SYNTHESIS OF BIOLOGICALLY ACTIVE COMPOUNDS

A THESIS

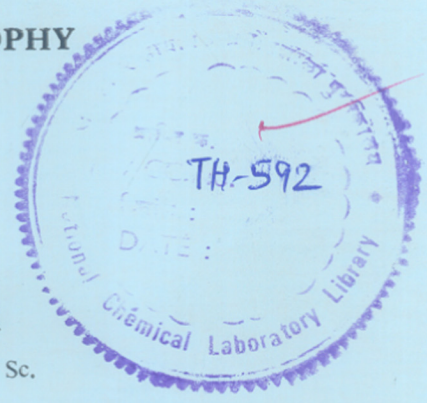
SUBMITTED TO THE

UNIVERSITY OF POONA

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)



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PUNE - 411 008 (INDIA)

JANUARY 1989

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DEDICATED TO MY PARENTS

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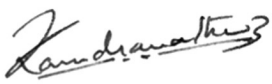
CERTIFICATE

Certified that the work incorporated in the thesis entitled **"Synthesis of Biologically Active Compounds"** by M. ANIL KUMAR was carried out by him under my supervision. Such material as has been obtained from other sources has been duly acknowledged in the thesis.



(DR. T. RAVINDRANATHAN)
Research Guide

January 1989

PREFACE

Malaria, still threatens the lives of the people especially in tropical countries due to the development of strains resistant to chloroquine treatment. Artemisinin - an active principle isolated from the Chinese herbal plant, Artemisia annua. L. - was found to be active against both chloroquine sensitive and chloroquine resistant strains of malaria parasite (Plasmodium falciparum). Artemisinin derivatives are also found to be very effective in cerebral malaria.

Structurally the artemisinin molecule is unique among antimalrials, being a sesquiterpene lactone peroxide. The present work embodies development of a short synthetic sequence and methodology for a stereospecific synthesis of artemisinin skeleton which is hopefully amenable for the synthesis of analogues as well.

In the first chapter of the thesis efforts are made to review all the chemical as well as biological properties of artemisinin.

The second chapter describes a stereospecific synthesis of artemisinin from a readily available cheap starting material like Δ^3-carene which can be modified to give a very practical synthetic route for the artemisinin.

The third chapter describes an attempt to synthesise artemisinin from achiral starting material like cyclopentenone through stereoselective reactions like ester enolate Claisen rearrangement, Diels-Alder reactions etc.

The approaches for the synthesis of artemisinin which is fairly complex in terms of stereochemical aspects (7 chiral centres) explained in Chapters II and III is based on the central theme in the stereo-specific synthesis, viz. recognition of the chirality in an easily available natural product and its translation into the required asymmetry in the biologically active products and use of highly stereo-regulated reactions in achieving stereochemical solution as applied to complex carbon framework like intramolecular Diels-Alder reaction and Claisen rearrangement.

While discussing the review and the work in the thesis, due credit has been given to other authors and their references have been appropriately noted wherever warranted. However, any information if taken for granted and no accreditation is made, it is requested to view the same as completely unintentional.

It gives me great pleasure to express my deep sense of gratitude and indebtedness to my guide, Dr. T. Ravindranathan, Assistant Director, Division of Organic Chemistry, National Chemical Laboratory, Pune for suggesting the problem and for his expert and inspiring guidance throughout this work.

I am equally indebted to Dr. S.V. Hiremath , Dr. P.R. Rajamohan and Dr. S.N. Kulkarni for their able support and suggestions throughout the course of my work. My heartfelt thanks are due to Drs. D. Rajagopala Reddy, Reddappa Reddy, and A.S. Phadke for helpful suggestions and valuable discussions. I wish to record my appreciation and grateful

thanks to all my colleagues and friends in National Chemical Laboratory particularly Ms. Annie Daniel, Ms. Rany Menon, Mr. R.B. Tejwani, Drs. A.M. Naik, S.V. Devasthale, A.M. Salunkhe, and G. Murlidhar from whom I received help and support in various ways during the course of the investigation of the work presented in the thesis. Finally, I would like to offer my gratitude to my uncle Dr. R. Soman for his never flagging encouragement.

The assistance rendered by the Microanalytical and Spectroscopic NMR, IR and Mass Sections of this laboratory is gratefully acknowledged. My thanks are due to Mr. M.V. Jayadevan and Mr. Bhujan for their technical assistance in preparing this thesis. Financial assistance from Council of Scientific & Industrial Research, New Delhi is gratefully acknowledged.

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

M. Anil

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National chemical Laboratory
Pune 411 008

January 23, 1989.

GENERAL REMARKS

All the boiling points and melting points are uncorrected. All solvents and reagents were purified and dried by standard procedures and techniques. All concentrations were done under reduced pressure on Buchi rotary evaporator below 50°C. Column chromatography was performed utilizing silica gel (60-120) mesh. Progess of the reactions was monitored by thin layer chromatography (TLC) on 0.2 mm layers of silica gel. The PMR spectra were recorded on Varian T-60, Jeol T-60, Brucker WH-90, Varian FT-80 or Brucker MSL-300 spectrometers using TMS as internal standard and chemical shifts are expressed in ppm downfield from TMS.

The following abreviations have been used while presenting the data:

s = singlet

d = doublet

t = triplet

q = quartet, and

m = multiplet

IR spectra (ν_{max} in cm^{-1}) were recorded in Nujol or neat or $CHCl_3$ on Perkin-Elmer model 683 spectrometer with sodium chloride optics. Mass spectra were recorded on Finnigan-Mat 1020 B instrument using direct inlet system at 70eV.

CONTENTS

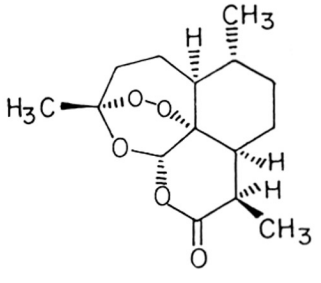
ABSTRACT

ABSTRACT

This thesis is divided into three chapters which are as follows:

CHAPTER I : Review on Artemisinin and its Derivatives

Artemisinin (Qinghaosu) (1) is an active antimalarial principle isolated from Qinghao (Artemisia annua L.) which is a traditional Chinese herbal medicine used in the treatment of malaria. This compound is a sesquiterpene lactone that bears a peroxide grouping and unlike other antimalarials lacks a nitrogen containing heterocyclic ring system. This compound has been used successfully in several thousand malaria patients in China including those with both chloroquine sensitive and chloroquine resistant strains of Plasmodium falciparum. Derivatives of artemisinin such as dihydroartemisinin (2), artemether (3) and the water soluble sodium artesunate (4) appear to be more potent than artemisinin itself.



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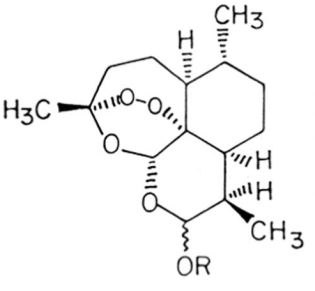


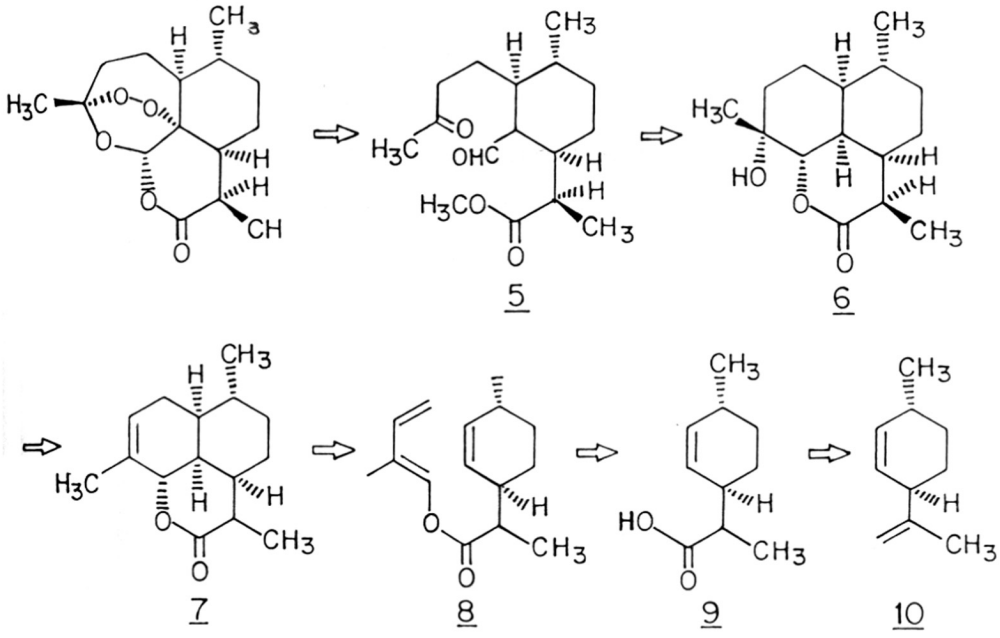
2: R = H
3: R = CH_3
4: R = $CO(CH_2)_2COONa$

This chapter summarises a brief review on the isolation, chemistry, pharmacology, clinical applications and various synthetic approaches reported for artemisinin.

CHAPTER II : Synthesis of Artemisinin from Δ^3 Carene

This synthesis starts with (+)(1R,4R)isolimonene (**10**) which can be obtained from naturally occurring Δ^3-carene which is abundantly available in India.

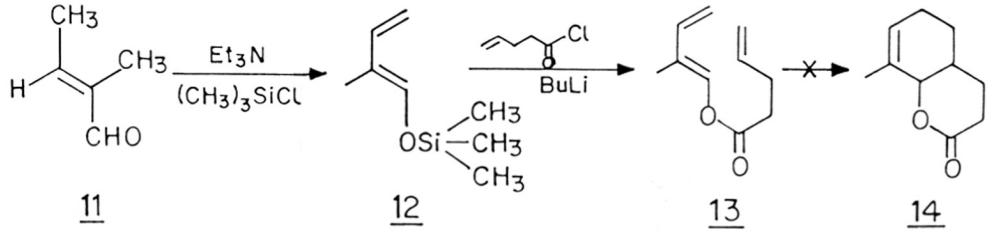
SCHEME-I



5 6 7 8 9 10

According to the above retrosynthetic analysis, the key reaction involves an intramolecular Diels-Alder reaction of butadienyl ester (**8**). In order to study the feasibility of this reaction, studies were carried out on the model compound (**13**), which was prepared according to the Scheme-II.

SCHEME-II



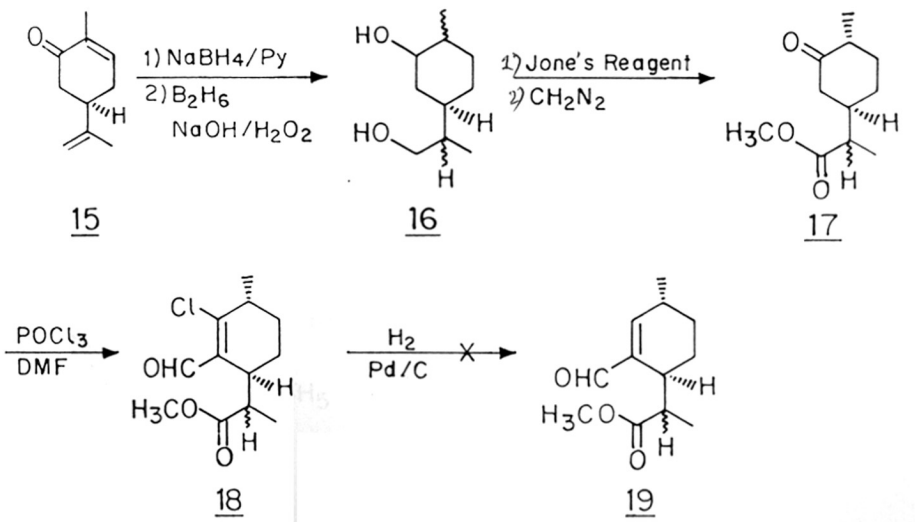
11 12 13 14

Tiglaldehyde (**11**) was converted to 2-methyl-1-trimethylsiloxy-butadiene, which on treatment with n-BuLi at room temperature generated the Li enolate. The Li enolate on reaction with pentenoic acid chloride gave the ester (**13**).

Since the ester (**13**) and also (**8**) failed to undergo Diels-Alder reaction under thermal as well as Lewis acid catalyzed reaction conditions, it was decided to modify the triene system (**8**) by activating the dienophile with an electron withdrawing group like (-CHO) regioselectivity, to give the desired product with right stereochemistry. In order to obtain such a triene system, two approaches were attempted starting from naturally occurring compounds such as R(-)carvone (**15**) (Scheme-III) and 1R,4S(-)isopulegol (**20**) (Scheme-IV).

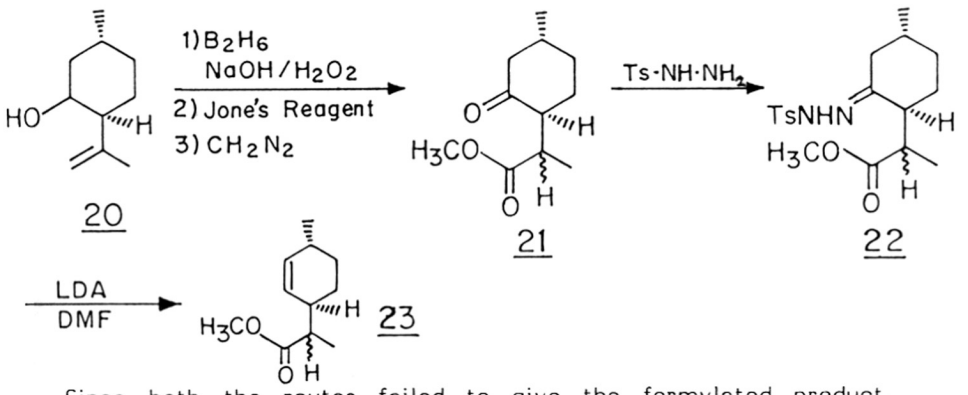
In the first approach R(-)carvone **15** was converted to the keto ester (**17**) as shown in the Scheme-III. The keto ester (**17**) under Vilsmeier formylation conditions gave the chloro aldehyde (**18**). Our attempts to hydrogenolyse the vinyl chlorine to obtain the α,β-unsaturated aldehyde (**19**) resulted in the recovery of the keto ester (**17**).

SCHEME - III



In the second approach (-)(1R,4S)isopulegol (**20**) was converted to the keto ester (**21**), which on treatment with tosyl hydrazine gave the corresponding hydrazone (**22**). This hydrazone on treatment with 4 equivalents of LDA and DMF however did not give the expected α,β-unsaturated aldehyde (**19**), but gave an olefin (**23**).

SCHEME-IV

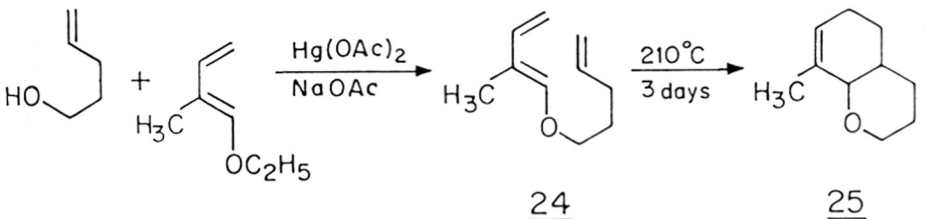


20 21 22 23

Since both the routes failed to give the formylated product, synthesis towards the triene system was not pursued further.

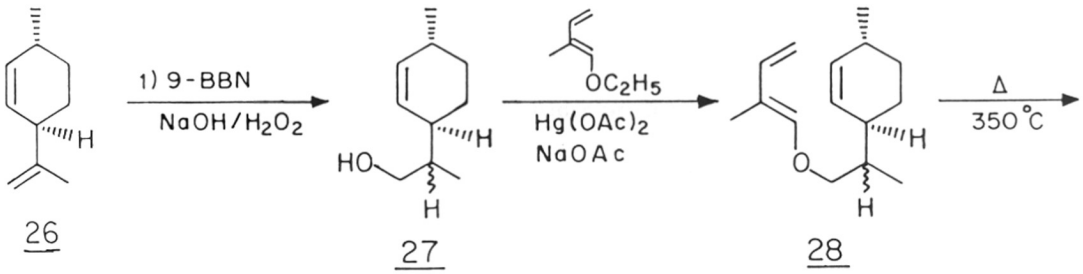
Butadienyl enol ethers possess a more electron-rich diene system compared to butadienyl enol esters. In order to study the feasibility of Diels-Alder reaction on this system, the model compound (**24**) was prepared as shown in Scheme-V.

SCHEME-V

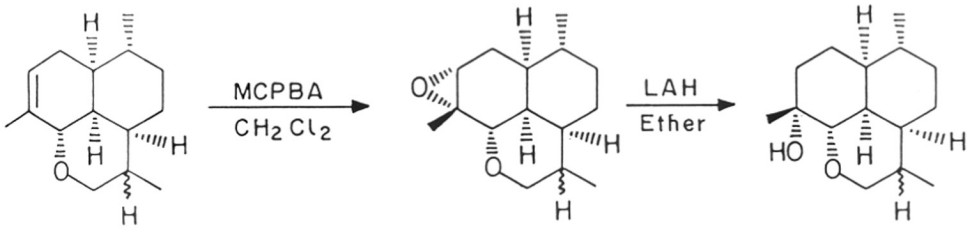


24 25

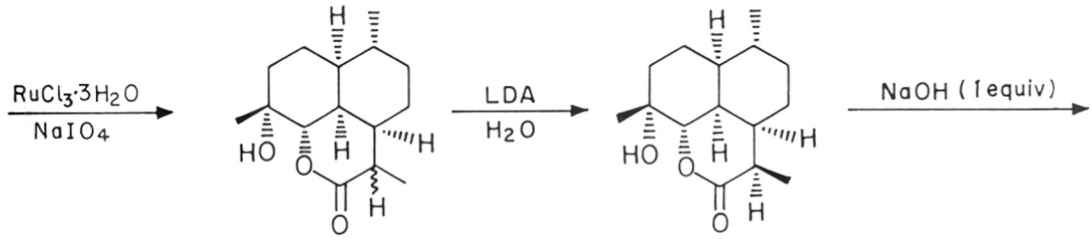
SCHEME-VI



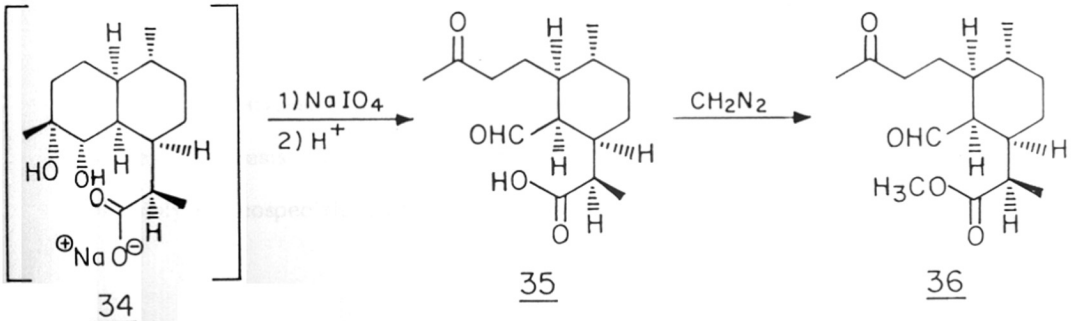
26 27 28



29 30 31



32 33



34 35 36

→ → → ARTEMISININ

A dilute solution of the ether (**24**) in benzene when heated in a sealed tube for 3 days gave the desired Diels-Alder product (**25**).

Accordingly, the intermediate enol ether (**28**) required for the synthesis of artemisinin was prepared as shown in the Scheme-VI. (+)(1R,4R)isolimonene (**26**) was regioselectively hydroborated at the terminal double bond using 9BBN, which on oxidation with alkaline hydrogen peroxide gave the alcohol (**27**). The alcohol was transetherified with 1-ethoxy-2-methylbutadiene to give the ether (**28**). Toluene solution of this ether was passed through a column preheated to 350°C to give the desired Diels-Alder product (**29**) in 25-30% yield.

The Diels-Alder product (**29**) was treated with 1.2 equivalents of MCPBA to give the epoxide (**30**) which on reduction with LAH gave the tertiary alcohol (**31**). This alcohol was oxidised with catalytic amount of $RuCl_3.3H_2O$ and 1 equivalent of $NaIO_4$ to give the lactone (**32**). The methyl α - to the carbonyl function was epimerized to give the more stable equatorial isomer by treating it with a base. The lactone (**33**) was then hydrolysed using 1 equiv. of NaOH to give the diol (**34**) which on oxidative cleavage with $NaIO_4$ and acidification gave the acid (**35**). The acid (**35**) was converted to its methyl ester (**36**) with diazomethane in ether. The ester (**36**) was identical in all properties with those reported earlier (IR, NMR & MS).

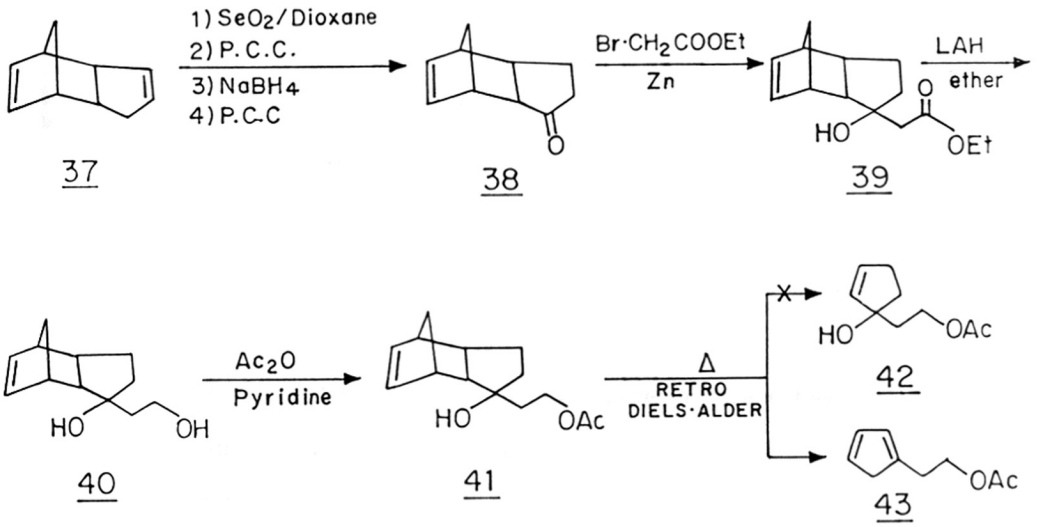
As the conversion of **36** into artemisinin was earlier reported, our new synthesis of **36** in effect constitutes one of the shortest and highly stereospecific synthesis of artemisinin.

CHAPTER III : Synthetic Approaches Towards- Artemisinin from Cyclopentenone

Chapter-II depicts a synthetic strategy which starts from a natural product with two chiral centres, which is translated into the target molecule. The following strategy involves building up of chiral centres from achiral starting materials.

The synthesis starts with dicyclopentadiene (37) which is converted to tricyclo[5.2.1.0]^{2,6} dec-8-ene-3-one (38). This ketone (38) is converted to the ester (41) as shown in the Scheme-VII. The ester on vacuum pyrolysis gave the cyclopentadiene derivative (43) instead of the expected compound (42).

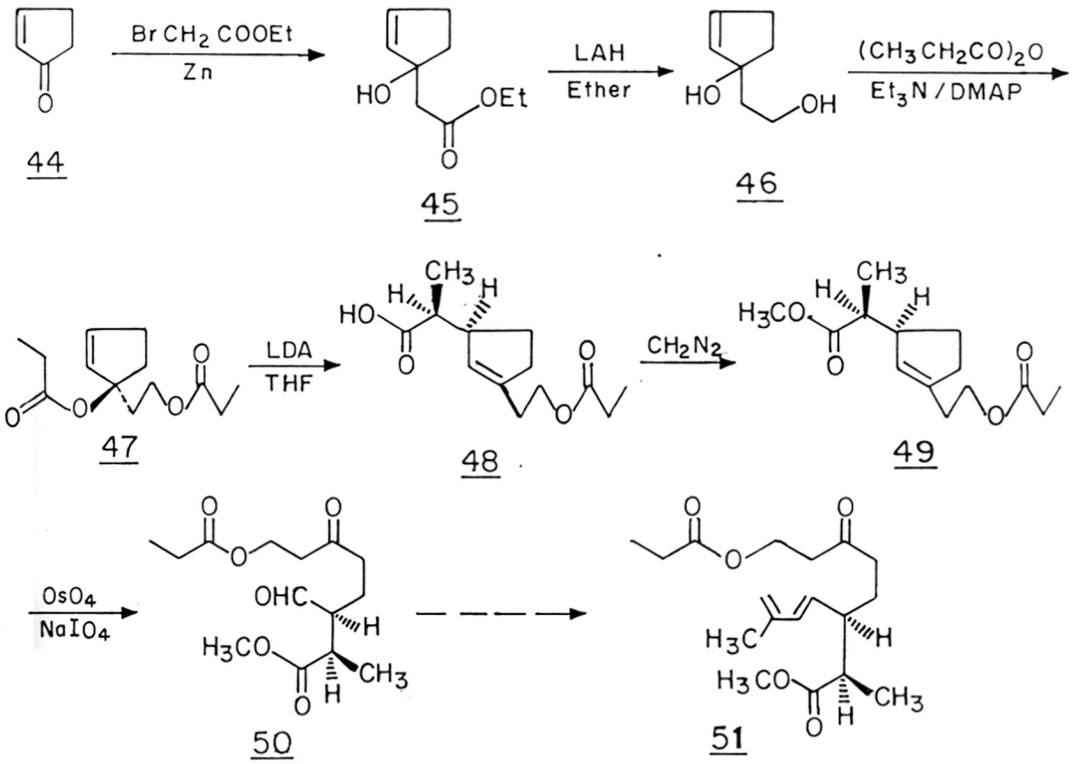
SCHEME-VII



37 38 39 40 41 42 43

So, the scheme was modified by starting with cyclopentenone (44) which can be prepared from pentenoic acid in two steps. Cyclopentenone on Reformatsky reaction gave the product (45) which on reduction with LAH yielded the diol (46).

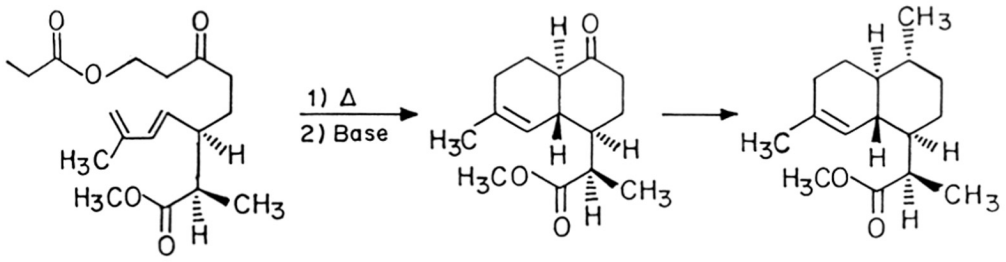
SCHEME-VIII



The diol (**46**) on treatment with propionic anhydride in triethylamine and catalytic amount of 4-N,N-dimethylaminopyridine gave the diester (**47**). The diester (**47**) underwent ester enolate Claisen rearrangement and gave the acid (**48**), which on treatment with diazomethane gave the methyl ester (**49**). This ester (**49**) on treatment with OsO_4 and $NaIO_4$ gave the keto aldehyde (**50**). All attempts to transform this keto aldehyde to the diene (**51**) by conventional methods like Wittig, Wittig-Horner, Peterson reactions were unsuccessful. Further studies

on this transformation is under progress. The diene **51** could be converted to a key intermediate in the synthesis of dl-artemisinin as shown below

SCHEME-IX



The key intermediate allyl alcohol **45** or **46** is amenable to kinetic resolution by Sharpless method and hence this scheme can be easily modified to give natural artemisinin.

CHAPTER 1·0·0
A REVIEW ON ARTEMISININ AND ITS DERIVATIVES

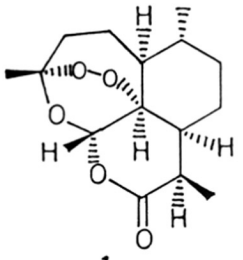
INTRODUCTION

1.1.0 History, Isolation and Structure:

Currently, world malaria infection still scores a high incidence rate. Global estimates[1] of acute and chronic malaria taken together amount to 210-220 million infections per year of which 85% are caused by Plasmodium falciparum, the most insidious species of malaria parasites. Furthermore, the development of strains resistant to chloroquine treatment, since 1960's, threatens the lives of the people in endemic areas including China more than ever. This calls for discoveries of newer and more efficient drugs.

In 1967, the government of the People's Republic of China embarked on a systematic examination of indigenous plants used in traditional remedies as sources of drugs. One such plant, a pervasive weed with a long history of use, is known as qing hao (Artemisia annua L., sweet worm wood, annual worm wood). Its earlier mention dates back to 2000 years in the "Recipes for 52 Kinds of Diseases" found in the Mawangdui Han dynasty tomb.[2] In that work the herb was recommended for use in hemorrhoids. This plant is mentioned further in the Zhou Hou Bei Ji Fang (Handbook of Prescriptions for Emergency Treatment) written in 340 AD. The author, Ge Hong, advised that to reduce fever one should soak one handful of qing hao in one sheng (about one litre) of water, strain the liquor and drink it all.[3] Later in 1956 Li Shizhen, the famous herbalist wrote in his 'Ben Cao Gang Mu' (Compendium of Material Medica) that chills and fever of malaria can be combated by qing hao preparations.[4] A decoction of Artemisia annua and Carapax trionycis was suggested in the Wenbing Tiaobian in 1798 as a treatment for malaria.[5]

Attempts to confirm the antipyretic and antimalarial activity of a hot water or ethanol extract of A. annua were disappointing. However, later extracts made from ethyl ether, which entailed operations at a lower temperature, produced promising results in both murine and simian malaria. The crystalline active principle **1** was then isolated in 1972 and named qinghaosu (an active principle of qing hao) or arteannuin and the more western sounding name "Artemisinine". Because the material is a terpene rather than an alkaloid or an amine which the 'ine' suffix suggests, the name artemisinin is preferred by chemical abstracts.



1

Systematically it is Octahydro-3,6,9-trimethyl-(3α, 5αβ, 6β, 8αβ 9α , 12β , 12α R*)-(+)-3,12-epoxy-12H-pyrano(4,3-j)-1,2-benzodioxepin 10(3H)-one; and the registry number is (63968-64-9). Various solvents including ethyl ether, petroleum ether and even gasoline have been used as solvents for the extractions. The yields from the dry herb vary between 0.01 - 0.6%[6] depending on the origin of the herb as well as the season of harvesting. The flowery plant seems to possess the highest content. Assays carried out on more than thirty species of Artemisia in China other than Artemisia annua failed to indicate the prevalence of the compound to date. Recently Klayman[9] et al. reported

the isolation of artemisinin in 0.06% yield, from the dried leaves or flowers of Artemisia annua growing in Washington DC vicinity.

It was found[7] out that the highest content of artemisinin in A. annua was found just before flowering. To possibly increase the amount of artemisinin during the growth period of the plant 2-hormone type growth regulators were tested on A. annua strain 811. One of them was able to increase the content of artemisinin by 30% over untreated plants. A study[8] of several physiological factors on artemisinin synthesis in A. annua showed that artemisinin content on the leaves of A. annua was effected by cultivation temperature and illumination. Higher temperature (≈30°) and illumination enhanced the accumulation of artemisinin to $>$ 32 mg/100 g. Other factors examined (substrate, plant height, developmental stage) had no effect on yield.

Other than indicating that ethyl ether extraction was used to prepare artemisinin from the aerial portions of A. annua, the Chinese literature provides no details of the isolation method. Investigators[9] at the Walter Reed Army Institute of Research extracted various air-dried components of the plant with several non-protic solvents, of which petroleum ether (30°-60°C) was the most satisfactory. The extract was then chromatographed on silica gel, with chloroform-ethyl acetate being used as an eluant. Fractions rich in artemisinin crystallised readily and recrystallisation was effected from cyclohexane or 50% ethanol to give fine colourless needles with m.p. 156-157°C and $[\alpha]_D^{17}$ = +66.3° (C - 1.64 $CHCl_3$).[1]

The amount of artemisinin in the extract can be measured by high performance liquid chromatography[2] and the use of an electrochemical

detector. Benzoyl peroxide is used as an internal standard. Another method is based on thin layer chromatography with visualization being achieved by means of p-dimethylaminobenzaldehyde.

Artemisia annua was found to have other terpenes and related compounds like 1,8-cineole, borneol acetate, 1- β -pinene, cuminal, β-caryophyllene, coumarin, stigmasterol, camphene, cadinene, arteannuin B, camphor, β-farnesene, arteannuin A, hydroarteannuin, scopolin, scopoletin, artemisia ketone, artemisinic acid and benzyl isovalerate.[5,12]

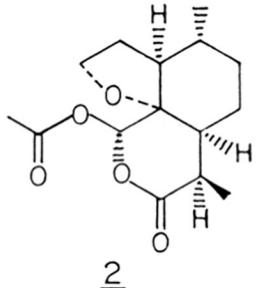
High resolution mass spectrum[11] (m/e 282.1742 M^+) combined with elemental analysis (C −63.72%; H −7.86%) led Chinese workers to assign an emperical formula of $C_{15}H_{22}O_5$ which indicated a possible sesquiterpenoid structure. The compound showed no absorption in the UV range while in the IR region there were absorption peaks at 1745 cm^{-1} (strong, delta-lactone) and at 722, 831, 881, 1115 cm^{-1} (peroxide). Then ^{1}H-NMR and ^{13}C-NMR spectra led to the assignment of three methyl groups (one tertiary and two secondary), an acetal function and several other carbon atoms. The presence of the lactone and peroxy groups was further corroborated by oxime formation and by quantitative reaction with triphenylphosphine respectively.

The structure of artemisinin together with its absolute configuration was finally resolved by X-ray diffraction studies.[16] Absolute configuration of the lactone ring has also been reached by a comparison of its ORD spectrum with a structurally related known sesquiterpene arteannuin B. The structure was later fully confirmed by synthesis.[13,14,15] Thus, artemisinin joins the terpene ascaridole and the sesquiterpenes

Yingzhaosu A and Benghalensin A, as one of the few naturally occurring endoperoxides. The compound is related to the cadinane or amorphane class of sesquiterpenes which are defined by their cis-decalin skeleton.

1.2.0 Stability:

Artemisinin is poorly soluble in water. It is soluble in most aprotic solvents and is unaffected by them upto 150°C[17] and is poorly soluble in oil. Unlike ascaridole, which is very sensitive to heat, artemisinin shows a remarkable thermal stability. It does not explode at its melting point, as one might expect, but rather can exist unchanged for about 3 minutes at 50°C above its melting point and can be purified by sublimation. It is reported[1] that no change was observed by refluxing a sample in toluene, ethanol, or isopropanol for several days. However, Luo[18] et al. reported that decomposition products were formed by refluxing in tetralin (200°C) for 5 h or by refluxing in xylene for 22 h. In the latter case, 6-7 spots were developed on TLC plates. Silica gel chromatography provided two crystalline compounds with the following structures (2) and (3).



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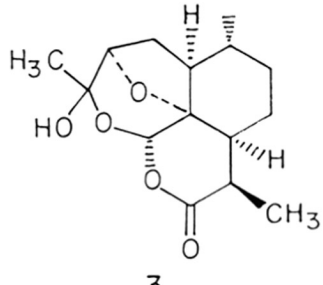

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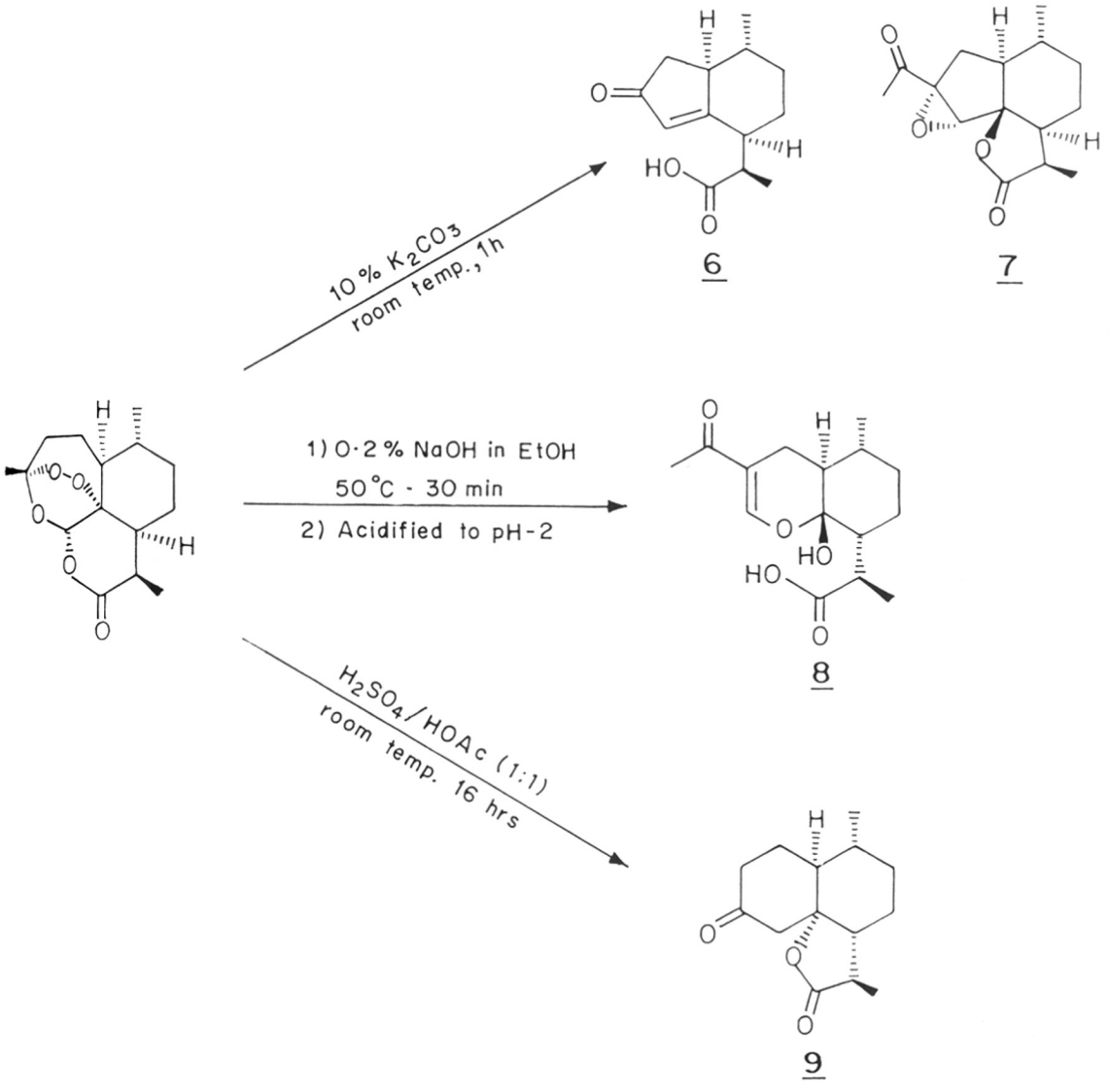
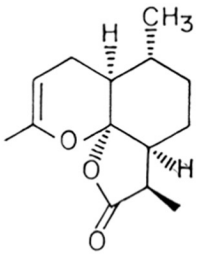
Lin and coworkers also reported that dry heating of artemisinin at 190°C for 10 min. produced numerous decomposition products from

SCHEME-I



which three have been isolated in the crystalline form. One was identified as 2 and the other two were characterised as 4 and 5.



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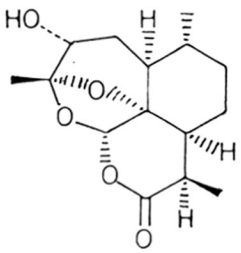


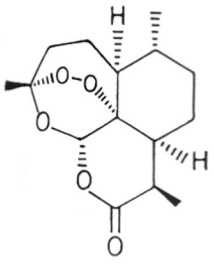
5

On the other hand, artemisinin is easily attacked by acid or alkali[17,19] even below room temperature. Products vary with the reaction conditions as shown in the Scheme-I.

The action of potassium carbonate in methanol at room temperature on artemisinin initially caused disruption of its lactone ring to give **10** where all interlocked functionalities are set free zipper-like. Subsequent condensation of the aldehyde group into the active methylene gave the unsaturated ketone **11** (Scheme II).

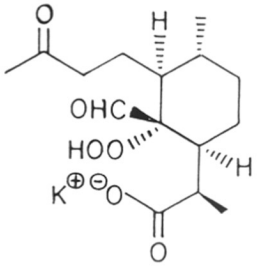
The hydroperoxy group at C_5 was then displaced by the carboxylate anion to give compound **12** along with a molecule of hydrogen peroxide which can readily epoxidise the $\alpha\beta$-unsaturated ketone to give **7** in about 10% yield. According to this mechanism the oxygen function at C_5 of compound **7** is β-oriented in contrast with α-orientation in artemisinin **1**. The α-configuration for the epoxide in **2** was assigned on steric grounds. The compound **6** was isolated in 1.6% yield and was formed via. Baeyer-Villiger type reaction of **12** to give an enol acetate **13** which on saponification gave **6**.

SCHEME-II

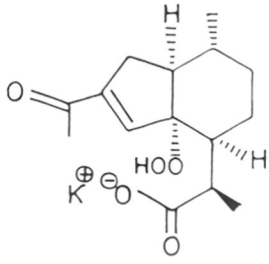


1

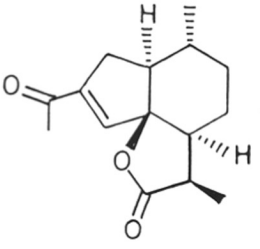
K_2CO_3
room temp.



