SYNTHESIS OF SOME BIOLOGICALLY ACTIVE COMPOUNDS

A THESIS

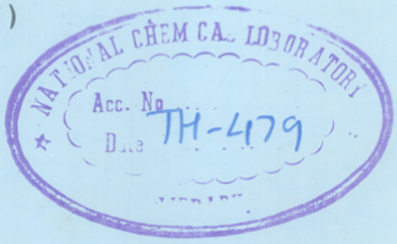
SUBMITTED TO THE

UNIVERSITY OF POONA

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)



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DECEMBER 1985

CERTIFICATE

Certified that the work incorporated in the thesis entitled SYNTHESIS OF SOME BIOLOGICALLY ACTIVE COMPOUNDS by Miss Kamini Garyali was carried out by the candidate under my supervision. Such material as had been obtained from other sources has been duly acknowledged in the thesis.

(A.V. RAMA RAO)
Supervisor

PREFACE

The work seen in the following pages reflects different facets of the preoccupation of an organic chemist of the day. Though the three chapters are of seemingly diverse topics, they all have the essential character of the basic common concern of an organic chemist practising his craft for a utilitarian goal.

The first chapter dealing with the synthesis of an interesting biologically active molecule of great potential in medical use, R-(+)-α-lipoic acid, describes different ways a problem of asymmetric synthesis can be solved.

The second chapter investigates the usefulness of a sulfur Wittig reaction towards the synthesis of the parent ester of pyrethroids.

The third chapter deals with the more practical aspects of a simple reaction in synthetic organic chemistry. Quite often, it is in such cases, where a simple reaction is shown to go efficiently using a practical system, that an organic chemist is called for to put his expertise to practical use.

In the reviews and discussions presented in the work, always due credit and references are given to other authors wherever warranted. If, by chance, any information is taken for granted and no accreditation is made, it is requested to view the same as completely unintentional.

I seek to express my very deep sense of esteem, debt and gratitude to Dr. A.V. Rama Rao, F.A.Sc., F.N.A, Director, Regional Research Laboratory, Hyderabad, formerly Dy. Director & Head, Division of Organic Chemistry II, NCL, for his inspiring guidance, the never-diminishing encouragement and his complete faith in my application to my work.

I consider myself privileged to have worked with Dr. T. Ravindranathan, who indeed patiently helped me speed up my work with his expertise.

I am also grateful to Dr. M.K. Gurjar for all the advice and suggestions that he rendered to me from time to time in the progress of my work and to Dr.M. Narayana Rao who enthused me to a good extent in the earlier stages of my work.

It is my pleasure to thank Dr. Jolly, Dr. Tripathi, Mr. Redkar, Mr. Devasthale and Dr.(Mrs) Wakharkar who rendered moral support and co-operation during the course of my work.

I am thankful to all my colleagues and friends in this laboratory for their willing assistance.

The assistance rendered by Microanalytical and Spectroscopic sections of this laboratory is gratefully acknowledged. My sincere thanks go to Mr.S. Venkataraman for his excellent technical help.

Finally I would like to offer my gratitude to my brothers for their never-flagging encouragement.

Financial assistance from Council of Scientific and Industrial Research, India, is gratefully acknowledged.

In the end, I wish to thank the Director, National Chemical Laboratory, Poona, for kindly allowing me to submit this work in the form of a thesis.

NCL, Poona 411 008
Dated 26th December 85

Garyali
(Miss) KAMINI GARYALI

GENERAL REMARKS

1. Proton Magnetic Resonance spectra were recorded on a Varian T-60 spectrometer, Varian FT-80 and a Bruker WH-90 FT-NMR Spectrometer using tetramethylsilane as the internal standard.

2. Infrared spectra were scanned on a Perkin-Elmer Infrared 683 spectrometer with sodium chloride optics.

3. The optical rotations were measured with a Jasco Dip 181 Digital Polarimeter.

4. Mass spectra were recorded on a CEC-21-110B double focussing mass spectrometer operating at 70 eV using a direct inlet system.

5. Melting points and boiling points are uncorrected.

6. Anhydrous solvents were prepared according to the procedure given in the Text Book of Practical Organic Chemistry by Vogel.

C O N T E N T S

ABSTRACT

ABSTRACT

Chapter 1.0.0 Asymmetric synthesis of R(+)-α-lipoic acid

The main emphasis in this chapter is on the development of approaches towards the asymmetric synthesis of the natural R(+)-α-lipoic acid 1. It is pertinent to mention here that when this work was initiated, no reported asymmetric synthesis of natural lipoic acid was known; only one report by Elliott et al. appeared just following the conclusion of this work.

Lipoic acid, a protein-bound coenzyme and a prosthetic group has been gaining increasing importance nowadays with the discovery of many new physiological activities being attributed to it for e.g. it has significant protective and curative effect, in heavy-metal poisoning and against liver toxicosis caused by Amanita phalloides poisoning; more recently it has been indicated to be effective in reducing the blood sugar level of diabetic rats during a glucose-tolerance test.

Herein, we have explored three different approaches for the synthesis of R(+)-α-lipoic acid viz. (i) from α-D-glucose (ii) an approach involving Sharpless asymmetric epoxidation (iii) use of 1,2R,4-butanetriol - a chiral synthon from RR-tartaric acid and cis-2-butene-1,4-diol towards the synthesis of +1.

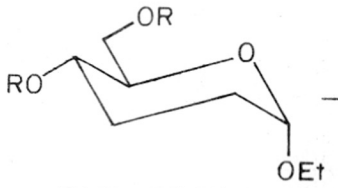
(i) From α-D-glucose

This synthesis involves use of an optically active

precursor, D-glucose, a cheap and easily accessible substrate. Triacetyl D-glucal, readily obtained from D-glucose was converted to the diacetyl derivative 2 (Chart 1) following Ferrier's procedure and hydrogenation. Zémplen deacetylation of 2 followed by benzylation afforded the dibenzyl derivative 3. Opening of the pyranose ring in 3 with propanedithiol gave a properly functionalised six-carbon derivative 4 with an extra hydroxy group at the 5-position. The free hydroxy group was reductively removed by Barton's deoxygenation, the resulting dithiane 5 was hydrolysed to the aldehyde which was immediately subjected to a two-carbon Wittig homologation to afford the required eight-carbon moiety with all necessary functionalities. Hydrogenation to 6, mesylation to 7, thiolation to 9 and hydrolysis afforded the title compound 1 in very high enantiomeric purity.

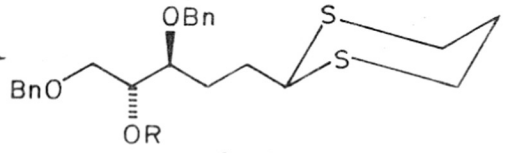
(ii) An approach involving Sharpless asymmetric epoxidation

The required eight-carbon moiety 12 was obtained by a simple alkylation of a tetrahydropyranylated derivative of bromopentanol on propargyl alcohol (Chart 1). Hydrogenation of the alkyne gave the corresponding trans allylic alcohol which is an ideal substrate for Sharpless asymmetric epoxidation. The α,β-epoxy alcohol 13 on 'Red-Al' reduction gave regioselectively the 1,3-diol 8. Mesylation, thiolation to 10 and detetrahydropyranylation gave the optically active 1,2-dithiolane-3-pentanol 11. Jones oxidation of 11 led to the title compound 1.



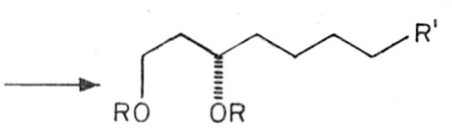
2: R = $COCH_3$

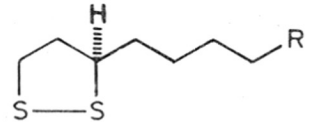
3: R = CH_2Ph



4 : R = H

5 : OR = H





9: R = CO_2Et

1: R = CO_2H

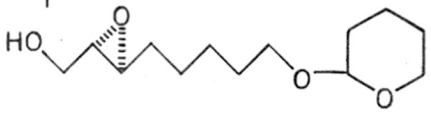
10: R = $-CH_2OTHP$

11: R = $-CH_2OH$

6: R = H, R' = CO_2Et

7: R = MS, R' = CO_2Et

8: R = H, R' = CH_2OTHP



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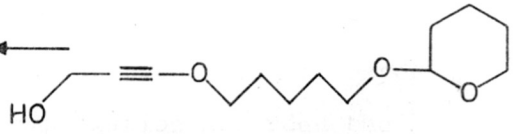

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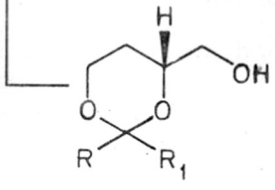
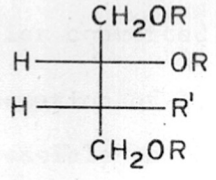
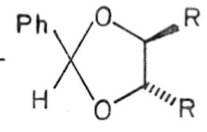






18: R = Ph, R_1 = H

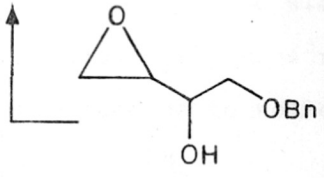
19: R = R_1 = CH_3

16: R = $-COPh$, R' = Br

17: R = R' = H

14: R = CO_2Et

15: R = CH_2OCOPh



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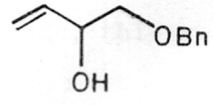

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CHART–1

(iii) Use of 1,2R,4-Butanetriol - a chiral synthon from RR-tartaric acid and cis-2-butene-1,4-diol towards (+)1

We envisaged the use of 'RR'-tartaric acid and cis-2-butene-1,4-diol for their conversion to the important intermediate butane triol 17 required in our synthetic sequence.

The diethyl tartarate was converted to the 1,2-dibenzylidene derivative 14 which on lithium aluminium hydride reduction followed by subsequent benzoylation afforded 15 (Chart 1). Opening of the 1,2-benzylidene derivative by N-bromosuccinimide afforded the bromotribenzoate 16 which on reductive debromination followed by Zémplen debenzoylation gave the required optically active butanetriol 17. Protection of the triol with α,α-dimethoxytoluene gave the 1,3-benzylidene alcohol 18. Oxidation of the above alcohol to the corresponding aldehyde followed by a four-carbon Wittig homologation afforded the eight-carbon moiety with required functionalities in the correct positions. Hydrogenation and hydrolysis led to the dihydroxy ester 6 which had been earlier converted to the title compound.

The possibility of formation of 1,2R,4-butanetriol from a cheap and easily accessible source - cis-2-butene-1,4-diol led to the following approach. Mercury-catalysed isomerisation of cis-butenediol followed by monobenzylation afforded 20, an allylic alcohol system. The possibility of using the above as a substrate for Sharpless asymmetric epoxidation prompted us to follow this approach, but, this reaction

was too slow for any practical conversion to the optically active epoxide. 'Red-Al' reduction of the dl epoxy alcohol 21 followed by protection with α,α-dimethoxyacetone and debenzylation gave the 1,3-acetonide alcohol 19. The conversion of this alcohol to the final compound follows essentially the same approach as before (Chart 1).

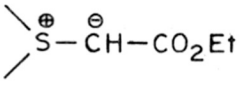
Chapter 2.0.0 - Synthesis of Ethyl trans (±)-chrysanthemate

This chapter essentially describes the development of a methodology towards a key component, ethyl trans (±)-chrysanthemate 25, of the important group of insecticides - pyrethroids - which are being widely used in agriculture.

The use of 'S' ylids in creation of cyclopropane moiety has been explored only recently and that too to a limited extent. In this context, the development of the methodology mentioned above can easily incorporate a cyclopropane reaction using a suitable ylid.

The choice of the sulfurane and its handling ease led us to take up the easily made sulfurane namely ethyldimethylsulfuranylidene acetate 22 [E.D.S.A.] (Chart 2). The choice of our ketone was a dimethylhexenone 23 whichwas prepared by an efficient sequence of reactions starting from a vinyl Grignard on isobutyraldehyde and PDC oxidation. The ketone obtained 23, had the requisite framework to give the isobutenyl chain of the chrysanthemate after cyclopropanation.

The reaction of an α,β-unsaturated ketone 23 with sulfurane



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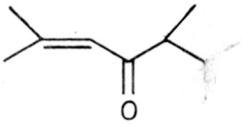

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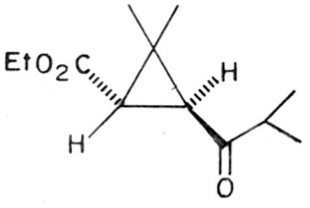

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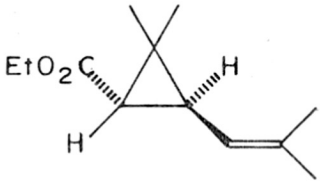

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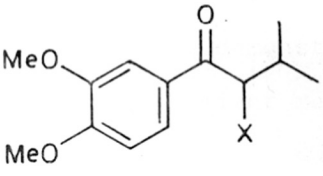
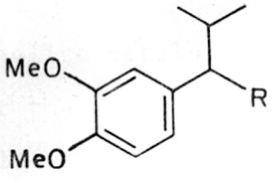


26: X = H

27: X = Cl

28: X = Br



29: R = COOH

30: R = $CONH_2$

31: R = CN

CHART – 2

E.D.S.A., 22 gave the required cyclopropane keto ester 24. α-Bromination of the ketone, followed by sodium borohydride reduction of the ketone and subsequent elimination led to the title compound 25 in a short reaction sequence.

Chapter 3.0.0 - Synthesis of Nitriles using Zeolites

This chapter highlights the potential use of zeolites in establishing a dehydration technique in organic synthesis. Nitriles are important organic intermediates for a variety of end products, especially required in the drug industry. Therefore, the manufacture or large scale preparation of nitriles requires an easy and simple method. Most of the known methods involve the dehydration of amides with a variety of reagents; but the practical application of these methods may suffer from a number of disadvantages such as use of expensive reagents, drastic reaction conditions, unsatisfactory yields, etc.

Herein, we demonstrate the use of zeolite catalysts in a simple and efficient reaction process for the above conversion which could be easily adapted to large scale manufacture. The general applicability of this process can be judged by an efficient conversion of various types of amides to the corresponding nitriles. This method was then extended very efficiently to the elimination reaction of aldoximes to again generate nitriles.

The application of this method was tested in the case of a verapamil intermediate 31 - a nitrile. The required acid 29 was obtained in a one-step conversion of α-chloro and

α-bromo ketones, 27 and 28 respectively (obtained from the corresponding ketone 26) involving a Favorskii rearrangement (Chart 2).

CHAPTER 1·0·0

ASYMMETRIC SYNTHESIS OF R (+)-α-LIPOIC ACID

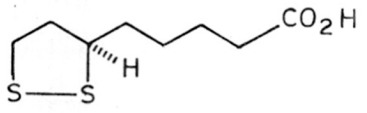
FOREWORD

This chapter deals with three approaches for the natural R(+)-α-lipoic acid starting from the natural chiral substrate, D-glucose, from a suitable allylic alcohol substrate for asymmetric epoxidation and from optically active 1,2R,4-butanetriol.

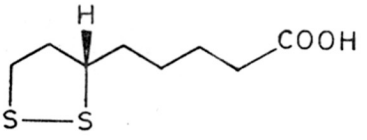
1.1.0 INTRODUCTION

α-Lipoic acid[1] (1), an important protein bound coenzyme, has become widely recognized as a prosthetic group and a substrate in plants, microorganisms and animal tissues. It has been identified as a vital cofactor in the multienzyme complexes that catalyze the oxidative decarboxylation of α-keto acids (for e.g. pyruvate, α-ketoglutarate and branched chain α-keto acids); it also occurs as the transacylating cofactor of several multienzymic α-keto acid dehydrogenase complexes. Evidence that it plays an important role in oxidative phosphorylation has also been given. It is also found to exhibit an essential role, not only in the tricarboxylic acid cycle [TCA], but also in photosynthesis, thus providing a connecting link between these two vital processes. Thus the importance of α-lipoic acid, also known widely as thioctic acid, in biochemical processes is well established.

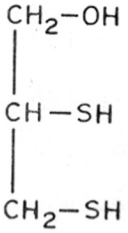
α-Lipoic acid (Chart 1.1.1) was first isolated from natural sources (liver) by Reed[2] et al. and on the basis of degradative, synthetic and spectroscopic evidence was characterised as the cyclic disulfide, 5-[3-(1,2-dithiolanyl)]-pentanoic acid 1[3]. This compound was named as α-lipoic acid in contrast to another cogener obtained which was later found to be the sulfoxide analog-β-lipoic acid[4]. The name lipoic acid was derived from the fact



(+) 1, R (+) – α – LIPOIC ACID



(–) 1, S (–) – α – LIPOIC ACID



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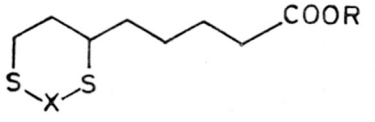

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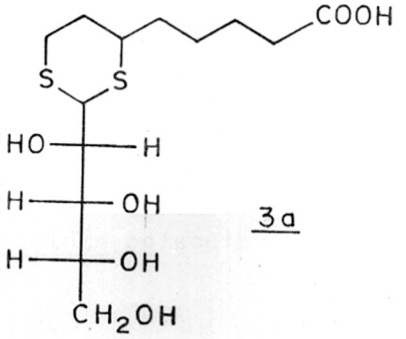
X = Radical of

D-glucose

D-arabinose

L-arabinose

R = H, Na



3a

CHART 1·1·1

that the compound is highly soluble in fat solvents, is acidic and is involved in oxidative decarboxylation of pyruvate in the formation of acetate, a precursor of fatty acids[5].

α- was designated to indicate that it is the first member in a series of chemically related substances which possess 'acetate replacing' and 'pyruvate oxidase factor' activity viz. biological activity.

BIOLOGICAL ACTIVITY

α-Lipoic acid has been shown to have significant physiological and pharmacological properties[1]. It is known to have protective and curative effect in heavy metal poisoning (for example, from As, Pb, Hg, Se, $Ni(CO)_4$) in animal tissues. This effect is frequently superior to that of BAL [Dimercaprol] 2 (Chart 1.1.1). A pharmacological study on the antidotal effects of α-lipoic acid on mercuric chloride-intoxicated rats showed that the mortality of the mice decreased from 60% to 40% by its administration[6]. A similar beneficial effect has been reported in liver damage, induced experimentally by CCl_4, allyl alcohol, and thiobarbiturate toxicity[1]. It is found to be very effective in the treatment of severe liver toxicosis caused by Amanita phalloides[7a]. Reports on therapeutic application of thioctic acid in the treatment of Amanita phalloides poisoning in children have also

appeared[7b]. The use of lipoic acid in correcting metabolic disturbances in rabbits inoculated by E. coli endotoxin has also been reported[7c]. It has also proved much more effective than BAL 2 alone, in the treatment of experimentally induced arsenite toxicosis in cattle by restoring the liver functions[7d]. It has also been demonstrated[8] to be an effective agent in preventing atherosclerosis in Japanese quails. Apart from its therapeutic use in liver-related maladies, recent reports[9] have indicated its effectiveness in reducing the blood sugar level of diabetic rats during a glucose tolerance test; reports on clinical trials on humans are being awaited.

An interesting cosmetic application[10] is that the 2-ethylhexyl and hexadecyl esters can be used as skin whitening cosmetics incorporated in creams etc.

There has been a discussion by Sigel et al.[11] on the hydrophobic interactions and metal-ion co-ordinating properties of α-lipoic acid. This accounts for its extremely high biological activity as it helps the free passage of the compound in various tissues. This cofactor, α-lipoic acid offers metal ions two different binding sites, the carboxylate group and the disulfide linkage. The carboxylate group dominates the co-ordinating properties of this ligand towards biologically important metal ions

but a disulfide metal ion interaction is still possible, and under sterically favourable conditions, may become very important; this could also be true under enzymic conditions when the carbonyl group is no longer free but amide-linked to the protein. Further, due to the valeric acid side chain, the lipoyl moiety is ideally suited to undergo hydrophobic ligand-ligand interaction in mixed ligand complexes. Such hydrophobic interactions seem to be ideal to allow migrations across cell membranes of the 14A° long lipoyl-lysyl moiety and also to facilitate the correct fixation at the surface of the enzyme.

Available evidence[12] suggests that the biological activity of α-lipoic acid is confined only to the naturally occurring 'R'isomer. In enzymatic pyruvate oxidation factor assays, the activity of synthetic R(+)-α-lipoic acid was double than that of (±)-α-lipoic acid. The activity of the S(-)isomer was found to be essentially zero. However, it is important to mention here that (±)-α-lipoic acid is equally important for pharmaceutical use because of the fact that the biological activity of the racemic is similar to that of the 'R' isomer and more importantly, without any concomitant side effects.

Optically active isomers of lipoic acid have been obtained by resolution of the intermediate stages in the synthetic sequence on using optically active amines. In 1979,

Chebotareva et al.[13] patented the synthesis of optically active lipoic acid from 2-(polyhydroxyalkyl)-1,3-dithiane-4-valeric acids or their sodium salts, 3, where X is a radical of D-glucose, D-arabinose and L-arabinose. In 1980, Chebotareva et al.[13] prepared the 'S' form through a resolution of the racemic compound by complexing it with a D(-)arabinose moiety to form the complex 3a (Chart 1.1.1).

Absolute Configuration and Stereochemistry

The absolute configuration of natural α-lipoic acid was assigned as 'R' by Mislow and Meluch[14] on the basis of comparison of the melting point composition diagrams for mixtures of R(+)3-methyl octanedioic acid with (+) and with (-)3-mercapto octanedioic acid respectively. These two mercapto acids have been correlated with (-) and (+)α-lipoic acid respectively.

In order to determine stereochemistry, White et al.[15a] have studied the biosynthesis of 1 by Escherichia coli from octanoic acid, which revealed that for α(+)-lipoic acid to have the 'R' configuration, the insertion of sulfur at the C-6 position of the derived octanoic acid must occur with an overall inversion of the stereochemistry at this carbon. Moreover, the insertion of each sulfur atom in lipoic acid has been demonstrated[15b] to occur at each of the saturated carbons, C_6 and C_8, with the loss of only that hydrogen atom which each sulfur replaces and without apparently involving the carbons C_5 and C_7. These observations are

consistent with a biosynthetic pathway of lipoic acid involving hydroxylated octanoic acids, which in turn, is consistent with the known ability of bacteria to perform ω or ω-2 hydroxylations.

SYNTHESIS OF RACEMIC AND OPTICALLY ACTIVE α-LIPOIC ACID : A REVIEW

Soon after its isolation, there were a spurt of synthetic methods and a number of patents on the synthesis of (±)-α-lipoic acid, its simple amide, amides of α-lipoic acid with other amino-acids and also mixed disulfides of lipoic acid and thiamine. These derivatives were specially synthesized for pharmaceutical use[1].

The naturally occurring isomer 'R' was previously obtained by the resolution of the racemic lipoic acid or via the resolution of some starting synthon or intermediate .

The first few syntheses were only of theretical interest which firmly established the structure of the compound and also the position of the two sulfur atoms on the octanoic acid chain. It is pertinent to mention and discuss in details, the numerous reported syntheses of α-lipoic acid.

These routes involved the preparation of octanoic acids having halogen, hydroxy, mercapto or ether groups on the carbon atoms 6 and 8 which by treatment with HI/thiourea, sodium disulfide, thiocyanate, thiosulfate or thioacetate led finally to the formation of dihydrolipoic acid or lipoic acid. For simplicity, the syntheses of α-lipoic acid have

been divided into four categories depending upon the reaction-type used:

a) Friedel-Craft's approach

b) Prins' approach

c) Baeyer-Villiger approach

d) Miscellaneous approach.

a) Friedel-Craft's approach[16]

Several syntheses involving the Friedel-Crafts reaction have been utilised for the synthesis of α-lipoic acid. It is interesting to note that in almost all the reported syntheses, the basic eight-carbon skeleton has been prepared by the alkylation of ethyl adipoyl chloride with ethylene. The eight-carbon intermediates were transformed into either the 6,8-dihydroxy or 6,8-dihalo or 6,8-thiohydroxy or other such derivatives which finally led to the 6,8-dihydrolipoic acid. Subsequent oxidation of this gave rise to the 1,2-dithiolane ring system.

In the first synthesis by Bullock et al.[16a] (Chart 1.1.2) the eight carbon chain of lipoic acid was obtained by the Friedel Craft's addition of ethyl adipoyl chloride to ethylene in the presence of $AlCl_3$. The resulting β-chloroketo ester 4 was dehydrohalogenated to ethyl 6-oxo-7-octenoate 5 by heating. Michael addition of thiolacetic acid to this vinyl ketone 5 gave ethyl 8-acetylthio-6-oxo-octanoate 6. Its subsequent reduction with sodium borohydride

SCHEME – I

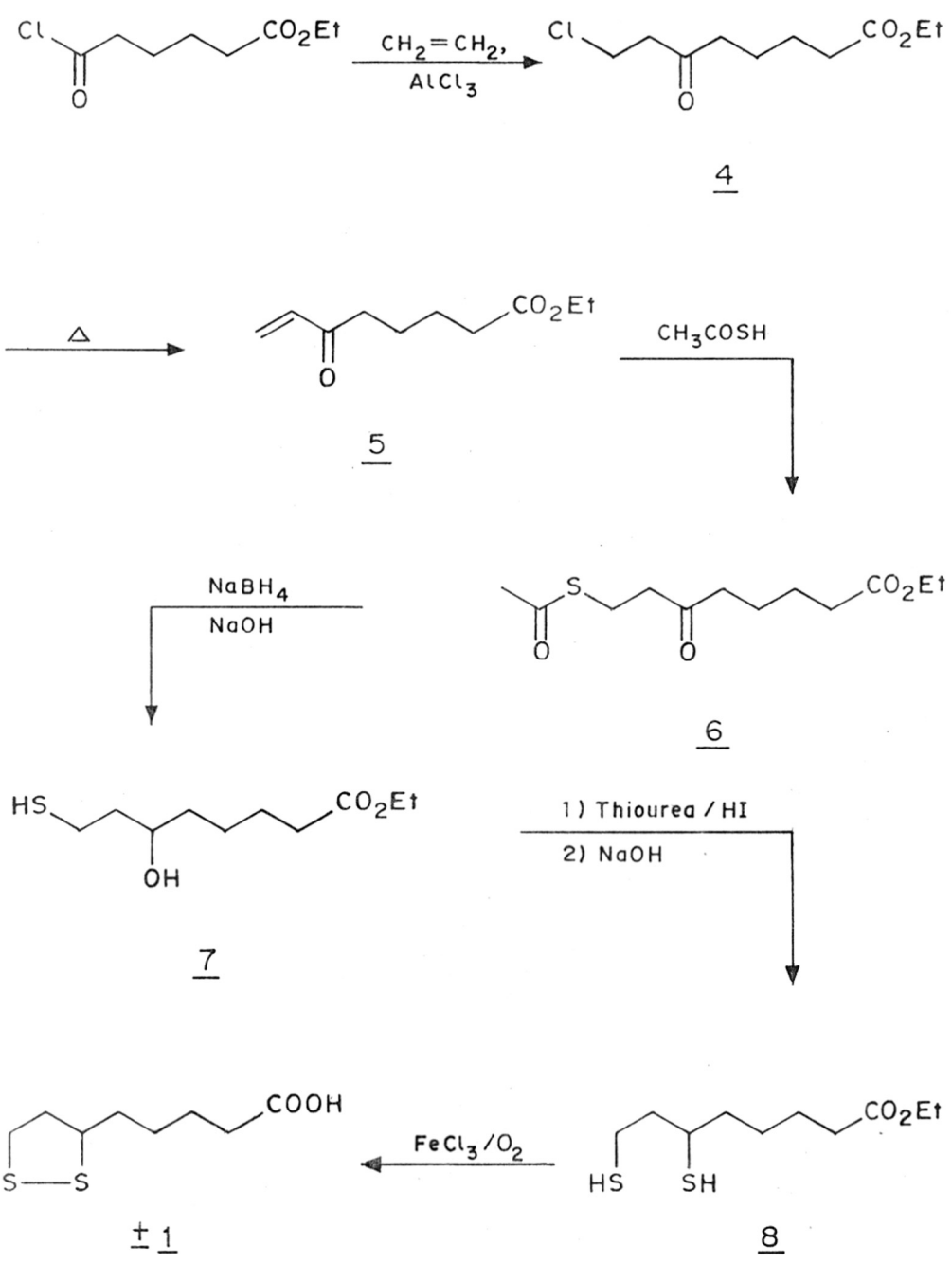


CHART 1·1·2

and alkaline hydrolysis afforded 8-mercapto-6-hydroxy-octanoic acid 7. 7 on treatment with thiourea in the presence of hydroiodic acid gave the key intermediate, 6,8-dimercapto octanoic acid 8. Oxidation of 8 with ferric chloride in the presence of oxygen afforded (±) α-lipoic acid in an overall yield of 8%.

Reed et al.[16b] (Chart 1.1.3) obtained the crystalline (±)-lipoic acid in much better yields (36% and 15% respectively) from the corresponding ethyl 6,8-dihalo octanoates 9 and 10. The dihalo esters (9 and 10) were obtained by two different routes. For example, the β-chloroketone 4 (obtained by earlier workers[16a]) was reduced with sodium borohydride and treated with thionyl chloride to give the dichloroester 9. In the second approach, the vinyl ketone 5 was successively treated with HBr, $NaBH_4$ and PBr_3 to yield the dibromo ester 10.

Final transformation of the dihalo esters into the dihydrolipoic acid ester 8 was carried out by nucleophilic displacement with potassium thiolacetate or sodium benzyl mercaptide, which on hydrolysis and oxidation gave ± 1.

In Acker's approach[16c] (Chart 1.1.4, Scheme III) methyl 8-thioacetyl-6 oxo-octanoate 6 (Bullock et al.) has been utilised as the starting material. The catalytic reductive thiolation of 6 with sulfur and cobalt polysulfide paste in acetic acid under hydrogen, followed by oxidation led to the manufacture of ± 1.

SCHEME – II

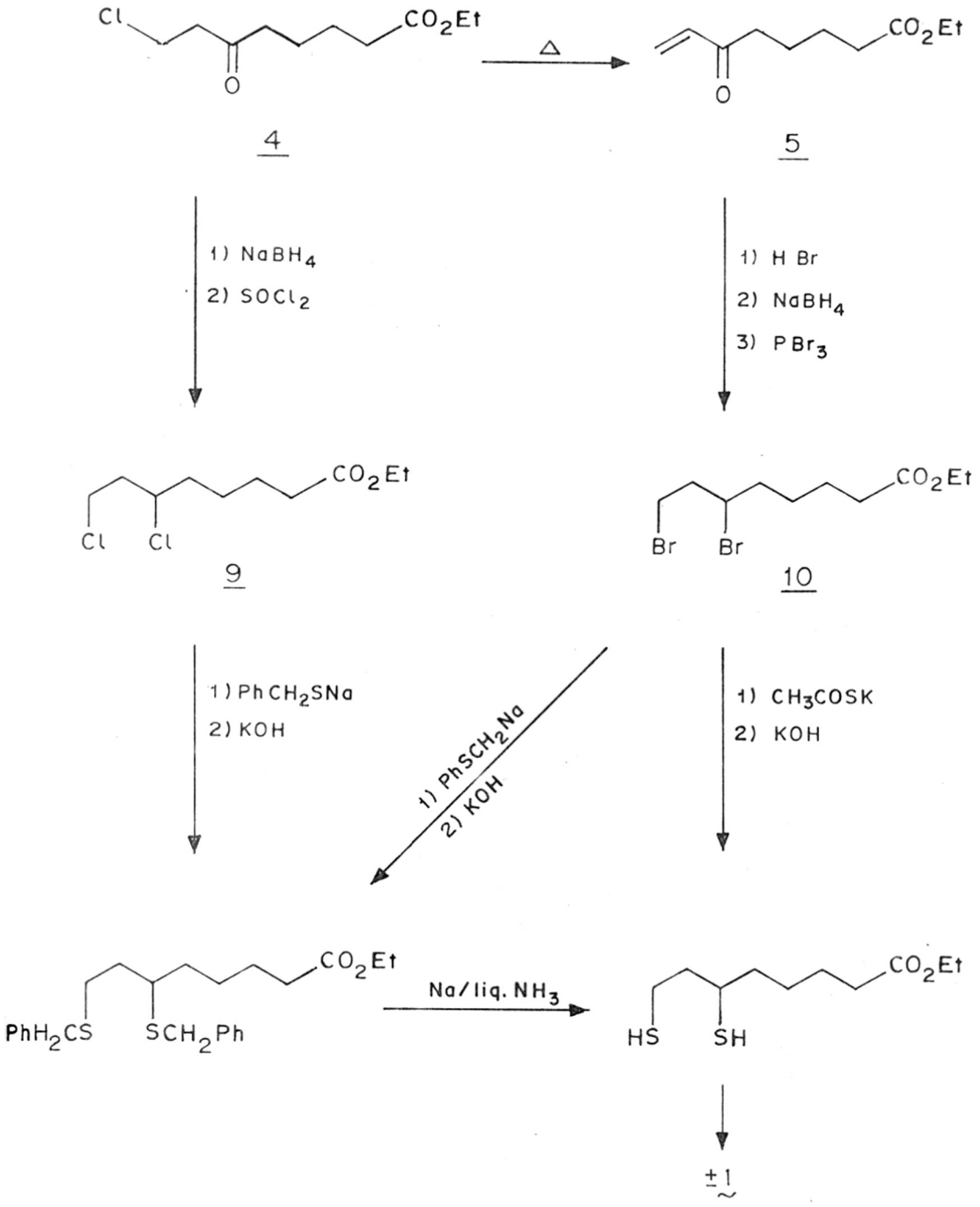
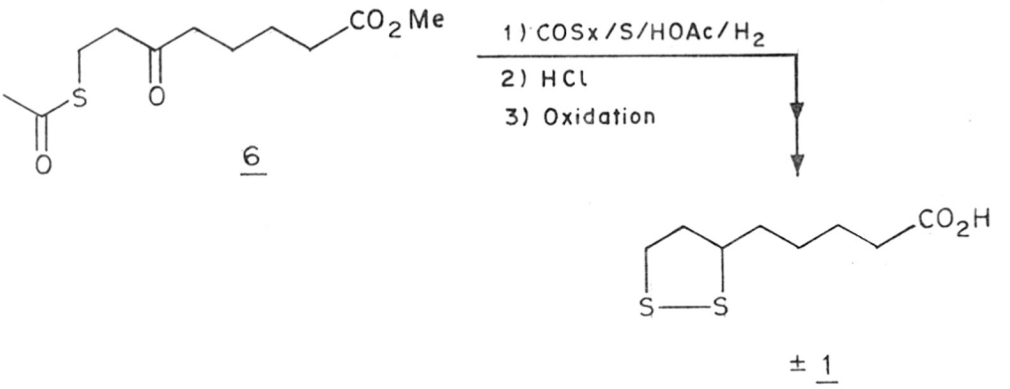


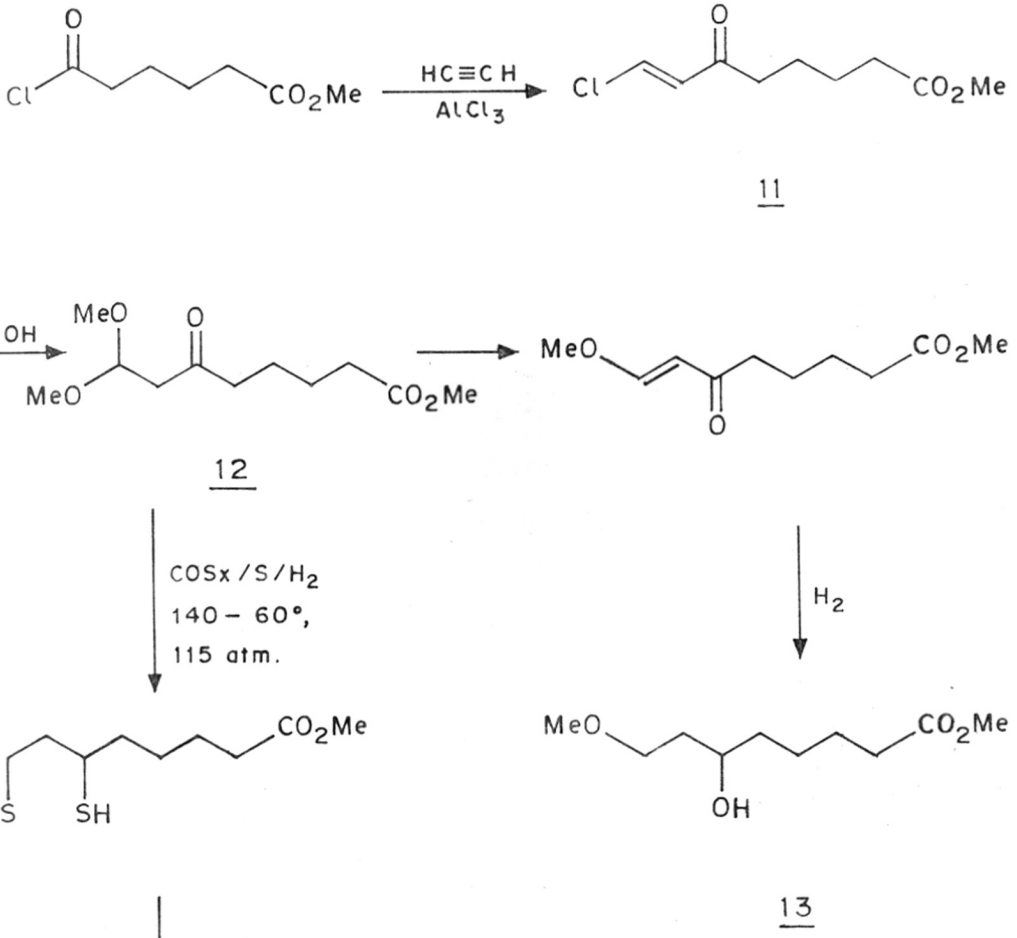
CHART 1·1·3

SCHEME — III



± 1

SCHEME — IV



± 1

CHART 1·1·4

A group of Japanese workers[16d] obtained the basic eight-carbon skeleton 11 of (±)α-lipoic acid by Friedel-Craft's addition of acetylene on ethyl adipoyl chloride (Chart 1.1.4, Scheme IV). Treatment of 11 with alcohol gave methyl 8,8-dialkoxy-6-oxooctanoate 12. 12 was converted in one step to dihydrolipoic acid by using sulfur in the presence of catalytic amount of cobalt polysulfide and hydrogen. In another approach by them, 11 was converted to methyl 8-alkoxy-6-hydroxy octanoate 13 by successive elimination and hydrogenation. This route was especially advantageous in the large scale manufacture of α-lipoic acid.

Based on essentially similar approach, there were many other methods reported for (±)-α-lipoic acid using Friedel-Craft's reaction[16e].

b) Prins' approach[17]

In this synthetic sequence, Prins reaction involving addition of paraformaldehyde on alkenes or acetylenes has been utilised for the hydroxy methylation and thereby 1,3-diol formation. For example, 1-bromo-4-pentyne 14 was treated with paraformaldehyde in the presence of an acid to afford the 4-substituted 1,3-dioxane derivative 15 (Chart 1.1.5). Its alkylation with diethylmalonate followed by decarbethoxylation and hydrolysis afforded 6,8-dihydroxy octanoic acid 16 in an overall yield of 26%[17a]. 16 was converted to (±) 1 by reported procedure.

SCHEME – V

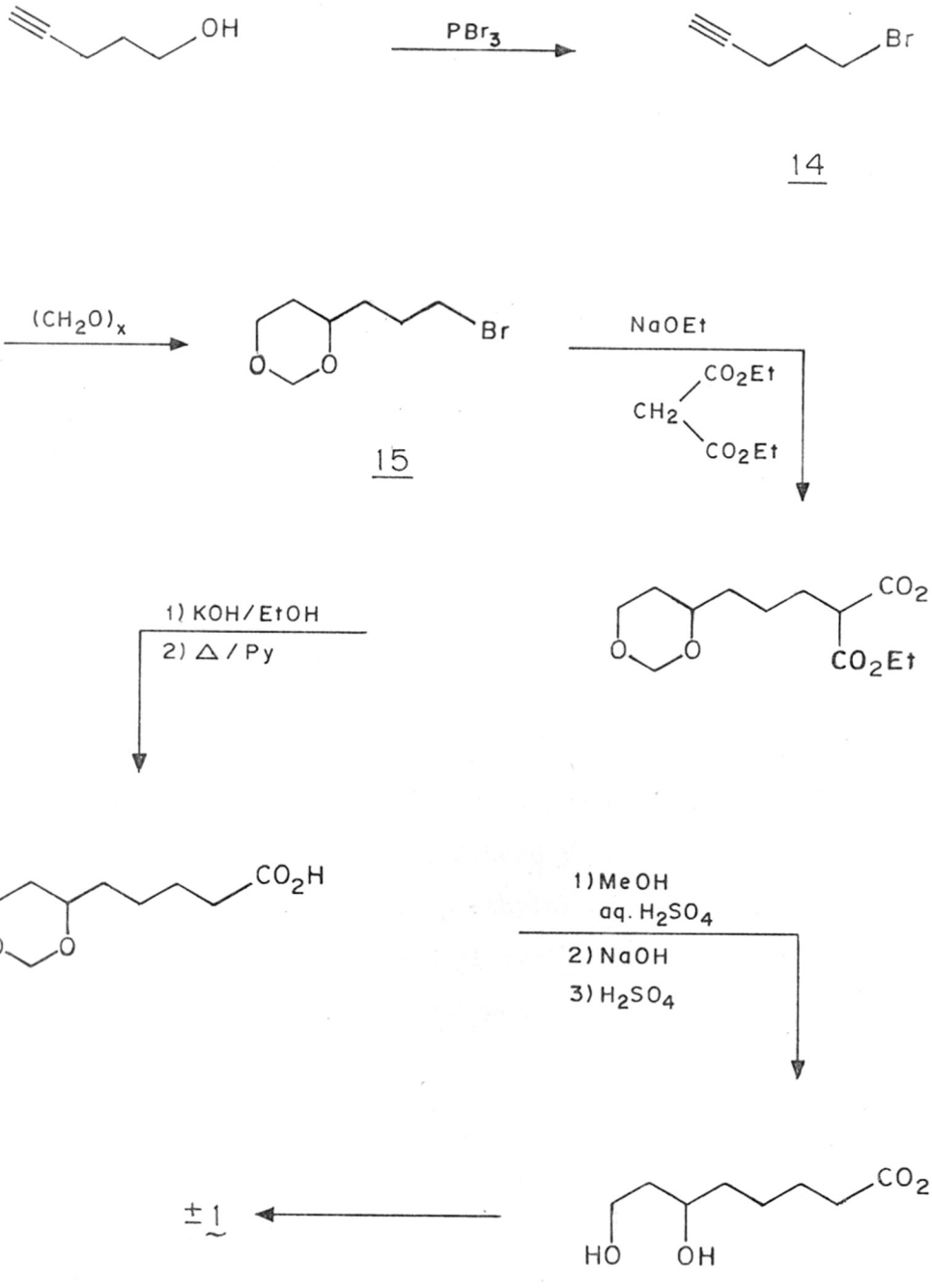


CHART 1·1·5

Braude et al.[17b] (Chart 1.1.6) carried out the Prins reaction for the 1,3 diol formation from 6-heptenoic acid 17. Prins' product afforded 6,8-dihydroxy octanoic acid 16 on hydrolysis. This route affords an overall 20-30% yield of α-lipoic acid from 6-heptenoic acid.

c) Baeyer Villiger approach[18]

The use of enamines for acylation or alkylation is one of the best methods for the homologative derivatisation of a cyclic ketone. Segre et al.[18a] (Chart 1.1.7) synthesised 2-ethoxy carbonyl methyl cyclohexanone 18 by alkylation of 1-morpholino cyclohexene with bromoethylacetate. The ketone 18 was protected and the ester group reduced and converted to acetate 19. Hydrolysis of the ketal followed by Baeyer-Villiger oxidation afforded the seven-membered lactone 20, which on opening with thiourea-HBr combination and oxidation gave ± 1 in 19% yield.

A more straightforward approach to ± 1 was reported by Ubatani[18b] (Chart 1.1.8, Scheme VIII). Alkylation of cyclohexanone with β-ethoxy ethylbromide in the presence of sodamide gave 2-β-ethoxyethyl cyclohexanone 21. Baeyer-Villiger oxidation of 21 followed by conventional reactions gave ± 1 in an over all yield of 10%.

Lewis and Raphael[18c] devised a novel route for the synthesis of ± 1 (Chart 1.1.8, Scheme IX). An interesting feature was the conversion of an aromatic compound into the

SCHEME – VI

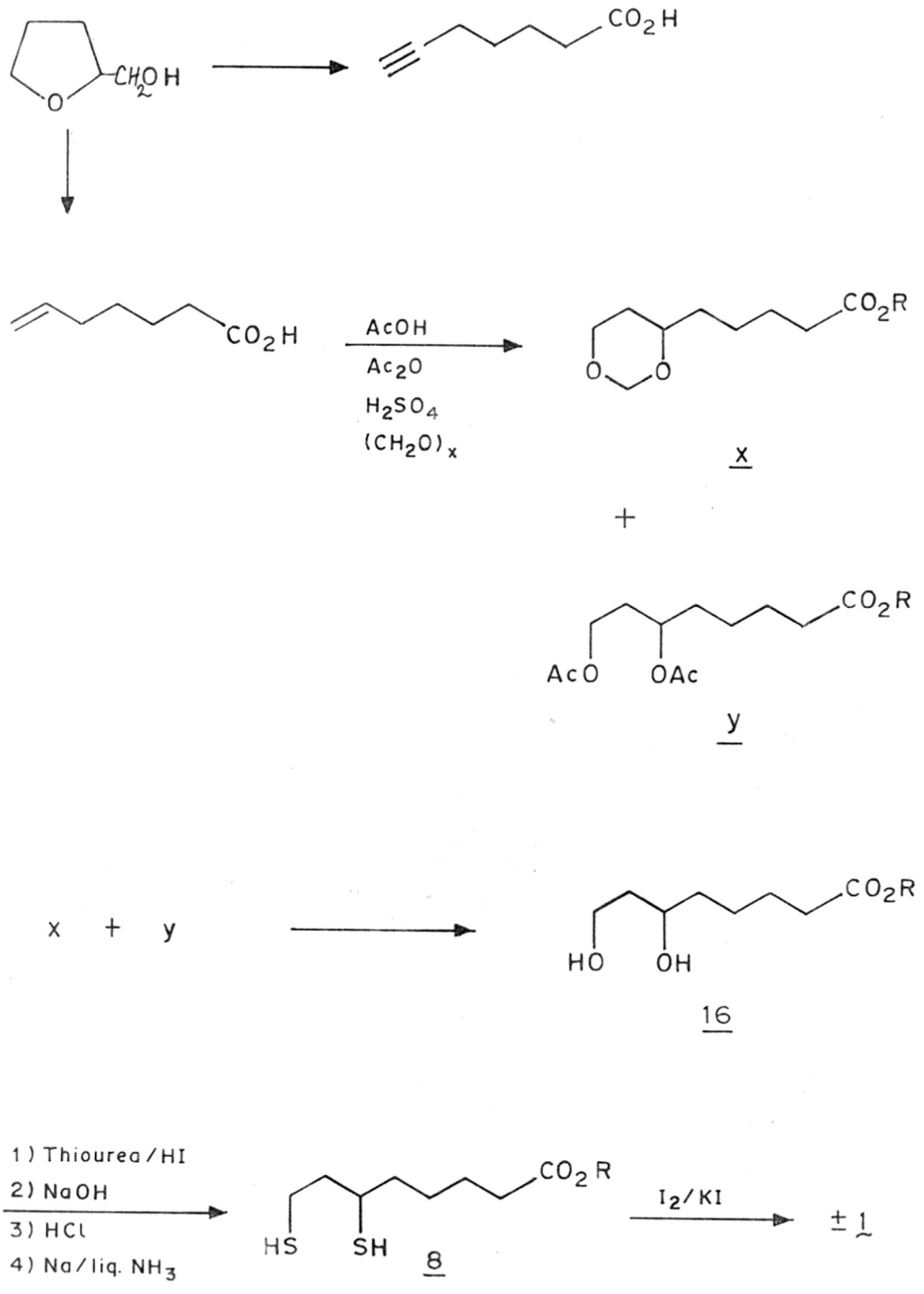
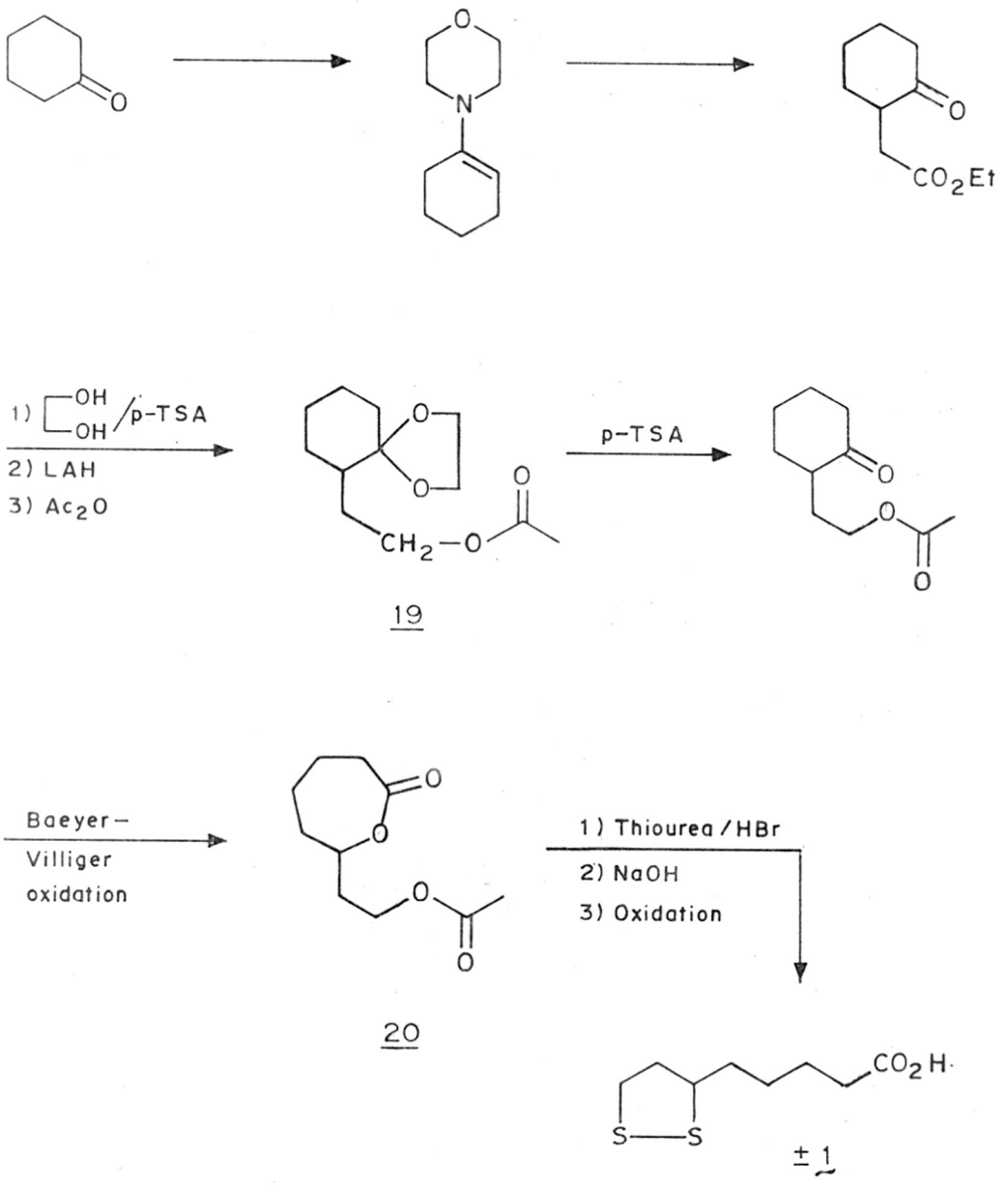


CHART 1·1·6

SCHEME– VII



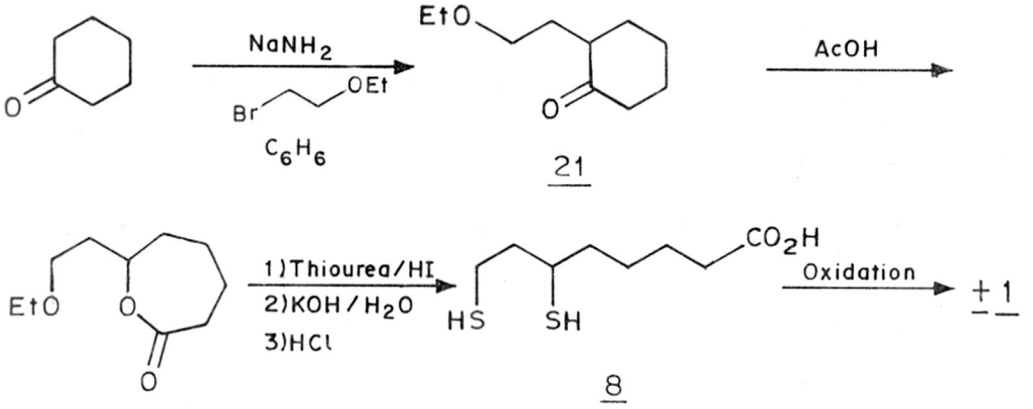
19

20

± 1

CHART 1·1·7

SCHEME – VIII



SCHEME – IX

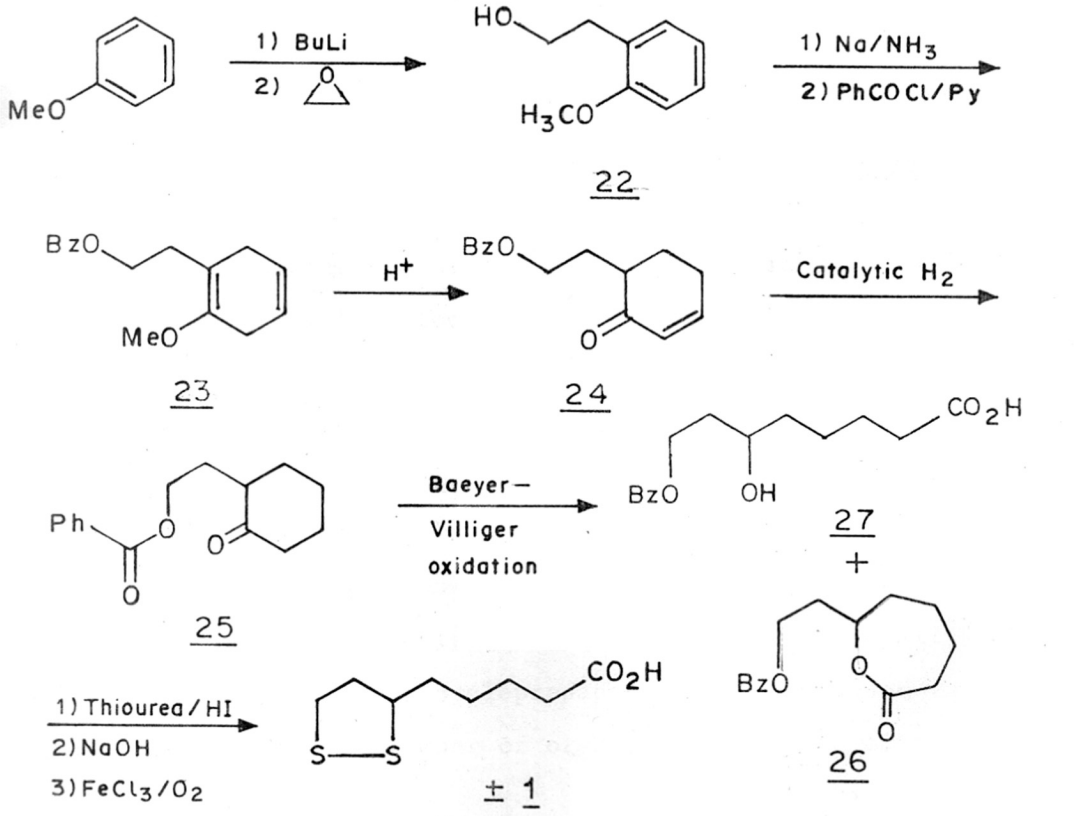


CHART – 1·1·8

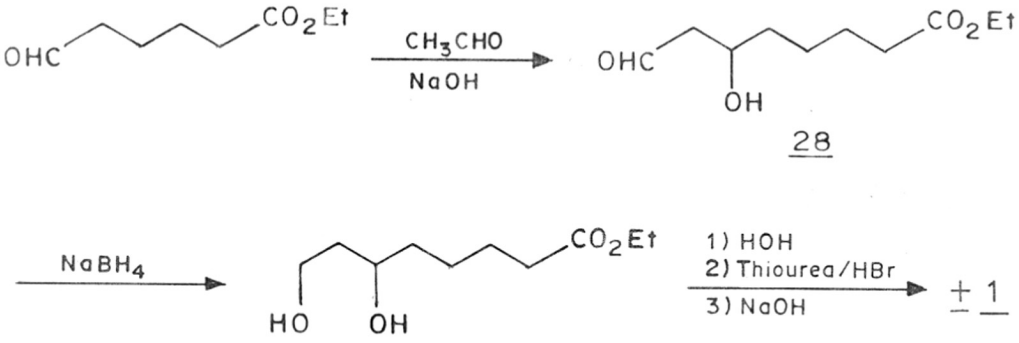
open chain aliphatic moiety. Addition of ethylene oxide to metallated anisole gave 2-hydroxyethyl anisole 22. Its Birch reduction afforded the expected dihydro derivative, which on benzoylation gave 23. Mild acidic hydrolysis of 23 then gave the expected α,β-unsaturated ketone 24. Hydrogenation of 24 to 25 and Baeyer-Villiger oxidation gave a mixture of lactone 26 and 8-benzyloxy-6-hydroxyoctanoic acid 27. Conventional thiolation and oxidation gave ± 1 in an overall yield of 26%.

d) Miscellaneous approaches[19]

Jones[19a] made use of the aldol condensation of δ-carbethoxyvaleraldehyde with acetaldehyde to give the expected β-hydroxyaldehyde 28 which on reduction gave the required 6,8-dihydroxyoctanoate ester (Chart 1.1.9, Scheme X).

In Brockman's approach[19b] (Chart 1.1.9, Scheme XI) the key intermediate namely 6,8-dibromooctanoic acid 10 was obtained from δ-cyclopropyl valeric acid 29. The latter derivative 29 was prepared by the diethylmalonate alkylation of 5-hexenyl bromide to afford 30 which on successive LAH reduction, mesylation and displacement by halogen gave 2-iodomethyl-7-octenyl iodide 31. A ring closure occurred when 31 and zinc dust were boiled in ethanol to afford 32 which on ozonolysis afforded 29 in 14% overall yield. This process of cyclopropanation has been used for the manufacture of a number of organic dihaloacids of the

SCHEME – X



SCHEME – XI

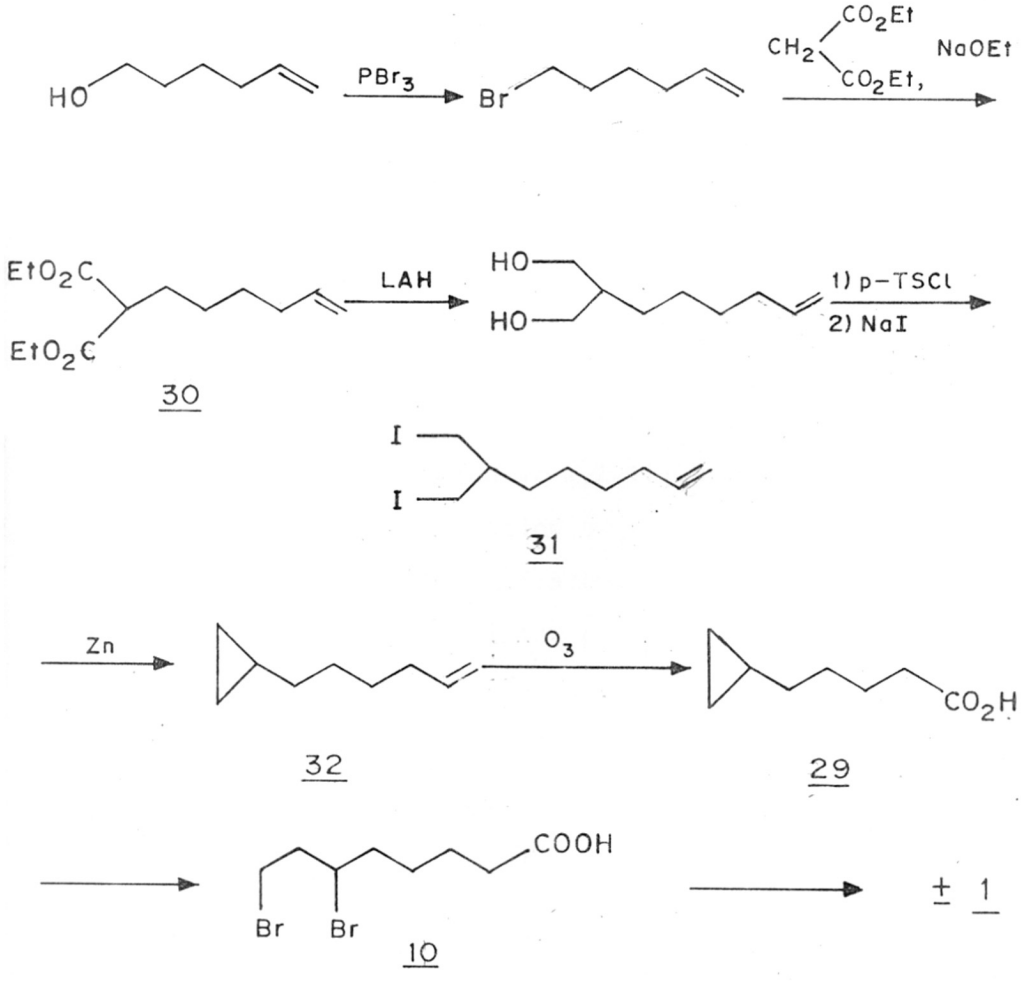


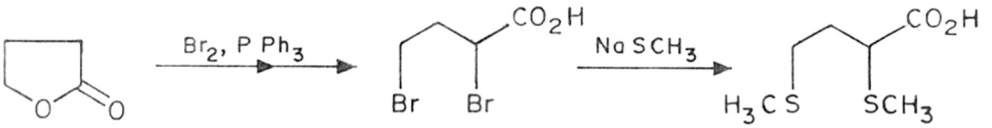
CHART 1·1·9

fatty acid series.

