SYNTHESIS OF SOME BIOLOGICALLY ACTIVE COMPOUNDS AND SOME NATURAL PRODUCTS

A THESIS

SUBMITTED TO THE

UNIVERSITY OF POONA

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

BY

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JANUARY 1986

Dedicated to my Parents

CERTIFICATE

Certified that the work incorporated in the thesis entitled "SYNTHESIS OF SOME BIOLOGICALLY ACTIVE COMPOUNDS AND SOME NATURAL PRODUCTS" by Mr. S. Pulla Reddy was carried out by the candidate under my supervision. Such material as had been obtained from other sources has been duly acknowledged in the thesis.

(A.V. RAMA RAO)
Supervisor

C O N T E N T S

ACKNOWLEDGEMENTS

It is with great pleasure that I wish to express my warm gratitude to Dr. A.V. Rama Rao, F.N.A., Director, Regional Research Laboratory, Hyderabad and formerly Dy.Director, and Head of the Organic Chemistry Division, National Chemical Laboratory, Poona, for suggesting the problem and for his inspiring guidance and enthusiastic encouragement.

I also owe a debt of gratitude to Dr.V.H. Deshpande for his valuable help and fruitful discussions throughtout the course of this work. I wish to thank Drs.T.Ravindranathan and J.S. Yadav for giving valuable suggestions.

I wish to record my appreciation and grateful thanks to all my colleagues in the laboratory, particularly to Mr. S.P. Chavan, Mr. D.R. Reddy, Mr. E.R. Reddy and Mr.U.R. Peshwe from whom I received help and support in various ways during the course of this work.

I am thankful to Dr.M.K. Gurjar for his constructive comments on the manuscript and to Mr. S.Venkataraman for technical assistance.

Assistance from spectroscopic and microanalytical sections of the laboratory is gratefully acknowledged.

I am thankful to the Director, National Chemical Laboratory, for allowing me to submit this work in the form of a thesis. Financial assistance from Council of Scientific and Industrial Research, New Delhi is gratefully acknowledged.

NCL, Poona 411 008
January 1986

S. Pulla Reddy
(S. PULLA REDDY)

ABSTRACT

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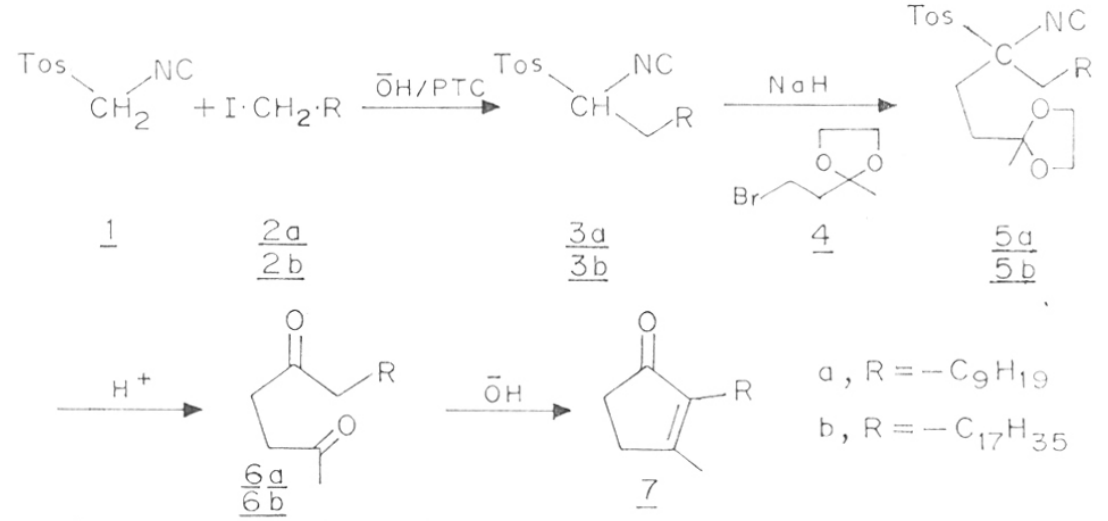
This thesis consists of three Chapters.

Chapter I - Synthesis of 1,4-dicarbonyl compounds: A new methodology

The utility of 1,4-dicarbonyl compounds in the synthesis of a variety of natural products having an incorporated cyclopentenone or a furan ring system has been well-documented in literature. In this chapter, a new methodology for obtaining 1,4-dicarbonyl compounds using TosMIC as a conjunctive reagent has been reported. TosMIC, which is a masked molecule of formaldehyde, can be successively alkylated and then TosMIC functionality could be converted into carbonyl functionality with the use of acid.

Synthesis of pentadecan-2,5-dione (6a) and triecoso-2,5-dione (6b)

Monoalkylation of TosMIC (1) with n-decyliodide (2a) in the presence of a phase transfer catalyst gave 3a. The second alkylation of 3a with the bromide 4 using NaH gave 5a, which on treatment with acid afforded the 1,4-diketone (6a). Base catalysed cyclisation of 6a gave 7. Similarly the 1,4-diketone 6b was synthesised from TosMIC by successive

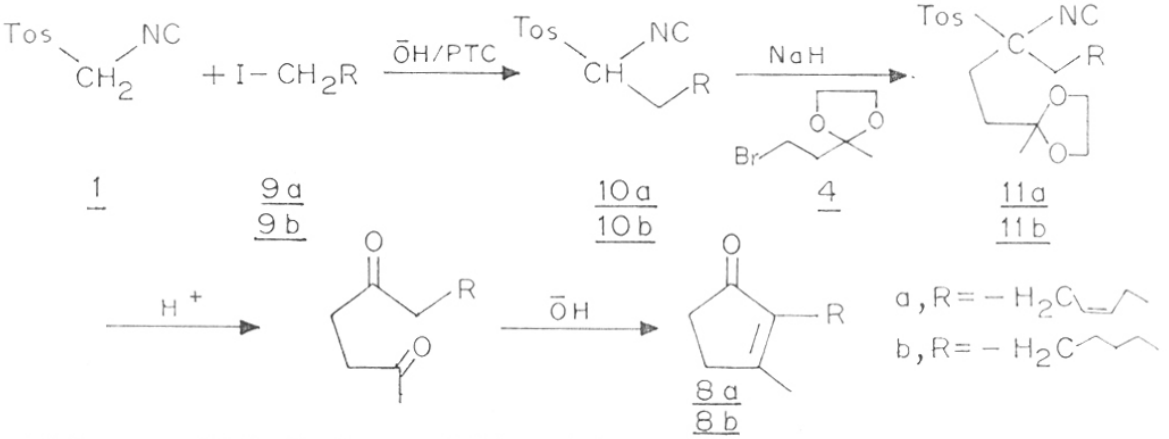


alkylation with halides 2b and 4 respectively.

Synthesis of cis-jasmone and dihydrojasmone

The importance of cis-jasmone and dihydrojasmone in perfume industry has been well recognised and well documented.

Based on the strategy described above cis-jasmone and dihydrojasmone were synthesised from TosMIC. For example, TosMIC was successively alkylated with the iodide 9a and the bromide 4 to afford the dialkylated TosMIC derivative 11a,



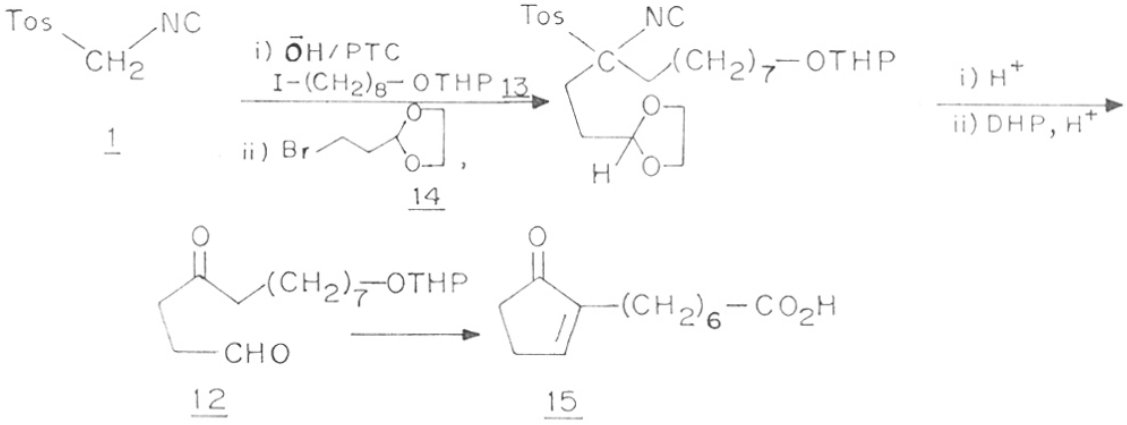
which on acid hydrolysis followed by cyclisation afforded jasmone

(8a). Adopting the same methodology with the alkylhalides, 9b and 4, dihydrojasmone was obtained.

Synthesis of a prostaglandin intermediate (15)

Apart from the fact that methods available for the synthesis of 1,4-diketones are numerous, several of them however could not be employed for the synthesis of 1,4-keto-aldehydes.

In a similar way 1,4-ketoaldehyde 12 was made from TosMIC by employing successive alkylations with the halides 13



and 14 followed by acid hydrolysis. Compound 12 was made use of in the synthesis of (±)-11,15-dideoxy PG_1 and (-)-11-deoxy PGE_1 via the intermediate 15.

Chapter II - Part A: Synthesis of some unsaturated hydroxy fatty acids

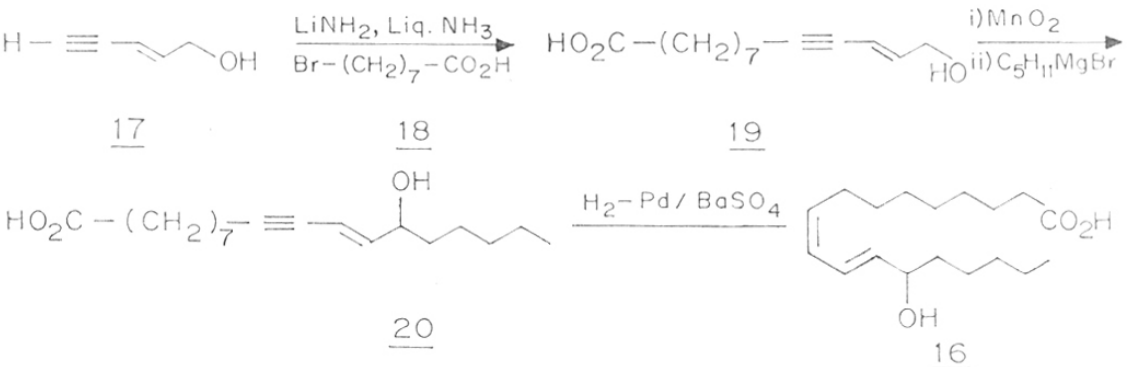
In recent years alkyne derivatives have been frequently used for the synthesis of natural products in particular unsaturated hydroxy fatty acids. Here this approach has been made use of for the synthesis of coriolic acid and recifeiolide.

Section 1 - A short and efficient approach to (±)-Coriolic acid

This section deals with the synthesis of (±)-coriolic acid (16), which is known to have ionophoretic properties coupled with self-defence activity against blast disease in rice plants.

The key intermediate in this synthesis is (E)-pent-2-en-4-yn-1-ol (17) which serves for the elaboration of aliphatic chain as desired and allows the acetylenic bond as a precursor for the cis-double bond.

Alkylation of 17 with the bromoacid 18 gave 19. This



17 18 19 20 16

on oxidation with MnO_2 followed by the treatment with n-pentyl magnesium bromide furnished 20, which on partial hydrogenation gave (±)-coriolic acid (16).

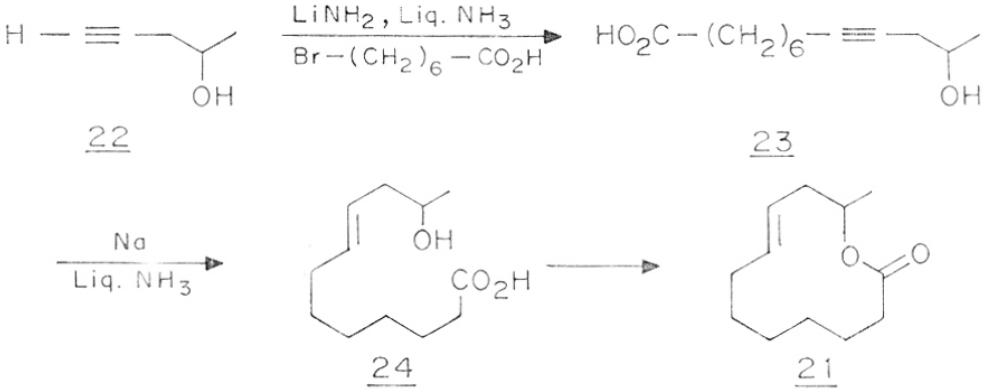
Section 2 - A short synthesis of (±)-recifeiolide

Recifeiolide [(21) 11-hydroxy-trans-8-dodecenoic acid lactone] has been isolated from a fungus, Cephalosporium recifei by Vesonder et al.

The salient features of the present synthesis are the conjunctive use of an acetylenic compound to get the recifeiolide

Chain with proper substituents and finally its conversion to a trans double bond.

Pent-1-yn-4-ol (22), on alkylation with 7-bromoheptanoic acid furnished 23. This on partial reduction with sodium in excess



22 23 24 21

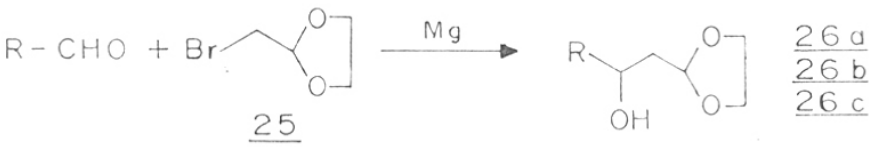
of liq. NH_3 gave 24, which was lactonised by several approaches to recifeiolide.

Part B: A methodology for two carbon homologation

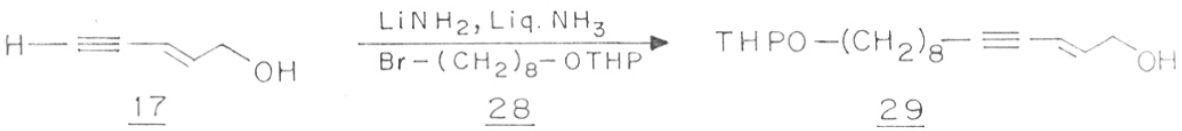
β-Hydroxy aldehydes are versatile intermediates for a variety of compounds such as 1,3-diols, 1,3-dicarbonyl compounds, α,β-unsaturated aldehydes. A method for β-hydroxy aldehydes (the aldehyde being in the protected form) has been developed by a Grignard reaction of 2-bromomethyl-1,3-dioxalane (25) with an aldehyde. To show the generality of this method the Grignard reaction was carried out with butanal, hexanal and decanal and the corresponding products 26a, 26b and 26c respectively were obtained.

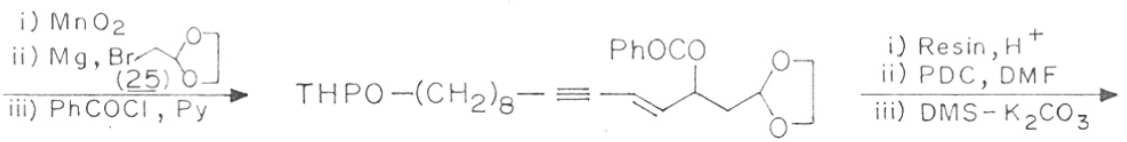
The efforts were made to utilise this methodology in the total synthesis of 27, which is active against blast disease in

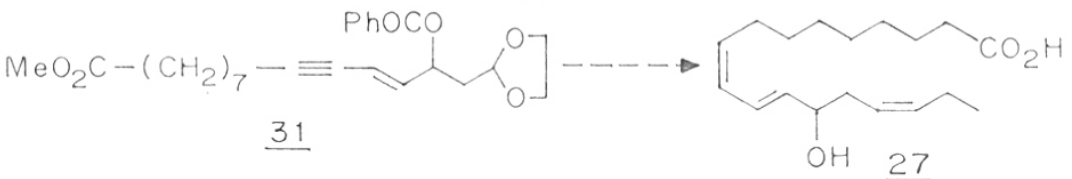
rice plants. Acetylenic alcohol (17), on alkylation with 28



a, R = $-C_3H_7$; b, R = $-C_5H_{11}$; c, R = $-C_9H_{19}$





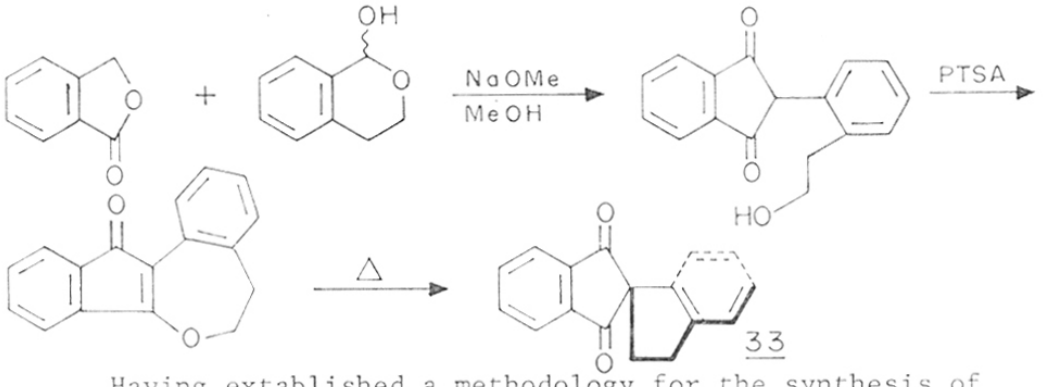


gave 29. This on oxidation with MnO_2 followed by the Grignard reaction with 25 and benzoyl protection afforded 30. Preferential removal of THP group in 30 followed by oxidation of the primary alcohol to the carboxyl group and esterification gave 31. Preliminary experiments to deprotect the ketal failed to give the desired aldehyde.

Chapter III - Synthetic approaches towards Fredericamycin A

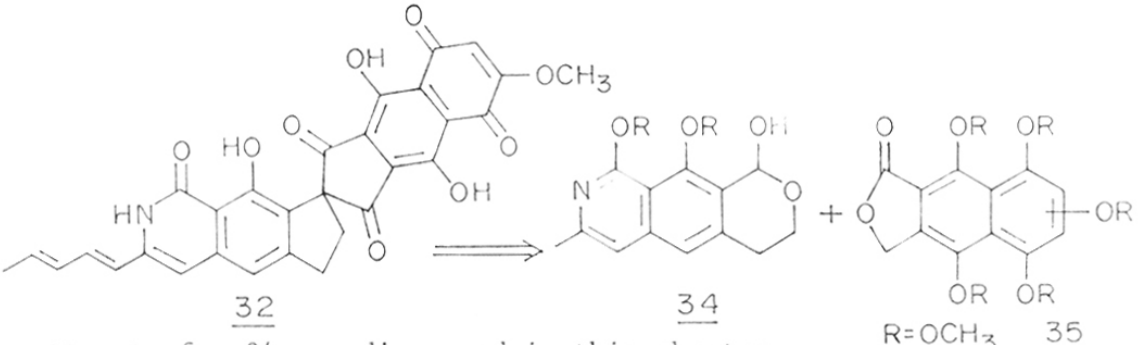
Fredericamycin-A (32) produced by Streptomyces griseus has been shown to be a potent antitumour agent. Its biological activity and important structural features called for its synthesis.

Methodology for the synthesis of spiro[4,4]nonane system present in 32 has recently been developed in these laboratories on a model spiro ring system 33.



33

Having extablished a methodology for the synthesis of spiro ring system, studies were directed towards the total synthesis of 32. Based on the above strategy the retrosynthesis of 32 reveals two key intermediates, 34 and 35. As the synthesis of 35 has already been completed in these laboratories various

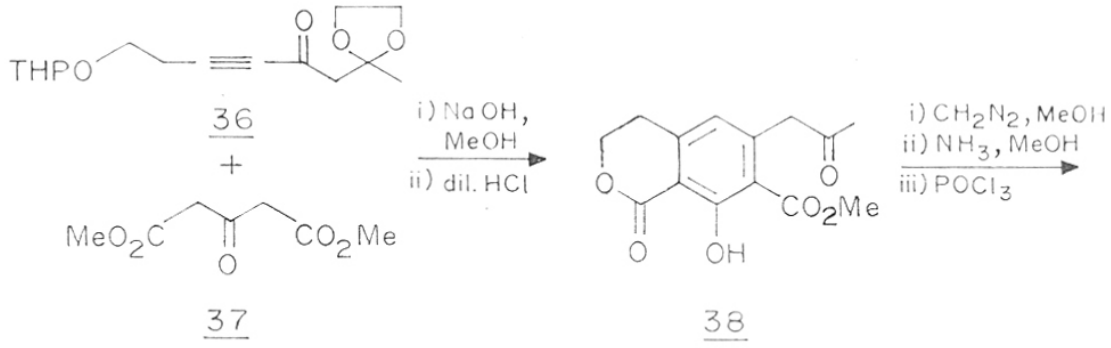


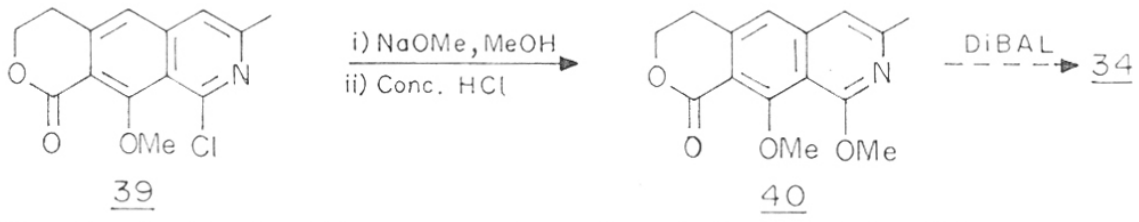
32 34 35

attempts for 34 are discussed in this chapter.

Here the main strategy involved the Michael addition followed by aldol condensation between the acetylenic ketone

36 and the diester 37 to give 38. The methyl ether of ketoester





38, on treatment with ammonia in methanol followed by $POCl_3$ gave the quinoline derivative 39. Compound 39 was treated with sodium methoxide in methanol to give the hydroxy acid, which on treatment with conc. HCl gave 40. Conversion of 40 to 34 is in progress.

Other studies related to the synthesis of intermediate 34 were also discussed.

CHAPTER I

SYNTHESIS OF 1,4-DICARBONYL COMPOUNDS; A NEW METHODOLOGY

INTRODUCTION

1,4-Dicarbonyl compounds are one of the most useful intermediates for the synthesis of a variety of natural products, having a cyclopentenone or a furan ring system[1]. The utility of 1,4-dicarbonyl compounds was realized because of their ability to form a number of ring systems, depending upon the reagent and of course the requirement.

Earlier methods for the synthesis of 1,4-dicarbonyl compounds

1,4-Dicarbonyl compounds have been prepared by numerous methods. However in this section to discuss all these methods together would be beyond the scope of this thesis and therefore those methods which are frequently utilised in the synthesis coupled with those pertinent with the work described in this section are only dealt with. The synthetic methods for 1,4-dicarbonyl compounds involved several reactions and reagents, it would be difficult to categorise these syntheses under certain headings. However, an attempt had been made to classify these methods by the reaction or by the intermediate, mainly involved in the synthesis.

I. From furan derivatives.

II. By alkylative assemblage.

III. Michael approach

IV. Ring cleavage routes

V. Grignard approach

VI. Miscellaneous methods.

I. From furan derivatives

Furans have been classified as latent 1,4-dicarbonyl compounds. 2,5-Disubstituted furan derivatives, on treatment with acid give rise to 1,4-dicarbonyl compounds.

This methodology has been elegantly used by Buchi-Wuest[2] in the synthesis of jasmonoids. For example 2-methyl furan was alkylated at 5-position with cis-3-hexenylbromide and n-butyl lithium. The resulting product 1, on treatment with acid furnished a 1,4-dicarbonyl compound, which was converted to cis-jasmone (Scheme 1). Later Crombie et al.[3] (Scheme 2), Sisido et al.[4] (Scheme 3), Fetizone-Schalbar[5] (Scheme 4) and Birch et al.[6] (Scheme 5) have made use of the similar strategy developed by Buchi-Wuest in the synthesis of jasmonoids. The difference was only in the formation of 2,5-disubstituted furan derivatives.

In case of the synthesis by Birch et al. the opening of furan was carried out by Collins reagent to generate the enedione 2, which on reduction furnished a 1,4-diketone.

