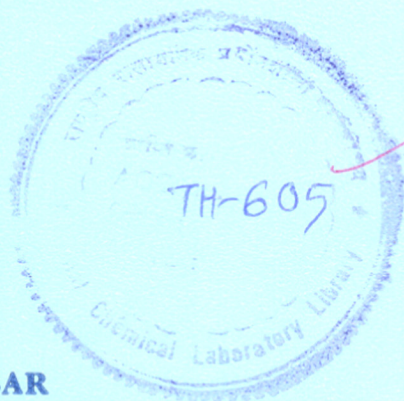


TOTAL SYNTHESIS OF MACROLIDES: R-(+)-PATULOLIDE A AND MONOCILLINS

A THESIS
SUBMITTED TO THE
UNIVERSITY OF POONA
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
(IN CHEMISTRY)

COMPUTERISED



BY
RAMESH A. KASAR

M. Sc.

547.473-314:615.779(043)
KAS

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

MAY 1991

COMPUTERISED

CERTIFICATE

Certified that the work incorporated in the thesis entitled
"Synthesis of Macrolides: R-(+)-Patulolide A and Monocillins" by
RAMESH A. KASAR was carried out by the candidate under my
supervision. Such material as had been obtained from other sources
has been duly acknowledged in the thesis.



(N. R. AYYANGAR)
Research Guide

May 1991

DEDICATED TO MY PARENTS

ACKNOWLEDGEMENTS

I have great pleasure in acknowledging my deep sense of gratitude and indebtedness to my revered supervisor, **Dr. N.R. Ayyangar**, former Deputy Director and Head, Division of Organic Chemistry-II, National Chemical Laboratory, Pune, for his inspiring guidance, keen interest and commitment to my work and helpful hints throughout my thesis work.

I am equally indebted to **Dr.(Mrs.) B. Chanda** for her constant encouragement and useful guidance. I also take this opportunity to thank her for the help rendered in preparation of this manuscript.

It is a privilege to acknowledge **Dr. V.H. Deshpande** for his valuable suggestions and discussions during the course of my work. I am also thankful to **Dr. (Mrs.) R.D. Wakharkar** for her useful advice from time to time.

I wish to take this opportunity to place on record the constant encouragement offered by **Dr. H.B. Boarate**. His helpful suggestions and painstaking efforts in proof-reading the manuscript are very much appreciated.

My sincere thanks to my colleague, **Mr. R.A. Khan** who has been a constant source of encouragement and support during my research tenure. The help rendered by my other esteemed colleagues **Mrs. Latha Sivadasan**, **Mrs. K. Balakrishnan**, **Mrs. Beena Rai**, **Ms. Neelam Gokhale**, **Mrs. Bela Goyal** and **Mr. D. Ravi** is also duly acknowledged. I am very much thankful to **IR, NMR, Mass, GC and Microanalysis groups of NCL** and **Mr. M.V. Jayadevan** for their cooperation.

My wife, **Mrs. Hemalata Kasar's** patience, perseverance and constant encouragement have assisted me throughout the research work and I am very much thankful to her. I am also thankful to my family members, in particular my brothers, **Mr. Prabhakar** and **Mr. Vishnu**.

Finally, I wish to thank the Council of Scientific and Industrial Research, New Delhi for financial assistance in the form of research award and the Director, National Chemical Laboratory, Pune for his permission to submit this research work in the form of a Ph.D. thesis.



Ramesh Annasaheb Kasar

May 1991,
National Chemical Laboratory,
Pune 411008.

INDEX

	<u>Page</u>
ABSTRACT	1-13
<u>CHAPTER I:</u>	
MACROLACTONIZATION IN THE SYNTHESIS OF BIOLOGICALLY ACTIVE MACROCYCLIC LACTONES – METHODOLOGIES AND REAGENTS: A REVIEW	14-40
<u>CHAPTER II:</u>	
SYNTHESIS OF PATULOLIDE A	41-103
<u>Part I : Total Synthesis of (±) Patulolide A</u>	
Introduction	41
Present Work	50
<u>Part II : Synthesis of R (+) Patulolide A</u>	
Introduction	66
Present Work	72
Experimental	86
References	100
<u>CHAPTER III :</u>	
SYNTHESIS OF R-(+) – RECIFEIOLIDE	104-136
Introduction	104
Present Work	114
Experimental	128
References	135
<u>CHAPTER IV :</u>	
STUDIES DIRECTED TOWARDS THE TOTAL SYNTHESIS OF MONOCILLIN IV, NORDINONE AND NORDINONEDIOL	137-190
<u>Part I : Synthesis of Monocillin IV</u>	
Introduction	137
Present Work	142

	<u>Page</u>
<u>Part II :</u> <u>synthesis of Nordinone and Nordinonediol</u>	
Present work	127
Experimental	171
References	188
 <u>CHAPTER V :</u>	
SYNTHESIS OF (±) DI- <u>Q</u> –METHYL-12-OXOCURVULARIN	191-216
Introduction	191
Present work	199
Experimental	210
References	215
LIST OF PUBLICATIONS	217

GENERAL REMARKS

1. All the solvent extracts were finally dried over anhydrous sodium sulphate.
2. All the temperatures are in °C. All the melting points and boiling points are in °C and are uncorrected.
3. Infra-red spectra (ν_{max} in cm^{-1}) were recorded as either liquid film or nujol mull on Perkin-Elmer Infra-red spectrometer model 683B.
4. ^1H -NMR spectra were recorded in CDCl_3 on Varian T-60, Bruker WH-90, FT-80 or WH-300 FT spectrometers, using TMS as internal standard downfield in δ value. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad.
5. GLC was carried out on Hewlett Packard 5890.
6. TLC was carried out on silica gel plates prepared by spreading the slurry (in CCl_4) and drying at room temperature.
7. Mass spectra were recorded on CES-21-110B spectrometer.
8. Microanalyses were carried out in the Microanalytical Section of NCL.
9. All solvents were dried as per standard procedures.
10. Column chromatography was performed on silica gel (60-120 mesh).

ABBREVIATIONS

Ac	:	Acetyl
Ar	:	Aryl
b.p.	:	Boiling point
CCl ₄	:	Carbon tetrachloride
CDCl ₃	:	Deuterated chloroform
DMAP	:	4-Dimethylaminopyridine
h	:	Hour/s
Et	:	Ethyl
g	:	Gram/s
IR	:	Infra-red
Me	:	Methyl
min	:	Minute/s
m.p.	:	Melting points
MS	:	Mass spectrum
nm	:	Nanometer
NMR	:	Nuclear Magnetic Resonance
Ph	:	Phenyl
TBDMS	:	<u>t</u> -Butyldimethylsilyl
DMSO	:	Dimethylsulphoxide

ABSTRACT

The thesis entitled "Synthesis of Macrolides: R-(+)-Patulolide A and Monocillins" is divided into five chapters.

Chapter I: Macrolactonization in the synthesis of biologically active macrocyclic lactones- Methodologies and reagents: A Review.

The term "macrolides" in general is attributed to a class of antibiotics isolated from the Streptomyces sp. but it also encompasses all natural products with large ring lactones. The crux of the macrolide synthesis lies in the macrolactonization of long chain hydroxy acid (seco-acid) by intramolecular esterification of secondary hydroxyl group with a suitably activated carbonyl group. The efficacy of the standard seco-acid approach is critically dependent on the existence of a low energy conformation of the seco-acid. Therefore, the yields in macrolactonization by the seco-acid approach are greatly dependent on the substitution pattern, nature of protecting groups and stereochemistry in seco-acid. In this chapter, the important macrolactonization reagents have been briefly reviewed. Some of these reagents are 2,2'-dipyridyldisulphide along with triphenylphosphine, 2,2'-bis-(4-t-butyl-N-isopropyl)imidazolyldisulphide/ PPh_3 , 2-chloropyridinium iodide and other related reagents developed by Mukaiyama, cyanuric chloride, diethylazodicarboxylate/triphenylphosphine, and 2,4,6-trichlorobenzoyl chloride in the presence of 4-dimethylaminopyridine. Most of these reagents

function by activating the carboxylic acid group of the seco-acid, while some are used to activate the hydroxyl group and some other reagents activate both the carboxylic acid group and hydroxyl group simultaneously.

Enzymes which are versatile reagents also bring about macrolactonization of ω -hydroxy acids. Biocatalytic lactonization of ω -hydroxy acid methyl ester in highly diluted solution has been recently reported.

Chapter II: Synthesis of Patulolide A.

This chapter is divided into two parts.

Part I: Total Synthesis of ($\pm$) Patulolide A

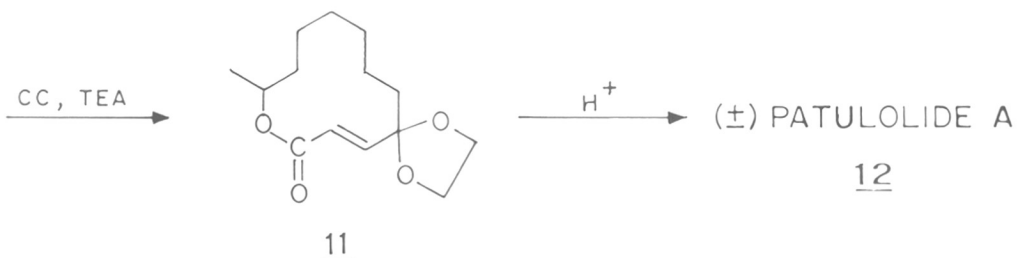
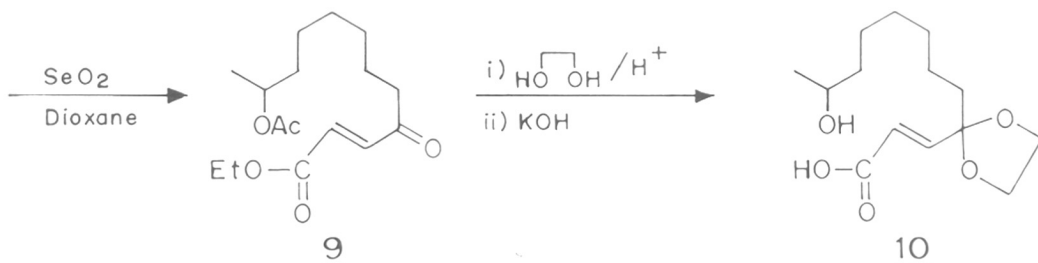
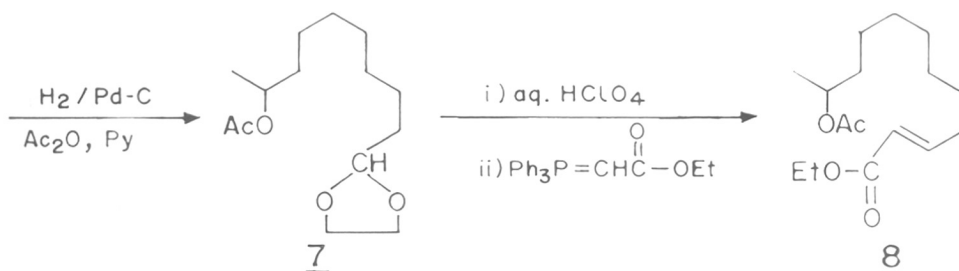
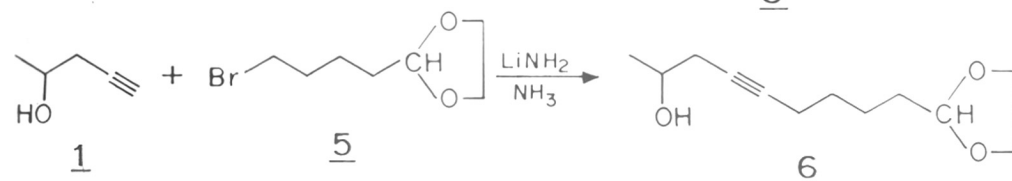
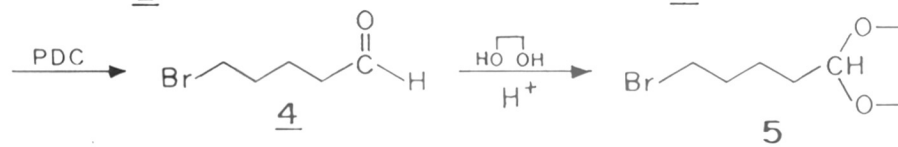
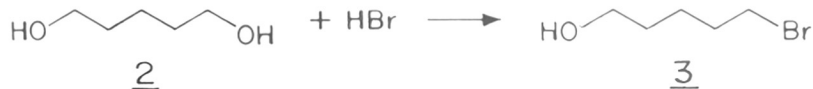
Patulolide A along with two closely related macrolides, patulolide B and patulolide C was isolated from the culture broth of Penicillium urticae S11 R59. Patulolide A is 12-membered lactone with characteristic structural features: a trans double bond flanked with lactone carbonyl and a keto group. It also exhibits antifungal activity. The total synthesis of ($\pm$)patulolide A was undertaken first in order to establish the methodology, to be applied later for the synthesis of R-(+)-patulolide A.

The C-12 unit of patulolide A was synthesized by coupling 4-pentyn-2-ol (**1**) with 2-(4-bromobutyl)-1,3-dioxolane (**5**) followed by two carbon homologation via Wittig reaction with stable phosphorane.

The alcohol (**6**) was prepared by condensing sodium acetylide and propylene oxide. The other C-5 counterpart,

SCHEME-I

3



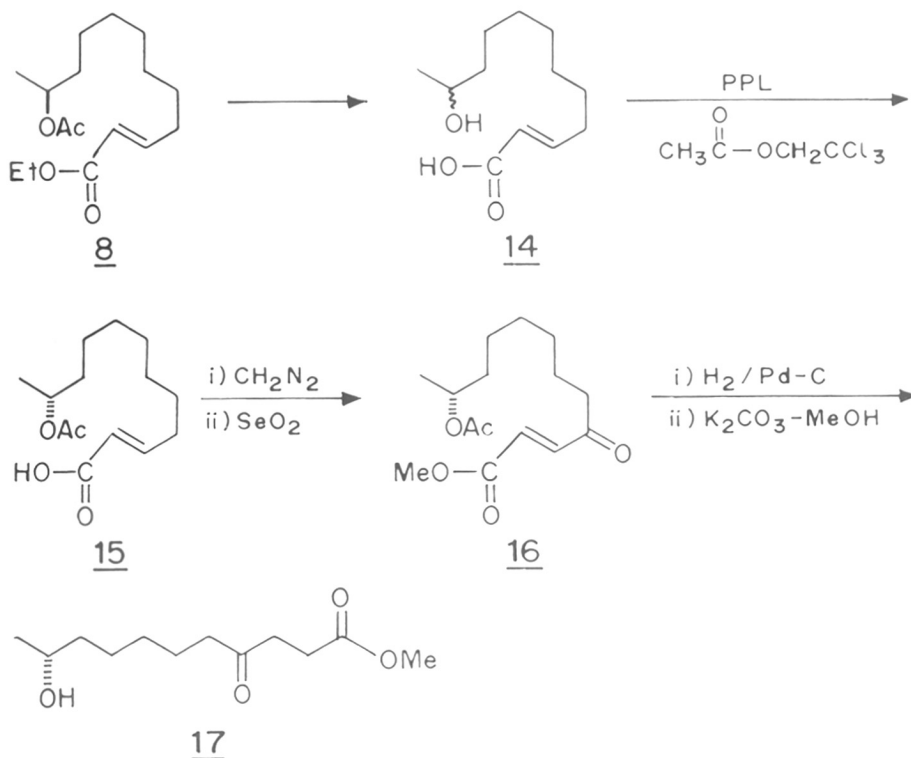
2-(4-bromobutyl)-1,3-dioxolane (5) was synthesized from 1,5-pentanediol (2) via its monobromination, followed by PDC oxidation. Coupling of (1) with (5) was effected with lithium amide in liq. ammonia to yield (6). Hydrogenation of the triple bond with Pd-C and hydrogen followed by acetylation gave saturated acetoxy acetal (7). Deprotection of the acetal gave the aldehyde, which upon Wittig reaction with the stable phosphorane, gave C-12 synthon (8). Allylic oxidation with SeO_2 in dioxane gave (9), which upon ketalisation and alkaline hydrolysis furnished the seco-acid (10) (SCHEME I). The macrolactonization of the seco-acid (10) was achieved with cyanuric chloride in the presence of triethylamine. As conversion of (11) to ($\pm$)patulolide A (12) is already reported, the present synthesis constitutes formally a total synthesis of ($\pm$)patulolide A.

Part II: Synthesis of R-(+)-patulolide A:

In Part I of this chapter, the total synthesis of ($\pm$)-patulolide A was reported. The work towards the total synthesis of R-(+)-patulolide A is the subject matter of Part II of this chapter.

In the present study, chirality in the molecule was introduced at a later stage via lipase-catalysed transesterification of hydroxy acid (14) in the presence of 1,1,1-trichloroethylacetate as an acyl donor under strictly anhydrous conditions. The required product R-(-)-11-acetoxy dodecen-2E-oic acid (15) was obtained in about 30% yield (SCHEME II).

SCHEME-II

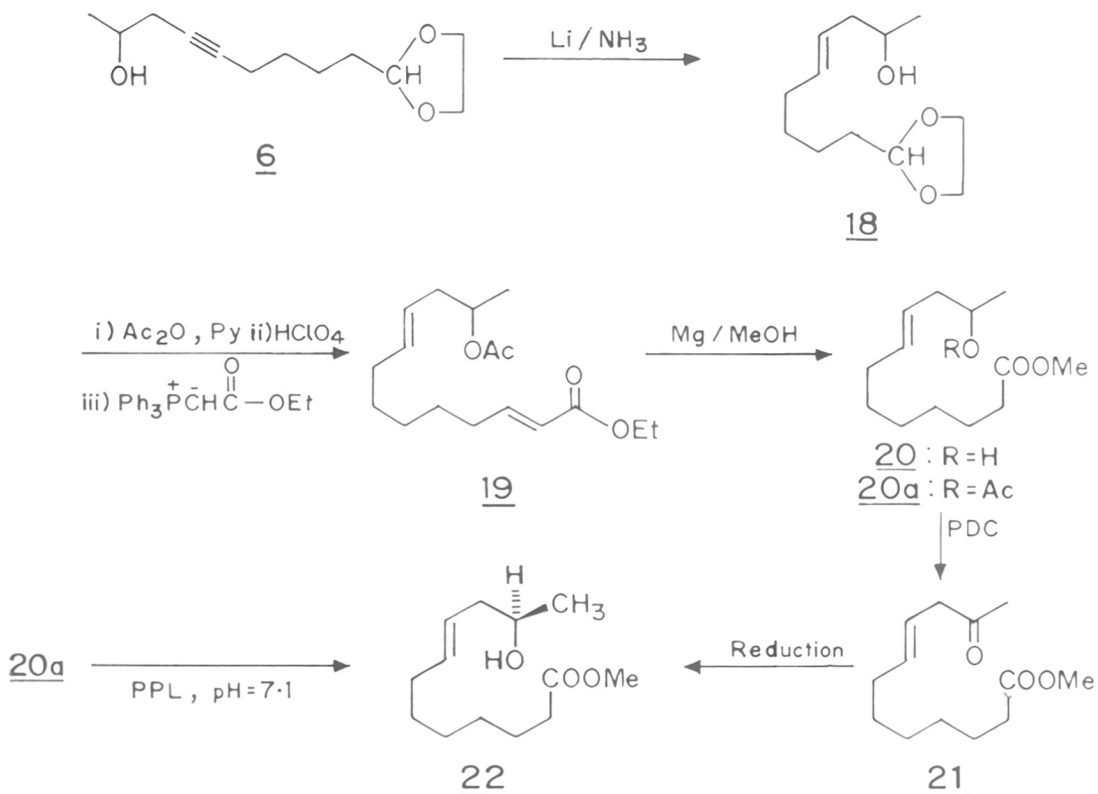


Esterification of (15) with diazomethane yielded the corresponding acetoxy ester. The latter was subjected to allylic oxidation with SeO_2 to furnish (16). Catalytic hydrogenation of (16) with 10% Pd-C gave fully hydrogenated product. Selective hydrolysis of acetate functionality in the presence of ester was achieved with anhydrous potassium carbonate in dry methanol. The product (17) was directly compared with the compound obtained during degradation studies of R-(+)-patulolide A. Its optical rotation, IR and ^1H -NMR values together with ^1H -NMR shift studies with $\text{Eu}(\text{hfc})_3$ (ee 95%) confirmed its identity and purity.

Chapter III: Synthesis of R-(+)-recifeiolide:

Recifeiolide is a 12-membered macrolide isolated from the fungus *Cephalosporium recifei*. NRRL 5161 and its structure was established by spectroscopic and chemical studies. Although it does not possess any biological activity like most of the macrolides, it has potential commercial application as a fixative in perfumes.

SCHEME-III



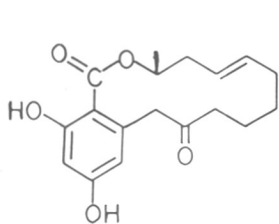
In this chapter, the strategy employed in the synthesis of R-(+)-recifeiolide involved introduction of chirality in the molecule, i.e. on achiral C-12 synthon (20). This was achieved by asymmetric reduction of the C-12 keto ester (21)

by chemical method as well as by enzyme-catalysed hydrolysis of racemic C-12 acetate ester (20a). The C-10 acetal (18) upon 2-carbon Wittig reaction furnished the α,β -unsaturated ester (19). The latter was subjected to selective reduction with activated magnesium in dry methanol to furnish the ester (20), which upon mild oxidation gave the keto ester (21). The latter was subjected to asymmetric reduction with Corey's catalyst and catecholborane. The product R-(-)-methyl 11-hydroxydodecen-8E-oate (22) was obtained in 51% yield along with 42% of (21). Enantiomeric excess of the magnitude of 76% was recorded after comparison with the optical rotation values of authentic (22) (SCHEME III).

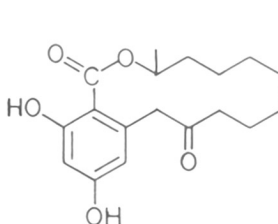
The other approach for the synthesis of (22) involved enantioselective hydrolysis with enzymes. For this purpose, compound (20) was acetylated to furnish (20a), the target compound for enzyme-mediated hydrolysis. Resolution of racemates by enantioselective ester hydrolysis employing lipases from various sources provides a powerful method for the preparation of chiral alcohol. In the present work, for hydrolysis of (20a), lipase derived from Candida cylindracea, PPL and Bacillus subtilis were employed. The most satisfactory and suitable enzyme was found to be PPL. Thus the hydrolysis of (20a) with PPL at pH 7 for 4 h gave a crude reaction product, from which pure R-(-)-methyl 11-hydroxydodecen-8E-oate (22) was isolated in 35% yield along with unhydrolysed ester (20a). Comparison of optical rotation of (22) with that reported showed an ee of 84%. As (22) has already been converted to R-(+)-recifeiolide, the work in this chapter in effect constitutes a total synthesis of R-(+)-recifeiolide.

Chapter IV: Studies directed towards the total synthesis of monocillin IV, nordinone and nordinonediol:

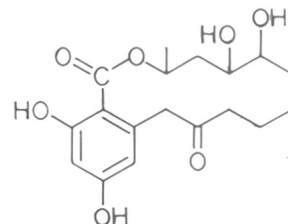
The first total synthesis of monocillin IV (23) and its chemical transformation to nordinone (24) and nordinonediol (25) is reported in this chapter.



23: MONOCILLIN IV



24: NORDINONE



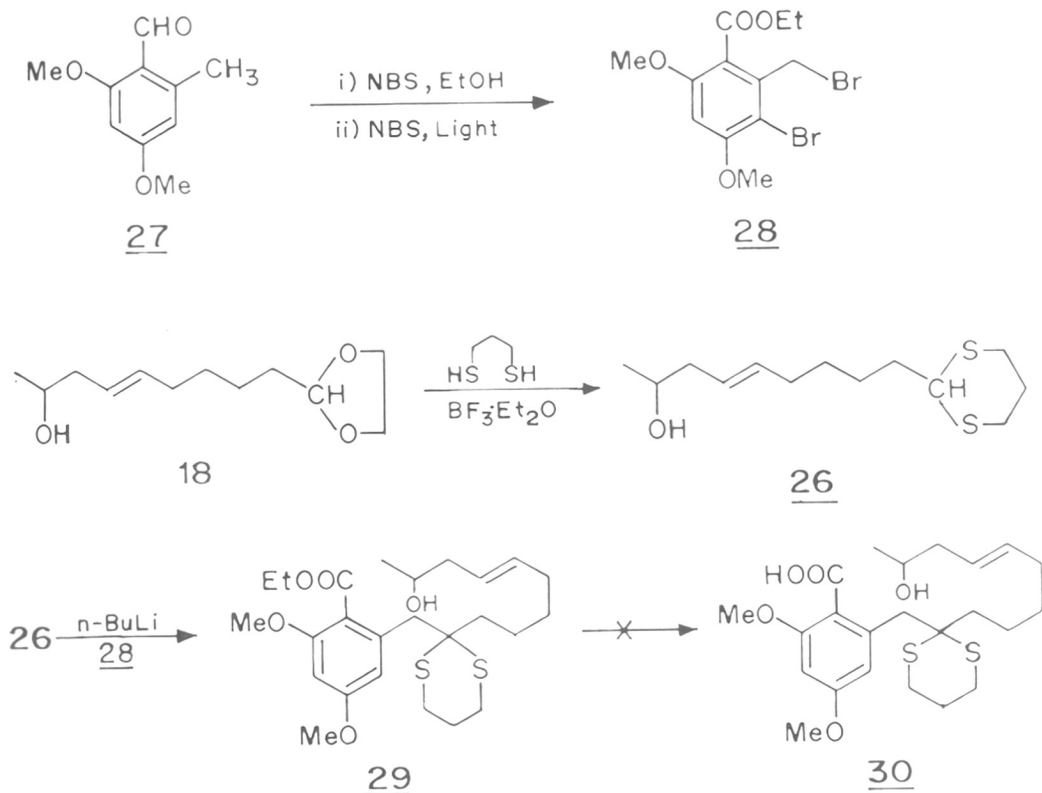
25: NORDINONEDIOL

For the synthesis of the aliphatic part, i.e. the C-10 unit (26) for monocillin IV, an "umpolung" approach was employed. The hydroxy acetal (18) was reacted with propane-1,3-dithiol in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to furnish (26). The aromatic synthon (28) was prepared from dimethylorcinal (27) by NBS bromination with 2.6 equivalent of NBS followed by ethanol. Further bromination with one more equivalent of NBS gave (28) (SCHEME IV).

Metallation of (26) with $n\text{-BuLi}$ followed by the addition of (28) yielded the desired C-C bond coupled product (29). The ester (29) resisted hydrolysis with reagents such as KOH -ethanol, KOH -aq. DMSO etc. to afford (30).

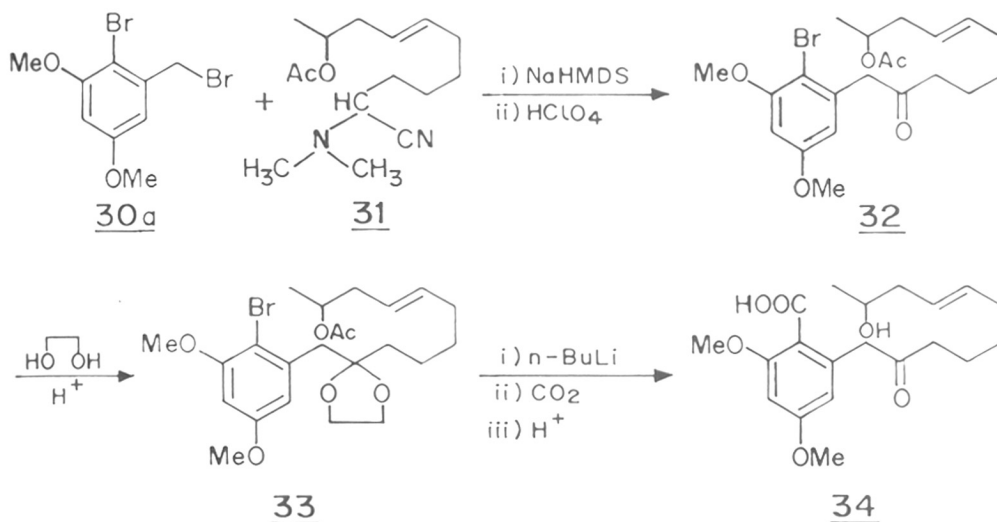
In an alternate approach, the aromatic synthon (30a) was conveniently prepared from 3,5-dimethoxybenzyl bromide by

SCHEME-IV



subjecting it to NBS-bromination. For the aliphatic counter-
 part, the "umpolung" α -aminonitrile (31) was used (SCHEME V).
 The required coupling between (30a) and (31) was effected
 with sodio derivative of hexamethyldisilazane. Deprotec-
 tion of the coupled product with aq. perchloric acid gave
 intermediate (32) which was reprotected with ethyleneglycol
 to yield the ketal (33). Introduction of carboxylic
 acid function was carried out by reacting (33) with n-BuLi
 followed by addition of solid carbondioxide. The carboxy

SCHEME-V



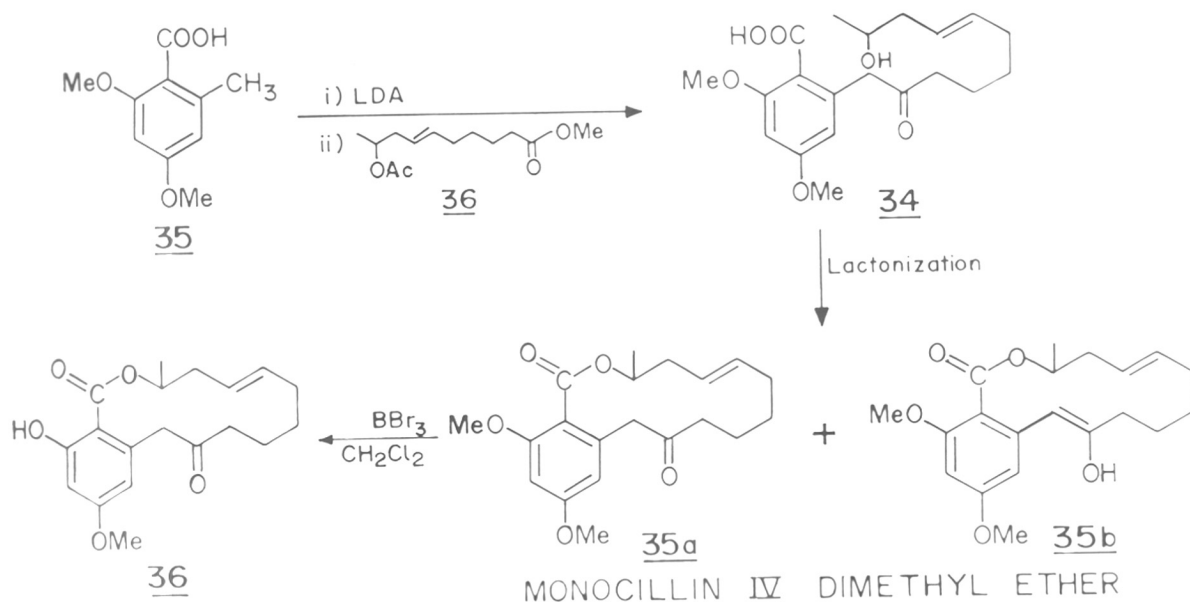
acid (34) was obtained in poor yields since the reaction with solid carbondioxide was sluggish (SCHEME V). Hence further steps in this scheme had to be abandoned.

The third approach was based on the observation made by Houser and Rhee that a carbanion can be generated from substituted o-toluic acid with LDA and this can be further reacted with dimethyl carbonate effecting a C-C bond formation.

Applying the same strategy, the aromatic acid (35) was reacted with 2.2 equiv. LDA. The acetoxy ester (36) was then added and the required coupled product (34) was obtained.

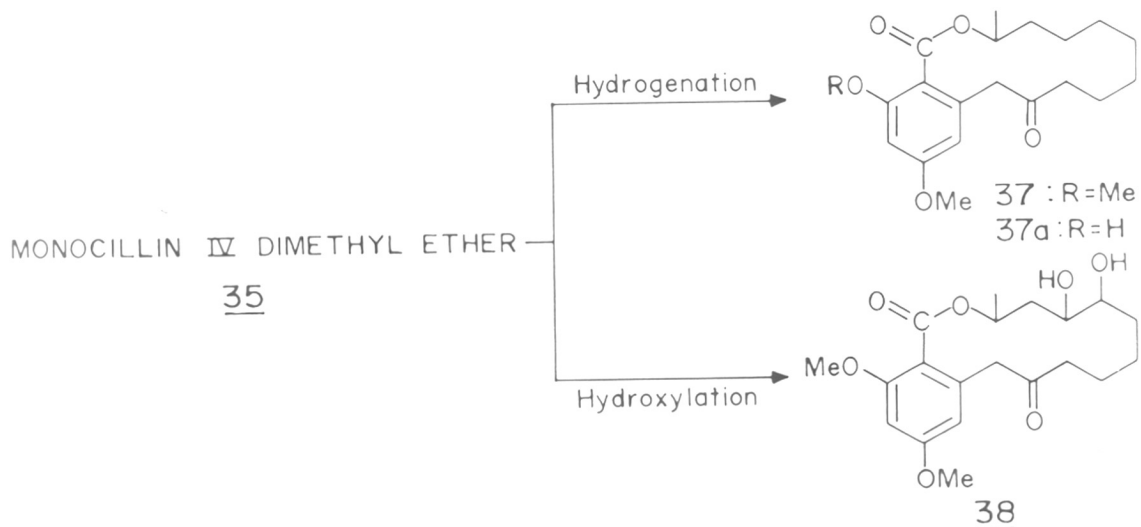
The crucial macrolactonization of the hydroxy acid (34) was carried out with the well-known reagents such as 2,2'-dipyridyldisulphide/ Ph_3P , 2,2'-bis(4-t-butyl-N-isopropyl)imidazolyl disulphide/ Ph_3P and 2,4,6-trichlorobenzoyl chloride/4-dimethylaminopyridine (4-DMAP).

SCHEME-VI



Monocillin IV dimethyl ether was obtained as an isomeric mixture of (**35a**) and (**35b**). Demethylation of (**35**) with BBr_3 produced only the monomethyl ether (**36**) (SCHEME VI).

SCHEME-VII

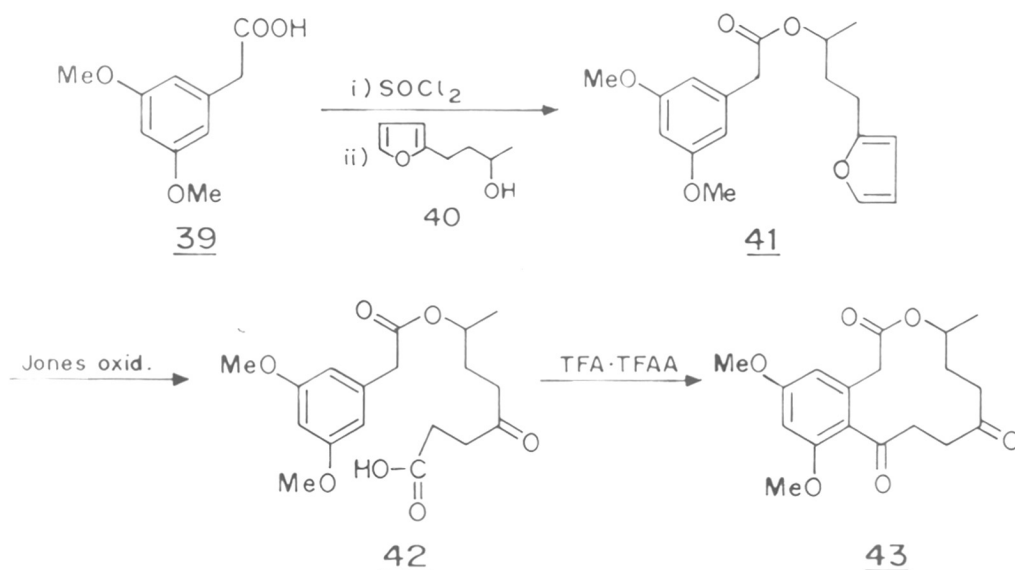


Conversion of monocillin IV dimethyl ether (35) to nordinone dimethyl ether (37) could be achieved easily by catalytic hydrogenation of (35). The nordinone dimethyl ether (37) formed upon demethylation with BBr_3 produced only monomethyl ether (37a). Osmium tetroxide hydroxylation of (35) in presence of N-methylmorpholine-N-oxide (NMO) furnished nordinonediol dimethyl ether (38) (SCHEME VII).

Chapter V: Synthesis of ($\pm$)di-O-methyl-12-oxo-curvularin:

Recently Yamamura et al. isolated 12-oxo-curvularin, curvularin-type metabolite of a hybrid strain ME 0005 derived from Penicillium cetero-viride B. In this chapter, the strategy employed in the synthesis of ($\pm$)di-O-methyl-12-oxo-curvularin (43) involved the use of (3,5-dimethoxyphenyl)

SCHEME-VIII



acetic acid (39) and 4-(2-furyl)-butan-2-ol (40) (SCHEME VIII). The acid (39) was reacted with thionyl chloride followed by the addition of alcohol (40) to afford (41). Jones oxidation of the resultant ester (41) gave the required acid (42) which was cyclized by a known method, i.e. by using trifluoroacetic acid and trifluoroacetic anhydride in 1:5 ratio at room temperature for 5 hr. Purification of the product by alumina column chromatography afforded (±)di-O-methyl-12-oxo-curvularin (43) in 16% isolated yield.

CHAPTER I

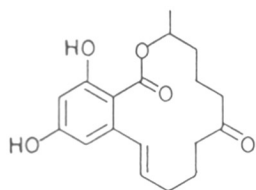
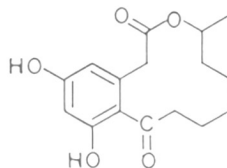
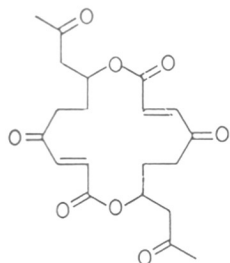
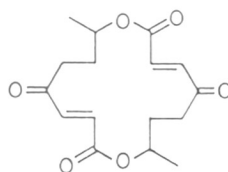
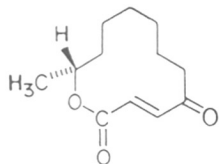
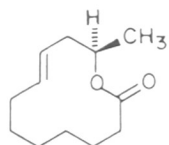
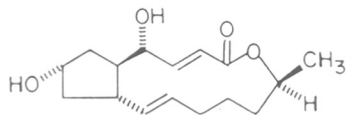
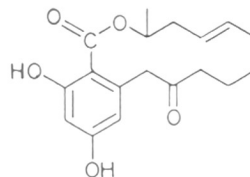
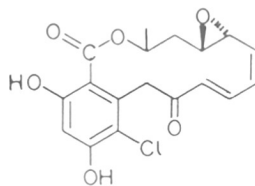
MACROLACTONIZATION IN THE SYNTHESIS OF BIOLOGICALLY ACTIVE MACROCYCLIC LACTONES - METHODOLOGIES AND REAGENTS: A REVIEW

INTRODUCTION:

The chemistry of macrocyclic compounds dates back to 1926 when the structures of civetone and muscone were elucidated.¹ The term "macrocyclic" most commonly refers to large-ring compounds, but in broader sense refers to medium ring compounds as well. In a classical sense "macrolides" refers to a class of antibiotics isolated from the Streptomyces species, with pikromycin being the first macrolide antibiotic to be isolated.² Wider application of the term "macrolides" now encompasses all natural products with large ring lactones. Macrocyclic lactams such as maytansinoides and rifamycins, which are useful drugs for leukemia and tuberculosis respectively, have also been classified as "macrolides".³ Intensive structural elucidation studies have led to unravelling the structures of methymycin, erythromycins A & B, carbomycin A, tylosin, etc.

There are several types of macrolides, viz. 12-, 14- and 16-membered macrolides, polyene macrolides, ionophoric



123467589 RADICOL

macrolides etc. The 12, 14, and 16-membered macrolides are also collectively called "polyoxo" macrolides. There are several lactonic compounds of either mould or bacterial origin which exhibit different biological activities. Some of the well known examples are zearalenone (1)⁴, curvularin (2)⁵, vermiculine (3)⁶, pyrenophorin (4)⁷, brefeldin A (5)⁸, patulolide A (6)⁹, recifeiolide (7)¹⁰, monocillin IV (8)¹¹, etc. Zearalenone (1), radicicol (9) and monocillin IV (8) are examples of " β -resorcylic acid group of macrolide antibiotics".¹¹ The polyene macrolide antibiotics belong to a group of compounds possessing strong antifungal activity. The group of ionophoric macrolides contains two or more lactone groups (oligonolides) in a large ring system. Total syntheses of several of these complex macrolides have been accomplished. It is not proposed to discuss in this chapter the various approaches to the synthesis of macrolides. At the same time, a few observations, which deserve mention have been included. Efforts directed towards the synthesis of polyoxomacrolides were started in mid-seventies and great strides have been made in this area since then.

New methods have been discovered and developed for the construction of the large ring lactones. Very efficient methods have been developed for the "crucial" macrolactonization of long chain hydroxy acids (seco-acids) by intramolecular esterification of secondary hydroxyl group with a suitably activated carbonyl group. The efficacy of the standard seco-acid approach is critically dependent on the

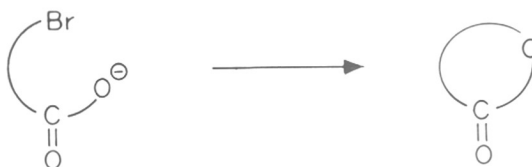
existence of a low energy conformation of the seco-acid in order to achieve efficient cyclisation by one of the methods. Hence the yields in macrolactonisation by the seco-acid approach are greatly dependent on the substitution pattern, nature of protecting groups and stereochemistry in seco-acid. The other approach which is not popular is where the macrocyclic lactones are synthesised by carbon-carbon bond formation.¹² Mostly 16-membered ring lactones have been synthesised in this manner.

Several exhaustive and excellent reviews are available in literature where various aspects of macrolide chemistry are described.¹² In the present chapter, attempts are made to trace the developments in "macrolactonization" reagents, applied in the seco-acid approach. Some of these reagents have been successfully used in the synthesis of various macrolides described in Chapters II & IV. The various reagents and their applications are presented in chronological order.

Macrolactonization reagents that activate carboxylic acid group:

One of the direct syntheses of simple macrolides involves cyclization of the corresponding ω -bromo¹³ or ω -iodo alkanolic acids¹⁴ (SCHEME I). The acids were heated with silver oxide or lactonized via their silver carboxylates. Russian workers¹⁵ obtained macrocyclic oxalactones by condensing diols with ω -chloroalkanoic acids. Due to their easy availability, ω -hydroxycarboxylic acids are more commonly used as the

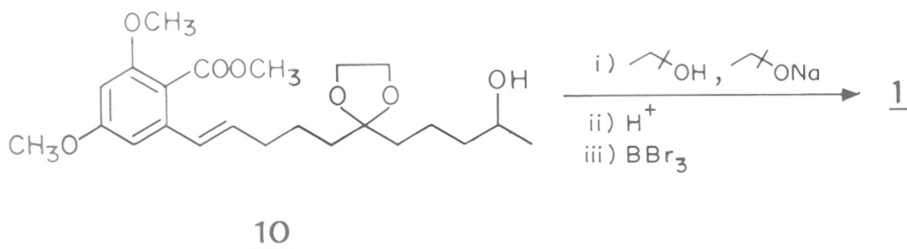
547.473-314:615.777(043)
PSE

SCHEME-I

starting materials for large ring lactones. Several techniques have also been developed and used for activation of the carboxylic acid group, hydroxyl moiety or both the functions simultaneously.

Intramolecular esterification of ω -hydroxyalkanoic acids originally reported by Stoll and Rouve¹⁶ is one of the direct routes for macrocyclic lactones. Alternatively, internal transesterification of esters of ω -hydroxy acids gives macrocyclic lactones. Internal transesterification of glycerides of ω -hydroxycarboxylic acids in the presence of sodium methoxide also affords the corresponding lactones in high yields.¹⁷ Zearalenone (1) was synthesised using a variation of this method but in poor yields.¹⁸ The hydroxy methyl ester (10) was cyclised by treating it with a dilute toluene solution of *t*-amyl alcohol and sodium *t*-amylate (SCHEME II).

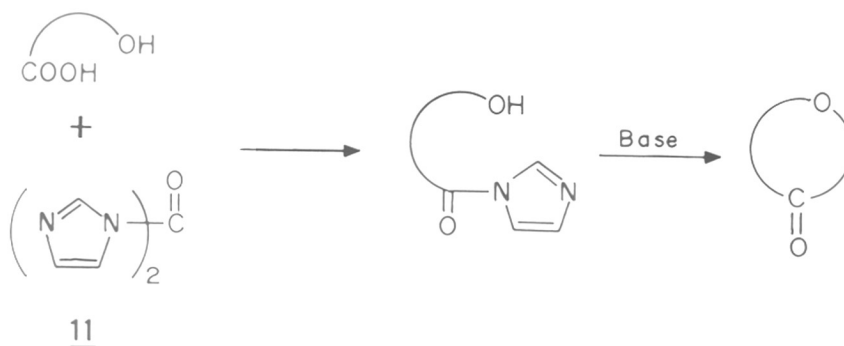
SCHEME-II



ω -Hydroxy acids have also been lactonised via mixed anhydride by their reaction with phosgene-triethylamine¹⁹ or trifluoroacetic anhydride.²⁰ The latter has also been applied to the synthesis of zearalenone. Two related techniques employ p-toluenesulphonyl chloride-triethylamine²¹ and thionyl chloride.²² The former technique has been utilised in the synthesis of a model compound of erythronolide B, which is the aglycone of the antibiotic erythromycin B.²¹

An alternative method for the activation of the carboxylic acids for esterification is by their conversion to N-acylimidazoles by treatment with N,N'-carbonyldiimidazole²³ (SCHEME III). ($\pm$)Pyrenophorin (**4**), an antifungal and cytostatic dilactone was synthesised,²⁴ using this reagent.

SCHEME-III



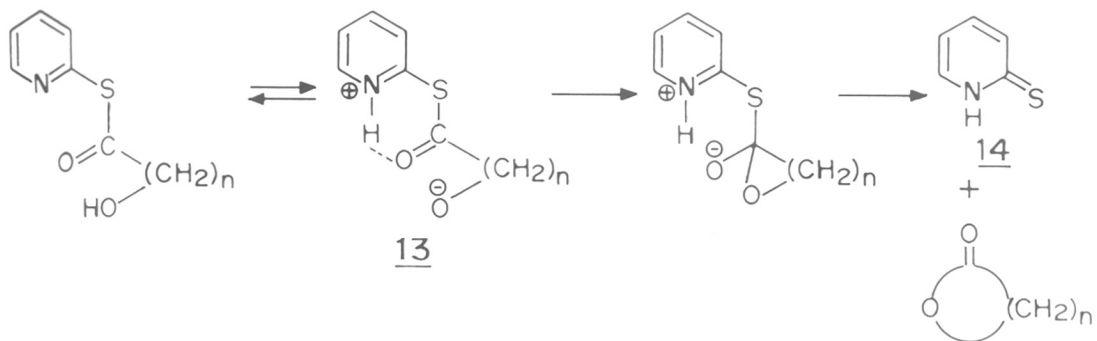
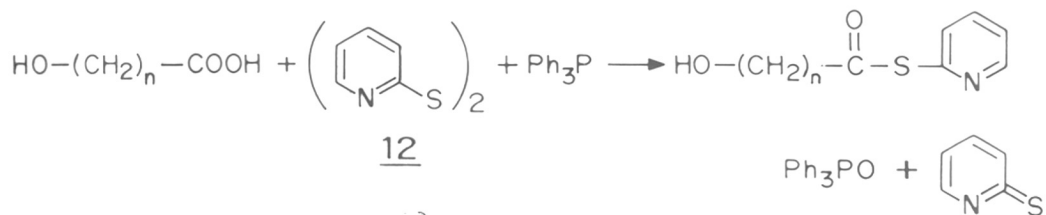
Macrolactonization reagents that employ "double activation":

Activation of a carboxylic acid function on a seco-acid prior to cyclization has several advantages. Simultaneous activation of both the hydroxyl and carboxyl groups leads to even better results in the macrolactonization step. Under milder conditions, efficient and rapid cyclizations can be achieved. Using this technique many complex polyfunctional lactones have been successfully synthesised.^{12d}

(i) Corey-Nicolaou method:

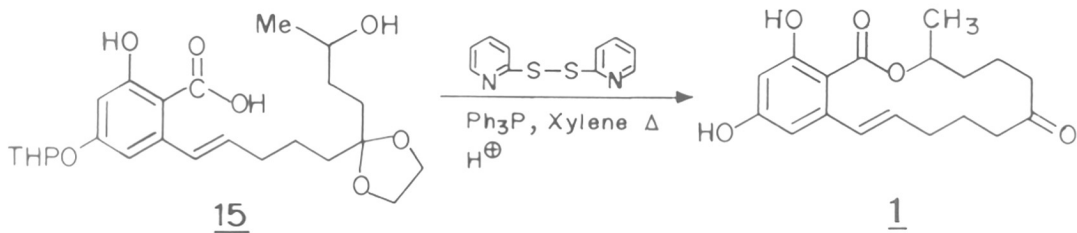
Corey and Nicolaou²⁵ observed that efficient "double-activation" could be achieved with 2-pyridinethiol esters of ω -hydroxyacids. The 2-pyridinethiol esters are readily prepared by well-known oxidation-reduction condensation method developed by Mukaiyama,²⁶ employing di(2-pyridyl) disulphide in the presence of triphenylphosphine (SCHEME IV). The proton transfer from the hydroxyl to the carbonyl group is a favourable reaction. Hence the dipolar intermediate (13) generated could undergo a facile "electrostatically driven" cyclization to the lactone by elimination of 2-pyridithione (14). This method was found to be efficient, useful and mild. The reactions were generally carried out by employing high dilution techniques. The lactonization reaction is generally performed in refluxing benzene or xylene without any acidic or basic catalysts and lactonization process could be accelerated using Ag(I) salt.²⁷

SCHEME-IV



Several macrocyclic lactones with 12 to 21-membered rings have been obtained employing this method. (+)Zearalenone (1) was obtained in 75% yield from the protected (±)hydroxy acid (15) (SCHEME V). Many macrocyclic dilactones

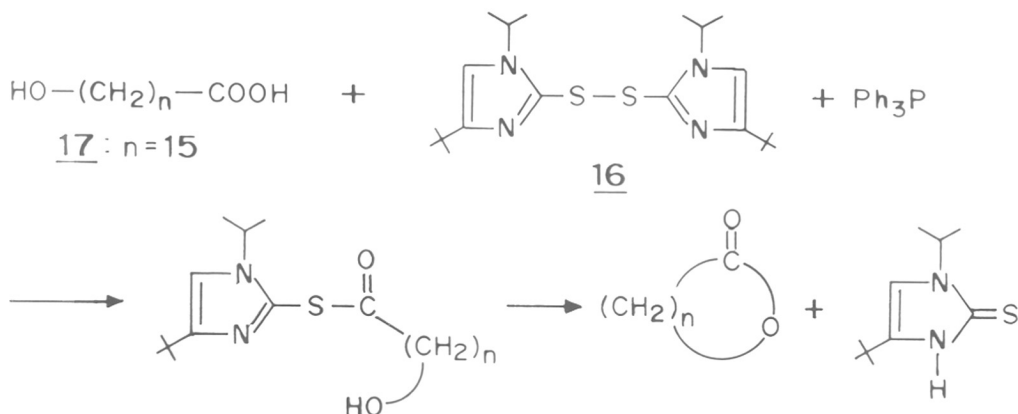
SCHEME-V



like vermiculine²⁸, carpaine²⁹, pyrenophorin, etc. have been synthesised via this method. Application of this lactonization technique in the prostaglandin series (PGF_{2α}) is also very well documented.^{30a} Among the many macrocyclic monolactone syntheses that have been achieved utilising this reagent, it is worth mentioning that of brefeldin A (5)²⁹, recifeiolide (7)^{30b}, erythronolide²⁹ B. etc.

After successful implementation of the above technique, several other heterocyclic disulphides were investigated by Corey and Brunelle³¹ in order to obtain maximum efficiency of the "double activation" method. A series of bis-1-alkyl-2-imidazolyldisulphides were explored for the same and the one that proved to be exceptionally good was 2,2'-bis-(4-t-butyl-N-isopropyl)imidazolyldisulphide (16) (SCHEME VI). Clearly the superiority of this reagent to others is because of the lower reaction temperatures (about 80°C, refluxing benzene) and higher yields. The lactones tetradecanolide,

SCHEME-VI

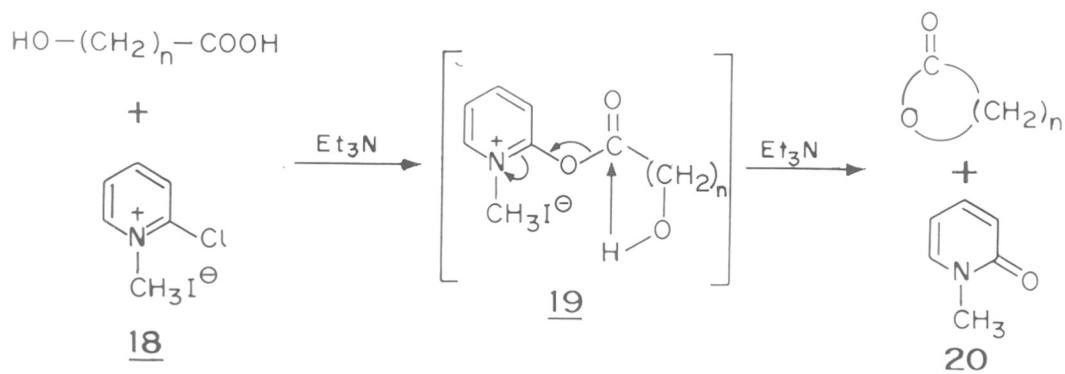


hexadecanolide and dodecanolide were generated from their corresponding ω -hydroxy acids using the reagent (16) in yields of 90%, 96% and 87% respectively. It is also pertinent to point out that at 80°C, the relative rates of cyclization of the thiol esters of 16-hydroxy-n-hexadecanoic acid (17) formed using the reagent (16) or 2,2'-dipyridyldisulphide (12) were found to be 100:1, thereby proving the high efficiency of the reagent (16).

(ii) Mukaiyama's method:

Macrolactonization via 2-chloropyridinium and 2-chloro-benzothiazolium salts was reported by Mukaiyama et al.³² The said reaction was accomplished by carboxyl activation with 1-methyl-2-chloropyridinium iodide (18) in the presence of triethylamine. The reaction proceeds via the pyridinium intermediate (19) in which nucleophilic attack by the hydroxyl group generates the lactone and the 2-pyridone (20). Thus when an acetonitrile solution of a long chain ω -hydroxycarboxylic acid and TEA was slowly added to a refluxing acetonitrile solution of 2-chloro-1-methylpyridinium iodide (SCHEME VII), the corresponding

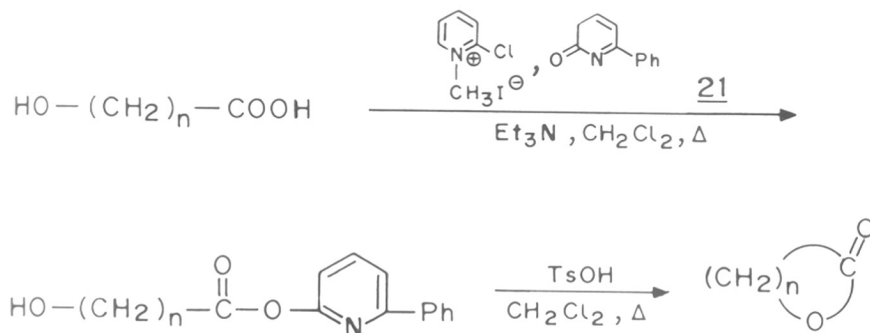
SCHEME - VII



macrocyclic lactone was obtained in good yields which is comparable to the results reported by Corey and Nicolaou.²⁵ Mukaiyama prepared several large ring lactones of upto 16-members in refluxing methylene chloride or acetonitrile.

In order to improve the yields of lactones, further investigations that were carried out revealed that use of 6-phenyl-2-pyridone (21) gave the best results.^{33a} When a ω -hydroxycarboxylic acid was added dropwise under reflux to a dichloromethane solution containing 2-chloropyridinium salt, 6-phenyl-2-pyridone (21) and triethylamine (SCHEME VIII), the

SCHEME-VIII

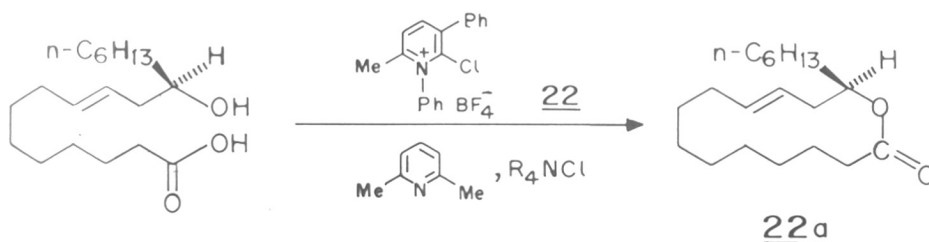


corresponding active ester was obtained in quantitative yield. This active ester was added to the dichloromethane solution of *p*-toluenesulphonic acid to give the desired cyclized macrocyclic lactone in high yield.

