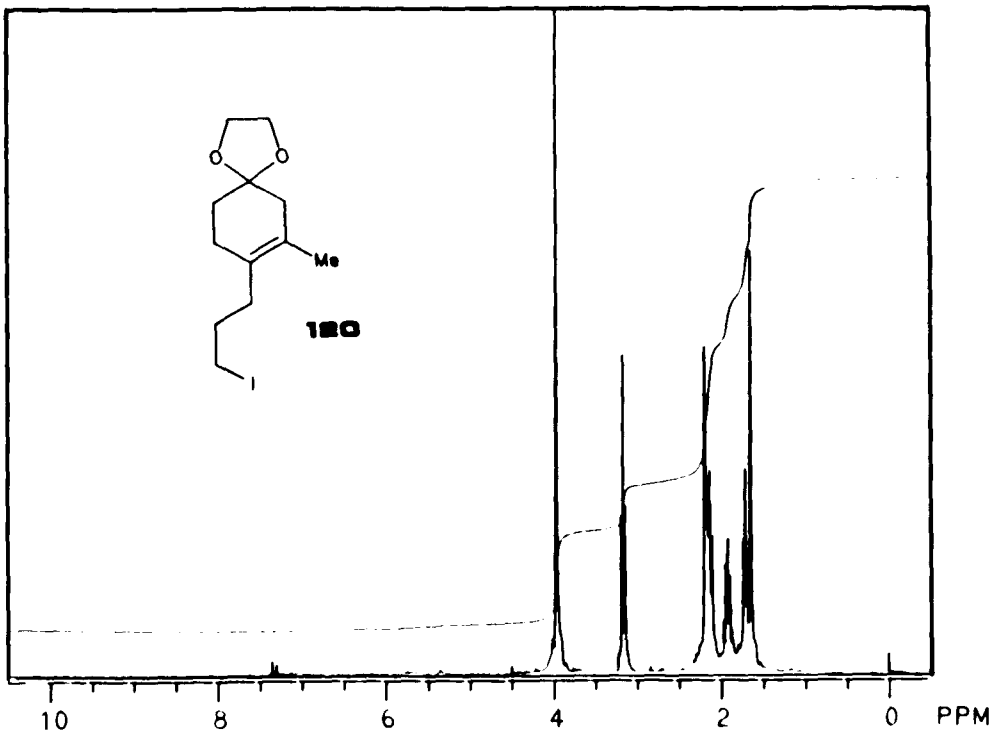
OMs
200
150
100
50
0
PPM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I
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8
6
4
2
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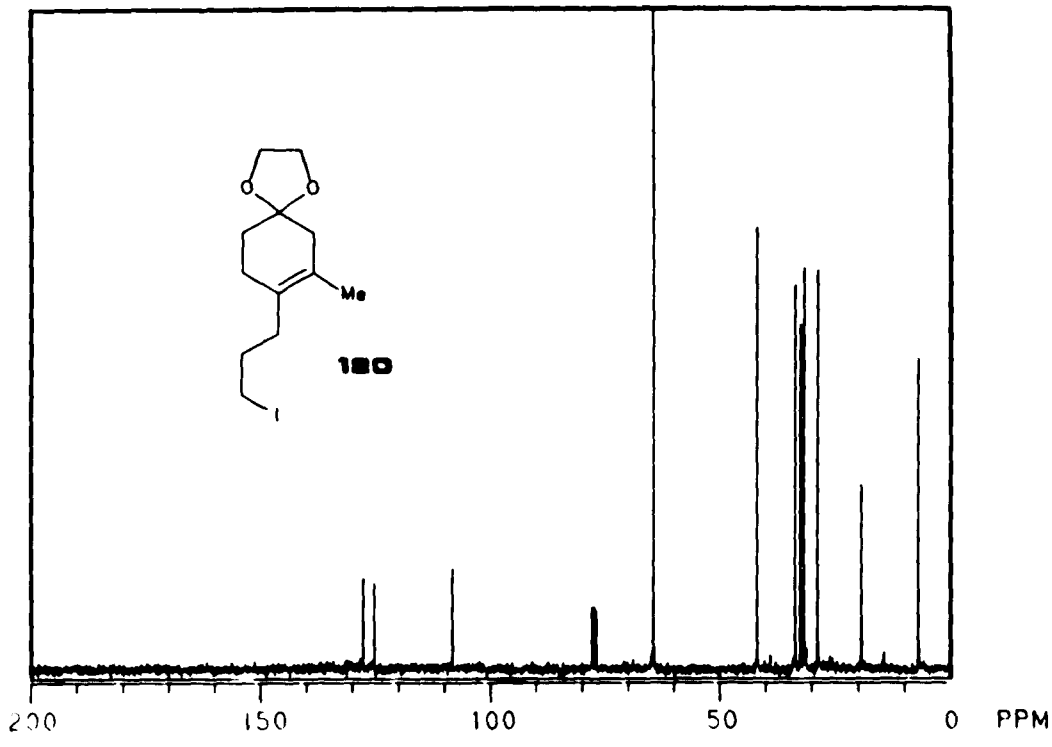
PPM



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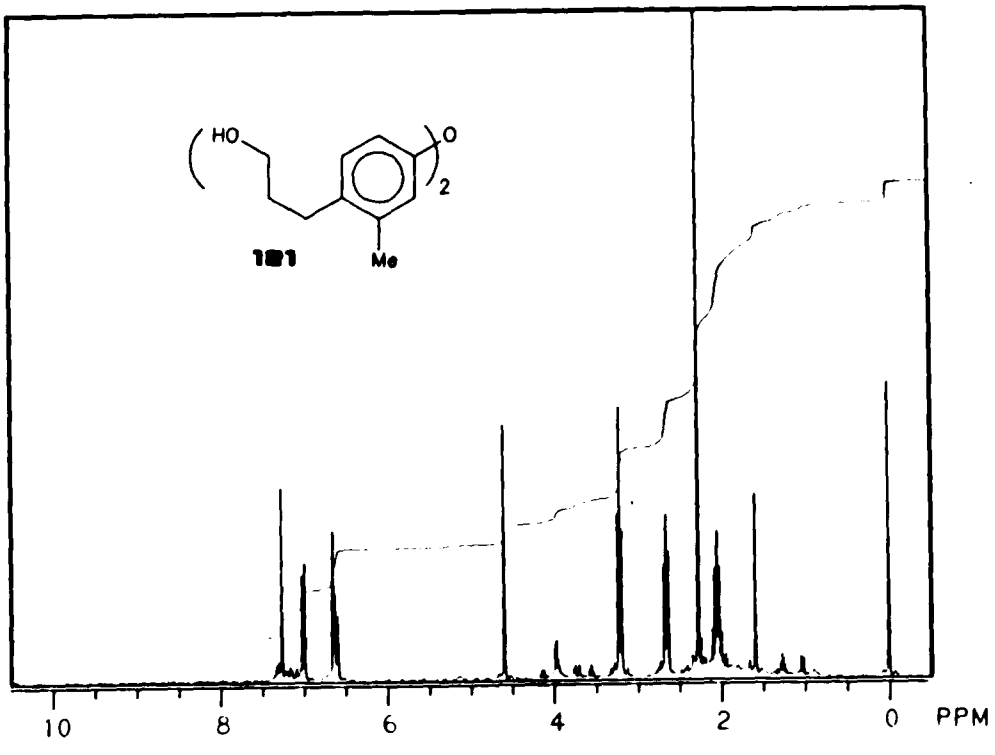

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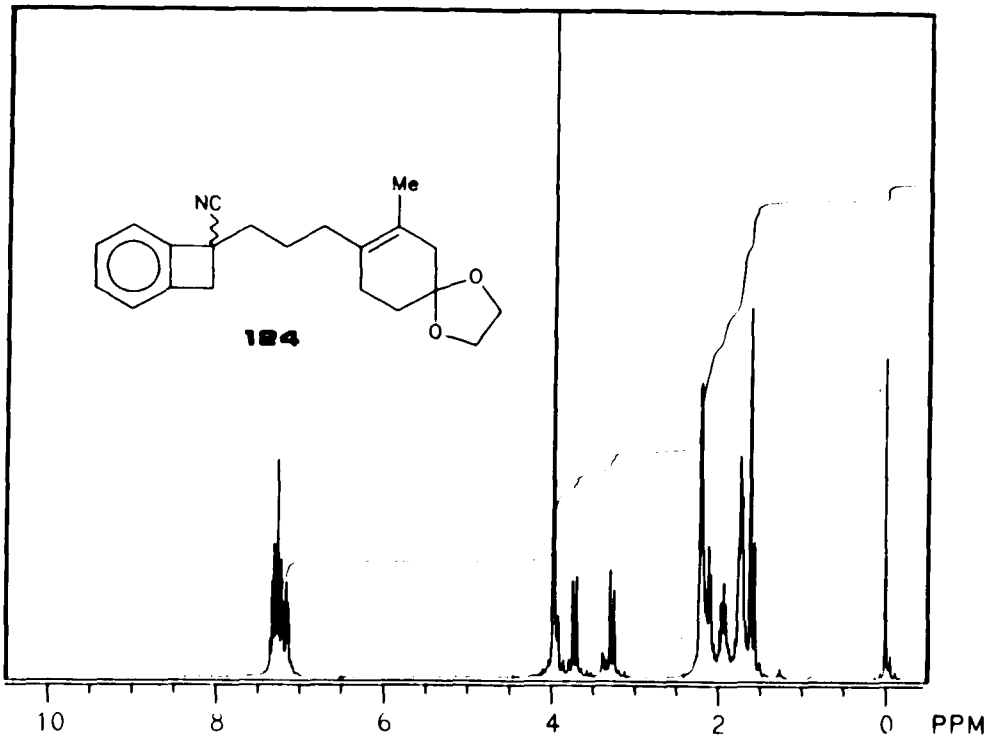
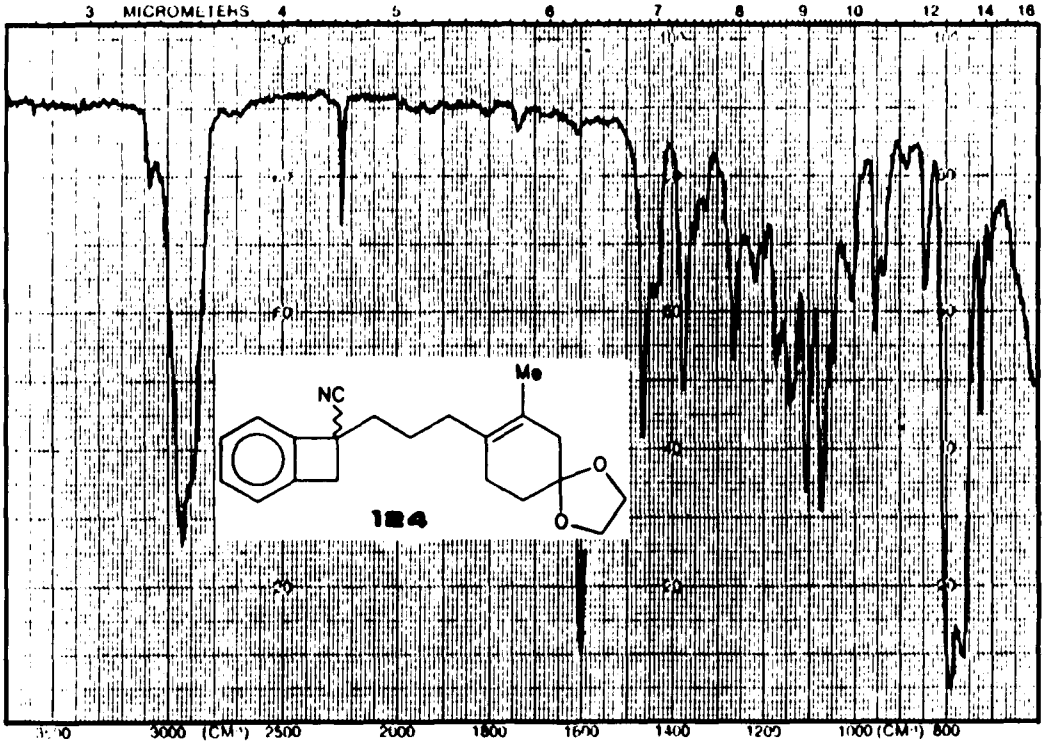

NC
Me
O
O
124
10
8
6
4
2
0
PPM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NC
Me
O
O
124
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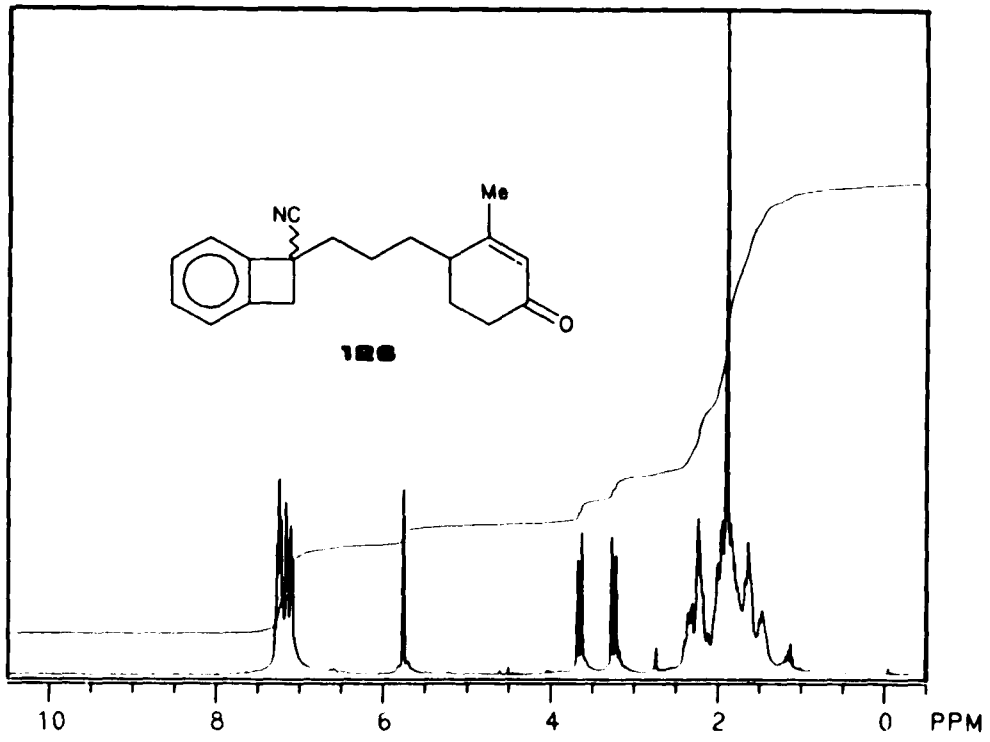
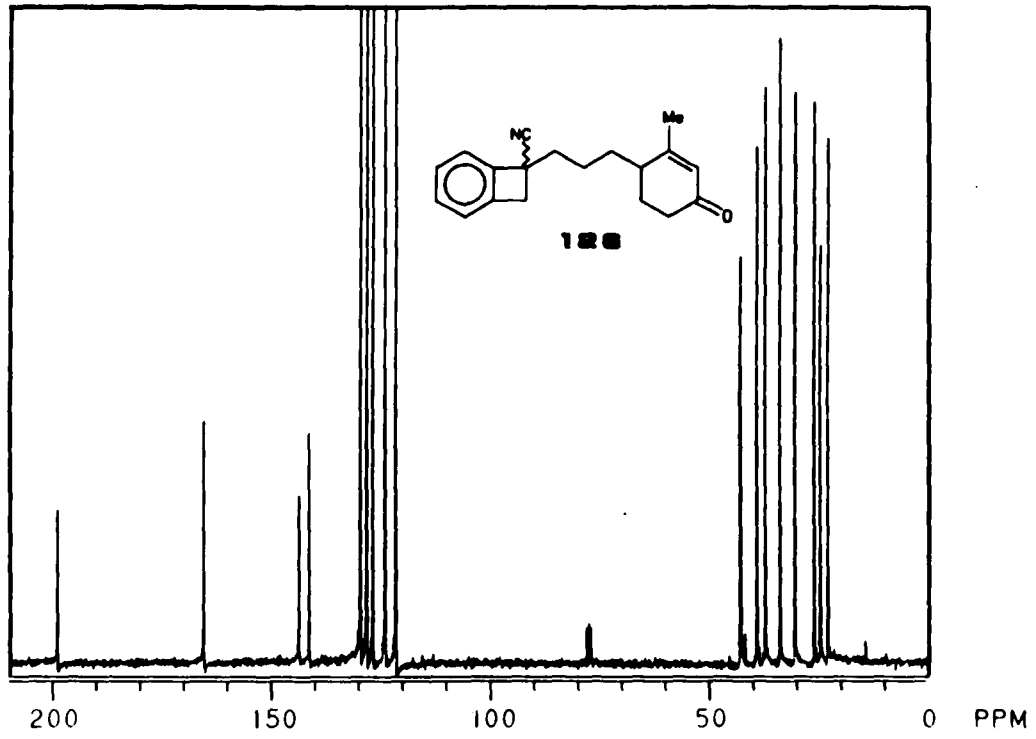
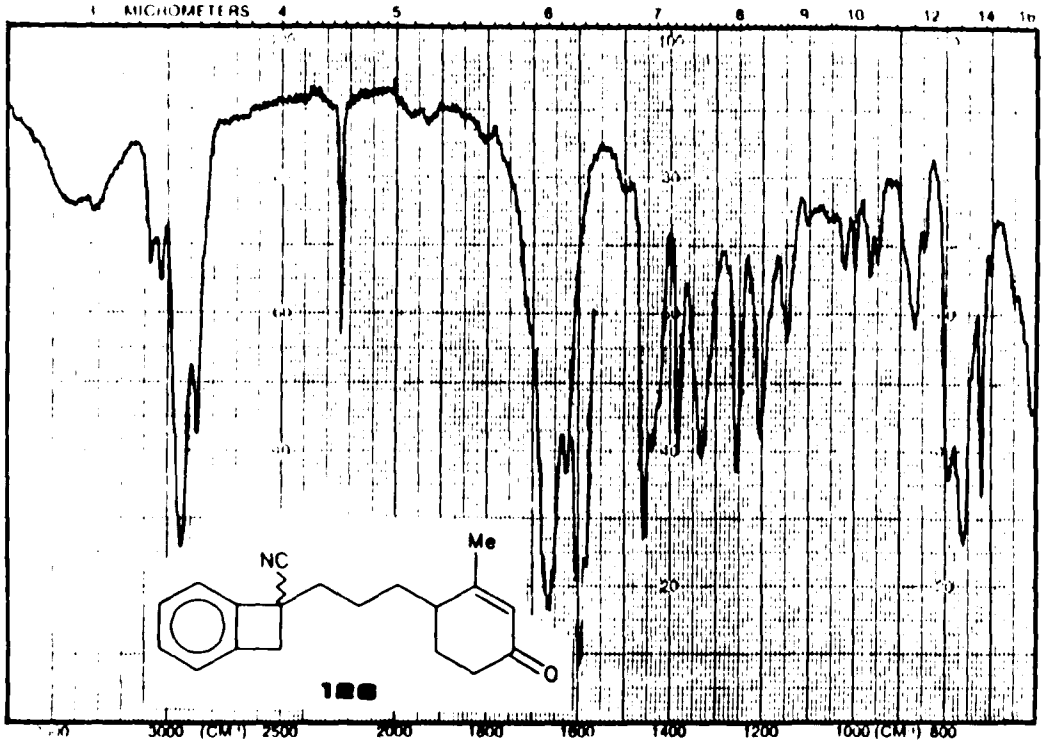
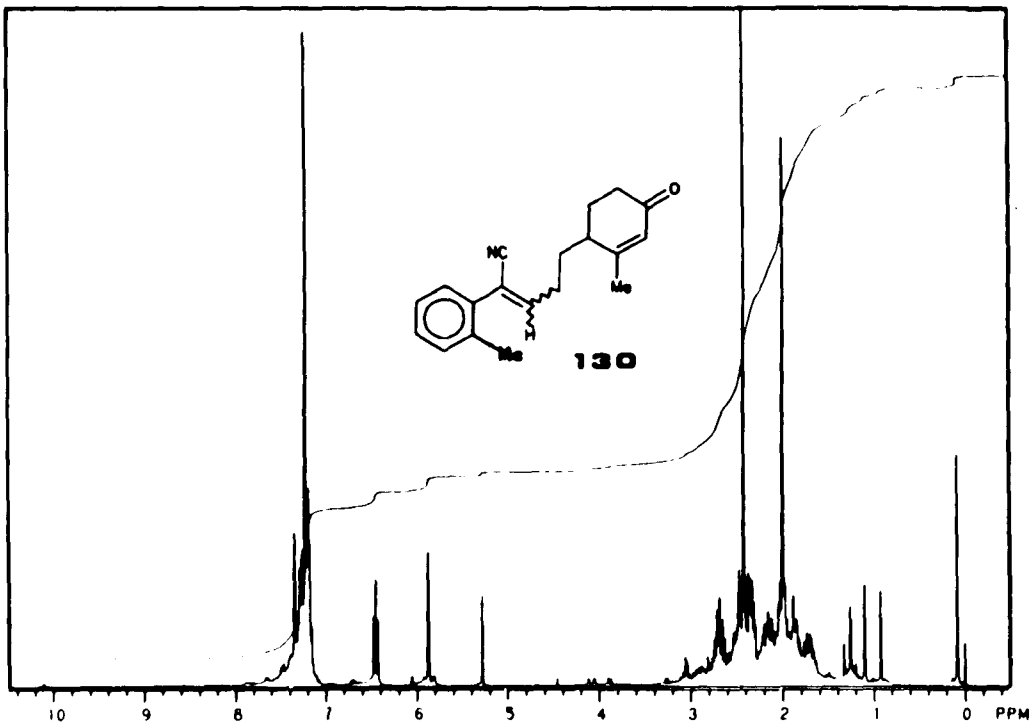

