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

A THESIS

SUBMITTED TO THE

UNIVERSITY OF POONA

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

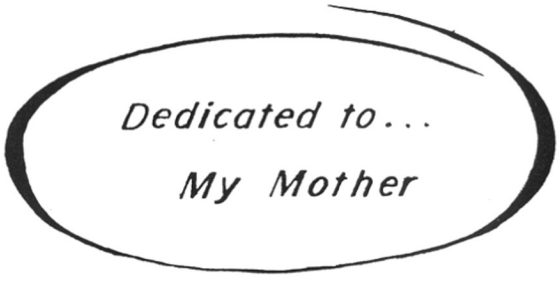
IN CHEMISTRY

BY

ABDUL RAKEEB ABDUL SUBHAN DESHMUKH
M. Sc.

DIVISION OF ORGANIC CHEMISTRY
NATIONAL CHEMICAL LABORATORY
POONA - 411 008 (INDIA)

JULY 1984


Dedicated to...
My Mother

Certified that the work incorporated in the thesis "Transformations of (+)-3-carene: Synthesis of Pyrethroids" submitted by Mr. Abdul Rakeeb Abdul Subhan Deshmukh was carried out by the candidate under my superivision. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

(Dr.R.B. Mitra)
Supervisor

A C K N O W L E D G E M E N T

I take this opportunity to express my deep sense of gratitude to Dr. R.B. Mitra, Deputy Director, National Chemical Laboratory, Poona, for his valuable guidance and keen interest throughout the course of this investigation.

I am indebted to Dr.(Miss) Z. Muljiani, Scientist, National Chemical Laboratory, Poona, for generous help, valuable suggestions, keen interest and constant encouragement.

I am also grateful to Drs. G.H. Kulkarni, A.S. Khanra, P.N. Khanna, B.V. Bapat and Dr.(Miss) M.V. Natekar for their generous help and valuable suggestions. I am thankful to Mrs. Smita Gadre and Mrs. Vijaya Joshi for their help and co-operation. I am also thankful to my wife for her patience and help.

Help from spectroscopic, microanalytical, GLC analysis and Entomology sections of this laboratory is gratefully acknowledged.

Thanks are due to all the staff members of the Division of Organic Chemistry (I) for constant co-operation.

Finally I am thankful to the Director, National Chemical Laboratory, Poona, for permitting me to submit this work in the form of a thesis.

(A.R.A.S. Deshmukh)

National Chemical Laboratory,
Poona-411008.
July 1984.

GENERAL REMARKS

1. All melting points and boiling points are uncorrected.
2. All temperatures are recorded on centigrade scale.
3. The compound numbers, scheme numbers and reference numbers etc. given in each chapter refer to that particular chapter only. The references and spectra are given at the end of each chapter.
4. All the solvents were distilled before use. Petroleum ether refers to the fraction boiling in the range 60-80°.
5. TLC analyses were carried out on glass plates with a mixture of silicic acid and plaster of paris (85:15, 200-300 mesh) and activated at 120° for 3 hrs. Solvent system used were pet.ether, benzene, ethyl acetate and acetone or a suitable mixture of two or more of these solvents depending upon the nature of the compound. The plates were developed by keeping in an iodine chamber or by spraying with sulfuric acid or ethanolic solution of phospho-molybdic acid.
6. Unless otherwise stated all optical rotations were measured in chloroform solution using sodium light (5893 A°) source on JASCO-181-digital polarimeter. Concentrations are expressed in gms/100 ml of the solution.
7. The IR spectra of liquids were recorded as smears (thin film) and of solids as nujol mulls on Perkin-Elmer "Infracord -137B", and/or 683 model spectrometer using NaCl optics. ν_{max} values are given in cm^{-1}.

8. The PMR spectra were taken in carbon tetrachloride, unless otherwise mentioned, using tetramethylsilane as the internal reference on Varian T-60 or Bruker WH-90 (spectrospin) or FT-80A varian spectrometers and the chemical shifts are measured in δ units. The ^{13}C NMR spectra were recorded on Bruker WH-90 spectrometer.

9. Mass spectra were recorded on CEC-21-110B and GC/MS model MS 30 of AEI mass spectrometers.

10. GLC was run on Hewlett-Packard 5730A and Fracto Vao-2450 Carlo Erba using nitrogen or helium as carrier gas and flame ionisation detector. Columns were selected as per requirements.

11. Column chromatography was carried out using silica gel (60-120 mesh) which was activated at 125-130° for 5 hours. Unless otherwise mentioned alumina refers to neutral alumina made in this laboratory.

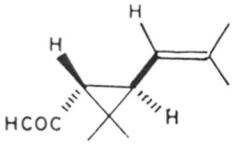
C O N T E N T S

CHAPTER - I

GENERAL INTRODUCTION TO PYRETHROIDS

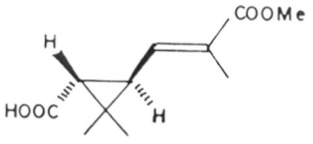
Natural products, isolated from plants have been the main subject of attraction for an organic chemist from ancient times. The natural products isolatedfrom plants have been utilized in oils, paints, pigments, medicines, insecticides etc. right from the old days. "Pyrethrum", a contact insecticide, obtained from the flower heads of chrysanthemum cinerariefolium, is one of them which has been used as an insecticide since ancient times. The plant appears to have originated from Middle and North East. At present Kenya is the major pyrethrum producing country. In 1965 the world output of pyrethrum was approximately 20,000 tonnes with Kenya producing some 10,000 tonnes[1-3].

The valuable insecticidal properties of pyrethrum were recognized in the 19th century and stimulated detailed examination of the chemical constitution of the active esters in the first quarter of 20th century. Staudinger and Ruzicka[4] for the first time isolated two active compounds from the pyrethrum extract and identified them as the esters of (+) trans-chrysanthemic acid (1) and (+) trans-pyrethric acid (2) with keto-alcohol, pyrethrolone (3) and named them as pyrethrin I (4) and pyrethrin II (5) respectively. Later on four more active esters viz. cinerin I (6), cinerin II[5] (7), jasmolin I (8) and jasmolin II[6-8] (9) were isolated from the pyrethrum extract. The insecticidal activity of pyrethrum is attributed to the presence of these



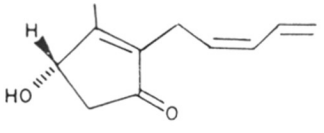
IR(+) Trans-Chrysanthemic acid

1



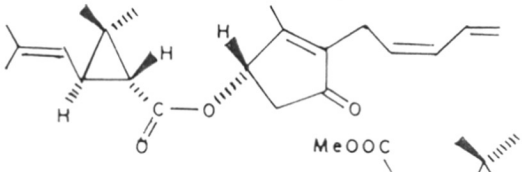
IR(+) Trans-Pyrethric acid

2



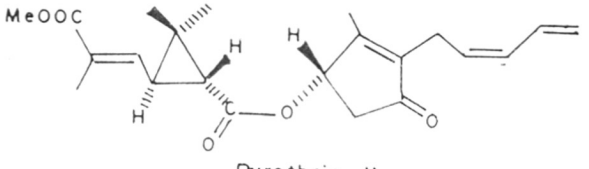
(+) Pyrethrolone

3



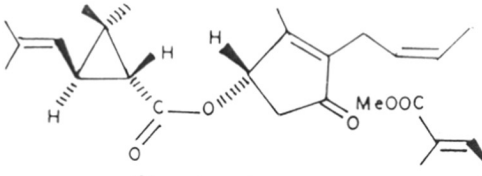
Pyrethrin-I

4



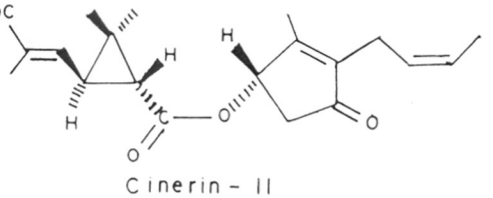
Pyrethrin-II

5



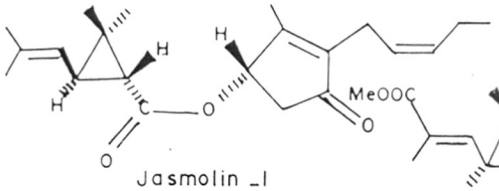
Cinerin-I

6



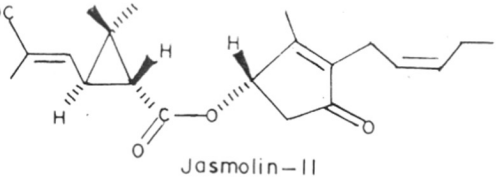
Cinerin-II

7



Jasmolin-I

8



Jasmolin-II

9

six esters. Out of these six esters pyrethrin I, cinerin I and jasmolin I contain (+) trans-crysanthemic acid as the common acid moiety. This class of active insecticidal esters occurring in pyrethrum was named as "pyrethroid". Now the word pyrethroid is not limited to natural pyrethrins alone, but is applied to biologically active Chrysanthemates and modified cyclopropane carboxylic acid, esters of various alcohols.

Pyrethroids, natural and synthetic ones, 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. Table I[9] demonstrates the relative advantage of pyrethroid over other classes of insecticides. Relative safety is indicated by the ratio of toxicities to rats and insects.

Table I

Clasa of insecticides	LD_{50} Rats mg/kg	LD_{50} Insects mg/kg	Ratio
Carbamate	45	2.8	16
Organophosphate	67	2.0	33
Organochlorine	230	2.6	91
Pyrethroid	2000	0.45	4500

The pyrethrin I is the most active of the natural pyrethroids. The acid components of natural pyrethroids are capable of existing as cis and trans geometrical isomers due to the presence of an olefinic double bond and each of the isomers can further exist in dextro (+) and Laevo (-) rotatory optical isomers. Similarly the alcohol can further exist in four stereoisomeric forms. The stereochemistry of pyrethroids has a vital influence on their insecticidal activity. Thus, (-) trans-chrysanthemates are practically inactive as compared with (+) trans-chrysanthemates. Elliot et al.[10, 11] have demonstratd that very small alteration in the structure and configuration can greatly influence the insecticidal potency. So the mechanism of the toxic action of pyrethroids probably involves a very specific interference with the biological system. For high insecticidal activity pyrethroid must have a precise steric relationship between an unsaturated centre in the alcohol moiety and the gem-dimethyl group or an equivalent substituent in the acid moiety[11]. This generally requires a 1R configuration in the cyclopropanecarboxylic acid and α-S-configuration in the alcohol. Inversion at these optical centres drastically alter the potency without greatly changing the physical properties.

Inspite of the high insecticidal activity and low mammalian toxicity of pyrethrum, a major disadvantage,

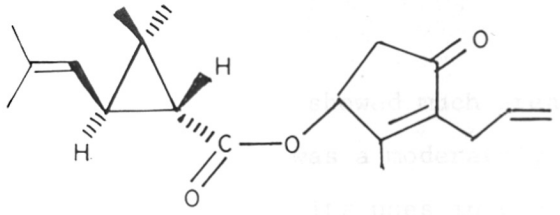
especially for use against agricultural pests lies in its lack of persistance due to its instability in the presence of air and light. For this reason it was necessary to modify the natural pyrethrin, keeping the appropriate stereochemistry necessary for biological activity, intact and increasing the photostability.

The synthesis of chrysanthemic acids and cyclopentenolones[12] opened up the possibility of obtaining synthetic pyrethroids. The first synthetic pyrethroid was allethrin (10)[13] prepared by esterification of synthetic (±) chrysanthemic acid with alcohol, allethrolone. The strong insecticidal activity of allethrin indicated that the side chain in the alcohol component may be modified without loss of activity. Barthel[14] showed that 2,4- and 3,4-dimethyl benzyl esters of chrysanthemic acids were insecticidal. Elliot and co-workers[15] concluded that the 4-methyl group was equivalent to a methylene group of the natural ester side-chain. On this basis, 4-allyl benzyl chrysanthemate, combining the structural features of allethrin and methyl benzyl chrysanthemate was synthesized and was shown to be appreciably more active against houseflies. Examination of number of methylbenzyl chrysanthemates showedthat 2,3,6- and 2,4,6-trimethyl substitution was particularly effective and so 4-allyl 2,6-dimethylbenzyl chrysanthemate was prepared which had a broader spectrum of insecticidal activity. This work

demonstrated that the cyclopentenone ring of the natural pyrethrin could be replaced by benzylic system without loss of activity[15]. The benzyl group can also be replaced by another aromatic system and this approach led to the discovery of 5-benzyl-3-furyl methyl (+)trans-chrysanthemate or bioresmethrin (11). This was an extremely potent insecticide (LD_{50} = 0.005 μg/ insect)[10]. Inspite of its high potency it was photosensitive and consequently was not persistent enough for agricultural use.

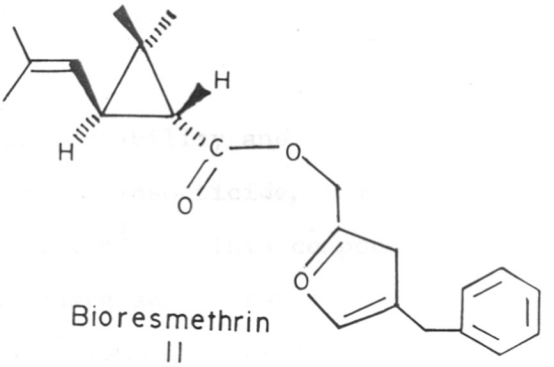
Insecticidal activity of 5-benzyl-3-furyl methyl (+)trans-chrysanthemate was raised even more by replacing the isobutenyl group by dichlorovinyl group. The resultant compound NRDC-134 (12), was found to be more toxic to houseflies and mustard beetles[16]. The dichlorovinyl side-chain in which the double bond is stabilized by the two electronegative atoms, replaces the photosenstive isobutenyl unit of chrysanthemic acid.

Chemical and spectroscopic evidence indicated that the furan ring in the ester of 5-benzyl-3-furylmethyl alcohol was the probable site of photosensitized oxidative decomposition. So, in an attempt to discover more stable pyrethroids, other esters of 2,2-dichlorovinyl cyclopropane carboxylic acid were synthesized. The ester from 3-phenoxybenzyl alcohol, biopermethrin (13), was as good against houseflies as bioresmethrin and 2.5 times more effective against mustard beetles.



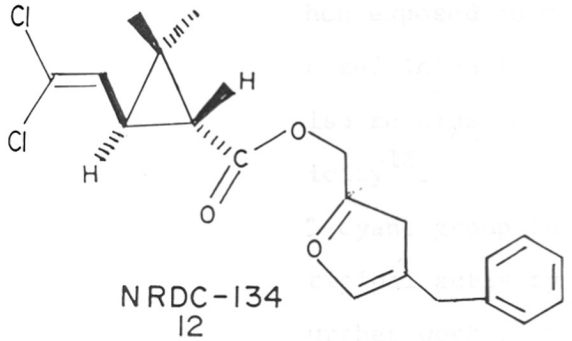
Allethrin

10



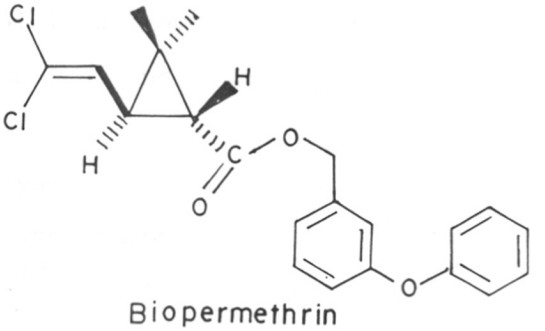
Bioresmethrin

11



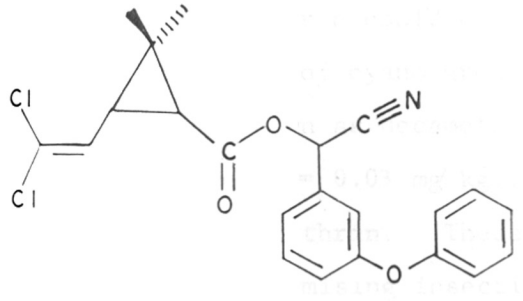
NRDC-134

12



Biopermethrin

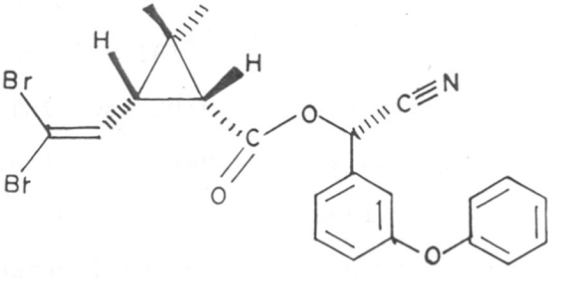
13



Cypermethrin

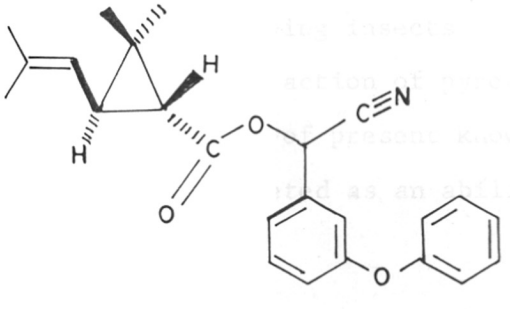
(±) cis - trans

14



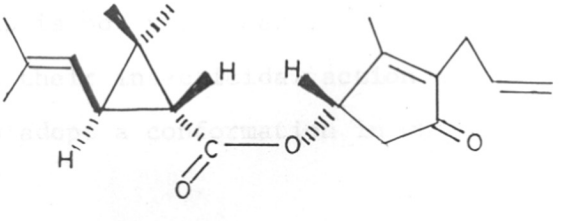
Decamethrin or NRDC - 161

15



Cyanophenothrin

18



S - Bioallethrin

25

This compound showed much greater photostability and consequently was a moderately persistent insecticide, which should extend its uses in crop protection[17]. This compound is more stable[16] than any organophosphate and carbamate. Nonetheless when exposed to micro-organisms in the soil, it is degraded sufficiently rapidly without any harmful residue and also retains the low oral and intravenous mammalian toxicity[16].

The α-cyano group in cypermethrin[18] (14) gave still greater insecticidal activity with somewhat increased mammalian toxicity. Further work showed[17] that the chlorine atoms of biopermethrin could be replaced by bromine and the introduction of cyano group led to an outstandingly active compound known as decamethrin or NRDC-161[19] (15)(LD_{50}= 0.0003 μg/housefly = 0.03 mg/kg). This was 20 times more active than bioresmethrin. These dihalovinyl pyrethroids appear extremely promising insecticides because of high activity combined with reasonable photostability and very low mammalian toxicity[20].

Most of the pyrethroids have a rapid "knock-down" action on flying insects. The exact mechanism of insecticidal action of pyrethroids is not yet clear . In the light of present knowledge their insecticidal action is best interpreted as an 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 of pyrethroids is the sensitivity of their insecticidal action to changes in substituents at certain important centres by which either the balance of conformers present is disturbed or contact of the molecule with receptor is obstructed. For the insecticidal activity the side-chain in the acid moiety must contain atleast one unsaturated centre, thus isobutyl (+)trans-chrysanthemates are much less active. The presence of the gem-dimethyl group and the carboxy moiety on the cyclopropane ring appears essential for the activity. This must be a cyclopropanecarboxylic acid. The alcoholic component must contain an unsaturated side-chain, which may be alkenyl, cycloalkenyl, benzyl or aromatic ring (e.g. furyl, benzyl or phenoxy). The whole cyclopentenolone ring can be replaced by structures that maintain the essential stereochemistry between the gem-dimethyl group on the cyclopropane ring and the unsaturated centre in the alcohol side-chain. For example (+) trans-chrysanthemates of 5-benzyl-3-furyl methyl and 3-phenoxybenzyl alcohol are active[11].

A significant feature of alcohol, leading to insecticidally potent pyrethroids, is the ability of unsaturated side-chain on the alcohol to adopt a conformation in which it is not coplanar with the ring. Thus, (+) chry-

santhemate of xanthene alcohol (16) is inactive because rotation about the band is prevented, whereas it can occur easily in the active esters from 3-phenoxybenzyl alcohol(17). Introduction of α-cyano group or α-ethynyl group[21] in the alcohol moiety increases the activity. Thus, -cyano-3-phenoxy benzyl chrysanthemate (18) showed increased activity. In the case of decamethrin or NRDC-161 (15), the two possible optical isomers were obtained. The crystalline α-S-isomer was found to be much more active than the liquid, α-R-isomer. This again emphasizes the importance of stereochemistry in the activity of pyrethroids.

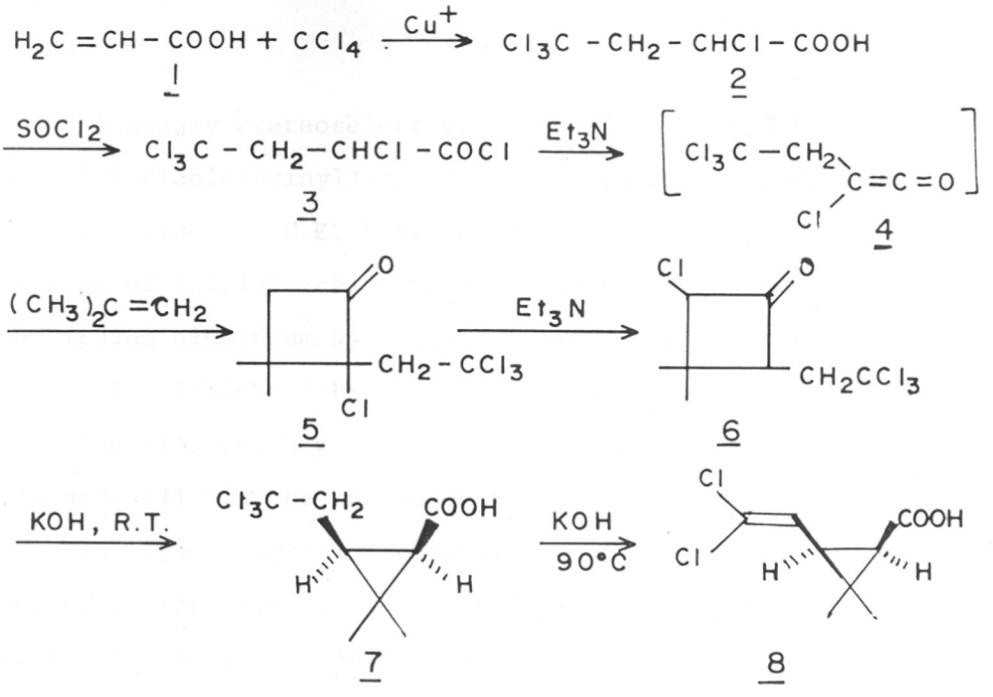
Due to the outstanding properties of the new pyrethroids, several research workers and industrial researches were attracted towards this field. Several new synthetic routes for pyrethroids were developed[22] and the work is still going on for the development and prepartion of new acid components of pyrethroids. Since the stereo-chemistry is very important for the insecticidal activity of pyrethroids, only stereo and enantioselective syntheses are described here.

Initially, for stereoselective and enantio-selective synthesis of pyrethroids, special reaction conditions have been applied to know methods that do not proceed very selectively without suitable modifications. Thus, in the reaction of tert-butyl diazo acetate with

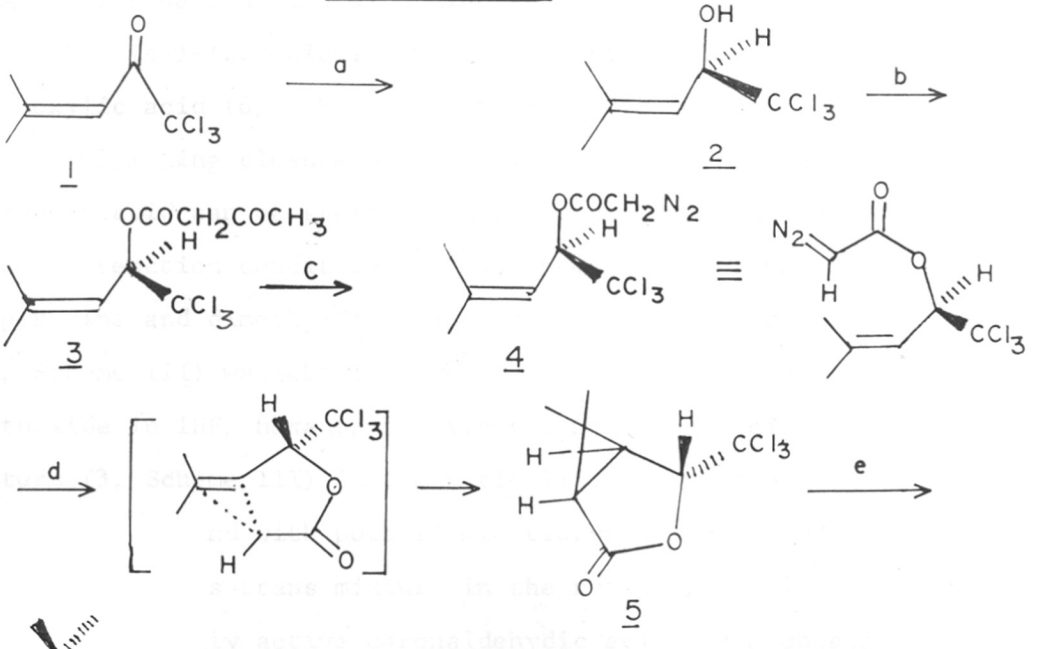
2, 5-dimethyl-2, 4-hexadiene the trans-chrysanthemic acid ester was obtained in high yield[23]. Copper (II) complexes with chiral ligands are used as catalyst for getting enantioselectivity. Thus, the synthesis of (1R)trans-acid was carried out by the addition of (-) menthyl diazo-acetate to 2, 5-dimethyl-2, 4-hexadiene, using chiral catalyst with an enantioselectivity of approximately 90%[24]. With rhodium (II) salts of carboxylic acids as catalysts e.g. the pivalate, cis enriched pyrethroid acid esters are obtained by diazoacetic ester addition to 1, 1-diholo-4-methyl-1, 3-pentadiene[25].

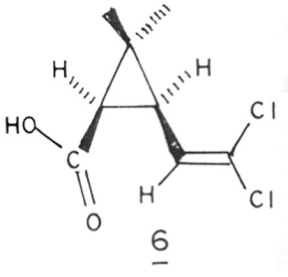
A Farorskii rearrangement of 2-chlorocyclobutanones also leads to stereoselective pyrethroid acids. Martin et al.[26] synthesized dichlorovinylcyclopropanecarboxylic acid by ring contraction of 2-chlorocyclobutanone as 80:20 cis-trans mixture. The cis compound predominently leads to cis-carboxylate in Farorskii rearrangement. The cyclo-butanone (5, Scheme I) was obtained by (2 + 2) cycloaddition of isobutylene with chloro-trichlorethyl ketene (4, Scheme I), which was isomerized by heating with cataltyic quantity of triethylamine in toluene to a more stable 2, 4-cis isomer (6, Scheme I), which readily underwent Farorskii rearrangement to predominently cis-dichlorovinylcyclopropane carboxylic acid by aquesous alkali.

SCHEME-I



SCHEME-II





6

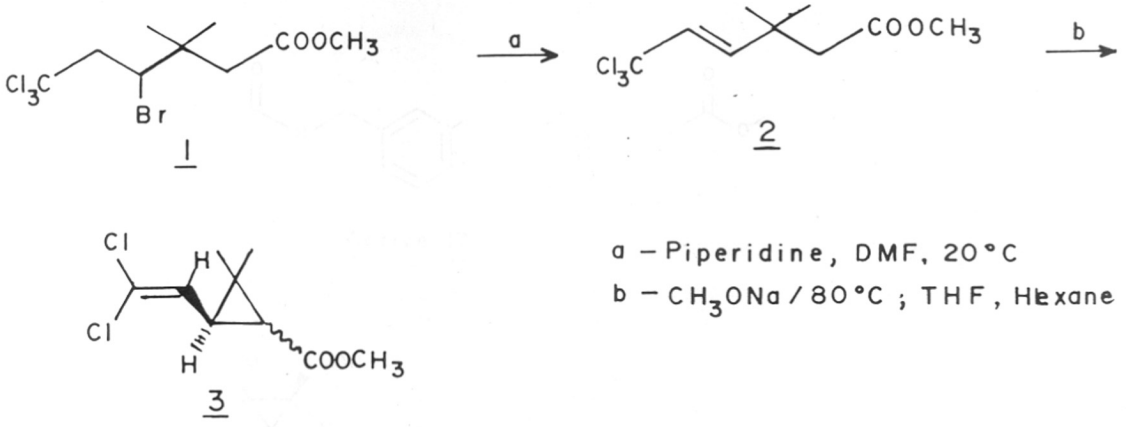
a – LAH, Ephedrine
b – Diketene
c – P-toluene sulfonyl azide or
P-acetamidobenzene sulfonyl azide
d – Cu (II), Δ
e – Zn / AcOH

A highly stereoselective synthesis of (1R, 3 R) cis-3-(2, 2-dichlorovinyl)-2, 2-dimethylcyclopropanecarboxylic acid was devised by C.E. Hatch et al.[27]. Asymmetric reduction of 1, 1, 1-trichloromesityl oxide (1, Scheme II) with lithium aluminium hydride-ephedrine complex produced (2R)-1, 1, 1-trichloro-2-hydroxy-4-methyl-pent-3-ene (2, Scheme II), which was transformed to a diazoacetate (4, Scheme II) via the corresponding diazoacetoacetate. Copper catalysed thermal decomposition of diazoacetate resulted in (2+ 1) cycloaddition of carbenoid on to the olefin with nearly quantitative stereoselectivity. The resultant bicyclic lactone (5, Scheme II) was ring opened via Boord type reaction with zinc and acetic acid, to afford (1R, 3R)-cis-3-(2, 2-dichlorovinyl)-2, 2-dimethylcyclopropane-carboxylic acid (6, Scheme II) in 98% optical purity.

1, 3-Ring closure of 4, 6, 6, 6-tetrahalo-3, 3-dimethyl hexanoic acid can be stereoselectively controlled using special reaction conditions[28, 29] (Scheme III). Thus using piperidine and dimethylformamide the unsaturated ester (2, Scheme III) was obtained which was cyclised using sodium methoxide in THF, hexane, to give the mixture of cis-trans esters (3, Scheme III) in the ratio 9:1. Corresponding 4-chloro compound with potassiumtertiarybutoxide in HMPT benzene gave cis-trans mixture in the ratio of 73:27.

Optically active caronaldehydic acid (19), obtained by ozonolysis of natural or synthetic enantiomerically pure

SCHEME - III

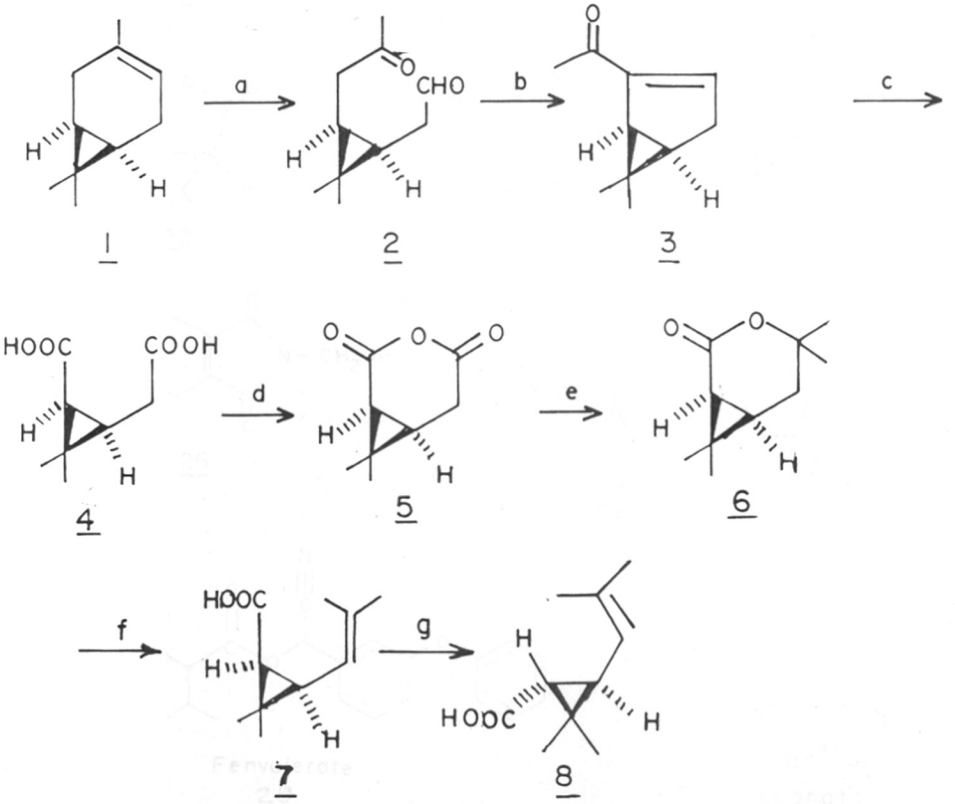


a – Piperidine, DMF, 20°C

b – CH_3ONa / 80°C ; THF, Hexane

Cis:trans = 9:1

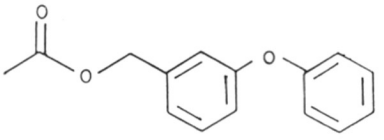
SCHEME - IV



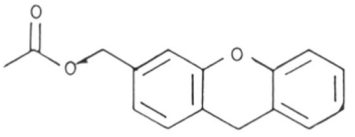
Cis-(1S, 3R) + trans-(1R, 3R)

a = O_3/Zn ; b = H$^+$; c = O_3/H_2O_2 ; d = Ac_2O ; e = CH_3MgI ;

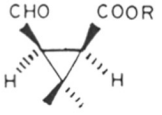
f = H$^+$; g = Base



Active 17

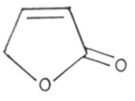


Inactive 16

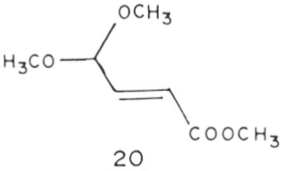


R = H, CH_3

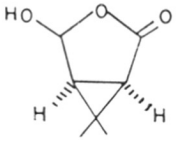
19



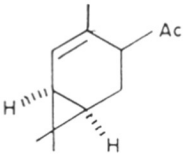
21



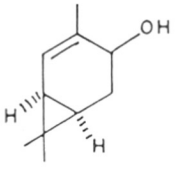
20



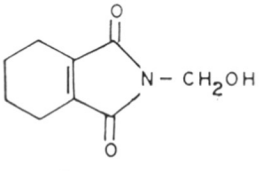
22



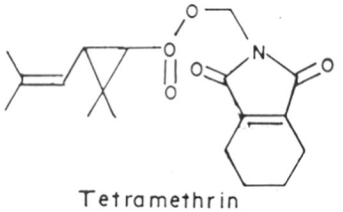
23



24

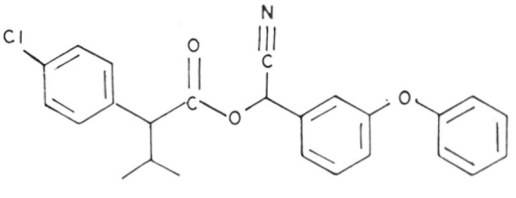


26



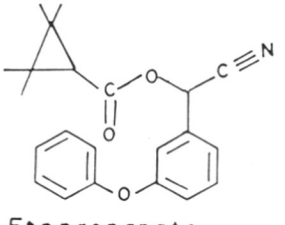
Tetramethrin

27



Fenvalerate

28



Fenpropanate

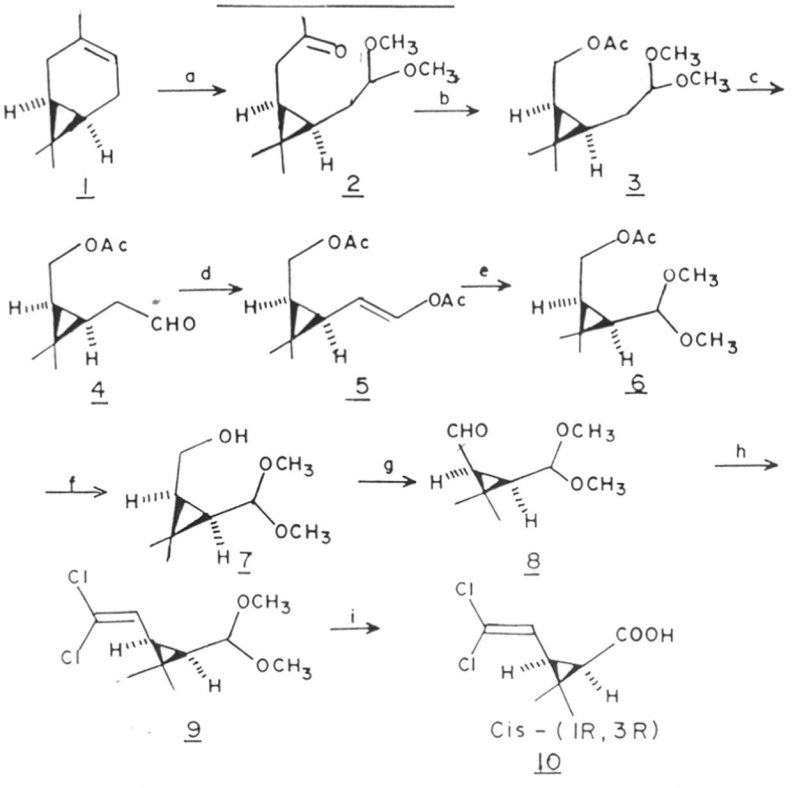
29

chrysanthemates, has been used to prepare several optically pure pyrethroid acids by Wittig reaction[30-32]. Krief et al.[33] have devised several synthetic path ways to trans- and cis-caronaldehydes, starting from 4,4-dimethoxycrotonic ester (20) or the butenolide (21). The caronaldehyde obtained so was utilized for synthesis of pyrethroids.

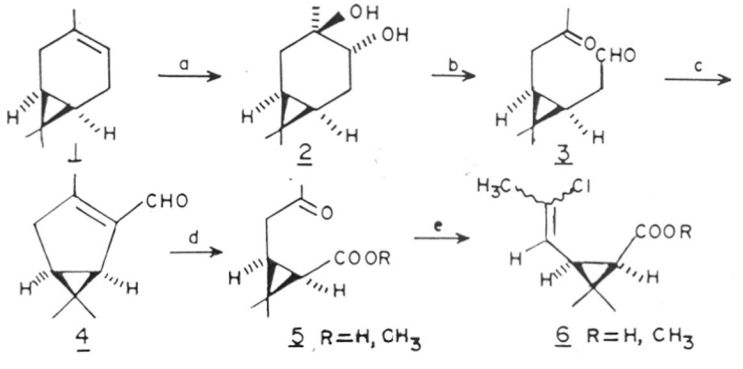
Optically active natural products such as (+)-3-carene ,(1R, 5R)(+)-α-pinene, (2R) (-)- and (2S)-(+)-pantolactones have been used successfully as starting materials for getting enantiomerically pure pyrethroid acids.

Matsui et al.[34] for the first time synthesized (1R, 3R) (+)-trans-chrysanthemic acid by degradation of (+) 3-carene (1, Scheme IV), which has already got a cis fused (1R, 6 S) cyclopropane ring. The complete reaction sequence is shown in Scheme IV. This synthetic route has since been improved upon by several working groups[35]. (+)-3--Carene was also utilized for the synthesis of (+) cis-permethrinic acid[36] (10, Scheme V) by a multistage pathway as shown in Scheme V. R. B. Mitra et al.[37] used (+)-3-carene for the synthesis of 2,2-dimethyl-3-(2-chloro-2-methyl vinyl) cyclopropanecarboxylic acid esters (6, Scheme VI). The key step of this synthesis is chlorination of ketoester (5, Scheme VI) by phosphorous pentachloride. The complete reaction sequence is shown in Scheme VI.

SCHEME V & VI

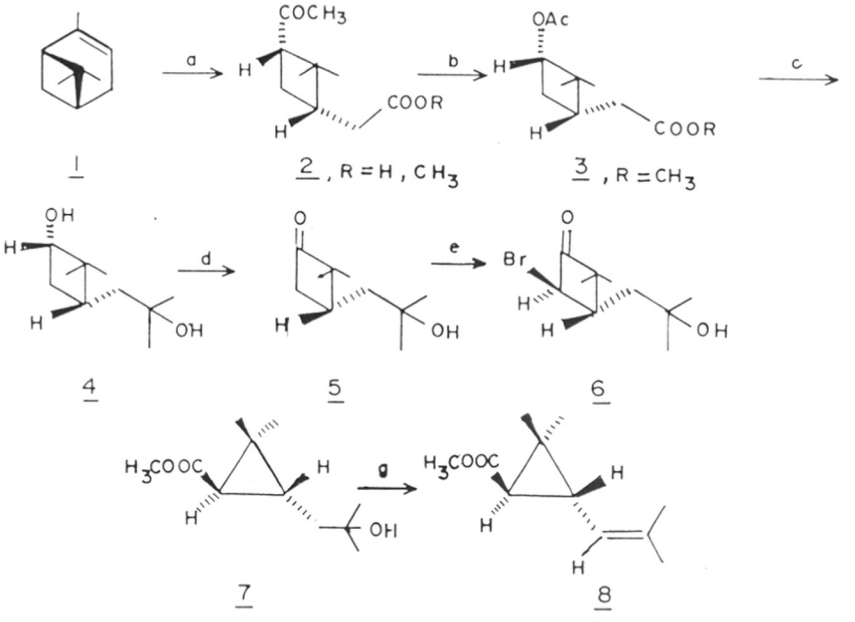


a = O_3 / $(CH_3)_2S$, CH_3OH / H^+ ; b = Per-acid ; C = H^+ ;
d = Ac_2O ; e = O_3/ $(CH_3)_2S$, CH_3OH / H^+ ; f = OH^- ; g = CrO_3/Py ;
h = Witting reaction ; i = H^+ / H_2O_2



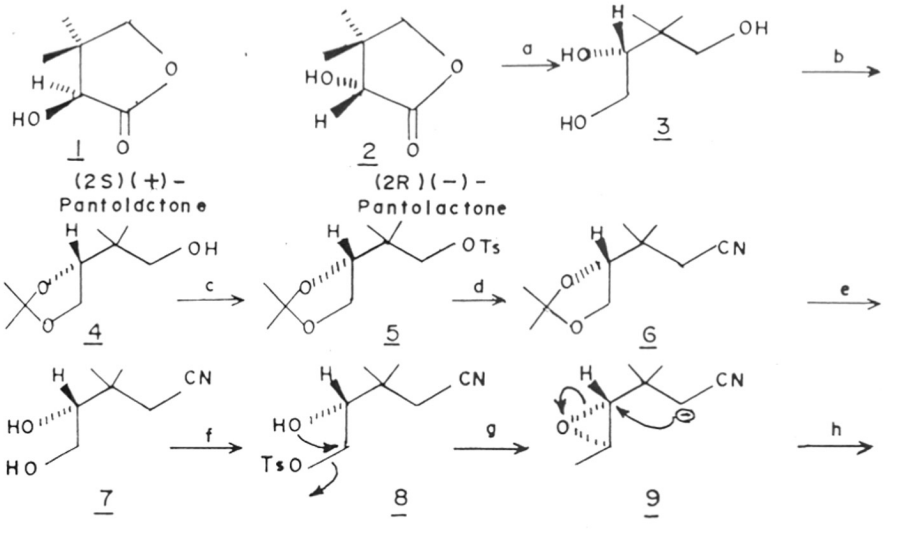
a = HCOOOH; b = $NaIO_4$; c = ACOH , Piperidine ; d = O_3 , e = PCl_5

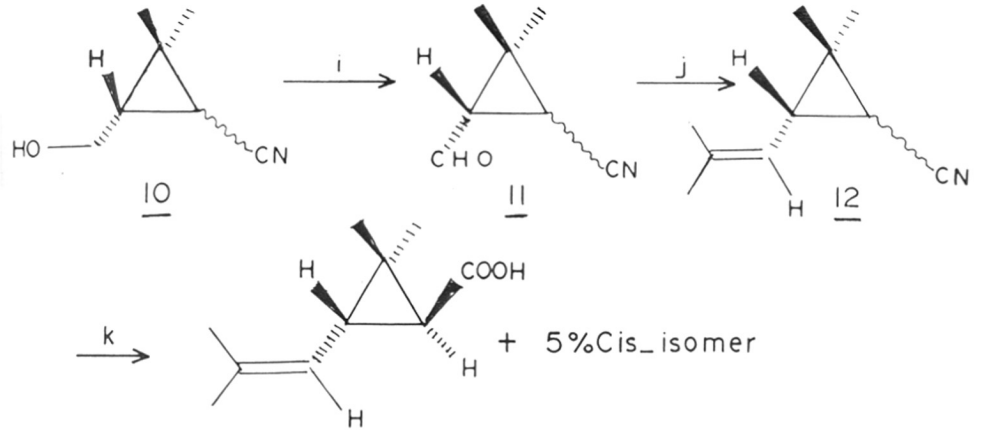
SCHEME VII



a = O_3 ; b = Bayer Villiger Oxdn, c = CH_3MgI ; d = Jones reagent ;
e = Br_2, f NaOMe ; g = $POCl_3$/Py

SCHEME VIII

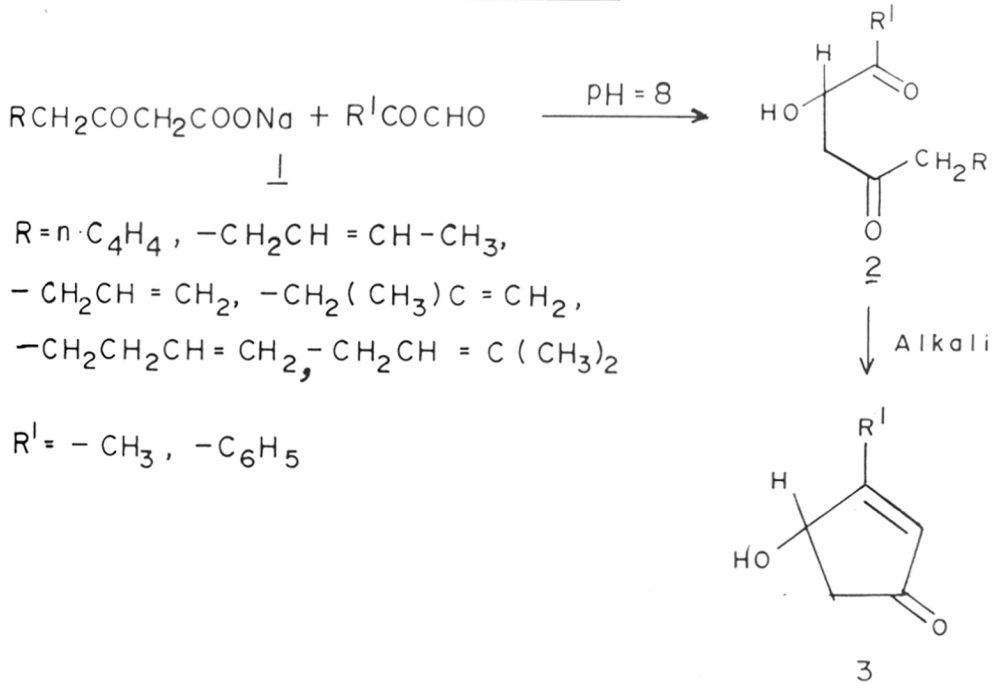




13 (1S,3S) (−) trans-chrysanthemic acid

a = LAH ; b = Acetone . PTS ; c = PTS-Cl . Py ; d = NaCN , DMSO ; e = AcOH
THF − H_2O , 45°C, 2 hr. ; f = PTS −Cl , Py ; − 10°C ; g = NaOMe , MeOH ;
h = $(Me_3Si)_2NLi$, Benzene , i = CrO_3 , Py j = (Ph_3PCHMe_2) Br ,
n-BuLi , Ether , R.T. , 24 hr ; K = KOH , Ethylene glycol , 200°C, 24 hr.

SCHEME − IX



R = n-C_4H_4 , $-CH_2CH=CH-CH_3$,
$-CH_2CH=CH_2$, $-CH_2(CH_3)C=CH_2$,
$-CH_2CH_2CH=CH_2$, $-CH_2CH=C(CH_3)_2$

R^1 = $-CH_3$, $-C_6H_5$

The cyclic hemiacetal or cis-(1R)-caronaldehyde (22) was also obtained from (+)-3-carene[38], which is an important intermediate for several pyrethroid acids. Similarly, derivatives of (+)-2-carene (23,24) were also used for getting permethrinic acid by multistage pathways[39].

(1R, 5R)-(+)-α-pinene was successfully utilized for the synthesis of (+)-trans-chrysanthemic acid by R.B. Mitra et al.[40] In this synthesis the decisive step is a Farorskii rearrangement as shown in Scheme VII.

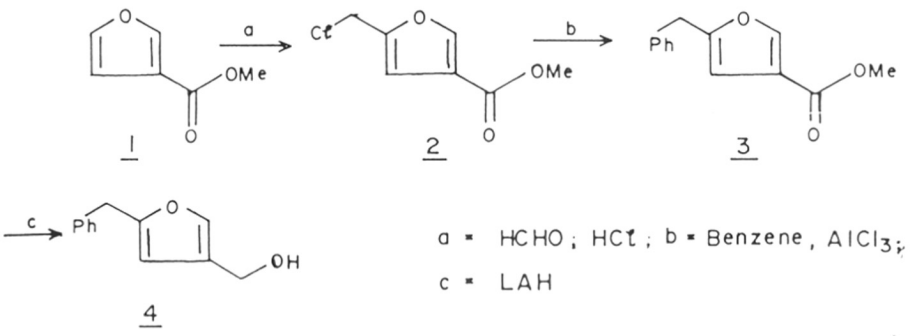
M. Matsui et al.[41] utilized optically active (2R) (-) and (2S) (+)-pantolactones for the synthesis of (+) trans-chrysanthemic acid (see Scheme (VIII). In this synthesis a crucial step is 1,3-ring closure to get the cyclo-propane ring. Epoxide (9, Scheme VIII) was opened by the internal attack of carbanion with Walden type inversion of configuration. So the (R) configuration of (2R) (-)-pantolactone changes to (S) in the nitrile (10, Scheme VIII). Thus there is a complete steric control in this reaction. The alcohol side-chain was oxidised by Corey's reagent to aldehyde (11, Scheme VIII) and isobutenyl side-chain was introduced by Wittig reaction. The final compound (1S, 3S) (-)-trans-chrysanthemic acid (13, SchemeVIII) was prepared by hydrolysis of nitrile group. On the same line, starting with (2S)(+)-pantolactone (1R, 3R) (+)-trans-chrysanthemic

acid was prepared. The pyrethroid acids so obtained are condensed with different alcohols to get the final pyrethroids. The first synthetic alcohol, allethrolone[13], was prepared by cyclisation of 1,4-diketone with aqueous alkali (Scheme IX) ,1,4-diketones were obtained by condesning ∝-alkenyl acetoacetic esters with substituted glyoxal. By this method several 2- and 3-substituted cyclopentenones were prepared (Scheme IX). Natural pyrethrin contains ∝-S-configuration, so the synthetic racemic mixture was resolved as hemisuccinate[42] or phthalate[43] derivatives. S-Isomer obtained so was utilized for the preparation of S-biallethrin[44] (25). The R-isomer was also utilized to get the corresponding ∝-S-configuration on the final pyrethroid by SN^2 reaction[45] of sodium chrysanthemate with the mesyl derivative of R-alcohol which took place by inversion of configuration.

N-Hydroxymethyl imide (26) which was used as an alcohol moiety for the synthesis of pyrethroids e.g. tetramethrin[46] (27), was prepared by condensation of maleic anhydride and butadiene followed by rearrangement, imide formation with urea and hydroxymethylation with formaldehyde[47].

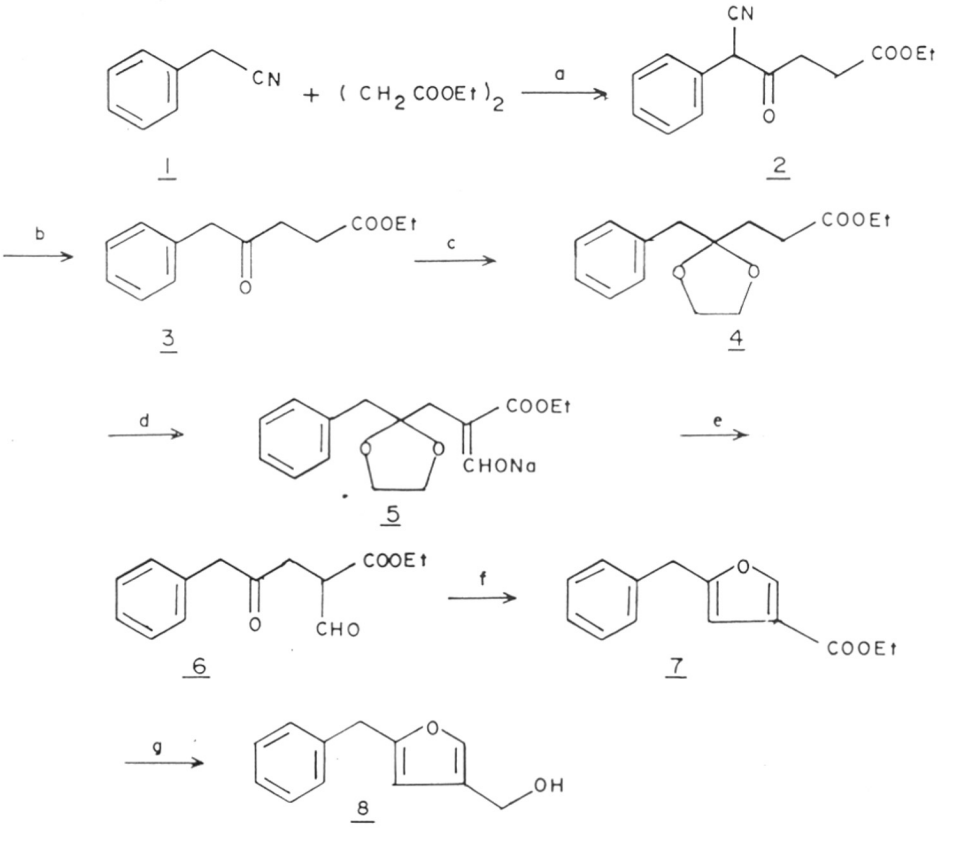
5-Benzyl-3-furylmethyl alcohol is a very important alcohol component of highly active pyrethroids. This alcohol was prepared[48] by chloromethylation of 3-furoates (Scheme X) followed by Friedel-Craft alkylation reaction.

SCHEME - X



a = HCHO ; HCℓ ; b = Benzene , $AlCl_3$;
c = LAH

SCHEME-XI



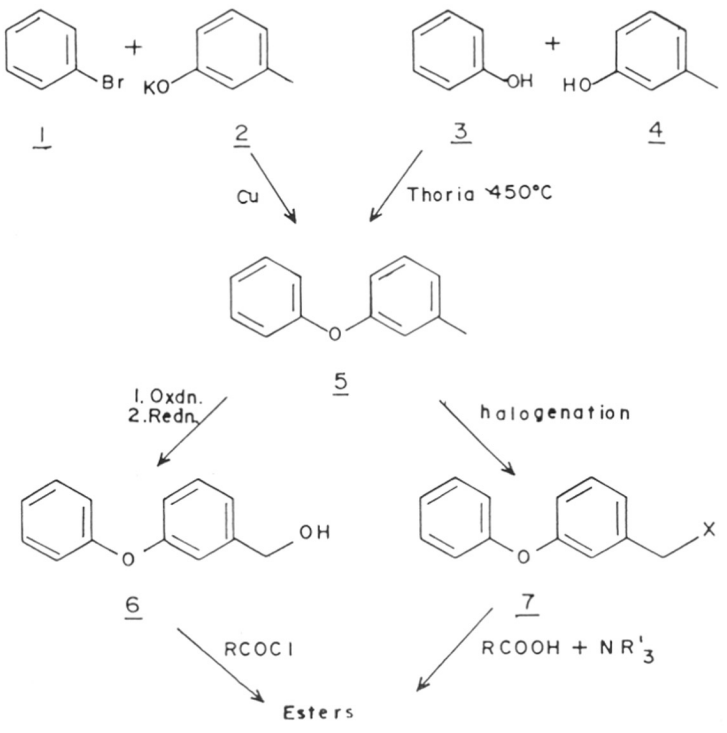
a = NaOEt ; b = i) H^+, H_2O ii) H, EtOH ; c = $(CH_2OH)_2$, H^+ ;
d = HCOOEt , NaH ; e = AcOH ; f = HCℓ ; g = LAH

5-Benzyl-3-furoate obtained so was reduced with lithium aluminium hydride to give the alcohol (Scheme X).

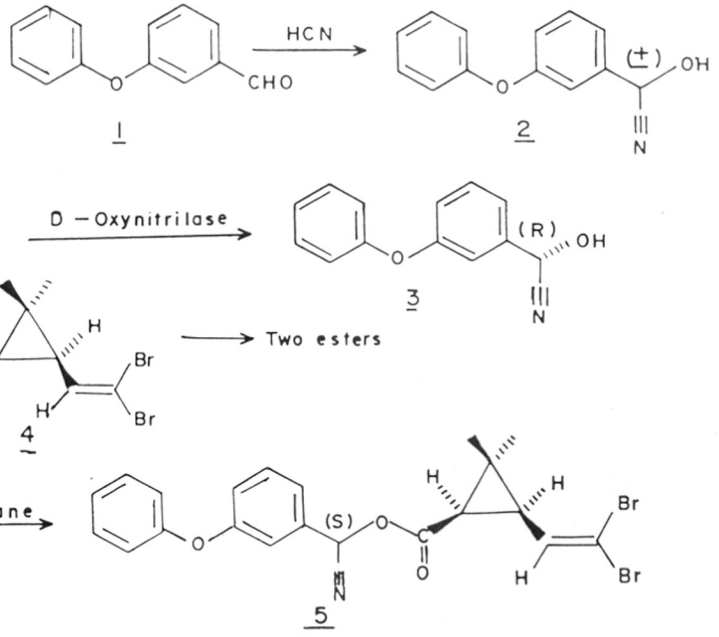
An alternative method (Scheme XI) was deviced by Elliot et al.[48]. They started with benzylcyanide, which was condensed smoothly with diethylsuccinate, hydrolysis and reesterification gave levulinic ester (3, Scheme XI). The keto-group of levulinic ester was protected as ethylene-ketal and then condensed with ethylformate using sodium-hydride. The formyl derivative (6, Scheme XI) was cyclised using concentrated hydrochloric acid to 5-substituted furoic ester (7, Scheme XI). This was reduced with lithium aluminium hydride to get 5-benzyl-3-furylmethyl alcohol. Several patented processess[49] are reported in the literature for preparation of this particular alcohol.

As we have seen earlier, 5-benzyl-3-furylmethyl alcohol was a probable site of photosensitized oxidative decomposition, another very important, although less toxic to insects as compared with 5-benzyl-3-furylmethyl alcohol derivatives, but more photostable 3-phenoxybenzyl alcohol was used for the synthesis of pyrethroids. Many patented processess are reported in the literature for the preparation of 3-phenoxybenzyl alcohol. In most of the cases (Scheme XII) sodium or potassium salts of metacresol were condensed with bromobenzene[50] and then the methyl group was either oxidised[51] and reduced to alcohol or halogenated[52] to

SCHEME XII



SCHEME XIII



3-phenoxybenzyl halide which can directly be used for the preparation of final pyrethroids. 3-Phenoxy benzyl alcohol was also obtained by hydrolysis of halides. A commercial process for 3-phenoxytoluene involves condensation of phenol and meta-cresol using catalyst like thoria and high temperature[53].

Cyanohydrin of 3-phenoxybenzaldehyde (2, Scheme XIII) was found to be a very potent synthon for pyrethroids. 3-Phenoxybenzaldehyde (1, Scheme XIII) was prepared either by direct oxidation of alcohol[19] or by Ulmann reaction[54]. When this aldehyde was treated with HCN, isomer mixture of cyanohydrins was obtained (Scheme XIII). This was used as such for the synthesis of pyrethroids or resolved. When this mixture was treated with D-oxynitrilase and the condensation was carried out only ester of R-isomer was obtained while the S-isomer was destroyed. Using this method Elliot et al.[55] prepared α-R-isomer of 2,2-dimethyl-3-(2,2-dibromovinyl) (1R, 3R) cis-cyclopropanecarboxylic acid. The isomeric mixture of alcohols, when treated with an acid-chloride of (1R, 3R) cis-2,2-dimethyl-3-(2,2-dibromovinyl)cyclopropanecarboxylic acid, isomeric mixture of esters was obtained. From this mixture a solid α-S-isomer was separated by crystallisation from hexane. The absolute configuration was assigned by comparing with α-R-conformer obtained earlier. It was observed that the

α-S-isomer was much more active than the liquid α-R-isomer. This clearly indicates the importance of stereochemistry for the insecticidal activity.

The alcohol moieties obtained as described above were condensed with the acid chlorides of pyrethroid acids to get the final pyrethroids. Several patented processes are reported in the literature for this condesnation reaction. The pyrethroid esters were also prepared by trans esterification of methyl ester with 3-phenoxybenzyl alcohol. Triethyl amine salts of halides e.g. 3-phenoxybenzyl triethyl ammonium bromide can directly be treated with sodium or potassium salts of pyrethroid acids to get the condensed esters.

Apart from the substituted cyclopropanecarboxylic acid derivatives some open chain compounds were also known to have appreciable insecticidal activity. Fenvalerate (28), an ester of α-(4-chlorophenyl) isovaleric acid is one of them which shows an insecticidal activity of similar magnitude to that of Permethrin[56]. This compound is photostable and has got sufficient field persistency. The isopropyl group is essential for the activity, the methyl and isobutyl compounds are practically inactive while the ethyl compound has got only half the activity of fenvalerate[56]. Fenpropanate[57] (29) is the ester of 2,2,3,3-tetramethyl-cyclopropane carboxylic acid. This compound, like fenvalerate, is also being assesssed to be a promising insecticide for agricultural use owing to its high potency and sufficient field prsistency.

REFERENCES

1. Naturally Occurring Insecticides. (Eds. M. Jacobson and D.G. Crosby), Dekker, New York (1971).
2. G.S. Hartley and T.F. West, Chemicals for Pest Control, Pergamon Press, Oxford, p.26 (1969).
3. A. Wood, Pest Control, McGraw-Hill, London, p.82 (1974).
4. H. Staudinger and L. Ruzicka, Helv.Chim.Acta., 7, 177 (1924).
5. F.B. La-Forge and W.F. Barthel, J.Org.Chem., 9, 242 (1944).
6. P.J. Godin, R.J. Sleeman, M. Snarey and E.M. Thain, Chem. and Ind., 371 (1964).
7. P.S. Beevor, P.J. Godin and M. Snarey, Chem. and Ind., 1342 (1965).
8. P.J. Godin, R.J. Sleeman, M. Snarey and E.M. Thain, J.Chem.Soc.(C), 332 (1966).
9. M. Elliott, 'Synthetic Pyrethroids" ACS-Symposium Series 42, p.2 (1977).
10. M. Elliott, Bull.Wld.Hlth.Org., 44, 315 (1970).
11. M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham and D.A. Pulman, Insecticidally active conformations of pyrethroids in mechanism of pesticide action, ACS-Symposium Series No.2, p.80 (1974).
12. H. Martin, The Scientific Principles of Crop Protection, 6th Edn., Arnold, London, p.179 (1973).
13. M.S. Schechter, M. Green, F.B. La-Forge, J.Am.Chem.Soc. 71, 3165 (1949).
14. F.W. Barthel, "Synthetic Pyrethroids", Advances in Pest Control Research, 4, 33 (1961).
15. M. Elliott, N.F. Janes and I.J. Graham-Bryce, Proc. 8th Brit.Insectic. and Fungic Conf. Brighton, 2, 373 (1975).
16. M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham, D.A. Pulman and J.H. Stevenson, Nature, London, 246, 169 (1973).
17. D.C. Griffith, G.C. Scott, K.A. Jeffs, F.F. Maskell and P.F. Robert, Proc. 8th Brit.Insectic. and Fungic. Conf. Brighton, 1, 213 (1975).
18. M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham and D.A. Pulman , Pestic.Sci., 6, 537 (1975).

19. M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham D.A. Pulman, Nature, 248, 710 (1974).

20. T.I. Watkins and D.M. Weighton, Repts. on Progr. Appl.Chem., 60, 404 (1975).

21. M. Elliott, N.F. Janes, B.P.S. Khambay and D.A. Pulman, Pestic.Sci., 14, 182 (1983).

22. D. Arlt, M. Jautelat and R. Lantzsch, Angew.Chim. 20, 703 (1981) and references cited therein.

23. T. Matsumoto, A. Nagai and Y. Takahashi, Bull.Chem.Soc.Jpn. 36, 481 (1963).

24. T. Aratani, Y. Yoneyoshi, T. Nagase, Tetrahedron Lett., 2599 (1977).

25. D. Holland and J. Milner, J.Chem.Res.(S), 317 (1979).

26. P. Martin, H. Greuter and D. Bellus, J.Am.Chem.Soc. 101, 5853 (1979).

27. C.E. Hatch, J.S. Baum, T. Takashima and K. Kondo, J.Org.Chem., 45, 3281 (1980).

28. K. Kondo, A. Negishi and K. Sugimoto, Eur.Pat. 3683 (1979), FMC Corp.

29. K. Kondo, T. Takashima, A. Negishi, K. Matsui, T. Fujimoto, K. Sugimoto, C.E. Hatch, J.S. Baum, Pestic.Sci., 11, 180 (1980).

30. M. Elliott, N.F. Janes and D.A. Pulman, J.Chem.Soc., Perkin Trans I, 2470 (1974).

31. W.G. Taylor, Synthesis, 554 (1980).

32. H. Hoffmann, F. Maurer, U. Priesnitz and H.J. Riebel, DOS. 2917620 (1980), Bayer A.G.

33. M.L. Sevrin, Hevsesi, A. Krief, Tetrahedron Lett., 3911, 3915 (1976).

34. M. Matsui, H. Yoshioka, H. Sakamoto, Y. Yamada, T. Kitahara, Agric.Biol.Chem., 29, 784 (1965); 31, 33, 1143 (1967).

35 a) R. Sobti and Sukh Dev, Tetrahedron 30, 2927 (1974).
(b) Y. Gopichand, A.S. Khanra, R.B. Mitra and K.K. Chakravarti, Indian J.Chem. 13, 433 (1975),
(c) A.S. Khanra, R.B. Mitra ibid. 14, 716 (1976),
(d) W. Cocker, H.S.J. Lander, P.V.R. Shannon, J.Chem.Soc., Perkin Trans I 337 (1975), 194 (1974),
(e) F. Horiuchi, N. Itaya, H. Yoshioka, DOS. 2261611 (1973), Sumitomo Chem.Co.,

36 a) P.A. Verbrugge, P.A. Kramer, J. Van Berkel, H.C. Kelderman, Eur.Pat. 2850 (1979). Shell Int.Res.
(b) S.A. Roman, DOS. 2942618 (1980), Shell Int.Res.