The utility of this reaction was clearly demonstrated^{33b} in the synthesis of ricifeiolide (7) and (+)ricinelaidic acid lactone (22a). The target lactones were both obtained in high

yields. As the applicability of the above reagent was limited, due to the use of p-toluenesulphonic acid in the cyclization step and also as a two step reaction was required to achieve lactonization, another reagent was developed which could bring about macrolactonization in a single step.³⁴ Thus 2-chloro-6-methyl-1,3-diphenylpyridinium tetrafluoroborate (22) transformed a long chain ω -hydroxycarboxylic acid smoothly in a single step to the corresponding macrocyclic lactone in high yield (SCHEME IX).

SCHEME-IX



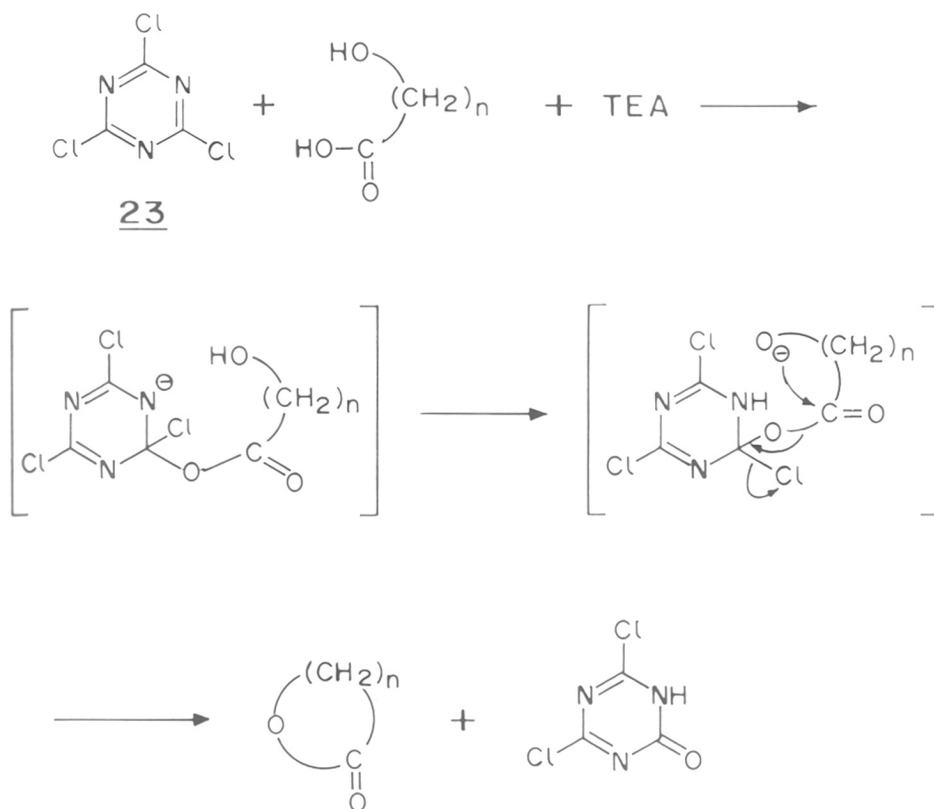
Macrolactonization of $\text{PGF}_{2\alpha}$ and its derivatives also proceeds smoothly, thereby demonstrating the wide applicability of this process.³⁴

(iii) Macrolactonization using cyanuric chloride (CC):

Cyanuric chloride (23) as a reagent for macrolactonization of ω -hydroxy acids was reported in 1980 by Venkataraman and Wagle.³⁵ They reported that cyanuric chloride and triethylamine in acetone at room temperature smoothly converted six ω -hydroxy acids to the corresponding lactones (SCHEME X). In the general procedure, to the acid in dry acetone cyanuric chloride was

added, followed by triethylamine. The reaction was complete in about 6 hours. When no more cyanuric chloride remained in solution, the precipitated chlorohydroxytriazine and triethylamine hydrochloride were removed and the corresponding lactone was isolated and purified.

SCHEME-X

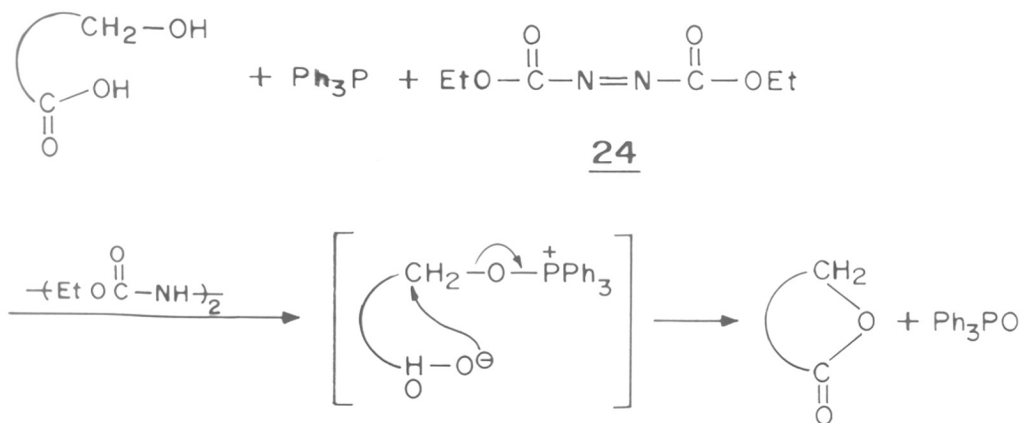


The mechanism of this reaction apparently involves "double activation" of the hydroxyl and carboxyl groups. Making use of the above reagent, a short convergent synthesis of the macro-lactide ($\pm$)patulolide A (6) was completed in 1988.³⁶ (see Chapter-II, Part I).

(iv) Mitsunobu method of macrolactonization by reverse addition:

Japanese workers³⁷ reported yet another general method for the synthesis of simple macrocyclic lactones from ω -hydroxy carboxylic acids by using the reagent, triphenylphosphine in combination with diethylazodicarboxylate (DEAD) (**24**) for the cyclization step (SCHEME XI). This method by Mitsunobu et al. is termed as a "reverse activation technique" for the ring closure as here the hydroxyl group is activated and the carboxylate anion functions as the nucleophile. At room temperature, in benzene or THF solution, a number of macrocyclic lactones

SCHEME-XI



and their corresponding dilides were formed in low to moderate yields depending on the ring size and the exact experimental conditions.

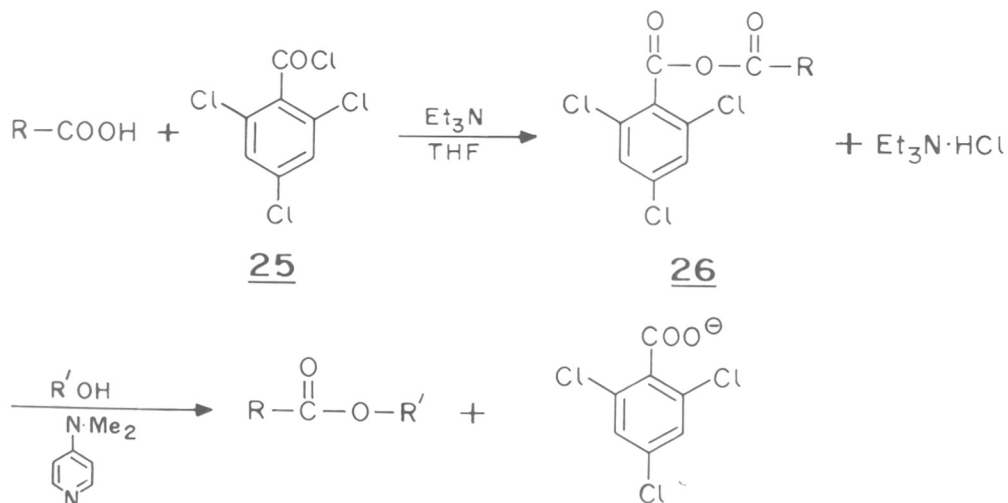
White et al.³⁸ applied this technique to the synthesis of ($\pm$)vermiculine (**3**). This intramolecular cyclization contrasts

with the dimerisation technique employed by Corey's group in their synthesis of vermiculine.²⁸

(v) Yamaguchi method of macrolactonization:

In the year 1979, Yamaguchi *et al.*³⁹ reported a rapid esterification method via a mixed anhydride derived from 2,4,6-trichlorobenzoyl chloride and an acid in the presence of 4-dimethylaminopyridine (4-DMAP) (SCHEME XII). Application of this method in the synthesis of (dl)-2,4,6-tridemethyl-3-deoxymethynolide (28) employing the seco-acid (27) and 2,4,6-trichlorobenzoyl chloride yielded the desired lactone (28) in 46% yield (SCHEME XIII). The esterification by means of mixed

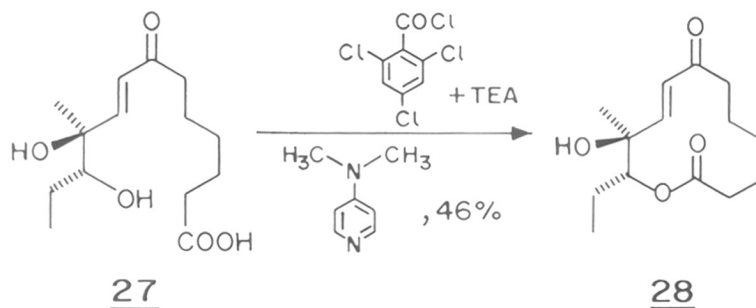
SCHEME-XII



anhydride consists of two steps: the formation of the mixed anhydride and the alcoholysis of the anhydride.⁴¹ The choice of the acid as 2,4,6-trichlorobenzoic acid was based on the fact

that it is a good leaving group and that the carbonyl group of the acid is sterically hindered to some extent for the nucleophilic attack. The amount of DMAP used in the reaction was found to have a significant influence on the rate of the reaction and normally more than one equivalent of the reagent per mole of the mixed anhydride was used when the method was applied to large ring lactonizations.

SCHEME-XIII

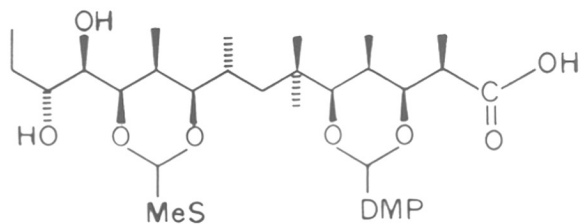


The usual procedure for mixed anhydride preparation was resorted to and after removal of triethylamine hydrochloride the solution of the mixed anhydride was diluted with toluene and slowly added to a refluxing solution of DMAP in toluene under high dilution conditions. In this manner, 9 to 13-membered ring lactones were prepared.

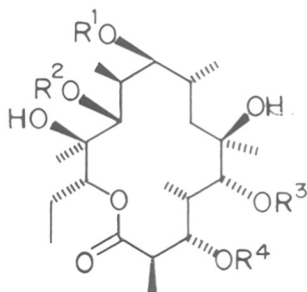
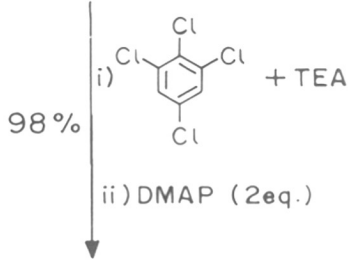
An extremely efficient macrolactonization by a modification of the above method (called modified Yamaguchi method) and its application to a stereoselective synthesis of erythronolide A (**30a**) was reported recently.⁴² Synthesis of (**30b**) was carried

out by cyclization of (29) using Corey,^{25,43} and Yamaguchi⁴⁴ methods, but with little success (SCHEME XIV). Only the Yamaguchi method augmented by a high concentration of DMAP⁴⁴ was successful in producing the desired lactone albeit in poor yields (27%). Perhaps the conformation of (29) was not conducive to the cyclization conditions requiring strong activation as one of the crucial requirements for achieving an efficient cyclization

SCHEME-XIV



29



30a : $R^1 = R^2 = R^3 = R^4 = H$

30b : R^1 and $R^2 = MES$, R^3 and $R^4 = DMP$

of seco-acid derivatives. Accordingly, the proper conformer (29) of the seco-acid was synthesised and when 4-DMAP (2 equiv.) was added to a 10 mM xylene solution of the mixed anhydride of (29) along with 2,4,6-trichlorobenzoyl chloride at room temperature, the lactonization proceeded extremely rapidly. The reaction was complete in $\sim$ 10 minutes to give an almost quantitative yield of the lactone (30). The excellent yield in the lactonization can be explained on the basis of suitable structure of the conformer (29) as well as efficient formation of the highly reactive acylpyridinium salt.⁴² In the present work, in the total synthesis of monocillin IV (8), a yield of 76% was achieved in a similar type of lactonization of seco-acid⁴⁵ (Chapter IV).

(vi) Macrolactonization of ω -hydroxy acids using enzymes:

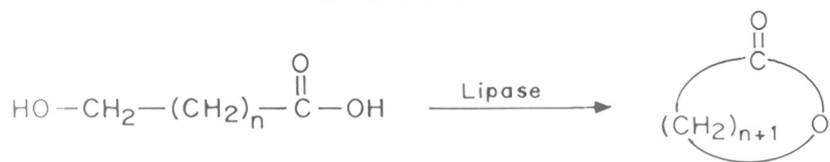
Enzymes which hydrolyse esters in aqueous media are also capable of catalysing esterification or transesterification reactions in monophasic organic solvents or in water-organic solvent biphasic media.⁴⁶ In 1984, it was first noted by Gatfield⁴⁷ that when certain hydroxy acids were exposed to the lipase of Mucor miehei, lactones were formed. This observation was subsequently confirmed by Yamada et al.⁴⁸ who reported the biocatalytic lactonization of ω -hydroxyacid methyl esters in highly diluted solutions. Very recently Gutmann et al.⁴⁹ found that porcine pancreatic lipase (PPL) in anhydrous organic solvents catalysed the lactonization of a number of esters of ω -hydroxyacids.

A novel method for the construction of macrocyclic lactones via direct condensation of diacids (31) and diols (32) catalysed by lipase in non-aqueous media was reported by Sih and co-workers.⁵⁰ In general, biocatalytic lactonization was less

SCHEME-XV

In order to study the stereospecificity of this unique biocatalytic lactonization process, many experiments were

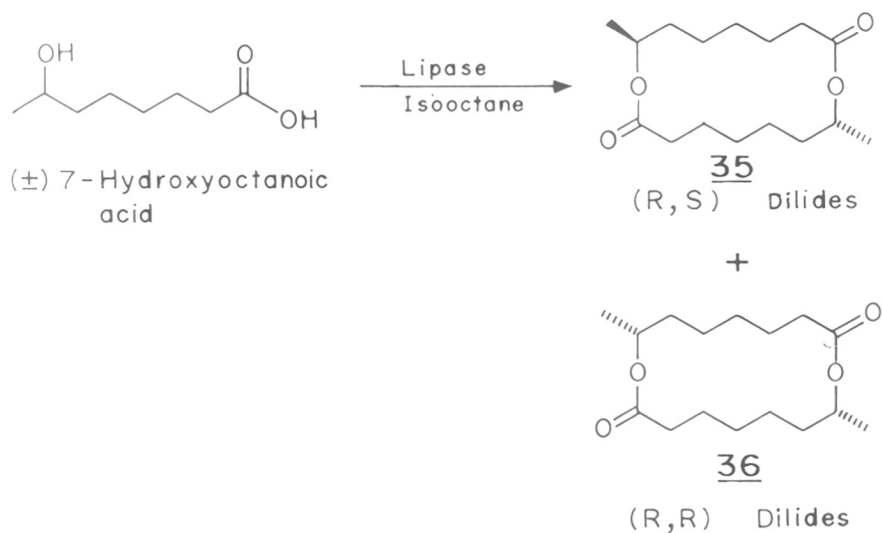
SCHEME - XVI



$n = 14$, 3-66% Yield

conducted. Thus in the case of chiral (ω -1)-hydroxy acid (SCHEME XVI) enzymatic lactonization afforded a complex mixture of diastereomeric lactones of varying ring sizes. Enzymatic

SCHEME - XVII



macrolactonization studies coupled with biocatalytic kinetic resolution of functionalised hydroxy alkanoates have been successfully applied in a chemoenzymatic synthesis of the dilides (35) and (36).⁵¹ (SCHEME XVII).

Conclusion: In this chapter, an attempt has been made to bring together the various important and highly efficient reagents for macrolactonization of seco-acids. Each one of these reagents has been used by many researchers successfully for the syntheses of several important macrolides. During the course of this thesis work, two of these reagents have been applied in the successful completion of the synthesis of (±)patulolide A [employing cyanuric chloride method] and monocillin IV (modified Yamaguchi method). A very exciting recent field is the use of the lipases in macrolactonization. Preliminary exploratory work on these lines and some applications have already been initiated as a sequel to the already completed works described in Chapters II to V.

REFERENCES

1. a) L. Ruzicka,
Helv. Chim. Acta, **9**, 230 (1926).
b) L. Ruzicka,
Ibid, **9**, 715 (1926).
2. H. Brockmann and W. Henkel,
Naturwissenschaften, **37**, 138 (1950).
3. a) W. Keller-Schierlein,
Fortsh. Chem. Org. Naturstoffe, **30**, 313 (1973).
b) W.D. Celmer,
Pure and Appl. Chem., **28**, 413 (1971).
4. W.H. Urry, H.L. Wehrmeister, E.B. Hodge and P.H. Hidey,
Tetrahedron Lett., 3109 (1966).
5. H.D. Munro, O.C. Musgrove and P. Templeton,
J. Chem. Soc. C, 947 (1967).
6. a) R.K. Boeckmann, Jr., J. Fayos and J. Clarady,
J. Am. Chem. Soc., **96**, 5954 (1974).
b) P. Sedmera, J. Vokoun, M. Podojil, Z. Vanek,
J. Fуска, P. Nemec and I. Kuhr,
Tetrahedron Lett., 1347 (1973).
7. a) S. Nozoe, K. Hirai, K. Ishibashi, M. Shrisasaka and
J.F. Grove,
Tetrahedron Lett., 4675 (1965).
b) J.F. Grove,
J. Chem. Soc. C, 2261 (1971).
8. H.P. Weber, D. Hauser and H.P. Sigg,
Helv. Chim. Acta, **54**, 2763 (1971).

9. J. Sekiguchi, H. Kurada, Y. Yamada and H. Okada,
Tetrahedron Lett., **26**, 2341 (1985).
10. R.F. Resonder, F.H. Stodola, L.J. Wickenham, J.J. Ellis
and W.K. Rohwedder,
Can. J. Chem., **49**, 2029 (1971).
11. W.A. Ayer, S.P. Lee, A. Tsuneda and Y. Hiratsuka,
Can. J. Microbiol., **26**, 766 (1980).
12. a) K.C. Nicolau,
Tetrahedron, **33**, 683 (1977).
b) T.G. Back,
Tetrahedron, **33**, 3041 (1977).
c) S. Masamune, G.S. Bates and J.W. Corcoran,
Angew. Chem. Int. Ed. Engl., **16**, 585 (1977).
d) I. Paterson and M.M. Mansuri,
Tetrahedron, **41**, 3569 (1985).
13. a) M. Kerschbaum,
Ber. Dtsch. Chem. Ges., **60B**, 902 (1927).
b) P. Baudart,
C.R. Acad. Sci., **221**, 205 (1945).
14. H. Hunsdiecker and H. Erlback,
Chem. Ber., **80**, 129 (1947).
15. S.A. Voitkevich, N.P. Solov'eva, L.P. Kizyakova and
A.G. Belfer,
Maslo-Zhir. Prom., **10**, 29 (1973).
16. M. Stoll and R. Rouve,
Helv. Chim. Acta, **17**, 1283 (1934).

17. a) C. Colland,
Helv. Chim. Acta, **25**, 945 (1942).
b) C. Colland,
Ibid, **26**, 849 (1943).
18. I. Vlatts, I.T. Harrison, L. Tokes, J.H. Fried and
A.D. Cross,
J. Org. Chem., **33**, 4176 (1968).
19. H.L. Wehrmeister and D.E. Robertson
J. Org. Chem., **33**, 4173 (1968).
20. D. Taub, N.N. Girotra, R.D. Hoffsomner, C.H. Kuo,
H.L. Slates, S. Weber and N.C. Wendler,
Tetrahedron, **24**, 2443 (1968).
21. J.D. White, S.N. Lodwig, G.L. Trammell and M.P. Fleming,
Tetrahedron Lett., 3263 (1974).
22. J.D. Wrobel and W.M. Golebiewski,
Tetrahedron Lett., 4293 (1973).
23. H.A. Staab,
Angew. Chem. Int. Ed., **1**, 351 (1962).
24. E.W. Colvin, T.A. Parcell and R.A. Raphael,
J. Chem. Soc., Chem. Commun., 1031 (1972).
25. E.J. Corey and K.C. Nicolaou,
J. Am. Chem. Soc., **96**, 5614 (1974).
26. a) T. Mukaiyama,
Synthetic Commun., **2**, 243 (1972).
b) T. Mukaiyama,
Angew. Chem. Int. Ed., **15**, 94 (1976).

27. H. Gerlach, K. Oertle, A. Thalmann and S. Servi,
Helv. Chim. Acta, **58**, 2036 (1975).
28. E.J. Corey, K.C. Nicolaou and T. Toru,
J. Am. Chem. Soc., **97**, 2287 (1975).
29. E.J. Corey, K.C. Nicolaou and L.S. Melvin,
J. Am. Chem. Soc., **97**, 654 (1975).
30. a) E.J. Corey, K.C. Nicolaou, L.S. Melvin,
J. Am. Chem. Soc., **97**, 653 (1975).
b) E.J. Corey, P. Ulrich and J.M. Fitzpatrick,
J. Am. Chem. Soc., **98**, 222 (1976).
31. E.J. Corey and D.J. Brunelle,
Tetrahedron Lett., 3409 (1976).
32. T. Mukaiyama, M. Usui and K. Saigo,
Chem. Lett., 49 (1976).
33. a) T. Mukaiyama, K. Narasaka and K. Kikuchi,
Chem. Lett., 441 (1977).
b) K. Narasaka, M. Yamaguchi and T. Mukaiyama,
Chem. Lett., 959 (1977).
34. K. Narasaka, K. Maruyama and T. Mukaiyama,
Chem. Lett., 885 (1978).
35. K. Venkataraman and D.R. Wagle,
Tetrahedron Lett., 1893 (1980).
36. N.R. Ayyangar, B. Chanda, R.D. Wakharkar and R.A. Kasar,
Synth. Commun., **18**, 2103 (1988).
37. T. Kurihara, Y. Nakajima and O. Mitsunobu,
Tetrahedron Lett., 2455 (1976).

38. Y. Fukuyama, C.L. Kirkema and J.D. White,
J. Am. Chem. Soc., **99**, 646 (1977).
39. J. Inanaga, K. Hirata, H. Saeki, T.Katsuki and
M. Yamaguchi,
Bull. Chem. Soc. Jpn., **52**, 1989 (1979).
40. a) G. Hofle and W. Steglich,
Synthesis, 619 (1972).
b) H. Vorbruggen,
Synthesis, 309 (1973).
41. N.F. Albertson,
Org. React., **12**, 157 (1962).
42. M. Hikota, H. Tone, K. Horita and O. Yonemitsu,
J. Org. Chem., **55**, 7 (1990).
43. E.J. Corey, P.B. Hopkins, S. Kim, S. Yoo,
P.K. Nambiar and J.R. Falk,
J. Am. Chem. Soc., **101**, 7131 (1979).
44. H. Tone, T. Nishi, Y. Oikawa, M. Hikota and O. Yonemitsu,
Chem. Pharm. Bull., **37**, 1160 (1989).
45. R.A. Kasar, R.D. Wakharkar, B. Chanda and N.R. Ayyangar,
Tetrahedron Lett., **31**, 6445 (1990).
46. a) A. Zake and A.M. Klibanov,
Science, **224**, 1249 (1984).
b) A.N. Semenov, Y.L. Khmel'nitski, I.V. Berezin and
K. Martinek,
Biocatalysis, **1**, 3 (1987).
47. I.L. Gatfield,
Ann. N.Y. Acad. Sci., **434**, 569 (1984).

48. A. Makita, T. Nihira and Y. Yamada,
Tetrahedron Lett., **28**, 805 (1987).
49. A.L. Gutman, K. Zuobi and A. Boltansky,
Tetrahedron Lett., **28**, 3861 (1987).
50. Z.W. Guo and C.J. Sih,
J. Am. Chem. Soc., **110**, 1999 (1988).
51. a) Z.W. Guo, T.K. Ngooi, A. Scilimati, G. Fulling and
C.J. Sih,
Tetrahedron Lett., **29**, 5583 (1988).
b) T.K. Ngooi, A. Scilimati, Z.W. Guo and C.J. Sih,
J. Org. Chem., **54**, 911 (1989).

CHAPTER II

SYNTHESIS OF PATULOLIDE A

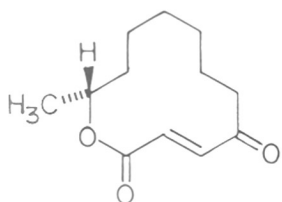
INTRODUCTION:

In 1985, during the course of isolating secondary metabolites from various mutant strains of Penicillium urticae, Yamada et al.¹ isolated a new 12-membered macrocyclic ring lactone, Patulolide A (1) from the culture broth of Penicillium urticae S11 R59. It belongs to a rather new group of macrolides comparable in structure to cladospolide A (5) and cladospolide B (6) produced by Cladosporium cladosporides² and recifeiolide (4) produced by Cladosporium recifei.³

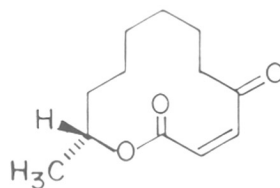
Structure and absolute configuration of patulolide A:

Yamada et al.¹ determined the structure and absolute configuration of patulolide A (1) from spectroscopic data and chemical degradation. It crystallised from n-hexane (m.p. 83°C), $[\alpha]_D^{25} = +30.1^\circ$ (C = 0.95 in EtOH). IR spectrum revealed absorptions at 1700 cm⁻¹ and 1680 cm⁻¹ indicating presence of lactone carbonyl and an α,β -unsaturated keto functionality. The absolute configuration at C-11 was determined by converting patulolide A (1) into methyl 4-oxo-11-hydroxydecanoate (8) as shown in SCHEME I.

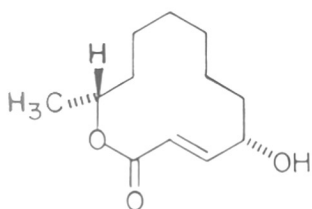
Patulolide A (1) was hydrogenated to dihydropatulolide A (7). This on hydrolysis and esterification yielded the required methyl ester (8). The latter was treated with 2-phenylbutanoic anhydride in pyridine according to Horeau's procedure⁵ and from the specific rotation of recovered 2-phenylbutanoic acid, absolute configuration at C-11 of patulolide A was deduced as 'R'.



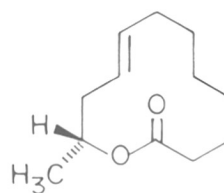
PATULOLIDE A (1)



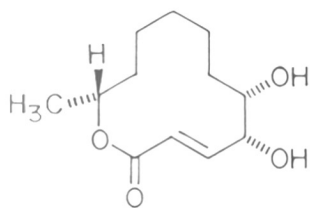
PATULOLIDE B (2)



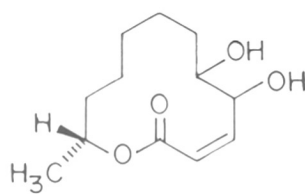
PATULOLIDE C (3)



RECIFEIOLIDE (4)



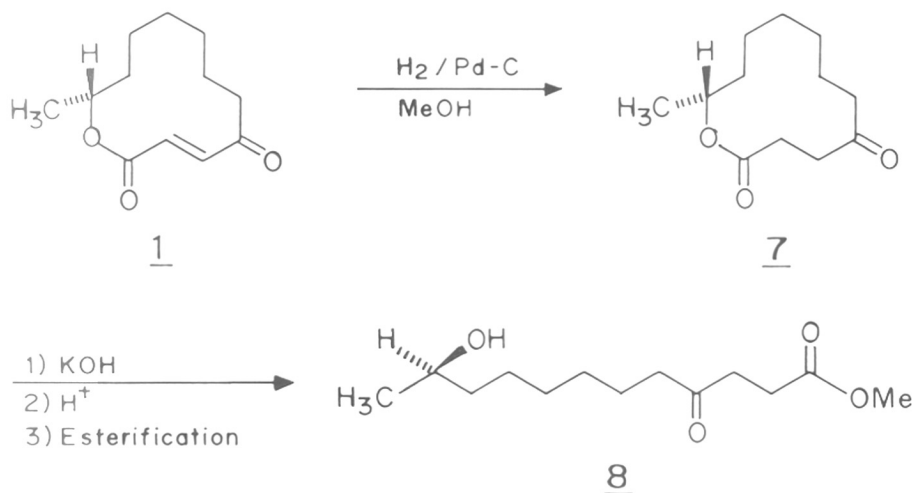
CLADOSPOLIDE A (5)



CLADOSPOLIDE B (6)

The ^1H -NMR spectrum of (1) indicated the presence of trans olefinic protons as doublets at δ 7.25 and at δ 6.45, each having a coupling constant of 16 Hz, a doublet at δ 1.35 ($J=6\text{Hz}$) and a multiplet at δ 4.91. Further, NMR studies showed the coupling between the protons at δ 1.35 and at δ 4.91. These data indicated the presence of $\text{CH}_3\text{CH-O}$ moiety in the structure of patulolide A (1). From the ^{13}C -NMR, presence of lactone carbonyl at δ 166.6 and ketocarbonyl at δ 202.4 were confirmed. On the basis of above spectroscopic data, the structure (1) was assigned to patulolide A.

SCHEME-I



Structure activity studies of patulolides:

Patulolides A, B and C exhibited different levels of antibacterial and antifungal activities.⁴ Of these, patulolide A (1) and patulolide B (2) inhibited various strains of fungi and yeasts and their effects were more potent than

that of patulolide C (3). Patulolide C (3) showed no antibacterial activity, while patulolide A (1) and patulolide B (2) exhibited some activity towards both Gram-negative and Gram-positive bacteria. From the result of these antimicrobial activities and the structures of these macrolides, the essential structural feature responsible for the activity appears to be a double bond flanked by carbonyl groups. Patulolide A and patulolide B have such structural features. The difference is that patulolide A has a trans geometry at the double bond, whereas patulolide B has a cis-geometry. Patulolide A is much more active than patulolide B, thus suggesting that trans-geometry at the double bond flanked with two carbonyl groups is essential for antibacterial and antifungal activity. In patulolide C (3) there is an α -hydroxyl group at C-4 position instead of a carbonyl function.

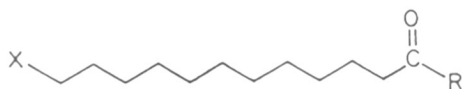
Synthesis of ($\pm$)patulolide A:

Under this sub-heading, only the total synthesis of ($\pm$)patulolide A is covered. This includes two approaches reported in the literature.^{6,7} The present work also describes total synthesis of ($\pm$)patulolide A. The synthesis of R-(+)-patulolide is described in Part-II of this chapter.

Makita's approach:

The first total synthesis of ($\pm$)patulolide A was reported by Makita et al.⁶ from 12-hydroxydodecanoic acid (SCHEME II). The hydroxy acid (9) was converted into methyl 12-bromododecanoate (11) via 12-bromododecanoic acid (10). The ester (11)

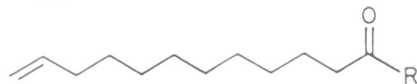
SCHEME - II



9: R=OH , X = OH

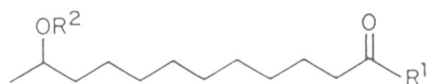
10: R=OH , X = Br

11: R=OMe, X = Br



12: R = OMe

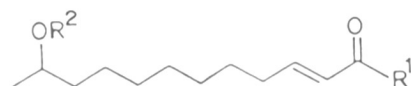
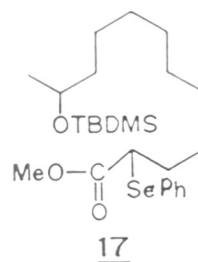
13: R = NMe₂



14: R¹ = OH , R² = H

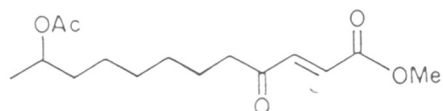
15: R¹ = OMe , R² = H

16: R¹ = OMe , R² = TBDMS

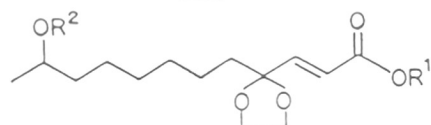


18: R¹ = OMe R² = TBDMS

19: R¹ = OMe R² = Ac



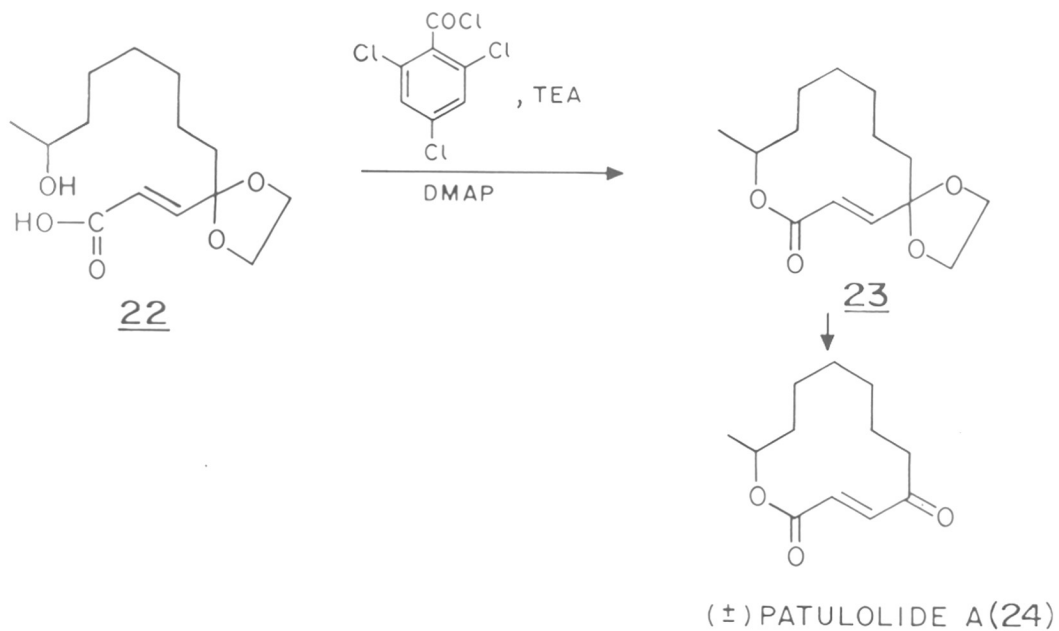
20



21: R¹ = Me R² = Ac

22: R¹ = H R² = H

was dehydrobrominated (NaI/HMPA) to give the ester (12) along with the corresponding dimethylamide (13). The ester (12) was converted into 11-hydroxydodecanoic acid (14) by treatment with mercuric acetate followed by NaBH_4 which was methylated to give the methyl ester (15). The amide (13) was converted into methyl 11-hydroxydodecanoate (15) in a similar manner. The latter was transformed to its silyl ether derivative (16) by treatment with TBDMS chloride. Introduction of double bond in the α,β -position of the ester (16) was effected by treatment with LDA in THF at -78°C followed by the addition of benzeneselenyl bromide. Oxidative elimination of the resultant product (17) was carried out with H_2O_2 /acetic acid at 0°C to give the desired α,β -unsaturated ester (18). Protection of the hydroxyl function by forming *t*-butyldimethylsilyl ether (TBDMS) gave unsatisfactory results in the subsequent allylic oxidation step, mainly due to the instability of the TBDMS group under acidic conditions. Hence as an alternative, acylation was carried out. The acetate (19) was subjected to allylic oxidation with chromium trioxide-acetic acid - acetic anhydride mixture to furnish the ketone (20) albeit in poor yield of 42%. The carbonyl group of (20) was protected as the ethylene ketal (21) by treatment with ethylene glycol and triethylorthoformate in the presence of traces of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in benzene. Alkaline hydrolysis of (21) with 2N KOH gave the required seco-acid (22) in quantitative yield.

SCHEME -II (Contd.)

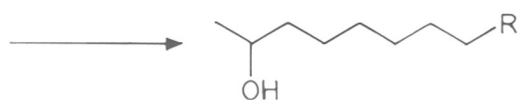
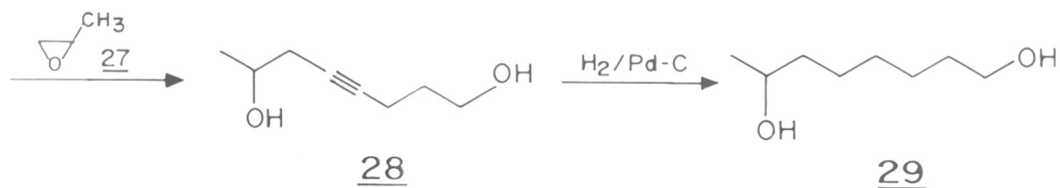
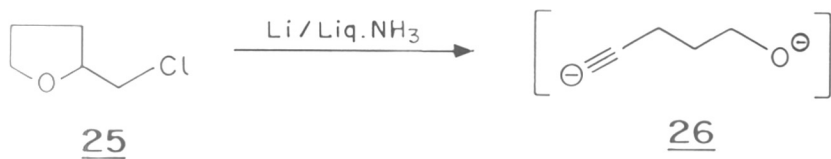
The key lactonization step was carried out by reaction of (22) with 2,4,6-trichlorobenzoyl chloride in the presence of triethylamine and the resulting mixed anhydride was refluxed in toluene using high dilution technique.²³ The lactone (23) failed to undergo deprotection under standard conditions, i.e. by using acetone-p-toluene sulphonic acid. Deprotection was, however, successfully carried out by Barton's method³⁴ using tritylfluoroborate in dichloromethane, although not in good yield. The synthetic (±)patulolide A (24) had m.p. 78-79°C which is about 4-5°C lower than that of (+)patulolide A. It was identical in all other respects (spectroscopy, TLC, etc.) with the natural product.

Yadav's approach:

A partial synthesis of ($\pm$)patulolide A (24) by application of a novel methodology for the synthesis of 1,7-dihydroxyhept-4-yne derivatives was reported recently by Yadav *et al.*⁷ (SCHEME III). The key reaction involved was the in situ alkylation of tetrahydrofurfuryl chloride (25) with methyloxirane (27). Thus the dianion of 1-pentyne-5-ol (26) generated from the tetrahydrofurfuryl chloride with lithium in liquid ammonia was alkylated in situ with methyloxirane to yield 1,7-dihydroxy-7-methylhept-4-yne (28). Catalytic hydrogenation of the latter yielded the corresponding saturated diol (29). Selective tosylation of the primary hydroxyl group with tosyl chloride - pyridine gave (30) which upon nucleophilic displacement with lithium bromide - acetone furnished the bromide (31). The alkylation of furan with (31) was effected with n-BuLi at -40°C to give the mono-alkylated product (32). Protection of the free hydroxyl group as the acetate (33) followed by oxidative ring cleavage with bromine-pyridine afforded the corresponding ene-dione derivative (34). Conversion of the aldehyde group in (34) to the acid (35) was carried out by employing sodium chlorite along with sodium dihydrogenphosphate as buffer and 2-methyl-2-butene as chlorine scavenger. Subsequent esterification of (35) with methanolic ferric chloride gave the ester (20). Since the latter has already been transformed to patulolide A⁶ the above synthetic route was taken as constituting a formal synthesis of ($\pm$)patulolide A (24).

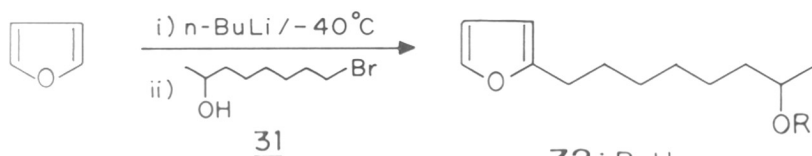
SCHEME-III

49



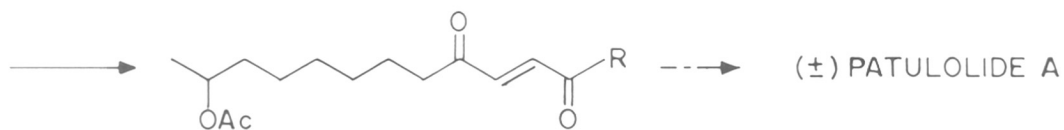
30 : R = OTs

31 : R = Br



32 : R = H

33 : R = Ac



34 : R = H

35 : R = OH

20 : R = OMe

PRESENT WORK:

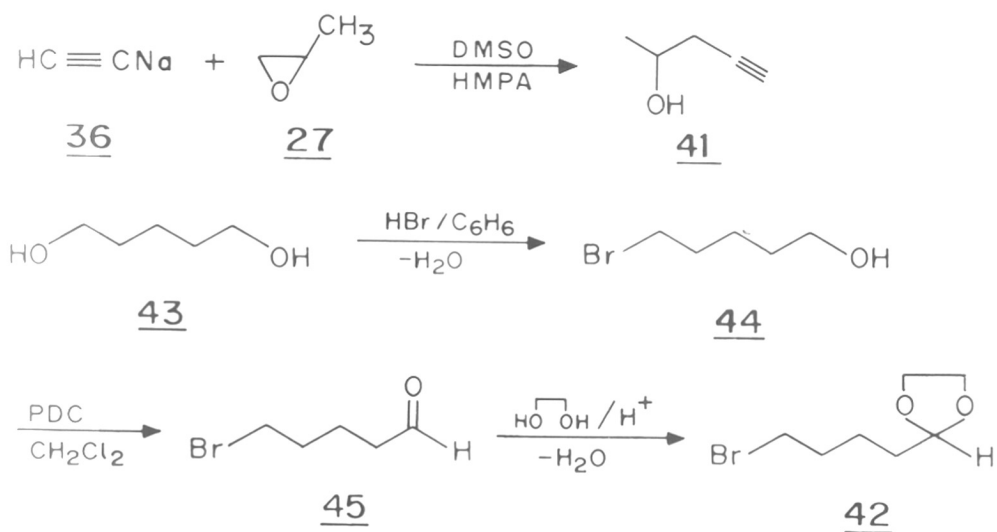
As is evident from what has been described so far, only one total synthesis of ($\pm$)patulolide A was reported in the year 1986, soon after the isolation and structure determination of patulolides A, B and C. The reported synthetic sequence⁶ involved about 15 steps starting from 12-hydroxydodecanoic acid, with fair to poor yields in a few steps. It was therefore felt that a better, more efficient synthesis of ($\pm$)patulolide A was necessary. With this in view, the synthesis was undertaken and the same is reported in the present work. The prime reason for undertaking the synthesis of ($\pm$)patulolide A was the biological activity (mainly antifungal) of R-(+)-patulolide A. Also, the synthetic scheme for ($\pm$)patulolide A would serve as a model, to be applied later, to the total synthesis of R-(+)-patulolide A. Soon after the completion and publication of the present work,⁸ Yadav et al.⁷ reported their partial synthesis of ($\pm$)patulolide A.

Retro-synthetic analysis (SCHEME IV) revealed that a C-10 synthon and a suitable C-2 synthon could be coupled appropriately to give the C-12 hydroxy acid (**37a**), precursor for patulolide A. Patulolide A is a 12-membered ring macrocyclic lactone. Its synthesis was therefore rationalised as arising out of C-12 hydroxy acid (**37a**) via the key lactonization step. The C-12 hydroxy acid (**37a**), in turn, could be derived from a functionalised C-10 synthon like (**39**) and a C-2 synthon. The choice for the latter fell heavily and appropriately on a stable phosphorane (**40**). The Wittig

reaction of the aldehyde (39) and the phosphorane (40) would yield (38). The reasons for choosing Wittig reaction were two-fold; Wittig reaction of (39) with a stable phosphorane (carbethoxymethylene triphenylphosphorane) (40) would result in the formation of the required α,β -unsaturated ester as in (38) and also the necessary trans-geometry of the double bond would be obtained exclusively as is required for the synthesis of ($\pm$)patulolide A.

The C-10 synthon (39) in turn could be obtained from two suitably functionalised C-5 units like (41) and (42). The starting materials for (41) would be the commercially and cheaply available acetylene gas and methyl oxirane (propylene oxide). For the synthesis of (42), the rightful choice was 1,5-pentanediol (43). A detailed reaction sequence is depicted in SCHEME V.

SCHEME-V



One of the required C-5 synthons, 4-pentyn -2-ol (41) was prepared starting from sodium acetylide (36) and propylene oxide (27). Several routes have been reported for the preparation of 4-pentyn -2-ol. Out of these the method reported by Mukaiyama et al.⁹ appeared to be the most suitable one. It involved the reaction of sodium acetylide with propylene oxide in the presence of HMPA. Later improvements in the method included use of DMSO as a solvent which resulted in increased yields.¹⁰ In the present work, yields were further improved from 50% to 64% by using HMPA as a co-solvent.

A detailed literature survey for the synthesis of 5-bromo-1-pentanol (44) revealed a few methods, one starting from 5-bromovaleronitrile, another from tetrahydropyran and a third from 1,5-pentanediol. The easy availability and comparatively low cost of 1,5-pentanediol enabled an efficient preparation of 5-bromo-1-pentanol for the present work. Although literature procedure¹¹ reported formation of 5-bromo-1-pentanol and 1,5-dibromopentane in 7:3 ratio, by judiciously altering the reaction time from 18 hr to 3-4 hr and also by employing high dilution technique, the required 5-bromo-1-pentanol was obtained in 95% yield.

Oxidation of (44) with PDC¹² yielded the corresponding unstable aldehyde, 5-bromopentanal (45). The infrared and ¹H-NMR spectra confirmed the structure of the aldehyde with IR absorption for the aldehyde carbonyl group at 1735 cm⁻¹ and ¹H-NMR chemical shift for the aldehyde function at δ 9.7.

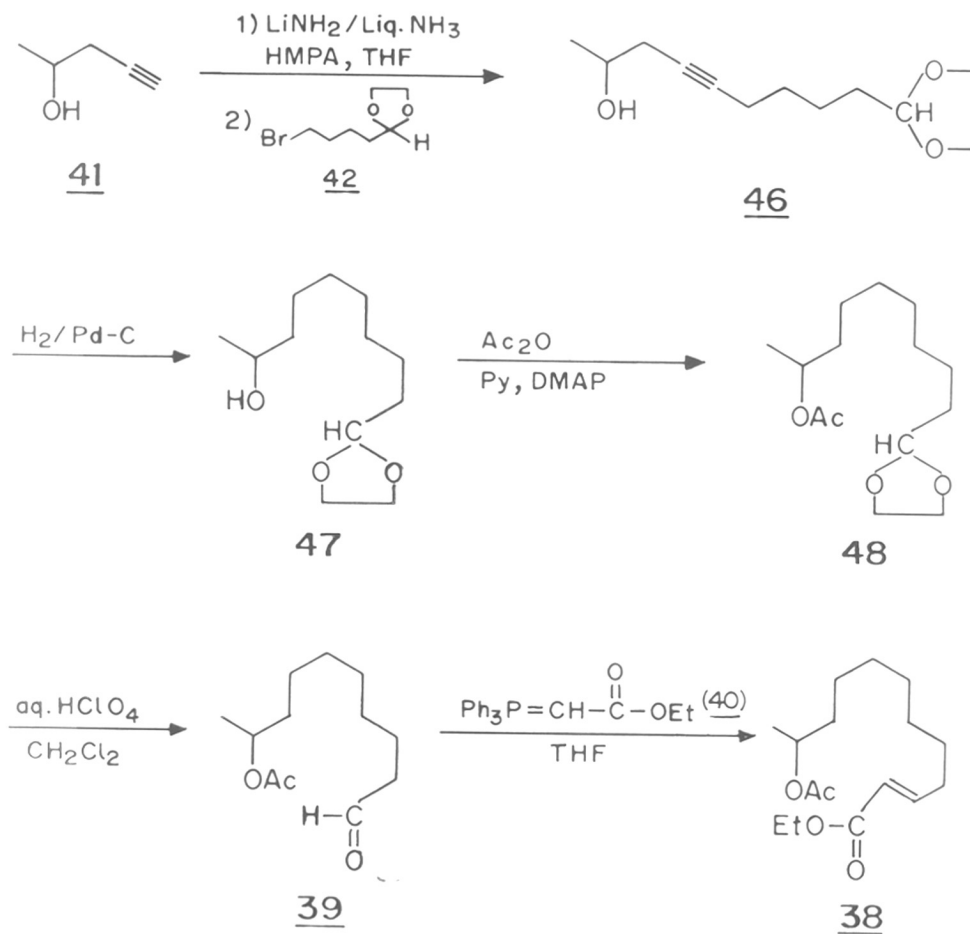
Hence the crude, unstable aldehyde was immediately converted to its ethylene acetal by reaction with ethylene glycol in benzene as solvent and in the presence of catalytic amounts of p-toluenesulfonic acid, with simultaneous azeotropic removal of water (Dean-Stark, 6 hr). The structure of the product, 2-(4-bromobutyl)-1,3-dioxolane (42) which was obtained in 73% overall yield from 5-bromo-1-pentanol was further confirmed by recording its ^1H -NMR and IR spectra. In the ^1H -NMR spectrum, characteristic peaks at δ 3.86 (m) for $-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-$ and a triplet at δ 4.8 for $-\text{O}-\text{CH}-\text{O}-$ were observed.

Having obtained the two key starting materials, viz. 4-pentyn-2-ol (41) and 2-(4-bromobutyl)-1,3-dioxolane (42), the next reaction of coupling was carried out. The dianion of 4-pentyn-2-ol (41) was generated with lithium amide in liquid ammonia in dry THF as a co-solvent over a period of 4 hr, followed by the addition of 2-(4-bromobutyl)-1,3-dioxolane (42) resulting in the formation of C-10 coupled product 2-(8-hydroxynon-5-ynyl)-1,3-dioxolane (46) along with unreacted (42). Maximum yield of $\sim$ 89% of the product (46) was obtained by employing THF-HMPA as solvents.

The compound 2-(8-hydroxy-non-5-yne)-1,3-dioxolane (46) was obtained as a colourless liquid, b.p. $121-24^\circ\text{C}/1\text{ mm}$ (lit.¹³ b.p. $88-91^\circ\text{C}/0.02\text{ Torr}$). The structure was fully confirmed by ^1H -NMR spectral data. The ^1H -NMR spectrum revealed a doublet at δ 1.22 for $\text{CH}_3-\text{CH}-$, a multiplet at δ 3.88 for $-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-$ and a triplet at δ 4.85 for $-\text{O}-\text{CH}-\text{O}-$ providing

necessary confirmation for the structure of (46). Further, IR spectrum showed a broad absorption at 3400 cm^{-1} for a hydroxyl function.

SCHEME-V (Contd.)



Reduction of the triple bond of (46) was achieved in the conventional manner. Thus hydrogenation of (46) in ethanol in the presence of 10% Pd-C at atmospheric pressure

resulted in a mixture containing the required saturated hydroxy acetal (47) along with starting material (46). However, when the same reduction was carried out at 30 psi for $\approx$ 30 min, (47) was the exclusive product (FIG. 1). Protection of the hydroxyl function in 2-(8-hydroxynonyl)-1,3-dioxolane (47) was necessary to enable a clean hydrolysis of the ethylene acetal to the aldehyde function required for further carbon extension from that end. The acetoxy group was the group of choice as it is more stable and also hydrolysis of acetate and ethyl ester groups in (38) could be carried out in one stroke. Thus, acetylation of (47) with acetic anhydride and pyridine in the presence of catalytic amounts of 4-DMAP furnished the acetate (48) in quantitative yield. Hydrolysis of the ethylene acetal function in (48) was effected with 35% aq. perchloric acid in dichloromethane at 0°C for 4 hr. Although several standard methods are available in literature for the hydrolysis step, viz. aq. HCl in methanol, p-toluenesulfonic acid in aq. acetone etc., they all resulted in a black gummy product which may be due to the presence of traces of acid in the reaction product. This was avoided during the two phase hydrolysis with HClO_4 and the reaction yielded the product (39) quantitatively. The 9-acetoxystyrene (39) was pure enough to be used for subsequent reactions and its structure was fully confirmed by $^1\text{H-NMR}$, IR and mass spectra. In the NMR, disappearance of signals at δ 3.86 and at δ 4.85 and appearance of a new signal at δ 9.80 confirmed the structure of the aldehyde (39).

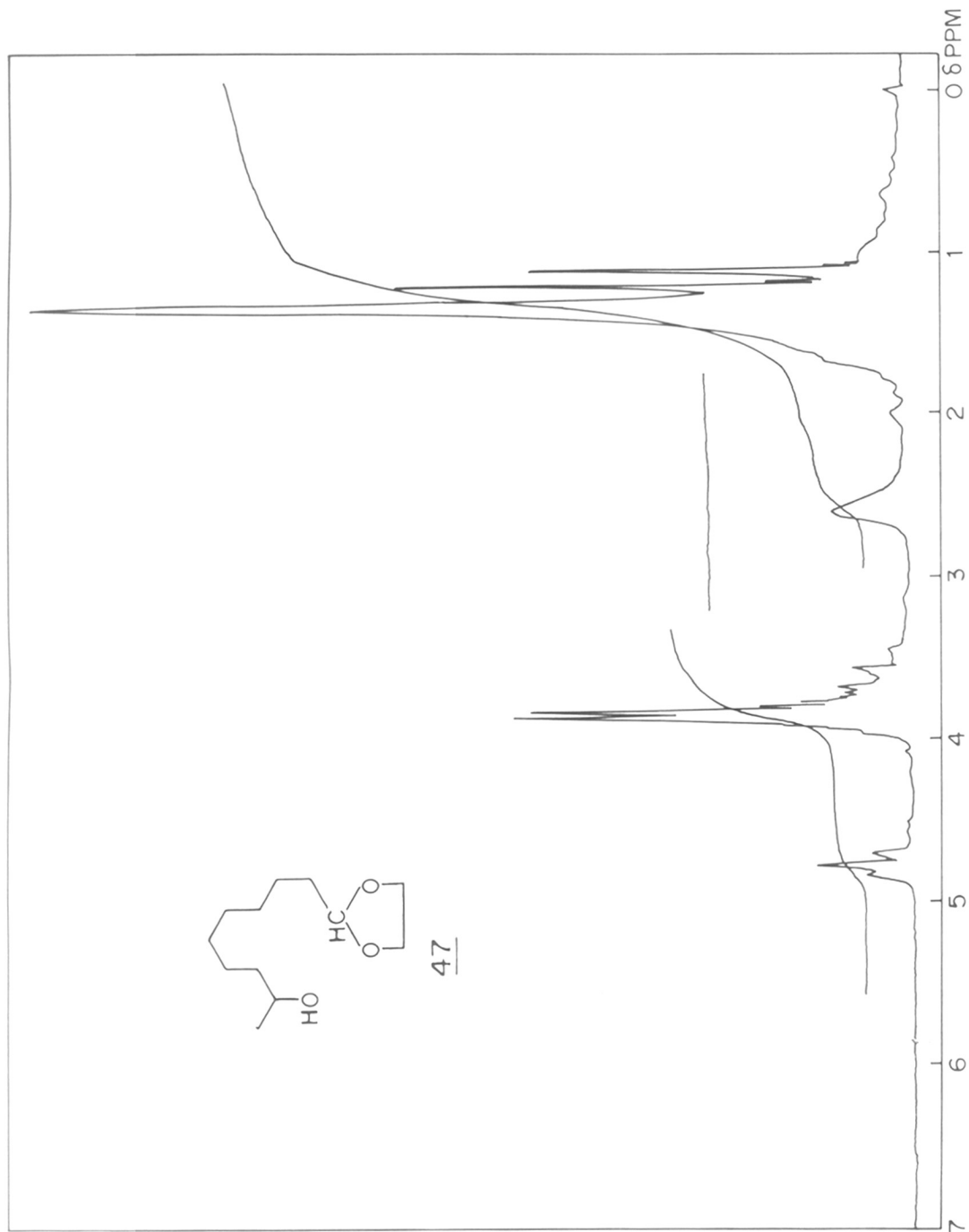
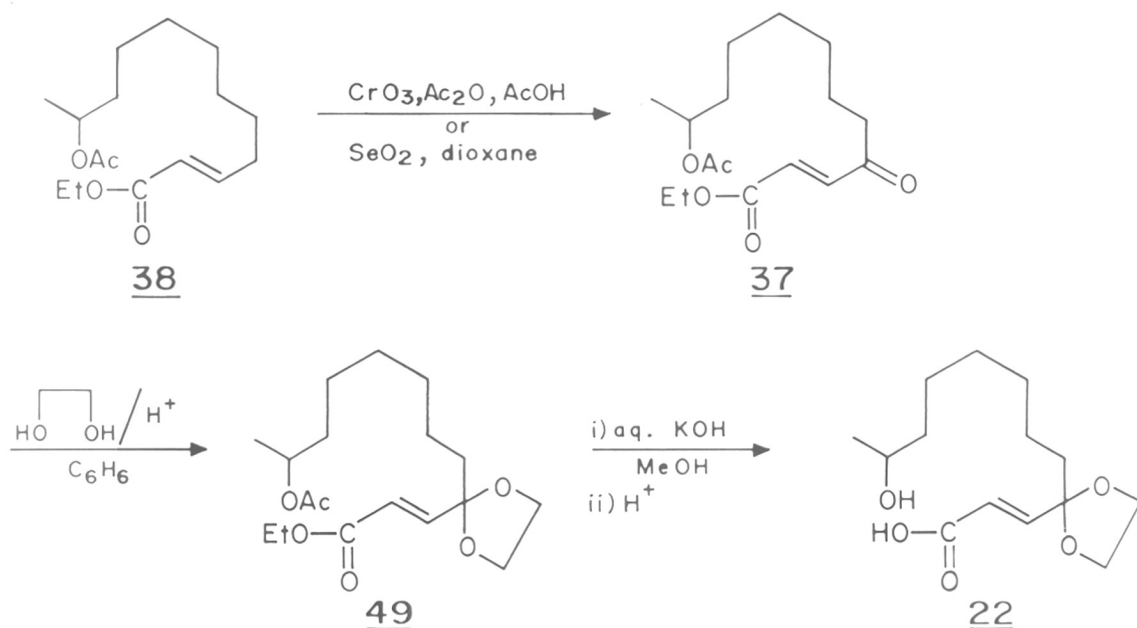


FIG. 1: ^1H -NMR SPECTRUM OF COMPOUND (47) IN CDCl_3

SCHEME -V (Contd.)