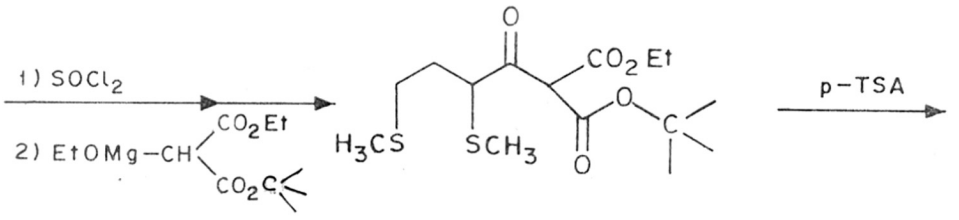
A somewhat longer route for the synthesis of ± 1 has been utilised by Wagner et al.[19c] (Chart 1.1.10). For instance, bromination of γ-butyrolactone was conducted to give 2,4-dibromobutyric acid 33 which on reaction with sodium methyl mercaptide gave 2,4-dimethylthiobutyric acid 34. The Grignard reaction of 34 with ethyl-t-butyl-α-ethoxymagnesio malonate yielded 35 which on decarboxylative elimination afforded the β-keto ester 36. Its alkylation with methyl β-chloropropionate afforded methyl-4-carbethoxy-4[2,4-di-(methylthio)-butyryl]-butyrate 37. Subsequent hydrolysis and decarboxylation gave the ω-keto acid 38 which on $NaBH_4$ reduction afforded the lactone 39. Opening of 39 in the presence of phosphorous and a calculated amount of iodine (weight ratio of iodine to lactone optimised as 1:10) gave 6,8-dimethyldihydrolipoic acid 40 whose oxidation yielded (±)-α-lipoic acid in extremely poor yields.

Tsuji et al.[19d] (Chart 1.1.11) have used a butadienetelomerization reaction as the main step towards the building of eight-carbon framework having the two functional groups located at the correct position and suitable for conversion to the required dihydrolipoic acid. Palladium catalysed butadiene telomerization afforded a mixture of 3-acetoxy-1,7-octadiene 41 and 1-acetoxy-2,7-octadiene 42. The latter compound was rearranged to 41 with

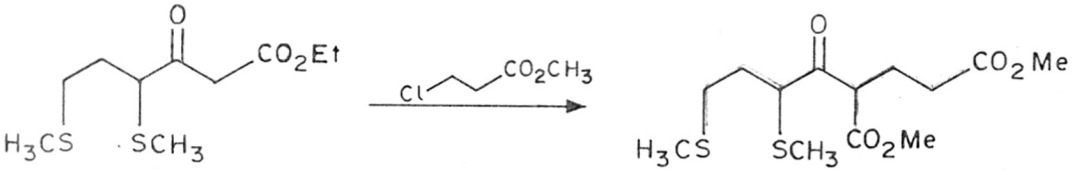
SCHEME — XII



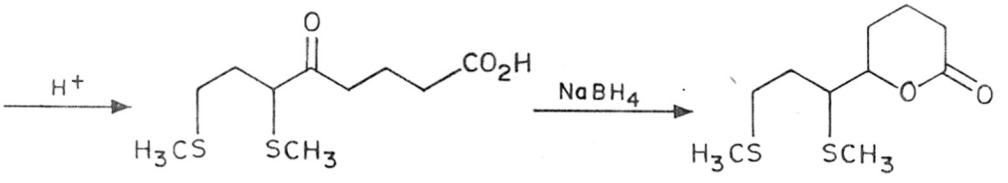
33 34



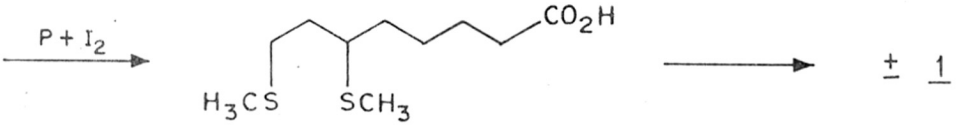
35



36 37



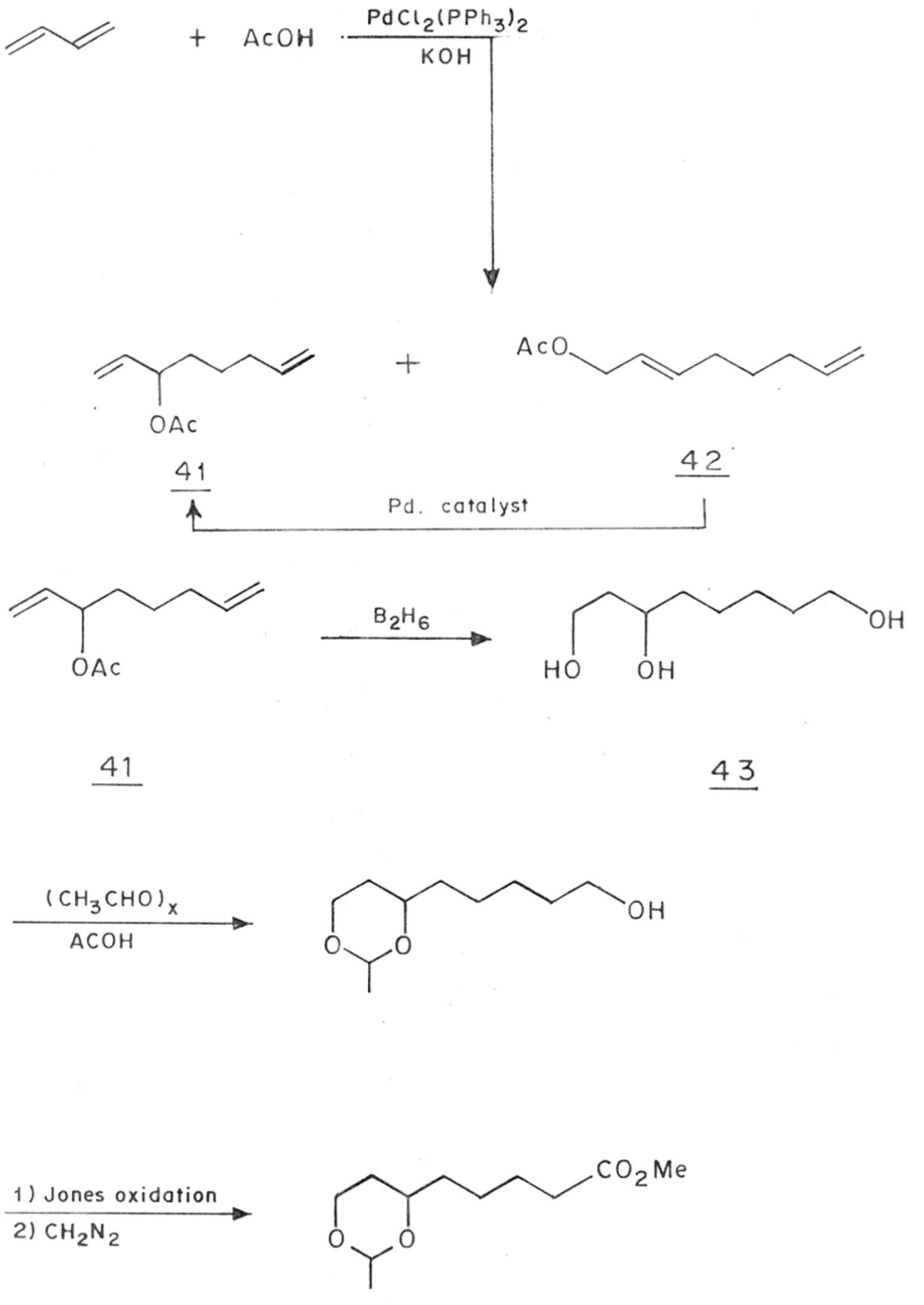
38 39



40

CHART 1·1·10

SCHEME – XIII



41 43

CHART – 1·1·11

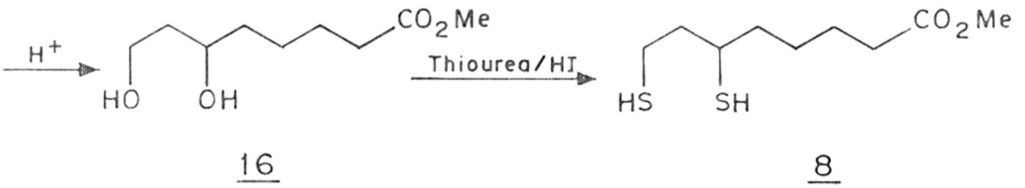
the same catalyst. 41 on hydroboration of the terminal double bonds with diborane complex afforded the 1,3,8-octanetriol 43 in good yields. The 1,3-diol segment in 43 was protected while the terminal hydroxyl group was oxidised to afford the 1,3-dihydroxy octanoic acid 16 which has been already converted into (±)-α-lipoic acid 1 by earlier workers. Herein, the final compound was obtained in 15% yield.

Asymmetric synthesis of α-lipoic acid[20,21]

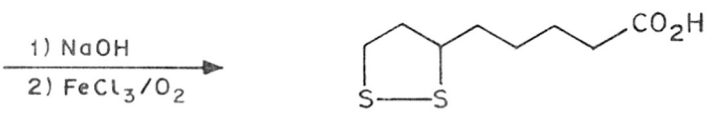
Although α-lipoic acid was isolated over three decades ago, no chiral approach towards its synthesis was known. Only recently, two approaches for the natural (R) and unnatural (S)-α-lipoic acid have appeared. The optically active R(+)-α-lipoic acid, in the past, was obtained by the resolution of the racemate. The only methods so far used for the asymmetric synthesis of α-lipoic acid is from either a chiral starting material or by the use of a chiral reagent.

Golding et al.[20] (Chart 1.1.12) were the first to synthesize the optical antipode, S(-)-α-lipoic acid, of the naturally occurring α-lipoic acid. The strategy employed in this synthesis was the organocuprate mediated opening of the (S)-(2-benzyloxyethyl)-oxirane 44 with but-3-enyl magnesium chloride to afford the eight-carbon framework 45 with proper functionalities for further

Scheme XIII contd.



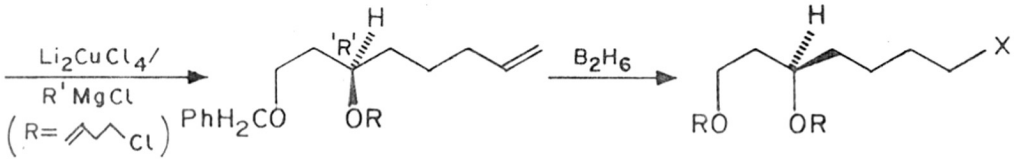
16 8



± 1

SCHEME – XIV

S-MALIC ACID 44



45, R=H

NaH / PhCH2Br

R=CH2Ph

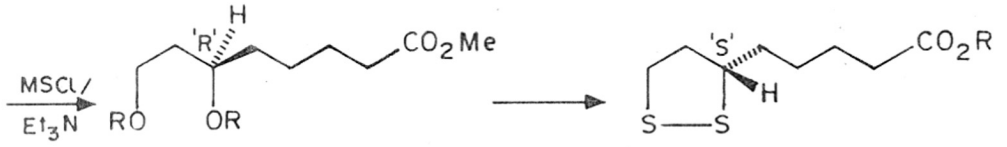
R=CH2Ph, X=CH2OH

PDC/DMF

46, R=CH2Ph, X=COOH

1) Pd/C/H2 2) CH2N2

16, R=H, X=CO2Me



R=SO2CH3

R=Me

0·1M KOH

+ 1, R=H

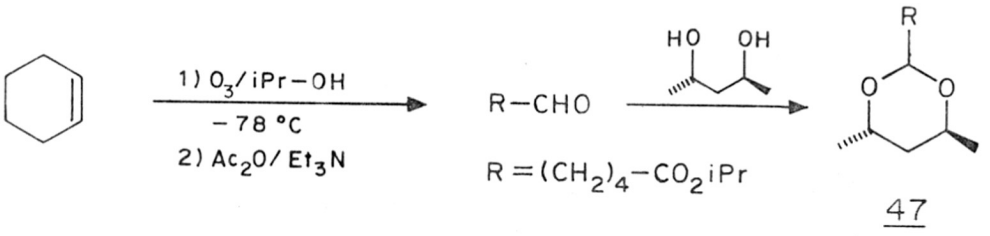
CHART 1·1·12

elaboration. 44 was obtained in two known steps from S(-)-malic acid. 45 on hydroboration-oxidation afforded the optically active triol derivative 46 which was converted to S(-)-α-lipoic acid by conventional route in an overall yield of 25% from 44. This synthesis unequivocally proved the absolute configuration of the natural (+)-α-lipoic acid to be 'R'.

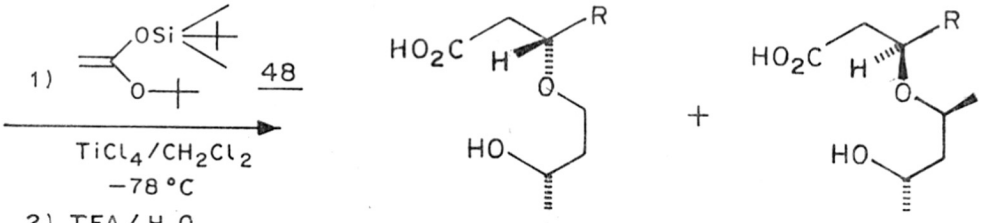
The first asymmetric synthesis of R(+)-α-lipoic acid was reported by Elliott et al.[21]. This route (Chart 1.1.13) was based on asymmetric synthesis of compounds via 'acetal templates'. A very high diastereoselectivity was realized in the $TiCl_4$-catalyzed aldol type coupling of chiral acetals with various chiral enol silanes leading to optically active β-hydroxy carboxylates of predictable absolute stereochemistry.

The required acetal 47 was obtained in two steps from cyclohexene by ozonolysis followed by acetalization with (S,S)-2,4-pentane diol. $TiCl_4$ mediated coupling of 47 with 48 afforded 49 and 50 in a very high diastereoselectivity (98:2). Jones oxidation followed by β-elimination using piperdinium acetate in boiling benzene yielded 51. Its reduction with borane gave the 6,8-dihydroxy ester 16. The dihydroxyester was straightaway transformed to R(+)-α-lipoic acid a la Golding's route in a highly efficient synthetic sequence in 37% yield.

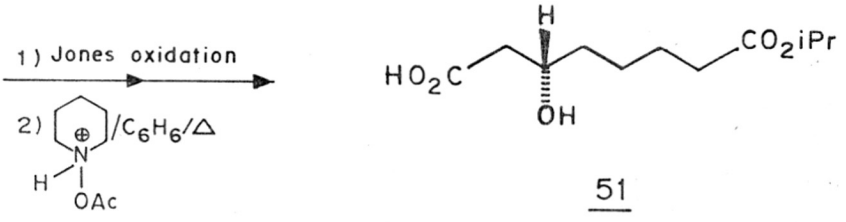
SCHEME – XV



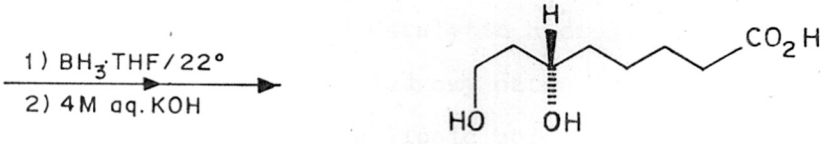
47



49 50



51



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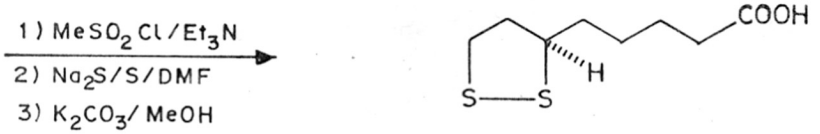


+ 1

CHART–1·1·13

CONCLUSION

The above routes lead to octanoic acids functionalised at carbon atoms 6 and 8, treatment of which with different thiolating agents led to the formation of dihydrolipoic or lipoic acid.

The lengthening of the carbon chain by means of Prins reaction or by acylation or alkylation of ketones and enamines, cannot compete on a technical scale with the synthesis by addition of ethyl adipoyl chloride to ethylene to form the ethyl 8-chloro-6-oxooctanoate. After elimination of HCl to form the 6-oxo-7-octenoic acid, dihydrolipoic acid is obtained directly by treatment with H_2S/H_2 in the presence of CoS$_x$ under vigorous conditions. However, it appears to be difficult to perform the reaction on a large scale. Reduction of the ethyl 8-chloro-6-oxooctanoate with $NaBH_4$ to form the 6-hydroxy compound, proceeds particularly readily. The latter is converted into lipoic acid via 6,8-dichloro-octanoic acid. Addition of alcohol or carboxylic acids to 6-oxo-7-octenoic acid and catalytic hydrogenation to form ethers or esters of 6,8-dihydroxy octenoic acids, followed by ready transformation to lipoic acid has also been achieved.

The same reaction sequence has been applied for large scale manufacture starting from acetylenes instead of ethylene. The Friedel-Craft's addition product of ethyl adipoyl chloride and acetylene formed 8,8-dialkoxy-6-oxo-

octanoic acid by treatment with alcohol. Esters of this acid or its lactones readily formed dihydrolipoic acid on treatment with thiourea/HI.

Almost all the above syntheses proceeded via dihydrolipoic acid which was subsequently oxidised with I_2/KI or $FeCl_3/O_2$ to α-lipoic acid.

All the above methods are for racemic lipoic acid and adapting the method for optically active synthesis would involve the asymmetric reduction of the keto function in 6-oxo-8-substituted octanoic acids, which however has not so far been tried.

1.2.0 PRESENT WORK

INTRODUCTION

Though the concept of asymmetric synthesis has a long standing, its application for effective and practical synthesis of biologically active compounds has started only recently. Many chiral substrates are available abundantly in nature and recognition of these materials as potential starting points for the synthesis of requisite compounds having desired chirality is crucial for the solutions of problems in asymmetric synthesis.

In this respect, carbohydrates have got a special place since they are practically cheap and a renewable natural source of pure chiral compounds. They are also available in a variety of chain lengths with varied functionalities. They are ideally suited for chemical manipulations and exploration of novel methods.

For the asymmetric synthesis of R(+)-α-lipoic acid our attention was naturally focussed on α-D-glucose and hydroxy acids like (RR)-tartaric acid.

Although there are a good number of synthesis reported for (±)-lipoic acid, interest in the synthesis of natural lipoic acid has started only very recently. When the present work was initiated, no reported asymmetric synthesis of natural lipoic acid was known. Only one asymmetric synthesis for natural lipoic acid by Elliott et al.[21]

appeared in 1985 when the present investigation was being concluded.

Although Elliott's[21] synthesis (Chart 1.1.13) was an elegant and efficient one, it involves expensive reagents including an expensive chiral auxillary namely (S,S)-pentane-1,4-diol. The other asymmetric synthesis known, namely that of Golding[20] (Chart 1.1.12) starts from the natural chiral starting material, S(-)malic acid, which leads to the optical antipode of α-lipoic acid. Starting from R-(+)-malic acid would have provided a convenient synthesis for R(+)-α-lipoic acid but R(+)-malic acid is expensive. This led us to look into the possibility of using cheap chiral sources from carbohydrates.

Since the biological activity of α-lipoic acid is confined only to the 'R' isomer, the present work was initiated for a chiral synthesis from glucose. Conceptually, suitability of glucose as a chiral starting material for 1 was ascertained by the recognition of C-4 of glucose as having the right configuration for conversion to the C-6 carbon atom of lipoic acid.

In addition to the above approach, we also studied the conversion from simpler chiral substrates like naturally occurring (RR)-tartaric acid. This chapter is therefore divided into three sections:

A) Asymmetric synthesis of R(+)-α-lipoic acid from α-D-glucose.

B) Synthesis of R(+)-α-lipoic acid involving Sharpless epoxidation on a suitably functionalized allylic alcohol.

C) 1,2R,4-Butanetriol as chiral synthon, from tartaric acid and cis-2-butene-1,4-diol, towards the synthesis of R(+)-α-lipoic acid.

Section A

R(+)-α-lipoic acid from α-D-glucose

Retrosynthetic analysis (Chart 1.2.1) of R(+)-α-lipoic acid (as revealed by earlier workers for racemic α-lipoic acid) indicated 6S,8-dihydroxy octanoic acid [A] as a key intermediate. The hydroxyl groups at C-6 and C-8 in [A] could be directly correlated with that of C-4 and C-6 of D-glucose. The absolute configuration at C_6 of [A] and its correlation with C-4 of D-glucose can be easily visualised by deoxygenation at C-2, C-3 and C-5 of D-glucose and subsequent two carbon homologation to result in the required eight-carbon dihydroxy octanoic acid [A] with the right stereochemistry at the lone chiral center.

This section deals with the first direct enantio-specific synthesis for R(+)-α-lipoic acid from D-glucose in a highly efficient synthetic sequence.

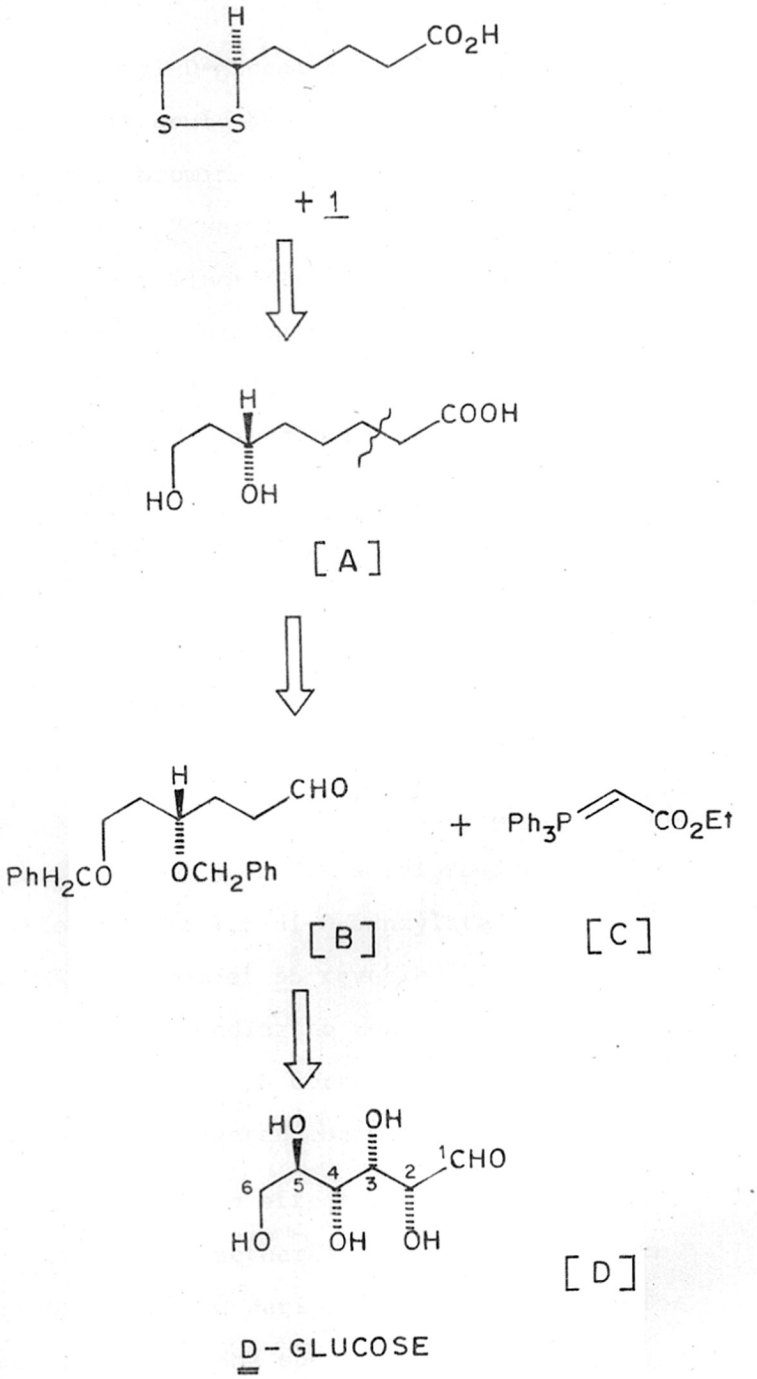
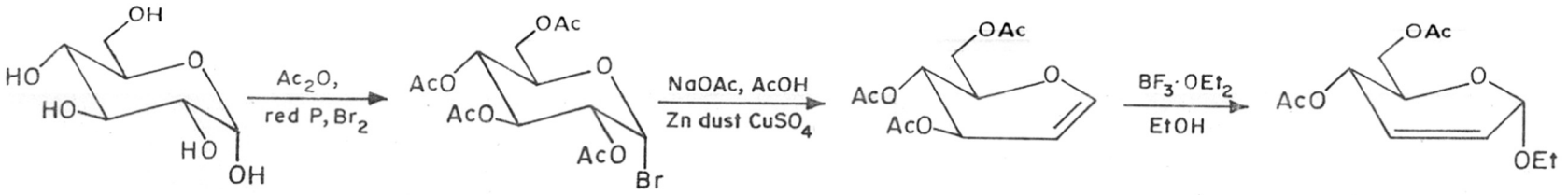

H
CO2H
S—S
+ 1
COOH
HO
OH
[A]
CHO
PhH2CO
OCH2Ph
+
Ph3P
CO2Et
[B]
[C]
HO
OH
1CHO
6
5
4
3
2
HO
OH
OH
[D]
D-GLUCOSE

CHART 1·2·1

3,4,6-Tri-O-acetyl-D-glucal 52[22] was chosen as a starting material as it could be directly derived from D-glucose by acetylation bromination and elimination all in one pot (Chart 1.2.2). 52 was treated with ethanol in the presence of boron-trifluorideetherate according to the procedure reported by Ferrier et al.[23] to afford the crystalline ethyl 4,6-di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-eno-pyranoside 53. Reduction of 53 over freshly prepared W-2 Raney nickel in ethyl acetate at 45 p.s.i. for 8 hr gave the 2,3-dideoxy compound 54 in 93% yield. The ^{1}H-NMR of 54 was in agreement with the assigned structure.

The compound 54 was then subjected to Zémplen de-acetylation in the presence of methanolic sodium ethoxide followed by deionisation with Amberlite-IR-120 (H^+) resin to give the diol 55[24] in almost quantitative yield. Treatment of the diol 55 with sodium hydride-benzylbromide under nitrogen then afforded the 4,6-di-O-benzylate 56 in 89% yield. The ^{1}H-NMR spectrum of 56 revealed two sets of AB quartets at δ 4.50 corresponding to two benzylic methylenes while a broad singlet at δ 4.76 corresponded to H-1. Other protons appeared at the expected chemical shifts (Fig.1.3.1).

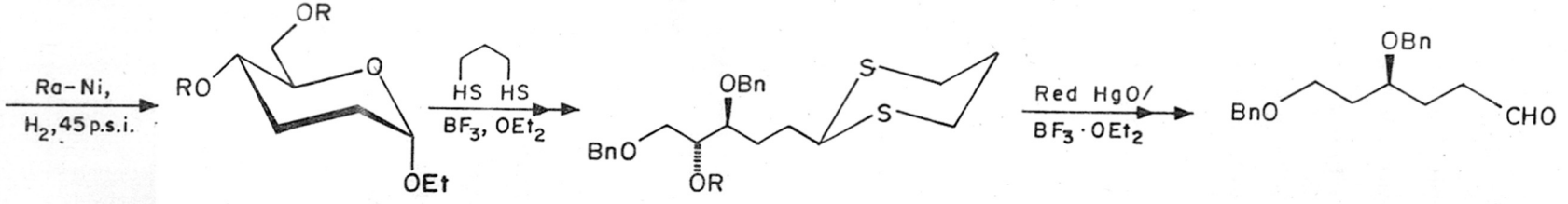
Ring opening of 56 was effected with propane-1,3-dithiol and borontrifluorideetherate at room temperature to give rise to the dithiane derivative in 80% yield. The salient features of its ^{1}H-NMR spectrum are as follows; a



D-GLUCOSE

52

53



54, R = Ac

$NaOCH_3$, MeOH

55, R = H

NaH, BnBr

56, R = Bn

57, R = H

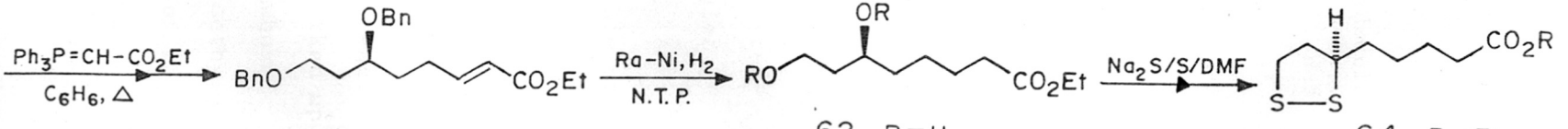
NaH, CS_2, MeI

58, $R = C(=S)-SMe$

nBu_3SnH

59, OR = H

60



61

62, R = H

Ms Cl, Et_3N

63, R = Ms

64, R = Et

0·1M KOH

+ 1, R = H

CHART - 1.2.2.

bunch of multiplets corresponding to methylenes at C-5, C-1' and C-2' were localised around δ2 whereas a quadruplet for methylenes at C-4 and C-6 appeared at δ 2.80. H-4, H-5 and H-5' appeared as multiplets around δ3.5 , H-2 and H-3' appeared as a complex multiplet at δ3.9 , and the two benzylic methylenes appeared as two singlets at δ 4.48 and δ 4.51. These NMR values clearly demonstrated the structure assigned for the compound 57.

The deoxygenation at C-4' of 57 was carried out by using the procedure developed by Barton and McCombie[25]. For instance, 57 was successively treated with sodium hydride, carbon disulfide and methyl iodide in tetrahydrofuran under nitrogen to afford the xanthate derivative 58 in 85% yield. In the ^{1}H-NMR spectrum of 58 (Fig.1.3.2) a singlet corresponding to S-methyl was observed at δ 2.56. A multiplet for H-4' was located in a downfield region of δ 5.95. A downfield shift for H-4' was expected because of deshielding effect due to the methyl dithiocarbonate group present at this center. Other ring protons resonated at the expected chemical shifts. The xanthate 58 was heated under reflux with freshly prepared tri-n-butyltinhydride[26] containing catalytic amount of α,α'-azobisisobutyronitrile in toluene and under nitrogen. After 18 hr, the reaction was worked up and then chromatographed to afford 59 in 96% yield, whose ^{1}H-NMR spectrum (Fig.1.3.3) revealed multiplets for methylene protons at C-5, 1',2',4' at around δ 2.0 and quadruplet for

methylenes at C-4,6 at δ 2.78. The triplet due to CH_2 at C-5' and H-3' proton appeared at δ 3.5 as multiplet. The dithiane proton H-2 appeared as triplet at δ 3.95 whereas benzylic methylenes appeared at δ 4.42 and 4.44 as a singlet and AB quartet.

Hydrolysis of dithiane 59 in the presence of red mercuric oxide and borontrifluoride etherate[27] in aqueous acetone then furnished the aldehyde 60 whose ^{1}H-NMR although complicated, did show a triplet due to aldehydic proton at δ 9.71. The aldehyde 60 was subjected to the Wittig reaction without delay with carbethoxymethylene triphenylphosphorane[28] in refluxing benzene to afford the α,β-unsaturated ester 61 in 80% yield. The ^{1}H-NMR spectrum of 61 was amenable to first order analysis. For example a triplet due to methyl of carbethoxy group was revealed at δ 1.24, multiplets due to the methylenes at around 2.0 ppm, a multiplet at δ 3.5 was assigned to H-6,8,8' protons, a quadruplet for CH_2 of ester function appeared at 4.13 ppm and a singlet due to benzylic methylenes at δ 4.42. The olefinic protons at H-2 indicated two sets of triplets at δ 5.71 with J value of 16 Hz clearly demonstrated the presence of trans double bond. This suggestion was further proved by the appearance of two sets of broad triplets with J value of 16 Hz at δ6.88 for H-3 proton. These NMR values were consistent with the product being ethyl 6,8-dibenzyloxy-2'-octanoate 61 (Fig.1.3.4).

Hydrogenation of 61 over excess of freshly prepared W-2 Raney nickel at normal pressure and temperature for 18 hr gave a saturated diol 62 in 90% yield which was transformed into the dimesylate 63 by the treatment with methanesulfonyl chloride, triethylamine in methylene chloride in almost quantitative yield. In the ^{1}H-NMR spectrum of the dimesylate 63, a singlet integrating for six protons due to two mesyloxy groups appeared at δ 3.00. A triplet corresponding to the methylene at C-8 resonated at δ 4.28 while a multiplet due to H-6 was at δ 4.80. The remaining protons had chemical shifts consistent with the assigned structure (Fig.1.3.5).

The dimesylate 63 was then heated with sodium sulfide nonahydrate[29], sulfur in N-N-dimethylformamide at 90° to afford after 24 hr the 1,2-dithiolane derivative 64 in 70% yield. The structure of 64 was demonstrated by its ^{1}H-NMR spectrum (Fig.1.3.6) in which a triplet due to H-8,8' and a multiplet due to H-6 appeared at δ 3.18 and δ 3.60 respectively. The upfield shift for these protons was expected because of the shielding effect of the sulfur atom. Mass spectrum of 64 revealed the molecular ion peak at m/z 234. All these evidences prove the structure of the dithiolane system 64.

Hydrolysis of the ester function in 64 was effected with 0.1M potassium hydroxide under nitrogen to afford R(+)-α-lipoic acid 1 together with the unhydrolysed ethyl

R(+)-α-lipoate 64. The overall yield of 1 based on recovered 64 was 75%. The specific rotation observed for 1 was $[\alpha]_D$ +95° (C_6H_6), Lit.[30] $[\alpha]_D$ +91°, +102°[21] (C_6H_6). The ^{1}H-NMR spectrum of 1 (Fig.1.3.7) revealed a triplet due to H-8,8' at 3.10 ppm and a multiplet for H-6 at δ 3.53, other protons resonating in the region of 1.3 to 2.8 ppm. Further proof for (+) 1 was gleaned from the mass spectrum which indicated the molecular ion peak at m/z 206.

Section B

Asymmetric synthesis of R(+)-α-lipoic acid involving Sharpless asymmetric epoxidation

We envisaged the possibility of using propargyl alcohol as the starting material on the basis of retro-synthetic fragmentation of lipoic acid.

It has been established by earlier synthesis that the key intermediate fragment is the 1,3-dihydroxy acid [A]. [A] can be visualised as being obtained by the selective reduction of an eight-carbon epoxy alcohol moiety [B] which suggests that the trans-allylic alcohol [C] could be a convenient precursor. [C], an eight carbon fragment can be easily obtained by alkylation of a five-carbon unit with propargyl alcohol (Chart 1.2.3). For this purpose, δ-valero-lactone seems to be the starting material of choice due to

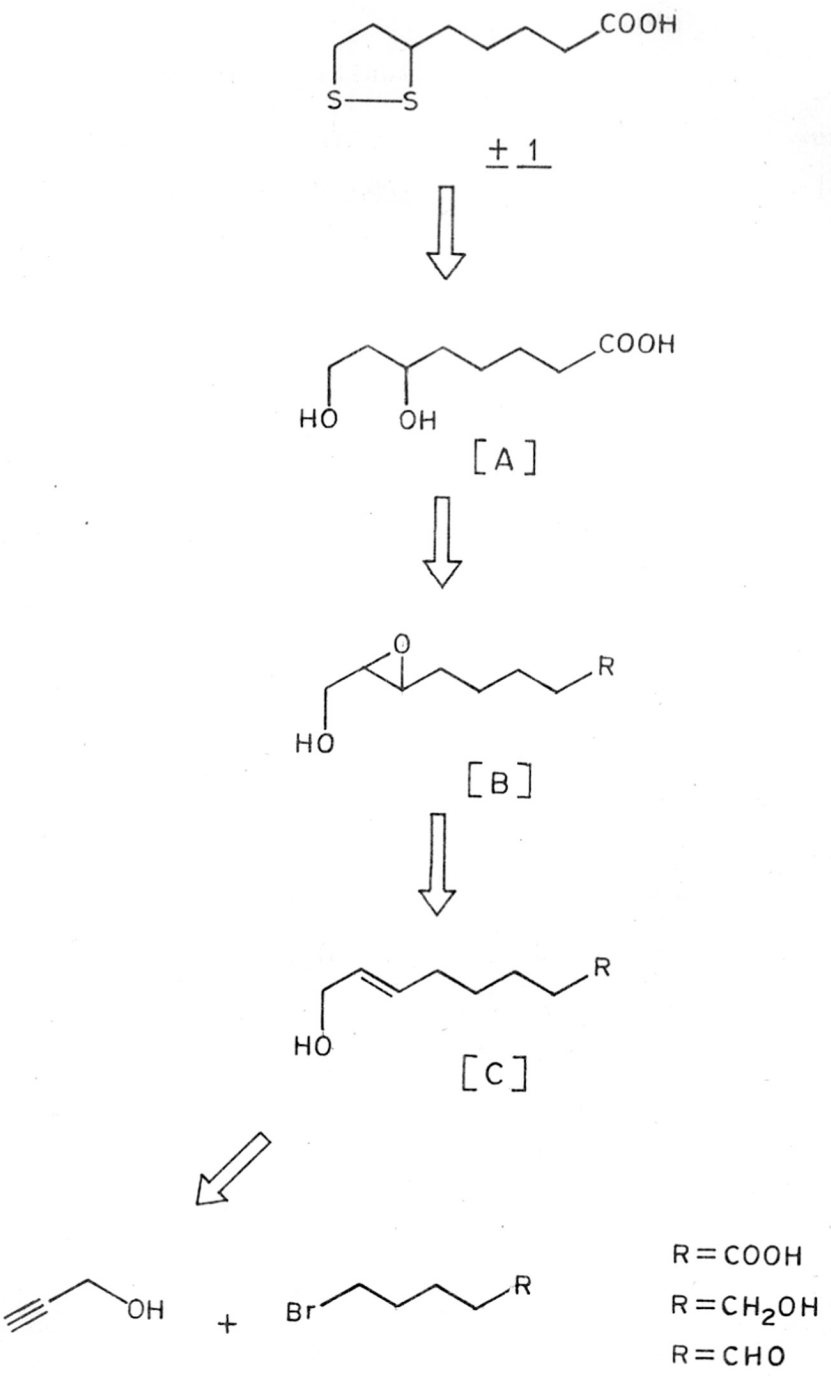


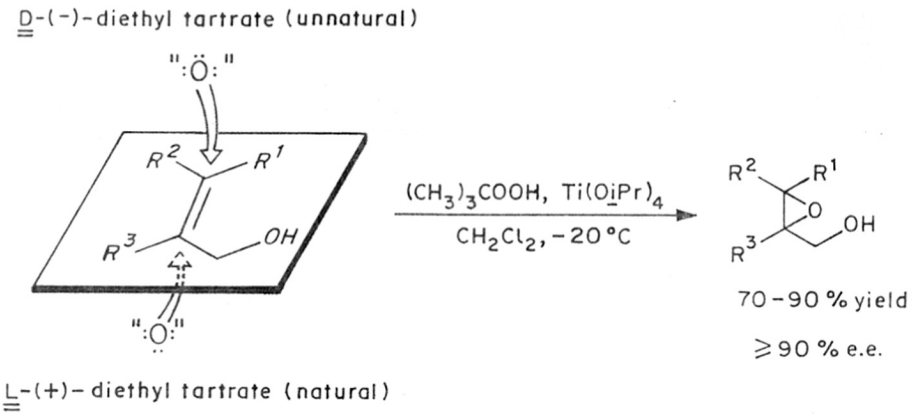
CHART 1·2·3

its ready and easy availability.

The precursor [C], being an allylic alcohol would be eminently suitable as a Sharpless substrate for epoxidation. Moreover, the optically active α,β-epoxy alcohol could be regio-selectively reduced to the 1,3-diol system [A] by the use of 'Red-Al'[31].

As per Sharpless rules[32], (+)diisopropyltartarate is supposed to give the correct configuration at C-6 of the α,β-epoxy alcohol [B] which would then lead to the R(+)-α-lipoic acid. Sharpless et al.[32] discovered a new metal catalyzed asymmetric epoxidation process which was far more selective than any of the previous known methods. The simplicity of the method is evident from the ready commercial availability of the requisite reagents at low costs. This chiral epoxidation system possesses two striking features: (a) It gives uniformly high asymmetric inductions throughout a range of substitution patterns (b) Upon use of a given tartarate enantiomer, the system seems obliged to deliver the epoxide oxygen from the same enantioface of the olefin regardless of the substitution pattern. This characteristic is highlighted in scheme below. When the olefinic unit is in the plane of the drawing with the hydroxymethyl substituent at the lower right side, the use of (+)-diethyltartarate leads to addition of epoxide oxygen from the bottom. Similarly when (-) diethyltartarate is employed,

the epoxide oxygen is added from the top.



Red-Al, [Na AlH_2 $(OCH_2CH_2OCH_3)_2$] is an effective reducing agent for the regioselective ring opening of α,β-epoxyalcohols to 1,3-diol systems[31a]. The primary factor controlling this remarkable regioselectivity seems to be the hydroxy group of the epoxy alcohol system. A mechanistic explanation for the above observation seems to be that 'Red-Al' initially complexes with the alcoholic group, followed by intramolecular hydride reduction to afford the 1,3-diol system. In the case of DIBAL, initial complexation of the alcohol with the reducing agent takes place and the aluminium in the complex serves as a Lewis acid to facilitate intermolecular hydride reduction. Thus, coupled with Sharpless asymmetric epoxidation, the 'Red-Al' reduction provides a methodology to synthesise 1,3-poly-hydroxylated systems which are the backbone of important natural products including polyene macrolide antibiotics[31b].

Accordingly, 5-bromopentanoic acid (65) was prepared from δ-valerolactone (Chart 1.2.4) by treatment with hydrogen bromide following the known procedure[33]. The alkylation[34] of propargyl alcohol with the bromo acid 65 was carried out in the presence of lithium in liquid ammonia to furnish the corresponding acetylenic derivative 66 (Fig. 1.3.8). The carboxylic group was protected as an oxazoline[35] group 67 (Fig.1.3.9) and then subjected to reduction over lithium aluminium hydride to afford the trans olefin 68.

Before trying the asymmetric epoxidation, model experiments were undertaken making use of m-chloroperbenzoic acid as the oxidant. Hence compound 68 with one equivalent of m-chloroperbenzoic acid gave a new product whose ^{1}H-NMR spectrum indicated olefinic protons which suggested that the required compound was not formed. There are reports in the literature[36] that the nitrogen of the oxazoline group undergoes N-oxide formation with m-chloroperbenzoic acid and therefore the structure 69 (Chart 1.2.4) was assigned. Due to the failure in epoxidising the olefin with one equivalent of m-CpBA, excess of m-CpBA was obviously necessary for the formation of N-oxide epoxy derivative 70. At this moment, it was realised that reduction of the epoxide with 'Red-Al' would lead to the N-hydroxy derivative 71 whose hydrolysis could lead to an aldehyde instead of the required acid.

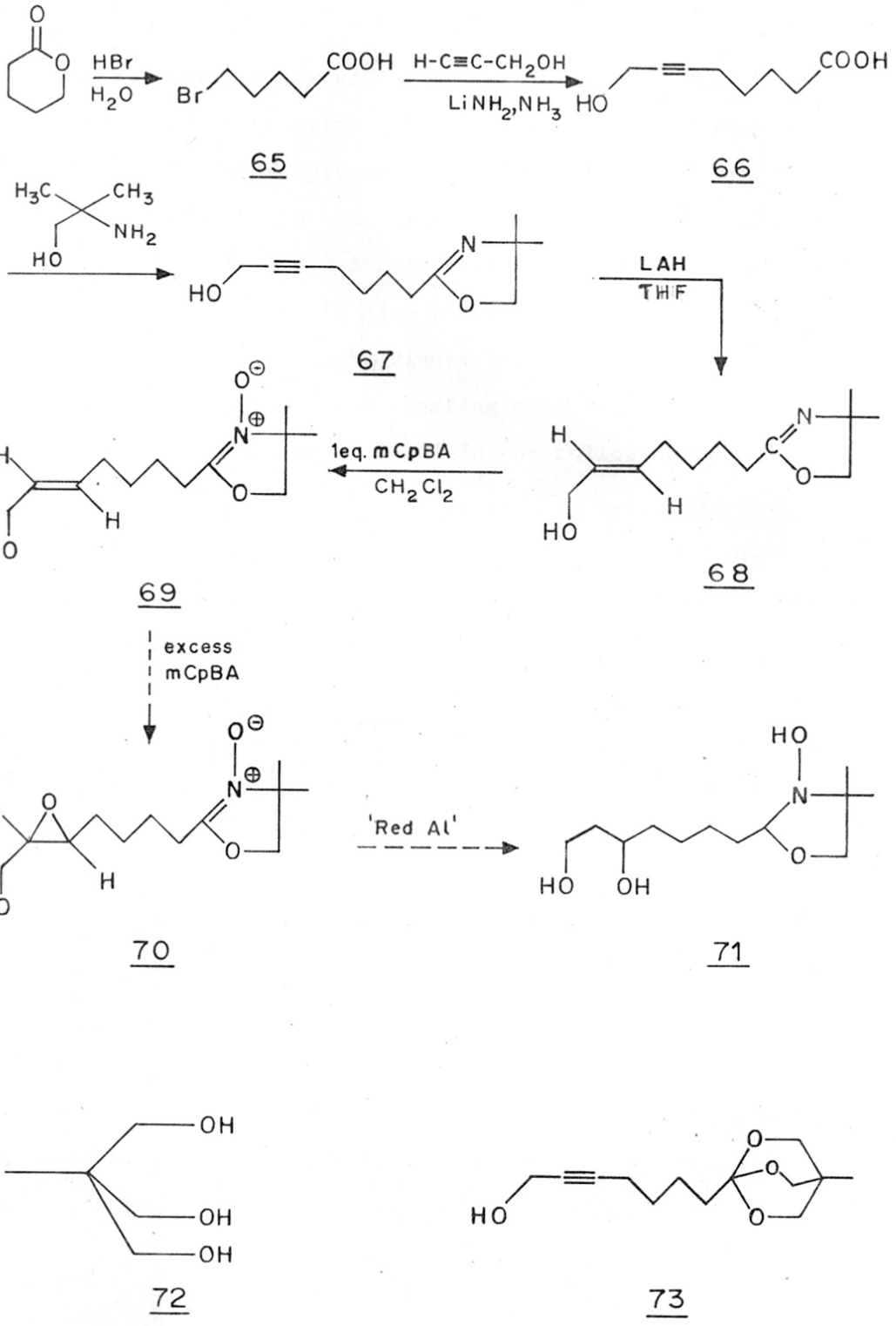

HBr
H2O
COOH
Br
H-C≡C-CH2OH
LiNH2,NH3
HO
COOH
65
66
H3C
CH3
NH2
HO
HO
N
O
67
LAH
THF
1eq. mCpBA
CH2Cl2
H
HO
H
68
69
excess
mCpBA
'Red Al'
HO
OH
70
71
OH
OH
OH
72
HO
O
O
O
73

CHART 1·2·4

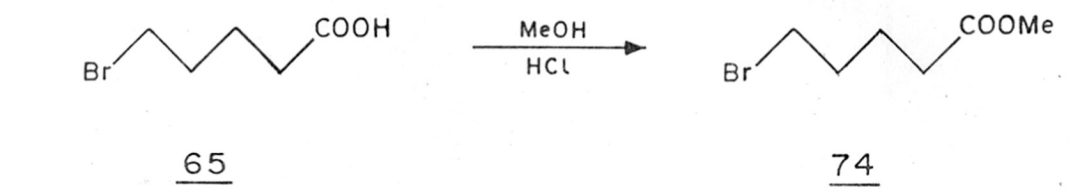
An alternate way would be the protection of the acid as the orthoester grouping. The triol, tris-trimethylol-ethane 72 was therefore prepared according to the known Cannizaro reaction[37], but the condensation of the acid 66 with the triol 72 failed. As an alternate way of obtaining the orthoester 73, we would have to start with a nitrile corresponding to 66 and apply Pinner reaction. However, instead of changing the basic starting material i.e. 5-bromo-pentanoic acid, it was made use of in the following manner.

Hence, based on the above experience, it was decided to execute the scheme with 5-bromopentanol 75 so that the primary alcohol present in 75 could be oxidised to the carboxylic acid at the end of the sequence and it could also be protected by a simple tetrahydropyranylation during the synthetic sequence. Alternatively, the bromopentanol could be oxidised to the aldehyde 76 and protected as the ethylene ketal 77 and used for alkylation with propargyl alcohol. It is pertinent to mention at this stage, that bromoketal[38] 77 (Chart 1.2.5) prepared in three steps from the methyl-bromopentanoate 74 was first subjected to alkylation with propargyl alcohol in the presence of lithium amide. Under standard conditions, a poor yield of the acetylenic product was realized but on optimisation of the reaction conditions, the yield of 79 (Fig.1.3.10) could be raised upto 50%. However, when the alkylation was performed with the tetrahydro-

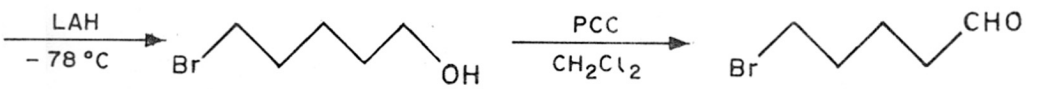
pyranylated derivative of 75, namely 78, an 80% yield of the acetylenic derivative 80 was obtained. Since the bromopentanol derivative 78 was a better alkylating agent, the synthetic sequence was modified as shown in the same scheme (Chart 1.2.5).

The bromopentanoic acid was esterified to 74 and then reduced to the corresponding alcohol 75 with LAH at -78°C[39] in 91% yield. The free alcohol 75 was protected as the THP derivative 78 and subsequently subjected to the alkylation reaction to realize 80 in 80% yield. The ^{1}H-NMR spectrum of 80 (Fig.1.3.11) indicated methylenes between δ 1.4 - 2.5 and a broad singlet due to OH group at δ 2.7. The methylenes adjacent to oxygen were observed as multiplets between δ 3.3 - 4 whereas the C_1-methylene, next to the acetylenic group was revealed as a triplet at δ 4.28. The appearance of a triplet for methylene at C-1 was due to the homoallylic coupling with methylene at C-4. The THP methine proton was seen as a broad singlet at δ 4.67.

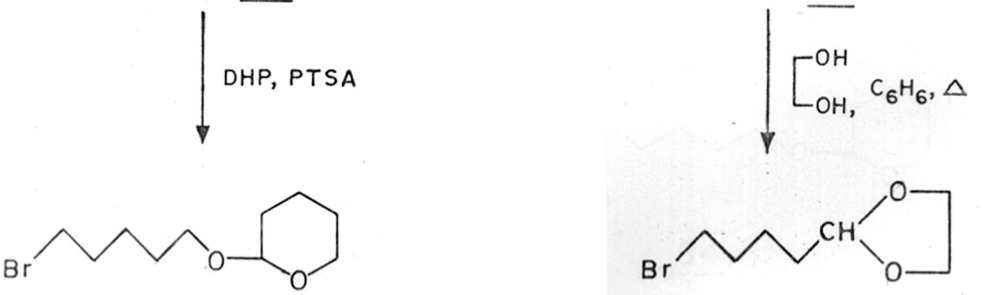
The compound 80 was reduced with LAH to afford the allylic alcohol 81[40] in 85% yield whose ^{1}H-NMR spectrum (Fig.1.3.12) revealed olefinic protons at δ 6.02 while remaining protons had chemical shifts comparable to 80. The structure of 81 was further substantiated by the molecular ion peak at m/z 228 in the mass spectrum. Treatment of the olefin with m-chloroperbenzoic acid gave a compound 82 in



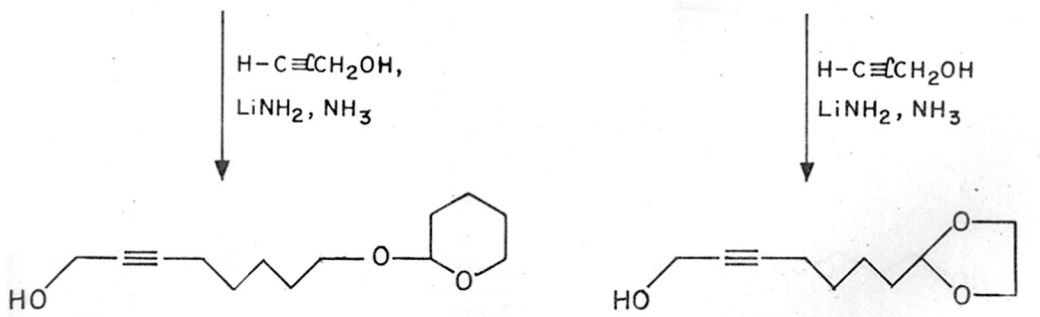
65 74



75 76



78 77



80 79

CHART 1·2·5 CONTD.

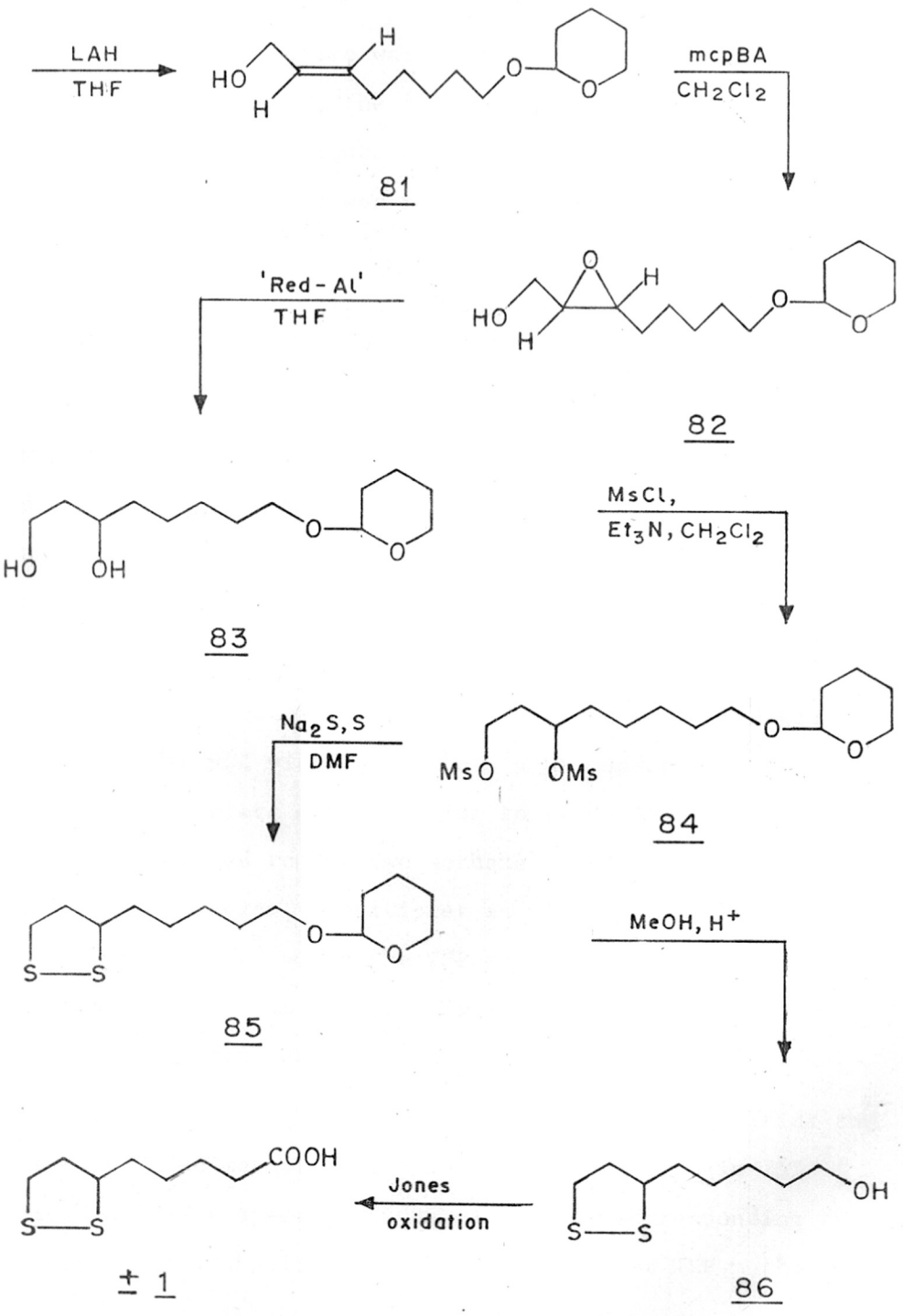

LAH
THF
HO
H
H
O
O
81
mcpBA
CH_2Cl_2
'Red-Al'
THF
O
H
HO
H
O
O
82
HO
OH
O
O
83
MsCl,
Et_3N, CH_2Cl_2
MsO
OMs
O
O
84
Na_2S, S
DMF
S—S
O
O
85
MeOH, H^+
COOH
S—S
Jones
oxidation
OH
S—S
± 1
86

CHART 1·2·5

80% yield whose structure was demonstrated by the ^{1}H-NMR spectrum. For example, the loss of olefinic protons and in addition, the appearance of multiplets for epoxy proton on C-2 and C-3 at δ 2.85 was observed (Fig.1.3.13).

Reduction of the epoxide with 'Red-Al' at -15°C for 5 hr gave the 1,3-diol 83 in 90% yield. It is well established that allylic epoxy alcohols undergo reduction with 'Red-Al'[31a] to give exclusively the 1,3-dihydroxy compounds in contrast to what is expected by a 'DIBAL' reduction of α,β epoxy alcohol[31a] which would give 1,2-diols. Based on this, the structure 83 was assigned as 8-tetrahydropyranyloxy-1,3,8-trihydroxyoctane[41].

The 1,3-dihydroxy compound 83 was mesylated with methane sulfonyl chloride and triethylamine to afford the mesylate 84 in 90% yield, in whose ^{1}H-NMR spectrum (Fig. 1.3.14) two singlets corresponding to six protons were located at δ 2.97 assigned to the two methane-sulfonyl groups. In the downfield region, a multiplet at δ 4.27 was seen which was assigned to H-3 while the THP methine proton was located as a broad singlet at δ 4.47. Mass spectrum also revealed the structure assigned.

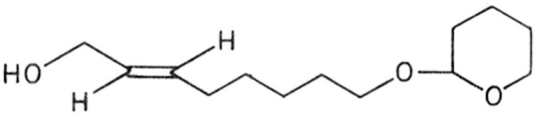
Treatment of the dimesylate 84 with sodium sulfide and sulfur in N,N-dimethylformamide[29] at 100° gave 85 in 75% yield. In ^{1}H-NMR spectrum of 85, a triplet corresponding to C-8 methylene at δ 3.13 and a broad singlet for THP methine

proton at δ 4.53 were observed. Other protons could not be defined because of second order splittings (Fig.1.3.15). However, mass spectrum revealed molecular ion peak at m/z 276. Methanolysis of 85 with Amberlite IR-120 (H^+) resin afforded the alcohol 86 whose ^{1}H-NMR spectrum (Fig.1.3.16) clearly suggested the assigned structure because a triplet for methylene at C-8 was visible at δ 3.17 and in addition, a triplet due to methylene at C-1 was located at δ 3.67. Also, a multiplet for H-6 at δ 3.54 which merged with the triplet at C-7 was observed. The mass spectrum also proved the structure of the molecule shown as 86.

