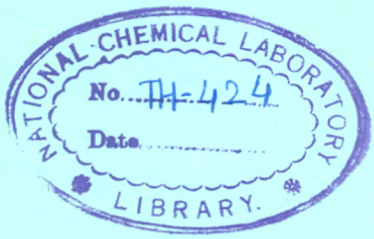
TRANSFORMATIONS OF (+) -3- CARENE : SYNTHESIS OF PYRETHROIDS

A THESIS
SUBMITTED TO THE
UNIVERSITY OF POONA

FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
IN CHEMISTRY



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MAY 1984

C E R T I F I C A T E

Certified that the work incorporated in the thesis "Transformations of (+)-3-carene: Synthesis of Pyrethroids" submitted by Shri Bharat Genuba Mahamulkar was carried out by the candidate under my supervision. Such material as has been obtained from other sources, has been duly acknowledged in the thesis.

(Dr.R.B. Mitra)
Research Guide
National Chemical Laboratory
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May 1984.

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(B.G. Mahamulkar)

NCL, Poona-411008
May 1984

C O N T E N T S

GENERAL REMARKS

1. All melting points and boiling points are uncorrected.
2. All temperatures are recorded on the centigrade scale.
3. Unless otherwise stated, all rotations were recorded in chloroform solutions. Concentrations are expressed in g /100 ml of the solution
4. The ultraviolet spectra were recorded in ethanol solution on a Perkin-Elmer 350 and Carl-Zeiss 445069 ratio recording spectrophotometers.
5. The infrared spectra of liquids were recorded as liquid films and that of solids as nujol mulls on a Perkin-Elmer Infracord Spectrophotometer- model 137-B or 683; ν_{max} values are given in cm^{-1}.
6. The PMR spectra were taken in carbontetrachloride solution, unless otherwise mentioned, using tetramethylsilane as the internal reference on a Varian T-60 or WH-90 FT or FT- 80A varian spectrometers and the chemical shifts are measured in δ units.
7. The mass spectra were recorded on a CEC-21-110B mass spectrometer.
8. Acid washed activated alumina standardised as per Brockmann's procedure and silicic acid for chromatographic purpose , after activation, were employed for column chromatography.
9. TLC analyses were carried out on glass plates coated with a mixture of silicic acid and plaster of paris (85:15; 200 mesh) and activated at 120° for 3 hr. Solvent systems used were pet.ether, benzene, ethylacetate and acetone or a suitable mixture of two or more of these solvents, depending upon the nature of the compounds. The plates were developed by keeping in an iodine chamber or by spraying with sulphuric acid.
10. The numbers assigned to the charts, structures and figures in each chapter of this thesis refer only to that particular chapter.
11. Pet.ether refers to the fraction boiling between 60-80°.
12. Unless otherwise stated, all solutions were dried over anhydrous sodium sulphate.
13. Unless otherwise stated, all b.ps. refer to the bath temperatures.
14. In the list of IR bands given in the experimental section, the significant bands described in the theory are underlined.
15. In the description of PMR signals, the abbreviations brs., br.d. and br.m. mean broad singlet, broad doublet and broad multiplet respectively.

CHAPTER - I

GENERAL INTRODUCTION

During the last decade a new class of agricultural insecticides, the synthetic pyrethroids has emerged as a complement to the organochlorines, organophosphates and carbamates. The history of the emergence of the synthetic pyrethroids as a result of extensive research on natural pyrethrins is now well documented[1,2,3]. The natural pyrethrins and the synthetic pyrethroids are superior to other classes of insecticides, because in addition to possessing high insecticidal activity, they have very low toxicity to mammals and plants and thus environmentally safe. The natural pyrethrins are esters of (+)-trans-chrysanthemic acid and (+)-trans-pyrethric acid, with alcohols, viz. pyrethrolone, cinerolone and jasmolone. The esters of (+)-trans-chrysanthemic acid are called pyrethrin I, cinerin I and jasmolin I respectively, whereas the esters of (+)-trans-pyrethric acid are called pyrethrin II, cinerin II and jasmolin II. Their structures are shown in Chart I. Table (I)[4] demonstrates the relative advantage of pyrethroids over other classes of insecticides. Relative safety is indicated by the ratio of toxicities to rat and insect (Column 4).

Table (I)

Class of insecticide	LD_{50} Rats mg/kg	LD_{50} Insects mg/kg	Ratio
Carbamates	45	2.8	16
Organophosphates	67	2.0	33
Organochlorine	230	2.6	91
pyrethroids	2000	0.45	4500

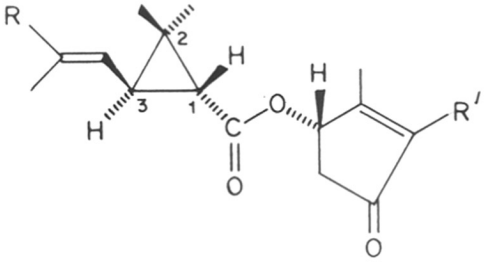
However, the natural pyrethrins[5] and the modified synthetic chrysanthemates are not suitable for agricultural use because of insufficient stability in light and air. Extensive research has been carried out in developing new pyrethroids, by replacing the photolabile groups in natural pyrethrins by others that give enhanced stability to the overall molecule and equal or increased insecticidal activity. The historical development of synthetic pyrethroids falls roughly into three stages. Initially, attention was mainly concentrated on the structural elucidation of the natural pyrethrins. This was followed by a search for simpler alcohol components from which active insecticidal esters derived from the natural acids could be obtained. In the last decade, considerable attention has been devoted towards developing a variety of cyclopropanecarboxylic acids that can give pyrethroid esters of significant insecticidal activity and sufficient photostability.

1) Natural Pyrethrins

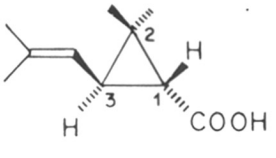
Pyrethrum represents the dried flowers of chrysanthemum cinerariae folium vis (Pyrethrum cinerariae folium Trev.), a member of the Compositae family. The powder of flowers has been used as an insecticide from ancient times[6]. The plant appears to have originated from the Middle and North East. At present Kenya is the major producing country. The discovery of pyrethrum as an

CHART–I

NATURAL PYRETHRINS

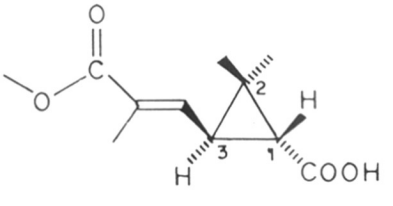


	R	R′
1. PYRETHRIN I	CH_3	
2. PYRETHRIN II	$COOCH_3$	
3. CINERIN I	CH_3	
4. CINERIN II	$COOCH_3$	
5. JASMOLIN I	CH_3	
6. JASMOLIN II	$COOCH_3$	



(+) 1R–TRANS–
CHRYSANTHEMIC ACID

7



(+) 1R–TRANS–
PYRETHRIC ACID

8

insecticide, its production and history of its uses are discussed by Gnadinger[7] and Shepard[6].

The insecticidal principles in pyrethrum are called "Pyrethrins" and for a long time have been considered harmless to mammals and plants while being very toxic to insects. Today they are becoming increasingly important as insect control agents because they possess a unique combination of desirable properties including exceptionally good insecticidal activity, low mammalian toxicity and rapid biodegradation. These features, combined with their broad spectrum of insecticidal activities and an unusually rapid paralytic effect or "knock down" effect on flying insects, have made them commercially successful and also environmentally safe.

These important properties of pyrethrum stimulated detailed examination of the chemical constitution of the active principles in the first quarter of 20th century. Staudinger and Ruzicka[8], for the first time, isolated two active compounds from the pyrethrum extract and identified them as esters of (+)-trans-chrysanthemic acid (7, Chart I) and (+)-trans-pyrethric acid (8, Chart I) with ketol pyrethrolone and named them as pyrethrin I and pyrethrin II respectively. Later on, four more active esters viz. cinerin I, cinerin II[9], jasmolin I and jasmolin II[10,11,12] were also isolated from pyrethrum extract (1 to 6, Chart I). Thus, the insecticidal activity of pyrethrum is attributed

to the presence of these six constituents. This class of active insecticidal esters, occurring in pyrethrum was named as "pyrethroids". Now, the word "Pyrethroid" is not limited to natural pyrethrins alone but is applied also to biologically active chrysanthemates and modified cyclopropanecarboxylic acid esters of various alcohols.

However, the natural pyrethrins are having limited use due to their high cost and because of insufficient stability in light and air.

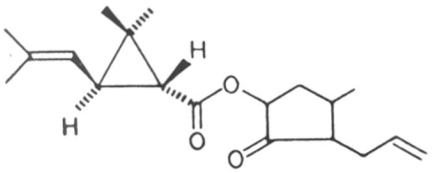
The monoterpene (+)-trans-chrysanthemic acid viz. 2,2-dimethyl-3-(2-methylprop-1-enyl)-1-cyclopropane-carboxylic acid occurs as an insecticidally active ester in pyrethrum extract. This fact has led to the preparation of many synthetic pyrethroids in which the acid moiety is (+)-trans-chrysanthemic acid (7, Chart I).

2) Evolution of Synthetic Pyrethroids

The valuable information obtained from the study of pyrethrins stimulated research in this field and as a result, a group of insecticides called "Synthetic Chrysanthemates" has developed. A close study of the structures of alcohol and acid moieties of the natural pyrethrins revealed that there are many photolabile centres in both the moieties, especially the allylic methyls and methylenes. These centres are likely to undergo autoxidation giving rise to hydroperoxides, alcohols etc. Since the insecticidal

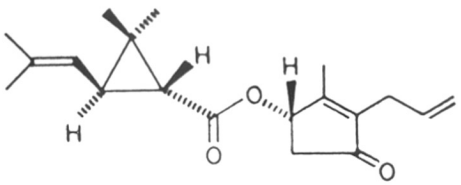
CHART-II

SYNTHETIC CHRYSANTHEMATES



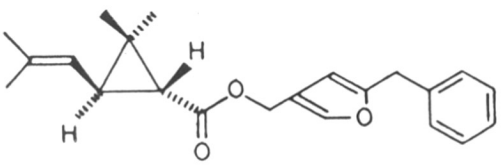
STAUDINGER & RUZICKA
(1924)

9



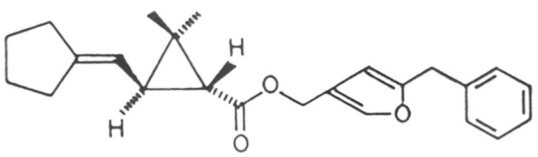
S-BIOALLETHRIN

10



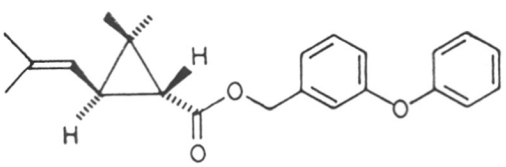
BIORESMETHRIN

11



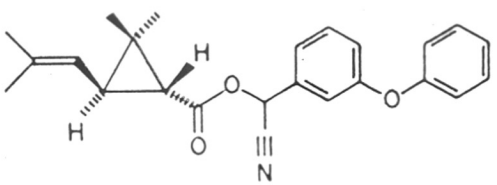
K-OTHRIN

12



BIOPHENOTHRIN

13



S-2703

14

activity is affected even due to minor structural changes in the molecule, the product resulting by autoxidation becomes inactive. As a first stage towards eliminating the photolabile centres in the alcohol moieties of natural pyrethrins, the normal pyrethrolone, cinerolone and jasmolone from natural pyrethrins were replaced by other photostable alcohols like 5-benzyl-3-furylmethyl alcohol, 3-phenoxybenzyl alcohol etc. As a restult of this modification, considerable progress has been made in developing new pyrethroids by replacing the alcohol moiety by the alcohols mentioned above which give enhanced stability to the overall molecule and equal or increased insecticidal activity.

Staudinger and Ruzicka[13], eminent pioneers of pyrethrum chemistry, detected insecticidal activity in the chrysanthemate of the cyclopentenolone (9, Chart II) which had an allyl rather than a pentadienyl side-chain. This fact was later used by Schechter, Green and La Forge[14] when they developed the first important synthetic pyrethroid "allethrin". S-Bioallethrin (10, Chart II) has faster knock-down but poorer killing power to most insects except house-flies[15]. Investigation with pure pyrethrin[16] and related compounds identified centres in the structure, sensitive to photosensitised attack by oxygen, the more important ones being the side-chain of chrysanthemic acid and the cis-pentadienyl side-chain. Modification in the

alcoholic component led to the compound bioresmethrin[17] (11, Chart II) and biophenothrin. In all these esters, the acid moiety is (+)-trans-chrysanthemic acid (7, Chart I) while the alcohol moiety is different. In bioresmethrin the cyclopentenolone nucleus of pyrethrolone has been replaced by the sterically equivalent furan ring and the photosensitive alkenyl side-chain by a stable aromatic nucleus. Bioresmethrin was the first synthetic pyrethroid to show equal or higher insecticidal activity than the natural pyrethrins against many insect species[17] in addition to possessing lower mammalian toxicity[18].

Using more lipophilic ethanochrysanthemic acid and the same furan alcohol, Martel and coworkers[19,20] developed the compound K-othrin (12, Chart II) which showed still more insecticidal activity but higher mammalian toxicity. (+) Trans-chrysanthemic acid esters with 3-phenoxybenzyl alcohol and its α-cyano derivative gave the potent pyrethroids biophenothrin[21] (13, Chart II) and S-2703[22] (14, Chart II) respectively in which the alcoholic components are stable but they still contain the photolabile isobutenyl side-chain at C_3 in the acid moiety. The photostabilities of these compounds had been assessed to be still insufficient under agricultural field conditions.

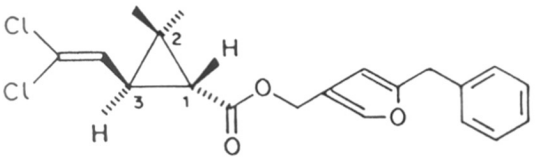
In order to develop more potent pyrethroids, modifications were also made in the acid moiety, so as to eliminate the photolabile centre in it. Thus, replacing the

methyl groups in the isobutenyl side-chain[23] by chlorine atoms, resulted in the pyrethroid NRDC-134 (15, Chart III). In NRDC-134 the alcohol moiety is 5-benzyl-3-furylmethyl alcohol and the acid moiety is 2,2-dimethyl-3 (dichlorovinyl)-cyclopropane carboxylic acid. In NRDC-134, a dichlorovinyl side-chain, in which the double bond is stabilized by the two electron withdrawing atoms, replaces the photo-sensitive isobutenyl unit of (+)-trans-chrysanthemic acid. Examining esters of this modified acid with other alcohols, Elliott and co-workers[24] developed biopermethrin (16, Chart III) in which 3-phenoxybenzyl alcohol replaces the photosensitive 5-benzyl-3-furylmethyl alcohol or other previous alcohols. Biopermethrin is more active than bioresmethrin or K-othrin and all the photolabile centres having been eliminated, the compound is more stable[24] than many organophosphates and carbamates. Nonethless, when exposed to microorganisms in the soil, it is degraded sufficiently rapid to allay any concern about undue accumulation. Biopermethrin also retains the low oral and intravenous mammalian toxicity[24].

The α-cyano group in cypermethrin (17, Chart III) gives still greater insecticidal activity, albeit with somewhat increased mammalian toxicity. Investigating a combination of optical and geometrical isomers, Elliott et al.[25] discovered the crystalline decamethrin (18, Chart III), the most potent pyrethroid yet synthesised

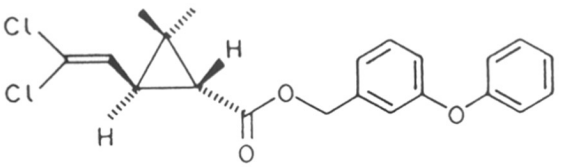
CHART – III

POTENT PYRETHROIDS



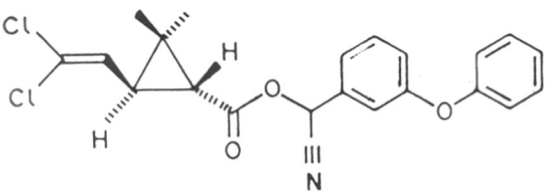
NRDC – 134

15



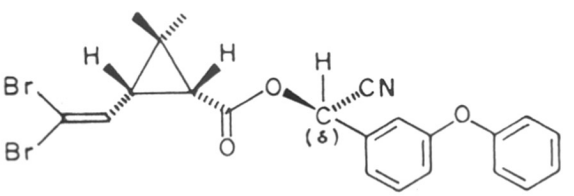
BIOPERMETHRIN – NRDC – 147

16



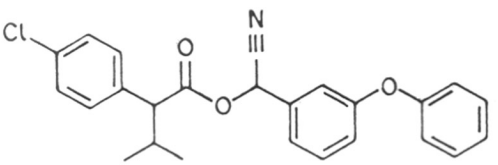
CYPERMETHRIN

17



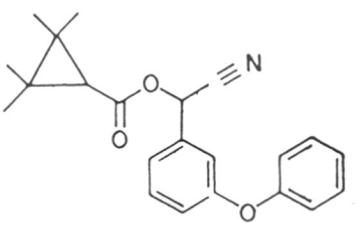
DECAMETHRIN

18



FENVALERATE

19



FENPROPANATE

20

(LD_{50} = 0.0003 μg/house-fly). Decamethrin is also adequately stable[26] for field use.

In addition to the compounds reported above many other pyrethroid esters possessing polyhalogenated vinyl side-chain at C_3 have been prepared. These include difluoro vinyl analogue[26], 2-(trifluoromethyl)-2-halo vinyl analogues[27] etc. In a few cases the double bond in the vinyl side-chain at C_3 of permethrin[28] and other related compounds[29] has been saturated with bromine to get pyrethroid esters with a polyhalogenated saturated side-chain at C_3. In recent patents esters of 2,2-dimethyl-3-(styryl) cyclopropanecarboxylic acids have been synthesised[30,31]. These compounds have been claimed to possess insecticidal and acaricidal activity. Besides pyrethroid esters having alkene side-chain at C_3, some compounds with alkyne side-chain[32] at C_3 have also been prepared.

Acid moieties recently developed i.e. α-(4-chlorophenyl)-isovaleric acid and 2,2,3,3-tetramethylcyclopropane carboxylic acid have no photolabile groups. Therefore, the esters of α-cyano-3-phenoxybenzyl alcohol with the above acids gave fenvalerate[33] (19, Chart III) and fenpropanate[34] (20, Chart III) respectively. These pyrethroids are much more stable to photoirradiation. These compounds are promising insecticides for agricultural use owing to their high potency and sufficient field persistency and are already well established in commerce.

As structural analogues of 2,2,3,3-tetramethylcyclopropanecarboxylic acid, several cyclopropanecarboxylic acids containing spirofused[35] cycloalkane rings have been synthesised. The esters of these acids with α-cyano-3-phenoxybenzyl alcohol have been tested for insecticidal activity.

3) Structure and Activity

The natural pyrethrins and the synthetic pyrethroids group of insecticides are flexible molecules. Their insecticidal action depends on their ability to adopt a conformation in which all the structural features, essential for potency are appropriately oriented with respect to each other and to a complementary receptor. A characteristic feature of the pyrethroids is the sensitivity of their insecticidal action to changes in the substituents at certain important centres, by which either the balance of conformers present, is disturbed or contact of molecule with a receptor is obstructed.

To possess high insecticidal activity, pyrethroids must have a precise steric relationship between an unsaturated centre in the alcohol moiety and gem-dimethyl group or an equivalent substituent in the acid moiety. This generally requires a 1R configuration in the cyclopropanecarboxylic acid[36,37]. Inversion at this optical centre drastically alters the potency without greatly

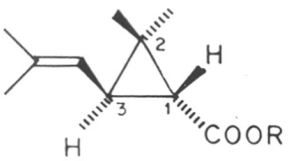
changing the physical properties. Thus (+)-*trans*-(1R, 3R) and (+)-*cis*-(1R, 3S) chrysanthemic acids (Fig. 1, Chart IV) possess 1R-configuration and their esters with suitable alcohols are found to be active insecticides whereas esters of (-)-*trans*-(1S, 3S) and (-)-*cis*-(1S, 3R) chrysanthemic acids (Fig. 2, Chart IV) which possess the 1S configuration are found to be inactive or much less active. In the case of pyrethroids possessing a dihalovinyl side-chain at C_3, the esters with the 1R *cis* absolute configuration are about twice active than the corresponding 1R *trans*[23] isomers.

Structurally, most of the synthetic pyrethroids are esters of 2,2-dimethyl-3-vinyl substituted cyclopropane-1-carboxylic acids with the alcohols like 3-phenoxybenzyl alcohol[15,21] as in permethrin or 5-benzyl-3-furylmethyl alcohol as in resmethrin[15]. Variation of the vinyl substituent at the C_3 position of the cyclopropanecarboxylic acid is possible while maintaining insecticidal activity. Using appropriate Wittig reagents Elliott et al.[38] have synthesised some fifty new esters related to the insecticide bioresmethrin by substituting the isobutenyl side-chain at C_3 with other side-chains[38].

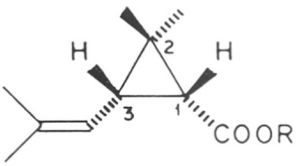
Thus in the acid moiety of the pyrethroids, the side-chain attached at C_3 position of the cyclopropane ring system is an important site where structural changes greatly influence insecticidal activity which in turn

CHART – IV

ACTIVE ISOMERS



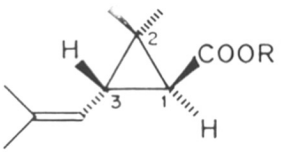
(+) – TRANS – (1R, 3R)
CHRYSANTHEMATE



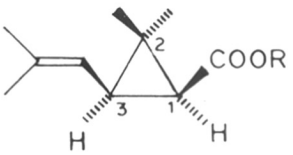
(+) – CIS – (1R, 3S)
CHRYSANTHEMATE

FIG. 1

INACTIVE ISOMERS



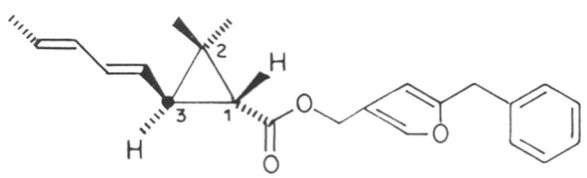
(–) – TRANS – (1S, 3S)
CHRYSANTHEMATE

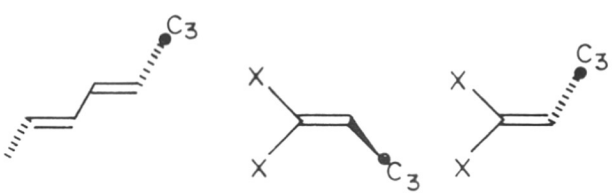


(–) – CIS – (1S, 3R)
CHRYSANTHEMATE

FIG. 2

C_3 SIDE-CHAIN EFFECTIVE FOR KILL





X = Cl or Br

FIG. 3

depends on the nature of the substituents in the side-chain.

Thus a simple modification in the structure of the side-chain at C_3 in bioresmethrin where isobutenyl group is replaced by but-1-enyl group produces still greater activity but retains low mammalian toxicity. Similarly esters with simple vinyl substituent were found to be less active than chrysanthemates but monoethyl vinyl esters were more active. Maximum activity[38] was observed in the case of esters with but-1-enyl side-chain at C_3.

Extremely high insecticidal activity is attained in esters with Z and E butadienyl and pentadienyl substituents[37] (Fig. 3, Chart IV) at C_3, trans and to a smaller extent cis to the 1R carboxylic centre, provided no methyl groups are there at C_3 or C_1 at the cyclopropane ring system. However, Matsui[39] observed that increase of the methyl substitution at C_3 contributes to the greater activity e.g. 2,2,3,3-tetramethylcyclopropanecarboxylic acid esters are found to be more active than the corresponding 3-monoethyl derivative which means presence of an unsaturated side-chain is not a must for the activity of pyrethroids. Further, some esters of 3-dihalovinyl[25,34,40] substituted acids (Fig. 3, Chart IV) were found to be outstandingly potent insecticides and in this class of insecticides, the 1R cis esters are usually more active than the 1R-trans esters. This observation also leads to

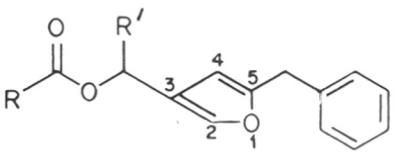
the conclusion that presence of methyl group on the vinyl side-chain at C_3 (as in chrysanthemic acid) is not essential for a pyrethroid to possess insecticidal activity as believed earlier.

The alcoholic constituents are equally sensitive. Esters of 5-benzyl-3-furylmethyl alcohol (1, R' = H, Fig. 4, Chart IV) are usually more active than those of 3-phenoxybenzyl alcohol (2, R' = H, Chart IV) or 5-benzylfurfuryl alcohol (3, R' = H, Chart IV). A methyl substituent (R' = Me) generally depresses the activity. The cyano substituent has little influence on the activity of 2,5-furan derivatives (3, R' = CN), depresses that of 3,5-furan (1,R' = CN) and increases the activity of 3-phenoxybenzyl esters[23,25] (2, R' = CN). Other bulky substituents have depressing effect[22]. Some unsaturation is present in the side-chain of the alcoholic component of all powerful pyrethroids, but again small changes removes activity as depicted in Fig. 5, Chart IV.

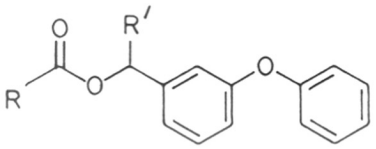
The relation between structure and photostability has already been discussed in the evolution of synthetic pyrethroids. Mammalian toxicity varies with substitution and conformation. Bioresmethrin (11, Chart II), an ester of the same trans substituted cyclopropane acids as in the natural pyrethrins is about sixty times less toxic to mammals than pyrethrin I (1, Chart I). But the toxicity of its cis isomer, cismethrin is similar to pyrethrin I[18]

CHART – IV (Contd.)

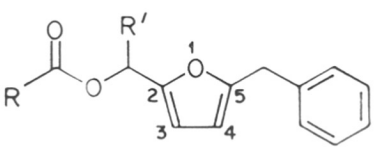
EFFECT OF SUBSTITUENT AT THE α-METHYLENE GROUP IN ALCOHOL MOIETY



1



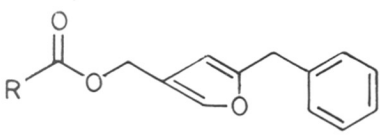
2

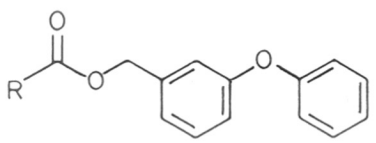


3

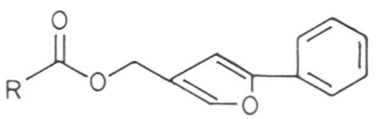
FIG. 4

ACTIVE





INACTIVE



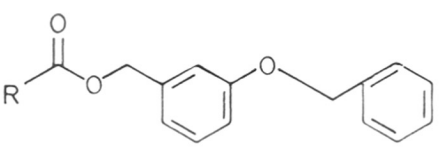


FIG. 5

and is somewhat increased by substituting chlorine for methyl groups. However, cis permethrin with 3-phenoxy-benzyl alcohol has low mammalian toxicity probably because another site at 4' position on the phenoxy ring is available for oxidative detoxification.

4) Synthesis of acid moieties

Numerous synthetic approaches[1,2,3], to acid components of synthetic pyrethroids have been described in literature. Many of these methods lead to dl mixtures of cis and trans cyclopropanecarboxylic acids. Some of the methods which lead to a mixture containing either cis or trans cyclopropanecarboxylic acid in predominance are described below.

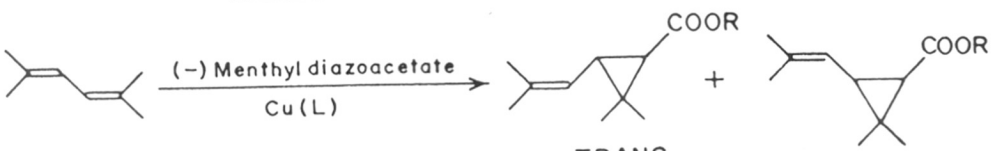
Diazoacetic ester addition

The reaction of tert-butyl diazoacetate[41] with 2,5-dimethyl-2,4-hexadiene afforded trans-chrysanthemic acid in high yield. In the presence of asymmetric copper complexes the reaction of the above diene proceeds enantioselectively[42] both with diazoacetic esters and with diazomalonic esters. The synthesis of trans-chrysanthemic acid was carried out by the addition of (-) menthyl diazoacetate[43] to the above diene, using chiral catalysts with an enantioselectivity of approximately 90% which is shown in Scheme A, Chart V.

CHART – V

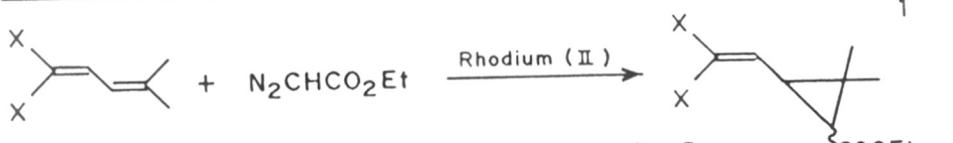
SCHEME A[43]

DIAZOACETIC ESTER ADDITION



TRANS 9 : CIS 1

SCHEME B[44]

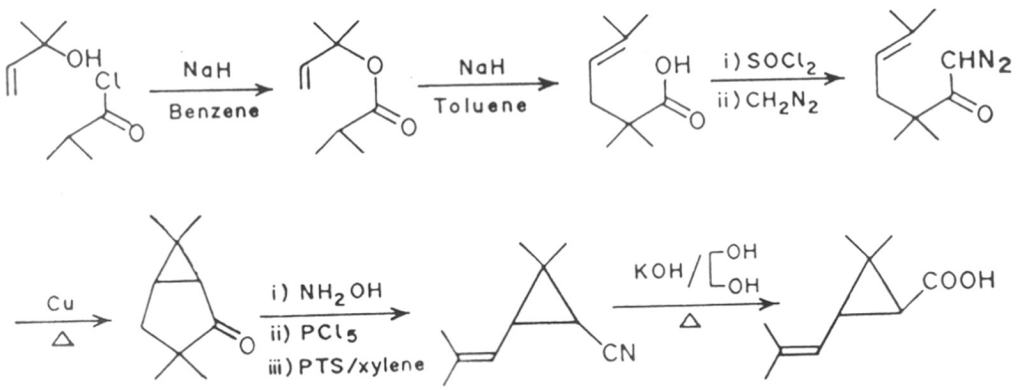


X = Cl, Br

CIS : TRANS 7 : 3

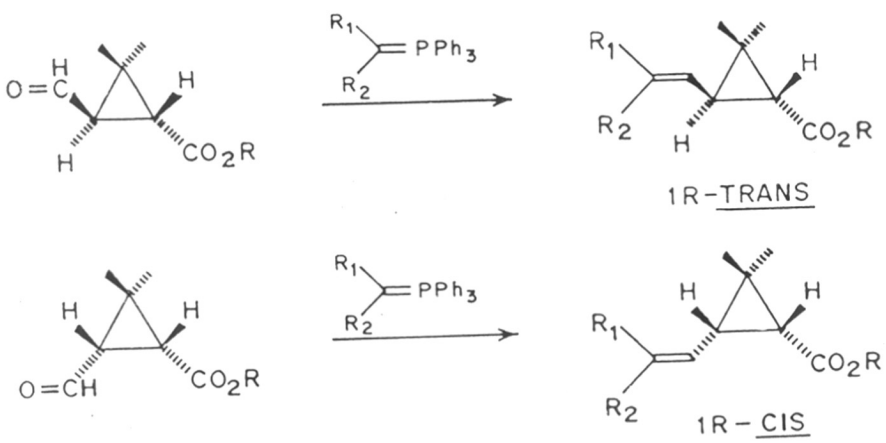
SCHEME C[45]

INTRAMOLECULAR ADDITION



SCHEME D[38]

NRDC – METHOD



David et al.[44] have synthesised cis enriched pyrethroid acid esters by addition of diazoacetic ester to 1,1-dihalo-4-methyl-1,3-pentadienes by using rhodium (II) salts of carboxylic acids as catalysts (Scheme B, Chart V).

Intramolecular addition

S. Julia et al.[45] synthesized a bicyclohexanone. The oxime gave the required chrysanthemate system directly with phosphorus pentachloride as shown in Scheme C, Chart V.

NRDC Method

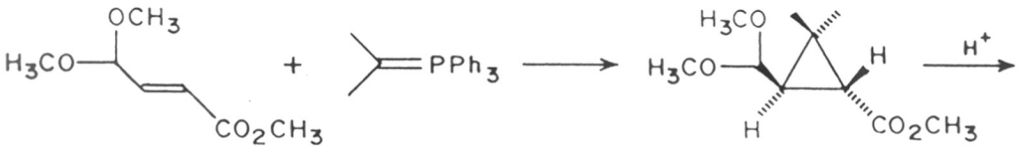
In this method[38] cis and trans 3-formyl-2,2-dimethyl-1-cyclopropanecarboxylic acid and its esters are obtained by ozonolysis of the corresponding chrysanthemates. Wittig reaction and analogous olefination lead directly to the required products with retention of configuration at cyclopropane ring (Scheme D, Chart V).

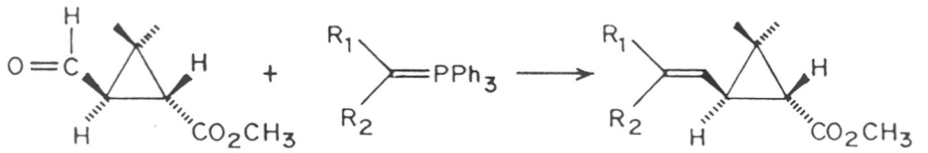
From isomerically pure precursors

Krief et al.[46] have devised several synthetic approaches to trans and cis 3-formyl-2,2-dimethyl-1-cyclopropanecarboxylates. The 1,4-addition of 4,4-dimethoxy-crotonic esters leads stereoselectively to the trans caronaldehyde dimethyl acetal, from which the aldehyde can be generated. Wittig reaction on the aldehyde using appropriate Wittig reagents leads to the trans-chrysanthemic acid or its analogues (Scheme E, Chart VI).

CHART–VI

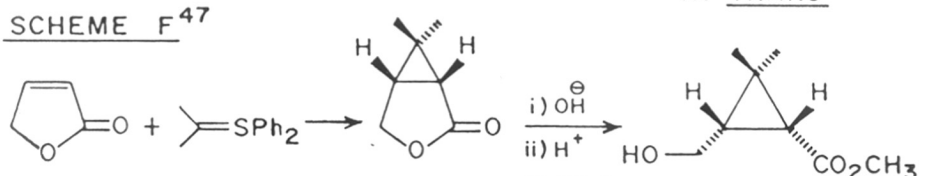
SCHEME E[46]



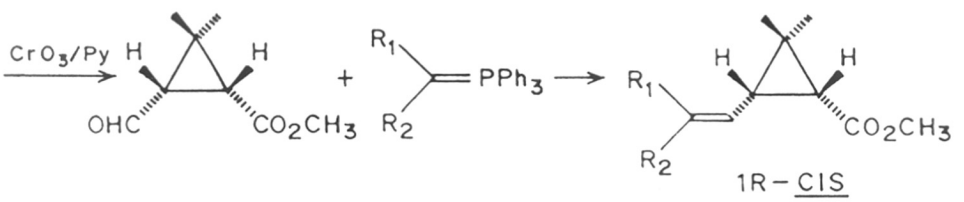


1R–TRANS

SCHEME F[47]



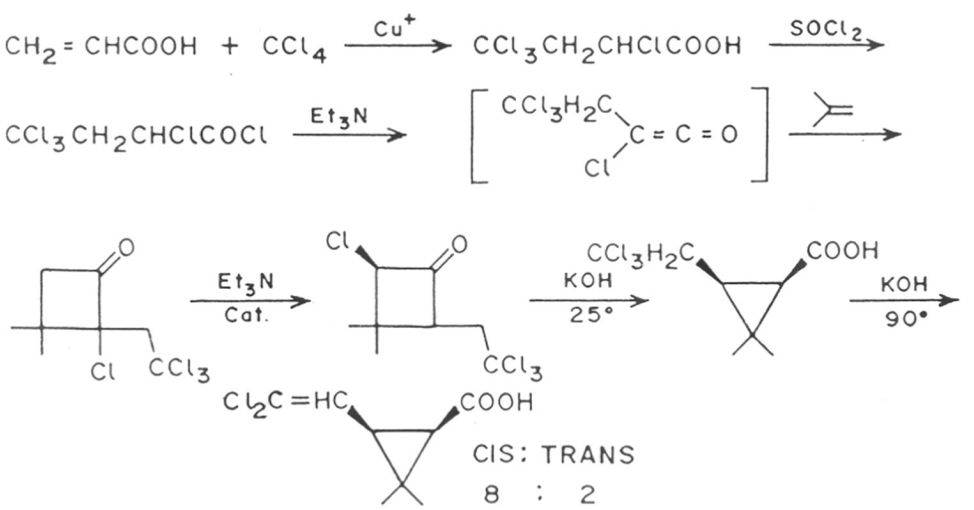
BUTENOLIDE



1R–CIS

SCHEME G[48]

FAVORSKII REARRANGEMENT



In another approach Krief et al.[47] have synthesised the cis-caronaldehyde ester starting from the butenolide. In this method isopropylidenediphenylsulfurane is used for building up the cyclopropane ring by taking advantage of the conjugated double bond in butenolide. This reaction leads stereoselectively to cis substituted cyclopropane derivatives (Scheme F, Chart VI).

Favorskii Rearrangement

Martin et al.[48] have synthesised 2,2-dimethyl-3-(2,2-dichlorovinyl)-cyclopropane-1-carboxylic acid, containing a high proportion of cis-cyclopropane isomer from acrylic acid as shown in(Scheme G Chart VI).

The above route can also be used for the synthesis of enantiomerically pure cis acid by effecting optical resolution[48] of the racemate obtained of the bisulphite adduct of tetrachlorocyclobutanone derivatives.

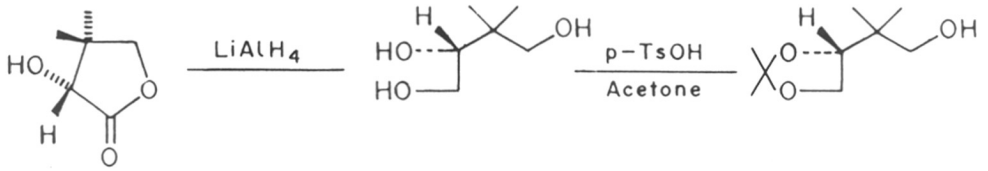
From optically active natural products

Enantiomerically pure pyrethroid acids have been also obtained from optically active natural products like (+) ∝-pinene, (+)-3-carene and (+) and (-) pantolactone.

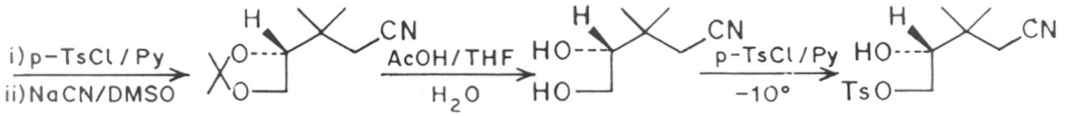
Matsuo et al.[49] have converted the readily available 2R(-) pantolactone into 1S, 3S(-)-trans-chrysanthemic acid and 2S (+) pantolactone into 1R, 3R (+)-trans chrysanthemic acid as shown in(Scheme H Chart VII).

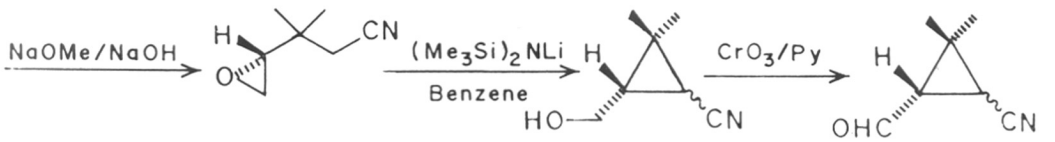
CHART- VII

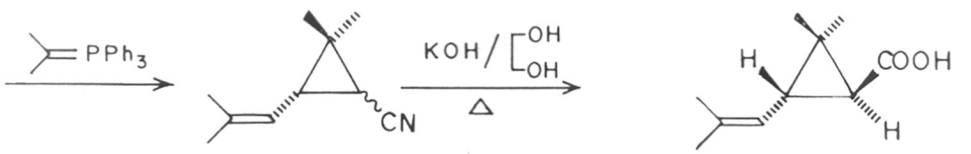
SCHEME H[49]



2R (−)-PANTOLACTONE

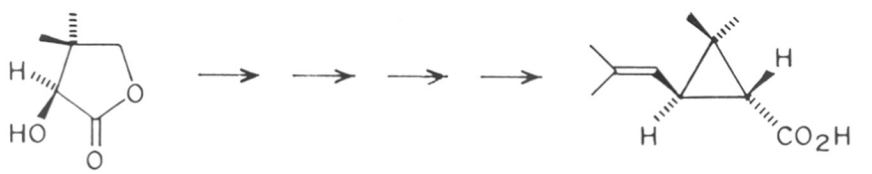






(−)-TRANS-CHRYSANTHEMIC ACID

SIMILARLY



2S (+)-PANTOLACTONE

(+)-TRANS-CHRYSANTHEMIC ACID

Synthesis of 2,2-dimethyl-3-(styryl)cyclopropane-1 carboxylates

Recently, synthesis of esters of 2,2-dimethyl-3(styryl) cyclopropane-1-carboxylate has been achieved starting from acyclic intermediates. Some of the approaches are described below.

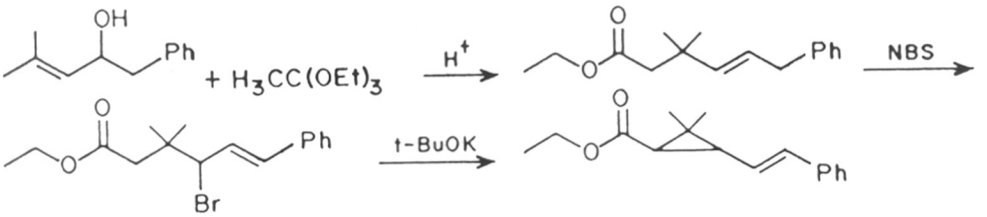
Condensation of substituted allylic alcohol and triethyl orthoacetate at 140° in presence of phosphoric acid or phenol gave the Y,δ-unsaturated esters. The unsaturated esters on bromination with N-bromosuccinimide and subsequent cyclization with base gave the styrylcyclopropane carboxylates[50] as shown in (Scheme I, Chart VIII).

The esters of 2,2-dimethyl-3(styryl)cyclopropane-1-carboxylate have also been prepared by Wittig reaction in its various forms[30,51,52] on ethyl-3-formyl-2,2-dimethyl-1-carboxylate (Scheme J, Chart VIII).

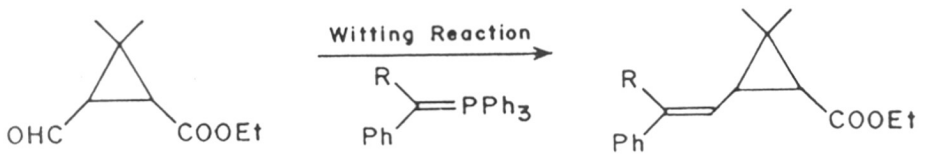
In another approach[53] for the synthesis of these compounds Claisen condensation of p-substituted acetophenone with isobutaraldehyde in presence of a base was effected to afford a mixture of conjugated and non-conjugated ketones. The mixture as such on treatment with phosphorous pentachloride afforded the conjugated diene, which on condensation with ethyl diazoacetate gave the α-halo(styryl)cyclopropanecarboxylate (Scheme K, Chart VIII).

CHART-VIII

SCHEME I[50]

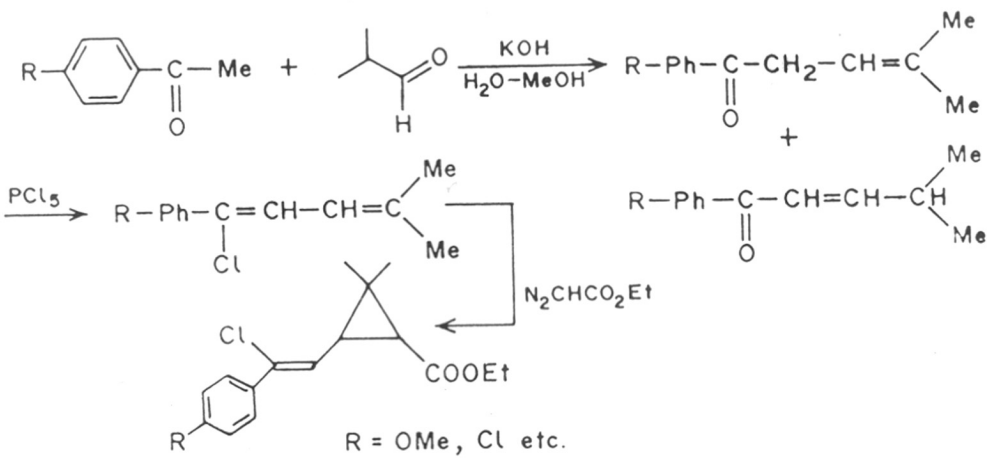


SCHEME J[30,51,52]



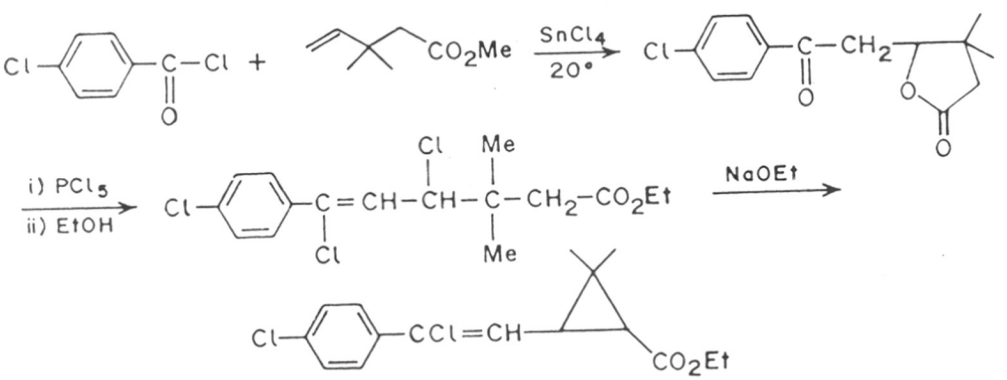
R = H, or Cl, or alkyl

SCHEME K[53]



R = OMe, Cl etc.

SCHEME L[54]



Prins reaction on methyl-3,3-dimethyl-pent-4-enoate using p-substituted benzoyl chloride[54] in presence of stannic chloride afforded the butyro-lactone which on treatment with phosphorous pentachloride followed by base treatment gave the 2,2-dimethyl-3(styryl)-cyclopropane-1-carboxylate. (Scheme L, Chart VIII).

In most of the above methods for styrylcyclopropane-carboxylate, cyclopropane ring is built up from an appropriate acyclic substrate leading to a mixture of cis and trans cyclopropane systems. In Chapters II and IV of this thesis, the synthesis of optically active pyrethroids has been described starting from abundantly available (+)-3-carene.

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CHAPTER – II

SYNTHESIS OF 1R – CIS – PYRETHROIDS FROM (+) – 3 – CARENE

SUMMARY

The trans caranediol 2 obtainable from (+)-3-carene 1, on oxidation with Jones chromic acid reagent gave the keto acid 3 (R=H) which on esterification ($MeOH/H^+$) afforded the keto ester 3 ($R=CH_3$). Treatment of the keto ester 3 ($R=CH_3$) with ethylene glycol and p-toluene sulphonic acid (PTS) gave the ketal ester 4. Grignard reaction on ketal ester 4, using methylmagnesium iodide gave a liquid ketal alcohol 5, which on deketalisation and dehydration with PTS furnished a mixture of two isomeric unsaturated ketones 6 and 7. These were separated by chromatography. Treatment of 6 with p-tolylmagnesium bromide afforded a mixture of diastereomeric alcohols 8. Potassium permanganate oxidation of diastereomeric alcohols 8 gave a mixture of diastereomeric hydroxy acids 9 (R'=H) along with the keto-diol 10. The acid 9 (R'=H) an esterification with an ethereal solution of diazomethane afforded a mixture of diastereomeric hydroxy methyl esters 9 ($R'=CH_3$). Dehydration of the methyl esters 9 ($R'=CH_3$) with $POCl_3$/Pyridine gave a mixture of two isomeric unsaturated esters 11 and 12. These were separated by chromatography. Unsaturated ester 11 was converted into the corresponding 3-phenoxybenzyl ester 13 by trans-esterification with 3-phenoxybenzyl alcohol.

By following analogous procedures 3-phenoxybenzyl esters 20, 27 and 33 have also been synthesised.

INTRODUCTION

"Synthetic Pyrethroids" which bear a close structural resemblance to natural pyrethrins and cinerins are increasingly becoming important as ideal Pest Control Agents. These pyrethroids belong to an almost ideal group of modern insecticides due to their high insecticidal activity, low mammalian toxicity and rapid biodegradability.[1,2] They are also superior to natural pyrethrins[3,4] in having higher photostability[5] and therefore applicable for agricultural use[6]. A number of synthetic pyrethroids[7,8] have been prepared and used with sucess during the last few years in UK, USA, Japan and other advanced countries. An important member of this group in commercial use is permethrin[9] (NRDC 143).

The natural pyrethrins and cinerins, which are found to be quite active against insects[10,11,12] are the esters of (+) trans-chrysanthemic acid and (+) trans-pyrethric acid with the alcohols like pyrethrolone and cinerelone[10]. These acids possess 1R trans configuration at the site bearing the carboxylic group. Much of the efforts were, therefore made for developing the methods for 1R trans-chrysanthemic acid, from naturally occurring compounds, containing a suitably substituted cyclopropane ring system and the required configuration. The absolute configuration

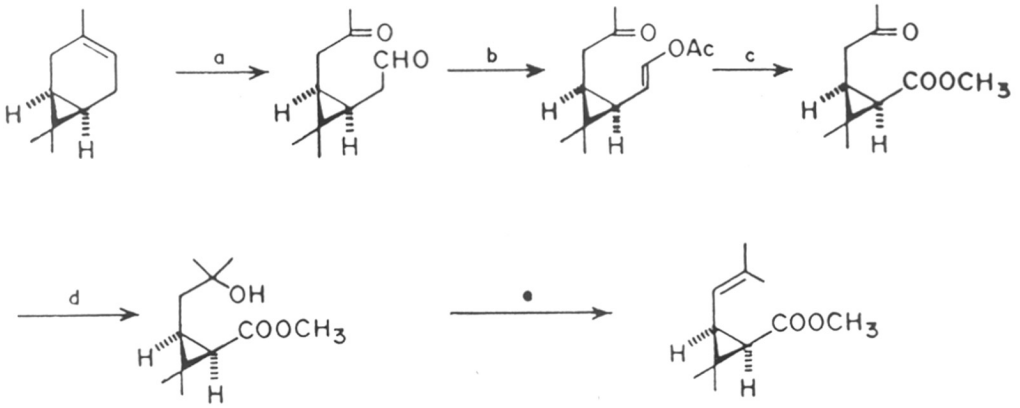
of (+)-3-carene 1 has been established as 1S, 6R[13]. The absolute configuration of (-) cis-chrysanthemic acid is 1S, 3R and that of (+) trans-chrysanthemic acid is 1R, 3R[14]. This resemblance in their configuration has been utilized by many workers[15-18] for the synthesis of 1R trans-chrysanthemic acid via the (-) 1S cis-chrysanthemic acid by epimerisation at C_1 centre, starting from (+)-3-carene 1, abundant in turpentine oil.

The insecticidal activity of pyrethroid esters depends, to a significant extent on the absolute configuration of the asymmetric carbon at C_1 of the cyclopropane system, which bears the ester function. Thus, the esters with absolute configuration 1R, irrespective of whether the cyclopropane ring is having a cis or a trans geometry, are active[19-22]. Whereas the corresponding 1S-isomers are either much less active or inactive. However, much attention was not given for the conversion of (+)-3-carene 1 into 1R (+) cis-chrysanthemic acid, the esters of which possess insecticidal activity. There are only two references[15,23] available in the literature for the conversion of (+)-3-carene 1 into 1R(+) cis-chrysanthemic acid. Matsui et al. synthesised selectively, the 1R(+) cis-chrysanthemic acid from (+)-3-carene 1 as shown in scheme I (Chart I).

In the case of highly potent pyrethroids like permethrin, cypermethrin and decamethrin, it has been

CHART - I

SCHEME I[15]



a. O_3

b. $Ac_2O/AcONa$

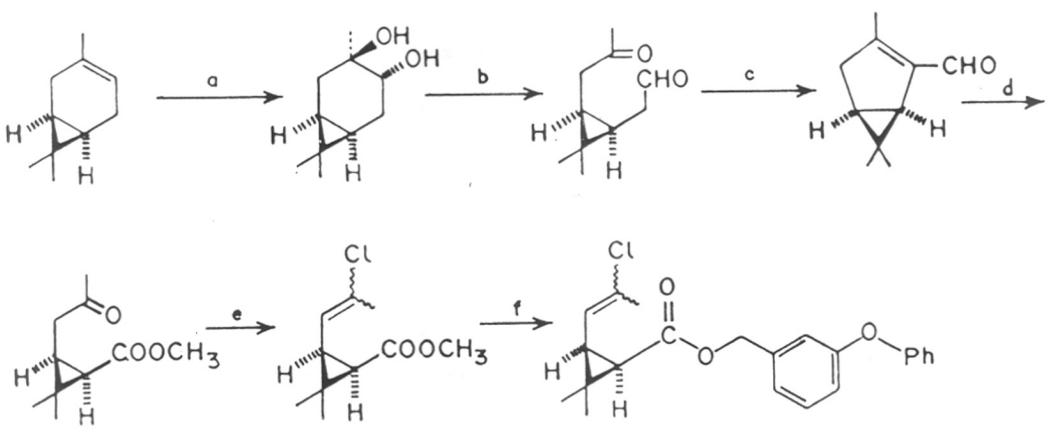
c.) i) O_3
ii) $KMnO_4$
iii) CH_2N_2

(+)- CIS - CHRYSANTHEMATE

d. Reverse Grignard with CH_3MgI

e. $POCl_3$ / Py or PTS

SCHEME II[25]



a. $HCOOH/H_2O_2$

b. $NaIO_4$

c. Piperidine/CH_3COOH

d. i) O_3
ii) Oxidation
iii) CH_2N_2

e. PCl_5

f. i) MeOH / KOH
ii) m - Phenoxybenzyl bromide / Triethylamine

observed that the 1R *cis* isomers are usually about twice as active[24] as the 1R *trans* pyrethroids.

In view of the above observations it was felt desirable to synthesise some 1R *cis* pyrethroids from (+)-3-carene 1. In our laboratory, a new synthetic pyrethroid[25] called "Indothrin" viz. 3-phenoxybenzyl 1R *cis*-2,2-dimethyl-3 (2-chloroprop-1-enyl) cyclopropane carboxylate (as a mixture of E and Z isomers) has been synthesised (Scheme II, Chart I) and found to possess almost similar type of insecticidal activity as permethrin. Also, 3-phenoxybenzyl 1R *cis*-2,2-dimethyl-3(2-cyanoprop-1-enyl) cyclopropanecarboxylate and α-cyano-3-phenoxybenzyl 1R *cis* 2,2-dimethyl-3(2-chloroprop-1-enyl)cyclopropane-carboxylate have been synthesised[26] and found to be almost as active as Indothrin. All these compounds have been synthesised starting from (+)-3-carene 1, a cheap, abundent, indigenous byproduct from pine oil (pinus longifolia).

Recently, in our laboratory Mane et al., synthesised selectively the 1R(+)-*cis*-chrysanthemic acid[23,27]. They have also synthesised[28,29] 1R (-) *cis*-2,2-dimethyl-3 (2-phenylprop-1-enyl)cyclopropanecarboxylate from (+)-3-carene 1.

In recent patents[30-32], esters of some 2,2-dimethyl -3(styryl)cyclopropanecarboxylic acid as dl-mixtures of both *cis* and *trans* isomers have been prepared and found to

possess good insecticidal and acaricidal activity.

In continuation of our efforts for the synthesis of better photostable pyrethroids from(+)-3-carene 1, we have now synthesised[33,34] some optically active 1R cis pyrethroids possessing p-substituted phenyl/cyclohexyl prop-1-enyl side chain at C_3, viz.

i) 3-Phenoxybenzyl 1R-cis-2,2-dimethyl-3-(2-p-tolylprop-1-enyl)cyclopropanecarboxylate.

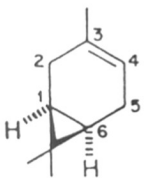
ii) 3-Phenoxybenzyl 1R-cis-2,2-dimethyl-3-(2-p-anisylprop-1-enyl)cyclopropanecarboxylate.

iii) 3-Phenoxybenzyl 1R-cis-2,2-dimethyl-3-(2-p-chlorophenylprop-1-enyl)cyclopropanecarboxylate.

and iv) 3-Phenoxybenzyl 1R-cis-2,2-dimethyl-3-(2-cyclohexylprop-1-enyl)cyclopropanecarboxylate.

All the above esters were tested for insecticidal activity and were found active.