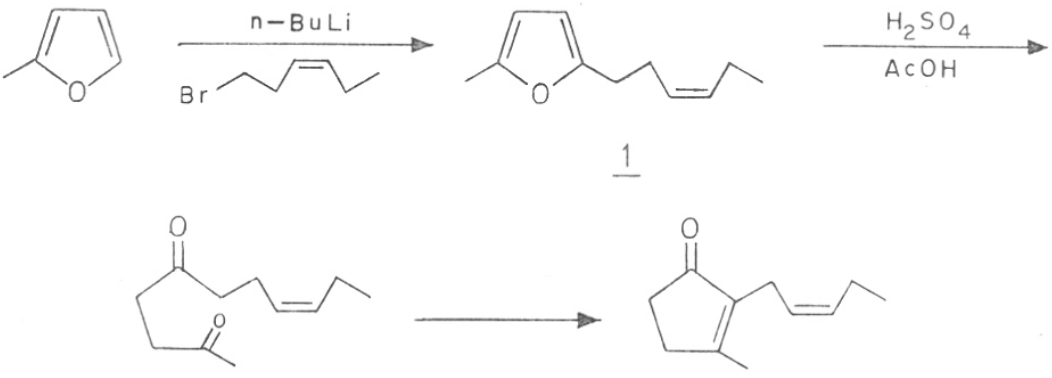
II. By alkylative assemblage

Several syntheses of 1,4-dicarbonyl compounds fall under this category, in which the salient feature is the alkylation of an active methylene or a methine carbon with alkyl halides under various conditions. For instance Crombie-Harper[7] prepared the ester 3 from ethylacetoacetate and carried out alkylation with bromoacetone in presence of sodium to afford the alkylated

SCHEME – 1

I FROM FURANS

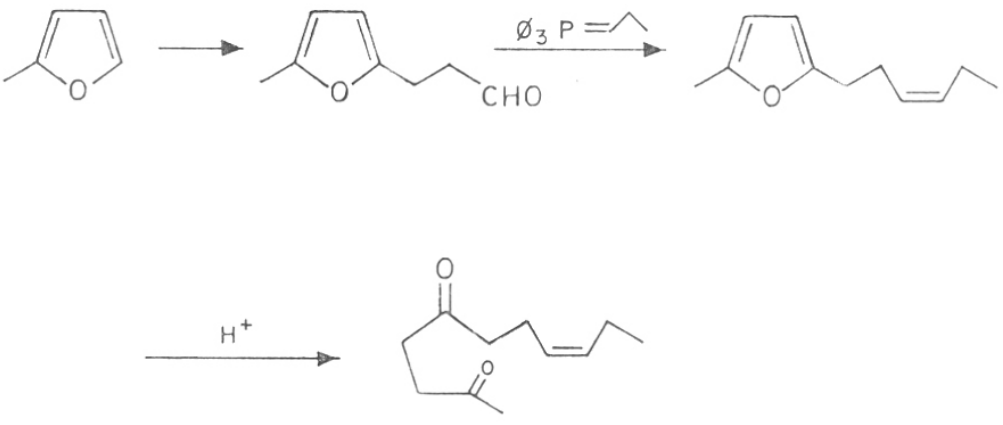
a) BUCHI – WUEST



1

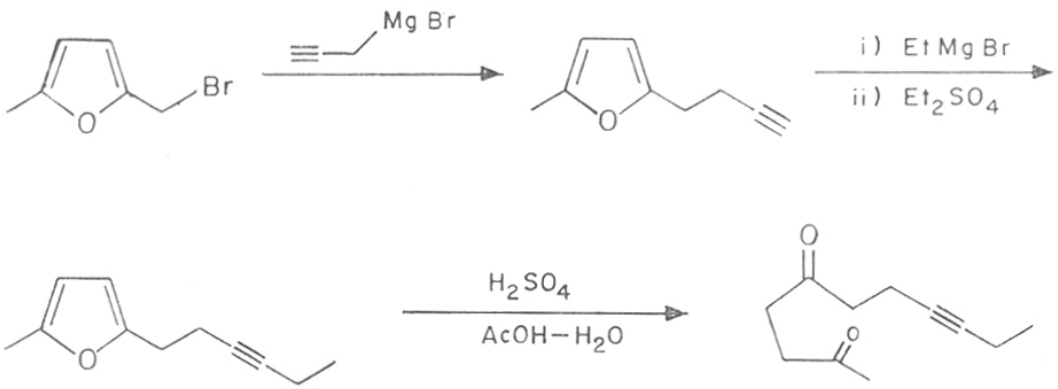
SCHEME – 2

b) CROMBIE et al



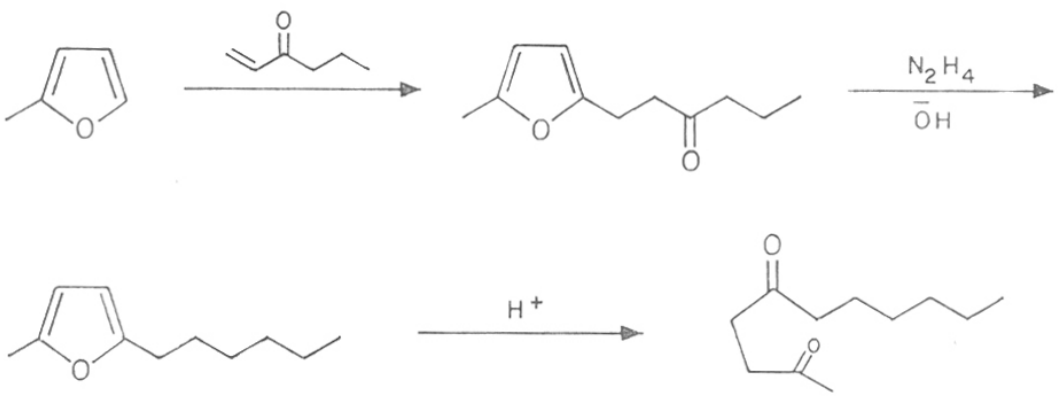
SCHEME – 3

c) SISIDO et al



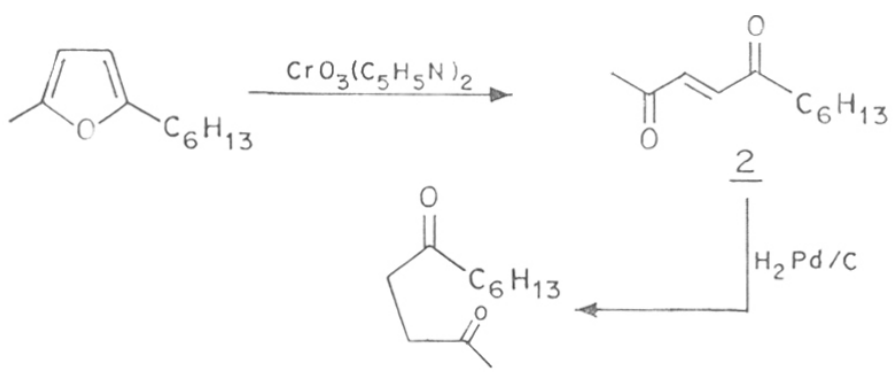
SCHEME – 4

d) FETIZONE – SCHALBAR



SCHEME – 5

e) BIRCH et al



product 4, which on treatment with base afforded cis-jasmone through its 1,4-diketone precursor (Scheme 6).

Ho et al.[8] prepared the 1,4-dicarbonyl compounds by making use of the Umpolung activity of 2-(n-hexyl)-1,3-dithiane. It was treated with 1,3-dichloro-but-2-ene in presence of a base to give the alkylated derivative 5, which on treatment with sulfuric acid effected the hydrolysis of both, the dithiane ring and vinylic chloride to furnish a 1,4-dicarbonyl compound (Scheme 7).

In another approach, Cuvigny et al.[9] carried out the alkylation of an enamine derivative 6 with 2,3-dichloroprop-1-ene to give the vinylic chloride derivative 7, which on acid treatment furnished a 1,4-diketone (Scheme 8).

In Takeda et al.[10] synthesis, methyl sulfinyl carbanion was allowed to react with the ester 8, followed by the reduction of the resulting sulfoxide 9 with aluminium amalgam and hydrolysis to give a 1,4-dicarbonyl compound (Scheme 9).

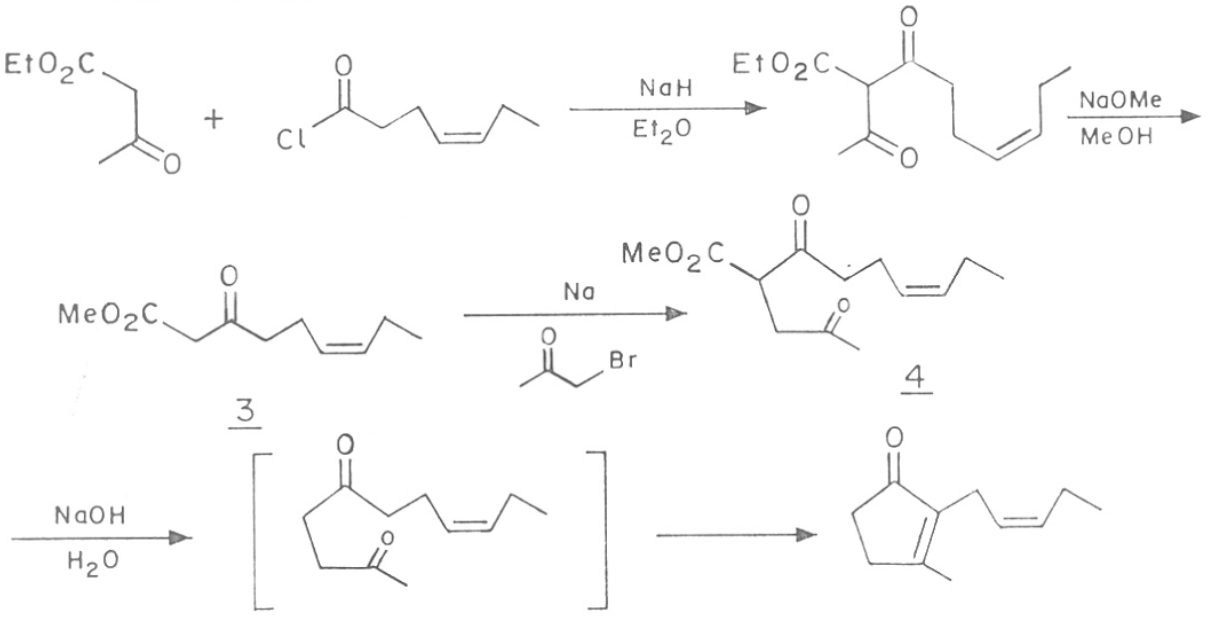
Opening of an epoxide with suitable carbanions to furnish γ-hydroxy ketone derivatives, has been the important feature for syntheses reported by Ho-Wong[11] (Scheme 10) and Grieco-Pogonowski[12] (Scheme 11). For example acetylacetone was allowed to react with 1,2-epoxy octane to furnish the corresponding hemiacetal derivative 10, which on Jones oxidation gave a 1,4-diketone (Scheme 10).

In case of the synthesis by Utimoto et al.[13] tri-n-hexylborane

SCHEME – 6

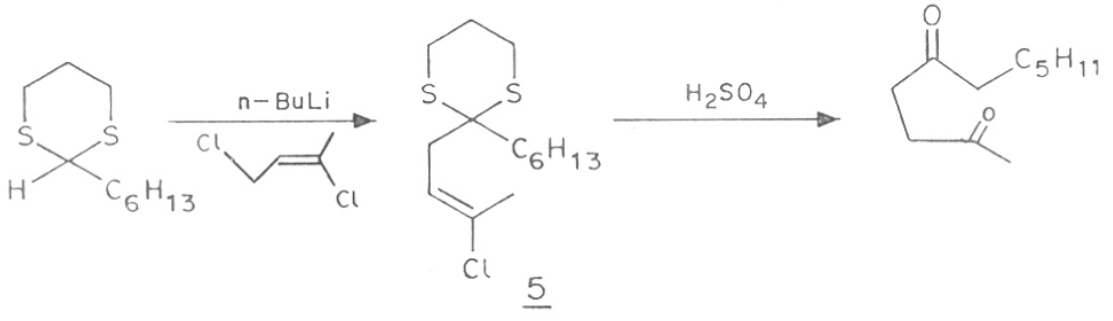
II. ALKYLATIVE ASSEMBLAGE :

a) CROMBIE – HARPER



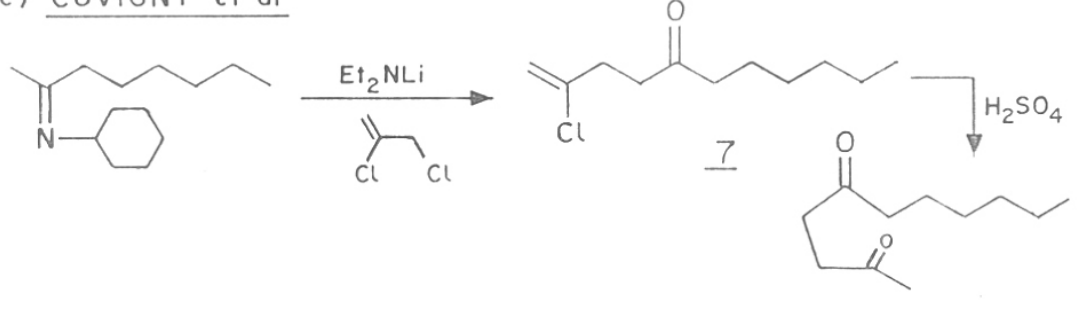
SCHEME – 7

b) HO et al



SCHEME – 8

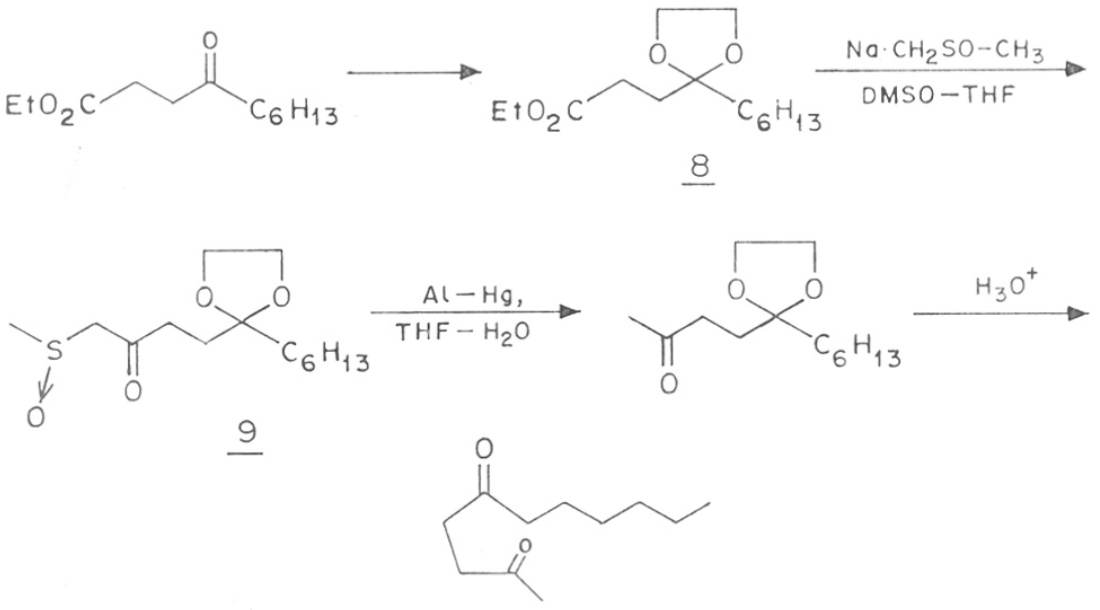
c) CUVIGNY et al



SCHEME – 9

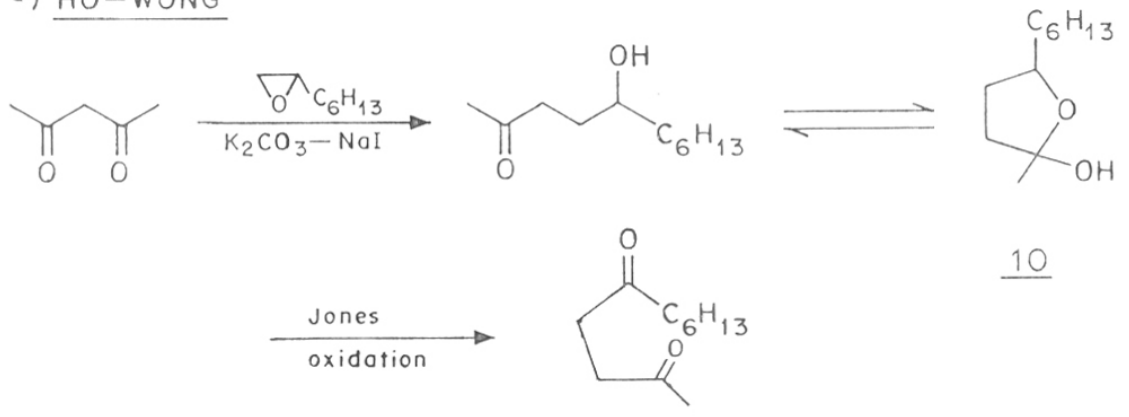
II ALKYLATIVE ASSEMBLAGE

d) TAKEDA et al



SCHEME – 10

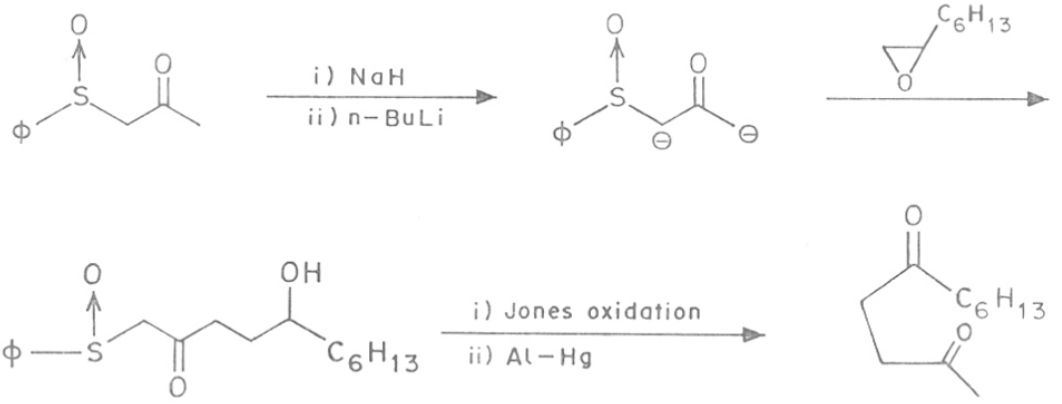
e) HO–WONG



SCHEME - 11

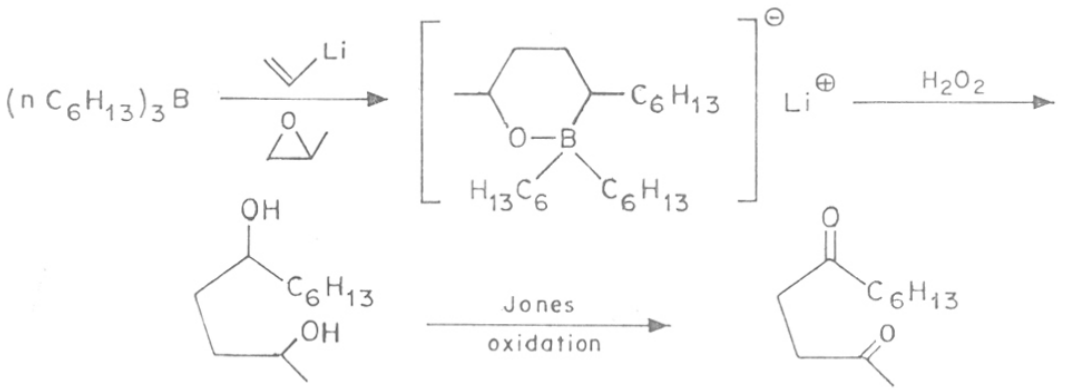
II ALKYLATIVE ASSEMBLAGE:

f) GRIECO-POGONOWSKI



SCHEME—12

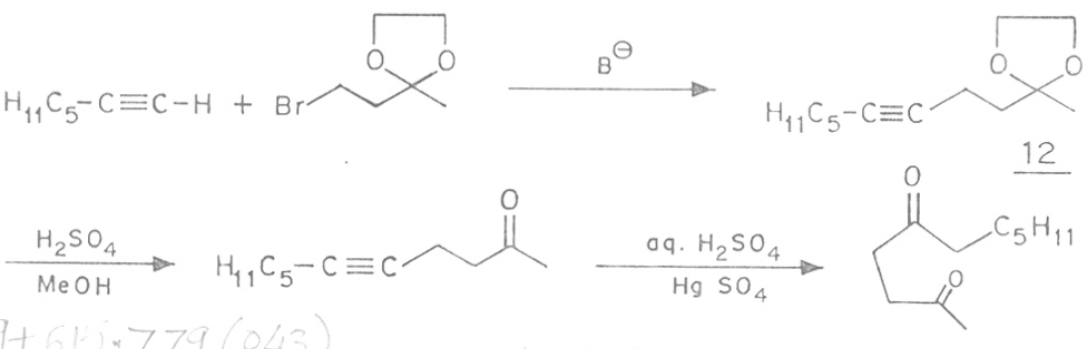
g) UTIMOTO et al



11

SCHEME—13

h) STORK-BORCH



12

was allowed to react with vinyl lithium followed by methyl-oxirane to give a 1,4-dihydroxy derivative 11 which on oxidation furnished a 1,4-dicarbonyl compound (Scheme 12).

Acetylenic derivatives have been used by Stork et al.[14] (Scheme 13) and Sum-Weiler[15] (Scheme 14) for the preparation of 1,4-dicarbonyl compounds. Stork et al. alkylated 1-heptyne with 3,3-ethylenedioxy butyl bromide in presence of a base to furnish the intermediate 12 which was deketalised and then hydrated to give a 1,4-diketone (Scheme 13).

III. Michael approach

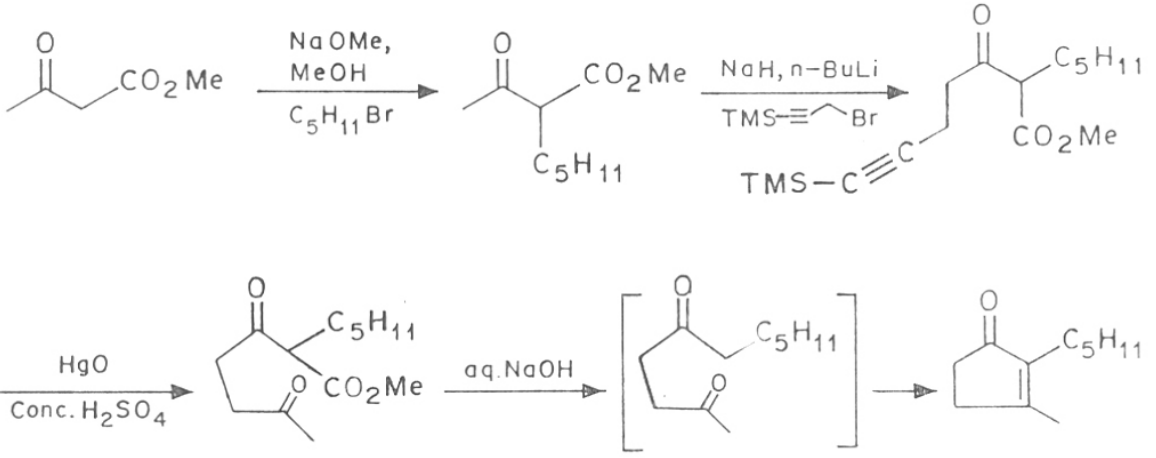
The 1,4-addition of an appropriate nucleophile on methyl vinyl ketone in presence of a base furnished an intermediate, which was transformed into a 1,4-dicarbonyl compound. This strategy was employed by Mc-Murry[16] (Scheme 15), Schlessinger[17] (Scheme 16), Mukaiyama[18] (Scheme 17) and their coworkers for the synthesis of 1,4-dicarbonyl compounds. For instance, Mukaiyama et al. had shown that the addition of diphenyl thioacetal derivative 13 on methyl vinyl ketone in presence of n-butyl lithium furnished the γ-keto thioketal intermediate 14, which on hydrolysis afforded a 1,4-dicarbonyl compound (Scheme 17).

IV. Ring cleavage routes

Cleavage of small rings to furnish 1,4-dicarbonyl compounds has been the strategy of Wenkert et al.[19] (Scheme 18) and Weinreb et al.[20] (Scheme 19) syntheses. Reaction of a diazoketone

SCHEME-14

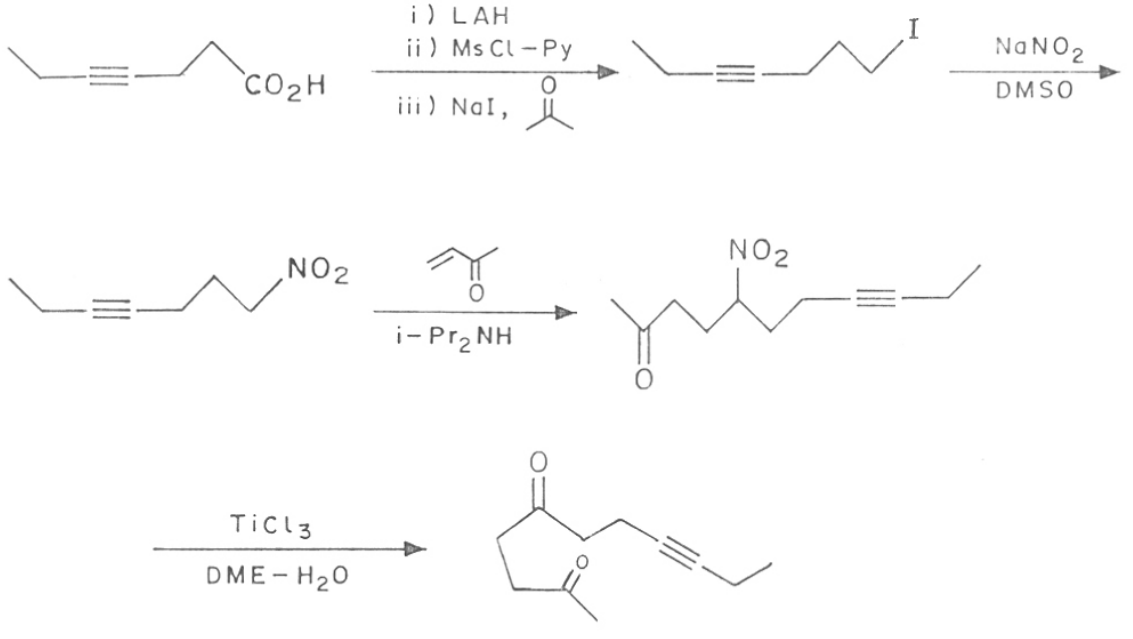
i) SUM-WEILER



SCHEME-15

III MICHAEL APPROACH

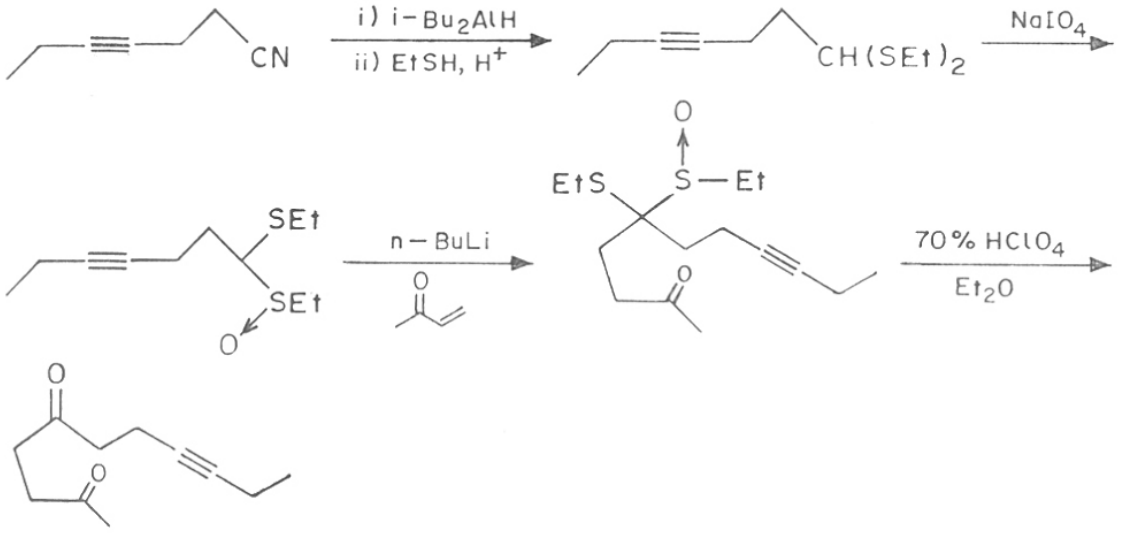
a) McMURRY-MELTON



SCHEME – 16

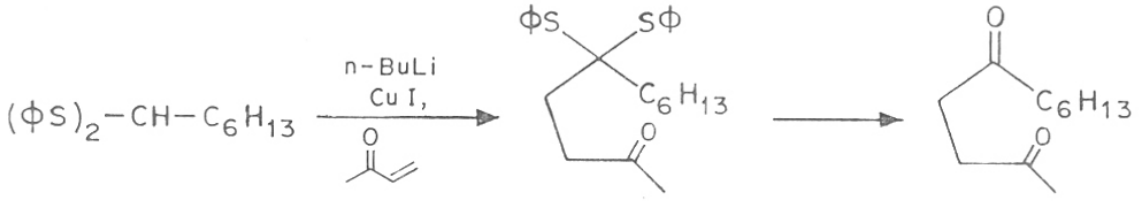
III MICHAEL APPROACH

b) SCHLESSINGER et al



SCHEME – 17

c) MUKAIYAMA et al

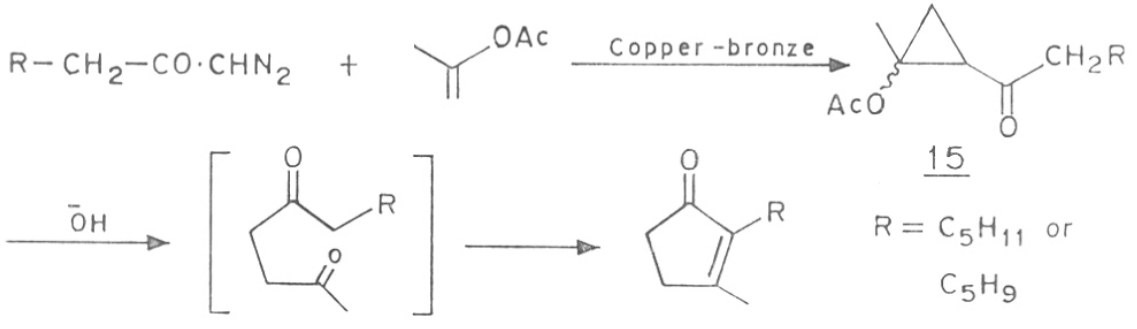


13 14

SCHEME – 18

IV RING CLEAVAGE ROUTES

a) WENKERT et al



with isopropenylacetate in presence of copper-bronze gave an acetoxy cyclopropane ketone 15, whose treatment with base furnished a 1,4-diketone, the latter concomitently underwent cyclization (Scheme 18). The utility of 2-hydroxy cyclobutanone 16 in the synthesis of 1,4-diketones was reported by Weinreb as shown in the Scheme 19.