37. R.B. Mitra, G.H. Kulkarni, K.G. Gore, A.S. Khanra, Z. Muljiani, P.N. Choudhari, B.M. Bhawal, G.D. Joshi, P.N. Khanna, Brit. U.K. Pat.Appl. 2034301 (1980), CSIR,India.

38. S.A. Roman, U.S. 415692 (1979) Shell Oil Co.

39. K. Arata, J.O. Bledsoc, K. Tanabe, Tetrahedron Lett., 3861 (1976).

40. R.B. Mitra, A.S. Khanra, Synth.Commun., 7, 245 (1977).

41. T. Matsuo, K. Mori, M. Matsui, Tetrahedron Lett., 1979 (1976).

42. B. Goffinet, Ger. Offen.2263880 (1973) Roussel UCLAF.

43. M. Matsui, F. Horiuchi, H. Hirai, N. Itaya, Ger.Offen 2414794 (1974), Sumitomo Chemic Co.Ltd.

44. W.A. Gersdorff and N. Mitlin, J.Econ.Entomol. 46, 999 (1953).

45. J. Martel, J. Tessier, J.P. Demoute, Ger.Offen 2740701 (1978), Roussel UCLAF.

46. T. Kato, K. Ueda and Fujimoto, Agric.Biol.Chem. 28, 914 (1964).

47. M.C. Bailey and E.D. Amstutz, J.Am.Chem.Soc. 78, 3828 (1956); T. Kato, K. Ueda, S. Horie and T. Mizutani, Jap. 22658 ('65) (1963), Sumitomo Chemical Co.Ltd.

48. M. Elliott, N.F. Janes and B.C. Pearson, J.Chem.Soc.(C), 2551 (1971); Anon, Chem.Eng.News (2), 32 (1971).

49. Fr. 1578377 (1969), Sumitomo Chemical Co.Ltd., G.R. Treves and P.A. Cruickshank Chem. and Ind. 544 (1971); F. Graf, H. Koenig, Ger.Offen 1935009 (1971), Badische Anilin und Soda Fabrik A.G.; V. Weberndoerfer, H. Koenig, Ger.Offen. 2122661 (1972), Badische Anilin und Soda-Fabrik A.G.; V. Weberndoerfer, H. Koenig, Ger.Offen. 2122822-3 (1972), Badische Anilin und Soda-Fabrik A.G.; J.B. Siddall, U.S. 3781308 (1973), Zoecon Corp.

50. F.F. Christopher, Fr. 1394557-8 (1965), British Petroleum Co.Ltd.

51. N. Itaya, T. Matsuo, T. Mizutani, Jap.Kokai. 7361450 (1973), Sumitomo Chemical Co.Ltd., J.H. Atkinson, D. Wright, Brit. 1489325 (1977), Imperial Chemical Ind. Ltd.

52. Y. Ume, T. Matsuo, N. Itaya, N. Ohno, Ger.Offen.2402457 (1974), Sumitomo Chemical Co.Ltd., T. Mizutani, N. Ohno, Y. Ume, T. Matsuo, Ger.Offen. 2437882 (1975), Sumitomo Chemical Co.Ltd.,

53, J.H. Atkinson, D. Wright, Ger.Offen. 2604474 (1976), Imperial Chemical Ind. Ltd.

54. R.A. Sheldon, J.W. Van der Meer, A.S. Mulder, Ger.Offen. 2624360 (1976), Shell Int.Res., A. Bader, Aldrichimica Acta. 9, 49 (1976).

55. M. Elliott, N.F. Janes, D.A. Pulman and D.M. Soderlund, Pestic.Sci. 9, 105, 112 (1978).

56. N. Ohno, K. Fujimoto, T. Mizutani, M. Hirano, N. Itaya, T. Honda, H. Yoshioka, Agric.Biol.Chem. 38, 881 (1974).

57. T. Matuo, N. Itaya, T. Mizutani, N. Ohno, K. Fujimoto, Y. Okuno, H. Yoshioka, Agric.Biol.Chem. 40, 247 (1976).

CHAPTER-II

STEREOSPECIFIC SYNTHESIS OF 1R-CIS-2,2-DIMETHYL-3-(2-OXOPROPYL)CYCLOPROPANECARBOXYLIC ACID AND ITS METHYL ESTER

SUMMARY

This chapter deals with the synthesis of 1R-cis--2,2-dimethyl-3-(2-oxopropyl)cyclopropanecarboxylic acid (8) starting from naturally occurring (+)-3-carene (4). The keto acid (8) was prepared by three different routes. In the first route, (+)-3-carene (4) was converted to carânediol (5) which was oxidized to ketol (10) by activated DMSO. Fufuryldine derivative (11) of ketol (10) was converted to hydroxy dicarboxylic acid (13) via an epoxide (12) by $KMnO_4$ oxidation. The hydroxy dicarboxylic acid gave the required keto acid (8) by acid-$KMnO_4$ oxidation.

In the second route, (+)-3-carene was transformed to -carene oxide by ethyl chloroformate and hydrogen peroxide. This epoxide (17) was opened up by thiophenol to afford sulfide (23). The sulfide (23) was oxidized to sulfoxide (24) by aqueous hydrogen peroxide. Sulfoxide (24) after pyrolysis gave the tertiary alcohol (14) which was oxidized to required keto acid (8) via hydroxy dicarboxylic acid (25).

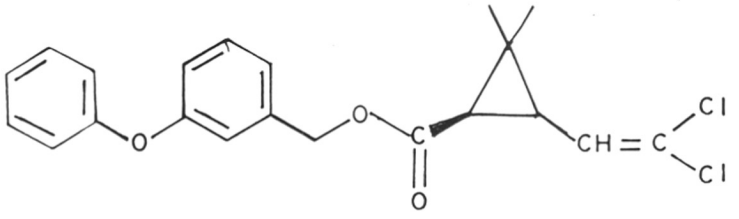
In the third route, ketol (10) was utilized to get keto acid (8). Oxime (30) was prepared from ketol (10) by using isoamyl nitrite. This oxime (30) was converted to nitrile (31) via the tosylate. The nitrile (31) was hydrolysed to hydroxy dicarboxylic acid (13) or an amide (32), which was converted to the required keto acid (8).

Present work and Discussion

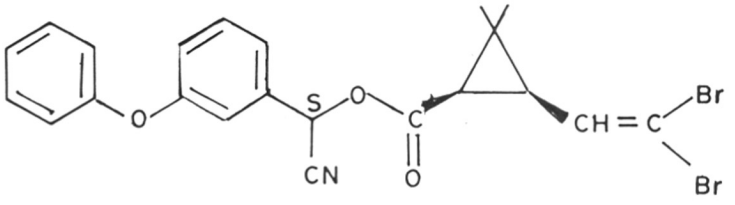
Pyrethroids, natural and synthetic are becoming increasingly important as insect control agents because they possess a unique combination of desirable properties including exceptionally good insecticidal activity, low mammalian toxicity and rapid biodegradation[1]. These features, combined with their broad spectrum of insecticidal activity, have made them commercially successful and also environmentally safe. Since the discovery of permethrin[2] (1) and its bromo analogue, decamethrin (2)[3], interest in the structural modification of natural pyrethroids has been renewed owing to their potential use as agricultural pesticides as well as house-hold insecticides.

A new insecticide of pyrethroid group, named "indothrin" (3) was synthesised in our laboratory[4]. Indothrin is 3-phenoxybenzyl ester of (1R) cis-2,2-dimethyl-3-(2-chloro-2-methylvinyl)cyclopropanecarboxylic acid. A naturally occurring monoterpene (+) 3-carene (4), was successfully utilized for the synthesis of acid moiety of indothrin (Scheme I). Indian turpentine oil is rich in (+) 3-carene as can be seen from Table I[5].

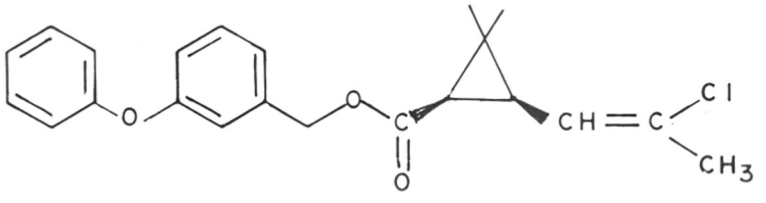
(+) 3-Carene was first converted to 3,4-carane-diol (5) using performic acid and then the diol (5) was cleaved by sodium metaperiodate to ketoaldehyde (6)/:



Permethrin 1

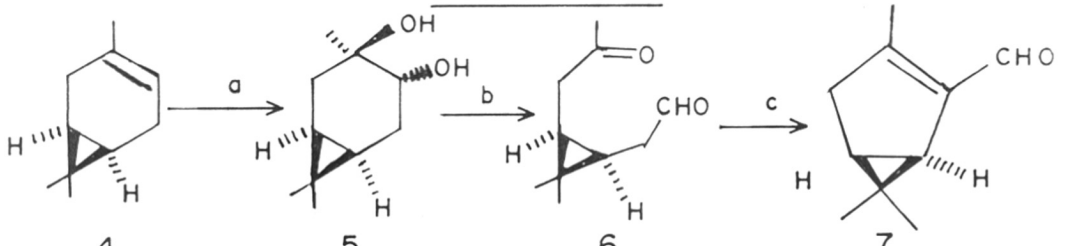


Decamethrin 2

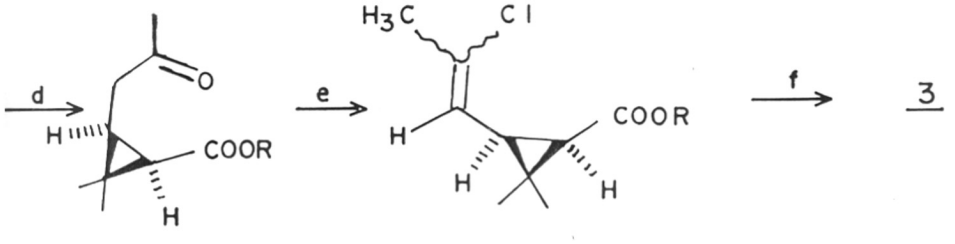


Indothrin 3

SCHEME - I



4 5 6 7



8, R=H, CH_3 9 R=H, CH_3

a = HCOOOH, b = $NaIO_4$, c = AcOH, Piperidine d = $KMnO_4$ Or O_3

e = PCl_5, f = K_2CO_3, 3-Phenoxybenzyl triethylammonium bromide

Table I

Typical Analysis of Turpentine

	USA %	France %	India %	USSR %	Portugese %	Sweden %	Japanese %
α-Pinene	65-75	60	20-30	75%	80	80	85
β-Pinene	20-30	25-30	5-10	-	15-17	5	10
Δ^3-Carene	-	-	55-65	15	-	15	5
Longifolene	-	-	2-5	-	-	-	-
Other terpenes	5	5-10	3-5	10	3-5	-	-

This ketoaldehyde (6) was cyclised to a cyclic aldehyde (7) using acetic acid and piperidine. This cyclic aldehyde (7) after ozonolysis and oxidative work up gave 2,2-dimethyl -3-(2-oxopropyl)cyclopropanecarboxylic acid (8). The methyl ester of this keto-acid after treatment with phosphrous pentachloride gave 2,2-dimethyl-3-(2-chloro-2-methylvinyl) cyclopropanecarboxylic acid ester (9). This was finally converted to the pyrethroid, indothrin (3).

In the above synthesis, the intermediate ketoester (8) is a very important intermediate. Apart from the use of this keto-ester in the above synthesis, several derivatives of this ketoester are known to have insecticidal activity[6]. (1R) cis-Chrysanthemic acid[7] can also be prepared from this ketoester. Although it is a very important intermediate, only one synthesis of this ketoester (8) is reported in literature by Matsui et al. and that too in very low yield. So, in view of its importance we tried to synthesize this particular compound starting from cheaply and abundantly available (+) 3-carene (4).

We thought, probably if we could functionalise C-5 of (+) 3-carene, then we could get this particular keto acid by oxidative degradation. With this strategy in mind we converted (+) 3-carene to caranediol (5) by usual method[8] using performic acid. Several reagents, like Jones reagent, pyridinium dichromate N-bromosuccinimide were

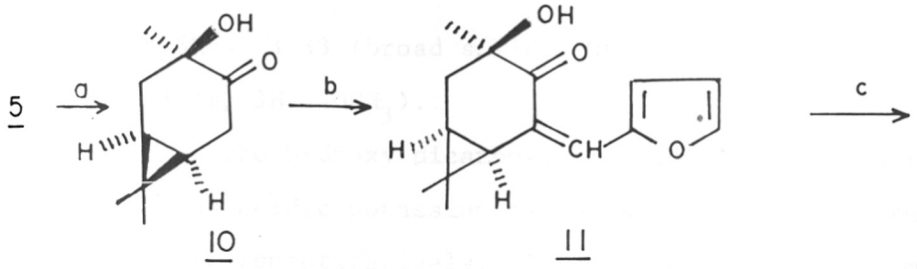
tried for the oxidation of caranediol (5) to ketol (10)[9,10], but the yields of ketol did not exceed above 30%. By using chromium trioxide in pyridine and dichloromethane as a solvent we could get ketol (10) in 50% yield[11]. But still it was not a satisfactory yield for the total synthesis of keto ester (8). Finally we could get the ketol (10) in 78% yield using dimethyl sulfoxide and oxalyl chloride[12], at -60° temperature and dichloromethane as solvent. The ketol was characterized by IR, PMR and specific rotation, which were comparable with the reported one[9,10].

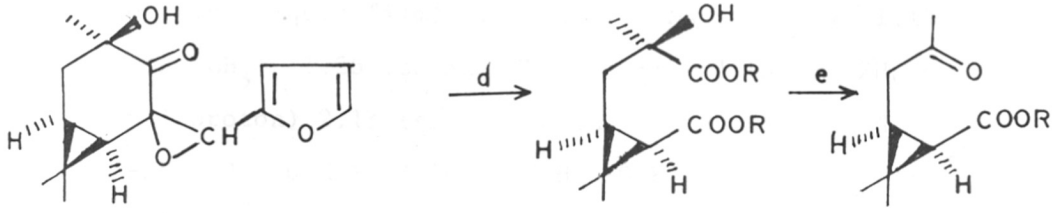
The ketol (10) has got the reactive methylene group adjacent to the carbonyl group. So, the furfurylidene derivative was prepared by stirring ketol (10) with 20% aqueous alcoholic sodium hydroxide and furfuraldehyde at room temperature for 5 hrs. It was diluted with water and extracted with ether. After drying over anhydrous sodium sulfate, solvent was removed to afford thick brown oil. It was purified by silica gel column chromatography with chloroform and pet. ether (1:3) as eluant to give yellow coloured solid m.p. 53-54°. This compound showed IR (Nujol): 3636, 1681, 1590 cm^{-1} and PMR (CCl_4, δ): 0.80 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.06 - 1.56 (m, 1H, cyclopropyl proton) 1.80 - 2.46 (m, 2H, $-CH_2-$), 3.66 (s, 1H, -OH), 6.39 (m, 1H, aromatic), 6.56 (d, 1H aromatic J = 4 Hz), 7.33 (m, 2H, aromatic and olefinic protons).

The crude furfurylidene derivative (11) was sufficiently pure as judged by its PMR spectrum. So it was utilized as such for further oxidation reaction. Several conditions for oxidation of furfurylidene derivative were tried e.g. neutral potassium permanganate, aqueous acetic acid and potassium permanganate, alkaline potassium permanganate ,but gave unsatisfactory results due to acid/ base catalysed retro-aldol reaction. The crude furfurylidene derivative was treated with alkaline hydrogen peroxide for 5 hr at room temperature. Formation of epoxide (12) was revealed by the PMR spectrum which showed a new singlet at δ 4.30 (1H, =-O-CH) and decrease in the peak intensity of the two-proton multiplet at δ 7.33 of (11) to a one-proton multiplet at δ 7.36 in (12). The epoxide was found to be unstable at room temperature so it was utilized immediately for further oxidation.

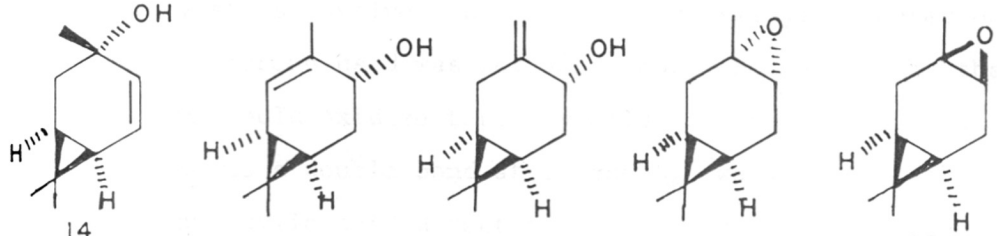
The epoxide (12) was taken in acetone and treated with powdered potassium permanganate (3 mol) at 15-20^{o} during 3 hrs. The hydroxy dicarboxylic acid (13) was recovered from the manganese dioxide precipitate by washing with warm water followed by acidification. It was characterized as dimethyl ester after purification by silica gel column chromatographed using 10% ethyl acetate in benzene as eluent . IR (liquid film): 3509, 1724 cm^{-1}. PMR (CCl_4, δ): 1.17 (s, 6H, two CH_3), 1.1 - 1.63 (m, 2H, cyclopropyl proton) 1.37 (s, 3H, CH_3) 2.03 (d, 2H, $-CH_2$,

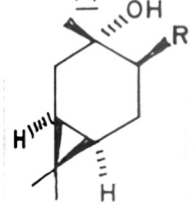
SCHEME-II





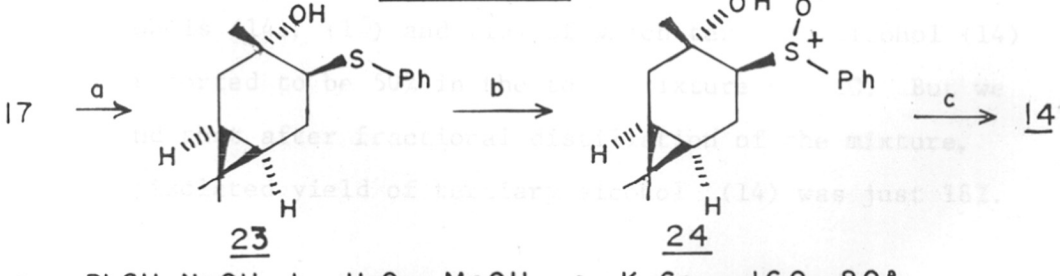
a = Oxalylchloride, DMSO ; b = NaOH, furfural dehyde; c = H_2O_2, NaOH ; d = $KMnO_4$; e = H^+, $KMnO_4$





18 R = $N(CH_3)_2$ 19, R = $-\overset{+}{N}(CH_3)_2 \rightarrow O^-$ 20, R = Se-Ph 21, R = $-\overset{+}{Se}\rightarrow O^-$-Ph

SCHEME-III



a = PhSH, NaOH; b = H_2O_2, MeOH ; c = K_2Co_3, 160-80°

J = 6Hz), 3.33 (broad s, 1H, -OH), 3.66 (s, 3H, $-OCH_3$), 3.83 (s, 3H, $-OCH_3$).

The hydroxy dicarboxylic acid (13) on oxidation with aqueous acidic potassium permanganate[13] gave the required keto acid quantitatively. It was characterized as methyl ester. IR (liquid film): 1724 cm^{-1}. PMR (CCl_4, δ): 1.13 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.33 - 1.63 (m, 2H, cyclopropyl proton) 2.13 (s, 3H, $-COCH_3$), 2.86 (broad, d, 2H, $-CH_2$; J = 6 Hz), 3.66 (s, 3H, $-OCH_3$). $(\alpha)_D^{28} = -31.3^\circ$ (c, 1.368, $CHCl_3$).

Although, we could get the required keto ester (8) by the above method, it was not a very good method as there were many steps involved and also the overall yield based on (+) 3-carene used was not very good. So we thought that if we could oxidize tertiary allylic alcohol (14), where there is a double bond at C_4 and C_5, we would get the hydroxy dicarboxylic acid directly. There are four different methods reported in the literature for the synthesis of this alcohol. The first method is the photosensitized oxygenation[14] of (+) 3-carene using rose-bengal as sensitizer. This methods leads to a mixture of three different allylic alcohols (14), (15) and (16) of which tertiary alcohol (14) is reported to be 50% in the total mixture by GLC. But we found that after fractional distillation of the mixture, the isolated yield of tertiary alcohol (14) was just 18%.

The second method[15] starts with α-epoxycarane (17). It is opened with dimethyl amine by heating under pressure to hydroxy amine (18) and then oxidized to corresponding N-oxide (19) by aqueous hydrogen peroxide. The N-oxide by Cope elimination gives the required alcohol (14).

The third method also starts with α-epoxycarane (17). Here it is opened up with diphenyl diselenide[16] and the corresponding selenide (20) is oxidized to selenoxide (21) by aqueous hydrogen peroxide. cis-Elimination of selenoxide (21) gives the required alcohol (14). In this synthesis the yield of tertiary alcohol is quite good starting with β -epoxy carane (22) but with α-epoxycarane yield is very poor.

The fourth method is the isomerization of α-epoxy-carane using strong base like isopropyl-lithium[17]. This method again gives a mixture of alcohols as in the case of photosensitized oxygenation reaction on (+) 3-carene.

We developed a new method to get this tertiary allylic alcohol (14) in quantitative yield (Scheme III) (+) 3-Carene was convert ed to α-epoxycarane in 100% yield using ethylchloroformate[18] and aqueous hydrogen peroxide. The clean α-epoxycarane so obtained was opened with thiophenol under alkaline condition to get phenyl sulfide (23) in 80% yield. The sulfide was characterized by IR (liquid film): 3663 cm^{-1}, PMR (CCl_4, δ): 0.56 - 0.93 (m, 2H, cyclopropyl

proton), 1.0 (s, 6H, two CH_3), 1.23 (s, 3H, CH_3), 1.63 - 2.5 (m, 4H, $-CH_2$), 3.26 (dd, 1H, -CH-S-, J = 6 Hz, 9 Hz), 7.4 (m, 5H, aromatic); $(\alpha)_D^{30}$ = + 73.6° (c, 2.366, $CHCl_3$).

The hydroxy sulfide (23) was oxidized to corresponding sulfoxide (24) by 30% hydrogen peroxide in methanol[19] at room temperature. Extractive work up with ethyl acetate gave a white solid in 100% yield, m.p.130-135°, IR (Nujol):3571, 1020 cm^{-1}, PMR (CCl_4, δ): 0.4 - 0.83 (m, 2H, cyclopropyl proton), 0.9 (s, 3H, $-CH_3$), 0.96 (s, 3H, CH_3), 1.03 - 2.33 (m, 4H, $-CH_2$) 1.56 (s, 3H, CH_3), 2.43 - 3.0 (m, 1H, -CH-S-), 3.73 (broad s, 1H, -OH), 7.17 - 8.03 (m, 5H, aromatic).

The hydroxy sulfoxide (24) was mixed thoroughly with anhydrous potassium carbonate and pyrolysed at 160-180° at 12 mm pressure to get (14) as colourless oil in 90% yield. It was characterized by IR (liquid film): 3509, 1639, 733 cm^{-1} and NMR ($CCl_4\delta$): 0.86 (s, 3H, $-CH_3$), 0.93-1.26 (m, 1H, cyclopropyl proton), 1.1 (s, 6H two $-CH_3$) 1.46 (d, 1H cyclopropyl proton, J = 4 Hz), 1.66 - 2.30 (m,2H, $-CH_2$), 1.66 (s, 1H, -OH, exchanged with D_20), 5.73 (s, 2H, olefinic), $(\alpha)_D^{28}$ = - 271° (benzene, c, 4.82) (HPLC pure); reported[14] $(\alpha)_D^{20}$ = - 289° (benzene, c, 3.6).

Thr methods described in literature for the synthesis of 14 suffer from serious drawbacks for large scale preparation. Alcohol (14) obtained by singlet oxygen reaction of 4 was combersome and uneconomical involving separation of isomers.

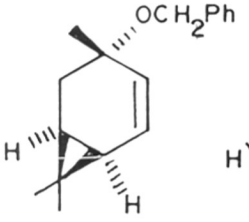
The rearrangement of α-epoxycarane (17) with strong base also results in a mixture of isomeric alcohols. Synthesis of 14 by Cope elimination of N-oxide (19), employs conditions of high pressure and temperature. Lastly the preparation of 14 involving the Sharpless method was unsuited for several reasons. Alcohol (14) by this method is reported in poor yields, attributed to steric factors, the cost and toxicity of selenium compounds are added disadvantages, especially for large scale preparation. So the method developed by us for getting alcohol (14) is definitely superior to all other reported methods as it gives pure compound, does not require high pressure and temperature, costly and hazardous diphenyl diselenide is avoided and alcohol (14) is obtained in very high yield.

Oxidation of alcohol (14) by potassium permanganate was tried by Volkov et al.[20] but they could not get hydroxy dicarboxylic acid (25), but the benzyl ether (26) was successfully oxidized by them to corresponding dicarboxylic acid (27) in just 19% yield,. While, we could oxidize alcohol (14) to hydroxy dicarboxylic acid using potassium permanganate as oxidizing agent. Acetone solution of alcohol (14) was treated with 3 moles of potassium permanganate at $0\text{-}5^{\circ}$ for 2 hrs and the mixture stirred at this temperature for another 3 hrs. The hydroxy dicarboxylic acid was recovered from the manganese dioxide residue by washing with

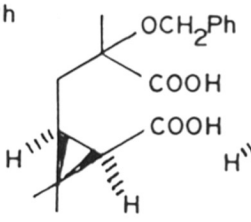
warm water, followed by acidification with 10% sulphuric acid. It was characterized as dimethyl ester after purification by silica gel column chromatography. IR Spectrum was identical with the IR spectrum of (13) but the PMR spectrum was slightly different from the PMR spectrum of (13) because there is a change in the stereochemistry of chiral centre bearing hydroxyl and carbomethoxy group. The doublet due to methylene protons of (13) appeared as a quartet in (25) while the remaining peaks are identical.

Hydroxy dicarboxylic acid (25) was further confirmed by preparing a lactone (28) which has the m.p. 174-75° like the reported one[13]. The hydroxy dicarboxylic acid (25) was then oxidized by aqueous acidic potassium permanganate to the required keto acid in quantitative yield. The overall yield of keto acid based on (+) 3-carene was about 42%.

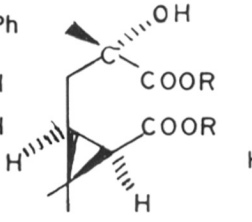
Ketol (10) was also utilized to get the required keto acid by another route as shown in Scheme IV. ∝-Oximino ketones can be prepared by treating ketones with isoamyl nitrite or isobutyl nitrite using potassium tertiary butoxide as base[21]. Accordingly ∝-oximino ketone (30) was prepared from ketol (10) using isoamyl nitrite and potassium tertiary butoxide. The crude brown oil of -oximino ketone (30) was purified by passing over silica gel and using 20% ethyl acetate in benzene as eluant to get white crystalline solid m.p.175-176°; IR (Nujol): 3330, 1706,



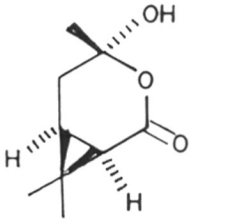
26



27



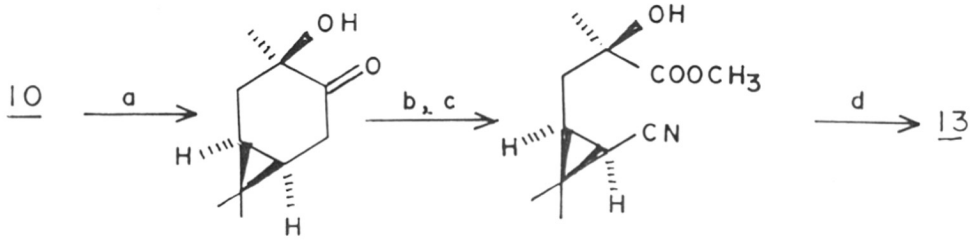
25, R=H, CH_3



28, R=H

29, R=CH_3

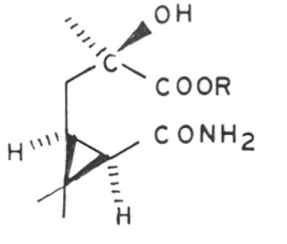
SCHEME - IV



30

31

13



32, R=H, CH_3

8

a = Isoamylnitrite, $Bu^t OK$; b = NaOH, PTs-Cl; c = CH_2N_2

d = NaOH; e = H_2O_2, NaOH. f = H^+, $KMnO_4$

1587 cm^{-1}; PMR ($CDCl_3$,δ); 0.96 (s, 3H, CH_3), 1.1-1.7 (m, 2H, cyclopropyl proton), 1.26 (s, 3H, $-CH_3$), 1.46 (s, 3H, CH_3), 1.76 (broad s, 1H, OH) 1.96 - 2.7 (m, 2H, $-CH_2$); $(\alpha)_D^{30}$ = + 37.56° ($CHCl_3$, c, 0.820).

The crude oxime (30) was taken in aqueous alkaline dioxane and p-toluene sulfonyl chloride added to it at room temperature under nitrogen atmosphere. This mixture was stirred at 50° for 2 hr. Then the solvent was removed completely at room temperature under vacuum. To the residue was added ice-cold water and extracted with ether. The aqueous solution was acidified with 10% sulfuric acid. The inorganic salts which separated out were filtered and the solid was washed with ether. Aqueous layer was extracted with ether and the combined ether extracts were washed with water and then with brine solution and dried over anhydrous sodium sulfate. Solvent was removed to afford brown oil in 43% yield which was esterified with diazomethane and distilled b.p.140-150°/2 mm to give pale yellow coloured oil. IR (liquid film): 3571, 2268, 1727 cm^{-1}; PMR (CCl_4,δ): 1.26-1.56 (m, 2H cyclopropyl proton), 1.27 (s, 6H, two-CH_3), 1.57 (s, 3H $-CH_3$), 1.76-2·10 (m, 2H, $-CH_2$), 3.30 (broad s, 1H, -OH); 4.07 (s, 3H,$-OCH_3$) $(\alpha)_D^{30}$ = - 4.00° ($CHCl_3$; c, 2.05).

Nitrile ester (31) so obtained was subjected to hydrolysis with methanolic hydrochloric acid but no clear

product was obtained. So alkaline hydrolysis was tried[22]. It was refluxed with 5 moles of potassium hydroxide in aqueous ethanol for 24 hrs. The hydroxy dicarboxylic acid was characterized as dimethyl ester which showed superimpossible IR and PMR spectra with (13). This hydroxy dicarboxylic acid was then converted to the final keto acid by usual aqueous acidic potassium permanganate. GLC of the keto ester revealed it as a mixture of 92% cis and 6% trans keto ester. It was purified by chromatography and checked IR, PMR and $(\alpha)_D$ which were comparable with the authentic.

The nitrile ester (31) when treated with aqueous alkaline hydrogen peroxide[23] gave a white solid amide (32) in 55% yield. It was esterified with diazomethane. IR (Nujol): 3446, 1751, 1667 cm^{-1}; PMR ($CDCl_3$, δ): 0.8-1.36 (m, 2H, cyclopropyl proton), 1.13 (s, 6H, two CH_3), 1.46 (s, 3H, $-CH_3$), 2.13 (d, 2H, $-CH_2$, J = 6 Hz), 3.23 (s, 2H, $-NH_2$), 3.86 (s, 3H, $-OCH_3$), 5.9 (broad s, 1H, -OH). From the spectral data it was found to be amide ester (32), which was confirmed by hydrolysing the amide (32) by alkali to hydroxydicarboxylic acid and finally to the keto acid. The overall yield of keto acid by the oximde route was not as good as the earlier two methods.

EXPERIMENTAL

4-Hydroxy-4,7,7-trimethyl bicyclo [4-1-0] heptan-3-one (10)

Oxalyl chloride (1.1 ml, 12.8 mmol) was taken in dichloromethane (25 ml) and cooled to -60°. A solution of dimethyl sulfoxide (1.85 ml, 26 mmol) in dichloromethane (5 ml) was added in five minutes. The mixture was stirred for 10 minutes at -60°, then added a solution of carane-diol (5) (1.7g, 10 mmol) in dichloromethane (30 ml) dropwise within 15 minutes and stirred for ½ hr. Trimethylamine (7.7 ml, 150 mmol) was added dropwise in five minutes. The cooling bath was removed and water (30 ml) was added at room temperature and stirred for 10 minutes . The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were washed with cold 1% aqueous hydrochloric acid, 5% aqueous sodium bicarbonate, water and with saturated brine solution. The ether extract was dried over anhydrous sodium sulfate and the solvent was removed to get a pale yellow oil (1.689 g) which was distilled to get colourless oil (1.310 g, 78.00%) b.p. 80-85°/4 mm (bath temp.). IR (liquid film): 3636, 3040, 1724, 1460, 1418, 1370, 1351, 1235, 1186, 1156, 1117, 1064, 1000, 990, 961, 943, 917, 806, 769 cm^{-1}. PMR (CCl_4,δ): 0.83 (s, 3H, $-CH_3$), 1.06 (s, 3H, $-CH_3$), 0.96-1.73 (m, 2H, cyclopropyl protons), 1.43 (s, 3H, $-CH_3$),

2.0-3.0 (m, 4H, $-CH_2$), 3.53 (broad s, 1H, -OH), $(\alpha)_D^{30}$= + 31.20° ($CHCl_3$, c, 2.413).

Analysis: Calcd. for $C_{10}H_{16}O_2$: C, 71.43; H, 9.52; observed C, 71.48; H, 9.70.

Furfurylidene derivative of 4-hydroxy-4,7,7-trimethyl bicyclo[4-1-0]heptan-3-one (11)

Ketol (10) (2.1 g, 12.5 mmol) was taken in ethanol (10 ml) and added aqueous sodium hydroxide solution (20%, 10 ml). This mixture was stirred for 5 minutes and freshly distilled furfuraldehyde (1.8 g, 18.75 mmol) was added to it. The reaction was stirred for 5 hrs at room temperature. It was diluted with ice-cold water and extracted with ether (3 x 25 ml). Ether extract was washed with water, dried over anhydrous sodium sulfate and solvent was removed to afford brown oil (2.56 g, 83.54%). It was purified by silica gel column chromatography using chloroform, pet.ether (1:3) as eluent to get yellow solid m.p.53-54°.

IR (Nujol): 3636, 3030, 1681, 1590, 1538, 1471, 1370, 1250, 1156, 1099, 1019, 990, 962, 943, 885, 811, 746, 704 cm^{-1}.

PMR (CCl_4, δ): 0.80 (s, 3H, $-CH_3$), 1.33 (s, 3H, $-CH_3$), 1.40 (s, 3H, $-CH_3$), 1.06 - 1.56 (m, 2H, cyclopropyl protons), 1.80-2.46 (m, 2H, $-CH_2$), 3.66 (s, 1H, -OH), 6.39 (m, 1H, aromatic), 6.56 (d, 1H, aromatic, J = 4 Hz), 7.33 (m, 2H, aromatic and olefinic protons).

Epoxidation of furfurylidene derivative (12)

A mixture of furfurylidene derivative (11) (2.46 g, 10 mmol), methanol (10 ml) and 30% hydrogen peroxide (2.85 ml, 30 mmol) was cooled to 15°C. Aqueous 6N sodium hydroxide (0.85 ml, 5 mmol) was added slowly without allowing the temperature to go above 20°C in about 20 minutes. The reaction was stirred at 20-25° for 5 hrs. and diluted with water (20 ml), extracted with ether (3 x 30 ml). The ether extract was washed with water and then with saturated brine solution, dried over anhydrous sodium sulfate and solvent was removed to get bronw coloured oil (12) (2.35 g, 90%).
IR (liq. film): 3571, 3012, 1724, 1667,1587, 1538, 1497, 1468, 1370, 1250, 1149, 1099, 1027, 988, 960, 885, 813, 746, 704 cm^{-1}.
PMR (CCl_4, δ): 0.60 (s, 3H, CH_3), 0.9 (s, 3H, $-CH_3$), 1.0 - 1.80 (m, 2H, cyclopropyl protons), 1.53 (s, 3H, $-CH_3$), 2.0 - 2.83 (m, 2H, $-CH_2$), 4.3 (s, 1H oxirane proton), 6.3 (m, 2H, aromatic), 7.36 (m, 1H, aromatic).

Methyl 1R-cis-2,2- dimethyl-3-(2-carbomethoxy-2-hydroxy-propyl)cyclopropanecarboxylate (13)

Epoxide (12) (10 g, 3.8 mmol) was taken in acetone (30 ml) and powdered potassium permanganate (1.8 g, 11.4 mmol) was added at 10-15° in about an hour. The mixture was stirred at this temperature for 3 hrs and then filtered through buchner funnel. The manganese dioxide

residue was extracted with hot water (3 x 15 ml) and the filtrate was cooled, acidified with 10% sulfuric acid, saturated with ammonium sulfate and extracted with ether (3 x 20 ml). The ether extract was washed with saturated brine solution and dried over anhydrous sodium sulfate. The solvent was removed to afford a thick brown oil 0.577 g (71%). It was characterized as dimethyl ester after purifying by silica gel column chromatography with 10% ethyl acetate in benzene as eluent.

IR (liq. film): 3509, 2985, 1724, 1667, 1587, 1429, 1370, 1266, 1236, 1205, 1176, 1124, 952, 886, 853, 758, 725 cm^{-1}.

PMR (CCl_4,δ): 1.10-1.63 (m, 2H, cyclopropyl protons), 1.17 (s, 6H, two /CH_3), 1.37 (s, 3H, -CH_3), 2.03 (d, 2H, -CH_2, J = 6 Hz), 3.33 (broad s, 1H, -OH), 3.66 (s, 3H, -OCH_3), 3.83 (s, 3H, -OCH_3)

$(\alpha)_D^{30}$ = - 10.18° ($CHCl_3$, c, 2.24).

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

Hydroxydicarboxylic acid (13) (850 mg, 3.9 mmol) was taken in water (5ml) and warmed it to 40°C. To this added a mixture of potassium permanganate (316 mg, 2 mmol), conc. sulfuric acid (300 mg, 3 mmol) and water (3 ml) dropwise and stirred at 40° for ½ hr. The temperature of the reaction was raised to 70° and kept at this temperature for 15 minutes. The clear solution was cooled

to $0^{o}C$, saturated with ammonium sulfate and extracted with ether (3 x 20 ml). The ether extract was washed with saturated brine solution and dried over anhydrous sodium sulfate. The solvent was removed to get a pale yellow oil 490 mg (73.24%) which was esterified with ethereal solution of diazomethane and distilled to get colourless oil (8) b.p.80-90^{o}/1 mm .

IR (liq. film): 3030, 1724, 1431, 1408, 1370, 1351, 1316, 1247, 1202, 1176, 1130, 1087, 1026, 962, 926, 855, 769, 725 cm^{-1}.

PMR (CCl_4,δ): 1.13 (s, 3H, $-CH_3$), 1.26 (s, 3H, $-CH_3$) 1.33-1.63 (m, 2H, cyclopropyl protons), 2.13 (s, 3H, $-COCH_3$), 2.86 (broad d, 2H, $-CH_2$, J = 6 Hz), 3.66 (s, 3H, $-OCH_3$).

$(\alpha)_D^{28}$ = -31.28^{o} ($CHCl_3$ c, 1.368).

Analysis: calculated for $C_{10}H_{16}O_3$: C, 65.21; H, 8.69;
observed C, 65.14; H, 8.71

α-Epoxycarane (17)

Trisodium phosphate (Na_3PO_4 12 H_2O) (68.4 g, 0.18 mol) was dissolved in hydrogen peroxide (30%, 150 ml) and a solution of (+)3-carene (12.0 g, 0.088 mol) and ethyl chloroformate (16.08 g, 0.148 mol) in methylene chloride (150 ml) was added gradually with stirring. The reaction was stirred at room temperature for 24 hrs. The organic layer was separated and the aqueous layer was extracted with methylene chloride (2 x 50 ml). The combined organic

extracts were washed with water, dried over anhydrous sodium sulfate and the solvent was removed at room temperature to afford a colourless oil 13.4 g (100%) b.p.90-108/18 mm (bath temp.).

IR (liq. film) : 2985, 1818, 1754, 1449, 1429, 1370, 1299, 1253, 1200, 1136, 1062, 1026, 990, 939, 840, 805, 762, 725 cm^{-1}.

PMR (CCl_4,δ):).43 (m, 2H, cyclopropyl protons), 0.7 (s, 3H, $-CH_3$), 1.10 (s, 3H, $-CH_3$), 1.16 (s, 3H, $-CH_3$), 1.23 - 2.46 (m, 4H, $-CH_2$), 2.6 (broad s, 1H, oxirane proton).

4-Thiophenyl-3,7,7-trimethylbicyclo[4-1-0]heptan-3-ol (23)

A homogeneous mixture of sodium hydroxide (3.36 g, 84 mmol), water (3 ml), thiophenol (8.58 g, 78 mmol), α-epoxycarane (17) (9.12 g, 60 mmol) in ethanol was refluxed for four hours under nitrogen. Ethanol was removed and extractive work up with ether gave a brown oil, which on distillation gave (23) as pale yellow oil (11.8 g, 76%) b.p.180/190°/1 mm (bath temp.).

IR (liq. film): 3663, 2985, 1587, 1471, 1449, 1429, 1370, 1230, 1130, 1111, 1081, 1064, 1020, 1005, 943, 917, 870, 840, 730, 690 cm^{-1}.

PMR (CCl_4,δ): 0.56 - 0.93 (m, 2H, cyclopropyl protons), 1.0 (s, 6H, $-CH_3$), 1.23 (s, 3H, $-CH_3$), 1.63 - 2.5 (m, 5H, $-CH_2$ and -OH), 3.26 (dd, 1H, -CH-S, J = 6, 9 Hz), 7.4 (m, 5H, aromatic).

$(\alpha)_D^{30}$ = + 73.6° ($CHCl_3$, c, 2.26).

Analysis: Calculated for $C_{16}H_{22}OS$: C, 73.28; H, 8.39;
S, 12.21; observed C, 73.07; H, 8.42; S, 11.81.

4-Sulfoxyphenyl-3,7,7-trimethylbicyclo[4-1-0]heptan-3-ol (24)

A solution of hydroxysulfide (23) (9.19 g, 35 mmol) in methanol was treated with hydrogen peroxide (30%, 12 ml, 0.105 mol) at room temperature for four hours. Extractive work up with ethyl acetate after dilution with water gave white solid (9.67 g, 100%) m.p. 130-135°.

IR (Nujol): 3571, 3030, 1639, 1471, 1449, 1379, 1307, 1235, 1143, 1087, 1070, 1020, 1000, 926, 877, 840, 752, 717 cm^{-1}.

PMR(CCl_4,δ): 0.4 - 0.83 (m, 2H, cyclopropyl protons) 0.9 (s, 3H, $-CH_3$), 0.96 (s, 3H, $-CH_3$), 1.03 - 2.33 (m, 4H, $-CH_2$), 1.56 (s, 3H, $-CH_3$), 2.43 - 3.0 (m, 1H, -CH-S-O), 3.73 (broad s, 1H, -OH), 7.16 - 8.03 (m, 5H, aromatic).

Analysis: Calculated for $C_{16}H_{22}O_2S$: C, 69.07; H, 7.91;
S, 11.51; observed C, 68.58; H, 7.96; S, 11.17.

3,7,7-Trimethyl bicyclo[4-1-0]hept-4-ene-3-ol (14)

Hydroxy sulfoxide (24) (9.0 g, 32.3 mmol) was mixed thoroughly with anhydrous potassium carbonate (6 g, 43.48 mmol) in a round bottom flask and heated at 160-180° in an oil bath at 12 mm for 1 hour with a distillation assembly attached. The receiver was cooled in an ice-salt bath. The distillate (4.428 g, 90%) was pure (14).

IR (liq. film): 3509, 3030, 1639, 1449, 1370, 1212, 1163, 1124, 1099, 1064, 985, 957, 935, 910, 851, 837, 794, 733, 709 cm^{-1}.

PMR (CCl_4, δ): 0.86 (s, 3H, $-CH_3$), 0.93-1.26 (m, 1H, cyclopropyl proton), 1.1 (s, 6H, $-CH_3$), 1.46 (d, 1H, cyclopropyl proton, J = 4 Hz), 1.66-2.30 (m, 2H, $-CH_2$), 1.66 broad s, 1H, -OH), 5.73 (s, 2H, olefinic).

$(\alpha)_D^{28} = -271^o$ (benzene c, 4.82) (HPLC- pure).

Reported[14] $(\alpha)_D^{20} = -289$ (benzene c, 3.6).

Analysis: Calculated for $C_{10}H_{16}O$: C, 78.96; H, 10.77;
observed C, 78.96; H, 10.70.

Methyl 1R-cis-2,2-dimethyl-3-(2-carbomethoxy-2-hydroxy propyl)-cyclopropanecarboxylate (25)

A mixture of alcohol (14 (2.0 g, 13 mmol), acetone (50 ml) and potassium carbonate (0.1 g) was cooled to 0^oC and powdered potassium permanganate (4.1 g, 26 mmol) was added portion wise over 2 hours at $0-5^oC$. The mixture was stirred at this temperature for 3 hours. The manganese dioxide residue was filtered through buchner funnel and the precipitate was washed with acetone. The residue was extracted with hot water (3 x 20 ml). The aqueous extract was cooled and acidified with 10% sulfuric acid, saturated with ammonium sulfate and extracted with ether (3 x 30 ml). The ether extract was washed with saturated brine solution, dried over anhydrous sodium sulfate and solvent was removed to get a thick pale yellow oil (1.76 g, 59.8%). It was esterified with diazomethane and purified by silica gel column chromatography using 10% ethyl acetate in benzene eluent.

IR (liq. film): 3636, 3030, 1730, 1439, 1377, 1318, 1274, 1242, 1217, 1176, 1108, 1080, 1053, 1000, 976, 952, 885, 855, 833, 787, 758 cm^{-1}.

PMR (CCl_4, δ): 1.03-1.53 (m, 2H, cyclopropyl proton), 1.20 (s, 6H, two $-CH_3$), 1.37 (s, 3H, $-CH_3$), 2.03 (dd, 2H, $-CH_2$, J = 6, 2 Hz), 3.13 (broad s, 1H, -OH), 3.63 (s, 3H,$-OCH_3$), 3.77 (s, 3H, $-OCH_3$).

$(\alpha)_D^{30} = -1.84^o$ ($CHCl_3$, c, 0.870).

Analysis: calculated for $C_{12}H_{20}O_5$: C, 59.01; H, 8.19; observed C, 58,78; H, 8.53.

δ-Lactone of 1R cis-2,2-dimethyl-3-(2-carbomethoxy-2-hydroxy propyl)cyclopropanecarboxylic acid (29)

Hydroxy dicarboxylic acid (25, R=H) (500 mg) was refluxed in benzene, with p-toluene sulfonic acid as catalyst, for 3 hrs. The mixture was cooled and washsed with water, dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to get white solid (400 mg) which was recrystallized from ether-pet.ether mixture to get 28 as white needles m.p.175-76. It was esterified with diazomethane to get (29) as white needles m.p.85-86^o.

IR (Nujol): 2985, 1730, 1449, 1370, 1333, 1316, 1279, 1258, 1235, 1163, 1117, 1075, 1053, 1015, 990, 962, 825, 806, 752 cm^{-1}.

PMR (CCl_4, δ): 1.1 (s, 3H, $-CH_3$), 1.26 (s, 3H, $-CH_3$), 1.3 - 1.56 (m, 2H, cyclopropyl protons), 1.63 (s, 3H, $-CH_3$), 1.73 - 2.23 (m, 2H, $-CH_2$), 3.8 (s, 3H $-OCH_3$).

2-Oximino-4-hydroxy-4,7,7-trimethyl bicyclo [4-1-0] heptan-3-one (30)

Potassium metal (12.5 g, 0.32 mol) was dissolved in dry t-butanol (375 ml) and ketol (10) (20.0 g, 0.119 mol) was added dropwise with stirring. The mixture was stirred at room temperature for ½ hr. Isoamyl nitrite (25 g, 0.213 mol) was added in one lot and stirred at room temperature for 1 hr. A second lot of isoamyl nitrite (25 g, 0.213 mol) was added and stirred for 2 hrs. Crushed ice (300 g) was added to the reaction mixture, stirred for 10 minutes and extracted with ether (2 x 200 ml). The aqueous layer was cooled and acidified with 1:1 sulfuric acid and extracted with ether (3 x 350 ml). The ether extract was washed with saturated brine solution, dried over anhydrous sodium sulfate and solvent was removed to get a thick brown oil (20 g, 85.2%), 1.4 g of the crude product was purified by silica gel column chromatography using 20% ethyl acetate in benzene as eluent, to get pale yellow solid, recrystallised from ether-pet.ether mixture to get white needles m.p.175-176°.

IR (Nujol): 3333, 2941, 1706, 1587, 1431, 1364, 1316, 1290, 1266, 1235, 1198, 1149, 1136, 1096, 1053, 1040, 1010, 967, 943, 926, 880, 843, 778, 752, 719 cm^{-1}.

PMR ($CDCl_3$, δ): 0.90 (s, 3H, $-CH_3$), 1.1-1.7 (m, 2H, cyclopropyl protons), 1.26 (s, 3H, $-CH_3$), 1.46 (s, 3H,$-CH_3$), 1.76 (broad s, 1H, -OH), 1.96-2.7 (m, 2H, $-CH_2$).

$(\alpha)_D^{30}$ = + 37.5° ($CHCl_3$ c, 0.820).

Analysis: Calculated for $C_{10}H_{15}NO_3$: C, 61.22; H, 7.90; N, 7.47 observed C, 60.91; H, 7.68; N, 7.10.

The crude oxime was used as such for further reaction.

1-Cyano-2,2-dimethyl-3-cis-(2-carbomethoxy-2-hydroxy-propyl)cyclopropane (31)

To a mixture of oxime (30) (9.3 g, 47.2 mmol), dioxane (270 ml) and water (45.6 ml), 3N sodium hydroxide (141 ml) was added dropwise below 40° under nitrogen atmosphere. p-Toluene sulfonyl chloride (29.7 g, 0.156 mol) was added portionwise without allowing the temperature to go above 40° in about 25 minutes. The mixture was stirred for 2 hrs. at 50° and the solvent was removed at room temperature under reduced pressure (1 mm). Cold water (75 ml) was added to the residue and extracted with ether (100 ml). The aqueous layer was cooled and acidified with 10% sulfuric acid, saturated with ammonium sulfate. Inorganic salts separated out were removed by filtration and washed with ether. The filtrate was extracted with ether (3 x 100 ml). The combined ether extracts were washed with saturated brine solution, dried over anhydrous sodium sulfate and solvent was

distilled off to afford brown oil (4.0 g, 43.2%) which was esterified with diazomethane and distilled to get pale yellow oil b.p.140-150°/2 mm (bath temp.). Analytical sample was prepared by silica gel column chromatography using 5% ethyl acetate in benzene as eluent.

IR (liq. film): 3571, 3030, 2268, 1727, 1449, 1379, 1244, 1204, 1124, 962, 886, 803, 762 cm^{-1}.

PMR (CCl_4, δ): 1.26-1.56 (m, 2H, cyclopropyl protons), 1.27 (s, 6H, $-CH_3$), 1.57 (s, 3H, $-CH_3$), 1.76-2.10 (m, 2H, $-CH_2$), 3.30 (broad s, 1H, -OH), 4.07 (s, 3H, $-OCH_3$).

$(\alpha)_D^{28}$ = -4° ($CHCl_3$, c, 2.04).

Analysis: Calculated for $C_{11}H_{17}NO_3$: C, 62.55; H, 8.05; N, 6.63; observed C, 62.32; H, 8.15; N, 6.32.

Methyl 1R-cis -2,2-dimethyl-3-(2-carbomethoxy-2-hydroxy propyl)cyclopropanecarboxylate (13)

To the mixture of potassium hydroxide (3.4 g, 60 mmol), water (10 ml) and ethanol (10 ml) was added nitrile ester (31) (1.0 g, 4.7 mmol). The clear solution was refluxed in an oil-bath for 24 hrs. Ethanol was removed under reduced pressure, the residue was cooled, acidified with 10% sulfuric acid, saturated with ammonium sulfate and extracted with ether (3 x 15 ml). The ether extract was washed with saturated brine solution and dried over anhydrous sodium sulfate. The solvent was removed to get a thick oil (0.9 g, 87.59%) which was esterified with

with diazomethane and purified by silica gel column chromatography using 10% ethyl acetate in benzene as eluent. Spectral data: Idential with that of authentic.

1R-cis-2,2-Dimethyl-3-(2-carbomethoxy-2-hydroxy propyl)-cyclopropanecarboxylic acid amide (32)

To a mixture of nitrile ester (31) (1.0 g, 4.7 mmol) hydrogenperoxide (30%, 8ml) and ethanol (12 ml) was added 6N potassium hydroxide (8 ml, 48 mmol) below 40°C within 15 minutes. The mixture was stirred at 50° for 3 hrs. and then at room temperature for 24 hrs. Ethanol was removed under vacuum and the aqueous residue was extracted with ether. The aqueous layer was cooled and acidified with 10% sulfuric acid, saturated with ammonium sulfate and extracted with ether (3 x 20 ml). The solvent was removed to afford white solid (622 mg) which was esterified with diazomethane to get white solid amide ester (32) (601 mg, 55.11%), m.p. 112°C.

IR (Nujol): 3446, 3030, 1751, 1667, 1613, 1460, 1379, 1307, 1206, 1163, 1122, 1075, 971, 893, 847. 833, 823, 806, 752 cm^{-1}.

PMR ($CDCl_3$, δ): 0.80 - 1.36 (m, 2H, cyclopropyl protons), 1.13 (s, 6H, two $-CH_3$), 1.46 (s, 3H, $-CH_3$), 2.13 (d, 2H, $-CH_2$, J = 6 Hz), 3.22 (s, 2H, $-NH_2$), 3.86 (s, 3H, $-OCH_3$), 5.9 (broad s, 1H, -OH).

$(\alpha)_D^{30}$ = 1.66° ($CHCl_3$, c, 2.46).

Analysis: Calculated for $C_{11}H_{19}O_4N$; C, 57.64; H, 8.24; N, 6.11; observed C, 57.34; H, 8.60; N, 6.01.

Methyl 1R-*cis*-2,2-dimethyl-3-(2-carbomethoxy-2-hydroxy propyl)cyclopropanecarboxylate (13)

Amide (32) (200 mg, 0.873 mmol) was taken in ethanol (2 ml) and 30% potassium hydroxide solution (2 ml) was added to it. The mixture was refluxed for 22 hrs. Ethanol was removed under vacuum and the residue was diluted with cold water (2 ml) and extracted with ether (10 ml). The aqueous layer was cooled and acidified with 10% sulfuric acid, saturated with ammonium sulfate and extracted with ether (3 x 15 ml). The ether extract was washed with saturated brine solution, dried over anhydrous sodium sulfate and solvent was distilled off to afford a thick oil (144 mg, 76.3%). It was esterified with diazomethane and characterized as (13) by IR and PMR spectra.

REFERENCES

1. L. M. Elliott, Synthetic Pyrethroids, ACS Symposium Series 42, 2 (1977).
2. M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham, D.A. Pulman, Nature, 246, 169 (1973).
3. M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham, D.A. Pulman, Nature, 248, 710 (1974).
4. R.B. Mitra, G.H. Kulkarni, K.G. Gore, A.S. Khanra, Z. Muljiani, P.N. Chaudhari, B.M. Bhawal, G.D. Joshi, P.N. Khanna, Brit., U.K. Patent Appl. 2,034,301 (1980), Indian Appl. 761/DEL/78, C.A. 94, 65195 (1981).
5. C.K. Atal, B.M. Kapur, Cultivation and utilization of aromatic plants, 349 (1982).
6. J.E. Powell, US. 4,225,612 (1980), Shell Oil Co.,Appl. 76,022 (1979), C.A. 94, 84095 (1981).
7. M. Matsui, H. Yoshioka, Y. Yamada, H. Sakamoto and T. Kitahara, Agric.Biol.Chem., 29, 784 (1965).
8. A.S. Khanra, R.B. Mitra, Indian J.Chem., 14B , 716 (1976).
9. H. Schmidt, P. Richter, M. Muehlstaedt, Ber., 96(10) , 2636 (1963).
10. M.S. Carson, W. Cocker, D.H. Grayson and P.V.R. Shannon, J.Chem.Soc.(C), 2220 (1969).
11. R.B. Mitra, A.S. Khanra, A.R.A.S. Deshmukh, Indian J.Chem., 20B, 436 (1981).
12. A.J. Mancuso, S.L. Huang, D. Swern, J.Org.Chem., 43, 2480 (1978).
13. J.L. Simonsen, M.G. Rau, J.Chem.Soc., 123, 549 (1923).
14. K. Gollnick, S. Schroeter, G. Ohloff, G. Schade, G.O. Schenck, Justus Leibigs Ann.Chem., 687, 14 (1965).

15. H. Kuczynski and A. Zabza, Rocz.Chem. 35. 1621 (1961).

16. A. Uzarewicz and E. Zientek, Rocz.Chem., 51, 181 (1977).

17. H. Kuczynski and K. Marks, Rocz.Chem., 43, 943 (1969).

18. R.D. Bach, M.W. Klein, R.A. Ryntz, J.W. Holbuka, J.Org.Chem., 44(14), 2569 (1979).

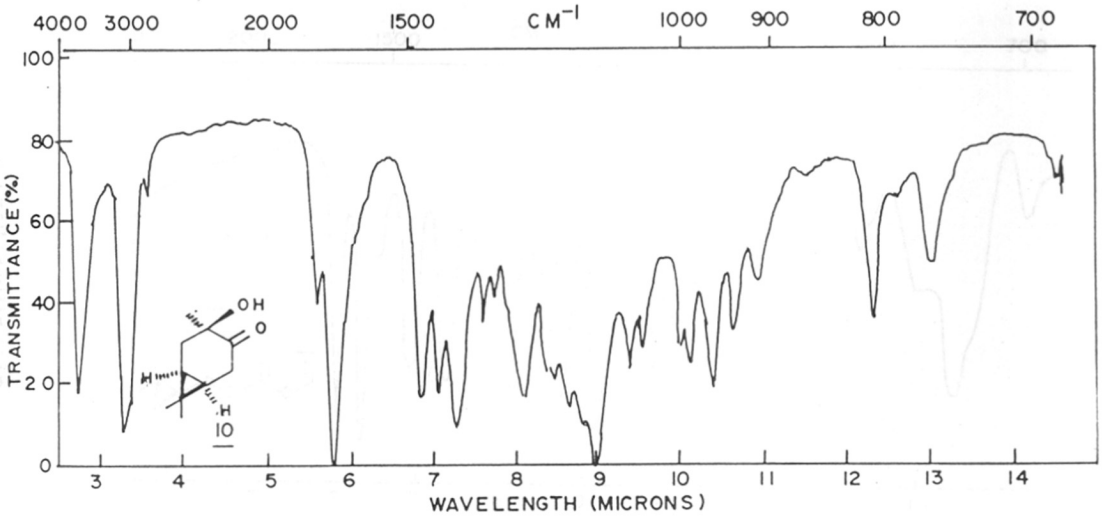
19. J. Drabowicz and M. Mikoajczyk, Synth.Commun., 11(12), 1025 (1981).

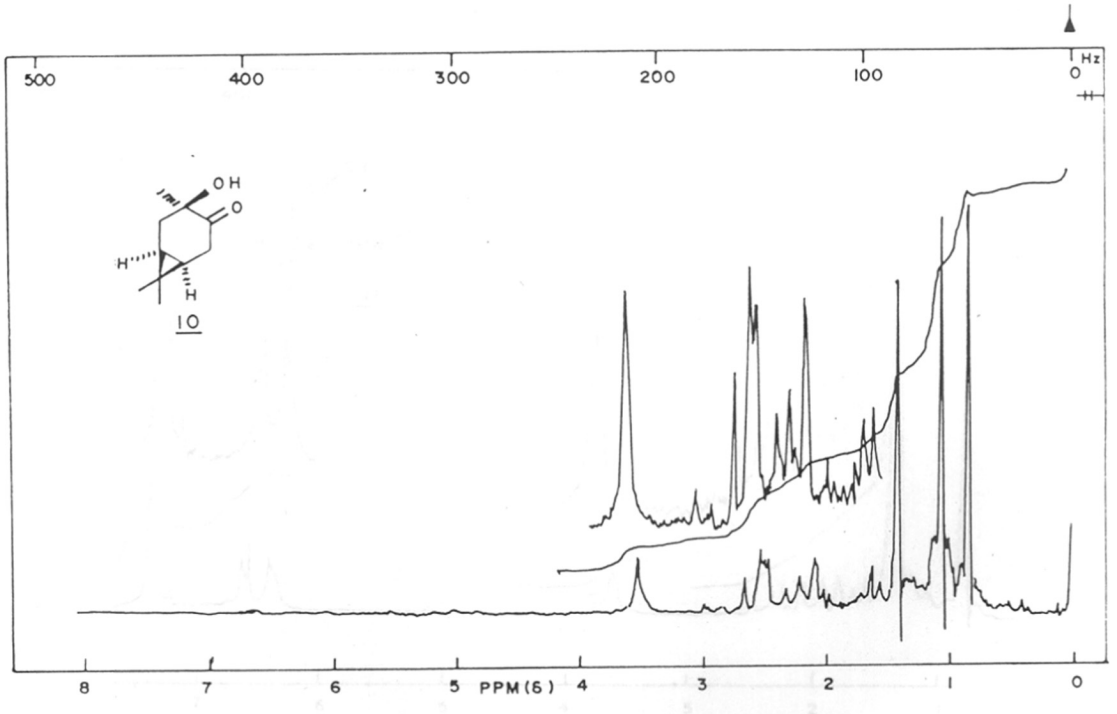
20. Yu. P. Volkov, L.N. Khachaturyan, Zh.Obshch.Khim., 37, 2358 (1967), C.A. 69, 10549 (1968).

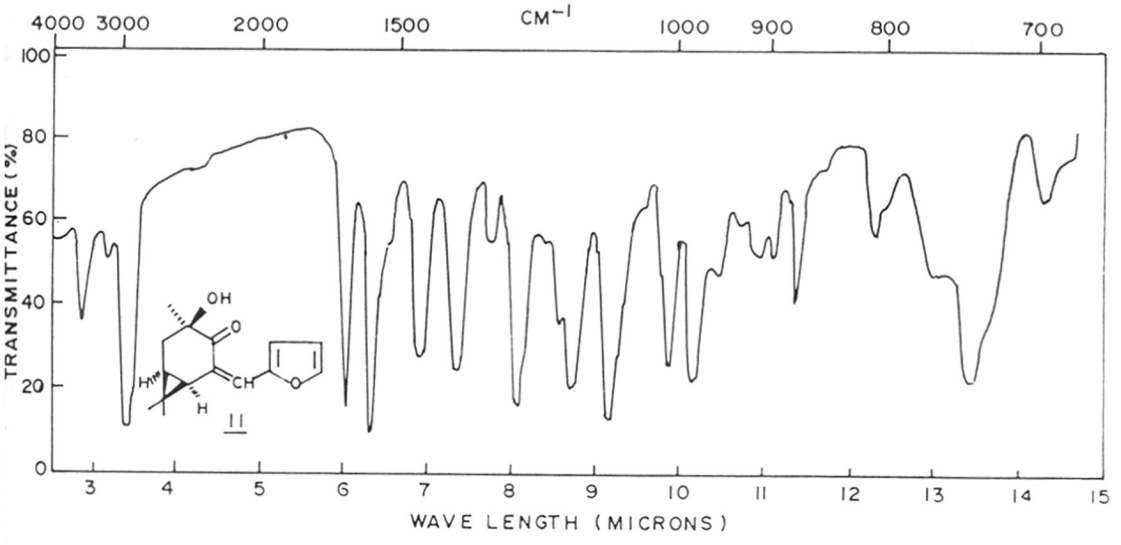
21. A. Hassner, I.H. Pomerantz, J.Org.Chem., 27, 1760 (1962).

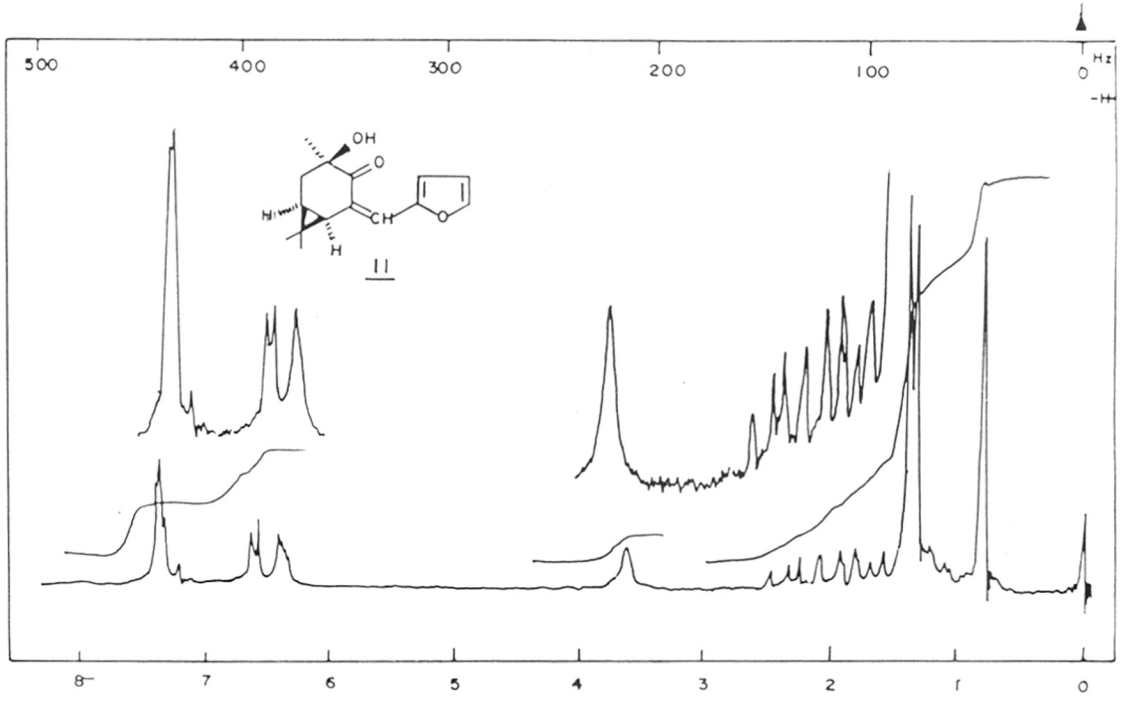
22. R.R. Sauers and G.P. Ahearn, J.Am.Chem.Soc., 83, 2759 (1961).

