

STUDIES ON NATURAL PRODUCTS

A THESIS SUBMITTED TO THE

GOA UNIVERSITY

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

BY



JOYDEEP BHATTACHARJEE, M.Sc.

GOVT. COLLEGE OF ARTS,
SCIENCE AND COMMERCE.
SANQUELIM, GOA

1993

547

BHA/stw
T-54

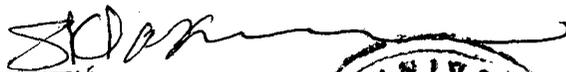
T-054

DEDICATED TO

MY PARENTS

STATEMENT REQUIRED TO BE SUBMITTED UNDER ORDINANCE
19.8 OF THE GOA UNIVERSITY.

No part of this thesis has been submitted for a degree or diploma or other academic award. The literature concerning the problems investigated has been surveyed and all the necessary references are incorporated in the thesis. The experimental work has been carried out independently and due acknowledgement has been made wherever outside facilities have been availed of.


(S.K. Paknikar)

Research Guide




(Joydeep Bhattacharjee)

Candidate

CONTENTS

Acknowledgements.	-----1
General Remarks.	-----3
Chapter - I	
Introduction.	-----5
<u>Section - 1</u>	
Synthesis of Coumarins by transfer of C-3 unit of cinnamic acids onto phenols.	-----7
<u>Section - 2</u>	
Characterisation of some abnormal products in the reaction of some phenols with p-methoxy cinnamic acid.	-----33
<u>Section - 3</u>	
Reinvestigation of the reaction between 2-acetyl-4-methyl phenol and 2-acetyl-5-methyl phenol with hexachloropropene in presence of aluminium chloride.	-----49

Experimental.	-----63
References.	-----106
 Chapter - II	
Introduction.	-----110
 <u>Section - 1</u>	
Reaction of cis-homochrysanthemic acid with lead tetraacetate.	-----112
 <u>Section - 2</u>	
Reaction of maaliol with lead tetraacetate.	-----145
 <u>Section - 3</u>	
Reaction of guaiol with lead tetraacetate.	-----157
Experimental.	-----164
References.	-----203

Chapter - III

Introduction. -----207

Section - 1

An attempted entry into the
Trixane carbon skeleton. -----210

Section - 2

Identity of the hydrocarbon
in the oil of the plant *Acorus calamus* -----220

Section - 3

Comments on the biogenesis
of patchoulenes. -----225

Section - 4

Revision of the structure
of Tanaphillin. -----234

Section - 5

A new biogenetic proposal
for 11-hydroxy jasionone. -----245

Section - 6

Oxidation products of furans :-

Butenolides or furanones. -----252

Section - 7

The decarboxylation step in the

bio-synthesis of Bakuchiol -----270

Experimental. -----286

References. -----293

Summary. -----298

ACKNOWLEDGEMENTS

I consider myself fortunate to have worked under Prof. (Dr.) S.K.Paknikar, Head, Dept. of Chem., Goa University. I am indebted to him for his constant encouragement and revealing discussions during the course of my work. ||

I thank C.S.I.R., New Delhi, for awarding a Research Fellowship and Dr. R. Sengupta, Head, Chemical Oceanographic Division, National Institute of Oceanography for providing facilities and taking keen interest in my work.

I am grateful to my former colleagues at N.I.O., Dr. S.Y.Kamat, Dr. C.G.Naik, Mr. P.S.Parameshwaran, Mrs. B.Das, Dr. (Mrs.) S.Wahidullah, Mrs. L.D'Souza and Mr. H.S.Dalvi for help, advice, critical comments and helpful discussions and to my present colleagues at Govt. College, Sanquelim, Prin. (Dr.) B.A.Gomes, Mr. J.P.P.Pacheco, Mr. Ashok Chodancar, Ms. Roslyn Pereira, Mr. Tensing Rodrigues and Dr. K.S. Muralidhar for taking interest in my work and constantly encouraging me.

I am indebted to my wife Dr. (Mrs.) Jivexa Bhattacharjee without whose help and support in the form of discussions, cheerful company and unstinted motivation, this work would not have been possible.

Thanks are also due to Dr. S.P.Kamat, Dr. V.P.Kamat, Dr. S.G.Tilve, Mr. K.K.Nadkarni, laboratory and office staff of the Goa University for many favours.

Spectral data on samples were obtained by the kind cooperation of late Dr. A.F.Thomas, Dr. A.W.Frahm, Prof. G. Rucker and Prof. R.D.H.Murray and Dr. A.E.Greene. These are gratefully acknowledged.

I am also thankful to Mr. Ramrao Wagh and Mr. Vithal Suctancar for help in word processing.

Finally I would like to thank Mr. K.G.Chitari for neat and prompt tracings and Mr. Fotu Gamas for clean photocopies.

Bhattachajin

GENERAL REMARKS

1. All figure, chart, scheme, table, structure and reference numbers in a chapter refer to that particular chapter only.
2. Organic extracts were dried over anhydrous Na_2SO_4 unless otherwise stated.
3. All melting and boiling points were recorded in degrees celsius and are uncorrected.
4. Petroleum ether refers to the fraction boiling between the range $60^\circ - 80^\circ$.
5. Silica gel used for column chromatography was of 60 - 120 mesh size and was activated at 110° for 5 hours before use.
6. Thin layer chromatography was done on glass plates coated with 0.25 mm. layer of TLC grade silica gel with 13% CaSO_4 as binder. Visualisation of the plates was done by spraying the plates with alcoholic solution of phosphomolybdic acid and warming the plates at 100° for 10 minutes, unless otherwise stated.
7. Spectral data on compounds were mainly obtained through the courtesy of various institutions.

No details of individual instruments are therefore given. These have been suitably acknowledged.

8. The chemical shift parameters in the PMR and ^{13}C MR spectra are expressed in ' δ ' ppm, with TMS as the internal standard. IR absorption bands are expressed in cm^{-1} .
9. All known compounds were identified by direct comparison of spectral data and physical constants reported in literature. Molecular formulae of the compounds were assigned on the basis of the molecular weight as obtained by mass spectrometry.

Introduction

Coumarins or 2H-1-benzopyran-2-ones are widely distributed in the plant kingdom especially in plants of families Umbelliferae and Rutaceae and some are also obtained from micro organisms. They have various structural modifications and the natural coumarins are classified into simple, " furanocoumarins, pyranocoumarins and coumarins substituted in the pyrone ring. Apart from the natural coumarins, there are also a very large number of synthetic coumarins.

Coumarins have a variety of biological functions. Aflatoxins are toxic, dicoumarol is anti-coagulant, furanocoumarins are photosensitizing and coumarin antibiotics such as novobiocin and coumarmycin are known.

Structurally the benzopyrone nucleus can be regarded as a derivative of 2'-hydroxy cinnamic acid, formed by the lactonization of the carboxyl and 2'-hydroxy functions. As such, the simple coumarin nucleus is phenylpropanoid having a C-6 benzene ring linked to a C-3 aliphatic side chain.

It has long been recognized that phenylpropanoids are most commonly derived via the shikimate-chorismate biosynthetic pathway.

The preparation of several coumarins, both natural and synthetic, by the reaction of p-methoxycinnamic acid with various phenols in the presence of polyphosphoric acid is described in the first section of this chapter. The second section deals with the formation of abnormal products during above reaction. The third section is on the reinvestigation of the reaction of certain phenols with hexachloropropene in presence of $AlCl_3$.

CHAPTER-I

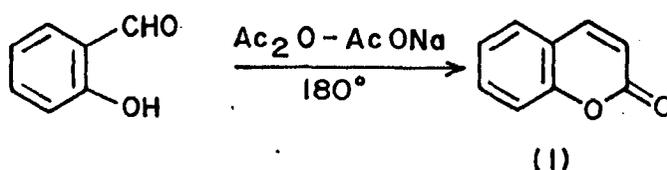
SECTION - I

SYNTHESIS OF COUMARINS BY TRANSFER OF C-3 UNIT OF
CINNAMIC ACIDS ONTO PHENOLS

Total synthesis of many coumarins have been achieved. The key step in many cases has been the formation of the pyrone ring. In some cases, a phenol containing the requisite substituents has been prepared prior to construction of the pyrone ring. In others, the coumarin nucleus has been prepared first and this then modified by steps such as nuclear oxygenation O- and/or C- alkylation and creation of additional rings.

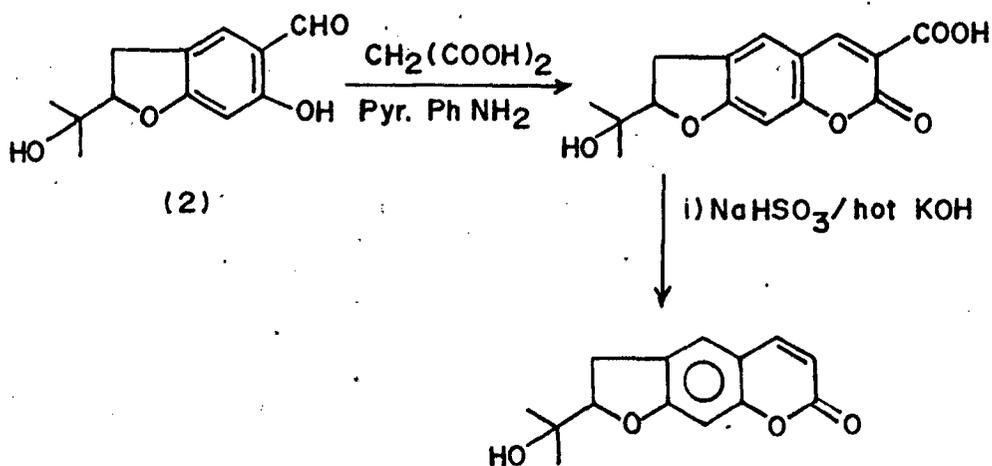
Since this section deals with a method of synthesis of the pyrone nucleus, it would be worthwhile to review the procedures available in literature for obtaining the same.

Many novel approaches have been developed for the formation of the pyrone ring from a suitably substituted phenol since Perkin¹ in 1868 discovered the famous synthesis which is now associated with his name. In Perkin's classical reaction, o-hydroxy benzaldehyde is heated with acetic anhydride and sodium acetate at 180°C to give coumarin (1).

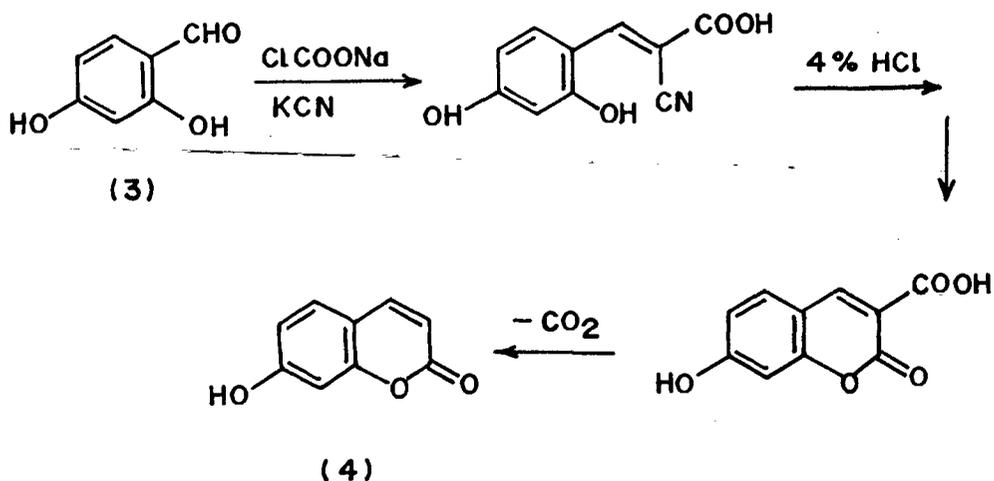


In a modern variation of the Perkin reaction, coumarin (1) was obtained when o-hydroxybenzaldehyde was heated with either 1,1-dimorpholino ethene² or 1-dimethyl amino-1-ethoxy ethene.³

A milder two step method for synthesis of coumarins unsubstituted in the pyrone ring involves condensation of an appropriate o-hydroxy benzaldehyde eg. (2) with malonic acid in the presence of pyridine and aniline at room temperature. This gives the coumarin-3-carboxylic acid, which is then decarboxylated⁴.

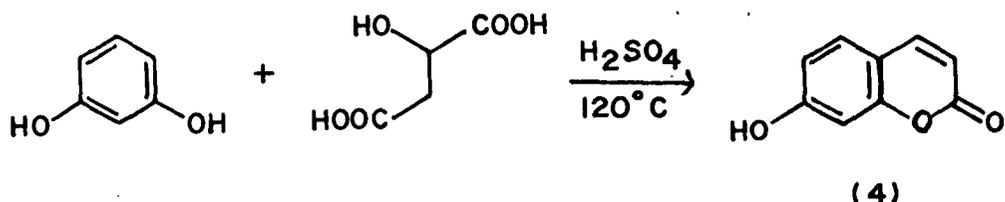


Alternatively a Knoevenagel condensation of the o-hydroxy benzaldehyde with diethyl malonate in hot pyridine gives the corresponding 3-carboethoxy coumarins which on hydrolysis and decarboxylation affords the coumarin in good yields⁵. A related approach was to react the dihydroxy benzaldehyde (3) with the cyanoacetate ion. The condensation product was heated under reflux with HCl to give 7-hydroxy coumarin-3-carboxylic acid which was then decarboxylated⁶.

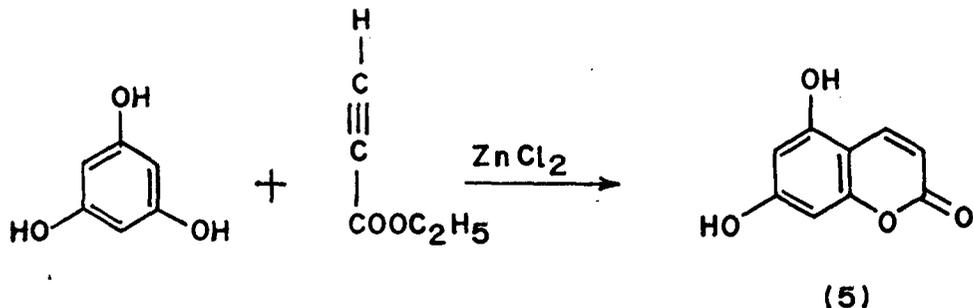


Sixteen years after Perkin reported his synthesis, Pechmann⁷ reported an alternative method in which a phenol is heated with malic acid and

sulphuric acid at about 120°C until gas evolution is complete. eg. the formation of 7-hydroxy coumarin (4) from resorcinol.



Kaufmann and Kelly⁸ found that 5,7-dihydroxy coumarin (5) could be prepared in one step by heating a mixture of phloroglucinol dihydrate, ethyl propynate and zinc chloride.



A related two step process of limited applicability has been developed in which a phenol is condensed with methyl acrylate⁹ or acrylonitrile¹⁰ under dry acidic conditions to give a 3,4-dihydro coumarin from which the coumarin is

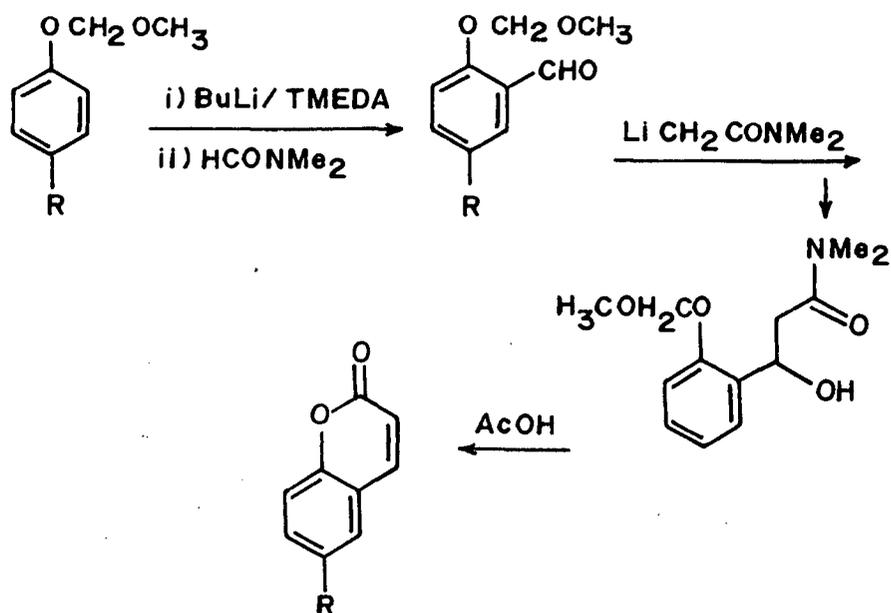
obtained by dehydrogenation over Pd/C in refluxing diphenyl ether.

The synthesis of coumarins by organolithiation reactions^{11, 12, & 13} are of interest because they provide compounds with methoxy substitution patterns not available by the usual acid catalysed methods such as Pechmann condensation.

Lithiation of phenol ethers (such as methyl or methoxy methyl) leads to ortho - lithiated phenols in excellent yields and further with appropriate electrophiles give o-hydroxy aromatic aldehydes which are starting points for many a coumarin synthesis.

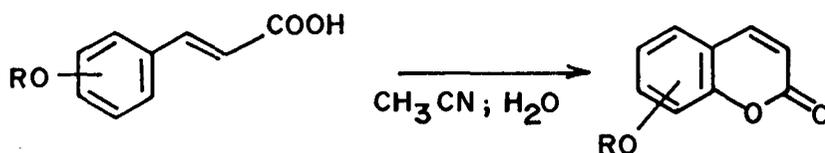
A recent application of this reaction is in the synthesis of polycyclic coumarin compounds with anticarcinogenic properties by Harvey et al¹⁴. This is based on the ortho-directed metallation of methoxy methyl phenyl ethers with alkyl lithium

reagents. Reaction of the ortho-aldehydes with lithio-N,N-dimethyl acetamides affords the addition products which on heating in refluxing acetic acid undergo smooth conversion to the coumarins.



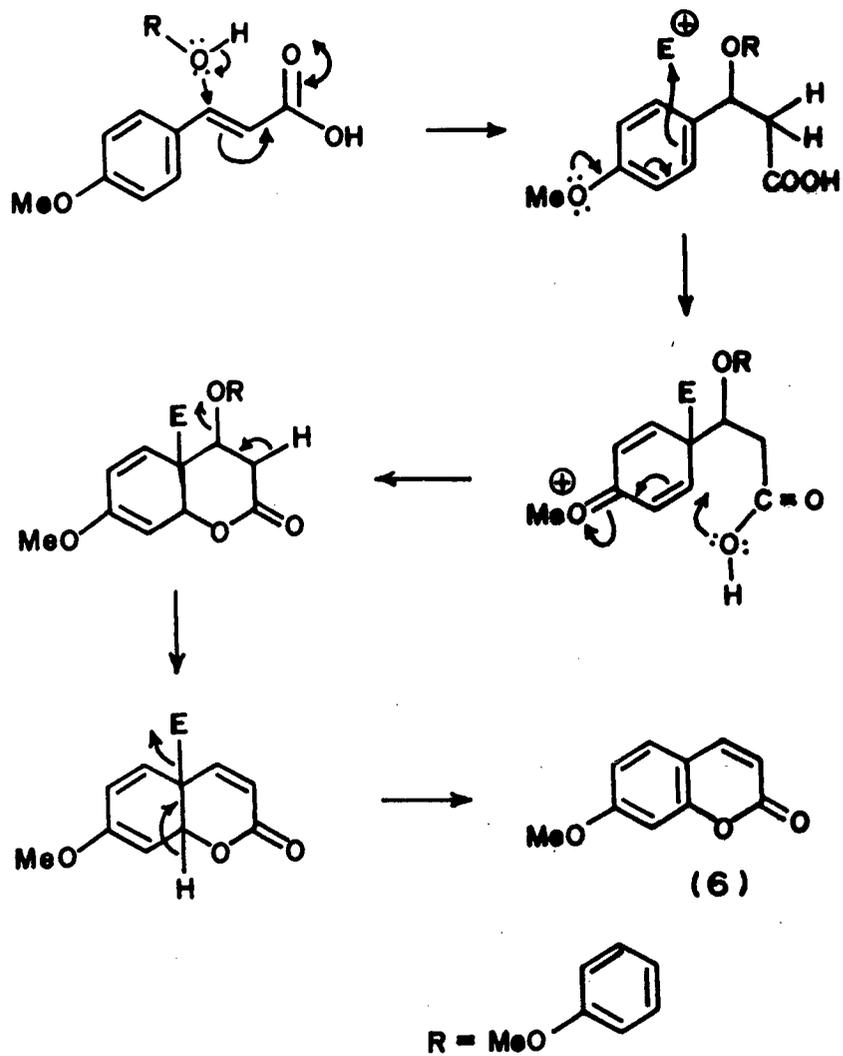
Panetta and Rapoport¹⁵ have synthesised 8-methoxy coumarin by treatment of guaiacol with triethyl orthoacrylate. Claisen rearrangement of the ether leads to the dihydro coumarin diethyl ketal which on hydrolysis and subsequent cyclization furnishes the 8-methoxy-3,4-dihydro coumarin which is dehydrogenated to 8-methoxy coumarin.

Yet another method pyrone ring formation in coumarins involves the single electron initiated photocyclization of substituted coumaric acids to the corresponding coumarins¹⁶.



Present study

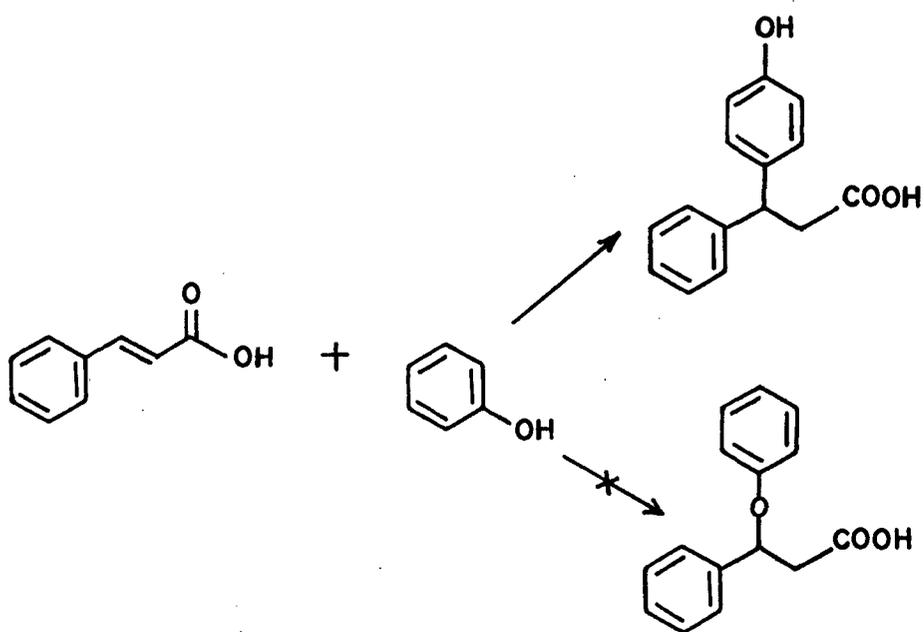
Ongoing research work in our laboratory on the reaction of phenols with acids in presence of polyphosphoric acid¹⁷ drew our attention to a report by Talapatra et al¹⁸. This report details the formation of 7-methoxy coumarin (6) during the reaction of p-methoxy cinnamic acid with resorcinol mono methyl ether in presence of polyphosphoric acid (PPA). These authors visualised an oxidative biogenetic type self-condensation of p-methoxy cinnamic acid to 7-methoxy coumarin. The mechanism proposed by the above authors (Scheme 1) bears a



Scheme - 1

close analogy to the biogenesis of 7-methoxy coumarin from p-methoxy cinnamic acid¹⁹.

The scheme albeit attractive was considered improbable by us due to various reasons. Previous experiments in our laboratory²⁰, on the reactions of phenol with cinnamic acid in presence of PPA led us to observe that phenol does not add across the double bond of cinnamic acid through the oxygen atom, but it adds through the carbon atom para to the phenolic hydroxyl group leading to β,β -diaryl propanoic acid.

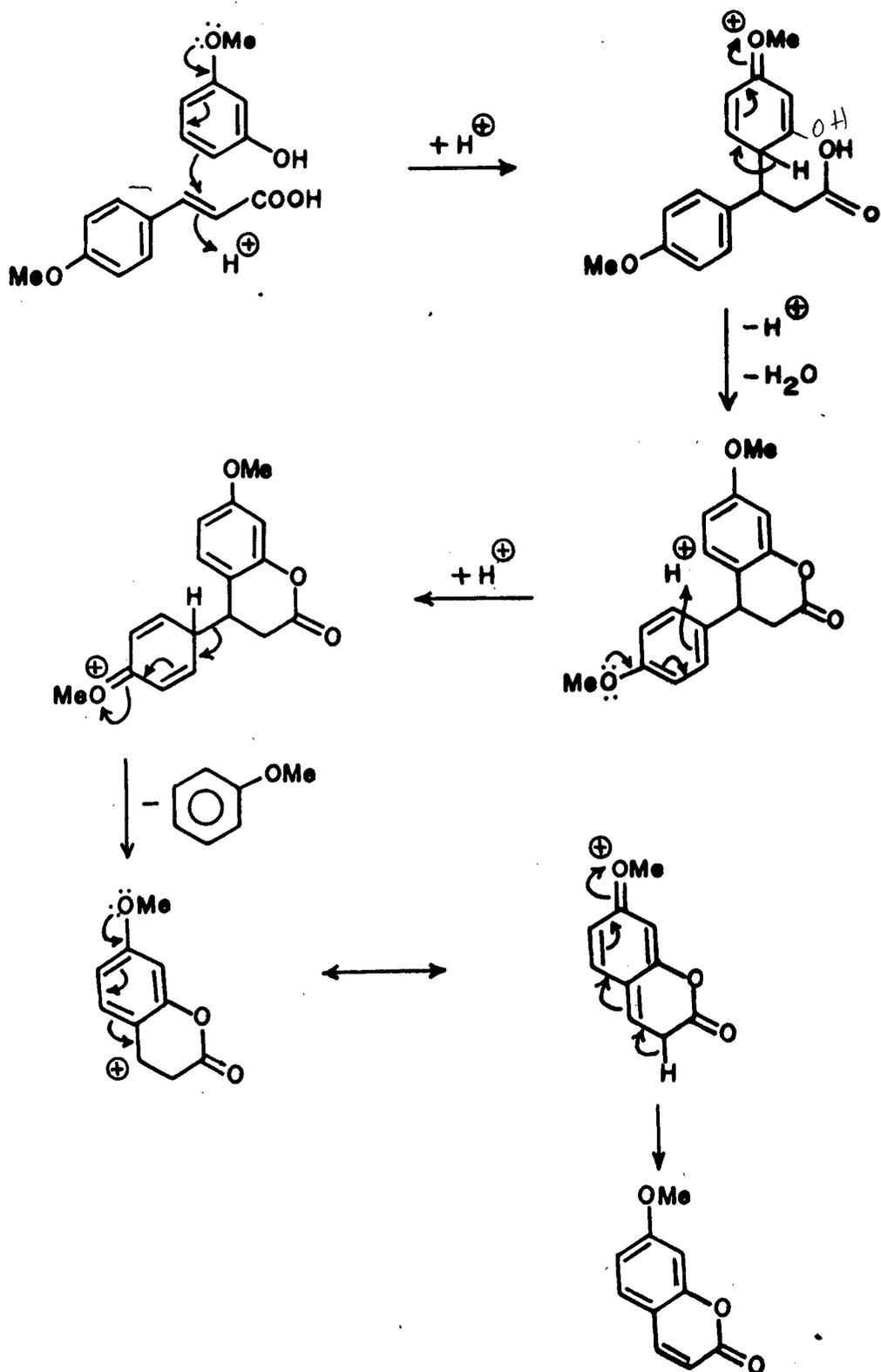


In other words, in the reaction of phenol with cinnamic acid in presence of PPA, C-alkylation of phenol predominates almost exclusively over O-alkylation. Although this observation was made in the case of simple phenol, there is no reason why other phenols should behave differently under similar conditions.

In light of the above, it seemed worthwhile to reinvestigate the above reaction, in order to delineate the actual mechanism. Theoretically, an alternative mechanism can be deemed to be operating. This alternative mechanism²¹ is depicted in Scheme 2.

The most noteworthy feature of this mechanism is that it envisages the fact that the aromatic ring of the coumarin originates (in this particular reaction) from the phenol and the remaining three carbon atoms of the heteroaromatic ring comes from the cinnamic acid. In other words, it is a transfer of C-3 unit from the cinnamic acid onto the C-6 unit of the phenol in presence of PPA.

Confirmation of this mechanism then consisted



Scheme - 2

(6)

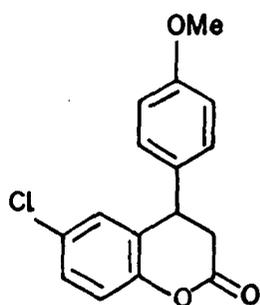
in labelling the phenolic hydroxyl group and confirming its presence in the coumarin formed as the ring oxygen. The simpler way to prove the mechanism is to simply repeating the reaction using conditions identical to those used by Talapatra and co-workers¹⁸, but with different phenols and different cinnamic acids and identifying the coumarin formed in each case.

From our results, tabulated in Table 1, it is evident that the aromatic ring of the cinnamic acid gets eliminated during the reaction leaving the C-3 unit with the phenol used, giving the corresponding coumarins. This observation is supported by the fact that reactions of resorcinol monomethyl ether with p-methoxy cinnamic acid, ferulic acid (3-methoxy-4-hydroxy cinnamic acid) and 3,4-dimethoxy cinnamic acid (entries 1,2 & 3 respectively, Table 1) gave 7-methoxy coumarin in each case rather than 6-methoxy,7-hydroxy coumarin (isoscopoletin) and 6,7-dimethoxy coumarin (scoparone) respectively in the latter two cases, which would have been the product, had the earlier mechanism been operative.

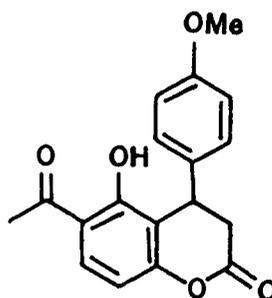
TABLE - 1

No.	PHENOL	CINNAMIC ACID	PRODUCT	M.P. (lit)	YIELD %
1.	Resorcinol mono methyl ether	p-methoxy-	6	118(118)	60
2.	--do--	Ferulic acid	6	--do--	55
3.	--do--	3,4-dimethoxy-	6	--do--	56
4.	P-chlorophenol	p-methoxy-	7	130	40
5.	Resacetophenone	-do-	8	173	30
6.	3,4-methylenedioxy	-do-	23	231(231)	45
7.	3,4,5-trimethoxy-	-do-	24	72(74)	55
8.	3,5-dimethoxy-	-do-	25	150(146)	50
9.	3,4-dimethoxy-	-do-	26	145(144)	55
10.	2-hydroxy-3,5-dimethoxy-	-do-	27	150(149)	50
11.	Orcinol	-do-	13 14	246(246) 215(dec)total	50
12.	1-naphthol	-do-	15	140(141)	35
13.	2-naphthol	-do-	16	118(118)	35
14.	1-bromo-2-naphthol	-do-	16	118	40
15.	2-phenyl-	-do-	--	--	--
16.	2,4-dimethoxy-	-do-	--	--	--

The intermediacy of the 4-aryl-3,4-dihydro coumarin system in the above reaction can be inferred from the isolation of 6-chloro-4-(4'-methoxy phenyl)-3,4-dihydro coumarin (7) from the reaction of p-chlorophenol and 6-acetoxy,5-hydroxy-4-(4'-methoxy phenyl)-3,4-dihydro coumarin (8) from the reaction of resacetophenone with p-methoxy cinnamic acid respectively (entries 4 & 5, Table 1).

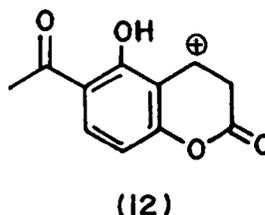
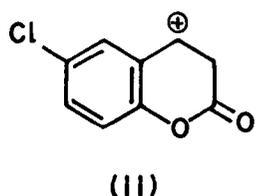
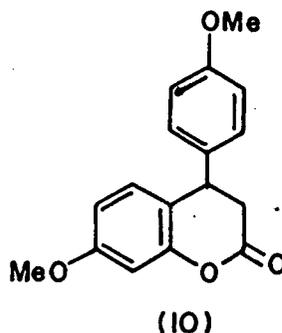
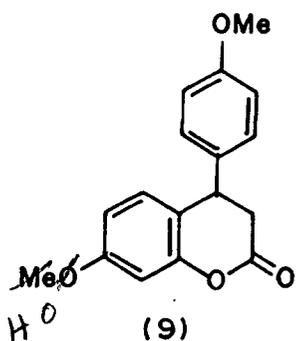


(7)



(8)

Talapatra and co-workers had in fact isolated 7-hydroxy-4-(4'-methoxyphenyl)-3,4-dihydro coumarin (9) and the corresponding 7-methoxy derivative (10) from the reaction of resorcinol and its monomethyl ether respectively with p-methoxy cinnamic acid



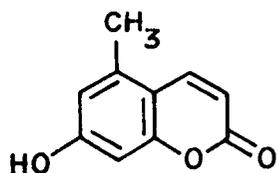
under shorter reaction periods. Our efforts to isolate similar intermediates from the reaction of phloroglucinol dimethyl ether and p-methoxy cinnamic acid, however were unsuccessful. The reaction could not be stopped at the appropriate stage and only the corresponding 5,7-dimethoxy coumarin could be isolated.

The isolation of the intermediates from reactions of phenols having electron withdrawing substituents in the para-position to the phenolic group (eg. p-chloro phenol and resacetophenone) can be explained due to the non formation of carbocations of the type (11 & 12) since the

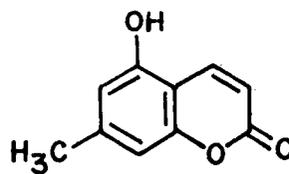
position of the electron withdrawing substituents preclude the stabilization of the cations.

An electron donating substituent eg. methoxyl at the meta position to the phenol appears to be beneficial to the course of the reaction. Such a substituent facilitates initial alkylation of the phenol at the ortho position to the phenolic hydroxyl (and para to itself). Also the same group appears at 7-position of the coumarin nucleus and aids in stabilisation of the intermediate cations during loss of the aryl group at the 4-position (see Scheme 2).

This observation is borne out by the fact that reactions with such phenols (those having electron donating function in meta position to phenolic hydroxyl) give a higher yield of the corresponding coumarin than other phenols (entries 1, 6, 7, 8, 9, 10 & 11, Table 1). In the case of orcinol (entry 11, Table 1), a mixture of two coumarin⁵ 5-methyl-7-hydroxy coumarin (13) and 5-hydroxy-7-methyl coumarin (14). This is due to the simultaneous



(13)

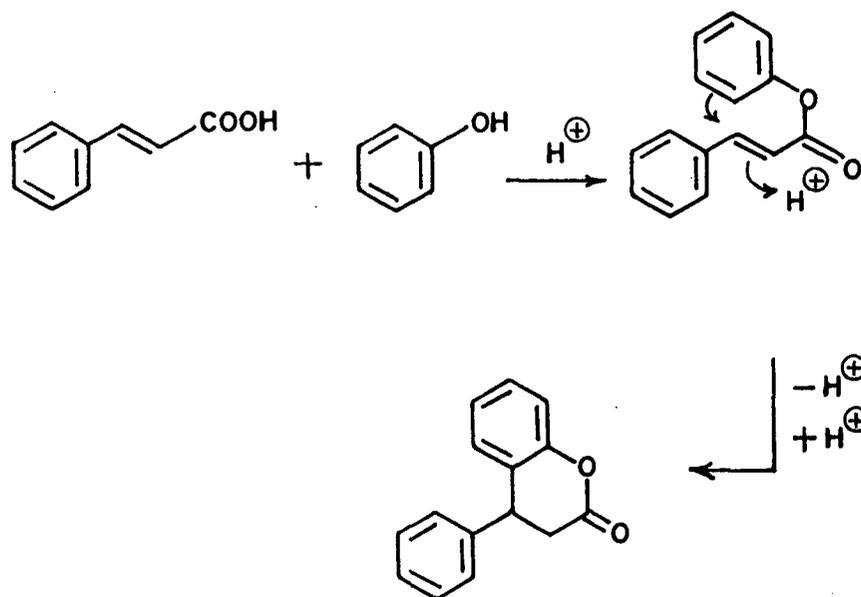


(14)

reactivity of orcinol at α and γ position. This was also observed earlier in the case of Friedel-Crafts²² and Pechmann reactions²³ of orcinol. The fact that (13 and 14) are obtained in the ratio of 4:1 leads support to our observation that there is participation of the electron donating substituent (in this case hydroxyl group) meta to the phenolic hydroxyl. *not clear*

An electron donating group (eg. methoxyl or hydroxyl) at the para position of the cinnamic acid also facilitates the reaction by assisting in the loss of the aryl group in the final step. In other words, reactions with cinnamic acid itself, should result in isolation of the intermediates, without the loss of the aryl group.

Reactions of phenols, thiophenols and anilines with cinnamic acids to give coumarins, thiacoumarins and carbostyrils respectively was earlier reported by Maniraman et al^{24, 25}. These authors used the method of Israeltam and Simpson²⁶ to obtain the 4-aryl-3,4-dihydro coumarin system, by reaction of phenols and cinnamic acid in presence of sulphuric acid. Presumably the phenyl cinnamate initially formed undergoes intramolecular cyclisation to the dihydro coumarin system. The



above authors have obtained the corresponding coumarins from the above reaction by treating the intermediate dihydro coumarin with $AlCl_3$ in refluxing chlorobenzene when the 4-aryl group is lost furnishing the coumarins.

Although this reaction is analogous to the method which we have developed, the significant difference is that, in the PPA reaction, there is concomitant dearylation leading to the coumarin in a single one-pot reaction whereas in the sulphuric acid reaction, the intermediate has to be treated subsequently with $AlCl_3$ to enforce dearylation. e ||

We presume that the acid catalysts used (H_2SO_4 or PPA) do not play any significant role in dearylation. Rather it seems that presence or absence of an electron donating substituent para to the cinnamic acid is a far more important factor. It would be safe to assume that in the reaction with sulphuric acid, if one uses p-methoxy cinnamic acid instead of simple cinnamic acid, one might end up with the corresponding coumarin instead of the intermediate 4-aryl-3,4-dihydro coumarins. We have

tried to substitute PPA with $\text{BF}_3/\text{Et}_2\text{O}$ as the acid catalyst in order to overcome some of the inherent problems in handling PPA. In the reaction of resorcinol mono methyl ether with p-methoxy cinnamic acid in presence of $\text{BF}_3/\text{Et}_2\text{O}$, we did obtain 7-methoxy coumarin but since the yields were not encouraging, the reaction was not investigated further. But this does confirm our assumption that it should be possible to synthesise coumarins from phenols and p-methoxy cinnamic acid by using many different acid catalysts rather than only PPA.

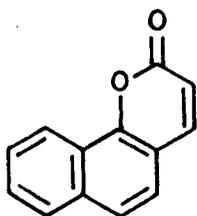
Most naturally occurring coumarins (in fact all but 35) have an oxygen functionality at the C-7 position. Since we have already stated that a meta-oxygen functionality in the phenol assists the reaction, and this functionality appears at the C-7 position in the coumarin nucleus, this method (PPA method) is a good general method for the synthesis of several naturally occurring coumarins. In fact, we have synthesised several natural coumarins by this method by using the appropriate phenols in their reaction with p-methoxy cinnamic acid. These

|| ?
where is
(35) ?

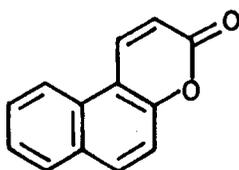
occurring

coumarins are 7-methoxy coumarin (herniarin)(6), 6,7-methylenedioxy coumarin (ayapin)(23), 5,6,7-trimethoxy coumarin(24), 5,7-dimethoxy coumarin (limmetin, citropten)(25), 6,7-dimethoxy coumarin (scopàrone)(26) and 5,7-dimethoxy-8-hydroxy coumarin (leptodactylone)(27) [entries 1,6,7,8,9 & 10 respectively, Table 1].

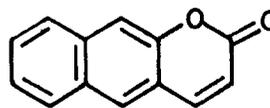
Among other phenols tried were α - and β -naphthols (entries 12 & 13, Table 1). α -Naphthol affords 7,8-benzo coumarin (15) whereas in the case of β -naphthol, the angular 5,6-benzocoumarin (16) rather than the 6,7-benzo coumarin (17) is obtained. This is explained by the fact that in 2-naphthols, the 1-position is more reactive and



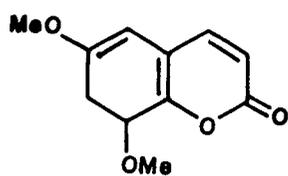
(15)



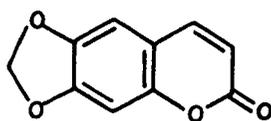
(16)



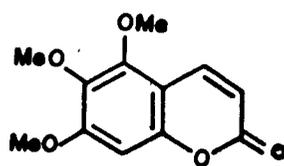
(17)



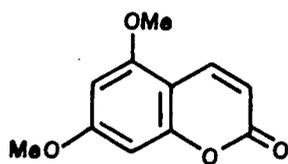
(22)



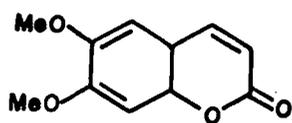
(23)



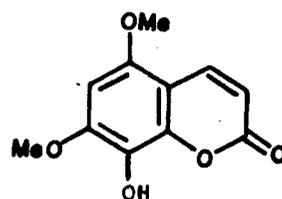
(24)



(25)

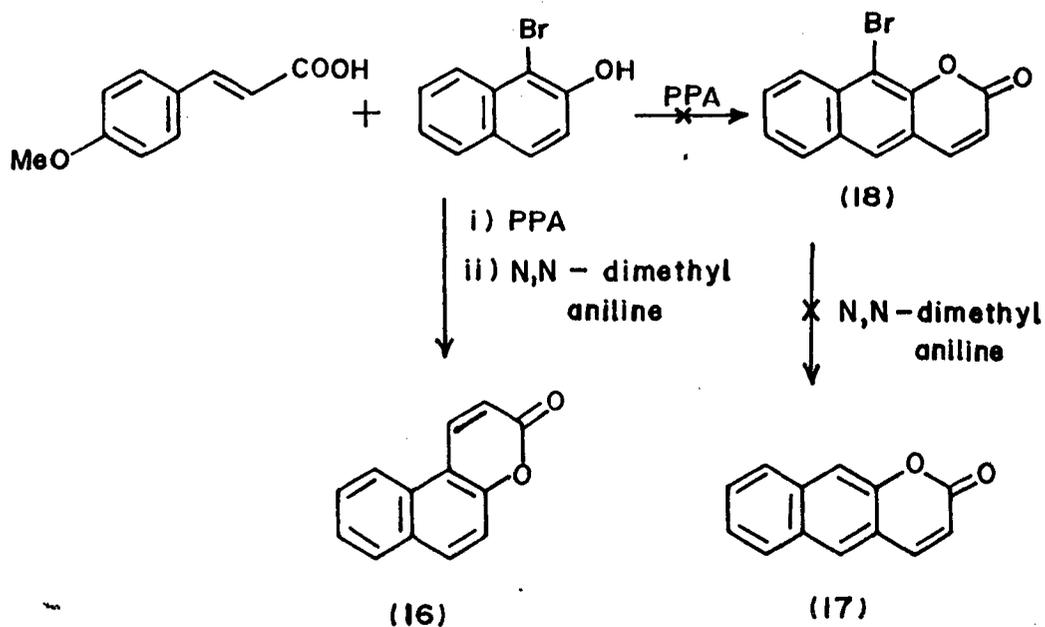


(26)



(27)

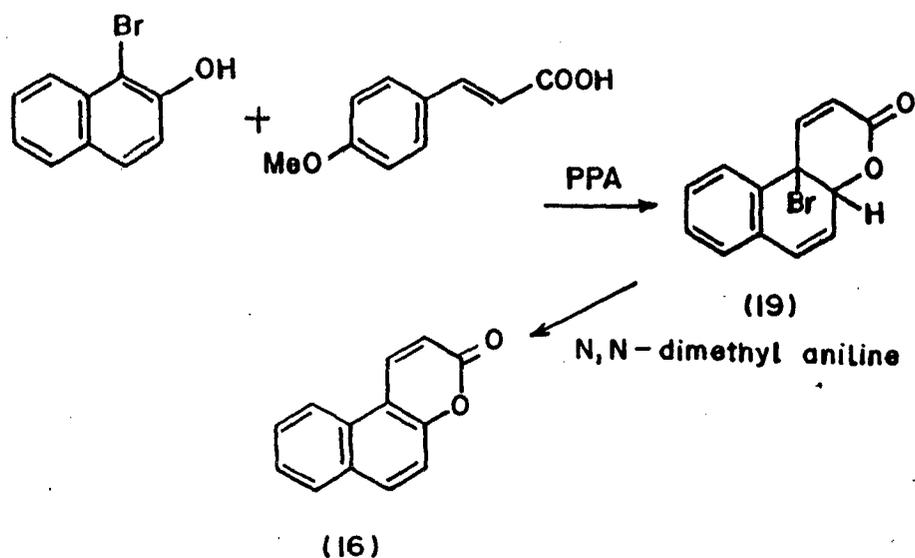
therefore alkylation takes place at the position preferentially. Efforts were made to synthesise the linear isomer (17) by blocking the 1-position of 2-naphthol by bromination and then using the 1-bromo-2-naphthol for the reaction (entry 14, Table 1). It was thought that bromine could be removed from the 8-bromo-6,7-benzocoumarin (18) by refluxing with N,N-dimethyl aniline according to the procedure of Ahluwalia and co-workers²⁷. It was indeed surprising to note that after carrying out all these steps, the final product was identified as



the angular 5,6-benzo coumarin (16) and not (17).

The formation of (16) and not (17) in the above reaction can be explained in two ways. Either initial alkylation of 1-bromo-2-naphthol takes place at the 1-position itself with removal of bromine at the first step, which would then lead to (16) by the usual route. The other possible route is that an intermediate of the type (19) could be involved which loses HBr during reflux with N,N-dimethyl aniline to furnish (16).

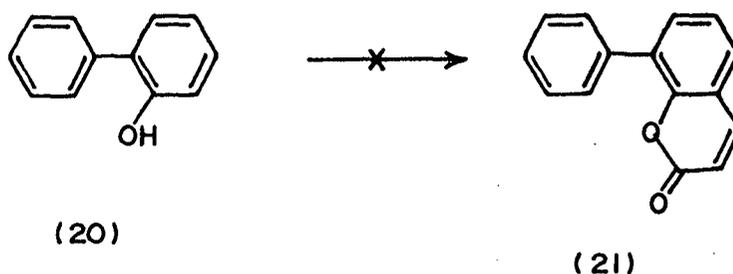
Since we did not characterize the intermediate (19), it is difficult to conclude with certainty which of the above routes ~~are~~ operative. It may be



noted that when we refluxed 1-bromo-2-naphthol

with N,N-dimethyl aniline, the product was β -naphthol.

Among the limitations of this method is that it seems to succeed only with more activated phenols. An example is that of 2-phenyl phenol (20) [entry 15, Table 1] which failed to give the required 8-phenyl coumarin (21).



2,4-Dimethoxy phenol : . [entry 16, Table 1] also failed to give the 6,8-dimethoxy coumarin (22).

From the above results, it seems obvious that the ideal situation for this reaction is an electron donating substituent in the meta position to the phenolic hydroxyl, which directs alkylation at the para position to itself and ortho to the

hydroxyl. Thus cyclisation can then take place leading to coumarins. Therefore alkylation takes place at the para position to the electron donating substituent if it is vacant. In the absence of such groups, alkylation takes place at the para position to the phenolic hydroxyl which cannot cyclise to coumarins.

Due to the strong acidic conditions of the reaction, any phenol which is sensitive to acids cannot be used.

In conclusion it may be said that this method is a good method for the synthesis of 7-oxygenated coumarins in general and certain other coumarins. The method is a single step reaction and is simple to carry out and does not ^{require} any special chemicals or glassware. The yields are however low as compared to some of the more modern methods.

Some of the abnormal products obtained in this reaction are discussed in the next section.

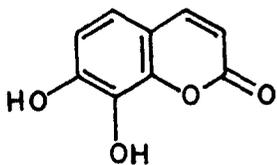
CHAPTER - I

SECTION - II

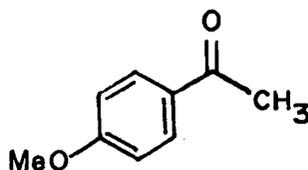
CHARACTERISATION OF SOME ABNORMAL PRODUCTS IN THE
REACTION OF SOME PHENOLS WITH P-METHOXY CINNAMIC
ACID

Towards the end of the earlier section, we have referred to some abnormal products in the reaction of phenols with p-methoxy cinnamic acid in the presence of PPA. The reactions discussed in this section refer to those cases where the normal expected coumarin was not obtained.

The first case was observed in the reaction of pyrogallol with p-methoxycinnamic acid. We expected the formation of 7,8-dihydroxy coumarin (28). No coumarin could be characterized from the above reaction. However, routine analysis of the different fractions obtained through column chromatography of the reaction product led to the identification of one of the products as p-methoxy acetophenone (29).



(28)



(29)

The formation of this compound was indeed intriguing. Obviously, the phenol (pyrogallol) used in the reaction is not responsible for the formation. The only other plausible explanation is that it is obtained in some way from the p-methoxy cinnamic acid used.

A literature survey on the behaviour of p-methoxy cinnamic acid in PPA showed that it sometimes formed p-methoxy cinnamic anhydride under the above conditions. This was the observation of Talapatra and co-workers¹⁸ whose work we have referred to earlier in the first section. These authors have observed that in the presence of phloroglucinol, p-methoxy cinnamic acid underwent self dimerization with the elimination of water to form p-methoxy cinnamic anhydride, under the standard experimental conditions. (PPA, 70°C, 4 hrs.).

It would be thus reasonable to assume that in the reaction of p-methoxy cinnamic acid in presence of pyrogallol also forms p-methoxy cinnamic anhydride. Thus, what remains to be explained was

the conversion of p-methoxy cinnamic anhydride to p-methoxy acetophenone.

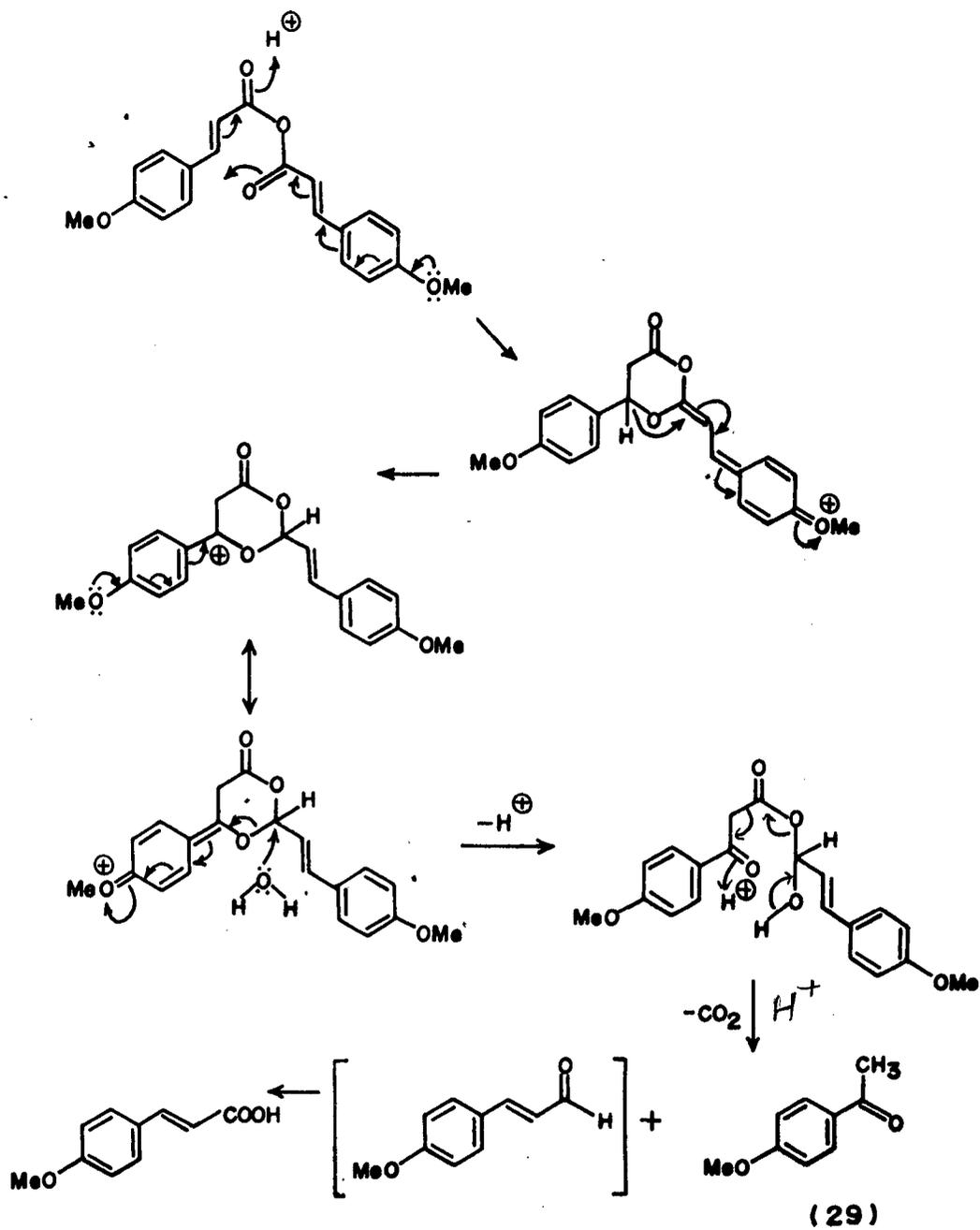
The pathway which we believe to be operating is shown in Scheme - 3. The other product as can be seen is p-methoxy cinnamaldehyde which is further oxidised to p-methoxy cinnamic acid which was always isolated from the reaction mixture whether the reaction proceeds normally or not (some p-methoxy cinnamic acid always remains unreacted).

The question remains as to why only in the case of highly reactive phenols eg. pyrogallol and phloroglucinol does p-methoxy cinnamic acid form its anhydride.

The next two cases are those in which products obtained show a selective loss of a hydroxy group from the starting phenol.

The first of the two cases deals with the reaction of guaiacol with p-methoxy cinnamic acid. The expected 8-methoxy coumarin is not obtained. However, a solid was obtained instead which had the following physical characteristics.

M.P. 130°C



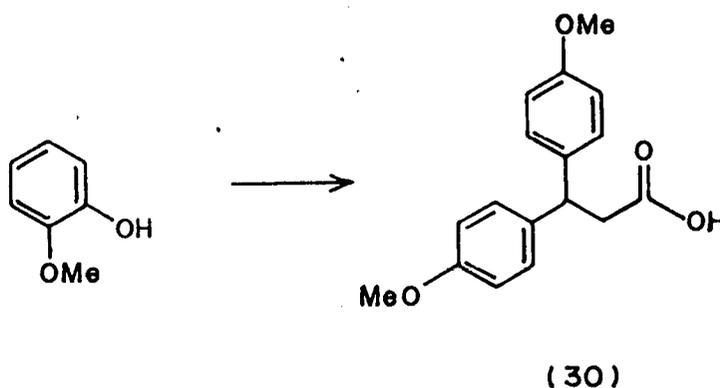
Scheme - 3

IR, λ_{\max} , 3600-3200, 3000, 1670, 1580, 1525, 1475, 1420, 1390, 1300, 1226, 1190, 1120, 1025, 850.

PMR (CDCl_3) 3.01 & 3.04 (d, 2H, $-\text{CH}_2$); 3.77(s, 6H, $-\text{OCH}_3$); 4.41 - 4.48 (t, 1H, $-\text{CH}$); 6.81 & 6.84 (d, 4H, aromatic protons); 7.12 & 7.16 (d, 4H, aromatic protons); 10 (br. s, $-\text{COOH}$)

Mass 286.12 (M^+); 227.10 (100%); 197.06; 168.05; 141.06; 113.55; 77.03.

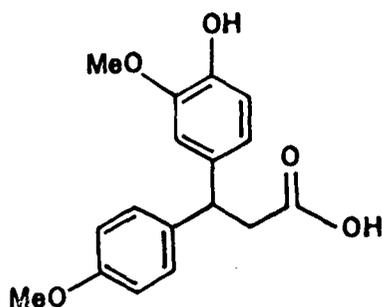
From the above data, the structure of the compound was deduced to be the acid^{*} (30).



The formation of compound (30) is explained in Scheme - 4. In this case, alkylation of the phenol takes place para to the phenolic hydroxyl. This is

* Formation of (30) amounts to conjugate addition of anisole to p-methoxy cinnamic acid.

followed by a) hydride transfer. The molecule receiving the hydride ion goes on to furnish (30) by the mechanism shown. The other molecule gives the expected product (31) with the hydroxy group intact.

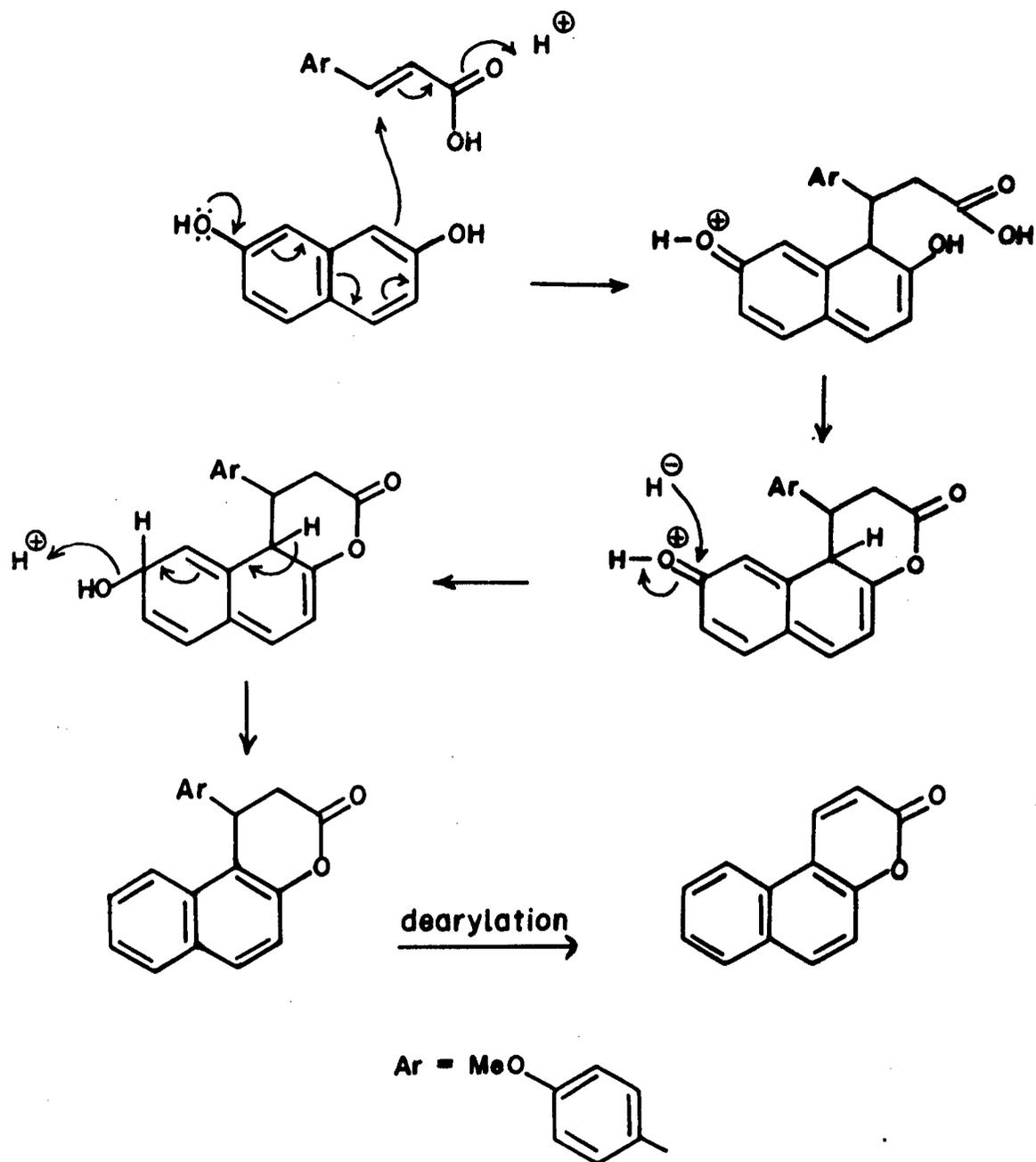


(31)

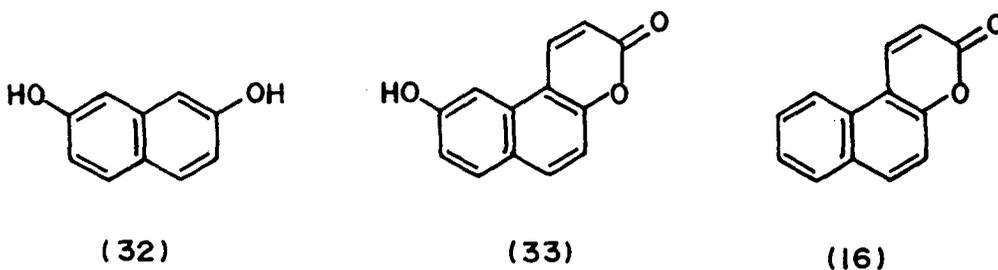
The presence of this product can be seen in traces in the mass spectrum of (30) [peaks at m/z 302.11 and 243.10].

The second case in which dehydroxylation was observed occurs in the reaction of 2,7-dihydroxy naphthalene (32) with *p*-methoxy cinnamic acid. Instead of the expected compound (33) 5,6-benzocoumarin (16) is formed in this reaction..

The formation of 5,6-benzo coumarin is explained in Scheme - 5. Hydride transfer from PPA

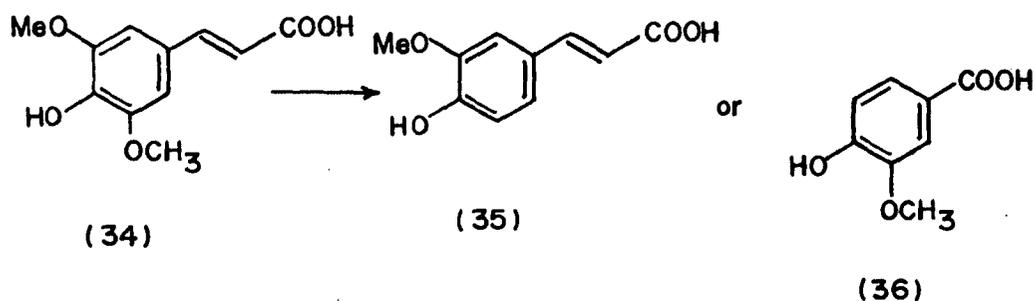


Scheme - 5

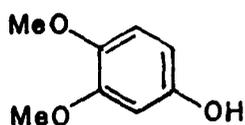


to the phenol assists in the initial alkylation of the phenol. The hydroxyl group is lost and the 5,6-benzocoumarin is obtained in the usual manner by dearylation of the intermediate 4-aryl-3,4-dihydrocoumarin.

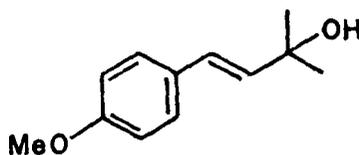
This loss of a hydroxyl group also occurs in nature eg. the conversion of sinapic acid (34) to ferulic acid (35) or vanillic acid (36) in *Hordeum*, *Oryza* and *Triticum*²⁸ species.



The last case of abnormal products being obtained is in the reaction of 3,4-dimethoxy phenol (37) and the tertiary alcohol (38) obtained from p-methoxy cinnamic acid methyl ester by a Grignard reaction.



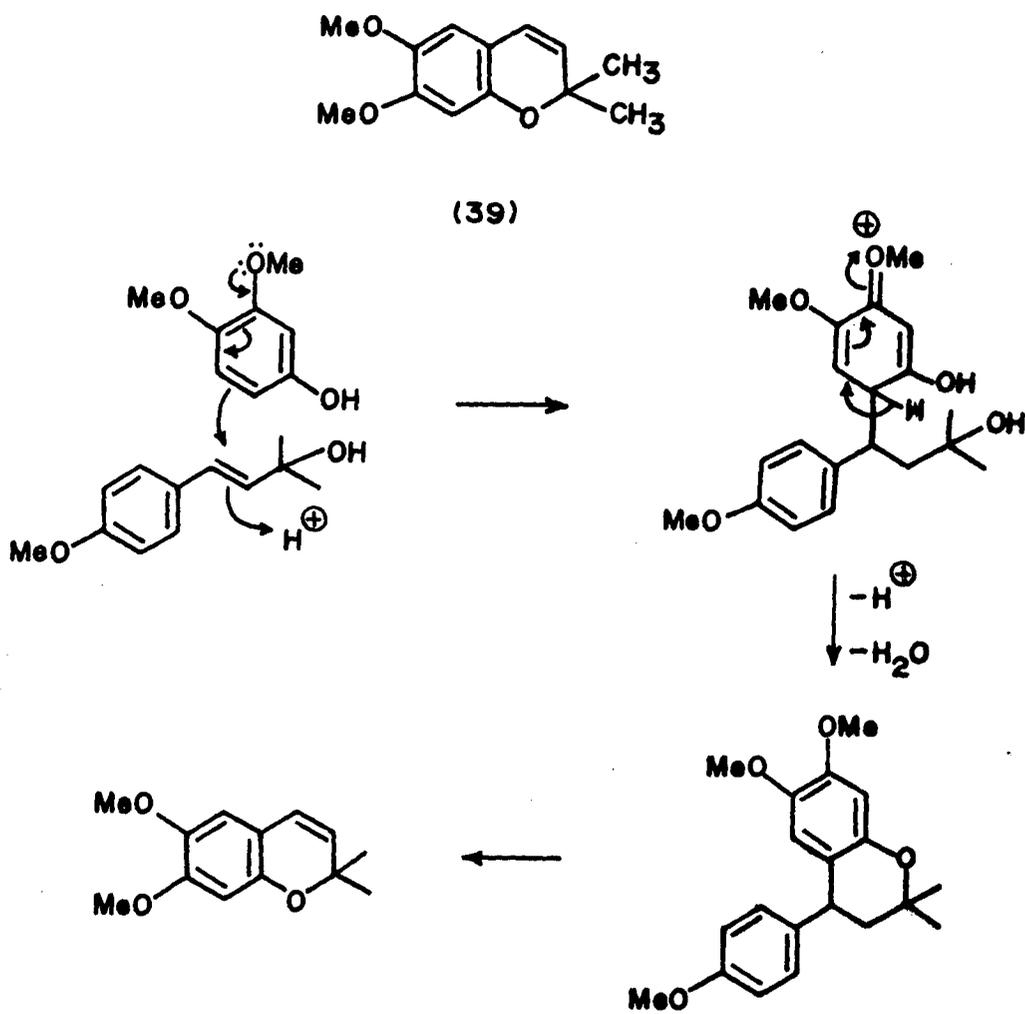
(37)



(38)

We were interested in synthesising the insecticide Precocene II (39) by a reaction similar to the one used to synthesize coumarins. Scheme - 6. Precocenes are compounds which have juvenile hormone activity. The above method would have been a simple single step synthesis of the compound.

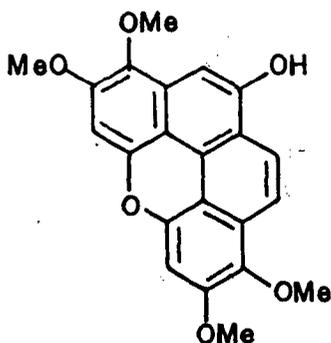
However no compound resembling Precocene II in



Scheme - 6

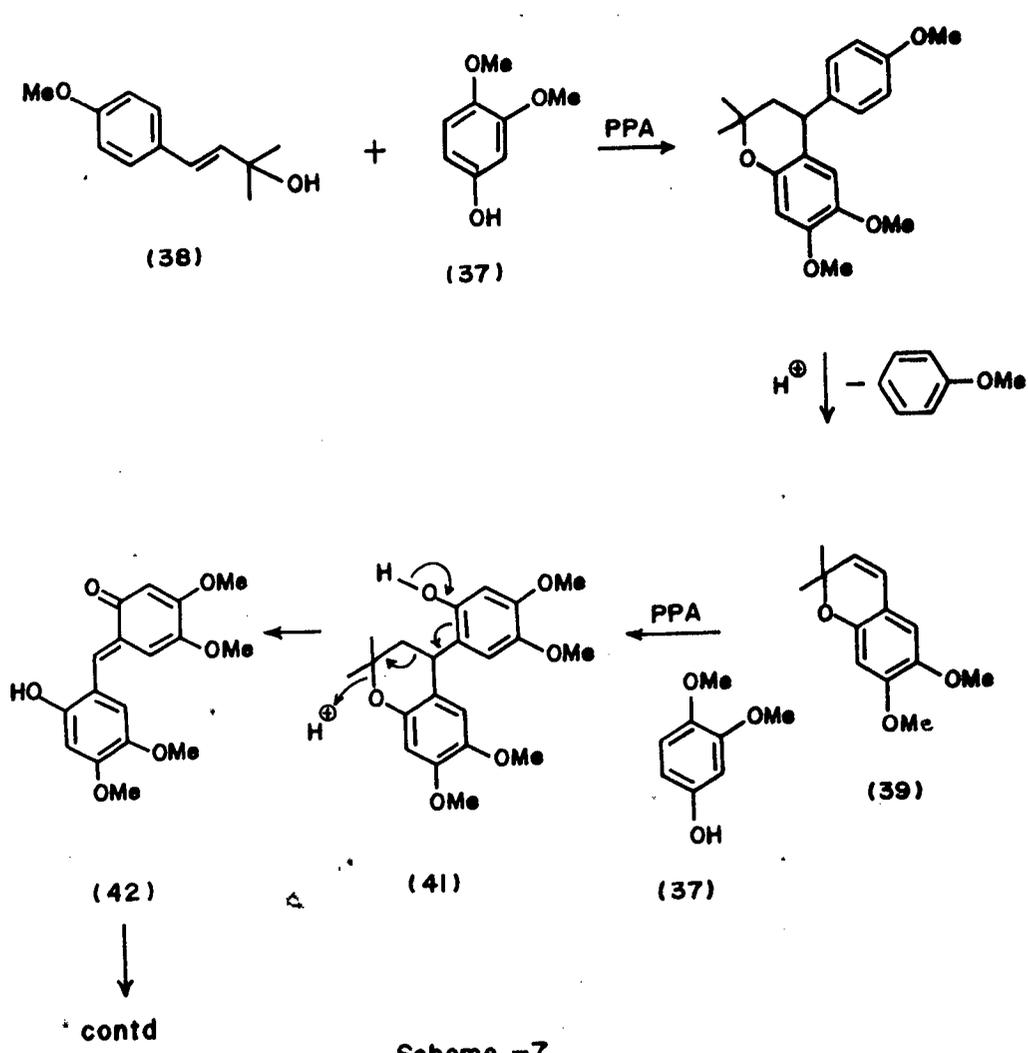
physical properties could be obtained. Instead a solid was obtained. The PMR data on the compound showed the presence of four methoxy groups and six protons in the aromatic region. The mass spectrum showed an unusually high molecular weight of 378, a fact which was confirmed by CIMS, EIMS and FAB.