The synthesis of Torssell et al.[21] involved the cleavage of 5-diethoxymethyl-2-isoxazoline (17) with titanium (III) ion in a weakly acidic solution to afford a 4-ketoaldehyde (Scheme 20).

V. Grignard approach

Ho et al.[22] chose levulonitrile as starting material and ceric ammonium nitrate has been used for dethioketalization (Scheme 21).

Mukaiyama et al.[23] carried out the Grignard reaction on S-(2-pyridyl)thioate 18 followed by dethioketalization of the resultant product 19 to furnish a 1,4-dicarbonyl compound (Scheme 22).

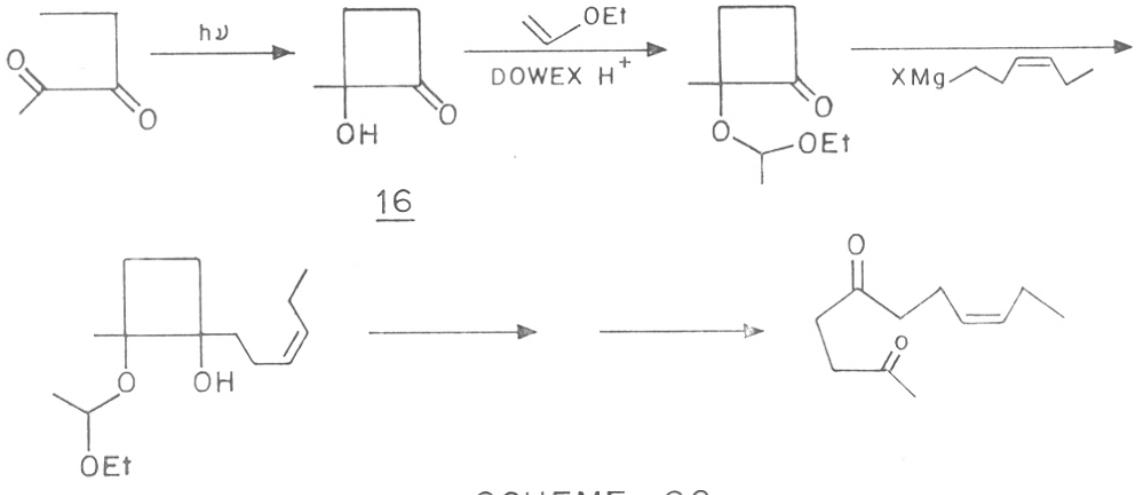
The synthesis of Bakuzis et al.[24] involved the Grignard reaction on an aldehyde 20 with a 3-thiophenyl alkylbromide 21 and further transformations to a 1,4-diketone (Scheme 23). The synthesis of Liu et al.[25] featured the Grignard reaction on 4,4-ethylenedioxypentanal (Scheme 24).

VI. Miscellaneous methods

Ficini et al.[26] have utilized ynamines as intermediates

SCHEME – 19

b) WEINREB – CVETOVICH



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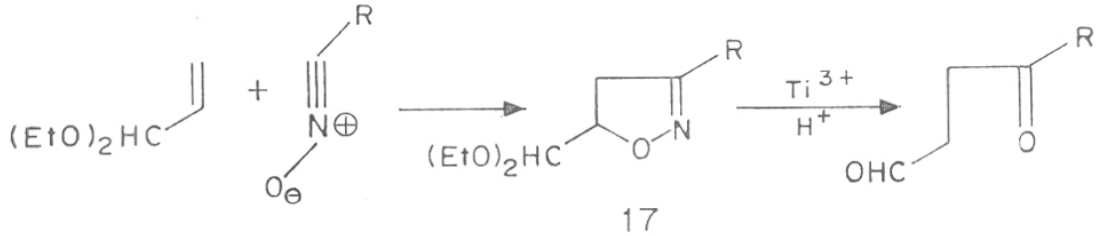
SCHEME – 20

c) TORSSELL et al



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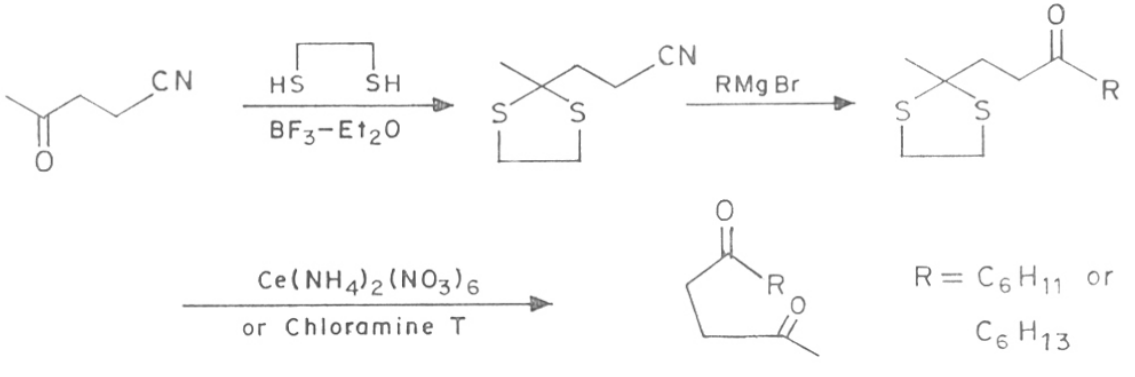
SCHEME – 21

V GRIGNARD APPROACH

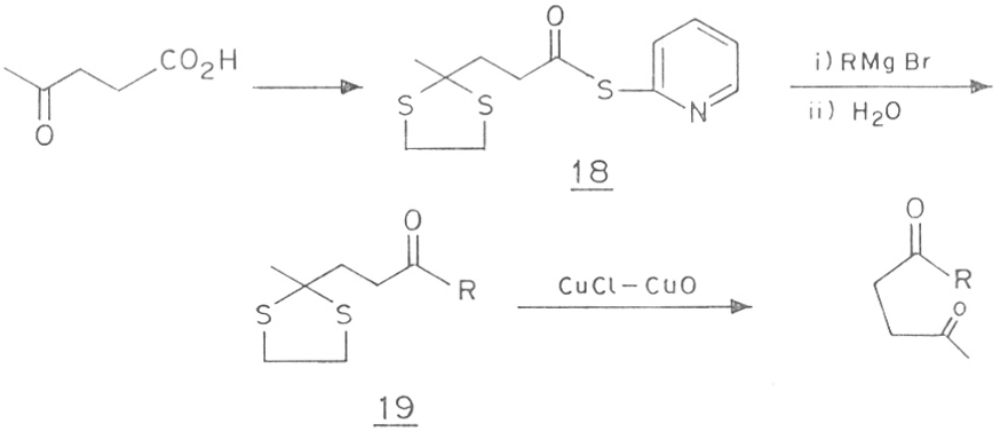
a) HO et al



SCHEME – 22

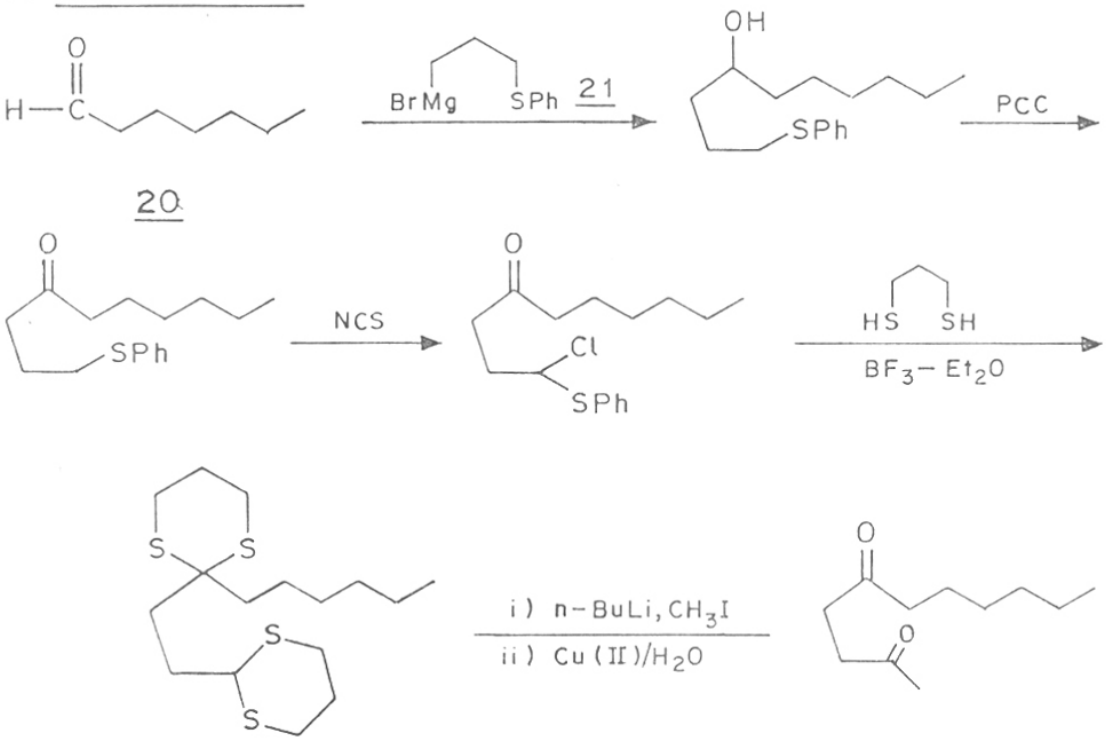
V GRIGNARD APPROACH

b) MUKAIYAMA et al



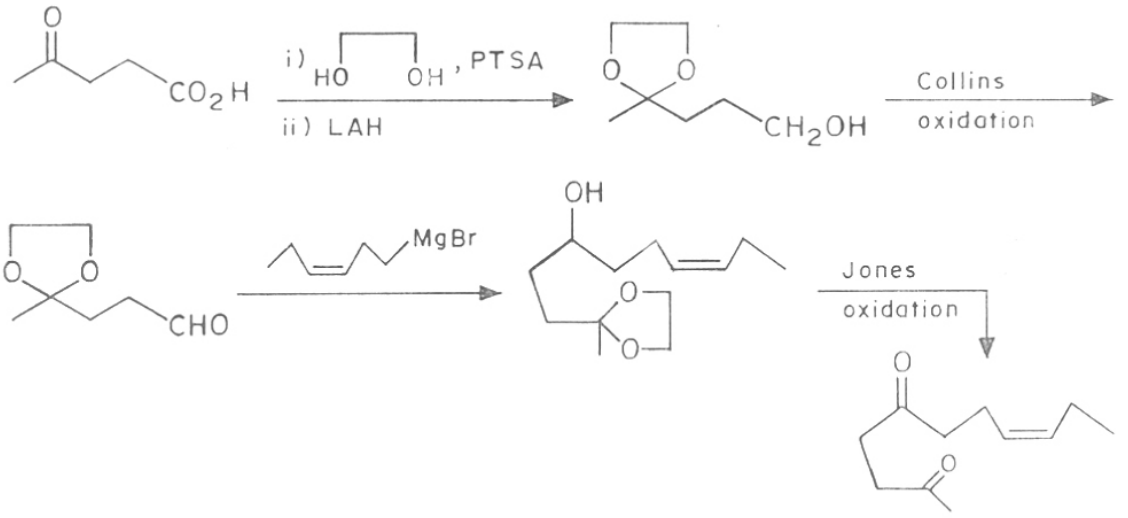
SCHEME – 23

c) BAKUZIS et al



SCHEME – 24

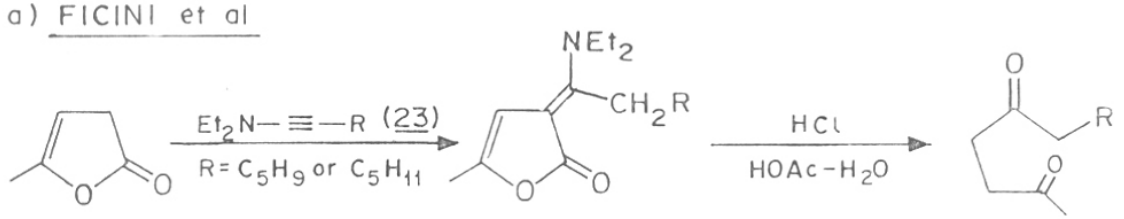
d) LIU–BULAT



SCHEME – 25

VI MISCELLANEOUS METHODS

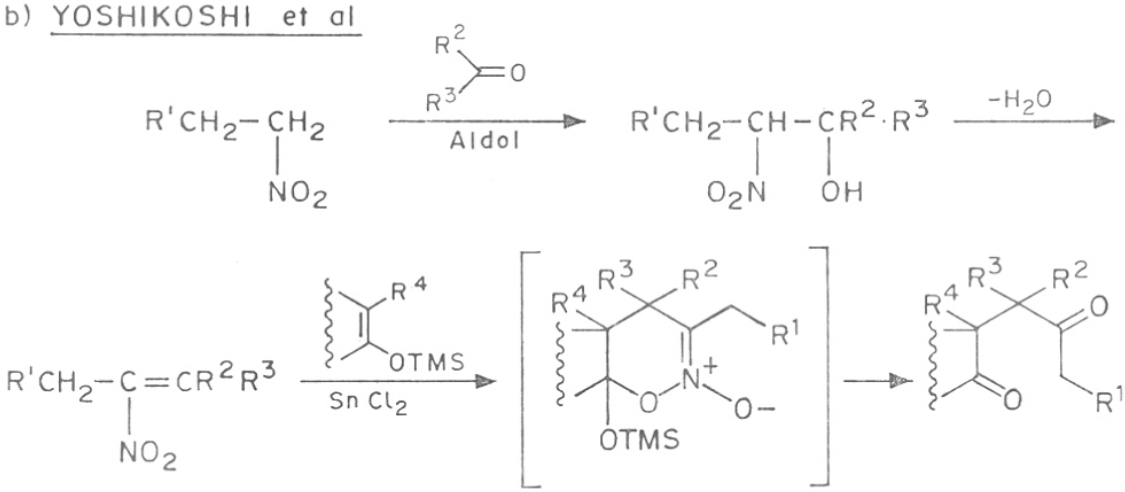
a) FICINI et al



22 24

SCHEME – 26

b) YOSHIKOSHI et al



for the synthesis of 1,4-dicarbonyl compounds. A γ-lactone 22 and an ynamine 23 were allowed to react to furnish an intermediate 24, which on hydrolysis afforded a 1,4-diketone (Scheme 25).

Yoshikoshi et al.[27] reported the synthesis of 1,4-dicarbonyl compounds by making use of α,β-unsaturated nitro compounds, in which a Michael type of addition was carried out between silyl enol ethers and nitro olefins (Scheme 26).

Umani-Ronchi et al.[28] had shown that the opening of a γ-valerolactone with dilithiosulfone furnished a γ-hydroxy ketosulfone 25, which was oxidised, followed by the desulfurisation of the resulting diketosulfone 26 afforded a 1,4-diketone (Scheme 27).

Utility of 1,4-dicarbonyl compounds in organic synthesis

1,4-Dicarbonyl compounds have been frequently utilised in the synthesis of organic compounds including natural products because of the ease with which they can be synthesised and more importantly because of the ease with which they undergo cyclization reactions in presence of various reagents and catalysts. Out of these reactions, perhaps synthesis of cyclopentenones is the most common. Briefly an attempt has been made in this section to highlight some basic transformations of 1,4-dicarbonyl compounds. They have been categorised according to the end products, which are as follows.

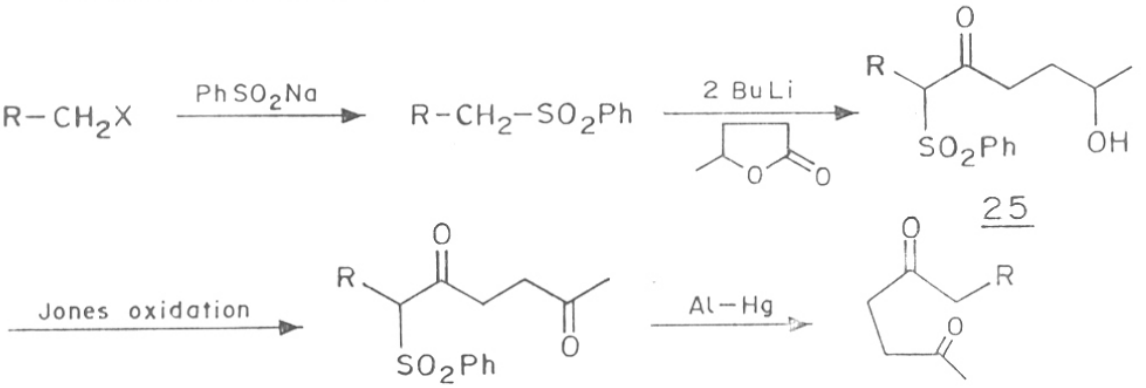
a) Cyclopentenones:

As reported earlier, cyclopentenones have been most

SCHEME-27

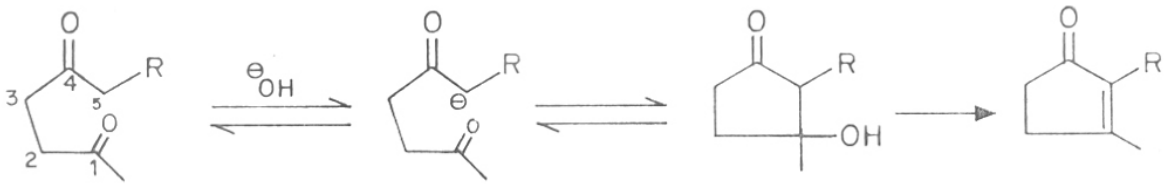
VI MISCELLANEOUS METHODS

c) UMANI-RONCHI et al

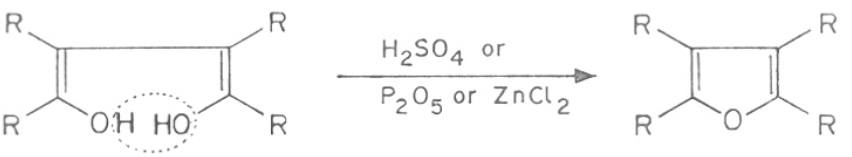


26

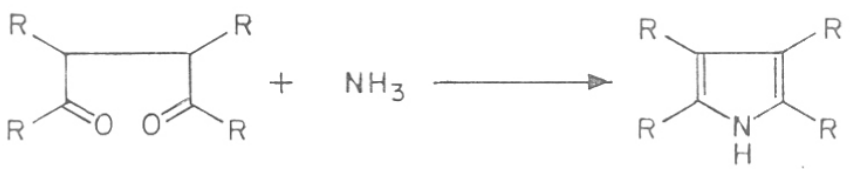
SCHEME-28



SCHEME-29



SCHEME-30



frequently obtained from 1,4-dicarbonyl compounds. The reaction involved is aldol condensation followed by dehydration under mild basic conditions to give cyclopentenones[29] (Scheme 28). For instance jasmonoids have been prepared from the corresponding 1,4-dicarbonyl compounds. In addition, in steroid chemistry the 'D' ring has been commonly prepared by making use of 1,4-dicarbonyl compounds.

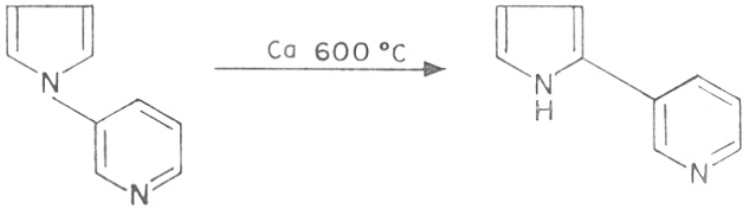
b) Furans:

Furan skeleton has been frequently observed in several natural products. Along with other methods generally adopted for furan synthesis, the use of 1,4-dicarbonyl compounds as intermediates for the same has made significant contribution. In presence of an acid, 1,4-dicarbonyl compounds undergo dehydration to furnish the furan derivatives[30] (Scheme 29). In this way several substituted 1,4-dicarbonyl compounds have been prepared and transformed to substituted furan derivatives, which otherwise are difficult to synthesise directly from furans. These furans are very good dienes in Diels-Alder approach for building six-membered rings, heterocycles as well as nonheterocycles.

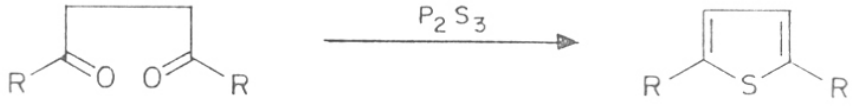
c) Pyrroles:

Treatment of 1,4-dicarbonyl compounds with ammonia gave rise to the pyrrole derivatives (Scheme 30).This method has normally been applied for the synthesis of N-substituted pyrroles, in which 1,4-dicarbonyl compounds and primary amines were utilised.

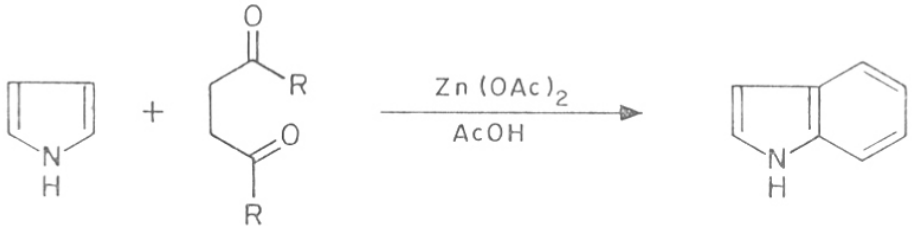
SCHEME – 31



SCHEME – 32



SCHEME – 33



An application is to the synthesis of nicotine[31], in which the mucate of β-aminopyridine is distilled to give N-β-pyridyl pyrrole (Scheme 31).

d) Thiophenes:

In accordance with the line of synthesis of furans and pyrroles, thiophene derivatives have been synthesised from 1,4-dicarbonyl compounds. In this case the mode of cyclization was effected in presence of phosphorous sulfides such as P_2S_3 or P_2S_4[32] (Scheme 32). Therefore this method has tremendous potential for the synthesis of substituted thiophene derivatives.

e) Miscellaneous ring systems:

1,4-Dicarbonyl compounds have significant utility in annelation reactions[33] (Scheme 33). For instance pyrrole and indole, when reacted with 1,4-dicarbonyl compounds give rise to indole and carbazole respectively. In a similar way hydroquinone gives rise to substituted naphthalene derivatives.

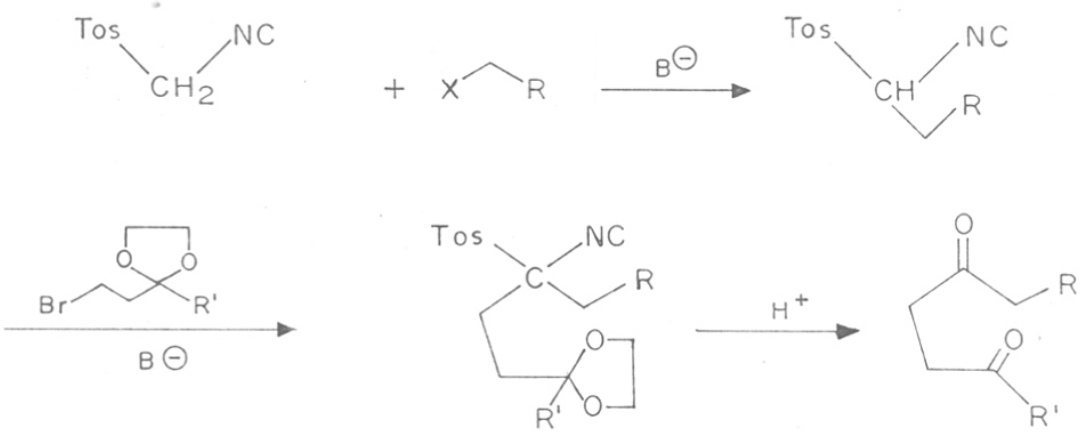
PRESENT WORK

Although there are several methods available for the synthesis of 1,4-dicarbonyl compounds as described in the previous section, a new method which should be simple and straightforward would always be welcome in synthetic chemistry. As a matter of fact, the importance of 1,4-dicarbonyl compounds as intermediates in natural products synthesis is so enormous that every now and then a new method is published for their synthesis. This aspect has been demonstrated in the last section. In the present work a new synthesis of 1,4-dicarbonyl compounds has been described by making use of TosMIC.

In these laboratories the potential of TosMIC as an intermediate in the synthesis of several organic compounds has been well documented. TosMIC (Tosylmethyl isocyanide) is basically a masked molecule of formaldehyde. The two electronegative functionalities facilitates the formation of TosMIC anion and in essence effect an Unpolung of carbonyl reactivity. Thus TosMIC can be successively alkylated efficiently both to mono and dialkyl derivatives[34]. The advantages of taking TosMIC as a conjunctive reagent are several. For instance, TosMIC can be easily prepared and handled and a carbonyl functionality could be generated out of it, whenever required by a brief treatment of acid.