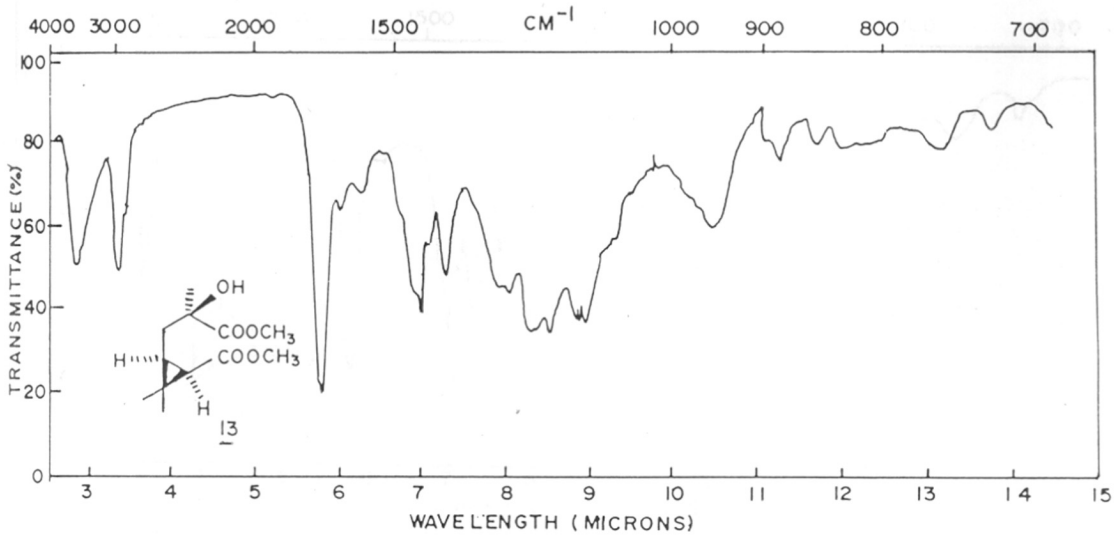
23. C.R. Noller, Org.Synth.Coll.Vol. 2, 586 (1943).

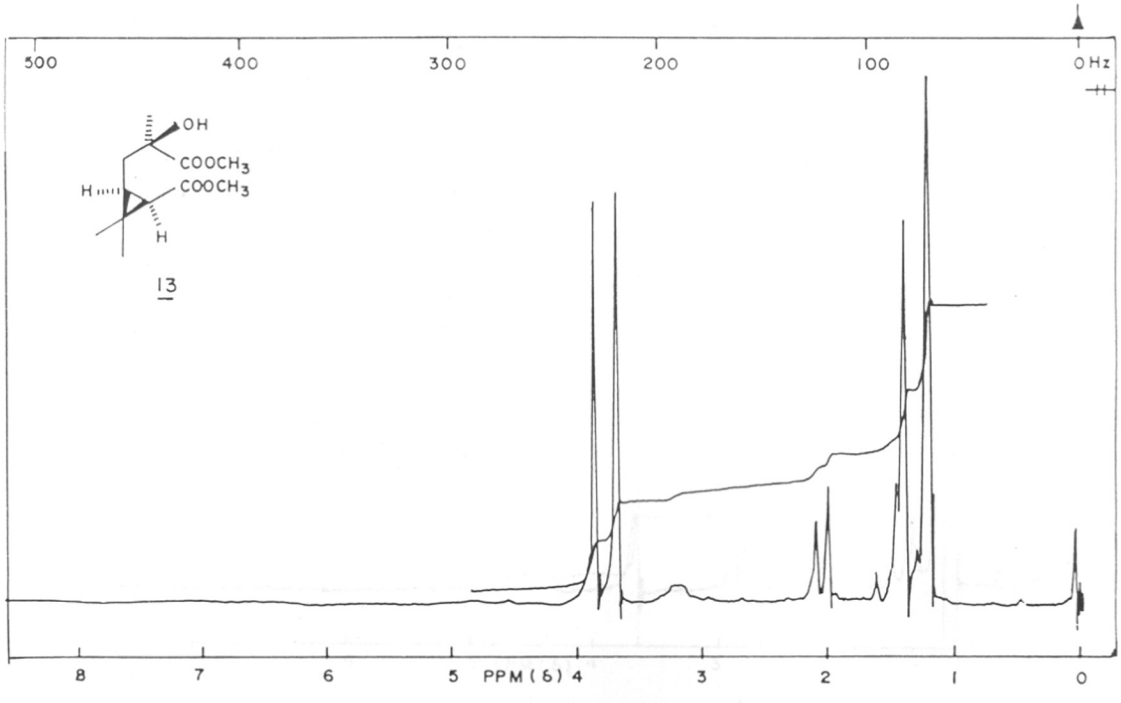

4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
OH
O
H
H
10
3 4 5 6 7 8 9 10 11 12 13 14
WAVELENGTH (MICRONS)

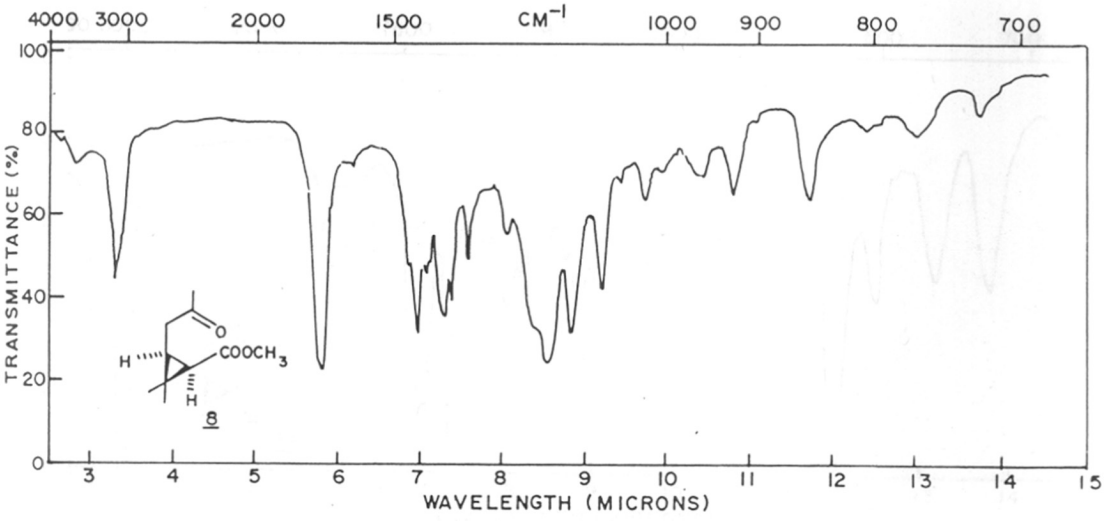

500 400 300 200 100 0 Hz
OH
O
H
H
10
8 7 6 5 PPM(δ) 4 3 2 1 0

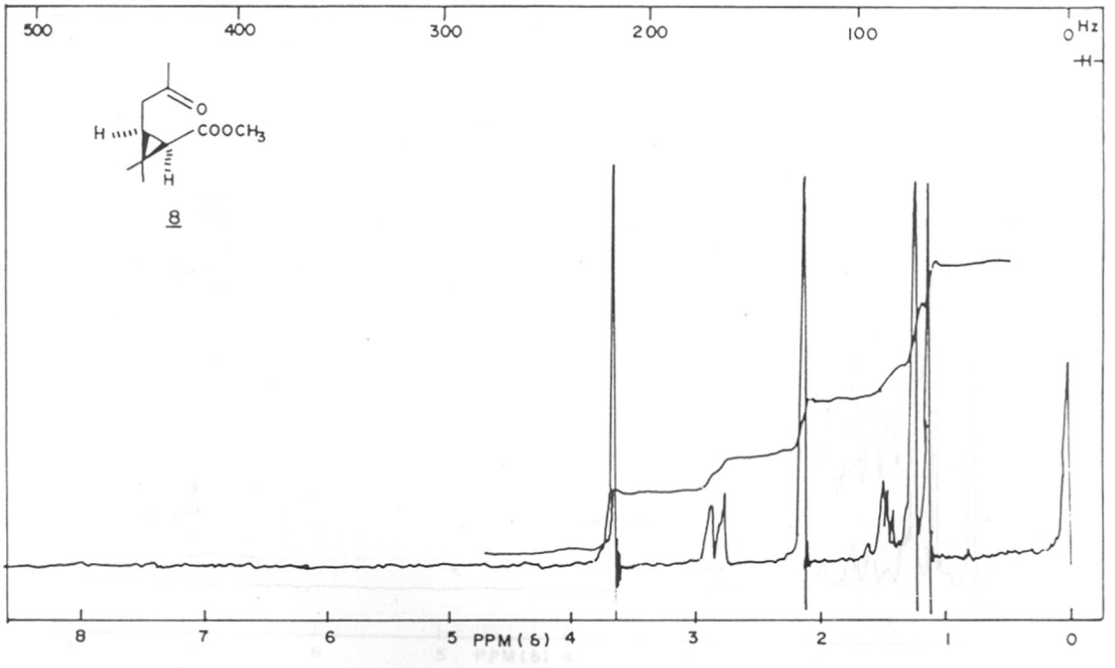

4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
OH
O
H
H
CH
O
II
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVE LENGTH (MICRONS)

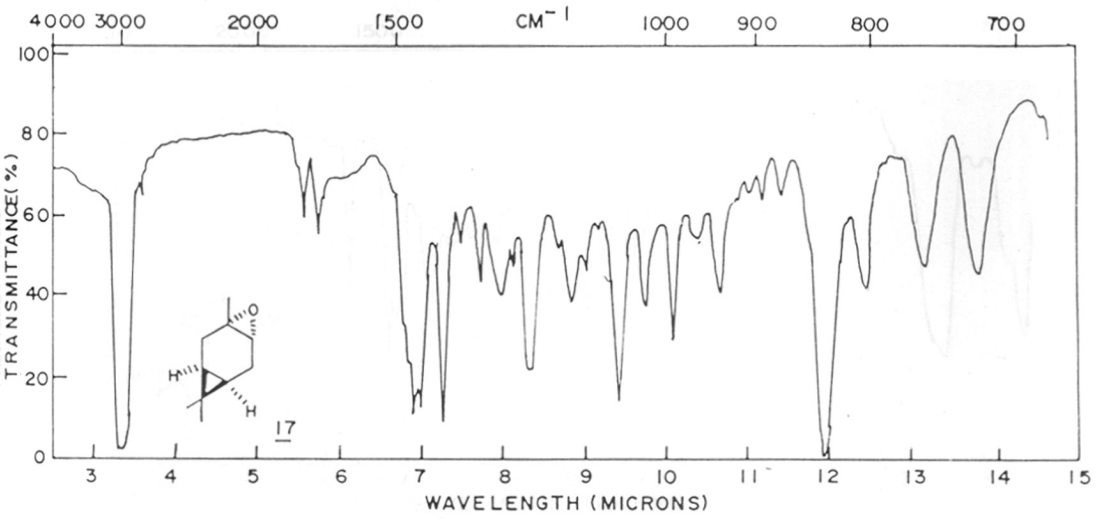

500 400 300 200 100 0 Hz
OH
O
H
H
CH
O
II
8 7 6 5 4 3 2 1 0

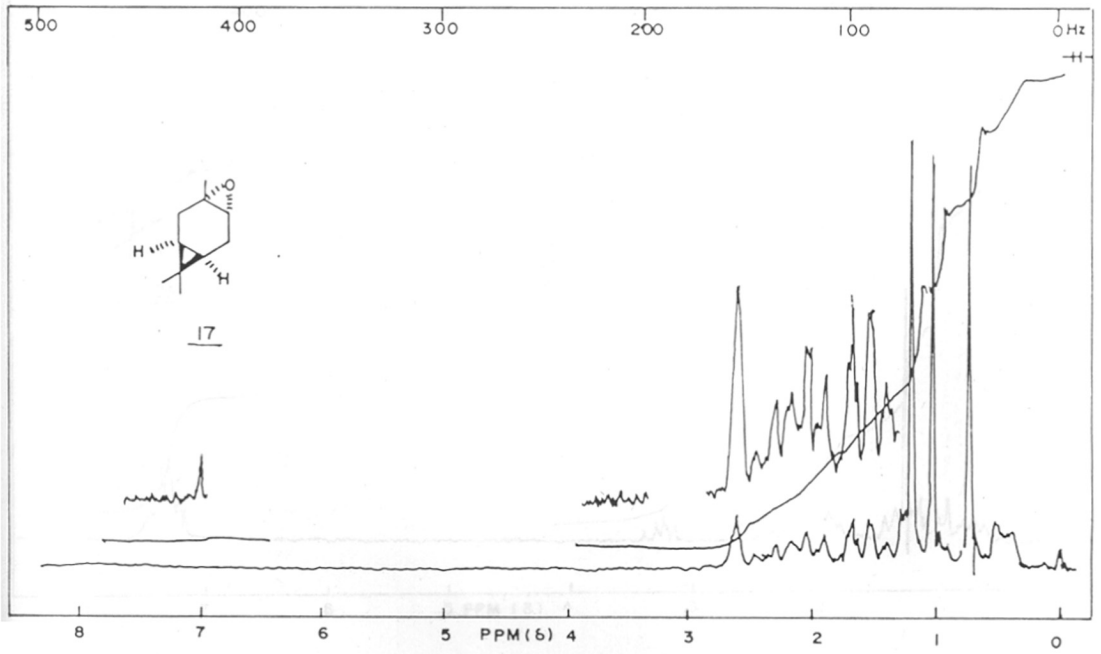

4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
OH
COOCH3
COOCH3
H
H
13
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVE LENGTH (MICRONS)

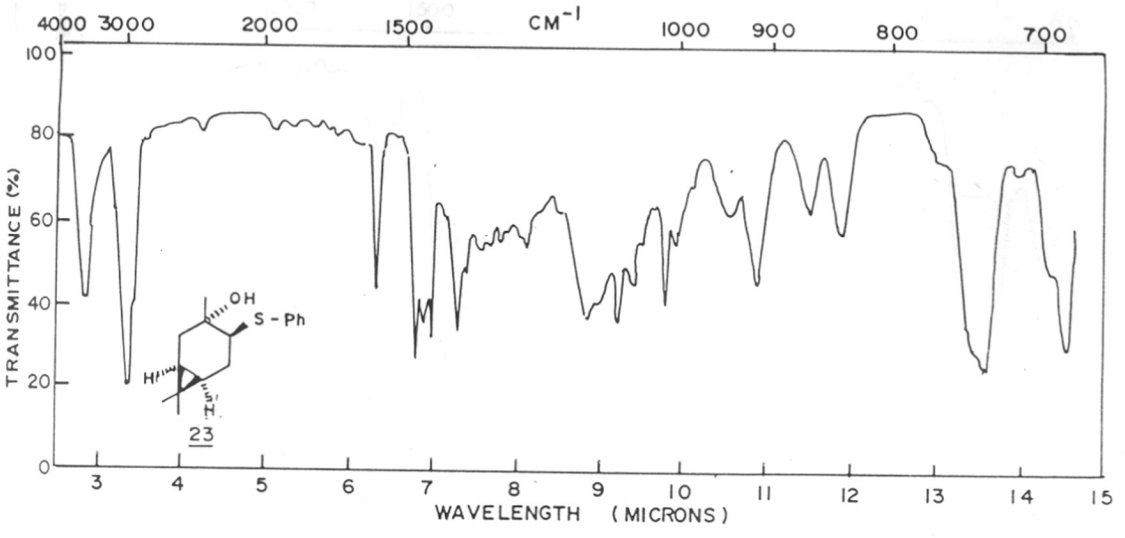

500 400 300 200 100 0 Hz
OH
COOCH3
COOCH3
H
H
13
8 7 6 5 PPM (δ) 4 3 2 1 0

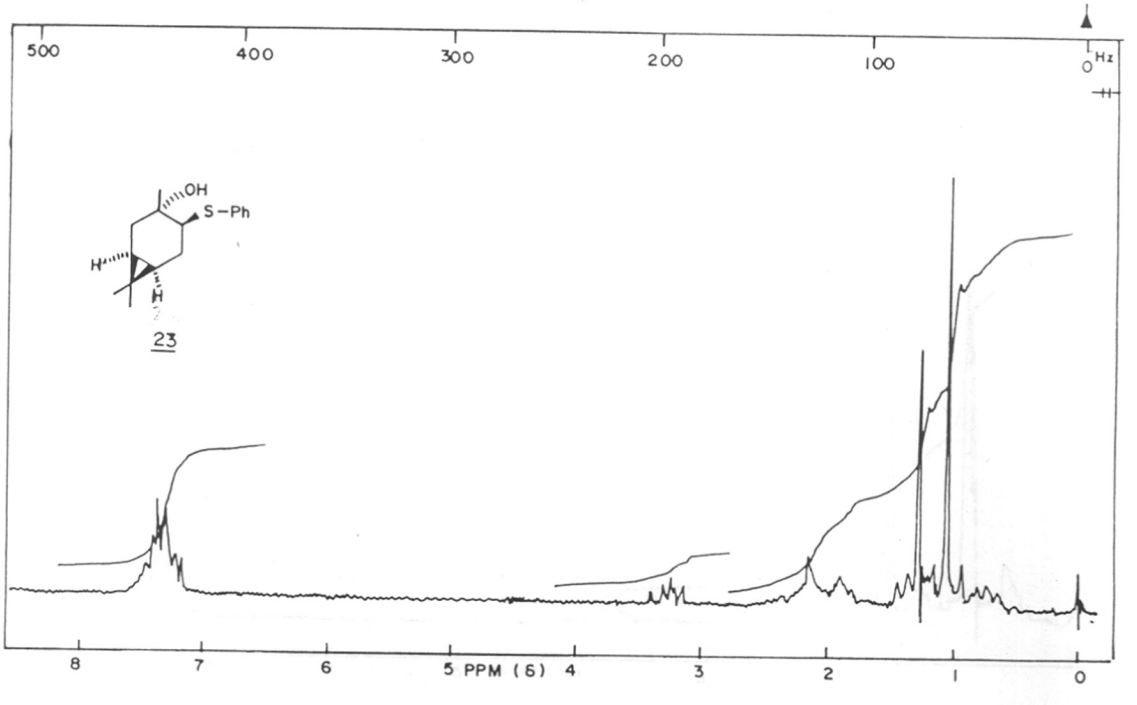

4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
O
H
COOCH3
H
8

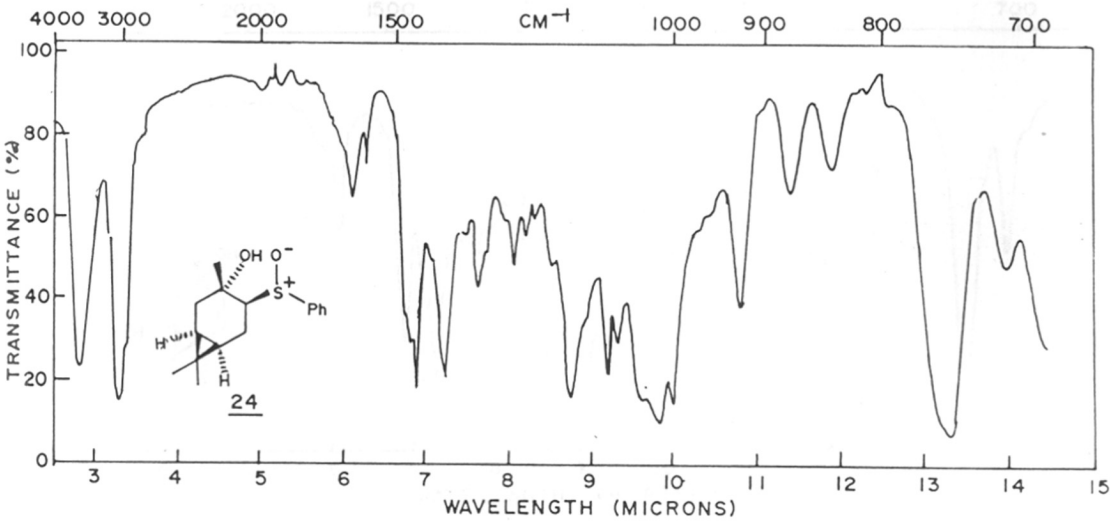

500 400 300 200 100 0 Hz
O
H
COOCH3
H
8
8 7 6 5 PPM (δ) 4 3 2 1 0

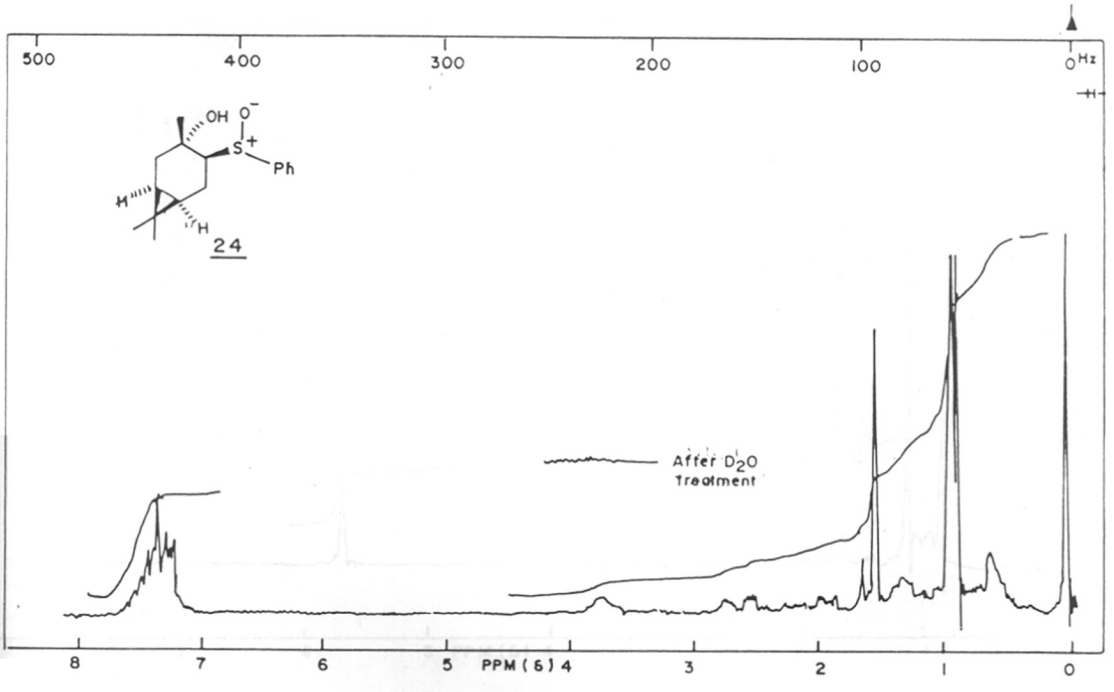

4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
O
H
H
17

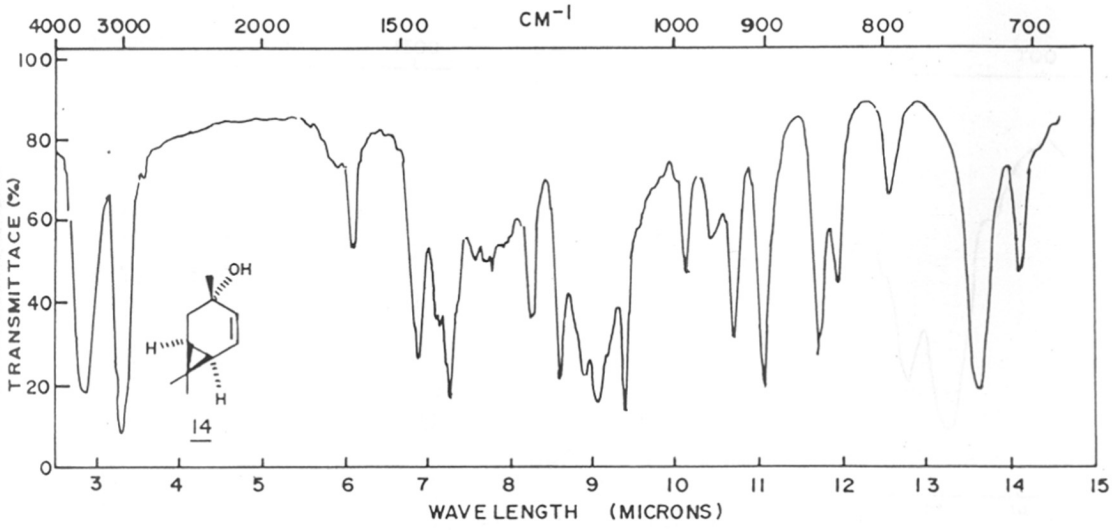

500 400 300 200 100 0 Hz
O
H
H
17
8 7 6 5 PPM(δ) 4 3 2 1 0

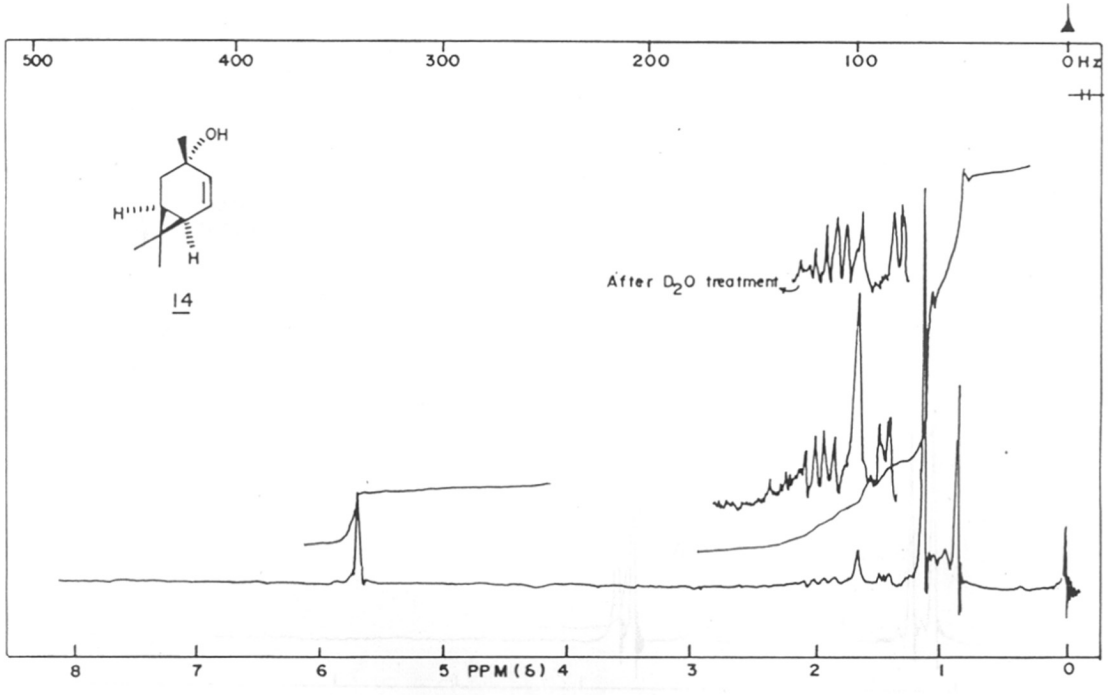

4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
OH
S - Ph
H
H
23
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

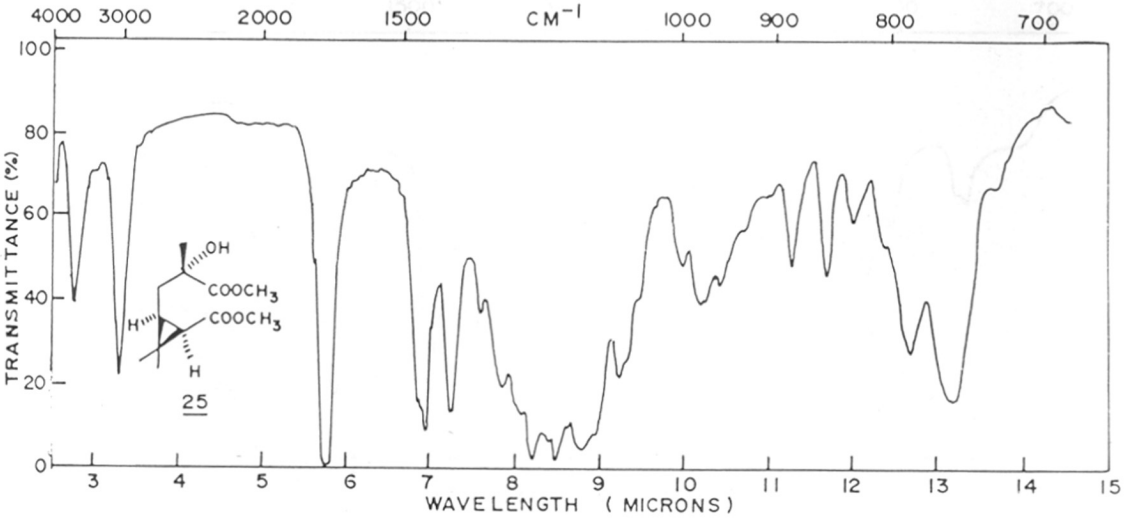

500 400 300 200 100 0 Hz
OH
S-Ph
H
H
23
8 7 6 5 PPM (δ) 4 3 2 1 0

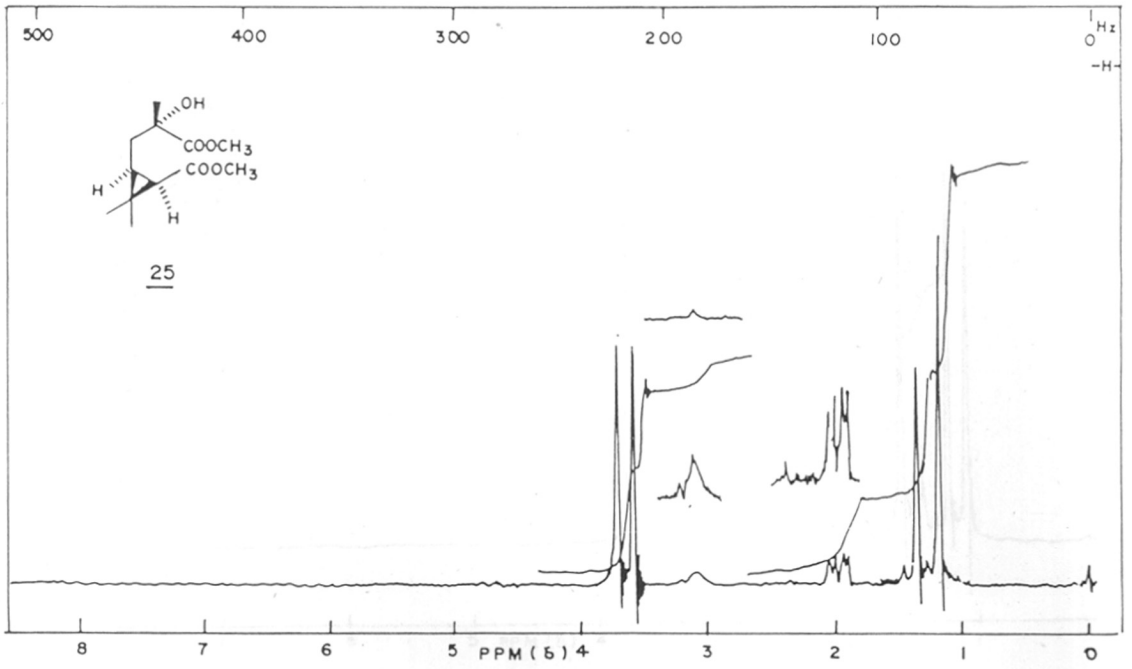

4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
OH O⁻
S⁺
Ph
H
H
24
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

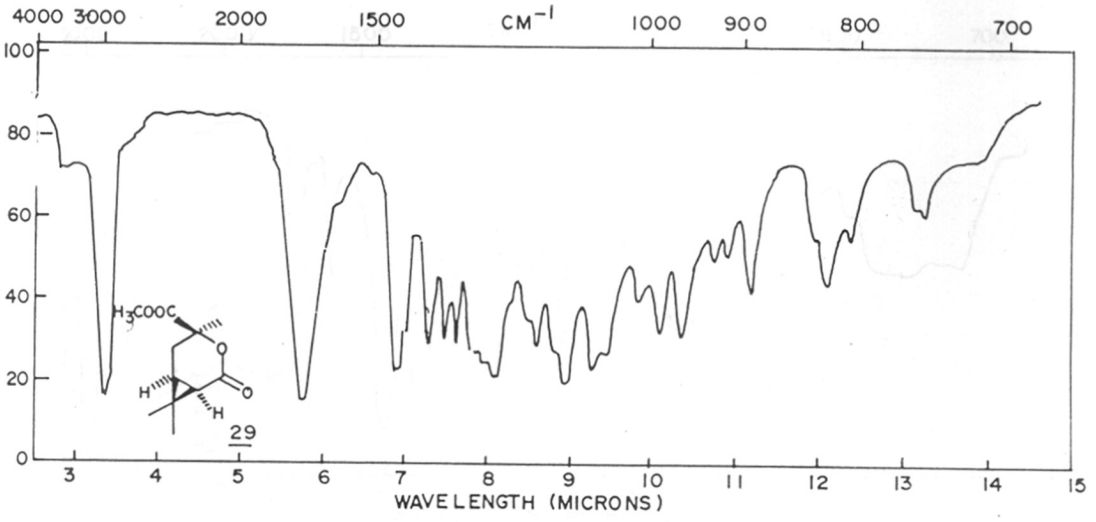

500 400 300 200 100 0 Hz
OH O⁻
S⁺
Ph
H
H
24
After D2O Treatment
8 7 6 5 PPM (δ) 4 3 2 1 0

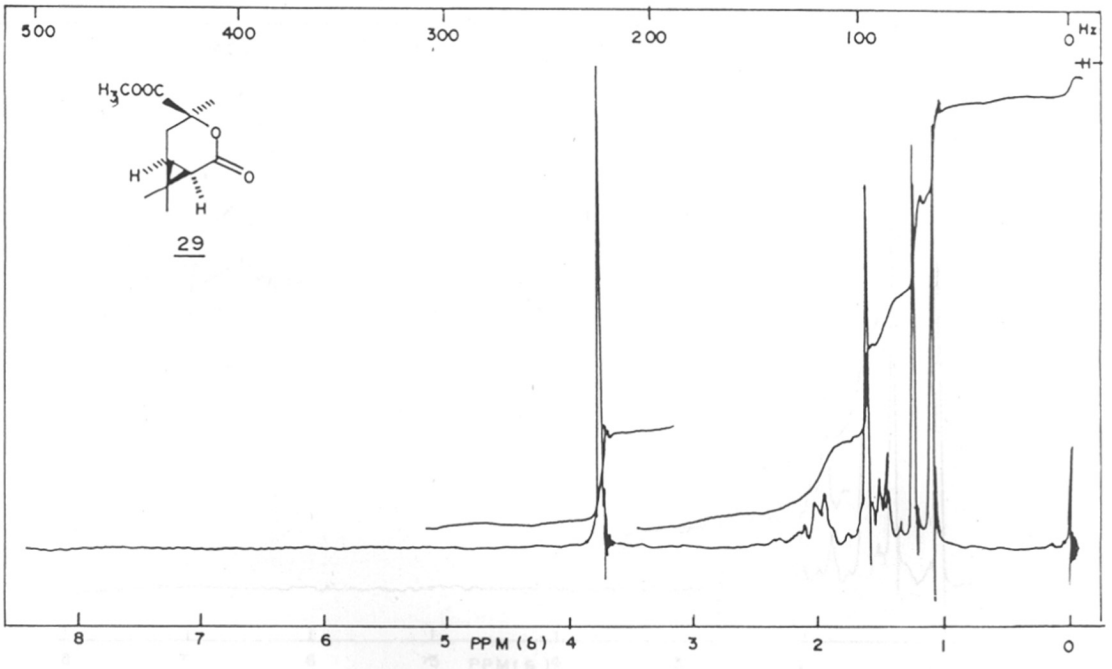

4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTACE (%)
OH
H
H
14
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVE LENGTH (MICRONS)

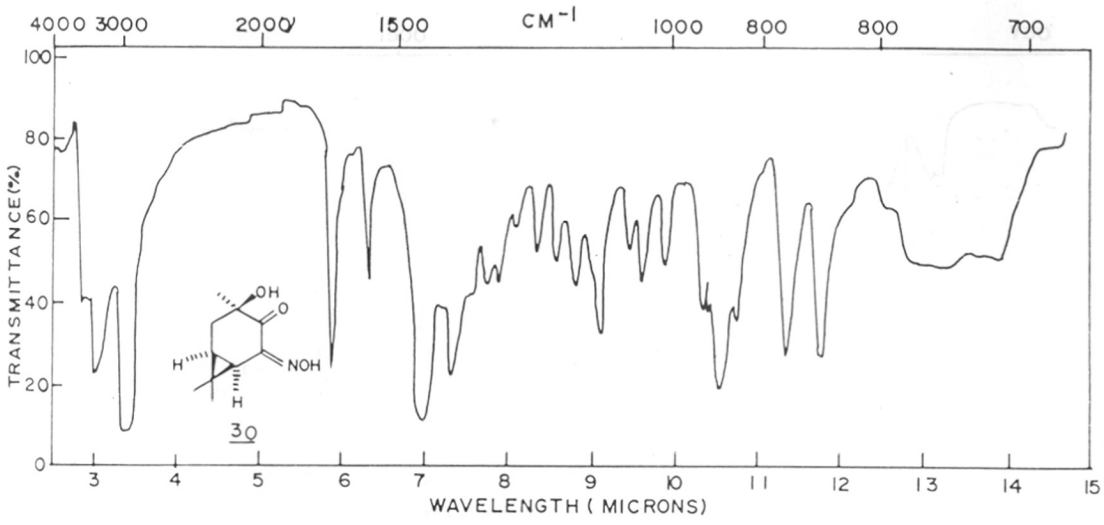

500 400 300 200 100 0 Hz
OH
H
H
14
After D2O treatment
8 7 6 5 PPM (δ) 4 3 2 1 0

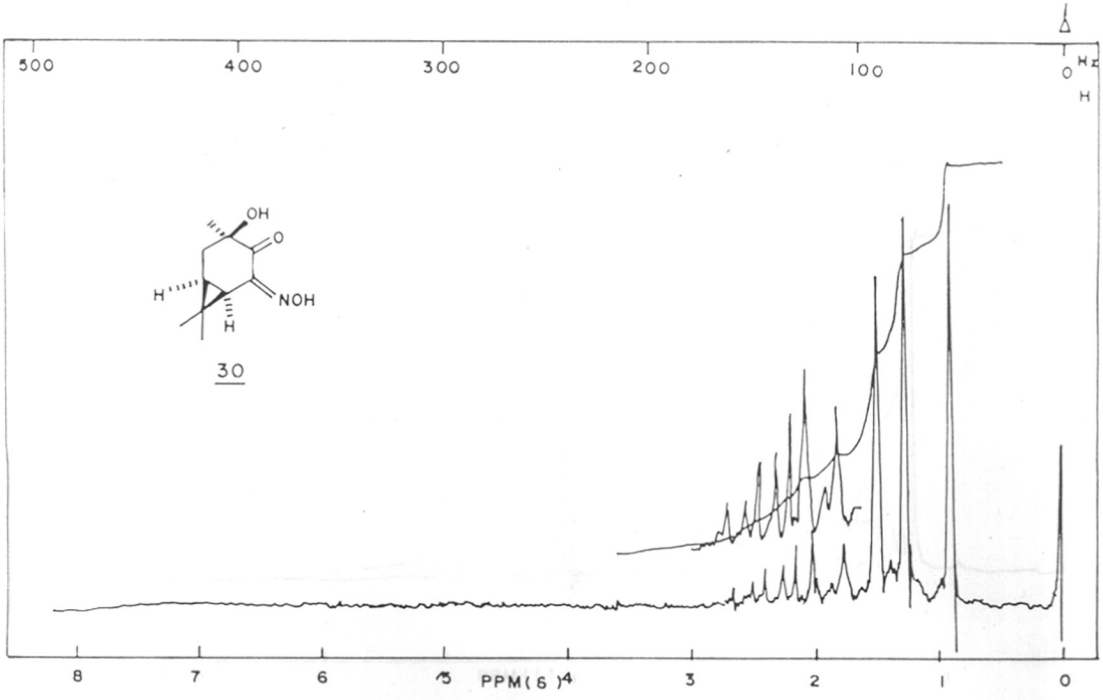

4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
OH
COOCH3
COOCH3
H
H
25
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

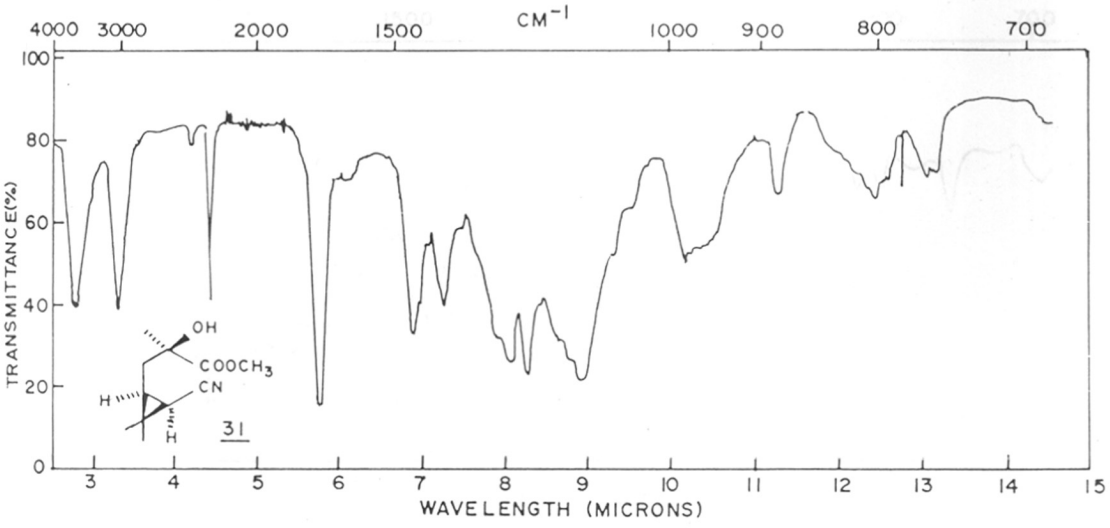

500 400 300 200 100 0 Hz
OH
COOCH3
COOCH3
H
H
25
8 7 6 5 PPM (δ) 4 3 2 1 0

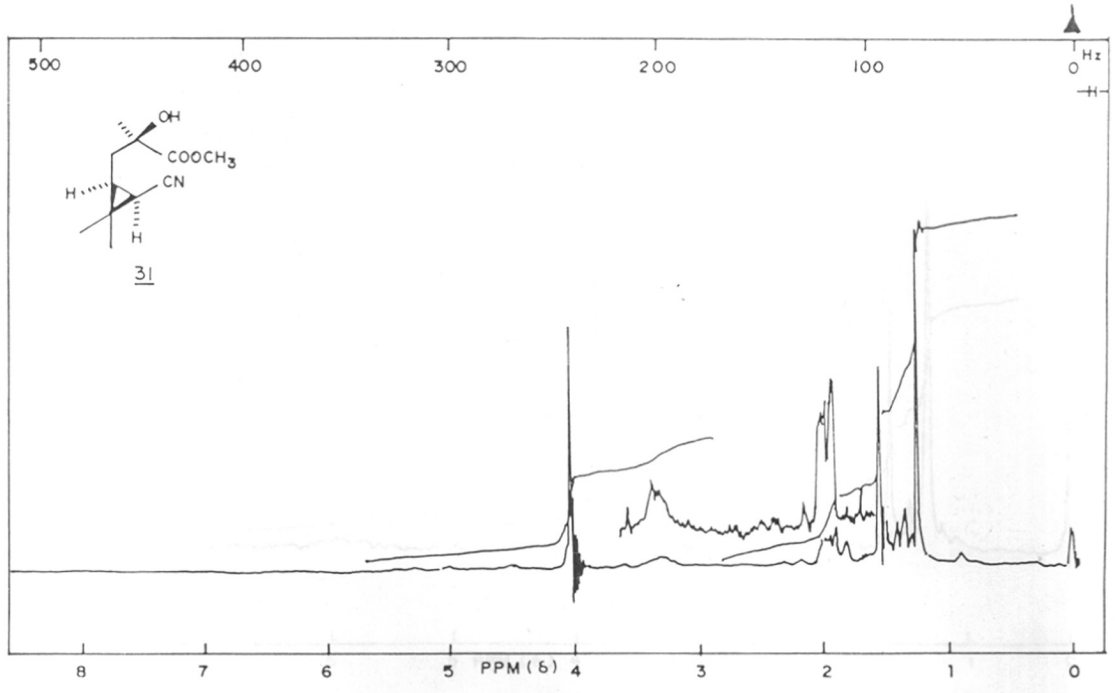

4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
H3COOC
O
O
H
H
29
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVE LENGTH (MICRONS)

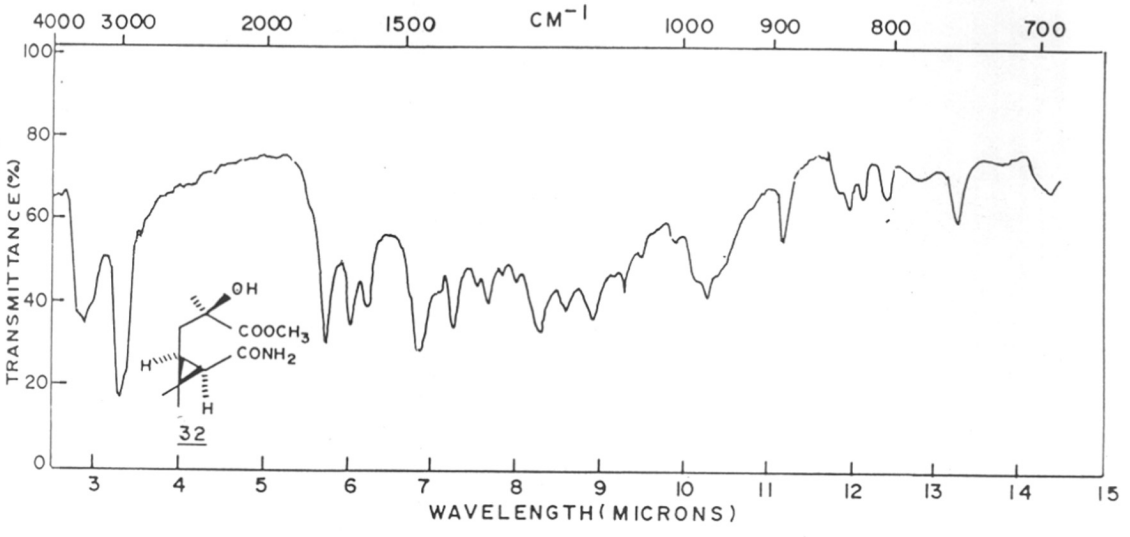

500 400 300 200 100 0 Hz
H3COOC
O
O
H
H
29
8 7 6 5 PPM (δ) 4 3 2 1 0

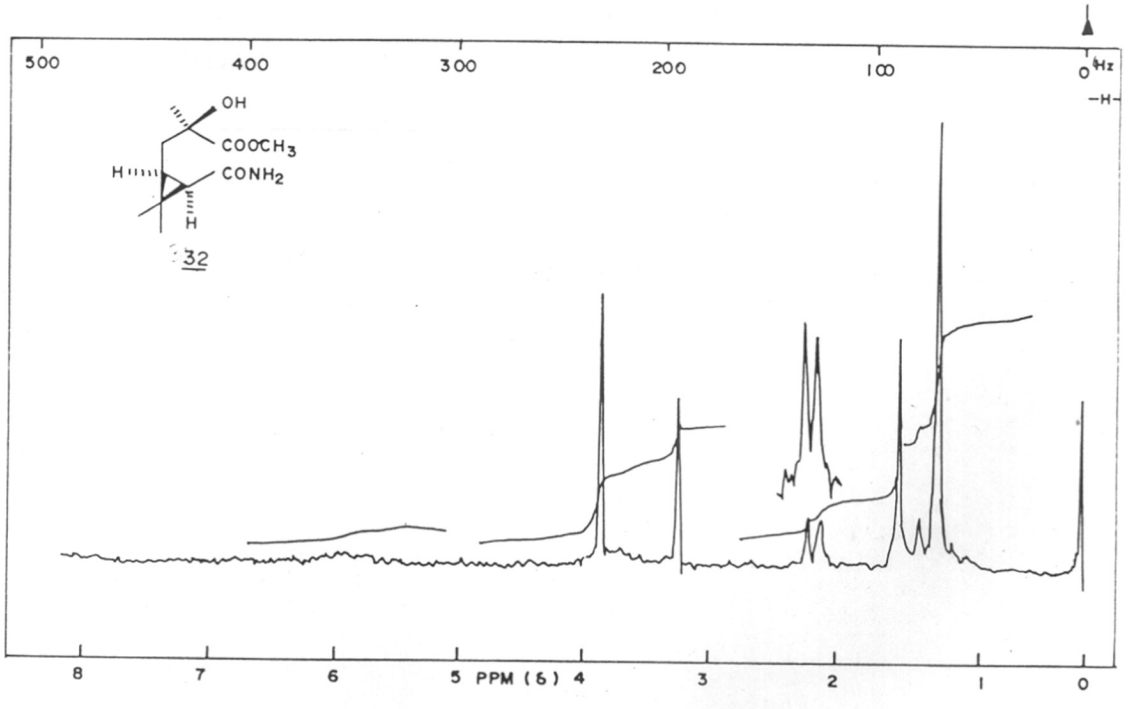

4000 3000 2000 1500 CM-1 1000 800 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
OH
O
H
NOH
H
30
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)


500 400 300 200 100 0 Hz
H
OH
O
H
NOH
H
30
8 7 6 5 PPM(δ) 4 3 2 1 0


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE(%)
OH
COOCH3
CN
H
H
31
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)


500 400 300 200 100 0 Hz
OH
COOCH3
CN
H
H
31
8 7 6 5 PPM (δ) 4 3 2 1 0


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
OH
COOCH3
CONH2
H
H
32
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)


500 400 300 200 100 0 Hz
OH
COOCH3
CONH2
H
H
32
8 7 6 5 PPM (δ) 4 3 2 1 0

CHAPTER-III

STEREOSPECIFIC SYNTHESIS OF 3-PHENOXYBENZYL CIS-(±)-2,2-DIMETHYL-3-(2-ARYL-2-CHLOROVINYL)CYCLOPROPANE-CARBOXYLATE

SUMMARY

3-Phenoxybenzyl esters of 2,2-dimethyl-3-(2-chloro-2-arylvinyl)cyclopropanecarboxylic acids are known to have very high insecticidal and acaricidal activity. So, the synthesis of such pyrethroids was undertaken starting from naturally occurring monoterpene (+)-3-carene (6).

The bromohydrin (9) was prepared from (+)-3-carene using NBS. The ring contraction reaction of bromohydrin using $AgNO_3$ afforded the acetyl compound (10). Bayer-Villiger oxidation gave an acetate (11) which on hydrolysis and Jones oxidation afforded a ketone (13). Grignard reaction of (13) with aryl-magnesium bromide gave tertiary alcohol (14,20). Dehydration using phosphorous oxychloride and pyridine gave an olefin (15,21) which was oxidized to keto-acid (16,22). Methyl ester of keto acid (16,22) when treated with phosphorous pentachloride gave isomeric mixture of vinyl ester (18,24) and (19,25). Trans esterification with 3-phenoxybenzyl alcohol using tetra-butyl titanate as catalyst afforded the final acaricide (7), (8).

Stereospecific synthesis of 3-phenoxybenzyl cis-(±) 2,2-dimethyl-3-(2-aryl-2-chlorovinyl)cyclopropanecarboxylate

Present work and discussion

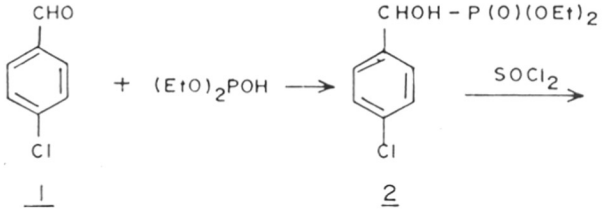
Synthetic pyrethroids belongs to an almost ideal group of modern insecticides due to their high insecticidal activity combined with low mammalian toxicity and rapid biodegradability. While several pyrethroid with potent insecticidal action have been synthesized[1], search for analogues with higher photo-chemical stability and other pesticidal activity continues. One major drawback of synthetic pyrethroids currently in use is their low acaricidal activity. In this connection some esters of 2,2-dimethyl-3-(2-aryl-2-chlorovinyl)cyclopropane-carboxylic acid have recently been reported to have good acaricidal activity[2-4].

As already mentioned in Chapter I of this thesis, esters of 3-vinyl substituted 2,2-dimethylcyclopropane-carboxylic acid with the carboxylic substituent in the 1R configuration, whether the side-chain at C-3 is trans- or cis- to the carboxylic group, are active[5-7], whereas esters of the 1S-epimer are inactive or much less active. The potency of such esters is also sensitive to the substituent on the side-chain at C-3[1,6,7]. Further, some esters of 3-dihalovinyl[8-10] substituted acids were

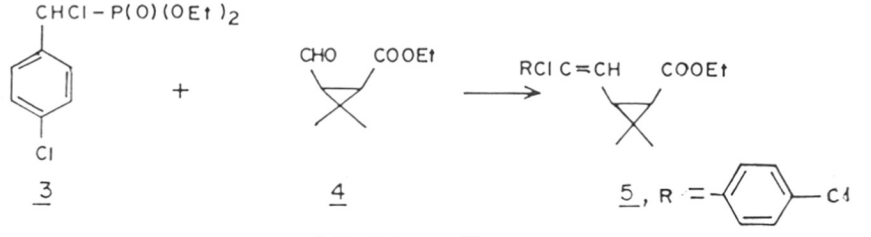
found to be outstandingly potent insecticides, the cis-esters being usually more active[11]. This observation leads to the conclusion that presence of methyl group on the vinyl side-chain at C-3 (as in chrysanthemic acid) is not essential for a pyrethroid to possess insecticidal activity as believed earlier.

In most of the synthesis of pyrethroids, derived from 2,2-dimethyl-3-(2-aryl-2-chlorovinyl)cyclopropane-carboxylic acid, the pyrethroid acids were prepared by Wittig reaction on caranoldehydic acid derivatives. The Wittig reagent was either $ArCHCl\text{-}P(O)(OEt)_2$[12] prepared from corresponding hydroxy compound by thionyl chloride reaction (Scheme-I) or $PhCH_2P(O)(OEt)_2$[13,14] (Scheme II) or $(PhCH_2)Ph_3P^+ Br^-$[15]. In a patented synthesis by R.A. Fuchs et al.[16] the cyclopropane ring was built up by diazo-ester addition over the double bond (Scheme - III). Thus, p-chlorobenzaldehyde was reacted with diethyl-phosphite to get the hydroxy compound (3, Scheme - III) which was converted to corresponding chloro compound (4, Scheme - III) by thionyl chloride and pyridine. This was then condensed with 2,2-dimethylacraldehyde in THF containing sodium ethoxide at 0-10°C to give (6, Scheme III) as cis-, trans-mixture. The cyclopropane ring was built up by reaction of ethyldiazo acetate in the presence of

SCHEME—I

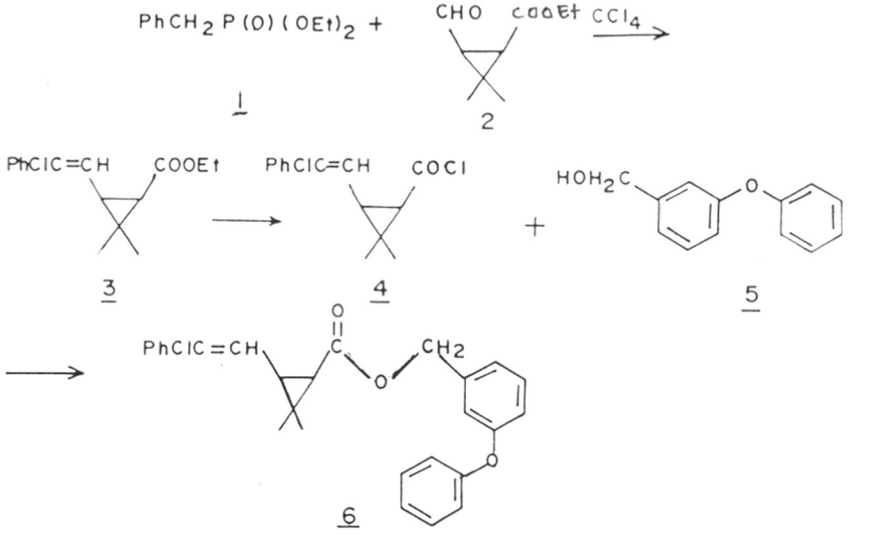


1 2

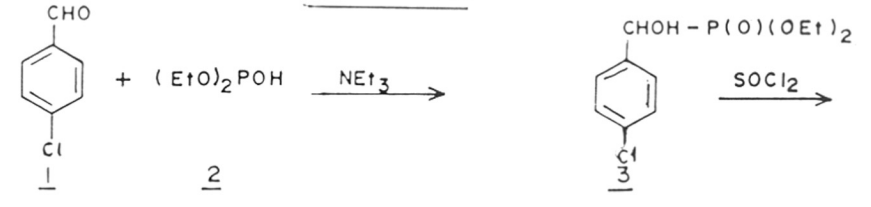


3 4 5

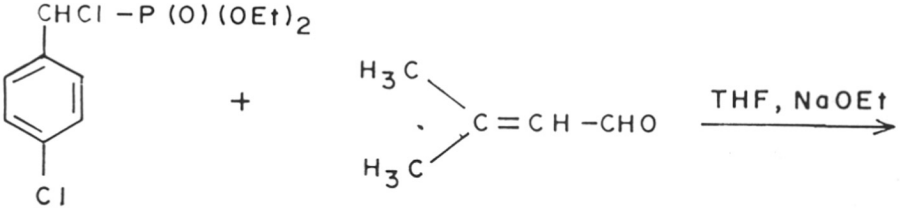
SCHEME – II



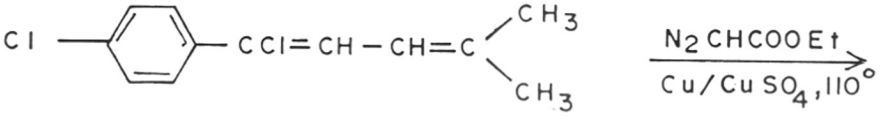
SCHEME –III



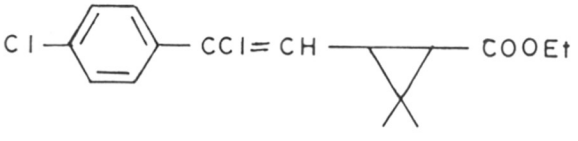
1 2 3


CHCl – P (O) (OEt)2
Cl
+
H3C
C = CH – CHO
H3C
THF, NaOEt

4 5


Cl
CCl = CH – CH = C
CH3
CH3
N2CHCOOEt
Cu/CuSO4, 110°

6

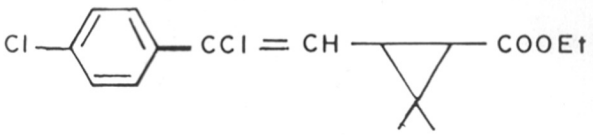

Cl
CCl = CH
COOEt

7

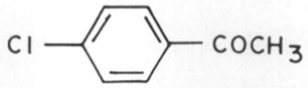
powdered copper and copper sulfate at 110°C over five hours to give styrylcyclopropanecarboxylate (7, Scheme III) as an isomeric mixture. In another synthesis reported by the same group of workers[17], the styryl cyclopropane-carboxylate (1) was prepared in seven steps starting from 4-chloroacetophenone (2) and isobutyraldehyde (3) via oxirane (4) and γ-butyro lactone (5). These syntheses, from acyclic starting materials always lead to isomeric mixture of pyrethroids.

As a part of our programme[18,19] for utilizing the abundantly available natural product (+)-3-carene (6) for the stereospecific synthesis of pyrethrodis containing the more active 3-substituted cis-cyclo-propanecarboxylate isomers, we have synthesized 3-phenoxy-benzyl cis (±)-2,2-dimethyl-3--(2-aryl-2-chloro vinyl) cyclopropanecarboxylate, where the aryl group is either phenyl (7) or 4-chlorophenyl (8).

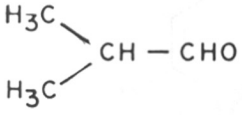
Thus, (+) 3-carene (6) was converted to bromo-hydrin (9) by a known method[20] using N-bromosuccinimide in aqueous t-butanol. The bromohydrin (9), without isolating was subjected to a modified solvolytic ring contraction reaction using aqueous silver nitrate[21]. The crude product obtained after extractive workup with ether, was distilled under vacuum to give 10, as a pale yellow oil M^+: 152; b.p. 70-75°/3.5 mm; IR (liquid film):



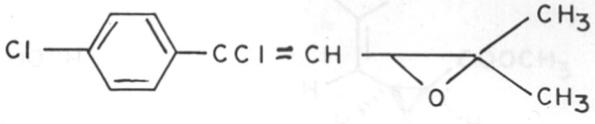
1



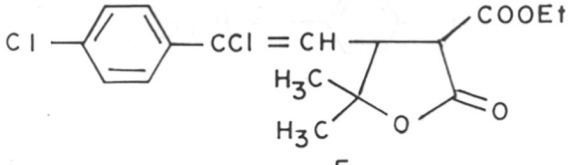
2



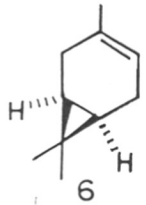
3



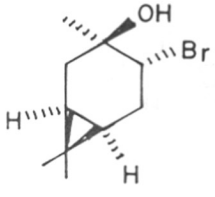
4



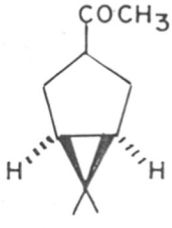
5



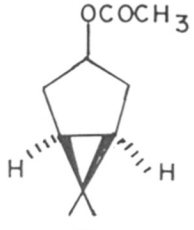
6



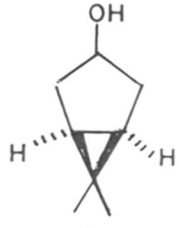
9



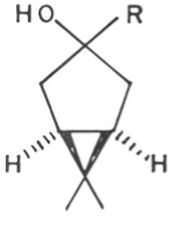
10



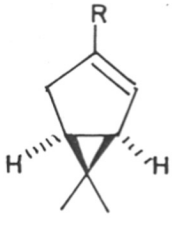
11



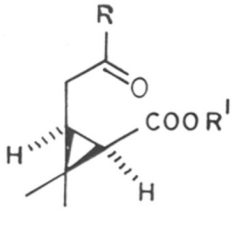
12



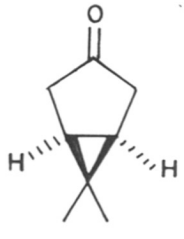
14, R = Ph



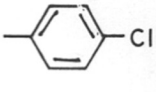
15, R = Ph

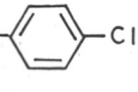


16, R = Ph, R' = H

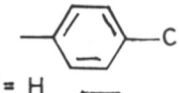


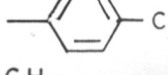
13

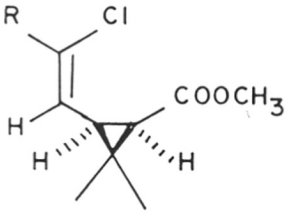
20, R = 

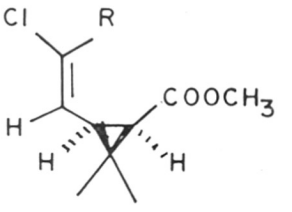
21, R = 

17, R = Ph, R' = CH_3

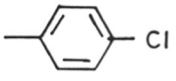
22, R =  , R' = H

23, R =  , R' = CH_3

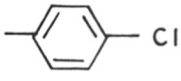


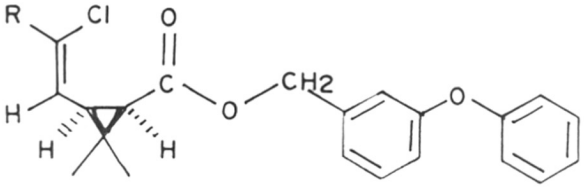


18, R = Ph

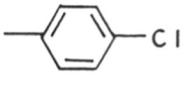
24, R = 

19, R = Ph

25, R = 



7, R = Ph

8, R = 

1710 cm^{-1} (carbonyl); PMR (CCl_4,δ): 0.83-1.17 (m,2H, cyclopropyl protons), 0.93 (s,6H, two-CH_3), 1.46-2.3 (m, 4H, -CH_2), 2.0 (s, 3H, -$COCH_3$), 2.37-2.86 (m, 1H, -CH).

The acetyl compound (10) was subjected to Bayer-Villiger oxidation[21,22] using perbenzoic acid in chloroform to afford an acetoxy compound (11) as an oil M^+: 168. IR (liquid film): 1724, 1220 cm^{-1}(acetate); PMR (CCl_4,δ): 0.90 (s, 3H, -CH_3), 1.0 (s, 3H, -CH_3), 1.03-1.4 (m, 2H, cyclopropyl proton) 1.5-2.36 (m, 4H,-CH_2), 1.93 (s, 3H, -$COCH_3$), 4.7-5.1 (m, 1H, -CH).

The acetate (11) was hydrolysed by aqueous alcoholic potassium hydroxide at room temperature to get a bicyclic alcohol (12) as a colourless oil. M^+: 126; IR (liquid film): 3400 (hydroxyl); PMR (CCl_4,δ): 0.87 (s, 3H, -CH_3), 1.03 (s, 3H, -CH_3), 1.07-1.40 (m, 2H, cyclopropyl protons), 1.80 (m, 4H, -CH_2), 3.70 (s, 1H -OH, exchanges with D_2O), 4.0 - 4.33 (m, 1H, -CH-O-). Jones chromic acid oxidation of the alcohol (12) gave a bicyclic ketone (13) as a colourless oil after vacuum distillation. M^+: 124; b.p. 130/15 mm; IR (liquid film): 1748 cm^{-1} (cyclopentanone); PMR(CCl_4,δ): 0.83-1.5 (m, 2H, cyclopropyl protons), 0.90 (s, 3H,-CH_3) 1.10 (s, 3H, -CH_3), 1.7 - 2.8 (m, 4H, -CH_2). This bicyclic ketone (13) is a very important intermediate in this pyrethroid synthesis.