NC
Me
O
10
8
6
4
2
0
PPM


NC
Me
O
200
150
100
50
0
PPM


MICROMETERS
3000 (CM⁻¹) 2500
2000
1800
1600
1400
1200
1000 (CM⁻¹) 800
NC
Me
O
128


O
NC
Me
H
Me
130
10
9
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4
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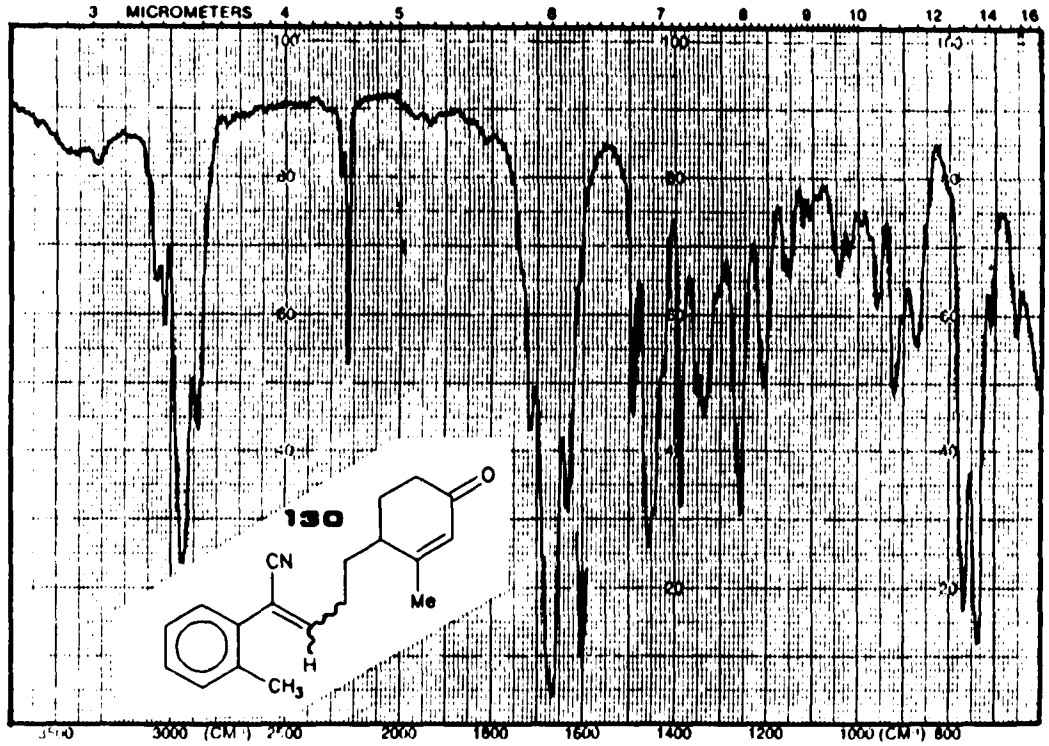
2
1
0
PPM


3 MICROMETERS 4 5 6 7 8 9 10 12 14 16
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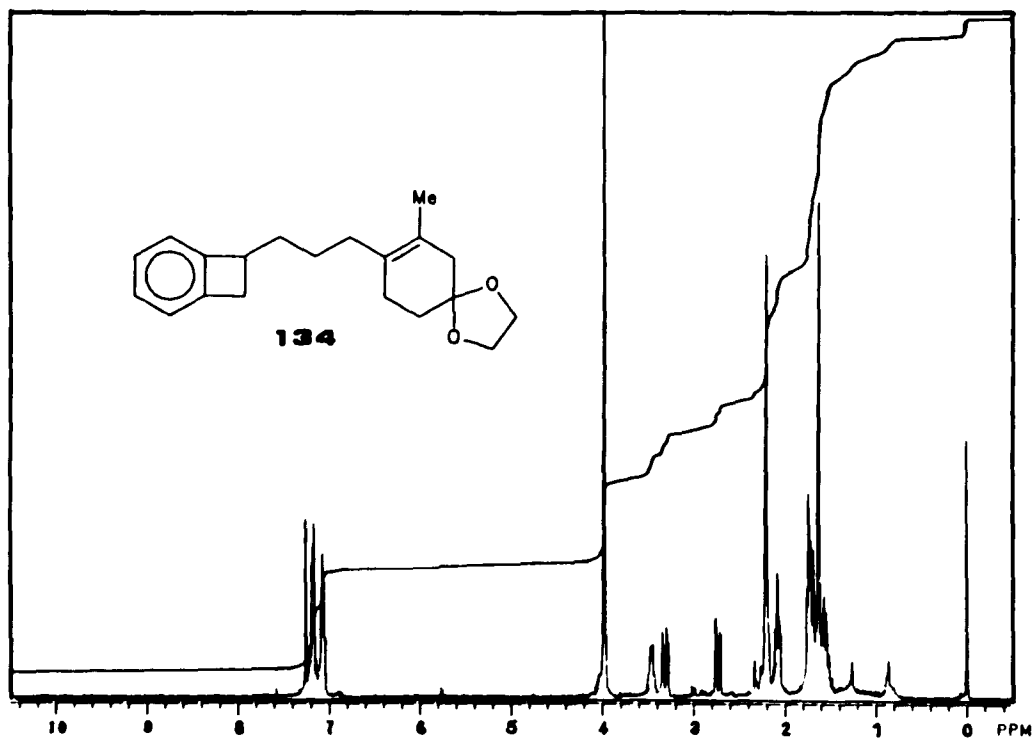
80
60
40
20
130
CN
Me
H
CH3
3000 (CM-1) 2000 1800 1600 1400 1200 1000 (CM-1) 800


Me
O
O
134
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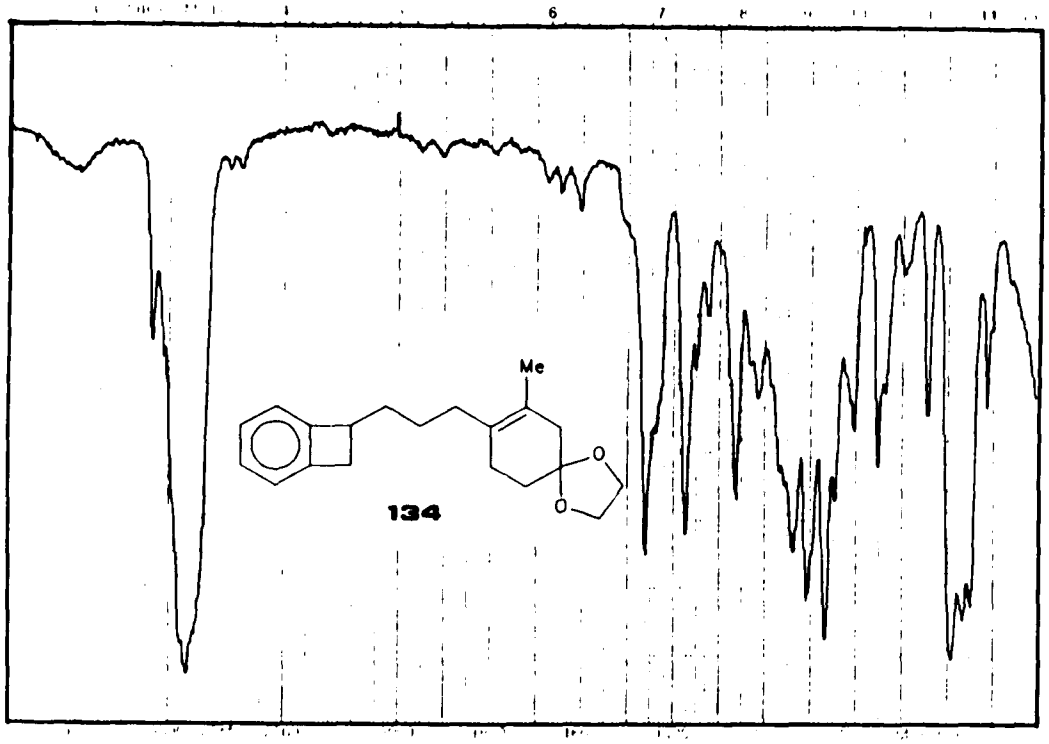

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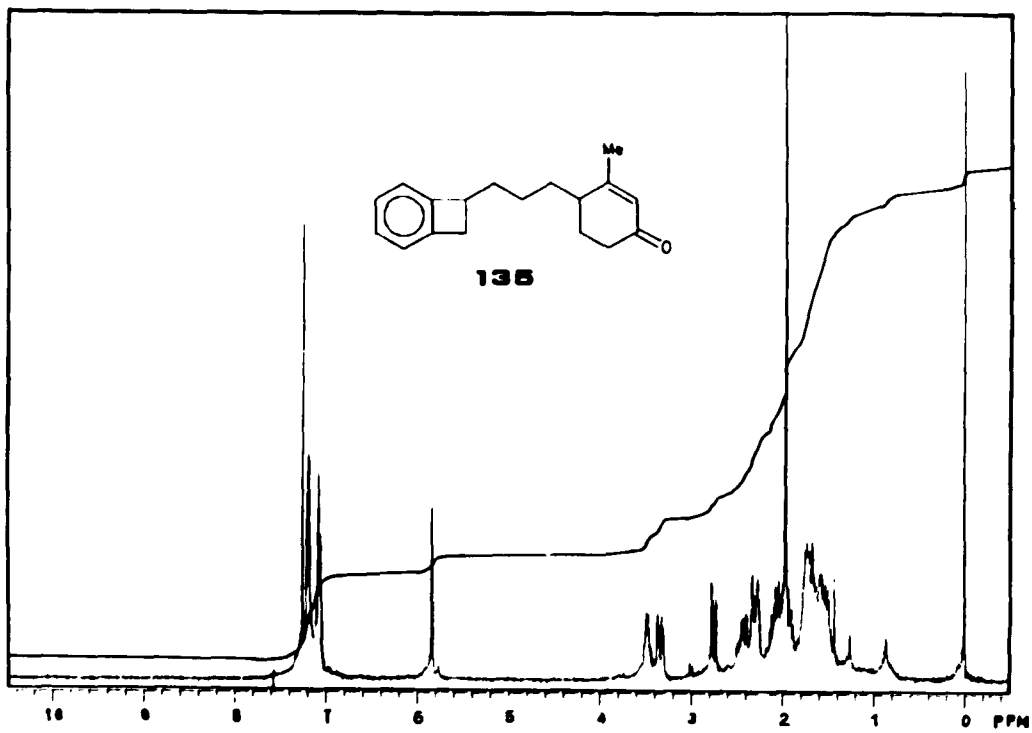

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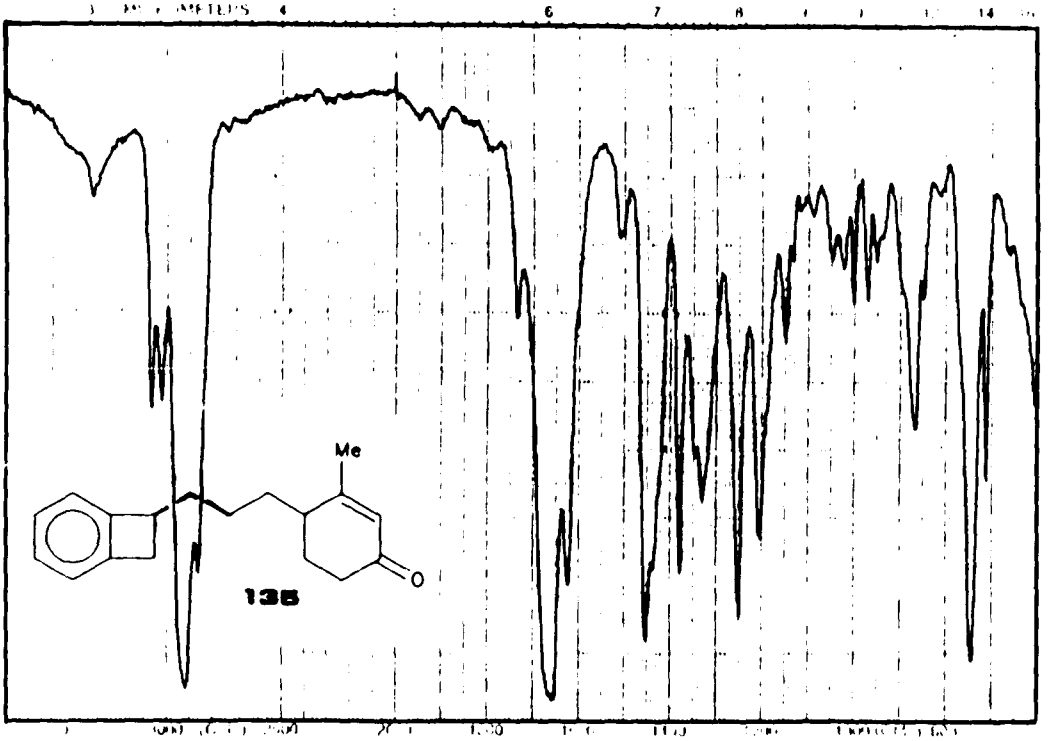