The product was identified as (40). This benzo-c-phenanthrene derivative satisfies the PMR data and the high molecular weight. The formation of this compound is indeed intriguing but a likely

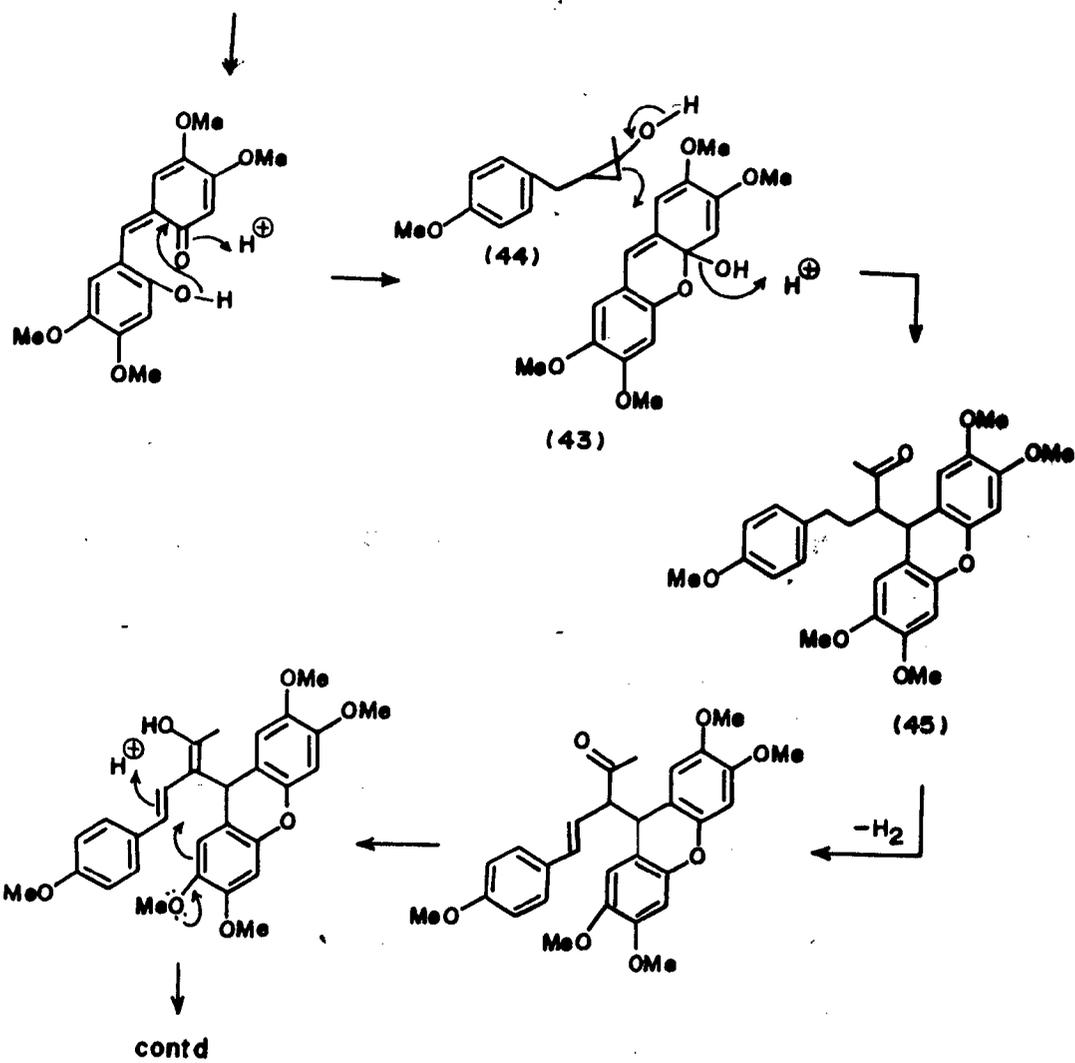


(40)

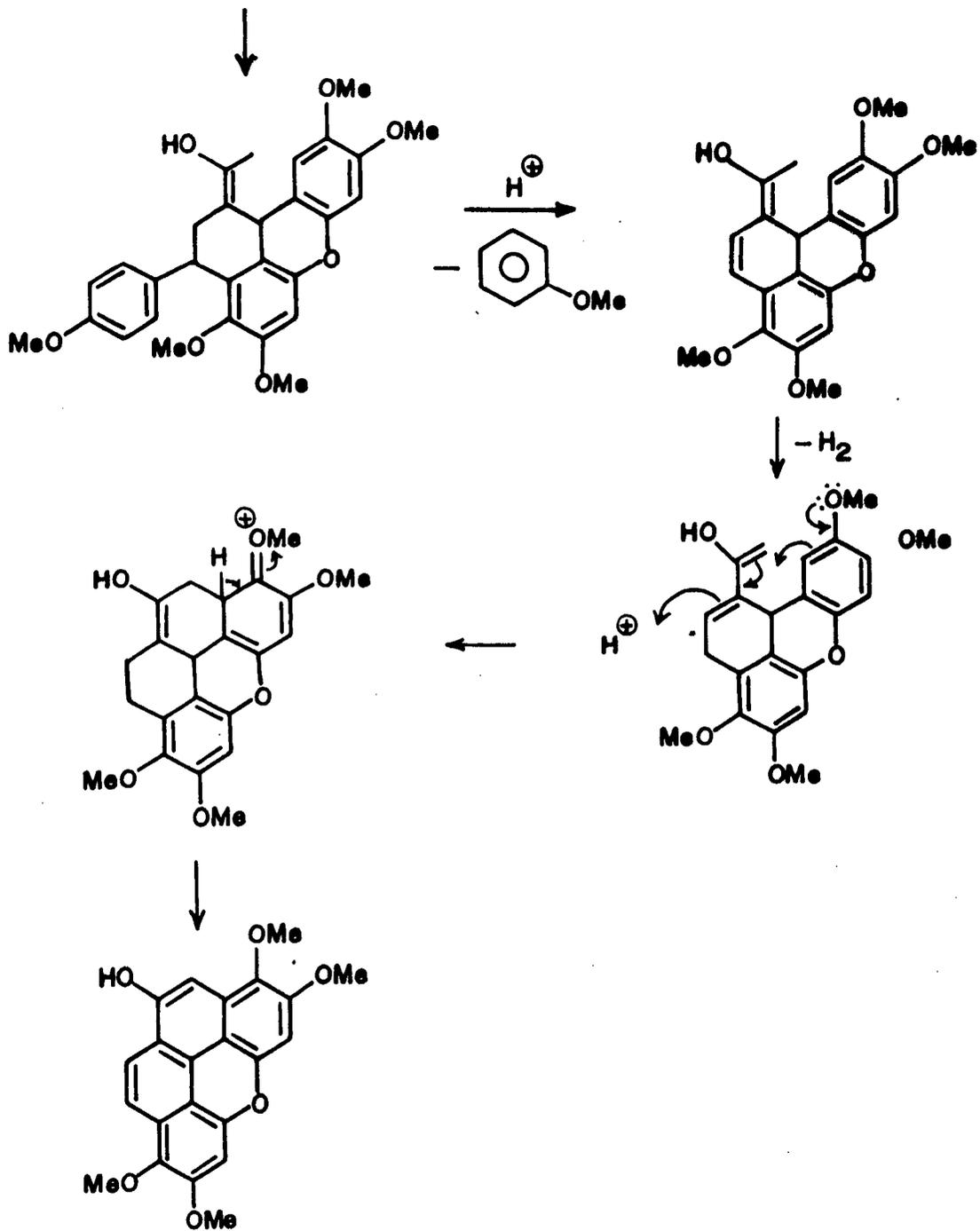
mechanism may be written if one considers that the desired product Precocene II is initially formed. The mechanism is shown in Scheme - 7.



Scheme -7



Scheme - 7 contd



(40)

Scheme - 7

Precocene II (39) which is initially formed, under the harsh reaction conditions adds on another molecule of the starting phenol (37) to furnish molecule (41) which loses isobutylene to afford (42). Ring closure then affords the xanthen derivative (43). This compound then adds on a modified derivative (44) of the starting tertiary alcohol (38) to afford (45). It may be noted that the formation of (44) from (38) is unprecedented. Compound (45) then through a series of oxidations and ring closures finally leads to the product (40).

We believe that if optimization of the reaction conditions are done then it would be possible to isolate the Precocene II as per our original synthetic plan.

Although this section deals with mainly those cases where the expected product is not obtained, some very interesting products were obtained and the explanations for the formation of these products brought to light some fascinating chemistry.

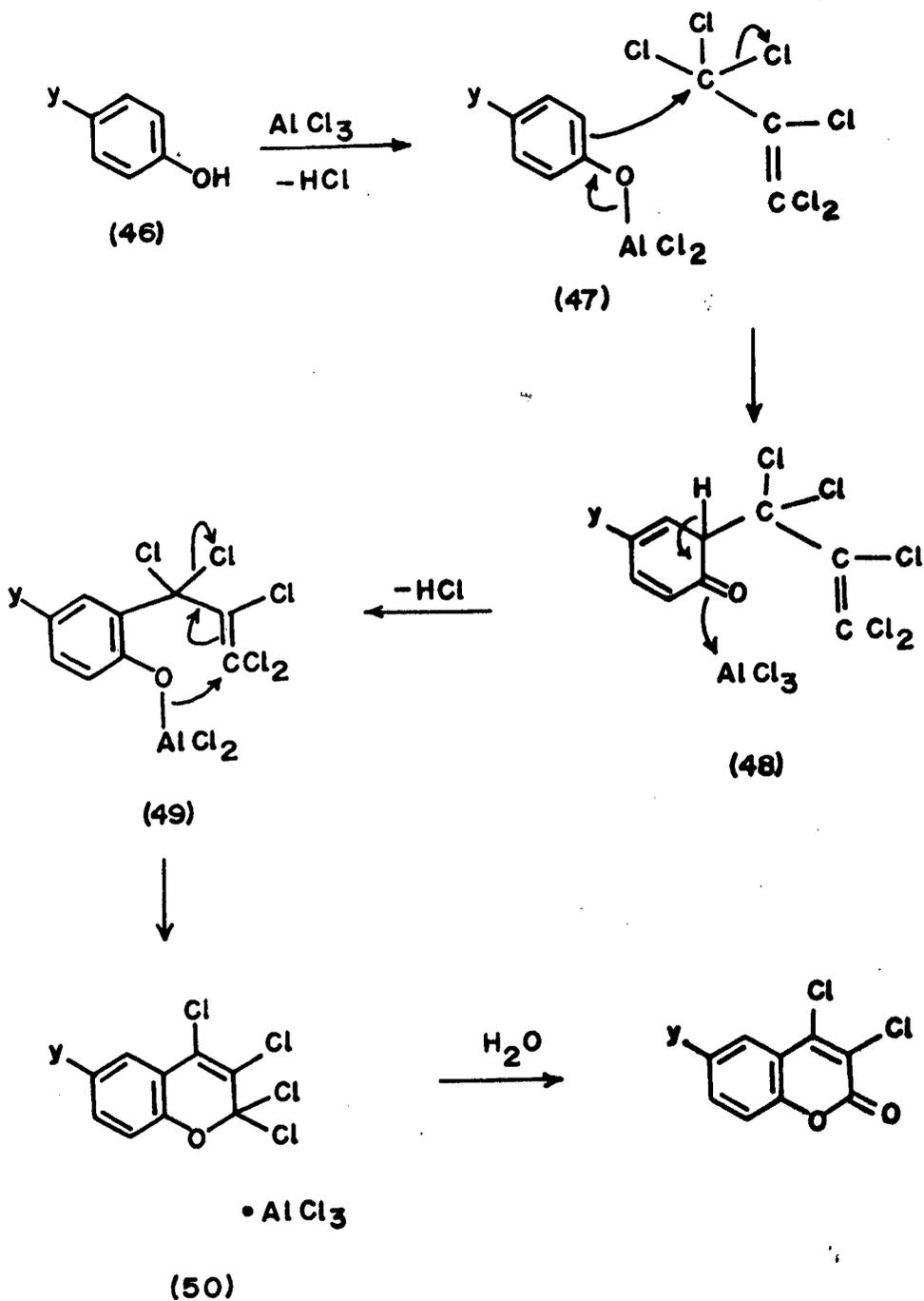
CHAPTER - I

SECTION - III

REINVESTIGATION OF THE REACTION BETWEEN 2-ACETYL
-4-METHYL PHENOL AND 2-ACETYL-5-METHYL PHENOL WITH
HEXACHLOROPROPENE IN PRESENCE OF ALUMINIUM CHLORIDE

The formation of 3,4-dichloro coumarins by the reaction of phenols with hexachloropropene in presence of AlCl_3 was first reported by Newmann and Schiff²⁹. According to these authors, who have studied the reaction in some detail, the mechanism of this reaction is as follows.

A phenol (46) reacts with one equivalent of AlCl_3 to yield the salt (47) which can react at the oxygen or at the ortho or para positions in the nucleus. The authors suggested that the reactions leading to the formation of the 3,4-dichloro coumarins occur by nucleophilic displacement of a chlorine of a trichloromethyl group of hexachloropropene by the anion of the salt (47) reacting at the ortho position to yield the cyclohexadienone intermediate (48). The latter reacts with AlCl_3 to form a new salt (49) and HCl . This then cyclizes to the complex (50) by an intramolecular $\text{S}_{\text{N}}2$ reaction. On hydrolysis with water, the final product, a substituted 3,4-dichloro coumarin, is obtained. These steps are shown in Scheme - 8.



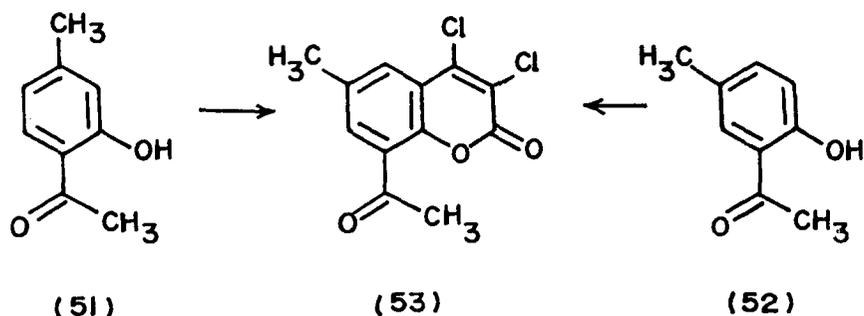
Scheme - 8

Newmann and Schiff have also commented that the yields of the reaction are good when there is a methyl or chlorine in the para position to the phenolic group. The electron withdrawing nature of the chlorine atom would facilitate the cleavage of the oxygen-hydrogen bond of the phenol assisting in the formation of the salt (47) and also the subsequent steps. However the effects of a methyl group in a similar position is not clear.

This is the only known method for the direct synthesis of 3,4-halogenated coumarins. It may be observed that these 3,4-dichloro coumarins are useful intermediates in the synthesis of 3,4-dimethoxy coumarins, a number of which are naturally occurring³⁰.

Merchant and Rege³¹ have studied the reaction of various phenols with hexachloropropene under the above conditions. Their aim was to study the Ullmann reaction on the dichlorocoumarins obtained. In one particular case, they have observed that 2-acetyl-5-methyl phenol (51) and 2-acetyl-4-methyl phenol (52) gave the same dichloro coumarin viz.

3,4-dichloro-6-methyl-8-acetyl coumarin (53).



This observation suggests that during the formation of (53) from (51), there is a migration of the methyl group from position 5 to 6 of the coumarin nucleus. The authors offer no comment on the cause of this migration .

Such a migration, if at all it occurs, is indeed intriguing since there is no apparent reason as to why it should occur during the comparatively mild reaction conditions. The reaction consists of adding a solution of the phenol in CS₂ to a slurry of AlCl₃ in the same solvent under stirring. Stirring is continued till the evolution of HCl is complete signalling completion of salt formation. Hexachloropropene is then added dropwise and

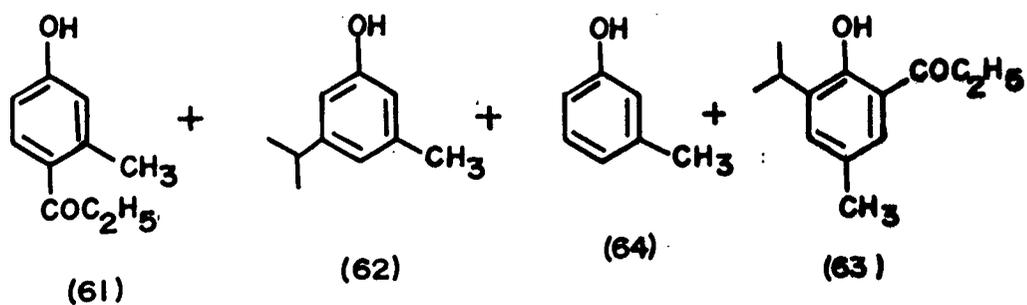
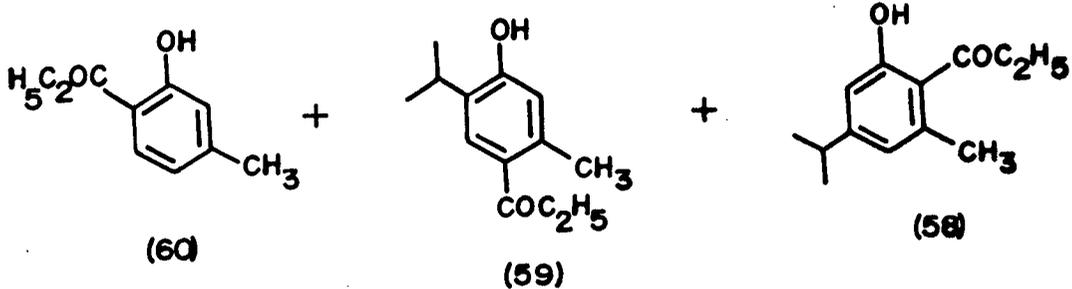
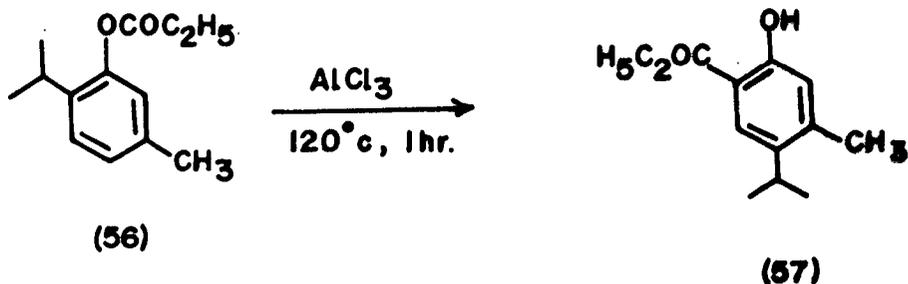
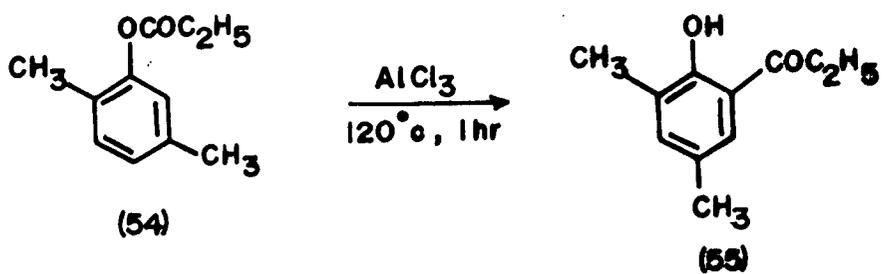
stirring is further continued till the evolution of HCl slows down or stops. The solvent is removed under reduced pressure and the residue hydrolysed with sulphuric acid and water. The coumarins are then purified by chromatography and finally *by* *//* recrystallization.

The observed methyl migration cannot be accommodated in the mechanistic scheme as given by Newmann and Schiff²⁹.

A literature survey of $AlCl_3$ catalysed reaction in general led us to a report by Martin and Demarseman³². These authors have studied the $AlCl_3$ -catalysed Fries rearrangement of phenyl esters. Their observations are summarised in Scheme - 9. *//*

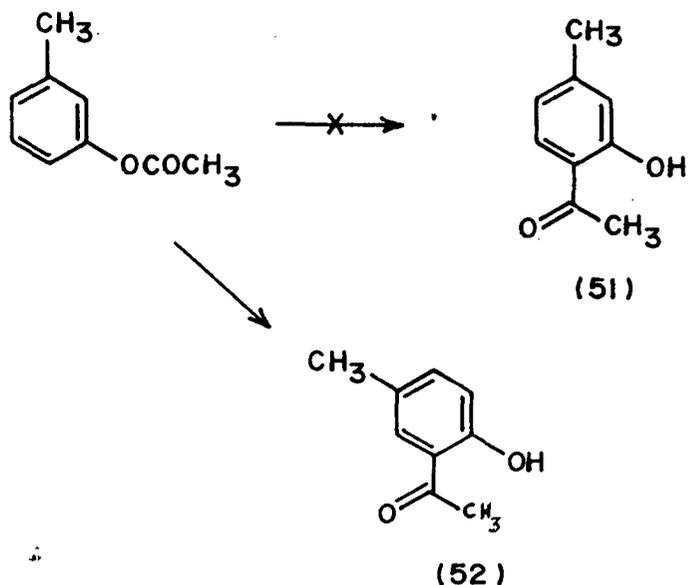
The products (55) and (63) in the above scheme are those arising from methyl group migration during the $AlCl_3$ catalysed Fries rearrangement.

In view of the above observation, the first explanation for the facts observed by Merchant and Rege³⁰ seemed that methyl group migration might be taking place during the preparation of 2-acetyl-5-



Scheme - 9

methyl phenol (51) obviously from m-cresyl acetate by an AlCl_3 catalysed Fries rearrangement.



Products (52) must then be affording 3,4-dichloro-6-methyl-8-acetyl coumarin (53) by the usual mechanism. Merchant and Rege however have not stated in their paper as to how they have obtained the phenols (51) and (52). It is entirely our conjecture that Fries rearrangement was used.

In view of the uncertain facts and observations given above, we thought of repeating these reactions ourselves in order to clarify some

of the observed facts.

2-acetyl-5-methyl phenol (51) and 2-acetyl-4-methyl phenol (52) were thus synthesised by us using the AlCl_3 catalysed Fries rearrangement of m-cresyl acetate and p-cresyl acetate respectively. The products were identified by their physical constants and spectral data. It is thus interesting to note that since normal Fries products are obtained, no methyl migration has taken place during the preparation of the starting phenols.

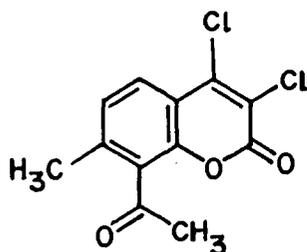
Reactions were then carried out on these phenols with hexachloropropene in presence of AlCl_3 . We first report the product of the reaction of 2-acetyl-5-methyl phenol.

m.p. 157°C

IR, λ_{max} , nujol: 1725 ($-\overset{\text{O}}{\parallel}{\text{C}}-\text{C}=\text{C}$), 1625 ($-\text{CO}-\text{CH}_3$) 1600, 1475, 1390, 1250, 1070, 1018, 905, and 755 cm^{-1} .

P.M.R. (CDCl_3) δ 2.44 (s, 3H, $-\text{CH}_3$), 2.74 (s, 3H, $-\text{COCH}_3$), 7.76 (s, 1H, H-6), 7.78 (s, 1H, H-5).

This product was identified as 3,4-dichloro-7-methyl-8-acetyl coumarin (65).



(65)

The product of the reaction of 2-acetyl-4-methyl phenol had the spectral characteristics given below.

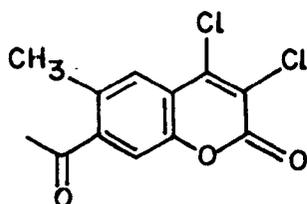
m.p. 155°C

IR, λ_{max} , nujol: 1725 ($-\text{CO}-\overset{\cdot}{\text{C}}=$), 1660 ($-\text{CO}-\text{CH}_3$), 1575, 1450, 1390, 1375, 1275, 1250, 1175, 1050, 1000, 975, 875, 812 and 752 cm^{-1} .

P.M.R. (CDCl_3), δ 2.58 (s, 3H, $-\text{CH}_3$), 2.62 (s, 3H, $-\text{COCH}_3$), 7.16 (s, 1H, H-5), 8.09 (s, 1H, H-8)

This product was identified as 3,4-dichloro-6-methyl-7-acetyl coumarin (66). d

From the above it is clear that the products of the above reactions are not identical as reported by Merchant and Rege³¹. These authors



(66)

have given the PMR data for a product which they have identified as 3,4-dichloro-6-methyl-8-acetylcoumarin (53). The reported data is reproduced below.

P.M.R. (CDCl_3) δ 2.5 (s, 3H, $-\text{CH}_3$), 2.76 (s, 3H, $-\text{COCH}_3$), 7.83 s, 2H, H-5 and H-7). It can be seen that the PMR data of (53) is very close to that of (65). We propose that these two are identical and explain the apparent misinterpretation of structure of (53) as follows.

Since the melting points of the products of reaction of (51) and (52) are very close as is their I.R., it is quite likely that these were

taken as identical by Merchant and Rege. Further once identity was assumed, it is presumed by us that PMR spectra was recorded on only one of these samples and this we suspect to be (65). The close chemical shift of the two aromatic protons as observed by us (7.76 and 7.78) appeared as a singlet (7.83) to the earlier authors. The chemical shifts of the methyl groups are also close to those observed by us.

Thus the product which is actually obtained from the reaction of 2-acetyl-5-methyl phenol with hexachloropropene is (65) and not (53). The close chemical shifts of the aromatic protons in product (63) can be explained because they are situated away from the acetyl group which would cause a downfield shift on the adjacent proton. This is clearly seen in the case of the product (66), the two protons appear 7.16 and 8.09 with the downfield signal attributable to the proton at position 8 in the coumarin nucleus, and adjacent to the acetyl group at position 7.

Thus what we have observed is in fact

migration of the acetyl group in both cases and not methyl migration. We have tried to explain this migration in the mechanistic scheme given below. Scheme - 10. We envisage that during alkylation of the salt of the phenol at the ortho position, with hexachloropropene, the acetyl group gets knocked out and this later gets reattached at other positions. A similar reaction sequence may be visualised for the conversion of (52) to (66).

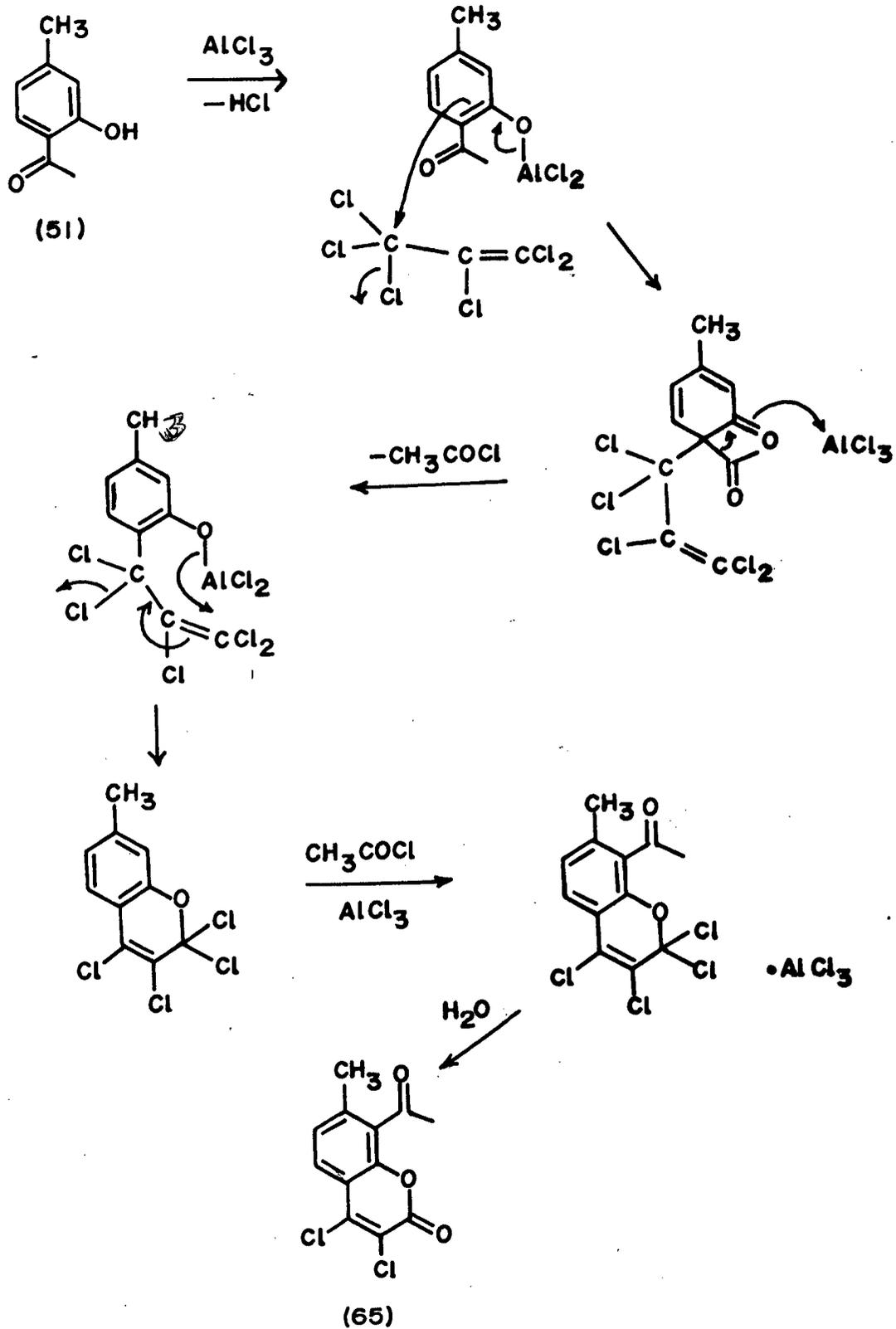
In another experiment done to check our earlier findings, 2-acetyl-5-methyl phenol (51) was again reacted with hexachloropropene. This time the product was a solid with the following characteristics.

m. p. 161°C

P.M.R. (CDCl_3) δ 2.5 (s, 3H, $-\text{CH}_3$), 7.2 (d, 2H, H-5 and H-7), 7.67 (s, 1H, H-8).

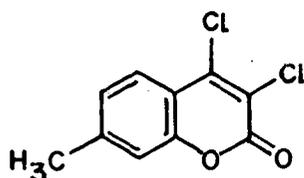
$^{13}\text{C.M.R.}$ δ 21 (CH_3), 115 (C-7), 117 (C-8), 125 (C-6), 127 (C-10), 151 (C-9), 156 (C-4), 160 (C-3), 170 ($\text{C}=\text{O}$).

From the above spectral data, it is clear that the product lacks the acetyl group. This compound



Scheme - 10

was thus identified as (67). The melting point and the spectral data are identical with 3,4-dichloro-7-methyl coumarin prepared from m-cresol.



(67)

The formation of this compound lends credence to our earlier observations that during the reaction, the acetyl group gets detached from the aromatic nucleus, and in the above case has not reattached.

Thus in conclusion, we may say that we have succeeded in shedding some light on the earlier work of Merchant and Rege on the reactions of phenols with hexachloropropene in presence of $AlCl_3$.

EXPERIMENTAL

Synthesis of coumarins from phenols and p-methoxy cinnamic acid.

General Procedure

A solution of polyphosphoric acid (PPA) was prepared by stirring a mixture of 10g P_2O_5 and 7-8 ml. orthophosphoric acid on a steam bath until a free flowing clear solution was obtained. This was then cooled to 70° in the same flask.

p-Methoxycinnamic acid (0.01 moles) and the appropriate phenol (0.01 moles) was then added in quick succession and the solution stirred at 70° for 4 hours.

The reaction mixture was then cooled to room temperature and poured into 250 ml. of ice-water and stirred. The resultant mixture was then extracted with $CHCl_3$. The $CHCl_3$ extracts were washed successively with water, and sat. brine and dried.

Concentration afforded an oil which was chromatographed over silica gel. Elution with petroleum ether containing increasing amounts of

ethyl acetate gave various fractions which were monitored by TLC, the plates visualised under UV light. The fractions showing the presence of coumarins were combined and concentrated. The solid coumarins were recrystallised in CHCl_3 - petroleum ether.

Spectral data of individual coumarins synthesised by the above method.

7-methoxy coumarin (herniarin)(6): 60%, m.p. 118°

IR. $\lambda_{\text{max.}}$, nujol. (Fig.1): 2880, 1725, 1620, 1510, 1470, 1400, 1350, 1280, 1230, 1200, 1150, 1125, 1090, 1025, 975, 890, 825, 760. cm^{-1}

PMR (80 MHz, CDCl_3 , δ)(Fig.2): 3.8 (s, 3H), 6.25 (d, $J=10$ Hz, 1H), 6.8 - 7.2(m, 3H), 7.6(d, $J=10$ Hz, 1H).

6-chloro-4-(4-methoxyphenyl)-3,4-dihydro coumarin
(7): 37%, M.P. 130° .

IR. $\lambda_{\text{max.}}$, nujol. (Fig.3): 2875, 1775, 1525, 1475, 1460, 1415, 1375, 1300, 1275, 1250, 1215, 1170, 1130, 1100, 1075, 1020, 960, 880, 875, 815, 750. cm^{-1} .

PMR (80 MHz, CDCl_3 , δ)(Fig.4): 2.9(d, $J=5$ Hz, 2H), 3.7(s, 3H), 4.2(t, $J=5$ Hz, 1H), 7-7.7(m, 7H).

Mass m/z (rel. int.)(Fig. 5): $[\text{M}^+]$ 288 (98), 270 (20), 245 (70), 215 (100), 152 (18), 139 (21).

6-acetyl-5-hydroxy-4-(4-methoxyphenyl)-3,4-dihydro coumarin (8): 25%, m.p. 173°

IR λ_{max} , nujol (Fig.6): 2920, 2850, 1780, 1640, 1610, 1520, 1490, 1460, 1390, 1325, 1250, 1190, 1120, 1075, 970, 890, 840, 800, $720. \text{cm}^{-1}$.

PMR (90 MHz, CDCl_3 , δ)(Fig.7): 2.5(s, 3H), 2.9(d, $J=5$ Hz, 2H), 3.7(s, 3H), 4.5(t, $J=5$ Hz, 1H), 6.5-7.6(m, 6H).

7-hydroxy-5-methyl coumarin (13) : 40%, m.p. 246°

IR λ_{max} , nujol : 3280, 2950, 1710, 1610, 1560, 1460, 1375, 1240, 1130, 1120, 900, 850, 825, $815. \text{cm}^{-1}$.

5-hydroxy-7-methyl coumarin (14): 10%, m.p. 215°
(dec).

IR λ_{max} , nujol : 3200, 2950, 1710, 1620, 1530, 1470, 1380, 1245, 1125, 1070, 900, $825. \text{cm}^{-1}$.

6,7-methylenedioxy coumarin (ayapin)(23): 45%,
m.p. 231^o.

IR λ_{\max} , nujol. (Fig.8): 2950, 1725, 1580, 1500,
1470, 1425, 1260, 1125, 1050, 950, 925, 880, 840,
750, 730. cm^{-1} .

PMR (90MHz, CDCl_3 , δ)(Fig.9): 6.15 (s, 2H), 6.3
(d, $J=10$ Hz., 1H), 6.9 (s, 2H), 7.5 (d, $J=10$ Hz.,
1H).

5,6,7-trimethoxy coumarin (24): 55%, m.p. 72^o

IR λ_{\max} ., nujol. (Fig.10): 2950, 1740, 1640,
1475, 1375, 1350, 1300, 1260, 1200, 1140, 1100,
1040, 1000, 940, 825, 815. cm^{-1} .

PMR (90 MHz, CDCl_3 , δ)(Fig.11): 3.70 (s, 3H), 3.75
(s, 1H), 3.9 (s, 3H), 6.2 (d, $J=10$ Hz, 1H), 6.5 (s,
1H), 7.8 (d, $J=10$ Hz, 1H).

5,7-dimethoxy coumarin (limettin) (25): 40%, m.p.
150^o.

IR, λ_{\max} , nujol. (Fig.12): 2900, 1720, 1620, 1500,
1470, 1400, 1360, 1320, 1240, 1230, 1220, 1150,
1120, 1050, 950, 900, 830. cm^{-1} .

PMR (80 MHz, CDCl_3 , δ)(Fig.13): 3.8 (d, 6H), 6.0 (d, $J=10$ Hz, 1H), 6.25 (s, 1H), 6.3 (s, 1H), 7.8 (d, $J=10$ Hz, 1H).

6,7-dimethoxy coumarin (scoparone) (26): 55%, m.p. 145 $^{\circ}$.

PMR (300 MHz, CDCl_3 , δ)(Fig.14): 3.75 (d, 6H), 6.1 (d, $J=10$ Hz, 1H), 6.58 (s, 1H), 6.72 (s, 1H), 7.5 (d, $J=10$ Hz, 1H).

5,7-dimethoxy-8-hydroxy coumarin (leptodactylone) (27): 50%, m.p. 150 $^{\circ}$.

IR, λ max, KBr (Fig.15): 1720, 1600, 1475, 1350, 1250, 1230, 1200, 1180, 1150, 1120, 950, 900, 820. cm^{-1} .

PMR (300 MHz, CDCl_3 , δ)(Fig.16): 3.85 (d, 6H), 6.1 (d, $J=10$ Hz, 1H), 6.25 (s, 1H), 6.37 (s, 1H), 7.9 (d, $J=10$ Hz, 1H).

7,8-benzocoumarin (15): 42%, m.p. 140 $^{\circ}$.

PMR (80 MHz, CDCl_3 , δ)(Fig.17): 6.5 (d, $J=10$ Hz, 1H), 7.2-8.0 (m, 7H).

5,6-benzocoumarin (16): 35%, m.p. 118^o.

IR, λ_{\max} , nujol. (Fig.18): 2875, 1750, 1575, 1475, 1390, 1180, 1125, 815, 780. cm^{-1} .

PMR (80 MHz, CDCl_3 , δ)(Fig.19): 6.6 (d, $J=9$ Hz, 1H), 7.4-7.8 (m, 3H), 7.9-8.1 (m, 2H), 8.25 (d, $J=10$ Hz, 1H), 8.5 (d, $J=9$ Hz, 1H).

Mass m/z (rel. int.)(Fig.20): 196.0532 (M^+ , 100%), 168.0581 (92), 139.056 (60), 113.0391 (9), 84.0286 (22), 70.0308 (19).

p-methoxy acetophenone (29) from pyrogallol.

To a stirred solution of PPA (10g P_2O_5 , 8ml. H_3PO_4) was added pyrogallol (1.26g, 0.01 moles) and p-methoxy cinnamic acid (1.78g, 0.01 moles) at 70^oC. Stirring was continued at 70^o for 4 hrs. The reaction mixture was then poured into water and extracted with CHCl_3 . CHCl_3 extracts were washed and dried. Concentration afforded an oil which was chromatographed over silica gel and eluted with petroleum ether with increasing amounts of ethyl acetate. Routine analysis of pure fractions by PMR

led to the identification of p-methoxy acetophenone. 0.450g. (30%) of (29) was obtained.

3,3-(bis-4'-methoxyphenyl)-propanoic acid (30)
from guaiacol.

To a stirred solution of PPA (10g P_2O_5 , 8ml. H_3PO_4) was added guaiacol (1.24g, 0.01 moles) and p-methoxy cinnamic acid (1.78g, 0.01 moles) at $70^\circ C$. Stirring was continued at 70° for 4 hrs. The reaction mixture was then poured into water and extracted with $CHCl_3$. $CHCl_3$ extracts were washed and dried. Concentration afforded an oil which was chromatographed over silica gel and eluted with petroleum ether with increasing amounts of ethyl acetate. 0.989g. (35%) of (30) was obtained.

IR, λ_{max} , nujol. (Fig.21): 3200, 2900, 1660, 1580, 1525, 1475, 1420, 1380, 1300, 1230, 1180, 1120, 1025, 970, 850. cm^{-1} .

PMR (300 MHz, $CDCl_3$, δ) (Fig.22): 3.05 (d, $J=5$ Hz, 2H), 3.8 (s, 6H), 4.25 (d, $J=5$ Hz, 1H), 6.8 (d, $J=5$ Hz, 4H), 7.2 (d, $J=5$ Hz, 4H), 9-10 (br s, 1H).

Mass m/z (rel.int.)(Fig.23): 286.1206 (M^+ , 30),
227.1077 (100), 197.0674 (17), 168.0575 (17),
141.0695 (10), 113.5535 (12).

5,6-benzocoumarin (16) from 2,7-dihydroxy
naphthalene.

In a similar experiment to the above with p-methoxy cinnamic acid (1.78g 0.01 moles) and 2,7-dihydroxy naphthalene (1.6g 0.01 moles), 0.560g (35%) of (16) was obtained.

For IR, PMR, Mass, refer Fig. nos. 18, 19, 20.

1,1-dimethyl-4'-methoxy cinnamyl alcohol (38) from
p-methoxy cinnamic acid.

p-methoxy cinnamic acid was converted into its methyl ester by refluxing with methanol in presence of H_2SO_4 . A solution of methyl magnesium iodide was prepared from 2g magnesium turnings in dry ether and methyl iodide. To this Grignard's solution was added 1.92g (0.01 moles) of methyl p-methoxy cinnamate. The mixture was stirred for 2 hours and then refluxed for 1 hr. Water was then added and

the ethereal layer separated, washed with water and brine and dried. Concentration afforded 1.5g (80%) of 1,1-dimethyl-4'-methoxy cinnamyl alcohol (38) as an oil.

IR, λ max, neat. : 3300, 2950, 1600, 1510, 1460, 1380, 1300, 1220, 1170, 1025, 970, 900, 810. cm^{-1} .

(40) from 1,1-dimethyl-4'-methoxy cinnamyl alcohol (38).

To a stirred solution of PPA (10g P_2O_5 , 8ml. H_3PO_4) was added (38) (1.4g, 0.007 moles) and 3,4-dimethoxy phenol (0.763g, 0.007 moles) at 70°C . Stirring was continued at 70° for 4 hrs. The reaction mixture was then poured into water and extracted with CHCl_3 . CHCl_3 extracts were washed and dried. Concentration afforded an oil which was chromatographed over silica gel and eluted with petroleum ether with increasing amounts of ethyl acetate. 0.989g. (30%) of a solid (40) was obtained.

IR, λ max, KBr (Fig.24) : 3200, 2650, 1610, 1490, 1475, 1425, 1320, 1200, 1150, 1120, 1070, 1000, 980, 750. cm^{-1} .

PMR (300 MHz, CDCl_3 , δ)(Fig.25): 4.0 (m, 12H), 7.1 (s, 1H), 7.2 (s, 1H), 7.35 (s, 1H), 7.45 (d, 1H), 7.6 (s, 1H), 7.8 (s, 1H).

Mass m/z (rel. int.) (Fig.26): 378 (M^+ , 100), 363 (10), 304 (15), 189 (10), 146 (5).

General Procedure for the synthesis of 3,4-dichloro coumarins.

A solution of 0.03 moles of the phenol in 25 ml. CS_2 was added dropwise to a slurry of 0.06 moles of AlCl_3 in 25 ml. CS_2 . The mixture was stirred at room temperature until the evolution of HCl was essentially complete and then, 0.03 moles of hexachloropropene was added dropwise during 10 mins. The colour always became dark and the reaction allowed to proceed at room temperature until the evolution of HCl slowed down or stopped.

The solvent was then removed under reduced pressure and the residue hydrolysed with ice and H_2SO_4 . The solids were washed well with dil. acid and water and then dried under vacuum. The coumarins purified by recrystallization from CHCl_3 -petroleum ether.

3,4-dichloro-7-methyl-8-acetyl coumarin (65): 55%,
m.p. 157°

IR, λ_{\max} , nujol. (Fig.27): 2900, 1725, 1675,
1625, 1600, 1475, 1400, 1390, 1325, 1250, 1170,
1070, 1050, 1018, 970, 905, 755. cm^{-1} .

PMR (200 MHz, CDCl_3 , δ)(Fig.28): 2.44 (s, 3H), 2.74
(s, 3H), 7.76 (s, 1H), 7.78 (s, 1H).

3,4-dichloro-6-methyl-7-acetyl coumarin (66): 60%,
m.p. 155°.

IR, λ_{\max} , nujol. (Fig.29): 2900, 1725, 1660,
1600, 1575, 1475, 1450, 1390, 1375, 1275, 1250,
1175, 1050, 1000, 975, 880, 875, 812, 752. cm^{-1} .

PMR (200 MHz, CDCl_3 , δ)(Fig.30): 2.58 (s, 3H),
2.62 (s, 3H), 7.16 (s, 1H), 8.09 (s, 1H).

3,4-dichloro-7-methyl coumarin (67): 40%, m.p.
161°.

PMR (90 MHz, CDCl_3 , δ)(Fig.31): 2.5 (s, 3H), 7.2
(d, 2H), 7.67 (s, 1H).

^{13}C MR (22.5 MHz, CDCl_3 , δ)(Fig.32): 21, 115, 117,
125, 127, 151, 156, 160, 170.

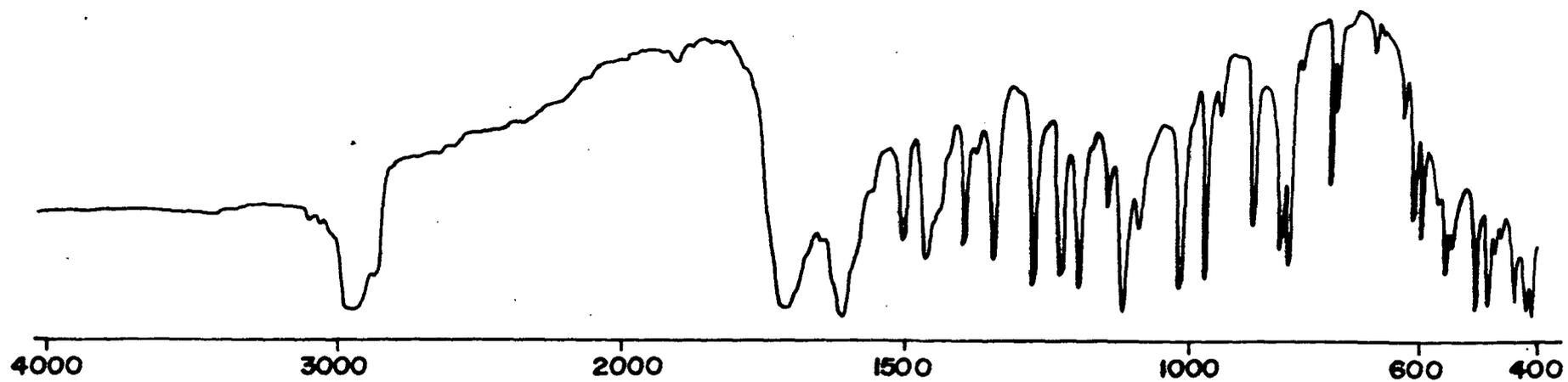
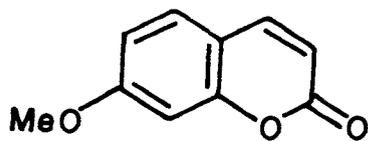


Fig. 1 IR spectrum of (6)

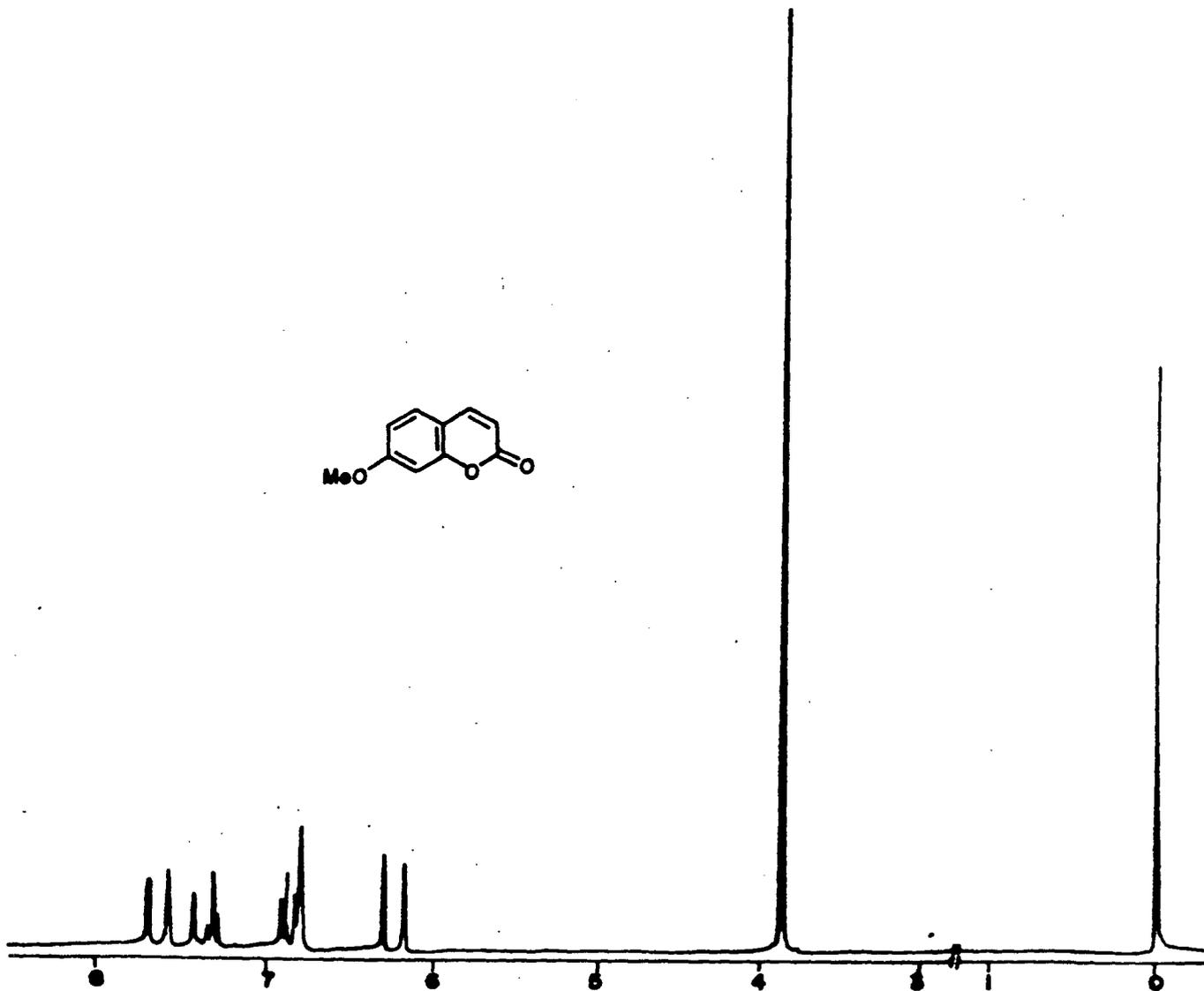
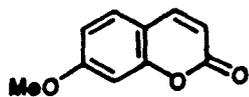


Fig. 2 NMR spectrum of (6)

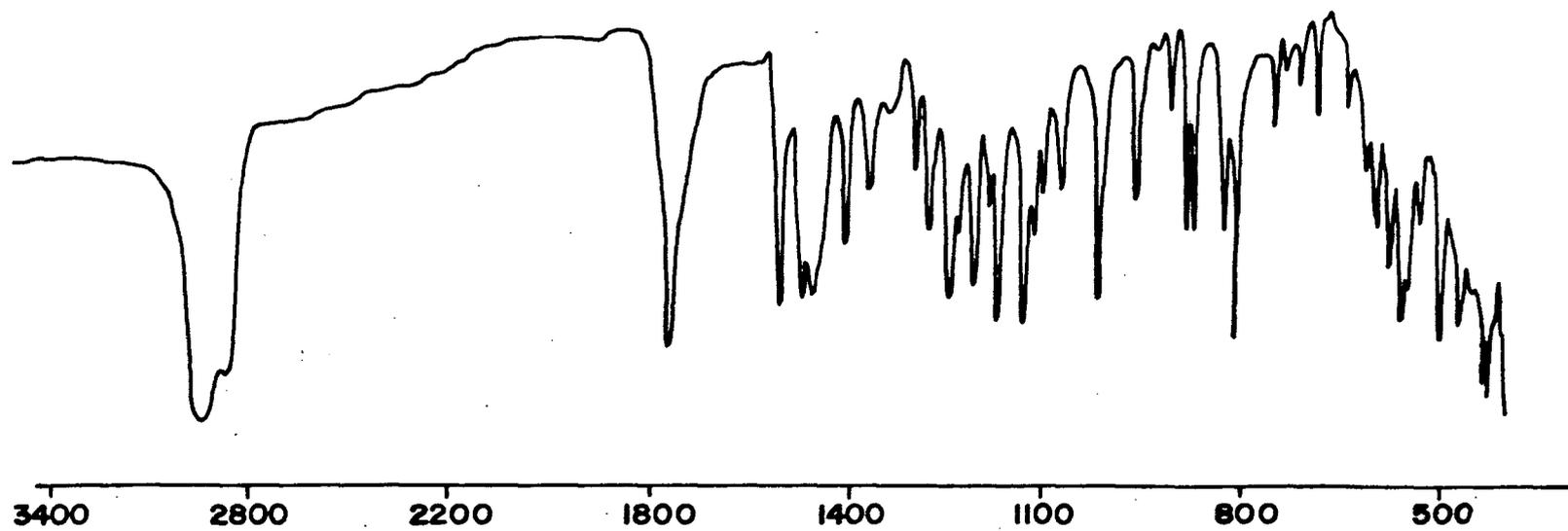
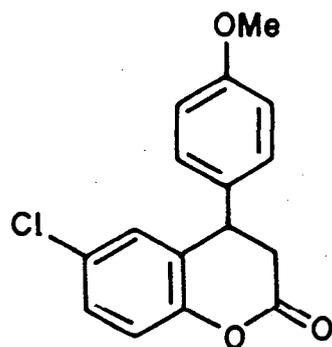


Fig. 3 IR spectrum of (7)

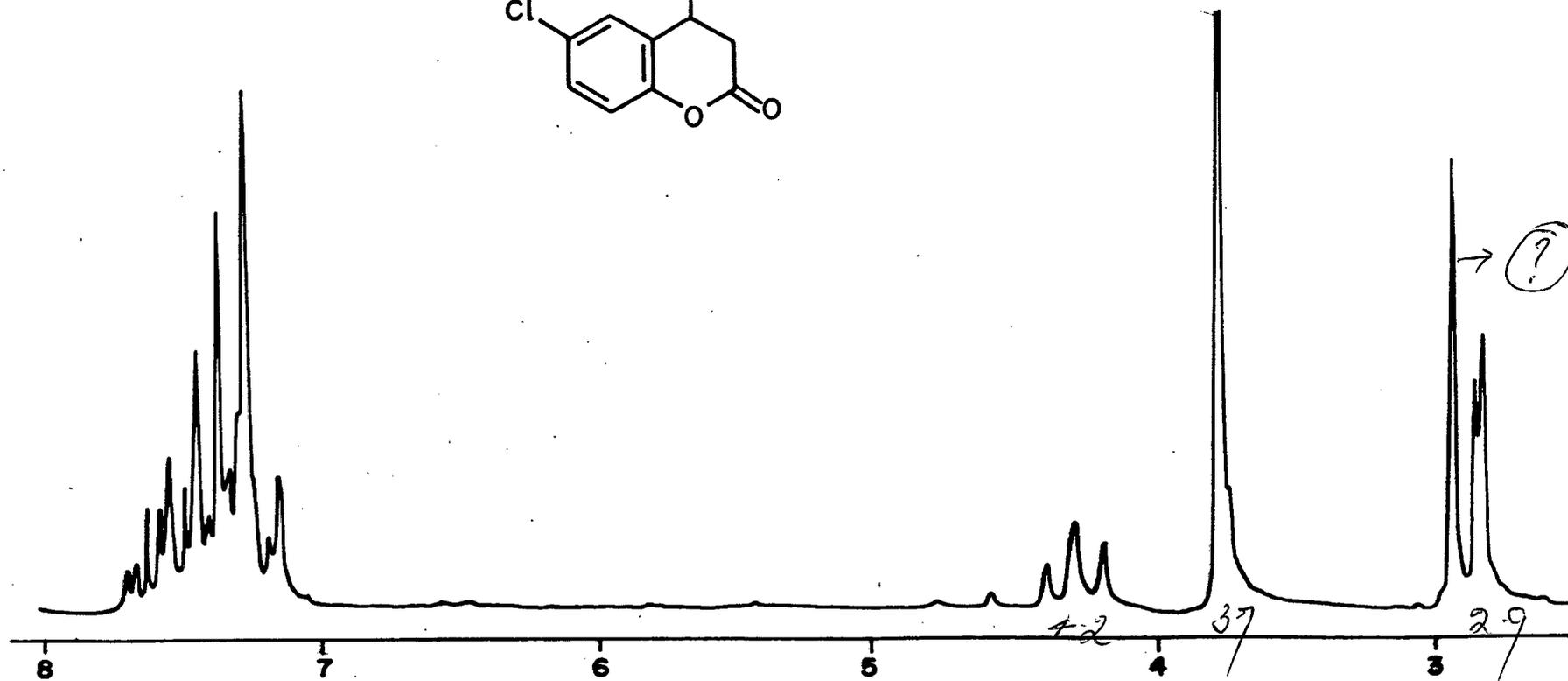
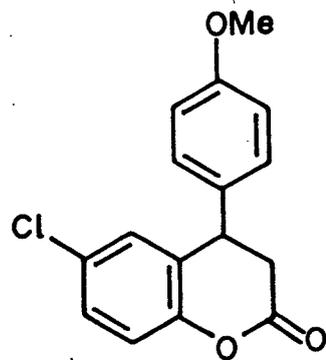


Fig. 4 NMR spectrum of (7)

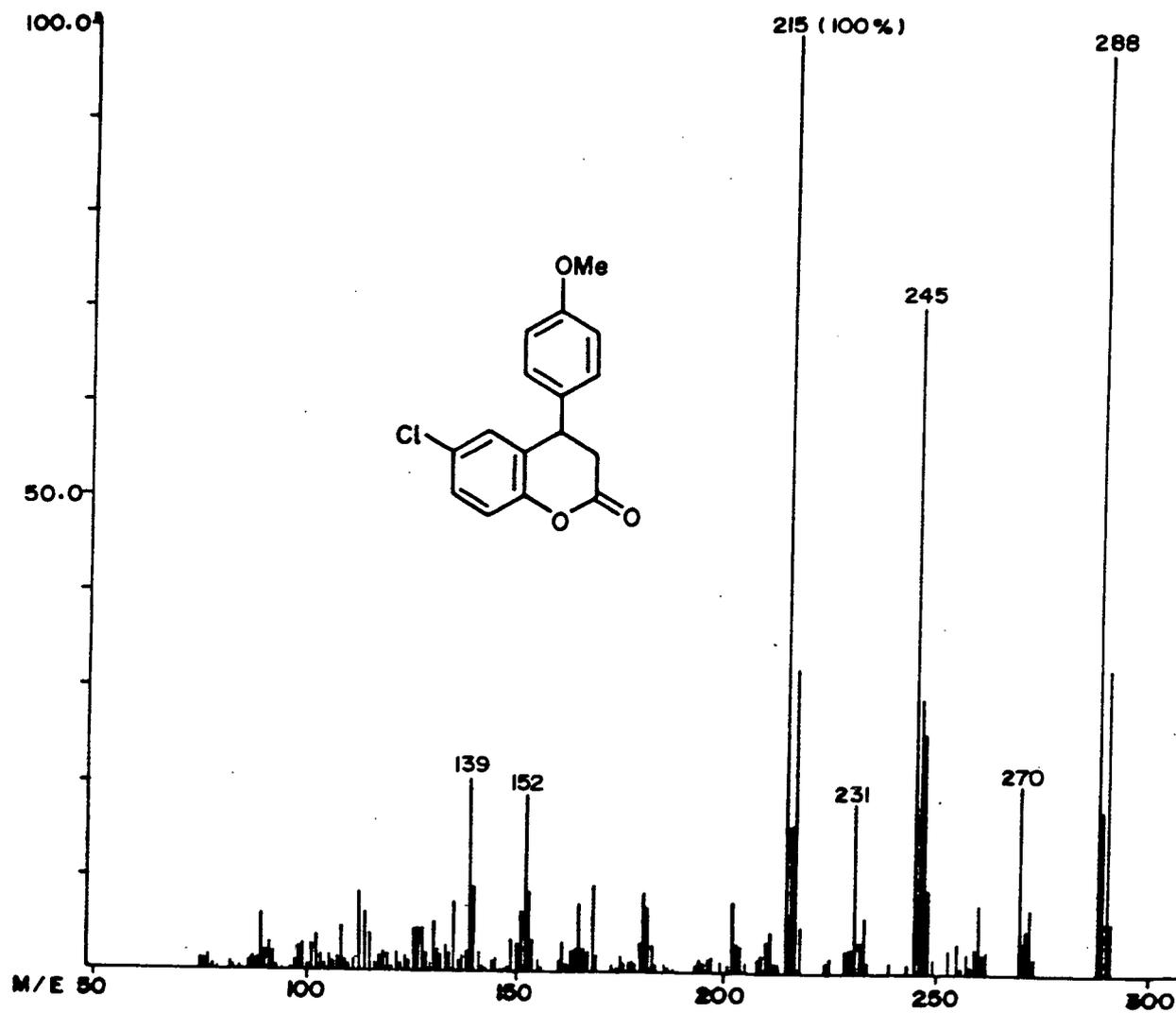


Fig. 5 Mass spectrum of (7)

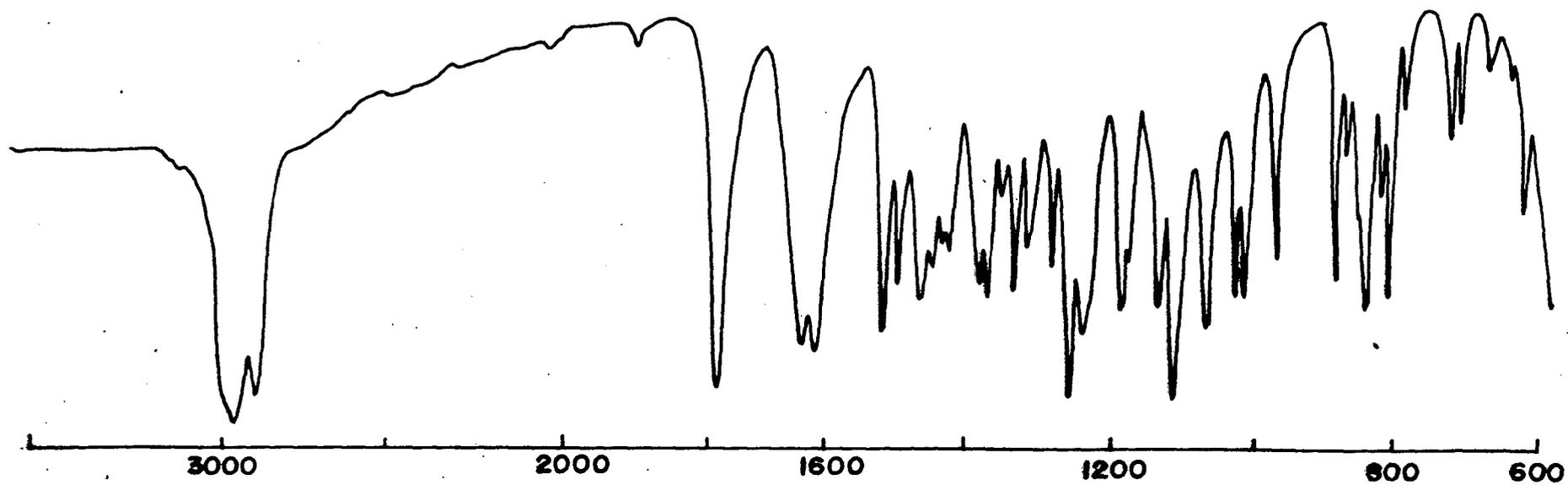
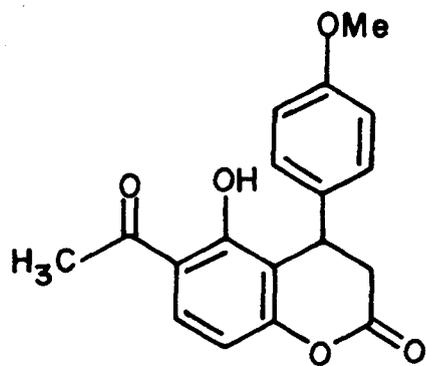


Fig. 6 IR spectrum of (8)

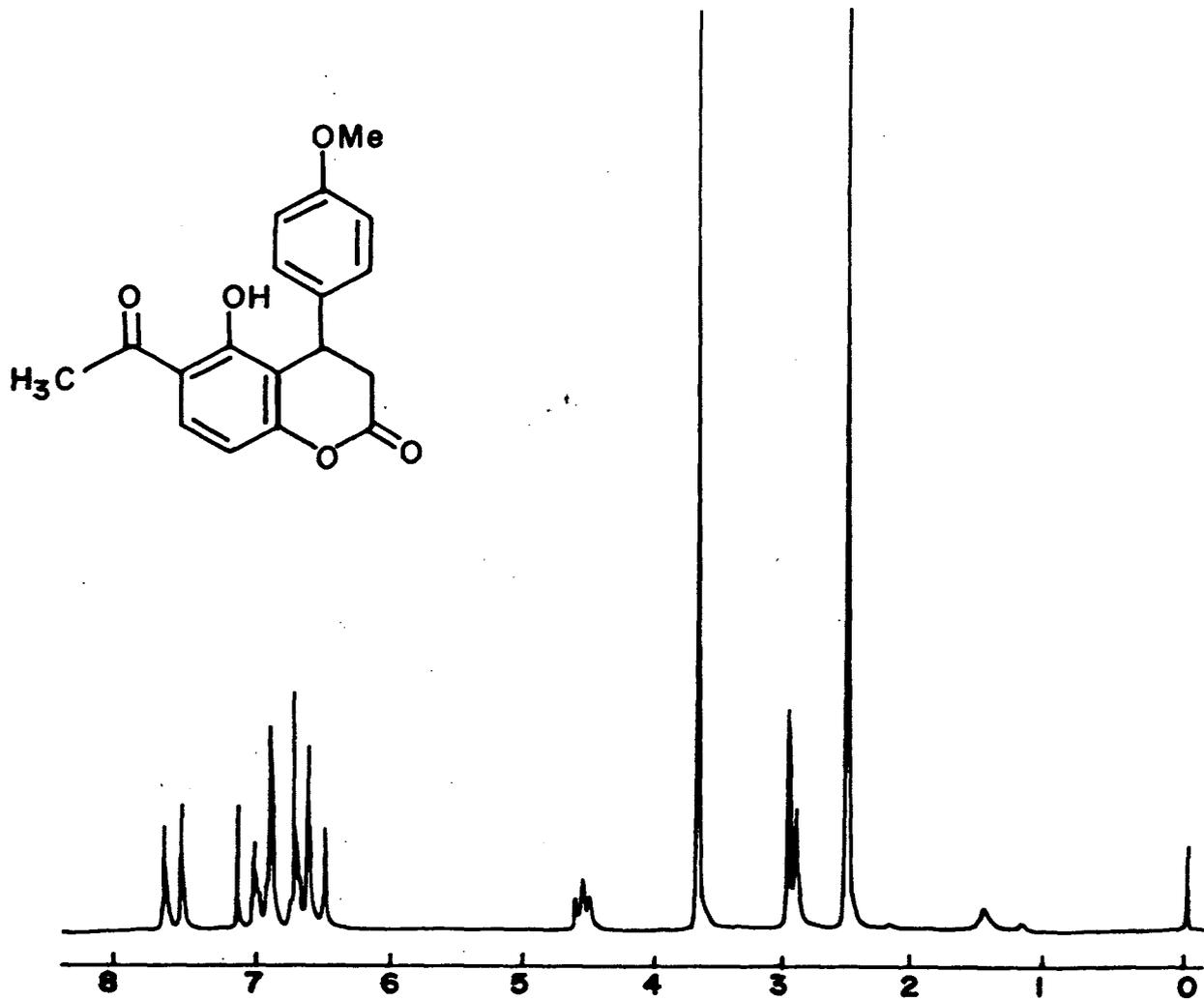


Fig. 7 NMR spectrum of (8)

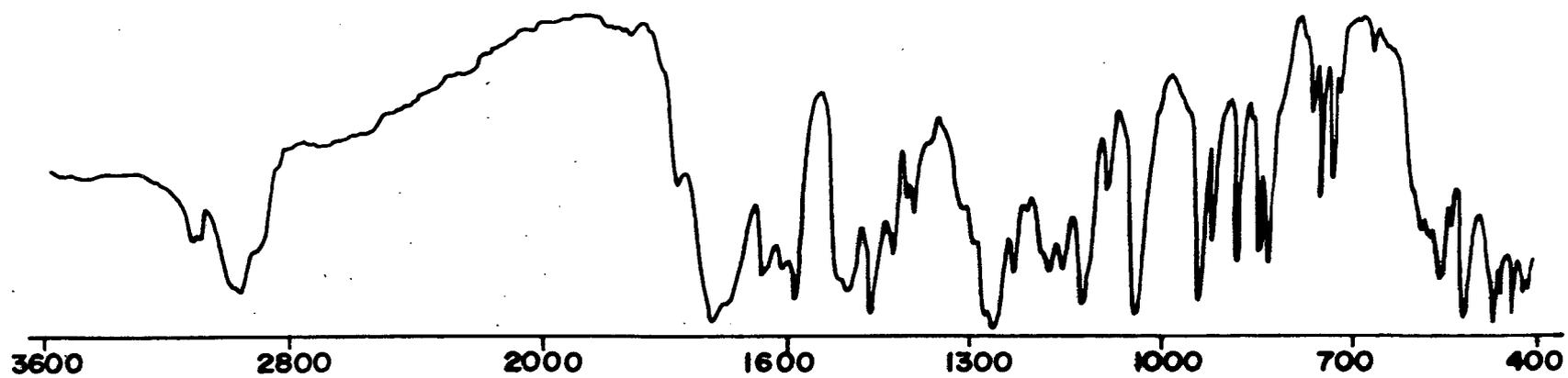
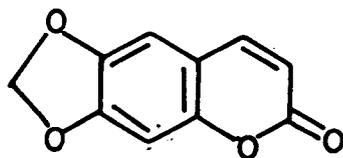


Fig. 8 IR spectrum of (23)

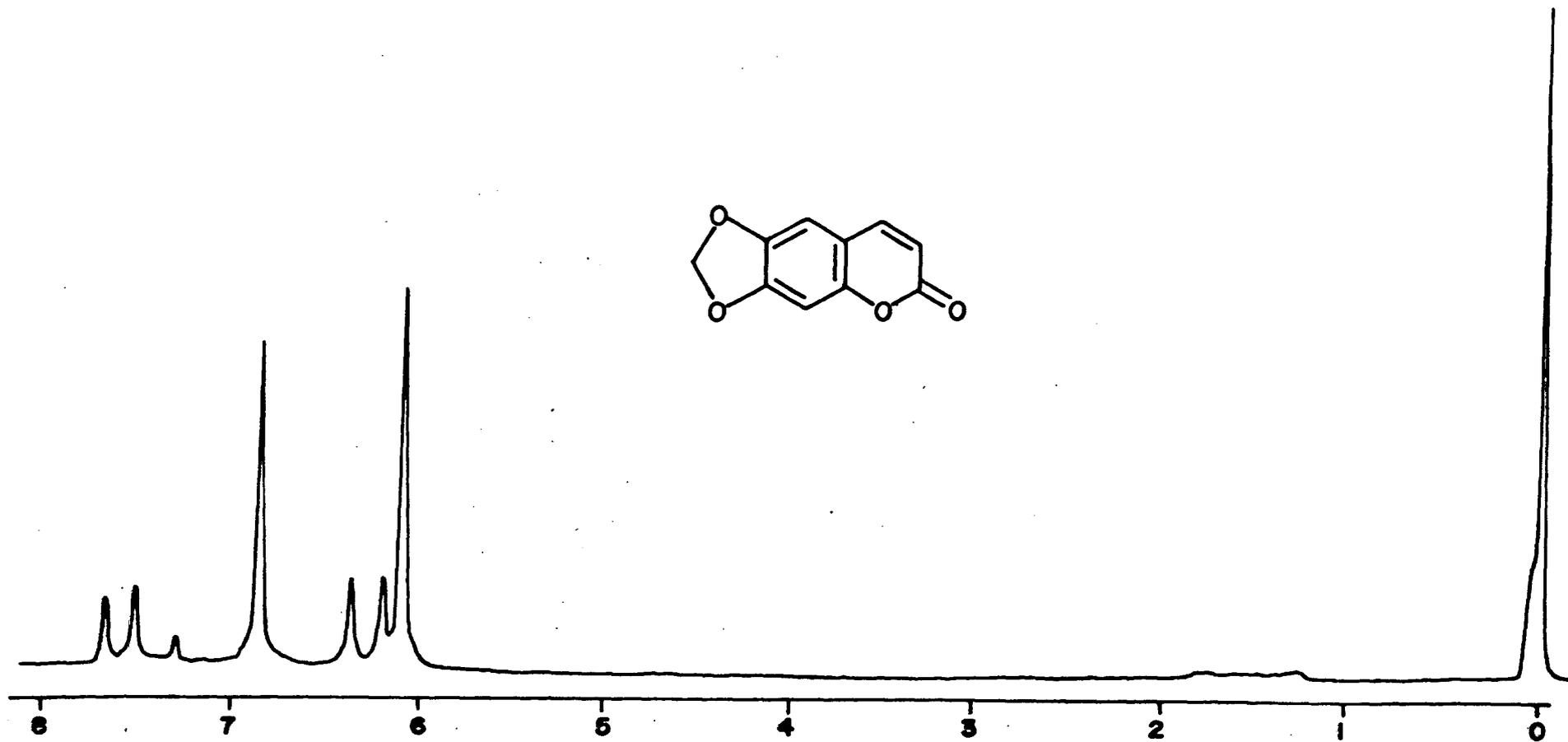


Fig. 9 NMR spectrum of (23)