10

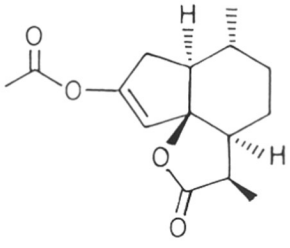


11

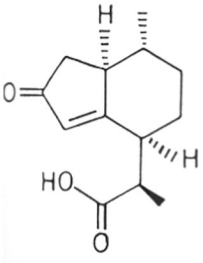


12

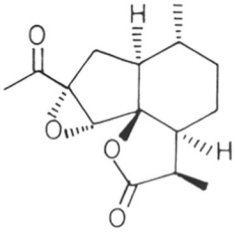
$+ OOH^{\ominus}$



13

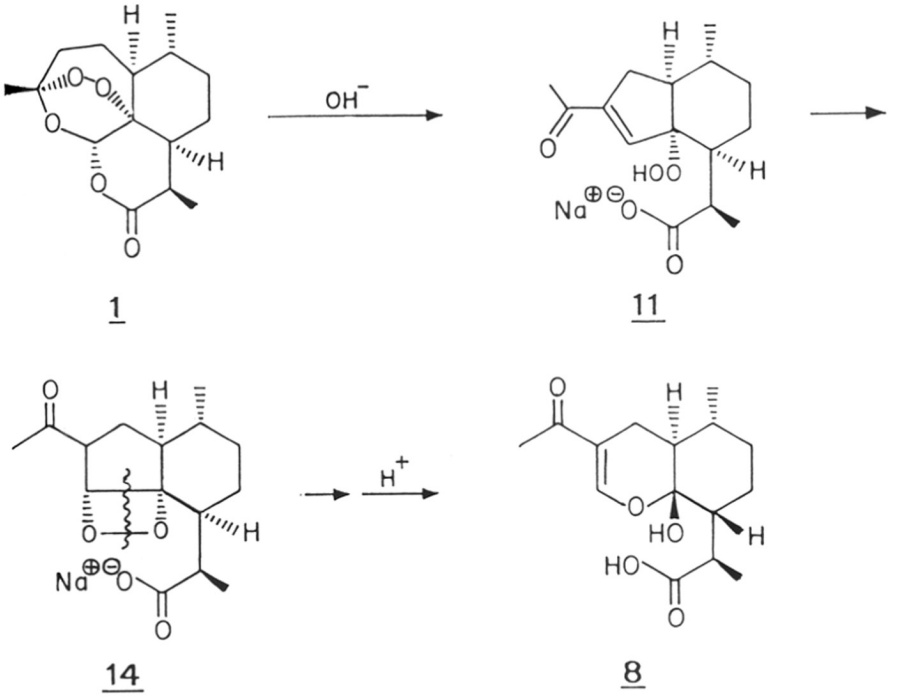


6



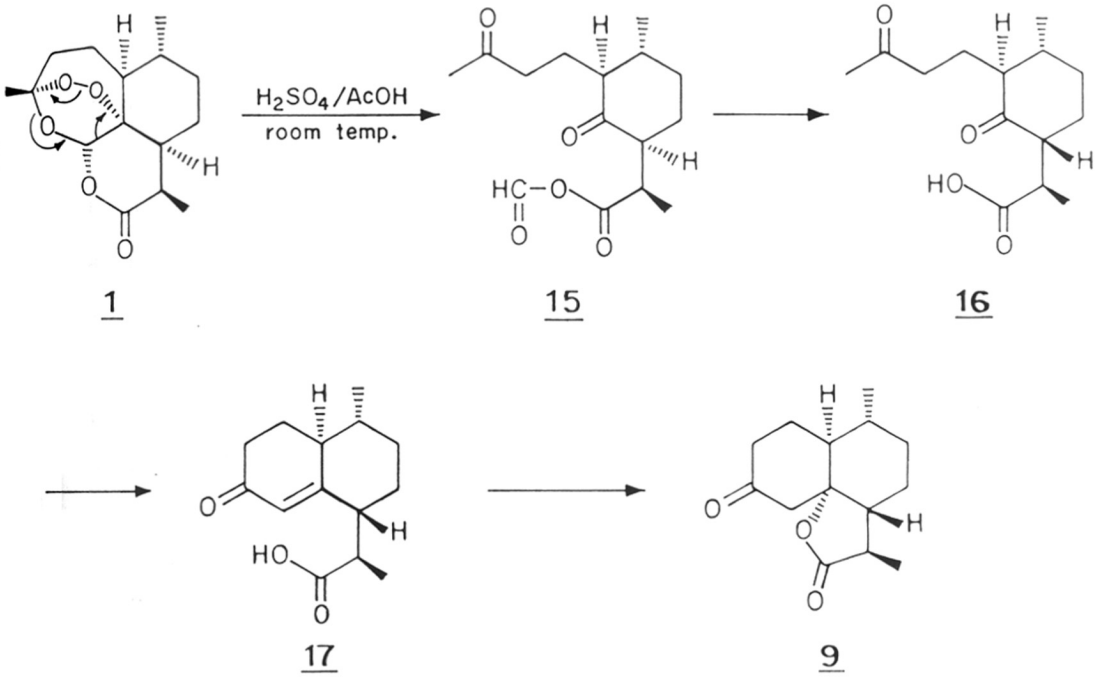
7

SCHEME-III



1 11 14 8

SCHEME-IV



1 15 16 17 9

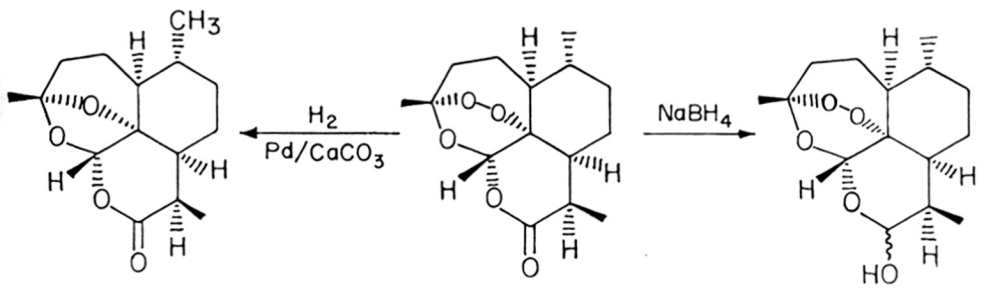
The mechanism of formation of **8** can be visualized as follows (Scheme III). In strong alkaline medium, the hydroperoxy group of **11** is sufficiently ionised to initiate an intramolecular Michael addition, forming the dioxetane ring of **14**. This ring, being fused into a tricyclic system, is strained and decomposes spontaneously to form **8**.

Treatment of artemisinin with a mixture of 10% sulphuric acid in glacial acetic acid at room temperature for 1 h caused the fission of the peroxide linkage with the loss of one carbon as formic acid (Scheme IV). The intermediate **15** formed has all three substituents equatorially disposed with the branched group at C_6 sterically interacting against the carbonyl oxygen. Enolisation-induced inversion at C_6 gave the less congested **16** which cyclised to afford **17** or its keto equivalent **9** with 5-α-hydroxyl.

1.3.0 Chemical Transformation:

Chemically the peroxy group is the most reactive site of the molecule. Catalytic hydrogenation in presence of palladium on calcium carbonate catalyst gave deoxyartemisinin,[12,20] an epoxide which is devoid of antimalarial activity. However, when reduced with sodium borohyride, the lactone function of the molecule was converted into a lactol, dihydro-artemisinin (dihydro QHS), in which the peroxide linkage is left intact. The lactol (hemiacetal) has even stronger antimalarial activity than artemisinin itself. It was reported[21] that in its crystalline form, the hydroxy is β but when in solution it is a mixture of epimers; thus a make and break of the multi-acetal linkage must be envisaged so that the composition of the epimers may vary with the nature of the medium.

SCHEME-V



19 1 18

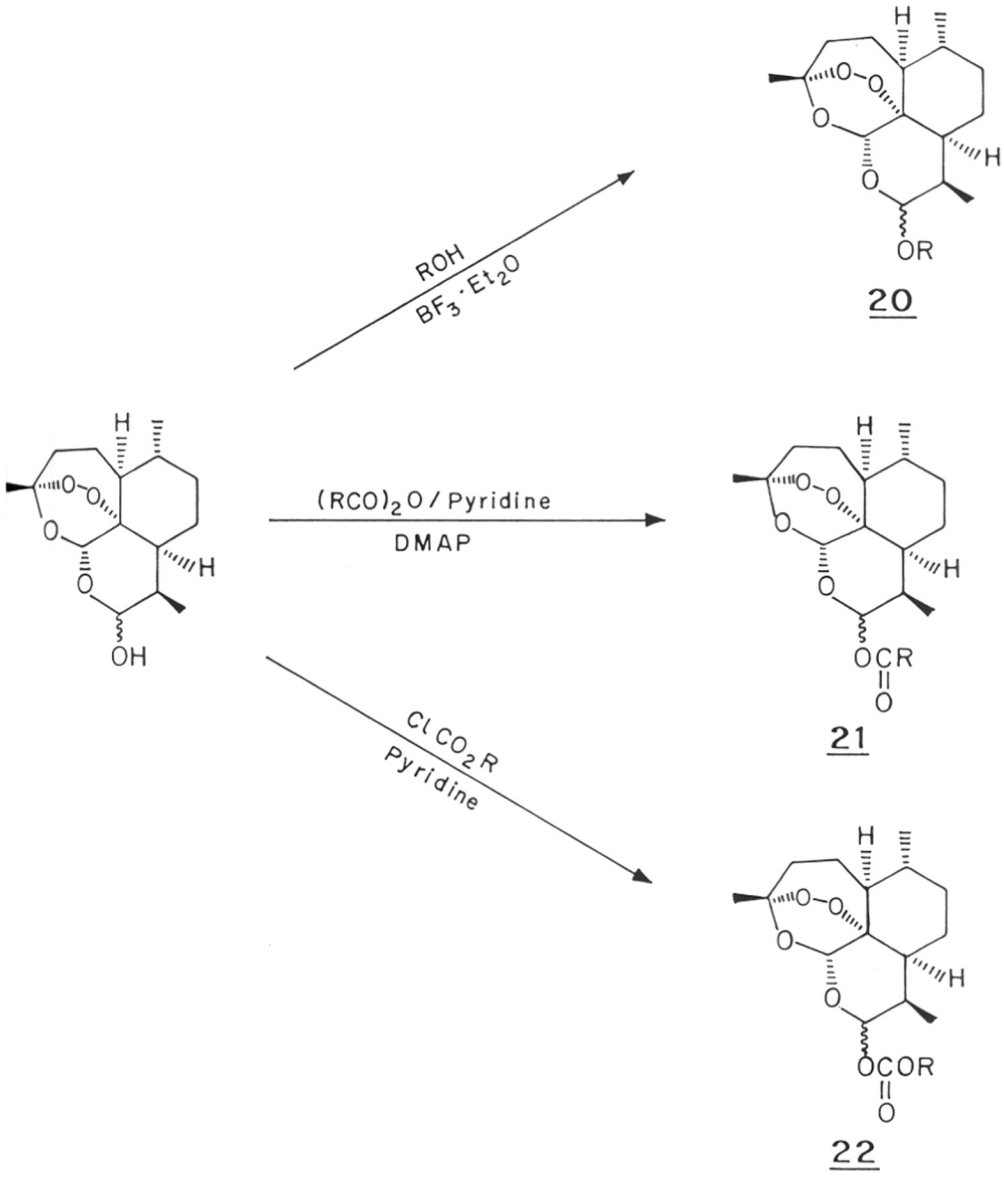
Dihydroartemisinin **18** can be converted to either ether by treating it with an alcohol in presence of borontrifluoride etherate or ester by treating it with an acid chloride in presence of pyridine and catalytic amount of dimethylaminopyridine as shown below.

As a rule, it appears that reaction in acidic media gives derivatives predominantly in the 12-β configuration and reaction in alkaline media provides products predominantly in 12-α configuration. Similarly, mixed α and β epimeric carbonates (**22**) were formed by reacting dihydroartemisinin with corresponding chloroformate (Scheme VI).

1.4.0 Biological Studies

In early studies[23,24,25] mice infected with P. berghei previously treated with artemisinin at different concentrations were compared with untreated mice as controls.[23] The appearance of parasitemia was greatly delayed in the group with treatment at a concentration of 25-50 μg/ml onwards. This indicated a direct attack of the drug against the parasite. More recent studies,[25,27,28] established its activity against strains resistant to primaquine, cycloguanil, pyrimethamine, sulfonamides,

SCHEME-VI


ROH
$BF_3 \cdot Et_2O$
$(RCO)_2O$ / Pyridine
DMAP
$ClCO_2R$
Pyridine
20
21
22

mefloquine and menoctone. Furthermore artemisinin and its derivatives showed only a low degree of cross resistance against highly chloroquine-resistant strains of P. berghei.

The development of resistance to artemisinin itself has been studied in parallel with chloroquine by repeated transfer of the parasite cultures in the presence of increasing concentration of drugs. It was demonstrated that with chloroquine a 52 x increase in inhibiting concentration was achieved after ten transfers while with artemisinin only 13 x after seventeen transfers. There was also a (3.6 - 3.9) x increase in ED_{50} (Median Effective Dose) of artemisinin towards the chloroquine resistant strain.[23,24] But artemisinin and its derivatives are active only against Plasmodia of the erythrocytic phase. They are inactive against parasites of the exoerythrocytic tissue phase, the sporozoites and the gametocytes. It was reported[23,24] that mature gametocytes have been observed in both experimental animals and humans following treatment with drugs. Therefore, the compound did not appear to offer a radical cure to either primary infection or recurrence caused by sporozoite. Artemisinin seems to be less prone to induce drug resistance in Plasmodia and the cross resistance with chloroquine and other classical antimalarials is only of a low order.

1.4.1 Toxicity[1,11,13]

Early reports[23] of the toxicity of artemisinin suggested that the compound was almost incapable of producing ill effects. Observations were carried out on oral, intramuscular or intraperitoneal administration of artemisinin to groups of cats, dogs, rabbits, rats and mice at dosages

ranging from 100-1600 mg/kg for three to seven consecutive days. Only the group of mice at 800 mg/kg showed bleeding spots in the brain, turbidity and edema of liver cells upon histological examination. Otherwise in all groups with dosage level below 70 X clinical dose, no abnormality was noted in EEG, ECG, hepatic functions, blood picture, total protein, classified protein, appetite and growth rate of the animals. However, when medication on dogs was prolonged to 21 consecutive days reversible pathological changes in sections of heart, liver and kidney were observed.[23,24,26]

Teratogenicity tests on mice were negative. The drug did not affect sperm of the males. Offsprings from the medicated mice were normal.[26] Since artemisinin exerted no influence on the micronuclear count of the polychromatic erythrocytes of the mice bone marrow, it was regarded as without carcinogenicity.

1.4.2 Phytotoxicity

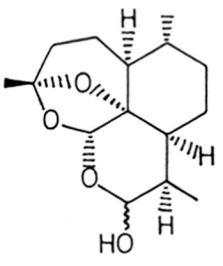
Artemisinin was tested for its phytotoxicity.[31] It inhibited germination of lettuce and annual worm wood and growth of roots and shoots of lettuce, red root pig weed etc. was inhibited at 33 μm. Chlorophyll was not affected in lettuce and chlorosis was not observed in any species tested. The probable biosynthetic precursors of artemisinin (arteannuin B and arteannuic acid) had no effect on growth and chlorophyll content of lettuce; however they inhibited seed germination. Respiration of lettuce roots was not inhibited by artemisinin. Artemisinin has marginally increased the mitotic index of lettuce root tips at 33 μm. Studies showed that artemisinin is a selective phytotoxin that reduces growth by a mechanism other than mitotic disruption or inhbition of protein synthesis.

1.4.3 Metabolism of Artemisinin

Pharmacokinetic studies with tritium-labelled compounds in mice revealed that artemisinin and dihydroartemisinin are similar in biological disposition. Upon oral administration artemisinin is rapidly absorbed from the G.I. tract, maximum blood concentration being attained one hour afterwards with a half-life of about 4 h. It is widely distributed in the body, but mostly accumulated in the liver, kidney and the bile. Approximately 80% of the radioactivity was excreted through the urine and feces within 24 h after administration.[23,24]

When administered by intravenous injection it disppears from the blood in 30 min. In vitro studies[28] revealed that when the drug was incubated with rat liver slices only 8.3% could be recovered after 1 h. as the unchanged compound. Both kidney and lung tissues were less effective while gut and whole blood were devoid of activity. The fact that the liver was the major organ where biotransformation occurred suggests a possible first-pass effect.[32]

After an oral dose of artemisinin to humans, four metabolites deoxyartemisinin **19**, deoxydihydroartemisinin **23** compound **24** and dihydroxydihydroartemisnin **25** were isolated from the urine.



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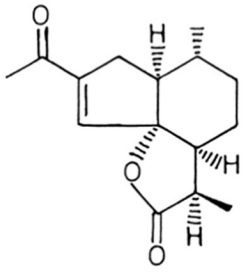

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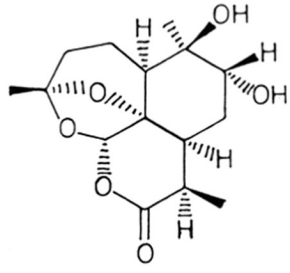


25

All have lost the peroxide moiety and were shown to be inactive towards P. berghei.[33,34]

1.4.4 Mode of Action

In an experiment with infected mice, p-aminobenzoic acid given prior to the administration of artemisinin did not counteract the suppressive activity of the latter on p. berghei.[35,36] This indicates that artemisinin and its derivatives act differently in mechanism from both chloroquine and the antifolate drugs.

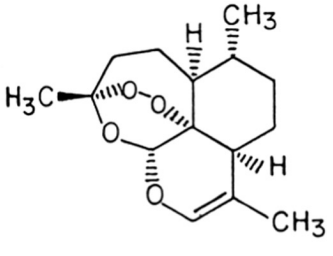
Electron microscope studies showed that artemisinin mainly interferes with membrane structures of the parasite. Changes occurred to trophozoites, i.e., the erythrocytic asexual form of the parasite in the sequence of: the appearance of whorled food vacuole membrane and limiting membranes, distended mitochondria, the swollen outer mitochondrial and nuclear membranes, dissociation of ribosomes with endoplasmic reticulum, altered endoplasmic reticulum leading to cytoplasmic vacuolization, and finally the formation of autophagic vacuoles which caused degeneration and eventually to death.[23,24,25] It has been observed that the drug inflicts similar morphological damages to all malaria species with the exception of P. falciparum in which the mitochondrial membrane was not affected.

1.5.0 Structure-Activity Relationship:

In accordance with the current trends,[37] in new drug research, artemisinin was subjected to molecular manipulations to improve its activity.[22,38] It soon became evident that the peroxide moiety of the structure is indispensable for antimalarial activity. Non-peroxy

metabolites as well as other sesquiterpenes isolated from Artemisia annua which lack a peroxy function all failed in antimalarial screening tests. On the other hand, the borohydride-reduction product of artemisinin, viz. dihydroartemisinin **18** in which the peroxide function is left intact exhibited almost twice the potency of the parent compound.

Dehydration of dihydroartemisinin gave an ethylenic compound **26** which was found to be inactive in antimalarial test. However,



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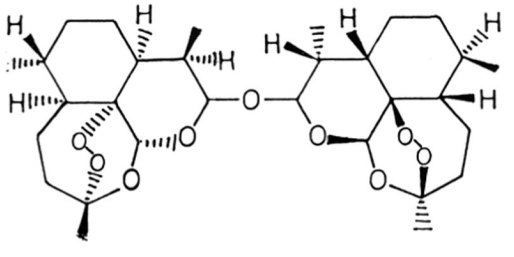


27

condensation of two molecules of dihydroartemisinin gave epimeric bisdihydroartemisinins - one composed of one molecule of α - and another molecule of β -dihydroartemisinin- **27**, was tested and found to be active at the dosage of 10 mg/kg.[38] Extensive investigations on variation of the ring systems have also pointed out that the integrity of the stereo structure of the ring system is mandatory to antimalarial activity.[40] The amphipathic nature of the molecule could be explained by examining its X-ray crystal structure. One can see that the five polar oxygen atoms are clustered on one side of the rather flattened molecule while the other side marks a nonpolar hydrocarbon skeleton. This forms a basis for the explanation of differences in the passage through and association with different biomembranes, in vitro and in vivo.

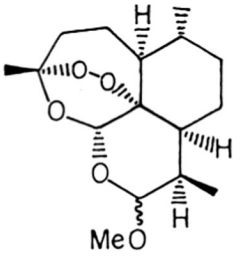
Three classes of compounds derived from dihydroartemisinin **18** ; the ethers, carboxylic esters and carbonates have been studied extensively. Their relative overall antimalarial potency can be arranged in the following order.[22,29]

Artemisinin < Dihydroartemisinin < Ethers

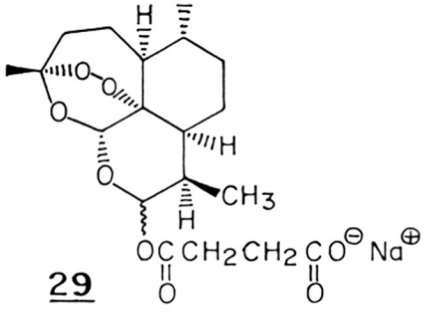
< Carboxylic esters < Carbonates

1.5.1 Ether

Ethers predominently in the β-configuration were made by reacting dihydroartemisinin with an alcohol in the presence of a Lewis acid like borontrifluoride etherate.[22,40] This class of compound being more oil-soluble, possesses better pharmacokinetic properties. The methyl ether, generically called Artemether **28**, is more active than



28



29

artemisinin. Its acute toxicity in laboratory animals, is lower than that of chloroquine but much higher than that of the parent compound.

1.5.2 Ester

Esters of dihydroartemisinin were usually made by treatment with an appropriate acid chloride or acid anhydride[40] in the presence of a Lewis base such as pyridine[41] or preferably 4-dimethylaminopyridine[22,30]

or treatment with carboxylic acids in the presence of dicyclohexylcarbodiimide.[38] Both gave esters predominently in the α -configuration. The half-ester of dihydroartemisinin **18** with succinic acid (hemisuccinate) generically called Artesunic acid, is one of the esters with notable merit. Due to water solubility of its sodium salt, known generally as sodium Artesunate **29** or 804-Na, the compound has been recommended for clinical trials as an intravenous injection. Sodium artesunate exhibited[42] more than five times suppressive activity than artemisinin against both chloroquine-resistant and chloroquine-sensitive strains of P. berghei. Eventhough it is more toxic than artemisinin, it is less toxic than Artemether. Sodium artesunate when injected in the middle and later stages of pregnancy in rats showed significant teratogenic effect. In monkeys it caused faster disappearance of parasitemia than artemisinin. A disadvantage of the compound as a drug is that an aqueous solution hydrolyses rapidly to deposit dihydroartemisinin on standing. In order to overcome this difficulty, a two ampule dosage form, with Artesunic acid and sodium bicarbonate, packed separately is being studied for clinical properties.

1.5.3 Carbonates[22,42]

The carbonates were prepared by treatment of dihydroartemisinin with the corresponding chloroformic esters in the presence of Lewis base such as triethylamine and 4-dimethylaminopyridine. α -Epimers predominated in the products. Although carbonates as a class were found to be most potent in vivo test against p. berghei, they have not been tested clinically due to difficulty in preparation.

1.6.0 Clinical Studies[23,24]

1.6.1 Treatment with Artemisinin[23,24]

According to data provided by The Coordinating Clinical Study Group on artemisinin, 1511 cases of vivax malaria and 588 cases of falciparum malaria were treated between 1973 and 1978 with artemisinin preparations. All achieved clinical cure. In addition, 143 cases of chloroquine-resistant falciparum malaria and 141 cases of cerebral malaria were also effectively treated with the drug.

Four different dosage forms and regimens have been used in clinical studies namely tablets given orally at a total dosage of (2.5 - 3.2) g. intramuscular injections of artemisinin in oil solution (0.5 - 0.8) g. and oil suspension (0.8 - 1.2) g. or water suspension (1.2) g. Each preparation was given in three divided doses, once daily for three successive days. Except for the tablets, administration was by intramuscular injection. The order of rapidity of action of each pharmaceutical form to effect fever subsidence and parasite clearance in P. vivax patients was tablets > oil > oil suspension > water suspension. The time required for a decline in the fever in vivax malaria was on the average within 20-30 h. and that for disappearance of parasitemia was 30-40 h. This demonstrated a quicker action exerted by artemisinin as compared with chloroquine. However, the recrudescence rate in the artemisinin group was 21% within a month but was zero in the chloroquine control group. On the other hand, in cases of falciparum malaria including chloroquine-resistant strains, the average time required for a decline in fever was 30-40 h. and that for disappearance of parasitemia was

30-50 h. Recrudescence rate in a month was 85% with tablets and 10-25% with other dosage forms.

No serious adverse effects have been observed during the treatment.. The drug was considered safe in patients complicated by liver, heart, and renal diseases of pregnancy.

Among the 141 cases of cerebral malaria from chloroquine-resistant falciparum treated with artemisinin, 131 achieved clinical cure and 10 died. The average time required for recovery from coma was (21.5-30.8) h; for fever subsidence was (34.1 - 56.7) h. and for disappearance of parasitemia was (33.3 - 64.5) h. These figures are much better than those achieved by either chloroquine or quinine dihydrochloride. The stronger activity of artemisinin against trophozoites can arrest the development of trophozoites at the small ring stage.[23]

1.6.2 Treatment with Artemether

Being much more oil-soluble, Artemether was administered as an oil solution by intramuscular injection. The total dosage was (0.24-0.64) g. given over a three day period. It was estimated that a 480 mg. dose of Artemether was similar in therapeutic efficacy to 900 mg. of artemisinin in oil suspension or solution.[43,28] However, a 600 mg/3 day treatment was suggested as the preferable regimen.

1.6.3 Treatment with Sodium Artesunate

On the other hand, sodium Artesunate,[43] distinguishes itself by water solubility. A total dose of 400 mg. in water solution was usually given intramuscularly or by intravenous dripping over a three day period.

The drug showed fast onset of action which is invaluable in potentially fatal cerebral malaria. The time for recovery from coma was reduced to about 12 h. although patients cured showed very high recrudescence rate. Therefore, combination therapy with appropriate antimalarial is necessary. As sodium Artesunate hydrolyses rapidly in water solution, a formulation of Artesunic acid and sodium bicarbonate packed in separate ampules is now under investigation.

1.7.0 Total Synthesis

The combination of an interesting biological activity, a novel chemical structure and a low yield from natural sources prompted scientists all over the world to search for a new synthesis of artemisinin and related products.

Working independently, both Zhou[13,14,45] et al. of the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences and Schmid and Hafheinz[13] of the F. Hoffman-La Roche Co., in Switzerland accomplished total synthesis of artemisinin in 1983 which provided definite proof of the structure and stereochemistry of the compound.

The Schmid's[13] synthesis which appeared four months earlier than Zhou's publication[14,45] started with (-)Isopulegol. On the other hand, Zhou's first synthesis[45] started with natural artemisinic acid as the starting material. Later his synthesis[14] of artemisinic acid from citronellal bridged the gap for the total synthetic programme (Scheme No. VIII).

Recently M.A. Avery[15] of Bio-organic Chemistry Laboratory of SRI International, California, reported its synthesis starting from a chiral cyclohexanone derivative. They have made use of an abnormal

course of reaction of vinylsilanes with ozone (as reported by Buchi[46]) for the formation of endoperoxide.

There are also reports of an unsuccessful approach by Jung et al.[47] starting from naturally occurring artemisinic acid.

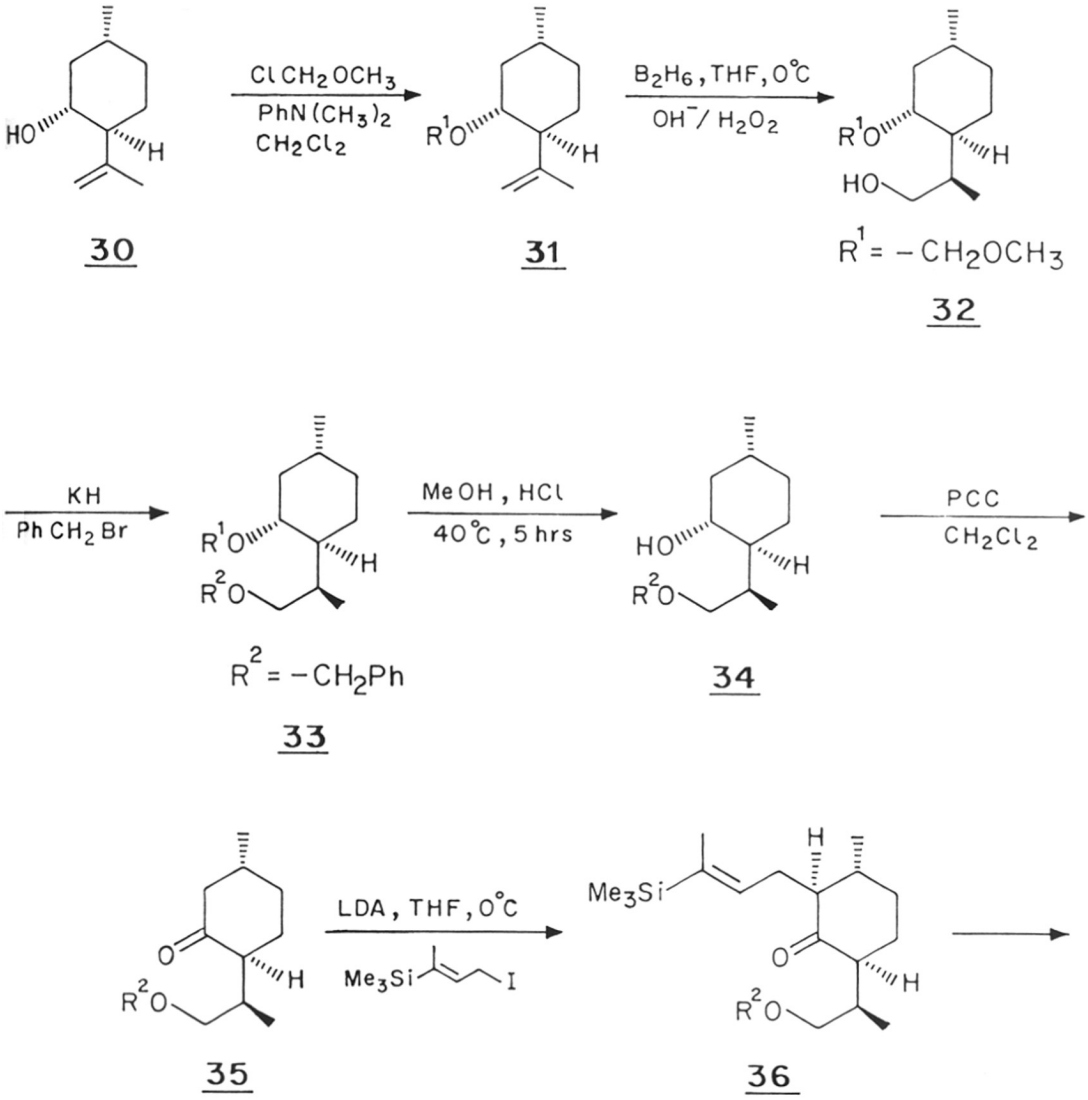
Recently, Yasuhira Imakura[48] reported the synthesis of Desethano-artemisinin **69**, a novel analogue of the antimalarial artemisinin, which contains the peroxide and the lactone functionalities intact, which are suspected to be necessary for its antimalarial activity according to the structure-activity studies. The compound is being studied for its expected activity.

A brief account of all synthetic approaches reported for artemisinin and its analogues is given in the following pages.

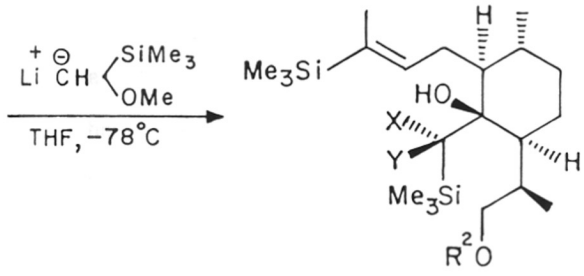
1.71 G. Schmid's Approach[13]

G. Schmid and W. Hofheinz started their synthesis with (-)Isopulegol **30** which was converted into its methoxymethyl ether **31**. The ether **31** was hydroborated with borane which on oxidative work-up with alkaline hydrogen peroxide gave the 8R alcohol **32** in 80% yield along with 10% of the 8S isomer. After the benzylation of the primary hydroxyl group, the methoxymethyl ether **33** was cleaved and the resulting alcohol **34** was oxidised to the benzyloxymenthone **35**. Kinetic deprotonation of **35** and treatment of the resulting enolate with (E-3-iodo-1-methyl-1-propenyl)-trimethylsilane provided a 6:1 mixture of epimeric alkylation products from which **36** was isolated in 62% yield. When ketone **35** was treated with 10 equiv. of lithium methoxy(trimethylsilyl)

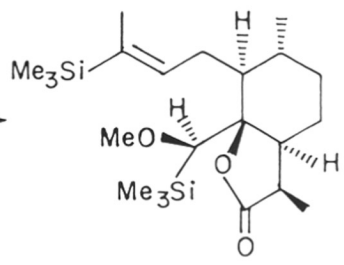
SCHEME VII


HO
H
30
ClCH2OCH3
PhN(CH3)2
CH2Cl2
R1O
H
31
B2H6, THF, 0°C
OH⁻/ H2O2
R1O
H
HO
R1 = −CH2OCH3
32
KH
PhCH2Br
R1O
H
R2O
R2 = −CH2Ph
33
MeOH, HCl
40°C, 5 hrs
HO
H
R2O
34
PCC
CH2Cl2
O
H
R2O
35
LDA, THF, 0°C
Me3Si
I
Me3Si
H
O
H
R2O
36

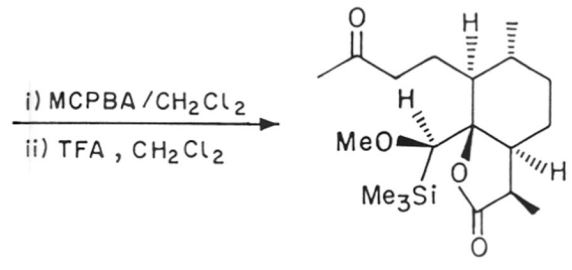
SCHEME -VII (Contd)



37 a) X=H, Y=OMe
b) X=OMe, Y=H



38



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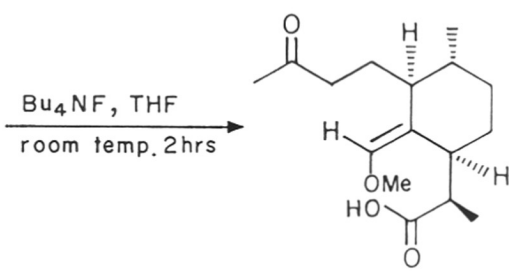

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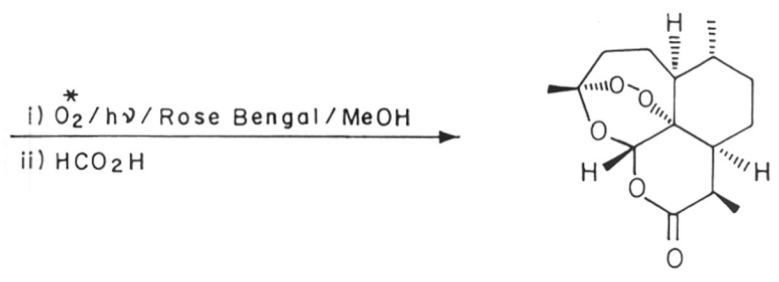


ARTEMISININ

methylide, two diastereomeric alcohols **37(a)** and **37(b)** were obtained in 8:1 ratio as a result of a kinetic resolution of the racemic organolithium reagent by the chiral ketone. Also since large nucleophiles are known to attack preferentially from the equatorial side of cyclohexanones, both **37(a)** and **37(b)** have the hydroxyl group in the axial position.

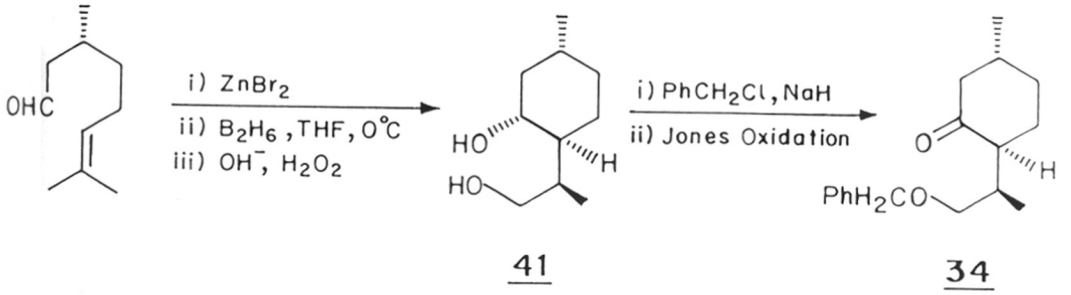
The compound **37(a)** was debenzylated and the resulting alcohol was oxidised to lactone **38**. The vinylsilane group of the lactone **38** was converted to ketone **39** by epoxidation and subsequent treatment with trifluoroacetic acid. The resulting ketone **39**, on treatment with tetrabutyl ammonium fluoride in tetrahydrofuran underwent a stereospecific β -elimination to give the enol ether **40**.

The sodium salt of the enol ether **40** on photooxygenation in methanol at -78°C gave a complex mixture of products which on treatment with formic acid in dichloromethane at 0°C gave artemisinin in 30% yield.

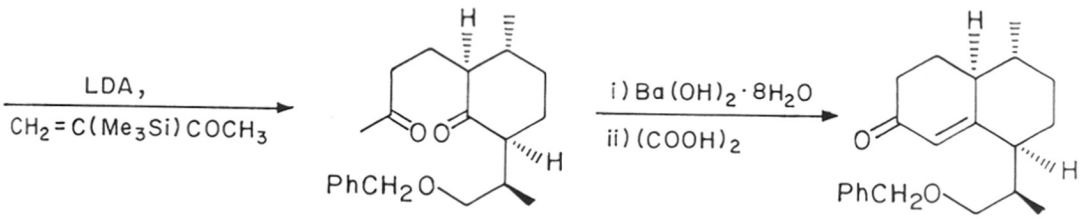
1.7.2 ZHOU Wei-Shan's Method[14]

(+)Citronellal on treatment with zinc bromide gave an alcohol which on hydroboration and subsequent oxidation gave the diol **41**. The diol was selectively benzylated at the primary alcohol group which was then oxidised with Jones reagent to give the ketone **34**. Kinetic deprotonation of **34** and the reaction of resulting enolate with silylated vinylketone gave the 1,5-diketone **42** with simultaneous cleavage of trimethylsilyl group. The diketone **42** was cyclised with barium hydroxide and on dehydration with 2.5% oxalic acid gave the α,β -unsaturated

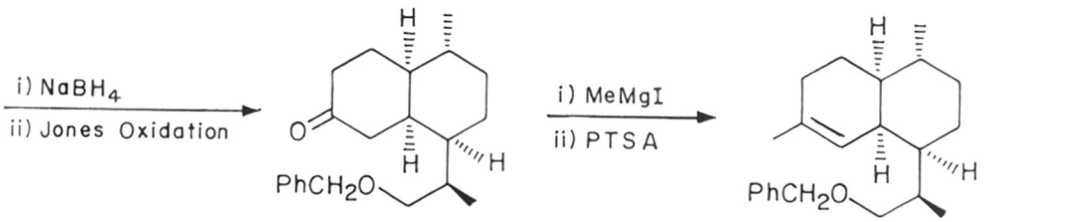
SCHEME - VIII



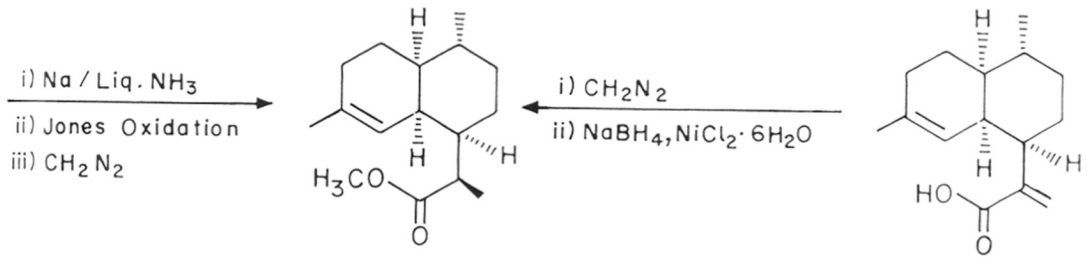
41 34



42 43

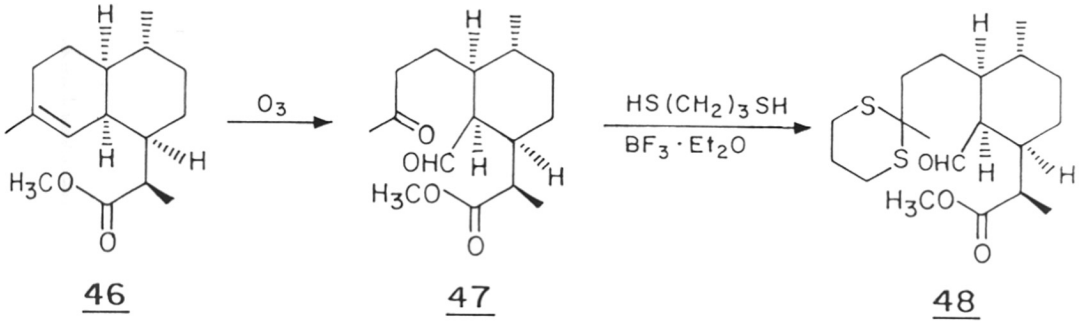


44 45

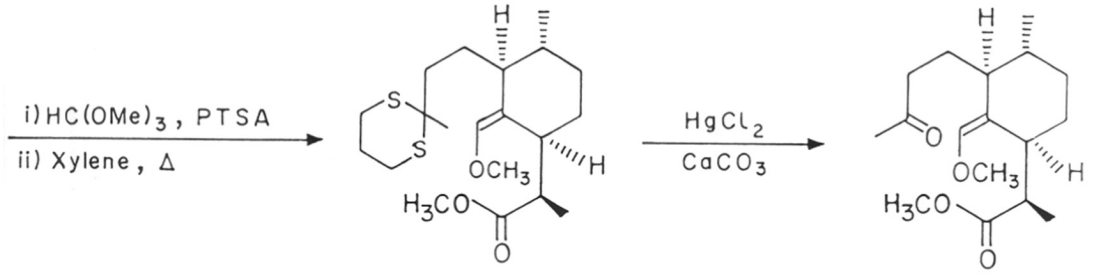


46 64

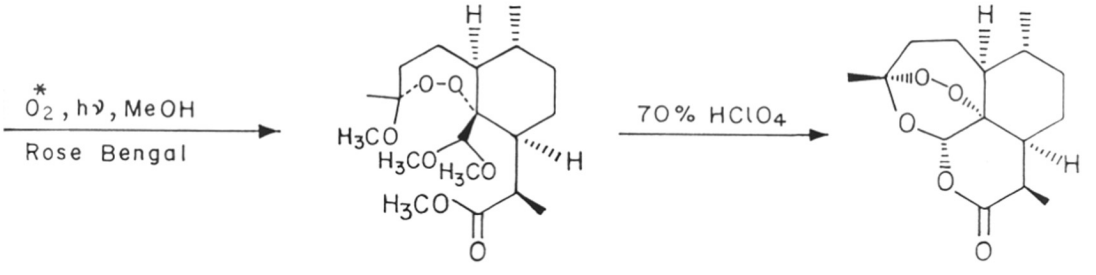
SCHEME-VIII (Contd.)



46 47 48



49 50



51 1

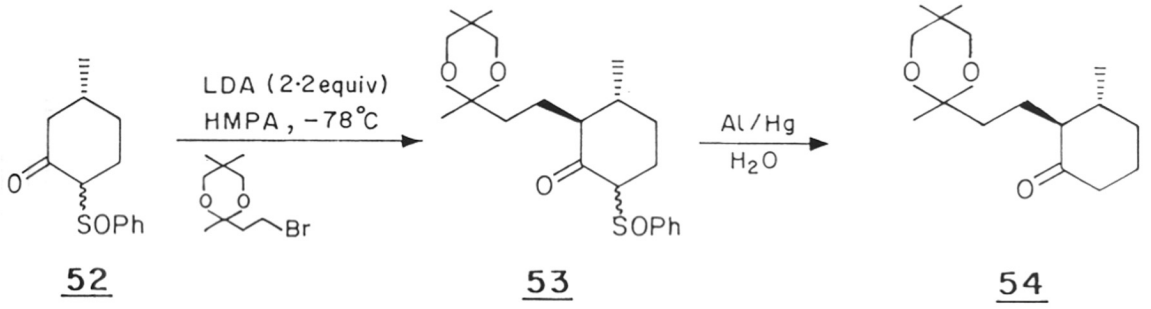
ketone **43**. This α,β -unsaturated ketone was converted to a saturated one **44** by reduction with sodium borohydride-pyridine followed by oxidation with Jones reagent. This ketone on treatment with methyl-magnesium iodide and subsequent dehydration gave a mixture of **45** and its Δ^3 -isomer in 1:1 ratio which was separated by flash chromatography. The **46** was debenzylated with sodium and liquid ammonia, then oxidised with Jones reagent and esterified with diazomethane to give **46** in 72% overall yield in three steps. **46** can also be obtained from the artemisinic acid **64** which exists together with artemisinin **1** in the same plant, first through esterification with diazomethane and then hydrogenation with sodium borohydride in the presence of nickel(II) chloride.

Ozonolysis of **46** afforded the keto-aldehyde **47** which on selective protection at the ketonic carbonyl gave **48** in 55% yield. The aldehyde was converted to its acetal by treatment with trimethylorthoformate, which on refluxing in xylene gave the enol ether **49**. The thioketal function was deprotected using mercuric chloride - calcium carbonate to give the intermediate **50**. Photo-oxidation of the methanolic solution of **50** in the presence of oxygen and Rose Bengal at -78°C followed by acid treatment gave **51** which on acid hydrolysis gave artemisinin in 28% yield.