CHART – II



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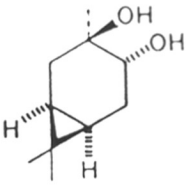

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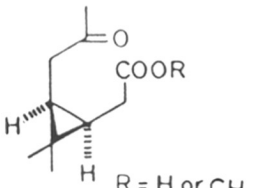

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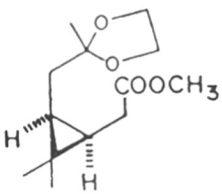

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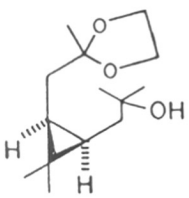

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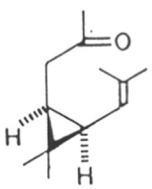

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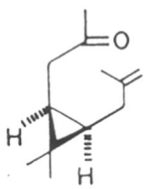

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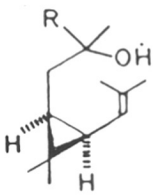
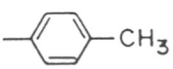
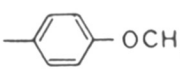
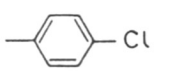


8 R = 

15 R = 

22 R = 

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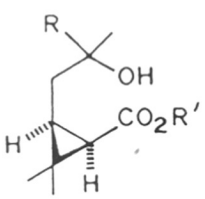

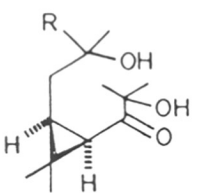

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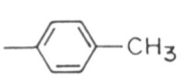
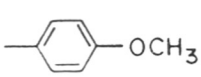
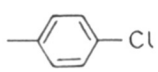
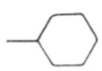
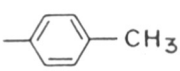
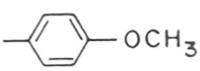
9		H or CH_3
16		H or CH_3
23		H or CH_3
29		H or CH_3

10 R = 

17 R = 

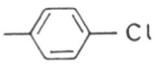
24 R = 

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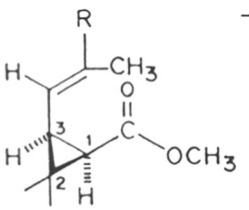
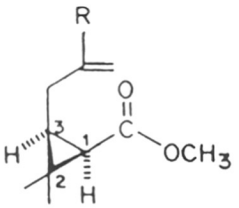
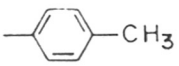
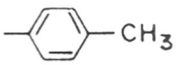
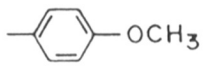
CHART – III

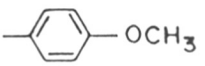


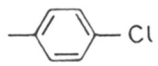


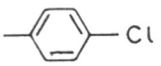
11 R = 

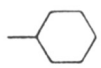
12 R = 

18 R = 

19 R = 

25 R = 

26 R = 

31 R = 

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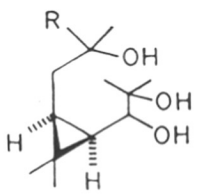
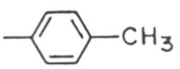
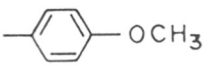
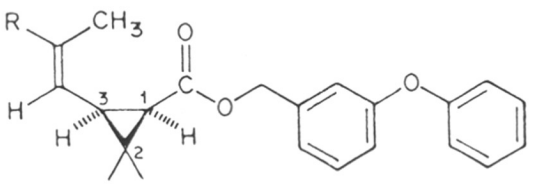
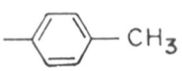
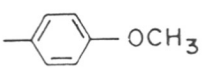


14 R = 

21 R = 



13 R = 

20 R = 

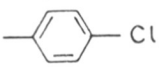
27 R = 

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CHART - IV

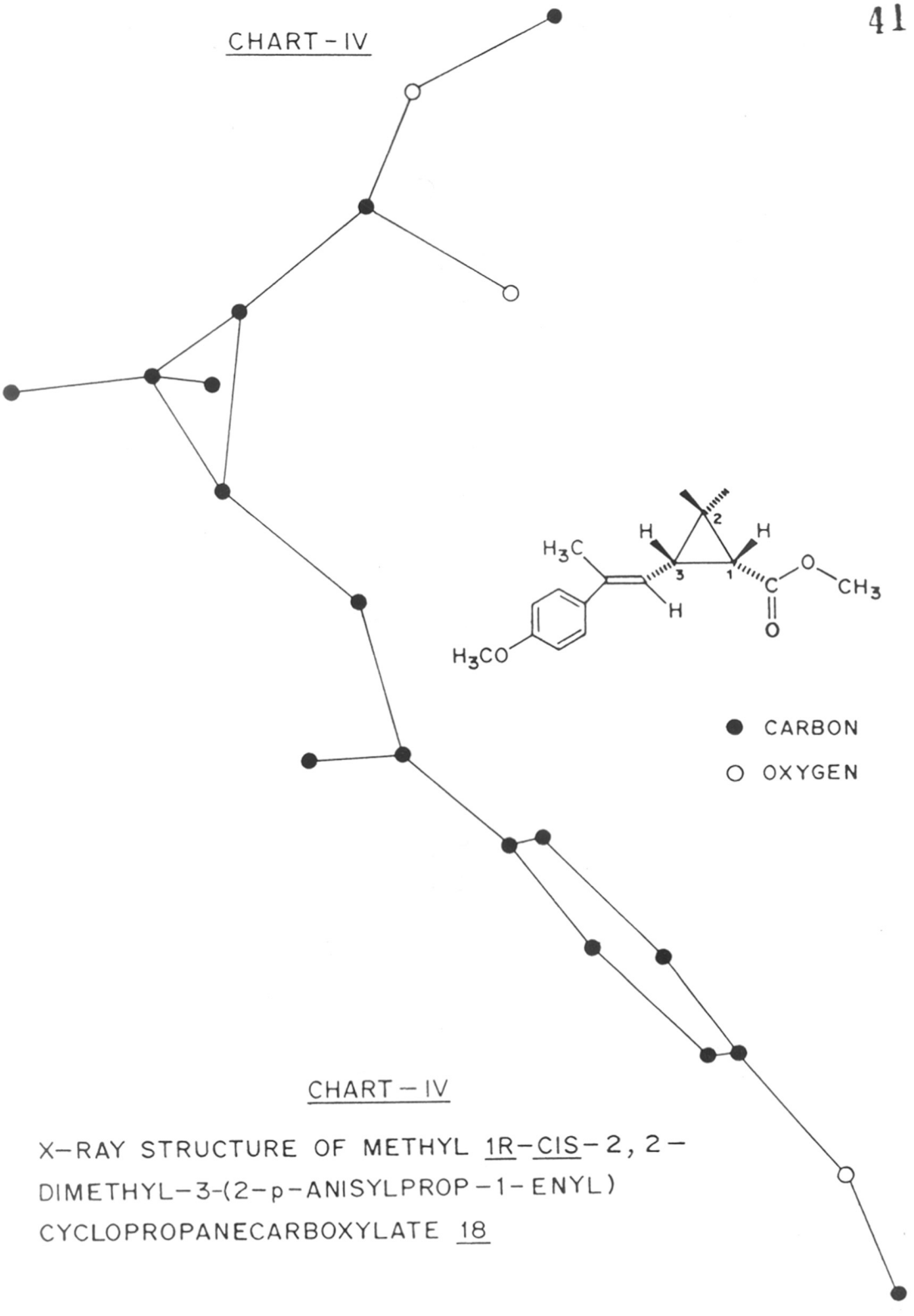

CHART – IV

X-RAY STRUCTURE OF METHYL 1R-CIS-2,2-DIMETHYL-3-(2-p-ANISYLPROP-1-ENYL) CYCLOPROPANECARBOXYLATE 18

PRESENT WORK

(+)-3-Carene 1, on treatment with performic acid was converted to the formyloxy hydroxy carane which on hydrolysis, gave the known[18] 3β,4α-caranediol 2 in 45% yield; m.p.82-83° (pet.ether) $C_{10}H_{18}O_2$, M^+ 170. It showed IR bands at 3448 (OH), 1058 (-C-O-) and PMR signals at 0.70 (2H, m, cyclopropane protons), 0.97 (6H, s, gem-dimethyl on cyclopropane), 1.17 (3H, s, $-CH_3$ at C_3), 1.73 to 2.23 (4H, m, $-CH_2$ protons), 3.27 (1H, q, proton at C_4) and 3.63 (2H, m, OH protons). Jones chromic acid oxidation of the diol 2 at 0° gave the keto carboxylic acid 3, (R=H) which was converted into its methyl ester 3 ($R=CH_3$)[16-18] by methanol and sulphuric acid in almost quantitative yield. The ester 3 ($R=CH_3$) $C_{11}H_{18}O_3$, M^+ 198, showed IR bands at 1739, 1150 (ester); 1709 (>C=O) and PMR signals at 0.67, 1.00 (1H each, m, protons at C_1 and C_3 of cyclopropane), 0.9, 1.13 (3H each, s each, gem dimethyl on cyclopropane), 2.10 (3H, s, $-\overset{O}{\overset{\|}{C}}CH_3$), 2.18, 2.30 (2H each, d each, J = 7 Hz, methylene protons adjacent to carbonyl group of ketone and ester) and 3.60 (3H, s, ester methyl).

The ester 3, ($R=CH_3$) was converted into its ethylene ketal ester 4 in 95% yield by treating it with ethylene glycol and catalytic amount of paratoluenesulphonic acid in benzene. The ketal ester 4, $C_{13}H_{22}O_4$, M^+ 242 showed

IR bands at 1739, 1163 (ester) and PMR signals at 0.72 (2H, m, cyclopropane protons at C_1 and C_3), 0.87, 1.07 (3H each, s each, gem-dimethyl on cyclopropane), 1.23 (3H, s, methyl attached to carbon bearing the ketal function), 1.47 (2H, d, J = 6 Hz, methylene α to ketal function), 2.17 (2H, d, J = 9 Hz methylene α to ester), 3.60 (3H, s, ester methyl) and 3.82 (4H, s, ketal methylene protons).

Grignard reaction on ketal ester 4 using excess of methylmagnesium iodide (3 moles) afforded in 90% yield the liquid ketal alcohol 5, $C_{14}H_{26}O_3$, M^+ 242. It showed IR bands at 3571, 1050 (-OH) and PMR signals at 0.57 (2H, m, cyclopropane protons), 0.88, 1.08 (3H each, s each, gem dimethyl on cyclopropane), 1.18 (6H, s, methyls of hydroxy isopropyl), 1.28 (3H, s, methyl on carbon bearing ketal function), 1.48 (4H, d, J = 6 Hz, $-CH_2$ protons at C_1 and C_3), 1.88 (1H, s, exchangeable with D_2O, OH proton) and 3.88 (4H, s, methylene protons of the ketal).

Dehydration and deketalisation of 5 was achieved in one step by treating it with PTS in refluxing benzene to afford a mixture of two liquid unsaturated ketones (double bond isomers) 6 and 7 in 73% yield, in which the former predominated. The ketones 6 and 7 were separated by chromatography over silica gel (1:15) impregnated with 10% silver nitrate and isolated in the TLC pure state. The earlier fractions eluted with pet.ether, pet.ether + 10% benzene gave a TLC pure liquid which was further purified

by distillation to afford pure unsaturated ketone 6, $C_{12}H_{20}O$, M^+ 180. It showed the following spectral properties, IR bands at 1710 (>C=O); PMR signals at 0.92, 1.13 (3H each, s, gem dimethyl on cyclopropane), 1.00 to 1.33 (2H, m, cyclopropane protons), 1.68, 1.73 (3H each, s, vinyl methyls), 2.07 (3H, s, $-COCH_3$), 2.28 (2H, d, J = 6.5 Hz, $-CH_2$ α to >C=O) and 4.80 (1H, d, J = 8 Hz, olefinic proton).

The isomeric ketone, eluted with pet.ether + benzene (1:1) and benzene (TLC single spot) was purified by distillation and identified as 7, $C_{12}H_{20}O$, M^+ 180, by spectral data showing IR bands at 1709 (>C=O), 1645, 885 (>C=CH_2) and PMR signals at 0.63 (1H, m, one of the cyclopropane proton), 0.87, 1.12 (3H each, s each, gem-dimethyl on cyclopropane), 1.23 (1H, s, another cyclopropane proton), 1.72 (3H, s, vinyl methyl), 1.87 (2H, d, J = 6 Hz, CH_2 allylic to double bond), 2.05 (3H, s, $-COCH_3$), 2.25 (2H, d, J = 7 Hz, CH_2 α to >C=O) and 4.67 (2H, s, olefinic protons of >C=CH_2).

Grignard reaction using p-tolylmagnesium bromide (1.3 mole) on the ketone 6 gave a mixture of diastereomeric alcohols 8 in 80.8% yield, $C_{19}H_{28}O$. It showed IR bands at 3448 (OH), 1504, 837 (aromatic) and PMR signals at 0.53 (1H, m, cyclopropane proton at C_3), 0.73, 0.83, 0.95, 1.03 (6H, all s, cyclopropane methyls of both the diastereomers), 1.23 (2H, d, J = 8 Hz $-CH_2$ protons), 1.46 (3H, s, methyl on carbon bearing hydroxy and p-tolyl), 1.66 (7H, br, m, vinyl methyls of diastereomers and allylic cyclopropane

proton), 2.30 (3H, s, methyl attached to phenyl), 4.73 (1H, br, m, olefinic proton) and 6.91, 7.15 (2H each, d each, J = 8 Hz, aromatic protons).

Oxidation of 8 with potassium permanganate in acetone-acetic acid-water mixture[35] afforded a mixture of two products, separated into acidic and neutral parts by aqueous sodium carbonate. The acidic part 9 (R'= H) was esterified with an ethereal solution of diazomethane and the resulting mixture of diastereomeric esters further purified by distillation to give hydroxy ester 9 (R' = CH_3), $C_{17}H_{24}O_3$. It showed IR bands at 3636 (OH), 1724, 1176 (ester), 1515, 819 (aromatic); and PMR signals at 0.93, 1.00, 1.06, 1.11 (6H, all s, cyclopropane methyls of both the diastereomers), 1.25 (2H, m, cyclopropane protons), 1.48 (3H, s, methyl on carbon bearing hydroxy and p-tolyl), 1.83 (1H, s, exchangeable with D_2O, OH proton), 2.03 (2H, br, m, CH_2- protons), 2.31 (3H, s, methyl attached to phenyl), 3.46, 3.56 (3H, s each, ester methyls of diastereomers) and 6.96, 7.20 (2H each, d each, J = 8 Hz, aromatic protons).

The neutral part was purified by chromatography and obtained as a thick liquid and was identified as keto-diol 10, $C_{19}H_{28}O_3$; IR bands at 3571 (OH), 1695 (>C=O), 1515, 816 (aromatic); PMR signals at 0.83, 1.00, 1.10, 1.13, 1.16, 1.23, 1.30 (12H, all s, cyclopropane methyls and hydroxy isopropyl methyls of both diastereomers), 1.45

(3H, s, methyl on carbon bearing hydroxy and p-tolyl), 1.76 (3H, m, CH_2-protons and C_1 cyclopropane proton), 2.06 (1H, d, J = 7 Hz, C_3 cyclopropane proton), 2.28 (3H, s, methyl attached to phenyl) and 6.86, 7.16 (2H each, d each, J = 8 Hz, aromatic protons).

Dehydration of hydroxy ester 9 ($R'=CH_3$) with $POCl_3$/ pyridine afforded mixture of two unsaturated esters (double bond isomers) 11 and 12 which were separated by chromatography over silica gel (1:10) impregnated with 10% silver nitrate. The less polar ester eluted with 20% benzene in pet.ether afforded a solid, m.p.64-65°(ethanol), identified as 11, $C_{17}H_{22}O_2$, M^+ 258 by spectral data. It showed IR bands at 1724 (ester >C=O), 1613, 813 (>C=C<H), 1499 (aromatic); PMR ($CDCl_3$, 90 MHz) signals at 1.28, 1.33 (3H each, s each, gem-dimethyl on cyclopropane), centered at 1.78 (1H, d, J = 9 Hz, cyclopropane proton at C_1) and centered at 2.07 (1H, t, J = 9 Hz, cyclopropane proton at C_3), 2.12 (3H, s, vinyl methyl), 2.34 (3H, s methyl attached to phenyl), 3.67 (3H, s, ester methyl), 6.08 (1H, d, J = 9 Hz, olefinic proton) and 7.12, 7.34 (2H each, d each, J = 9 Hz, aromatic protons). The unsaturated ester 11 has been assigned the E configuration on the basis of the value of chemical shift of the olefinic proton (6.08δ), which is in close agreement with the calculated value[40] (6.07δ). It is interesting to note that by this method only one pure geometric isomer is obtained.

The polar compound 12 was eluted later but not characterised.

The ester 11 on trans-esterification[36-38] with 3-phenoxybenzyl alcohol in presence of butyl titanate afforded the 3-phenoxybenzyl ester 13, $C_{29}H_{30}O_3$, M^+ 426, purified by chromatography. It showed IR bands at 1724 (ester >C=O), 1585, 813, 784 (aromatic); PMR ($CDCl_3$; 90 MHz) signals at 1.23, 1.27 (3H each, s each, gem dimethyl on cyclopropane), 1.82(1H, d, J = 9 Hz, cyclopropane proton at C_1), 2.04(3H, s, vinyl methyl), 2.06 (1H, t, J = 9 Hz, cyclopropane proton at C_3), 2.31 (3H, s, methyl attached to phenyl), 5.06 (2H, s, benzylic methylene protons), 6.05 (1H, d, J = 9 Hz, olefinic proton) and 7.15 (13H, m, aromatic protons).

The keto-diol 10 on sodium borohydride reduction gave the triol 14, as a thick liquid, $C_{19}H_{30}O_3$. It showed the following spectral properties, IR bands at 350 (OH), 1515, 816, 752 (aromatic) and PMR signals at 0.80, 0.83, 0.93, 1.00, 1.10, 1.23 (12H, all s, cyclopropane methyls and methyls of hydroxy isopropyl of both the diastereomers), 1.46 (3H, s, methyl attached to carbon bearing hydroxy and p-tolyl groups), 2.26 (3H, s, methyl attached to phenyl), 3.06 (3H, br, m, exchangeable with D_2O, OH protons), 3.31 (1H, d, J = 8 Hz, $-O-\overset{|}{C}-H$, at C_1) and 6.83, 7.08 (2H each, d each, J = 8 Hz, aromatic protons).

Jones chromic acid oxidation of the triol 14, gave a hydroxy acid 9 (R' = H) along with other products. The hydroxy acid 9, (R' = H) was converted into its methyl ester by an ethereal solution of diazomethane and identified as 9 (R' = CH_3), $C_{17}H_{24}O_3$ by spectral data. The IR and PMR spectra of 9 (R' = CH_3) were superimposable with those described earlier in this chapter.

The ketone 6, when subjected to Grignard reaction using p-anisylmagnesium bromide (1.3 mole) afforded the liquid alcohol 15 in 90% yield, $C_{19}H_{28}O_2$. It showed IR bands at 3646 (OH), 1613, 1508, 826 (aromatic) and PMR signals at 0.73, 0.83, 0.96, 1.05 (6H, all s, cyclopropane methyls of both the diastereomers), 1.20 (2H, d, J = 7.8 Hz, CH_2-protons), 1.46 (3H, s, methyl on carbon bearing hydroxy and p-anisyl group), 1.66 (7H, br, m, vinyl methyls of both diastereomers and C_1 cyclopropane proton), 1.95 (1H, s, exchangeable with D_2O, OH proton), 3.73 (3H, s, methoxy attached to phenyl), 4.76 (1H, br, m, olefinic proton) and 6.66, 7.18 (2H each, d each, J = 8 Hz, aromatic protons).

Oxidation of the alcohol 15, with potassium permanganate[39] in dry acetone, with catalytic amount of anhydrous potassium carbonate, afforded mainly a mixture of two products, separated into acidic and neutral parts. The acidic part 16 (R' = H) was converted into its methyl ester 16 (R' = CH_3), $C_{17}H_{24}O_4$ by an ethereal solution of diazomethane. It showed IR bands at 3546 (OH), 1724,

1163 (ester), 1608, 826 (aromatic) and PMR signals at 0.96, 1.03, 1.13 (6H, all s, cyclopropane methyls of both diastereomers), 1.26 (1H, m, C_3 cyclopropane proton), 1.50 (3H, s, methyl on carbon bearing hydroxy and p-anisyl), 2.00 (3H, m, CH_2-protons and C_1 cyclopropane proton), 3.48, 3.56 (3H, each s, ester methyls of diastereomers), 3.76 (3H, s, methoxy attached to phenyl), 6.73 (2H, d, J = 9 Hz, aromatic protons) and 7.23 (2H, m, aromatic protons).

The neutral part was purified by chromatography to give a thick liquid, identified as keto-diol 17, $C_{19}H_{28}O_4$, by spectral data. IR: 3646 (OH), 1669 (>C=O), 1610, 1504, 826 (aromatic); PMR signals at 0.83, 1.01, 1.13, 1.18, 1.23, 1.31 (12H, all s, cyclopropane methyls and hydroxy isopropyl methyls of both diastereomers), 1.46 (3H, s, methyl attached to carbon bearing hydroxy and p-anisyl), 1.78 (2H, m, cyclopropane protons), 2.08 (2H, m, CH_2-protons), 3.70 (3H, s, methoxy attached to phenyl) and 6.63, 7.10 (2H each, m each, aromatic protons).

Dehydration of the ester 16 (R' = CH_3) using $POCl_3$/ pyridine gave a mixture of two unsaturated esters 18 and 19 (double bond isomers), which were separated by chromatography over silica gel impregnated with 20% silver nitrate. The less polar ester 18, $C_{17}H_{22}O_2$ eluted with pet.ether gave a solid m.p.61° (ethanol), M^+ 274. It displayed the following spectral properties; IR bands at 1742, 1163 (ester), 1613, 830 (>C=C<^{H}), 1515, 785 (aromatic),

PMR ($CDCl_3$; 90 MHz) signals at 1.28, 1.33 (3H each, s each, gem-dimethyl on cyclopropane), 1.78 (1H, d, J = 9 Hz, cyclopropane proton at C_1), 2.07 (1H, t, J = 9 Hz, cyclopropane proton at C_3), 2.10 (3H, s, vinyl methyl), 3.67 (3H, s, ester methyl), 3.82 (3H, s, methoxy attached to phenyl), 6.05 (1H, d, J = 9 Hz, olefinic proton) and 6.92, 7.44 (2H each, m each, aromatic protons). The E-geometry for the double bond in the ester 18 has been assigned on the basis of chemical shift (6.05 δ) of olefinic proton which is in close agreement with calculated value[40] (6.07 δ).

The fractions eluted with 10% benzene in pet.ether gave the TLC pure isomeric liquid ester 19, $C_{17}H_{22}O_3$. It showed IR bands at 1724 (ester), 1669, 885 ($>C=CH_2$), 1600, 1504, 833 (aromatic) and PMR ($CDCl_3$; 90 MHz) signals at 1.18, 1.26 (3H each, s each, gem-dimethyl on cyclopropane), 1.42 (1H, dd, J_1 = 4 Hz, J_2 = 12 Hz, cyclopropane proton at C_3), 1.65 (1H, d, J = 10 Hz, cyclopropane proton at C_1), 2.84 (2H, d, J = 7 Hz, CH_2-protons), 3.66 (3H, s, ester methyl), 3.83 (3H, s, methoxy attached to phenyl), 5.16 (2H, m, $>C=CH_2$ protons) and 6.92, 7.43 (2H each, m each, aromatic protons).

However, ester 16 (R' = CH_3) on dehydration with PTS in refluxing benzene, gave the E and Z isomers of 18 as indicated by PMR doublets at 5.73 δ and 5.50 δ with J = 8 Hz for olefinic protons.

The ester 18 was converted to the corresponding 3-phenoxybenzyl ester by trans-esterification with 3-phenoxybenzyl alcohol and identified as 20, $C_{29}H_{30}O_4$ by spectral data. It showed IR bands at 1730 (ester), 1590, 826 (aromatic) and PMR ($CDCl_3$; 90 MHz) signals at 1.21, 1.31 (3H each, s each, gem-dimethyl on cyclopropane), 1.82 (1H, d, J = 9 Hz, cyclopropane proton at C_1), 2.06 (1H, t, J = 9 Hz, cyclopropane proton at C_3), 2.08 (3H, s, vinyl methyl), 3.80 (3H, s, methoxy attached to phenyl), 5.09 (2H, s, benzylic methylene protons), 6.01 (1H, d, J = 9 Hz, olefinic proton) and 7.11 (13H, br, m, aromatic protons).

The keto-diol 17 on reduction with sodium borohydride gave the triol as thick liquid 21, $C_{19}H_{30}O_4$. It showed IR bands at 3509 (OH), 1616, 1587, 1515, 830 (aromatic). Jones chromic acid oxidation of the triol 21 gave a hydroxy acid 16 (R'= H), which was converted to methyl ester by diazomethane and identified as 16 (R' = CH_3), $C_{17}H_{24}O_4$ by spectral data. The IR and PMR spectra of 16 (R'=CH_3) were superimposable with those described in this chapter.

The ketone 6, when subjected to Grignard reaction using p-chlorophenylmagnesium bromide (1.3 mole) gave the liquid alcohol 22, $C_{18}H_{25}OCl$, in 87% yield. It showed the IR bands at 3521 (OH), 1608, 829 (aromatic) and PMR signals at 0.60 (1H, m, cyclopropane proton at C_3), 0.79, 0.87, 0.99, 1.07 (6H, all s, cyclopropane methyls of both the diastereomers), 1.23 (2H, d, J = 8 Hz, CH_2-protons), 1.50

(3H, s, methyl on carbon bearing hydroxy and p-chlorophenyl), 1.70 (6H, br, m, vinyl methyls of diastereomers), 1.93 (1H, d, J = 8 Hz, allylic cyclopropane proton), 4.80 (1H, br, m, olefinic proton) and 7.30 (4H, m, aromatic protons).

Oxidation of the alcohol 22 with potassium permanganate in dry acetone, gave a mixture of two products, viz. acidic and neutral. The acidic part 23 (R' = H) was converted into its methyl ester 23 (R' = CH_3), $C_{16}H_{21}O_3Cl$ by an ethereal solution of diazomethane. It exhibited spectral properties as follows: IR bands 3559 (OH), 1712 (ester >C=O), 1600, 1490, 829 (aromatic) and PMR signals at 1.00, 1.07, 1.16 (6H, all s, cyclopropane methyls of both the diastereomers), 1.30 (1H, m, cyclopropane proton at C_3), 1.57 (3H, s, methyl on carbon bearing hydroxy and p-chlorophenyl), 2.14 (3H, m, CH_2-protons and cyclopropane proton at C_1), 3.55, 3.63 (3H, each s, ester methyls of diastereomers) and 7.40 (4H, m, aromatic protons).

The neutral part was chromatographed and characterised as keto-diol 24, $C_{18}H_{25}O_3Cl$; IR bands at 3484 (OH), 1669 (>C=O), 1590, 866 (aromatic). The PMR signals at 0.90, 1.06, 1.08, 1.20, 1.26, 1.28, 1.36 (12H, all s, cyclopropane methyls and hydroxy isopropyl methyls of both the diastereomers), 1.51 (3H, s, methyl attached to carbon bearing hydroxy and p-chlorophenyl), 1.80 (2H, m, cyclopropane protons), 2.16 (2H, m, CH_2-protons) and 7.26

(4H, m, aromatic protons).

Dehydration of the ester 23 (R'= CH_3), using $POCl_3$/ pyridine gave a mixture of two isomeric unsaturated esters, separated by chromatography over silica gel impregnated with 15% silver nitrate. The fractions eluted with pet.ether gave ester 25, $C_{16}H_{19}O_2Cl$, M^+ 278, 280 (due to Cl^{37}) as a solid m.p.70° (ethanol). It showed IR bands at 1718 (ester), 1587, 823 (aromatic) and PMR ($CDCl_3$; 90 MHz) signals at 1.29, 1.32 (3H each, s each, gem dimethyl on cyclopropane), 1.82 (1H, d, J = 9 Hz, cyclopropane proton at C_1), 2.06 (1H, t, J = 9 Hz, cyclopropane proton at C_3), 2.11 (3H, s, vinyl methyl), 3.69 (3H, s, ester methyl), 6.13 (1H, d, J = 9 Hz, olefinic proton) and 7.22 (4H, m, aromatic protons).

During the dehydration of hydroxy methyl ester 23 to give 25, two double bond geometric isomers are possible. It appears from the PMR spectrum of 25 that only one thermodynamically stable isomer is formed and this isomer has been assigned stereostructure 25 on the basis of chemical shift of olefinic proton i.e. 6.13δ which is in good agreement with calculated value[40] (6.07δ).

The fractions eluted with 10% benzene in pet.ether gave the isomeric ester 26, $C_{16}H_{19}O_2Cl$. It showed IR bands at 1724 (ester >C=O), 1629, 893 (>C=CH_2), 1590, 831 (aromatic) and PMR ($CDCl_3$; 90 MHz) signals at 1.19, 1.24 (3H each, s each, gem-dimethyl on cyclopropane), 1.40

(1H, m, cyclopropane proton at C_3), 1.63 (1H, d, J = 8 Hz, cyclopropane proton at C_1), 2.82 (2H, d, J = 8 Hz, CH_2-protons), 3.64 (3H, s, ester methyl), 5.20 (2H, m, $>C=CH_2$ protons) and 7.19 (4H, m, aromatic protons).

The ester 25 was trans-esterified with 3-phenoxybenzyl alcohol to afford the 3-phenoxybenzyl ester 27, $C_{28}H_{27}O_3Cl$, M^+ 446, 448 (due to chlorine isotopes). It showed the following properties: IR bands at 1730, (ester >C=O), 1587, 824, 787 (aromatic) and PMR ($CDCl_3$; 90 MHz) signals at 1.25, 1.28 (3H each, s, gem-dimethyl on cyclopropane), 1.84 (1H, d, J = 9 Hz, cyclopropane proton at C_1), 2.02 (1H, t, J = 9 Hz, cyclopropane proton at C_3), 2.04 (3H, s, vinyl methyl), 5.05 (2H, s, benzylic $-CH_2-$), 6.05 (1H, d, J = 9 Hz, olefinic proton) and 7.14 (13H, m, aromatic protons).

Similarly, Grignard reaction using cyclohexyl-magnesium bromide (2 moles) on the ketone 6 gave the alcohol 28, $C_{18}H_{32}O$, in 78% yield. Unlike other alcohols like 9, 16 and 23, 28 was obtained only as a single diastereomer as indicated by PMR spectral data. It showed IR bands at 3509 (OH); PMR signals at 0.90, 1.00 (6H, both s, cyclopropane methyls), 1.11 (3H, s, methyl on carbon bearing hydroxy and cyclohexyl), 1.21 (1H, exchangeable with D_2O, OH proton), 1.30 - 2.30 (15H, m, CH_2 at C_3, cyclopropane protons and cyclohexane methine and methylenes), 1.76 (6H, br, m, vinyl methyls) and 4.80

(1H, br, m, olefinic proton).

Oxidation of 28 with potassium permanganate as in previous cases gave the mixture of acid and neutral parts. The acidic part 29 (R'= H) was esterified with an ethereal solution of diazomethane to give hydroxy ester 29 (R' = CH_3), $C_{16}H_{28}O_3$. It showed IR bands at 3636 (OH), 1724, 1170 (ester >C=O); PMR signals at 1.00, 1.05 (6H, both s, cyclopropane methyls), 1.10 (3H, s, methyl on carbon bearing hydroxy and cyclohexyl), 1.13 2.65 (15H, CH_2-protons at C_3, cyclohexane methine and methylenes and cyclopropane protons) and 3.65 (3H, s, ester methyl).

The neutral part was chromatographed to give the keto-diol 30, $C_{18}H_{32}O_3$. It showed IR bands at 3571 (OH), 1686 (>C=O); PMR signals at 0.96, 1.03 (6H, both s, cyclopropane methyls), 1.10 (3H, s, methyl on carbon bearing hydroxy and cyclohexyl), 1.28, 1.33 (6H, both s, hydroxy-isopropyl methyls), centered at 1.83 (15H, br, m, $-CH_2$ at C_3, cyclohexane methine and methylene protons and cyclopropane protons) and 3.83 (1H, s, exchangeable with D_2O, OH proton).

Dehydration of the ester 29 (R' = CH_3) with $POCl_3$/pyridine gave a mixture of two isomeric unsaturated esters, which were separated by chromatography over silica gel impregnated with 15% silver nitrate. The fractions eluted with pet.ether gave a liquid 31, $C_{16}H_{26}O_2$, M^+ 250. It showdd IR bands at 1742, 1170 (ester >C=O);

PMR ($CDCl_3$; 90 MHz) signals at 1.20, 1.21 (6H, each s, gem-dimethyl on cyclopropane), 1.65 (3H, s, vinyl methyl), 1.41 - 2.42 (13H, br, m, cyclopropane protons and cyclohexane methine and methylene protons), 3.62 (3H, s, ester methyl) and 5.40 (1H, d, J = 8 Hz, olefinic proton). The E configuration has been assigned to the double bond on the basis of value of the chemical shift of the olefinic proton (5.40 δ) which is in close agreement with the calculated[40] value (5.37 δ).

The fractions eluted with pet.ether + 10% benzene gave the isomeric ester 32, $C_{16}H_{26}O_2$. It showed IR bands at 1742, 1170 (ester >C=O), 1653, 886 (>C=CH_2) and PMR ($CDCl_3$; 90 MHz) signals at 1.18 (6H, s, cyclopropane methyls), 1.93 - 1.22 (13H, br, m, cyclopropane protons, cyclohexane methine and methylene protons), 2.26 (2H, m, CH_2-protons at C_3), 3.62 (3H, s, ester methyl) and 4.73 (2H, m, >C=CH_2 protons).

Similarly ester 31 was trans-esterified with 3-phenoxybenzyl alcohol to give the 3-phenoxybenzyl ester 33, $C_{28}H_{34}O_3$, M^+ 418. It showed IR bands at 1736 (ester >C=O), 1590, 786, 755 (aromatic) and PMR ($CDCl_3$, 90 MHz) signals at 1.19, 1.23 (3H each, s, cyclopropane methyls), 1.63 (3H, s, vinyl methyl), 1.44 - 2.40 (13H, br, m, cyclopropane protons and cyclohexane methine and methylene protons), 5.05 (2H, s, benzylic -CH_2), 5.35 (1H, d, J = 7 Hz, olefinic proton) and 7.18 (9H, br, m, aromatic protons).

Regarding, the stereochemistry of esters 11, 18, 25 and 31 at the double bond, an E (CH_3, H trans) configuration is assigned to the double bond, on the basis of PMR chemical shifts [40] of the olefinic protons, which are in close agreement with the calculated values. For example in case of ester 25 the chemical shift for the olefinic proton is observed at 6.13 δ which is in close agreement with the calculated value 6.07δ.

The above conclusions regarding the stereochemistry of cyclopropane as well as of the double bond have been confirmed by X-ray crystallographic analysis of compound 18. The crystals of 18 belong to the space group $P2_1\ 2_12_1$ with a = 6.711(1), b = 8.133 (2) and C = 28.740(5) Å. The intensity data (1631 reflections) were collected on a a CAD_4F-11M diffractometer with MoKα radiation (λ= 0.7107 Å) using the $\omega/2\Theta$ scan technique. The structure was solved by direct methods. The substituents at 1 and 3 are α with respect to the planes through the cyclopropane ring. Refinement of the structure is in progress with the current R value of 0.147 for 953 reflections with $|Fo| > 3\sigma|Fo|$. A view of the molecule is shown in Chart IV.

EXPERIMENTAL

Preparation of 3β 4α-caranediol 2

In a 2 litre 3-necked round bottom flask, equipped with a mechanical stirrer and a dropping funnel, was placed formic acid (90%, 525 ml) and freshly distilled (+) 3-carene 1 (200 g) was added with stirring through a dropping funnel. Hyderogen peroxide (30%, 300 ml) was then added, dropwise, maintaining the temperature of the reaction mixture between 30-40° (2 hr). Stirring was continued at that temperature for 6 hr and the reaction mixture was allowed to stand overnight. A solution of sodium hydroxide (160 g in 400 ml water) was added slowly to the reaction mixture under stirring, keeping the temperature around 25° (1 hr). The reaction mixture was transferred to a two litre separating funnel and the layers were allowed to separate. The upper oily layer (approx. 250 g) was transferred back to the reaction flask and further amount of a solution of sodium hydroxide (40 g in one litre water) was added slowly, under vigorous stirring, maintaining the temperature at 25-30°. After stirring for 1/2 hr and cooling to 5 to 10°, the solid diol separated. It was filtered, the residue washed with cold water and dried; yield 120 g, m.p.68°. The crude diol was crystallised from pet.ether + 5% ethylacetate to give

110 g of diol 2 (45%) m.p.87-88°. (Found: C, 70.81; H, 10.52; $C_{10}H_{18}O_2$ requires C, 70.54; H, 10.66%). IR bands at: 3448, 2900, 1460, 1375, 1058, 945 and 815 cm^{-1}.

Methyl (-) 2,2-dimethyl-3-(2-oxopropyl)cyclopropane-cis-1-acetate 3 (R=CH_3)

To a vigorously stirred solution of diol, 2 (51 g, 0.3 mole) in acetone (300 ml) was added Jones chromic acid reagent (136 ml, 0.36 mole), dropwise, maintaining the temperature below 0° (1.5 hr). After the addition, it was stirred for 2 hr at room temperature, diluted with water (500 ml) and extracted with chloroform (100 ml x 3). The chloroform layer was washed with water and extracted with 10% sodium hydroxide solution (100 ml x 3). The aqueous alkaline portion was cooled to 5°, acidified with 20% sulphuric acid and extracted with chloroform (100 ml x 3). The chloroform layer was washed with water, dried and evaporated to furnish the keto acid 3 (R=H), (33.10 g, 60%).

The above keto acid 3 (R=H; 33.10 g) was refluxed in dry methanol (200 ml) with catalytic amount of conc.sulphuric acid (1 ml) for 5 hr. Most of the methanol was removed under reduced pressure, diluted with water (200 ml) and extracted with chloroform (100 ml x 3). The chloroform layer was washed with water, dried. Evaporation of chloroform furnished the keto ester 3 (R=CH_3) which was further purified by distillation to give a colourless liquid

(32.5 g), b.p.92°(vapour)/1.5 mm, $(\alpha)_D^{28}$ - 26.1° (c, 5.22).
(Found: C, 66.48; H, 9.32; $C_{11}H_{18}O_3$ requires C, 66.64;
H, 9.15%).
IR bands at: 3077, 2985, 1739, 1709, 1600, 1429, 1346,
1150, 1010 and 833 cm^{-1}.

The neutral material (7.00 g) in the chloroform layer was not investigated further.

Methyl 2,2-dimethyl-3-(2,2-ethylenedioxypropyl)cyclopropane-cis-1-acetate 4

A mixture of keto ester 3 (R=CH_3, 29.7 g, 0.15 mole), freshly distilled ethylene glycol (15.5 g, 0.25 mole), PTS (0.40 g) and dry benzene (300 ml) was taken in a 500 ml round bottom flask fitted with a Dean-Stark unit for azeotropic distillation. The mixture was then heated under reflux till no more water collected (6 hr). The reaction mixture wasthen washed with water (150 ml x 2) to remove unreacted ethylene glycol and PTS and dried. Evaporation of benzene afforded the ketal ester 4 which was purified by distillation, b.p.104°(vapour)/1.50 mm;
Yield 32.7 g (90%), $(\alpha)_D^{28}$ + 18.9° (c, 3.17).
(Found: C, 64.65; H, 9.42; $C_{13}H_{22}O_4$ requires C, 64.44;
H, 9.15%).
IR bands at: 3030, 2985, 1739, 1418, 1361, 1299, 1163,
1036, 935, 837 and 755 cm^{-1}.

2,2-Dimethyl-3(2,2-ethylendioxypropyl)-cis-1-(2-methyl-2-hydroxypropyl) cyclopropane 5

(A) Preparation of methylmagnesium iodide reagent

In a one-litre three necked flask fitted with an overhead mechanical stirrer, a reflux condenser and a dropping funnel,were taken magnesium turnings (7.2 g, 0.3 mole), dry ether (150 ml) and a crystal of iodine. A few drops of methyl iodide in ether were slowly introduced in the reaction mixture when the colour of iodine disappeared. The remaining solution of methyl iodide (42.6 g, 0.3 mole) in dry ether (150 ml) was then added, dropwise, under stirring. After the addition, the reaction mixture was stirred at room temperature for 1 hr when most of the magnesium dissolved to give a solution of methyl-magnesium iodide in ether.

(B) Preparation of 5

A solution of ketal ester 4 (24.2 g, 0.1 mole) in ether (100 ml) was then added dropwise to the above Grignard reagent at 0° under vigorous stirring. Stirring was continued for 1 hr at room temperature and 2 hr under reflux. Excess of the reagent and magnesium complex were decomposed by adding dropwise, a saturated solution of ammonium chloride (200 ml) at 0 to 5° and was stirred for 30 minutes at room temperature. The ether layer was separated and the aqueous portion extracted with ether

(100 ml x 2). The combined ether layer was washed with water, dried and evaporated to furnish the ketal alcohol 5 (21.8 g, 90%), b.p.120-130°/1 mm, $(\alpha)_D^{28}$ - 5.30° (c, 3.70). (Found: C, 69.12; H, 10.76; $C_{14}H_{26}O_4$ requires C, 69.38; H, 10.81%).

IR bands at: 3571, 3030, 1460, 1376, 1299, 1218, 1135, 1107, 1050, 944, 907 and 844 cm^{-1}.

2,2-Dimethyl-3-(2-methylprop-1-enyl)-cis-1-(2-oxopropyl)-cyclopropane 6

A mixture of ketal alcohol 5 (18 g 0.075 mole), PTS (0.2 g) in dry benzene (300 ml) was heated under reflux for 16 hr, with an arrangement for removing the water formed, azeotropically. Water (10 ml) was then added and the mixture refluxed for additional 4 hr. It was then washed repeatedly with water to remove PTS and ethylene glycol, dried and evaporated to give a mixture of two unsaturated ketones 6 and 7 (10 g, 75%), b.p.115-120°/2 mm. (TLC on SiO_2 + $AgNO_3$ plate, 5% ethylacetate in benzene, two spots). The above mixture of ketones was chromatographed on silica gel (180 g) impregnated with silver nitrate (20 g) and eluted with pet.ether, pet.ether + benzene mixtures and benzene. The fractions eluted with pet.ether and pet.ether + 10% benzene gave TLC pure liquid 6 (7.5 g, 75% of the mixture) $(\alpha)_D^{28}$ - 76.8° (c, 1.20); (Found: C, 79.85; H, 11.20; $C_{12}H_{20}O$ requiresC, 79.74; H, 11.18%).

IR bands at: 2967, 1710, 1439, 1368, 1342, 1215, 1149 and 825 cm^{-1}.

The fractions eluted with pet.ether + benzene (1:1) and benzene gave the TLC pure ketone 7 which was further purified by distillation, b.p.115-120°/2 mm. (Found: C, 79.60; H, 11.02; $C_{12}H_{20}O$ requires C, 79.74; H, 11.18%). IR bands at: 2985, 1709, 1645, 1445, 1370, 1351, 1220, 1160, 1047 and 885 cm^{-1}.

2,2-Dimethyl-1(2-methylprop-1-enyl)-cis-3-(2-p-tolyl-2-hydroxypropyl)-cyclopropane 8

To an ice-cooled solution of p-tolylmagnesium bromide in dry ether, prepared from magnesium (2.35 g; 0.097 mole) and p-bromotoluene (16.6 g; 0.097 mole), a solution of the ketone 6 (13.5 g; 0.075 mol) in dry ether (150 ml) was added dropwise under stirring. After the complete addition, the reaction mixture was refluxed for 2 hr and kept overnight, decomposed with aqueous ammonium chloride solution at 5-10°. The ether layer was separated and the aqueous layer was extracted with ether (100 ml x 2). The combined ether layer was washed with water (100 ml x 2), dried and distilled to give the crude liquid mixture of diastereomeric unsaturated alcohols 8 (18 g), which was purified by chromatography (Al_2O_3; 1:15) to eliminate less polar impurities. Elution with pet.ether + benzene (1:1) and benzene gave pure liquid, 8 (16.5 g, 80.8%), b.p.175-85°/

0.5 mm, $(\alpha)_D^{27}$ - 15.25°(c, 1.18); (Found: C, 83.58; H, 10.39; $C_{19}H_{28}O$ requires C, 83.77; H, 10.36%).

IR bands at: 3448, 2985, 1504, 1439, 1364, 1081, 1011, 930, 837, 813 and 719 cm^{-1}.

Methyl 1R-cis-2,2-dimethyl-3-(2-p-tolyl-2-hydroxypropyl) cyclopropanecarboxylate 9 (R' = CH_3)

To a solution of the unsaturated alcohol 8 (10.2 g, 0.036 mole) in acetone (75 ml) acetic acid (15 ml) and water (50 ml), powdered potassium permanganate (9.0 g, 0.057 mol) was added, portionwise, under stirring during 1 hr at 30°. Stirring was continued for 2 hr more and the reaction mixture wastreated simultaneously with sodium nitrite (6 g) and sulphuric acid (1:10), till all the manganese dioxide dissolved and a cleer yellow solution obtained. It was then diluted with water (200 ml) and extracted with chloroform (100 ml x 3). The chloroform layer was washed with water (75 ml x 2) and extracted with 10% aqueous sodium carbonate solution (25 ml x 3). The carbonate layer was cooled, acidified with (1:1) hydrochloric acid to 2 pH and extracted with ether (75 ml x3). The ether layer was washed with water (50 ml x 2), dried and distilled to give the hydroxy acid 9 (R' = H; 2.5 g) which was esterified with an ethereal solution of diazomethane to give a liquid,purified by chromatography over (Al_2O_3, 25 g) and elution with pet.ether + benzene and benzene to

give ester 9 (R' = CH_3, 2.1 g, 20.3%); b.p.160-65°/0.6 mm; $(\alpha)_D^{27}$ -30.9° (c, 0.84); (Found: C, 74.18; H, 8.79; $C_{17}H_{24}O_3$ requires C, 73.88; H, 8.75%).
IR bands at: 3636, 3030, 1724, 1515, 1439, 1379, 1176, 952, 870, 851 and 819 cm^{-1}.

The chloroform layer after extraction with sodium carbonate solution was repeatedly washed with water (50 ml x 3), dried and evaporated to give mainly the keto diol 10 in the neutral part. The neutral part 6 g was chromatographed over (Al_2O_3, 100 g) and the fractions eluted with benzene and chloroform gave a TLC pure thick liquid 10 (5 g, 43.8%), $(\alpha)_D^{28}$ - 56.5° (c, 0.93); (Found: C, 74.72; H, 8.92; $C_{19}H_{28}O_3$ requires C, 74.96; H, 9.27%).
IR bands at: 3571, 3058, 1695, 1515, 1460, 1370, 1015, 967, 870, 816 and 758 cm^{-1}.

Methyl 1R-cis-2,2-dimethyl-3-(2-p-tolylprop-1-enyl) cyclopropanecarboxylate 11

To an ice-cooled solution of 9 (R' = CH_3, 1.4 g) in dry pyridine (10 ml) was added $POCl_3$ (2.5 g), dropwise with shaking and maintaining temperature at 0-5°. The reaction mixture was allowed to stand at 10° for 24 hr, poured over crushed ice with stirring and the organic matter extracted with chloroform (75 ml x 3). The chloroform layer was washed successively with water, 10% hydrochloric acid to remove excess of pyridine and water, dried and distilled to furnish the dehydrated product (1.1 g, 84%, TLC on SiO_2 +

10% $AgNO_3$, 4% ethyl-acetate in benzene, two spots). The above mixture of unsaturated esters was chromatographed over silica gel impregnated with 10% silver nitrate (12 g) and eluted with pet.ether, pet.ether + benzene mixtures. The fractions eluted with pet.ether + 20% benzene gave 11 as a white solid (0.8 g, 61%), crystallised from alcohol m.p.64-65°, $(\alpha)_D^{28}$ -18.2° (c, 3.07); (Found: C, 79.30; H, 8.57; $C_{17}H_{22}O_2$ requires C, 79.07; H, 8.58%).

IR bands at: 2967, 1724, 1613, 1499, 1418, 1361, 1163, 1130, 1075, 885 and 813 cm^{-1}.

The polar compound 12 was eluted later but not characterised.

3-Phenoxybenzyl 1R-cis-2,2-dimethyl-3-(2-p-tolyl-prop-1-enyl)cyclopropanecarboxylate 13

To a solution of methyl ester 11 (0.13 g, 0.5 mmol) in dry xylene (20 ml) were added 3-phenoxybenzyl alcohol (0.25 g, 1.25 mmol), butyl tianate (0.05 g) and the mixture refluxed for 10 hr. Xylene was removed under reduced pressure and the reaction mixture chromatographed over (Al_2O_3; 25 g). The fractions eluted with 10% benzene in pet.ether gave TLC pure liquid 13 (0.19 g, 89%), $(\alpha)_D^{31}$ -32° (c, 0.79); (Found: C, 81.55; H, 7.18; $C_{29}H_{30}O_3$ requires C, 81.66; H, 7.09%).

IR bands at: 2985, 1724, 1585, 1475, 1439, 1250, 1208, 1170, 1129, 1075, 813 and 784 cm^{-1}.

2,2-Dimethyl-3-(2-p-tolyl-2-hydroxypropyl)-cis-1-(2-methyl-1,2-dihydroxypropyl)cyclopropane 14

To a stirred solution of 10 (5 g) in dry methanol (100 ml), was added portionwise, sodiumborohydride (1g) during 1/2 hr. Stirring was continued for 65 hr, the reaction mixture diluted with water (200 ml) and extracted with ether (100 ml x 3). The ether layer was washed with water (75 ml x 2), dried and evaporated to give 14 (4 g, 79.5%) as a thick liquid. (Found: C, 74.20; H, 9.60; $C_{19}H_{30}O_3$ requires: C, 74.47; H, 9.87%). IR bands at: 3509, 3030, 1515, 1449, 1370, 1020, 952, 866, 816, 752 and 722 cm^{-1}.

Methyl 1R-cis-2,2-dimethyl-3-(2-p-tolyl-2-hydroxypropyl) cyclopropanecarboxylate 9 (R' = CH_3) from 14

To an ice-cooled solution of 14 (4 g) in acetone (50 ml), Jones chromic acid reagent was added dropwise till a brown colour persisted. The reaction mixture was kept at 0° for 2 hr, diluted with water and extracted with chloroform (50 ml x 3). The chloroform layer was washed with water and extracted with 10% aqueous sodium carbonate (20 ml x 2). The carbonate layer was cooled, acidified with hydrochloric acid (1:1) to 2 pH and extracted with ether (50 ml x 3). The ether layer was washed with water, dried and distilled to give a liquid acid (1 g) which was esterified with an ethereal

solution of diazomethane to give the hydroxy methyl ester (9 (R' = CH_3; 0.9 g, 24.9%), $(\alpha)_D^{28}$ - 30° (c, 0.70). (Found: C, 74.18; H, 8.79; $C_{17}H_{24}O_3$ requires C, 73.88; H, 8.75%).

IR bands at : 3636, 3030, 1724, 1515, 1439, 1379, 1176, 952, 870, 851 and 819 cm^{-1}

2,2-Dimethyl-1-(2-methylprop-1-enyl)-cis-3-(2-p-anisyl-2-hydroxypropyl)cyclopropane 15

A solution of ketone 6 (9 g, 0.05 mol) in dry ether (100 ml) was introduced, dropwise with stirring into a cooled solution of p-anisylmagnesium bromide, prepared from magnesium (1.6 g; 0.065 mol) and p-bromoanisole (12.2 g; 0.065 mol) in dry ether. After the complete addition, the reaction mixture was refluxed for 3 hr, kept overnight and decomposed by aqueous ammonium chloride at 5 to 10°. The ether layer was separated and the aqueous layer extracted with ether (100 ml x 3). The combined ether layer was washed with water, dried and evaporated to give a liquid (15 g), which was chromatographed over (Al_2O_3, 300 g). The fractions eluted with pet.ether-benzene (4:1), pet.ether-benzene (1:1) and benzene gave TLC pure alcohol 15 (13 g, 90.26%), b.p.160-65°/0.4 mm, $(\alpha)_D^{28}$ -23.12° (c, 3.46). (Found: C, 78.98; H, 9.91; $C_{19}H_{28}O_2$ requires C, 79.12; H, 9.79%).

IR bands at: 3646, 2985, 1613, 1508, 1449, 1370, 1294, 1242, 1172, 1031 and 826 cm^{-1}.

Methyl 1R-*cis*-2,2-dimethyl-3-(2-p-anisyl-2-hydroxy-propyl) cyclopropanecarboxylate 16 ($R' = CH_3$)

To an ice-cooled solution 15 (7.2 g, 0.025 mol) in dry acetone (175 ml) containing anhydrous potassium carbonate (0.05 g), finely powdered potassium permanganate (8 g, 0.05 mol) was added portionwise under stirring during 2 hr. Stirring was continued for 3 hr, the reaction mixture filtered and the residue washed with dry acetone (100 ml). The residue was then extracted with hot water (75 ml x 3), the aqueous extract cooled, acidified with dil. hydrochloric acid and extracted with ether (100 ml x 3). The ether layer was washed with water, dried and the solution of hydroxy acid in ether was as such immediately treated with an ethereal solution of diazomethane to give after workup the ester 16 ($R' = CH_3$, 4.2 g, 57.5%). It was chromatographed over (Al_2O_3, 80 g). The fractions eluted with pet.ether + benzene (1:1) and benzene gave pure ester b.p.150-55°/0.5 mm, $(\alpha)_D^{26}$ -9.5° (c, 2.94). (Found: C, 70.08; H, 8.40; $C_{17}H_{24}O_4$ requires C, 69.83; H, 8.27%).

IR bands at: 3546, 2994, 1724, 1608, 1497, 1429, 1370, 1235, 1163, 1029 and 826 cm^{-1}

Acetone was distilled from the neutral portion and the residue was taken in ether (100 ml). The ether solution was washed with water (50 ml x 3), dried and

distilled to give the keto diol 17 (3 g). It was chromatographed over (Al_2O_3; 45 g) and eluted with benzene and chloroform to give TLC pure 17 (2.5 g, 31.25%), $(\alpha)_D^{28}$ -23.8° (c, 1.37); (Found: C, 71.01; H, 9.00; $C_{19}H_{28}O_4$ requires C, 71.22; H, 8.81%).
IR bands at: 3546, 3003, 1669, 1610, 1504, 1449, 1359, 1290, 1235, 1026, 962 and 826 cm^{-1}.

Methyl 1R-cis-2,2-dimethyl-3-(2-p-anisylprop-1-enyl)cyclopropanecarboxylate 18

Method A - To an ice cooled solution of the ester 16 (2.9 g) in dry pyridine (20 ml), $POCl_3$ (3.5 g) was added dropwise with shaking at 0-5°. The reaction mixture kept for 24 hr, poured on to crushed ice and the organic matter extracted with chloroform (100 ml x 3). The chloroform layer was washed successively with water, dil. HCl, water and dried. Removal of solvent gave a mixture of two unsaturated esters (2.6 g, 94.8%) (TLC on SiO_2 + 20% $AgNO_3$; 30% pet.ether in benzene; two spots). The mixture was chromatographed on silica gel impregnated with 20% silver nitrate (35 g) and eluted with pet.ether and 10% benzene in pet.ether. The fractions eluted with pet.ether gave 18 as solid, crystallised from ethyl alcohol; m.p.61°, $(\alpha)_D^{27}$ - 58.2° (c, 2.4). (Found: C, 74.70; H, 8.18; $C_{17}H_{22}O_3$ requires C, 74.42; H, 8.08%).
IR bands at: 3030, 1742, 1613, 1515, 1449, 1379, 1290, 1250, 1163, 1083, 1025, 917, 830 and 785 cm^{-1}.

The fractions eluted with 10% benzene in pet.ether gave TLC pure isomeric ester 19, b.p.180-85°/1 mm; $(\alpha)_D^{27}$ - 19.7° (c, 2.13). (Found: C, 74.60; H, 8.30; $C_{17}H_{22}O_3$ requires C, 74.42; H, 8.08%).
IR bands at: 3003, 1724, 1669, 1600, 1504, 1429, 1366, 1235, 1163, 1124, 1026, 885 and 833 cm^{-1}.

Method B- Solution of 16 (1 g) in dry benzene (75 ml) was refluxed with PTS (0.1 g) for 8 hr. It was washed with water (100 ml x 2), dried and distilled to give dehydrated product (0.8 g, 77.8%; TLC on SiO_2 + 20% $AgNO_3$; 30 pet.ether in benzene, single spot). This on chromatography over silica gel (10 g) and elution with pet.ether, pet.ether + 10% benzene, gave in the middle fractions a solid which was crystallised from ethyl alcohol to give anester 18 m.p. and m.m.p.61°.

3-Phenoxybenzyl 1R-cis-2,2-dimethyl-3(2-p-anisyl-prop-1-encyl)cyclopropanecarboxylate 20

To a solution of methyl ester 18 (0.14 g,0.51 mmol) in dry xylene (25 ml), 3-phenoxybenzyl alcohol (0.3 g, 1.5 mmol) and butyl titanate (0.05 g) were added and the reaction mixture refluxed for 15 hr. Xylene was distilled under reduced pressure. The reaction mixture chromatographed over (Al_2O_3, 30 g). The fraction eluted with 20% benzene in pet.ether gave TLC pure liquid 20 (0.19 g, 84.5%).
$(\alpha)_D^{31}$ -57° (c, 0.20). (Found: C, 78.90; H, 6.85;

$C_{29}H_{30}O_4$ requires C, 78.70; H, 6.83%).

IR bands at: 3030, 1730, 1613, 1590, 1515, 1493, 1250, 1176, 1134, 1081, 1031 and 826 cm^{-1}.

2,2-Dimethyl-3-(2-p-anisyl-2-hydroxypropyl)-cis-1-(2-methyl-1,2-dihydroxypropyl)cyclopropane 21

To a well stirred solution of 17 (2.5 g) in methanol (75 ml) was added sodiumborohydride (0.5 g) during 1/2 hr. Stirring was continued for 72 hr. The reaction mixture was diluted with water and extracted with ether (75 ml x 3). The ether layer was washed with water, dried and distilled to give a thick liquid 21 (2.0 g, 79.4%). (Found: C, 70.53; H, 9.11; $C_{19}H_{30}O_4$ requires C, 70.77; H, 9.38%).

IR bands at: 3509, 3030, 1616, 1587, 1515, 1471, 1370, 1299, 1250, 1031, 952 and 830 cm^{-1}.

Methyl 1R-cis-2,2-dimethyl-3-(2-p-anisyl-2-hydroxypropyl) cyclopropanecarboxylate 16 from 21

To an ice-cooled solution of 21 (2 g) in acetone (30 ml), Jones chromic acid reagent was added till a brown colour persisted. The reaction mixture was stirred for 2 hr at 0°, diluted with water and extracted with chloroform (50 ml x 3). The chloroform layer was washed with water and extracted with 10% aqueous sodium carbonate (10 ml x 2). The carbonate layer was cooled, acidified with hydrochloric acid and extracted with ether (50 ml x 3). The ether

layer was washed with water, dried and solution of hydroxy acid 16 (R' = H) in ether was esterified with an ethereal solution of diazomethane to give the corresponding ester 16 (R' = CH_3; 0.48 g; 26.6%). It was chromatographed over (Al_2O_3, 10 g) and elution with pet.ether-benzene (1:1) and benzene gave TLC pure ester $(\alpha)_D^{26}$ -11.2° (c, 1.40); (Found: C, 70.08; H, 8.40; $C_{17}H_{24}O_4$ requires C, 69.83; H, 8.27%).

IR bands at: 3546, 2994, 1724, 1608, 1497, 1429, 1370, 1235, 1163, 1026 and 826 cm^{-1}.

2,2-Dimethyl-1-(2-methylprop-1-enyl)-cis-3-(2-p-chlorophenyl-2-hydroxypropyl)cyclopropane 22

To an ice-cooled solution of p-chlorophenylmagnesium bromide in dry ether, prepared from magnesium (0.76 g, 0.032 mol) and p-chlorobromobenzene (6.03 g, 0.032 mol), a solution of ketone 6 (4.5 g, 0.025 mol) in dry ether (75 ml) was added dropwise under stirring. After complete addition, the reaction mixture was refluxed for 2 hr, kept overnight, decomposed with aqueous ammonium chloride (5 g in 100 ml) at 5-10°. The ether layer separated and the aqueous layer extracted with ether (100 ml x 2). The combined ether layer was washed with water, dried and distilled to give 22 as a liquid (9 g), which was purified by chromatography over (Al_2O_3, 180 g), to eliminate less polar impurities. The fractions eluted with pet.ether +

benzene (1:1) and benzene gave TLC pure 22 (6.4 g, 87.3%); b.p.165-70°/0.6 mm; $(\alpha)_D^{25}$ - 9.3° (c, 2.16); (Found: C, 74.13; H, 8.82; Cl, 12.38, $C_{18}H_{25}OCl$ requiresC, 73.87; H, 8.54; Cl, 12.14%).

IR bands at: 3521, 3012, 1608, 1493, 1449, 1374, 1089, 1010, 935, 829, 750 and 719 cm^{-1}.

Methyl 1R-cis-2,2-dimethyl-3-(2-p-chlorophenyl-2-hydroxypropyl)-cyclopropanecarboxylate 23 (R' = CH_3)

To an ice cooled solution of 22 (6 g, 0.20 mol) in dry acetone (150 ml), containing anhydrous potassium carbonate (0.5 g) was added finely powdered potassium permanganate (6.6 g, 0.42 mol) under stirring during 2 hr. Stirring was continued for 3 hr, the reaction mixture filtered and the residue washed with dry acetone (75 ml). The residue was extracted with hot water (75 ml x 3), the aqueous extract cooled, acidified with hydrochloric acid (1:1) and extracted with ether (75 ml x 3). The ether layer was washed with water, dried and the solution of hydroxy acid 23 (R' = H) in ether was treated with an ethereal solution of diazomethane to give the methyl ester 23 (R' = CH_3, 3.5 g, 57.5%). It was chromatographed over (Al_2O_3, 70 g). The fractions eluted with pet.ether + benzene (4:1), pet.ether + benzene (1:1) and benzene gave TLC pure ester b.p.175-85°/0.7 mm, $(\alpha)_D^{25}$ - 1.7° (c, 3.5). (Found: C, 64.86; H, 7.36; Cl, 11.45, $C_{16}H_{21}O_3Cl$ requires C, 64.76; H, 7.08; Cl, 11.98%).