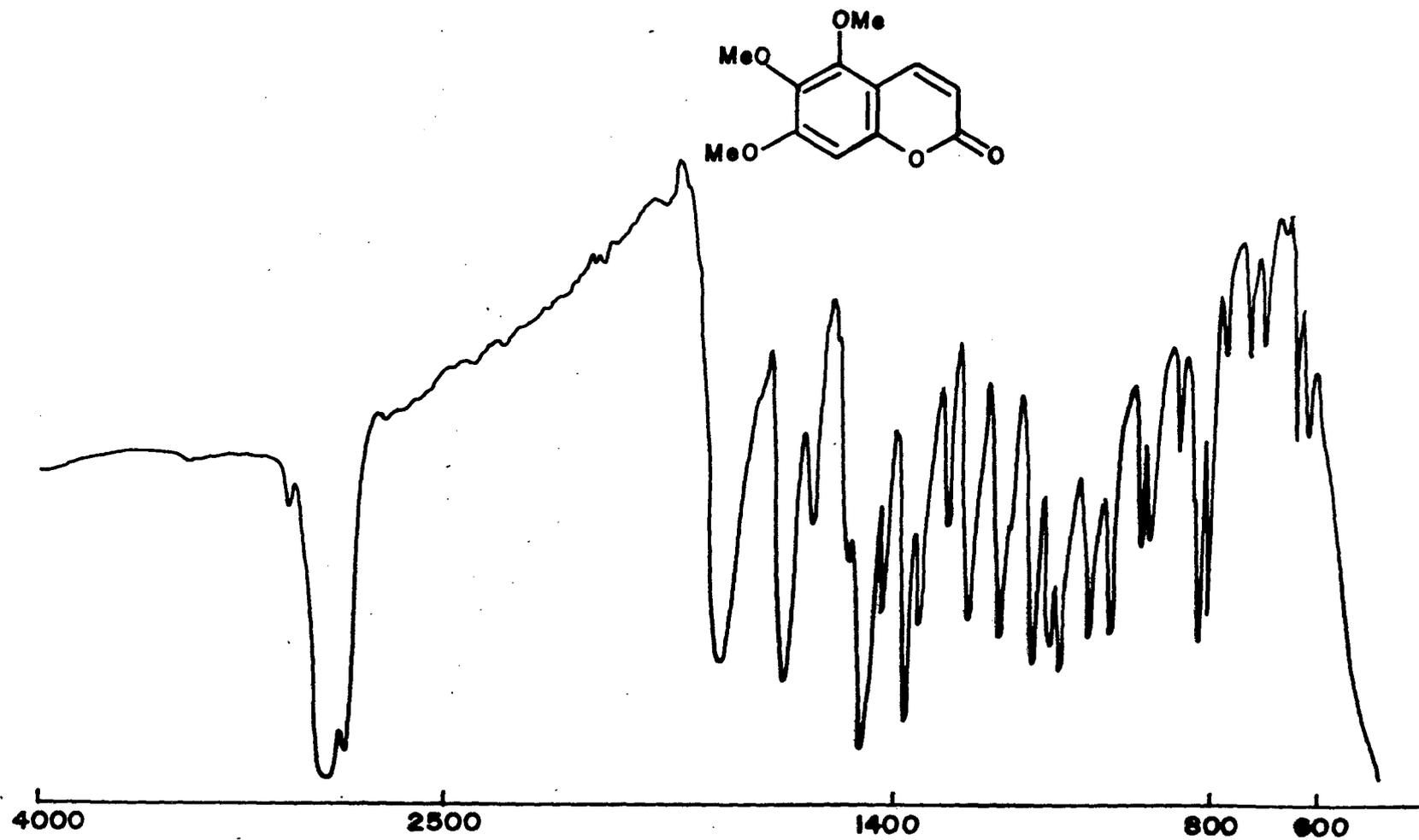


Fig. 10 IR spectrum of (24)

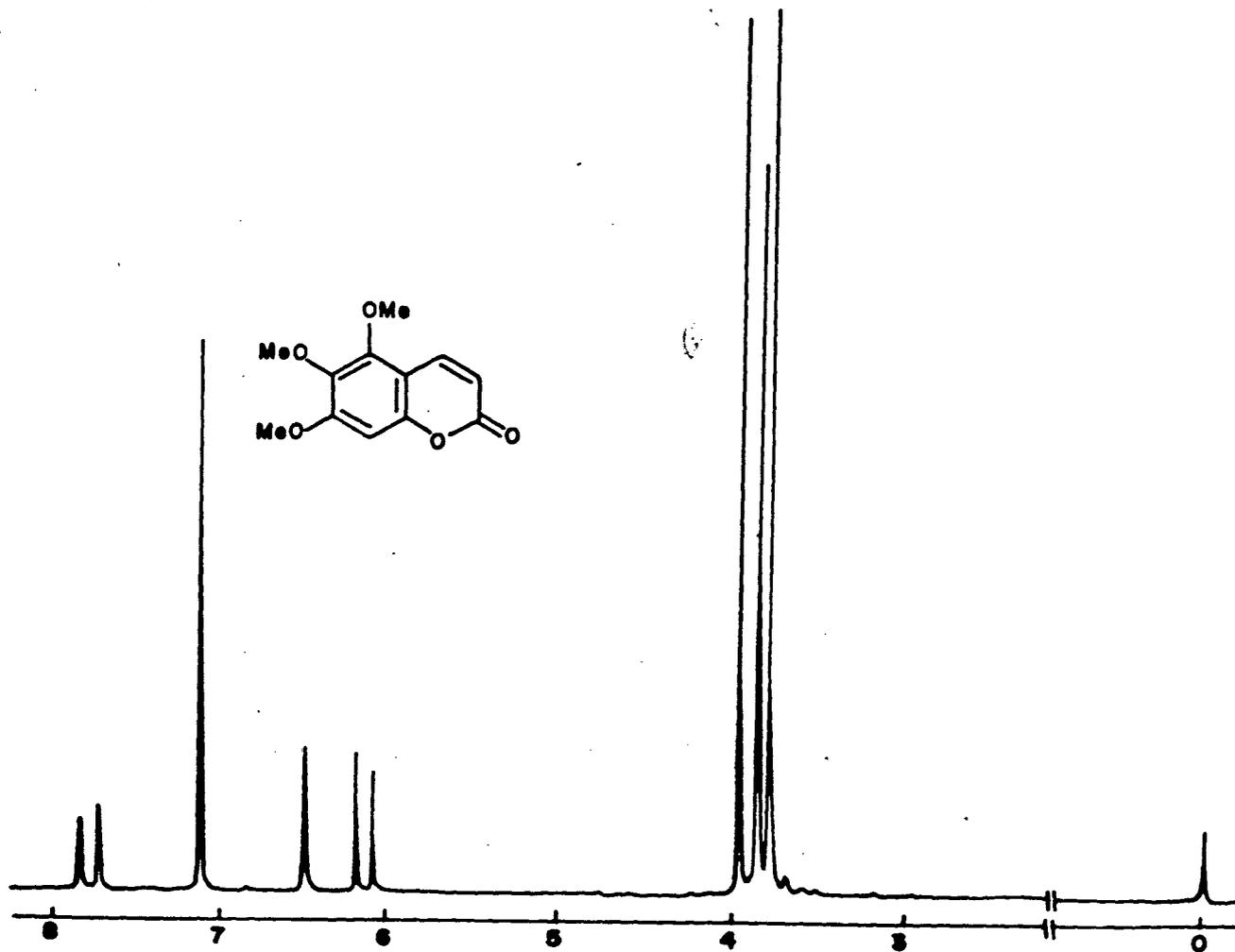
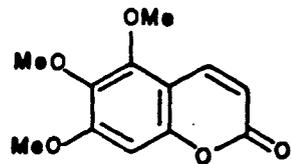


Fig. 11 NMR spectrum of (24)

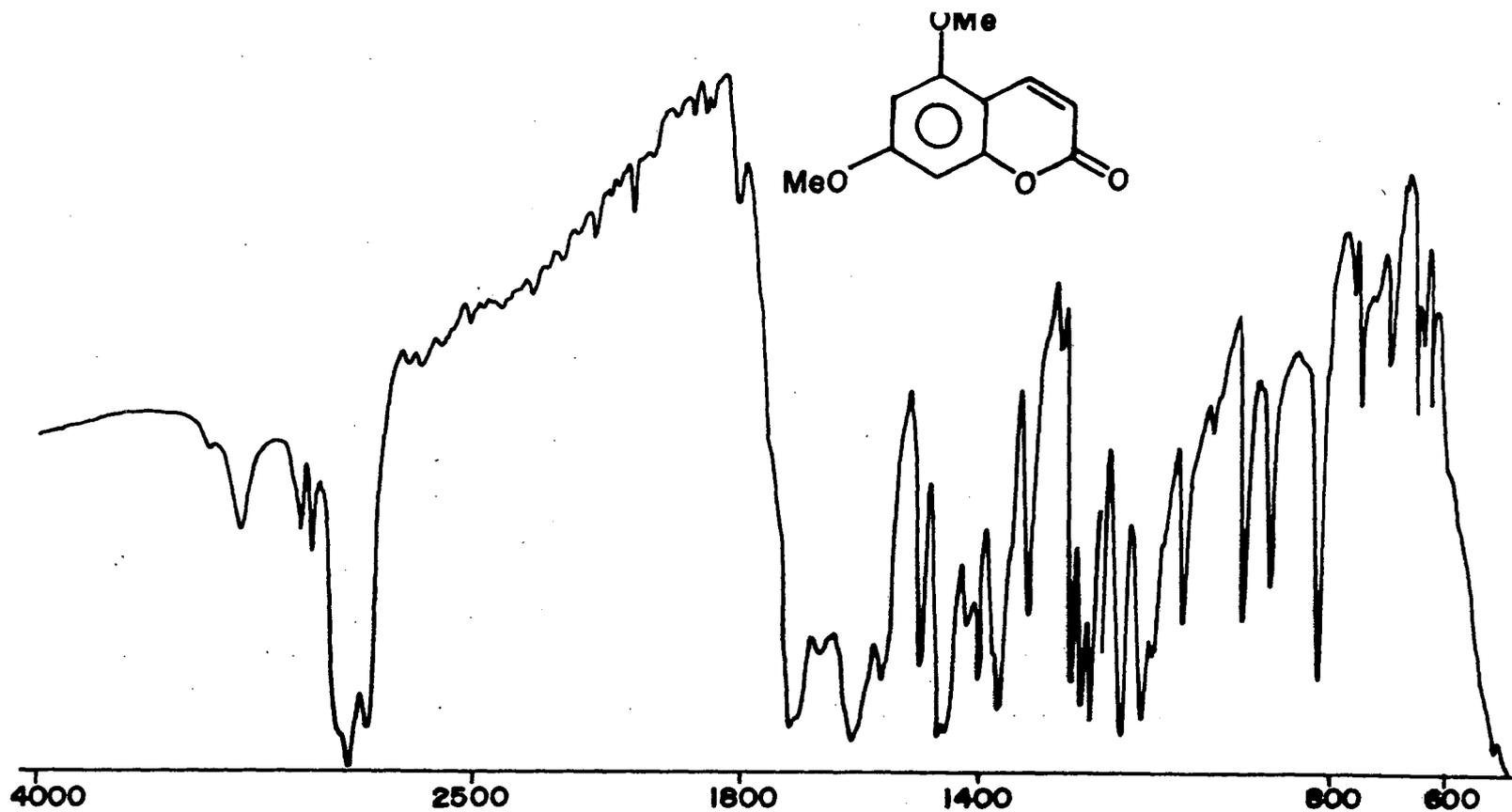


Fig. 12 IR spectrum of (25)

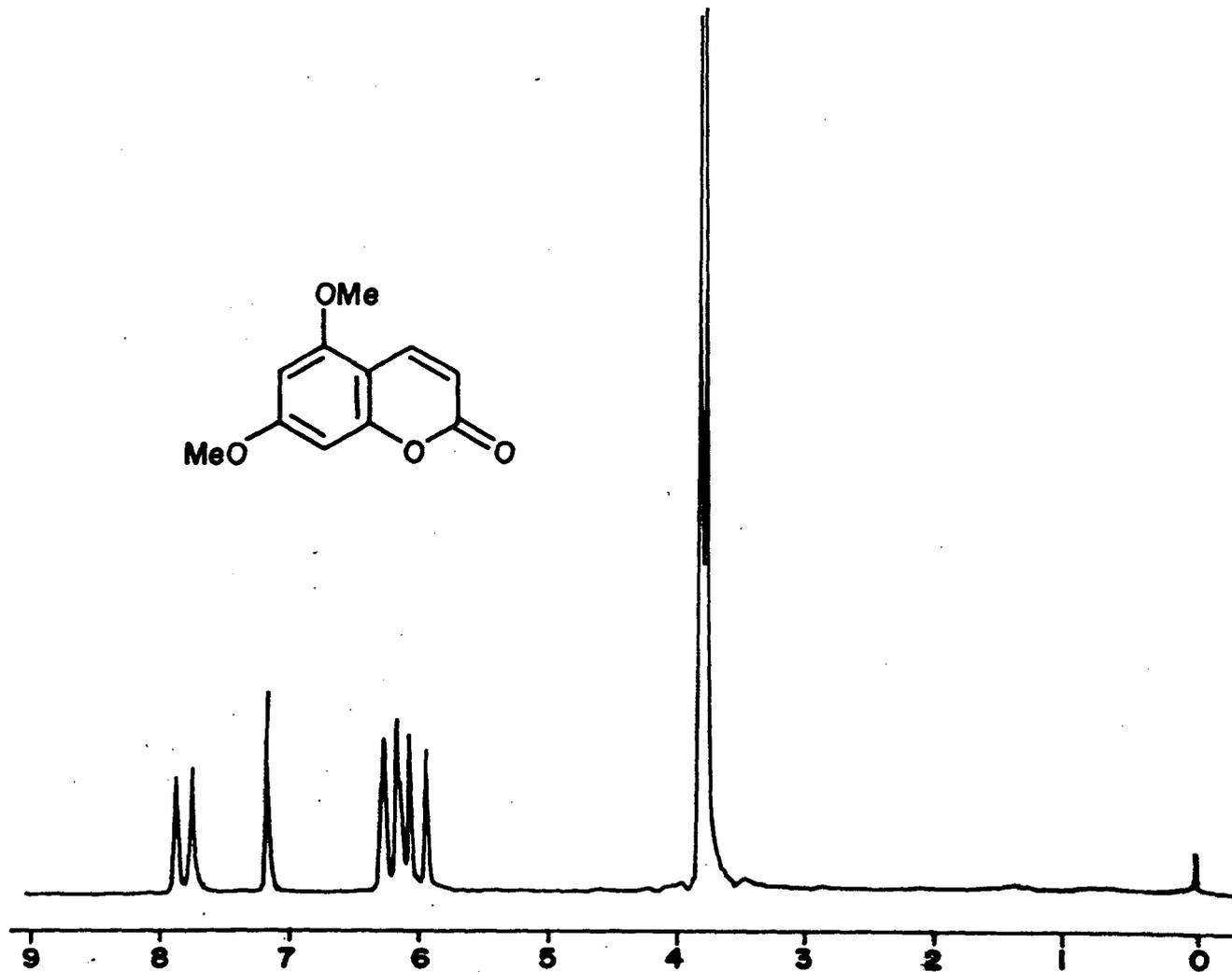
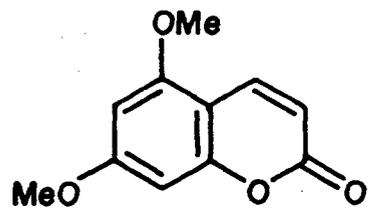


Fig. 13 NMR spectrum of (25)

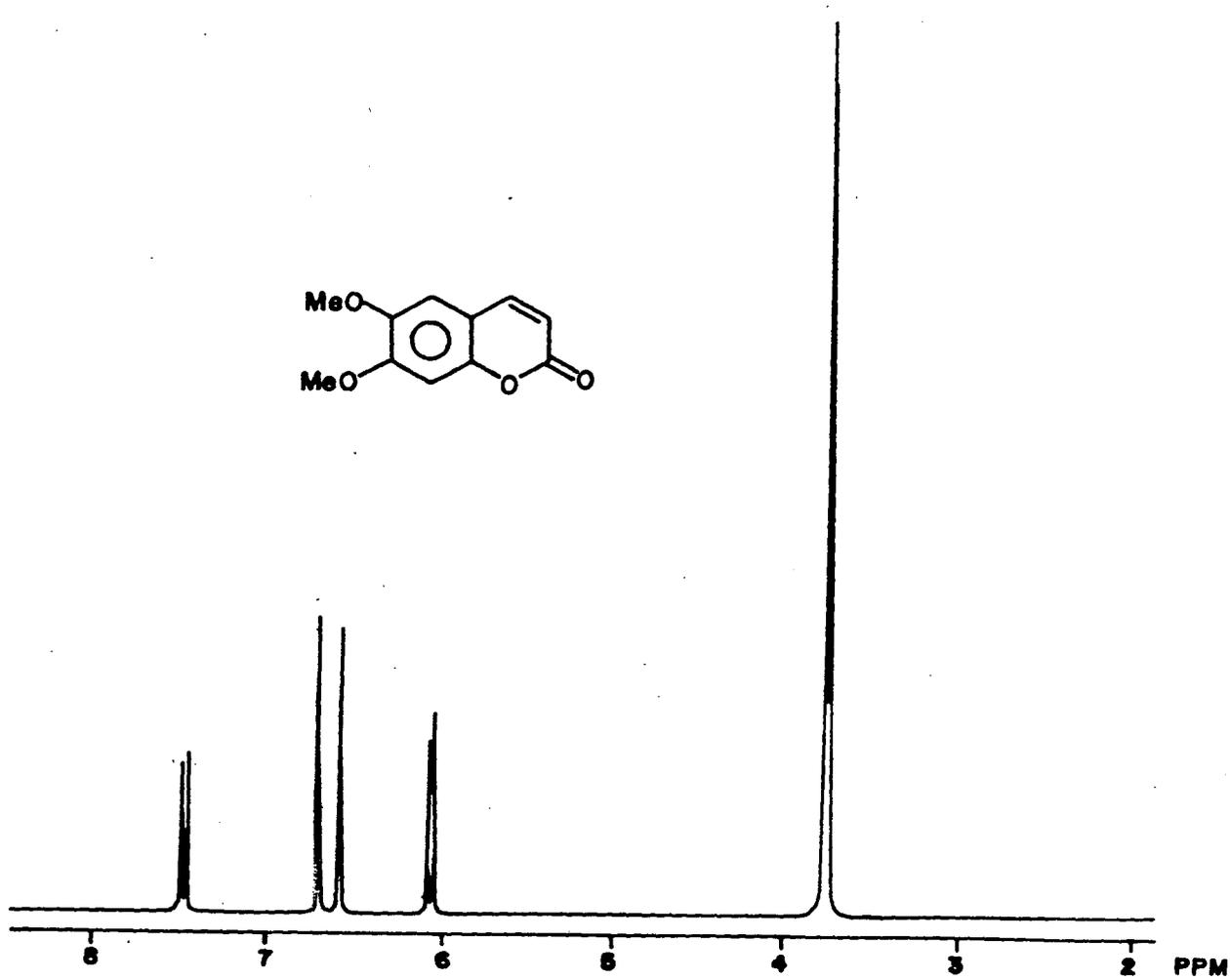
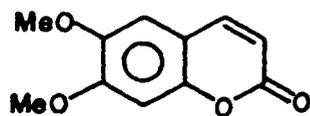


Fig. 14 NMR spectrum of (26)

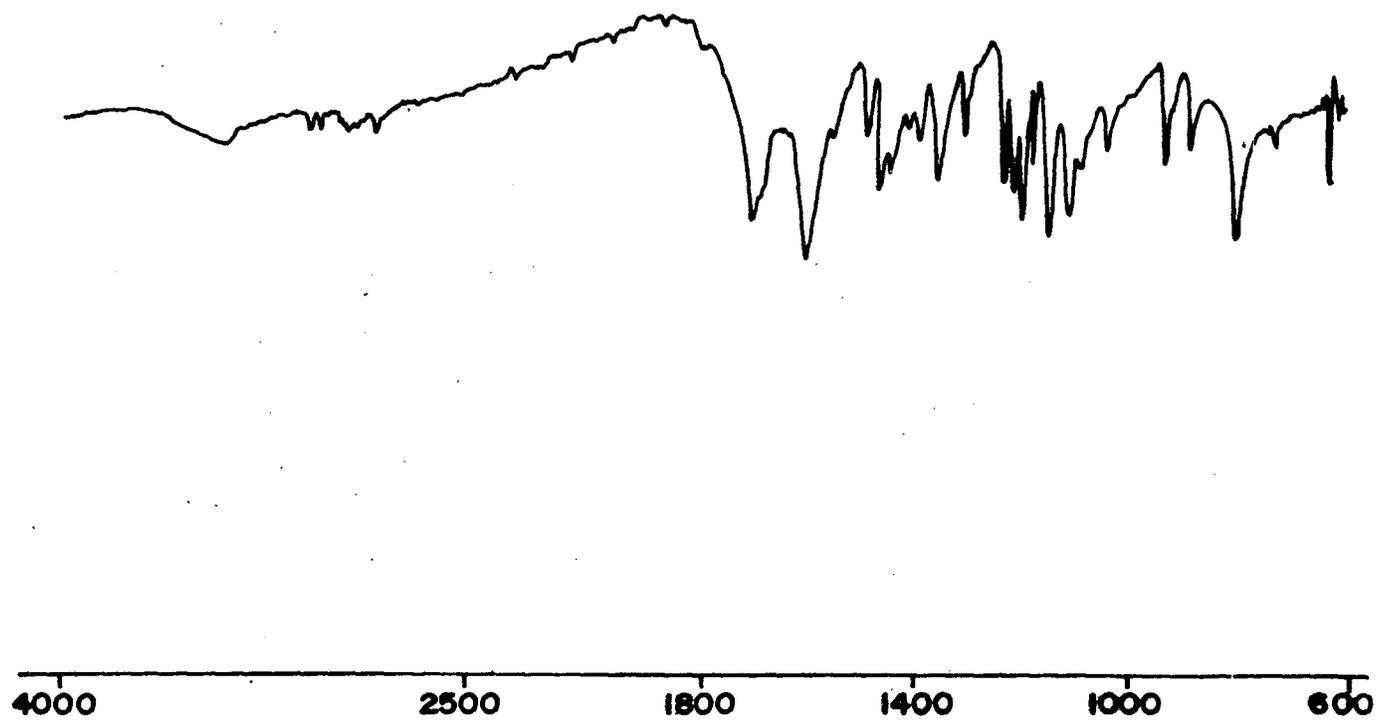
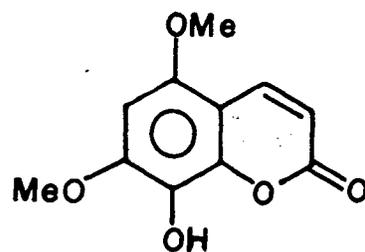


Fig. 15 IR spectrum of (27)

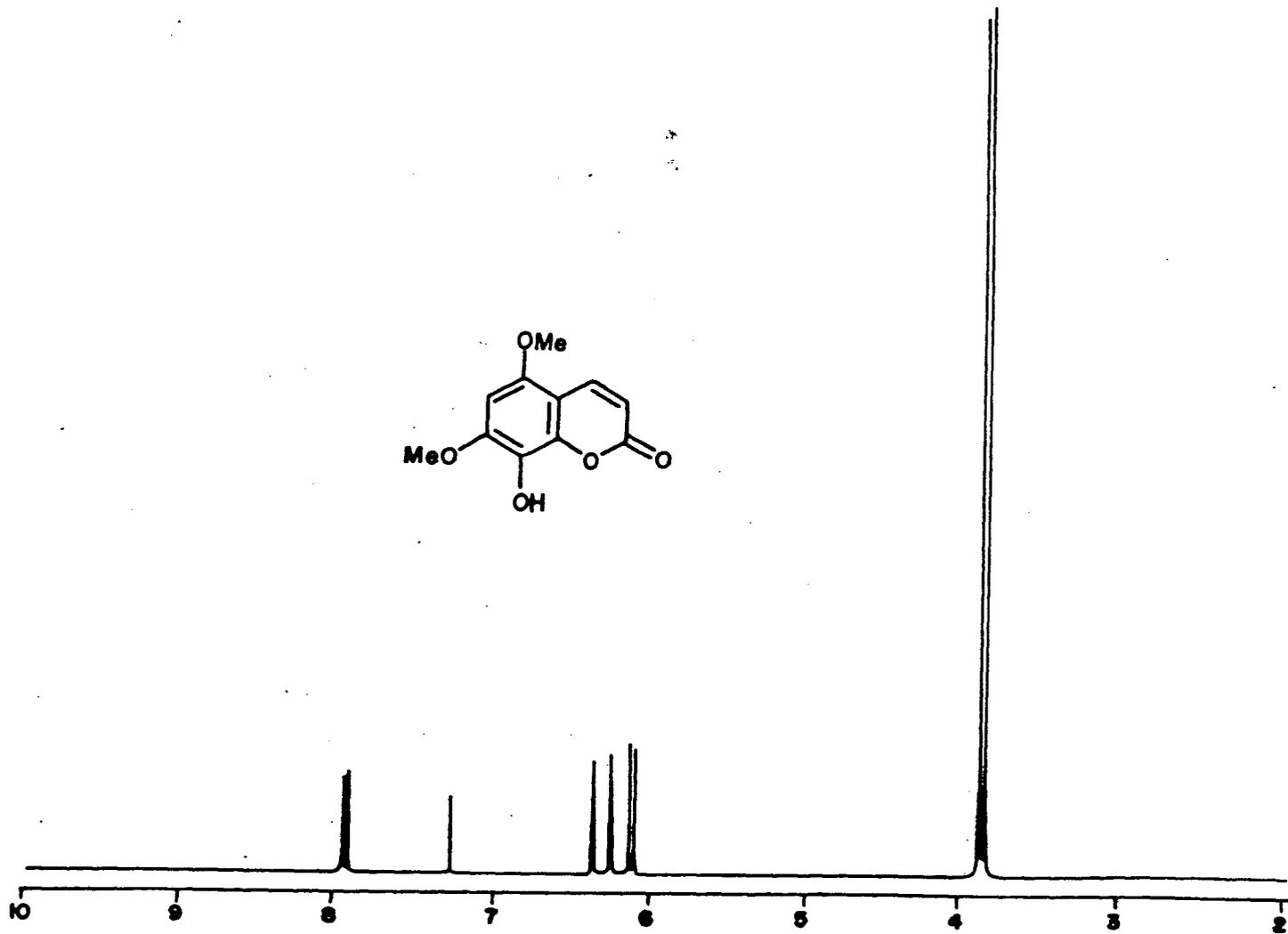
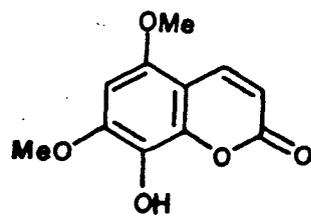


Fig. 16 NMR spectrum of (27)

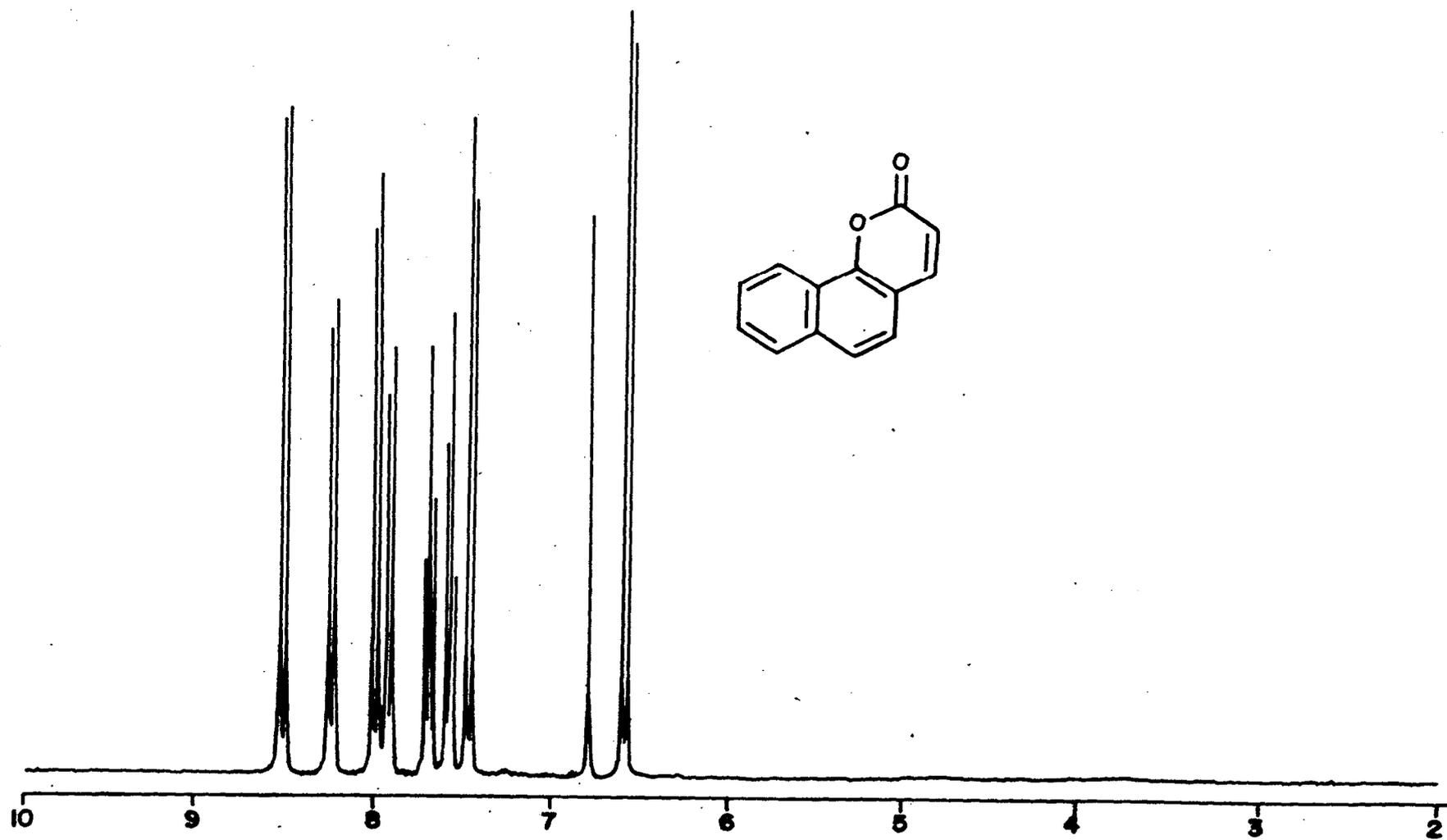


Fig. 17 NMR spectrum of (15)

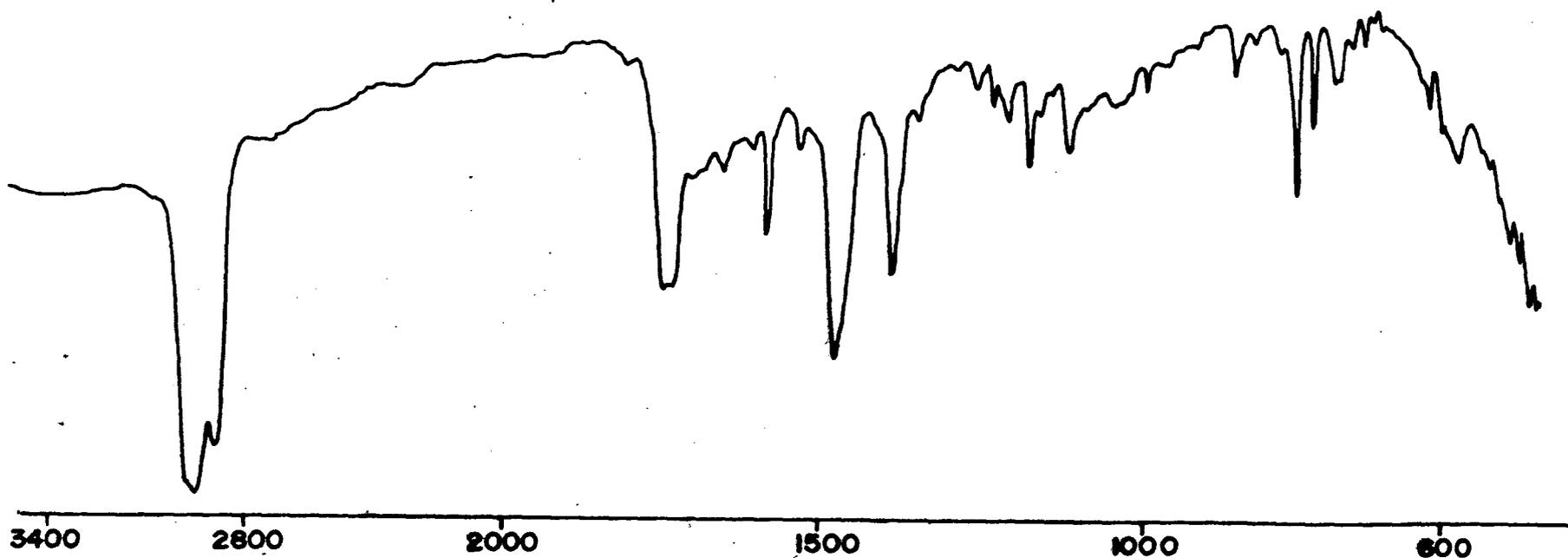
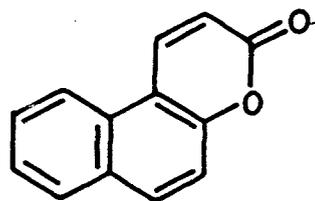


Fig. 18 IR spectrum of (16)

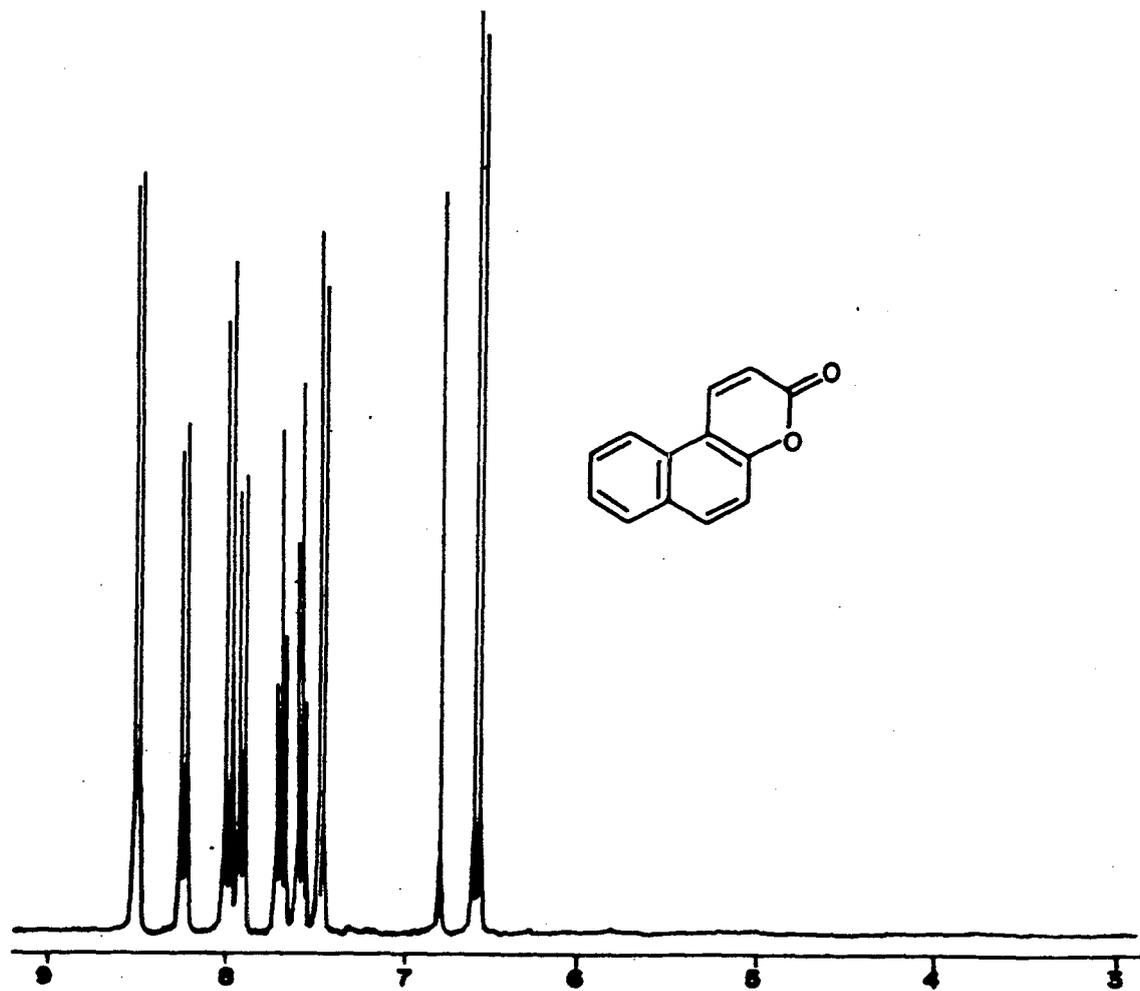


Fig. 19 NMR spectrum of (16)

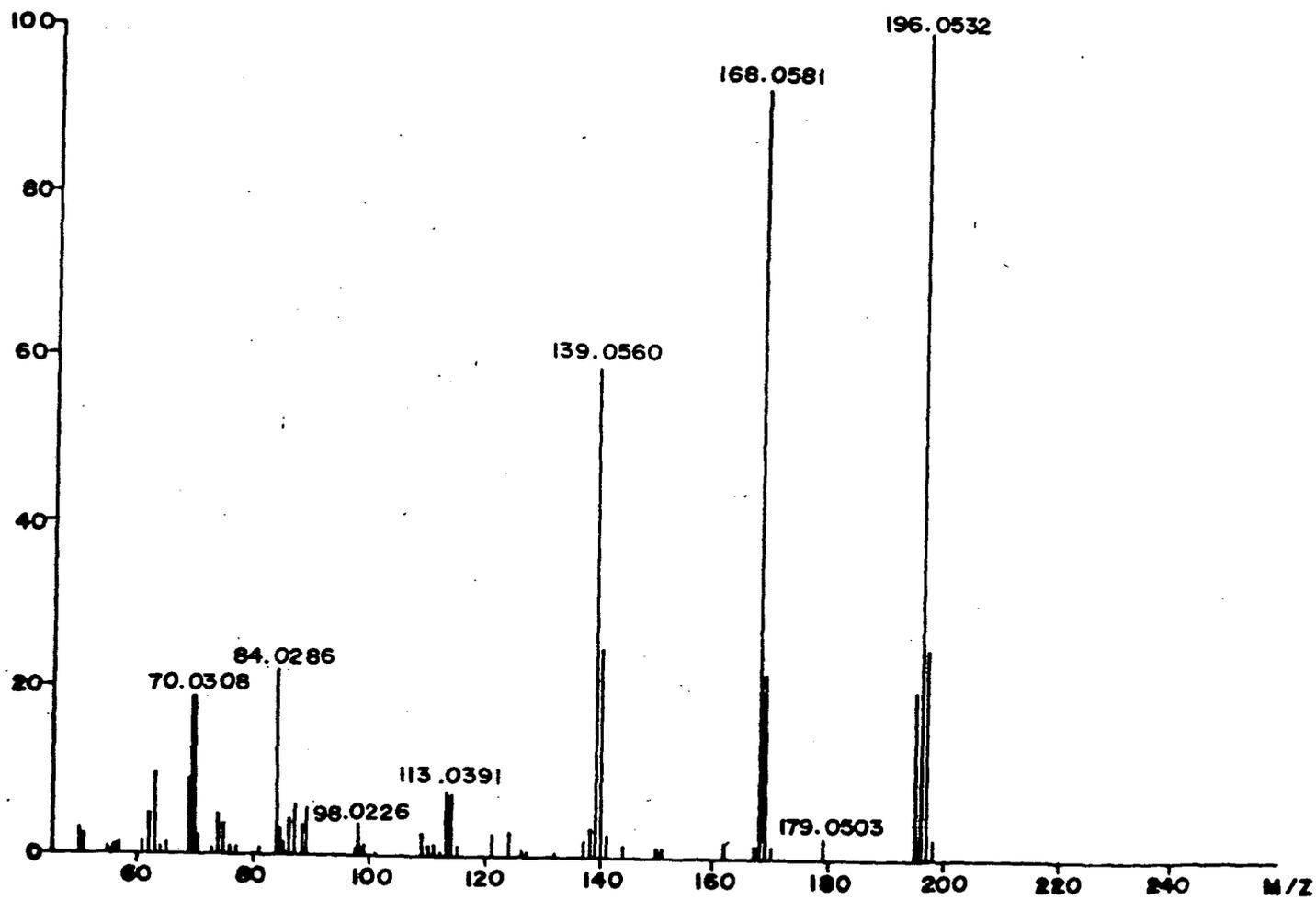


Fig. 20 Mass spectrum of (16)

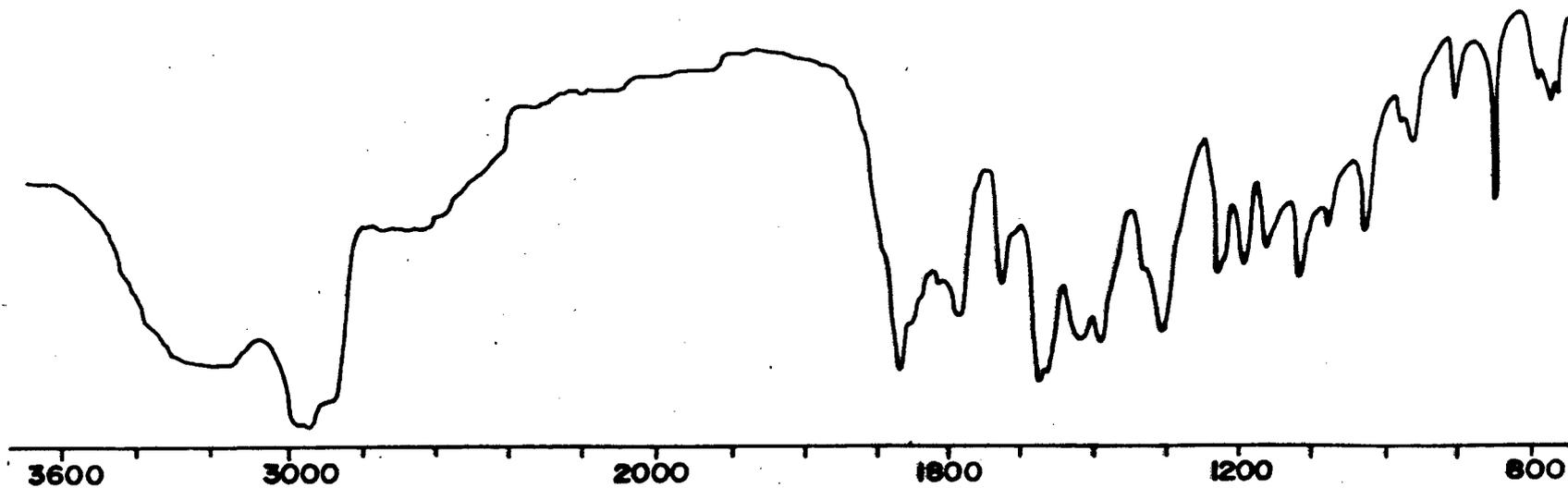
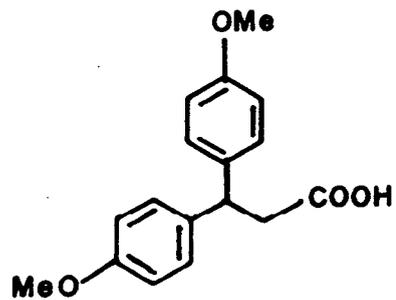


Fig. 21 IR spectrum of (30)

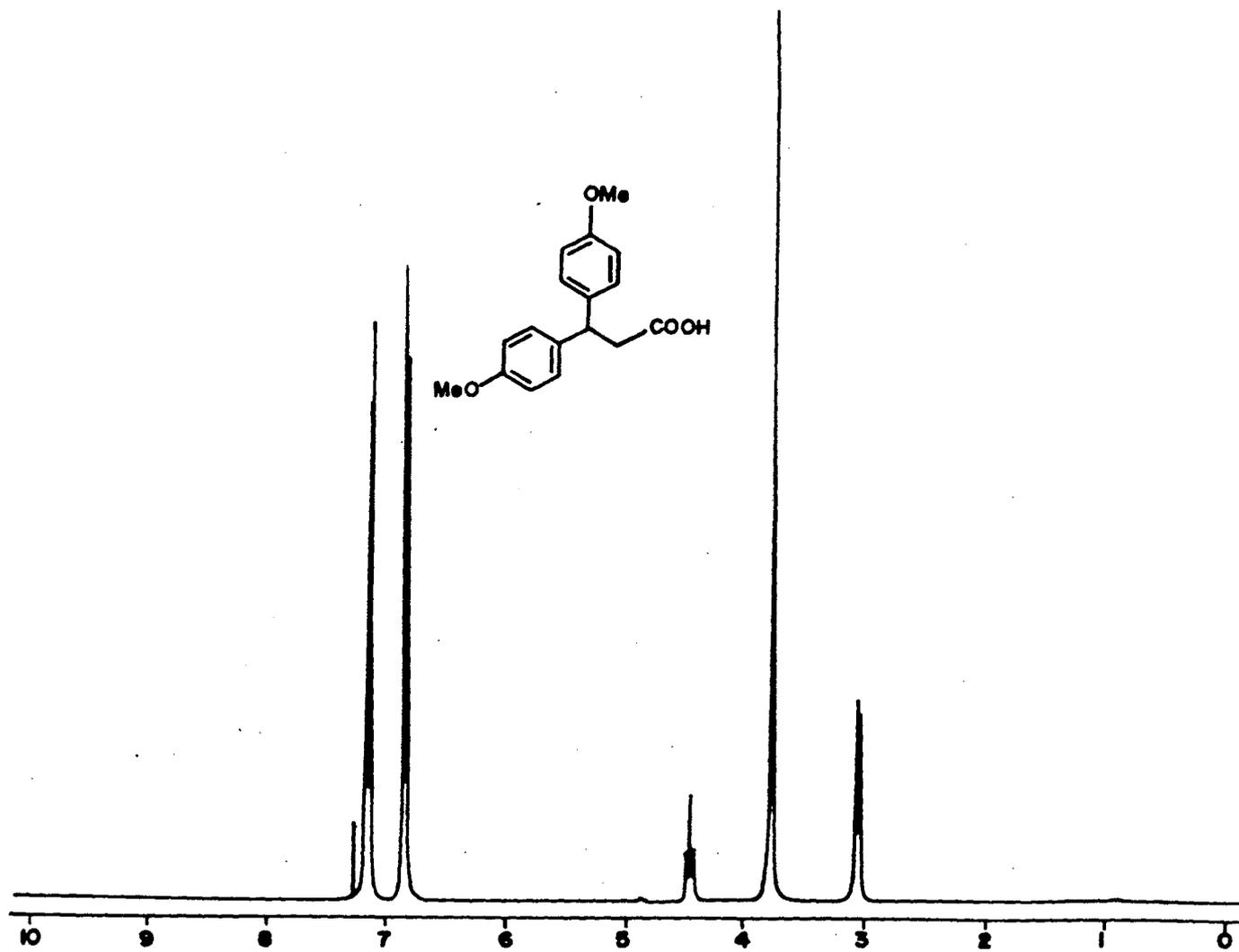


Fig. 22 NMR spectrum of (30)

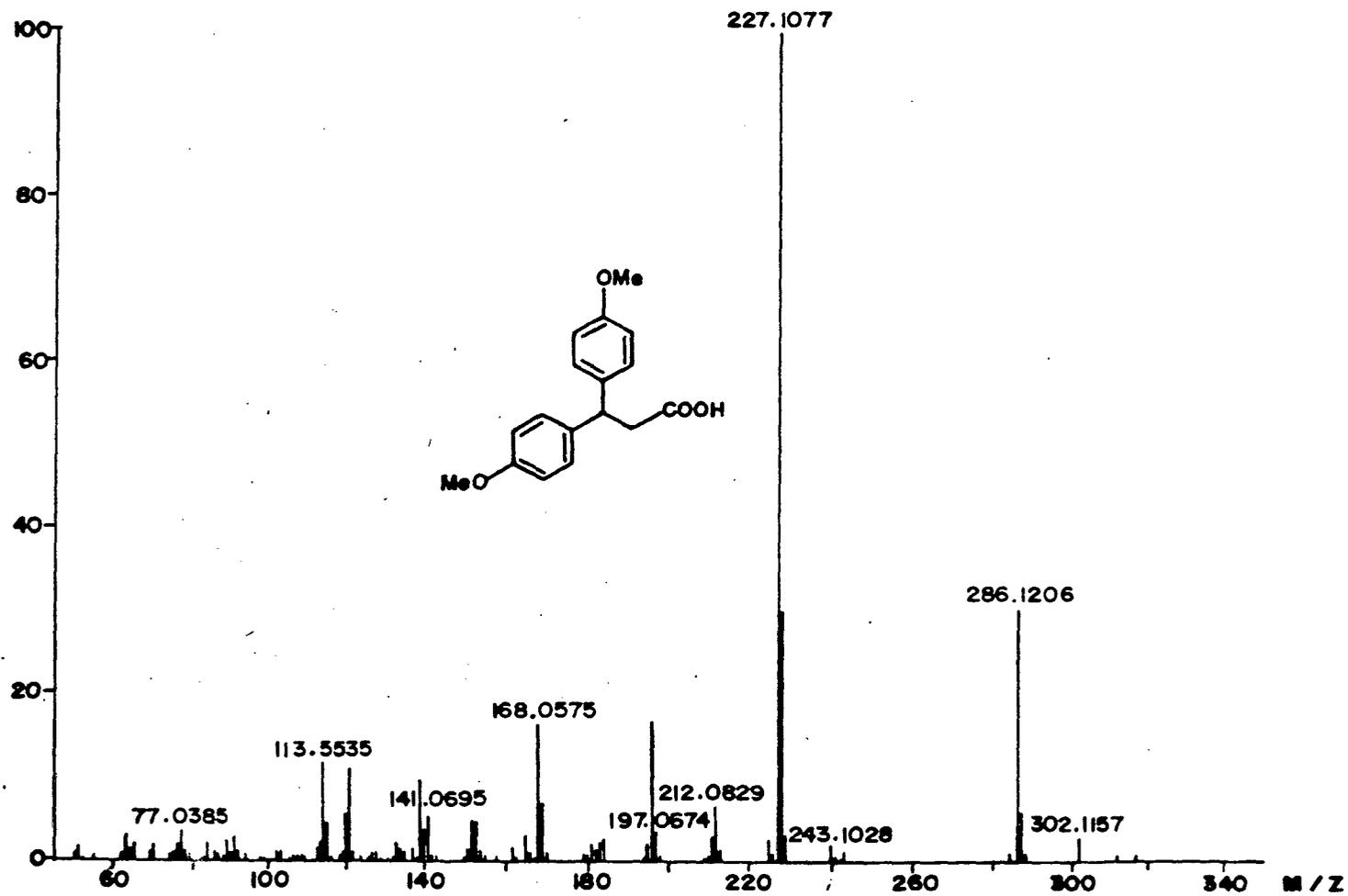


Fig. 23 Mass spectrum of (30)

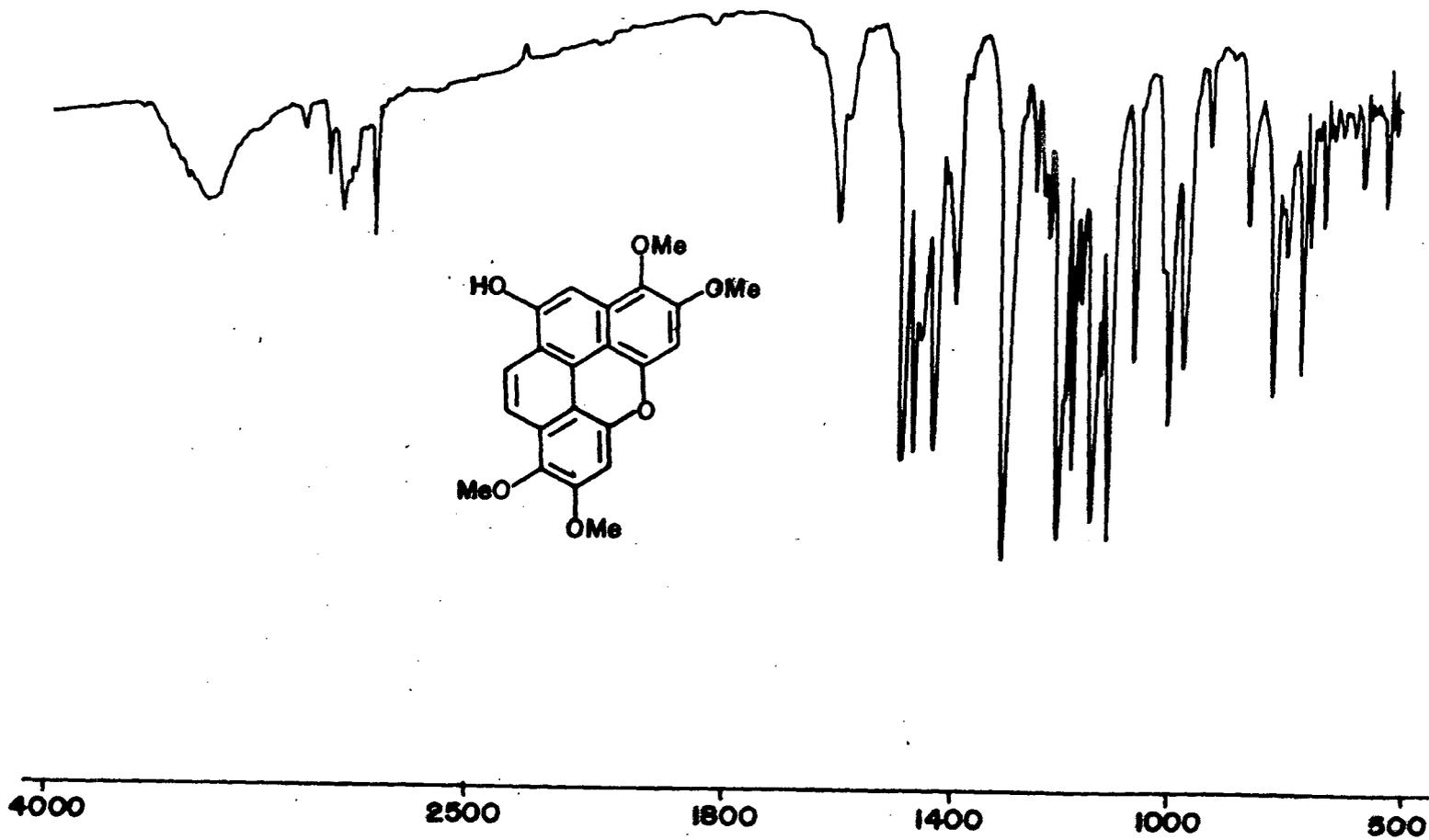


Fig. 24 IR spectrum of (40)

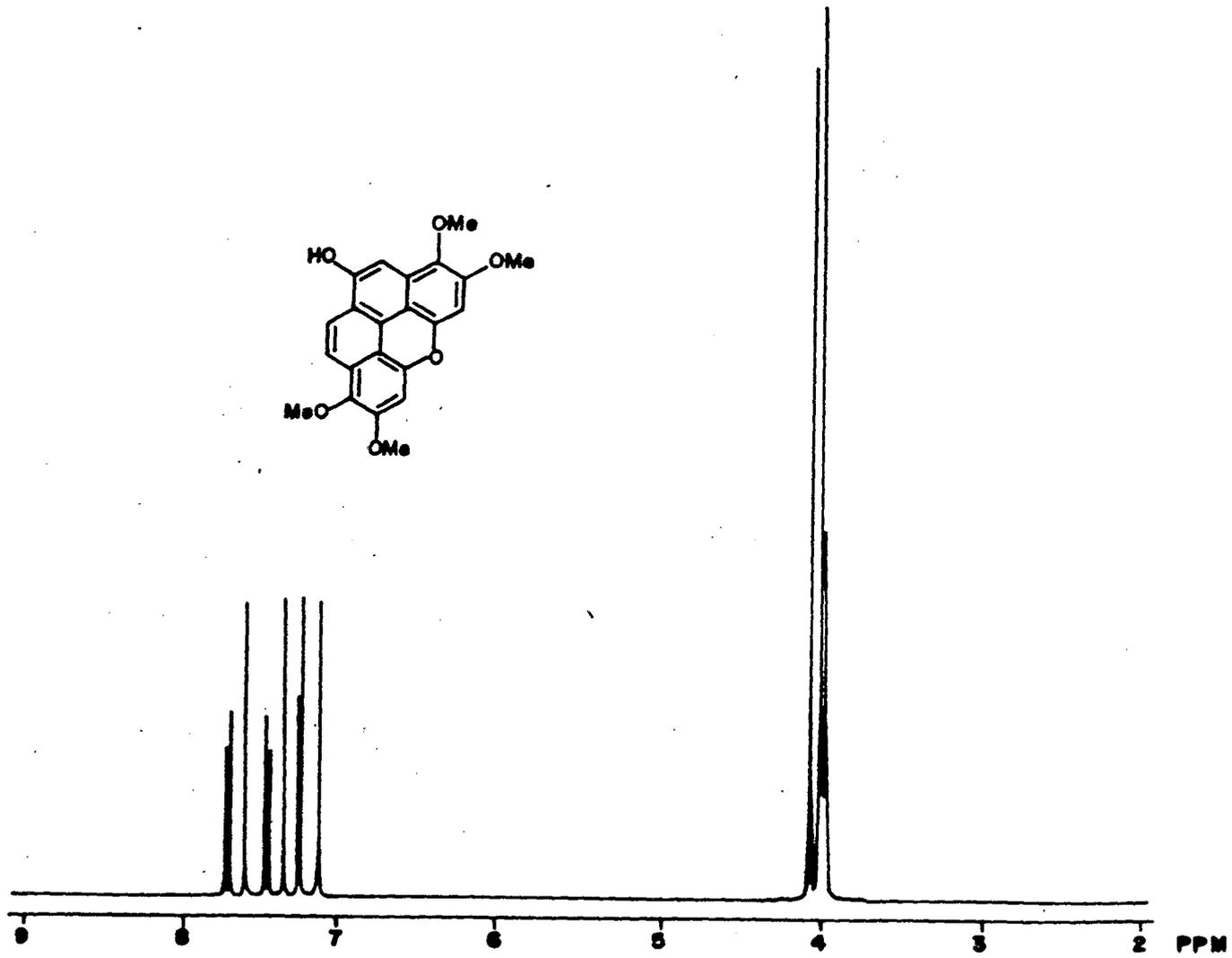


Fig. 25 NMR spectrum of (40)

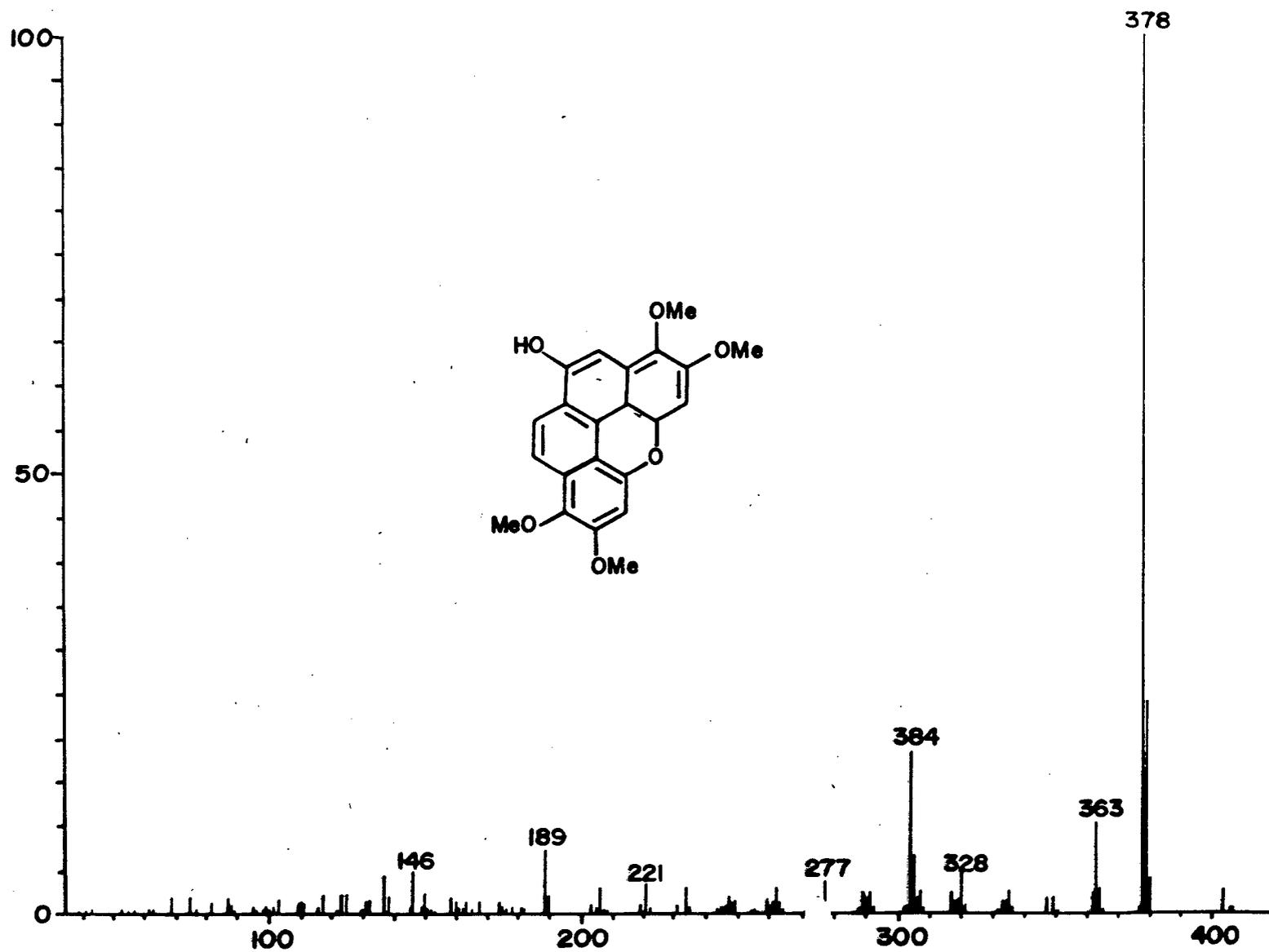


Fig. 26 Mass spectrum of (40)

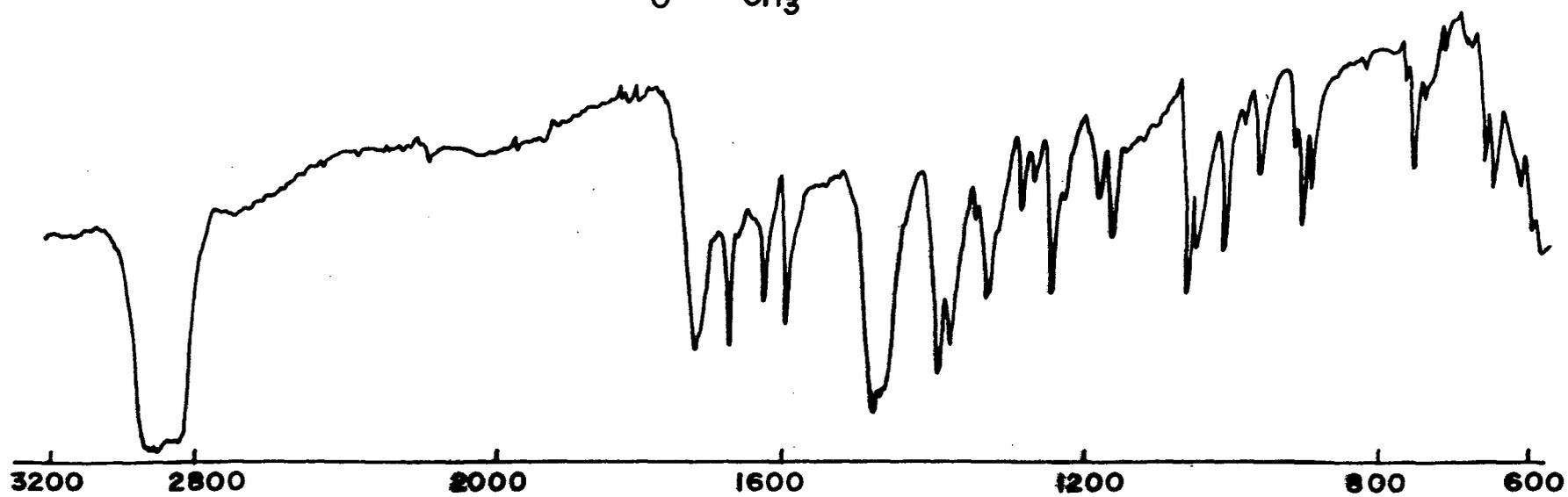
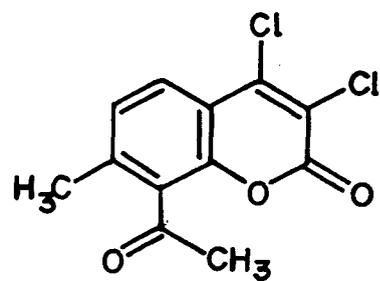


Fig. 27 IR spectrum of (65).