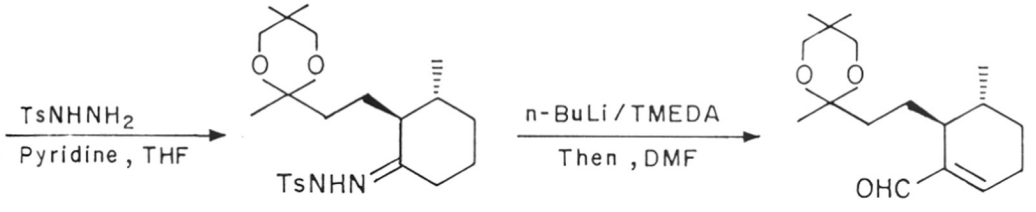
1.7.3 Avery's Approach[15]

Mitchell A. Avery converted the chiral sulphoxide **52** to its dianion with lithium diisopropylamide-hexamethylphosphoramide and alkylated with 2-(2-bromoethyl)-2,5,5-trimethyl-1,3-dioxane to give a mixture

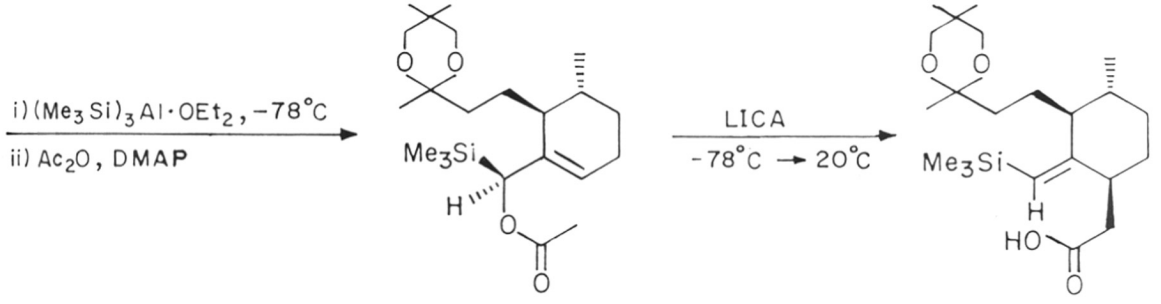
SCHEME - IX



52 53 54

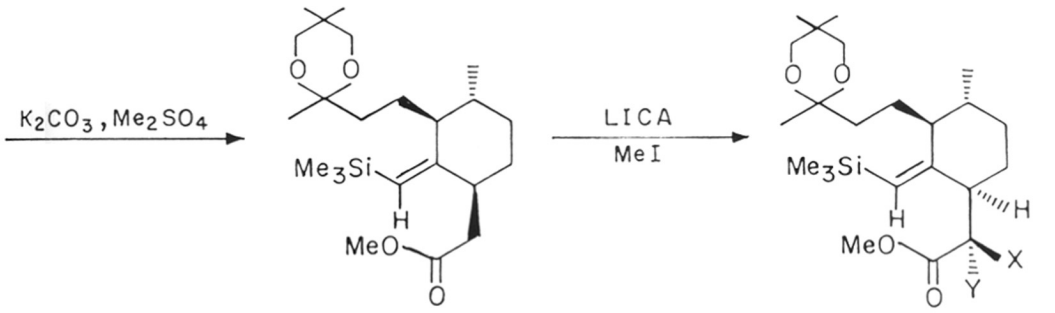


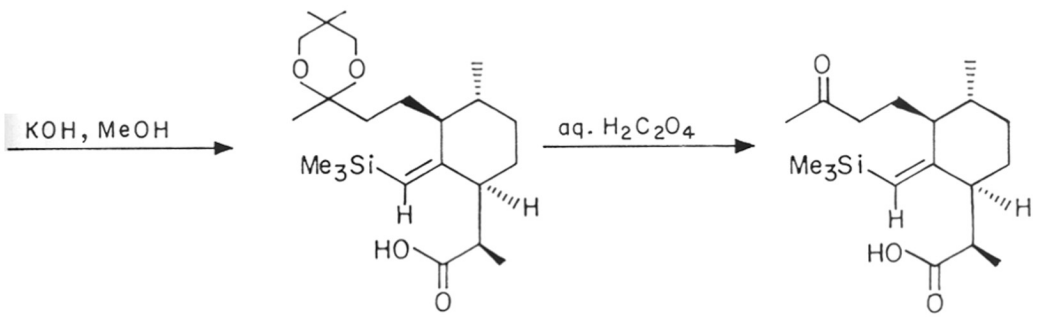
55 56

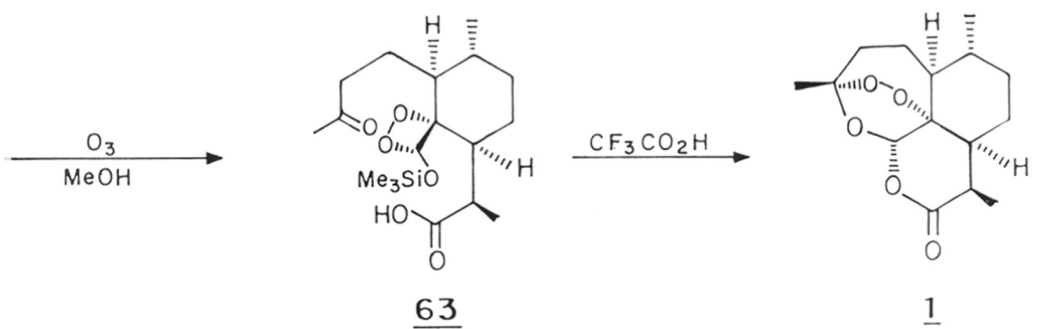


57 58

SCHEME-IX (Contd.)





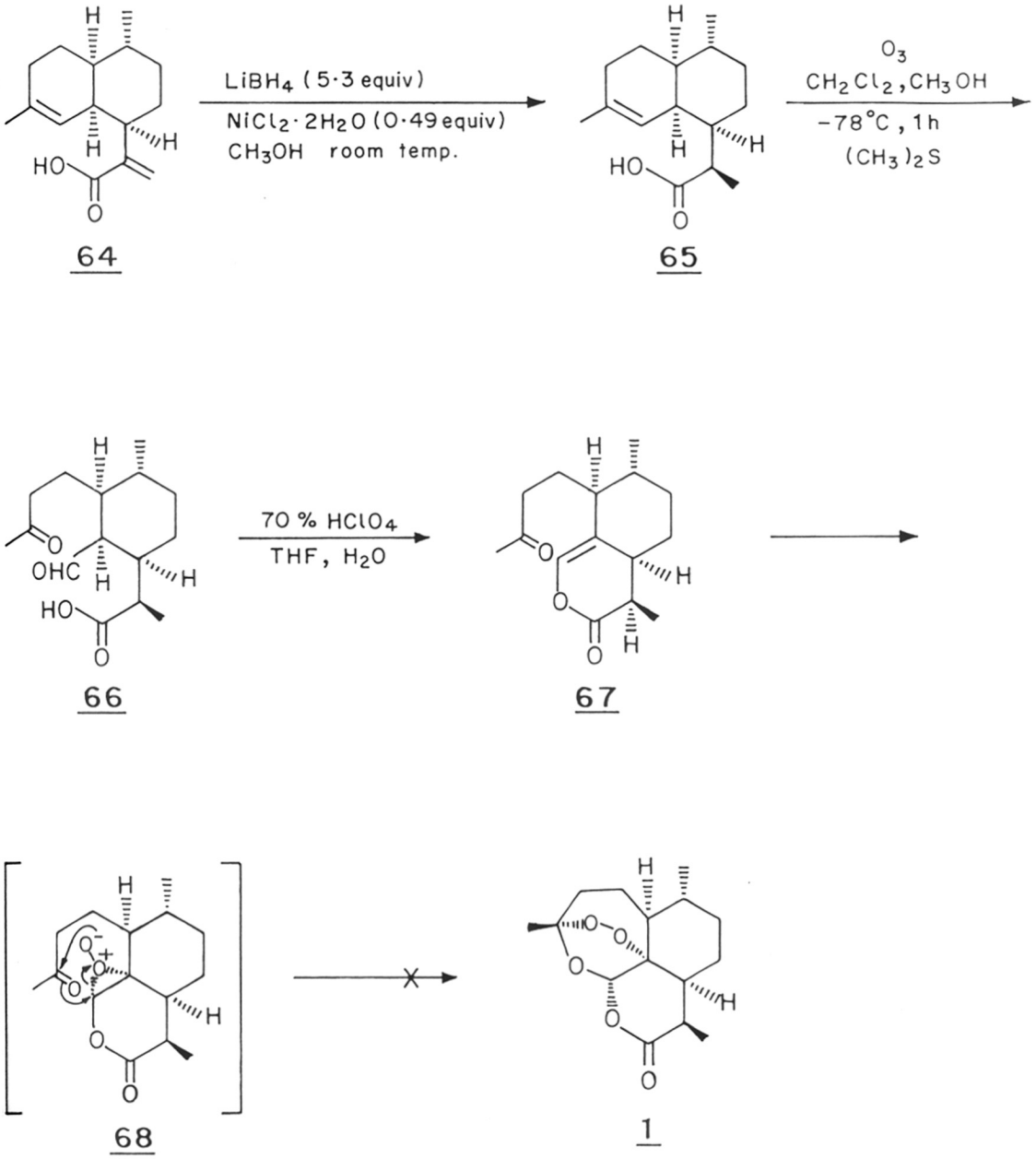


of diastereomers which on desulfurization with aluminium amalgum provided the ketone **54** in 50% yield along with a small amount of the unwanted isomer. Treatment of **54** with tosylhydrazide and pyridine in refluxing tetrahydrofuran gave hydrazone **55** in 94% yield which was then converted to a vinylanion upon reaction with four equivalents of n-butyllithium in tetramethylethylenediamine. After trapping the vinylanion with dimethylformamide, the diastereomerically pure aldehyde **56** was separated from the C_2 epimer by flash chroamtography.

The aldehyde **56** underwent a diastereoselective addition reaction with tris-(trimethylsilyl)-aluminium etherate which on treatment with acetic anhydride and 4-dimethylaminopyridine gave diastereomerically pure silyl acetate **57**.

The silyl acetate **57** on treatment with lithium isopropylcyclohexylamide (LICA) in tetrahydrofuran underwent Ireland's ester enolate Claisen rearrangement to give **58**, which was converted to its methyl ester by treatment with potassium carbonate and dimethylsulphate. The methyl ester **59** was deprotonated with LICA and then alkylated with methyl iodide to give 7:3 mixture of **60(a)** and **60(b)** respectively. Alkaline hydrolysis of the ester mixture of **60(a)** and **60(b)** in methanolic potassium hydroxide followed by deketalisation gave the desired keto ester **62** (56%) along with the undesired isomer (15%). This mixture on ozonisation underwent an abnormal course of reaction[46] leading to an oxetane **63** which on acidification with trifluoroacetic acid gave (+)artemisinin and 9-isoartemisinin from which artemisinin was obtained in 37% yield from **62**.

SCHEME-X

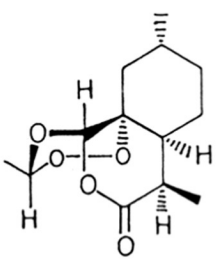

LiBH4 (5·3 equiv)
NiCl2·2H2O (0·49 equiv)
CH3OH room temp.
O3
CH2Cl2, CH3OH
-78°C, 1h
(CH3)2S
70 % HClO4
THF, H2O
64
65
66
67
68
1

1.7.4 Jung's Approach

M. Jung et al.[47] attempted to synthesise artemisinin from a natural product, artemisinic acid **64** which is present in A. annua 8-10 times more than artemisinin itself. Artemisinic acid **64** was stereoselectively reduced with lithium borohydride in presence of nickel chloride to give dihydroartemisinic acid **65** in quantitative yield which on ozonolysis gave the keto aldehyde **66** in 75% yield. The keto-aldehyde **66** was converted to the enol lactone **67** by treatment with 70% perchloric acid at room temperature. But attempts to convert **67** into artemisinin by photooxygenation failed due to the decreased electron density of the double bond in the enol-lactone ring.

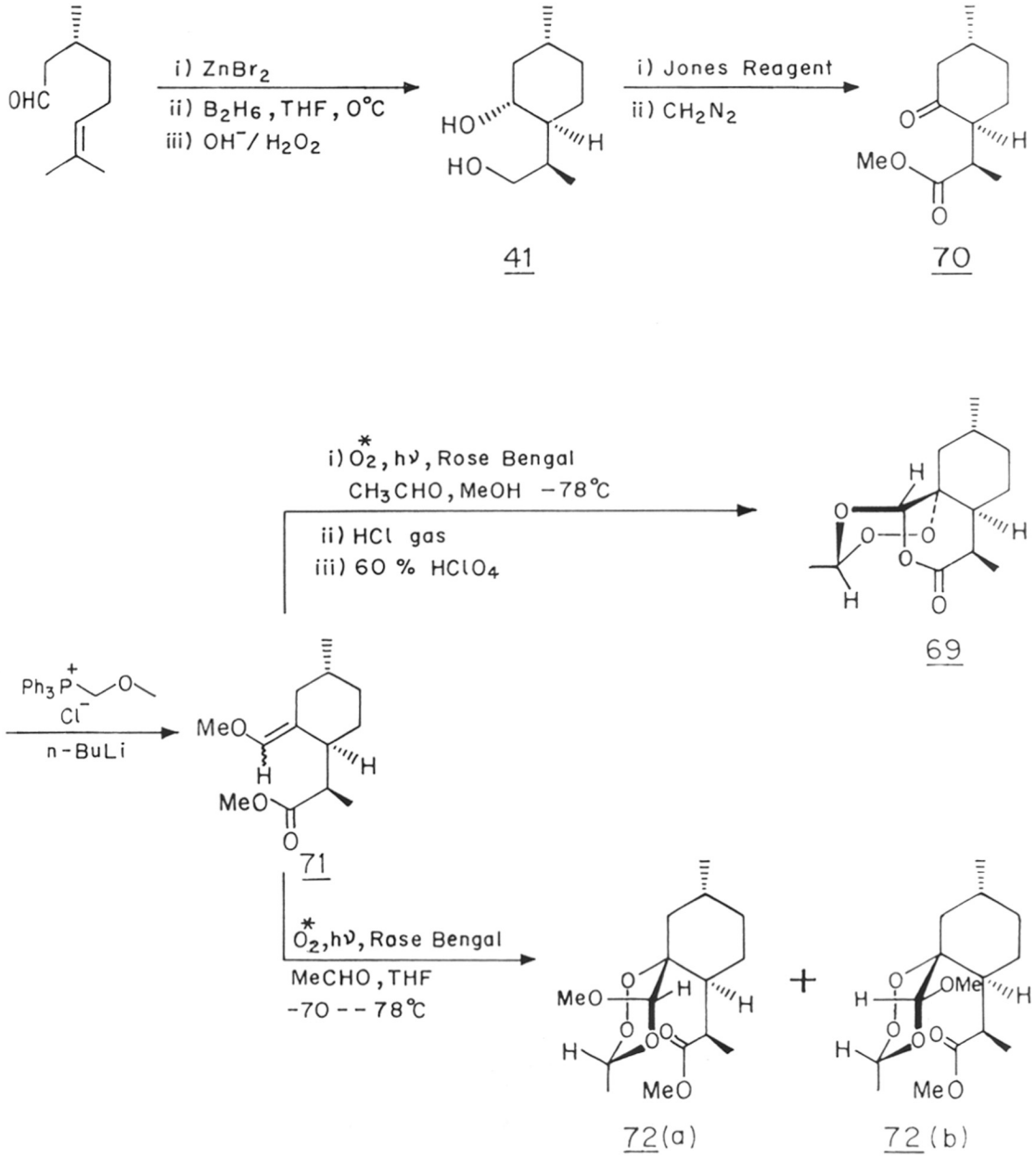
1.8.0 Synthesis of a Novel Analogue of Artemisinin[48]

Studies on structure-activity relationships on artemisinin and its analogues showed that the antimalarial activity might involve the unique C-O-O-C-O-C-O-C=O- moiety found in artemisinin. A.T. McPhaill et al. synthesised stereoselectively a simple analogue known as desethanoqinghaosu which contains this structural feature. Citronellal was converted to the dihydroxy compound **41** as in the Zhou-Weisshan's approach which was oxidised with Jone's reagent and esterified with diazomethane to give the ester **70.**

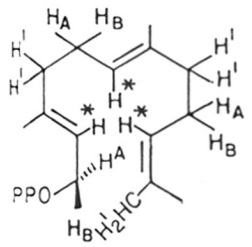


69

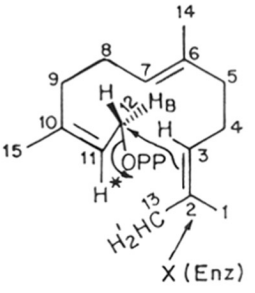
SCHEME-XI

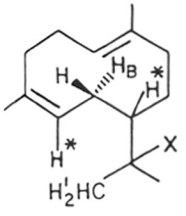

OHC
i) ZnBr2
ii) B2H6, THF, 0°C
iii) OH⁻/ H2O2
HO
HO
H
41
i) Jones Reagent
ii) CH2N2
O
MeO
O
H
70
i) O2*, hν, Rose Bengal
CH3CHO, MeOH −78°C
ii) HCl gas
iii) 60 % HClO4
H
O
O
O
O
O
H
H
69
Ph3P
O
Cl⁻
n-BuLi
MeO
H
MeO
O
H
71
O2*, hν, Rose Bengal
MeCHO, THF
-70 - - 78°C
MeO
O
O
H
O
O
H
MeO
72(a)
+
H
O
O
OMe
H
O
O
O
H
MeO
72(b)

SCHEME-XII BIOSYNTHESIS OF ARTEMISININ



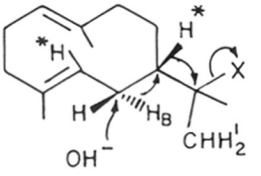
Farnesyl pyrophosphate



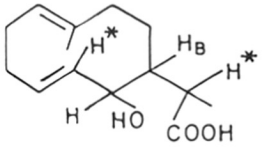


75

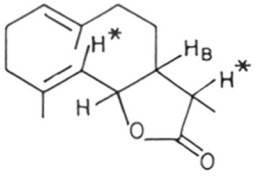
Germacrane



or its biogenetic equiv

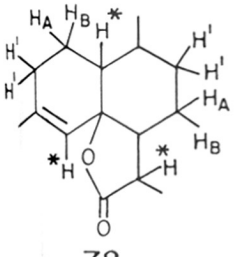


76



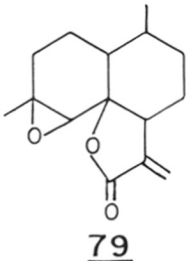
77

Dihydrocostunolide



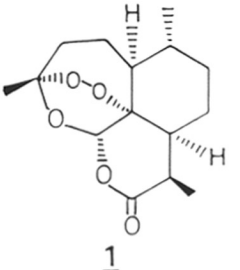
78

Cadinanolide



79

Arteannuin B



1

Artemisinin

Wittig reaction of **70** with methoxymethyltriphenylphosphonium chloride and n-butyllithium afforded an enol methylether **71.** Photo-oxygenation of a methanolic solution of **71** with acetaldehyde in the presence of oxygen and Rose bengal at -78°C followed by hydrogen chloride gas treatment and acidic hydrolysis with 60% perchloric acid produced desethanoqinghaosu **69** in 15% yield. When the compound **71** was photo-oxygenated in tetrahydrofuran instead of methanol with acetaldehyde and Rose bengal as sensitiser at -70°C to -78°C a mixture of diastereomers **72(a)** and **72(b)** respectively were obtained.

1.9.0 Biosynthesis of Artemisinin

The isotope ratios (^{3}H : ^{14}C) in arteannuin B and artemisnin biosynthesised in A. annua from [4R-^{3}H, 2-^{14}C] - [5-$^{3}H_2$, 2-^{14}C] and [2-$^{3}H_2$, 2-^{14}C] (3RS) mevalonate have suggested the following biosynthetic scheme. Two specific 1,2-hydride shifts take place during the oxidation and lactonization of the germcrane skeleton to yield dihydrocostunolide.

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CHAPTER 2·0·0
SYNTHESIS OF ARTEMISININ FROM Δ^3 CARENE

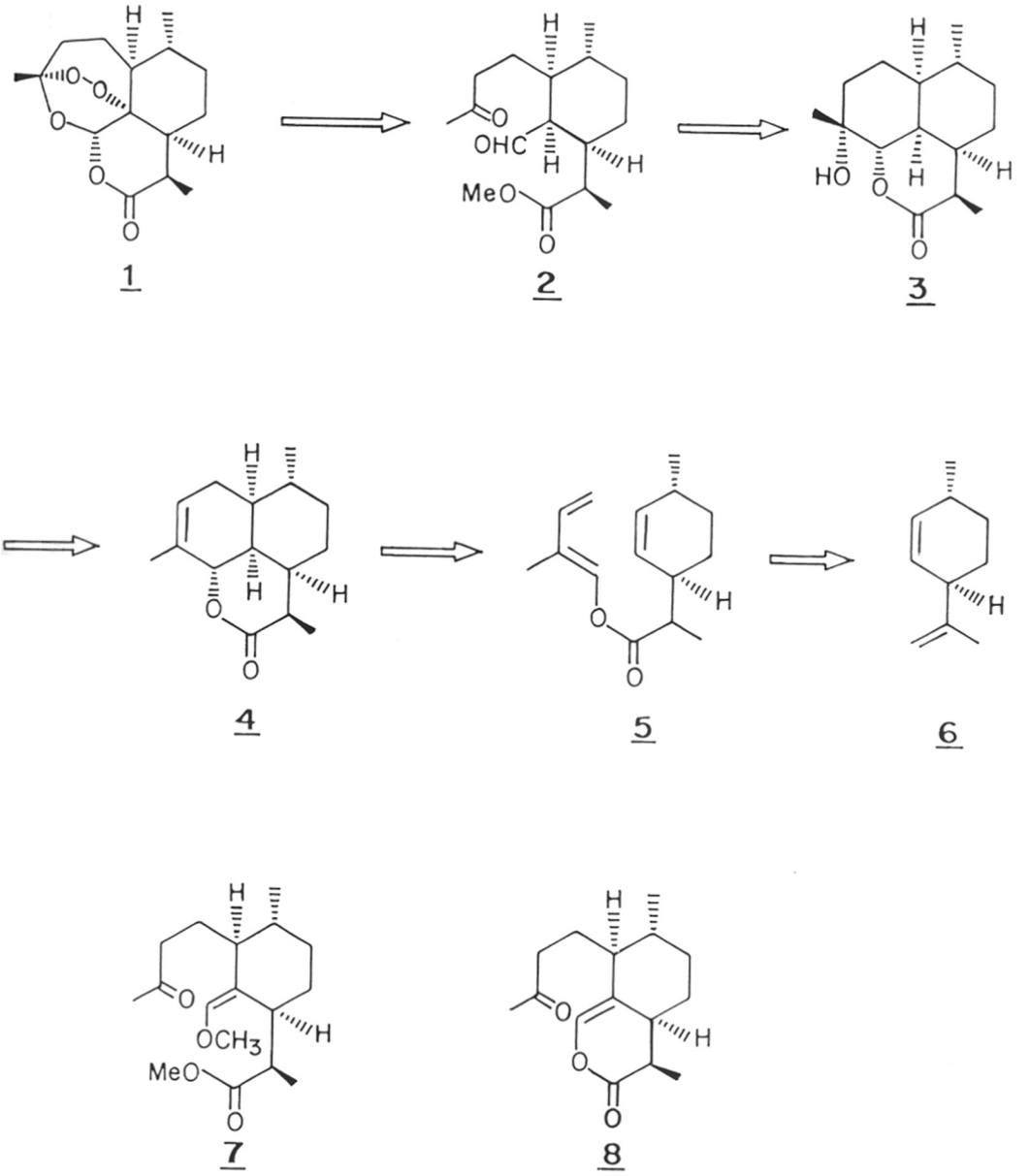
2.1.0 RESULTS AND DISCUSSION

Biological activity of compounds (pharmacological as well as pheromonal) is more often than not, dependent on the shape and structure. The main parameter affecting the shape of the organic molecule is stereochemistry of the different carbon centres. Hence the absolute configuration of carbons in the biologically active compounds is of utmost concern for synthetic organic chemist preparing them. The most direct method for preparing chiral compounds is resolution of racemic mixtures obtained by synthesis. This has been the traditional method which suffers from the disadvantage of abandoning the undesired optical antipode, that one ends up in the resolution step. If this unwanted enantiomer is not recycled by racemisation and repeated resolutions, all the efforts in the synthesis of the racemic compound and half of the end result itself become a colossal waste. An elegant solution to avoid this is the synthesis of organic molecule stereoselectively *via.* asymmetric methods. The latter is practised by the organic chemists by starting with naturally occurring chiral substrates of known absolute stereochemistry or by the use of suitable auxillaries for chiral induction.

On the basis of above facts a retrosynthetic analysis of the target molecule artemisinin was planned, so as to provide an asymmetric route for the same which is as shown below (Scheme-I).

In 1986 W. Zhou[1] reported the conversion of the intermediate 2 to artemisinin through the intermediate enol ether **7**. Our synthetic strategy for the conversion of the intermediate **2** to artemisinin was through the enol lactone **8** which is much easier to prepare than the

SCHEME-I


H
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1
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OHC
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HO
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H
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3
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O
O
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5
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OCH3
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MeO
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7
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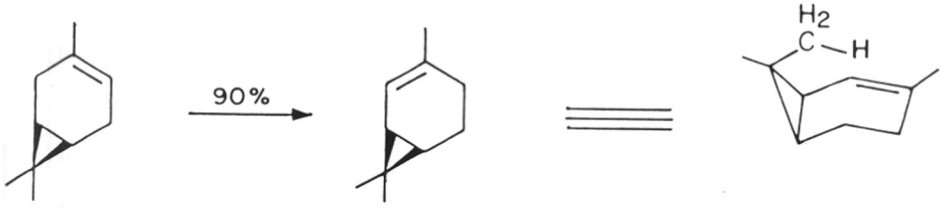
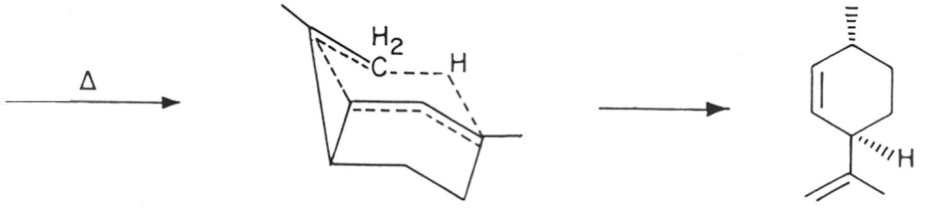
H
O
8

SCHEME-II



9 10



11 6

enol ether. But, later M. Jung et al.[2] reported their unsuccessful attempt to prepare artemisinin from **2** through this enol lactone by photooxygenation. Hence it was decided to convert the keto aldehyde **2** to artemisinin as reported earlier.[1]

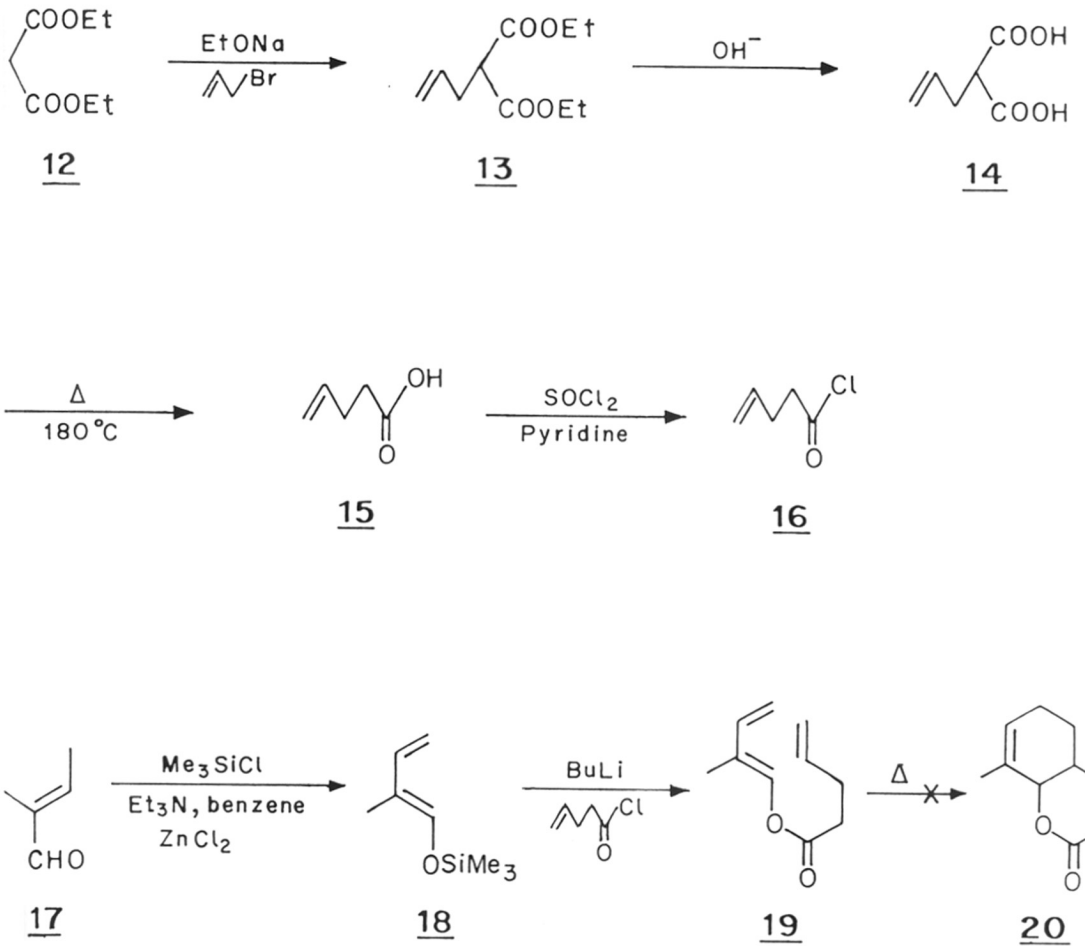
(+)(1R:4R)-Trans-$\Delta^{2,8}$-p-menthadiene (isolimonene) **6** forms a suitable starting material for the synthesis of artemisinin since it possesses two asymmetric carbon atoms having the same absolute configuration as in the target molecule. Moreover it can be obtained[3] in enantiomerically pure form from Δ^3 carene (Scheme-II) which is indigenously available in abundant quantities.

Δ^3-Carene was isomerised to Δ^2-carene which, being thermally unstable, rearranges via a cyclic transition state **11** by simultaneous shift of hydrogen and cleavage of cyclopropane ring to give (1R,4R)-trans-$\Delta^{2,8}$-p-menthadiene **6**.

In the above retrosynthetic analysis of artemisinin the intramolecular Diels-Alder reaction of the intermediate enol ether **5** is the key step since three new chiral centres could be formed in this reaction. The intramolecular Diels-Alder reaction involving an 1-acyloxybutadiene with an unactivated dienophile as in the intermediate **5** has not been reported in the literature. In order to study the feasibility of the intramolecular Diels-Alder reaction of the above type a simpler model system was prepared as shown in Scheme-III.

Diethyl malonate **12** on alkylation with allyl bromide gave the diester **13** which on alkaline hydrolysis gave the dicarboxylic acid **14**. The decarboxylation of **14** by pyrolysis at 180°C gave 4-pentenoic

SCHEME-III



12 13 14

15 16

17 18 19 20

acid **15** in 70% yield. The 4-pentenoic acid **15** was converted to its acid chloride **16** in about 80-85% yield by treating it with thionyl chloride in presence of pyridine at 0°C.

2-Methyl-but-2-enal **17** (Tiglaldehyde) on treatment with triethylamine and trimethylsilyl chloride in presence of catalytic amount of zinc chloride was converted to its silyl enol ether[5] **18** which was characterised by its PMR and IR spectra. Its PMR spectrum showed a singlet at 0.16 ppm for (9H, -OSi$\underline{Me}_3$), a doublet at 1.61 ppm for (3H, J=2Hz) for vinylic methyl, a multiplet between (5 - 6.36) ppm for four olefinic protons. In addition IR spectrum showed a band at 1640 cm^{-1} of medium intensity for the diene system.

Silyl enol ether **18** on treatment with 1 equiv. of alkyllithium resulted in the fission of the silicon-oxygen bond with the concomitant formation of lithium enolate[6] of tiglaldehyde which was cooled to -78°C and treated with 4-pentenoyl chloride to give enol ester **19** in 50% yield. (Our earlier attempt to prepare enol ester of the aldehyde by treating it with lithium diisopropylamide and pentenoyl chloride resulted in the formation of pentenoyldiisopropylamide due to faster reaction of acid chloride with amine). The PMR spectrum of the ester **19** showed a doublet at 1.82 ppm, (3H, J=2Hz) for the methyl on the double bond, a multiplet between (2.31-2.57) ppm (4H) for two methylenes, a multiplet between (4.9-5.35) ppm (4H) for two terminal methylenes(=CH_2), a multiplet between (5.66-6.1) ppm for one olefinic proton of the pentenoic acid moiety, a quadruplet between (6.22-6.5) ppm for the one hydrogen on C_3 carbon of the butadiene moiety and

a singlet at 7.2 ppm for one hydrogen on C_1 carbon of the butadiene. IR spectrum showed strong absorption band at 1750 cm^{-1} for enol ester carbonyl and a medium absorption band at 1640 cm^{-1} corresponding to the diene.

In order to study the feasibility of the intramolecular Diels-Alder reaction of the enol ester **19**, it was subjected to various thermal and Lewis acid catalysed conditions. Thus a 0.02 M solution of the enol ester **19** (the high dilution was used to reduce the polymerisation) in different solvents like toluene (b.p. 111°C), xylene (b.p. 143°C) orthodichlorobenzene (b.p. 180°C) and tetralin (b.p. 207°C) were prepared and heated to their reflux temperatures under nitrogen atmosphere. (A catalytic amount of hydroquinone was added to reduce the polymerisation and a small amount of pyridine was also used to maintain the reaction medium basic). The reaction was monitored by thin layer chromatography (TLC). It was found that below 200°C the enol ester **19** remained unchanged and above 200°C and also on prolonged heating it underwent polymerisation.

After failing to achieve the intramolecular Diels-Alder reaction thermally, the above model reaction was carried out under Lewis acid catalysed conditions.[7] To begin with the triene system **19** was treated with readily available catalysts like borontrifluoride etherate, Tin (IV) chloride, aluminium chloride. Since it is known that the enol esters undergo decomposition in the presence of Lewis acids, the reaction was carried out at a very low concentration of the triene **19** in dichloromethane, initially with only catalytic amount and subsequently with

equivalent amount of Lewis acid at various temperatures ranging from -78°C to room temperature. The reaction was monitored by TLC. Initially there was no change at lower temperature but on prolonged keeping and above 0°C, the triene **19** slowly underwent decomposition. So the use of still milder Lewis acid catalysts such as ethylaluminium chloride,[8] diethylaluminium chloride, menthoxyaluminium chloride[9] were tried. The Diels-Alder reaction of the triene **19** with these catalysts were tried as in the case of other Lewis acids like borontrifluoride etherate, etc. Reaction was monitored by TLC. No change was observed below 0°C, but on prolonged keeping, above 0°C it underwent polymerisation.

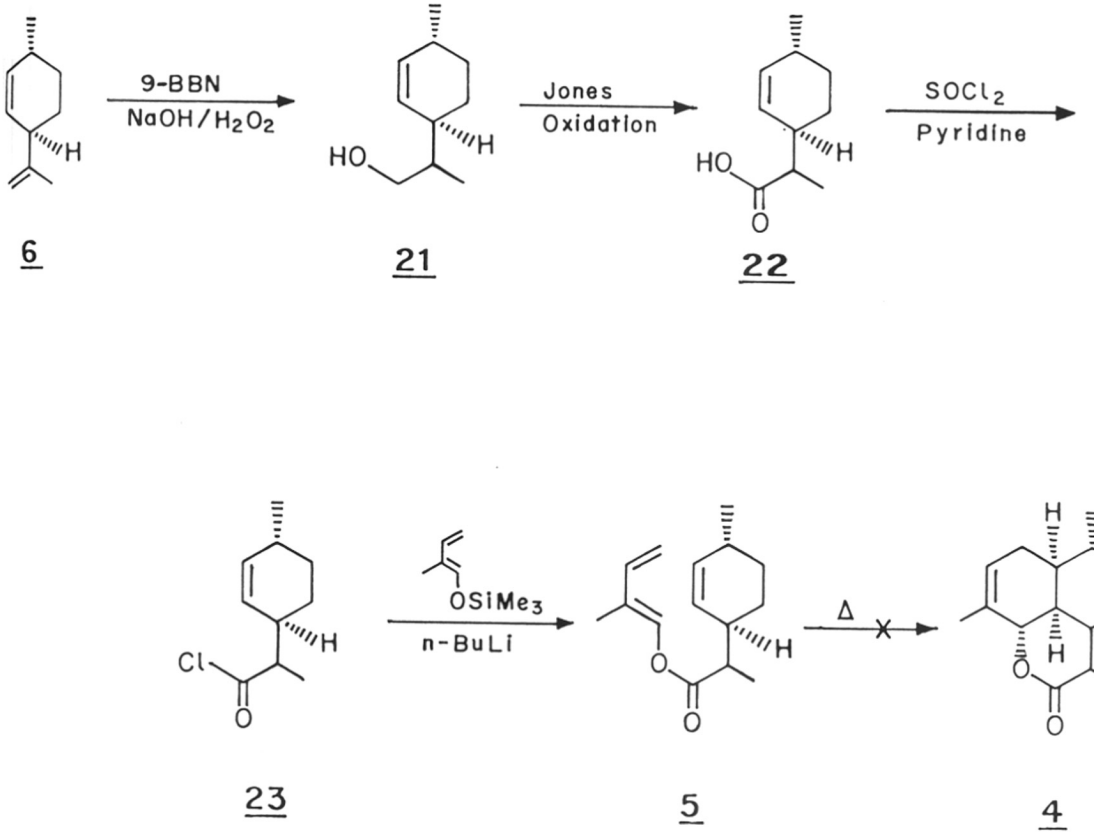
Since reaction did not proceed under Lewis acid catalysis, cation-radical catalysed Diels-Alder reaction,[10] which is found to be complementary to above, was tried. Cation-radical catalysis is considered complementary to the Lewis acid catalysis since it is known to catalyse the Diels-Alder reactions of neutral or electron-rich dienes whereas Lewis acids are known to catalyse the reaction of electron deficient dienophiles. The principle behind the cation-radical catalysis is to convert the dienophile into a cation-radical, which could be obtained using a cation-radical initiator like tris-(p-bromophenyl) aminium hexachlorostibnate,[11] which (cation radical) being a highly electron-deficient species will add to appropriate cisoid dienes to yield the Diels-Alder product. Since the dienophile in the triene **19** is an unactivated one, the compound **19** was also subjected to cation-radical catalysis conditions as follows.[10]

A solution (0.05 M) of triene **19** in dichloromethane was treated with 10 mole % of tris-(p-bromophenyl)aminium hexachlorostibnate at various temperatures ranging from -78°C to room temperature. But the results were same as in the case of Lewis acid catalysis. There was no change at -78°C and on prolonged keeping or on raising the reaction temperature to 0°C, the triene underwent only polymerisation. In dealing with the theoretical analysis of selectivity in the cation-radical catalysed Diels-Alder reactions, Bauld[12] has reported that the cycloaddition is role-selective being allowed for the addition of an ionised dienophile to a neutral diene component, but forbidden for the addition of a neutral dienophile to an ionised diene component. On this basis, failure of the triene to react under cation-radical catalysis could be understood as the triene **19** belongs to the latter category, i.e. having an ionised diene component and a neutral dienophile, thus supporting Bauld's hypothesis.

The intramolecular Diels-Alder reaction of the triene **5** (Scheme-I, retrosynthetic analysis) required for the synthesis of target molecule artemisinin, was also tried under thermal, Lewis acid catalysis and cation-radical catalysis conditions as described above. The triene was prepared according to the scheme shown (Scheme-IV).

(IR:4R)-Trans- $\Delta^{2,8}$-p-menthadiene (isolimonene) on regioselective hydroboration at the terminal double bond with 9-borabicyclo[3.3.1]nonane (9-BBN)[13] and subsequent oxidative hydrolysis using alkaline hydrogen peroxide gave the alcohol **21** in 60% yield. The stereochemistry of the newly formed asymmetric centre cannot be controlled since the

SCHEME-IV



6 21 22

23 5 4

addition of borane can take place from both sides of the plane containing the olefin resulting in the formation of both the epimers. However, this was not considered a limitation because of the opportunity, the structure will present itself at a later stage in the synthesis, for equilibration and recycling. The alcohol showed a rotation of $[\alpha]_D^{25^\circ} = +70^\circ$ (C = 2.1). The PMR spectrum (Fig. 2.1) showed a multiplet between (0.8 - 1) ppm (6H) for two methyls, a multiplet (1 - 2) ppm (5H) for methylene and methine protons, a multiplet (2 - 2.35) ppm (2H) for allylic protons, a multiplet (3.45 - 3.65) ppm for ($-CH_2-O$) and an unresolved doublet at 5.5 ppm for olefinic protons. IR spectrum (Fig. 2.2) showed absorption band at 3350 cm^{-1} for hydroxyl group and mass showed (m/e) at 154 (M^+).

The alcohol **21** thus obtained was oxidised with Jone's reagent[14] at 0°C to give the acid **22** in 70% yield. The PMR spectrum of the acid **22** (Fig. 2.3) showed a doublet at 0.85 ppm (J = 6.5 Hz) of the methyl group in the cyclohexane ring and two doublets at 1.1 ppm (J = 6Hz) for the methyl α - to the carbonyl, a multiplet between (1.5 - 2.35) ppm (7H), a multiplet at 5.4 ppm for the olefinic protons and a broad singlet at 10 ppm for the acidic proton. IR spectrum (Fig. 2.4) showed a broad absorption band at 3000 cm^{-1} for ($-\overset{O}{\overset{\|}{C}}-OH$) and a strong acid carbonyl absorption at 1700 cm^{-1} and mass spectrum showed M^+ peak at 168.

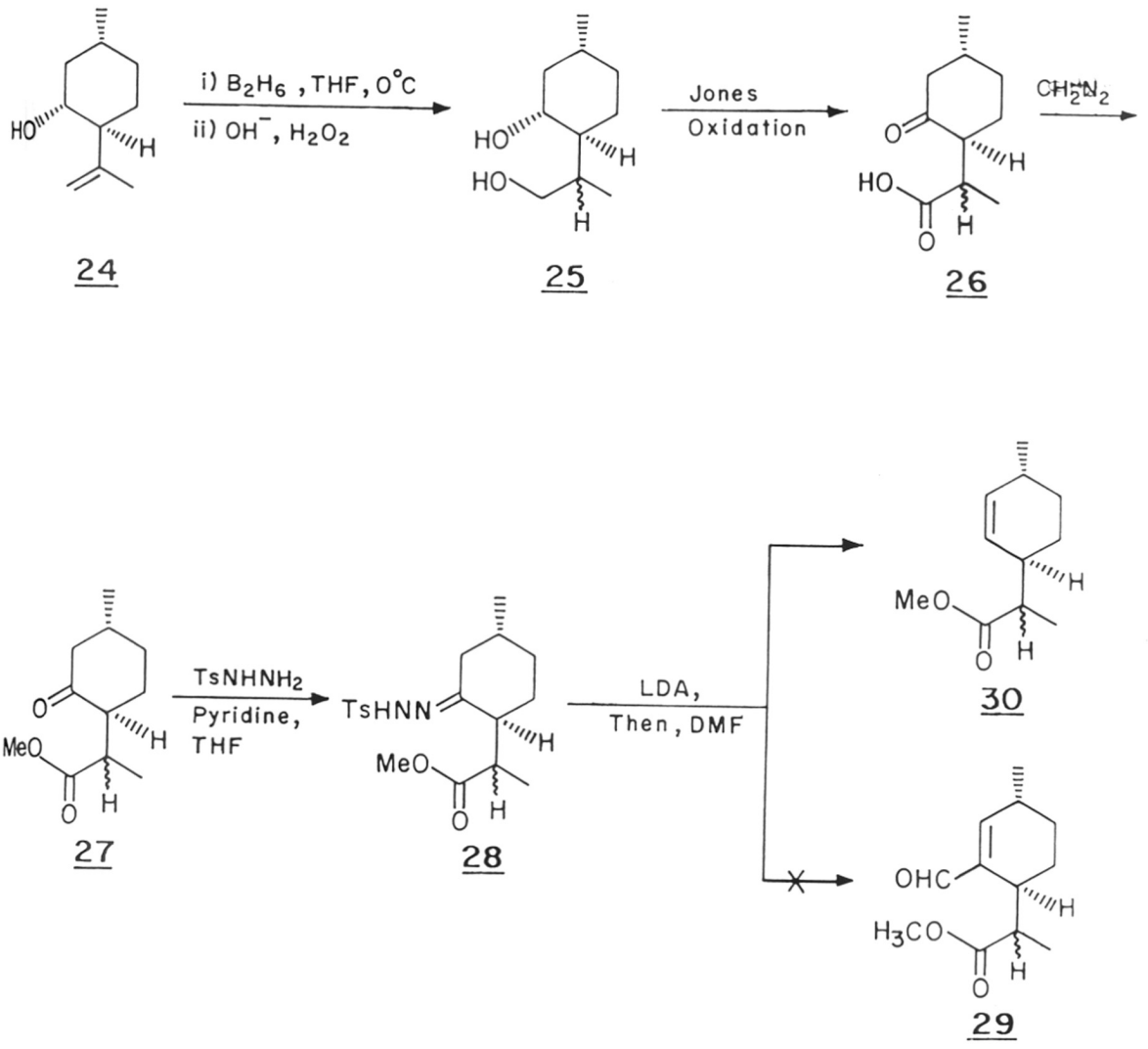
The acid **22** was converted to acid chloride **23** by treatment with one equivalent of thionyl chloride in presence of one equivalent of pyridine at 0°C. The lithium enolate[6] of the tiglaldehyde was

prepared as described earlier (Scheme-IV) and then treated with the acid chloride **23** at -78°C to afford the triene **5** in 50% yield. The triene was characterised by its PMR spectra (Fig. 2.5) which showed a doublet at 1.02 ppm (3H; J=7Hz) for methyl on the cyclohexane ring, a doublet of doublet at 1.33 ppm (3H; J=4Hz, J=4Hz), for the methyl α- to the carbonyl group, a doublet at 1.92 ppm (3H; J=2Hz) for the methyl connected to the double bond, a multiplet between (1-2.62) ppm for (7H), a broad doublet at 5.62 (2H) for the olefinic protons in the cyclohexane ring and characteristic pattern for the butadiene moiety seen earlier for **19**. Also IR spectrum (Fig. 2.6) showed a strong absorption band at 1750 cm^{-1} for the carbonyl of the ester group and a medium absorption band at 1640 cm^{-1} corresponding to the diene system.