The last stage of 2-carbon homologation was achieved via a Wittig reaction of (39) with the stable phosphorane (40) [carbethoxymethylene triphenylphosphorane] in dry THF for 6 hr under reflux temperature. The required C-12 synthon (38) was obtained in 82% yield and was characterised fully from its spectral data. The corresponding ester was also reported by Makita *et al.*⁶ The characteristic pattern for the α,β -unsaturated (E)-ester was seen at δ 5.77 and δ 6.93 (FIG.2). Further confirmation was obtained from its IR spectrum which revealed absorptions at 1730 and 1660 cm^{-1} respectively. In order to introduce a carbonyl function at C-4 position, allylic oxidation of (38) with chromium trioxide in acetic acid - acetic anhydride mixture^{14a} was carried out. The required keto ester (37) was obtained in 38% yield after

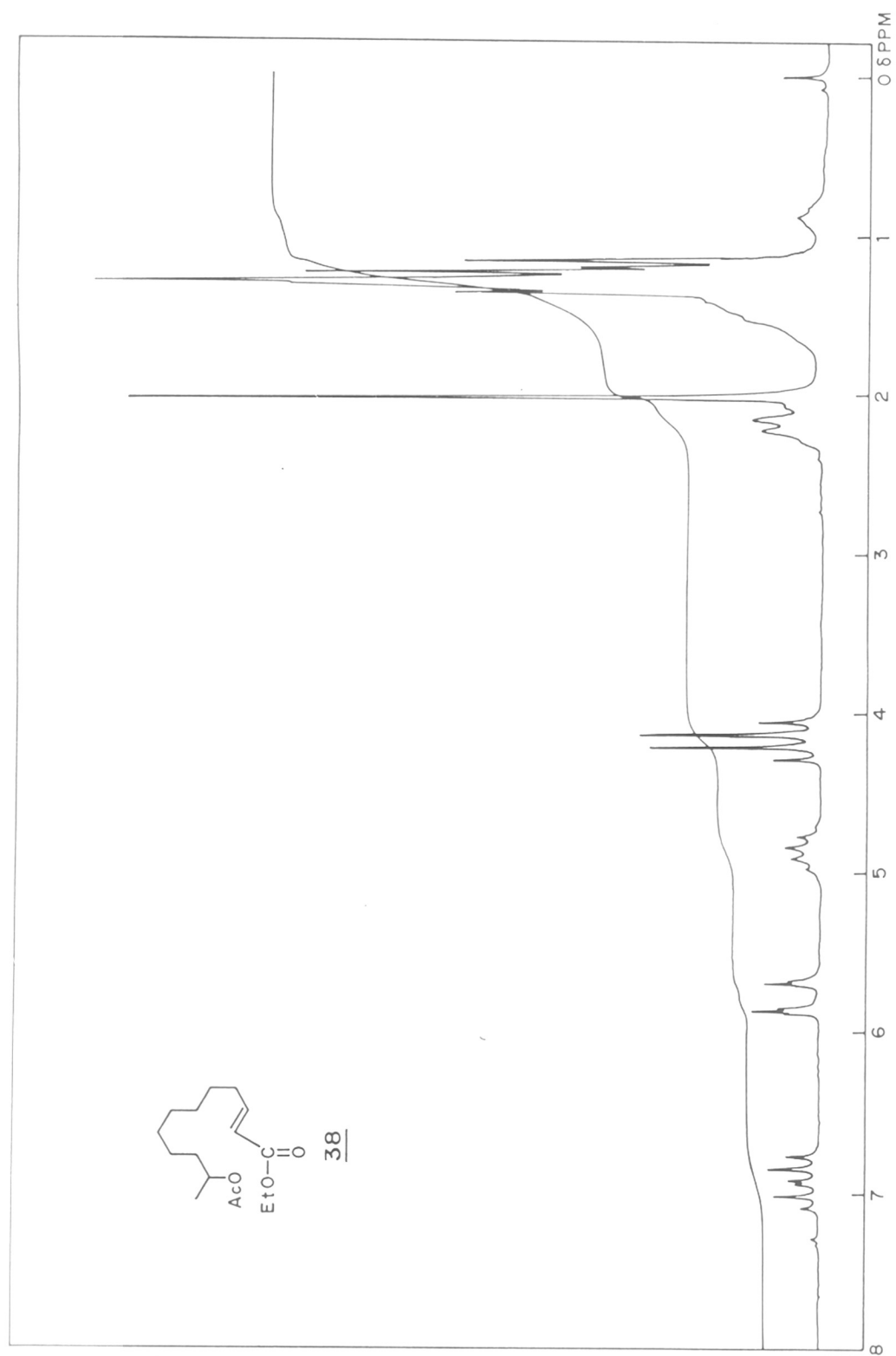
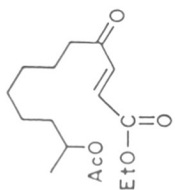
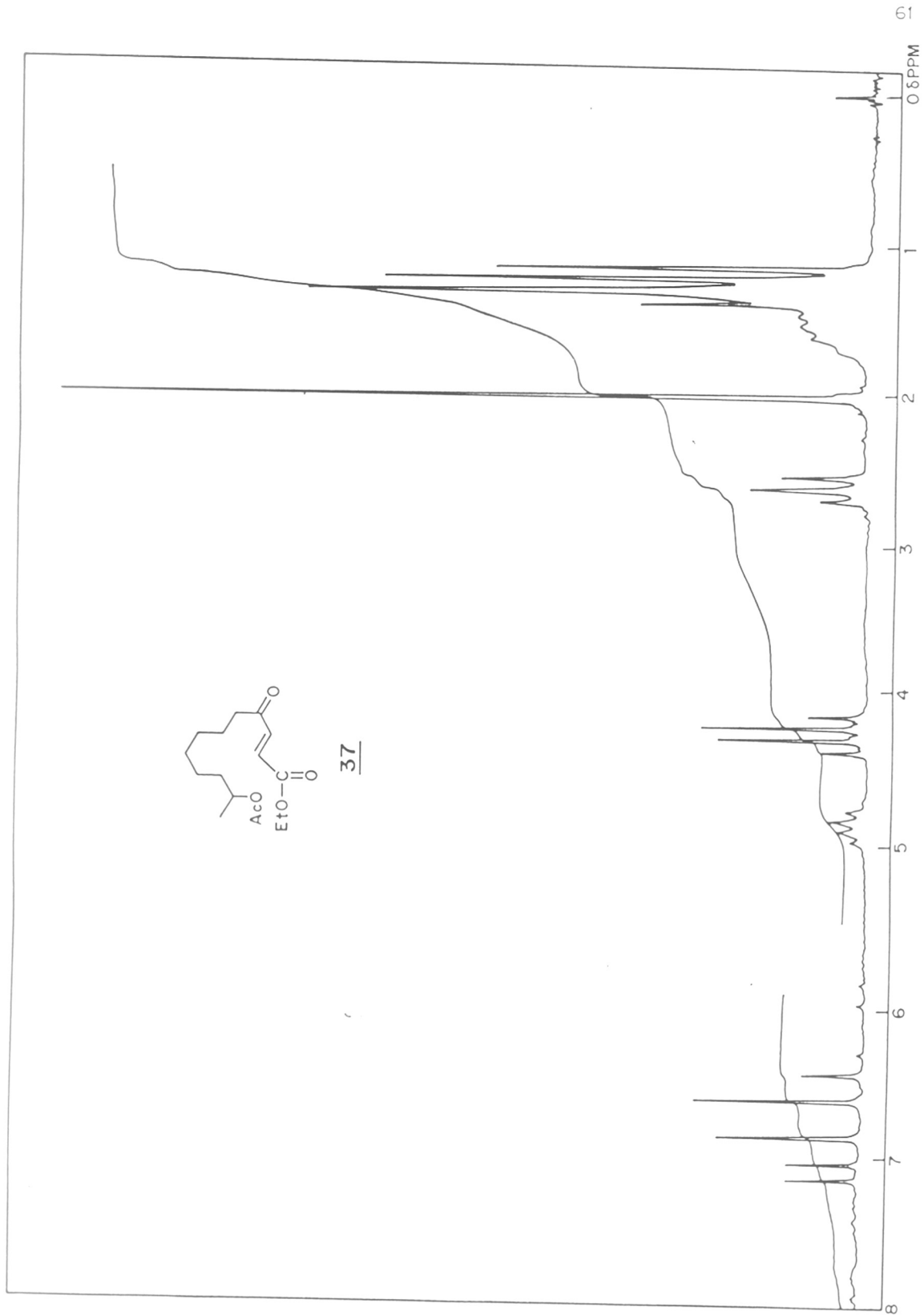


FIG. 2: ^1H -NMR SPECTRUM OF COMPOUND (38) IN CDCl_3

column chromatographic purification of the crude product along with an equal amount of the starting material (38). As the yield was very poor, some modification was carried out. Thus oxidation with selenium dioxide in dry dioxan at reflux temperature^{14b} furnished (37) in 92% yield. ¹H-NMR chemical shifts at δ 6.62 and at δ 7.06 (each d, J=16Hz) were assigned to C-2 and C-3 protons (FIG. 3). Appearance of an additional carbonyl at 1710 cm^{-1} in the IR spectrum was indicative of keto-carbonyl in the oxidised product (37). Further confirmation was also obtained from its mass spectrum (M^+ , 298).

In order to effect smooth hydrolysis of acetate and ester functionalities, protection of keto carbonyl was necessary. In the absence of such a protection, the trans double bond protons were not seen at all after hydrolysis. Makita et al.⁶ employed ethylorthoformate and ethylene glycol in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ for the protection of keto group in (37). However, this method did not give satisfactory yields. Hence, the usual ketalisation method was employed wherein (37) was refluxed in benzene containing ethylene glycol and catalytic amounts of p-toluenesulfonic acid, with azeotropic removal of water (Dean-Stark, 6 hr). The structure of the product (49) was confirmed by its spectral analysis. ¹H-NMR revealed doublets at δ 5.97 (J=16Hz) and at δ 6.68 (J=16Hz) and a multiplet at δ 3.82, the latter is for $-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-$. Having thus the protected ketoester (49) in hand, the next hydrolysis step was carried out

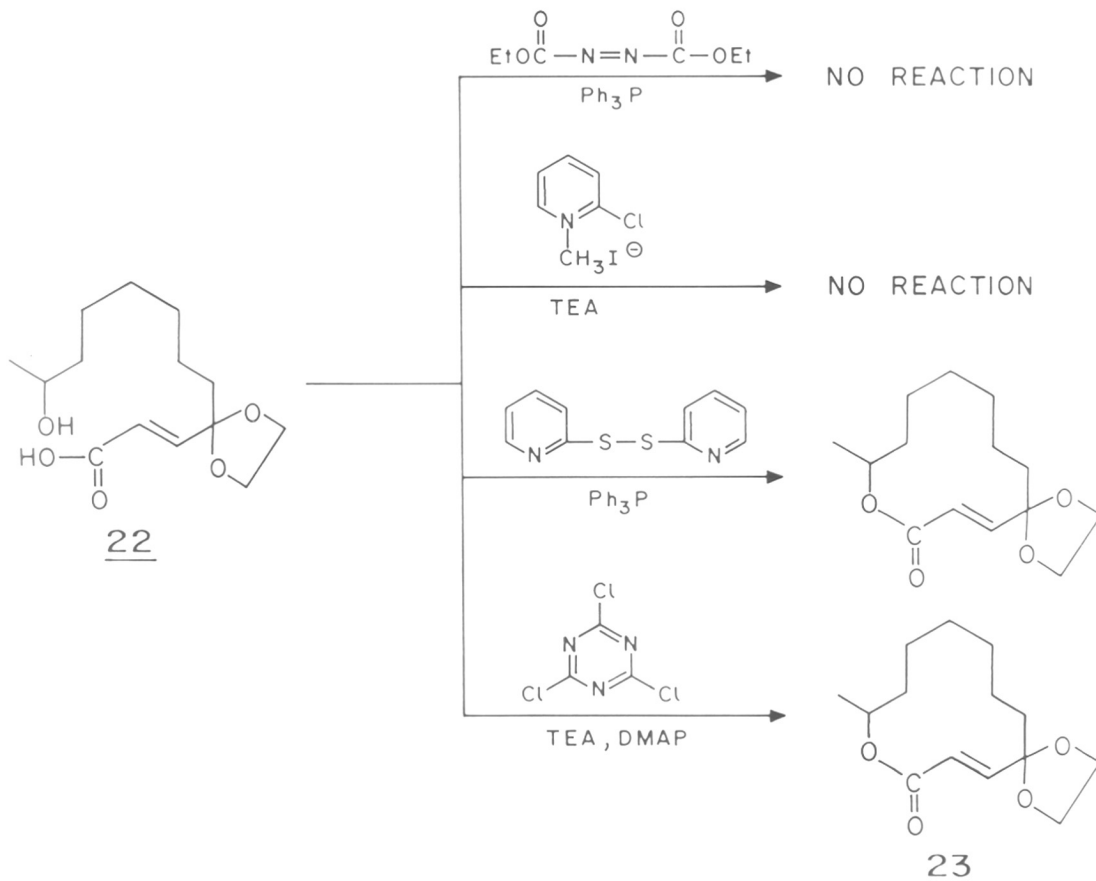


37

FIG.3: $^1\text{H-NMR}$ SPECTRUM OF COMPOUND (**37**) IN CDCl_3

smoothly with 2N KOH in methanol. The required seco-acid (**22**) was obtained as a colourless solid, m.p. 54-55°C in almost quantitative yield (NMR: FIG. 4).

SCHEME-V (Contd.)



The crucial macrolactonization reaction was finally successful after attempting several reactions with well known reagents employed in literature (also see Chapter I of this thesis). Among the known methods that were employed were Mukaiyama's method (2-chloro-1-methyl pyridinium iodide),¹⁵

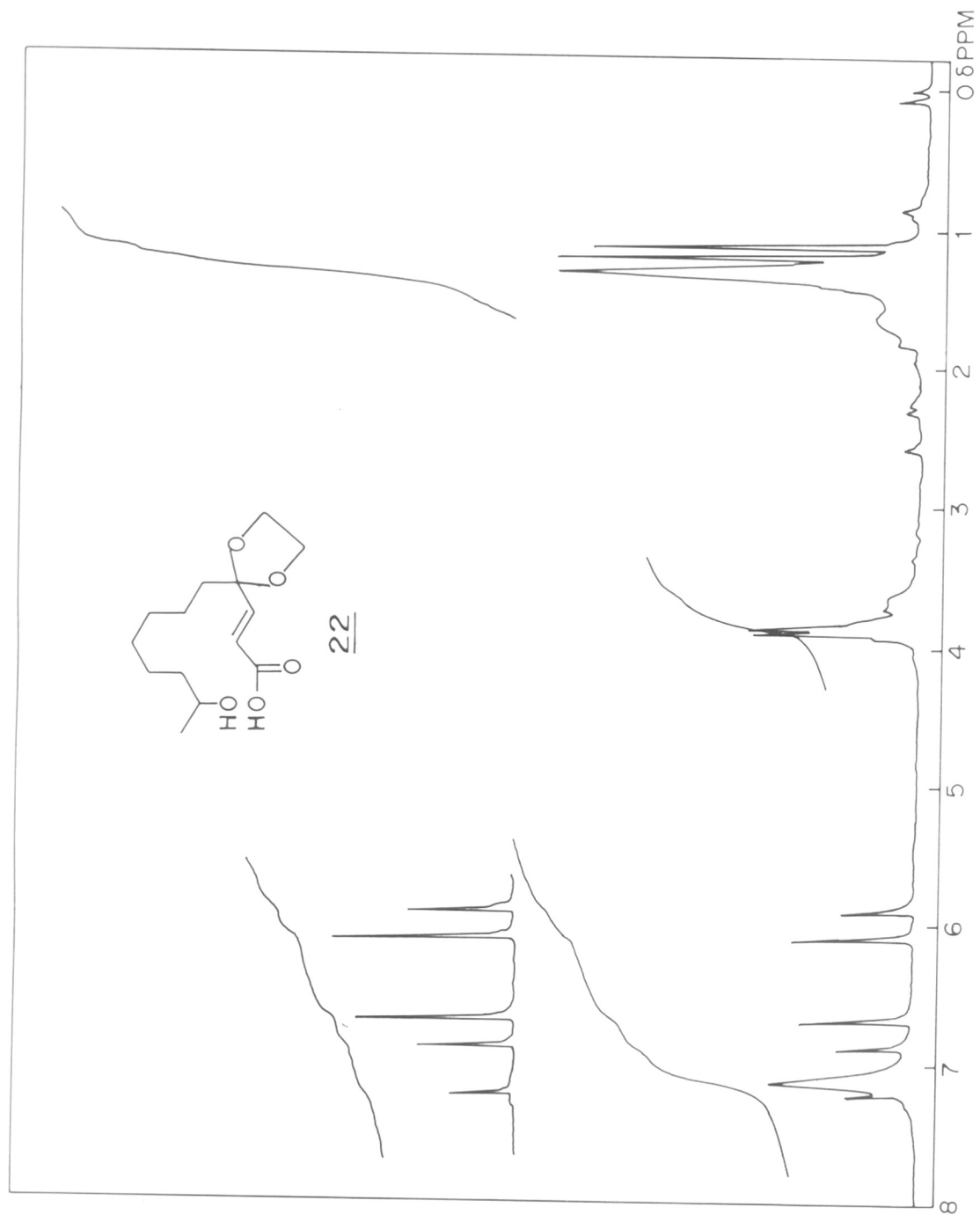
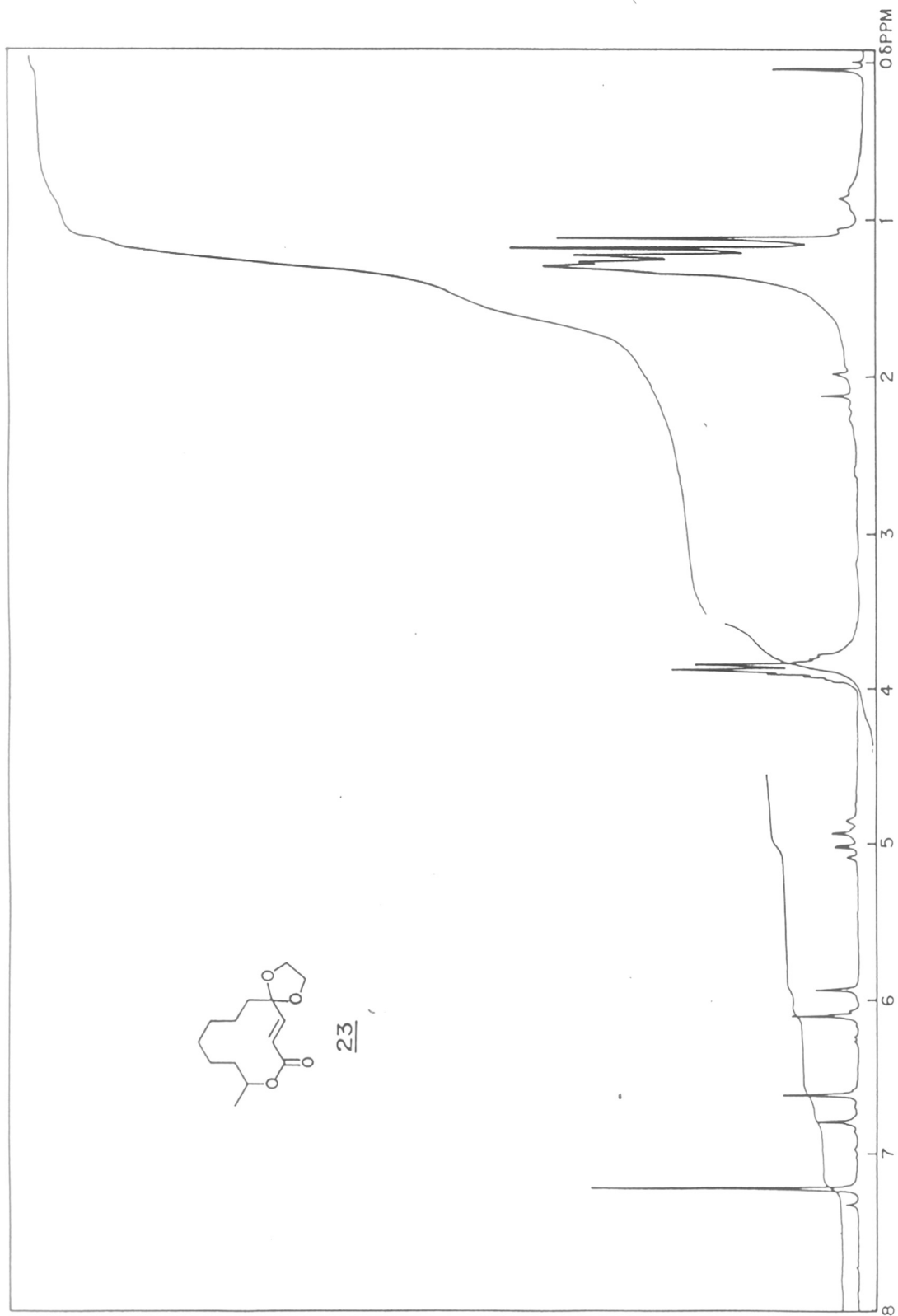


FIG. 4: ^1H -NMR SPECTRUM OF COMPOUND (22) IN CDCl_3

Mitsunobu's method (diethylazodicarboxylate, triphenyl phosphine),¹⁶ Corey's lactonisation method (2,2'-dipyridyl disulphide and triphenylphosphine)¹⁷ etc. Satisfactory yields of the required lactone (23) could however not be obtained from any of these methods. Some years back, an efficient lactonisation procedure using cyanuric chloride, a cheaply available commercial product was reported by Venkataraman and Wagle¹⁸, which proved to be the best for the preparation of lactone (23). Thus a mixture of (22) and triethylamine in dry acetone was added to a stirred solution of freshly crystallized cyanuric chloride in acetone at room temperature. (±)Patulolide A as the protected cyclic ketal (23) was obtained after purification by column chromatography (FIG.5). As deprotection of (23) to give (±)patulolide A (24) has already been carried out by Makita et al.⁶ the present work in effect constitutes a total synthesis of (±)patulolide A (24).

FIG.5: ^1H -NMR SPECTRUM OF THE COMPOUND (23) IN CDCl_3

PART-II

INTRODUCTION:

In the earlier part of this chapter, a short and convergent synthesis of (+)patulolide A was discussed. This synthesis was carried out as an exercise, to be applied later on, to the synthesis of the naturally occurring R-(+)-patulolide A. When the present work was initiated in late 1987, no synthesis of R-(+)-patulolide A was reported. Subsequently, in 1988, an enantioselective synthesis of patulolides A, B and C from ethyl (R)-3-hydroxybutyrate was reported by Mori and Sakai.¹⁹ A year later, in 1989, Zwanenburg²⁰ reported an enantioselective total synthesis of macrolide patulolide C involving nucleophilic ring opening of R-(+)-methyloxirane with a lithium acetylide, Sharpless epoxidation, photochemical rearrangement and macrolactonization using 2,6-dichlorobenzoyl chloride.

A study of the structure and activity of R-(+)-patulolide A is worth mentioning here. Patulolide A is a 12-membered macrolide which has a double bond flanked by carbonyl groups. It belongs to a rather new group of simple macrolides like cladospolide A (5), cladospolide B (6)² and recifeiolide (4).³ The marked antifungal activity of patulolide A was attributed to the presence of a trans double bond flanked by two carbonyl groups. Patulolides B and C are relatively less active, as the former has a cis double bond and two carbonyl functions and the latter has a trans double bond along with a α -hydroxy function. Further, patulolide C has already been transformed to patulolide A (Mori, loc. cit.).

Synthesis of R-(+)-patulolide A:

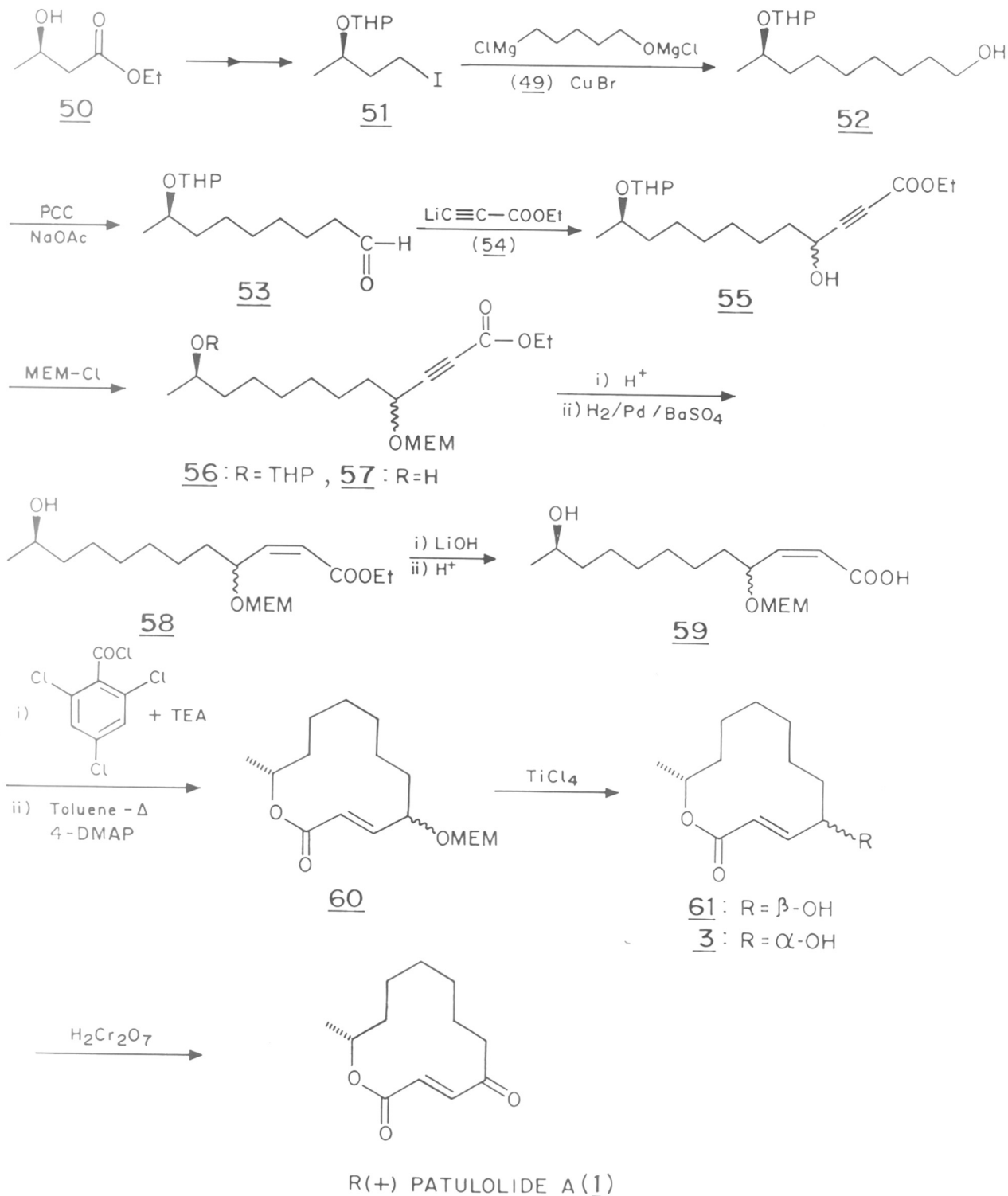
(i) Mori's approach:

The first total synthesis of R-(+)-patulolide A along with patulolides B and C was reported by Mori and Sakai.¹⁹ The utility of ethyl (R)-3-hydroxybutanoate as a chiral building block was amply demonstrated in their synthesis. This versatile chiral building block²¹ was obtained from cell-free PHB [poly-(R)-3-hydroxybutanoate] or from dried cells of Alcaligenes eutrophus H16, which had been grown in an aqueous fructose solution. Enantiomerically pure ethyl, methyl, butyl (R)-3-hydroxybutanoates were obtained in yields ranging from 75-90%. Depolymerization was achieved by heating the PHB containing material to temperatures of 80°-160°C in the corresponding alcohols in the presence of sulphuric acid or tetraethoxy titanium catalyst.

Ethyl (R)-3-hydroxybutanoate (50) was subjected to Grignard reaction (via the iodide 51) with the reagent (49) derived from 5-chloro-1-pentanol. PCC oxidation of the resultant THP-alcohol (52) gave the aldehyde (53) which upon condensation with ethyl lithiopropiolate (54) afforded (55) as a mixture of diastereomers. The free hydroxyl function of (55) was protected as the MEM ether to furnish (56) and the latter was deprotected to yield (57). Hydrogenation of the latter using Lindlar catalyst gave the (Z)-olefinic ester (58) as a sole product. The seco-acid (59) was obtained by alkaline hydrolysis of (58) (SCHEME VI).

MORI and SAKAI¹⁹

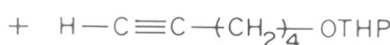
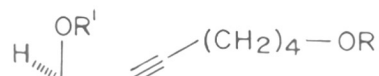
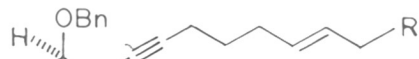
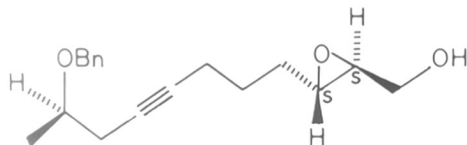
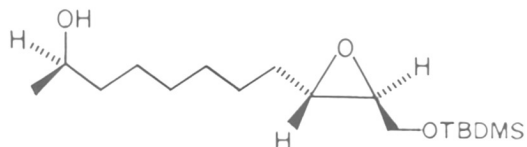
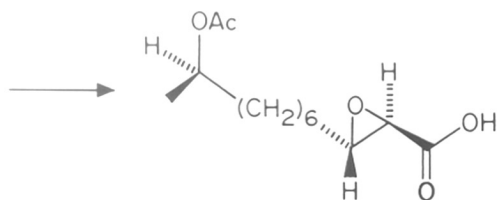
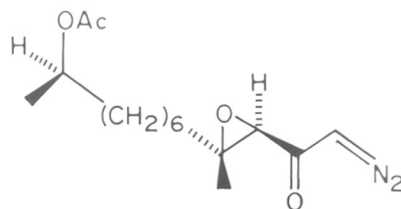
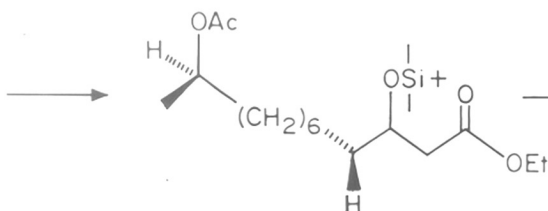
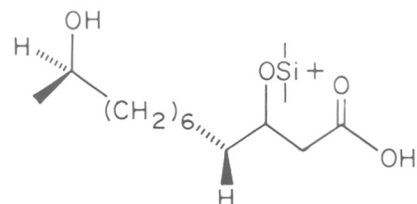
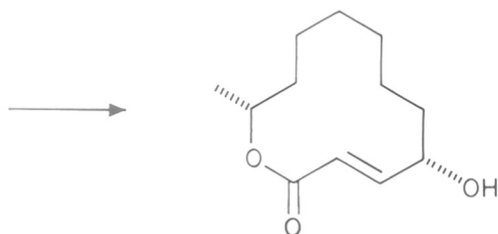
SCHEME-VI



Lactonization of (59) was accomplished by Yamaguchi method.²³ The mixed anhydride was derived from 2,4,6-trichlorobenzoyl chloride and the acid (59) in the presence of triethylamine in THF and the resultant reaction mixture in toluene was added to a refluxing solution of 4-DMAP in toluene (high dilution). During the course of the reaction, the double bond's geometry was found to be (E) instead of (Z) (NMR studies). The basic condition due to 4-DMAP was probably the causative factor for the olefin isomerization during the course of lactonization. The lactone (60) was obtained as a mixture of diastereoisomers. Deprotection of the MEM ether with TiCl_4 furnished patulolide C (3) and its epimer (61). Oxidation of the mixture of (3) and (61) gave R-(+)-patulolide A. The synthesis of patulolide A was effected in an overall yield of 10% from (50) in 14 steps.

(ii) Zwanenburg's approach:

It was demonstrated in Mori's approach that patulolide C (3) on oxidation gave patulolide A (1). Hence, it was felt necessary to include Zwanenburg's approach²⁰ for an enantioselective total synthesis of patulolide C (3) (SCHEME VII). The essential features of this synthesis include nucleophilic ring opening of R-(+)-methyloxirane (62) with the lithium acetylide of THP-protected 5-hexyn-1-ol (63) to give (64a) which was further protected as the benzyl ether (64b). Hydrolysis of the THP group in (64b) furnished (64c) which was subjected to Swern oxidation to give the intermediate

ZWANENBURG et al.²⁰626364a: R = THP, R' = H64b: R = THP, R' = Bn64c: R = H, R' = Bn65a: R = COOEt, 65b: R = CH₂OH6667686970713Ref.¹⁹R-(+)-PATULOLIDE A

aldehyde ; Wittig-Horner 2-carbon chain extension of the aldehyde furnished the α,β -unsaturated ester (65a). The DIBAL reduction of the latter gave the allylic alcohol (65b), which upon enantiospecific Sharpless epoxidation, produced the epoxy alcohol (66). Protection of the free hydroxyl group as t-butyldimethylsilyl ether followed by hydrogenation of the triple bond and debenzylation yielded the epoxy alcohol (67). Acetylation of the secondary hydroxyl group, desilylation, Collins oxidation of the resultant alcohol and further oxidation of the intermediate aldehyde furnished the epoxy acid (68). The diazoketone (69) was obtained from the acid (68) via the mixed anhydride procedure. The key step involving photo-induced rearrangement of the diazo compound (69) was accomplished cleanly and the acetate ester formed (70) was transformed to the seco-acid (71) by consecutive removal of the acetate function and the ester group. The ultimate lactonization step was achieved with 2,6-dichlorobenzoyl chloride in a modified Yamaguchi procedure.²³ Final removal of the silyl protecting group resulted in patulolide C (3). The latter has already been converted to patulolide A (1) (Mori, loc. cit.).

PRESENT WORK:

The two syntheses of R-(+)-patulolide A (1) and R-(-)-patulolide C (3) mentioned earlier utilise two different chiral synthons, viz. ethyl (R)-3-hydroxybutanoate and R-(+)-methyloxirane as the starting materials. Hence, chirality which was introduced right from the first step was carried through the entire synthesis. It was felt that a very apt alternative would be to introduce chirality at a later stage in the synthesis. Retrosynthetic analysis (see part I) readily revealed that the C-12 seco-acid (37a) is one of the intermediates where the chirality could be introduced. The choice was either asymmetric reduction or enzyme mediated enantioselective resolution of the racemate. The latter approach was selected as the method of choice based on which the present synthesis was completed successfully. Therefore, a short introduction on biotransformations using enzymes, in particular lipases is discussed first.

Biotransformations using enzymes:

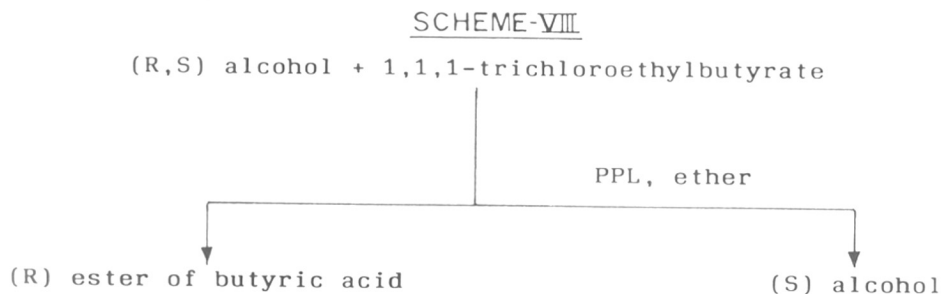
Enzymes are efficient biocatalysts, which exhibit high specificity and play a significant role in asymmetric synthesis. Innumerable biotransformations have been reported and reviewed in literature.²⁴ Several of them have been applied successfully on a preparative or even an industrial scale. Nearly unlimited reservoir of different enzyme activities exist in nature; there is thus an enormous potential available for onward progress in the field of biotransformations. A variety of

enzymes are catalytically active in apolar media. Enantio-selective biocatalysis in non-aqueous media is becoming increasingly important in organic synthesis.

The field of applications of biotransformations includes the introduction of a chiral centre, resolution of racemates, reaction under milder conditions etc. In the present work in this part and in the subsequent chapter lipases have been used for the introduction of asymmetry in the molecule via ester hydrolysis²⁵ and transesterification.²⁶ A brief introduction, therefore, to this fascinating group of enzymes is desired.

Lipases are abundant, stereospecific, stable and highly versatile enzymes. Transformations possible with lipases include esterification, transesterification, acyl exchange, lypolysis, oximolysis etc. Lipases are also unique, they are stable in non-polar organic solvents. About 20 different²⁷ commercially available lipases from microbial, plant and animal sources are available. Enantioselective ester synthesis and ester interchange are most popular and have been exploited largely for the preparation of optically active acids and alcohols. The choice of organic solvent plays a crucial role in lipase catalysed reactions. For instance, esterification and transesterification can be carried out with lipases under anhydrous conditions or under two phase system. There is also general consensus that some water is absolutely necessary for the catalytic function of the enzymes.²⁸

Lipase is a hydrolytic enzyme and it was found that porcine pancreatic lipase (PPL) and yeast lipases can vigorously function and catalyse numerous reactions. PPL was found to be both quite active and stereoselective in the transesterification reactions. Thus, in the PPL catalysed transesterification of racemic alcohols, only the (R)-isomer of the alcohol reacts²⁹ leaving behind the (S)-alcohol (SCHEME VIII).



The most commonly used solvents are ether, heptane, water-immiscible solvents (paraffins, toluene, carbontetrachloride), water-miscible solvents (acetone, acetonitrile, dioxane) etc. As water has a detrimental effect in the transesterification reaction due to the dominance of the competing hydrolysis, all transesterification reactions²⁷ are carried out under anhydrous condition. Lipases are generally stable from 25°C to 60°C with virtually no loss in catalytic activity.

In conclusion, one might observe that there are many advantages of the lipase catalysed resolution in organic media. Operationally, the lipase reactions are very simple to carry out. A suspension of lipase powder in a substrate

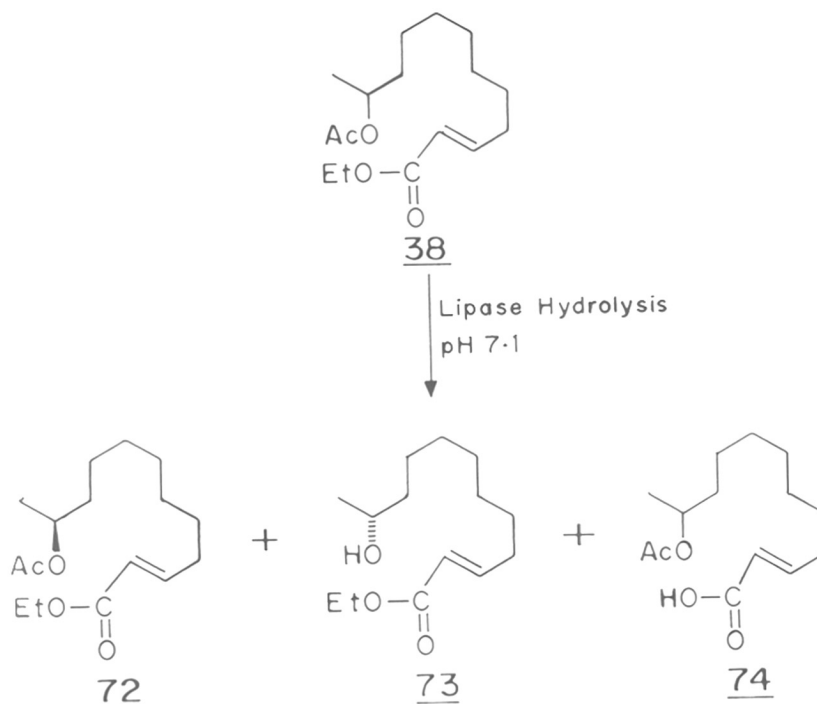
mixture in an organic solvent is shaken at room temperature, the enzyme is then filtered for reuse and the organic phase is separated by conventional techniques.

Lipase-catalysed hydrolysis studies towards the synthesis R-(+)-patulolide:

As has been mentioned in the earlier introduction, only two main applications of lipases have been exploited in organic synthesis so far, viz., hydrolysis and transesterification. Initially, it was decided to attempt hydrolysis of acetate ester (38) using lipases like PPL, Bacillus 2010, pig pancreatin (NF-14) etc. and the results are presented here.

Hydrolysis of acetate ester (38) with PPL, Bacillus 2010 and pig pancreatin (NF-14) was carried out in the usual manner. In each case, in a typical experiment, the compound (1 mmol) dissolved in a minimum quantity of acetone was added to a stirred suspension of the lipase (10% by weight) in a phosphate buffer of pH 7.1 at room temperature. The reaction was usually complete in about 5-6 hours (in all the cases) with the disappearance of the starting material. In each case the reaction mixture did not appear to contain any of the desired products (72) or (73) but was a complex mixture from which a major compound was isolated and characterised by silica gel column chromatography. Its structure was confirmed as the acid (74) by IR and ^1H -NMR studies, (SCHEME IX). Apparently, during lipase-catalysed

SCHEME - IX



hydrolysis, the α,β -unsaturated ester function hydrolyses faster than the desired resolution of acetate functionality. Such reactions have also been reported earlier in some other examples.^{30d} However, when there was no α,β -unsaturated ester moiety in the system, lipase-catalysed hydrolysis proceeded enantioselectively yielding (R)-hydroxyester and (S)-acetate (for details, see Chapter III).

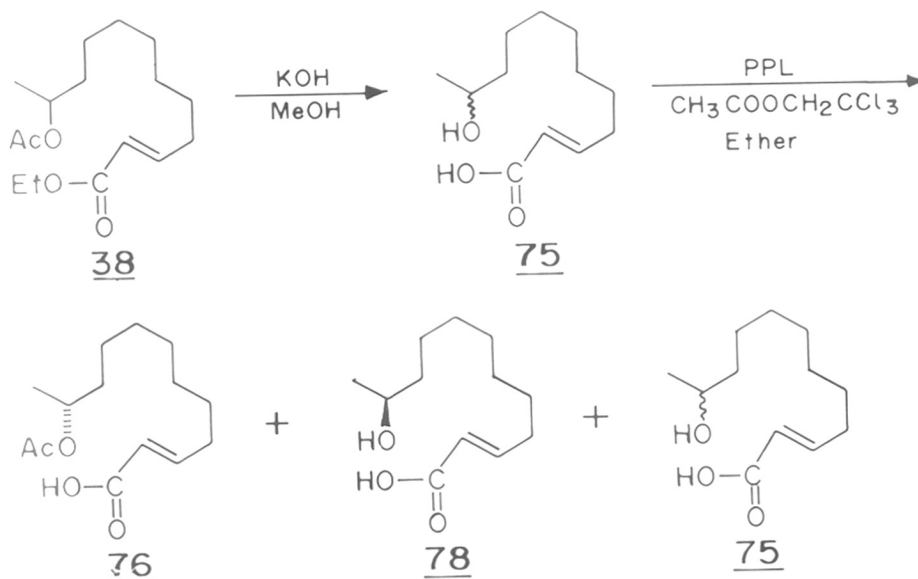
Application of transesterification in the synthesis of R-(+)-patulolide using lipases:

In the present work, lipases derived from at least three to four different sources were used in the crucial transesterification reaction. Initially, lipase from Candida cylindracea and lipase derived from mycelium (No.1201) were used. As an acyl donor, 1,1,1-trichloroethylbutyrate along with acetic anhydride, vinyl acetate, ethyl acetate as well as 1,1,1-trichloroethyl acetate have been reported.²⁶ It was found in the present work that during transesterification of the racemic hydroxy acid (75) and lipase from Candida cylindracea in the presence of 1,1,1-trichloroethyl butyrate as the acylating agent, there was no product formed even after 2-3 days. With mycelium (No.1201) also similar results were observed. Perhaps, the small amount of water which was added to catalyse the reaction was sufficient to hydrolyse 1,1,1-trichloroethylbutyrate in both the cases. There are reports available in literature,²⁶ where perfect anhydrous conditions are recommended for lipase catalysed transesterification mainly to avoid the hydrolysis of the ester.

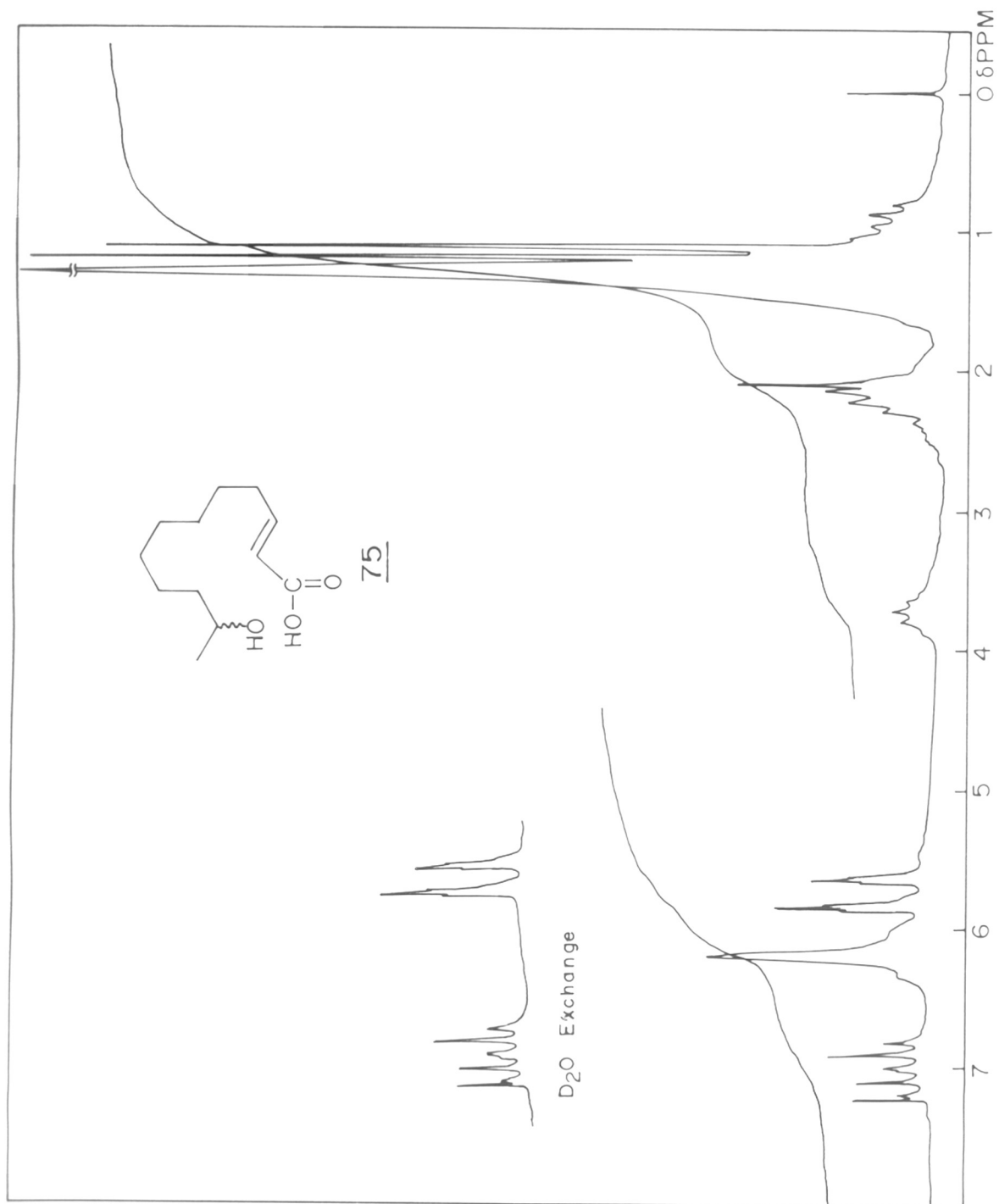
Transesterification of (75) in the presence of crude pig pancreatin (source: Loba Chemie) with 1,1,1-trichloroethylbutyrate and 1,1,1-trichloroethylacetate did not result in any product formation. On the other hand, when transesterification of the hydroxy acid (75) with 1,1,1-trichloroethylacetate in the presence of PPL under strictly

anhydrous conditions was carried out (dry ether solvent, 3A molecular sieves, argon atmosphere), the expected reaction proceeded as described below. In order to obtain products of high enantiomeric purity, the reaction was carried out under kinetic conditions,³² (SCHEME X), i.e. termination of the reaction after about 45% of starting material was utilised (monitored by GLC). The course of the reaction was also followed by TLC. After 48 hours, the reaction was discontinued. The crude lipase suspension was

SCHEME-X



filtered through celite and celite was washed with more ether. The required product R-(-)-11-acetoxydodecen -2E-oic acid (**76**) was obtained in about 30% yield and about 70% of

FIG. 6: ^1H -NMR SPECTRUM OF COMPOUND (**75**) IN CDCl_3

the unreacted acid as a mixture of (78 and 75) was recovered. Such reactions are known to proceed at a slow rate, some of them are lasting for about 4-5 days²⁶ resulting in low ee. Thus, the optimum time and the reaction conditions appear to play a crucial deciding role in the transesterification reaction.

IR spectrum of the product (76) revealed a broad absorption at 3500 cm^{-1} , thereby indicating the presence of a free carboxylic acid group. $^1\text{H-NMR}$ showed singlet at $\delta 1.97$ and a multiplet at $\delta 4.87$ indicating an acyl methyl function and a methine proton at C-11, respectively. Shift reagent studies in $^1\text{H-NMR}$ with Eu(hfc)_3 showed an enantiomeric purity of 95%. Further confirmation was also obtained from the mass spectrum of (76). Optical rotation studies of the 11-acetoxy acid (76) gave a rotation of -47° ($C=1$, CHCl_3). In conformity with the stereospecificity²⁶ of the enzyme PPL, the R-configuration was assigned to (76).

Further steps during the course of the synthetic scheme included esterification of acetoxy acid (76) with diazomethane to yield the corresponding acetoxy ester (79). The product was purified by silica gel column chromatography in the usual manner. $^1\text{H-NMR}$ showed a singlet at $\delta 3.63$ for the newly introduced ester function in addition to the other required peaks. A rotation value of $+23.2^\circ$ ($C=0.84$, CHCl_3) was also recorded.

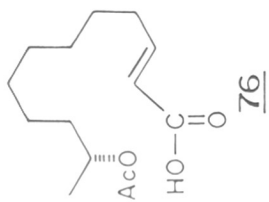
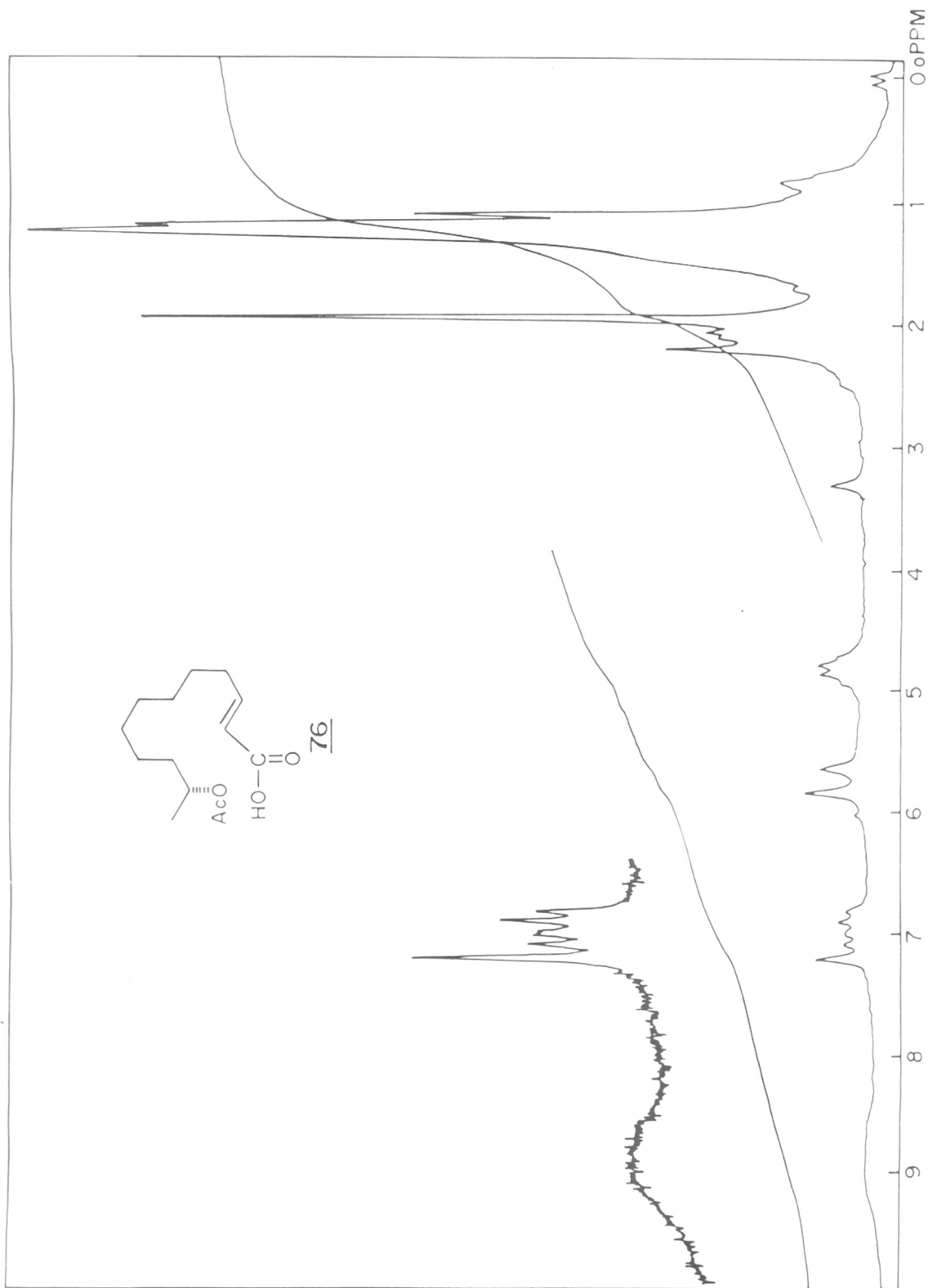
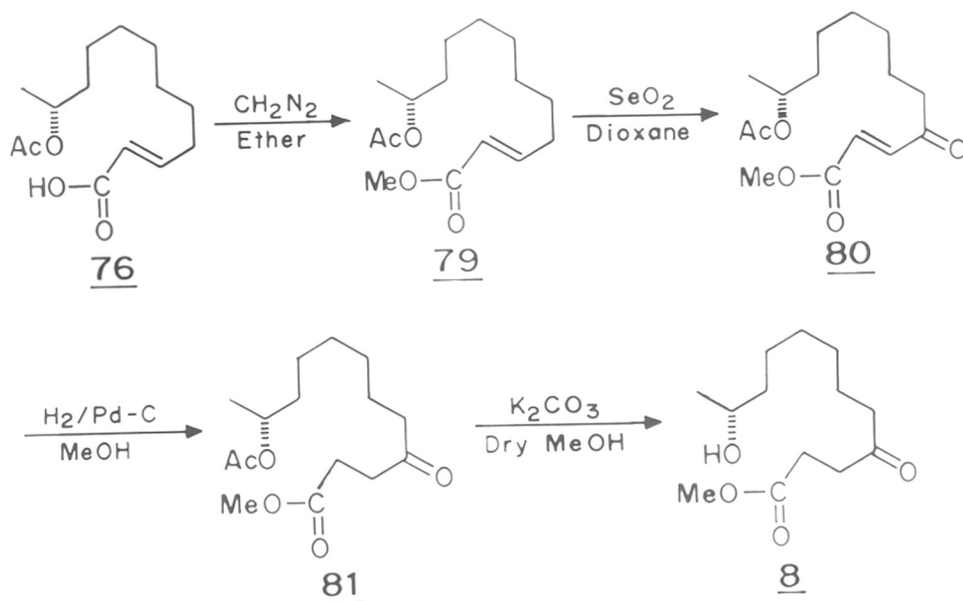


FIG. 7 : ^1H -NMR SPECTRUM OF COMPOUND (76) IN CDCl_3

SCHEME-X (Contd.)



Allylic oxidation of (79) was carried out with selenium dioxide in dry dioxane^{14b} under reflux. The product (80) formed was characterised by $^1\text{H-NMR}$ which showed the appearance of two sets of doublets at δ 6.86 ($J=16$ Hz) and at δ 7.05 ($J=16$ Hz) for two trans-olefinic protons. The singlets at δ 2.02 and δ 3.64 indicated the presence of $-\text{OCOCH}_3$ and $-\text{COOCH}_3$, respectively ($^1\text{H-NMR}$: FIG.8).