All these compounds, acetyl (10), acetate (11), hydroxy (12) and ketone (13) are optically inactive as they are all having a plane of symmetry. Eventhough, they are optically inactive, the absolute stereochemistry at C-1 and C-5 is not disturbed during all these reactions.

Grignard reaction of phenyl magnesium bromide on the ketone (13) afforded tertiary alcohol (14) as a pale yellow coloured thick oil. IR (liquid film): 3448 cm^{-1} (hydroxyl), PMR (CCl_4,δ): 1.0 (s, 3H, $-CH_3$), 1.13 (s, 3H, $-CH_3$), 1.5-2.4 (m, 4H, $-CH_2$), 2.57 (broad s, 1H, -OH, -OH, exchanges with D_2O), 6.7-7.43 (m, 5H, aromatic). This tertiary alcohol (14) was dehydrated with phosphorous oxychloride and pyridine at 0^oC, to give pale yellow coloured oil, bicyclohexene (15), b.p.90-120^o/1 mm (bath temp.); IR (liquid film): no hydroxyl group; PMR (CCl_4,δ): 0.87 (s, 3H, $-CH_3$), 1.10 (s, 3H, $-CH_3$), 1.17 - 1.53 (m, 1H, cyclopropyl proton), 1.63 - 2.00 (m, 1H, cyclopropyl proton), 2.07 - 2.83 (m, 2H, $-CH_2$), 6.0 (m, 1H, olefinic), 7.0 - 7.57 (m, 5H, aromatic). This bicyclohexene(15) was found to be very unstable and was used soon after preparation. It could be prepared in the cold, sealed in vacuum.

Attempts to oxidize 16 to (±) cis-2,2-dimethyl-3-(2-oxo-2-phenylethyl)cyclopropanecarboxylic acid (16) using potassium permanganate with various reaction conditions were fruitless. Finally the Lemieux-Von-Rudolf's method[23], using

catalytic amount of potassium permanganate and excess sodium metaperiodate, had worked well and gave a yellow coloured solid (16) m.p.135-136°, in 40% yield which was esterified to(17)with ethereal solution of diazomethane. The methyl ester (17) was purified by silica gel column chromatography using 30% chloroform-pet.ether as eluant, to get pale yellow oil. IR (liquid film): 1725 (ester), 1690 cm^{-1} (ketone), 1605, 1580 cm^{-1} (aromatic); PMR (CCl_4, δ): 1.20 (s, 3H, $-CH_3$), 1.30 (s, 3H, $-CH_3$), 1.57 (m, 2H, cyclopropyl protons), 3.37 (m, 3H, $-CO-CH_2-$), 3.90 (s, 3H, $-OCH_3$), 7.37 (m, 3H, aromatic), 7.87) (m, 2H, aromatic).

The keto ester (17) when treated with phosphorous pentachloride in methylene chloride as solvent gave pure chlorovinyl compound as a mixture of geometric isomsers (18) and (19) in a ratio of 2:3 as judged from PMR spectrum. The mixture showed a pair of doublets at δ 6.5 and δ 5.2 for the vinyl protons. The doublet at δ 6.5 was attributed to (18), where due to the deshielding effect of the adjacent phenyl ring, the vinyl proton appears at low field as compared to the other isomer (19). From the mixture pure (19) was isolated by repeated crystallisation as white needles, m.p.99-100°; M^+: 264; IR (Nujol): 1710 cm^{-1} (ester); PMR ($CDCl_3$,δ): 1.33 (s, 3H, $=CH_3$), 1.2 (s, 3H, $-CH_3$), 1.7 (d, 1H, J = 8 Hz,

cyclopropyl proton), 1.98 (dd, 1H, J = 10, 8 Hz, cyclopropyl proton), 3.55 (s, 3H, $-OCH_3$), 5.33 (d, 1H, J = 10 Hz, vinyl proton), 7.3 (m, 3H, aromatic), 7.7 (m, 2H, aromatic).

Treatment of keto ester (17) with neat phosphorous pentachloride in the absence of solvent, gave one single isomer (18), as could be seen from the PMR spectrum of the crude product, which showed only one doublet at δ 6.5 and no absorption at δ 5.2. The crude product was purified by silica gel column chromatography using 1:1 benzene, pet.ether as eluant to get colourless oil in 48% yield. IR (liquid film): 1710 cm^{-1} (ester); PMR (CCl_4, δ): 1.3 (s, 6H two $-CH_3$), 1.80 (d, 1H, J = 9 Hz, cycloropyl proton), 2.3 (dd, 1H, J = 9, 9 Hz, cyclopropyl proton), 3.57 (s, 3H, $-OCH_3$), 6.5 (d, 1H, J = 9 Hz vinyl proton), 7.03 - 7.5 (m, 5H, aromatic).

The chlorovinyl ester (18) was transesterified with 3-phenoxybenzyl alcohol by refluxing in xylene with tetrabutyl titanate[24] as catalyst, to afford the final pyrethroids (7) as a colourless thick oil. M^+: 432; IR (liquid film): 1750 cm^{-1} (ester); PMR ($CDCl_3$, δ): 1.30 (s, 6H, two $-CH_3$), 1.95 (d, 1H, J = 9 Hz, cyclopropyl proton), 2.50 (dd, 1H, cyclopropyl proton, J = 9, 9 Hz), 5.04 (s, 2H, $-O-CH_2-$), 6.51 (d, 1H, vinyl proton,

J = 9 Hz), 6.8 - 7,6 (m, 14H, aromatic).

Similarly, the Grignard reaction with 4-chlorophenyl magnesium bromide, on ketone (13) afforded tertiary alcohol (20) as yellow coloured thick oil. IR (liquid film): 3509 cm^{-1} (hydroxyl); PMR (CCl_4,δ): 1.07 (s, 3H, $-CH_3$), 1.20 (s, 3H, $-CH_3$), 1.47 - 2.53 (m, 5H, $-CH_2$ and -OH), 7.1 - 7.7 (m, 4H, aromatic). This tertiary alcohol (20) on dehydration with phosphorous oxychloride and pyridine gave the bicyclohexene (21). This was also found to be very unstable and was utilized soon after preparation. IR (liquid film): showed absence of hydroxyl group. PMR (CCl_4,δ): 0.80 (s, 3H, $-CH_3$), 1.10 (s, 3H, $-CH_3$), 1.2-1.9 (m, 2H, cyclopropyl protons), 2.03-2.83 (m, 2H, $-CH_2$), 6.0 (m, 1H, olefinic), 7.1 (s, 4H, aromatic).

Oxidation of bicyclohexene (21) by Lemieux-Von-Rudolf's method gave acid (22). The crude acid (22) was esterified with diazomethane. The PMR of the crude ester (23) showed an extra signal atδ3.67, this was due to the presence of methyl p-chlorobenzoate as an impurity in the crude product. So, it was purified by column chromatography using silica gel and 30% chloroform, pet.ether as eluant, to afford an oil. IR (liquid film): 1724 cm^{-1} (ester), 1695 cm^{-1} (ketone), 1597, 1493 cm^{-1} (aromatic); PMR (CCl_4, δ): 1.17 (s, 3H, $-CH_3$), 1.30 (s, 3H, $-CH_3$), 1.57 (m, 2H, cyclopropyl protons), 3.03 (m, 2H, $-COCH_2$), 3.57 (s, 3H, $-O-CH_3$), 7.4

(d, 2H, aromatic J = 8 Hz), 7.93 (d, 2H, aromatic, J = 8 Hz).

The keto ester (23) was treated with phosphorous penta chloride in methylene chloride under similar conditions as used for (17), gave geometric isomers in the same proportion of 2:3. Structures for each isomer were assigned on the same line as in (18) and (19). The vinyl proton doublets appeared at δ6.5 and δ5.2 are for compound (24) and (25) respectively.

The two geometric isomer could not be separated from mixture so, the final pyrethroid (8) was prepared by trans-esterification with 3-phenoxybenzyl alcohol using tetrabutyltianate as catalyst. The PMR spectrum showed only one doublet at δ6.5 for vinyl proton while there was no absorption at δ5.2. This shows that there is isomerization of double bond to a thermodynamically more stable product (8) where the bulkyl cyclopropyl ring and 4-chlorophenyl groups are trans to each other.
IR (liquid film): 1754 cm^{-1} (ester); PMR ($CDCl_3$,δ): 1.26 (s, 6H, $-CH_3$), 2.0 (d, 1H, cyclopropyl proton, J = 9 Hz), 2.35 (dd, 1H, cyclopropyl proton, J = 9, 9 Hz), 5.1 (s, 2H, $-O-CH_2-$), 6.6 (d, 1H, olefinic, J = 9 Hz), 6.9 - 7.7 (m, 3H, aromatic).

E X P E R I M E N T A L

6,6-Dimethyl-3-acetyl bicyclo[3-1-0]hexane (10)

(+) 3-Carene (69.0 g, 0.507 mol) was taken in t-butanol (240 ml) and water (75 ml) was added to it. N-Bromosuccinimide (95.0 g, 0.521 mol) was added portion-wise without allowing the temperature of the reaction mixture to go above 50°C, in about half hour. The mixture was then stirred for another one hour and left overnight at room temperature. The mixture was cooled using ice-water-bath and a solution of silver nitrate (105.0 g, 0.618 mol) in water (150 ml) was added dropwise without allowing the temperature to go above 30°C in ½ hour. The mixture was stirred at room temp. for one hour and filtered through buchner funnel, the residue washed with ether. The filtrate was diluted with water (500 ml) and extracted with ether,. Combined ether extracts were washed with water, then with saturated brine solution dried over anhydrous sodium sulfate and solvent was distilled off to get yellow oil (68.00 g) This oil was fractionally distilled at 3.5 mm pressure.

Fractions	Temperature	Amount collected
Fr.I	65-70°C	8.3 g
Fr. II	70-75°C	25.1 g
Fr.III	above 75°C	2.3 g

Fr. I and Fr. II were the required acetyl compound (10) while Fr. III was not analysed further.

IR (liquid film): 2950, 1710, 1625, 1440, 1350, 1260, 1170, 838, 785 cm^{-1}..

PMR (CCl_4, δ): 0.83-1.17 (m, 2H, cyclopropyl protons), 0.93 (s, 6H, $-CH_3$), 1.46 - 2.3 (m, 4H, $-CH_2$), 2.0 (s, 3H, $-COCH_3$), 2.37 - 2.86 (m, 1H -CH).

6,6-Dimethyl-3-acetoxy bicyclo[3-1-0]hexane (11)

To an ice-cooled and stirred solution of acetyl compound (10), (15.0 g, 0.098 mol) in chloroform (25 ml), a solution of perbenzoic acid (12.25 g, 0.89 mol) in chloroform (100 ml) and paratoluene sulfonic acid (0.5 g) were added and the contents stirred at 10-15°C for 24 hours. Another portion of perbenzoic acid (12.25 g, 0.89 mol) in chloroform (100 ml) was added and the stirring continued for 24 hours. After 48 hours the chloroform solution was washed with saturated solution of sodium carbonate (100 ml x 2), water (100 ml x 2) and dried over anhydrous sodium sulfate. Removal of the chloroform by distillation afforded pale yellow oil (12.8 g, 77.2%). It showed a single spot on TLC (10% ethyl acetate in benzene).

IR (liquid film): 2930, 1724, 1420, 1360, 1220, 1210, 1170, 1025, 840, 750, 700 cm^{-1}.

PMR (CCl_4, δ): 0.90(s, 3H, $-CH_3$), 1.0 (s, 3H, $-CH_3$), 1.03 - 1.4 (m, 2H, cyclopropyl protons), 1.5 - 2.36 (m, 4H, $-CH_2$), 1.93 (s, 3H, $-COCH_3$), 4.7 - 5.1 (m, 1H - CH).

6,6-Dimethyl bicyclo[3-1-0]hexan-3-ol (12)

The acetate (11) (13.0 g, 0.077 mol) was dissolved in ethanol (30 ml) and aqueous solution of potassium hydroxide (10 g, 0.178 mol) in water (10 ml) was added to it. This mixture was stirred at room temperature for 24 hours, ethanol was removed under suction and the residue was diluted with water (50 ml) and extracted with ether (75 ml x 3). The ether extract was washed with water and then with saturated brine solution, dried over anhydrous sodium sulfate and solvent was distilled off to afford an oil (8.5 g, 89.48%).

IR (liquid film): 3400, 2960, 1425, 1360, 1333, 1290, 1275, 1124, 1080, 1010, 920, 838, 813, 787, 730 cm^{-1}.

PMR (CCl_4, δ): 0.87 (s, 3H, $-CH_3$), 1.03 (s, 3H, $-CH_3$), 1.07 - 1.40 (m, 2H, cyclopropyl proton), 1.80 (m, 4H, $-CH_2$), 3.70 (s, 1H, -OH, exchanges with D_2O), 4.0 - 4.33 (m, 1H -CH).

6,6-Dimethyl bicyclo[3-1-0]hexan-3-one (13)

To an ice cooled solution of bicyclic alcohol (12) (8.5 g) in acetone (200 ml) was added Jones reagent dropwise till brown colour persisted (15 ml). After the addition, reaction mixture was stirred for ½ hour at 5-10°C, diluted with water (400 ml) and extracted with ether (200 ml x 3). The ether extract was washed with water and then with saturated brine solution, dried over

anhydrous sodium sulfate ; solvent was removed to get pale yelllow oil (7.2 g, 86.0%). Distilled at 130/140°/ 15 mm to get colourless oil.

Analysis: Calculated for $C_8H_{12}O$: C, 77.39; H, 9.67.
Found: C, 76.97; H, 9.52.

IR (liquid film): 3030, 1748, 1639, 1449, 1404, 1370, 1256, 1145, 1093, 1030, 1000, 950, 930, 833, 816, 775, 758 cm^{-1}.

PMR (CCl_4, δ): 0.83 - 1.5 (m, 2H, cyclopropyl protons), 0.90 (s, 3H, $-CH_3$), 1.10 (s, 3H, $-CH_3$), 1.7 - 2.8 (m, 4H, $-CH_2$).

cis(±)-6,6-Dimethyl bicyclo[3-1-0]hexan-3-phenyl-3-ol (14)

Phenyl magnesium bromide (63.8 mmol), prepared in ether under anhydrous condition and in an atmosphere of nitrogen, was cooled in an ice-bath and the ketone (13) (5.8 g, 46.8 mmol), dissolved in ether, was added to it dropwise with stirring. After addition was complete, the ice-bath was removed and the reaction left stirring overnight. After cooling in an ice-bath, the reaction mixture was decomposed with saturated ammonium chloride solution. The ether layer was separated and the aqueous layer extracted twice with ether. The combined ethereal layer was washed with water, brine, dried over anhydrous sodium sulfate and evaporated to give pure (14) as a pale

yellow oil (8.3 g, 88.4%).

IR (liquid film): 3448, 3030, 1613, 1449, 1379, 1282, 1176, 1053, 1015, 917, 840, 813, 741, 694 cm^{-1}.

PMR (CCl_4, δ): 1.0 (s, 3H, $-CH_3$), 1.13 (s, 3H, $-CH_3$), 1.5 - 2.4 (m, 4H, $-CH_2$), 2.57 (broad s, 1H, -OH), exchanges with D_2O), 6.7 - 7.43 (m, 5H, aromatic).

cis (±)-6,6Dimethyl bicyclo[3-1-0]hex-3-phenyl-3-ene (15)

Alcohol (14) (1 g, 4.95 mmol) was dissolved in pyridine (3.2. ml), cooled in an ice-bath and phosphorous oxychloride (0.48 ml, 5.2 mmol) was added. The reaction was stirred in the cold for three hours and excess pyridine removed under vacuum (1 mm). The residue was cooled, treated with water and extracted with ether three times. The ether layer was washed with water, brine, dried over anhydrous sodium sulfate and evaporated to give pure (15) as a pale yellow oil (620 mg, 68%) b.p.90-120/1 mm (bath temperature).

PMR (CCl_4, δ): 0.87 (s, 3H, $-CH_3$), 1.10 (s, 3H, $-CH_3$), 1.17 -2 (m, 2H, cyclopropyl protons), 2.07 - 2.83 (m, 2H, $-CH_2$), 6.0 (m, 1H, olefinic), 7.0 - 7.57 (m, 5H, aromatic).

cis(±)-2,2-Dimethyl-3-(2-oxo-2-phenyl ethyl)cyclopropane-carboxylic acid (16) and methyl ester (17)

To bicyclohexene (15) (480 mg, 2.6 mmol) in t-butanol (100 ml) was added a solution of potassium

permanganate (10 mg catalytic), sodium metaperiodate (3.42 g, 15.9 mmol) in water (200 ml). The pH of the reaction mixture was adjusted to nine with 5% potassium carbonate solution, and the reaction stirred for forty eight hours at room temperature. The pH was maintained at nine during this time, by adding 5% potassium carbonate solution whenever necessary. Butanol was removed under vacuum and the reaction mixture acidified with 10% sulfuric acid and extracted with ether several times. The ether layer was washed with brine solution and then extracted with potassium carbonate solution . The alkaline solution was cooled, acidified with 10% sulfuric acid and extracted with ether. The ether layer was washed with brine solution, dried over anhydrous sodium sulfate and evaporated to give (16) as a white solid m.p.135-136^{o}, (240 mg, 40%). Esterification with diazomethane gave (17) as a pale yellow oil which was used without further purification. An analytical sample was prepared by column chromatography (silica gel, 30% chloroform, pet.ether).

Analysis: Calculated for $C_{15}H_{18}O_3$; C, 73.18; H, 7.32;
Found: C, 73,44; H, 7.64.

IR (liquid film): 3030, 1724, 1695, 1613, 1449, 1370, 1333, 1215, 1198, 1176, 1081, 1000, 985, 930, 847, 794, 749, 730, 690 cm^{-1}.

PMR (CCl_4, δ): 1.17 (s, 3H, $-CH_3$), 1.30 (s, 3H, $-CH_3$), 1.50 (m, 2H, cyclopropyl protons), 3.27 (m, 2H, $-COCH_2-$), 3.60 (s, 3H, $-OCH_3$), 7.27 (m, 3H, aromatic), 7.83 (m, 2H, aromatic).

Methyl cis (±)-2,2-dimethyl-3-(2-phenyl-2-chlorovinyl)-cyclopropanecarboxylate (18)

To keto ester (17) (120 mg, 0.48 mmol) cooled in ice was added all at once phosphorous pentachloride (240 mg, 0.91 mmol). The reaction was gradually brought to room temperature and left overnight. After adding some crushed ice to the reaction mixture, it was extracted with ether. Ether layer was washed with water, brine, dried over anhydrous sodium sulfate and evaporated to give an oil (120 mg). The oil was purified by column chromatography using silica gel. The product was eluted out with 1:1 benzene, pet.ether, (18) was obtained as colourless oil (60 mg, 48%).

M/e: 264 (M^+), 229 (M^+ - Cl), 205 (M^+ $-COOCH_3$).

IR (liquid film): 3000, 1710, 1600, 1440, 1370, 1280, 1200, 1130, 1080, 1000, 930, 840, 815, 760, 690 cm^{-1}.

PMR (CCl_4, δ): 1.3 (s, 6H, $-CH_3$), 1.80 (d, 1H, cyclopropyl proton, J = 9 Hz), 2.3 (dd, 1H, cyclopropyl proton, J = 9, 9 Hz), 3.57 (s, 3H, $-OCH_3$), 6.53 (d, 1H, olefinic, J = 9 Hz), 7.03 - 7.5 (m, 5H, aromatic).

Methyl cis (±)-2,2-dimethyl-3-(2-phenyl-2-chloro-vinyl)cyclopropanecarboxylate (19)

To the keto ester (17) (196 mg, 0.8 mmol) in methylene chloride (5 ml) was added phosphorous pentachloride (362 mg, 1.7 mmol) and the reaction refluxed for twenty hours. Crushed ice was added to the reaction mixture and the organic layer separated. The aqueous layer was extracted twice with methylene chloride. The combined organic layer was washed with water, brine, dried over anhydrous sodium sulfate and evaporated to give an oily residue, which consisted of a pure mixture of (18) and (19). (202 mg, 96%). On leaving it in the refrigerator overnight a small quantity of solid precipitated which was separated and crystallised several times from petroleum ether to give (19)as white needles m.p. 99-100°C.

M/e: 264 (M^+), 229 (M^+ -Cl), 205 (M^+ -$COOCH_3$).

IR (Nujol): 2990, 1710, 1425, 1360, 1180, 1130, 990, 928, 838, 792, 780, 768, 755, 705, 685 cm^{-1}.

PMR ($CDCl_3$,δ): 1.33 (s, 3H, -CH_3), 1.2 (s, 3H, -CH_3), 1.7 (d, 1H, cyclopropyl proton, J = 8 Hz), 1.98 (dd, 1H, cyclopropyl proton, J = 10, 8 Hz), 3.55 (s, 3H, -OCH_3), 5.33 (d, 1H, vinyl, J = 10 Hz), 7.3 (m, 3H, aromatic), 7.7 (m, , 2H, aromatic).

3-Phenoxybenzyl cis (±)-2,2-dimethyl-3-(2-phenyl-2-chlorovinyl) cyclocpropanecarboxylate (7)

Ester (18) (90 mg, 0.34 mmol), m-phenoxybenzyl alcohol (100mg , 0.5 mmol), tetrabutyl titanate (9 mg, catalytic), was refluxed in xylene (4 ml) for fourteen hours. After cooling to room temperature, the solution was passed over a short column of silica gel and eluted with petroleum ether. The colourless eluant was evaporated to give (7) as a colourless oil (100 mg, 62%).

M/e : 432 (M^+), 397 (M^+ - Cl), 205 (M^+ -$COOCH_2$-C_6H_4-0-C_6H_5), 183 (C_6H_5-0- $C_7H_6^+$).

IR (liquid film): 3150, 3000, 1750, 1600, 1500, 1450, 1260, 1220, 1175, 1070, 815, 785, 700, 695 cm^{-1}.

PMR ($CDCl_3$, δ): 1.30 (s, 6H, $-CH_3$), 1.95 (d, 1H, cyclopropyl proton, J = 9 Hz), 2.50 (dd, 1H, cyclopropyl proton, J = 9, 9 Hz), 5.04 (s, 2H, $-COCH_2$), 6.51 (d, 1H, vinyl, J = 9 Hz), 6.8 - 7.6 (m, 14H, aromatic).

cis (±)-6,6-Dimethyl bicyclo[3-1-0]hexan-3-(4-chlorophenyl)-3-ol (20)

4-Chlorophenyl magnesium bromide (30 mmol) prepared in ether under anhydrous condition and in an atmosphere of nitrogen was cooled in an ice-bath and the ketone (13) (3.1 g, 25 mmol) dissolved in ether was added to it dropwise with stiring. After addition was complete the ice-bath was removed and the reaction mixture left

stirring overnight. After cooling in an ice-bath, the reaction mixture was decomposed with saturateed ammonium chloride solution. The ether layer was separated and the aqueous layer extracted with ether, washed with water and brine solution, dried over anhydrous sodium sulfate. Solvent was removed to afford pure (20) as pale yellow oil (5.018 g, 84.85%).

IR (liquid film): 3509, 3030, 1600, 1493, 1449, 1399, 1370, 1282, 1205, 1124, 1087, 1064, 1010, 943, 909, 855, 826, 749, 738 cm^{-1}.

PMR (CCl_4, δ): 1.07 (s, 3H, $-CH_3$), 1.20 (s, 3H, $-CH_3$), 1.47-2.53 (m, 5H, $-CH_2$ and -OH), 7.1 - 7.7 (m, 4H, aromatic).

cis(±)-6,6-Dimethylbicyclo [3-1-0]hex-3-(4-chlorophenyl)-3-ene (21)

Alcohol (20) (1.08 g, 5 mmol) was dissolved in pyridine (3.2 ml), cooled in an ice-bath and phosphorous oxychloride (0.48 ml, 5.2 mmol) was added slowly. The reaction was stirred in the cold for three hours and excess pyridine was removed under vacuum (1 mm). The residue was cooled, treated with water and extracted with ether three times. The ether layer was washed with water and brine solution, dried over anhydrous sodium sulfate. The solvent was evaporated off to afford bicyclohexene (21) as yellow oil (681 mg, 68%).

b.p. 120/130°/1 mm (bath temp.)

PMR (CCl_4, δ): 0.80 (s, 3H, $-CH_3$), 1.10 (s, 3H, $-CH_3$), 1.2 - 1.9 (m, 2H, cyclopropyl protons), 2.03 - 2.83 (m, 2H, $-CH_2$), 6.0 (m, 1H, olefinic), 7.1 (s, 4H, aromatic).

cis(±)-2,2-Dimethyl-3-[2-oxo-2-(4-chlorophenyl)ethyl]-cyclopropanecarboxylic acid (22) and methyl ester (23)

To bicyclohexene (21) (1.042 g, 5 mmol) in t-butanol (200 ml) was added a solution of potassium permanganate (20 mg), sodium metaperiodate (6.417 g, 30 mmol) in water (400 ml). The pH of the reaction mixture was adjusted to nine with 5% potassium carbonate solution and the reaction stirred for forty-eight hours at room temperature. The pH was maintained at nine during this time by adding 5% potassium carbonate solution whenever necessary. Butanol was removed under vacuum and the reaction mixture acidified with 10% sulfuric acid and extracted with ether several times. The ether layer was washed with water and extracted with aqueous potassium carbonate solution. The alkaline solution was cooled and acidified with 10% sulfuric acid, extracted with ether. The ether layer was washed with brine, dried over anhydrous sodium sulfate and distilled off solvent to give (22) as semisolid. Esterification with diazomethane gave (23) (475 mg, 34.7%) as pale yellow oil.

It was purified by passing over silica gel column with 30% chloroform, pet.ether as eluant.

Analysis: Calculated for $C_{15}H_{17}ClO_3$; C, 64.16; H, 6.06; Cl, 12.66; Found: C, 64.36; H, 6.17; Cl, 12.31.

IR (liquid film): 3030, 1724, 1695, 1597, 1493, 1429, 1397, 1374, 1342, 1325, 1258, 1242, 1190, 1163, 1134, 1111, 1087, 1026, 1005, 995, 897, 820, 791, 769, 738 cm^{-1}.

PMR (CCl_4, δ): 1.17 (s, 3H, $-CH_3$), 1.30 (s, 3H, $-CH_3$), 1.57 (m, 2H, cyclopropyl protons), 3.03 (m, 2H, $-COCH_2-$), 3.57 (s, 3H, $-O-CH_3$), 7.4 (d, 2H, aromatic J = 8 Hz), 7.93 (d, 2H, aromatic, J = 8 Hz).

Methyl cis (±)-2,2-dimethyl-3-[2-(4-chlorophenyl)-2-chlorovinyl]cyclopropanecarboxylate (24) and (25)

To the keto ester (23) (350 mg, 1.24 mmol) in methylene chloride (6 ml)was added phosphorous pentachloride (442 mg, 2.12 mmol) and the reaction mixture refluxed for 20 hours. Crushed ice was added to the reaction mixture and the organic layer separated. The aqueous layer was extracted with methylene chloride twice. The combined organic layer was washed with water, brine and dried over anhydrous sodium sulfate, solvent was removed to furnish an oily residue (285 mg, 76.38%).

GLC: Column- S.E. 30(10%), temperature - 200°C, nitrogen flow- 30 ml/min, detector- FID; two peaks with ret ention time 9.74' and 12.14' in the ratio 2:3.

M/e: 298 (M^+), 263 (M^+ - Cl), 239 (M^+ -$COOCH_3$).

IR (liquid film): 3030, 1736, 1605, 1493, 1439, 1399, 1379, 1282, 1196, 1176, 1143, 1117, 1092, 1053, 1010, 1000, 930, 873, 847, 787, 760, 741, 714 cm^{-1}.

PMR (CCl_4, δ): 1.0 - 1.4 (m, 6H, $-CH_3$), 1.53 - 2.50 (m, 2H, cyclopropyl protons), 3.6, 3.67 (two s, 3H, $-OCH_3$), 5.23, 6.53 (two d, 1H, olefinic, J = 9, 9 Hz), 7.1 - 7.83 (m, 4H, aromatic).

3-Phenoxybenzyl cis(±)-2,2-dimethyl-3-[2(4-chlorophenyl)-2-chlorovinyl]cyclopropanecarboxylate (8)

Mixture of chloroester (24 and 25) (140 mg, 0.468 mmol), m-phenoxybenzyl alcohol (300 mg, 1.5 mmol), tetrabutyl titanate (15 mg, catalytic) was refluxed in xylene (5 ml) for fourteen hours. After cooling to room temperature, the solution was passed over a short column of silica gel and eluted with petroleum ether. The colourless eluant was evaporated to give (8) as a pale yellow coloured thick oil (134 mg, 61.3%).

M/e: 466 (M^+), 431 (M^+ - Cl), 239 (M^+ - $COOCH_2$-C_6H_4-O-C_6H_5), 183 (C_6H_5-O-$C_7H_6^+$).

IR (liquid film): 3067, 1754, 1613, 1504, 1449, 1408, 1389, 1316, 1290, 1266, 1205, 1190, 1149, 1124, 1099, 1058, 1020, 1005, 935, 855, 833, 791, 766, 719 cm^{-1}.

PMR ($CDCl_3$, δ): 1.26 (s, 6H, $-CH_3$), 2.0 (d, 1H, cyclopropyl proton, J = 9 Hz), 2.35 (dd, 1H, cyclopropyl proton, J = 9, 9 Hz), 5.1 (s, 2H, $-OCH_2$), 6.6 (d, 1H, olefinic, J = 9 Hz), 6.9 - 7.7 (m, 13H, aromatic).

REFERENCES

1. M. Elliott, Synthetic Pyrethroids, ACS Symposium series 42, ACS Washington D.C. (1977).
2. J.F. Engel, Ger.Offen, 2,738,150 (1978), FMC Corpn., C.A. 89, 42821.
3. R. Fuchs, I. Hammann, W. Stendel, Ger.Offen, 2,730,515 (1979), Bayer A-G., C.A. 90, 151658.
4. J.F. Engel, U.S. Patent, 4,157,447 (1979), FMC Corpn., C.A. 91, 107712.
5. M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham D.A. Pulman, ACS Symposium series No.2, 80 (1974).
6. D. Owen John, J.Chem.Soc.Perkins Trans I, 1231 (1976).
7. M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham and D.A. Pulman, Pestic.Sci. 7, 499 (1976).
8. M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham D.A. Pulman, Nature, 248, 710 (1974).
9. M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham D.A. Pulman, Nature, 244, 456 (1973).
10. P.E. Burt, M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham and D.A. Pulman, Pestic.Sci., 5. 791 (1974).
11. M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham and D.A. Pulman, Pestic.Sci., 6, 537 (1975).
12. H.J. Diehr, R. Fuchs, Ger.Offen 2,827,101 (1980), Bayer A.G., C.A. 92, 215078.
13. J.F. Engel, U.S. 4,183,942 (1980), FMC Corpn., C.A. 92, 215077.
14. J.F. Engel, U.S. 4,157,447 (1979) FMC Corp., C.A. 91, 107712.

15. J.F. Engel, Ger.Offen, 2,738,150 (1978), FMC Corp., C.A. 89, 42821.

16. R. Fuchs, H. Harnisch, R. Lantzsch, K. Naumann, H.J. Riebel, R. Schroeder, Ger.Offen. 2,916,357 (1980), Bayer A.-G., C.A. 94, 139469.

17. M. Jautelat, D. Arlt, R. Lantzsch, R. Fuchs, H.J. Riebel, R. Schroeder, H. Harnisch, Ger.Offen. 2,916,401 (1980), Bayer A.G. C.A. 94, 139468.

18, B.M. Mane, P.P. Pai, G.H. Kulkarni and R.B. Mitra, Indian J.Chem., 19B, 710 (1980).

19, R.B. Mitra, G.H. Kulkarni, K.Gore, A.S. Khanra, P.N. Khanna, Z. Muljiani, P.N. Choudhari, B.M. Bhawal, G.D. Joshi, Brit. U.K. Patent Appl. 2,034,301 (1980), Indian Appl. 761/DEL/78. C.A. 94, 65195.

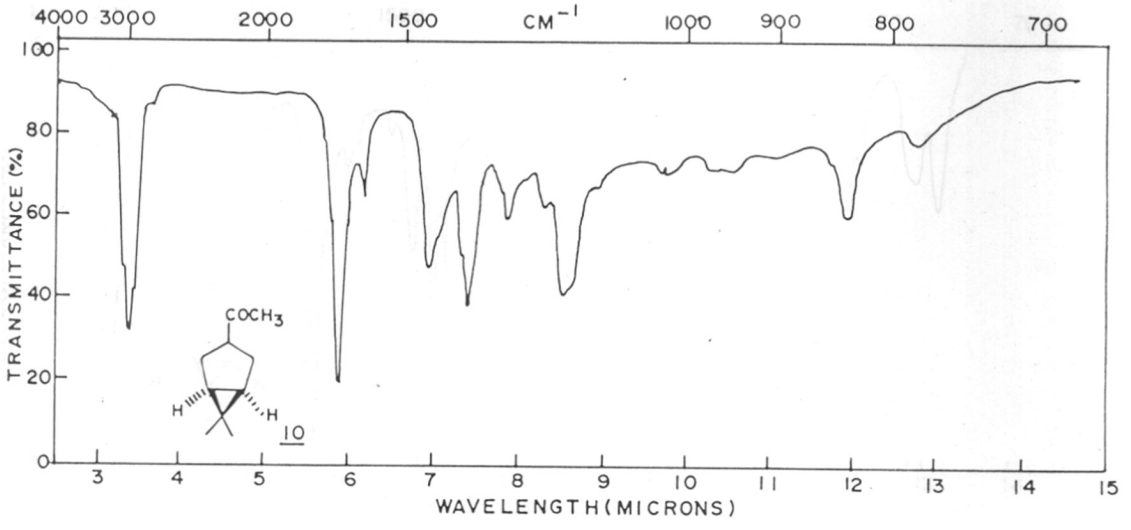
20. W. Cocker, D.H. Grayson, Tet.Lett., 4451 (1969).

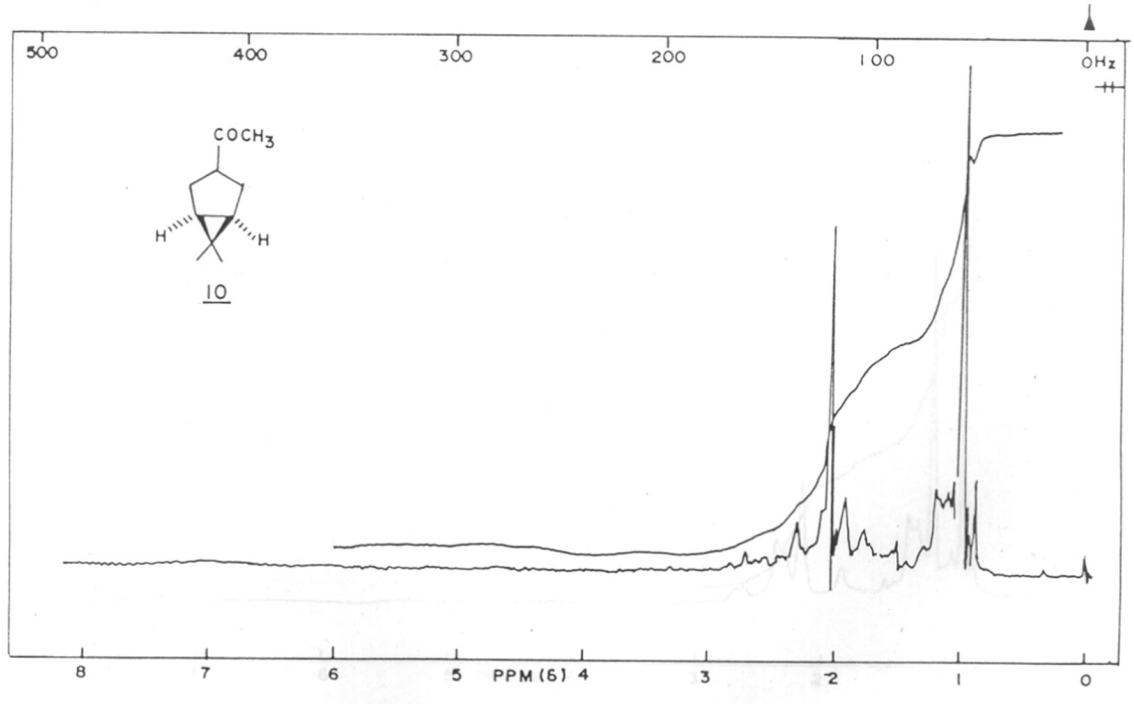
21. B.M. Mane, G.H. Kulkarni, Curr.Sci. 50, 715 (1981).

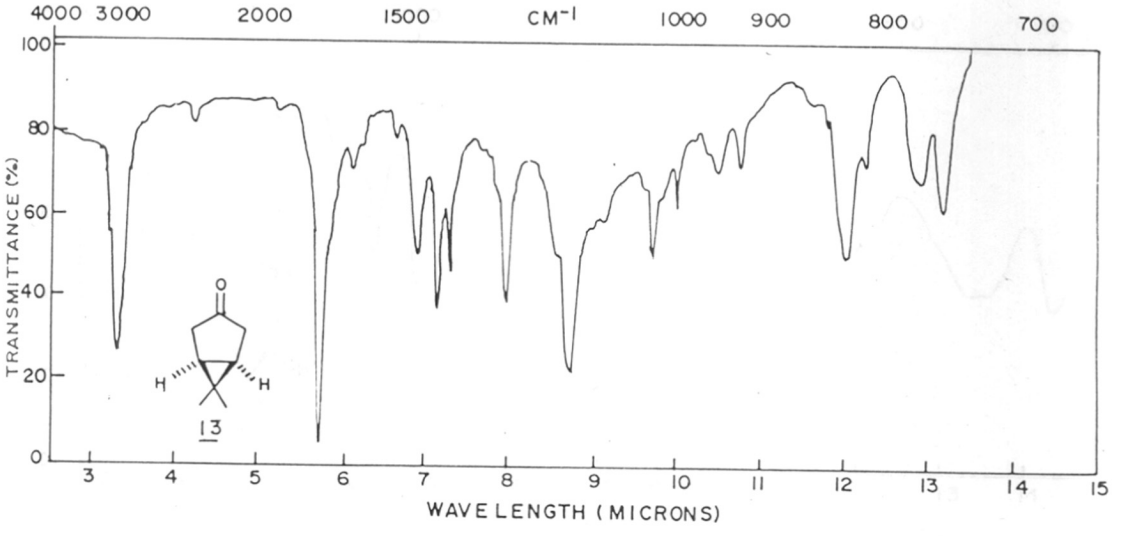
22. M. Walkowicz, H. Kuczynski and C. Walkowicz, Rocz.Chem. 41(5), 927 (1967).

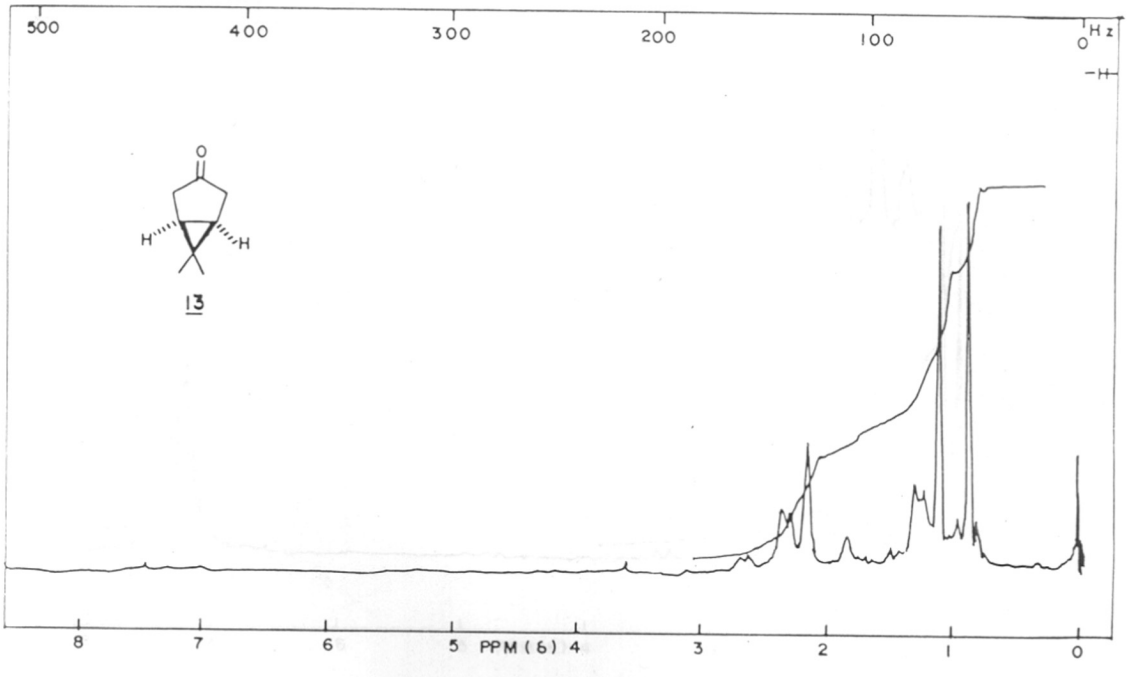
23. U.R. Lemieux, E. Von Rudloff, Can.J.Chem., 33, k701, 1710, 1714 (1955).

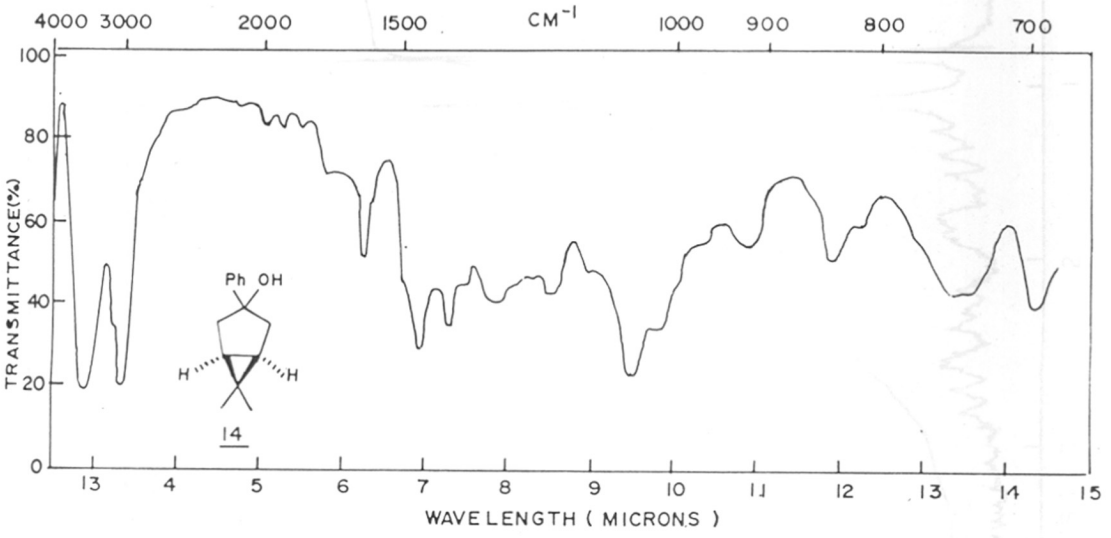
24. M.Halfon, W.G. Seharp, Brit.U.K. Pat ent Appl.2005269 (1979), FMC Corpn., C.A. 92, 22138.

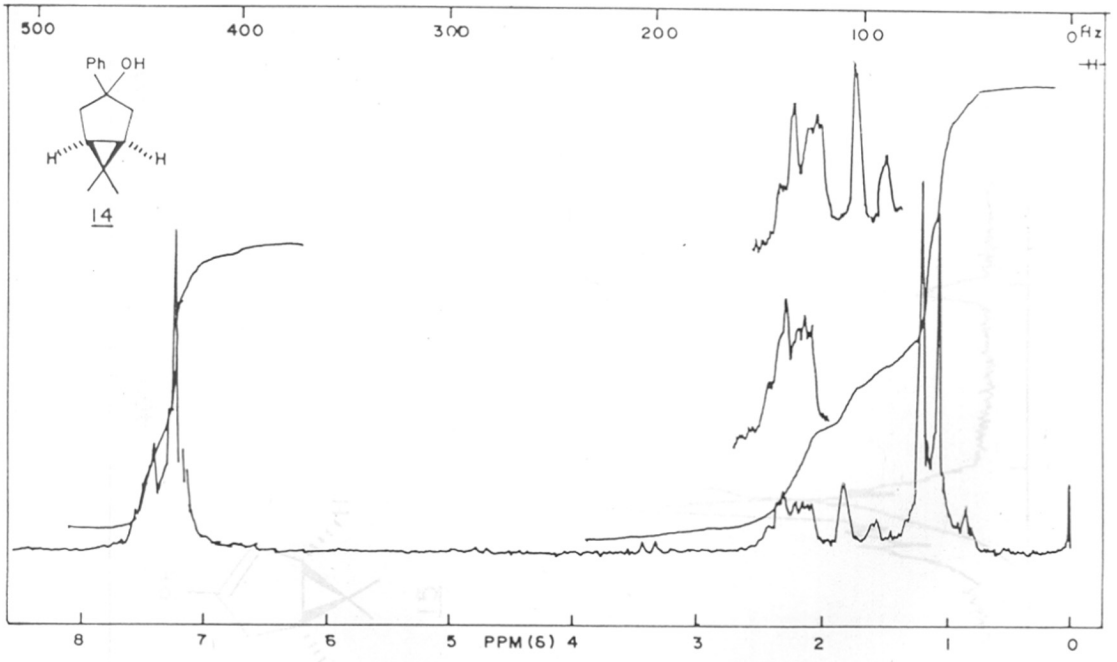

4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
COCH3
H
H
10
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

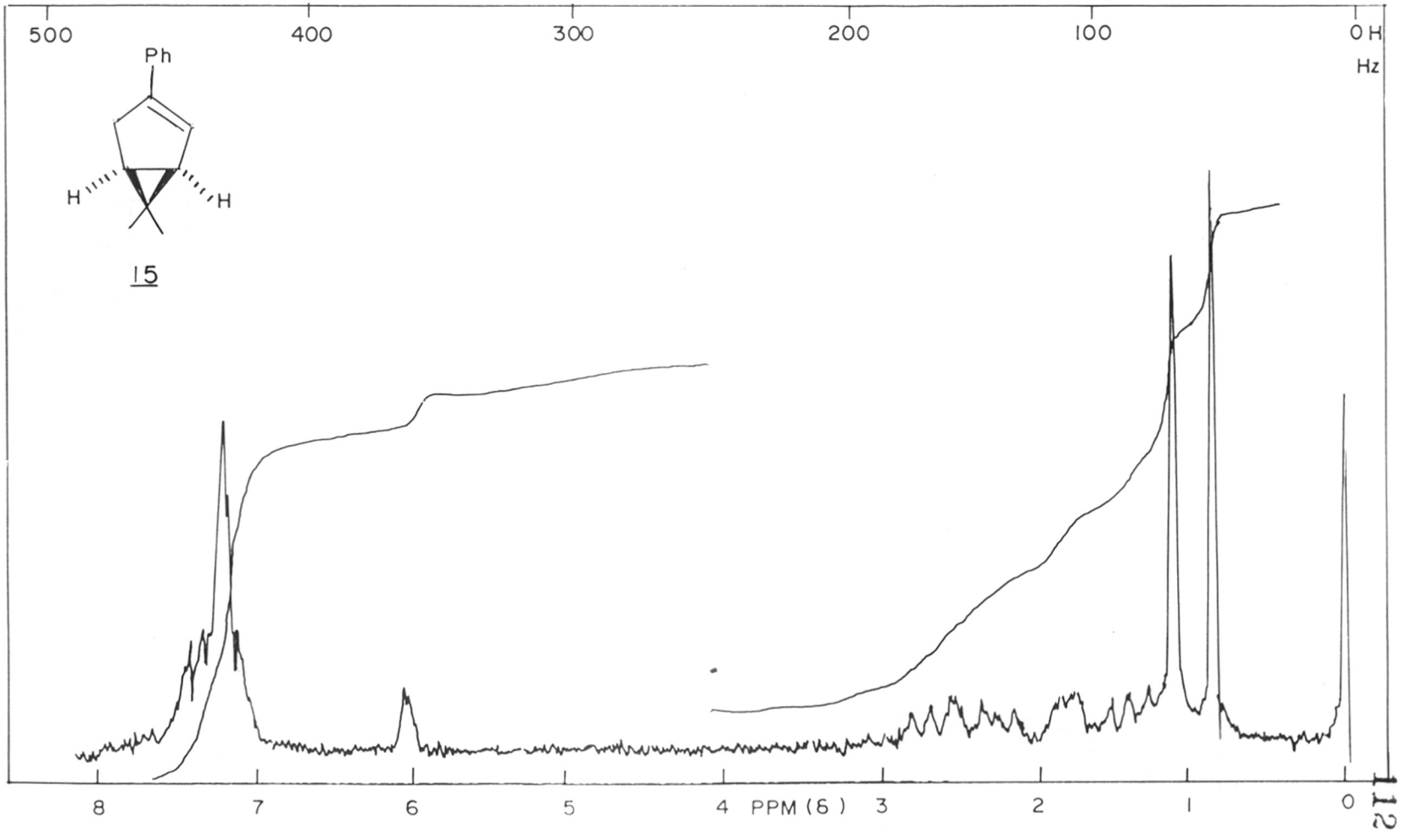

500 400 300 200 100 0Hz
COCH3
H
H
10
8 7 6 5 PPM (δ) 4 3 2 1 0


4000 3000
2000
1500
CM⁻¹
1000
900
800
700
100
80
60
40
20
0
TRANSMITTANCE (%)
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVE LENGTH (MICRONS)
O
H
H
13

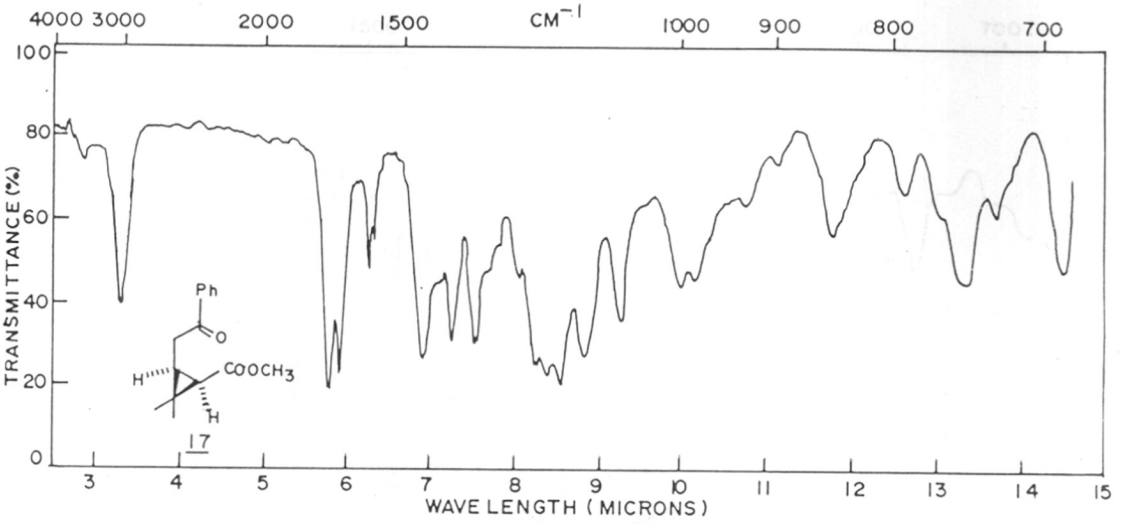

500
400
300
200
100
0 Hz
O
H
H
13
8
7
6
5 PPM (δ) 4
3
2
1
0

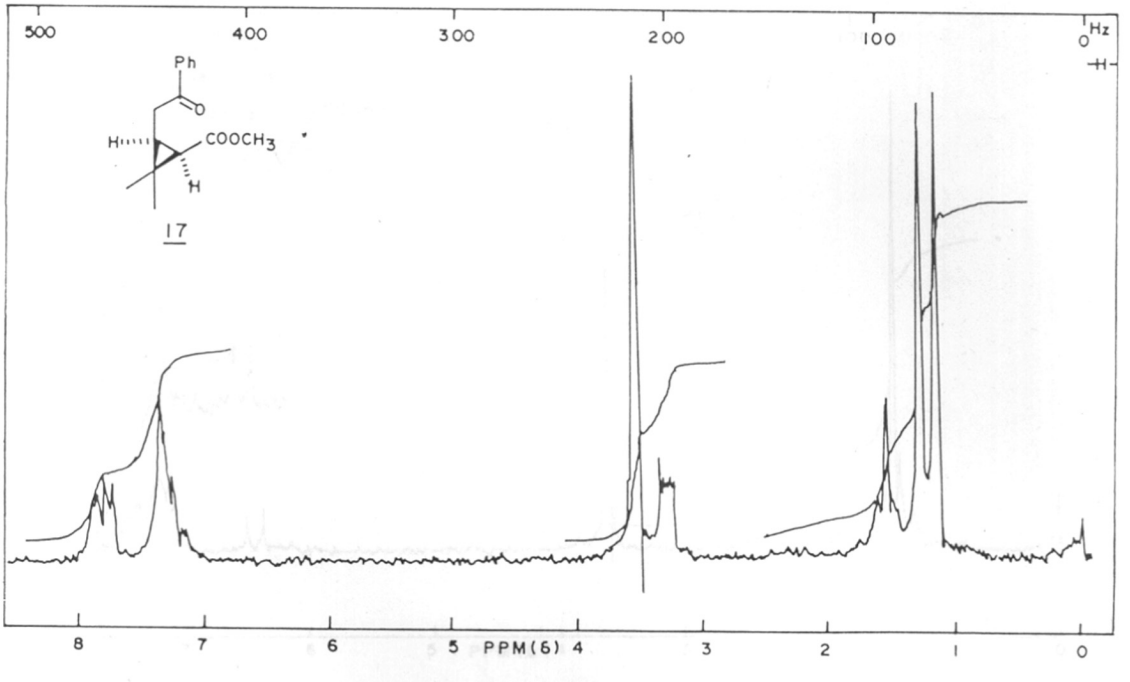

4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE(%)
Ph OH
H
H
14
13 4 5 6 7 8 9 10 11 12 13 14 15
WAVE LENGTH (MICRONS)

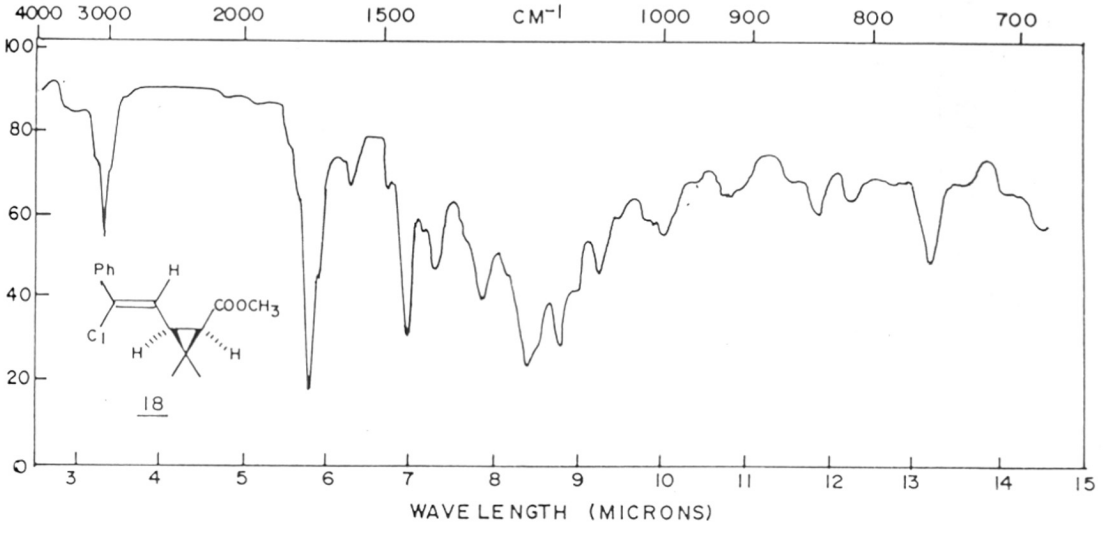

500 400 300 200 100 0 Hz
Ph OH
H
H
14
8 7 6 5 PPM(δ) 4 3 2 1 0

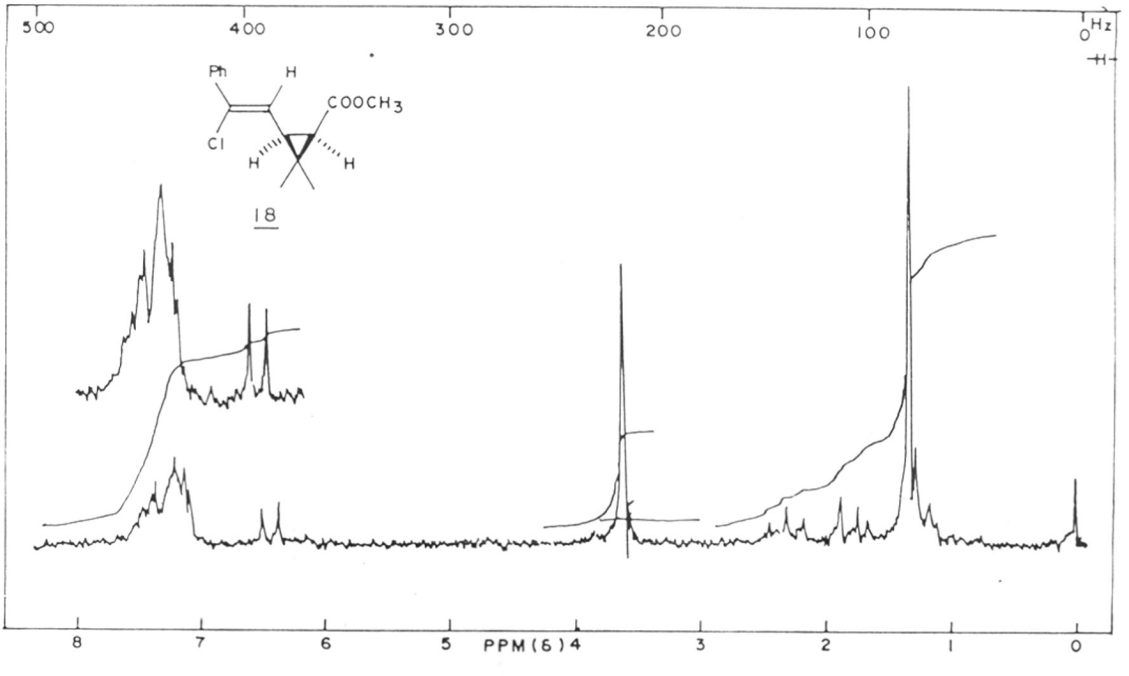


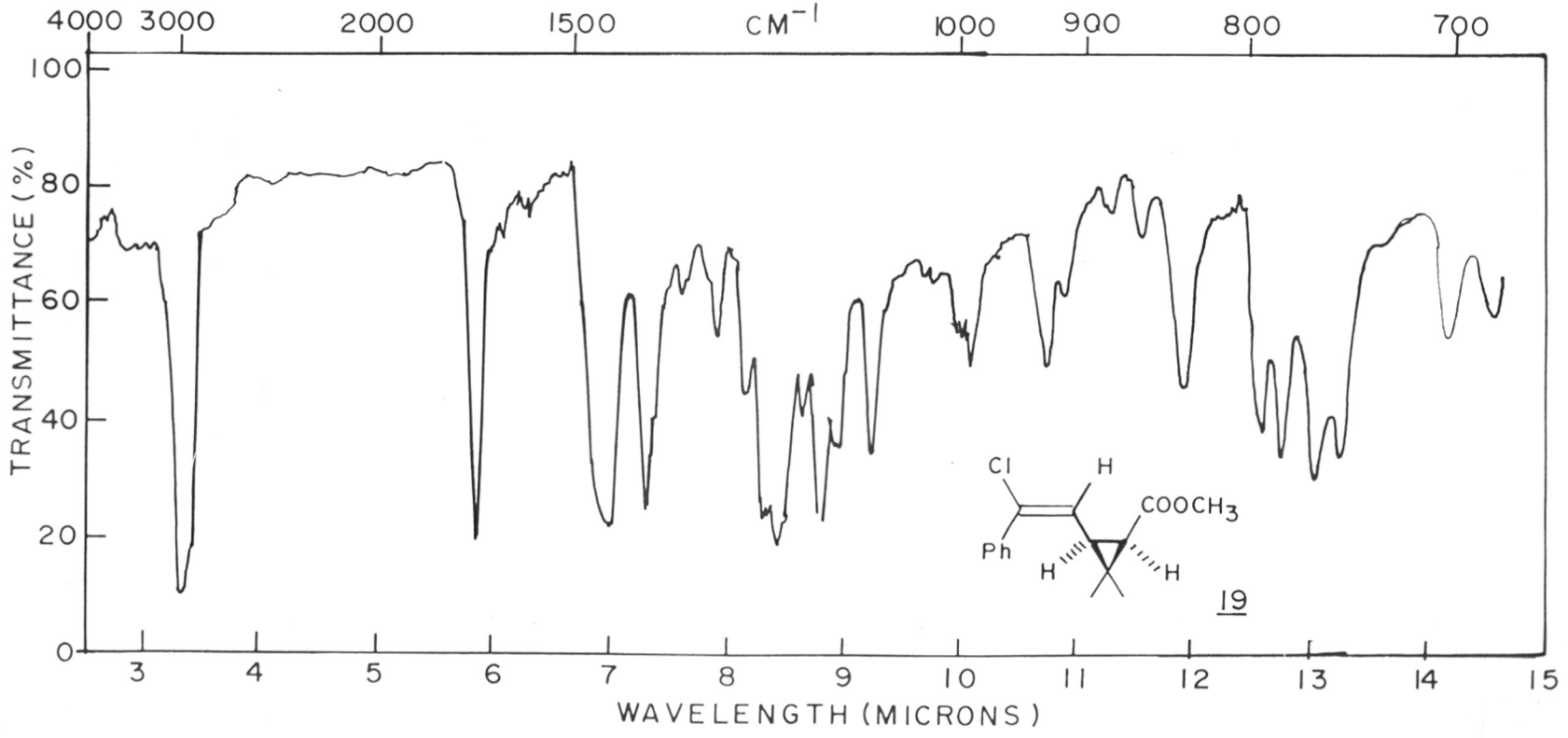
15


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
Ph
O
H
COOCH3
H
17
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVE LENGTH (MICRONS)

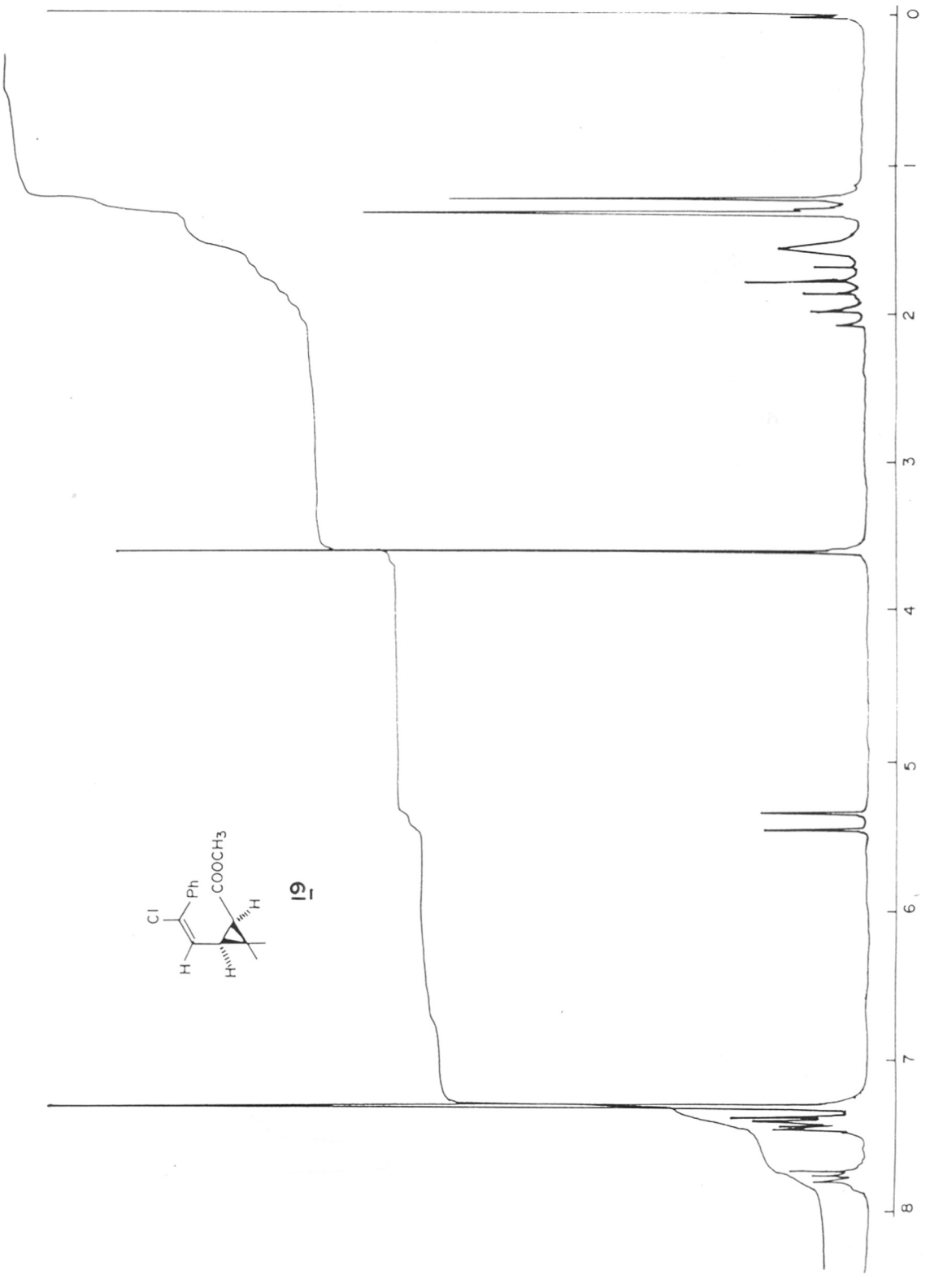

500 400 300 200 100 0 Hz
Ph
O
H
COOCH3
H
17
8 7 6 5 PPM(δ) 4 3 2 1 0


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
Ph
H
COOCH3
Cl
H
H
18
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVE LENGTH (MICRONS)