The attempts to bring about intramolecular Diels-Alder reaction with the triene **5** under thermal, Lewis acid catalysed as well as cation-radical catalysed conditions were unsuccessful. The triene **5** also behaved in the same way as the model compound (**21**) i.e. giving rise to decomposition products under the above mentioned conditions.

Since electron-withdrawing group in the dienophile and electron-donating group in the diene or vice versa can accelerate the rate of Diels-Alder reaction, activation of the triene system **5** by introduction of an electron-withdrawing substituent like (-CHO) in the dienophile was attempted. To get Diels-Alder product with correct stereochemistry, this introduction of -CHO to give an α, β-unsaturated aldehyde has to be regioselective. Therefore, Scheme-V was planned.

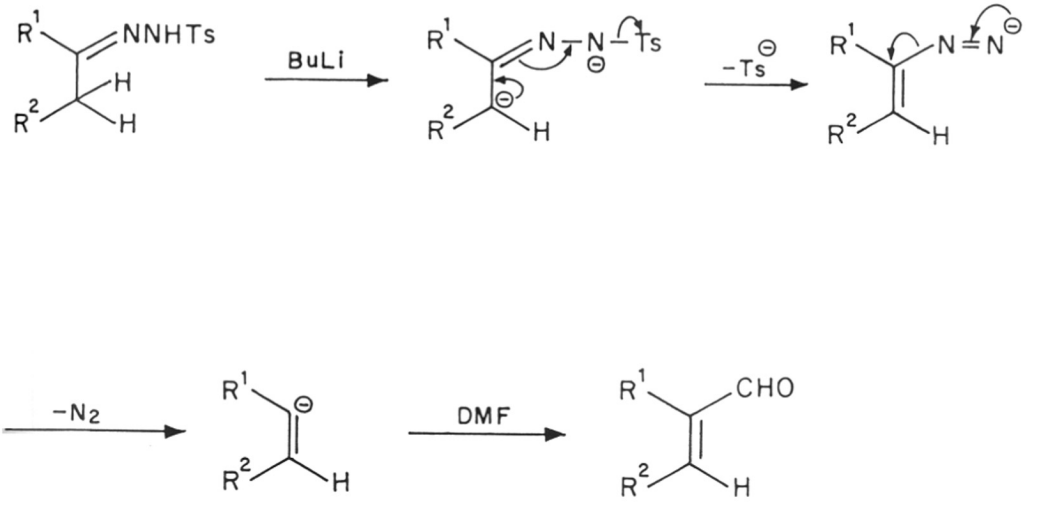
SCHEME-V


i) B_2H_6 , THF, 0°C
ii) OH^-, H_2O_2
Jones
Oxidation
CH_2N_2
TsNHNH$_2$
Pyridine,
THF
LDA,
Then , DMF
24
25
26
27
28
30
29

(-)(1R, 4S) Isopulegol **24** on hydroboration[15] with sodium borohydride and borontrifluoride etherate and subsequent hydrolysis with alkaline hydrogen peroxide gave diol **25** which was identified as the structure **25** by PMR, IR and mass spectra. The diol **25** was further oxidised with Jone's reagent[14] to give the keto acid **26** which was esterified with diazomethane[16] in ether to give its methyl ester **27** which was characterized by its PMR, IR and mass spectra. The keto ester **27** was converted to its corresponding tosylhydrazone[17], **28** by refluxing it with one equivalent of tosylhydrazine in tetrahydrofuran in presence of pyridine. The PMR spectrum of tosylhydrazone **28** showed a singlet at 2.35 ppm for the methyl on the aromatic ring, a singlet at (3.6) ppm for the methyl of the ester, a multiplet between (0.65-2.8) ppm for (15H) and two sets of multiplet between (7.1-7.9) ppm for aromatic protons. IR spectrum showed a strong absorption at 1735 cm^{-1} indicating the presence of the ester carbonyl, a weak absorption at 1600 cm^{-1} for aromatic ring and a medium absorption band at 3220 cm^{-1} for NH functionality.

Trass et al.[18] reported the conversion of tosylhydrazone to α,β-unsaturated aldehyde by treating it with four equivalents of alkyllithium in tetramethylethylenediamine and formylating the vinyllithium intermediate with dimethylformamide, as explained mechanistically in Scheme-VI. Since the hydrazone **28** contains an ester group, lithium diisopropylamide (LDA) was chosen instead of alkyllithium as base for the above reaction. However, the reaction failed to give the desired α,β-unsaturated aldehyde **29**, instead an olefin **30** was isolated. This

SCHEME-VI

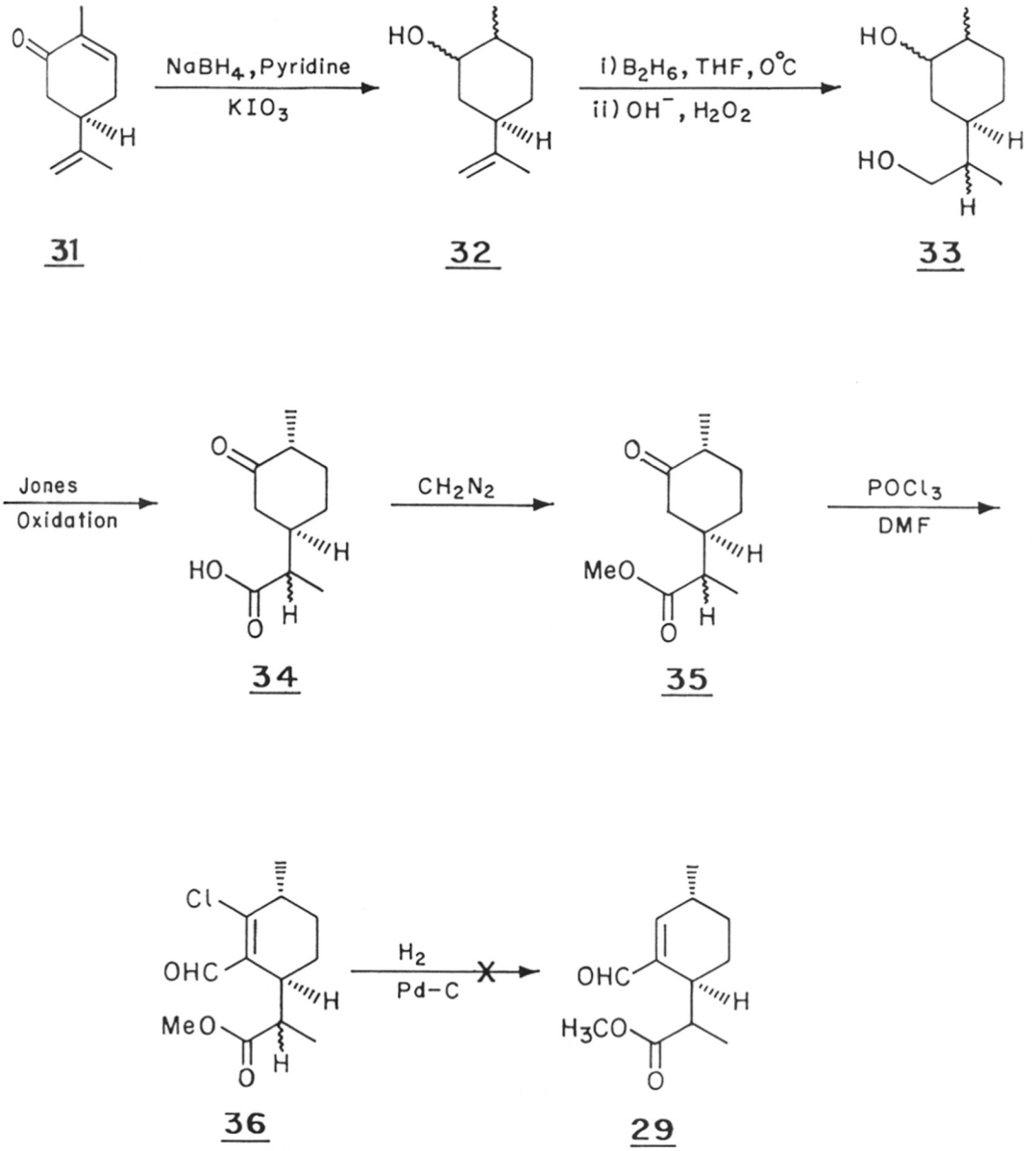


may be due to the protonation of the intermediate vinyllithium by diisopropylamine since the former is more basic than LDA. The olefin was identified by its PMR, IR and mass spectral data. PMR spectrum showed a multiplet between (0.09 - 1.1) ppm (6H) for the two methyls, a multiplet between (1.2 - 2.5) ppm (10H) for all methylene and methine protons, a singlet at 3.55 ppm for (3H, $COOCH_3$) and a multiplet between (5.2-5.6) ppm for olefinic protons. IR spectrum showed a strong absorption band at 1735 cm^{-1} for ester carbonyl and mass spectrum showed (m/e) at 182 (M^+).

Hence in order to get α,β -unsaturated aldehyde **29** another approach (Scheme-VII) was tried starting from carvone **31**.

(-)(R)Carvone **31** on reduction with sodium borohydride-pyridine complex[19] and subsequent work-up with potassium iodate gave the alcohol **32**. This alcohol was then hydroborated and subsequent oxidative hydrolysis gave the diol **33**. The diol on oxidation and esterification gave the keto ester **35** in which the methyl group and propionic residue were trans to each other, both being equatorial with respect to the ring. This was evident from its PMR spectrum which showed a doublet at 0.98 ppm (J=6Hz) and two doublets at 1.11 ppm (J=7Hz, J=7Hz) indicating both types of diastereomers at the asymmetric carbon α - to ester carbonyl. In addition, PMR spectrum showed a multiplet between (1.11 - 2.5) ppm (9H) for methylene and methine protons and singlet at 3.64 ppm for the ($-\overset{O}{\overset{\|}{C}}-OCH_3$) group of the ester. IR spectrum showed absorption bands at 1710 cm^{-1} and 1735 cm^{-1} for the two types of carbonyl and mass spectrum showed (m/e) peak at 198 (M^+).

SCHEME-VII



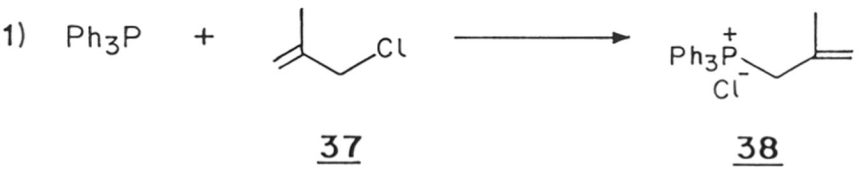
31 32 33 34 35 36 29

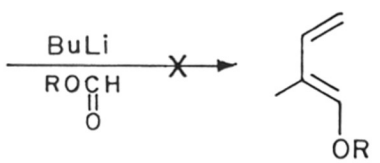
The keto ester **35** on treatment with phosphorus oxychloride-dimethylformamide complex[20] (Vilsmeier reagent) at 70°C for 2 hours gave the β-chloro α,β-unsaturated aldehyde **36**, PMR spectrum of which showed a triplet at 1.2 ppm for (6H), a singlet at 3.63 ppm (3H), (-$COOCH_3$) of the ester, a multiplet between (1.5-2.66) ppm (7H) for methylene and methine protons and a singlet at 9.26 ppm for aldehydic proton. IR spectrum showed absorption band at 1715 cm^{-1} for aldehydic carbonyl and an absorption band at 1740 cm^{-1} for ester carbonyl.

Trass et al.[21] reported reductive dehalogenation of β-chloro-α,β-unsaturated aldehyde without the saturation of the double bond using palladium on charcoal in methanol and using triethylamine as hydrogen chloride scavenger. All the attempts to achieve a similar conversion using the intermediate **36** were unsuccessful resulting only in the formation of the keto ester **35** (as a result of solvolysis and deformylation). Later it was found out that compound **36** on keeping in methanol underwent similar changes to give the keto ester **35**. Attempts to carry out the hydrogenation in other solvents were also unsuccessful. Also the attempts to reduce vinylic-chlorine with other reducing agents like zinc-silver couple[22] and zinc[23] did not effect the required conversion.

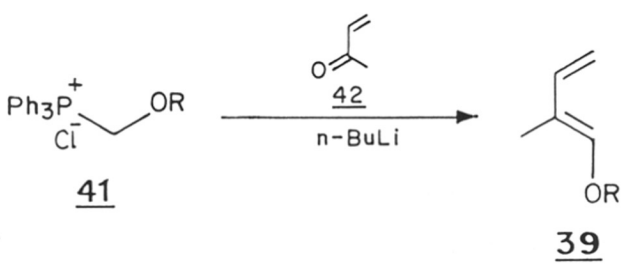
Since both the routes failed to give the αβ-unsaturated product **29**, the synthesis towards artemisinin via the enol ester was not pursued further.

SCHEME-VIII


1) Ph3P +
Cl
Ph3P
Cl
37
38


BuLi
ROCH
O
X
OR
39


2) ROH + CH2O + HCl
ROCH2Cl
Ph3P
40


Ph3P
Cl
OR
41
O
42
n-BuLi
OR
39

Another option was considered at this juncture, viz. making the diene more electron-rich to facilitate the Diels-Alder reaction. Butadienyl enol ethers possess a more electron-rich diene system compared to the corresponding enol esters due to the absence of carbonyl group. In order to study the feasibility of intramolecular Diels-Alder reaction on enol ether system a model compound **53** was prepared and studied under various conditions as earlier.

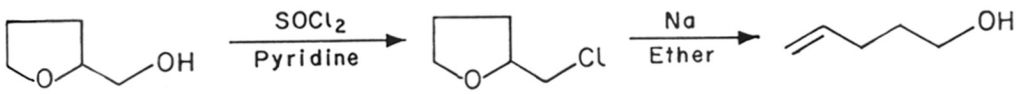
Attempts to prepare the model enol ether by Wittig olefination on formyl esters[24] as reported did not succeed. Also Wittig olefination[25] with triphenylphosphine salt of chloromethyl ether **41** of corresponding alcohol on methylvinyl ketone resulted in a very low yield, (Scheme-VIII).

Finally the enol ether **53** was prepared in moderate yields by transetherification[26] of 1-ethoxy-2-methylbutadiene **52** with 4-pentenol **45** in presence of mercuric acetate and sodium acetate.

4-Pentenol[27] **45** (Scheme IX) starting from furfuryl alcohol and 1-ethoxy-2-methylbutadiene[26] **52** (Scheme X) were prepared according to reported procedures.

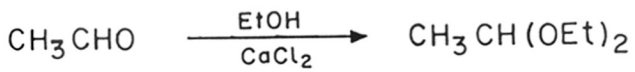
4-Pentenol on treatment with 1-ethoxy-2-methylbutadiene in presence of mercuric acetate and sodium acetate underwent transetherification to give the enol ether **53** (Scheme XI) which was characterised by its PMR spectrum which showed a multiplet between (1.11-1.4) ppm (2H) for homoallylic protons, a doublet at 1.66 ppm (J=2Hz) for the methyl on the double bond, a multiplet

SCHEME-IX

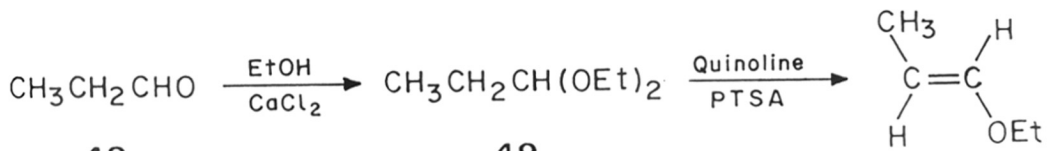


43 44 45

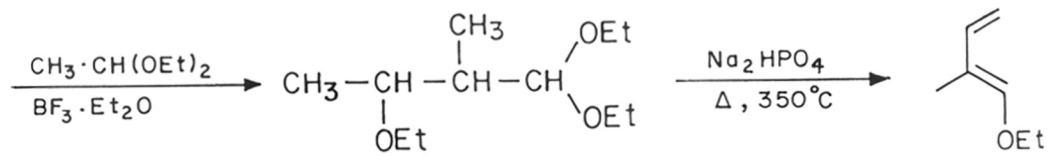
SCHEME-X



46 47

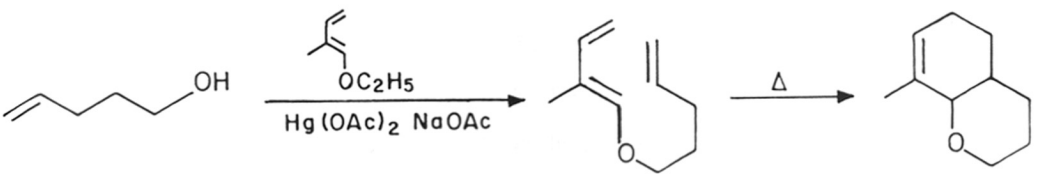


48 49 50



51 52

SCHEME-XI

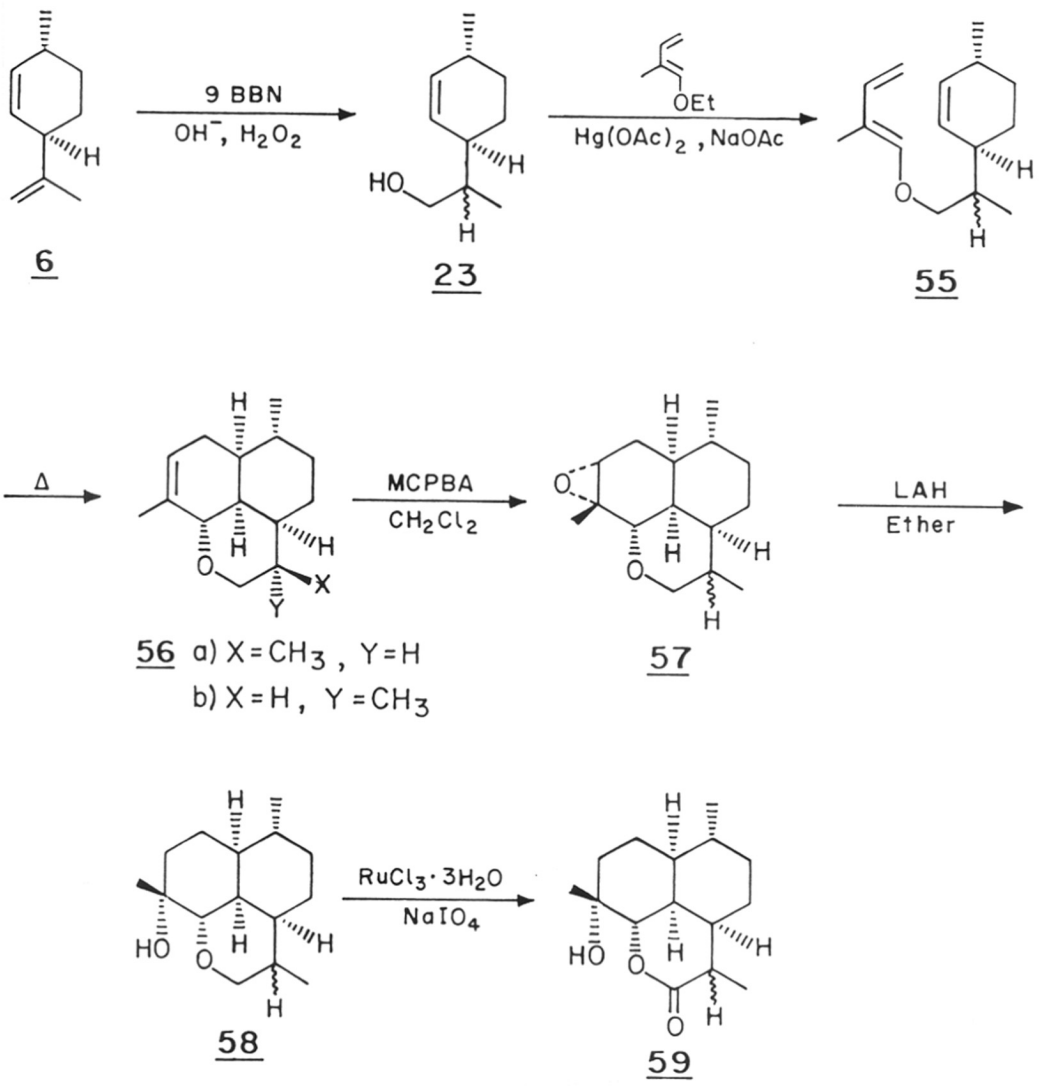


45 53 54

between (2 - 2.28) ppm (2H) for allylic protons, a triplet between (3.66 - 4) ppm for two protons (-O-$\underline{CH_2}$-), a multiplet between (4.5-5.22) ppm (4H) for terminal olefinic (=CH_2) protons, a multiplet between (5.22 - 6) ppm (1H) for the single olefinic hydrogen in the pentenol moiety, a quartet between (6.1-6.42) ppm for a proton on the C_3 carbon of butadiene part and a singlet at 6.17 ppm for a proton on the C_1 carbon of the butadiene (whereas the corresponding proton appeared at 7.2 ppm for the ester **19** in Scheme III). In addition, IR spectrum showed an absorption band at 1650 cm^{-1} for the diene system.

A very dilute solution (.01 M) of this triene (**53**) was prepared in different solvents like toluene, xylene, orthodichlorobenzene and heated to its reflux temperature as in the case of enol esters The reaction was monitored by TLC. When the triene was heated in orthodichlorobenzene (b.p. 180°C) for 72 hours it underwent Diels-Alder reaction to give the compound **54** in 25-30% yield. However, when the triene **53** was exposed to Lewis acid as well as cation-radical catalysed conditions as earlier, it resulted only in polymerisation. The Diels-Alder product was characterised by its PMR and mass spectra. PMR spectrum showed a multiplet between (1-2) ppm (9H), a doublet at 1.55 ppm (J=2Hz) for vinylic methyl, a multiplet in the range (3.2 - 3.55) ppm (2H) for methylene α to the oxygen atom, a multiplet between (3.85-4.1) ppm (1H) for the methine proton, α- to oxygen atom and a broad singlet at 5.3 ppm for the olefinic proton. IR spectrum showed the disappearance of the absorption

SCHEME-XII


9 BBN
OH⁻, H₂O₂
OEt
Hg(OAc)₂ , NaOAc
Δ
MCPBA
CH₂Cl₂
LAH
Ether
RuCl₃·3H₂O
NaIO₄
6
23
55
56 a) X=CH₃ , Y=H
b) X=H , Y=CH₃
57
58
59

band corresponding to the diene (1650 cm^{-1}) and mass spectra showed M^+ peak at 152.

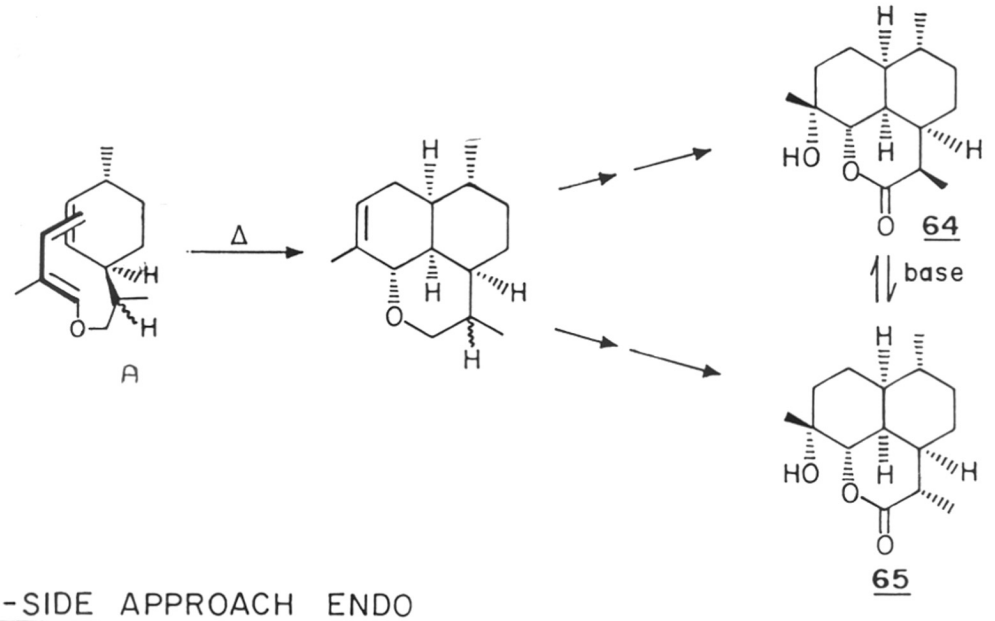
After achieving the intramolecular Diels-Alder reaction of the triene **53** thermally, the triene system required for the synthesis of the target molecule artemisinin was prepared by transetherifying the alcohol **23** from isolimonene with 1-ethoxy-2-methylbutadiene in presence of mercuric acetate and sodium acetate as earlier (Scheme-XII).

The PMR spectrum of the triene **55** (Fig. 2.7 showed a triplet at 0.9 ppm (6H) for two methyls, a multiplet between (1-2.3) ppm for (7H), a doublet at 1.7 ppm (J=2Hz, 3H) for the vinylic methyl, a multiplet between (3.55-3.9) ppm (2H) for the methylene protons adjacent to oxygen atom, a triplet between (4.72-5.13) ppm (2H) for olefinic methylene protons, a multiplet at 5.5 ppm for olefinic protons in the cyclohexane ring, a quartet between (6.1-6.44) for (1H) on C_3 carbon atom and an unresolved doublet at 6.2 for (1H) on C_1 atom of the butadiene moiety. Also IR spectrum showed an absorption band at 1640 cm^{-1} for the diene system.

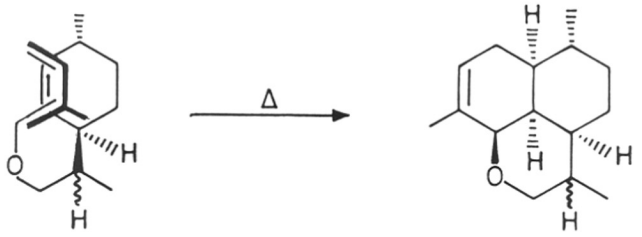
A 0.02 M solution of the triene **55** in benzene was heated in a sealed tube at 210°C for 72 hrs to give the desired Diels-Alder product in 25-30% yield. The TLC of the above product showed two closely moving spots which were separated by flash chromatography. The ^1H, ^{13}C NMR studies as well as mass spectra showed them to be two diastereomers **56a&b**. Considering the possible transition states in the Diels-Alder reaction (Scheme-XIII) the approach of the diene

SCHEME-XIII

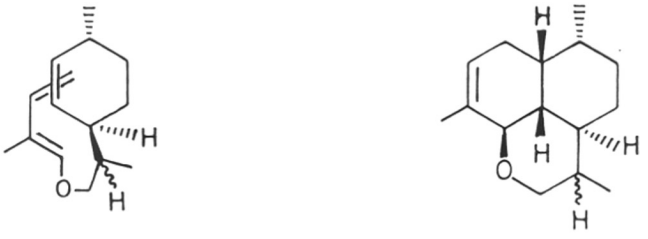
β-SIDE APPROACH EXO



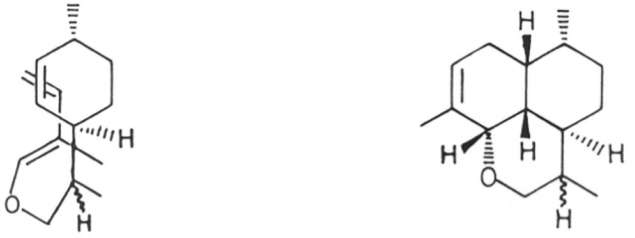
β-SIDE APPROACH ENDO



α-SIDE APPROACH EXO



α-SIDE APPROACH ENDO



from below the plane of the dienophile is not possible since the diene is attached to the isopropyl group which is β- to the cyclohexane ring. Also the endo attack is ruled out because of steric reasons; so the most favoured transition state will be A in which the diene approaches the dienophile from above the plane of the dienophile in an exo fashion. The diastereomers formed therefore is expected to be only due to the difference in configuration of methyl at the isopropyl carbon atom.

^{1}H NMR spectra of two diastereomers are shown in the Figs. 2.9 and 2.10. Fig. 2.9 shows a broad singlet between (5.15-5.36) ppm for one olefinic hydrogen on C_{10} carbon atom, a broad doublet between (3.75-4.1) ppm for one allylic methine proton on C_{12} carbon atom and a multiplet of seven lines between (3.16-3.75) ppm for two methylenic protons on C_2 carbon atom of the ether **56(a)**. Since the methylene protons adjacent to the oxyen atom are not equivalent, they couple themselves (geminal coupling) and also with the methine proton on C_3 carbon atom giving rise to a multiplet. The multiplicity of seven lines can be explained as follows: Thre three lines coming at a high field (3.16-3.4) ppm are due to one of the methylene proton for which the vicinal coupling constant (11 Hz) is equal to the geminal coupling constant. The remaining four lines are due to the other methylene proton for which the vicinal coupling constant (6.2 Hz) is much less than the geminal coupling constant (11 Hz). This can be explained by considering the model in which the methyl group is in the equatorial position which can give rise to two different

dihedral angle between the methylene and methine protons on C_2 and C_3 carbon atoms and hence two coupling constants J=11Hz, J=6.2Hz. The coupling constant 11Hz observed is similar to vicinal coupling constant that can be expected between two diaxial protons. In this spectra the signals corresponding to the methyl on C_3 carbon atom and on C_7 carbon atoms appears between (0.7-0.9) ppm whereas the vinylic methyl comes at 1.65 ppm. All other protons appear as multiplet between (0.7-2.35) ppm.

Fig. 2.10 shows the spectrum of other diastereomer. Here the methylene proton signals on C_2 carbon atom is quite different from the above spectrum. Here the methylene protons show only six lines. By considering the coupling cosntants, this can be divided into two groups - one consists of two signals between (3.45-3.65) ppm and the other consists of four signals between (3.7-4.1) ppm. This is because the high field proton does not show any vicinal coupling whereas the low field one showed a small vicinal coupling of the order of 2.65 Hz. This in turn means the high field methylene proton makes a dihedral angle closer to 90°C with the methine proton on C_3 carbon atom. This splitting pattern of methylene proton is quite different from what is expected (from models) when the methyl group at C_3 carbon is axial. These observations imply a twist for the tetrahydropyran ring from the expected chair conformation which is probably due to steric reasons. In this spectra the signals corresponding to the methine proton on C_{12} carbon atom is merging with the low field signals of the methylene protons on C_2 carbon atom. The signal

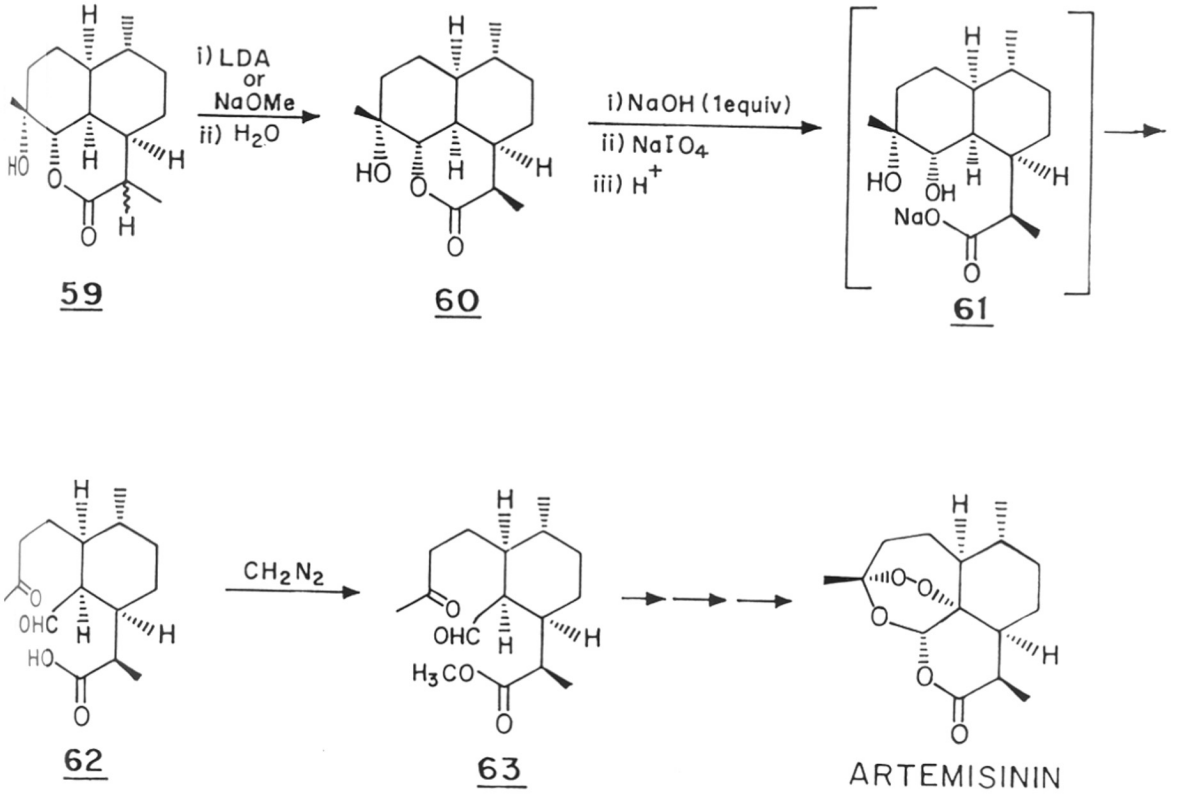
corresponding to methyl on the C_3 carbon atom comes at 1.15 ppm compared to the other diastereomer where it appears at 0.8 ppm.

The ^{13}C spectra of the diastereomers also show the changes in the chemical shifts of the ring carbons as expected. The ^{13}C chemical shifts of the diastereomer **56(a)** are 132.29(C), 121.19(CH), 71.38(CH), 69.47(CH_2), 42.00 2(CH), 38.62(CH), 34.63(CH_2), 33.92(CH), 28.84(CH), 26.25(CH_2), 19.36(CH_3), 18.98(CH_2), 17.61(CH_3), 12.70 (CH_3). The ^{13}C chemical shifts for the diastereomer **56(b)** are as follows: 132.59(C), 121.05(CH), 72.51(CH), 69.27(CH_2), 41.62(CH), 39.79(CH), 36.17(CH), 35.01(CH_2), 34.04(CH), 28.86(CH), 26.26(CH), 26.07(CH_2), 19.36(CH_3), 18.26(CH_3), 17.51(CH_3).

It can be seen that for the diastereomer **56(a)**, a methyl group and a methylene group resonates respectively at 12.70 and 18.98 ppm. Such upfield shifts are characteristic of gamma-gausche interactions. In this diastereomer eventhough the methyl group is equatorial, there is a likelihood of such interactions with the gamma methylene carbon (C-5).

Attempts to hydroxylate the double bond of the Diels-Alder product (mixture of diastereoisomers) at the tertiary carbon atom by treating it with mercurry(II)acetate[28] in aqueous tetrahydrofuran and subsequent reduction of the resulting mercurial intermediate by alkaline sodium borohydride solution (oxymercuration-demercuration) did not succeed. However, the alcohol **58** was obtained in good yield

SCHEME-XII (Contd.)



by epoxidation of the double bond in (**56**) with m-chloroperbenzoic acid in dichloromethane (to give the epoxide **57**) and subsequent reduction of **57** with lithium aluminium hydride in ether. The alcohol **58** was characterised by its PMR spectrum which showed a triplet at 0.85 ppm for (6H) for two secondary methyl groups, a singlet at 1.15 ppm (3H) for the tertiary methyl, a multiplet between (1 - 2.25) ppm for (13H) and a multiplet between (3.15-3.95) ppm for three protons on the carbon atoms attached to the oxygen atom. IR spectrum also showed an absorption at 3450 cm^{-1} for (-OH) group. From models it was clear that this epoxidation could occur from the α-face of the Diels-Alder adduct. It was proved from the periodate cleavage done subsequently (see below) after oxidation to lactone **59** and also from the X-ray data of lactone **59** that the configuration of the alcohol **58** is as shown in the Scheme-XII. The CH_2 group α to the ring oxygen in **58** was oxidised with sodium metaperiodate in presence of a catalytic amount of ruthenium trichloride[29] in a solution of carbontetrachloride-acetonitrile-water in the ratio of 1:1:1.5. This oxidation gave a mixture of diastereomers which were separated by column chromatography.

The ^1H NMR spectrum of the isolated diastereomeric lactones are shown in the Fig. 2:13 and 2:14. The striking features of this spectra are the nature and position of the methine proton α to the carbonyl group. In Fig. 2.13, the methine proton on C_3 carbon atom showed a multiplet centered at 2.25 ppm consists of 8 lines (doublet of quartet) J=9Hz, J=3Hz. Only the six lines of the multiplet can

be clearly seen since it is merging with the signal corresponding to the methine proton on ^{13}C carbon atom. In the spectrum of the other diastereomer (Fig. 2.14) the methine proton α -to the carbonyl group showed up as a quintet centred at 2.7 ppm, J=12Hz. In the former case the methine proton α to the carbonyl (i.e. proton on C_3 carbon atom) has two different vicinal coupling, i.e. one with the methyl protons (7Hz) and the other with the proton on the C_4 carbon atom (J=3Hz). In the latter case the magnitude of the vicinal coupling is same J=5Hz, resulting in five lines. This change in the splitting pattern is obviously due to the change in the dihedral angle. Here the J value observed is typical of vicinal coupling constant between an axial and equatorial protons. By studying the model such a situation can be envisaged by considering the methyl group in the equatorial position.

The methyl group in the axial position may not give rise to a stable chain conformation due to steric reasons, and hence the molecule may try to relieve the strain by changing into a quasi-chair form. [Such a change in the conformation is not possible when the methyl is in the equatorial position, since it will lead to a more unstable system].

In fact X-ray data showed that the diastereomer corresponding to the Fig. 2.14 prefers to exist in the quasi-chair form. In such conformation the dihedral angle between the two methine protons on C_3 and C_4 atoms may give rise to small coupling constant (J=3Hz). Change in the chemical shift of the methine proton α- to the carbonyl

group from 2.7 in the chair conformer to 2.25 in the quasi-chair conformer might be due to an effect or effects accompanying the change in the conformation. Apart from these major difference one can also see a small change in the chemical shifts of the methyl group from 1.31 to 1.22 ppm. Also the chemical shifts of the methine proton on C_{12} changes from 4.23 to 4.32 ppm. The ^{13}C chemical shifts for the diastereomer corresponding to the Fig. 2.14 are as follows: 18.64(CH_3), 20.04(CH_3), 21.79(CH_2), 27.43(CH_3), 28.11(CH_2), 29.72 (CH_2), 32.01(CH_2), 34.70(CH), 34.76(CH), 40.19(CH), 42.16(CH), 42.39 (CH), 70.60(C), 80.29(CH), 175.56(C=O). The ^{13}C chemical shifts for the other isomer shows corresponding signals at 13.18, 19.85, 22.11, 22.77, 27.35, 29.56, 32.55, 34.85, 37.21, 39.23, 40.32, 43.17, 70.56, 80.83, 174.99.

The diastereomer in which the methyl is in the axial position was converted to the other diastereomer with methyl in the equatorial position by treating it with sodium methoxide.

Attempts to cleave the lactone with sodium methoxide to afford dihydroxyester did not succeed. Although the lactone was saponified with alkali, neutralisation and work up resulted in the recovery of **59** as a result of facile relactonisation. Attempts to prepare the methyl ester by alkylation of the potassium salt with methyl iodide in hexamethylphosphoramide also resulted in the recovery of the lactone.

Treatment of the lactone **59** with transesterification catalyst titanium tetraisopropoxide in isopropanol, with methanol and triethyl-amine[35], with trimethylsilyl iodide[32] and with borontribormide[33]

resulted in a mixture of products instead of ring-opened ester. Finally the lactone **60** was converted to the keto aldehyde **62** by hydrolysis with exactly one equivalent of sodium hydroxide in situ oxidative cleavage of the diol carboxylate with sodium metaperiodate,[34] and neutralisation with dilute acid. The compound **62** was converted to its methyl ester (**63**) by treating it with diazomethane in ether.

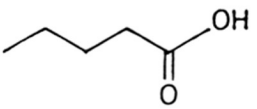
Its PMR spectrum showed a doublet at 0.96 ppm (J=5.7Hz, 3H), for the methyl on the C_6 carbon atom, a doublet at 1.15 ppm (J=7Hz, 3H) for the methyl on the C_2 carbon atom, a singlet at 2.1 ppm (3H) for three protons on C_{12} carbon atom, a singlet at 3.66 ppm (3H) for the methyl ester, a multiplet between (1-3) ppm for 13H and a doublet at 9.96 ppm for aldehyde proton. IR spectrum showed a broad, absorption band between 1700-1735 cm^{-1} and mass spectrum showed M^+ peak at 281 (M^+ +1).

As the conversion of **63** into artemisinin was earlier reported,[1] our new synthesis of **63** in effect constitutes one of the shortest and highly stereoselective syntheses of artemisinin.

EXPERIMENTAL

2.2.0 EXPERIMENTAL

Preparation of 4-Pentenoic Acid 15

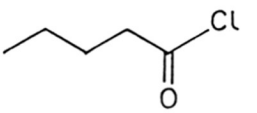


4-Pentenoic acid was prepared according to the reported procedure[4] by a three step synthesis starting with diethyl malonate and allyl bromide.

B.P. : 91°C/17 mm (lit.[4] b.p. 83-84°C/12 mm)

PMR ($CDCl_3$) δ : 2.33 (m, 4H), 4.76-5.11 (m, 2H), 5.24-6 (m, 1H).

Preparation of Pentenoyl Chloride 16

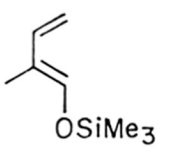


To a mixture of 4-pentenoic acid (10 g, 0.1 mole) and pyridine (7.9 g, 0.1 mole) cooled to 0 - -5°C, thionyl chloride (11.9 g, 0.1 mole) was added very slowly. The reaction mixture was stirred at room temperature overnight. Dry ether was added and the precipitated pyridine hydrochloride was separated by filtration. The pentenoyl chloride was purified by fractional distillation.

Yield: 8.2 g (74%)

B.P. : 127°C (lit.[36] b.p. 128°C)/760 mm.

Preparation of 2-Methyl-1-(Trimethylsilyloxy)butadiene[5] 18



Zinc chloride (250 mg) was added to triethylamine (23 g, 0.22 mole) and the mixture was stirred for 1 hr. at room temperature

until the salt was suspended in the amine. A solution of 2-methyl-but-2-en-1-al (Tiglaldehyde) (8.4 g, 0.1 mole) in benzene (30 ml) was added to the suspended salt in triethylamine followed by chloro-trimethyl silane (25.3 ml, 0.20 mole). After stirring at room temperature (28°C) for 30 min. the reaction mixture was stirred at 40°C overnight. After cooling the reaction mixture, dry ether was added to precipitate out triethylamine hydrochloride. Then it was filtered and concentrated. 2-Methyl-1-trimethylsilyloxybutadiene was purified by repeated distillation.

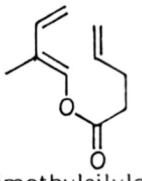
B.P. : 135°C/760 mm

Yield: 7.5 g (50%).

PMR ($CDCl_3$) δ : 0.16 (s, 9H), 1.61 (d, J=2Hz, 3H), 4.6-5 (m, 2H), 5.86-6.36 (q, 1H), 6.23 (s, 1H)

IR (neat) : 1640 cm^{-1}.