IR bands at: 3559, 3003, 1712, 1600, 1490, 1370, 1163, 1010, 948, 870, 829 and 784 cm^{-1}.

The acetone was distilled from the neutral part and the residue was taken in ether (100 ml) and ether solution was washed with water, dried and evaporated to give neutral (3 g). It was chromatographed over (Al_2O_3, 60 g) and elution with benzene, benzene + chloroform (1:1) gave pure keto-diol 24 (2.7 g, 40.5%). $(\alpha)_D^{26}$ -33° (c, 2.4) (Found: C, 66.15; H, 7.97; Cl, 10.78. $C_{18}H_{25}O_3Cl$ requires C, 66.58; H, 7.70; Cl, 10.94%).
IR bands at: 3484, 2985, 1669, 1590, 1449, 1370, 1220, 1010, 962 and 866 cm^{-1}.

Methyl 1R-cis-2,2-dimethyl-3-(2-p-chlorophenyl-prop-1-enyl)-cyclopropanecarboxylate 25

To an ice cooled solution of 23 (2.9 g) in dry pyridine (15 ml), $POCl_3$ (3 g) was added. The reaction mixture was allowed to stand at room temperature for 24 hr, and worked up as described in case of 18 to give a mixture of two unsaturated esters (2.5 g; 91.6%). (TLC on SiO_2 + 15% $AgNO_3$; 20% pet.ether in benzene, two spots). The mixture was separated by chromatography over silica gel impregnated with 15% $AgNO_3$ (25 g) and elution with pet.ether gave TLC pure ester 25 as a solid, which was crystallised from ethyl alcohol, m.p.70°, $(\alpha)_D^{26}$ -9.9° (c, 1.7 g). (Found: C, 68.98; H, 6.96; Cl, 12.50; $C_{16}H_{19}O_2Cl$ requires C, 68.95; H, 6.82; Cl, 12.75%).

IR bands at: 2914, 1718, 1587, 1488, 1429, 1825, 1163 1136, 1111, 1087, 1000, 917, 823 and 730 cm^{-1}.

The fractions eluted with 10% benzene in pet.ether gave the TLC pure isomeric ester 26, b.p.170-75°/0.5 mm, $(\alpha)_D^{26}$ - 1.3° (c, 1.44). (Found: C, 68.72; H, 6.63; Cl, 12.60. $C_{16}H_{19}O_2Cl$ requires C, 68.95; H, 6.82; Cl, 12.75%).

IR bands at: 3012, 1724 , 1629, 1590, 1488, 1429, 1370, 1163, 1127, 1087, 1006, 893 and 831 cm^{-1}.

3-Phenoxybenzyl 1R-cis-2,2-dimethyl-3-(2-p-chlorophenyl-prop-1- enyl)cyclopropanecarboxylate 27

To a solution of unsaturated ester 25 (0.15 g, 0.54 mmol) in dry xylene (20 ml), were added 3-phenoxybenzyl alcohol (0.250 g, 1.25 mmol) and butyl titanate (0.05 g) and the mixture refluxed for 10 hr. Xylene was removed under reduced pressure and the reaction mixture chromatographed over (Al_2O_3, 30 g). The fractions eluted with 15% benzene in pet.ether gave TLC pure 27 thick liquid (0.19 g, 79.07%). $(\alpha)_D^{31}$ - 28° (c, 1.0). (Found: C, 75.25; H, 6.22; Cl, 7.49; $C_{28}H_{27}O_3Cl$ requires C, 75.25; H, 6.04; Cl, 7.95%). IR bands at 3030, 1730, 1587, 1481, 1439, 1391, 1250, 1212, 1176, 1133, 1087, 1005, 824 and 787 cm^{-1}.

2,2-Dimethyl-1-(2-methylprop-1-enyl)-cis-3-(2-cyclohexyl-2-hydroxypropyl)cyclopropane 28

The reaction between cyclohexylmagnesium bromide, prepared under nitrogen atmosphere from magnesium (1.8 g;

0.075 mol) and cyclohexyl bromide (12.2 g; 0.075 mol) and unsaturated ketone 6 (6.8 g; 0.037 mol) was carried out exactly as described in in the preparation of 22. In this case refluxing period was 5 hr. Workup as described for 22 gave 28 as a liquid (10.5 g), which was purified by chromatography over (Al_2O_3, 200 g) and eluting with pet.ether + benzene (4:1) and pet.ether + benzene (1:1) to give TLC pure 28 (7.8 g, 78.8%), b.p.170-75°/0.8 mm, $(\alpha)_D^{25}$ -50° (c, 2.80). (Found: C, 81.54; H, 11.86; $C_{18}H_{32}O$ requires C, 81.75; H, 12.20%).
IR bands at: 3509, 3030, 1449, 1374, 935, 893 and 844 cm^{-1}.

Methyl 1R-cis-2,2-dimethyl-3-(2-cyclohexyl-2-hydroxypropyl)-cyclopropanecarboxylate 29 (R' = CH_3)

Oxidation of 28 (5.12 g, 0.019 mol) in dry acetone (125 ml) using potassium permanganate (6.12 g,; 0.038 mol) was carried out as described in the preparation of 23 and after usual workup, gave the hydroxy acid in the acid part. This was treated with an ethereal solution of diazomethane to obtain the ester. It was purified by chromatography over (Al_2O_3; 60 g) to give 29 (3.10 g; 49.9%), b.p.160-70°/1 mm, $(\alpha)_D^{25}$ -5° (c, 1.6); (Found: C, 71.32; H, 10.63; $C_{16}H_{28}O_3$ requires C, 71.60; H, 10.52%).
IR bands at: 3636, 3030, 1724, 1433, 1370, 1170, 1124, 1075, 935, 881 and 847 cm^{-1}.

The neutral part (3 g) was chromatographed over (Al_2O_3, 60 g) and eluted with benzene and chloroform to give TLC pure keto-diol 30 (2.1 g; 36.8%); (Found: C, 72.55; H, 10.81; $C_{18}H_{32}O_3$ requires C, 72.92; H, 10.88%).

IR bands at: 3571, 3030, 1686, 1449, 1370, 1212, 1163, 1124, 1070, 1053, 1010, 971, 917, 893, 847 and 826 cm^{-1}.

Methyl 1R-cis-2,2-dimethyl-3-(2-cyclohexylprop-1-enyl)-cyclopropanecarboxylate 31

Dehydration of 29 (2 g) in dry pyridine (15 ml) and $POCl_3$ (2.5 g) was carried out as described in the case of 25, to give after usual workup, a mixture of two unsaturated esters (1.68 g,; 90%) (TLC on SiO_2 + 15% $AgNO_3$, 30% pet.ether in benzene; two spots). The mixture was chromatographed on silica gel impregnated with 15% silver nitrate (17 g) and eluted with pet.ether and 10% benzene in pet.ether. The fractions eluted with pet.ether gave TLC pure ester 31 as a liquid, b.p.155-65°/0.1 mm; $(\alpha)_D^{25}$ +36° (c, 2.45). (Found: C, 77.29; H, 10.38; $C_{16}H_{26}O_2$ requires C, 76.75; H, 10.47%).

IR bands at: 3030, 1742, 1667 , 1439, 1379, 1170, 1143, 1124, 1079, 1000 and 847 cm^{-1}.

The fractions eluted with pet.ether + 10% benzene gave the TLC pure isomeric ester 32, b.p.165-75°/0.8 mm; $(\alpha)_D^{25}$ -3° (c, 1.56) (Found: C, 77.13; H, 10.58. $C_{16}H_{26}O_2$ requires C, 76.75; H, 10.47%).

IR bands at: 3030, 1742, 1653, 1439, 1379, 1333, 1170, 1136, 1124, 1087, 886 and 851 cm^{-1}.

3-Phenoxybenzyl-1R-cis-2,2-dimethyl-3-(2-cyclohexylprop-1-enyl)cyclopropanecarboxylate 33

To a solution of methyl ester 31 (0.125 g; 0.5 mmol) in dry xylene (15 ml), 3-phenoxybenzyl alcohol (0.3 g; 1.5 mmol) and butyl titanate (0.05 g) were added and the mixture refluxed for 12 hr. The reaction mixture was worked-up as previously described and purified by chromatography over (Al_2O_3; 35 g). The fractions eluted with pet.ether + 10% benzene gave TLC pure liquid 33 (0.16 g, 76.56%). $(\alpha)_D^{31}$ -2^o (c, 1.58). (Found: C, 80.51; H, 8.14. $C_{28}H_{34}O_3$ requires C, 80.34; H, 8.19%).
IR bands at: 3012, 1736, 1590, 1488, 1449, 1408, 1389, 1351, 1256, 1212, 1163, 1136, 1075, 1020, 870, 786 and 755 cm^{-1}.

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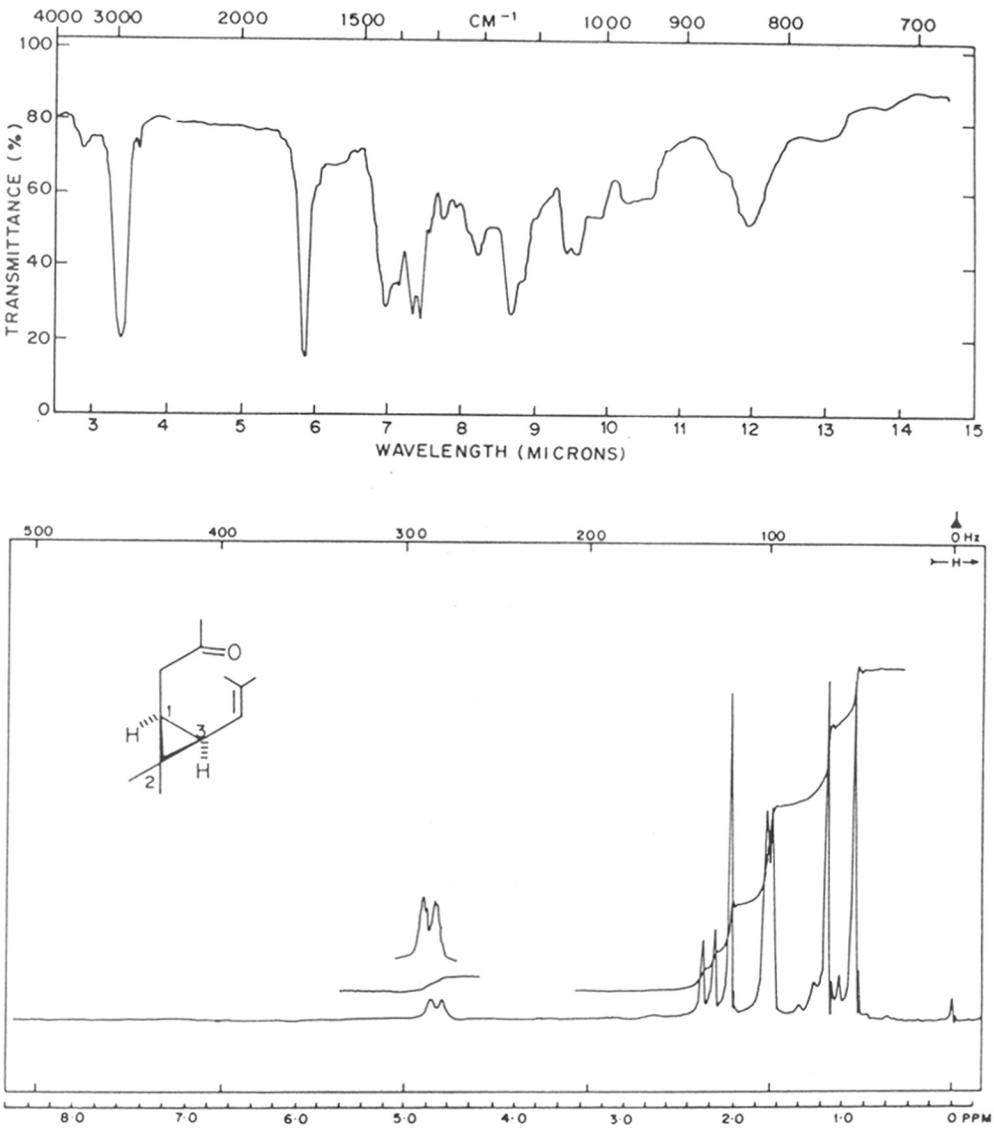
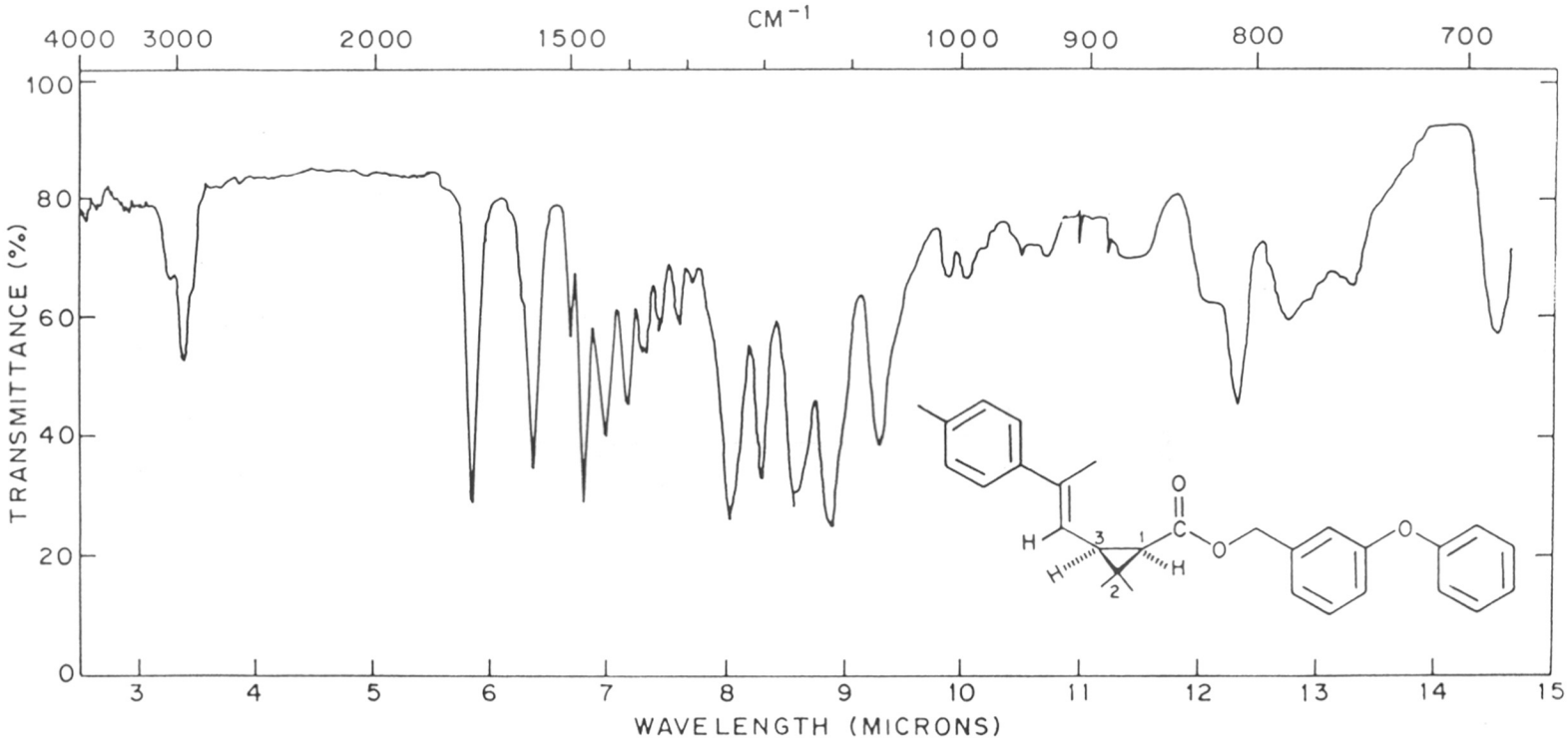
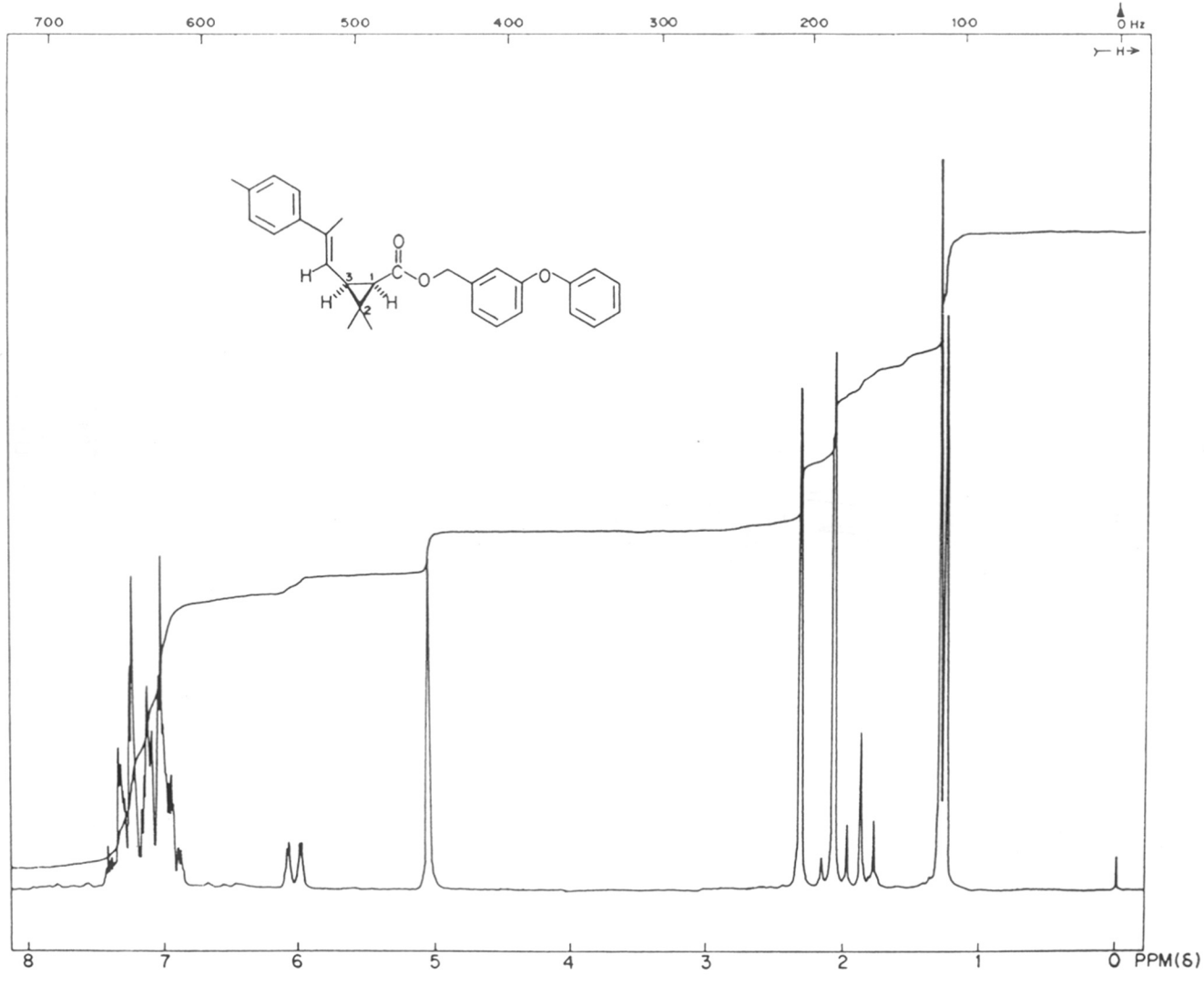


IR & PMR OF 2,2-DIMETHYL-3-(2-METHYLPROP-1-ENYL)-

CIS-1-(2-OXOPROPYL) CYCLOPROPANE 6.



IR SPECTRUM OF 3-PHENOXYBENZYL 1R-CIS-2,2-DIMETHYL-3-(2p-TOLYL-PROP-1-ENYL) CYCLOPROPANECARBOXYLATE 13



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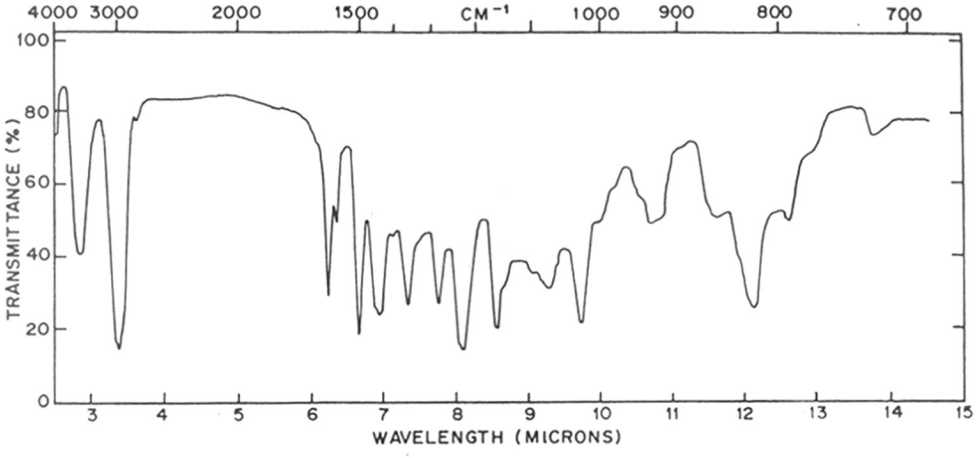
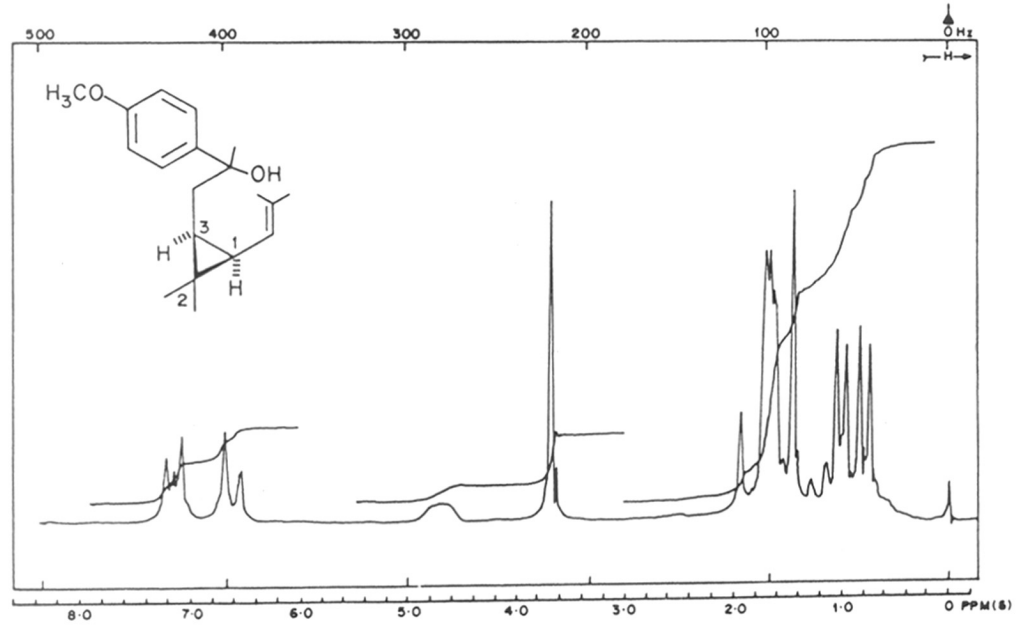
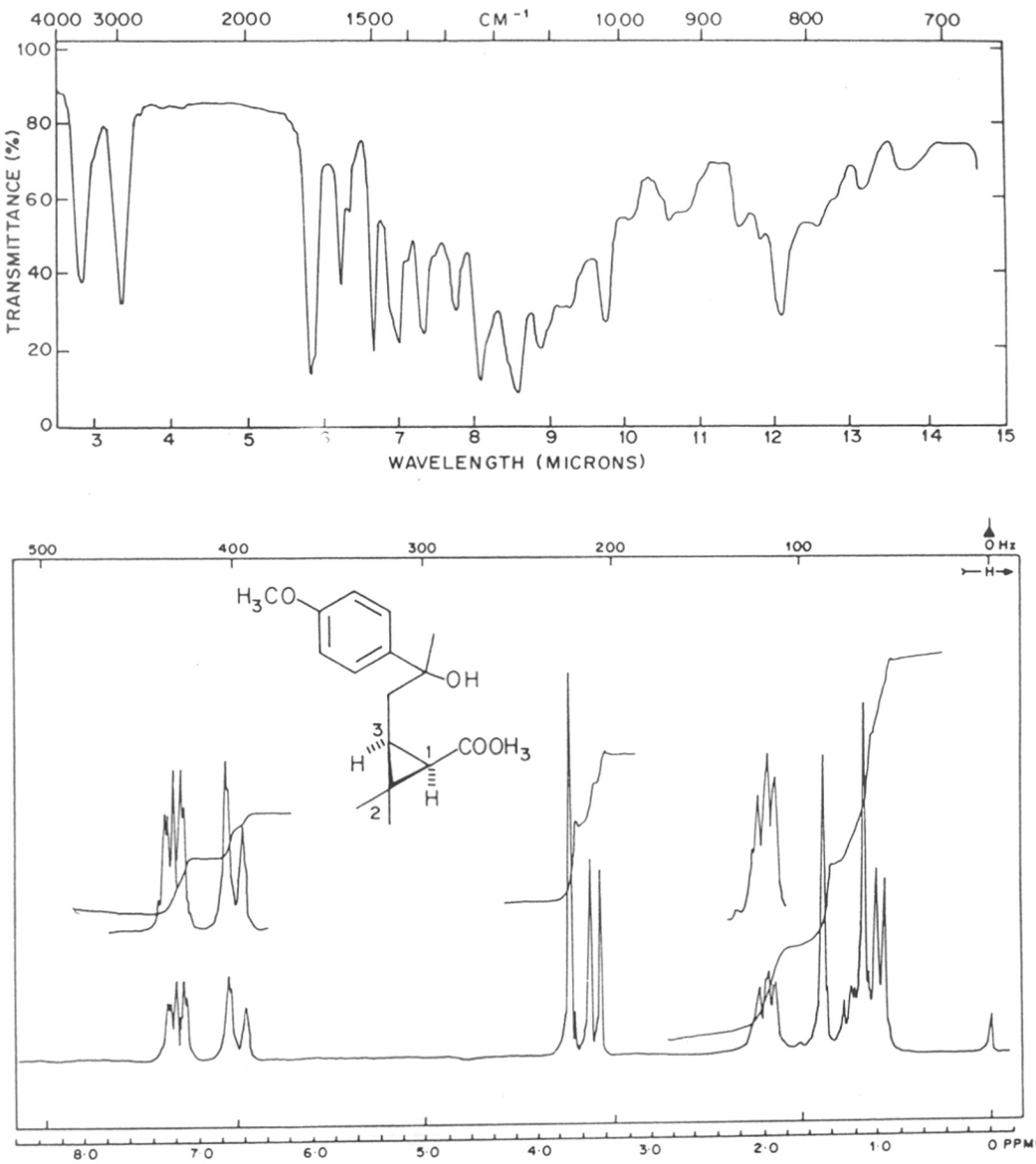
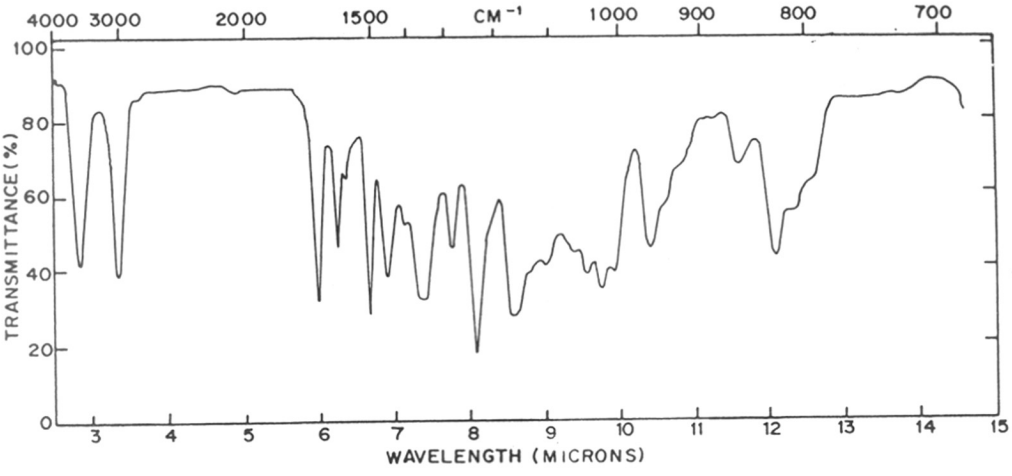


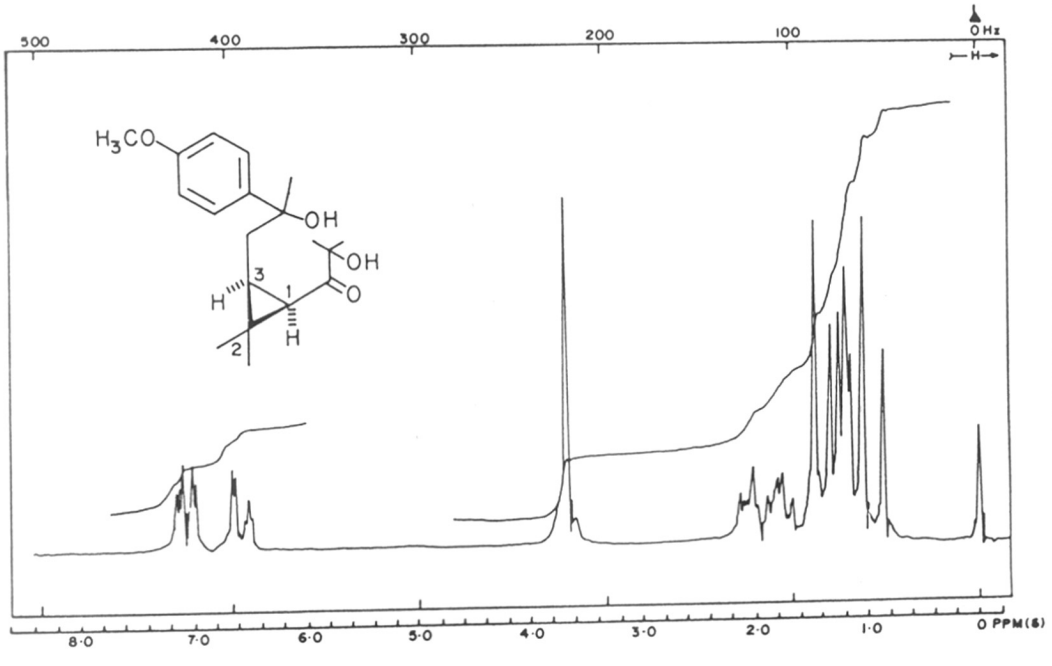


IR & PMR OF 2,2-DIMETHYL-1-(2-METHYLPROP-1-ENYL)-CIS-3-(2-p-ANISYL-2-HYDROXYPROPYL) CYCLOPROPANE 15.

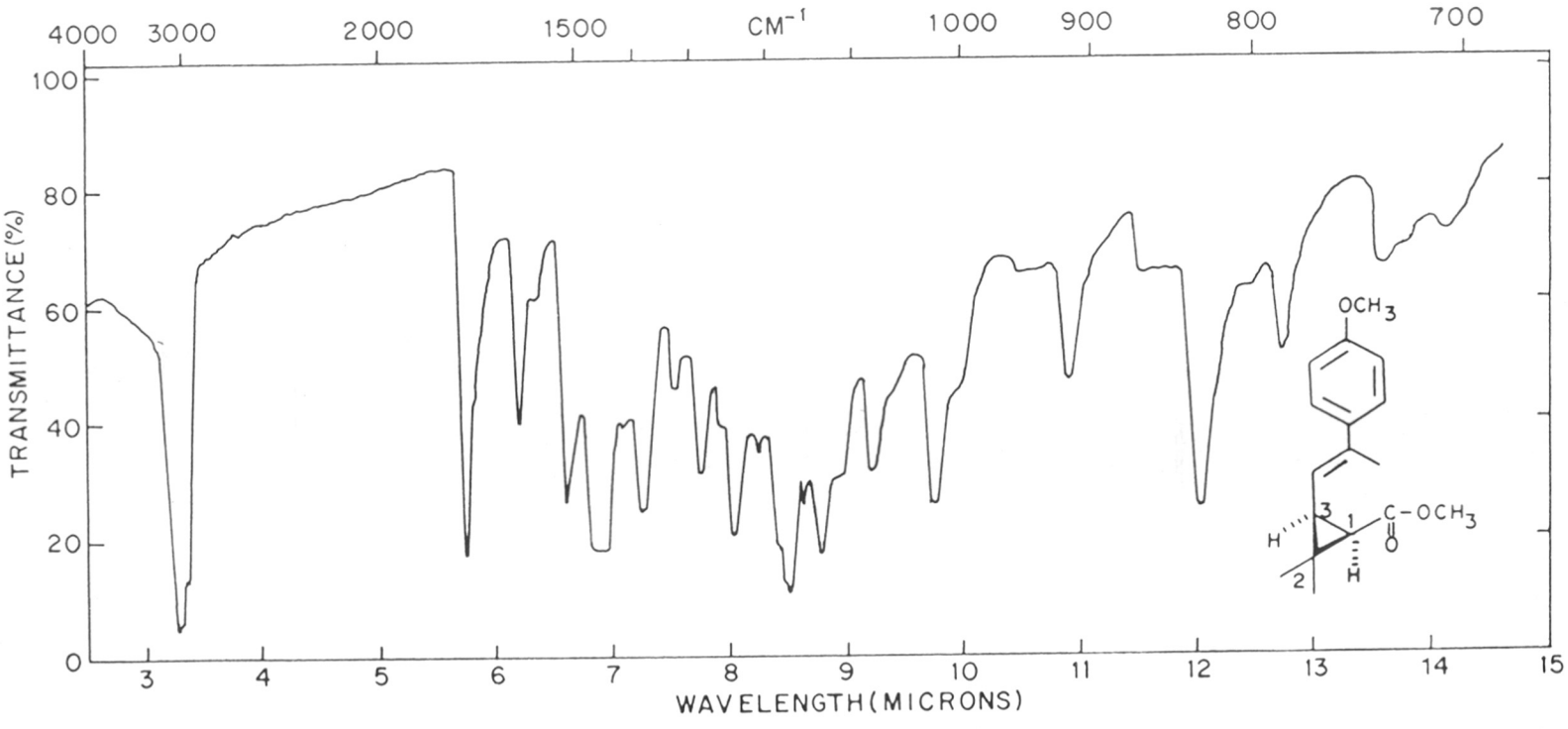


IR & PMR OF METHYL 1R-CIS-2,2-DIMETHYL-3-(2-p-ANISYL-2-HYDROXYPROPYL) CYCLOPROPANECARBOXYLATE 16

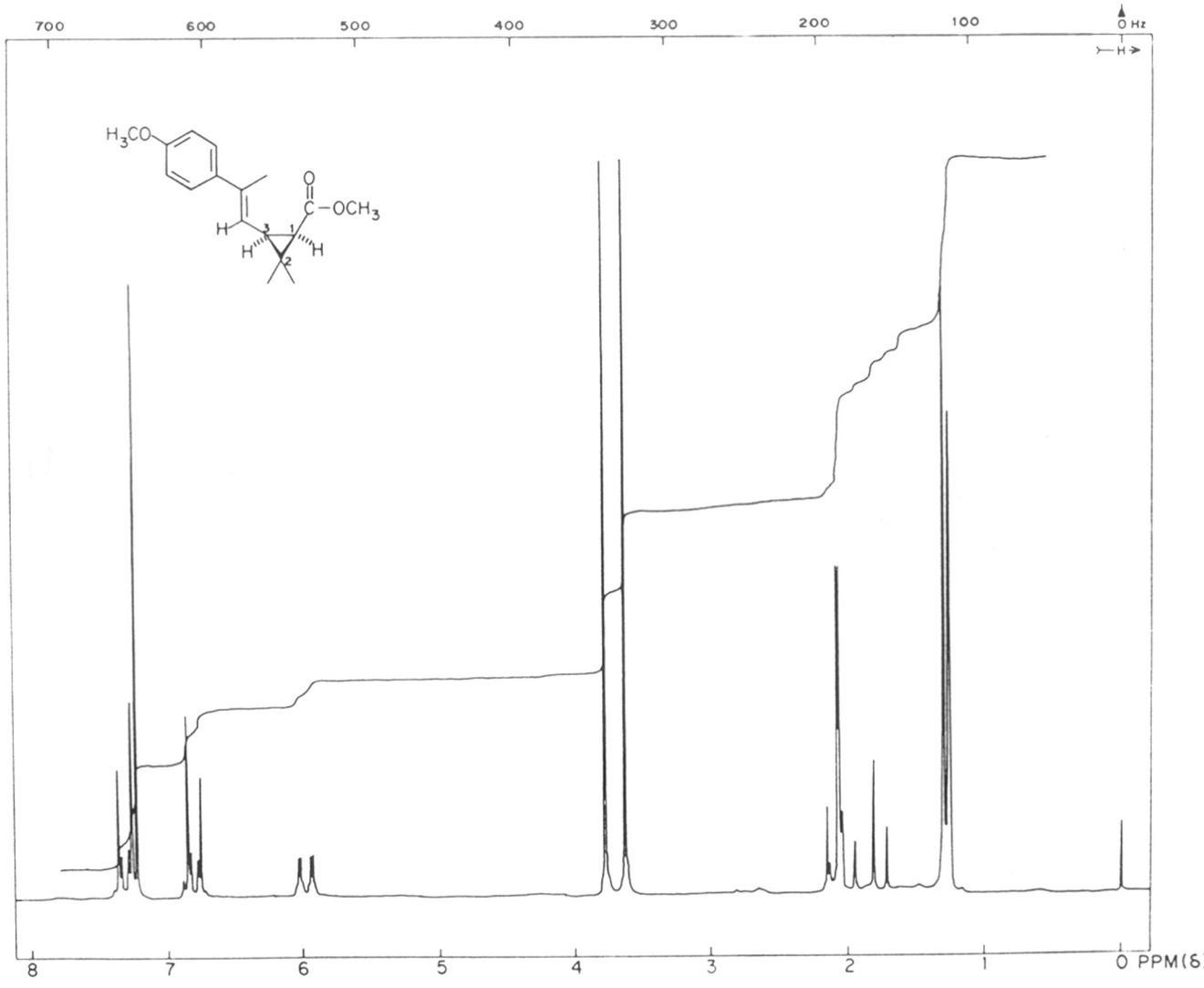




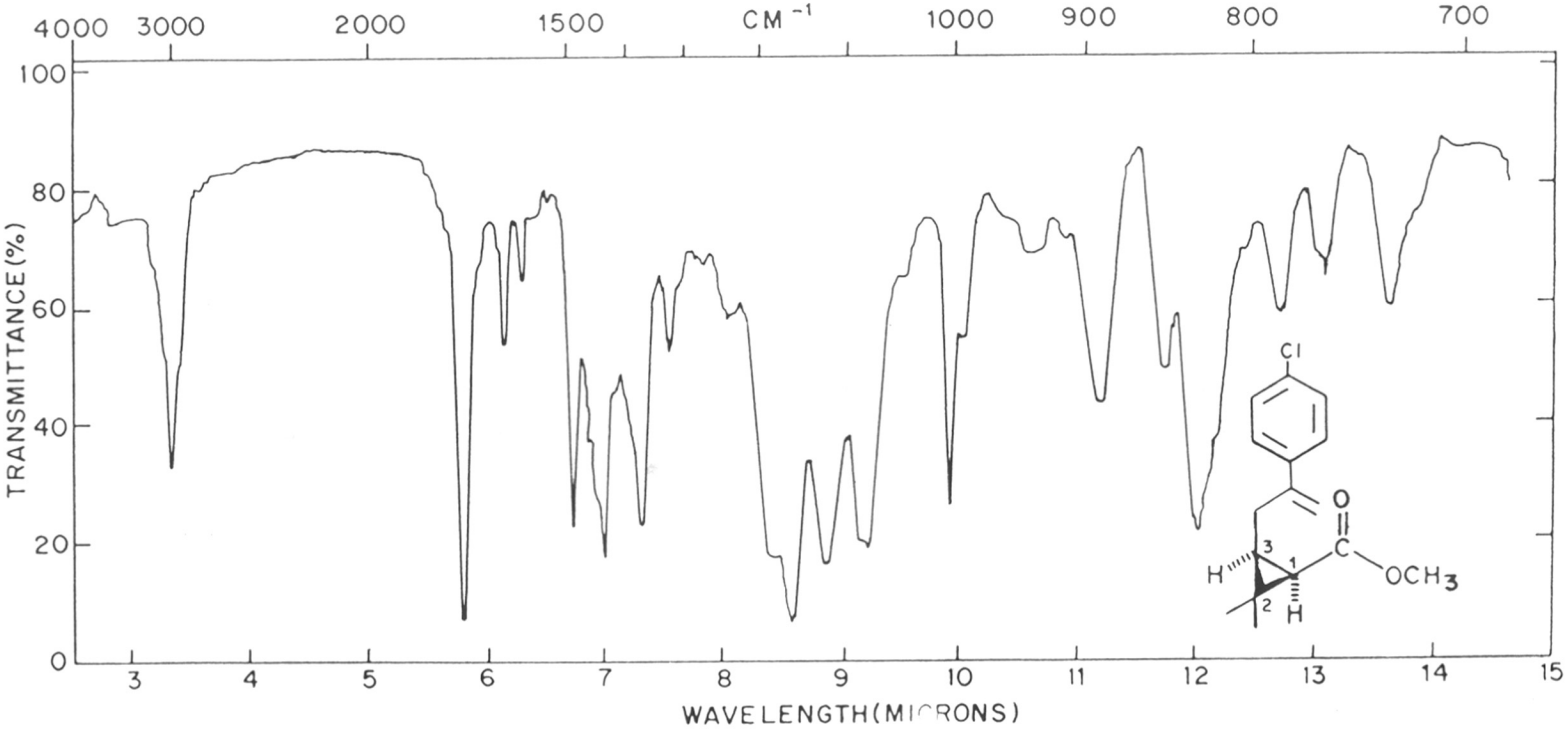
IR & PMR OF 2,2-DIMETHYL-3-(2-p-ANISYL-2-HYDROXYPROPYL) -CIS-1-(2-METHYL-2 HYDROXY-1-OXOPROPYL) CYCLOPROPANE 17.



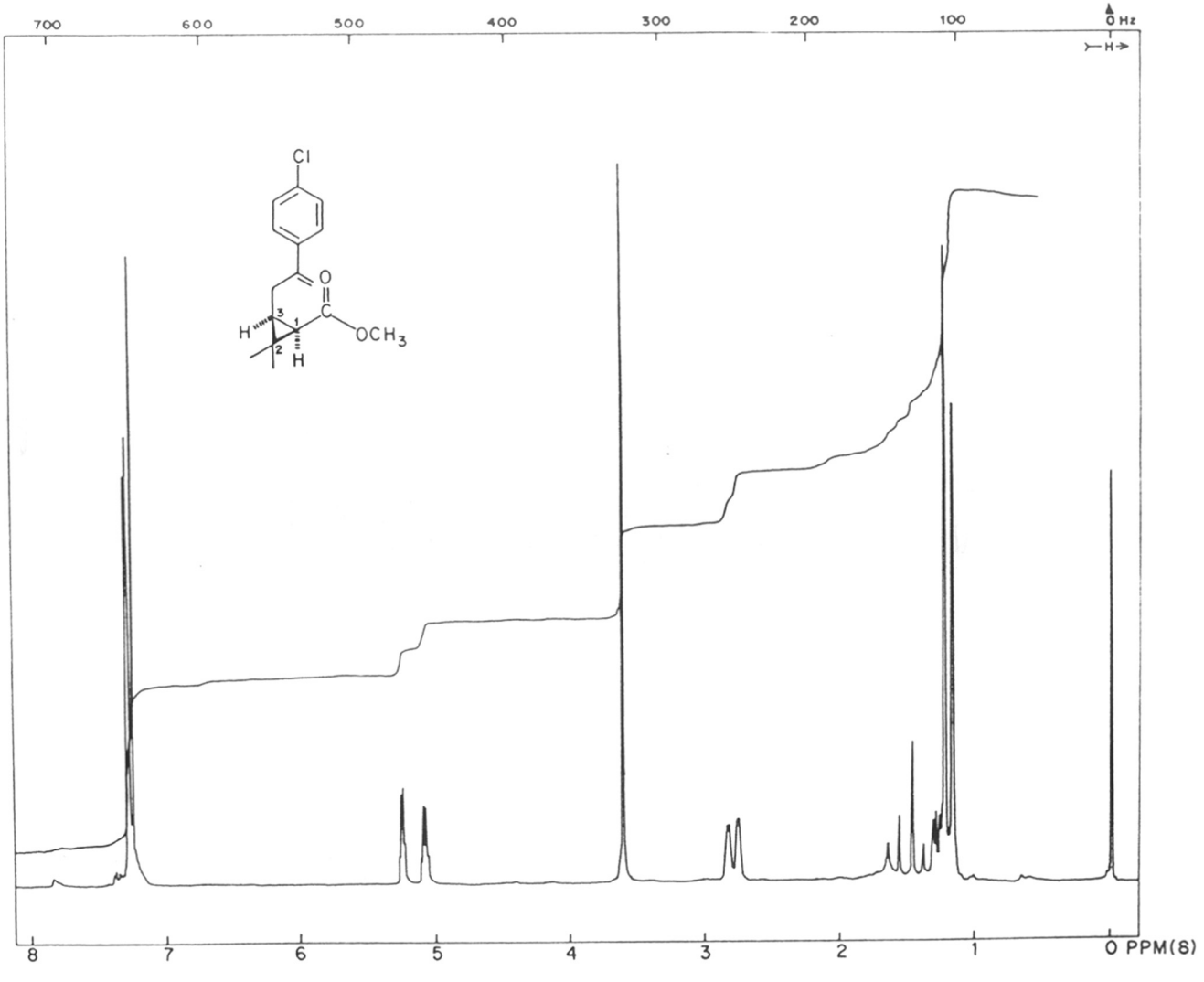
IR SPECTRUM OF METHYL IR-CIS-2,2-DIMETHYL-3-(2-p-ANISYLPROP-1-ENYL) CYCLOPROPANECARBOXYLATE 18



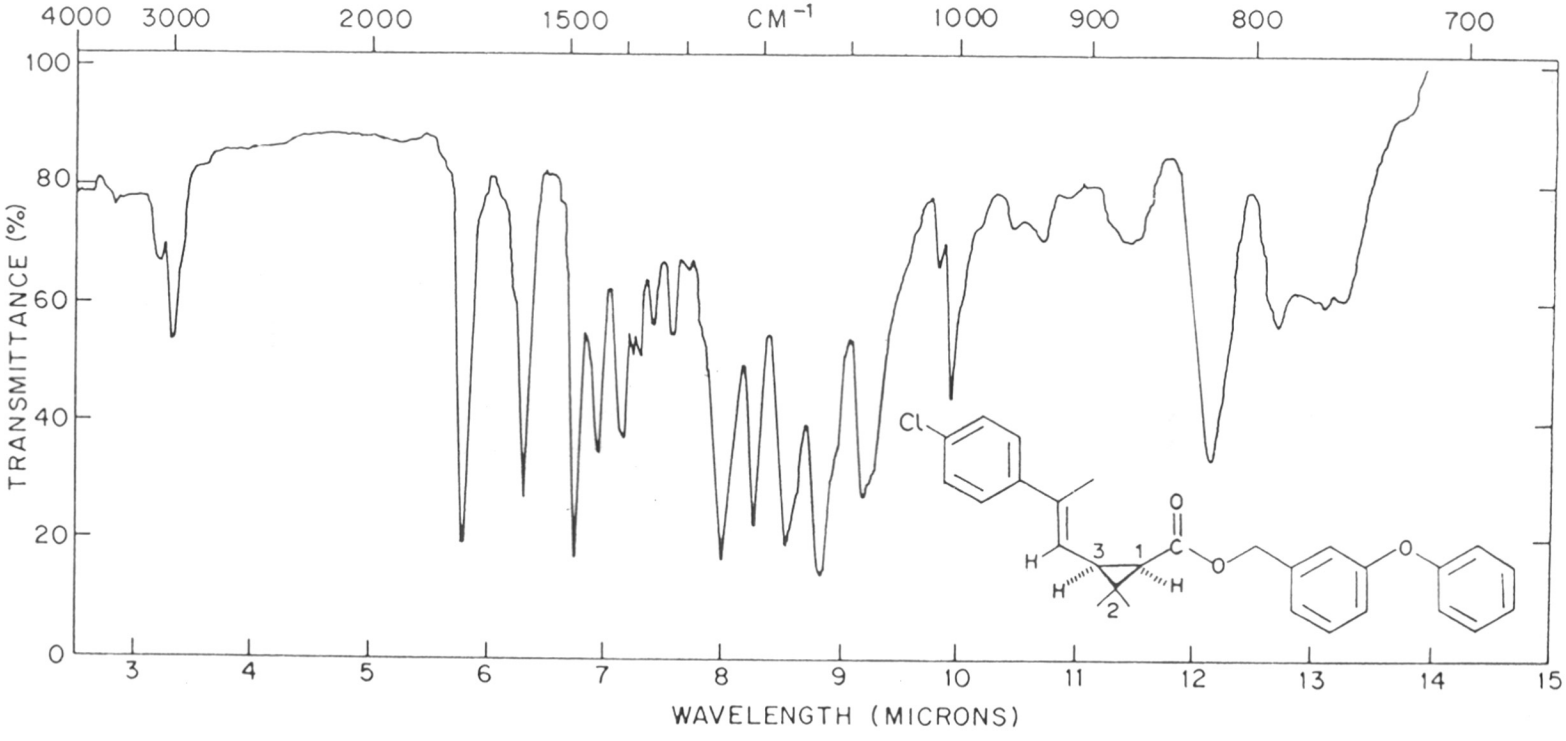
PMR SPECTRUM OF METHYL 1R-CIS-2,2-DIMETHYL-3-(2-p-ANISYLPROP-1-ENYL) CYCLOPROPANECARBOXYLATE 18



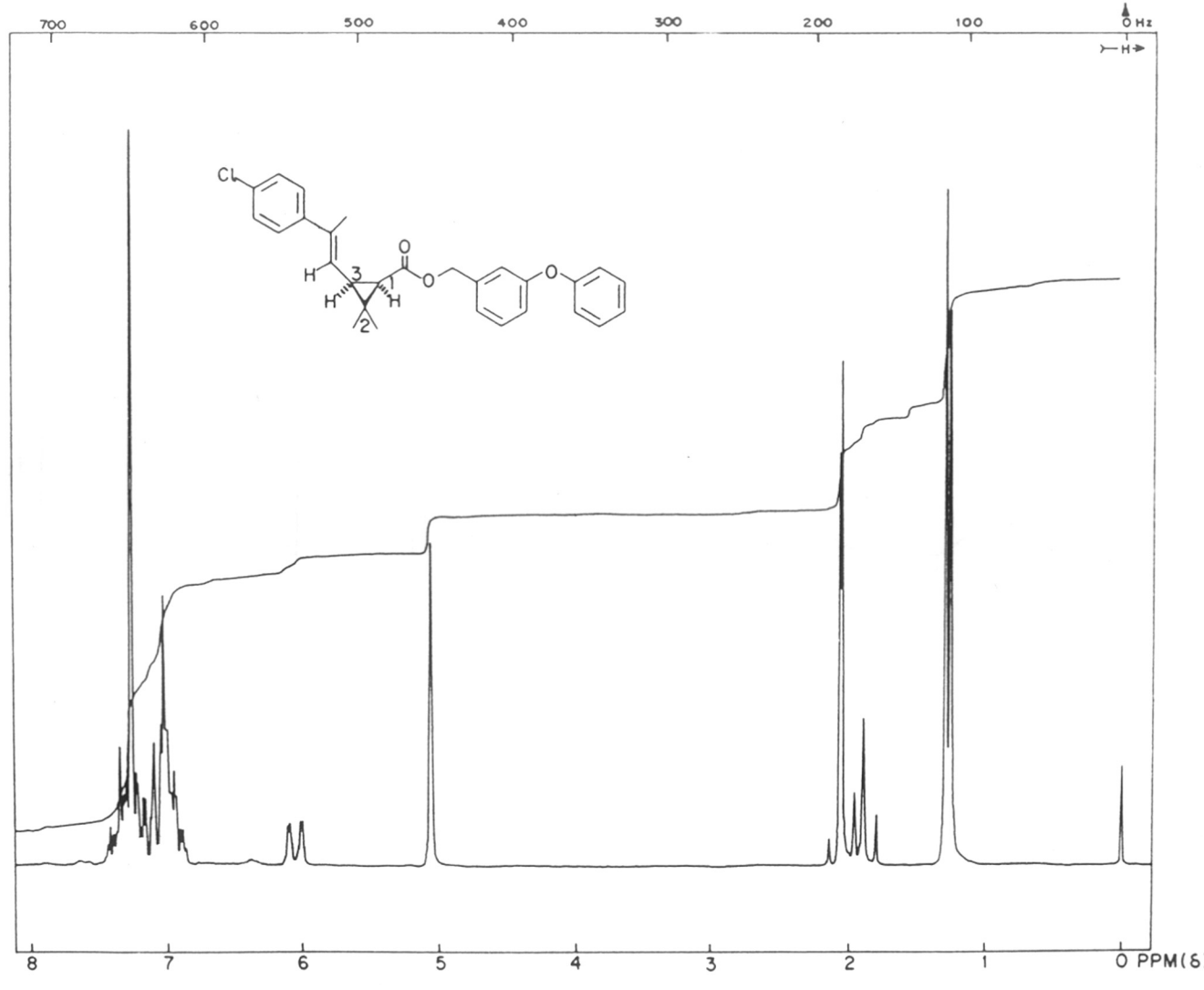
IR OF METHYL 1R-CIS-2,2-DIMETHYL-3-(2-p-CHLOROPHENYL-PROP-2-ENYL) CYCLOPROPANECARBOXYLATE 26.



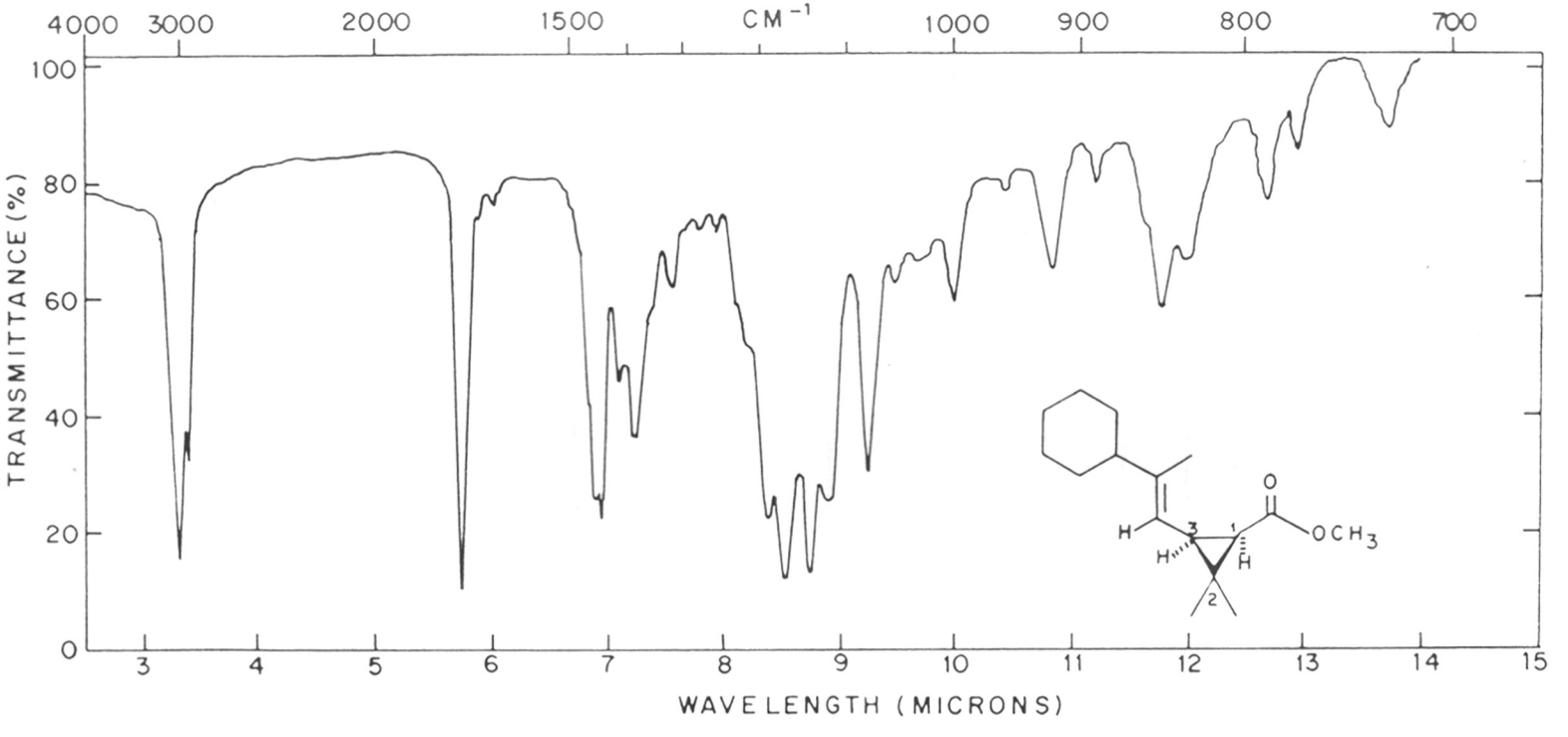
PMR OF METHYL 1R-CIS-2,2-DIMETHYL-3-(2-p-CHLOROPHENYL-PROP-2-ENYL) CYCLOPROPANECARBOXYLATE 26.