The strategy of present synthesis of 1,4-dicarbonyl compounds involved successive alkylations with alkyl halides (the

second halide with a masked carbonyl functionality) to give the dialkylated TosMIC derivatives, which on acid treatment gave 1,4-dicarbonyl compounds (Scheme 34).



SCHEME - 34

In order to check the efficacy of this methodology a number of 1,4-dicarbonyl compounds were synthesised, which are described below.

i) Pentadecan-2,5-dione (27a)

ii) Triecoso-2,5-dione (27b)

iii) 8-Undecen-2,5-dione (28a), the precursor of cis-jasmone.

iv) Undecan-2,5-dione (28b), the precursor of dihydro-jasmone.

v) 4-oxo-12[(tetrahydro-2H-pyran-2-yl)oxy]dodecanal (29), a prostaglandin intermediate.

Synthesis of pentadecan-2,5-dione (27a) and triecoso-2,5-dione (27b) (Scheme 35)

Monoalkylation of TosMIC (30) was carried out with

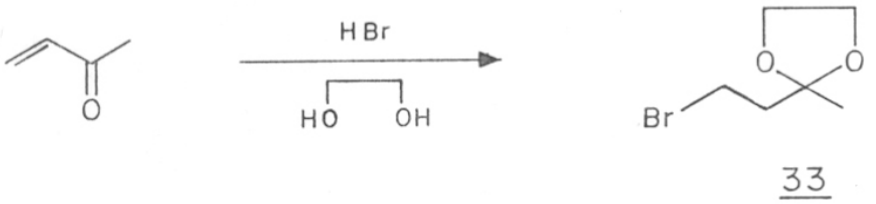
decyl iodide (31a) in presence of a phase transfer catalyst namely, tetrabutyl ammoniumbromide to give a monoalkylated TosMIC derivative 32a in 80% yield. The appearance of a multiplet in the region of 4.2 - 4.5 ppm for the methine proton in ^{1}H-NMR spectrum of 32a clearly indicated that only monoalkylation had occurred. The rest of the protons appeared at the expected chemical shift values.

Subsequent alkylation of the monoalkylated TosMIC derivative 32a was effected with the bromide 33 (obtained by passing hydrogenbromide to methyl vinyl ketone in ethylene glycol)[35] in presence of sodium hydride in DMSO:ether mixture at 10-15° to furnish the dialkylated-TosMIC derivative 34a. In ^{1}H-NMR spectrum of 34a the two methylene protons of the ketal protection resonated at 3.90 ppm as a singlet, which suggested that the alkylation had occurred.

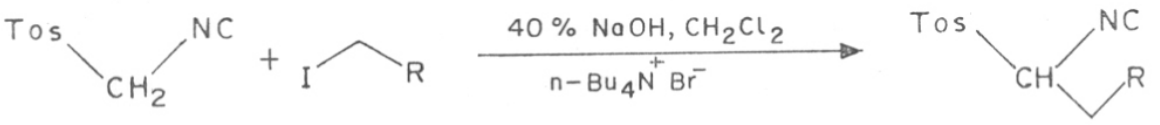
Hydrolysis of 34a with a few drops of conc.hydrochloric acid in ether:dichloromethane mixture afforded the diketone 27a in 90% yield. The ^{1}H-NMR spectrum of 27a showed a singlet for methyl group at 2.10 ppm and a singlet integrating for four protons at 2.70 ppm was assigned to the two methylenes at C-2 and C-3. These PMR values clearly indicated the structure assigned. In addition, the IR spectrum showed the presence of a carbonyl frequency at 1720 cm^{-1} and the absence of the isonitrile band at 2130 cm^{-1}.

Based on the above strategy triecoso-2,5-dione (27b) was synthesised by successive alkylations of TosMIC with

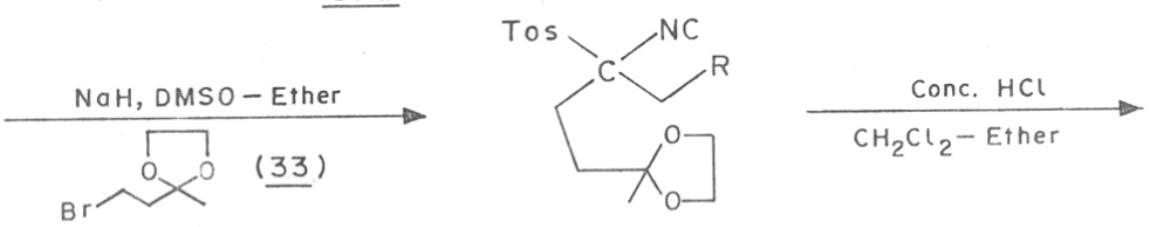
SCHEME–35



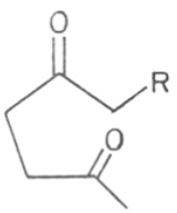
33



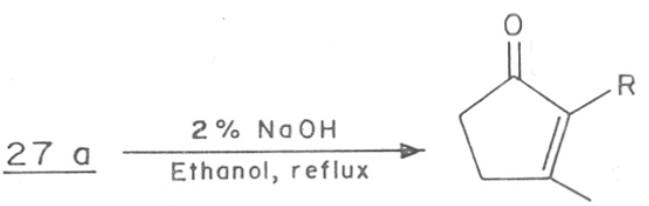
30 31 a 31 b 32 a 32 b



34 a 34 b



27 a 27 b



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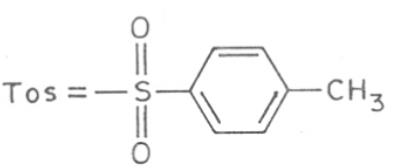


a, $R = -CH_2-(CH_2)_7-CH_3$

b, $R = -CH_2-(CH_2)_{15}-CH_3$

1-iodo octadecane (31b) and the bromide 33, followed by acid hydrolysis.

The diketone 27a on treatment with 2% aqueous sodium hydroxide in ethanol underwent a smooth cyclization to afford a 2,3-disubstituted cyclopentenone 35, whose structure was based on the spectral studies.

Synthesis of cis-jasmone (36a) and dihydrojasmone (36b)

cis-jasmone (36a) and dihydrojasmone (36b), the odoriferous constituents of jasminium family are important ingredients, both in the production of high grade fragrances in the perfume industry and as enhancing agents for spearmint and pepperment flavours in the food industry. Because of their commercial importance and limited availability from natural sources, synthetic efforts for these compounds are still popular even though the pioneering work of Treff and Werner[36] was nearly fifty years ago. Their syntheses were carried out by a number of investigators in the last few decades and reviewed from time to time[1]. Many of the existing methods were however concerned with the development of new or improved methods for the construction of 1,4-diketones and cyclopentenones using cis-jasmone and dihydrojasmone, only as testing models for their synthetic applicability. Whenever there is a discovery of a new methodology to 1,4-diketones or cyclopentenones, chemists can hardly resist the temptation of applying it to the synthesis of these molecules. Often these procedures, as well as being lengthy, require costly and/or

difficultly accessible chemicals and thus are not economically viable for the large scale production of these products. Consequently there is a lot of demand for the development of their effective syntheses. In this section, therefore, a simple synthesis of cis-jasmone and dihydrojasmone has been described using TosMIC as a conjunctive reagent (Scheme 36).

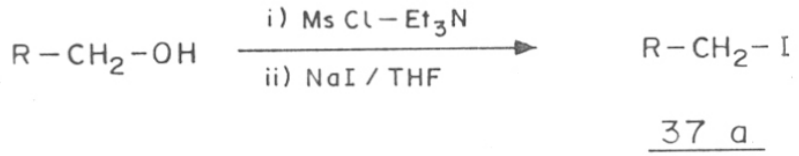
Having successfully carried out the synthesis of 27a and 27b using TosMIC as an intermediate it was felt worthwhile to extend this methodology for the synthesis of 1,4-diketones, which can directly lead to the synthesis of jasmonoids.

Accordingly (Scheme 36) the requisite alkyl halides cis-3-hexenyl iodide (37a), 1-iodohexane (37b) and 3,3-ethylenedioxy butylbromide (33) were prepared according to the literature procedure.

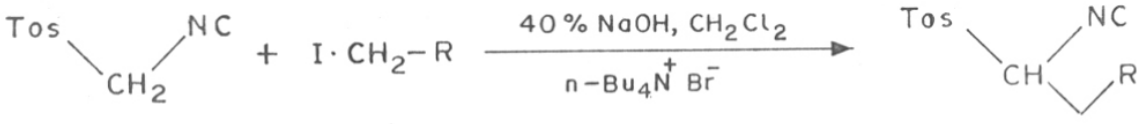
The first alkylation of TosMIC was carried out with cis-3-hexenyl iodide (37a) in presence of a phase transfer catalyst as mentioned earlier to give in 80% yield the mono-alkylated TosMIC derivative 38a, whose ^{1}H-NMR spectrum (Fig.1) revealed the characteristic multiplet for methine proton in the region of 4.1 - 4.3 ppm, which confirmed the formation of the monoalkylated derivative.

The second alkylation with the bromide 33 in presence of sodium hydride afforded the dialkylated TosMIC derivative 39a in 95% yield. The structure of 39a was governed by its

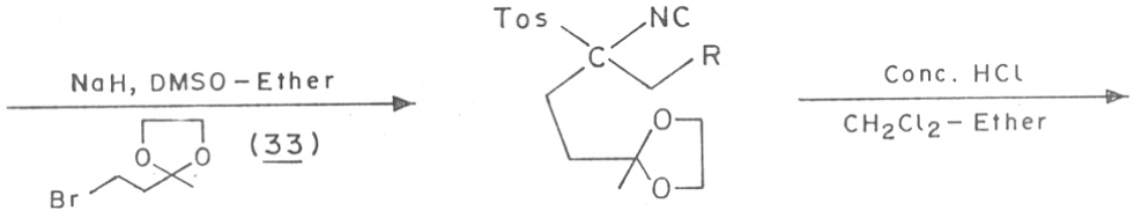
SCHEME – 36



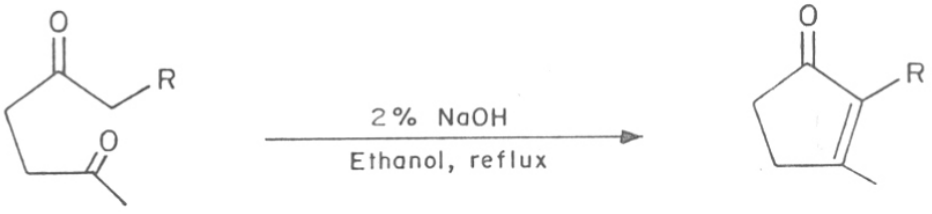
37 a



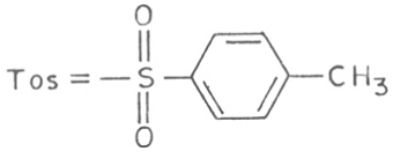
30 | 37 a, 37 b | 38 a, 38 b



39 a, 39 b



28 a, 28 b | 36 a, 36 b



a, R = 

b, R = 

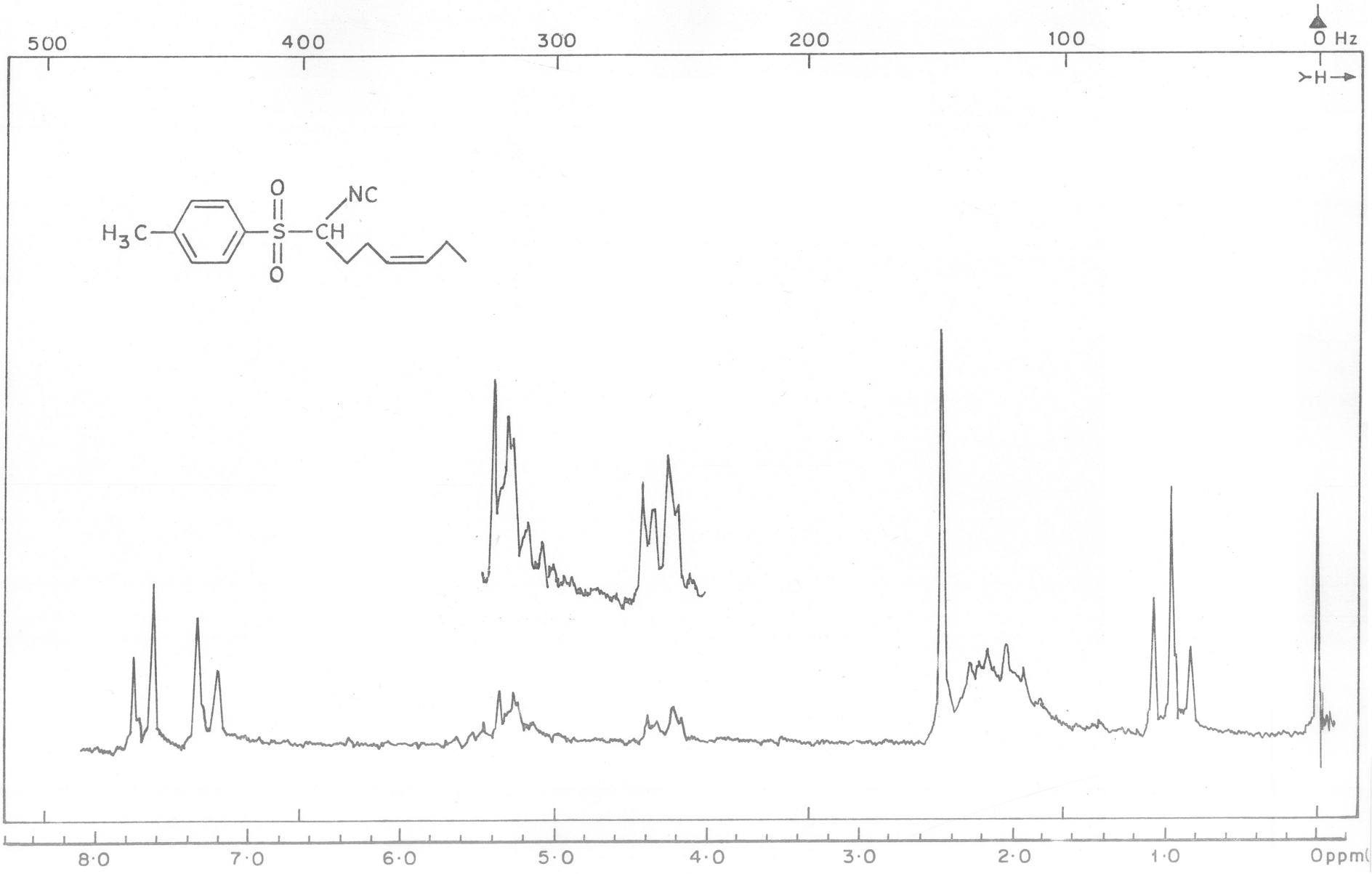


FIG. 1. ^{1}H-NMR SPECTRUM OF COMPOUND (38a) IN CCl_4

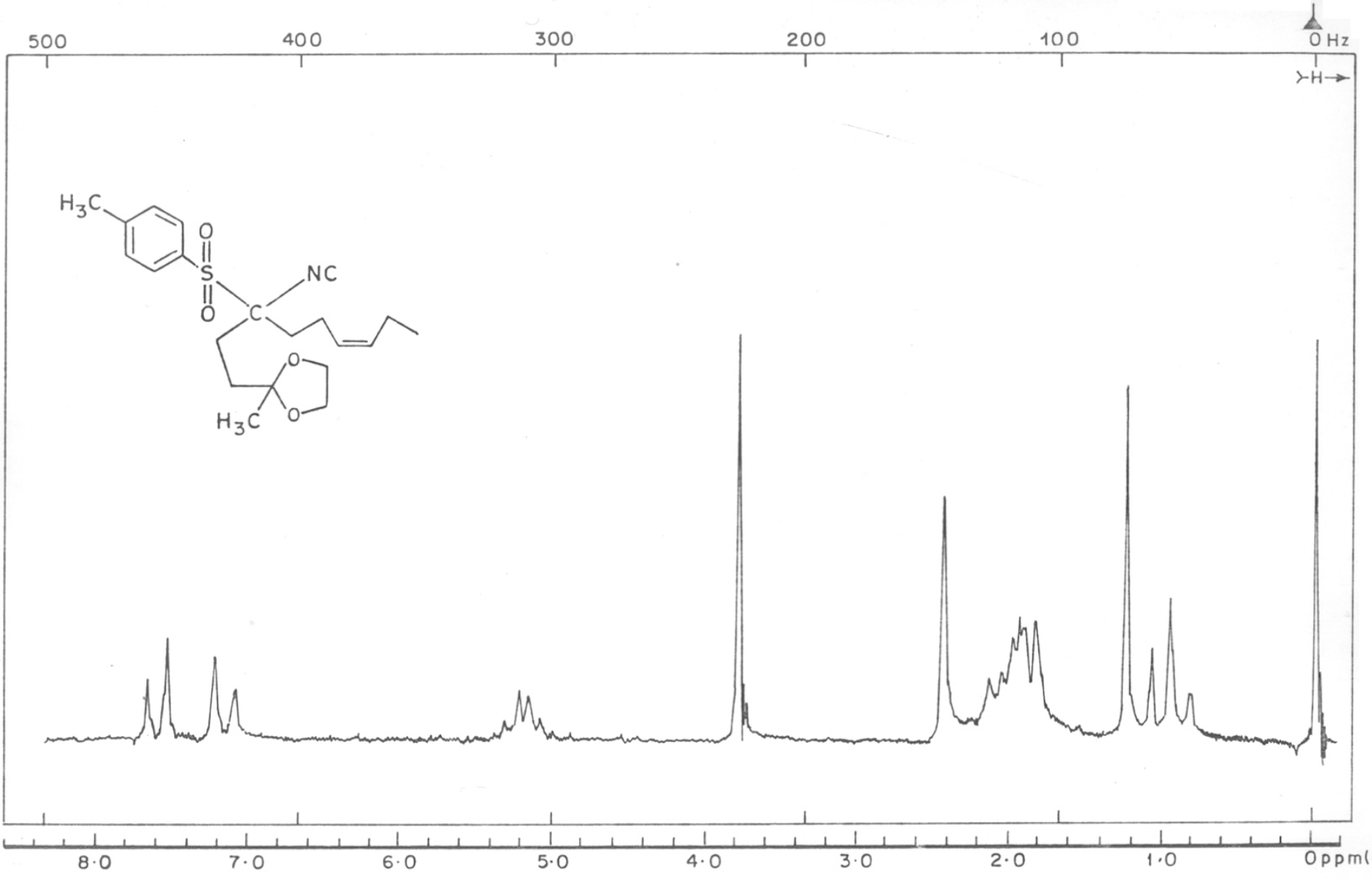


FIG. 2. ^{1}H-NMR SPECTRUM OF COMPOUND (39a) IN CCl_4

spectral studies (Fig.2).

39a was subjected to acid hydrolysis and the corresponding 1,4-diketone 28a was isolated in 90% yield and further characterised by spectral data (Fig.3).

Cyclization of 28a was realized by refluxing it with 2% sodiumhydroxide in ethanol to afford the cis-jasmone (36a), whose physical and spectral data (Fig.4) corresponded well with the reported values.

In a similar way, dihydrojasmone (36b) was also synthesised from TosMIC by selective monoalkylation with 1-iodohexane (37b) followed by subsequent dialkylation with the bromide 33 to afford the dialkylated TosMIC derivative 39b, which on hydrolysis and cyclization gave the expected dihydrojasmone (36b), the properties of which coincided with the reported data (Fig.5).

Synthesis of a prostaglandin intermediate (40)

Although methods available for the synthesis of 1,4-diketones are several, many of them are not particularly suited for the synthesis of 1,4-ketoaldehydes. 1,4-Keto-aldehydes are of great assistance, if one has to synthesise 2-substituted cyclopentenones. It was thought to extend the present methodology to prepare a 1,4-ketoaldehyde which could in turn be elaborated in the synthesis of a prostaglandin intermediate.