Further steps in conversion of (80) to R-(+)-patulolide A (1) would involve the same sequence of reactions as reported for ($\pm$)patulolide A (see Part I). But as in the latter, the yield in the deketalisation step leading to (24) was extremely poor; it was not desirable to obtain

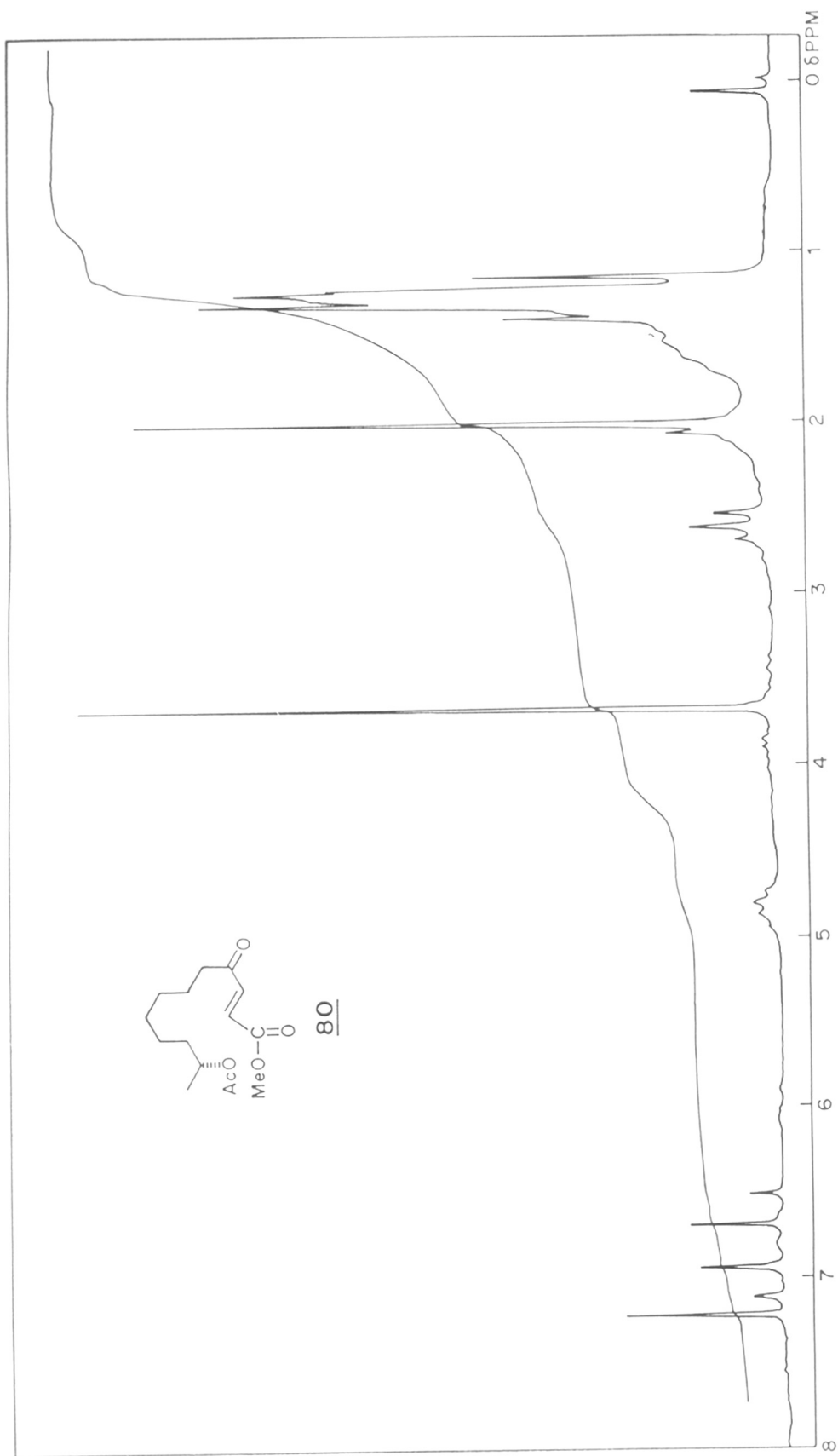


FIG. 8: ^1H -NMR SPECTRUM OF COMPOUND (80) IN CDCl_3

R-(+)-patulolide A (1) following the same route. Instead, the intermediate optically active keto ester (8) which is also known¹ has been obtained in an efficient manner by conversion of (80) in two steps, involving hydrogenation and hydrolysis.

Thus hydrogenation of the α,β -unsaturated keto ester (80) was carried out in the usual fashion in the presence of 10% Pd-C as a catalyst and in solvent methanol. The fully hydrogenated product (81) revealed in its ¹H-NMR, absence of trans olefinic protons and appearance of an additional signal at δ 2.22 which was assigned to CH₂ α -to the ester functionality. Other spectral data were also in full conformity with the structure (81).

Selective hydrolysis of the acetate functionality in the presence of ester in (81) was necessary to obtain the optically active hydroxy ester (8) for direct comparison with reported value.¹ This could be achieved with anhydrous potassium carbonate as the base in the presence of dry methanol.³³ The reaction proceeded smoothly to yield the desired product in 86% yield. ¹H-NMR showed the absence of signal at δ 2.02 and also upfield shift of methine proton from δ 4.86 in the acetate ester (81) to δ 3.74 in the hydroxy ester. Further confirmation of the hydroxy function was also obtained from the IR spectrum which indicated a broad absorption for hydroxyl function at 3400 cm⁻¹. Direct comparison of the optical rotation exhibited by (8) as $[\alpha]_D^{25}$ -7.08° (C=0.96, methanol) with that reported for the same

compound $[\alpha]_D^{25} -5.64^\circ$ (C=1.16, methanol) obtained during degradation studies of R-(+)-patulolide A, revealed that the data were in full agreement with each other.

Further, ^1H -NMR shift reagent studies with Eu(hfc)_3 showed an enantiomeric purity of $\geq 95\%$.

In conclusion, it has been demonstrated that lipase catalysed transesterification is a very efficient and useful method for resolution of racemic hydroxy acid and here in the present work, the same has been successfully applied towards a synthesis of R-(+)-patulolide A. Further work in this area and on macrolides is in progress in our laboratory.

EXPERIMENTAL

4-Pentyn-2-ol (41):

Sodium acetylide was prepared by simultaneous bubbling of acetylene gas and addition of sodium metal (23 g, 1 g. atom) into the liquid ammonia (100 ml) at -33°C over a period of 2 h. Dry DMSO (230 ml) was then added slowly followed by the addition of dry HMPA (100 ml). The reaction mixture was then warmed to 50°C with vigorous swirling to drive off the traces of ammonia. It was cooled to 0°C and propylene oxide (68 g, 1.17 mmol) was added with vigorous shaking for 1 h. Shaking was continued for another 1 h. The reaction mixture was poured into ice-cold saturated NH_4Cl solution (500 ml) and extracted with ether (12 x 100 ml). The combined ether solution was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The product was distilled as a colourless liquid (b.p. 112°C , lit.⁹ b.p. 115°C) in 64% (54 g).

IR (neat): 3400 (OH), 3300 ($=\text{C}-\text{H}$) and 2110 cm^{-1} .

$^1\text{H-NMR}$: δ 1.26 (d, $J=6\text{Hz}$, 3H), 2.08 (t, 1H, $\underline{\text{CH}} \equiv \text{C}-$), 2.35 (m, 2H) and 3.95 (m, 1H).

5-Bromo-1-pentanol (44):

A mixture of 1,5-pentanediol (20.8 g, 200 mmol) and aq. HBr (48%, 30 g, 200 mmol) in benzene (500 ml) was vigorously stirred under reflux with azeotropic removal of water (Dean-Stark) for 4 h. The reaction mixture was cooled to room temperature, quenched with solid NaHCO_3 and stirred for 15 min. The organic layer was decanted, concentrated

and distilled under reduced pressure to afford 30.5 g (91%) of 5-bromo-1-pentanol (b.p. 67°C/4mm).

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

$^1\text{H-NMR}$: δ 1.30-2.20 (m, 6H, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$), 3.20-3.70 (m, 5H, CH_2-Br , CH_2-OH and OH).

Mass (m/e): 167 (M^+), 165, 159, 149, 137, 135, 69 and 55.

5-Bromopentanal (45):

To a mechanically stirred slurry of pyridinium dichromate (72.5 g, 192.7 mmol) in CH_2Cl_2 (250 ml) containing molecular sieves (5A, 50 g) was added 5-bromo-1-pentanol (20.1 g, 120 mmol) at 0°C over 20 min. The stirring was continued at room temperature for a further period of 4.5 h. The reaction mixture was filtered through celite, the residue was washed with CH_2Cl_2 (2 x 100 ml) and the combined solution was concentrated under reduced pressure. The crude concentrate was triturated with ether. The ethereal solution was concentrated under reduced pressure to yield the pure aldehyde **45** (16 g, 80%).

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

$^1\text{H-NMR}$: δ 1.50-2.10 (m, 6H), 2.40 (t, 2H, $-\text{CH}_2-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-\text{H}$), 3.33 (t, 2H, $-\text{CH}_2\text{Br}$) and 9.70 (t, $-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-\text{H}$).

Mass (m/e): 165 (M^+), 163, 101 and 55.

2-(4-Bromobutyl) 1,3-dioxolane (42):

A mixture of 5-bromopentanal **45** (15.7 g, 95.15 mmol), ethylene glycol (7 g, 112.9 mmol) and p-toluenesulphonic acid (100 mg) in dry benzene (500 ml) was refluxed with

azeotropic removal of water (Dean-Stark) for 6 h. The reaction mixture was cooled and washed with saturated NaHCO_3 (50 ml), brine and dried (Na_2SO_4). Concentration afforded 2-(4-bromobutyl)-1,3-dioxolane as a light yellow liquid (18.2 g, 91.5%), b.p. 120-122/6mm.

$^1\text{H-NMR}$: δ 1.35-2.10 (m, 6H, $\text{CH}_2\text{-CH}_2\text{-CH}_2$), 3.43 (t, 2H, $\text{CH}_2\text{-Br}$), 3.86 (m, 4H, $\text{O-CH}_2\text{-CH}_2\text{-O}$) and 4.80 (t, 1H, O-CH-O).

Mass (m/e): 209 (M^+), 148, 73 and 55.

2-(8-Hydroxynon-5-ynyl)-1,3-dioxolane (**46**):

Fresh lithium amide was prepared by dissolving lithium metal (4.16 g, 0.59 g. atom) in liquid ammonia (500 ml) in the presence of catalytic amount of ferric nitrate at -33°C . To this solution was added dropwise with stirring, 4-pentyn-2-ol **41** (20 g, 238 mmol) in dry THF (25 ml) over 30 min. After 2 h at -33°C , dry HMPA (20 ml) was added followed by the addition of bromoacetal **42** (41.8 g, 200 mmol) in dry THF (50 ml) over 20 min. The reaction mixture was stirred for further 2 h at -33°C . Ammonia was evaporated off, excess lithium amide was destroyed with MeOH followed by saturated NH_4Cl solution (100 ml). It was extracted with ethylacetate (3 x 200 ml), washed with brine and dried (Na_2SO_4). The product obtained was purified by silica gel column chromatography to afford **46** (38 g, 89%), b.p. 121-124/1mm; lit.¹³ b.p. $88\text{-}91^\circ\text{C}/0.01\text{mm}$).

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

$^1\text{H-NMR}$: δ 1.22 (d, $J=6\text{Hz}$, 3H), 1.25-1.57 (m, 6H), 2.22 (m, 4H & OH), 3.88 (m, 5H, $\text{-OCH}_2\text{-CH}_2\text{-O}$ & $\text{CH}_3\text{-CH-OH}$), 4.85

(t, 1H, -OCHO-).

Mass (m/e): 212 (M^+), 211, 197, 167 and 73.

2-(8-Hydroxynonyl)-1,3-dioxolane (47):

2-(8-Hydroxynon-5-ynyl)-1,3-dioxolane **46** (7.2 g, 34 mmol) in ethanol (50 ml) was hydrogenated in the presence of Pd-C (5%, 0.700 g) in a Parr-shaker apparatus at 30 psi for 30 min. The catalyst was filtered through celite and washed with ethanol (2 x 10 ml). The combined filtrate was concentrated under reduced pressure to yield **47** (7.3 g, 100%) as a colourless liquid pure enough to be used as such. IR (neat): 3400 cm^{-1} (OH).

$^1\text{H-NMR}$ (CDCl_3): δ 1.18 (t, $J=6\text{Hz}$, 3H), 1.20-1.80 (br.m, 14H), 2.60 (br.s, 1H, OH), 3.70-3.90 (m, 5H, $\text{O-CH}_2\text{-CH}_2\text{-O-}$, $\text{CH}_3\text{CH-OH}$) and 4.82 (t, 1H, O-CH-O-).

Mass (m/e): 216 (M^+), 215 and 73.

Analysis Calc. for $\text{C}_{12}\text{H}_{24}\text{O}_3$: C, 66.66; H, 11.11;

Found: C, 66.32; H, 10.98%.

2-(8-Acetoxyonyl)-1,3-dioxolane (48):

2-(8-Hydroxynonyl)-1,3-dioxolane **47** (10 g, 46.2 mmol), pyridine (5.00 ml, 69.3 mmol) and 4-DMAP (50 mg) in dry CH_2Cl_2 (10 ml) were stirred together at room temperature and acetic anhydride (6.5 ml, 69.3 mmol) was added dropwise over a period of 10 min. Stirring was continued for 2 h, water (20 ml) was added to the reaction mixture, extracted with CH_2Cl_2 (100 ml) and washed with cold 5% aq. HCl followed by brine. The dried (Na_2SO_4) solution upon concentration yielded the pure acetate **48** (11 g, 92%).

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

$^1\text{H-NMR}$: δ 1.20 (d, $J=6\text{Hz}$, 3H), 1.25-1.85 (m, 14H), 1.97 (s, 3H, OCOCH_3), 3.86 (m, 4H, $\text{OCH}_2\text{-CH}_2\text{-O}$) and 4.83 (m, 2H, O-CHO- , $\text{CH}_3\text{-CH-O}$).

Mass (m/e): 258 (M^+), 257, 215, 169, 87, 73 and 55.

9-Acetoxydecanal (39):

To a stirred solution of 2-(8-acetoxynonyl)-1,3-dioxolane (8 g, 31 mmol) in dichloromethane (150 ml) at 0°C , was added aq. HClO_4 (35%, 25 ml) over 30 min. The stirring was continued at 0°C for another 2.5 h. The organic layer was separated, washed with saturated NaHCO_3 (20 ml) followed by brine and dried (Na_2SO_4). Concentration under reduced pressure yielded 6.40 g (96%) of aldehyde **39** sufficiently pure (TLC) for further reaction.

IR (neat): 1740 and 1730 cm^{-1} .

$^1\text{H-NMR}$: δ 1.18 (d, $J=6\text{Hz}$, 3H), 1.20-1.90 (br.m, 10H), 2.33 (m, 2H, $\text{CH}_2\text{-}\overset{\text{O}}{\parallel}\text{C-H}$), 4.80 (m, 1H) and 9.80 (t, $\text{CH}_2\text{-}\overset{\text{O}}{\parallel}\text{C-H}$).

Mass (m/e): 214, 213, 185, 171, 154, 81, 55.

Ethyl 11-acetoxydodecen-2E-oate (38):

To a stirred solution of phosphorane **40** (11.7 g, 33.6 mmol) in dry THF (20 ml) was added the solution of 9-acetoxydecanal **39** (6 g, 28 mmol) in dry THF (15 ml) at room temperature over 20 min. The reaction mixture was then refluxed while the progress of reaction was monitored by TLC. After 4 h, THF was distilled off & the crude product was purified by silica gel column chromatography (pet.

ether - ethylacetate, 95:5) to afford the acetate ester **38** (6.52 g, 82%) as colourless liquid.

IR (neat): 1740, 1730 and 1660 cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3): δ 1.15 (t, 3H), 1.17 (d, $J=6\text{Hz}$, 3H), 1.20-1.75 (br.m, 1H), 2.02 (s, 3H, COCH_3), 2.17 (m, 2H), 4.16 (q, 2H, $\text{OCH}_2\text{-CH}_3$), 4.86 (m, 1H), 5.77 (dt, $J=16\text{Hz}$ and $J=2\text{Hz}$, 1H) and 6.93 (dt, $J=16\text{Hz}$ and 8Hz , 1H).

Mass (m/e): 284 (M^+), 242, 239, 197, 169, 87 and 55.

Analysis Calc. for $\text{C}_{16}\text{H}_{28}\text{O}_4$: C, 67.60; H, 9.85;

Found: C, 67.32; H, 9.70%

Ethyl 11-acetoxy-4-oxo-dodecen-2E-oate (**37**):

(a) Chromium trioxide oxidation of (**38**):

To a vigorously stirred mixture of CrO_3 (5 g, 50 mmol), acetic anhydride (13 ml) and acetic acid (26 ml) at 0°C was added the solution of the acetate ester **38** (2.84 g, 10 mmol) in benzene (25 ml) over 5 min. The reaction mixture was allowed to come to room temperature over 30 min. and stirred further at room temperature for 1.5 h. After addition of water (20 ml), organic layer was separated and stirred with solid NaHCO_3 (15 g) for 30 min. It was then washed with water (20 ml) and the organic layer was extracted with ether (2 x 25 ml). The combined ether extract was washed with brine, dried (Na_2SO_4) and concentrated to furnish the crude product. Purification by silica gel column chromatography (eluent: pet. ether - ethylacetate, 98:2) yielded a viscous oil (1.15 g, 38%) which was identified as **37**.

(b) SeO₂ oxidation of (38):

A mixture of ethyl 11-acetoxydodecen-2E-oate **38** (2 g, 7.07 mmol) and SeO₂ (0.940 g, 8.46 mmol) in dry dioxane (20 ml) was refluxed under N₂ for 14 h. Dioxane was distilled off under reduced pressure and the residue was dissolved in ether (50 ml). Water (20 ml) was added to the mixture and stirred for 2 h. at room temperature. The organic layer was separated and dried (Na₂SO₄) to give a red oil which on silica gel column chromatography (5% ethylacetate in pet. ether) furnished **37** as a reddish yellow liquid (1.92 g, 92%). IR (neat): 1740, 1730 and 1710 cm⁻¹.

¹H-NMR: δ 1.15 (t, 3H, OCH₂-CH₃), 1.20 (d, J=6Hz, 3H), 1.20-1.84 (br.m, 10H), 2.00 (s, 3H), 2.62 (t, 2H), 4.26 (q, 2H), 4.86 (m, 1H), 6.62 (d, J=16Hz, 1H, CH=CH-^OC) and 7.06 (d, J=16Hz, 1H, CH=CH-^OC).

Mass (m/e): 298 (M⁺), 296, 243, 171, 99 and 55.

Analysis Calc. for C₁₆H₂₆O₅: C, 64.42; H, 8.72;

Found: C, 64.10; H, 8.66%

Ethyl 11-acetoxy-4-ethylenedioxydodecen-2E-oate (49):

A mixture of keto ester **37** (1.5 g, 5.03 mmol), ethylene glycol (0.624 g, 10 mmol) and catalytic amount of p-toluene sulphonic acid in dry benzene (30 ml) was refluxed for 16 h. with azeotropic removal of water (Dean-Stark). The reaction mixture was then washed with saturated NaHCO₃ (10 ml) and extracted with ether (2 x 50 ml). The combined organic layer was washed with brine, dried (Na₂SO₄) and concentrated

to yield the protected ester **49** (1.35 g, 78.4%) as a light yellow liquid.

IR (neat): 1740 ($\text{O}=\text{C}-\text{CH}_3$) and 1730 ($\text{O}=\text{C}-\text{OEt}$) cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3): δ 1.08 (t, 3H, $\text{CH}_3-\text{CH}_2-\text{O}$), 1.18 (d, $J=6\text{Hz}$, 3H, $\text{CH}_3-\text{CH}-$), 1.20-1.95 (br.m, 12H), 1.95 (s, 3H, CH_3-COO), 3.82 (m, 4H, $\text{OCH}_2-\text{CH}_2-\text{O}$), 4.13 (q, 2H, $\text{CH}_3-\text{CH}_2-\text{O}$), 4.78 (m, 1H), 5.97 (d, $J=16\text{Hz}$, 1H, $-\text{CH}=\text{CH}-\text{C}=\text{O}$) and 6.68 (d, $J=16\text{Hz}$, 1H, $-\text{CH}=\text{CH}-\text{C}=\text{O}$).

Mass (m/e): 342, 314, 297, 259, 254, 158, 113, 98.

11-Hydroxy-4-ethylenedioxy-dodecen-2E-oic acid (**22**):

The ester **49** (1.30 g, 3.8 mmol) was dissolved in ethanol (10 ml) and 2N KOH (13 ml) was added with stirring at room temperature over 10 min. and the stirring was continued for 6 h. The reaction mixture was then diluted with water and washed with benzene. The aqueous solution was cooled to 0°C and acidified to pH 4 with 2N HCl. The acidified solution was then extracted with CH_2Cl_2 (3 x 100 ml) and organic layer was dried (Na_2SO_4). The solvent was evaporated under reduced pressure to give the required acid **22** (0.96 g, 93%) as a cream coloured solid, m.p. $56-57^\circ\text{C}$ (lit.⁶ m.p. $54-55^\circ\text{C}$).

IR (nujol): 3400 and 1700 cm^{-1} .

$^1\text{H-NMR}$: δ 1.15 (d, $J=6\text{Hz}$, 3H), 1.18-1.90 (br.m, 12H), 3.64-3.95 (m, 5H, $\text{OCH}_2-\text{CH}_2-\text{O}$ and $\text{CH}_3-\text{CH}-\text{OH}$), 6.04 (d, $J=16\text{Hz}$, 1H), 6.82 (d, $J=16\text{Hz}$, 1H) & 7.10 (br.s, 1H, OH).

Mass (m/e): 272 (M^+), 254, 201, 143 and 99.

Attempted lactonization of seco-acid 22 with cyanuric chloride:

To a stirred solution of hydroxy acid **22** (100 mg, 0.36 mmol) in dry acetone (4 ml) under nitrogen was added freshly crystallized cyanuric chloride (67 mg, 0.36 mmol) followed by the addition of triethylamine (73 mg, 0.73 mmol) and 4-DMAP (100 mg). The reaction mixture was stirred at room temperature for 6 h. The colourless solid formed was filtered off. The filtrate was concentrated and to the residue, water (5 ml) was added. It was extracted with CHCl_3 (2 x 50 ml), dried (Na_2SO_4) and concentrated. The product was purified by silica gel column chromatography (hexane - acetone, 9:1) to give 40 mg (43%) of the lactone **23** as a semi-solid.

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

$^1\text{H-NMR}$ (CDCl_3): δ 1.25 (d, $J=6\text{Hz}$, 3H), 1.30-1.86 (br.m, 12H), 3.95 (m, 4H, $-\text{OCH}_2-\text{CH}_2-\text{O}-$), 5.00 (m, 1H), 6.10 (d, $J=16\text{Hz}$, 1H) and 6.75 (d, $J=16\text{Hz}$, 1H).

Mass (m/e): 254 (M^+), 239, 210, 143, 125, 113 and 98.

Analysis Calc. for $\text{C}_{14}\text{H}_{22}\text{O}_4$: C, 66.14; H, 8.66;

Found: C, 66.24; H, 8.58%

11-Hydroxydodecen-2E-oic acid (75):

An aqueous solution of KOH (2N, 11.5 ml) in methanol (5 ml) was slowly added over 10 min to a stirred solution of ethyl 11-acetoxydodecen-2E-oate **38** (3.150 g, 11.09 mmol) in methanol (5 ml). The resultant solution was stirred for a further period of 10 h. It was then diluted with water (10 ml) and extracted with benzene (20 ml). The aqueous layer was acidified with 5% dil. HCl to pH 4 and extracted with CHCl_3 (4 x 50 ml) followed by washing with brine and drying (Na_2SO_4). Evaporation of the solvent afforded a low melting solid (1.84 g, 77.6%).

IR (neat): 3500 (br.), 1730, 1720 and 1660 cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3): δ 1.18 (d, $J=6.2\text{Hz}$, 3H), 1.19-1.72 (m, 12H), 2.20 (m, 2H), 3.78 (m, 1H), 5.70 (td, $J=16\text{Hz}$ and 2Hz , 1H), 7.05 (dt, $J=16\text{Hz}$ and 8Hz , 1H) and 6.20 (br.s, 1H, D_2O exchangeable, OH).

Mass (m/e): 214 (M^+), 197 (M-OH), 181, 170, 136, 109, 99 and 55.

R(-)-11-Acetoxydodecen-2E-oic acid (76):

A solution of 11-hydroxydodecen-2E-oic acid **75** (0.630 g, 2.94 mmol) and 1,1,1-trichloroethylacetate (1 g, 4.51 mmol) in dry ether (5 ml) was added to a stirred suspension of porcine pancreatic lipase (PPL, Sigma, 0.5 g) in dry ether (10 ml) containing molecular sieves 4A (1 g).

The reaction mixture was stirred under nitrogen atmosphere at 27°C for 4 h, after which it was filtered through celite and celite was washed with ether. Ether was removed under reduced pressure and the crude reaction mixture was purified by silica gel column chromatography (10% acetone in pet. ether). The required acetoxy acid **76** was obtained as a semi-solid (0.234 g, 31%) along with 0.385 g of unreacted acid (**75**); $[\alpha]_D^{25} -47^\circ$ (C=1, CHCl₃).

IR (neat): 3500 (br.) 1730, 1720 and 1660 cm⁻¹.

¹H-NMR (CDCl₃): δ 1.20 (d, J=6.1Hz, 3H), 1.25-1.80 (m, 12H), 2.00 (s, 3H), 2.20 (m, 2H), 4.84 (m, 1H), 5.74 (dt, J=16Hz and J=2Hz, 1H), 7.02 (dt, J=16Hz and 8Hz, 1H) and 9.00 (br.s, D₂O exchangeable, 1H, OH).

Mass: 256 (M⁺), 224, 215, 195, 181, 152, 101, 73 and 55.

Analysis Calc. for C₁₄H₂₄O₄: C, 78.50; H, 9.37;

Found: C, 78.65; H, 9.25%

R-(+)-Methyl 11-acetoxydodecen-2E-oate (**79**):

Freshly prepared solution of diazomethane in ether (100 ml) was added slowly at 0°C to the solution of acid **76** (0.190 g, 0.7 mmol) in ether (5 ml). The reaction mixture was kept at 0°C for 2 h and excess diazomethane (CH₂N₂) was then destroyed with glacial acetic acid (0.2 ml). The product was purified by column chromatography (5% acetone in pet. ether) to yield 0.174 g (87%) of (**79**) as a viscous yellow oil; $[\alpha]_D^{25} +23.2^\circ$ (C=0.84, CHCl₃).

IR (neat): 1740, 1730 and 1660 cm⁻¹.

$^1\text{H-NMR}$ (CDCl_3): δ 1.18 (d, $J=6\text{Hz}$, 3H), 1.20-1.80 (m, 12H), 1.98 (s, 3H), 3.63 (s, 3H, COOCH_3), 5.65 (d, $J=16\text{Hz}$, 1H) and 6.82 (dd, $J=16\text{Hz}$ and 8Hz , 1H).

Mass (m/e): 270 (M^+), 239 ($\text{M}-\text{OCH}_3$), 195, 151, 136, 113, 87, 75.

R-(-)-Methyl 11-acetoxy-4-oxo-dodecen-2E-oate (80):

R-(+)-Methyl 11-acetoxydodecen-2E-oate **79** (0.138 g, 0.51 mmol) and powdered SeO_2 (0.067 g, 0.61 mmol) in dry dioxane (10 ml) was refluxed under nitrogen atmosphere for 17 h. Dioxane was distilled off under reduced pressure and the residue was dissolved in ether (25 ml). Water (15 ml) was added to the mixture and stirred for 2 h at room temperature. The organic layer was separated, dried (Na_2SO_4) and concentrated to give a red oil which was then purified by silica gel column chromatography (5% ethylacetate in pet. ether) to afford **80** as a reddish yellow liquid (0.128 g, 88%); $[\alpha]_{\text{D}}^{25} -14.5^\circ$ ($C=0.56$, CHCl_3).

IR (neat): 1745, 1730 and 1645 cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3): δ 1.18 (d, $J=6\text{Hz}$, 3H), 1.20-1.77 (m, 10H), 2.02 (s, 3H, OCOCH_3), 2.62 (t, 2H), 6.60 (d, $J=16\text{Hz}$, 1H), and 7.03 (d, $J=16\text{Hz}$, 1H).

Mass (m/e): 284 (M^+), 241, 224, 215, 152, 101, 73, 69 and 55.

R-(+)-Methyl 11-acetoxy-4-oxo-dodecanoate (81):

R-(-)-Methyl 11-acetoxy-4-oxo-dodecen-2E-oate **80** (0.128 g, 0.45 mmol) in dry methanol (10 ml) was subjected to hydrogenation at atmospheric pressure over Pd-C (10%, 50 mg)

for 8 h. The catalyst was filtered off and methanol was removed under reduced pressure. The required product was obtained in quantitative yield (0.123 g) as a colourless oil; $[\alpha]_D^{25} +13.04$ (C=0.42, MeOH).

IR (neat): 1750, 1740 and 1735 cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3): δ 1.20 (d, J=6Hz, 3H), 1.24-1.80 (m, 10H), 2.02 (s, 3H, OCOCH_3), 2.22-2.60 (m, 6H), 3.66 (s, 3H, $-\text{COOCH}_3$) and 4.86 (m, 1H).

Mass (m/e): 286 (M^+), 256 ($\text{M}+1 - \text{OCH}_3$), 243, 227, 199, 171, 150, 75.

Analysis Calc. for $\text{C}_{15}\text{H}_{26}\text{O}_5$: C, 62.93; H, 9.09;

Found: C, 62.78; H, 9.12%

R-(-)-Methyl 11-hydroxy-4-oxo-dodecanoate (8):

To a stirred solution of R-(+)-methyl 11-acetoxy-4-oxo-dodecanoate **81** (0.108 g, 0.37 mmol) in dry methanol (5 ml), anhydrous potassium carbonate (.2 g) was added and the stirring was continued for 6 h at room temperature. Excess methanol was removed and the mixture was diluted with water (10 ml), extracted with ethylacetate (2 x 20 ml) and dried (Na_2SO_4). The crude product obtained was purified by silica gel column chromatography (5% acetone in pet. ether) to yield **8** as a light yellow liquid (76 mg, 82%); $[\alpha]_D^{25} -7.08^\circ$ (C=0.96, MeOH) (lit.¹ $[\alpha]_D^{25} -5.64^\circ$, C=1.16 MeOH).

IR (neat): 3400, 1740 and 1730 cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3): δ 1.20 (d, J=6Hz, 3H), 1.30-1.80 (m, 10H), 2.22-2.84 (m, 6H), 3.65 (s, 3H, COOCH_3) and 3.74 (m, 1H).

Mass (m/e): 244 (M^+), 226, 213, 196, 152, 95, 81 and 55.

Analysis Calc. for $C_{13}H_{24}O_4$: C, 63.93; H, 9.93;

Found: C, 63.68; H, 9.74%

REFERENCES

1. J. Sekiguchi, H. Kuroda, Y. Yamada and H. Okada,
Tetrahedron Lett., **26**, 2341 (1985).
2. a) A. Hirota, H. Sakai and A. Isogai,
Agric. Biol. Chem., **43**, 731 (1985).
b) A. Hirota, H. Sakai, A. Isogai, Y. Kitano, T. Ashida,
H. Hirota and T. Takahashi,
Ibid, **43**, 903 (1985).
c) A. Hirota, H. Hirota, H. Sakai, A. Isogai and
T. Takahashi,
Bull. Chem. Soc. Jpn., **58**, 2147 (1985).
d) A. Hirota, A. Isogai and H. Sakai,
Agric. Biol. Chem., **43**, 799 (1985).
3. R.F. Vesonder, F.H. Stodola, L.J. Wickenham,
J.J. Ellis and W.K. Rohwedder,
Can. J. Chem., **49**, 2029 (1971).
4. D. Rodphaya, J. Sekiguchi and Y. Yamda,
J. Antibiot., **39**, 629 (1986).
5. A. Horeau,
Stereochemistry Fundamentals and Methods Vol.3,
Determination of Configuration by Chemical Methods,
Ed. by H.B. Kagan, p.51, George Thieme Publishers,
Suttgart (1977).
6. A. Makita, Y. Yamada and H. Okada,
J. Antibiot., **39**, 1257 (1986).

7. J.S. Yadav, P. Radhakrishna and M.K. Gurjar,
Tetrahedron, **45**, 6263 (1989).
8. N.R. Ayyangar, B. Chanda, R.D. Wakharkar and R.A. Kasar,
Synth. Commun., **18**, 2103 (1988).
9. K. Narasaka, M. Yamaguchi and T. Mukaiyama,
Chem. Lett., 959 (1977).
10. Preparative Acetylenic Chemistry
L. Brandsma, Ed.,
Elsevier (1971).
11. S.K. Kang, W.S. Kim and B.H. Moon,
Synthesis, 1161 (1985).
12. E.J. Corey, G. Schmidt,
Tetrahedron Lett., 399 (1979).
13. H.J. Bestmann and R. Schobert,
Synthesis, 419 (1989).
14. a) M. Nakayama, S. Shinke, Y. Matsushita, S. Ohira and
S. Hayashi,
Bull. Chem. Soc. Jpn., **52**, 184 (1979).
b) H.J. Bestmann and R. Schobert,
Angew. Chem. Int. Ed. Engl., **24**, 791 (1985).
15. T. Mukaiyama, M. Usui and K. Saigo,
Chemistry Letters, 2455 (1976).
16. T. Kurihara, Y. Nakajima and O. Mitsunobu,
Tetrahedron Lett., 2456 (1976).
17. E.J. Corey and K.C. Nicolaou,
J. Am. Chem. Soc., **96**, 5614 (1974).
18. K. Venkataraman and D.R. Wagle,
Tetrahedron Lett., **21**, 1893 (1980).

19. K. Mori and T. Sakai,
Liebigs Ann. Chem., 13 (1988).
20. L. Thijs, D.M. Egenberger and B. Zwanenburg,
Tetrahedron Lett., 30, 2153 (1989).
21. D. Seebach and M. Zuger,
Helv. Chim. Acta, 65, 495 (1982).
23. J. Inanaga, K. Hirata, H. Saeiki, T. Katsuki and
M. Yamaguchi,
Bull. Chem. Soc. Jpn., 52, 1989 (1979).
24. a) Lipases,
B. Borgstrom and H.L. Brockmann (Eds.)
Elsevier, p.151 (1984).
b) J.B. Jones,
Tetrahedron, 42, 3351 (1988).
c) H.G.W. Leuenberger,
Pure and Appl. Chem., 62, 753 (1990).
25. K. Laumen and M. Schneider,
Tetrahedron Lett., 26, 2073 (1985).
26. G. Kirchner, M.P. Scollar and A.M. Klibanov,
J. Am. Chem. Soc., 107, 7072 (1985).
27. C.H. Chen and C.J. Sih,
Angew. Chem. Int. Ed. Engl., 28, 695 (1989).
28. H.L. Goderic, G. Ampe, M.P. Feyten, B.L. Fouwe,
W.M. Guffens, S.M.V. Cauwenbergh and P.P. Tobback,
Biotechnol. Bioeng., 30, 258 (1987).
29. A.M. Klibanov,
Chem. Tech., 354 (1986).

30. a) J.S. Wallace, K.B. Reda, M.E. Williams and
C.J. Morrows,
J. Org. Chem., 55, 3544 (1990).
- b) A.L. Gutmann, K. Zuobi and T. Bravdo,
J. Org. Chem., 55, 3546 (1990).
- c) P. Ciuffreda, D. Colombo, F. Ronchetti and L. Toma,
J. Org. Chem., 55, 4187 (1990).
- d) C. Shin, M. Seki and N. Takahashi,
Chemistry Letters, 2089 (1990).
31. F. Theil, S. Ballschuh, H. Schick, M.Haupt, B. Hafner
and S. Schwarz,
Synthesis, 540 (1988).
32. K. Mori and R. Bernotas,
Tetrahedron Asymmetry, 1, 87 (1990).
33. H. Suemune, Y. Mizuhara, H. Akita and K. Sakai,
Chem. Pharm. Bull., 34, 3440 (1986).
34. D.H.R. Barton, P.D. Magnus, G. Smith and D. Zurr,
J.C.S. Chem. Commun., 861 (1971).

CHAPTER III

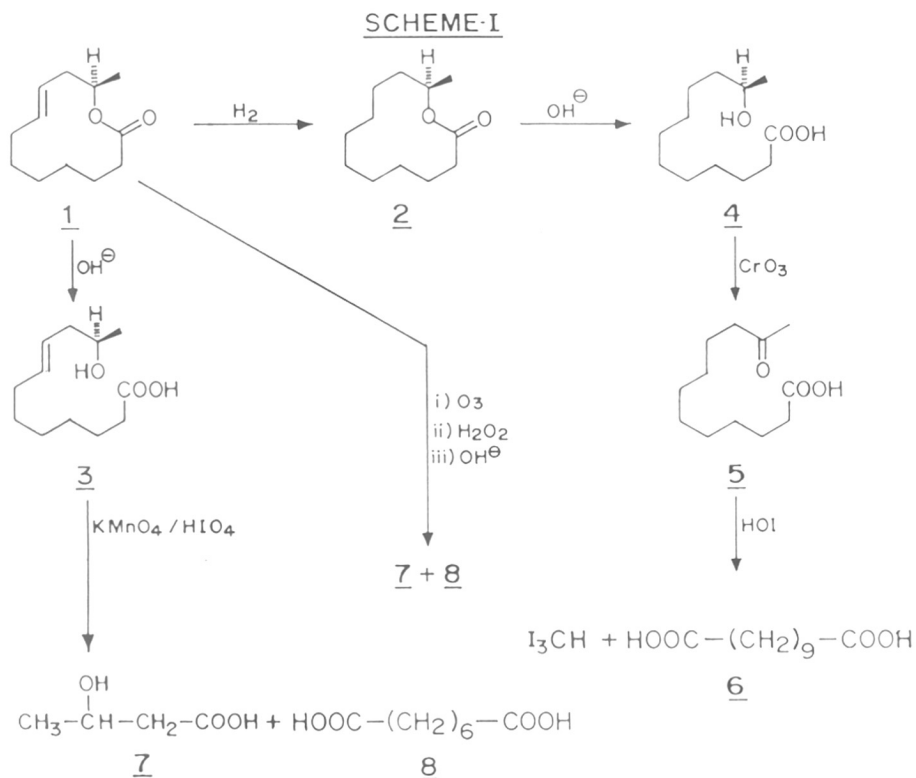
SYNTHESIS OF R-(+)-RECIFEIOLIDE

INTRODUCTION:

The isolation and chemistry of large ring lactones have been known for more than 60 years. These were first described by Kerschbaum¹ in 1927; since then many more examples of this class of compounds have appeared. Most of these lactones are macrolides and one such macrolide is recifeioidide (1), isolated from the fungus Cephalosporium recifei NRRL 5161, after growing the strain on malt-glucose medium for 35 days. From a crude colourless mobile liquid, pure lactone (1) was obtained in about 50% yield by preparative GLC.

Vesonder et al.² established the structure of recifeioidide utilising spectroscopic and chemical studies. Elementary analyses and molecular ion peak (m/e 196) in the mass spectrum corresponded to the molecular formula $C_{12}H_{20}O_2$. In the infra-red spectrum, absorption bands at 1735 cm^{-1} indicative of either a lactone or an ester and at 975 cm^{-1} , characteristic of a trans double bond were seen. Chemical degradations described below further lent support to the structure. Saponification of (1) gave a 12-carbon hydroxy acid (3). Asymmetry in the molecule (1) was indicated by its optical activity, $[\alpha]_D^{25} +73.2^\circ$. Hydrogenation of (1) afforded the saturated lactone (2) which on saponification yielded the 12-carbon hydroxy acid (4). Chromium trioxide oxidation of (4) gave the keto acid 5 which was converted to (6) and CHI_3 by treatment with hypoiodite (SCHEME I). The position of the double bond in (1) was established by subjecting it to ozonolysis and to oxidation with $KMnO_4-HIO_4$ which gave 3-hydroxybutyric

acid (**7**) and suberic acid (**8**). The structure proposed was found to be in full conformity with the spectral data and chemical degradation studies.



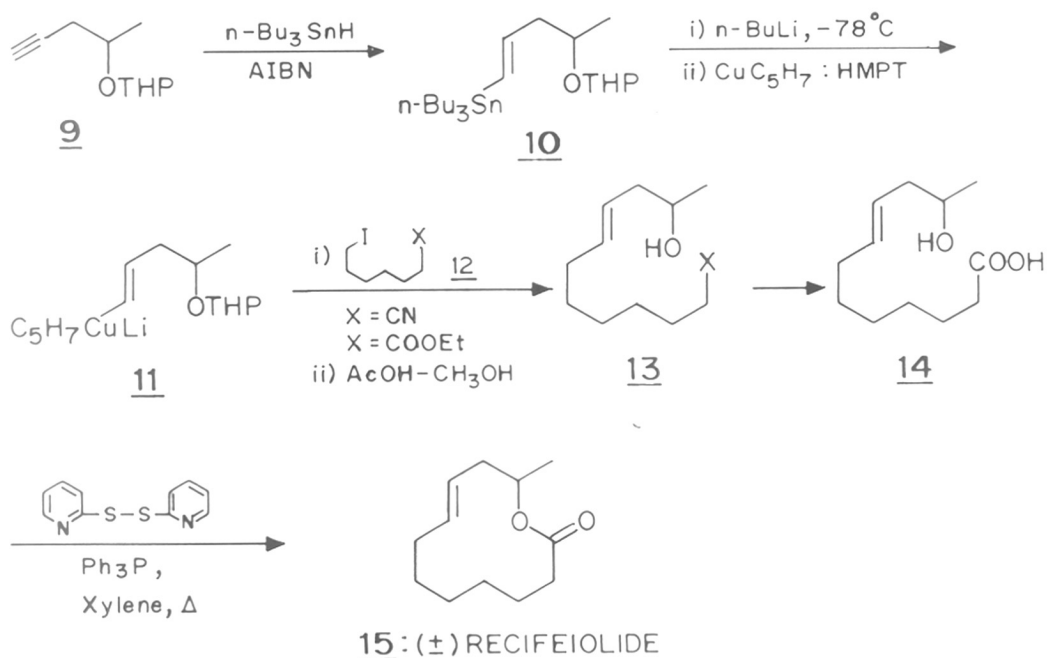
Recifeiolide (**1**) is not known to possess any biological activity unlike most of the macrolides. Yet, due to the fact that use of simple large-ring lactones has found commercial application as fixative in perfumes, the synthesis of recifeiolide has evoked considerable interest. Soon after its isolation and structure determination in 1971, Corey and Ulrich³ reported the first synthesis of ($\pm$)recifeiolide. Since

then to date six more syntheses of racemic recifeiolide and two syntheses of R(+)recifeiolide have been reported. For the sake of brevity, the important strategies applied in these syntheses will be highlighted here.

The main strategy involved in the reaction sequence of Corey's approach³ was the use of acetylinic precursor (**9**) for the creation of trans double bond followed by lactonization using dipyridyldisulphide (DPDS) (SCHEME II). The cuprate (**11**) was obtained by the reaction of the vinyl stannane (**10**) with $\text{CuC}_5\text{H}_7\text{:HMPT}$. Coupling of (**11**) with the iodonitrile (**12**)

SCHEME-II

E J. COREY et.al.³

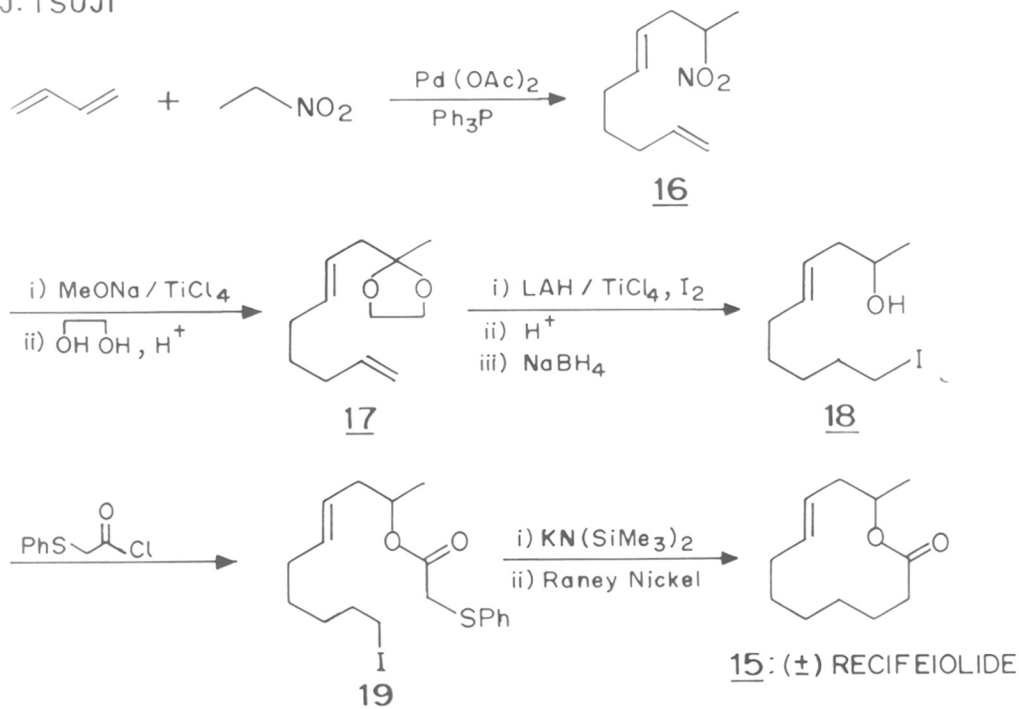


followed by hydrolysis gave 11-hydroxy-dodecen-8E-oic acid (14). Lactonization was carried out by the procedure developed by Corey using dipyridyldisulphide to yield racemic recifeiolide (15).

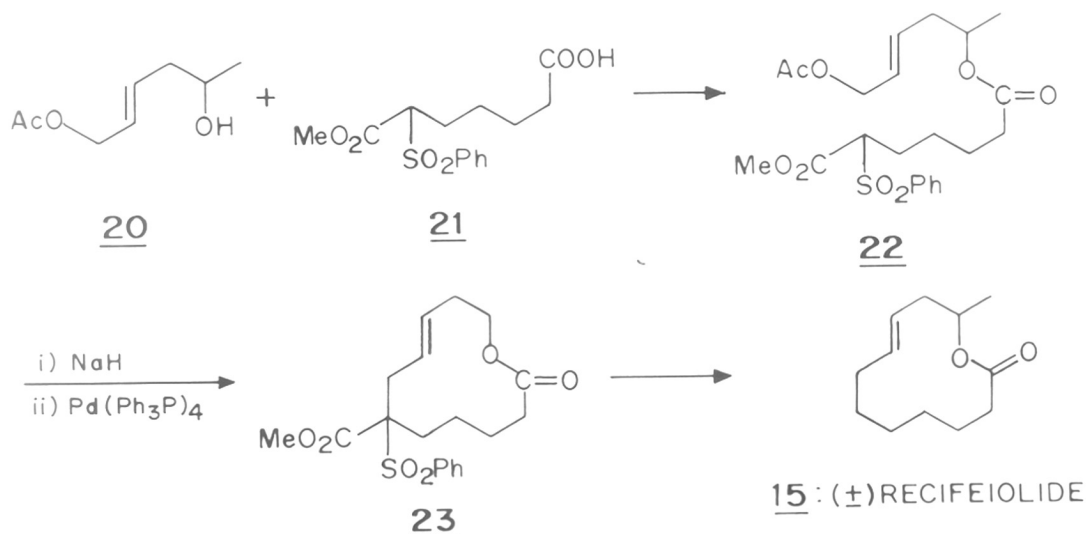
Tsuij⁴ has reported a new method for the formation of hydroxyacid carbon skeleton and has applied the same for the synthesis of (±)recifeiolide (SCHEME III). The key reaction involved was telomerization of two molecules of butadiene and one of nitroethane catalysed by $\text{Pd}(\text{OAc})_2/\text{PPh}_3$ to furnish (16). Nef reaction ($\text{MeONa}/\text{TiCl}_4$) followed by protection of the resultant ketone gave (17). Functionalization of the terminal double bond and reduction of the ketone formed followed by

SCHEME-III

J. TSUJI⁴



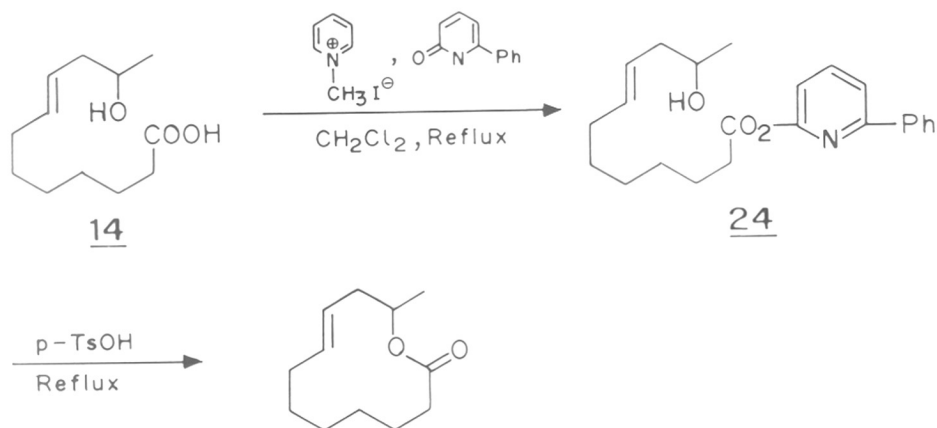
Another stereocontrolled synthesis of ($\pm$)recifeiolide via organopalladium chemistry was reported by Trost and Verhoeven.⁵ The usual method of macrolactonization was avoided by forming a C-C bond using $\text{Pd}(\text{Ph}_3\text{P})_4$ (SCHEME IV). Thus the ester (22) was obtained by reacting the alcohol (20) with the acid chloride of (21). The anion of (22) was generated with NaH and subsequently reacted with $\text{Pd}(\text{Ph}_3\text{P})_4$ to produce the 12-membered lactone (23) as the sole product. The reaction was both regio- and stereospecific. Decarbomethoxylation followed by reductive desulphonylation gave ($\pm$)recifeiolide (15) identical in all respects with an authentic sample.

TROST and VERHOEVEN⁵

Mukaiyama *et al.*⁶ have reported the total synthesis of (±)recifeiolide by applying their own method developed for lactonization (SCHEME V). Thus 11-hydroxydodecen-8E-oic acid (**14**) was cyclised to (±)recifeiolide in excellent yield, via its 6-phenyl-2-pyridyl ester (**24**).

SCHEME-V

T. MUKAIYAMA⁶

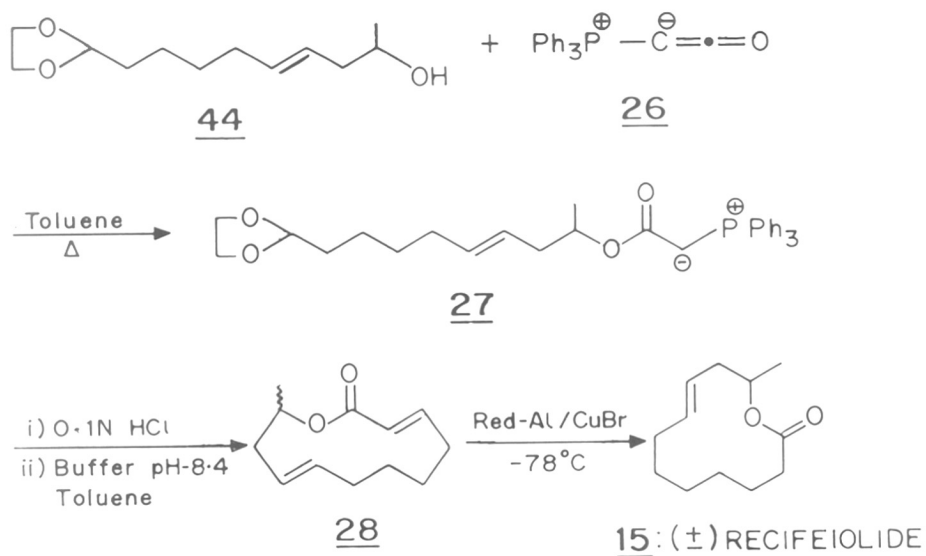


15: (±) RECIFEIOLIDE

Application of intramolecular Wittig reaction of (ω-oxoalkoxy)carbonylmethylene triphenylphosphoranes (**27**) for closure of macrocyclic lactones for recifeiolide synthesis was recently reported by Bestmann and Schobert⁷ (SCHEME VI). The intermediate (**27**) was obtained by addition of 2-(8-hydroxynon-5E-enyl) - 1,3-dioxolane (**44**) to the cumulated ylide, triphenylphosphoranylidene ketene (**26**). Deprotection of acetal in (**27**) followed by intramolecular Wittig reaction furnished the lactone (**28**) which on selective reduction with Red-Al afforded (±)recifeiolide (**15**).

SCHEME-VI

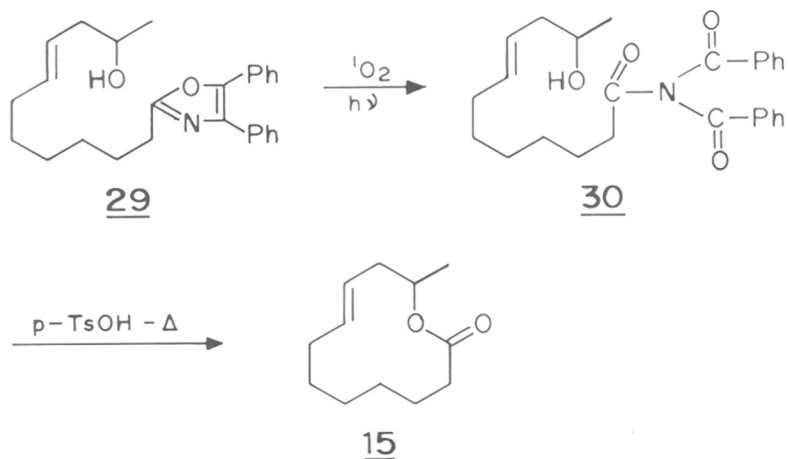
BESTMANN and SCHOBERT⁷



The conversion of oxazoles to triamides by dye-sensitized photo-oxidation is one of the interesting reactions of singlet oxygen with heterocyclic system reported by Wasserman⁸ (SCHEME VII). The said rearrangement occurs under mild conditions. This reaction has been applied to the synthesis of (±)recifeiolide. Thus photo-oxidation of the isoxazole (29) and cyclisation of the intermediate triamide (30) gave a mixture of E and Z (±)recifeiolide from which pure E-form was isolated by chromatography on silver nitrate-impregnated silica gel.

SCHEME-VII

WASSERMAN et.al⁸



Other synthetic methodologies for (±)recifeiolide include application of "ene" reactions by aldehydes with non-nucleophilic alkenes catalysed by ethylaluminium chloride, and palladium-catalysed alkylation of (E)-alkenylpentafluoro-silicates for the preparation of 1,4-diones. Yet another synthesis starting from pent-1-yn-4-ol (**41**, Chapter II) was reported in 1986 by Rama Rao and Pulla Reddy.¹¹

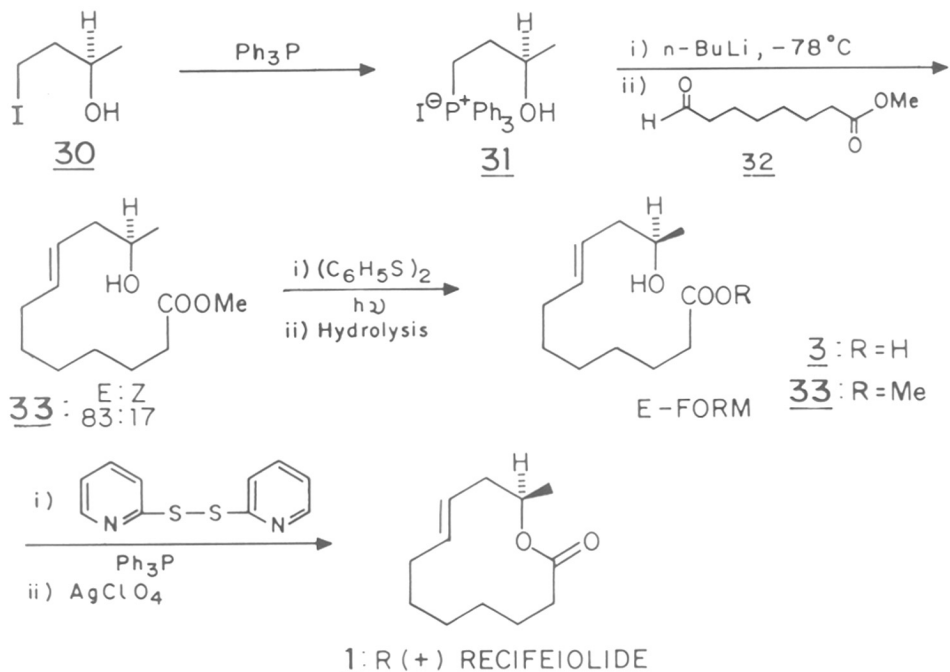
Synthesis of R(+)-recifeiolide:

Only a few of the methods described for the synthesis of (±)recifeiolide can be considered for a parallel synthetic scheme for R(+)-recifeiolide. The other methods are based on the resolution of racemic recifeiolide. Two asymmetric syntheses of R(+)-recifeiolide have been reported so far^{12,13} utilising the chiral starting materials R(+)-methyloxirane and R(-)-1,3-butanediol, respectively.