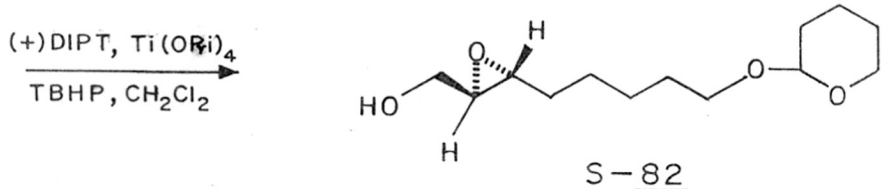
Jones oxidation[42] of the alcohol 86 afforded (±)-α-lipoic acid whose ^{1}H-NMR spectrum was identical with the spectrum of the compound prepared earlier from D-glucose (Chart 1.2.2).

For the generation of the asymmetric diol 83, the above reaction sequence was studied using Sharpless reagent for epoxidation of 81 instead of m-chloroperbenzoic acid. As per Sharpless rules, (+) diisopropyltartarate is supposed to give the correct configuration at C-6 of the epoxy alcohol 82 which would lead to R(+)-α-lipoic acid (Chart 1.2.6).

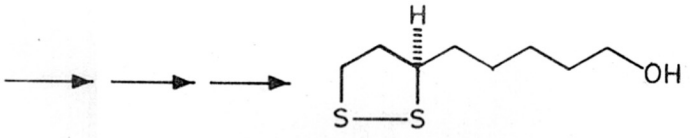
Accordingly, the allylic alcohol 81 in dry dichloromethane was added to the complex of titanium isopropoxide and (+)-diisopropyltartarate followed by oxidation of tert-butylhydroperoxide at -23°C. The reaction was stirred at -15°C



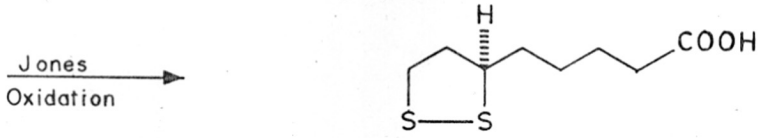
81



S-82



R-86



R(+)1

CHART 1·2·6

and followed by TLC. It was found to be very slow and after 72 hr, the product (S)-82 was isolated by chromatography in 65% yield (based on the recovered olefin) (Chart 1.2.6).

The epoxy derivative, (S)-82 was detetrahydropyranylated in methanol using Amberlite IR-120 (H^+) resin to afford the optically active 2,3 epoxy, 1,8-octane diol in 80% yield, which shows $[\alpha]_D$ -4.3° ($CHCl_3$).

The epoxide S-82 was subjected to the same set of reactions as the racemic one to obtain the 1,2-dithiolane-3-pentanol, (R)-86. The $[\alpha]_D$ of this alcohol was found to be -12.5° ($CHCl_3$). Jones oxidation of this alcohol led to the title compound, R(+)-1.

Section C

1,2R,4-Butanetriol as chiral synthon for R(+)-α-lipoic acid

(i) From Tartaric Acid

Natural (R,R)-tartaric acid[43] has been recognized as a cheap, versatile and useful chiral building block for a number of natural product syntheses. As a matter of fact, with tartaric acid as starting material, the synthetic chemists have a choice of synthesizing the chiral target structure as also its enantiomer because both (R,R) and (S,S) tartaric acids are readily available.

Retrosynthetic analysis of R(+)-α-lipoic acid as reported earlier reveals the key fragment [A], (Chart 1.2.7), namely the [S]-6,8-dihydroxyoctanoic acid. [A] in turn can be visualised as being obtained by four-carbon homologation of the aldehyde [B] via a Wittig reaction. [B] could be obtained from R(+)-1,2,4 butane triol - a key fragment in this synthesis, which in turn could be realized from (R,R)-tartaric acid.

Diethyl (R,R)-(+)-tartarate (Chart 1.2.8) was converted into the benzylidene derivative 87 by treatment with $\alpha\alpha$-dimethoxytoluene in refluxing dry acetonitrile containing traces of toluene-p-sulfonic acid. After 8 hr, the product was distilled as an oil which immediately crystallised. The physical and spectroscopic data of 87 were identical with the reported values[44].

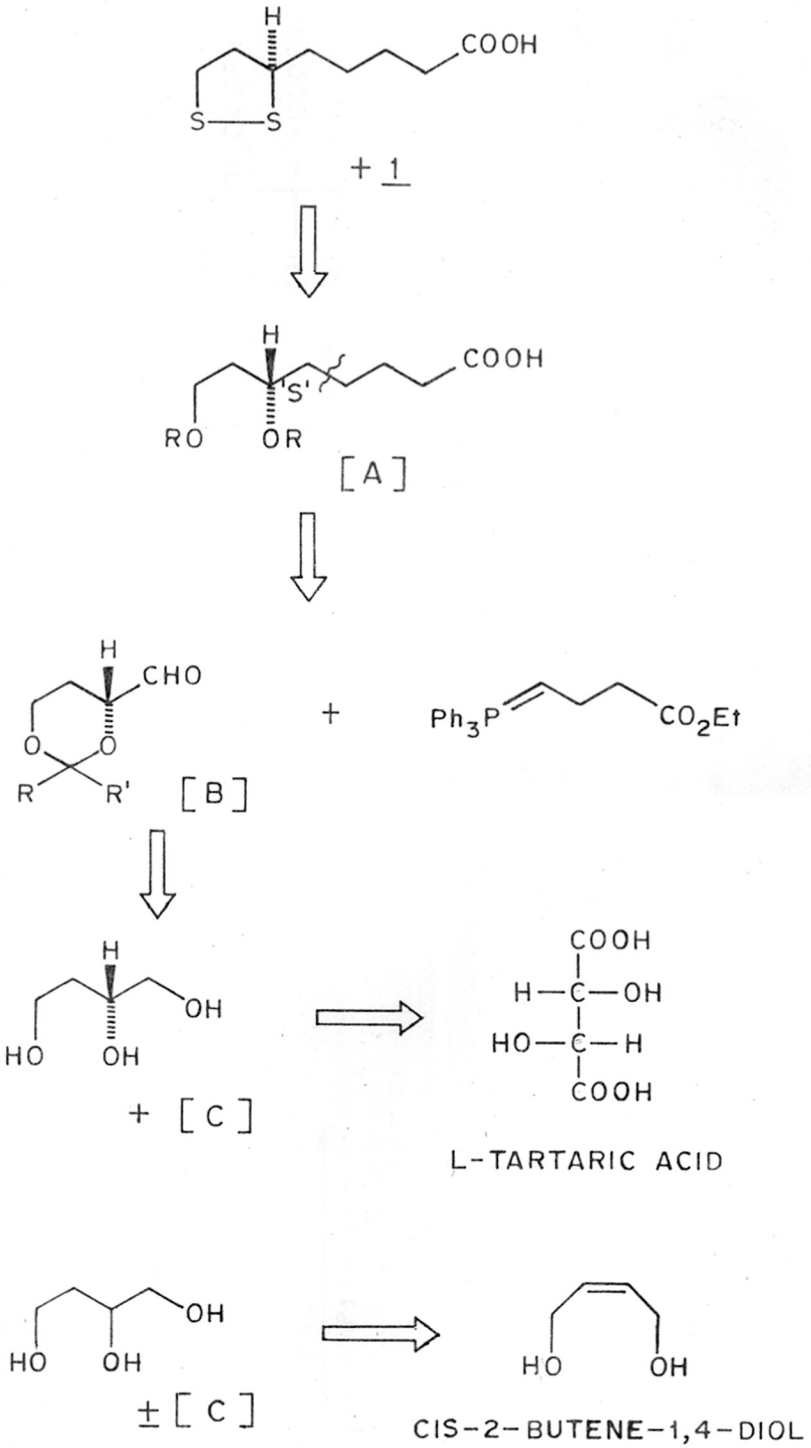

H
COOH
S—S
+ 1
H
COOH
S'
RO
OR
[A]
H
CHO
O
O
R
R'
[B]
+
Ph3P
CO2Et
H
OH
HO
OH
+ [C]
COOH
H—C—OH
HO—C—H
COOH
L-TARTARIC ACID
OH
HO
OH
± [C]
HO
OH
CIS-2-BUTENE-1,4-DIOL

CHART 1·2·7

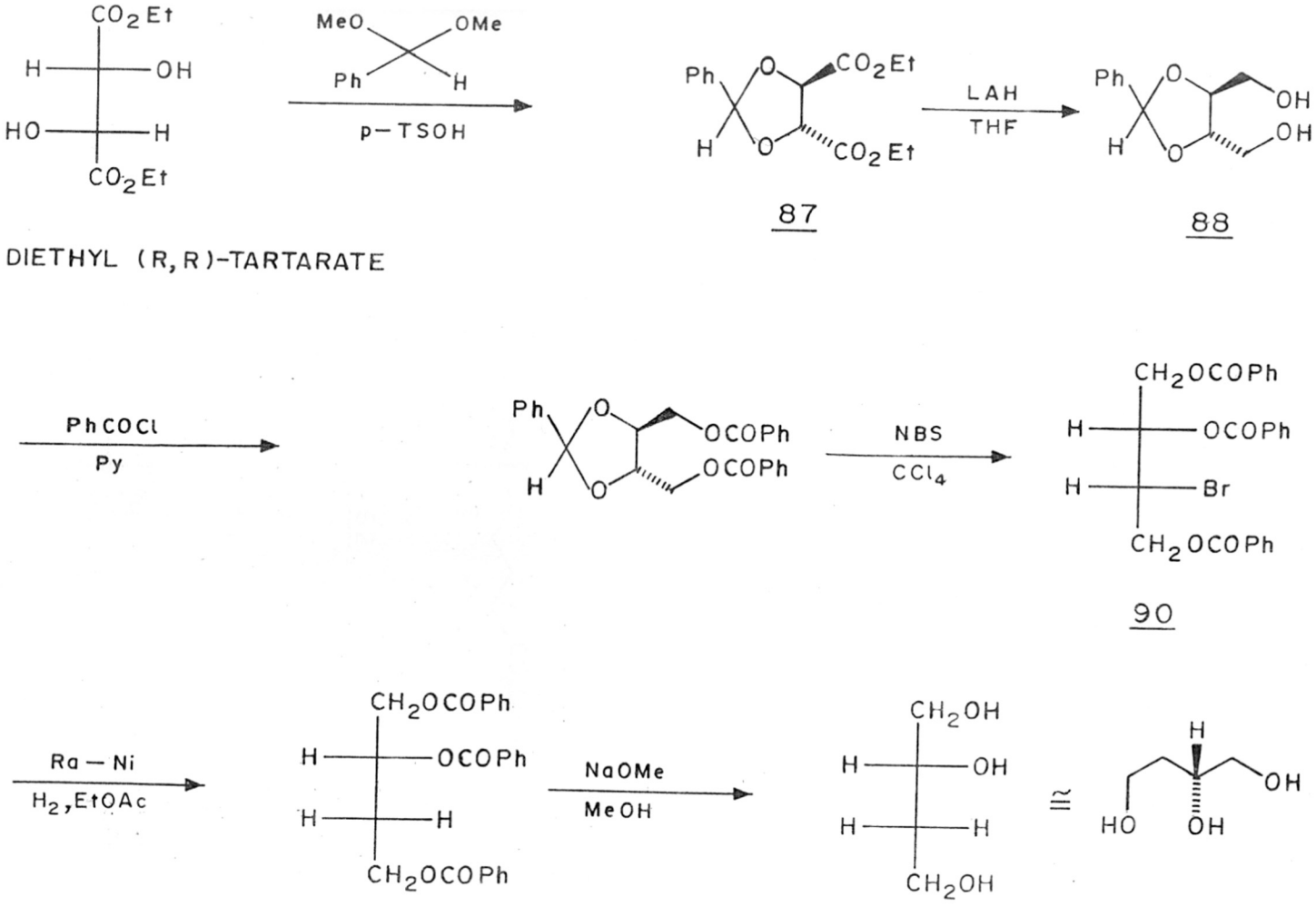
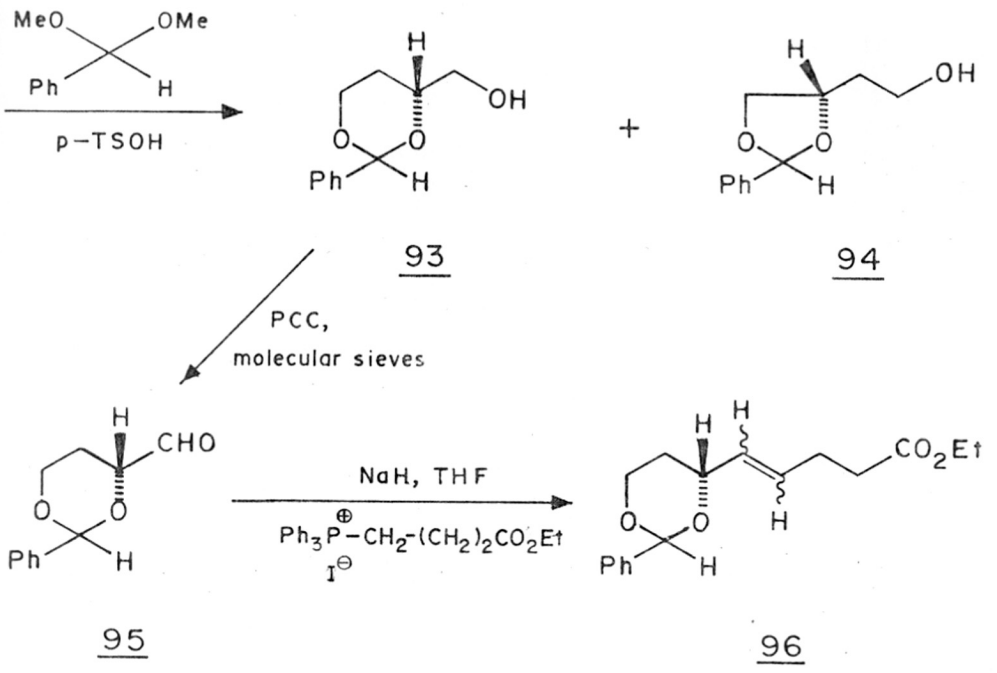
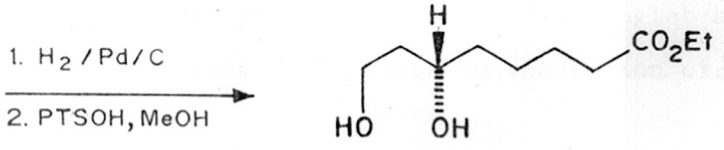
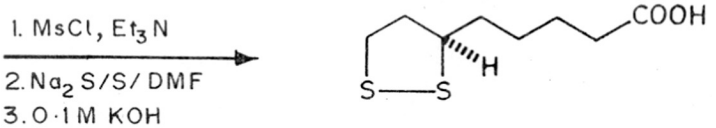


CHART 1·2·8 CONTD.





62



+ 1

CHART 1·2·8

Reduction of 87 with lithium aluminium hydride in dry tetrahydrofuran for 6 hr afforded the diol 88 in 85% yield. The loss of absorption due to the carbethoxy signal in the IR spectrum clearly indicated the reduction had occurred which was further substantiated by the presence of hydroxyl absorption. In addition, physical data also coincided with the reported values[44].

The hydroxyls of 88 were converted into their O-benzoates 89 by treatment with benzoyl chloride in pyridine in 90% yield. Its IR spectrum revealed absorption around 1730 cm^{-1} which corresponded with the absorption of the benzoates; loss of absorption due to hydroxyl groups was clearly visible. The ^{1}H-NMR spectrum of 89 revealed a broad singlet corresponding to the six protons present in the molecule at δ 4.45, whereas the benzylidene proton resonated as a singlet at δ 5.98 and aromatic protons appeared in the region of δ7-8 (Fig. 1.3.17).

Treatment of 89 with N-bromo succinimide in refluxing carbon tetrachloride opened the 1,3-dioxolane ring to afford the bromide 90 whose ^{1}H-NMR spectrum (Fig.1.3.18) revealed a multiplet for the methine proton at C-2 adjacent to bromine at δ3.81. The methine proton at C-3 came at a downfield region as a multiplet at δ 5.81 and the C-1 and C-4 methylenes were bunched as a multiplet around δ4.7. The aromatic protons resonated at expected chemical shift.

The bromobenzoate 90 was reductively debrominated in the presence of excess of W-2 Raney nickel at 45 p.s.i. for 5 hours to afford the tribenzoate 91 (Fig.1.3.19) which was subjected to Zémplen debenzoylation[24] using sodium methoxide to afford the [R]-1,2,4-butanetriol, 92 whose ^{1}H-NMR spectrum was scanned in deuterated acetone and was in agreement with the assigned structure. Moreover the b.p. and other physical data matched with the reported values[45].

An alternate way from tartaric acid to malic acid, which would lead to the same triol, was reported earlier by a longer reaction sequence[46].

The triol 92 was treated with α,α-dimethoxytoluene in refluxing acetonitrile in the presence of toluene-p-sulfonic acid to afford two products as judged by TLC. The major product 93 isolated after chromatography was revealed as the 1,3-benzylidene derivative, whereas the other product was the 1,2-benzylidene derivative in a ratio of 9:1 respectively. The R_f value of the 2R-phenyl-4R-hydroxymethyl-1,3-dioxane 93 was lower than that of the isomeric 1,3-dioxolane 94.

Identity of 93 as the 1,3-isomer was deduced by a comparative study of the ^{1}H-NMR splitting pattern between 1-2 δ for the methylenes (C-3 of 93 and C-2 of 94). 93 (Fig.1.3.20) had a multiplet ranging from 1.2 to 2.2 δ which

was identical with the reported spectrum of 93 as its tosylate[47] or as the mesylate prepared by us (Fig.1.3.21). Also the corresponding methylenes of 94 appearing as a multiplet around 1.5 δ (Fig.1.3.22) were identical with those of the corresponding acetonide[48].

The oxidation of the 1,3-benzylidene derivative 93 was attempted with several reagents such as PDC, PCC/NaOAc/Celite, DMS/NCS, $RuCl_3/NaIO_4$, but in all the cases, the corresponding aldehyde 95 was either obtained in negligible amounts or no reaction was observed. However, with PCC in the presence of molecular sieves[49], the alcohol 93 afforded the required aldehyde, albeit in poor yields (20%). The aldehyde 95 showed an IR signal of carbonyl at 1725 cm^{-1} and was immediately subjected to Wittig olefination with carbethoxypropyltriphenylphosphorane[50] in the presence of sodium hydride in tetrahydrofuran. The product 96 was obtained in very low yield after chromatographic purification. Its ^{1}H-NMR spectrum (Fig.1.3.23) was complicated because of cis and trans mixture which was of no consequence because the product was reduced to afford a saturated derivative whose acid-catalysed methanolysis followed by purification with chromatography gave the required diol, ethyl[S]-6,8-dihydroxy octanoate 62 (Fig.1.3.24). The comparison of this diol with that prepared earlier indicated that both are

identical. The diol had earlier been transformed into R(+)-α-lipoic acid (Chart 1.2.2).

Although the above account showed the synthesis of 1,2R,4 butanetriol 92 and its potential use for the synthesis of the key intermediate Ethyl[S]-6,8-di-hydroxy-octanoate 62 for R(+)-α-lipoic acid, the oxidation and Wittig sequence was vitiated by poor yields. A suitable oxidation method for better yields of the aldehyde 95 would constitute an efficient entry into the lipoic acid eight carbon skeleton from tartaric acid. In fact, such a method for oxidation was reported very recently[51], where the benzylidene alcohol 93 was oxidised by sulfurtrioxide-pyridine complex in satisfactory yields.

(ii) 1,2R,4-Butane triol from cis-2-butene-1,4-diol

An alternate approach for 1,2R,4-butanetriol - a useful chiral synthon for R(+)-α-lipoic acid would be starting from easily available and cheap cis-2-butene-1,4-diol. Cis-2-butene-1,4-diol can be easily isomerised to 1-butene-3,4-diol[52] giving a suitable allylic alcohol for Sharpless epoxidation. The α,β-epoxy alcohols are in principle vital precursors[31a] for 1,3-diol systems as shown earlier (Chart 1.2.5). This would constitute an easy access to 1,2R,4-butanetriol from the cheap cis-2-butene-1,4-diol in a short sequence using a chiral reagent.

1-Butene-3,4-diol 97 was obtained by mercuric catalysed rearrangement of cis-2-butene-1,4-diol as reported[52] (Chart 1.2.9) in 35% yield. Selective benzylation of 97 was carried out with 1.2 equivalents of benzyl bromide in refluxing acetone containing excess of potassium carbonate to yield the monobenzylated derivative 98 whose spectroscopic data coincided well with the expected.

Epoxidation of the allylic alcohol 98 with m-chloroperbenzoic acid occurred in 18 hr to afford the epoxide 99 in 75% yield. The ^{1}H-NMR spectrum of 99 showed a doublet for C-4 methylene protons at δ 2.62, a multiplet for C-3 methine proton at δ 2.95 and a multiplet for C-1 and C-2 at δ 3.52. Two singlets for the benzylic and aromatic protons were also seen at the expected chemical shifts (Fig.1.3.25).

Selective ring opening of the epoxide functionality in 99 with 'Red-Al'[31a] gave two products (100, 101) which were treated with α,α-dimethoxypropane in the presence of p-toluenesulfonic acid to afford a mixture of isopropylidene derivatives 1,3 102[54] and 2,3 103[54] in a ratio of 75:25. The regioselectivity of the Red-Al reduction was poorer than seen earlier (Chart 1.2.5) and reported[53] in many other cases possibly because of the fact that the oxirane under question is only a monosubstituted and not 1,2-disubstituted as in other cases.

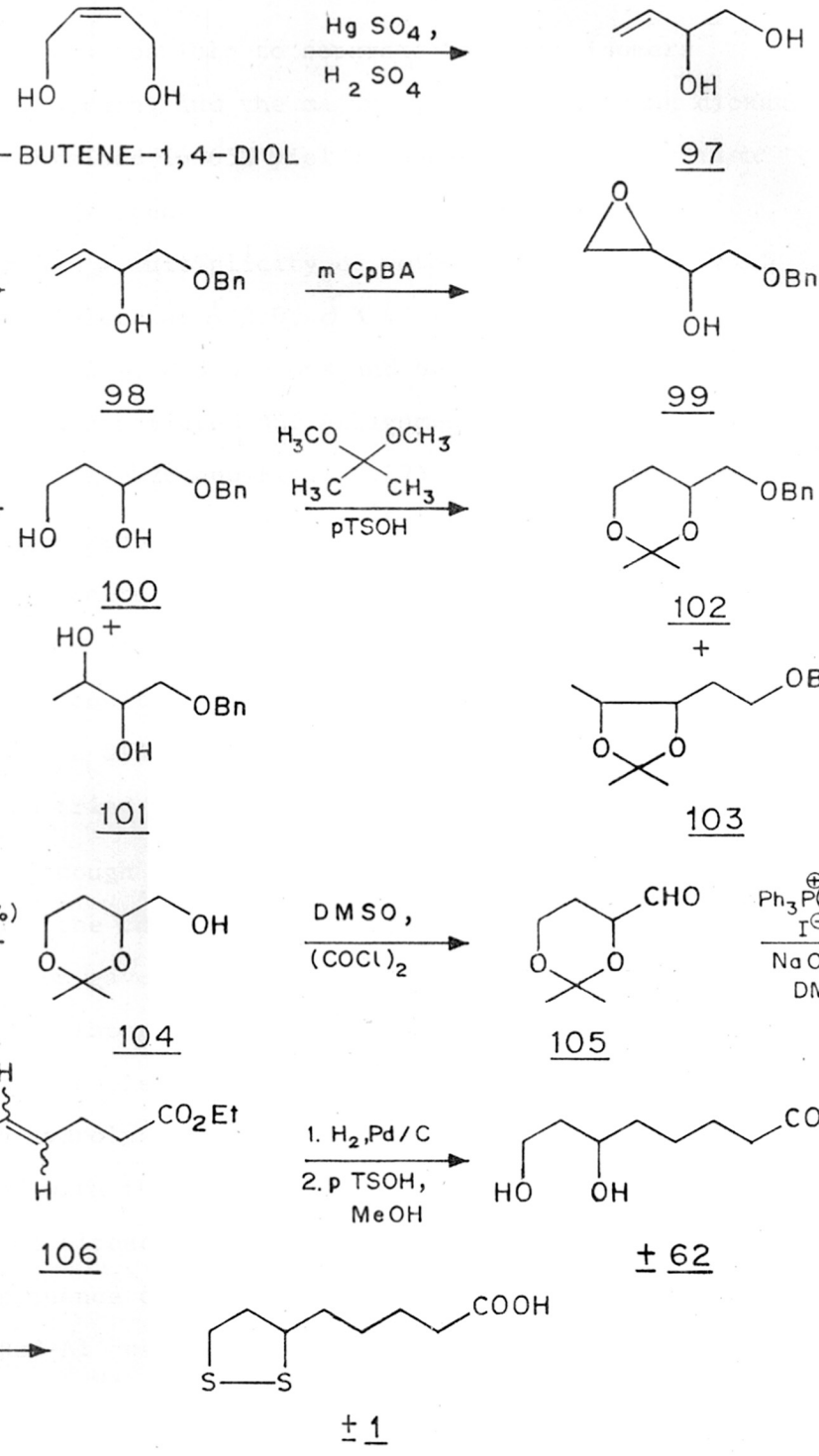

Hg SO4 ,
H2 SO4
CIS-2-BUTENE-1,4-DIOL
97
NaH ,
BnBr,THF
m CpBA
98
99
'Red-Al'
pTSOH
100
102
+
101
103
102
Pd/C (10%)
H2
DMSO,
(COCl)2
Ph3P(CH2)3CO2Et
I
NaOEt,
DMF
104
105
106
1. H2,Pd/C
2. p TSOH,
MeOH
± 62
± 1

CHART 1·2·9

It was possible to separate both the isomers by chromatography and the major 1,3-isopropylidene dioxane 102 was obtained in 65% yield. Subsequently comparison of the ^{1}H-NMR spectrum of 102 with the minor isomer 103 which showed a multiplicity of methyl signals around δ1.5 , three multiplets at δ 3.0, δ 3.42 and δ 3.82 corresponding to the C-1, C-2, C-3 protons and benzylic methylene at δ 4.48, substantiated our assignment of the major isomer as 102 (Fig.1.3.26 and Fig.1.3.27).

Hydrogenolysis of benzyl group in 102 using 10% palladised charcoal at normal pressure and temperature afforded the alcohol 104[55]. Oxidation of 104 under Swern's[56] condition using DMSO-oxalyl chloride combination afforded the aldehyde 105 in very low yield. Other reagents were also tried for the same oxidation without better results.

Although the aldehyde 105 showed the requisite IR spectrum, the compound was not pure enough as Wittig olefination gave an extremely poor yield of the α,β-unsaturated ester 106, the reaction thus being of no practical use. However, the olefinic ester was hydrogenated and subjected to mild hydrolysis to the dihydroxyester 62 which was TLC compared with the same ester 62 prepared earlier. The diol ester had already been transformed into lipoic acid. The above sequence of epoxidation with m-CpBA and reduction with 'Red-Al' was planned by first treating 98 with Sharpless

asymmetric reagent. The reaction was found to be too slow for any practical conversion to the asymmetric epoxy alcohol 99.

1.3.0 EXPERIMENTAL

SECTION A: From D-glucose

3,4,6-Tri-O-acetyl-D-glucal (52)

∝ -D-glucose monohydrate (55 g) was added in 1 hr to a stirred mixture of acetic anhydride (200 ml) and perchloric acid (1.2 ml) at 30-40°. 15 g of red phosphorous was then added to it and after the reaction flask was cooled to -10°C, bromine (29 ml) was added dropwise at such a rate as to keep the internal temperature at less than 20°C. Water (15 ml) was added with careful control of temperature over 30 min. and the flask was stoppered and kept for 3 hr at room temperature. It was then filtered and the residue washed with a little glacial acetic acid. The filterate contains tetra-O-acetyl-∝-D-glucopyranosyl bromide.

Meanwhile, to a cooled (-10°C) solution of sodium acetate trihydrate (200 g) in water (290 ml) and glacial acetic acid (200 ml), a solution of Zn dust (110 g) and cupric sulfate pentahydrate (11 g) in water (40 ml) was added. After the blue colour had disappeared, the above solution containing the ∝-D-glucosyl bromide was added over 1 hr at -10°. The reaction mixture was then stirred for 3 hr at 0° and filtered. The residue was washed with 50% acetic acid. Water (500 ml) was added to the filterate which was then repeatedly extracted with chloroform. The chloroform layer was washed with cold water, Na_2CO_3 and cold water, dried ($CaCl_2$), decanted and evaporated under

reduced pressure. The resulting syrup was codistilled with dry benzene (50 ml). Tri-O-acetyl-D-glucal 52 (58 g, 70%) m.p. 54-55° was crystallised from the residual syrup by ether/light petrol. Lit.[22] m.p. 56°C.

Ethyl 4,6-di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (53)

To a stirred solution of 3,4,6-triacetyl-D-glucal 52 (10 g), absolute ethanol (6 ml) and benzene (60 ml) was added borontrifluoride-etherate (2 ml) and the reaction stirred for 8 hr at room temperature. The acidity was neutralized with excess of solid Na_2CO_3, filtered and the residue was washed with absolute ethanol. The crude product obtained on concentration of the organic layer was chromatographed on a silica column (eluant: light petrol, benzene, 1:1) to afford 53 in quantitative yields. m.p. 77-78°; lit.[23] m.p. 78-79°; $[\alpha]_D$ +105° (c 2.0, C_6H_6); lit.[23] $[\alpha]_D$ 107° (C_6H_6).

Ethyl 4,6-di-O-acetyl-2,3-dideoxy-α-D-erythrohexopyranoside (54)

Ethyl 4,6-di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside 53 (7.0 g, 27 mmol) was hydrogenated over freshly prepared W2 Raney nickel (28 g) in ethyl acetate (50 ml) at 45 p.s.i. for 8 hr. The catalyst was filtered through a bed of celite and the filterate concentrated to afford 54 (6.6 g, 93%), $[\alpha]_D$ +120.5° (c 1.2, chloroform), Lit.[57] $[\alpha]_D$ +118° (ethanol). ^{1}H-NMR ($CDCl_3$): δ 1.20 (t, 3H, $OCH_2\underline{CH_3}$), 1.8 (m, 4H, H-2,2', 3,3'), 2.00, 2.03 (2s, 6H, 2X $OCOCH_3$), 3.3-4.2 (m, 5H, H-5,6,6' and $O\underline{CH_2}CH_3$), 4.63 (m, 1H, H-4), 4.80 (bs, 1H, H-1).

Ethyl 4,6-di-O-benzyl-2,3-dideoxy-α-D-erythrohexopyranoside (56)

To the diacetate 54 (10.4 g, 40 mmol) in dry methanol (50 ml) was added sodium (40 mg). After 18 hr, the reaction was deionised with Amberlite IR 120 (H^+) resin, concentrated, and codistilled with benzene to afford the diol 57 (7.0 g, 100%).

To the diol 55 (5 g, 28.4 mmol) in dry tetrahydrofuran (50 ml) under nitrogen was added sodium hydride (50% dispersion, 5 g, 210 mmol) over 1 hr. The solution was cooled and benzyl bromide (7 ml, 58 mmol) was introduced and then left overnight at room temperature. Methanol (5 ml) was carefully added and solution concentrated to afford a residue which was partitioned between ethyl acetate and water. The ethyl acetate layer was dried, concentrated and the residue was chromatographed over a column of silica gel using ethyl acetate-light petroleum (gradient, 1:10, 1:4) to afford the 4,6-dibenzylate 56 (8.9 g, 89%), $[\alpha]_D$ +100.5 (c 0.8, chloroform), ^{1}H-NMR ($CDCl_3$): δ 1.19 (t, 3H, $CH_2\underline{CH_3}$), 1.7 (m, 4H, H-2,2',3,3'), 3-4 (m, 6H, H-4,5,6,6' + $\underline{CH_2}CH_3$), 4.1-4.6 (m, 4H, 2X CH_2Ph), 4.76 (bs, 1H, H-1), 7.21 (d, 10H, 2 Ph) (Fig.1.3.1).

Analysis: Calculated for $C_{22}H_{28}O_4$: C, 74.2; H, 7.9. Found: C, 74.0; H, 7.7%.

2-(3'(S),5'-di-O-benzyl-4'(R)-hydroxypentyl)-1,3-dithiane (57)

To the dibenzyl derivative 56 (5 g, 14 mmol) in dichloromethane (20 ml) was added propane-1,3-dithiol (2 g, 18.5 mmol) and borontrifluorideetherate (2 ml). After 2 hr of

stirring at room temperature, the reaction was neutralised with sodium carbonate. The solution was filtered, concentrated and the residue was chromatographed on silica gel column with ethyl acetate-light petroleum (gradient, 1:10, 1:1) to afford 57 (4.6 g, 80%), $[\alpha]_D$ +8.3° (c 1, chloroform), ^{1}H-NMR ($CDCl_3$): δ 1.4-2.4 (m, 7H, 3X CH_2 at C-1', C-2', C-5 + OH), 2.80 (q, 4H, CH_2 at C-4 and C-6), 3.5 (m, 3H, CH_2 at C-5' + H-4'), 3.9 (m, 2H, H-2, H-3'), 4.48 (s, 2H, CH_2Ph), 4.51 (s, 2H, CH_2Ph), 7.3 (d, 10H, 2X Ph).

Analysis: Calculated for $C_{23}H_{30}O_3S_2$: C, 66.0; H, 7.2; S, 15.3. Found: C, 66.4; H, 7.2; S, 15.1%.

2-(3'(S),5'-Di-O-benzyl-pentyl)-1,3-dithiane (59)

To á stirred solution of 57 (2.5 g, 6 mmol) in dry tetrahydrofuran (30 ml) under nitrogen was added sodium hydride (50% oil dispersion, 1.2 g, 25 mmol). After 1 hr, dry carbon disulfide (2 ml) was added, followed by after 20 min. methyl iodide (2 ml). After stirring for 24 hr at room temperature, methanol (3 ml) was carefully introduced. The reaction was concentrated and the residue was partitioned between chloroform and water. The chloroform layer was dried, concentrated and the resulting residue was chromatographed on a short column of silica gel using ethyl acetate-light petroleum (1:4) as eluant to obtain 58 (2.65 g, 85%), ^{1}H-NMR ($CDCl_3$): δ 1.7-2.4 (m, 6H, 3X CH_2 at C-1', C-2', C-5), 2.56 (s, 3H, SMe), 2.75 (q, 4H, 2X CH_2 at C-4, C-6), 3.8 (m, 4H, CH_2 at C-5, H-2,3'), 4.50 (s,

2H, CH_2Ph), 4.53 (dd, 2H, CH_2Ph), 5.94 (m, 1H, H-4'), 7.25 (d, 10H, 2 Ph) (Fig.1.3.2).

The above xanthate 58 (2.1 g, 4.13 mmol) in dry toluene (30 ml) containing a pinch of α,α'-azabisisobutyronitrile was heated under nitrogen and then freshly prepared tri-n-butyltin hydride[26] (3 ml) was added. After 18 hr of refluxing, the reaction mixture was concentrated and the residue was purified by column chromatography on silica gel using ethyl acetate-light petroleum (gradient, 0:1, 1:9) to afford 59 (1.61 g, 96%), $[\alpha]_D$ +14.5° (c 0.7, chloroform), ^{1}H-NMR ($CDCl_3$): δ 1.6-2.3 (m, 8H, 4X CH_2 at C-1', C-2', C-4' and C-5), 2.78 (q, 4H, 2X CH_2 at C-4, C-6), 3.5 (m, 3H, CH_2 at C-5' + H-3'), 3.95 (t, 1H, H-2), 4.42 (s, 2H, $PhCH_2$), 4.44 (dd, 2H, CH_2Ph), 7.25 (s, 10H, 2 Ph) (Fig.1.3.3).

Analysis: Calculated for $C_{23}H_{30}O_2S_2$: C, 68.7; H, 7.5; S, 15.9. Found: C, 68.1; H, 7.2; S, 15.8%.

Ethyl (S)-6,8-di-O-benzyl-oct-2-enoate (61)

To a suspension of red mercuric oxide (1.06 g, 3.5 equivalents) and borontrifluoride (0.52 ml, 3 equivalents) in 17% aqueous acetone (15 ml) was added 59 (0.56 g, 1.4 mmol) in tetrahydrofuran (3 ml) dropwise with efficient stirring and under nitrogen. After 20 hr, the reaction was neutralised with sodium hydroxide dissolved in 75% aqueous acetone. The greyish precipitate was filtered and the filterate concentrated to a minimum amount. It was extracted repeatedly with chloroform. The aqueous layer was concentrated to dryness and the residue

extracted with chloroform. The combined chloroform layer was dried and concentrated to afford the compound 60 which was found chromatographically homogeneous and used without further purification. ^{1}H-NMR ($CDCl_3$): δ 9.71 (t, 1H, -CHO).

The above aldehyde (0.35 g, 1.12 mmol) dissolved in dry benzene (5 ml) was treated with carbethoxymethylenetriphenylphosphorane (1.17 g, 3 equivalents). The mixture was heated under reflux for 10 hr and then concentrated. The residue was chromatographed on a silica gel using ethyl acetate-light petroleum (1:20) to give the α,β-unsaturated derivative 61 (0.30 g, 80%), $[\alpha]_D$ +3° (c 1.1, chloroform), ^{1}H-NMR ($CDCl_3$): δ 1.24 (t, 3H, CH_3CH_2), 1.4-2.0 (m, 4H, H-5,5',7,7'), 2.3 (m, 2H, H-4,4'), 3.5 (m, 3H, H-6,8,8'), 4.13 (q, 2H, CH_3CH_2), 4.42 (s, 4H,2X CH_2Ph), 5.71 (dt, 1H, H-2, J=16 and 1.5 Hz), 6.88 (dt, 1H, H-3, J=16 and 6.5 Hz), 7.24 (d, 10H, 2 Ph) (Fig.1.3.4).

Analysis: Calculated for $C_{24}H_{30}O_4$: C, 75.4; H, 7.9. Found: C, 75.3; H, 7.9%.

Ethyl (S)-6,8-di-O-mesyl-octanoate (63)

The dibenzylate 61 (0.4 g, 1.05 mmol) in ethanol (10 ml) was hydrogenated over freshly prepared W2 Raney nickel (4 g) at normal pressure and temperature for 18 hr. The reaction was filtered through celite and filterate concentrated to afford the saturated diol 62 (0.192 g, 90%), b.p.153°/0.1 mm Lit.[57] b.p.150-158°/0.1 mm. IR: ν_{max} (neat): 3400, 1735 cm^{-1}.

To the above diol (0.102 g, 0.5 mmol) in dry dichloromethane

(2 ml) at 0° was added triethylamine (1 ml) and methanesulfonyl chloride (0.24 ml, 3 mmol). After 4 hr at 0°, the reaction mixture was poured over aqueous sodium bicarbonate and extracted with methylene chloride, dried and concentrated. The residue was purified by column chromatography over silica gel using ethyl acetate-light petroleum (1:1) to obtain the dimesylate 63 (0.18 g, 100%), $[\alpha]_D$ +17° (c 1, chloroform), ^{1}H-NMR ($CDCl_3$): δ1.22 (t, 3H, $C\underline{H}_3CH_2$), 1.3-2.5 (m, 10H, 5X CH_2), 3.00 (s, 6H, 2X OSO_2CH_3), 4.15 (q, 2H, $CH_3C\underline{H}_2$), 4.28 (t, 2H, H-8,8'), 4.80 (m, 1H, H-6) (Fig.1.3.5).

Analysis: Calculated for $C_{12}H_{24}O_8S_2$: C, 40.0; H, 6.7; S. 17.8. Found: C, 40.0; H, 6.7; S, 17.5%.

Ethyl R(+)-α-Lipoate (Ethyl (R)-1,2-dithiolane-3-pentanoate) (64)

A solution of the dimesylate ester 63 (0.36 g,1 mmol) in dry dimethylformamide (3 ml) containing powdered sodium sulfide monohydrate (0.24 g, 1 mmol) and sulfur (0.032 g, 1 mmol) was heated at 90° for 24 hr. The mixture was poured over ice-water and extracted with light petroleum. The organic layer was washed with water, dried and concentrated to afford a residue which was purified on a short column of silica gel with benzene as eluant to afford 64 (0.164 g, 70%), $[\alpha]_D$ +61° (c 0.34, chloroform), IR (neat): 1730 cm^{-1} (COOEt); ^{1}H-NMR ($CDCl_3$): δ1.27 (t, 3H, $C\underline{H}_3CH_2$), 1.4-2.8 (m, 10H, 5X CH_2), 3.18 (t, 2H, H-8,8'), 3.6 (m, 1H, H-6), 4.13 (q, 2H, $CH_3C\underline{H}_2$) (Fig.1.3.6). Mass spectrum: m/z 234.

Analysis: Calculated for $C_{10}H_{18}O_2S_2$: C, 51.3; H, 7.7; S, 27.35. Found: C, 51.2; H, 7.8; S, 27.1%.

R(+)-α-lipoic acid (R(+)-1,2-dithiolane-3-pentanoic acid (1)

The ester 64 (0.117 g, 0.5 mmol) in ethanol (5 ml) was treated with 0.1M aqueous potassium hydroxide (5.5 ml) in dark and under nitrogen at room temperature. After 24 hr, ethanol was evaporated and extracted with light petroleum. The aqueous layer was carefully acidified with 5N hydrochloric acid to pH 1 and then repeatedly extracted with ether. The ethereal layer concentrated and the semisolid residue was purified through a short column of silica gel using benzene-ethyl acetate (70:1) to afford 1 (0.063 g, 75% based on recovered 14) m.p. 44°, lit.[21] m.p. 43-45°, $[\alpha]_D$ +95° (c 0.11, benzene), lit.[30] $[\alpha]_D$ +91° (C_6H_6); lit.[21] +102° (C_6H_6); IR (neat): 1695 cm^{-1} (COOH); ^{1}H-NMR ($CDCl_3$): δ 1.3-2.8 (m, 10H, 5X CH_2), 3.10 (t, 2H, H-8,8'), 3.53 (m, 1H, H-6) (Fig.1.3.7). Mass spectrum: m/z 206 (M^+).

Analysis: Calculated for $C_8H_{14}O_2S_2$: C, 46.6; H, 6.8; S, 31.1. Found: C, 46.55; H, 6.6; S, 30.7%.

SECTION B: ASYMMETRIC SYNTHESIS INVOLVING SHARPLESS ASYMMETRIC EPOXIDATION

5-Bromopentanoic acid 65 was prepared from δ-valerolactone by the method reported in the literature[33]. 5-Bromopentanol 75 was prepared by lithium aluminium hydride reduction of methyl-5-bromopentanoate 74 at -78°C by following the reported method[39]. Trimethylolethane 72 was prepared from propionaldehyde by Cannizaro reaction with formaldehyde by the literature method[37].

8-Hydroxy-Oct-6-yne-oic acid (66)

A litre of ammonia was collected in a 3-necked flask, and a catalytic amount of ferric nitrate was added to it. To a stirred solution of the above, lithium metal (7 g, 1 m) was added in small cut portions for 30 minutes and the reaction was refluxed (at -30°C) for 45 minutes until greyish white precipitate was formed. Propargyl alcohol (28 g, 0.5 m) in dry tetrahydrofuran (100 ml) was then added dropwise to this freshly formed lithium amide and the reaction was refluxed for 1 hr. A solution of the 5-bromopentanoic acid 65 (9 g, 0.05 m) in 300 ml dry tetrahydrofuran was then added to the above which was then refluxed for 8 hours at -30°C. 5N HCl (500 ml) was added to it and left stirring overnight to allow the ammonia to evaporate. Repeated extraction with ether of the acidic solution gave a crude product which on chromatographic purification gave 66 (6.94 g, 89%) which solidified slowly on standing. IR ν_{max} ($CHCl_3$): 3400, 2220, 1710 cm^{-1};

^{1}H-NMR ($CDCl_3$) (Fig.1.3.8): δ 1.5-1.9 (m, 4H, 2X CH_2 at C-3,4), 2.0-2.5 (m, 4H, 2X CH_2 at C-2,5), 4.17 (t, J=3Hz, 2H, CH_2-8), 6.7 (bs, 2H, -OH, COOH, exchanges with D_2O).

8-Hydroxy-oct-6-ene-oic acid (67)

Freshly distilled ammonia (25 ml) was collected in a flask to which a solution of 67 (1 g, 6.4 m.mol) in dry tetrahydrofuran (10 ml) was added. Pieces of sodium metal (3.0 g, 130 m.mol) were added to the above at intervals and the reaction was refluxed for 4 hr. A saturated solution of ammonium chloride was then added to it and ammonia was allowed to evaporate. Ether extract of the above after drying and concentration gave 67 (842 mg, 85%). IR ν_{max} (neat): 3400, 950 1710 cm^{-1}; ^{1}H-NMR (CCl_4): δ 1.4-1.8 (m, 4H, 2X CH_2 at C-3,4), 1.9-2.5 (m, 4H, 2X CH_2 at C-2,5), 4.13 (bd, 2H, CH_2-OH), 5.67 (bt, 2H, olefinic protons), 7.1 (brs, 2H, -OH, -COOH, exchanges with D_2O).

Formation of the oxazoline (68) from olefinic acid of 66 or 66

The olefinic acid of 66/ itself was used for the above condensation by following an analogous procedure[35]. 66 (1.56 g, 10 m.mol) and freshly distilled 2-amino-2-methyl-1-propanol (0.89 g, 10 m.mol) were heated for 2 hrs upto a temperature of 170°C. The oxazoline was distilled off in a receiver containing hexane where water separated out as the lower layer. The aqueous layer was repeatedly extracted with hexane/light petrol, dried (NaOH) and concentrated to afford the pure product

68 in quantitative yields. IR ν_{max} ($CHCl_3$): 3400,1665 cm^{-1}. ^{1}H-NMR (CCl_4) (Fig.1.3.9).

Attempted preparation of orthoester 73

To a sample of the compound 66 or 67 (474 mg, 0.063 m) in 2 ml dry xylene, tris-trimethylolethane 72 (378 mg, 0.0032 m) and toluene p-sulfonic acid were added and the reaction refluxed using a Dean-Stark extractor. There was no separation of water and no reaction (TLC) even after 48 hours. The same reaction was repeated by mixing both the reactants with a catalytic amount of toluene p-sulfonic acid and heating the solid mixture at 200-250°C for 10 hrs. The triol 72 sublimes and condenses on the upper sides of the flask and there is no trace of product on TLC.

5-Bromopentanal (76)

To a solution of pyridinium chlorochromate (32.3 g, 0.15 m) in 200 ml dry methylene chloride stirred at room temperature, 5-bromopentanol 75 (16.6 g, 0.1 m) in dry dichloromethane (25 ml) was added in one portion and the reaction was stirred for 2 hr. Dry ether (200 ml) was admixed with the above and after stirring, the supernatant liquid was decanted from the black gummy residue, which was washed repeatedly with dry ether. The organic layer was passed through a short pad of silica gel and eluted with ether to afford on concentration, a pale yellow oil, 5-bromopentanal 76 (12.3 g, 75%). IR ν_{max} (neat): 2740, 1730, 765 cm^{-1}. ^{1}H-NMR (CCl_4): δ1.88

(m, 4H, 2X CH_2), 2.49 (t, J= 6.5 Hz, 2H, $-\underline{CH_2}CHO$), 3.47 (t, J= 6.5 Hz, 2H, CH_2-Br), 9.81 (t, J= 2 Hz, 1H, CHO).

2-(4'-Bromobutyl)-1,3-dioxolane(77)

A solution of the bromopentanal 76 (8.2 g, 0.05 m) ethylene glycol (9.3 g, 0.15 m) and toluene-p-sulfonic acid (15 mg) in dry benzene (30 ml) was refluxed using a Dean-Stark apparatus for constant azeotropic removal of water, for 6 hr. On cooling, the organic layer was washed with water, 5% $NaHCO_3$, dried and evaporated in vacuo to afford a crude product which was chromatographically purified on a silica gel column (eluant, light petrol + benzene, 1:1) to afford 77[38] (7.8 g, 75%). ^{1}H-NMR (CCl_4): δ 1.60 (m, 6H, 3X CH_2 at C-1',2',3'), 3.25 (t, J= 6.5 Hz, 2H, $\underline{CH_2}$-Br), 3.67 (s, 2H, $-OCH_2$), 3.73 (s, 2H, $-OCH_2$), 4.58 (t, J= 4 Hz, 1H, $-CH<^{O}_{O}$).

5-Bromo-1-tetrahydropyranyloxypentane(78)

To 5-bromopentanol 75 (8.4 g, 0.05 m) and catalytic amount of toluene-p-sulfonic acid, 2,3-dihydropyran (4.62 g, 0.11 m) was added with cooling (0°C). After the exothermic reaction subsided, the reaction mixture was stirred for 2 hr at room temperature. Anhydrous potassium carbonate (1 g) was added to the above, reaction stirred for 30 minutes, filtered and residue was washed with ether. The crude product obtained on concentration of the organic layer was purified on a silica gel column (eluant, benzene) to afford 78 (11.5 g) in almost quantitative yield. ^{1}H-NMR (CCl_4): δ 1.3-2.0 (m,

12H, 6X CH_2, C-2,3,4,4',5',6'), 3.13-3.63 (m, 6H, 3X CH_2, C-5,1,3'), 4.35 (bs, 1H, H-1').

7-(1',3'-Dioxolan-2'-yl)-hept-2-yne-1-ol (79)

To a solution of lithium amide [made from lithium (300 mg, 43 m.mol) in condensed ammonia (30 ml) containing a pinch of ferric nitrate, was added propargyl alcohol (1.12 g, 20 m.mol). After 45 min. reflux, a solution of the bromoketal 77 (2.08 g, 10 m.mol) in dry tetrahydrofuran (10 ml) was added to it. After 2 hr reflux (-33°C) a saturated solution of ammonium chloride was added to the above and ammonia was allowed to evaporate overnight at room temperature. Ether extraction of the above gave a crude oil which was purified on a silica gel column (eluant, benzene + acetone, 9:1) to afford pure 79 (920 mg, 50%). IR ν_{max} (neat): 3400 cm^{-1}. ^{1}H-NMR (CCl_4): δ 1.57 (brs, 6H, 3X CH_2 at C-5,6,7), 2.20 (m, 2H, CH_2-4), 3.33 (br, 1H, -OH, exchanges with D_2O), 3.82 (s, 2H, OCH_2), 3.85 (s, 2H, OCH_2), 4.12 (bs, 2H, $\underline{CH}_2$-OH), 4.78 (m, 1H, $\underline{CH}<^{O}_{O}$) (Fig.1.3.10).

1-Hydroxy-8-tetrahydropyranyloxy-oct-2-yne (80)

Liquid ammonia (200 ml) was condensed in a 3-necked flask and a catalytic amount of ferric nitrate added to it. To a stirred and refluxed solution of the above, small pieces of lithium metal (1.4 g, 0.2 m) were added in portions over 20 minutes. After 30 minutes reflux, a greyish suspension of lithium amide in ammonia was formed to which a solution of propargyl alcohol (5 g, 90 m.mol) in dry tetrahydrofuran

(10 ml) was added. After 0.5 hr reflux, the protected bromopentanol 78 (20 g, 80 m.mol) in dry tetrahydrofuran (50 ml) was added dropwise to the propargylic dianion generated above. After 8 hr reflux the excess of base was decomposed by slow addition of a saturated solution of ammonium chloride and ammonia was allowed to evaporate overnight at room temperature. Ether extract of the above was dried, concentrated and purified on a short silica gel column (eluant, light petrol + benzene, 1:1) to afford 80 (14.5 g, 80%). IR ν_{max} (neat): 2220, 3400 cm^{-1}. ^{1}H-NMR (CCl_4): δ 1.4 - 1.8 (m, 12H, 6X CH_2 at C-5,6,7,4',5',6'), 2.23 (brt, 2H, 4-CH_2), 2.73 (bs, 1H, -OH, exchanges with D_2O), 3.33 - 3.93 (m, 4H, 2X CH_2 at C-8,3'), 4.28 (t, J= 2 Hz, 2H, 1-CH_2), 4.67 (bs, 1H, H-1') (Fig.1.3.11). Mass m/z: 226 (M^+).

Analysis: Calculated for $C_{13}H_{22}O_3$: C, 69.02; H, 9.73; Found: C, 68.73; H, 9.71%.

1-Hydroxy-8-tetrahydropyranyloxy-oct-2E-ene (81)

A solution of alkyne 80 (11.3 g, 0.05 m) in dry tetrahydrofuran (50 ml) was added to a stirred slurry of lithium aluminium hydride (1.9 g, 0.05 m) in dry tetrahydrofuran (200 ml) at room temperature under N_2. After 8 hr reflux, excess hydride was decomposed by slow addition of water, while cooling the receiving flask, till granular solid was formed. The suspension was filtered, residue was washed with chloroform and the combined organic layer dried and evaporated in vacuo to afford a chromatographically homogenous product

81[40] (10.1 g, 85%). IR ν_{max} (neat): 3400 cm^{-1}, 950. ^{1}H-NMR(CCl_4): δ 1.40 - 1.80 (m, 12H, 6X CH_2 at C-5,6,7,4',5',6'), 2.17 (m, 2H, 4-CH_2), 3.47 - 4.07 (m, 4H, 2X CH_2 at C-8,3'), 4.27 (d, 2H, 1-CH_2), 4.87 (bs, 1H, H-1'), 6.62 (bt, 2H, H-2 and H-3) (Fig.1.3.12). Mass m/z: 228 (M^+).

Analysis: Calculated for $C_{13}H_{24}O_3$: C, 68.42; H, 10.53; Found: C, 67.91; H, 10.50%.

2,3-Epoxy-1-hydroxy-8-tetrahydropyranyloxy octane (82)

m-Chloroperbenzoic acid (7.6 g, 0.044 m) was added in portions to a stirred and cooled (0°C) solution of the alkynol (81) (9.0 g, 0.04 m) in dry dichloromethane (50 ml). After 3 hr at 0°C and 18 hr at room temperature, a 10% solution of sodium sulfite was added to it. The organic layer was separated, dried and evaporated in vacuo to afford 82 (7.72 g, 80%). IR ν_{max} ($CHCl_3$): 3400 cm^{-1}. ^{1}H-NMR (CCl_4): δ 1.4 - 1.8 (m, 14H, 7X CH_2 at C-4,5,6,7,4',5',6'), 2.85 (m, 2H, -CH at C-2,3), 3.3 - 4.3 (m, 6H, 3X CH_2 at C-1,8,3') 4.63 (bs, 1H, H-1') (Fig.1.3.13). Mass m/z: 244 (M^+).

Analysis: Calculated for $C_{13}H_{24}O_4$: C, 63.93; H, 9.84; Found: C, 63.71; H, 9.62%.

Sharpless asymmetric epoxidation of 81

Dry dichloromethane (150 ml, freshly distilled from calcium hydride) was introduced in an oven dried, nitrogen flushed, single necked flask fitted with a septum. The flask was cooled to -23°C and titanium isopropoxide (2.42 ml,

15 m.mol) was added to it. After stirring for 10 minutes, (+)diisopropyltartarate (3.4 ml, 16.5 m.mol) was added and the reaction stirred for 10 min. The allylic alcohol 81 (3.39 g, 15 m.mol) in dry dichloromethane (15 ml) was then added to the above complex, followed after 10 minutes by a 4.25 M solution of tert-butylhydroperoxide (TBHP) in dichloromethane (7.2 ml, containing 30 mmol of anhydrous TBHP). The resulting homogenous solution was stored at -15°C for 72 hrs. It was recooled to -23°C and a solution of 10% aqueous tartaric acid (50 ml) was added while stirring. After 30 min. at -23°, the solution was stirred for 1 hr at room temperature until the aqueous layer becomes clear. The organic layer was separated, washed with water, dried and concentrated to afford a pale yellow oil. A solution of this oil in excess ether (150 ml) was cooled to 0°C and 1N NaOH solution (60 ml) was added to it. The resulting two phase mixture was stirred at 0° for 30 minutes. The ether layer was separated, washed with brine, dried and concentrated to afford an oil. Chromatographic purification of the above (eluant benzene + ethyl acetate 5:1) afforded the asymmetric epoxy alcohol 82 whose spectroscopic properties coincided with the racemic 82 obtained earlier.

1,3-Dihydroxy-8-tetrahydropyranyloxy-octane (83)

To a stirred and cooled solution (-23°C) of epoxide (82) (1.8 g, 7.4 m.mol) in dry tetrahydrofuran (20 ml) was added a 3.5 M solution of Red-Al in toluene (3 ml, 3 m equivalent)

under nitrogen. After 4 hr, the excess of hydride was decomposed by dropwise addition of a saturated solution NaCl till granular solid forms. The resulting suspension was filtered, residue washed with chloroform and the combined organic layer was dried and concentrated in vacuo to afford chromatographically homogenous mono- protected triol 83. IR ν_{max} (neat): 3400 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ1.2 - 1.7 (m, 16H,8X CH_2 at C-2,4,5,6,7,4',5',6'), 3.1 - 3.9 (m, 7H, CH_2 at C-1,8,3' and H-3), 4.47 (bs, 1H, H-1'). Mass m/z: 246 (M^+).

Analysis: Calculated for $C_{13}H_{26}O_4$: C, 63.41; H, 10.57; Found: C, 63.40; H, 10.51%.

1,3-Dimesyloxy-8-tetrahydropyranyloxy-octane (84)

Triethylamine (3.1 ml, 30 m.mol) was added to a stirred and cooled (0°C) solution of the diol 83 (1.23 g, 5 m.mol) in dry dichloromethane (5 ml). After 15 min, methane sulfonyl chloride (0.81 ml, 10.5 mmol) was added to the above. After 4 hr at 0°, the reaction mixture was poured into 10% aqueous $NaHCO_3$ extracted with dichloromethane, dried and concentrated in vacuo. The crude product was purified through a short column of silica gel (eluant ethyl acetate + light petrol,1:20) to afford the pure dimesylate 84 (1.81 g, 90%). ^{1}H-NMR ($CDCl_3$): δ1.3 - 1.7 (m, 16H, 8X CH_2 at C-2,4,5,6,7,4',5',6'), 2.97 (s, 6H, 2X $-OSO_2CH_3$), 3.3 - 3.7 (m, 6H, CH_2 at C-1,8,3'), 4.27 (m, 1H, H-3), 4.47 (bs, 1H, H-1') (Fig.1.3.14). Mass m/z: 402 (M^+).

Analysis: Calculated for $C_{15}H_{30}O_8S_2$: C, 35.82; H, 7.46; S, 15.92; Found: C, 35.43; H, 7.42; S, 15.23%.

3-(5'-tetrahydropyranyloxypentyl)-1,2-dithiolane (85)

A solution of the dimesylate 84 (402 mg, 1 m.mol) in dry N,N-dimethylformamide (3 ml) containing powdered sodium sulfide nonahydrate (240 mg, 1 m.mol) and sulfur (32 mg, 1 mmol) was heated at 100° for 24 hr, then poured into ice water and extracted with light petrol. The extract was washed once with water, dried and concentrated. Purification of the crude product on a silica column (eluant, benzene) afforded the protected lipoyl alcohol 85 (207 mg, 75%). ^{1}H-NMR ($CDCl_3$): δ 1.4 - 1.8 (m, 14H, 7X CH_2 at C-1',2',3',4' + 3 CH_2 on THP); 2.41 (m, 2H, CH_2-4), 3.13 (t, J=5 Hz, 2H, CH_2-5), 3.4 - 3.8 (m, 5H, CH_2-5' + H-3 + THP -CH_2-O), 4.53 (bs, 1H, THP methine proton) (Fig.1.3.15). Mass m/z: 276 (M^+).

Analysis: Calculated for $C_{13}H_{24}O_2S_2$: C, 56.52; H, 8.70; S, 23.19; Found: C, 56.11, H, 8.52; S, 22.83%.

3-(5'-hydroxypentyl)-1,2-dithiolane (86)

To a solution of the protected lipoyl alcohol 85 (207 mg, 0.75 mmol in dry methanol (1 ml), a catalytic amount of amberlite IR-120 (H^+) resin was added and the reaction was stirred at room temperature for 20 hr. It was then filtered, residue was repeatedly washed with methanol and the solvent was evaporated in vacuo. Purification of the resulting oil on a silica gel column (eluant, light petrol + ethyl acetate 9:1)

afforded the pure alcohol 86 (130 mg, 90%), IR ν_{max} ($CHCl_3$): 3450 cm^{-1}. ^{1}H-NMR[58] ($CDCl_3$): δ1.4-1.7 (m, 8H, 4X CH_2 at C-1',2',3',4'), 2.44 (q, J= 7 Hz 2H, 4-CH_2), 3.17 (dt, J= 7 Hz, J= 9 Hz, 2H, 5-CH_2), 3.59 (t, J= 7 Hz, 1H, C-3 methine), 3.67 (t, J= 7 Hz, 2H, CH_2-5') (Fig.1.3.16). Mass m/z: 192 (M^+).