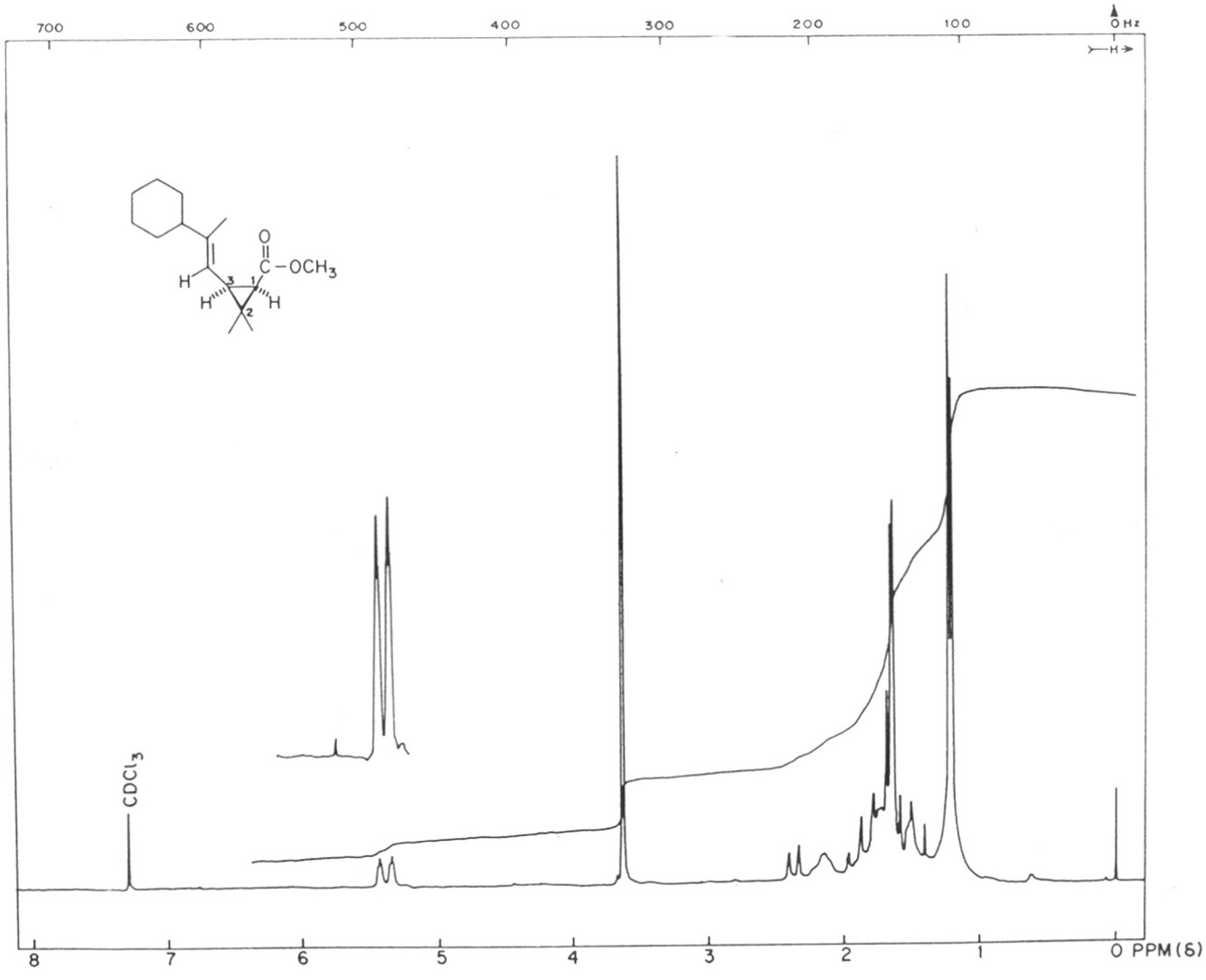
IR SPECTRUM OF 3-PHENOXYBENZYL 1R-CIS-2,2-DIMETHYL-3-(2p-CHLORO-PHENYLPROP-1-ENYL)-CYCLOPROPANECARBOXYLATE 27.



PMR SPECTRUM OF 3-PHENOXYBENZYL 1R-CIS-2,2-DIMETHYL-3-(2-p-CHLOROPHENYLPROP-1-ENYL)-CYCLOPROPANECARBOXYLATE 27



IR SPECTRUM OF METHYL 1R-CIS-2,2-DIMETHYL-3-(2-CYCLOHEXYLPROP-1-ENYL) CYCLOPROPANECARBOXYLATE 31.



PMR SPECTRUM OF METHYL 1R – CIS – 2,2 – DIMETHYL – 3-(2-CYCLOHEXYLPROP-1-ENYL) CYCLOPROPANECARBOXYLATE 31.

CHAPTER – III

SYNTHESIS OF IMPORTANT SYNTHONS FOR PYRETHROIDS FROM (+)-3-CARENE

SUMMARY

Friedel-Craft acylation of (+)-3-carene 1 with acetic anhydride and zinc chloride gave (+)-4α-acetylcar-2-ene 2. Methylation of 2 using methyl iodide and potassium t-butoxide afforded 4-methyl-4-acetylcar-2-ene 3. Ozonolysis of 3, followed by oxidative work-up with Jones chromic acid reagent gave the diketo acid 4 (R=H), characterised through its methyl ester 4 ($R=CH_3$). Treatment of diketo ester 4 ($R = CH_3$) with sodium methoxide, followed by esterification (CH_2N_2) gave the keto ester 5 ($R=CH_3$). Baeyer-Villiger oxidation of the keto ester 5 ($R=CH_3$) with m-chloroperbenzoic acid furnished the acetoxy ester 6. Saponification of 6 with methanolic potash, followed by esterification (CH_2N_2) gave hydroxy ester 7 ($R=CH_3$) which, on Jones chromic acid oxidation afforded the keto ester 8. By following analogous procedures keto esters 14 and 20 have also been synthesised.

INTRODUCTION

The naturally occurring insecticides like pyrethrin I[1], Cinerin I[2] and jasmolin I[3,4,5] are all esters of (+)-1R-*trans*-chrysanthemic acid with different alcohols like pyrethrolone, cinerolone and jasmolone respectively. These naturally occurring insecticides have drawn increasing attention due to the unique combination of their insecticidal properties, knock down effect, low mammalian toxicity and biodegradability. For these reasons they are environmentally safe and are still being used even today in some countries. The synthetic chrysanthemates like bioresmethrin[6], biophenothrin[7] and bioallethrin[8,9], which show higher and selective insecticidal activity than the naturally occurring esters have attracted the attention towards new synthetic approaches to (+)-1R-*trans*-chrysanthemic acid.

A number of ingenious synthesis of the racemic chrysanthemic acids[10-19] and also of the (+) *trans*-chrysanthemic acid[13,20] are on record, so also their resolution forms the subject matter of several patents[21-24] and papers[25]. In most of these methods, a substituted cyclopropane ring is built up, starting with suitable acyclic substrate. As a result, in many of these methods, a mixture of *cis* and *trans* isomers is obtained.

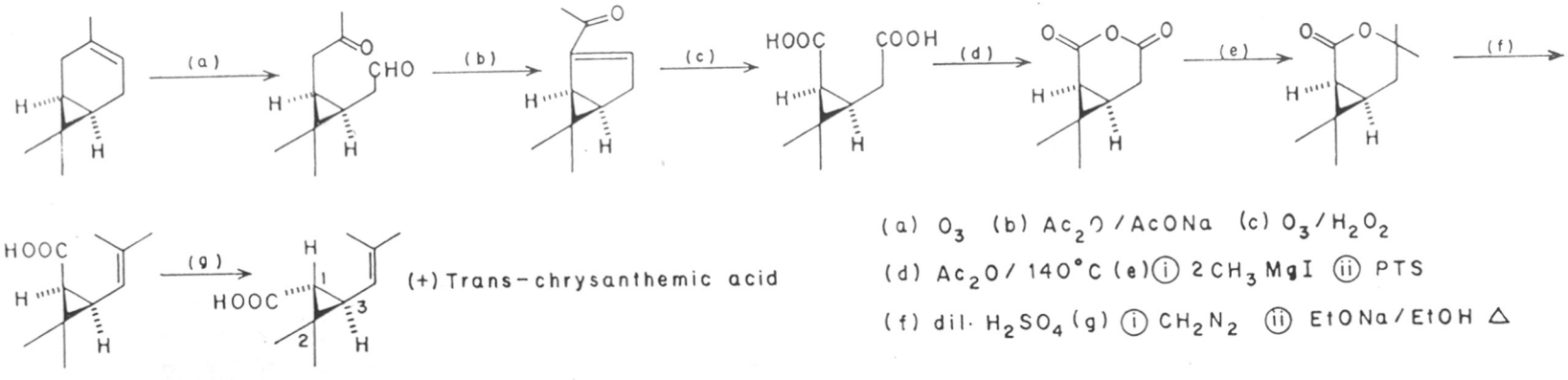
Some of the approaches towards the synthesis of (+)-trans-chrysanthemic acid starting from optically active naturally occurring substrates like (+)-3-carene[26-33], (+)α-pinene[34], (-) carvone[35], (+) limonene and α-terpineol[36] etc. described in literature have been presented below.

Matsui et al.[26] were the first to synthesise (+)-1R-trans-chrysanthemic acid from the (+)-3-carene, a naturally occurring monoterpene which is abundantly available and possesses the desired stereochemistry. The key intermediate in these synthesis was (+)-cis-homocaronic acid, which was converted to (-) 1S-cis- chrysanthemic acid, which in turn was converted to (+) 1R-trans-chrysanthemic acid by inversion of configuration at C_1 centre by epimerisation as shown in Scheme I, Chart I.

Cocker et al.[31] have converted (+)-3-carene into (+)-cis-homocaronic acid via (+)-4α-acetoxymethyl-car-2-ene and (+)-4α-acetylcar-2-ene by ozonolysis. The synthesis of (+) 1R-trans-chrysanthemic acid from (+)-cis-homocaronic acid has been achieved by the previous workers[26]. In a subsequent communication[32], they have converted methyl (+)-cis-2,2-dimethyl-3-(2-oxopropyl)cyclopropanecarboxylate, obtained as one of the products of transformation of (+)-3-carene, to methyl (-) cis-chrysanthemate (Scheme II, Chart I).

CHART I

Scheme I[26]

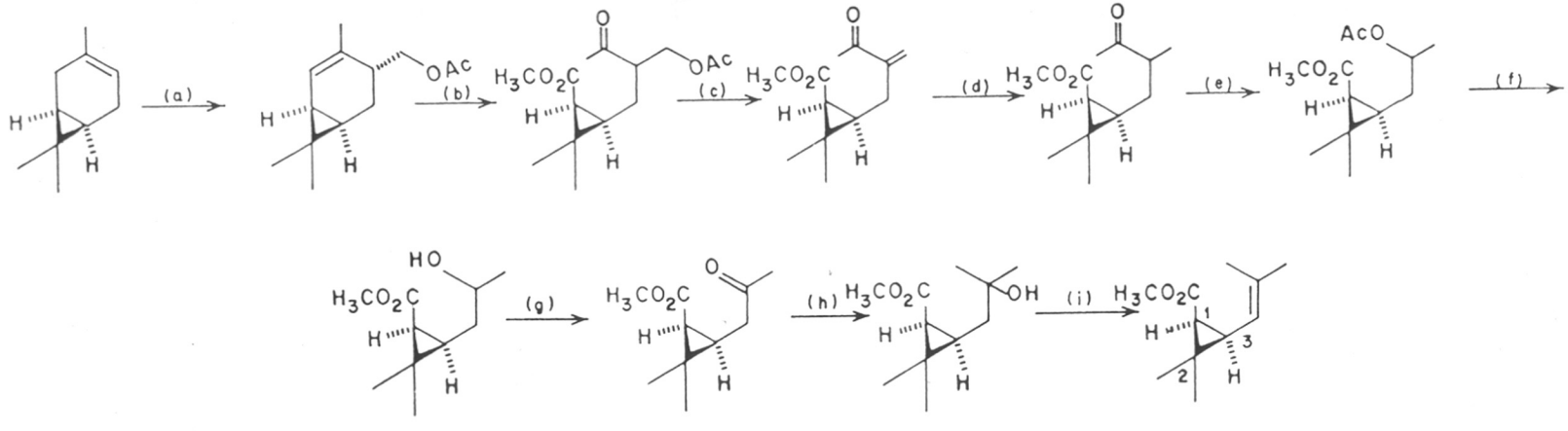


(a) O_3 (b) Ac_2O / AcONa (c) O_3/H_2O_2

(d) Ac_2O / 140°C (e) ⓘ $2CH_3MgI$ ⓘⓘ PTS

(f) dil. H_2SO_4 (g) ⓘ CH_2N_2 ⓘⓘ EtONa/EtOH △

Scheme II[32]



(a) HCHO/CH_3COOH (b) ⓘ O_3/H_2O_2, ⓘⓘ CH_2N_2 (c) Base (d) H_2/Pd-C (e) MCPBA (f) ⓘ Alkali ⓘⓘ CH_2N_2

(g) CrO_3 (h) Reverse Grignard CH_3MgI (i) PTS

Sukh Dev et al.[28] and Mitra et al.[29] have independantly developed a more efficient route to (+) 1R-trans-chrysanthemic acid from (+)-3-carene as shown in Scheme III, Chart II.

Mitra et al.[34] stereospecifically converted (+) α-pinene to (+) 1R-trans-chrysanthemic acid. In this synthesis the decisive step is a Favorskii rearrangement of substituted α-bromocyclobutanone (Scheme IV, Chart II).

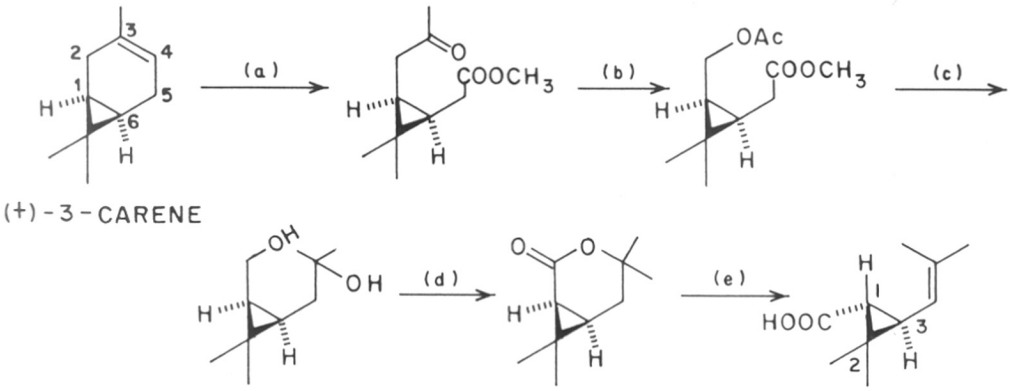
(+)-cis-Homocaronic acid and (-) cis-dihydrochrysanthemolactone which were employed by previous groups[26,31] for the synthesis of (+)-1R-trans chrysanthemic acid, have been prepared from (+)-3-carene by Ho et al.[33] from a common intermediate car-2-ene-4-one (Scheme V, Chart III).

Subsequently the same group achieved the synthesis of methyl (+) cis 2,2-dimethyl-3-(2-oxopropyl)cyclopropane-carboxylate from (-) carvone[35] as shown in Scheme VI, Chart III. Later on, they have also transformed (+) limonene[36] to (+) cis-homocaronic acid (Scheme VII, Chart IV) and α-terpineol[36] to Julia's bicyclic ketone[37,38] (Scheme VIII, Chart IV), both of which have been converted to 1R trans-chrysanthemic acid.

For effecting epimerisation of 1S cis compounds Sukh Dev et al.[28] have used (-) dihydrochrysanthemolactone. We have observed[39] that in addition to the lactone the corresponding 1S-cis-hydroxy acid or its methyl ester can

CHART II

Scheme III [28,29]

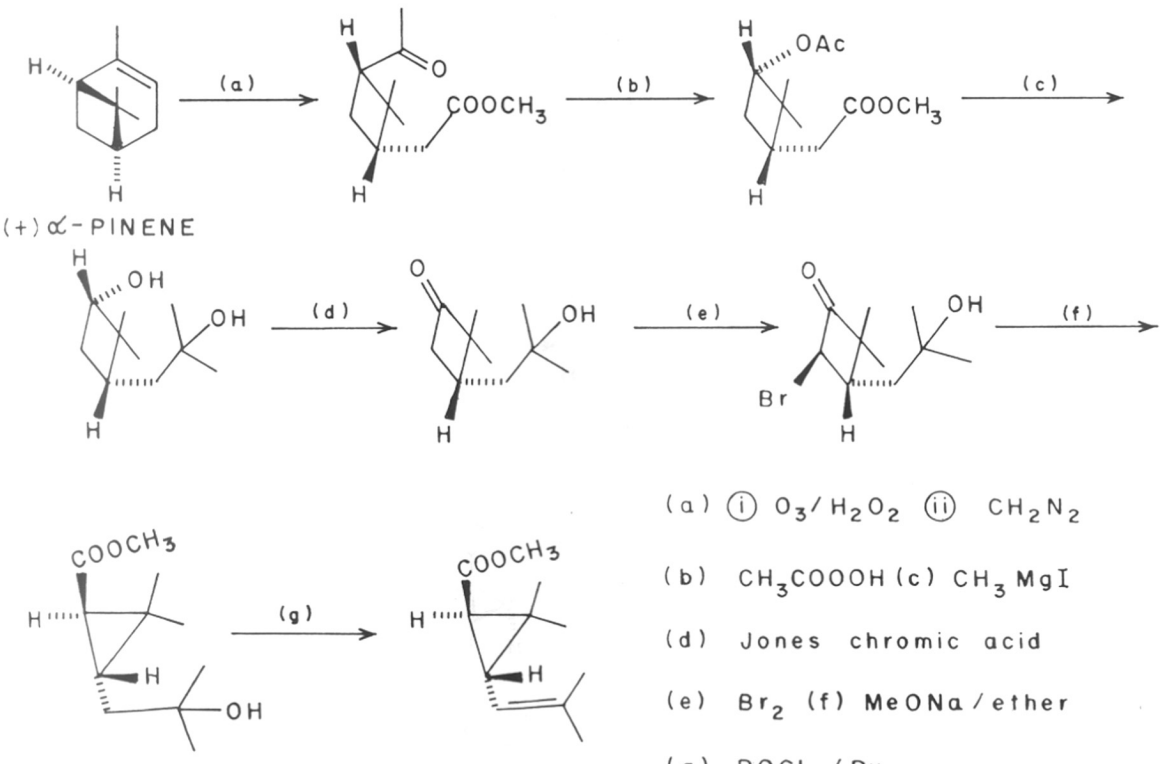


(+)-3-CARENE

(a) (i) O_3, CrO_3 (ii) MeOH, HCl (b) $CH_3-\overset{O}{\overset{\|}{C}}-O-OH$ (c) CH_3MgI

(d) (i) CrO_3 (ii) PTS (e) KOH / Diethylene glycol △

Scheme IV [34]



(+) α-PINENE

(a) (i) O_3/H_2O_2 (ii) CH_2N_2

(b) CH_3COOOH (c) CH_3MgI

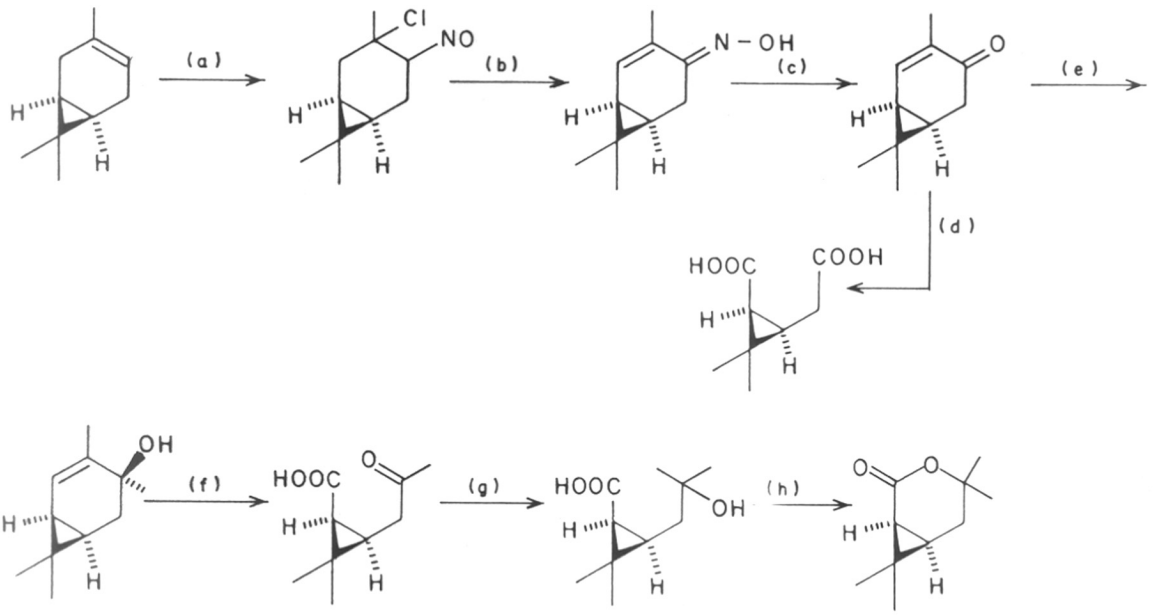
(d) Jones chromic acid

(e) Br_2 (f) MeONa / ether

(g) $POCl_3$ / Py

CHART III

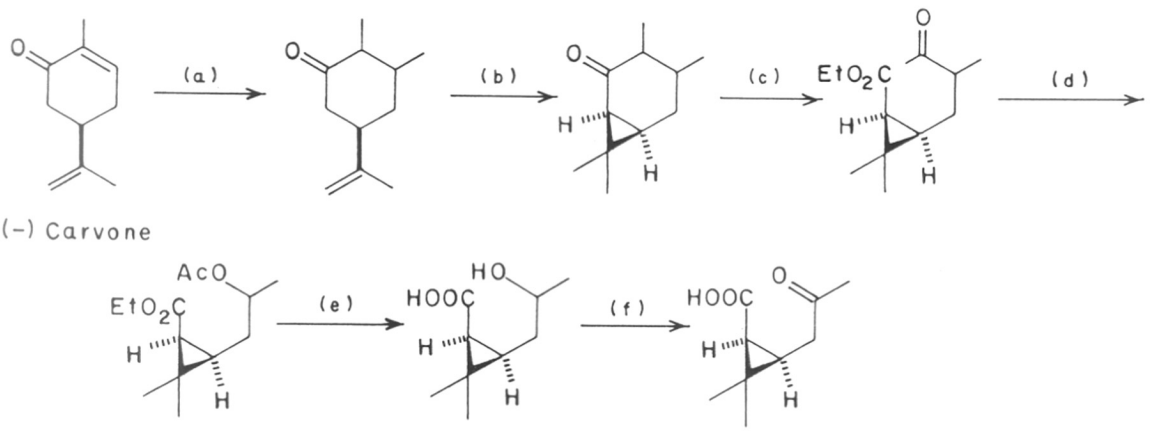
Scheme V [33]



(a) Nitrosyl chloride (b) Na_2CO_3 / iPrOH (c) Sodium bisulfite /aq. EtOH

(d) O_3 / H_2O_2 (e) MeLi (f) O_3 / H_2O_2 (g) CH_3MgI (h) PTS / Toluene

Scheme VI [35]



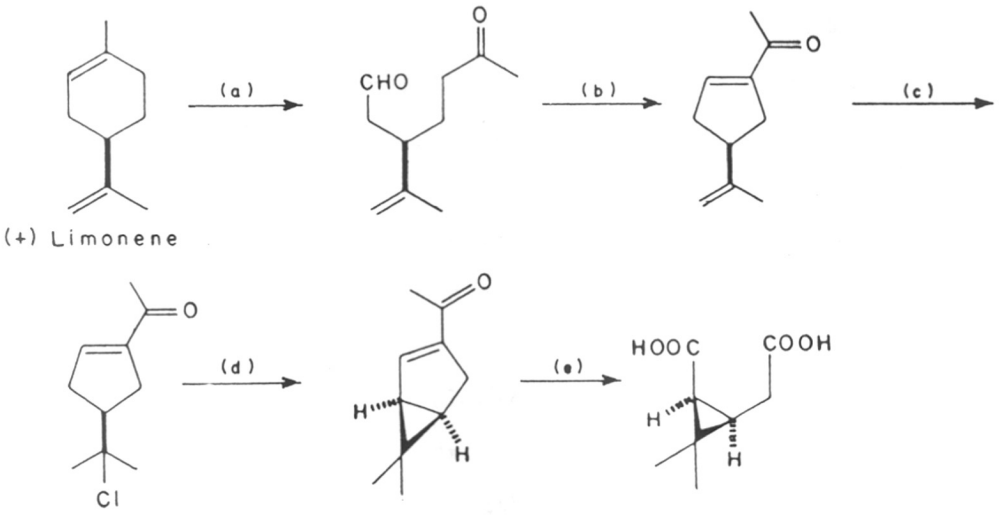
(–) Carvone

(a) CH_3MgI / CuCl (b) (i) HCl (ii) NaOH / MeOH (c) EtONO / EtONa

(d) CH_3COOOH (e) NaOH / aq. EtOH (f) CrO_3

CHART IV

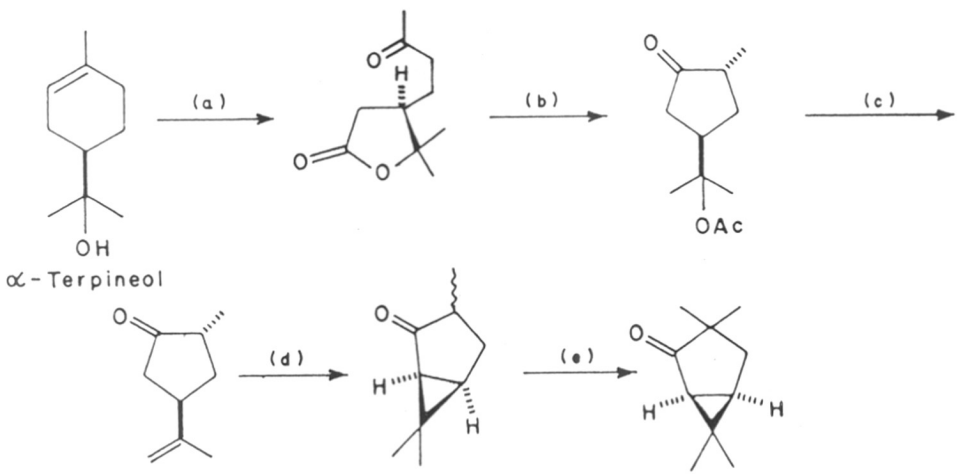
Scheme VII [36]



(a) $O_3/(CH_3)_2S$ (b) 50 % NaOH in CH_2Cl_2 (c) HCl

(d) NaOH / MeOH (e) O_3/H_2O_2

Scheme VIII [36]



(a) Oxidation

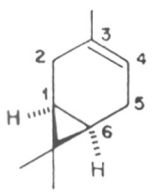
(b) (i) NaH / THF (ii) CH_3I

(c) Pyrolysis

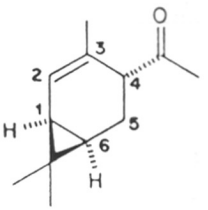
(d) (i) HCl / cat. $AlCl_3$ (ii) NaOH / MeOH (e) CH_3I / LDA

also be employed for epimerisation at C_1 centre to give the corresponding 1R trans-hydroxy esters (as described in Chapter IV) under slightly modified conditions.

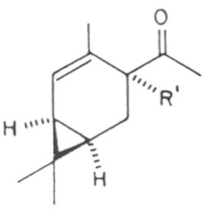
The high insecticidal activity of some esters[40,41] of (+) 1R-trans-chrysanthemic acid and its analogues[42,43], prompted us to investigate a new generalised and more efficient synthetic route[44] for the synthesis of methyl (+)-1S-cis-2,2-dimethyl-3-(2-oxo-alkyl/aralkyl)cyclopropanecarboxylate, which are precursors for the corresponding 1R-trans-chrysanthemates and its analogues from (+)-3-carene, a cheap, abundant, indigenous byproduct from pine oil (pinus longifolia).



1



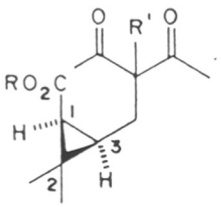
2



3 R' = CH_3

9 R' = C_2H_5

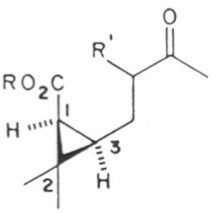
15 R' = CH_2Ph



4 R' = CH_3 ; R = H or CH_3

10 R' = C_2H_5 ; R = H or CH_3

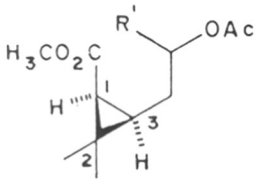
16 R' = CH_2Ph ; R = H or CH_3



5 R' = CH_3 ; R = H or CH_3

11 R' = C_2H_5 ; R = H or CH_3

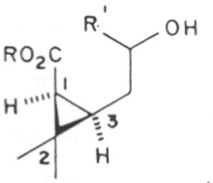
17 R' = CH_2Ph ; R = H or CH_3



6 R' = CH_3

12 R' = C_2H_5

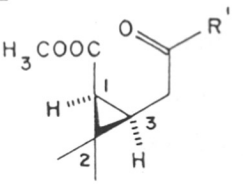
18 R' = CH_2Ph



7 R' = CH_3 ; R = H or CH_3

13 R' = C_2H_5 ; R = H or CH_3

19 R' = CH_2Ph ; R = H or CH_3



8 R' = CH_3

14 R' = C_2H_5

20 R' = CH_2Ph

PRESENT WORK

(+)-3-Carene 1, on treatment with acetic anhydride in presence of Lewis acid like anhydrous zinc chloride, afforded in fairly good yield (+)-4α-acetylcar-2-ene 2[45], $C_{12}H_{18}O$, M^+ 178 . IR Spectrum showed bands at 1704 (>C=O), 1661 (C=C) and 830 (trisubstituted double bond) and PMR spectrum showed signals at 0.9, 1.13 (3H each, s each, gem-dimethyl on cyclopropane ring), 1.76 (3H, s, vinyl methyl), 2.10 (3H, s, acetyl methyl) and 5.56 (1H, m, olefinic proton). Methylation of 2 using methyl iodide and potassium t-butoxide followed by chromatographic purification gave 4-methyl-4-acetylcar-2-ene 3, $C_{13}H_{20}O$, M^+ 192 in 65% yield. The compound 3 showed IR bands at 1706 (>C=O), 1653 (C=C) and 823 (trisubstituted double bond) and PMR spectrum showed signals at 0.8 to 1.06 (2H, m, cyclopropane protons at C_1 and C_6) 1.00, 1.16 (9H, s each, gem-dimethyl on cyclopropane and methyl at C_4), 1.56 (3H, s, vinyl methyl), 1.73 (2H, m, methylene protons at C_5), 2.03 (3H, s, $-\overset{O}{\overset{\|}{C}}-CH_3$) and 5.53 (1H, m, olefinic proton). Methylated product 3 on ozonolysis in ethylacetate at -10°, followed by oxidative work-up of the ozonide by Jones chromic acid reagent[46] furnished 1S-cis-2,2-dimethyl-3-(2,2-diacetylpropyl)cyclopropanecarboxylic acid 4 (R=H), which was esterified with an ethereal solution of diazomethane. The neutral part was not characterized.

The resulting ester 4 (R = CH_3) was purified by chromatography to give TLC pure ester 4 (R=CH_3) in 52% yield, $C_{14}H_{22}O_4$, M^+ 254. It exhibited IR bands at 1730, 1176 (ester >C=O), 1706 (>C=O) and PMR spectrum showed signals at 0.83 (1H, m, cyclopropane proton at C_3), 1.16 (6H, s, gem-dimethyl on cyclopropane), 1.25 (3H, s, methyl group flanked by two >C=O), 1.40 (1H, d, J = 8 Hz, cyclopropane proton at C_1), 2.05 (6H, s, two $-\overset{O}{\overset{\|}{C}}-CH_3$), 2.16 (2H, m, methylene protons) and 3.60 (3H, s, ester methyl).

Diacetyl ester 4 (R=CH_3) possessing a β-diketone grouping on heating with sodium methoxide in methanol gave keto acid 5 (R=H), which was esterified with an ethereal solution of diazomethane to give methyl ester 5 (R=CH_3), $C_{12}H_{20}O_3$, M^+ 212 in almost quantitative yield. It showed IR bands at 1721, 1163 (>C=O of ester and ketone) and PMR signals at 1.03 (3H, d, J = 7 Hz, methyl attached to carbon bearing acetyl group), 1.12, 1.14 (3H each, s each, gem-dimethyl on cyclopropane), 1.33 (1H, d, J = 8 Hz, cyclopropane proton at C_1), 1.76 (2H, m, methylene protons), 2.00 (3H, s, acetyl methyl), 2.26 (1H, m, proton on carbon bearing acetyl group and methyl) and 3.48 (3H, s, ester methyl).

Methyl ester 5, on Baeyer-Villiger oxidation using m-chloroperbenzoic acid afforded in 65% yield, the methyl 1S-cis 2,2-dimethyl-3-(2-acetoxypropyl)cyclopropane-

carboxylate 6, $C_{12}H_{20}O_4$, M^+ 228. IR Spectrum showed bands at 1730, 1176 (>C=O), 1242 (acetate) and PMR signals at 0.93 (1H, m, cyclopropane proton at C_3), 0.96 to 1.20 (9H, m, gem-dimethyl on cyclopropane and methyl attached to carbon bearing acetoxy group), 1.35 (1H, d, J = 8 Hz, cyclopropane proton at C_1), 1.78 (2H, t, J = 6 Hz, methylene protons), 1.90 (3H, s, acetate methyl), 3.46 (3H, s, ester methyl) and 4.66 (1H, m, proton attached to carbon bearing acetate function).

Saponification of 6 at room temperature with aqueous methanolic potassium hydroxide furnished the hydroxy acid 7 (R=H), which on esterification with an ethereal solution of diazomethane gave hydroxy ester 7 ($R=CH_3$), $C_{10}H_{18}O_3$, M^+ 186. It showed following spectral properties: IR bands at 3509 (OH), 1724, 1170 (ester >C=O) and PMR signals at 1.11 (3H, d, J = 5 Hz, methyl attached to carbon bearing hydroxy group), 1.16 (7H, br s, gem-dimethyl on cyclopropane and cyclopropane proton at C_3), 1.40 (1H, d, J = 8 Hz, cyclopropane proton at C_1), 1.71 (2H, t, J = 6 Hz, methylene protons), 2.06 (1H, s, exchangeable with D_2O, OH proton) and 3.55 (3H, s, ester methyl).

Jones chromic acid oxidation of the hydroxy ester 7 ($R=CH_3$) gave in good yield the keto ester 8, $C_{10}H_{16}O_3$, M^+ 184. It showed IR bands at 1721, 1163 (>C=O) and PMR spectrum showed signals at 1.13, 1.24 (3H each, s each, gem-dimethyl on cyclopropane), 1.45 (2H, m, cyclopropane

protons at C_1 and C_3), 2.10 (3H, s, acetyl methyl), 2.80 (2H, d, J = 6 Hz, methylene protons) and 3.60 (3H, s, ester methyl).

Similarly, base catalysed reaction of compound 2 using ethyl iodide and potassium t-butoxide afforded 4-ethyl-4-acetylcar-2-ene 9, $C_{14}H_{22}O$, M^+ 206. It showed IR bands at 1695 (>C=O), 1639 (C=C) and 813 (trisubstituted double bond) and PMR spectrum showed signals at 0.86 (4H, t, J = 8 Hz, $-CH_2-CH_3$ and cyclopropane proton at C_6), 1.00, 1.13 (3H each, s each, gem-dimethyl on cyclopropane), 1.60 (3H, s, vinyl methyl), 1.75 (4H, m, methylene protons), 2.01 (3H, s, acetyl methyl and 5.66 (1H, m, olefinic proton).

Ozonolysis of 9 in ethylacetate followed by oxidative workup of the ozonide by Jones chromic acid reagent furnished 1S-cis-2,2-dimethyl-3-(2,2-diacetyl-butyl)cyclopropanecarboxylic acid 10 (R=H), which was esterified with an ethereal solution of diazomethane. The resulting methyl ester 10 was purified by chromatography to give TLC pure ester 10 ($R=CH_3$) in 50% yield, $C_{15}H_{24}O_4$, M^+ 268. It showed IR bands at 1721, 1170 (ester >C=O), 1695 (>C=O) and PMR ($CDCl_3$, 80 MHz) signals at 0.75 (4H, m, $-CH_2-CH_3$ and cyclopropane proton at C_3), 1.08, 1.14 (3H each, gem-dimethyl on cyclopropane), 1.42 (1H, d, J = 7 Hz, cyclopropane proton at C_1), 1.87 (2H, t, J =6 Hz, $-CH_2-CH_3$), 2.06 (6H, s, acetyl methyls), 2.19 (2H, m, methylene protons adjacent to cyclopropane ring) and 3.59 (3H, s, ester methyl).

Diacetyl ester 10 ($R=CH_3$) on treatment with sodium methoxide in refluxing methanol gave acid 11 (R=H), which was converted to methyl ester 11 ($R=CH_3$) with an ethereal solution of diazomethane. It was characterised through mass, IR and PMR spectral data. Mass spectrum showed M^+ 226. IR spectrum showed bands at 1724, 1170 (>C=O of ester and ketone); PMR spectrum showed signals at 0.9 (4H, m, $-CH_2-CH_3$ and cyclopropane proton at C_3), 1.23, 1.26 (3H each, s each, gem-dimethyl on cyclopropane), 1.33 to 1.96 (5H, m, methylene protons and cyclopropane proton at C_1), 2.13 (3H, s, acetyl methyl), 2.33 (1H, m, proton on carbon bearing ethyl and acetyl groups) and 3.70 (3H, s, ester methyl).

Baeyer- Villiger oxidation of 11 ($R=CH_3$) with m-chloroperbenzoic acid in refluxing methylene chloride furnished the acetate ester 12, $C_{13}H_{22}O_4$, M^+ 242. It showed IR bands at 1718, 1163 (ester >C=O), 1235 (acetate) and PMR signals at 0.91 (3H, t, J = 7 Hz, $-CH_2-CH_3$), 1.16, 1.21 (3H each, s each, gem-dimethyl on cyclopropane), 1.35 to 1.86 (5H, m, cyclopropane proton at C_1 and four methylene protons), 2.00 (3H, s, $-\overset{\overset{O}{\|}}{C}-CH_3$), 3.63 (3H, s, ester methyl) and 4.86 (1H, m, proton on carbon bearing -OAc group).

Saponification of 12 at room temperature gave the hydroxy acid 13 (R=H), which was esterified with an ethereal solution of diazomethane to give hydroxy ester 13 ($R=CH_3$), $C_{11}H_{20}O_3$, M^+ 200. It showed IR bands at 3448 (OH),

1712, 1163 (ester >C=O) and PMR signals at 0.9 (4H, m, $-CH_2-CH_3$ and cyclopropane proton at C_3), 1.15 (6H, s, gem-dimethyl on cyclopropane), 1.39 to 1.86 (5H, m, cyclopropane proton at C_1 and four methylene protons), 1.48 (1H, hump, exchangeable with D_2O, OH proton) and 3.50 (3H, s, ester methyl).

Jones chromic acid oxidation of 13 (R=CH_3) furnished the liquid keto ester 14, $C_{11}H_{18}O_3$, M^+ 198. It displayed the following spectral properties IR: 1724 (>C=O); PMR signals at 1.03 (3H, t, J = 8 Hz, $-CH_2-CH_3$), 1.13, 1.25 (3H each, s each, gem-dimethyl on cyclopropane), 1.48 (2H, m, cyclopropane protons at C_1 and C_3), 2.41 (2H, q, J = 7 Hz, $-\overset{O}{\overset{\|}{C}}-CH_2-CH_3$), 2.80 (2H, d, J = 6 Hz, methylene protons adjacent to cyclopropane ring) and 3.63 (3H, s, ester methyl).

Base catalysed alkylation of compound 2 with benzyl bromide furnished the product 15, $C_{19}H_{24}O$, M^+ 268, in good yield. It showed IR bands at 1718 (>C=O), 1653, 833 (trisubstituted double bond), 1608, 755, 701 (aromatic) and PMR signals at 0.70 (2H, m, both the cyclopropane protons), 0.96, 1.06 (3H each, s each, gem-dimethyl on cyclopropane), 1.40 (3H, s, vinyl methyl), 1.83 (2H, m, methylene protons at C_5), 2.03 (3H, s, $-\overset{O}{\overset{\|}{C}}-CH_3$), 3.01 (2H, s, benzylic methylene protons), 5.76 (1H, m, olefinic protons) and 7.33 (5H, s, aromatic protons).

Ozonolysis of 15 in ethylacetate at -10°, followed by oxidative workup of the ozonide by Jones chromic acid reagent gave in the acid part 1S-*cis*-2,2-dimethyl-3-(2,2-diacetyl-3-phenylpropyl)cyclopropanecarboxylic acid 16 (R=H), which was characterised through its methyl ester 16 (R=CH_3), $C_{20}H_{26}O_4$, M^+ 330. It showed IR bands at 1724, 1176 (>C=O), 1613, 1538, 760, 704 (aromatic) and PMR signals at 0.95 (1H, m, cyclopropane proton at C_3), 1.13, 1.18 (3H each, s each, gem-dimethyl on cyclopropane), 1.46 (1H, d, J = 9 Hz cyclopropane proton at C_1), 2.00, 2.03 (3H each, s each, acetyl methyls), 2.06 (2H, m, methylene protons adjacent to cyclopropane ring), 3.21 (2H, s, benzylic methylene protons), 3.63 (3H, s, ester methyl) and 7.20 (5H, m, aromatic protons). The neutral part was not characterised.

Treatment of 16 (R=CH_3) with sodium methoxide in refluxing methanol gave the keto acid 17 (R=H), which was esterified with an ethereal solution of diazomethane to give methyl ester 17 (R=CH_3), $C_{18}H_{24}O_3$, M^+ 288. It showed IR bands at 1730, 1163 (>C=O), 1613, 1504, 755, 700(aromatic) and PMR spectrum showed signals at 0.95 (1H, m, cyclopropane proton at C_3), 1.16 (6H, s, gem-dimethyl on cyclopropane), 1.38 (1H, d, J = 8 Hz, cyclopropane proton at C_1), 1.86 (3H, s, $-\overset{\overset{O}{\|}}{C}-CH_3$), 1.86 (2H, m, methylene protons adjacent to cyclopropane ring), 2.71 (3H, m, benzylic methylene protons and proton on carbon bearing acetyl group), 3.56 (3H, s, ester methyl) and 7.10 (5H, s, aromatic protons).

The ester 17 (R=CH_3), on Baeyer-Villiger oxidation using m-chloroperbenzoic acid in refluxing methylene chloride afforded the acetate ester 18, $C_{18}H_{24}O_4$, M^+ 304, as a liquid. It showed the following spectral properties: IR bands at 1733, 1163 (>C=O), 1235 (acetate) 1613, 1587, 748, 699 (aromatic) and PMR signals at 0.83 (1H, m, cyclopropane proton at C_3), 1.11, 1.15 (3H each, s each, gem-dimethyl on cyclopropane), 1.40 (1H, d, J = 8 Hz, cyclopropane proton at C_1), 1.70 to 2.03 (2H, br, m, CH_2 protons adjacent to cyclopropane ring), 1.88 (3H, s, -acetate methyl), 2.78 (2H, d, J = 7 Hz, benzylic methylene protons), 3.55 (3H, s, ester methyl), 4.95 (1H, m, proton attached to carbon bearing -OAc group) and 7.03 (5H, s, aromatic protons).

Saponification of 18 with aqueous methanolic potash furnished the hydroxy acid 19 (R=H), which was esterified with an ethereal solution of diazomethane to give hydroxy ester 19 (R=CH_3), $C_{16}H_{22}O_3$, M^+ 262. It showed IR bands at 3448 (OH), 1727 (ester >C=O), 1600, 750, 700 (aromatic) and PMR spectrum showed signals at 1.13 (6H, s, gem-dimethyl on cyclopropane), 1.36 (2H, m, cyclopropane protons at C_1 and C_3), 1.76 (2H, m, methylene protons adjacent to cyclopropane ring), 2.03 (1H, hump, exchangeable with D_2O, -OH proton), 2.60 (2H, d, J = 6 Hz, benzylic methylene protons), 3.50 (3H, s, ester methyl), 3.56 (1H, m, protons attached to carbon bearing hydroxy group) and 6.96 (5H, s, aromatic protons).

Jones chromic acid oxidation of the hydroxy ester 19 ($R=CH_3$) gave the keto ester 20, $C_{16}H_{20}O_3$, M^+ 260. It was identified as 20 on the basis of spectral data: IR bands at 1727, 1170 (>C=O), 1613, 1499, 743, 699 (aromatic); PMR spectrum signals at 1.03, 1.14 (3H each, s each, gem-dimethyl on cyclopropane), 1.41 (2H, m, cyclopropane protons at C_1 and C_3), 2.80 (2H, d, J = 7 Hz, methylene protons adjacent to cyclopropane ring), 3.50 (3H, s, ester methyl), 3.56 (2H, s, benzylic methylene protons) and 7.10 (5H, s, aromatic protons).

The stereochemistry of compounds 3, 9 and 15 at asymmetric centre C_4 has been tentatively assigned as shown in stereostructures. The incoming alkyl group attacks from the less hindred α-side, since the β-face of the 4- α-acetylcar-2-ene 2 was shielded by cyclopropanyl methyl groups.

EXPERIMENTAL

(+)-4α-Acetylcar-2-ene 2

A mixture of acetic anhydride (220 ml, 2.33 moles), (+)-3-carene 1 (136 g, 1 mole) was heated to 50° with stirring in an atmosphere of nitrogen. Anhydrous zinc chloride (24 g, 0.18 mole) was then added portionwise over a period of 2 hr maintaining the temperature 50°. The mixture was stirred at the same temperature for additional 3 hr and then poured into water (300 ml). The organic layer was extracted with ether (150 ml x 3). The ether layer was washed with aqueous sodium bicarbonate solution 5%, water and dried. Evaporation of ether furnished the crude product, which was fractionated and the fractions boiling at 60 to 70° (vapour)/0.8 mm was collected. This fraction consisted chiefly of compound 2 (97 g). This fraction showed 98% purity by GLC. (Found: C, 81.15; H, 9.78; $C_{12}H_{18}O_2$ requires C, 80.85; H, 10.18%).
IR bands at: 2985, 1704, 1661, 1439, 1350, 1244, 1189, 1168, 1140, 1029, 971 and 830 cm^{-1}.

4-Methyl-4-acetylcar-2-ene 3

To an ice-cooled and stirred solution of potassium t-butoxide (8.4 g, 75 mmol) and 4-α-acetylcar-2-ene 2 (8.9 g, 50 mmol) in t-butanol (100 ml), methyl iodide (10.65 g, 75 mmol) was added in one lot and the mixture

stirred at 0° for 2 hr and at room temperature for 24 hr. The reaction mixture was filtered, t-butanol removed by distillation under reduced pressure, the residue diluted with water and extracted with ether (100 ml x 3). The ether layer was washed with water (100 ml x 2) and dried. Removal of the ether furnished the crude product (9 g), which was purified by chromatography over silica gel (180 g) and eluted with pet.ether + benzene (4:1) and pet.ether + benzene (1:1) successively to give compound 3; yield 6.3 g (65%); b.p.102-107°/0.1 mm;$(\alpha)_D^{28}$ + 133° (c, 2.0). (Found: C, 81.69; H, 10.59; $C_{13}H_{20}O$ requires C, 81.20; H, 10.48%).

IR bands at: 3012, 1706, 1653, 1449, 1370, 1351, 1220, 1091 and 823 cm^{-1}.

Methyl 1S-cis-2,2-dimethyl-3-(2,2-diacetylpropyl)cyclopropanecarboxylate 4 (R=CH_3)

A stream of ozonised oxygen was passed through a cooled (-10°) solution of compound 3 (4.8 g, 25 mmol) in ethylacetate (100 ml) till the absorption of ozone was completed (tested by starch iodide paper). The solution of the ozonide was treated with Jones chromic acid reagent at 0° (10 ml) for 2 hr. It was washed with water (100 ml x 2) and the organic layer was extracted with 10% aqueous sodium carbonate (15 ml x 2). The carbonate layer was cooled and acidified with dilute hydrochloric acid,

extracted with ether (100 ml x 3). The ether layer was washed with water (50 ml x 2) and dried. Evaporation of the solvent furnished the diketo acid 4 (R=H). This was converted to the methyl ester 4 ($R=CH_3$) by an ethereal solution of diazomethane and purified by chromatography over silica gel (45 g). The fractions eluted with benzene gave a TLC pure ester 4 ($R=CH_3$). Yield 3.3 g (52%); b.p.118-20°/0.3 mm; $(\alpha)_D^{28}$ -0.4° (c, 1.55). (Found: C, 65.92; H, 8.77; $C_{14}H_{22}O_4$ requires C, 66.11; H, 8.72%).
IR bands at: 3021, 1730, 1706, 1439, 1379, 1355, 1176, 1136, 1099, 962 and 853 cm^{-1}.

Methyl 1S-*cis*-2,2-dimethyl-3-(2-methyl-3-oxobutyl)cyclopropanecarboxylate 5 ($R=CH_3$)

A solution of diketo ester 4 (2.5 g, 10 mmol) in methanol (50 ml) containing sodium methoxide (1.6 g, 30 mmol) was refluxed for 6 hr. Methanol was removed under reduced pressure, residue diluted with water, cooled, acidified with dilute hydrochloric acid and extracted with ether (50 ml x 3). The combined ether was washed with water (50 ml x 2) and dried. Evaporation of ether furnished the keto acid 5 (R=H), which was esterified with an ethereal solution of diazomethane to give crude ester 5 ($R=CH_3$). The product was purified by chromatography over silica gel (25 g) and elution with pet.ether + benzene (1:1) gave ester 5 ($R=CH_3$); yield 1.6 g (75%); b.p.100-5°/0.13 mm;

$(\alpha)_D^{28}$ + 28.5° (c, 1.81). (Found: C, 67.57; H, 9.47; $C_{12}H_{20}O_3$ requires C, 67.89; H, 9.50%).

IR bands at: 3003, 1721, 1429, 1370, 1163, 1130, 952, 930 and 847 cm^{-1}.

Methyl 1S-cis-2,2-dimethyl-3-(2-acetoxypropyl)cyclopropane-carboxylate 6

To a solution of methyl ester 5 (1.5 g; 7.0 mmol) in dry dichloromethane (25 ml), m-chloroperbenzoic acid (1.8 g, 10.3 mmol) was added and the mixture refluxed for 6 hr. The reaction mixture was cooled, filtered and the filtrate was washed with 10% aqueous sodium carbonate, water and dried. Removal of the solvent gave the crude acetate ester, which was purified by chromatography over (Al_2O_3, 25 g). The fractions eluted with pet.ether + benzene (4:1) and pet.ether + benzene (1:1) gave TLC pure acetate ester 6; yield 1.0 g (65%); b.p.105-10°/0.2 mm; $(\alpha)_D^{28}$ + 21.1° (c, 1.45). (Found: C, 62.89; H, 8.50; $C_{12}H_{20}O_4$ requires C, 63.13; H, 8.83%).

IR bands at: 2994, 1730, 1429, 1370, 1242, 1176, 1136, 1080, 952, 935 and 850 cm^{-1}.

Methyl 1S-cis-2,2-dimethyl-3-(2-hydroxypropyl)cyclopropane-carboxylate 7 (R=CH_3)

To a solution of compound 6 (0.82 g, 3.6 mmol) in methanol (10 ml) a solution of potassium hydroxide (0.6 g, 10.7 mmol) in water (2 ml) was added and the

mixture stirred for 24 hr at room temperature. Methanol was removed by distillation under reduced pressure. The residue was diluted with water (50 ml), acidified with dilute hydrochloric acid and extracted with ether (50 ml x 3). The combined ether layer was washed with water (50 ml x 2) and dried. Evaporation of ether furnished the hydroxy acid 7 (R=H), which was esterified with an ethereal solution of diazomethane to give the hydroxy methyl ester 7 ($R=CH_3$); yield 0.45 g (67%); b.p.115-20°/0.2 mm; $(\alpha)_D^{28}$ + 5.2° (c, 1.2). (Found: C, 64.41; H, 9.91; $C_{10}H_{18}O_3$ requires C, 64.49; H, 9.74%). IR bands at: 3509, 3012, 1724, 1429, 1370, 1235, 1170, 1130, 935, 885 and 851 cm^{-1}.

Methyl 1S-*cis*-2,2-dimethyl-3-(2-oxopropyl)cyclopropane-carboxylate 8

To an ice-cooled and stirred solution of hydroxy ester 7 ($R=CH_3$, 0.75 g, 4.02 mmol) in acetone (5 ml), Jones chromic acid reagent was added dropwise until a pale orange colour persisted. The reaction mixture was stirred at 0° for 3 hr, diluted with water (25 ml) and extracted with ether (50 ml x 3). The ether layer was washed with water (50 ml x 2) and dried. Removal of ether gave crude ester 8, purified by chromatography over silica gel (10 g). The fractions eluted with pet.ether + benzene (1:1) gave colourless liquid keto ester 8; yield 0.46 g (63%); b.p.90-95°/0.15 mm; $(\alpha)_D^{28}$ + 35° (c, 2.32). (Found: C, 64.92;

H, 8.93; $C_{10}H_{16}O_3$ requires C, 65.19; H, 8.75%).
IR bands at: 3012, 1721, 1431, 1330, 1351, 1361, 1163, 1130, 1085, 1022, 957, 926 and 853 cm^{-1}.

4-Ethyl-4-acetyl car-2-ene 9

To an ice-cooled and stirred solution of potassium t-butoxide (8.4 g, 75 mmol) and 4∝-acetyl car-2-ene 2 (8.9 g, 50 mmol) in t-butanol (150 ml), ethyl iodide (11.7 g, 75 mmol) was added in one lot. The reaction mixture was stirred at 0° for 2 hr and at room temperature for 24 hr. The reaction mixture was filtered, t-butanol removed by distillation under reduced pressure. The residue was diluted with water (100 ml) and extracted with ether (100 ml x 3). The combined ether layer was washed with water (75 ml x 2) and dried. Removal of ether gave the crude liquid product (10 g), which was purified by chromatography over silica gel (200 g). The fractions eluted with pet.ether + benzene (4:1) and pet.ether + benzene (1:1) gave TLC pure 9; yield 7.1 g (69%); b.p.110-15°/0.35 mm; $(\alpha)_D^{28}$ + 106.3° (c, 4.5). (Found: C, 81.77; H, 10.96; $C_{14}H_{22}O$ requires C, 81.50; H, 10.75%). IR bands at: 2959, 1695, 1639, 1439, 1364, 1339, 1206, 1190, 1099 and 813 cm^{-1}.

Methyl 1S-cis-2,2-dimethyl-3-(2,2-diacetylbutyl)-cyclopropanecarboxylate 10 ($R=CH_3$)

Ozonised oxygen was passed through cooled (-10°) solution of compound 9 (5.3 g, 25.7 mmol) in ethylacetate (125 ml) till the absorption of ozone was completed. The cold solution of the ozonide was treated with Jones chromic acid reagent (15 ml) for 2 hr. The reaction mixture was washed with water (75 ml x 2) and the organic layer extracted with 10% aqueous solution of sodium carbonate (25 ml x 3). The combined aqueous layer was cooled and acidified with dilute hydrochloric acid and extracted with ether (75 ml x 3). The ether layer was washed with water (50ml x 2) and dried. Evaporation of the solvent gave the diketo acid 10 (R=H), which was esterified with an ethereal solution of diazomethane to give the crude diketo ester (4 g). The diketo ester was purified by chromatography over silica gel (50 g) and the fractions eluted with benzene and benzene + chloroform (4:1) gave TLC pure ester 10 ($R=CH_3$); yield 3.45 g (50%); b.p.127-32°/0.3 mm; $(\alpha)_D^{28}$ + 7.2° (c, 2.4). (Found: C,66.75; H, 9.16; $C_{15}H_{24}O_4$ requires C, 67.13; H, 9.02%), IR bands at: 2994, 1721, 1695, 1429, 1374, 1351, 1190, 1170, 1130, 943 and 847 cm^{-1}.

Methyl 1S-cis-2,2-dimethyl-3-(2-acetylbutyl)-cyclopropane-carboxylate 11 ($R=CH_3$)

A solution of 10 ($R=CH_3$, 2.68 g, 10 mmol) in methanol (50 ml) containing sodium methoxide (1.89 g, 35 mmol) was

refluxed for 6 hr. Solvent was removed, residue diluted with water (50 ml), cooled, acidified with dilute hydrochloric acid and extracted with ether (75 ml x 3). The combined ether layer was washed with water (50 ml x 2) and dried. Distillation of ether gave the acid 11 (R=H), which was esterified with an ethereal solution of diazomethane to give the crude ester (2.1 g). This was chromatographed over silica gel (25 g) and the fractions eluted with pet.ether + benzene (1:1) and benzene gave pure ester 11 ($R=CH_3$); yield 1.75 g (78%); b.p.115-25°/0.2 mm; $(\alpha)_D^{28}$ + 22.3° (c, 1.9). (Found: C, 69.31; H, 10.00; $C_{13}H_{22}O_3$ requires C, 68.99; H, 9.80%).
IR bands at: 3003, 1724, 1431, 1374, 1170, 1131 and 848 cm^{-1}.

Methyl 1S-cis-2,2-dimethyl-3-(2-acetoxybutyl)cyclopropane-carboxylate 12

To a solution of methyl ester 11 (1.7 g, 7.5 mmol) in dry dichloromethane (25 ml) m-chloroperbenzoic acid (1.94 g, 11.25 mmol) was added and the reaction mixture refluxed for 6 hr. The product on usual workup gave the crude acetoxy ester 12. This was chromatographed over silica gel (25 g) and the fractions eluted with pet.ether + benzene (1:1) and benzene gave pure liquid acetoxy ester 12, yield 1.16 g (64%); b.p.110-15°/0.15 mm; $(\alpha)_D^{28}$ + 19.2° (c, 1.35). (Found: C, 64.11, H, 9.50; $C_{13}H_{22}O_4$ requires C, 64.40; H, 9.15%).

IR bands at: 2985, 1718, 1429, 1361, 1235, 1163, 1130, 1081, 1015, 952 and 847 cm^{-1}.

Methyl 1S-*cis*-2,2-dimethyl-3-(2-hydroxybutyl)cyclopropane-carboxylate 13 (R=CH_3)

To a solution of acetoxy ester 12 (0.97 g, 3.9 mmol) in methanol (20 ml) solution of potassium hydroxide (0.8 g, 15.9 mmol) in water (4 ml) was added and stirred for 24 hr at room temperature. Methanol was removed by distillation under reduced pressure. The residue was diluted with water (50 ml), cooled, acidified with dilute hydrochloric acid and extracted with ether (50 ml x 3). The combined ether layer was washed with water (50 ml x 2) and dried. Removal of the solvent gave the hydroxy acid 13 (R=H), which was esterified with an ethereal solution of diazomethane. The methyl ester 13 thus obtained was purified by chromatography over (Al_2O_3, 20 g). The fractions eluted with benzene and benzene + chloroform (4:1) afforded colourless liquid; yield 0.52 g (65%); b.p.110-15°/0.15 mm; $(\alpha)_D^{28}$ + 3.8° (*c*, 1.10). (Found: C, 65.68; H, 9.85; $C_{11}H_{20}O_3$ requires C, 65.17; H, 10.07%). IR bands at: 3448, 1712, 1429, 1364, 1190, 1163, 1126, 1081, 1020, 926 and 847 cm^{-1}.

Methyl 1S-*cis*-2,2-dimethyl-3-(2-oxobutyl)cyclopropane-carboxylate 14

To an ice-cooled and stirred solution of hydroxy ester 13 (R=CH_3, 0.69 g, 3 mmol) in acetone (5 ml), Jones

chromic acid reagent was added dropwise, with shaking till the brown colour persisted. The mixture was stirred at 0° for 3 hr, diluted with water (25 ml) and extracted with ether (50 ml x 3). The combined ether layer was washed with water (50 ml x 2) and dried. Evaporation of the solvent gave crude ester 14. It was chromatographed over silica gel (15 g) and fractions eluted with pet.ether + benzene (1:1) and benzene gave TLC pure keto ester 14; yield 0.38 g (65%); b.p.100-105°/0.15 mm; $(\alpha)_D^{28}$ + 33.6° (c, 3.8). (Found: C, 66.57; H, 9.37; $C_{11}H_{18}O_3$ requires C, 66.64; H, 9.15%).

IR bands at: 3012, 1724, 1431, 1324, 1190, 1170, 1133, 1111, 1087, 980, 935 and 847 cm^{-1}.