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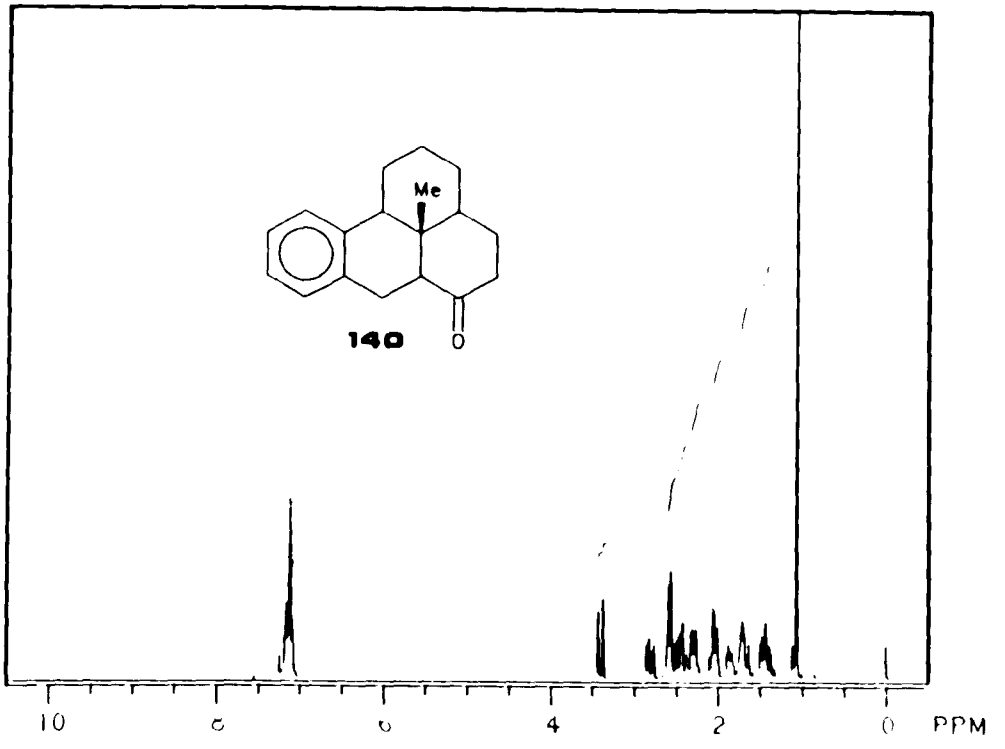

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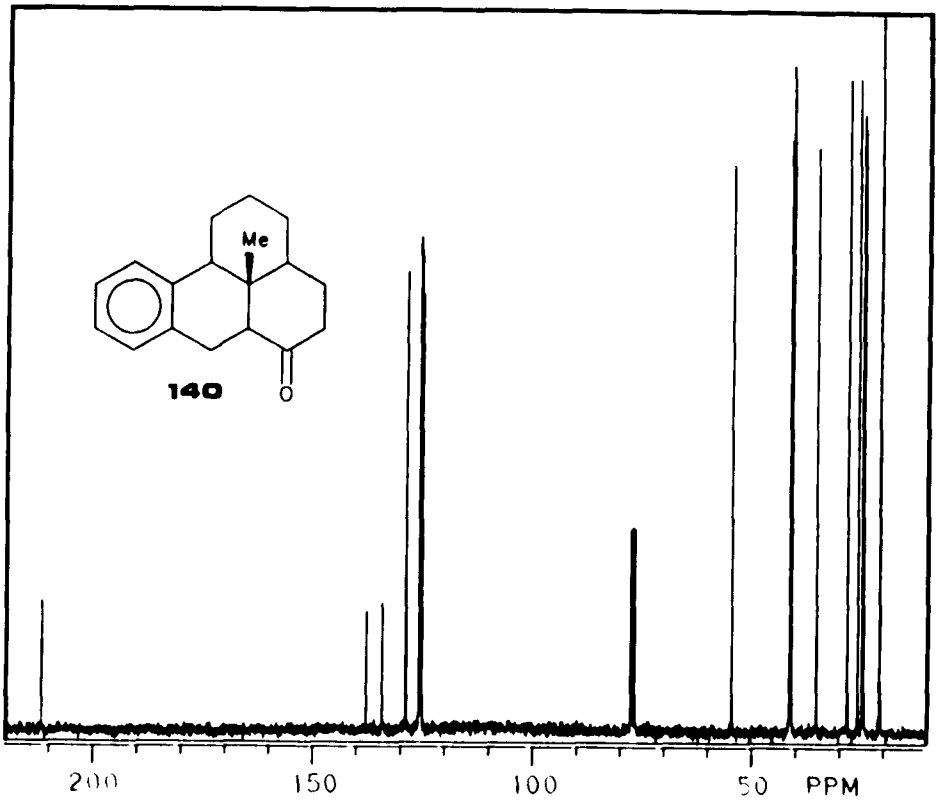

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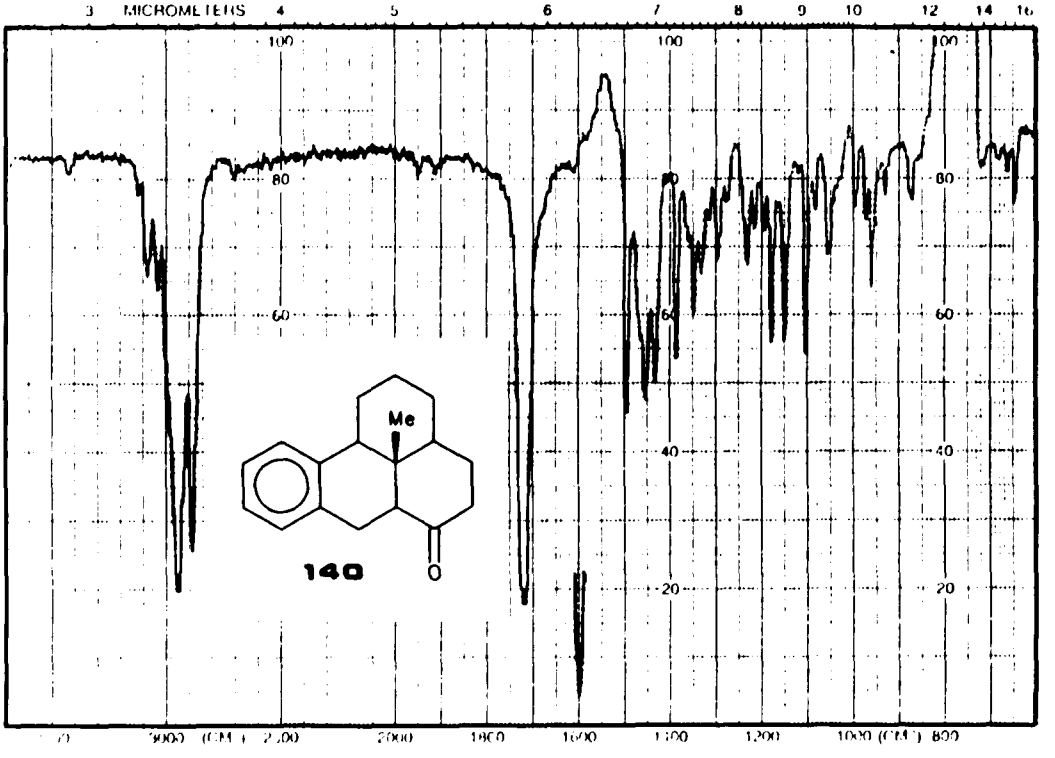

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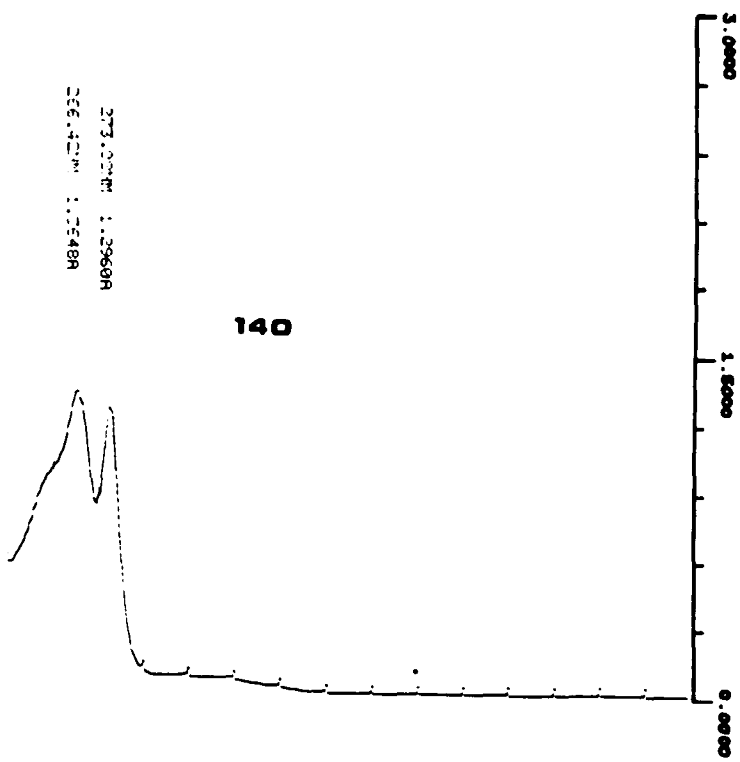
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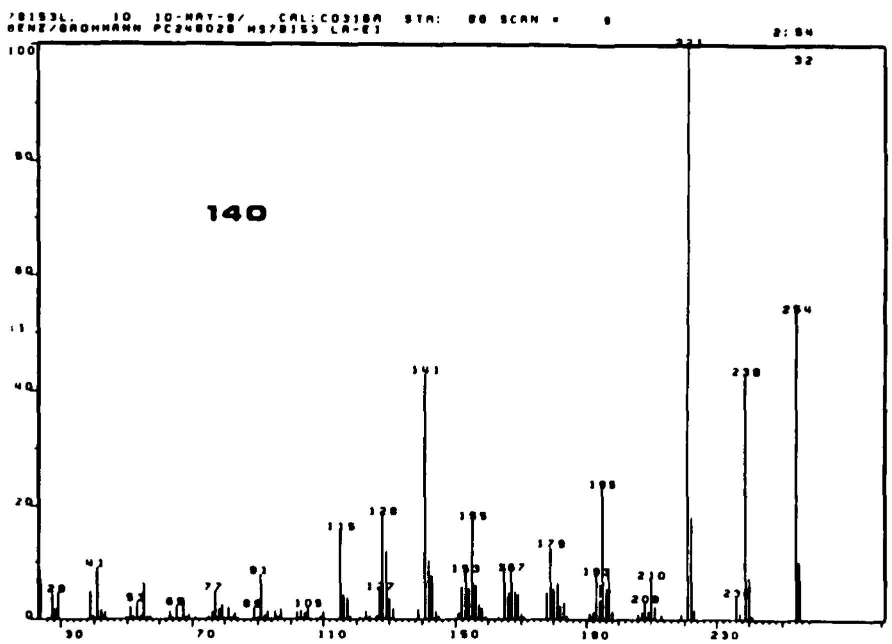
273.02NM 1.2960A
140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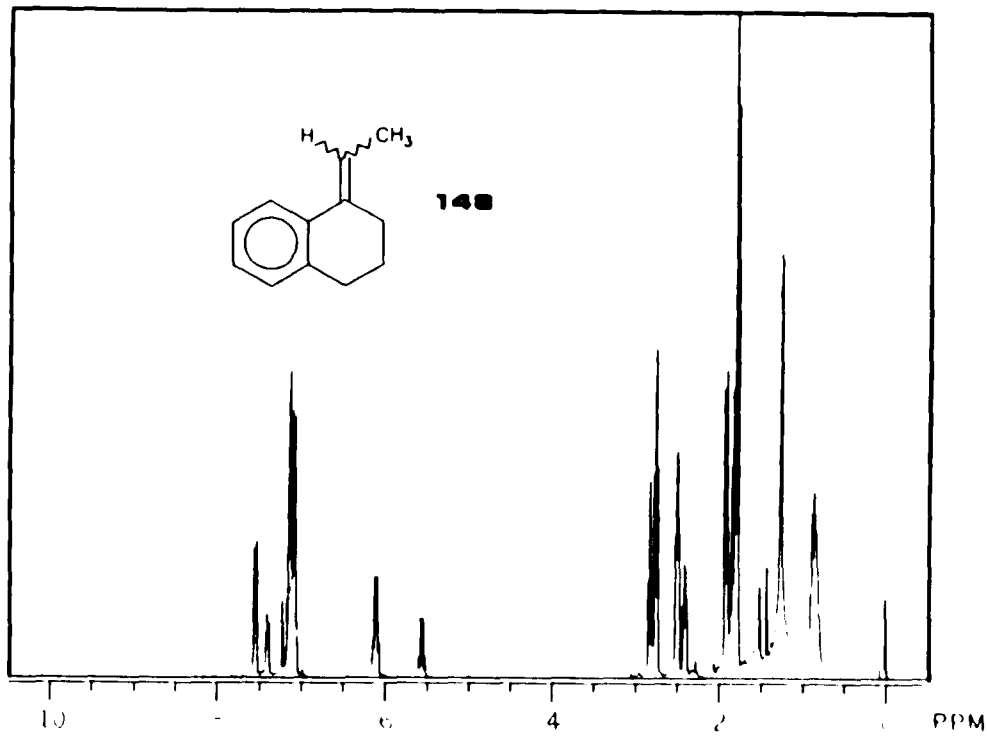
230
341
238
254