Preparation of 1-(Pent-4'-en acyloxy)-2-methylbutadiene 19



2-Methyl-1-trimethylsilyloxybutadiene (3.23 g, 0.02 mole) was dissolved in tetrahydrofuran (30 ml) and introduced into a two necked 100 ml flask flushed with nitrogen. A speck of bipyridyl was added as an indicator which gives a dark red colour in presence of alkyllithium. 1.66 M butyllithium (12 ml, 0.02 mole) was added to the silyloxyether at room temperature and the colour of the reaction mixture turned dark red showing the presence of alkyllithium. Stirring was continued until the dark red colour of the reaction

mixture faded to light yellow showing the absence of alkyllithium. Lithium enolate thus prepared was cooled to -78°C and pentenoic acid chloride (2.37 g, 0.02 mole) was added. After stirring for 30 min. at -78°C the reaction mixture was quenched with saturated NH_4Cl solution, extracted with petroleum ether thoroughly and the petroleum ether layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure.

The enol ester **19** formed was further purified by passing through a column of silica gel (TLC grade) loaded on sintered funnel and eluting with petroleum ether under suction so as to reduce the time of contact of the ester with silica gel. The petroleum ether solution thus obtained was concentrated under reduced pressure to give enol ester **19.**

Yield : 2.1 g (60%)

PMR ($CDCl_3$)δ: 1.82 (d, J=3Hz, 3H), 2.31-2.5 (m, 4H), 4.9-5.35 (m, 4H), 5.66-6.0 (m, 1H), 6.22-6.5 (q, 1H), 7.2 (s, 1H).

IR (neat) : 1750, 1640 cm^{-1}.

Diels-Alder Reaction under Thermal Condition

The triene (**21**) (0.166 g, 1 mmole) was dissolved in a mixture of toluene (50ml) and pyridine (3 ml) and refluxed under nitrogen atmosphere in presence of catalytic amount of hydroquinone (to prevent polymerisation). The reaction was monitored by TLC. The reaction was repeated in different solvents like xylene, orthodichlorobenzene, tetralin etc. Below 200°C on prolonged heating the triene

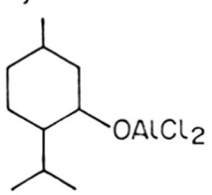
underwent polymerisation and above 200°C (i.e. when heated in tetralin) the polymerisation was fast.

Preparation of Ethylaluminium dichloride[8] $EtAlCl_2$

$$CH_3CH_2AlCl_2$$

To a suspension of aluminium chloride (13.3 g, 0.1 mole) in n-hexane (20 ml) a solution of diethylaluminium chloride (12.0 g, 0.1 mole) in n-hexane (20 ml) was added slowly. The reaction mixture was stirred until most of the aluminium chloride dissolved. Then the reaction mixture was filtered through a sintered funnel under nitrogen atmosphere to give a solution of ethylaluminium dichloride (25.4 g) in 40 ml of hexane (theoretical).

Preparation of Menthoxyaluminium Chloride[9]



To a solution of ethylaluminium chloride (12.75 g, 0.1 mole) in n-hexane (20 ml) taken in a two necked flask flushed with nitrogen, menthol (15.6 g, 0.1 mole) was added slowly at -78°C. After stirring at room temperature for 2 hrs, the hexane solution was concentrated, the white residue formed was crystallised from toluene.

M.P. 72-75°C

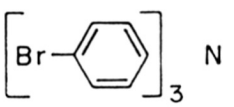
Yield: 15.25 g (60%).

Diels-Alder Reaction under Lewis Acid Catalysed Conditions[7]

The triene **21** (0.166 g, 1 mmole) was dissolved in dichloromethane (50 ml) and cooled to -78°C and borontrifluoride etherate (0.028 g, 0.2 mmole) in dichloromethane (3 ml) was added. Reaction was monitored by TLC. After stirring for 2 hrs, borontrifluoride etherate (0.113 mg, 0.8 mmole) in dichloromethane (12 ml) was added in 4 parts at an interval of 2 hrs at -78°C and monitoring by TLC. Even after the addition of 1 equiv. there was no change in the TLC. On raising the temperature to 0°C the triene **21** got polymerised. The experiment was repeated with other Lewis acids like $SnCl_4$, $AlCl_3$, $EtAlCl_2$, Et_2AlCl and menthoxyaluminium chloride without any success.

Preparation of Tris(p-bromophenyl)aminium hexachlorostibnate[11]

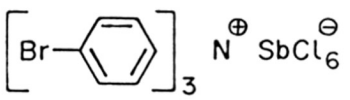
(a) Preparation of tris-p-bromophenylamine[11]



A solution of bromine (13 ml, 0.24 mole) in chloroform (50 ml) was added slowly to triphenylamine (19.6 g, 0.08 mole) dissolved in chloroform (50 ml) at 0°C. After addition the mixture was stirred at room temperature for 12 hrs. The chloroform was removed under reduced pressure and the residue was recrystallised from n-heptane.

M.P. : 145°C (lit.[11] m.p. 144.5-146.5°C).
Yield: 26 g (65%).

(b) Preparation of tris(p-bromophenyl) aminium hexachlorostibnate[11]



Tris(p-bromophenyl)amine (12 g, 0.0248 mole) was dissolved in dichloromethane (50 ml) and a solution of $SbCl_5$ (5 ml) in dichloromethane (50 ml) was slowly added. The deep blue mixture was poured in dry ether (100 ml). The blue precipitate was filtered and washed with dry ether and dried at room temperature under vacuum.

M.P. : 140°C (lit.[11] m.p. 141-142°C) decomp.

Yield : 16 g (80%).

Diels-Alder Reaction under Cation Radical Catalysis[10]

A solution of 1-(pent-4'-enacyloxy)-2-methylbutadiene (0.166 g, 1 mmole) in dichloromethane (20 ml) was treated with tris-(p-bromophenyl)aminium hexachlorostibnate (0.040 g, 0.05 mmole) under nitrogen atmosphere at -78°C. Reaction was monitored by TLC. Since there was no change, the temperature was slowly raised to 0°C. But on raising the temperature to 0°C, the triene underwent decomposition to give a complex mixture of products.

Preparation of Borane-dimethyl sulphide[13]

Borane-dimethyl sulphide solution was prepared by the procedure[13] reported for the preparation of borane-tetrahydrofuran solution. The borane was absorbed in dimethyl sulphide cooled to -78°C. The concentration of the borane in dimethyl sulphide was estimated

by measuring the hydrogen evolved during the hydrolysis of known volume of the solution as described below.

Standardisation of Borane-dimethyl sulphide Complex

Borane-dimethyl sulphide solution (1 ml) was diluted with tetra-hydrofuran to 10 ml under nitrogen atmosphere. Standardisation of borane-dimethyl sulphide solution was done according to the reported procedure,[13] by hydrolysing 1 ml of this diborane solution with a solution of glycerol, water and methanol mixture in the ratio of 1:1:1. The liberated hydrogen was measured with a gas burette. The molarity of hydride was calculated according to the following equation.

$$\text{Hydride molarity} = \frac{(P_i - P_{H_2O})\ 273 \times (V_{H_2})}{760\ (T)\ 22.4\ (V_A)}$$

Where T = temperature of water on the burette °K

P_i = atmospheric pressure

P_{H_2O} = vapour pressure of H_2O at T

V_{H_2} = volume of hydrogen liberated

V_A = volume of aliquot injected

Substituting the experimental values:

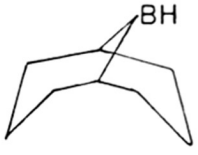
$$H^- \text{ molarity} \quad \frac{711 \times 273 \times 38.5}{760 \times 301 \times 22.4 \times 1} = 1.458$$

So the concentration of the borane dimethyl complex

$$= 1.458 \times 10 = 14.58$$

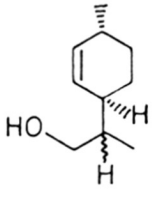
$$\therefore \quad \text{Borane molarity } [BH_3] = \frac{14.58}{3} = 4.86$$

Preparation of 9-Borabicyclo[3.3.1]nonane[13] (9-BBN)



A two necked flask (50 ml) fitted with a reflux condenser, a three way stopcock and a septum was flushed with nitrogen. Dimethyl sulphide-borane complex (4.8 M) (2.67 ml, 13 mmole) and tetrahydrofuran (5 ml) were introduced into the flask with syringe. The flask was cooled in a water bath, and 1,5-cyclooctadiene (1.406 g, 13 mmole) in tetrahydrofuran (5 ml) was added dropwise with stirring. The reaction mixture was stirred for 1 hr. at room temperature and refluxed for another 2 hrs. The solvent was removed by distilling under nitrogen atmosphere during which the solid 9-BBN separated out. This was used for the reaction without purification.

Preparation of Alcohol 21[13]



A solution of (1R, 4R)-trans- $\Delta^{2,8}$ menthadiene (1.496 g, 11 mmole) in tetrahydrofuran (15 ml) was introduced into a two necked 100 ml flask under nitrogen atmosphere. The 9-borabicyclo-[3.3.1]nonane (13 mmole) obtained from the above reaction was dissolved in tetrahydrofuran (15 ml) and added slowly in 1 hr. with stirring. The reaction mixture was stirred for another 2 hrs. Then

3M NaOH (6 ml) was added rapidly followed by slow dropwise addition of 30% H_2O_2 (6 ml) at a rate such that the temperature did not rise above 50°C. The reaction mixture was stirred at room temperature for 5 hrs. The aqueous phase was saturated with NaCl and extracted thoroughly with ether. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. The alcohol **21** was separated from cyclooctanediol by column chromatography over silica gel eluting with petroleum ether containing 6% ethylacetate as solvent.

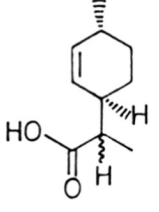
Yield : 1.2 g (75%)

PMR ($CDCl_3$) δ **:** 0.8-1 (m, 6H), 1-2 (m, 5H), 2-2.35 (m, 2H), 3.45-3.6 (m, 2H) and 5.5 (m, 2H). (Fig. 2.1)

IR (neat): 3350 cm^{-1} (-OH). (Fig. 2.2).

MS: (m/e) 154 (M^+).

Preparation of Acid 22



The alcohol **21** (1.2 g, 7.8 mmol) was dissolved in acetone (20 ml) and cooled to 0°C. Jone's reagent was added dropwise until orange brown colour of the reagent persisted. The reaction mixture was stirred for another 2 hrs. Ether (40 ml) was added to precipitate out the chromous salts. The reaction mixture was filtered and the residue was washed with ether. The organic layer was dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography over silica gel.

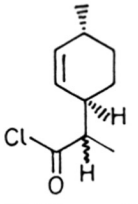
Yield : 0.780 g (62%)

PMR ($CDCl_3$) δ : 0.85 (d, J = 6.5Hz, 3H), 0.94-1.3 (dd, J = 6Hz, J = 6Hz, 3H), 1.5-2.35 (m, 7H), 5.45 (m, 2H). (Fig.2.3).

IR (neat): 3000 cm^{-1} (-C(=O)-OH), 1700 cm^{-1} -C=O. (Fig. 2.4).

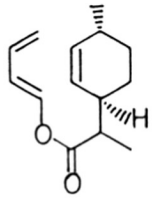
MS (m/e): 167 ($M^+ - 1$)

Preparation of Acid Chloride 23



To a solution of the acid **22** (0.33 g, 2 mmole) in dry ether (5 ml), pyridine (0.158 g, 2 mmole) was added and the reaction mixture was cooled to 0°C. A solution of thionyl chloride (0.238 g, 2 mmole) in dry ether (3 ml) was added slowly with stirring. The reaction mixture was stirred for 3 hrs. at room temperature. 10 ml of dry ether was added, filtered to remove pyridinium hydrochloride under dry conditions and concentrated to give 0.340 g of crude acid chloride which was used as such for next reaction.

Preparation of the Triene 5



The lithium enolate of the 2-methylbut-2-ene-al (Tiglaldehyde) (2 mmole) was generated as discussed earlier for the preparation of **21** and cooled to -78°C. The crude acid chloride (2 mmole)

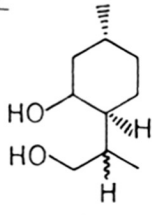
obtained from the above experiment was dissolved in tetrahydrofuran (5 ml) and added slowly to the enolate at -78°C with stirring. After stirring for another 30 min. the reaction mixture was quenched with NH_4Cl. The petroleum ether layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product thus obtained was further purified by passing through a column (2 inches) of silica gel (TLC grade) loaded on a sintered funnel and eluting it with petroleum ether under suction. The petroleum ether eluate was concentrated under reduced pressure to give the triene **5**.

Yield : 0.280 g (64%)

PMR ($CDCl_3$) δ : 1.02 (d, J = 7Hz, 3H), 1.33 (dd, J = 4Hz, J = 4Hz, 3H), 1.92 (d, J = 2Hz, 3H), 1-2.62 (m, 7H), 5.51-5.71 (m, 2H), 5.08-5.42 (t, 2H), 6.35-6.62 (q, 1H), 7.2 (s, 1H). (Fig. 2.5).

IR (neat): 1640, 1750 cm^{-1}. (Fig. 2.6).

Preparation of the Diol 25



The diol **25** was prepared according to a reported procedure[15] by hydroborating isopulegol (6.16 g, 0.04 mole) which on oxidative hydrolysis with alkaline hydrogen peroxide gave the diol **25**.

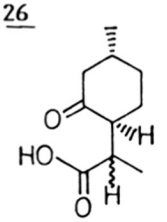
Yield : 4.5 g (66%)

PMR ($CDCl_3$) δ : 0.85 ppm (d, J=7Hz, 6H), 1-1.9 (m, 6H) 2.5 (s, 2H, D_2O exchangeable), 3.15-3.73 (m, 3H).

IR (neat): 3320 cm^{-1}.

MS (m/e): 172 (M^+).

Preparation of the Keto Acid 26



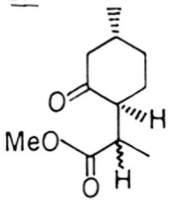
The diol **25** (4 g, 0.023 mole) was dissolved in acetone (50 ml) and was cooled to 0°C. To this solution Jone's reagent was added dropwise until the colour of the reagent persists. The reaction mixture was stirred at room temperature for another 2 hrs. The dissolved chromium salts were precipitated out by the addition of 60 ml of ether. The chromium salts were removed by filtration, and washed with ether. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. The keto acid **26** was purified by column chromatography over silica gel.

Yield : 2.5 g (60%).

PMR ($CDCl_3$) δ : 0.8-1.2 (m, 6H), 1.3-2.7 (m, 9H), 9.1 (s, 1H).

IR (neat) : 3100, 1700 cm^{-1}.

Preparation of Keto ester 27



An ether solution of acid **26** (2.0 g, 11 mmole) was treated with diazomethane (prepared from nitrosomethylurea (2 g) and 30% aquous KOH (6 ml). The reaction mixture was kept overnight to remove the excess diazomethane. The ether layer was concentrated and the keto ester was purified by chromatography over silical gel.

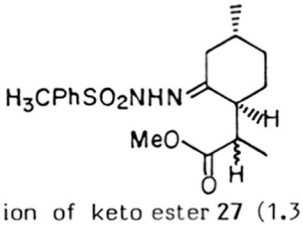
Yield : 1.5 g (70%)

PMR ($CDCl_3$) δ : 0.8-1.25 (m, 6H), 1.35-2.8 (m, 9H), 3.6 (s, 3H).

IR (neat) : 1710 (>C=O), 1740 ($\overset{O}{\overset{\|}{C}}$-$OCH_3$) cm^{-1}.

MS (m/e) : 198 (M^+).

Preparation of the Hydrazone 28



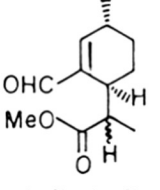
To a solution of keto ester **27** (1.3 g, 6.5 mmole) and pyridine (0.79 g, 10 mmole) in THF (10 ml), tosyl hydrazide (1.21 g, 6.5 mmole) was added. The reaction mixture was refluxed for 18 hrs. The solvent was removed under reduced pressure and the hydrazone was separated by column chromatography over silica gel.

Yield : 1.6 g (66%)

PMR ($CDCl_3$) δ : 0.65-1.25 (m, 6H), 2.0-2.8 (m, 10H), 2.35 (s, 3H), 3.65 (s, 3H), 7.1-7.4 (m, 2H), 7.65-7.9 (m, 2H).

IR (neat) : 1600, 1735, 3220 cm^{-1}.

Attempted Synthesis of α,β-Unsaturated Aldehyde 29



A two necked 50 ml flask fitted with a three way stop-cock and a septum was flame-dried and flushed with nitrogen. A solution

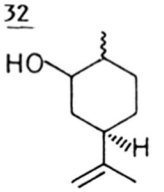
of diisopropylamine (0.889 g, 8.8 mmole) in tetrahydrofuran (10 ml) was introduced and cooled to 0°C. 1.6 M Butyllithium (5 ml, 8 mmole) was added slowly and the reaction mixture was stirred for 30 min. Tetramethylethylenediamine (20 ml) was added and the reaction mixture was cooled to -78°C. A suspension of tosylhydrazone (732 mg, 2 mmole) in tetramethylethylenediamine (5 ml) was added and the clear red solution thus formed was allowed to come to room temperature. When the evolution of nitrogen stopped, dimethylformamide (292 mg, 4 mmole) was added at 0°C and the mixture was stirred for 1 hr. The reaction mixture was quenched with NH_4Cl and the product was extracted with ehter. The ether layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. It was further purified by column chromatography over silica gel to get 80 mg of olefin **30**. The product was characterised by its PMR, IR and mass spectra.

PMR ($CDCl_3$) δ : 0.9-1.1 (m, 6H), 1.2-2.5 (m, 10H), 3.55 (s, 3H), 5.2-5.6 (m, 2H).

IR (neat) : 1735 cm^{-1}.

MS (m/e): 182 (M^+).

Preparation of Dihydrocarveol[19] **32**

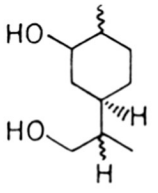


Dihydrocarveol was prepared from carvone according to the reported procedure[19] in 80% yield.

PMR ($CDCl_3$) δ : 0.66-1.11 (m, 3H), 1.66 (s, 3H), 1-2.1 (m, 8H), 2.9 (broad singlet, 1H), 4.56 (s, 2H).

IR (neat): 3400 cm^{-1}.

Preparation of the diol 33



Dihydrocarveol **32** (3.08 g, 20 mmole) in tetrahydrofuran (30 ml) was taken in a flame dried two necked (50 ml) flask under nitrogen atmosphere. Borane-dimethyl sulphide solution (4.86 M) (4.20 ml, 25 mmole) was added dropwise at 0°C. The reaction mixture was stirred at room temperature for another 2 hrs. The residual hydride was decomposed by the addition of water (5 ml) followed by rapid addition of 3M NaOH (20 ml). The flask was cooled to 0°C and hydrogen peroxide (30%) (20 ml) was added dropwise and reaction mixture was stirred for anotehr 4 hrs. at room temperature. The aqueous solution was saturated with sodium chloride and extracted thoroughly with ether. The combined ether layer was dried over anhydrous Na_2SO_4 and concentrated to give the diol **33**.

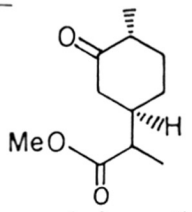
Yield : 2.9 g (85%)

PMR ($CDCl_3$) δ : 0.8-1.05 (m, 6H), 1-2 (m, 11H), 3.2-3.6 (m, 3H).

IR (neat) : 3320 cm^{-1}.

MS (m/e) : 172 (M^+).

Preparation of the Keto ester 35



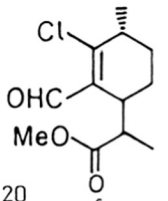
The keto ester **35** was prepared from the diol **33** by oxidising it with Jone's reagent and then esterifying with diazomethane as described earlier (for the conversion of diol **25** to **27**) in an overall yield of 50%.

PMR ($CDCl_3$) δ : 0.98 (d, J=6Hz, 3H), 1.11 (d d, J=7Hz, J=7Hz, 3H), 1.11-2.5 (m, 9H), 3.64 (s, 3H).

IR (neat) : 1710, 1735 cm^{-1}.

MS (m/e) : 198 (M^+).

Preparation of β-Chloro-α,β-Unsaturated Aldehyde 36



Vilsmeier reagent[20] was formed by the addition of $POCl_3$ (3.825 g, 25 mmole) to dimethylformamide (2.19 g, 30 mmole) at 0°C and stirring at room temperature for 30 min. The reaction mixture was again cooled to 0°C and keto ester **35** (1.97 g, 10 mmole) was added with stirring. After stirring at room temperature for 1 hr. the reaction mixture was heated to 70°C for 4 hrs. The reaction mixture was then cooled to room temperature, quenched with ice cold Na_2CO_3 solution, extracted with ether and dried over anhydrous Na_2SO_4 and distilled to give β-chloro-α,β-unsaturated aldehyde.

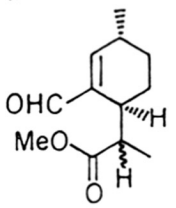
Yield : 1.5 g (65%)

B.P. : 112°C at 10 mm

PMR ($CDCl_3$) δ : 1 - 1.33 (m, 6H), 1.5-2.66 (m, 7H), 3.63 (s, 3H), 9.26 (s, 1H).

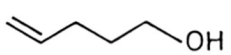
IR (neat) : 1715, 1740 cm^{-1}.

Attempted Synthesis of α,β-Unsaturated Aldehyde 29



Aldehyde **37** (1.2 g, 5 mmole) was dissolved in a mixture of methanol (15 ml) and triethylamine (2 ml) and hydrogenated at atmospheric pressure in presence of palladium on charcoal as catalyst. After 30 min. all starting material disappeared and a new spot was formed (TLC). After work-up the newly formed compound was characterised as keto ester **36** by comparing the PMR, IR and mass spectra with that of authentic sample. The reaction was repeated with ethyl acetate as solvent but was unsuccessful.

Preparation of Pentenol 45

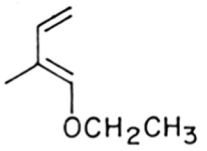


4-Pentenol was prepared from furfuryl alcohol by the reported procedure.[27]

B.P. : 134°C (lit.[27] b.p. 135-37°C).

PMR ($CDCl_3$) δ : 1.23-1.83 (m, 2H), 1.83-2.40 (m, 2H), 3.4-3.92 (t, J=6Hz, 2H), 4.15 (s, 1H, D_2O exchangeable), 4.8-5.2 (m, 2H), 5.4-6.13 (m, 1H).

Preparation of 1-Ethoxy-2-Methylbutadiene 52



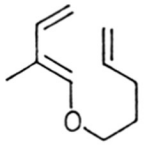
1-Ethoxy-2-methylbutadiene **52** was prepared by a reported procedure[26] in five steps starting with acetaldehyde and propionaldehyde;

B.P. : 145°C/760 mm.

PMR ($CDCl_3$) δ : 1.27 (t, J=7Hz, 3H), 1.72 (d, J=2Hz, 3H), 3.86 (q, J=7Hz, 2H), 4.75-5.04 (m, 2H), 6.13-6.44 (q, 1H), 6.22 (m, 1H).

IR (neat) : 1640 cm^{-1}.

Prepartion of the Enol ether 53



Mercuric acetate (0.265 g, 0.6 mmole) and sodium acetate (0.032 g, 0.39 mmole) was taken in a two necked flask (25 ml) flushed with nitrogen. A mixture of 4-pentenol (0.172 g, 2 mmole), 1.-ethoxy-2-methylbutadiene (0.896 g, 8 mmole) and a catalytic amount of hydroquinone was added and stirred for 3 hrs. at room temperature.

The reaction mixture was quenched by adding anhydrous K_2CO_3. Dry ether was added to precipitate out mercury salts and the reaction

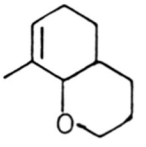
mixture was filtered and concentrated. The excess 1-ethoxy-2-methyl-butadiene was removed under reduced pressure. The enol ether **53** was further purified by flash chromatography over silica gel.

Yield : 0.180 g (62%).

PMR ($CDCl_3$) δ : 1.11-1.4 (m, 2H), 1.66 (d, J=2Hz, 3H), 2 - 2.28 (m, 2H), 3.66-4 (t, 2H), 4.5-5.22 (m, 4H), 5.22-6 (m, 1H), 6.1-6.42 (q, 1H), 6.17 (s, 1H).

IR (neat) : 1650 cm^{-1}.

Preparation of the Ether 54



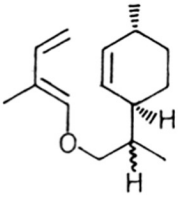
A solution of the triene **53** (0.152 g, 1 mmole) in orthodichlorobenzene (50 ml) was refluxed for 72 hrs. The orthodichlorobenzene was removed under reduced pressure and the residue was purified by column chromatography over silica gel by eluting with petroleum ether-benzene mixture.

Yield : 0.035 g (25%)

PMR ($CDCl_3$) δ : 1-2.2 (m, 9H), 1.55 (d, J=2Hz, 3H), 3.2-3.55 (m, 2H), 3.85-4.1 (m, 1H), 5.3 (broad s, 1H).

MS (m/e) : 152 (M^+).

Preparation of the Enol ether 55



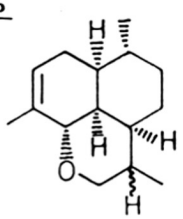
The alcohol **23** (0.308 g, 2 mmole) was transetherified according to the procedure discussed for the enol ether **53**.

Yield : 0.250 g (53%).

PMR ($CDCl_3$) δ : 0.9 (t, 6H, 1-2.3 (m, 7H), 1.7 (d, J=2Hz, 3H), 3.55-3.9 (m, 2H), 4.72-5.13 (t, 2H), 5.5 (m, 2H), 6.1-6.44 (q, 1H), 6.2 (m, 1H).

IR (neat): 1640 cm^{-1}.

Preparation of the Ether 56



The enol ether **55** (0.468 g, 2 mmole) was dissolved in a mixture of degassed dry benzene (100 ml) and dry pyridine (5 ml). A catalytic amount of hydroquinone was added to prevent polymerisation. This mixture was filled upto 3/4th of an ampule and sealed under nitrogen atmosphere. The sealed ampule was placed in a steel bomb and heated upto 210°C for 72 hrs. The solvent was then removed under reduced pressure. The residue on TLC showed two closely moving spots which were separated by flash chromatography over silica gel and characterised by their NMR (^{13}C & ^{1}H), IR and mass spectra. The two spots were found to correspond to the two diastereomers from its PMR, IR and mass spectra, (**56a** and **56b**).

PMR : see Fig. 2.9 and Fig. 2.10

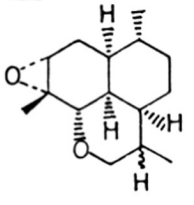
IR : see Fig. 2.11 and 2.12

MS (me/) : 220 (M^+) for both products

Attempt to prepare the Alcohol 58 by Oxymercuration - Demercuration

Mercuric acetate (0.320 g, 1 mmole) was added rapidly to a mixture of water (1 ml) and tetrahydrofuran (1 ml). An orange yellow suspension was formed immediately. After stirring for 15 min. the Diels-Alder product 56 (0.220 g, 1 mmole) was added and there was no immediate change in the colour of the reaction mixture. The mixture was stirred for 12 hrs. during which time the colour of the solution faded. To this 3M NaOH solution (1 ml) and a solution of $NaBH_4$ (20 mg, 0.5 mmole) in 3M NaOH (1 ml) was added. After stirring overnight the aqueous phase was saturated with NaCl and extracted twice with ether. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. But TLC did not show any change in the starting material.

Preparation of the Epoxide 57



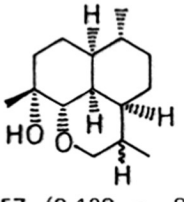
Diels-Alder product (0.110 g, 0.5 mmole, mixture of diastereomers) was dissolved in dichloromethane (3 ml) and cooled to 0°C. m-Chloroperbenzoic acid (MCPBA) (0.172 g, 1 mmole) was added slowly to the solution with stirring at 0°C. After 5 hrs. the excess MCPBA was decomposed by stirring with 10% sodium sulphite (3 ml) solution. The organic layer was washed successively with 5% aqueous $NaHCO_3$, water, followed by saturated sodium chloride solution.

The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give crude epoxide (0.120 g).

PMR ($CDCl_3$) δ : 0.8-2.2 (m, 17H), 2.9 (m, 1H), 3.45-3.85 (m, 3H).

IR (neat) : 755 cm^{-1}.

Preparation of the Alcohol 58



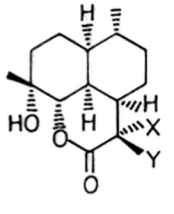
A solution of epoxide **57** (0.120 g, 0.5 mmole) in ether was added dropwise to lithium aluminium hydride (0.030 g, 0.75 mmole) in 5 ml of ether at 0°C. After the addition the reaction mixture was refluxed for 4 hrs. The excess hydride was decomposed by careful addition of saturated solution of sodium sulphate. After stirring for another one hour the ether layer was decanted, the solid residue was washed with ether, the ether layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatogrphy over silica gel.

Yield : 0.080 g (65%)

PMR ($CDCl_3$) δ : 0.85 (t, 6H), 1.15 (s, 3H), 1 - 2.25 (13H), 3.15-3.95 (m, 3H).

IR (neat) : 3450 cm^{-1}. (-OH).

Preparation of the Lactone 59



64) X=H Y=CH_3

65) X=CH_3 ,Y=H

The alcohol **58** (0.169 g, 0.5 mmole) was dissolved in a mxiture of CCl_4 (4 ml), CH_3CN (4 ml) H_2O (6 ml) and sodium metaperiodate (0.428 g, 2 mmole) was added. To this solution $RuCl_3 \cdot 3H_2O$ (5 mg) was added. The reaction mixture was stirred for 6 hrs. at room temperature. Dichloromethane (10 ml) was added and the two phases were separated. The aqueous layer was extracted three times with ether and the combined organic layer was dried over anhydrous Na_2SO_4 and purified by column chromatography over silica gel.

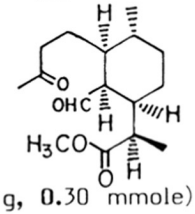
Yield : 0.130 g (71%)

PMR ($CDCl_3$) : see Fig. 13 and 14.

IR ($CHCl_3$): see Fig. 15.

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

Preparation of the Keto aldehyde 63



The lactone **60** (0.075 g, 0.30 mmole) was stirred with 0.1M solution of NaOH (3 ml) for about 12 hrs. The flask was then cooled to 0°C and $NaIO_4$ (0.070 g, 0.32 mmole) in water (3 ml) was added and stirred at 10-20°C for 12 hrs. $BaCl_2$ (100 mg) in water (2 ml) was then added to precipitate out the dissolved iodate. The reaction mixture was filtered through celite, the filtrate was acidified with dil. HCl, the aqeuous layer was saturated with NaCl and extracted with ethylacetate. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated. The crude acid **62** was taken in

ether and treated with ethereal solution of diazomethane until the colour of the reagent persists. The solvent was removed and the keto aldehyde **63** was purified by column chromatography over silica gel.

Yield : 0.050 g, (62%0

PMR ($CDCl_3$) δ : 0.96 (d, J=5Hz, 3H), 1.15 (d, J=7Hz, 3H), 1-3 (m, 13H), 3.66 (s, 3H), 9.96 (d, J=5Hz, 1H), 2.15 (s, 3H).

IR (neat): 1715, 1735 cm^{-1}.

MS (m/e): 281 (M^{+} +1).