Analysis: Calculated for $C_8H_{16}OS_2$: C, 56.00; H, 8.33; S, 33.33; Found: C, 49.98;H, 8.31; S, 33.11%.

3-(1,2-dithiolanyl)-pentanoic acid (1)

The alcohol 86 (100 mg, 0.52 m.mol) was dissolved in acetone (0.5 ml) and stirred at 0°C. Jones reagent[42] was added slowly to the above with a syringe when the colour of the solution turned to green. The reagent was added dropwise until red-brown colour remained. The solution was dissolved in dichloromethane and washed with saturated brine. The aqueous layer was re-extracted with dichloromethane and the combined organic layer was washed once with saturated brine, dried, concentrated *in vacuo* and purified on a silica gel column to afford lipoic acid 1 (30 mg) whose spectroscopic data coincided well with that of the compound prepared earlier (Section A).

The asymmetric epoxide (obtained after Sharpless reaction), (S)-82 when subjected to detetrahydropyranylation with Amberlite IR-120(H^+) resin by following the same method as before gave the 2S,3S-epoxy-1,8-dihydroxy octane in 80% yield which showed $[\alpha]_D$ -4.3° (c 0.14, $CHCl_3$).

(S)-82 when subjected to the same set of reactions as (±)-82 above gave 3R-(1,2-dithiolanyl)-pentanol 86 having $[\alpha]_D$ -12.5° (c 0.8, $CHCl_3$).

(R)-86 on Jones oxidation gave R-1, $[\alpha]_D$ +30° (c, 0.12, C_6H_6).

SECTION C

(i) From tartaric acid

(RR)-Diethyl tartarate[59] and α,α-dimethoxy toluene[60] were prepared according to the reported procedures.

Ethyl 1,3-dioxolane-2-phenyl-4R,5R-dicarboxylate (87)

α,α-Dimethoxytoluene (29.64 g, 0.195 m) was added to a solution of diethyl tartarate (30.9 g, 0.150 m) in 300 ml of dry acetonitrile and a catalytic amount of toluene p-sulfonic acid, under nitrogen. After 8 hr reflux, the reaction was neutralized by addition of triethylamine and concentrated under reduced pressure. The crude product was distilled at b.p. 140°/0.2 mm to afford an oil which crystallised on cooling 87 (39.7 g, 90%), $[\alpha]_D$ -30.5°(c, 1.5, $CHCl_3$), lit.[44] b.p. 146°/0.2 mm, $[\alpha]_D$ -33.1°, IR ν_{max} ($CHCl_3$): 1740, 1595, 1580 cm^{-1}. ^{1}H-NMR (CCl_4): δ 1.28, 1.33 (2t, 6H, J=7 Hz 2X CH_3 of ester group), 4.25, 4.32 (2 q, J=7 Hz, 4H, 2X CH_2 of ethyl ester group), 4.75, 4.88 (2d, 2H, J=4 Hz, H-2, H-3), 6.15 (s, 1H, benzylic proton), 7.47 (m, 5H, Ph). Mass m/z: 294 (M^+).

Analysis: Calculated for $C_{15}H_{18}O_6$: C, 61.22; H, 6.12; Found: C, 61.01; H, 6.11%.

1,3-Dioxolane-2-phenyl-4S,5S-dimethanol (88)

To a stirred slurry of 7.6 g (0.2 m) of lithium aluminium hydride in dry tetrahydrofuran (300 ml), 29.4 g (0.1 m) of 87 in dry tetrahydrofuran (100 ml) was added

dropwise, at room temperature over a period of 30 minutes under nitrogen. After 6 hr reflux, the reaction was worked up by slow addition of water till granular solid separates out, and then filtered. The residue was washed repeatedly with chloroform and the filterate was dried and concentrated in vacuo to afford 88 (18.0 g, 85%) as an oil which solidified after long standing, $[\alpha]_D$ +7.1 (c 1.0, $CHCl_3$), lit.[44] $[\alpha]_D$ +7.4°. IR ν_{max} (neat): 3340 cm^{-1}; ^{1}H-NMR (CCl_4): δ 3.22 (s, 4H, 2X CH_2-OH), 5.30 (m, 2H, H-2,3), 5.82 (s, 1H, benzylic proton), 7.27 (m, 5H, Ph), Mass m/z: 210 (M^+).

Analysis: Calculated for $C_{11}H_{14}O_4$: C, 62.86; H, 6.67; Found: C, 62.81; H, 6.63%.

4R,5R-Dibenzoyloxymethyl-2-phenyl-1,3-dioxolane (89)

To a stirred solution of the diol 88 (10.5 g, 0.05 m) in dry pyridine (16.2 ml, 0.2 m) at 0°C, benzyl chloride (11.2 ml, 0.1 m) was added dropwise. After 2 hr at 0° and 20 hr at room temperature, reaction mixture was poured over water and extracted with chloroform. The organic layer was washed with 10% sodium bicarbonate, water, dried and concentrated in vacuo to afford a residue which after a silica column chromatography (eluant light-petrol + benzene, 1:1) gave a white crystalline solid 89 (18.8 g, 90%); m.p. 62-63°, $[\alpha]_D$ +8.2 (c 0.1, $CHCl_3$). IR ν_{max} ($CHCl_3$): 1730, 1610, 1590 cm^{-1}. ^{1}H-NMR (CCl_4): δ 4.47 (bs, 6H, 2X CH_2OCOPh and H-2,3), 5.98 (s, 1H, benzylic proton), 7.30, 7.96 (m, 15H, 3X Ph) (Fig.1.3.17). Mass m/z: 418 (M^+), 296 [M^+-(OCOPh+H)]

Analysis: Calculated for $C_{25}H_{22}O_6$: C, 71.77; H, 5.26; Found: C, 71.74; H, 5.23%.

2*R*-Bromo-tri-O-benzoyl-butane-1,3*S*,4-triol (90)

A solution of the dibenzoate 89 (16.72 g, 0.04 m) in dry carbon tetrachloride (80 ml) was added to a stirred suspension of N-bromosuccinimide (8.54 g, 0.048 m) and excess of anhydrous barium carbonate (20 g) in dry carbon tetrachloride (100 ml). After 5 hr reflux, the suspension was filtered and the residue was washed with chloroform. The filterate was concentrated in vacuo and crude product chromatographed on a silica column (eluant, light petrol + benzene, 1:1) to afford the bromotribenzoate 90 (17.8 g, 90%), m.p. 141-142°C, $[\alpha]_D$ +7.4 (c 0.12, $CHCl_3$). IR ν_{max} ($CHCl_3$): 1730, 1600,1580 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ3.81 (m, 1H, CH-Br), 4.75 (m, 4H, 2X CH_2 at C-1,4), 5.81 (m, 1H, -CH- at C-3), 7.44, 8.00 (2 m, 15H, 3X Ph) (Fig.1.3.18). Mass m/z: 496, 498 (M^+), 417 (M^+ - Br).

Analysis: Calculated for $C_{25}H_{21}BrO_6$: C,60.48; H, 4.23; Found: C, 60.13; H, 4.21%.

(+)1,2R,4-Butanetriol (92)

45 g of freshly prepared W-2 Raney nickel was added to a solution of the bromobenzoate 90 (9.96 g, 0.02 m) in hot acetic acid free,ethyl acetate (200 ml). The suspension was stirred mechanically at 45 p.s.i. for 20 hr and then filtered. The filterate was evaporated in vacuo to afford

the tribenzoate 91 in almost quantitative yield. IR ν_{max} (neat) 1730, 1600, 1580 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 2.34 (m, 2H, CH_2 at C-3), 4 - 4.81 (m, 4H, 2X CH_2 at C-1,4), 5.66 (m, 1H, CH at C-2), 7.31, 8.00 (2 m, 15H, 3X Ph) (Fig.1.3.19). Mass spectrum m/z: 418 (M^+). Sodium pieces in catalytic amounts, were added to a stirred solution of the above tribenzoate 91 (8.3 g, 0.02 m) in dry methanol (50 ml) and the reaction stirred overnight at room temperature. It was then deionised by Amberlite IR-120 (H^+) resin and the solvent evaporated in vacuo to afford a fruity odoured two layered immiscible suspension. It was purified on a short pad of neutral alumina to afford the triol (eluant, methanol), which was distilled at b.p. 138°/0.9 mm to give 92 (1.67g, 80%), $[\alpha]_D$ +21.3 (c 2, EtOH), lit.[45] b.p. 140-143/0.9 mm $[\alpha]_D$ +22.5. IR(Nujol): 3380(s) cm^{-1}. ^{1}H-NMR (CD_3COCD_3): δ 1.66 (m, 2H, CH_2 at C-3), 3.4 - 3.8 (m, 5H, 2X CH_2 at C-1,4 and H-2), 4.00 (bs, 1H, -OH, exchanges with D_2O).

Mass m/z: 194 (M^+).

Analysis: Calculated for $C_4H_{10}O_3$: C, 45.28; H, 9.43; Found: C, 45.23; H, 9.41%.

4R-(Hydroxymethyl-2R-phenyl-1,3 dioxane (93)

α,α-Dimethoxytoluene (4.56 g, 30 m.mol) was added to a stirred solution of the butanetriol (2.12 g, 20 m.mol) in 20 ml dry acetonitrile with traces of toluene p-sulfonic acid under nitrogen. After 8 hr reflux, the reaction was

basified with triethylamine and the solvent evaporated in vacuo. The residue was chromatographed on a silica gel column (eluant light petrol + ethylacetate) to afford first the 1,3-dioxolane 94 (0.31 g, 10%) and then the 1,3-dioxane 93[46] (2.79 g, 90%) in an overall yield of 80%. 1,3 dioxolane 94, IR ν_{max} (neat): 3400, 1600 cm^{-1}, ^{1}H-NMR spectrum ($CDCl_3$): δ 1.2 - 1.5 (m, 2H, CH_2 at C-1'), 3.4 - 4.3 (m, 5H, CH_2 at C-5, C-2' and H-4), 5.50 (s, 1H, benzylic proton), 7.48 (m, 5H, Ph) (Fig.1.3.22). Mass m/z: 194 (M^+).

Analysis: Calculated for $C_{11}H_{14}O_3$: C, 68.04; H, 7.22; Found: C, 67.91; H, 7.22%.

1,3-dioxane 93, IR ν_{max} (neat): 3400, 1600 cm^{-1}. ^{1}H-NMR spectrum ($CDCl_3$): δ 1.3 - 2.1 (m, 2H, CH_2 at C-5), 3.5 - 4.4 (m, 5H, 4-CH_2, CH_2-OH and H-6), 5.53 (s,1H, benzylic proton), 7.41 (m, 5H, Ph) (Fig.1.3.20), Mass m/z: 194 (M^+).

Analysis: Calculated for $C_{11}H_{14}O_3$: C, 68.04; H, 7.22; Found: C, 67.91; H, 7.22%.

Ethyl 1-(2'-phenyl-1',3'-dioxane-4'-yl)-pent-1-enoate (96)

To a stirred and cooled (0°C) solution of pyridinium chlorochromate (3.24 g, 15 m.mol) and powdered molecular sieves (3A), (6 g, 2 g per mmol of alcohol) in dry dichloromethane (16 ml), a solution of the alcohol 93 (582 mg, 3 mmol) in dichloromethane (2 ml) was added in one lot. After 2 hr stirring at 0°C, dry ether was added to the reaction mixture

which was then filtered through a short column of silica gel and washed thoroughly with ether. The solvent was concentrated in vacuo and purified by a dry column chromatography on silica gel (eluant, ether) to afford the aldehyde 95 (115 mg, 20%) which was immediately used for the Wittig reaction. IR ν_{max} (neat) 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ1.3 - 1.7 (m, 2H, 5-CH_2), 3.6-4.6 (m, 2H, 6-CH_2), 5.21 (m, 1H, H-4), 5.91 (s, 1H, benzylic proton), 7.4 (m, 5H, Ph), 9.71 (s, 1H, CHO). Sodium hydride (316 mg, 22 mm 50% mineral dispersion) was washed repeatedly with dry pet. ether and then covered with 1 ml of dry tetrahydrofuran. The phosphonium salt (1.5 g, 5 m.mol) was added to a stirred solution of the above under nitrogen at room temperature. After 2 hr stirring, the above aldehyde (115 mg, 0.6 m.mol) 1 ml dry tetrahydrofuran was added to the ylid and reaction mixture was stirred for 20 hr at room temperature. Methanol was then slowly added to it with cooling and the solvent concentrated in vacuo to afford an oil which was chromatographed on silica column (eluant, pet ether ± ethylacetate, 20:1) to afford the α,β-unsaturated ester 96 (20 mg, 12%). IR ν_{max} ($CHCl_3$): 1730, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.21 (bt, J=7 Hz, 5H, CH_3 + CH_2-5'), 1.9 - 2.3 (m, 4H, CH_2 at C-3,4), 3.7 - 4.3 (m, 4H, 6'-CH_2 and $CO_2\underline{CH_2}CH_3$), 4.72 (m, 1H, $\underline{CH}$-4'), 5.79 (s, 1H, H-2'), 5.91 (m, 2H, H-1,2), 7.48 (m, 5H, Ph) (Fig.1.3.23). Mass m/z: 290 (M^+).

Analysis: Calculated for $C_{17}H_{22}O_4$: C, 70.34; H, 7.59; Found: C, 70.14; H, 7.31%.

Ethyl (s)-6,8-dihydroxy octanoate(62)

The α,β-unsaturated ester 96 (20 mg, 69 m.mol)in ethanol (1 ml) was hydrogenated over 10% palladised charcoal (20 mg) at normal pressure and temperature. After 4 hr, the solution was filtered, residue washed repeatedly with ethanol and the filterate was concentrated to afford the saturated ester.

The above compound was stirred in methanol (1 ml) and a catalytic amount of toluene-p-sulfonic acid was added to it. After 20 hr stirring at room temperature, it was neutralized with triethylamine and concentrated in vacuo to afford the diol ester 62, distilled at 153° at 0.1 mm, lit.[57] b.p. 150-8° (0.1 mm), IR ν_{max} ($CHCl_3$): 3400, 1735 cm^{-1}, ^{1}H-NMR($CDCl_3$): Figure 1.3.24.

4R-(Mesyloxymethyl)-2R-phenyl-1,3-dioxane (93b).

To a stirred and cooled (-10°C) solution of the 1,3-dioxane alcohol 93 (388 mg, 2 m.mol)in dry dichloromethane (2 ml), triethylamine (0.85 ml, 6 m.mol)was added. After 10 minutes, methanesulfonyl chloride (0.25 ml, 3 m.mol)was added dropwise to the above and reaction stirred for 4 hr at 0°C. It was then poured into a solution of 10% aqueous $NaHCO_3$ and extracted with dichloromethane. The organic layer was washed once with water, dried and concentrated to afford a crude oil which on purification through a silica gel column (eluant, light petrol + ethyl acetate, 20:1) afforded pure mesylate 93b (489 mg, 90%), ^{1}H-NMR ($CDCl_3$): Figure 1.3.21. δ 1.1 - 2.2 (m,

2H, 5-CH_2), 3.02 (s, 3H, $OSO_2\underline{CH_3}$), 3.8-4.6 (m, 3H, 6-CH_2 + H-4), 5.58 (s, 1H, benzylic methine), 7.49 (m, 5H, Ph).

(ii) From cis-2-Butene 1,4 diol:

3,4-Dihydroxy-but-1-ene was prepared from cis-2-butene-3,4-diol according to the reported procedure through a mercuric ion catalysed rearrangement[52].

4-Benzyloxy, 3-hydroxy-but-1-ene (98)

To a mechanically stirred and refluxing suspension of anhydrous potassium carbonate (100 g) in dry acetone (250 ml), the butene diol 97 (17.6 g, 0.2 m) in dry acetone (50 ml) was added. Benzyl bromide (23.7 ml, 0.2 m.) was added dropwise to the reaction mixture along with a catalytic amount of sodium iodide (2 g). The suspension was refluxed for 72 hr to allow completion and filtered. The solvent was evaporated in vacuo and the residue was purified on a column of silica gel (eluant light petrol) to afford 98 (25 g, 70%). IR ν_{max} (neat): 3420 cm^{-1}; ^{1}H-NMR (CCl_4): δ 3.45 (m, 2H, 4-CH_2), 4.53 (dd, 2H, benzylic methylene), 5.6 (m, 3H, olefinic protons H-1,2,2'), 7.27 (s, 5H, Ph). Mass m/z: 178 (M^+).

Analysis: Calculated for $C_{11}H_{14}O_2$: C, 74.16; H, 7.87; Found: C, 74.00; H, 7.71%.

1,2-Epoxy-3-hydroxy-4-benzyloxybutane (99)

m-Chloroperbenzoic acid (85%, 26 g, 0.13 m) was added in small portions to a stirred and cooled (0°) solution of the olefin 98 (21 g, 0.12 m) in dry dichloromethane

(100 ml). After the addition, the reaction was stirred at room temperature for 18 hr when a 10% solution of $NaHCO_3$ was added to it. The organic layer was separated, washed repeatedly with 10% $NaHCO_3$, H_2O, dried and concentrated. The crude oil was purified by passing through a silica gel column (eluant, light petrol, ethyl acetate, 7:1) to afford the epoxide 99 (19.5 g, 85%). IR ν_{max} (neat): 3400, 1600 cm^{-1}; ^{1}H-NMR (CCl_4): Fig.1.3.25. Mass m/z: 194 (M^+).

Analysis: Calculated for $C_{11}H_{14}O_3$: C, 68.04; H, 7.22; Found: C, 67.91; H, 7.21%.

'Red-Al' reduction of the epoxide 99

A solution of the epoxide 99 (7.76 g, 0.04 m) in dry tetrahydrofuran (40 ml) was cooled to -23°C under nitrogen. 3.5M solution of 'Red-Al' in toluene (12.26 g, 17.34 ml, 3 m.eq.) was added to the above and the reaction mixture was stirred for 2 hr at -23°C. It was decomposed by slow addition of a saturated solution of brine till a granular solid was obtained. The suspension was filtered and the residue washed with chloroform. The combined organic layers were dried and evaporated in vacuo to afford a mixture of isomeric diols, 100 and 101[53] (6.7 g, 86%. IR ν_{max} (neat): 3400 cm^{-1}. Mass m/z: 196 (M^+).

4-Benzyloxymethyl-2,2-dimethyl-1,3-dioxane (102)

The above mixture of diols 100 and 101 (6.5 g, 0.033 m) 2,2 dimethoxypropane (7 g, 8.2 ml, 0.066 m) and toluene

p-sulfonic acid (100 mg) were stirred in dry acetonitrile (30 ml) under nitrogen for 24 hr. The acidity of the medium was neutralized by a few drops of triethylamine and the solvent was concentrated. The oily residue was purified on a silica gel column to afford first, the 1,3-dioxane 102[54] as an oil (4.66 g), eluant (light petrol) and next the 1,3-dioxolane 103[54] (1.55 g) in an overall yield of 80% and a ratio of 3:1.

102, ^{1}H-NMR (CCl_4): Fig.1.3.26; Mass m/z: 226 (M^+).

Analysis: Calculated for $C_{14}H_{20}O_3$: C, 71.19; H, 8.47; Found: C, 70.96; H, 8.36%.

103, ^{1}H-NMR (CCl_4): Fig.1.3.27; Mass m/z: 226 (M^+).

Analysis: Calculated for $C_{14}H_{20}O_3$: C, 71.19; H, 8.47; Found: C, 70.85; H, 8.43%.

4-methanol-2,2-dimethyl-1,3-dioxane (104)

To the 1,3-dioxane 102 (2 g, 8 m.mol) in ethylacetate (5 ml) was added 10% palladised charcoal (100 mg) and the reaction was stirred at room temperature for 4 hr under hydrogen. It was then filtered and concentrated in vacuo to afford 104 (0.99 g, 80%). IR ν_{max} (neat): 3400 cm^{-1}. ^{1}H-NMR ($CDCl_3$) (Fig.1.3.28): δ 1.2-1.5 (m, 8H, 2X CH_3 + 5-CH_2), 2.8 (br, 1H, -OH- exchanges with D_2O), 3.4-4.3 (m, 5H, 6-CH_2 + H-4 + CH_2-OH). Mass m/z: 146 (M^+).

Analysis: Calculated for $C_7H_{14}O_3$: C, 57.53; H, 9.59; Found: C, 57.41; H, 9.52%.

Ethyl 1-(2',2'-dimethyl-1',3'-dioxan-4'-yl)-pent-1-enoate (106)

To a solution of methylene chloride (8 ml) and oxalyl chloride (0.35 ml, 3.85 m.mol) at -60°C was added dimethylsulfoxide (0.6 ml, 7.7 m.mol) dissolved in dichloromethane (0.5 ml). After 5 minutes, the alcohol 104 (0.5 g, 3.4 m.mol) in dichloromethane (1 ml) was added to the above and the reaction stirred for 1 hr at -23°C. Then triethylamine (2.5 ml, 17.5 m.mol) was added, stirred for 5 minutes and then allowed to warm to room temperature. H_2O (1 ml) was added and aqueous layer was re-extracted with dichloromethane, washed with saturated sodium chloride, dried and concentrated. The oil was purified on column (eluant, light petrol) to afford 105 (123 mg) which was immediately subjected to Wittig reaction. IR ν_{max} (neat): 1710 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.2 - 1.5 (m, 8H, 2X CH_3 + 5-CH_2), 3.6 - 4.7 (br.m, 3H, 6-CH_2 + H-4), 9.60 (d, 1H, -CHO).

The Wittig salt, carbethoxypropyltriphenylphosphorane[50] (5 g, 0.01 m) in dry N,N-dimethylformamide (5 ml) was stirred with a 2.5M solution of NaOEt (4 ml, 0.011 m) at room temperature. To the above, the aldehyde 105 (120 mg, 0.83 m.mol) in dry N,N-dimethylformamide (1 ml) was added and the reaction stirred at room temperature for 20 hr. It was then poured into cold water and extracted with hexane, dried and concentrated in vacuo to afford an oil which was purified on a short column (eluant, benzene) to afford the product 106 (40 mg, 20%).

IR ν_{max} ($CHCl_3$): 1735 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.1-1.4 (m, 11H, 3X CH_3 + 5'-CH_2), 2.28 (m, 4H, CH_2 at C-3,4), 3.5 - 4.4(m, (4H, 6'-CH_2 + $C\underline{H}_2CH_3$), 5.2-5.6 (m, 3H, H-4',1,2). Mass m/z: 242 (M^+).

Analysis: Calculated for $C_{13}H_{22}O_4$: C, 64.46; H, 9.09; Found: C, 64.39; H, 9.01%.

Ethyl 6,8-dihydroxyoctanoate (62)

The α,β-unsaturated ester 106 (40 mg, 0.165 m.mol) in ethanol (1 ml) was hydrogenated over 10% palladised charcoal (10 mg) at normal pressure and temperature. After 4 hr, the solution was filtered, residue washed repeatedly with ethanol and the filterate concentrated to afford the saturated ester. It was stirred in methanol (1 ml) and a catalytic amount of toluene-p-sulfonic acid was added to it. After 4 hr at room temperature, it was neutralized with triethylamine and concentrated in vacuo to afford the diol ester 62 (5 mg) after distillation at 150°/0.1 mm, lit.[57] b.p.150-8° (0.1 mm). IR ν_{max} ($CHCl_3$): 3400,1735 cm^{-1}; ^{1}H-NMR ($CDCl_3$): Fig.1.3.24.

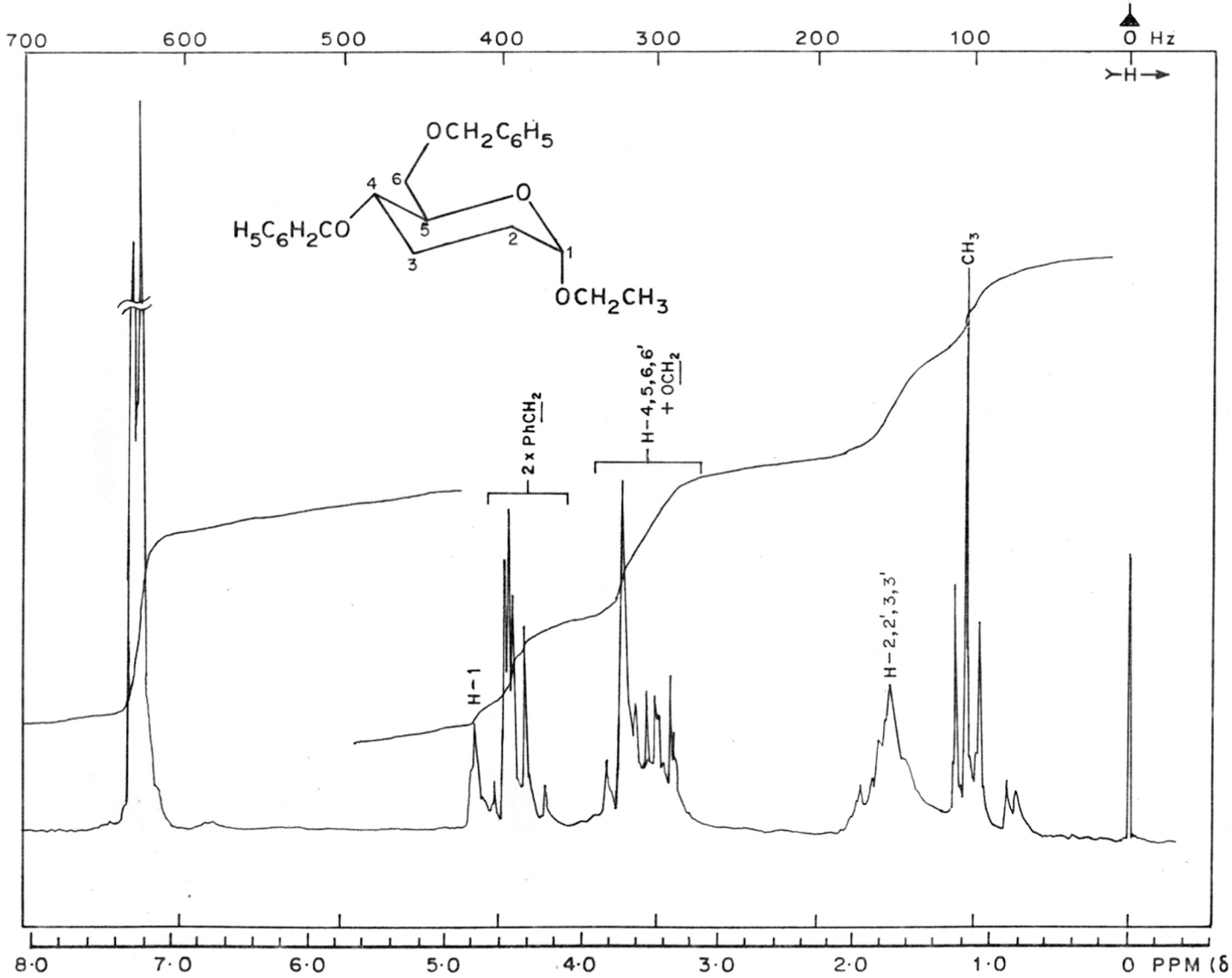

700
600
500
400
300
200
100
0 Hz
→H←
OCH2C6H5
H5C6H2CO
OCH2CH3
4
6
5
3
2
1
O
CH3
2 x PhCH2
H-4,5,6,6'
+ OCH2
H-1
H-2,2',3,3'
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM (δ)

FIGURE 1·3·1

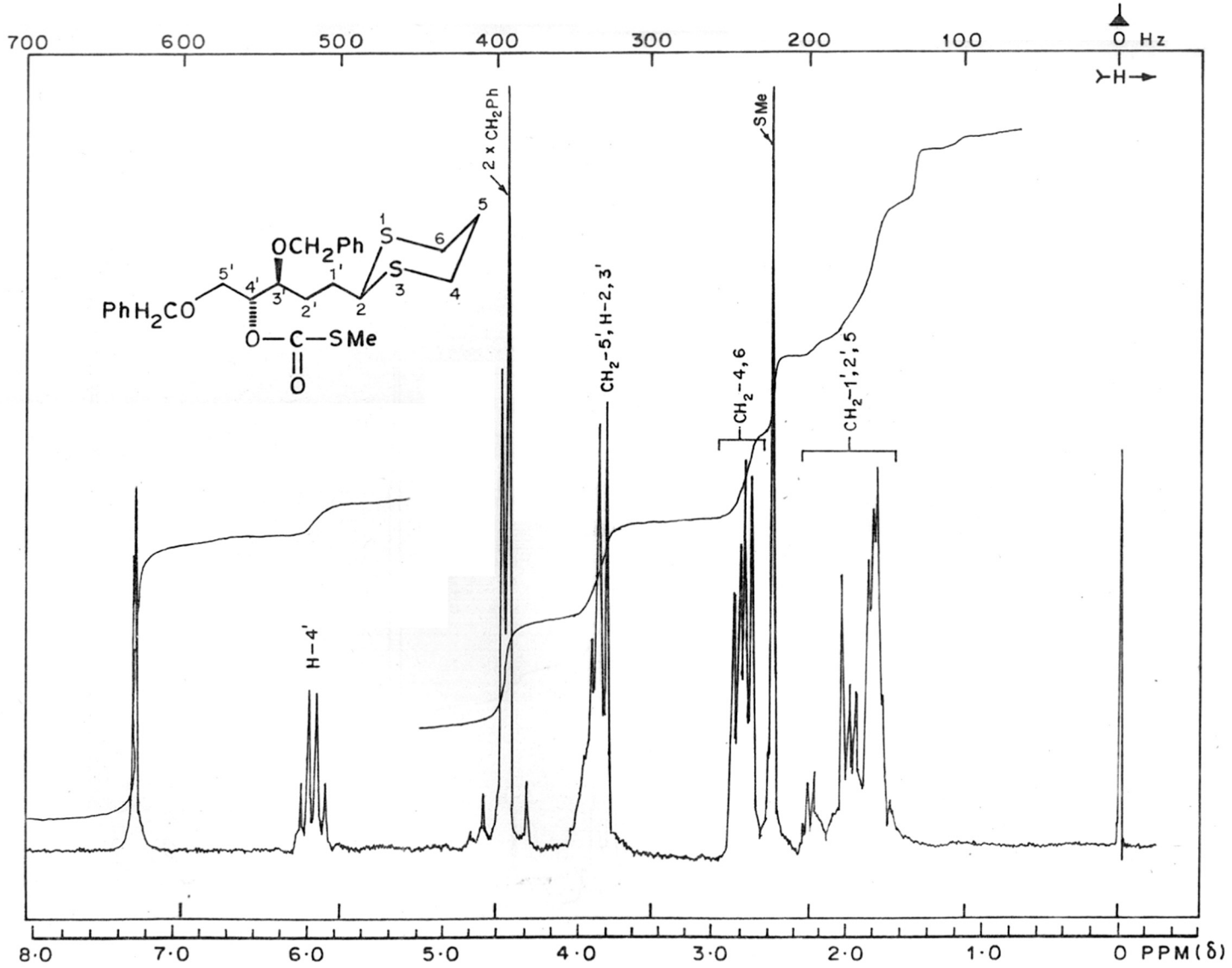

700
600
500
400
300
200
100
0 Hz
→H←
2 x CH2Ph
SMe
CH2-5', H-2, 3'
CH2-4, 6
CH2-1', 2', 5
H-4'
OCH2Ph
PhH2CO
O—C—SMe
O
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM(δ)

FIGURE 1·3·2

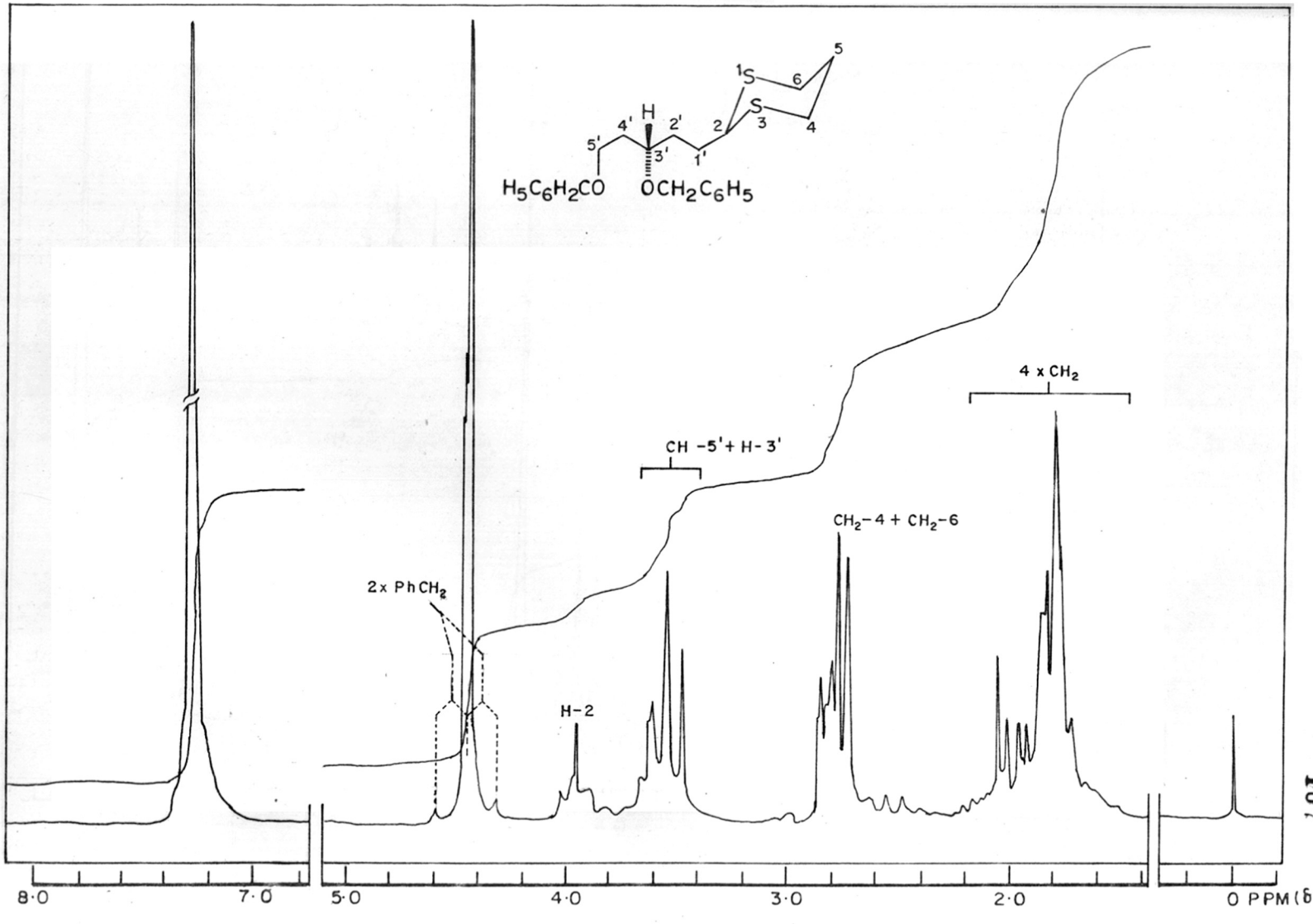

H5C6H2CO
OCH2C6H5
2x PhCH2
H-2
CH -5'+ H-3'
CH2-4 + CH2-6
4 x CH2
8·0
7·0
5·0
4·0
3·0
2·0
0 PPM(δ)

FIGURE 1·3·3

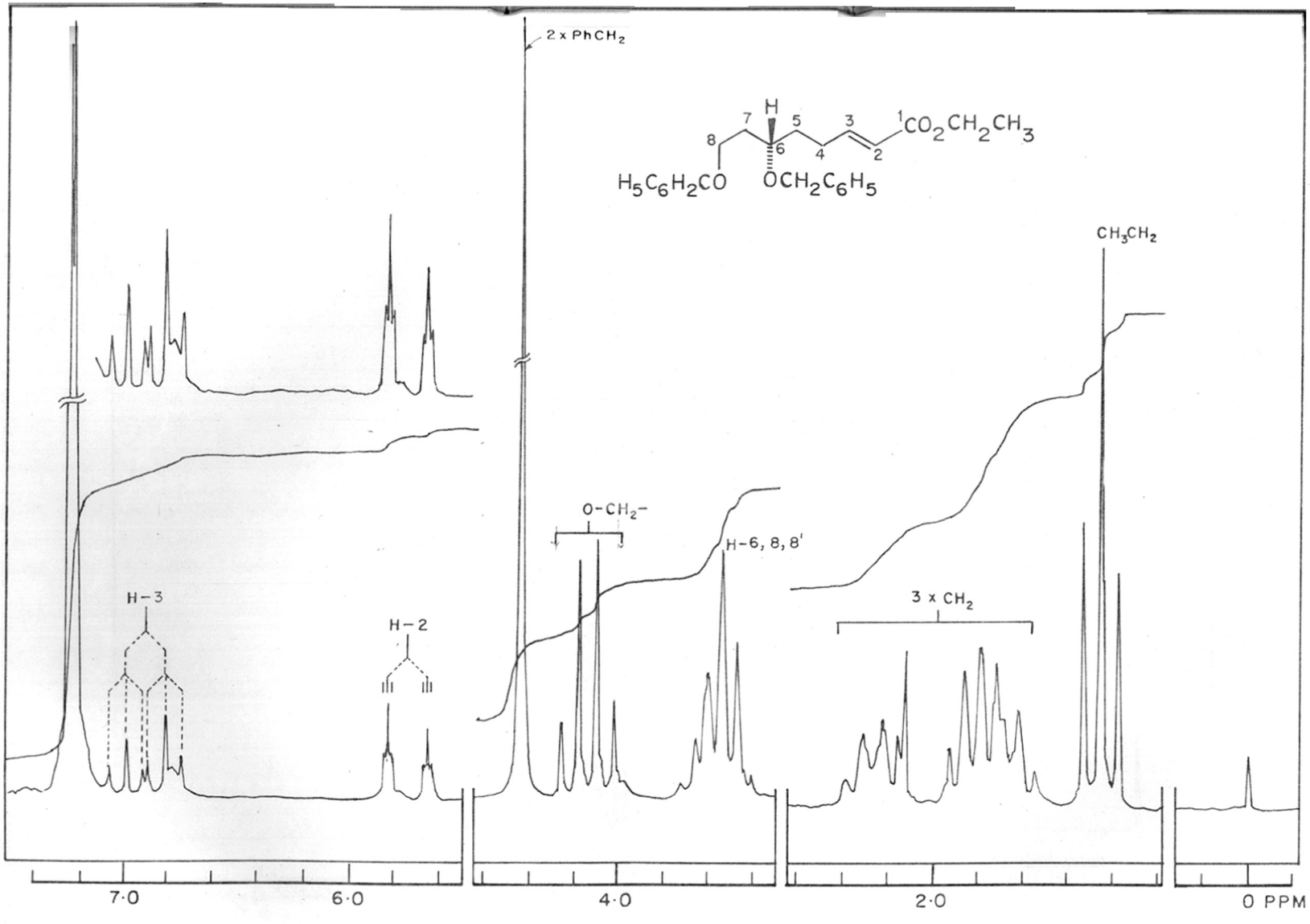

2 x PhCH2
H
7
5
3
1CO2CH2CH3
8
6
4
2
H5C6H2CO
OCH2C6H5
CH3CH2
O-CH2-
H-6, 8, 8'
H-3
H-2
3 x CH2
7·0
6·0
4·0
2·0
0 PPM(δ)

FIGURE 1·3·4

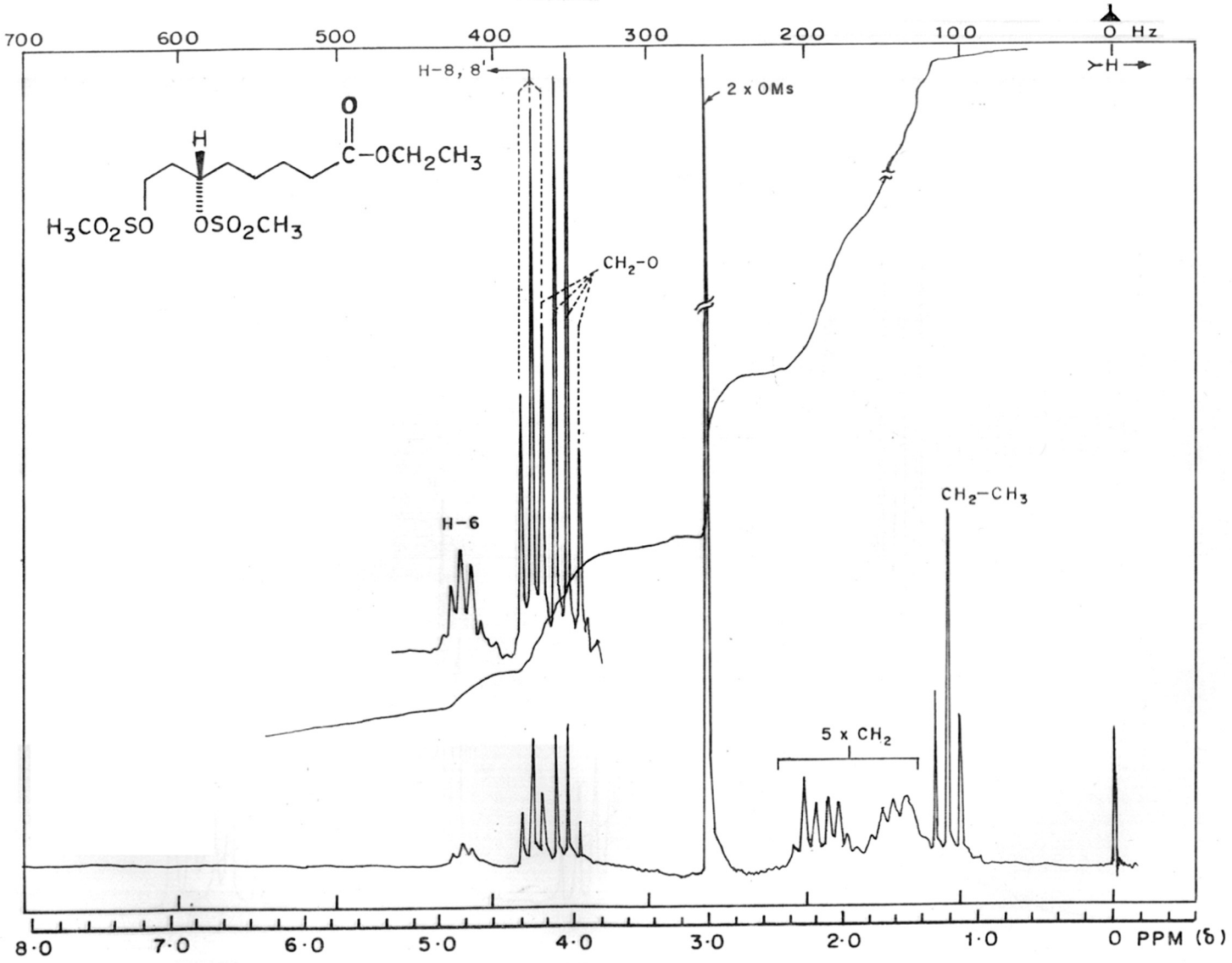

700
600
500
400
300
200
100
0 Hz
H-8, 8'
2 x OMs
CH2-O
H-6
CH2-CH3
5 x CH2
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM (δ)

FIGURE 1·3·5

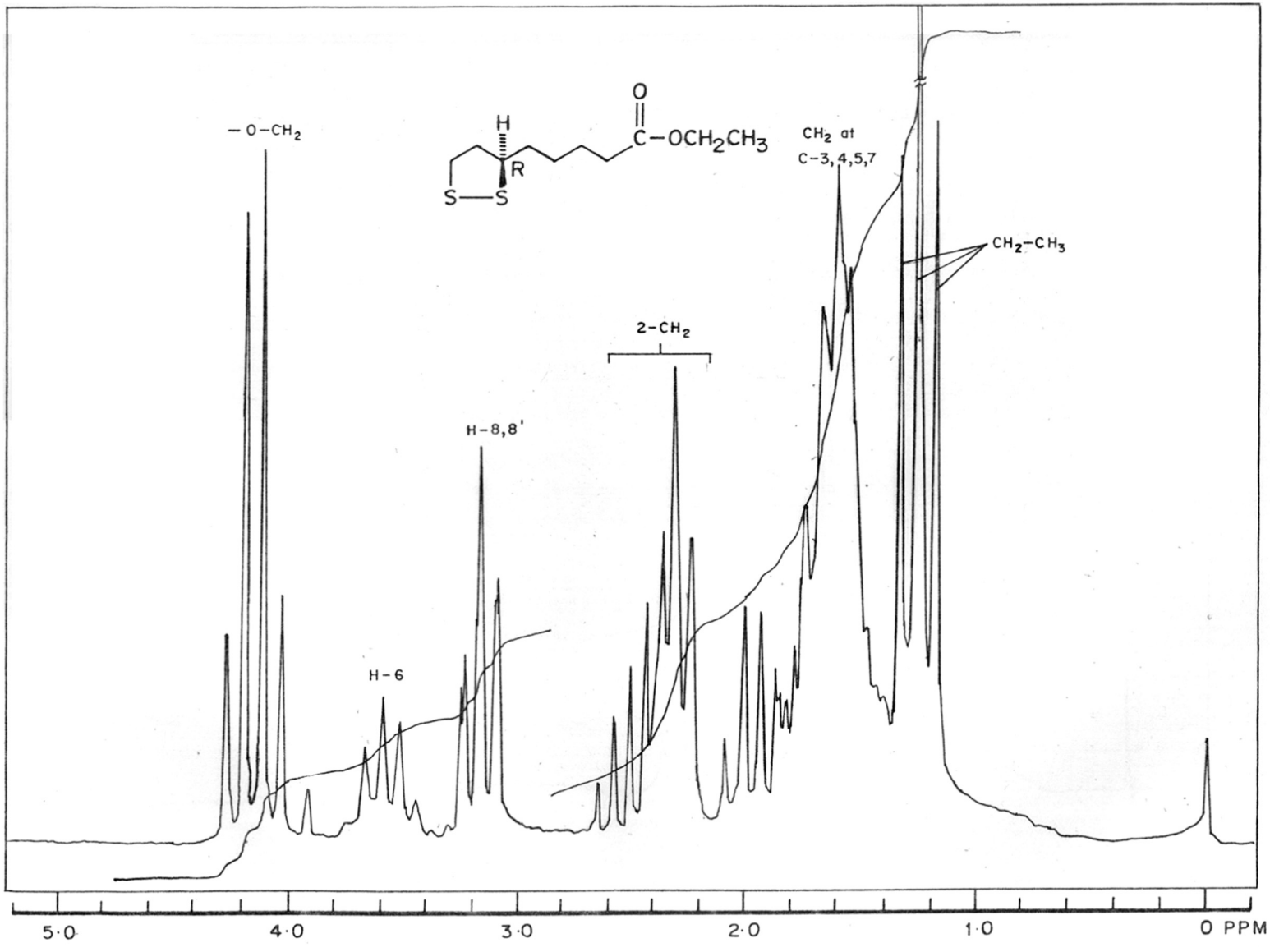

−O−CH2
H
R
S—S
O
C−OCH2CH3
CH2 at
C-3,4,5,7
CH2−CH3
2-CH2
H-8,8'
H-6
5·0
4·0
3·0
2·0
1·0
0 PPM(δ)

FIGURE 1·3·6

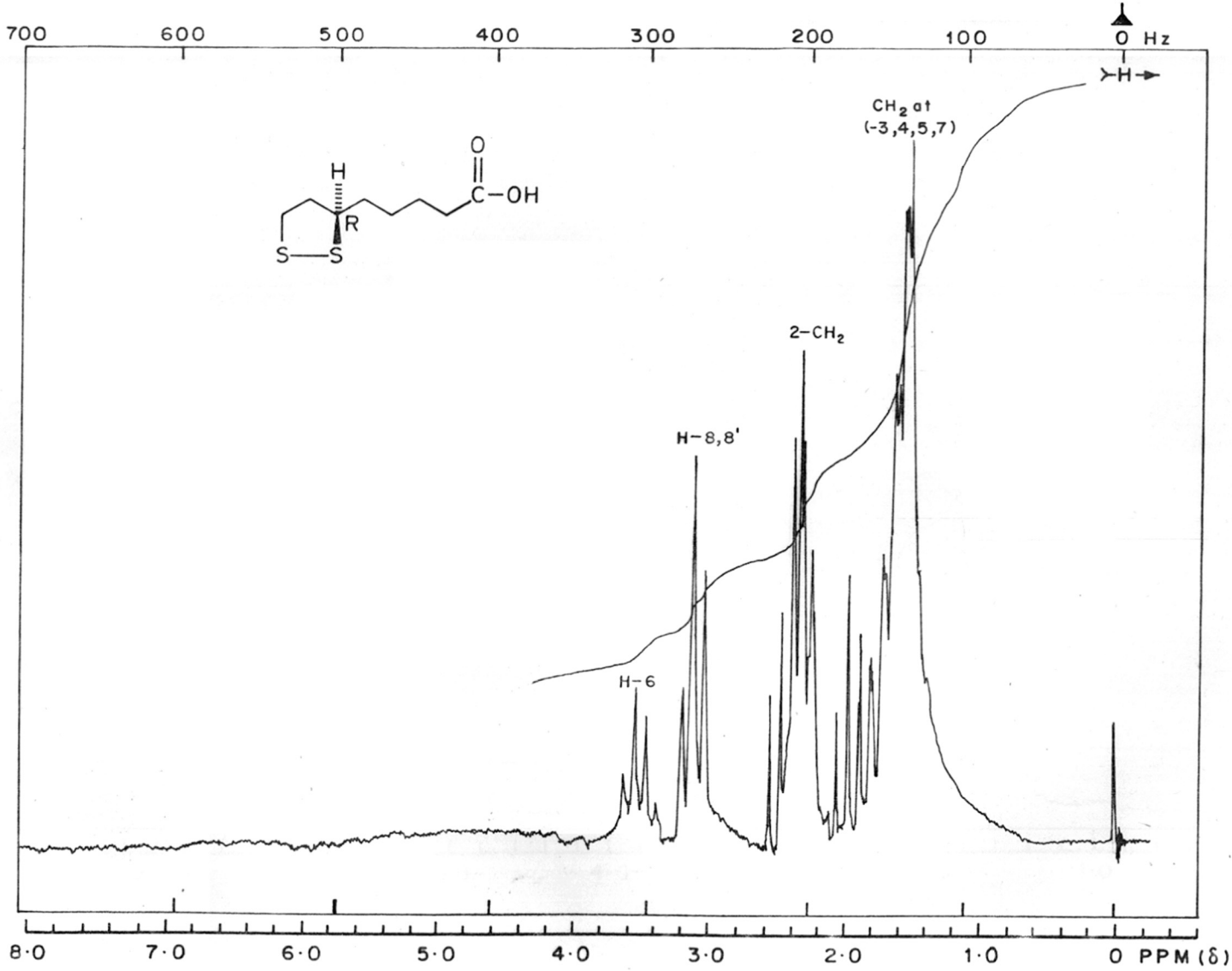

700
600
500
400
300
200
100
0 Hz
H
CH2 at
(-3,4,5,7)
O
H
C–OH
R
S—S
2–CH2
H–8,8'
H–6
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM (δ)

FIGURE 1·3·7

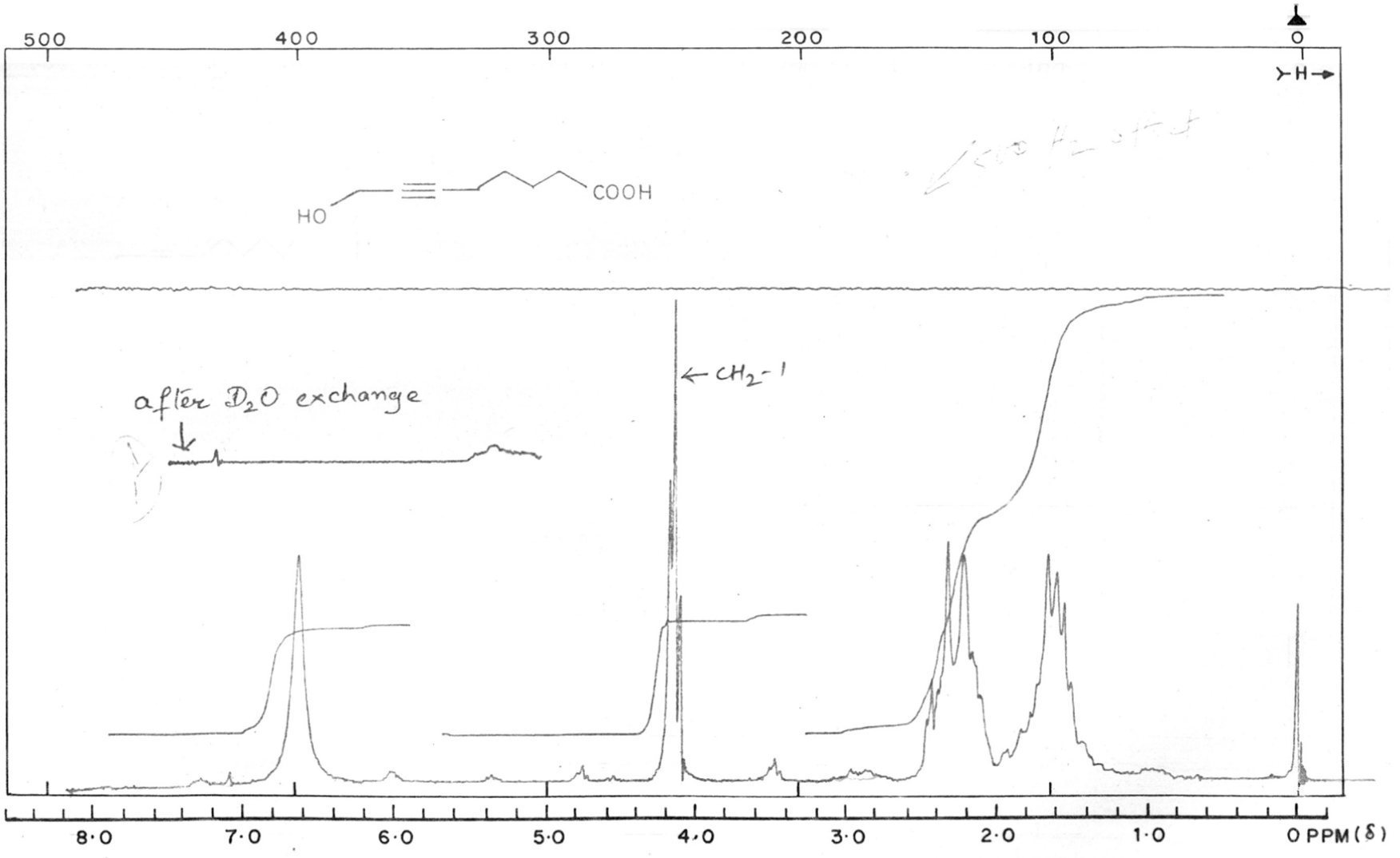

500
400
300
200
100
0
H
HO
COOH
after D_2O exchange
CH_2-1
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM(δ)

FIGURE. 1·3·8.

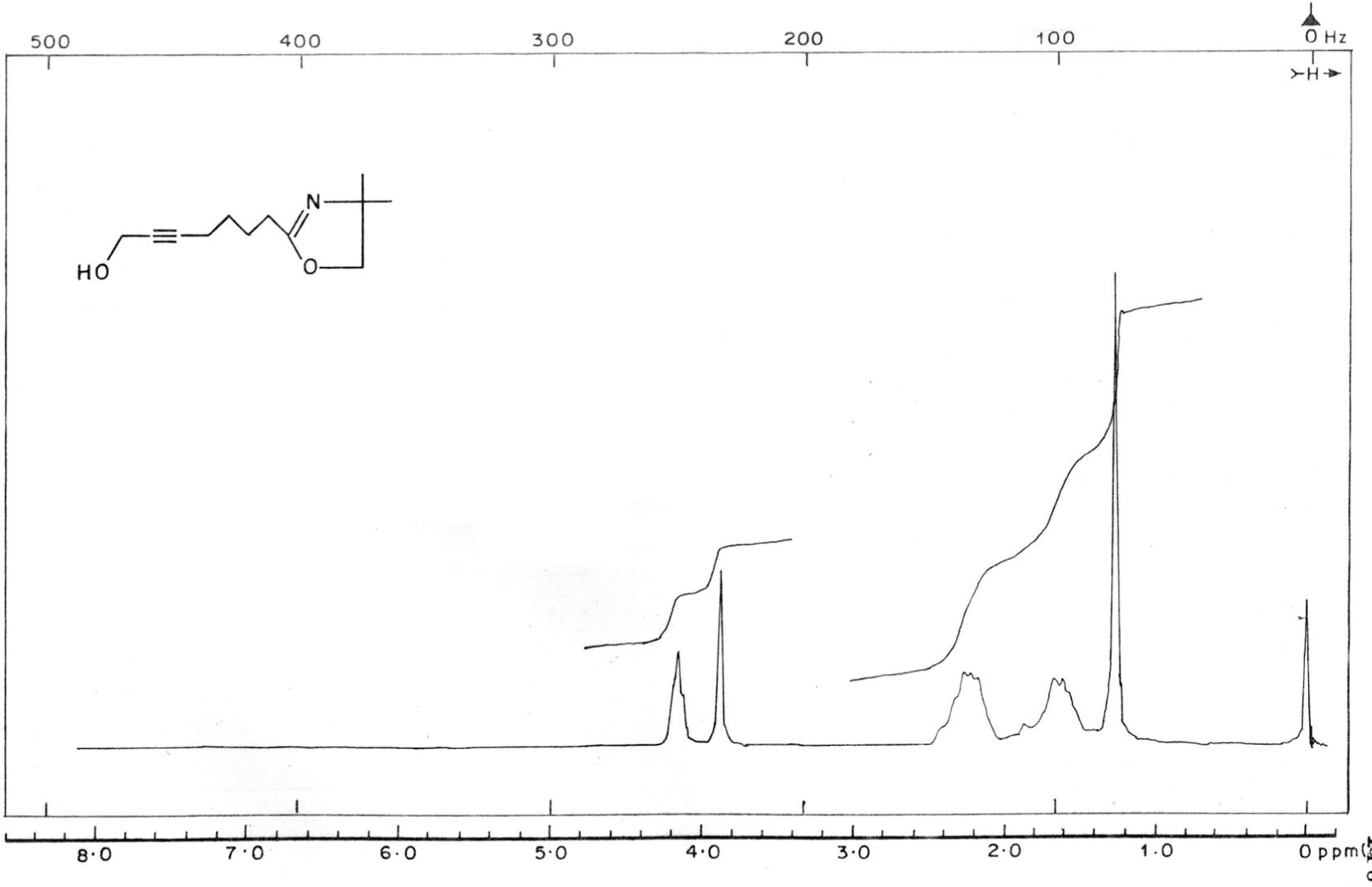


FIGURE . 1·3·9 .