Prostaglandins are a family of compounds, which have

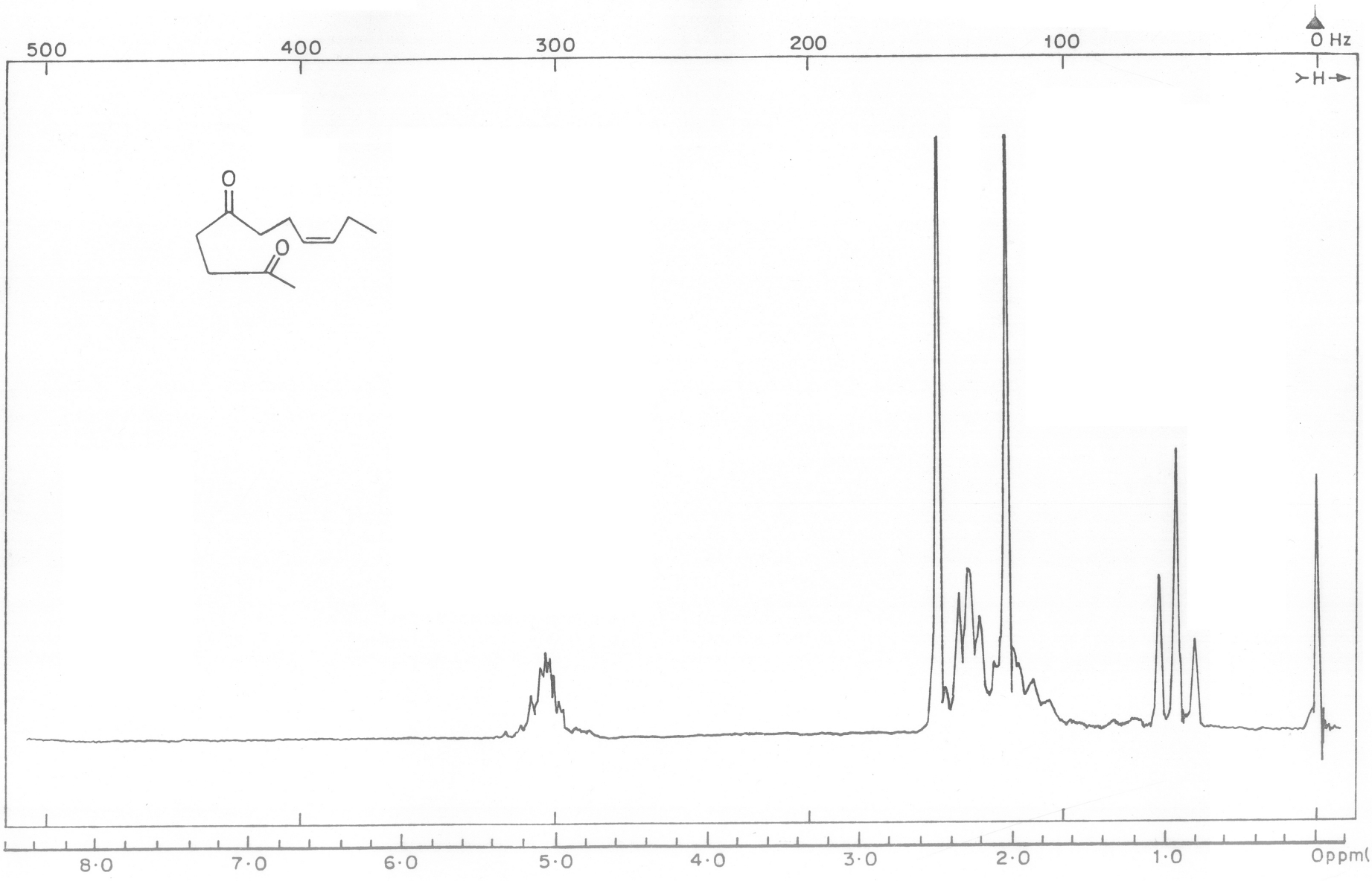


FIG. 3. ^{1}H-NMR SPECTRUM OF COMPOUND (28a) IN CCl_4

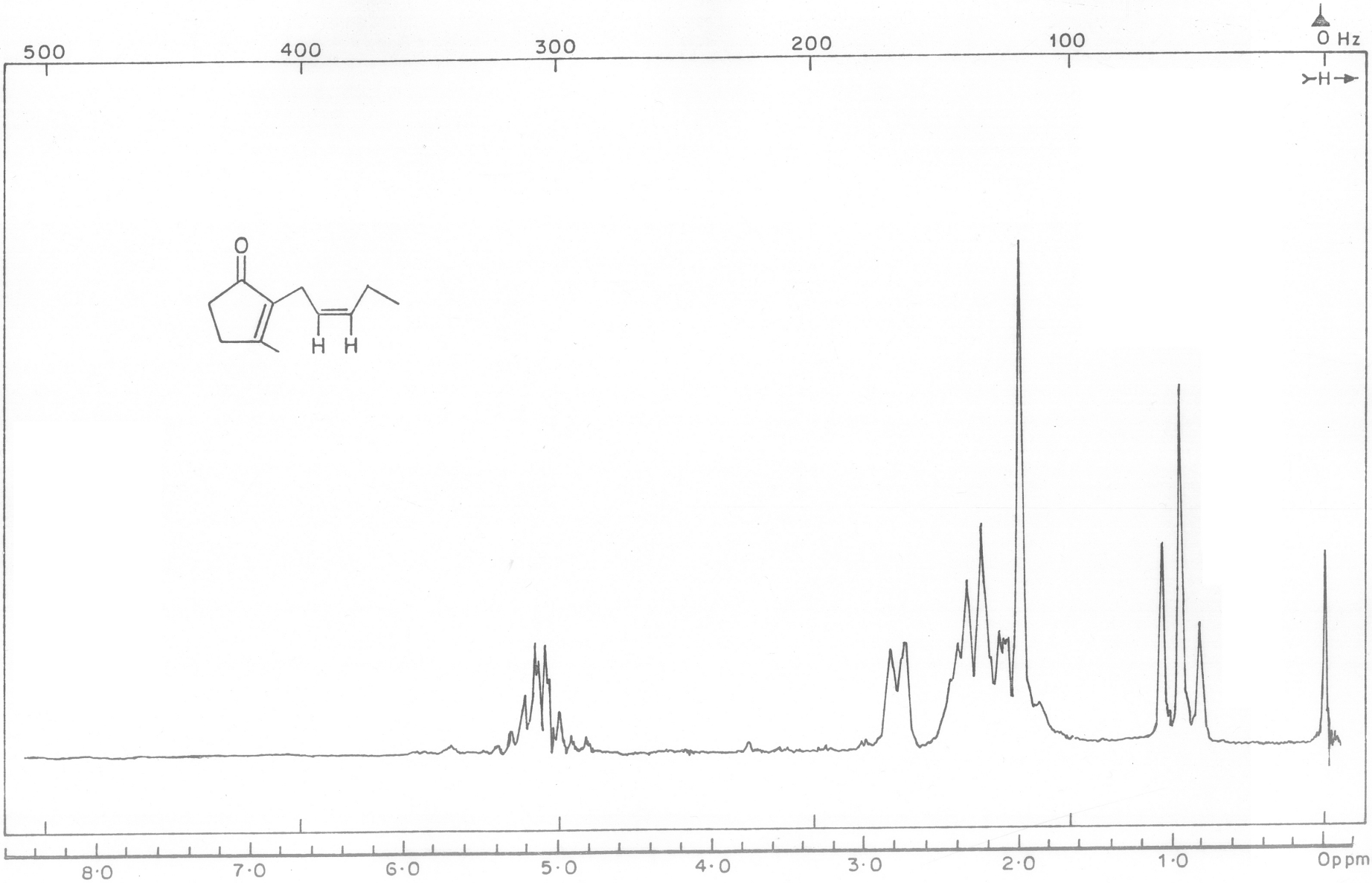


FIG. 4. ^{1}H-NMR SPECTRUM OF COMPOUND (36a) IN $CDCl_3$

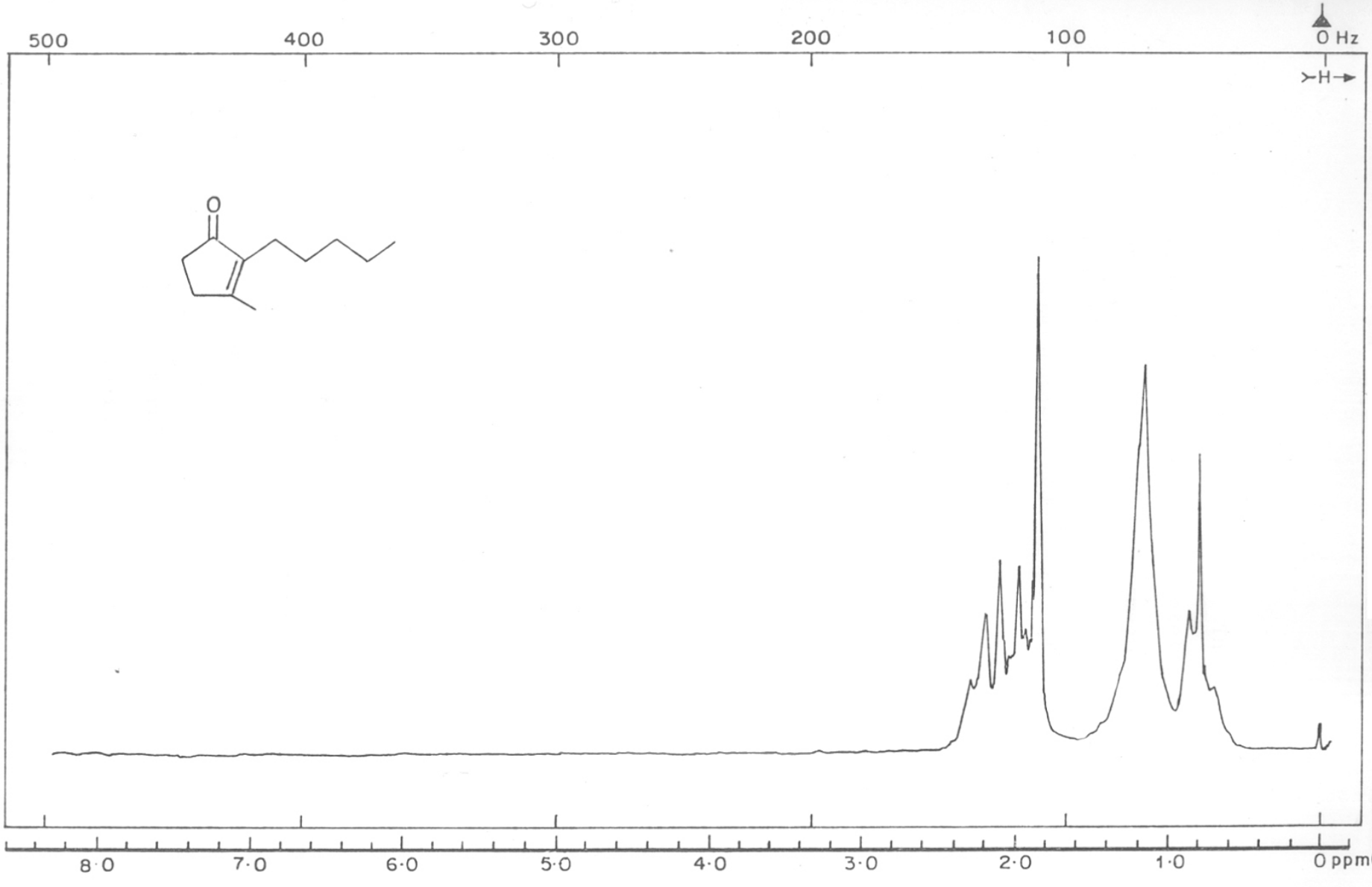


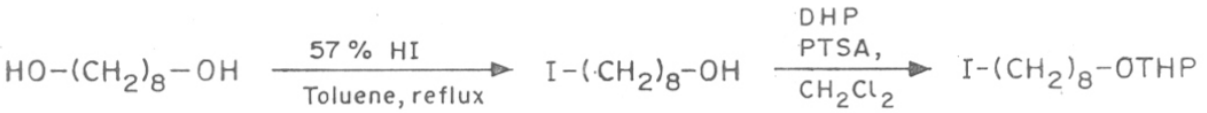
FIG. 5. ^{1}H-NMR SPECTRUM OF COMPOUND (36b) IN CCl_4

a wide spectrum of physiological uses. They act as a vasodilator, decongestant, improved platelet mobility and stability and can be used in the treatment of stomach ulcers and as an abortifacient or bith control agents. The discovery of prostaglandins as pharmaceutical agents has motivated tremendous amount of research in the synthetic organic chemistry, pharmacology and clinical medicine. The natural prostaglandins fall into six classes of compounds named as prostaglandin-A through F series of compounds. The classification is based on the structure of the cyclopentyl group in prostanoic acid.

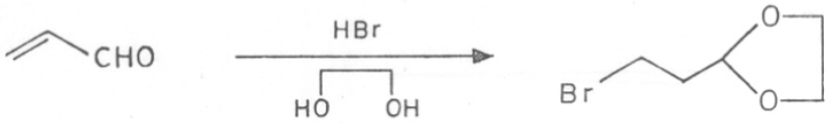
According to the planned strategy as shown in the scheme 37, the required alkyl halides,tetrahydropyranyl ether of 8-iodooctanol (41) and 3,3-ethylenedioxy propyl bromide (43) were first synthesised. The iodide 41 was synthesised from octane-1,8-diol by treatment with 57% hydroiodic acid in toluene, followed by the protection of free hydroxyl group with dihydropyran. The bromide 43 was obtained[37] in one step from acrolein by the reaction with hydrogenbromide in ethyleneglycol.

Selective monoalkylation of TosMIC (30) with iodide 41 was achieved in the presence of a phase-transfer catalyst (tetrabutyl ammonium bromide) to give in 80% yield of the corresponding product 42. In the ^{1}H-NMR spectrum of 42, signals due to THP (tertiary) proton and methine proton were overlapping in the region of 4.0 - 4.4 ppm, while other protons

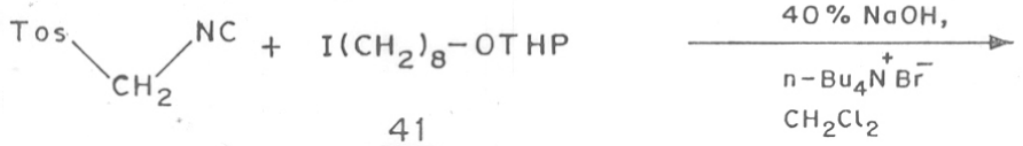
SCHEME-37



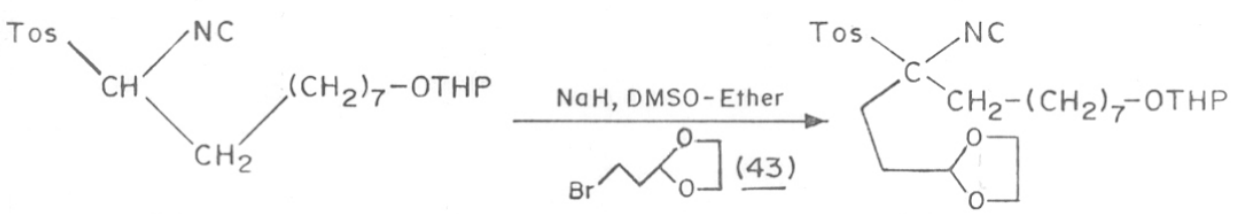
41



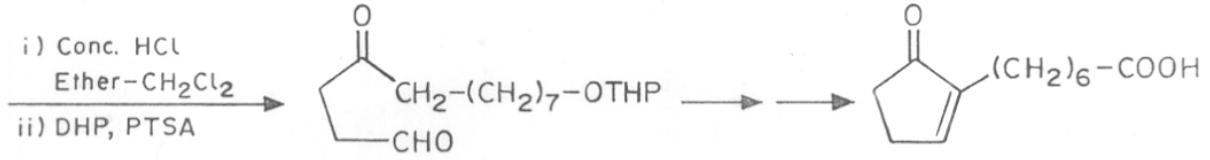
43



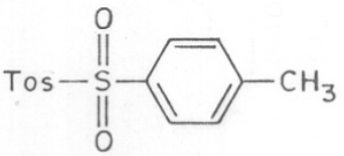
41



42 44



29 40



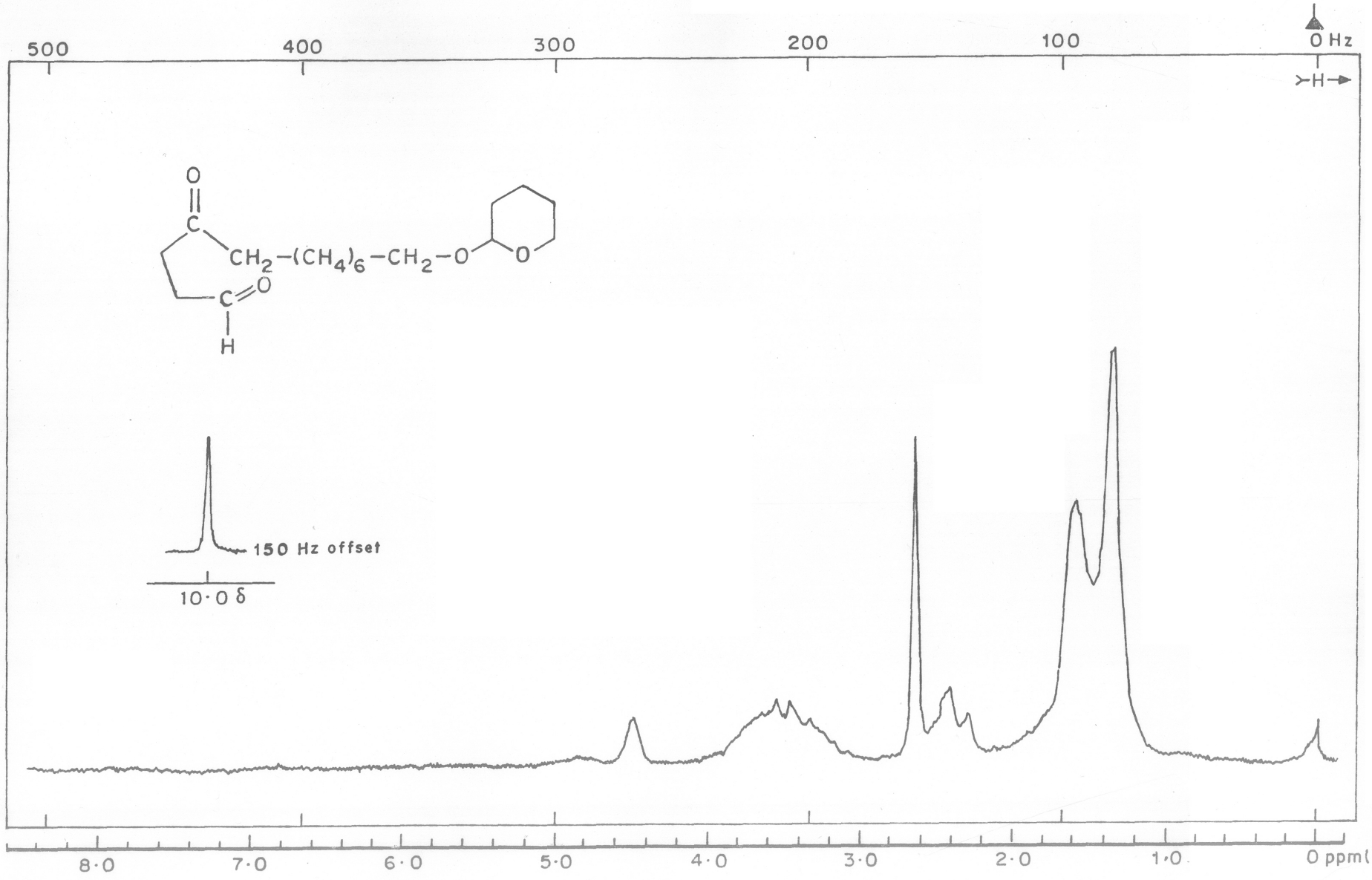


FIG. 6. ^{1}H-NMR SPECTRUM OF COMPOUND (29) IN CCl_4

resonated at the expected chemical shifts.

The dialkylation of 42 was effected with the bromide 43 using sodium hydride as base to afford the product 44 in 90% yield. In the ^{1}H-NMR spectrum of 44, peaks corresponding to the ketal group and THP group were localized, which indicated that the alkylation had occurred.

Hydrolysis of the dialkylated TosMIC derivative 44 with conc. hydrochloric acid gave a product, which was immediately protected with dihydropyran to afford the THP protected ketoaldehyde 29 in an overll yield of 75%. The physical and spectral data (Fig.6) of this compound coincided with the authentic sample reported earlier, which proved the structure. The transformation of the ketoaldehyde 29 into cyclopentenone derivative 40 has already been carried out by Umani-Ronchi et al.[38]. This intermediate has been utilized for the synthesis of (±)-11,15-dideoxy PGE, and (-)-11-deoxy PGE_1.

GENERAL REMARKS

Melting points are uncorrected. IR spectra ($_{max}$ in cm^{-1}) were recorded in nujol or chloroform or neat on a Perkin-Elmer Model 683 spectrophotometer with sodium chloride optics.

^{1}H-NMR spectra were obtained on Varian T-60 or Varian FT-80A or Bruker WH-90 spectrometer in $CDCl_3$ or CCl_4 solutions containing TMS as an internal standard with chemical shifts ( ) expressed in ppm downfield from TMS.

Mass spectra were run on AEI MS 30 double beam mass spectrometer or CEC 21-110B spectrometer.

All solvents and reagents were purified and dried by standard techniques. Solvents were removed on rotary evaporator at temperatures between 40-50°.

Progress of the reactions was checked by TLC on 0.2 mm layers of silica gel, using iodine chamber for visualisation.

EXPERIMENTAL

Tosylmethyl isocyanide (30)

40% solution of formaldehyde (116 ml, 1.5 mol), formamide (226 g, 5 mol) and formic acid (81 g, 1.8 mol) were added to an aqueous solution of sodium p-toluenesulphinate (89 g, 0.5 mol) in water (250 ml). The reaction mixture was heated at 90-95° with vigorous stirring. After 2 hr, it was cooled in an ice salt bath and further left overnight in a freezer. The solid separated was filtered, washed with ice water and dried over P_2O_5 at 70° to give N-(p-tolylsulphonylmethyl) formamide (51.1 g) in 40% yield. m.p.108° (lit.[39] 106-110°).

A solution of $POCl_3$ (16 ml, 0.18 mol) in 1,2-dimethoxyethane (20 ml) was added dropwise to a cooled and stirred suspension of crude N-(ptolylsulphonylmethyl) formamide (35 g, 0.16 mol), DME (80 ml), dry ether (35 ml) and triethylamine (115 ml, 0.8 mol). After being stirred for further 30 min. at 0°, ice cold water (500 ml) was added with stirring. The brown crystalline solid separated in the reaction mixture was filtered and washed with 75 ml of cold water. The wet product was dissolved in 125 ml of warm benzene (40-60°) and the aqueous layer was separated. The dark brown benzene solution was dried (Na_2SO_4) and the crude product was precipitated by adding petroleum ether to give 30 (26 g) in 82% yield, m.p. 113° (dec.) [lit.[39] m.p. 111-114°(dec.)].

1-Tosylundecyl isocyanide (32a)

A mixture of tosylmethyl isocyanide (TosMIC) (30) (0.975 g, 5 m.mol), n-decyliodide (31a) (1.34 g, 5 m.mol), tetrabutylammonium bromide (0.320 g, 1.0 m.mol), 40% aqueous sodium hydroxide (12 ml) and dichloromethane (15 ml) was stirred at 0°C for two hr and then at room temperature for 12 hr. The reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was washed with water, brine and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a solid which was crystallised from ether-petroleum ether mixture to give 32a (1.5 g) in 80% yield, m.p. 55-57°. IR(nujol): 2120 cm^{-1} (N=C). ^{1}H-NMR ($CDCl_3$): δ 0.9 (distorted t, 3H, CH_3), 1.33 (bs, 18H, 9X $-CH_2$), 2.43 (s, 3H, Ar-CH_3), 4.20 - 4.50 (m, 1H, -CHNC), 7.20 (d, J=8 Hz, 2H, Ar-H), 7.60 (d, J=8 Hz, 2H, Ar-H).

Analysis: Calculated for $C_{19}H_{29}NO_2S$: C, 68.66; H, 8.66; N, 4.12; S, 9.55. Found: C, 68.53; H, 8.63; N, 4.08; S, 9.48%.

1-Tosyl Nonadecyl isocyanide (32b)

A mixture of TosMIC (30, 0.97 g, 5 m.mol), 1-iodooctadecane (31b, 1.9 g, 5 m.mol) and tetrabutyl ammonium bromide (0.32 g, 1 m.mol) in 40% aqueous sodium hydroxide solution (12 ml) and dichloromethane (15 ml) was stirred at 0° for 2 hr and then at room temperature for 9 hr. The reaction mixture was worked up as mentioned above to furnish 32b (1.82 g) in 80% yield, which was crystallised from benzene-pet.ether (3:1)

into colourless needles m.p. 77°. ^{1}H-NMR (CCl_4): δ 0.90 (dist.t, 3H, $-CH_3$), 1.30 (br.s, 34H, 17X $-CH_2-$), 2.50 (s, 3H, Ar-CH_3), 4.20 - 4.50 (m, 1H, -CHNC), 7.33 (d, J=8 Hz, 2H, aromatic), 7.76 (d, J=8 Hz, 2H,aromatic). IR (nujol): 2140 cm^{-1} (N=C): M^+ 447.

Analysis: Calculated for $C_{27}H_{45}O_2NS$: C, 72.48; H, 10.06; Found: C, 72.37; H, 10.10%.

3,3-Ethylenedioxy butylbromide (33)

To a solution of HBr (12.6 g, 0.14 mol) in ethyleneglycol (24.8 g, 0.4 mol) was added dropwise methylvinyl ketone (7.0 g, 0.1 mol) at 0°. The reaction mixture was stirred at room temperature for 1 hr and then extracted with hexane. The extracts were washed with 5% $NaHCO_3$ solution and dried over anhyd. Na_2SO_4. Evaporation of the solvent and distillation of the resulting residue gave 33 (8.87 g) in 46% yield, b.p. 69-73°/10 mm (lit.[35] b.p. 88-94°/27 mm). ^{1}H-NMR (CCl_4): δ 1.30 (s, 3H, $-CH_3$), 2.20 (t, 2H, $-CH_2$), 3.40 (t, 2H, $-CH_2Br$), 3.90 (s, 4H, $-OCH_2.CH_2O-$).

1-(3',3'-ethylenedioxybutyl)-1-tosylundecylisocyanide (34a)

A solution of 32a (1.34 g, 4 m.mol) in 1:10 DMSO-ether (20 ml) was added dropwise, to a stirred suspension of prewashed sodium hydride (0.14 g, 6 m.mol) in ether (10 ml) during 10 min. at 10-15° under nitrogen atmosphere. Bromide 33 (0.78 g, 4 m.mol) in ether (8 ml) was added to the reaction mixture and stirring continued at 10-15° for an additional 3 hr. The reaction mixture was poured into cold water (20 ml) and extracted with ether.

The organic extract was washed with water, brine and dried (Na_2SO_4). The solvent was removed to give 34a (1.72 g) in 96% yield as a gummy material. IR (nujol): 2130 cm^{-1} (N=C); ^{1}H-NMR (CCl_4):δ0.95 (distorted t, 3H, $-CH_3$), 1.15 - 1.40 (br.s, 19H, 8X $-CH_2$ and $-CH_3$), 1.75 - 2.0 (m, 6H, 3X $-CH_2$), 2.50 (s,3H, Ar-CH_3), 3.90 (s, 4H, $-OCH_2.CH_2O$), 7.25 (d, 2H, Ar-H), 7.75 (d, 2H, Ar-H).

1-(3,3-ethylenedioxybutyl)-1-tosylnonadecylisocyanide (34b)

A solution of 32b (1.75 g, 4 m.mol) in 1:10 DMSO-ether (20 ml) was added dropwise, to a stirred suspension of prewashed sodiumhydride (0.14 g, 6 m.mol) in ether (10 ml) during 10 min. Bromide 33 (0.78 g, 4 m.mol) in ether (8 ml) was added to the reaction mixture and stirring was continued for an additional 3 hr. The reaction mixture was worked up as mentioned earlier to afford 34b (2.086 g) in 92% yield as gummy material. IR(neat): 2120 cm^{-1}; ^{1}H-NMR (CCl_4):δ0.9 (distorted t, 3H, $-CH_3$), 1.2 - 1.4 (br.s, 35H, 16X CH_2 and $-CH_3$), 1.75 - 2.05 (m, 6H, 3X $-CH_2$), 2.45 (s, 3H, Ar-CH_3), 3.9 (s, 4H, $-OCH_2-CH_2O-$), 7.30 (d, 2H, Ar-H), 7.8 (d, 2H, Ar-H).

Pentadecan-2,5-dione (27a)

Compound 34a (1.57 g, 3.5 m.mol) was dissolved in a mixture of ether-dichloromethane (21: 7 ml) and treated with conc. hydrochloric acid (0.4 ml) at room temperature for 30 min. The reaction mixture was diluted with ether and washed successively

with water, 5% sodium bicarbonate and brine. The organic layer was dried and solvent was removed to afford 27a (0.75 g) in 90% yield.. IR(nujol): 1725 cm^{-1} (-C=O); ^{1}H-NMR (CCl_4): δ 0.92 (distorted t, 3H, $-CH_3$), 1.10 - 1.40 (br.s, 16H, 8X $-CH_2$), 2.10 (s, 3H, $CO-CH_3$), 2.45 (dist.t, 2H, $CO-CH_2$), 2.70 (s, 4H, $CO-CH_2.CH_2CO-$).

Triecoso-2,5-dione (27b)

Compound 34b (1.96 g, 3.5 m.mol) was dissolved in a mixture of ether-dichloromethane (30 ml) and treated with conc. HCl (0.4 ml) at room temperature for 30 min. The reaction mixture was worked up as described above to furnish 27b (1.103 g) in 89.6% yield. IR (nujol): 1720 cm^{-1} (C=O); ^{1}H-NMR (CCl_4): δ 0.95 (distorted t, 3H, $-CH_3$), 1.25 - 1.55 (br.s, 32H, 16X $-CH_2$), 2.15 (s, 3H, $CO-CH_3$), 2.50 (dist.t, 2H, $CO-CH_2$), 2.75 (s, 4H, $-COCH_2.CH_2.CO$); Mass: M^+ 352.

2-Nonyl-3-methylcyclopent-2-enone (35)

A mixture of 27a (0.48 g, 2 m.mol), 0.5N sodium hydroxide solution (4 ml) and ethanol (2 ml) was allowed to reflux under nitrogen for 6 hr. The reaction mixture was allowed to cool, extracted with ether, the ether extracts were washed with water and dried (Na_2SO_4). The solvent was removed and the residue was eluted through a short column of silica gel to furnish pure 35 (0.335 g) in 75% yield. IR (neat): 1650 and 1705 cm^{-1}; ^{1}H-NMR (CCl_4): δ 0.90 (distorted t, 3H, $-CH_3$), 1.15 - 1.50 (br.s, 14H, 7X $-CH_2$), 2.04 (s, 3H, $-CH_3$), 2.10 - 2.60 (m, 6H, 3X $-CH_2$).

(Z)-1-Iodo-3-hexene (37a)

To a cooled solution of cis-3-hexenol (4.0 g, 0.040 mol) in dry dichloromethane (40 ml) containing triethylamine (12.1 g, 0.12 mol) was added a solution of methanesulfonylchloride (6.87 g, 0.06 mol) in dichloromethane (10 ml) over a period of 10 min. Stirring was continued for further 1 hr and the reaction mixture was washed with ice water followed by 10% HCl, 5% aq. sodiumbicarbonate and brine. The organic phase was dried (Na_2SO_4) and concentrated to give the mesylate.

The crude mesylate was treated with sodium iodide (12.0 g, 0.08 mol) in anhydrous THF (50 ml) at room temperature for 12 hr. The solvent was removed, the residue dissolved in ether and washed successively with water, aq. sodium thiosulfate, brine and dried (Na_2SO_4). The solvent was removed to afford 37a (5.88 g) in 70% yield. ^{1}H-NMR (CCl_4): δ 1.02 (t, 3H, CH_3), 1.70 - 2.20 (m, 2H, $-CH_2-CH_3$), 2.4-2.8 (m, 2H, $-CH_2$), 3.01 (t, 2H, $-CH_2I$), 4.95-5.6 (m, 2H, olefinic).

(Z)-1-Tosyl hept-4-enylisocyanide (38a)

A mixture of TosMIC (30, 1.56 g, 8 m.mol), iodide 37a (1.68 g, 8 m.mol) and tetrabutylammonium bromide (0.51 g, 1.6 m.mol) in 40% aq. sodium hydroxide solution (20 ml) and dichloromethane (25 ml) was stirred at 0° for 2 hr and then at room temperature for 12 hr. The reaction mixture was worked up as mentioned earlier to furnish 38a (1.77 g) in 80% yield. IR (neat): 2120 cm^{-1} (N=C); ^{1}H-NMR (CCl_4): δ 1.0 (t, 3H, $-CH_3$), 1.7 - 2.5 (m, 6H, 3X CH_2), 2.5 (s, 3H, Ar-CH_3), 4.10 - 4.30 (m,

1H, -CH), 5.0 - 5.6 (m, 2H, olefinic), 7.25 (d, 2H, Ar-H), 7.8 (d, 2H, Ar-H).

Analysis: Calculated for $C_{15}H_{19}NO_2S$: C, 64.98; H, 6.85; N, 5.05. Found: C, 64.83; H, 6.82; N, 5.07%.

1-Tosylheptylisocyanide (38b)

A mixture of TosMIC (30, 1.95 g, 10 m.mol), 1-iodohexane (1.02 g, 10 m.mol) and tetrabutylammonium bromide (0.64 g, 2 m.mol) in 40% aq. NaOH solution (24 ml) and dichloromethane (30 ml) was stirred at 0° for 2 hr and then at room temperature for 12 hr. The reaction mixture was worked up as described earlier to afford 38b (2.26 g) in 81% yield. IR (neat): 2120 cm^{-1} (NC). ^{1}H-NMR (CCl_4): δ 0.90 (distorted t, 3H, $-CH_3$), 1.1 - 1.5 (br.s, 8H, 4X CH_2), 1.60 - 2.00 (m, 2H, $-CH_2$), 2.42 (s, 3H, Ar-CH_3), 4.05 - 4.25 (m, 1H, -CH), 7.10 (d, 2H, Ar-H), 7.50 (d, 2H, Ar-H).