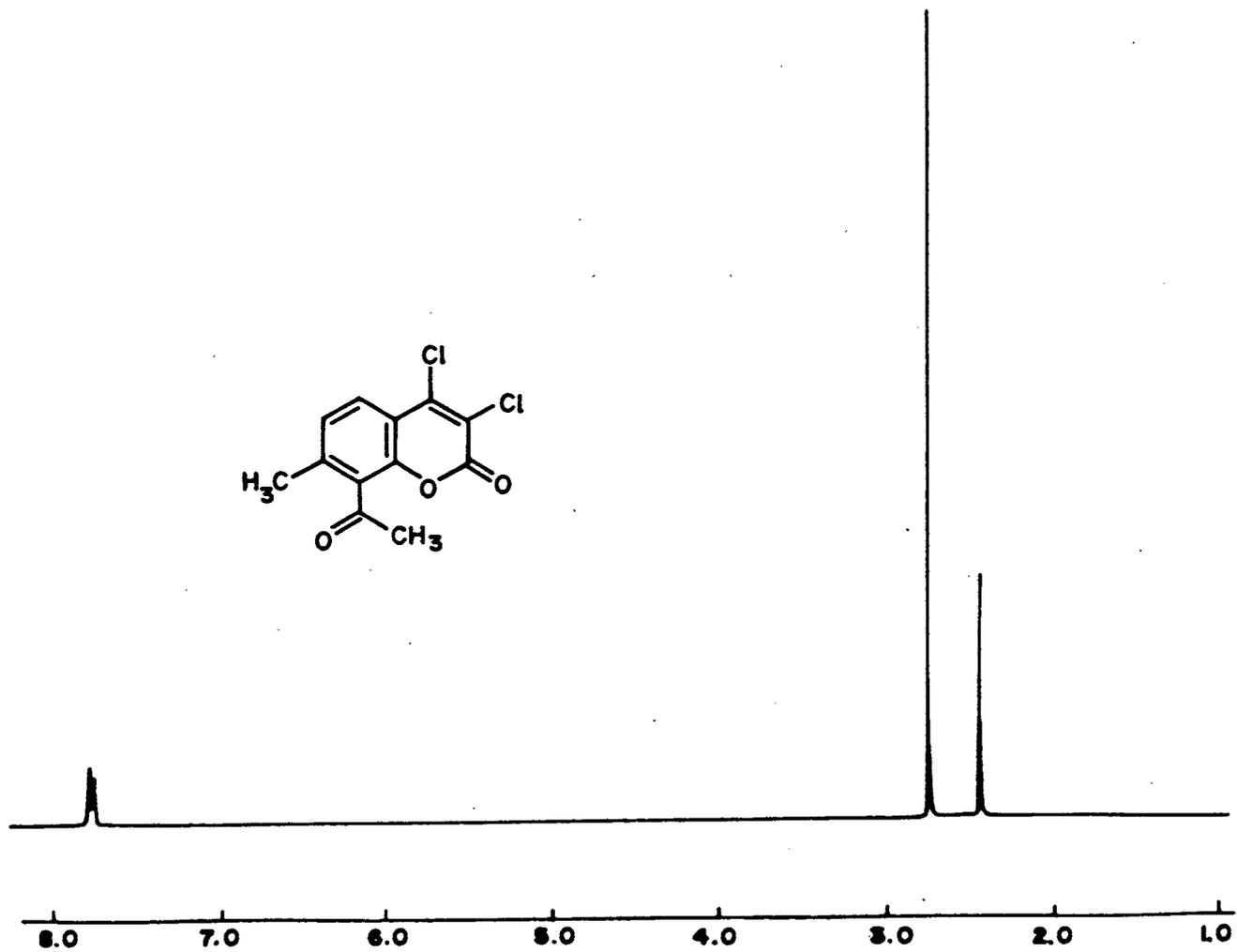
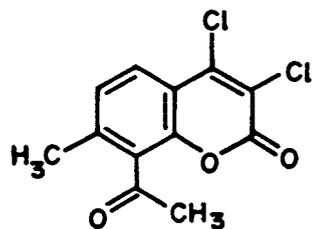


Fig. 28 NMR spectrum of (65)

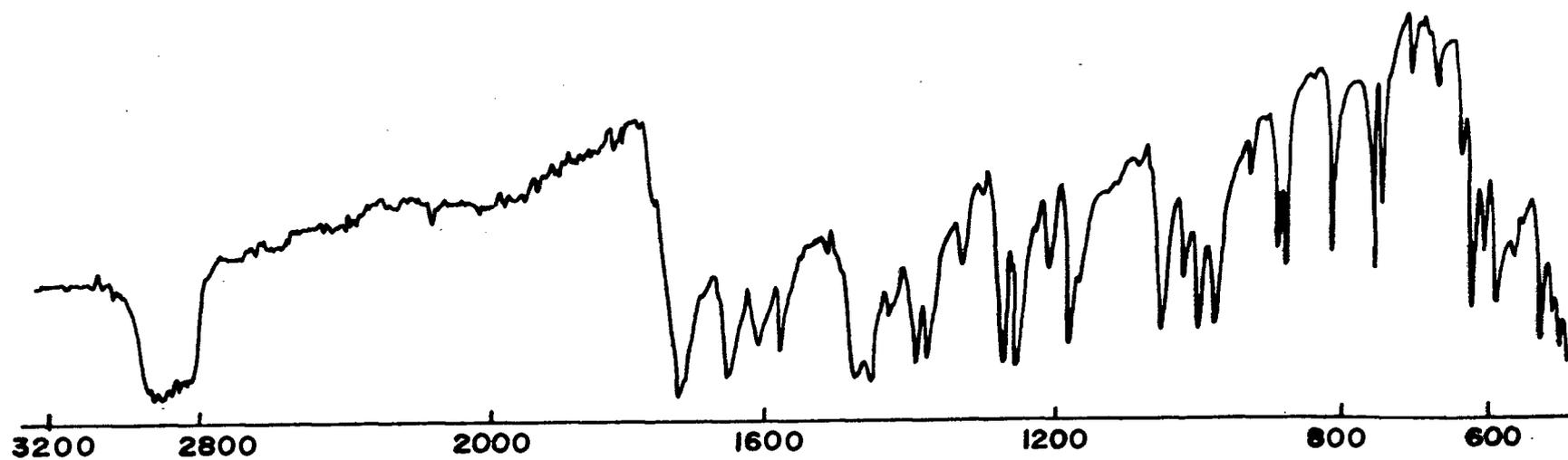
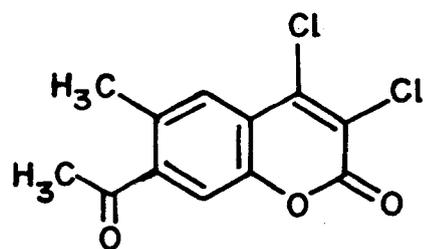


Fig. 29 IR spectrum of (66)

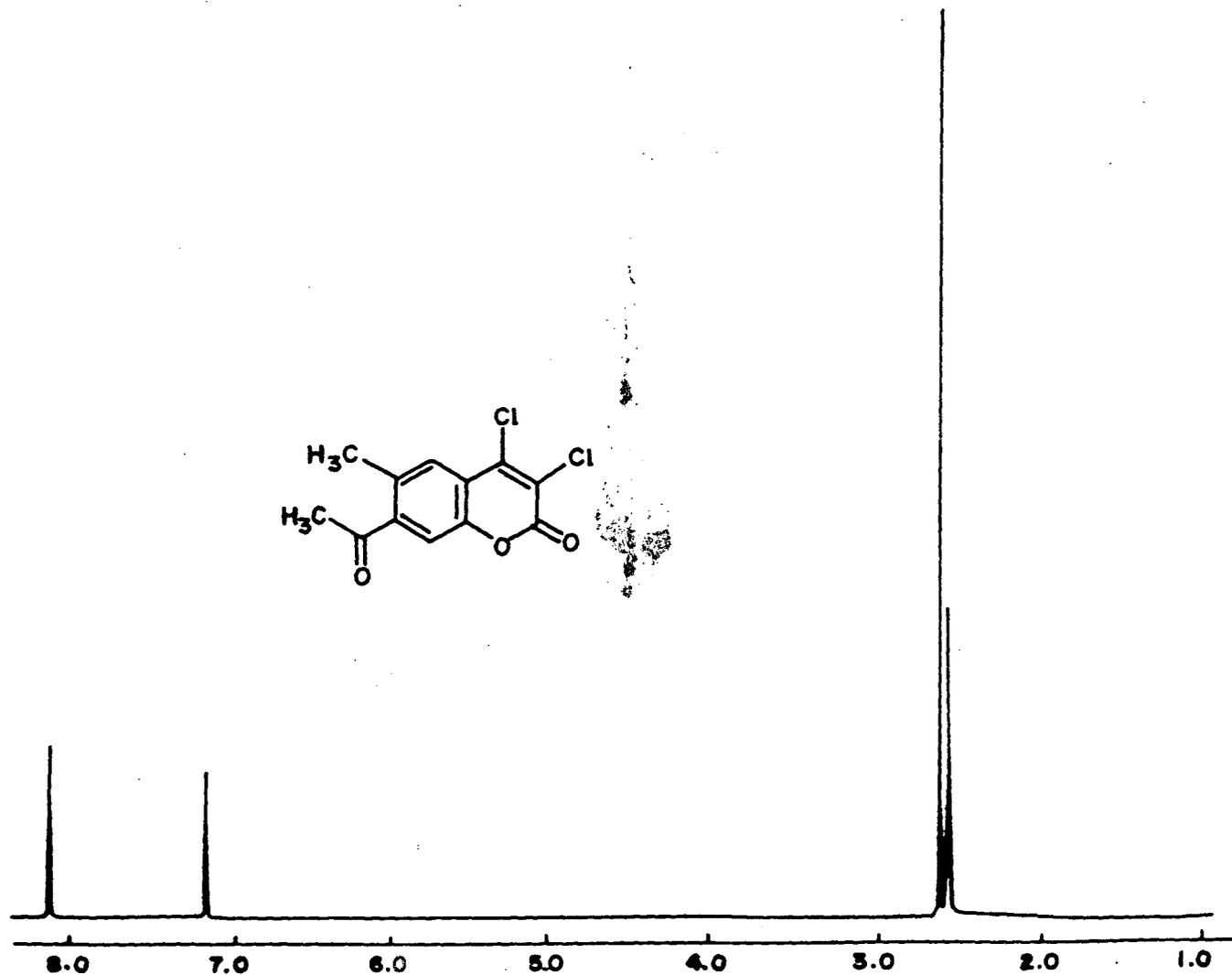
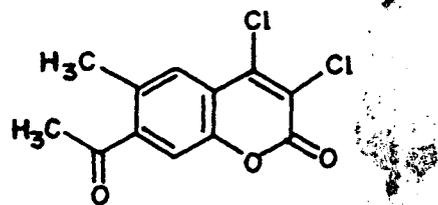


Fig. 30 NMR spectrum of (66)

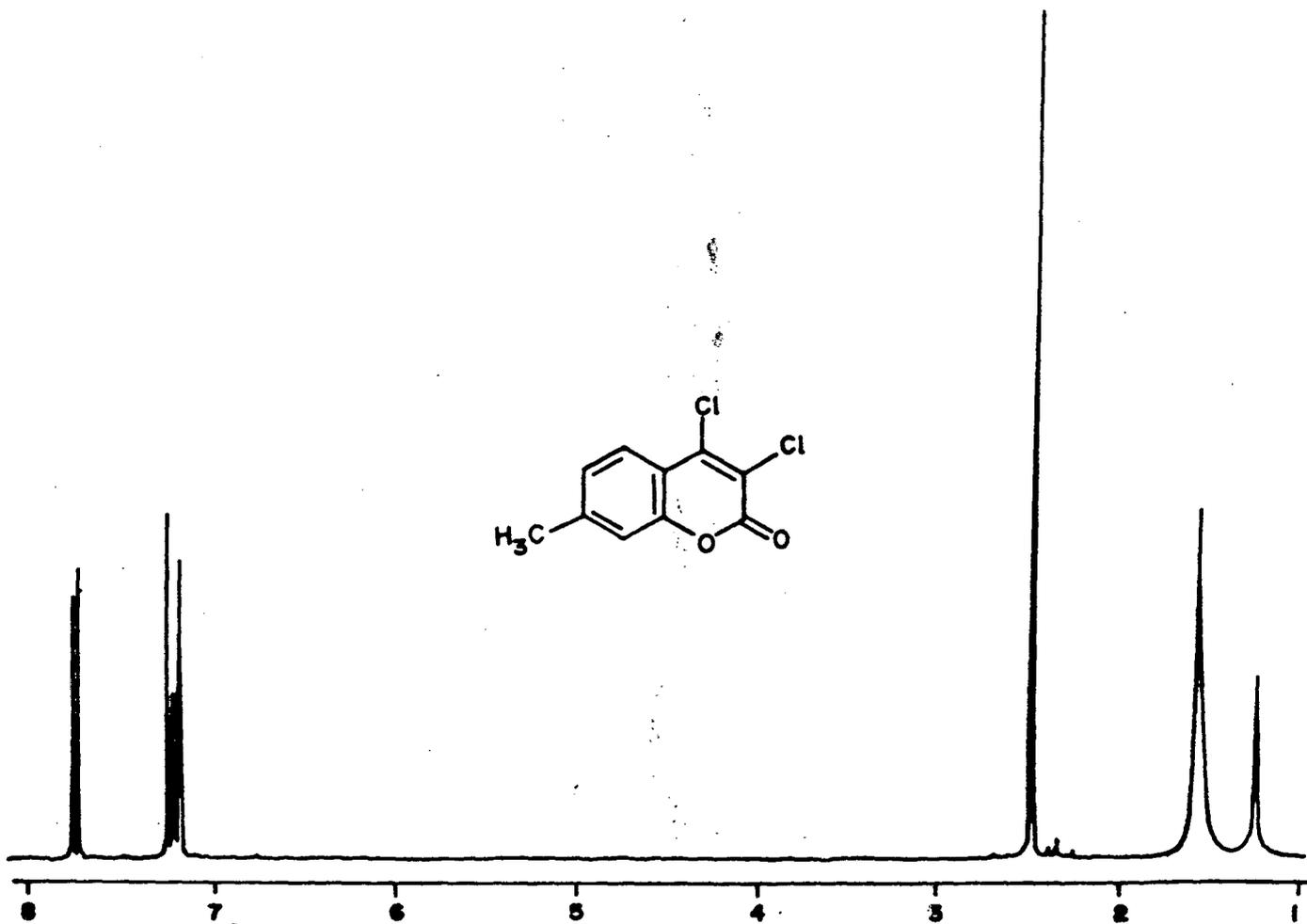


Fig. 31 NMR spectrum of (67)

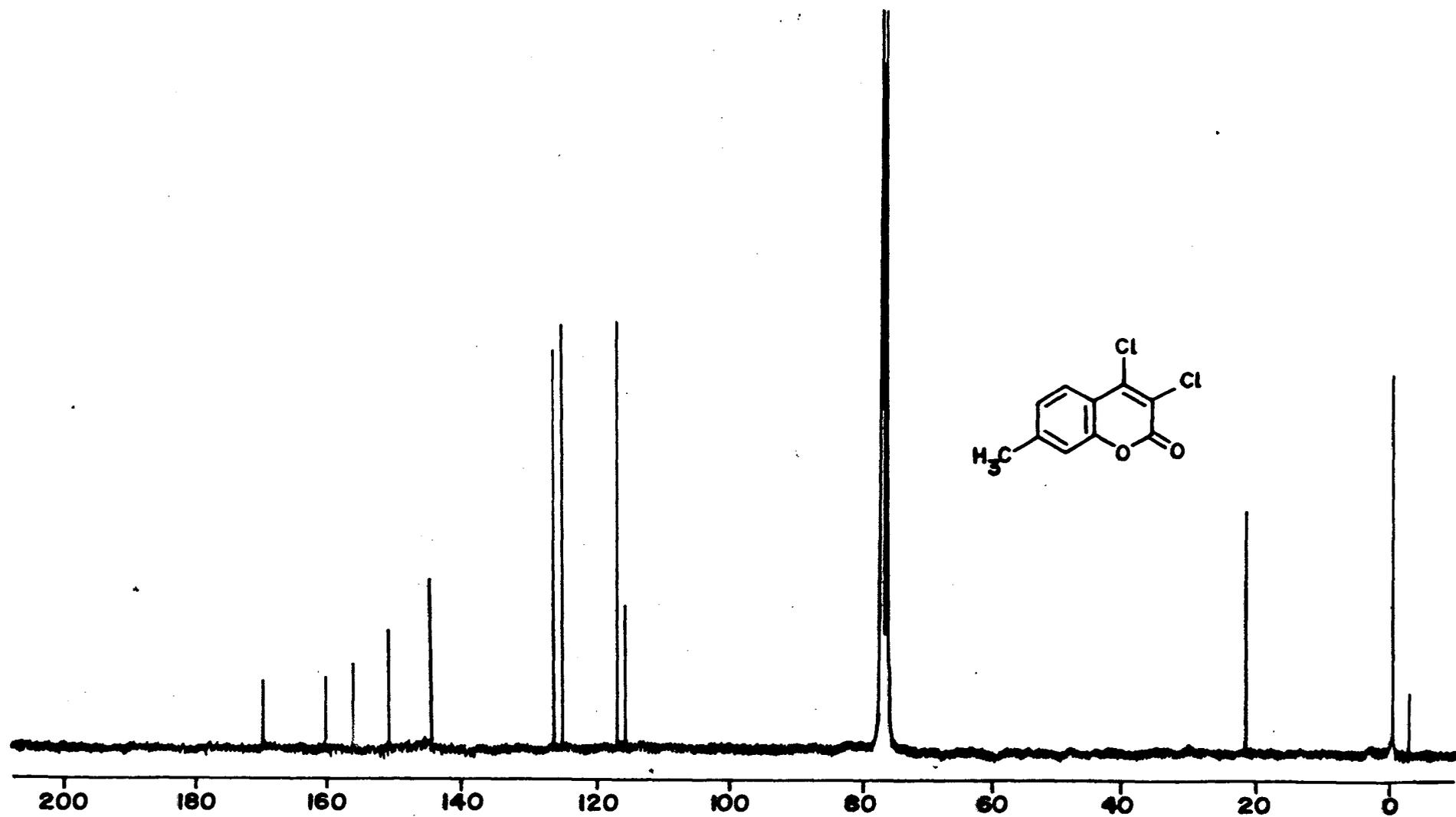


Fig. 32 ^{13}C NMR spectrum of (67)

REFERENCES

1. Perkin, W.H., J. Chem. Soc., 21, 53, (1968).
2. Barton, D.H.R., Hewitt, G. and Sommes, P.G. J. Chem. Soc. Chem. Comm., 16, (1969).
3. Effenberger, F. and Maier, R., Justus Liebigs Ann. Chem., 729, 246, (1969).
4. Wawzonek, S. in Heterocyclic Compounds Vol. 2 (R.C. Elderfield ed.) Wiley N.Y. (1951) pp 173.
5. Cardillo, G., Crichio, R., Merlina, L. and Nasini, G., Gazz. Chim. Ital., 99, 308, (1969).
6. Brown, S.A., Phytochemistry, 2, 137, (1963).
7. Pechmann, H. von., Ber. Deutsch Chem. Ges., 17, 929, (1884).
8. Kauffman, K.D. and Kelly, R.C., J. Heterocycl. Chem., 2, 91, (1965).
9. Das Gupta, A.K. and Das, K.R., J. Chem. Soc. Chem. Comm., 33, (1969).
10. Chatterjee, D.K. and Sen, K., Tett. Lett., 5223, (1969).
11. Kelkar, S.L., Phadke, C.P. and Marina, S., Ind. J. Chem., 23B,458, (1984).

12. Narasimhan, N.S. and Bhide, B.H., *Tett. Lett.* 4159, (1968).
13. Narasimhan, N.S., Mali, R.S. and Barve, M.V., *Synthesis*, 906, (1979).
14. Harvey, R.G., Cortez, C., Ananthanarayan, T.P. and Schmolka, S., *J. Org. Chem.*, 53, 3936, (1988).
15. Panetta, J.A., and Rapoport, H., *J. Org. Chem.*, 47, 946, (1982).
16. Pandey, G., Krishna, A. and Rao, J.M., 27, 4075, (1986).
17. Paknikar, S.K. and Kamat, S.P., *Ind. J. Chem.*, 27B, 773, (1988).
18. Talpatra, B., Deb, T. and Talapatra, S., *Ind. J. Chem.* 25B, 1122, (1986).
19. Bunton, C.A., Kenner, G.W., Robinson, M.J.T. and Webster, B.R., *Tetrahedron*, 19, 100, (1963).
20. Kamat, S.P. and Paknikar, S.K., Unpublished Results.

21. Bhattacharjee, J. and Paknikar, S.K., *Ind. J. Chem.*, 28B, 205, (1989).
22. Desai, R.D. and Vakil, V.M., *Proc. Indian Acad. Sci.*, 12A, 391, (1940).
23. Ahluwalia, V.K., Dhingra, S. and Kapur, K., *Ind. J. Chem.* 18B, 79, (1979).
24. Maniraman, T., Thiruvengadam, T.K. and Ramakrishnan, V.T., *Synthesis*, 739, (1975).
25. Maniraman, T, and Ramakrishnan, V.T., *Ind. J. Chem.*, 18B, 324, (1979).
26. Simpson, J.D. and Israeltam, S.S., *Chem. Abstr.*, 45, 6196d, (1951).
27. Ahluwalia, V.K., Prakash, C. and Bala, S., *Monate. fur Chemie*, 111, 877, (1980).
28. El-Basyouni, S.Z., Chen, D., Ibrahim, R.K., Neish, A.C. and Towers, G.H.N., *Phytochemistry*, 3, 485, (1964).
29. Newmann, M.S. and Schiff, S., *J. Amer. Chem. Soc.*, 81, 2266, (1959).
30. Zdero, C., Bohlmann, F., King, R.M. and Robinson, H., *Phytochemistry*, 25, 2873, (1986).

31. Merchant, J.R. and Rege, D.V., *Ind. J. Chem.*,
1419, (1971).
32. Martin, R. and Demarseman, P., *Synthesis*, 25,
(1989).

Introduction

Lead tetraacetate is undoubtedly one of the most versatile reagents used in organic chemistry. Its use ranges from the more common oxidative cleavages of 1,2-diols, α -hydroxy ketones, 1,2-diketones and hydroxy acids to the uncommon conversion of olefins to γ -lactones and aldehydes to nitriles.

Some of the above reactions are similar to those with periodates, the only difference being that periodates are predominantly used in aqueous media while lead tetraacetate mainly in non-aqueous solvents.

The other useful applications of lead tetraacetate are acetylation at allylic and benzylic positions, cyclisation of alcohols having a hydrogen, oxidative decarboxylation of carboxylic acids, the conversion of cyclopropanes to bisacetates and olefins to bisacetates of glycols.

Nitrogen containing functional groups also react with lead tetraacetate, the more notable

examples are the conversion of primary amines to azo compounds and the degradation of amides to amines via isocyanates.

This chapter deals with the use of lead tetraacetate to effect some selective oxidations in the terpenoids - cis-homochrysanthemic acid, maaliol and guaiol.

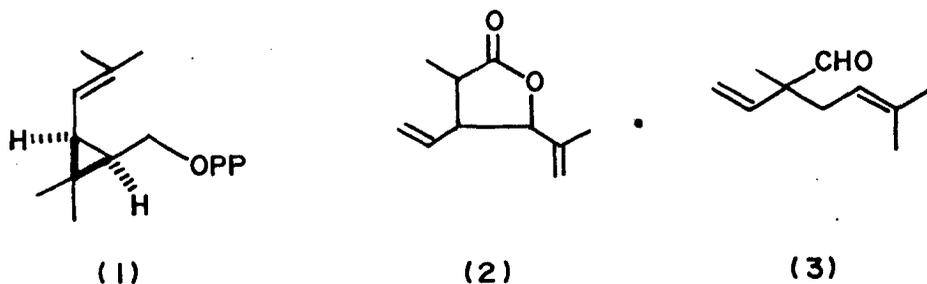
CHAPTER - II

SECTION - I

REACTION OF CIS-HOMOCHRYSANTHEMIC ACID WITH LEAD
TETRAACETATE

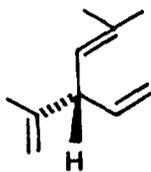
Terpenoids whose carbon skeletons do not fit into the biogenetic isoprene rule are called irregular terpenoids. Their biogenesis almost always involves rearrangements, cleavages of C-C bonds of the "regular" precursors and several interesting modifications. Due to their departure from the biogenetic isoprene rule, irregular terpenoids have always posed challenges to chemists with respect to their structures, biogenesis and synthesis.

We have been interested in the chemistry of irregular terpenoids which are derived from chrysanthemyl pyrophosphate (1). Since the original biogenetic proposal¹, we have extended these ideas to propose the correct structure for the C-10 lactone (2), isolated from *Artemesia tridentata* by



Hoerger² and the biogenesis³ of 2,5-dimethyl-2-vinyl-4-hexenal (3), an irregular monoterpene isolated by Corbier and Teisseire⁴.

Santolina triene (4), the parent member of the group of irregular monoterpene having the santolinyll skeleton was first isolated by Thomas and Willhalm from the oil obtained from flowers of Santolina chamaecyparissus⁵. The structure was



(4)

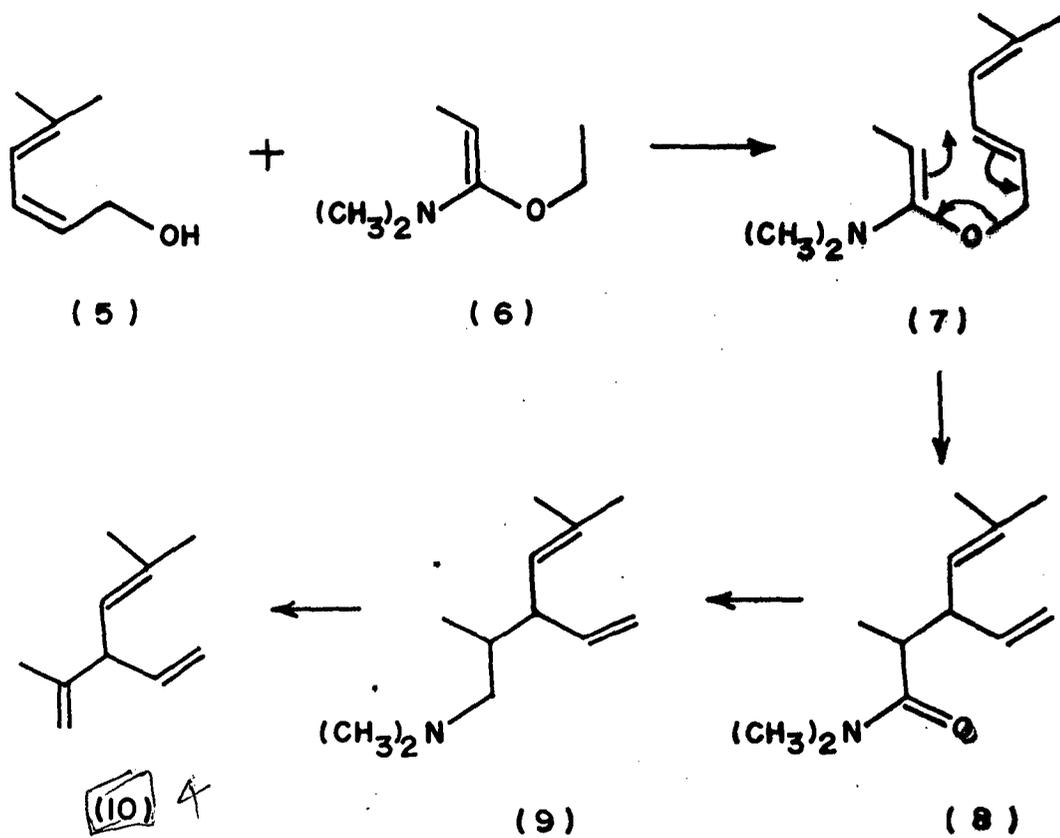
assigned on the basis of mass, NMR. and IR. data.

The absolute configuration was fixed as S-(+) by the application of the sequence rule. Recently Epstein and Gaudioso⁶ isolated santolina triene from the neutral pentane extract of the leaves and flowerheads of Artemesia tridentata rothrockii.

Because of our continued interest in biogenetically aberrant terpenoids, we chose to synthesise optically active santolina triene.

Santolina triene was first synthesised by Sucrow⁷ in 1968, from 5-methyl-2,4-hexadiene-1-ol (5). This on heating with a twofold excess of 1-ethoxy-1-dimethyl aminoprop-1-ene (6) in xylene, underwent Claisen's reaction of the initially formed ketene - O,N - acetal (7) leading to the dimethyl amide (8). Reduction of the amide to the amine (9) followed by pyrolysis of the corresponding N-oxide afforded santolina triene. (Scheme - 1).

Thomas⁸ in 1970 synthesised santolina triene from yomogi alcohol epoxide (10). On treatment with p-toluene sulphonic acid, the epoxide (10) yields the santolinyl skeleton either as cyclised substances (14 & 15) or as a diol (13). However acid catalysed rearrangement of the epoxide (10) in presence of excess benzaldehyde furnishes two acetals (16 & 17) as the major products which on treatment with n-butyl lithium in hexane affords



Scheme - I

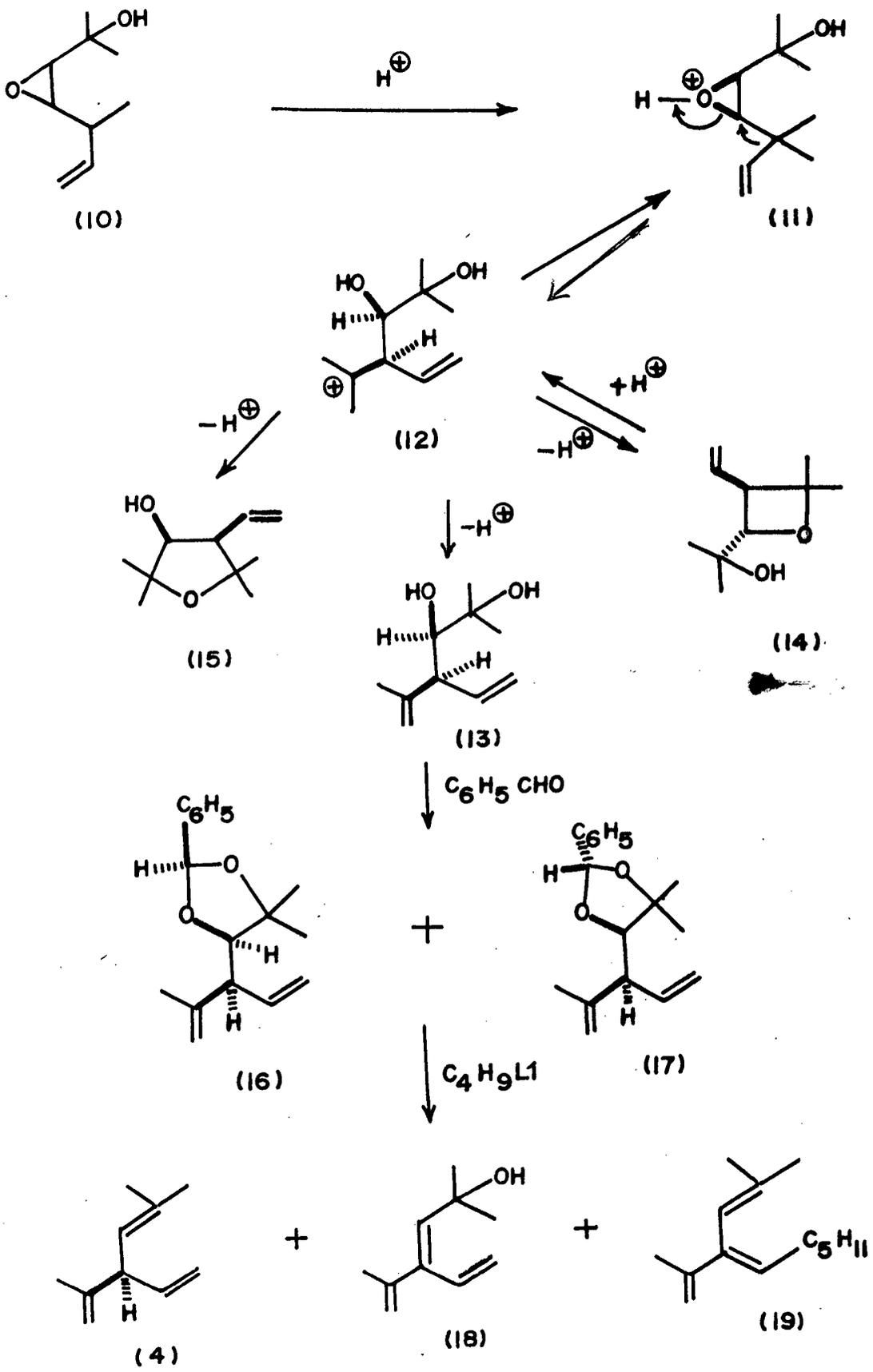
santolina triene (4) in low yields. (Scheme - 2).

Another entry into the santolinyl skeleton is a synthesis of santolina alcohol by Moiseenkov et al⁹. They utilised the cyclopropyl carbonyl - homo allyl rearrangement of adducts which are produced by tandem addition of vinyl magnesium bromide and an appropriate carbonyl compound to the cyclopropane. ^e

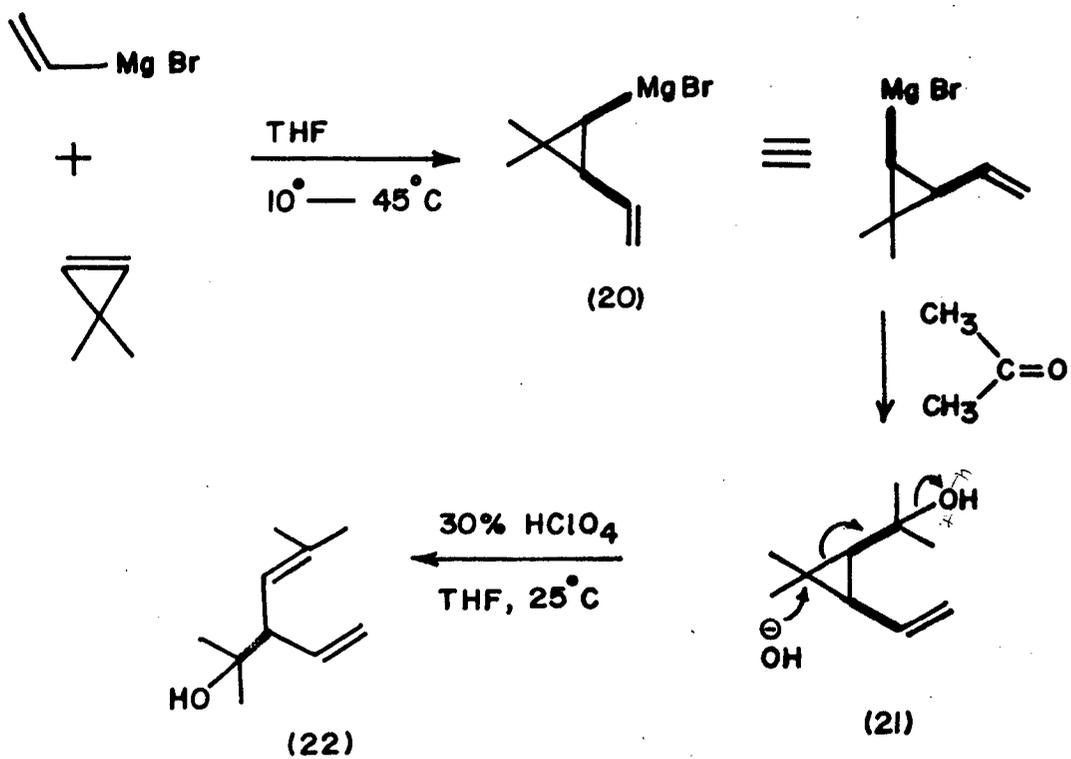
The Grignard reagent (20) obtained from methyl cyclopropane and vinyl magnesium bromide in THF was treated with acetone gave the tertiary alcohol (21) in about 20% yield. Acid catalysed rearrangement of the tertiary alcohol (21) gave (\pm) - santolina alcohol (22) in 87% yield. The alcohol may be in principle be dehydrated to santolina triene.

(Scheme - 3).

Synthesis of optically active santolina triene was first achieved by Takano et al¹⁰. They reported the synthesis of R-(-)-santolina triene (4) in 15% yield from (S)-O-benzyl glycidol (23) via the γ -lactone intermediate (29). Reduction of (29) with DIBAL-H yielded (30) which on Wittig reaction with



Scheme -2

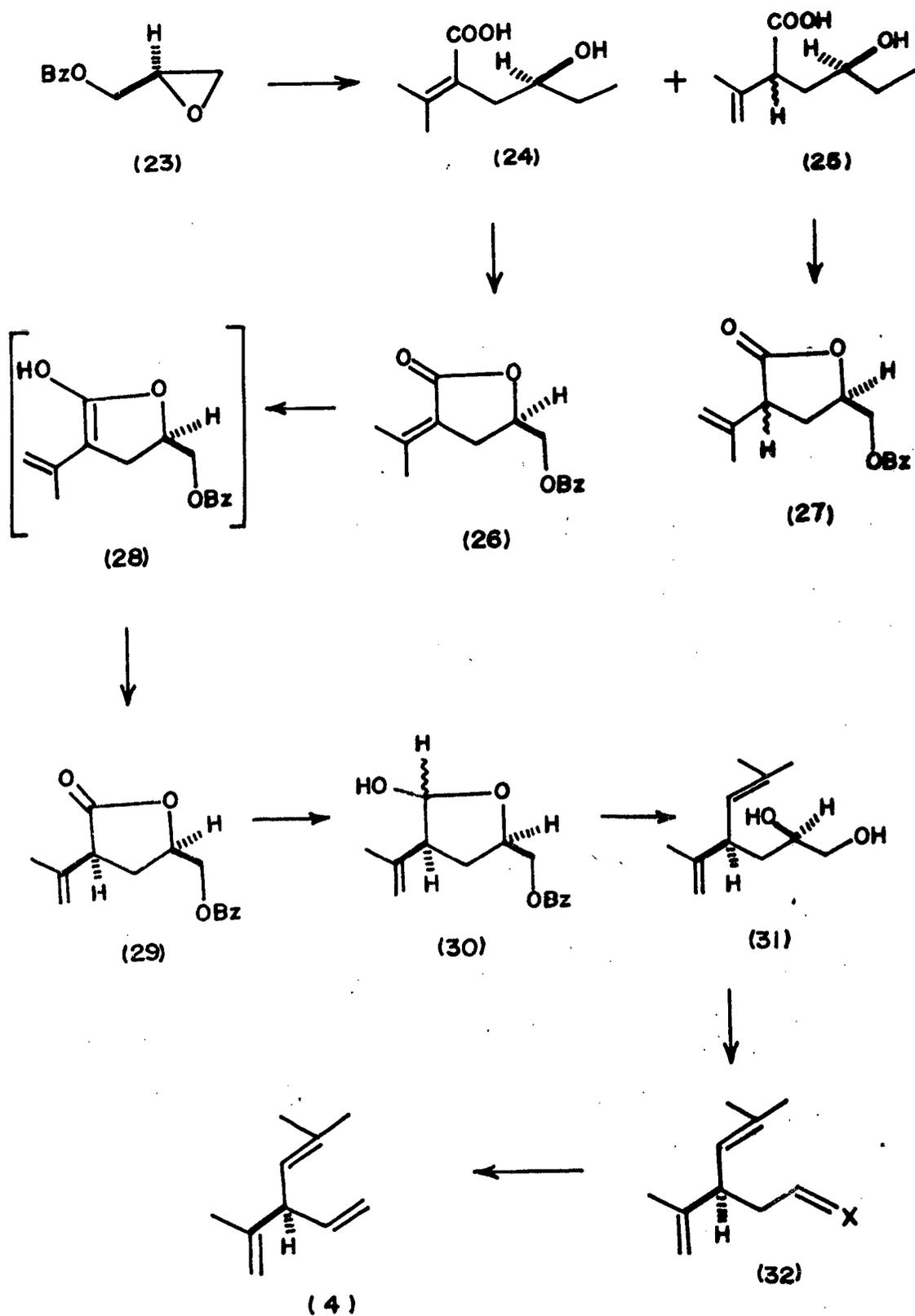


Scheme -3

isopropylidene triphenyl phosphorane furnished (31). This on treatment with Li/liq. NH_3 , aq. NaIO_4 and NaBH_4 yielded (32). The alcohol (32, X=OH) could be transformed into R(-)-santolina triene via the selenide (32, X=H, o- $\text{NO}_2\text{C}_6\text{H}_4\text{Se}$) by employing the Sharpless-Grieco olefination reaction. (Scheme - 4).

Previous work in our laboratory concerned the synthesis of R(-)-santolina triene from (+)-3-carene¹¹. (+)-3-carene, the main constituent of turpentine oil of Eastern Europe and India, has been used extensively in the synthesis of many natural products because of its ready accessibility.

The keto acid (35) previously prepared from (+)-3-carene (33)¹² seemed to be an ideal point of departure. It had been reported earlier that cyclopropane acetic acid on reaction with lead tetraacetate in presence of pyridine and added copper(II) salts (Kochi reaction¹³) yields butadiene and not methylene cyclopropane¹³. By analogy, the keto acid (35) on Kochi's reaction should furnish the unsaturated ketones (36) and



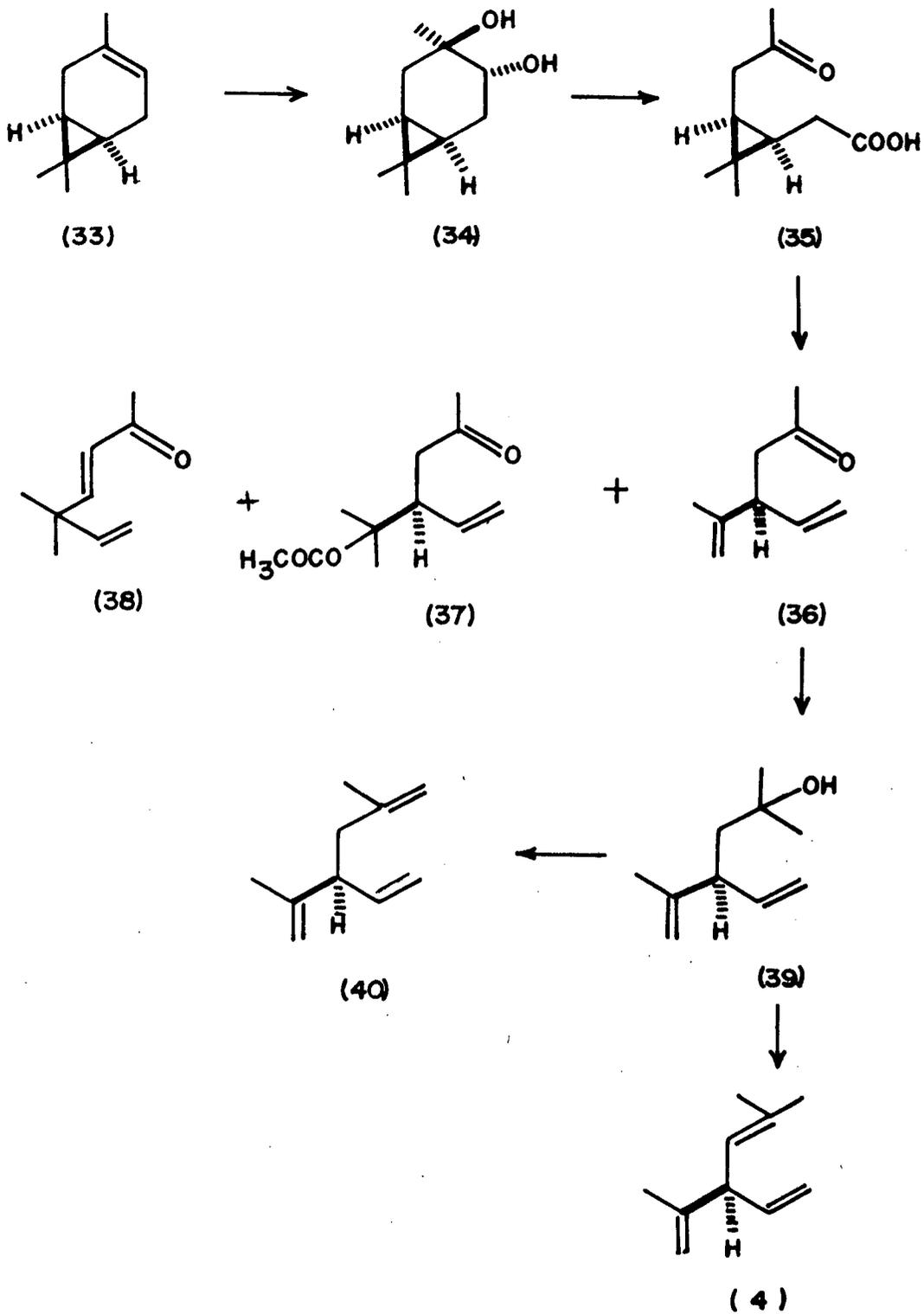
X = O
 X = H, OH
 X = H, O-NO₂ C₆H₄SO₂

Scheme - 4

(38). It should then be possible to obtain santolina triene (4) by dehydrating the tertiary alcohol (39), obtained from ketone (36) by a Grignard reaction (Scheme - 5).

Jones' oxidation on the diol (34) obtained from (+)-3-carene (33) afforded the ketocarboxylic acid (35). This on treatment with lead tetraacetate in dry benzene containing the catalytic amount of pyridine and cupric acetate gave a mixture of two products, subsequently identified as the ketone (36) and the keto acetate (37). These products could be separated by column chromatography, the ketone (36) being less polar is eluted out first. a

Treatment of the ketone(36) with excess methyl magnesium iodide in dry ether gave the tertiary alcohol (39). The remaining part of the synthesis of santolina triene consisted in then dehydrating the alcohol (39) to the desired compound (4). This part proved to be ^{the} most difficult in the whole synthesis. Acidic conditions had to be rigorously excluded since santolina triene was known to be unstable in such conditions.



Scheme - 5

The first method tried was the POCl_3 -pyridine method. This gave the undesired isomer (40) predominantly. Dimethyl sulphoxide has been used to dehydrate tertiary alcohols¹⁴. A comparative study showed that in 1-methyl cyclopentanol and 1-methyl cyclohexanol, dehydration with DMSO at 175°C gives about 90 % of the endocyclic trisubstituted olefin. Thus alcohol (39) was expected to give santolina triene (4) preferentially. Unfortunately, reaction of alcohol (39) with DMSO at 175°C gave a tarry product from which sufficient quantity of hydrocarbons could not be obtained for characterization.

Alcohols can also be dehydrated by thionyl chloride-pyridine at low temperatures. Dehydration of alcohol (39) under the above conditions, gave, on usual workup a viscous oil. It appeared that hydrochloric acid used for washing the organic extract free of pyridine, had caused polymerization of the product. Therefore, in the next experiment the organic extract was concentrated as such and the concentrate was subjected to preparative GLC.

The PMR of the hydrocarbon fraction showed that it was a mixture of santolina triene (4) and its isomer (40). These could not be separated further on GLC. However, GCMS on a supelcowax column lead to resolution of the two. The mass spectrum of the minor fraction (30%) was shown to be identical to santolina triene. a

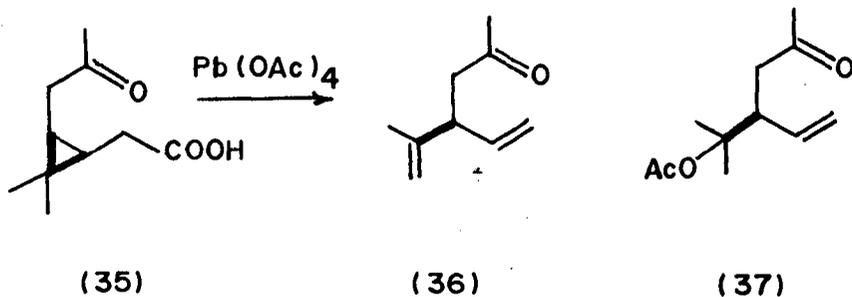
It was not possible, in this study, to determine the optical rotation of the synthetic santolina triene since its formation could be proved only by GCMS. However, since the starting material was (+)-3-carene and subsequently the stereochemistry of C-1 was kept intact throughout the synthesis, it is obvious that the product is R-(-)-santolina triene - the antipode of the naturally-occurring substance. /

Present study

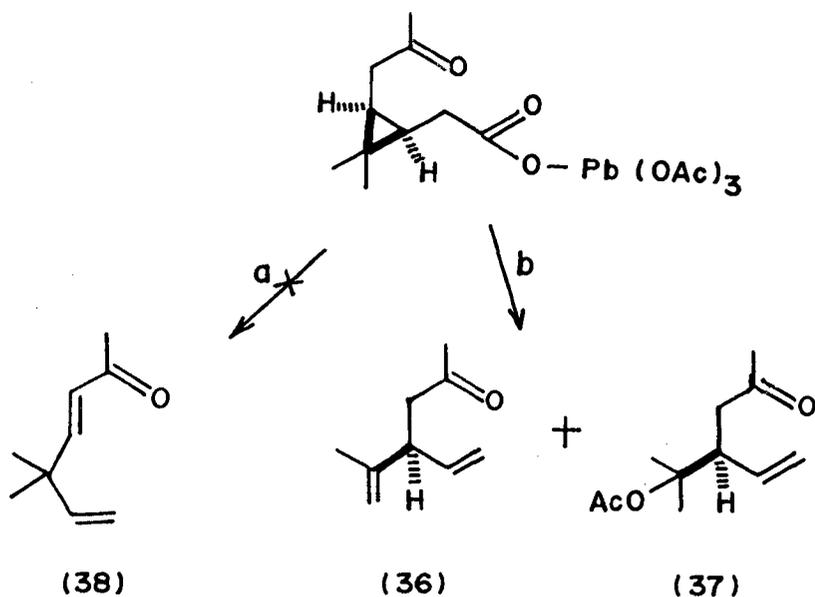
Since, in the above synthesis, pure sample of santolina triene (4) was not obtained for measurement of optical rotation, an alternative synthesis was planned. The major snag in the above synthesis is the failure to separate the double a

bond isomers (4) and (40). It was therefore decided that this problem was best nipped in the bud. If one starts with the desired double bond isomer for further transformations, then the problem of separation does not exist.

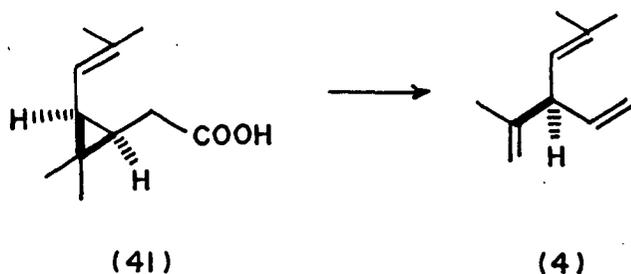
Another noteworthy feature of the above synthesis is the cyclopropane ring cleavage of the keto acid (35) to (36) and (37) with lead



tetraacetate. Although cleavage can take place in two directions giving (36) and (37) in one and (38) in another, (38) is not obtained in any significant amount and (36) and (37) are the only products.



This unidirectional cleavage of the cyclopropane ring in the ketoacid (35), together with the earlier problem of separation of the double bond isomers (4) and (40) encouraged us to consider the lead tetraacetate decarboxylation of cis-homochrysanthemic acid (41) as a viable means of obtaining santolina triene. Also starting with optically active cis-homochrysanthemic acid should lead to optically active R-(-)-santolina triene.



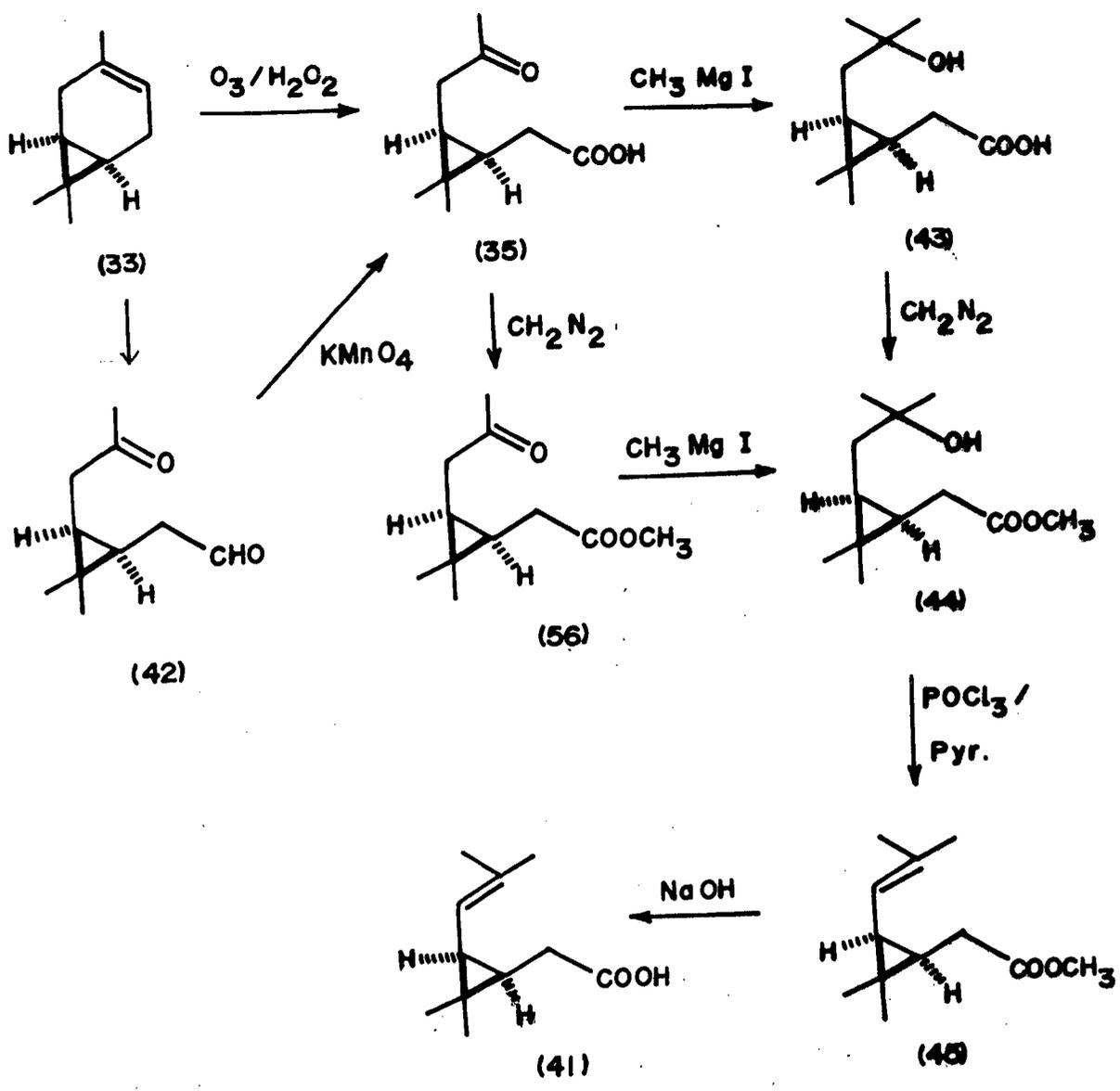
Thus effort was directed towards synthesis of cis-homochrysanthemic acid. This acid was synthesised in 1969 by Sasaki et al¹⁵ from (+)-3-carene. Naik and Kulkarni¹⁶ have synthesised methyl cis-chrysanthemate and methyl cis-homochrysanthemate (45) also from (+)-3-carene. cis-Chrysanthemic acid has also been homologated to cis-homochrysanthemic acid (41) by Crombie et al¹⁸.

The route followed by Sasaki et al¹⁵ involved cleavage of the double bond of (+)-3-carene by ozonolysis. Both oxidative and reductive decomposition of the ozonide were carried out using H_2O_2 and $(CH_3)_2S$ to give keto acid (35) and 3,3-dimethyl-2-(2-oxopropyl) cyclopropyl acetaldehyde

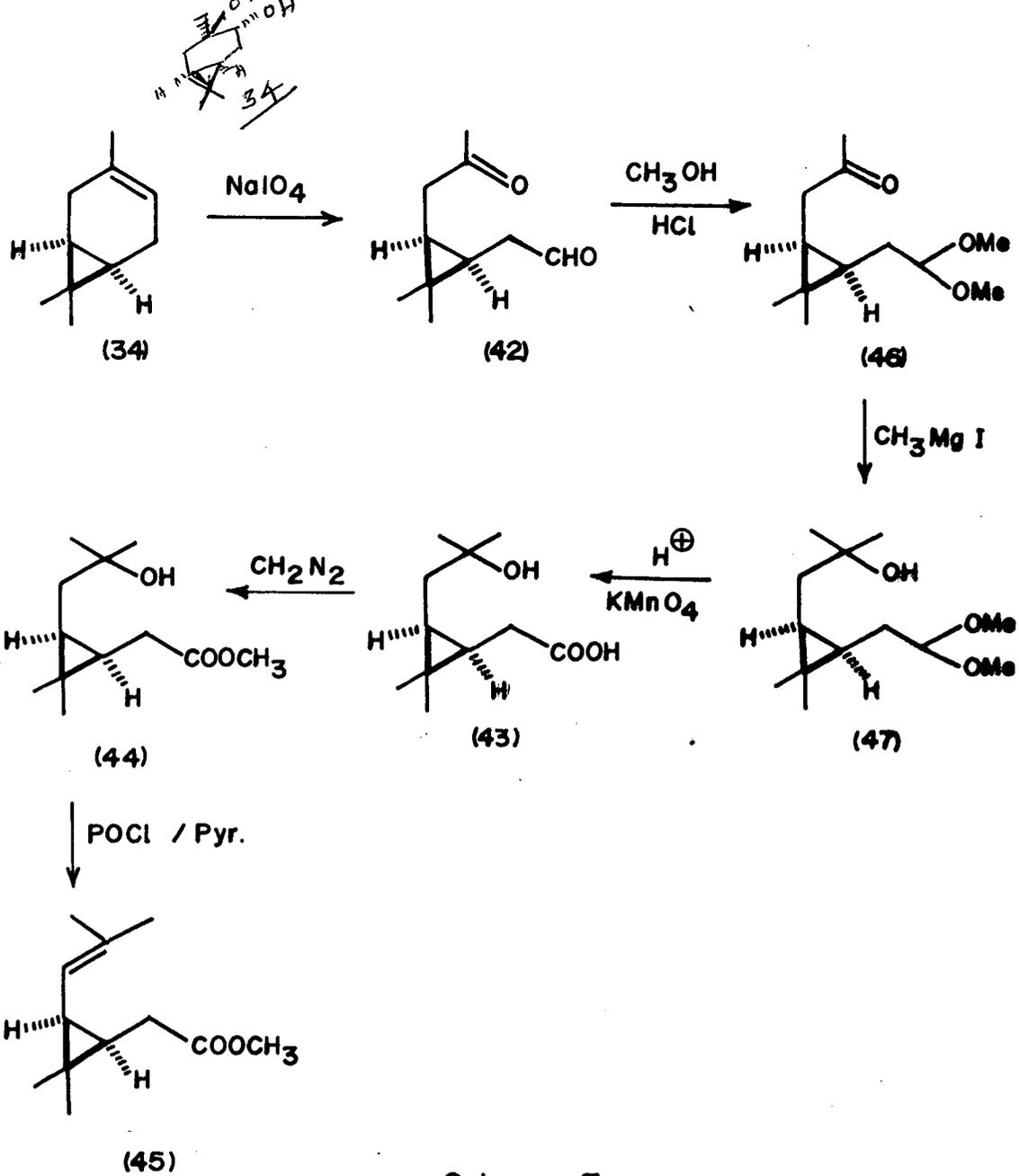
(42) respectively. Another method involved direct cleavage of the double bond with KMnO_4 to give the keto acid (35) directly. Out of these the authors preferred ozonolysis with oxidative cleavage as a better method.

The keto acid (35) was converted to the hydroxy acid (43) through a Grignard reaction. The acid (43), a crystalline solid was esterified to the hydroxy ester (44) and then dehydrated to methyl cis-homochrysanthemate (45) which was then hydrolysed to cis-homochrysanthemic acid (41). (Scheme - 6).

Naik and Kulkarni¹⁶ have followed a different method for cleaving the six membered ring of 3-carene. Oxidation of 3,4-carene diol (34) with sodium metaperiodate afforded the ketoaldehyde (42). The aldehyde was protected as its dimethyl acetal (46) and then subjected to Grignard reaction to give (47). Regeneration of the aldehyde group followed by oxidation afforded hydroxy acid (43). This was then esterified and dehydrated to give methyl cis-homochrysamthemate (45). (Scheme - 7).



Scheme - 6

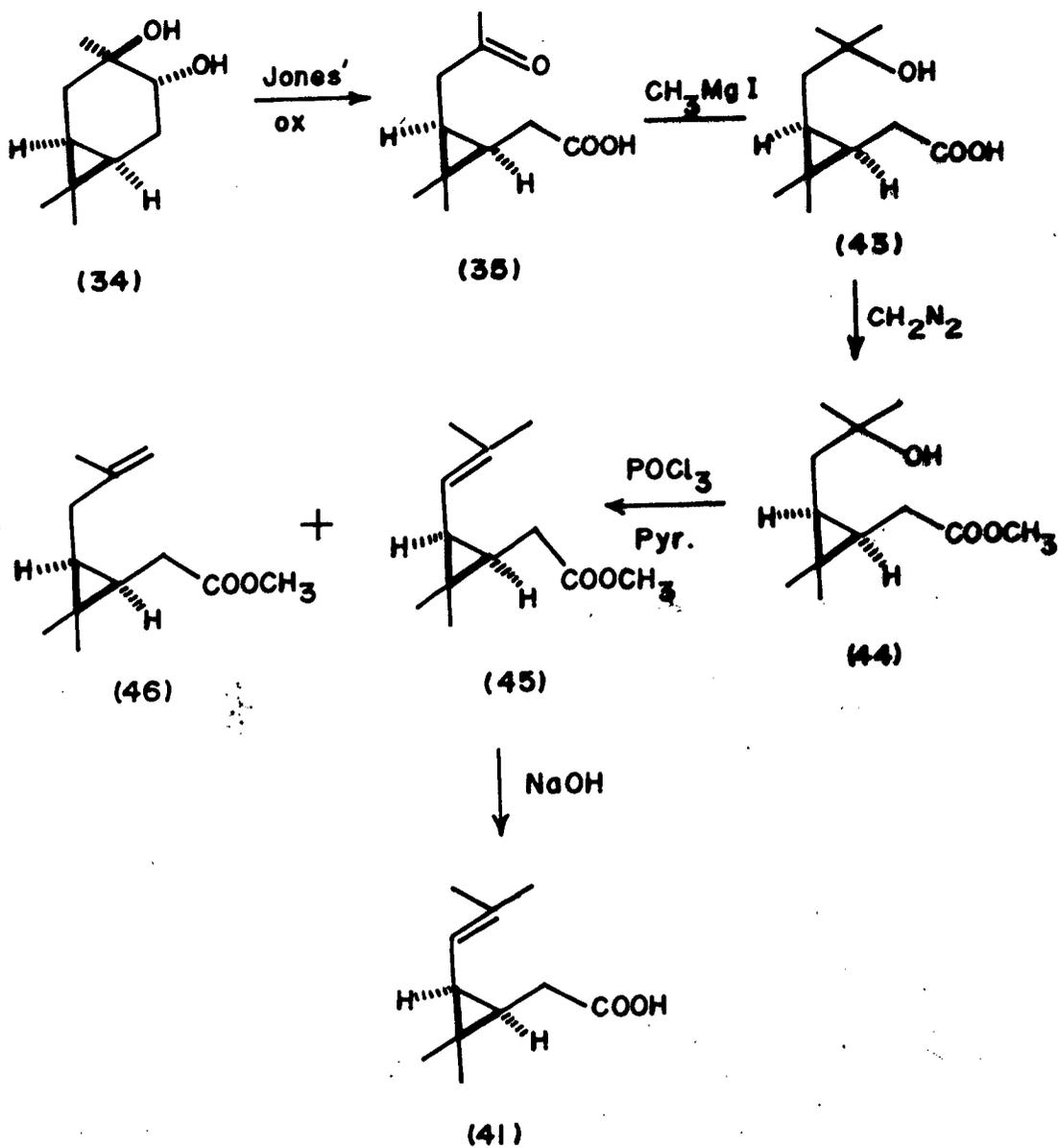


Scheme -7

We decided to follow the method of Sasaki et al ¹⁵ for the synthesis of cis-homochrysanthemic acid. Since we had already observed that the keto acid (35) could be readily obtained from carane diol (34) by Jones' oxidation (see scheme - 5), it was decided to obtain keto acid (35) and then proceed on the lines of Sasaki et al ¹⁵. (Scheme - 8).

Carane diol (34) was subjected to Jones' oxidation to give keto acid (35) as a yellow oil. Grignard reaction with a two fold excess of CH_3MgI was then carried out by using the reverse addition procedure. The Grignard reagent was added slowly to the solution of keto acid in ether. The hydroxy acid (43) obtained initially as an oil was purified by column chromatography to give a crystalline solid, m.p. $87-88^\circ$.

$\text{POCl}_3/\text{pyridine}$ dehydration of the corresponding methyl ester (44) gave methyl cis-homochrysanthemate (45) and its double bond isomer (46), which were separated by column chromatography over silica gel impregnated with AgNO_3 . The desired



Scheme - 8

isomer (45) is eluted out first.

The claim of Sasaki et al ¹⁵ that dehydration of (44) would most likely yield (45) rather than (46), since the double bond introduced is in conjugation with the cyclopropane ring, is not borne out by our observations. In our experience (and also of Naik and Kulkarni ¹⁶), almost equal quantities of (45) and (46) are obtained and rigorous separation is always necessary to separate them. The cyclopropane ring exerts almost no influence on the dehydration.

The methyl cis-homochrysanthemate (45) is obtained as an oil. It was well characterized by IR and PMR since it was imperative for our synthetic plan, that we obtain pure cis-homochrysanthemic acid uncontaminated by its double bond isomer.

IR λ_{max} , neat.(Fig.2): 1740 and 1065 ($-\text{COOCH}_3$), 1650 and 840 [$(\text{CH}_3)_2\text{C}=\text{CH}$].

PMR (300 MHz, CDCl_3 , δ)(Fig.3) : 0.96 & 1.16 (each 3H, each s, cyclopropane ring methyls), 1.04 - 1.6 (2H, m, cyclopropane ring protons), 1.75 & 1.79 (each 3H, each s, vinyl methyls), 2.36(2H, d, J =

8Hz., -CH₂-COOCH₃), 3.85 (3H, s, -COOCH₃), 5.0 (1H, d, J = 6Hz., vinyl protons¹).

[α]_D + 80.85° in CCl₄ (lit.¹⁶ [α]_D + 68°).

Hydrolysis of methyl cis-homochrysanthemate (45) with 5% NaOH for 12 hrs. at room temperature furnished cis-homochrysanthemic acid (41). Having obtained pure cis-homochrysanthemic acid, lead tetraacetate decarboxylation was the next step. Reaction of (41) with Pb(OAc)₄ in benzene containing catalytic amount of pyridine afforded a brown oil on work up. Preliminary GC showed the material to be a complex mixture.

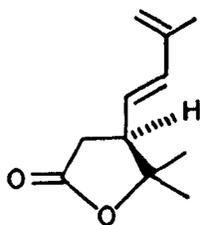
Chromatographic separation on silica gel with 98:2 cyclohexane-ether in the beginning followed by progressively increasing amounts of ether step wise through 95:5 , 9:1, 8:2 and 7:3 gave various fractions.

Any hydrocarbons present should have been eluted out in the earlier fractions. GCMS of the fraction however showed that it still contained cyclohexane and only traces of compounds of MW. 136. Most of the material was eluted in the

fractions eluted with 95:5 and 90:10 of cyclohexane-ether. The former fraction was almost pure (fraction A).

The second fraction (fraction B) consisted of three substances, the major one of which was separated by preparative GLC. on carbowax column (compound B₁). The three isomers could not be separated altogether on GCMS. (Supelcowax column) as seen by their mass spectra (Fig.7). However, these could be separated on an apolar column coupled with a FTIR instrument and their IR spectra could be recorded (Fig.8).

Fraction A was shown to contain the γ -lactone 4,4-dimethyl-3-(3-methylbuta-1,3-dienyl)butanolide (47) as its major component.

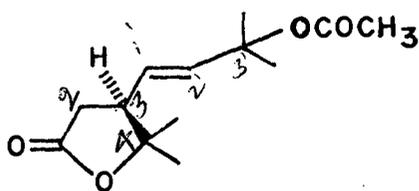


(47)

PMR (300 MHz, CDCl₃, δ)(Fig.6) : 1.26 & 1.36 (each 3H, each s, gem dimethyl group), 1.85 (3H, s, CH₃-C=C), 2.51 - 2.73 (m, 2H, C-2 H), 2.88 - 2.99 (m, 1H, C-3 H), 5.0 (d, 2H, C=CH₂), 5.49 (dd, 1H, J = 14.4 Hz. & J = 7.2 Hz., $\begin{matrix} \text{H} \\ \diagup \\ \text{C}=\text{C} \\ \diagdown \\ \text{H} \end{matrix}$), 6.25 (d, J = 14.4 Hz., 1H, $\begin{matrix} \text{H} \\ \diagdown \\ \text{C}=\text{C} \\ \diagup \\ \text{H} \end{matrix}$).

Mass m/z (rel. int)(Fig.7): 180(M⁺,2), 165 (2), 122 (10), 94 (80), 79(100), 65 (5), 53 (5), 43 (12).

Compound B₁ was identified as 4,4- dimethyl-3-(3'-acetoxy-3'-methylbut-1-eneyl)butanolide (48).



(48)

GCFTIR λ_{max}, (Fig.8): 2986, 1809, 1790, 1377, 1232, 1128, 963 cm⁻¹.

PMR (300 MHz, CDCl₃,δ)(Fig.9) 1.23 & 1.43 (each 3H, each s, gem dimethyl on C-4), 1.5 & 1.52 (each 3H,

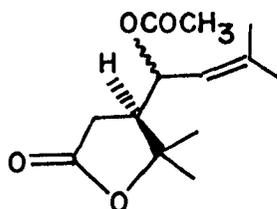
each s, gem dimethyl on C-3'), 1.99 (s, 3H, -
 OCOCH₃), 2.46 - 2.71 (m, 2H, CH₂), 2.79 - 2.9 (m,
 1H, CH), 5.48 (dd, 1H, J = 7.2, 14.4 Hz., C-1'H),
 5.85 (d, 1H, J = 14.4 Hz., C-2'H)

¹³CMR (75 MHz, δ)(Fig.10): 22.1 (-OCOCH₃), 22.5 &
 26.7 (methyls on C-4), 27.0 & 27.1 (methyls on C-
 3'), 34.7 (C-2), 48.7 (C-3), 79.7 (C-3'), 86.7 (C-
 4), 124.5 (C-1'), 138.6 (C-2'), 169.9 (acetate
 carbonyl carbon), 175.1 (lactone carbonyl).

Mass m/z (rel. int.)(Fig.11): 240(M⁺,2), 154 (20),
 122 (28), 112 (30), 94 (70), 85 (73), 79(100), 69
 (15), 55 (18), 43 (87).

The structure was conclusively established by
 2D NMR (COSY) spectra (Fig.12).

The allylic rearrangement product of (48)
 namely (49) was also shown to be formed in the
 above reaction. [¹³CMR spectra (Fig.13)]

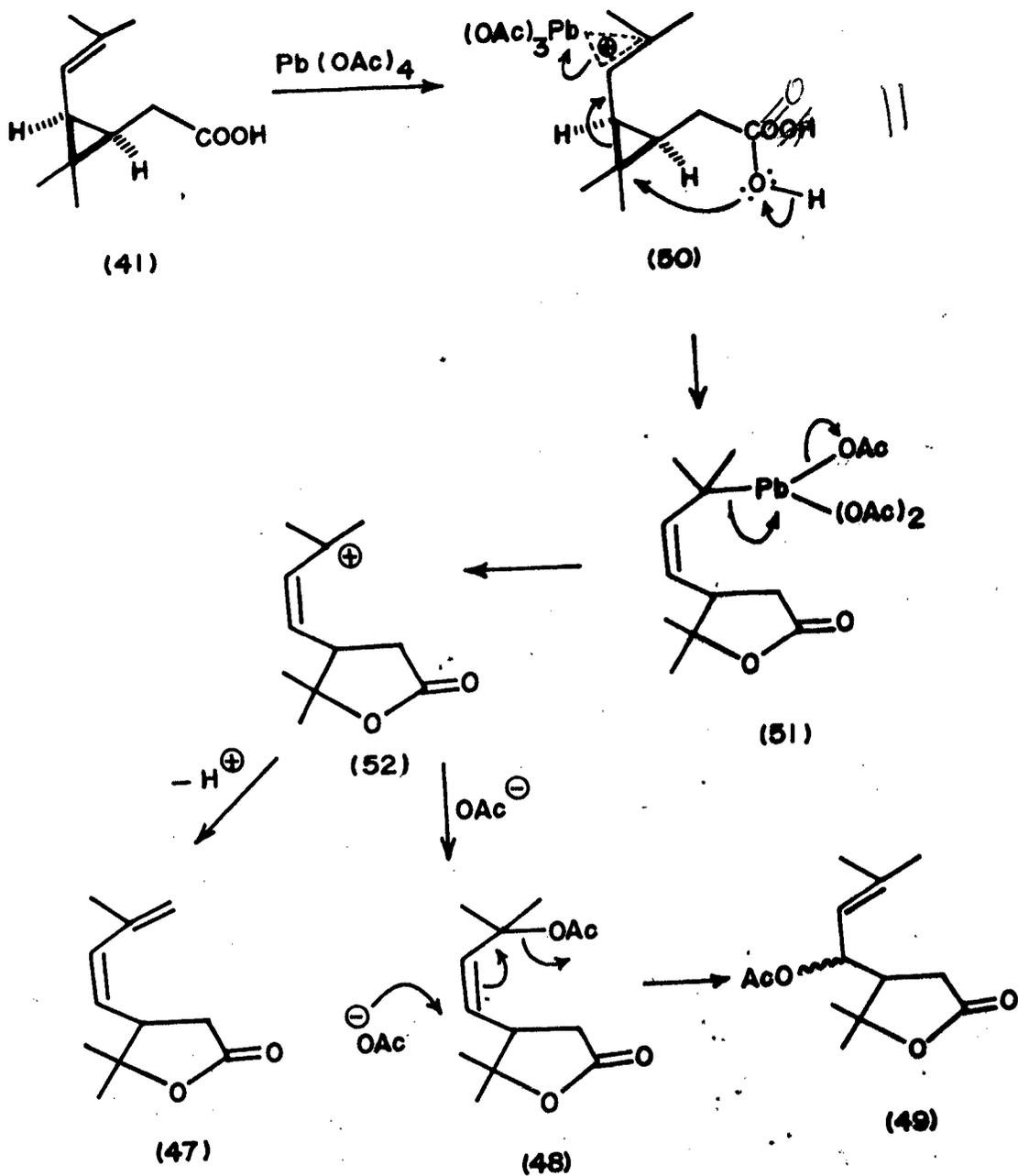


(49)

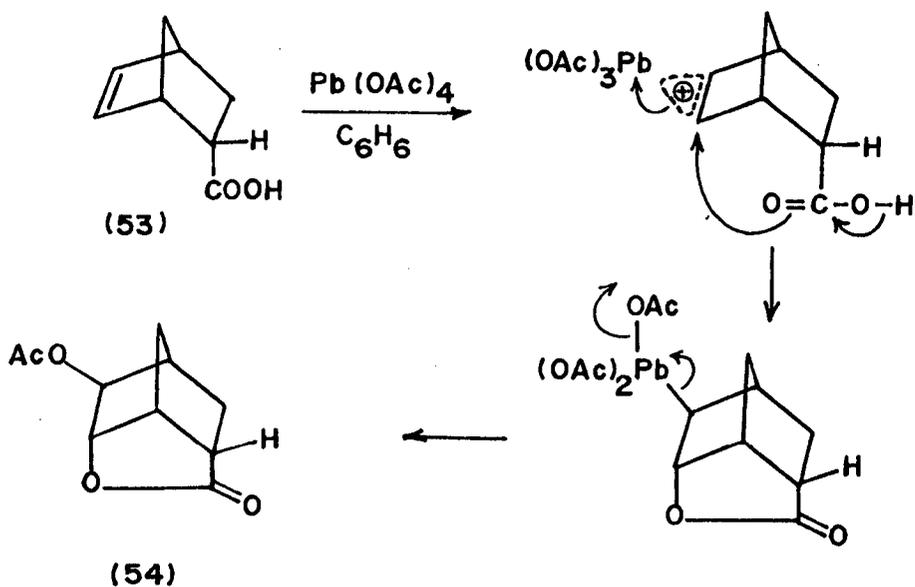
The formation of lactones, rather than simple decarboxylation products in the above reaction can be explained as shown in Scheme - 9. Lead tetraacetate attacks the double bond of cis-homochrysanthemic acid to form a electrophilic lead complex (50) which then gives the lead compound (51) by cleavage of the cyclopropane ring and nucleophilic attack of the carboxyl group leading to lactone formation. Loss of lead diacetate from (51) gives the carbocation (52) which can give (47) by elimination of a proton or (48) by intramolecular transfer of an acetate ion. Allylic rearrangement of the cation may lead to product (49).

Formation of these lactones is by no means serendipitous. There is an exactly analogous case in literature, and that involves the formation of lactone (54) from the unsaturated acid (53) on treatment with lead tetraacetate¹⁷.

It is pertinent to note that similiar lactones were obtained by Sasaki et al¹⁵ as well as Naik and Kulkarni¹⁶ either when dehydration of the



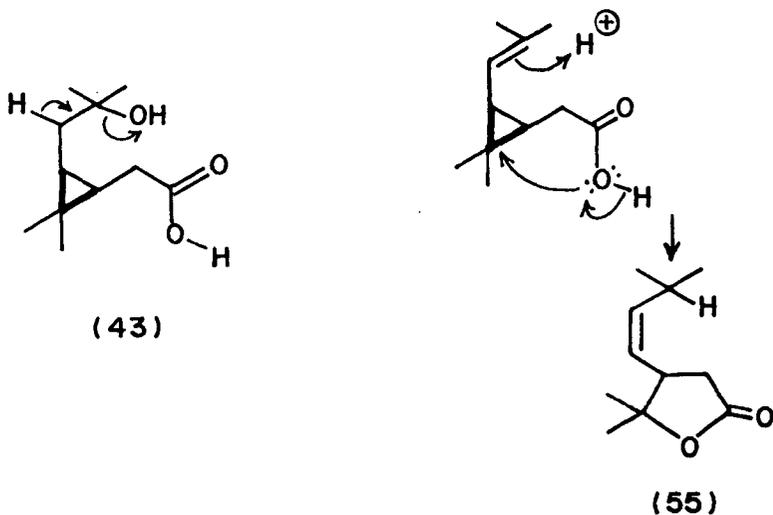
Scheme - 9



hydroxy acid (43) was attempted or during the hydrolysis of methyl cis-homochrysanthemate under acidic conditions.

The formation of lactone (55) during dehydration of (43) can be explained as follows. The initially formed carbocation rearranges with cleavage of the cyclopropyl ring and the resulting cation is attacked nucleophilically by the carboxyl group.

The formation of lactones (47), (48) and (49)



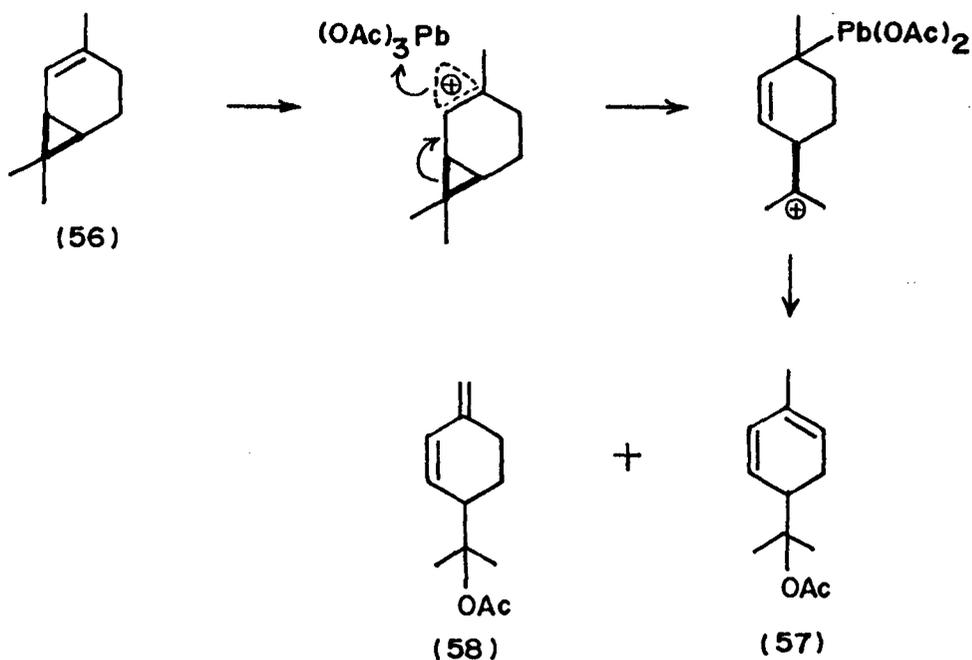
can be considered analogous to the formation of lactone (55). In the former case, there is a positively charged lead atom whereas in the latter, it is a protonated double bond.

Thus it is not possible to synthesise santolina triene by the lead tetraacetate decarboxylation of cis-homochrysanthemic acid. Probably if the double bond is protected by some means and the decarboxylation carried out and then deprotection should furnish santolina triene.

We realized that cis-homochrysanthemic acid and 2-carene (56) have similar part structures especially when the cyclopropyl ring and the double bond are concerned. Therefore it was considered interesting to know the effect of lead tetraacetate

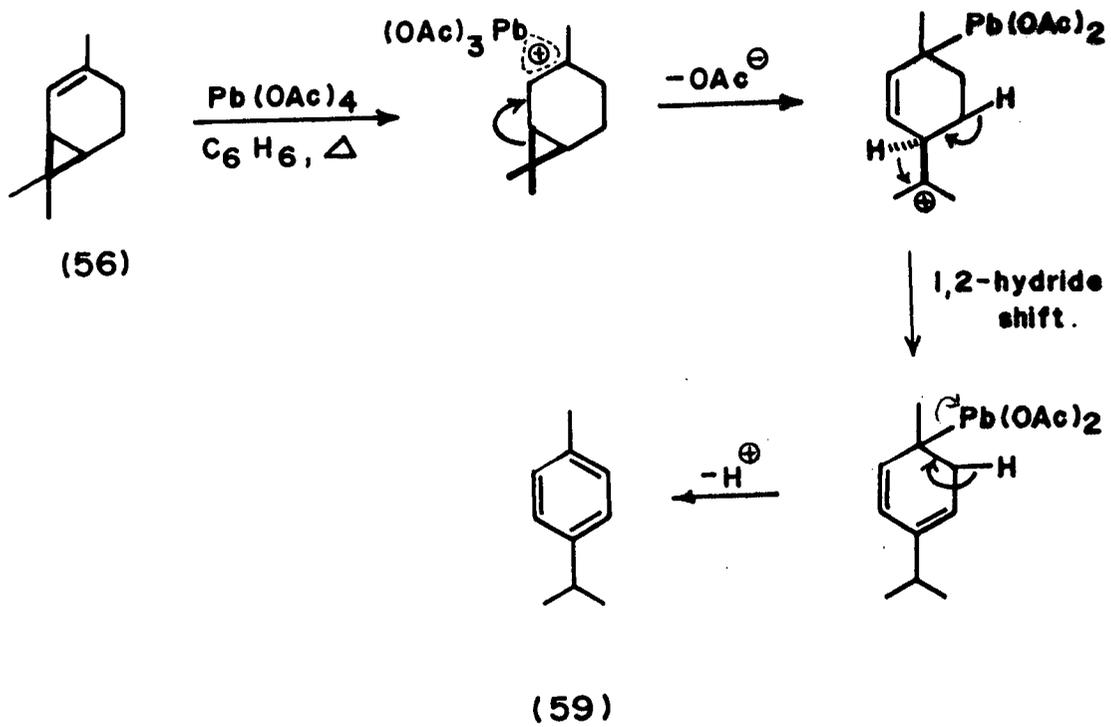
on 2-carene.