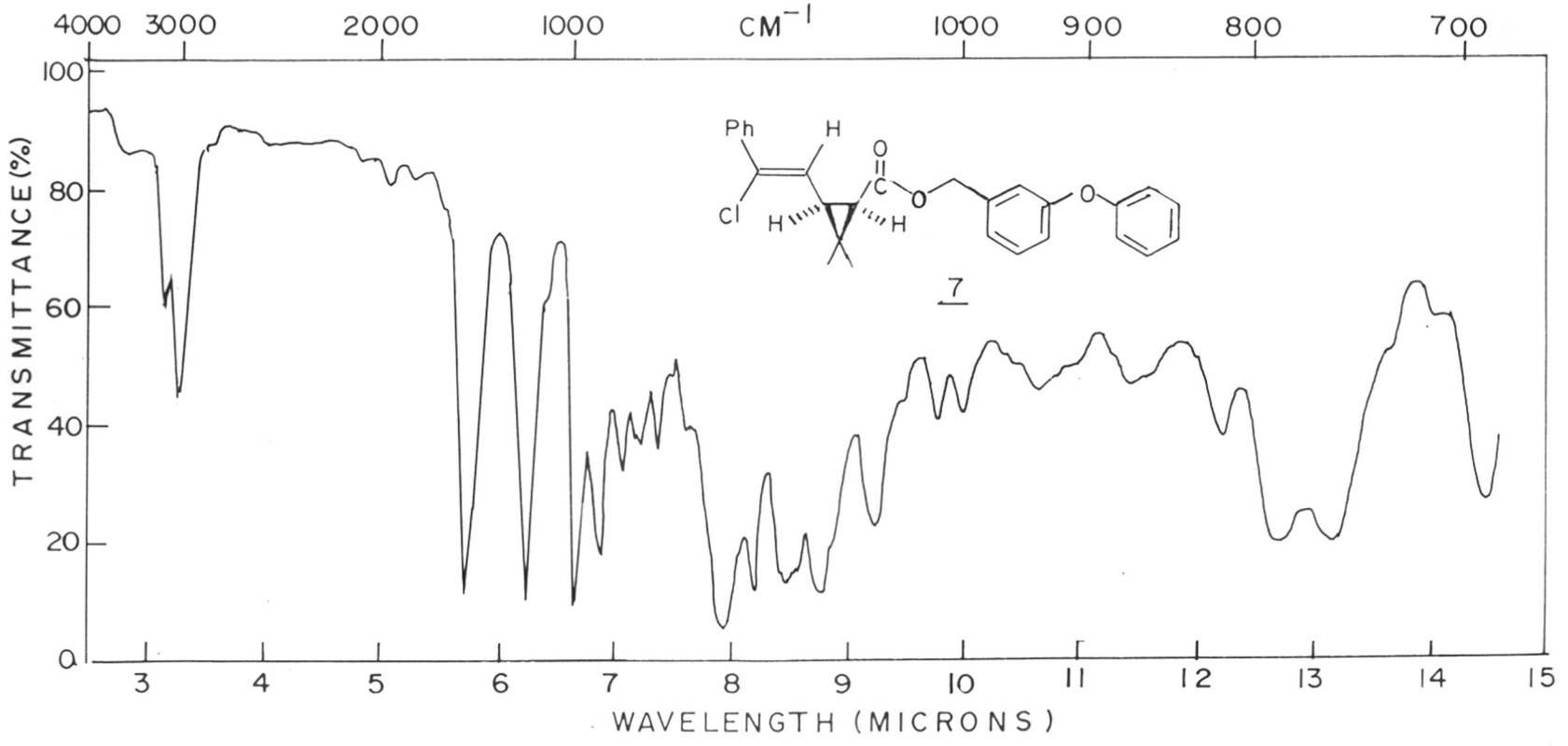

500 400 300 200 100 0 Hz
Ph
H
COOCH3
Cl
H
H
18
8 7 6 5 PPM(δ) 4 3 2 1 0

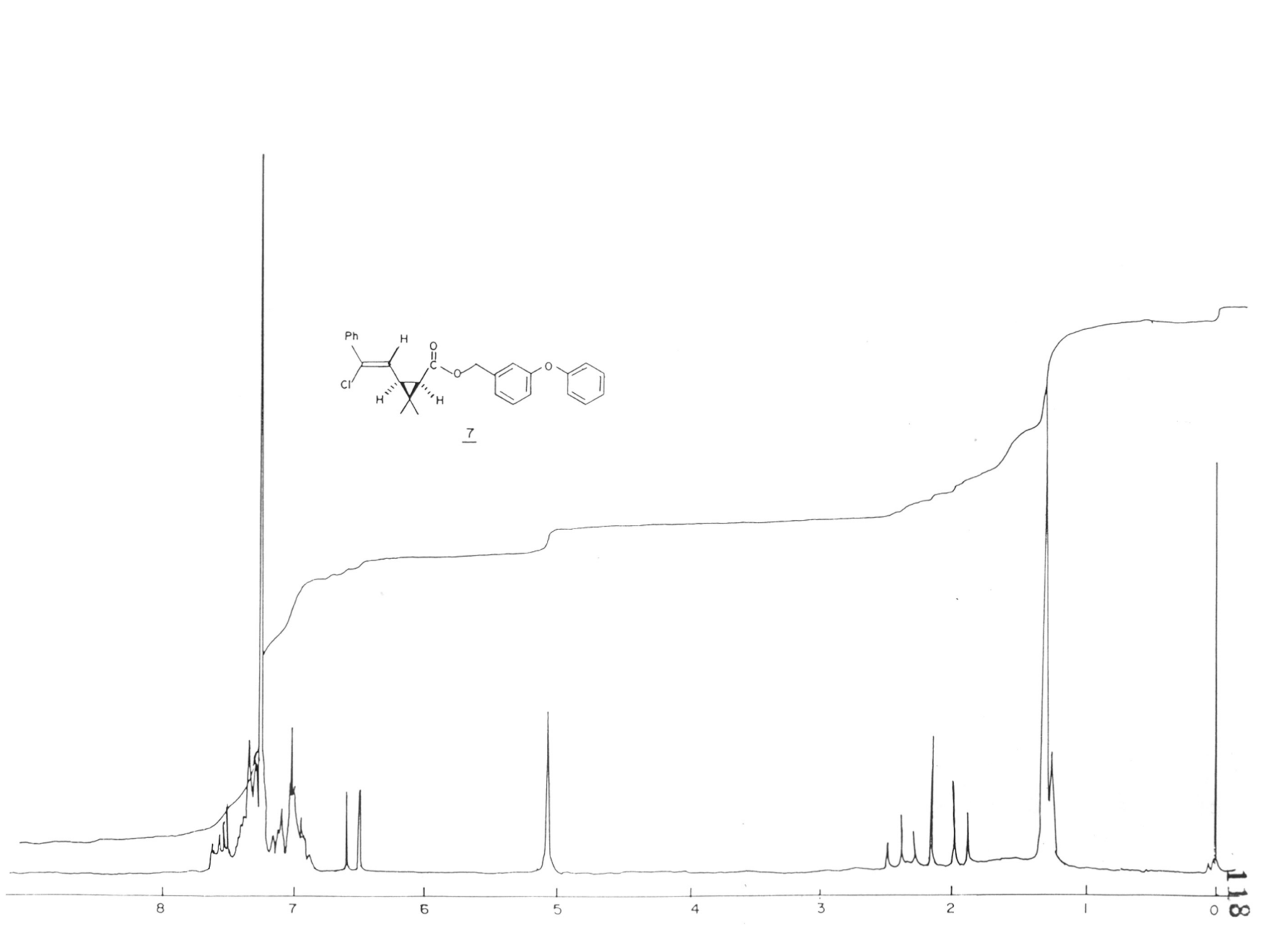

4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
Cl
H
COOCH3
Ph
H
H

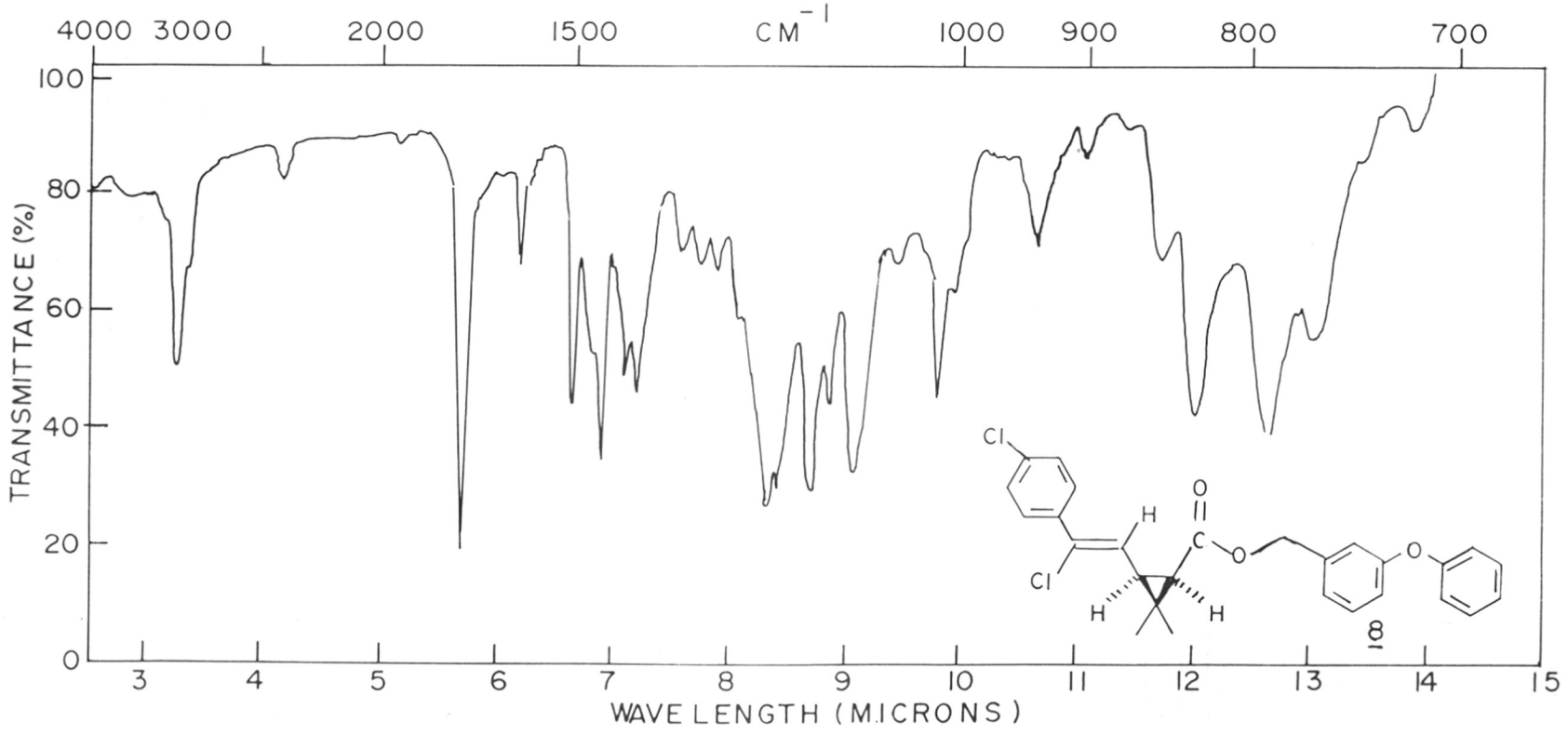
19

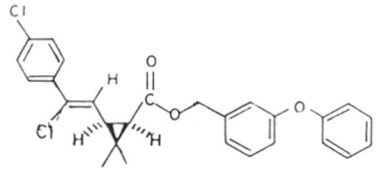


19


4000 3000 2000 1000 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
Ph
H
Cl
H
H
O
C
O
O
7


Ph
H
Cl
O
C
O
O
H
H
7
8
7
6
5
4
3
2
1
0


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVE LENGTH (MICRONS)
Cl
H
O
C
O
Cl
H
H
O
81



8

CHAPTER - IV

STEREOSPECIFIC SYNTHESIS OF 3-PHENOXYBENZYL-1R-TRANS AND 1S-CIS-2,2-DIMETHYL-3-(2-CHLORO-1-PROPENYL)CYCLOPROPANECARBOXYLATE

SUMMARY

3-Phenoxybenzyl-1R-cis-2,2-dimethyl-3-(2-chloro-1-propenyl)cyclopropanecarboxylate is known to have very good insecticidal activity. In view of this, 1R-trans and 1S-cis-3-phenoxybenzyl-2,2-dimethyl-3-(2-chloro-1-propenyl)cyclopropanecarboxylates were synthesized.

Carane diol (2) was oxidized to keto aldehyde (3) by sodium metaperiodate. This keto aldehyde (3) when treated with excess methylmagnesium iodide gave a dihydroxy compound (4). Jones oxidation and dehydration using PTS and benzene gave keto olefin (6). 1S-cis-Keto ester (8) was obtained from keto olefin (6). The dihydroxy compound (4) was acetylated to mono acetate (19) which after dehydration and oxidation gave acetate acid (21). Hydrolysis and lactonization using PTS gave δ-lactone (13) which was epimerized to 1R-trans-hydroxy acid (18, R=H). This was also obtained by refluxing hydroxy acid (11, R=H) or acetate (21) in alkaline ethylene glycol.

Jones oxidation of hydroxy ester (18) gave 1R-trans-keto ester (16). This 1R-trans-keto ester was converted to vinyl chloro esters (23,24,25) using phosphorous pentachloride. Trans esterification with 3-phenoxybenzyl alcohol gave the final pyrethroid (26,27). Similarly 1S-cis/isomer (9c, d) was prepared from 1S-cis-keto ester (8).

Stereospecific synthesis of 3-phenoxybenzyl-1R-trans and 1S-cis-2,2-dimethyl-3-(2-chloro-1-propenyl)cyclopropanecarboxylate

Present work and discussion

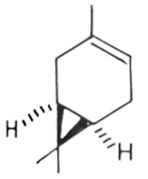
Stereochemistry is playing a vital role for the insecticidal activity in synthetic pyrethroids[1]. In most of the synthetic as well as natural pyrethroids, 1R-configuration in the acid part is one of the essential requirements for the higher insecticidal activity[2-5]. Pyrethroids with 1S-configuration are almost inactive. Insecticidal potency differences are observed between distereomeric pyrethroids having the R-configuration at C-1 but differing in configuration at C-3. In most insect species, the 1R-cis isomer of a distereomer pair is more toxic than the corresponding 1R-trans isomer. The toxicity difference can be as much as 10-fold, depending on both the species and pyrethroid examined. In American cockroaches, the toxicity ratio in favour of the cis-isomer has been found to range from 1.7 fold to 5-fold for a variety of pyrethroid esters[6]. D.M. Soderlund[7] explored the relative internal availability of 3-phenoxybenzyl-1R-cis-2,2-dimethyl-3-(2-dibromovinyl)cyclopropane-carboxylate acid its 1R-trans-isomer in the individual tissues of adult male American cockroaches, by

determining the accumulation of parent compounds in homolymph, nerve cord and fat body, after the administration of equitoxic doses. Eventhough, the just lethal dose of 1R-trans isomer was more than 3-fold higher than the equitoxic dose of 1R-cis-, the level of 1R trans were similar to those found for 1R-cis in both the nerve cord and fat body. The fact that steady state levels of 1R-trans in the nerve cord were less than one-half of those found for 1R-cis at an equitoxic dose suggests that the trans isomer is intrinsically more toxic than the cis-isomer and that its lower insecticidal activity results from the intervening influence of pharmacokinetic processes. So, although it looks from the bioassay that 1R-cis isomer is more toxic, but actually 1R-trans isomer is more toxic to the insect species.

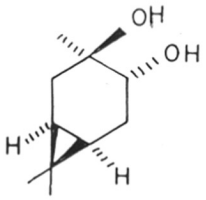
Synthetic pyrethroids, currently in use, combine both low mammalian toxicity and biodegradability with high activity against a large number of insect types. However, they exhibit high toxicity to fish[8] which limits their application in rice-paddy fields. In view of this, we synthesized pyrethroidal esters whose acid moiety has a hybrid structure of chrysanthemic acid and 3-dihalovinyl-2,2-dimethyl cyclopropanecarboxylate, i.e. 3-phenoxybenzyl cis and trans-2,2-dimethyl-3-(2-chloropropenyl)cyclo-

propanecarboxylate, starting from naturally occurring monoterpene, (+) 3-carene (1). The photostability and fish toxicity data has already been reported by the Japanese group of workers[9]. It has been shown that these esters possess very good photostability, low fish toxicity and comparable insecticidal activity, with that of permethrin.

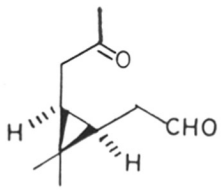
The synthesis of 3-phenoxybenzyl-1R-cis-2,2-dimethyl-3-(2-chloropropenyl)cyclopropanecarboxylate, "Indothrin"[10] has already been reported by R.B. Mitra et al. starting from (+) 3-carene (see Chapter II). Another non stereospecific synthesis of this particular pyrethroid is already on record[11] by Japanese group of workers. This synthesis gives a mixture of cis- and trans and also E & Z double bond geometric isomers. We have synthsized 1R-trans as well as 1S-cis-3-phenoxybenzyl esters of 2,2-dimethyl-3-(2-chloropropenyl)cyclopropanecarboxylic acid starting from (+) 3-carene. Thus, (+) 3-carene was converted to carane diol (2) by a known method[12] using performic acid. The carane diol (2) was cleaved with sodium metaperiodate to afford quantitatively keto-aldehyde (3). This keto-aldehyde was reacted with excess methyl magnesium iodide to get dihydroxy compound (4) as a thick oil IR (liquid fil): 3448 cm^{-1}, (hydroxyl). PMR (CCl_4, δ): 0.53 (m, 2H, cyclopropyl protons), 0.87 (s, 3H, $-CH_3$), 1.03 (s, 3H, $-CH_3$), 1.17 (m, 9H, $-CH_3$ attached to carbon bearing oxygen),



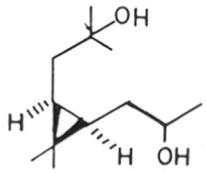
1



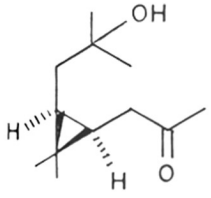
2



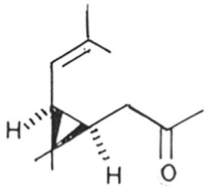
3



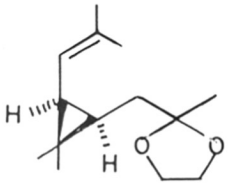
4



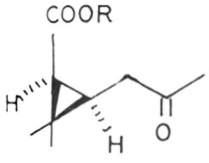
5



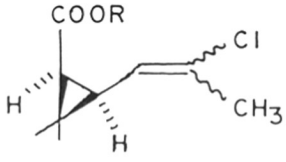
6



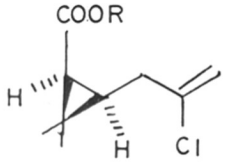
7



8 R=H, CH_3

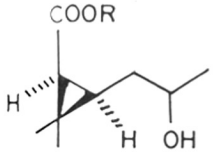


9a R = CH_3



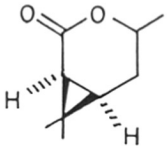
9b R = CH_3

9c, R = 3-PHENOXYBENZYL 9d, R=3-PHENOXYBENZYL

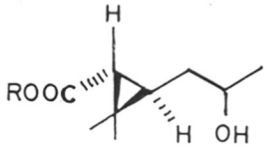


11, R = H

12 R = CH_3

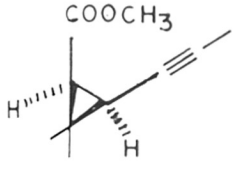


13

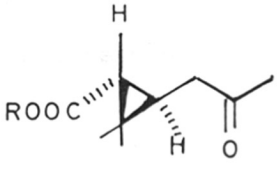


14, R = $-C(CH_3)_3$

18 R = CH_3

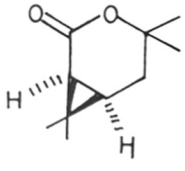


10



15 R = $-C(CH_3)_3$

16 R = CH_3



17

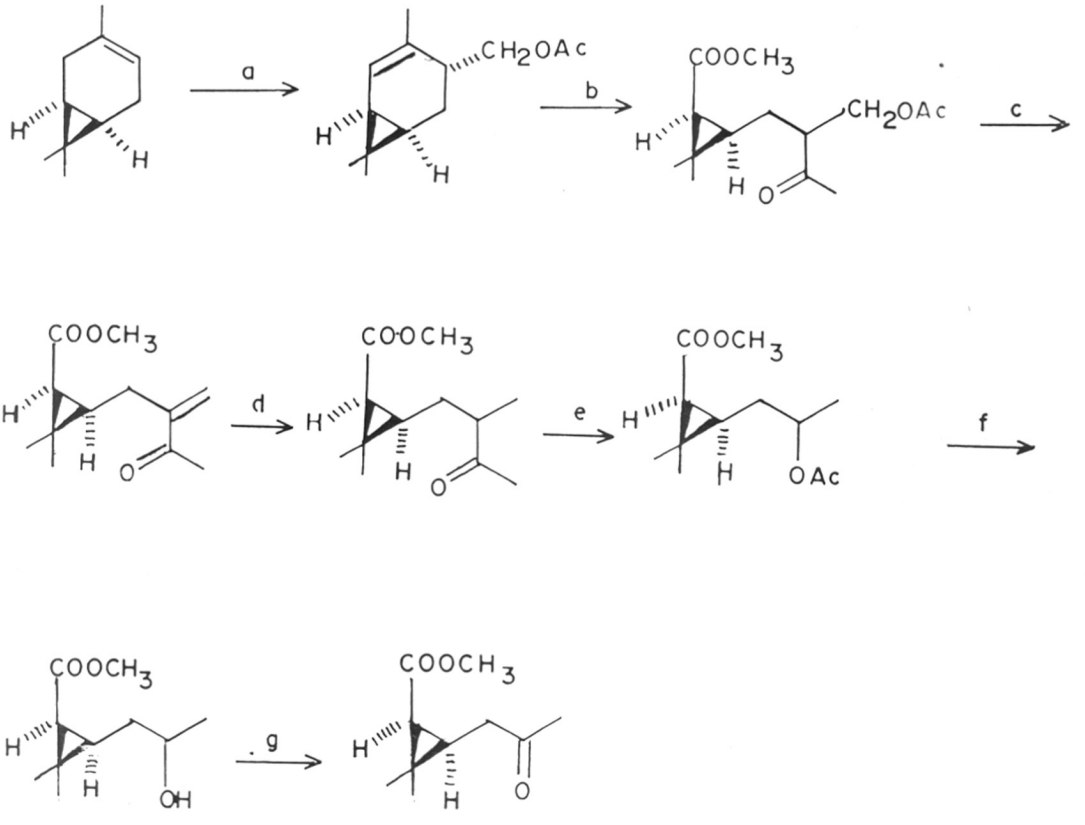
3.73 (m, 3H, -OH, and -CH-OH). This dihydroxy compound (4) was having one secondary hydroxyl group and the other tertiary hydroxyl group. The secondary hydroxyl group was selectively oxidized to ketone (5) by Jones chromic acid reagent at 0-5°C. IR (liquid film): 3509 cm^{-1} (hydroxyl) and 1739 cm^{-1} (ketone); PMR (CCl_4, δ); 0.7 (m, 2H, cyclopropyl protons), 0.83 (s, 3H, $-CH_3$), 1.06 (s, 3H, $-CH_3$), 1.10 (s, 6H, $-CH_3$), 1.27 (m, 2H, $-CH_2$), 1.83 (broad s, 1H, -OH), 2.03 (s, 3H, $-COCH_3$), 2.23 (d, 2H, $-COCH_2$, J = 6Hz). Dehydration of this hydroxy ketone (5) was achieved by refluxing in benzene azeotropically for 24 hours using p-toluenesulfonic acid as catalyst. Unlike the dehydration with phosphorous oxychloride and pyridine[12], only one double bond isomer (6) was obtained quantitatively. The crude keto-olefin (6) was distilled under vacuum b.p.80-110°/2 mm (bath temp.) to give pale yellow oil. IR (liquid film): 1724 cm^{-1}.(ketone), 1672 and 840 cm^{-1} (C=C). PMR (CCl_4, δ): 0.9 (s, 3H, $-CH_3$) 1.13 (s, 3H, $-CH_3$), 1.0 - 1.5 (m, 2H, cylopropyl protons), 1.66 and 1.73 (s, each, 6H, $=C(CH_3)_2$), 2.03 (s, 3H, $-COCH_3$), 2.26 (d, 2H, $-COCH_2$, J = 6 Hz), 4.08 (d, 1H, olefinic, J = 7 Hz).

Attempts to oxidize the keto-olefin (6) using potassium permanganate with various reaction conditions

failed but when the keto group was protected as diethylene ketal (7), 1S-keto acid (8) was obtained in 40% yield;with potassium permanganate as oxidant, the deketalization occurred during workup of the reaction. This keto acid (8) was also obtained by ozonolysis of keto olefin (6), after oxidative workup of the ozonoid with Jones reagent. It was characterized as a methyl ester. IR (liquid film): 1745 cm^{-1} (ester, and ketone); PMR (CCl_4,δ): 1.1 (s, 3H, $-CH_3$), 1.2 (s, 3H, $-CH_3$), 1.33 - 1.63 (m, 2H, cyclopropyl protons), 2.06 (s, 3H, $-COCH_3$), 2.83 (d, 2H, $-COCH_2$, J = 6 Hz), 3.60 (s, 3H, $-OCH_3$); $(\alpha)_D^{30}$ = + 34.54° ($CHCl_3$; c, 2.64), reported[13] $(\alpha)_D^{20}$ = + 38.2 ($CHCl_3$; c, 1.6).

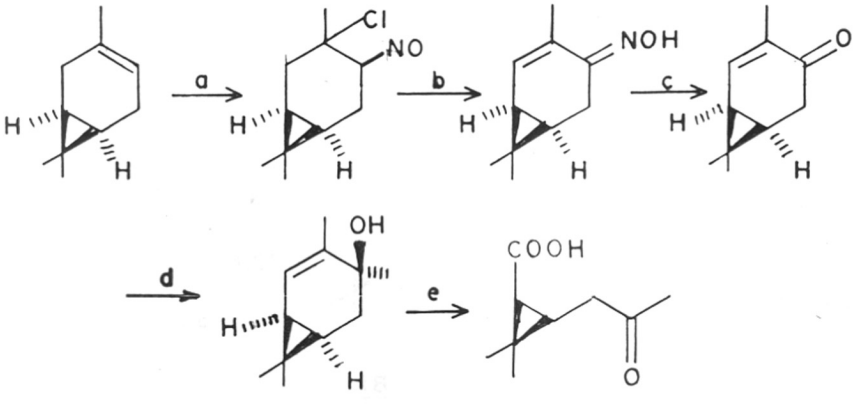
This keto ester (8) is a very important intermediate for the synthesis of 1R-trans-chrysanthemic acid. Synthesis of this keto-ester was already reported by W. Cocker et al.[13] by a multistep reaction sequences starting from (+) 3-carene and that too in very low yields (Scheme I). T.L. Ho et al. also reported the synthesis of this important intermediate starting from (+) 3-carene[14] (Scheme II) and carvone[15] (Scheme III). In the synthesis of (8) starting from (+) 3-carene by T.L. Ho, the first step is to be carried out with great care and also the alkylation of car-2-ene-4-one is done by methyl lithium at very low temperature. The other synthesis

SCHEME – I



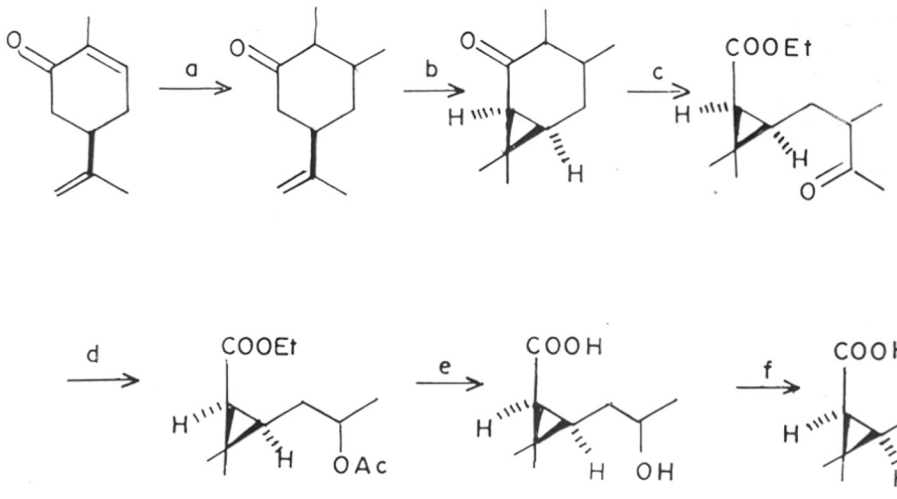
a = HCHO , CH_3COOH ; b = i) O_3, H_2O_2 ii) CH_2N_2 ; c = BASE d = H_2, Pd-C ;
e = MCPBA ; f = BASE , CH_2N_2 ; g = JONES REAGENT

SCHEME – II



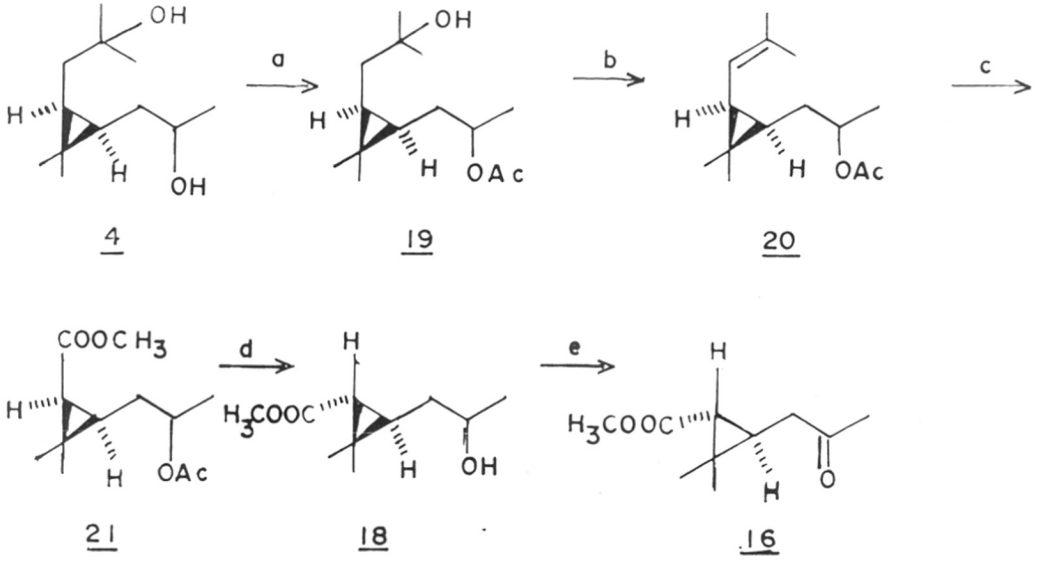
a = NOCl ; b = Na_2CO_3, iPrOH ; c = $NaHSO_3$; aq. EtOH ; d = MeLi
e = O_3, MeOH, –78°, H_2O_2, NaOH

SCHEME-III



a = CuCl , CH_3MgI ; b = i) HCl , ii) NaOH , MeOH ; c = EtONO , EtONa , d = CH_3COOOH ; e = 50% NaOH , aq EtOH
f = Cl_2/ Py

SCHEME – IV



a = Ac_2O, Py. ; b = PTS, BENZENE ; c = $KMnO_4$, CH_2N_2 ; d = KOH, ETHYLENE GLYCOL, CH_2N_2; e = JONES REAGENT

starting with carvone is again a multi-step, low yielding synthesis, while, in our synthesis, the reactions involved are comparatively simple and can be done at moderate reaction conditions with high yields.

Once the keto ester (8) was ready, it was converted to vinyl chloro ester (9a, 9b) by a well-known phosphorous pentachloride reaction[16]. An isomeric mixture was obtained in the ratio 35:27:38 as in the case of 1R-cis-2,2-dimethyl-3-(2-chlorpropenyl)cyclopropanecarboxylic acid ester[16]. This mixture was not separated further as it was expected to be an inactive and also separation and characterization of individual isomer from the mixture was already done in case of 1R-cis-vinyl chloro esters. So the 3-phenoxybenzyl esters were prepared by trans esterification[17] and the insecticidal activity checked. It was found to be inactive as expected.

Our main interest was to get biologically active 1R-trans-ester. So, we tried to epimerize methyl-1S-cis-2,2-dimethyl-3-(2-chloropropenyl)cyclopropanecarboxylate using various reaction conditions. The Julia's method[18] of epimerization using potassium tertiary butoxide in benzene did not work. Some how it gave unepimerized vinyl chloro acid which was confirmed by

PMR spectrum after re-esterification. When the chloro-ester (9) was subjected to Sukh Dev's[19] reaction condition of epimerization using diethylene glycol and sodium hydroxide a dark coloured tarry material was obtained. When this 1S-chloro ester (9) was refluxed in tertiary butanol and potassium tertiary butoxide dehydro halogenation was observed and an acetylenic compound (10) was obtained. PMR showed no olefinic proton absorption. Mass spectrum showed molecular ion peak at 166.

So, our next choice was to epimerize the 1S-keto ester (8). But unfortunately this keto ester was reported to be very sensitive to alkali and cyclopropane ring was known to open up with alkali[20]. Therefore, the keto group was reduced by sodium borohydride to hydroxyl. The hydroxy ester (11) obtained so was having identical IR and PMR spectra as reported by W. Cocker[13] for the same compound. This hydroxy ester (11) was then subjected to epimerization using Julia's[18] conditions, but again it did not work. The ester was then hydrolysed to hydroxy acid (12) by aqueous ethanolic sodium hydroxide. The hydroxy acid was lactonized by refluxing with benzene, containing catalytic amount of p-toluenesulfonic acid, for three hours. After usual workup, lactone (13) was obtained as colourless oil

IR (liquid film): 1730 cm^{-1} (δ-lactone). PMR (CCl_4, δ): 0.9 (m, 1H, cyclopropyl proton), 1.08 (s, 3H, $-CH_3$), 1.22 (s, 3H, $-CH_3$), 1.17 (d, 3H, CH_3-CH, J = 6 Hz), 1.37 (m, 2H, $-CH_2$), 1.87 (m, 1H, cyclopropyl proton), 4.3 (m, 1H, -ĊH-O-).

The lactone (13) was refluxed with potassium tertiary butoxide in t-butanol, with the idea of getting alkali stable t-butyl ester. After working up the reaction 20% neutral portion and 80% acidic portion was obtained. The acidic part was nothing but the unepimerized hydroxy acid (12) which was confirmed by relactonization using p-toluenesulfonic acid and benzene. The 20% neutral portion was characterized as hydroxy t-butyl ester (14). IR (liquid film): 3509 cm^{-1} (hydroxyl) and 1718 cm^{-1} (ester); PMR (CCl_4, δ): 0.96 - 1.36 (complex m, 13H), 1.43 (s, 9H, t-butyl), 2.16 (broad s, 1H, -OH), 3.8 (m, 1H, -CH-O-).

Jones oxidation of t-butyl ester (14) at $0^{o}C$ gave keto ester (15) as an oil IR (liquid film): 1724 cm^{-1} (ketone, ester); PMR (CCl_4, δ): 0.96 - 1.33 (m, 2H, cyclopropyl protons)), 1.06 (s, 3H, $-CH_3$), 1.20 (s, 3H, $-CH_3$), 1.43 (s, 9H, t-butyl), 2.06 (s, 3H, $-COCH_3$), 2.36 (m, 2H, $-COCH_2$). This t-butyl ester (15) was hydrolysed by treating with a saturated solution of dichloromethane with dry hydrogen chloride gas, at

0-5°C for 32 hours. It was then re-esterified with diazomethane to get keto ester (16). It was purified by passing over silica gel column with 5% ethyl acetate in benzene as eluant to get colourless oil. PMR spectrum of this keto ester (16) showed a pair of doublet at δ 2.4 for $-CO-CH_2-$ protons, while in PMR spectrum of 1S-keto ester (8) a broad doublet was seen at δ 2.83 for $-CO-CH_2-$ and it was downfield because of deshielding effect of carbomethoxy group at C-1. In case of keto-ester (16), the carbomethoxy group must be trans to the side chain at C-3, therefore $-COCH_2-$ signal appeared upfield as compared to 1S-keto ester. The specific rotation also agreed with the trans configuration of carbomethoxy group $(\alpha)_D^{30} = -32.3^\circ$ for 1R-trans keto ester (16) while $(\alpha)_D^{30} = +34.5^\circ$ for 1S-cis-keto ester (8). IR (liquid film): 1724 cm^{-1} (ketone and ester); PMR (CCl_4, δ): 1.1 (s, 3H, $-CH_3$), 1.23 (s, 3H, $-CH_3$), 1.37 - 1.73 (m, 2H cyclopropyl protons), 2.13 (s, 3H, $-COCH_3$), 2.4 (dd, 2H, $-COCH_2$), 3.7 (s, 3H, $-OCH_3$).

Although we got the 1R-trans-keto ester (16) in hand, yield was not good enough to proceed further. Sukh Dev et al.[13] could cleanly and quantitatively convert dihydrochrysanthemo lactone (17) to 1R-trans-chrysanthemic acid by refluxing with diethylene glycol

and sodium hydroxide. Our lactone (13) was similar to dihydrochrysanthemo lactone, except a methyl group at C-5 was missing. So, the lactone (13) which was somewhat similar to chrysanthemo lactone was refluxed in ethylene glycol containing potassium hydroxide under nitrogen atmosphere for six hours. It was cooled to room temperature and diluted with water; extractive workup with ether after acidification gave brown oil which was esterified with diazomethane. GLC of the crude ester revealed only 4% unepimerized hydroxy ester (11). This crude hydroxy ester was oxidized by Jones chromic acid reagent to get trans-keto ester (16). This was purified by silica gel column chromatography using 5% ethyl acetate-benzene as eluant. GLC showed it to be 99% pure trans keto ester (16). IR and PMR data was identical with that of authentic.

It was interesting to note that no olefinic proton signal was seen in the PMR spectrum of crude hydroxy ester (18), as in the case of trans-chrysanthemic acid obtained from dihydrochrysanthemo lactone (17). That means, the first step is hydrolysis of the lactone (13) and then it is epimerized. The dehydration in dihydro-chrysanthemo lactone during epimerization may be due to tertiary -OH in the hydrolysed acid, which can easily undergo dehydration under such drastic reaction conditions.

While, in case of lactone (13) there is no dehydration under these reaction conditions as there is a secondary -OH in the hydrolysed acid. Accordingly, when 1R-cis-hydroxy ester (11) was subjected to epimrization under similar conditions, similar results were obtained as in the case of lactone (13).

Once the epimerization was achieved, the complete route to methyl- 1R-trans-2,2-dimethyl-3-(2-oxopropyl)-cyclopropanecarboxylate was established as shown in the Scheme IV. The dihydroxy compound (4) was acetylated with acetic anhydride and pyridine. The usual workup of the reaction gave hydroxy acetate (19) as thick pale yellow oil IR (liquid film): 3571 cm^{-1} (hydroxyl) and 1724 cm^{-1} (acetate), PMR (CCl_4, δ): 0.53 (m, 2H, cyclopropyl protons), 0.9 (s, 3H, $-CH_3$), 1.07 (s, 3H, $-CH_3$), 1.17 (s, 6H, $-CH_3$), 1.33 (d, 3H, $\underline{CH_3}$-CH-), 2.0 (s, 3H, $-OCOCH_3$), 2.63 (broad s, 1H, -OH), 4.83 (m, 1H, -CH-O-).

The hydroxy acetate (19) was subjected to dehydration using p-toluene sulfonic acid as catalyst, by refluxing for 48 hrs in benzene to get brown oil in 87.7% yield. It was distilled to get pale yellow oil b.p. $98^{o}/2$ mm. IR (liquid film): 1748 cm^{-1} (acetate), PMR (CCl_4, δ): 0.43 - 0.87 (m, 1H, cyclopropyl proton) 0.93 (s, 3H, $-CH_3$), 1.10 (s, 3H, $-CH_3$), 1.13 - 1.16

(m, 6H, $-CH_3$, $-CH_2$ adnd cyclopropyl proton) 1.70 and 1.73 (s, each, 6H, $= C(CH_3)_2$), 1.96 (s, 3H, $-COCH_3$), 4.6 - 5.1 (m, 2H, olefinic and -CH-O-), the acetate (20) was oxidized by potassium permanganate in acetone to furnish acetate acid (21) in about 60% yield. It was esterified with diazomethane to get (21, R = CH_3), as pale yellow oil. IR and PMR spectral data was identical with the reported data for the same compound by Cocker et al.[13].

The crude acetate acid (21, R = H, obtained as above was taken in ethylene glycol containing excess potassium hydroxide and refluxed for six hours under nitrogen atmosphere. Ethylene glycol was distilled off and the residue was diluted with water and extractive workup with ether after acidification gave brown oil, which was esterified with diazomethane. GLC analysis of the crude product showed it to be about 90% 1R-trans hydroxy ester (15). It was oxidized to keto ester and purified as usual to get pure 1R-trans keto ester (16). All the spectral data were found to be identical with that of authentic 1R-trans keto ester (16).

The 1R-trans-keto ester (16) was treated with neat phosphorous pentachloride with initial cooling and then left at room temperature overnight. The reaction mixture was poured over crushed ice and extracted with

ether, the ether layer washed with water, dried over anhydrous sodium sulfate and solvent was removed to get brown oil. It was distilled under vacuum to get colourless oil in about 70% yield b.p.80-90°/1 mm. The GLC analysis showed it to be a mixture of four compounds.

Compouned	Retention time	% Composition
A	9.77'	21.5%
B	10.90'	12.2%
C	11.43'	35.2%
D	18.79'	28.1%

GCMS-analysis showed molecular ion peak for compound A, B and C at m/e 202, while for compound D fragments ion peak were seen at m/e 207, 203 and 127. The peak at m/e 207 might not be the molecular ion peak but it might have arised by loss of CH_3 from the molecular ion m/e 238 and the next peak at m/e 203 might be due to loss of chlorine from the molecular ion m/e 238. From this fragmentation pattern, compound D might have the structure (22) and the fragment ion peak m/e 127 might be due to loss of $CH_2 - \underset{Cl}{\overset{Cl}{C}} - CH_3$.

Compound D was separated from the mixture by preparative GLC and its mass spectrum showed the molecular ion peak at m/e 238. It also gave satisfacory

elemental analysis.

IR (liquid film): 1736 cm^{-1} (ester); PMR ($CDCl_3$, δ): 1.20 (s, 3H, $-CH_3$), 1.28 (s, 3H, $-CH_3$), 1.32 - 2.0 (m, 2H, cyclopropyl protons), 2.20 (s, 3H, $-CH_3$), 2.24 - 2.76 (m, 2H, $-CH_2$), 3.76 (s, 3H, $-OCH_3$). The mixture was treated with sodium hydroxide in methanol at reflux when compound D (22) was dehydrochlorinated to give the following product distribution by GLC:

Compound A (27%), compound B (16%) and compound C (50%).

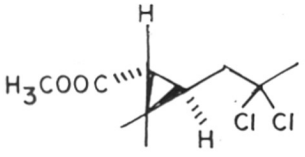
By careful chromatography of the mixture over silica gel, impregnated with 30% silver nitrate, and pet.ether as eluent, three enriched fraction were obtained.

Fractions	% A	% B	% C
I	4%	94%	2%
II	11.4%	11.3%	76.9%
III	56%	-	43%

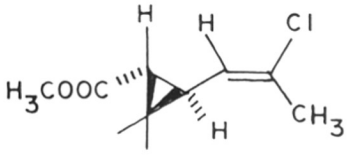
Fraction I was obtained as 94% pure B.

IR (liquid film): 1730 cm^{-1} (ester); PMR ($CDCl_3$, δ): 1.17 (s, 3H, $-CH_3$), 1.26 (s, 3H, $-CH_3$), 1.56 (d, 1H cyclopropyl proton, J = 5.5 Hz), 2.05 (dd, 1H, cyclopropyl proton, J = 8.5, 5.5 Hz), 2.14 (s, 3H, $>C = C'-CH_3$), 3.70 (s, 3H, $-OCH_3$), 5.4 (d, 1H, olefinic, J = 8.5 Hz).

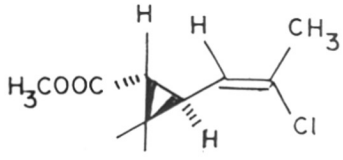
The singlet at δ 2.14 is for the methyl on double bond and it shows further fine splitting due to long range



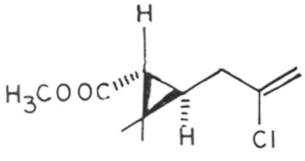
22



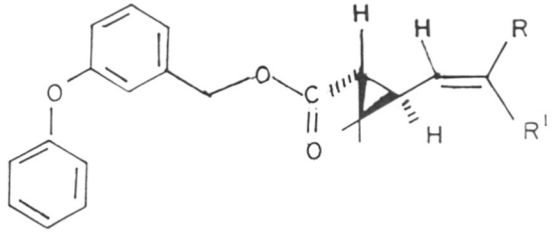
23



24



25



26 R = Cl, $R^1 = CH_3$

27 R = CH_3, R^1 = Cl

allylic coupling . Similarly the doublet at δ 5.4 for vinyl proton also shows further splitting due to long range allylic coupling.

The fraction II which was rich in compound C showed major absorption peaks in PMR spectrum as follows: PMR ($CDCl_3$, δ): 1.15 (s, 3H, $-CH_3$), 1.28 (s, 3H, $-CH_3$), 1.5 (d, 1H, cyclopropyl proton, J = 5.5 Hz), 2.12 (s, 3H, $C=C-CH_3$), 2.32 (dd, 1H, cyclopropyl proton, J = 8, 5.5 Hz), 3.70 (s, 3H, $-OCH_3$), 5.25 (d, 1H, olefinic J = 8 Hz). The singlet at δ 2.12 and doublet at δ 5.25 further splitted due to long rangeallylic coupling.

The doublet at δ 5.4 due to vinyl proton of compound B appeared little down-field as compared to the doublet at δ 5.25 at compouned C. It may be due to the deshielding effect of chlorine which is cis to the hydrogen on the double bond. Similarly cyclopropyl proton at carbon-3 of compound C appeared little downfield as compared to the cyclopropyl proton at carbon-3 of compound B. Again it may be due to the deshielding effect of chlorine which comes closer to the hydrogen of carbon-3 for compound C. So the structures for compound B and C were assigned as (23) and (24) respectively. The compound 24, of 80% purity with 23 (10%) and 25 (10%) was obtained by preparative GLC. The Z stereochemistry (chlorine and cyclopropane cis) for 24 was concluded

from ^{13}C NMR where the vinyl methyl appears at 26.3 ppm as reported[21] and from NOE which showed 17% enhancement for the vinyl proton when vinyl methyl was irradiated (6% for 23).

The structure for compound A was assigned as (25) based on the PMR spectrum of fraction III. The absorption signals due to compound A are as follows: PMR ($CDCl_3$,δ): 1.16 (s, 3H, $-CH_3$), 1.24 (s, 3H, $-CH_3$), 1.47 - 1.78 (m, 2H, cyclopropyl protons), 2.33 (d, 2H, $-CH_2$, J = 7 Hz), 3.70 (s, 3H, $-OCH_3$), 5.24 (m, 2H, olefinic). The doublet at δ 2.33 is further splitted due to long range allylic coupling.

The trans esterification of 23 with m-phenoxybenzyl alcohol using tetrabutyl titanate as catalyst gave 3-phenoxybenzyl-1R-trans-2,2-dimethyl-3-(2-chloropropenyl)-cyclopropanecarboxylate (26) as an oil. IR (liquid film): 1724 cm^{-1} (ester), 1580, 1486 cm^{-1} (aromatic); PMR ($CDCl_3$,δ), 1.15 (s, 3H, $-CH_3$), 1.25 (s, 3H, $-CH_3$), 1.55 (d, 1H, cylopropyl proton, J = 5.5 Hz), 2.05 (dd, 1H, cyclopropyl proton, J = 8.5, 5.5 Hz), 2.13 (s, 3H, $>C=C-CH_3$), 5.4 (s, 2H, $-O-CH_2-$), 5.40 (d, 1H, olefinic, J = 8.5 Hz), 6.93 - 7.6 (m, 9H, aromatic), the singlet at δ 2.13 and doublet at δ 5.4 further splitted due to long range allylic coupling.

Similarly, trans esterification of (24) with m-phenoxybenzyl alcohol gave (27). PMR ($CDCl_3$,δ):

1.15 (s, 3H, $-CH_3$), 1.28 (s, 3H, $-CH_3$), 1.50 (d, 1H, cyclopropyl proton, J = 5.5 Hz), 2.12 (s, 3H, $-CH_3$), 2.32 (dd, 1H, cyclopropyl proton, J = 5.5, 8 Hz), 5.17 (s, 2H, $-CH_2$), 5.25 (d, 1H, olefinic, J = 8 Hz), 6.98 - 7.6 (m, 9H, aromatic). The singlet at δ 2.12 and doublet at δ5.25 further splitted due to long range allylic coupling.

EXPERIMENTAL

3,3-Dimethyl-2-(2'-oxopropyl)-1-acetaldehydecyclopropane (3)

Carane diol (2) (30.0 g, 0.176 mol) was dissolved in acetone (560 ml) and water (170 ml). Powdered sodium metaperiodate (60.0 g, 0.28 mol) was added portionwise with stirring at room temperature in about one hour. The mixture was stirred at room temperature for two hours. The sodium iodate separated out was removed by filtration and the filtrate was concentrated to 200 ml at room temperature. Cold water (200 ml) was added to the residue and extracted with ether (3 x 150 ml). The ether extract was washed with water and dried over anhydrous sodium sulfate. The solvent was removed at room temperature to get colourless oil (26.0 g, 87.7%), b.p.85-87°/1.5 mm.

IR (liquid film): 3000, 1725, 1375, 1175, 955 cm^{-1}.

PMR (CCl_4, δ): 0.87 (m, 2H, cyclopropyl proton), 0.91 (s, 3H, $-CH_3$), 1.12 (s, 3H, $-CH_3$), 2.08 (s, 3H, $-COCH_3$), 2.27 (m, 4H, $-CH_2$).

Analysis: Calculated for $C_{10}H_{16}O_2$; C, 71.39; H, 9.59;
observed C, 70.92; H, 9.45.

3,3-Dimethyl-2-(2'-hydroxy-2'-methyl-n-propyl)-1-(2'-hydroxy-n-propyl)cyclopropane (4)

A grignard reagent, prepared from 0.3 mol of methyl iodide and 0.3 mol of magnesium was taken in dry ether (200 ml) and cooled to 0°C by ice-bath. To this added dropwise a solution of keto aldehyde (3) (16.8 g, 0.1 mol) in ether (25 ml). Stirred the reaction at 0-5° for one hour and then left stirring at room temperature, overnight. It was then decomposed by saturated solution of ammonium chloride after cooling. The organic layer was separated and the aqueous layer was extracted with ether (2 x 200 ml). The combined ether extracts were washed with water, then with brine, dried over anhydrous sodium sulfate and solvent was removed to get colourless thick oil (20 g, 100%). Analytical sample was prepared by distillation, b.p.150%/0.5 mm.

IR (liquid film): 3448, 2985, 1450, 1370, 1124, 1064, 935, 909, 844, 763 cm^{-1}.

PMR (CCl_4, δ):).53 (m, 2H, cyclopropyl proton), 0.87 (s, 3H, $-CH_3$), 1.03 (s, 3H, $-CH_3$), 1.17 (9H, $-CH_3$), 3.73 (m, 3H, -OH and -CH-OH).

Analysis: Calculated for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08;
observed C, 72.01; H, 12.10.

3,3-Dimethyl-2-(2'-hydroxy-2'-methyl-n-propyl)-1-(2'-oxopropyl)cyclopropane (5)

The diol (4) (14.00 g, 0.07 mol) was taken in distilled acetone (200 ml) and cooled it to 0°C. Jones reagent (28 ml) was added dropwise with vigorous stirring without allowing the temperature to go above 5°C. The mixture was stirred at 0°C for ½ hour. The brown coloured reaction mixture was diluted with water (300 ml) and extracted with ether (3 x 200 ml), washed with water brine, dried over anhydrous sodium sulfate. Solvent was removed to get pale yellow coloured oily residue (13.0 g, 93.8%), b.p. 120°/1.5 mm.

IR (liquid film): 3509, 3003, 1739, 1460, 1370, 1220, 1156, 1099, 962, 909, 758 cm^{-1}.

PMR (CCl_4,δ): 0.7 (m, 2H, cyclopropyl protons), 0.83 (s, 3H, $-CH_3$), 1.06 (s, 3H, $-CH_3$), 1.10 (s, 6H, $-CH_3$), 1.27 (m, 2H, $-CH_2$), 1.83 (broad s, 1H, -OH), 2.03 (s, 3H, $-COCH_3$), 2.23 (d, 2H, $-COCH_2$, J = 6 Hz).

Analysis: Calculated for $C_{12}H_{22}O_2$: C, 72.68; H, 11.8;
observed C, 72.61; H, 11.12.

3,3-Dimethyl-2-(2'-methyl-prop-1'-enyl)-1-(2'-oxopropyl)-cyclopropane (6)

Keto alcohol (5) (18.0 g, 0.09 mol) was taken in one litre round bottom flask, attached with azeotropic distillation unit and reflux condensor. Dry benzene (300 ml)

and p-toluenesulfonic acid (0.5 g) was added to it and refluxed for 24 hours. The reaction was cooled to room temperature and the solution was washed with water, dried over anhydrous sodium sulfate and benzene was distilled off under reduced pressure to furnish brown coloured oil (15.2 g, 92.8%). It was distilled to get pale yellow oil b.p. 80-110°/2 mm.

IR (liquid film): 3030, 1724, 1672, 1449, 1370, 1159, 966, 885, 833 cm^{-1}.

PMR (CCl_4, δ): 0.9 (s, 3H, $-CH_3$), 1.13 (s, 3H, $-CH_3$), 1.0 - 1.5 (m, 2H, cyclopropyl protons), 1.66 and 1.73 (s, each, 6H = $C(CH_3)_2$), 2.03 (s, 3H, $-COCH_3$), 2.26 (d, 2H, $-COCH_2$, J = 6 Hz), 4.8 (d, 1H, olefinic, J = 7 Hz).

Analysis: Calculated for $C_{12}H_{20}O$: C, 79.94; H, 11.18;
observed C, 79.91; H, 11.13.

3,3-Dimethyl-2-(2'-methyl-prop-1'-enyl)-1-(2'ethylenedioxy-n-propyl)cyclopropane (7)

Keto olefin (6) (10.8 g, 0.06 mol) was taken in one litre round bottom flask, attached with reflux condensor and azeotropic distillation unit. To this added dry benzene (250 ml), ethylene glycol (7.44 g, 0.12 mol) and p-toluene sulfonic acid (0.2 g) and refluxed for 24 hours. The reaction mixture was cooled and washed with water, dried over anhydrous sodium sulfate. Solvent was removed under reduced pressure to afford brown oil (12.2 g, 90.7%),

b.p. 120/130°/1 mm (bath temp.).

IR (liquid film): 3125, 1681, 1493, 1399, 1319, 1235, 1163, 1111, 1064, 956, 926, 893, 855, 791 cm^{-1}.

PMR (CCl_4, δ): 0.9 (s, 3H, $-CH_3$), 1.1 (s, 3H, $-CH_3$), 1.2 (s, 3H, $-CH_3$), 1.46 (d, 2H, $-CH_2$, J = 6 Hz), 1.66 and 1.7 (s, each, 6H = $C(CH_3)_2$), 3.8 (s, 4H, $-O-CH_2-$), 4.73 (d, 1H, olefinic, J = 7 Hz).

Analysis: Calculated for $C_{14}H_{24}O_2$: C, 75.00; H, 10.71; observed C, 74.98; H, 10.49.

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

Ketal (7) (4.0 g, 17.8 mmol) was taken in distilled acetone (100 ml) and 0.5 gm of potassium carbonate was added to it. The mixture cooled to 0°C and powdered potassium permanganate (8.0 g, 50 mmol) was added portion-wise at 0-5° in 2 hours. The mixture was stirred at 0-5° for three hours. It was filtered through buchner funnel and the manganese dioxide residue was washed with distilled acetone and then extracted with hot water (3 x 20 ml). The aqueous extract was cooled and acidified with 10% sulfuric acid, saturated with ammonium sulfate and extracted with ether (3 x 25 ml). It was washed with saturated brine solution, dried over anhydrous sodium sulfate and the solvent was distilled off to get pale yellow oil (1.762 g, 58.0%). It was esterified with diazomethane and distilled under vacuum

to get colourless oil b.p. 80-90/1 mm (bath temp.).

IR (liquid film): 3049, 1745, 1449, 1429, 1389, 1370, 1250, 1220, 1183, 1143, 1094, 1034, 966, 932, 868, 775, 730 cm^{-1}.

PMR (CCl_4, δ): 1.1 (s, 3H, $-CH_3$), 1.2 (s, 3H, $-CH_3$), 1.33-1.63 (m, 2H, cyclopropyl protons), 2.06 (s, 3H, $-COCH_3$), 2.83 (d, 2H, $-COCH_2$, J = 6 Hz), 3.60 (s, 3H, $-OCH_3$).

$[\alpha]_D^{30}$ = + 34.54 ($CHCl_3$, c, 2.64).

Analysis: Calculated for $C_{10}H_{16}O_3$: C, 65.21; H, 6.89.
observed C, 64.91; H, 8.32.

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

Keto-olefin (6) (3.0 g, 0.016 mol) was taken in ethyl acetate (150 ml) and cooled in an ice-salt bath. Ozone gas (O_3 = 1.0 gm/hr) was passed through the solution for 1½ hours. The ozonoid was decomposed by Jones reagent (8 ml). The reaction mixture was washed with water, dried over anhydrous sodium sulfate and solvent was removed under reduced pressure. The residue was taken in ether and extracted sodiumbicarbonate solution. The alkaline extract was cooled and acidified with 10% sulfuric acid, saturated with sodium chloride and extracted with ether (3 x 25 ml). The organic layer was washed with brine solution, dried over anhydrous sodium-

sulfate and solvent was removed to get pale yellow oil which was esterified with diazomethane (1.7 g, 55.4%). IR and PMR spectra were identical with that of (8), obtained by $KMnO_4$ oxidation of (7).

Reaction of 1S-cis-keto ester (8) with phosphorous pentachloride

Keto ester (8) (0.5 g, 2.71 mmol) cooled in an ice bath, was added phosphorous pentachloride (1.13 g, 5.42 mmol) and the reaction left at room temperature overnight. The reaction mixture was poured over ice. Extractive workup followed by distillation of crude product gave colourless oil (386 mg) b.p.80-90°/1 mm (bath temp.).

GLC analysis : Column - SE 30 (10%), column temp. =90°, carrier gas -N_2, flow rate - 71 ml/min, chart speed -30"/hr. Detector - TCD

GLC showed it to be a mixture of three compounds with retention times (tRs) 12 min, 15 min and 21 min in the ratio of 35:27:38.

IR (liquid film): 1730, 1640 cm^{-1}.

PMR (CCl_4, δ): 1.2 (s, 6H), 1.4 - 1.8 (m, 2H), 2.1 merged singlets), 2.67 (m), 3.57 (s, 3H), 5.03 (s), 5.73 (d).

Mixture of 3-phenoxybenzyl esters (9c,[9]d)

A solution of chloro esters (9a, b) (202 mg), 3-phenoxybenzyl alcohol (300 mg) and tetrabutyl titanate

(catalytic) in xylene (6 ml) was refluxed for 12 hrs. Xylene was removed under vacuum and the residue was passed through a short column of silica gel with 1:1 pet.ether benzene as eluant to afford 3-phenoxybenzyl esters (9c, d) (300 mg, 80.6%).

IR (liquid film): 1730, 1595 cm^{-1}.

PMR (CCl_4, δ): 1.2 (s, 6H), 1.35 - 2.0 (m, 2H), 2.1 (merged singlets), 2.63 (d), 4.9 (s, 2H), 5.0 (s), 5.63 (d), 6.6 - 7.3 (m, 9H), signals at δ 5.0 and δ 5.63 in the approximate ratio of 1:2.

Methyl 2,2-dimethyl-3-(2-propynyl)cyclopropane-carboxylate (10)

A mixture of methyl esters (9a) (9b) (160 mg, 0.8 mmol) was added to a solution of potassium (156 mg, 4 mmol) in t-butanol (10 ml) and refluxed under nitrogen atmosphere for 12 hrs. t-Butanol was removed under vacuum and the residue was diluted with water (5 ml). It was acidified with 10% sulfuric acid and extracted with ether (3 x 20 ml). The ether extract was washed with water, dried over anhydrous sodium sulfate and solvent was removed to get pale yellow oil which was esterified with diazomethane and distilled to get colourless oil (110 mg, 83,8%), b.p. 100/110°/1 mm (bath temp.).

GLC: showed it to be 83% major compound along with some minute impurities.

Column- OV - 101, 3%; column temp. 120°C, flow rate N_2 - 30 ml/min; detector - FID, tR - 4.38 min.

MS: m/e 166.

IR (liquid film): 2985, 1724, 1587, 1429, 1399, 1370, 1351, 1282, 1250, 1215, 1190, 1143, 1111, 1070, 990, 952, 917, 826, 800 cm^{-1}.

PMR (CCl_4, δ): 1.17 (s, 3H, $-CH_3$), 1.3 (s, 3H, $-CH_3$), 1.6 (s, 2H, cyclopropyl protons), 1.8 (s, 3H, $-CH_3$), 3.6 (s, 3H, $-OCH_3$).

Methyl 1S-cis-2,2-dimethyl-3-(2-hydroxy propyl)cyclopropanecarboxylate (12)

1S-Keto ester (8) (1.0 g, 5.4 mmol(20 ml) and water (0.3 ml) was added to it. To this stirred mixture added slowly a solution of sodium borohydride (0.4 gm, 10.5 mmol) in water (0.3 ml). The mixture was stirred for three hours at room temperature. Then it was concentrated to 5 ml under reduced pressure and diluted with cold water (20 ml), saturated with sodium chloride and extracted with ether (3 x 20 ml), washed with brine, dried over anhydrous sodium sulfate and solvent was distilled off to get colourless oil (0.948 g, 93.7%).

IR (liquid film): 3546, 3030, 1739, 1443, 1383, 1250, 1198, 1176, 1136, 1093, 1042, 939, 893, 855 cm^{-1}.

PMR (CCl_4, δ): 1.13 (d, 3H, $-CH_3$, J = 6 Hz), 1.2 (s, 6H, $-CH_3$), 1.26 - 1.53 (m, 2H, cyclopropyl protons), 1.6 - 2.23 (m, 3H, $-CH_2$ and -OH), 3.53 - 3.93 (m, 1H, -CH-O-), 3.63 (s, 3H $-OCH_3$).

δ -Lactone of 1S-cis-2,2-dimethyl-3-(2-hydroxypropyl) cyclopropanecarboxylic acid (13)

To a solution of potassium hydroxide (700 mg, 12.5 mmol) in water (2 ml) and ethanol (10 ml), hydroxy ester (12) (700 mg, 3.7 mmol) was added and stirred the mixture at room temperature overnight. Ethanol was removed under reduced pressure and to the residue added cold water (5 ml), cooled it to 0°C and acidified with 10% sulfuric acid. The mixture was saturated with ammonium sulfate and extracted with ether (3 x 20 ml), washed with saturated brine solution (20 ml), dried over anhydrous sodium sulfate and solvent was removed to get pale yellow oil (11) (619 m.g., 95.6%). This hydroxy acid (11) was taken in dry benzene (25 ml) and p-toluene sulfonic acid (50 mg) was added to it. It was refluxed for 3 hrs. It was cooled to room temperature, washed with water, dried over anhydrous sodium sulfate and solvent was removed to get pale yellow oil (13) (378 mg, 68.2%).

IR (liquid film): 3030, 1730, 1449, 1370, 1333, 1282, 1176, 1124,, 1053, 976, 901 cm^{-1}.

PMR (CCl_4, δ): 0.9 (m, 1H, cyclopropyl proton), 1.08 (s, 3H, $-CH_3$), 1.22 (s, 3H, $-CH_3$), 1.17 (d, 3H, $-CH_3$, J = 6 Hz), 1.37 (m, 2H, $-CH_2$), 1.87 (m, 1H, cyclopropyl proton), 4.3 (m, 1H, -CH-0-).

t-Butyl 1R-trans-2,2-dimethyl-3-(2-hydroxy propyl)-cyclopropanecarboxylate (14)

Potassium (390 mg, 10 mmol) was dissolved in dry t-butanol (20 ml) and to this added lactone (13) (304 mg, 1.97 mmol). The mixture was refluxed for 18 hrs under nitrogen atmosphere. The solvent was removed under reduced pressure and then 10 ml of cold water was added to the residue, extracted with ether (3 x 15 ml). The ether layer washed with water, dried over anhydrous sodium sulfate and solvent was removed to get colourless oil (84 mg).

IR (liquid film): 3509, 3030, 1718, 1449, 1429, 1357, 1282, 1235, 1212, 1149, 1111, 1053, 1042, 1020, 1010, 976, 952, 943, 847, 813, 769, 752, 735 cm^{-1}.

PMR (CCl_4, δ): 0.96 - 1.36 (complex m, 13H), 1.43 (s, 9H, t-butyl), 2.16 (broad s, 1H, -OH), 3.8 (m, 1H, -CH-0-).

The aqueous layer from above was cooled and acidified with 10% sulfuric acid, saturated with sodium chloride and extracted with ether (3 x 20 ml), dried over anhydrous sodium sulfate and solvent was removed

to afford pale yellow hydroxy acid (256 mg). The acid (11) was lactonized by refluxing with benzene and p-toluene sulfonic acid as catalyst to get pale yellow oil (158 mg, 69%). IR and PMR spectra were identical with that of lactone (13).

t-Butyl 1R-trans-2,2-dimethyl-3-(2-oxopropyl)cyclopropanecarboxylate (15)

t-Butyl hydroxy ester (14) (60 mg) was taken in distilled acetone (1 ml) and cooled the mixture to 0°c. The Jones reagent (0.5 ml) was added slowly to it and stirred at 0°C for 15 minutes. The reaction mixture was diluted with cold water (5 ml) and extracted with ether (3 x 15 ml). The ether layer was washed with water, brine and dried over anhydrous sodium sulfate. The solvent was removed to get colourless oil (54 mg, 90.79%).