4-Benzyl-4-acetyl car-2-ene 15

To an ice-cooled and stirred solution of potassium t-butoxide (10.5 g, 93.75 mmol) and compound 2 (11.12 g, 62.45 mmol) in dry t-butanol (150 ml), benzyl bromide (16 g, 93.75 mmol) was added in one lot. The reaction mixture was stirred at 0° for 2 hr and at room temperature for 24 hr. The reaction mixture was filtered, t-butanol removed under suction. The residue diluted with water (150 ml) and extracted with ether (100 ml x 3). The combined ether was washed with water (75 ml x 2) and dried. Removal of the solvent gave the crude product 15 g. It was chromatographed over silica gel (300 g). The fractions eluted with pet.ether + benzene (4:1) and

pet.ether + benzene (1:1) gave TLC pure compound 15; yield 11.7 g (70%); b.p.145-50°/0.3 mm; $(\alpha)_D^{28}$ + 140.4° (c, 2.4). (Found: C, 84.84; H, 9.05; $C_{19}H_{24}O$ requires C, 85.02; H, 9.01%).

IR bands at: 3030, 1718, 1653, 1608, 1497, 1449, 1374, 1351, 1190, 1205, 943, 833, 755, and 701 cm^{-1}.

Methyl 1S-cis-2,2-dimethyl-3-(2,2-diacetyl-3-phenylpropyl)-cyclopropanecarboxylate 16 (R=CH_3)

Compound 15 (6.7 g, 25 mmol) in ethylacetate (125 ml) was ozonised at -10°. The solution of the ozonide was treated with Jones chromic acid reagent at 0° (15 ml) for 2 hr. It was washed with water (100 ml x 2) and the organic layer extracted with 10% aqueous sodium carbonate solution (20 ml x 2). The carbonate layer was cooled, acidified and extracted with ether (100 ml x 3). The combined ether layer was washed with water (75 ml x 2) and dried. Removal of solvent gave the diketo acid 16 (R=H), which was esterified with an ethereal solution of diazomethane. The methyl ester 16 (R=CH_3) thus obtained, was purified by chromatography over silica gel (50 g). The fractions eluted with benzene and benzene + chloroform (4:1) gave TLC pure ester 16 (R=CH_3); yield 3.8 g (47%); b.p.175-80°/0.2 mm; $(\alpha)_D^{28}$ + 4.8° (c, 1.86). (Found: C,72.42; H, 8.11; $C_{20}H_{26}O_4$ requires C, 72.70; H, 7.93%).

IR bands at: 3030, 1724, 1613, 1538, 1439, 1381, 1357, 1176, 1134, 1087, 1031, 957, 856, 760 and 704 cm^{-1}.

Methyl 1S-*cis*-2,2-dimethyl-3-(2-acetyl-3-phenylpropyl) cyclopropanecarboxylate 17 ($R=CH_3$)

A solution of diketo ester 16 ($R=CH_3$, 3.3 g, 10 mmol) in methanol (75 ml) containing sodium methoxide (1.8 g ,g, 35 mmol) was refluxed for 6 hr. The solvent was removed under reduced pressure, residue diluted with water (50 ml), cooled, acidified and extracted with ether (75 ml x 3). The combined ether layer was washed with water (50 ml x 2) and dried. Distillation of ether furnished the acid 17 (R=H), which was esterified with an ethereal solution of diazomethane to give crude ester 17 ($R=CH_3$). It was purified by chromatography over silica gel (30 g) and elution with pet.ether + benzene (1:1) and benzene gave pure ester 17 ($R=CH_3$); yield 2.2 g (77%); b.p. 150-55°/0.13 mm; $(\alpha)_D^{28}$ + 15.8° (c, 1.14). (Found: C, 74.63; H, 8.62; $C_{18}H_{24}O_3$ requires C, 74.97; H, 8.39%).
IR bands at: 3030, 1730, 1613 , 1504, 1439, 1163, 1087, 851, 755, and 700 cm^{-1}.

Methyl 1S-*cis*-2,2-dimethyl-3-(2-acetoxy-3-phenylpropyl)-cyclopropanecarboxylate 18

To a solution of compound 17 ($R = CH_3$, 1.4 g; 4.86mmol) in dry dichloromethane (30 ml), m-chloroperbenzoic acid (1.26 g, 7.3 mmol) was added and the solution refluxed for 6 hr. The reaction mixture was cooled, filtered and the filtrate washed with 10% aqueous sodium carbonate, water

and dried. Evaporation of the solvent gave the crude product, which was purified by chromatography over silica gel (20 g). Elution with pet.ether + benzene (1:1) and benzene gave TLC pure acetoxy ester 18; yield 0.87 g (59%); b.p.150-55°/0.13 mm; $(\alpha)_D^{28}$ + 0.5° (c, 1.08). (Found: C, 69.89; H, 7.69; $C_{18}H_{24}O_4$ requires C, 71.02; H, 7.95%).

IR bands at: 3012, 1733, 1613, 1587, 1433, 1370, 1235, 1163, 1026, 926, 851, 748 and 699 cm^{-1}.

Methyl 1S-cis-2,2-dimethyl-3-(2-hydroxy-3-phenylpropyl)cyclopropanecarboxylate 19 (R=CH_3)

To a solution of potassium hydroxide (0.73 g, 13 mmol) in water (5 ml) and methanol (20 ml), was added acetoxy ester 18 (1.0 g, 3.3 mmol). The homogeneous solution was stirred for 24 hr at room temperature. Most of the methanol was removed under suction. The residue was diluted with water (25 ml) acidified with dilute hydrochloric acid and extracted with ether (50 ml x 3). The combined ether layer was washed with water, dried and distilled to furnish hydroxy acid. It was esterified with an ethereal solution of diazomethane. The hydroxy methyl ester was purified by distillation to give colurless liquid 19 (R=CH_3); yield 0.53 g (62%); b.p.160-65°/0.13 mm; $(\alpha)_D^{28}$ + 4.6° (c, 1.4). (Found: C, 72.99; H, 8.15; $C_{16}H_{22}O_3$ requires C, 73.25; H, 8.45%).

IR bands at: 3448, 2925, 1727, 1600, 1500, 1440, 1380, 1175, 1130, 1100, 850, 750 and 700 cm^{-1}.

Methyl 1S-*cis*-2,2-dimethyl-3-(2-oxo-3-phenylpropyl)cyclopropanecarboxylate 20

To an ice-cooled solution of hydroxy ester 19 ($R=CH_3$, 0.65 g, 2.48 mmol) in acetone (5 ml), Jones chromic acid reagent was added dropwise till a brown colour persisted. The reaction mixture was stirred at 0° for 3 hr, diluted with water (25 ml) and extracted with ether (50 ml x 3). The ether layer was washed with water (30 ml x 2) and dried. Evaporation of the ether gave a liquid keto ester 20, which was chromatographed over silica gel (10 g). The fractions eluted with pet.ether + benzene (1:1) and benzene gave TLC pure keto ester 20; yield 0.39 g (61%); b.p.140-45°/0.15 mm; $(\alpha)_D^{28}$ + 9° (c, 1.54). (Found: C, 73.59; H, 7.46; $C_{16}H_{20}O_3$ requires C, 73.82; H, 7.74%).

IR bands at: 3030, 1727, 1613, 1499, 1433, 1377, 1325, 1170, 1131, 1081, 855, 743 and 699 cm^{-1}.

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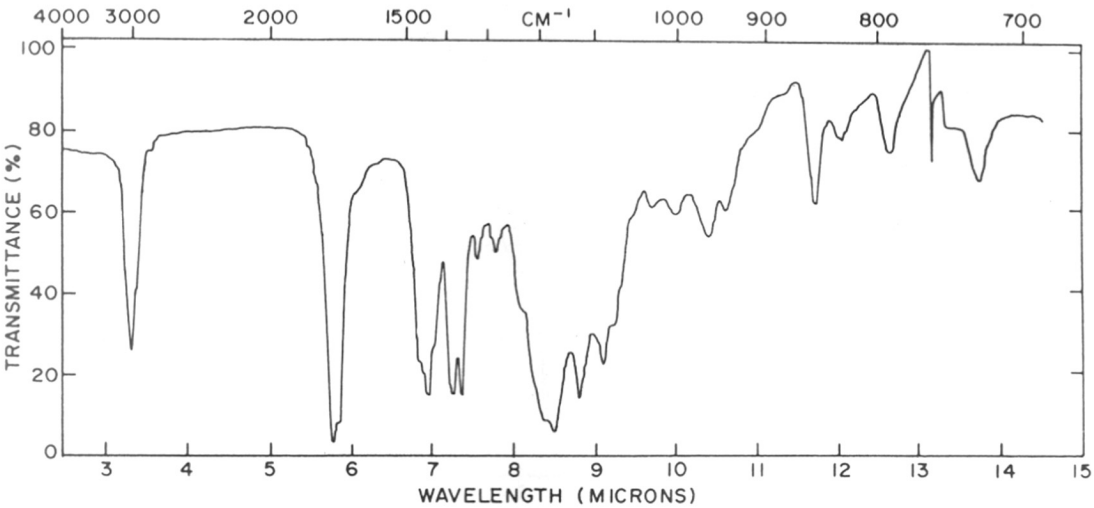
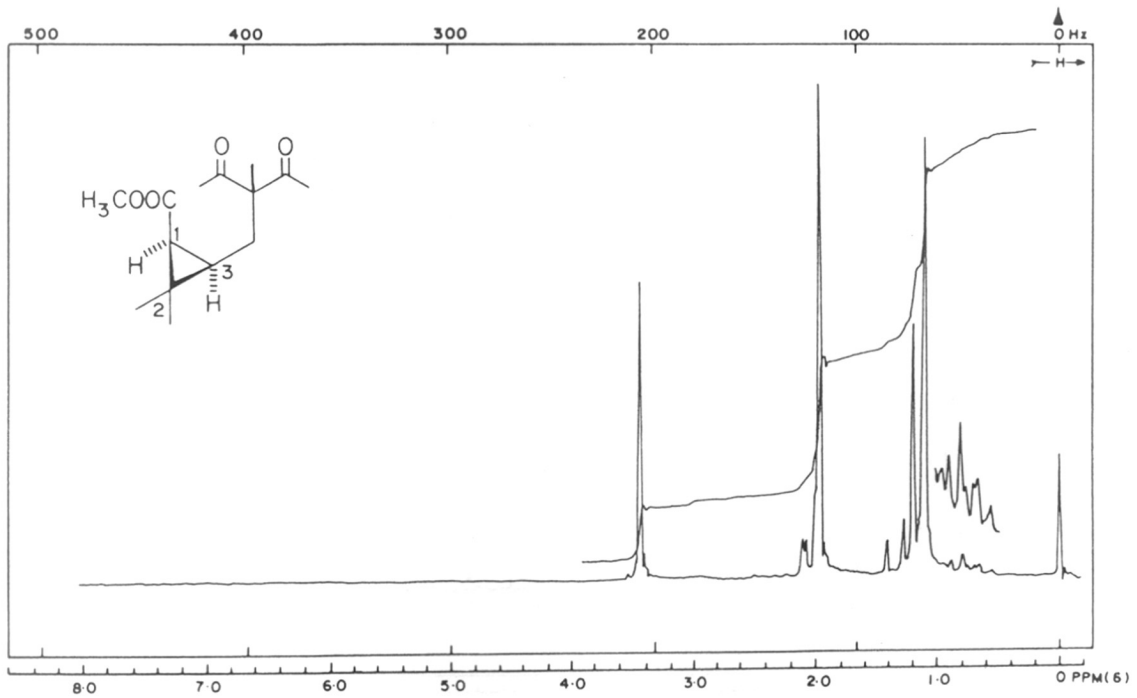
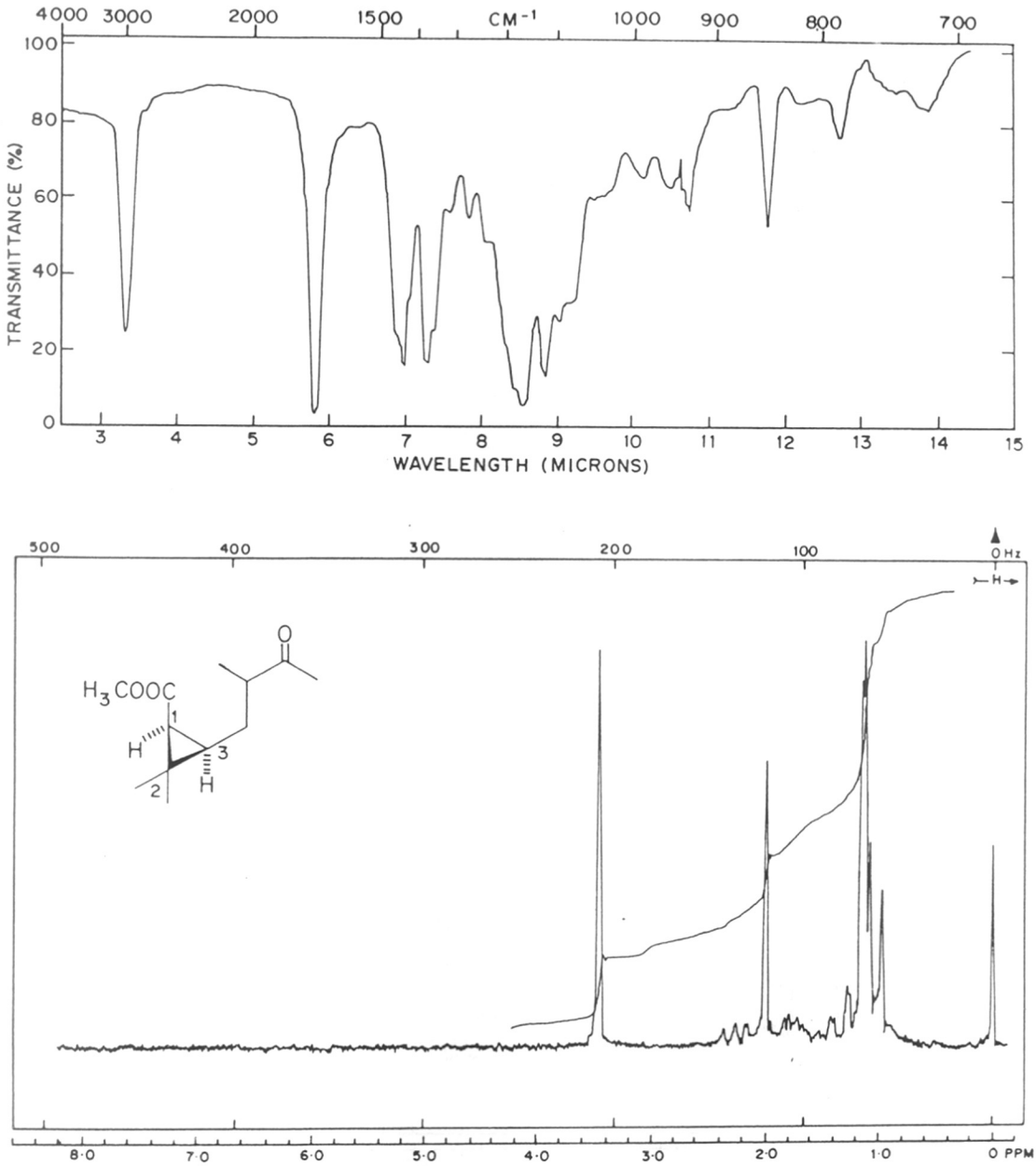
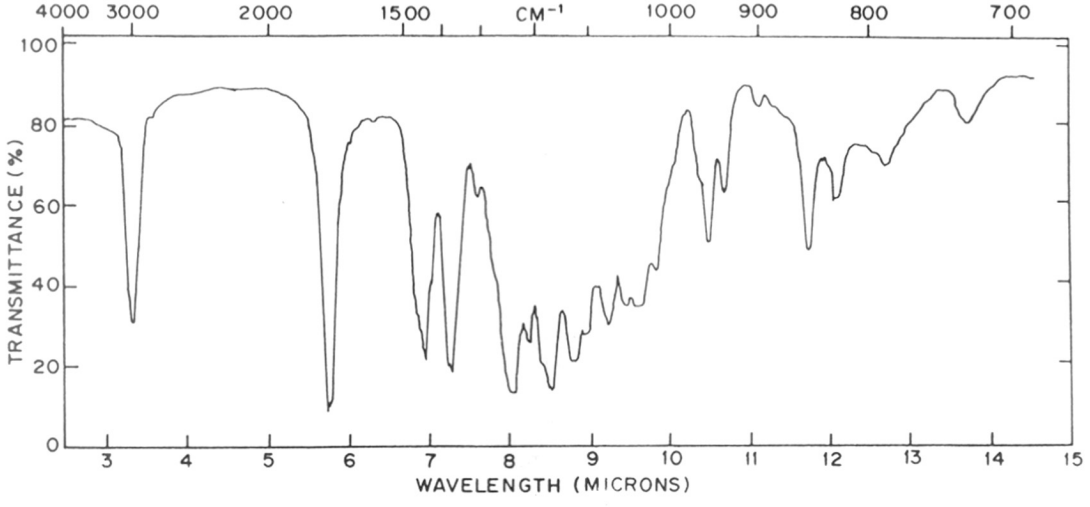


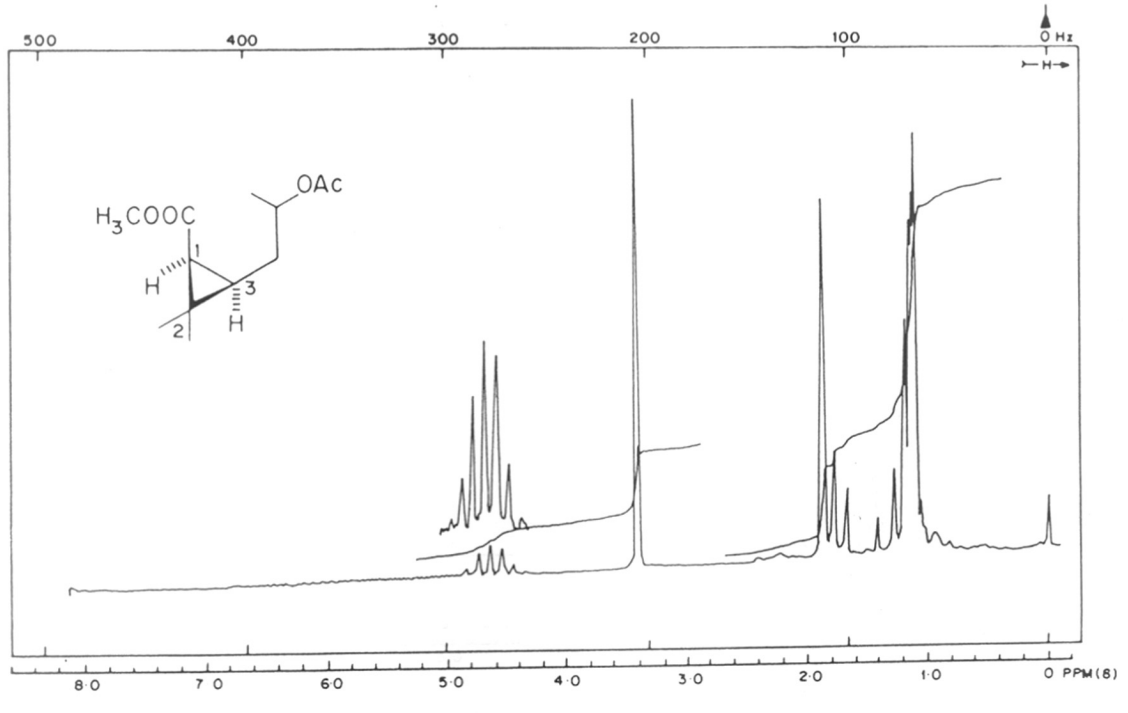


IR & PMR OF METHYL 1S-CIS-2,2-DIMETHYL-3-(2,2-DIACETYLPROPYL) CYCLOPROPANECARBOXYLATE 4.



IR & PMR OF METHYL 1S-CIS-2,2-DIMETHYL-3-(2-METHYL-3-OXOBUTYL) CYCLOPROPANECARBOXYLATE 5.





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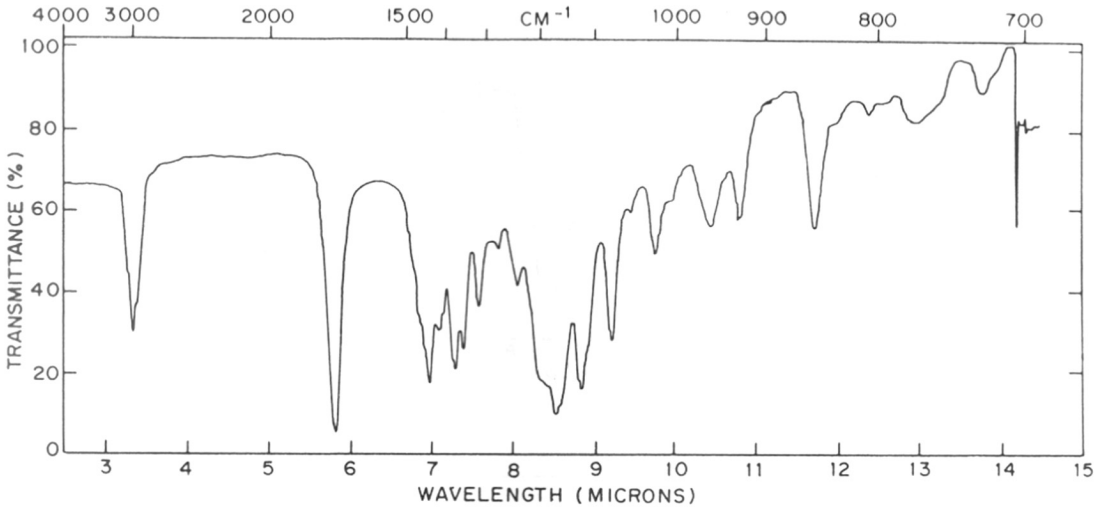
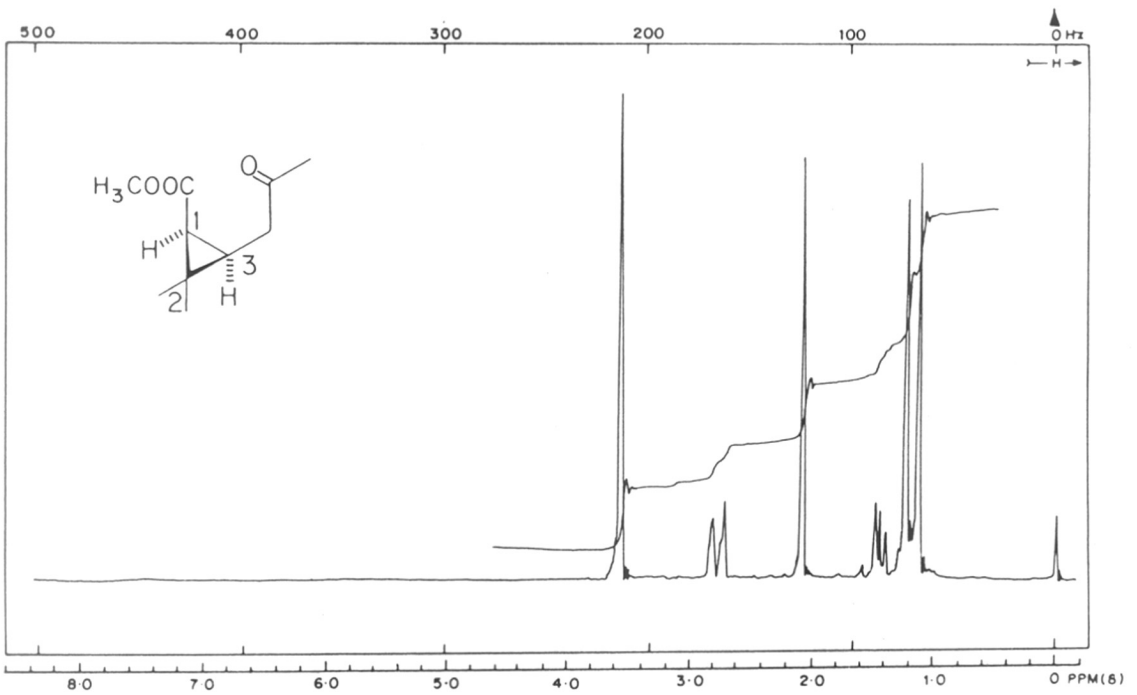
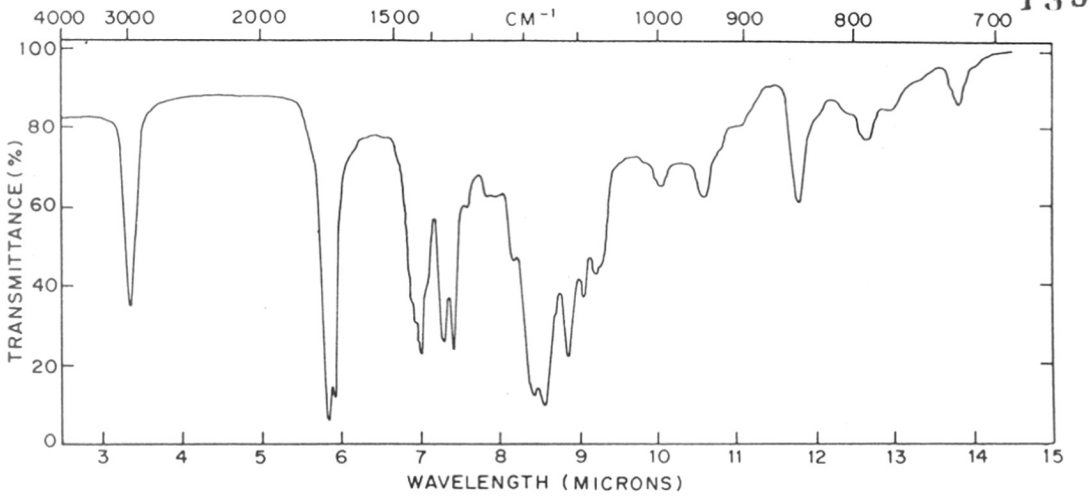
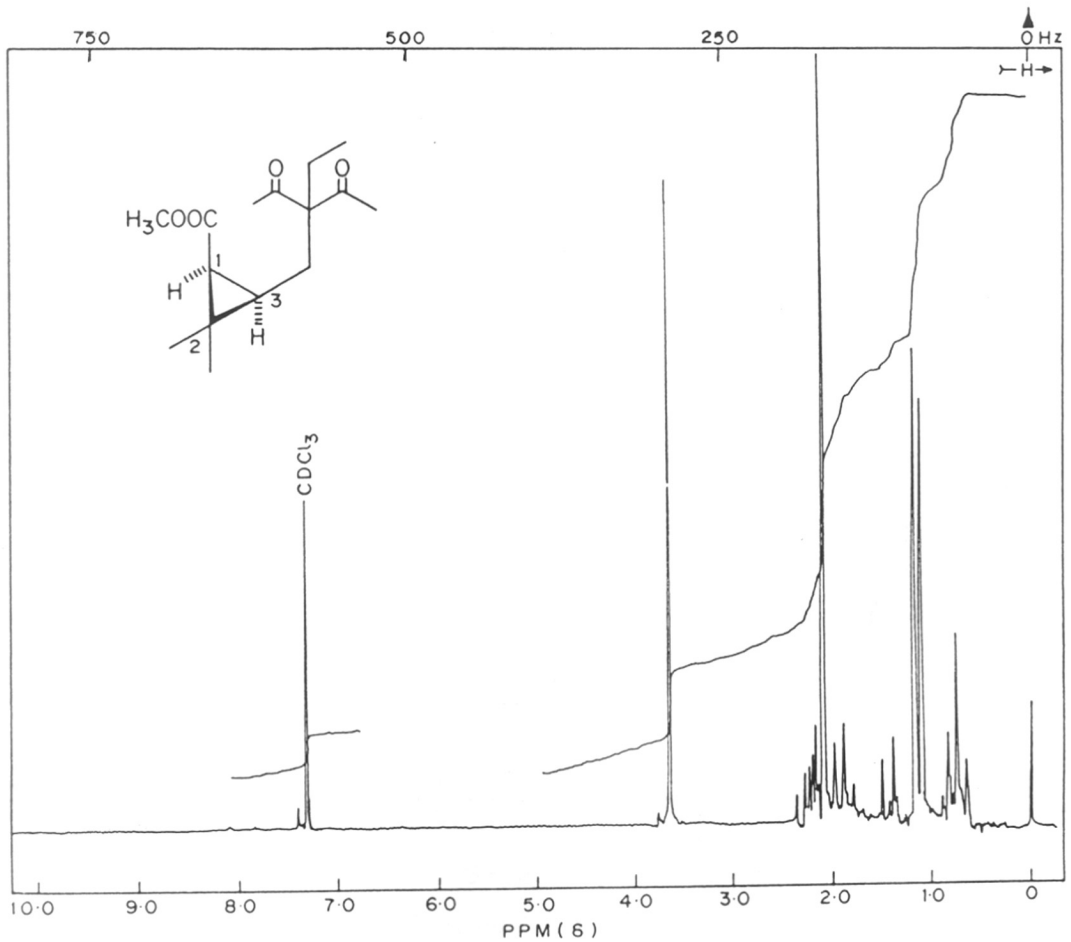




IR & PMR OF METHYL 1S-CIS-2,2-DIMETHYL-3-(2-OXOPROPYL) CYCLOPROPANECARBOXYLATE 8.





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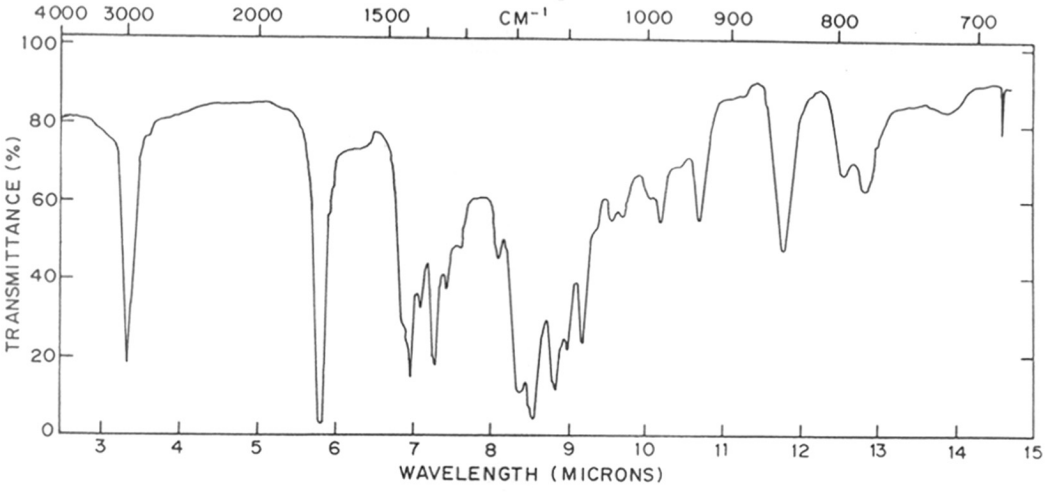
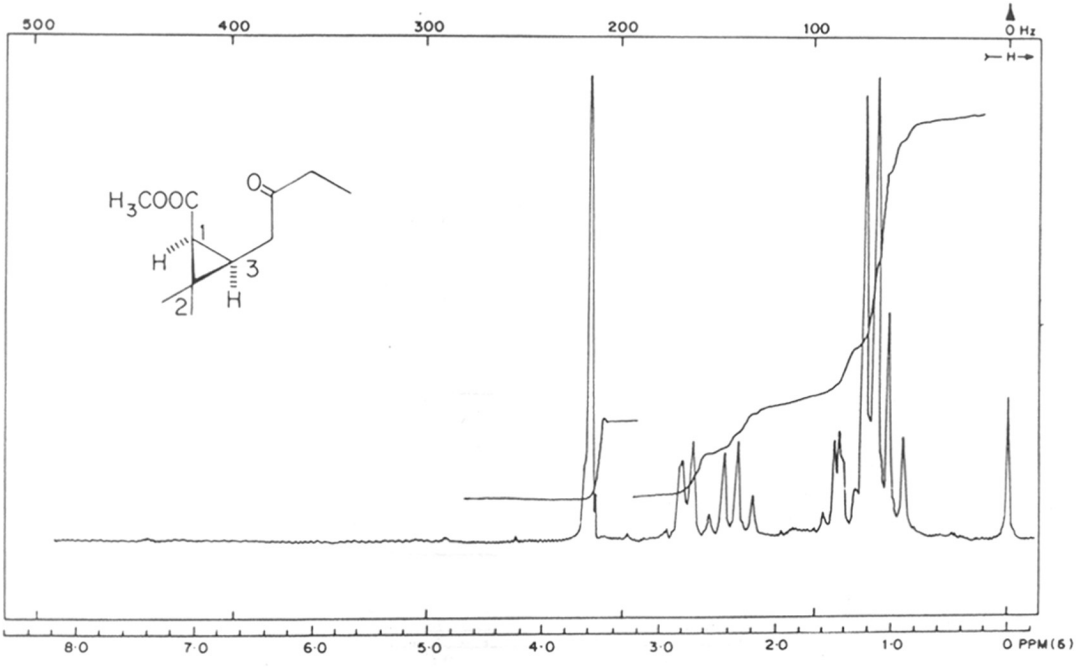
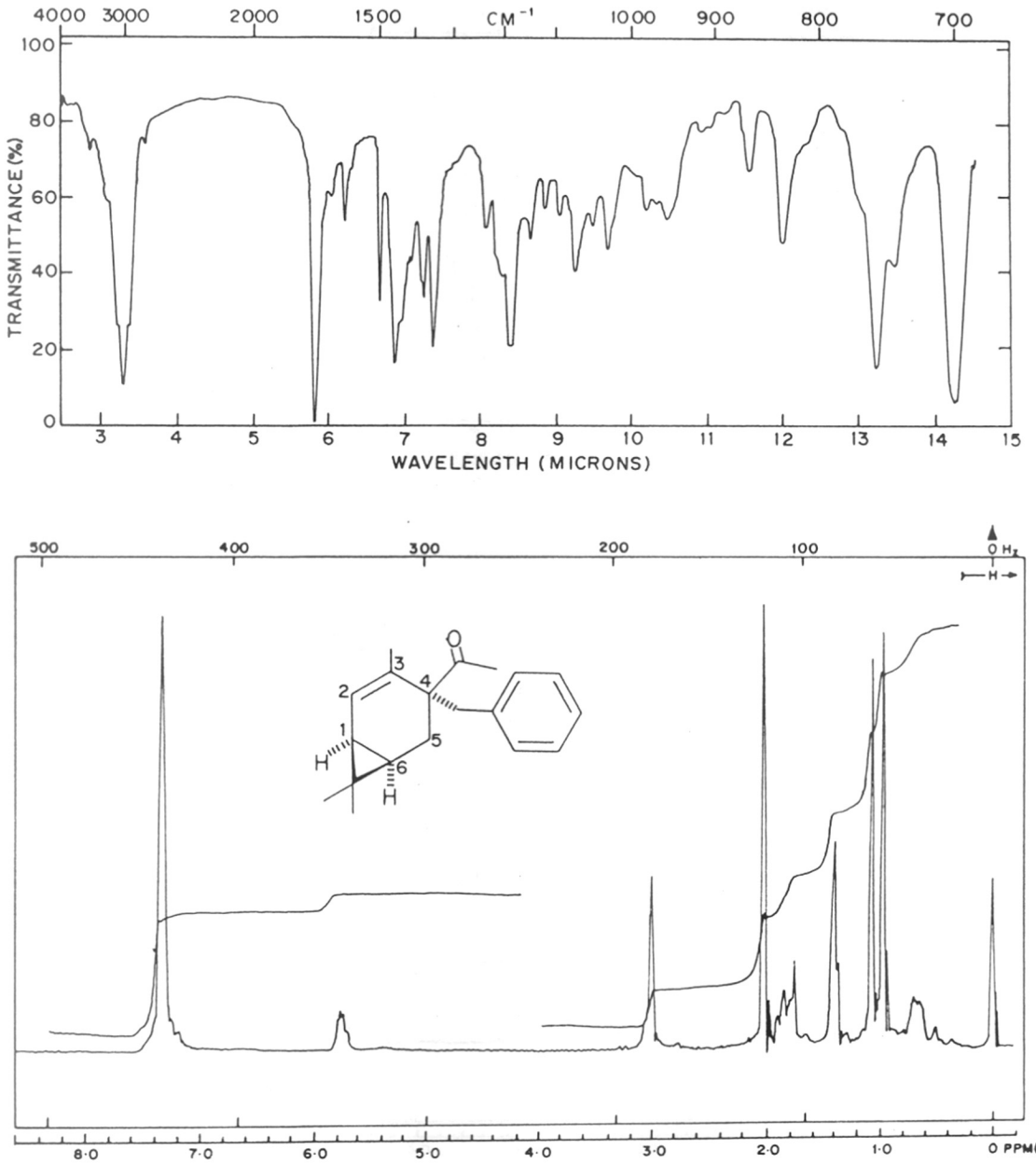
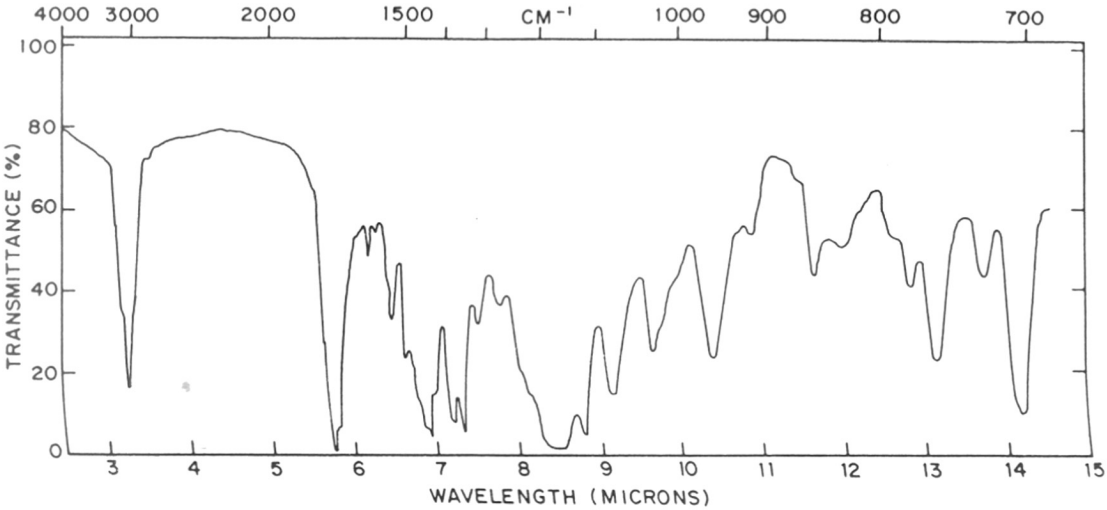


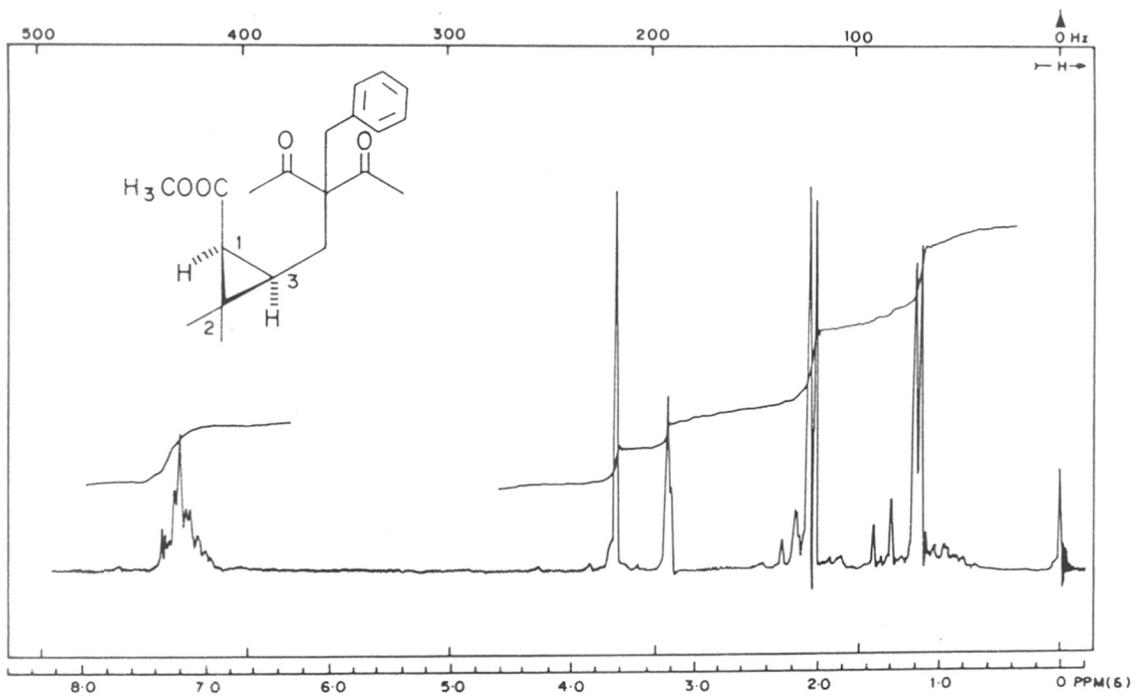


IR & PMR OF METHYL 1S-CIS-2,2-DIMETHYL-3-(2-OXOBUTYL) CYCLOPROPANECARBOXYLATE 14



IR & PMR OF 4-ACETYL-4-BENZYLCAR-2-ENE 15.





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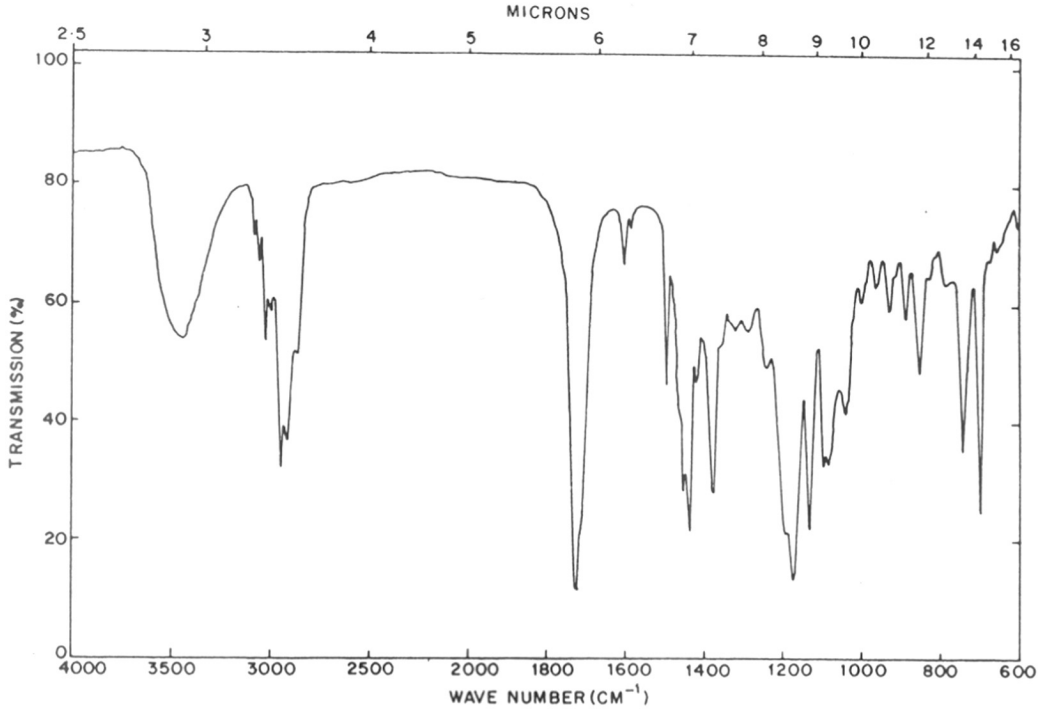
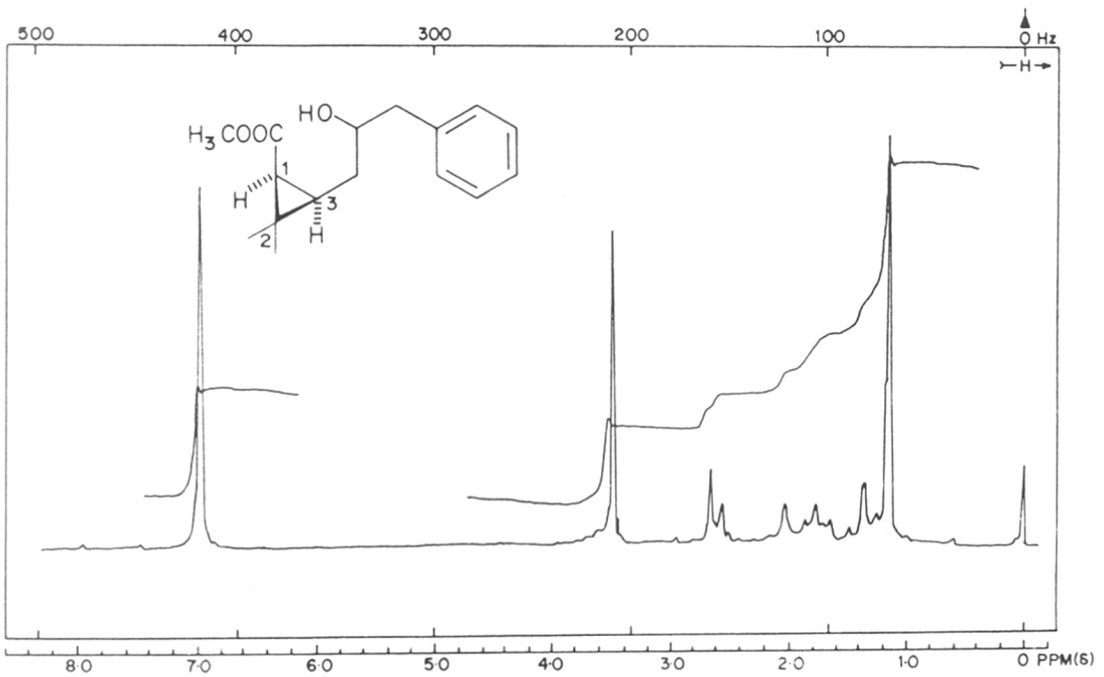
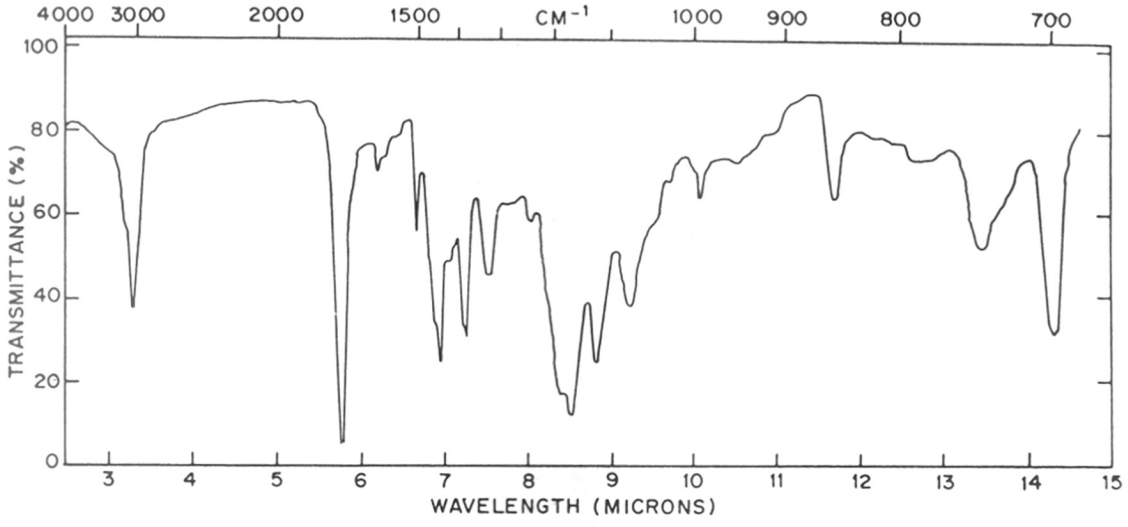
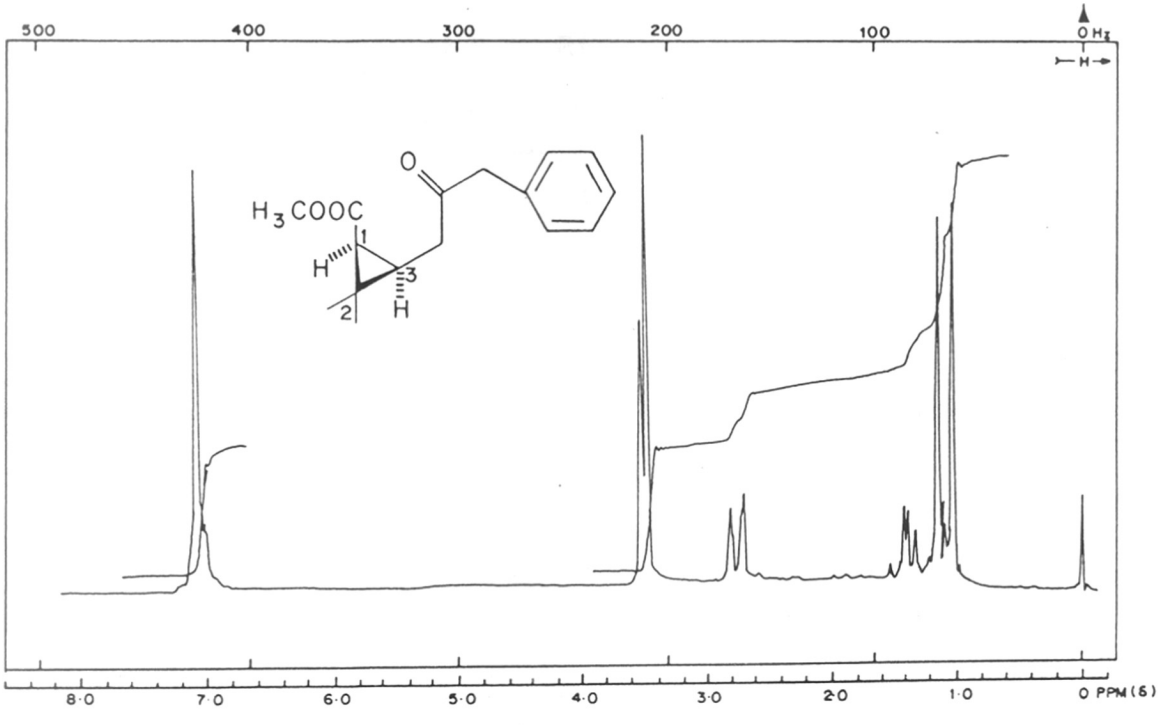




IR & PMR OF METHYL 1S-CIS-2,2-DIMETHYL-3-(2-HYDROXY-3-PHENYLPROPYL) CYCLOPROPANECARBOXYLATE 19.





IR & PMR OF METHYL 1S-CIS-2,2-DIMETHYL-3-(2-OXO-3-PHENYLPROPYL)CYCLOPROPANECARBOXYLATE 20.

CHAPTER-IV

SYNTHESIS OF OPTICALLY ACTIVE (+) 1R-TRANS PYRETHROIDS FROM (+)-3-CARENE

SUMMARY

The trans caranediol 2 obtainable from (+)-3-carene 1, on oxidation with sodium meta periodate, gave the keto aldehyde 3 which, on Grignard reaction with phenyl-magnesium bromide, afforded a mixture of diastereomeric diols 4. Acetylation of the diols 4 gave the hydroxy acetate 5 which, on dehydration with PTS, afforded the unsaturated acetate 6. Potassium permanganate oxidation of 6 followed by esterification of the resulting acetate acid 7 (R=H) gave an acetate ester 7 ($R=CH_3$). Saponification of the acetate ester 7 ($R=CH_3$) followed by esterification of the hydroxy acid 8 (R=H) gave hydroxy ester 8 ($R=CH_3$). Jones chromic acid oxidation of 8 ($R=CH_3$) gave the keto ester 9. Acid catalysed dehydration of the ester 8 ($R=CH_3$) gave exclusively the E geometric isomer of unsaturated ester 10. The hydroxy acid 8 (R=H) on refluxing with PTS in benzene afforded the δ-lactone 11.

The δ-lactone 11 on heating with potassium hydroxide in ethylene glycol gave the trans-hydroxy acid 12 (R=H) which on esterification gave the hydroxy ester 12 ($R=CH_3$). Jones chromic acid oxidation of 12 ($R=CH_3$) gave the keto ester 13, which on treatment with phosphorous pentachloride furnished the mixture of E and Z isomers of 15 in 65:35 proportion by GLC. Transesterification of 15 (E and Z isomers) with 3-phenoxybenzyl alcohol gave

3-phenoxybenzyl 1R(+)-trans-2,2-dimethyl-3-(2-phenyl-2-chlorovinyl)cyclopropanecarboxylate 16 (as a mixture of E and Z isomers).

Acid catalysed dehydration of 12 ($R=CH_3$) gave exclusively the E geometric isomer of unsaturated ester 17 which, on transesterification with 3-phenoxybenzyl alcohol afforded the 3-phenoxybenzyl 1R-(+)-trans-2,2 dimethyl-3-(2E-styryl)cyclopropanecarboxylate 18.

INTRODUCTION

The natural insecticides isolated from pyrethrum flowers like pyrethrins[1] and cinerins[2] are the esters of (+) trans-chrysanthemic acid and (+) trans pyrethric acid. Both the above acid moieties are trans cyclopropane derivatives possessing 1R configuration at the site bearing the carboxylate function. As already stated in Chapter I, for insecticidal activity pyrethroids must have 1R configuration at the site bearing the ester function, irrespective of whether the cyclopropane ring is having a cis or a trans geometry[3]. The corresponding 1S epimers are either much less active or inactive. In view of these observations many efforts have been made to develop suitable synthetic routes for (+) trans chrysanthemic acid starting from the abundent and naturally occurring substrates possessing suitably substituted cyclopropane ring system and required configuration. One such important substrate is (+)-3-carene 1 which, occurs in the pine oil (Pinus longifolia). Matsui et al.[4,5], for the first time realised the possibility of getting (+) trans chrysanthemic acid from (+)-3-carene 1 as shown in Scheme I, in Chapter III (page No.101). Later on, many workers have converted (+)-3- carene 1 selectively into 1S(-) cis chrysanthemic acid[6,7,8] which could be readily epimerised to the 1R (+) trans isomer, a desired isomer for the

synthesis of pyrethroids as shown in Chapter III. Its synthesis has also been achieved from (+)α-pinene[9] in this laboratory as shown in Chapter III.

Besides (+)-3-carene 1 and (+)α-pinene other substrates like limonene, α-terpineol[10] and carvone[11] have also been utilised for the synthesis of (+) trans chrysanthemic acid as shown in previous chapter III. In addition, its synthesis has also been achieved starting from acyclic[12-15] substrates.

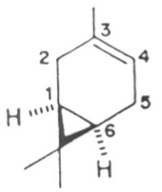
It is known that many esters of (+) trans chrysanthemic acid with relatively more photostable alcohols like 3-phenoxybenzyl and 5-benzyl-3-furylmethyl alcohols also possess good insecticidal activity, such as biophenothrin[16], bioresemethrin[17] etc. In addition, biopermethrin[18] and biodecamethrin[19], possessing the 1R trans configuration, have also been synthesised which are potent photostable pyrethroids.

During the last decade many new pyrethroids[20-25] which, are the esters of 2,2-dimethyl-3-(2-chloro-2-phenyl-vinyl/2-styryl/2-cyano-2-phenylvinyl)cyclopropane carboxylic acids with alcohols like 3-phenoxybenzyl alcohol, 3-(4-fluorophenoxy) benzyl alcohol have been reported to possess high insecticidal and acaricidal activities. Most of these compounds are obtained as dl mixtures of both cis and trans isomers. Recently[26,27] α-cyano-3-phenoxy-benzyl-trans-(±)-2,2-dimethyl-3-(2 E-phenylalk-1-enyl)cyclo-

propanecarboxylates have been synthesised and reported to possess ectoparasiticidal activity. Later, the corresponding optically active[28] *trans* isomers have also been synthesised. In our laboratory, 3-phenoxybenzyl *cis* (±) 2,2-dimethyl-3- (2-phenyl-2-chlorovinyl)cyclopropanecarboxylate has been synthesised[29] from (+)-3-carene 1.

In this chapter a new approach for the synthesis of optically active (+) 1R *trans* pyrethroids in the form of 3-phenoxybenzyl esters are described from (+)-3-carene 1, viz. (i) 3-phenoxybenzyl-1R(+) *trans* 2,2-dimethyl-3-(2-chloro-2-phenylvinyl)cyclopropanecarboxylate and (ii) 3-phenoxybenzyl-1R(+) *trans* 2,2-dimethyl-3-(2E-styryl)-cyclopropanecarboxylate.

CHART I



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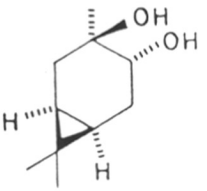

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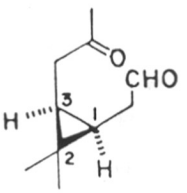

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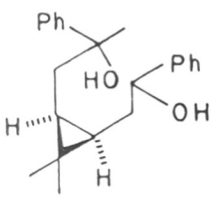

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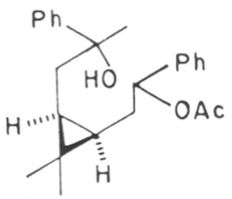

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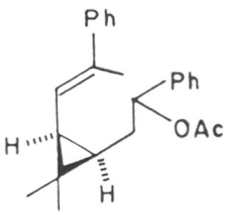

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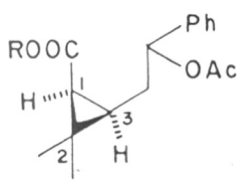
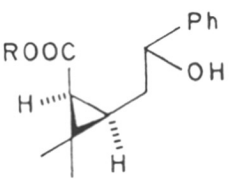


7 R = H or CH_3



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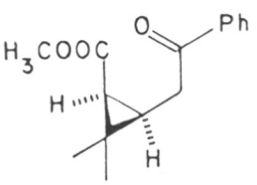

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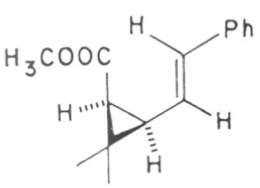

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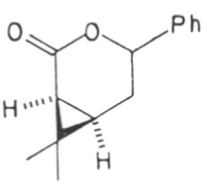

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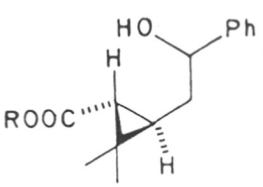
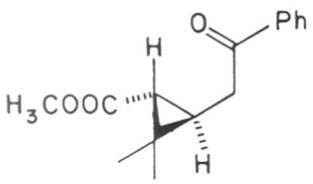


12 R = H or CH_3

CHART II



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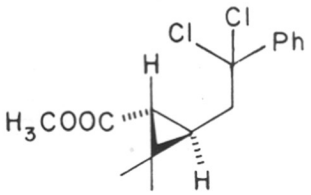

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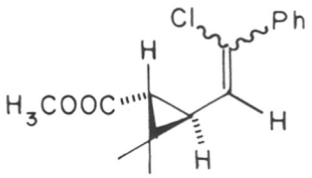

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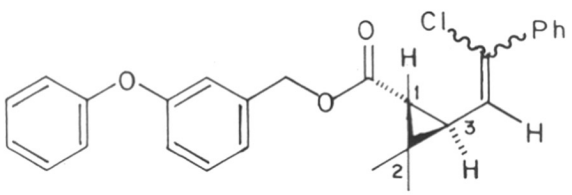

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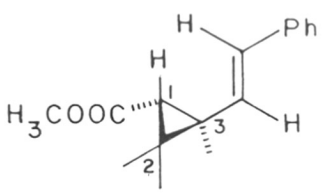

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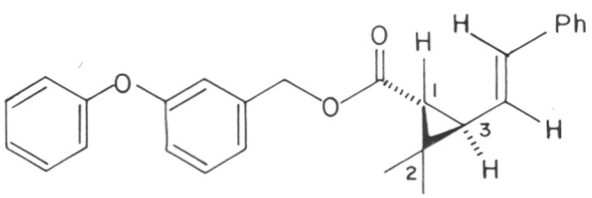

18

PRESENT WORK

(+)-3-Carene 1 was converted into trans 3β, 4α-caranediol 2, $C_{10}H_{18}O_2$, M^+ 170, m.p.82-83°, by a known method in 45% yield[7]. The vicinal diol 2 was cleaved by sodium meta periodate to afford the keto aldehyde 3[7] in 82% yield, $C_{10}H_{16}O_2$, M^+ 168. It showed IR bands at 2740 (-CHO), 1724 (>C=O) and PMR signals at 0.83 (2H, m, cyclopropane protons at C_1 and C_3), 1.0, 1.13 (3H each, s each, gem-dimethyl on cyclopropane), 2.10 (3H, s, $-COCH_3$) and 2.33 (4H, m, methylene protons α to >C=O).