It was expected that acetates (57) and (58), which can be considered as and phellandrene derivatives, would be the products.



2-carene (56) on oxidation with lead tetraacetate gave an oil whose IR spectra showed the presence of small amounts of acetates. This oil was further purified by preparative GLC. The major fraction was interestingly identified as p-cymene (59) from its PMR spectra.

PMR (300 MHz, CDCl_3 , δ)(Fig.14): 1.25 (d, 6H), 2.35 (s, 3H), 2.9 (m, 1H), 7.1 (d, 4H).



Scheme - 10

The formation of p-cymene from 2-carene is explained in Scheme - 10. The reaction is indeed similar to the one with cis-homochrysanthemic acid (41). Initial attack takes place on the double bond followed by opening of the cyclopropyl ring. A 1,2-hydride shift followed by aromatization affords p-cymene.

Thus, although we were unable to synthesise santolina triene by the lead tetraacetate decarboxylation of cis-homochrysanthemic acid, could get valuable insight into the relative reactivities of a double bond and a carboxyl group towards lead tetraacetate.

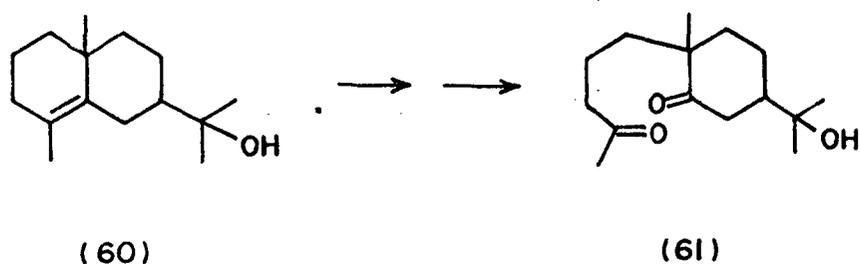
CHAPTER - II

SECTION - II

REACTION OF MAALIOL WITH LEAD TETRAACETATE

The modified terpenoids are of special importance in view of their biosynthetic modifications from the normal precursors and also due to their novel carbon skeletons. One of the well known example is that of seco-loganin from the monoterpene group.

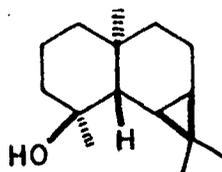
In view of our continued interest, the carbon skeletons of certain seco-sesquiterpenoids attracted our attention. In recent years several 4,5-secoeudesmane sesquiterpenoids have been isolated. An entry into the 4,5-secoeudesmanes can be made by cleavage of the 4,5-bond of a normal eudesmane e.g. (60) in all probability in a manner analogous to the biosynthetic transformation.



Alternatively a 4-hydroxyeudesmane when

subjected to oxidation with lead tetraacetate should furnish 4,5-secoeudesmanes. As a part of our programme on oxidation of terpenoids with lead tetraacetate we selected the sesquiterpene alcohol maaliol (62) for the preparation of 4,5-secoeudesmanes.

We expected that concomitant to the cleavage of the C₄-C₅ bond, there will be cleavage of the C₆-C₁₁ bond thus furnishing a monocyclic skeleton from the tricyclic precursor in a single step. The results obtained have been described in this section.

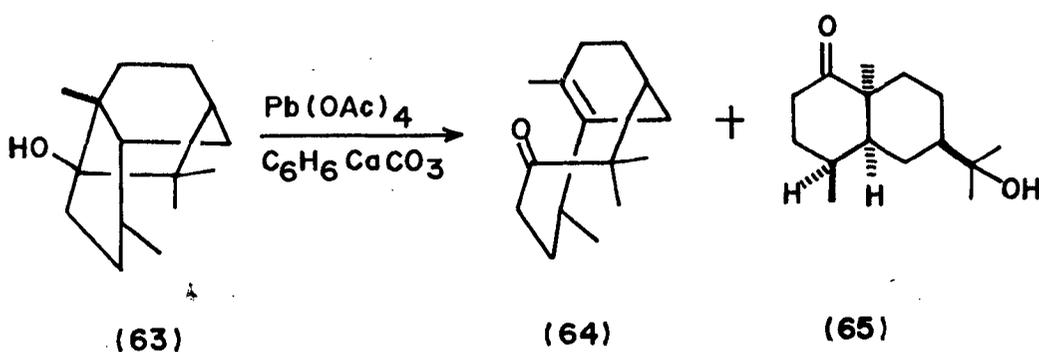


(62)

Maaliol, first isolated from Valeriana officinalis L. by Stoll et al²⁰ was assigned the stereostructure (62) by Buchi and co-workers²¹ on

chemical degradation, spectral analysis and by an unambiguous synthesis.

Thomas and Ozainne²² had earlier carried out a regioselective fragmentation of patchouli alcohol (63), the structurally most important component of the oil from Pogostemon cablin (Patchouli oil). These authors have used lead tetraacetate for the reaction and the reaction sequence is shown in Scheme - 11.



Scheme-II

A similar reaction was carried out on maaliol by us, using lead tetraacetate in refluxing benzene. Usual workup provided a brown oil, which on column chromatography over silica gel furnished two clearly separable fractions.

The first fraction was further purified by preparative GLC. This showed the presence of one major compound (92.13%) and a minor (6.635%). The second fraction also purified by preparative GLC showed a major component (81.487%) in addition to unreacted maaliol (14.378%). This separation scheme is shown in Scheme - 12. a

The spectral data on the various fractions and products are discussed below.

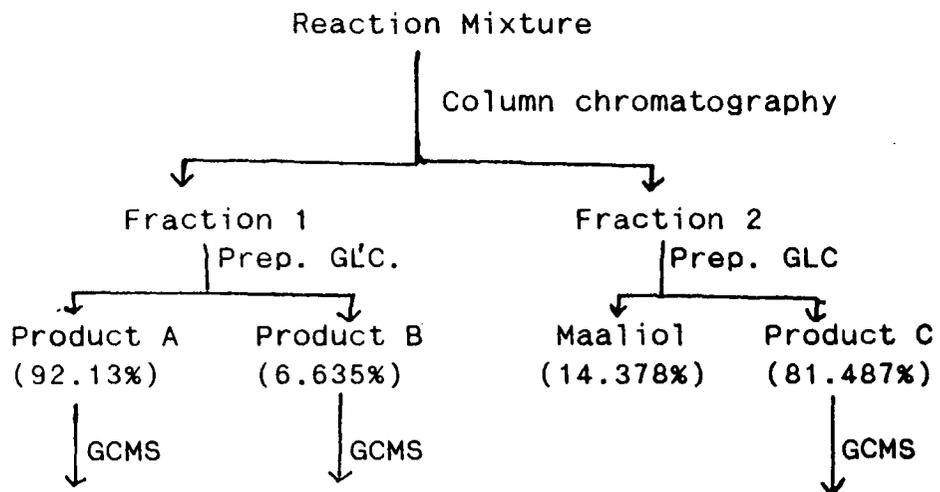
Fraction - 1

IR λ_{\max} , neat. (Fig.15): 2950, 1716, 1642, 1452, 1369, 1222, 1165, 891, 741 cm^{-1} .

PMR (300 MHz, CDCl_3 , δ)(Fig.16): 0.98 (s, 3H), 1.75 (s, 3H), 2.15 (s, 3H), 4.7 (d, 2H), 5.5 (s, 2H).

Mass m/z (rel. int.) (Fig.17): 220 (M^+ , 2), 162 (30), 147 (12), 135 (97), 107 (85), 93 (95), 85 (25), 79 (75), 67 (15), 55 (25), 43 (100) (100).

All the above data is consistent with the structure (66) (Product A).



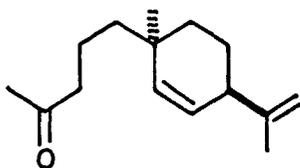
Mass spectra

Mass spectra

IR spectra were recorded on Fractions 1 & 2.

P.M.R. spectra were recorded on the purified GLC eluent from fraction 1 and on Product C (from fraction 2).

Scheme -12



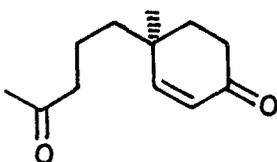
(66)

The mass fragmentation pattern of (66) is discussed in Scheme - 13.

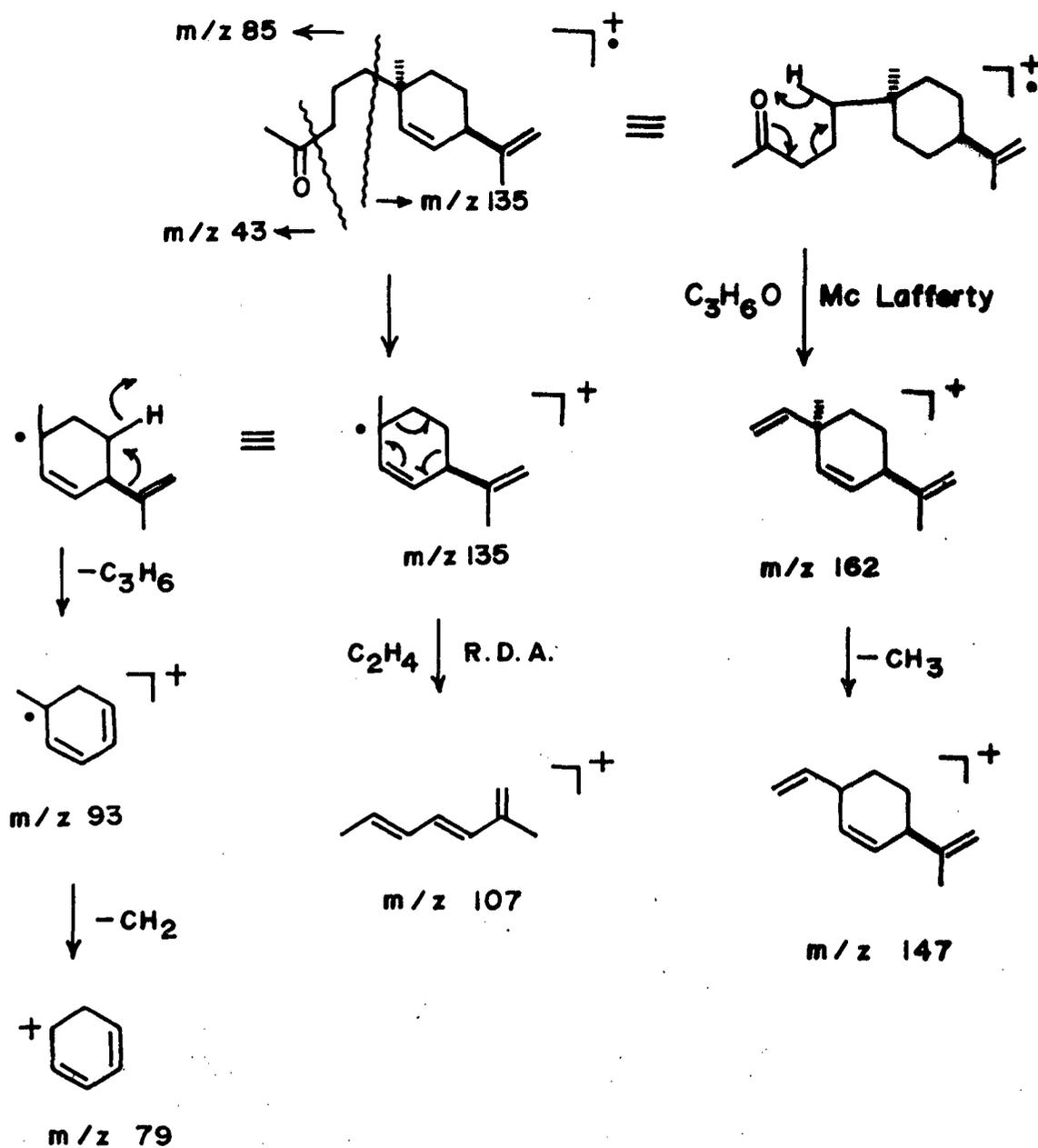
The second minor component of Fraction 1 i.e. Product B (6.635%) could be identified by GCMS only although traces of this compound could be seen in the PMR ~~spectra~~ ^{spectrum} of Product A.

Mass m/z (rel. int)(Fig.18): 194 (M^+ , 5), 179 (8), 136 (20), 123 (30), 109 (52), 95 (40), 79 (50), 67 (38), 53 (20), 43 (100).

The structure of this minor product was assigned to be (67).



(67)



Scheme -13

The mass fragmentation pattern of this compound is shown in Scheme - 14.

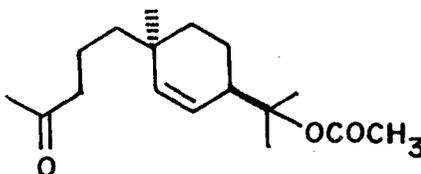
The other fraction (Fraction 2) contained a major compound (81.487%) (Product C) in addition to unreacted maaliol. The spectral data of this compound is discussed below. *presented*

IR, λ_{\max} , neat. (Fig.19): 2950, 1728, 1462, 1367, 1257, 1137, 1019, 941, 737 cm^{-1}

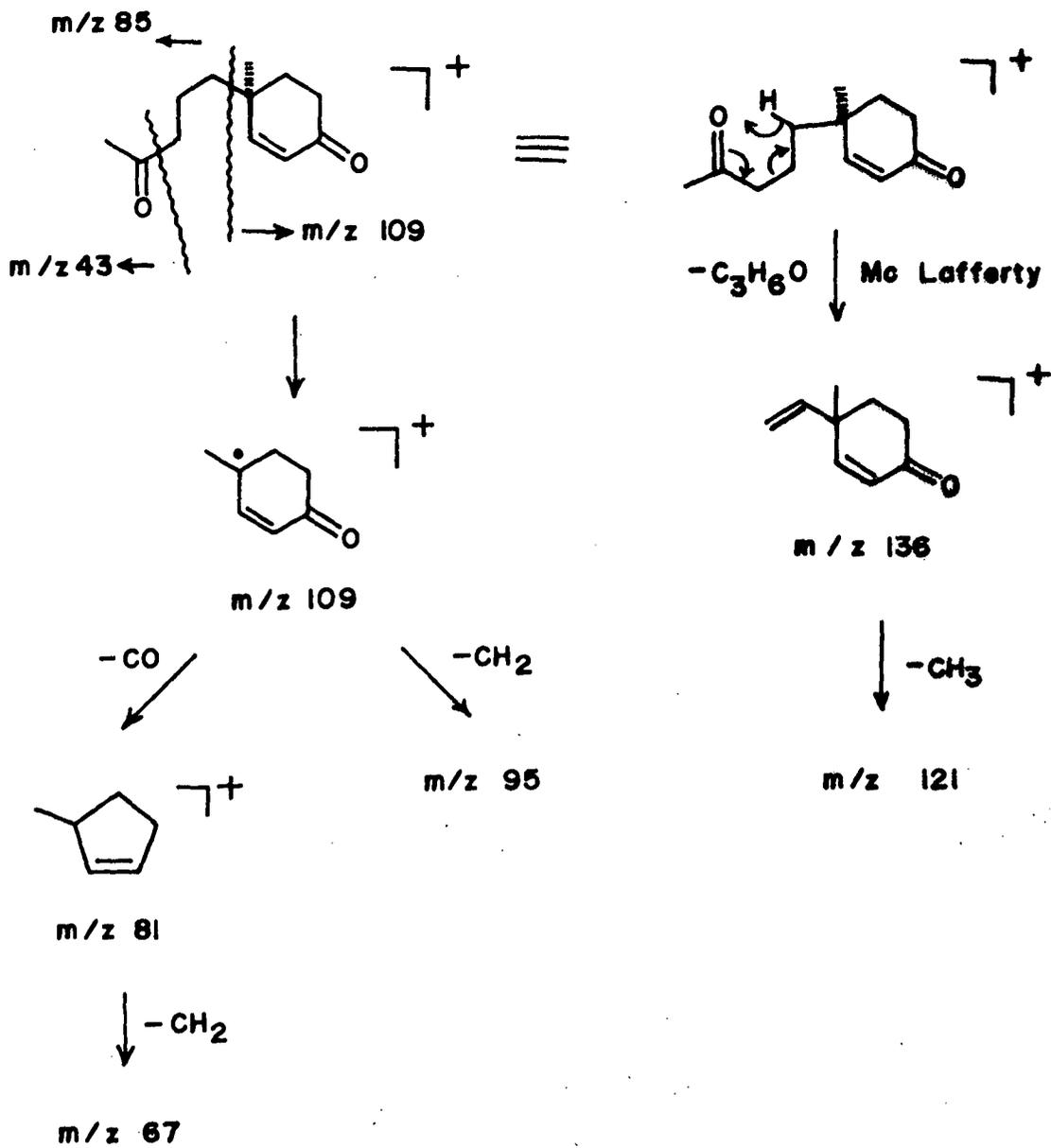
PMR (300 MHz, CDCl_3 , δ) (Fig.20): 0.95 (s, 3H), 1.4 (d, 6H), 1.97 (s, 3H), 2.13 (s, 3H), 2.4 (t, 2H), 5.52 (q, 2H).

Mass m/z (rel. int.) (Fig.21): 220 ($\text{M}^+ - \text{CH}_3\text{COOH}$, 8), 162 (28), 135 (97), 119 (18), 107 (50), 93 (15), 85 (15), 79 (50), 43 (100).

The above data is consistent with the structure (68).



(68)



Scheme - 14

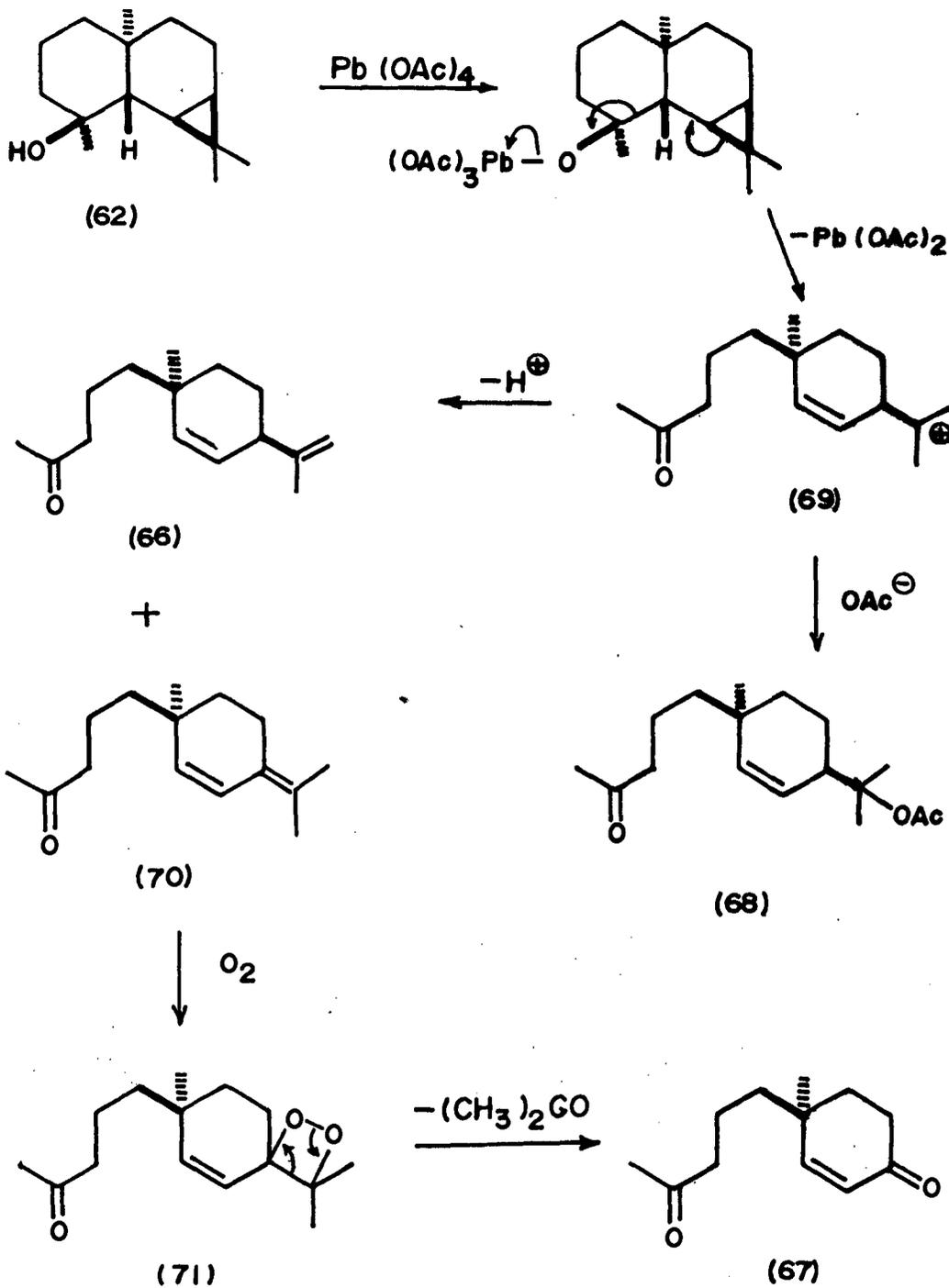
The mass fragmentation pattern is also similar to that of compound (66) (see Scheme - 13) since after initial loss of acetic acid, (68) would give (66).

In all the above products, cleavage of the cyclopropyl ring is observed along with the cleavage of the 4,5-bond as expected. The formation of these products is explained in the unified Scheme - 15.

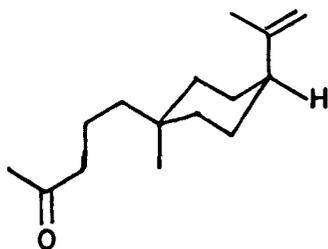
Maaliol (62) forms the lead ester which cleaves to give the cation (69). This cation if trapped by an acetoxy anion would furnish acetate (68). Loss of a proton in (69) would afford a mixture of (66) and (70). Since we have not excluded oxygen from the reaction mixture, the alkene (70) would furnish diketone (67) via the dioxetane intermediate (71). It has been reported^{23,24} that the dioxetanes of the type (71) may cleave to a diketone in non polar solvents.

The configurations at C₁₀ and C₇ are not affected during the lead tetracetate oxidation and conformation (72) is preferred over the alternative (73) assuming the C₅ side chain equatorial.

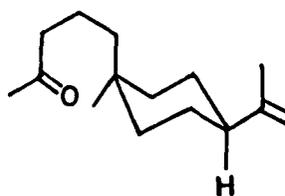
numbers
in sketch
is needed



Scheme -15



(72)



(73)

Thus in conclusion we have achieved a regioselective cleavage of the 4,5-bond of maaliol to synthesize compounds having the 4,5-seco sesquiterpenoid carbon skeleton

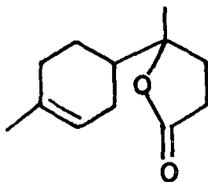
CHAPTER - II

SECTION - III

REACTION OF GUAIOL WITH LEAD TETRAACETATE

Among the degraded sesquiterpenes, there is a small but conspicuous group of tris-nor sesquiterpenes. The three carbon atoms that are eliminated in the process of biogenetic evolution belong to the isopropylidene end of the acyclic farnesyl pyrophosphate though, the exact stage at which the elimination takes place is not clear. Some of the C-12 compounds which can be regarded as representatives examples of this group are listed in Chart - 1.

Oxidative removal of the isopropyl group from the naturally occurring sesquiterpenes appears to be an attractive route for entry into the corresponding C-12 framework of the degraded sesquiterpenes. A successful application of this idea can be seen in the reported biogenetic type synthesis of the C-12 lactone (74)²⁵



(74)

C-12 Carbon
framework

Tris-norsesquiterpene

Parent C-15 Carbon
framework

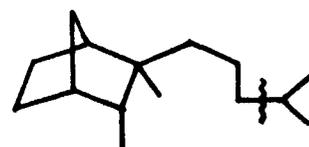
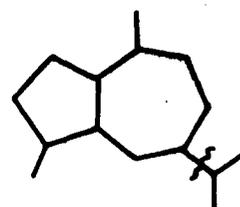
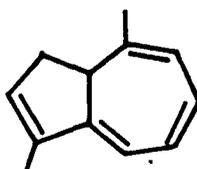
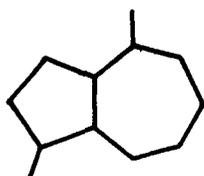
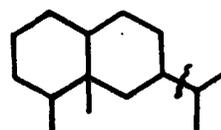
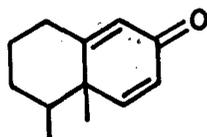
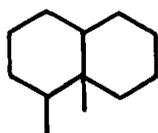
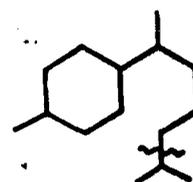
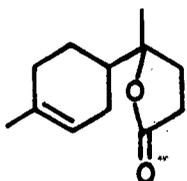
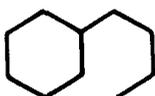
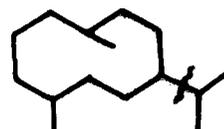
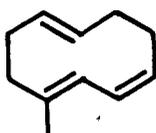
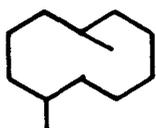
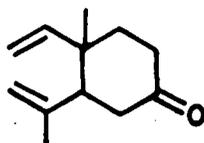
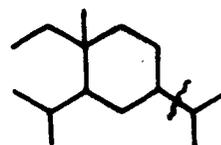
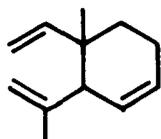
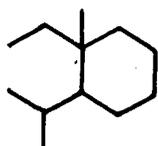
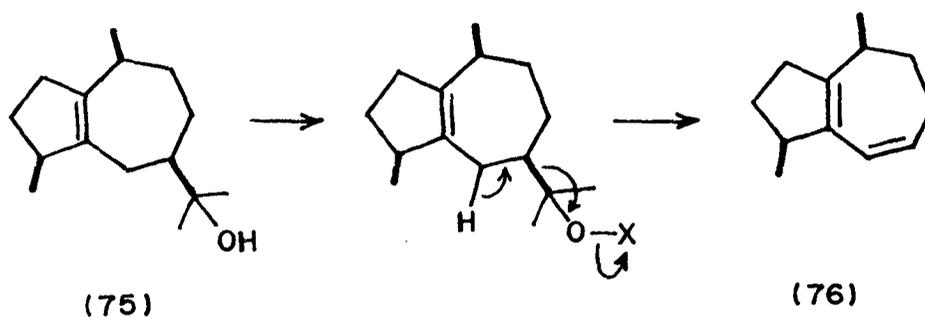


Chart - I

As a part of our research programme on transformation studies on natural sesquiterpenes, we chose to prepare the C-12 hydrocarbon (76) from guaicol (75), the main component of guaic wood oil. We envisaged the preparation of (76) as indicated in the scheme given below.



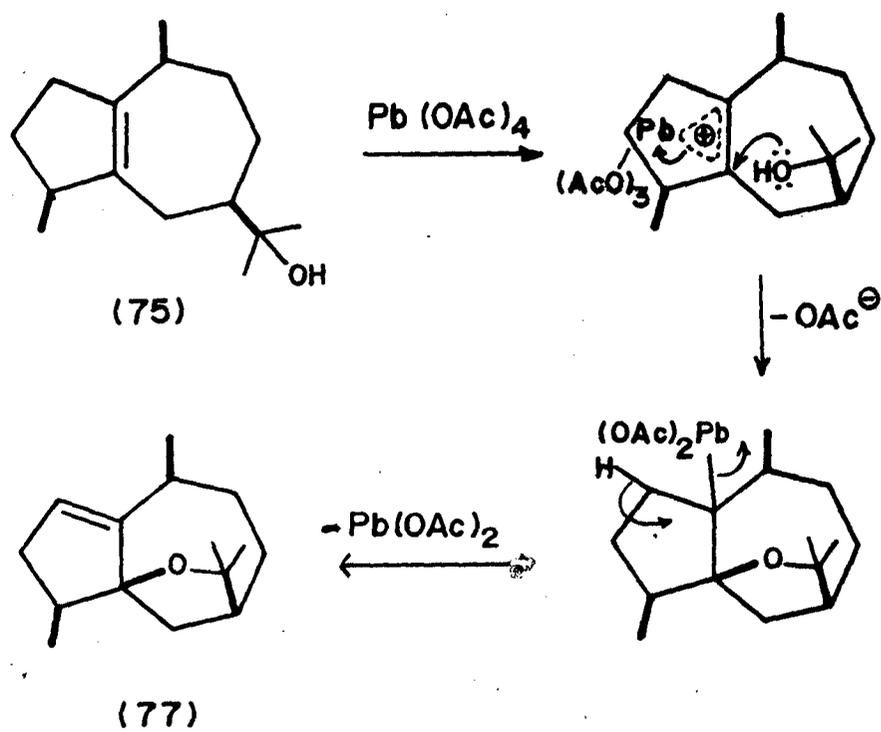
Tertiary alcohols can be oxidatively degraded with lead tetraacetate^{26a-f}. The lead alkoxide intermediates have been found to decompose thermally or photolytically in a variety of ways as illustrated in Scheme - 16. The fragmentation of lead alkoxide intermediates becomes more favourable with alkoxides from secondary and tertiary alcohols and is especially important if a relatively stable tertiary alkyl, benzyl or allyl fragment may be

lost^{26d-f}. This fragmentation may become the major reaction path for tertiary alcohols where a relatively stable alkyl radical may be lost and where competing abstraction of a nearby C-H bond is not sterically feasible.

• It is pertinent to note that the reaction of guaiol with lead tetraacetate was earlier studied by Ourisson and Ehret²⁷. They had characterized a product, dehydroguaioxide (77) from the reaction. We thought it worthwhile to reinvestigate the reaction and to characterize the hydrocarbon fraction if any from the above reaction.

Reaction of guaiol with lead tetraacetate in refluxing benzene with a catalytic amount of pyridine, afforded on usual workup an oil which on column chromatography failed to yield any hydrocarbon. The only compound which could be isolated from the reaction mixture was again dehydroguaioxide (77).

The formation of this compound is explained in Scheme - 17. Initial attack of lead tetraacetate on guaiol takes place at the double bond rather than



Scheme - 17

on the tertiary alcoholic group. Subsequent trapping of the cationic lead species by the tertiary alcohol and further loss of the lead dioxide yields dehydroguaiooxide (77).

Although our aim to synthesise the C-12 hydrocarbon (76) was unsuccessful, we could gather additional spectral data on dehydroguaiooxide. These include ^{13}C NMR, 2D COSY, HETCOR and mass spectra in addition to PMR and IR., many of the above data were not available in earlier literature and hence incorporated in this section.

EXPERIMENTAL

3,4 -carane diol (34) from (+) 3-carene (33)

In a two liter, Three necked flask, eqipped with a mechanical stirrer and a dropping funnel was placed formic acid (90%, 52.5 ml., 12.5 moles) and freshly distilled (+) 3-carene (200g. 1.47 moles) was added with stirring. H_2O_2 (30%, 300 ml.) was then added dropwise, maintaining the temperature at 34-35°C. Stirring was carried on for 6 hours and the mixture kept overnight. NaOH, solution (160g. in 400 ml. water) was added slowly to the reaction mixture under stirring, keeping the temperature around 25°C. The reaction mixture was then transfered to a 2-liter separeting funnel and the upper oily layer (approx. 180g.) was separeted and transfered back to the same reaction vessel and the remaining amount of NaOH (40g. in 1 liter water) was added slowly under vigorous stirring maintaining the temperature between 25-30°C. After stirring for 1 hour and cooling to 5°C, the solid diol separeted out. This was filtered, washed with

cold water and dried. Recrystallization from 5% ethyl acetate-petroleum ether furnished 127g. of the diol (34). Melting point : 87-88° (lit¹⁹ 87-88°). The spectral data were identical with those reported in the above literature.

Keto-carboxylic acid (35) from Carane diol (34).

To a vigorously stirred solution of carane diol (51g., 0.3 moles) in acetone (275ml.), was added Jones' reagent (136ml., 0.36 moles) dropwise maintaining temperature at 5-10°C (1.5 hours). Stirring was continued further for two hours at room temperature and then the excess reagent destroyed by adding methanol. 400ml. of water was added to the reaction mixture and it was extracted with CHCl₃ (2 X 150ml.). The organic layer was washed well with water (4 X 100ml.) and then extracted with sat. Na₂CO₃ (4 X 75ml.). The CHCl₃ layer was not investigated further.

The aqueous portion was acidified with 50% HCl, dropwise at 5-10°C and extracted with CHCl₃ (4 X 50ml.). The CHCl₃ layer was washed with water (4 X 75ml.), then with brine and dried. Evaporation of

the solvent gave a brown oily liquid 42g. (76%).

IR. λ max., film : 3540, 3000, 1738, 1720, 1425, 1390, 1370, 1315, 1170, 1110. cm^{-1} .

Esterification of acid (35).

10g. of the above acid was dissolved in ether and an ethereal solution of diazomethane was added slowly till a yellowish green colour persisted. The reaction mixture was left for 3 hours and then dried and concentrated. 10g. (92%) of the methyl ester was obtained as a light yellow oil.

IR. λ max., film (Fig.1): 2950, 1720, 1600, 1460, 1370, 1275, 1175, 990, 815, 760, 725, 660. cm^{-1} .

Grignard reaction on keto-carboxylic acid (35).

Magnesium (3g., 0.12 g atoms) was suspended in 200ml. Dry ether and to this added a solution of methyl iodide (18g., 0.127 moles) in 75ml. ether according to the general procedure for the preparation of Grignard's reagent. This reagent was

then siphoned into a dropping funnel using dry nitrogen gas.

10g. (0.054 moles) of the keto-carboxylic acid (35) was dissolved in 100ml. dry ether. The Grignard reagent was added very slowly to the above solution during 4 hours at room temperature. Stirring was continued overnight, and water was added to produce a turbid solution to which aqueous NH_4Cl was added. This was then cautiously acidified with 10% HCl . The ether layer was separated and dried. Removal of the ether afforded 9.8g (90%) of the 3,3-dimethyl-2-(2-methyl-2-hydroxypropyl)cyclopropyl acetic acid (43) as a crystalline solid. This was recrystallized from n-hexane to obtain 9g. of colourless needles.

M.P. $87-88^\circ$ (lit.¹⁵ $87-88^\circ$).

IR. $\lambda_{\text{max.}}$, KBr: 3300, 3000-2500, 1680, 1150. cm^{-1} .

PMR (80 MHz, CDCl_3 , δ): 0.68-1 (m, 2H), 0.92 and 1.1 (each s, each 3H), 1.28 (s, 6H), 1.46 (d, $J=6\text{Hz}$, 2H), 2.93 (d, $J=7\text{Hz}$, 2H), 7.1 (s, 2H).

Esterification of the hydroxy acid (43).

A solution of (43) (1g., 0.005 moles) was treated with an ethereal solution of diazomethane and left for 3 hours. Drying and concentration gave an almost quantitative yield of the hydroxy ester (44).

IR $\lambda_{\max.}$, film: 3550, 1740, 1450, 1170, 1029, 910, 770. cm^{-1} .

Grignard's reaction on the ketocarboxylic ester (56).

To a stirred solution of (56) (8g., 0.043 moles) in 50ml. of dry ether was added slowly the Grignard's reagent prepared from 0.945g (0.043g atom) of magnesium and 6.11g. (0.043 moles) methyl iodide in 100ml. ether. Stirring was continued at room temperature overnight and aqueous NH_4Cl was added to the reaction mixture which was then acidified with 10% HCl . The ether layer was separated washed and dried. Removal of ether afforded 7g. (81%) of the hydroxy ester (44) as an oil. Its IR spectrum was superimposable on that of

the sample prepared earlier from (43).

Dehydration of the hydroxy ester (44).

To a stirred solution of (44) (2g., 0.0092 moles) in 20ml. of dry pyridine was added 1.2ml. of POCl_3 at 0°C , dropwise during 30 minutes. Stirring was continued at 0°C for another 2.5 hours. The reaction mixture was poured on crushed ice and extracted with benzene. The benzene extracts were washed with 10% HCl, water and dried. Evaporation gave 0.8g (50%) of an oil.

T.L.C. of this oil over AgNO_3 impregnated silica gel showed two spots. Column chromatography over silica gel impregnated with AgNO_3 , with petroleum ether as eluent afforded 0.5g. of methyl cis-homochrysanthemate (45). Later fraction eluted with 1-2% ethyl acetate-petroleum ether gave 0.250g. of the double bond isomer (46).

Methyl cis-homochrysanthemate (45): IR. λ max., film (Fig.2): 1740, 1650, 1065, 840. cm^{-1} .

PMR (80 MHz, CDCl_3 , δ) (Fig.3): 0.96 and 1.16 (each s, each 3H,), 1.04-1.6 (m, 2H), 1.75 and 1.79

(each s, each 3H), 2.36 (d, J=8Hz, 2H), 3.85 (s, 3H), 5.0 (d, J=6Hz, 1H).

$[\alpha]_D +80.85^\circ$ in CCl_4 (lit.¹⁶ $+68^\circ$)

Double bond isomer of methyl cis-homochrysanthemate

(46): IR. $\lambda_{max.}$, film (Fig. 4): 1740, 1655, 890. cm^{-1} .

Hydrolysis of methyl cis-homochrysanthemate (45).

A suspension of the ester (45)(2g., 0.01 moles) in 50ml. of 5% NaOH was stirred at room temperature for 12 hours. The reaction mixture then cooled to $10^\circ C$ and carefully acidified with 10% HCl and extracted with $CHCl_3$ (5 x 20ml.). $CHCl_3$ extracts were washed with water and dried. Removal of $CHCl_3$ afforded 1.6g (85%) of cis-homochrysanthemic acid (41) as an oil.

IR. $\lambda_{max.}$, film (Fig.5): 3100-2729, 1703, 1648, 840. cm^{-1} .

Reaction of cis-homochrysanthemic acid with lead tetraacetate.

The acid (41)(1.5g., 0.008 moles), 0.4g. cupric acetate and pyridine 0.25g. was taken in 25

ml. of dry benzene and to this added 6g. of lead tetraacetate. The mixture was stirred for 45 minutes in an nitrogen atmosphere and then refluxed for two hours. The mixture was cooled and the excess of $Pb(OAc)_4$ destroyed by the careful addition of ethylene glycol (5 ml.). Water was added and the benzene layer separated and washed well with water. Drying and evaporation gave a reddish oil.

Column chromatography over silica gel with cyclohexane - ether gave two major fractions. Fraction A (95.5:5 cyclohexane-ether) was almost pure and Fraction B (90:10 cyclohexane-ether) which consisted of three substances. The major component of fraction B was separated by preparative GLC over Carbowax column (compound B₁). The other two could not be separated even on GCMS. However their IR spectra could be recorded on an FTIR instrument coupled to an apolar column.

Fraction A was identified mainly as 4,4-dimethyl-3-(3-methylbuta-1,3-dienyl) butanolide. (47).

PMR (360 MHz., $CDCl_3$, δ)(Fig.6): 1.26 and 1.36

(each s, each 3H), 1.85 (s, 3H), 2.51 - 2.73 (m, 2H), 2.88 - 2.99 (m, 1H), 5.0 (d, J= 7.2Hz, 2H), 5.49 (dd, J= 14.4 and 7.2 Hz., 1H), 6.25 (d, J= 14.4 Hz., 1H)

Mass m/z (rel. int)(Fig.7): 180 (M^+ , 2), 165 (2), 122 (10), 94 (80), 79 (100), 65 (5), 53 (5), 43 (12).

Compound B₁ 4,4-dimethyl-3-(3'acetoxy-3'-methylbut-1-enyl)butanolide (48).

GCFTIR $\lambda_{max.}$, (Fig.8): 2986, 1809, 1790, 1377, 1232, 1128, 963. cm^{-1} .

PMR (360 MHz, $CDCl_3$, δ)(Fig.9): 1.23 and 1.43 (each s, each 3H), 1.5 and 1.52 (each s, each 3H), 1.99 (s, 3H), 2.46 - 2.71 (m, 2H), 2.79 - 2.9 (m, 1H), 5.48 (dd, J= 14.4 and 7.2 Hz, 1H), 5.85 (d, J= 14.4 Hz, 1H).

^{13}C MR (90MHz, $CDCl_3$, δ)(Fig. 10): 22.1, 22.5, 26.7, 27.0, 27.1, 34.7, 48.7, 79.7, 86.7, 124.5, 138.6, 169.9 and 175.1.

Mass m/z, (rel. int.)(Fig.11): 240 (M^+ , 2), 154 (20), 122 (28), 112 (30), 94 (70), 85 (73), 79

(100), 69 (15), 55 (18), 43 (87).

COSY (Fig.12)

¹³CMR spectra of (49) (Fig.13):

Lead tetraacetate reaction on 2-carene (56).

2-carene (2.72g., 0.02 moles) was added to a mixture of lead tetraacetate (1.5g) and benzene (25ml) and the mixture refluxed for 2 hours. Excess lead tetraacetate was decomposed by the careful addition of ethylene glycol. The mixture was cooled and the benzene layer was separated and washed with NaHCO₃, water and brine. Concentration afforded an oil which was purified by column chromatography over silica gel with ethyl acetate - petroleum ether as eluent. 0.938g (35%) of a pure fraction was obtained which was identified as p-cymene (59).

PMR (300 MHz, CDCl₃, δ)(Fig.14): 1.3 (d, 6H), 2.05 (s, 3H), 2.95 (m, 1H), 7.05 (s, 4H).

Lead tetraacetate reaction on maaliol (62).

Maaliol (2.22g., 0.01 moles) was added to a mixture of lead tetraacetate (1.5g) and benzene

(25ml) and the mixture refluxed for 2 hours. Excess lead tetraacetate was decomposed by the careful addition of ethylene glycol. The mixture was cooled and the benzene layer was separated and washed with NaHCO_3 , water and brine. Concentration afforded an oil which was purified by column chromatography over silica gel with ethyl acetate - petroleum ether as eluent. Two fractions were obtained. Both were further subjected to preparative GLC.

The first fraction showed the presence of two compounds, one major (92.13%) and a minor (6.635%). The major compound was identified as (66).

IR, λ_{max} , neat. (Fig.15): 2950, 1716, 1642, 1452, 1369, 1222, 1165, 891 and 741 cm^{-1} .

PMR (300 MHz, CDCl_3 , δ)(Fig.16): 0.98 (s, 3H), 1.75 (s, 3H), 2.15 (s, 3H), 4.7 (d, 1H), 5.5 (s, 2H).

Mass m/z (rel. int.)(Fig.17): 220 (M^+ , 2), 162 (30), 147 (12), 135 (97), 119 (20), 107 (85), 93 (95), 85 (25), 79 (75), 67 (15), 55 (25), 43 (100).

The minor compound was identified as (67).

Mass m/z (rel. int.)(Fig.18): 194 (M^+ , 5), 179

(50), 67 (38), 53 (20), 43 (100).

The second fraction showed the presence of a major fraction in addition to unreacted maaliol. the compound was identified as (68).

IR, λ_{\max} , neat. (Fig.19): 2950, 1728, 1462, 1367, 1257, 1137, 1019, 941 and 737 cm^{-1} .

PMR (300 MHz, CDCl_3 , δ)(Fig.20): 0.95 (s, 3H), 1.4 (d, 6H), 1.97 (s, 3H), 2.13 (s, 3H), 2.4 (t, 2H), 5.52 (q, 2H).

Mass m/z (rel. int.)(Fig.21): 220 ($\text{M}^+ - \text{CH}_3\text{COOH}$, 8), 162 (28), 135 (97), 119 (18), 107 (50), 93 (15), 85 (15), 79 (50), 43 (100).

Lead tetraacetate reaction on guaiol (75).

Guaiol (2.24g., 0.01 moles) was added to a mixture of lead tetraacetate (1.5g) and benzene (25ml) and the mixture refluxed for 2 hours. Excess lead tetraacetate was decomposed by the careful addition of ethylene glycol. The mixture was cooled and the benzene layer was separated and washed with NaHCO_3 , water and brine. Concentration afforded an

oil which was purified by column chromatography over silica gel with ethyl acetate - petroleum ether as eluent. 0.425g (20%) of dehydroguaiooxide (77) was obtained.

PMR (300 MHz, CDCl_3 , δ)(Fig.22): 1.12 (d, 3H), 1.17 (d, 3H), 1.2 (s, 3H), 1.35 (s, 3H), 1.4-1.6 (m, 3H), 1.7-1.9 (m, 3H), 1.9-2.4 (m, 7H).

^{13}C MR (75 MHz, CDCl_3 , δ)(Fig.23): 13.2, 20.47, 23.6, 31.1, 31.4, 33.3, 33.8, 38.1, 38.3, 42.5, 45.1, 81.8, 93.5, 123.8, 153.6.

Mass m/z (rel. int.)(Fig.24): 221 (M^+ , 10), 220 (80), 205 (100), 187 (25), 177 (15), 159 (32), 147 (62), 131 (25), 119 (45), 105 (45), 91 (65), 79 (38), 69 (35), 55 (65), 43 (85).

Cosy spectra (Fig.25)

HETCOR spectra (Fig.26)

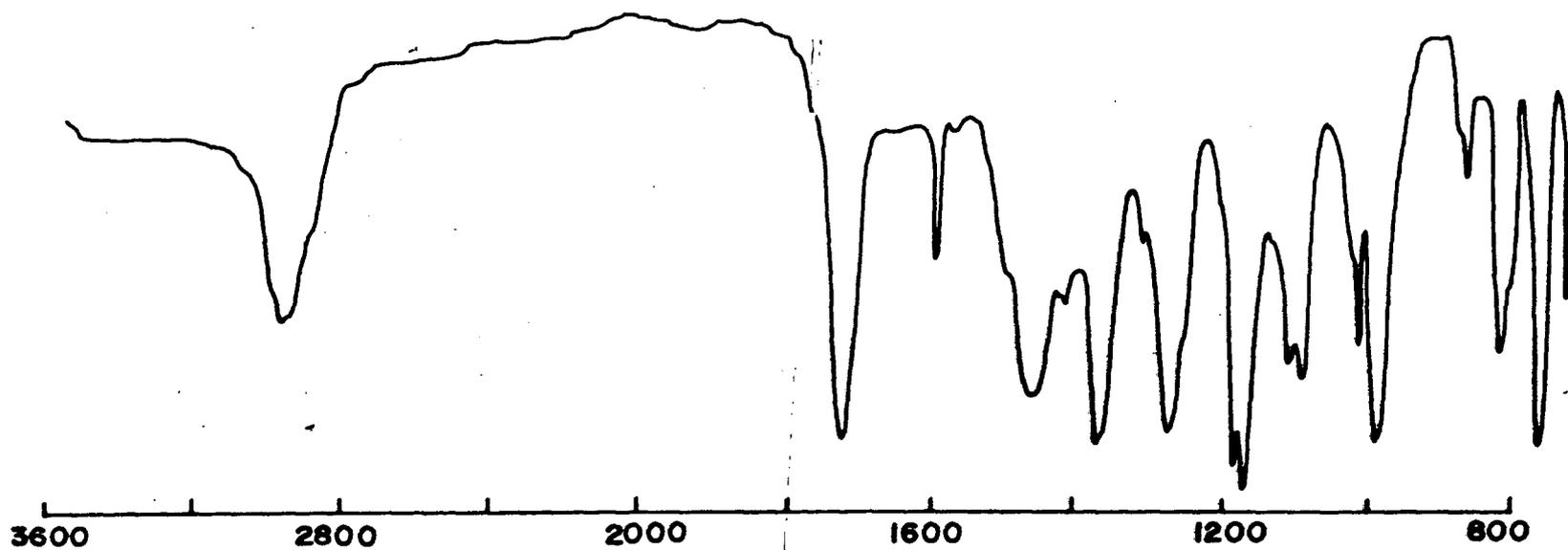
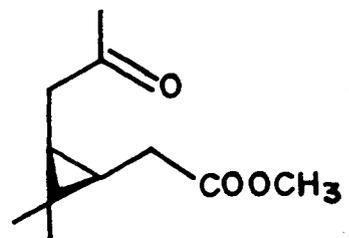


Fig. 1 IR spectrum of (56)

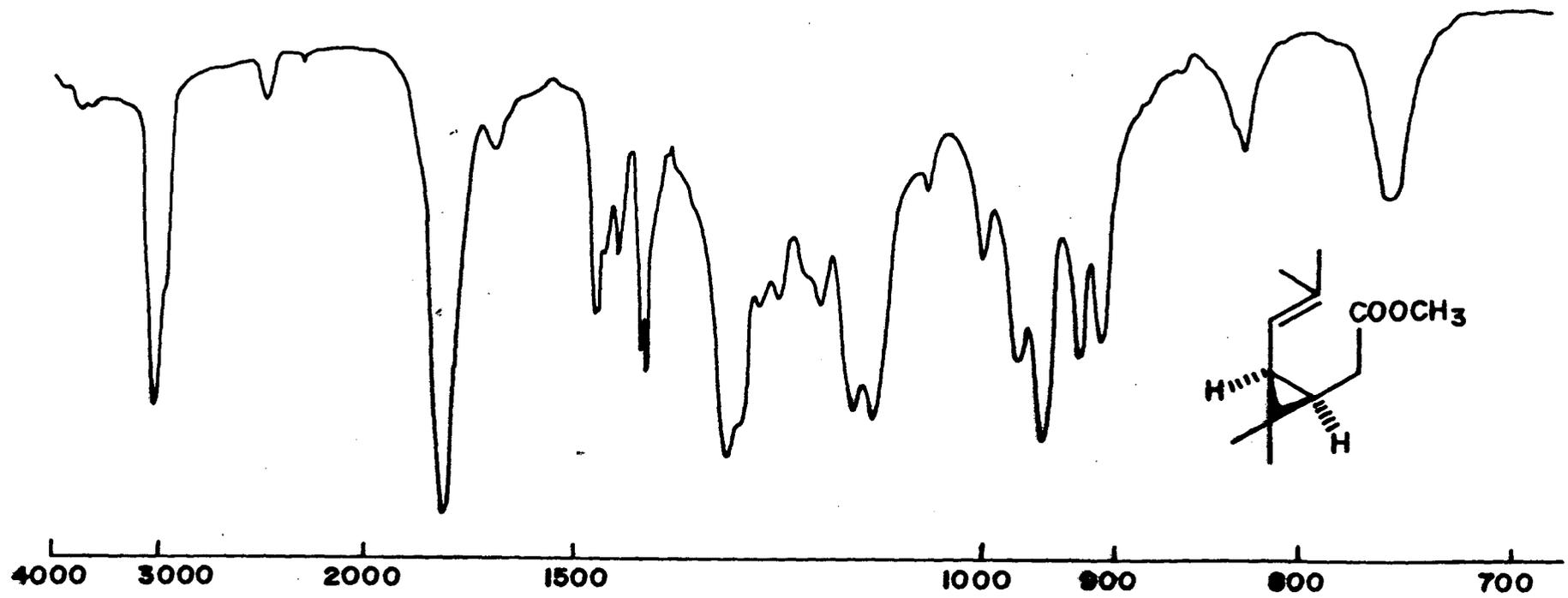


Fig. 2 IR spectrum of (45)

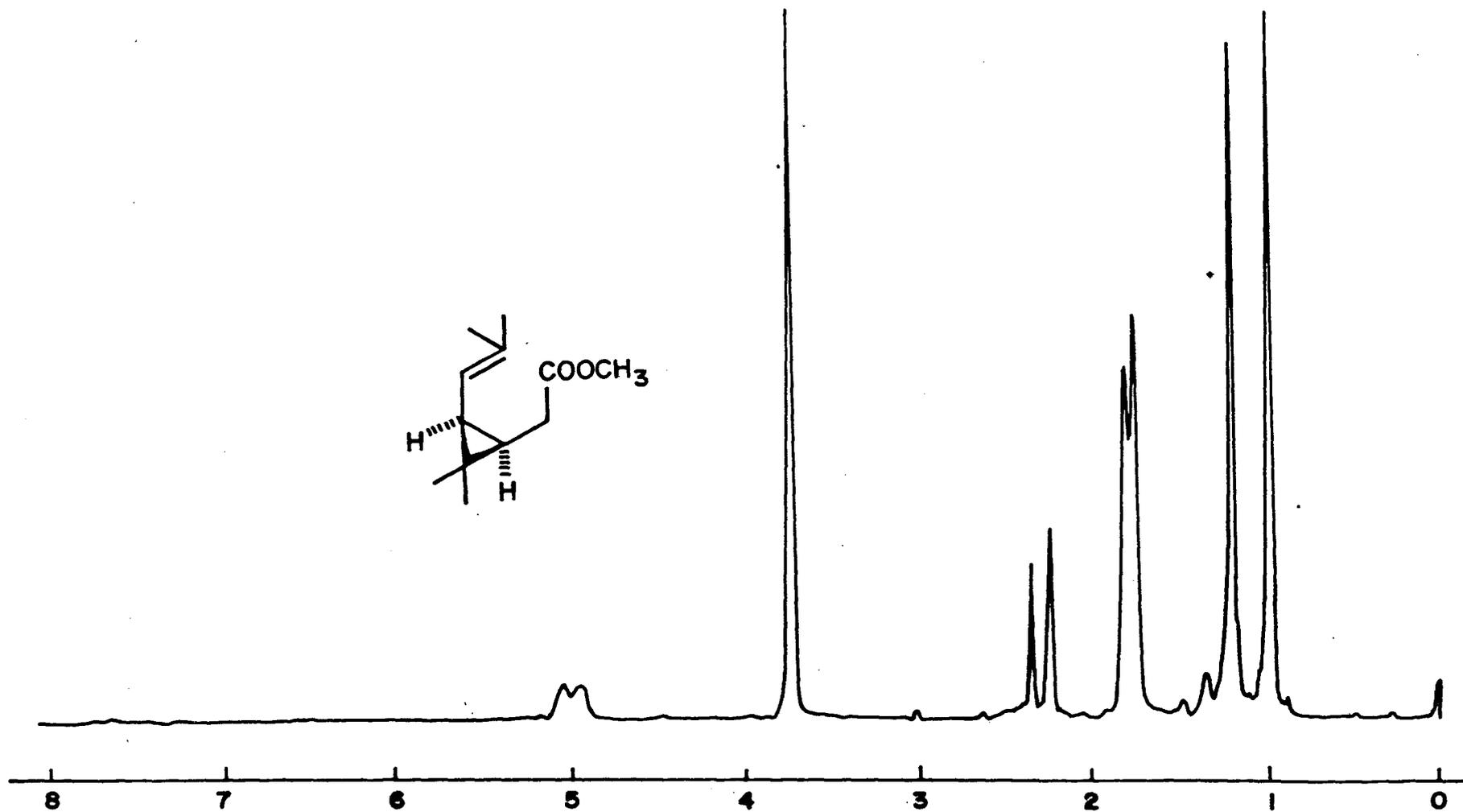


Fig. 3 NMR spectrum of (45)

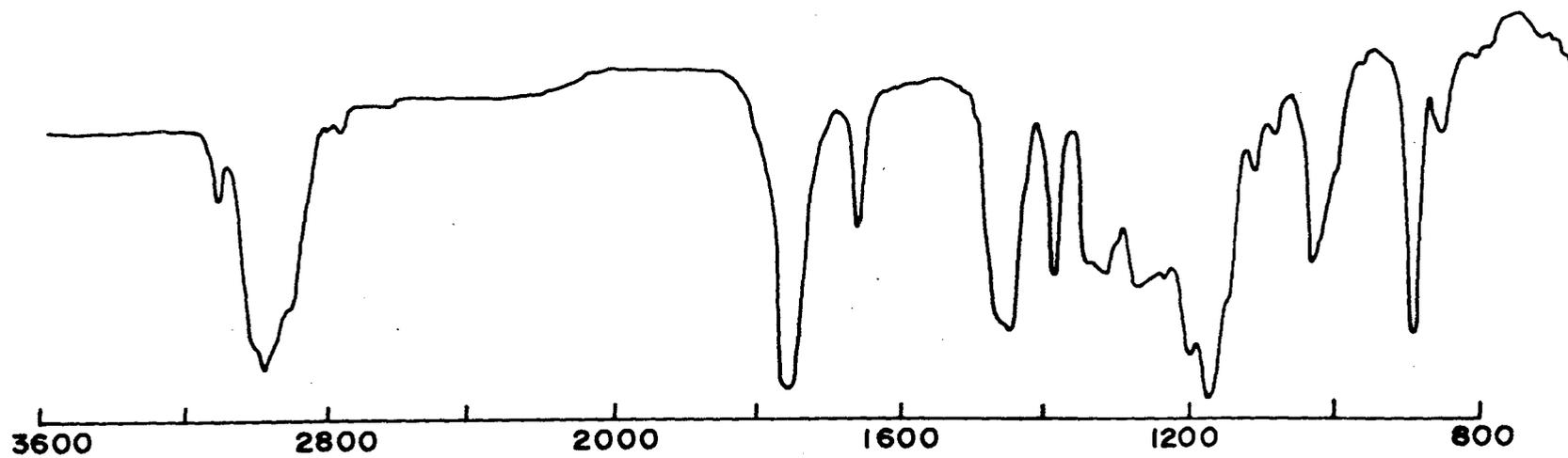
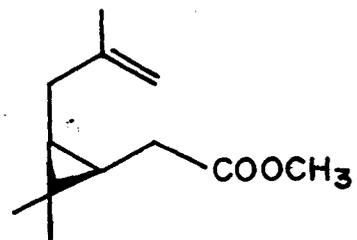


Fig. 4 IR spectrum of (46)

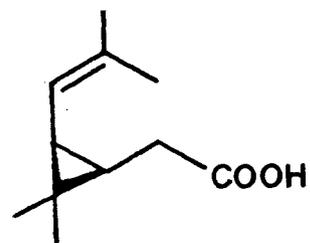


Fig. 5 IR spectrum of (41)

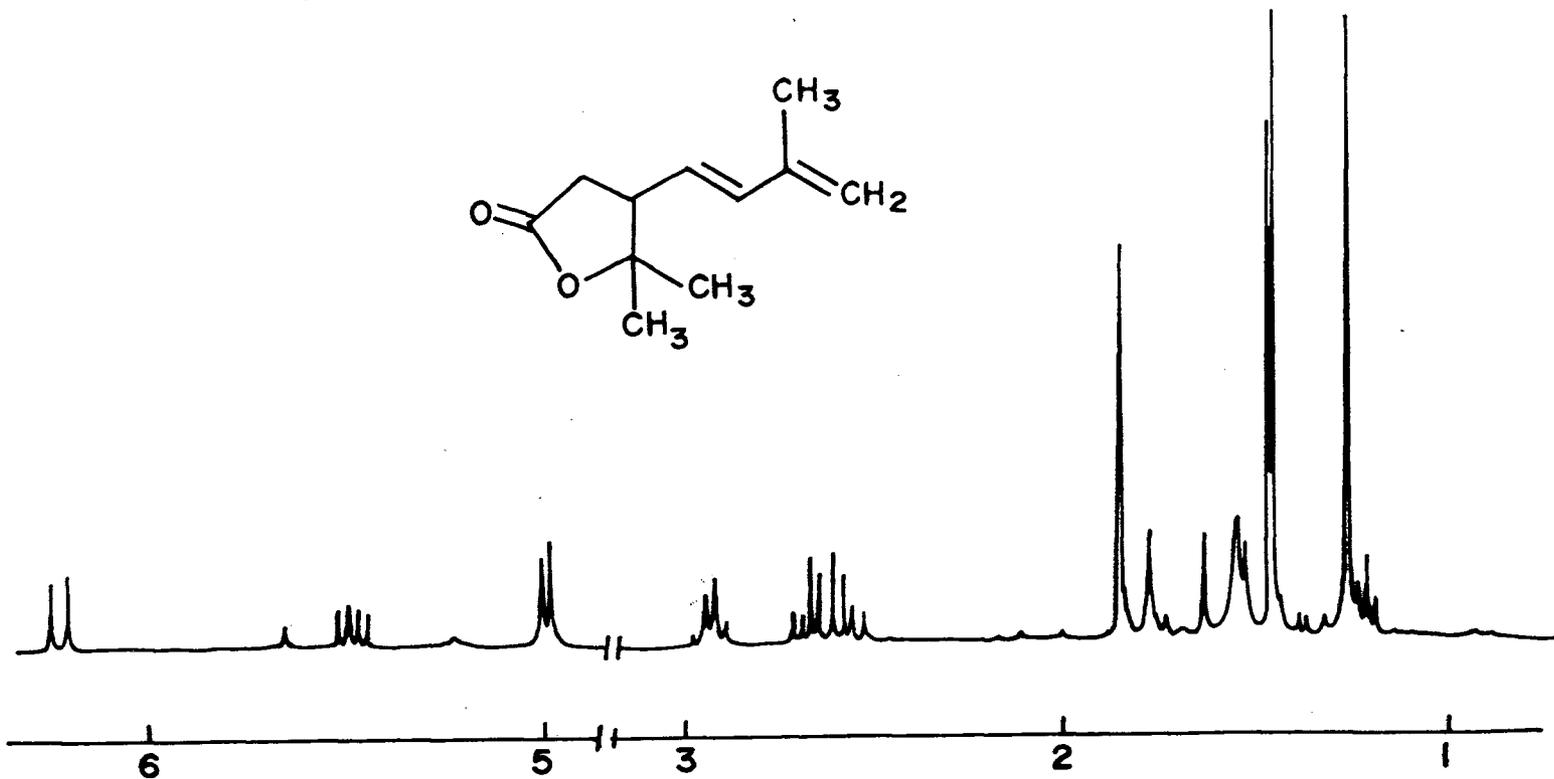


Fig. 6 NMR spectrum of (47)

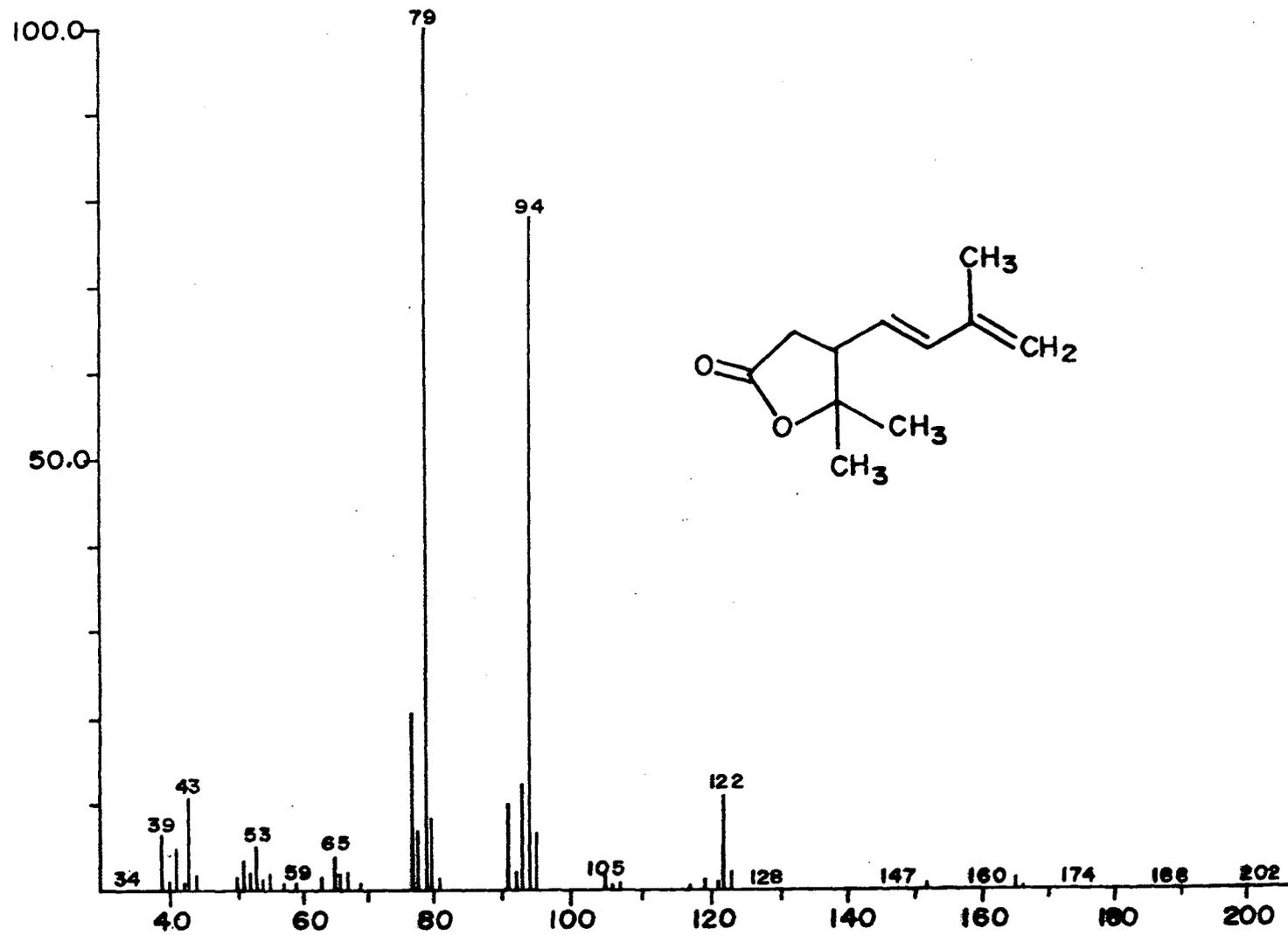


Fig. 7 Mass spectrum of (47)

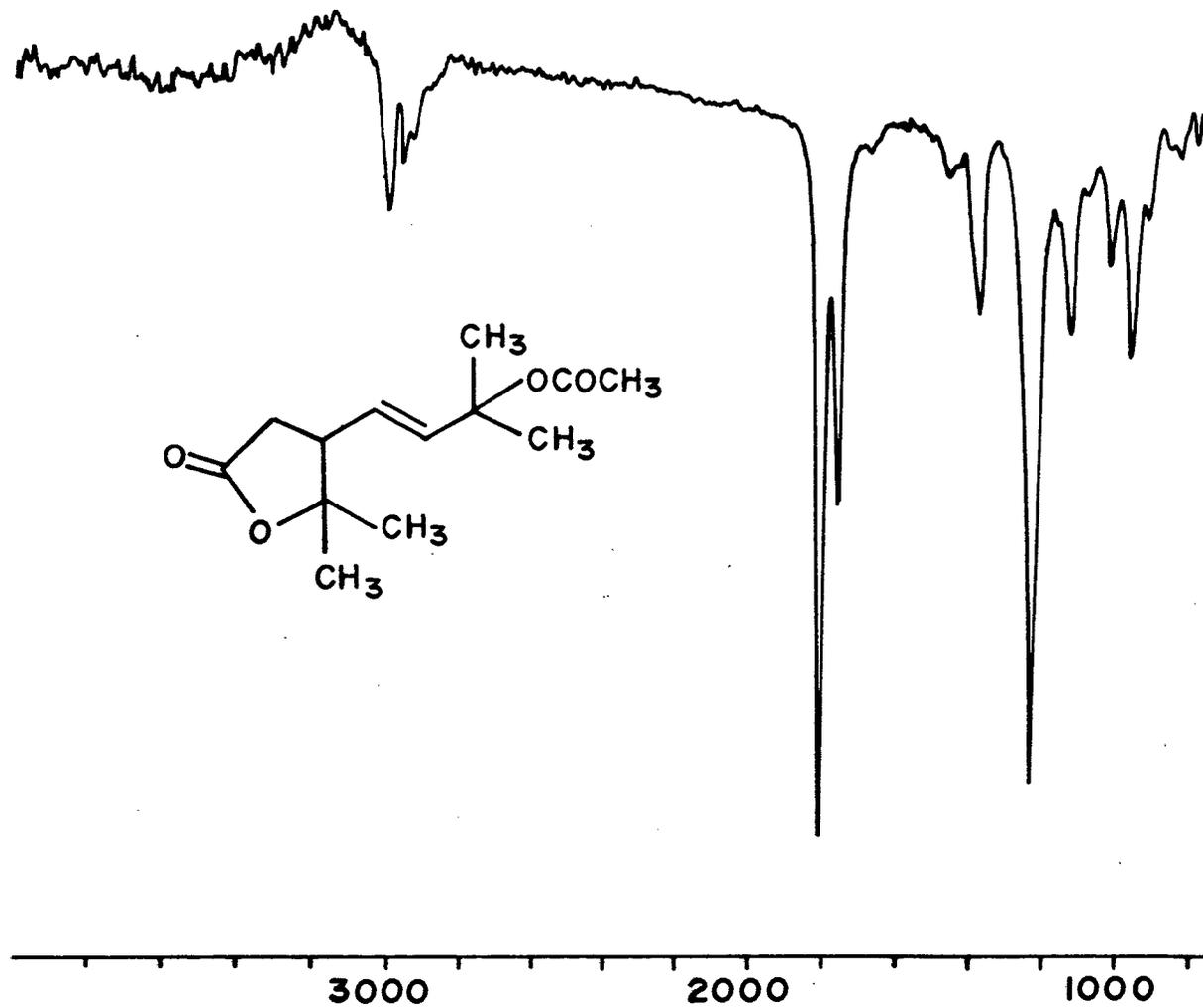


Fig. 8 IR spectrum of (48)

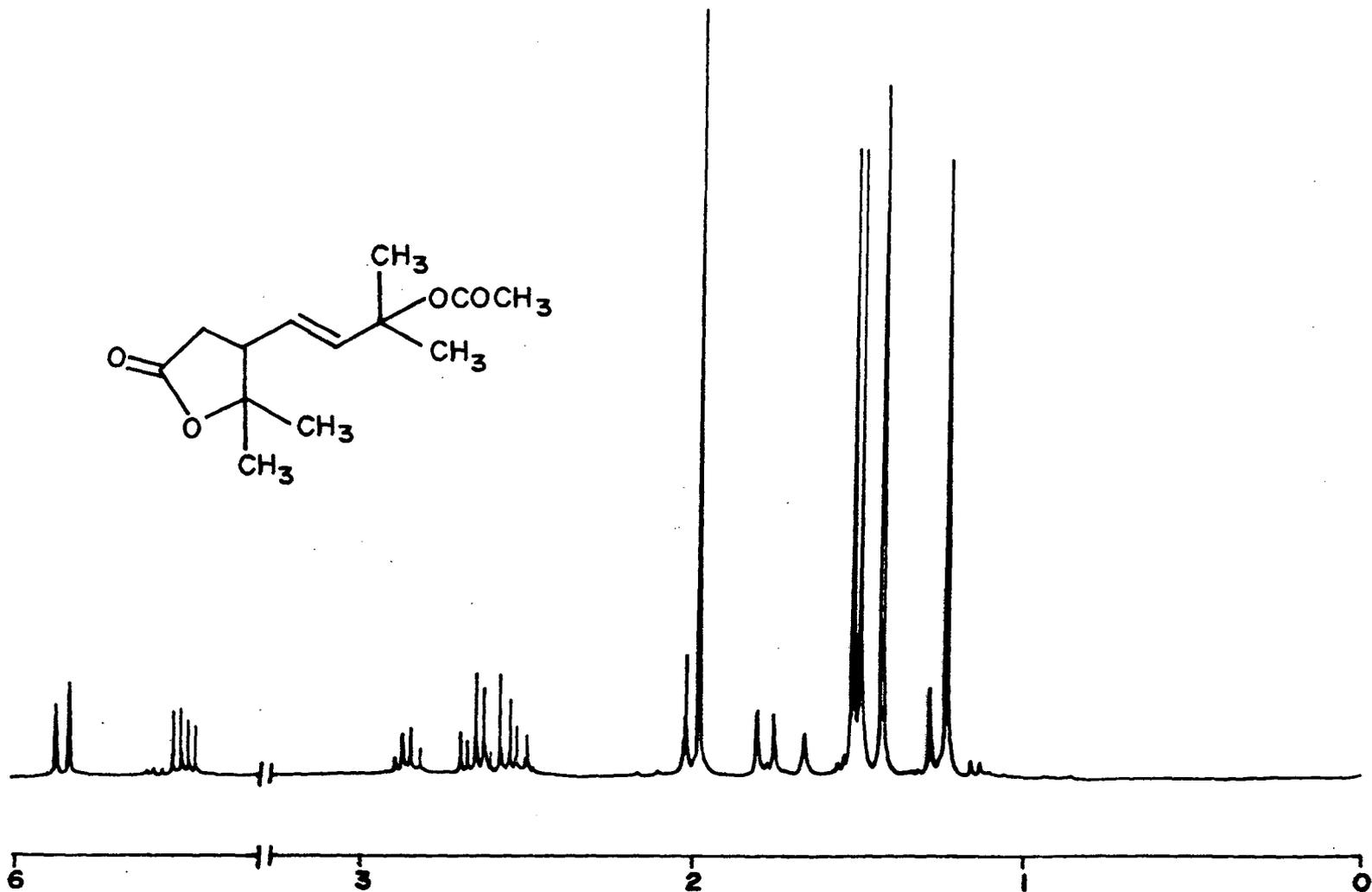
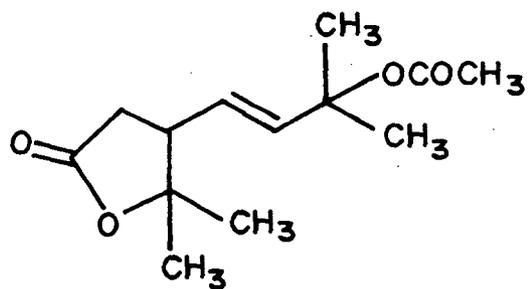