IR (liquid film): 3030, 1724, 1460, 1429, 1370, 1316, 1282, 1250, 1212, 1149, 1111, 1042, 1026, 957, 926, 847, 772, 737 cm^{-1}.

PMR (CCl_4, δ): 0.96 - 1.33 (m, 2H, cyclopropyl protons), 1.06 (s, 3H, $-CH_3$), 1.20 (s, 3H, $-CH_3$), 1.43 (s, 9H, t-butyl), 2.06 (s, 3H, $-COCH_3$), 2.36 (m, 2H, $-COCH_2$).

Methyl 1R-trans-2,2-dimethyl-3-(2-oxopropyl)cyclopropanecarboxylate (16)

t-Butyl ether (15) (50 mg) was taken in dry methylene chloride (5 ml). This solution was cooled to

0°C and saturated with dry hydrogen chloride gas. The acidic solution was then kept at 0-5°C for 32 hrs. Then the solution was washed with cold water, dried over anhydrous sodium sulfate and solvent was removed under reduced pressure to afford pale yellow oil which was esterified with diazomethane to get methyl ester (34 mg, 83.52%).

IR (liquid film): 3030, 1724, 1453, 1381, 1351, 1316, 1282, 1250, 1198, 1114, 1033, 957, 923, 855, 769, 746, 727, 704 cm^{-1}.

PMR (CCl_4, δ): 1.1 (s, 3H, $-CH_3$), 1.23 (s, 3H, $-CH_3$), 1.37 - 1.73 (2H, m, cyclopropyl protons), 2.13 (s, 3H, $-COCH_3$), 2.4 (dd, 2H, $-COCH_2-$, J = 3,7 Hz), 3.7 (s, 3H, $-OCH_3$).

$[\alpha]_D^{30}$ = -32.29° ($CHCl_3$, c, 0.842).

Analysis: Calculated for $C_{10}H_{16}O_3$; C, 65.27; H, 8.69;
observed C, 65.06; H, 9.08.

Epimerization of δ-lactone (13) with potassium hydroxide in ethylene glycol

Potassium hydroxide (400 mg, 7.1 mmol) was dissolved in ethylene glycol (5 ml) and added -lactone (13) (100 mg, 0.65 mmol) to it. The mixture was refluxed for 5 hours. Cooled it to room temperature and diluted with water (15 ml), acidified with 10% sulfuric acid, saturated with ammonium sulfate and extracted with ether (3 x 20 ml). The organic layer was washed with

brine solution, dried over sodium sulfate and solvent was removed to get thick oil (90 mg) which was esterified with diazomethane to get pale yellow ester (90 mg, 74.51%). GLC: showed 4% unepimerized product. (Column- OV-101, 3%, colum temp. 105°, flow rate - 30 ml/min, chart speed- 1 cm/min, tRs: 8.1 min (cis) and 8.7 min (trans).

The hydroxy ester (18) was taken in acetone (1 ml) and cooled to 0°C. Jones reagent (0.5 ml) was added to it slowly and stirred the mixture for 15 minutes at 0-5°, diluted with water (5 ml) and extracted with ether. The organic layer was washed with water, brine and dried over anhydrous sodium sulfate. Solvent was removed to get pale yellow oil (80 mg) which was purified on silica gel column using 5% ethyl acetate-benzene as eluant to get 99% GLC pure 1R-trans-keto ester (16). IR and PMR spectra[1] data were identical with that of authentic.

Epimerization of methyl 1S-cis-2,2-dimethyl-3-(2-hydroxy propyl)cyclopropanecarboxylate (12) with potassium hydroxide in ethylene glycol

Potassium hydroxide (1.0 g, 17.8 mmol) was dissolved in (8 ml) ethylene glycol and added hydroxy ester (12) (400 mg, 2.15 mmol) to it. The mixture was refluxed under nitrogen for 5 hours. It was cooled to room temperature and then diluted with water (20 ml) and extracted with ether to remove neutral impurity if any. The aqueous

layer was cooled and acidified with 10% sulfuric acid and saturated with ammonium sulfate, extracted with ether (3 x 20 ml),washed the ether layer with saturated brine solution. The ether layer was dried over anhydrous sodium sulfate and the solvent was removed to get pale yellow oil (365 mg, 92%) which was esterified with diazomethane to get the methyl ester.

GLC: Analysis showed it to be 90% pure trans ester column- OV-101, 3%, column temp. - 105°, flow rate- 30 ml/min, chart speed - 1 cm/min, tRs: 8.10' (cis) and 8.75' (trans).

3,3- Dimethyl-2-(2'-hydroxy-2'-methyl-n-propyl)-1-(2'-acetoxy-n-propyl)cyclopropane (19)

Diol (4) (43.0 g, 0.215 mol) was dissolved in pyridine (58 ml). To this added acetic anhydride (70 ml) portionwise at room temperature. This mixture was kept at room temperature for 48 hours. Then water (26 ml) was added dropwise to the mixture and stirred for 1 hr to hydrolyse excess acetic anhydride, 300 ml of cold water was added to the reaction mixture and extracted with ether (3 x 200 ml). The ether extract was washed with water, 1% hydrochloric acid and then with water. Solvent was removed after drying over anhydrous sodium sulfate to get pale yellow oil (51.4 g, 98.3%).

IR (liquid film): 3571, 3030, 1724, 1449, 1370, 1242, 1124, 1047, 1010, 948, 909, 760, 702 cm^{-1}.

PMR (CCl_4, δ): 0.53 (m, 2H, cyclopropyl protons) 0.9 (s, 3H, $-CH_3$), 1.07 (s, 3H, $-CH_3$), 1.17 (s, 6H, $-CH_3$), 1.33 (d, 3H, $-CH-\underline{CH_3}$), 2.0 (s, 3H, $-COCH_3$), 2.63 (broad s, 1H, -OH), 4.83 (m, 1H, -CH-O-).

3,3-Dimethyl-2-(2'-methyl-prop-1'-enyl)-1-(2'-acetoxy-n-propyl)cyclopropane (20)

Hydroxy acetate (19) (27.00 g) was taken in (600 ml) dry benzene in one litre round bottom flask, attached with azeotropic distillation unit and reflux condensor. p-Toluene sulfonic acid (1.0 gm) was added and refluxed for 48 hrs, with azeotropic removal of water. The content of the flask was cooled to room temperature and it was taken in a separatory funnel and washed with water (2 x 500 ml), dried over anhydrous sodium sulfate and distilled off benzene to get dark brown oil (25.00 gm). It was distilled to get pale yellow oil (20) (19.5 gm, 78%).

b,p. 78-80°/0.5 mm.

IR (liquid film): 3030, 1748, 1449, 1370, 1242, 1136, 1047, 1010, 952, 889, 840 cm^{-1}.

PMR (CCl_4, δ): 0.43 - 0.87 (m, 1H, cyclopropyl proton), 0.93 (s, 3H, $-CH_3$), 1.10 (s, 3H $-CH_3$), 1.13 - 1.6 (m, 6H, $-CH_3$, $-CH_2$ and cyclopropyl proton), 1.7 and 1.73 (s, each, 6H = $C(CH_3)_2$), 1.96 (s, 3H, $-COCH_3$), 4.6 - 5.1 (m, 2H, olefinic and -CH-O-).

Analysis: Calculated for $C_{14}H_{24}O_2$: C, 75.00; H, 10.71; observed C, 75.13; H, 10.83.

2,2-Dimethyl-3-(2-acetoxy propyl)cyclopropane-carboxylic acid (21)

Acetate (20) (10.0 g, 44.6 mmol) was dissolved in acetone (200 ml), potassium carbonate (0.5 g) was added to it. This mixture was cooled to 0°C. Then powdered potassiumpermanganate (21.3 g, 0.134 mol) was added portionwise with stirring in about 1½ hr at 0-5°C. The reaction mixture was stirred at room temperature for three hours and filtered through buchner funnel. The manganese dioxide residue was washed with acetone and then extracted with hot water (3 x 50 ml). The aqueous alkaline extract was cooled and acidified with 10% sulfuric acid, saturated with ammonium sulfate and extracted with ether (3 x 100 ml). Ether extract was washed with saturated brine solution, dried over anhydrous sodium sulfate and distilled off the solvent to get colourless oil (5.5 g, 53.33%). Aliquot of the above acid was esterified with diazomethane, and purified by silica gel column chromatography with 10% ethyl acetate, benzene as eluant.

IR (liquid film): 3030, 1724, 1439, 1370, 1250, 1170, 1136, 1087, 1031, 950, 931, 888, 847, 820, 781 cm^{-1}.

PMR (CCl_4, δ): 1.23 - 1.6 (complex m, 11H, $-CH_3$ and cyclopropyl protons), 1.76 - 2.1 (m, 2H, $-CH_2$), 2.03 (s, 3H, $-OCOCH_3$), 3.7 (s, 3H, $-OCH_3$), 5.0 (m, 1H, -CH-O-).

Analysis: Calculated for $C_{12}H_{20}O_4$; C, 63.15; H, 8.77;
observed C, 63.51; H, 8.49.

Epimerization of 2,2-dimethyl-3-(2-acetoxy propyl)cyclo-propanecarboxylic acid (21)

Potassium hydroxide (5.81 g, 0.103 mol) was dissolved in ethylene glycol (30 ml). To this added acetate (21) (3.66 g, 17.1 mmol) and heated it to reflux. Ethylene glycol (10 ml) was distilled out so that reflux temperature reached to 185°. The refluxtion was continued for six hours. Then ethylene glycol (8 ml) was distilled out and the residue was cooled to room temperature, poured it over crushed ice (30 gm). The aqueous reaction mixture was washed with ether to remove neutral impurities. The alkaline aqueous solution was cooled and acidified with 10% sulfuric acid, saturated with ammonium sulfate and extracted with ether (3 x 50 ml). Organic layer was washed with saturated brine solution, dried over anhydrous sodium sulfate and solvent was removed to get thick oil (2.362 g.). It was esterified with diazomethane to get pale yellow oil (2.370 gm, 74.5%).

GLC: showed it to be 90% trans ester.

Column OV-101, 3%, column temp. - 125°, flow rate - 30 ml/min, chart speed - 1 cm/min, Detector - FID)

tRs - 4.9' (cis) and 5.35' (trans).

It was taken as such for Jones oxidation.

Reaction of 1R-trans-keto ester (16) with phosphorous pentachloride

Keto ester (16) (982 mg, 5.53 mmol) cooled in an ice bath, was added phosphorous pentachloride (2.3 g, 11.6 mmol) and the reaction left at room temperature overnight. The reaction mixture was poured over ice. Extractive workup followed by distillation of crude product gave a pale yellow oil (720 mg) b.p.80-90°/1 mm (bath temp.)

GLC analysis: Column - OV-101, 3% HP (2 mm x 180 cm); Column temp. 110°; carrier gas -N_2; flow rate - 30 ml/min; Detector - FID.

GLC showed it to be a mixture of four compounds.

Compound	Retention time (tR)	% composition
A	9.77 min.	21.5%
B	10.90 min.	12.2%
C	11.43 min.	35.2%
D	18.79 min.	28.1%

GCMS analysis: MS 30 AEI, England.

Column - 5% carbowax 20 m; column temp. 130°; source temp. - 250°; Helium flow - 30 ml/min; Electron energy- 32 eV.

tRA = m/e 202
tRB = m/e 202
tRC = m/e 202
tRD = m/e 207, 203, 127

Preparative GLC: Fractovap- 2450, column- all glass OV-1, 20% on chromosorb W- AW, 30-60 mesh; Prog. 80-150°;

Carrier gas- helium; flow rate- 140 ml/min;

Detector- TCD.

Compound D (22) was obtained in pure form while compound C(24) was obtained in 80% purity.

Compound D (22)

IR (liquid film): 3030, 1736, 1439, 1379, 1359, 1282, 1266, 1220, 1190, 1170,, 1117, 1075, 1055, 922, 855, 775, 755, 733 cm^{-1}.

PMR ($CDCl_3$, δ): 1.20 (s, 3H, $-CH_3$), 1.28 (s, 3H, $-CH_3$), 1.32 - 2.0 (m, 2H, cylopropyl protons), 2.20 (s, 3H, $-CH_3$), 2.24 - 2.76 (m, 2H, $-CH_2$), 3.76 (s, 3H, $-OCH_3$).

Analysis: Calculated for $C_{10}H_{16}Cl_2O_2$: C, 50.20; H, 6.69; Cl, 29.7; observed C, 50.55; H, 6.81; Cl, 30.11.

MS: m/e 238 (m^+), 207 ($m^+ - OCH_3$), 203 (m^+ - cl), 127 ($m^+ - CH_2CCl_2CH_3$).

Compound C (24)

IR (liquid film): 1730, 1661 cm^{-1}.

PMR ($CDCl_3$, δ): 1.15 (s, 3H, $-CH_3$), 1.28 (s, 3H $-CH_3$), 1.5 (d, 1H, cyclopropyl proton, J = 5.5 Hz), 2.12 (s, 3H, $-CH_3$), 2.32 (dd, 1H, cyclopropyl proton, J = 8, 5.5 Hz), 3.70 (s, 3H, $-OCH_3$), 5.25 (d, 1H, olefinic, J = 8 Hz).

^{13}C NMR: 20.40, 22.68, 26.32, 28.66, 32.92, 34.83, 51.66, 123.02, 133.22, 172.41.

MS: m/e 202 (m^+), 171 ($m^+ - OCH_3$), 167 (m^+ - Cl), 143 ($m^+ - COOCH_3$).

Column chromatography of mixture (A + B + C)

A careful chromatography of the mixture of chloro ester A, B and C was done over silica gel (1:100 ratio) impregnated with 30% silver nitrate and pet.ether as eluant. Several fractions were collected, out of which three enriched fractions were as follows:

Fractions	% of A (25)	% of B (23)	% of C (24)
I	4%	94%	2%
II	11.4%	11.3%	76.9%
III	56.4%	-	43.4%

Fraction I (23)

IR (liquid film): 3030, 1730, 1661, 1439, 1383, 1351, 1282, 1227, 1190, 1167, 1143, 1116, 1099, 1058, 1025, 990, 954, 909, 866, 769, 728, 697 cm^{-1}..

PMR ($CDCl_3$, δ): 1.17 (s, 3H, $-CH_3$), 1.26 (s, 3H, $-CH_3$), 1.56 (d, 1H, cyclopropyl proton, J = 5.5 Hz), 2.05 (dd, 1H, cyclopropyl proton, J = 8.5, 5.5 Hz), 2.14 (s, 3H, $-CH_3$), 3.70 (s, 3H, $-OCH_3$), 5.4 (d, 1H, olefinic, J = 8.5 Hz).

Fraction III

IR (liquid film): 1730, 1661 cm^{-1}.

PMR ($CDCl_3$, δ): signals for isomer A (25); 1.16 (s, 3H, $-CH_3$), 1.24 (s, 3H, $-CH_3$), 1.47 - 1.78 (m, 2H, cyclopropyl protons), 2.33 (d, 2H, $-CH_3$, J = 7 Hz), 3.70 (s, 3H, $-OCH_3$), 5.24 (m, 2H, olefinic).

3-Phenoxybenzyl-1R-trans-2,2-dimethyl-3-(2-chloro-1-propenyl)cyclopropanecarboxylate (26) and (27)

A mixture of chloroester (24) (101 mg), 3-pheoxybenzyl alcohol (150 mg), tetrabutyl titanate (catalytic) and xylene (3 ml) was refluxed for 12 hours. Xylene was removed under vacuum and the residue was passed through a short column of silica gel with 1:1 pet.ether benzene as eluant to afford pure ester (27) (145 mg, 78.3%).

PMR ($CDCl_3$, δ): 1.15 (s,3H, $-CH_3$), 1.28 (s, 3H, $-CH_3$), 1.50 (d, 1H, cylopropyl proton, J = 5.5 Hz), 2.12 (s, 3H, $-CH_3$), 2.32 (dd, 1H, cyclopropyl proton, J = 5.5, 8 Hz), 5.17 (s, 2H, $-CH_2$), 5.25 (d, 1H, olefinic J = 8 Hz), 6.98 - 7.6 (m, 9H, aromatic)

$[\alpha]_D^{30}$ = - 18.21 ($CHCl_3$, c, 2.12).

Analysis: Calculated for $C_{22}H_{23}ClO_3$: C, 71.36; H, 6.21; Cl, 9.58; observed C, 71.37; H, 6.47; Cl, 9.36.

Similarly (26) was prepared as above from (23).

PMR ($CDCl_3$, δ): 1.17 (s, 3H, $-CH_3$), 1.26 (s, 3H, $-CH_3$), 1.56 (d, 1H, cyclopropyl proton, J = 5.5 Hz), 2.05 (dd, 1H, cylopropyl proton, J = 8.5, 5.5 Hz), 2.14 (s, 3H, $-CH_3$), 5.14 (s, 2H, $-CH_2$), 5.4 (d,1H olefinic, J = 8.5 Hz), 6.93 - 7.6 (m, 9H, aromatic).

Analysis: Calculated for $C_{22}H_{23}ClO_3$: C, 71.36; H, 6.21; Cl, 9.58; observed C, 71.83; H, 6.85; Cl, 9.08.

REFERENCES

1. M. Elliott and N.F. Janes, Chem.Soc.Review, 7, 473 (1978).
2. M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham and D.A. Pulman, ACS Symposium Series No.2, 80 (1974).
3. M. Elliott and N.F. Janes, ACS Symposium No.42, 29 (1977).
4. D. Owen John, J.Chem.Soc.Perkin Trans I, 1231 (1976).
5. M. Elliott, A.W. Farnham, N.F. Janes, P.H. Needham and D.A. Pulman, Pestic. Sci. 7, 499 (1976).
6. P.E. Burt and R.E. Goodchild, Pestic. Sci., 8, 681 (1977).
7. Pesticide Chemistry. Human Welfare and the Environment, Vol. 3, page 69, Eds. J. Miyamoto and P.C. Kearney..
8. G. Carson, Bull.Environ.Contam. Toxicol, 21, 338 (1979).
9. J. Ide, Y. Nakada, R. Endo, S. Muramatsu, K. Konishi, T. Mizuno, S. Ohno, Y. Yamazaki, H. Endo, K. Fujita, H. Tsuji, Agric. Biol.Chem. 47, 927 (1983).
10. R.B. Mitra, G.H. Kulkarni, K.G. Gore, A.S. Khanra, Z. Muljiani, P.N. Choudhari, B.M. Bhawal, P.N. Khanna, G.D. Joshi, Brit.UK. Pat. Appl. 2,034,301 (1980), Council of Scientific and Industrial Research (India), Indian Appl. 761/DEL/78 (1978), C.A. 94, 65195 (1981).
11. J. Ide, Y. Inoue, Y. Nakada, T. Mizuno, R. Endo, S. Ohno, Jpn.Kokai, Tokkyo. Koho 7,887,337 (1978), Sankyo Co.Ltd., C.A. 90, 22567 (1979).
12. A.S. Khanra and R.B. Mitra, Indian J.Chem., 14B, 716 (1976).
13. W cocker and H.J. Lauder, J.Chem.Soc. Perkin Trans I, 332 (1975).

14. T.L. Ho and Z.U. Din, Synth.Commn. 10, 921 (1980).

15. T.L.Ho and Z.U. Din Synth.Commn. 12, 257 (1982).

16, P.N. Khanna, Ph.D. thesis, page 37 (1979).

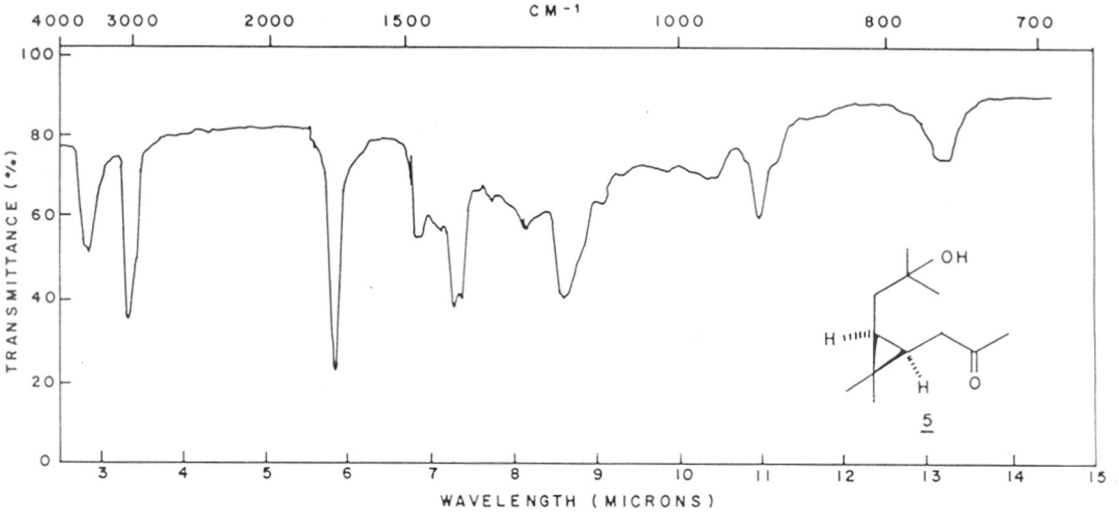
17. M. Halfon, W.G. Scharp, Brit. U.K. Patent Appl. 2005269 (1979), FMC Corp., C.A. 92, 22138 (1980).

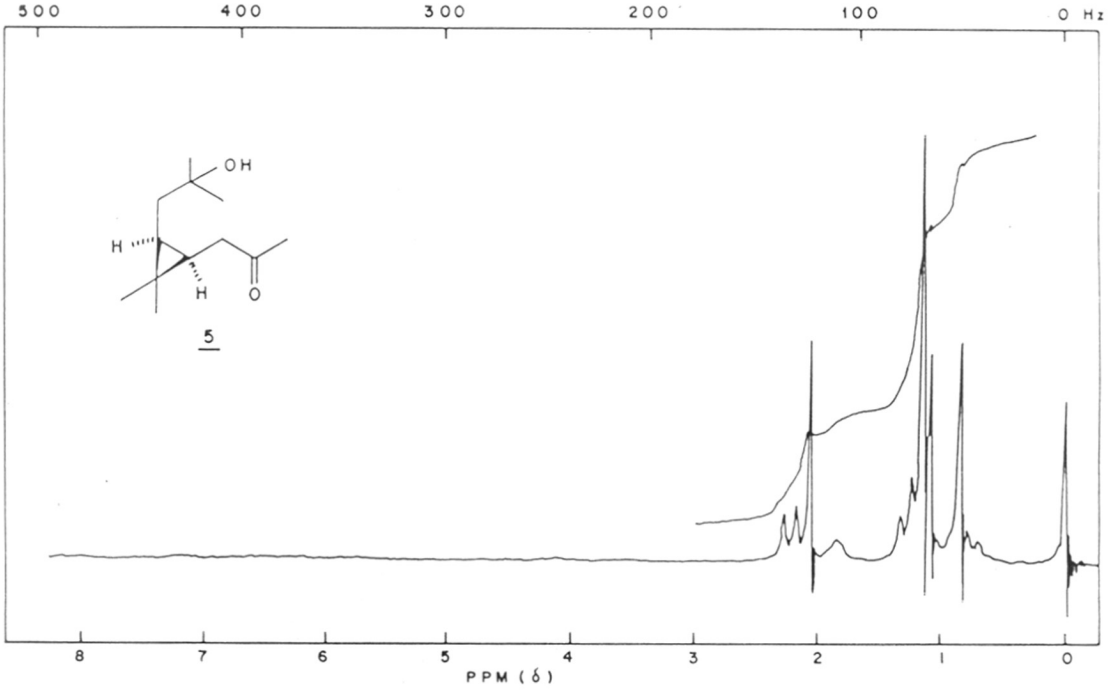
18. M. Julia, S. Julia, B. Bemont, G. Tchernoff, Compt. Rend. 248, 242 (1959); M. Julia, Fr. 1,203,902 (1960); C.A. 55, 13338 (1961).

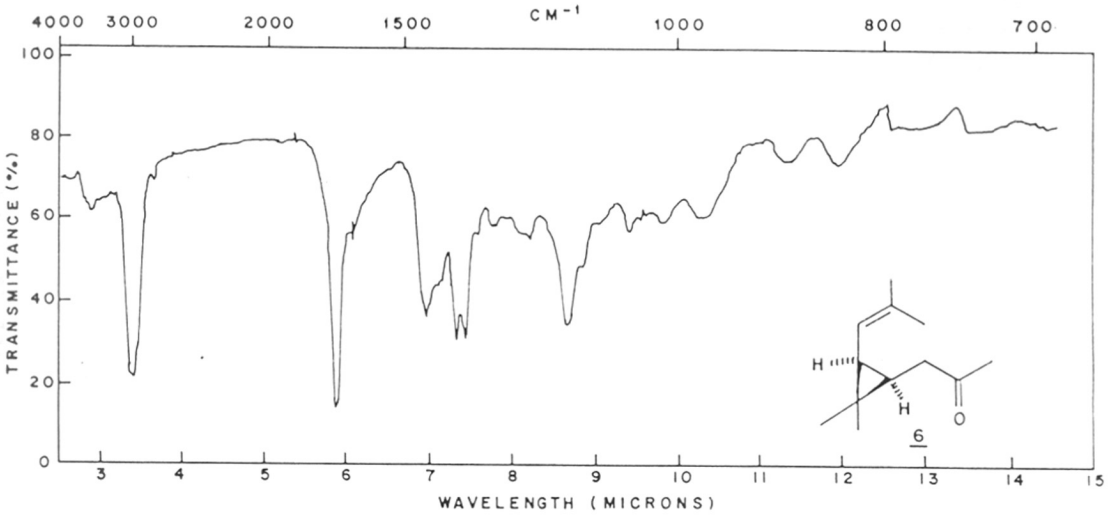
19. R. Sobti and Sukh Dev, T;trahedron, 30. 2927 (1974).

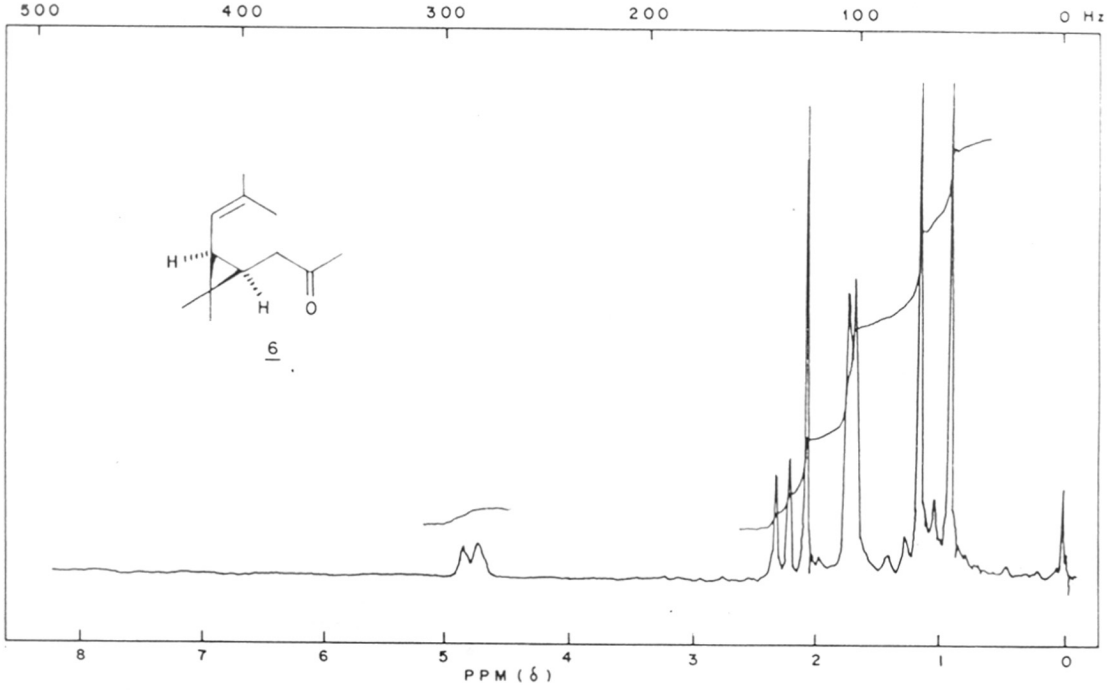
20. B.M. Mane, B.G. Mahamulkar, P.P. Pai, G.H. Kulkarni and R.B. Mitra, Indian J.Chem. 20B, 1029 (1981).

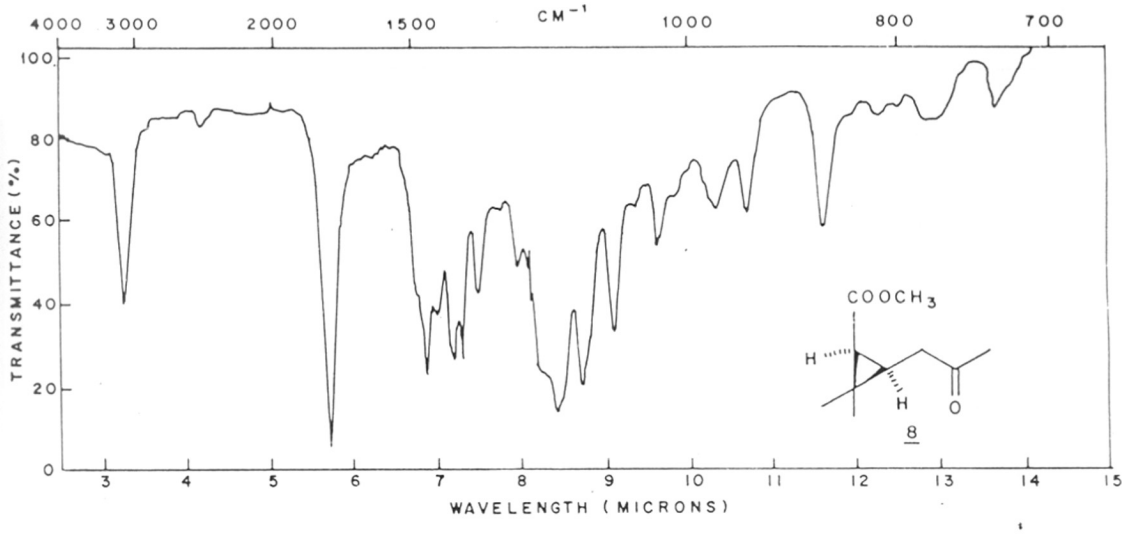
21. T. Iwaoka, H.Kuwano, S. Muramatsu, R. Endo, Y. Nakada, J. Ide and M. Kondo, Agric.Biol.Chem., 45, 1381 (1981).

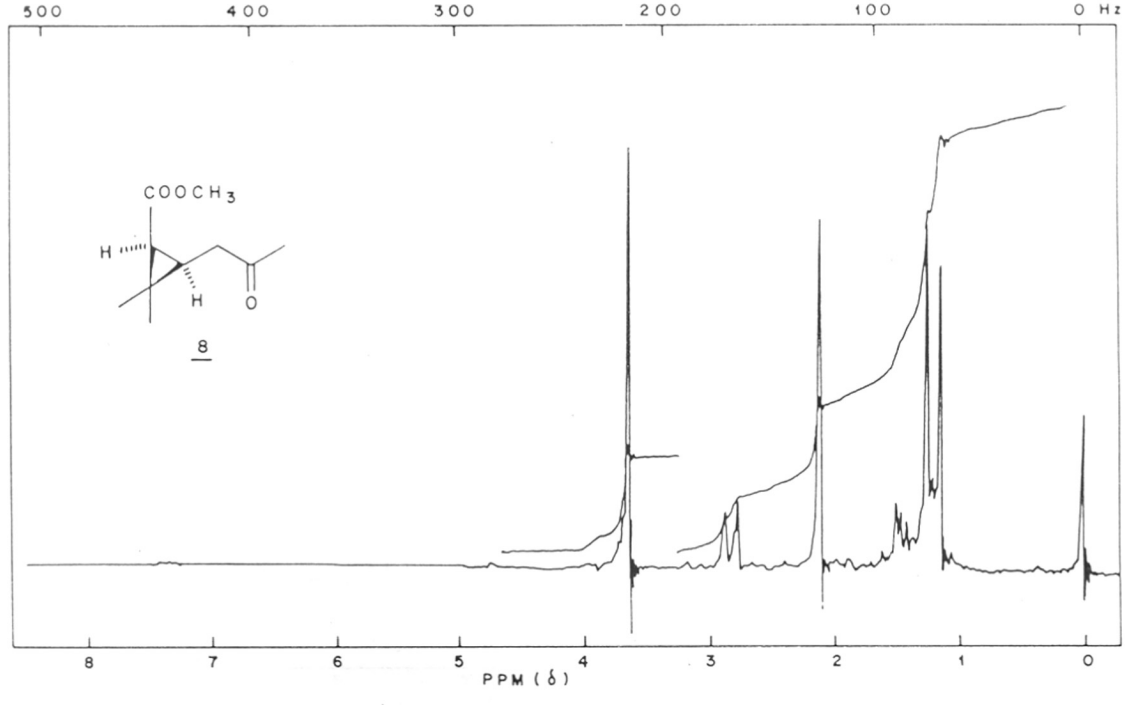

4000 3000 2000 1500 CM-1 1000 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
OH
H
H
O
5

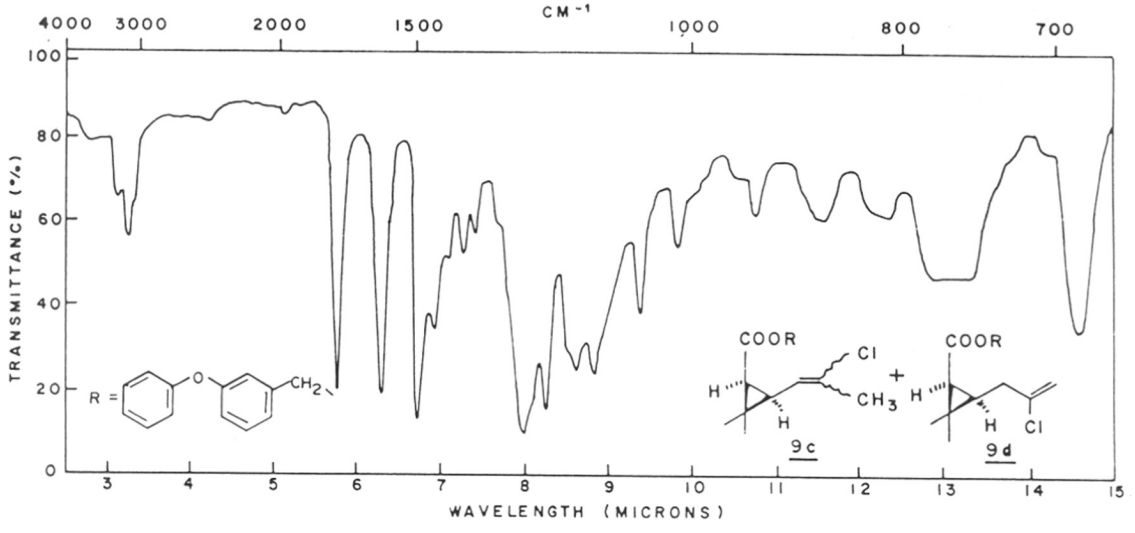

500 400 300 200 100 0 Hz
OH
H
H
O
5
8 7 6 5 4 3 2 1 0
PPM (δ)

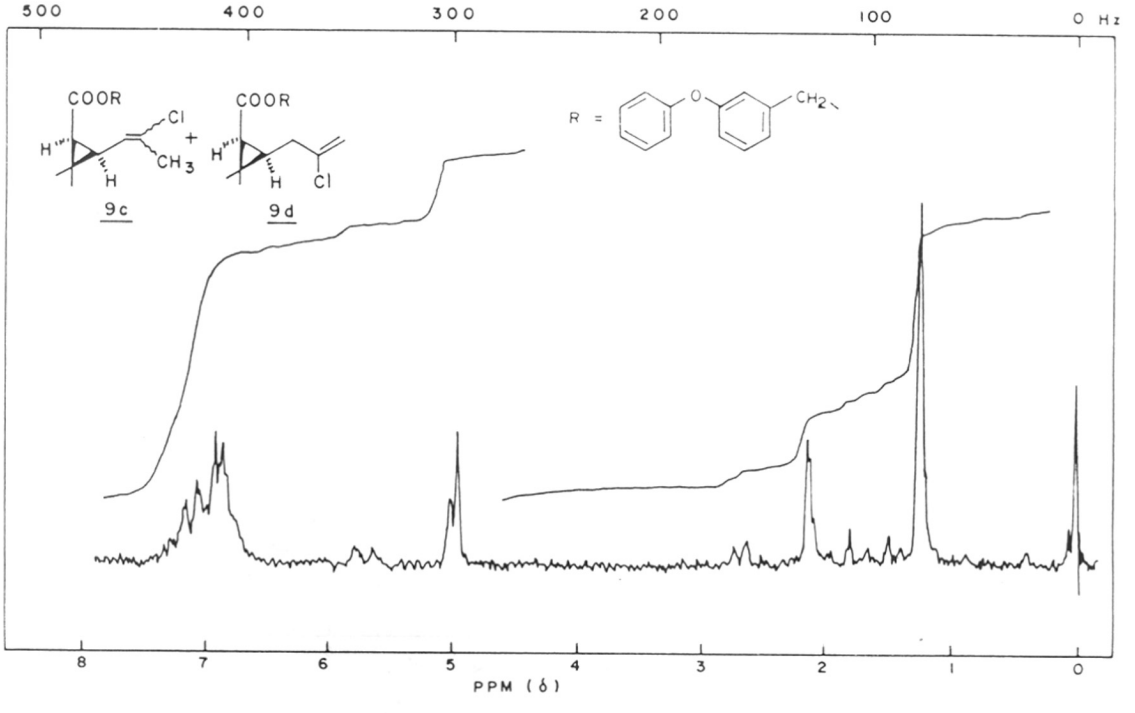

4000 3000 2000 1500 CM⁻¹ 1000 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
H
H
O
6

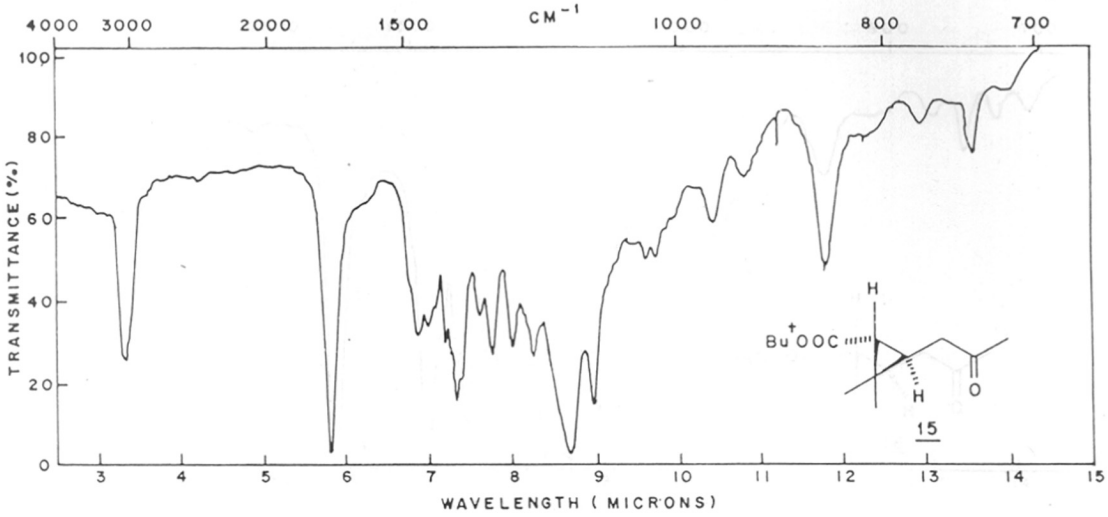

500 400 300 200 100 0 Hz
H
H
O
6
8 7 6 5 4 3 2 1 0
PPM (δ)

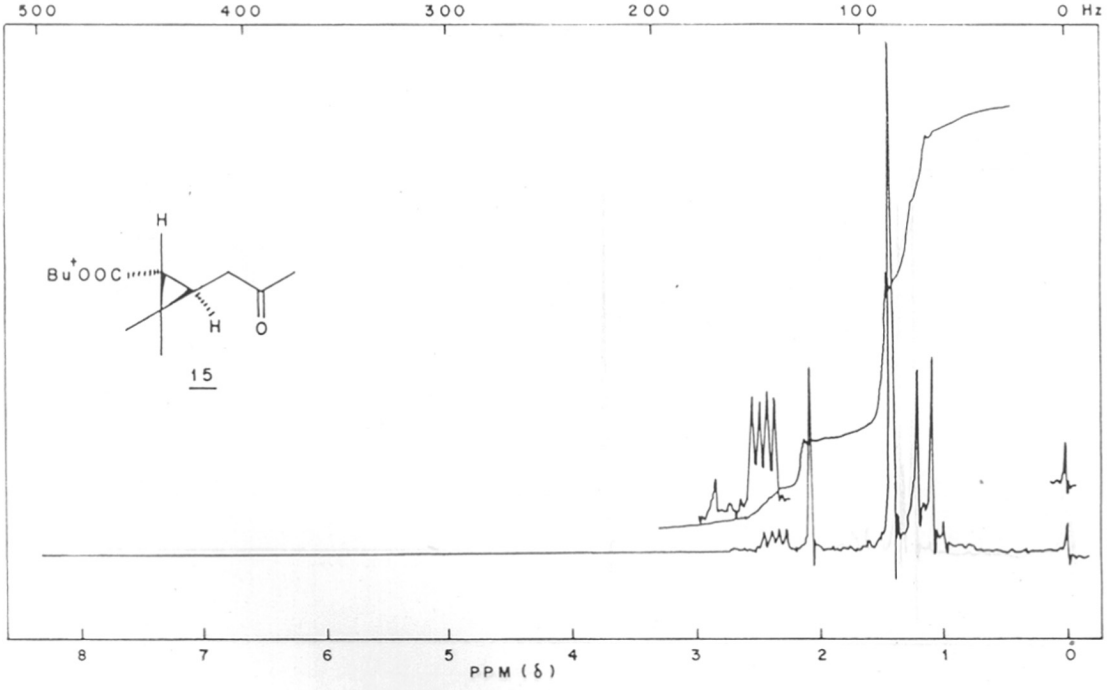

4000 3000 2000 1500 CM⁻¹ 1000 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
COOCH3
H
H
O
8

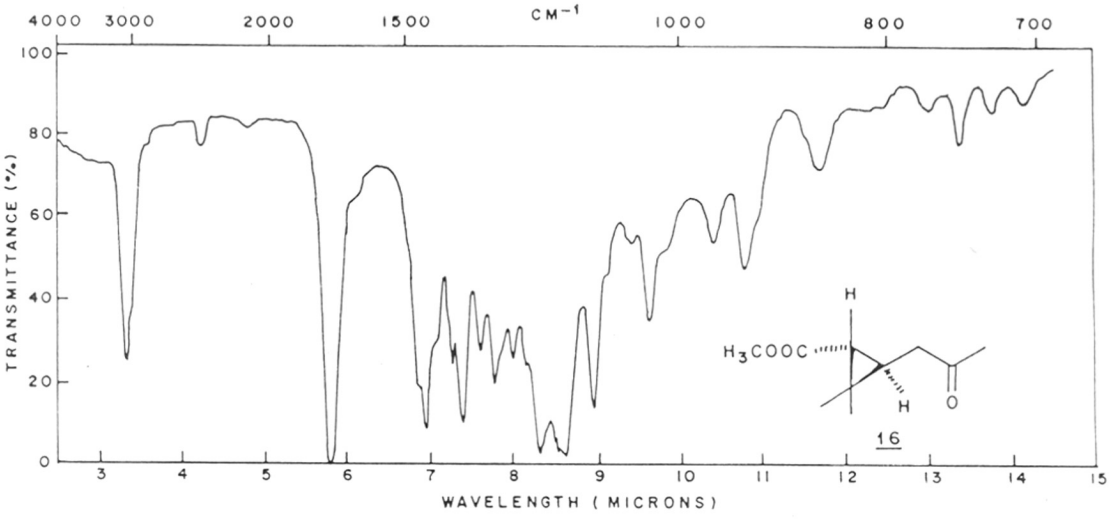

500 400 300 200 100 0 Hz
COOCH3
H
H
O
8
8 7 6 5 4 3 2 1 0
PPM (δ)

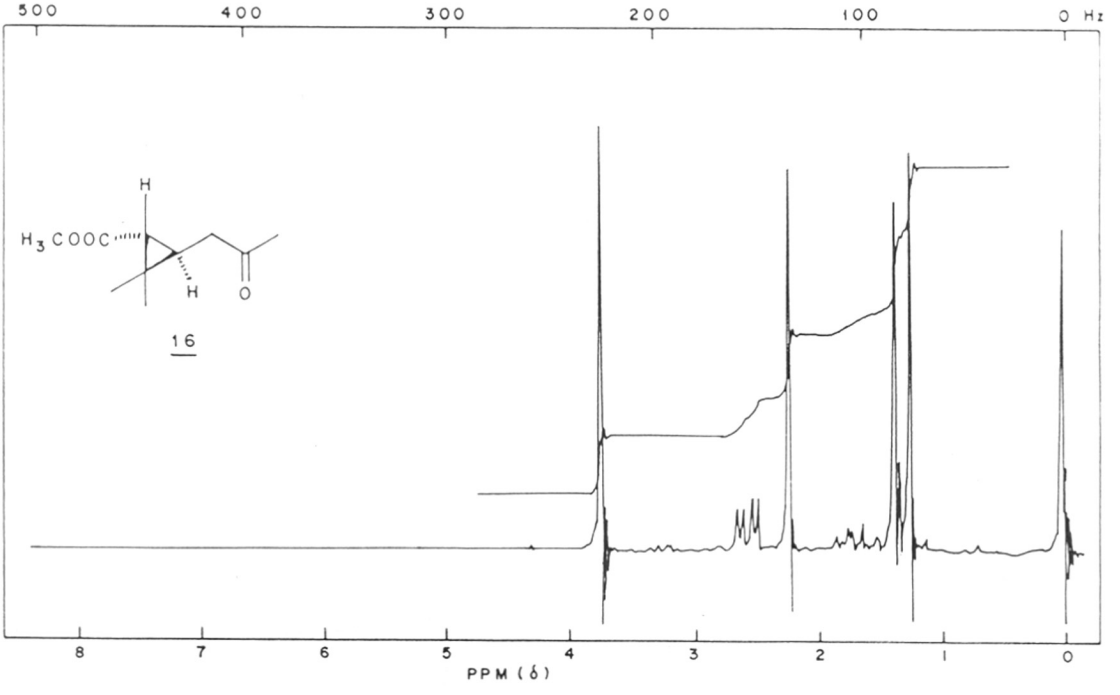

4000 3000 2000 1500 CM⁻¹ 1000 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
R =
O
CH2
COOR
Cl
H
CH3
H
9c
+
COOR
H
H
Cl
9d
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

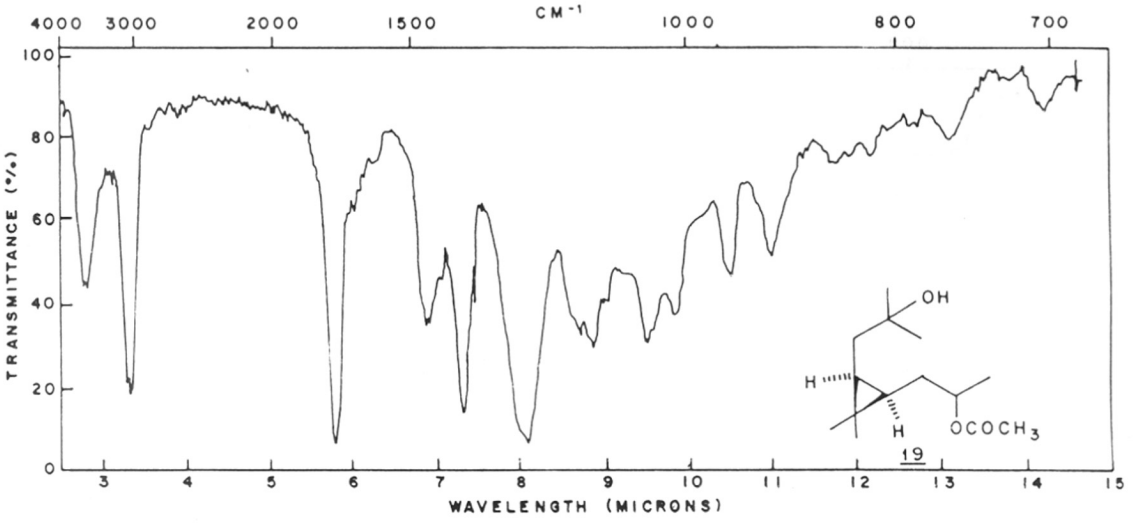

500 400 300 200 100 0 Hz
COOR
Cl
H
CH3
H
9c
+
COOR
H
H
Cl
9d
R =
O
CH2
8 7 6 5 4 3 2 1 0
PPM (δ)

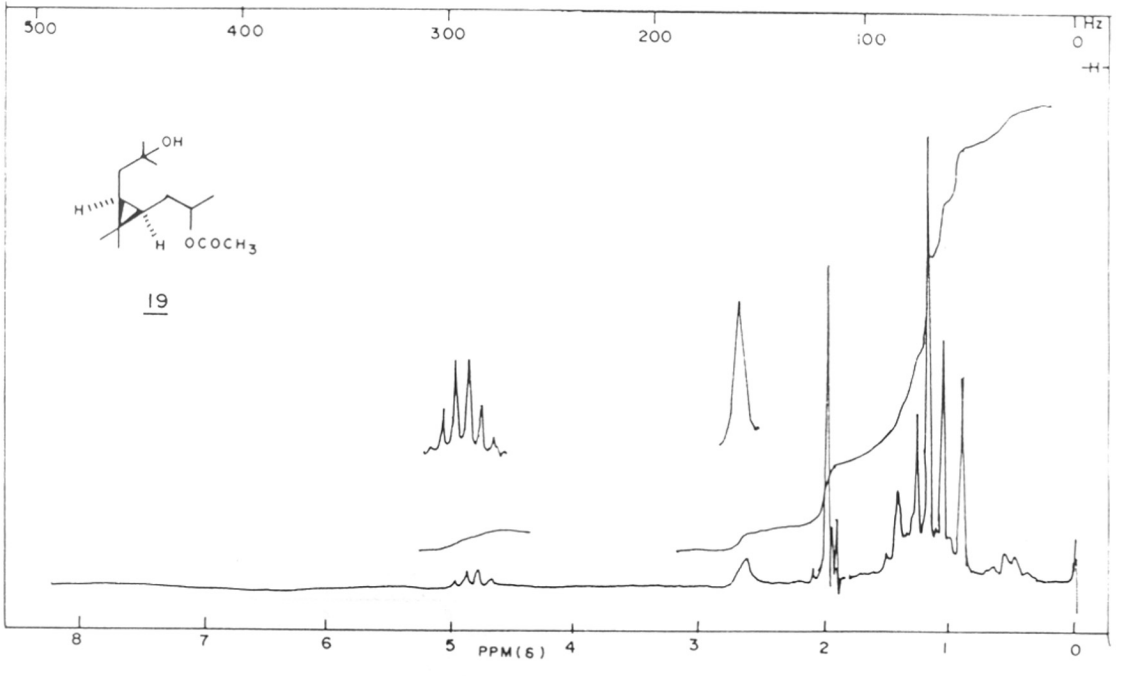

4000 3000 2000 1500 CM⁻¹ 1000 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
H
Bu⁺OOC
H
O
15

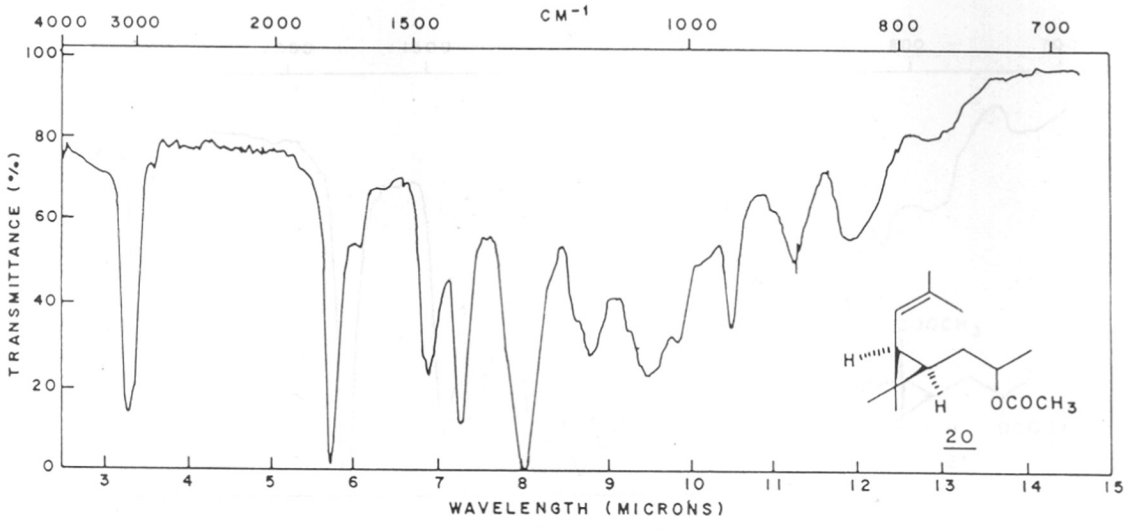

500 400 300 200 100 0 Hz
H
Bu⁺OOC
H
O
15
8 7 6 5 4 3 2 1 0
PPM (δ)

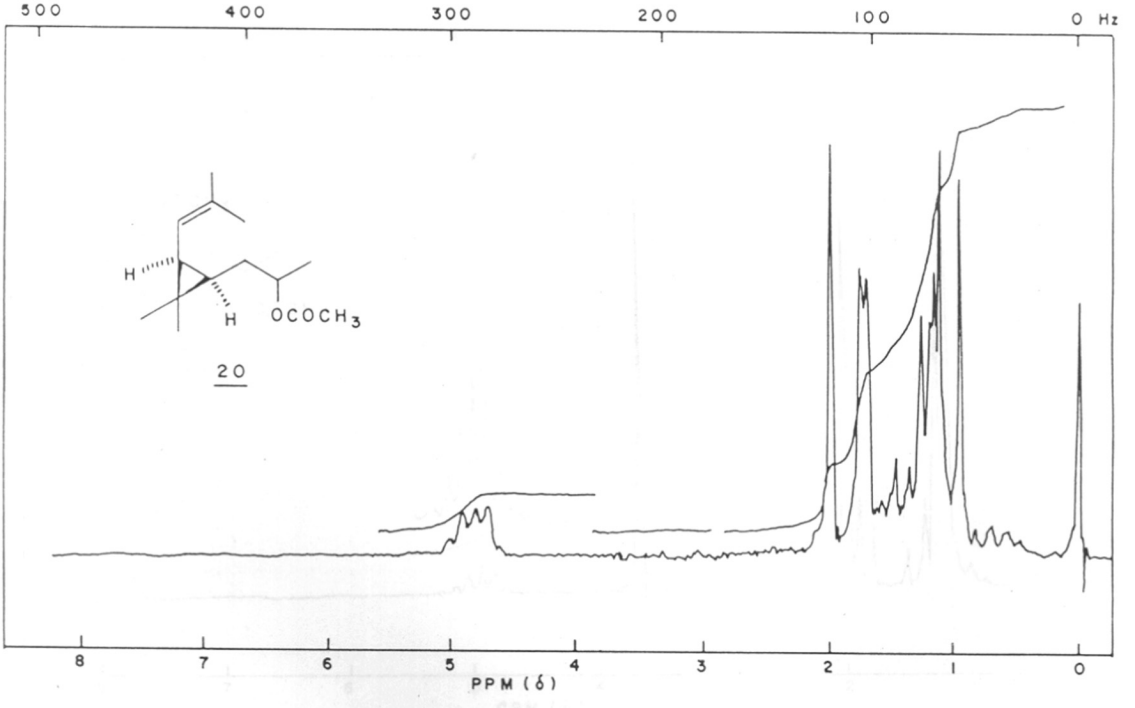

4000 3000 2000 1500 CM⁻¹ 1000 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
H
H3COOC
H
O
16

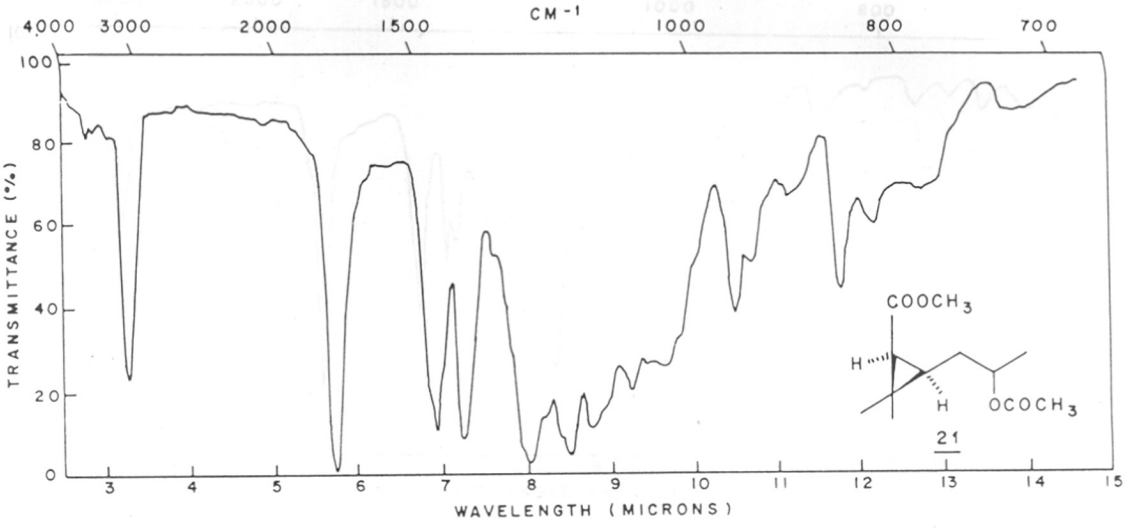

500 400 300 200 100 0 Hz
H
H3COOC
H
O
16
8 7 6 5 4 3 2 1 0
PPM (δ)

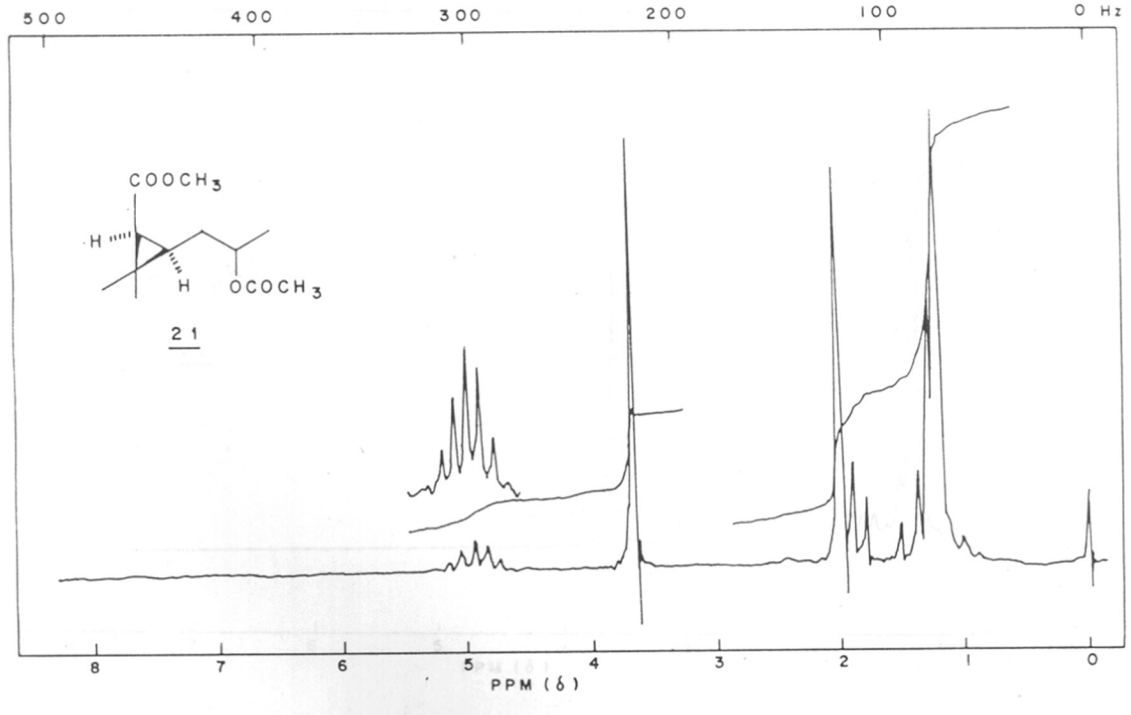

4000 3000 2000 1500 CM⁻¹ 1000 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
OH
H
H
OCOCH3
19

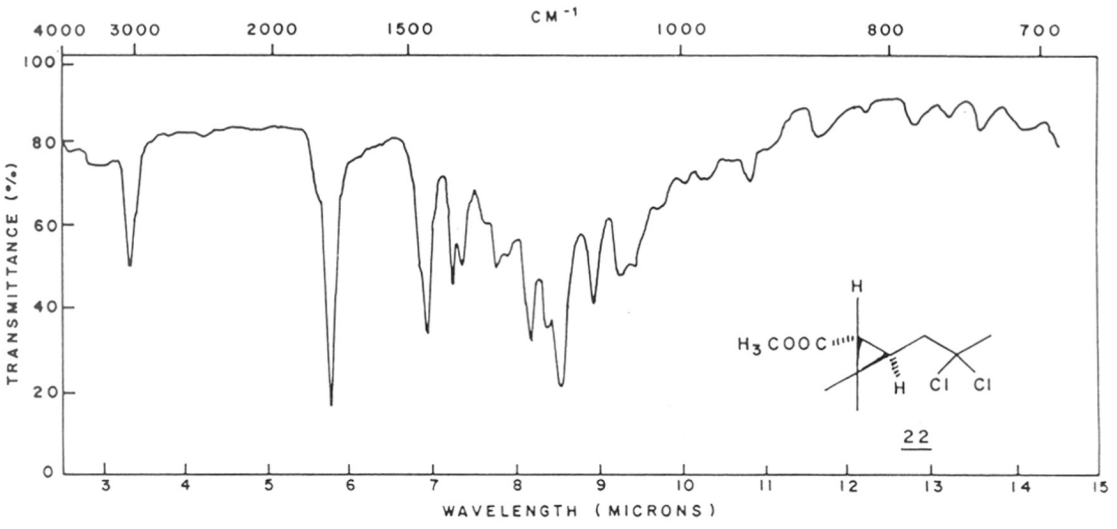

500 400 300 200 100 0 Hz
OH
H
H
OCOCH3
19
8 7 6 5 PPM(δ) 4 3 2 1 0


4000 3000 2000 1500 CM-1 1000 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
H
H
OCOCH3
20

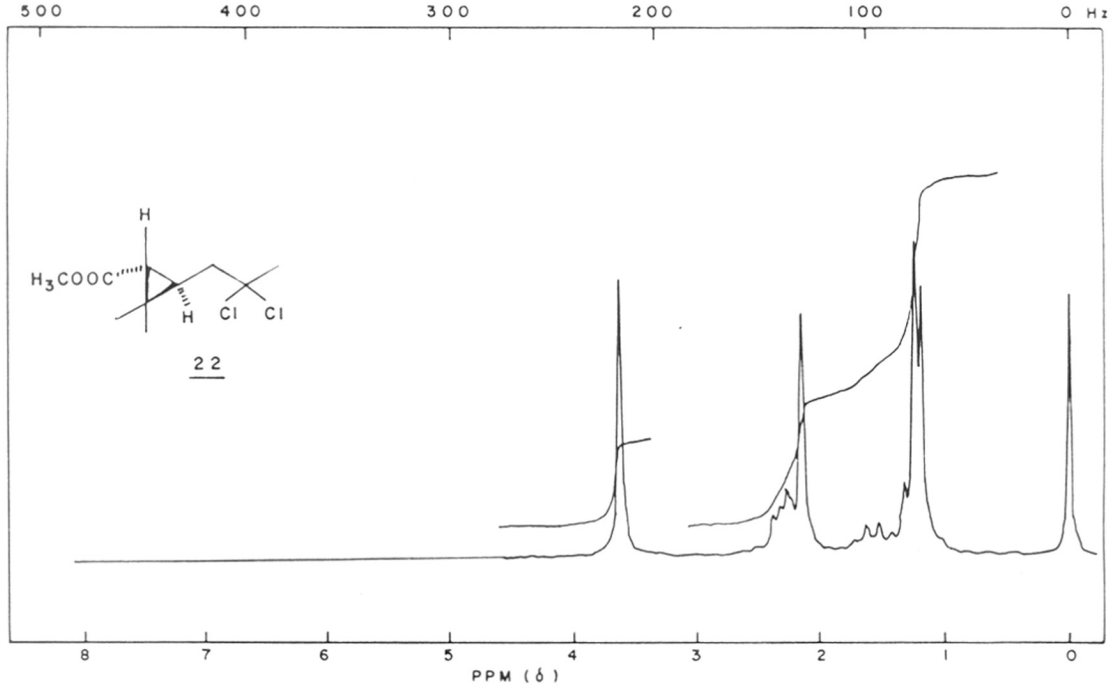

500 400 300 200 100 0 Hz
H
H
OCOCH3
20
8 7 6 5 4 3 2 1 0
PPM (δ)


4000 3000 2000 1500 CM-1 1000 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
COOCH3
H
H
OCOCH3
21