In the first approach,¹² (SCHEME VIII), 1,3-butanediol was resolved with (-)-camphanic acid to a mixture of diastereomeric esters. The R(-)enantiomer was converted via (R)-1-iodo-3-butanol (**30**) to 3-hydroxybutyl triphenylphosphonium iodide (**31**). Wittig condensation of the phosphorane

SCHEME - VIII

GERLACH et.al.¹²

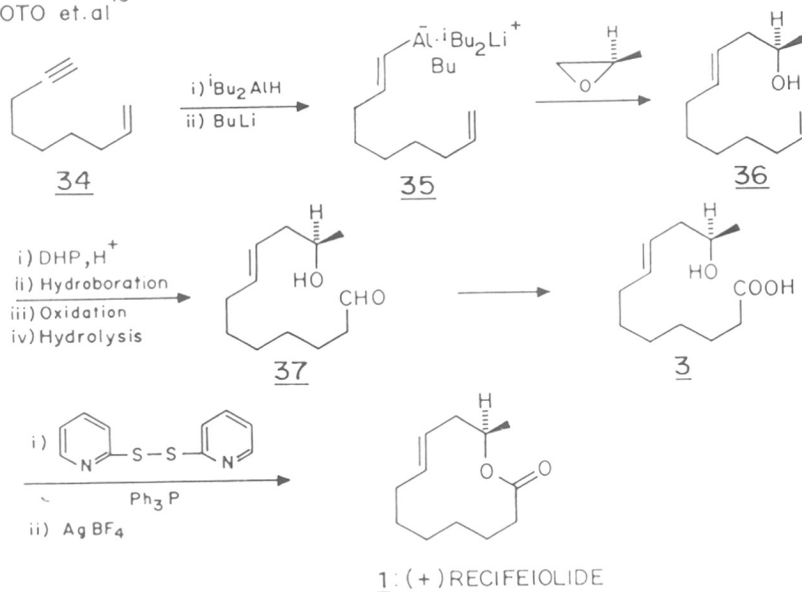


derived from (**31**) with methyl 8-oxooctanoate (**32**) led to a mixture of E and Z isomers of (**33**). The latter mixture of isomers on photo-irradiation led to methyl 11-hydroxydodecen-8E-oate (**33**). Hydrolysis of the latter gave the corresponding hydroxy acid (**3**) which was transformed into the (2-pyridyl) ester. Cyclisation of the latter under the influence of silver perchlorate yielded R(+)-recifeiolide (**1**).

Utimoto et al. have reported¹³ yet another synthesis of R(+)-recifeiolide (SCHEME IX) employing R(+)-methyl oxirane as the chiral source. The key reaction involved was stereoselective reductive alkenylation of 1-nonen-8-yne via hydralumination. Thus treatment of 1-nonen-8-yne with DIBAL-H followed by lithiation with n-BuLi furnished lithium vinyl-alanate (35). The latter was reacted with R(+)-methyloxirane to yield the alcohol (36) with 99% E-selectivity. The chiral centre was not disturbed as was evident from ¹H-NMR studies with Eu(hfc)₃ reagent. Protection of the hydroxy group of (36) as the THP ether, hydroboration of the terminal olefin

SCHEME - IX

UTIMOTO et al.¹³



followed by oxidation and hydrolysis gave the hydroxy aldehyde (37). Further oxidation to acid (3) and lactonization as per the procedure by Gerlach¹² afforded R(+)-recifeiolide (1).

PRESENT WORK

Introduction:

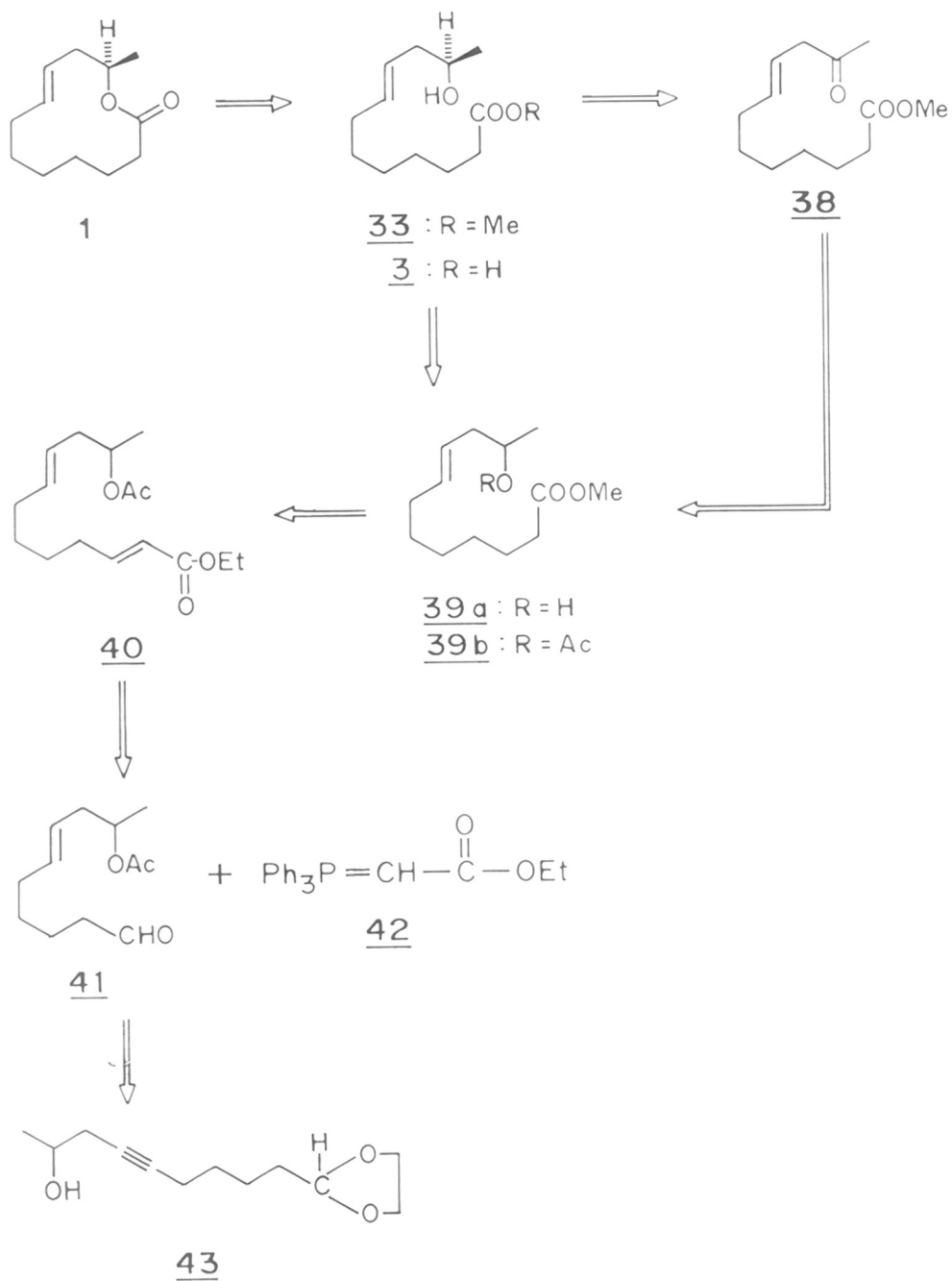
As was described earlier, only two syntheses of R(+) recifeiolide have been reported so far. The two main requirements for synthesising R(+)recifeiolide are: stereoselective introduction of the double bond and fixation of the chiral centre. In the two earlier syntheses, chirality was introduced from the beginning in the form of R(-)-1,3-butanediol and R(+)methyloxirane as the C-4 and C-3 synthons respectively. In these cases, possibilities of partial racemization cannot be discounted. Hence introduction of chirality at a later stage was desirable. In the present work, synthesis of R(+) recifeiolide was effected by introduction of chirality at a later stage on a C-12 synthon. This was achieved by asymmetric reduction of the required C-12 ketoester by chemical method as well as by enzyme catalysed hydrolysis of racemic C-12 acetate ester.

Retrosynthetic analysis of (1)

A study of retrosynthetic analysis (SCHEME-X) reveals that a good strategy for synthesising a racemic C-12 synthon of the type (39a) would be a 2-carbon Wittig reaction with the C-10 aldehyde (41). The latter in turn could be derived from the C-10 acetylenic ketal (43) by selective reduction. Synthesis of (43) was already achieved and utilised in the synthesis of (±) patulolide A (see Chapter II). Partial reduc-

RETROSYNTHETIC ANALYSIS

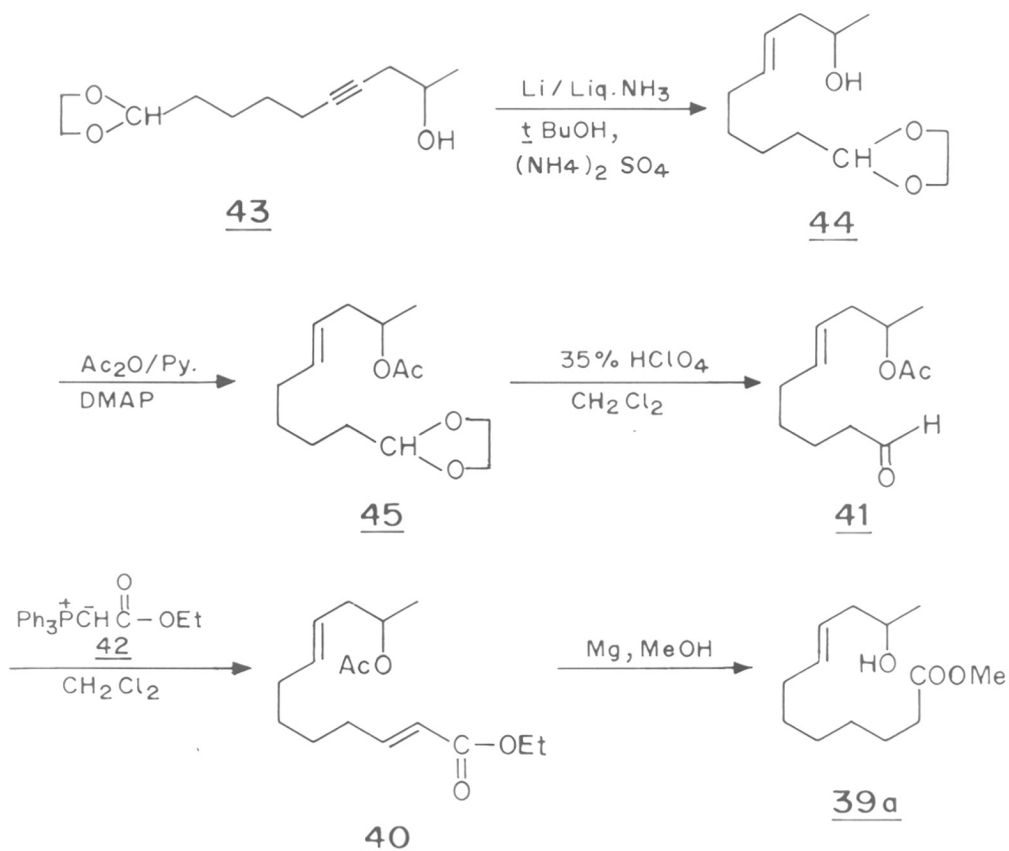
SCHEME-X



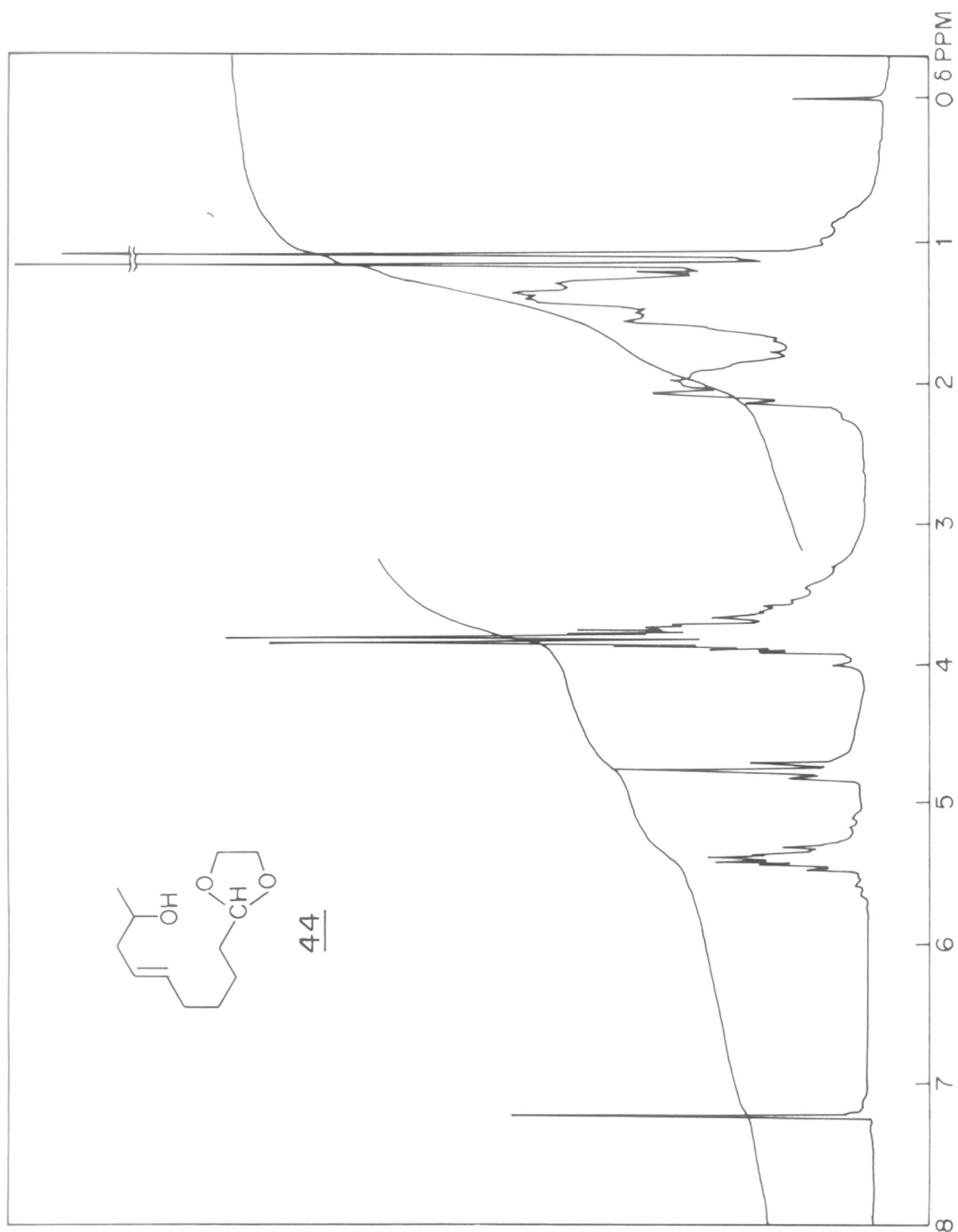
tion of the α, β -unsaturated ester (40) to the ester (39a) followed by mild oxidation of the latter would furnish the keto ester (38), the target molecule for asymmetric reduction. Similarly acetylation of (39a) would provide the right compound (39b) for attempting an enzyme mediated hydrolysis.

Stereoselective reduction of 2-[8-hydroxynon-5-ynyl]-1,3-dioxolane (43) was achieved with Li/NH_3 ¹⁴ in the presence of *t*-butanol and solid ammonium sulphate (SCHEME-XI). This method was found to be superior to the conventional Na/NH_3 ⁶ and LAH-diglyme¹⁵ reductions. Work-up procedures were simpler and easier with Li/NH_3 and also yield of the product formed was found to be good, giving exclusively the desired trans-isomer. Thus 2-[8-hydroxynon-5E-enyl]-1,3-dioxolane (44) was obtained as a colourless liquid in more than 90% yield. Further, the product was fully characterized by spectral data. Its ¹H-NMR showed a multiplet centered at δ 5.34 indicative of a trans double bond.⁷ (Fig.1). Protection of the hydroxy group in (44) as acetate followed by mild acid-catalysed hydrolysis of acetal yielded the acetate aldehyde (41) quantitatively. Wittig reaction of the latter with the phosphorane (42) in methylene chloride at room temperature yielded the unsaturated ester (40) as a viscous oil. Purification by column chromatography furnished the pure ester in 78% yield. Its ¹H-NMR revealed a triplet of doublet centered at δ 5.73 ($J=16\text{Hz}$, $J=2\text{Hz}$) and another triplet of doublet at δ 6.88 ($J=16\text{Hz}$, $J=8\text{Hz}$) indicative of an α, β -unsaturated trans-double bond (FIG.2). Further confirmation was also provided by IR and mass spectral studies.

SCHEME -XI



Selective reduction of α, β -unsaturated trans double bond of (**40**) keeping the other trans double bond intact was achieved by reacting it with activated magnesium in dry methanol.¹⁶ Similar type of reductions have been reported with Red-Al (Aldrich).⁷ Thus methyl 11-hydroxydodecen-8E-oate (**39a**) was obtained in 80% yield as a colourless liquid. During the course of this reaction, transesterification, reduction of α, β -unsaturated double bond and deacetylation took place (Fig.3). The appearance of a singlet at δ 3.65 ($-\text{COOCH}_3$), a

FIG.1: ^1H -NMR SPECTRUM OF COMPOUND (44) IN CDCl_3

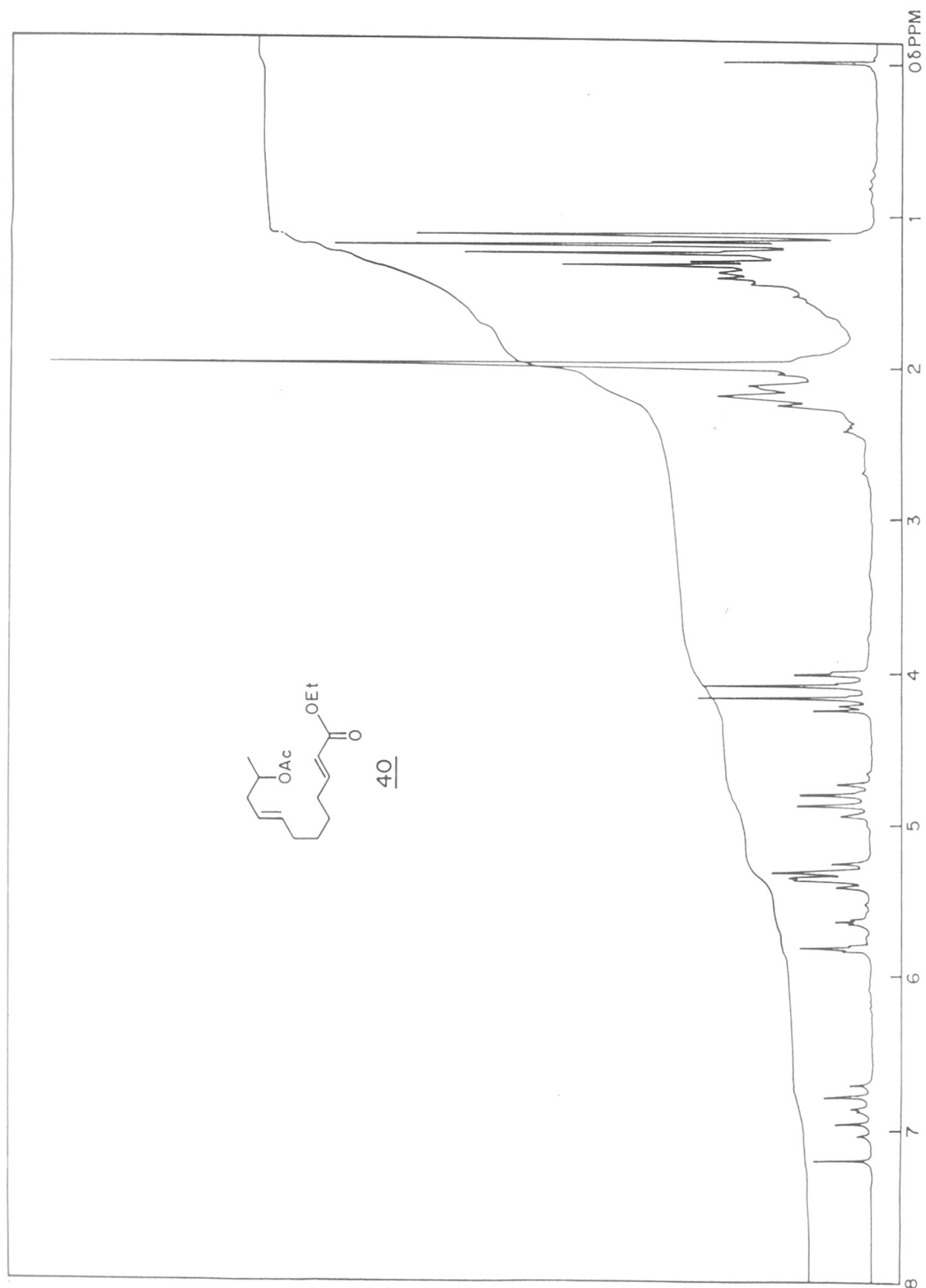


FIG.2: ^1H -NMR SPECTRUM OF COMPOUND (40) IN CDCl_3

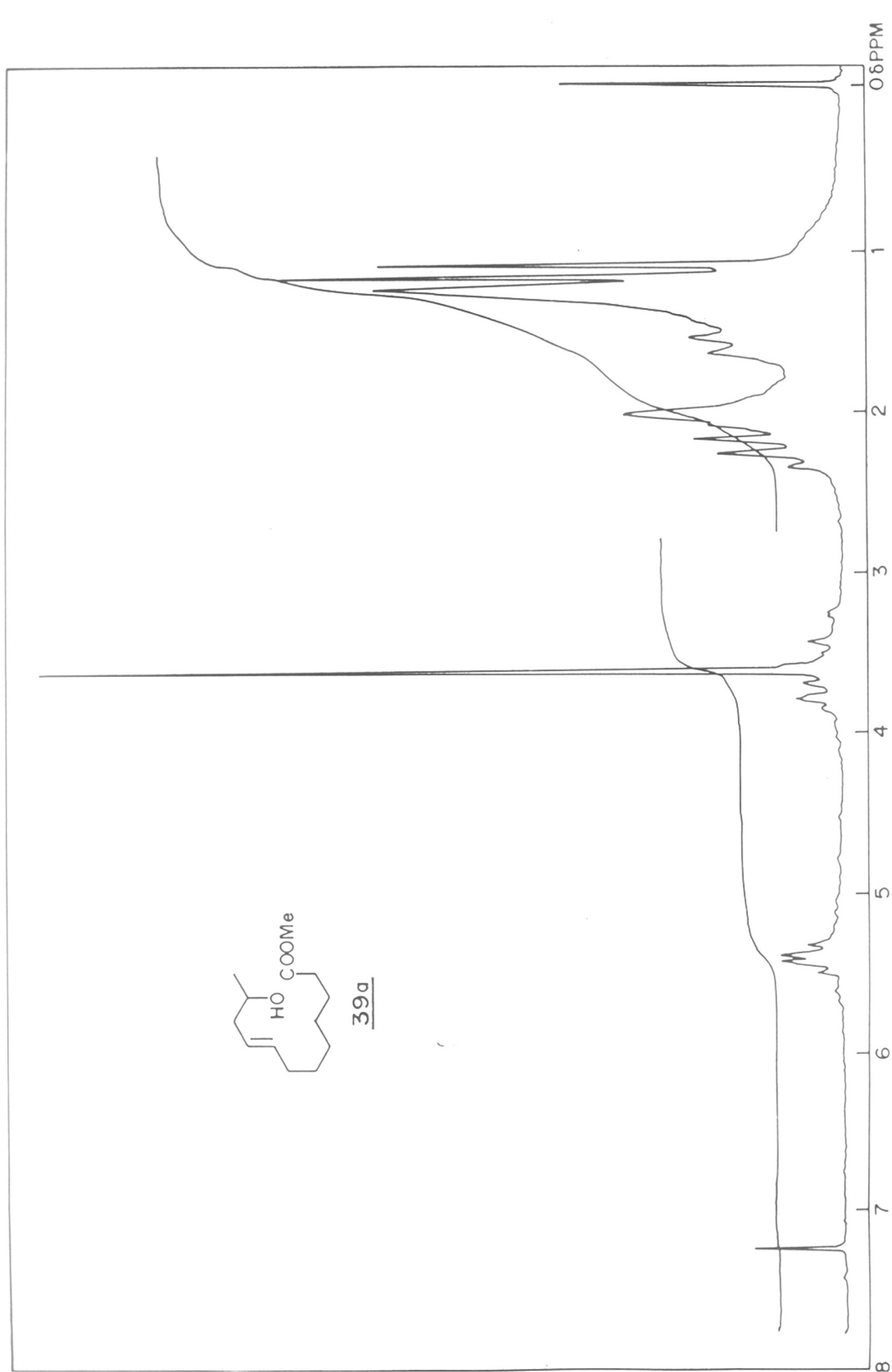


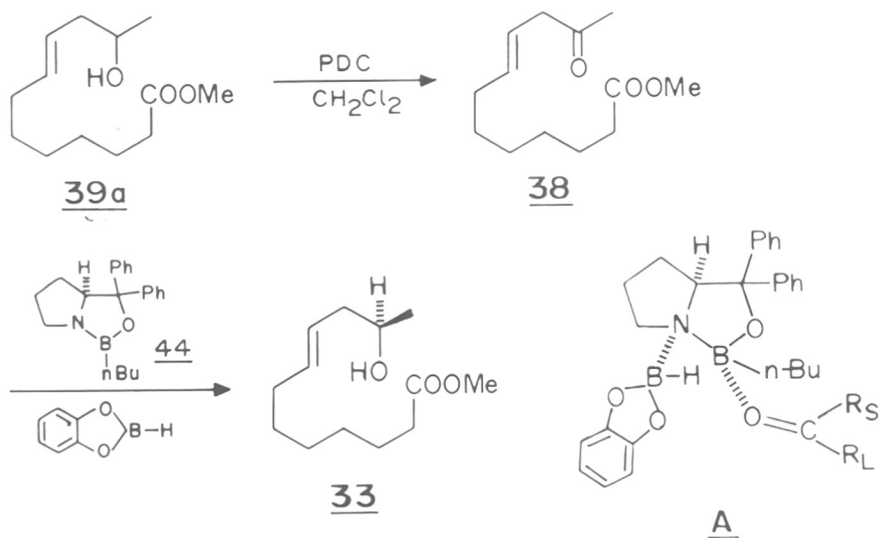
FIG. 3: $^1\text{H-NMR}$ SPECTRUM OF COMPOUND (**39a**) IN CDCl_3

multiplet at δ 3.78 ($\text{CH}_3\text{-}\underline{\text{CHOH}}$) and disappearance of signals due to α, β -unsaturated trans double bond confirmed the formation of (**39a**). Oxidation of (**39a**) with PDC in the conventional manner gave methyl 11-oxododecen-8E-oate (**38**) in 76% yield as a colourless viscous liquid. Its $^1\text{H-NMR}$ showed the required chemical shifts in agreement with the structure of (**38**) including a singlet at δ 2.11 for acetyl methyl protons.

Enantioselective reduction of (38**) by chiral catalyst:**

One of the methods envisaged and discussed earlier to obtain chiral hydroxy ester (**33**) was the asymmetric reduction of (**38**) with chiral catalysts (chemzymes). Many borane reagents¹⁷ are well known to effect this type of reduction smoothly, yielding the corresponding hydroxy compound in high enantiomeric excess (ee). A new system for catalytic enantioselective

SCHEME-XII



reduction of achiral ketones to chiral alcohols has been reported recently by Corey and Bakshi.¹⁸ This method which involves a transition state assembly (A) (SCHEME-XII) is advantageous in many ways, viz. wide scope, predictable absolute stereochemistry, ready availability of the chiral catalyst in either enantiomeric form, easy and efficient recoverability of the chiral amino alcohol (catalyst precursor), high yields, experimental simplicity and economy.

The original procedure¹⁷ involved (44) as the catalyst and BH_3 as stoichiometric reductant but later modifications¹⁸ used catecholborane at low temperature. A recent paper by Rama Rao et al.¹⁹ reported α -picolinic acid based boron reagent for similar reductions.

Reduction of methyl 11-oxododecen-8E-oate (38) with the chiral catalyst (44) at -20°C yielded R(-)-methyl 11-hydroxy-dodecen-8E-oate (33) in 51% yield along with 42% of (38). Enantiomeric excess was found to be 76% by comparison of the optical rotation of (33) with authentic value.¹²

Enantioselective hydrolysis of 39b by enzymes:

Microorganisms are capable of performing a vast number of chemical reactions. In fact, there exists an enzyme catalysed equivalent for almost every type of chemical reaction.²⁰ Bio-transformations have successfully been employed to introduce chiral centres, to resolve racemates, to functionalise a non-activated carbon regioselectively etc. Till now

more than 2000 enzymes have been catalogued. The role of a microorganism or an enzyme in a biotransformation is to simply act as a catalyst.

Some of the advantages of using enzymes as catalysts are: mild reaction conditions, kinetic resolution (substrate enantioselectivity), diastereoisomeric product formation etc.^{20,21} One can obtain reaction specificity, stereospecificity and regiospecificity also. Various biotransformations have successfully been carried out with bio-catalysts which are commercially available, such as several enzymes and Baker's yeast.

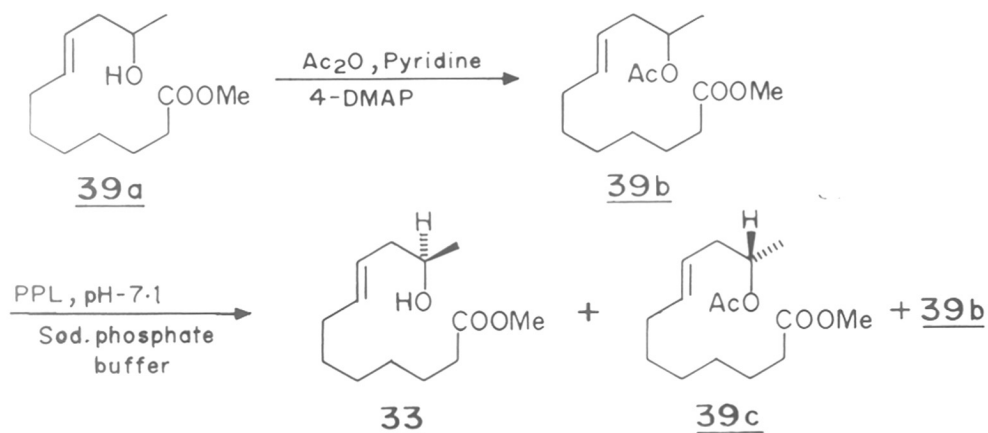
Resolution of racemates by stereospecific ester hydrolysis using lipases from various sources provides a powerful method for the preparation of chiral alcohols (see also Chapter II, Part-II). The most commonly used lipase for this purpose is porcine pancreatic lipase (PPL). Lipases are particularly useful enzymes as they are relatively stable in aqueous and even in organic media; PPL is stable for several hours in toluene or decanol even at 100°C.²⁰ Lipases catalyse reactions such as transesterification, esterification, aminolysis and hydrolysis in organic media^{21,22} which are rarely possible in water.

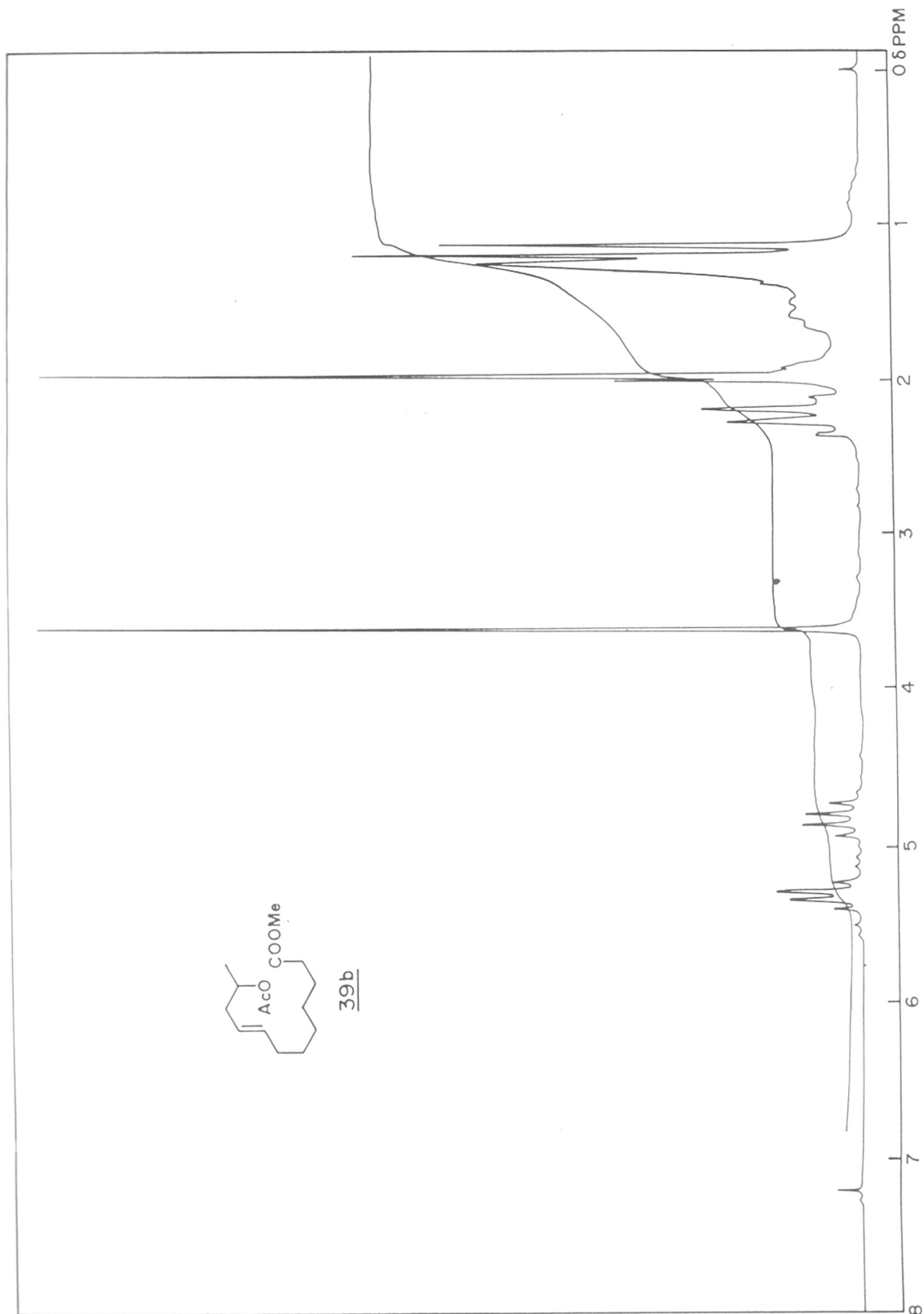
For the present work, microorganism derived from Bacillus subtilis, lipase derived from Candida cylindracea and PPL were used for hydrolysis of acetate derived from (39a). With Bacillus subtilis, the methyl ester of (39b) was hydrolysed

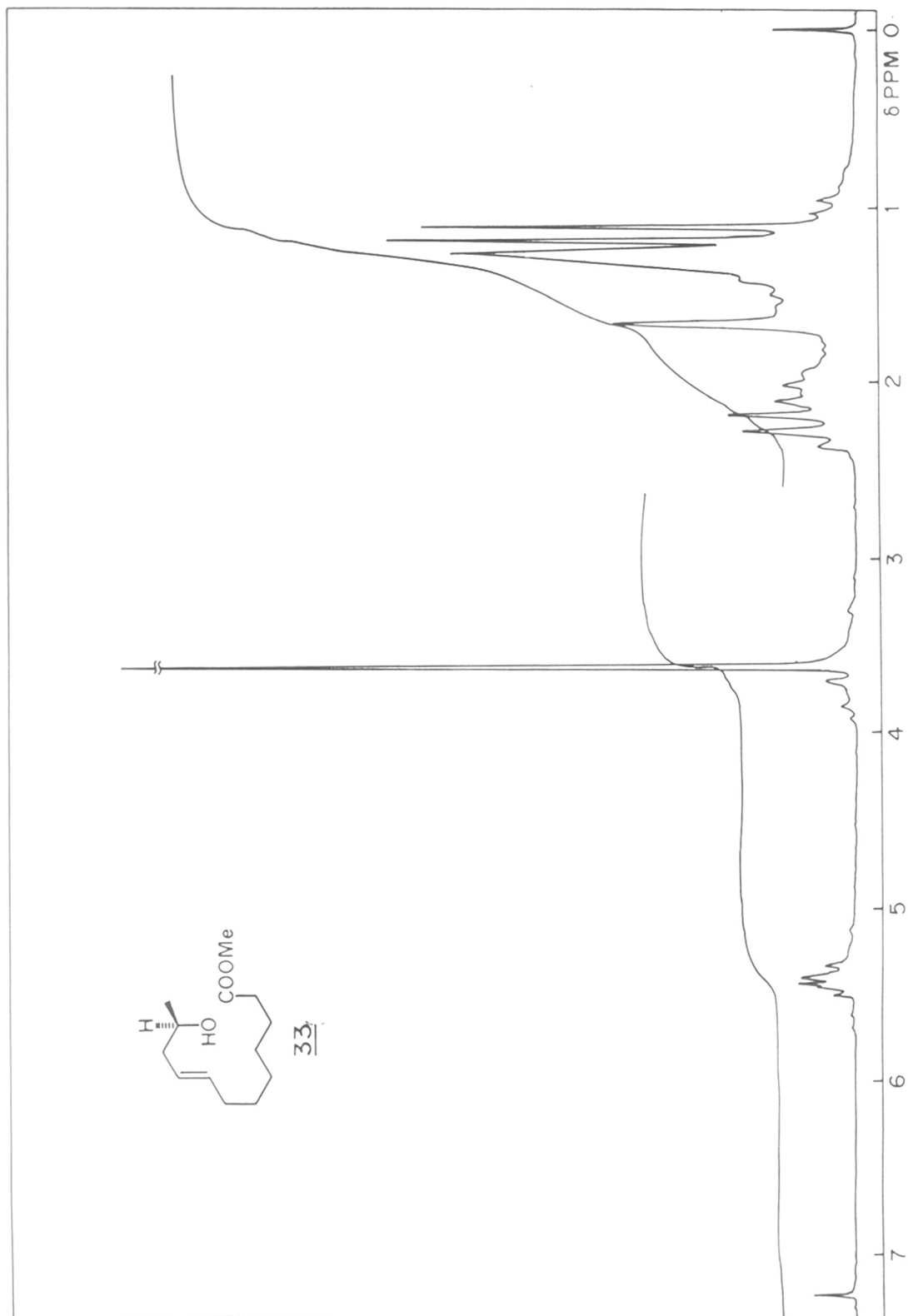
whereas with Candida cylindracea lipase no satisfactory result could be obtained. Hence hydrolysis with PPL was effected and was found to be a very satisfactory and a most suitable procedure.

Thus acetylation of (39a) with acetic anhydride, pyridine and 4-DMAP gave the required acetate ester (39b) (FIG. 4), suitable for PPL catalysed hydrolysis (SCHEME XIII). Treatment of the acetate (39b) with PPL in minimum quantity of acetone at pH 7.1 (sodium phosphate buffer) for 4 h at room temperature gave a crude reaction product which upon purification by silica gel column chromatography yielded R-(-)-11-hydroxydodecen-8E-oate (33) in 35% yield (NMR: FIG. 5) along with unhydrolysed acetate ester (39c) and some starting material. Comparison of optical rotation with that reported¹² showed an enantiomeric excess of 84%.

SCHEME-XIII





FIG. 5: ^1H -NMR SPECTRUM OF COMPOUND (33) IN CDCl_3

From the above discussion, one can surmise that PPL catalysed hydrolysis of (39b) to give (33) in high enantiomeric excess is a better method in comparison to asymmetric reduction of (38) with chiral catalyst. As (33) has already been converted to R(+)recifeiolide, the present work in effect constitutes a total synthesis of R(+)recifeiolide (1).

EXPERIMENTAL

2-(8-Hydroxy-nonen-5E-yl)-1,3-dioxolane (44):

Lithium metal (0.462 g) was added in small pieces to liquid ammonia (300 ml) in a 500 ml 3-necked RB flask over a period of 20 min. at -33°C followed by ammonium sulphate (5 g) and *t*-butanol (1 ml). The compound **43** (3.50 g, 16.5 mmol) in dry THF (5 ml) was then added through a dropping funnel over a period of 10 min at -33°C with stirring. The stirring was continued for another 3 h. After evaporation of ammonia, excess of lithium was destroyed with dry MeOH (10 ml) followed by the addition of saturated solution of ammonium chloride. The product was extracted with CHCl_3 (3 x 100 ml), washed with brine, dried and concentrated under reduced pressure to afford **44** (3.28 g, 93%) as a colourless liquid, b.p. $112^{\circ}\text{C}/6\text{ mm}$ (lit.⁷ b.p. $68-70^{\circ}\text{C}/0.01\text{ mm}$).

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

$^1\text{H-NMR}$: δ 1.18(d, $J=6.1\text{Hz}$, 3H), 1.20-1.80 (m, 6H), 1.80-2.25 (m, 5H, $2\times\text{CH}_2$ and OH), 3.50-3.97 (m, 5H, $\text{O-CH}_2\text{-CH}_2\text{-O}$ and $\text{CH}_3\text{-CH-OH}$), 4.78 (t, 1H, OCHO), 5.45 (m, 2H, $-\text{CH}=\text{CH}-$).

Mass (m/e): 214 (M^+), 213, 155, 137, 108 and 99.

Analysis Calc. for $\text{C}_{12}\text{H}_{22}\text{O}_3$: C, 67.28; H, 10.28;

Found: C, 67.08; H, 10.14%.

2-(8-Acetoxy-nonen-5E-yl)-1,3-dioxolane (45):

Acetic anhydride (2.5 ml, 24.5 mmol) was added to a stirred solution of alcohol **44** (5 g, 23.36 mmol) containing pyridine (1.84 g, 23.36 mmol) and catalytic amount of 4-DMAP

in CH_2Cl_2 (10 ml) at 0°C over a period of 10 min. The reaction mixture was stirred at room temperature for 14 h. Water (50 ml) was added, extracted with CH_2Cl_2 (2 x 50 ml), the combined extract was washed with ice-cold dil. HCl (5%, 10 ml) followed by brine and dried (Na_2SO_4). Concentration of the organic solution gave 5.15 g, (86%) of the pure acetate **45** as a viscous liquid.

IR (Neat): 1745 cm^{-1} .

$^1\text{H-NMR}$: δ 1.20 (d, $J=6.1\text{Hz}$, 3H), 1.20-1.84 (m, 6H), 1.84-2.31 (m, 4H), 2.00 (s, 3H, OCOCH_3), 3.88 (m, 4H, $\text{O-CH}_2\text{-CH}_2\text{-O}$), 4.80 (t, 1H, O-CH-O), 4.88 (m, 1H, $-\text{CH}-\text{CH}_3$) and 5.42 (m, 2H, $-\text{CH}=\text{CH}-$).

Mass (m/e): 256 (M^+), 196, 149, 108 and 87.

9-Acetoxy decen-6E-al (**41**):

Aqueous perchloric acid (35%, 15 ml) was added at 0°C with stirring to the compound **45** (2.8 g, 10.93 mmol) in CH_2Cl_2 (50 ml) and the stirring was continued for 3 h. The organic layer was separated, washed with saturated NaHCO_3 solution (20 ml) followed by brine and dried (Na_2SO_4). Concentration under reduced pressure yielded the pure aldehyde **41** (2.6 g, 93%) which was used immediately for further reaction.

Ethyl 11-acetoxy-dodeca-2E,8E-dienoate (**40**):

To a stirred solution of carboethoxymethylene triphenyl phosphorane (**42**, 4.56 g, 13.10 mmol) in CH_2Cl_2 (10 ml), 9-acetoxydecen-6E-al **41** (2.16 g, 10.18 mmol) in CH_2Cl_2 (5 ml)

was added at room temperature over 10 min. The stirring was continued at room temperature for a further period of 10 h, while the progress of the reaction was monitored by TLC. The CH_2Cl_2 was distilled off and the crude product was purified by silica gel column chromatography using pet. ether-ethyl acetate as eluent (95:5) to afford the acetate ester **40** (2.4 g, 83%) as colourless thick liquid.

IR (Neat): 1745, 1730 and 1660 cm^{-1} .

$^1\text{H-NMR}$: δ 1.18 (t, 3H), 1.20 (d, $J=6\text{Hz}$, 3H), 1.20-1.80 (m, 4H), 1.84-2.30 (m, 6H), 1.98 (s, 3H), 4.13 (q, 2H, $\text{O-CH}_2\text{-CH}_3$), 4.84 (m, 1H, $\text{CH}_3\text{-CH-OAc}$), 5.34 (m, 2H, -CH=CH-) 5.73 (dt, $J=16\text{Hz}$, $J=2\text{Hz}$, 1H) and 6.88 (dt, $J=16\text{Hz}$ and 8Hz , 1H).

Mass (m/e): 282 (M^+), 268, 252, 242, 239, 223, 197, 164 and 81.

Analysis Calc. for $\text{C}_{16}\text{H}_{26}\text{O}_4$: C, 68.08; H, 9.21,

Found: C, 68.26; H, 9.42.

Methyl 11-hydroxy-dodecen-8E-oate (**39a**):

A solution of the acetate ester **40** (1.74 g, 6.17 mmol) in dry CH_3OH (20 ml) was cooled to 0°C and the activated magnesium turnings (1.48 g, 6.7 mg. atom) were added with stirring. After 1 h at 0°C , further stirring was continued for 5 h. at room temperature. Excess methanol was removed in vacuo and the residue was treated with dil. HCl (5%, 50 ml). It was then extracted with CHCl_3 (3 x 50 ml), washed with brine and dried (Na_2SO_4). The chloroform solution was concentrated under reduced pressure and the crude product was purified by silica gel column chromatography using pet.

ether - ethyl acetate (80:20) as eluent. A colourless viscous liquid (1.125 g, 80%) was obtained which was identified as **39a**.

IR (Neat): 3450 (OH) and 1745 cm^{-1} (C=O).

$^1\text{H-NMR}$: δ 1.18 (d, $J=6\text{Hz}$, 3H), 1.20-1.70 (m, 8H), 1.80-2.20 (m, 5H, $2\times\text{CH}_2$ and OH), 2.25 (t, 2H), 3.65 (s, 3H, $-\text{COOCH}_3$), 3.78 (m, 1H, $-\text{CHOH}$) and 5.38 (m, 2H, $-\text{CH}=\text{CH}-$).

Mass (m/e): 228 (M^+), 210, 197, 167, 152 and 84.

Analysis Calc. for $\text{C}_{13}\text{H}_{24}\text{O}_3$: C, 68.42; H, 10.52;

Found: C, 68.63; H, 10.38.

Methyl 11-oxo-dodecen-8E-oate (38):

Pyridinium dichromate (7.9 g, 21 mmol) in dry CH_2Cl_2 (25 ml) and 5A molecular sieves (2 g) were vigorously stirred and the solution of hydroxy ester **39a** (3.2 g, 14 mmol) in CH_2Cl_2 (5 ml) was added in one portion. The reaction mixture was stirred at room temperature for 4 hr. The solution was filtered through celite and the residue was washed with CH_2Cl_2 (2 x 25 ml). The combined filtrate was concentrated under reduced pressure. It was then triturated with ether (50 ml), ether layer was concentrated and the crude product was purified by silica gel column chromatography (eluent, pet. ether-acetone, 90:10). Methyl 11-oxo-dodecen-8E-oate **38** (2.42 g, 76%) was obtained as a colourless oil.

IR (Neat): 1740 and 1718 cm^{-1}

$^1\text{H-NMR}$: δ 1.15-1.44 (m, 8H), 1.45-1.85 (m, 2H), 2.11 (s, 3H,

-COCH₃), 2.40-2.65 (m, 4H), 3.64 (s, 3H, COOCH₃) and 5.41 (m, 2H, -CH=CH-).

Mass (m/e): 226 (M⁺), 211, 196, 152, 108 and 87.

Methyl 11-acetoxy-dodecen-8E-oate (39b):

To methyl 11-hydroxy-dodecen-8E-oate (300 mg, 1.3 mmol) in pyridine (2 ml) containing catalytic amount of 4-dimethylaminopyridine (4-DMAP) was added acetic anhydride (1 ml) at 0°C. It was allowed to come to room temperature and the stirring was continued at room temperature for 16 h after which the reaction mixture was poured on ice. It was extracted with CH₂Cl₂ (3 x 50 ml), combined extract was washed with dil. HCl (5%, 10 ml) followed by brine and dried (Na₂SO₄). Concentration of CH₂Cl₂ solution afforded the acetate **39b** (280 mg, 83.5%) as a light yellow liquid.

IR (neat): 1750 and 1740 cm⁻¹.

¹H-NMR: δ 1.20 (d, J=6Hz, 3H), 1.22-1.82 (m, 8H), 1.85-2.20 (m, 4H), 2.00 (s, 3H, OCOCH₃), 2.28 (t, 2H), 3.63 (s, 3H, COOCH₃), 4.84 (m, 1H, CH₃-CH-O) and 5.33 (m, 2H, -CH=CH).

Mass (m/e): 270 (M⁺), 260, 238, 210 and 197.

Analysis Calc. for C₁₅H₂₆O₄: C, 66.66; H, 9.62;

Found: C, 66.18; H, 9.48.

Asymmetric reduction of ketone 38:

Corey's catalyst was prepared by reacting S-(-)-2-(diphenyl-hydroxymethyl)pyrrolidine (15 mg, 0.057 mmol) with n-butylboronic acid (9 mg, 0.057 mmol) in dry toluene (10 ml) under argon and the resultant solution was refluxed for

5 h. with azeotropic removal of water (Dean-Stark trap). Toluene was distilled off and a solution of methyl 11-oxo-dodecen-8E-oate (0.130 g, 0.57 mmol) in dry THF (5 ml) was added. Catechol borane (0.1 ml) in dry THF (2 ml) was added slowly at -20°C over 5 min. After 5 min, reaction mixture was quenched with saturated ammonium chloride. It was extracted with CHCl_3 (3 x 25 ml), dried (Na_2SO_4) and concentrated. Purification by silica gel column chromatography (pet. ether - acetone, 90:10) furnished alcohol ester **34** in 51% yield (67 mg) along with starting material (55 mg).

$[\alpha]_{\text{D}}^{25} = -6.86^\circ$ (C=0.67, CHCl_3); Lit.¹² $[\alpha]_{\text{D}}^{28} = -9^\circ$ (C=1, CHCl_3); 76% ee based on rotation.

Enantioselective hydrolysis of **39b** with PPL:

Methyl 11-acetoxy-dodecen-8E-oate (0.130 g, 0.48 mmol) in acetone (0.5 ml) was added to a stirred suspension of PPL (porcine pancreatic lipase, 100 mg) maintaining the pH at 7.1 (sodium phosphate buffer, 0.5 M, 20 ml). Stirring was continued for 4 h at pH 7.1 and the reaction was monitored by GLC. The reaction mixture was filtered through celite, washed with ether and further extracted with ether. Distillation of ether yielded 0.115 g crude product which on silica gel column chromatographic purification (eluent: pet. ether - ethyl acetate, 80:20) yielded the R-(-)-methyl 11-hydroxy dodecen-8E-oate (**34**, 38 mg, 35%).

$[\alpha]_{\text{D}}^{25} -7.6$ (C=0.46, CHCl_3); lit.¹² $[\alpha]_{\text{D}}^{28} -9$ (C=1, CHCl_3) .

IR (neat); 3440 (OH) and 1745 cm^{-1} .

$^1\text{H-NMR}$: δ 1.18 (d, $J=6\text{Hz}$, 3H), 1.20-1.70 (m, 8H), 1.77-2.20 (m, 5H, $2\times\text{CH}_2$ and OH), 2.25 (t, 2H), 3.64 (s, 3H, $-\text{COOCH}_3$), 3.70 (m, 1H) and 5.38 (m, 2H, $-\text{CH}=\text{CH}-$).

Mass (m/e): 228 (M^+), 226, 210, 197, 152, 111 and 87.

REFERENCES

1. M. Kerschbaum,
Ber., **60B**, 902 (1927).
2. R.F. Vesonder, F.H. Stodola, L.J. Wickherham, J.J.Ellis,
and W.K. Rohwedder,
Can. J. Chem., **49**, 2029 (1971).
3. E.J. Corey, P. Ulrich and J.M. Fitzpatrick,
J. Am. Chem. Soc., **98**, 222 (1976).
4. J. Tsuji,
Pure and Appl. Chem., **51**, 1235 (1979).
5. B.M. Trost and T.R. Verhoeven,
Tetrahedron Lett., 2275 (1978).
6. K. Narasaka, M. Yamaguchi and T. Mukaiyama,
Chemistry Letters, 959 (1977).
7. H.J. Bestmann and R. Schobert,
Synthesis, 419 (1989).
8. H.H. Wasserman, R.J. Gambale and M.J. Pulwar,
Tetrahedron Lett., **22**, 1737 (1981).
9. B.B. Snider and G.B. Phillips,
J. org. Chem., **48**, 464 (1983).
10. J. Yoshida, K. Tamao, M. Takahashi and M. Kumada,
Tetrahedron Lett., 2161 (1978).
11. A.V. Rama Rao and S. Pulla Reddy,
Synth. Commun., **16**, 1149 (1986).
12. H. Gerlach, K. Oertle and A. Thalmann,
Helv. Chim. Acta, **59**, 755 (1976).

13. K. Utimoto, K. Uchida, M. Yamaya and H. Nozaki,
Tetrahedron Lett., 3641 (1977).
14. R.K. Boeckmann, Jr. and E.W. Thomas,
J. Am. Chem. Soc., **99**, 2805 (1977).
15. E.F. Magoon and L.H. Slaugh,
Tetrahedron, **23**, 4509 (1967).
16. T. Hudlicky, G.S. Zingde and M.G. Natchus,
Tetrahedron Lett, **28**, 5287 (1987).
17. a) E.J. Corey, R.K. Bakshi and S. Shibata,
J. Am. Chem. soc., **109**, 5551 (1987).
b) E.J. Corey, R.K. Bakshi, S. Shibata, C.P. Chen and
V.K. Shingh,
J. Am. Chem. Soc., **109**, 7925 (1987).
18. E.J. Corey and R.K. Bakshi,
Tetrahedron Lett., **31**, 611 (1990).
19. A.V. Rama Rao, M.K. Gurjar, P.A. Sharma, V. Kaiwar,
Tetrahedron Lett., **31**, 2341 (1990).
20. H.G.W. Leuenberger,
Pure and Appl. Chem., **62**, 753 (1990).
21. C.S. Chen and C.J. Sih,
Angew. Chem. Int. Ed. Engl., **28**, 695 (1989).
22. J.B. Jones,
Tetrahedron, **42**, 3351 (1986).
23. A.M. Klivanov,
Chemtech, 354 (1986).
24. K. Laumen and M. Schneider,
Tetrahedron Lett., **26**, 2073 (1985).

CHAPTER IV

*STUDIES DIRECTED TOWARDS THE TOTAL SYNTHESIS OF
MONOCILLIN IV, NORDINONE AND NORDINONEDIOL*

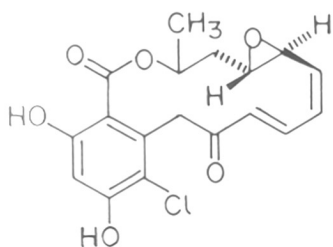
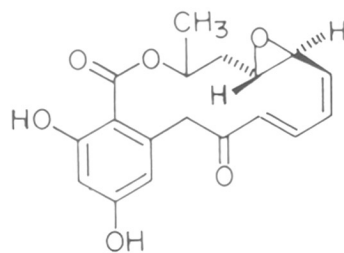
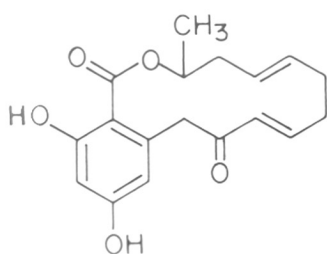
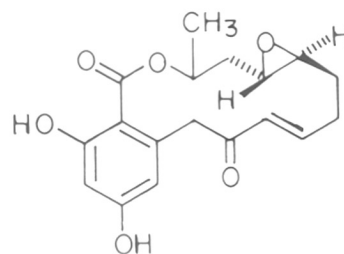
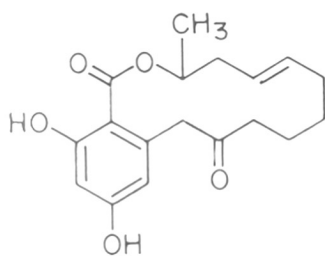
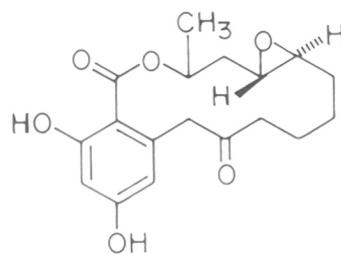
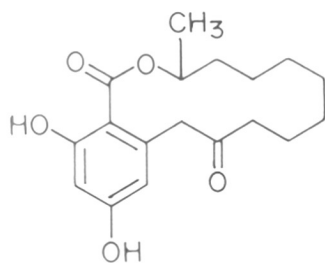
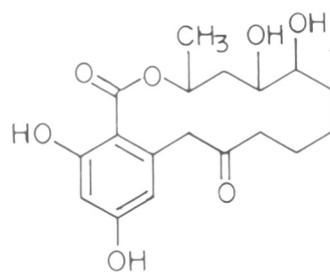
INTRODUCTION:

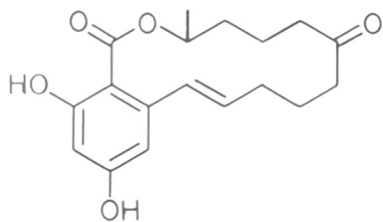
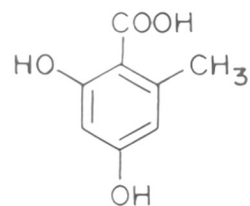
Monocillium nordinii (Bourchier) W. Gams is a destructive mycoparasite of pine stem rusts. In the year 1980 Ayer et al.¹ isolated the crude ether soluble metabolites that were produced when Monocillium nordinii was grown on potato dextrose agar. These metabolites were active against a wide variety of fungi and were generally found to have anti-fungal properties. A total of five new substances termed monocillins I-V (2-6) were isolated and characterised in addition to the already known monorden² (1). A few years later³ two more minor metabolites produced in liquid still culture by Monocillium nordinii were isolated and reported by the same authors. They were named nordinone (7) and nordinonediol (8). Monorden (1) is identical in structure with radicicol,^{4,6} an antibiotic produced by Cylindrocarpon radicicola (Nectria radicicola).