Fig. 9 NMR spectrum of (48)

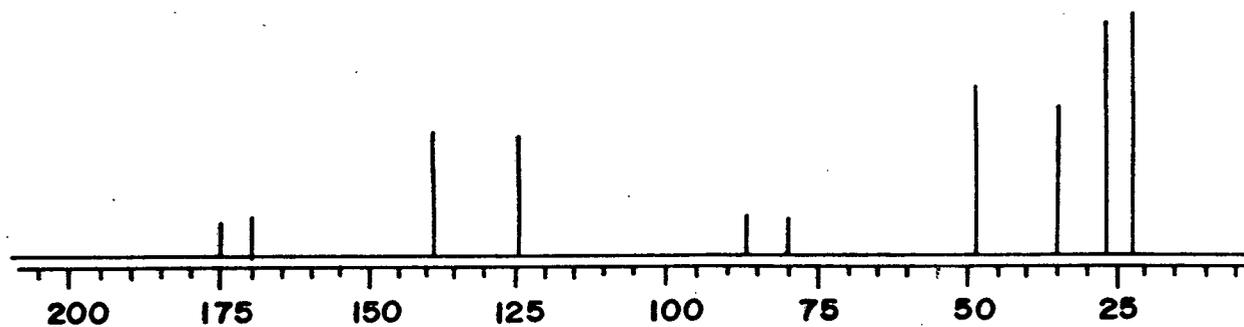
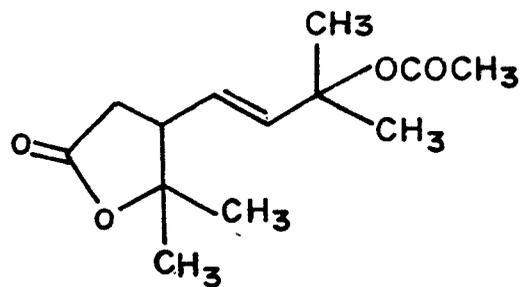


Fig. 10 ¹³C NMR spectrum of (48)

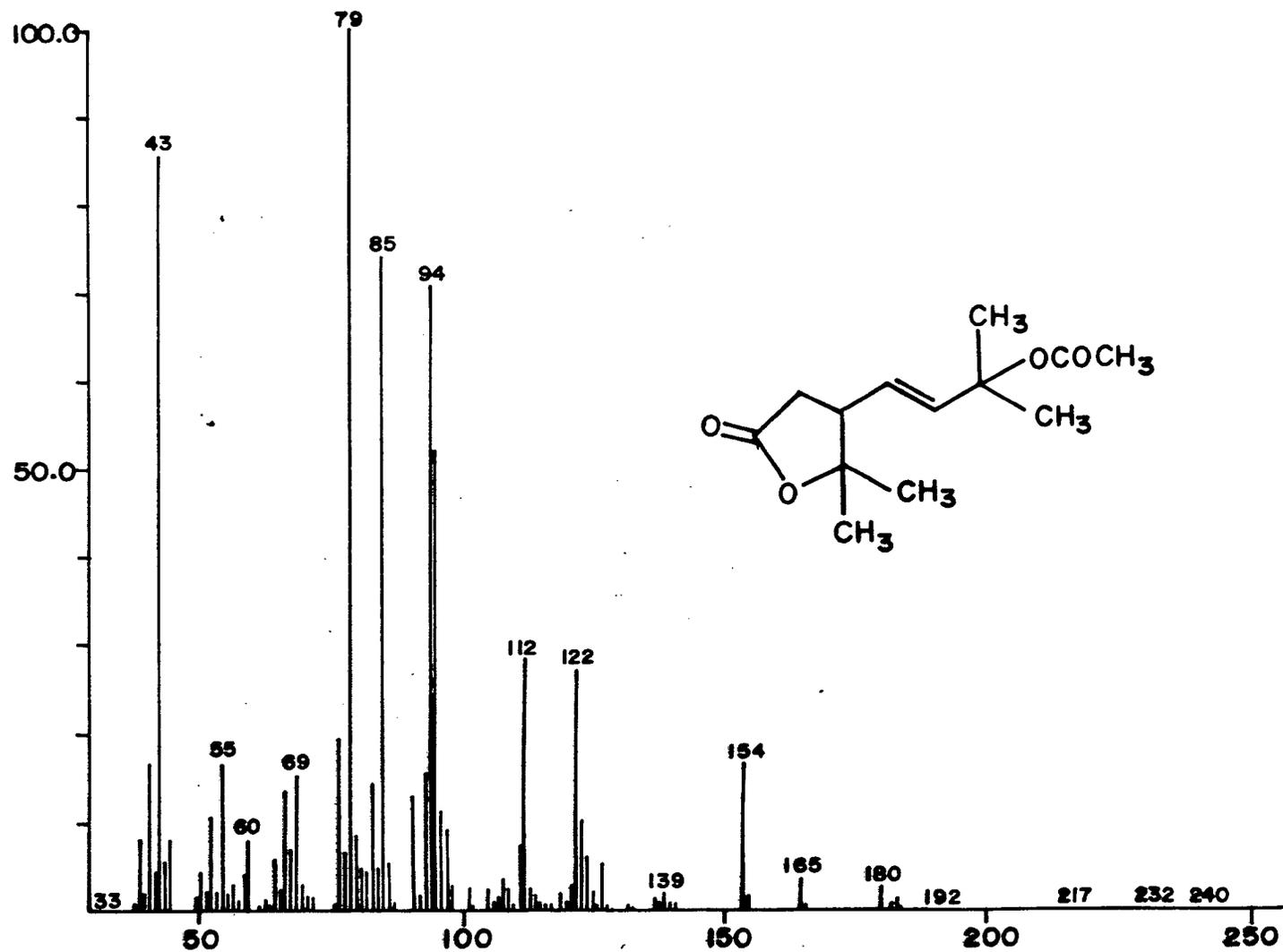


Fig. II Mass spectrum of (48)

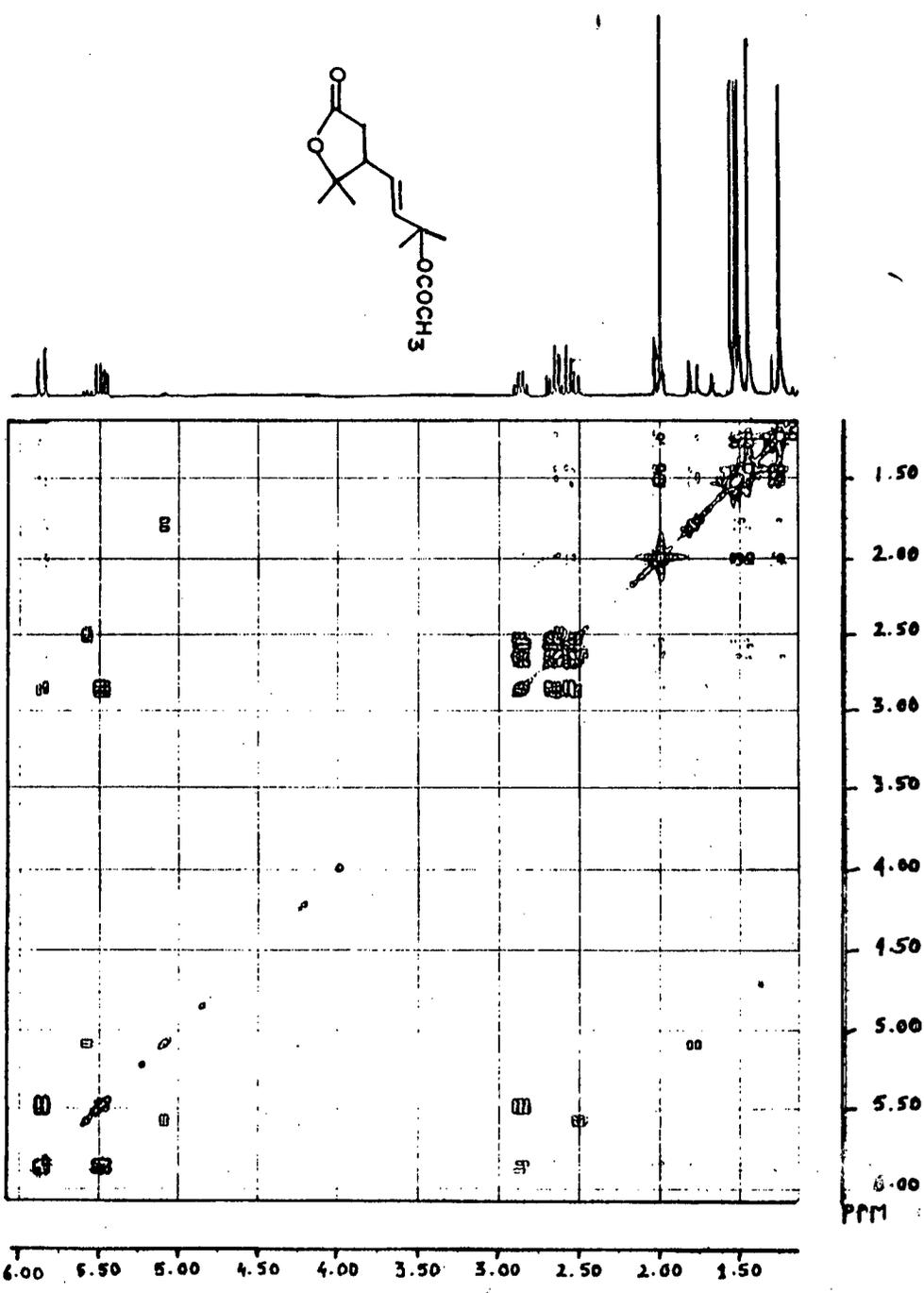


Fig. 12 Cosy spectrum of (48)

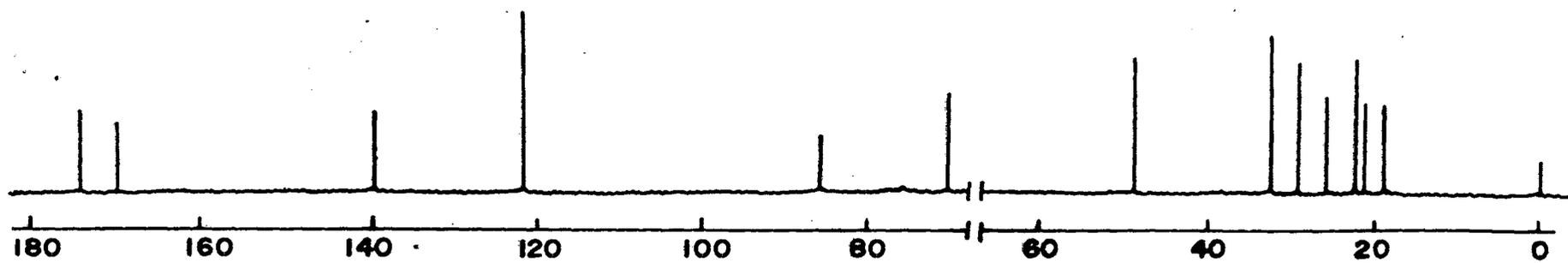
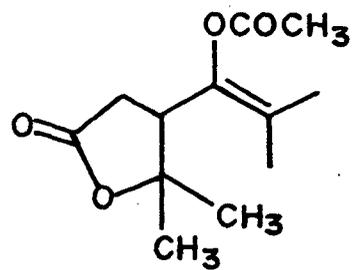


Fig. 13 CMR spectrum of (49)

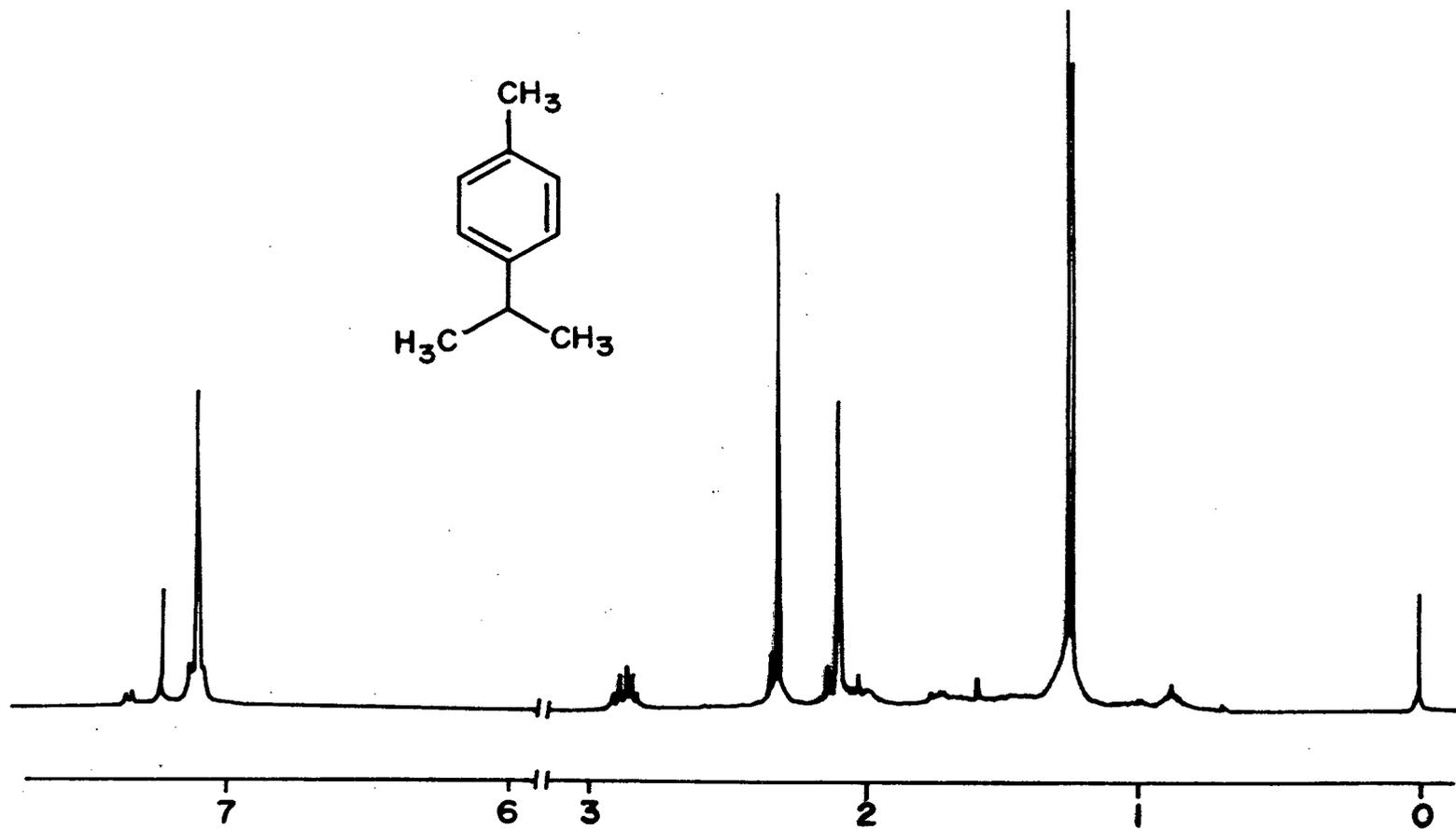


Fig. 14 NMR spectrum of (59)

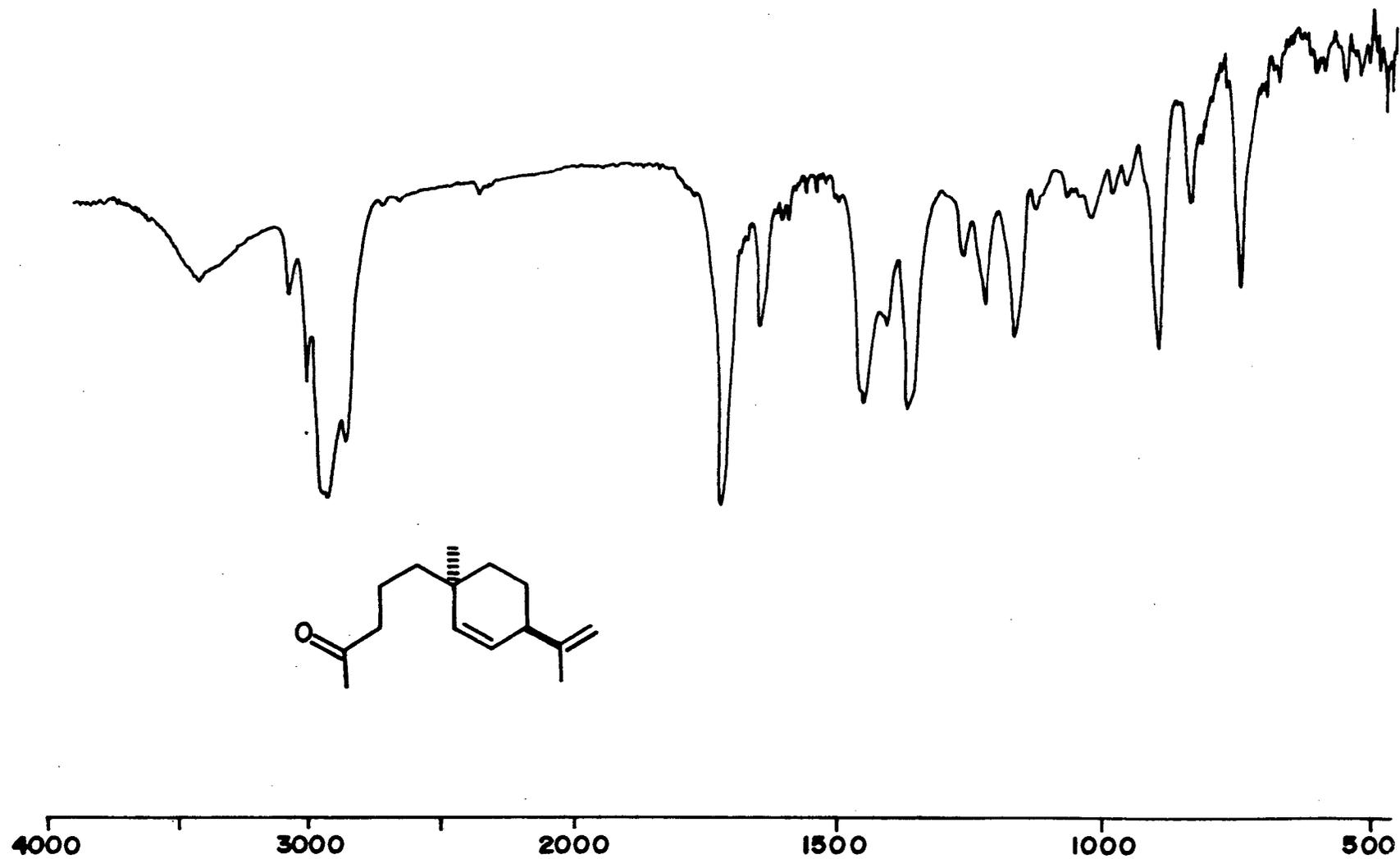


Fig. 15 IR spectra of (66)

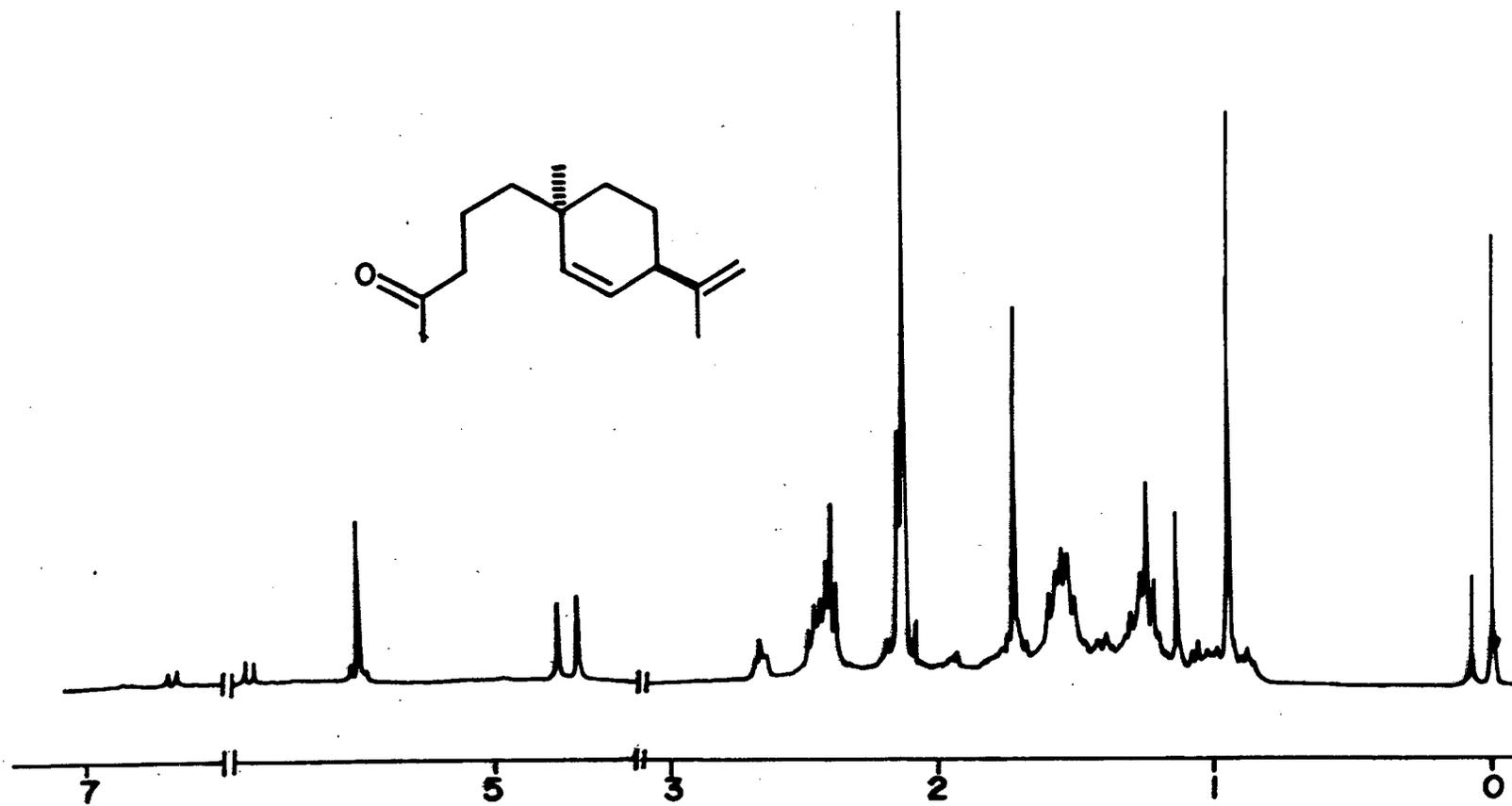


Fig. 16 NMR spectrum of (66)

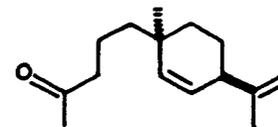
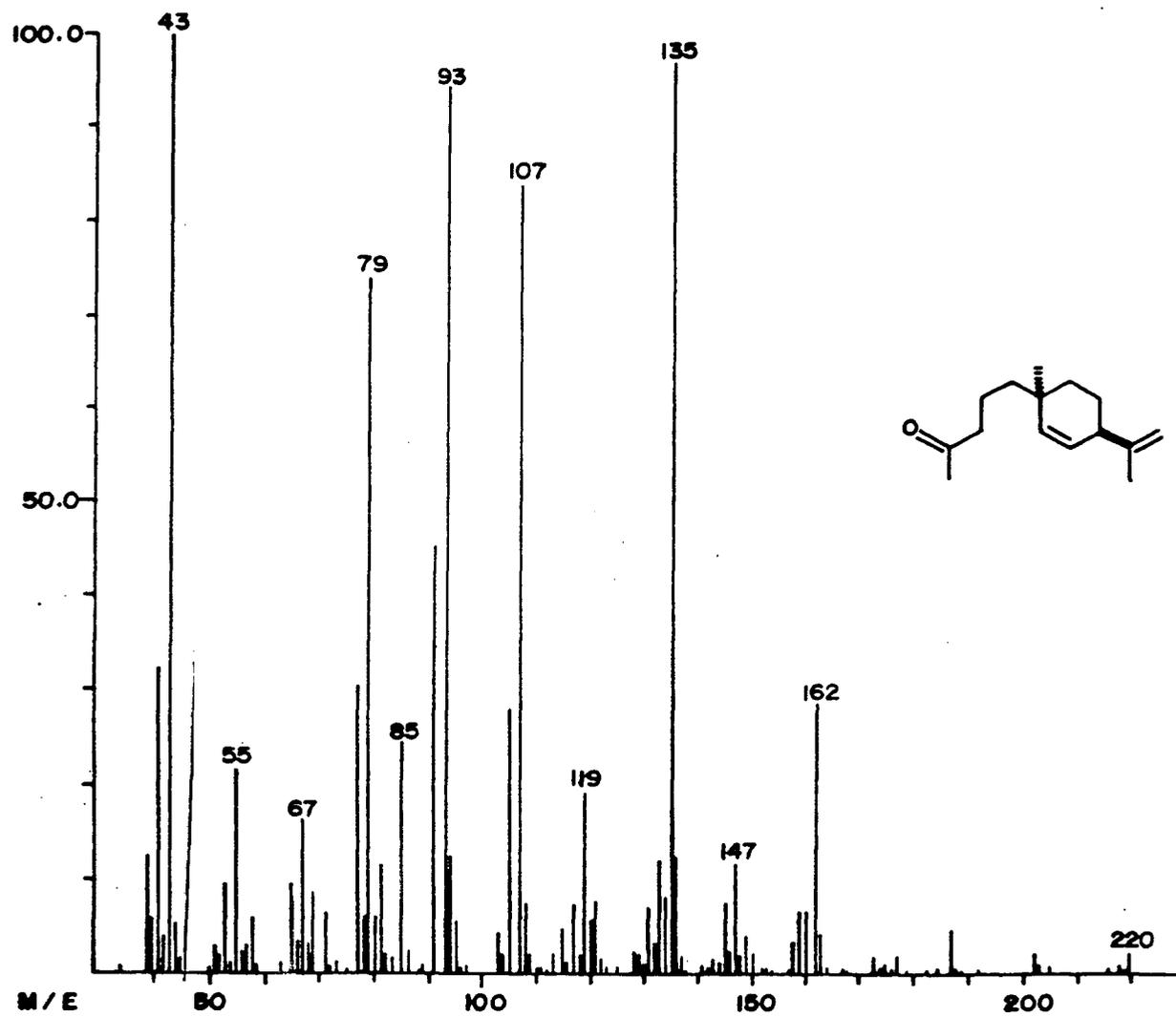


Fig. 17 Mass spectrum of (66)

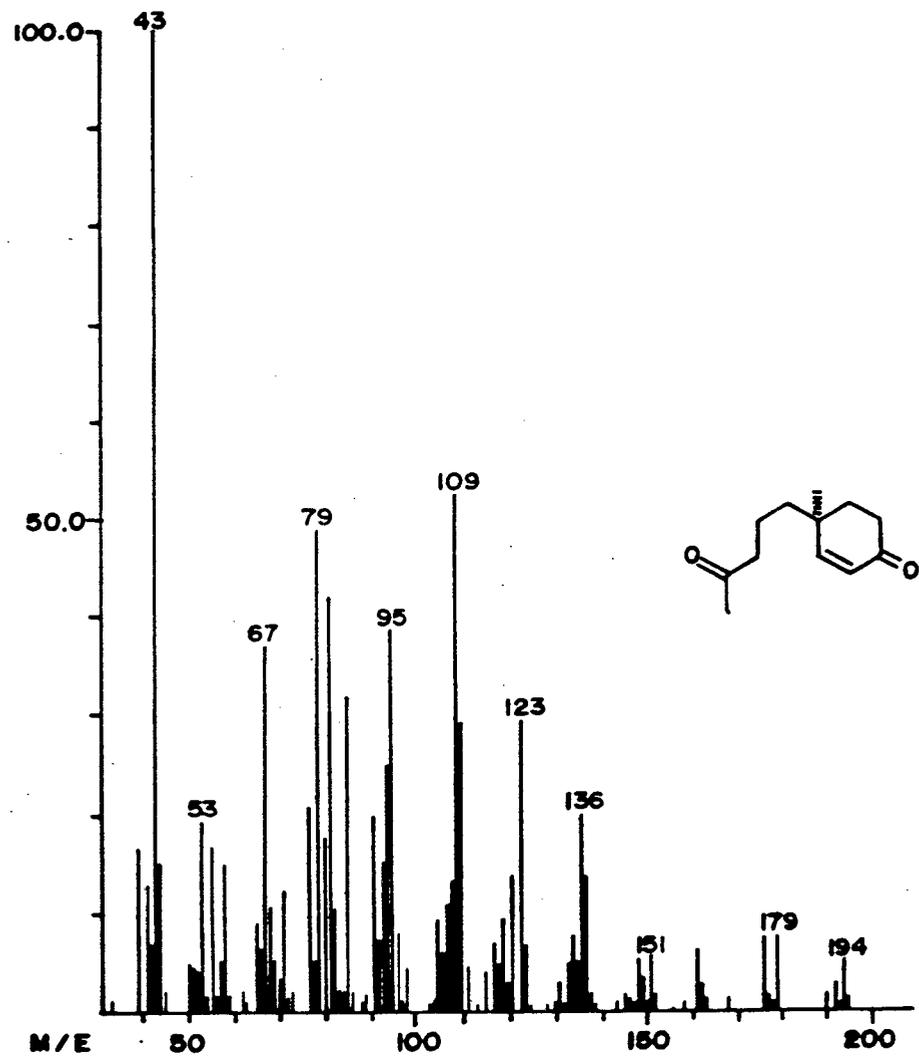


Fig. 18 Mass spectrum of (67)

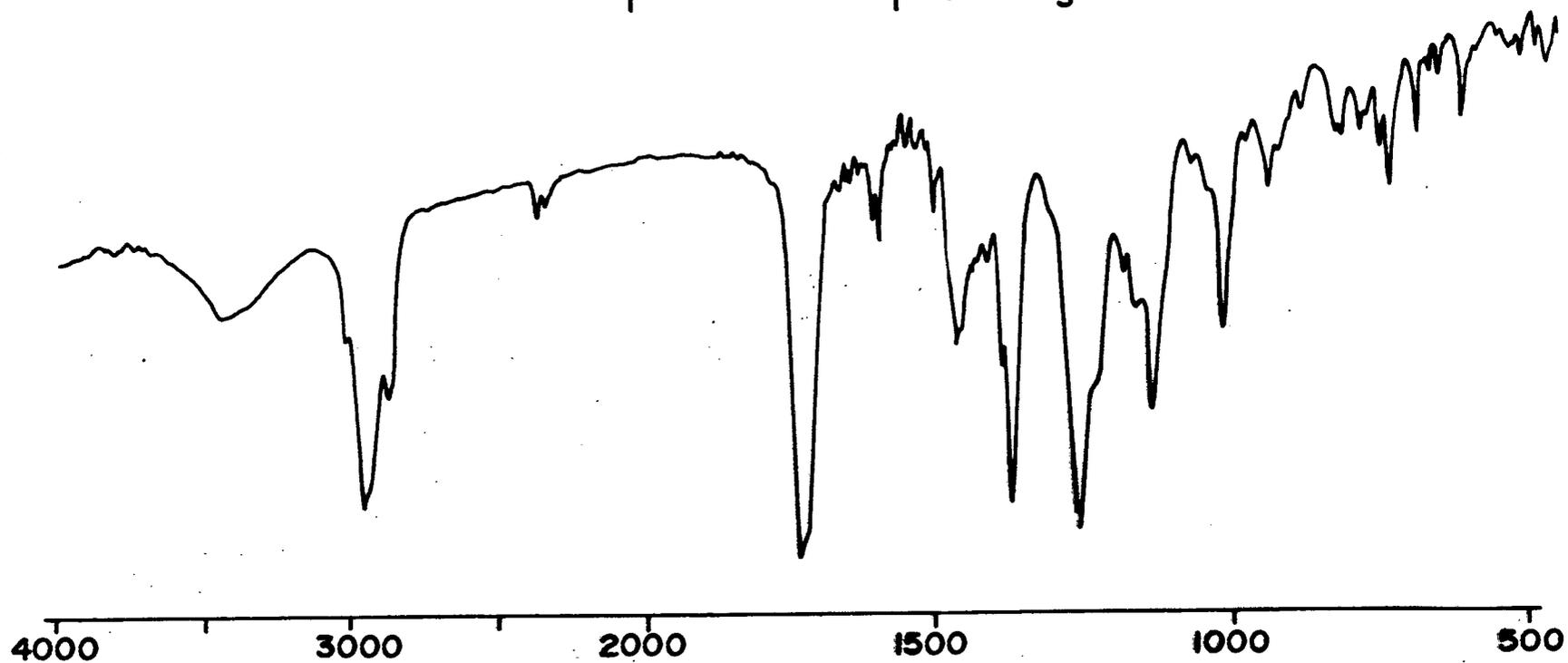
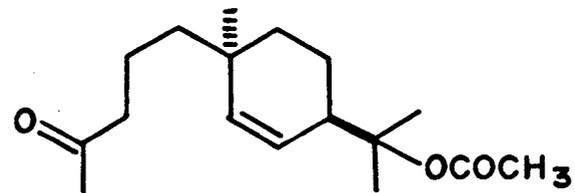


Fig. 19 IR spectrum of (68)

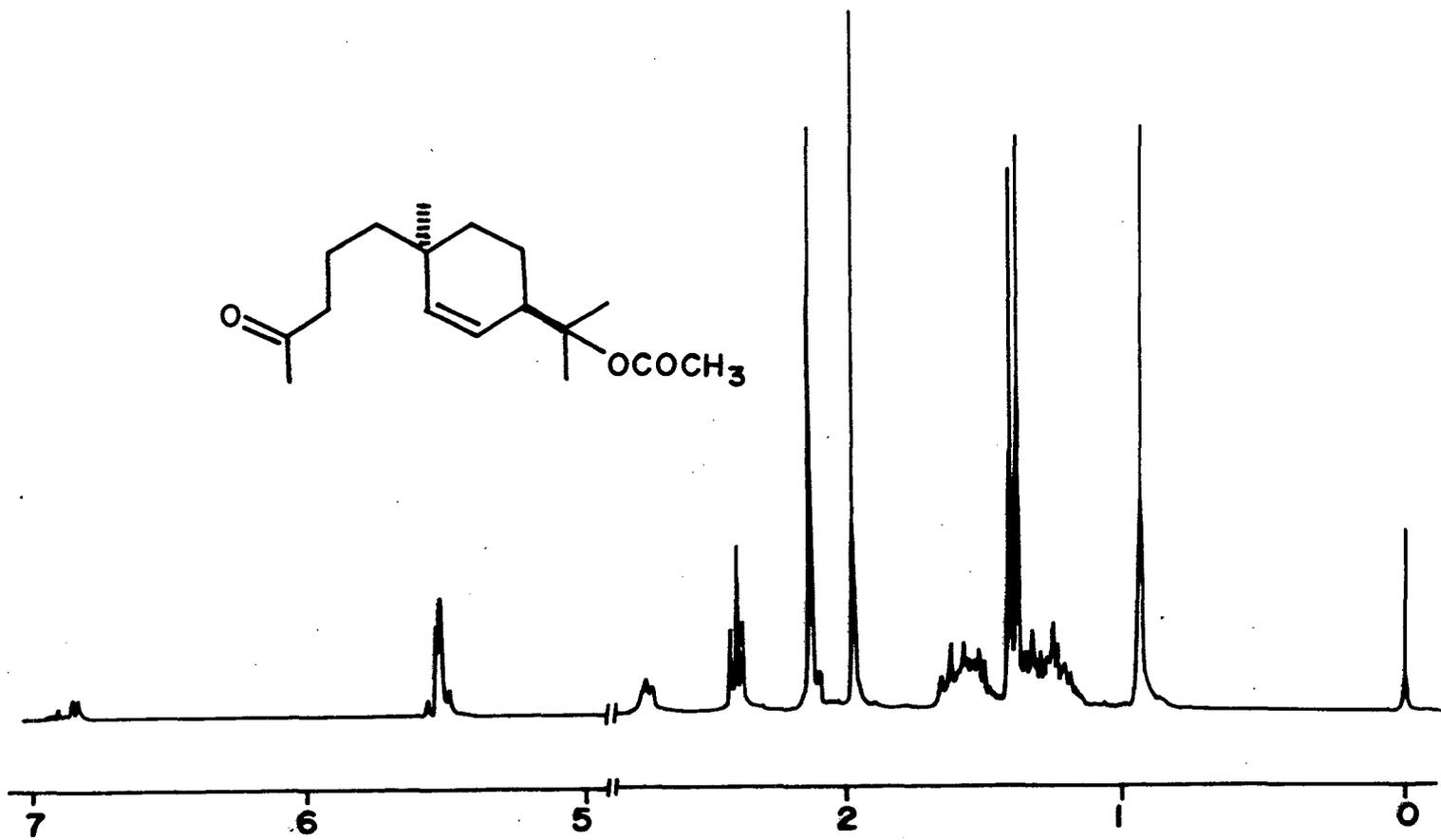


Fig. 20 NMR spectrum of (68)

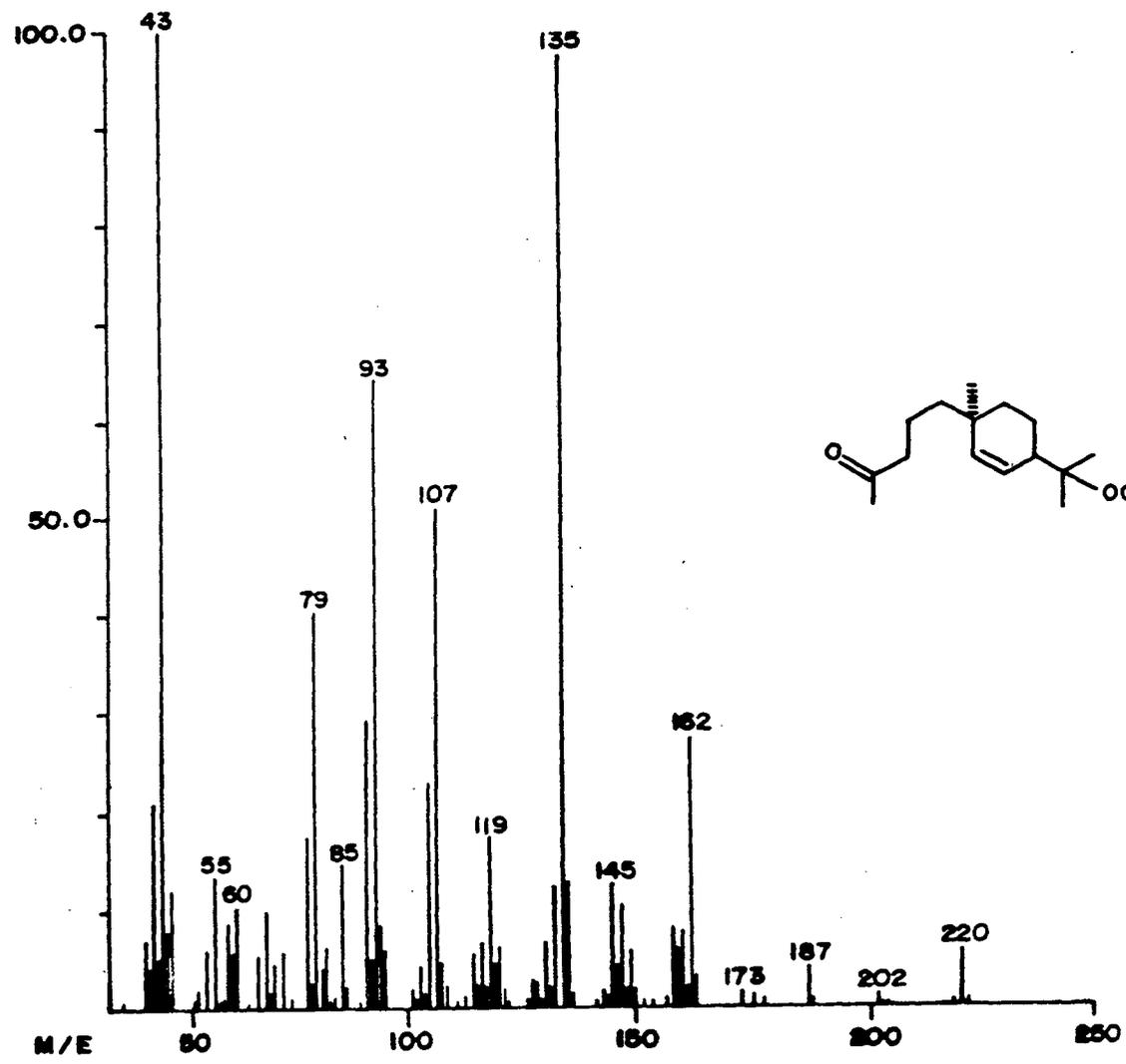
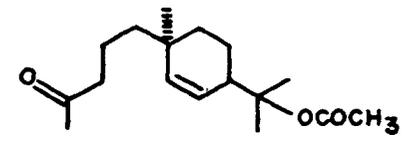


Fig. 21 Mass spectrum of (68)

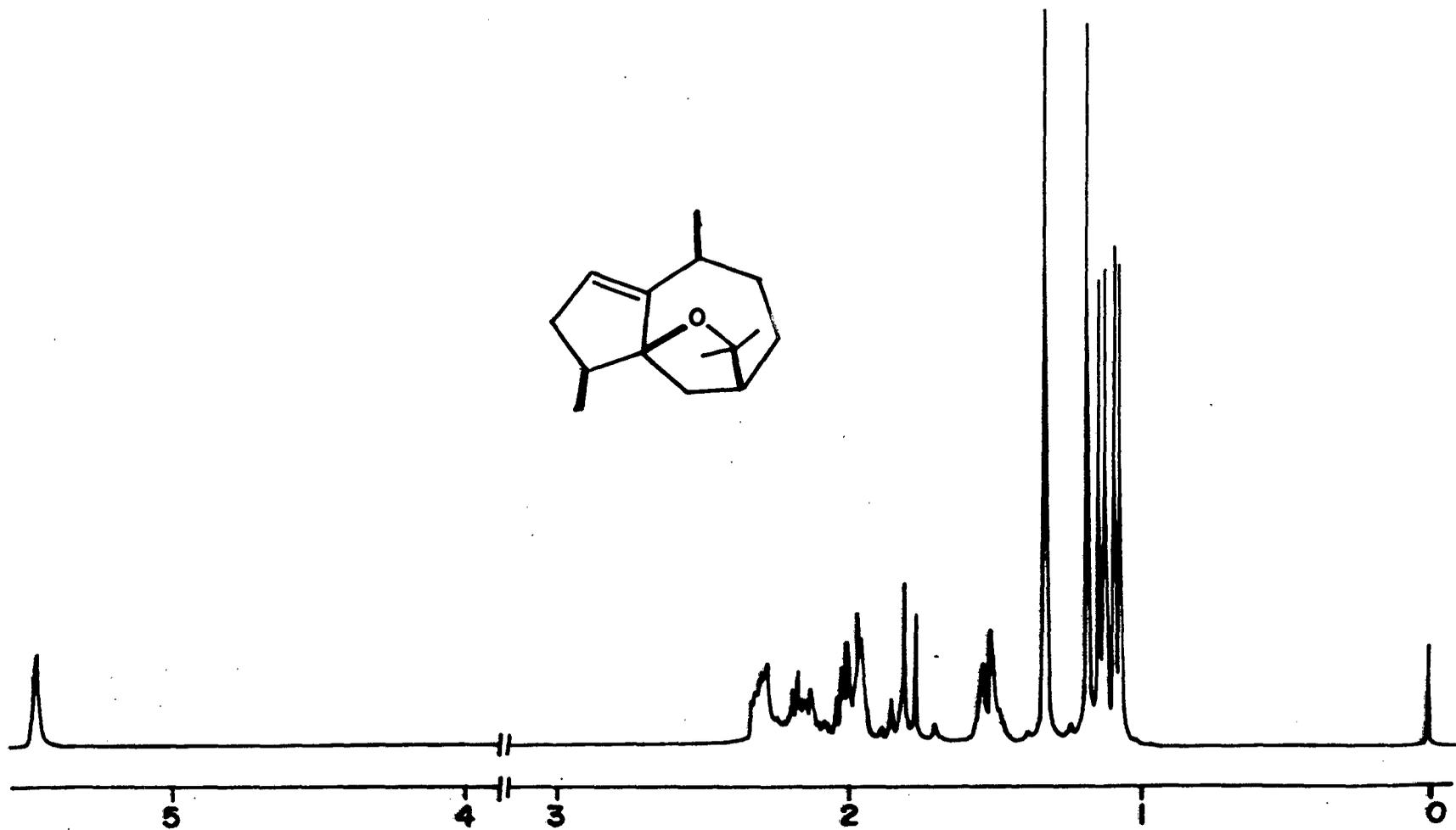
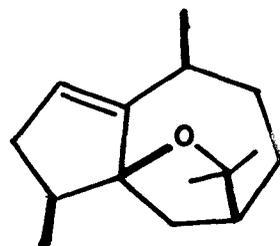


Fig. 22 NMR spectrum of (77)

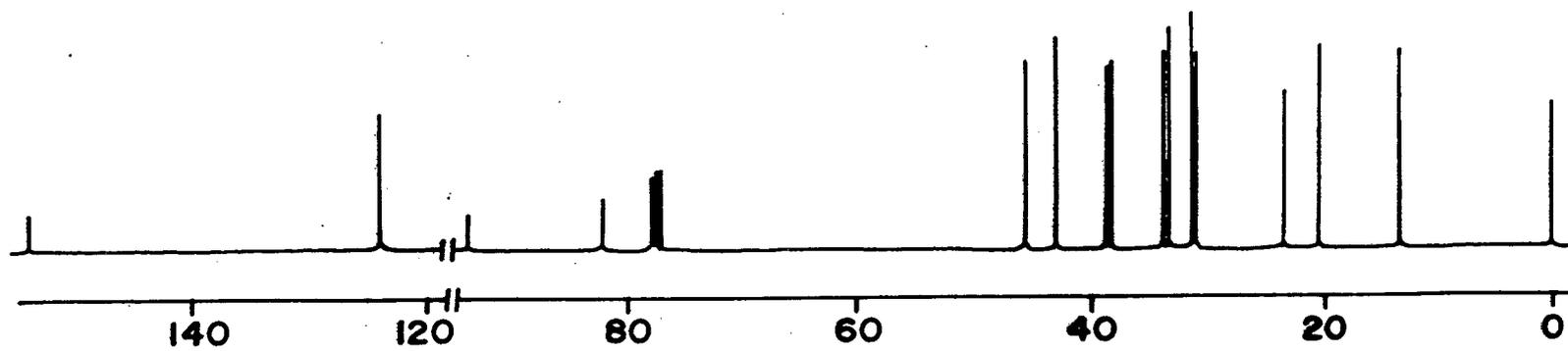
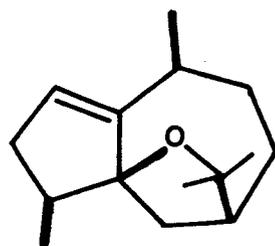


Fig. 23 ^{13}C NMR spectrum of (77)

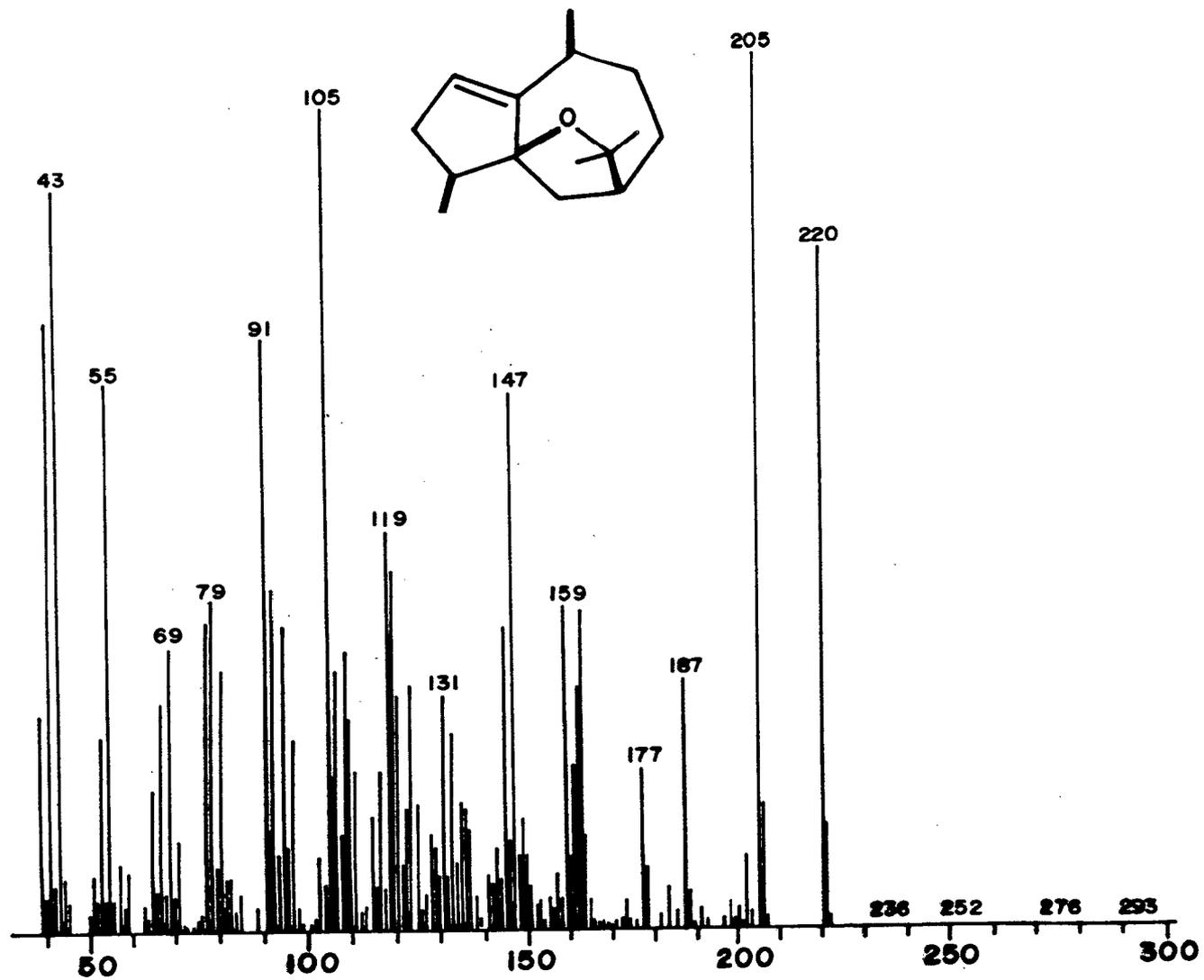


Fig. 24 Mass spectrum of (77)

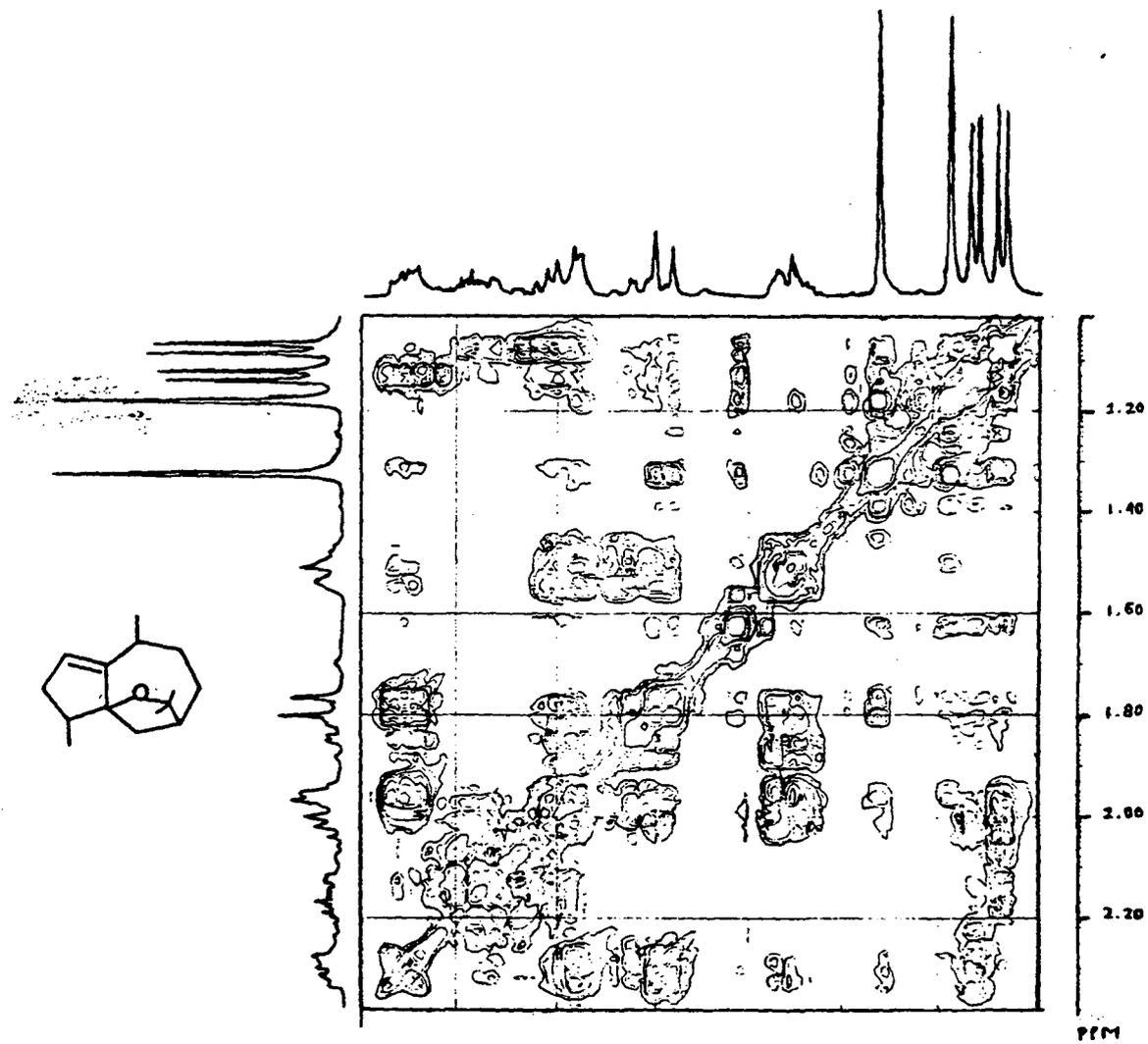


Fig. 25 Cosy spectrum of (77)

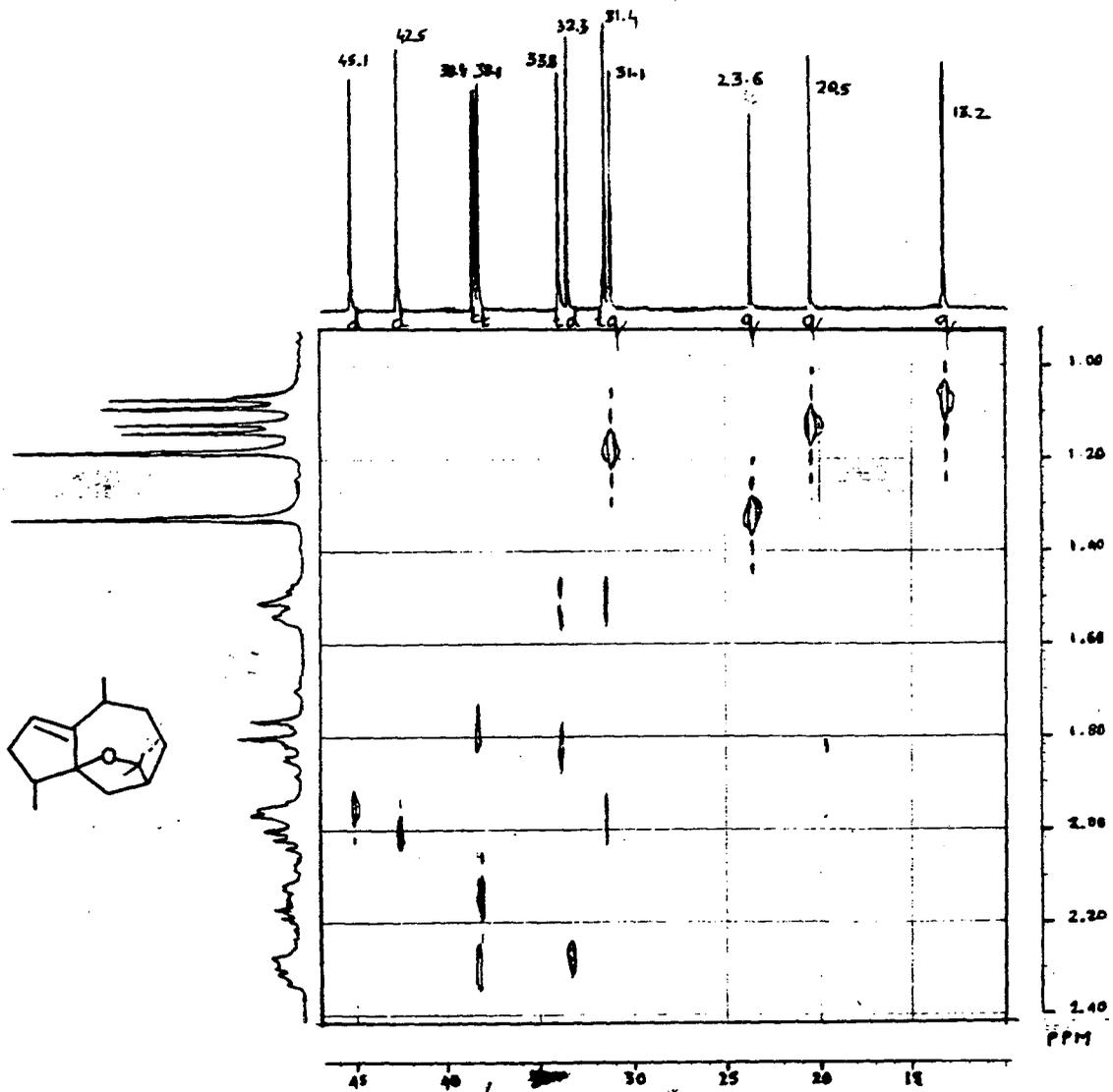


Fig. 26 HETCOR spectrum of (77)

References

1. Bates R.B. and Paknikar, S.K., *Tett. Lett.* 1453, (1965).
2. Hoerger, E.H., *Proc. Mont. Acad. Sci.*, 33, 97, (1973).
3. Paknikar, S.K. and Veeravali, J., *Ind. J. Chem.*, 18, 269, (1979).
4. Corbier, B. and Teisseire, P., *Recherches*, 19, 289, (1974).
5. Willhalm, B. and Thomas, A.F., *Tett. Lett.*, 3775, (1964).
6. Epstein, W.W., Gaudioso, L.A. and Brewster, G.B., *J. Org. Chem.*, 49, 2748, (1984).
7. Sucrow, W., *Agnew. Chem. Int. Ed.*, 7, 629, (1968).
8. Thomas, A.F., *Chimia*, 24, 452, (1970) and unpublished work.
9. Moiseenkov, A.M., Czeskis, B.A. and Semenovskiy, A.V., *J. Chem. Soc. Chem. Comm.*, 109, (1982).
10. Takano, S., Tanaka, M., Seo, K., Hirama, M. and Ogasawara, K., *J. Org. Chem.*, 50, 931, (1985).

11. Naik, U.S., Ph.D. Thesis, University of Bombay, (1987).
12. Mitra, R.B., Joshi, B.N., Khanra, A.S. and Saxena, A.P., Ind. J. Chem., 16, 842, (1978).
13. Sheldon, R.A. and Kochi, J.K., Org. Reactions, 19, 279, (1972).
14. Traynelis, V.J., Hergenrother, W.L., Hanson, H.T. and Valicenti, J.A., J. Org. Chem., 29, 123, (1964).
15. Sasaki, T., Eguchi, S., Ohno, M. and Oyobe, T., Bull. Chem. Soc. Jpn., 42, 3582, (1969).
16. Naik, R.H. and Kulkarni, G.H., Ind. J. Chem., 22B, 859, (1983).
17. Moriarty, R.M., Walsh, H.G. and Gopal, H., Tett. Lett., 36, 4363, (1966).
18. Crombie, L., Crossley, J. and Mitchard, D.A., J. Chem. Soc., 4957, (1963).
19. Shinde, D.D., Ph.D. Thesis, University of Poona, (1986).
20. Stoll, A., Seebach, E. and Stauffacher, D., Helv. Chim. Acta., 40, 1205, (1957).

21. Buchi, G., Schach, M., Wittenau, V. and White, D.M., J. Amer. Chem. Soc., 81, 1968, (1959).
22. Thomas. A.F. and Ozainne, M., Helv. Chem. Acta., 62, 361, (1979).
23. Schultz, A.G. and Schlessinger, R.H., Tett. Lett., 32, 2731, (1970).
24. Foote, C.S. and Lin, J.W.P., Tett. Lett., 29, 3267, (1968).
25. Sampath, V., Ph.D. Thesis, I.I.T. Bombay, (1970).
- 26a. Partch, R. and Monthony, J., Tett. Lett., 45, 4427, (1967).
- 26b. Fieser, L.F. and Fieser, M., Reagents for Organic Synthesis., Wiley. New York., (1967), pp. 537-563.
- 26c. Crigee, R. in Wiberg, K., ed. Oxidation in Organic Chemistry. Part A. Academic Press, New York. (1965), pp 277.
- 26d. Heusler, K. and Kolvoda, J., Agnew. Chem. Intern. Ed. Engl. 3, 525, (1964).
- 26e. L' Homme, J. and Ourisson, G., Tetrahedron, 24, 3177, (1968).

26f. Partch, R.E., J. Org. Chem., 30, 2498,
(1965).

27. Ourisson, G. and Ehret, E., Bull. Chim. Soc.
Fr., 2629, (1968).

Introduction

The manner in which natural substances are produced in nature differs greatly, at first sight, from synthetic procedures used in the laboratory. Yet organic chemists have traditionally accepted biosynthesis as part of the study on natural products. The main reason for this is that reactions occurring in the living cells should be able to be rationalised in terms of the same principles used to govern reactions in the laboratory.

The methods by which biosynthetic processes are studied can be broadly divided into four categories. First, circumstantial evidence for biosynthetic pathways can be obtained by considering the structural relationships between natural products. In recent years, very complete analyses have been made of the metabolites produced by the individual organisms and such sequences can provide very powerful evidence for postulated biosynthetic pathways. In the same way, common structural features in a series of compounds can

• suggest possible common precursors.

Secondly, reactions in vitro which leads to compounds or structural features which also occur among natural products often suggest the operation of the same type of reaction on similiar precursors in vivo. However, it is extremely doubtful if any cellular reaction, no matter how facile it may seem in the laboratory, takes place completely independent of enzyme control.

The third and more recent method which provides direct evidence involves the use of radioactive tracers. The incorporation of activity from a suitably labelled precursor provides direct evidence for the utilisation of the precursor in the biosynthesis of a metabolite.

The fourth approach also called the 'biological' method, embraces a wide variety of experimental techniques ranging from the investigation of the properties of isolated enzyme systems to the use of microbial mutants which have genetic deficiencies resulting in the deletion or inactivation of enzymes responsible for specefic

steps in a biosynthetic sequence.

The first two approaches, however, can at best provide only circumstantial evidence for biosynthetic pathways. Their great value lies in the understanding they bring to biosynthetic reactions from investigations of similar reactions in the laboratory and in the stimulus they provide for experimentation that can lead to direct proof.

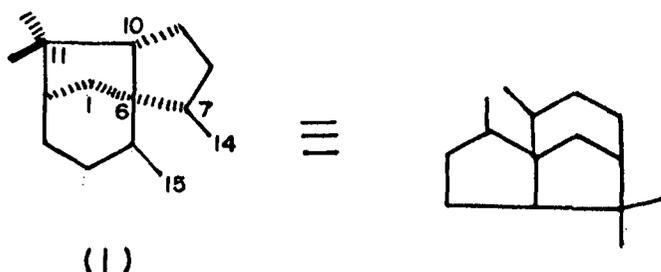
The biosynthesis and structure elucidation or revision of various natural products, based on biosynthetic interrelationships is discussed in this chapter.

CHAPTER - III

SECTION - I

AN ATTEMPTED ENTRY INTO THE TRIXANE CARBON SKELETON

Sesquiterpenes based on the unusual carbon skeleton (1) have been isolated from many sources in nature eg. from several Trixis species¹⁻⁵.

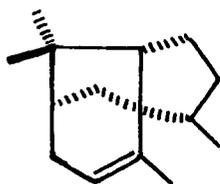


Bohlmann and co-workers had earlier named this skeleton as iso-cedrane. However this is inappropriate⁶, since the term iso-cedrane has been used for the C-3 epimer of cedrane.

It was considered interesting to devise a synthesis of this hydrocarbon or a derivative on biogenetic lines which would illuminate the probable biogenesis of the trixane skeleton.

Thomas and Ozainne⁷ had earlier obtained an unsaturated hydrocarbon of the trixane skeleton (2) during their study of the reaction of patchoulool (3) with lead tetraacetate. This compound (2) was named as 2-exo-6,6,10-tetra methyl tricyclo

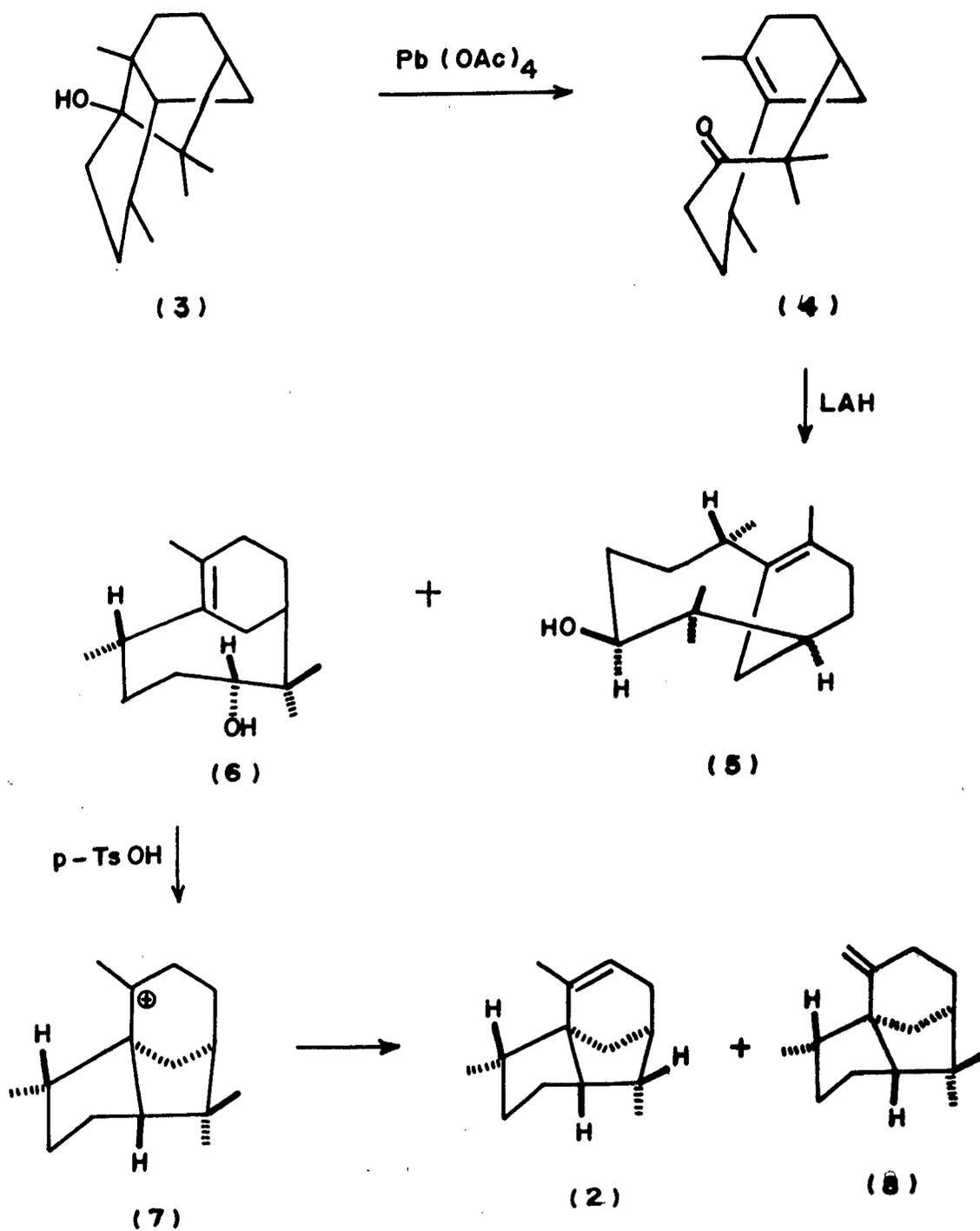
[5,3,1,0^{1,5}]undec-9-ene by the above authors who make no comment on its relation with either "isocedrene" or trixene. (Scheme - 1)



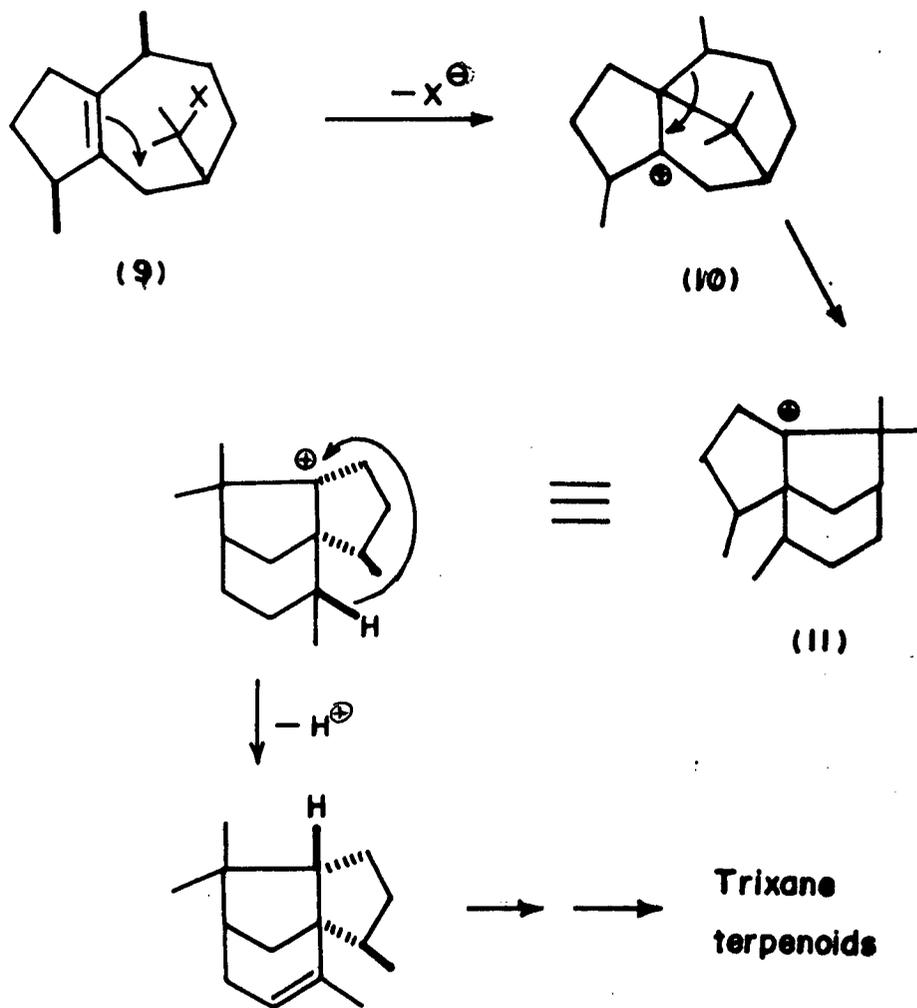
(2)

Patchoulol (3) on treatment with lead tetraacetate gave a ketone (4) which was characterized as 2,2,6-exo,8-tetra methyl bicyclo [5,3,1] undec-7-ene-3-one. This on reaction with LiAlH_4 gave a mixture of isomeric alcohols (5 & 6). Very brief treatment of alcohol (6) with p-toluene sulphonic acid or passage of (6) or its acetate through a GC. apparatus leads to the formation of two hydrocarbons (2 & 8).