Analysis: Calculated for $C_{19}H_{31}NO_2S$: C, 64.52; H, 7.52; N, 5.02; Found: C, 64.71; H, 7.54; N, 5.03%.

(Z)-1-(3,3-Ethylenedioxybutyl)-1-tosylhept-4-enyl isocyanide (39a)

A solution of 38a (1.66 g, 6 m.mol) in 1:10 DMSO-ether (20 ml) was added dropwise to a suspension of prewashed sodium hydride (0.216 g, 9 m.mol) in ether (5 ml) during 5 min. at 10° under nitrogen atmosphere. Bromide 33 (1.170 g, 6 m.mol) in ether (8 ml) was added dropwise to the reaction mixture and the stirring continued at the same temperature for further 3 hr. The reaction mixture was worked up as described earlier to furnish 39a (2.23 g) in 95% yield as gummy material. IR(neat):

2115 cm^{-1} (N=C). ^{1}H-NMR (CCl_4): δ 1.00 (t, 3H, $-CH_3$), 1.20 (s, 3H, $-CH_3$), 1.74 - 2.25 (m, 10H, 5X $-CH_2$), 2.52 (s, 3H, $ArCH_3$), 3.88 (s, 4H, $-OCH_2.CH_2O-$), 5.05 - 5.40 (m, 2H, olefinic), 7.23 (d, 2H, Ar-H), 7.75 (d, 2H, Ar-H).

Analysis: Calculated for $C_{21}H_{29}NO_4S$: C, 64.45; H, 7.42; N, 3.58. Found: C, 64.34; H, 7.43; N, 3.56%.

1-(3,3-Ethylenedioxybutyl)-1-tosylheptylisocyanide (39b)

A solution of 38b (2.20 g, 8 m.mol) in 1:10 DMSO-ether (30 ml) was added dropwise to a suspension of NaH (0.288 g, 12 m.mol) in ether (8 ml) during 10 min. at 10°. Bromide 33 (1.56 g, 8 m.mol) in ether (10 ml) was added dropwise to the reaction mixture and the stirring continued for further 3 hr. Usual work up gave 39b (3.0 g) in 95.5% yield. IR (neat): 2120 cm^{-1} (N=C). ^{1}H-NMR (CCl_4): δ 0.90 (distorted t, 3H, $-CH_3$), 1.05 - 1.45 (m, 11H, 4X CH_2 and $-CH_3$), 1.70 - 1.90 (m, 6H, 3X $-CH_2$), 2.40 (s, 3H, Ar-CH_3), 3.86 (s, 4H, $-OCH_2-CH_2O-$), 7.13 (d, 2H, Ar-H), 7.62 (d, 2H, Ar-H).

(Z)-Undec-8-ene-2,5-dione (28a)

To the solution of 39a (2.15 g, 5.5 m.mol) in 1:3 dichloromethane-ether (40 ml) mixture, conc. HCl (0.8 ml) was added and stirred for 30 min. at 20°. It was diluted with ether and washed successively with water, 5% aq. $NaHCO_3$, brine and dried (Na_2SO_4). The solvent was evaporated to give 28a (0.9 g) in 90% yield. IR (neat): 1720 cm^{-1} (C=O). ^{1}H-NMR (CCl_4): δ 0.95 (t, 3H, $-CH_3$), 1.70 - 2.10 (m, 4H, 2X $-CH_2$), 2.0 (s, 3H, $-CO.CH_3$),

2.25 (t, 2H, $-COCH_2$), 2.55 (s, 4H, $-CO.CH_2.CH_2.CO$), 4.90 - 5.15 (m, 2H, olefinic); Mass: M^+ 182.

Analysis: Calculated for $C_{11}H_{18}O_2$: C, 72.52; H, 9.89; Found: C, 72.42; H, 9.92%.

Undecan-2,5-dione (28b)

To the solution of 39b (2.94 g, 7.5 m.mol) in dichloromethane-ether mixture (45 ml), conc. HCl (1.0 ml) was added and stirred for 30 min. The reaction mixture was worked up as mentioned above to afford 28b (1.25 g) in 91% yield. IR (neat): 1720 cm^{-1} (-C=O). ^{1}H-NMR (CCl_4): δ 0.87 (dist.t, 3H, $-CH_3$), 1.10 - 1.30 (br.s, 8H, 4X $-CH_2$), 1.97 (s, 3H, $CO.CH_3$), 2.15 (dist.t, 2H, $CO.CH_2$), 2.45 (s, 4H, 2X $-CH_2$); Mass: M^+ 184.

(Z)-Jasmone (36a)

A mixture of 28a (0.73 g, 4 m.mol), 0.5N NaOH (8 ml) and ethanol (4 ml) was allowed to reflux under N_2 for 6 hr. The cooled reaction mixture was acidified with dil. HCl and extracted with ether. The ethereal extracts were washed with water and dried (Na_2SO_4). The solvent was evaporated and the resulting residue was eluted through a short silica gel column to give pure (Z)-jasmone (0.525 g) in 80% yield. IR (neat): 1650, 1705 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.02 (t, 3H, $-CH_3$), 2.10 (s, 3H, $-CH_3$), 2.10 - 2.60 (m, 6H, 3X $-CH_2$), 2.90 (d, 2H, $-CH_2$), 5.0 - 5.35 (m, 2H, olefinic); Mass: M^+ 164.

Analysis: Calculated for $C_{11}H_{16}O$: C, 80.48; H, 9.75; Found: C, 80.26; H, 9.78%.

Dihydrojasmone (36b)

A mixture of 28b (1.10 g, 6 m.mol), 0.5 N NaOH (12 ml) and ethanol (6 ml) was agitated under reflux for 6 hr. The reaction mixture was worked up as described above to afford dihydrojasmone (36b, 0.795 g) in 80% yield. IR (neat): 1650, 1705 cm^{-1}; ^{1}H-NMR (CCl_4): δ 0.85 (dist.t, 3H, $-CH_3$), 1.0 - 1.45 (m, 6H, 3X $-CH_2$), 1.90 (s, 3H, $-CH_3$); 1.90 - 2.40 (m, 6H, 3X $-CH_2$). Mass: M^+ 166.

Analysis: Calculated for $C_{11}H_{18}O$: C, 79.50; H, 10.84; Found: C, 79.17; H, 10.84%.

8-[(Tetrahydro-2H-pyran-2-yl)-oxy]octyliodide (41)

A mixture of octane-1,8-diol (7.3 g, 0.05 mol) and 57% hydroiodic acid (9.5 ml, 0.07 mol) in toluene (60 ml) was allowed to reflux for 6 hr. The cooled reaction mixture was diluted with water and the organic layer was washed with 5% aq. $NaHCO_3$ solution, 10% $Na_2S_2O_3$ solution and brine. The dried (Na_2SO_4) organic layer was evaporated and the resulting residue passed through a silica gel column to afford pure 8-iodo-octanol (9.6 g) in 75% yield.

A mixture of 8-iodooctanol (9.6 g, 0.0375 mol), dihydropyran (4.7 g, 0.056 mol) and p-toluenesulfonic acid (0.10 g) in dry dichloromethane (100 ml) was stirred at room temperature for 6 hr. The reaction mixture was diluted with CH_2Cl_2, washed with 5% aqueous Na_2CO_3 and dried (K_2CO_3). Evaporation of the solvent and chromatographic purification (silica gel) of the residue gave 41 (11.47 g) in 90% yield. ^{1}H-NMR (CCl_4): δ 1.20 -

1.70 (m, 18H, 9X $-CH_2$), 3.0 - 3.70 (m, 6H, 3X $-CH_2$), 4.42 (br.s, 1H, O.CH.O).

1-Tosyl-9-[(tetrahydro-2H-pyran-2-yl)-oxy]nonylisocyanide (42)

A mixture of TosMIC (30, 0.97 g, 5 m.mol), iodide 41 (1.70 g, 5 m.mol) and tetrabutylammonium bromide (0.32 g, 1 m.mol) in 40% aqueous NaOH (12 ml) and dichloromethane (15 ml) was stirred at 0° for 2 hr and then at room temperature for 12 hr. The reaction mixture was worked up as described earlier to give 42 (1.63 g) in 80% yield as a gummy product. ^{1}H-NMR (CCl_4): δ 1.15 - 1.65 (m, 20H, 10X $-CH_2$), 2.38 (s, 3H, Ar-CH_3), 2.85 - 3.75 (m, 4H, 2X $-CH_2$), 4.0 - 4.4 (m, 2H, 2X -CH), 6.98 (d, 2H, Ar-H), 7.47 (d, 2H, Ar-H).

Analysis: Calculated for $C_{22}H_{33}NO_4S$: C, 64.86; H, 8.11; Found: C, 64.90; H, 8.12%.

3,3-Ethylenedioxypropylbromide (43)

To a stirred solution of HBr (24 g, 0.3 mol) in ethylene glycol (55 g, 0.9 mol) was added dropwise acrolein (11.2 g, 0.2 mol) at 5°. After stirring for 1 hr at room temperature, the mixture was extracted twice with hexane. The organic layer was washed with 5% $NaHCO_3$, dried (Na_2SO_4) and evaporated. Distillation of the residue afforded 43 (22.25 g) in 64% yield. b.p. 80°/15 mm (lit.[37] b.p. 68-70°/8 mm). ^{1}H-NMR (CCl_4): δ 2.10 (d of t, 2H, $-CH_2$), 3.38 (t, 2H, $-CH_2$), 3.80 (m, 4H, $OCH_2.CH_2O-$), 4.80 (t, 1H, OCH.O).

1-(3,3-Ethylenedioxypropyl)-1-tosyl-9-[(tetrahydro-2H-pyran-2-yl)-oxy]nonylisocyanide (44)

A solution of 42 (1.42 g, 3.5 m.mol) in 1:10 DMSO-ether (20 ml) was added dropwise to a stirred suspension of NaH (0.12 g, 5 m.mol) in ether (10 ml) during 10 min. at -5 to 0° under N_2. Bromide 43 (0.65 g, 3.55 m.mol) in ether (6 ml) was added dropwise to the reaction mixture and stirring was continued for 3 hr at 10°. The reaction mixture was worked up as mentioned earlier to give 44 (1.81 g) in 88% yield as a gummy material. IR (neat): 2140, 1600 cm^{-1}; ^{1}H-NMR (CCl_4): δ 1.2 - 2.0 (m, 24H, 12X CH_2),2.4 (s, 3H, Ar-CH_3), 3.2 - 3.6 (m, 4H, 2X -OCH_2-), 3.9 (d, 4H, -O-CH_2.CH_2O-), 4.5 (br.s, 1H, -CH), 4.8 (br.t, 1H, -CH), 7.2 (d, 2H, Ar-H), 7.65 (d, 2H, Ar-H).

Analysis: Calculated for $C_{27}H_{41}NO_6S$: C, 63.90; H, 8.09; Found: C, 63.60; H, 8.14%.

4-oxo-12-[(tetrahydro-2H-pyran-2-yl)-oxy]dodecanal (29)

To the solution of 44 (1.52 g, 3 m.mol) in 1:3 CH_2Cl_2-ether (32 ml) mixture, conc. HCl (1.5 ml) was added and stirred for 1 hr. After usual work up the product was dissolved in CH_2Cl_2 (30 ml), cooled to 0° and added dihydropyran (0.34 g, 4.0 m.mol) and PTS-acid (20 mg). After stirring the reaction mixture for 4 hr, the usual work up gave the product 29 (0.8 g) in 75% yield as an oil. ^{1}H-NMR (CCl_4):δ 1.2 - 1.8 (m, 18H, 9X -CH_2), 2.2 - 2.6 (m, 2H, CO.CH_2), 2.65 (s, 4H, CO.CH_2.CH_2.CO), 3.1 - 3.9 (m, 4H, 2X OCH_2-), 4.55 (s, 1H, OCHO), 9.8 (s, 1H, -CHO).

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CHAPTER II

PART-A

SYNTHESIS OF SOME UNSATURATED HYDROXY FATTY ACIDS

INTRODUCTION

The utility of acetylenic derivatives in the synthesis of unsaturated fatty acids has been well realised by the work done in these laboratories as well as in other laboratories. The advantages of having acetylenic intermediates lie in their ability to produce cis or trans double bond with ease and with high degree of selectivity, depending upon the reaction conditions and reagent employed. For example, substituted acetylenes undergo partial reduction with sodium in liquid ammonia[1,2], organo aluminium compounds[3], organozirconium compounds[4] and organoboranes[5,6] to afford trans olefins, while partial hydrogenation over Lindlar catalyst[7,8] or P-2 nickel[9] furnishes exclusively cis- olefins. In general, unsaturated hydroxy fatty acids are synthesised from the corresponding acetylenic hydroxy acids because partial reduction at this stage would lead to the desired product.

Formation of acetylenic hydroxy acids are generally visualised from the alkylation of corresponding terminal acetylenic compounds with hydroxy alkyl halides (the hydroxyl group being in the protected form) followed by oxidation of the primary alcoholic group (Scheme 1). By this approach the main

$$R-\equiv-H + X-(CH_2)_n-CH_2OR' \longrightarrow R-\equiv-(CH_2)_n-CH_2OR'$$

$$\longrightarrow R-\equiv-(CH_2)_n-CH_2OH \longrightarrow R-\equiv-(CH_2)_n-COOH$$

drawback is that the carboxyl functionality is generated from the

protected primary alcoholic group, which first needed deprotection followed by oxidation. The yields are normally moderate and the steps involved are more.

Although alkylation of acetylenic compounds with halo-acids to form directly the corresponding acetylenic hydroxy-acids has been reported[10], its use in the synthesis of natural products is rarely encountered. In this part of thesis, this particular strategy has been exploited for the synthesis of (±)-coriolic acid and (±)-recifeiolide.

Section 1 : A short and efficient approach to (±)-coriolic acid

INTRODUCTION

The isolation of small molecular weight ion carriers from biological system has within past few years began to achieve the documentation that has been awaited, since the introduction of the concept by Osterhout[11] in 1933. The molecules present in the biological systems and responsible for the ion-transport are first termed as "ionophores" by Pressmann[12,13] in 1964. The general description of an ionophore is "the ability of a molecule to complex with an ion and assist in the transport of the ion through a lipophilic interface. "Complexone" perhaps accentuating more the process of complexation is employed by Ovchinnikov[14] *et al*. to describe the same molecule. Ionophore is a device for filtering the cation away from its anion.

This class of molecules, the biological ion carriers coined as ionophores have a diversity of structural types. The presence of a hetero atom in their structures, which is capable of acting as a ligand for an ion is the common feature for all these molecules. Another equally important feature is the 3-dimensional capability and an inward orientation of the ligand in an appropriate geometry for the ion, simultaneously exposing a relatively lipophilic exterior.

The interest in the field of naturally occurring ionophores is not only due to their ionophoretic activity, but also

due to their antibiotic activity along with other pharmacological effects[15,16] such as +ve ionotropic effect and a decrease in coronary resistance. Other effects such as distribution of radio nucleides and lowering of intramolecular pressure have also been noticed.

Coriolic acid (1) and dimorphecolic acid (2) are the examples of octadecadienoic acid type of ionophores. This section mainly deals with the synthesis of coriolic acid (1).

Coriolic acid (1) with its ionophoretic activity was isolated from beef heart mitochondria by Blondin[17]. It also occurs in Coriaria nepalensis[18], Xeranthemum annuum seed oils, Monnina emarginate seed oil etc.

The structure of 1 was determined spectroscopically as 13-hydroxy-9-cis-11-trans-octadecadienoic acid (13-HOD) by Blondin[17]. It is an intermediate[19] in the biogenetic conversion of linoleic acid to conjugated trienoic acids. The configuration of the lone chiral centre in 1 was established as (R)[20].

The ionophoretic properties of the neutral mitochondrial divalent cation ionophores 1,2 etc. (Fig.1) were studied by Blondin[17]. From the structure of 1, the isolated oxyoctadecadienoic acid congener should possess divalent cation ionophoretic properties, which are different from those of ordinary fatty acids such as oleic acid and cis-linoleic acids. 13-HOD (1) is a potent inducer of mitochondrial swelling in the presence of Mg^{+2} ions. 1 is also capable to restore the

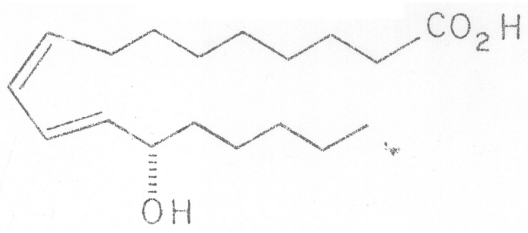
transport of Ca^{+2} and associated swelling of mitochondrial even in the presence of ruthenium red, a calcium transport inhibitor.

Coriolic acid (1) was also isolated recently from Fukuyuki (Oryza sativa L.) by Kato et al.[21,22,23] along with other oxygenated unsaturated fatty acids. They acted as self-defensive substances against rice blast disease. These acids (1 to 5, Fig.1) inhibit the spore germination and germ tube growth of rice blast fungus. These acids seem to play a role as defensive substances in the rice plant without being affected from the disease.

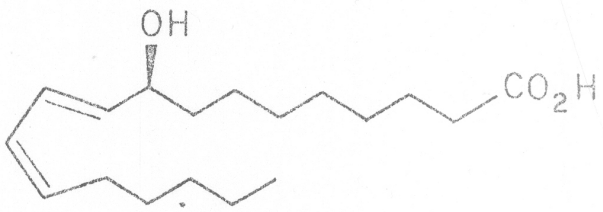
The ionophoretic properties of coriolic acid, its structural features and recent report by Kato et al.[23] (activity against rice blast disease) led to embark on its total synthesis.

The first total synthesis of coriolic acid has been achieved from this laboratory[24] starting from the known compounds 6 and 7 (Scheme 2a). Treatment of acetylenic alcohol 6 with the halide 7 in presence of lithium amide in liquid ammonia furnished the corresponding alkylated derivative 8. Oxidation of the allylic alcohol 8 with manganese dioxide followed by the treatment with the Grignard reagent, prepared from amylbromide and magnesium to give the carbinol 9. The free hydroxyl in 9 was protected as benzoate followed by the removal of THP ether gave the primary alcohol 10. Stepwise

FIGURE - 1



1



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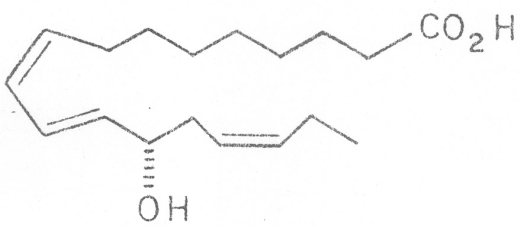

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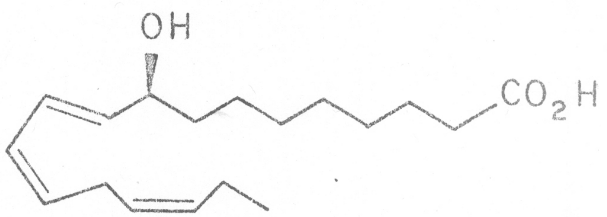

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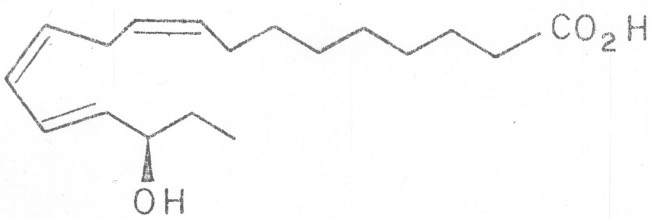
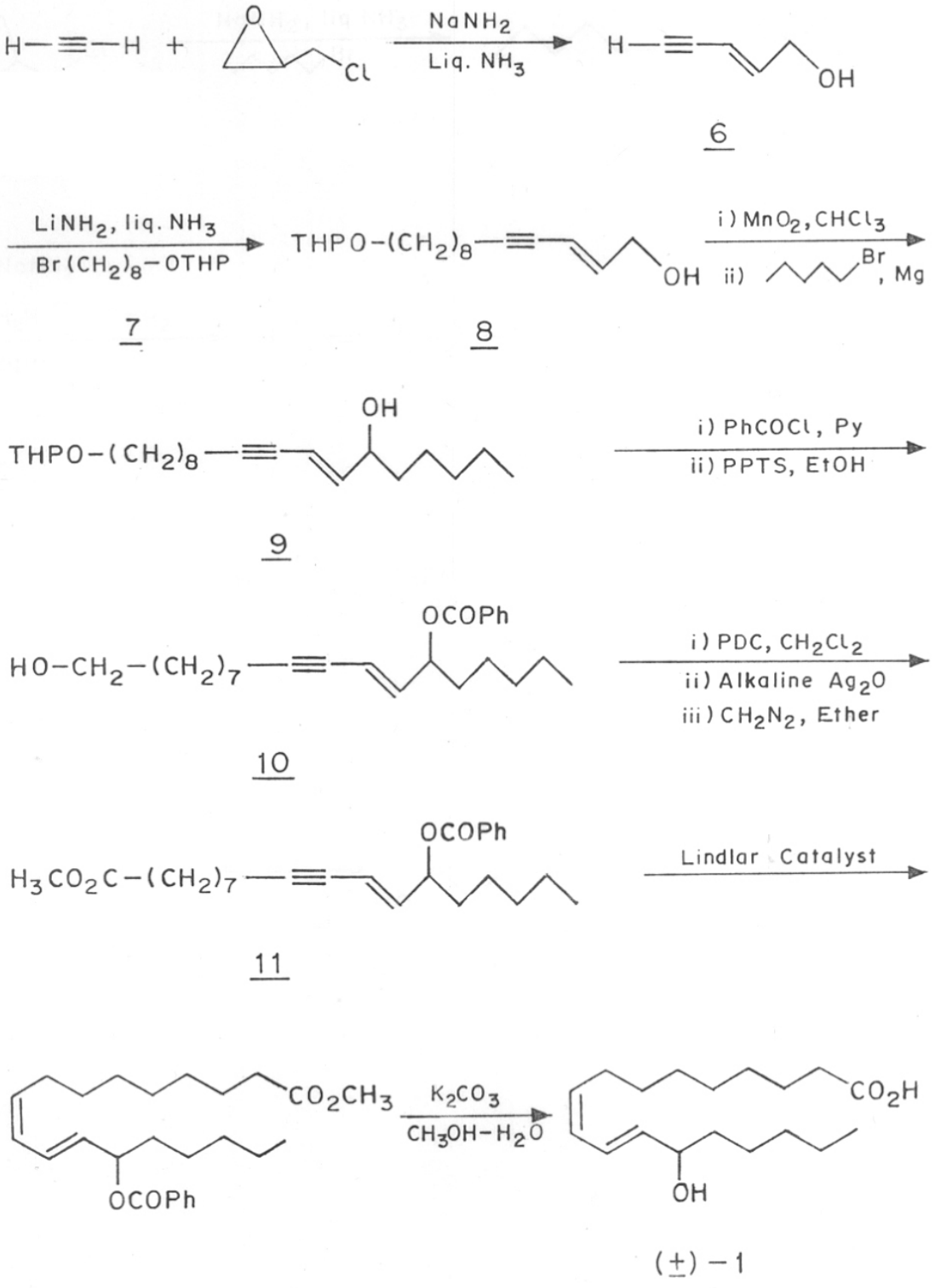
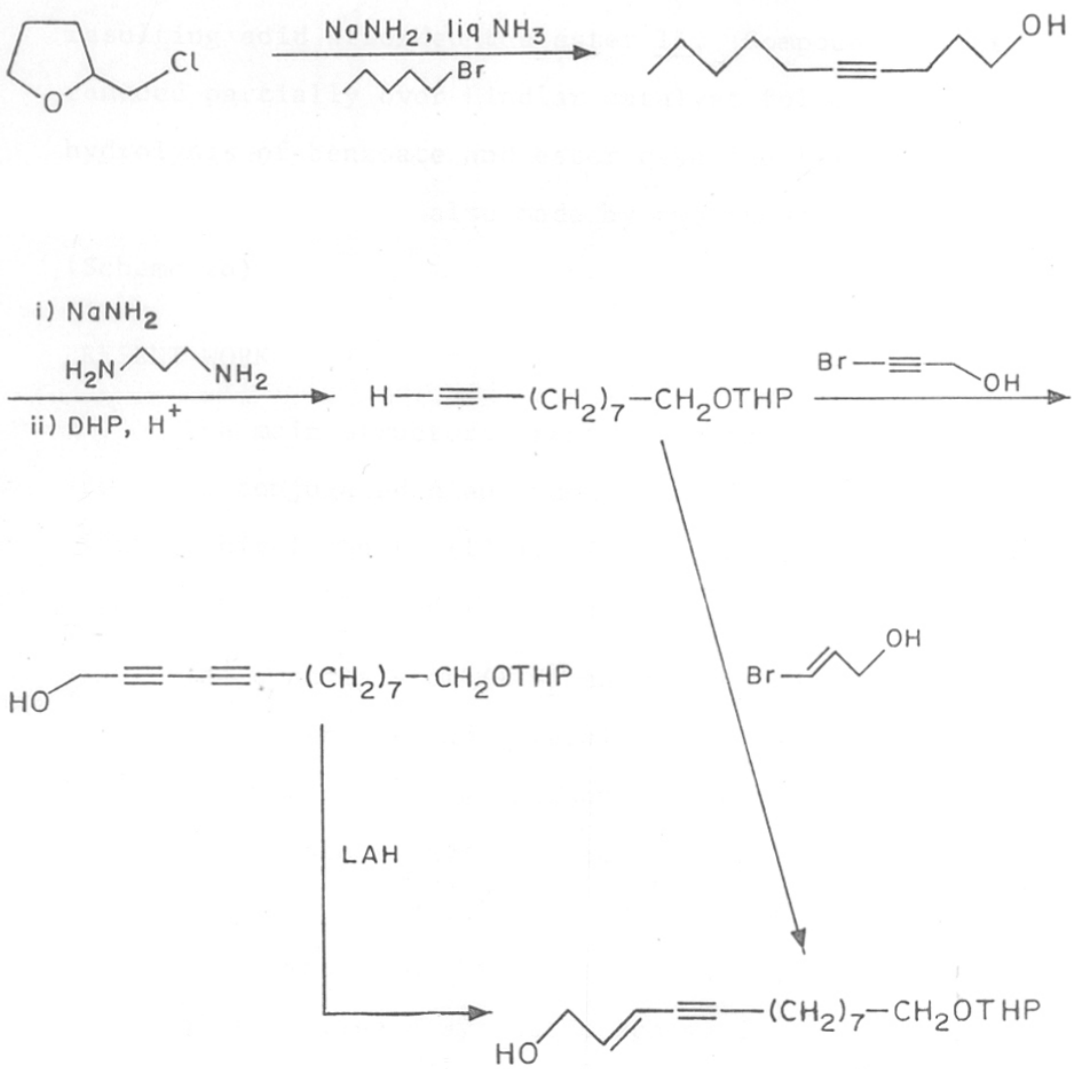


5

SCHEME-2a


NaNH2
Liq. NH3
OH
6
LiNH2, liq. NH3
Br(CH2)8–OTHP
THPO–(CH2)8
OH
7
8
i) MnO2, CHCl3
ii)
Br
, Mg
OH
THPO–(CH2)8
9
i) PhCOCl, Py
ii) PPTS, EtOH
OCOPh
HO–CH2–(CH2)7
10
i) PDC, CH2Cl2
ii) Alkaline Ag2O
iii) CH2N2, Ether
OCOPh
H3CO2C–(CH2)7
11
Lindlar Catalyst
CO2CH3
OCOPh
K2CO3
CH3OH–H2O
CO2H
OH
(±) – 1

SCHEME-2b


NaNH2, liq NH3
Br
Cl
O
OH
i) NaNH2
H2N
NH2
ii) DHP, H+
H—≡—(CH2)7—CH2OTHP
Br—≡—OH
HO—≡—≡—(CH2)7—CH2OTHP
Br
OH
LAH
HO
(CH2)7—CH2OTHP

8

oxidation of 10 followed by the esterification of the resulting acid afforded the ester 11. Compound 11 was reduced partially over Lindlar catalyst followed by the hydrolysis of benzoate and ester gave the (±)-coriolic acid (1). Compound 8 was also made by two other approaches (Scheme 2b).