The freshly prepared keto aldehyde 3 on treatment with phenylmagnesium bromide (2.5 mol), afforded the liquid diol 4 as a mixture of diastereomers, in 90% yield, $C_{22}H_{28}O_2$. It showed IR bands at 3448 (OH), 1058 (-C-O-) 1600, 755, 694 (aromatic) and PMR signals at 0.3 (2H, m, cyclopropane protons), 0.58, 0.65, 0.72, 0.88 (6H, s each, gem-dimethyls diastereomers), 1.42 (3H, s, $H_3C-\overset{|}{C}-OH$), 1.53 (4H, m, methylene protons), 4.61 (1H, m, benzylic proton), 7.16, 7.25 (10H, each s, aromatic protons). Attempts to separate diastereomers were not successful. The diol 4 was used for preparing two different pyrethroids viz. 16 and 18.

The diol 4 on treatment with Ac_2O/pyridine, gave a mixture of the diastereomeric hydroxy monoacetates 5 as a thick liquid $C_{24}H_{30}O_3$. It showed IR bands at 3509, 1015(OH)

1724, 1227 (acetate), 1587, 758, 694 (aromatic) and PMR signals at 0.37 (2H, m, cyclopropane protons at C_1 and C_3), 0.62, 0.77, 0.80, 0.92 (6H total, s each, gem-dimethyls of both diastereomers), 1.45 (3H, s, methyl attached to carbon bearing hydroxyl and phenyl), 1.60 (4H, m, methylene protons at C_1 and C_3), 1.95 (3H, s, acetate methyl), 5.66 (1H, m, benzylic proton i.e. H- C - OAc) and 7.18 (10H, s, aromatic protons). The acetate 5, obtained as a mixture of diasteromers could not be separated into its isomers.

The acetates 5 were dehydrated by paratoluene sulphonic acid in refluxing benzene to afford the mixture of diastereomeric unsaturated acetates 6 $C_{24}H_{28}O_2$, obtained as a viscous liquid. It showed IR bands at 1739, 1220 (acetate), 1587, 755, 694 (aromatic) and PMR signals at 0.60 (1H, m, cyclopropane proton at C_3), 0.85, 1.00, 1.07, 1.13 (6H total, s. each, gem-dimethyls of both diastereomers), 1.33 (1H, d, J = 8 Hz, allylic cyclopropane proton at C_1), 1.77 (2H, m, methylene protons), 2.00 (3H, s, acetate methyl), 2.07 (3H, s, vinyl methyl), 5.45 (2H, m, benzylic and olefinic protons) and 7.20, 7.23 (10H total, s each, aromatic protons).

The mixture of unsaturated acetates 6 was subjected to oxidation by potassium permanganate[30] in acetone in the presence of acetic acid and water to afford the acetoxy acid 7 (R=H) in 45% yield. This was converted into its

methyl ester by an ethereal solution of diazomethane to give acetoxy ester 7 (R=CH_3), $C_{17}H_{22}O_4$ as a liquid. It showed IR bands at 1730 (>C=O), 1235 (acetate), 1163 (ester), 1613, 758, 699 (aromatic) and PMR signals at 0.95 (1H, m, cyclopropane proton at C_3), 1.06, 1.13 (3H each, s each, gem-dimethyl on cyclopropane), 1.36 (1H, d, J = 8 Hz, cyclopropane proton at C_1), 2.03 (3H, s, acetoxy methyl), 2.16 (2H, m, methylene protons), 3.56 (3H, s, ester methyl), 5.63 (1H, t, J = 7 Hz, benzylic proton, i.e. H-C-OAc) and 7.20 (5H, s, aromatic protons).

The acetoxy ester 7 (R=CH_3) on saponification with aqueous potassium hydroxide in methanol gave hydroxy acid 8 (R=H) which, was esterified with an ethereal solution of diazomethane to give hydroxy ester 8 (R=CH_3). The purified ester 8 (R=CH_3), $C_{15}H_{20}O_3$ obtained as a thick liquid showed IR bands at 3509. 1124 (OH), 1724, 1162 (ester), 750, 694 (aromatic) and PMR signals at 0.80 (1H, m, cyclopropane proton at C_3), 1.05, 1.10 (3H each, s each, gem-dimethyl on cyclopropane), 1.32 (1H, br, d, cyclopropane proton at C_1), 1.98 (2H, br, m, methylene protons), 2.67 (1H, br, s, exchangeable with D_2O, -OH proton), 3.55 (3H, s, ester methyl), 4.53 (1H, t, J = 6 Hz, benzylic proton) and 7.22 (5H, s, aromatic protons).

Jones chromic acid oxidation of 8 (R=CH_3) at 0^o afforded the keto ester 9 in 85% yield, $C_{15}H_{18}O_3$, M^+ 246, m.p.61^o. It showed IR bands at 1725 (ester), 1695

(-C-ph), 1605, 1587, 760, 705 (aromatic) and PMR signals at 1.15, 1.26 (3H each, s each, gem-dimethyl on cyclopropane), 1.53 (2H, m, cyclopropane protons at C_1 and C_3), 3.26 (2H, m, methylene protons), 3.50 (3H, s, ester methyl) and 7.23, 7.76 (5H total, m, aromatic protons).

Dehydration of hydroxy ester 8 ($R=CH_3$) with PTS in refluxing benzene gave methyl 1S-(+)-cis 2,2-dimethyl-3-(2E-styryl)cyclopropanecarboxylate 10 in 50% yield, $C_{15}H_{18}O_2$, M^+ 230. It showed IR bands at 1724, 1176 (ester >C=O), 1654, 966 (trans-disubstituted double bond). 1499, 755 (aromatic) and PMR ($CDCl_3$, 80 MHz) signals at 1.22, 1.34 (3H each, s each, gem-dimethyl on cyclopropane), 1.79 (1H, d, J = 8 Hz, cyclopropane proton at C_1), 1.90 (1H, m, cyclopropane proton at C_3), 3.59 (3H, s, ester methyl), 6.50 (2H, m, olefinic protons) and 7.18 (5H, m, aromatic protons). The E-geometry for the double bond in 10 has been assigned on the basis of chemical shift (6.56) of olefinic protons which is in close agreement with the calculated value[31] (6.36δ) for the E isomer. The calculated value for Z isomer is 5.89δ. No other peak corresponding to Z isomer was seen in the PMR spectra of 10. Further, the chemical shift of 6.56 is also in close agreement with the reported value[29] for similarly situated olefinic protons in methyl cis(+) 2,2-dimethyl-3-(2-phenyl-2-chlorovinyl)cyclopropanecarboxylate, where the down-field shift has been attributed to the deshielding

effect of the adjacent phenyl ring on the vinyl proton, cis to it. The trans geometry of the double bond is also supported by the presence of a strong band at 966 cm^{-1} in the IR spectrum of compound 10.

The cis relationship between carboxylic group at C_1 and side chain at C_3 was proved by preparing the solid lactone 11 from hydroxy acid 8 (R=H) obtainable from hydroxy ester 8 ($R=CH_3$). Thus, the ester 8 ($R=CH_3$) on saponification, afforded the hydroxy acid which was treated with paratoluene sulphonic acid in dry benzene under reflux to furnish solid lactone 11, $C_{14}H_{16}O_2$, M^+ 216, m.p.136° (benzene + pet.ether). It showed IR bands at 1724, 1220 (δ-lactone), 758, 699 (aromatic) and PMR ($CDCl_3$) signals at 1.17, 1.23 (3H each, s each, gem-dimethyl on cyclopropane), 1.60 (3H, m, methylene protons and cyclopropane proton at C_3), 2.15 (1H, s, cyclopropane proton at C_1), 5.22 (1H, dd, J_1 = 4 Hz, J_2 = 12 Hz, benzylic proton) and 7.23 (5H, s, aromatic protons).

It has been reported[6] that (-) dihydrochrysanthemolactone, on heating with potassium hydroxide in diethylene glycol gave (+) trans-chrysanthemic acid in good yields. Therefore, for obtaining 1R-trans acid 12 (R=H) the δ-lactone 11 was considered as a suitable intermediate. Thus when lactone 11 was heated with potassium hydroxide in ethylene glycol a mixture of two acids was obtained, which was esterified with an ethereal solution of diazomethane

and separated by chromatography. The less polar fraction (20%), $C_{15}H_{18}O_2$, M^+ 230 was characterised as the dehydrated ester by spectral data. However, the GLC analysis indicated it to be a mixture of the double bond geometric isomers of both the epimerised 17 ($R=CH_3$) and unepimerised 10 ($R=CH_3$) dehydrated esters. The polar fraction (65%), $C_{15}H_{20}O_3$ was characterised as 12 ($R=CH_3$) by spectral data. It showed IR bands at 3546 (OH), 1724 (ester $\rangle$C=O), 1600, 758, 700 (aromatic) and PMR signals at 0.86, 1.05 (3H each, s each, gem-dimethyl on cyclopropane), 1.40 (4H, br m, cyclopropane protons and methylene protons), 3.03 (1H, hump, exchangeable with D_2O, OH proton), 3.50 (3H, s, ester methyl), 4.56 (1H, t, J = 6 Hz, benzylic proton) and 7.10 (5H, s, aromatic protons).

Jones chromic acid oxidation of 12 furnished the keto ester 13 in 90% yield as a solid, $C_{15}H_{18}O_3$, M^+ 246, m.p.100° (pet.ether). It showed IR bands at 1730 (ester $\rangle$C=O), 1690 (ph-$\underset{\underset{O}{\|}}{C}$-), 1600, 1580, 750, 703 (aromatic) and PMR signals at 1.13, 1.36 (3H each, s each, gem-dimethyl on cyclopropane), 1.73 (2H, m, cyclopropane protons at C_1 and C_3), 3.0 (2H, m, methyleneprotons), 3.61 (3H, s, ester methyl) and 7.43, 7.93 (5H, m, aromatic protons).

Reaction of phosphorous pentachloride[32,33] on keto ester 13, gave a mixture of products, which was subjected to chromatography. The earlier fractions afforded the dichloro ester 14, 10% yield, $C_{15}H_{18}O_2Cl_2$, M^+ 300, 302 (due to chlorine isotopes), m.p. 110°(pet.ether). It showed IR bands at 1727, 1176 (ester >C=O), 746, 709 (aromatic) and PMR ($CDCl_3$, 80 MHz) signals at 1.22, 1.33 (7H, s, gem-dimethyl on cyclopropane and cyclopropane proton at C_3), 1.50 (1H, s, cyclopropane proton at C_1), 2.03, 2.59 (1H each, d, J = 7 Hz, methylene protons), 3.67 (3H, s, ester methyl) and 7.17, 7.31 (5H, br, s, aromatic protons).

The middle fractions gave a mixture of E, Z isomers of the chloroester 15 in the ratio of 65:35 (GLC), $C_{15}H_{17}O_2Cl$, M^+ 264, 266 (due to chlorine isotopes). It showed IR bands at 1742 (ester >C=O), 1639, 1499, 763, 694 (aromatic) and PMR ($CDCl_3$, 80 MHz) signals at 1.18, 1.21, 1.23, 1.34 (all s, gem-dimethyls of E, Z isomers), 1.50 1.64 (d each, J = 5 Hz each, cyclopropane proton at C_1 of E, Z isomers), 2.06, 2.51 (dd each, J_1 = 5 Hz, J_2 = 8 Hz, cyclopropane protons at C_3 of E, Z isomers), 3.59, 3.67 (s each, ester methyls of E, Z isomers), 5.68, 5.81 (d each, J = 8 Hz, olefinic protons of E, Z isomers) and 7.32 (m, aromatic protons).

Transesterification [34] of 15 with 3-phenoxybenzyl alcohol furnished the 3-phenoxybenzyl ester 16 as a mixture of E, Z isomers; $C_{27}H_{25}O_3Cl$, M^+ 432, 434 (due to chlorine istopes). It showed following spectral properties, IR bands at 1724 (ester >C=O), 1587, 760 (aromatic) and PMR ($CDCl_3$, 80 MHz) signals at 1.05, 1.15, 1.22, 1.31 (all s, gem-dimethyls of E, Z isomers), 1.56, 1.68 (d each, J = 5 Hz each, cyclopropane protons at C_1 of E, Z isomers), 2.06, 2.50 (dd each, J_1= 5 Hz, J_2 = 8 Hz each, cyclopropane protons at C_3 of E, Z isomers), 5.0, 5.09 (s each, benzylic methylene protons of E, Z isomers), 5.67, 5.84 (d each, J = 8 Hz each, olefinic protons of E, Z isomers) and 7.12 (m, aromatic protons).

The pure 1R trans dehydrated ester 17 was independantly prepared by the acid-catalysed dehydration (PTS in refluxing benzene) of the hydroxy ester 12 (R=CH_3). The chromatographic purification gave in the middle fractions a TLC pure liquid ester, characterised as methyl 1R (+) trans 2,2-dimethyl-3-(2E-styryl)cyclopropane-carboxylate 17, $C_{15}H_{18}O_2$, M^+ 230. It showed IR bands at 1721 (ester >C=O), 1639, 956 (trans-disubstituted double bond), 1592, 750, 692 (aromatic) and PMR ($CDCl_3$, 80 MHz) signals at 1.19, 1.28 (3H each, s each, gem-dimethyl on cyclopropane), 1.62 (1H, d, J = 5 Hz, cyclopropane proton at C_1), 2.17 (1H, dd, J_1 =5 Hz, J_2 = 8 Hz, cyclopropane proton at C_3), 3.64 (3H, s, ester methyl), 5.89 (1H, dd,

J_1 = 8 Hz, J_2 = 15 Hz, olefinic proton adjacent to cyclopropane ring), 6.50 (1H, d, J = 15 Hz, olefinic proton adjacent to phenyl ring) and 7.25 (5H, m, aromatic protons).

Dehydrated ester 17 was converted by transesterification[34] into 3-phenoxybenzyl 1R-(+)-trans 2,2-dimethyl-3-(2E-styryl)cyclopropanecarboxylate 18 as a colourless liquid, $C_{27}H_{26}O_3$, M^+ 398. It showed IR bands at 1724, 1163 (ester >C=O), 1653, 958 (trans-disubstituted double bond), 1587, 755, 690(aromatic) and PMR ($CDCl_3$, 80 MHz) signals at 1.20, 1.27 (3H each, s each, gem-dimethyl on cyclopropane), 1.72 (1H, d, J = 6 Hz, cyclopropane proton at C_1), 2.17 (1H, dd, J_1 = 6 Hz, J_2 = 9 Hz, cyclopropane proton at C_3), 5.02 (2H, s, benzylic methylene protons), 5.85 (1H, dd, J_1 = 9 Hz, J_2 = 16 Hz, olefinic proton adjacent to cyclopropane ring), 6.48 (1H, d, J = 16 Hz, olefinic proton adjacent to phenyl ring) and 7.08 (14H, m, aromatic protons).

Compound 12 (R=CH_3) was also obtained by epimerisation of the corresponding 1S-cis hydroxy ester 8 (R=CH_3), under conditions similar to those employed for lactone 11. In this case also a mixture of dehydrated esters 10 and 17 was produced in about 15% as indicated by GLC analysis. However, the trans hydroxy ester 12 (R=CH_3) that was obtained from hydroxy ester 8 (R=CH_3) was found to be a mixture of diastereomers as indicated by the PMR spectra. It showed PMR signals at 0.9, 1.00, 1.06, 1.11 (6H, s, gem-

dimethyls of diastereomers), 1.53 (3H, br, m, methylene protons and cyclopropane proton at C_1), 2.86 (1H, hump, exchangeable with D_2O, OH proton), 3.46, 3.51 (3H, s, ester methyls of diastereomers), 4.56 (1H, t, J = 6 Hz, benzylic proton), 7.13, 7.20 (5H, s, aromatic protons). In the case of epimerisation of lactone 11 only one diastereomer of 12 ($R=CH_3$) was obtained as indicated by PMR spectra. The diastereomeric mixture of trans hydroxy ester 12 ($R=CH_3$) obtained from hydroxy ester 8 ($R=CH_3$) on oxidation with Jones chromic acid gave the same keto ester 13 m.p. and m.mp. 100° (superimposable PMR and IR spectra)

EXPERIMENTAL

2,2-Dimethyl-3-(2-oxopropyl)cyclopropane-1-acetaldehyde 3

In a 1-litre 3-necked flask equipped with an overhead mechanical stirrer, were taken caranediol 2 (51 g, 0.3 mol), methanol (200 ml) and water (75 ml). The contents were stirred at room temperature for ten minutes. Finely powdered sodium meta periodate (70.6 g, 0.33 mol) was then added, portionwise to the above solution under stirring. After the addition ($\frac{1}{2}$ hr) the reaction mixture was stirred for 2 hr, filtered and the residue washed with methanol (50 ml). The combined filtrate was diluted with water (350 ml) and extracted with chloroform (150 ml + 75 ml x 2). The chloroform layer was washed with water (250 ml x 3), dried and evaporated to give the keto aldehyde 3 (41.50 g, 82%), b.p.85-87°(vapour)/1.5 mm; (Found: C, 70.95; H, 9.48; $C_{10}H_{16}O_2$ requires C, 71.39; H, 9.59%). IR bands at: 2985, 2740, 1724, 1439, 1351, 1163, 1124, 1047 and 962 cm^{-1}.

2,2-Dimethyl-3-(2-phenyl-2-hydroxypropyl)-cis-1-(2-phenylethane-2-ol)cyclopropane 4

A solution of keto aldehyde 3 (33.6 g, 0.2 mol) in dry ether (100 ml) was introduced, dropwise, under stirring into an ice-cooled solution of phenylmagnesium bromide prepared from magnesium turnings (10.8 g, 0.45 mol) and

bromobenzene (70.65 g, 0.45 mol) in dry ether (250 ml). After the complete addition, it was stirred for 1 hr at room temperature and 3 hr under reflux and kept overnight The reaction mixture was cooled at 0° and a saturated solution of ammonium chloride (300 ml) was introduced, dropwise, with vigorous stirring. After the addition, it was stirred for ½ hr at room temperature and transferred to a separating funnel. The ether layer was separated and the aqueous portion extracted with ether (100 ml x 2). The combined ether extract was washed with water (200 ml) and dried. Ether was distilled to give the crude product (66 g).

This product showed on TLC (18% ethylacetate in benzene) one main spot, along with minor quantities of less polar impurities. The less polar impurities were separated from main product viz. the diol 4 by chromatography over (Al_2O_3, 660 g). The less polar impurities (not investigated) were removed by eluting the column with pet.ether + benzene (1:1) and benzene while the main product was eluted with chloroform to give diol 4 (62.5 g, 96.4%) as a gummy liquid; $(\alpha)_D^{28}$ + 3.72° (c, 3.76), (Found: C, 80.96; H, 8.84; $C_{22}H_{28}O_2$ requires C, 81.44; H, 8.70%).

IR bands at: 3448, 2967, 1600, 1493, 1443, 1370, 1058, 1022, 939, 909, 870, 755 and 694 cm^{-1}.

2,2-Dimethyl-3-(2-acetoxy-2-phenylethyl)-cis-1-(2-phenyl-2-hydroxypropyl)cyclopropane 5

To a solution of the diol 4 (32.4 g, 0.1 mol) in dry pyridine (60 ml) was added acetic anhydride (35 ml) and the mixture was kept at room temperature for 24 hr. It was then diluted with ice cold water (250 ml) and kept at room temperature for 2 hr when the excess amount of acetic anhydride was hydrolysed. The mixture was extracted with ether (150 ml + 100 ml x 2), the ether layer washed successively with water, 10% hydrochloric acid, saturated solution of sodium carbonate and finally with water. The ether layer was dried and evaporated to furnish the pure monoacetylated product 5 as a thick liquid in almost quantitative yield (32.9 g, 90%); $(\alpha)_D^{25}$ 5.3° (c, 2.65); (Found: C, 78.24; H, 8.42; $C_{24}H_{30}O_3$ requires C, 78.65; H, 8.25%).

IR bands at: 3508, 2985, 1724, 1587, 1481, 1429, 1361, 1227, 1053, 1015, 930, 758 and 694 cm^{-1}.

2,2-Dimethyl-3-(2-acetoxy-2-phenylethyl)-cis-1-(2-phenylprop-1-enyl)cyclopropane 6

A solution of hydroxy acetate 5 (27.5 g, 0.075 mol) in dry benzene (250 ml) was refluxed with catalytic amount of PTS (0.3 g) for 6 hr. The reaction mixture was washed with water (100 ml x 2) to remove PTS and the benzene layer dried. Removal of benzene afforded the dehydrated

product (26 g) which was purified by chromatography on silica gel impregnated with 10% silver nitrate (400 g). The fractions eluted with pet.ether + benzene (1:1) and benzene afforded TLC pure (8% ethylacetate in benzene) unsaturated acetate 6 (20 g, 80%); $(\alpha)_D^{28}$ + 8.6° (c, 2.8); (Found: C, 82.58; H, 8.34; $C_{24}H_{28}O_2$ requires C, 82.72; H, 8.10%).

IR bands at: 2985, 1739, 1587, 1481, 1439, 1361, 1220, 1015, 755 and 694 cm^{-1}.

Methyl 1S-cis-2,2-dimethyl-3-(2-acetoxy-2-phenylethyl)-cyclopropanecarboxylate 7 (R=CH_3)

In a one litre, three necked round bottom flask equipped with overhead stirrer, was placed the unsaturated acetate 6 (17.4 g, 0.05 mol), acetone (200 ml), water (25 ml) and acetic acid (15 ml). To the above stirred solution was added powdered potassium permanganate (12 g, 0.075 mol), during ½ hr at room temperature. After the addition, the stirring was continued for 1.5 hr at room temperature. It was then treated simultaneously with sodium nitrite (8 g) and sulphuric acid (1:10), when all the manganese dioxide dissolved and a clear solution was obtained. The colourless solution was diluted with water (300 ml) and extracted with ether (150 ml + 100 ml x 2). The ethereal solution was concentrated to 150 ml and extracted with 10% aqueous sodium carbonate solution

(50 ml x 3). The neutral part was not investigated. The aqueous alkaline portion was cooled, acidified with 20% sulphuric acid and extracted with ether (100 ml x 3). The combined ether layer was washed with water (100 ml x 3), dried and evaporated to furnish the acid 7 (R=H) which was converted into its methyl ester 7 ($R=CH_3$, 6.5 g, 45%). The acetoxy ester was further purified by chromatography over (Al_2O_3; 130 g) and the fractions eluted with pet.ether + benzene (1:1) and benzene gave TLC pure acetoxy ester 7 ($R=CH_3$); b.p.150-55°/0.15 mm; (Found: C, 69.94; H, 7.45; $C_{17}H_{22}O_4$ requires C, 70.30; H, 7.64%).
IR bands at: 2985, 1730, 1613, 1493, 1439, 1370, 1235, 1190, 1163, 1130, 1089, 1020, 847, 758 and 699 cm^{-1}

Methyl 1S-*cis*-2,2-dimethyl-3-(2-hydroxy-2-phenylethyl)cyclopropanecarboxylate 8 ($R=CH_3$)

To a solution of the acetoxy ester 7 (5.8 g, 0.02 mol) in methanol (200 ml) was added 20% aqueous solution of sodium hydroxide (25 ml) and the mixture refluxed for 5 hr. Methanol was removed under reduced pressure and the residue diluted with water (100 ml), acidified with dilute hydrochloric acid and extracted with ether (100 ml x 3). The combined ether layer was washed with water (100 ml x 2), dried and the solution of hydroxy acid 8 (R=H) in ether was esterified with an ethereal solution of diazomethane to give the hydroxy ester 8 ($R=CH_3$, 4.4 g, 90%). It was

chromatographed over silica gel (50 g) and fractions eluted with benzene, benzene + chloroform (3:1) furnished the TLC pure hydroxy ester 8 ($R=CH_3$) as a thick liquid; b.p.160-65°/0.2 mm; $(\alpha)_D^{28}$ - 2.25° (c, 2.67); (Found: C, 72.74; H, 7.95; $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.12%). IR bands at: 3509, 3030, 1724, 1613, 1538, 1504, 1449, 1383, 1250, 1162, 1124, 1094, 1053, 957, 862, 750 and 694 cm^{-1}.

Methyl 1S-cis-2,2-dimethyl-3-(2-oxo-2-phenylethyl)cyclopropanecarboxylate 9

To a solution of hydroxy ester 8 ($R=CH_3$, 2.5 g, 0.01 mol) in acetone (30 ml), cooled at -10° was added Jones chromic acid reagent till brown colour persisted. The reaction mixture was allowed to remain at 0 to 5° for 2 hr. It was then diluted with water (50 ml) and extracted with ether (50 ml x 3). The combined ether layer was washed with water (50 ml x 2), dried and evaporated to furnish a semisolid. It was chromatographed over silica gel (25 g) and fractions eluted with pet.ether + benzene (1:1) and benzene gave a white solid, which was crystallised from pet.ether to afford white crystalline keto ester 9 (2.0 g, 85%); m.p. 61°, $(\alpha)_D^{25}$ + 60.3° (c, 2.32). (Found: C, 73.34; H, 7.26; $C_{15}H_{18}O_3$ requires C, 73.14; H, 7.37%).

IR bands at: 2940, 1725 , 1695, 1605, 1587, 1455, 1387, 1345, 1255, 1205, 1145, 1097, 863, 785, 760 and 705 cm^{-1}.

Methyl 1S (+) cis 2,2-dimethyl-3-(2E-styryl)cyclopropane-carboxylate 10

The hydroxy ester 8 ($R=CH_3$, 0.75 g), in dry benzene (100 ml) was refluxed with catalytic amount of PTS (0.05 g) for 8 hr using azeotropic unit. It was then washed with water (50 ml x 2), dried and distilled to give the dehydrated ester. It was chromatographed over silica gel impregnated with 10% silver nitrate (12 g) and fractions eluted with pet.ether + benzene (4:1) and pet.ether + benzene (1:1) gave the liquid dehydrated ester 10 (0.34 g, 50%); b.p.125-30°/0.2 mm;$(\alpha)_D^{25}$ + 43° (c, 1); (Found: C, 78.27; H, 7.82; $C_{15}H_{18}O_2$ requires C, 78.23; H, 7.88%).

IR bands at: 3030, 1724, 1654, 1608, 1499, 1439, 1408, 1370, 1309, 1266, 1176, 1136, 966, 926, 755 and 694 cm^{-1}.

8-Lactone of 1S-cis-2,2-dimethyl-3-(2-hydroxy-2-phenylethyl)-cyclopropane carboxylic acid 11

To a solution of hydroxy ester 8 ($R=CH_3$, 4.9 g, 0.02 mol) in methanol (100 ml), was added 25% aqueous solution of sodium hydroxide (20 ml) and refluxed for 5 hr. The methanol was distilled under reduced pressure and the reaction mixture was cooled, diluted with water (50 ml) and extracted with ether (50 ml x 2) to remove neutral part.

The aqueous alkaline portion was cooled, acidified with 20% sulphuric acid and extracted with ether (50 ml x 3). The combined ether layer was washed with water (40 ml x 2), dried and evaporated to furnish the hydroxy acid 8 (R=H, 4.3 g) as a thick liquid. The acid 8 (R=H) was taken in dry benzene (100 ml) and the solution refluxed with paratoluene sulphonic acid (0.05 g) for 8 hr. The benzene solution was washed with water (30 ml x 2), dried and the solvent evaporated to furnish the solid (2.6 g, 60%). It was crystallised from 15% pet.ether in benzene to furnish crystalline δ-lactone 11, m.p.136°; $(\alpha)_D^{28}$ + 49° (c, 1.14); (Found: C, 77.68; H, 7.52; $C_{14}H_{16}O_2$ requires C, 77.75; H, 7.46%).

IR bands at: 2941, 1724, 1481, 1439, 1370, 1342, 1266, 1220, 1111, 1042, 1015, 925, 830, 758 and 699 cm^{-1}.

Methyl 1R trans-2,2-dimethyl-3-(2-hydroxy-2-phenylethyl)-cyclopropanecarboxylate 12 (R=CH_3) from lactone 11

δ-Lactone 11 (0.432 g, 2 mmol) was refluxed for 30 minutes with potassium hydroxide (0.448 g, 8 mmol) in ethylene glycol (20 ml). After distillation of 8 ml of the solvent, the mixture was heated at 190-95° for 5 hr in nitrogen atmosphere. It was cooled and diluted with water (30 ml) and extracted with ether (25 ml) to remove the neutral portion. The alkaline portion was cooled, acidified with dilute sulphuric acid and extracted with

ether (50 ml x 3). The combined ether layer was washed with water (25 ml x 2) and dried. The solution of acid in ether was esterified with an ethereal solution of diazomethane to give the methyl ester. It showed two spots on TLC (4% ethyl acetate in benzene). It was separated by chromatography over silica gel (8 g). The fractions eluted with pet.ether + benzene (4:1) gave the mixture of dehydrated esters (20%) 10 and 17 as indicated by GLC analysis. The polar fractions eluted with benzene and chloroform gave the TLC pure trans hydroxy ester 12 ($R=CH_3$, 0.27 g; 65%) b.p.145-50°/0.1 mm; $(\alpha)_D^{24}$ + 45° (c, 2.4); (Found: C, 72.25; H, 8.22; $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.12%).

IR bands at: 3546, 3030, 1724, 1600, 1499, 1439, 1361, 1282, 1198, 1163, 1117, 1047, 758 and 700 cm^{-1}.

Methyl 1R-trans-2,2-dimethyl-3-(2-hydroxy-2-phenylethyl)-cyclopropanecarboxylate 12 ($R=CH_3$) from hydroxy ester 8 ($R=CH_3$)

Hydroxy ester 8 ($R=CH_3$, 1 g, 4 mmol) was refluxed for ½ hr with potassium hydroxide (0.89 g, 16 mmol) in ethylene glycol (25 ml) under nitrogen atmosphere. After distillation of 12 ml of the solvent, the mixture was heated at 190-95° for 5 hr. The reaction mixture was worked-up as described above to give the mixture of esters. It was separated by chromatography over silica gel (15 g).

The fractions eluted with pet.ether + benzene (4:1) gave the mixture of dehydrated esters (15%) 10 and 17 as indicated by GLC analysis. The polar fractions eluted with benzene and chloroform gave the TLC pure trans hydroxy esters 12 (R=CH_3, 0.79 g, 70%), b.p.145-50°/0.1 mm.

Methyl 1R trans 2,2-dimethyl-3-(2-oxo-2-phenylethyl)-cyclopropanecarboxylate 13

To a solution of hydroxy ester 12 (R=CH_3, 1.0 g, 4 mmol) in acetone (20 ml), cooled at -10°, was added Jones chromic acid reagent till brown colour persisted. The reaction mixture was allowed to remain at 0 to 5° for 2 hr. It was then diluted with water (30 ml) and extracted with ether (30 ml x 3). The combined ether layer was washed with water (25 ml x 2), dried and distilled to furnish a solid which was crystallised from pet.ether to furnish white crystalline keto ester 13(0.89 g, 90%); m.p.100°; $(\alpha)_D^{24}$ - 1° (c, 1); (Found: C, 73.36; H, 7.48; $C_{15}H_{18}O_3$ requires C, 73.14; H, 7.37%).

IR bands at: 2985, 1730, 1690, 1600, 1580, 1470, 1380, 1335, 1200, 1160, 750 and 703 cm^{-1}

Methyl 1R(+)-trans-2,2-dimethyl-3-(2-chloro-2-phenylvinyl)-cyclopropanecarboxylate 15

To a solution of keto ester 13(0.5 g, 2 mmol) in dry dichloromethane (20 ml) was added phosphorous pentachloride (1.6 g, 7.6 mmol) and the mixture was refluxed for 7 hr.

The reaction mixture was then poured on to crushed ice (20 g) with stirring, allowed to attain room temperature and extracted with dichloromethane (30 ml x 3). The combined dichloromethane layer was washed with water, aqueous sodium bicarbonate and water, dried and evaporated to give a mixture of two products (TLC). They were separated by chromatography over silica gel (10 g). The less polar, the minor one (10%), eluted with pet.ether + 10% benzene gave a solid, crystallised from pet.ether to furnish dichloroester 14; m.p.110°; (Found: C, 59.43; H, 5.50; Cl, 23.14; $C_{15}H_{18}O_2Cl_2$ requires C, 59.80; H, 5.98; Cl, 23.59%). IR bands at: 3030, 1727, 1449, 1389, 1299, 1220, 1176, 1117, 862, 806, 746, and 709 cm^{-1}.

The more polar, the major product was eluted with pet.ether + 25% benzene to afford the pure chloroester 15, as a liquid (0.35 g, 62%); b.p.140-45°/0.1 mm; $(\alpha)_D^{25}$ 65° (c, 0.9); (Found: C, 68.36; H, 6.08; Cl, 13.66; $C_{15}H_{17}O_2Cl$ requires C, 68.06; H, 6.42; Cl, 13.42%). IR bands at: 3030, 1742, 1639, 1499, 1449, 1282, 1235, 1174, 1117, 763 and 694 cm^{-1}.

3-Phenoxybenzyl 1R(+)-trans-2,2-dimethyl-3-(2-chloro-2-phenylvinyl)cyclopropanecarboxylate 16

To a solution of methyl ester 15 (0.132 g; 0.5 mmol) in dry xylene (20 ml), 3-phenoxybenzyl alcohol (0.25 g, 1.25 mmol) and butyl titanate (0.05 g) were added and the

reaction mixture refluxed for 10 hr. The reaction mixture was worked up and purified as previously described in Chpater II of the thesis to give TLC pure 16 as thick liquid (0.15 g, 73%); $(\alpha)_D^{26}$ + 25° (c, 2.2); (Found: C, 74.83; H, 5.76; Cl, 8.46; $C_{27}H_{25}O_3Cl$ requires C, 74.91; H, 5.78; Cl, 8.20%).

IR bands at: 3030, 1724, 1587, 1488, 1445, 1250, 1212, 1163, 1112, 877 and 760 cm^{-1}.

Methyl 1R(+)-trans-2,2-dimethyl-3-(2E-styryl)cyclopropane-carboxylate 17

A solution of hydroxy ester 12 (R=CH_3, 0.5 g) in dry benzene (100 ml) was refluxed on a water bath with PTS (0.10 g) for 8 hr. It was then washed with water (50 ml x 2), dried and distilled to furnish the crude unsaturated ester 17. It was chromatographed over silica gel impregnated with 10% silver nitrate (20 g) and the fractions eluted with pet.ether + 10% benzene and pet.ether + 25% benzene gave a TLC pure liquid ester 17 (0.23 g, 50%); b.p.145-50°/0.15 mm; $(\alpha)_D^{26}$ + 126° (c, 2.6); (Found: C, 78.12; H, 8.09; $C_{15}H_{18}O_2$ requires C, 78.23; H, 7.88%).

IR bands at: 2967, 1721, 1639, 1592, 1493, 1429, 1370, 1342, 1274, 1205, 1163, 956, 909, 750 and 692 cm^{-1}.

3-Phenoxybenzyl 1R(+)-trans-2,2-dimethyl-3-(2E-styryl)-cyclopropanecarboxylate 18

To a solution of methyl ester 17 (0.147 g, 0.64 mmol) in dry xylene (20 ml), 3-phenoxybenzyl alcohol (0.26 g, 1.3 mmol) and butyl titanate (0.05 g) were added and the reaction mixture refluxed for 12 hr. Xylene was removed under reduced pressure and the residue chromatographed over (Al_2O_3, 25 g). The fractions eluted with pet.ether + 10% benzene and pet.ether + 20% benzene gave TLC pure ester 18 (0.19 g, 78%) as colourless liquid; $(\alpha)_D^{26}$ + 78° (c, 1.0); (Found: C, 80.96; H, 6.62; $C_{27}H_{26}O_3$ requires C, 81.38; H, 6.58%).

IR bands at: 3012, 1724, 1653, 1587, 1484, 1447, 1376, 1342, 1250, 1208, 1163, 958, 862, 755 and 690 cm^{-1}.

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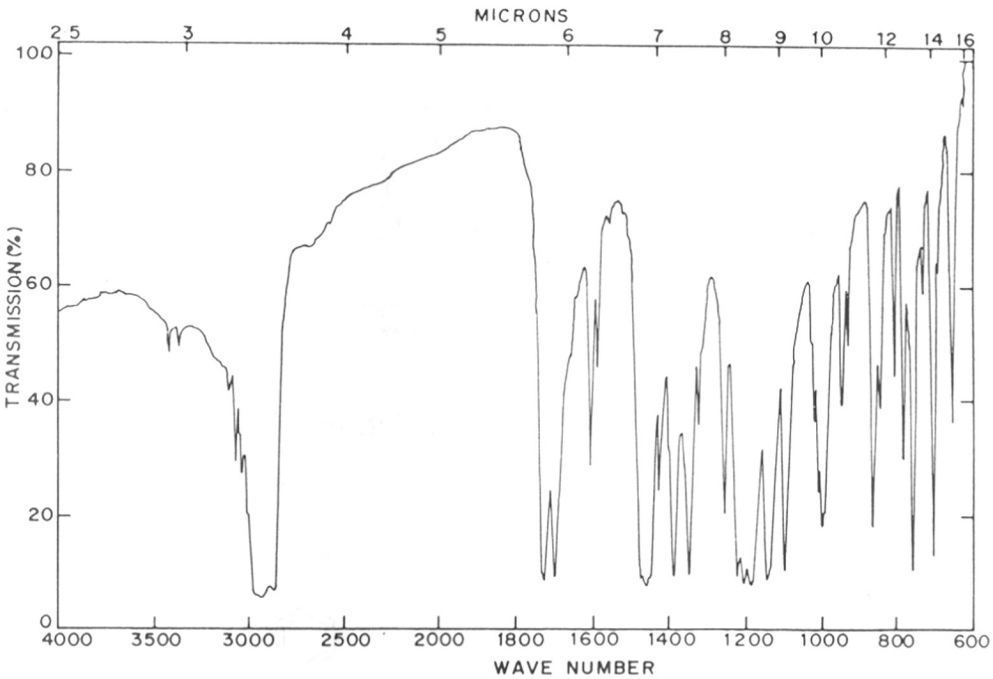
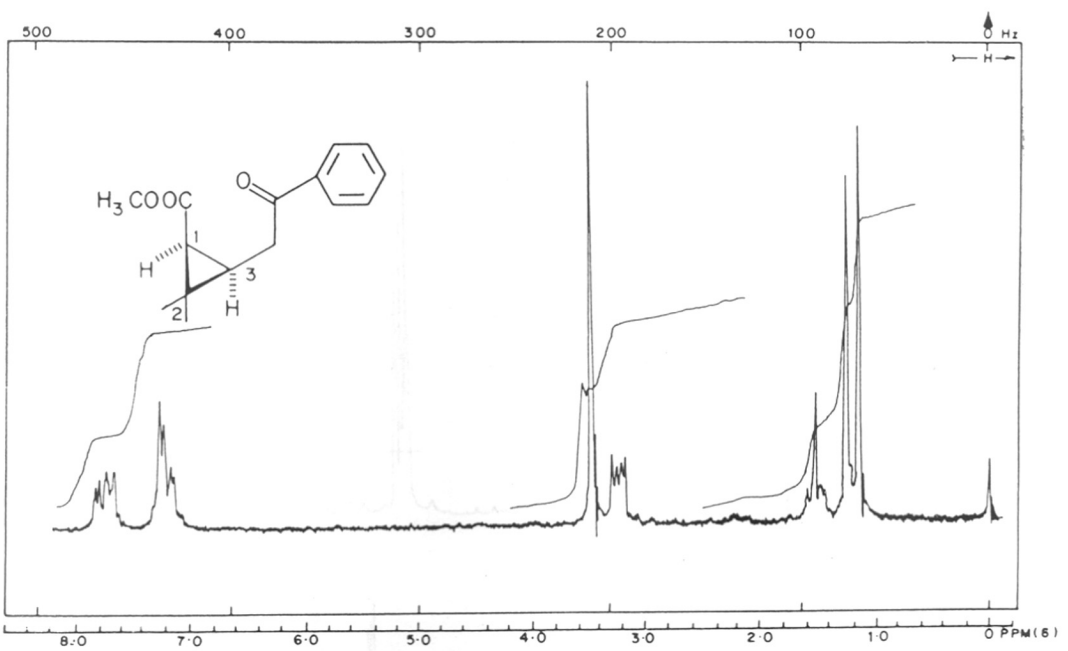
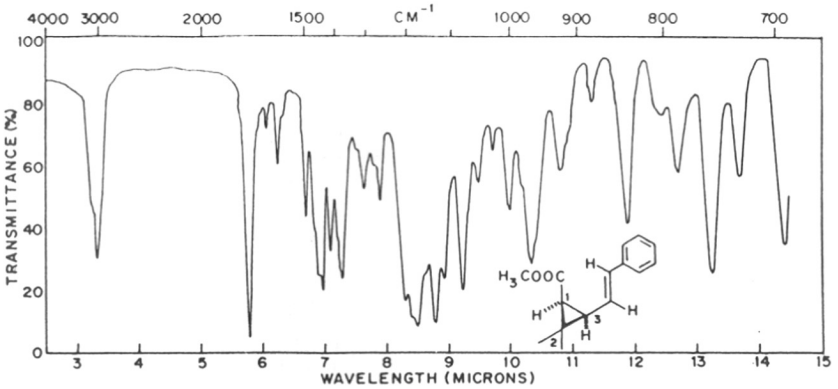
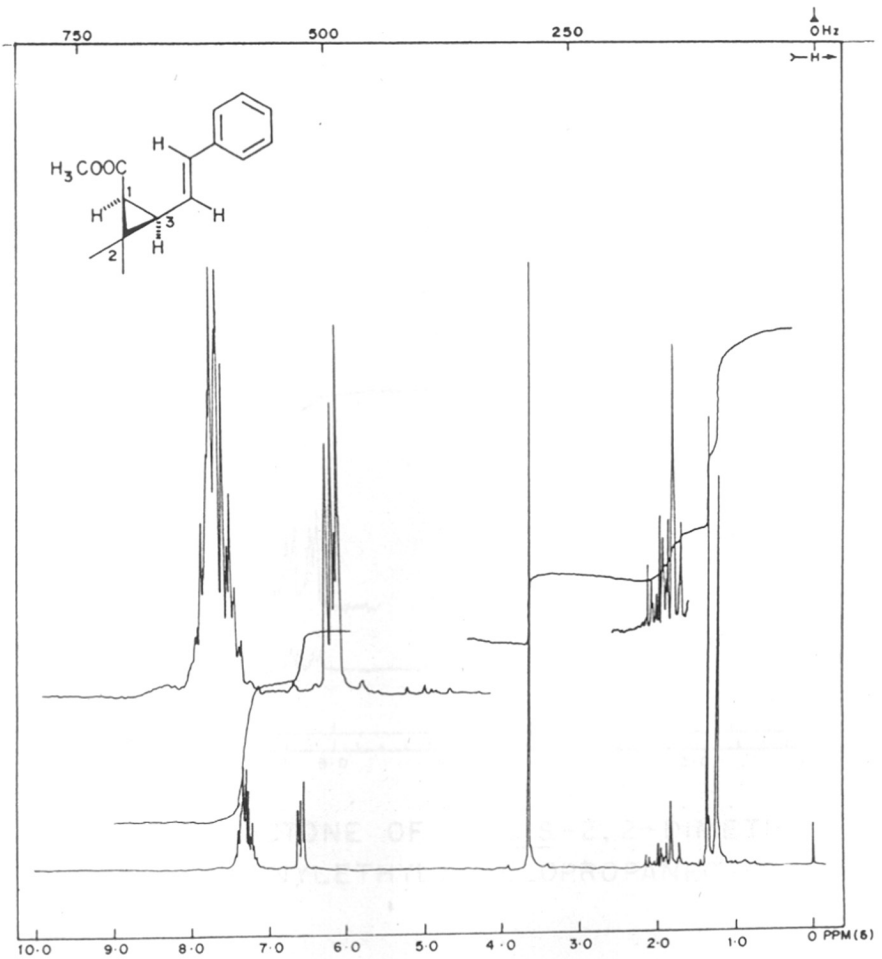




IR & PMR OF METHYL IS CIS-2,2-DIMETHYL-3-(2-OXO-2-PHENYLETHYL) CYCLOPROPANECARBOXYLATE 9



IR SPECTRUM OF METHYL 1S(+) CIS 2,2-DIMETHYL-3-(2E-STYRYL) CYCLOPROPANE-CARBOXYLATE 10.



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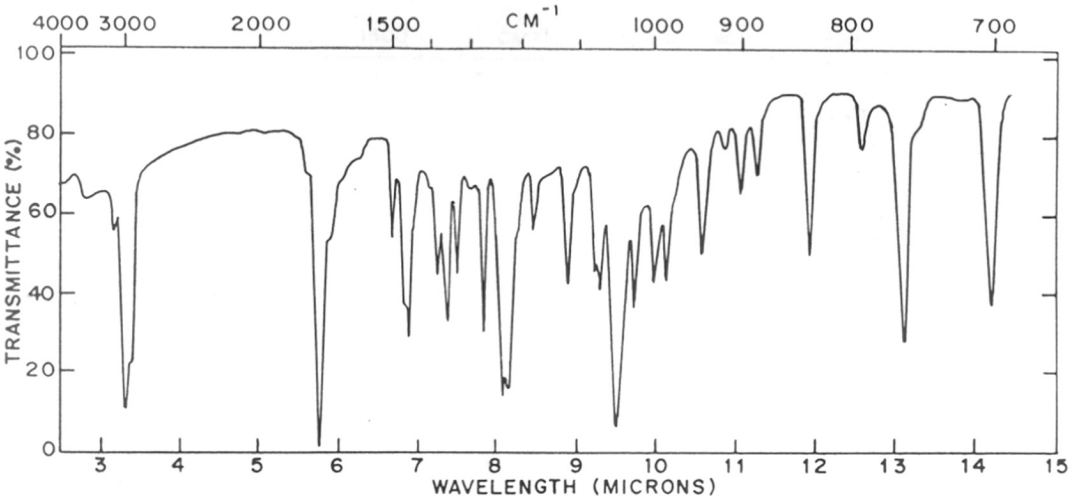
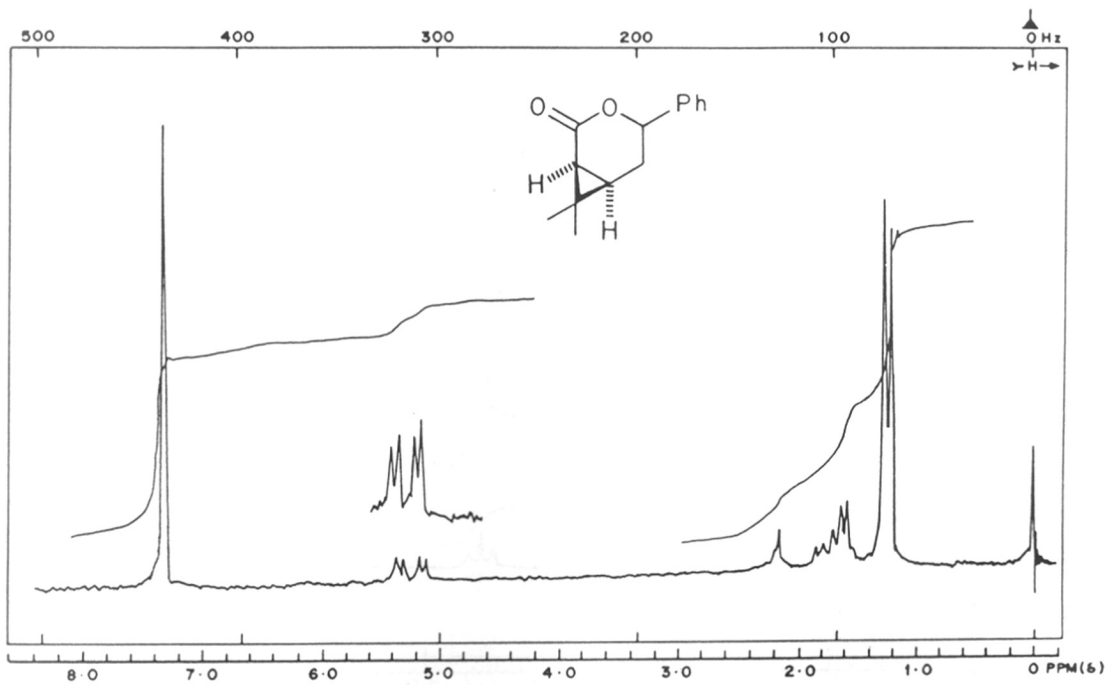
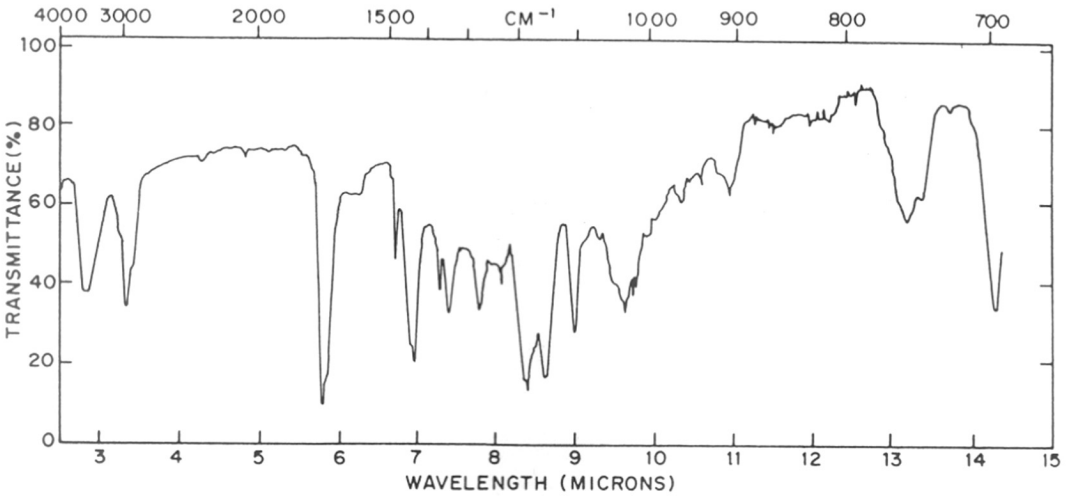
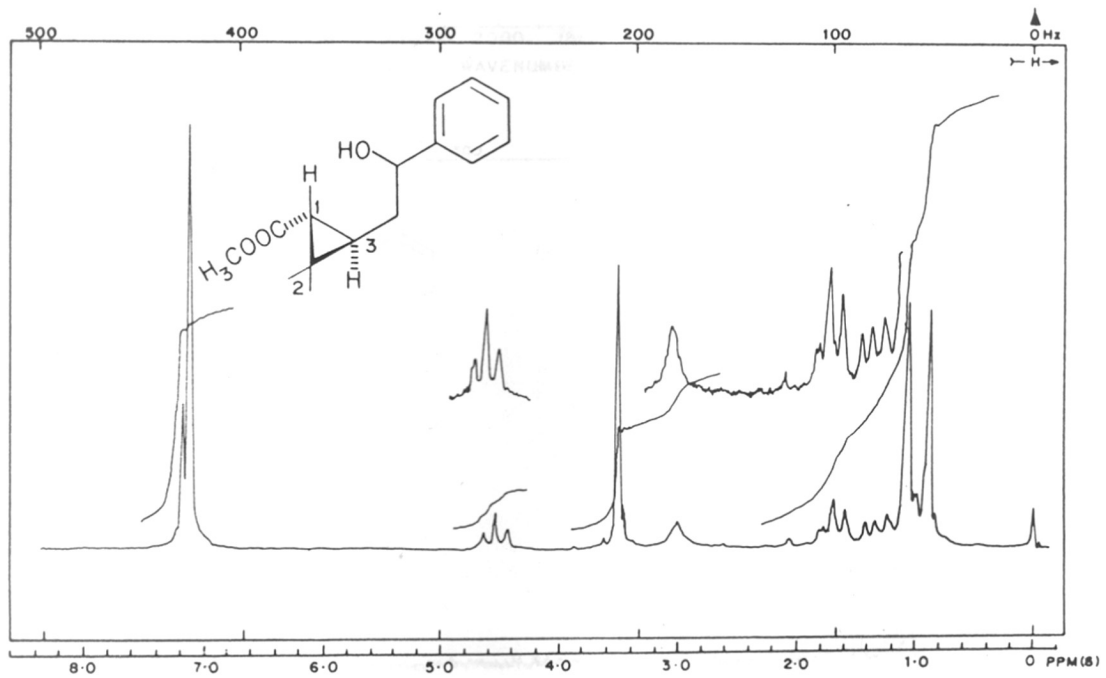


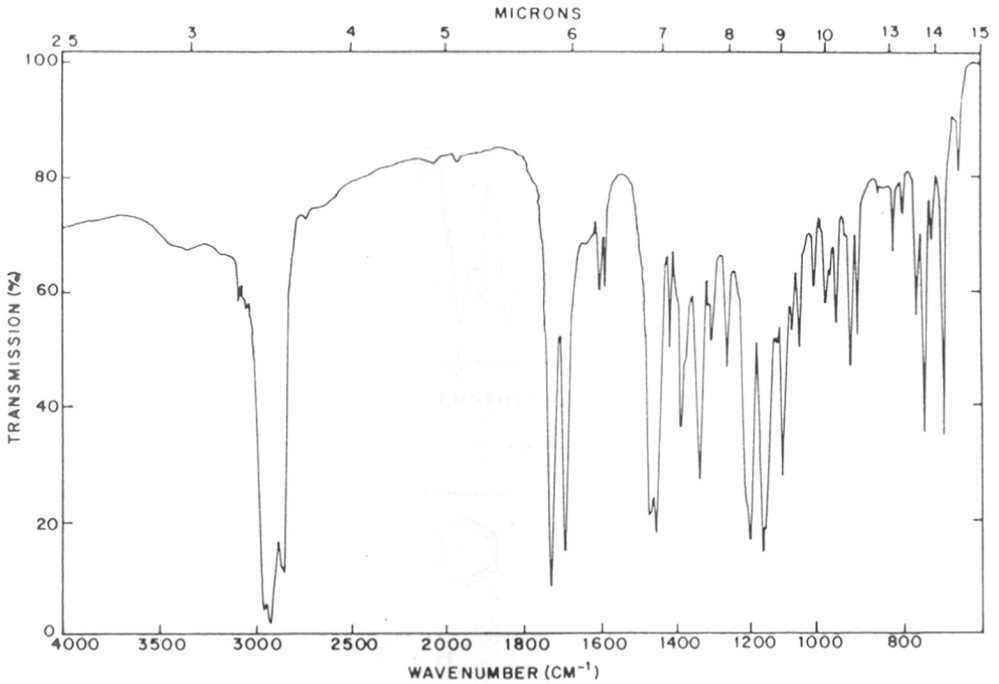


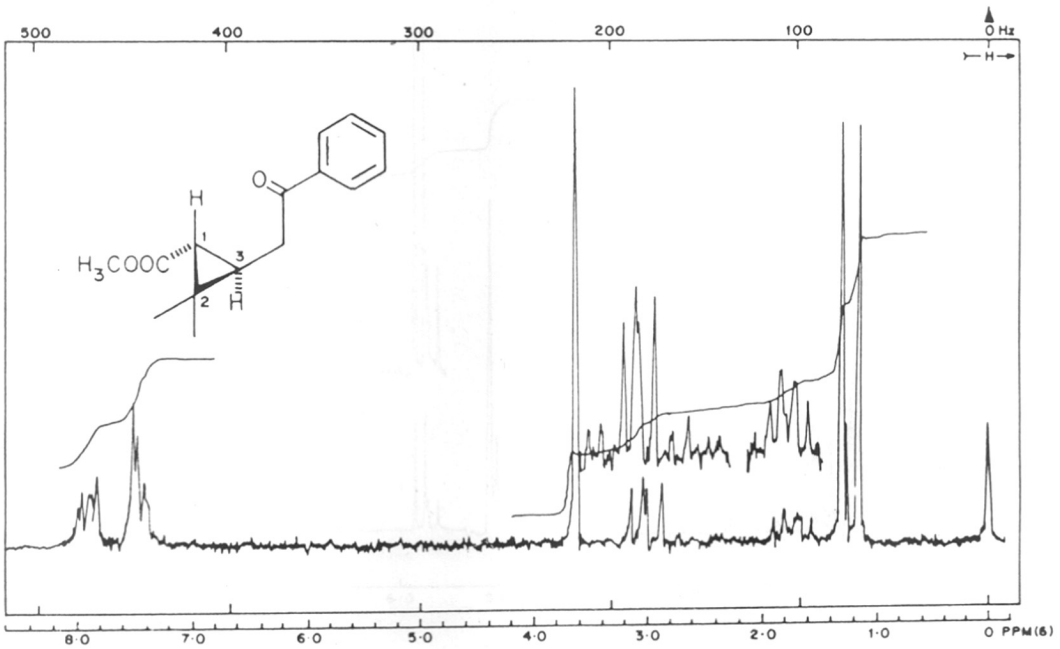
IR & PMR OF δ-LACTONE OF 1S-CIS-2,2-DIMETHYL-3-(2-HYDROXY-2-PHENYLETHYL) CYCLOPROPANECARBOXYLIC ACID 11





IR & PMR OF METHYL 1R - TRANS - 2,2 DIMETHYL-3-(2-HYDROXY-2-PHENYLETHYL) CYCLOPROPANECARBOXYLATE 12.