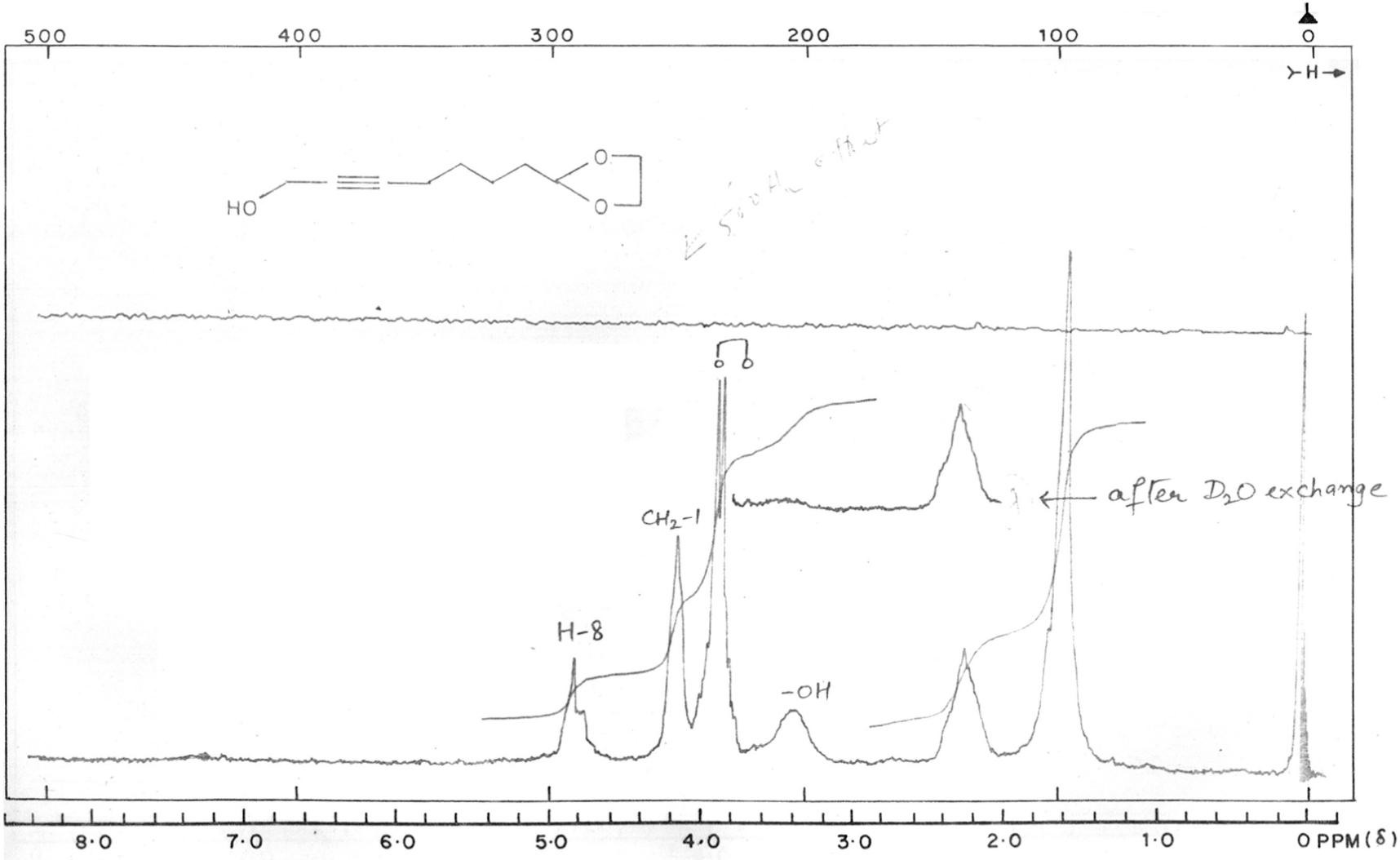

500
400
300
200
100
0
>H→
HO
O
O
CH2-1
H-8
-OH
after D2O exchange
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM(δ)

FIGURE. 1·3·10.

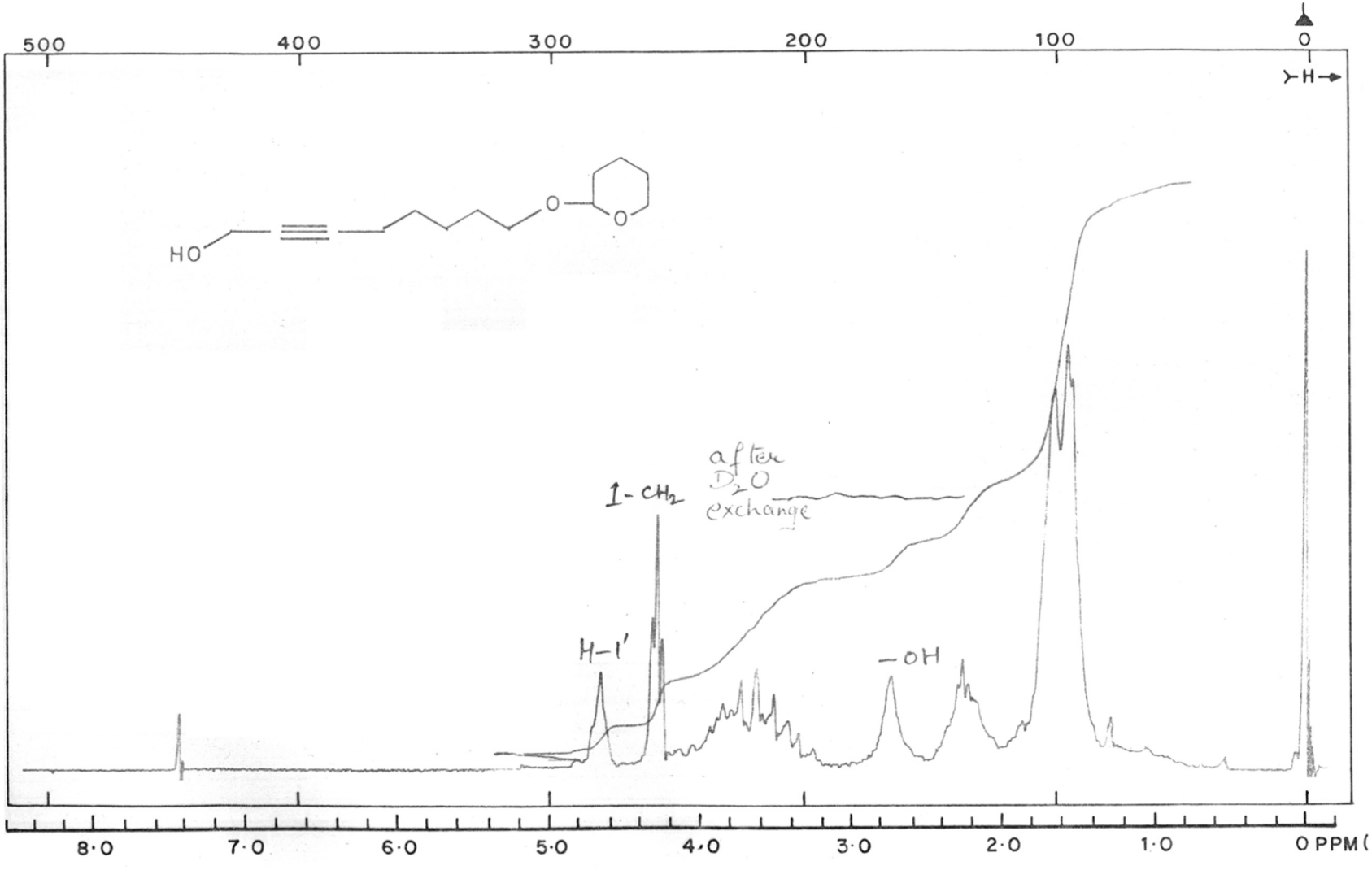

500
400
300
200
100
0
H
HO
O
O
1-CH2
after D2O exchange
H-1'
-OH
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM (δ)

FIGURE. 1·3·11.

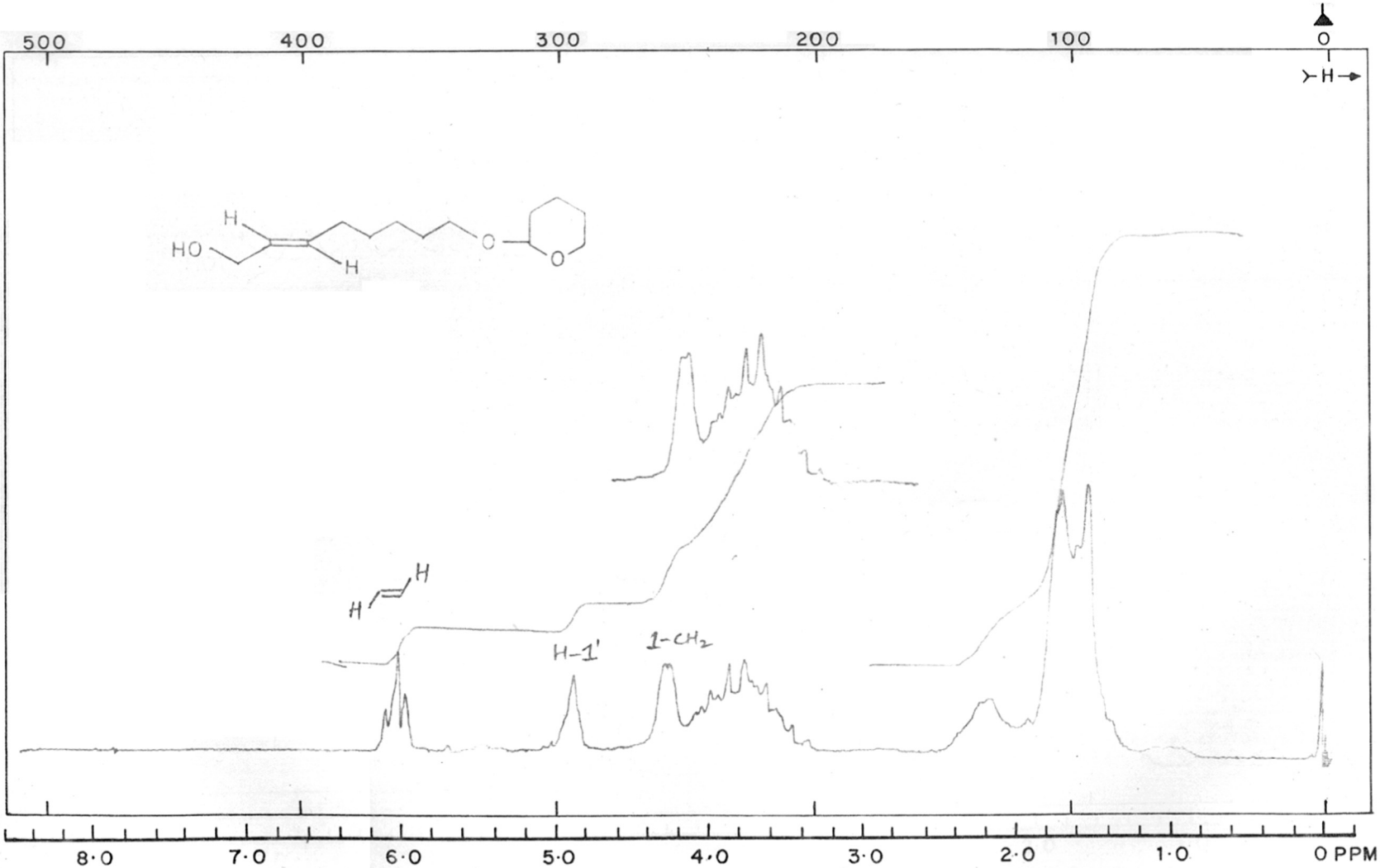

500
400
300
200
100
0
Y H
HO
H
H
O
O
H
H
H-1'
1-CH2
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM (δ)

FIGURE. 1·3·12.

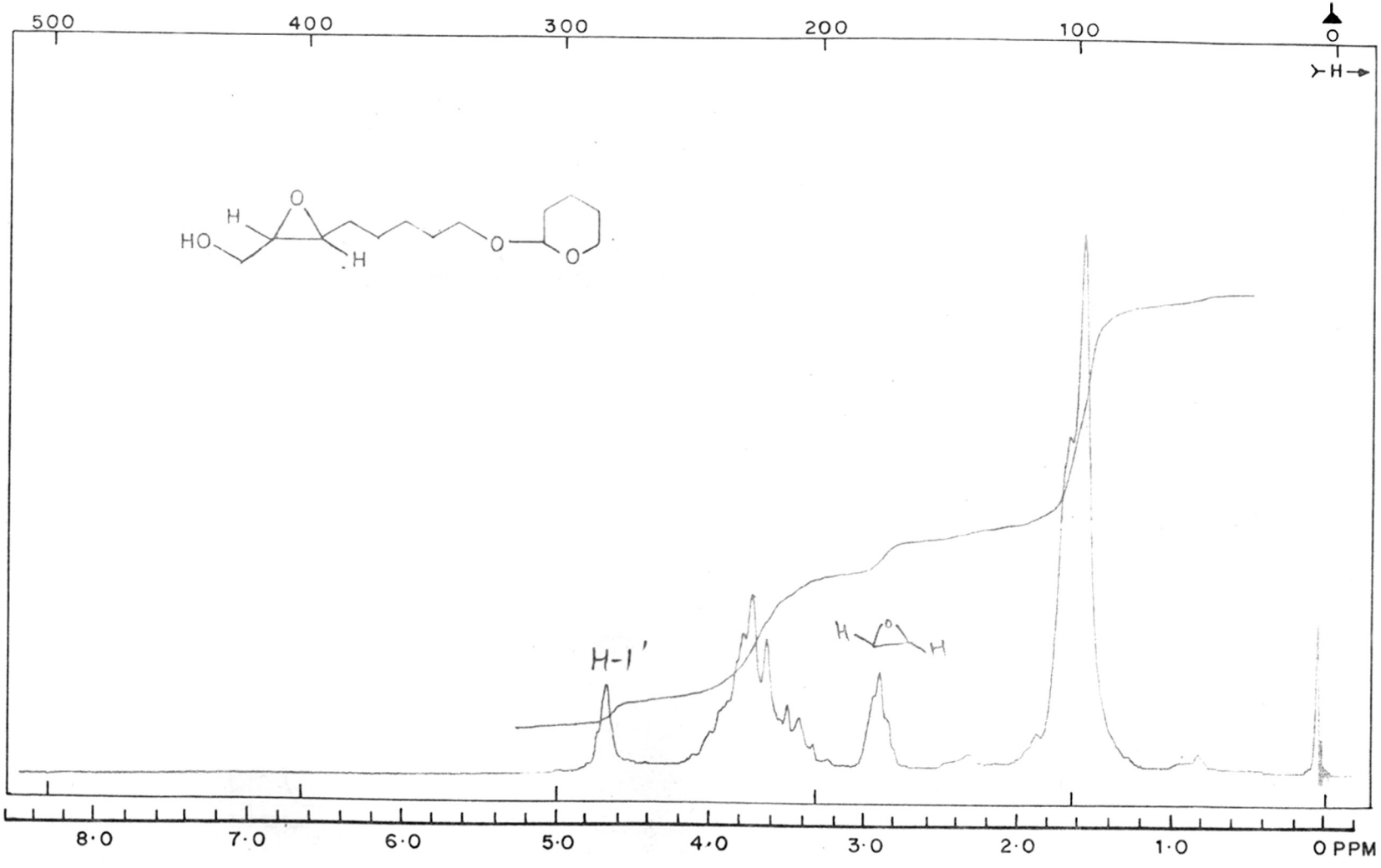

500
400
300
200
100
0
Y H
HO
H
O
H
O
O
H-1'
H
O
H
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM (δ

FIGURE 1·3·13.

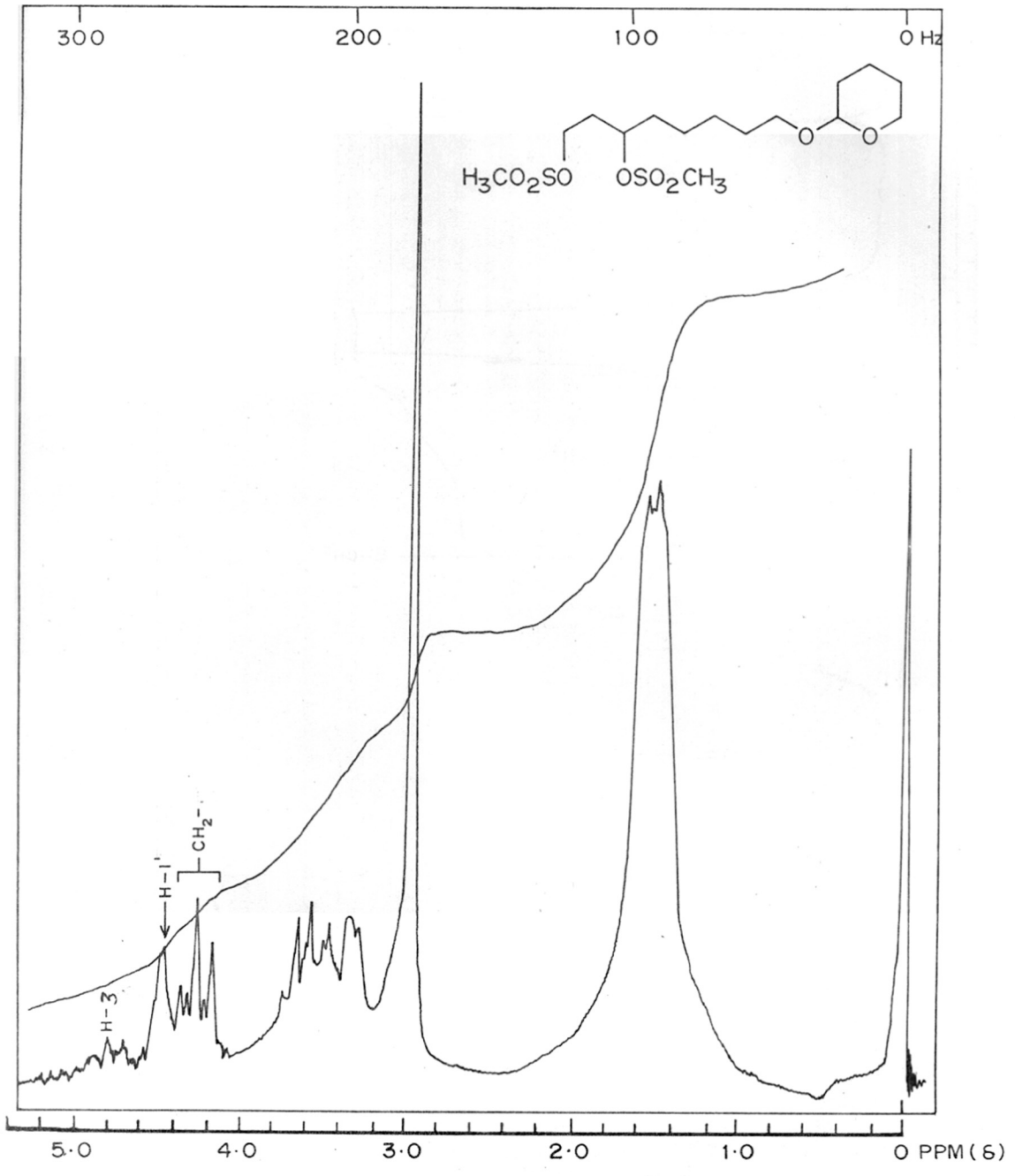

300
200
100
0 Hz
H3CO2SO
OSO2CH3
O
O
H-3
H-1'
CH2
5·0
4·0
3·0
2·0
1·0
0 PPM (δ)

FIGURE 1·3·14

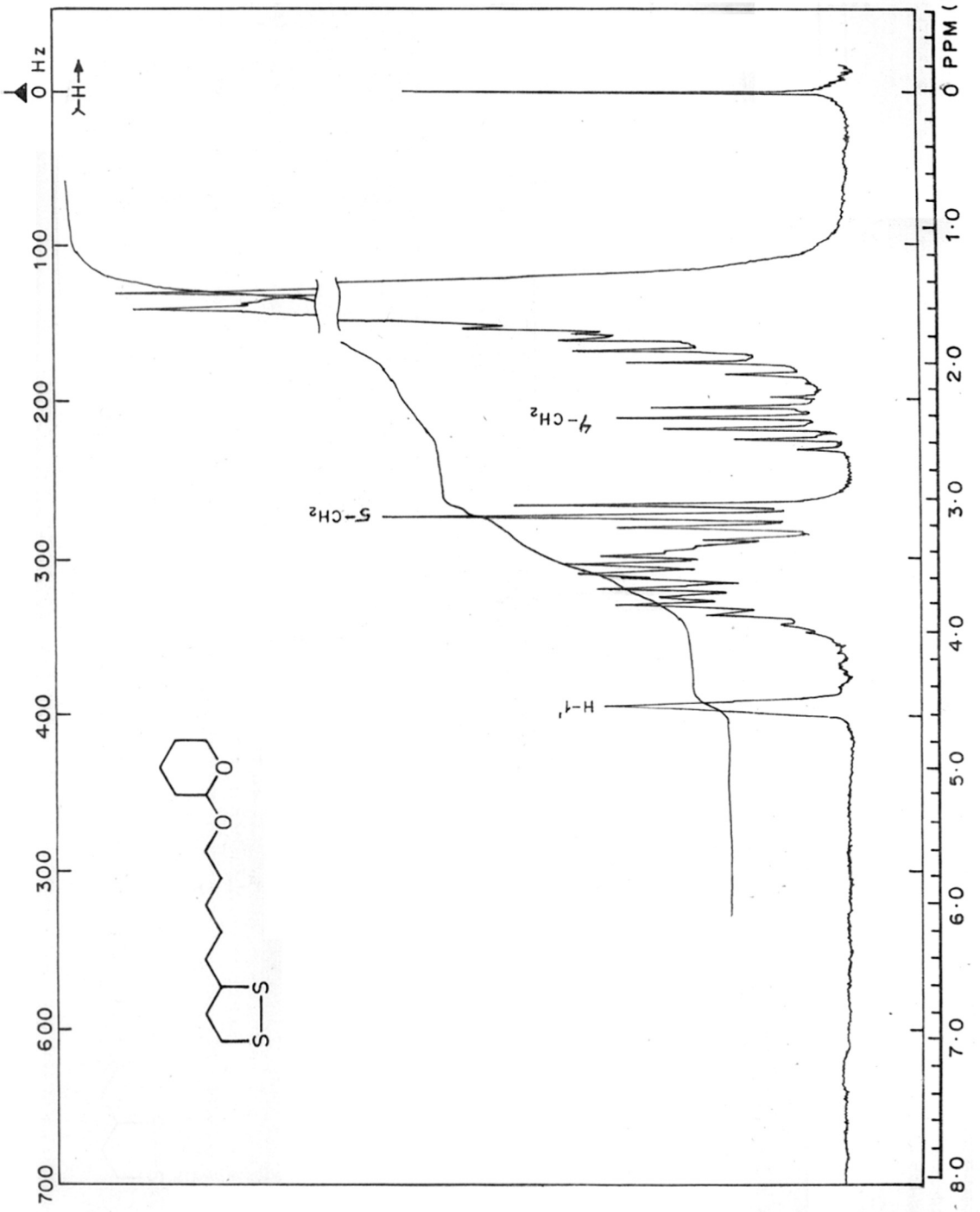

0 Hz
100
200
300
400
600
300
600
700
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM (δ)
H-1'
5-CH2
4-CH2
O
O
S
S

FIGURE 1·3·15

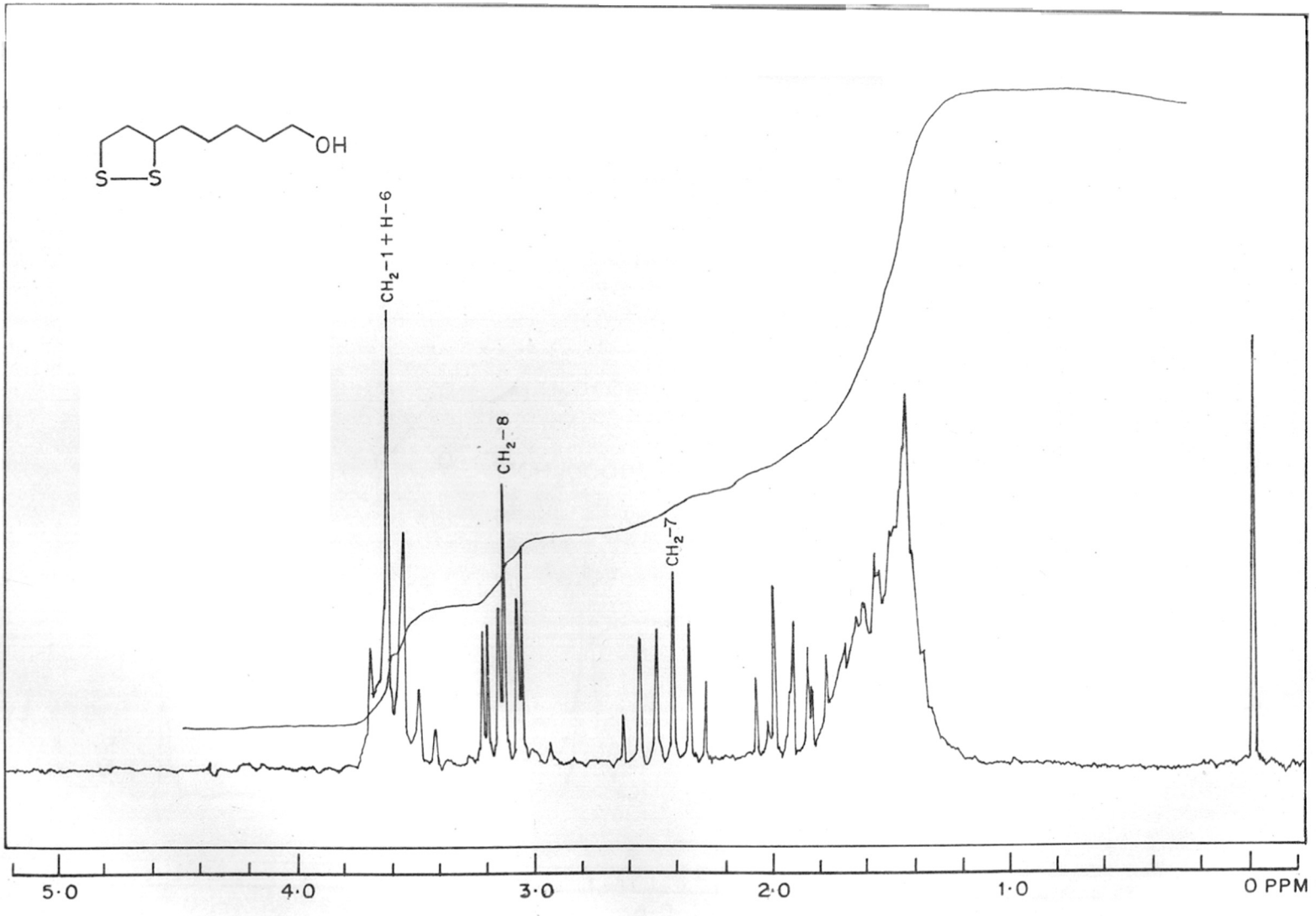


FIGURE 1·3·16

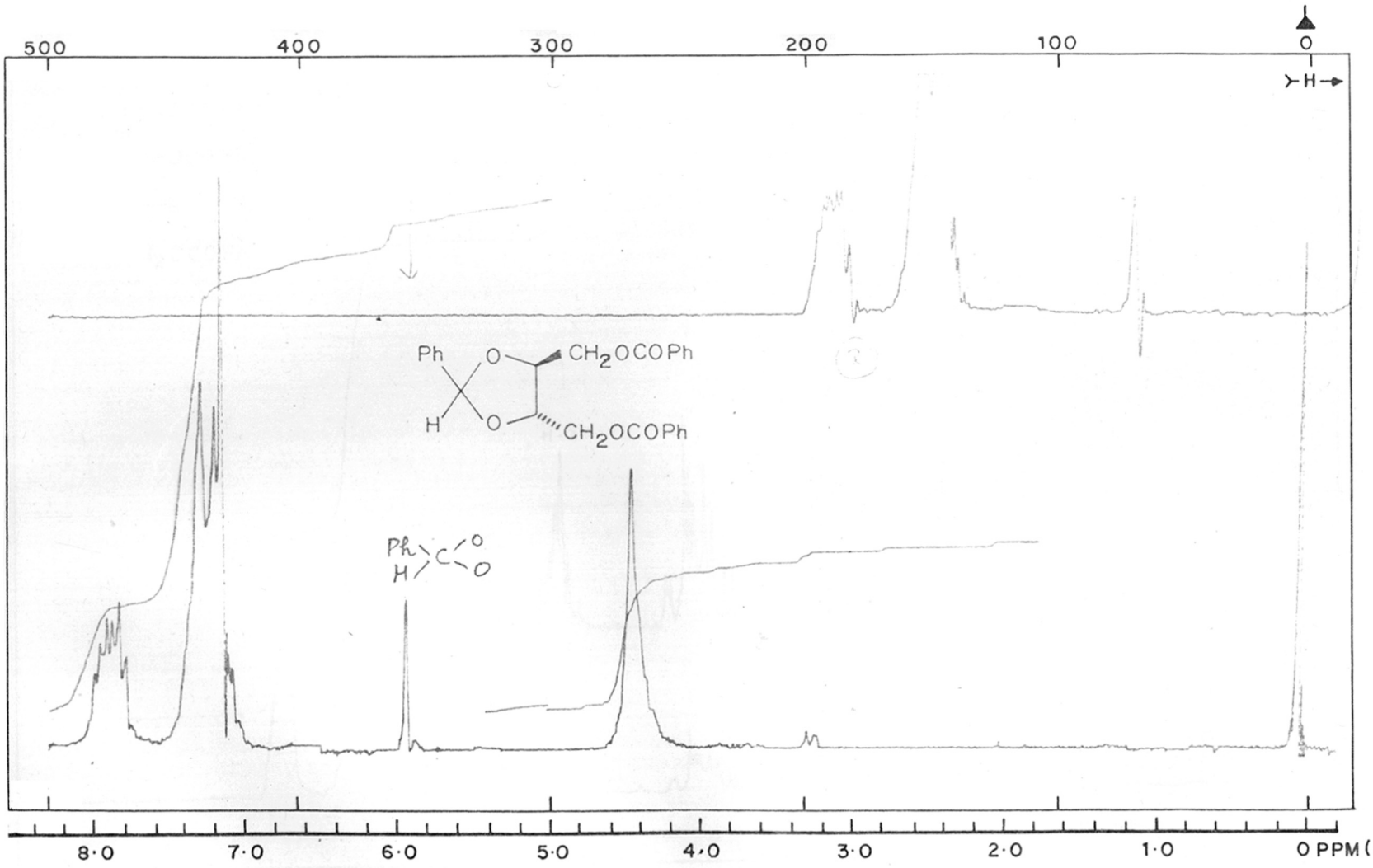

500
400
300
200
100
0
H
Ph
O
CH2OCOPh
H
O
CH2OCOPh
Ph
H
C
O
O
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM(δ)

FIGURE 1·3·17

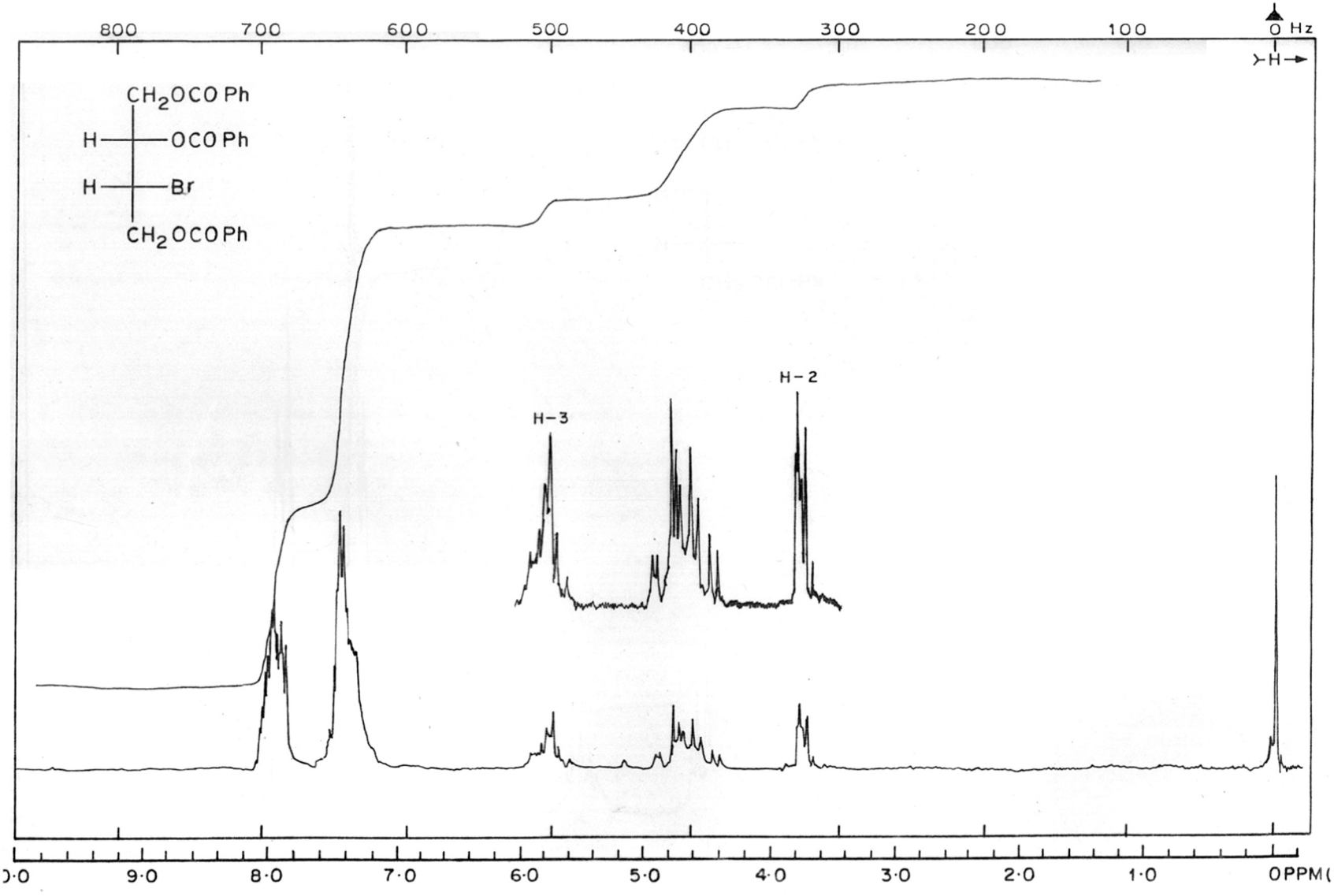
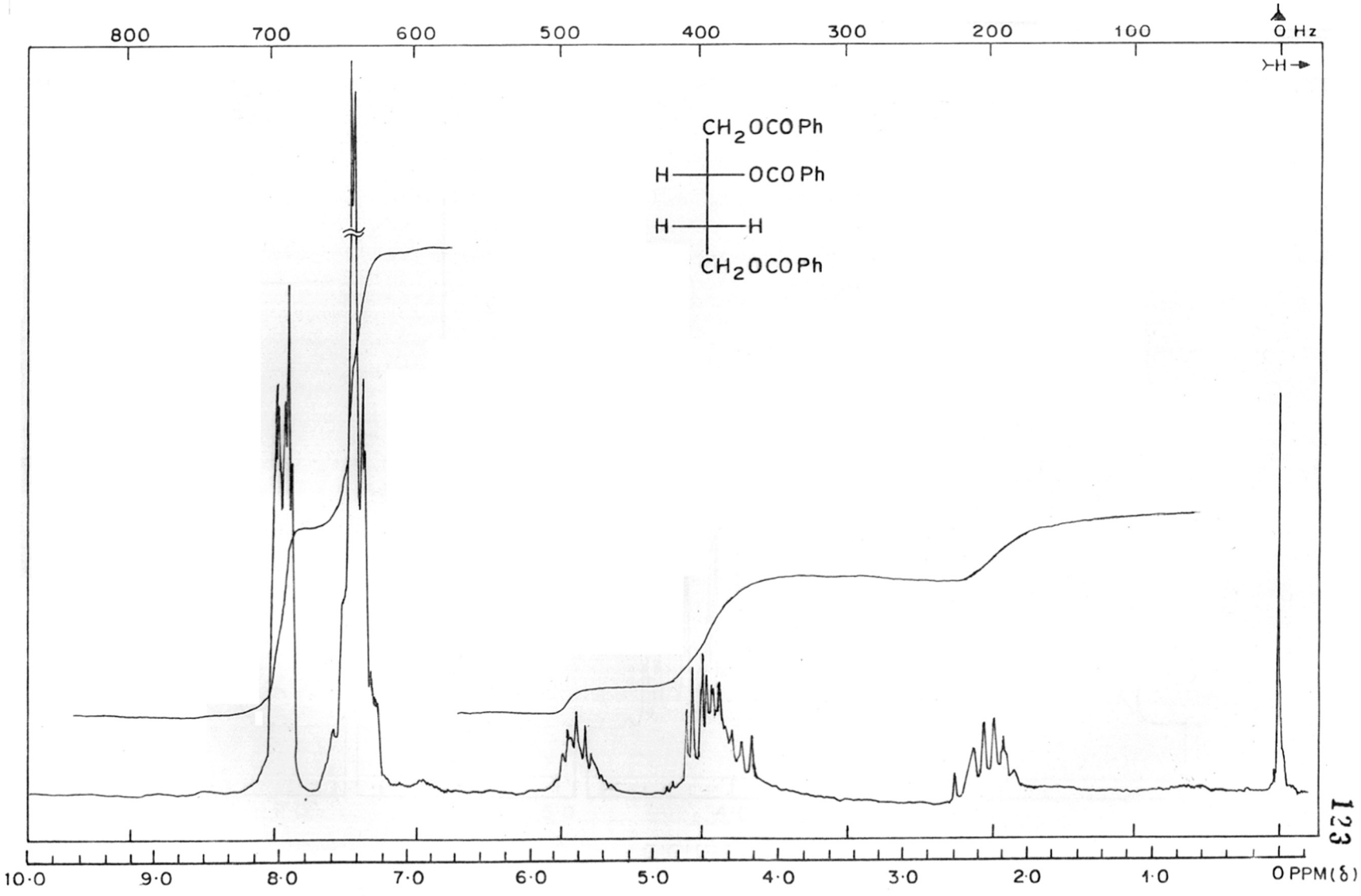

800
700
600
500
400
300
200
100
0 Hz
TMS
CH2OCOPh
H
OCOPh
H
Br
CH2OCOPh
H-3
H-2
9·0
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0PPM(δ)

FIGURE 1-3-18



123

FIGURE 1·3·19

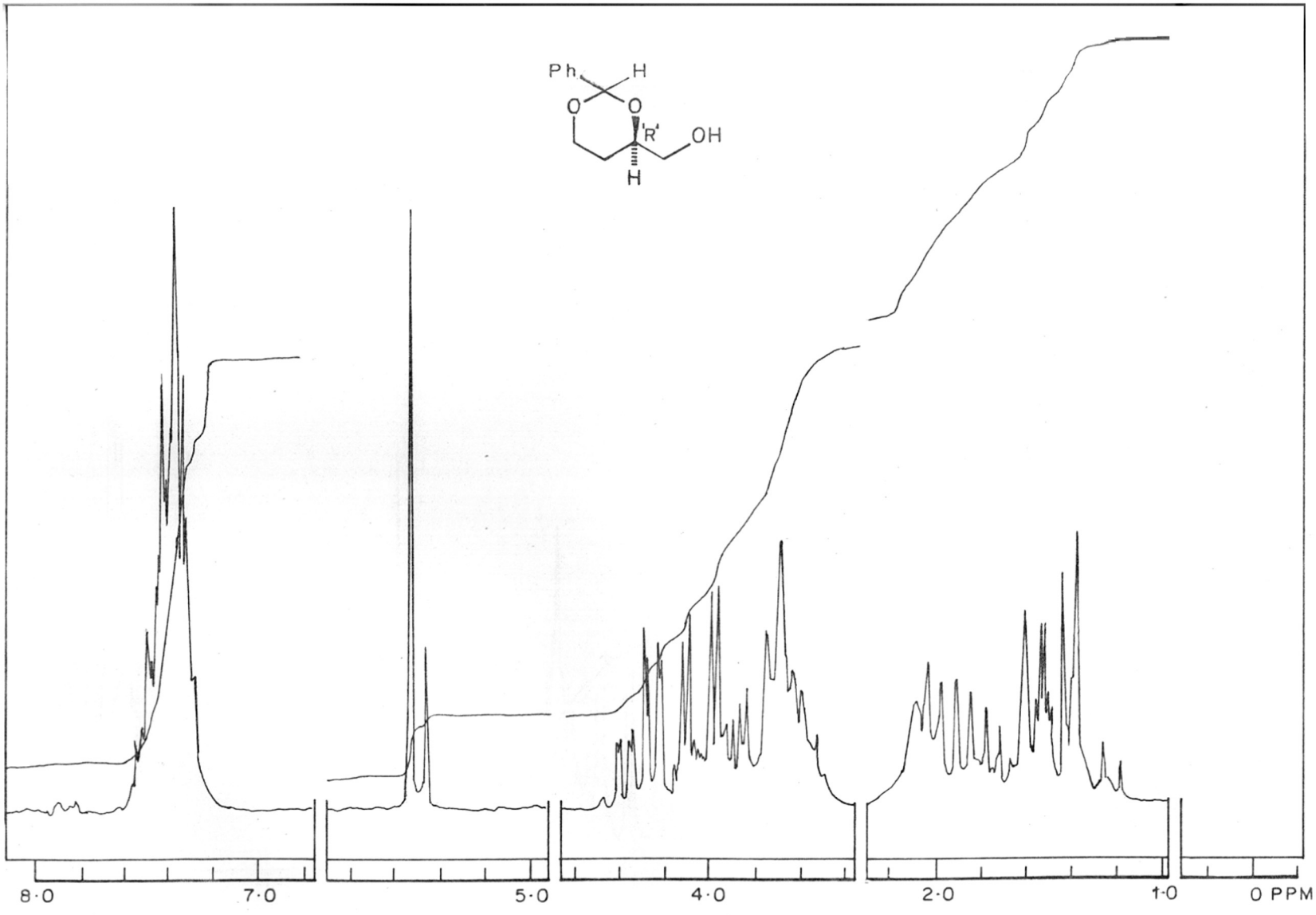


FIGURE 1·3·20

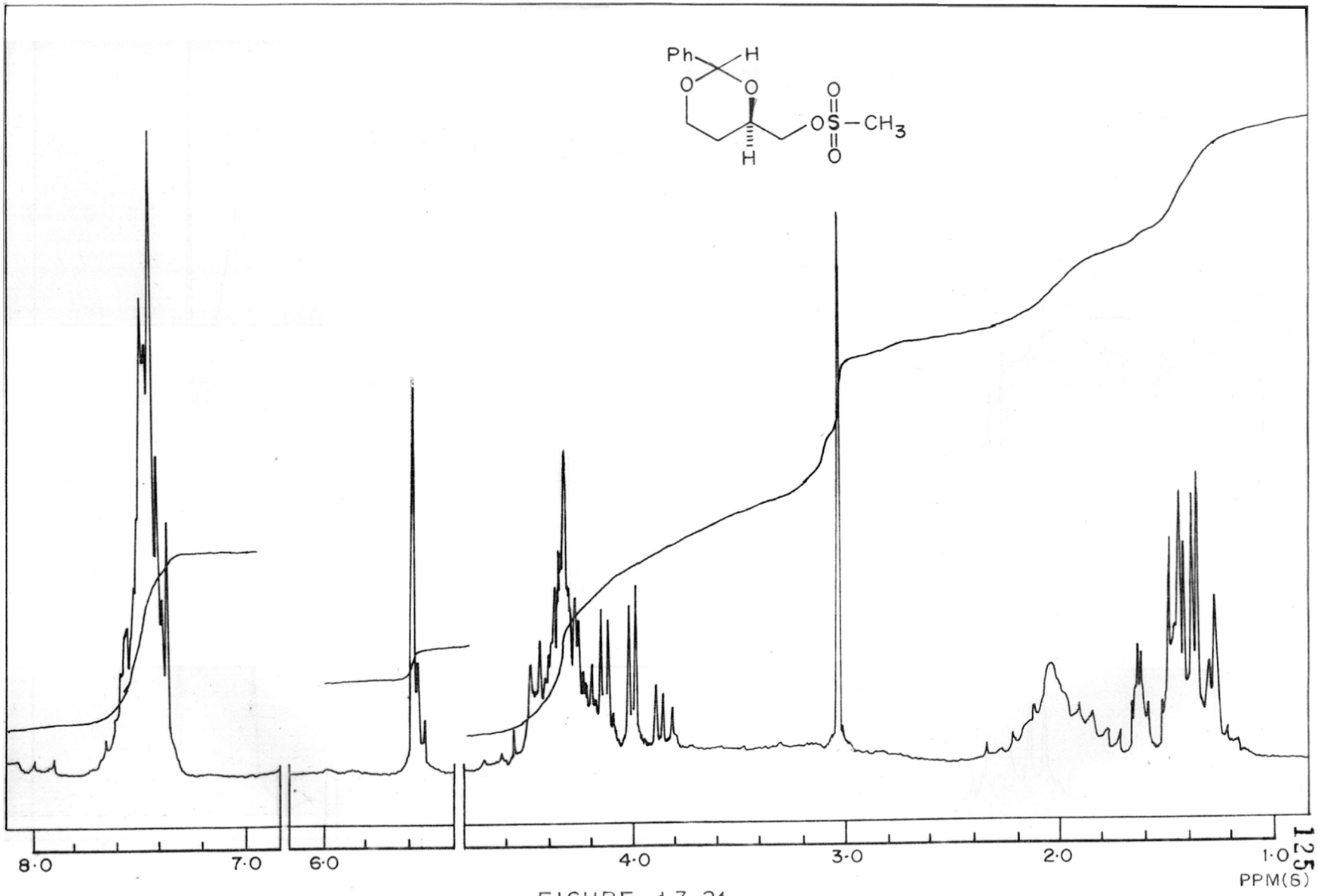


FIGURE 1·3·21

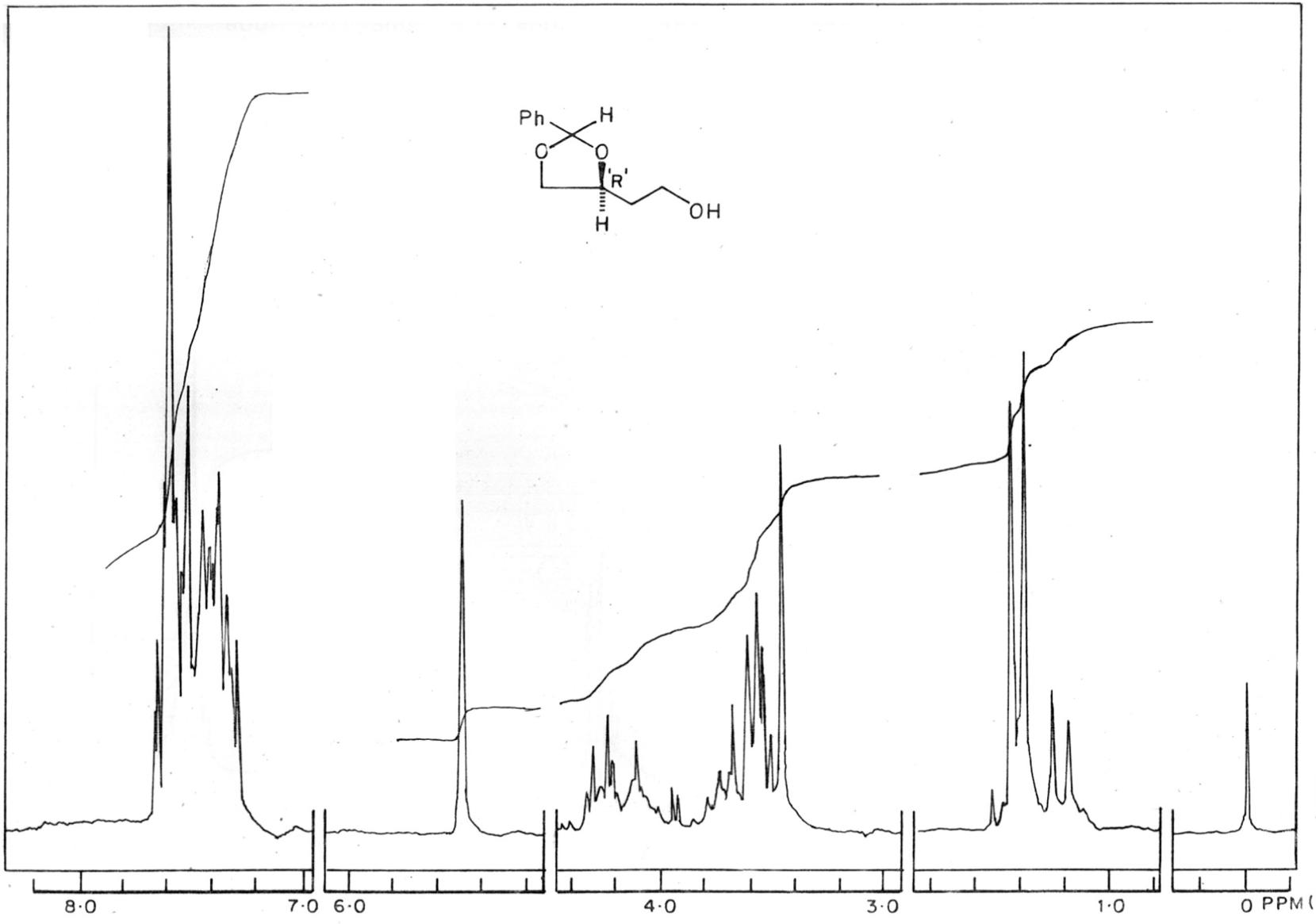


FIGURE 1·3·22

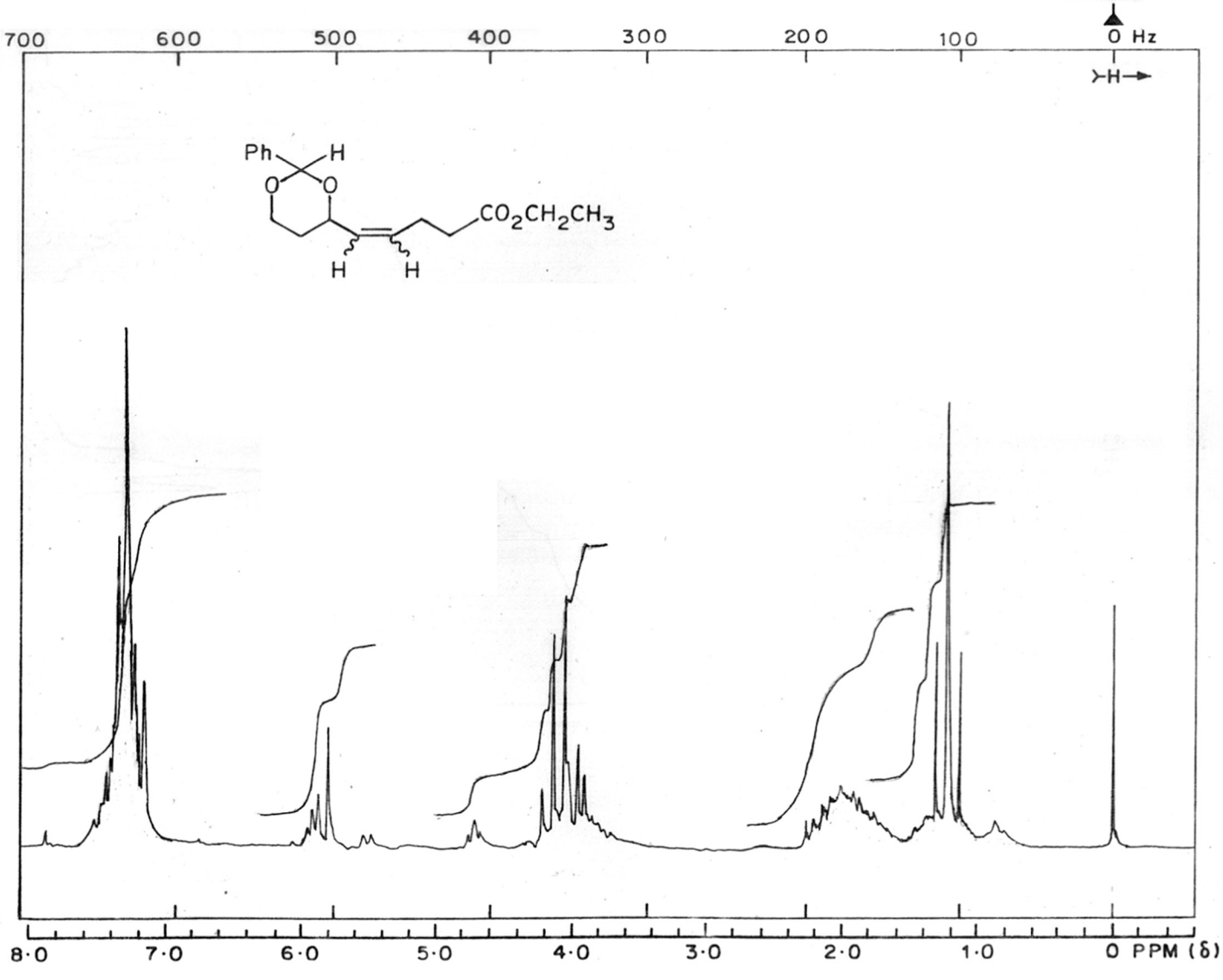

700
600
500
400
300
200
100
0 Hz
H
Ph
H
O
O
CO2CH2CH3
H
H
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM (δ)

FIGURE 1·3·23

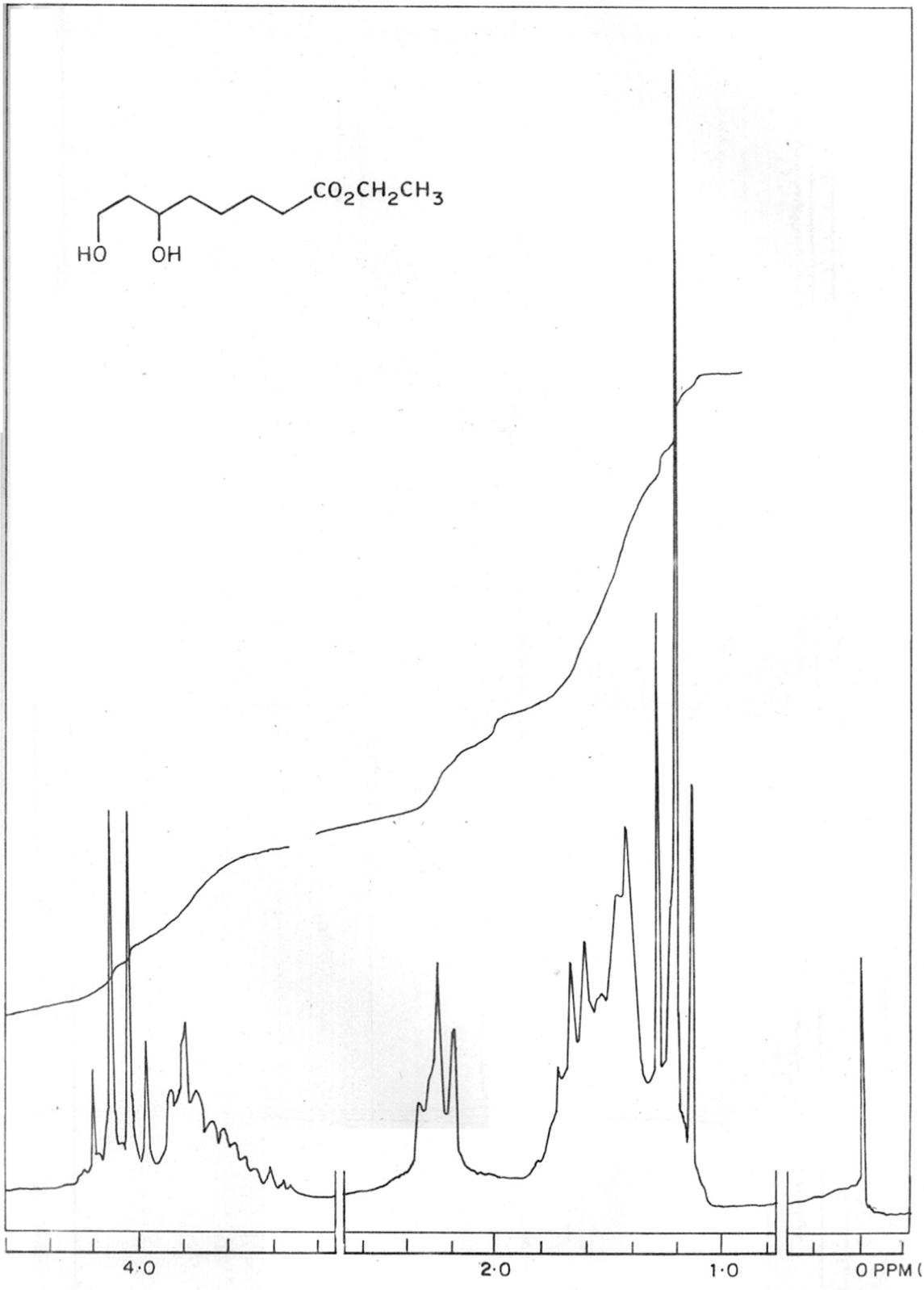


FIGURE 1·3·24.