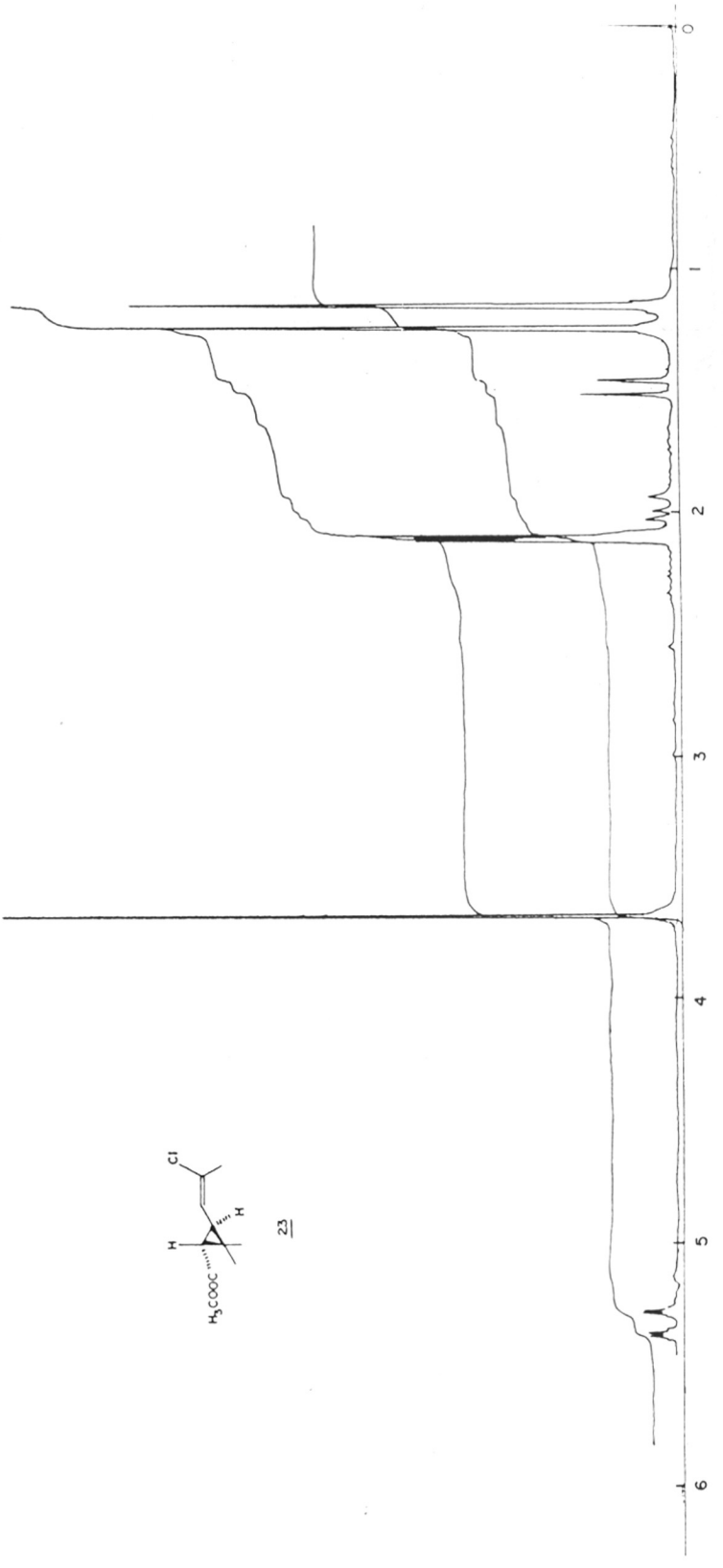

500 400 300 200 100 0 Hz
COOCH3
H
H
OCOCH3
21
8 7 6 5 4 3 2 1 0
PPM (δ)


4000 3000 2000 1500 CM⁻¹ 1000 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
H
H3COOC
H Cl Cl

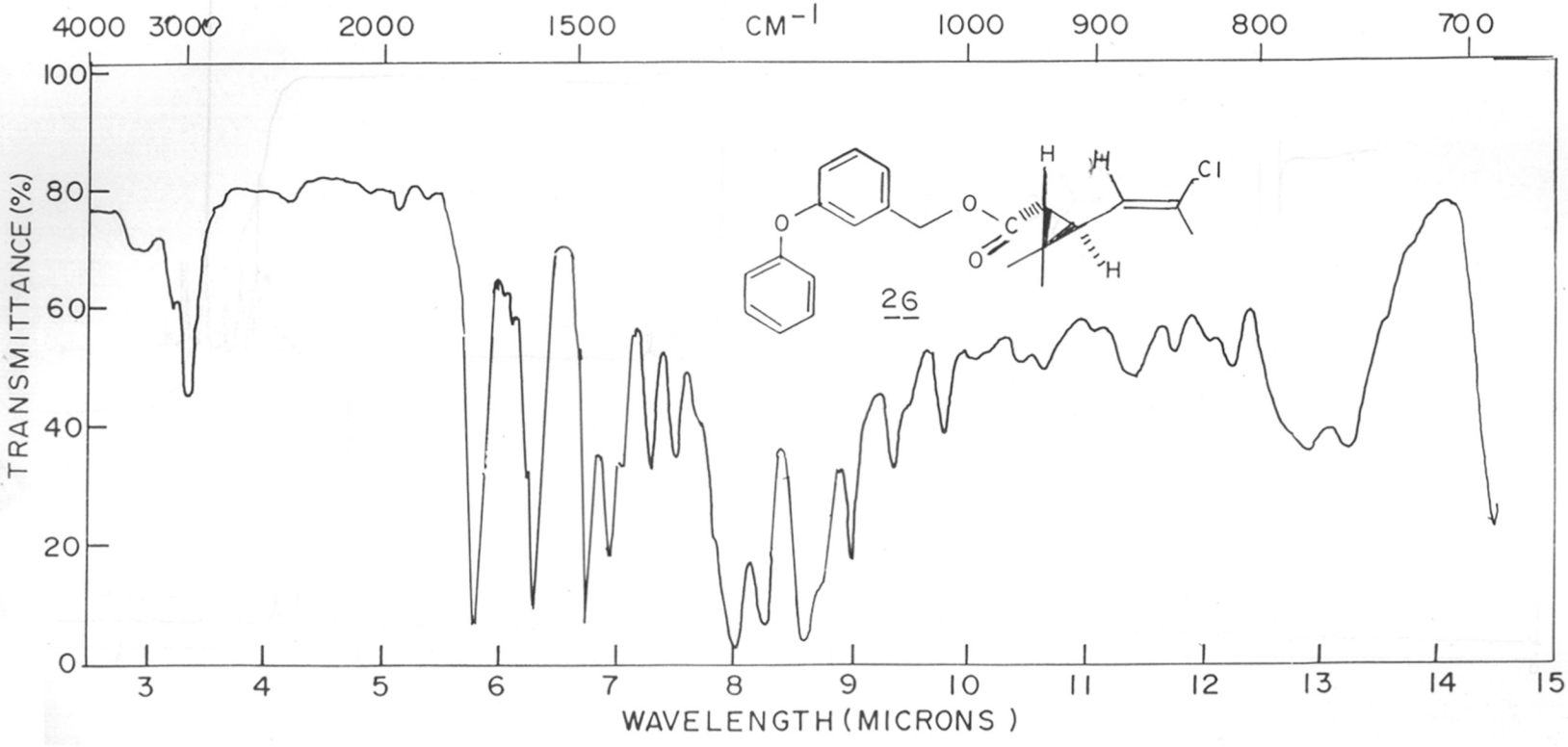
22


500 400 300 200 100 0 Hz
H
H3COOC
H Cl Cl
8 7 6 5 4 3 2 1 0
PPM (δ)

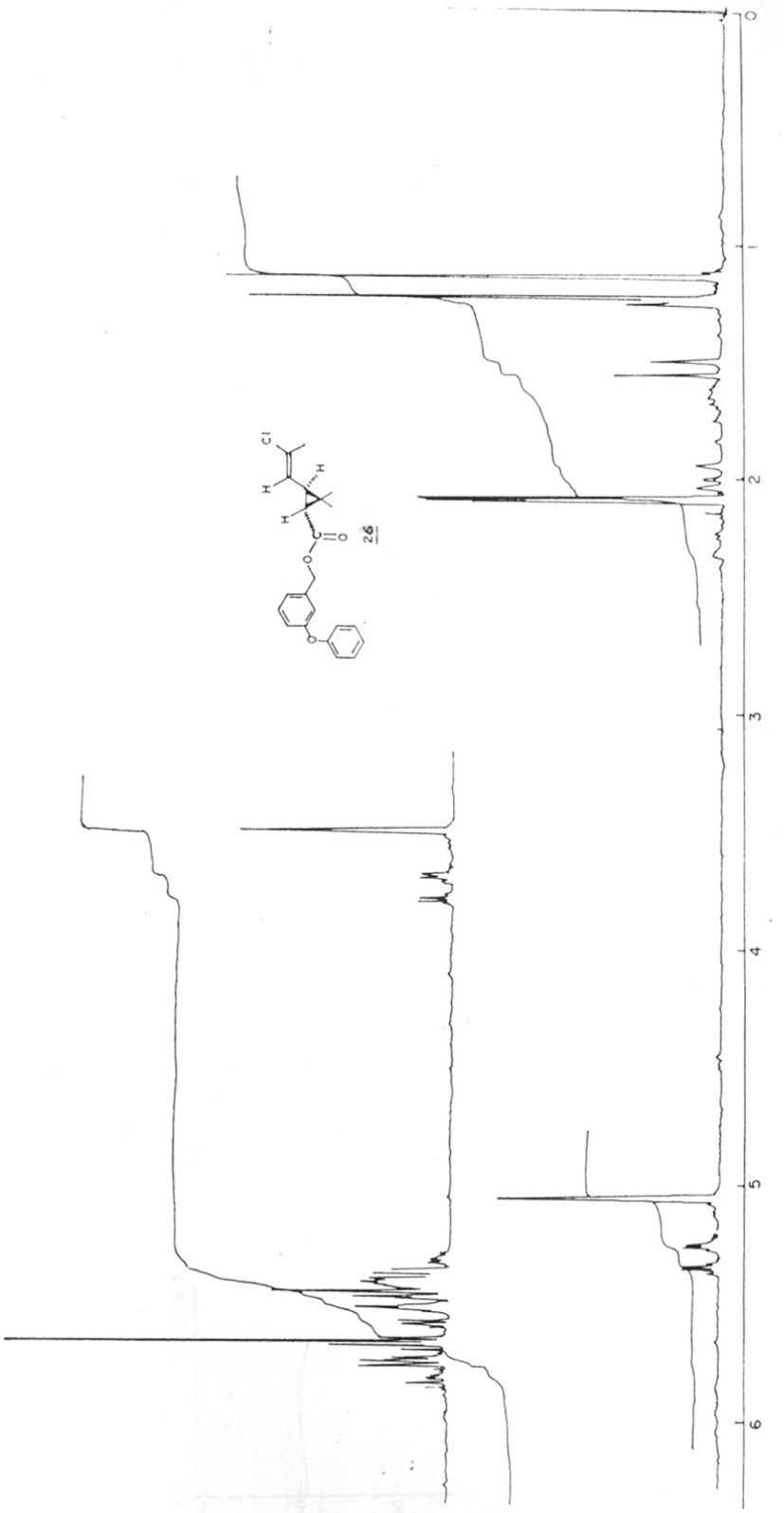
22

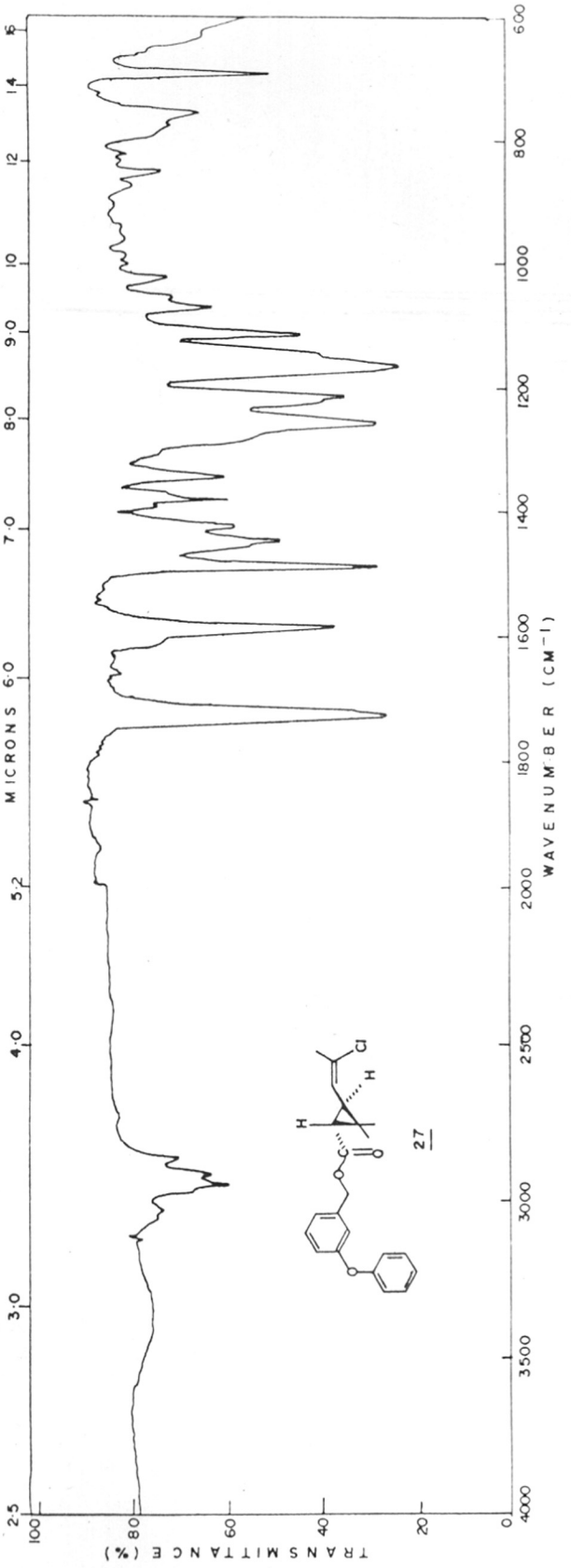

Cl
H
H
H3COOC
23
0
1
2
3
4
5
6

24

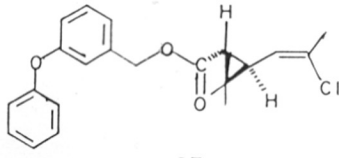

4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
O
O
C
O
H
H
H
Cl

26


Cl
H
H
H
O
O
O
26
0
1
2
3
4
5
6


TRANSMITTANCE (%)
MICRONS
WAVENUMBER (CM⁻¹)
2.5
3.0
4.0
5.2
6.0
7.0
8.0
9.0
10
12
14
15
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
100
80
60
40
20
0
Cl
H
H
O
O

27



27

CHAPTER - VA

A CONVENIENT SYNTHETIC METHOD FOR ALLYL ALCOHOLS

SUMMARY

A convenient synthetic method for the preparation of allyl alcohols was developed. Alkenes were epoxidated by hydrogen peroxide and ethyl chloroformate. The epoxides so obtained were opened by sodium thiophenoate to corresponding hydroxy sulfides. Hydroxysulfides were converted to hydroxy sulfoxides and the pyrolysis of sulfoxides gave the corresponding allyl alcohols. Compounds (1), (2), (11), (14) and (17) were prepared by this method. The tertiary allyl alcohol (2) was also prepared by addition of phenyl sulfenyl chloride to (+)-3-carene. The addition product was converted to hydroxy sulfide (6) via the acetate (7). Pyrolysis of sulfoxide (8) obtained from hydroxy sulfide (6) gave the tertiary allyl alcohol (2).

INTRODUCTION

(-) Car-4-ene-3α-ol (1) and its C-3 epimer (-) car-4-ene-3β-ol (2) are very important intermediates for the synthesis of bioactive synthetic pyrethroids (see Chapter II), starting from (+) 3-carene (3). So, we required a facile practical route for the conversion of (+) 3-carene into these alcohols.

There are a number of methods[1-6] known in literature to get allylic alcohols, but at the same time there are limitations for their application as a general method of synthesis. The most widely used general method is conversion of epoxide to allyl alcohol, discovered by Cope et al.[7-9] and it was thoroughly developed by Crandall[10-12] and Rickborn[13-16]. Sharpless[17] for the first time introduced organoselenium reagent for getting allyl alcohols from epoxides.

The methods described in literature for the synthesis of (1) and (2) suffer from serious drawbacks. Alcohol (1) obtained by singlet oxygen reaction[18] of (3) was cumbersome and uneconomical involving separation of isomers. The rearrangement of α-epoxycarane (4) with strong base[19] also results in a mixture of isomeric alcohols. Synthesis of (1) and (2) by Cope elimination of N-oxides, employs conditions of high pressure and

temperature and in our hands, resulted in very poor yields,contrary to what is reported[20]. Lastly, the preparation[21] of (1) involving Sharpless[17] sequence- phenyl selenation- oxidation-elimination was unsuited for several reasons: Alcohol (1) by this method is reported in poor yield, attributed to steric factors[20,23]. Preparation of (2) requires (-)-3β, 4β-epoxycarane (5) which is itself obtained from (+) 3-carene in modest yield; the cost and toxicity of selenium compounds are added disadvantages, especially for large scale preparation.

The syn-elimination of sulphenic acid by the pyrolysis of sulfoxides has been widely used for the synthesis of α-enone systems[23] and continues to find wide application for the introduction of double bond in natural product synthesis. However, unlike the Cope elimination and selenium methodology, the pyrolysis of sulfoxides has not been developed[24] as a method for the preparation of allylic alcohols, except for a report[25] describing the preparation of primary and secondary allylic alcohols.

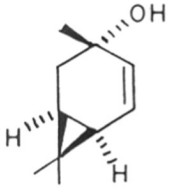
We have developed a simple and practical method for preparing allylic alcohols including both the bicyclic tertiary alcohols (1) and (2), by the pyrolysis of sulfoxides. Although sulfoxides require a higher temperature for pyrolysis than the corresponding selenoxides, for the specific synthesis of (1) and (2)

the sulfoxide method proved to be definitely superior, when toxicity due to selenium compounds has to be avoided or where complications arise, either due to steric factors or by further oxidation[26] of the product catalysed by benzene-selenenic acid.

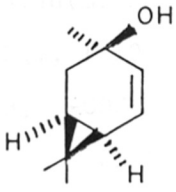
Present work and discussion

We have already seen the preparation of (-) car-4-ene-3α-ol (1) (Chapter II) starting from α-epoxy-carane (4). The bicyclic tertiary alcohol (-) car-4-ene-3β-ol (2) was prepared from β-epoxycarane (5). The -epoxide (5) required for the preparation of (2) was prepared by Ohloff's method[18], starting from 3β,4α-carane diol, by tosylation and detosylation. The mixture of β-epoxy carane (5), thiophenol and aqueous sodium hydroxide, in ethanol was refluxed under nitrogen atmosphere for four hours. Ethanol was removed and extractive workup with ether after dilution with water, gave brown oil which was distilled under vacuum to give (6) as a colourless oil in 78% yield, b.p.170-190°/1 mm (bath temp.). IR (liquid film): 3571 cm^{-1} (hydroxyl); PMR (CCl_4,δ); 0.4 - 0.97 (m, 2H, cyclopropyl protons), 1.03 (s, 6H, $-CH_3$), 1.3 (s, 3H, $-CH_3$), 1.4 - 2.43 (m, 4H, $-CH_2$), 3.03 (dd, 1H -CH-S-, J = 8, 12 Hz), 7.43 - 7.47 (m, 5H, aromatic).

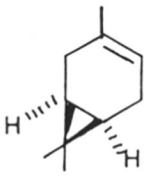
The same hydroxy sulfide (6) was prepared in quantitative yield from (+) 3-carene. The stereo-specific addition of phenyl sulfenyl chloride followed by sulfur assisted solvolysis with sodium acetate and acetic acid gave acetate (7) as colourless oil in 94% yield. IR (liquid film): 1736 cm^{-1} (acetate); PMR(CCl_4,



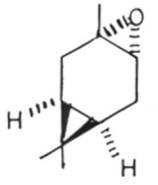
1



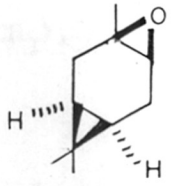
2



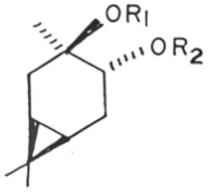
3



4



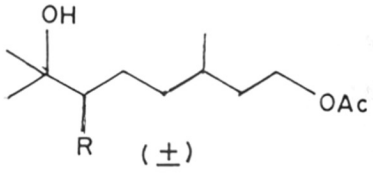
5



6, R_1 = H, R_2 = −SPh

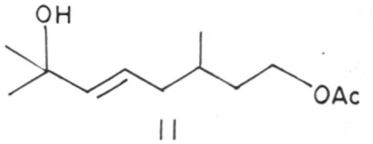
7, R_1 = Ac, R_2 = −S(O)Ph

8, R_1 = H, R_2 = −S(O)−Ph

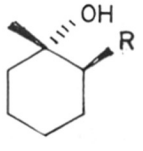


9, R = −SPh

10, R = −S(O)−Ph

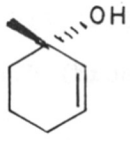


11

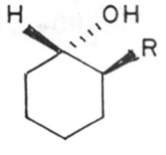


12, R = −SPh

13, R = −S(O)−Ph

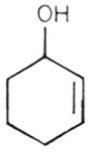


14

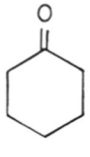


15, R = −SPh

16, R = −S(O)−Ph



17



18

δ): 0.5 - 0.46(m, 2H, cyclopropyl protons), 1.00 (s, 3H, $-CH_3$), 1.10 (s, 3H, $-CH_3$), 1.50 (s, 3H, $-CH_3$), 1.70 (s, 3H, $-COCH_3$), 1.73 - 2.40 (m, 4H, $-CH_2$), 3.83 (dd, 1H, -CH-S-, J = 8, 12 Hz), 6.46 - 7.6 (m, 5H, aromatic). The above acetate was hydrolysed by stirring with aqueous methanolic sodium hydroxide at room temperature to get quantitatively hydroxy sulfide (6) which was having identical spectral data with that of authentic, obtained from β-epoxy carane.

The methanolic solution of hydroxy sulfide (6) was stirred with 30% aqueous hydrogen peroxide at room temperature for four hours. Extractive workup after dilution with cold water gave semisolid hydroxy sulfoxide (8) in 99% yield. IR (nujol): 3509 (hydroxyl), 1020 cm^{-1} (sulfoxide); PMR (CCl_4, δ): 0.4 - 0.66 (m, 2H, cyclopropyl protons), 0.76 (s, 3H, $-CH_3$), 0.93 (s, 3H, $-CH_3$), 1.07 - 1.93 (m, 4H, $-CH_2$), 1.50 (s, 3H, $-CH_3$), 2.0 - 2.57 (m, 1H, -CH-S-), 4.5 (broad s, 1H, -OH), 7.17 - 7.70 (m, 5H, aromatic).

Pyrolysis of hydroxy sulfoxide (8) at 160-200°/6 mm gave semisolid material which was dissolved in ether, dried over sodium sulfate, ether was removed and residue distilled to give colourless liquid (9) in 64% yield b.p.100-110°/6 mm, (bath temp.), solidified after seeding m.p. 47-48° (reported m.p.49-51°). IR (liquid film): 3448 (hydroxyl) 1639, 725 cm^{-1} (double bond).

PMR (CCl_4, δ): 0.6 - 1.0 (m, 2H, cyclopropyl proton), 0.97 (s, 3H, $-CH_3$), 1.07 (s, 3H, $-CH_3$), 1.23 (s, 3H, $-CH_3$), 1.33 - 2.23 (m, 2H, $-CH_2$), 3.73 (broad s, 1H, -OH), 5.2 (dd, 1H, olefinic, J = 10, 2 Hz), 5.53 (d, 1H, olefinic J = 10 Hz), $[\alpha]_D^{28}$ = 204° (methanol, c, 4.15). Reported $[\alpha]_D^{20}$ = -187.13± (methanol, c, 3.34) and $[\alpha]_D^{20}$ = - 197.8° (methanol, c, 3.0).

In order to test the generality of this method for getting allylic alcohols, sulfoxide (10), (13) and (16) were prepared and pyrolysed. These were obtained as in the case of (1) from corresponding epoxides in about 80% overall yield. Pyrolysis of sulfoxide (10) gave (11)[27] in 87% yield which was having identical spectral data with that of the reported one. The corresponding route is reported to give (11) in 72% yield from epoxide. Pyrolysis of (13) gave 2-cyclohexen-1,methyl-1-ol[26] (14) in 53% yield. GLC analysis of the product showed it to be 90% pure, contaminated with 3% 1,2-epoxy-1-methyl cyclohexane and other minute impurities. The corresponding selenoxide route is reported to yield about 15% impure product[26]. The sulfoxide (16) (reported m.p.155°C)[28] was obtained as distereomers (16a) m.p.160° and (16b) m.p. 140°. It was interesting to find that (16) pyrolysed at 200°C to give 46% product, while (16b) pyrolysed at 160-170°C to give 80% product. In each case the product consisted of 90% 2-cyclohexene-1-ol and 10% cyclohexanone by GLC and PMR.

EXPERIMENTAL

Epoxides

A procedure described[29] for the synthesis of epoxides was adopted for the preparation of epoxides used in this work. They were obtained in 95-100% yield and gave satisfactory spectral data. β-Epoxy carane was prepared by Ohloff's method[18], from 3β,4α-carane diol.

Hydroxy sulfide (6)

A homogeneous mixture of sodium hydroxide (1.68 g, 42 mmol), water (1.5 ml), thiophenol (4.29 gm, 39 mmol), β-epoxy carane (5) (4.56 g, 30 mmol) in ethanol (25 ml) was refluxed for four hours under nitrogen. Ethanol was removed and extractive workup with ether gave a brown oil, which on distillation b.p.170-190°/1 mm (bath temp) gave (6) as colourless oil (6.13 g, 78%).

IR (liquid film): 3571, 2985, 1587, 1471, 1429, 1370, 1220, 1200, 1130, 1111, 1083, 1064, 1020, 1000, 948, 926, 889, 840, 806, 766, 741, 714, 690 cm^{-1}.

PMR (CCl_4, δ): 0.4 - 0.97 (m, 2H, cyclopropyl protons), 1.03 (s, 6H, $-CH_3$), 1.3 (s, 3H, $-CH_3$), 1.4 - 2.43 (m, 4H, $-CH_2$), 3.03 (dd, 1H, -CH-S-, J = 8, 12 Hz), 7.43 - 7.97 (m, 5H, aromatic)

$[\alpha]_D^{30}$ = - 60.67° ($CHCl_3$; c, 2.426).

Analysis: Calculated for $C_{16}H_{22}OS$: C, 73.28; H, 8.39;
S, 12.21.
Found: C, 73.57; H, 8.61; S, 12.52.

Hydroxy sulfide (6) from (+) 3-carene

Phenyl sulfenyl chloride (10.8 g, 74.73 mmol) was added to (+) 3-carene (3) (12.5 g, 91.91 mmol) at 0°C. To the product was added acetic acid (50 ml, 0.87 mol) and sodium acetate (14.8 g, 0.180 mol) and the reaction stirred overnight at room temperature. Extractive workup with ether, after dilution with water gave the acetate (7) (26.25 g, 93.93%).

IR (liquid film): 3030, 1736, 1587, 1479, 1437, 1370, 1247, 1198, 1170, 1145, 1087, 1020, 959, 935, 847, 810, 743 cm^{-1}.

PMR (CCl_4, δ): 0.5 - 0.96 (m, 2H cyclopropyl protons), 1.00 (s, 3H, $-CH_3$), 1.10 (s, 3H, $-CH_3$), 1.50 (s, 3H, $-CH_3$), 1.70 (s, 3H, $-COCH_3$), 1.73 - 2.40 (m, 4H, $-CH_2$), 3.83 (dd, 1H, -CH-S, J = 8, 12 Hz), 6.46 - 7.6 (m, 5H, aromatic).

Acetate (7) (26.0 g, 85.53 mmol) in methanol (350 ml) was treated with aqueous 10% sodium hydroxide (52 ml, 0.13 mol) at room temperature overnight. Extractive workup with ether after dilution with water gavea pale yellow oil (6) (21.86 g, 91.68% from (+) 3-carene).

Spectral data- identical with that of hydroxy sulfide obtained from β-epoxy carane (5).

Hydroxy sulfoxide (8)

A solution of hydroxy sulfide (6) (7.0 g, 25.1 mmol) in methanol was treated with hydrogen peroxide (30%, 9.14 ml, 80 mmol) at room temperature for 4 hours. Extractive workup with ethyl acetate after addition of water gave (8) as sticky solid (7.35 g, 99%).

IR (nujol): 3509, 2985, 1587, 1433, 1397, 1370, 1333, 1307, 1280, 1220, 1190, 1136, 1111, 1075, 1020, 990, 952, 926, 883, 833, 812, 751, 709, 692 cm^{-1}.

PMR (CCl_4, δ): 0.4 - 0.66 (m, 2H, cyclopropyl protons), 0.76 (s, 3H, $-CH_3$), 0.93 (s, 3H, $-CH_3$), 1.07 - 1.93 (m, 4H, $-CH_2$), 1.50 (s, 3H, $-CH_3$), 2.0 - 2.57 (m, 1H, -CH- S-), 4.5 (broad s, 1H, -OH), 7.17 - 7.70 (m, 5H, aromatic).

Analysis: Calculated for $C_{16}H_{22}O_2S$: C, 69.07; H, 7.91; S, 11.51.
Found: C, 69.09; H, 8.18; S, 11.20.

Pyrolysis of sulfoxide (8)

Hydroxy sulfoxide (8) (6.3 g, 24 mmol) was mixed thoroughly with anhydrous potassium carbonate (5.0 g, 36 mmol) in a round bottom flask and heated at 160-200°C in an oil bath at 6 mm for 1 hour, with a distillation assembly attached, the receiver was cooled in an ice-salt bath. The distillate was dissolved in ether, dried over anhydrous sodium sulfate, ether removed and residue distilled to give colourless liquid (2) (2.2 g, 64.0%)

b.p. 100-110°/6 mm (bath temp.). Solidified after seeding m.p. 47-48° (reported m.p. 49-51°).

IR (liquid film): 3448, 2985, 1639, 1449, 1370, 1325, 1285, 1250, 1205, 1149, 1134, 1099, 1053, 1000, 980, 962, 948. 917, 889, 791, 725 cm^{-1}.

PMR (CCl_4, δ): 0.6 - 1.0 (m, 2H, cyclopropyl protons), 0.97 (s, 3H, $-CH_3$), 1.07 (s, 3H, $-CH_3$), 1.23 (s, 3H, $-CH_3$) 1.33 - 2.33 (m, 2H, $-CH_2$), 3.73 (broad s, 1H, -OH), 5.2 (dd, 1H, olefinic, J = 10, 2 Hz), 5.53 (d, 1H, olefinic, J = 10 Hz).

$[\alpha]_D^{28}$ = 204° (methanol; c, 4.15) (HPLC- pure)

Reported $[\alpha]_D^{20}$ = -187.13° (methanol; c, 3.34) and $[\alpha]_D^{20}$ = - 197.8° (methanol, c, 3.0).

Analysis: Calculated for $C_{10}H_{16}O$; C, 78.96; H, 10.77

Found: C, 78.77; H, 10.90.

Hydroxy sulfide (9)

Reaction of (±) epoxy citronellyl acetate (6.421 g, 30 mmol) with thiophenol (3.90 g, 35.46 mmol) as described earlier gave after acetylation (9) (8.43 g, 81.7%) as a thick pale yellow liquid, b.p. 150-160°/1 mm (bath temp.)

IR (liquid film): 3434, 2985, 1724, 1580, 1460, 1429, 1359, 1235, 1157, 1120, 1081, 1042, 1020, 952, 893, 792, 741 cm^{-1}.

PMR (CCl_4, δ): 0.93 (broad s, 3H, CH_3), 1.2 (s, 3H, $-CH_3$), 1.27 (s, 3H, $-CH_3$), 1.33 - 1.77 (m, 7H, $-CH_2$, -C-H), 1.93

(s, 3H, $-OCOCH_3$), 2.8 - 3.14 (m, 1H, -CH-3-), 3.57 (broad s, 1H, -OH), 3.83 - 4.23 (m, 2H, $-CH_2-O-$), 7.03-7.6 (m, 5H, aromatic).

Hydroxy sulfoxide (10)

Procedure same as for (8).

Hydroxy sulfide (9) (3.1 g) gave hydroxy sulfoxide (10) as thick liquid (3.17 g, 100%).

IR (liquid film): 3571, 3030, 1754, 1613, 1486, 1429, 1374, 1247, 1176, 1087, 1026, 962, 896, 756, 699 cm^{-1}.

PMR (CCl_4, δ): 0.73 (broad s, 3H, $-CH_3$), 1.20 (s, 3H, $-CH_3$), 1.5 (s, 3H, $-CH_3$), 0.87 - 1.77 (m, 7H, $-CH_2$ and -CH-), 1.97 (s, 3H, $-CH_3$), 2.37 - 2.77 (m, 1H, -CH-S-), 3.54 - 4.0 (m, 2H, $-CH_2-O-$, 4.9 (broad s, 1H, -OH), 7.23 - 7.97 (m, 5H, aromatic).

Pyrolysis of (10)

Pyrolysis was carried as described for (8), with hydroxy sulfoxide (10) (1.3 g) at 160/170°/6 mm. Residue was extracted with ether and mixed with distillate. The product contaminated with diphenyl disulfide was purified by column chromatography (silica gel, eluant, 30% ethyl acetate in hexane) to give (11) (0.703 g, 86%) as an oil.

IR (liquid film): 3448, 2985, 1724, 1575, 1449, 1429, 1351, 1230, 1136, 1025, 966, 912, 781, 73 cm^{-1}.

PMR (CCl_4, δ): 0.97 (d, 3H, $-CH_3$, J = 6 Hz), 1.27 (s, 6H, $-CH_3$), 1.33 - 1.77 (m, 4H, $-CH_2$), 2.0 (s, 3H, $-OCOCH_3$), 1.83 - 2.07 (m, 1H, -CH-), 4.07 (t, 2H, $-O-CH_2$, J = 6 Hz), 5.5 (broad s, 2H, olefinic).

Hydroxy sulfide (12)

Reaction of 1-methylcyclohexene-1,2-oxide (4.5 g, 40.18 mmol) with thiophenol (5.28 g, 48.22 mmol) as described for (6) gave (12) (7.1 g, 79.6%) as an oil.

IR (liquid film): 3571, 3125, 3030, 2941, 1587, 1493, 1443, 1379, 1351, 1149, 1136, 1111, 1087, 1047, 1025, 980, 975, 930, 920, 897, 877, 847, 810, 746, 714, 690 cm^{-1}.

PMR (CCl_4, δ): 1.3 (s, 3H, $-CH_3$), 1.36 - 2.13 (m, 8H $-CH_2$), 2.73 (s, 1H, -OH), 3 - 3.33 (m, 1H, -CH-S-), 7.13 - 7.73 (m, 5H, aromatic).

Hydroxy sulfoxide (13)

Procedure same as described for (8).

Hydroxy sulfide (12) (2.717 g) gave hydroxy sulfoxide (13) as white solid (2.832 g, 97.23%), m.p. 128-136°.

IR (nujol): 3461, 2941, 1449, 1429, 1370, 1316, 1299, 1279, 1250, 1220, 1199, 1136, 1075, 1045, 1013, 990, 934, 917, 854, 763, 751, 714 cm^{-1}.

PMR (CCl_4, δ)^{30}: 1.06 - 1.87 (m, 8H, $-CH_2$), 1.57 (s, 3H, $-CH_3$), 2.53 - 2.9 (m, 1H, -CH-S-), 5.13 (s, 1H, -OH), 7.4 - 8.0 (m, 5H, aromatic).

Analysis: Calculated for $C_{13}H_{18}O_2S$: C, 65.54; H, 7.56; S, 13.45;

Found: C, 65.35; H, 7.71; S, 13.62.

Pyrolysis of (13)

Pyrolysis was carried out as earlier with hydroxy sulfoxide (13) (3.5 g) at 170-200°/20.30 mm for 1 hr. The receiver was cooled to -75°. Colourless oil (0.871 g, 53.4%) was obtained. The product was 90% pure by GLC (column: 2 mm x 180 cm, OV - 225-31).

IR (liquid film): 3571, 3030, 1449, 1370, 1183, 1124, 1099, 1020, 990, 961, 909, 847, 735 cm^{-1}.

PMR (CCl_4, δ)[26]: 1.26 (s, 3H, $-CH_3$), 1.4 - 2.13 (m, 6H, $-CH_2$), 2.4 (s, 1H, -OH), 5.66 (s, 2H, olefinic).

Hydroxy sulfide (15)

Reaction of cyclohexene oxide (2.941 g, 30 mmol) with thiophenol (4.4 g, 40 mmol) as described for (6) gave hydroxy sulfide (15) (4.21 g, 67.44%). b.p.117-125/1 mm (bath temp).

IR (liquid film): 3571, 3125, 2985, 2924, 1587, 1471, 1435, 1383, 1351, 1299, 1266, 1227, 1198, 1152, 1117, 1064, 1036, 1008, 962, 893, 867, 843, 813, 787, 738 cm^{-1}.

PMR (CCl_4, δ): 0.9 - 2.3 (m, 8H, $-CH_2$), 2.43 - 2.93 (m, 2H, -CH-S- and -OH), 3.0 - 3.43 (m, 1H, -CH-O-) 6.96 - 7.4 (m, 5H, aromatic).

Hyroxy sulfoxide (16a), (16b)

A solution of 2-(phenyl thio)cyclohexanol[31] (15) (11.36 g, 54.62 mmol) in methanol (100 ml) was treated with hydrogen peroxide (30%, 35 ml, 0.309 mol) for 4 hours.

The reaction mixture was diluted with water (100 ml) and left overnight. The white crystals (6.51 g, 53.23%) obtained, were filtered and crystallised from ethyl acetate to give a sharp melting compound (16a) m.p.160°.

IR (nujol): 3448, 3003, 1449, 1383, 1551, 1333, 1307, 1285, 1266, 1235, 1215, 1134, 1111, 1075, 1037, 1008, 956, 948, 917, 893, 873, 847, 797, 746, 723, 690 cm^{-1}.

PMR ($CDCl_3$, δ): 0.7 - 2.2 (m, 8H, $-CH_2$), 2.4 - 2.93 (m, 1H, -CH- S-), 3.6 - 4.33 (m, 1H, -CH-O-), 5.08 (s, 1H, -OH), 7.33 - 8.03 (m, 5H, aromatic).

Analysis: Calculated for $C_{12}H_{16}O_2S$: C, 64.30; H, 7.14; S. 14.29.

Found: C, 64.13; H, 7.30; S, 14.62.

MS: m/e 224 (M^+), 126 ($C_6H_5SOH^+$, 100%).

The aqueous solution from above after extraction with chloroform gave a white solid (16b) (4.14 g, 33.9%), recrystallised from ethyl acetate m.p.140°.

IR and PMR of (16b) was the same as described for (16a).

Analysis: Calculated for $C_{12}H_{16}O_2S$: C, 64.30; H, 7.14; S, 14.29;

Found: C, 64.59; H, 7.21; S, 14.68.

MS: m/e 224 (M^+), 126 ($C_6H_5SOH^+$, 100%).

Pyrolysis of (16b)

Pyrolysis was carried out as described for (13) with hydroxy sulfoxide (16b) (1.0 g) at 170-180°/20 mm. Distillate

was dissolved in ether, dried over anhydrous sodium sulfate, ether was removed and residue distilled to give colourless liquid (0.343 g). GLC showed the product to consists of 90% cyclohexanol and 10% cyclohexanone (column, 6 mm x 180 cm, OV - 225-31).

IR (liquid film): 3448, 3115, 2899, 1667, 1449, 1429, 1389, 1282, 1220, 1163, 1136, 1053, 1000, 959, 926, 917, 897, 883, 861, 847, 805, 726 cm^{-1}.

PMR (CCl_4, δ)[32]: 1.47 - 2.13 (m, 6H, $-CH_2$), 3.00 (broad s, -1H, -OH), 3.93 - 4.2 (m, 1H, -CH-O-), 5.7 (s, 2H, olefinic).

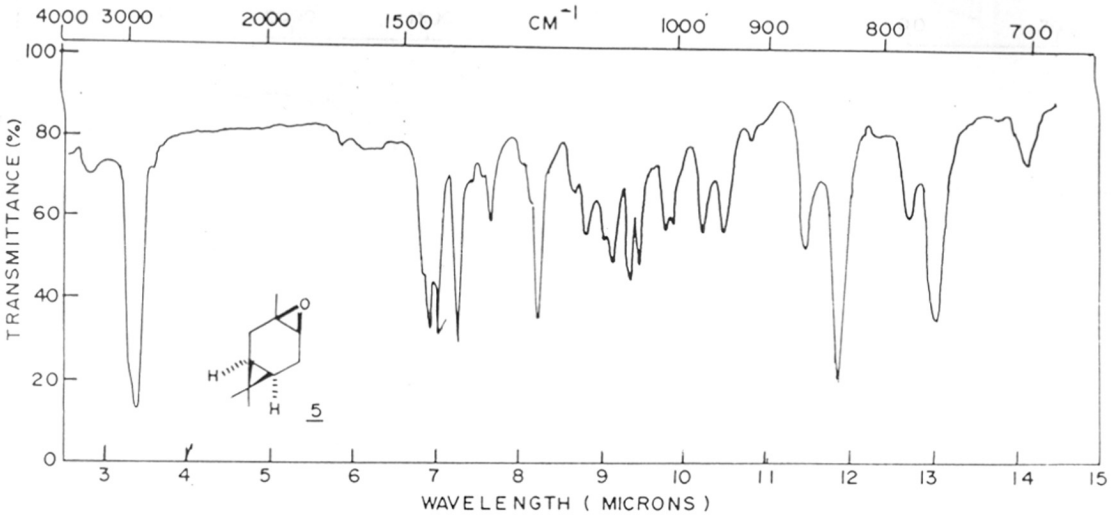
Pyrolysis of (16a)

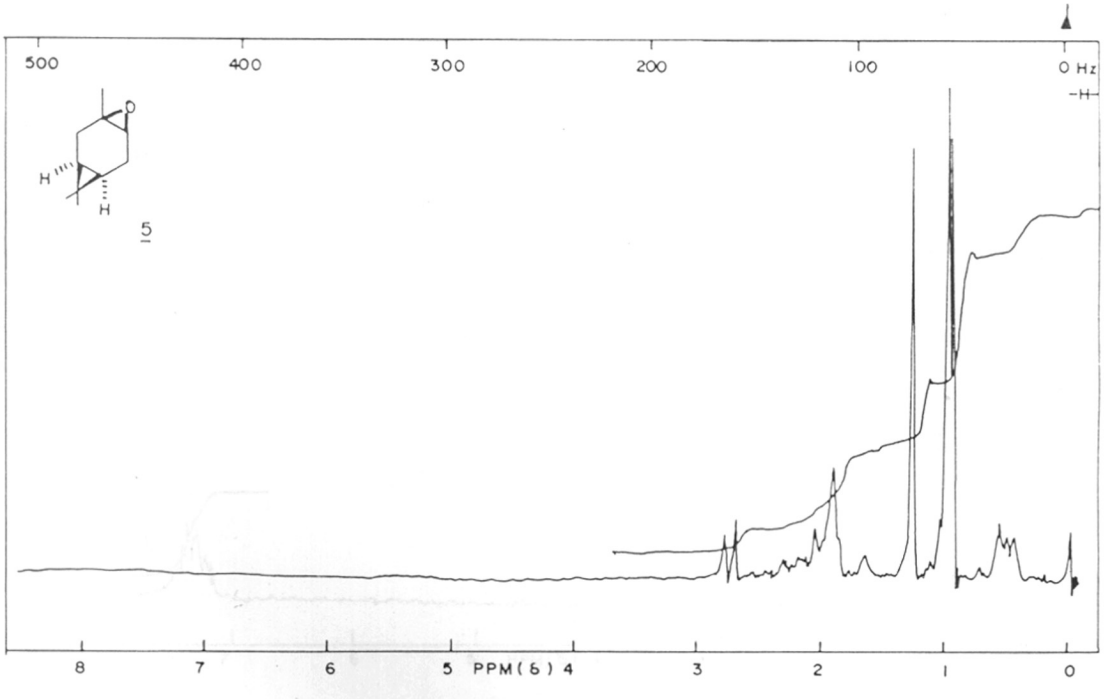
Pyrolysis was carried out with hydroxy sulfoxide (16a) (2 g) at 190-210°/20 mm and worked up as above to give colourless liquid (0.408 g) consisting of 90% cyclohexenol and 10% cyclohexanone.

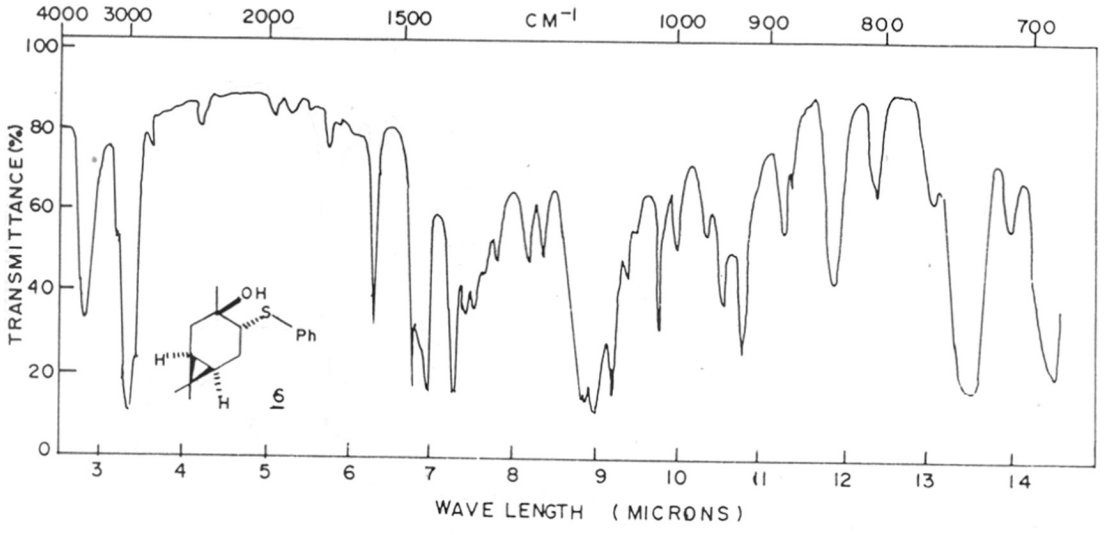
REFERENCES

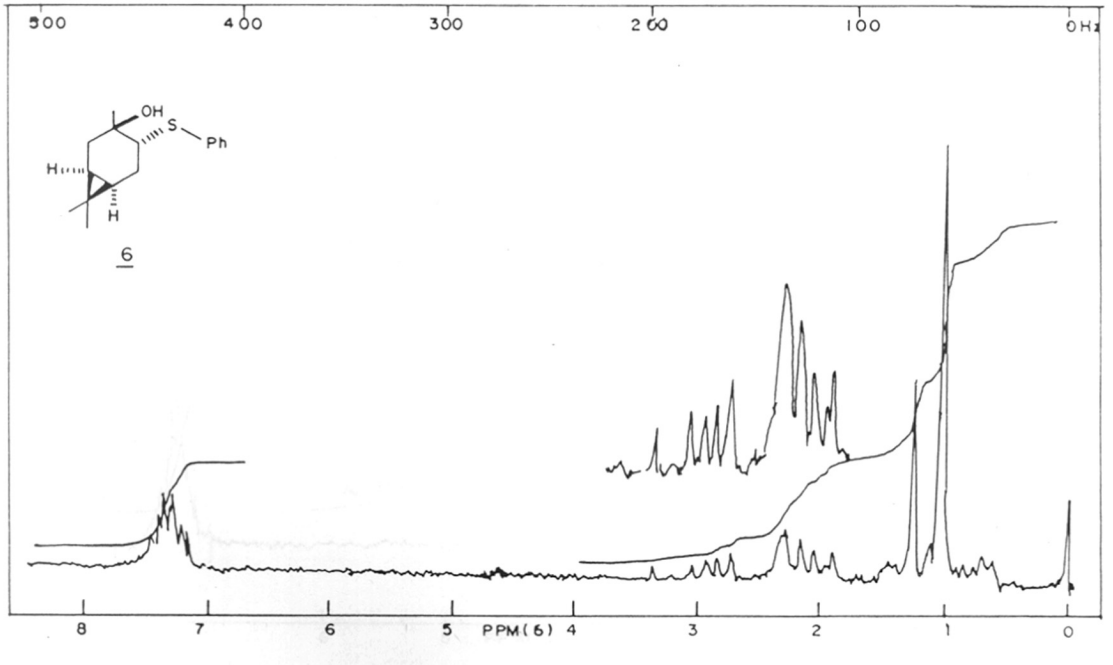
1. P.D. Sleezer, S. Winstein, W.G. Young, J.Am.Chem.Soc., 89, 1890 (1963).
2. W. Dumont, P. Bayet and A. Krief, Angew.Chem.internat.Ed. 13, 804 (1974).
3. D. Seebach and A.K. Beck, Angew.chem.internat.Ed. 13, 806 (1974).
4. A. Yasuda, S. Tanaka, K. Ohima, H. Yamamoto and H, Nozaki, J.Am.Chem.Soc., 96, 6513 (1974).
5. G. Rauchschwalbe and M. Schlosser, Helv.Chim.Acta., 58, 1094 (1975).
6. E.J. Corey and R.H. Wollenberg, J.Org.Chem., 40, 2265 (1975).
7. A.C. Cope, H.H. Lee and H.E. Petree, J.Am.Chem.Soc., 80, 2849 (1958).
8. A.C. Cope, G.A. Berchtold, P.E. Peterson and S.H. Sharman, J.Am.Chem.Soc., 82, 6370 (1960).
9. A.C. Cope, M. Brown and H.H. Lee, J.Am.Chem.Soc., 80, 2855 (1958).
10. J.K. Crandall, J.Org.Chem., 29, 2830 (1964).
11. J.K. Crandall and L. Chang, J.Org.Chem., 32. 435, 532 (1967).
12. J.K. Crandall and L.C. Lin, J.Am.Chem.Soc., 89, 4526, 4527 (1967).
13. B. Rickborn and R.P. Thummel, J.Org.Chem., 34, 3583 (1969).
14. R.P. Thummel and B. Rickborn, J.Am.Chem.Soc., 92. 2064 (1970).
15. R.P. Thummel and B. Rickborn, J.Org.Chem., 36, 1365 (1971).
16. C.L. Kissel and B. Rickborn, J.Org.Chem. 37. 2060 (1972).

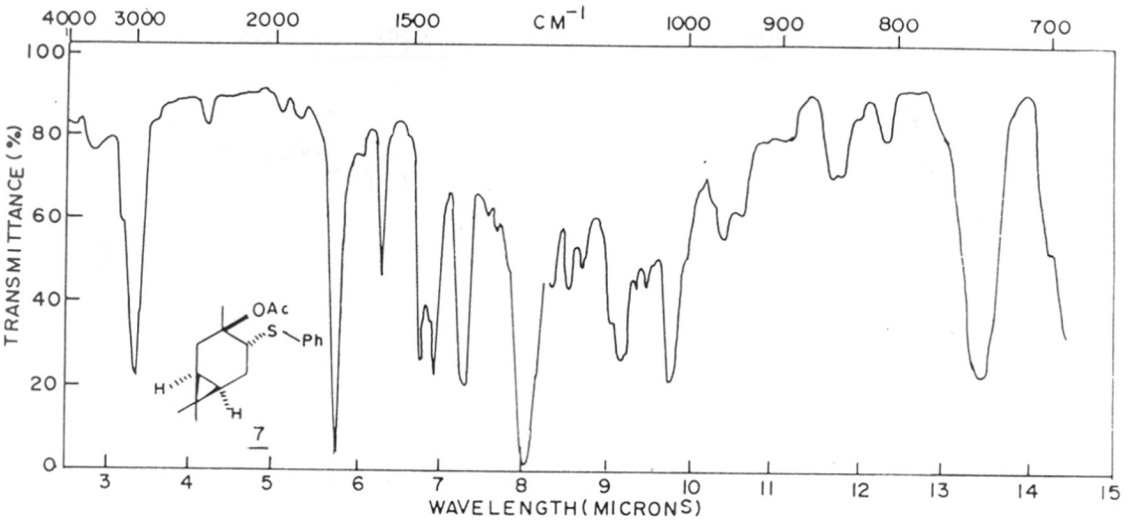
17. K.B. Sharpless and R.F. Lauer, J.Am.Chem.Soc., 95, 2697 (1973).
18. K. Golluick, S. Schroeter, G. Ohloff, G. Schade and G.O. Schenck, Justus Liebigs, Ann.Chem., 687, 14 (1965).
19. H. Kuczynski and K. Marks, Rocz.Chem., 43, 943 (1969).
20. H. Kuczynski and A. Zabza, Rocz.Chem., 35, 1621 (1961).
21. A. Yzarewicz and E. Zientek, Rocz.Chem. 51. 181 (1977).
22. W. Cocker and D.H. Grayson, Tet.Lett., 4451 (1969).
23. B.M. Trost, Accounts Chem.Research 11, 453 (1978).
24. H.J. Reich, Accounts Chem.Research, 12, 22 (1979).
25. J. Nokami, K. Ueta and R. Okawara, Tet.Lett., 49. 4903 (1978).
26. T. Hori and K.B. Sharpless, J.Org.Chem., 43. 1989 (1978).
27. K. Mori, T. Suguro and Uchida, Tetrahedron, 34. 3119 (1978).
28. Y. Uneo, T. Inoue and M. Okawara, Tet.lett., 2413 (1977); Y. Uneo, T. Miyano and Okawara, Bull.Chem.Soc.Jpn., 53, 3615 (1980).
29. R.D. Bach, M.W. Klein, R.A. Ryntz and J.W. Holubka, J.Org.Chem., 44, 2569 (1979).
30. G.H. Posner and D.Z. Rogers, J.Am.Chem.Soc., 99. 8208 (1977).
31. J.J. Uebel, R.F. Milaszewski and R.E. Arlt, J.Org.Chem., 42, 585 (1977).
32. R. Menicagli and O. Piccolo, J.Org.Chem, 45, 2581 (1980); W.E. Fristand, T.R. Bailey and L.A. Paquette, ibid., 45, 3028 (1980).

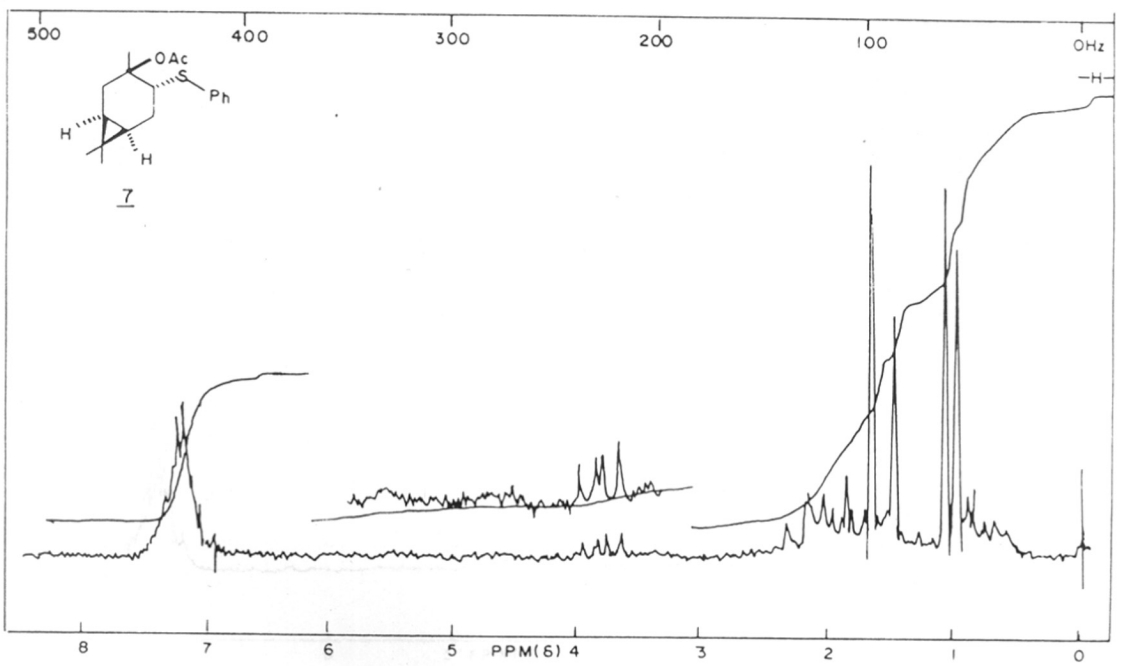

4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
O
H
H
5
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

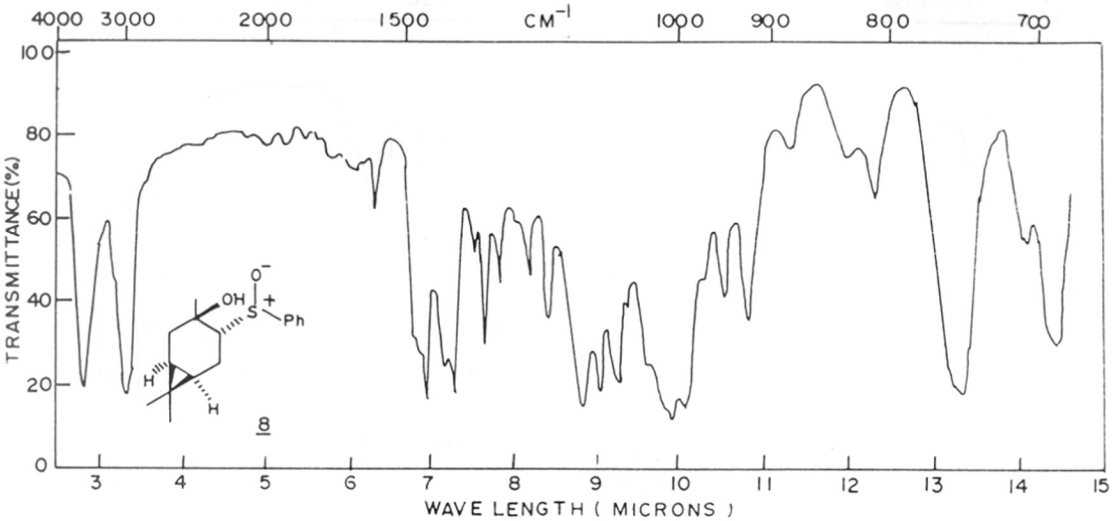

500 400 300 200 100 0 Hz
-H-
O
H
H
5
8 7 6 5 PPM(δ) 4 3 2 1 0

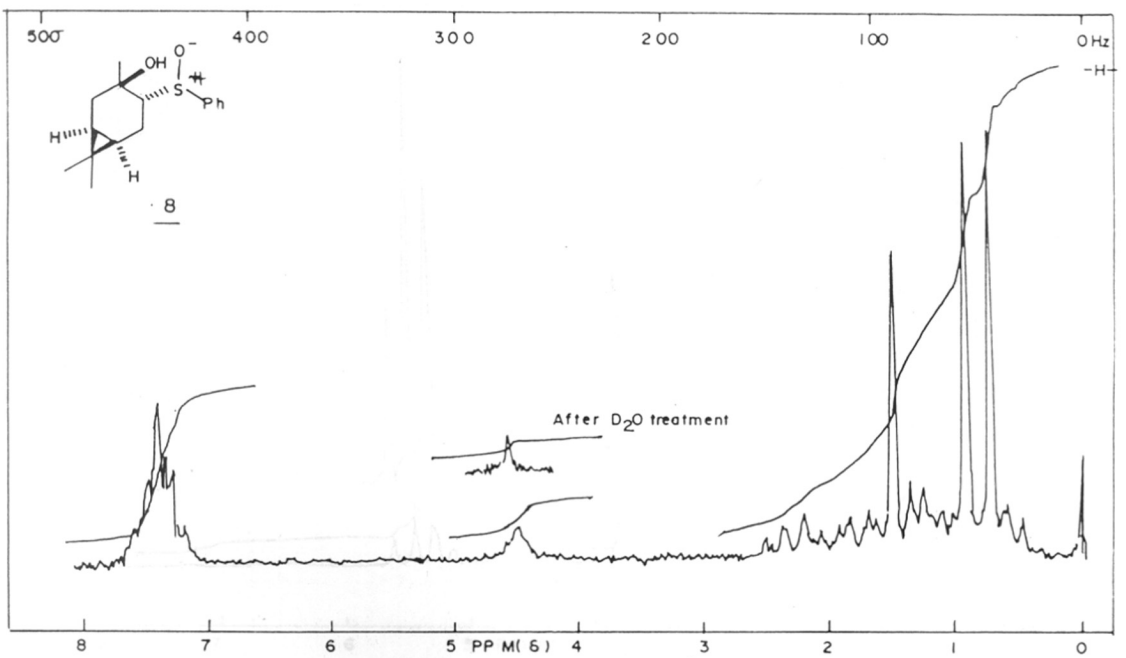

4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
OH
S
Ph
H
H
6
3 4 5 6 7 8 9 10 11 12 13 14
WAVE LENGTH (MICRONS)

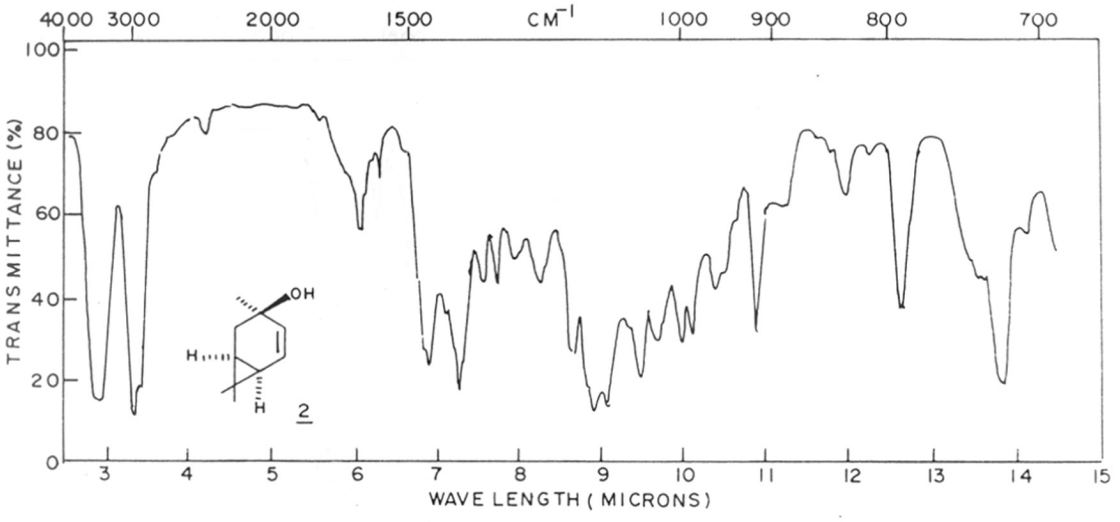

500 400 300 200 100 0Hz
OH
S
Ph
H
H
6
8 7 6 5 PPM(δ) 4 3 2 1 0

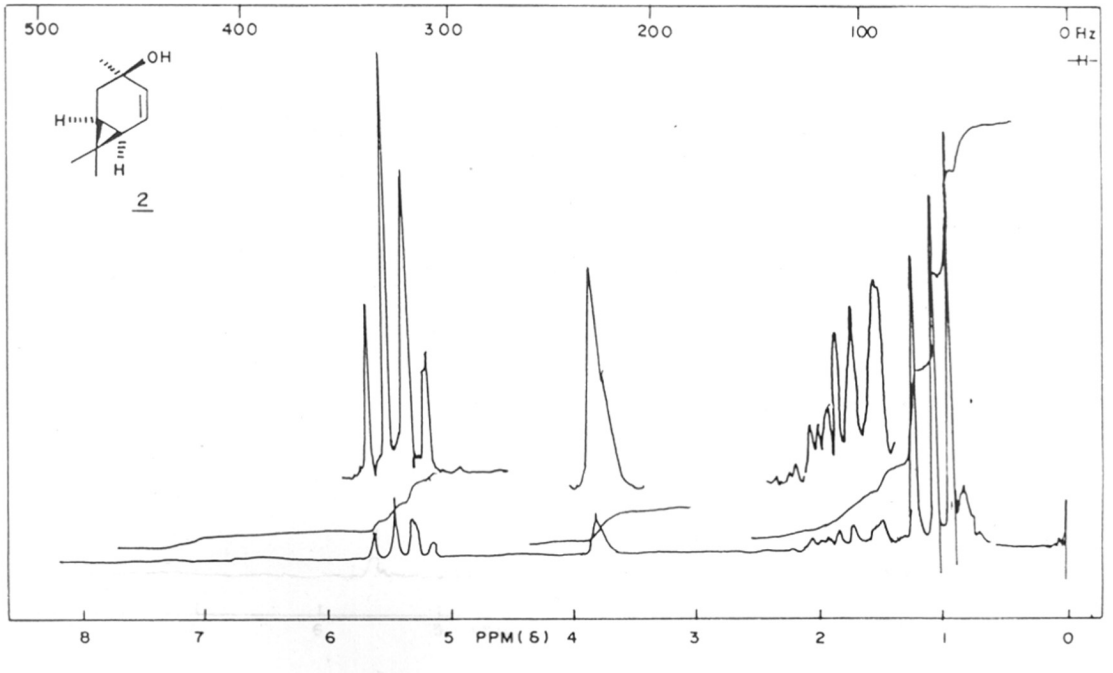

4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
OAc
S
Ph
H
H
7
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

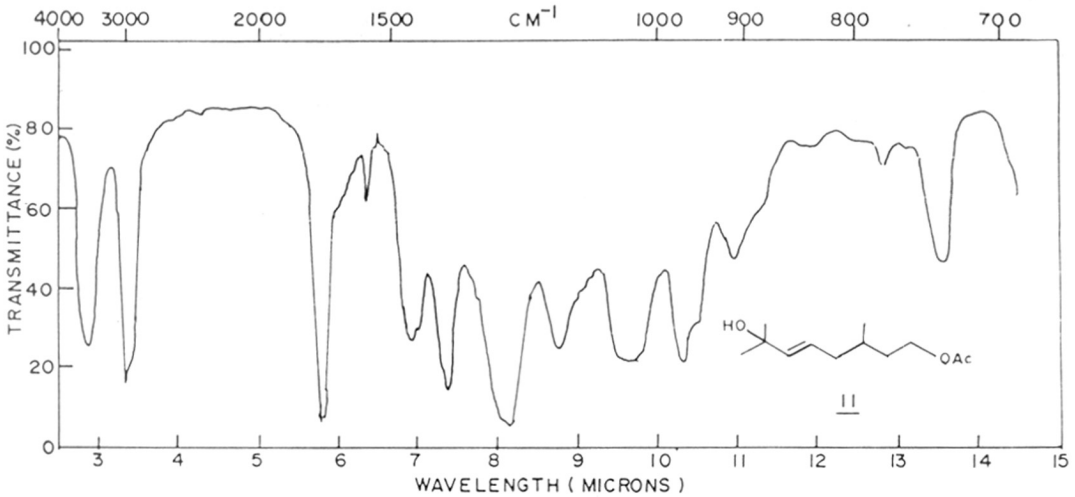

500 400 300 200 100 0Hz
OAc
S
Ph
H
H
7
8 7 6 5 PPM(δ) 4 3 2 1 0

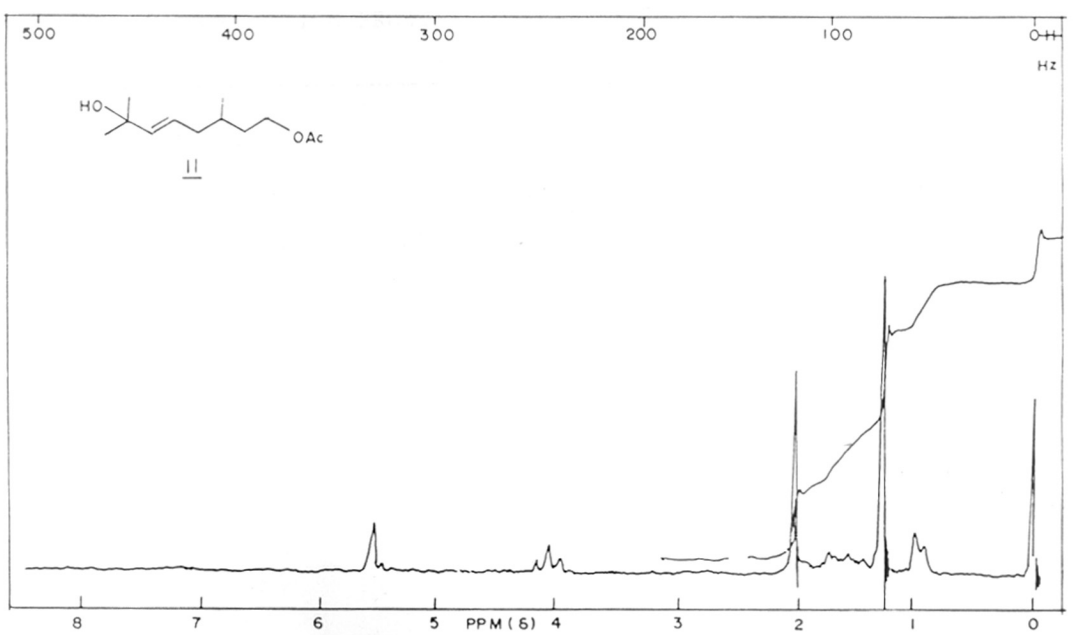

4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE(%)
OH
O⁻
S
+
Ph
H
H
8
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVE LENGTH (MICRONS)


500 400 300 200 100 0 Hz
OH
O⁻
S
+
Ph
H
H
8
After D2O treatment
8 7 6 5 PP M(δ) 4 3 2 1 0


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVE LENGTH (MICRONS)
OH
H
H
2


500 400 300 200 100 0 Hz
OH
H
H
2
8 7 6 5 PPM(δ) 4 3 2 1 0


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
HO
OAc
II


500 400 300 200 100 0 Hz
HO
OAc
II
8 7 6 5 PPM (δ) 4 3 2 1 0

CHAPTER - VB

TRANSFORMATION PRODUCTS OF CARENE DERIVATIVES

SUMMARY

The tertiary allyl alcohol (15) obtained from (+)-3-carene (1) was epoxidated using perbenzoic acid. When this epoxide (26) was treated with Jones reagent a rearranged dihydroxy ketone (27) was isolated. Similarly when this epoxide (26) was stirred with methanol containing traces of p-toluene sulfonic acid a rearranged methoxy compound (28) was obtained. A similar cyclopropane ring participation was observed when the epoxide (26) was treated with alkali, to give a trihydroxy compound (29).