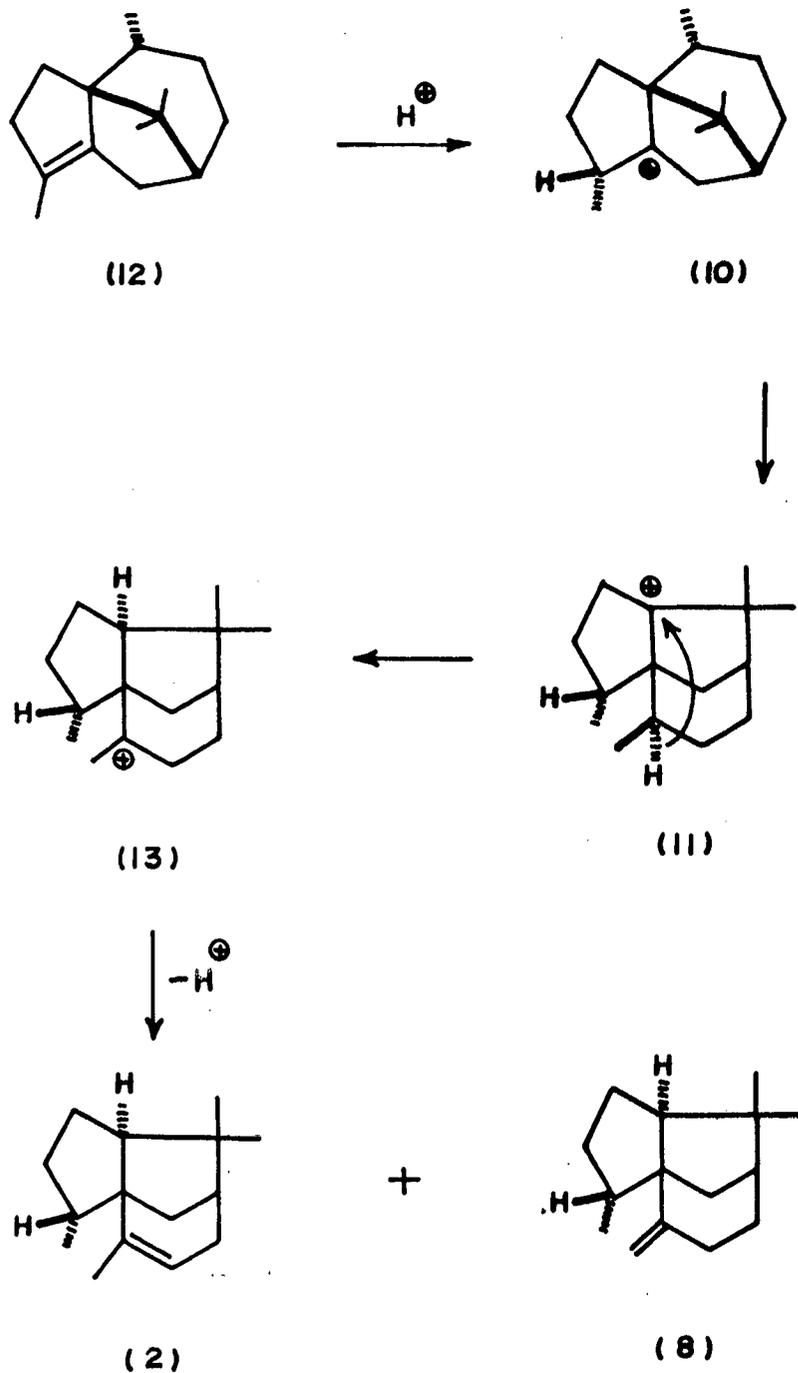
Herz et al⁶ have commented that the trixane system may originate from a guaiane precursor (9).



Scheme - 1

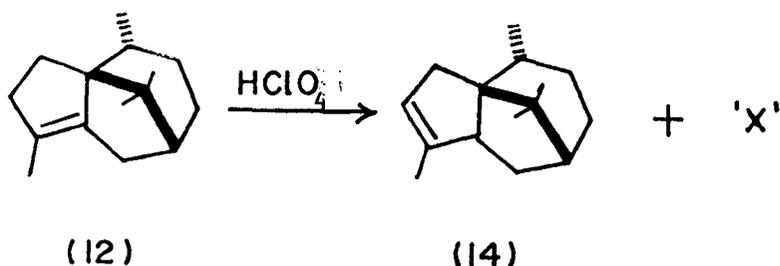


Scheme -2



Scheme-3

gave iso-cyperene (14) and another unidentified product 'X'.



It was therefore imperative to repeat the above reaction to know the nature of the unidentified product since it may be trixane derivative appearing according to the reaction outlined in Scheme - 3.

Cyperene was therefore treated with HClO_4 in aqueous dioxane. The product on purification on GLC. gave a hydrocarbon of molecular formula $\text{C}_{15}\text{H}_{24}$. The PMR. (Fig.1) of this compound was encouraging. However the mass spectrum of this compound was not identical to that of the hydrocarbon (2) as given by Thomas and Ozainne⁷.

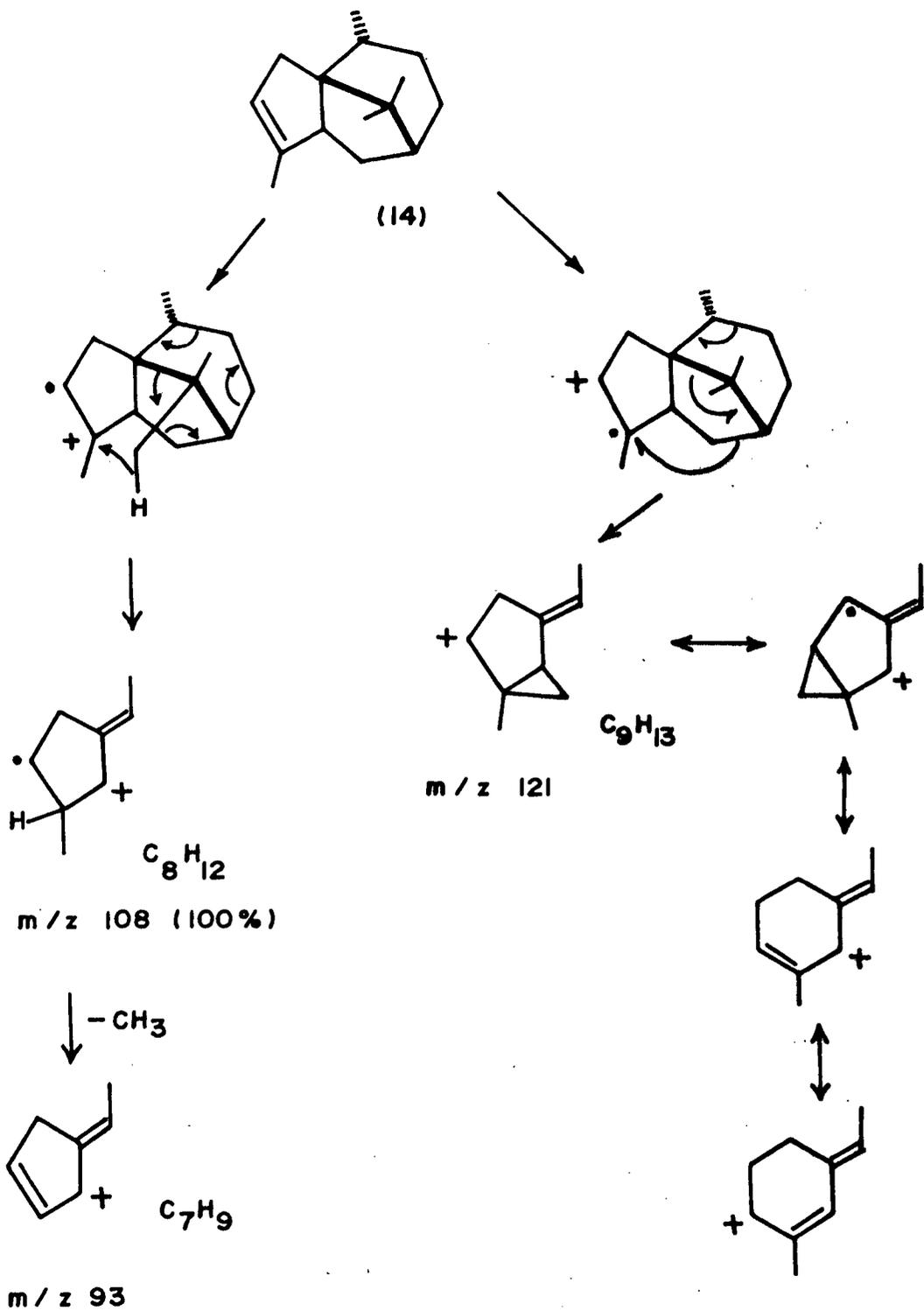
Mass spectrum of hydrocarbon (2) showed fragments of m/z 204 (M^+), 124, 123, 119, 107, 105, 93, 91, 81 and 80.

The mass spectrum of the hydrocarbon (Fig.2) obtained from cyperene by treatment with $HClO_4$ showed fragments of m/z 204(M^+), 189, 175, 162, 121, 108, 93, 79, 67, 55 and 41 which clearly indicated its nonidentity with hydrocarbon (2) or trixene if it may be so called.

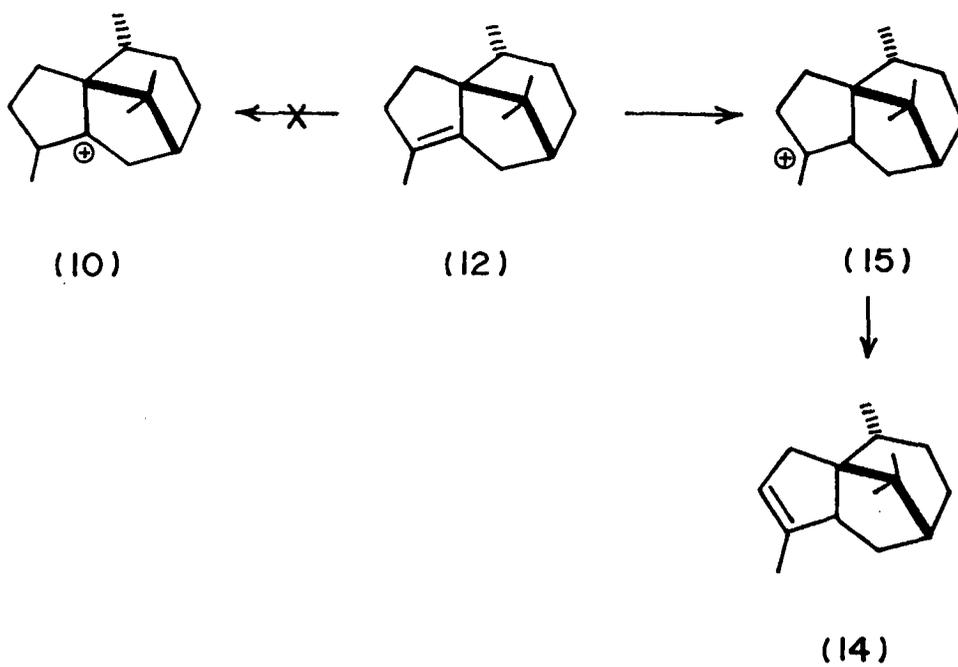
The hydrocarbon was identified as isocyperene from its mass spectrum. The origin of the various fragments is shown in Scheme - 4. The PMR. and ^{13}C MR. (Figs.1 & 3) of this compound was also completely assignable to iso-cyperene.

The failure to obtain trixene from cyperene by treatment with $HClO_4$ can be attributed to protonation occurring in only one direction in cyperene generating only (15) and not cation (10).

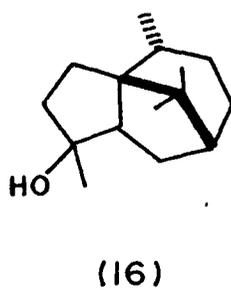
Another compound obtained from the above reaction was identified as a tertiary alcohol. Though the structure of this alcohol could not be ascertained with certainty, we tentatively propose



Scheme - 4



structure (16) resulting by trapping of the carbocation (15) by water.



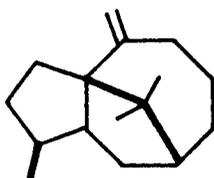
CHAPTER - III

SECTION - II

IDENTITY OF THE HYDROCARBON IN THE OIL OF THE PLANT

ACORUS CALAMUS

The oil of the plant Acorus calamus L. has yielded a number of sesquiterpenes [Chart I]⁹. One of the sesquiterpene hydrocarbons was tentatively identified as Υ -patchoulene (17)⁹ on the basis of physical constants d_4^{20} 0.9421; n_D^{20} 1.5050 and $[\alpha]_D^{20}$ +2.1° together with the IR spectra.



(17)

A cursory look at the structures of the genuine constituents of oil of A. calamus L. [Chart I], would show the absence of patchoulane based sesquiterpenes and probably warrant further rechecking of the identity of Υ -patchoulene (17).

Recently, the dehydration of patchouli alcohol (18) with DMSO was studied in our laboratory. Υ -patchoulene (17) was shown to be one of the reaction products. This gave us an opportunity to

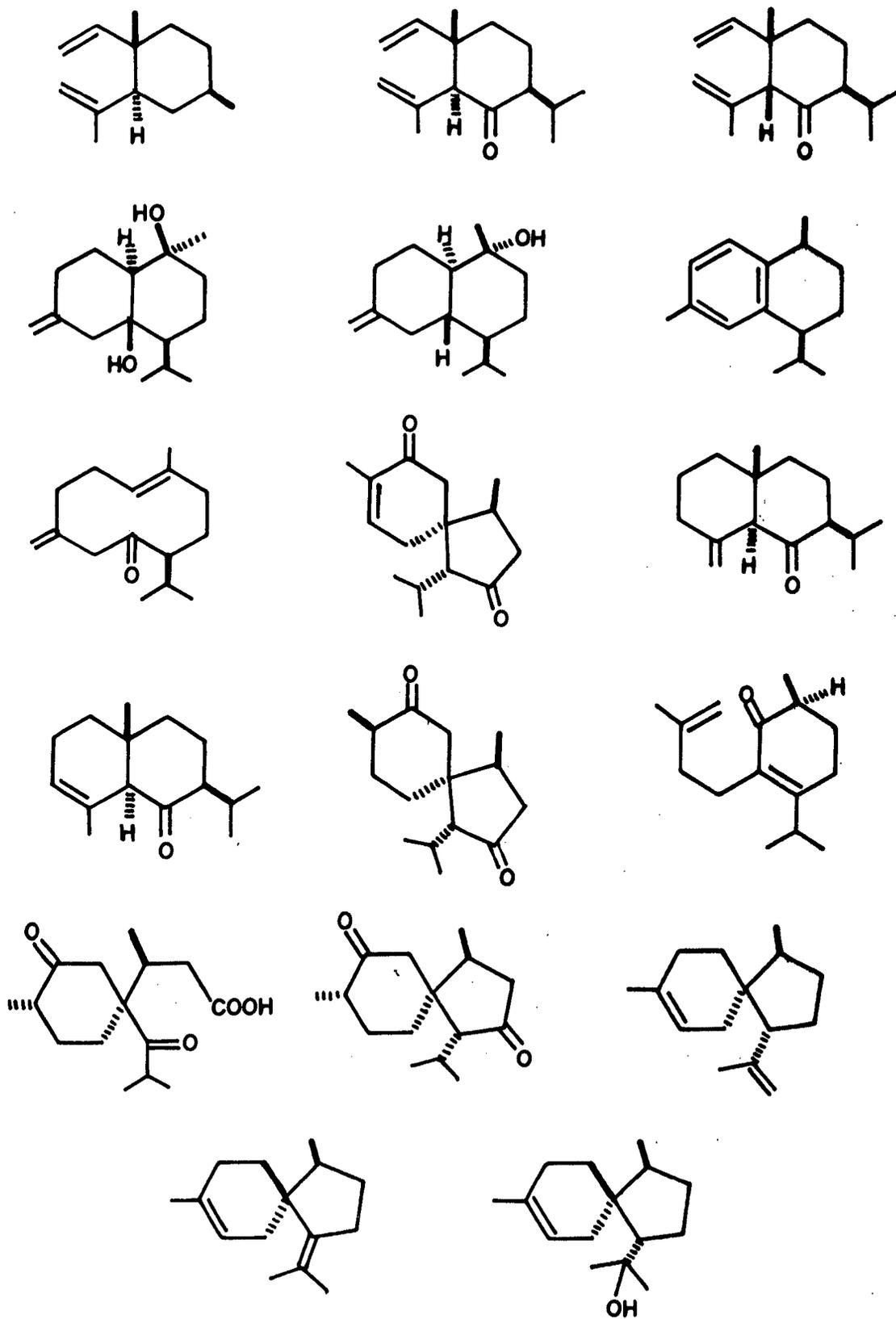
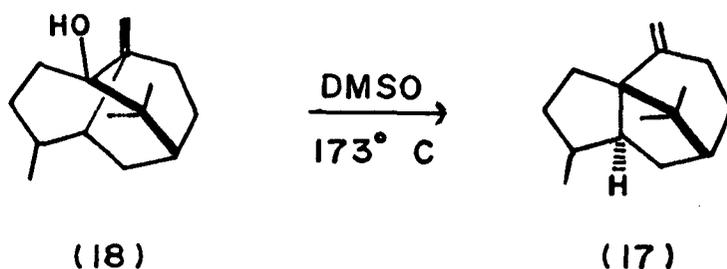


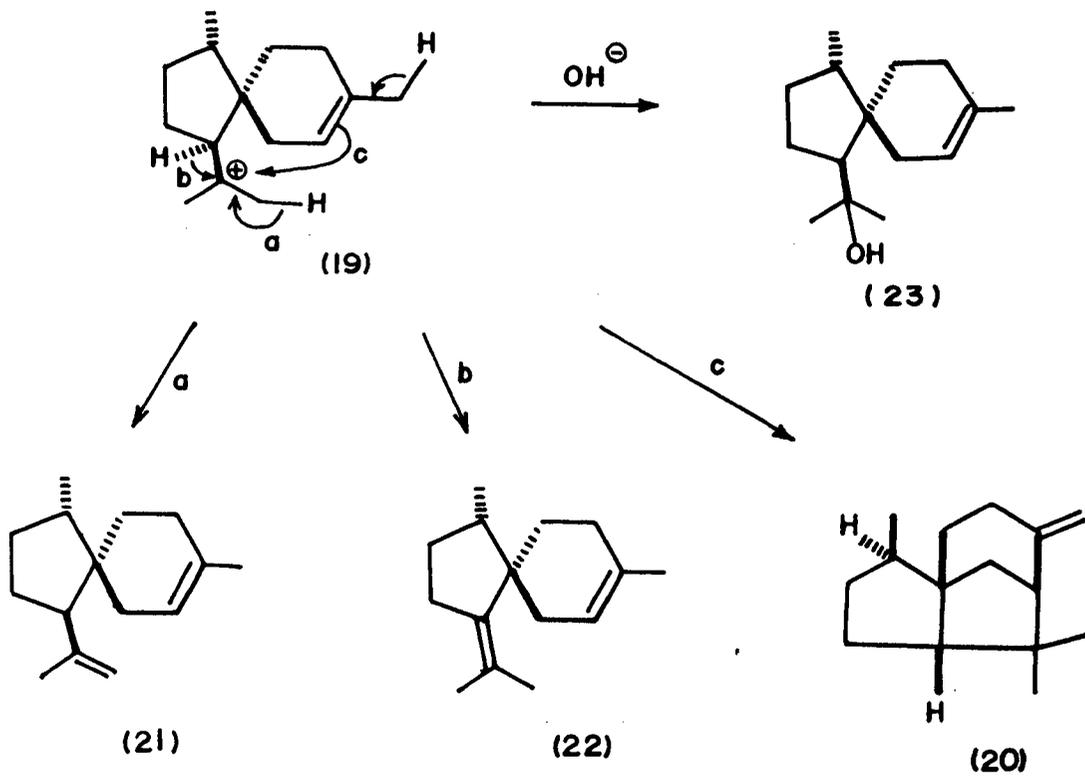
Chart - 1

compare the IR spectra of γ -patchoulene (17) and the hydrocarbon from A. calamus L. oil.



Comparison of the IR spectra of this hydrocarbon with that of the hydrocarbon from A. calamus L. (Fig. 3), however showed dissimilarities which confirmed its nonidentity with γ -patchoulene. *spectroscopy*

It was therefore considered worthwhile to delve into the structure of the hydrocarbon. Acoradienes (21 & 22) and acorenol (23) are the major constituents of A. Calamus L. oil. It is well known from biogenetic studies, that cedrenes eg. (20) and acoradienes (21 & 22) as well as acorenol



Scheme - 5

(23) can arise from a common precursor (19) (Scheme - 5).

It was therefore considered that the hydrocarbon originally designated as γ -patchoulene by Sorm et al could be β -cedrene (20).

The IR spectra of β -cedrene* (Fig. 4) was compared with that of the hydrocarbon from oil of A. calamus L. However, they were not superimposable and so the two compounds are not identical. So the question still remains as to what is the structure of the hydrocarbon from the oil of Acorus calamus L.

spectrum

* Prepared from cedrol. We thank Dr. Daldrup for a sample of β -cedrene.

CHAPTER - III

SECTION - III

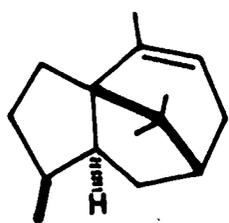
COMMENTS ON THE BIOGENESIS OF PATCHOULENES

The oil of Pogostemon cablin (patchouli oil) contains several interesting sesquiterpenes^{10,11,12} such as α -, β -, γ - and δ - patchoulenes (24,25,26 & 27), seychellene (28), patchouli alcohol (29) and the norsesquiterpene, norpatchoulol (30). [see Chart 2]

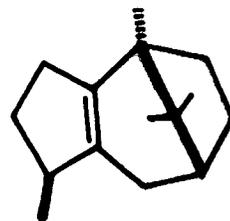
The hypothetical biogenetic pathways which appeared in the literature seem to have a common agreement that all these compounds are derived from the bonafide biogenetic precursor viz. farnesyl pyrophosphate (31) [see Chart 2] and involve intricate molecular rearrangements. The most reasonable and commonly accepted proposal is due to Wolff and Ourisson¹³ and is given in Scheme - 6.

The key feature is the involvement of the carbocation (33) derived from the bulnesyl cation (32) by cyclisation. Simple elimination of a proton from (33) then produces α - and γ - patchoulenes (24 and 26) while Wagner-Meerwein rearrangement of (33), then results in the production of other compounds.

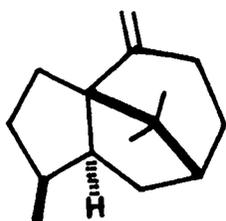
Validity of the hypothetical proposals were



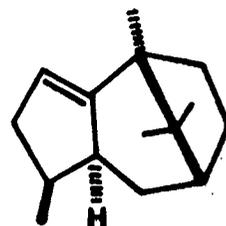
(24)



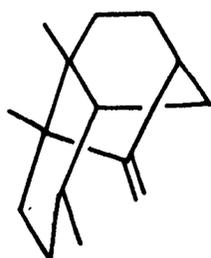
(25)



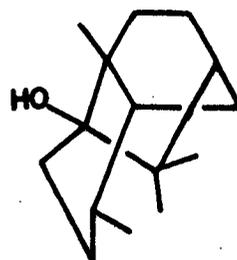
(26)



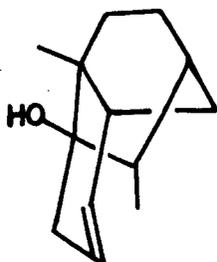
(27)



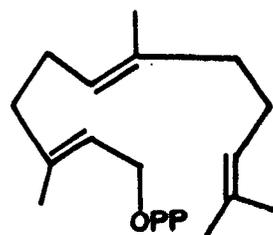
(28)



(29)

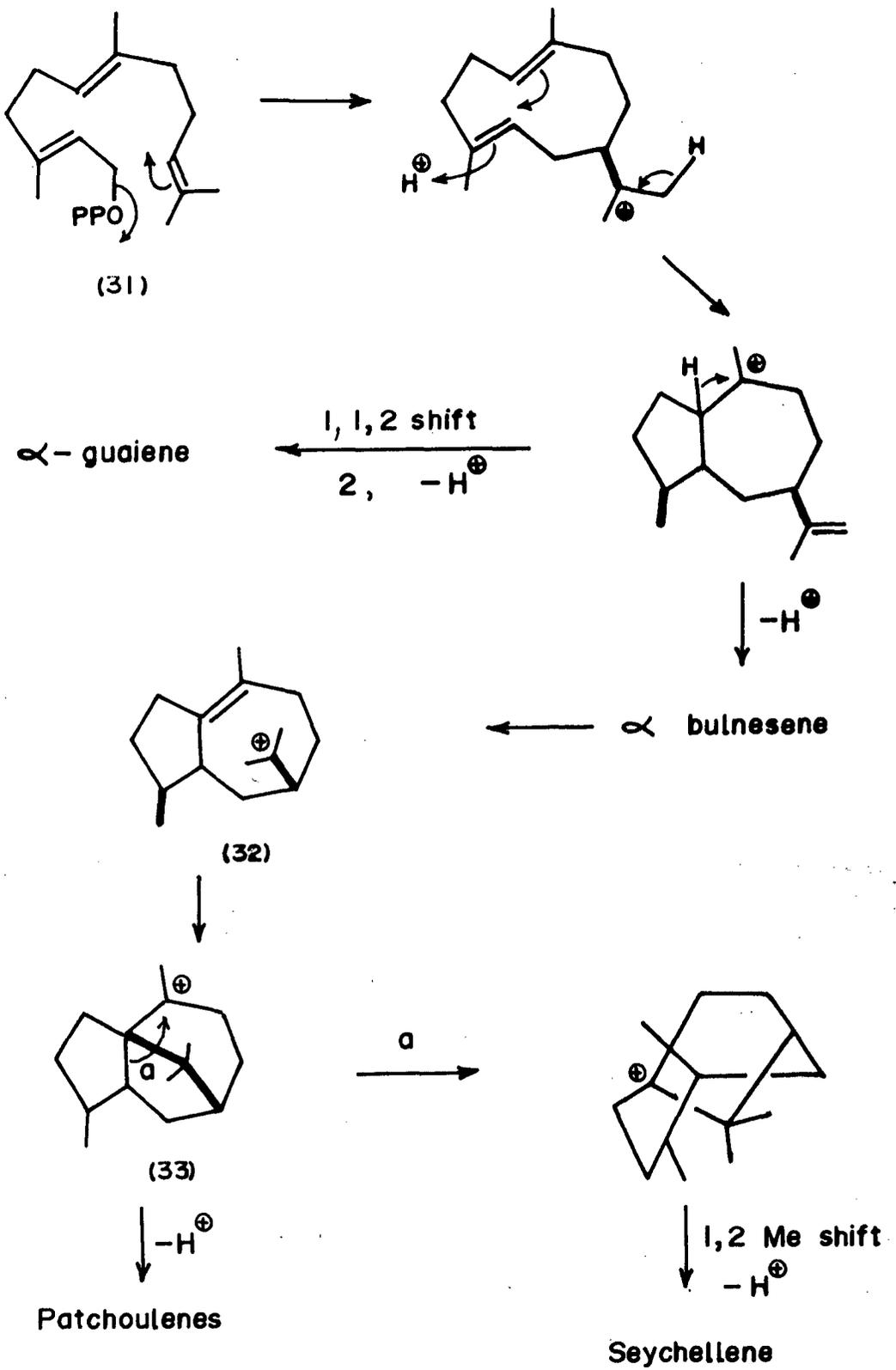


(30)



(31)

Chart - 2



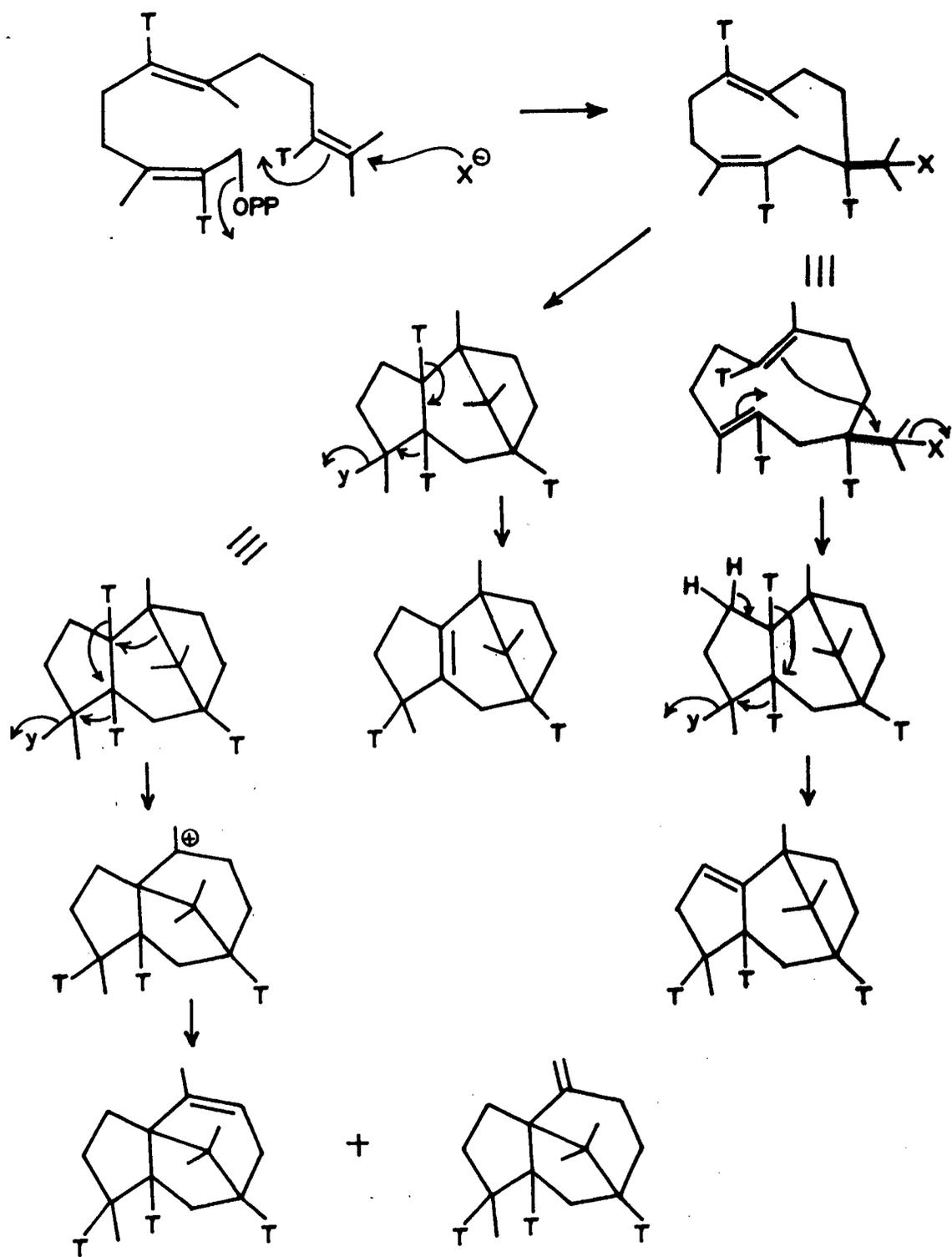
Scheme - 6

not tested experimentally except for some preliminary reports. Some experimental support to Scheme - 6 was advanced by the laboratory synthesis of patchoulenes from the bulnesyl cation (32) by Bates and Slegal¹⁴.

This problem has been studied in detail by Akhila and his colleagues¹⁵. This recent work on the biosynthesis of patchoulenes in Pogostemon cablin using labelled cis-farnesyl pyrophosphate however sheds some different light on the topic. The above authors have proposed a scheme, based on tracer studies, for the biogenesis of patchoulenes (Scheme - 7).

The earlier scheme by Wolff and Ourisson (Scheme -6) fails to account for the retention of three tritium atoms in the α -, β - and δ -patchoulenes. Hence the bulnesyl cation is definitely not the precursor of the patchoulenes. However, there is another important aspect that has to be considered and that is the stereochemical aspect.

The stereochemistry at C-4, C-5 and C-7 in α -



Scheme -7

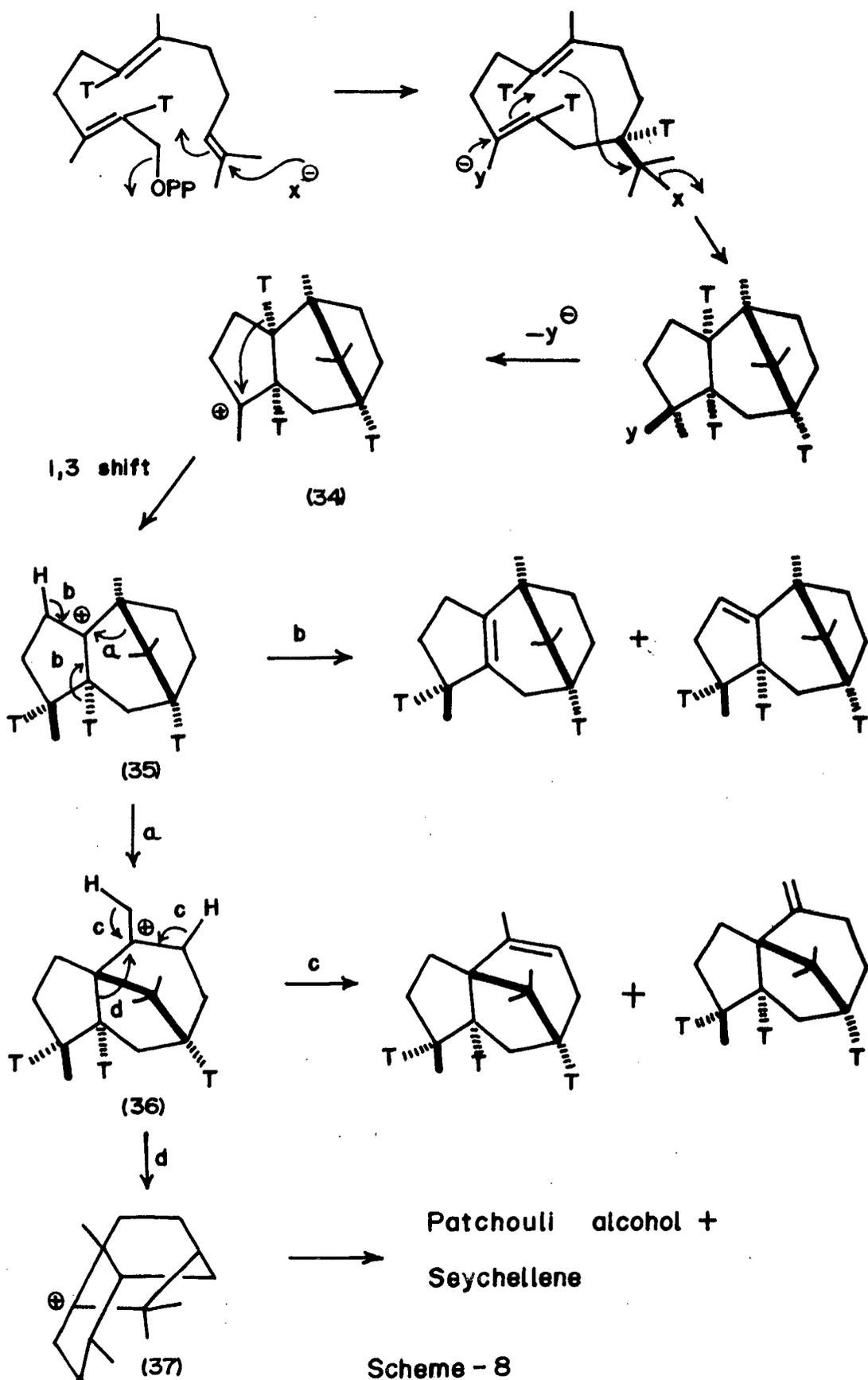
γ - and δ - patchoulenes (24, 25 and 27) has been assigned unambiguously and in this respect the 1,2 shifts (Scheme - 7) suggested by Anand et al are not acceptable if one considers the stereochemical requirements of Wagner-Meerwein rearrangements.

We envisage the biogenesis of patchoulenes as shown in Scheme - 8. Examination of the model of cation (33) showed that a 1,3 hydride shift is very likely and this would also account for the observed stereochemistry of patchoulenes.

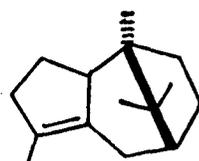
The cation (35) obtained after the 1,3 hydride shift, on elimination would be expected to give β - and ζ - patchoulenes. Further rearrangement of the cation (35) to (36) followed by elimination would furnish α - and γ - patchoulenes. Still further rearrangement to cation (37) furnishes the precursor of patchouli alcohol, seychellene and cycloseychellene.

Thus it is neither bulnesyl cation (32) nor the 10-membered germacryl cation which is the precursor of the patchoulenes.

It would be pertinent to note that the missing

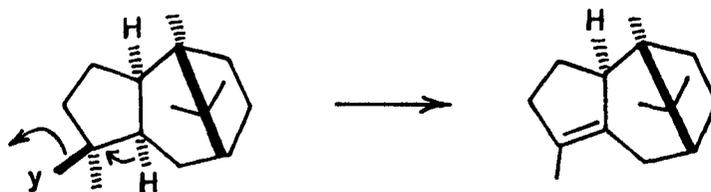


member among the patchoulenes viz. ϵ - patchoulene (38) has not so far been isolated.



(38)

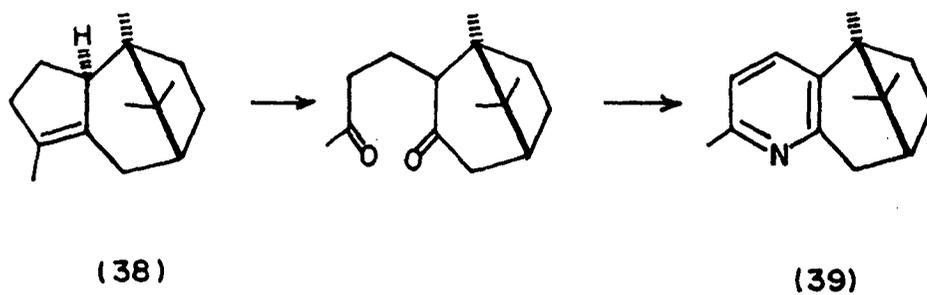
However its natural existence may be easily conjectured from the existing intermediates as follows.



(38)

There is however indirect evidence for the anticipated natural occurrence of the compound (38)

as patchouli pyridine (39), a component of patchouli oil could arise from a 3,4 - bond cleavage of (38) leading to a 1,5 - diketone which could then furnish (39) by a reaction similar to the Hantzche pyridine synthesis.



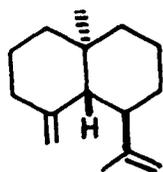
CHAPTER - III

SECTION - IV

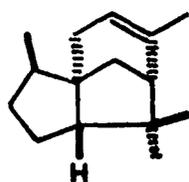
REVISION OF THE STRUCTURE OF TANAPHILLIN

The modified terpenoids are of special importance in view of their biosynthetic modifications from the normal precursors and also due to their novel carbon skeletons. One of the well known example is that of seco-loganin from the monoterpene group. The incorporation of geranyl pyrophosphate in the carbon skeleton of reserpine and other structurally related indole alkaloids is now unequivocally demonstrated¹⁶. The biosynthetic origin of the santolenyl and artemesyl skeletons from chrysanthemyl pyrophosphate has also been established beyond doubt¹⁷.

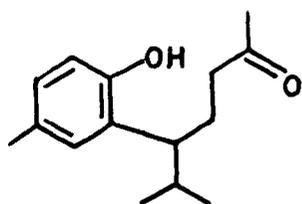
The last twenty five years have witnessed an advancement of detailed hypothetical biogenetic proposals for a large number of modified terpenoids. Some of these biogenetic proposals have been substantiated by simple and straight forward biogenetic type syntheses of β -gorgonene (40)¹⁸, α -funebrene (41)¹⁹, sesquichamaenol (42)²⁰, himasecolone (43)²⁰ and (\pm) 3,10 - dihydroxydielmentha -5,11-diene-4,9-dione (44)²¹
[Chart-3].



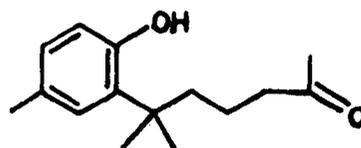
(40)



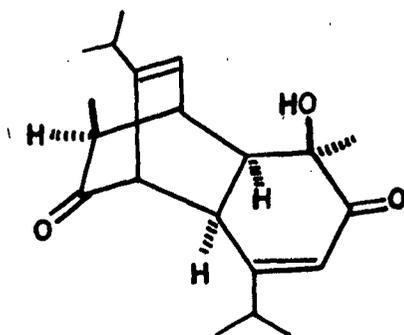
(41)



(42)



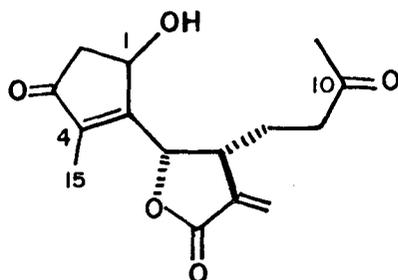
(43)



(44)

Chart - 3

In view of our continued interest, the carbon skeletons of certain seco-sesquiterpenoids attracted our attention (Chart-4). In this section, we propose to comment on the structure of the 1,10-seco-guánolide, tanaphillin (45) and discuss its biogenesis.



(45)

Tanaphillin (45) was isolated from the plant Tanacetum macrophyllum L. fam. Asteraceae. by Todorova and Ognyanov²². Earlier there was no report about the chemical composition of the plant and the authors report that compound (45) is one the first known 1,10-seco-guánolides.

Before proceeding to the biogenesis of the above compound, we would like to comment on the structure which was assigned on the basis of

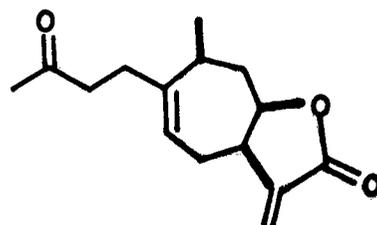
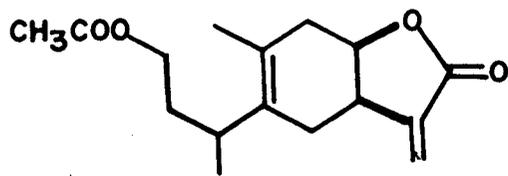
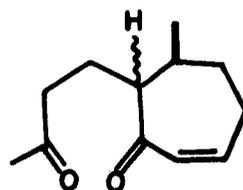
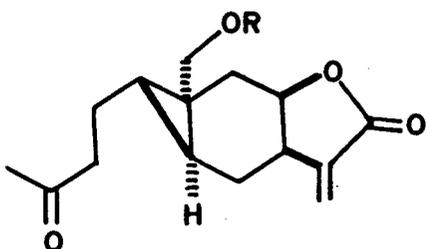
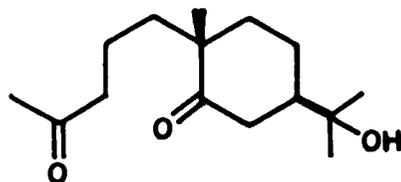
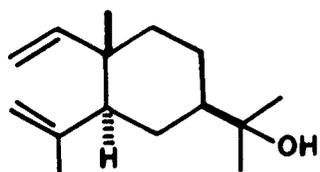
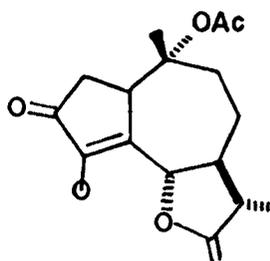
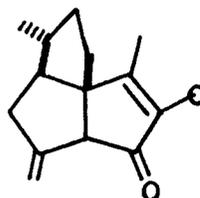


Chart - 4

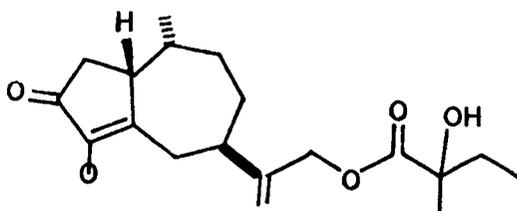
spectral data. The PMR shift of the C-15 methyl protons was reported as 2.20. We have compared the chemical shift values of a similiarly placed methyl group i.e. 'alpha' to a carbonyl and on a double bond. These values are all in the region 1.7 - 1.9. (see Table 1 below).



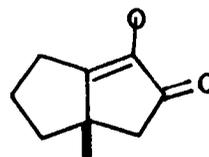
$$\delta \text{CH}_3 = 1.86$$



$$\delta \text{CH}_3 = 1.7$$



$$\delta \text{CH}_3 = 1.7$$

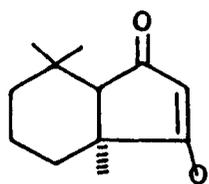


$$\delta \text{CH}_3 = 1.77$$

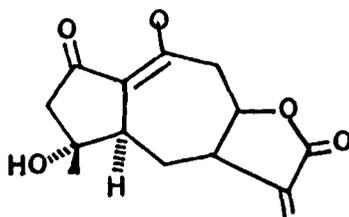
Chemical shifts refer to encircled methyls

Table - 1

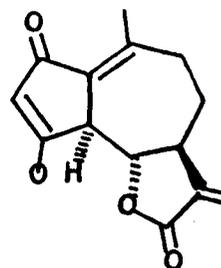
On the other hand, compounds in which the methyl is placed on a double bond but 'beta' to a carbonyl have chemical shifts much downfield in the region 2.0 - 2.5. (see Table 2 below).



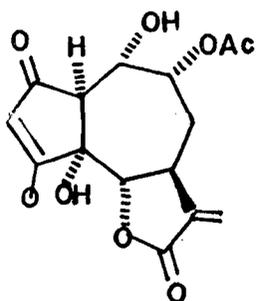
$$\delta \text{CH}_3 = 1.99$$



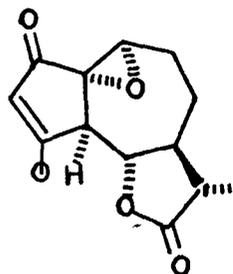
$$\delta \text{CH}_3 = 2.24$$



$$\delta \text{CH}_3 = 2.34$$



$$\delta \text{CH}_3 = 2.32$$



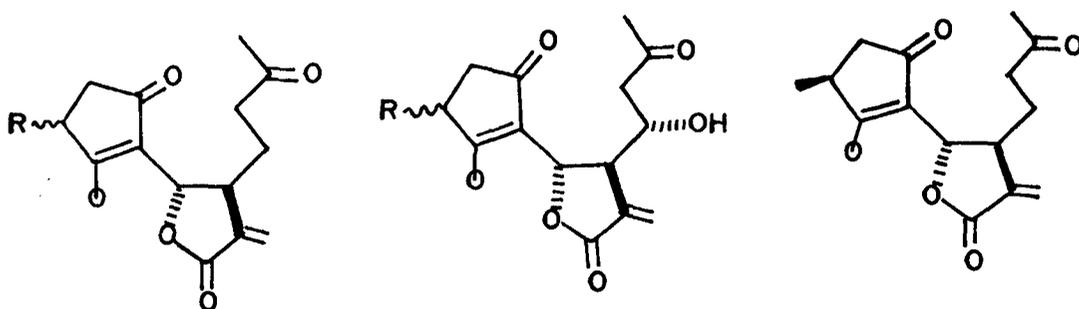
$$\delta \text{CH}_3 = 2.43$$

Chemical shifts refer to encircled methyls

Table - 2

Taking note of the value given Todorova and Ognyanov²² for the C-15 methyl group i.e. 2.2, it is more likely that it is situated 'beta' to a carbonyl and on a double bond.

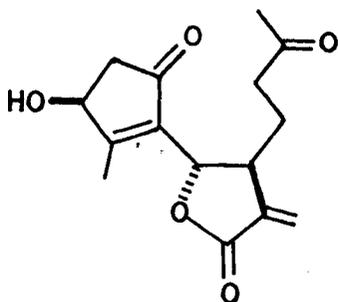
Further comparison with the chemical shift of C-15 methyl group of 1,10-seco-guanolides gave additional support to the above fact.



<u>R</u>	<u>δ CH₃</u>	<u>R</u>	<u>δ CH₃</u>	δ CH ₃ = 2.14
β - OMe	2.15	H	2.16	
α - OMe	2.13	α - OH	2.18	
β - OAc	2.12	β - OH	2.18	
α - OAc	2.13			

Chemical shifts refer to encircled methyls

In view of the above, we would like to propose a revised structure for tanaphillin (45) and this structure is actually identical to the C-3 epimers of iso-secotanaparholide (46) (i.e. 3 α -hydroxy and 3 β -hydroxy). These compounds was isolated by Bohlmann et al ²³ from Artemesia species fam. Compositae. It may be noted that the two families Asteraceae and Compositae are identical.



(46)

The PMR spectra of tanaphillin (45) and 3- β -hydroxy-iso-secotanaparholide show remarkable similarity and are reproduced below which almost conclusively prove their identity.

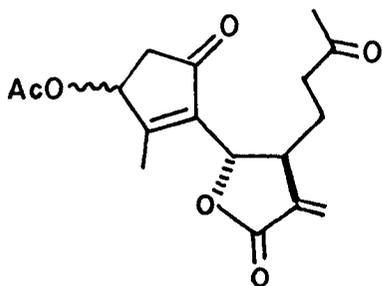
H	Tanaphillin	(46)
2a	2.33 d	2.31 dd
2b	2.78 dd	2.82 dd
3	4.70 bs	4.72 brd
6	4.94 d	4.97 d
7	3.12 m	3.09 dddt
8	1.90 m	1.94 ddt
8		1.85 ddt
9	2.55 m	2.59 dt
9		2.54 dt
13	6.32 d	6.35 d
14	2.15 s	2.12 s
15	2.20 s	2.14 s

Also, Todorova and Ognyanov comment that the lactone (45) is a mixture of two diastereomers because almost all ^1H and ^{13}CMR signals are doubled with a difference of 0.02 - 0.15 ppm. They propose the names tanaphillin A for the diastereomer with C-1 α OH and B with C-1 β OH.

We would like to presume that these authors were actually handling the C-3 diastereomers and would like to name the compounds as 3 α -hydroxy-iso-secotanapartholide and 3 β -hydroxy-iso-secotanapartholide. The minor differences in the chemical shifts observed in the PMR spectra of (45) and (46) is understandable since the chemical shift

of (46) is that of the 3 β -hydroxy epimer and not of the mixture of epimers as in the case of tanaphillin.

Todorova and Ognyanov²² have acetylated (45) to the acetates (47a & b). It is interesting to note that these acetates were also earlier isolated by Bohlmann and co-workers²⁴ from Artemisia rutifolia.

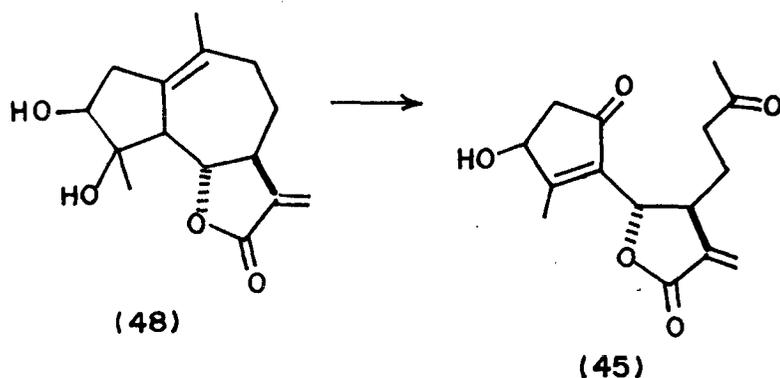


47 a - 3 α OAc
47 b - 3 β OAc

The PMR spectra of the acetates prepared by Todorova and Ognyanov and those isolated by Bohlmann et al also show close similarity thus conclusively proving the identity of (45) with (46). The PMR spectra are given below for comparison.

H	47	Compds. isolated by Bohlmann	
		A	B
2a	2.29 d	2.32 d	2.28 d
2b	2.92 dd	2.90 dd	2.90 dd
3	5.70 d	5.75 brd	5.66 brd
6	5.00 d	5.44 brd	4.95 brd
7	3.14 m	3.29 m	3.13 m
8a	1.94 m	1.96 ddt	1.96 ddt
8b		1.88 ddt	1.89 ddt
9a	2.57 m	2.46 dt	2.53 dt
9b		2.39 dt	2.63 dt
13a	5.70 d	5.64 d	5.69 d
13b	6.37 d	6.34 d	6.37 d
14	2.18 s	2.13 s	2.16 s
15	2.14 s	2.13 s	2.12 s
OAc	2.11 s	2.11 s	2.09 s

Having proved the identity of tanaphillin (45) with C-3 epimers of iso-secotanaparholide (46), we would now like to comment on its probable biogenesis. The diketolactone (45) would most probably originate by an oxidative cleavage of the 1,10-double bond of a precursor of the type (48).



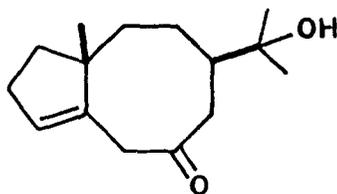
CHAPTER - III

SECTION - V

A NEW BIOGENETIC PROPOSAL FOR 11-HYDROXY JASIONONE

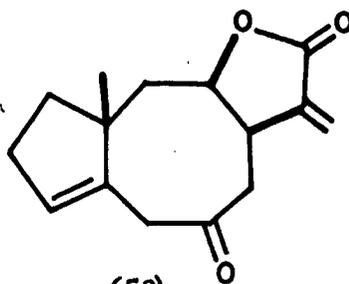
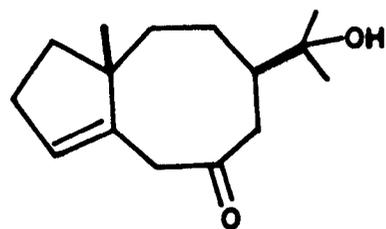
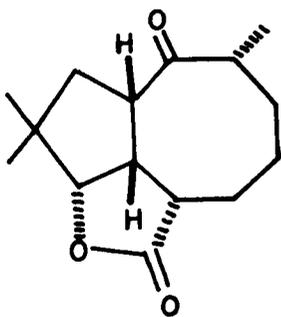
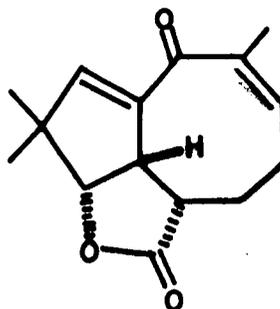
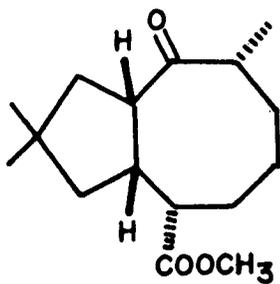
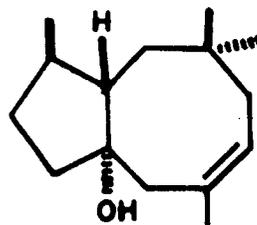
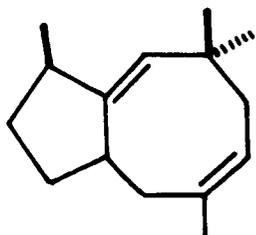
Biosynthetic reactions in terpenoids give rise to a variety of structures. Among the sesquiterpenoids alone, structures ranging from acyclic to tricyclic are found. Sesquiterpenoids possessing the bicyclo [3,6,0] undecane (the 5,8 ring fused system) are however rare. (See Chart 5 for some examples).

All these sesquiterpenoids are biogenetically derived by structural modifications of the bonafide precursor viz. farnesyl pyrophosphate. In 1988, Jakupovic et al.²⁵ reported the isolation of 11-hydroxy jasionone from Jasonia montana. They proposed structure (49) based on extensive spectral analysis.



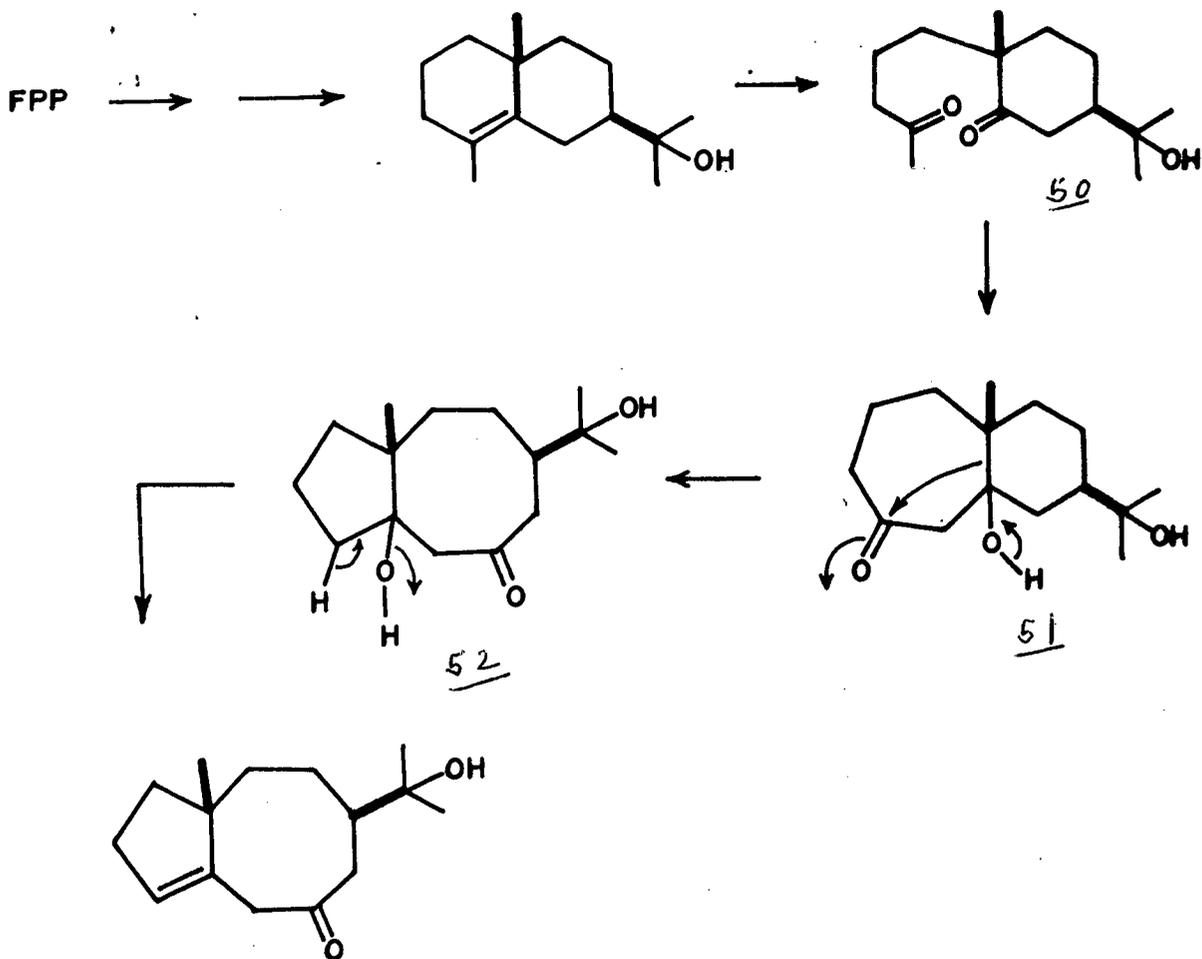
(49)

The biogenesis of this compound was suggested by the above authors to be as shown in Scheme - 9.



(59)

Chart -5



Scheme -9

This scheme has several drawbacks. Firstly, it is known that base catalysed cyclisation of 1,6-diketones eg. of (50) to (51) usually afford five membered rings rather than seven membered rings as shown. Secondly, the 1,3 - shift of the ring residue [(52) to (53)] is also a highly improbable step. //

51 - 52

It was therefore obvious that a different biogenetic proposal was needed which would be simple in principle as well have some literature support.

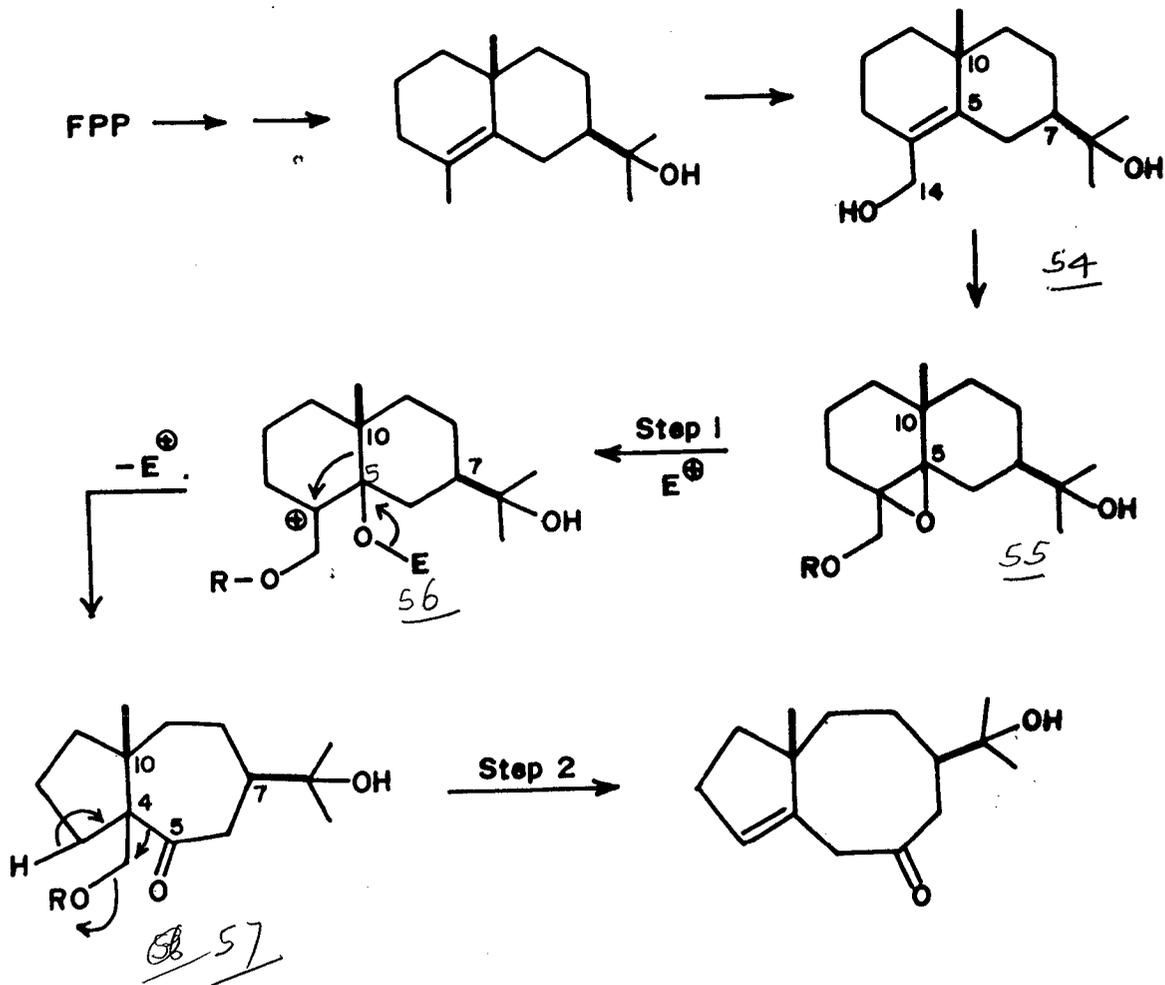
In this section, we suggest a new biogenetic proposal for 11-hydroxy jasionone. This is given in Scheme - 10.

It appears that γ -hydroxy eudesmol gets functionalised at C₁₄ to produce (54). Oxidation of the double bond linkage of (55) would give rise to the intermediate (56). Electrophilic attack of E⁺ on (56) and 1,2-shift of the C₅-C₁₀ bond with concomitant loss of the E⁺ would result in the formation of the intermediate (57). 11-hydroxyjasionone (49) would then be produced by

54

55

55

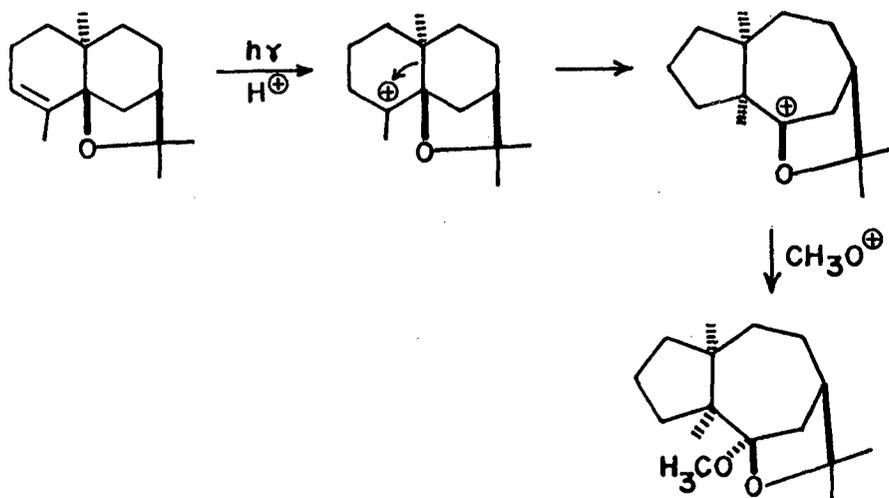


Scheme - 10

loss of a proton, the shift of the C₄-C₅ bond onto C₁₄ and loss of the functionality at that carbon.

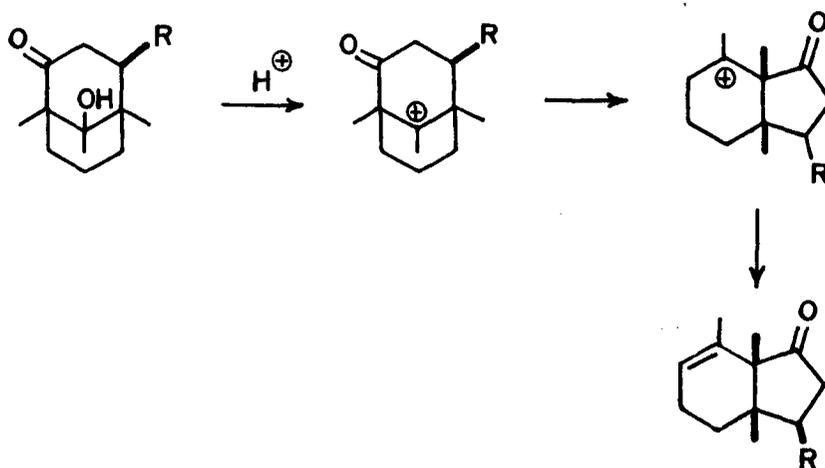
There exists a precedent in the literature where a similar contraction of ring A and expansion of ring B with the formation of a perhydroazulene derivative has been observed experimentally²⁶. See below.

We believe that the perhydroazulene intermediate (58) then gets transformed into the bicyclo [3,6,0] undecane skeleton of 11-hydroxy



jasioneone by the preferential migration of the C₄-C₅ bond followed by elimination of a proton.

Such a preferential migration of acyl bonds over alkyl and α -substituted alkyl groups have been reported before by Gambcorta and co-workers²⁷. Further support to these observations has been obtained by Vogel and co-workers²⁸.



Subsequently, another sesquiterpene having the bicyclo [3,6,0] undecane skeleton, 9-oxojasoniolide (59)^{*} has been isolated by Bohlmann et al²⁹. The biogenesis of this compound is also expected to proceed along similar lines as proposed by us for 11-hydroxy jasionone.

Thus an attractive scheme to account for the biogenesis of sesquiterpenes having the bicyclo [3,6,0] undecane skeleton has been proposed.

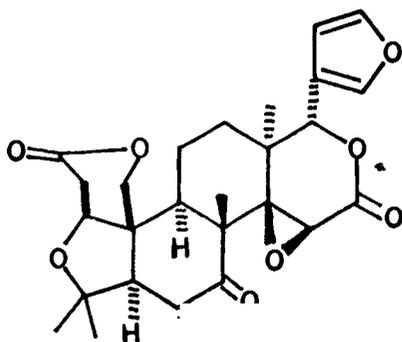
* see Chart 5

CHAPTER - III

SECTION - VI

OXIDATION PRODUCTS OF FURANS - BUTENOLIDES OR
FURANONES

Since the isolation of limonin, the first tetranortriterpene (60), a very large number of highly oxygenated tetranortriterpenoids have been isolated and fully characterized. Practically all these compounds possess a β -substituted furan or a butenolide moiety. Some of these compounds are available in substantial quantities and can be used for transformation and/or correlation purposes.

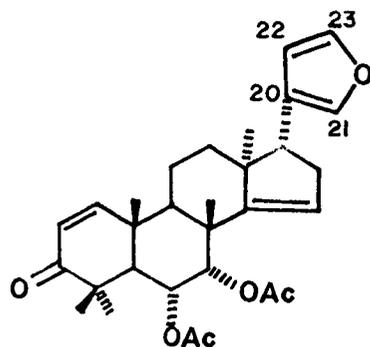


(60)

Such interconversions provide unambiguous support to the assigned structures including absolute stereochemistry, particularly when the structural assignments are based entirely on spectral analysis.

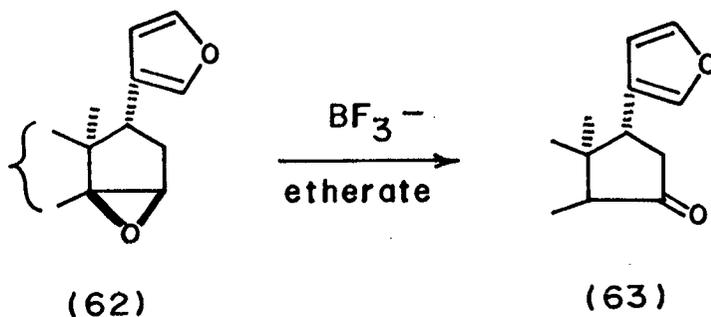
In the course of their studies on the reactions and rearrangements of

tetranortriterpenoids, Chatterjee et al³⁰ selected 6 α -acetoxy azadirone (61) as a starting material.



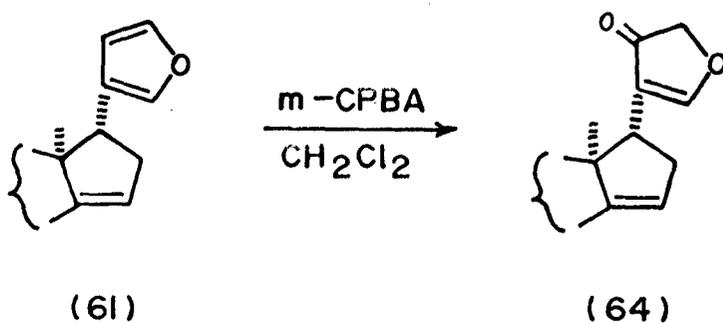
(61)

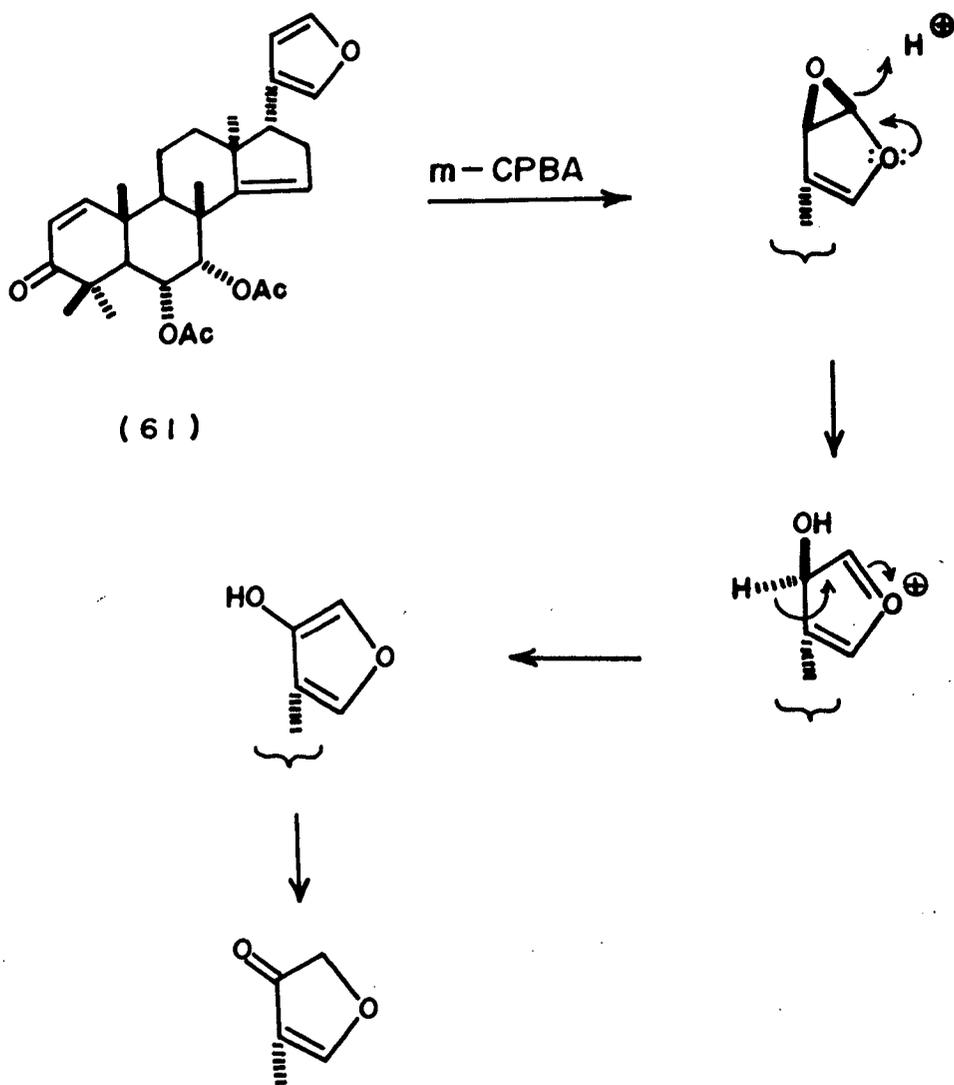
Of the several reactions reported those involving oxidation of (61) with i) m-CPBA in CH_2Cl_2 and ii) NBS in aqueous acetone in the presence of a catalytic amount of CH_3COOH attracted our attention. The above authors aimed at the



preparation of ^{14,15} epoxide (62) by the reaction of (61) with m-CPBA, and its further rearrangement with BF₃-etherate to obtain the rearranged compound (63).