Structure and inter-relation of monocillins, nordinone and nordinonediol:

All the monocillins are structurally related and belong to the important class of "orsellinic acid type macrolides"; members of this class include zearalenone⁵ (9), monorden (radicicol)^{4,6} (1), trans and cis resorcylicides⁷ etc.

The structure of monocillin I (2) is similar to monorden (1, radicicol) but without the chlorine atom. The structure was already established from its 400 MHz ¹H-NMR spectrum. On the other hand, monocillin III (4) has one unsaturation less as compared to monocillin I (2), as confirmed from its spectroscopic studies. Chemically, monocillin I (2) was hydrogenated

1 : MONORDEN (RADICICOL)2 : MONOCILLIN I3 : MONOCILLIN II4 : MONOCILLIN III5 : MONOCILLIN IV6 : MONOCILLIN V7 : NORDINONE8 : NORDINONEDIOL

9 ZEARALENONE10 ORSELLINIC ACID

with Pd-C in ethanol till one equivalent of hydrogen was absorbed. It gave monocillin III (4) in high yield. Monocillin II (3) has one double bond extra in addition to the conjugated carbonyl function of monocillin III. The $^1\text{H-NMR}$ signals in monocillin II (3) showed no peaks attributable to epoxide protons. Epoxidation of monocillin II (3) with m-chloroperbenzoic acid (m-CPBA) gave monocillin III (4) exclusively, thus confirming the structure of monocillin II as (3). Monocillin IV (5) and monocillin V (6) showed saturated ketone absorption in the infrared spectrum. To determine the position of the double bond in monocillin IV (5), monocillin II (3) was hydrogenated in the presence of Raney-nickel in chloroform:ethanol (1:19). The product formed was identical with monocillin IV (5). Similar hydrogenation of monocillin III (4) gave monocillin V (6). Chemical correlation of monocillin I (2) with monorden (1) was achieved³ by treatment of monocillin I (2) with N-chlorosuccinimide in dimethylformamide. The product was identical with natural monorden (1) in all respects.

The absolute stereochemistry for the epoxide ring of monorden (1), monocillin I (2) and monocillin V (6) was arrived at, by application of Brewster's benzoate rule.⁸

Nordinone (7), isolated as a solid, m.p. 130-134°C showed in its high resolution mass spectrum, molecular ion peak at m/e 320 and the base peak of m/e 150, characteristic of monocillins. Further, its IR spectrum was very similar to that of monocillin IV (5) and monocillin V (6). In the ¹H-NMR spectrum, no vinylic protons were observed thereby indicating a structure having one unsaturation less than monocillin IV (5). The structure was also confirmed by a chemical correlation. Hydrogenation of monocillin II (3) gave nordinone (7).

Nordinonediol (8) also had in its high resolution mass spectrum, a base peak characteristic of monocillins at m/e 150. A diol structure based on spectral data was assigned to (8). It had resulted by opening of the epoxide ring in monocillin V (6). Assuming a trans-opening of the epoxide, nordinonediol was assigned a cis-diol structure but absolute stereochemistry at C-4 and C-5 has not been established yet.

Antifungal activity of the three major metabolites of M. nordinii:

Monorden (radicicol, 1), monocillin I (2) and monocillin III (4) are the three major metabolites which exhibit encouraging antifungal activity. However, their antifungal activities were found to be non-specific.¹ In monorden (1), the presence of chlorine atom in the aromatic nucleus did not seem to have

any significant effect in increasing the antifungal activity. The activities of monorden (1) and monocillin I (2) were therefore found to be similar. The antifungal activities of monocillins II to V were found to be negligible.

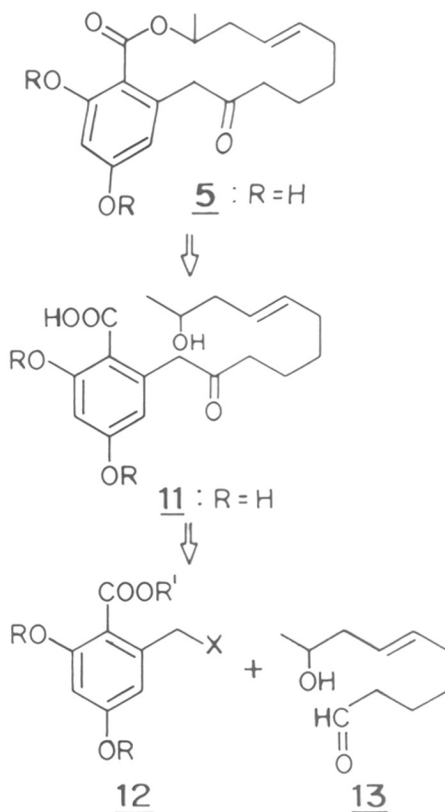
PRESENT WORK:

PART I:

Although radicicol^{4,6} (1) was isolated in 1964 and the group of monocillins¹ in 1980 (along with monorden which was found to be identical with radicicol), no synthesis of any of them was reported when the present work on the synthesis of monocillins was undertaken in late 1988. In addition, two compounds closely related to monocillins were isolated from Monocillium nordinii in 1987³ and were named nordinone (7) and nordinonediol (8). An examination of the structures of monocillins and the minor metabolites nordinone (7) and nordinonediol (8) readily revealed that monocillin IV (5) was the simplest member of the group. Further, it can also be transformed to nordinone (7) and nordinonediol (8) via simple reactions like hydrogenation, opening of the epoxide ring etc. It was therefore considered appropriate to undertake first the total synthesis of monocillin IV (5) followed by nordinone (7) and nordinonediol (8). Successful completion of these syntheses are reported in this chapter.

Monocillin IV (5) has a 14-membered lactone ring which could be derived from orsellinic acid (10), a possible biogenetic precursor. Other important features in the molecule include a trans double bond, a keto-functionality and a C-10 unit. A retrosynthetic analysis readily suggested the orsellinic acid (12) and the C-10 aldehyde (13) as the logical starting materials (SCHEME I). The latter aldehyde has already

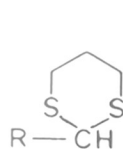
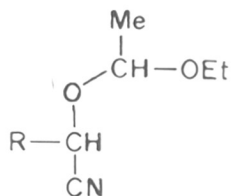
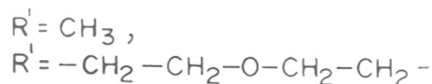
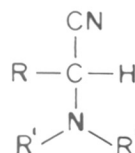
SCHEME-I
RETROSYNTHETIC ANALYSIS



WHERE R=Me or H , $\text{R}'=\text{Et}$, X=Br

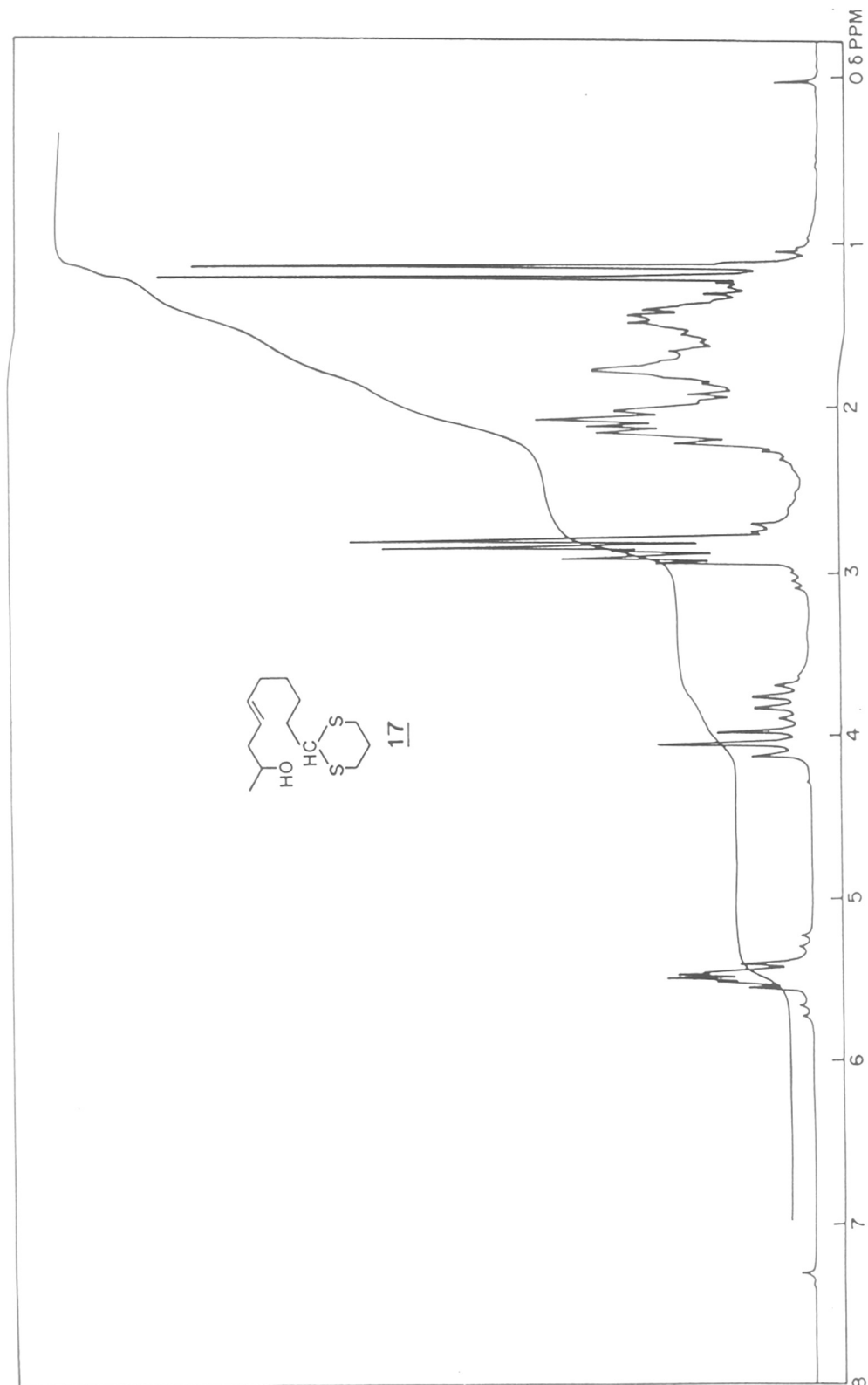
been synthesised and utilised in the total synthesis of R(+) recifeiolide (Chapter III). Thus one can envisage a C-C bond coupling reaction between a suitably substituted orsellinic acid ester derivative like (12) and an activated carbonyl function like (13), resulting in the intermediate hydroxyketo acid (11). The latter could then be subjected to macrolactonization with conventional reagents.

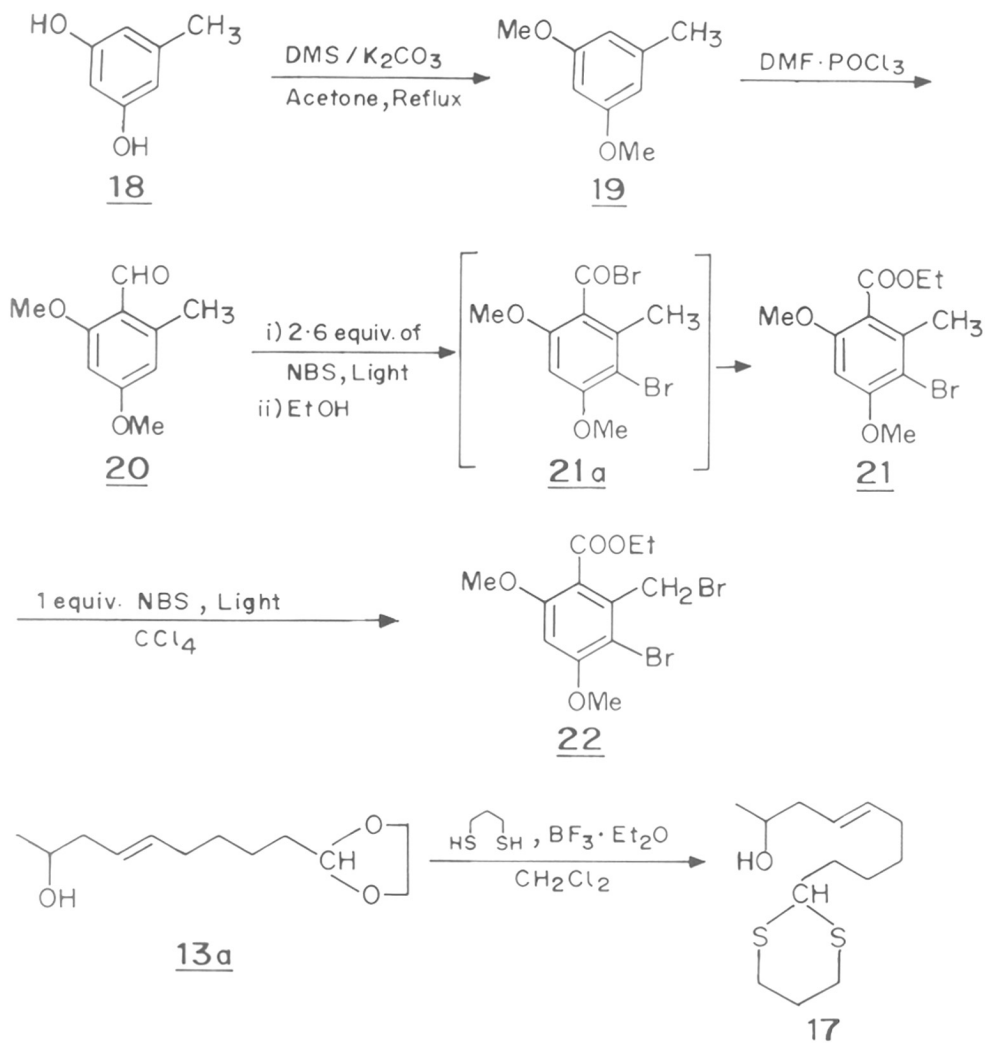
Suitable activation of the carbonyl function in (13) to convert it to a nucleophilic centre was achieved by utilising "umpolung" approach. Some of the common umpolungs are 1,3-dithiane⁹ (14), α -hydroxynitrile¹⁰ (15), α -aminonitrile¹¹ (16) etc. In all these cases after the required coupling reaction,

141516

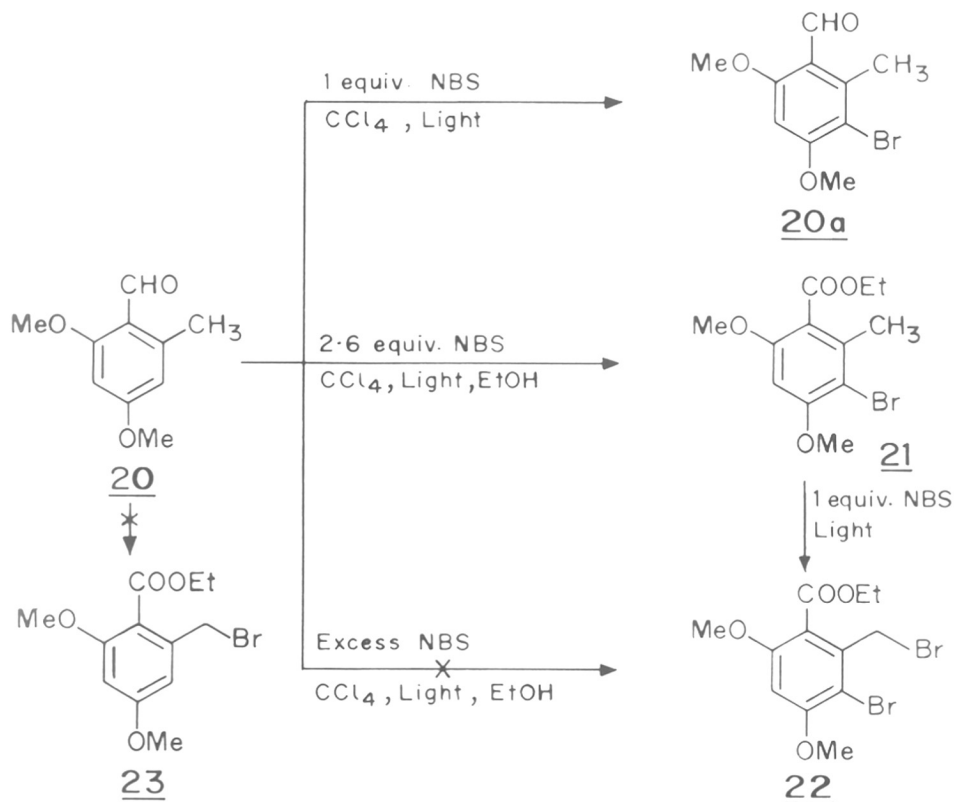
an aldehyde group is effectively converted into a keto function. Thus the hydroxy acetal (13a) whose preparation has already been described in Chapter III, was subjected to the reaction with propane 1,3-dithiol in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}^9$ (SCHEME II). The product, hydroxythioacetal (17) was obtained in 84% yield and its structure was confirmed from $^1\text{H-NMR}$. It showed a relatively upfield multiplet centred at $\delta 2.82$, and a multiplet at 1.90 to $\delta 2.40$. The methine proton of the dithiane appeared at $\delta 4.03$ as a triplet (FIG. 1).

The aromatic synthon (12) required for coupling reaction with the aliphatic counterpart (17) could be obtained from orcinol (18) (SCHEME II). Thus, methylation of orcinol with dimethyl sulphate in the presence of potassium carbonate in acetone gave the dimethyl ether (19) which was subjected to Vilsmier-Haack reaction¹² to furnish the aldehyde (20). In

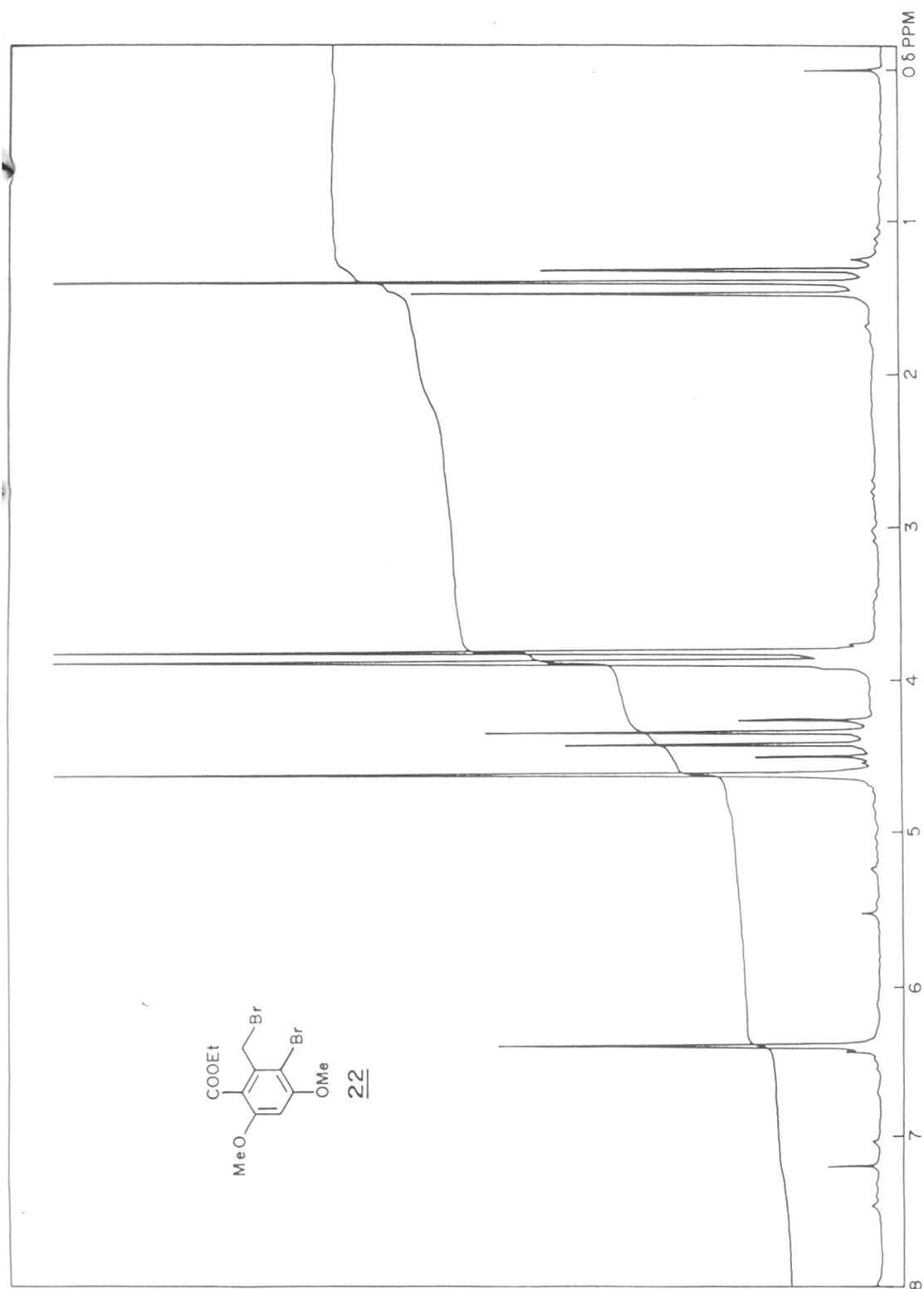
FIG.1: ^1H -NMR SPECTRUM OF THE COMPOUND (**17**) IN CDCl_3



order to obtain the aromatic part, ethyl 6-bromomethyl-2,4-dimethoxybenzoate (23) directly from the above aldehyde (20) the obvious choice of reaction was bromination with N-bromosuccinimide followed by esterification in situ of the intermediate acid bromide (21a) with ethanol. Aromatic aldehydes are known¹³ to undergo transformation to acid bromides with NBS. Thus NBS bromination of (20) in carbon tetrachloride and in the presence of light afforded different products depending on the amount of NBS utilised and on the time given to the reactions (SCHEME III). In all the cases nuclear bromination

SCHEME-III

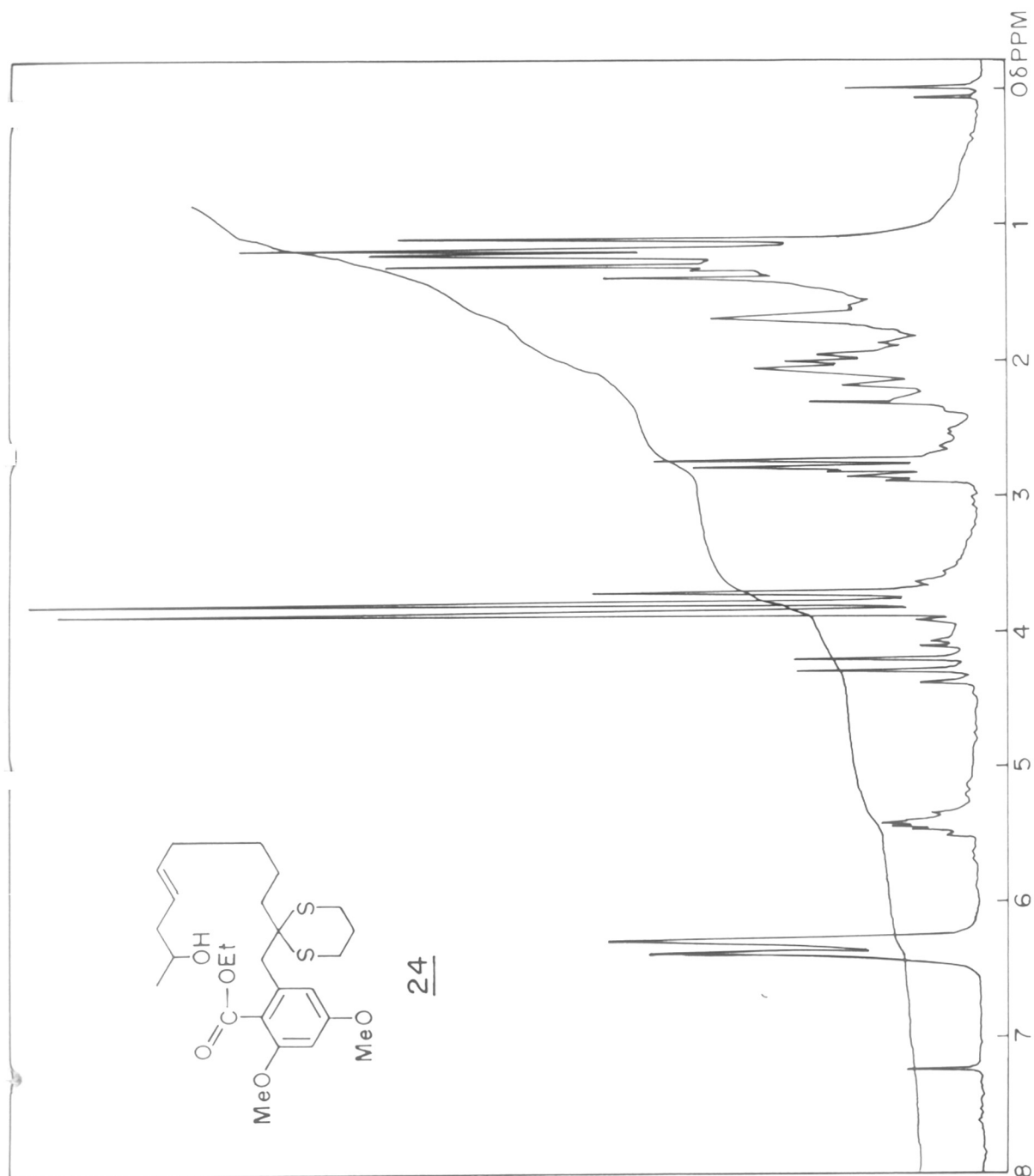
preceded other reactions and this could not be averted. When the aldehyde (20) was subjected to bromination with 2.6 equivalents of NBS followed by treatment with ethanol, instead of the required ester (23), the ester ethyl 5-bromo-2,4-dimethoxy-6-methyl benzoate (21) was obtained. Further bromination of (21) with one equivalent of NBS afforded ethyl 5-bromo-6-bromo-methyl-2,4-dimethoxybenzoate (22) (FIG. 2). The formation of (21) is envisaged to take place via the acid bromide (21a) which was esterified in situ with dry ethanol. All the spectral

FIG. 2. ^1H -NMR SPECTRUM OF THE COMPOUND (22) IN CDCl_3

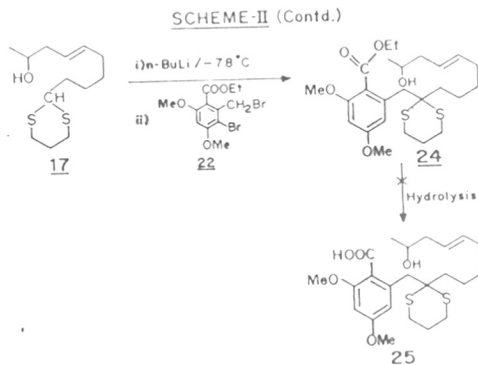
data for (22) were in conformity with the structure assigned (see Experimental). Although nuclear bromination reaction of (20) with NBS could not be avoided, nevertheless it did not present difficulties in subsequent steps as it was removed during the metalation reaction described below.

Metalation of the thioacetal (17) with *n*-BuLi at -78°C followed by the addition of ethyl 5-bromo-6-bromomethyl-2,4-dimethoxybenzoate (22) in THF yielded the desired C-C coupled product (24) (SCHEME II). The latter was purified in the usual manner (silica gel column chromatography). Its IR spectrum revealed hydroxyl group at 3450 cm^{-1} and an ester carbonyl at 1730 cm^{-1} . The mass spectrum and the ^1H -NMR spectrum were in full agreement with the structure (24). In the ^1H -NMR, there was an upfield shift from δ 4.64 to δ 3.88 of the benzylic protons as compared to the starting material (22). The methine proton adjacent to the thio group appearing at δ 4.08 in (17) was absent (FIG. 3). That the bromo group at C-5 was removed could be confirmed from the appearance of a meta-coupled doublet at δ 6.40 integrating for two protons.

Further reactions in this scheme involved hydrolysis of the ester functionality to acid (25) followed by macrolactonization. Hydrolysis of (24) with refluxing methanolic KOH resulted in quantitative recovery of the starting material. Other well-known reagents like KOH-ethylene glycol under reflux, KOH-aq.DMSO under reflux,¹⁴ chlorotrimethylsilane-NaI¹⁵ etc. also gave back the unreacted ester (24). Perhaps steric

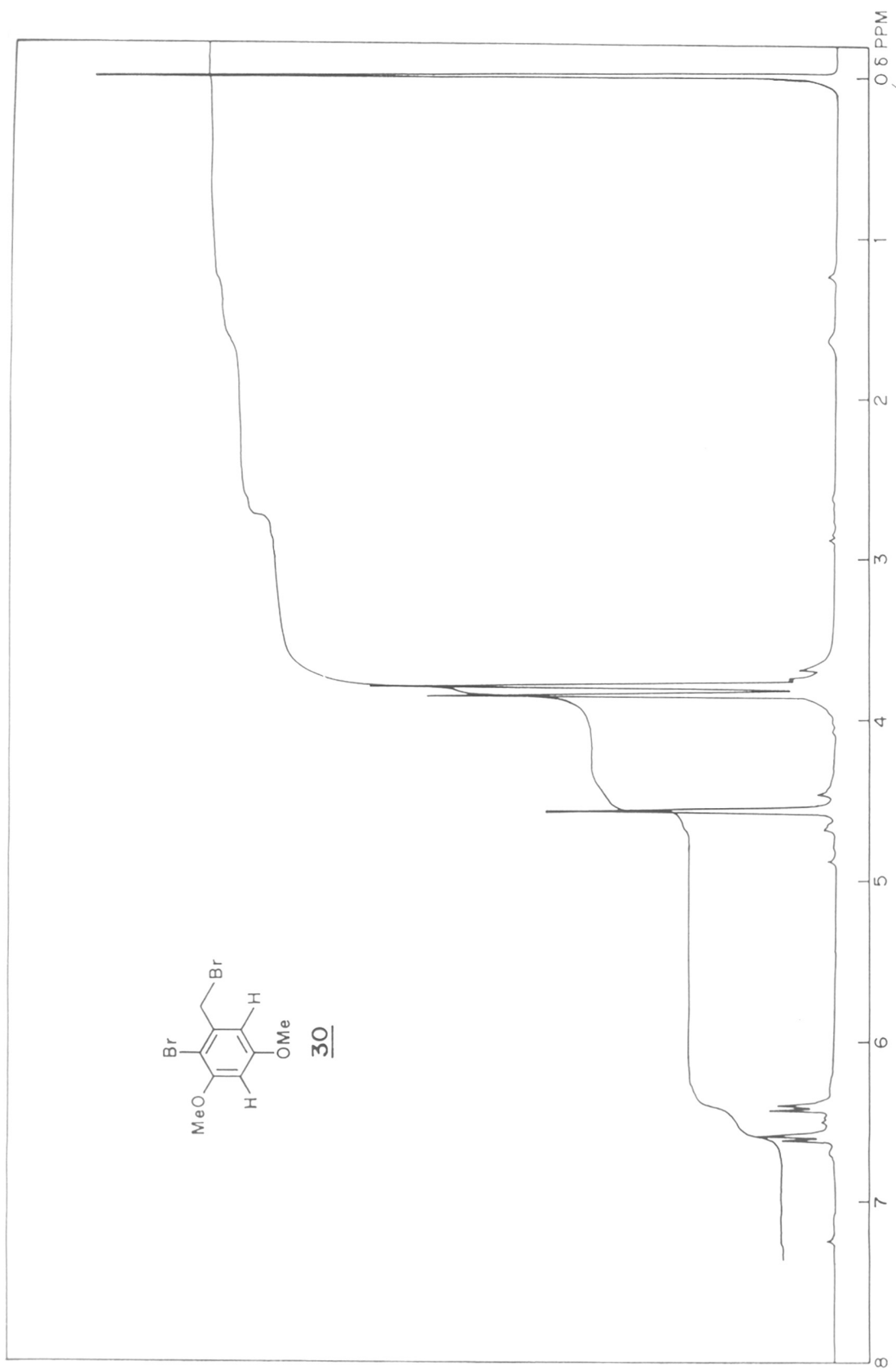
FIG. 3: ^1H -NMR SPECTRUM OF THE COMPOUND (24) IN CDCl_3

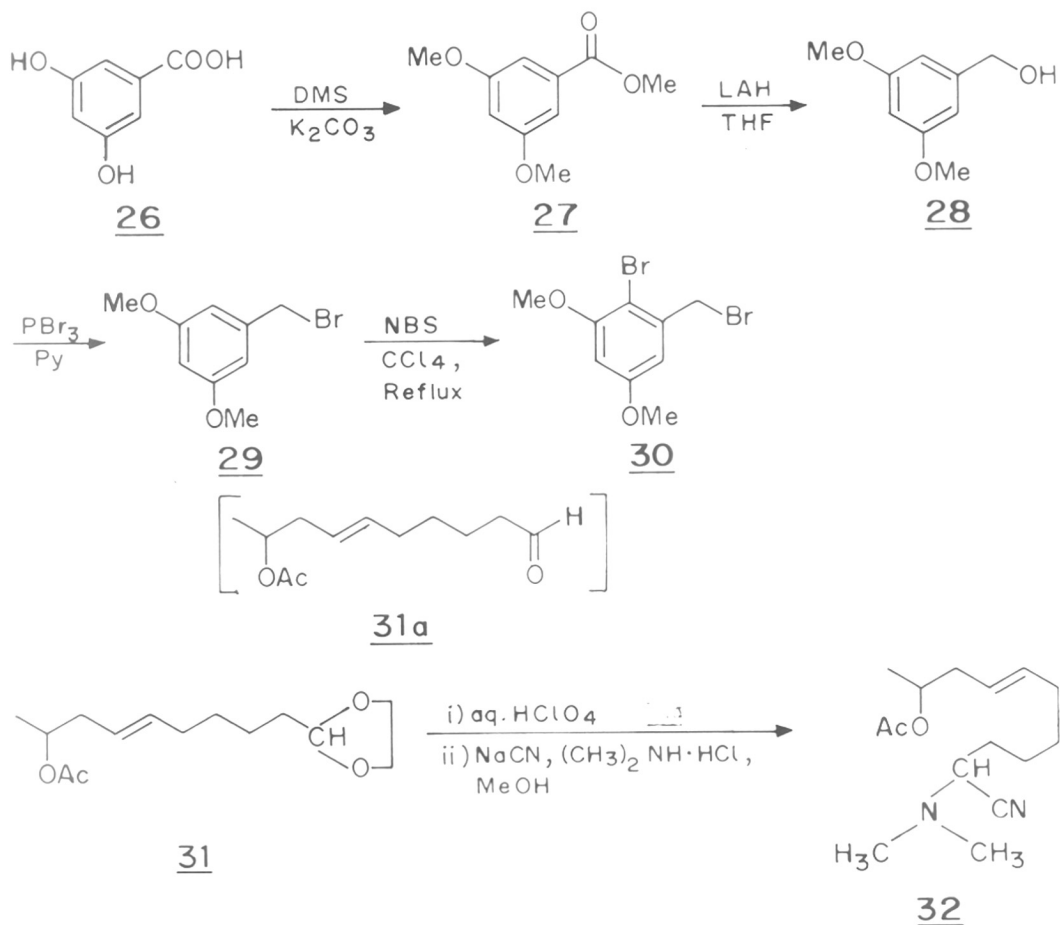
hindrance¹⁶ due to methoxyl group adjacent to the ester function prevented the hydrolysis of (24).



As the hydrolysis of ester moiety in (24) posed problems, it was decided to have a free acid function and with this in view, an alternate scheme was attempted. Thus, 3,5-dimethoxybenzyl bromide (29) obtained from (26) was subjected to NBS bromination¹⁷ in refluxing CCl_4 under high dilution and the product 2-bromo-3,5-dimethoxybenzyl bromide (30) was obtained in quantitative yield (SCHEME IV). Its structure was further confirmed by spectral studies (FIG. 4).

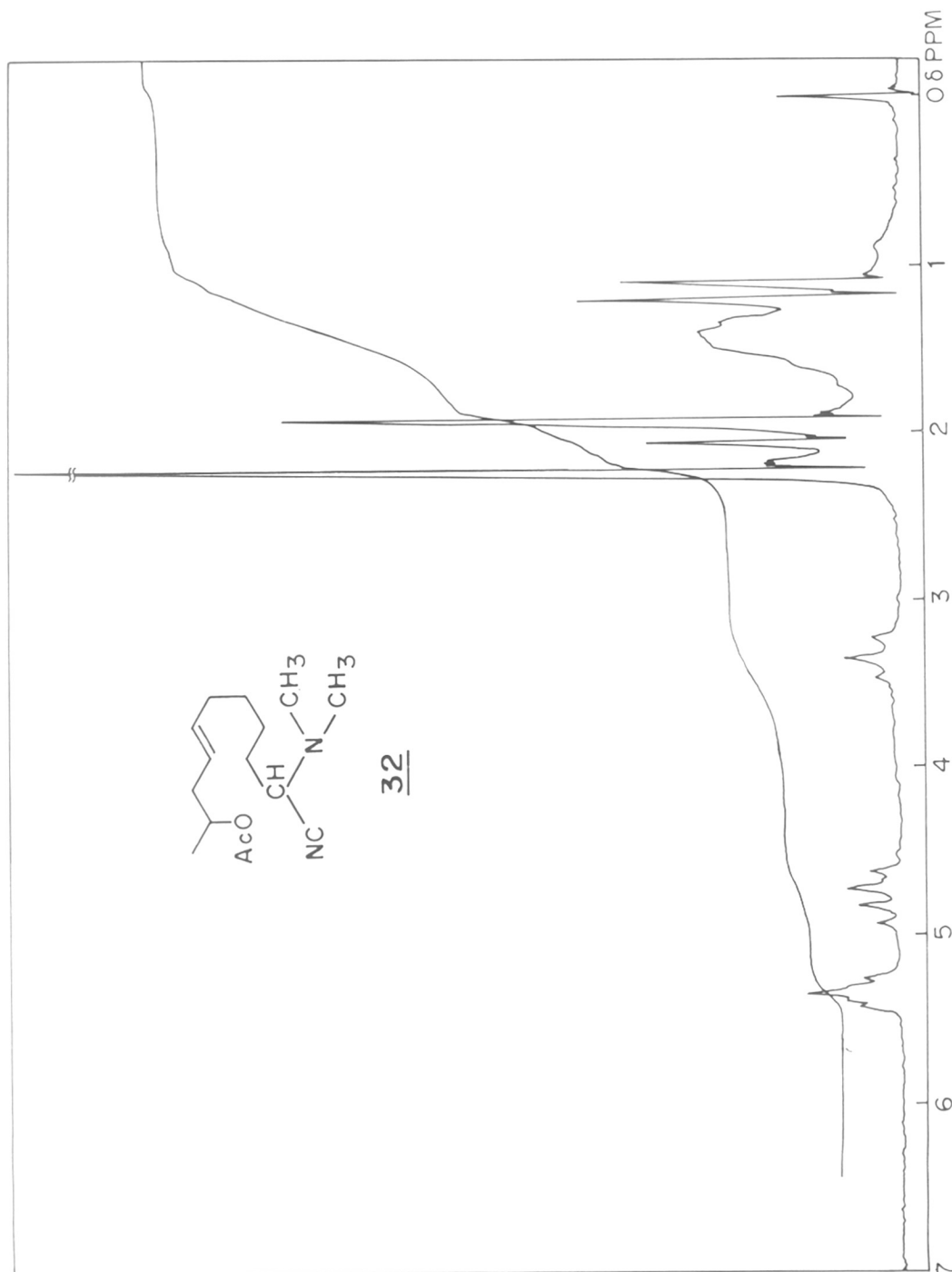
The thioacetal (17) as an umpolung in the coupling reaction with (30) would necessitate use of $n\text{-BuLi}$ as the base which would readily undergo metal-halogen exchange with the 2-bromo group in (30). To overcome this problem, an alternate umpolung like the α -aminonitrile (32) was proposed to be used which would involve a relatively milder base. Thus the α -aminonitrile (32) was prepared from the known acetal (31) (see Chapter III) by reacting the latter with aq. HClO_4 followed by treatment with NaCN and dimethylamine hydrochloride in aqueous

FIG.4: ^1H -NMR SPECTRUM OF THE COMPOUND (30) IN CDCl_3

SCHEME-IV

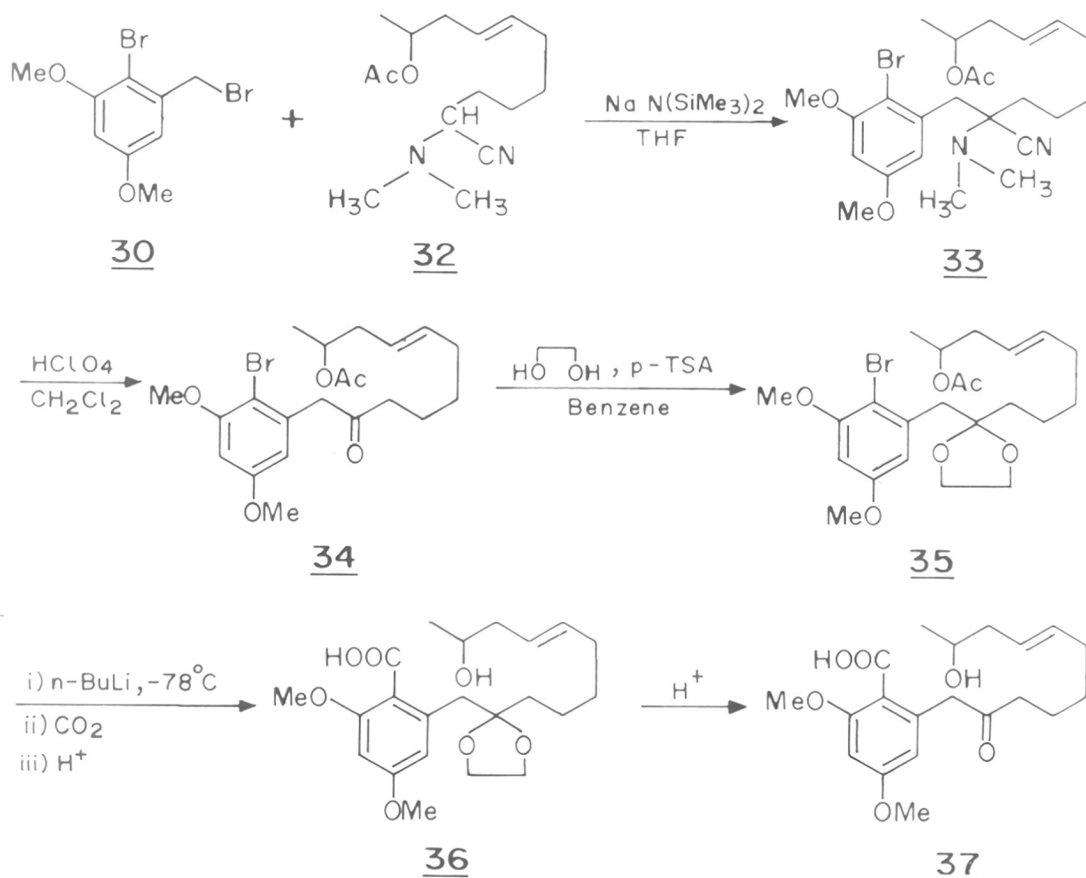
methanol at room temperature.¹⁰ The spectral data of (**32**) were in full agreement with the structure (FIG. 5).

The coupling reaction between (**30**) and (**32**) was first attempted with the base sodium hydride in DMF. Both the starting materials were recovered unchanged and no trace of the coupled product (**33**) was observed. A survey of literature



revealed that sodio-derivative of hexamethyldisilazane¹⁸ could be an ideal base for such reactions. Thus addition of α -amino-nitrile (32) and the aromatic dibromide (30) to a cooled solution of sodio-N-hexamethyldisilazane in THF and usual work up resulted in the required product (33) in 86% yield. The latter without further purification was subjected to hydrolysis with 35% HClO_4 to yield the ketone (34) quantitatively.

SCHEME-IV (Contd.)

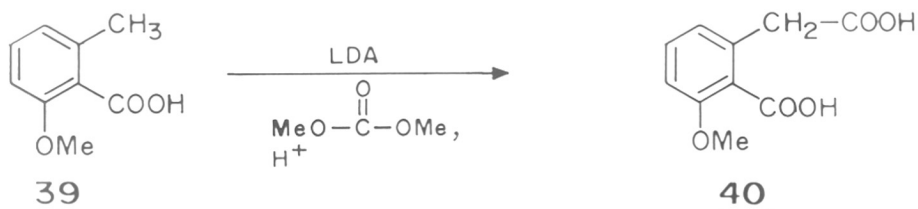


In the IR spectrum, the compound (34) exhibited a band at 1730 cm^{-1} for a keto group. Its $^1\text{H-NMR}$ indicated absence of singlet at $\delta 4.27$ and appearance of a new singlet at $\delta 4.05$. The signals for aromatic protons were similar to those of (30). The mass spectrum confirmed the presence of nuclear bromine atom (SCHEME IV). In order to introduce the carboxyl function in the 2-position by lithiation of bromo compound (35) and subsequent reaction of the intermediate lithio-derivative with solid carbon dioxide,¹⁷ protection of the keto-function was necessary. It was achieved by the reaction of (34) with ethylene glycol in the presence of p-toluenesulfonic acid. The bromo ketal (35) was lithiated under argon atmosphere with n-BuLi (hexane solution) in THF followed by addition of solid carbon dioxide. Usual work up and purification gave the required acid (36) whose IR spectrum revealed bands at 3450 cm^{-1} and 1730 cm^{-1} for hydroxyl and carboxyl groups respectively. $^1\text{H-NMR}$ did not have any signals due to the acetate function, since it was hydrolysed during aqueous work up. A broad signal at $\delta 8.5$ for the carboxylic proton and a singlet at $\delta 3.72$ for the methylene protons of the ketal were also present. The mass spectrum also contained the expected fragmentation pattern (vide Experimental).

The above reaction proceeded, albeit in poor yield. As the yield could not be improved by altering the experimental parameters, an alternate route for the acid (37) was worked out. The rationale behind this approach was: effective generation of carbanion at the methyl carbon of orsellinic acid

derivative (38) for the coupling reaction with (42). A detailed study of literature revealed that Houser and Rhee^{14,19} had generated such a carbanion from the substituted *o*-toluic acid (39) with LDA as the base and subsequent reaction of the carbanion formed with dimethyl carbonate (SCHEME V). A similar strategy was also utilised by Kelly *et al.*²⁰

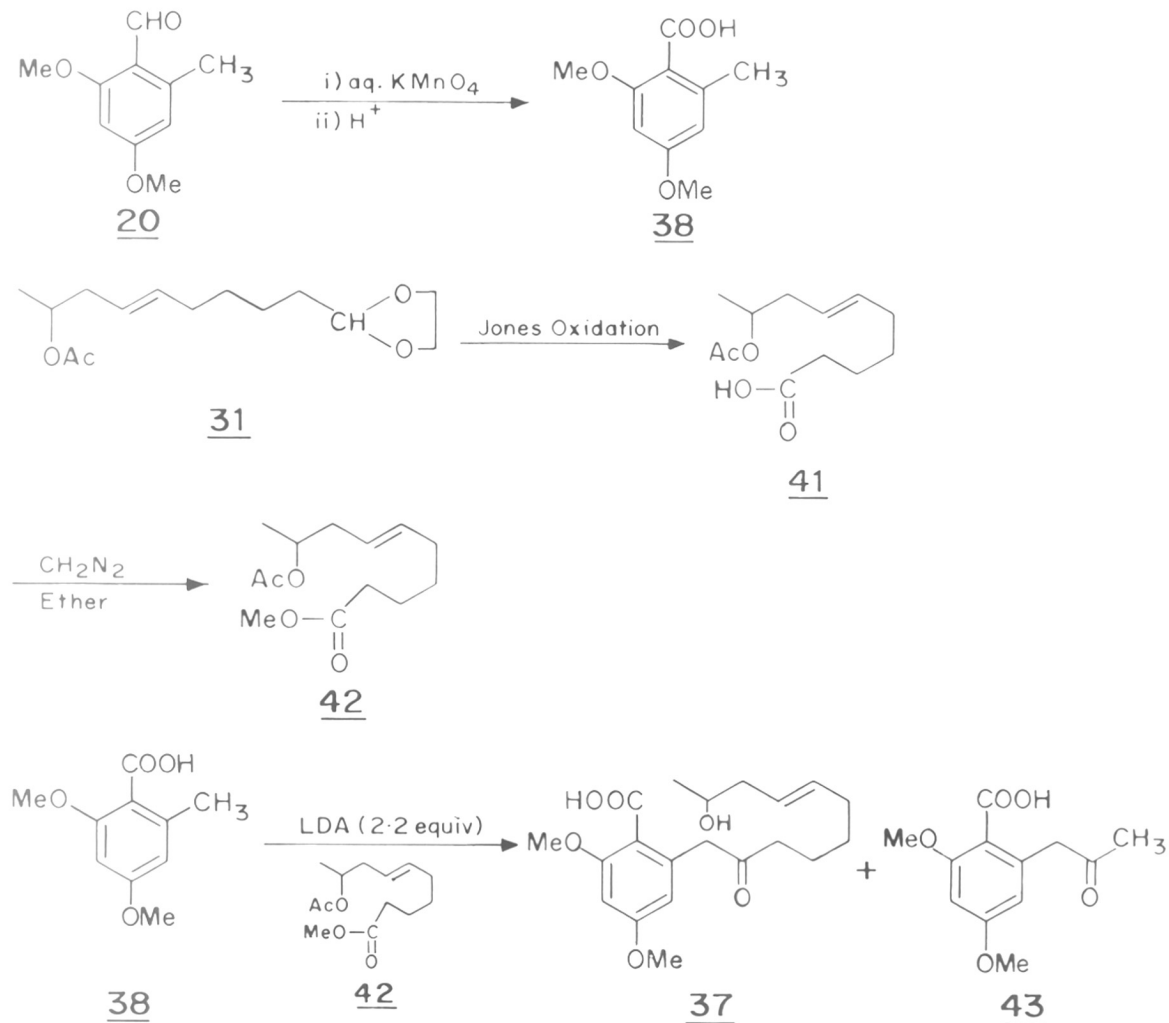
SCHEME-V



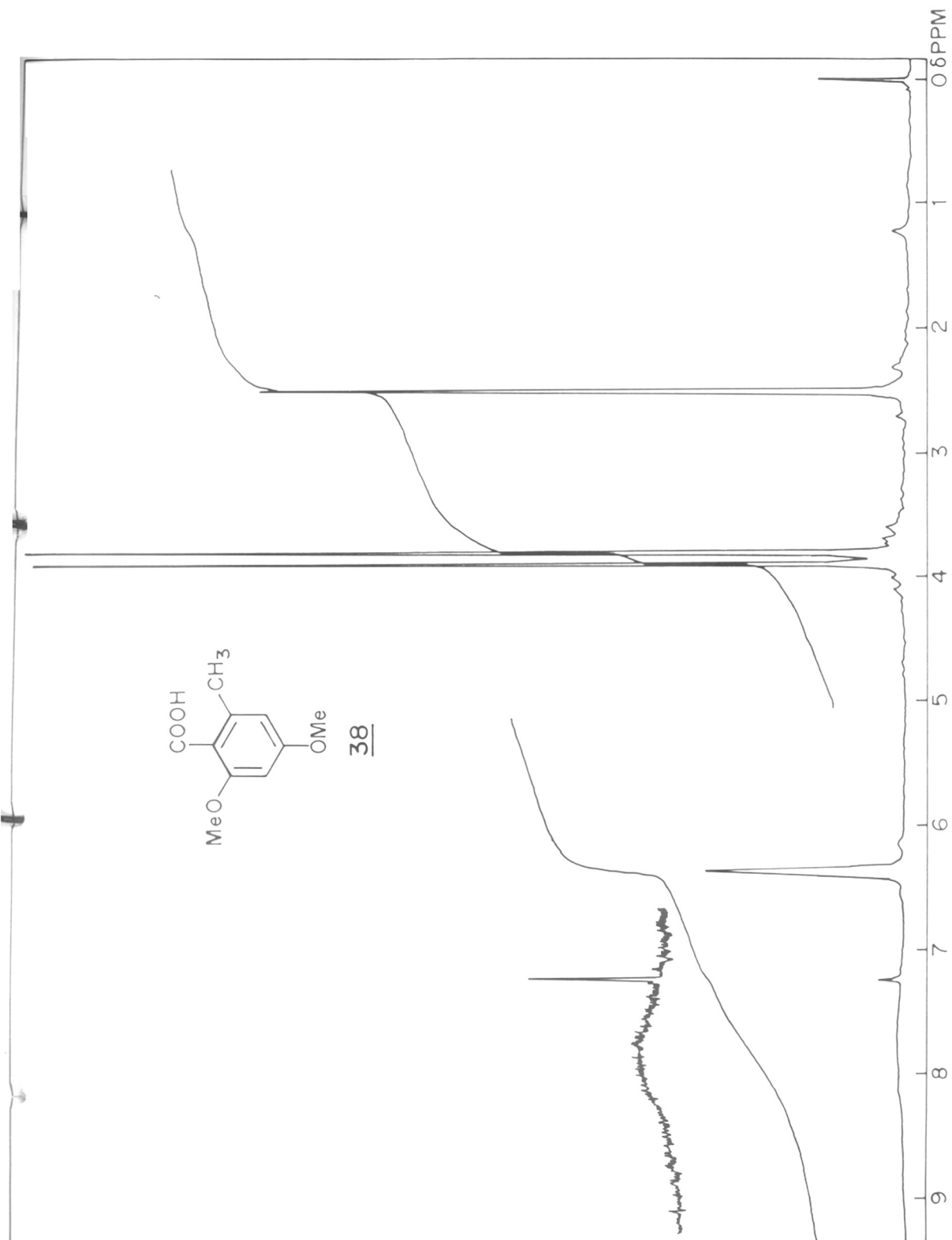
in the synthesis of cervinomycin. Thus it is feasible to generate the carbanion and utilise it to displace the methoxy group of the ester function. These observations lent support to the present approach and accordingly a synthetic scheme was envisaged as shown below.

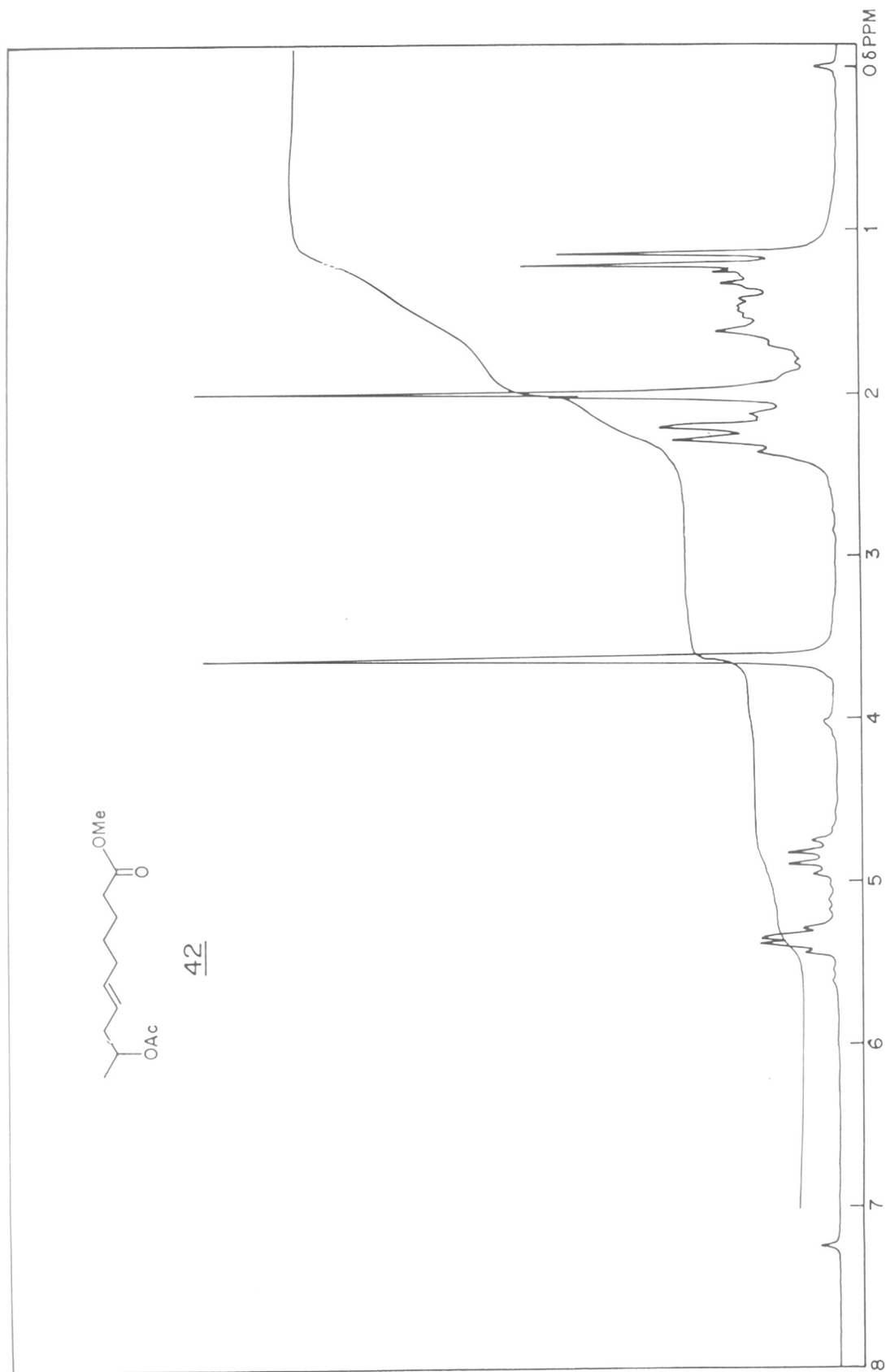
The requisite aromatic acid (38) was prepared from orcinolaldehyde (20) by permanganate oxidation.^{21a} The physical and spectral properties of the product dimethylorsellinic acid (38) compared favourably with those reported (FIG. 6). The aliphatic counterpart, methyl 9-acetoxydecen-6E-oate (42) (FIG. 7) was conveniently prepared from the corresponding acetoxy acetal (31) by Jones oxidation^{21b} followed by esterification of the acid formed (41) with diazomethane (SCHEME VI).