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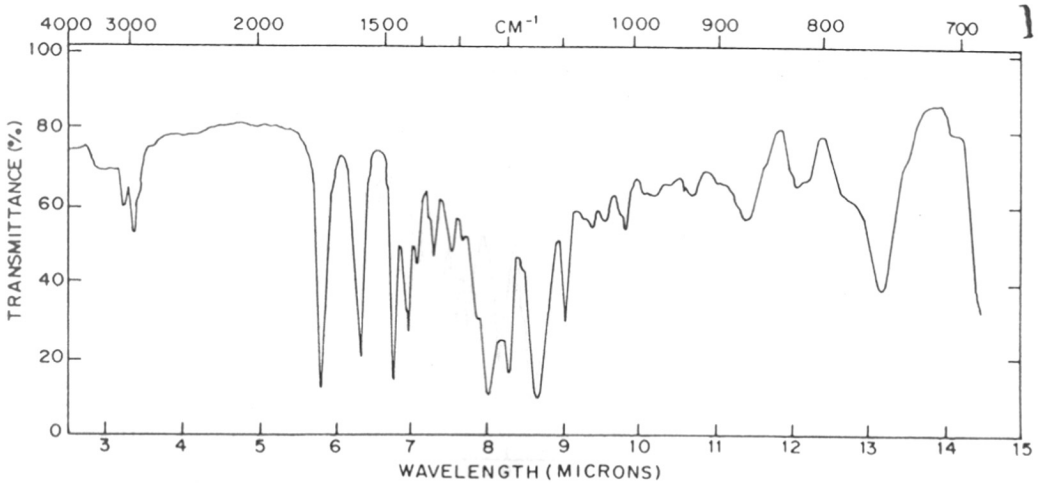
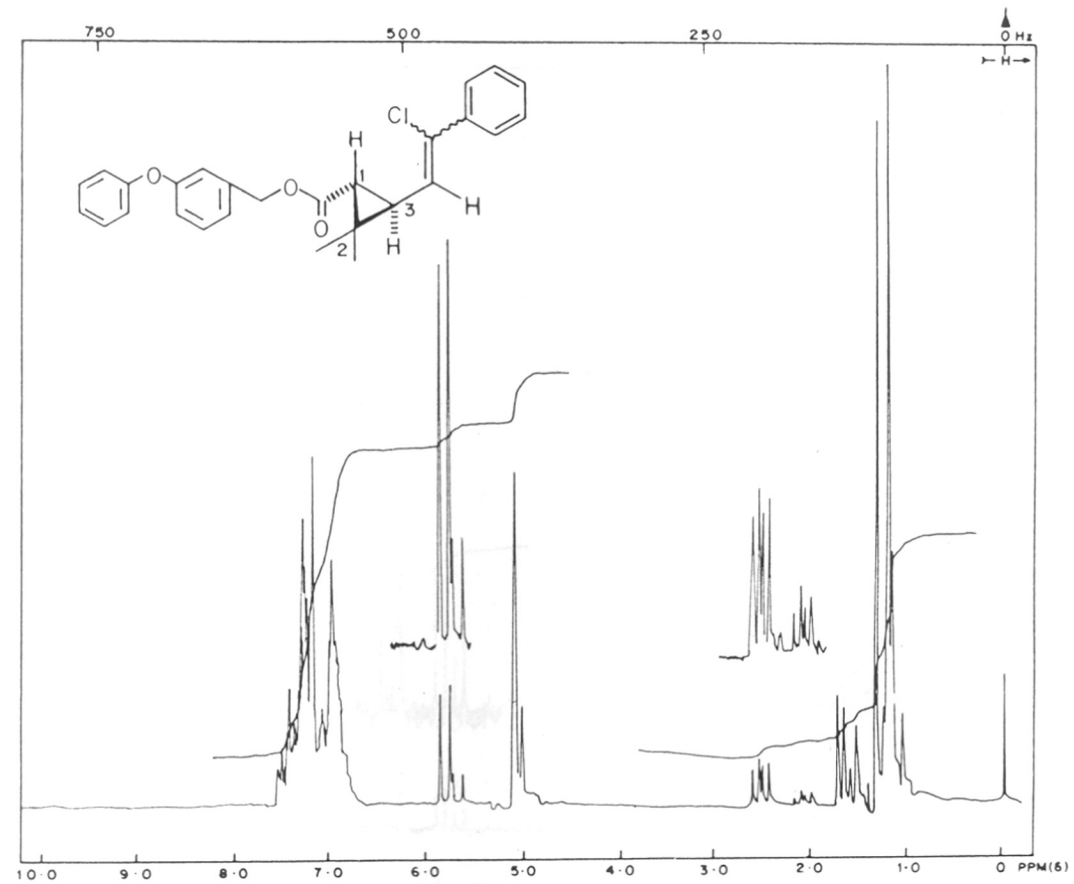
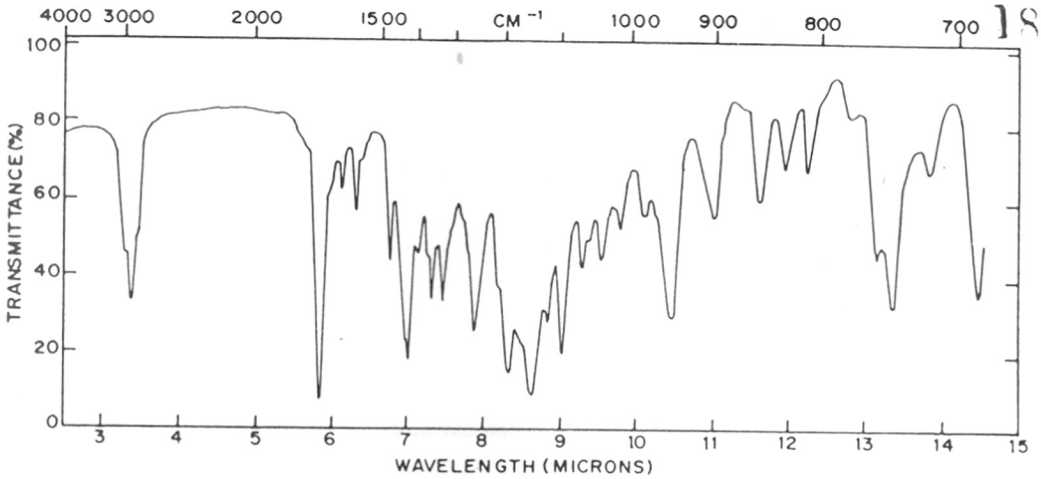
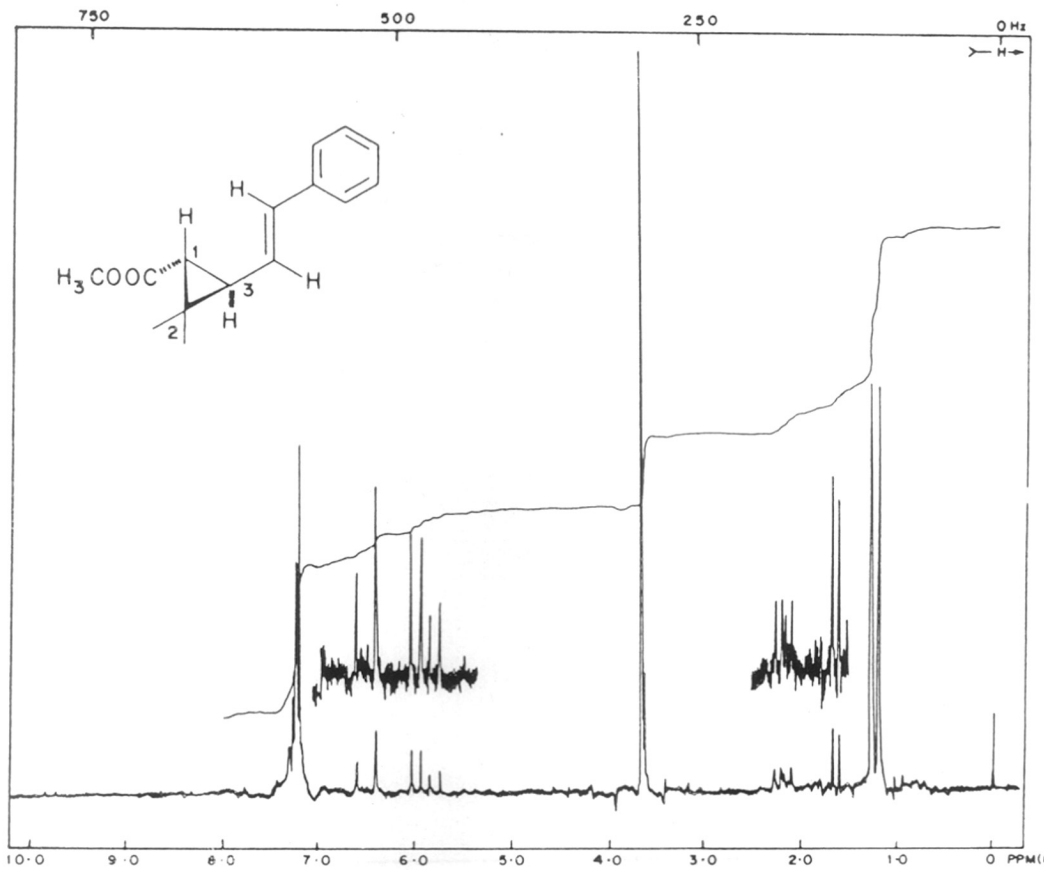




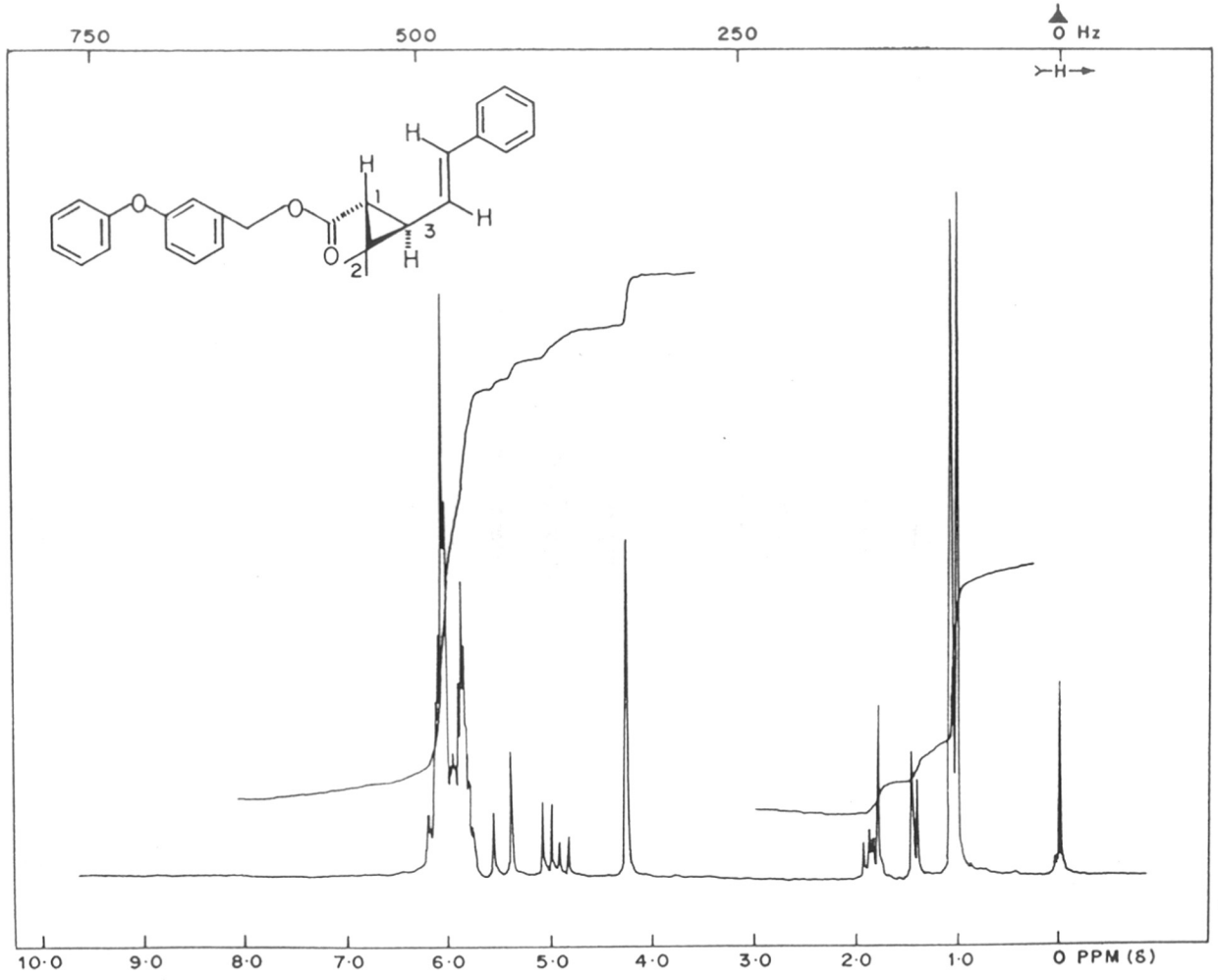
IR & PMR SPECTRUM OF 3-PHENOXYBENZYL 1R (+) TRANS-2,2-DIMETHYL-3-(2-CHLORO-2 PHENYLVINYL) CYCLOPROPANECARBOXYLATE

16.





IR & PMR SPECTRUM OF METHYL 1R(+)-TRANS-2,2 DIMETHYL-3-(2E-STYRYL) CYCLOPROPANECARBOXYLATE 17.



PMR SPECTRUM OF 3-PHENOXYBENZYL 1R-(+) TRANS 2,2-DIMETHYL -3-(2E-STYRYL) CYCLOPROPANECARBOXYLATE 18.

CHAPTER–V

TRANSFORMATIONS OF (+)-3-CARENE INTERMEDIATES

PART–A

BASE-CATALYSED REARRANGEMENTS

SUMMARY

The trans caranediol 2 obtainable from (+)-3-carene 1, on oxidation with sodium meta periodate, gave the keto aldehyde 3 which, on treatment with piperidine and acetic acid in dry benzene, afforded the aldehyde 4. Potassium permanganate oxidation of aldehyde 4 gave the keto acid 5 (R=H), which on esterification with ethereal solution of diazomethane afforded the keto ester 5 ($R=CH_3$).

Wittig reaction on keto ester 5 ($R=CH_3$) using methylene-triphenylphosphorane, gave instead of the normal expected product (6), the acyclic diene ester 8. Keto ester 5 ($R=CH_3$) on treatment with potassium t-butoxide at 0° underwent base catalysed retro-Michael type rearrangement to afford the acyclic α,β-unsaturated keto ester 9. This on Wittig reaction with methylenetriphenylphosphorane gave the expected diene ester 8.

Similar results were obtained when the keto ester 10 was subjected to Wittig reaction using methylenetriphenyl-phosphorane reagent to give diene ester 11 via the acyclic α,β-unsaturated keto ester 13.

An attempt to epimerise the 1S cis keto ester 10 to the corresponding 1R trans isomer by sodium methoxide resulted in the formation of conjugated diketone 14. The formation of conjugated diketone 14 has been explained by the initial base-catalysed retro-Michael type rearrangement

of 10 to the corresponding acyclic α,β-unsaturated ester 13. The keto ester 13 in the presence of methoxide ion undergoes combined Michael and internal Claisen condensation to give conjugated diketone 14. Similar results were obtained on the keto ester 5 ($R=CH_3$).

INTRODUCTION

As already mentioned in Chapter III of the thesis, there are several approaches[1,2] for the synthesis of 1R(+) trans-chrysanthemic acid, which is a component of natural insecticides[3].

However, not much attention was given for the conversion of (+)-3-carene 1 into 1R(+)-cis-chrysanthemic acid 6 (R=H). There are only few references available in the literature[4-6] for the conversion of (+)-3-carene 1 into 1R (+) cis-chrysanthemic acid 6 (R=H). Matsui et al.[4] synthesised selectively, the 1R(+)-cis-chrysanthemic acid 6 (R=H) from (+)-3-carene 1. Recently, in our laboratory, Mane et al.[5,6], synthesised, selectively, the 1R(+)-cis-chrysanthemic acid from (+)-3-carene 1.

Recently, it has been reported[7-9] that esters of 1R(+)-cis-chrysanthemic acid with the alcohols like 3-phenoxybenzyl alcohol, 3-thiophenoxybenzyl alcohol and 3-benzylbenzyl alcohol possess insecticidal activity. This has prompted us to develop other synthetic routes for 1R(+)-cis-chrysanthemic acid and its analogues starting from (+)-3-carene 1.

Methyl 1R-cis-2,2-dimethyl-3-(2-oxopropyl)cyclopropane-carboxylate 5 ($R=CH_3$) can be obtained from (+)-3-carene 1 by various methods[10-12]. Recently, the keto ester 5 ($R=CH_3$) has been employed for the synthesis of some new

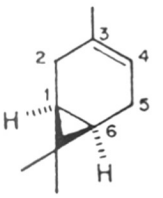
pyrethroids like 3-phenoxybenzyl 1R cis-2,2-dimethyl-3-(2-chloroprop-1-enyl)cyclopropanecarboxylate[13] viz. "Indothrin" in our laboratory. So, it was of interest to try the synthesis of 1R(+)cis-chrysanthemic acid 6(R=H) from this intermediate keto ester 5 ($R=CH_3$).

For this purpose, Wittig reaction was considered as an ideal reaction on the keto ester 5 ($R=CH_3$), which could give the double bond isomer 7 of 1R(+) cis-chrysanthemic acid. From the double bond isomer 7, the 1R(+) cis-chrysanthemate 6 ($R=CH_3$) could be obtained by the isomerisation of the double bond by the method already reported in the literature[14].

With this object in view, the keto ester 5 ($R=CH_3$) and its analogues were subjected to Wittig reaction using methylenetriphenylphosphorane. But instead of the desired product 7, reaction led to the formation of conjugated diene ester 8, in which cyclopropane ring was cleaved.

In a recent communication[15], Julia et al. have converted the diene ester 8 into trans-chrysanthemate, by hydrogen chloride addition followed by cyclization with potassium t-butoxide shown in Scheme I, Chart II.

CHART I



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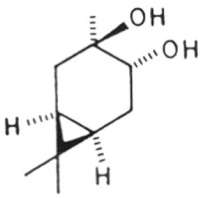

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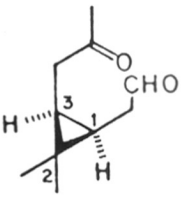

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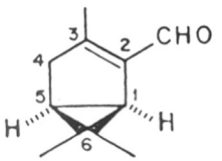

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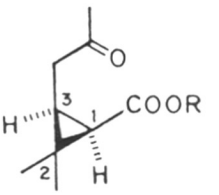
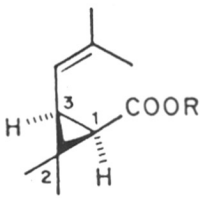
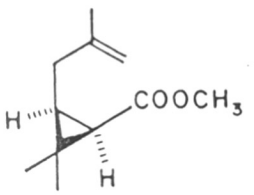


5 (R = H or CH_3)



(6) R = H or CH_3



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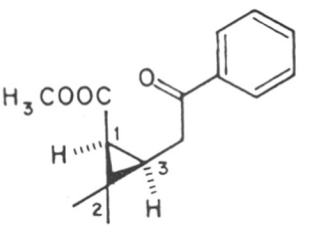

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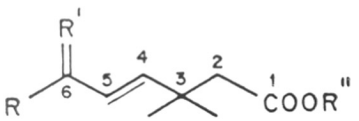


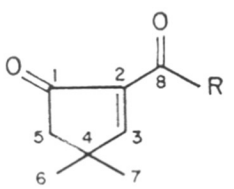
8 R = CH_3 ; R' = CH_2 ; R'' = CH_3

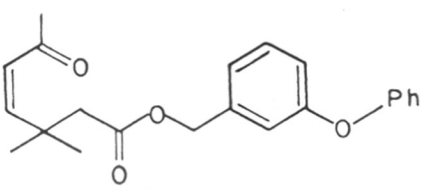
9 R = CH_3 ; R' = O ; R'' = CH_3

11 R = ; R' = CH_2 ; R'' = CH_3

12 R = ; R' = CH_2 ; R'' = $C(CH_3)_3$

13 R = ; R' = O ; R'' = CH_3





16

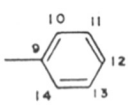
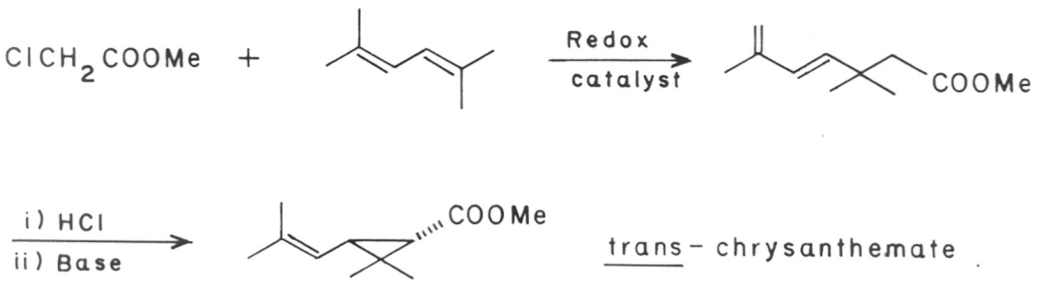
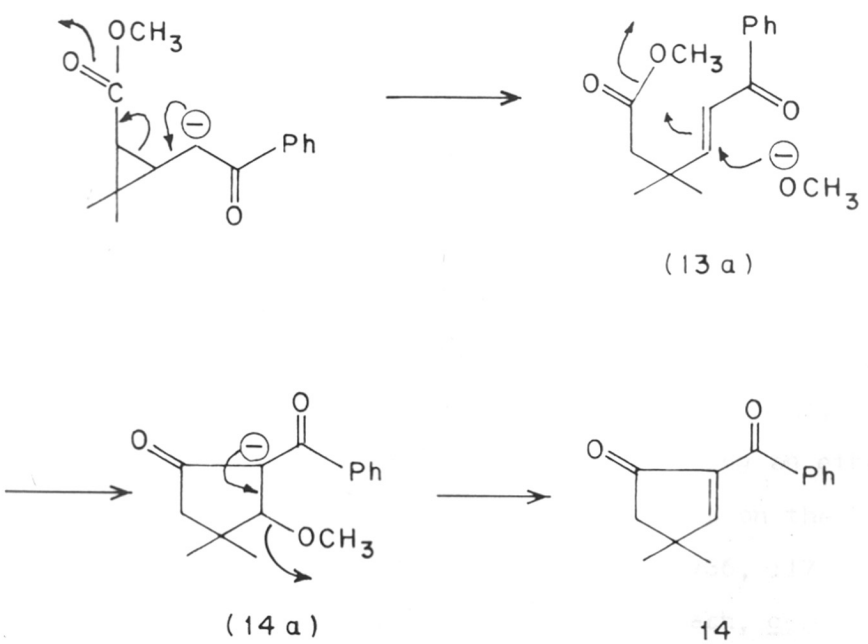
14 R =  , 15 R = CH_3

CHART II

Scheme I [15]



Scheme II [16]



The treatment of (+)-3-carene 1, with performic acid gave the known 3β,4α-caranediol 2 in 45% yield; m.p.82-83°(pet.ether), which on cleavage with sodium meta periodate afforded 2,2-dimethyl-3-(2-oxopropyl)cyclopropane cis-1-acetaldehyde 3, in 82% yield, b.p.85-87°/1.5 mm. Aldol cyclisation of 3, using piperidine and acetic acid in catalytic amount gave 2-formyl-3,6,6-trimethylbicyclo (3,1,0) hex-2-ene 4 as the major product (50%) which was separated from the other high boiling fractions, by fractional distillation. Aldehyde 4, b.p.49-55°/0.5 mm; single spot in TLC showed IR bands at 2778 (-CHO), 1667, 1618 (conjugated aldehyde >C=O) and PMR signals at 0.68, 1.06 (3H each, s each, gem-dimethyl on cyclopropane), 1.20 (1H, m, cyclopropane proton at C_5), 2.03 (4H, multiplet overlapping a singlet, vinyl methyl and allylic cyclopropane proton at C_1), 2.50 (2H, m, methylene protons at C_4) and 9.83 (1H, s, aldehyde proton).

Oxidation of the aldehyde 4 with potassium permanganate in acetone-acetic acid-water mixture gave the keto acid 5 (R=H), in the acidic part. The keto acid 5 (R=H) was converted into its methyl ester 5 ($R=CH_3$), $C_{10}H_{16}O_3$, M^+ 184, $(\alpha)_D^{28}$ - 36.7° (c, 4.6), using an ethereal solution of diazomethane. It was identified on the basis of spectral data. It showed IR bands at 1736, 1176 (>C=O) and PMR signals at 1.08, 1.19 (3H each, s each, gem-dimethyl on cyclopropane), 1.45 (2H, m, cyclopropane protons at C_1 and C_3), 2.03 (3H, s, $-COCH_3$), 2.73 (2H, d,

J = 6 Hz, methylene protons), and 3.53 (3H, s, ester methyl).

Methyl 1R cis-2,2-dimethyl-3-(2-oxopropyl)cyclopropanecarboxylate 5($R=CH_3$) is an important intermediate in the synthesis of some active insecticidal esters of the pyrethroid groups, like Indothrin[13] and other related compounds. With the object of converting keto ester 5 ($R=CH_3$) into methyl 1R(+) cis-chrysanthemate 6 ($R=CH_3$) via the double bond isomer(7) it was subjected to Wittig reaction using methylenetriphenylphosphorane generated from triphenylmethylphosphonium iodide and potassium tertiary butoxide. Instead of getting the desired ester(7), this reaction led to the formation of an isomeric ester, $C_{11}H_{18}O_2$, M^+ 182, which was assigned structure 8 on the basis of spectral properties. It showed IR band at 1730 (ester $\rangle C=O$), 1610 ($\rangle C=C\langle$), 1642, 883 ($\rangle C=CH_2$), 964 (trans disubstituted double bond) and PMR signals at 1.15 (6H, s, gem-dimethyl at C_3), 1.78 (3H, s, vinyl methyl at C_6), 2.23 (2H, s, $-CH_2$ protons adjacent to $-COOCH_3$), 3.55 (3H, s, ester methyl), 4.80 (2H, m, $\rangle C=CH_2$) and a pair of doublets at 5.43, 6.03 (1H each, J = 16 Hz each, conjugated olefinic protons at C_4 and C_5); UV λ_{max} 234 nm, ε_{max} 24,270. All the above physical properties were in good agreement with reported data in the literature[15].

The formation of diene ester 8 from keto ester 5 ($R=CH_3$) can be explained by its initial base catalysed

retro-Michael type rearrangement to give unsaturated keto ester 9, which then undergoes Wittig reaction to give ultimately diene ester 8. This fact was verified by treating keto ester 5 ($R=CH_3$) with potassium t-butoxide at 0°, when it was smoothly converted in almost quantitative yield into 9, $C_{10}H_{16}O_3$, M^+ 184, characterised by spectral data. It showed IR bands at 1736 (ester >C=O), 1672 (conjugated >C=O), 1626 (conjugated C=C), 984 (trans disubstituted double bond) and PMR signals at 1.23 (6H, s, gem-dimethyl at C_3), 2.21 (3H, s, $-COCH_3$), 2.38 (2H, s, methylene protons adjacent to ester function), 3.70 (3H, s ester methyl) and a pair of doublets centred at 5.96, 6.88 (1H each, J = 16 Hz each, conjugated olefinic protons at C_4 and C_5); UV λ_{max} 227 nm, ε_{max} 10,700. It gave a solid 2,4-DNP derivative, $C_{16}H_{20}O_6N_4$, m.p. 140°.

Wittig reaction on conjugated keto ester 9 using methylenetriphenylphosphorane gave as predicted the diene ester 8, identified by comparative spectral data with those of authentic sample. However, it was not possible to get the normal Wittig product 7, even when lesser quantity of potassium t-butoxide was used. In this case also, the product was diene ester 8 along with the unchanged keto ester 5 ($R=CH_3$).

Similar rearrangement was also observed when keto ester 10 (for preparation please refer to Chapter IV of the thesis) was subjected to Wittig reaction using methylene-

triphenylphosphorane . In this case also diene ester 11, $C_{16}H_{20}O_2$, M^+ 244 was isolated as the major product of reaction (80%). It showed IR bands at 1736 (ester $\rangle C=O$), 1645, 893 ($\rangle C=CH_2$), 974 (trans disubstituted double bond), 1600, 775, 704 (aromatic) and PMR spectrum showed signals at 1.16 (6H, s, gem-dimethyl at C_3), 2.83 (2H, s, methylene protons adjacent to ester group), 3.56 (3H, s, ester methyl), 5.10 (2H, m, $\rangle C=CH_2$ protons), a pair of doublets at 5.60, 6.20 (1H each, J = 16 Hz each, conjugated olefinic protons at C_4 and C_5) and 7.23 (5H, s, aromatic protons); $UV\lambda_{max}$ 227 nm; ε_{max} 15,130.

The minor product of the Wittig reaction was identified as the t-butyl ester 12, $C_{19}H_{26}O_2$, M^+ 286. It showed IR bands at 1721 (ester $\rangle C=O$), 1639, 889 ($\rangle C=CH_2$), 971 (trans disubstituted double bond), 1590, 771, 703 (aromatic) and PMR signals at 1.13 (6H, s, gem-dimethyl at C_3), 1.33 (9H, s, methyls of t-butyl), 2.13 (2H, s, methylene protons adjacent to ester function), 5.03 (2H, m, $\rangle C=CH_2$ protons), a pair of doublets 5.53, 6.10 (1H each, J = 16 Hz each, conjugated olefinic protons at C_4 and C_5) and 7.10 (5H, s, aromatic protons). The formation of t-butyl diene ester 12 could be explained from diene ester 11 by transesterification catalysed by potassium t-butoxide.

The formation of diene ester 11 can similarly be explained from keto ester 10, via its initial base catalysed rearrangement to give keto ester 13, which then

undergoes Wittig reaction to afford diene ester 11.

The above assumption was further proved by the reaction of keto ester 10 with potassium t-butoxide at 0^{o}. In this reaction the rearranged ester 13, $C_{15}H_{18}O_3$, M^{+} 246 was isolated as the major product. It showed IR bands at 1736 (ester $\rangle C=O$), 1670 (conjugated $\rangle C=O$), 1620 (conjugated $\rangle C=C\langle$), 1600, 1580, 780, 700 (aromatic) and PMR signals at 1.20 (6H, s, gem-dimethyl at C_3), 2.30 (2H, s, methylene protons adjacent to ester function), 3.50 (3H, s, ester methyl), a pair of doublets 6.46, 6.76 (1H each, J = 16 Hz each, conjugated olefinic protons at C_4 and C_5) and 7.20, 7.66 (5H, m, aromatic protons); UV λ_{max} 257 nm, ε_{max} 22,550. The keto ester 13 gave a solid 2,4-DNP derivative $C_{21}H_{22}O_6N_4$, m.p.181^{o}.

Further, Wittig reaction on keto ester 13 using methylenetriphenylphosphorane, gave as expected the diene ester 11, identified by spectral data (IR, PMR, UV and mass) and comparative TLC with authentic sample.

Attempts[16] to epimerise the 1S cis keto ester 10 to the corresponding 1R trans isomer by treatment with sodium methoxide in methanol under refluxing conditions, gave a conjugated diketone, $C_{14}H_{14}O_2$, M^{+} 214. It was identified as 14 by spectral data. It showed IR bands at 1720 (cylopentenone $\rangle C=O$), 1665 (cross conjugated dienone), 1610 (conjugated C=C), 1410 ($-CH_2-\overset{\overset{O}{\|}}{C}-$) and it showed PMR

signals at 1.33 (6H, s, gem-dimethyl at C_4), 2.33 (2H, s, methylene protons α to $>C=O$), 7.50 (1H, s, doubly conjugated olefinic proton at C_3) and 7.30, 7.60 (5H, m, aromatic protons).

The structure of diketone 14 was further confirmed by C^{13} NMR spectrum. The C^{13} NMR ($CDCl_3$) spectrum of diketone 14 showed chemical shifts at δ ppm) with multiplicities (from TMS internal standard) as follows: C_1(s), 204; C_8(s), 191; C_3 (d, β to both the carbonyls), 175.7; C_2(s), 141.8; C_9(s), 136.9; C_{12} (d), 133.8; C_{11},C_{13}(d), 128.3; C_{10}, C_{14}(d), 128.6; C_5(t), 51.01; C_4(s), 39.78 and C_6 and C_7 (q), 27.82.

The diketone 14 gave a mono2,4-DNP derivative, $C_{20}H_{18}O_5N_4$, m.p.197-98°, the IR spectrum of which showed strong absorption at 1720 indicating that cyclopentene $>C=O$ does not form the derivative.

The above rearrangement was also observed in the case of 1R cis keto ester 5 ($R=CH_3$), when treated with sodium methoxide under similar conditions. It gave as the major product, liquid diketone 15, $C_9H_{12}O_2$, M^+ 152. It showed IR bands at 1724 (cyclopentenone $>C=O$), 1695 (conjugated $>C=O$ of $-COCH_3$), 1613 ($-CH=C<$ doubly conjugated to carbonyls), 1408 ($-\overset{O}{\overset{\|}{C}}-CH_2-$) and PMR signals at 1.30 (6H, s, gem-dimethyl at C_4), 2.33 (5H, s, $-COCH_3$ and $-COCH_2$) and 7.96 (1H, s, doubly conjugated olefinic proton at C_3). Unlike the diketone 14, the diketone 15 gave a 2,4-DNP

derivative $C_{21}H_{20}O_8N_8$ m.p.255°, in which both the carbonyls have formed the derivative (absence of 1720 cm^{-1} peak in the IR spectrum). This observation clearly indicates that phenyl group in diketone 14 is obstructing the attack of reagent on cyclopentenone (>C=O).

The probable mechanism of formation of the diketone 14 from keto ester 10 by sodium methoxide in methanol is shown in Scheme II, Chart II. The anion formed from keto ester 10 by the action of base rearranges to the conjugated keto ester (13a). A similar type of base catalysed rearrangement has been observed[17] in the case of keto acid 5 (R=H) during its esterification with 3-phenoxy-benzyl triethyl ammonium bromide, under alkaline conditions to give the rearranged conjugated keto ester (16). Keto ester (13a) with methoxide ion undergoes a combined Michael and internal Claisen condensation to give the methoxy β-diketone (14a). Loss of methanol from (14a) furnishes diketone 14. A similar mechanism operates in the case of keto ester 5 ($R=CH_3$) to give diketone 15.

The validity of the above assumption was further proved by treating α,β-unsaturated keto ester 13 with sodium methoxide under reflux when diketone 14 was isolated as the only product. It was characterised by physical constants, spectral data (IR, PMR) and also by m.m.p. of the 2,4-DNP derivative.

Similarly keto ester 9 on treatment with sodium methoxide in methanol under reflux gave diketone 15, characterised by spectral data (IR, NMR) and m.m.p. of 2,4-DNP derivative. These observations proved that the conjugated keto esters 13 and 9 are the intermediates in the formation of diketones 14 and 15 respectively from the corresponding keto esters 10 and 5 ($R=CH_3$).

EXPERIMENTAL

2-Formyl-3,6,6-trimethyl-bicyclo(3.1.0)-hex-2-ene 4

A solution of keto aldehyde 3 (50 g, 0.3 mol) in dry benzene (300 ml) containing piperidine (3 ml) and acetic acid (3 ml), was refluxed for 4 hr, using a Dean-Stark unit for removal of water. The reaction mixture was cooled and washed with dilute hydrochloric acid, dilute solution of sodium carbonate, water and dried. Removal of benzene gave a residue (45 g) which was fractionally distilled. The first fraction boiling between 49-55°/5 mm, (22.3 g) was found to be TLC pure compound 4; $(\alpha)_D^{25}$ -134° (c, 1.9); (Found: C, 79.69; H, 9.14; $C_{10}H_{14}O$ requires C, 79.95; H, 9.39%).

IR bands at: 2985, 2778, 1667, 1618, 1449, 1414, 1370, 1351, 1235, 1176, 859 and 797 cm^{-1}.

The higher boiling fraction was not characterised.

Methyl 1R cis-2,2-dimethyl-3-(2-oxopropyl)cyclopropane-carboxylate 5 (R=CH_3)

To a solution of aldehyde 4 (11.2 g, 0.075 mol) in acetone (125 ml), water (15 ml) and acetic acid (10 ml), powdered potassium permanganate (17.7 g, 0.11 mol) was added portion wise under stirring during ½ hr maintaining the temperature 25 to 30°. Stirring was continued further for 1.5 hr at room temperature. It was then treated

simultaneously with sodium nitrite and dilute sulphuric acid, till all the manganese dioxide dissolved and a clear solution obtained. It was diluted with water (100 ml) and extracted with ether (100 ml x 3). The combined ether layer was washed with water (75 ml x 2) and extracted with 10% aqueous sodium carbonate solution (50 ml x 2). The carbonate layer was acidified with dilute hydrochloric acid and extracted with chloroform (75 ml x 3). The chloroform layer was washed with water (50 ml x 2), dried and distilled to give the keto acid 5 (R=H). The keto acid 5 (R=H) was esterified with an ethereal solution of diazomethane to give the keto ester 5 ($R=CH_3$, 6.2 g, 45%); b.p. 105-110°/5 mm, $(\alpha)_D^{28}$ -36.7° (c, 4.6). (Found: C, 65.37; H, 8.92; $C_{10}H_{16}O_3$ requires C, 65.19; H, 8.75%).

IR bands at: 3030, 1736, 1439, 1355, 1325, 1176, 1087, 1029, 926 and 855 cm^{-1}.

Methyl 3,3,6-trimethylhepta-4,6-dienoate 8 from keto ester 5 ($R=CH_3$)

To an ethereal solution of methylenetriphenylphosphorane, prepared from triphenylmethylphosphonium iodide (9.0 g, 22 mmol) and potassium t-butoxide (2.6 g, 23 mmol), a solution of keto ester 5 ($R=CH_3$, 2.7 g, 15 mmol) in dry ether (50 ml) was added dropwise during ½ hr with stirring under nitrogen atmosphere. The reaction mixture was refluxed for 3 hr, filtered and the residue washed

repeatedly with ether. The combined filtrate was washed with water (50 ml x 2), dried and evaporated to give a liquid residue (3 g). It was distilled to furnish TLC pure diene ester 8 (2.1 g, 80%); b.p.130-40°/12 mm; (Found: C, 72.44; H, 9.89; $C_{11}H_{18}O_2$ requires C, 72.49; H, 9.96%).

IR bands at: 3003, 1730, 1642, 1610, 1429, 1333, 1248, 1192, 1156, 1117, 1015, 964 and 883 cm^{-1}.

The above procedure when repeated using lesser quantity of t-BuOK (0.9 g, 8 mmol) afforded diene ester 8 along with unchanged keto ester 5 ($R=CH_3$). These esters were separated by chromatography over silica gel, eluting the column with pet.ether + 10% benzene, pet.ether + benzene (1:1) and benzene. The fractions eluted with pet.ether + 10% benzene gave TLC pure diene ester 8 and the fractions eluted with benzene gave TLC pure keto ester 5 ($R=CH_3$), identified by spectral data (IR, PMR).

Methyl-3,3-dimethyl 6- oxohepta-4-enoate 9 from keto ester 5 ($R=CH_3$)

To an ice cooled solution of keto ester 5 (2.7 g, 15 mmol) in dry ether (50 ml) was added potassium t-butoxide (0.84 g, 7.5 mmol) in dry tertiary butanol (40 ml), dropwise with stirring under nitrogen atmosphere. The reaction mixture was stirred for 2 hr, diluted with water (100 ml), cooled to 0° and acidified with dilute hydrochloric acid to pH 4. The ether layer was separated

and the aqueous layer extracted with ether (50 ml x 3). The combined ether layer was washed with water (50 ml x 2), dried and evaporated to give a liquid keto ester 9 (2 g, 74%). It was further purified by chromatography over silica gel (20 g) and fractions eluted with pet.ether + benzene (1:1) and benzene gave TLC pure liquid keto ester 9; b.p.135-40°/13 mm; (Found: C, 65.43; H, 8.76; $C_{10}H_{16}O_3$ requires C, 65.19; H, 8.75%).
IR bands at: 3012, 1736, 1672, 1626, 1453, 1429, 1351, 1250, 1198, 1156, 984 and 922 cm^{-1}.

It gave 2,4-DNP derivative, m.p.140° (Found: C, 52.49; H, 5.28; N, 15.53; $C_{16}H_{20}O_6N_4$ requires C, 52.74; H, 5.53; N, 15.38%).
IR bands at: 2976, 1733, 1616, 1590, 1515, 1460, 1418, 1370, 1325, 1149, 1093, 1015, 917, 833 and 746 cm^{-1}.

Methyl-3,3,6-trimethylhepta-4,6-dienoate 8 from α,β-unsaturated keto ester 9

To an ethereal solution of methylenetriphenylphosphorane, prepared from triphenylmethylphosphonium iodide (3.06 g, 7.5 mmol) and potassium t-butoxide (0.84 g, 7.5 mmol), a solution of α,β-unsaturated keto ester 9 (0.92 g, 5 mmol) in dry ether was added dropwise during 30 minutes with stirring under nitrogen atmosphere. The reaction mixture was refluxed for 2.5 hr, filtered and the residue repeatedly washed with ether. The combined filtrate

was washed with water (30 ml x 2), dried and evaporated to give a liquid residue, which was distilled to give TLC pure diene ester 9 (0.72, 76%), identified by comparative spectral data with the one obtained above.

Methyl-3,3-dimethyl 6-phenylhepta-4,6-dienoate 11 from keto ester 10

To an ethereal solution of methylenetriphenylphosphorane, prepared from triphenylmethylphosphonium iodide (5.3 g, 13 mmol) and t-BuOK (1.5 g, 1.3 mmol), a solution of 10 (2.46 g, 10 mmol) in dry ether (50 ml) was added dropwise during ½ hr with stirring under nitrogen atmosphere. The reaction mixture was refluxed for 3 hr, filtered and the residue washed with ether. The combined filtrate was washed with water (50 ml x 2), dried and evaporated to give a liquid mixture (4 g). It was distilled to give (1.8 g, 74%), b.p.130-40°/0.3 mm; (TLC on SiO_2 + 10% $AgNO_3$ in 30% pet.ether in benzene; two spots). These were separated by chromatography over silica gel impregnated with 10% silver nitrate (20 g) and eluted with pet.ether, pet.ether + 10% benzene and pet.ether + 20% benzene. The fractions eluted with pet.ether + 10% benzene gave TLC pure diene ester 12 (0.3 g) (Found: C, 79.95; H, 9.20; $C_{19}H_{26}O_2$ requires C, 79.68; H, 9.15%).
IR bands at: 3012, 1721, 1639, 1590, 1493, 1429, 1385, 1361, 1242, 1156, 971, 889, 840, 771, and 703 cm^{-1}.

The fractions eluted with 20% benzene in pet.ether gave TLC pure diene ester 11 (1.2 g); (Found: C, 78.51; H, 8.07; $C_{16}H_{20}O_2$ requires C, 78.65; H, 8.25%).
IR bands at: 3021, 1736, 1645, 1600, 1495, 1439, 1332, 1124, 1026, 974, 893, 775 and 704 cm^{-1}.

Methyl 3,3-dimethyl 6-phenyl-6-oxo-hepta-4-enoate 13 from keto ester 10

To an ice cooled solution of keto ester 10 (1.2 g; 5 mmol) in dry ether (50 ml), was added t-BuOK (0.28 g, 2.5 mmol) in dry t-butanol (25 ml), dropwise with stirring under nitrogen atmosphere. The reaction mixture was stirred for 2 hr, diluted with water (50 ml), cooled to 0° and acidified with dilute hydrochloric acid to pH 4. Ether layer was separated and aqueous layer extracted with ether (50 ml x 2). The combined ether layer was washed with water (40 ml x 2), dried and evaporated to give a liquid (0.9 g, 75%). It was further purified by chromatography over silica gel (10 g) and fractions eluted with pet.ether + benzene (1:1) gave TLC pure liquid ester 13, b.p.140-50°/0.5 mm; (Found: C, 72.82; H, 7.39; $C_{15}H_{18}O_3$ requires C, 73.14; H, 7.37%).
IR bands at: 2980, 1736, 1670, 1650, 1620, 1600, 1580, 1450, 1332, 1310, 1225, 1130, 780 and 700 cm^{-1}.

It gave 2,4-DNP derivative, m.p.181°; (Found: C, 59.56; H, 5.31; N, 13.15; $C_{21}H_{22}O_6N_4$ requires C, 59.15; H, 5.20; N, 13.14%).

IR bands at: 3012, 1742, 1621, 1595, 1471, 1333, 1307, 1212, 1136, 1111, 769 and 742 cm^{-1}.

Methyl-3,3-dimethyl,6-phenyl-hepta 4,6-dienoate 11 from 13

To an ethereal solution of methylenetriphenylphosphorane, prepared from triphenylmethylphosphonium iodide (1.3 g, 3.2 mmol) and t-BuOK (0.36 g, 3.2 mmol), a solution of keto ester 13 (0.6 g, 2.5 mmol) in dry ether (30 ml) was added dropwise during ½ hr with stirring under nitrogen atmosphere. The reaction mixture was refluxed for 2.5 hr, filtered and the residue repeatedly washed with ether. The combined filtrate was washed with water (40 ml x 2), dried and evaporated to give a liquid residue (1.5 g) which was distilled to give TLC pure diene ester 11 (0.45 g, 75%). All the spectral properties were identical with one obtained above.

2-Benzoyl-4,4-dimethyl-cyclopent-2-ene-1-one 14 from keto ester 10

Sodium methoxide was prepared by dissolving sodium (1 g) in dry methanol (50 ml). Keto ester 10 (2.5 g) was added to the sodium methoxide solution and refluxed on a water bath for 6 hr. Methanol was removed under suction, residue diluted with water (100 ml) and acidified with dilute hydrochloric acid to pH 4 and extracted with chloroform (50 ml x 3). The chloroform layer was washed with water (50 ml x 2), dried and evaporated to furnish

crude diketone 14. It was purified by chromatography over silica gel (25 g). The fractions eluted with pet. ether + benzene (1:1) and benzene gave TLC pure diketone 14 as a colourless liquid (2 g, 90%); (Found: C, 78.25; H, 6.65; $C_{14}H_{14}O_2$ requires C, 78.58; H, 6.59%).

IR bands at: 3030, 1720, 1665, 1610, 1587, 1449, 1410, 1316, 1235, 1176, 1070, 1020, 893 and 855 cm^{-1}.

It gave a mono 2,4-DNP derivative, m.p.197-198°; (Found: C, 60.72; H, 4.75; N, 13.98; $C_{20}H_{18}O_5N_4$ requires C, 60.91; H, 4.57; N, 14.21%).

IR bands at: 3030, 1721, 1626, 1600, 1515, 1468, 1333, 1302, 1220, 1136, 831, 775 and 741 cm^{-1}.

2-Acetyl-4,4-dimethyl cyclopent-2-ene-1-one 15 from keto ester 5

Keto ester 5 (1 g) was added to sodium methoxide solution prepared by dissolving sodium (1 g) in dry methanol (50 ml). It was refluxed on a water bath for 6 hr, and worked-up as described above. The crude diketone 15 (0.8 g) was purified by chromatography over silica gel (10 g). The fractions eluted with pet.ether + benzene (1:1) and benzene gave TLC pure diketone 15 (0.6 g, 60%) as a liquid; b.p.110-120°/2 mm; (Found: C, 71.28; H, 8.07; $C_9H_{12}O_2$ requires C, 71.02; H, 7.95%).

IR bands at: 3030, 1724, 1695, 1613, 1471, 1408, 1370, 1299, 1186, 1093, 1020, 922 and 820 cm^{-1}.

It gave a bis 2,4-DNP derivative, m.p.255°; (Found: C, 49.45; H, 4.12; N, 17.20; $C_{21}H_{20}O_8N_8$ requires C, 49.21; H, 3.91; N, 17.50%).

IR bands at: 2985, 1618, 1590, 1515, 1460, 1408, 1374, 1333, 1307, 1266, 1131, 833 and 741 cm^{-1}.

2-Benzoyl-4,4-dimethyl-cyclopent-2-ene-1-one 14 from α,β -unsaturated keto ester 13

Keto ester 13 (0.6 g) was added to sodium methoxide solution, prepared by dissolving sodium (0.5 g) in dry methanol (40 ml). It was refluxed on a water-bath for 5 hr and worked-up as described earlier. The crude diketone 14 (0.5 g) was purified by chromatography over silica gel (6 g). The fractions eluted with pet.ether + benzene (1:2) and benzene gave TLC pure diketone 14 (0.4 g, 80%) as a colourless liquid, b.p.145-50°/8 mm.

The diketone 14 was characterised by comparative spectral data and 2,4-DNP derivative, $C_{20}H_{18}O_5N_4$, m.p. and m.m.p. 197-98°.

2-Acetyl- 4,4-dimethyl-cyclopent-2-ene-1-one 15 from α,β -unsaturated keto ester 9

The keto ester 9 (0.9 g) was added to sodium methoxide solution prepared by dissolving sodium (1 g) in dry methanol (50 ml). It was refluxed on a water bath for 6 hr. It was worked-up and purified as previously described to give diketone 15 (0.5 g, 67%). All the spectral properties were identical with one obtained from keto ester 5. It gave a bis 2,4-DNP derivative, m.p. and m.m.p.255°

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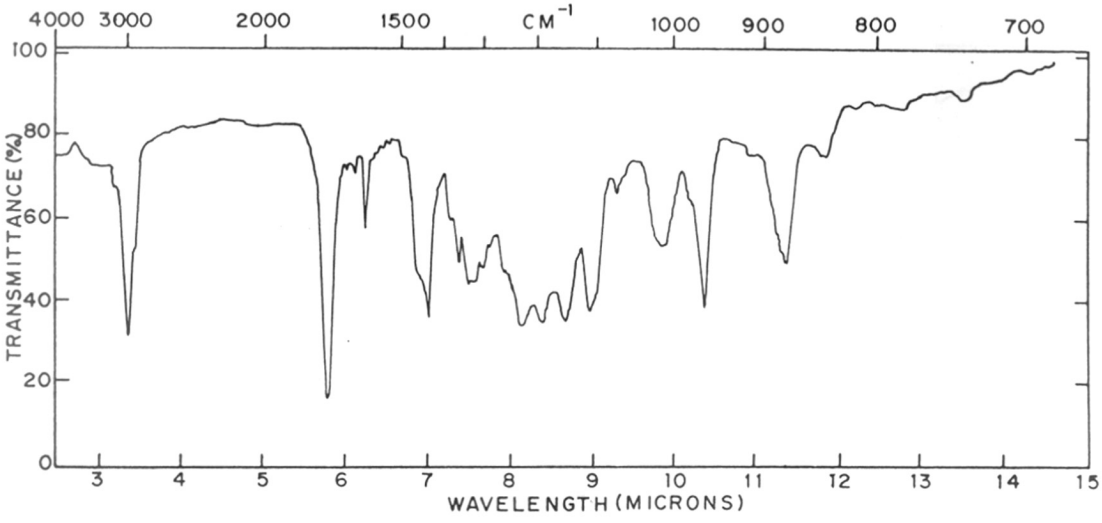
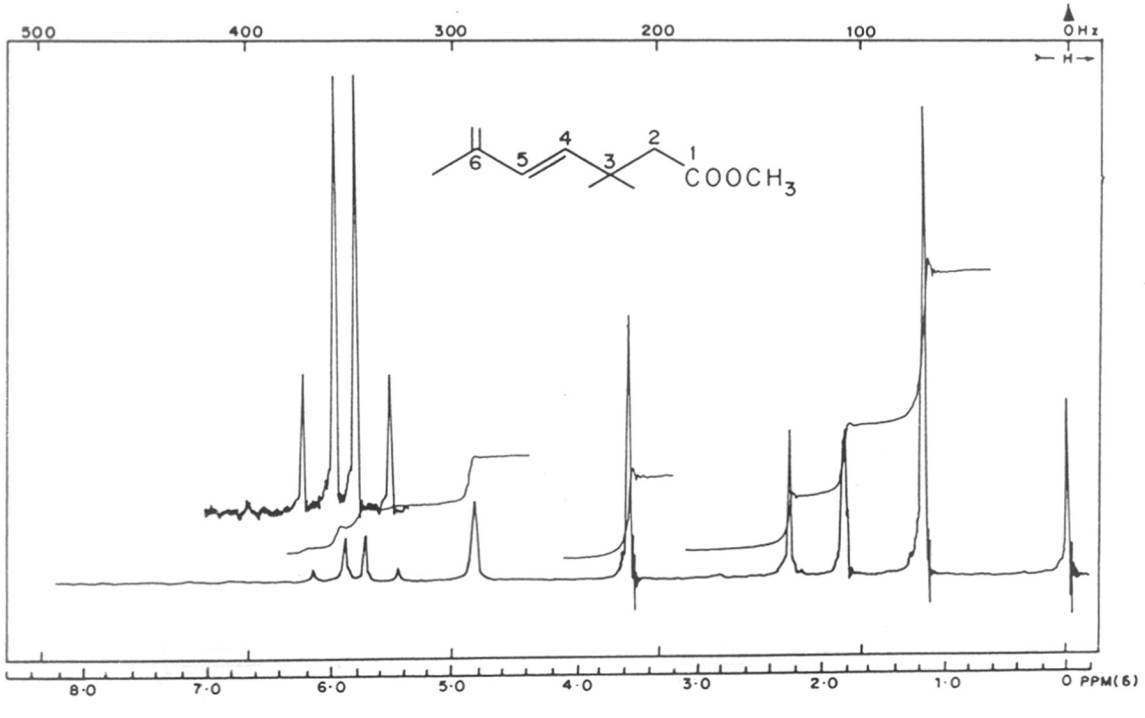
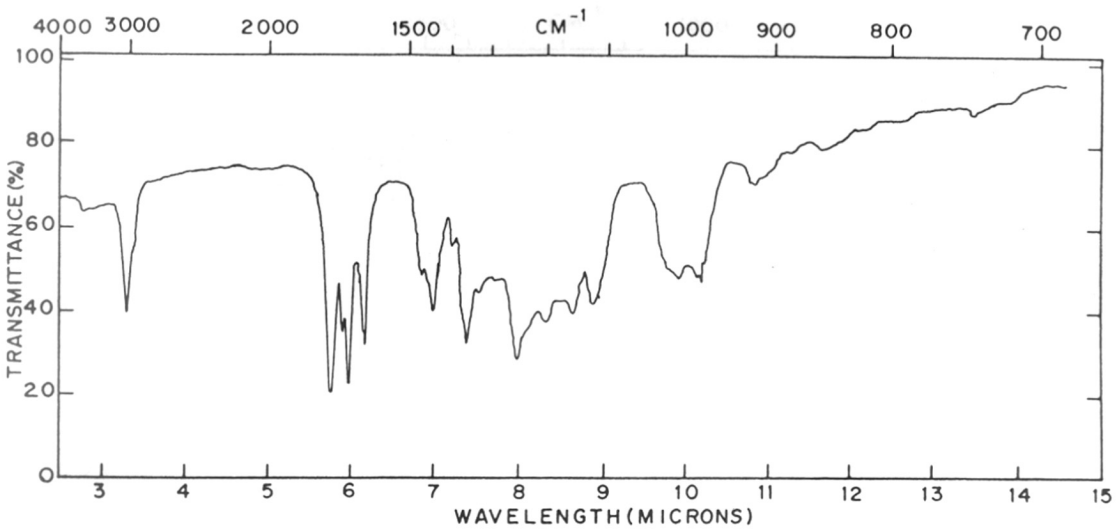
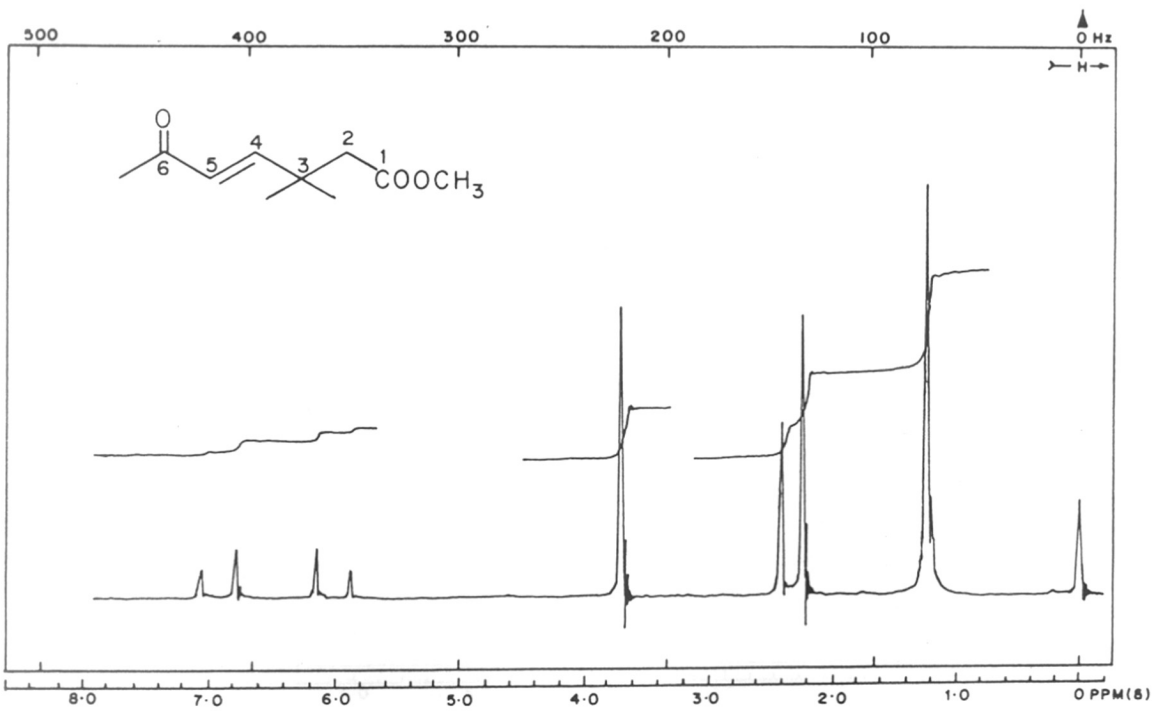




IR & PMR OF METHYL 3,3,6-TRIMETHYL-HEPTA-4,6-DIENOATE 8.