PRESENT WORK

The main structural features present in the molecule are (i) a conjugated dienol unit (ii) a carboxyl group and (iii) a chiral centre (13R). The geometry of the conjugated diene system is 9Z and 11E.

The synthesis of (±)-1 carried out in these laboratories as described earlier had several drawbacks which were realized later and overcome in the present synthesis. For instance, the number of steps involved are too many and because of this, overall yield is very low. In order to get coriolic acid in substantial amount for biological testing, it is felt most essential to devise a synthetic scheme for (±)-coriolic acid in which the steps should be less and yield of each of the step should be of high order. With this view in mind, a short synthesis of coriolic acid was planned as shown in Scheme 3.

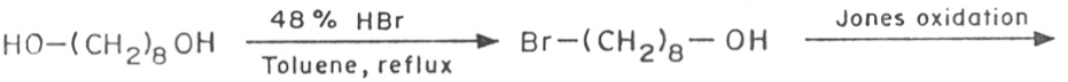
The strategy is based on the reaction in which the alkylation of an acetylenic alcohol was carried out with a haloalkanoic acid in presence of excess of base. This reaction would definitely reduce the number of steps as the requisite

carboxyl functionality was directly incorporated. Accordingly the required (E)-pent-2-en-4-yn-1-ol (6) was prepared[25] by opening of epichlorohydrin with sodiumacetylide in liquid ammonia. The alkylation of acetylenic alcohol 6 was carried out with 8-bromooctanoic acid (12) (prepared from octane 1,8-diol) in the presence of lithiumamide in liquid ammonia to furnish the unsaturated hydroxy acid 13 in 85% yield, on the basis of the bromoacid used. In ^{1}H-NMR spectrum (Fig.2) of 13, a doublet due to the terminal methylene protons (-C$\underline{H}_2$OH) was observed at 4.15 ppm, olefinic protons were located in the region of 5.4 - 6.4 ppm as multiplet and other protons resonated at the expected chemical shifts. The IR spectrum indicated a broad band at 3250 cm^{-1} indicating the presence of -COOH and -OH groups.

Oxidation of 13 with activated manganese dioxide in chloroform at room temperature afforded the aldehyde 14 in 60% yield. In the ^{1}H-NMR spectrum of 14 the aldehyde proton was observed at 9.50 ppm as a doublet, besides the absence of doublet for allylic methylene protons was noticed.

Aldehyde 14 was treated with the Grignard reagent (prepared from amylbromide and magnesium) to furnish the carbinol 15 in 75% yield. The structure of this compound was demonstrated by the spectroscopic data. For example, in ^{1}H-NMR spectrum (Fig.3) the methine proton (C$\underline{H}$-OH) was revealed at 4.0 - 4.2 ppm as a multiplet and rest of the protons appeared at the expected chemical shifts. The final confirmation

SCHEME – 3

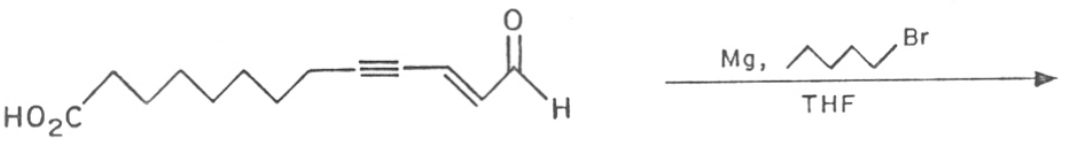


$Br-(CH_2)_7-COOH$

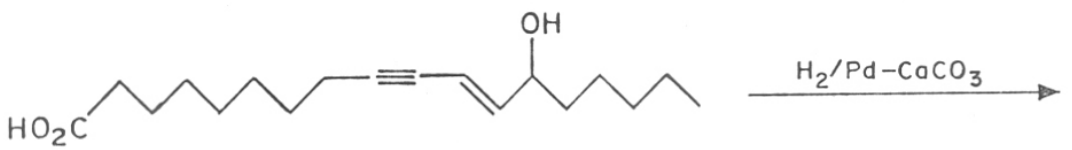
12

6

12 13



14



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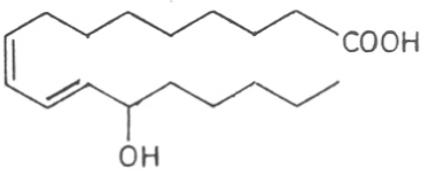


1

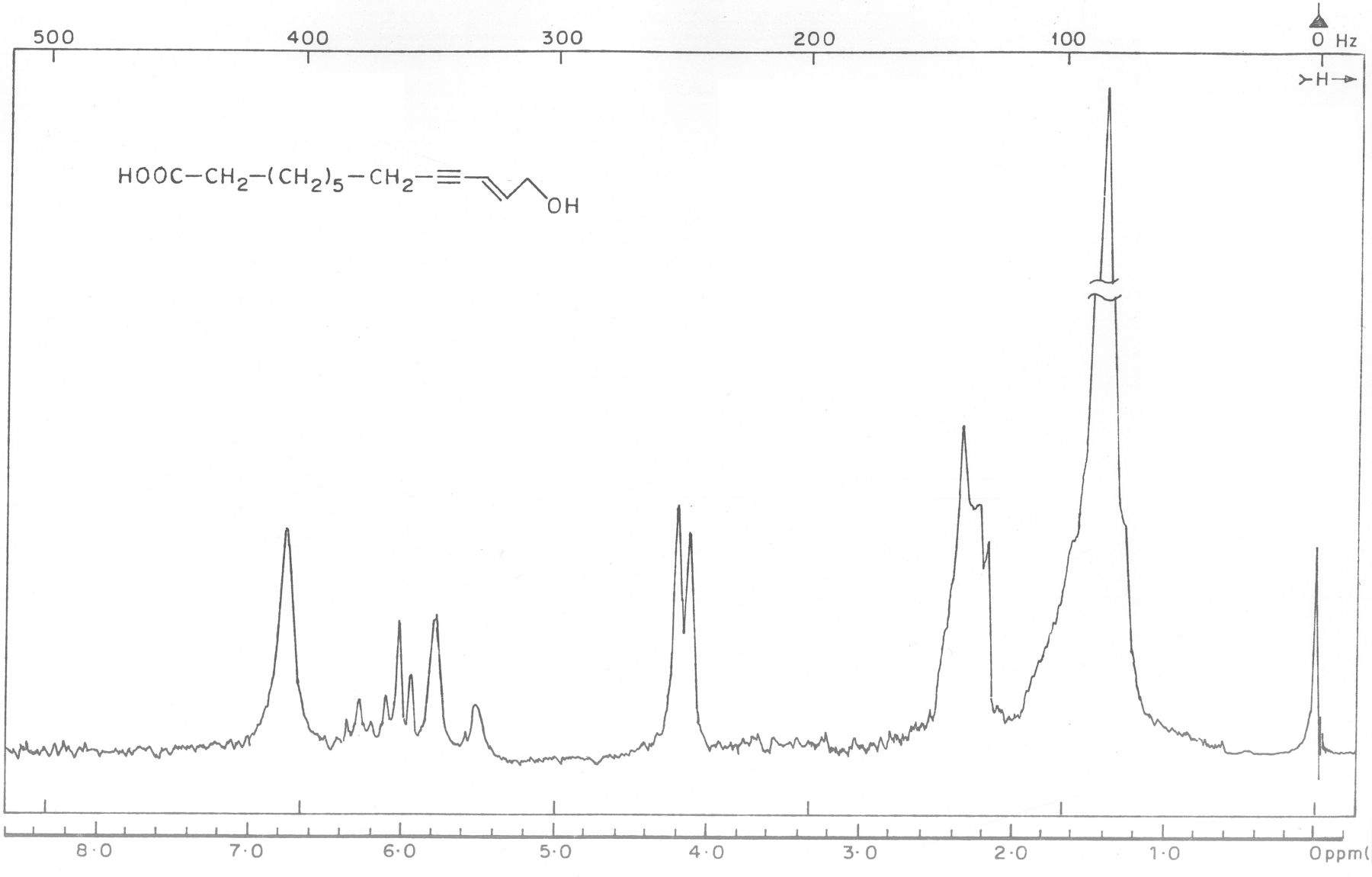


FIG. 2. ^{1}H-NMR. SPECTRUM OF COMPOUND (13) IN $CDCl_3$

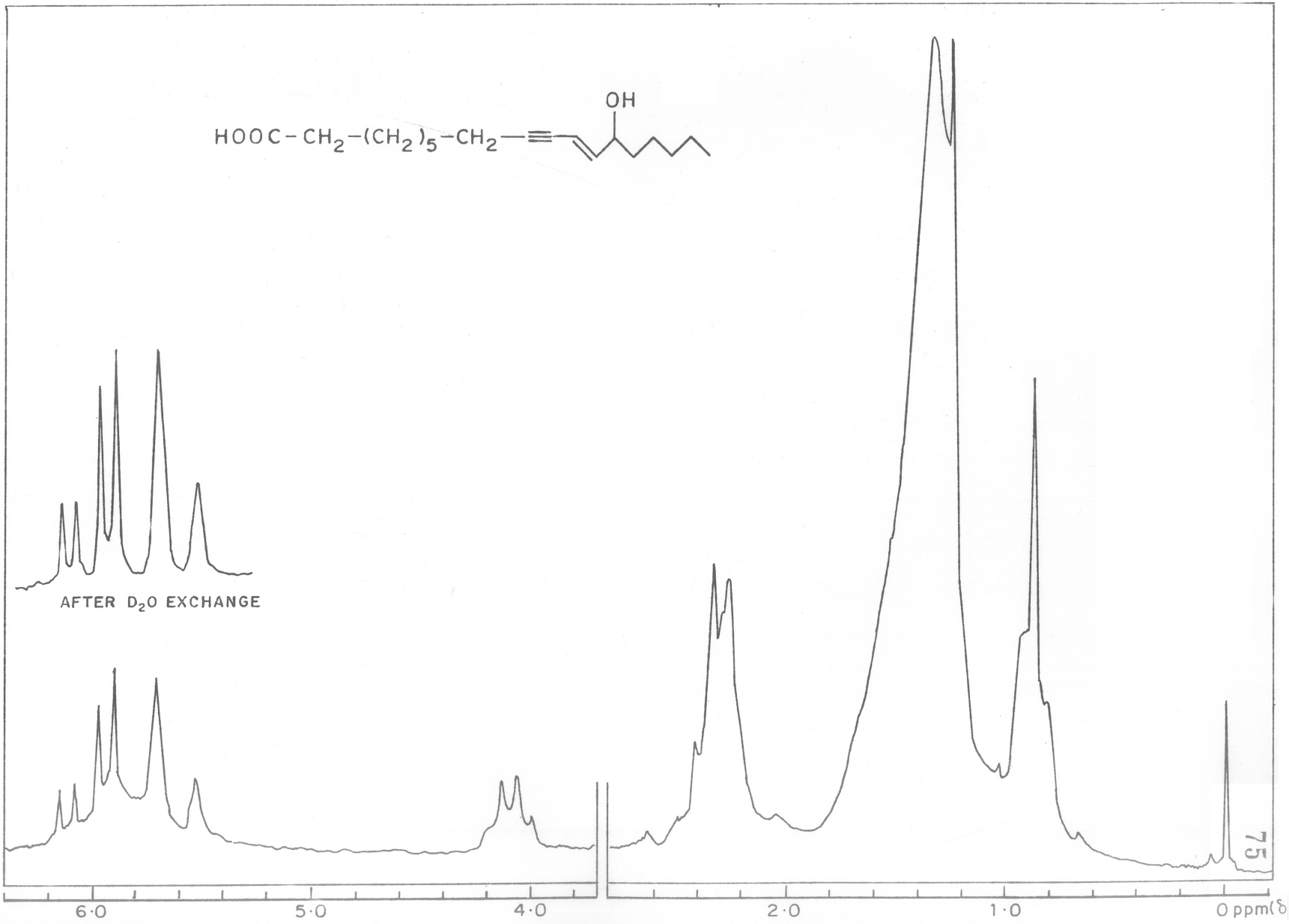


FIG. 3. ^{1}H-NMR SPECTRUM OF COMPOUND (15) IN $CDCl_3$

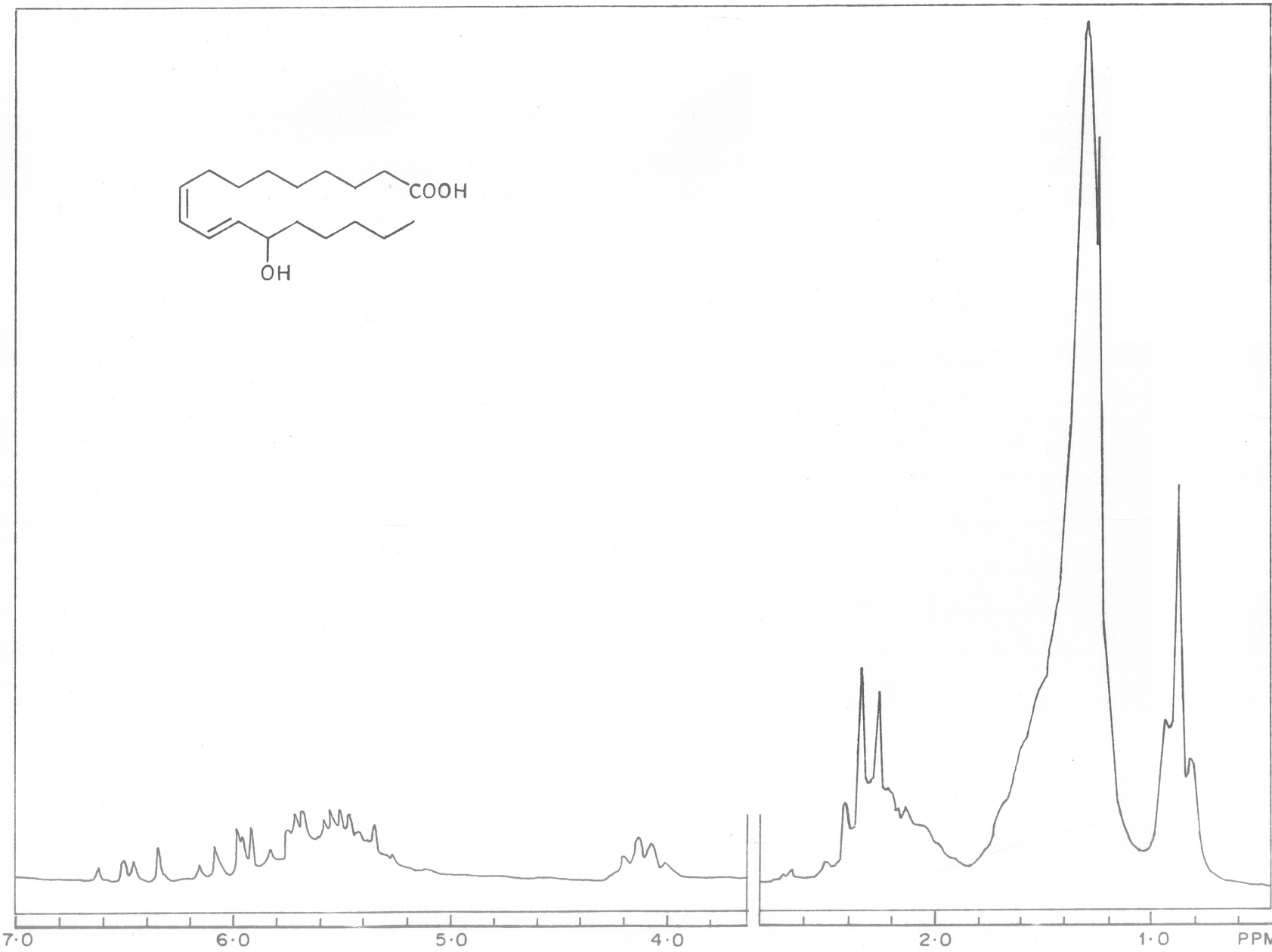


FIG. 4. ^{1}H-NMR SPECTRUM OF COMPOUND (1) IN $CDCl_3$

for the structure of 15 was indicated by its mass spectrum in which the molecular ion peak was observed at m/e 294.

After obtaining the complete carbon skeleton with the requisite number of carbon atoms, it was aimed at the conversion of acetylenic bond to cis-olefin. Thus 15 on partial hydrogenation with Lindlar catalyst in ethanol containing quinoline furnished coriolic acid (1) in 95% yield. In the ^{1}H-NMR spectrum (Fig.4) of 1 the four olefinic protons appeared in the region of 5.30 - 6.60 ppm as a complex pattern (multiplet). IR showed the absence of absorption at 2200 cm^{-1} assignable for -C≡C- was a clear indication of the reduction. The molecular ion peak in its mass spectrum at m/e 296 was in agreement with the assigned structure.

In conclusion it could be suggested that the present synthesis is better in several respects. The number of steps has been reduced in the present synthesis because of the use of 8-bromooctanoic acid as alkylating agent, which directly gave the corresponding acid. In the previous synthesis three steps were involved in order to get the carboxyl group at the right position. This method enabled us to synthesise coriolic acid (1) in sufficient amount for its further study.

Section 2 : A short synthesis of (±) recifeiolide

INTRODUCTION

The macrolide[26] class of antibiotics is perhaps one of the richest in natural product chemistry. It consists of a wide variety of molecules with variable structures and diversified biological and physiological activities. The constitutional structures and intriguing conformational features of macrolide antibiotics have been the subject of elegant studies over the years. Their chemistry has been recently highlighted by the development of indigenous macrolactonisation methods[27,28,29]. These land mark achievements as well as important contributions in the field of macrolide chemistry have been largely responsible for a renewed interest in this general area.

The synthesis of macrolides is associated with a wide range of problems. Amongst them, the foremost being the construction of medium to large sized macrocyclic ring along with the correct stereochemistry, besides the preservation and creation of various functionalities and chiral centres. The developments in this area of macrolides in recent years have certainly simplified the problems to a considerable extent.

Recifeiolide (16) is a naturally occurring 12-membered ring macrolide isolated from the fungus Cephalosporium recifei which grows on malt glucose medium[30]. Vesonder et al.[30] have assigned the structure of recifeiolide on the basis of its

degradation and spectral studies. The same workers also established the chiral centre as (R)-configuration.

The simple large ring lactones have found commercial application as fixatives in perfumes. This usage stimulated considerable interest in their synthesis and properties.

The synthesis of recifeiolide has attracted the attention of many well known schools throughout the world and as a result several syntheses of recifeiolide have been reported. All the earlier syntheses have been reviewed briefly because detailed studies is beyond the scope of this thesis.

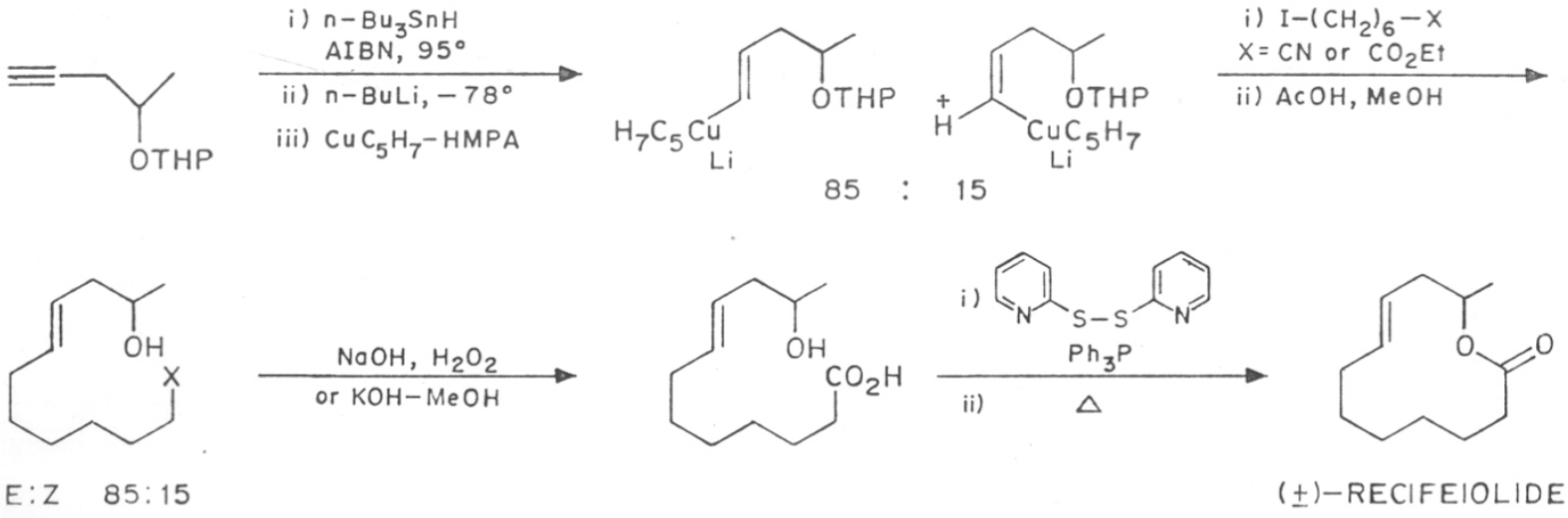
The first total synthesis (Scheme 4) of recifeiolide as recemate was reported by Corey et al.[31] in 1976. This synthesis featured the use of an acetylenic precursor for the creation of trans double bond, besides the double activation method for the final lactonization.

The second total synthesis (Scheme 5) was due to Gerlach et al.[32], in which the 12-membered lactone was prepared in its optically pure form starting from (R)-1,3-butanediol. The strategy involved in the synthesis was the condensation of the phosphonium salt 17 and the aldehyde 18 to give rise to the hydroxy acid 19 which was lactonized to (R)-recifeiolide.

In the synthesis of Utimoto et al.[33] the (R)-methyl oxirane has been used as the source of chiral centre (Scheme 6). It featured a stereoselective alkenylation of the acetylenic

SCHEME–4

COREY et al (1976)



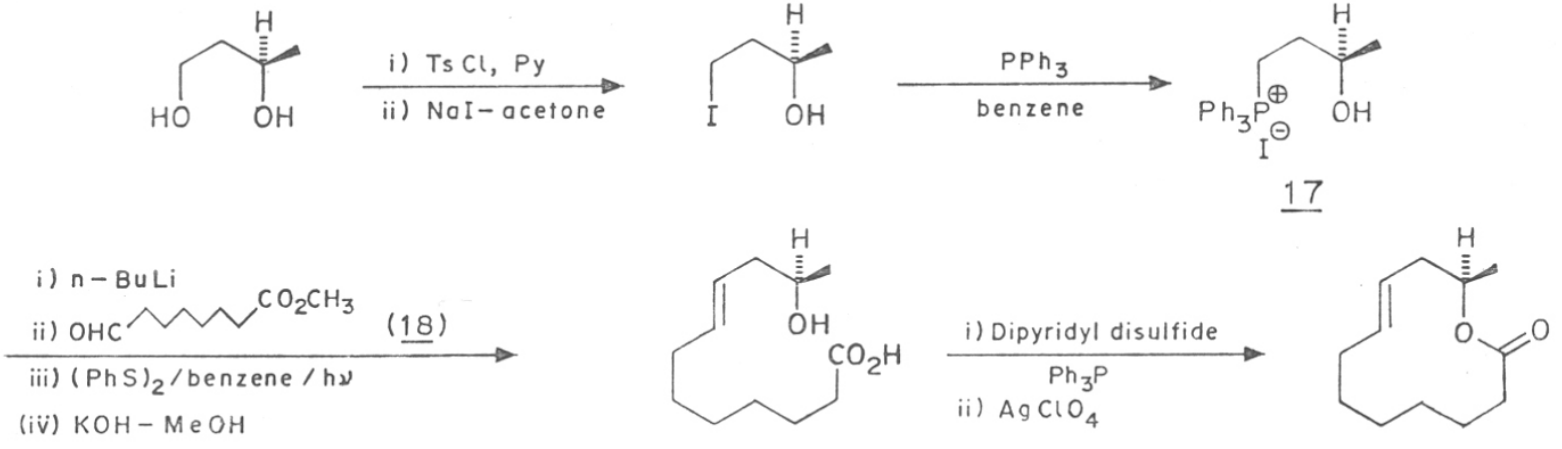
E:Z 85:15

X=CN, CO_2Et

(±)–RECIFEIOLIDE

SCHEME–5

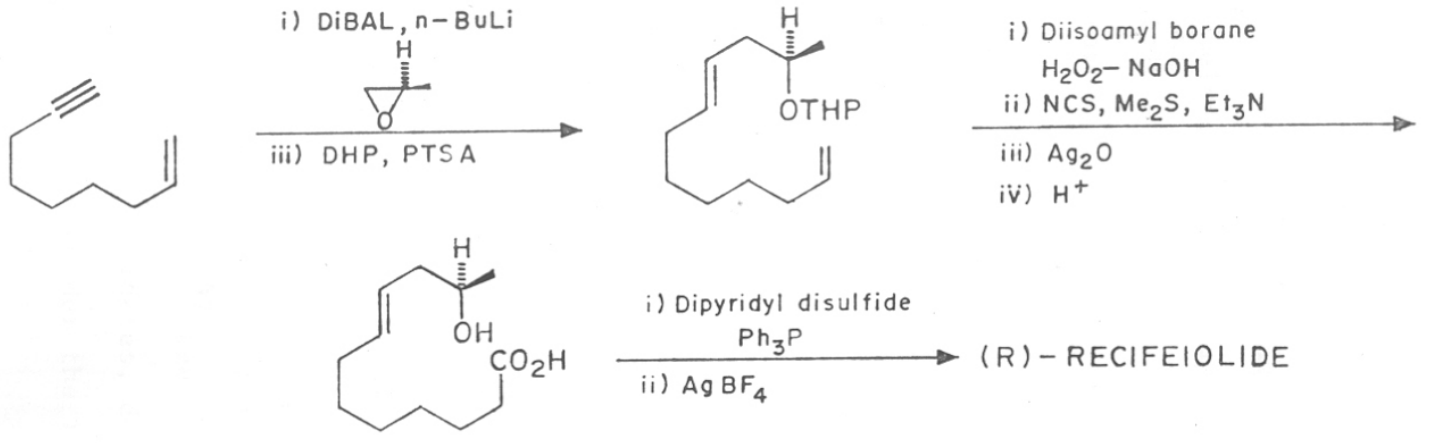
GERLACH et al (1977)



(R)–RECIFEIOLIDE

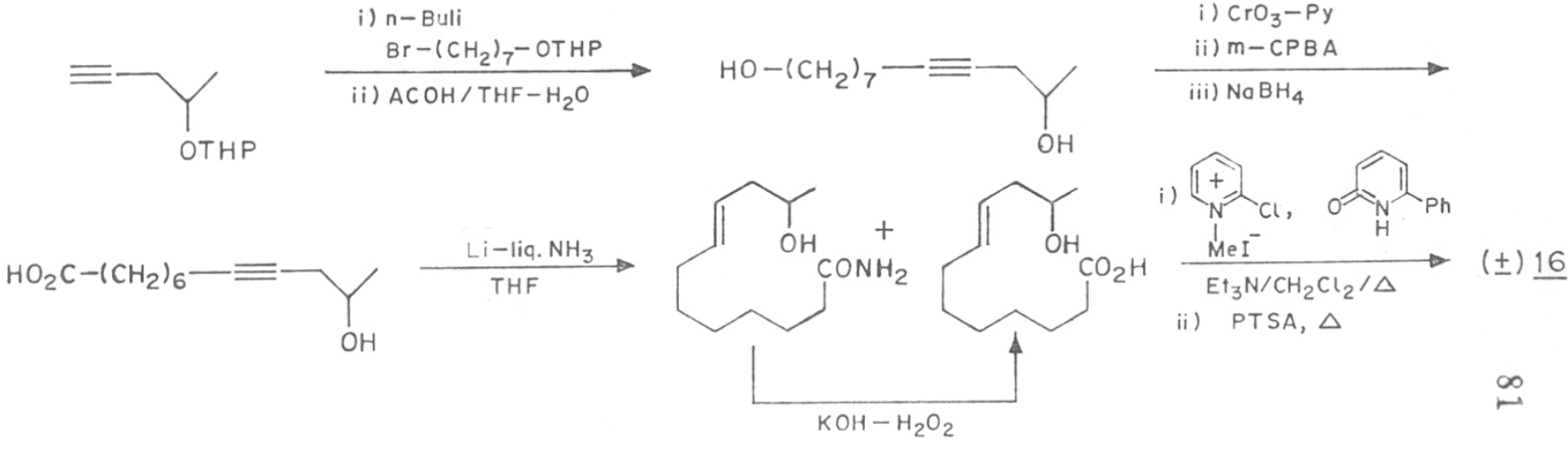
SCHEME-6

UTIMOTO et al (1977)



SCHEME-7

MUKAIYAMA et al (1977)



compound via hydroalumination.