H
CH3
14a
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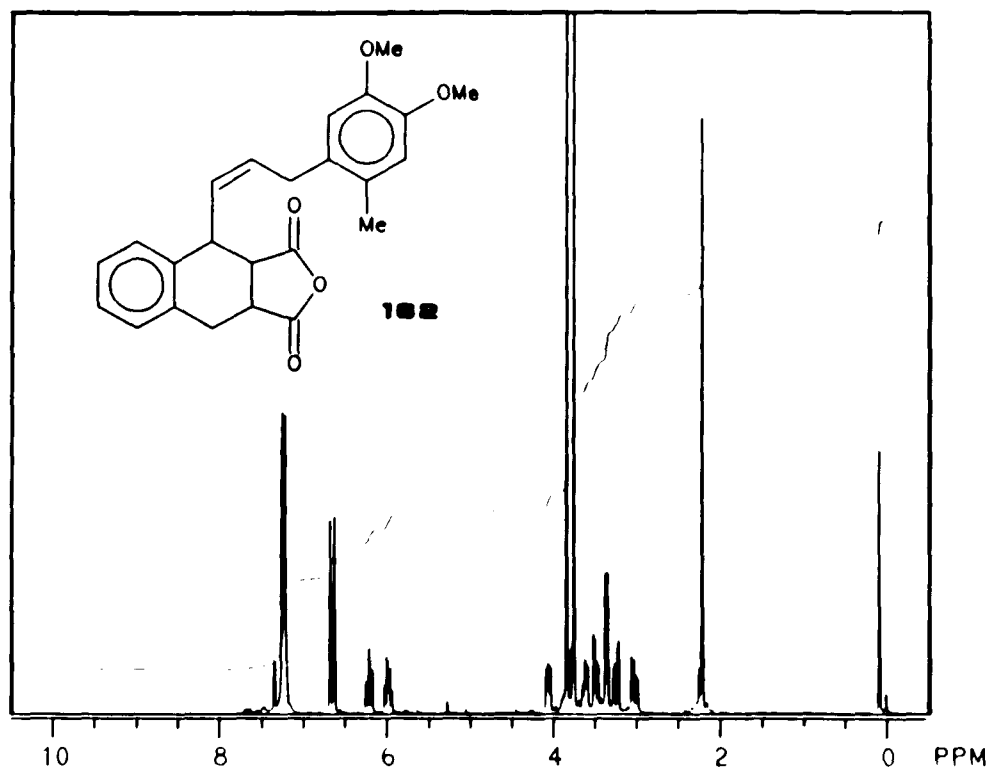
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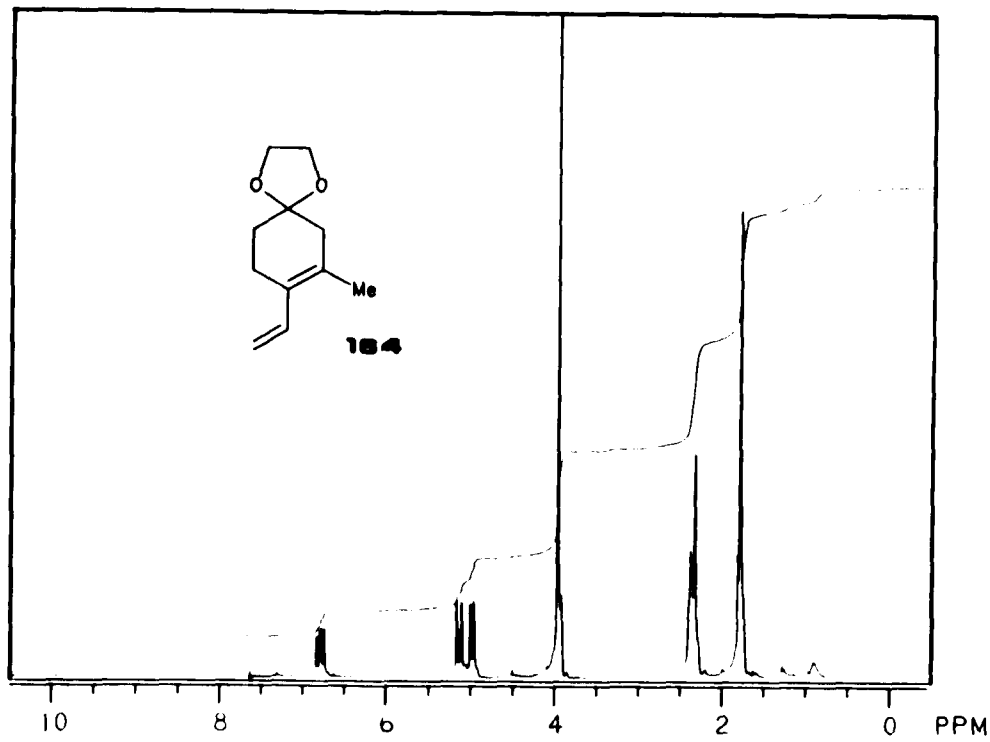
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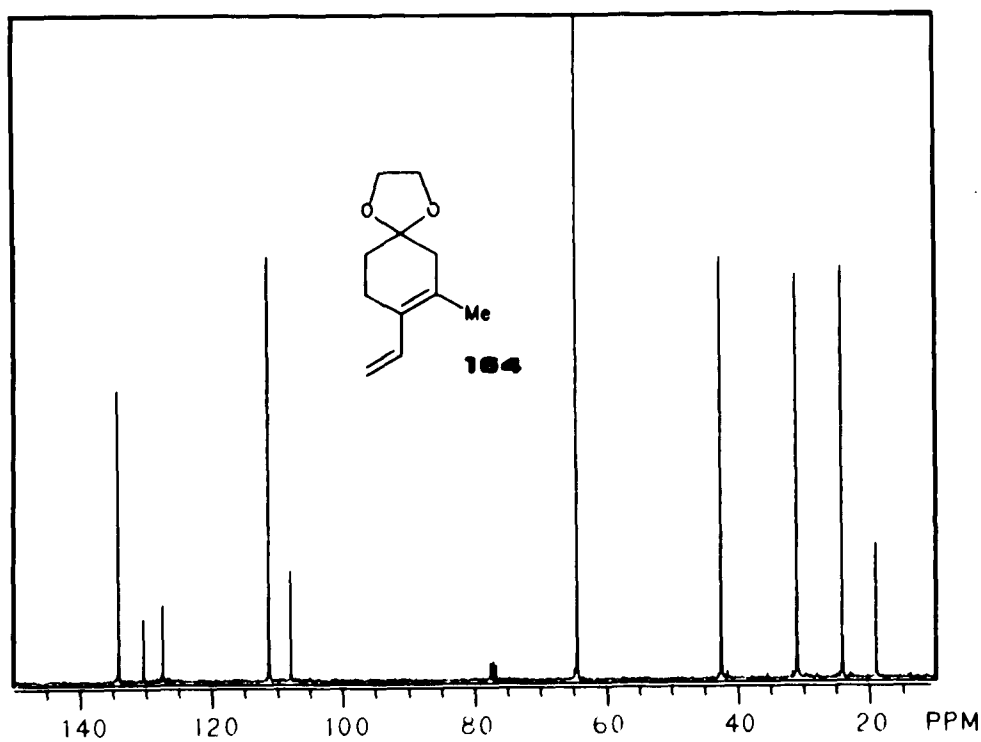
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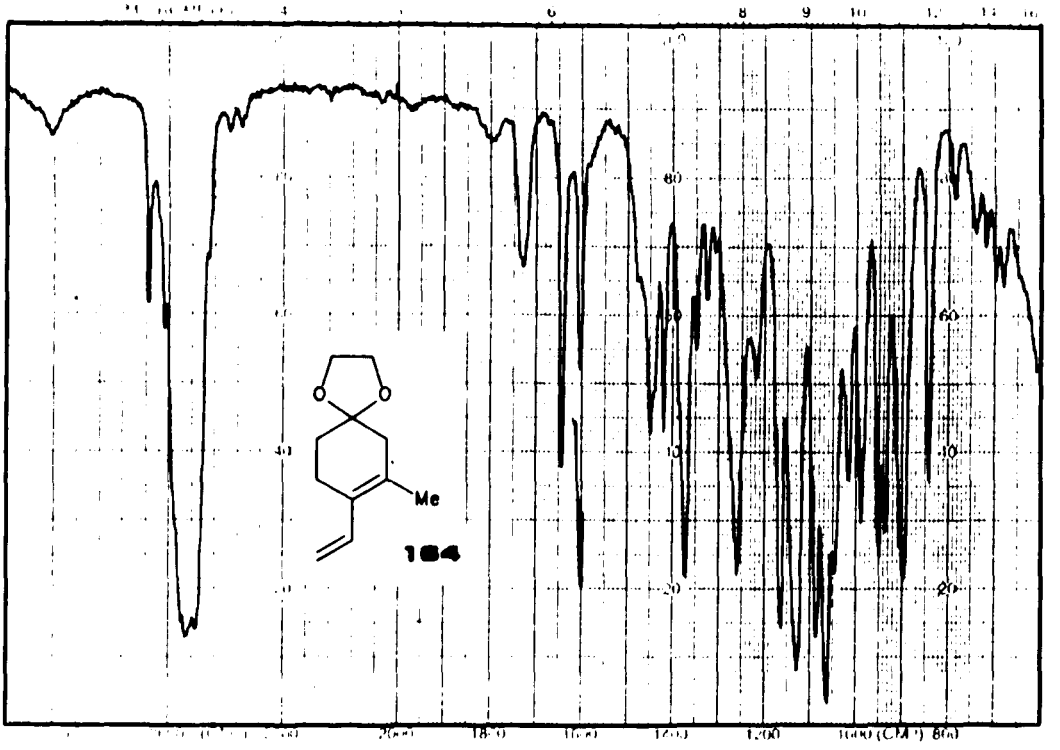
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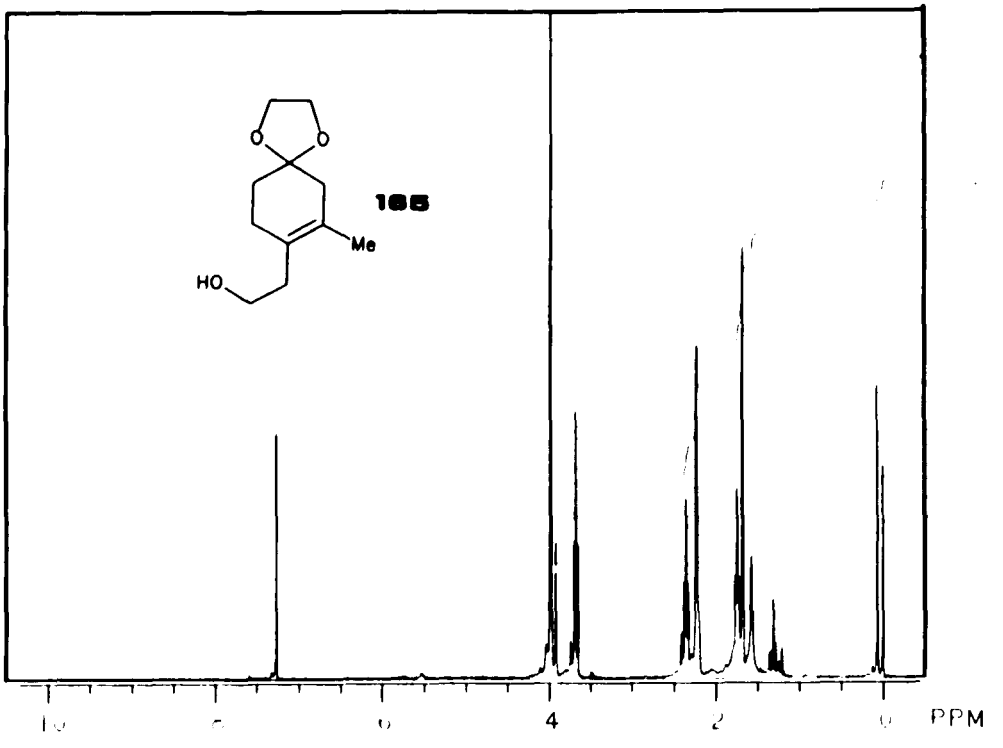
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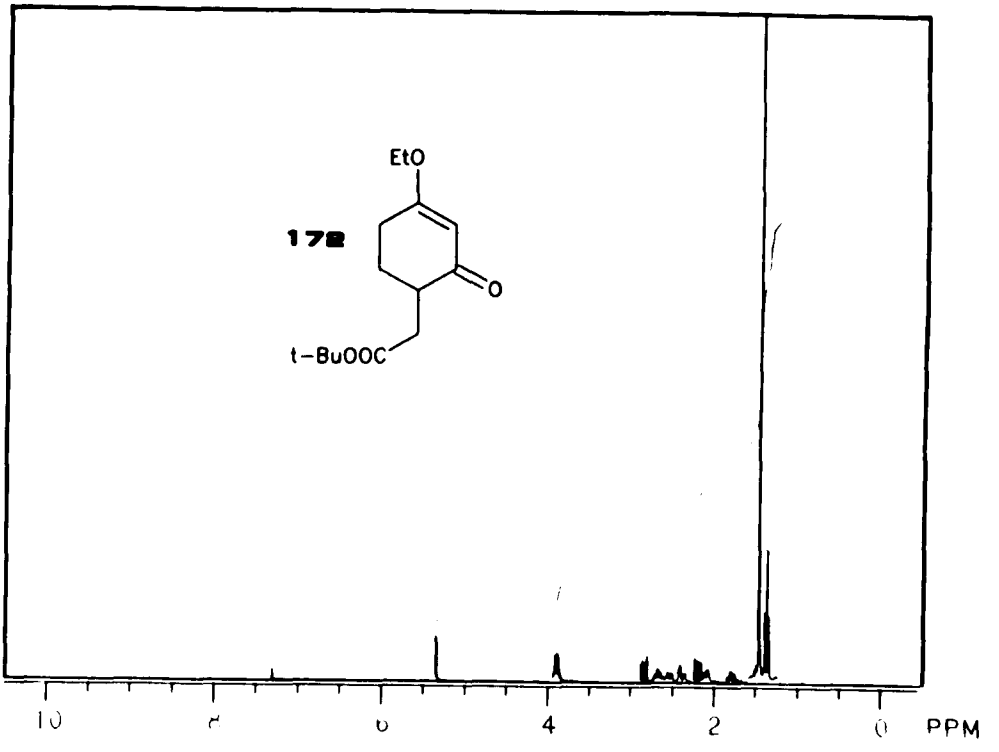
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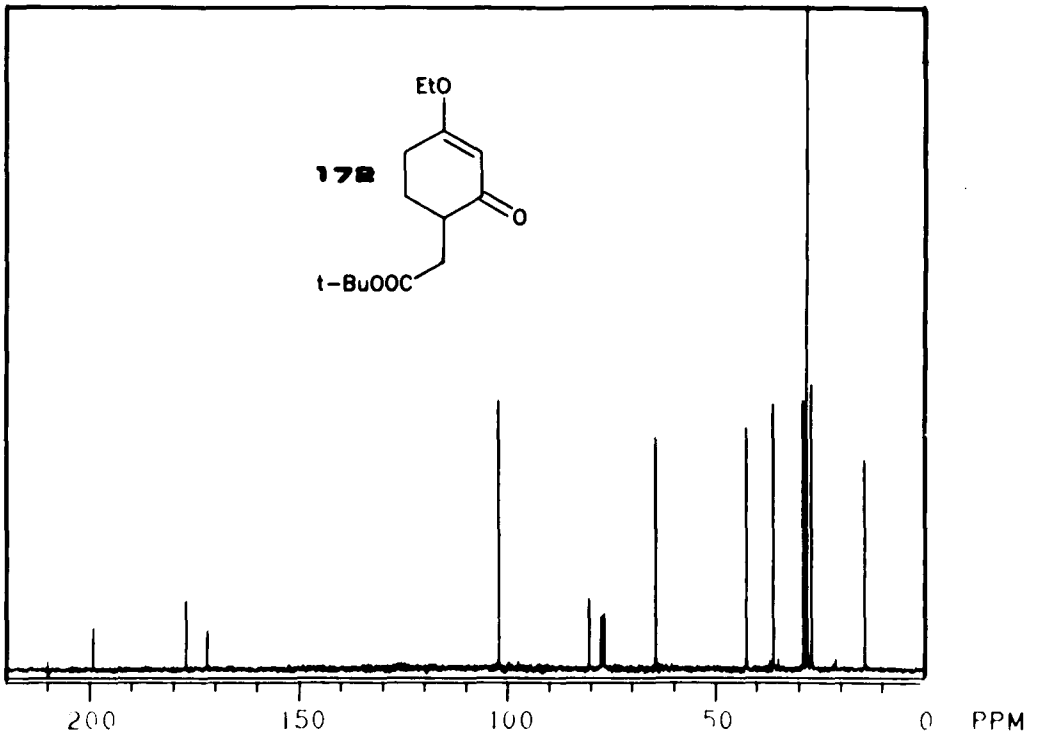
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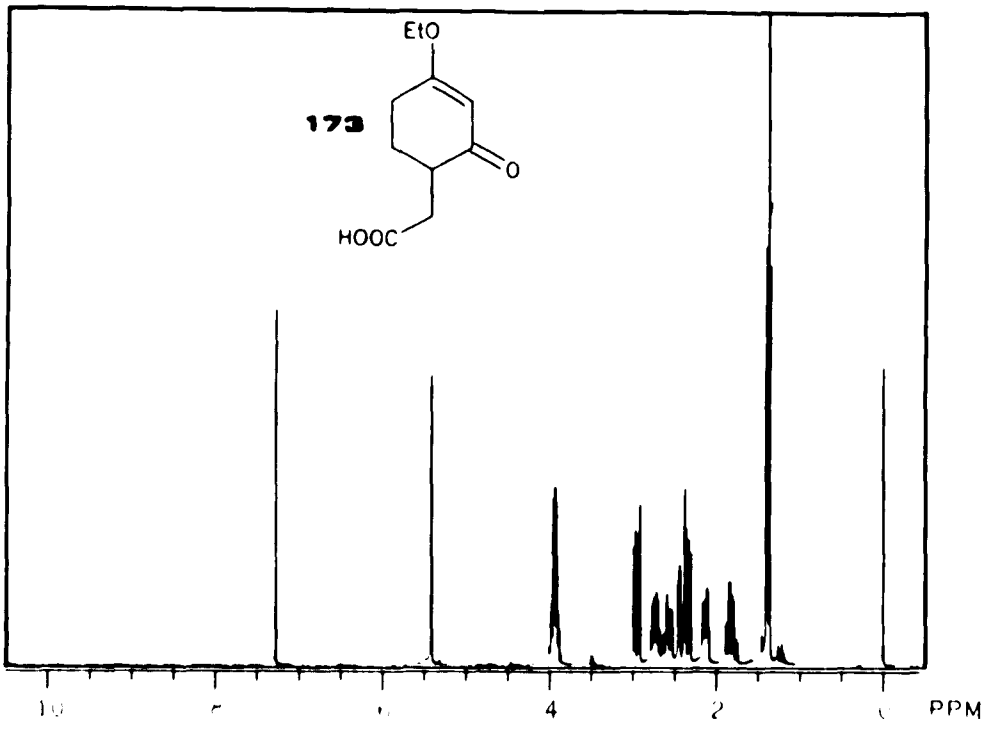
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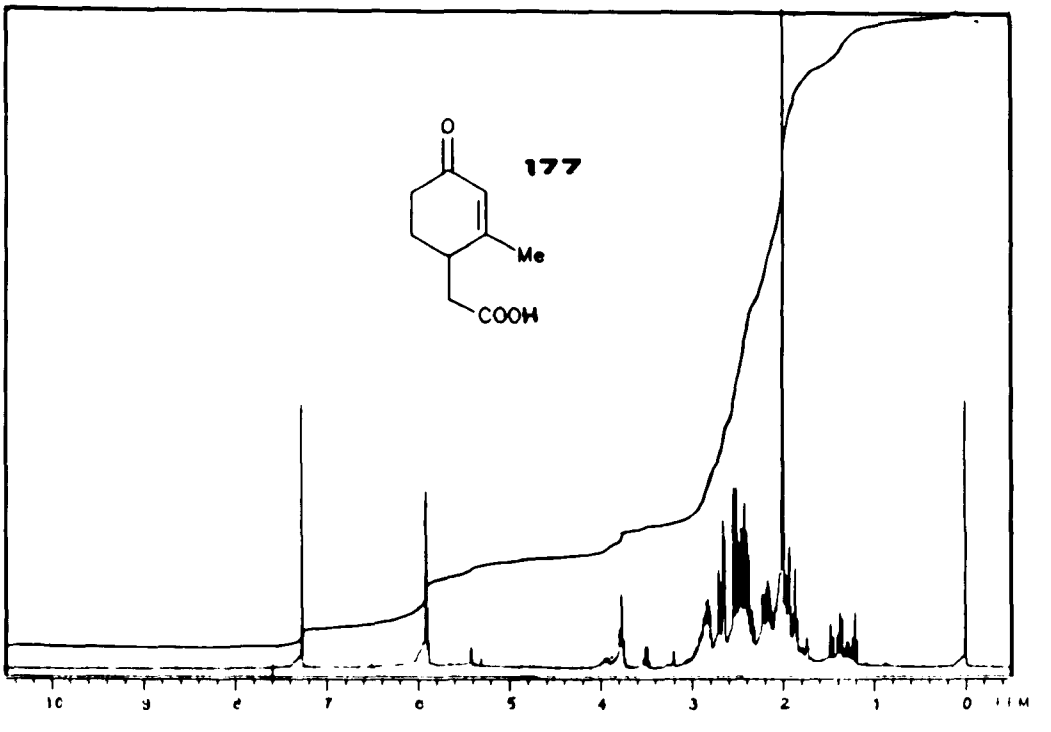
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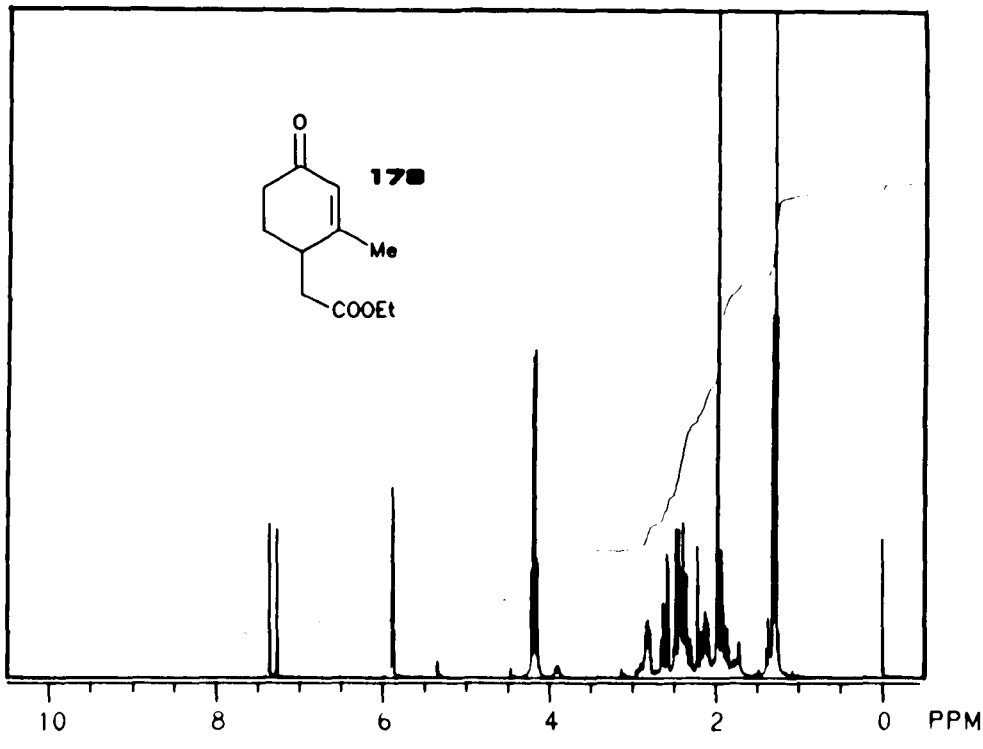
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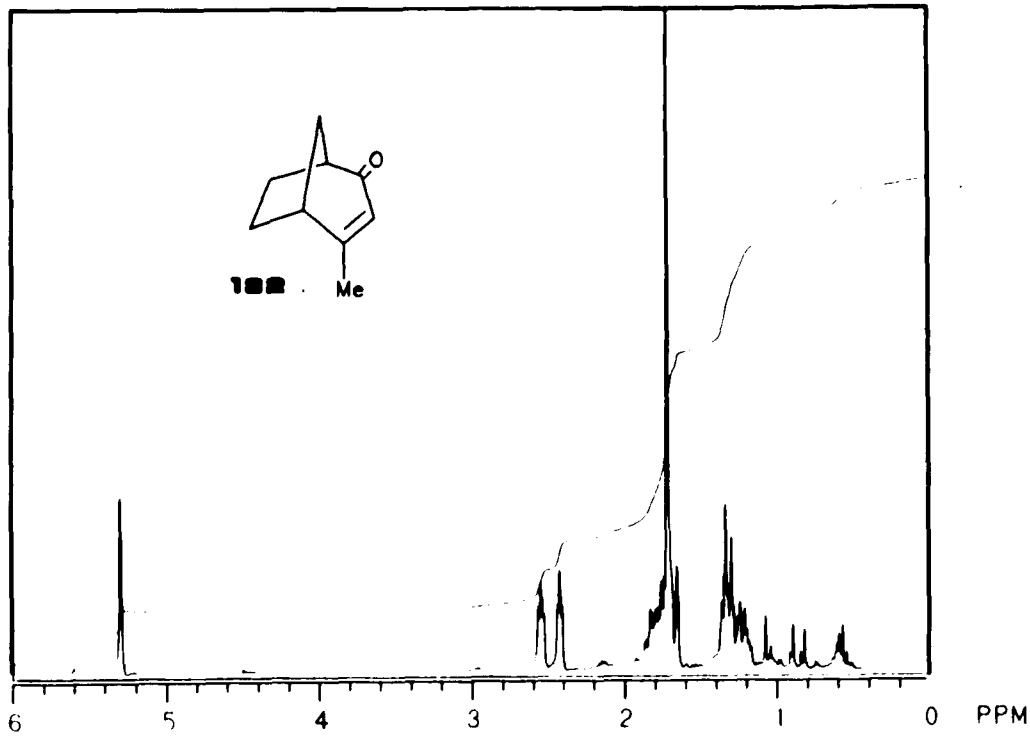
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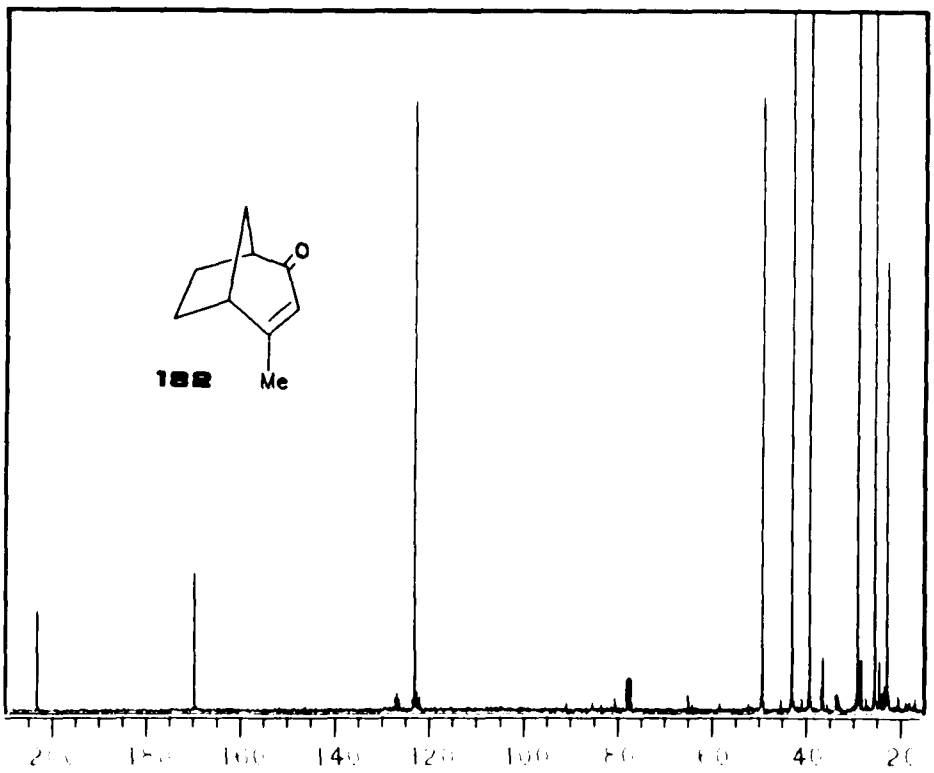
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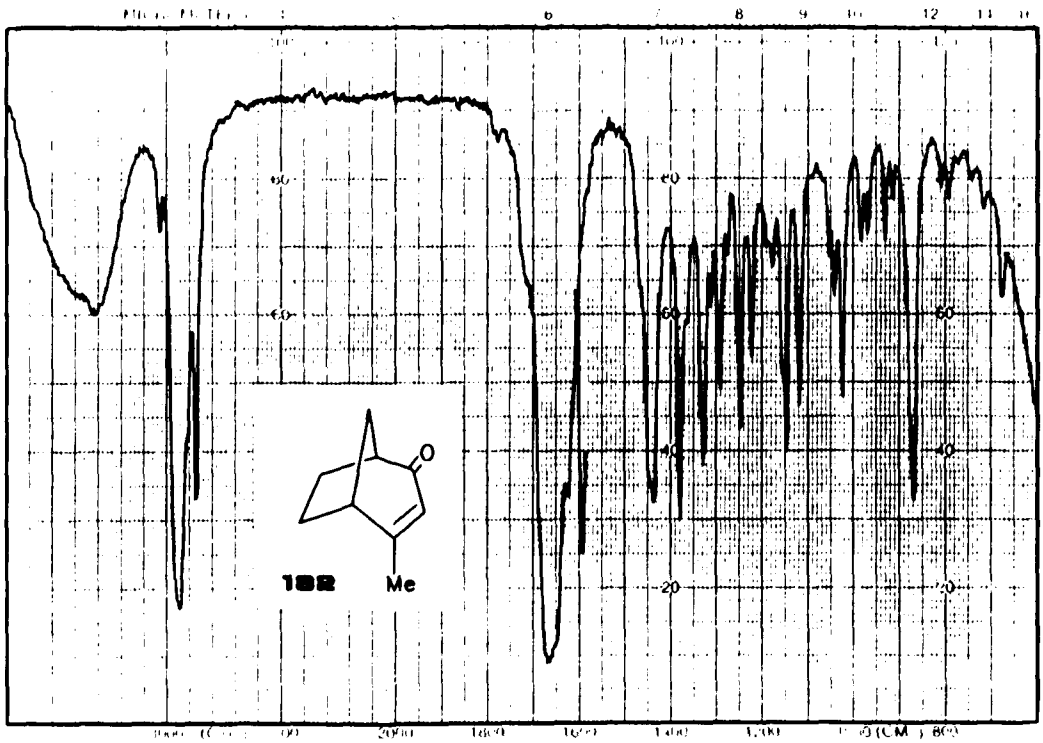
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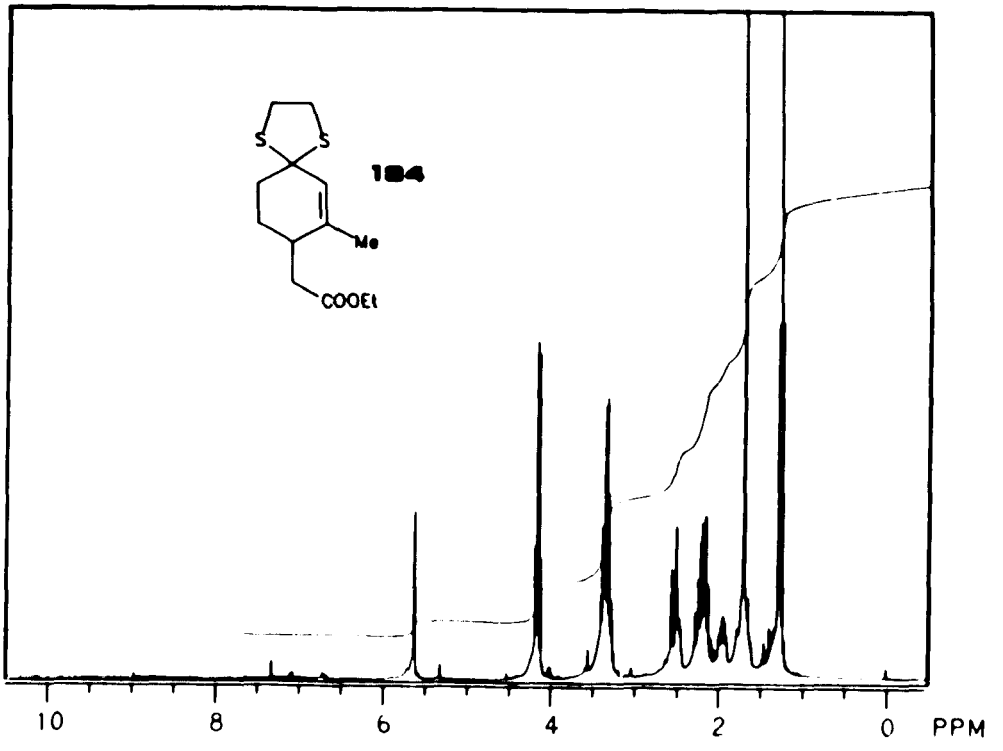
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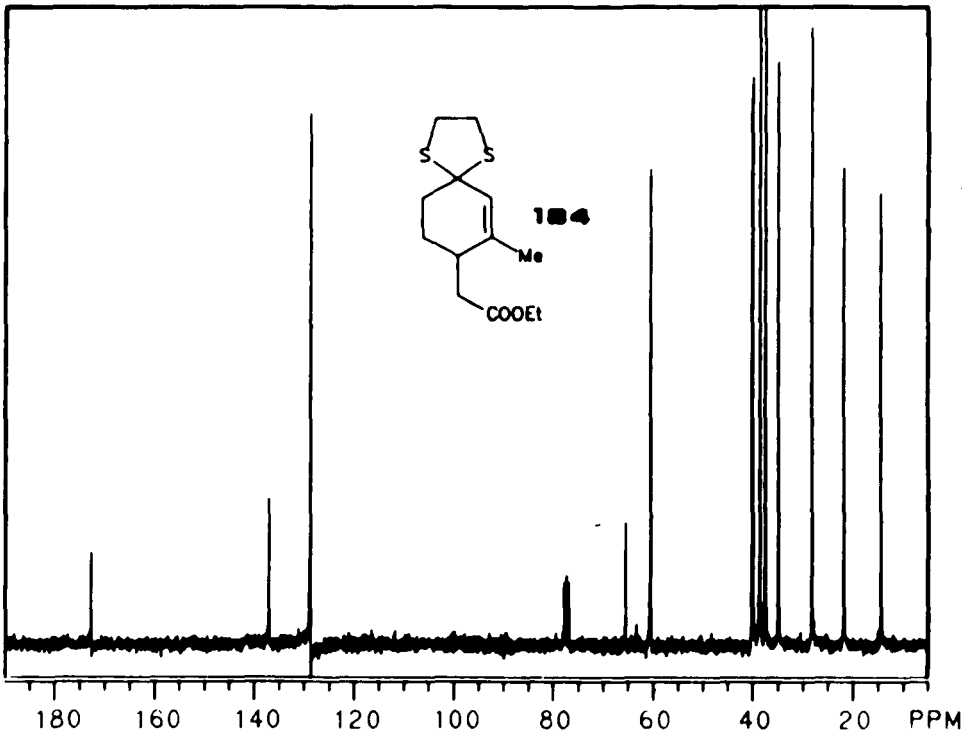
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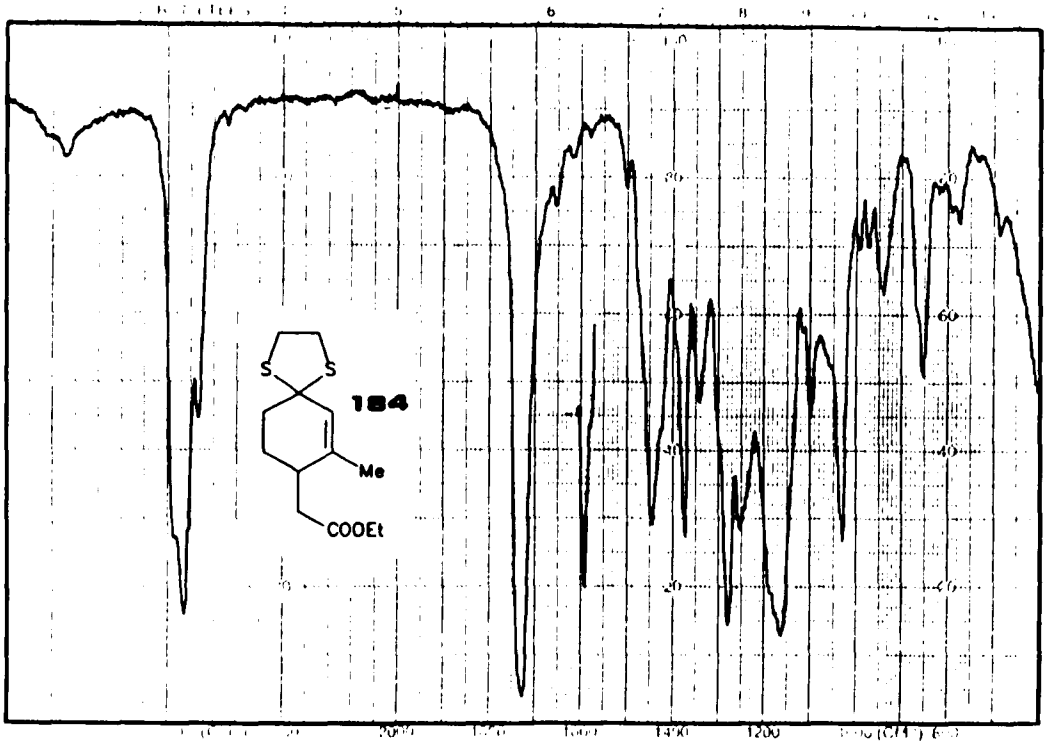
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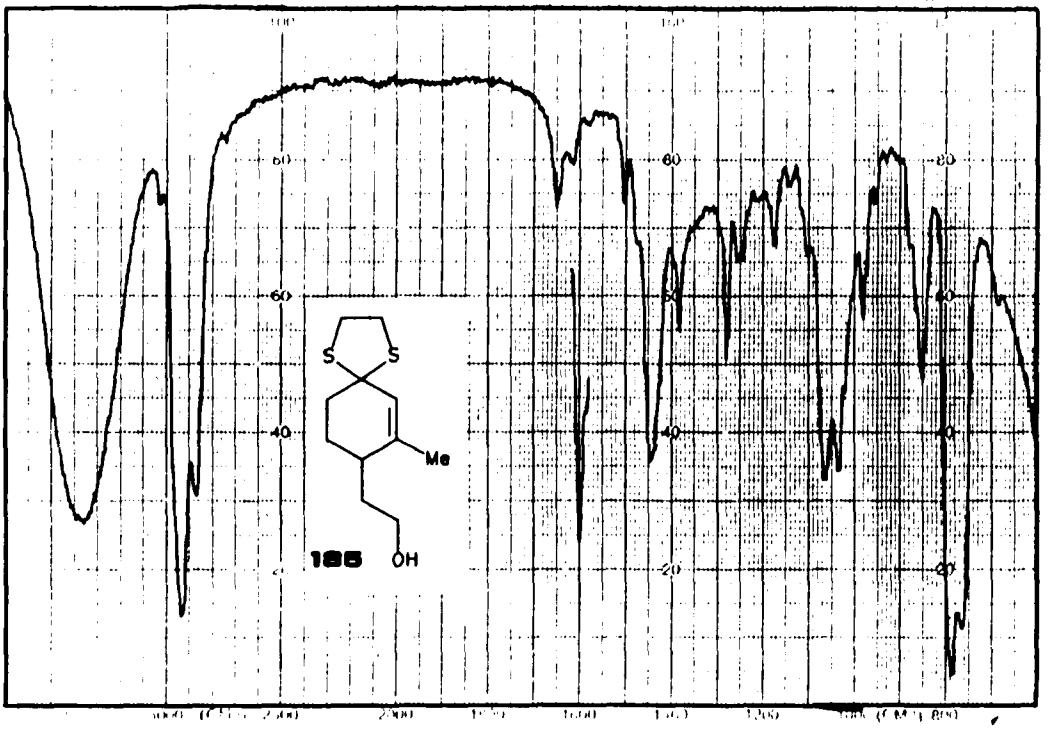
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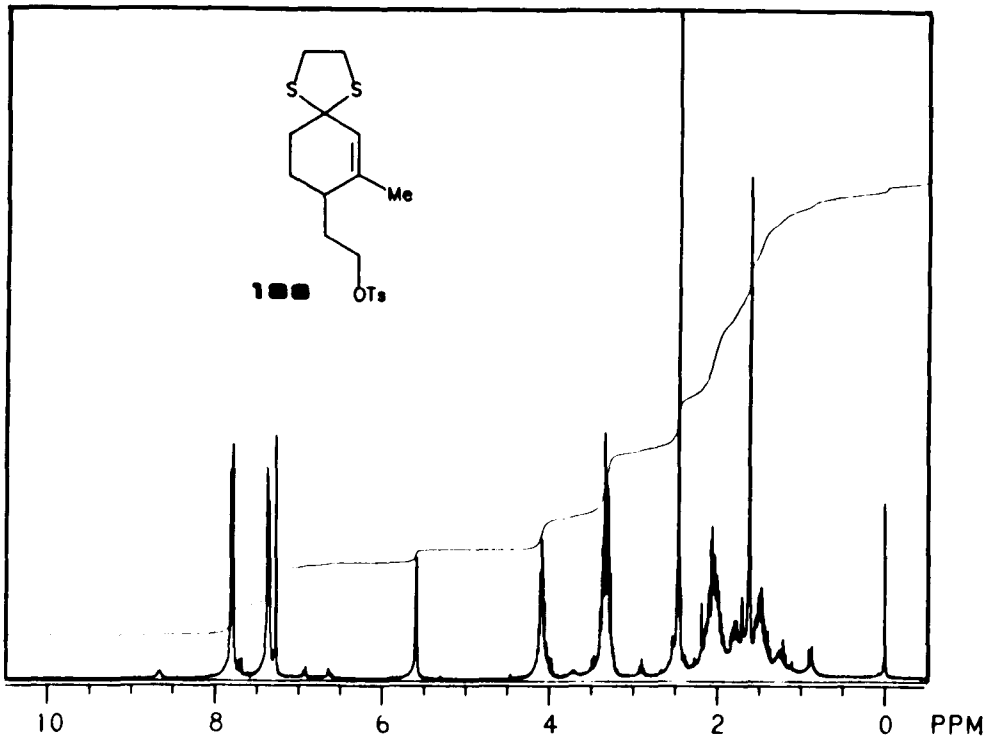
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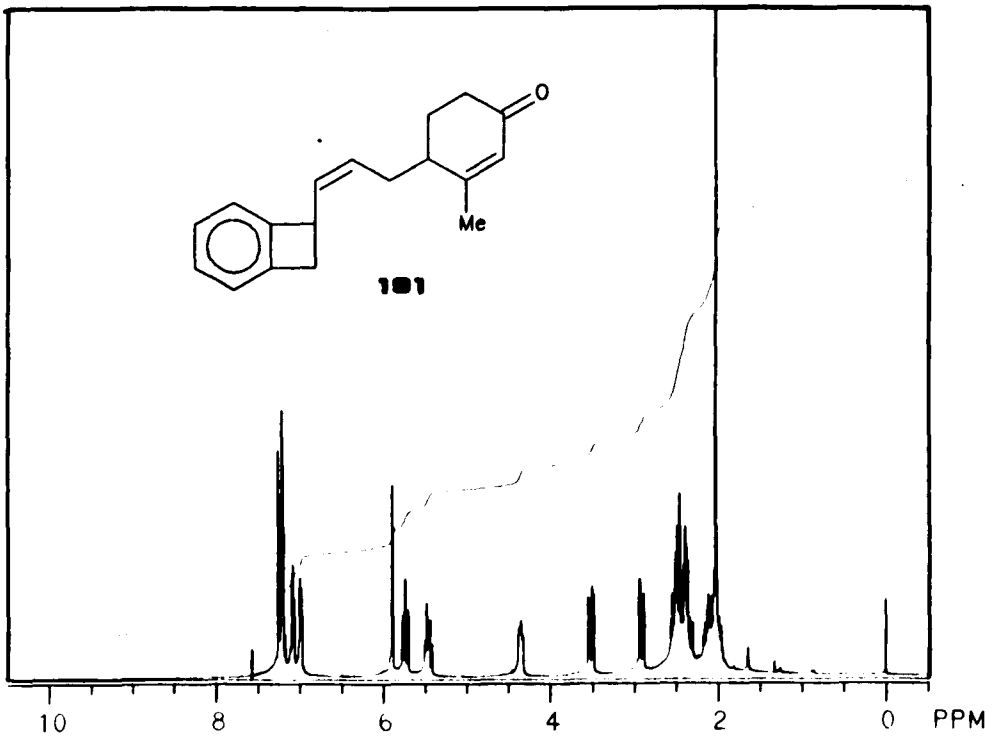
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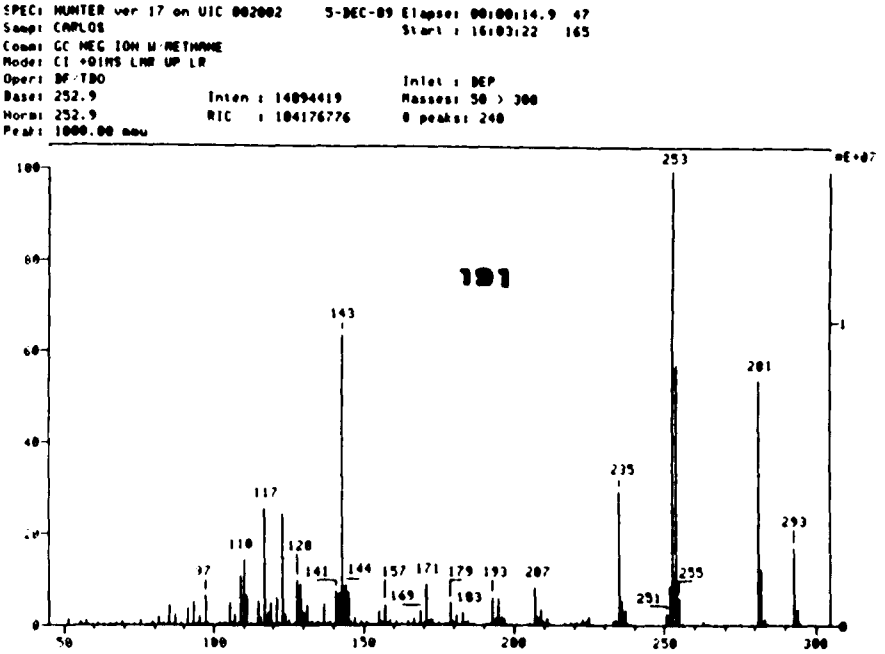
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Oper: BF/TDO Inlet : DEP
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Norm: 252.9 RIC : 104176776 0 peaks: 240
Peak: 1000.00 amu
mE+07
191
253
143
201
235
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293
110
128
97
141
144
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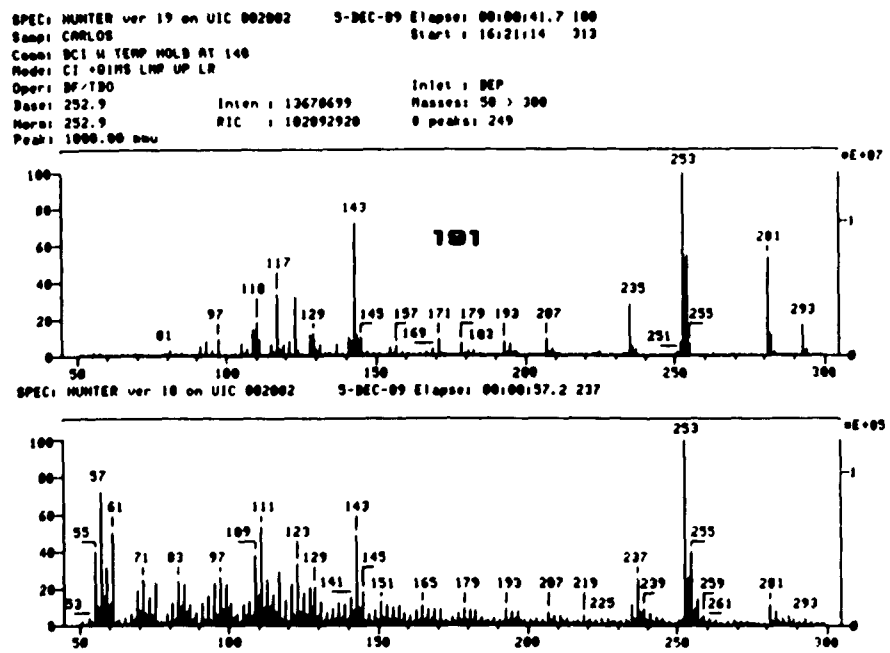
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Norm: 252.9 RIC : 102092920 0 peaks: 249
Peak: 1000.00 amu
mE+07
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mE+05
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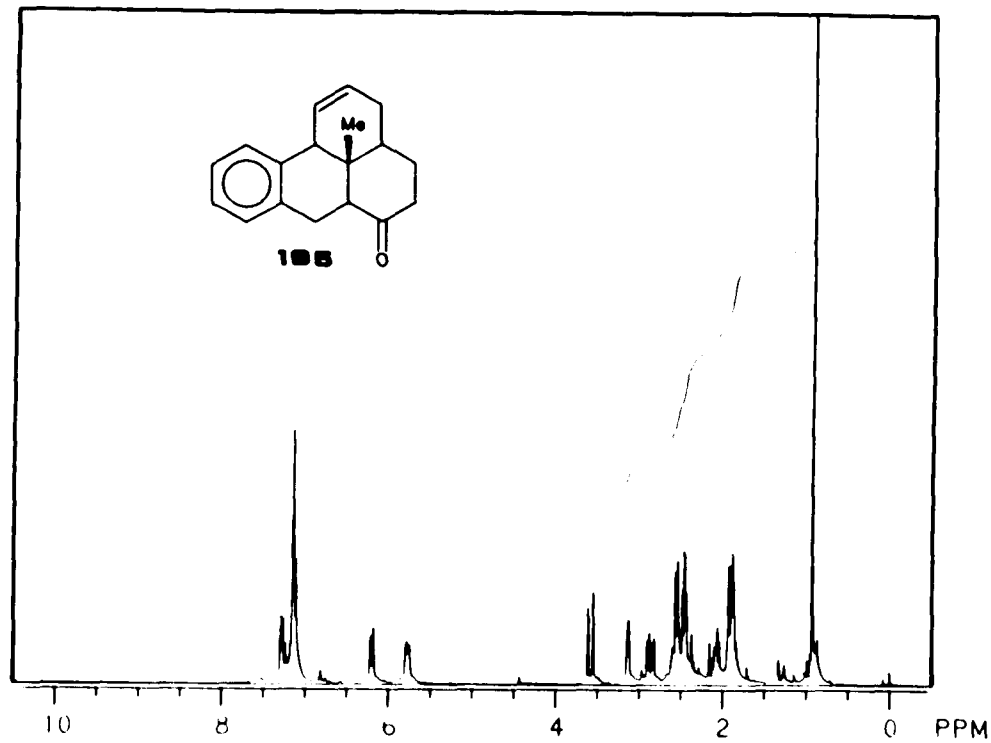