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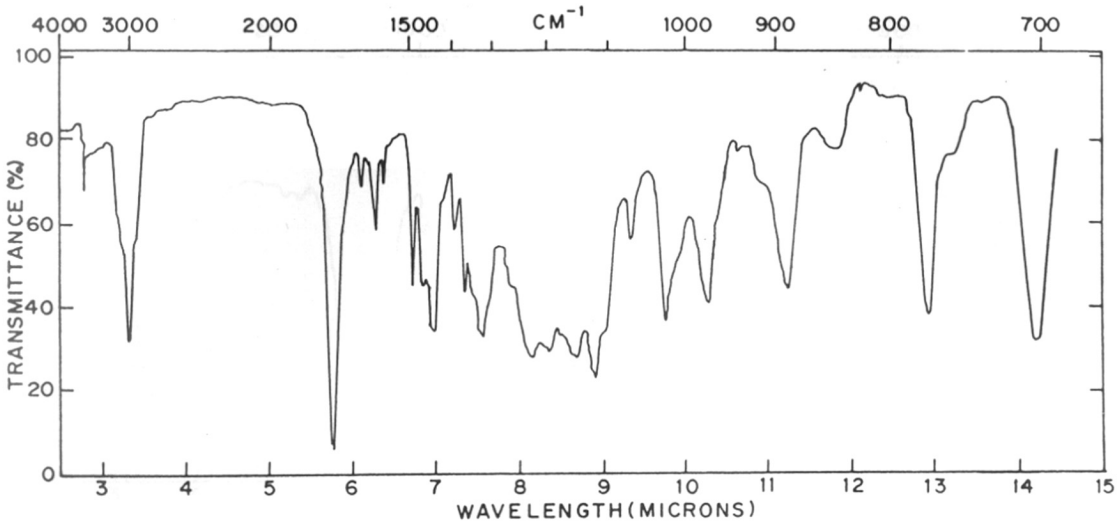

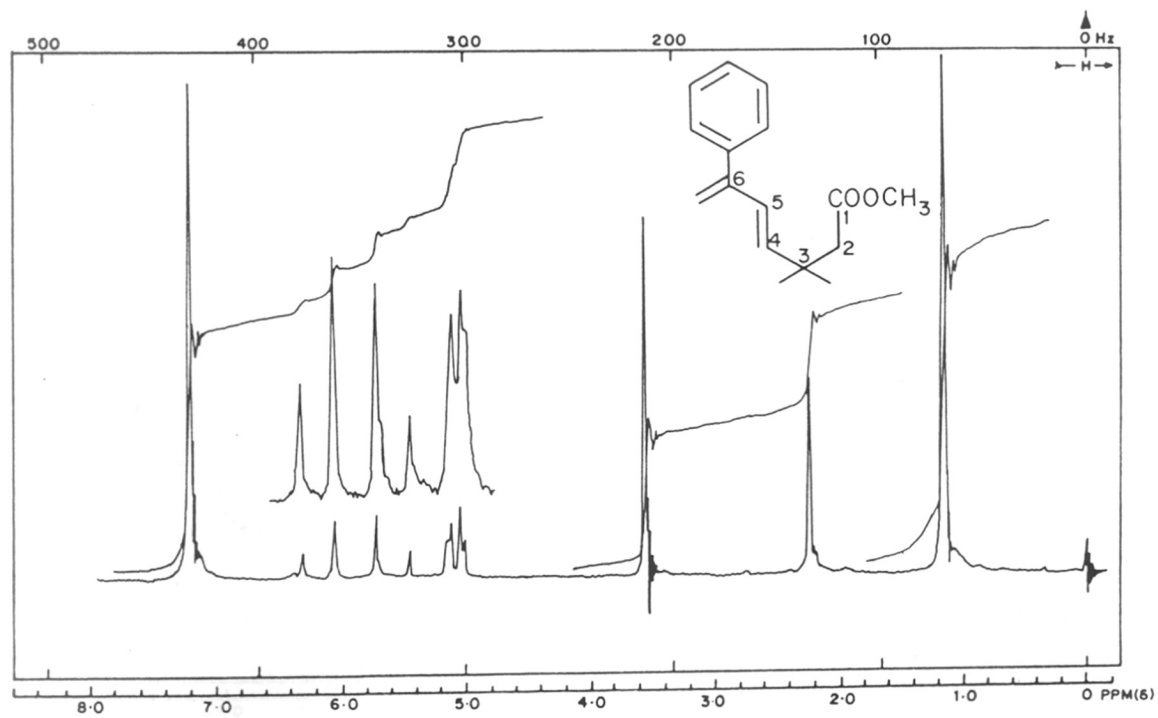

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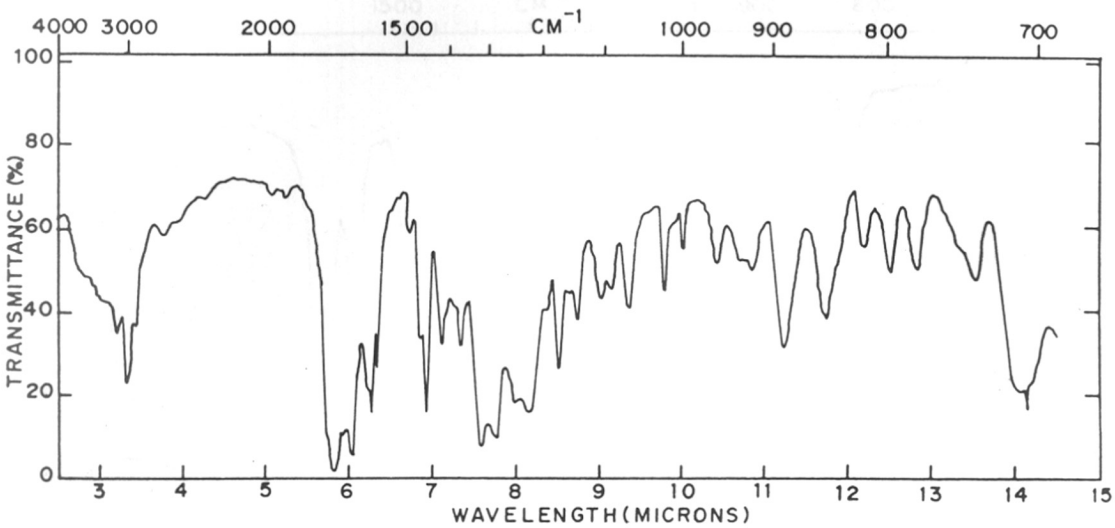
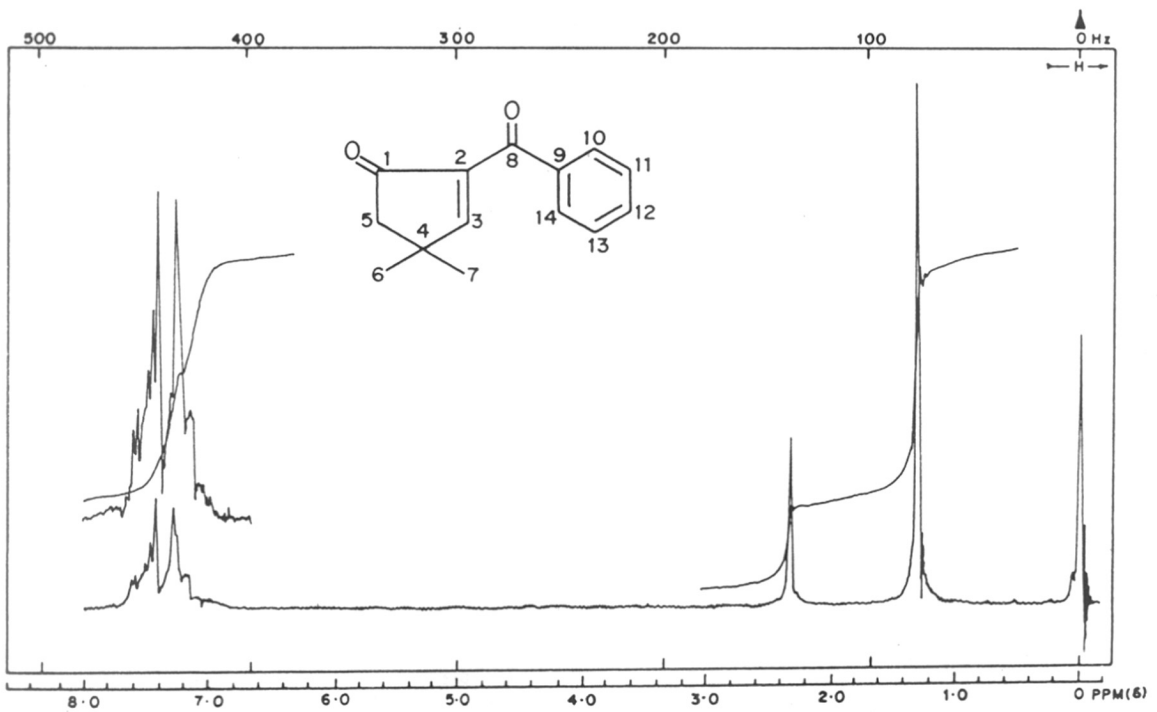
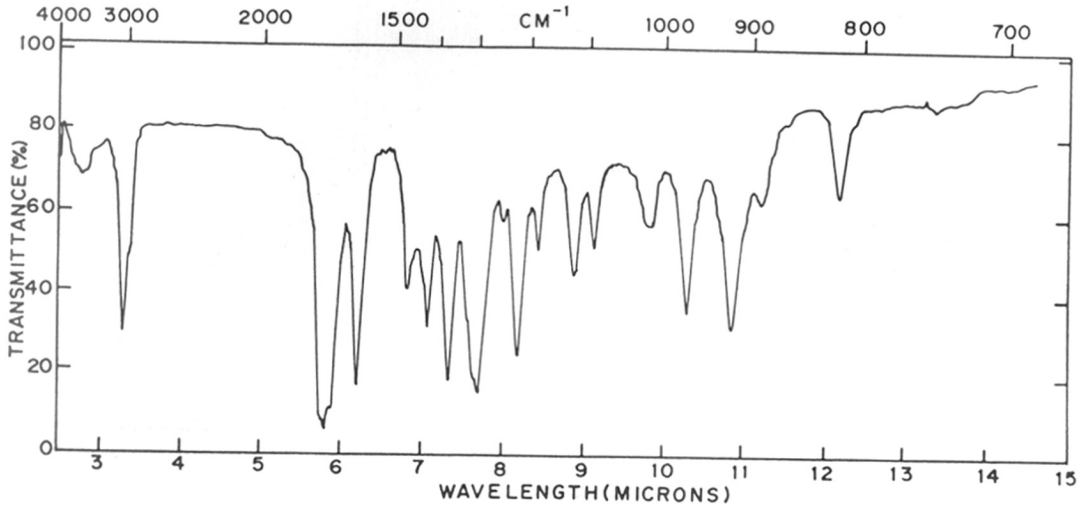
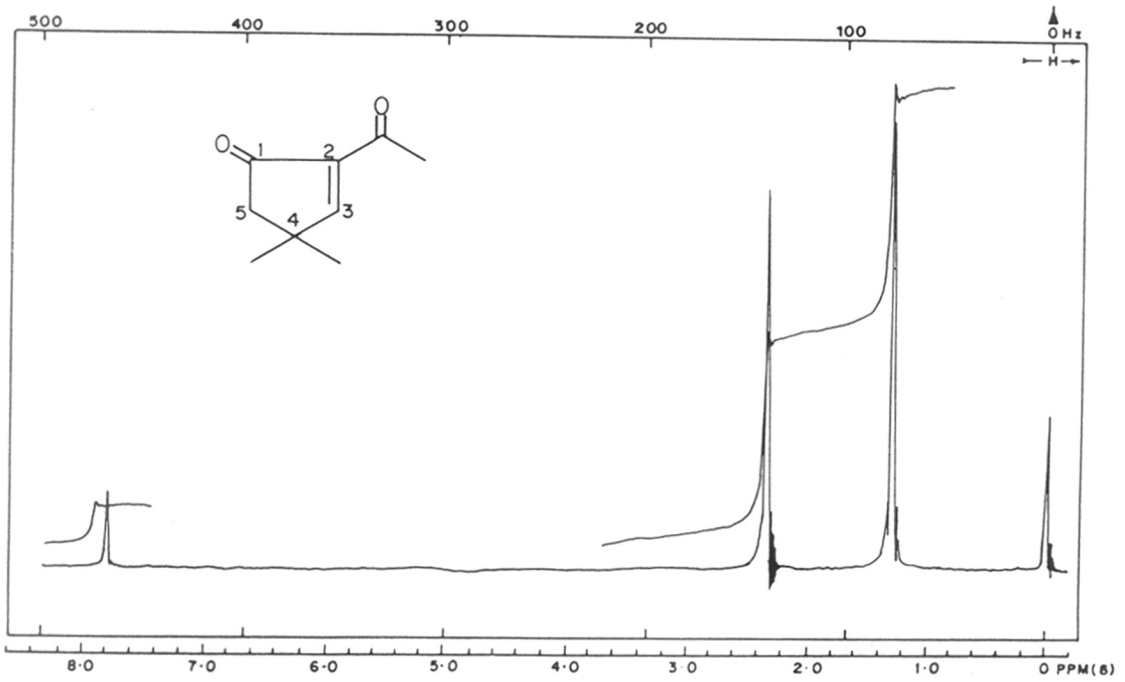




IR & PMR OF 2-BENZOYL-4,4-DIMETHYL-CYCLOPENT-2-ENE-1-ONE 14.





IR & PMR OF 2-ACETYL-4,4-DIMETHYL-CYCLOPENT-2-ENE-1-ONE

15.

CHAPTER – V

PART – B

ACID – CATALYSED REARRANGEMENTS

SUMMARY

The trans caranediol 2, obtainable from (+)-3-carene 1, on Jones chromic acid oxidation gave the keto acid 3 (R=H) which, on esterification ($MeOH/H^+$) afforded the keto ester 3 ($R=CH_3$). Treatment of the keto ester 3 ($R=CH_3$) with phosphoric acid gave the (+) homoterpenyl methyl ketone 4. Bromination of keto ester 3 ($R=CH_3$) in presence of sodium acetate afforded 2,4-dimethylphenyl-acetate 11 ($R=CH_3$) as one of the products. Treatment of keto acid 3 (R=H) and keto lactone 4 with bromine and hydrochloric acid gave 2,4-dimethylphenylacetic acid 10 (R=H). Keto ester 12 when heated with phosphoric acid for a short period gave the conjugated keto ester 13. However, the keto ester 12 on prolong heating with excess of phosphoric acid gave butyrolactone 14 ($R=CH_3$). Conjugated keto ester 13 on further treatment with phosphoric acid gave butyrolactone 14 ($R=CH_3$). Similarly, keto ester 15 on treatment with phosphoric acid afforded butyrolactone 16 (R=Ph).

INTRODUCTION

Gibson and Simonsen[1] reported that oxidation of (+)-3-carene 1 by Beckmanns chromic acid mixture, afforded as one of the products, (+)-homoterpenyl methyl ketone 4. The formation of 4 was explained by them, on the basis of the initial oxidation of (+)-3-carene 1 to keto acid 3 (R=H), which under the acidic conditions of the reaction rearranged to 4. However, the isolation of keto acid 3 (R=H) was not reported by them.

Later, (-) homoterpenyl methyl ketone (5) has been reported[2] to be formed from (+)-α-terpineol (6) by potassium permanganate oxidation. Recently[3] (-)-homoterpenyl methyl ketone (5) has been utilized for the synthesis of trans-chrysanthemic acid.

Owen and Simonsen[4], reported that (±) 2,2-dimethyl-3-(3-oxobutyl)cyclopropanecarboxylic acid (7) obtainable from (+)-2-carene (8) (referred to as Δ^4 by the authors) gave (±)-homoterpenyl methyl ketone(4) on heating with mineral acids. The same keto lactone (4) was later reported to be obtained by heating pinonic acid[5] (9) with mineral and organic acids as shown in Scheme I, Chart II.

Barbier et al.[6] found that pinonic acid (9) on treatment with bromine gave 2,4- dimethylphenylacetic acid 10 (R=H). Later on, Harispe[7] increased the yield of 2,4-dimethylphenylacetic acid 10 (R=H) by reacting pinonic

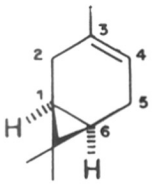
acid with bromine in presence of concentrated hydrochloric acid. Further Arcus et al.[8] suggested a mechanism for the rearrangement of pinonic acid (9) to 2,4-dimethylphenylacetic acid 10 (R=H) which is shown in Scheme II, Chart II. They have suggested that pinonic acid is initially converted by acid-catalysed rearrangement to homoterpenyl methyl ketone (4), which after bromination gives a bromo homoterpenyl methyl ketone. The latter was then converted to 2,4-dimethylphenylacetic acid 10 (R=H). However, Toshi et al.[9] suggested that the rate of formation of bromo homoterpenyl methyl ketone is too slow for it to be a possible intermediate in the formation of 2,4-dimethylphenylacetic acid 10 (R=H). They suggested a somewhat different mechanism for the formation of 2,4-dimethylphenylacetic acid 10 (R=H), which is shown in Scheme III, Chart II.

We have now observed that 2,2-dimethyl-3-(2-oxopropyl)-cis-cyclopropane—1-acetic acid 3 (R=H) or its methyl ester[10] 3 ($R=CH_3$) obtainable from (+)-3-carene 1, on heating with phosphoric acid gave (+)-homoterpenyl methyl ketone 4. This observation confirms the assumption of Gibson and Simonsen[1], that keto acid 3 (R=H) is an intermediate in the formation of (+)-homoterpenyl methyl ketone 4 from (+)-3-carene 1. We have also observed that keto ester 3 ($R=CH_3$), when brominated under mild conditions in presence of sodium acetate in carbontetra-

chloride, afforded as one of the products, methyl 2,4-dimethylphenylacetate 11 ($R=CH_3$). The probable mechanism of formation of 11 ($R=CH_3$) from keto ester 3 ($R=CH_3$) is discussed later in this chapter.

The keto ester[11] 12 and its phenyl analogue 15 also undergo acid-catalysed rearrangement to give keto γ-lactones 14 ($R=CH_3$) and 16 (R=Ph) respectively. The formation of 14 ($R=CH_3$) has been explained on the basis of initial formation of conjugated keto ester 13, from keto ester 12, which then undergoes an internal Michael addition to afford the keto γ-lactone 14 ($R=CH_3$). Recently, such keto γ-lactones 16 (R=Ph) have been utilized[12,13] for the preparation of styrylcyclopropanecarboxylic acids which are the acid moities of active insecticidal esters.

CHART – I



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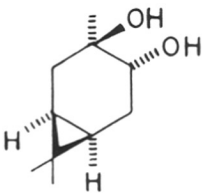

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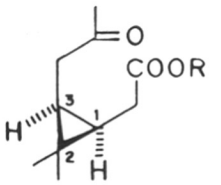
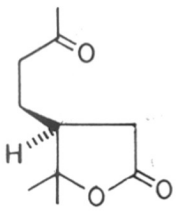


(R = H or CH_3) 3



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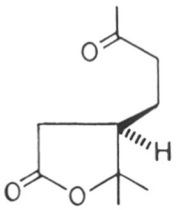

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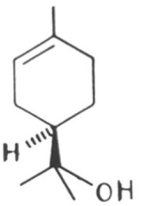

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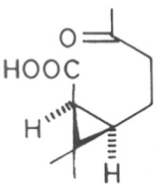

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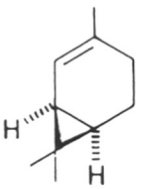

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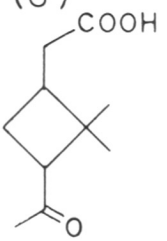

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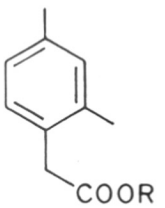
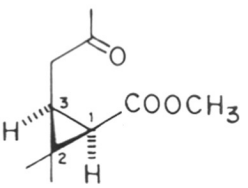


10 R = H

11 R = CH_3



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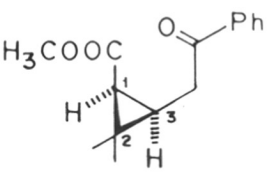

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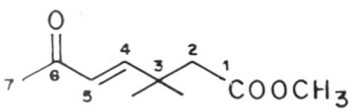

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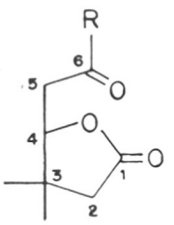
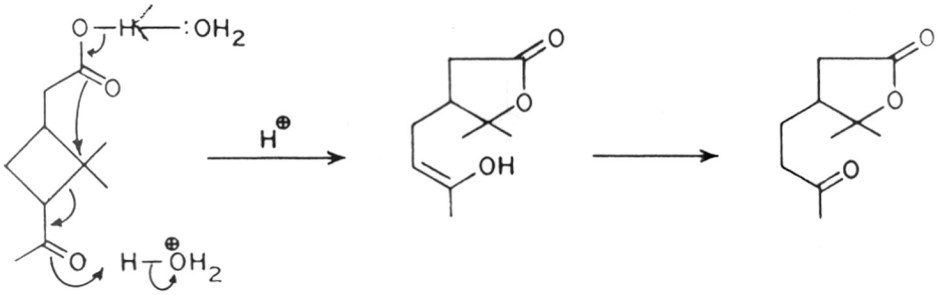


14 R = CH_3

16 R = Ph

CHART – II

SCHEME – I[5]



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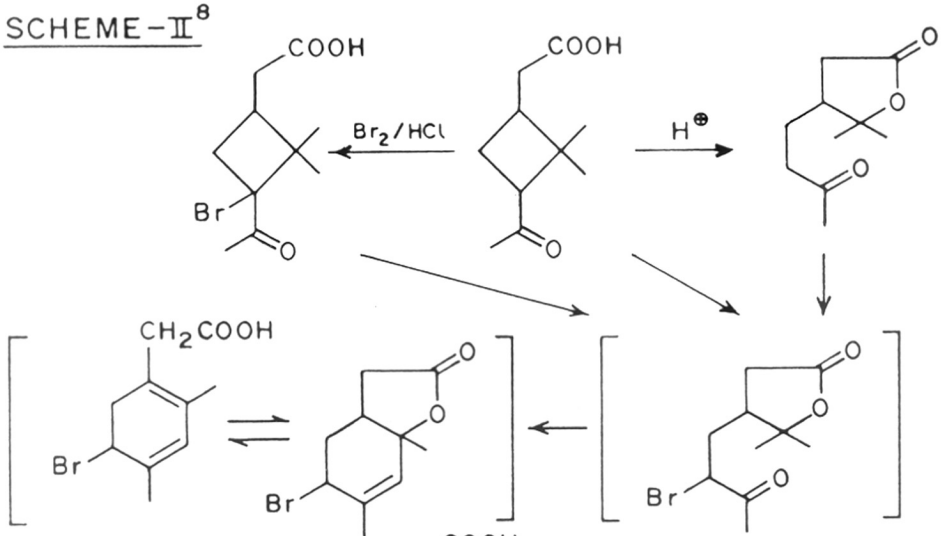

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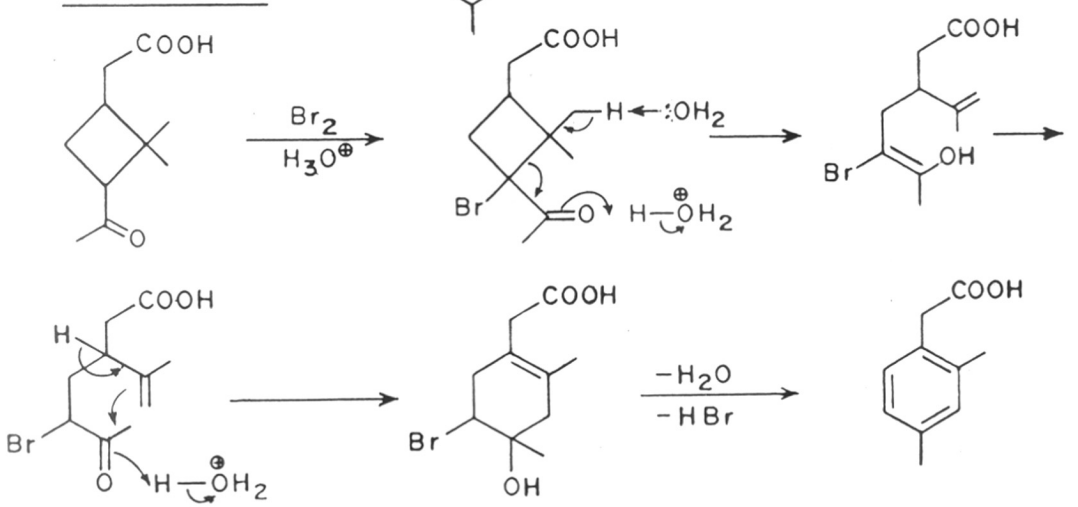
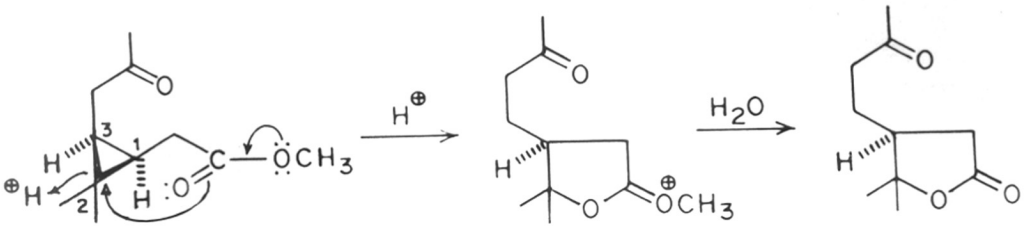


CHART – III

SCHEME – IV



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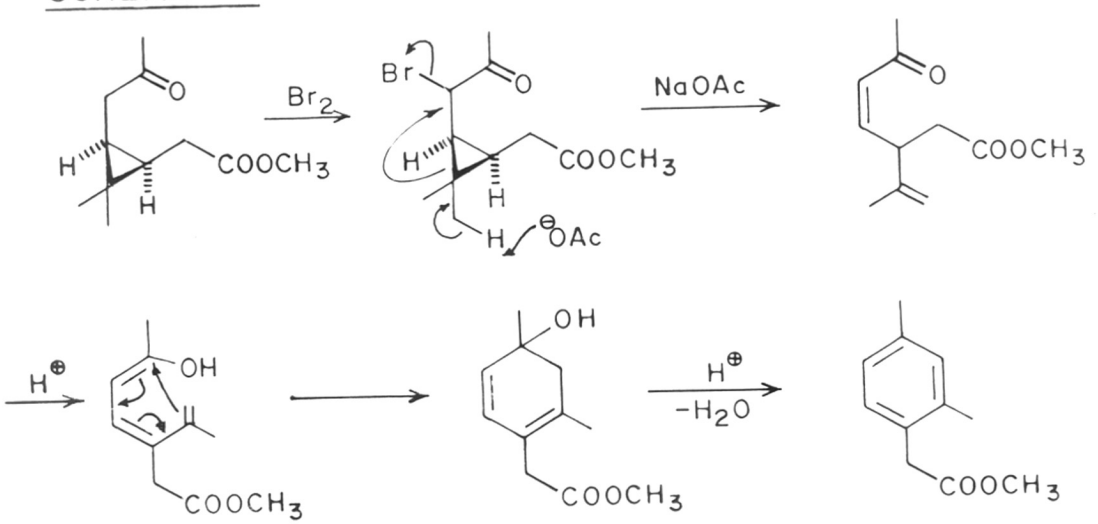

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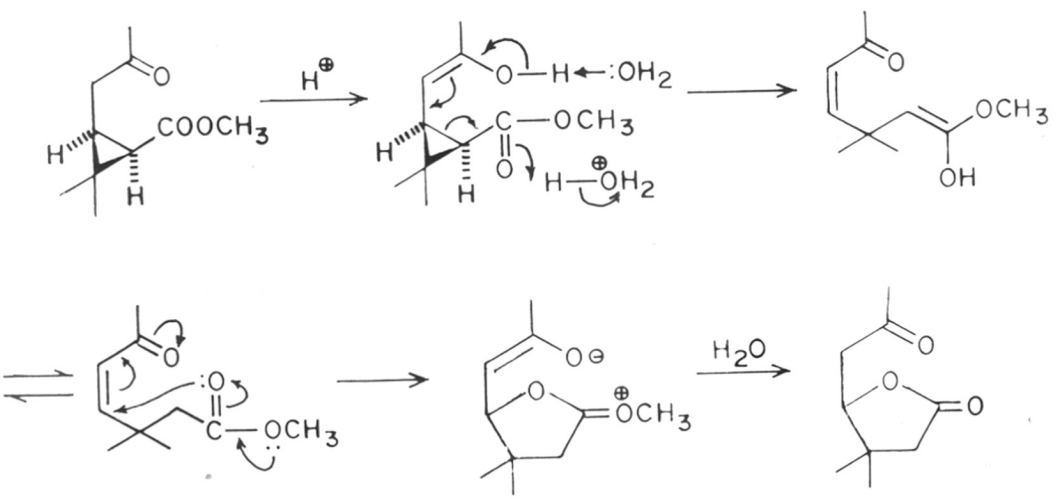

PRESENT WORK

3β ,4∝-caranediol 2, obtainable from (+)-3-carene 1 in 45% yield by a known method,was oxidised by Jones chromic acid reagent to give the keto carboxylic acid 3 (R=H) in 60% yield. The keto acid 3 (R=H) was converted into its methyl ester 3 ($R=CH_3$) by methanol and sulphuric acid in almost quantitative yield (see Chapter II of this thesis).

2,2-Dimethyl-3-(2-oxopropyl)-cis-cyclopropane-1-acetic acid 3 (R=H) or its methyl ester 3 ($R=CH_3$), on heating with phosphoric acid gave (+)-homoterpenyl methyl ketone 4, m.p.46-47° (aq.alcohol), $C_{10}H_{16}O_3$, M^+ 184. It showed IR bands at 1773 (γ -lactone >C=O). 1724 (>C=O), 1408 ($-\overset{O}{\overset{\|}{C}}-CH_2-$) and PMR signals at 1.16, 1.33 (3H each, s each, gem-dimethyl), 1.63 (3H, m, $-CH_2$ protons at C_4 and proton at C_3), 1.93 (3H, s, $-\overset{O}{\overset{\|}{C}}-CH_3$) and 2.06 (4H, m, $-CH_2-$ adjacent to >C=O). It gave 2,4-DNP derivative, m.p.171° (lit.[5] records m.p.168.5°). This observation of the formation of keto lactone 4 from keto acid 3 (R=H) or keto ester 3 ($R=CH_3$) confirms the findings of Gibson and Simonsen. A probable mechanism of formation of keto lactone 4 from keto ester 3 ($R=CH_3$) is shown in Scheme IV, Chart III.

During the formation of keto lactone 4 from keto ester 3 ($R=CH_3$) the bond between C_1 and C_3 of the cyclopropane ring in keto ester 3 ($R=CH_3$) is not disturbed. The absolute configuration of (+)-3-carene 1 is 1S, 6R, which is well established[14]. These facts can be used to assign tentatively the stereochemistry of keto lactone 4, $(\alpha)_D^{25}$ + 52° at the assymetric carbon atom C_3, as shown in the stereostructure 4, which corresponds to S configuration at C_3. Such an assignment is further supported by the fact that enantiomeric keto lactone (5) prepared from (+) α-terpineol[2] (6) showing $(\alpha)_D$-48° has already been assigned the opposite stereochemistry.

With a view to ascertaining in which position the substitution takes place, the keto ester 3 ($R=CH_3$) was subjected to bromination at 0° in presence of sodium acetate. It afforded a mixture of products, from which methyl 2,4-dimethylphenylacetate 11 ($R=CH_3$), $C_{11}H_{14}O_2$, M^+ 178, b.p.135-40°/25 mm was isolated as one of the products. It showed IR bands at 1745 (ester >C=O), 1613, 787 (aromatic) and PMR signals at 2.23 (6H, s, methyls attached to phenyl ring), 3.33 (2H, s, benzylic -CH_2-), 3.53 (3H, s, ester methyl) and 6.83 (3H, m, aromatic protons).

In confirmation of structure 11 ($R=CH_3$), the compound gave on saponification, the acid 10 (R=H), $C_{10}H_{12}O_2$ as a solid, m.p.104° (lit. records[8] m.p.103°).

It showed IR bands at 1686 (>C=O), 1647, 1493, 833, 794 aromatic) and PMR signals at 2.21 (6H, s, methyls attached to phenyl ring), 3.43 (2H, s, benzylic $-CH_2-$ protons), 6.73 (3H, m, aromatic protons) and 10.9 (1H, m, acid proton).

The formation of methyl 2,4-dimethylphenylacetate 11 ($R=CH_3$) from keto ester 3 ($R=CH_3$) appears to proceed by a mechanism, somewhat analogous to the one reported by Toshi et al.[9] for the formation of 10 (R=H) from pinonic acid (9). A probable mechanism is shown in Scheme V, Chart III. This involves initial bromination of keto ester 3 ($R=CH_3$) at methylene adjacent to carbonyl, solvolysis of the resulting bromide with ring opening and subsequent cyclisation of trienol followed by dehydration to give ultimately 11 ($R=CH_3$).

Treatment of keto acid 3 (R=H) with bromine and hydrochloric acid gave 2,4-dimethylphenylacetic acid 10 (R=H). It was characterised by comparative spectral data m.p. and m.m.p. 104°. Similarly, the keto lactone 4 on treatment with bromine and hydrochloric acid afforded 2,4-dimethylphenylacetic acid 10 (R=H) as reported by Arcus et al; identified by spectral data (IR, PMR).

The base-catalysed rearrnagement of methyl 1R cis2,2-dimethyl-3-(2-oxopropyl)cyclopropanecarboxylate 12 and related compounds have been discussed in Chapter V, Part A of this thesis. These rearrangements prompted us to

study the acid-catalysed rearrangements of the keto esters 12 and its phenyl analogue 15.

Keto ester 12 obtainable from (+)-3-carene 1 (see Chapter V, Part A of this thesis), when heated with phosphoric acid for a short period (10 minutes), afforded the conjugated keto ester 13, $C_{10}H_{16}O_3$, M^+ 184. It showed IR bands at 1737 (ester $\rangle$C=O), 1672 (conjugated $\rangle$C=O) 1626 (conjugated C=C) and 984 (trans-disubstituted double bond and PMR signals at 1.23 (6H, s, gem-dimethyl at C_3), 2.21 (3H, s, $-COCH_3$), 2.38 (2H, s, methylene protons adjacent to ester $\rangle$C=O), 3.70 (3H, s, ester methyl) and a pair of doublets centered at 5.96, 6.88 (1H each, J = 16 Hz each, olefinic protons at C_4 and C_5). It gave a solid 2,4-DNP derivative, $C_{16}H_{20}O_6N_4$, m.p. and m.m.p. 140°. The same conjugated keto ester 13 has been obtained by base catalysed rearrangement from keto ester 12.

However, when keto ester 12, was heated with excess of phosphoric acid for ½ hr, it exclusively gave a solid keto lactone 14 (R=CH_3) viz. 3,3-dimethyl-4-(2-oxopropyl)-butyrolactone $C_9H_{14}O_3$, M^+ 170, m.p. 52° (benzene + hexane). It showed IR bands at 1770 (γ-lactone $\rangle$C=O), 1724 ($\rangle$C=O) and PMR ($CDCl_3$) signals at 0.96, 1.10 (3H each, s each, gem dimethyls at C_3), 2.06 (3H, s, $-COCH_3$), 2.18 (2H, s, $-CH_2$ protons at C_2), 2.43 (2H, m, $-CH_2$ protons at C_4) and 4.25 (1H, dd, J = 4 Hz, C_4 proton). It gave 2,4-DNP derivative, $C_{15}H_{18}O_6N_4$, m.p. 110°.

During the formation of butyrolactone 14 ($R=CH_3$) from keto ester 12, conjugated keto ester 13 appears to be an intermediate as it could be isolated, when reaction was carried out for a short duration with limited quantity of phosphoric acid. It was further confirmed that keto ester 13 on heating with phosphoric acid was completely converted to the keto lactone 14 ($R=CH_3$), characterised by spectral data and also by m.p. and m.m.p.

Similarly, methyl 1S-cis-2,2-dimethyl-3-(2-oxo-2-phenylethyl)cyclopropanecarboxylate 15 (for preparation, see Chapter IV of this thesis) obtainable from (+)-3-carene 1, on heating with phosphoric acid for 15 minutes gave a solid keto lactone 16 (R=Ph) viz. 3,3-dimethyl-4-(2-oxo-2-phenylethyl)butyrolactone, $C_{14}H_{16}O_3$, M^+ 232, m.p. 95° (benzene + 20% hexane). It showed IR bands at 1770 (γ-lactone >C=O), 1701 (>C=O), 1605, 1587, 706 (aromatic) and PMR ($CDCl_3$) signals at 1.10, 1.20 (3H each, s each, gem-dimethyl at C_3), 2.36 (2H, s, $-CH_2$ protons at C_2), 3.13 (2H, m, $-CH_2$- attached to C_4), 4.80 (1H, dd, J = 4 Hz, proton at C_4) and 7.40 (5H, m, aromatic protons). It gave a solid 2,4-DNP derivative, $C_{20}H_{20}O_6N_4$, m.p.215°.

The formation of keto lactones 14 ($R=CH_3$) and 16 (R=Ph) which proceeds by identical mechanisms is represented in Scheme VI, Chart III. This involves an acid-catalysed ring opening to give the conjugated acyclic keto ester 13, which then undergoes, an internal Michael addition to give ultimately the γ-butyrolactone 14 ($R=CH_3$).

EXPERIMENTAL

Heptanoic acid-3-(1-hydroxy-1-methylethyl)6-oxo Y-lactone 4 or (+)homoternenyl methyl ketone 4 from keto ester 3 (R=CH_3)

Keto ester 3 (R=CH_3, 6.0 g) was dissolved in phosphoric acid (30 ml) and the solution heated on steam bath for 15 minutes. It was cooled, poured on ice cold water (150 ml) and extracted with methylene chloride (75 ml x 3). The organic layer was washed with water (50 ml x 2) and dried. Evaporation of the solvent gave the crude keto lactone 4 (5.5 g), which was purified by chromatography over silica gel (60 g). The fractions eluted with pet.ether + benzene (1:1) and benzene gave TLC pure keto lactone 4 (3.6 g, 65%). It was crystallised from hot water m.p.46-47° (lit.[5] records m.p.48-52°); $(\alpha)_D^{25}$ + 52° (c, 2.0); (Found: C, 65.17; H, 8.69; $C_{10}H_{16}O_3$ requires C, 65.19; H, 8.75%).

IR bands at: 3049, 1773, 1724, 1408, 1370, 1319, 1274, 1258, 1199, 1163, 1129, 1099, 957, 939, 922 and 820 cm^{-1}.

It gave 2,4-DNP derivative, m.p.171° (lit.[5] records m.p.168.5°); (Found: C, 52.38; H, 5.69; N, 15.12; $C_{16}H_{20}O_6N_4$ requires C, 52.74; H, 5.53; N, 15.38%).

IR bands at: 3030, 1776, 1637, 1608, 1524, 1471, 1429, 1379, 1335, 1316, 1149, 1105, 957, 939, 917, 855 and 833 cm^{-1}.

(+)-Homoterpenyl methyl ketone 4 from keto acid 3 (R=H)

Keto acid 3 (R=H, 4.5 g) was dissolved in phosphoric acid (25 ml) and the solution heated on steam bath for 15 minutes. The reaction mixture worked up and purified as described above to give lactone 4 (2.7 g, 60%); m.p. and m.m.p. 48-49° (superimposable IR and PMR spectra).

Methyl, 2:4-dimethylphenylacetate 11 ($R=CH_3$) from keto ester 3 ($R=CH_3$)

To an ice cooled and stirred solution of keto ester 3 ($R=CH_3$, 5.9 g) in carbontetrachloride (30 ml) containing sodium acetate (3.6 g), bromine (4.8 g) in carbontetrachloride (20 ml) was added during 1 hr and mixture stirred at 0° for 3 hr. It was then washed with water, aqueous sodium sulphite solution followed by water and dried. Removal of solvent gave a residue (7 g) which was shown to be a mixture of five compounds (TLC 8% ethylacetate + benzene, 5 spots). The mixture was chromatographed over silica gel (70 g). The fractions eluted with pet.ether + benzene (3:1) and pet.ether + benzene (1:1) gave TLC pure liquid ester 11 ($R=CH_3$, 1.3 g; 25%); b.p.135-40°/25 mm; (Found: C, 74.98; H, 8.09; $C_{11}H_{14}O_2$ requires C, 74.13; H, 7.92%).

IR bands at: 2994, 1745, 1613, 1497, 1429, 1325, 1258, 1149, 1105, 1010 and 787 cm^{-1}.

The other products could not be isolated pure.

2,4-Dimethylphenylacetic acid 10 (R=H) from 11 (R=CH_3)

The ester 11 (R=CH_3, 0.8 g) was dissolved in methanolic potassium hydroxide (KOH 2 g, water 2 ml and methanol 20 ml) and refluxed for 5 hr. Methanol was removed under reduced pressure, residue diluted with water (20 ml), acidified with dilute hydrochloric acid. It was extracted with ether (50 ml x 3). The ether layer was washed with water, dried and evaporated to give a residue (0.5 g), crystallised from alcohol-water to give 10 (R=H) as a solid, m.p.104° (lit.[8] records m.p.103°); (Found: C, 73.27; H, 7.69; $C_{10}H_{12}O_2$ requires C, 73.14; H, 7.37%). IR bands at: 3125, 2941, 1686, 1647, 1493, 1449, 1366, 1212, 1166, 1020, 889, 833 and 794 cm^{-1}.

It gave the amide derivative m.p.184° (Found: C, 73.30; H, 8.38; N, 8.40; $C_{10}H_{13}ON$ requires C, 73.59; H, 8.03; N, 8.58%).

2,4-Dimethylphenylacetic acid 10 (R=H) from keto acid 3 (R=H)

The keto acid 3 (R=H, 2.9 g) was suspended in concentrated hydrochloric acid (4 ml) and bromine (2.5 g) was added in one lot under stirring. The mixture was heated on water bath for 4 hr. It was poured over crushed ice and extracted with ether (50 ml x 3). The combined ether layer was washed with water, aqueous sodium sulphite solution, followed by water. The ether

layer was extracted with aqueous 10% sodium carbonate (15 ml x 2). The sodium carbonate layer was acidified with dilute hydrochloric acid, extracted with chloroform (40 ml x 3). The chloroform layer was washed with water, dried and evaporated to give a solid residue (1.4 g, 60%). It was purified by chromatography over silica gel (15 g). The fractions eluted with benzene gave pure solid 10 (R=H), m.p. and m.m.p. 104° (superimposable IR and PMR spectra).

2,4-Dimethyl-phenylacetic acid 10 (R=H) from keto lactone 4

The keto lactone 4 (1.0 g) was suspended in concentrated hydrochloric acid (2 ml) and bromine (1 g) was added in one lot under stirring. The mixture was heated for 4 hr and worked up and purified as described above to give 10 (R=H, 0.5 g, 56%) m.p. and m.m.p. 104° (superimposable IR and PMR spectra).

Methyl 3,3-dimethyl 6-oxo- hepta-4-enoate 13 from keto ester 12

Keto ester 12 (1.0 g) was heated with phosphoric acid (5 ml) on steam bath for 10 minutes, cooled, poured on ice cold water (40 ml) and extracted with ether (30 ml x 3). The organic layer was washed with water (25 ml x 2) and dried. Removal of solvent gave the crude ester 13 (0.8 g), which was purified by column chromatography over silica gel (10 g) and fractions eluted with pet.ether + benzene (1:1) and benzene gave TLC pure liquid ester 13 (0.55 g, 55%);

(Found: C, 65.43; H, 8.76; $C_{10}H_{16}O_3$ requires C, 65.19; H, 8.75%).

IR bands at: 3012, 1736, 1672, 1626, 1453, 1429, 1351, 1250, 1198, 1156, 984 and 922 cm^{-1}.

It gave 2,4-DNP derivative, m.p. and m.m.p.140°.

3,3-Dimethyl-4-(2-oxopropyl)-butyrolactone 14 (R=CH_3) from keto ester 12

Keto ester 12 (1.8 g) was heated with phosphoric acid (20 ml) for 30 minutes and worked up as described above, the residue chromatographed over silica gel (20 g). The fractions eluted with pet.ether + benzene (1:2) and benzene gave solid butyrolactone 14 (R=CH_3, 1.2 g, 70%). It was crystallised from benzene + 20% pet.ether, m.p.52°; (Found: C, 63.25; H, 8.31; $C_9H_{14}O_3$ requires C, 63.51; H, 8.29%).

IR bands at: 2985, 1770, 1724, 1464, 1385, 1366, 1307, 1290, 1242, 1204, 1170, 1149, 1053, 930, 901 and 800 cm^{-1}.

It gave 2,4-DNP derivative m.p.110°: (Found: C, 51.44; H, 5.03; N, 15.83; $C_{15}H_{18}O_6N$ requires C, 51.42; H, 5.18; N, 15.99%).

IR bands at: 2914, 1770, 1613, 1587, 1449, 1351, 1319, 1299, 1266, 1136, 1093, 844, 826, 743 and 725 cm^{-1}.

3,3-Dimethyl-4-(2-oxopropyl)-butyrolactone 14 (R=CH_3) from keto ester 13

Conjugated keto ester 13 (0.46 g) was heated with phosphoric acid (10 ml) for 30 minutes. The reaction was

worked-up and product purified as above to give solid butyrolactone 14 (R=CH_3, 0.27 g, 65%), m.p. and m.m.p. 53° (superimposable IR and PMR spectra).

3,3-Dimethyl-4-(2-oxo-2-phenyl ethyl) butyrolactone 16 (R=Ph) from keto ester 15

Keto ester 15 (1.2 g) was heated with phosphoric acid (15 ml) for 15 minutes. The reaction mixture was cooled, poured on ice cold water (50 ml) and extracted with ether (50 ml x 3). The combined ether layer was washed with water (50 ml x 2) and dried. Evaporation of the solvent gave lactone 16 (R=Ph, 0.9 g, 80%). It was further purified by chromatography over silica gel (10) and fractions eluted with pet.ether + benzene (1:1) and benzene gave solid lactone, which was crystallised from benzene + 20% pet.ether; m.p.95°$(\alpha)_D^{27}$3.6° (c, 2.6); (Found: C, 72.61; H, 6.93; $C_{14}H_{16}O_3$ requires C, 72.39; H, 6.94%).

IR bands at: 3012, 1770, 1701, 1605, 1449, 1389, 1351, 1242, 1205, 1149, 1031, 1010, 980, 940, 833 and 760 cm^{-1}.

It gave 2,4-DNP derivative, m.p.215° (Found:C, 58.83; H, 4.63; N, 13.40; $C_{20}H_{20}O_6N_4$ requires C, 58.25; H, 4.89; N, 13.58%).

IR bands at: 2950, 1779, 1610, 1449, 1370, 1326, 1217, 1136, 1042, 917, 846, 763 and741 cm^{-1}.

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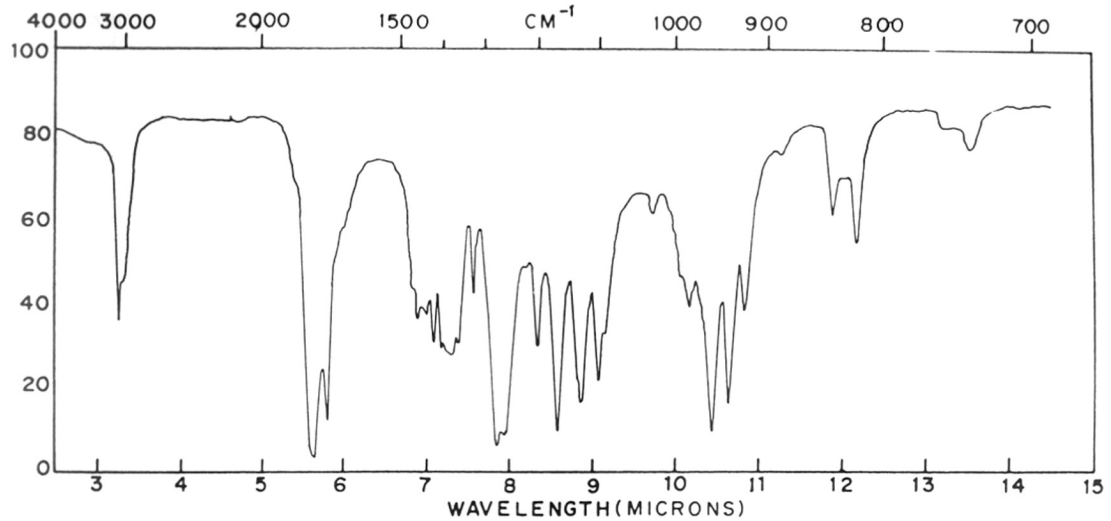
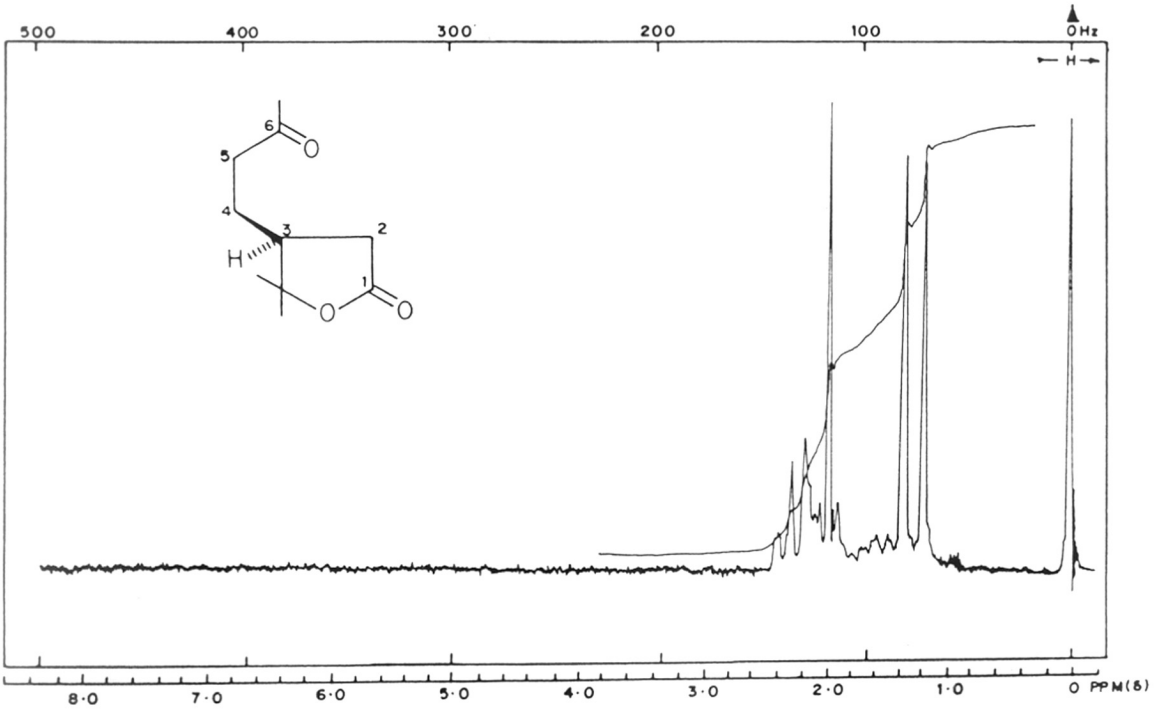
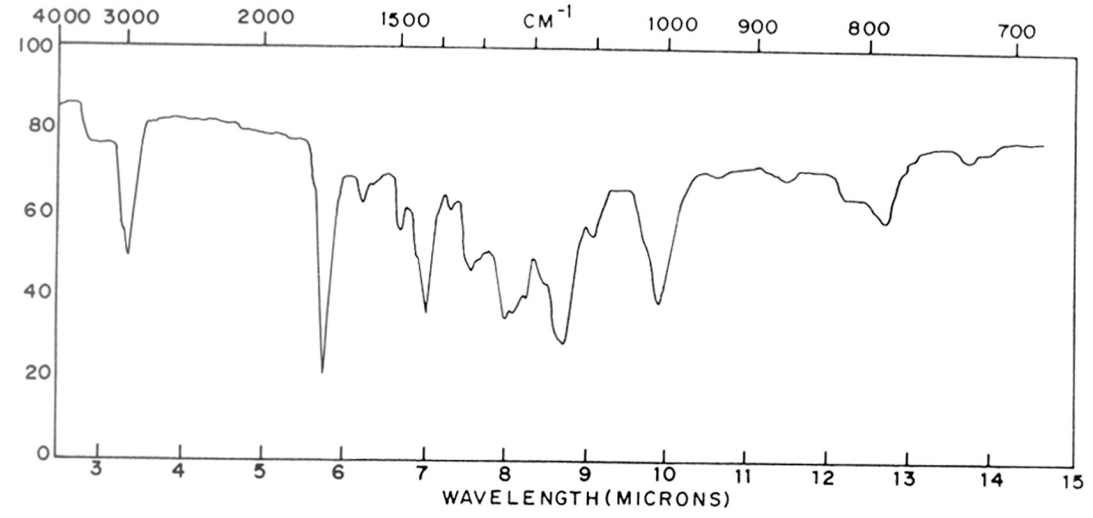
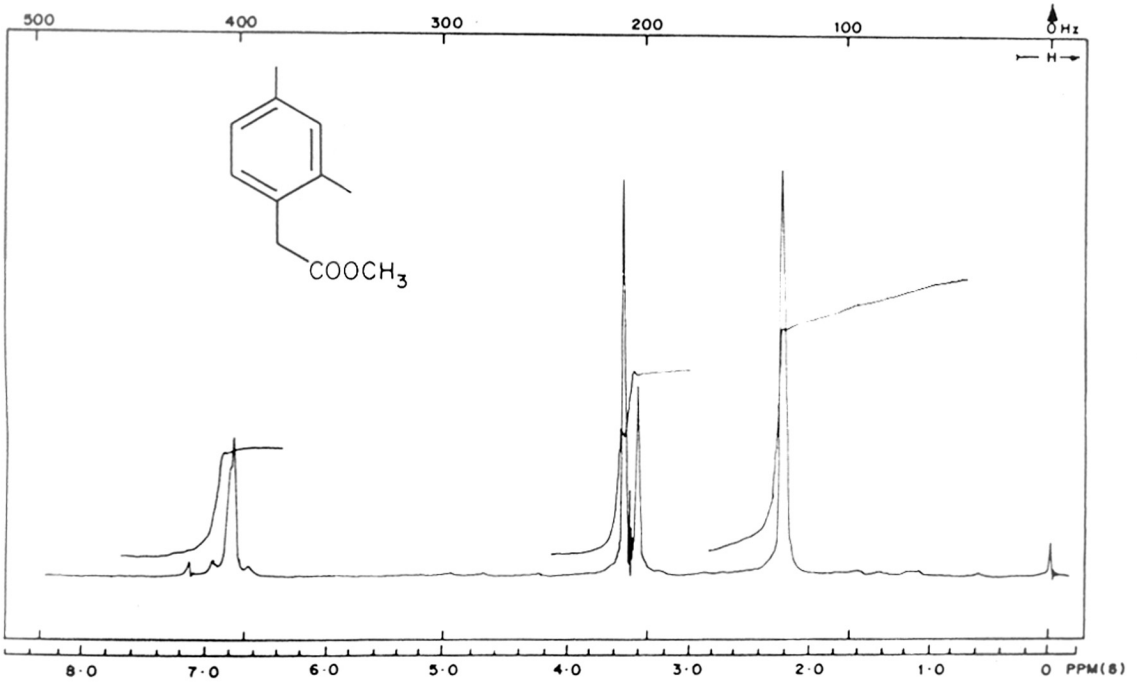


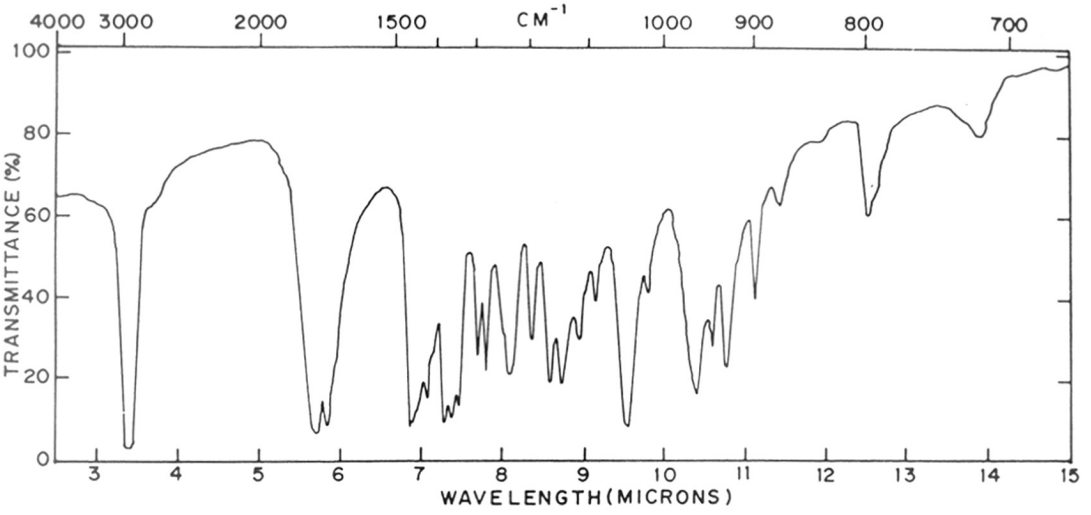


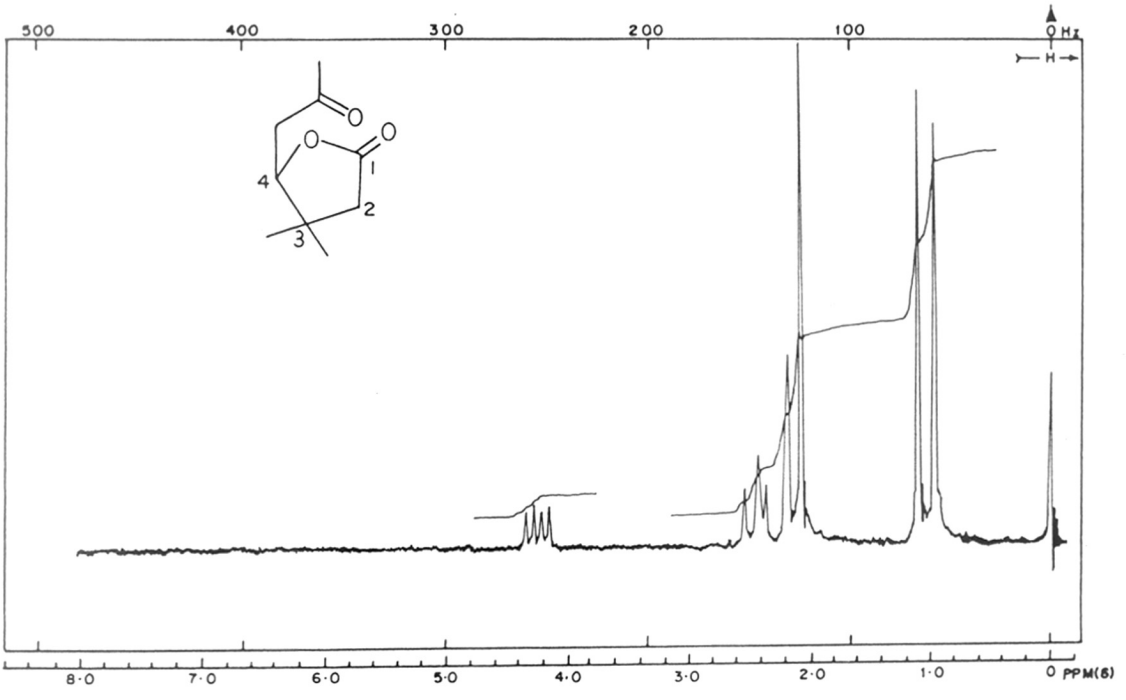
IR & PMR OF HEPTANOIC ACID-3-(1-HYDROXY-1-METHYLETHYL) 6-OXO-γ-LACTONE OR (+) HOMOTERPENYL METHYL KETONE 4.





IR & PMR OF METHYL 2,4-DIMETHYLPHENYLACETATE 11.





IR & PMR OF 3,3-DIMETHYL-4-(2-OXOPROPYL)-BUTYROLACTONE 14.

LIST OF PUBLICATIONS

1. Synthesis of methyl 1S-*cis*-2,2-dimethyl-3-(2-chloro-2-phenylvinyl)cyclopropanecarboxylate from (+)-3-carene, B.M. Mane, B.G. Mahamulkar, P.P. Pai, G.H. Kulkarni and R.B. Mitra, Indian J.Chem., 20B, 1029 (1981).

2. Synthesis of chrysanthemic acid analogues from (+)-3-carene, B.G. Mahamulkar, P.P. Pai, G.H. Kulkarni and R.B. Mitra, Indian J.Chem., 21B, 286 (1982).

3. Synthesis of some pyrethroids from (+)-3-carene, B.G. Mahamulkar, P.P. Pai, G.H. Kulkarni and R.B. Mitra, Indian J.Chem., 22B, 355 (1983).

4. Some interesting rearrangements of methyl 1R-*cis*-2,2-dimethyl-3-(2-oxopropyl)cyclopropanecarboxylate and related compounds, B.G. Mahamulkar, P.P. Pai, K.G. Gore, G.H. Kulkarni and R.B. Mitra, Indian J.Chem., 22B, 341 (1983).

5. Acid-catalysed rearrangements of methyl 1R-*cis*-2,2-dimethyl-3-(2-oxopropyl)cyclopropanecarboxylate and related compounds, B.G. Mahamulkar, G.H. Kulkarni and R.B. Mitra, Indian J.Chem., 22B, 910 (1983).

6. Synthesis of some optically active 1R-*trans*-pyrethroids from (+)-3-carene, B.G. Mahamulkar, G.H. Kulkarni and R.B. Mitra, Indian J.Chem. (in press).

7. Synthesis of 3-phenoxybenzyl 1R-*cis*-2,2-dimethyl-3-(acyloxy or alkoxy methyl)cyclopropanecarboxylate from (+)-3-carene, S.S. Bhosale, B.G. Mahamulkar, K.G. Gore, G.H. Kulkarni and R.B. Mitra, Indian J.Chem., (in press).

8. A new approach to the synthesis of methyl 1S-*cis*-3-(2-acetoxyalkyl/2-hydroxyalkyl/2-oxoalkyl) 2,2-dimethyl-cyclopropane carboxylate from (+)-3-carene, R.B. Mitra, B.G. Mahamulkar, G.H. Kulkarni, Synthesis (in press)