SCHEME-VI



Reaction of dimethylorsellinic acid (**38**) with LDA at -78°C in THF under argon atmosphere, followed by addition of the acetoxy ester (**42**) in THF gave after standard work up, the hydroxyketo acid (**37**) in 84% yield. It was accompanied by traces of dimethylorsellinic acid and another acidic

FIG. 6: ^1H -NMR OF SPECTRUM OF THE COMPOUND (**38**) IN CDCl_3

FIG. 7: ^1H -NMR SPECTRUM OF THE COMPOUND (42) IN CDCl_3

component ($\sim 10\%$), which was characterised as (43) from its IR, $^1\text{H-NMR}$ and mass spectra. Formation of the minor product (43) could be rationalised by assuming attack of the anion generated with LDA, on the acetoxy carbonyl²⁰ and subsequent O-C bond cleavage.

Complete characterisation of the required product (37) was obtained from its IR, $^1\text{H-NMR}$ and mass spectral data (FIG. 8). The IR spectrum showed typical bands for the hydroxyl and carboxyl functions at 3600 cm^{-1} and 1730 cm^{-1} respectively. In addition, a medium band at 1620 cm^{-1} for an olefin and an intense absorption at 1710 cm^{-1} for the keto function were observed. The $^1\text{H-NMR}$ spectrum was fully compatible with the structure (37). A methyl doublet at $\delta 1.18$, a multiplet at $\delta 3.78$ (methine) and another multiplet at $\delta 5.40$ (olefinic) were observed. The two benzylic protons were observed as a singlet at $\delta 3.94$ and meta coupled aromatic protons appeared as a doublet centred at $\delta 6.38$.

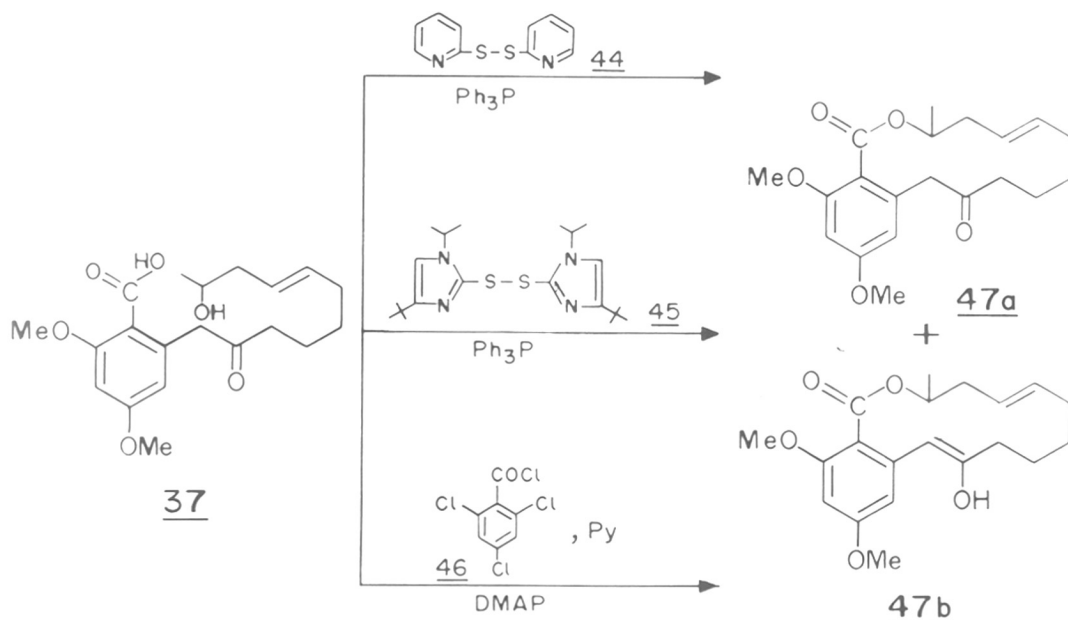
In the present proposed scheme, after realising the requisite coupling reaction in good yields, the stage was set for the macrolactonization step (which is also a key step in any macrolide synthesis). For this purpose, various reagents have been developed over the years (see Chapter I for details). These reagents in general either activate the hydroxyl group or the carboxyl functionality or both of them. Three of these reagents, *viz.* 2,2'-dipyridyl disulphide (44)/triphenyl phosphine (Ph_3P)²², 2,2'-bis(4-*t*-butyl,N-isopropyl)imidazolyl disulphide (45)/ Ph_3P ²³ and 2,4,6-trichlorobenzoyl

FIG.8: ^1H -NMR SPECTRUM OF THE COMPOUND (**37**) IN CDCl_3

chloride (**46**)/4-dimethylaminopyridine (4-DMAP)²⁴ were utilised in the lactonization step for monocillin IV and the results are discussed below.

The hydroxy acid (**37**) and 1.2 equivalents of 2,2'-dipyridyl disulphide (**44**) were dissolved in toluene under argon atmosphere and 1.2 equivalents of Ph_3P was added to it. The resultant solution was added slowly (17-18 hrs) to a refluxing solution of toluene. After 3-4 hr of further reflux, the reaction mixture was worked up and the product characterised. Only about 5-7% of the required lactone (**47**) could be realised and more than 90% of the hydroxy acid was recovered unchanged.

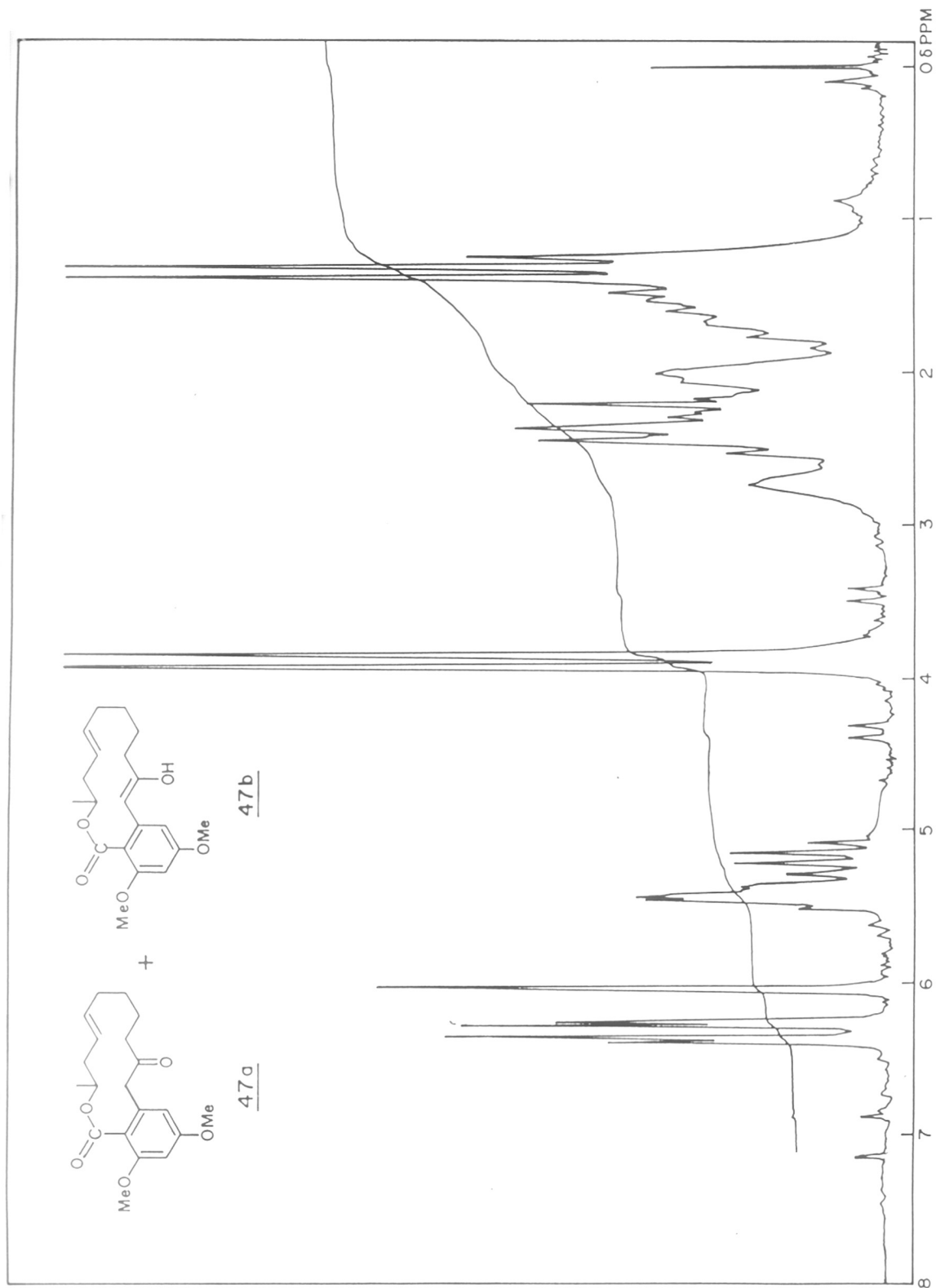
SCHEME-VI



With 2,2'-bis(4-t-butyl-N-isopropyl)imidazolyl disulphide (45), the reaction was carried out under similar conditions but employing 2.5 equivalents of the reagent instead of 1.2 equivalents. Considerably improved yield of the product (65% by GLC) was observed, but still good quantity of the starting material was recovered unchanged.

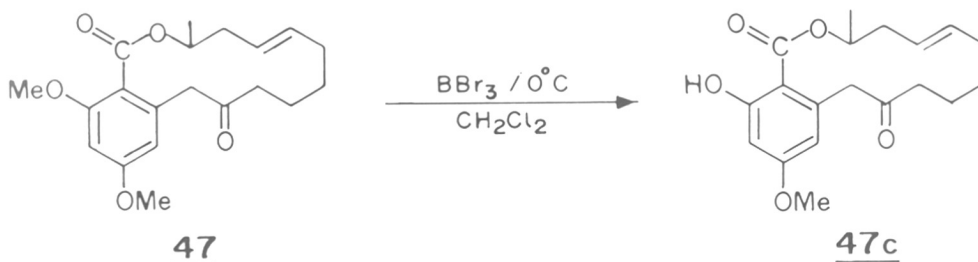
Yet another reagent attempted for the cyclisation of the hydroxy acid (37) was 2,4,6-trichlorobenzoyl chloride (46) in the presence of 4-dimethylaminopyridine (DMAP). This method introduced by Yamaguchi^{24a} for macrolactonisation was later modified by Yonemitsu et al.^{24b,c} The latter successfully applied the modified procedure (wherein high concentration of DMAP was used instead of a dilute solution) in the synthesis of erythronolide A. Thus the hydroxy acid (37) in xylene was stirred with pyridine and 2,4,6-trichlorobenzoyl chloride (46) for 24 hrs. The mixed anhydride thus formed was slowly added over 1 hr to two equivalents of DMAP in xylene. Lactone (47) as a tautomeric mixture (47a, 47b) was obtained in 76% yield after conventional work up and purification (FIG. 9).

Monocillin IV dimethyl ether (47) prepared as above displayed in its ¹H-NMR a multiplet at δ 5.25 characteristic of a lactone, and doublets due to benzylic protons at δ 3.44 and at δ 4.33 each having a coupling constant of 8 Hz. This was perhaps due to coupling in space of the benzylic protons with the methine proton at C-2. Additionally a singlet was observed at δ 6.01 integrating for one proton and it was

FIG. 9: ^1H -NMR SPECTRUM OF THE COMPOUND (47a+47b) IN CDCl_3

assigned to the enol proton of monocillin IV dimethyl ether (47). That monocillin IV dimethyl ether (47) obtained synthetically was a mixture of keto-enol tautomers (47a,47b) (in roughly equal proportions) was further confirmed from its IR spectrum which showed broad absorption at 3400 cm^{-1} for hydroxyl group, a lactone carbonyl at 1740 cm^{-1} and a keto carbonyl at 1720 cm^{-1} . The characteristic mass spectral pattern reported for monocillins³ was also observed in the dimethyl ether which recorded a base peak at m/e 178 and molecular ion at m/e 346. The formation and stability of the enol form of monocillin IV dimethyl ether is apparently due to the extended conjugation of the double bond with the aromatic ring.

SCHEME-VI (Contd.)



The demethylation of monocillin IV dimethyl ether (47a, 47b) was carried out employing BBr_3 in dichloromethane at 0°C ^{25a,b}, but only monocillin IV monomethyl ether (47c) was obtained. Hence, direct comparison with natural monocillin IV (5) was not possible.

PART II: Synthesis of nordinone and nordinonediol:

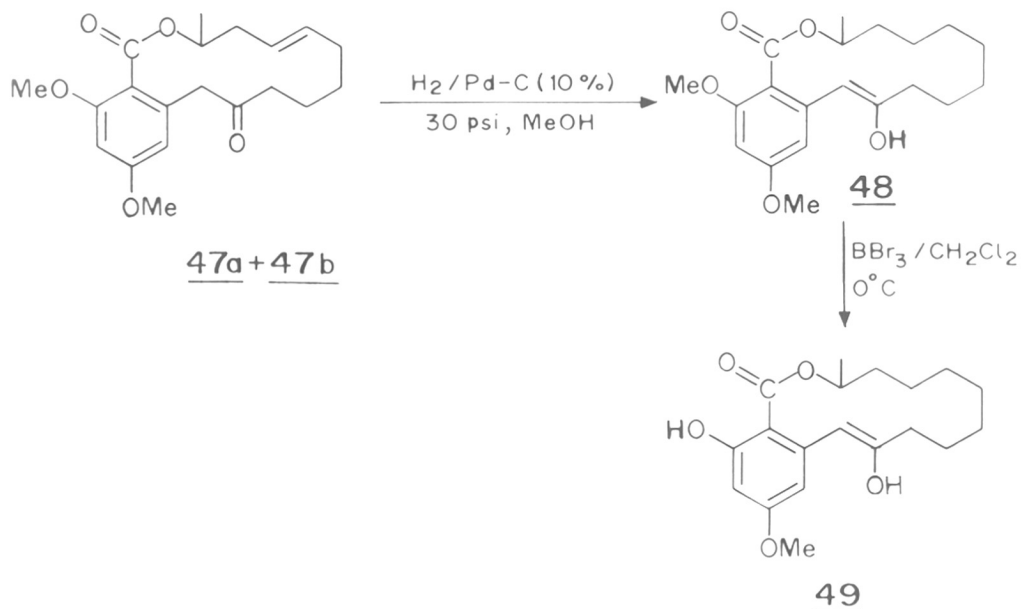
In the earlier part of this chapter, it was mentioned that along with the simplest member of this series, monocillin IV (5), synthesis of the other two minor metabolites, viz. nordinone (7) and nordinonediol (8) will also be carried out. The results of these attempts and achievements are described in this part of the chapter.

Nordinone (7), as may be recalled, does not possess any unsaturation in its aliphatic part. It was therefore envisaged that total synthesis of nordinone dimethyl ether (48) could be achieved via a simple hydrogenation of monocillin IV dimethyl ether (47a, 47b). Demethylation of (48) would then lead to nordinone (7) itself.

Thus monocillin IV dimethyl ether (47a, 47b) was hydrogenated in the presence of Pd-C (10%) at 30 psi for 1 hr (SCHEME VII). The product in its $^1\text{H-NMR}$ showed absence of trans double bond as was evident by the disappearance of the multiplet centred at δ 5.45. All other peaks were assignable to the remaining protons in nordinone dimethyl ether (48) (FIG.10). Mass spectral fragmentation was also characteristic of the monocillins with the base peak at m/e 178. Molecular ion at m/e 348 also lent support to the formation of nordinone dimethyl ether.

Attempts were directed towards demethylation of nordinone dimethyl ether (48) to the natural product nordinone (7) so that a direct comparison with the natural product could be

SCHEME-VII

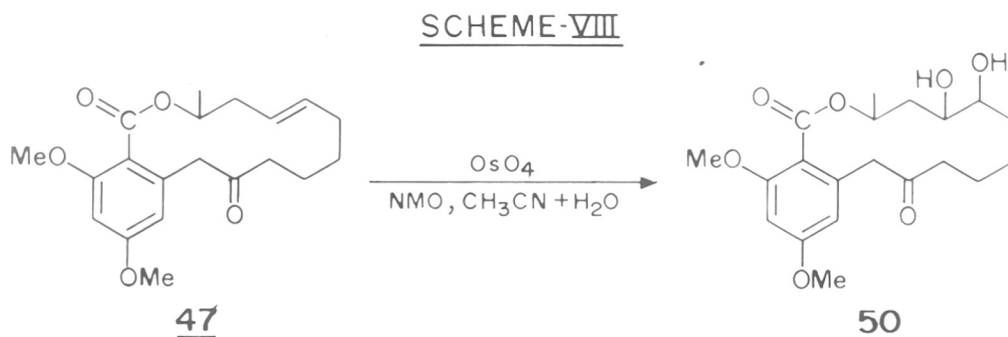


carried out. Accordingly, nordinone dimethyl ether (48) was demethylated with boron tribromide in dichloromethane^{25a,b} at 0°C . The product formed was identified and characterised as the monomethyl ether (49) and not nordinone (7) itself thereby indicating that only partial demethylation was possible. Only the methoxy group adjacent to the lactone carbonyl group got demethylated.

Nordinonediol (8), the other minor metabolite isolated along with nordinone (7), has similar structural pattern as the monocillins and nordinone (7), but possesses two hydroxy groups cis to each other at carbons 4 and 5. The absolute stereochemistry has not been determined yet. A simple OsO_4 catalysed cis-hydroxylation of monocillin IV dimethyl ether was envisaged to give nordinonediol dimethyl ether. Thus

FIG. 10: $^1\text{H-NMR}$ SPECTRUM OF THE COMPOUND (48) IN CDCl_3

monocillin IV dimethyl ether was reacted with OsO_4 in presence of N-methylmorpholine N-oxide (NMO) in aqueous acetonitrile at room temperature for 6 hr²⁶ (SCHEME VIII).



A major product was isolated by chromatographic purification and its structure was confirmed as nordinonediol dimethyl ether (50) on the basis of spectral evidence. The IR spectrum indicated a broad absorption at 3400 cm^{-1} for a hydroxyl group. In the $^1\text{H-NMR}$ the multiplet centred at δ 5.45 for trans-double bond was absent and a multiplet at δ 3.60 appeared which was assigned to protons at carbons 4 and 5. Further confirmation was also obtained from the mass spectral data which revealed a base peak at m/e 178 and a molecular ion at m/e 380.

In conclusion, as a part of the programme of work, the first total synthesis of monocillin IV dimethyl ether (47a, 47b), monocillin IV monomethyl ether (47c), nordinone dimethyl ether (48), nordinone monomethyl ether (49) and nordinonediol dimethyl ether (50) have been achieved. The biological activity of these synthetic products is being evaluated.

EXPERIMENTAL

3,5-Dimethoxytoluene (19):

A mixture of orcinol **18** (10 g, 80.64 mmol), potassium carbonate (27.8 g, 201.6 mmol) and dimethyl sulphate (18.5 ml, 193.5 mmol) in dry acetone (100 ml) was heated under reflux for 16 h on a waterbath. Excess acetone was distilled off and residue was poured into ice water. The mixture was stirred overnight to decompose excess dimethyl sulphate. It was then extracted with ethylacetate (2 x 100 ml) and the combined extract was dried (Na_2SO_4). Distillation under reduced pressure gave 10.4 g (83%) of pure dimethyl ether **19**, b.p. 91-92/4 mm (lit.²⁷ 67.5-68.5/.2 mm) as a pale yellow liquid.

IR (Neat): 1610 cm^{-1} .

$^1\text{H-NMR}$: δ 2.20 (s, 2H), 3.63 (s, 6H, $2\times\text{OCH}_3$) and 6.10 (s, 3H, Ar-H).

Mass (m/e): 152 (M^+), 137, 123, 109, 91 and 77.

2,4-Dimethoxy-6-methyl-benzaldehyde (20):

A complex was prepared from POCl_3 (4.47 ml, 49.34 mmol) and DMF (3.6g, 49.31 mmol) at 0°C and to this complex was added 3,5-dimethoxytoluene (5 g, 32.89 mmol) with cooling (0°C). The mixture was allowed to warm to room temperature and stirring was continued for 5 h. The reaction product was cooled to 0°C and then decomposed with 10% NaOAc solution (100 ml). A white solid was obtained which was filtered, washed with water and air dried. Recrystallization from the hot pet. ether ($60\text{-}80^\circ\text{C}$) yielded 4.7 g. (79%) of the

required aldehyde as a colourless crystalline solid, m.p. 59-60°C (lit.¹² m.p. 62°C).

IR (Nujol): 1680 and 1610 cm^{-1} .

¹H-NMR: δ 2.71 (s, 3H), 3.91 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 6.37 (s, 2H, aromatic) and 10.40 (s, 1H, CHO).

Mass (m/e): 180 (M^+), 179, 163, 149, 155 and 77.

Ethyl 5-bromo-2,4-dimethoxy-6-methylbenzoate (21):

A mixture of 2,4-dimethoxy-6-methylbenzaldehyde **20** (3 g, 20 mmol), N-bromo-succinimide (9.2 g, 52 mmol) and catalytic amount of benzoyl peroxide in dry CCl_4 (50 ml) was irradiated with light (300 watts) for 20 min. Dry ethanol (2 ml) was added to the reaction mixture at 0°C and the reaction mixture was stirred for another 2 h at room temperature. Succinimide was filtered off and the organic solution was concentrated to yield a crude product which was purified by silica gel chromatography to yield a white solid (4.8 g, 79%), m.p. 108°C.

IR (CHCl_3): 1730 and 1600 cm^{-1} .

¹H-NMR: δ 1.33 (t, 3H, $\text{OCH}_2\text{-CH}_3$), 2.35 (s, 3H), 3.82 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.37 (q, 2H, $\text{-OCH}_2\text{-CH}_3$) and 6.40 (s, 1H, Ar-H).

Mass (m/e): 304 (M^+), 302, 275, 273 and 215.

Ethyl 5-bromo-6-bromomethyl-2,4-dimethoxybenzoate (22):

The ester **21** (4.4 g, 14.5 mmol) and NBS (2.83 g, 15.95 mmol) in dry CCl_4 was irradiated with light (300 watts) for 4 h (monitored by ¹H-NMR). Succinimide was filtered off and

the CCl_4 solution was concentrated under reduced pressure to yield brown solid. The product was purified by silica gel column chromatography (5% acetone in pet. ether) to yield (22) as a semi-solid (5.2 g, 94%).

IR (CHCl_3): 1740 and 1620 cm^{-1} .

$^1\text{H-NMR}$: δ 1.40 (t, 3H, $\text{O-CH}_2\text{-CH}_3$), 3.84 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.33 (q, 2H, $\text{-OCH}_2\text{-CH}_3$), 4.64 (s, 2H, $\text{CH}_2\text{-Br}$) and 6.44 (s, 1H, Ar-H).

Mass (m/e): 382 (M^+), 380, 357, 326, 323, 222, 150 and 77.

2-(8-Hydroxy non-5E-enyl)-1,3-dithiane (17):

$\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.55 ml, 12.6 mmol) was added to a stirred solution of 2(8-hydroxy non-5E-enyl)1,3-dioxolane 13a, (1.8 g, 8.41 mmol) and 1,3-propanedithiol (1 g, 10 mmol) in dry CH_2Cl_2 (20 ml) at 0°C over 10 min. The stirring was continued at room temperature for 14 h. Excess 1,3-propanedithiol was removed with saturated solution of K_2CO_3 (10 ml) and the reaction mixture was stirred for 2 h at room temperature. It was then extracted with CH_2Cl_2 (2 x 30 ml), the combined extract was washed with brine and dried (Na_2SO_4). Concentration of the solvent gave crude product which upon purification by silica gel column chromatography (10% acetone in pet. ether) afforded 1.35 g of required thioacetal 17 in 84% yield as yellow liquid.

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

$^1\text{H-NMR}$: δ 1.15 (d, $J=6\text{Hz}$, 3H), 1.20-1.90 (m, 6H), 1.90-2.40 (m, 6H), 2.68-3.11 (m, 4H, $\text{S-CH}_2\text{-CH}_2\text{-CH}_2\text{-S}$), 3.73 (m, 1H), 4.03

(t, 1H, S-CH-S) and 5.44 (m, 2H, -CH=CH-).

Mass (m/e): 260 (M^+), 242, 215, 185 and 199.

Analysis Calc. for $C_{13}H_{24}OS_2$: C, 60.00; H, 9.23;

Found : C, 60.24; H, 9.18%

Alkylation of dithiane 17 with bromide 22:

n-BuLi (1.2M in hexane, 10.90 ml, 13 mmol) was added to a stirred solution of the dithiane 17 (1.7 g, 6.53 mmol) in dry THF (10 ml) at -78°C . The reaction mixture was stirred at -78°C for 2 h. The bromo ester 22 (2.4g, 6.53 mmol) in dry THF (10 ml) was slowly added at -78°C over 20 min. and the stirring was continued for 1 h. at the same temperature. The reaction mixture was warmed to room temperature and was quenched with saturated NH_4Cl (10 ml). It was then extracted with ethyl acetate (2 x 50 ml). The solvent was distilled off and the crude product obtained was purified by silica gel column chromatography (10% acetone in benzene) to yield the required product 24 (1.65 g, 54%) as a gummy solid.

IR (Neat): 3450, 1730 and 1600 cm^{-1} .

$^1\text{H-NMR}$: δ 1.15 (t, 3H, O-CH₂-CH₃), 1.20 (d, J=6Hz, 3H), 1.25-1.80 (m, 5H, 2xCH₂ and OH), 1.80-2.45 (m, 6H), 2.66-2.90 (m, 4H, 2xSCH₂), 3.70 (s, 2H, Ar-CH₂), 3.75 (m, 1H), 3.80 (s, 3H, OCH₃), 3.88 (s, 3H, OCH₃), 4.22 (q, 2H, OCH₂-CH₃), 5.39 (m, 2H, -CH=CH-), 6.45 (br. d, 2H, Ar-H).

Mass (m/e): 482 (M^+), 449, 435, 418 and 259.

Analysis Calc. for $C_{24}H_{38}O_5S_2$: C, 59.75; H, 7.88; S, 13.2;

Found: C, 60.09; H, 7.78; S, 13.4%

10-Acetoxy-2-(N,N-dimethylamino)undec-7E-nonitrile (32):

Aqueous perchloric acid (35%, 20 ml) was slowly added to a stirred solution of acetate **31** (2.8 g, 10.93 mmol) in CH_2Cl_2 (25 ml) at 0°C over 10 min. The reaction mixture was stirred for a further period of 3 h, the aqueous layer was separated and the organic layer was washed with saturated NaHCO_3 solution (10 ml), dried (Na_2SO_4) and concentrated to give the aldehyde (**31a**). This aldehyde in methanol (5 ml) was added with stirring to a solution of NaCN (0.649 g, 13.06 mmol) and dimethylamine hydrochloride (1.06 g, 13.06 mmol) in water (10 ml) at room temperature. The reaction mixture was stirred at room temperature for 16 h. Water (50 ml) was then added and the product was extracted with pet. ether (2 x 100 ml), washed with water, dried (Na_2SO_4) and concentrated under reduced pressure to give the pure amino nitrile (**32**) (2.4 g, 82.7%) as yellow oil.

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

$^1\text{H-NMR}$: δ 1.16 (d, $J = 6\text{Hz}$, 3H), 1.20-1.80 (br.m, 4H), 1.98 (s, 3H), 2.00-2.24 (m, 6H), 2.80 (s, 6H, $\text{N}(\text{CH}_3)_2$), 3.35 (t, 1H), 4.74 (m, 1H) and 5.36 (m, 2H, $-\text{CH}=\text{CH}-$).

Mass (m/e): 266 (M^+), 251, 196 and 134.

Analysis Calc. for $\text{C}_{15}\text{H}_{26}\text{N}_2\text{O}_2$: C, 67.66; H, 9.77;

Found : C, 67.54; H, 9.68%

Methyl 3,5-dimethoxybenzoate (27):

A mixture of 3,5-dihydroxybenzoic acid **26** (25 g, 162.3 mmol), dimethylsulphate (53.8 ml, 568 mmol) and potassium

carbonate (78.3 g, 568 mmol) in dry acetone (250 ml) was refluxed for 6 h. Acetone was distilled off, the residue was poured into ice water and the resultant solid was filtered, washed with water and air dried to yield **27** (30.2 g, 95%) as a white solid, m.p. 39-40°C (lit.²⁸ m.p. 42-43°C).

IR (nujol): 1730 and 1610 cm^{-1} .

¹H-NMR: δ 3.75 (s, 6H, 2xOCH₃), 3.88 (s, 3H, COOCH₃), 6.58 (m, 1H), and 7.12 (d, J=1.2Hz, 2H).

Mass (m/e): 196 (M⁺), 182, 152.

3,5-Dimethoxybenzyl alcohol (**28**):

LiAlH₄ (0.484 g, 12.73 mmol) was added slowly over 30 min. to a stirred solution of ester **27** (5 g, 25.5 mmol) in dry THF (30 ml) at 0°C. The reaction mixture was stirred for 10 h and the excess LAH was destroyed by the addition of ethyl acetate (10 ml) followed by saturated Na₂SO₄ solution (10 ml). The solid cake formed was filtered, the residue was washed with ethyl acetate and dried (Na₂SO₄). Concentration of the solvent under reduced pressure yielded 3,5-dimethoxybenzyl alcohol **28** (3.25 g, 95%); m.p. 47-48°C (lit.²⁹ 47-50°C).

IR (nujol): 3400 and 1610 cm^{-1} .

¹H-NMR: δ 2.65 (br.t, OH), 3.78 (s, 6H, 2xOCH₃), 4.44 (d, J=6Hz, 2H), 6.28 (t, 1H, Ar-H) and 6.45 (d, J=1.5Hz, 2H, Ar-H).

Mass (m/e): 168 (M⁺), 153.

3,5-Dimethoxybenzyl bromide (**29**):

PBr₃ (13.8 ml, 142.8 mmol) was added slowly to a stirred solution of alcohol **28** (20 g, 119 mmol) and pyridine (9.6 ml,

119 mmol) in dry ether (100 ml) at 0°C over 15 min. The reaction mixture was stirred at room temperature for 16 h. The ether solution was poured into ice water and the organic layer was separated, dried (Na_2SO_4) and concentrated under reduced pressure. It yielded the required benzyl bromide **29** (21 g, 76%) as a pale yellow solid, m.p. 98-101°C.

IR (nujol): 1600 cm^{-1} .

$^1\text{H-NMR}$: δ 3.70 (s, 6H, $2\times\text{OCH}_3$), 4.30 (s, 2H, $\text{CH}_2\text{-Br}$), 6.20 (d, $J=1.5\text{Hz}$, 2H, Ar-H) and 6.40 (dd, $J=1.5\text{Hz}$ and $.6\text{Hz}$, 1H, Ar-H).

Mass (m/e): 230 (M^+), 199, 151 and 120.

2-Bromo-3,5-dimethoxybenzyl bromide (**30**):

A mixture of 3,5-dimethoxybenzyl bromide (**29**, 2.5 g, 10.86 mmol) and dry N-bromosuccinimide (1.93 g, 10.86 mmol) in dry CCl_4 (230 ml) was refluxed in oil bath for 40 min. Succinimide was filtered off and CCl_4 solution on distillation produced the bromide **30** as a white solid (3.20 g, 95%); m.p. 112-114°C.

IR (nujol): 1600 cm^{-1} .

$^1\text{H-NMR}$: δ 3.80 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.27 (s, 2H, $\text{CH}_2\text{-Br}$), 6.40 (d, $J=2.2\text{Hz}$, 1H) and 6.60 (d, $J=2.2\text{Hz}$, 1H).

MS (m/e): 310 (M^+), 309, 229 and 151.

Alkylation of the α -aminonitrile **32** with the bromide **30**:

Sodium salt of hexamethyldisilazane (HMDS) was prepared by refluxing hexamethyldisilazane (1.8 ml) and NaNH_2 (0.283 g, 7.25 mmol) in dry THF (10 ml) for 1 h. To this stirred solution, a mixture of bromide **30** (1 g, 3.22 mmol) and

α -aminonitrile **32** (0.975 g, 3.66 mmol) in dry THF (10 ml) was added at room temperature over a period of 1 h. Stirring was continued for 8 h. The reaction mixture was then quenched with saturated NH_4Cl (10 ml), extracted with ethylacetate (2 x 50 ml), washed with water and dried (Na_2SO_4). The crude product was purified by column chromatography on alumina (neutral) using acetone - pet. ether as eluent (1:9) to afford **33** as a gummy solid (1.6 g, 86%) which was taken to the next step without further purification.

Deprotection of **33**:

Aqueous HClO_4 (35%, 20 ml) was added dropwise over 10 min to a stirred solution of **33** (1.5 g, 3 mmol) in CH_2Cl_2 (25 ml) at 0°C . The mixture was stirred at room temperature for 2 h, the aqueous layer was separated and the organic layer was washed with saturated NaHCO_3 solution (10 ml), brine and dried (Na_2SO_4). Concentration under reduced pressure gave a crude product which was purified by silica gel column chromatography (benzene-acetone, 95:5). The required product (**34**) was obtained in 86% yield (1.23 g) as a semi-solid.

IR (Neat): 1750, 1730 and 1600 cm^{-1} .

$^1\text{H-NMR}$: δ 1.20 (d, $J=6\text{Hz}$, 3H), 1.25-1.78 (br.m, 4H), 2.01 (s, 3H, OCOCH_3), 2.10-2.40 (br.m, 6H), 3.75 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.05 (s, 2H), 4.80 (m, 1H), 5.38 (m, 2H, CH=CH) and 6.36 (d, $J=1.5\text{Hz}$, 2H).

MS (m/e): 440 (M^+), 439, 437, 358, 341, 230, 151 and 135.

Ketalisation of 34:

A solution of ketoacetate **34** (1.15 g, 2.61 mmol), ethylene glycol (1 g, 16 mmol) and a catalytic amount of p-toluene sulphonic acid in dry benzene (50 ml) was refluxed with azeotropic removal of water (Dean-Stark) for 10 h. The reaction mixture was cooled, diluted with ethyl acetate (20 ml), washed with cold saturated NaHCO_3 solution (10 ml) followed by brine and dried (Na_2SO_4). The solvent was distilled off under reduced pressure to yield the required ketal **35** (1.15 g, 91%) as a semi-solid.

IR (neat): 1745 and 1600 cm^{-1} .

$^1\text{H-NMR}$: δ 1.21 (d, $J=6\text{Hz}$, 3H), 1.24-1.91 (m, 4H), 2.00 (s, 3H, OCOCH_3), 2.05-2.46 (m, 6H), 3.04 (br.d, 2H), 3.62 (s, 4H, $\text{OCH}_2\text{-CH}_2\text{-O}$), 3.80 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.80 (m, 1H), 5.37 (m, 2H, -CH=CH-) and 6.33, (br.d, 2H, Ar-H).

Mass (m/e): 484 (M^+), 426, 382, 323, 231, 191 and 152.

Carboxylation of 35:

To a stirred solution of ketal acetate **35** (1.20 g, 2.48 mmol) in dry THF (5 ml) at -78°C , n-BuLi (1.6M in hexane, 2 ml, 3.2 mmol) was added over 10 min. The reaction mixture was stirred at -78°C for a further period of 1 h. To this stirred solution solid CO_2 (dry ice) ($\sim 10\text{ g}$) was added in small pieces in one lot under argon atmosphere and kept at -78°C for 1 h. It was then warmed upto room temperature and the reaction mixture was quenched with saturated NH_4Cl .

solution (10 ml). Water (20 ml) was added and the mixture was extracted with benzene (30 ml). The aqueous layer was cooled to 0°C and was acidified with cold dil. HCl (5%) to pH=2. Extraction with CH₂Cl₂ (2x50 ml) followed by routine washing, drying and concentration yielded the pure hydroxy acid **36** (0.419 g, 41.5%) as a colourless semi-solid.

IR (CHCl₃): 3450 (br), 1730 and 1610 cm⁻¹.

¹H-NMR: δ 1.18 (d, J=6Hz, 3H), 1.20-2.00 (m, 6H), 2.10-2.45 (m, 4H), 3.72 (s, 4H, -OCH₂-CH₂-O), 3.80 (s, 6H), 3.85 (s, 2H), 5.40 (m, 2H, -CH=CH-), 6.31 (d, J=1.5Hz, 1H, Ar-H) & 6.39 (d, J=1.5Hz, 1H, Ar-H).

Mass (m/e): 408 (M⁺), 361, 312, 294, 207, 198 and 149.

Deketalisation of **36**:

Aqueous perchloric acid (35%, 5 ml) was added to stirred solution of the hydroxy acid **36** (400 mg, 0.98 mmol) in CH₂Cl₂ (10 ml) at 0°C and stirred at the same temperature for 6 h. The organic layer was separated, washed with brine and dried (Na₂SO₄). Concentration of the solvent gave pure hydroxy acid **37** (330 mg, 92%). (For spectral data, please see page 183).

9-Acetoxydecen-6E-oic acid (**41**):

To an ice cold solution of 2-(8-acetoxynon-5E-enyl)-1,3-dioxolane (**31**, 2 g, 8.77 mmol) in acetone (20 ml) was added Jones reagent^{21b} (8 ml) over a period of 20 min. Stirring continued at 0°C for 4 h. The chromium salt was separated by filtration through celite pad and was further washed with acetone (50 ml). Acetone was distilled off under reduced

pressure, the resultant residue was diluted with water (20 ml) and extracted with CHCl_3 (2x50 ml). The chloroform solution was washed with brine, dried (Na_2SO_4) and concentrated. The crude product was purified by silica gel column chromatography to yield 1.58 g (88%) of the acid **41**.

IR (neat): 3400 (br.), 1750 and 1730 cm^{-1} .

$^1\text{H-NMR}$: δ 1.18 (d, $J=6\text{Hz}$, 3H), 1.20-1.85 (m, 4H), 1.98 (s, 3H, OCOCH_3), 2.00-2.50 (m, 6H), 4.82 (m, 1H), 5.35 (m, 2H, CH=CH) and 6.50 (br.s, 1H, D_2O exchangeable, $-\text{COOH}$).

Mass (m/e): 228 (M^+), 227, 198, 150.

Methyl 9-acetoxystecaric acid (**42**):

An ethereal solution of diazomethane (prepared from 1.70 g, nitrosomethyl urea) was added to a solution of 9-acetoxystecaric acid **41** (2.50 g, 10.96 mmol) in ether (5 ml) at 0°C and kept at the same temperature for 4 h, after which excess diazomethane was destroyed with glacial acetic acid (0.5 ml). Ether was distilled off at low temperature and the crude product obtained was purified by silica gel column chromatography (eluent 5% acetone in pet. ether). The required ester **42** was obtained as a light yellow liquid (2.2 g, 83%).

IR (neat): 1745 and 1730 cm^{-1} .

$^1\text{H-NMR}$: δ 1.20 (d, $J=6\text{Hz}$, 3H), 1.26-1.77 (br.m, 4H), 1.98 (s, 3H), 2.0-2.46 (br.m, 6H), 3.64 (s, 3H, COOCH_3), 4.86 (m, 1H) and 5.37 (m, 2H, CH=CH).

Mass (m/e): 242 (M^+), 240, 227, 211, 199, 198, 182, 150 and 108.

Analysis Calc. for $\text{C}_{13}\text{H}_{22}\text{O}_4$: C, 64.46; H, 9.07;

Found: C, 64.50; H, 9.07%

2,4-Dimethoxy-6-methylbenzoic acid (38):

To a stirred solution of 2,4-dimethoxy-6-methylbenzaldehyde **20** (2 g, 11.11 mmol) in acetone (10 ml) was added an aqueous solution of KMnO_4 (3.5%, 100 ml) till the KMnO_4 colour persisted. The mixture was stirred for 2h. at room temperature and finally heated on the water bath for 2h. The MnO_2 that was formed was filtered off through celite pad and residue was washed with water (100 ml). Acidification of the aqueous layer with dil. HCl (2N) to pH 2 gave a solid which was filtered, washed with cold water and dried to afford **38** as a white solid; m.p. 137-138°C (lit.^{21a} m.p. 140°C).

IR (Nujol): 3400 (br), 1680 and 1610 cm^{-1} .

$^1\text{H-NMR}$: δ 2.53 (s, 3H), 3.84 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.38 (br.s, 2H).

Mass (m/e): 196 (M^+), 178, 149, 135, 120 and 77.

Analysis Calc. for $\text{C}_{10}\text{H}_{12}\text{O}_4$: C, 61.22; H, 6.12;

Found: C, 61.01; H, 6.45%.

Seco-acid of monocillin IV dimethyl ether (37):

LDA solution was prepared by reacting the n-BuLi in hexane [2.5M, 4.5 ml] with dry diisopropyl amine (1.75 ml, 11.22 mmol) in dry THF (5 ml) at 0°C under argon. This solution was cooled to -78°C and a solution of 2,4-dimethoxy-6-methyl benzoic acid **38** (1 g, 5.10 mmol) in dry THF (5 ml) was added slowly over 20 min. A deep red solution

was formed and the mixture was stirred for a further period of 2 h at -78°C . The acetate ester **42** (0.617 g, 2.55 mmol) in dry THF (5 ml) was added slowly over 5 min. Stirring was continued at -78°C for 1 h and the mixture was warmed to room temperature and stirred further for 1 h. the reaction was quenched with saturated NH_4Cl solution, diluted with water (10 ml) and extracted with ether (20 ml). The aqueous layer was acidified with cold dil. HCl (5%) to pH 2. The crude acid obtained was purified by silica gel column chromatography (20% acetone in pet. ether) to give 1.25 g (68%) of seco-acid **37** as a semi-solid.

IR (CHCl_3): 3400 (br.), 1730, 1620 and 1590 cm^{-1} .

$^1\text{H-NMR}$: δ 1.18 (d, $J=6.2\text{Hz}$, 3H), 1.2-1.75 (br.m, 4H), 1.80-2.60 (br.m, 6H), 3.78 (m, 1H), 3.80 (s, 6H, $2\times\text{OCH}_3$), 3.94 (s, 2H, Ar-CH_2), 5.40 (m, 2H, CH=CH), 6.38 (br.d, 2-H, Ar-H).

Mass (m/e): 364 (M^+), 238, 234, 221, 193, 178, 147 and 138.

Monocillin IV dimethyl ether (47a, 47b):

Lactonization of **37** using 2,2'-dipyridyl disulphide:

The hydroxy acid **37** (100 mg, 0.274 mmol), 2,2'-dipyridyl disulphide (72 mg, 0.329 mmol) and triphenylphosphine (86 mg, 0.329 mmol) were dissolved in dry xylene (10 ml) under argon and stirred for 8 h. The reaction mixture was diluted to 20 ml with dry xylene and added slowly (syringe pump) over 17 h to refluxing xylene (100 ml) under argon atmosphere. Refluxing was continued for additional 3 h. Xylene was distilled off

under reduced pressure and the product was purified by column chromatography (5% acetone in benzene) to afford lactone **47a**, **47b** as a keto-enol tautomer (6 mg, 7%).

Lactonization of 37 using 2,2'-bis(4-t-butyl-N-isopropyl) imidazolyl disulphide

The hydroxy acid **37** (0.120 g, 0.329 mmol) in dry benzene (5 ml) was added to a stirred solution of 2,2'-bis(4-t-butyl-N-isopropyl) imidazolyl disulphide (0.324 g, 0.824 mmol) in 5 ml dry benzene followed by addition of triphenylphosphine (0.215 g, 0.824 mmol) in one lot at room temperature under argon. Stirring was continued for 2 h till the faint yellow colour disappeared. The thiol ester formed was diluted with dry benzene (10 ml) and added to a refluxing dry benzene (100 ml) over 10 h (syringe pump). Refluxing was continued for another 2 h. Benzene was distilled off and the residue was chromatographed to afford 10-15 mg of pure lactone (**47**). The remaining product could not be separated from imidazothione.

Lactonization of 37 using 2,4,6-trichlorobenzoyl chloride:

To a stirred solution of the seco-acid **37** (0.23 g, 0.631 mmol) and pyridine (49 mg, 0.631 mmol) in dry xylene (10 ml) at room temperature was added 2,4,6-trichlorobenzoyl chloride (113 μ L, 0.69 mmol) under argon atmosphere. The reaction mixture was stirred further at room temperature for 18 h and the resultant mixed anhydride that was formed was added to a stirred solution of 4-dimethylaminopyridine (0.155 g, 1.26 mmol)

in dry xylene (20 ml) over 1 h at room temperature under argon atmosphere. The xylene was distilled off under reduced pressure and the crude product was purified by silica gel column chromatography (10% acetone in pet. ether). The required lactone (**47a**, **47b**) was obtained as a semi-solid in 76% yield (0.167 g). IR (CHCl_3): 3400, 1740, 1720 and 1610 cm^{-1} .

$^1\text{H-NMR}$ (300 MHz): δ 1.35 (d, $J=6.2\text{Hz}$, 3H), 1.20-1.80 (br.m, 4H), 1.95-2.57 (br.m, 6H), 2.75 (br.s, 1H, D_2O exchangeable, OH), 3.44 (d, $J=8\text{Hz}$, 1H), 3.87 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.33 (d, $J=8\text{Hz}$, 1H), 5.25 (m, 1H), 5.45 (m, 2H, $-\text{CH}=\text{CH}-$), 6.07 (s, 1H, enolic), 6.31 (d, $J=1.5\text{Hz}$, 1H) and 6.41 (d, $J=1.5\text{Hz}$, 1H).

Analysis Calc. for $\text{C}_{20}\text{H}_{26}\text{O}_5$: C, 69.39; H, 7.5;

Found: C, 69.42; H, 7.49%

Monocillin IV monomethyl ether **47c**:

To a stirred solution of monocillin IV dimethyl ether **47a**, **47b** (50 mg, 0.14 mmol) in dry CH_2Cl_2 (2 ml) at 0°C under argon atmosphere, was added cooled solution of BBr_3 in CH_2Cl_2 (1M, 0.4 ml). The reaction mixture was stirred at 0°C for 1 h and at room temperature for 2 h. It was then quenched with water (1 ml). The product was extracted with ethylacetate (2x5 ml), washed with brine and dried (Na_2SO_4). Concentration of solvent and purification of the crude product on silica gel column chromatography (10% ethylacetate in pet. ether) afforded monocillin IV monomethyl ether (**47c**), (18 mg, 38%) as a semi-solid.

IR (neat): 3440, 1735, 1720 and 1610 cm^{-1} .

$^1\text{H-NMR}$: δ 1.30 (d, $J=6.2\text{Hz}$, 3H), 1.25-1.85 (br.m, 4H), 1.90-2.58 (br.m, 6H), 3.42 (d, $J=8\text{Hz}$, 1H), 4.30 (d, $J=8\text{Hz}$, 1H), 3.85 (s, 3H, OCH_3), 5.20 (m, 1H), 6.02 (s, 1H, enotic), 6.33 (d, $J=1.5\text{Hz}$, 1H), 6.42 (d, $J=1.5\text{Hz}$, 1H) and 10.15 (br.s, 1H, OH, D_2O exchangeable).

Nordinone dimethyl ether (48):

Monocillin IV dimethyl ether as a mixture of keto-enol tautomers (40 mg, 0.115 mmol) was hydrogenated at 30 psi over Pd-C (10%, 30 mg) in ethyl acetate (10 ml) for 1 h. The catalyst was filtered off and ethylacetate was removed by distillation under reduced pressure. Nordinone dimethyl ether (48) (38 mg, 94%) was obtained as colourless semi-solid.

IR (CHCl_3): 3400, 1735, 1720 and 1600 cm^{-1} .

$^1\text{H-NMR}$: δ 1.28 (d, $J=6.2\text{Hz}$, 3H), 1.30-1.84 (br.m, 12H), 2.13-2.51 (m, 3H, CH_2 and OH), 3.84 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 5.13 (m, 1H), 6.04 (s, 1H, enolic), 6.26 (d, $J=1.5\text{Hz}$, 1H) and 6.37 (d, $J=1.5\text{Hz}$, 1H).

Mass (m/e): 348 (M^+), 330, 260, 178, 151, 135 and 77.

Nordinone monomethyl ether (49):

To a stirred solution of nordinone dimethyl ether 48 (20 mg, 0.057 mmol) in dry CH_2Cl_2 (2 ml), was added BBr_3 in CH_2Cl_2 (1M, .25 ml) at 0°C under argon atmosphere. The stirring was continued at 0°C for 2 h and at room temperature for 2 h. Water (1 ml) was added and the reaction mixture was extracted with ethylacetate (2 x 5 ml), washed with brine and dried (Na_2SO_4). Ethylacetate extract was filtered through a pad of

silica gel. Concentration of the solvent afforded nordinone monomethyl ether (**49**).

IR (neat): 3450 (br.), 1730, 1720 and 1610 cm^{-1} .

$^1\text{H-NMR}$: δ 1.25 (d, $J=6.2\text{Hz}$, 3H), 1.28-1.90 (br.m, 12H), 2.10-2.60 (br.m, 3H), 3.80 (s, 3H, OCH_3), 5.00 (m, 1H), 6.01 (s, 1H, enolic), 6.28 (d, $J=1.5\text{Hz}$, 1H), 6.38 (d, $J=1.5\text{Hz}$, 1H), 10.5 (br.s, 1H, OH, D_2O exchangeable).

Nordinonediol dimethyl ether (50):

To a stirred solution of monocillin IV dimethyl ether **47** (60 mg, 0.173 mmol) and N-methylmorpholine oxide (30 mg, 0.26 mmol) in a mixture of acetonitrile and water (9:1, 4 ml) was added the OsO_4 solution (0.05M in toluene, 0.1 ml) at room temperature. The reaction mixture was stirred at room temperature for 6 h, after which it was quenched with sodium thiosulphate and extracted with ethylacetate (3x10 ml). Filtration through a short silica gel column and concentration afforded nordinonediol dimethyl ether (**50**, 17 mg, 26%) as a semi-solid.

IR: 3400 (br.), 1730, 1715 and 1610 cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3): δ 1.22 (d, $J=6.2\text{Hz}$, 3H), 1.30-1.60 (br.m, 4H), 2.22-2.80 (br.m, 6H), 3.60 (m, 2H), 3.78 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 5.20 (m, 1H), 6.05 (s, 1H, enolic), 6.30 (d, $J=1.5\text{Hz}$, 1H) and 6.66 (d, $J=1.5\text{Hz}$, 1H).

Mass (m/e): 380 (M^+), 349, 346, 318, 207, 178, 150, 135 and 78.

REFERENCES

1. W.A. Ayer, S.P. Lee, A. Tsuneda and Y. Hiratsuka,
Can. J. Microbiol., **26**, 766 (1980).
2. R.N. Mirrington, F. Ritche, C.W. Shoppee, S. Strenhell
and W.C. Taylor,
Aust. J. Chem., **19**, 1265 (1966).
3. W.A. Ayer and L.P. Rodriguez,
Phytochemistry, **26**, 1353 (1987).
4. G. Evans and N.H. White,
Trans Br. Micol. soc., **49**, 563 (1966).
5. W.H. Urry, H.L. Wehrmeister, E.B. Hodge and P.H. Hide,
Tetrahedron Lett., 3109 (1966).
6. a) R.N. Mirrington, E. Ritchie, C.W. Shoppee,
W.C. Taylor and S. sternhell,
Tetrahedron Lett., 365 (1964).
b) F. McCapra, A.I. Scott, P. Delmotte and J. Delmotte-
plaguee,
Tetrahedron Lett., 869 (1964).
7. H. Oyama, T. Sassa and M. Ikeda,
Agri. Biol. Chem., **42**, 2407 (1978).
8. J.H. Brewster,
Tetrahedron, **13**, 106 (1961).
9. E.J. Corey and D. Seebach,
J. Org. Chem., **40**, 231 (1975).
10. G. Stork and L. Maldonado,
J. Amer. Chem. Soc., **93**, 5286 (1971).

11. a) S.F. Dyke, E.P. Tiley, A.W.C. White and D.P. Gale,
Tetrahedron, **31**, 1219 (1975).
b) P.P.Latey and V.H. Deshpande,
Indian J. Chem., **25(B)**, 299 (1986).
12. I.M. Godfrey, M.V. Sargent and J.A. Elix,
J. Chem. Soc., Perkin-I, 1353 (1974).
13. Y.F. Cheung,
Tetrahedron Lett., 3809 (1979).
14. F.M. Houser and R.P. Rhee,
J. Org. Chem., **42**, 4155 (1977).
15. G.A. Olah, A. Husain, B.P. Singh and A.K. Mehrota,
J. Org. Chem., **48**, 3667 (1983).
16. Stereoelectronic effects in organic chemistry,
Chapter 3,
P. Deslongchamps, Pergamon Press (1983).
17. R.W. Noire and R.W. Rranck,
Synthesis, 882 (1980).
18. a) U. Wannagat and H. Niederprum,
Chem. Ber., **94**, 1540 (1961).
b) T. Takahashi, I. Minami and J. Tsuji,
Tetrahedron Lett., 2651 (1981).
19. a) F.M. Hauser and R.P. Rhee,
Synthesis, 245 (1977).
b) F.M. Hauser and R.P. Rhee,
J. Am. Chem. Soc., **99**, 4533 (1977).
20. T.R. Kelly, C.T. Jagoe and Q. Li,
J. Am. Chem. Soc., **111**, 4522 (1989).

21. a) R. Robertson and R. Robinson,
J. Chem. Soc., 2196 (1927).
b) R.G. Curtis, I. Heibron, E.R.H. Jones and G.F. Woods,
J. Chem. Soc., 457 (1953).
22. E.J. Corey and K.C. Nicolaou,
J. Am. Chem. Soc., **96**, 5614 (1974).
23. E.J. Corey and D.G. Brunelle,
Tetrahedron Lett., 3409 (1976).
24. a) J. Inanaga, K. Hirata, H. Saeki, T. Katsuki and
M. Yamaguchi,
Bull. Chem. Soc. Jpn., **52**, 1989 (1979).
b) M. Hikota, H. Tone, K. Horita and O. Yonemitsu,
J. Org. Chem., **55**, 7 (1990).
c) M. Hikota, H. Tone, K. Horita and O. Yonemitsu,
Tetrahedron, **46**, 4613 (1990).
25. a) P.A. Grieco, M. Nishizawa, T. Oguri, S.D. Burke,
N. Marinovic,
J. Am. Chem. Soc., **99**, 5778 (1977).
b) G. Solladie, A. Rubio, M. Carreno and J.L.G. Ruano,
Tetrahedron Asymmetry, **1**, 187 (1990).
26. E.N. Jacobsen, I. Marko, W.S. Mungall, G. Schroder and
K.B. Sharpless,
J. Am. Chem. Soc., **110**, 1968 (1988).
27. Organic Synthesis, **53**, 90 (1973).
28. J.F. Kingston and L. Weiter,
Can. J. Chem., **55**, 785 (1977).
29. H. Brockmann, F. Kluge and H. Muxfeldt
Chem. Ber., **90**, 2302 (1957).

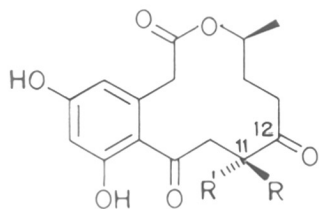
CHAPTER V

SYNTHESIS OF ($\pm$)DI-O-METHYL-12-OXOCURVULARIN

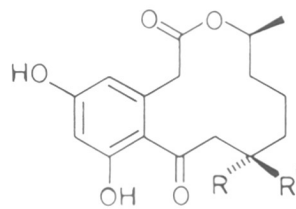
INTRODUCTION:

Recently Yamamura et al.¹ reported several curvularin-type metabolites of a hybrid strain ME 0005 derived from Penicillium citreo-viride B. In addition to the known curvularin (3) and trans-dehydrocurvularin (6), a number of new metabolites, viz. 12-oxocurvularin (1), 11- β -hydroxy-12-oxocurvularin (2), 11- α -hydroxycurvularin (4), 11- β -hydroxycurvularin (5), cis-dehydrocurvularin (7) and citreofuran (8) have been isolated. Their structures have been elucidated on the basis of chemical evidence together with spectral data. Curvularin and trans-dehydrocurvularin were isolated in 1956 from the curvularin species.² However, no curvularin-type metabolite was isolated from the mycelium of P. citreo-viride B. till now. This is the first instance, where the isolation of a curvularin-type metabolite from P. citreo-viride B. has been reported. Among the curvularins, 12-oxo-curvularin, citreofuran, 11- α and 11- β -hydroxy curvularins show remarkable activity against sea urchin embryo cell.¹ Interestingly, 12-oxo-curvularin, citreofuran and 11- β -hydroxy-12-oxo-curvularin possess an unusual oxygen function at C-12 position in their structures. It has been shown that 12-oxocurvularin (1) on treatment with cesium hydroxide in benzene gets readily converted into citreofuran (8).