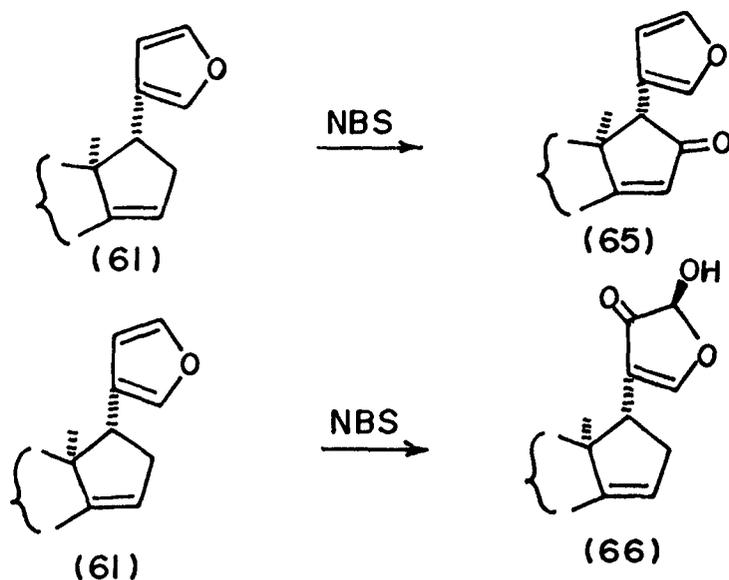
However, it was observed that ^{14,15} olefin linkage of 6 α -acetoxy azadirone remains intact on treatment with m-CPBA in CH₂Cl₂, and the oxidation product is a result of oxidation of the β -substituted furan ring. The crystalline product, C₃₀H₃₈O₇, m.p. 230^o was assigned the ketodihydrofuran (β -furanone) structure (64) on the basis of PMR data. The mechanism of formation of (64) as given by Chatterjee et al¹ is given in Scheme - 11.



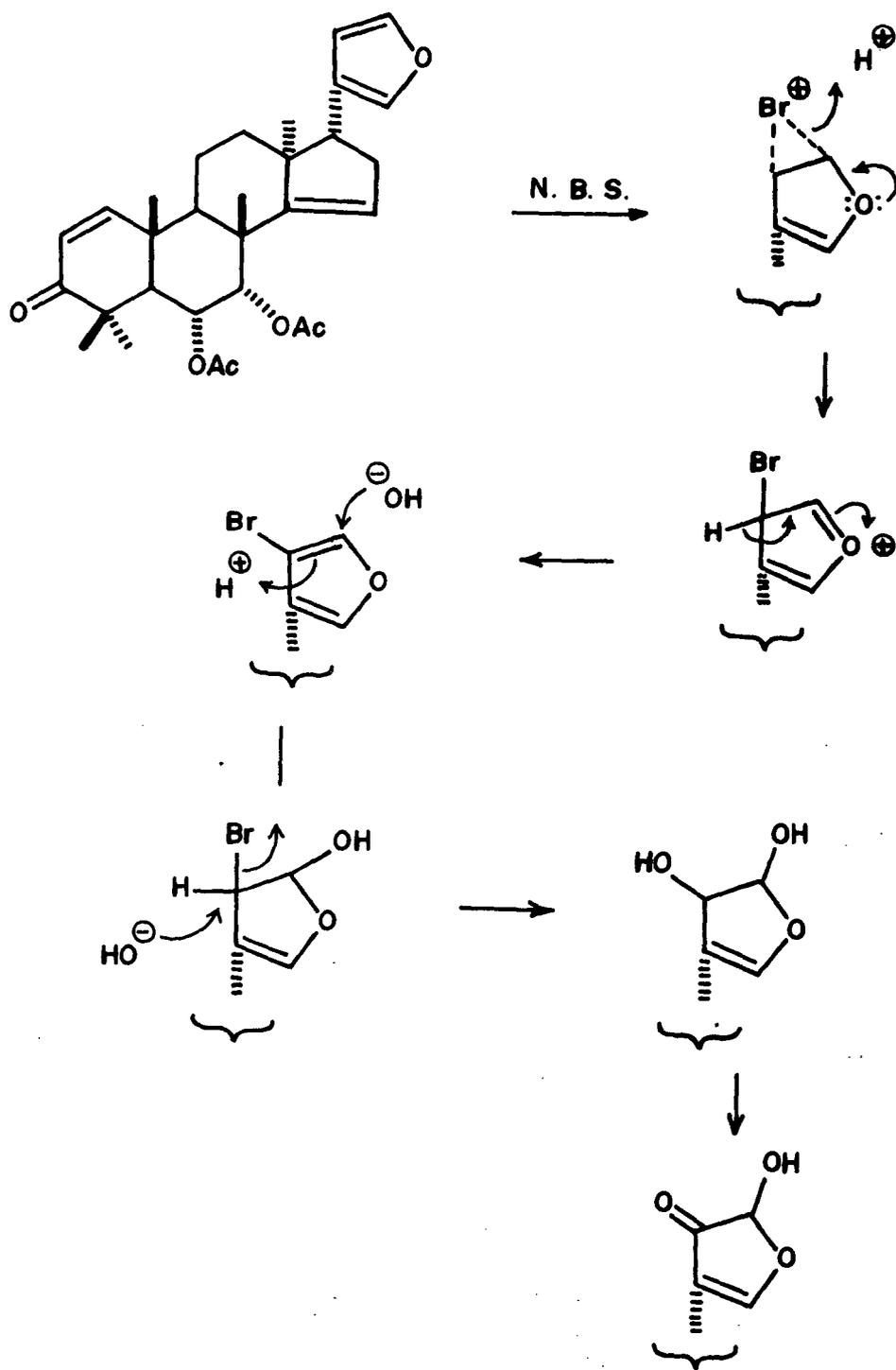


Scheme — 11

Further in an attempt to transform 6 α -acetoxy azadirone (61) into (65) a naturally occurring



compound, it was reacted with NBS in aqueous acetone. In this case also their expectation was not realized and the results showed that once again the furan ring has reacted under these experimental conditions. The product a crystalline solid, $C_{30}H_{38}O_8$, m.p. 330° , was assigned structure (66) on the basis of PMR and ^{13}C MR data. The formation of this compound is shown in Scheme - 12.



Scheme - 12

The spectral data assigned to compounds (64) and (66) are summarized below.

Compound (64)

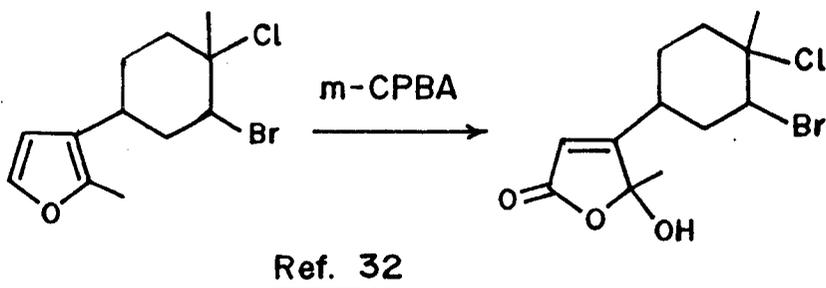
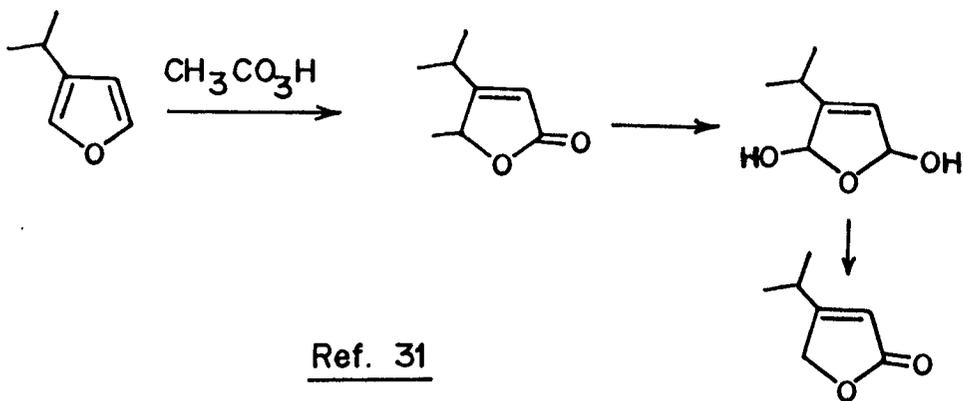
PMR, δ . 0.86(s, 3H, -CH₃), 1.18(s, 6H, 2 -CH₃), 1.26(s, 3H, -CH₃), 1.33(s, 3H, -CH₃), 2.00(s, 3H, -OCOCH₃), 2.04(s, 3H, -OCOCH₃), 4.83(br s, 2H, H-23), 5.42(m, 3H, H-6,7,15), 5.91(d, 1H, J=10 Hz, H-2), 7.12(d, 1H, J=10 Hz, H-1), 7.20(s, 1H, H-21).

Compound (66)

PMR, δ . 0.92(s, 3H, -CH₃), 1.01(s, 3H, -CH₃), 1.22(s, 3H, -CH₃), 1.31(s, 3H, -CH₃), 1.40(s, 3H, -CH₃) 2.06(s, 3H, -COCH₃), 2.12(s, 3H, -COCH₃) 2.63(d, 1H, J=12.2 Hz, H-5), 5.34(m, 1H, H-15), 5.62(dd, 1H, J=12.2, 2.5 Hz, H-6), 5.72(d, 1H, J=2.5Hz, H-7), 6.05(d, 1H, J=10 Hz, H-2), 6.18(s, 1H, H-23), 6.52(br s, 1H, H-21), 7.14(d, 1H, J=10 Hz, H-1).

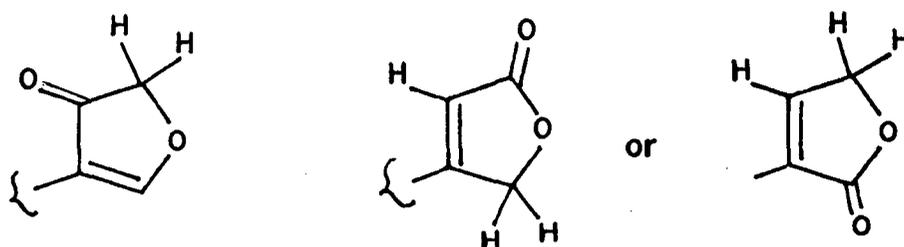
$^{13}\text{CMR}, \delta$. 157.7(d, C-1), 126.3(d, C-2), 203.8(s, C-3), 41.0(s, C-4), 48.4(d, C-5), 70.4(d, C-6), 74.7(d, C-7), 43.5(s, C-8), 37.6(d, C-9), 45.3(s, C-10), 16.6(t, C-11), 33.3(t, C-12), 47.7(s, C-13), 158.3(s, C-14), 119.6(d, C-15), 33.5(t, C-16), 54.0(d, C-17), 126.3(s, C-20), 121.1(d, C-21), 168.0(s, C-22), 100.6(d, C-23), 170.6, 170.5(s, -COCH₃), 20.9, 21.3(q, -OCOCH₃), 32.1(q, -CH₃), 26.8(q, -CH₃), 21.4(q, -CH₃), 20.9(q, -CH₃), 20.7(q, -CH₃).

First we would like to discuss the structure of the compound (64), the m-CPBA oxidation product of (61). A survey of the literature on the oxidation of β -substituted furans with peracids showed that oxidation takes place at the less hindered 5 position followed by nucleophilic attack at the 2 position. This pattern of oxidation is seen in many cases. Some representative examples are given below. The product in both cases is a butenolide and not a furanone.

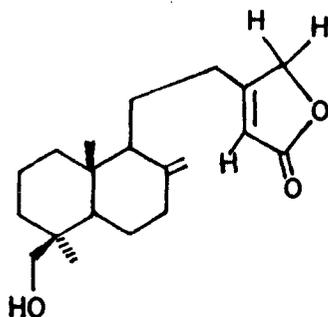


In view of the above facts, we thought it worthwhile to have a closer look at the structure of compound (64). It appears that this compound is not a furanone but a butenolide. To support our speculation, we gathered PMR data on various butenolides and we would like to show that the PMR data assigned to the compound (64) is consistent with an alternative butenolide structure.

The deciding factor between the two structures is the chemical shift of the proton on C-23 of the furanone structure and C-22 of the butenolide structure [all numbering as in structure (61)].

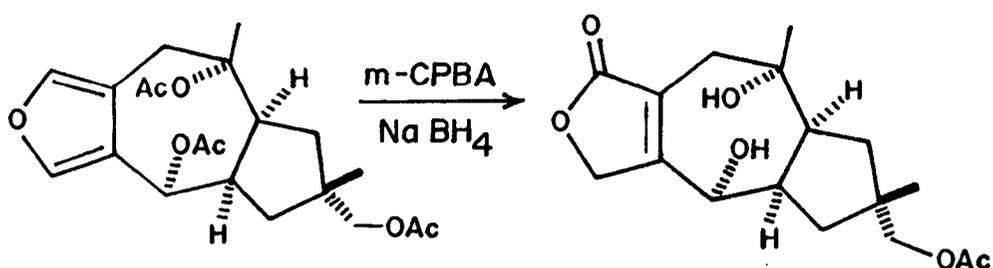


The PMR chemical shift values for the protons on carbon atoms 22 and 21 or 23 (butenolide structure) as available in the literature for a representative compound eg. as below³³ are given as



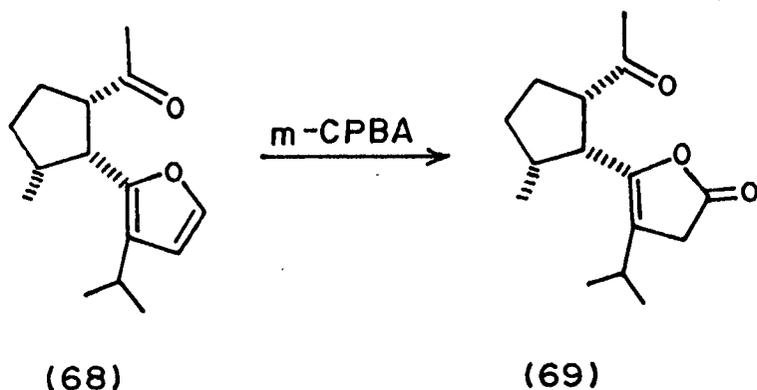
4.73 (d, $J=7$ Hz, 1H) and 5.86 (t, $J=2$ Hz, 1H). The signal at 4.73 can be assigned to the proton on C-21 in the butenolide structure.

There are also numerous other examples where the oxidation of a β -substituted furan ring has given a butenolide rather than a β -furanone.



Ref. 34

Another case was the oxidation of furopelargone B (68) with m -CPBA³⁵. The oxidation product was the butenolide (69).



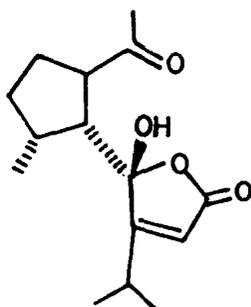
Now we would like to comment on the structure of compound (66) obtained by the NBS oxidation of (61). Chatterjee et al³⁰ have suggested a ketohydroxy dihydrofuran structure (66) for the product. Again on the strength of existing literature on the oxidation of furans with NBS, we will propose an alternative structure, a hydroxy butenolide for the same.

Our main argument in support of a butenolide is the ¹³CMR chemical shift reported for the ester carbonyl of the butenolide moiety is around 160-175 units whereas a keto group of a β -furanone eg. (66) always resonates above 200 as given in several cases in literature.

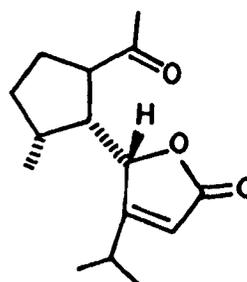
The chemical shift of the carbonyl group obtained by the NBS oxidation of the furan ring as reported by Chatterjee et al³⁰ is 168 which agrees well with the butenolide structures proposed by us 73a or 73b.

Existing literature on butenolides, some examples of which are given below invariably put the ¹³C chemical shift of the lactone carbonyl

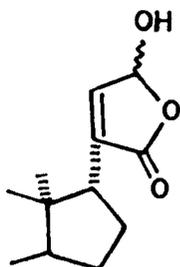
below 180.



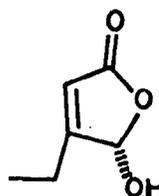
¹³CMR carbonyl
 δ 177.5



δ 178.8

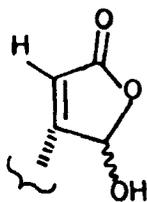


δ 169.5

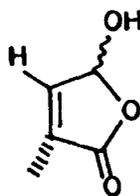


δ 172

In order to decide between alternative structures 73a and 73b, one has to look at the chemical shift of the vinyl proton in the butenolide ring. In one case (structure 73a), it is to the carbonyl and in the other (structure 73b) it is to the carbonyl. Thus PMR would be able to distinguish between them.



73 a

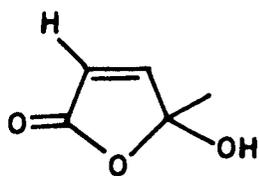


73 b

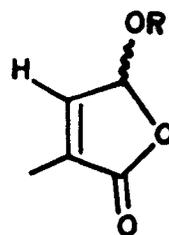
A comparison of the chemical shifts of the above types of protons in representative compounds is given in Chart 6. The chemical shift $\delta 6.18$ given for H-22 (numbering as in structure 61) agrees well with a vinyl proton to a carbonyl and therefore we decide in favour of structure 73a for the NBS oxidation product of (61). The mechanism of formation of these compounds are shown in Schemes - 13 and 14.

There are other considerations which would support butenolide structures for compounds (64) and (66). When one delves into the literature of natural furans, the co-occurrence of furans and butenolides is quite common. On the other hand, there is no report of a co-occurrence of furanone and a furan. This would suggest that oxidation-reductions in nature also involve butenolides and not furanones.

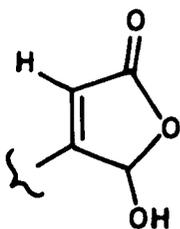
However if one sees the number of natural furans and compares with the number of natural butenolides, the ratio of furans to butenolides is about 9:1. This can be explained if one considers



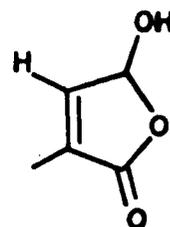
δ_H 5.8



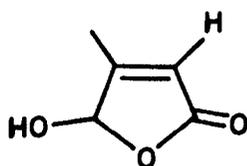
δ_H 6.96



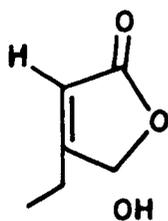
δ_H 6.07



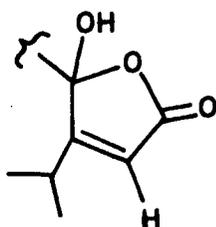
δ_H 6.78



δ_H 5.96

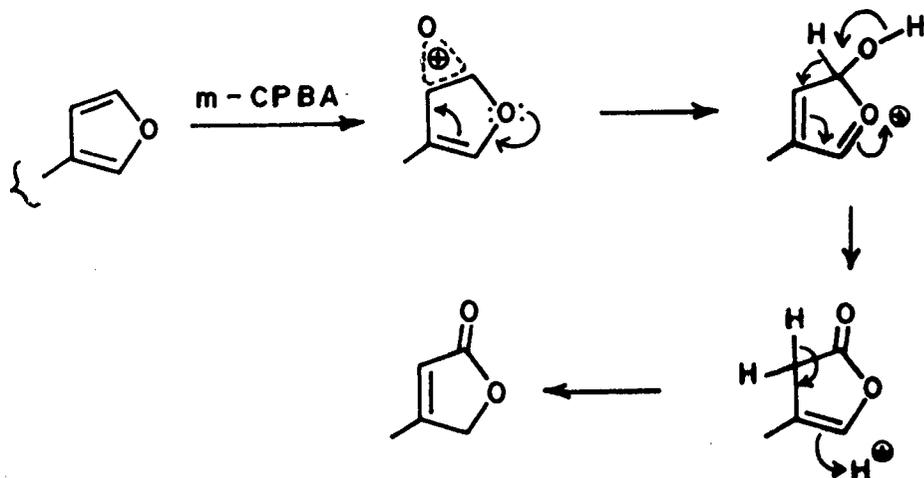


δ_H 5.83

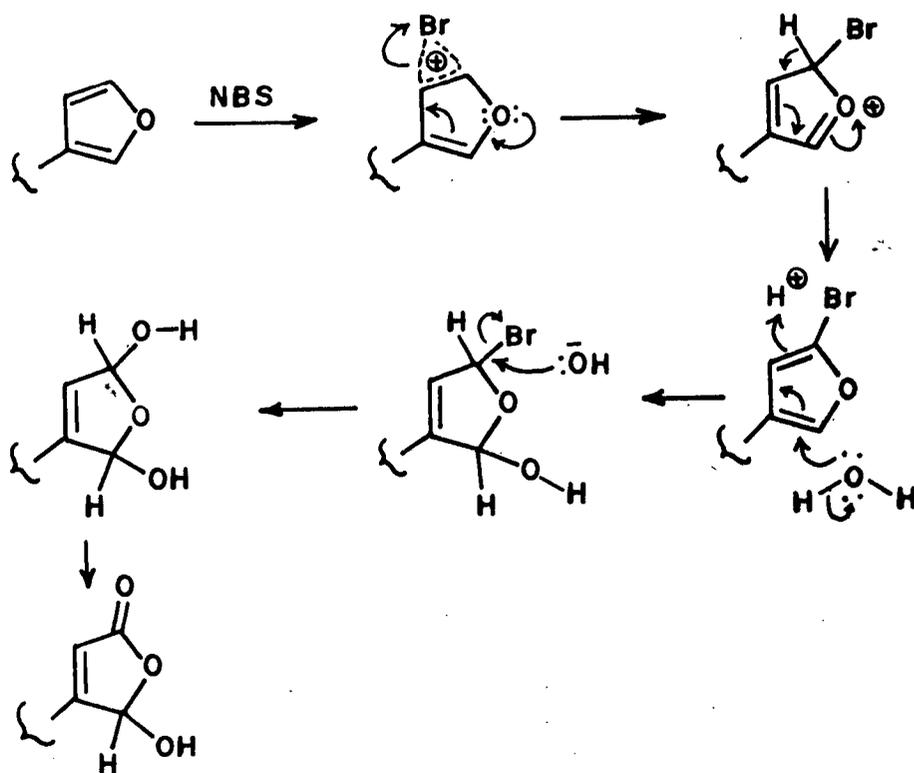


δ_H 5.77

Chart - 6



Scheme - 13



Scheme - 14

that butenolides are not formed in nature by oxidation of furans, rather, it is the furans which are end products of the redox systems involving butenolides and both furans and butenolides can originate from a common precursor.

The natural tetranortriterpenoids have highly oxygenated rings with the furan ring intact. The furan ring being highly susceptible to oxidation even in presence of other oxidisable group, it is practically impossible that compounds such as (61) and (63) and many others could have originated by the oxidation of furans.

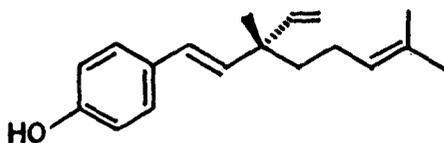
In conclusion, we have revised the structures of the oxidation products of 6 α -acetoxyazadirone (61) with m-CPBA and NBS.

CHAPTER - III

SECTION - VII

THE DECARBOXYLATION STEP IN THE BIO-SYNTHESIS OF
BAKUCHIOL

Bakuchiol (74), isolated from the seeds of the Indian medicinal plant, Psoralea corylifolia L.³⁶ is a novel phenolic compound with a monoterpene sidechain.



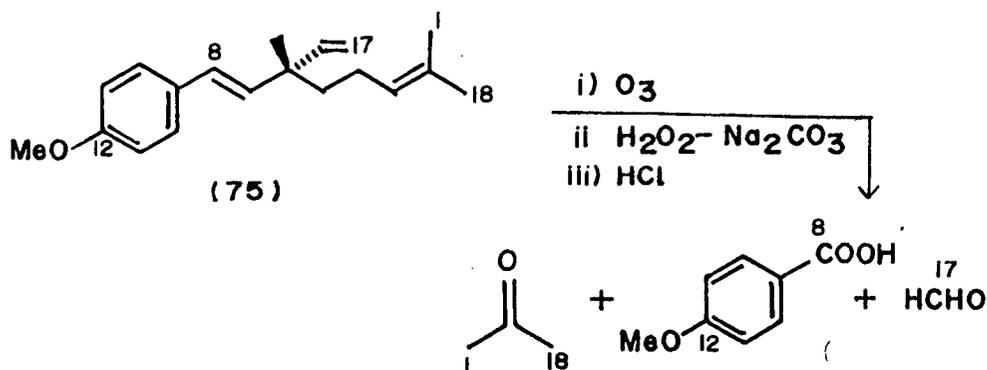
(74)

In addition to reported antimicrobial activity^{36,37}, bakuchiol also exhibits insect juvenile hormone (JH) properties and is more potent than the naturally occurring JH mimic, juvabione.

Inspection of the structure (74) suggests that 10 out of 12 carbon atoms of the sidechain are isoprenoid in nature. The aromatic ring, along with the two carbon sidechain may be considered to be derived from a phenylpropane unit or from a polyketide chain.

Because of the interesting structural features present in bakuchiol, Banerjee and co-workers^{38,39,40,41} have extensively studied the biogenesis of bakuchiol using labelled precursors.

Bakuchiol methyl ether (75) prepared from biosynthesised (74) from D,L-[U-¹⁴C]-phenylalanine on degradation gave radioactive anisic acid which carried 81% of the radioactivity of the parent compound. Considering the loss of one carbon atom, (i.e. carbon-7) out of the eight labelled carbon atoms of (75), this amounts to 93% of expected retention of the radioactivity. Other degradation products, namely, formaldehyde and acetone did not contain significant amount of labels. The specific incorporation of phenylalanine into the aromatic ring thus establishes the phenylpropanoid origin of the non-isoprenoid part of (74).



Loss of the carboxyl group during the biosynthesis of bakuchiol from phenylalanine has been shown by experiments where D,L-[1-¹⁴C]-phenylalanine was used. Bakuchiol isolated from the treated plant did not possess any significant radioactivity though expected incorporations into other phenylpropanoids like psoralen and angelecin were observed in the same experiment. Thus, the carboxyl of phenylalanine is lost during the biosynthesis of (74). Further proof for the loss of the carboxyl carbon has been obtained by using [4-³H,1-¹⁴C]-phenylalanine as substrate. Loss of ¹⁴C was indicated by the increase in the ratio of ³H/¹⁴C in the biosynthesised bakuchiol.

Information about the biosynthesis of the side chain carbon atoms 1-6 and 15-18 could be obtained by using [1-¹⁴C] and [2-¹⁴C]-acetates as substrates. The major pathway leading to the biosynthesis of MVA involves the condensation of three acetate units. In the first specific step in the biosynthesis of terpenoids, one carboxyl carbon of MVA is lost during the formation of isopentenyl

pyrophosphate. Thus if the side chain of (74) is isoprenoid in nature, the distribution of the labels from [1-¹⁴C] and [2-¹⁴C] acetates will be expected in the positions shown Scheme-15.

Bakuchiol methyl ether, obtained from (74) biosynthesised from sodium [1-¹⁴C] acetate, on degradation gave radioactive formaldehyde and acetone. In the corresponding experiment, where sodium [2-¹⁴C] acetate was used as a substrate, formaldehyde did not show significant radioactivity while acetone was labelled with ¹⁴C. This pattern of labelling is consistent with the terpenic origin of the sidechain (C-atoms 1-6 and 15-18).

Definite proof of the terpenic origin of the sidechain was obtained by using [2-¹⁴C]-MVA as a substrate. Degradation of (75) obtained from biosynthesised (74) gave acetone containing 45% of the total incorporated radioactivity (expected 50%). This indicates that two units of MVA are involved in the biosynthesis of (74). Anisic acid and formaldehyde, the other isolable degradation products did not show significant labelling. Since

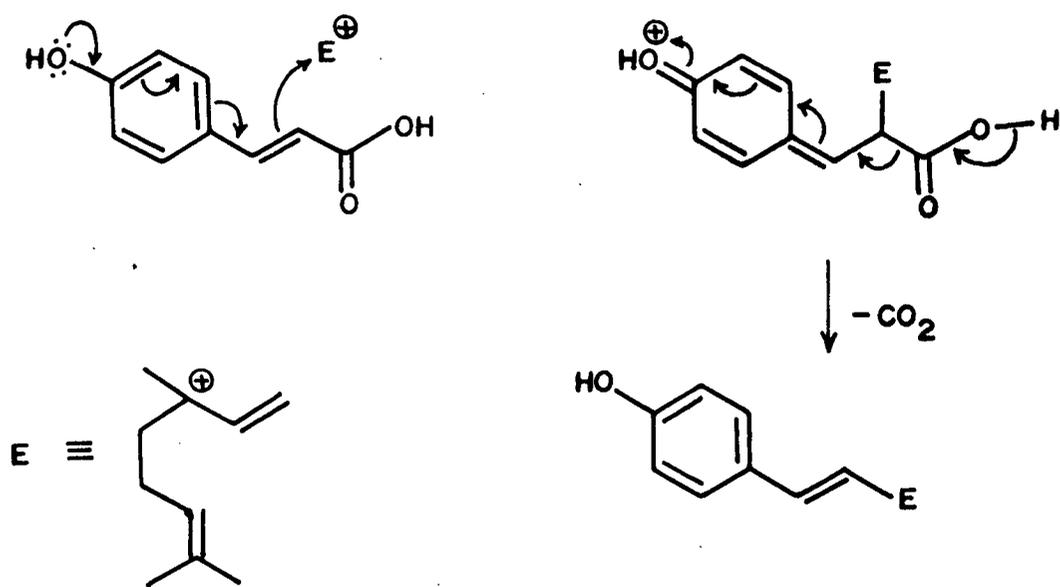
radioactive acetone is obtained from the DMAPP derived part of (74), this experiment also establishes that DMAPP derived moiety of (74) is also biosynthesised from MVA.

Though it is quite clear from the above results that phenylalanine and MVA are involved in the biosynthesis of bakuchiol, the sequence of biosynthetic events which finally lead to bakuchiol are yet to be finalised.

In view of our continued interest in the biogenesis of terpenoids, we thought it worthwhile to postulate the biosynthetic pathway including the mode of elimination of the carboxyl carbon in the form of carbon dioxide.

If the carbocation derived from linalyl pyrophosphate (76) attacks p-hydroxy cinnamic acid, in the manner shown (Scheme - 16), then the resultant end product should be bakuchiol.

A similar reaction may be assumed for the formation of bis (4-methoxybenzal)acetone (77) from p-methoxy cinnamic acid when heated with PPA at 60-70° for 4 hours⁴². The reaction may be considered



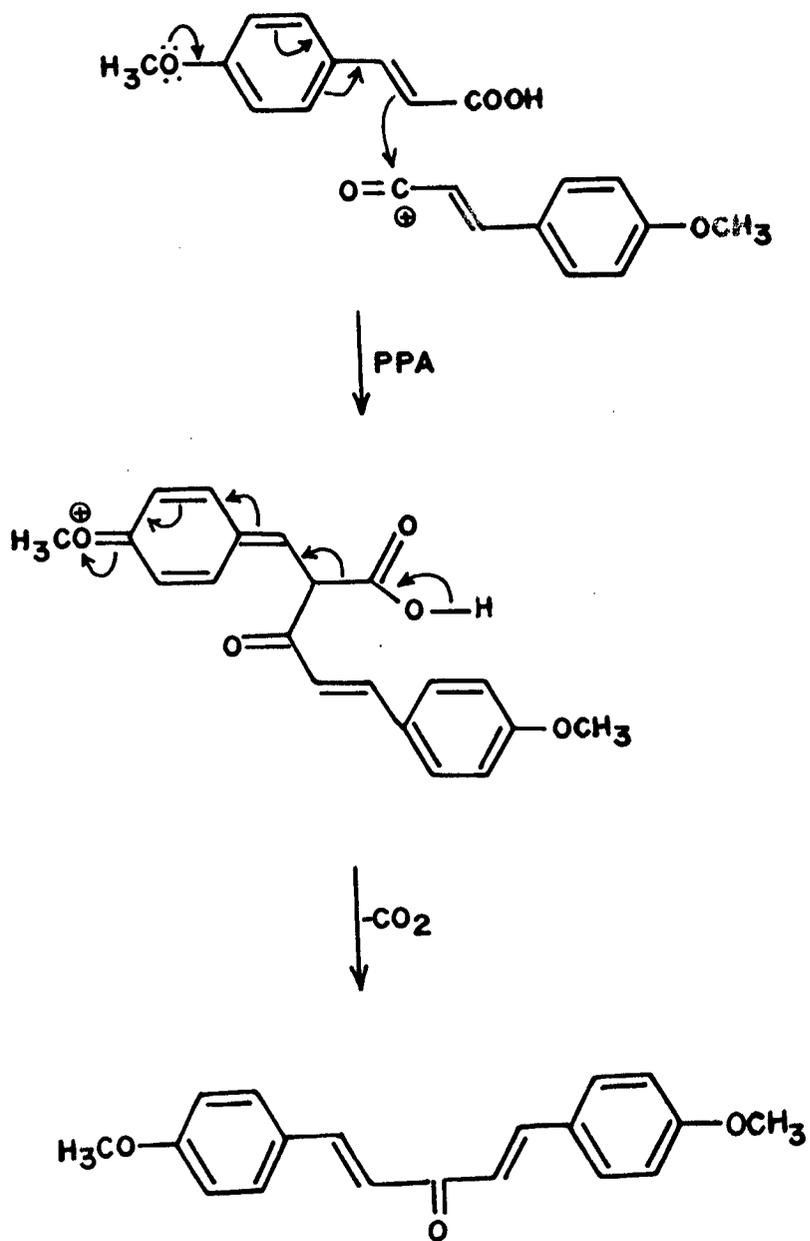
Scheme - 16

to be an attack of p-methoxy cinnamic acid on an electrophilic species derived from itself. (Scheme - 17)

In an attempt to synthesise bakuchiol methyl ether, p-methoxycinnamic acid and linalool were heated with aqueous citric acid. We failed to detect any bakuchiol methyl ether in the reaction product which mainly consisted of a mixture of C₁₀ hydrocarbons together with a hydroxylic fraction. These observations suggest that the penultimate step in the biosynthesis of bakuchiol may involve the formation of a meroterpenoid precursor. The immediate outcome of this consideration is the involvement of p-hydroxycinnamyl ester of an acyclic terpene alcohol such as linalool, geraniol or nerol.

Literature survey indicated the natural occurrence of a very large number of p-hydroxycinnamyl esters of terpene alcohols (see Chart-7 for representative examples).

The reported isolation of geranyl p-hydroxy cinnamate (78) in Calocedrus formosana by Chang et



Scheme - 17

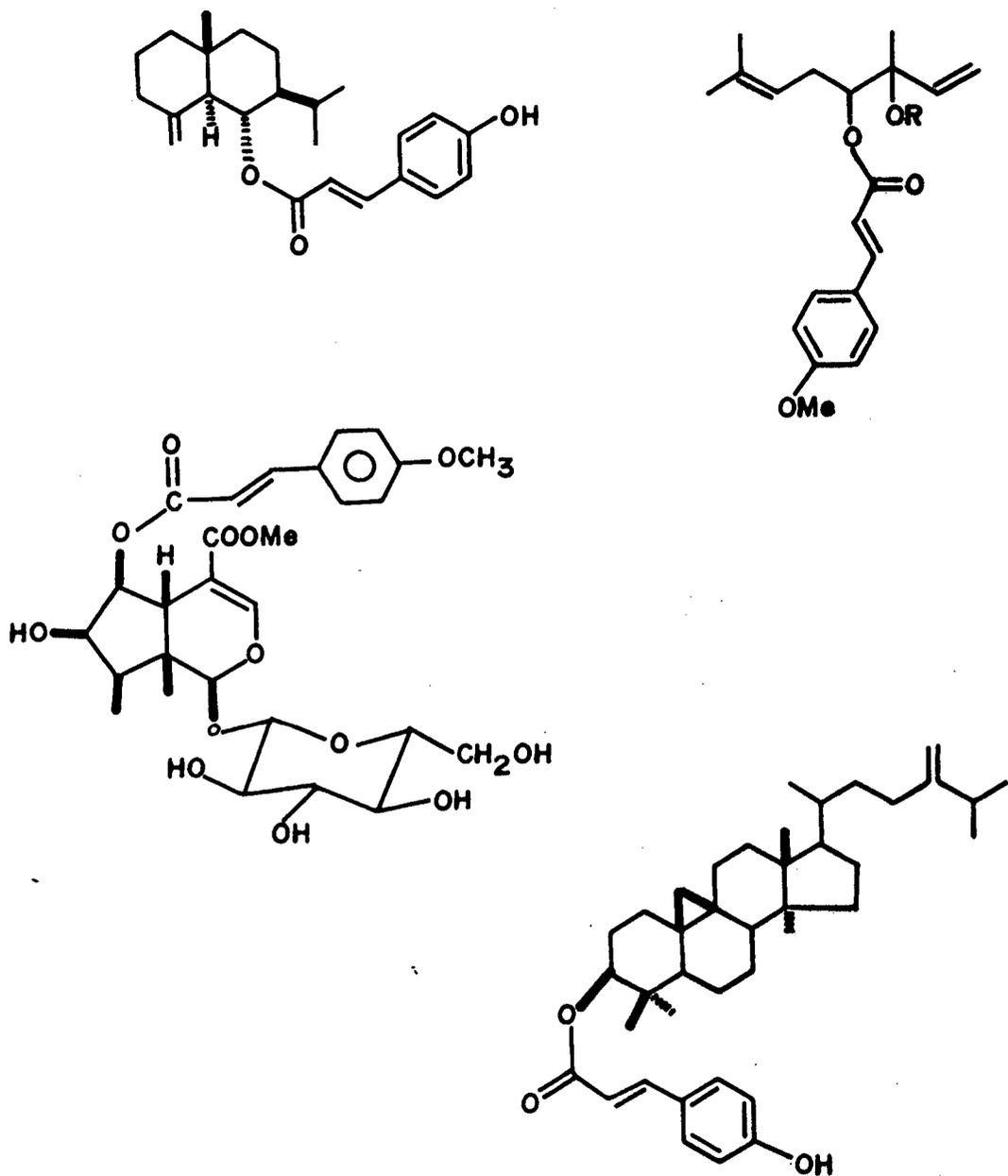
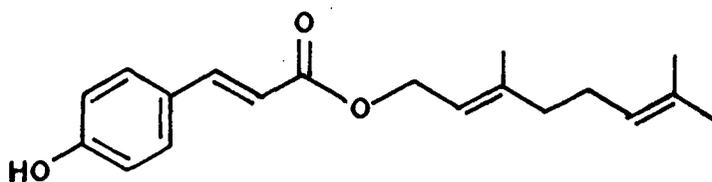


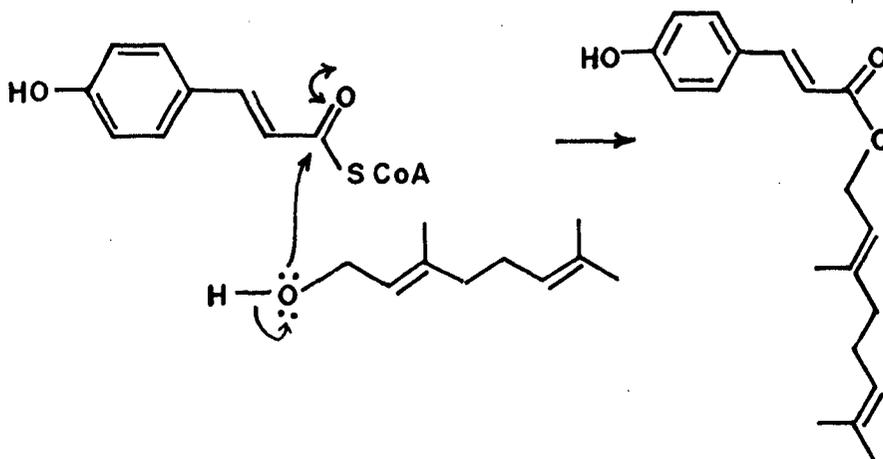
Chart - 7

al⁴³ is of special significance in this connection.



(78)

The formation of this ester can be speculated as a result of a transesterification reaction between hydroxy cinnamoyl-CoA and geraniol both of which are naturally occurring.



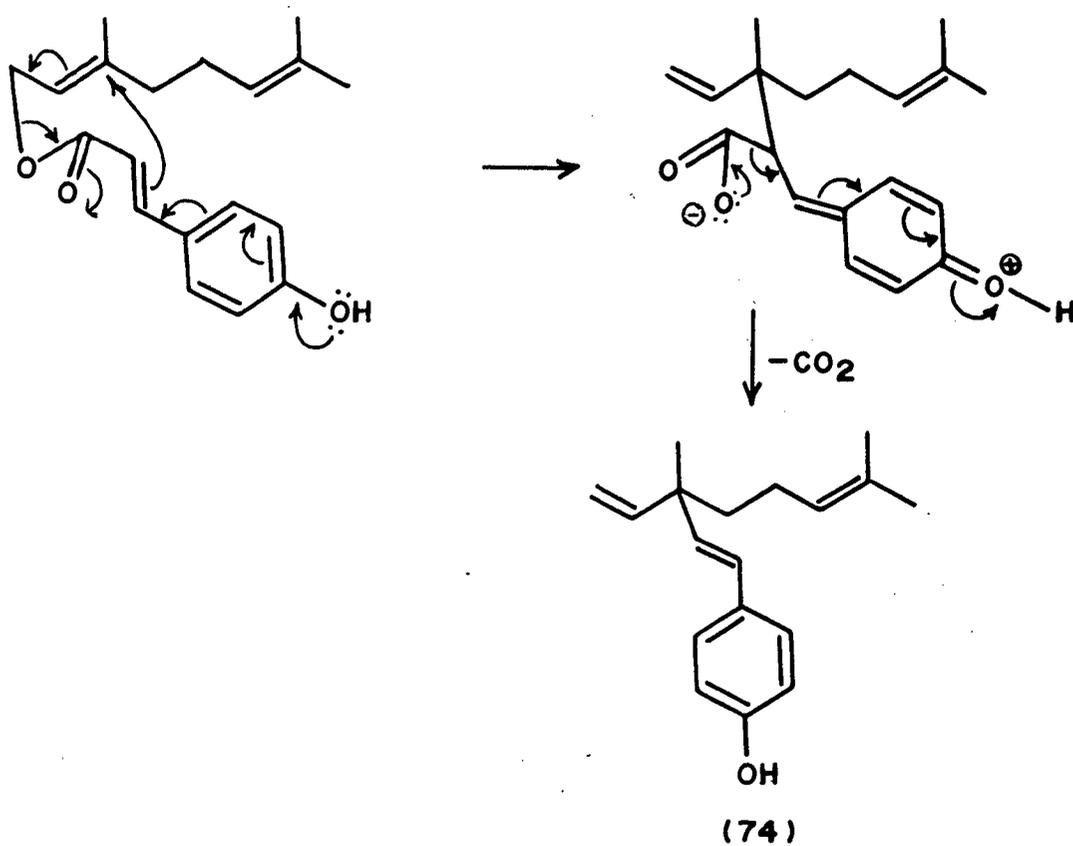
(78)

We envisage the biosynthesis of bakuchiol from geranyl p-hydroxycinnamate (78) as shown in Scheme - 18.

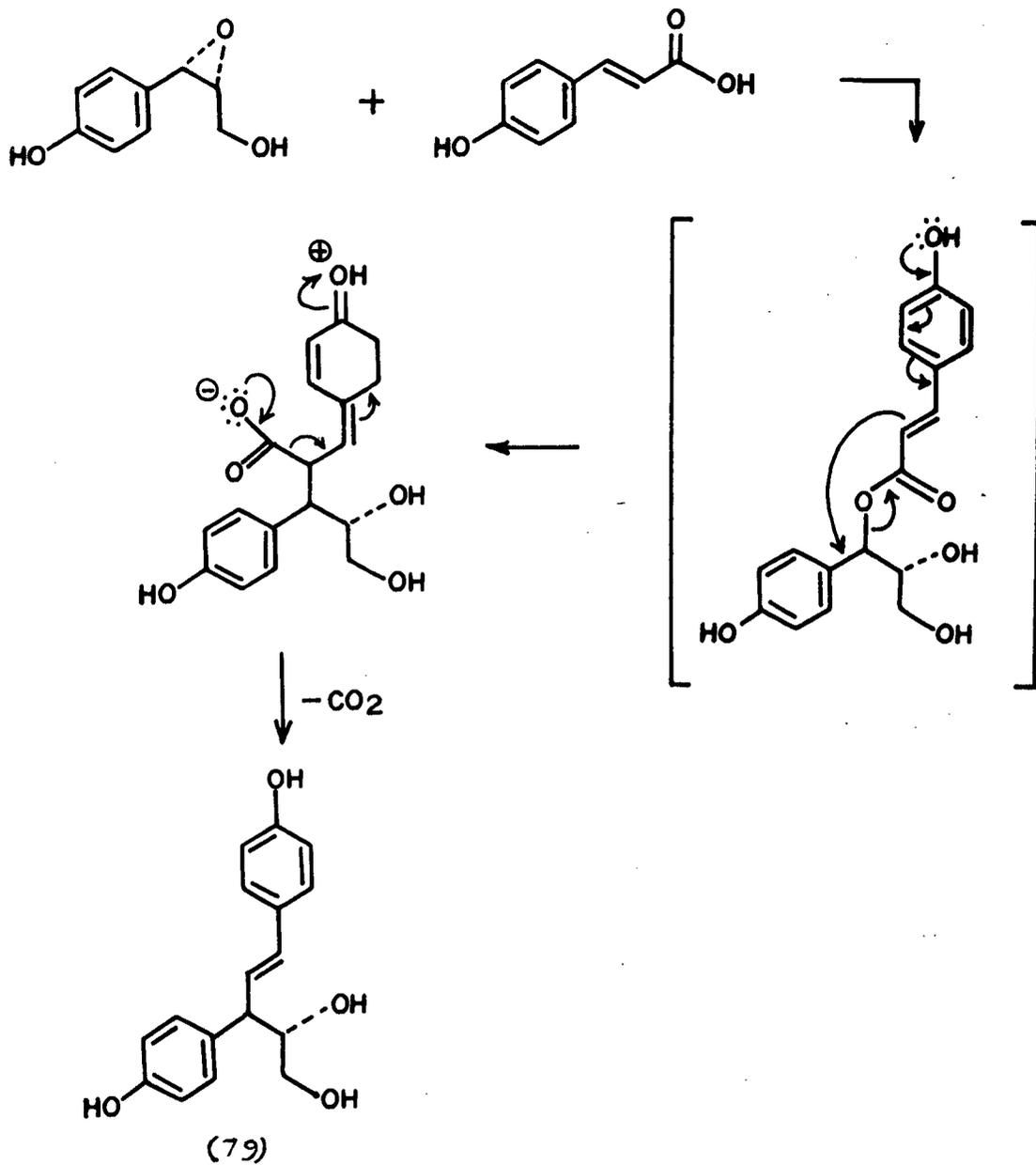
In order to obtain experimental proof for our proposed biosynthesis of bakuchiol, we have synthesised the geranyl ester of p-methoxycinnamic acid. Efforts are now on to convert it into bakuchiol methyl ether under a variety of acid catalysts. Reaction of geranyl p-hydroxy cinnamate with BF₃-etherate in benzene at room temperature did not lead to bakuchiol methyl ether but led to the hydrolysis of the ester.

The assigned structure (79) of agatharesinol, a norlignan is of interest in this connection. An analogous biogenetic pathway can easily be proposed for agatharesinol. (Scheme - 19)

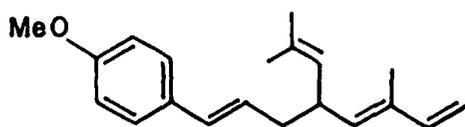
A reference to two other meroterpenoids (80 and 81) where the monoterpene and phenylpropanoid (C₆-C₃) units are intact may be in order. These are juvocimene 1 (80) and juvocimene 2 (81). They are



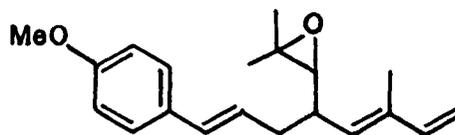
Scheme -18



Scheme - 19



(80)

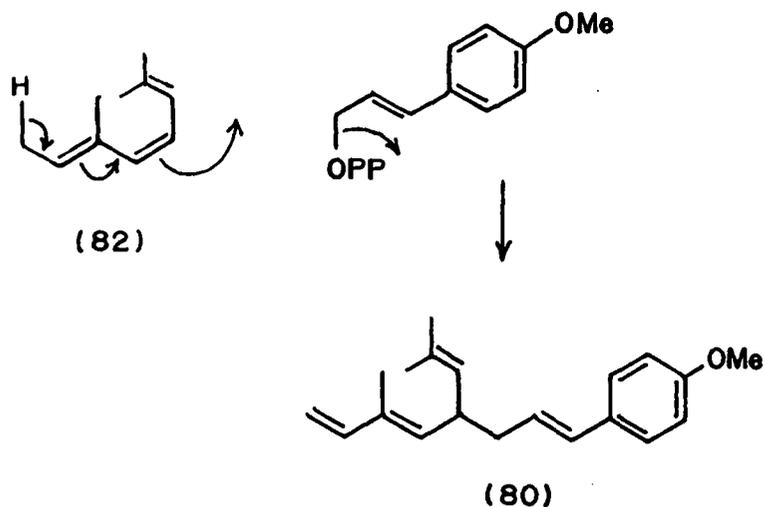


(81)

compounds with highly potent juvenile hormone activity, isolated from the oil of the sweet basil, Ocimum basilicum L. They contain ocimene as a portion of their chemical structure and appear to have resulted from the condensation of a monoterpene and a cinnamoyl moiety. This speculation is supported by the presence of β -ocimene, methyl chavicol and methyl cinnamate as important constituents of the sweet basil oil distillate.

The major difference between the structures of bakuchiol (74) and (80) is that in the latter case the electrophilic species is derived from the

phenylpropanoid precursor viz. p-hydroxycinnamyl pyrophosphate. The probable biogenesis of juvocimene 1 (80) may be as follows.



An attack of allocimene (82) on p-methoxy cinnamyl pyrophosphate may afford (80).

Though there is no experimental proof for the decarboxylation step suggested by us in the biosynthesis of bakuchiol, it in all probability would be correct.

EXPERIMENTAL

Attempted preparation of hydrocarbon (2) from cyperene (12).

Cyperene (1g. 0.005 mole) was dissolved in aqueous dioxane (5ml.) and perchloric acid (0.5ml.) was added dropwise while the mixture was stirred magnetically. Stirring was continued for 1 hour. The mixture was then poured into 20 ml. water and extracted with ether. Ether extracts were washed with sat. NaHCO_3 , water and brine. Drying and concentration gave an oil which was purified by column chromatography over silica gel. The hydrocarbon fraction was further subjected to GLC. A hydrocarbon of M.W. 204 was found in addition to unreacted cyperene. This was identified as isocyperene (14).

PMR (360 MHz, CDCl_3 , δ)(Fig.1): 0.77 (d, 3H); 0.8 & 0.9 (each s, each 3H); 1.0-2.2 (m); 2.8 (br s, 1H); 5.0 (s, 1H)

Mass m/z (rel. int)(Fig.2): 204 (M^+ , 8); 189 (10); 121 (30); 108 (100); 93 (55); 79 (15); 67 (10).

Geranyl p-methoxycinnamate from geraniol

P-methoxy cinnamic acid (1.78g, 0.01 mol) was first converted into p-methoxyl cinnamoyl chloride by treatment with SOCl_2 (10ml.) and refluxing. The product was distilled under vacuum after SO_2 and HCl were boiled out.

Geraniol (1.54g, 0.01 mol) was taken in 10 ml. dry pyridine and stirred magnetically. To this was added the p-methoxyl cinnamoyl chloride dropwise. The mixture was stirred for an hour and then poured into water (25 ml.) and extracted with ether. Ether extracts washed free of pyridine with 10% HCl and then with water. Drying and concentration afforded 1.876g (60%) of geranyl p-methoxy cinnamate.

Attempted conversion of geranyl p-methoxy cinnamate into bakuchiol methyl ether (75).

Geranyl p-methoxy cinnamate (1g, 0.0032 mol) was dissolved in 5 ml. benzene and treated with 0.5 ml. BF_3 -etherate under stirring. After stirring for 30 minutes, the mixture was poured into 10 ml. of

ice water and the benzene layer separated. Drying and concentration gave an oil which was chromatographed on silica gel. Elution with petroleum ether-ethyl acetate afforded a solid (200mg., 35%) which was identified as p-methoxy cinnamic acid.

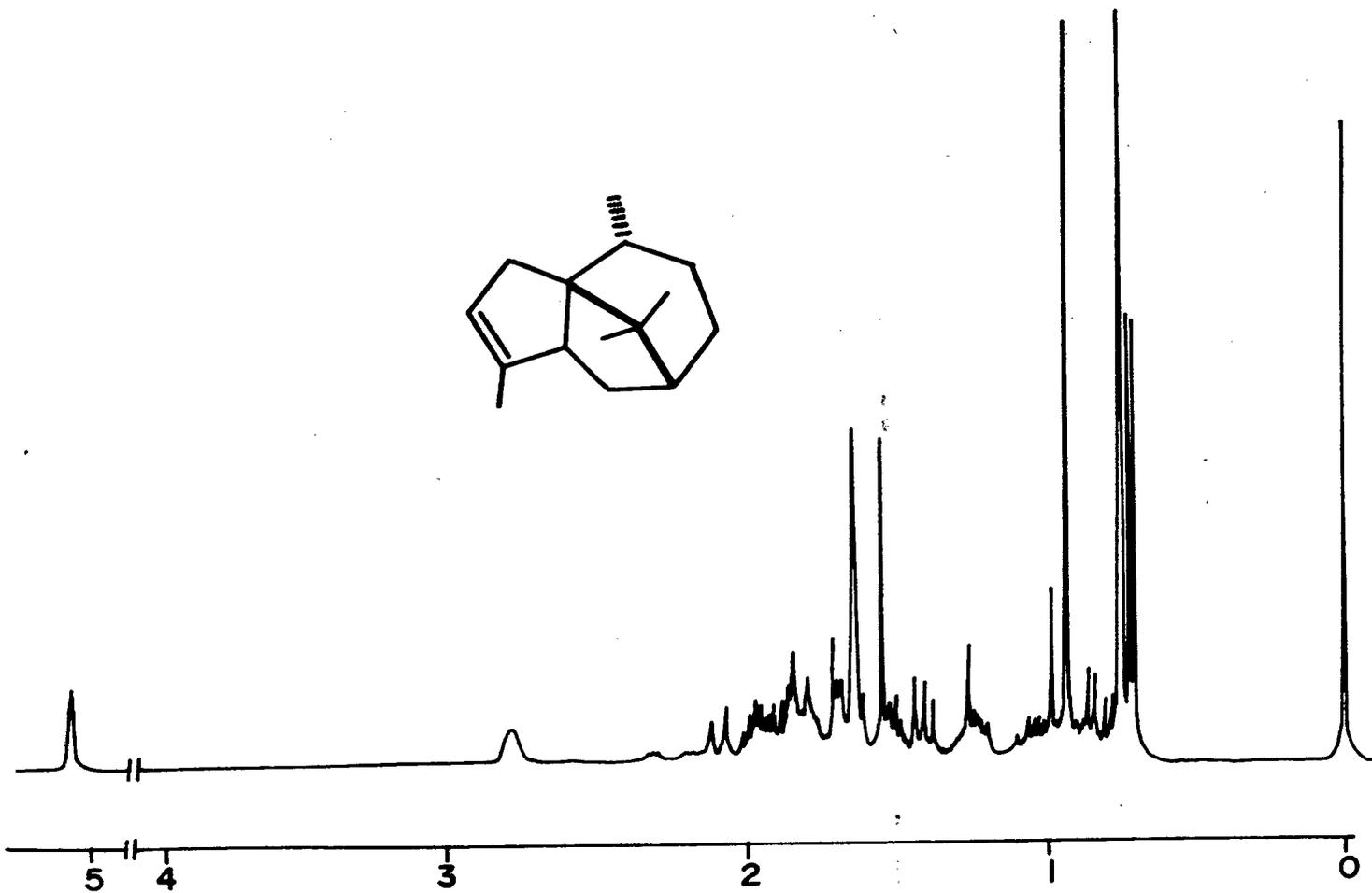


Fig. 1 NMR spectrum of (14)

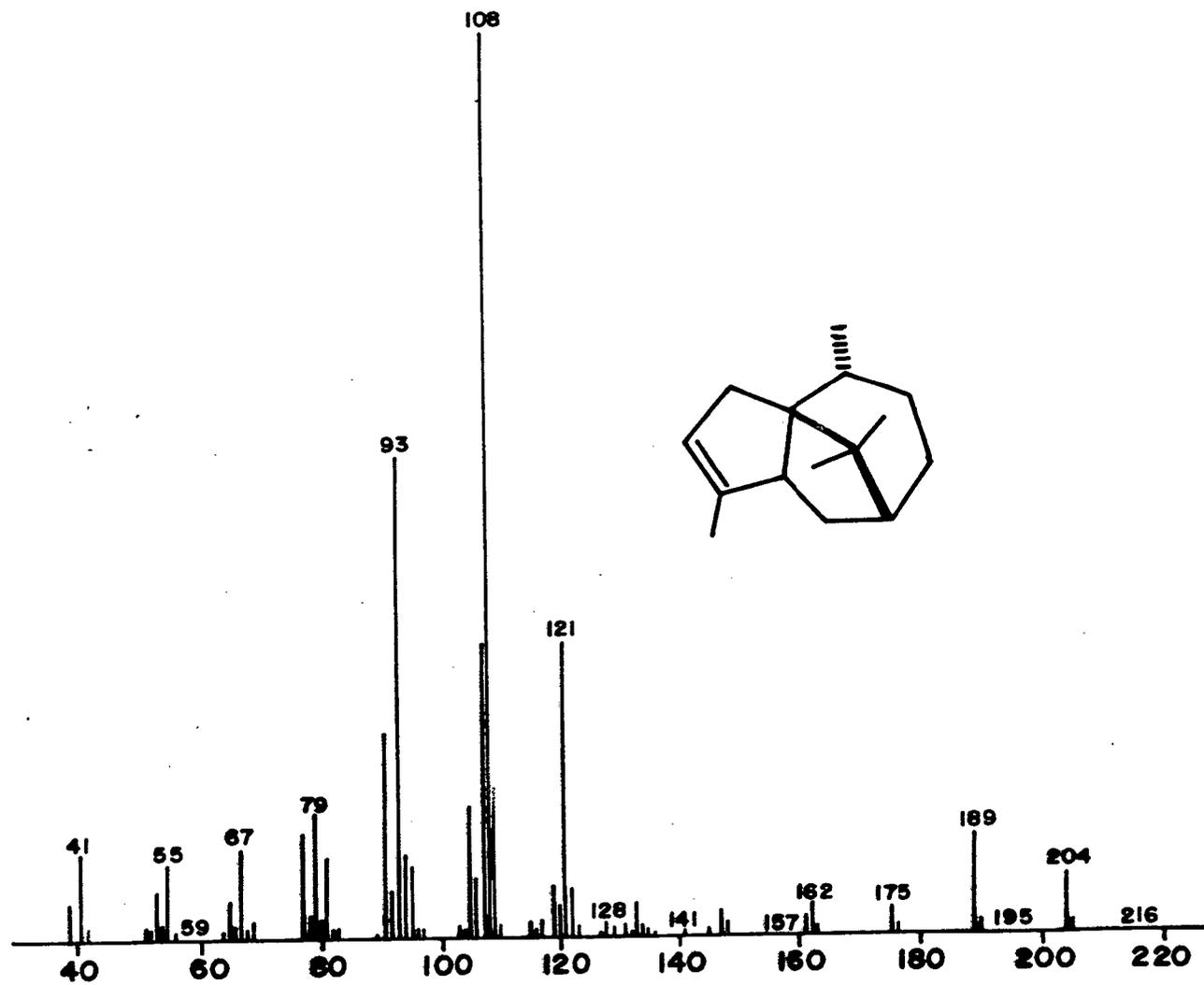


Fig. 2. Mass spectrum of (14)

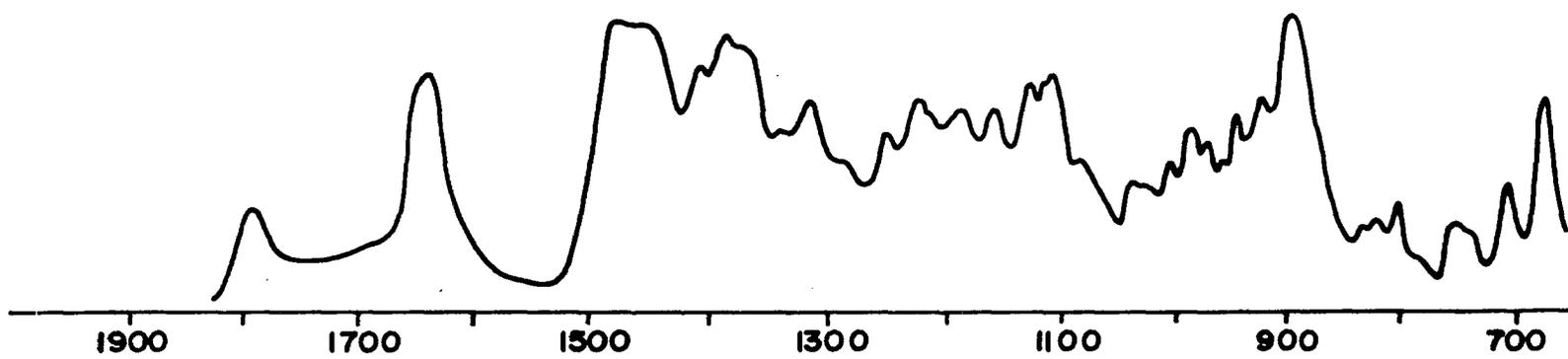


Fig. 3 IR spectrum of (17)

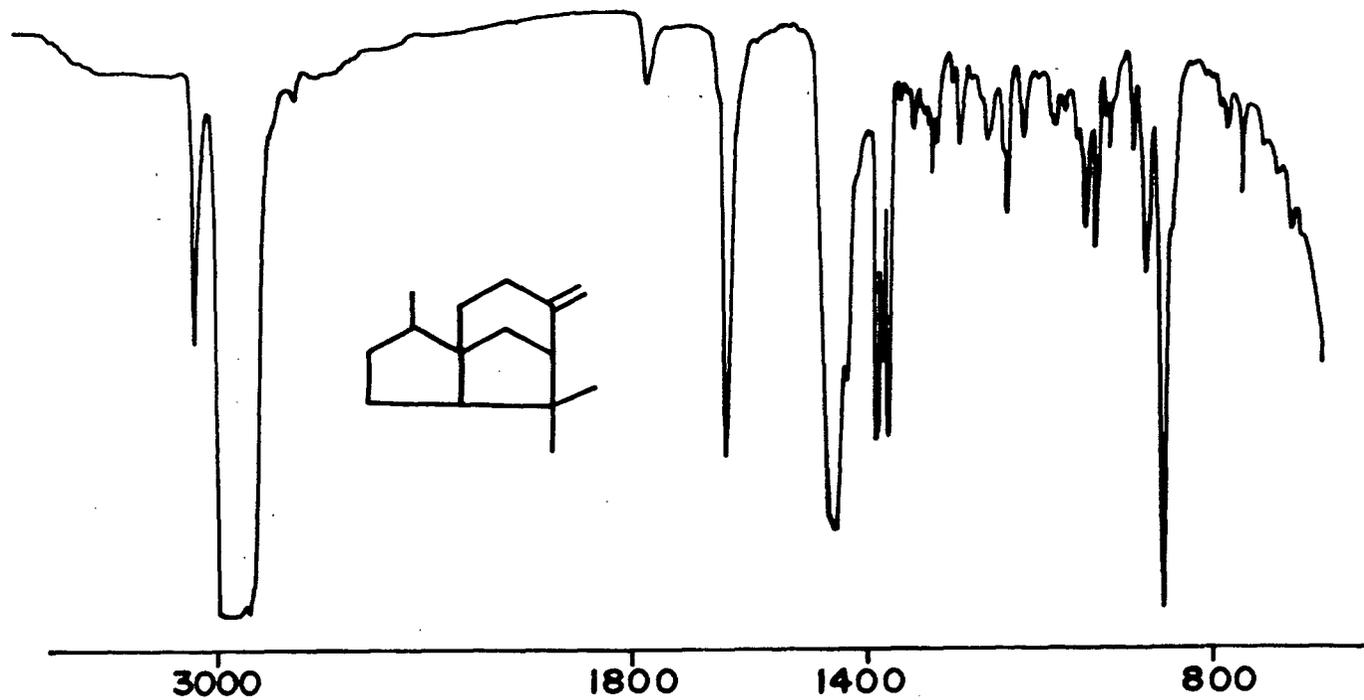


Fig. 4 IR spectrum of (20)

REFERENCES

1. Bohlmann, F. and Zdero, C., Chem. Ber., 112, 427, (1979).
2. Bohlmann, F. and Zdero, C., Chem. Ber., 112, 435, (1979).
3. Bohlmann, F., Zdero, C., King, R.M. and Robinson, H., Phytochemistry, 18, 855, (1979).
4. Singh, P., Jakupovic, J. and Bohlmann, F., Phytochemistry, 24, 1525, (1985).
5. Zdero, C., Bohlmann, F., King, R.M. and Robinson, H., Phytochemistry, 25, 2873, (1986).
6. DeRiscala, E.C., Catalan, C.A.N., Sosa, V.E., Gutierrez, A.B and Herz, W., Phytochemistry, 27, 2343, (1988).
7. Thomas, A.F. and Ozainne, M., Helv. Chim. Acta., 62, 361, (1979).
8. Teissere, P., Maupetit, P., Corbier, B. and Rouillier, P., Recherches, 19, 36, (1974).
9. Sorm, F., Holub, M., Sykora, V., Mleziva, J., Streibl, J., Schneider, B. and Herout, V., Coll. Czech. Chem. Revs. 512, (1953).

10. Akhila, A. and Nigam, M.C., *Fitoterapia*, LV, 363, (1984).
11. Tsubaki, N., Nishimura, K. and Hirose, Y., *Bull. Chem. Soc. Jpn.*, 40, 597, (1967).
12. Teissere, P., Maupetit, M. and Corbier, B., *Recherches*, 19, 8, (1974).
13. Ourisson, G. and Wolffe, G., *Tetrahedron*, 25, 4903, (1969).
14. Bates, R.B. and Slegal, R.C., *Chemistry and Industry*, 1715, (1962).
15. Akhila, A., Sharma, P.K. and Thakur, R.S., *Phytochemistry*, 26, 2705, (1987).
16. Battersby, A.R., *Pure Appl. Chem.*, 14, 117, (1976).
17. Bates, R.B. and Paknikar, S.K., *Tett. Lett.*, 1453, (1965).
18. Paknikar, S.K. and Sood, V.K., *Tett. Lett.*, 4853, (1973).
19. Paknikar, S.K. and Kirtany, J.K., *Ind. J. Chem.*, 20B, 438, (1981).

20. Kamat, V.P., Ramannama, C.V., Naik, C.G. and Paknikar, S.K., Presented at the Post - IUPAC symposium on Natural Products, Feb. 1990, Bangalore, India.
21. Paknikar, S.K. and Patel., J., Chemistry and Industry, 523, (1988).
22. Todorova, M. and Ognyanov, I., Planta Medica, 174, (1985).
23. Huneck, S., Zdero, C. and Bohlmann, F., Phytochemistry, 25, 883, (1986).
24. Tan, R.X., Jia, Z.J., Jakupovic, J., Bohlmann, F. and Huneck, S., Phytochemistry, 30, 3033, (1991).
25. Ahmed, A.A., Jakupovic, J., Eid, F. and Ali, A.A., Phytochemistry, 27, 3875, (1976).
26. Thomas, A.F. and Ozainne, M., Helv. Chim. Acta., 59, 1243, (1976).
27. Alessandri, P., DeAngelis, F. and Gambcorta, A., Tetrahedron, 41, 2831, (1985).
28. LeDrian, C. and Vogel, P., Tett. Lett., 28, 1523, (1987).

29. Jakupovic, J., Ganzer, U., Pritschlow, P.,
Lehmann, L., Bohlmann, F. and King, R. M.,
Phytochemistry, 31, 863, (1992).
30. Chatterjee, A., Nayak, L., Das, B., Patra, A.,
Dhara, K.P., Mukherjee, K. and Banerji, J.,
Ind. J. Chem., 26B, 231, (1989).
31. Kehrl, A.R.H. and Taylor, D.A.H., J.C.S.
Perkin Trans., 2067, (1990).
32. Gonzales, A.G., Darries, J. and Martin, J.D.,
Tett. Lett., 3625, (1973).
33. Sethi, A., Khare, A. and Khare, M.P.,
Phytochem., 27, 2255, (1990).
34. Daniewski, W.M., Gomulka, M. and Skibicki, P.,
Phytochem., 29, 527, (1990).
35. Itokawa, H., Morita, H., Osawa, K., Watanabe,
K. and Iitaka, Y., Chem. Pharm. Bull., 35,
2859, (1987).
36. Mehta, G., Nayak, U.R. and Dev, S.,
Tetrahedron, 29, 1119, (1973).
37. Prikhodko, V.A. and Bondarenko, A.S.,
Microbiol. Zh. (Kiev), 41, 400, (1979).

38. Banerjee, A. and Chintalwar, G.J.,
Phytochemistry, 22, 1945, (1983).
39. Banerjee, A. and Chintalwar, G.J.,
Phytochemistry, 23, 1605, (1984).
40. Banerjee, A and Chintalwar, G.J., Proc. Indian
Acad. Sci. (Chem. Sci.), 93, 1171, (1984).
41. Banerjee, A. and Chintalwar, G.J., Indian
Jour. Biochem. and Biophysics. 26, 394, (1989).
42. Talapatra, B., Deb, T. and Talapatra, S., Ind.
J. Chem., 25B, 1122, (1986).
43. Cheng, Yu-Shia, Hsu, Kuo-Chio and Fang, Jim-
Min., Phytochemistry, 28, 1173, (1989).
44. Bowers, W.S. and Nishida, R., Science, 209,
1030, (1980).

SUMMARY

This thesis is on synthesis, synthetic transformations and biogenesis of natural products.

It is divided into three chapters.

Chapter I includes studies on coumarins. It is composed of three sections.

Section 1 :- Deals with a new method of synthesis of coumarins by the transfer of C-3 unit of p-methoxy cinnamic acid onto phenols. The synthesis of many natural and synthetic coumarins by the above method is discussed in this section.

Section 2 :- Discusses the formation of certain unexpected products in the reaction of some phenols with p-methoxy cinnamic acid. Some intriguing dehydroxylations and rearrangements are described in this section.

Section 3 :- Reinvestigates the reaction of 2-acetyl-4-methyl phenol and 2-acetyl-5-methyl phenol with hexachloropropene in the presence of $AlCl_3$. The structures of the products have been reassigned to fit in the available spectral data.

Chapter II describes the reactions of various terpenoids with lead tetraacetate. It is divided into three sections.

Section 1 :- Deals with the attempted preparation of santolina triene by the lead tetraacetate decarboxylation of cis-homochrysanthemic acid. Instead of the desired product, three lactones are obtained by the initial attack of lead tetraacetate on the double bond of cis-homochrysanthemic acid and not on the carboxylic acid group.

Section 2 :- Describes the synthesis of 4,5-secoeudesmanes by the regioselective cleavage of the 4,5- and the 6,11- bonds of maaliol by reaction with lead tetraacetate.

Section 3 :- Deals with the attempted preparation of a C-12 hydrocarbon by the reaction of guaicol with lead tetraacetate. The product dehydroguaioxide which was earlier reported by Ourisson et al was characterized and additional spectral data on it was gathered.

Chapter III describes biogenetic studies on various natural products. It consists of seven sections.

Section 1 :- Deals with an attempted entry into the trixane skeleton by the protonation of cyperene. The only product characterized was isocyperene.

Section 2 :- Discusses the identity of the hydrocarbon isolated from the oil of the plant Acorus calamus L. Its identity with patchoulene or cedrene was conclusively disproved.

Section 3 :- Comments on the biogenesis of patchoulenes. A new unified proposal is put forward which also takes into account the stereochemical aspect which was lacking in earlier schemes.

Section 4 :- Discusses the structure revision of tanaphillin, a 1,10-secoguanolide isolated from the plant Tanacetum macrophyllum. A new structure is proposed which fits in with existing spectral data and biogenetic relationships.

Section 5 :- Describes new biogenetic proposal for 11-hydroxyjasione and 9-oxojasoniolide - sesquiterpenoids which have the rare bicyclo[3,6,0]undecane carbon skeleton (or the 5,8 ring fused ring system).

Section 6 :- Revises the structures of the oxidation products of 6 α -azadirone with m-CPBA and NBS. The proposed structures which were furanones are revised to butenolides in accordance with reported spectral data and mechanistic aspects.

Section 7 :- Describes the decarboxylation step in the biogenesis of bakuchiol a phenolic with a monoterpene side chain. The biogenesis of bakuchiol from geranyl p-hydroxy cinnamate is described and this scheme is extended to the biogenesis of the meroterpenoids, agatharesinol and juvocimene 1 and 2.