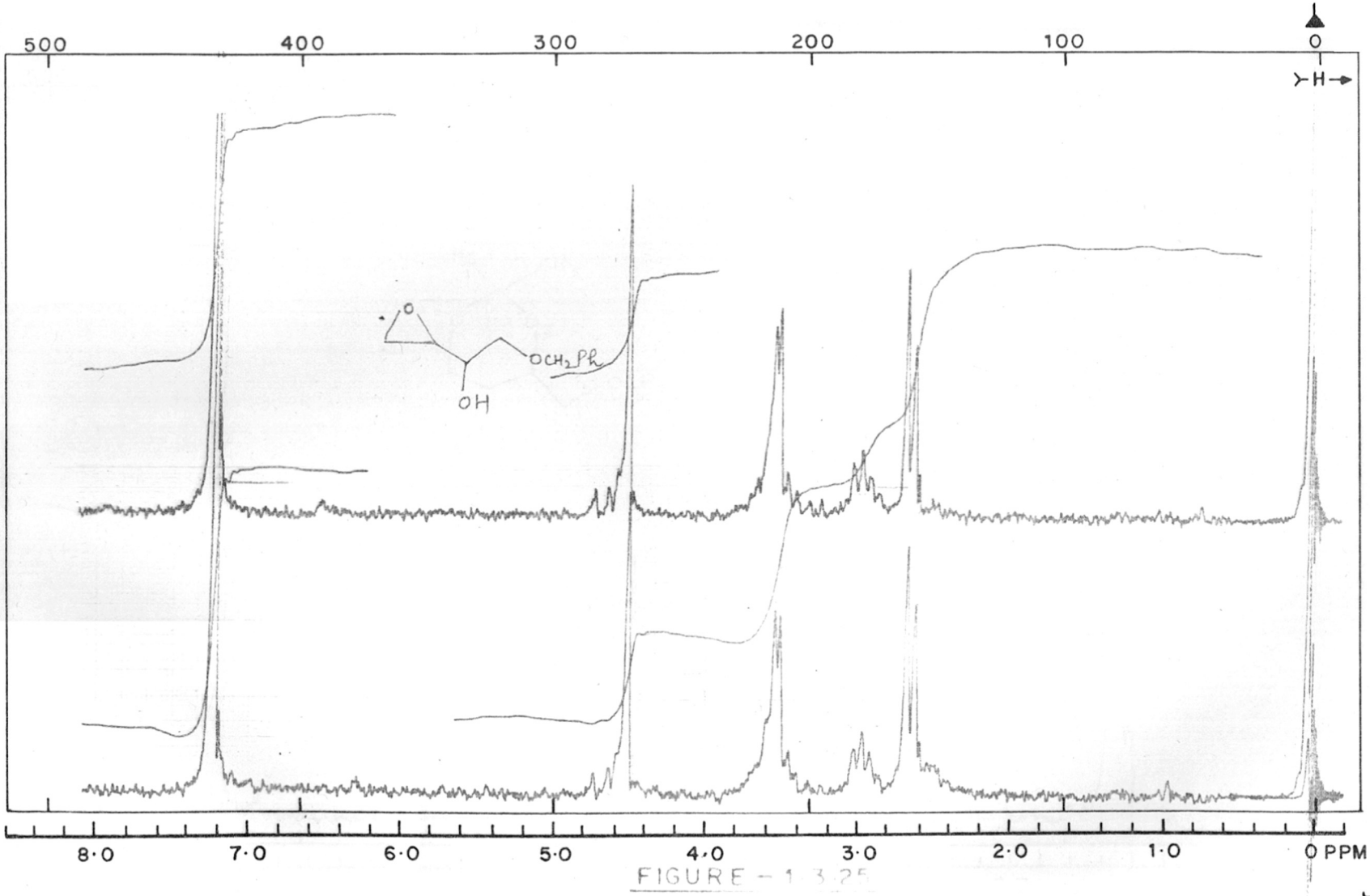


FIGURE – 1.3.25

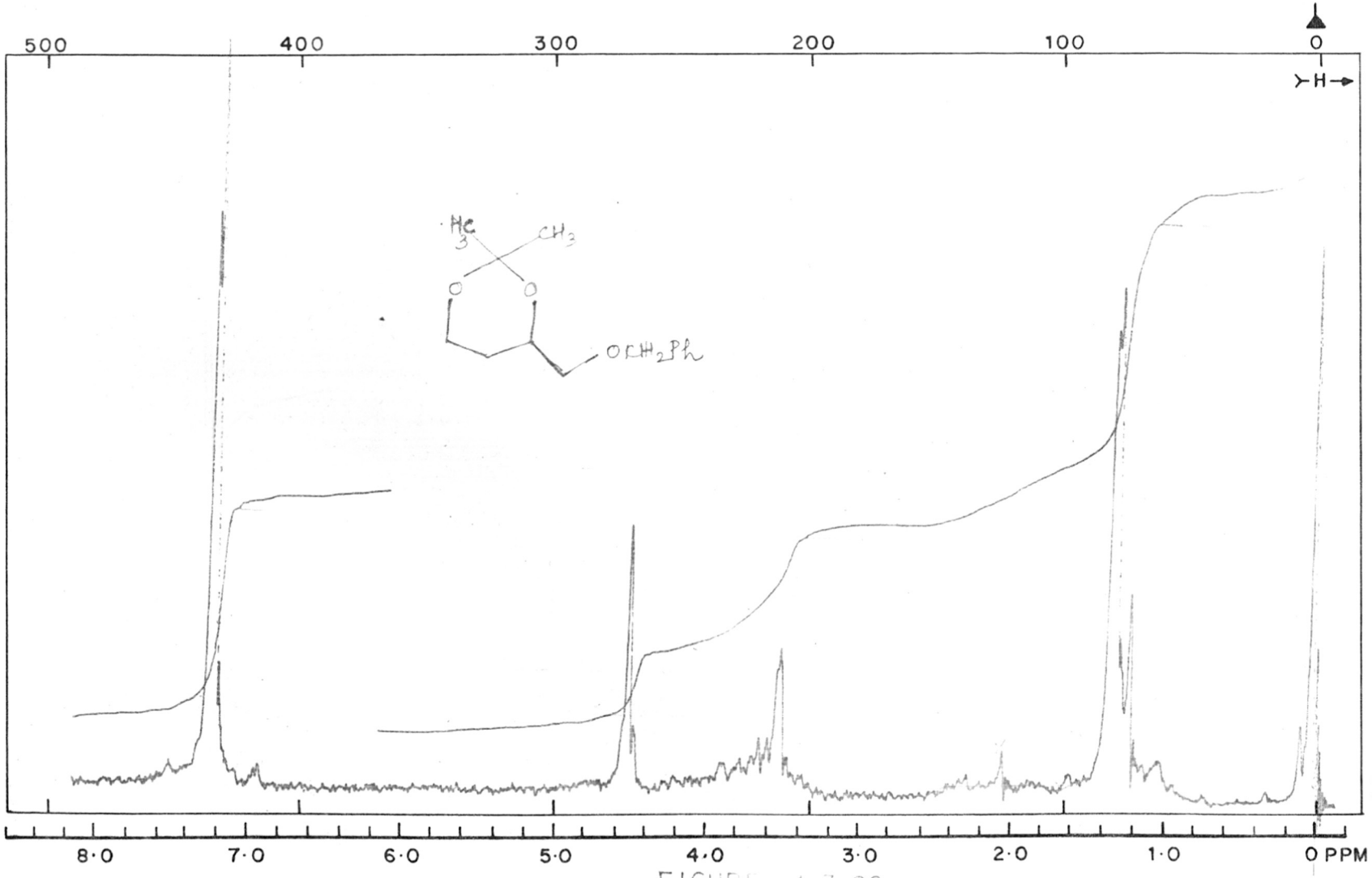


FIGURE - 3.26

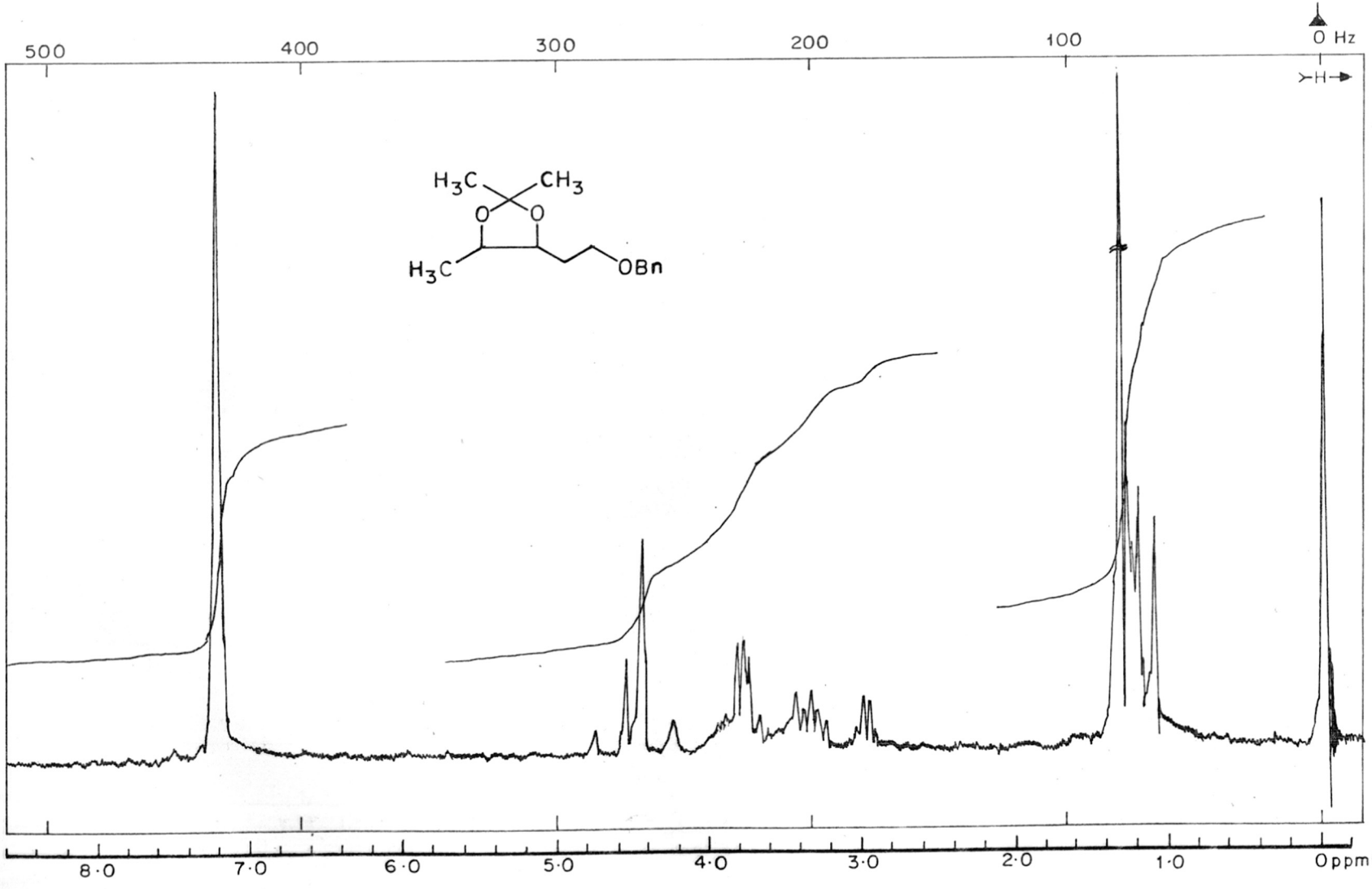

500
400
300
200
100
0 Hz
H
H_3C
CH_3
O
O
H_3C
OBn
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0ppm(δ)

FIGURE 1·3·27

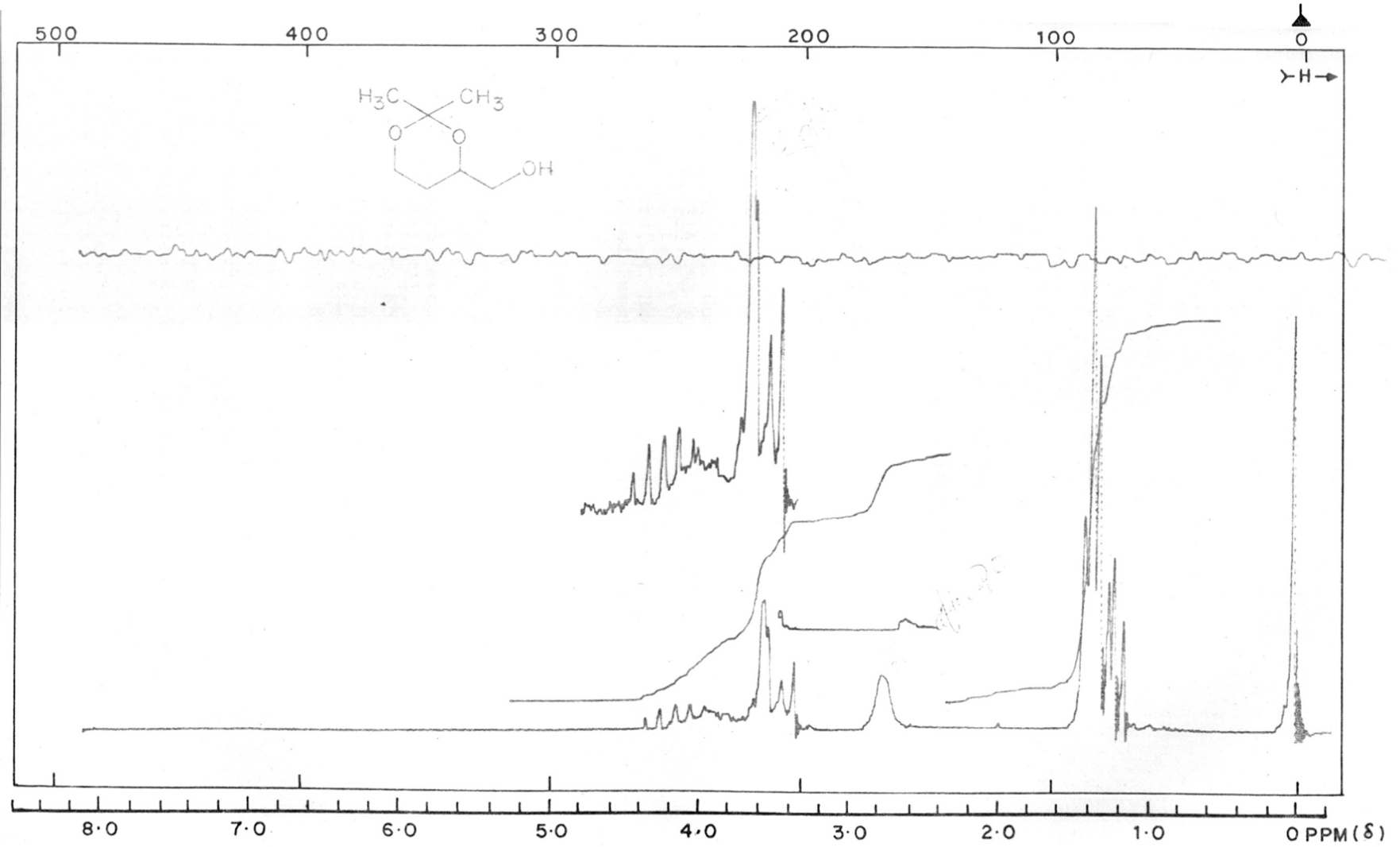


FIGURE 1·3·28

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CHAPTER 2·0·0

SYNTHESIS OF ETHYL TRANS-(±)-CHRYSANTHEMATE

FOREWORD

This chapter investigates the applicability of 'S' ylid in cyclopropane formation for synthesis of ethyl trans (±)-chrysanthemate.

2.1.0 INTRODUCTION

One of the most controversial subjects in recent years has been the use of chemical insecticides in pest control. An ideal insecticide must have a number of biological and chemical properties along with effective insecticidal activity. An essential requirement of insecticides is that they should not be toxic to humans exposed to them, either on short or long term basis. They should also have a physiological specificity in that all the beneficial microorganisms, insects and exposed plants must be spared of their effect. Moreover, the residues of the compound must dissipate by physical or chemical means so that hazardous levels do not accumulate which could disrupt the natural balance maintained in the food chain.

Insecticides with a wide range of physical, chemical and biological properties will be required for as long as present methods of crop protection continue and until diseases transmitted by insects no longer affect mankind and his livestock.

The commercial insecticides being used were carbamates, organophosphates and organochlorine compounds. The discovery of synthetic pyrethroids with increased insecticidal activity and low mammalian toxicity led to an abundance of new synthetic results in the chemistry of pyrethroids[1]. The

evolution of pyrethroids and their identification on the basis of synthetic, spectroscopic and degradative properties have been reviewed comprehensively by Casida[2] and also by Elliott et al.[3].

Pyrethrum[1], a natural product fits in the correct concept of an ideal pest control agent. Since it has been identified as an insecticide with one of the longest history of safety in use, scientists have directed all efforts to improve upon its structure through preparation of its analogues. An interesting fact that surfaced was that few classes of biologically active compounds have such great potential for structure variation with retention or enhancement of insecticidal potency as pyrethrum[3].

Natural pyrethrins, derived from the daisy-like flowers of Chrysanthemum cinerariefolium, have been widely used as a domestic insecticide since the 19th century in Europe and even earlier than that in Persia.

Pyrethrum flowers yield pyrethrum extract of which the insecticidal constituents are collectively called the 'natural pyrethrins'. Pyrethrins are esters formed by combination of two acids, chrysanthemic and pyrethric acid and three alcohols, pyrethrolone, cinerolone and jasmolone.

The esters of chrysanthemic acid are called 'pyrethrin I' 1, cinerin I 3 and jasmolin I 5 together known as 'Pyrethrins I' fraction; whereas the esters of pyrethric

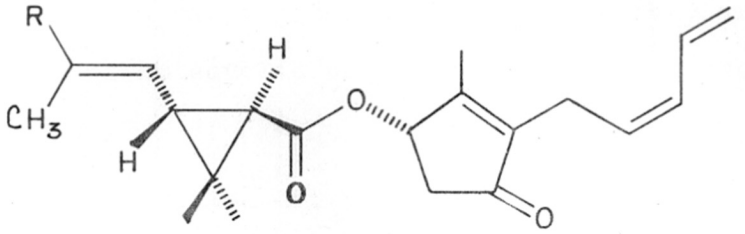
acid are pyrethrin II 2, cinerin II 4 and jasmolin II 6, together representing the 'Pyrethrin II' fraction (Chart 2.1.1). These six constituents together account for the kill and knock-down properties of the pyrethrin extract.

Pyrethrins I and II are the most active and constitute 40% of the refined pyrethrum extract, cinerins I and II and jasmolins I and II together constitute about 15% and the rest consists of 20% fatty acids and 25% other unidentified components.

Structure-Activity relationship

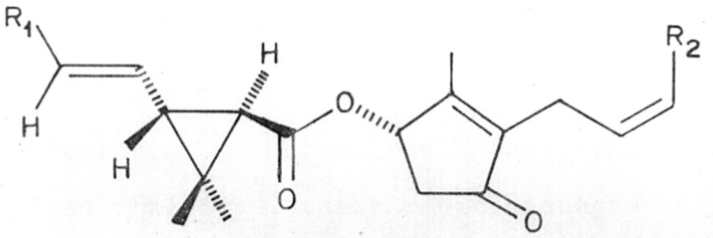
The essential features of potential pyrethroids were proved to be the two centers of unsaturation at the extremities of the pyrethroids and a gem-dimethyl or sterically equivalent group β to the ester group on the cyclopropane ring.

Insecticidal activity of pyrethroids depends to a significant extent on the absolute configuration at C-1 viz. the site being the ester function. Thus, esters with absolute configuration 1R, irrespective of whether the cyclopropane ring possesses a cis- or trans- geometry are active, while the corresponding 1S isomers are either inactive or much less active. The natural pyrethrins are esters of (+)1R-trans chrysanthemic acid and (+)1R-trans pyrethric acids. It has also been observed in the case of pyrethroids possessing a C-3 dihalovinyl side chain, that the 1R-cis compounds are about twice as active as the corresponding 1R-trans compounds. Commercially established pyrethroids like permethrin etc. are usually dl mixtures of both cis and trans cyclopropane carboxylic



1, PYRETHRIN I, R = CH_3

2, PYRETHRIN II, R = $CH_3OC(=O)-$



3 CINERIN I, $R_1 = CH_3$; $R_2 = CH_3$

4, CINERIN II, $R_1 = CH_3OC(=O)-$; $R_2 = CH_3$

5, JASMOLIN I, $R_1 = CH_3$; $R_2 = CH_3CH_2-$

6, JASMOLIN II, $R_1 = CH_3OC(=O)-$; $R_2 = CH_3CH_2-$

CHART – 2·1·1

acid esters, in varying proportions, since they are synthesized from acyclic precursors, involving cyclopropane ring closure.

For effective activity, pyrethroids depend on at least two centers having appropriate chirality[3] i.e. in chrysanthemates - the gem-dimethyl cyclopropane acids, the configuration at C-1 carbon must be 'R' and the unsaturated side chain at C-3 must be trans to the C_1-carboxylic group. Mainly the alcohol component, methyl cyclopentenolones should have 'S' configuration at the site of attachment of the alcoholic oxygen. It has been conclusively proved that C-1 'S' cyclopropane acids or 'R' alcohols give almost inactive esters. Though natural pyrethrins are excellent insecticides with practically no mammalian toxicity[2], their rapid biodegradability mainly due to photolability make them unsuitable for agricultural use.

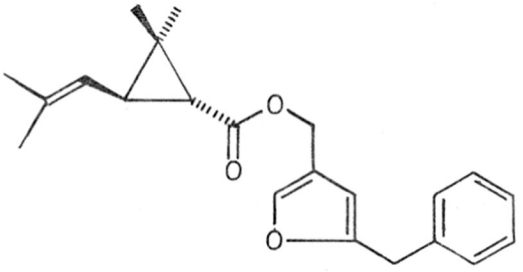
As soon as the nature of active constituents were known, analogues were investigated in attempts to elucidate principles governing activity and to discover simple or more potent insecticides. Initial indications of the valuable influence of changing the 3-substituent in the chrysanthemic acid stimulated synthesis of other analogues.

Hence synthetic pyrethroids, structurally related to natural pyrethrins or cinerins are increasingly becoming important as ideal pest control agents for they possess a unique combination of the desirable properties of an ideal insecticide,

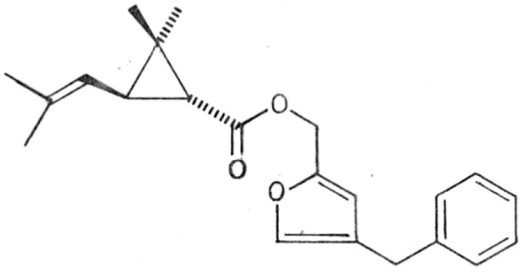
such as high and selective insectidal activity, low mammalian toxicity, greater biodegradability. In addition, they are more superior to natural pyrethrins in the fact that they are comparatively more photostable. For this reason, they are very suitable for use in agriculture.

During the course of varying the structure to obtain increased activity, many new synthetic pyrethroids with greater potency have emerged. Amongst them in chronological order of evolution were resmethrin 7, bioresmethrin 8, permethrin 9, cypermethrin 11, deltamethrin 10 and fenvalerate 12[3] (Chart 2.1.2). The latter four compounds are photostable, highly active synthetic pyrethroids developed by the end of 1970s and are called as the first generation synthetic pyrethroids[4]. It is appropriate, at this stage, to mention that at National Chemical Laboratory, work had been initiated by Mitra et al.[4] towards the conversion of a cheap and abundant constituent of turpentine oil viz. carene to active pyrethroid insecticides which culminated in the preparation of a new and potent insecticide named Indothrin[5] 13.

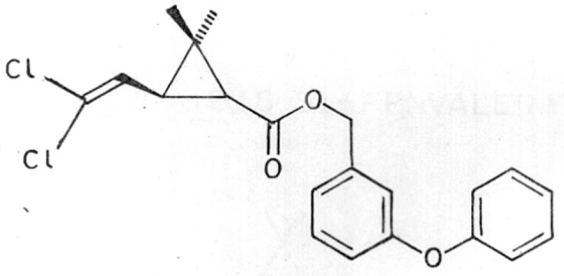
All the above compounds are esters of different alcohols with chrysanthemic acids, especially the trans isomer or its halo analogues of the olefinic substituents at the 3-position of the cyclopropane ring, with the exception of fenvalerate which was developed with the intent of knowing the level of activity with cyclopropane ring being substituted by a similar



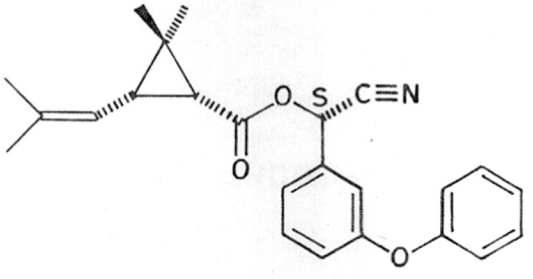
7, RESMETHRIN



8, BIORESMETHRIN

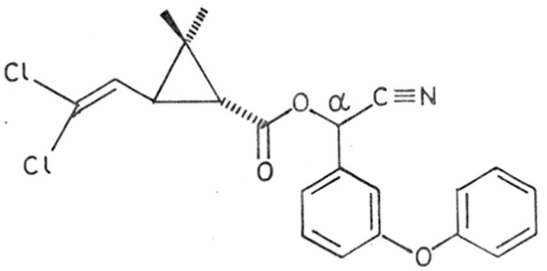


9, (±)-PERMETHRIN

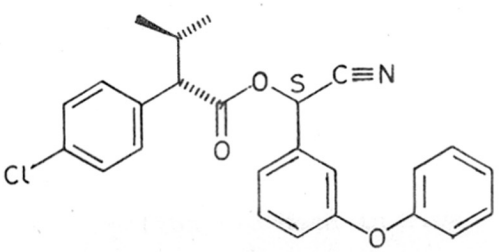


10, (1R, 3R, αS) DELTAMETHRIN

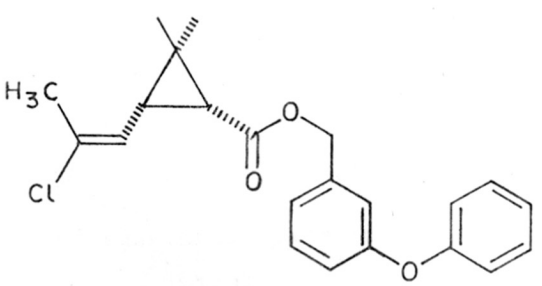
CHART – 2·1·2



11, (±) CYPERMETHRIN



12,(S, S)-FENVALERATE



13, INDOTHRIN

CHART-2·1·2 (contd.)

acyclic moiety.

Chrysanthemic acid 14 was the first component of the 5 of the natural esters to be synthesised. It has been thoroughly and conclusively established as the most accessible and generally effective acid component of the synthetic pyrethroids.

The units from which the cyclopropane ring in chrysanthemic acid has been constructed are shown in the Chart (Chart 2.1.3).

Synthesis of chrysanthemic acid using ylids

As it is not related to our work, we would not like to go into the details of the various modes for the cyclopropane ring formation. There are numerous methods reported for the synthesis of chrysanthemic acids[1] but the use of ylids based on S and P for cyclopropanation has been involved in a few synthesis todate.

We envisaged the use of a stabilized sulfonium ylid as a useful synthetic intermediate towards the key step in our synthesis viz. cyclopropanation.

Hence, a brief discussion on sulfur ylids and previous methods of synthesis pertaining to the use of ylids, in general, towards the total synthesis of chrysanthemic acid is relevant.

The term ylid was first coined by George Wittig[6] in the context of phosphorous ylids in 1944 and with the introduction of the Wittig synthesis of olefins, the usefulness of ylids captured the imagination of organic chemists all over the world.

The outcome was the discovery and use of sulfur ylids.

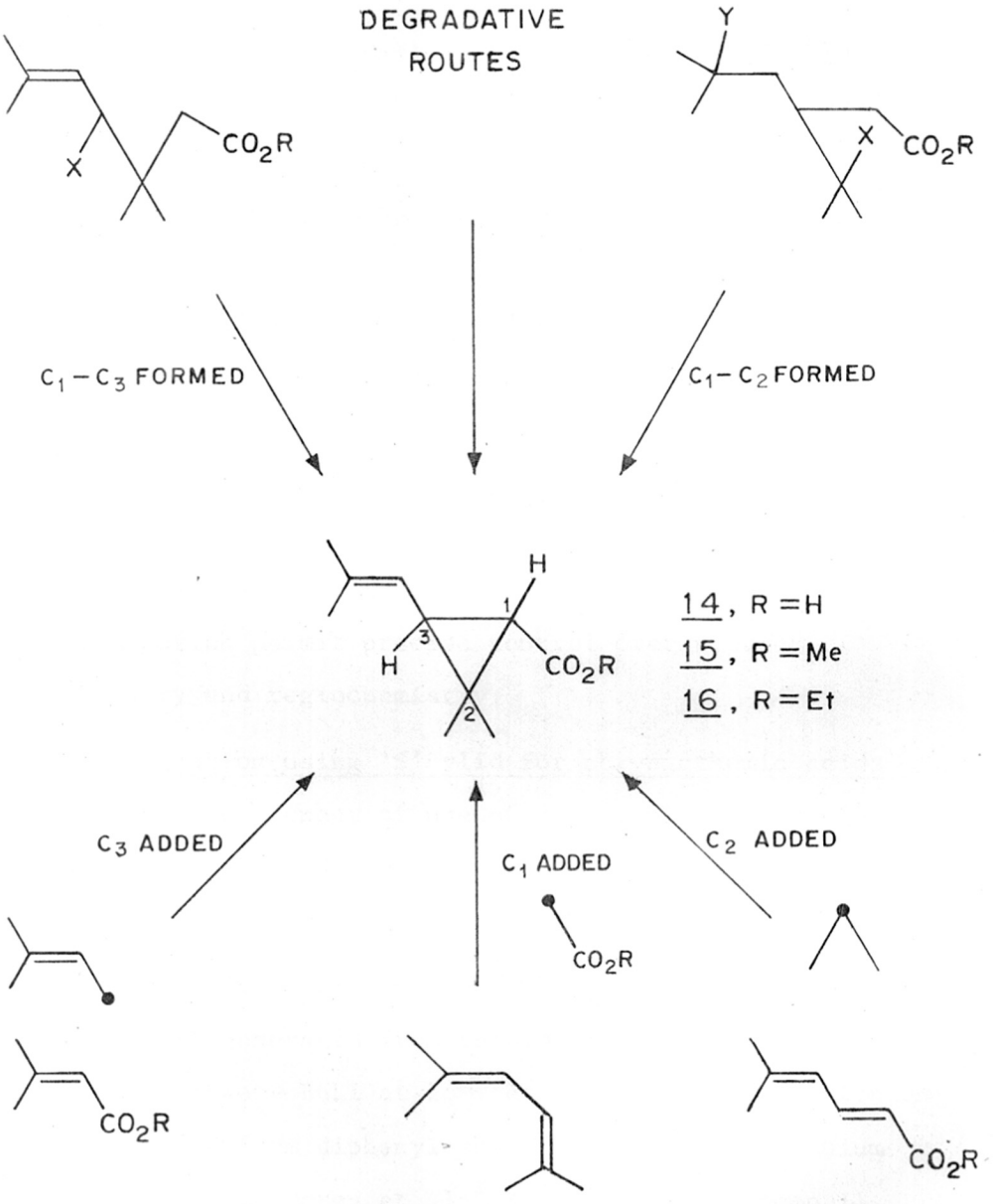

DEGRADATIVE
ROUTES
X
CO2R
Y
X
CO2R
C1 – C3 FORMED
C1 – C2 FORMED
H
1
3
H
2
CO2R
14, R = H
15, R = Me
16, R = Et
C3 ADDED
C1 ADDED
C2 ADDED
CO2R
CO2R
CO2R

CHART-2·1·3

These are a class of compounds in which a carbanion is stabilized by an adjacent positively charged sulfur; being in the most formal sense, neutral compounds viz. sulfuranes.

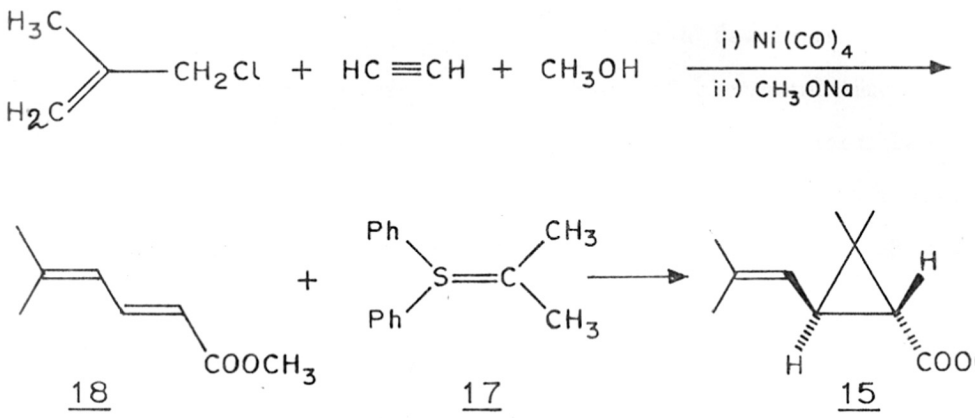
Sulfur ylids[7] are nucleophilic reagents, their most characteristic reaction being the transfer of an alkylidene group to an electrophilic double bond with the resultant formation of a cyclopropane ring. Depending on the structure of the ylid and substrate, diastereomeric or structurally isomeric betaines result as the intermediate from the addition of the ylid, leading to a distribution of products on the collapse of the betaines. As the formation of the betaines is a reversible reaction, the conditions of the reaction and the ylid formation permit precise control over product stereochemistry and regiochemistry.

(i) Cyclopropanation using 'S' ylid for chrysanthemic acids

Corey, the pioneer of use of sulfur ylids in cyclopropanation, demonstrated at an early stage the possibility of effectively using sulfuranes for the synthesis of chrysanthemates.

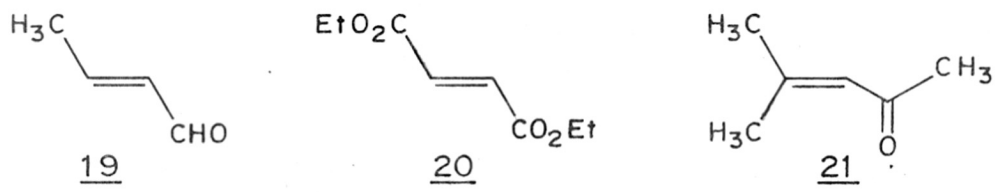
The reactive sulfur ylid, diphenyl sulfoniumisopropylide 17 was generated from the corresponding sulfonium salt using a strong base - BuLi at low temperatures. The sulfonium salt was prepared from diphenyl sulfide and triethyloxonium fluoborate and LDA. Corey et al.[8] (Chart 2.1.4, Scheme I) used this ylid in conjunction with a number of substrates essentially towards cyclopropanation at temperature of -70

SCHEME – I

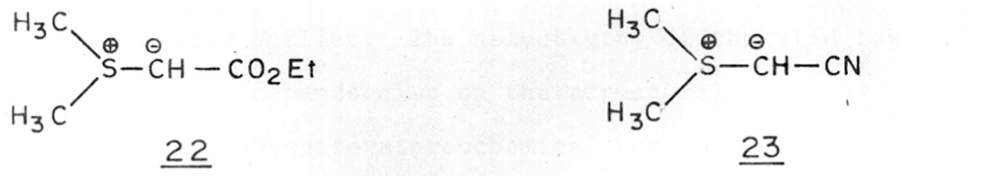


18 17 15

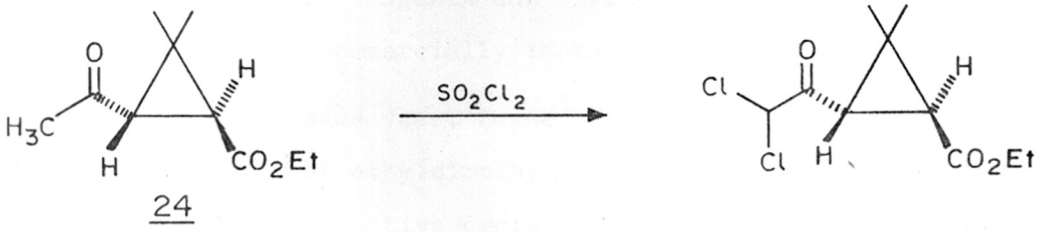
SCHEME – II



19 20 21



22 23



24 25

CHART – 2·1·4

to -20°C, the reaction being over within a few hours. For the olefin substrate for the synthesis of chrysanthemate ester, the nickel carbonyl catalyzed addition of acetylene on methallyl chloride afforded the starting dienoic ester 18. Reaction of this conjugated carbonyl derivative 18 with the sulfurane 17 led to a novel and direct approach to the required gem-dimethyl cyclopropane system of various compounds. Hence, equivalent amounts of the ylid and the α,β-unsaturated carbonyl compounds at -70° to -20° under nitrogen gave the corresponding trans ester 15 on distillation.

This reaction of the sulfurane 17 with the conjugated ketone revealed a greater tendency of the ylid for 1,4-addition leading to cyclopropanes, than the 1,2-addition which would lead to the oxirane as was the case with diphenyl sulfonium-methylide used earlier. The selectivity of the ylid towards 1,4- over 1,2- depends also on the structural features of the enone system. Despite stereochemical purity of products, the complexity of the reagents and stringent reaction conditions make this route commercially impracticable.

In the same year, Payne[9] (Chart 2.1.4, Scheme II) demonstrated that ethyldimethylsulfuranylidene acetate (E.D.S.A.) 22 could be an effective cyclopropanating agent. The reaction of 22 with crotonaldehyde 19, diethylfumarate 20, mesityl oxide 21 and a number of other enone systems led to an array of substituted cyclopropanes in comparatively good yields.

An analogous route was published in 1982[9b] using dimethylsulfuranylidene acetonitrile 23, on mesityl oxide to obtain the corresponding cyclopropane derivative which was converted by a series of reactions into chrysanthemic acid.

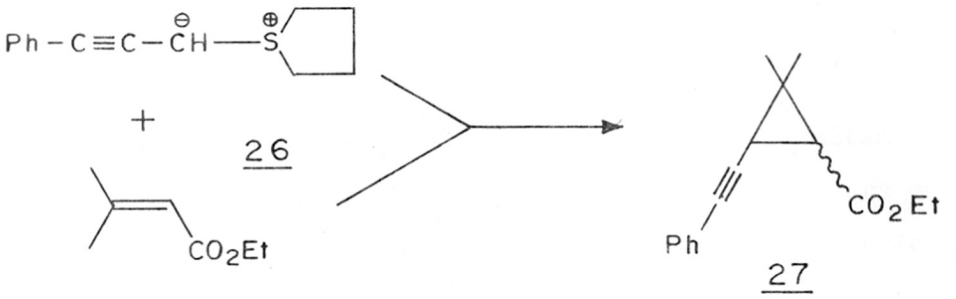
A decade after Payne's paper, Lee and coworkers[10] made use of the same methodology to obtain the permethrinic ester 25. In this patent, the addition of the sulfurane, E.D.S.A. 22 with mesityl oxide gave the corresponding cyclopropane ester 24 in one step. α-Dichlorination of the keto group by sulfurylchloride followed by sodium borohydride reduction of the ketone and subsequently acid catalysed elimination led to the dichlorovinyl ester 25 (Chart 2.1.4, Scheme II).

Another synthetic route to an analogous chrysanthemate was from the propargyl sulfonium salt 26. This salt was treated with ethyl 3-methylcrotonate to afford the 2,2 dimethyl 3-(phenyl ethynyl) cyclopropane carboxylic ester 27[11] (Chart 2.1.5, Scheme III).

(ii) Cyclopropanation using 'P' ylid for chrysanthemic acids

Use of 'P' ylids in conventional ketone olefinations are well studied, but its application for cyclopropanation was first demonstrated by Krief et al. in a series of papers and patents during the late seventies (references cited in 1).

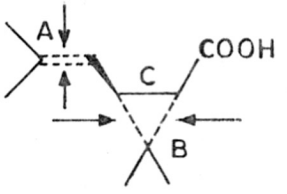
SCHEME – III

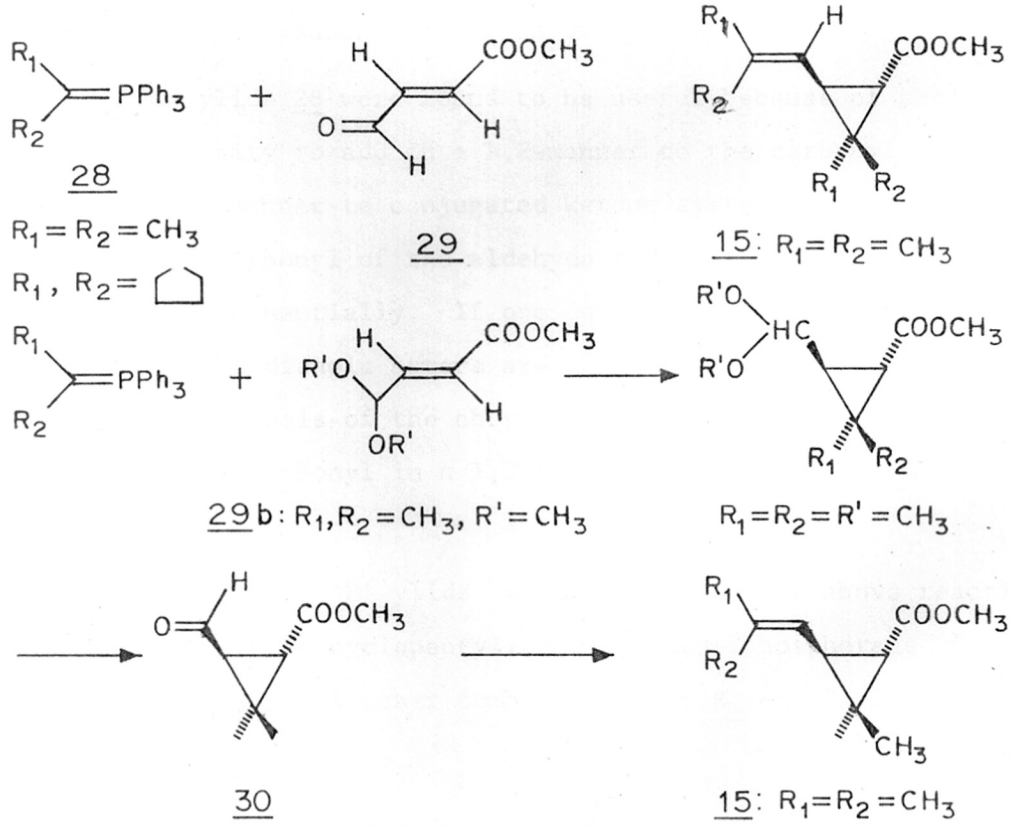


26

27

SCHEME – IV





28

$R_1 = R_2 = CH_3$

$R_1, R_2 =$

29

15: $R_1 = R_2 = CH_3$

29b: $R_1, R_2 = CH_3$, $R' = CH_3$

$R_1 = R_2 = R' = CH_3$

30

15: $R_1 = R_2 = CH_3$

CHART – 2·1·5

In the first paper, Krief et al.[12] has shown the use of isopropylidenetriphenylphosphorane 28 where simultaneous isopropylidination of the double bond and ketone occurs on methyl 4-oxocrotonoate 29 yielding directly chrysanthemic acid derivatives (Chart 2.1.5, Scheme IV).

The basis of the above reaction was an appreciation of the chrysanthemic acid molecule dissecting into two isopropylidene moieties as A and B. Accordingly, they used sorbic esters as starting points. Ozonolysis of sorbic esters yields the required methyl 4-oxo-butenoate 29 which corresponded well with fragment C. Reaction of 29 with more than two equivalents of the phosphorane 28 at -78° gave stereospecifically methyl trans chrysanthemate 15 in 60% yield.

The ylids 28 were found to be useful because of their known propensity to add in a 1,2-manner to the carbonyl group and in a 1,4-manner to conjugated ketone systems. They react both on the carbonyl of the aldehyde and on the carbon carbon double bond sequentially. If one equivalent of phosphorane was used, only dienoic esters are obtained proving that in the total synthesis of the chrysanthemate, the ylid first reacts on the carbonyl in a 1,2-manner and then on the double bond.

A number of 'P' ylids were studied in the above reaction, but except for the cyclopentylidene triphenylphosphorane 25 (R_1R_2= -$(CH_2)_5$-) all other combinations of R_1 and R_2 led only

to dienoic esters.

In this paper, Krief et al. also reported the first synthesis of methyl 2,2-dimethyl-3-formyl cyclopropane carboxylate 30 and its analogs by the reaction of the acetal 29b with the ylid 28 to obtain 30 in 83% yield.

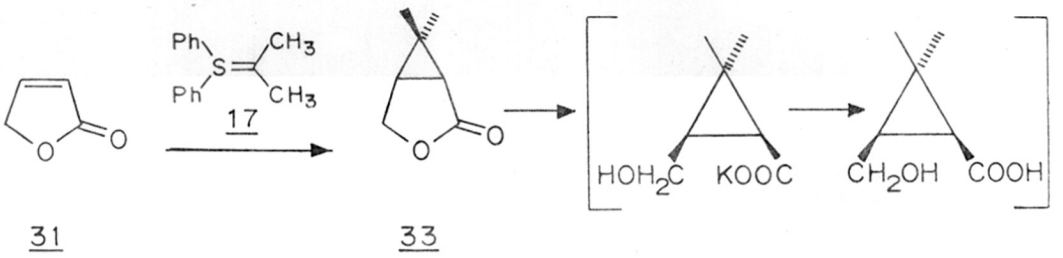
A similar methodology as above was reported by Krief et al.[13] (Chart 2.1.6, Scheme V) for the first total stereospecific synthesis of the unnatural cis chrysanthemic esters from cis olefins 31 and 32; the only difference being that the sulfur ylid 17 was used instead of a phosphorous ylid. It is interesting to see that this is the first example of cyclopropanation of an α,β-unsaturated lactone.

Thus, the addition of 17 to the easily accessible γ-butenolide led to the bicyclic lactone 33 which was converted in one pot to the methyl, 2,2-dimethyl-3-hydroxymethyl 3-cyclopropane carboxylate 34 in 55% yield on successive treatments with potassium hydroxide, acid and diazomethane.

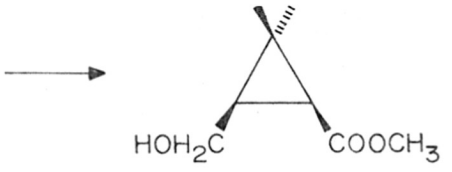
The addition of 17 to the methyl-4-(tetrahydropyranyloxy)-2Z-butenoate 30 (obtained from propargyl alcohol) leads to the stereospecific formation of the cis derivative 34 and its lactone 33 on detetrahydropyranylation.

The alcohol 34 was easily converted to the required cis ester 15b via oxidation to 30b and Wittig olefination using isopropylidene triphenylphosphorane in the presence of

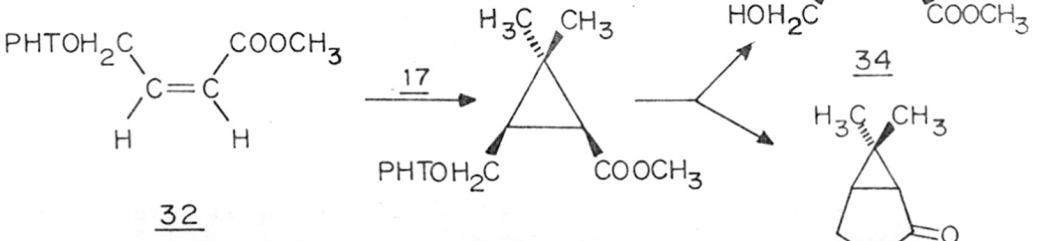
SCHEME - V



31 33

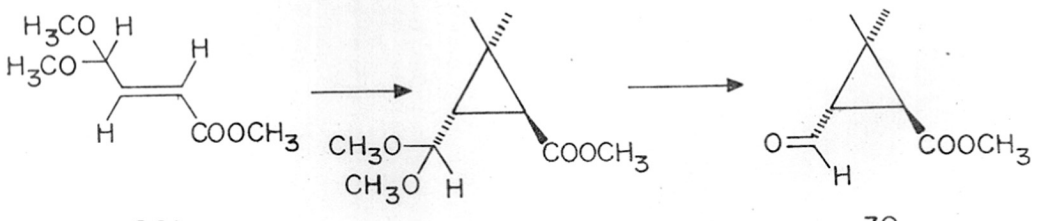


34



32

34 30b 15a



29b 30

CHART - 2·1·6

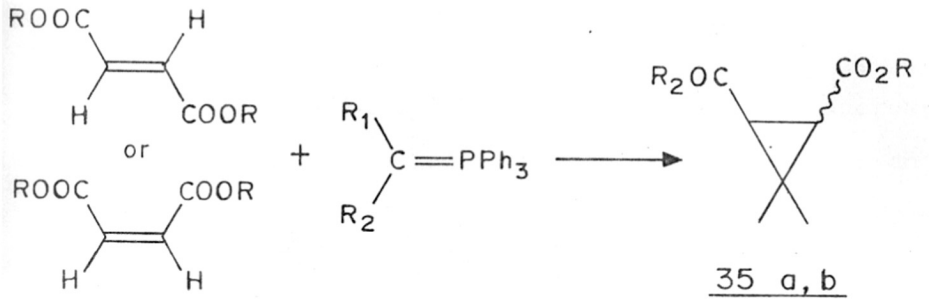
dimethoxyethane.

The addition of the sulfurane 17 on the acetal of the oxobutenoate, 29b, followed by hydrolysis led to the trans caronaldehyde ester 30 which had been previously converted to the trans chrysanthemic ester.

Krief et al.[14] extended the phosphorane approach to synthesis , not otherwise easily accessible cyclopropane derivatives from fumaric and maleic esters using a series of phosphoranes including cyclohexylidene and cyclopentylidene analogs.

The cis and trans diesters 35a and b obtained from maleates and fumarates are converted to cis and trans-chrysanthemates respectively via hydrolysis to half ester 36, diborane reduction to 34b and oxidation to 30 by chromic acid in pyridine (Chart 2.1.7, Scheme VI).

SCHEME – VI



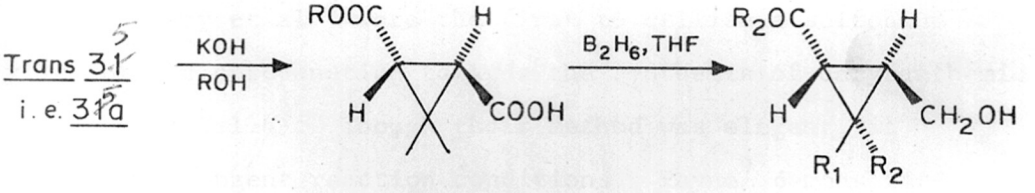
35 a, b

R = Et $R_1 = R_2 = CH_3$

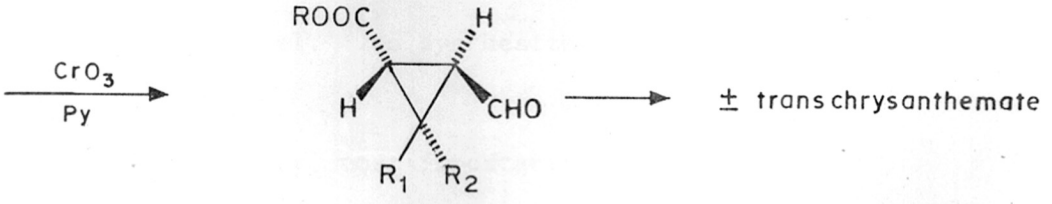
R = Et $R_1 = R_2 = Et$

$R = CH_3$ $R_1 = R_2 =$ 

R = Et $R_1 = R_2 =$ 



36 34 b



30

CHART – 2·1·7

2.2.0 PRESENT WORK

The discovery of synthetic pyrethroids with increased insecticidal activity and low mammalian toxicity led to an abundance of new synthetic results in the chemistry of pyrethroids. Many of these methods adapted on an industrial scale make use of sigmatropic rearrangement, radical addition and nucleophilic ring closure with carbanions. There have been quite a few synthesis utilizing ylids especially phosphorous and sulfur ylids. In Krief's method[12] the addition of the C-2 carbon (refer retrosynthetic Chart No.2.1.3) to form the cyclopropane moiety, was amply demonstrated by the use of both dialkyl and cyclic phosphonium ylids.

Corey et al.[8] were the first to utilise a sulfonium ylid for cyclopropanation towards the synthesis of chrysanthemic acid (Chart 2.1.4). Though their method was elegant, it involved stringent reaction conditions. Payne[9] demonstrated the use of ethyldimethylsulfuranylideneacetate [EDSA] as an effective cyclopropanating agent on a number of α,β-unsaturated carbonyl substrates and this methodology was made use of by Lee et al.[10] to synthesize permethric acid (Chart 2.1.4).

One of the primary, most important and useful acid component of synthetic pyrethroids is the trans chrysanthemic acid and a lot of effort is directed towards its synthesis by more innovative routes which would thereby lead to simpler

approaches towards the manufacture of pyrethroids.

The use of sulfonium ylids or sulfuranes in the cyclopropanation of substrates represents an important synthetic methodology in organic synthesis. The use of ethyldimethylsulfuranylideneacetate 22 (EDSA) in the formation of cyclopropanes prompted us to look into the possibility of utilizing EDSA in preparing a properly functionalized and substituted cyclopropane, which could be transformed into chrysanthemic acid.

We envisaged the possibility of using three substrates; ethyl-3-methylcrotonoate 37, ethyl 3,3-dimethyl acrylate 38 and 2,5-dimethyl-hex-4-ene-3-one 39 for the cyclopropanation reaction with E.D.S.A. It was realised that the expected reaction of the aldehyde 37 with E.D.S.A. could lead to caronaldehyde in just one step which could be converted to either chrysanthemic acid or indothrin acid moiety. Similarly, the ester 38 on reaction with E.D.S.A. would afford the chrysanthemum dicarboxylic ester which also could be converted to chrysanthemic acid. The reaction of the ketone 39 with E.D.S.A. would give a keto ester which could be transformed to ± 14.

Surprisingly, the reaction of E.D.S.A. with both the aldehyde 37 and ester 38 went so poorly as to be of no practical use. In contrast to the above, the reaction of E.D.S.A. with the α,β-unsaturated ketone 39 gave far

better results. The reason for the poor reactivity of the above compounds could be the steric effect due to the β-dialkyl group but as reaction with 39 occurred, we proceeded as in Chart 2.2.1.

Accordingly the α,β-unsaturated ketone 39 had to be prepared. The possibility of using a vinyl Grignard reaction using isobutenyl bromide 40 on isobutyraldehyde to give the required allylic alcohol 41 occurred. Hence isobutenyl bromide 40 was prepared from t-butanol in two steps by the known procedure.[15a] It involved bromination of t-BuOH to 1,2-dibromo-2-methyl-propane and selective dehydrohalogenation of the dibromo compound in presence of potassium hydroxide.

The Grignard reaction of magnesium isobutenyl bromide on isobutyraldehyde at 0° for 5 hr afforded on distillation 2,5 dimethyl-4-hexen-3-ol/$\overline{\text{in}}^{(41)}$ 75% yield (Chart 2.2.1). The previous report[15b] had suggested a very poor yield. The IR spectrum of 41 showed the presence of OH group at 3400 cm^{-1} and its ^{1}H-NMR spectrum showed the presence of all the signals at expected chemical shifts.

Oxidation of this allylic alcohol with pyridinium dichromate in dichloromethane for 18 hr under reflux afforded the required α,β-unsaturated ketone substrate 39 for our synthesis, namely 2,5-dimethyl-4-hexen-3-one/$\overline{\text{in}}^{(39)}$ 66% yield. This compound had been obtained earlier[16] by Friedel Craft's

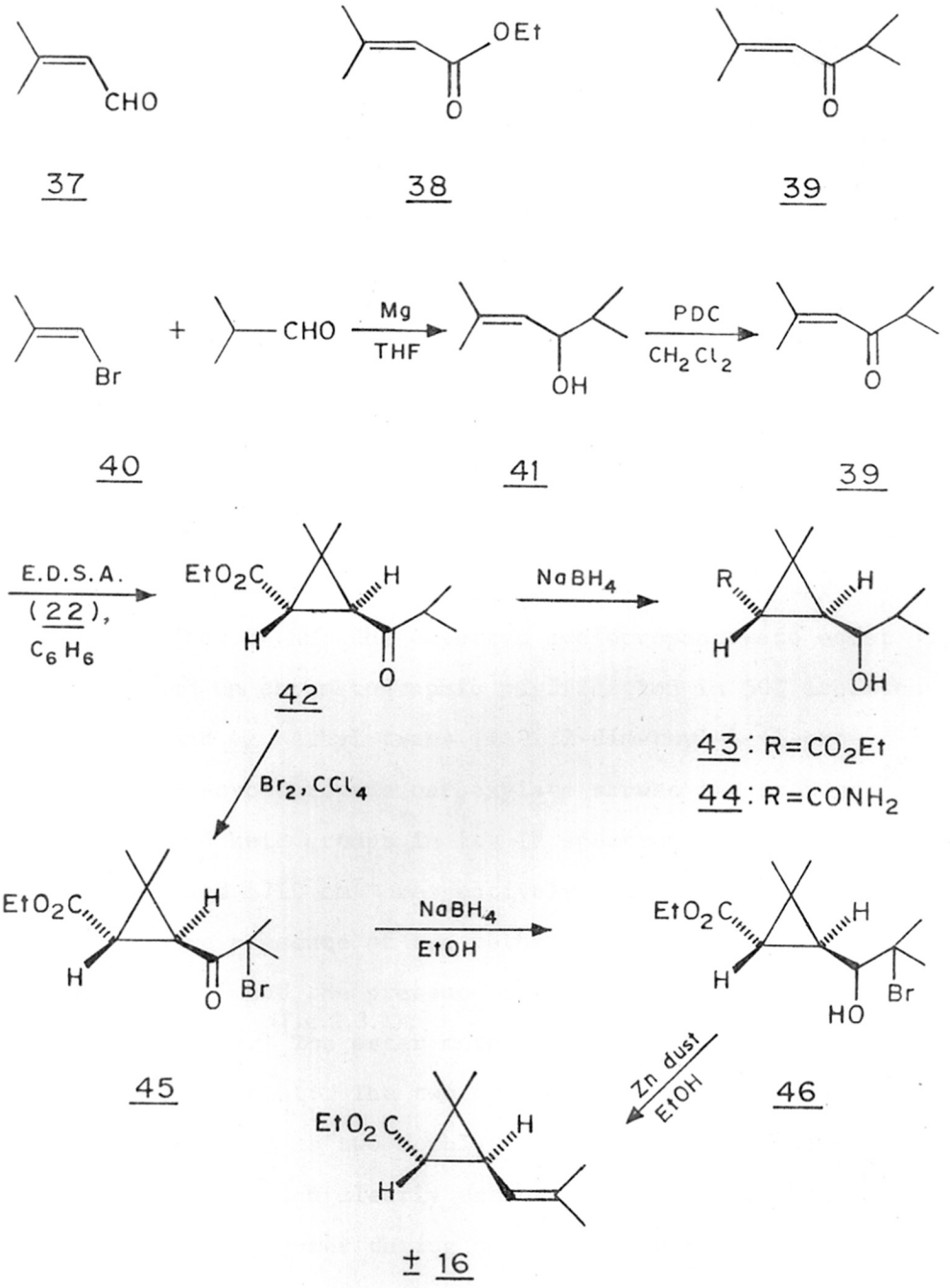

CHO
OEt
O
37
38
39
Br
+
CHO
Mg
THF
OH
PDC
CH_2Cl_2
40
41
39
E.D.S.A.
(22),
C_6H_6
EtO_2C
H
O
42
$NaBH_4$
R
43 : R=CO_2Et
44 : R=$CONH_2$
Br_2, CCl_4
Br
45
$NaBH_4$
EtOH
HO
46
Zn dust
EtOH
± 16

CHART-2·2·1

acylation of isobutryl chloride on isobutene, followed by dehydrohalogenation. The IR and ^{1}H-NMR spectra of 39 coincided well with the expected values.

The next step was the treatment of E.D.S.A. on the above ketone. E.D.S.A. 22 a stabilised sulfurane was prepared by the reported two step procedure; viz. the condensation of dimethylsulfide with ethylbromoacetate gave the stable sulfonium salt which on treatment with a saturated solution of K_2CO_3 gave the required sulfurane, E.D.S.A. which was immediately used for cyclopropanation.

Unsaturated ketone 39 was added to a nitrogen flushed flask, containing a refluxing solution of E.D.S.A. in dry benzene and after 24 hr, the expected cyclopropane keto ester 42 was obtained on chromatographic purification in 50% isolated yield. Compound 42, ethyl trans (±)-2,2-dimethyl-3-(1-oxo-2-methylpropyl)-cyclopropane carboxylate showed the presence of the ester and keto groups in its IR spectrum with absorption bands at 1740 and 1710 cm^{-1} respectively. The ^{1}H-NMR spectrum of 42 showed the presence of two methyl singlets on C-2 around δ 1.04 and δ 1.14 and the presence of two isopropyl methyl doublets at δ 1.23. (Fig.2.3.1). The ester methyl was clearly differentiated at δ 1.33 as a triplet. The two cyclopropyl protons at C-1 and C-3 were located as two doublets at δ 2.23 and δ 2.42 having J value of 5.6 Hz which clearly demonstrates the formation of the expected trans isomer during the Michael addition of the

stabilised sulfurane on the α,β-unsaturated ketone. The other protons were located at the expected chemical shifts. The mass spectrum of 42 showed a strong molecular ion peak at m/z 212 and a parent peak at m/z 141 which indicates the radical formed on loss of the carbethoxy group.

The next step would be a short approach towards ± 14 from this ketone 42. Earlier workers had tried to effect the above conversion to chrysanthemic acid and its analogues through the alcohol 43 obtained on sodium borohydride reduction of the above ketone (42).

Dehydration of this alcohol 43 was known[17] to result in the cleavage of the cyclopropane ring, although similar conversion was earlier achieved very efficiently by Majewskii et al.[18] using Martin's sulfurane reagent $Ph_2S[O(CF_3)_2Ph]_2$ on the corresponding amide 44.

The ketone corresponding to 42 obtained on degradation, was also converted to the olefin ± 14 by Matsui et al.[19] by α-bromination, hydrolysis to α-hydroxy ketone and treatment with hydrazine hydrate and potassium hydroxide. An alternate and simpler route was followed by us. The keto ester 42 was treated with bromine in carbon tetrachloride at 20-30° and after 5 hr, the bromo derivative 45 was afforded in 90% yield. The ^{1}H-NMR spectrum of 45 (Fig.2.3.2) revealed a set of singlets for 4 methyl groups, two C-2 methyls at δ 1.09, the isopropyl methyl adjacent to bromine at δ 1.77 and δ 1.84 and a triplet

at δ 1.27 for the ester methyl protons. The cyclopropyl proton H-3 shifts downfield to δ 2.83 probably due to the deshielding effect of the bromine atom. The other protons resonated at expected chemical shifts. The mass spectrum of 45 reveals molecular ion peaks of equal intensity at m/z 290 and 292, strong peaks at m/z 217, 219 for the loss of carbethoxy group and another intense peak at m/z 211 for the loss of bromine atom.

The reduction of the above bromoketone 45 with sodium borohydride at 0° for 4 hr afforded the bromohydrin 46 in 90% yield. IR spectrum demonstrates the presence of the hydroxy group at 3400 cm^{-1}. Mass spectrum confirmed the presence of bromohydrin as molecular ion peaks at m/z 292 and 294 were clearly visible. The bromohydrin was immediately treated with excess of freshly activated zinc dust in refluxing ethanol for 12 hr to afford after chromatographic purification, the title compound, ethyl trans (±)chrysanthemate 16 in 60% yield. The IR, NMR and mass spectral data of 16 coincide well with the reported values[20] (^{1}H-NMR, Fig.2.3.3).

In conclusion, it may be added that since the hydrolysis of the ethyl trans chrysanthemate 16 to the trans-chrysanthemic acid 14 was already well known[21] the above synthesis is, in effect, a formal synthesis of the trans-chrysanthemic acid 14.

2.3.0 EXPERIMENTAL

2-Methyl but-2-ene-3-bromide (40)

Isobutenyl bromide (40) was prepared from t-butanol in a two step sequence according to the reported procedure.[15a]

2,5-dimethyl-4-hexen-3-ol (41)

Isobutenyl bromide (40) (16.75 g, 0.125m.mol) was added dropwise to a stirred refluxing mixture of magnesium turnings (3.3 g, 138m.mol) and a trace of iodine in tetrahydrofuran (40 ml). The mixture was refluxed until the magnesium turnings were completely dissolved. Then it was cooled to 0° and isobutyraldehyde (4.5 g, 62.5 m.mol) in tetrahydrofuran (25 ml) was added dropwise over 15 minutes. The reaction mixture was stirred for 5 hr and then decomposed with saturated ammonium chloride solution. Extractive work up with chloroform and fractional distillation of the crude product gave (41) (6 g, 75%), b.p. 39-40°C/3 mm, lit.[15b] b.p. 161-163°. IR: ν_{max} (neat): 3400, 1600 cm^{-1}; ^{1}H-NMR (CCl_4): δ 0.79, 0.95 (6H, 2d, J value = 7Hz, 2X CH_3), 1.47 (1H, m, $CH(CH_3)_2$), 1.65,1.70 (6H, 2d, 2X CH_3 on double bond), 3.86 (1H, dd, J=6 and 8 Hz, CH-OH), 5.09 (1H, dm, J=8 Hz, CH on double bond). Mass m/e: 128 (M^+), 85 ($M^+ - C_3H_7$).