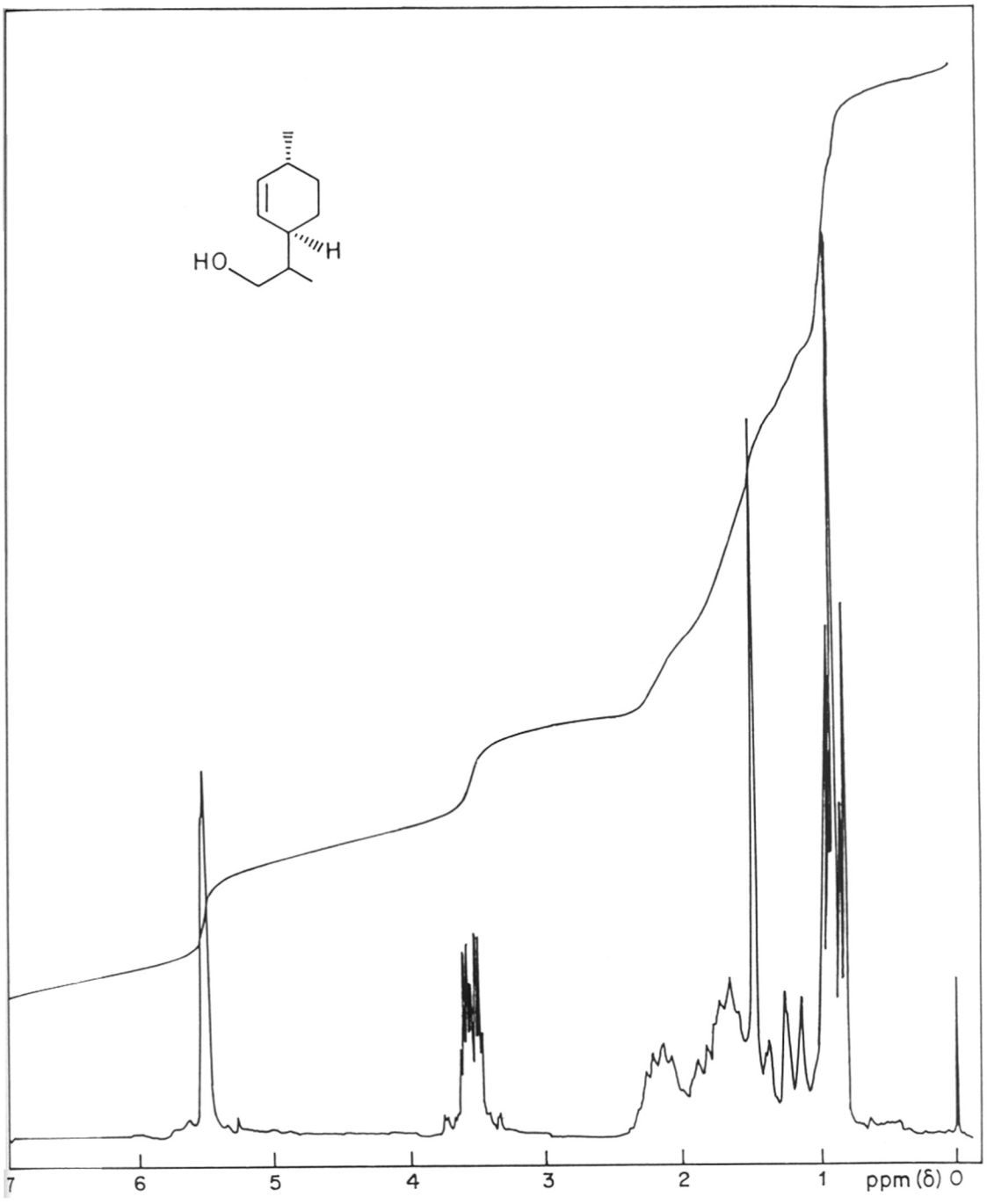


FIG. 2·1 : NMR OF THE ALCOHOL 21

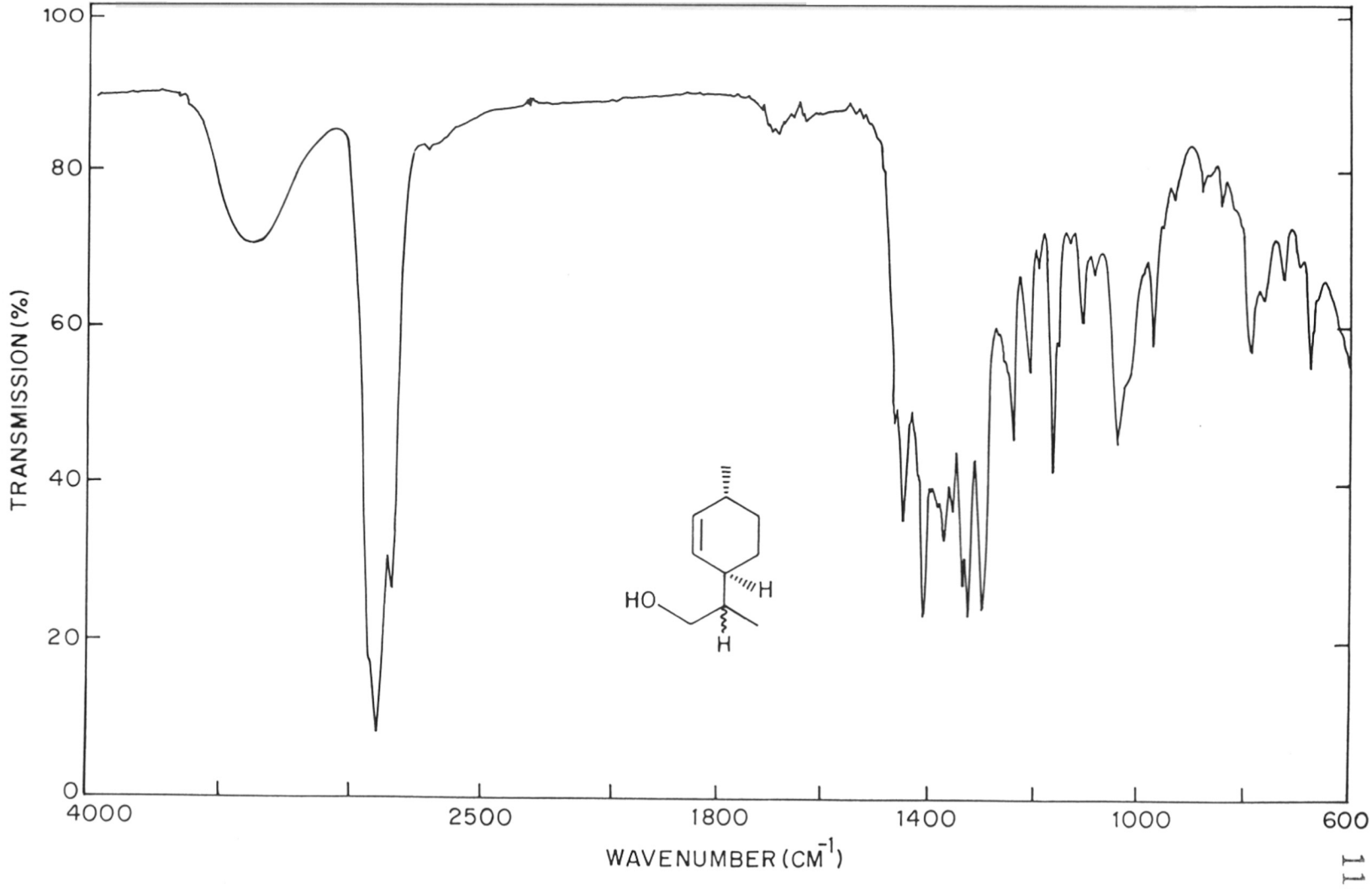


FIG. 2·2 : IR OF THE ALCOHOL 21

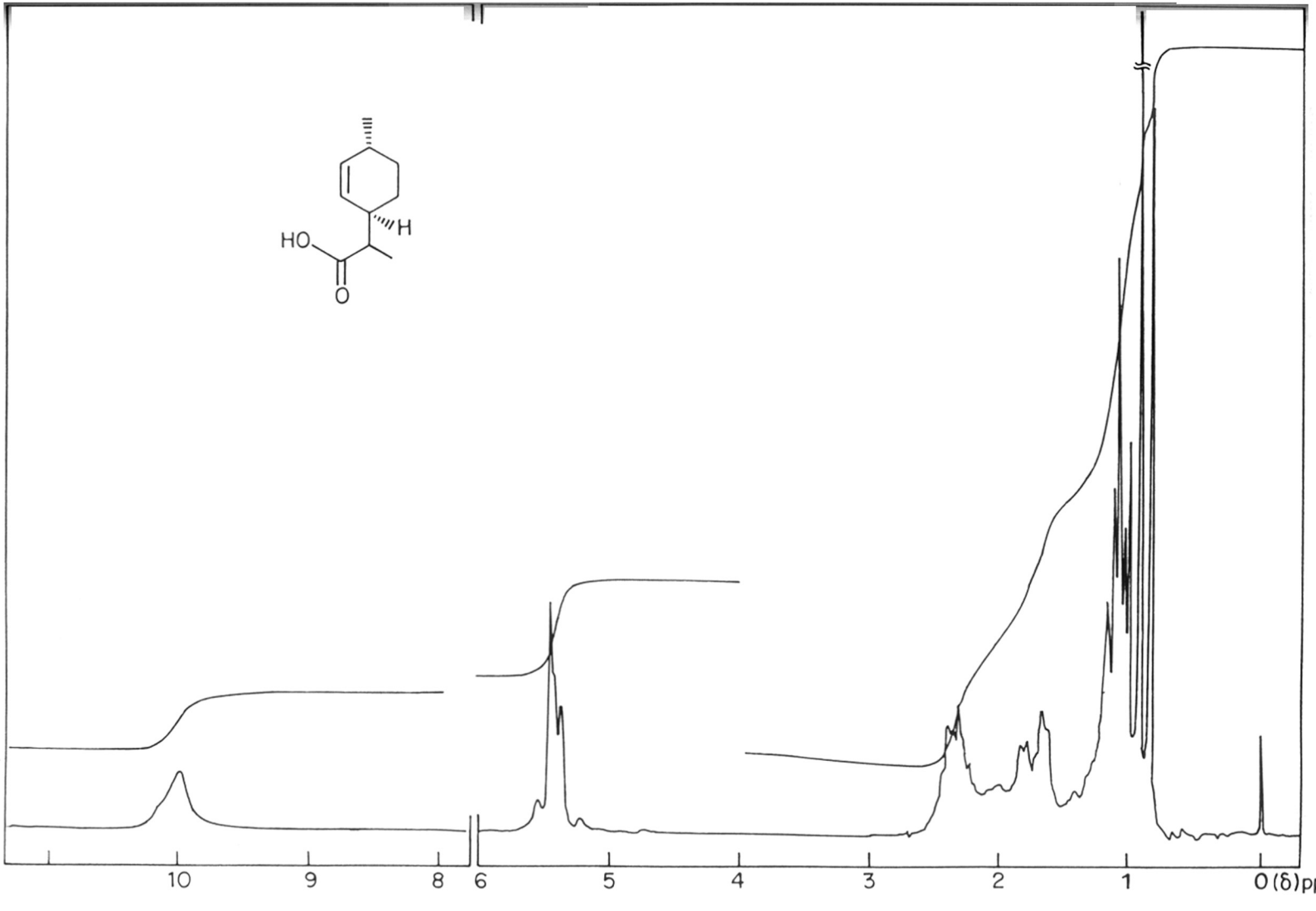


FIG. 2·3 : NMR OF THE ACID 22

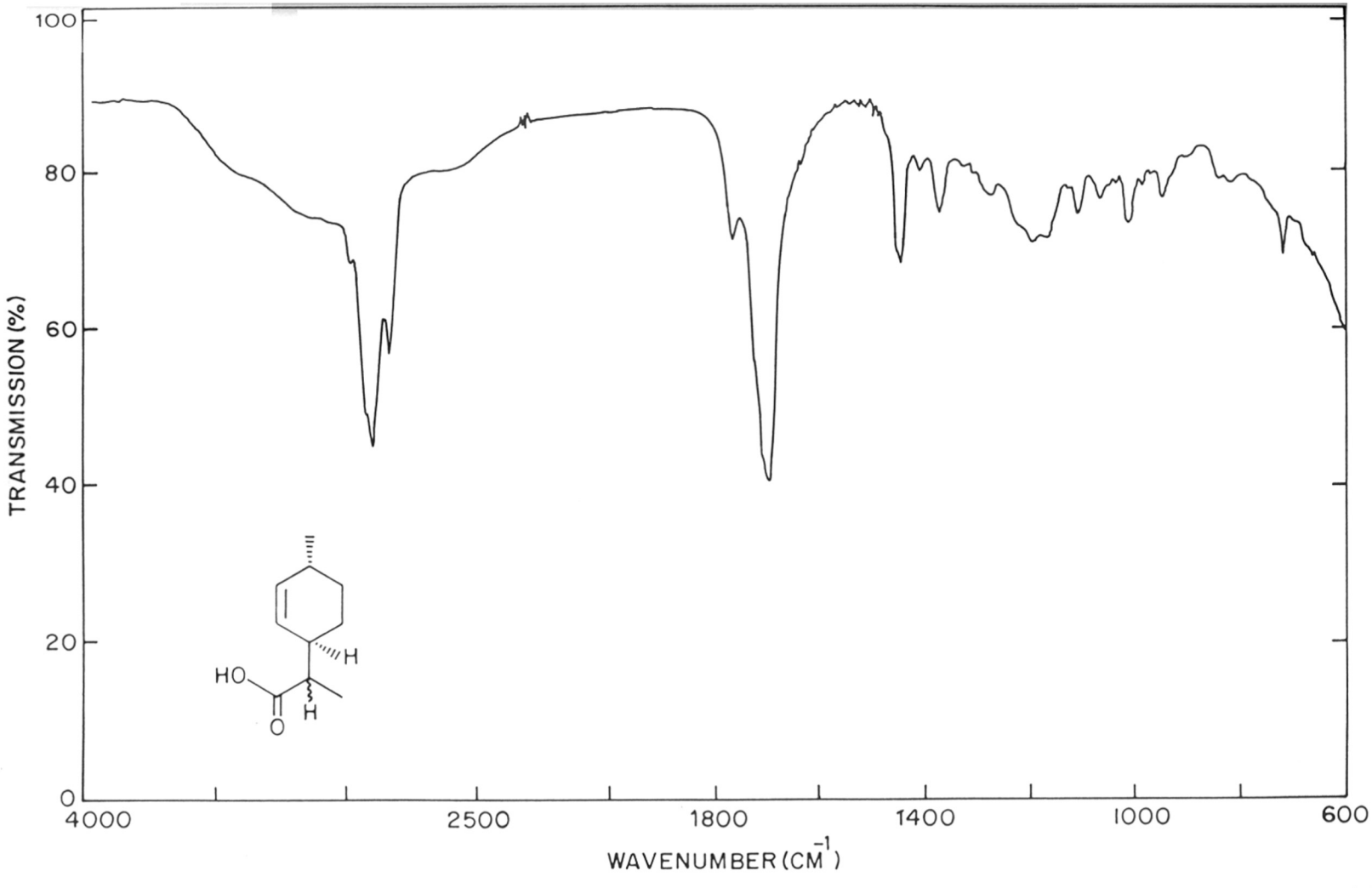


FIG. 2·4 : IR OF THE ACID 22

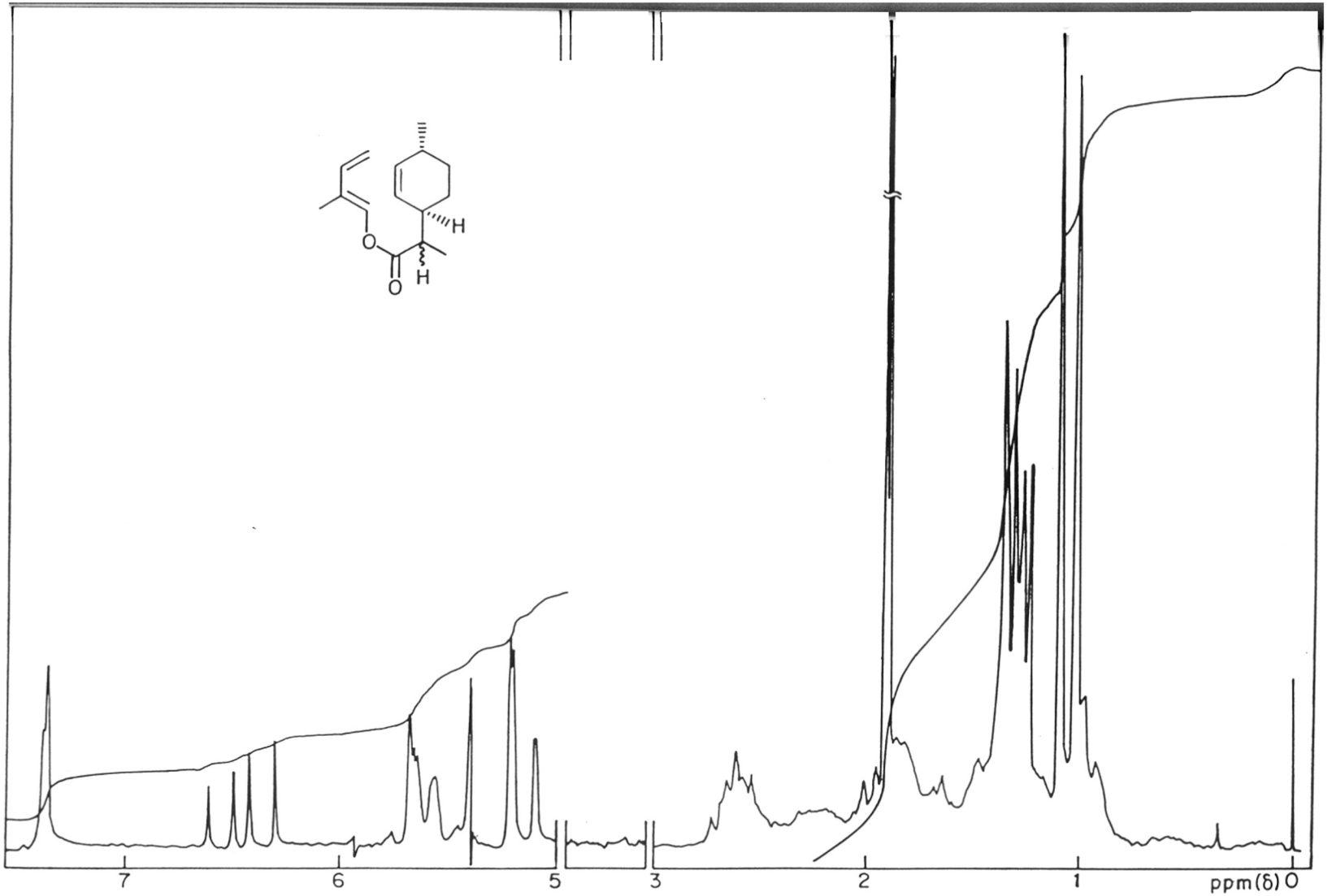


FIG. 2·5 : NMR OF THE ENOLESTER 5

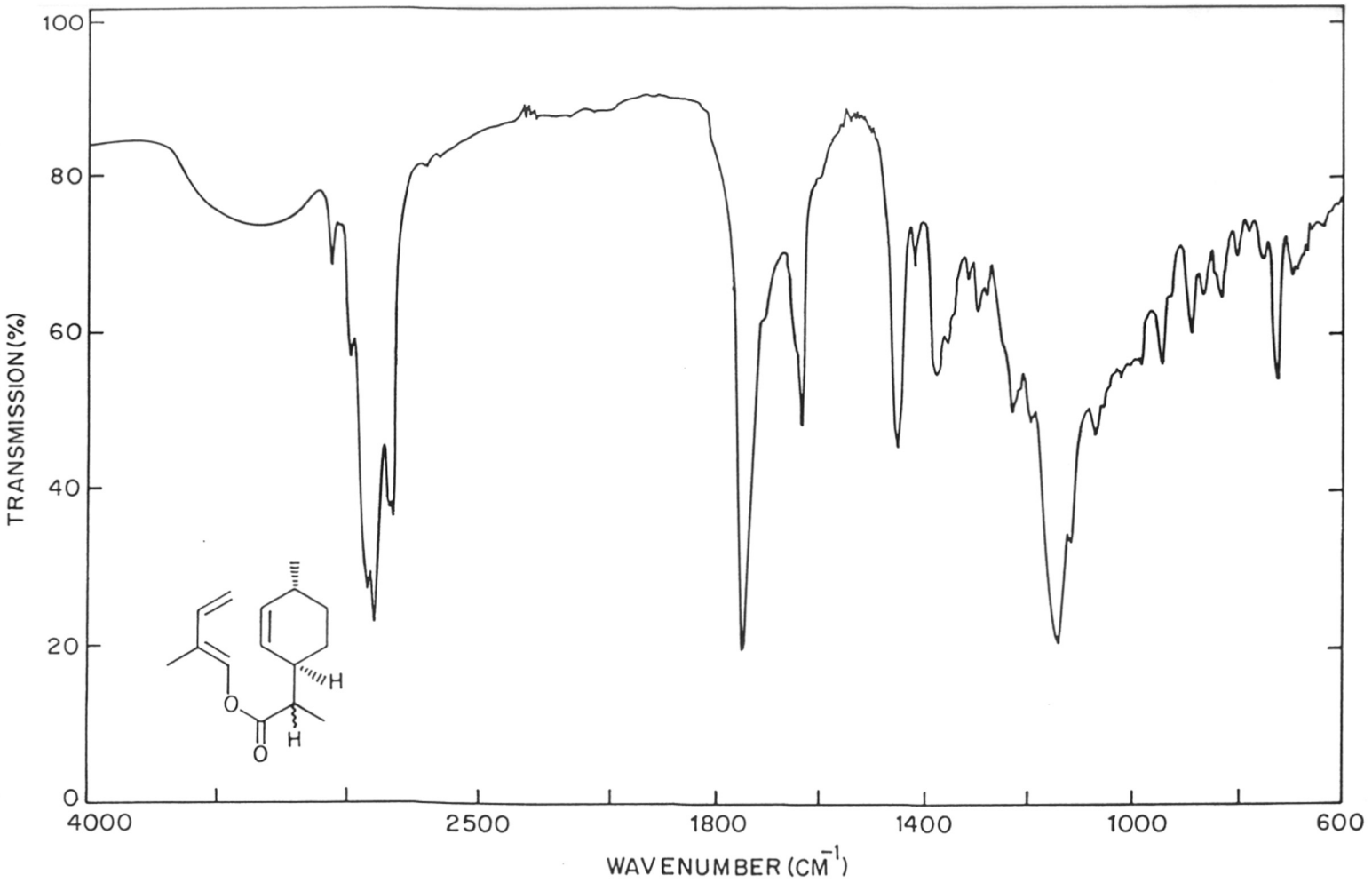


FIG. 2·6 : IR OF THE ENOL ESTER 5

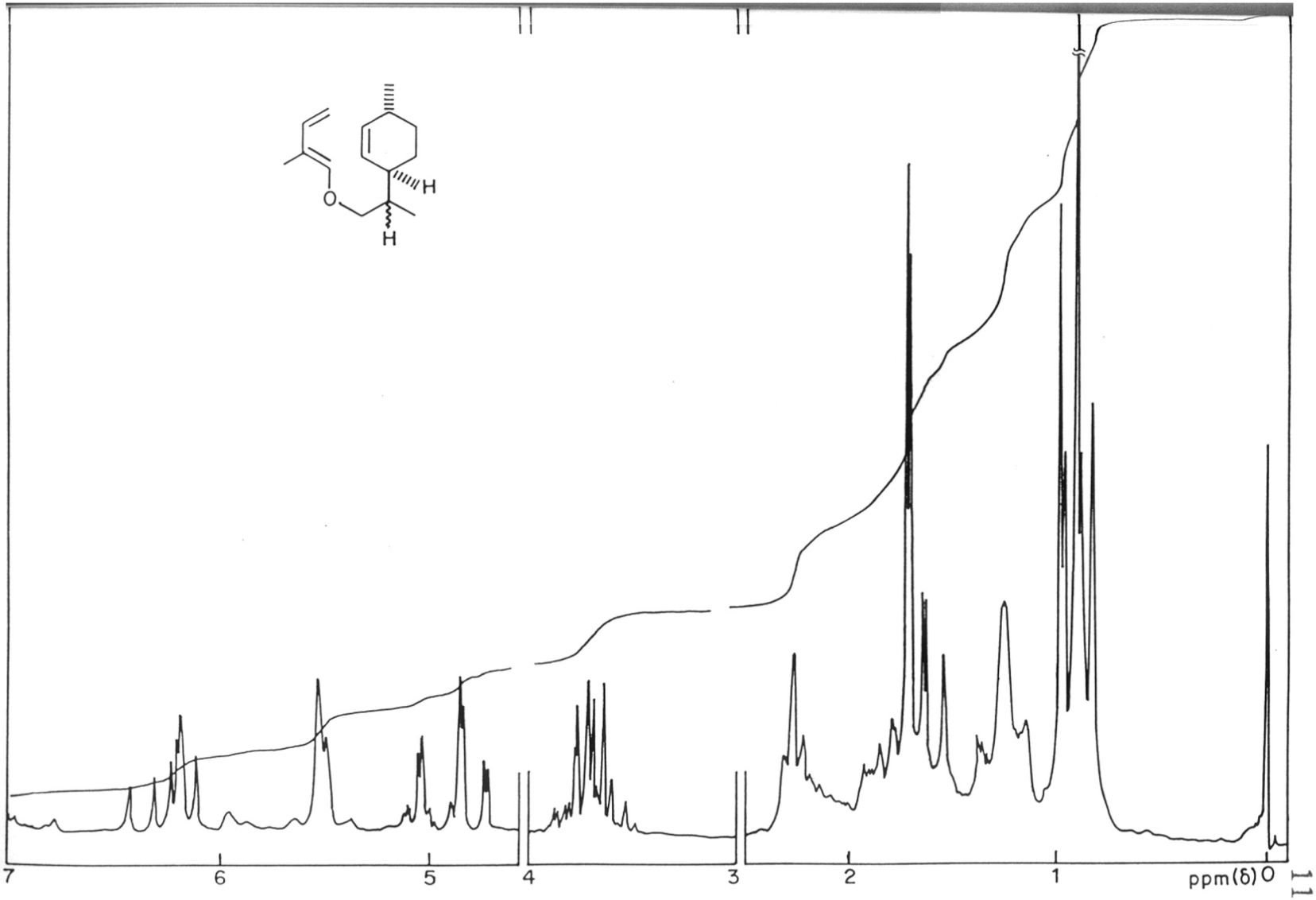


FIG. 2·7 : NMR OF THE ENOL ETHER 55

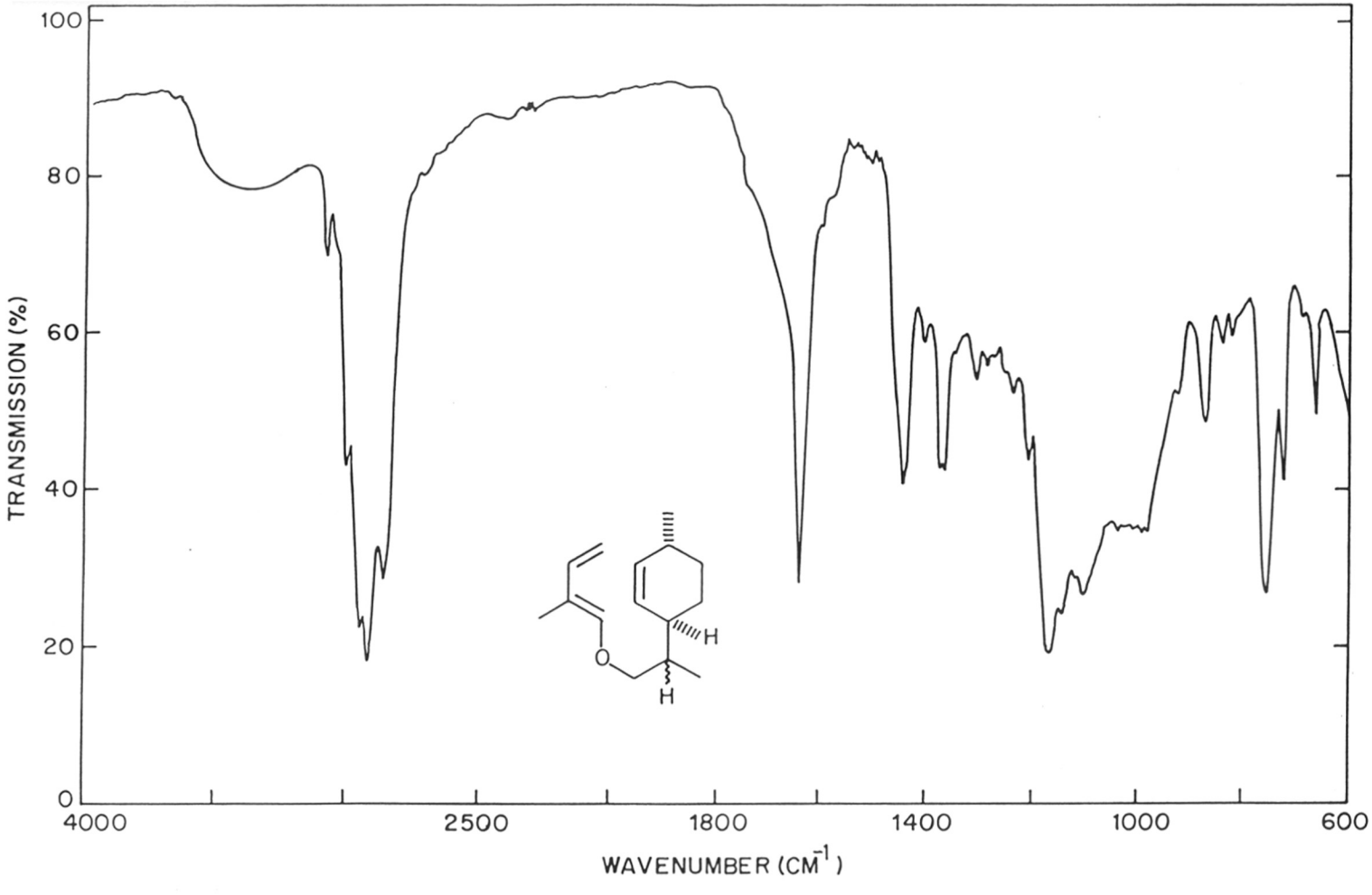


FIG. 2·8 : IR OF THE ENOL ETHER 55

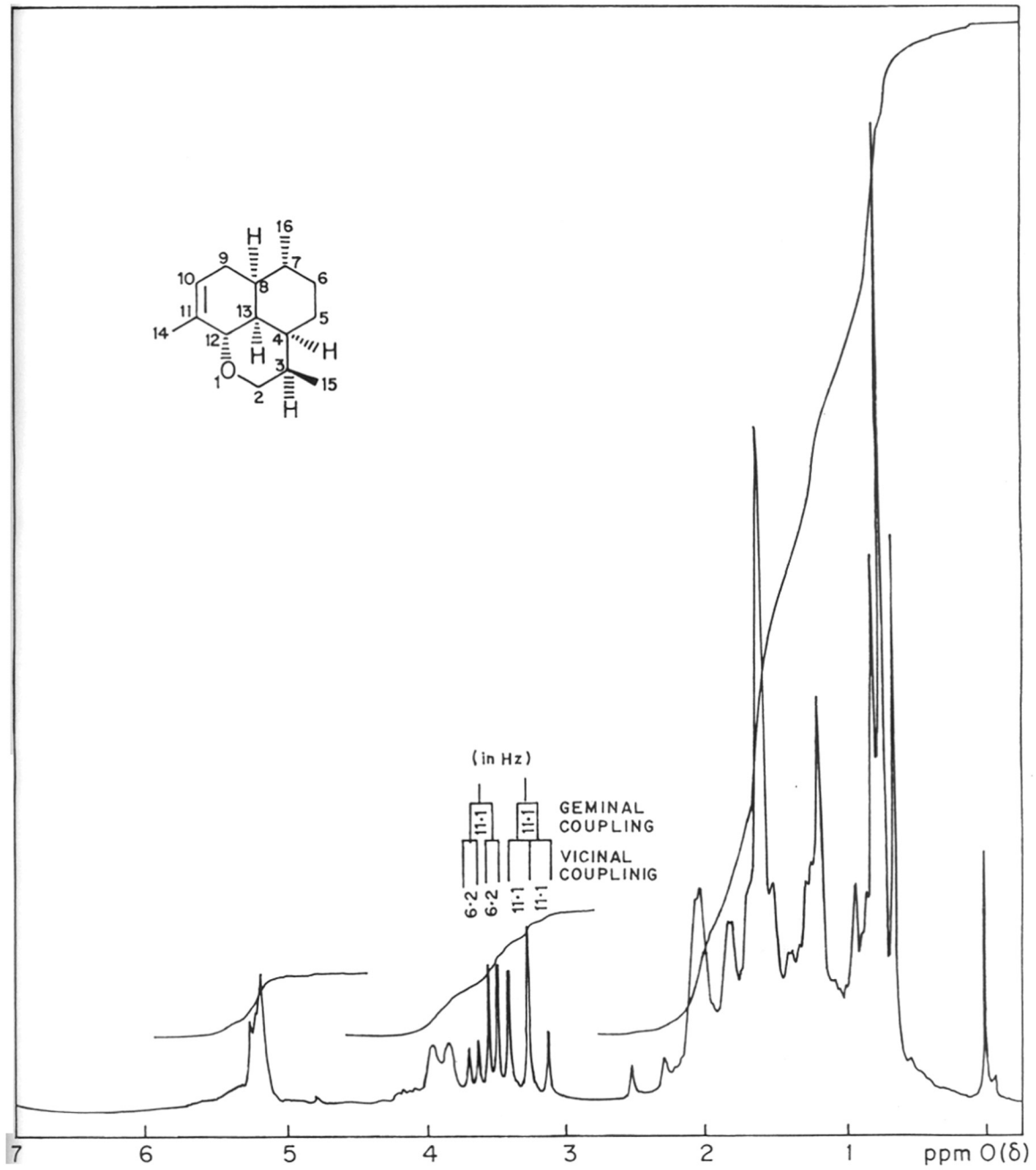


FIG.2·9 : NMR OF THE DIELS-ALDER PRODUCT 56a

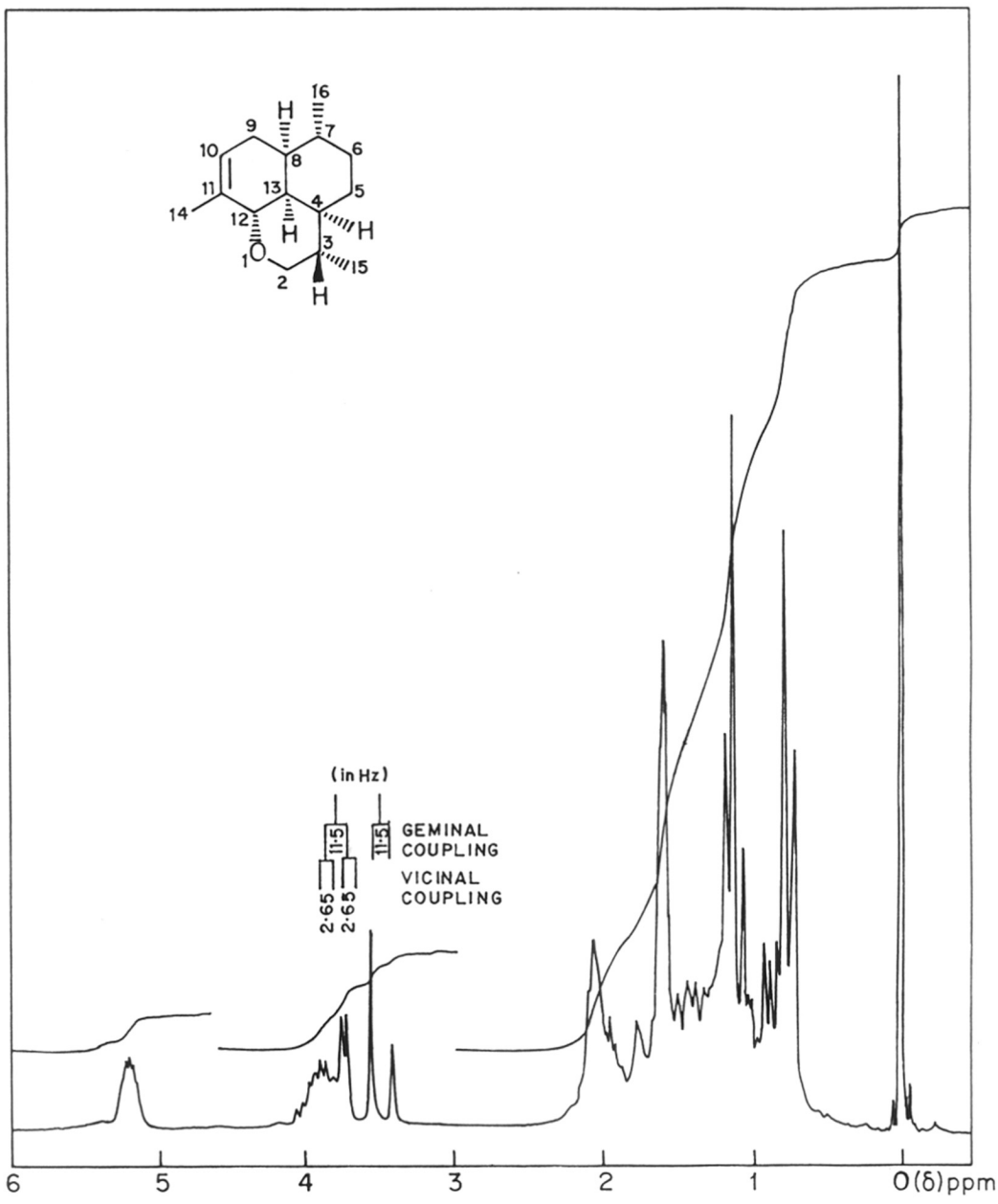


FIG. 2·10: NMR OF THE DIELS-ALDER PRODUCT 56b

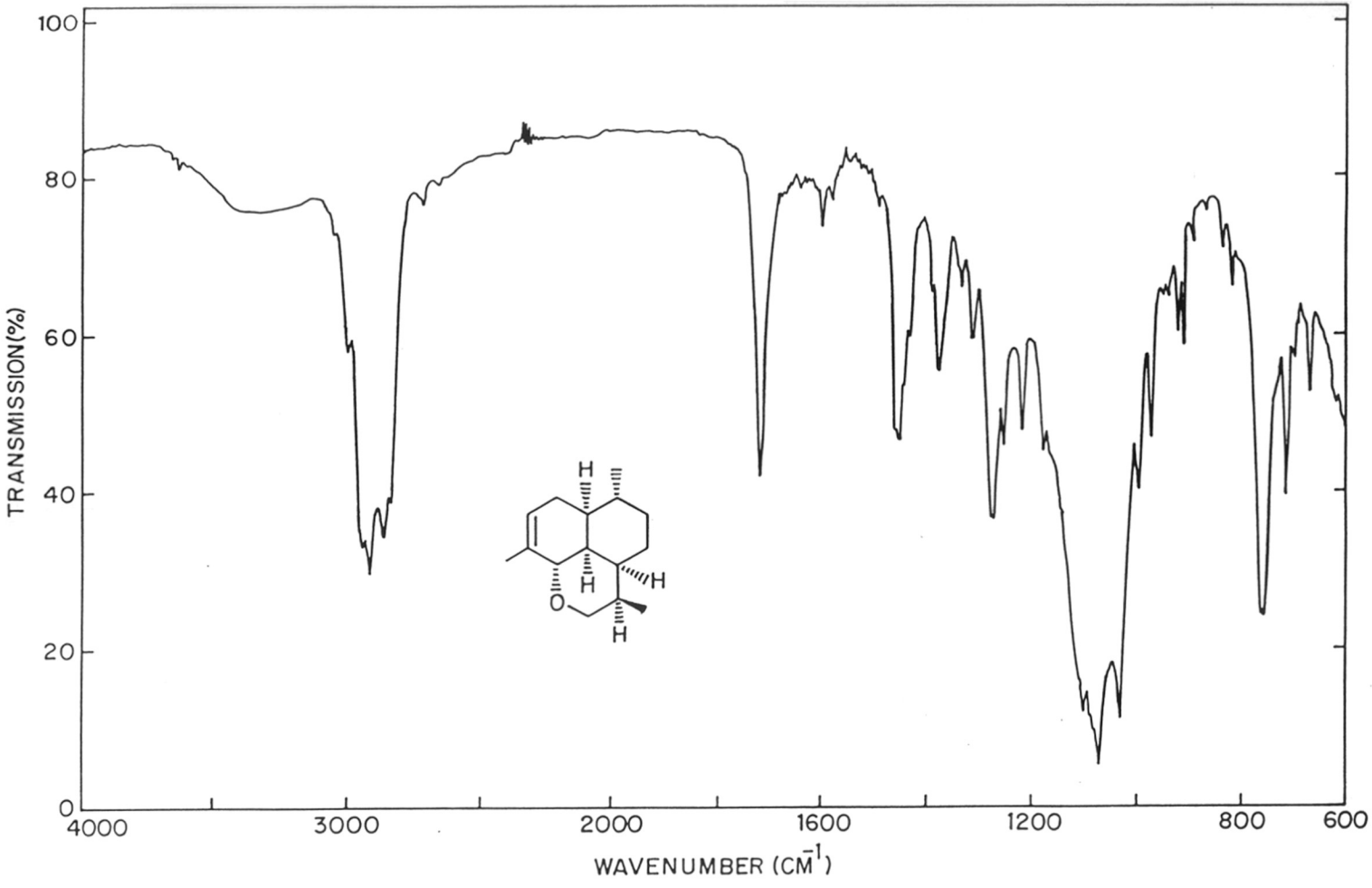


FIG. 2·11: IR OF THE DIELS-ALDER PRODUCT 56(a)

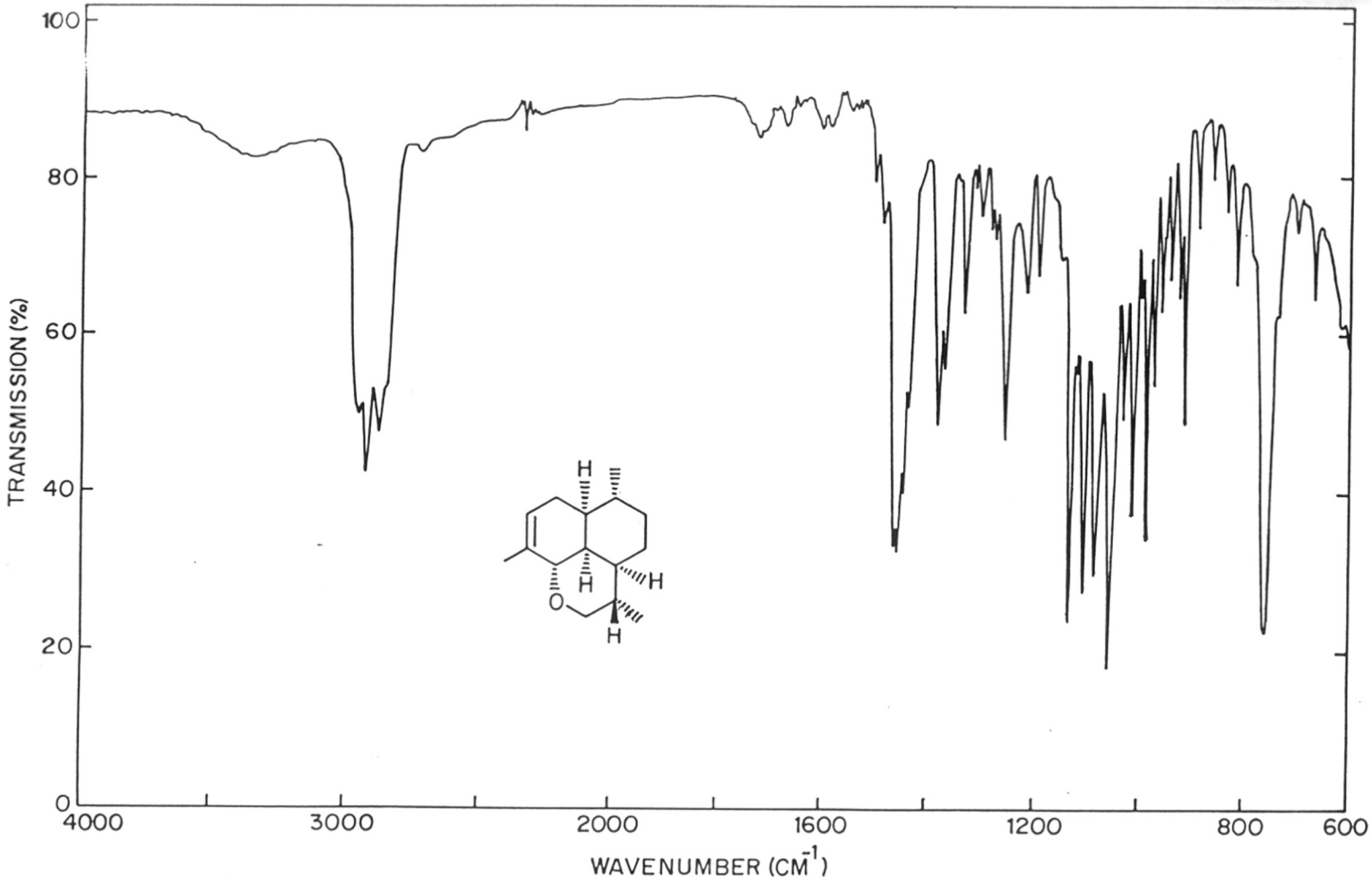


FIG. 2·12: IR OF THE DIELS-ALDER PRODUCT 56(b)