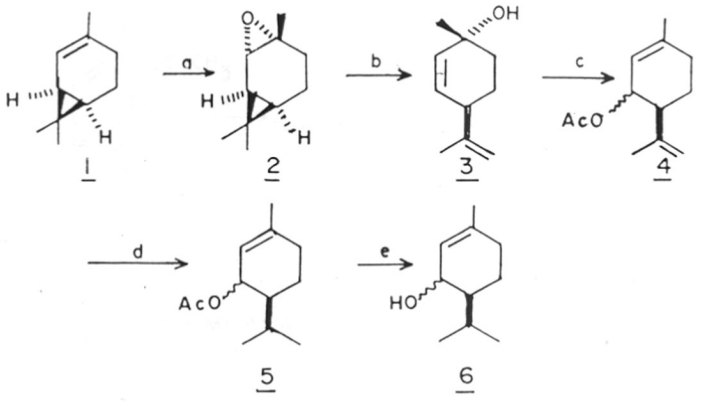
Two main products (36) and (37) were isolated when allyl acetate (32), obtained from (+)-3-carene, was treated with hydrogen peroxide and formic acid and the product was cleaved by sodium metaperiodate.

INTRODUCTION

(+)3-Carene, a naturally occurring monoterpene, is a very sensitive molecule. Several derivatives of (+) 3-carene have been prepared and are subjected to a variety of reactions leading to a variety of products[1]. It is a general observation that whenever there is a double bond at C-2 or C-4 in the carene derivatives (i.e. a vinylcyclopropane group) then the molecule has strong tendency to rearrange with cyclopropane ring participation under acidic conditions. Epoxides of such derivatives are even much more sensitive to acidic conditions. Thus, when car-2-ene (1) was treated with peracetic acid, a rearranged product (3) was obtained[2]. This fact has been utilized by Sukh Dev et al.[3] for the preparation of piperitol (6) from car-2-ene. Epoxide(2) of car-2-ene when treated with m-titanic acid, gave a cyclopropane ring opened product (3) which was then converted to piperitol (6) by a series of reactions (Scheme I).

G. Ohloff et al.[2] prepared epoxide (8) of car-4-ene(7) and treated this with acid. They isolated number of products, (Scheme II) out of which the major was a cyclopropane ring opened product (11). Gollnick et al.[4] found that when car-4-ene-3α-ol (15) was heated with

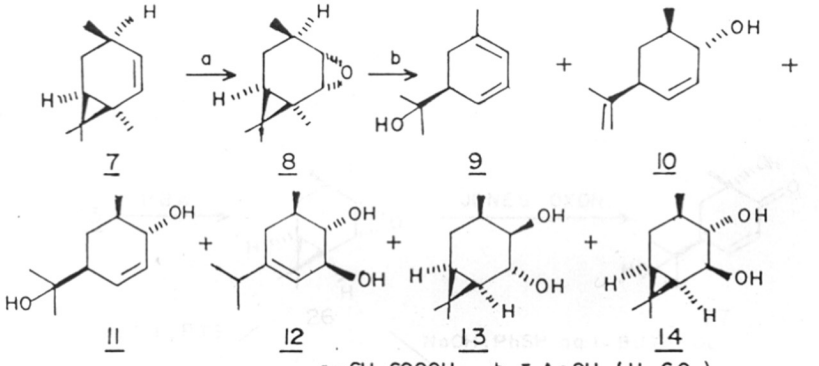
SCHEME - I



1 2 3 4 5 6

a = CH_3COOOH ; b = m - titanic acid ; c = AcOH, AcONa ; d = H_2, e = LAH

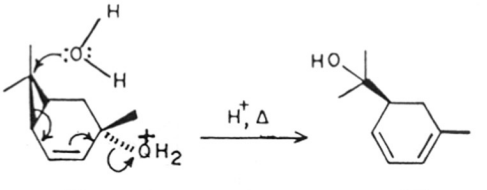
SCHEME - II



7 8 9 10 11 12 13 14

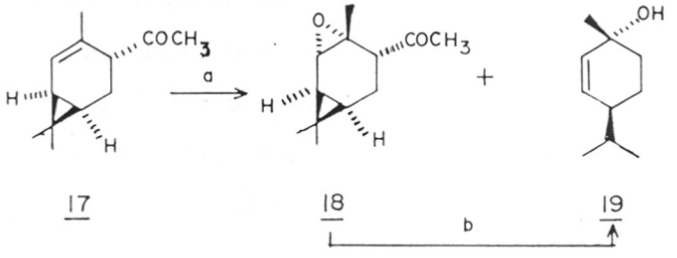
a = CH_3COOOH ; b = AcOH (H_2SO_4)

SCHEME - III



15 16

SCHEME-IV

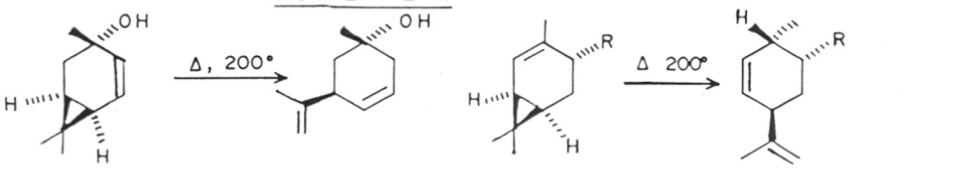


17 18 19

b

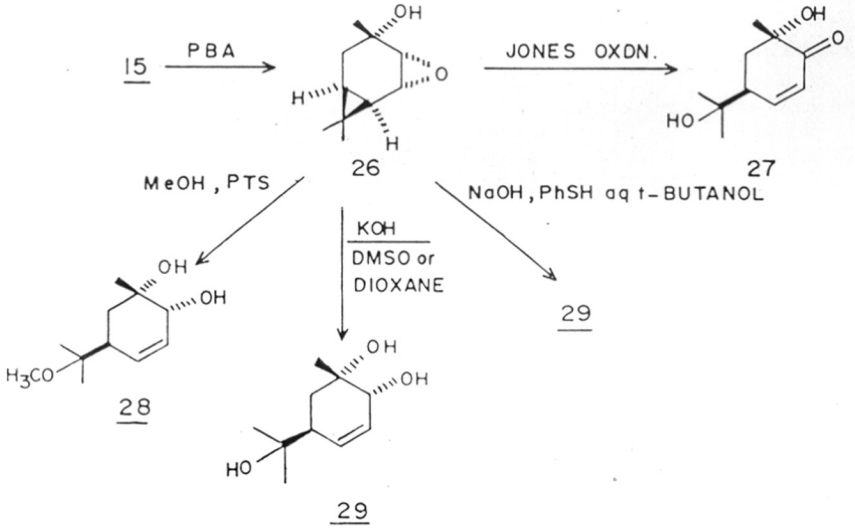
a = MCPBA , b = H^+

SCHEME-V



15 20 21 R = H, OH, CH_2OH 22 R = H, OH, CH_2OH

SCHEME-VI



aqueous acid, a similar type of rearrangement was observed (Scheme III).

Recently G.H. Kulkarni et al.[5] isolated a rearranged product (19) during epoxidation of 4-acetyl-car-2-ene (17). Apart from these acid catalysed rearrangements of 2- and 4-carene derivatives, the thermal rearrangement[6,7] of these derivatives was also observed when they are heated above 200°C (Scheme V).

Present work and discussion

(A) Methyl-1R-cis-2,2-dimethyl-3-(2-oxo-propyl)-cyclopropanecarboxylate (23) is a very important intermediate for bioactive synthetic pyrethroids[8,9] (see Chapter II). Therefore, we wanted to get this intermediate in good yield from car-4-ene-3α-ol (15). It is wellknown that when 3α,4α-epoxy carane (24) is treated with Jones reagent it gives keto acid[10] (25) quantitatively. With this idea we prepared epoxide of car-4-ene-3α-ol using perbenzoic acid. The epoxide (26) was characterized by spectral data IR (liquid film): 3664 cm^{-1} (hydroxyl); PMR (CCl_4, δ): 0.66 - 0.9 (m, 2H, cyclopropyl protons), 0.96 (s, 3H, $-CH_3$), 1.13 (s, 3H, $-CH_3$), 1.33 (s, 3H, $-CH_3$), 1.73 - 2.26 (m, 2H, $-CH_2$), 2.43 (broad s, 1H, -OH), 2.80 (d, 1H, $-C\overset{O}{\diagdown\!\diagup}CH-$, J = 4 Hz) 3.06 (d, 1H, $-C\overset{O}{\diagdown\!\diagup}CH-$, J = 4 Hz), the PMR spectrum showed two doublets at δ2.80 and δ3.06 for two oxirane protons and absence of olefinic protons absorption. This epoxide must be having the structure (26), where the epoxide ring is -α and the cyclopropane ring is -β, since the β-side is sterically hindered due to cyclopropyl methyls.

The acetone solution of this epoxide (26) was treated with Jones reagent at 0°C for 15 minutes. The reaction mixture was diluted with cold water and

extracted with ether, the aqueous layer was saturated with ammonium sulfate and again extracted with ether. The combined ether extract was washed with saturated brine solution. After drying over anhydrous sodium sulfate, solvent was removed to afford colourless oil IR (liquid film): 3509 cm^{-1} (hydroxyl), 1721 and 1669 cm^{-1} (conjugated ketone); PMR ($CDCl_3$, δ): 1.16 (s, 3H, $-CH_3$), 1.26 (s, 3H, $-CH_3$), 1.3 (s, 3H, $-CH_3$), 1.53 - 2.5 (m, 2H, $-CH_2$), 2.6 - 3.0 (m, 1H, -CH-), 3.76 (broad s, 2H, -OH), 6.03 (broad d, 1H, olefinic, J = 11 Hz), 7.23 (broad d, 1H, olefinic, J = 11 Hz). The IR spectrum showed absorption bands at 1721 cm^{-1} and 1669 cm^{-1} which are typical absorptions bands for α,β-unsaturated ketone. PMR spectrum also showed two doublets at δ 6.03 and δ 7.23. The doublet at δ 7.23 must be due to β-hydrogen of α,β-unsaturated ketone system, and the doublet at δ 6.03 must be for α-hydrogen. On the basis of IR and PMR spectra, the structure for this compound was assigned as (27). The first step of this reaction might be the protonation of epoxide ring and then it was opened up by participation of cyclopropane ring leading to trihydroxy compound (29) and then the secondary hydroxyl group might be oxidized to ketone due to excess Jones reagent.

If the above mechanism is correct then we must get methoxy compound (28) when the epoxide is stirred with

methanol containing traces of acid. It was indeed found to be the case when epoxide (26) was stirred with methanol containing catalytic amount of p-toluene sulfonic acid. IR (liquid film): 3509 cm^{-1} (hydroxyl); PMR (CCl_4, δ): 1.03 (s, 6H, $-CH_3$), 1.26 (s, 3H, $-CH_3$), 1.6 - 2.20 (m, 2H, $-CH_2$), 2.6 (m, 1H, -CH-), 3.0 (broad s, 2H, -OH), 3.16 (s, 3H, $-OCH_3$), 3.86 (broad s, 1H, -CH-O-), 5.53 (broad d, 1H, olefinic, J = 11 Hz), 5.87 (broad d, 1H, olefinic, J = 11 Hz) .

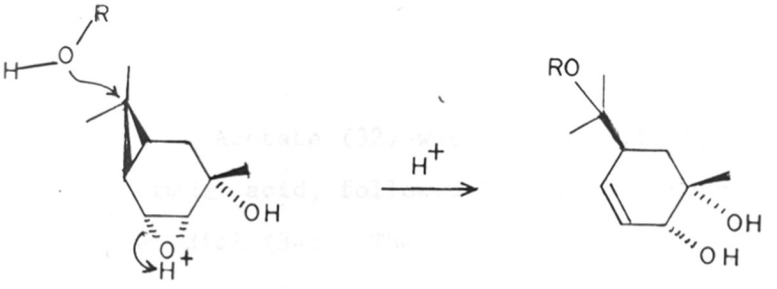
Since acidic conditions resulted in the rearrangement described above, an attempt was made to open the epoxide ring under basic conditions to get the corresponding triol. Accordingly,, the epoxide (26) was heated with aqueous alkaline dimethylsulfoxide or dioxane. Here too a rearrangement product similar to that obtained in acidic conditions was observed. Instead of the expected triol, triol (29) was obtained IR (liquid film): 3561 cm^{-1} (hydroxyl); PMR ($CDCl_3$, δ): 1.13 (s, 3H, $-CH_3$), 1.20 (s, 3H, $-CH_3$), 1.3 (s, 3H, $-CH_3$), 1.5 - 2.53 (m, 3H, $-CH_2$, and -CH-), 2.73 (broad s, 3H, -OH), 3.83 (broad s, 1H, -CH-O-), 5.43 (broad d, 1H, olefinic, J = 10 Hz), 5.76 (broad d, 1H, olefinic, J = 10 Hz). This is probably due to the fact that an SN_2 opening of the epoxide ring is precluded due to steric reasons, the β face of the molecule being hindered by the cyclopropyl ring; and this encourages a solvolytic type of ring opening even under

basic conditions, assisted by the formation of an incipient cyclopropyl carbinyl cation.

Since sulphur is a better nucleophile than oxygen, the epoxide was refluxed with aqueous sodium thiophenate in t-butanol, expecting to get the corresponding phenylthio compound. But instead of incorporation of phenylthio group, the triol (29) was obtained. Perhaps the thiophenoxide anion is too bulky to react at the isopropyl centre.

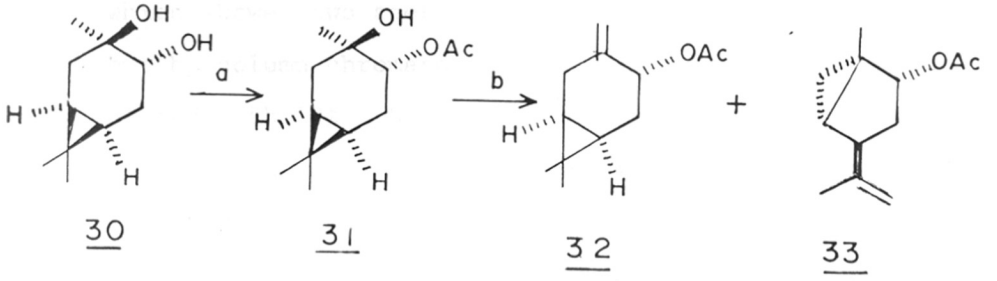
(B) Another interesting transformation was observed during the preparation of 7,7-dimethyl-4-acetoxy bicyclo(4-1-0)heptan-3-one (36) from the acetate (32) (Seheme VII). The synthesis of ketoacetate (36) was taken up as it would prove to be a useful intermediate for the preparation of analogues of the keto ester(23), described in Chapter - II.

Acetate (32) needed for the preparation was obtained as reported[12] and as shown in Scheme VII. The carane diol (30) obtained from (+) 3-carene[11] was acylated with acetic anhydride and pyridine[12,13]. The hydroxy acetate (31), so obtained was subjected to dehydration using phosphorous oxychloride and pyridine to get a mixture of acetates (32) and (33), from which pure (32) was obtained by column chromatography over silica gel impregnated with 10% silver nitrate.

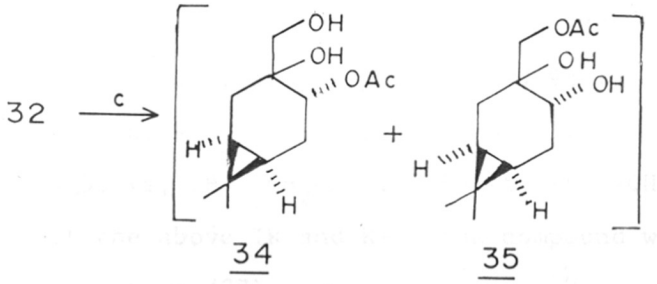


R = H, CH_3 R = H, CH_3

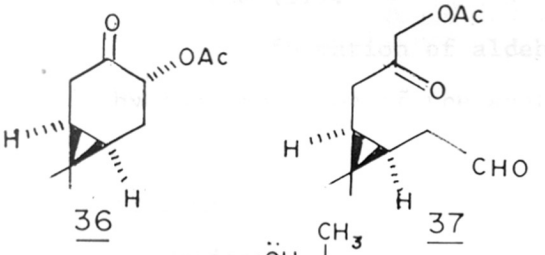
SCHEME–VII



30 31 32 33



34 35



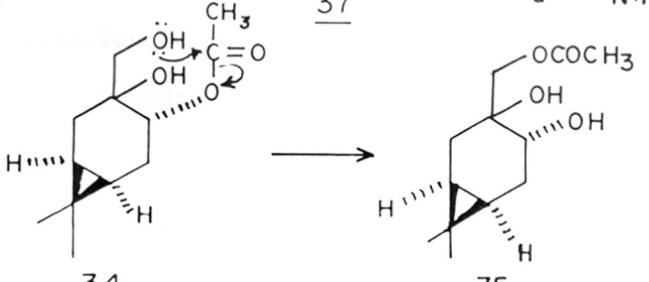
36 37

a = Ac_2O, Py

b = $POCl_3$, Py

c = $HCOOH$, H_2O_2, aq Na_2CO_3

d = $NaIO_4$



34 35

Acetate (32) was treated with hydrogen peroxide and formic acid, followed by alkaline hydrolysis in order to get diol (34). The reaction product yielded a mixture of hydroxyl compounds which without separation were subjected to sodium metaperiodate oxidation. After usual workup of the reaction, a pale yellow oil was obtained which showed two spots on TLC. Purification was carried out by column chromatography. The less polar compound was eluted with 10% ethylacetate in benzene and found to be the keto acetate (36). IR and PMR spectra were comparable with those reported[13]. The more polar compound was eluted with 20% ethylacetate in benzene. IR (liquid film): 2740 cm^{-1} (aldehyde), 1724 cm^{-1} (ketone). PMR (CCl_4, δ): 0.76-1.37 (m, 2H, cyclopropyl protons), 0.93 (s, 3H, $-CH_3$), 1.17 (s, 3H, $-CH_3$), 2.1 (s, 3H, $-OCOCH_3$), 2.3 (m, 4H, $-CH_2-CO$), 4.53 (s, 2H, $-CH_2OAc$), 9.66 (t, 1H, -CHO). On the basis of the above IR and NMR, the compound was assigned structure (37).

The formation of aldehyde (37) can be explained by the migration of the acetyl group in the expected diol (34) to give the rearranged hydroxy acetate (35) leading to a mixture of (34) and (35); sodium metaperiodate oxidation would then give (36) and (37) as observed.

E X P E R I M E N T A L

4α,5α-Epoxycaran-3α-ol (26)

Car-4-ene-3α-ol (15) (6.8 g, 44.7 mmol) was taken in chloroform (50 ml) and cooled the solution to 0°C. To this added chloroform solution of perbenzoic acid (1.7N, 120 ml) carefully with stirring. This mixtue was kept at 0°C for 48 hours. Then it was washed with aqueous sodium bicarbonate solution and then with water. The organic layer was dried over anhydrous sodium sulfate and solvent was removed under reduced pressure to give a colourless oil (6.7 g, 89.1%) b.p.70-75°/0.5 mm (bath temp.)
IR (liquid film): 3664, 3030, 1667, 1449, 1416, 1379, 1312, 1250, 1189, 1163, 1149, 1124, 1093, 1042, 990, 943, 920, 903, 877, 840, 824, 787, 703 cm^{-1}.
PMR (CCl_4, δ): 0.66 - 0.9 (m, 2H, cyclopropyl protons), 0.96 (s, 3H, $-CH_3$), 1.13 (s, 3H, $-CH_3$), 1.33 (s, 3H, $-CH_3$), 1.73 - 2.26 (m, 2H, $-CH_2$), 2.43 (broad s, 1H, -OH), 2.8 (d, 1H, $-C\overset{O}{\diagdown\!\diagup}CH-$, J = 4 Hz), 3.06 (d, 1H, $C\overset{O}{\diagdown\!\diagup}CH-$, J = 4 Hz).

1-Methyl-1-hydroxy-5-(α-hydroxy propyl)cyclohex-3-ene-2-one (27)

Epoxide (26) (1.0 g) was taken in acetone (10 ml) and cooled this solution to 0°C. Jones reagent (1.5 ml) was added slowly at 0°C and stirred the mixture at this temperature for 15 minutes. The reaction mixture was

diluted with equal volume of water and extracted with ether. The aqueous layer was saturated with ammonium sulfate and extracted with ether. The combined ether extract was washed with saturated brine solution and dried over anhydrous sodium sulfate, the solvent was distilled off to afford colourless oil (726 mg, 71.9%).

IR (liquid film): 3509, 3030, 1721, 1669, 1449, 1370, 1290, 1250, 1212, 1130, 1087, 1064, 980, 943, 917, 862, 830 cm^{-1}.

PMR ($CDCl_3$, δ): 1.16 (s, 3H, $-CH_3$), 1.26 (s, 3H, $-CH_3$), 1.3 (s, 3H, $-CH_3$), 1.53 - 2.5 (m, 2H, $-CH_2$), 2.6 - 3.1 (m, 1H, -CH-), 3.76 (broad s, 2H, -OH), 6.03 (broad d, 1H, olefinic, J = 11 Hz), 7.23 (broad d, 1H, olefinic, J = 11 Hz).

1-Methyl-1,2-dihydroxy-5-(α-methoxy isopropyl)cyclohex-3-ene (28)

A solution of epoxide (26) (1.0 g) in methanol (25 ml) and p-toluene sulfonic acid (100 mg) was stirred at room temperature for two hours. Solvent was removed under reduced pressure and the residue was diluted with water and extracted with chloroform. The chloroform layer was washed with saturated brine solution, dried over anhydrous sodium sulfate. The solvent was removed to get brown oil which was distilled under reduced pressure to get colourless oil (589 mg, 49.47%), b.p.130-140/0.5 mm

(bath temp.).

IR (liquid film): 3509, 3003, 1645, 1449, 1370, 1282, 1235, 1182, 1143, 1087, 1058, 1015, 956, 941, 901, 877, 862, 826, 781, 725 cm^{-1}.

PMR (CCl_4, δ): 1.03 (s, 6H, $-CH_3$), 1.26 (s, 3H, $-CH_3$), 1.6 - 2.20 (m, 2H, $-CH_2$), 2.6 (m, 1H, -CH-), 3.0 (broad s, 2H, -OH), 3.16 (s, 3H, $-O-CH_3$), 3.86 (broad s, 1H, -CH-O-), 5.53 (broad d, 1H, olefinic, J = 11 Hz), 5.87 (broad d, 1H, olefinic, J = 11 Hz).

1-Methyl-1,2-dihydroxy-5-(α-hydroxy isopropyl)cyclohex-3-ene (29)

(A) A homogeneous solution of epoxide (26) (355 mg, 2.11 mmol), potassium hydroxide (0.336 g, 6 mmol), water (4 ml) and dimethyl sulfoxide (6 ml) was heated in an oil-bath at 100°C for 4 hours. Dimethyl sulfoxide was removed under reduced pressure and water (3 ml) was added to the residue and extracted with ether. The ether extract was dried over anhydrous sodium sulfate and solvent was removed to afford thick oil (131 mg, 33.4%), the aqueous layer was saturated with ammonium sulfate and extracted with ethyl acetate to give a thick oil (173 mg, 44%). The PMR spectra of both the extracts were found to be identical b.p.120/130°/2 mm (bath temp.).

IR (liquid film): 3448, 2985, 2500, 1695, 1439, 1351, 1250, 1205, 1136, 1081, 1047, 1010, 939, 817, 885, 862, 831, 787, 752 cm^{-1}.

PMR ($CDCl_3$, δ): 1.13 (s, 3H, $-CH_3$), 1.20 (s, 3H, $-CH_3$), 1.3 (s, 3H, $-CH_3$), 1.5 - 2.53 (m, 3H, $-CH_2$ and -CH-), 2.73 (broad s, 3H, -OH), 3.83 (broad s, 1H, -CH-O-), 5.43 (broad d, 1H, olefinic, J =10 Hz), 5.76 (broad d, 1H, olefinic, J = 10 Hz).

(B) A homogeneous solution of epoxide (26) (350 mg, 2 mmol), potassium hydroxide 2.0 g. 35 mmol), water (15 ml) and dioxane (20 ml) was heated for 3 hours at 90°C in an oil-bath. Dioxane and water was removed under reduced pressure. The residue was extracted with ether, dried over anhydrous sodium sulfate and solvent was removed to get thick oil (61 mg, 16.4%), the aqueous layer was saturated with ammonium sulfate and extracted with ethyl acetate to get a thick oil (231 mg, 62%).

IR and PMR spectra were identical with that of triol (29) from procedure A.

3,7,7-Trimethyl-4α-acetoxy bicyclo[4-1-0]heptan-3β-ol (31)

To a solution of 3β,4α-caranediol (30) (85 g, 0.5 mol) in dry pyridine (100 ml) was added acetic anhydride (75 g, 0.75 mol). The reaction mixture was kept at room temperature for 48 hours. Then it was poured over crushed ice (500 g) with stirring and allowed to stand at room temperature for one hour. The diluted solution was then extracted with chloroform (3 x 300 ml).

The organic layer was washed with water, then with 20% aqueous hydrochloric acid, again washed with water. It was dried over anhydrous sodium sulfate and solvent was removed to give solid monoacetate (31) (75 g , 70.76%) It was recrystallised from pet.ether to get white needles, m.p.71-72°.

IR (nujol): 3509, 2946, 1700, 1449, 1364, 1266, 1129, 1111, 1087, 1031, 1004, 971, 952, 912, 813, 719 cm^{-1}.

PMR (CCl_4, δ): 0.70 (m, 2H, cyclopropyl protons), 0.96 (s, 3H, $-CH_3$), 1.0 (s, 3H, $-CH_3$), 1.3 - 2.36 (m, 4H, $-CH_2$), 1.96 (s, 3H, $-COCH_3$), 2.5 (s, 1H, -OH), 4.46 (dd, 1H, -CH-O-, J = 7, 10 Hz).

7,7-Dimethyl-4α-acetoxy bicyclo[4-1-0]hept-3(10)-ene (32)

Hydroxy acetate (31) 27.5 g, 0.129 mol) was dissolved in dry pyridine (100 ml) and cooled the solution to 0°C. To this solution was addded phosphorous oxychloride (17.2 ml, 0.185 mol) dropwise with stirring. Stirred the reaction mixture at 0-5°C for 80 minutes and then at room temperature for 6 hrs. Pyridine was removed under vacuum and the residue was diluted with cold water, extracted with ether. Ether extract was washed with water and then with brine solution, dried over anhydrous sodium sulfate. Solvent was removed to get brown oil (21.0 g). This was chromatographed over silica gel (250 g) impregnated with 10% silver nitrate.

Pure (32) (5.0 g, 19.8%) was eluted with pet.ether-benzene (1:1). The later fractions were not analysed. IR (liquid film): 3030, 1733, 1639, 1429, 1361, 1227, 1170, 1053, 1010, 962, 889, 826, 808, 746 cm^{-1}. PMR (CCl_4, δ): 0.7 (m, 2H, cyclopropyl protons), 0.90 (s, 3H, $-CH_3$), 1.0 (s, 3H, $-CH_3$), 1.98 (s, 3H, $-O-COCH_3$), 4.8 (m, 2H, olefinic), 5.07 (t, 1H, -CH-O-, J = 4 Hz).

7,7-Dimethyl-4-acetoxy bicyclo [4-1-0] heptan-3-one (36) and 3,3-dimethyl-2-(3'-acetoxy-2'-oxopropyl)-1-acetaldehyde cyclopropane (37)

Acetate (32) (5.86 gm) was taken in formic acid (90%, 10 ml). Hydrogen peroxide (30%, 6 ml) was added slowly at 40° in about ½ hr to the reaction mixture. The clear solution was stirred at room temperature for 6 hrs and then left over night at room temperature. A solution of sodium hydroxide (0.32 gm) in water (2 ml) was added to the reaction mixture and stirred for ½ hr. The mixture was diluted with water and extracted with ether. The ether layer was washed with water, dried over anhydrous sodium sulfate and solvent was removed to get brown oil (3.2 gm). The brown oil was taken in water (10 ml) containing sodium carbonate (2.4 gm) and stirred for 2 hrs. The aqueous mixture was saturated with sodium chloride and extracted with ether. The ether layer was washed with

saturated brine solution, dried over anhydrous sodium sulfate and solvent was removed to get thick brown oil (2.430 gm, 35.31%). TLC of this product was not very clear. So, this crude product was taken in acetone (30 ml) and water (10 ml). To this clear solution , sodium meta-periodate (3.6 gm) was added portionwise in about ½ hr. and stirred for 2 hrs at room temperature. The sodium iodate separated out was filtered and the filtrate was concentrated to 10 ml. It was diluted with water (10 ml) and extracted with ether. The ether layer was washed with water, dried over anhdryous sodium sulfate and solvent was removed to get brown oil (1.6 gm). It showed two spots on TLC (20% ethyl acetate-benzene). It was purified by column chromatography over silica gel. The less polar compound eluted out with 10% ethyl acetate in benzene (0.44 gm) while, the polar compound was eluted with 20% ethyl acetate in benzene (0.53 gm). The less polar compound was (36).

IR (liquid film): 3030, 1754, 1429, 1370, 1235, 1149, 1036, 952, 909, 787, 757 cm^{-1}.

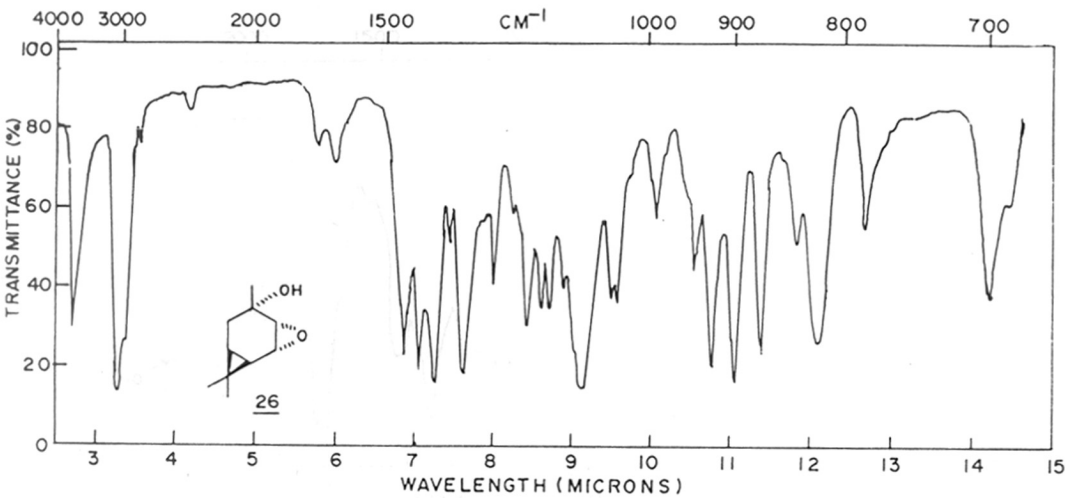
PMR (CCl_4, δ) 0.6 - 1.27 (m, 2H, cyclopropyl protons), 1.0 (s, 3H, $-CH_3$), 1.06 (s, 3H, CH_3), 1.63 - 2.9 (m, 4H, $-CH_2$), 2.03 (s, 3H, $-OCOCH_3$), 4.53 (t, 1H, -CH-O-, J = 5 Hz), while, the more polar compound was (37).

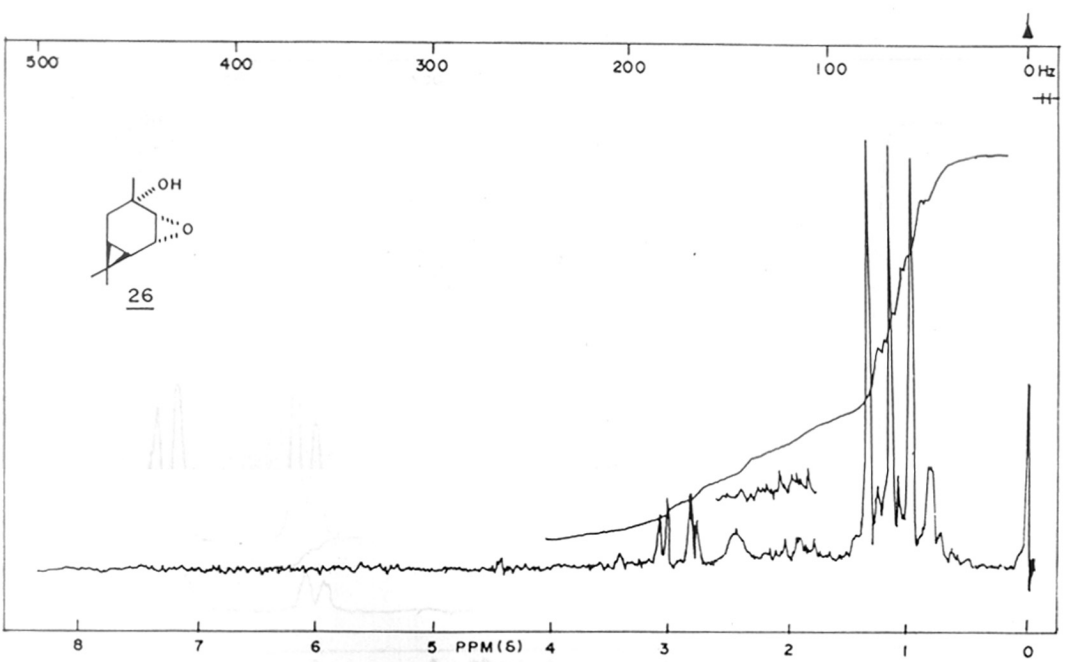
IR (liquid film): 2941, 2740, 1724, 1399, 1361, 1220, 1031, 970, 909, 847 cm^{-1}.

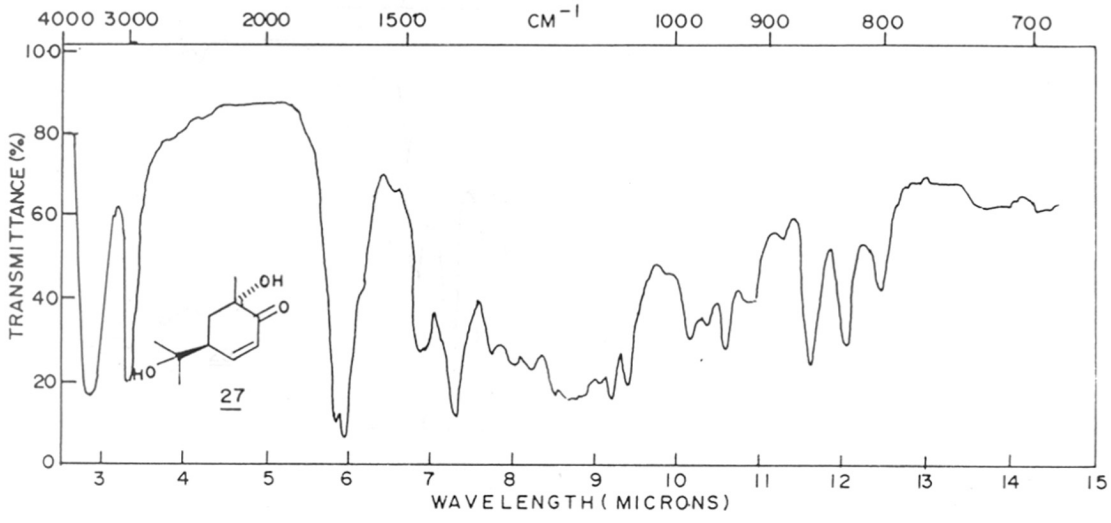
PMR (CCl_4, δ): 0.76 - 1.37 (m, 2H, cyclopropyl protons), 0.93 (s, 3H, $-CH_3$), 1.17 (s, 3H, $-CH_3$), 2.1 (s, 3H $-O-COCH_3$, 2.3 (m, 4H, $-CH_2-CO-$), 4.53 (s, 2H, $-CH_2-O$), 9.66 (t, 1H, -CHO).

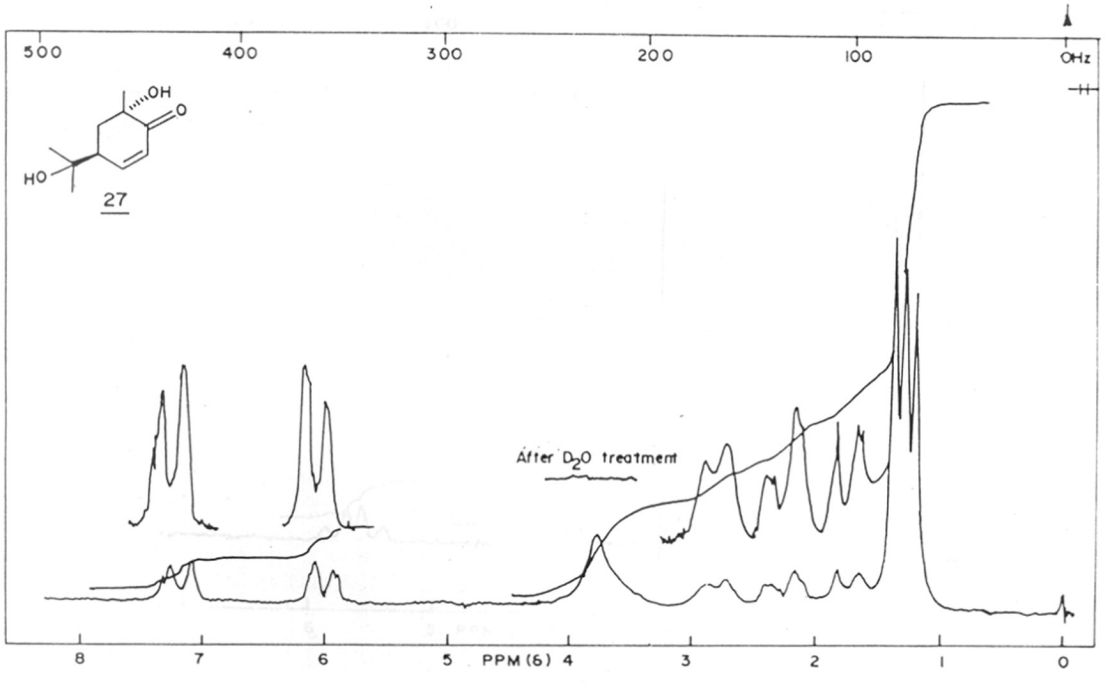
REFERENCES

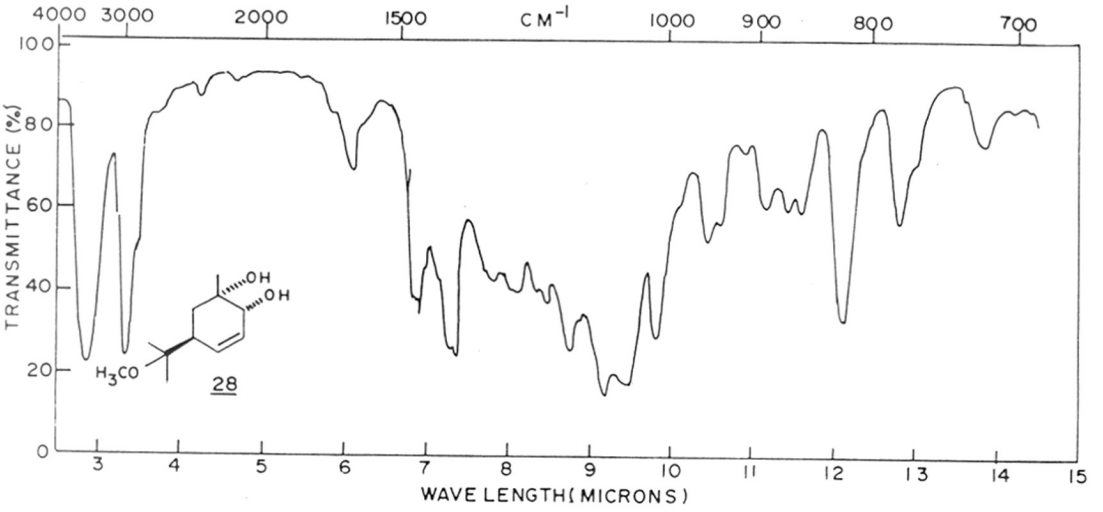
1. W. Cocker, J.Soc.Cosmetic Chemists, 22, 249 (1979).
2. G. Ohloff, W. Giersch, Helv.Chim.Acta., 51, 1328 (1968).
3. R.S. Prasad, Sukh Dev, Tetrahedron, 32. 1437 (1976).
4. K. Gollnick, G. Schade, S. Schroeter, Tetrahedron, 22, 139 (1966).
5. P.P. Pai, G.D. Joshi, K.G. Gore, G.H. Kulkarni, Indian J.Chem., 18B, 549 (1979).
6. G. Ohloff, Tet.Lett., 1395 (1965).
7. K. Gollnick, Tet.Lett., 327 (1966).
8. R.B. Mitra, G.H. Kulkarni, K.G. Gore, A.S. Khanra, Z. Muljiani, P.N. Chaudhari, B.M. Bhawal, G.D. Joshi, P.N. Khanna, Brit.U.K. Patent Appl. 2,034,301 (1980); Indian Appl. 761/DEL/78, C.A. 94, 65195 (1981).
9. M. Matsui, H. Yoshioka, Y. Yamada, H, Sakamoto, T. Kitahara, Agric.Biol.Chem. 29, 784 (1965).
10. R. Sobti, Sukh Dev, Tetrahedron, 30, 2927 (1974).
11. A.S. Khanra, K.K. Chakravarti, R.B. Mitra, Indian J.Chem., 13, 314 (1975).
12. P.J. Kropp, J.Am.Chem.Soc., 88, 4926 (1966).
13. B.M. Mane, K.G. Gore, G.H. Kulkarni, Indian J.Chem., 18B , 395 (1979).

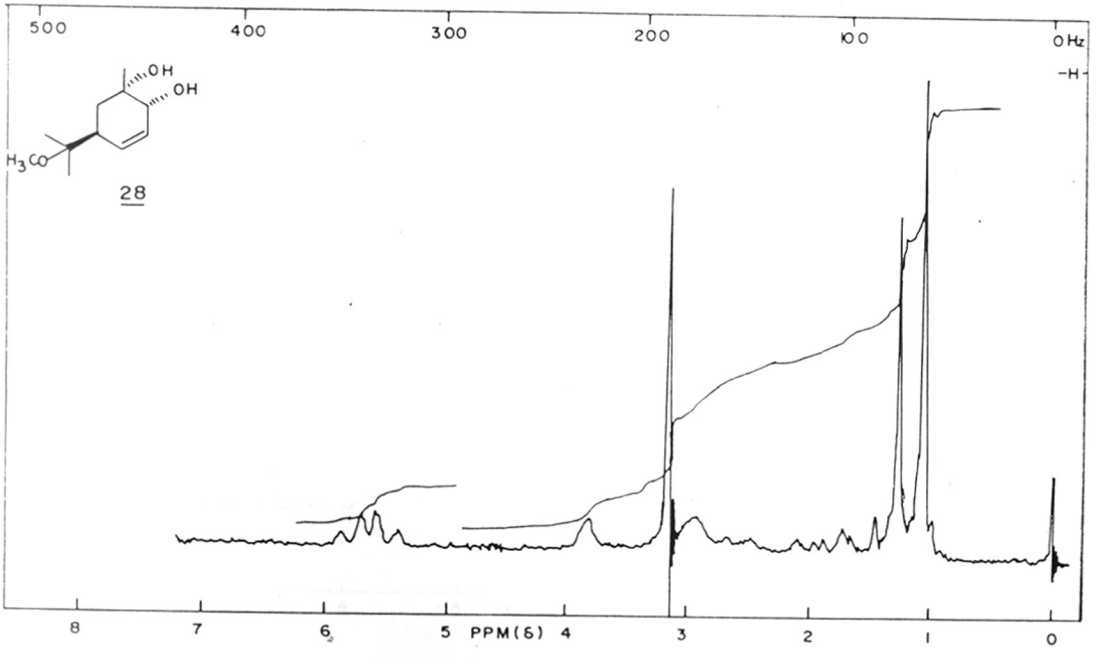

4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
OH
O
26
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)

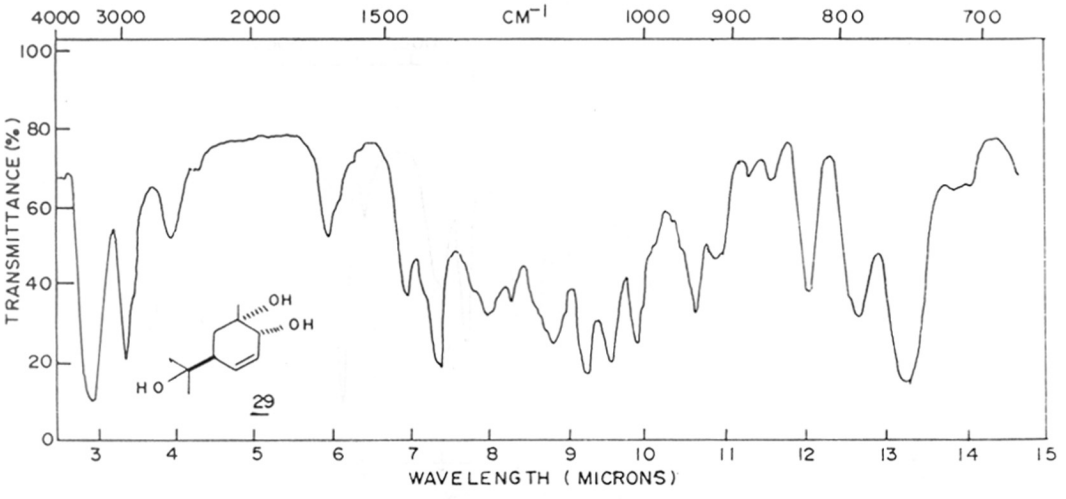

500 400 300 200 100 0 Hz
OH
O
26
8 7 6 5 PPM(δ) 4 3 2 1 0

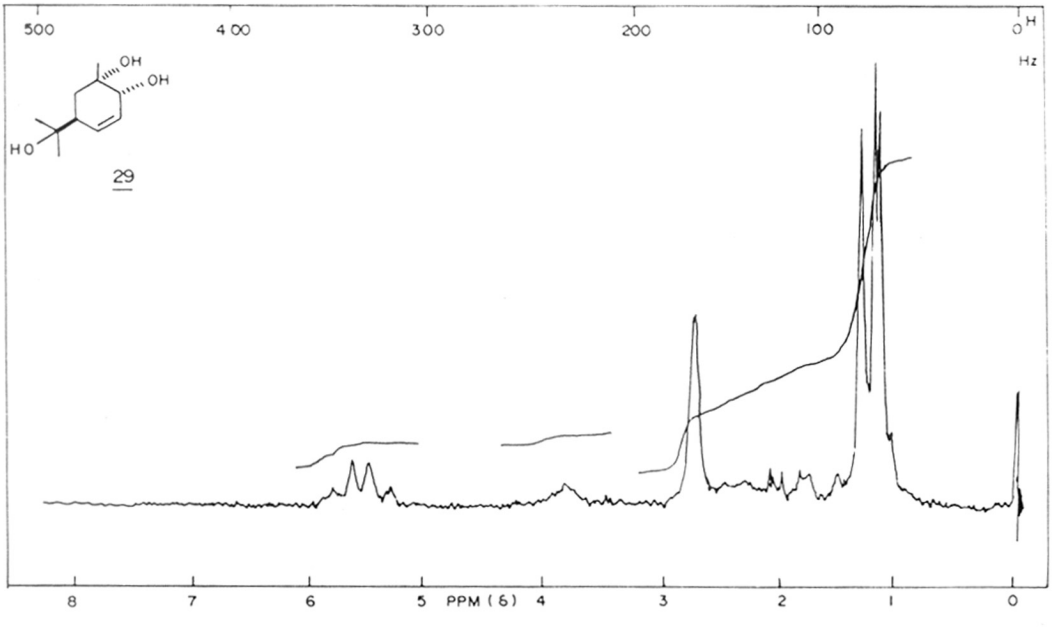

4000 3000
2000
1500
CM⁻¹
1000
900
800
700
100
80
60
40
20
0
TRANSMITTANCE (%)
OH
O
HO
27
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)

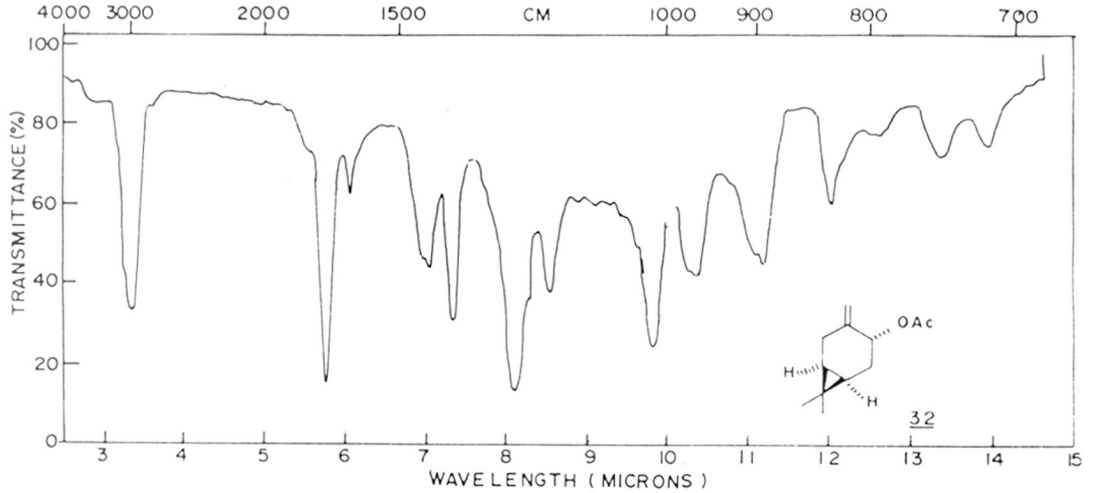

500
400
300
200
100
0Hz
OH
O
HO
27
After D2O treatment
8
7
6
5
PPM (δ) 4
3
2
1
0

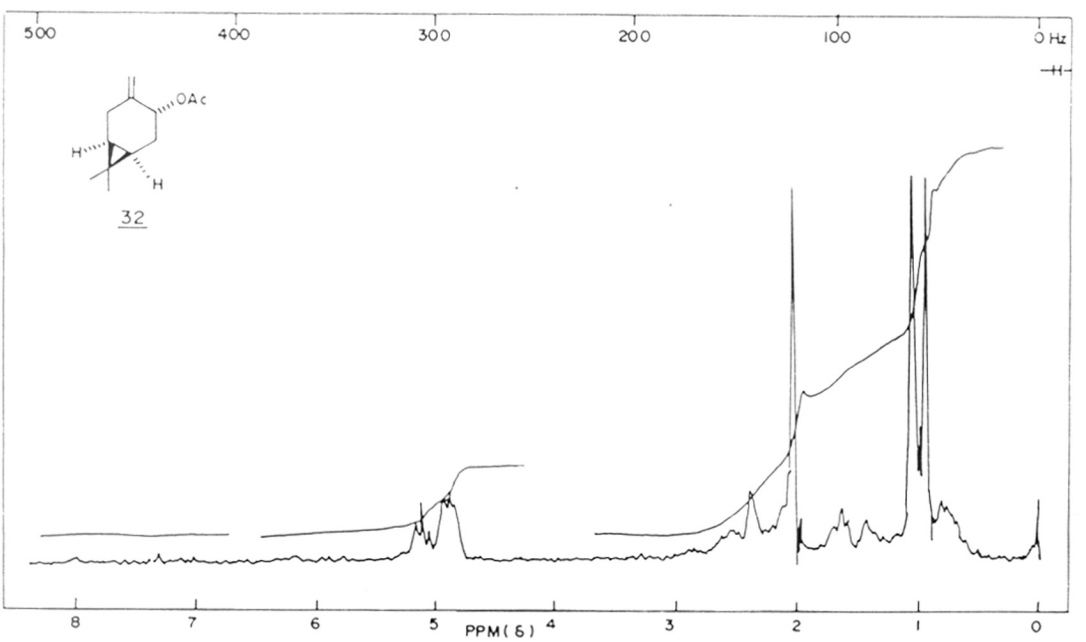

4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
OH
OH
H3CO
28
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVE LENGTH(MICRONS)

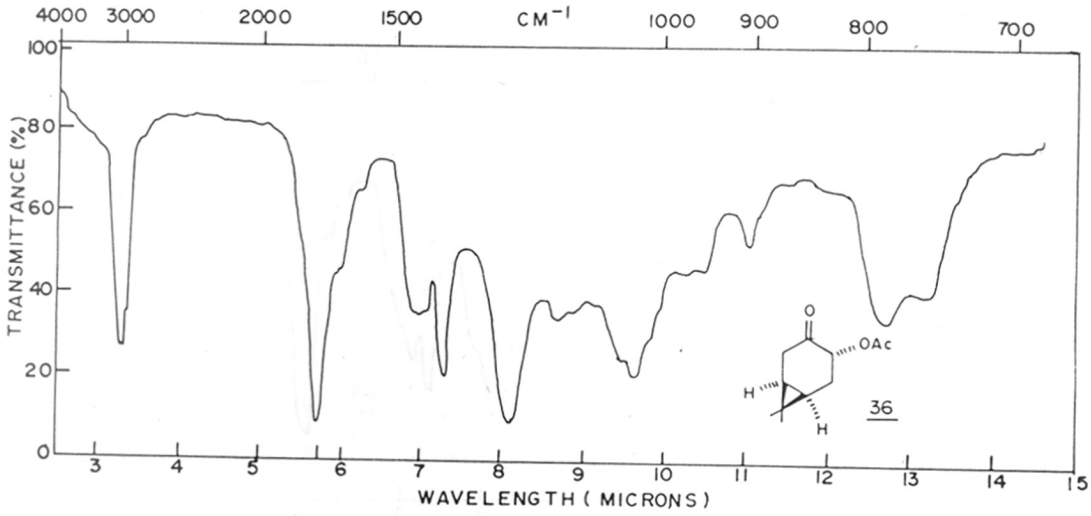

500 400 300 200 100 0Hz
-H-
OH
OH
H3CO
28
8 7 6 5 PPM(δ) 4 3 2 1 0

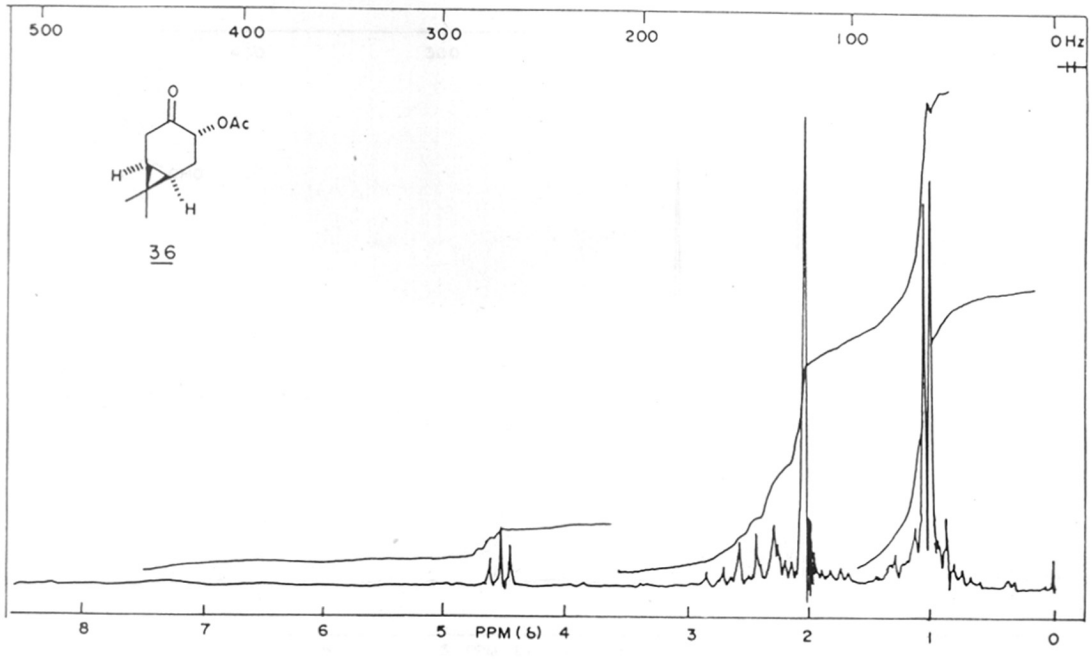

4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
OH
OH
HO
29
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVE LENGTH (MICRONS)

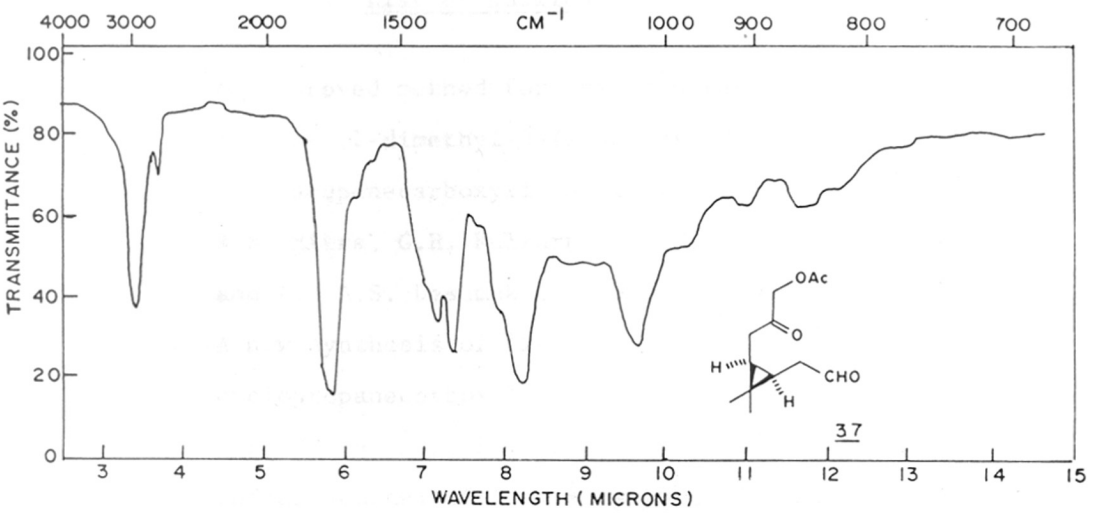

500 400 300 200 100 0 H
Hz
OH
OH
HO
29
8 7 6 5 PPM (δ) 4 3 2 1 0

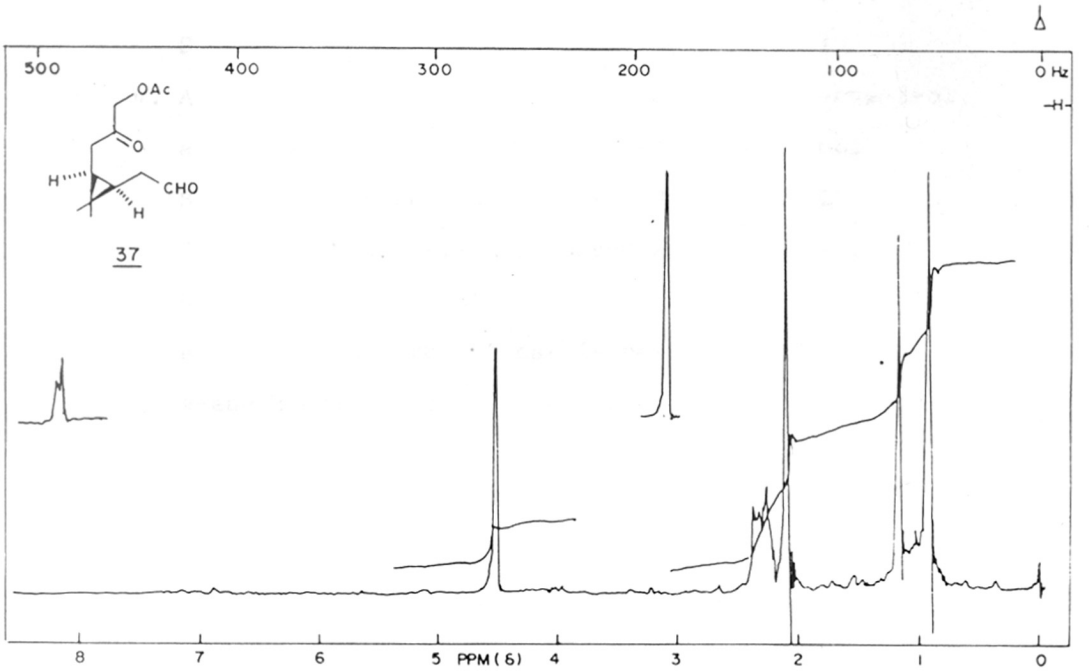

4000 3000 2000 1500 CM 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVE LENGTH (MICRONS)
OAc
H
H
32


500 400 300 200 100 0 Hz
OAc
H
H
32
8 7 6 5 PPM(δ) 4 3 2 1 0


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
100
80
60
40
20
0
TRANSMITTANCE (%)
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
O
OAc
H
H
36


500 400 300 200 100 0 Hz
O
OAc
H
H
36
8 7 6 5 PPM (δ) 4 3 2 1 0


4000 3000 2000 1500 CM⁻¹ 1000 900 800 700
TRANSMITTANCE (%)
100
80
60
40
20
0
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)
OAc
O
H
CHO
H
37


500 400 300 200 100 0 Hz
OAc
O
H
CHO
H
37
8 7 6 5 PPM (δ) 4 3 2 1 0

List of publications

1. An improved method for the preparation of 1R-cis-2,2-dimethyl-3-(2-hydroxy-2-carboxypropyl)-cyclopropanecarboxylic acid from car-4-ene-3-ol, R.B. Mitra, G.H. Kulkarni, Z. Muljiani, V.G. Naik, and A.R.A.S. Deshmukh, Patent Appl.No.425/DEL/80 (1980).
2. A new synthesis of 1R-cis-2,2-dimethyl-3-(2-oxopropyl)-cyclopropanecarboxylic acid from (+)-3-carene, R.B. Mitra, A.S. Khanra and A.R.A.S. Deshmukh, Indian Journal of Chemistry 20B, 436 (1981).
3. A new route to 3-phenoxybenzyl cis-(±)-2,2-dimethyl-3-(2-phenyl-2-chlorovinyl)cyclopropanecarboxylate, R.B. Mitra, Z. Muljiani and A.R.A.S. Deshmukh, Synthetic Communication 12(B), 1063-1070 (1982).
4. A new process for the preparation of car-4-ene-3-ol, an important intermediate in the synthesis of Synthetic Pyrethroids insecticides, R.B. Mitra, Z. Muljiani and A.R.A.S. Deshmukh, Patent Appl. No.140/DEL/83 (1983).
5. A facile route to (-) car-4-ene-3α-ol and (-)car-4-ene-3β-ol, intermediates for bioactive synthetic pyrethroids, synthesis of tertiary allylic alcohols by pyrolysis of sulfoxides, R.B. Mitra, Z. Muljiani, A.R.A.S. Deshmukh, V.S. Joshi and S.R. Gadre, Synthetic Communication 14, 101 (1984).
6. Synthesis of bioactive pyrethroid, 3-phenoxybenzyl-1R-trans-2,2-dimethyl-3-(2-chloro-1-propenyl)cyclopropanecarboxylate, Z. Muljiani, A.R.A.S.Deshmukh and V.S. Joshi (communicated).