Analysis: Calculated for $C_8H_{16}O$: C, 74.94; H, 12.58; Found: C, 75.25; H, 12.52%.

2,5-dimethyl-4-hexen-3-one (39)

A solution of the alcohol (41) (4.8 g, 37.5m.mol) in dry dichloromethane (25 ml) was added dropwise to a stirred

suspension of pyridinium dichromate (42 g, 112.5 m.mol) in dry dichloromethane (125 ml) under nitrogen. The reaction mixture was refluxed for 18 hr, admixed with dry ether (125 ml) and filtered. The filtrate was passed through a short silica gel column, eluted with ether and solvents evaporated in vacuo to give (39) (3.13 g, 66%). IR: ν_{max} (neat): 1700,1630 cm^{-1}; ^{1}H-NMR (CCl_4): δ 0.90 (6H, d, J=7Hz, 2X CH_3), 1.65, 1.88 (6H, 2d, 2X CH_3 on double bond), 2.18 (1H,m, $C\underline{H}(CH_3)_2$), 5.42 (1H, m, $C\underline{H}$ on double bond); Mass m/e: 126 (M^+).

Analysis: Calculated for $C_8H_{14}O$: C, 76.14; H, 11.18; Found: C, 75.89; H, 11.29%.

Ethyl trans-(±)-2,2-dimethyl-3-(1-oxo-2-methylpropyl)-cyclopropane carboxylate (42)

To a stirred refluxing solution of ethyl dimethyl sulfuranylidene acetate 22[9](4.0 g, 25m.mol)(prepared according to Payne's method), in dry benzene (80 ml) was added, dropwise over 5 minutes, a solution of (39) (1.6 g, 12.7 m.mol) in dry benzene (10 ml) under nitrogen. The reaction mixture was refluxed for 24 hr, the solvent removed and the resulting dark yellow oil was purified on a silica gel column (eluant, light petrol) to give (42) (1.34 g, 50%); IR: ν_{max} (neat): 1740, 1710 cm^{-1}; ^{1}H-NMR (CCl_4): δ 1.04 (3H, s, CH_3), 1.14 (3H, s, CH_3), 1.18 (3H, d, CH_3), 1.28 (3H, d, CH_3), 1.33 (3H, t, $COOCH_2C\underline{H}_3$), 2.23 (1H, d, J=5.6 Hz, $C\underline{H}$-CO_2Et; 2.42

(1H, d, J=5.6 Hz, CH-C-), 2.67 (1H, m, CH-$(CH_3)_2$), 4.09 (2H, q, $CO_2\underline{CH}_2$-CH_3); Mass m/e: 212 (M^+), 141 (M^+ -CO_2Et). (Fig.2.3.1)

Analysis: Calculated for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50; Found: C, 67.99; H, 9.38%.

Ethyl trans-(±)-2,2-dimethyl-3-(1-oxo-2-bromo-2-methylpropyl)-cyclopropanecarboxylate (45)

Bromine (0.2 ml, 1.2 eq) in carbon tetrachloride (2 ml) was added dropwise to a stirred solution of 42 (500 mg, 2.5 m.mol) in carbon tetrachloride (5 ml), maintaining the temperature between 20-30°. The reaction mixture was stirred for 5 hr and excess bromine and solvent were removed in vacuo to give a pure white semisolid 45 (620 mg, 90%). IR: $\nu_{max}(CCl_4)$: 1740, 1710 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.09 (6H, s, 2XCH_3), 1.27 (3H, t, $CO_2CH_2\underline{CH}_3$), 1.77 (3H, s, CH_3), 1.84 (3H, s, CH_3), 2.15 (1H, d, J=5.6 Hz, CH-CO_2Et), 2.83 (1H, d, J=5.6 Hz, CH-C-), 4.08 (2H, q, $CO_2\underline{CH}_2$-CH_3); Mass m/e: 290, 292 (M^+), 217, 219 (M^+-CO_2Et), 211 (M^+-Br). (Fig.2.3.2)

Analysis: Calculated for $C_{12}H_{19}BrO_3$: C, 49.48; H, 6.53; Found: C, 49.25; H, 6.45%.

Ethyl trans-(±)-2,2-dimethyl-3-(1-hydroxy-2-bromo-2-methyl-propyl)-cyclopropane carboxylate (46)

Sodium borohydride (30 mg, 0.79 m.mol) was added in small portions to a cooled (0°) solution of 46 (180 mg, 0.62 m.mol) in methanol (5 ml) while stirring. The reaction

mixture was stirred for 4 hr at 0°, solvent removed *in vacuo* and unreacted sodium borohydride decomposed with water. The aqueous layer was extracted with chloroform. The organic extract was dried and the solvent removed to give the bromohydrin 46 (163 mg, 90%); IR: ν_{max} (CCl_4): 3400, 1740 cm^{-1}; Mass m/e: 292, 294 (M^+).

Analysis: Calculated for $C_{12}H_{21}BrO_3$: C, 49.15; H, 7.17. Found: C, 49.33; H, 7.30%.

Ethyl trans-(±)-chrysanthemate (16)

To a refluxing solution of 46 (180 mg, 0.62 m.mol) in absolute ethanol (5 ml), freshly activated zinc dust (500 mg) was added in one lot. The reaction mixture was refluxed for 12 hr, filtered and the residue washed with dry ether. The solvents were evaporated *in vacuo* and the resulting oil purified on a silica gel column (eluant, benzene) to yield 16 [40 mg, 60% based on recovered starting material (80 mg)], IR: ν_{max} (CCl_4): 1725, 850 cm^{-1}; ^{1}H-NMR[20] ($CDCl_3$): δ 1.10 (3H, s, CH_3), 1.20 (3H, s, CH_3), 1.21 (3H, t, $CO_2CH_2\underline{CH}_3$), 1.70 (6H, d, 2X CH_3), 1.80 (1H, d, J=5.6 Hz, CH-CO_2Et), 2.01 (1H, dd, J=5.6, 8 Hz, $\underline{CH}$-CH=), 4.08 (2H, q, $CO_2\underline{CH}_2CH_3$), 4.80 (1H, dm, J=8 Hz, CH on double bond); Mass m/e: 196 (M^+), 123 (M^+ - CO_2Et). (Fig.2.3.3)

Analysis: Calculated for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.18; H, 9.91%.

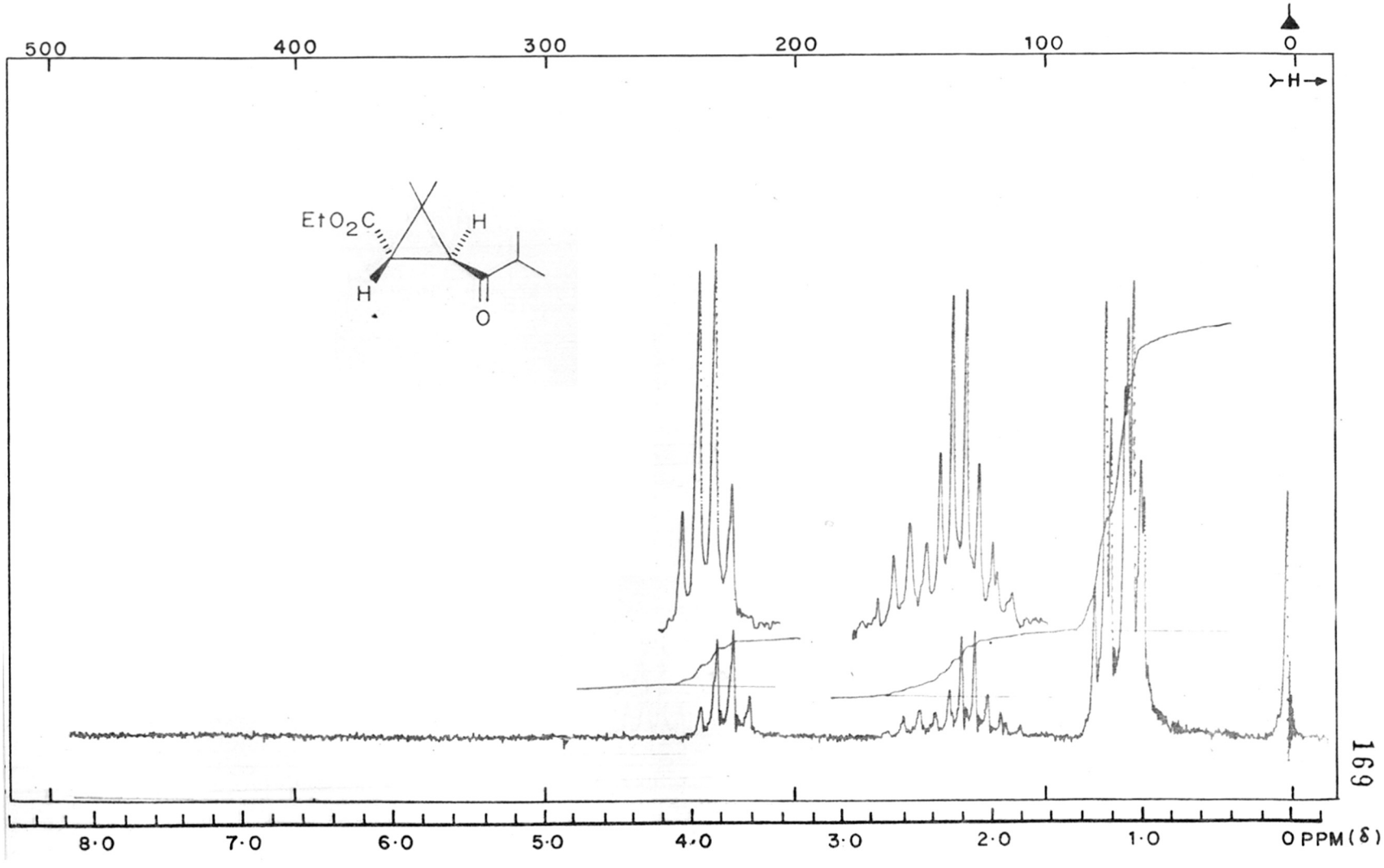


FIGURE 2·3·1

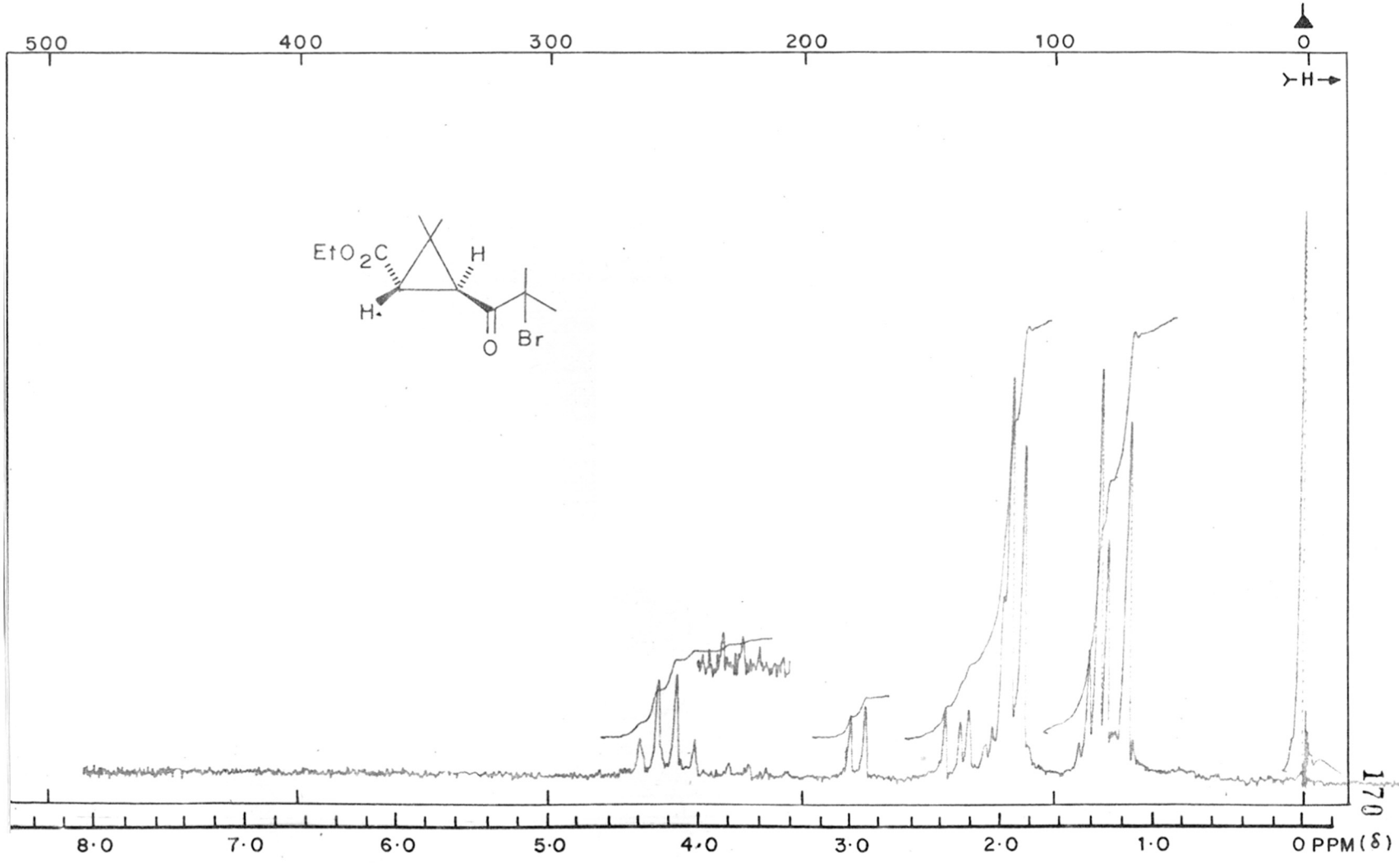

500
400
300
200
100
0
H
EtO2C
H
H
O
Br
170
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM (δ)

FIGURE 2·3·2

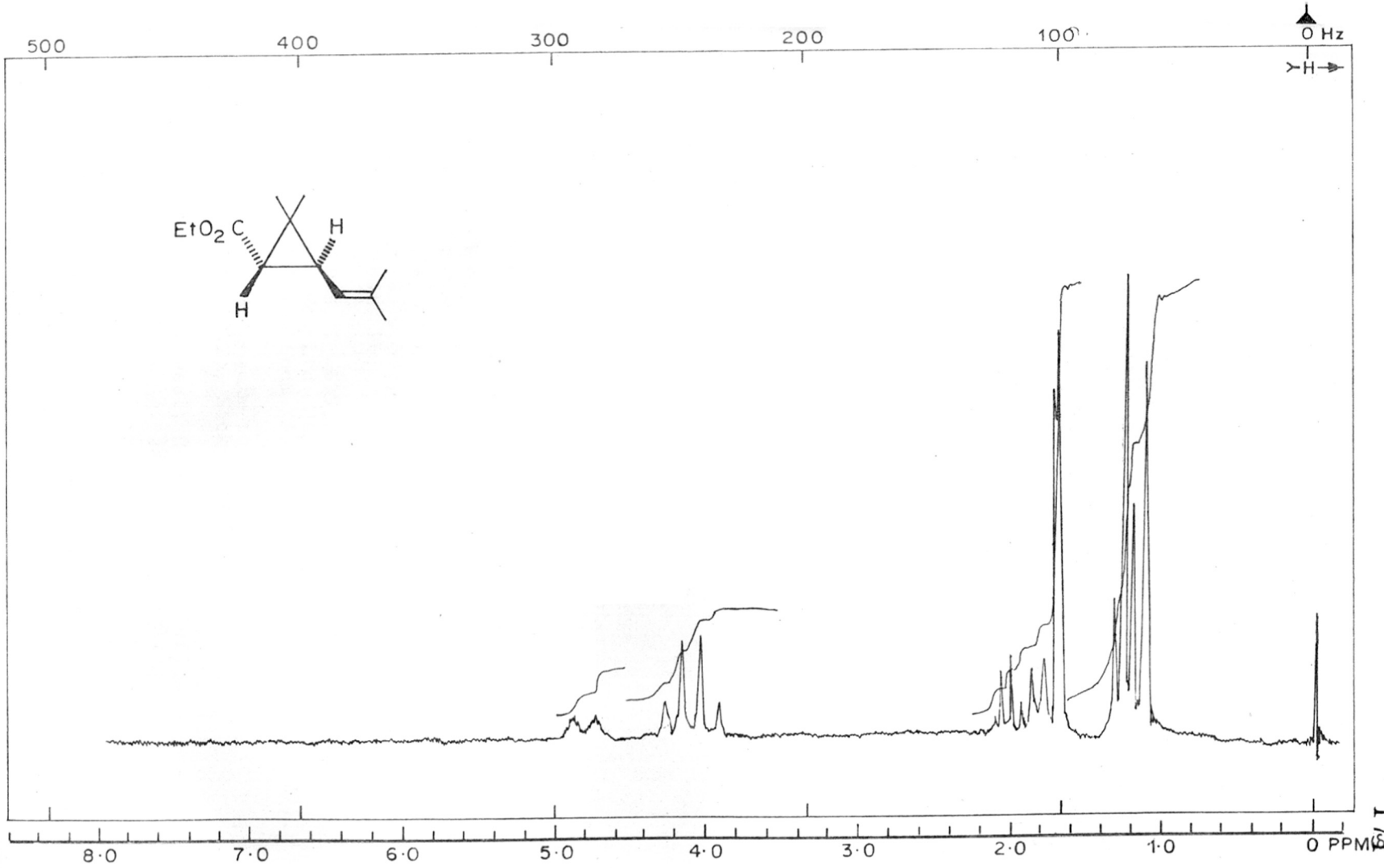


FIG. 2·3·3

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CHAPTER 3·0·0

SYNTHESIS OF NITRILES USING ZEOLITES

FOREWORD

This chapter explores the dehydration techniques of amides and aldoximes which can find practical use for nitriles of interest as drug intermediates.

3.1.0 INTRODUCTION

This chapter highlights the potential use of zeolites in establishing a dehydration technique in organic synthesis.

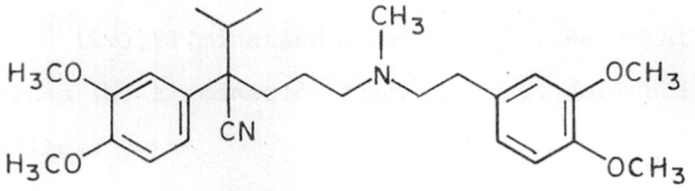
Nitriles are important organic intermediates for a variety of end products. A few compounds containing a nitrile group have been found to have potent medicinal characteristics for e.g. verapamil (1), isoaminile (2) and toyocamycin (3)[1].

Nitriles are widely being used as intermediates in the synthesis of many types of heterocycles and other compounds of medicinal interest for e.g. 3,4-dihydroisoquinolines, imidazoles, indoles, lactim ethers, naphthyridines, pyridones, pyrido-pyrmidines, pyrmidines, quinazolines, quinazolones, quinolines, 1,2,4,5-tetrazines, tetrazoles, 1,2,4-triazoles, N-substituted amides, amidines and basic esters[1].

The chemistry of the cyano group and recent methods of preparing these important intermediates have been reviewed comprehensively[1,2].

General Methods of Preparation of Nitriles[2]

The synthetic methods for the preparation of nitriles can be related mainly to four reaction types: (i) addition of hydrogen cyanide to multiple bonds (ii) substitution reactions viz. displacement by the cyano group (iii) conversion from



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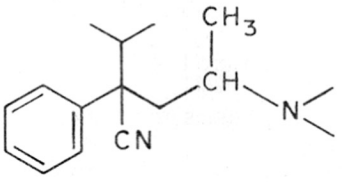

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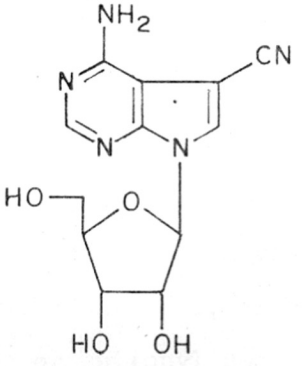

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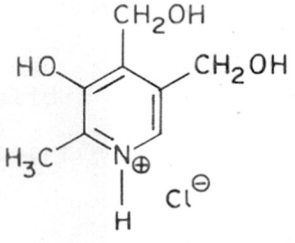

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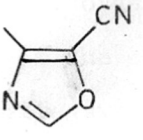

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CHART-3·1·1

other nitriles (iv) Elimination reactions (a) Dehydration of carboxamides (b) Elimination from carbonyl derivatives mainly aldoximes.

Methods used for the generation of nitriles other than the dehydration methods will be first dealt with briefly.

(i) Addition of hydrogen cyanide to multiple bonds

Though the nucleophilic addition of HCN or its salts to multiple bonds, results in the formation of nitriles, either directly or on subsequent rearrangement, it is an unsatisfactory reaction even in the presence of catalysts and high temperatures as yields are low.

While there have been few innovations of value to laboratory scale synthesis, the addition of HCN on an alkene or alkyne remains an important industrial process e.g. the manufacture of acrylonitrile[2b].

Base catalysed addition of HCN across multiple bonds particularly when such bonds are substituted by electron withdrawing groups (as in Michael additions),also gives rise to nitriles,which can be saturated or unsaturated nitriles, esters,ketones, nitro or sulfonyl compounds.

(ii) Substitution reactions

The reaction of a suitable leaving group viz. organic halides or sulfonates with a metal cyanide, is one of the most frequently used and convenient methods of nitrile synthesis.

A variety of reagents e.g. sodium cyanide, potassium cyanide, cuprous cyanide, sodium dicyano cuprate etc. are being used.

(iii) Conversion from other nitriles

This class belongs to generation of nitriles by derivatisation of simpler nitriles.

One such major reaction involves aldol type condensation of nitriles with ketones or aldehydes leading to unsaturated nitriles and α-alkylation of nitriles to generate homologues. α,β-Unsaturated nitriles by virtue of being good dienophiles generate new nitrile derivatives on cycloaddition.

(iv) Elimination Reactions

This type of reaction generating nitriles are very common and will be the subject matter of this chapter. Elimination of water from carboxamides and aldoximes are effected efficiently using different reagents.

a) Dehydration of carboxamides

The most important method for the conversion of carboxylic acids into the corresponding nitriles consists in the dehydration of their amides.

The variety of reagents which were being used for the dehydration, have recently increased and milder reaction conditions than were previously possible, have evolved.

A good number of reagents[3] like P_2O_5[3], $SOCl_2$, PCl_5,

$POCl_3$, $AlCl_3$, $SOCl_2$-DMF complex, PTS chloride/pyridine, benzenesulfonyl chloride, polyphosphoric acid, its ethyl ester [PPE], ethylchloroformate/triethylamine, DCC, triphenylphosphine/CCl_4 and titanium tetrachloride/Et_3N are well known in literature.

More recently, reagents like $SOCl_2$-$(COCl)_2$[4], trimethyl silylpolyphosphate [PPSE][4], silazones[5] and phase transfer catalysts[6] have been reported.

The catalytic dehydration[7] of amides too, has been reported using charcoal, graphite, alumina, silicic acid gel and silica gel/$SiCl_4$.

The direct conversion of carboxylic acids to nitriles, can be done by treating the acid at sufficiently high temperature with dry ammonia or urea, or by subjecting the ammonium salt of an acid to dehydration thermally or by chemical means[2].

b) Elimination from aldoximes

One of the most frequently used method to convert aldehyde to nitriles is via the dehydration of their oximes. Numerous methods for the conversion of aldoximes to nitriles have been described in the literature. Some of them appear to be of theoretical interest to the medicinal chemist, while others offer distinct advantages over earlier methods.

This conversion may be effected by a number of reagents[8] for e.g. Ac_2O, trifluoroacetic anhydride/pyridine

triflic anhydride, trichloroacetyl chloride/Et_3N, Ph_3P/CCl_4, N-trifluoroacetyl imidazole, PTS-chloride, Et_3N-SO_2 complex, Vilsmeir reagents, cyanuric chloride, selenium dioxide, PPA, PI_3, P_2I_4/pyridine, chlorosulfonyl isocyanate, DCC, benzene-sulfonyl chloride, KCN/PTC and $Cu(OAc)_2$.

Some of the recent reagents include titanium chloride in pyridine, diphenylphosphoric acid and hexamethyl cyclotrisilazones[1].

A facile one-step conversion of aliphatic aldehydes to nitriles can also be effected by treatment with hydroxylamine hydrochloride and hydrochloric acid in ethanol[1].

Compared with the above methods, the catalytic dehydration of oximes at elevated temperatures in presence of alumina or thoria catalysts appear to be less important.

Herein, it is demonstrated for the first time that zeolites could be used for the dehydration of carboxamides and elimination reactions of aldoximes to nitriles in quantitative yields in a process which could be easily adapted to large scale manufacture as required in the drug industry.

ZEOLITES

Zeolites[9] are hydrated crystalline aluminosilicates composed of SiO_4 and AlO_4 tetrahydra arranged in various geometric patterns. The tetrahydra are linked together at the corners by shared oxygen ions to form ordered lattices which

are often best visualised as three-dimensional combination of chains, layers and polyhedra.

The unit cell formula of zeolites is

M x/n $[(AlO_2)_x (SiO_2)_y] WH_2O$, where M is a metal ion, x, y and n are integers. The bracketed portion describes the framework composition, and the values of x and y are such that y/x is usually greater than 1 and they represent the number of tetrahedra in the zeolite. W is the number of water molecules in the zeolite.

Although natural zeolites and their properties were known more than 200 years ago, their unique properties came to receive increasing attention only in the 1940s. With the advent of X-ray crystallography further studies on zeolites were possible which led to synthetic zeolites for commercial use. Some of those synthesised were analogs of zeolite minerals and not found in nature.

The earliest uses of these zeolites were for adsorption and drying of gases, separation of gases and ion exchange. Soon, their importance as catalysts for reactions were realized. They were first employed as cracking catalysts in 1964. The beginning, development, synthesis and various recent applications of zeolites have been reviewed[10].

At present, there exist numerous species of natural and synthetic zeolites. The classification of zeolites[9] is based on the structural units and their linkage and X-ray

analysis of the framework structure. The classification based on X-ray divides zeolites into a number of groups, the more important ones being synthetic faujasites (x and y), mordenite, zeolites T,A and L and clinoptile and later ZSM-5 and silicalite have been discovered.

The subsequent success of zeolites as catalysts has been primarily due to the discovery of new zeolites - those containing high silica, in the early 1970s. The most important of these, ZSM-5 was discovered by Argauer & Landolt[11] in 1972. The generic name "pentasil zeolites" has been used to refer to ZSM-5 type zeolites. The other members of the pentasil family are ZSM-8, ZSM-11 and silicalite. Silicalite contains essentially no aluminium.

PROPERTIES OF ZEOLITES[9]

From the point of view of catalysis, zeolites are molecular sieves having variable dimensions that are admirably suited to manipulating molecular rearrangements. Their main properties are:

(1) High density of active sites

(2) Stereospecificity

(3) Sites for occluded species.

(4) Controllable potential energy fields.

Most of the zeolites are very acidic and all efforts were previously focussed on acid catalysed reactions.

With the development of high silica/alumina ratio

zeolites, several zeolites with low or no acidity - ZSM-5 being the most important, have been synthesized.

Such products may develop hydrophobic properties, more so when they approach the pure silica end-member of the structure, as in silicalite.

ZSM-5 has been undoubtedly established as the most interesting and important catalytic material to be found among the zeolites so far.

ZSM-5 combines the advantages of low acidity, high pore volume and moderated pores with a degree of hydrophobicity. Such products are ideal for petrochemical processing. These properties of ZSM-5 combine to make it an excellent dehydration and polymerization catalyst.

SCOPE OF ZEOLITES[9]

Zeolite catalysts have been applied to the following four general areas of industrial processes:

a) Petroleum processing

b) Petrochemicals

c) Chemical synthesis

d) Pollution control

Zeolites, as catalysts, have been well exploited in petroleum processing for a number of operations, such as cracking, isomerisation, alkylation and polymerization. Development of zeolite applications in other areas are still in their infancy but seem poised for major expansions.

Organic reactions using zeolites

Venuto and Landis[12] have enumerated various organic reactions being catalysed by zeolites, prominent among them being olefin-forming eliminations, polymerizations, isomerizations and aromatic alkylations.

Some of the other reactions catalysed by zeolites are:

a) Condensation and cyclization reactions which include aldol condensation, Cannizaro reaction, Prins reaction and Beckmann rearrangement.
b) Epoxide transformations
c) Oxygen-sulfur exchange reactions
d) Olefin-carbonylation
e) Amination reactions
f) Hydrogenation, dehydrogenation and related reactions.

3.2.0 PRESENT WORK

Though zeolites have been used in some organic reactions, the main reactions being, olefin formation via dehydration, aromatic alkylations and isomerisations, their potential in general organic synthesis has not been fully exploited.

This chapter demonstrates the effectiveness of zeolites in quantitative conversions of amides and aldoximes to nitriles.

As mentioned earlier, there have been numerous methods reported for the above conversions, but, most of the methods have limitations and are not suitable for large scale preparations.

Further, the practical applications of these methods in synthesis may suffer from various disadvantages such as use of expensive and unusual reagents or less easily available reagents, prolonged heating, drastic reaction conditions, tedious work up procedure, unsatisfactory yields and those inherent in batch-type processes.

Few of these methods also may require the use of strong bases, acids or oxidizing agents i.e. conditions which may be incompatible with sensitive substrates or less stable groups in the substrate and may thus lead to the formation of side products. For example, for the preparation of the important B_6 intermediates 5 (Chart 3.1.1) from the corresponding

amide, drastic chemical conditions as above are extremely unsuitable. Hence we thought we should develop methods for facile conversion of amides to nitriles under nearly neutral conditions using the zeolite catalyst, ZSM-5. We took up as examples for this study, amides such as benzamide, nicotinamide, isovaleramide and phenacetamide.

Further we wanted to take up an example of a drug intermediate to apply the result of these dehydration studies. In this context, we prepared 3',4'-dimethoxy- -(1-methylethyl)-benzene acetic acid 8 by the use of a Favorskii reaction on 2-chloro, 3-methyl-3',4'-dimethoxy-butyrophenone 10 (Chart 3.2.2). This method of preparation of the acid was general and can be applied to the preparation of other carboxylic acid intermediates required for example in the drug industry viz. α-(4-isobutylphenyl)propionic acid or used as acid moiety of synthetic pyrethroids viz. α -[4-(tert-butyl)phenyl] isovaleric acid[13]. These type of compounds were prepared by multistep synthesis whereas here we have a single Favorskii reaction leading directly to the carboxylic acid. The use of zeolites as effective dehydrating agents was later extended to the process of nitrile formation from aldoximes.

Section A

Experimental set up for carboxamide dehydration

As amides, in general, are not soluble in hydrocarbon solvents, it was not possible to pass a solution of an amide

on the catalyst column in an experimental set-up generally used. Use of chlorinated solvents for dissolution of amides is not feasible as the passing of such solvents on zeolites heated to such high temperatures (400°C) as in the present set-up, would result in alkylations thus leading to a number of side products.

The general set up involves the passage of liquified amide (through which a continuous flow of nitrogen was being passed) through a preheater (which vapourises the amide) to the zeolite catalyst bed in a flow reactor. The end of the catalyst column was connected to a receiver through a cooled condensor.

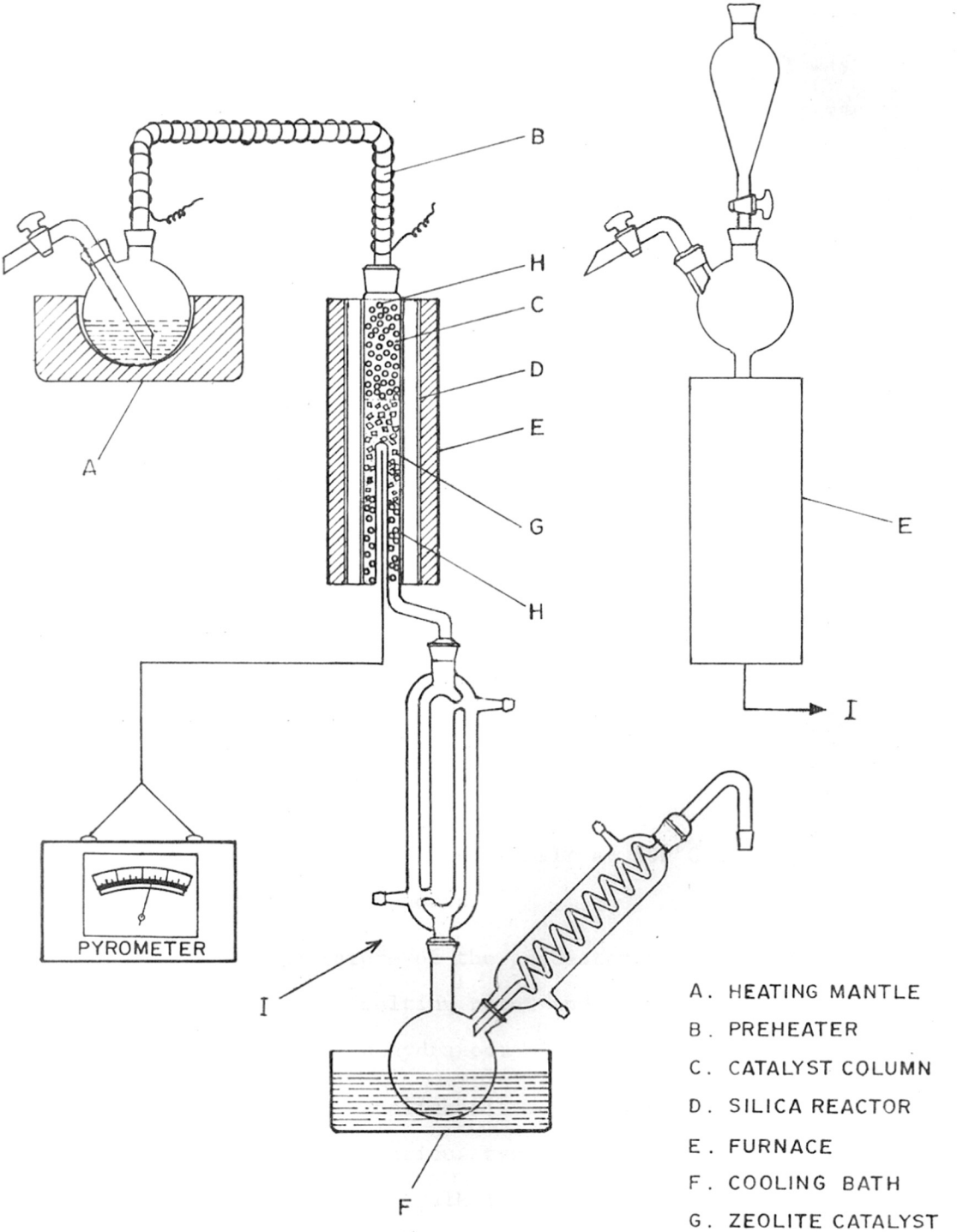
In the modified experimental set-up, the preheater was designed in such a way that the amide vapours would not solidify in the stop-cock, by covering the preheater by the heating element and insulation upto its joint which, in turn, enters the hot joint of the catalyst column.

This set-up (Fig. in Chart 3.2.1) involved the use of a two necked round bottomed flask with a nitrogen inlet at one end, the other neck was extended into a fissured tube, surrounded by nichrome wire for heating. This served as the preheater and was fitted into the joint of the column in the reactor. The reactor consists of a silica tube or column (length 14", internal diameter, 15 mm) kept in a cylindrical furnace (Description*)The required quantity of the catalyst,

*The furnace comprises of a cylindrical silica tube surrounded by nichrome ribbon and a glass sleeve, around which asbestos rope is bound and the whole is covered by a thick paste of asbestos powder.

SET UP FOR

(a) CARBOXAMIDES TO NITRILE (b)ALDOXIMES TO NITRILES



A. HEATING MANTLE
B. PREHEATER
C. CATALYST COLUMN
D. SILICA REACTOR
E. FURNACE
F. COOLING BATH
G. ZEOLITE CATALYST
H. PORCELAIN BEADS
I. RECEIVING SYSTEM

CHART. 3·2·1

ZSM-5 here, in the form of pellets (1/16" diameter) was kept in the center of the catalyst column so that it was in the middle isothermal region of the furnace. The catalyst was packed with porcelain beads at both ends of the column. Provision was made for measuring the inside temperature of the catalyst bed by means of inserting a thermocouple in the column. The catalyst column was heated to a temperature of 400°C while passing a stream of nitrogen, in 2 hours / The preheater was heated to 250°C and the column at 400°C was connected through a double surface condensor to a two-necked flask, the other neck of which had a coiled condensor with a nitrogen outlet at the top end.

fractionation.

The work up procedure was very simple and uncomplicated in that,the product collected in the receiving flask was taken up in benzene, dried and concentrated to yield the pure nitrile. In our 5 g batches, the whole operation was over within an hour's time. After each reaction, the catalyst was reactivated by passing CO_2-free air at 500°C through the catalyst tube for 3-4 hours.

The temperature of the preheater could be changed depending upon the melting point and vapourisation temperature of the amide being dehydrated.

The general applicability of this method was ably demonstrated by the various types of amides used for the reaction viz. aromatic, alkyl aromatic, heterocyclic as well

as aliphatic (Table I, Chart 3.3.1). These amides were dehydrated in very high yields to the corresponding nitriles.

Section B

Experimental set up for aldoxime dehydration

The experimental set up for the conversion of aldoximes (Fig. in Chart 3.2.1) was much simpler as aldoximes are readily soluble in benzene and a solution of the oxime in benzene could be directly passed from a dropping funnel, through a flask having a N_2 vent, to the catalyst column; the upper portion of the column packed with beads, serving as the preheater.

The benzene solution collected at the end of the reaction was dried (Na_2SO_4) and concentrated to afford excellent ($\geqslant 90\%$) yields of the pure and clean product in a relatively short time; the whole operation was over within an hour in our reactions.

The high yields obtained are due to the fact that a solution of the substrate was passed on the zeolite; the solution allowing nothing to remain adsorbed on the catalyst bed. The catalyst can even be taken in the powder form to provide similar yields, through the pellet form was definitely better.

This conversion was base catalysed, the catalyst used was Cs-NaX type [14].

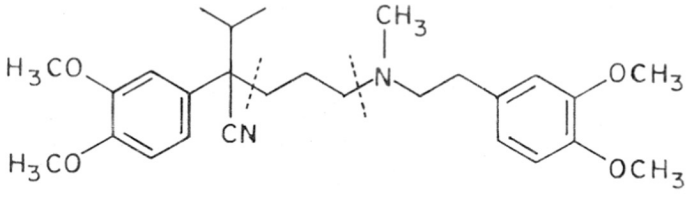
This method was of general applicability. It could be used for aliphatic, aromatic and heterocyclic aldoximes.

Both (E) & (Z) isomers of oximes could be used for the conversion. Even a mixture of E & Z isomers could be used to obtain complete and quantitative conversion (Table II, Chart 3,3,1).

In conclusion, Sections A and B unequivocally show that zeolites could be used in the exclusive and quantitative conversion of carboxamides and aldoximes to nitriles.

The use of the zeolite column has a distinct advantage over other reagents and catalysts known as this process offers operational advantages, wherein no purification of the product formed is necessary. Also, this process can be very easily extended to large scale manufacture as required in the drug industry. The process of manufacture can be a continuous one if two columns of catalyst beds are kept available so that while one is being reactivated (by air oxidation at 500°C), the other column can be put to use and vice versa, thus allowing for a steady flow of material for further reactions.

That the method is operationally viable has been proved in the Section C of this chapter wherein, 3,4-dimethoxy-2'-isopropyl benzene acetonitrile (6) (Chart 3.2.2) a key intermediate in the manufacture of Verapamil (1), a coronary vasodilator, has been obtained in high yields from the corresponding amide (14) (Chart 3.2.3) by passing it over a zeolite bed.



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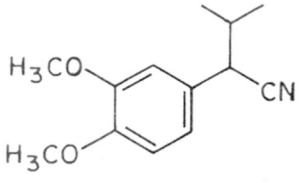

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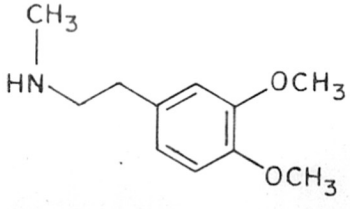

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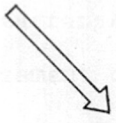

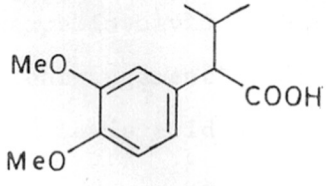

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CHART-3·2·2

Section C

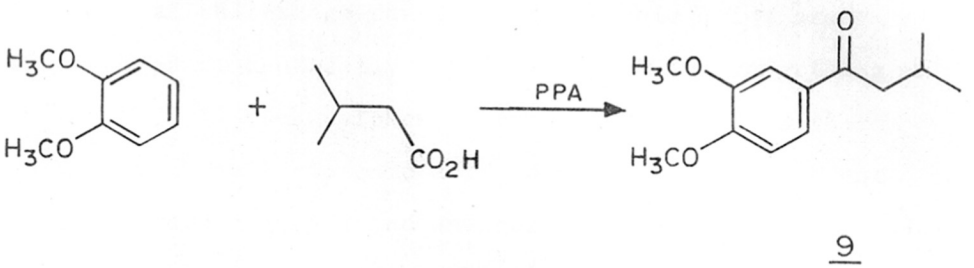
Preparation of the Verapamil intermediate (6)

Verapamil (1) is an important drug used worldwide as a coronary vasodilator.

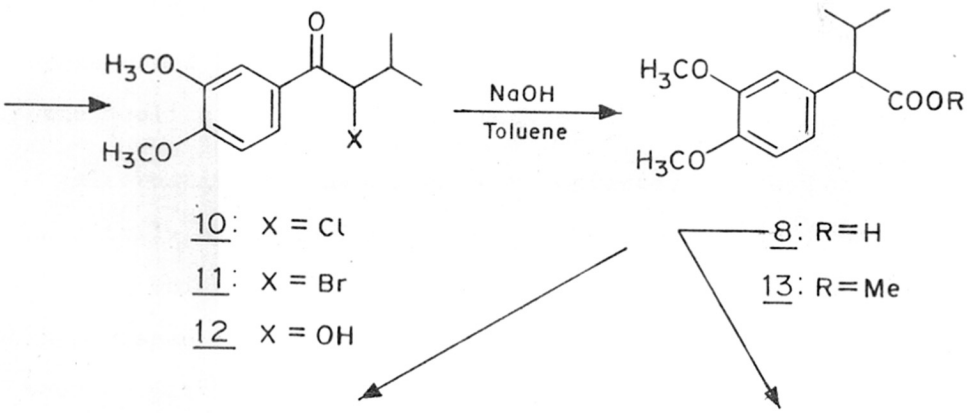
An antithetic fragmentation of Verapamil (Chart 3.2.2) demonstrates that two main fragments 6 and 7 are required for its synthesis. This section deals with the synthesis of the key intermediate 6 via a short route involving a Favorskii rearrangement. It may be mentioned here that the nitrile 6 was earlier synthesized by alkylation of 3,4-dimethoxy benzene acetonitrile, during the course of the total synthesis of verapamil.

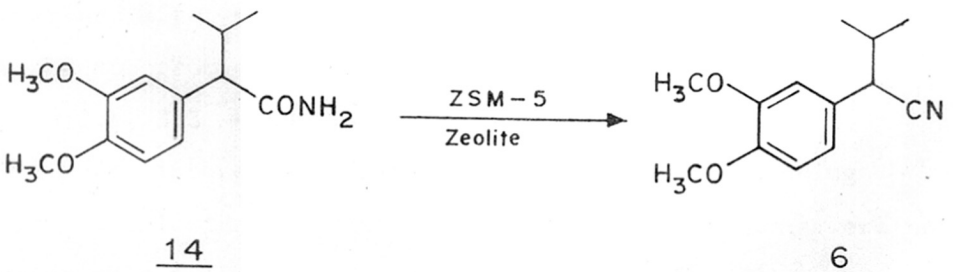
2-Methyl-(3',4'-dimethoxy)butyrophenone 9 (Chart 3.2.3) obtained earlier[15] by the polyphosphoric acid catalysed condensation of isovaleric acid with veratrole was halogenated to afford the α-haloketones 10 and 11. The next step was the Favorskii rearrangement of the α-haloketone to the acid. 1,2-rearrangement of α-haloketones to α-arylalkanoic acids has been previously reported[13] in multistep sequences; a three step sequence involving acetalization, tosylation and base catalysed rearrangement[13a] or a two step process involving acetalization and Lewis acid promoted rearrangement[13b].

α-Chloro and α-bromoketones 10 and 11 were simply refluxed with 2 molar equivalents of powdered sodium hydroxide in dry toluene following the procedure of Stevens and Farkas[16],



9





14 6

CHART- 3·2·3

to afford the α-aryl alkanoic acid 8. It is pertinent to mention at this stage that α-aryl alkanoic acids are a class of pharmaceutically important compounds comprising of for e.g. 2-(4-isobutylphenyl)propionic acid and 2-(6-methoxy-2-naphthyl)propionic acid (Naproxen) - both potent anti-inflammatory agents and analgesics and also α-isopropyl, 4-chlorophenyl acetic acid and α-[4(tert-butyl)phenyl]isovaleric acid - active acid moieties of synthetic pyrethroids.

The acid 8[17] was esterified with diazomethane at 0°C for 5 hr to afford the methyl ester 13[17] which was treated with liquor NH_3 (25%) to afford the amide 14. This amide 14 was transformed to the nitrile 6 in high yields by passing over the zeolite (ZSM-5) column described before (Section A).

Alternatively 8 has also been converted in one pot to the nitrile by employing the procedure reported by Dunn et al.[18] in which the acid 8 was first mesylated and ammonia was then passed through it to afford the amide. The amide was treated with excess mesylchloride and kept at RT for 24 hr to afford after workup the nitrile 6 in 70% yield. The IR and ^{1}H-NMR spectrum of the amide 14 and nitrile 6 are shown in Fig.3.3.4, 3.3.5 and Fig.3.3.6, 3.3.7 respectively.

An interesting feature of the chlorination using sulfuryl chloride was that if the reaction conditions were not stringently followed, the product obtained after Favorskii rearrangement contained an additional acid. It was isolated and

esterified and ^{1}H-NMR of the ester (Fig.3.3.8) showed that it could be an α-phenyl acrylic acid ester system - such a system could arise only from the Favorskii rearrangement of $\alpha\alpha'$-dichloro compound formed during the chlorination.

3.3.0 EXPERIMENTAL

Section A

Carboxamides to Nitriles

General Experimental Procedure

Benzamide (5 g) was heated in a round bottomed flask and a slow stream of nitrogen was bubbled through the melted amide. The vapours of the amide were passed through a preheater (250°C) to a silica column (length, 14 inches, internal diameter 15 mm) packed with the zeolite (ZSM-5 type) catalyst in the form of extrudates (1/16" diameter), kept in a reactor heated at 400°C. The end of the column was connected to a coiled condensor fitted to a flask to collect the nitrile formed together with water vapour. The product was dried (Na_2SO_4) and distilled at 70°/10 mm to give benzonitrile (3.83 g, 90%), lit.[19] b.p. 69°/10 mm; IR ν_{max} (neat): 2240 cm^{-1} (C≡N)

Similarly phenacetonitrile[19] (ν_{max} 2260 cm^{-1}), nicotinnitrile[19] (ν_{max} 2230 cm^{-1}); isovaleronitrile[19] (ν_{max} 2240 cm^{-1}) were prepared from the corresponding amides.* A tabular survey of the conversions is given overleaf (Table 1, Chart 3.3.1).

---

* Phenacetamide[20a] and isovaleramide[20b] were prepared by the reported methods. Benzamide and nicotinamide are commercially available.

TABLE – 1

AMIDE	YIELD OF NITRILE PERCENT	m.p. or b.p./torr (°C)	
		FOUND	LIT. VALUE
BENZAMIDE	90	70/10 mm	69/10 mm
PHENACETAMIDE	85	107/12 mm	107/12 mm
NICOTINAMIDE	89	m.p. 49–50	m.p. 49–50
ISOVALERAMIDE	85	52/50mm	52·5–53·5/50 mm
α–ISOPROPYL, 3,4–DIMETHOXY–BENZENE ACETAMIDE	88	m.p. 46	m.p. 46–49

TABLE – 2

ALDOXIME	YIELD OF NITRILE (PERCENT)	m.p. or b.p./torr (°C)	
		FOUND	LIT. VALUE
BENZALDOXIME	92	70/10 mm	69/10 mm
FURFURALDOXIME	95	147	146/738
VERATRALDOXIME	90	m.p. 68	m.p. 67–68
DECANALDOXIME	93	117	118
n–BUTYRALDOXIME	85	105/10 mm	106/10 mm

CHART – 3·3·1

Section B

Aldoximes to nitriles

Benzaldoxime[21a], furfuraldoxime[21b], vetraldoxime[21c], n-butyraldoxime[21d] and decanaldoxime[21e] were prepared according to known methods.

General Experimental Procedure

A solution of benzaldoxime (5 g) in benzene (50 ml) was added dropwise through a preheater (heated to 250°C) through which a steady stream of nitrogen was being passed, to a silica column (length, 14"; internal diameter, 15 mm) packed with the zeolite catalyst (Cs-Nax type) in the form of pellets, kept in a reactor heated to 350°C. The end of the column was connected to a coiled condensor fitted to a flask to collect a solution of the nitrile formed, in benzene, together with water vapour. The benzene layer was dried (Na_2SO_4) and evaporated in vacuo to afford a product which was distilled at 70°/10 mm to give benzonitrile[19] (3.84 g, 92%). Similarly, 2-furfuryl cyanide[19], veratronitrile[19], n-butyronitrile[19] and decanonitrile[19] were prepared from the corresponding oximes as has been tabulated (Table 2, Chart 3.3.1).

The IR spectra of veratraldoxime and the corresponding nitrile are represented in Fig.3.3.1 and Fig.3.3.2 respectively.

Section C

Preparation of the verapamil intermediate 6

1-(3,4-dimethoxyphenyl)-3-methyl-butanone (9)

Polyphosphoric acid was prepared by mixing phosphorous pentoxide (135 g) and orthophosphoric acid (85%, 58 cc) in a three-necked flask fitted with a mechanical stirrer and the reaction was maintained, with stirring, at a temperature of 80° for 1 hour. The temperature of the bath was brought down to 60° and a solution of the two reactants, veratrole (13.8 g, 0.1 m) and isovaleric acid (10.2 g, 0.1 m) was added to the swirling, viscous, polyphosphoric acid in one lot. The reaction was maintained at 60° with stirring for 4 hours and then ice cold water was added to it. Ether extract of the above was washed with 10% solution of sodium bicarbonate, dried (Na_2SO_4) and evaporated in vacuo to afford a yellow solid 9 (20.4 g, 92%), m.p. 90°C, lit.[15] m.p. 91.6°C; IR: ν_{max} (nujol): 1685, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 0.85, 0.95 (2s, 6H, 2 CH_3), 2.07 (m, 1H, $CH\lessdot$), 2.62 (d, J=6 Hz, 2H, CH_2-C(=O)-), 3.73 (s, 6H, 2XOCH_3), 6.53 (d, 1H, J=9 Hz, H-5'), 7.17 (m, 2H, H-2',6); Mass m/e: 222 (M^+), 165 ($M^+ - C_4H_9$).

Analysis: Calculated for $C_{13}H_{18}O_3$: C, 70.27; H, 8.11; Found: C, 70.01; H, 8.10%.

1-(3,4-dimethoxyphenyl)-2-chloro-3-methyl-butanone (10)

To a stirred and cooled (0°C) solution of the above ketone 9 (11.1 g, 0.05 m) in 100 ml dry (over P_2O_5) carbon tetrachloride, sulfuryl chloride (4.5 ml, 0.055 m) was added dropwise. After stirring for 2 hours at 0°C, reaction was stirred for 18 hours at room temperature. The solvent was evaporated in vacuo to afford pure 10 as a viscous oil (12 g, 93%). (Fig.3.3.3): IR: ν_{max} (neat): 1690, 1605, 1595 cm^{-1}; ^{1}H-NMR (CCl_4)/δ 0.95, 1.10 (dd, 6H, J=7 Hz, 2XCH_3), 2.23 (m, 1H, C<u>H</u><); 3.73 (s, 6H, 2 X OCH_3), 4.57 (d, J=8 Hz, 1H, C(=O)-C<u>H</u>-Cl); 6.52 (d, J=9 Hz, 1H, H-5'); 7.16 (m, 2H, H-2',6). Mass m/e: 256, 258 (M^+).

Analysis: Calculated for $C_{13}H_{17}O_3Cl$: C, 60.94; H, 6.64; Found: C, 60.51; H, 6.23%.

1-(3,4-dimethoxyphenyl)-2-bromo-3-methyl-butanone (11)

To an ice cooled (0°C) and stirred solution of 9 (11.1 g, 0.05 m) in 100 ml dry CCl_4, bromine (3.3 ml, 0.055 m) was added dropwise. After the addition, solution was stirred at RT for 4 hours and solvent was then evaporated in vacuo to afford pure 11 as a viscous oil (14.3 g, 95%); IR: ν_{max} (neat): 1690, 1605, 1595 cm^{-1}; ^{1}H-NMR (CCl_4): δ 0.97, 1.17 (2d, J=6 Hz, 6H, 2XCH_3), 2.22 (m, 1H, C<u>H</u><), 3.73 (s, 6H, 2X OCH_3), 4.58 (d, J=8 Hz, 1H, C(=O)-C<u>H</u>-Br), 6.43 (d, J=9 Hz, 1H, H-5'), 7.12 (m, 2H, H-2',6). Mass m/e: 300, 302 (M^+).

Analysis: Calculated for $C_{13}H_{17}O_3Br$: C, 52.00; H, 5.67; Found: C, 51.76; H, 5.61%.

3,4-dimethoxy,α-(1-methylethyl)-benzeneacetic acid (8)

A suspension of finely ground sodium hydroxide (3.6 g, 90 m.mol) and chloroketone 10 (11.5 g, 45 m.mol) in 250 ml dry toluene was stirred and heated to reflux for 30 hours. The reaction mixture was cooled, water was added to it and the organic layer was separated. The aqueous layer was acidified and extracted with ether to afford the 1,2 rearranged acid 8 (3.65 g, 55%), m.p. 82-83°C, lit.[17] m.p. 85°C. IR ν_{max} (CCl_4): 3350,1710 cm^{-1}; ^{1}H-NMR (CCl_4): δ 0.71, 1.02 (6H, 2d, 2X CH_3), 2-2.6 (1H, m, C<u>H</u>$\prec$), 3.11 (1H, d, J=10.4 Hz), 3.83 (6H, bs, 2X OCH_3), 6.5-7.1 (3H, m, $-C_6H_3-$); Mass m/e: 238 (M^+).
The toluene layer was dried and concentrated to afford the α-hydroxyketone 12 (4.2 g, 40%); IR ν_{max} (neat): 3400,1720 cm^{-1}. Similarly the bromoketone 11 (13.5 g, 45 m.mol) gave rearranged acid 8 (4.2 g, 40%) and α-hydroxyketone 12 (3.75 g, 35%).

Methyl 3,4-dimethoxy, α-(1-methylethyl)-benzene acetate (13)[17]

The acid 8 was esterified with diazomethane in ether at 0°C for 4 hours to afford after removal of diazomethane and ether, the ester 13 in quantitative yields, b.p. 130°/0.1 mm, lit.[17] b.p. 133°/0.1 mm. IR ν_{max} (neat): 1740 cm^{-1}. ^{1}H-NMR (CCl_4): δ 0.72, 1.02 (6H, 2d, J=6.5 Hz, 2X CH_3), 2-2.6 (1H, m, C<u>H</u>$\prec$), 3.12 (1H, d, J=10.4 Hz, C<u>H</u>-$COOCH_3$), 3.64 (3H, s, $COOCH_3$), 3.85 (6H, bs, 2X OCH_3), 6.5-7.1 (3H, m, $-C_6H_3-$);

Mass m/e: 252 (M^+).

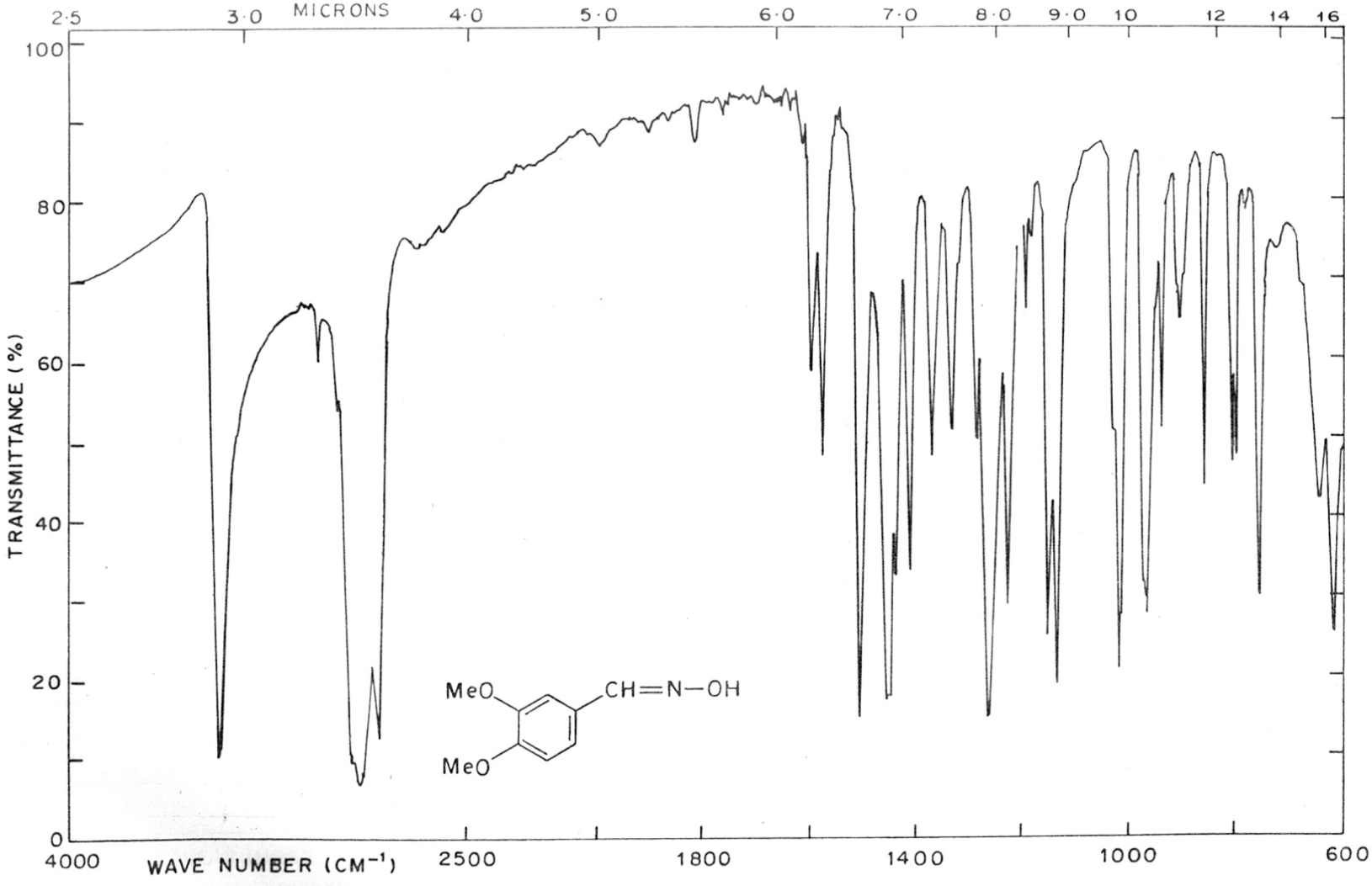
3,4-dimethoxy-α-(1-methylethyl)-benzene acetamide (14)

The ester 13 was stirred with 25% liquor ammonia at room temperature for 24 hr and filtered to afford the amide 14 in 50% yield, m.p. 139°C (recrystallised from benzene, methanol). The unreacted ester was obtained on concentration of the filterate. 14, IR ν_{max} (nujol): 3410, 3160, 1680, 1600 cm^{-1} (Fig.3.3.4), ^{1}H-NMR ($CDCl_3$) (Fig.3.3.5): δ 0.72, 1.07 (2d, 6H, 2X CH_3), 2-2.6 (m, 1H, $-CHMe_2$, 2.87 (d, J=10.4 Hz, 1H, $-\underline{CH}CONH_2$), 3.83 (bs, 6H, 2X OCH_3), 5.83 (brs,2H, exchanges with D_2O-$CONH_2$), 6.5-7.1 (m, 3H, $-C_6H_3-$).
Mass m/e: 237 (M^+).
Analysis: Calculated for $C_{13}H_{19}NO_3$: C, 65.82; H, 8.02; N, 5.91; Found: C, 65.45; H, 8.00; N, 5.80%.