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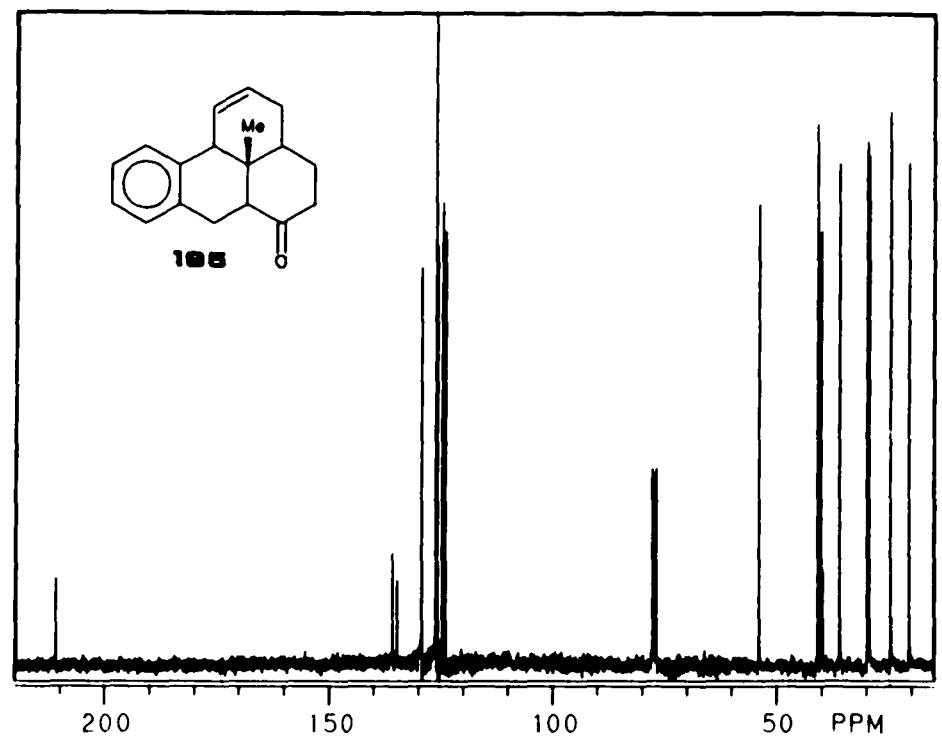