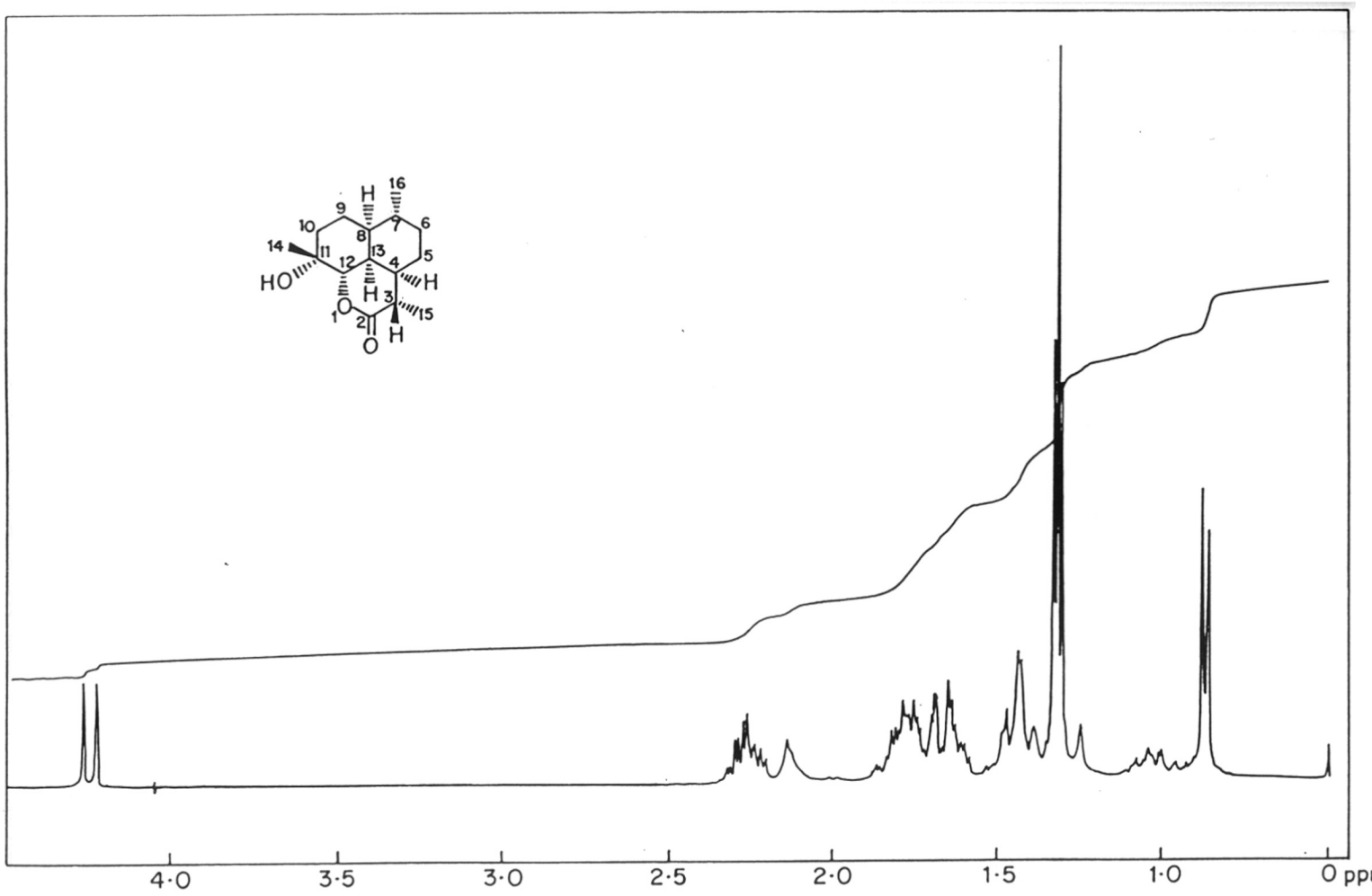


FIG. 2·13 : NMR OF THE LACTONE 65

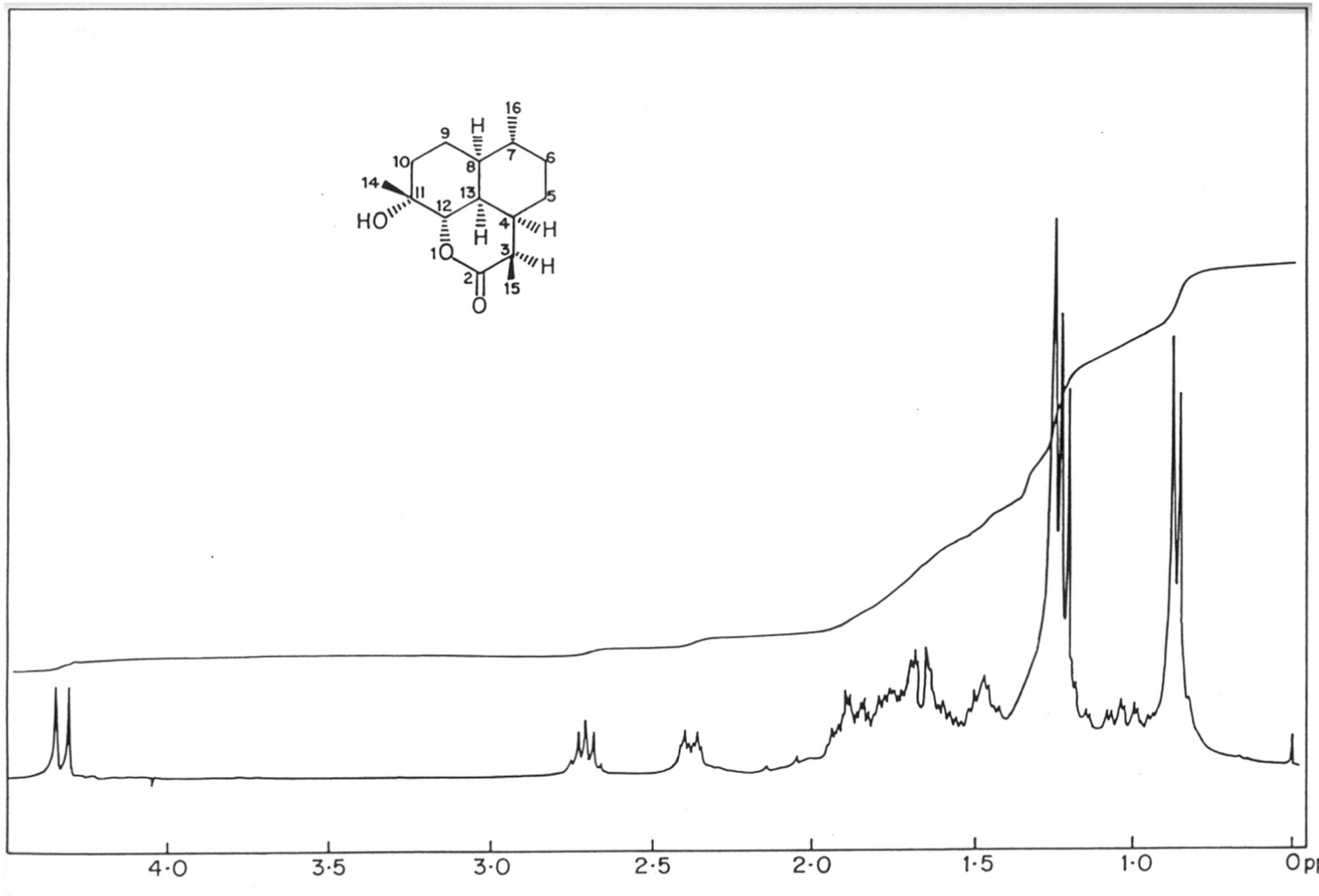


FIG. 2·14 : NMR OF THE LACTONE - 64

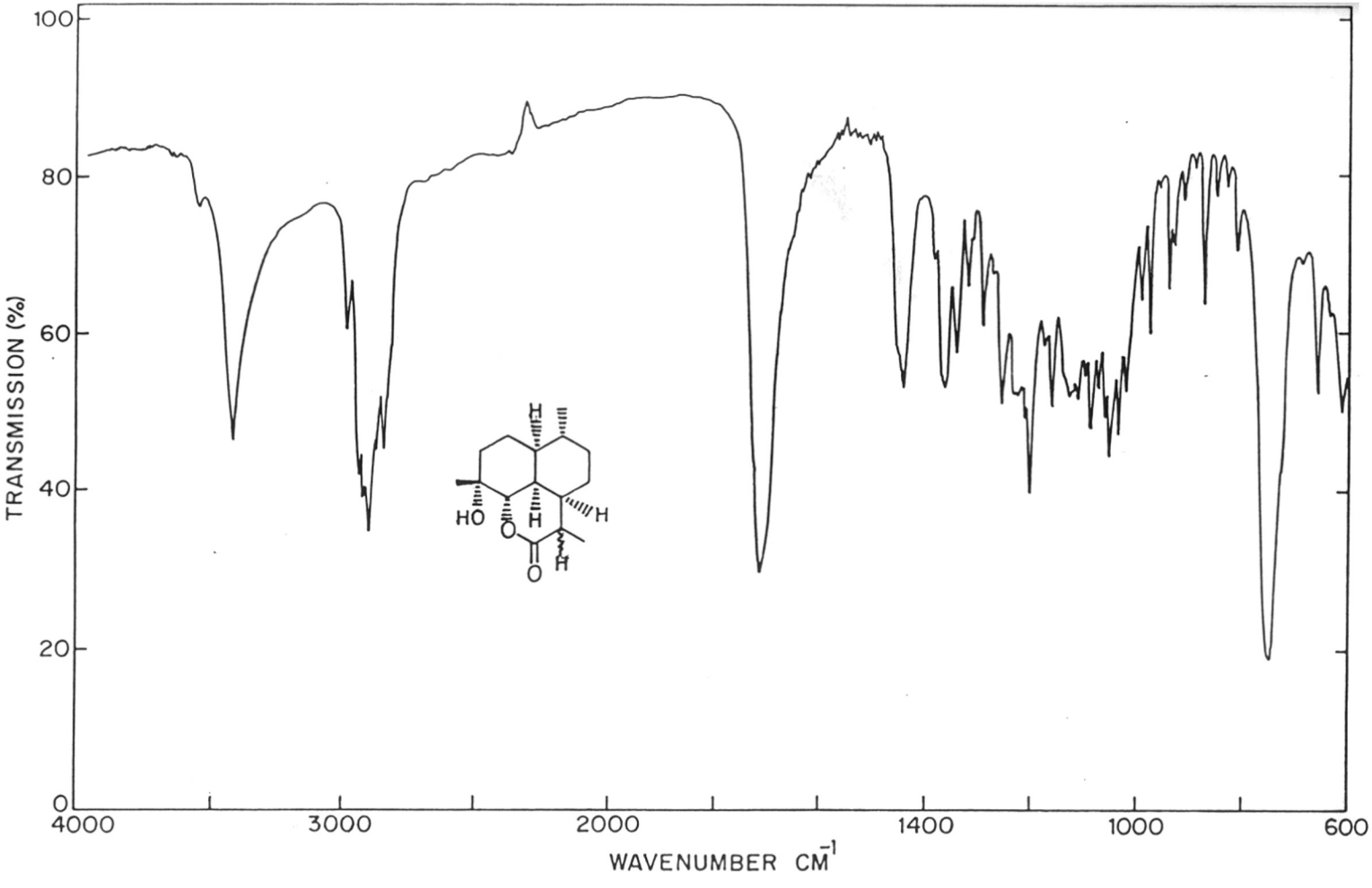


FIG. 2·15 : IR OF THE LACTONE 59

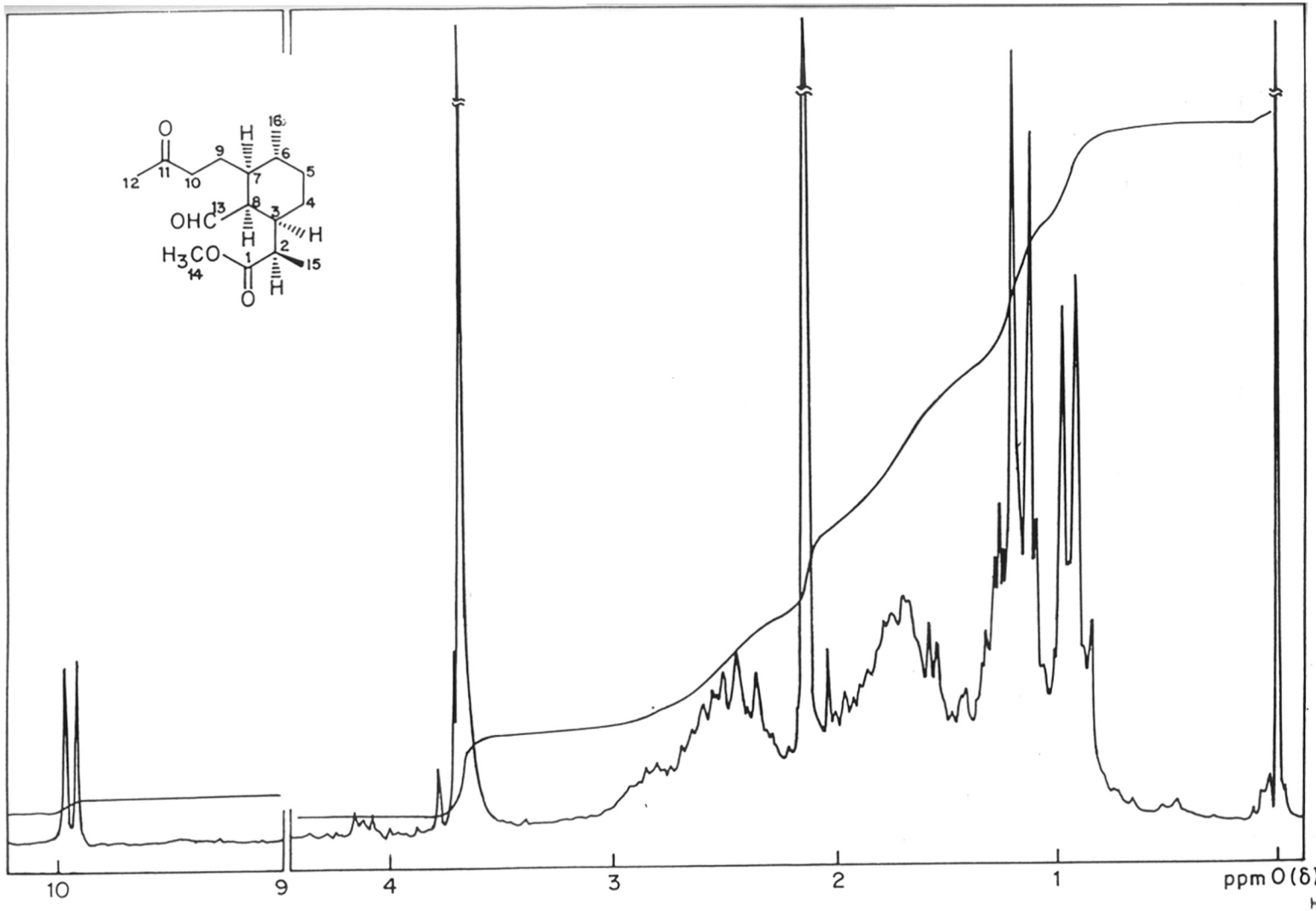


FIG. 2·16 : NMR OF THE KETO ALDEHYDE 63

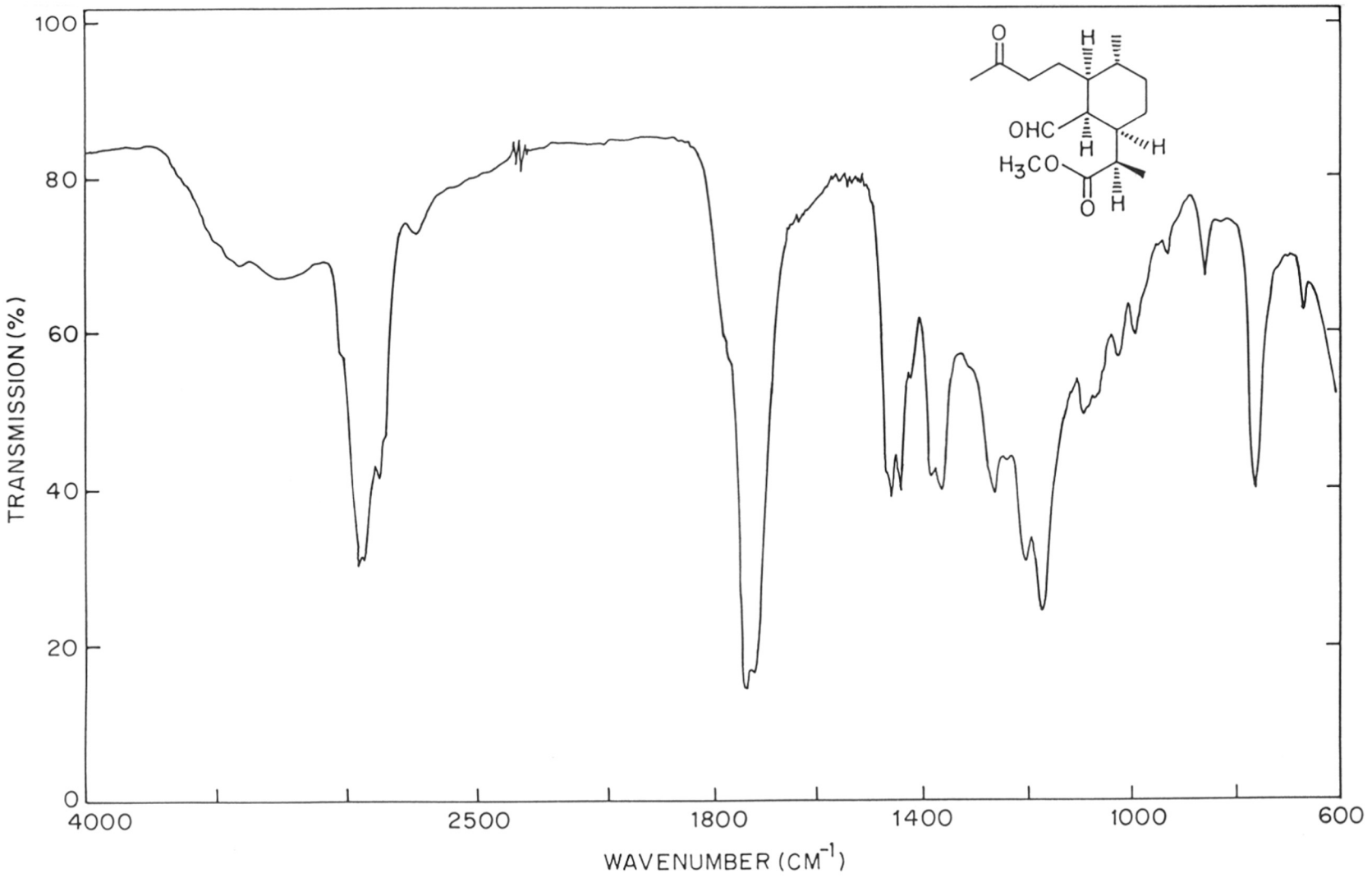


FIG.2·17: IR OF THE KETO ALDEHYDE 63

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CHAPTER 3·0·0
SYNTHETIC APPROACHES TOWARDS ARTEMISININ FROM CYCLOPENTENONE

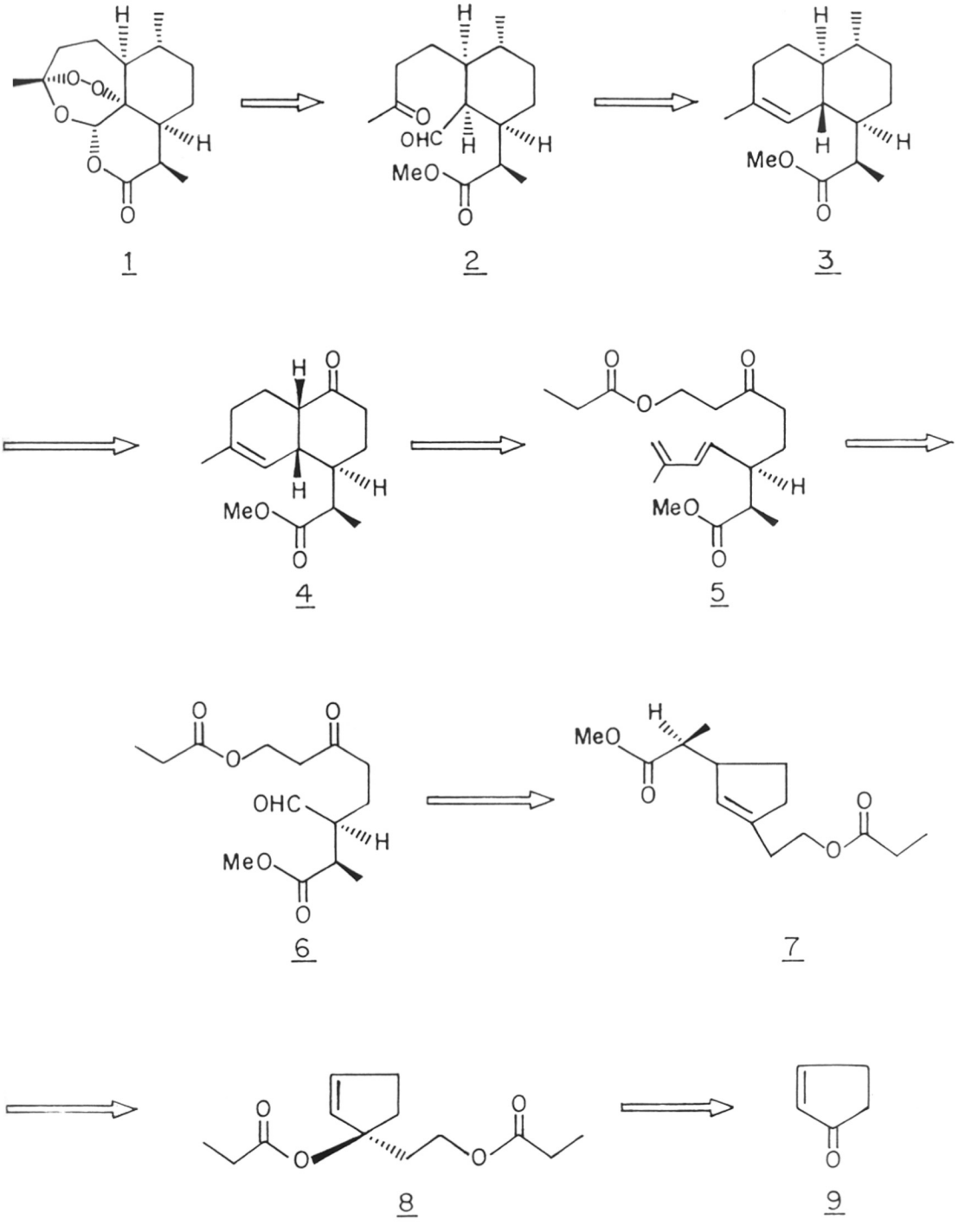
3.0.0 RESULTS AND DISCUSSION

The strategy involved in the earlier synthesis (Chapter II), two chiral centres present in the starting material, viz. trans-$\Delta^{2,8}$-p-menthadiene were translated into target molecule, artemisinin. In the present synthetic strategy of artemisinin, attempts were made to build up all chiral centres from achiral starting material like cyclopentenone. Though resolution was involved in this strategy, it could be done at an early stage of the synthesis. Further transformations were designed to build up other stereocentres by stereoselective reactions like ester enolate Claisen rearrangement, Wittig, Diels-Alder reactions etc. The retrosynthetic analysis which connects the target structure with cyclopentenone is shown in the Scheme-I.

The synthetic sequence suggested by the above analysis involves two key synthetic reactions well-known for generation of asymmetric centres, viz. Claisen rearrangement and Diels-Alder reaction. Claisen rearrangement in this context can be performed through stereospecific enolate generation and Diels-Alder reaction effects creation of the stereocentres, and a properly functionalised bicyclic system which can easily be manipulated to the target molecule.

Though different methods are known for the preparation of cyclopentenone **9** still there is a lack of a practical and facile route for large scale preparations. Also there is a possibility of getting both 1,2- and 1,4-addition products during Reformatsky reaction on cyclopentenone **9**. Hence it was decided to protect the double bond by suitable protecting group so that it can be regenerated

SCHEME-I

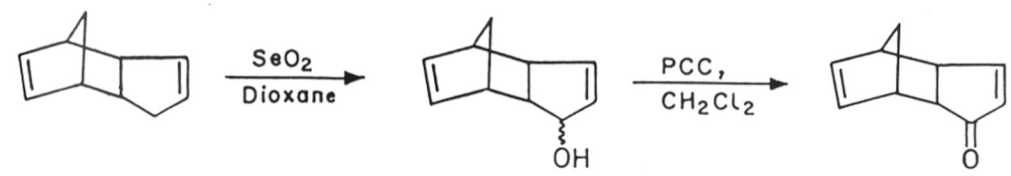


after Reformatsky reaction. Tricyclo(5,2,1,$0^{2,6}$)dec-8-ene-3-one **14** forms a suitable starting material since it can be prepared in large quantities and also it can be considered as cyclopentenone with a masked double bond. The double bond can be regenerated after the Reformatsky reaction on **14** by retro Diels-Alder reaction, thereby eliminating the possibility of 1,4- addition. The compound **14** can be prepared from readily available cheap starting material like dicyclopentadiene in four steps by reported procedure[1,2] after modification (Scheme-II).

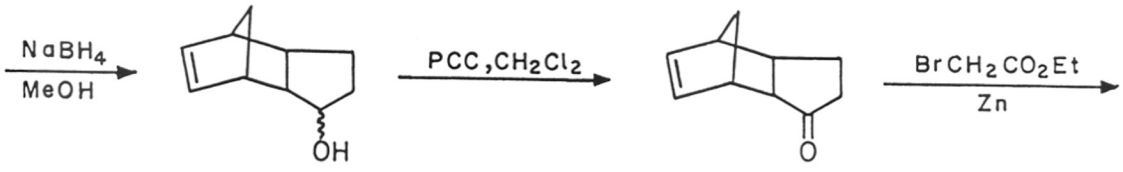
Dicyclopentadiene **10** on selenium dioxide oxidation[1,2] in dioxan in the presence of potassium dihydrogen phosphate gave the alcohol **11** which on oxidation with pyridiniumchlorochromate (PCC) in dichloromethane gave the ketone **12** in 75-80% yield. This α,β-unsaturated ketone[2] **12** was reduced with sodium borohydride in methanol to give the saturated alcohol **13** which was further oxidised with PCC in dichloromethane to give the ketone **14** in 70% yield which was identified by PMR, IR, Mass spectra as reported earlier.[1,2]

The ketone **14** on treatment with activated zinc[3] and ethyl bromoacetate[4] in a mixture of benzene and ether in the ratio of 8:2 gave the β-hydroxy ester **15** in 60% yield, the PMR spectrum of which showed a multiplet between (1.15-1.9) ppm for 8H, a singlet at 2.5 ppm for a methylene α to the carbonyl of the ester group a singlet at 3.65 for ester methyl group, a multiplet between (2.4-3) ppm for two allylic protons and a multiplet between (5.95-6.3) ppm for two olefinic protons. IR spectrum showed an absorption

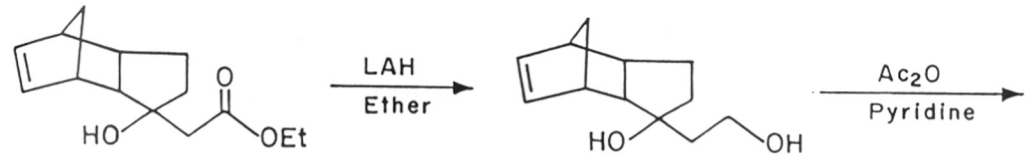
SCHEME-II



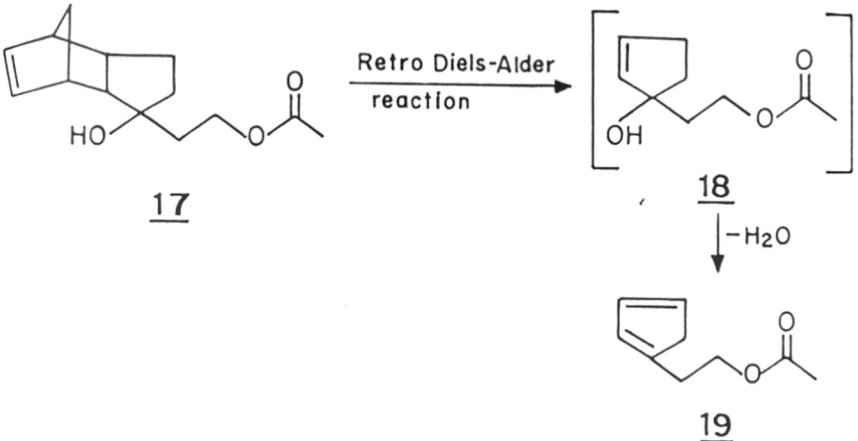
10 11 12



13 14



15 16



17 18 19

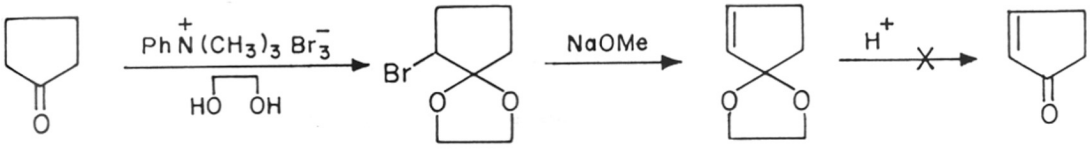
band at 1720 and 3500 cm^{-1} for carbonyl and hydroxyl group respectively. Mass spectrum showed (M^+) peak at 186.

The β -hydroxy ester **15** was reduced with lithium aluminium hydride to give the diol **16** which was esterified with acetic anhydride in presence of pyridine. The ester was characterised by its PMR and IR spectra. PMR spectrum showed a multiplet between (1-1.8) ppm for 8H, a triplet at 1.9 ppm (J=7Hz, 2H) for two protons on the carbon atom β to both oxygen atoms, a singlet at 2.1 ppm for 3H ($O-COCH_3$) a multiplet at (2.4-3) ppm (6H) for two allylic and one hydroxyl protons a triplet at 4.3 ppm (J=7Hz, 2H) for methylene connected to oxygen atom and a multiplet between (6.13-6.44) ppm for the two olefinic protons. IR spectrum showed an absorption band at 1730 and 3440 cm^{-1} for ester carbonyl and hydroxyl group respectively.

The ester **17** was flash-pyrolysed under vacuum by passing its dilute solution through a glass tube filled with glass beads, heated to 250°C under a vacuum of 6mm of Hg and condensing the vapours in a trap cooled to -78°C. But unfortunately the allylic alcohol **18** formed by retro Diels-Alder reaction underwent further dehydration to give the diene ester **19** which was characterised by its PMR and IR spectra.

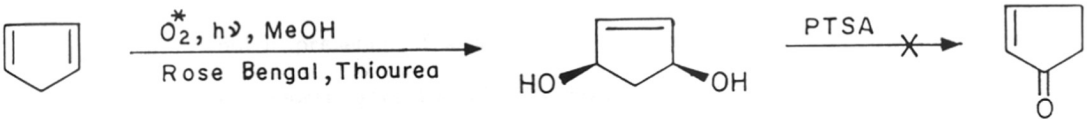
Assuming the dehydration to be highly acid-catalysed the pyrolysis was done under basic conditions using a pyridine solution of the ester **17**. But since the results were same as earlier, it was decided to prepare the ester **17** from cyclopentenone.

SCHEME-III



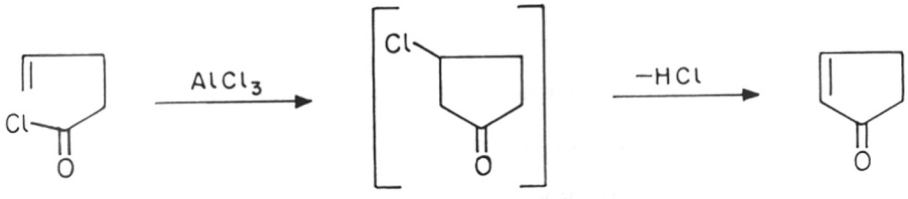
20 21 22 9

SCHEME-IV



23 24 9

SCHEME-V



25 9

Various attempts were made to prepare cyclopentenone in large scale according to the reported procedures as shown in the following schemes (Schemes III, IV & IV).

Cyclopentanone **20** was converted to its bromoketal[6] by brominating it in ethyleneglycol using the brominating agent phenyltrimethylammonium tribromide.[5] It was dehydrobrominated[7] by treatment with sodium methoxide in dimethylsulphoxide. However, on deketalisation of **22** by shaking with 3% sulphuric acid at room temperature no change was observed and only polymerisation was noticed on raising the temperature.

Second attempt was to prepare cyclopentenone from cyclopentadiene as reported.[8] The cyclopentadiene on photooxygenation[11] in methanol in presence of a sensitizer like Rose Bengal and reducing agent like thiourea gave the diol **24** which on distillation in presence of p-toluenesulphonic acid underwent polymerisation resulting in very poor yields of cyclopentenone.

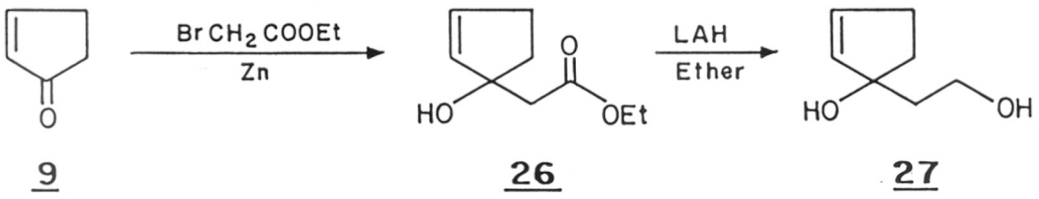
Finally it was prepared from 4-pentenoyl chloride according to a patented procedure.[9] 4-Pentenoyl chloride on treatment with aluminium chloride in chloroform underwent intramolecular acylation and simultaneous dehydrohalogenation to give cyclopentenone in 50% yield. (Pentenoyl chloride was prepared[10] from diethylmalonate in four steps as described in the second chapter.) The physical and spectral properties of cyclopentenone thus prepared were in full agreement with those reported. Cyclopentenone on treatment with ethyl bromoacetate and activated zinc in a mixture

of benzene and ether in the ratio of 8:2 gave the β-hydroxy ester **26**[12] in 60% yield. Fortunately no 1,4-addition product was observed. The yield increased to 80-85% when the reaction was done using trimethylborate[13] as solvent. No improved yield was observed when the reaction was done using ultrasound and using dioxane as solvent as claimed in the literature.[14]

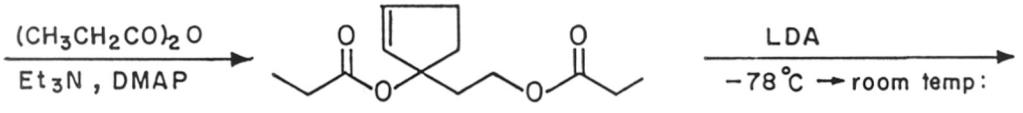
The PMR spectrum of β-hydroxy ester **26** (Fig. 3.1) showed a triplet centered at 1.26 ppm (J=7Hz, 3H) for a methyl and a quartet between (4.05-4.28) ppm (2H, J=7Hz) for methylene of the ether ester, a singlet at 2.64 ppm for methylene α- to the ester carbonyl, a multiplet between (1.86-2.57) ppm (4H) for two methylenes in the cyclopentene ring and a multiplet between (5.66-6) ppm (2H) for two olefinic protons. IR spectrum showed absorption bands at 3450 and 1730 cm^{-1} for hydroxyl and ester carbonyl group respectively (Fig. 3.2). Also mass spectrum showed weak M^+ peak at 170 (M^+) and strong peak at 152 (M^+ - $-H_2O$).

The β-hydroxy ester **26** on reduction with lithium aluminium hydride in ether gave the diol **27** which was characterised by its PMR and IR spectra. PMR spectrum in D_2O showed a multiplet between (1.62-1.93) ppm (4H), a multiplet between (2.1-2.4) ppm for two allylic protons, a triplet centered at 3.64 ppm (2H, J=7Hz) for methylene adjacent to the oxygen atom and a multiplet between (5.46-5.9) ppm for two olefinic protons. IR spectrum showed disappearance of absorption band at 1730 cm^{-1} for ester carbonyl and showed a strong absorption at 3320 cm^{-1} for hydroxyl group and mass spectrum showed M^+ peak at 128.

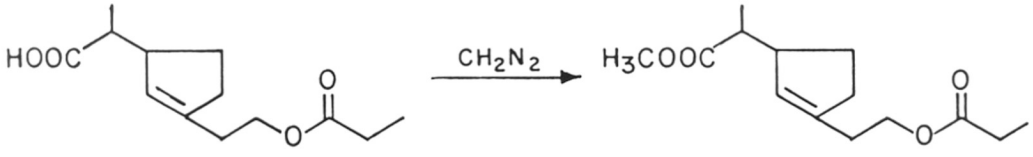
SCHEME-VI



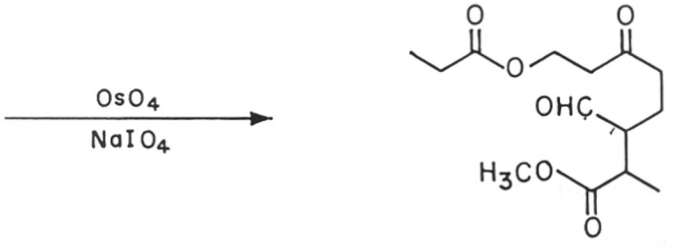
9 26 27



28



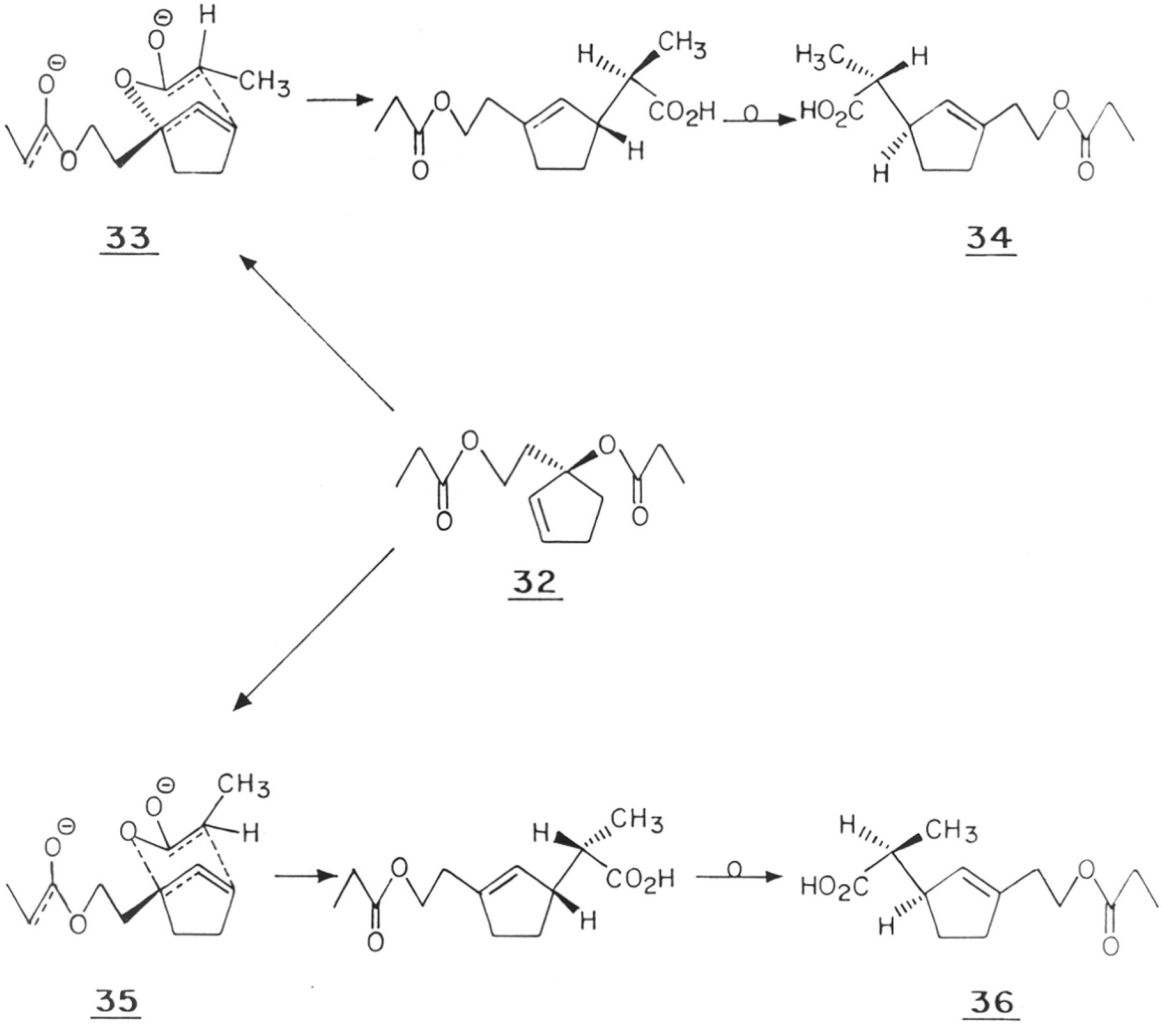
29 30



31

. All attempts to esterify the hydroxyl groups of the diol **27** using acylating agents like acid chloride or acid anhydride in presence of organic bases like pyridine, triethylamine, dimethylaniline were unsuccessful. Although the primary hydroxyl group was esterified under above reaction conditions, the tertiary hydroxyl group underwent dehydration to give a cyclopentadienyl derivative **19** which was characterised by its PMR and IR spectra. PMR spectrum showed a triplet centered at 1.1 ppm (J=6Hz) for the methyl, a quartet between (2.1-2.4) ppm for methylene of the ethyl ester, a multiplet between (2.5-3) ppm for four allylic protons, a triplet between (4.1-4.3) ppm for methylene adjacent to oxygen atom and a multiplet between (6-6.5) ppm for olefinic protons. Also attempts to esterify the diol **27** using strong bases like sodium hydride, potassium hydride, n-butyllithium, lithiumdiisopropylamide and acylating agents like acid chloride and acid anhydride resulted in the eliminated product. Finally, the diol **27** was esterified using propionic anhydride in presence of triethylamine and catalytic amount of dimethylaminopyridine.[15,16] Though the reaction can be monitored by TLC, the product on purification (distillation, column chromatography over silica, alumina, etc.) underwent decomposition. Hence the product was characterised by further chemical transformation. The diester **28** thus prepared was treated with two equivalents of lithiumdiisopropylamide in tetrahydrofuran at -78°C. On warming up the reaction mixture upto room temperature, it underwent ester enolate Claisen rearrangement[17] to give the acid **29** (on acidification of the reaction mixture). The acid **29** was converted to its methyl ester **30** by treatment with

SCHEME-VII

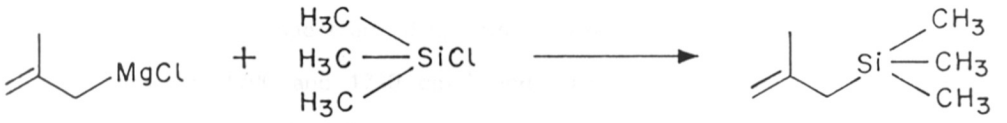


diazomethane in ether. The PMR spectrum of **30** (Fig. 3.3) showed a multiplet between (1-1.2) ppm (6H) for two methyls, a multiplet between (1.2 - 2.1) ppm for 2H, a multiplet between (2.05-2.5) ppm (8H) for 5 allylic protons and for 3 protons in the carbon atom α to the carbonyl group, a singlet at 3.6 ppm for 3H (-COO$\underline{CH_3}$), a triplet between (4 - 4.25) ppm for a methylene adjacent to oxygen atom and a multiplet between (5.15-5.4) ppm for one olefinic proton. IR spectrum (Fig. 3.4) showed absorption at 1750 cm^{-1} for ester carbonyl and mass spectrum showed M^+ peak at 254.

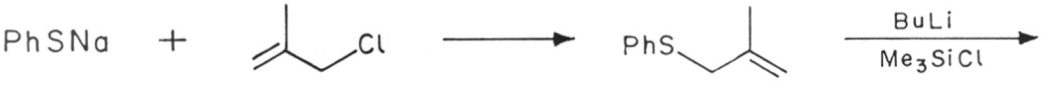
The stereochemistry of the two newly formed asymmetric centres in **29** can be controlled by starting with an optically active intermediate **32** which can be obtained from the allylic alcohol **26** by Sharpless kinetic resolution method. The ester **32** on treatment with lithiumdiisopropylamide gives rise to E enolate in tetrahydrofuran and Z enolate in tetrahydrofuran -23% hexamethylphosphoramide mixture which in turn undergoes ester enolate Claisen rearrangement to give **34** and **36** respectively through a chair-like transition state as shown in the scheme.

The configuration required for the synthesis of natural artemisinin can be obtained by generating enolate of **32** in tetrahydrofuran which will give rise to **34**. Attempts to cleave the olefinic bond of **30** by ozonolysis to get the keto aldehyde gave a complex mixture of products. But the required transformation was achieved by treating the ester **30** with osmium tetroxide and sodium metaperiodate.[18] The keto aldehyde **31** formed was characterised by PMR, IR and

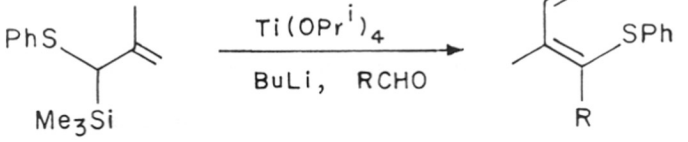
SCHEME - VIII



39 40 41



42



43

44a R = $(CH_2)_6 CH_3$

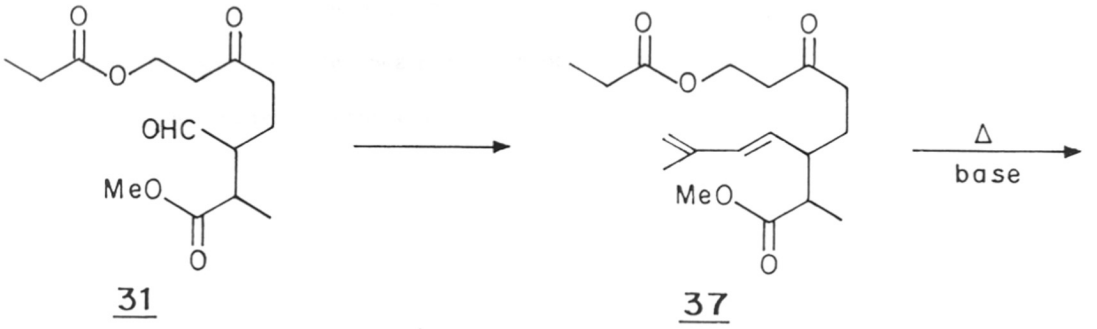
b R = $CH(CH_3)_2$

mass spectra. PMR spectrum (Fig. 3.5) showed a multiplet for 6H between (0.9-1.3) ppm for two methyls, a multiplet for 10H between (1.6-3) ppm, a singlet for 3H at 3.6 ppm for the ester methyl group, a triplet for 2H centered at 4.25 ppm (J = 7Hz) for hydrogens adjacent to oxygen atom and a multiplet (1H) at 9.6 ppm for aldehyde proton. IR spectrum (Fig. 3.6) showed a broad absorption band between 1700 and 1770 cm^{-1} and mass spectrum showed a peak at 212 (M^{+} -CH_3-CH_2-COOH).

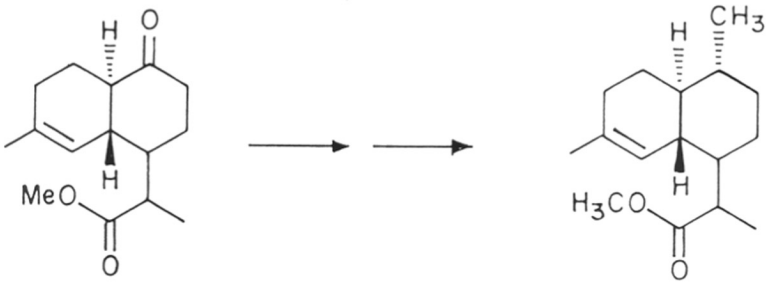
Attempts to convert the keto aldehyde **31** into the diene **37** by chemoselective Wittig olefination[19] with methyallyltriphenylphosphonium chloride did not succeed. Also attempts to prepare the diene with methallylphosphonamide[20,23] met with failure. Then it was decided to make use of Peterson reaction[21] for the above conversion. Eventhough the generation of trimethylsilylallyl anion with n-butyllithium or sec. butyllithium was reported, attempts to generate the anion of methallyltrimethylsilane with these bases were not successful. So the proton α to the silicon was activated by introducing a thiophenyl group[22] as shown in Scheme-VIII. Eventhough the reaction worked with a model compound like isobutyraldehyde and octanal, it failed to give the required diene with keto-aldehyde (**31**); instead it gave a complex mixture of products. Further studies on this transformation is going on in our laboratory.

The diene **37** can be converted to a key intermediate **45** in the synthesis of artemisinin as shown in Scheme-IX.

SCHEME-IX



31 37



38 3

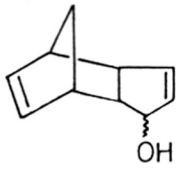
The Diels-Alder reaction could be achieved thermally in presence of a base which would go through a cis-decalin structure and could be epimerised under base catalysis (which will undergo base catalysed epimerisation) to the more stable trans-structure shown in Scheme-IX).

Since the key intermediate allyl alcohol **26** is amenable to kinetic resolution by Sharpless method, this scheme can be easily modified to give natural artemisinin.

EXPERIMENTAL

3.2.0 EXPERIMENTAL

Preparation of the Alcohol 11



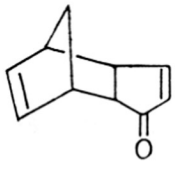
The alcohol (**11**) was prepared according to the reported procedure[1] starting from dicyclopentadiene.

Yield : 60%

B.P. : 82°C/3 mm (lit. b.p. 84°C/3 mm)

PMR ($CDCl_3$) δ : 0.33-0.6 (m, 2H), 2.3-3.5 (m, 5H), 3.8-4.06 (broad singlet, IH), 5.33 - 6 (m, 4H).

Preparation of the Ketone 12



The alcohol **11** (34.5 g, 0.23 mole) was dissolved in dichloromethane (500 ml) and cooled to 0°C. Pyridinium chlorochromate (85 g) was added with stirring. After the initial exothermic reaction the reaction mixture was stirred for another 6 hrs. Dry ether (400 ml) was added to precipitate out the chromium salt, then it was decanted, the residue was washed four times with dry ether (4 x 100 ml). The combined extract was concentrated under reduced pressure and purified by column chromatography over silica gel.

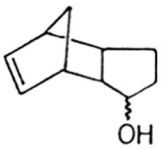
Yield : 27 g (79%).

PMR ($CDCl_3$) δ : 1.55-1.7 (m, 2H), 2.65-2.8 (t, J=4.8, 1H), 2.8-3.45 (m, 3H), 5.6-5.95 (m, 3H), 7.2-7.35 (m, 1H, J=6.4, J = 3.2).

IR (neat): 1690 cm^{-1}.

MS (m/e) : 146 (M^+).

Preparation of the Alcohol 13



The alcohol **13** was prepared from the ketone **12** by reduction with sodium borohydride in methanol according to a reported procedure[2].

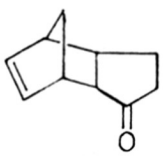
Yield: 65%

PMR ($CDCl_3$) δ : 1.15-1.75 (m, 8H), 2.45-3 (m, 2H), 4.05-4.35 (m, 2H), 6-6.3 (m, 2H)

IR (neat): 3390 cm^{-1}

MS (m/e): 150 (M^+).

Preparation of the Ketone 14



The ketone **14** was prepared from the alcohol **13** by oxidation with pyridinium chlorochromate in dichloromethane as described earlier.

Yield: 70%

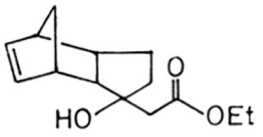
PMR ($CDCl_3$) δ: 1.36-2.1 (m, 7H), 2.46-3.26 (m, 3H), 6.03-6.25 (m, 2H).

IR (neat): 1730 cm^{-1}.

Activation of Zinc[3]

The zinc dust was activated by washing rapidly with dilute sodium hydroxide solution, water, dilute acetic acid, ethanol, acetone and ether. It was finally dried in a vacuum oven at 100°C.

Preparation of β-Hydroxyester 15



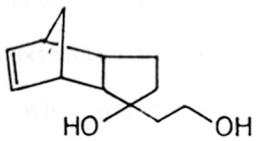
Activated zinc (1.96 g, 30 mmole) was placed in a two necked R.B. flask fitted with a reflux condenser and a dropping funnel under dry conditions. A solution of ethyl bromoacetate (5 g, 30 mmole) and ketone **14** (1.48 g, 10 mmole) in a mixture of benzene (50 ml) and ether (12 ml) was prepared and 5 ml of this solution and a speck of iodine crystals were added to initiate the reaction. After the initial vigorous exothermic reaction, rest of the solution was also added dropwise in about 2 hrs. The reaction mixture was refluxed for another 3 hrs, cooled to 0°C and was quenched with ammonium chloride. The organic layer was removed and the aqueous phase was extracted with ether (50 x 4). The combined organic layer wad dried (anhyd. Na_2SO_4) and concentrated. The crude product was purified by column chromatography over silica gel.

Yield: 1.416 g (60%).

PMR ($CDCl_3$) δ : 1.15-1.9 (m, 8H), 2.5 (s, 2H), 2.4-3 (m, 2H) 3.65 (s, 3H), 5.95-6.3 (m, 2H)

IR (neat): 1720, 3500 cm^{-1}.

Preparation of the diol 16



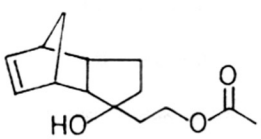
A solution of the ester **15** (14.2 g, 60 mmole) in ether (75 ml) was slowly added to a solution of lithium aluminium hydride (2.5 g, 65 mmole) in ether (50 ml), cooled to 0°C. The reaction mixture was stirred for 6 hrs at room temperature. The excess hydride was decomposed by adding hydrated sodium sulphate. The reaction mixture was filtered, the solid precipitate was washed with ether, the combined organic layer was dried (anhyd. Na_2SO_4) and concentrated under reduced pressure.

Yield: 9.8 g (83%)

PMR ($CDCl_3$) δ : 1.22-1.9 (m, 8H), 2.33-3 (m, 6H), 3.77-3.96 (t, J=6Hz, 2H), 6.1-6.42 (m, 2H).

IR (nujol): 3200 cm^{-1}.

Preparation of the Ester 17



A solution of the diol **16** (2.86 g, 14 mmole) in pyridine (20 ml)

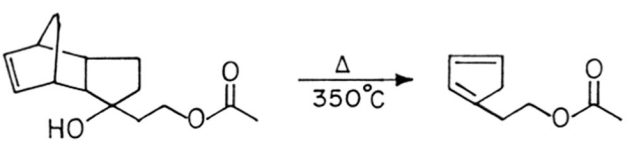
was cooled to 0°C and acetic anhydride (3 g, 29 mmole) was added dropwise. The reaction mixture was stirred at room temperature and the progress of the reaction was monitored by TLC. After stirring the reaction mixture for 6 hrs, methanol (10 ml) was added to decompose the excess acetic anhydride. The excess methanol was removed under reduced pressure. The reaction mixture was diluted with water and extracted thoroughly with ether. The ether layer was then washed with water, very dilute hydrochloric acid and water successively. The ether layer was dried (anhydrous Na_2SO_4) and concentrated under reduced pressure. Further purification was done by column chromatography over silica gel.

Yield: 2.43 g (70%)

PMR ($CDCl_3$) δ : 1-1.8 (m, 8H), 1.8-2 (t, J=7Hz, 2H), 2.1 (s, 3H), 2.4-3 (m, 3H), 4.2-4.34 (t, J = 7Hz, 2H), 6.13-6.44 (m, 2H)

IR (neat): 1730, 3440 cm^{-1}.

Pyrolysis of the Ester 17



17 19

A dropping funnel carrying a nitrogen inlet was connected to a 50 cm long pyrolysis tube filled with glass beads. The lower end of the pyrolysis tube was connected to a condenser, which in turn was connected to a two necked receiver, cooled to -78°C. The other end of the receiver flask was connected to the vacuum pump. The system was flushed with nitrogen, after a while the

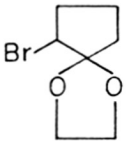
nitrogen inlet was closed and the system was kept under a vacuum of 6 mm of Hg and the pyrolysis tube was slowly heated to 250°C. A dilute solution of the ester **17** (5 gms/21 mmole) in benzene (100 ml) was added over a period of 6 hrs and the vapours were condensed in the receiver flask. When the addition was over the vacuum was released and the system was again flushed with nitrogen to remove the vapours from the pyrolysis tube. The solution collected in the receiver flask was concentrated under reduced pressure and purified by column chromatography over silica gel. The product formed was identified as the diene ester **19** by its PMR and IR spectra.