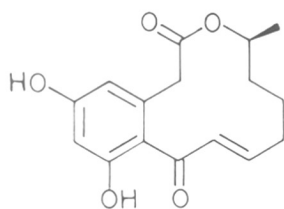
Although several syntheses of curvularin (3) are known, the synthesis of 12-oxo-curvularin (1) has not been reported. In the present work the synthesis of ($\pm$)-di-O-methyl-12-oxocurvularin (43) is described.



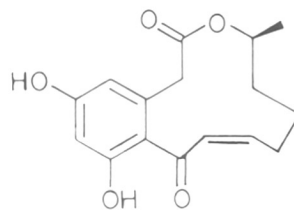
- 1 $R = R' = H$
2 $R = OH, R' = H$



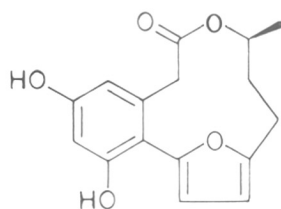
- 3 $R = R' = H$
4 $R = OH, R' = H$
5 $R = H, R' = OH$



6

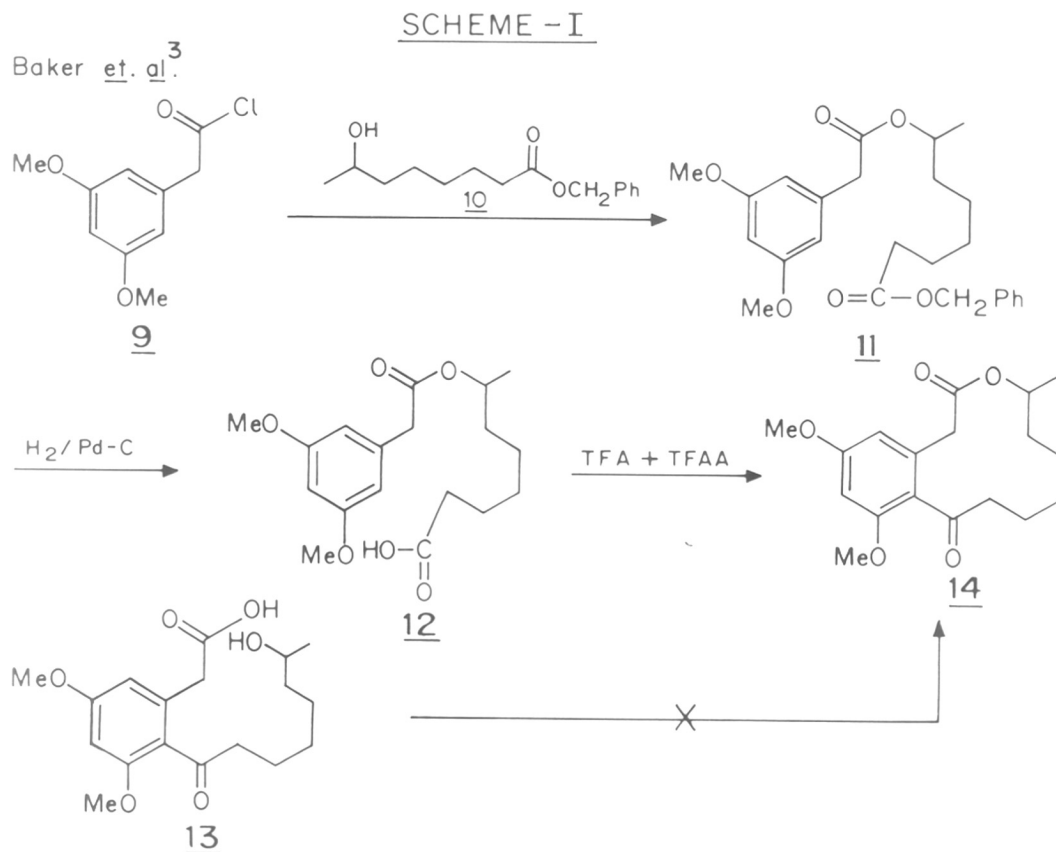


7



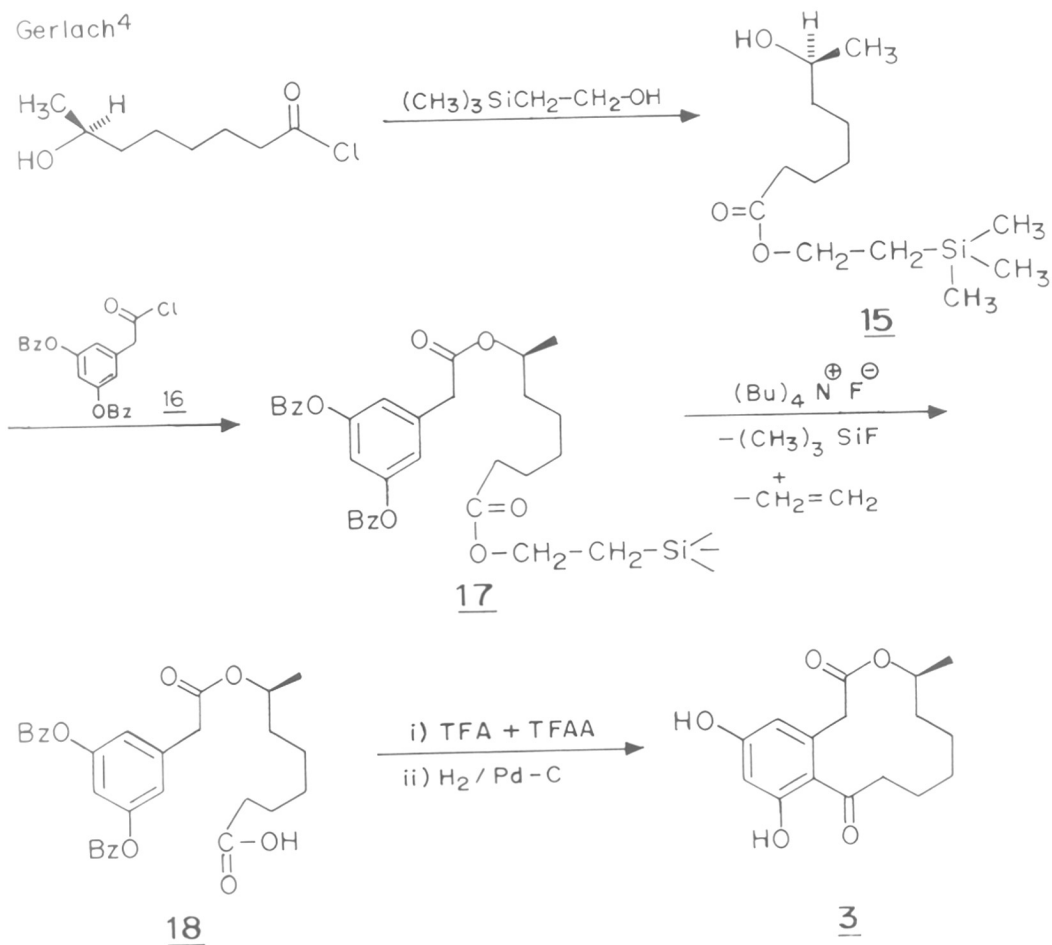
8

The first synthesis of ($\pm$)-di-O-methyl curvularin (**14**) was reported in 1967 by Baker *et al.*³ (SCHEME I). Initially, they attempted macrolactonization of the hydroxy acid (**13**) with trifluoroacetic anhydride and dicyclohexylcarbodiimide under a variety of conditions. Finally the synthesis of (**14**) was successfully achieved by intramolecular Friedel-Crafts acylation. Benzyl 7-hydroxyoctanoate (**10**) was treated with 3,5-dimethoxyphenylacetyl chloride (**9**) to yield the ester (**11**) which on hydrogenolysis afforded the acid (**12**). Its intramolecular Friedel-Crafts acylation with TFA-TFAA afforded ($\pm$)-di-O-methyl curvularin (**14**) in 14% yield (SCHEME I).



Total synthesis of naturally occurring S-(-)-curvularin was reported by Gerlach.⁴ He made use of S-(-)- γ -valerolactone. S-(+)-2-(Trimethylsilyl)ethyl 7-hydroxyoctanoate (**15**) prepared from S-(-)- γ -valerolactone was esterified with 3,5-dibenzyl-oxyphenyl acetyl chloride (**16**) to form (**17**) having two different ester groups. The selective deprotection of the 2-(trimethylsilyl) ethyl ester with tetrabutylammonium fluoride in THF gave the acid (**18**), which on intramolecular acylation (TFA + TFAA) followed by debenzoylation (10% Pd-C, MeOH-THF) afforded the desired S-(-)-curvularin (**3**) (SCHEME II).

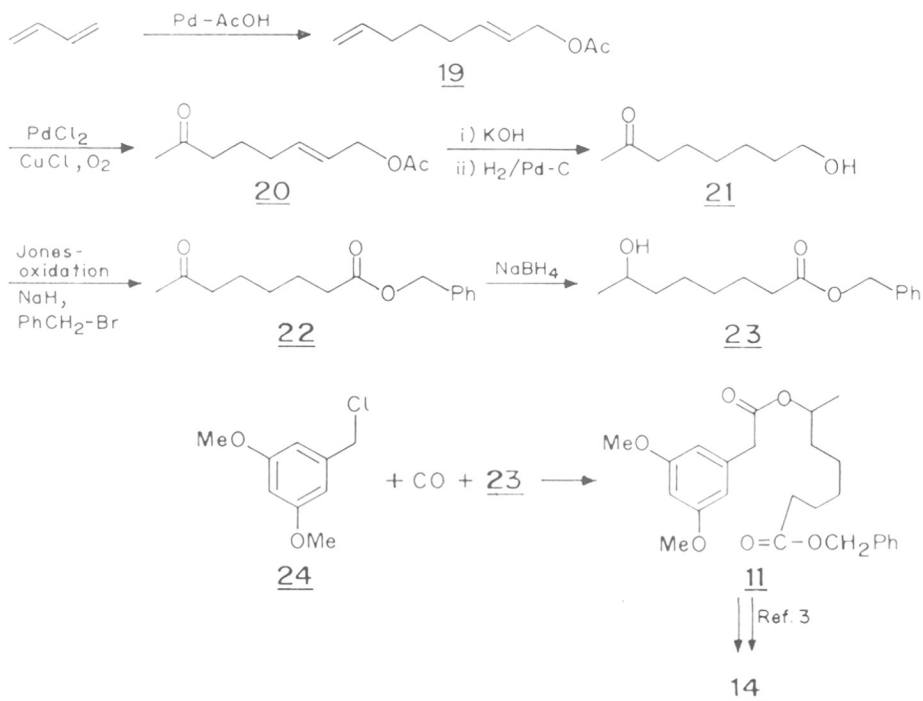
SCHEME-II



Synthesis of (+)di-O-methyl curvularin reported by Tsuji et al.⁵ was based on the palladium-catalysed carbonylation of 3,5-dimethoxybenzyl chloride (**24**) using a butadiene telomer as a building block (SCHEME III). The Pd-catalysed telomerization of butadiene with acetic acid afforded the telomer (**19**) which was converted into benzyl 7-hydroxyoctanoate (**23**) in four steps. Palladium-catalysed carbonylation of 3,5-dimethoxybenzyl chloride (**24**) with benzyl 7-hydroxyoctanoate (**23**) afforded the benzyl 7(3,5-dimethoxyphenyl acetoxyl) octanoate (**11**) in good yield. The conversion of (**11**) to (+)di-O-methylcurvularin is a known process.³

SCHEME-III

Tsuji et.al.⁵

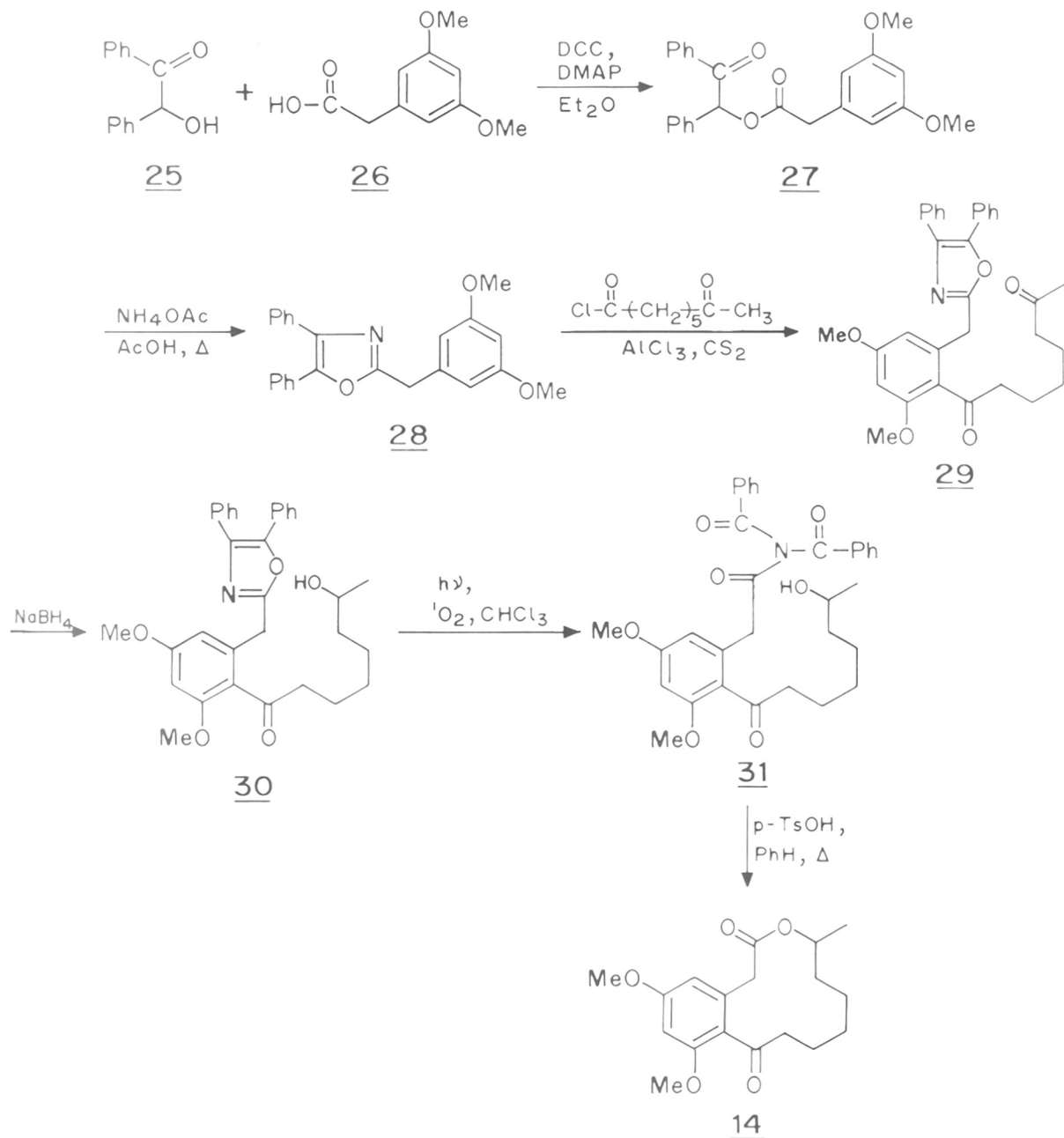


Wasserman *et al.*⁶ reported the synthesis of (±)-di-O-methyl curvularin by intramolecular esterification of an activated carboxylate derived from the photo-oxygenation of an oxazole precursor (SCHEME IV). Earlier workers achieved the synthesis of curvularin through an intramolecular acylation reaction. However, despite a number of attempts, the formation of curvularin system via macrolactonization with various reagents from the hydroxy acid precursor was not successful.

The treatment of 3,5-dimethoxyphenyl acetic acid (26) with benzoin (25) in the presence of DCC/DMAP gave ester (27) which on refluxing with ammonium acetate in acetic acid gave oxazole (28). The Friedel-Crafts acylation of (28) with 7-oxo-octanoyl chloride using aluminium trichloride in carbon disulphide gave diketo oxazole (29), which on selective reduction of the aliphatic ketone provided hydroxy oxazole (30). Photo-oxygenation of the hydroxy oxazole readily yielded triamide intermediate (31). It was then allowed to cyclize under high dilution conditions in presence of *p*-toluene sulphonic acid in refluxing benzene to afford (±)di-O-methyl curvularin (14) (30%) (SCHEME IV).

Recently Subba Rao *et al.*⁷ reported the formal synthesis of (±)curvularin involving the preparation of an acyclic precursor (34) using one pot[^] Alder-Rickert reaction from 1,3-dimethoxy cyclohexa-1,3-diene (32) and long chain acetylenic dienophile (33). The cycloaddition reaction with a mixture of conjugate diene (32) and acetylenic dienophile (33) afforded a product which on hydrolysis gave aromatic acyclic precursor (34).

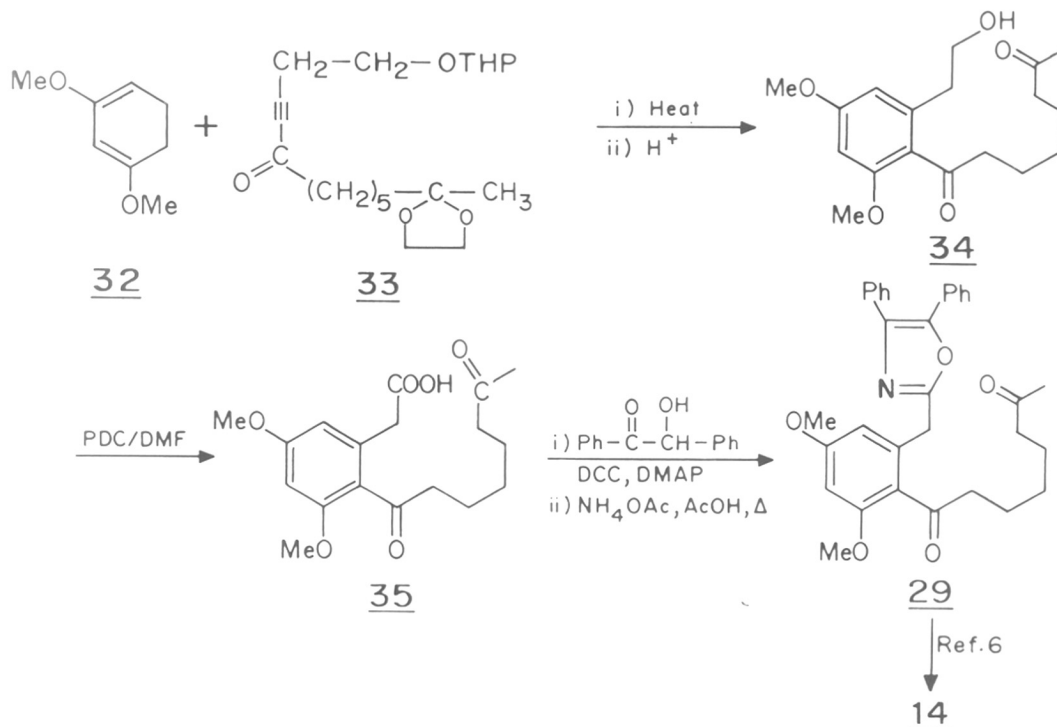
SCHEME-IV

Wasserman and Gambale⁶

Mild oxidation of (34) using PDC in DMF furnished diketo acid (35) in good yield. The reaction of the diketo acid (35) with benzoin afforded the benzoin ester which was refluxed with NH_4OAc in AcOH to give diphenyl oxazole (29). Since the same intermediate has been converted into ($\pm$)-14 by Wasserman *et al.*⁶ this was taken to constitute a formal synthesis of ($\pm$)-di-O-methyl curvularin (SCHEME V).

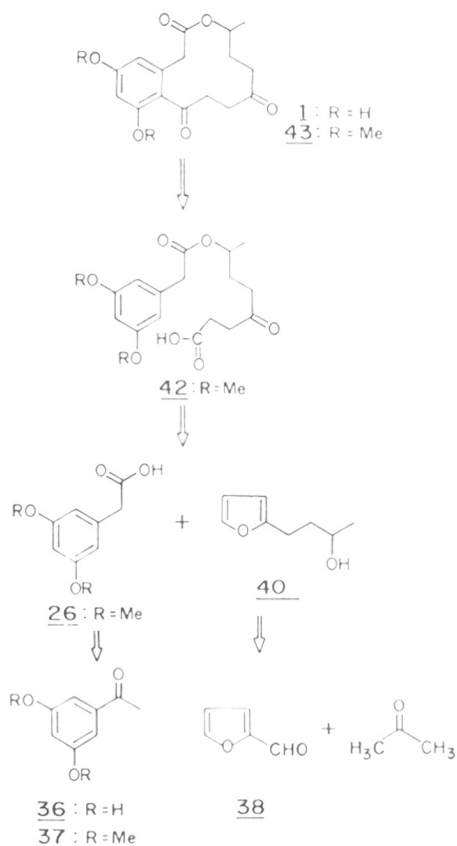
SCHEME -V

Subba Rao *et al.*⁷



PRESENT WORK:

12-Oxo-curvularin is a 12-membered macrolide containing 1,4-diketo system in the macrocyclic ring. Retrosynthetic analysis, as shown in the SCHEME VI, clearly indicates that it can be synthesised from the substituted phenylacetic acid (26) and C-8 carbon unit (40). The desired phenylacetic acid can be easily prepared from 3',5'-dihydroxyacetophenone while C-8 carbon unit (40) could be obtained from the condensation product of 2-furfural (38) and acetone.

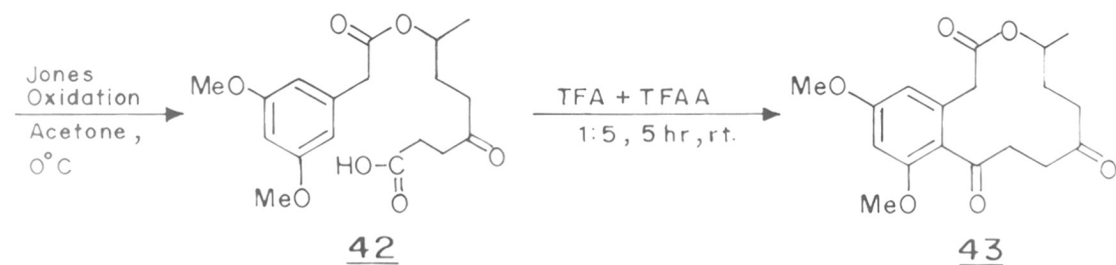
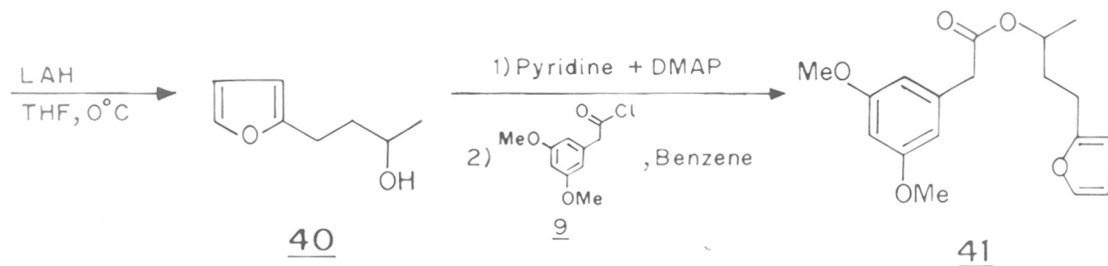
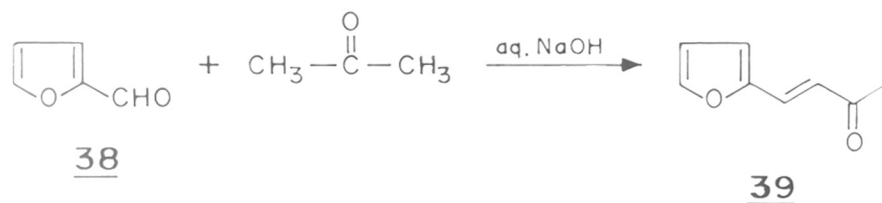
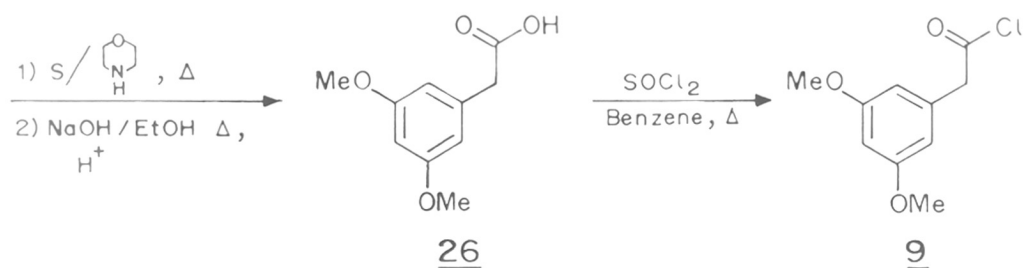
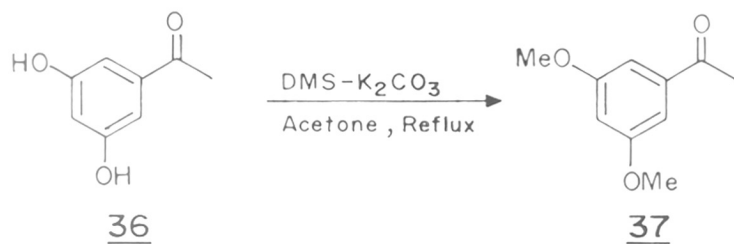
RETROSYNTHETIC ANALYSISSCHEME VI

Methylation of 3',5'-dihydroxyacetophenone (36) with dimethylsulphate and potassium carbonate in refluxing acetone afforded 3',5'-dimethoxyacetophenone (37) in quantitative yield. The treatment of 3',5'-dimethoxyacetophenone with sulphur and morpholine (Willgerodt reaction)⁹ at reflux temperature for 18 hours followed by hydrolysis with sodium hydroxide in ethanol at reflux temperature for 12 hours and acidification gave (3,5-dimethoxyphenyl)acetic acid (26) in 54% yield. It was characterised by spectral analysis. In the ¹H-NMR spectrum it showed singlet at δ 3.54 for the presence of ArCH₂. Infra-red spectrum showed a broad absorption at 3400 cm⁻¹ (-COOH) and at 1720 cm⁻¹ for the carboxyl group. The mass spectrum showed a molecular ion at 196 (M⁺). The acid (26) showed m.p. 100-101°C in agreement with the reported literature⁸ value of 100-102°C. (SCHEME VII).

In order to obtain the C-8 unit of the aliphatic portion, 4-(2-furyl)butan-2-ol (40) was prepared by condensation of 2-furfural (38) and acetone.⁹ The treatment of acetone with 2-furfural (38) in presence of aqueous NaOH afforded after distillation 4-(2-furyl)-3-buten-2-one (39) as a low melting solid. The reduction of the α,β -unsaturated ketone (39) with lithium aluminium hydride in THF at 0°C furnished the saturated alcohol (40).

(3,5-Dimethoxyphenyl)acetic acid (26) was converted into its acid chloride (9) with thionyl chloride in refluxing benzene. The resulting acid chloride (9) was added to the alcohol (40) in dry benzene containing equimolar quantity of

SCHEME-VII



pyridine and catalytic amount of DMAP. The crude product was purified by silica gel column chromatography to give the desired ester (**41**) as a low melting solid in 75% yield (NMR: FIG. 1).

The crucial step in the synthesis was the oxidative ring cleavage of 2-substituted furan to give 4-keto acid system. A number of methods have been used to perform this type of reaction. Considerable attention has been paid to synthesise cis or trans enediones by oxidative ring cleavage or acid catalysed hydrolysis of furans especially 2,5-di-substituted furans. The methods that have been used successfully are as follows.

1. **Oxidative conversion of 2,5-disubstituted furans into 1,4-enediones and 1,4-diketones:**

(a) Oxidation of 2,5-disubstituted furans with acetyl nitrate¹⁰ or bromine in methanol¹¹ followed by hydrogenation produced 1,4-diketones (SCHEME VIII).

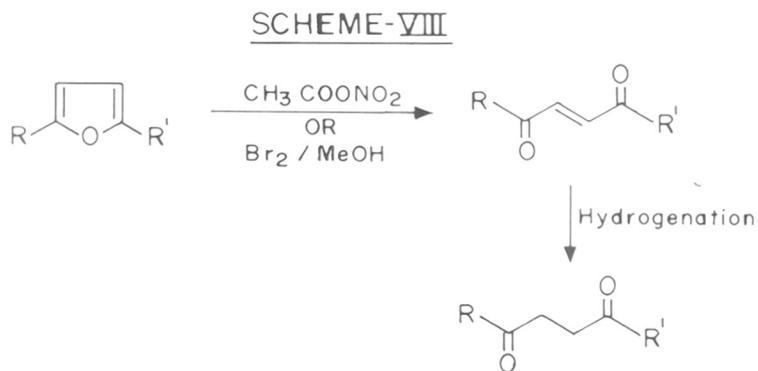
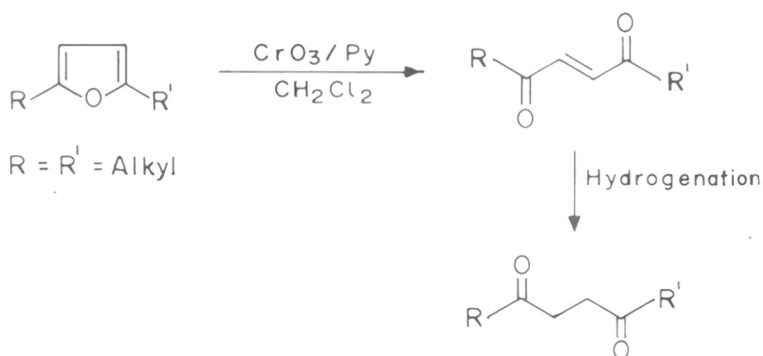


FIG.1: ^1H -NMR SPECTRUM OF THE COMPOUND (41) IN CDCl_3

These methods are unsatisfactory in certain cases because of poor yields in oxidation, necessity to carry out a catalytic hydrogenation which may possibly affect other double bond in the system or the competitive bromination or oxidation of other reaction centres.

(b) Oxidation of substituted furans with Collin's reagent¹² converts 2,5-dialkylfurans into enediones. The enediones on hydrogenation afford 1,4-diketo systems (SCHEME IX).

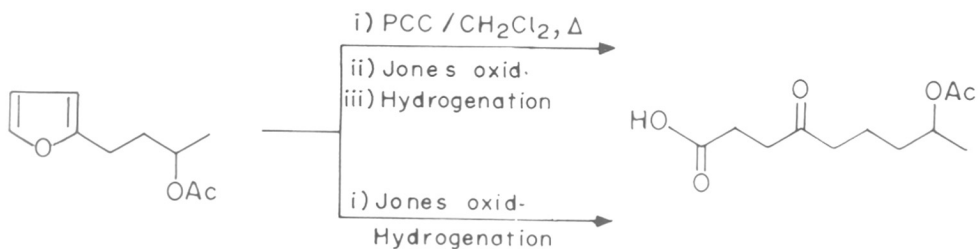
SCHEME - IX



(c) Oxidation of furan ring by PCC/Jones reagent:

Monosubstituted furan on treatment with PCC in refluxing CH_2Cl_2 yielded 1,4-enedione system,^{9a,b} which on treatment with Jones reagent followed by hydrogenation gave 4-keto acid (SCHEME X).

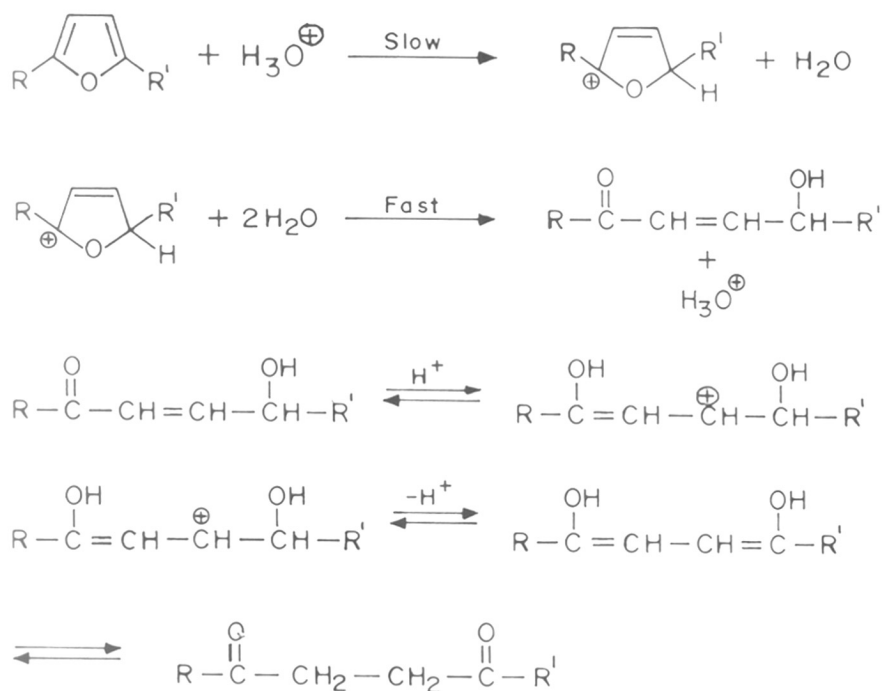
SCHEME - X



2. Hydrolytic cleavage of furans:

Alkylfurans may be readily opened to 1,4-diketones under acidic conditions.^{13,14} Furans with electron-withdrawing substituents are generally resistant to acid-attack. The first step of the reaction involves the protonation at an α -position rather than oxygen (SCHEME XI).

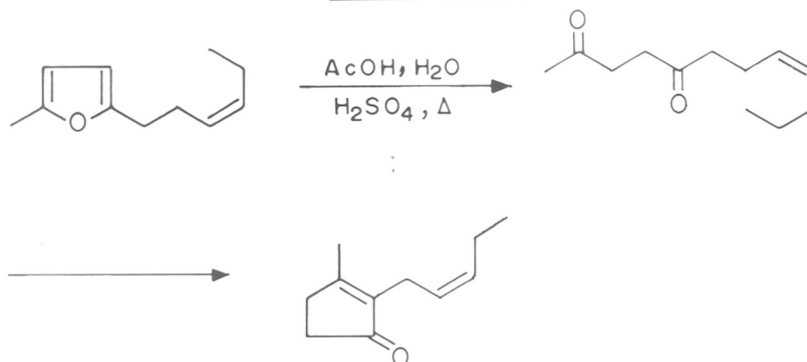
SCHEME -XI



Where $\text{R} = \text{H}$, Alkyl ; $\text{R}' = \text{CH}_3$

On the similar line, disubstituted furans were opened in the synthesis of cis-Jasmone¹⁵ (SCHEME XII).

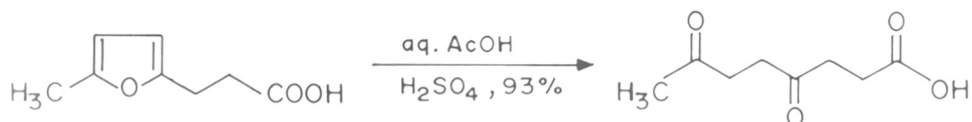
SCHEME-XII



Cis - JASMONE

Hydrolytic cleavage of 2,5-disubstituted furan in aqueous acetic acid containing a few drops of sulphuric acid led directly to saturated diketo acid in 93% yield (SCHEME XIII).

SCHEME-XIII



From the above reactions, disubstituted furans can be opened to a saturated 1,4-dicarbonyl functionality where the substituent may be either R=H or alkyl (SCHEME XI). If the R=H, it would be possible to get the aldehyde. The resulting aldehyde could then be converted into acid. Therefore it was decided to use Jones reagent ($\text{CrO}_3/\text{H}_2\text{SO}_4/\text{H}_2\text{O}$) in acetone as solvent which would open the 2-substituted furan ring to saturated 4-keto-aldehyde derivative; the Jones reagent present in the system may convert it into 4-keto acid.

Thus the furan ester (41) (SCHEME VII) was treated with Jones reagent at 0°C for 2 hours. Usual work up and chromatographic purification gave an acid which was characterised as (42) with the help of spectral studies. The $^1\text{H-NMR}$ spectrum of the acid showed the absence of protons due to furan as well as olefinic protons and showed the presence of three methylene protons at δ 2.17-2.48 ($2 \times \text{CH}_2$) and δ 2.50-2.84 ($-\text{CH}_2$). The broad absorption in IR spectrum at 3400 cm^{-1} indicated the presence of COOH group. Mass spectrum revealed molecular ion at m/e 352 (M^+) along with other characteristic peaks (FIG. 2).

Having thus obtained the required 4-keto acid system (42), its cyclization was carried out by known method i.e. by using trifluoroacetic acid and trifluoroacetic anhydride in 1:5 ratio at room temperature for 5 hours. Purification of the product by alumina column chromatography afforded 12-oxo-curvularin as a dimethyl ether (43) in 16% isolated yield.

The spectral data of (43) were in full agreement with the assigned structure. In the IR spectrum, the compound exhibited bands at 1745, 1730 and 1610 cm^{-1} . Its $^1\text{H-NMR}$ spectrum showed a broad doublet centred at 6.34 for two aromatic protons along with other required peaks (FIG. 3). The mass spectrum showed the molecular ion at m/e 334.

In conclusion, a short, simple and the first synthesis of di-O-methyl-12-oxo-curvularin (43) has been described in this chapter. The highlight of the methodology is that the use of protection-deprotection in the synthetic sequence has been completely avoided.

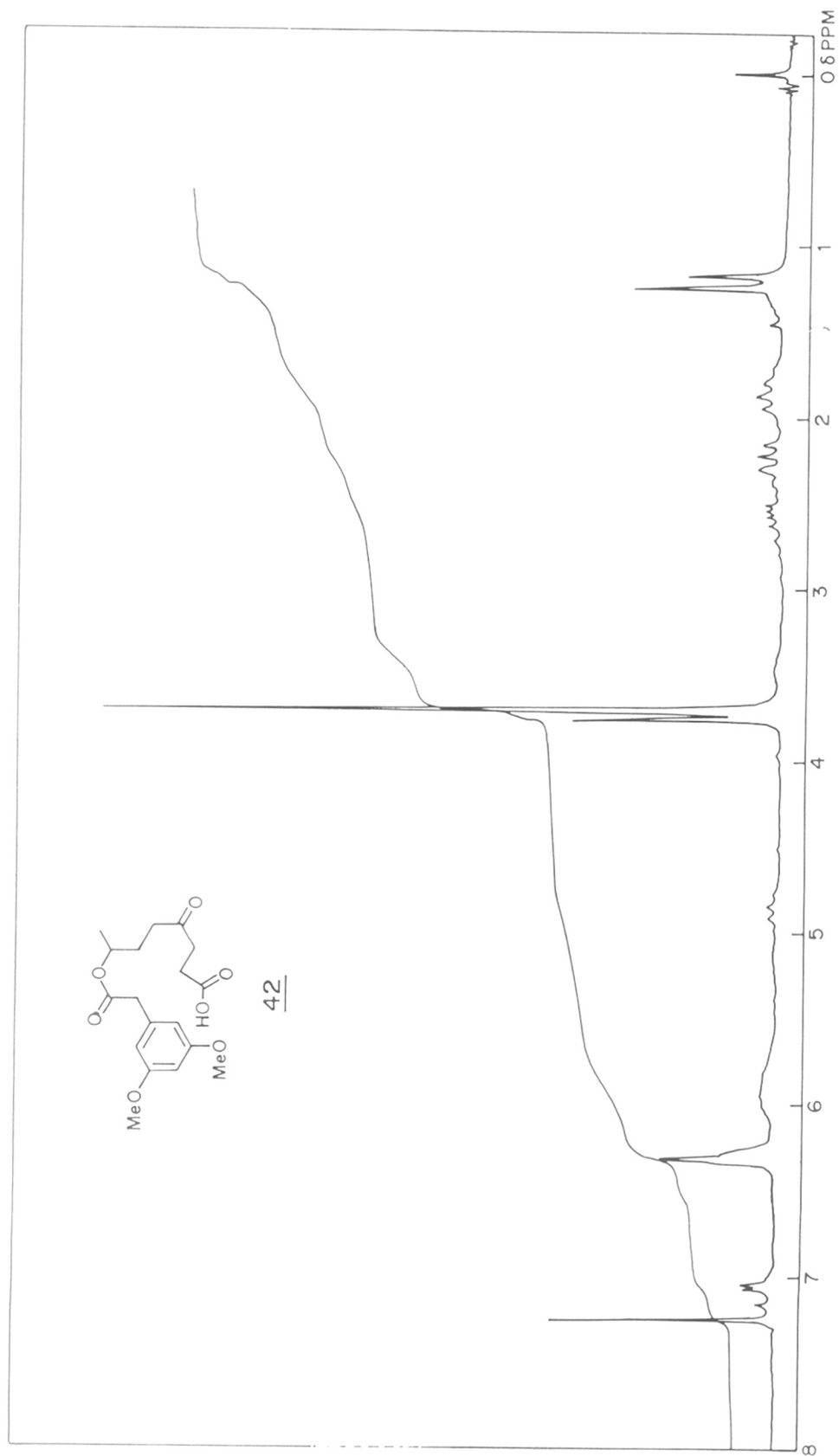


FIG. 2: ¹H-NMR SPECTRUM OF THE COMPOUND (42) IN CDCl₃

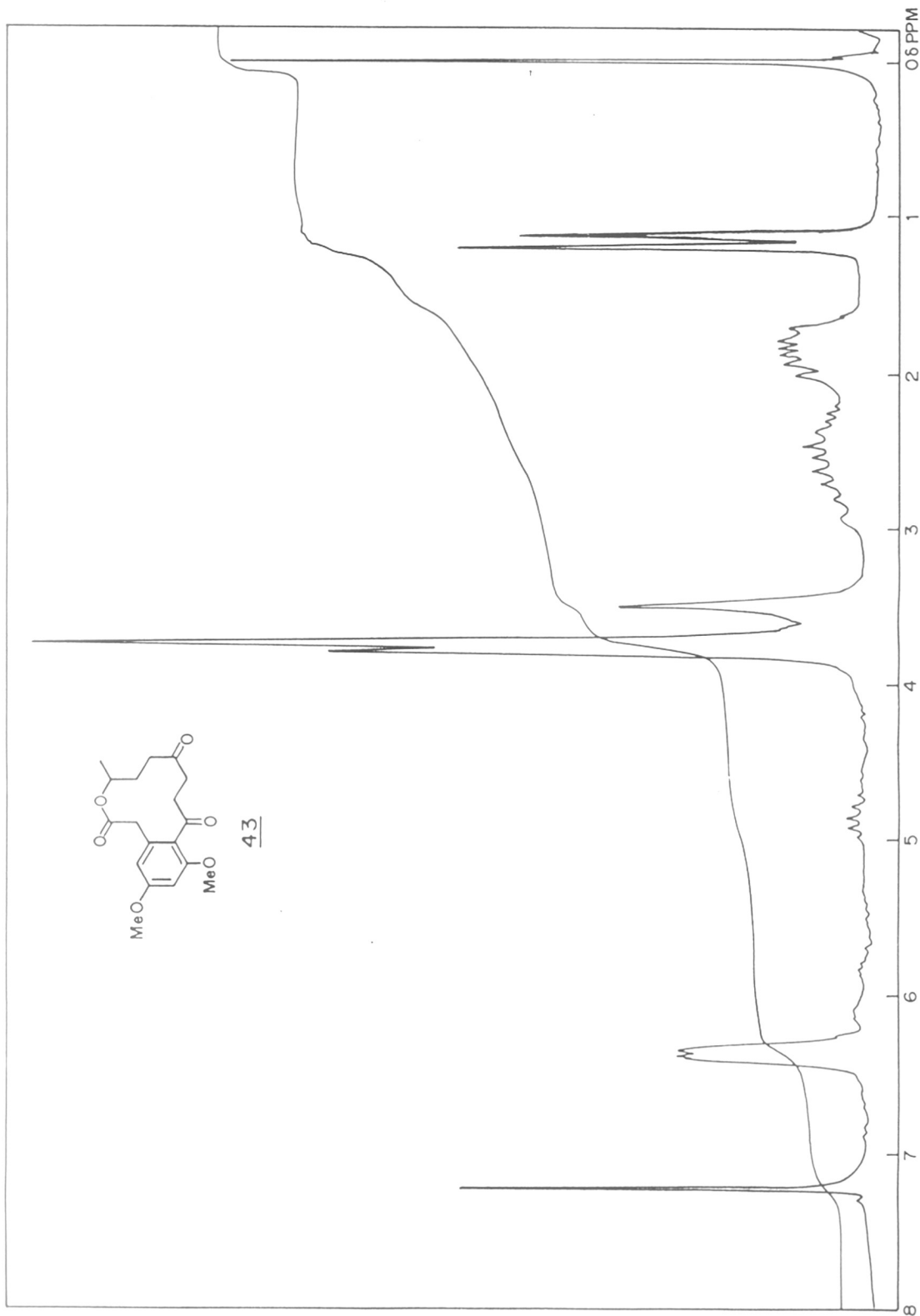


FIG.3: ¹H-NMR SPECTRUM OF THE COMPOUND (43) IN CDCl₃

EXPERIMENTAL

3',5'-Dimethoxyacetophenone (37):

A mixture of the 3',5'-dihydroxyacetophenone **36** (40 g, 0.263 mol), dimethylsulphate (73 g, 0.579 mol) and potassium carbonate (80 g, 0.579 mol) in dry acetone (500 ml) was heated at reflux temperature for 10 h. The acetone was distilled off, water was added into the reaction mixture and stirred for 2 h. It was extracted with ethyl acetate (2 x 200 ml), washed with brine, dried (Na_2SO_4) and the solvent was removed under reduced pressure to afford 3',5'-dimethoxyacetophenone as a yellow viscous oil (46 g, 97%) which was used for next step without further purification.

$^1\text{H-NMR}$: δ 2.55 (s, 3H, COCH_3), 3.82 (s, 6H, $2\times\text{OCH}_3$), 6.62 (t, $J=2\text{Hz}$, 1H), 7.06 (d, $J=2\text{Hz}$, 2H).

Mass (m/e): 180 (M^+), 165, 137, 122, 107 and 77.

(3,5-Dimethoxyphenyl)acetic acid (26):

A mixture of 3',5'-dimethoxyacetophenone **37** (45 g, 0.25 mol), sulphur powder (12 g, 0.375 mol) and morpholine (27 g, 0.31 mol) was heated under reflux for 18 h and poured in cold water. The brown coloured thick semi-solid obtained was washed thoroughly with water. To the crude thiomorphonilide so obtained was added 10% ethanolic sodium hydroxide (500 ml) and the mixture was heated at reflux temperature for 12 h. The excess ethanol was removed under reduced pressure, the residue was diluted with water and acidified with concentrated HCl. The

precipitated solid was filtered, washed with cold water and dried to afford (3,5-dimethoxyphenyl) acetic acid **26** (26.5 g, 54%) after crystallisation from water; m.p. 100-101°C (lit.^{8b} m.p. 100-102°C).

IR (nujol): 3400 (br), 1710 and 1610 cm^{-1} .

¹H-NMR: δ 3.54 (s, 2H, Ar-CH₂), 3.73 (s, 6H, 2xOCH₃), 6.38 (m, 3H, Ar-H).

Mass (m/e): 196 (M⁺), 182, 152, 121, 91, 77.

4-(2-Furyl)-3-buten-2-one (**39**):

To a stirred solution of furfural **38** (40 g, 416.1 mmol), water (300 ml) and acetone (62 ml, 1.06 mol) at 0°C was added dropwise an aqueous solution of sodium hydroxide (7 ml, 33%) over 30 min. The stirring was continued for additional 4 h at room temperature. It was then acidified with dil. H₂SO₄ (10%) to pH 5. The organic layer was separated, dried (Na₂SO₄) and distilled under reduced pressure to yield the low melting solid **39** (36.8 g, 65%); b.p. 86-89°C/2 mm; m.p. 36-38°C (lit.^{9a} b.p. 114-116°C/10 mm; lit.^{9a} m.p. 37-39°C).

¹H-NMR: δ 2.30 (s, 3H, COCH₃), 6.44-6.68 (m, 3H), 7.20-7.8 (m, 2H).

4-(2-Furyl)-buten-2-ol (**40**):

To a stirred slurry of LAH (0.7 g, 18.38 mmol) in dry THF (40 ml) under nitrogen atmosphere, was added 4-(2-furyl)-3-buten-2-one **39** (5 g, 36.38 mmol) in dry THF (10 ml) at 0°C over 30 min. The stirring was continued for additional 2 h. The excess LAH was destroyed with ethyl acetate (10 ml) followed by

a saturated solution of sodium sulphate (20 ml). The resultant solid was filtered through celite and washed with ethyl acetate (100 ml). The filtrate was dried (Na_2SO_4) and the solvent was removed on rotavapour. The residue was distilled under reduced pressure to yield a colourless liquid **40** (2.6 g, 50%); b.p. 81-84°C/2.5 mm (lit.^{9a} b.p. 71-72°C/2 mm).

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

¹H-NMR: δ 1.17 (d, $J=6.5\text{Hz}$, 3H, CH_3), 1.77 (m, 2H, CH_2), 2.73 (t, 2H, CH_2), 3.80 (m, 1H, CH), 5.93 (m, 1H, Fu-H), 6.20 (m, 1H, Fu-H), 7.20 (m, 1H, Fu-H).

(±)[4-(2-Furyl)-butan-2-ol]]3,5-dimethoxyphenyl acetate (**41**):

Thionyl chloride (4.3 ml, 39.2 mmol) was added to a stirred solution of (3,5-dimethoxyphenyl)acetic acid **26** (7.69 g, 39.2 mmol) in dry benzene (50 ml) at room temperature. It was then refluxed for 2 h. The excess thionyl chloride along with the benzene was distilled off. The resultant acid chloride was dissolved in dry benzene (10 ml) and added to the stirred solution of alcohol **40** (5 g, 35.7 mmol), pyridine (4 g, 50.63 mmol) and catalytic amount of 4-DMAP in dry benzene (40 ml) under nitrogen atmosphere. The stirring was continued for 10 h at room temperature. The reaction mixture was quenched with water and the product was extracted with ethyl acetate (2x100 ml). The ethyl acetate extract was dried (Na_2SO_4) and the solvent was distilled off. The residue was purified by silica gel column chromatography (eluent 5% acetone in pet. ether) to afford **41** as a viscous oil (8.6 g, 75.7%).

IR (neat): 1735, 1610 cm^{-1} .

$^1\text{H-NMR}$: δ 1.22 (d, $J=6\text{Hz}$, 3H, CH_3), 1.88 (m, 2H, CH_2), 2.57 (t, 2H, CH_2), 3.78 (s, 6H, $2\times\text{OCH}_3$), 3.80 (s, 2H, Ar- CH_2), 4.88 (m, 1H, CH-CH_3), 5.88 (m, 1H, Fu-H), 6.11 (m, 1H, Fu-H), 6.36 (m, 2H, Ar-H) and 7.10-7.31 (m, 2H, Ar-H and Fu-H).

Mass (m/e): 318, 304, 196, 151, 122, 107, 91, 81, 77.

Analysis Calc. for $\text{C}_{18}\text{H}_{22}\text{O}_5$: C, 67.92; H, 6.91;

Found: C, 67.88; H, 6.89%

7-(3,5-Dimethoxyphenylacetoxy)-4-oxo-octanoic acid (42):

To an ice-cold solution of the furan ester **41** (4.2 g, 13.20 mmol) in acetone (150 ml) was added Jones reagent⁹ (6.5 ml) with stirring over 20 min and further stirred at the same temperature for 2 h. The supernatant clear solution was decanted and the residue was washed with acetone (2 x 20 ml). The combined acetone solution was distilled under reduced pressure and the residual product was purified by column chromatography (eluent 30% ethyl acetate in pet. ether) to give required acid **42** (3.1 g, 67%) as viscous oil.

IR (neat): 3500 (br), 1735, 1730, 1715 and 1610 cm^{-1} .

$^1\text{H-NMR}$: δ 1.22 (d, $J=6.2\text{Hz}$, 3H, $-\text{CH}_3$), 1.67-1.95 (m, 2H, $-\text{CH}_2-$), 2.15-2.66 (m, 4H, $2\times\text{CH}_2$), 2.66-2.84 (m, 2H, CH_2), 3.78 (s, 6H, $2\times\text{OCH}_3$), 3.84 (s, 2H, Ar- CH_2), 4.91 (m, 1H), 6.37 (br.s, 2H, Ar-H) and 7.11 (dd, 1H, Ar-H).

Mass (m/e): 353 (M^+), 296, 282, 216, 196, 178, 139, 101, 77.

Analysis Calc. for $\text{C}_{18}\text{H}_{24}\text{O}_7$: C, 61.36; H, 6.81;

Found: C, 61.06; H, 6.80%

(±)3,5-Di-O-methyl-12-oxocurvularin (43):

Trifluoroacetic acid (1 ml) was added to a solution of the acid 42 (0.130 g, 0.369 mmol) in trifluoroacetic anhydride (5 ml) at room temperature and stirred for 6 h. The reaction mixture was quenched with ice water and the product was extracted with chloroform (2x50 ml). Evaporation of the dried (Na_2SO_4) chloroform solution gave a residue which was purified by column chromatography over neutral alumina (eluent: 20% ethyl acetate in pet. ether) to get the required 3,5-di-O-methyl-12-oxocurvularin (43) (20 mg, 16%).

IR (neat): 1745, 1730, 1610 cm^{-1} .

UV (MeOH, λ max): 220, 275, 300 nm.

$^1\text{H-NMR}$ (CDCl_3): δ 1.17 (d, $J=6.2\text{Hz}$, 3H), 1.72-2.1 (m, 2H), 2.1-2.75 (m, 4H), 3.00 (m, 2H), 3.60 (bs, 2H), 3.71 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.92 (m, 1H), and 6.34 (br.d, 2H, Ar-H).

Mass (m/e): 334 (M^+), 296, 196, 178, 165, 151, 138, 111, 91, and 77,

Analysis Calc. for $\text{C}_{18}\text{H}_{22}\text{O}_6$: C, 64.67; H, 6.58;

Found: C, 64.47; H, 6.60% .

REFERENCES

1. a) S. Lai, Y. Shizuri, S. Yamamura, K. Kawai, Y. Terada
and H. Furukowa,
Tetrahedron Lett., **30**, 2241 (1989).
b) S. Lai, Y. Shizuri, S. Yamamura, K. Kawai, Y. Terada
and H. Furukowa,
Chemistry Lett., 589 (1990).
2. a) O.C. Musgrave,
J. Chem. Soc., 4301 (1956).
b) O.C. Musgrave,
J. Chem. Soc., 1104 (1957).
c) A.J. Birch, O.C. Musgrave, R.W. Rickards and H. Smith,
J. Chem. Soc., 3146 (1959).
3. P.M. Baker, B.W. Bycroft and J.C. Roberts,
J. Chem. Soc. (C), 1913 (1967).
4. H. Gerlach,
Helv. Chem. Acta, **60**, 3039 (1977).
5. T. Takahashi, H. Ikeda and J. Tsuji,
Tetrahedron Lett., **21**, 3885 (1980).
6. H.H. Wasserman and R.J. Gambale,
Tetrahedron Lett., **22**, 4849 (1981).
7. A.J. Birch, N.S. Mani and G.S.R. Subba Rao,
J. Chem. Soc. Perkin Trans-I, 1423 (1990).
8. a) O.P. Vig, S.D. Sharma, N.K. Varma and V.K. Handa,
Indian J. Chem., **15B**, 988 (1977).
b) A.J. Birch and F.W. Donovan,
Austral. J. Chem., **6**, 373 (1953).

9. a) M. Petrini, R. Ballini, G. Rosini and E. Merotta,
Tetrahedron, **42**, 151 (1986).
b) T.K. Ngnooi, A. Scilimati, Z.W. Guo and C.J. Sih,
J. Org. Chem., **54**, 911 (1989).
10. K.Y. Novitskii, V.P. Volkov, Y.M. Il'ina and Y.K. Yur'ev,
J. Gen. Chem. USSR, **33**, 1128 (1963).
11. J. Levisalles,
Bull. Soc. Chim. Fr., 997 (1957).
12. R. Ratcliff and R. Rodehorst,
J. Org. Chem., **35**, 4000 (1970).
13. E.J. Stamhuis, W. Drenth and H. Vandenberg,
Rueueil, **83**, 167 (1964).
14. A.J. Birch, K.S. Koegh and V.R. Mamdapur,
Aust. J. Chem., **26**, 2671 (1973).
15. G. Buchi and Wuest,
J. Org. Chem., **31**, 977 (1966).
16. R.A. Kasar, R.A. Khan, V.H. Deshpande and N.R. Ayyangar,
Tetrahedron Lett., **32**, 1599 (1991).

Publications:

1. A short convergent synthesis of R(±)patulolide A
N.R.Ayyangar, B.Chanda ,R.D.Wakharkar and R.A.Kasar,
Synth.Comm.,**18**,2103 (1988).
2. The synthetic approach to Monocillins.
R.A.Kasar ,R.D.Wakharkar,B.Chanda and N.R.Ayyangar,
17th IUPAC Synposium,New Delhi, 1990.
3. Total Synthesis of Monocillin IV Dimethyl Ether.
R.A.Kasar, R.D.Wakharkar, B.Chanda and N.R.Ayyangar,
Tetrahedron Lett.,**31** 6445 (1990).
4. Total syntheses of Monocillin IV, Nordinone and Nordinone diol
(To be communicated shortly to Tetrahedron)
5. Synthesis of 12-oxo-di-O-methyl curvularin.
R.A.Kasar, R.A.Khan, V.H.Deshpande and N.R.Ayyangar
Tetrahedron lett.**32**,1599 (1991)