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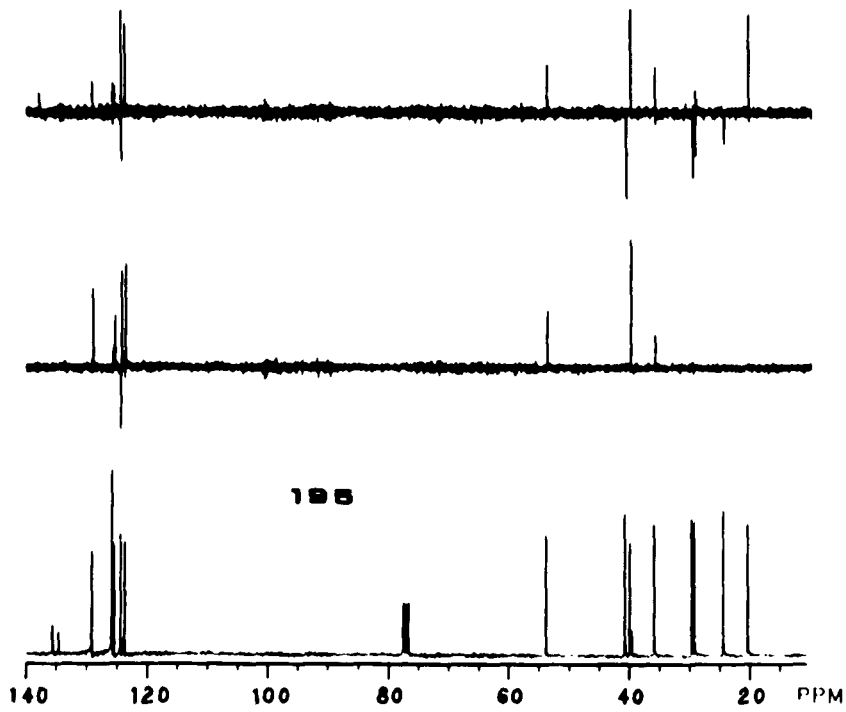
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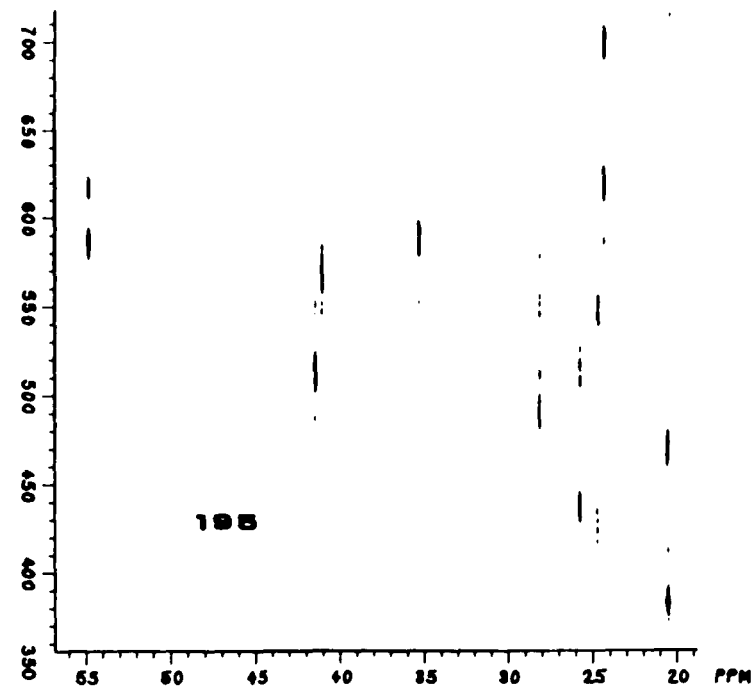
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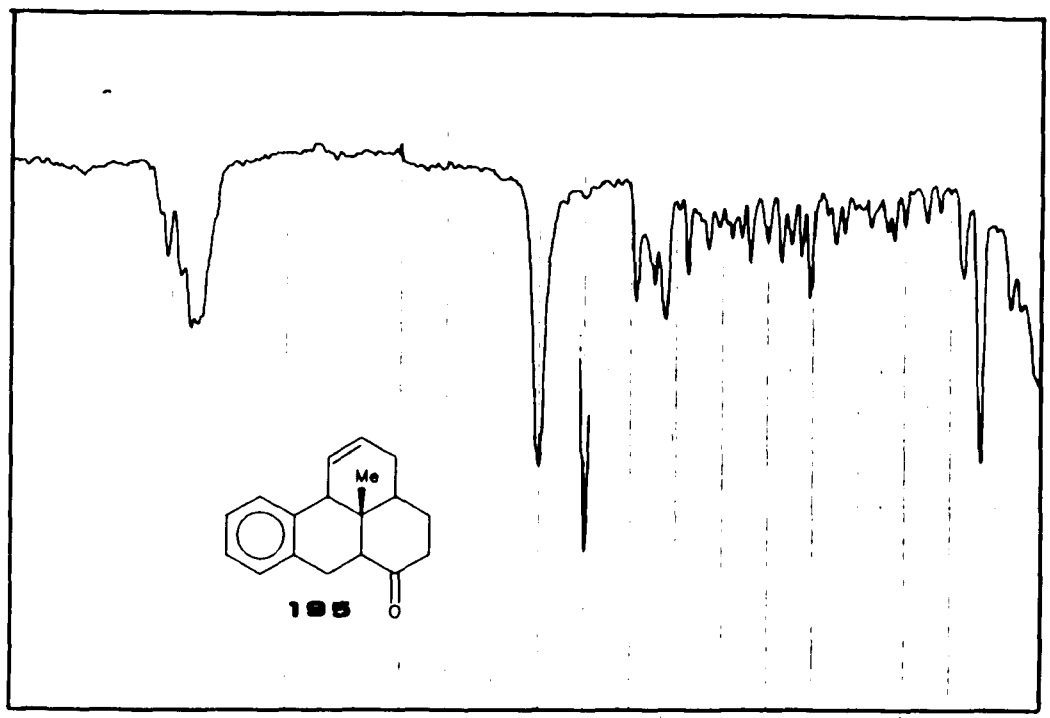