3,4-dimethoxy, α-(1-methylethyl)-benzene acetonitrile (6)

The acid 8 (1.19 g, 5 m.mol) and dry pyridine (20 ml 0.25 m) were stirred at 0°C and methane sulfonyl chloride (0.44 ml, 5m.mol)was added dropwise to it. After 1 hour at 0°C, dry ammonia gas was passed into the reaction mixture for 2 minutes and then the excess ammonia was removed on rotavapour (kept for 5 minutes). The mixture was recooled to 0°C, methane sulfonylchloride (2.8 ml,32 m.mol) added to it and then the reaction was stirred at room temperature for 24 hours. It was then poured into dil. HCl, pH was adjusted to 7 and it was repeatedly extracted with ethylacetate.

The organic layer was dried and concentrated to afford a crude nitrile which was recrystallised (benzene, light petrol) to afford 6 (0.77 g, 70%), m.p. 46°C, lit.[18] m.p. 45.5-49°C. IR ν_{max} (neat): Fig.3.3.6; ^{1}H-NMR (CCl_4): Fig.3.3.7.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3·0
MICRONS
4·0
5·0
6·0
7·0
8·0
9·0
10
12
14
16
100
80
60
40
20
0
TRANSMITTANCE (%)
MeO
CH=N—OH
MeO
4000
WAVE NUMBER (CM⁻¹)
2500
1800
1400
1000
600

FIGURE 3·3·1

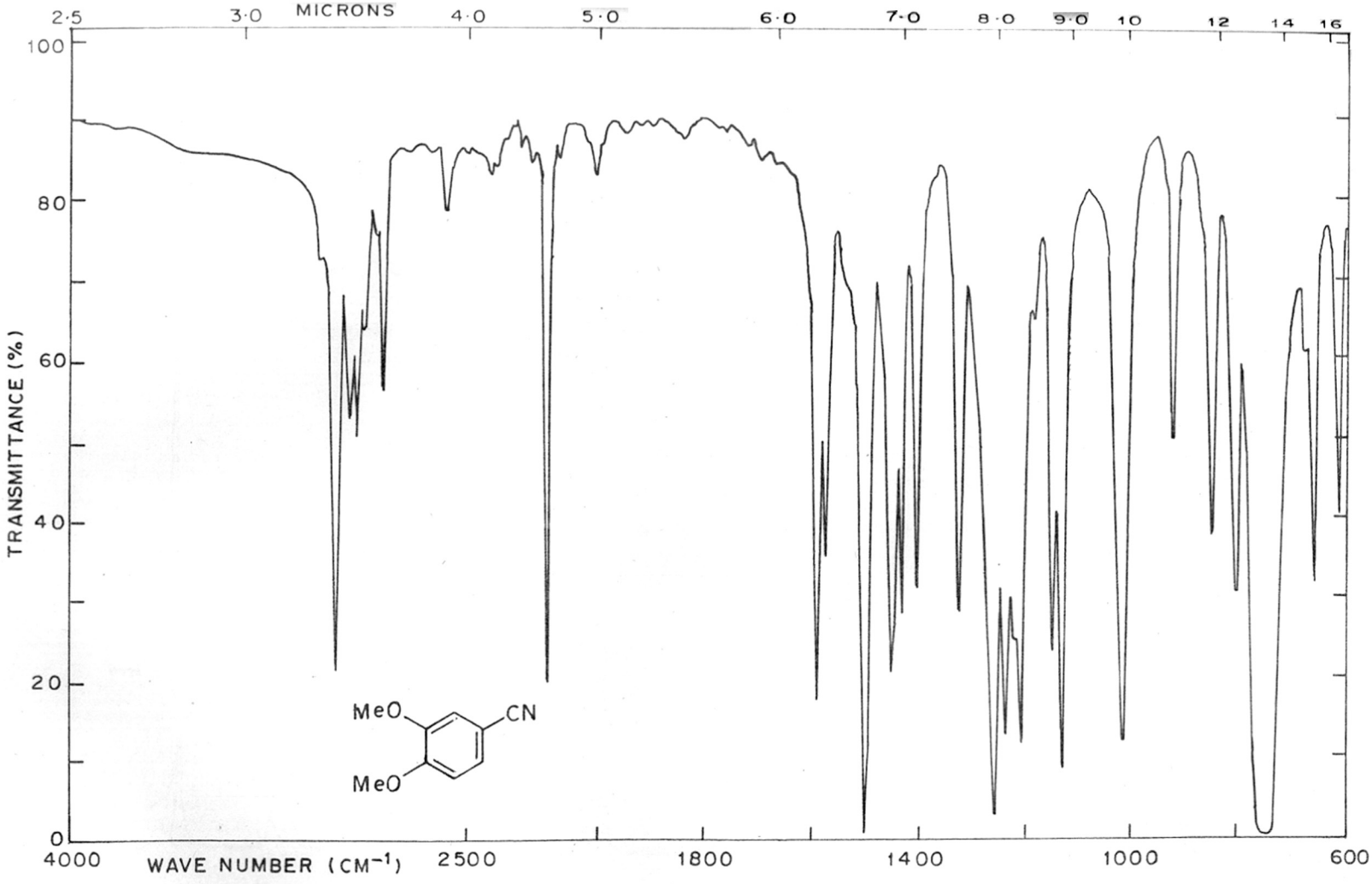

2·5
3·0
MICRONS
4·0
5·0
6·0
7·0
8·0
9·0
10
12
14
16
100
80
60
40
20
0
TRANSMITTANCE (%)
MeO
CN
MeO
4000
WAVE NUMBER (CM⁻¹)
2500
1800
1400
1000
600

FIGURE 3·3·2

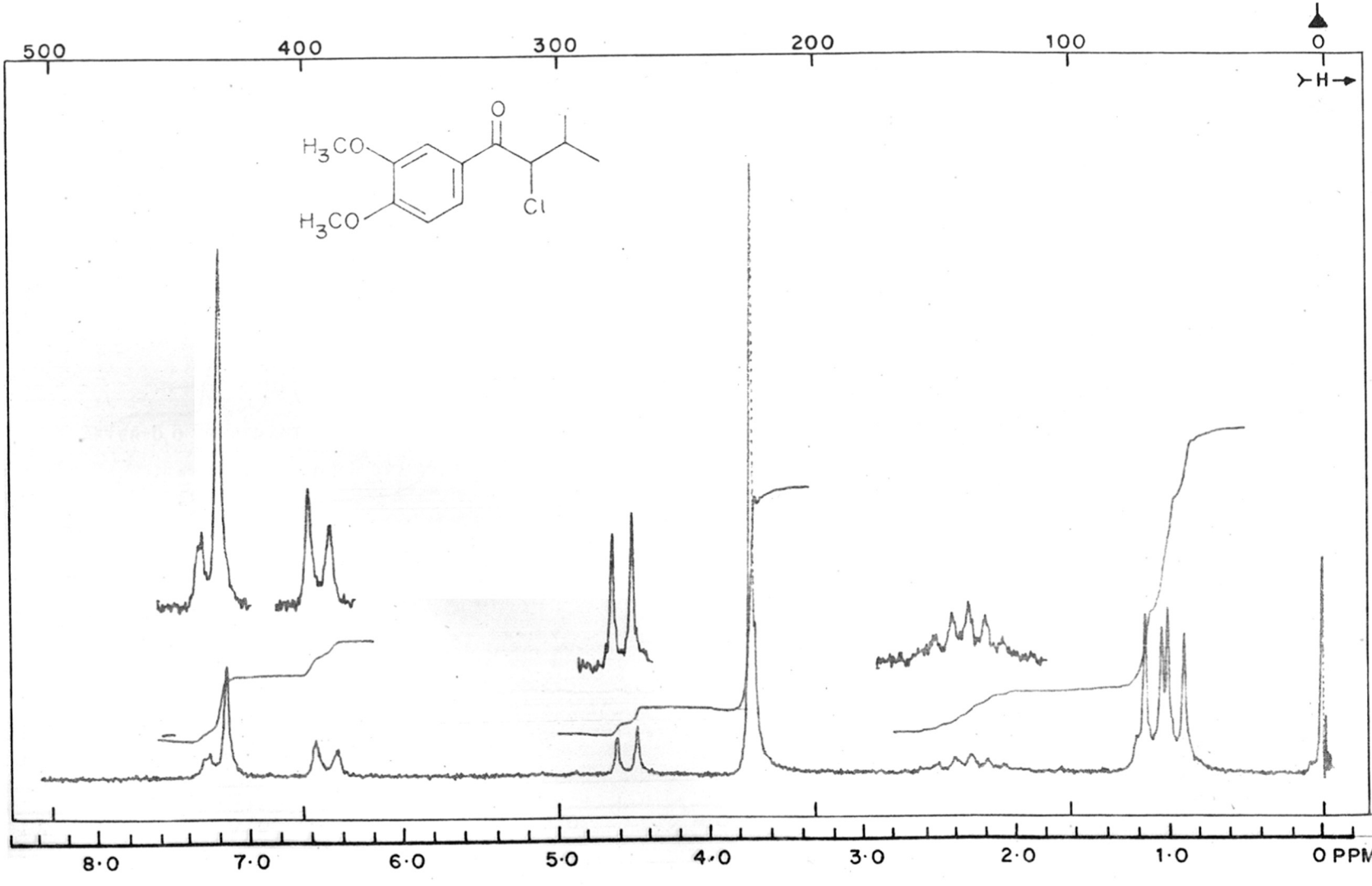
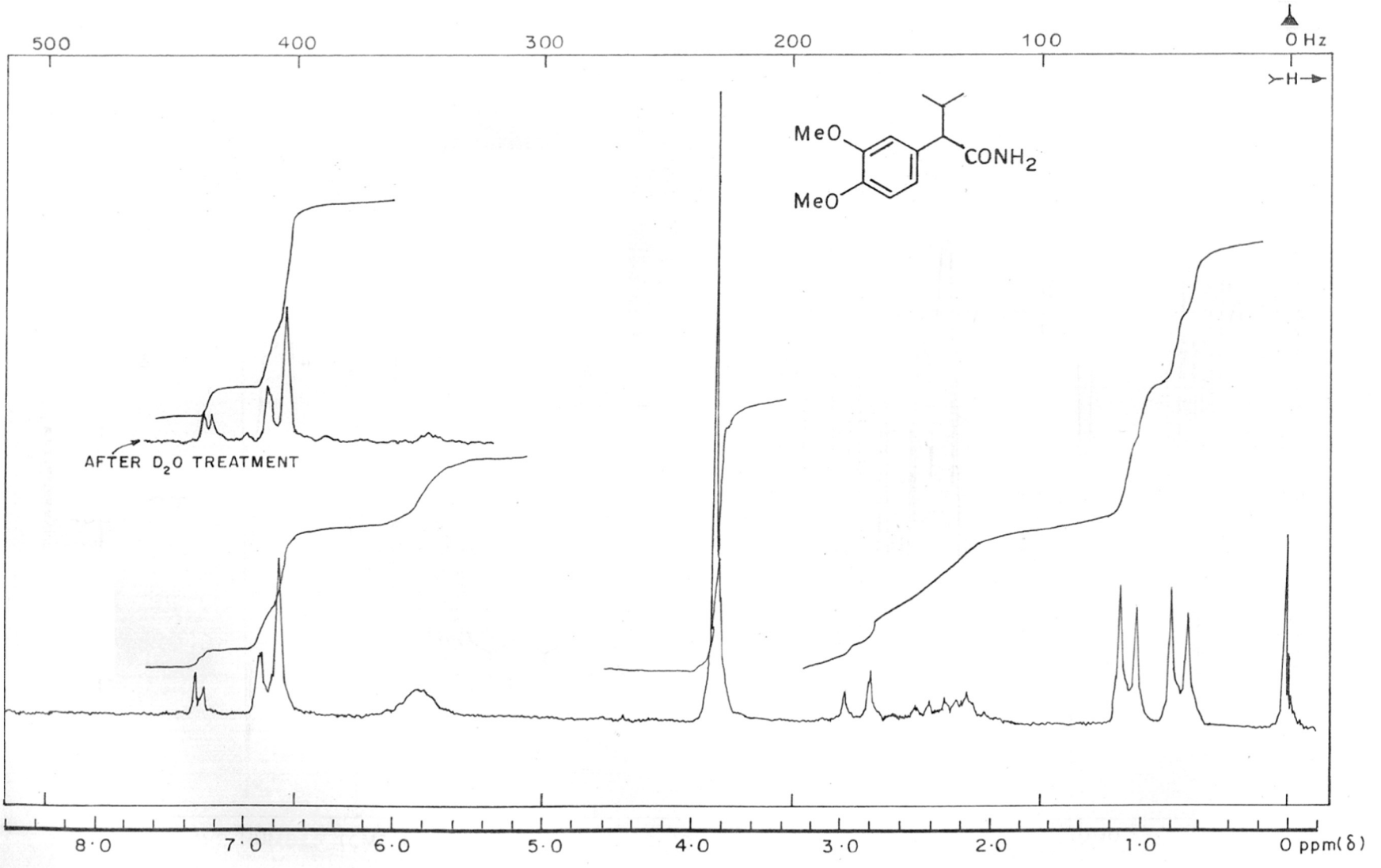


FIGURE 3·3·3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400
300
200
100
0 Hz
TMS
MeO
MeO
CONH2
AFTER D2O TREATMENT
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 ppm(δ)

FIGURE 3·3·4

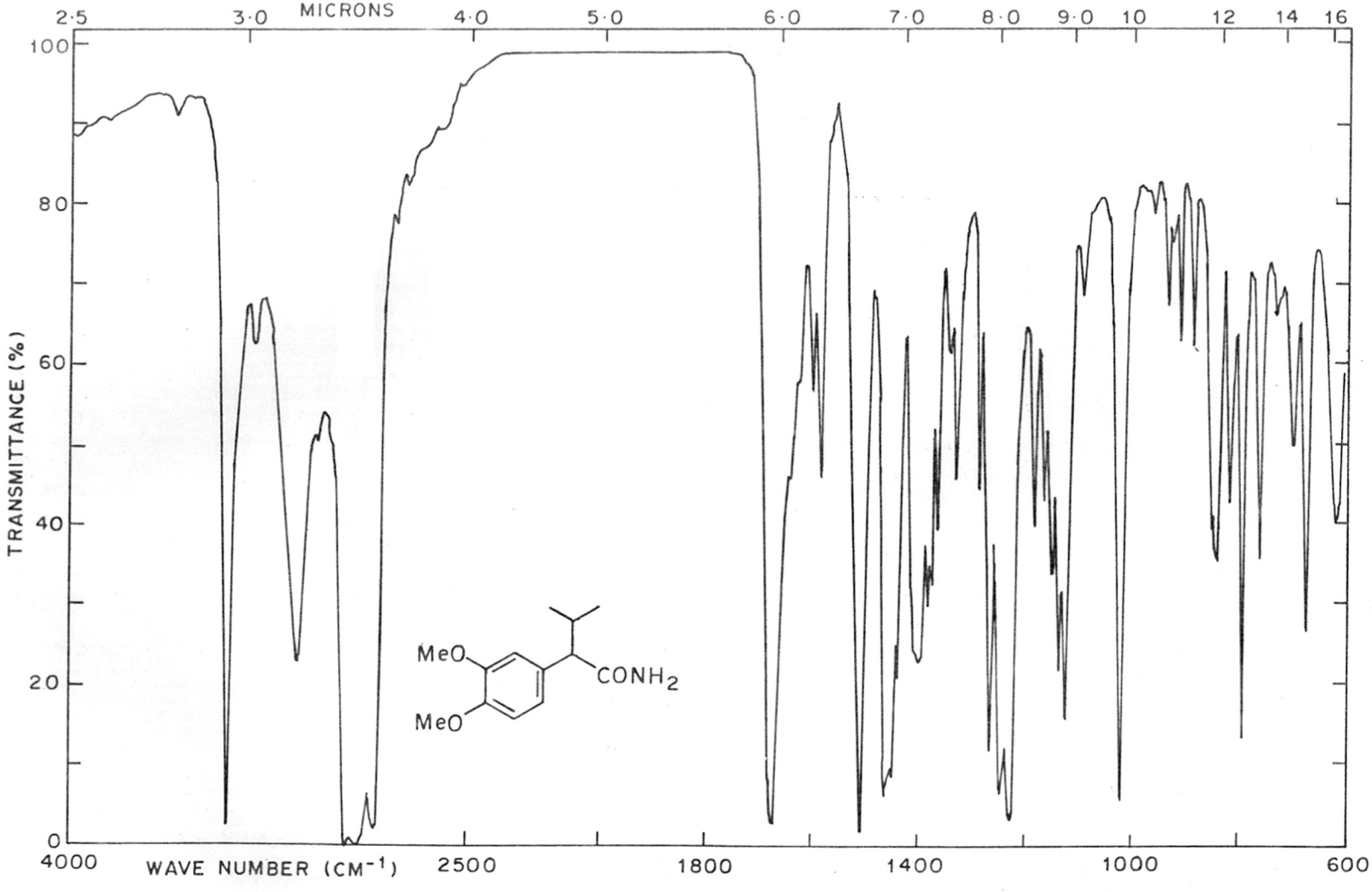

2·5
3·0
MICRONS
4·0
5·0
6·0
7·0
8·0
9·0
10
12
14
16
100
80
60
40
20
0
TRANSMITTANCE (%)
MeO
MeO
CONH2
4000
WAVE NUMBER (CM-1)
2500
1800
1400
1000
600

FIGURE 3·3·5

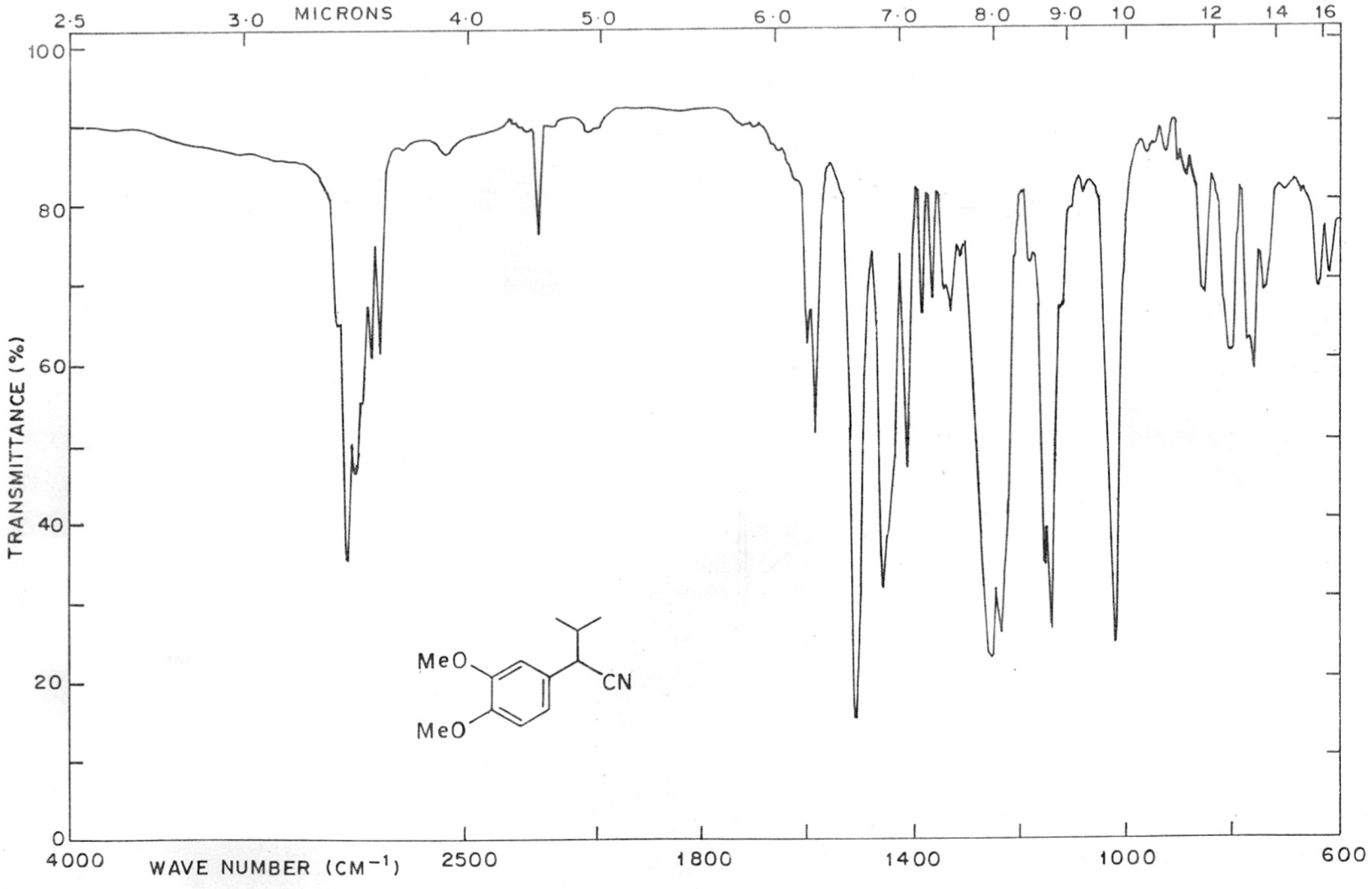
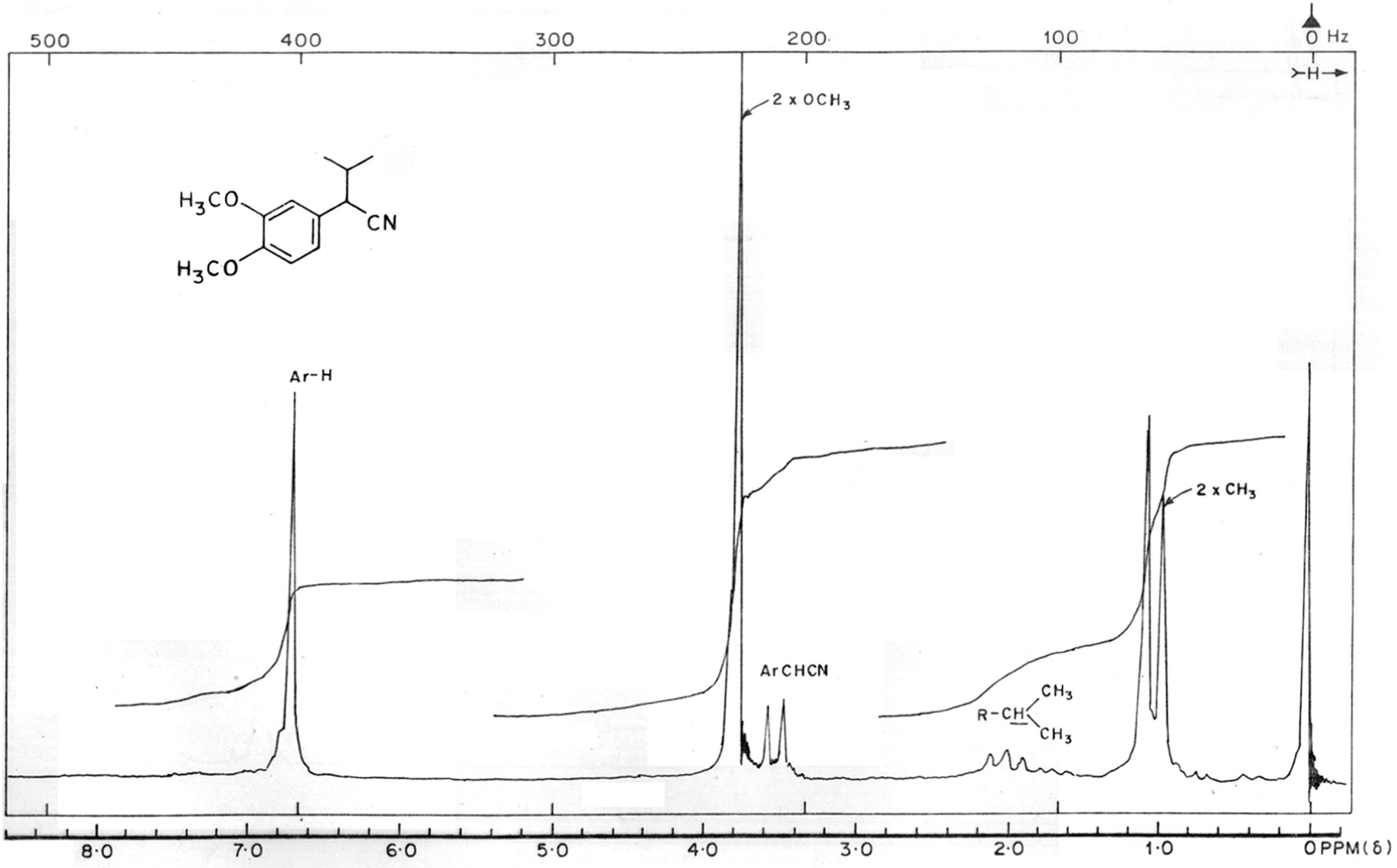

2·5
3·0
MICRONS
4·0
5·0
6·0
7·0
8·0
9·0
10
12
14
16
100
80
60
40
20
0
TRANSMITTANCE (%)
MeO
MeO
CN
4000
WAVE NUMBER (CM⁻¹)
2500
1800
1400
1000
600

FIGURE 3·3·6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400
300
200
100
0 Hz
H
2 x OCH3
H3CO
H3CO
CN
Ar-H
ArCHCN
R-CH
CH3
CH3
2 x CH3
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM(δ)

FIGURE 3·3·7

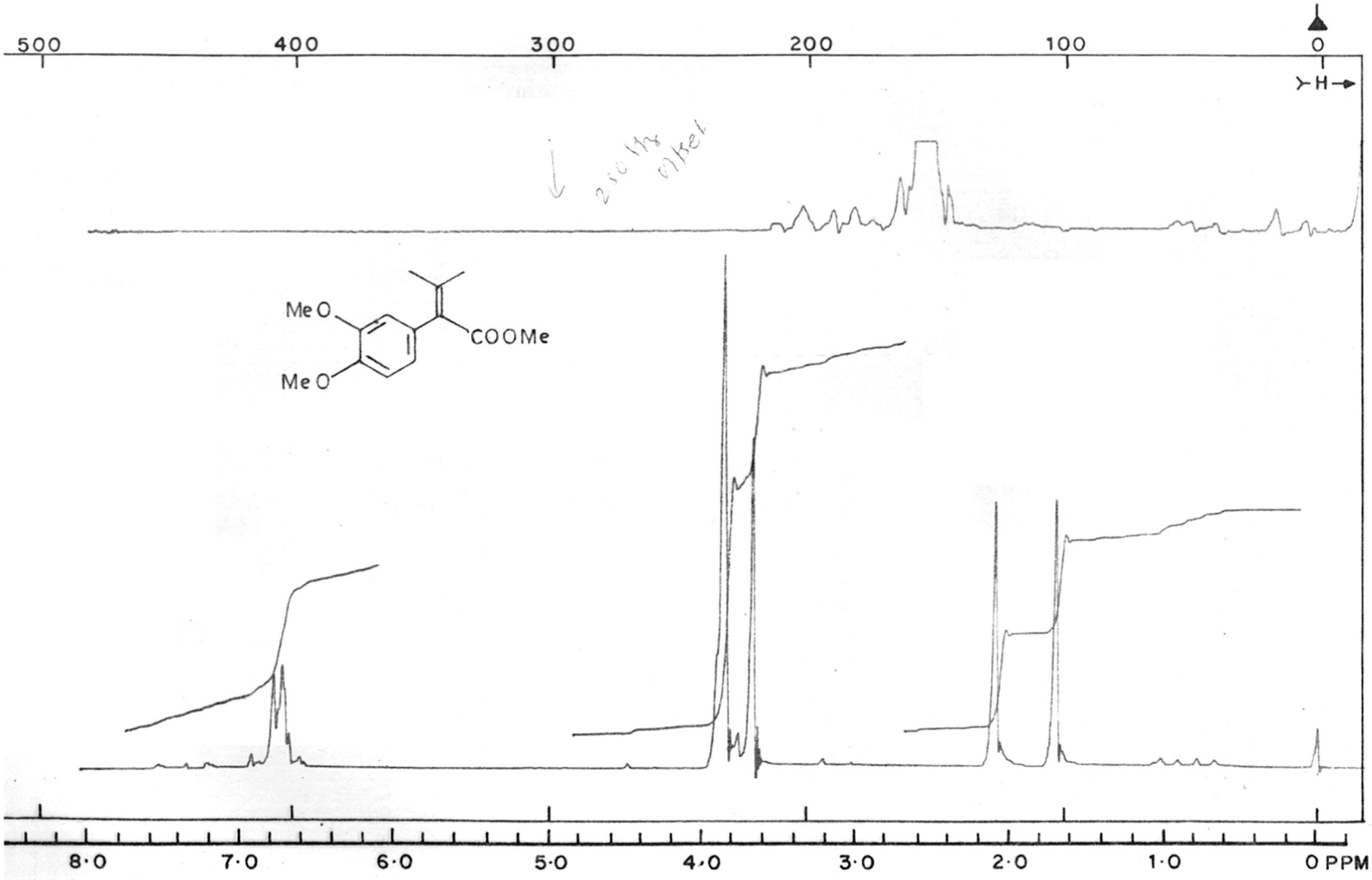
500
400
300
200
100
0
δH
Me O
Me O
COOMe
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM (δ)

FIGURE 3·3·8

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PUBLICATIONS

synthetic communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

SYNTHETIC COMMUNICATIONS, 14(6), 557-564 (1984)

A SHORT NEW SYNTHESIS OF ETHYL trans-CHRYSANTHEMATE

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National Chemical Laboratory, Pune 411 008.

The discovery of synthetic pyrethroids with increased insecticidal activity and low mammalian toxicity led to abundance of new synthetic results in the chemistry of pyrethroids[1]. Many of these methods adopted on an industrial scale make use of sigmatropic rearrangement, radical addition and nucleophilic ring closer with carbanions. Herein we report a simple and stereospecific route for the synthesis of ethyl trans-chrysanthemate (1) by utilizing carbonyl stabilized sulphuranes. Although the use of sulphurane was demonstrated at a much earlier stage for the synthesis of methyl trans-chrysanthemate[2], the present approach makes use of simple reagents and offers some operational advantages.

Our present approach for the synthesis of 1 is depicted in Scheme I. 2,5-Dimethyl-4-hexen-3-

*To whom correspondence should be addressed.

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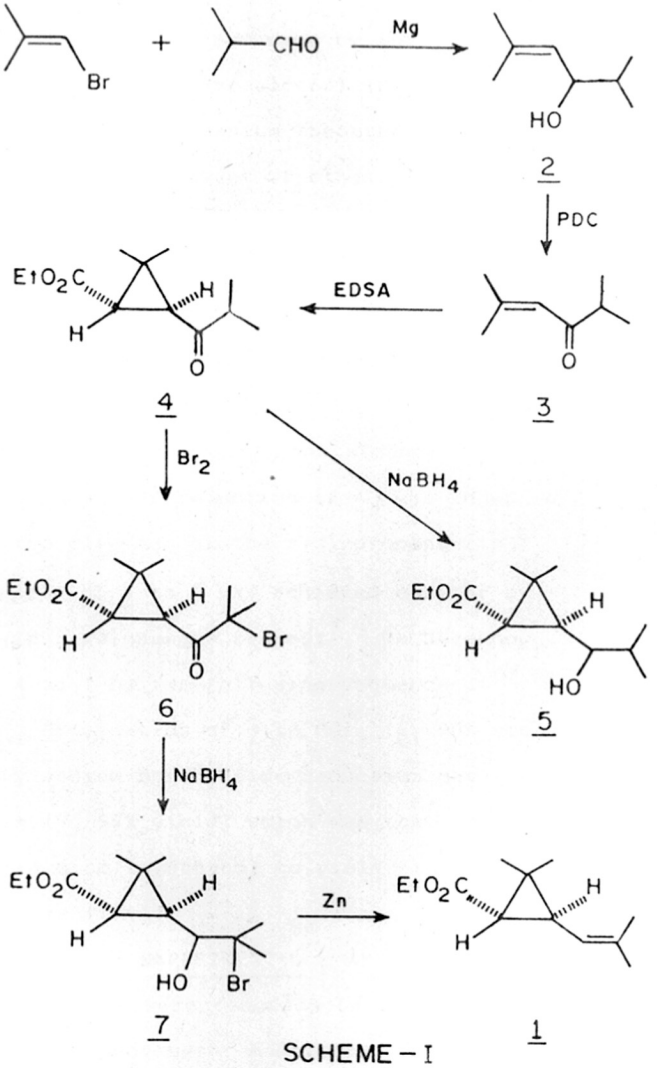
Br
+
CHO
Mg
HO
2
PDC
EtO2C
H
H
O
EDSA
O
4
3
Br2
NaBH4
EtO2C
H
H
O
Br
EtO2C
H
H
HO
6
5
NaBH4
EtO2C
H
H
HO
Br
Zn
EtO2C
H
H
7
1

SCHEME – I

one (3), obtained earlier by Friedel-Crafts acylation of isobutyryl chloride on isobutene followed by dehydrohalogenation[3], is now made by the pyridinium dichromate oxidation of the alcohol (2), prepared by Grignard reaction of magnesium isobutenyl bromide on isobutyraldehyde[4]. Treatment of ethyl dimethylsulphuranylidene acetate (EDSA)[5] with the α,β - unsaturated ketone(3) in benzene at reflux followed by silica gel column chromatography resulted in the formation of the cyclopropane carboxylic acid ester (4).

As the dehydration of the alcohol (5), obtained by sodium borohydride reduction of 4, was known to result in the cleavage of the cyclopropane ring[6], the conversion of 5 to 1 was achieved earlier by using Martin's sulphurane reagent[7]. We have now converted 4 to 1 by the following sequence of reactions : Bromination of 4 in CCl_4 (6, 90% yield) followed by sodium borohydride reduction gave the bromohydrin (7, 90% yield) which was then subjected to activated zinc in ethanol to yield ethyl trans-chrysanthemate (1).

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer infrared spectrophotometer model 683. NMR were recorded on Varian T-60 and FT-80 spectrometers with TMS

as standard. Mass spectra were recorded on CEC 21-11013 mass spectrometer.

2,5-dimethyl-4-hexen-3-ol (2)

Isobutenyl bromide (16.75 g, 0.125 mol) was added dropwise to a stirred refluxing mixture of magnesium turnings (3.3 g, 0.138 mol) and a trace of iodine in tetrahydrofuran (40 ml). The mixture was refluxed until the magnesium turnings were completely dissolved. Then it was cooled to 0° and isobutyraldehyde (4.5 g, 0.0625 mol) in tetrahydrofuran (25 ml) was added dropwise over 15 min. The reaction mixture was stirred for 5 hr and then decomposed with saturated ammonium chloride solution. Extractive work up with chloroform and fractional distillation of the crude product gave pure 3 (6 g, 75%). b.p. $39\text{-}40^{\circ}/3$ mm. IR: ν_{max}(neat) : 3400, 1600 cm^{-1}. NMR $\delta(CCl_4)$: 0.79, 0.95 (6H, 2d), 1.47 (1H, m), 1.65, 1.70 (6H, 2d), 3.86 (1H, dd, J = 6,8 Hz), 5.09 (1H, dm, J = 8 Hz). MS m/e: 128(M^+), 85($M^+ - C_3H_7$). Analysis: Calcd. for $C_8H_{16}O$: C, 74.94; H, 12.58; Found: C, 75.25; H, 12.52%.

2,5-dimethyl-4-hexen -3-one (3)

A solution of the alcohol (2) (4.8 g, 0.0375 mol) in dry dichloromethane (25 ml) was added dropwise to a stirred suspension of pyridinium dichromate (42 g, 0.1125 mol) in dry dichloromethane (125 ml)

under nitrogen. The reaction mixture was refluxed for 18 hr, admixed with dry ether (125 ml) and filtered. The filtrate was passed through a short silica gel column, eluted with ether and solvents evaporated in vacuo to give 3 (3.13 g, 66%).
IR: ν_{max} (neat): 1700, 1630 cm^{-1}. NMR: $\delta(CCl_4)$: 0.90 (6H, d), 1.65, 1.88 (6H, 2d), 2.18 (1H, m), 5.42 (1H,m). MS m/e: 126 (M^+). Analysis : Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18; Found: C, 75.89. H, 11.29%.

Ethyl trans-(±)-2,2-dimethyl-3-(1-oxo-2-methylpropyl)-cyclopropane carboxylate (4)

To a stirred refluxing solution of EDSA(4.0 g, 25 m. mol) (prepared according to Payne's method[5]) in dry benzene (80 ml) was added, dropwise over 5 min., a solution of 2 (1.6 g, 12.7 m. mol) in dry benzene (10 ml) under nitrogen. The reaction mixture was refluxed for 24 hr, the solvent removed and the resulting dark yellow oil was purified on a silica gel column (eluent, petroleum ether) to give 4 (1.34 g, 50%).
IR: ν_{max} (neat): 1740, 1710 cm^{-1}. NMR: $\delta(CCl_4)$: 1.04 (3H, s), 1.14 (3H, s), 1.18 (3H, d), 1.28 (3H, d), 1.33 (3H, t), 2.23 (1H, d, J = 5.6 Hz), 2.42 (1H, d, J = 5.6 Hz), 2.67 (1H, m), 4.09 (2H, q). MS (m/e): 212 (M^+), 141 ($M^+ - CO_2Et$). Analysis : Calcd. for

$C_{12}H_{20}O_3$: C, 67.89; H, 9.50; Found : C, 67.99; H, 9.38%.

Ethyl trans - (±) -2,2-dimethyl-3-(1-oxo-2-bromo-2-methylpropyl) -cyclopropane carboxylate (6)

Bromine (0.2 ml, 1.2 eq.) in carbon tetrachloride(2 ml) was added dropwise to a stirred solution of 4 (500 mg, 2.5 m. mol) in carbon tetrachloride (5 ml), maintaining the temperature between 20-30° The reaction mixture was stirred for 5 hr and excess bromine and solvent were removed in vacuo to give a pure, white semi-solid 6 (620 mg, 90%). IR: $\nu_{max}(CCl_4)$: 1740, 1710 cm^{-1}. NMR : $\delta(CDCl_3)$: 1.09 (6H, s), 1.27 (3H, t), 1.77 (3H, s), 1.84 (3H,s), 2.15 (1H, d , J = 5.6 Hz), 2.83 (1H, d, J = 5.6 Hz), 4.08 (2H, q). MS m/e: 290, 292 (M^+), 217, 219 ($M^+ - CO_2Et$), 211 ($M^+ - Br.$). Analysis: Calcd. for $C_{12}H_{19}BrO_3$: C, 49.48; H, 6.53; Found : C, 49.25; H, 6.45%.

Ethyl trans-(±)-2,2 dimethyl-3-(1-hydroxy-2-bromo-2-methylpropyl)-cyclopropane carboxylate (7)

Sodium borohydride (30 mg, 0.79 m. mol) was added in small portions to a cooled (0°) solution of 6 (180 mg, 0.62 m. mol) in methanol (5 ml) while stirring. The reaction mixture was stirred for 4 hr at 0°, solvent removed in vacuo and unreacted sodium borohydride decomposed with water. The aqueous layer was extracted with chloroform. The organic extract

was dried and the solvent removed to give the bromohydrin 7 (163 mg, 90%).

IR: ν_{max} (CCl_4) : 3400, 1740 cm^{-1}. MS m/e: 292, 294 (M^+). Analysis : Calcd. for $C_{12}H_{21}BrO_3$: C, 49.15; H, 7.17; Found : C, 49.33; H, 7.30%.

Ethyl trans-(±)-chrysanthemate (1)

To a refluxing solution of 7 (180 mg, 0.62 m. mol) in absolute ethanol (5 ml), freshly activated zinc dust (500 mg) was added in one lot. The reaction mixture was refluxed for 12 hr, filtered and the residue washed with dry ether. The solvents were removed and resulting oil purified on a silica gel column (eluent. benzene) to yield 1 [40 mg, 60%, based on recovered starting material (80 mg)]. IR ν_{max} (CCl_4) : 1725, 850 cm^{-1}. NMR: δ($CDCl_3$) : 1.10 (3H, s), 1.20 (3H, s), 1.21 (3H, t), 1.70 (6H, d), 1.80 (1H, d, J = 5.6 Hz), 2.01 (1H, dd, J = 5.6, 8 Hz), 4.08 (2H, q), 4.80 (1H, dm, J = 8 Hz). MS m/e: 196 (M^+), 123 ($M^+ - CO_2Et$). Analysis : Calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27; Found : C, 73.18; H, 9.91%.

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Contributions should have novelty and must be brief. Manuscripts must be submitted in accordance with the instructions to authors, which are published in the 20 February 1984 issue (p146). Authors are requested to note that manuscripts which do not accord with these instructions are currently being returned without consideration; in the case of overseas contributions return is by *seamail*. In order to expedite publication of accepted manuscripts, proofs are not circulated to authors outside the UK.

Synthesis of nitriles from carboxamides with zeolites*

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Nitriles are important organic intermediates for a variety of end products. One of the methods widely adopted for their preparation is dehydration of the corresponding carboxamide derivative. A variety of dehydrating agents may be used, e.g. P_2O_5, PCl_5, $POCl_3$, $AlCl_3$, $SOCl_2$-DMF complex, PTS chloride/pyridine, benzenesulphonyl chloride, polyphosphoric acid ethyl ester (PPE), silazanes, dicyclohexylcarbodiimide, triphenyl phosphine/CCl_4, titanium tetrachloride/Et_3N, $SOCl_2$-$(COCl)_2$ and trimethylsilyl polyphosphate.[1-3] Many of these methods have limitations and are not suitable for large-scale preparations. Now, a convenient method for large-scale manufacture of nitriles from the corresponding carboxamides utilising zeolite as the catalyst is reported.

Use of zeolites as catalysts in petroleum processing for a wide variety of operations is well-known.[4] However, their potential in general organic synthesis has not yet been fully realised. Now it is demonstrated for the first time that dehydration of carboxamides by passage as vapour over a zeolite (ZSM-5 type) catalyst column heated to 400°C, gives nitriles in almost quantitative yield. The catalyst can be used repeatedly. Some examples are given in the Table.

General experimental procedure

Benzamide (5g) was heated in a round-bottomed flask and a slow stream of nitrogen was bubbled through the melted amide. The vapours of the amide were passed through a preheater (250°C) to a silica column (length 14 inches, internal dia. 15mm) packed with the zeolite (ZSM-5 type) catalyst in the form of extrudates (1/16″ dia.), kept in a reactor heated at 400°C. The end of the column was connected to a coiled condenser fitted to a flask to collect the nitrile formed together with water vapour. The product was dried (Na_2SO_4) and distilled at 70°/10mm to give benzonitrile (3.83g, 90 per cent).

The authors thank Dr Paul Ratnasamy for the zeolite sample.

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Table

Amide	Yield of nitrile (per cent)[a]	mp or bp/torr (°C) Found	Lit. value[5]
Benzamide	90	70°/10mm	69°/10mm
Phenacetamide	85	107°/12mm	107°/12mm
Nicotinamide	89	mp 49-50°[b]	mp 49-50°
Isovaleramide	85	52°/50mm	52.5-53.5/50mm

[a]All the nitriles were characterised by mp/bp and infrared p.m.r. and mass spectral measurements and by comparison with authentic samples; [b]purified by crystallisation

NCL Communication No. 3450

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Carbohyd. Research (In Press)

ENANTIOSPECIFIC SYNTHESIS OF R(+)-α-LIPOIC ACID FROM D-GLUCOSE*

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ABSTRACT

First enantiospecific synthesis of natural R(+)-α-lipoic acid in 13 steps starting from D-glucose is described.

INTRODUCTION

Interest in the total synthesis of α-lipoic acid (1) arose because of its physiological properties[1]. It is a cofactor in the biochemical decarboxylation of α-keto acids, a growth factor for a variety of microorganisms, and reduces the blood sugar of diabetic rabbits during glucose tolerance test[2]. Although several synthesis of (±)-α-lipoic acid have been reported, natural R(+)-α-lipoic acid (1) has been obtained by resolution of the racemate[3]. A recent communication[4] on the asymmetric synthesis of R(+)-α-lipoic acid prompted this report of an enantiospecific synthesis.

RESULTS AND DISCUSSION

In planning our synthesis of 1, the first objective was the aldehyde 10, a useful precursor for C-C bond formation.

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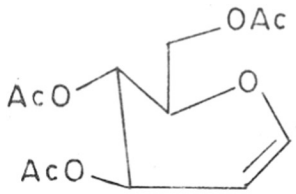
*NCL Communication No. 3852

3,4,6-Tri-O-acetyl-D-glucal (2) was converted[5] into crystalline ethyl 4,6-di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (3). Hydrogenation of 3 over freshly prepared Raney nickel afforded 93% of the 2,3-dideoxy derivative 4. Zemplén deacetylation[6] of which (→5) followed by conventional benzylation afforded 89% of the 4,6-di-O-benzyl derivative 6. Treatment of 6 with propanedithiolborontrifluoride etherate-dichloromethane at room temperature afforded 80% of the dithiane derivative 7, the ^{1}H-n.m.r. spectrum of which was consistent with the assigned structure.

Using the procedure of Barton and McCombie[7], 7 was converted into 85% of the xanthate derivative 8 by reaction with sodium hydride-carbon disulfide-methyl iodide. The ^{1}H-n.m.r. spectrum of 8 contained a downfield signal at δ5.95 (m) for H-4'. Treatment of 8 with a boiling mixture of tri-n-butyltin hydride-toluene-α,α-azabisisobutyronitrile for 18 h gave 96% of 9, hydrolysis of which with mercuric oxide-borontrifluoride etherate in aqueous acetone yielded the desired aldehyde 10.

The next stage involved C_2 homologation of 10. Accordingly 10 and carbethoxymethylenephosphorane were heated under reflux in benzene to give the α,β-unsaturated ester 11 (80%). The large $J_{2,3}$ value (16 Hz) of 11 confirmed the trans configuration. Hydrogenation of 11 over excess of Raney nickel effected the reduction of the double bond and debenzylation to give 90% of the diol 12 which was converted into R(+)-α-lipoic acid (1) following the strategy developed by Golding et al[8].



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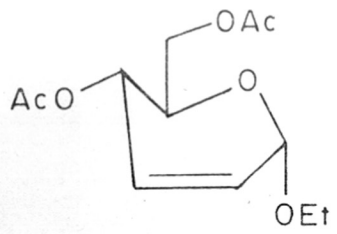
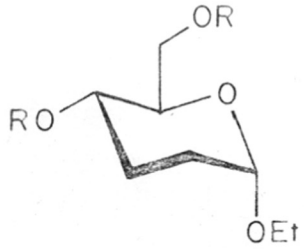


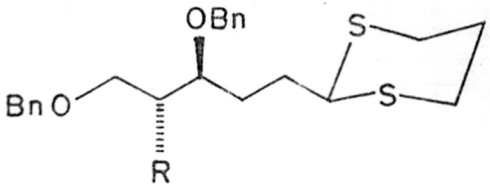
3



4 R = Ac

5 R = H

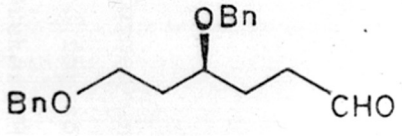
6 R = Bn



7 R = OH

8 R = OC(=S)—SMe

9 R = H



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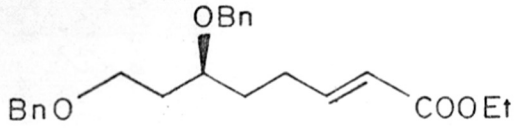
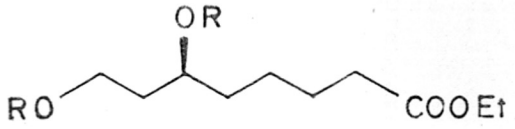
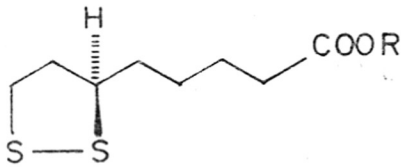


11



12 R = H

13 R = Ms



1 R = H

14 R = Et

Treatment of 12 with methanesulfonyl chloridetriethylamine in dichloromethane gave the dimesylate 13 in almost quantitative yield. The ^{1}H-n.m.r. spectrum of 13 contained two singlets for mesyl groups and signals at δ4.28 (t) and 4.80 (m) for H-8,8' and H-6, respectively. Reaction of 13 with sodium sulfide and sulphur in N,N-dimethylformamide at 90° afforded 70% of the expected ethyl R(+)-α-lipoate (14) which gave n.m.r. signals at δ3.18 (t) and 3.60 (m) for H-8,8' and H-6, respectively. The upfield shifts of the signals for these protons were expected because of shielding effect due to the sulfur atom. Hydrolysis of 14 with 0.1M potassium hydroxide in ethanol at room temperature afforded 75% R(+)-α-lipoic acid (1), $[\alpha]_D$ +95° (benzene); lit.[3] +91°, lit.[4] +102°.

EXPERIMENTAL

All evaporations were performed under diminished pressure. ^{1}H-N.m.r. spectra were recorded for solutions in $CDCl_3$ (internal Me_4Si) with Varian FT-80A or Bruker WH-90 spectrometers. Optical rotations were measured with a JASCO DIP-181 polarimeter. All solvents were purified and dried. Light petroleum refers to the fraction b.p. 60-80°. Dry-packed column chromatography was performed on silica gel (60-120 mesh).

Ethyl 4,6-di-O-benzyl-2,3-dideoxy-α-D-erythro-hexopyranoside (6).- To a solution of the diacetate 4[6] {10.4 g, 40 mmol; $[\alpha]_D$ +120.5° (c 1.2, chloroform); lit.[6] $[\alpha]_D$ +118° (ethanol)} in dry methanol (50 mL) was added sodium (40 mg). After 18 h, the mixture was

neutralised with Amberlite IR-120 (H^+) resin, concentrated, and benzene was distilled from the residue to afford the diol 5[6] (7.0 g, 100%).

To a solution of 5 (5 g, 28.4 mmol) in dry tetrahydrofuran (50 mL) under nitrogen was added sodium hydride (50% dispersion, 5 g, 210 mmol) during 1 h. The solution was cooled, benzyl bromide (7 ml, 58 mmol) was added, and the mixture was left overnight at room temperature. Methanol (5 mL) was added, the solution was concentrated and the residue was partitioned between ethyl acetate and water. The ethyl acetate layer was dried and concentrated. Column chromatography (ethyl acetate-light petroleum, 1:10→1:4) of the residue afforded 6 (8.9 g, 89%), $[\alpha]_D$ +100.5° (c 0.8 chloroform), ^{1}H-N.m.r. data: δ 1.19 (t, 3 H, $CH_2\underline{CH}_3$), 1.7 (m, 4 H, H-2,2',3,3'), 3-4 (m, 6 H, H-4,5,6' and $\underline{CH}_2CH_3$), 4.1-4.6 (m, 4 H, 2 $\underline{CH}_2$Ph), 4.76 (bs, 1 H, H-1), 7.21 (d, 10 H, 2 Ph).

Anal. Calc. for $C_{22}H_{28}O_4$: C, 74.2; H, 7.9. Found: C, 74.0; H, 7.7.

2-[3'(S),5'-Di-benzyloxy-4'(R)-hydroxypentyl]-1,3-dithiane (7). - To a solution of 6 (5 g, 14 mmol) in dichloromethane (20 mL) was added propane-1,3-dithiol (2 g, 18.5 mmol) and borontrifluoride etherate (2 mL). The mixture was stirred for 2 h at room temperature, then neutralised with sodium carbonate, filtered and concentrated. Column chromatography (ethyl acetate-light petroleum, 1:10→1:1) of the residue

afforded 7 (4.6 g, 80%), $[\alpha]_D$ +8° (c 1, chloroform), ^{1}H-N.m.r. data: δ 1.4-2.4 (m, 7 H, 3 CH_2 at C-1,2',5 and OH), 2.80 (q, 4 H, CH_2 at C-4,6), 3.5 (m, 3 H, CH_2 at C-5' and H-4'), 3.9 (m, 2 H, H-2,3'), 4.48 (s, 2 H, $C\underline{H}_2Ph$), 4.51 (s, 2 H, $C\underline{H}_2Ph$), 7.3 (d, 10 H, 2 Ph).

Anal. Calc. for $C_{23}H_{30}O_3S_2$: C, 66.0; H, 7.2; S, 15.3. Found: C, 66.4; H, 7.2; S, 15.1.

2-[3'(S),5'-Di-benzyloxypentyl]-1,3-dithiane (9). - To a stirred solution of 7 (2.5 g, 6 mmol) in dry tetrahydrofuran (30 mL) under nitrogen was added sodium hydride (50% oil dispersion, 1.2 g, 25 mmol). After 1 h, dry carbon disulfide (2 mL) was added, followed, after 20 min, by methyl iodide (2 mL). The mixture was stirred for 24 h at room temperature, methanol (3 mL) was added, the mixture was concentrated, and the residue was paritioned between chloroform and water. The chloroform layer was dried and concentrated. Short-column chromatography (ethyl acetate-light petroleum, 1:4) of the residue gave the xanthate 8 (2.65 g 85%). ^{1}H-N.m.r. data δ 1.7-2.4 (m, 6 H, 3 CH_2 at C-1',2',5), 2.56 (s, 3 H, SMe), 2.75 (q, 4 H, 2 CH_2 at C-4,6), 3.8 (m, 4 H, CH_2 at C-5 and H-2,3'), 4.50 (s, 2 H, $C\underline{H}_2Ph$), 4.53 (dd, 2 H, $C\underline{H}_2Ph$), 5.95 (m, 1 H, H-4'), 7.25 (d, 10 H, 2 Ph).

A solution of 8 (2.1 g, 4.13 mmol) in dry toluene (30 mL) containing α,α-azabisisobutyronitrile (15 mg) was heated under nitrogen and freshly prepared tri-n-butyltin hydride (3 mL)

was then added. The mixture was boiled under reflux for 18 h then concentrated. Column chromatography (ethyl acetate-light petroleum, 0:1→1:9) of the residue afforded 9 (1.61 g, 96%), $[\alpha]_D$ +14.5° (c 0.7, chloroform), ^{1}H-N.m.r. data: δ1.6-2.3 (m, 8 H, 4 CH_2 at C-1',2',4',5), 2.78 (q, 4 H, 2 CH_2 at C-4,6), 3.5 (m, 3 H, CH_2 at C-5' and H-3'), 3.95 (t, 1 H, H-2), 4.42 (s, 2 H, CH_2Ph), 4.44 (dd, 2 H, CH_2Ph), 7.25 (s, 10 H, 2 Ph).

Anal. Calc. for $C_{23}H_{30}O_2S_2$: C, 68.7; H, 7.5; S, 15.9. Found: C, 68.1; H, 7.2; S, 15.8.

Ethyl (S)-6,8-dibenzyloxy-oct-2-enoate (11). - To a stirred suspension of red mercuric oxide (1.06 g, 3.5 equiv.) and boron trifluoride (0.52 mL, 3 equiv.) in aqueous 17% acetone (15 mL) under nitrogen, a solution of 9 (0.56 g, 1.4 mmol) in tetrahydrofuran (3 mL) was added dropwise. After 20 h, the mixture was neutralised with a solution of sodium hydroxide in aqueous 75% acetone. The precipitate was removed, the acetone was evaporated, the aqueous solution was extracted repeatedly with chloroform, then concentrated to dryness. The residue was extracted with chloroform, the extract was dried and concentrated to afford 10 which was chromatographically homogeneous and used without further purification.

A solution of 10 (0.35 g, 1.12 mmol) in dry benzene (5 mL) was treated with carbethoxymethylenetriphenylphosphorane (1.17 g, 3 equiv.). The mixture was heated under reflux for 10 h and then concentrated. Column chromatography (ethyl

acetate-light petroleum, 1:20) of the residue gave 11 (0.30 g, 80%), $[\alpha]_D$ +3° (c 1.1, chloroform). ^{1}H-N.m.r. data: δ 1.24 (t, 3 H, CH_3CH_2), 1.4-2.0 (m, 4 H, H-5,5',7,7'), 2.3 (m, 2 H, H-4,4'), 3.5 (m, 3 H, H-6,8,8'), 4.13 (q, 2 H, CH_3CH_2), 4.42 (s, 4 H, 2 CH_2Ph), 5.71 (dt, 1 H, J 16 and 1.5 Hz, H-2), 6.88 (dt, 1 H, J 16 and 6.5 Hz, H-3), 7.24 (d, 10 H, 2 Ph).

Anal. Calc. for $C_{24}H_{30}O_4$: C, 75.4; H, 7.9. Found: C, 75.3; H, 7.9.

Ethyl (S)-6,8-dimesyloxy-octanoate (13). - A solution of 11 (0.4 g, 1.05 mmol) in ethanol (10 mL) was hydrogenated over freshly prepared W2 Raney nickel (4 g) at normal pressure and temperature for 18 h, then filtered through Celite, and concentrated to afford the saturated diol 12 (0.192 g, 90%).

To a solution of 12 (0.102 g, 0.5 mmol) in dry dichloromethane (2 mL) at 0° was added triethylamine (1 mL) and methanesulfonyl chloride (0,24 mL, 3 mmol). After storage for 4 h at 0° the mixture was poured into aqueous sodium hydrogen carbonate, extracted with methylene chloride, and the extract was dried, and concentrated. Column chromatography (ethyl acetate-light petroleum, 1:1) of the residue gave 13 (0.18 g, 100%), $[\alpha]_D$ +17° (c 1, chloroform), ^{1}H-N.m.r. data: δ 1.22 (t, 3 H, CH_3CH_2), 1.3-2.5 (m, 10 H, 5 CH_2), 3.00 (s, 6 H, 2 OMs), 4.15 (q, 2 H, CH_3CH_2), 4.28 (t, 2 H, H-8,8'), 4.80 (m, 1 H, H-6).

Anal. Calc. for $C_{12}H_{24}O_8S_2$: C, 40.0; H, 6.7; S, 17.8. Found: C, 40.0; H, 6.7; S, 17.5.

Ethyl R(+)-α-lipoate [ethyl (5R)-5-(1,2-dithiolan-3-yl)-pentanoate] (14). - A solution of 13 (0.36 g, 1 mmol) in dry N,N-dimethylformamide (3 mL) containing powdered sodium sulfide monohydrate (0.24 g, 1 mmol) and sulfur (0,032 g, 1 mmol) was heated at 90° for 24 h, then poured into ice-water, and extracted with light petroleum. The extract was washed with water, dried, and concentrated. Short-column chromatography (benzene) of the residue afforded 14 (0.164 g, 70%), $[\alpha]_D$ +61° (c 0.3, chloroform); ν_{max}^{liquid} 1730 cm^{-1} (COOEt). ^{1}H-N.m.r. data: δ 1.27 (t, 3 H, CH_3CH_2), 1.4-2.8 (m, 10 H, 5 CH_2), 3.18 (t, 2 H, H-8,8'), 3.6 (m, 1 H, H-6), 4.13 (q, 2 H, CH_3CH_2), Mass Spectrum: m/z 234 (M^+).

Anal. Calc. for $C_{10}H_{18}O_2S_2$: C, 51.3; H, 7.7; S, 27.35. Found: C, 51.2; H, 7.8; S, 27.1.

R(+)-α-lipoic acid [5R)-5-(1,2-dithiolan-3-yl)-pentanoic acid] (1). - A solution of 14 (0.117 g, 0.5 mmol) in ethanol (5 mL) was treated with 0.1M potassium hydroxide (5.5 mL) in the dark and under nitrogen at room temperature. After 24 h, ethanol was evaporated, the aqueous solution was extracted with light petroleum, then acidified with 5M hydrochloric acid to pH 1, and repeatedly extracted with ether. The combined extracts were concentrated and short-column chromatography (benzene-ethyl acetate, 20:1) of the residue afforded 1 (0.063 g, 75% based on recovered 14), m.p. 44°, $[\alpha]_D$ +95° (c 0.1, benzene); ν_{max}^{liquid} 1695 cm^{-1} (COOH); lit.[4] m.p. 43-45°, lit.[3] $[\alpha]_D$ +91°; lit.[4] 102°, ^{1}H-N.m.r. data: δ 1.3-2.8 (m, 10 H,

5 CH_2), 3.10 (t, 2 H, H-8,8'), 3.53 (m, 1 H, H-6), Mass spectrum: m/z 206 ($M^{\cdot+}$).

Anal. Calc. for $C_8H_{14}O_2S_2$: C, 46.6; H, 6.8; S, 31.1. Found: C, 46.55; H, 6.6;S, 30.7.

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