Yield: 800 mg (25%).

PMR ($CDCl_3$) δ : 2.1 (s, 3H), 2.53-2.85 (m, 2H), 2.85-2.95 (m, 2H), 4.1-4.28 (dt, J=7Hz, J=2Hz, 2H), 6-6.42 (m, (3H).

IR (neat): 1735 cm^{-1}.

Preparation of the Bromoketal 21



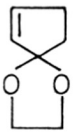
Phenyltrimethylammonium tribromide (14.27 g, 38 mmole) was added to a stirred solution of cyclopentanone (1.68 g, 20 mmole) in tetrahydrofuran (25 ml) and ethyleneglycol (25 ml). Stirring was continued for 36 hrs at room temperature. Then it was poured to a solution of 10% sodium bicarbonate (500 ml) and 5% sodium thiosulphate (50 ml) and extracted thoroughly with ether. The ether

layer was washed with water, brine solution, dried (anhydrous Na_2SO_4) and concentrated under reduced pressure. Further purification was done by column chromatography over silica gel.

Yield: 3.2 g (77%)

PMR (CCl_4) δ : 1.5-2.4 (m, 6H), 3.26-3.8 (m, 1H), 3.8-4.33 (m, 4H).

Preparation of Cyclopentenone Ketal 22



The bromoketal **21** (3 g, 15 mmole) was refluxed with a solution of sodium hydroxide (2 g, 50 mmole) in methanol (25 ml) for 6 hrs. The reaction mixture was poured into 50 ml of water saturated with sodium chloride and extracted thoroughly with petroleum ether. The combined extracts were dried (anhyd. Na_2SO_4), concentrated under reduced pressure and further purified by column chromatogrphy over silica gel.

Yield: 1.1 g (65%)

PMR ($CDCl_3$) δ : 2.36-2.9 (m, 4H), 3.53-4 (m, 4H), 5.3-6.1 (m, 2H).

Attempted Deketalization of 22

The ketal **22** (1.26 g, 10 mmole) was stirred with 3% H_2SO_4 (5 ml). Since TLC did not show any change, the reaction was continued for several days. Finally the reaction mixture was extracted with

ether and the combined extracts were washed with dilute sodium bicarbonate, dried over anhydrous Na_2SO_4 and concentrated. The PMR spectrum of the product showed partial deketalization. The reaction was carried out at elevated temperature (60°C); prolonged stirring resulted in the polymerisation. The experiment was repeated with p-toluenesulphonic acid without success.

Preparation of Cyclopentadiene 23

It was prepared by the pyrolysis of dicyclopentadiene at 240-250°C as described in the procedure reported in the literature.[9]

Preparation of Cyclopent-4-ene 1,3-diol 24

Cyclopent-4-ene 1,3-diol was prepared by irradiating a solution of cyclopentadiene (32 g, 0.48 mole) and thiourea (25 g) in methanol (4 lit.) in presence of sensitizer (rose bengal, 400 g) according to the reported procedure.[8] Work up and subsequent distillation of the reaction mixture gave 20 g of cyclopent-4-ene 1,3-diol.

Yield : 20 g (41%)

PMR (D_2O) δ : 1.1 - 1.56 (dt, J=14Hz, J=5Hz, 1H), 2.5 - 3 (dt, J=14Hz, J=7Hz, 1H), 4.5-4.85 (Peaks masked by signals of water), 5.73-6.1 (s, 2H).

IR (neat): 3440 cm^{-1} (strong absorption).

Attempted Synthesis of cyclopentenone 9[8] from Diol 24

Cyclopent-4-ene-1,3-diol (10 g, 0.1 mole) was placed in a 25 ml R.B. flask fitted with a distillation condenser which in turn was connected to a receiver cooled in ice. The mixture was heated to 50-55°C and p-toluenesulphonic acid (150 mg) was added. The pressure was reduced to (10-15) mm and the flask was heated to 65-70°C, but very little distillate was obtained. The residue in the distillation flask became very thick. The distillate was extracted with ether, dried over sodium sulphate and concentrated to give 500 mg of cyclopentenone.

Yield: 500 mg (6%).

Preparation of Cyclopentenone[9] from 4-Petenoic Acid

9

A solution of 4-pentenoyl chloride (prepared as described in the second chapter) (10.5 g, 0.088 mole) in chloroform (50 ml) was added to a solution of aluminium chloride (24 g, 0.179 mole) in chloroform (150 ml). The temperature of the reaction mixture was maintained at 35-40°C by external cooling with water. When the evolution of hydrogen chloride gas ceased, the reaction mixture was poured in crushed ice, the chloroform layer was separated, and washed thoroughly with 5% sodium bicarbonate solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. It was further purified by fractional distillation under reduced pressure.

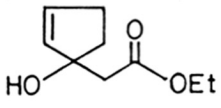
B.P. : 72-73°C at 30 mm

Yield: 3.89 g (53%)

PMR ($CDCl_3$) δ: 2.11-2.33 (m, 2H), 2.46-2.76 (m, 2H), 5.9-6.15 (m, 1H), 7.4-7.66 (m, 1H).

IR (neat): 1710 cm^{-1}.

Preparation of β-Hydroxy Ester 26



β-Hydroxy ester was prepared by treating activated zinc (1.96 g, 30 mmole) with a mixture of cyclopentenone (0.820 g, 10 mmole) and ethyl bromoacetate (5.01 g, 30 mmole) as described for the preparation of ester **15**.

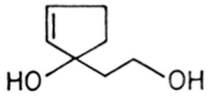
Yield: 1.02 g (60%).

PMR ($CDCl_3$) δ : 1.26 (t, J=7Hz, 3H), 1.86-2.57 (m, 4H), 2.64 (s, 2H), 3.42-3.77 (broad singlet, D_2O exchangeable, 1H), 4.05-4.31 (q, J=7Hz, 2H), 5.66-6.0 (m, 2H).

IR (neat): 3450, 1730 cm^{-1}

MS (m/e): 170 (M^+).

Preparation of the Diol 27



The ester **26** (1 g, 5.8 mmole) was reduced with lithium aluminium hydride (0.250 g, 6.5 mmole) in ether as described in the

preparation of the diol **16.**

Yield: 620 mg (82%)

PMR (D_2O) δ : 1.62-1.93 (m, 4H), 2.1-2.4 (m, 2H), 3.4-3.66 (t, 2H), 5.44-5.62 (m, 1H), 5.7-5.88 (m, 1H).

IR (neat): 3340 cm^{-1}.

MS (m/e): 128 (M^+).

Attempted Synthesis of the Diester 28 from the diol 27

(a) Using organic bases:

A solution of the diol **27** (0.256 g, 2 mmole) in pyridine (5 ml) and ether (5 ml) was cooled to 0°C and propionyl chloride (0.600 g, 6 mmole) was added dropwise. The reaction mixture was stirred for 4 hrs. at 0°C during which time the primary hydroxyl group was esterified which was evident by comparing with authentic sample. No change was observed on prolonged keeping at 0°C but on stirring at room temperature for a long time, a spot corresponding to the cyclopentadienyl ester **19** was formed which was confirmed by comparing its PMR and IR spectra with authentic sample.

The experiment was repeated using triethylamine, dimethylaniline and with acylating agent like propionic anhydride, without any success.

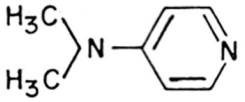
(b) Using inorganic bases:

Sodium hydride (50-60%) (720 mg, 15 mmole) was washed with dry petroleum ether under nitrogen atmosphere, three times in a two necked RB flask fitted with septum and three way stop cock.

A solution of diol **27** (896 mg, 7 mmole) in dry tetrahydrofuran (10 ml) was added slowly after cooling the flask to 0°C. After stirring for 30 min. propionyl chloride (1.29 g, 14 mmole) in tetrahydrofuran (5 ml) was added slowly. Stirring was continued at 0°C for 2 hrs, the reaction mixture was quenched with ice cold water and extracted with ether. The ether extract was washed with 10% sodium bicarbonate solution and water, dried (anhyd. Na_2SO_4) and concentrated under reduced pressure. PMR and IR spectra showed it as the eliminated product (i.e. ester **19**).

The experiment was repeated using other bases like KH, butyl lithium, lithium diisopropylamide etc. without success.

Preparation of Dimethylaminopyridine[15,16]



Pyridinylpyridiniumchloride hydrochloride was prepared by adding thionyl chloride (238 g, 2 moles) dropwise to dry pyridine (79 g, 1 mole) and working up according to the procedure as reported in the literature.[15] Pyridinylpyridiniumchloride hydrochloride (35 g) thus prepared was refluxed with dimethylformamide (250 ml) over 4 hrs. The flask was cooled and 20% aqueous sodium hydroxide solution (100 ml) was added and stirred overnight. The reaction mixture was diluted with water and extracted with ether four times. The ether layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude dimethylaminopyridine formed

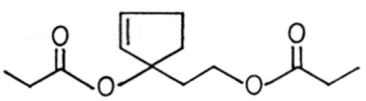
was purified by repeated crystallisation from n-hexane.

Yield: 4 g

M.P. : 108°C

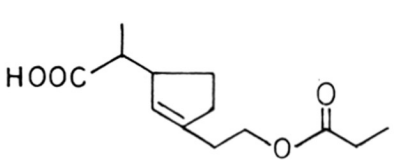
PMR ($CDCl_3$)δ: 3 (s, 6H), 6.2-6.43 (m, 2H), 7.86-8.16 (m, 2H).

Preparation of the Diester 28



A solution of the diol 27 (0.512 g, 4 mmole) and 4-dimethyl-aminopyridine (0.322 g, 2.6 mmole) in triethylamine (15 ml) was cooled to 0°C and propionic anhydride (1.7 g, 13 mmole) was added dropwise. The reaction mixture was stirred for 12 hrs. and the progress of the reaction was monitored by TLC. When the reaction was over the excess propionic anhydride was decomposed with methanol. Excess methanol was removed under reduced pressure. The reaction mixture was poured in water and extracted thoroughly with petroleum ether. The combined petroleum ether layer was dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure and the product as such was used for the next reaction without further purification.

Preparation of the Acid 29

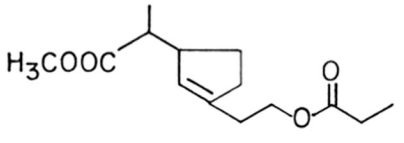


Lithium diisopropylamide (7 mmole) was prepared by adding a solution of n-butyllithium in n-hexane (2.36 M) (3 ml, 7 mmole) to a solution of diisopropylamine (0.808 g, 8 mmole) in tetrahydrofuran (10 ml) at 0°C and stirring it at 0°C for 30 min. Then it was cooled to -78°C and a solution of the ester **28** (1.44 g, 6 mmole) in 10 ml of tetrahydrofuran was added slowly. After the addition, the reaction mixture was stirred for 30 min. at -78°C and slowly warmed to room temperature. Above 0°C a thick white precipitate came out of the solution. The reaction mixture was cooled to -20°C and quenched with diluted hydrochloric acid so that the pH of the reaction mixture was around 2. The reaction mixture was diluted with water and extracted four times with ether. The combined ether layer was dried (anhyd. Na_2SO_4) and concentrated under reduced pressure. Further purification was done by column chromatography over silica gel.

Yield: 920 mg (64%)

PMR ($CDCl_3$) δ : 0.9-1.15 (m, 6H), 2-2.4 (m, 8H), 1.15-2 (m, 2H), 3.9-4.15 (t, J=7Hz, 2H), 5.5-5.7 (s, 1H), 7.9-8.1 (broad s, 1H, D_2O exchangeable).

Preparation of the Ester 30



An ethereal solution of diazomethane was added to a solution of acid **29** (1.2 g, 5 mmole) in dry ether until the colour of the reagent persists. The excess reagent was removed, concentrated and purified by column chromatography over silica gel.

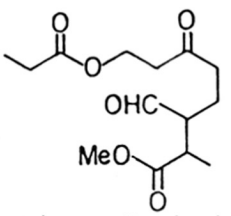
Yield: 0.950 g (74%)

PMR ($CDCl_3$) δ : 1-1.2 (m, 6H), 1.2-2.1 (m, 2H), 2.1-2.5 (m, 8H), 3.6 (s, 3H), 4-4.25 (t, J=6.4Hz, 3H), 5.15-5.4 (m, 1H).

IR (neat): 1750 cm^{-1}

MS (m/e) : 254 (M^+).

Preparation of the Keto aldehyde 31



The ester **30** (80 mg, 0.34 mmole) was dissolved in tetrahydrofuran (5 ml) and water (1 ml) and stirred under nitrogen atmosphere. Osmium tetroxide (2 mg) was added and the solution turned dark brown. To this solution sodium metaperiodate (0.2 g, 0.93 mmole) was added and stirred for 4 hrs. The solvent was removed under reduced pressure. Water was added and the product was extracted with ether four times, dried (anhydrous Na_2SO_4) and concentrated under reduced pressure. Further purification was achieved by column chromatography over silica gel.

Yield : 0.062 g (68%)

PMR ($CDCl_3$) δ : 1 - 1.31 (m, 6H), 1.64 - 3 (m,10H), 3.73 (s, 3H), 4.26 - 4.44 (t, J = 6Hz, 2H), 9.66 - 9.75 (m, 1H)

IR (neat) : 1700-1780 cm^{-1}, broad signal.

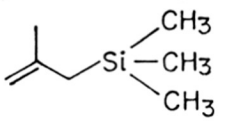
MS (m/e): (M^{+} -CH_3-CH_2-COOH)

Attempt to Prepare the Diene Using Wittig Reaction

The methallyltriphenylphosphonium chloride was prepared by refluxing a solution of triphenylphosphine (10 g, 38 mmole) and methallyl chloride (3.5 g, 38 mmole) in benzene for 7 days.

was warmed to room temperature. The saturated $NaHCO_3$ (10 ml) solution was added and the reaction mixture was extracted with ether. The ether layer was dried (anhyd. Na_2SO_4) and concentrated. The crude product obtained showed a number of spots which were very difficult to characterize.

Preparation of Methallyltrimethylsilane 41



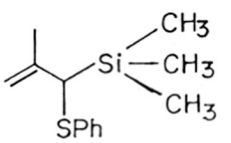
Grignard reagent (0.2 mole) was prepared by treating magnesium (4.86 g, 0.2 mole) with methallyl chloride (18.1 g, 0.2 mole) in 500 ml of ether. The reaction mixture was cooled to -5°C and chlorotrimethylsilane (21.6 g, 0.2 mole) was added slowly. The reaction mixture was cooled to -15°C with ice-salt mixture and quenched by adding saturated NH_4Cl dropwise. The organic layer was separated, the aqueous phase was washed with ether three times. The combined organic phase was dried over anhyd. Na_2SO_4, concentrated under reduced pressure and purified by distillation.

B.P. : 92 - 96°C/760 mm.

Yield: 17 g (66%)

PMR(CCl_4) δ : 0.06 (s, 9H), 1.7 (s, 3H), 2.1 (s, 2H), 4.6 (s, 2H).

Preparation of the Silane 43



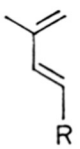
Thiophenol (2.41 g, 22 mmole) was treated with sodium ethoxide prepared from sodium (0.53 g, 23 mmole) and ethanol 20 ml and cooled to 0°C. Methallyl chloride (1.983, 22 mmole) was added dropwise and stirred for 12 hrs. The reaction mixture was quenched with saturated ammonium chrloride and extracted with ether. The ether layer was dried (anhyd. Na_2SO_4) and concentraed.

PMR ($CDCl_3$) δ : 1.8 (s, 3H), 3.4 (s, 2H), 4.73 (s, 2H), 7.1 (m, 5H).

Lithiumdiisopropylamide (0.25 mole) was prepared by adding n-butyllithium 2.36M (10.6 ml, 25 mmole) dropwise to a solution of diisopropylamine (2.72 g, 0.27 mole) in tetrahydrofuran at 0°C under nitrogen atmosphere. The reaction mixture was stirred for 30 min. at 0°C, then cooled to -78°C. A solution of crude allyl thioether in tetrahydrofuran (10 ml) was added over a period of 20 min. The reaction mixture was stirred at -78°C for 30 min. and allowed to warm to room temperature. Reaction mixture was quenched with ammonium chloride and extracted with ether. The ether layer was dried (anhyd. Na_2SO_4), concentrated and purified by column chromatography.

PMR ($CDCl_3$) δ : 1.7-2 (m, 5H), 4.7 (s, 2H), 7 (broad singlet, 5H).

Preparation of the Diene



To a solution of the silane (0.216 mg, 1 mmole) in tetrahydrofuran (5 ml) n-butyllithium 2M (0.5 ml, 1 mmole) was added slowly

at -30°C and stirred for 2 hrs. The reaction mixture was then cooled to -78°C and titanium tetraisopropoxide (284 mg, 1 mmole) was added and stirred for half an hour. A solution of isobutyraldehyde (72.11 mg, 1 mmole) in tetrahydrofuran (1 ml) was added. After 1 hr. the temperature was slowly raised to room temperature. The reaction mixture was quenched with diluted HCl and extracted with ether. The ether layer was dried over anhydrous Na_2SO_4 and concentrated. It was purified by column chromatography over silica gel.

Yield: 78 mg (35%)

PMR ($CDCl_3$) δ : 0.9 (d, 6H, J=6.5Hz), 1.9 (d, 3H, J=3Hz), 2.4-3 (m, 1H), (4.6-6.1) (m, 3H), 7.35 (m, 5H).

The experiment was repeated with other aldehyde like octanal. The δ value for the signals of the corresponding diene is given below. (Fig. 3.7).

PMR ($CDCl_3$) δ : 0.9 (t, 3H), 1.28 (s, 14H), 1.95 (d, J=2Hz, 3H), 2.24 (t, 2H), 4.77-6.13 (m, 3H), 7.3 (m, 5H).

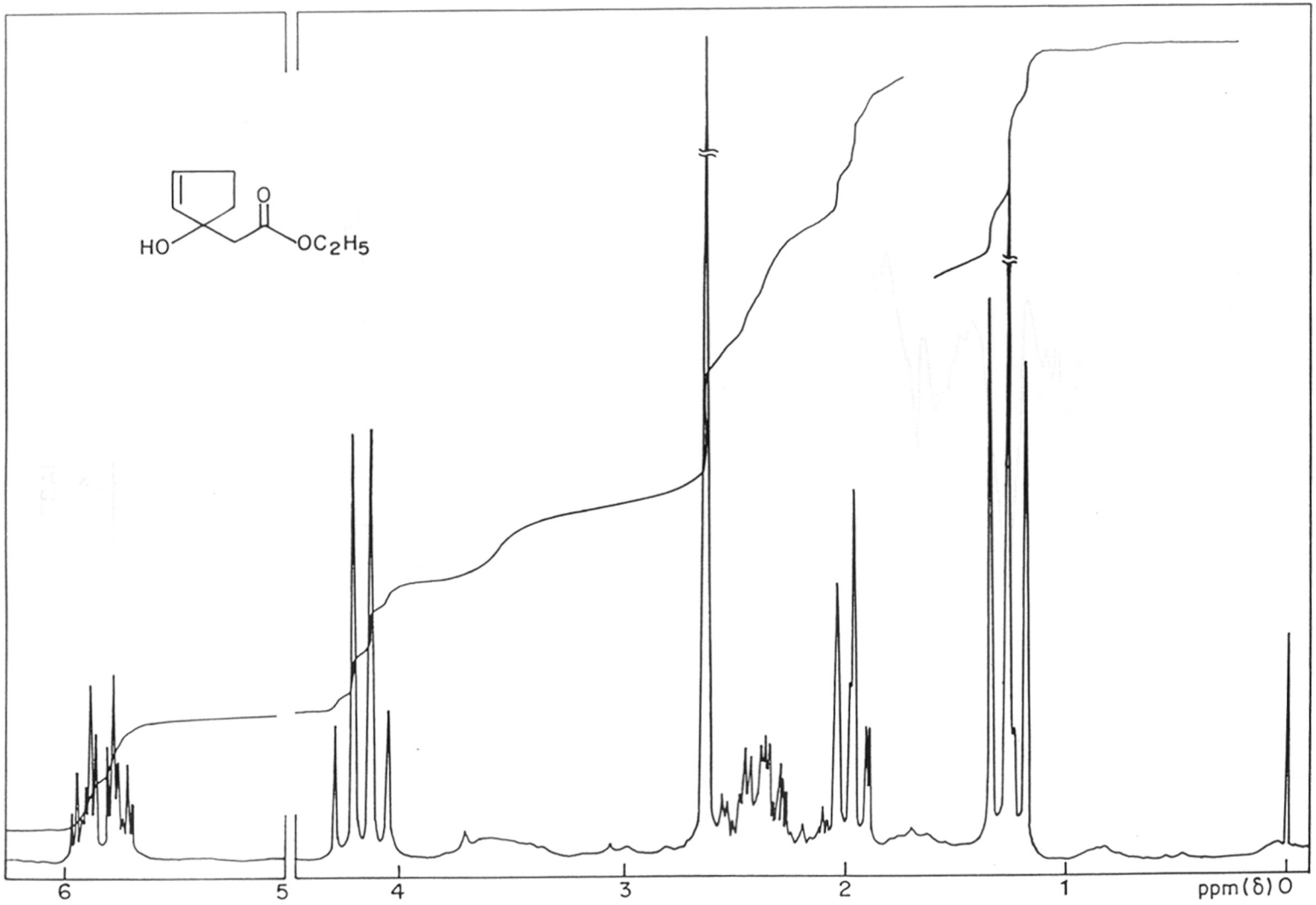


FIG. 3·1 : NMR OF THE ALCOHOL 26

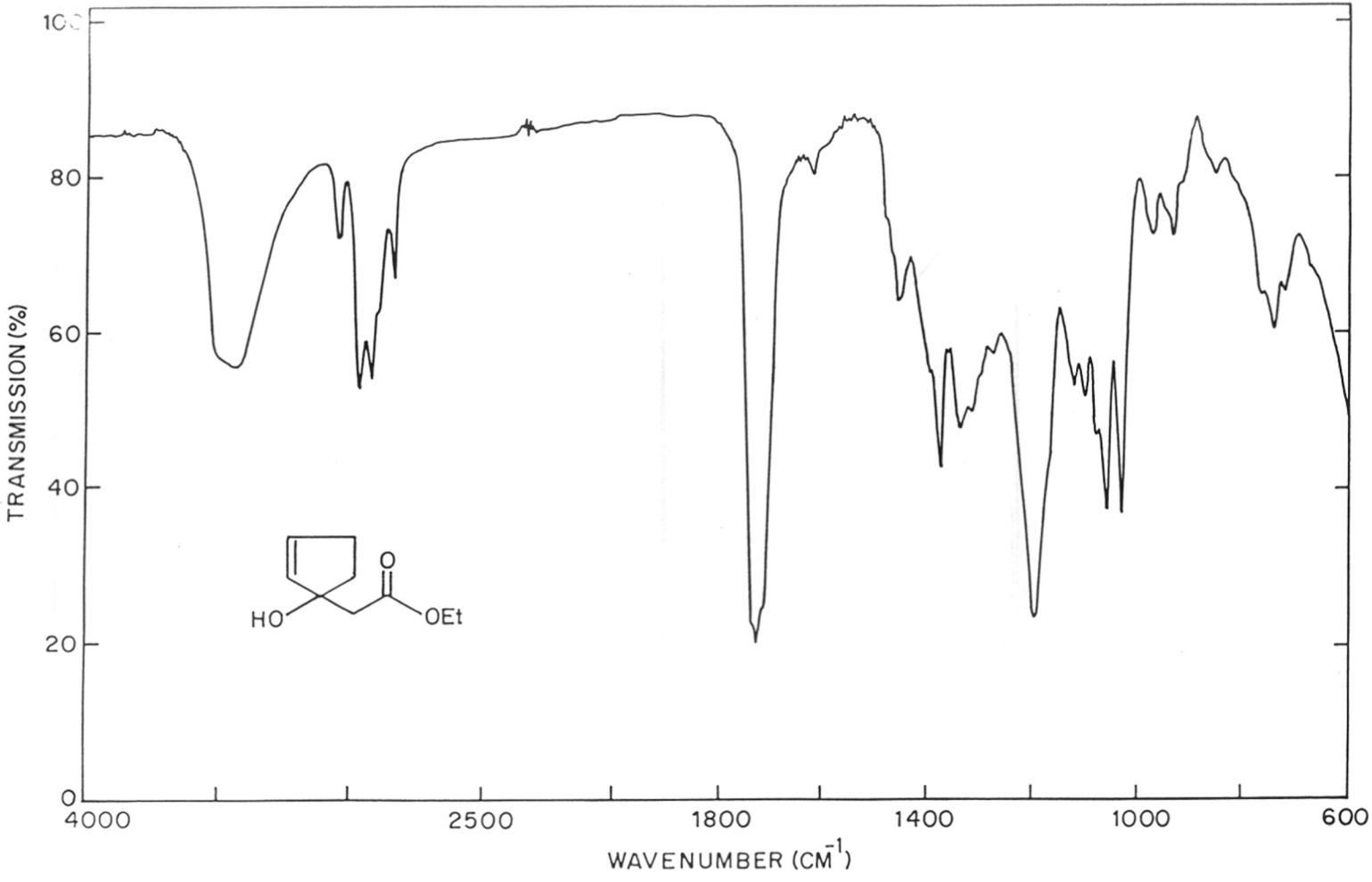


FIG.3·2 : IR OF THE ALCOHOL **26**

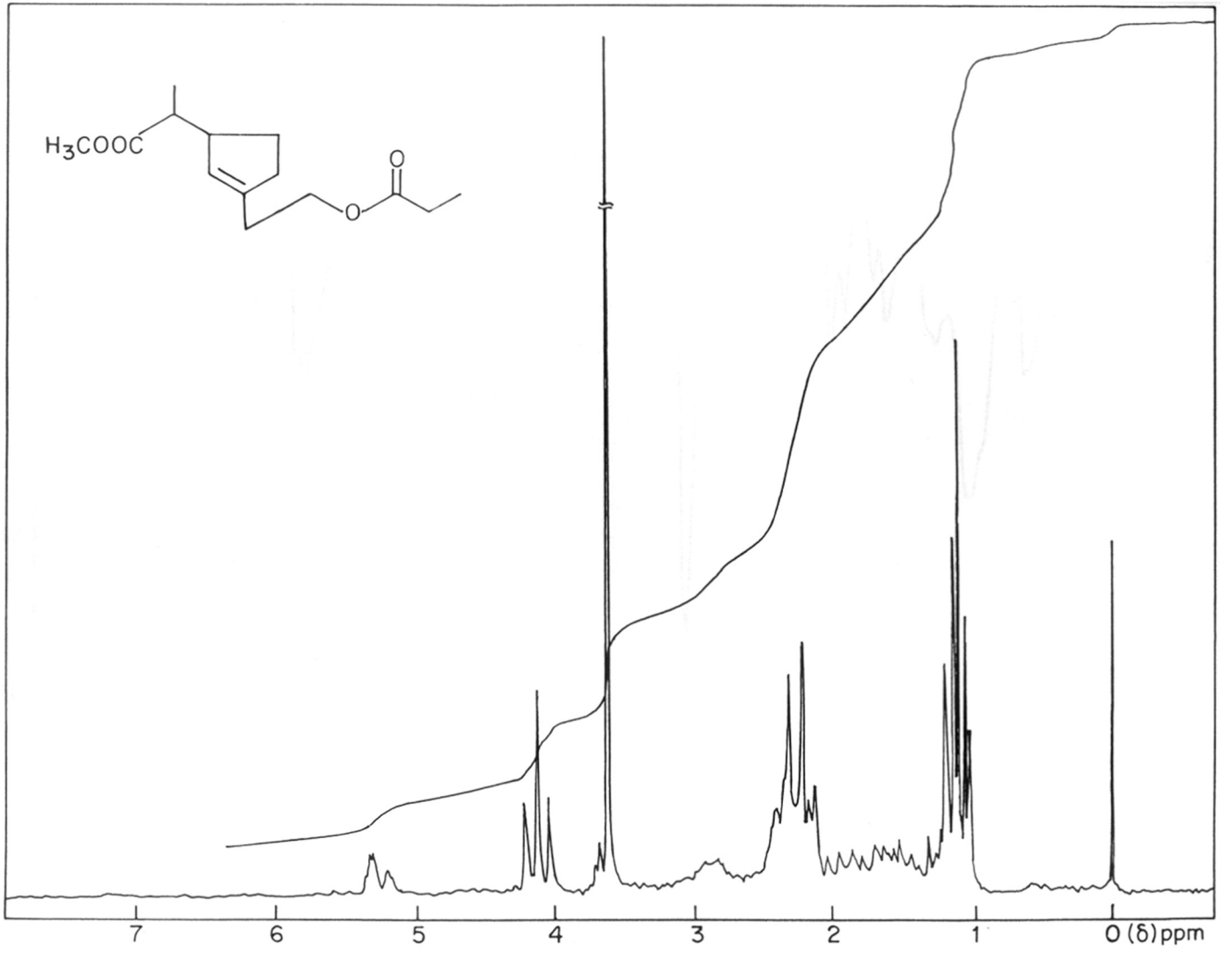


FIG. 3·3 : NMR OF THE ESTER 30

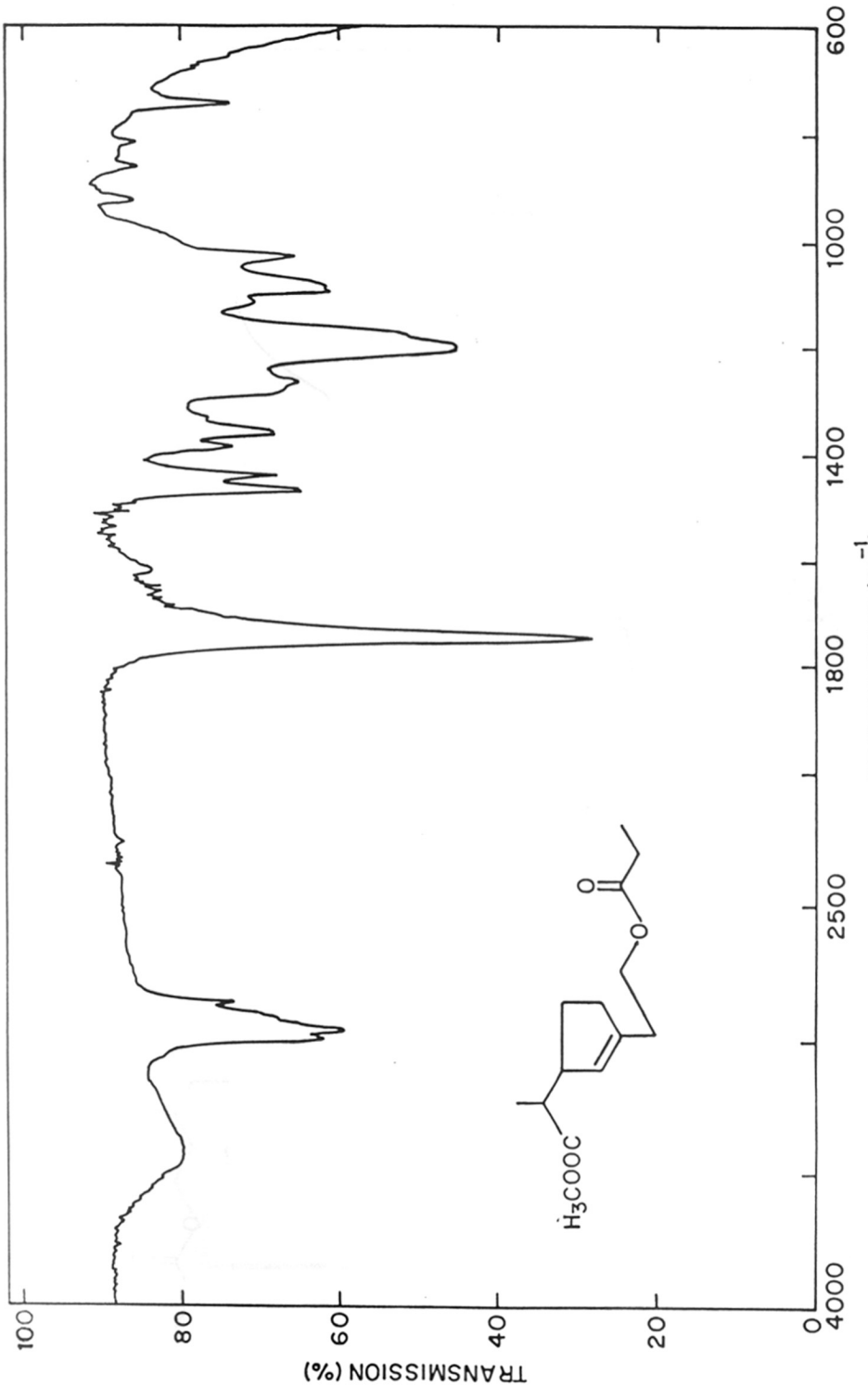


FIG. 3·4: IR OF THE ESTER 30

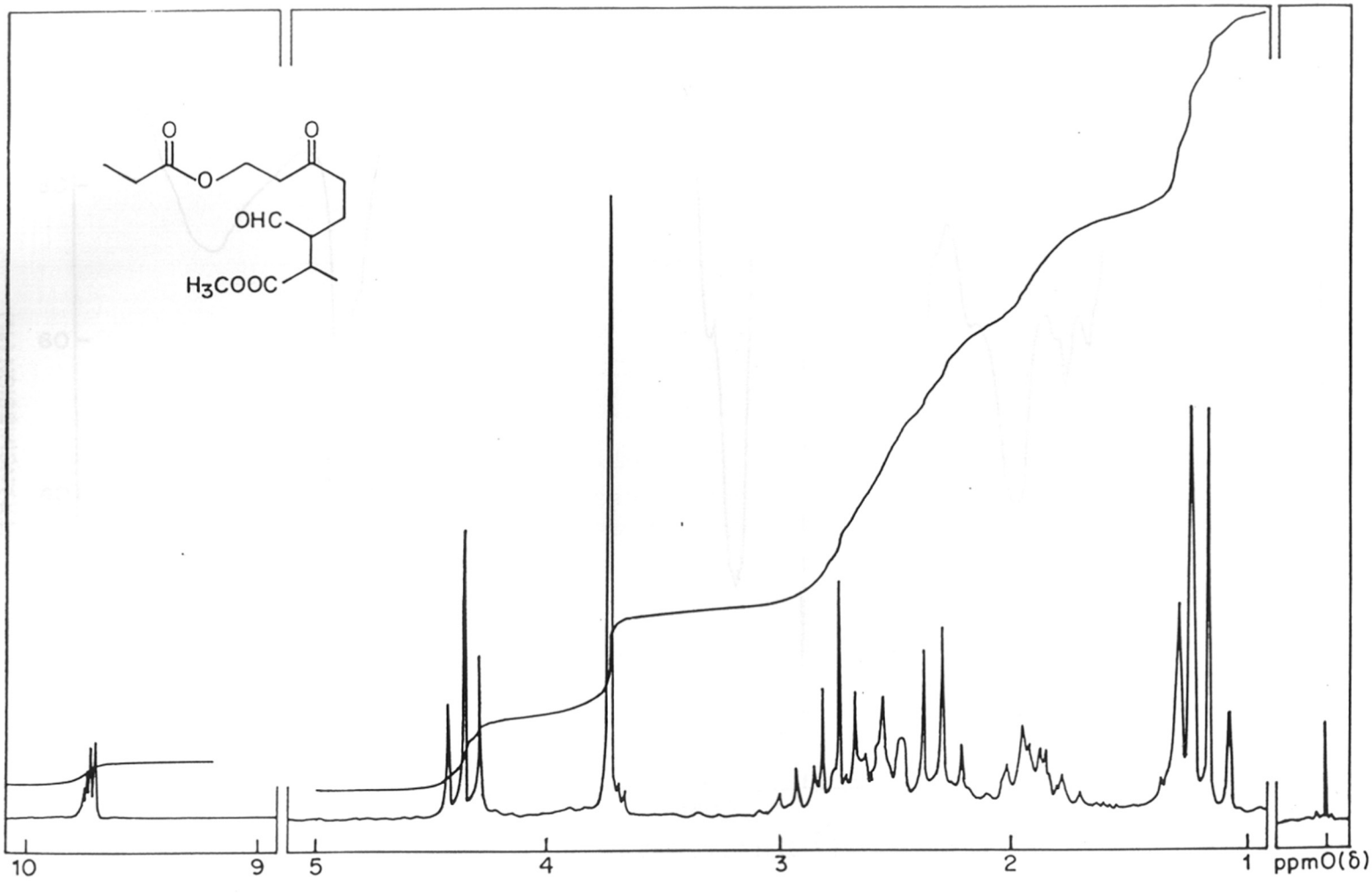


FIG. 3·5 : NMR OF THE KETO-ALDEHYDE 31

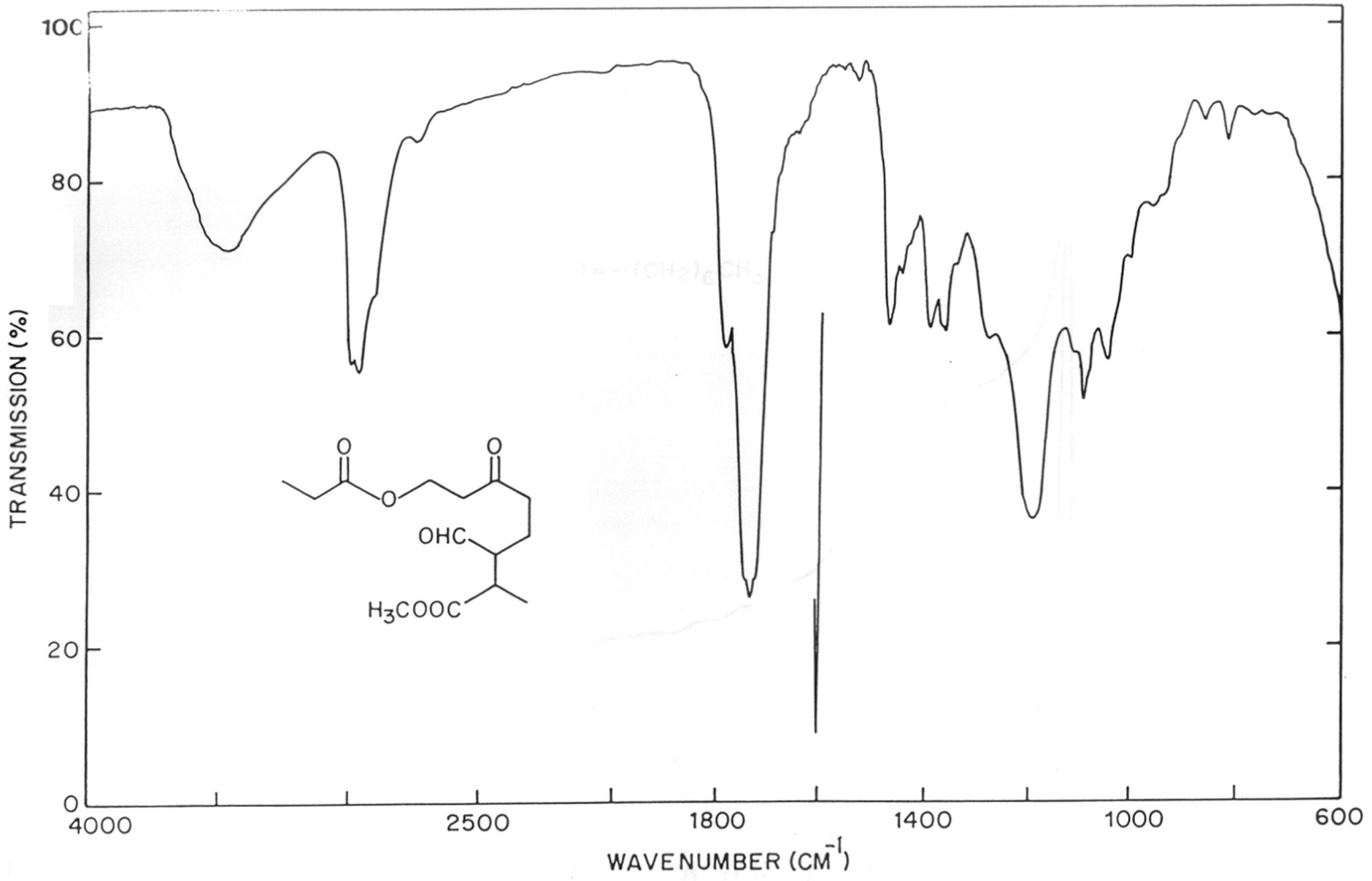


FIG. 3·6 : IR OF THE KETO ALDEHYDE 31

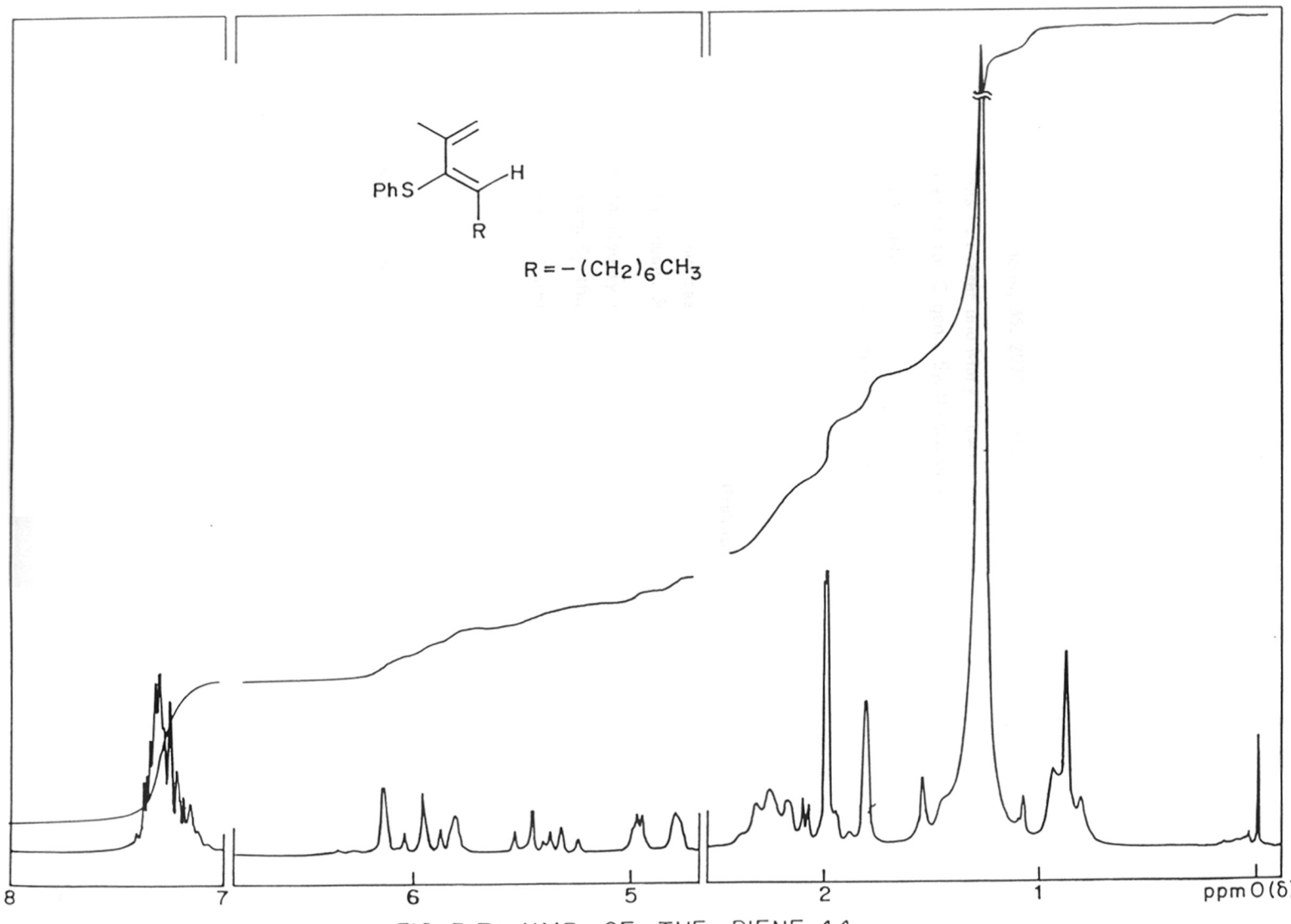


FIG. 3·7 : NMR OF THE DIENE 44

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