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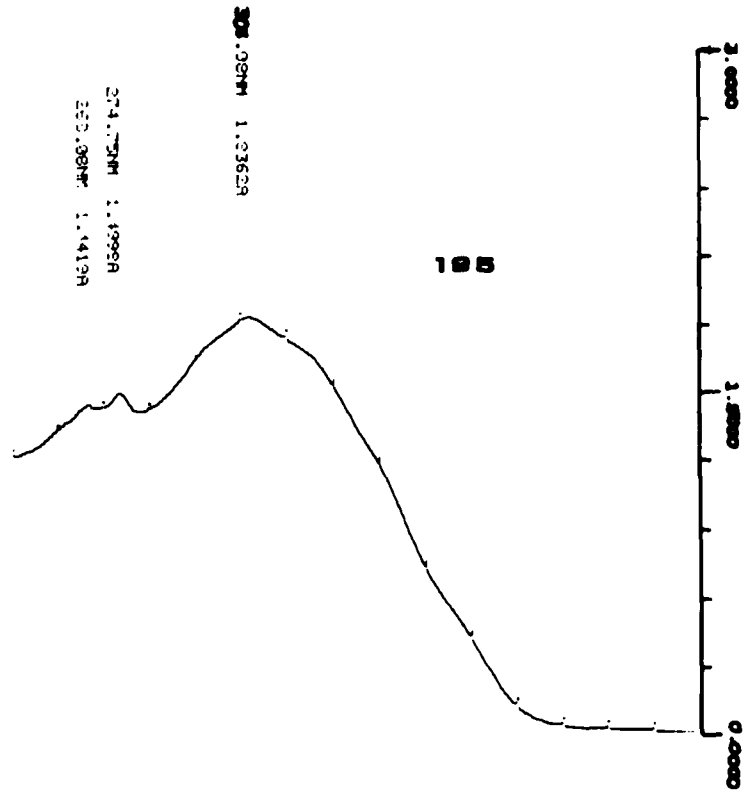

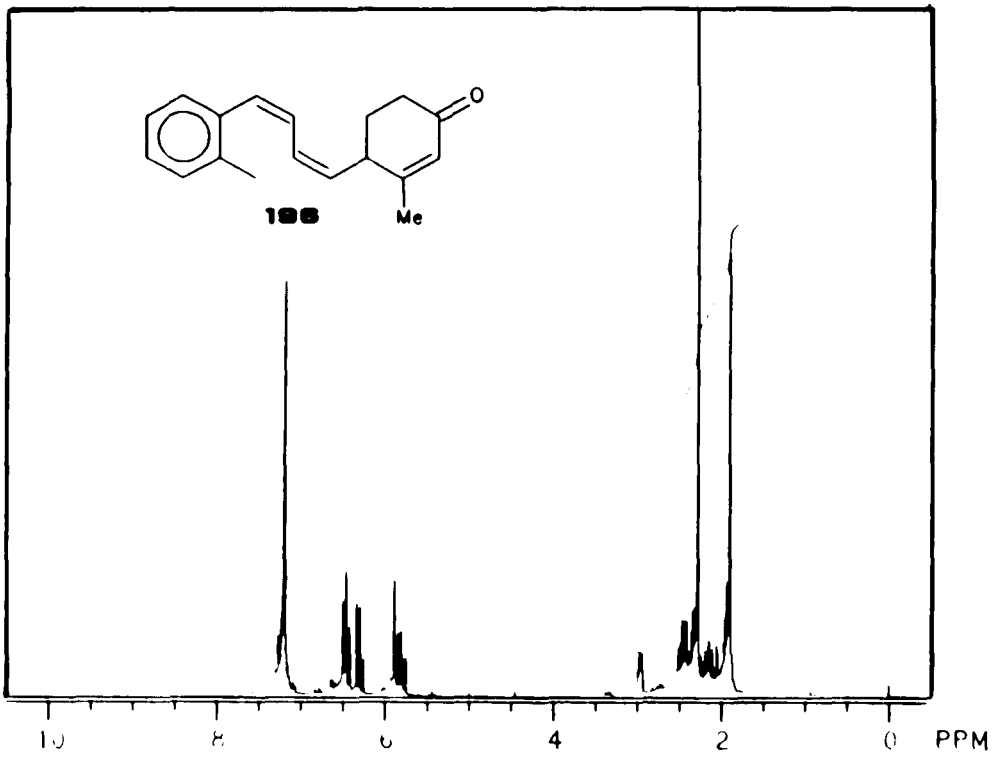

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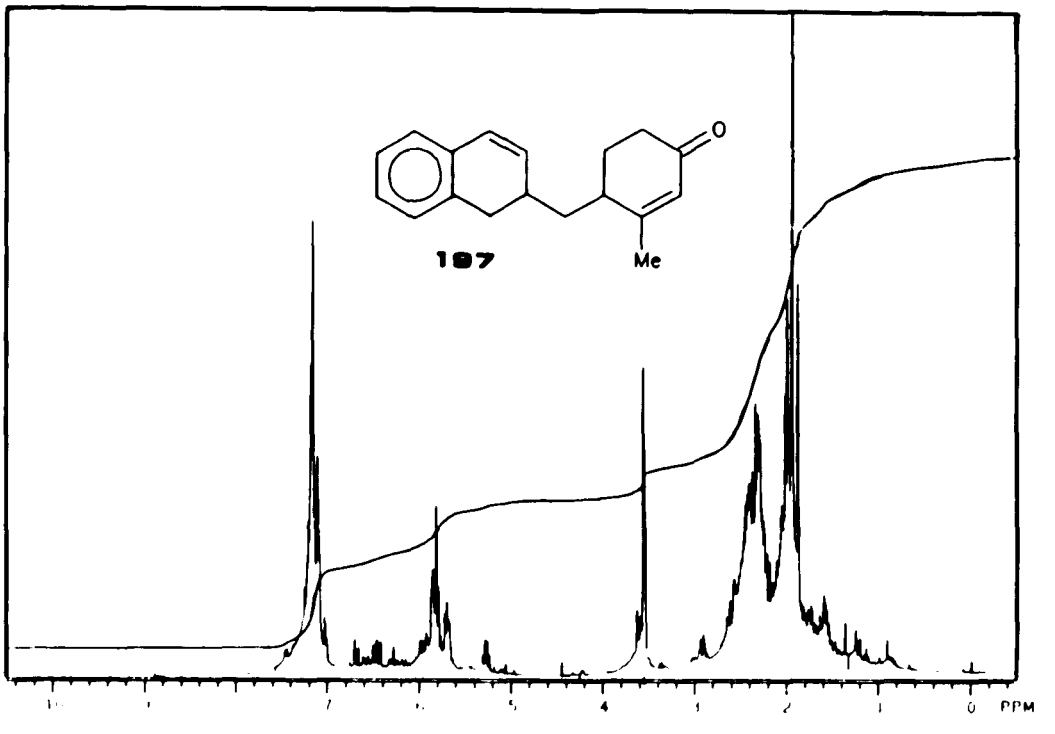

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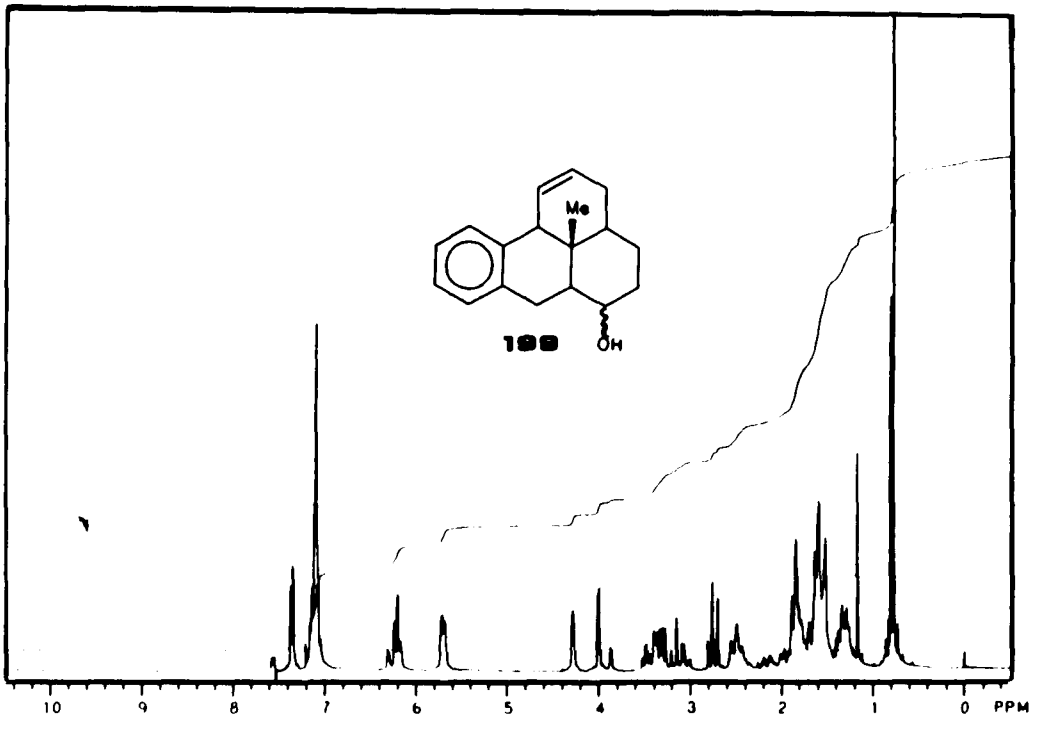
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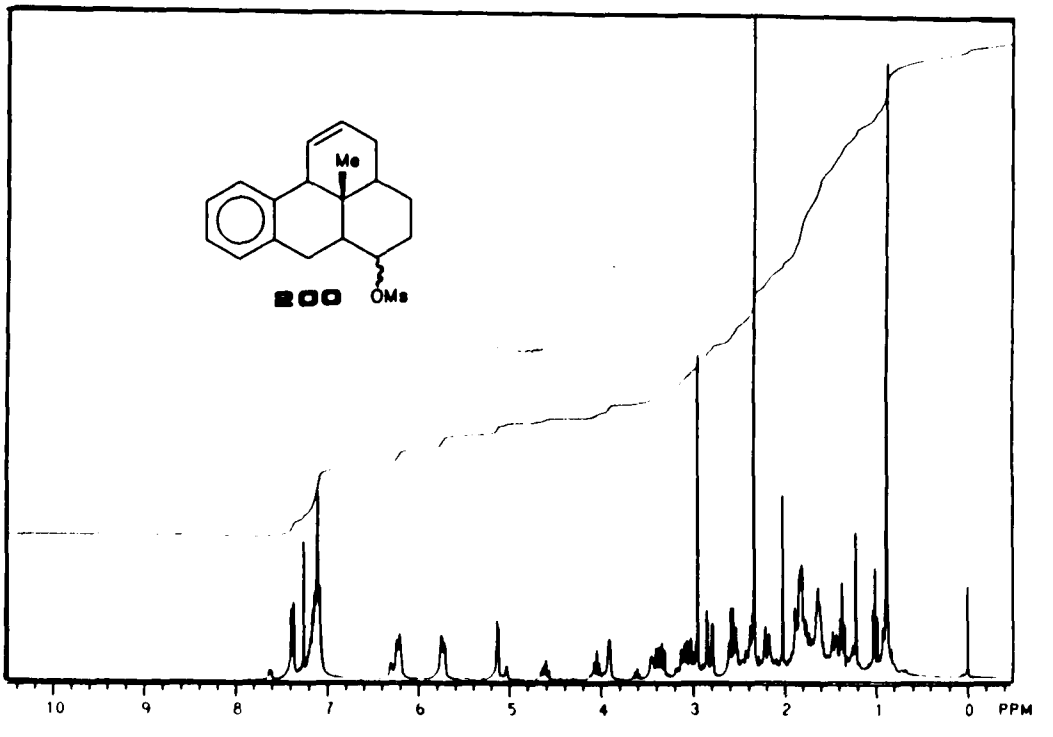
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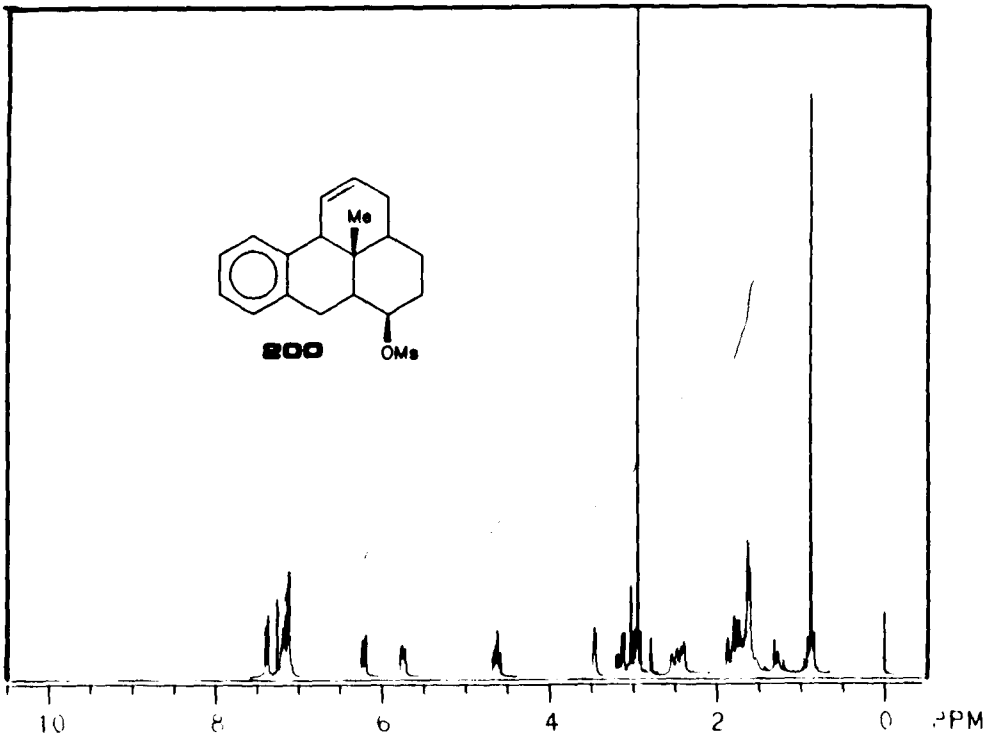

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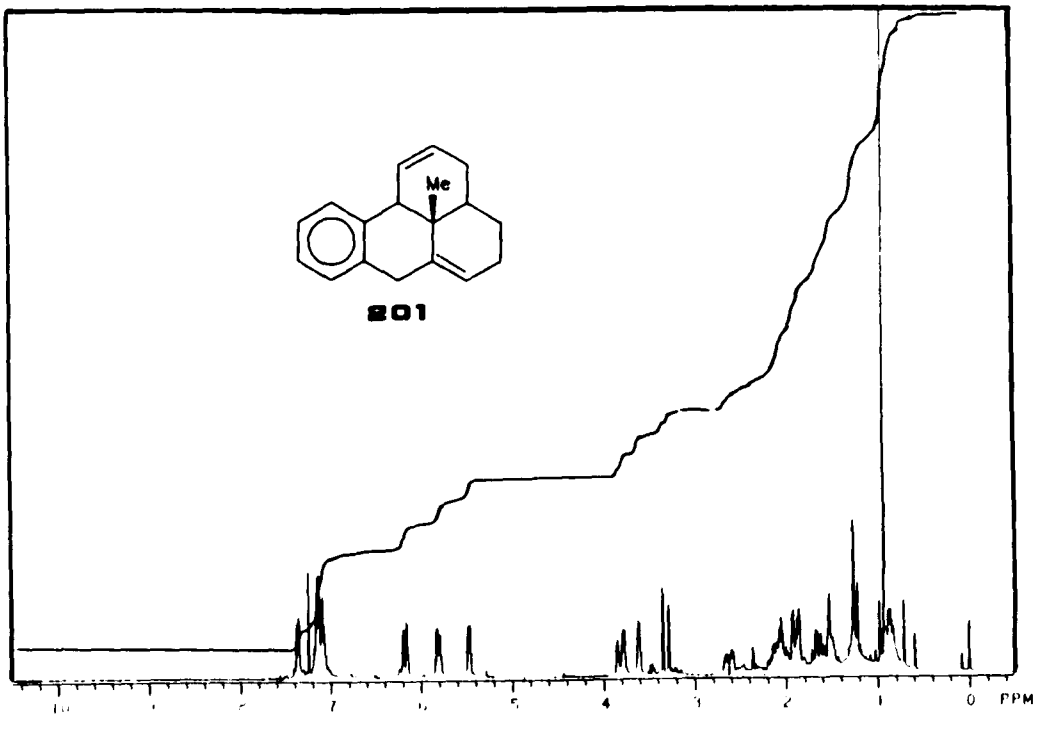

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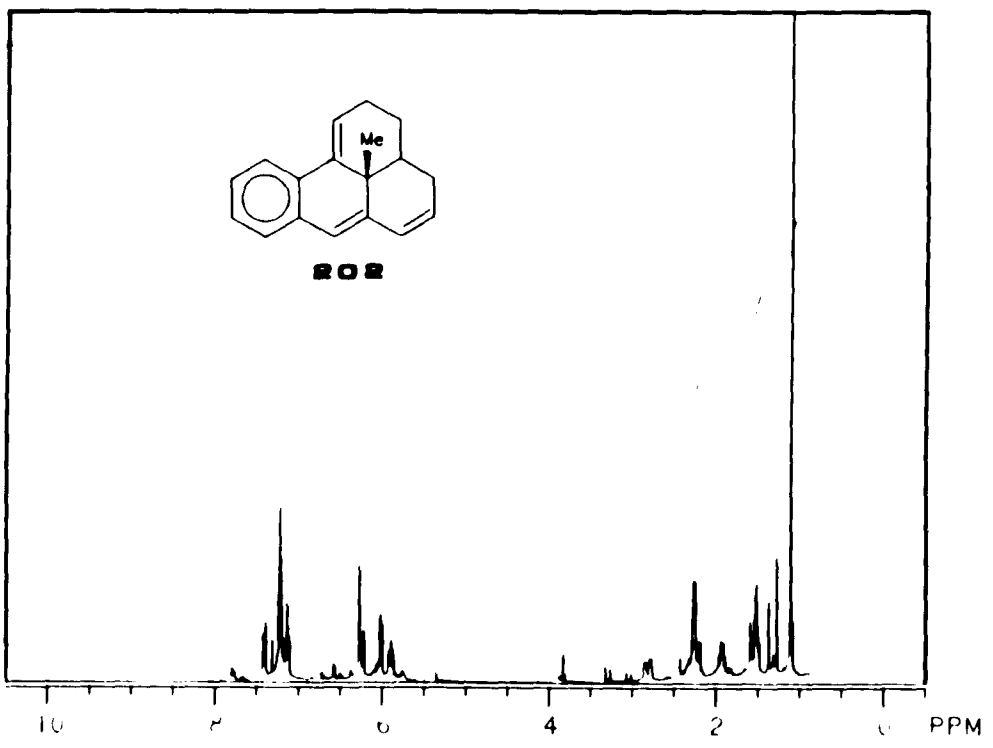
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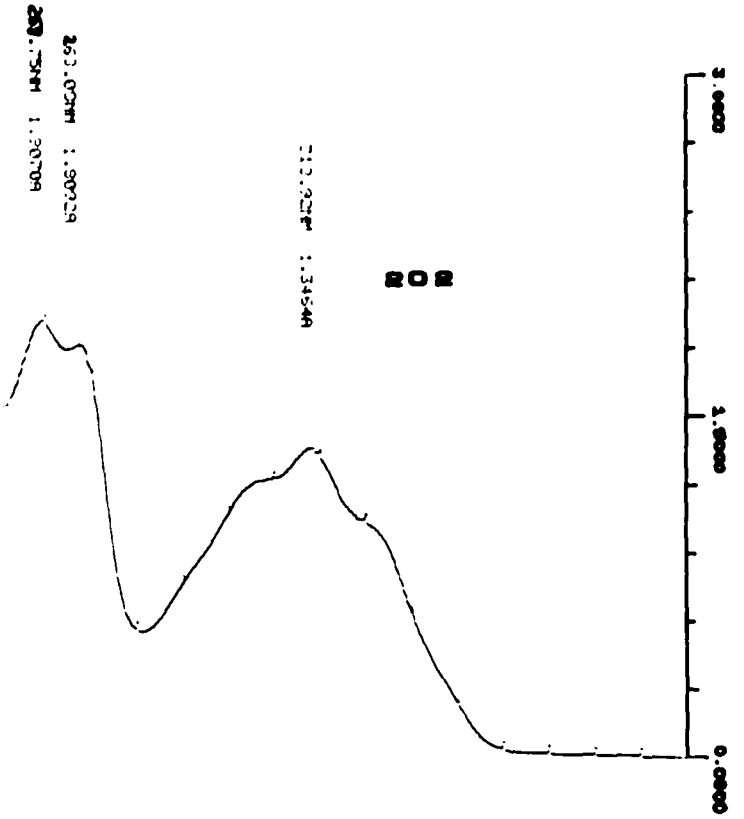
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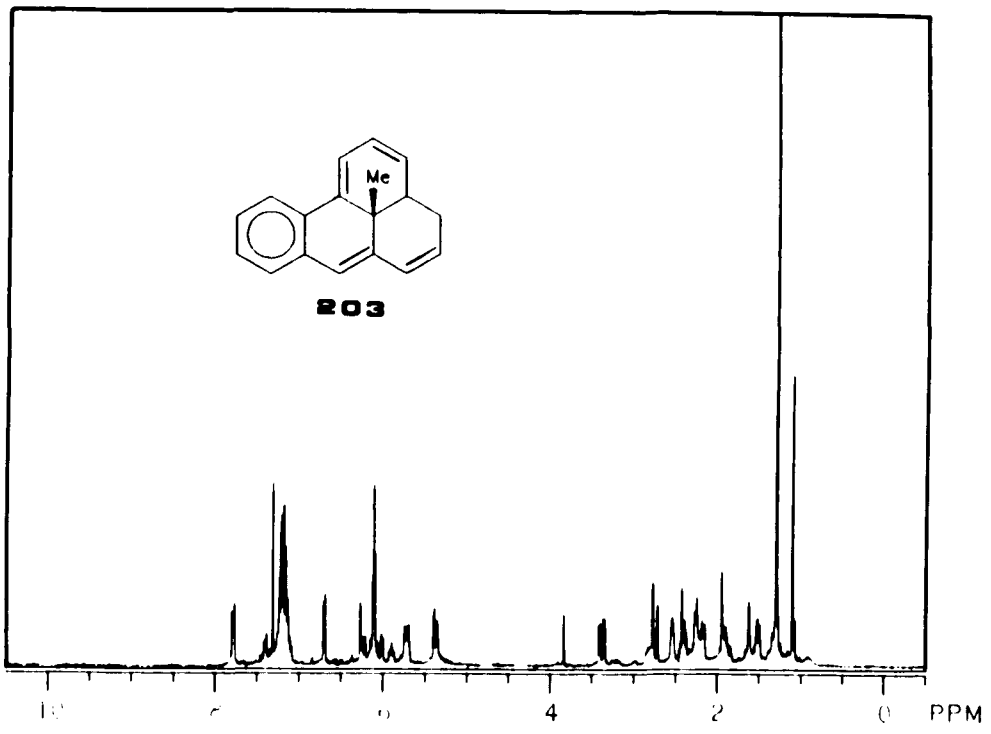
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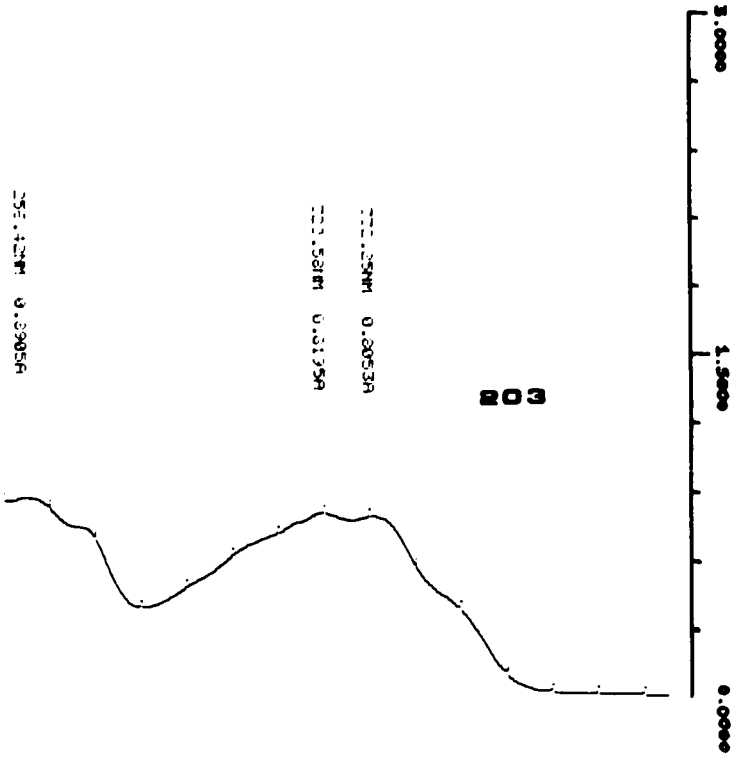
203

APPENDIX B

The crystal data[1] are summarized in Table I. Final atomic parameters, thermal factors, bond lengths, and bond angles are listed in Tables II through V, respectively. The intensity data were measured on an Enraf-Nonius CAD4 diffractometer (graphite-monochromated Cu Kα radiation, w-2θ scans). The size of the crystal used for data collection was approximately 0.11 x 0.24 x 0.50 mm; the data were not corrected for absorption. Of the 2074 independent reflections for $\theta<60°$, 1663 were considered observed [$I>3.0\sigma(I)$].

The structure was solved by a multiple-solution procedure[2] and was refined by full-matrix least squares. One reflection, which was strongly affected by extinction, was excluded from the final refinement and difference map. In the final refinement, the nonhydrogen atoms were refined anisotropically. The hydrogen atoms were included in the structure-factor calculations but their parameters were not refined. The final discrepancy indices are R=0.047 and wR=0.067 for the 1662 observed reflections. The final difference map has no peaks greater than ±0.2 e $Å^{-3}$.

Table I. Crystal Data

Compound	140
Formula	$C_{18}H_{22}O$
Formula weight	254.38
Crystal system	Triclinic
Space group	P1
a	7.473(1)Å
b	9.982(1)Å
c	11.103(1)Å
α	113.31(1)°
β	97.40(1)°
γ	2
d_{calc}	1.206 g cm^{-3}
μ(Cu Kα)	5.2 cm^{-1}

Table II. Final Atomic Parameters[3,4,5] for 140

Atom	x	y	z	B(A2)
O5	0.7531(2)	0.4154(2)	-0.0235(1)	5.35(4)
C1	0.5150(3)	0.3553(2)	0.2368(2)	3.42(4)
C2	0.6526(3)	0.2859(2)	0.2080(2)	4.02(5)
C3	0.8535(3)	0.3764(2)	0.2086(2)	4.67(5)
C4	0.8826(3)	0.5387(2)	0.2196(2)	3.70(4)
C5	0.8246(3)	0.5362(2)	0.0829(2)	3.97(5)
C6	0.8640(3)	0.6946(2)	0.0892(2)	4.97(5)
C7	0.7679(3)	0.7852(2)	0.1886(2)	4.83(5)
C8	0.8148(3)	0.7887(2)	0.3287(2)	4.30(5)
C9	0.7032(3)	0.8726(2)	0.4200(3)	5.56(7)
C10	0.4871(3)	0.7717(2)	0.3761(2)	5.11(6)
C11	0.4505(3)	0.6072(2)	0.3612(2)	4.39(5)
C12	0.5595(2)	0.5253(2)	0.2667(2)	3.28(4)
C13	0.7803(3)	0.6246(2)	0.3195(2)	3.53(4)
C14	0.8682(3)	0.6418(3)	0.4618(2)	5.13(6)
C15	0.6060(4)	0.1291(2)	0.1786(2)	5.89(6)
C16	0.4244(4)	0.0381(2)	0.1748(3)	6.47(7)
C17	0.2875(4)	0.1051(2)	0.2003(2)	5.67(6)
C18	0.3316(3)	0.2607(2)	0.2310(2)	4.35(5)
H3A	0.879	0.313	0.122	5.6
H3B	0.949	0.389	0.288	5.6
H4	1.026	0.600	0.258	4.4
H6A	0.811	0.682	-0.004	6.0
H6B	1.007	0.755	0.121	6.0
H7A	0.624	0.735	0.148	5.8
H7B	0.814	0.896	0.202	5.8
H8	0.957	0.850	0.372	5.2
H9A	0.718	0.973	0.415	6.7
H9B	0.760	0.897	0.516	6.7
H10A	0.426	0.763	0.286	6.1
H10B	0.426	0.825	0.446	6.1
H11A	0.308	0.543	0.322	5.3
H11B	0.495	0.614	0.453	5.3
H12	0.509	0.519	0.176	3.9
H14A	0.805	0.697	0.528	6.2
H14B	0.846	0.535	0.455	6.2
H14C	1.011	0.704	0.492	6.2
H15	0.706	0.081	0.160	7.1
H16	0.393	-0.074	0.154	7.8
H17	0.155	0.040	0.196	6.8
H18	0.230	0.307	0.250	5.2

Table III. Final Anisotropic Thermal Parameters[6]

(U's) for 140

Atom	U(1,1)	U(2,2)	U(3,3)
O5	0.0628(8)	0.0707(7)	0.0589(7)
C1	0.0403(8)	0.0464(7)	0.0481(8)
C2	0.0516(8)	0.0539(7)	0.0621(9)
C3	0.0512(9)	0.0714(8)	0.080 (1)
C4	0.0307(8)	0.0570(8)	0.0583(8)
C5	0.0336(8)	0.0631(8)	0.0626(9)
C6	0.057 (1)	0.0700(9)	0.080 (1)
C7	0.053 (1)	0.0531(8)	0.089 (1)
C8	0.0391(9)	0.0454(8)	0.065 (1)
C9	0.060 (1)	0.046 (1)	0.081 (1)
C10	0.057 (1)	0.0469(9)	0.085 (1)
C11	0.0450(9)	0.0563(9)	0.068 (1)
C12	0.0318(8)	0.0432(7)	0.0492(8)
C13	0.0321(8)	0.0493(8)	0.0489(8)
C14	0.048 (1)	0.084 (1)	0.054 (1)
C15	0.086 (1)	0.0661(9)	0.104 (1)
C16	0.100 (2)	0.0528(9)	0.109 (1)
C17	0.071 (1)	0.055 (1)	0.089 (1)
C18	0.047 (1)	0.0503(8)	0.067 (1)

Atom	U(1,2)	U(1,3)	U(2,3)
O5	0.0191(6)	0.0111(6)	0.0247(6)
C1	0.0149(6)	0.0125(7)	0.0269(5)
C2	0.0249(6)	0.0195(8)	0.0359(6)
C3	0.0347(7)	0.0263(8)	0.0483(7)
C4	0.0155(6)	0.0103(7)	0.0324(6)
C5	0.0167(7)	0.0193(7)	0.0356(6)
C6	0.0210(8)	0.0262(9)	0.0512(7)
C7	0.0170(7)	0.0214(9)	0.0445(7)
C8	0.0060(7)	0.0067(8)	0.0207(7)
C9	0.0123(9)	0.015(1)	0.0134(9)
C10	0.0219(7)	0.0263(9)	0.0207(9)
C11	0.0213(7)	0.0216(8)	0.0274(7)
C12	0.0122(6)	0.0087(7)	0.0228(6)
C13	0.0100(6)	0.0050(7)	0.0240(6)
C14	0.0186(9)	0.0010(9)	0.0319(6)
C15	0.0419(8)	0.041 (1)	0.0556(7)
C16	0.0261(9)	0.041 (1)	0.0497(8)
C17	0.0110(9)	0.030 (1)	0.0385(8)
C18	0.0108(7)	0.0178(8)	0.0299(7)

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(13) Any solvent containing a proton that could interfere in the ^1H NMR analysis was removed this way.

(14) Two equivalents were enough when fresh hydride was used.

(15) This compound must be purified before reduction. Several reductions were tried with impure material resulting in loss of time and hydride.

(16) If the aqueous solution was added too fast, an extremely violent reaction was observed, with ether boiling and foaming at an uncontrollable rate.

(17) T.M. Cresp, M.V. Sargent, and P. Vogel, J. Chem. Soc. Perkin I, 37 (1974).

REFERENCES for APPENDIX B

(1) The structute of 140 was determined by a single-crystal X-ray analysis performed at Hoffmann-LaRoche Inc. by Mr. Louis J. Todaro.

(2) P. Main, S. Fisky, S. Hull, L. Lessinger, G. Germain, J.P. Declercq, M. Woolfson, (1982). MULTAN 11/82. University of York, England and University of Louvain, Belgium.

(3) The parameters of the hydrogen were not defined.

(4) Standard deviations are in parentheses.

(5) Anisotropically defined atoms are given in the form of the isotropic equivalent displacement parameter defined as:

(4/3)*[a2*B(1,1) + b2*B(2,2) + c2*B(3,3) +
ab(cos gamma)*B(1,2) + beta)*B(1,3) +
bc(cos alpha)*B(2,3)]

(6) The form of the anisotropic displacement parameter is:

exp[-2PI2{h2a2U(1,1) + k2b2U(2,2) + 12c2U(3,3) +
2hjabU(1,2) + 2h1acU(1,3) + 2k1bcU(2,3)}]

where a,b,and c are reciprocal lattice constants.