Mukaiyama et al.[34] have reported a total synthesis of (±)16 (Scheme 7) which featured a new and different lactonization method, utilising 1-methyl-2-chloropyridinium iodide, developed by his group earlier[29]. This synthesis also utilised an easily available acetylenic alcohol. Here the drawback is, the methyl-7-bromoheptanoate was reduced to bromoalcohol and then after protection, was used for alkylation on an acetylenic alcohol. After alkylation, the alcohol was deprotected and oxidised to acid. Thus it consists of number of steps, thereby decreasing the overall yield.

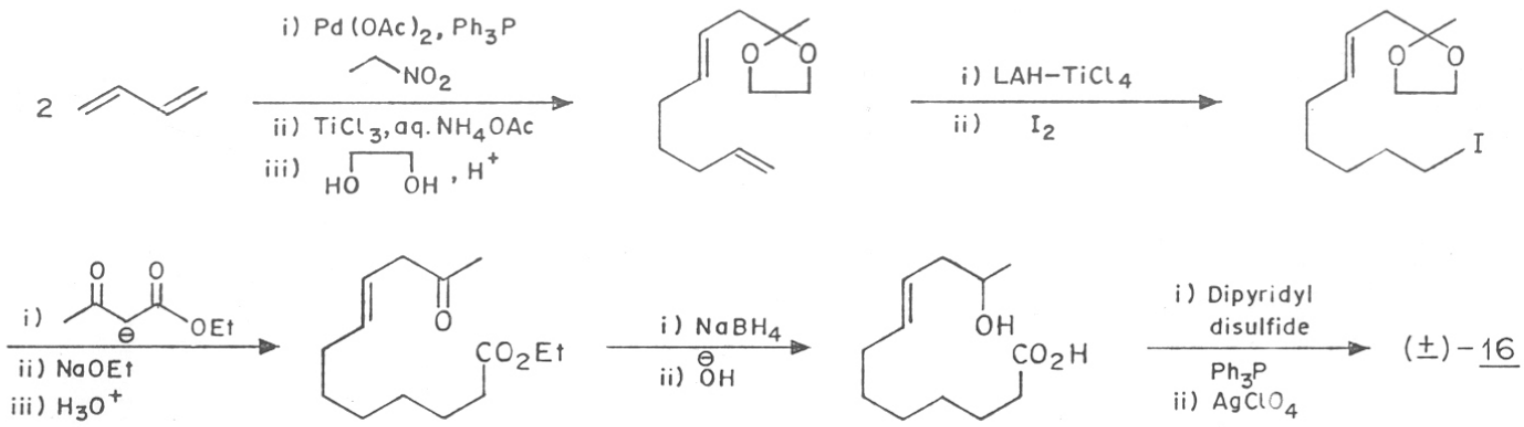
The synthesis of Tsuji et al.[35] (Scheme 8) featured a palladium catalysed telomerisation of butadiene with nitroethane to a stereoselective synthesis of hydroxy acid 19.

All the syntheses discussed so far involved the conventional internal lactonization of ω-hydroxy acid by different reagents. Tsuji et al.[36] (1978) have differed this approach and built the macrocyclic lactones, involving C-C bond formation based on intramolecular alkylation of carbanion generated onω-halophenylthioacetates (Scheme 9).

Synthesis of (±)recifeiolide (Scheme 10) developed by Kumada et al.[37] featured the C-C bond formation of alkenyl pentafluoro silicates, derived from terminal acetylenes with allyl halides under the influence of palladium salts.

SCHEME-8

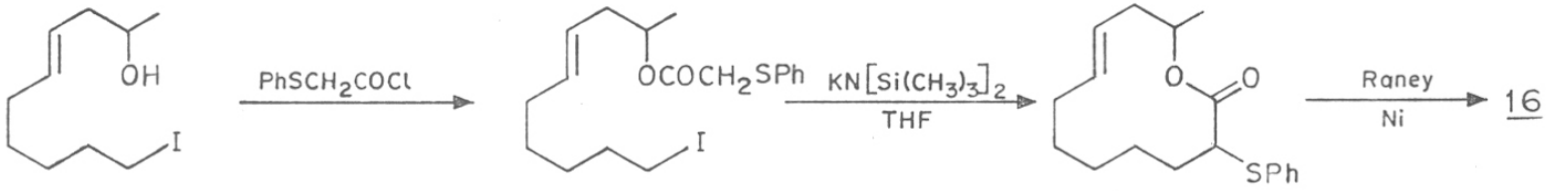
TSUJI et al (1978)



19

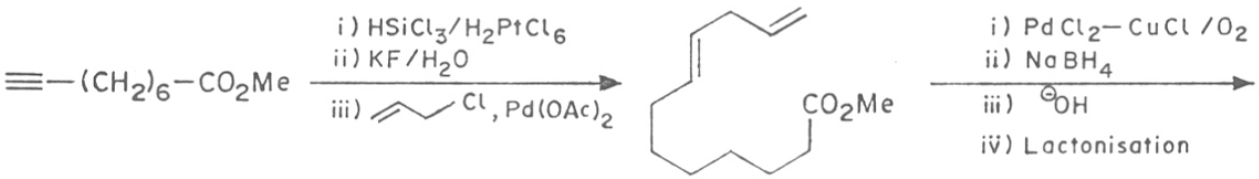
SCHEME-9

TSUJI et al (1978)



SCHEME-10

KUMADA et al (1978)



Trost and Verhoeven[38] have reported a different approach for the synthesis of (±)recifeiolide by making use of organopalladium chemistry. This synthesis (Scheme 11) featured a C-C bond fusion for the lactone formation rather than the conventional lactonization route.

Schreiber[39] developed a synthetic sequence to (±)-recifeiolide (Scheme 12), which featured the generation and usefulness of α-alkoxyhydroperoxides and their fragmentation under the influence of metal catalysts.

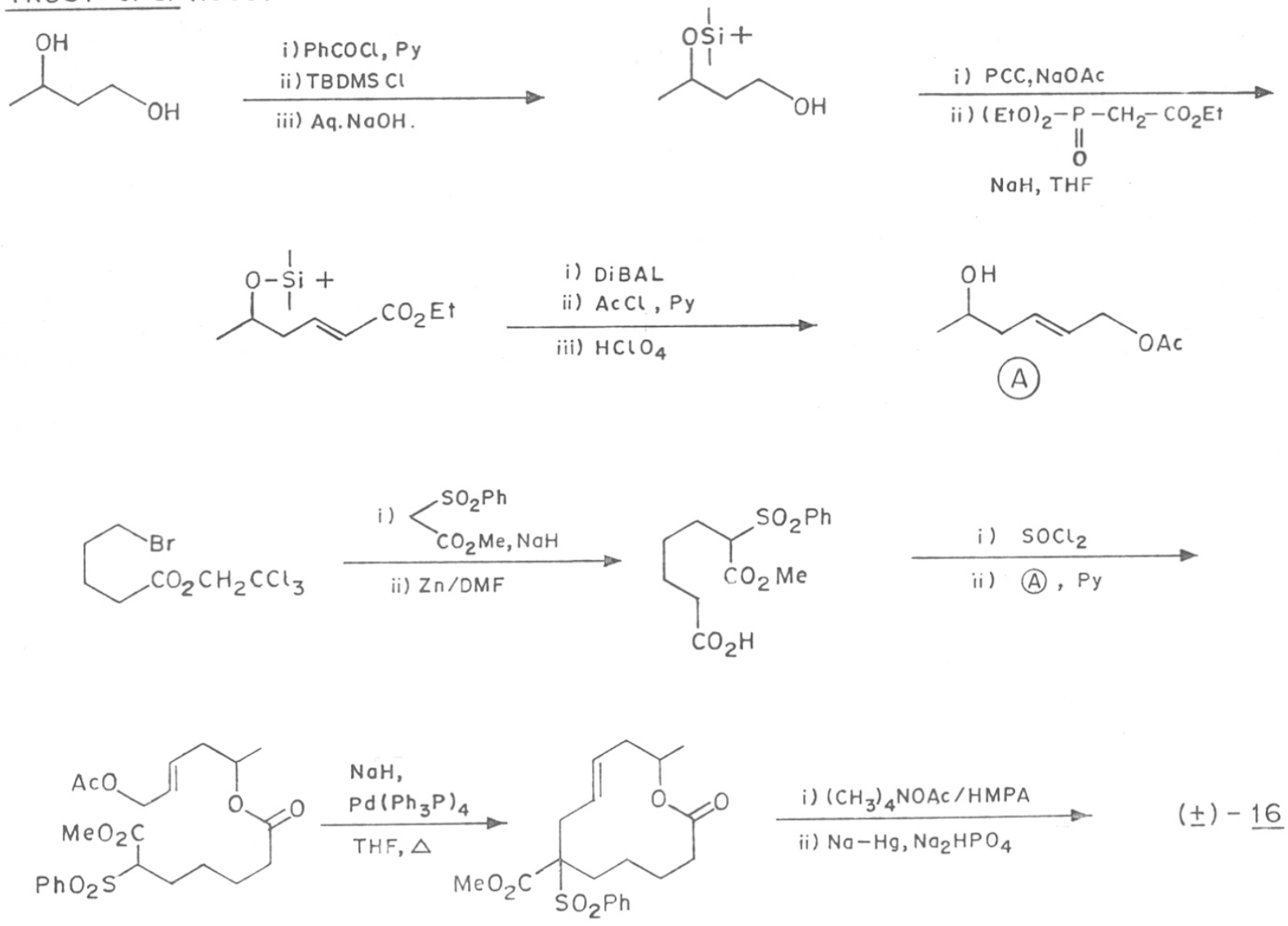
The synthesis of (±) recifeiolide reported by Wassermann *et al.*[40] utilised the substituted oxazoles, where the masked carbonyl function as oxazole was generated under mild conditions of photoxygenation to afford reactive triamides (Scheme 13).

Snider and Phillips[41] developed a general synthetic approach (Scheme 14) for the preparation of homoallylic alcohols by the ene reaction of aldehydes with non-nucleophilic alkenes, under the influence of ethylaluminium dichloride.

The earlier synthesis from this laboratory[42] (Scheme 15) featured the "acetylene-zipper reaction" of an internal acetylenic alcohol. The terminal acetylene thus obtained was used for C-C bond formation by hydroxyalkylation as well as for the stereoselective introduction of *trans* double bond.

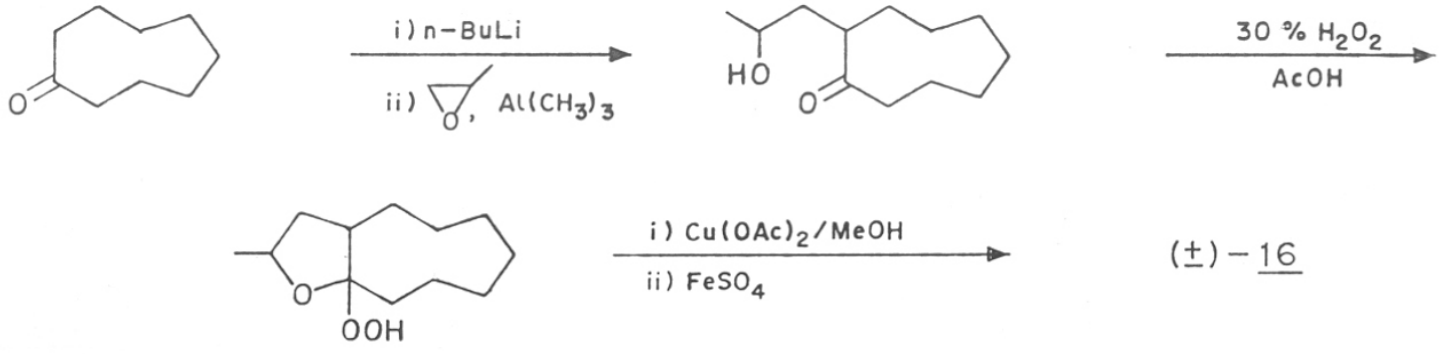
SCHEME-11

TROST et al (1980)



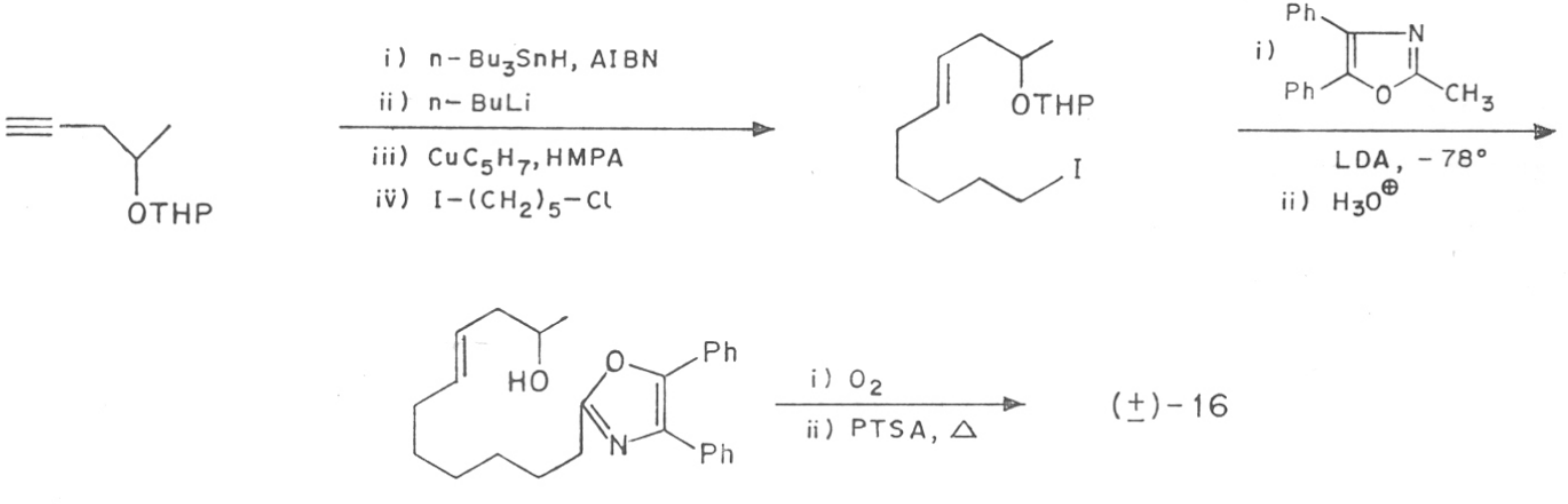
SCHREIBER (1980)

SCHEME-12



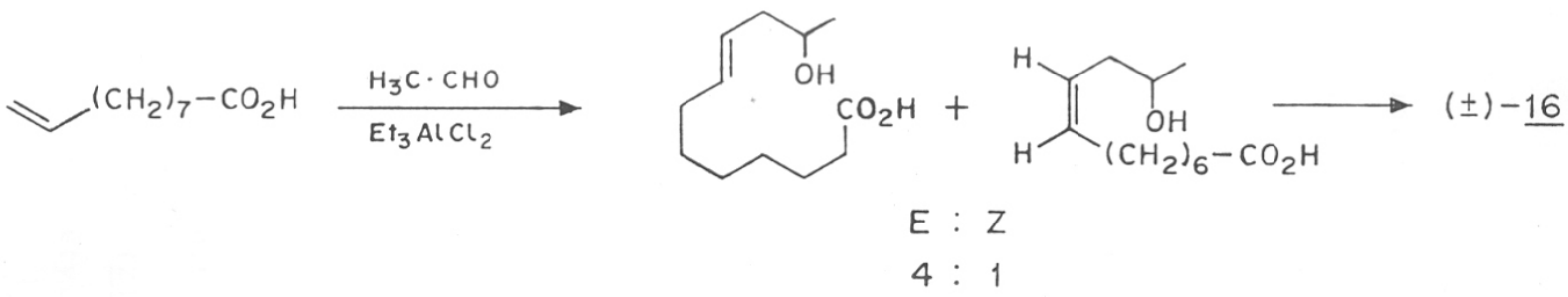
SCHEME-13

WASSERMAN et al (1981)



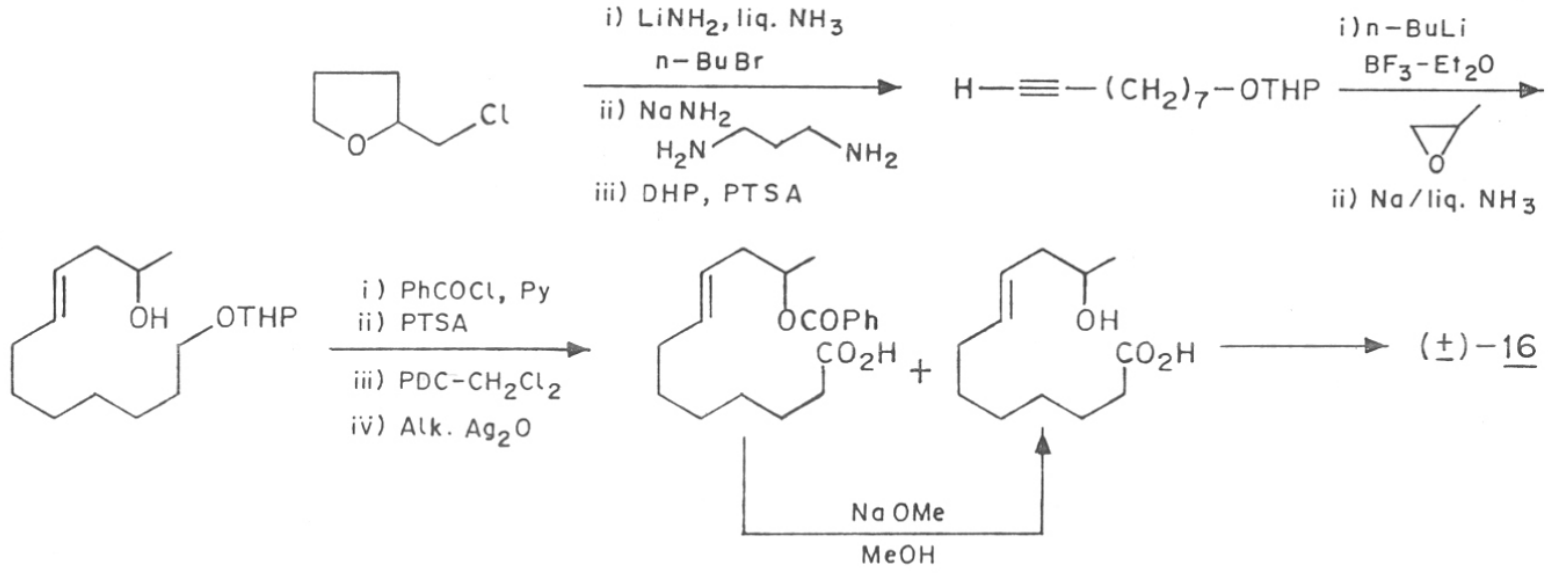
SCHEME-14

SNIDER and PHILLIPS (1983)



SCHEME-15

RAMA RAO et al (1984)



PRESENT WORK

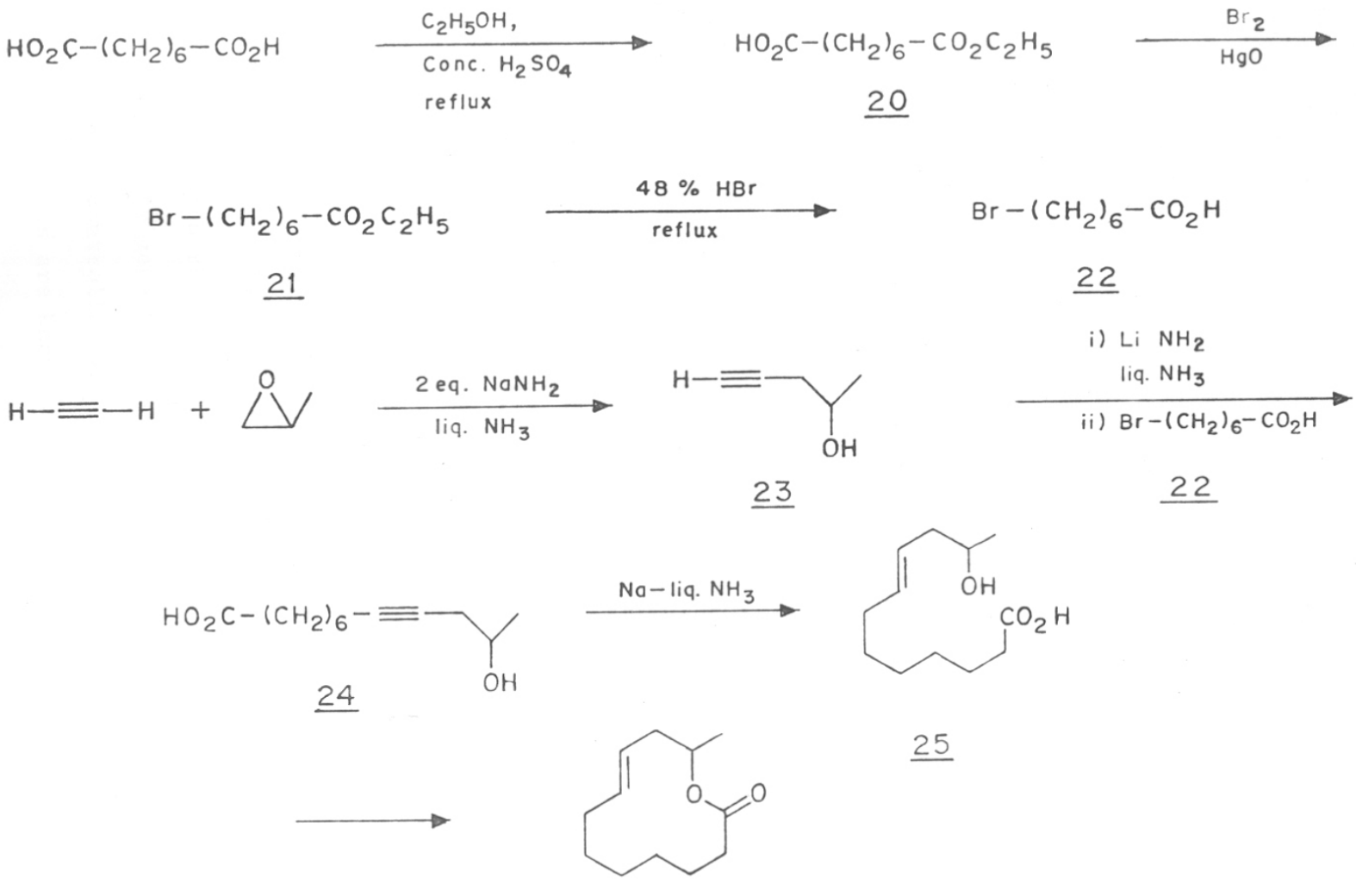
Recifeiolide (16) is a naturally occurring 12-membered ring lactone, isolated from Cephalosporium recifei. Although it is not known much for its biological and physiological activities, its structural features attracted several groups of workers all over the world. Many stereoselective syntheses have been reported for recifeiolide by adopting various methods for ring closure. All precedent syntheses of 16 suffered from multistep functional group manipulations and poor overall yields. This section is dealing with a short and stereoselective synthesis of (±)-16, useful for multigram scale preparation.

The main structural features present in the synthesis of recifeiolide are the stereoselective introduction of trans double bond and fixation of chiral centre. The important feature of this synthesis involves the use of acetylene which not only assist to elongate the carbon chain of required number but also assist to introduce stereocontrolled trans-double bond.

The main strategy in this synthesis is the alkylation of pent-1-yn-4-ol (23) with 7-bromoheptanoic acid (22) followed by metal ammonia reduction of triple bond to trans double bond.

Pent-1-yn-4-ol (23) was prepared[43] by opening of propylene-oxide with sodium acetylide in liq. ammonia (prepared by passing

SCHEME–16


HO2C–(CH2)6–CO2H
C2H5OH,
Conc. H2SO4
reflux
HO2C–(CH2)6–CO2C2H5
20
Br2
HgO
Br–(CH2)6–CO2C2H5
21
48 % HBr
reflux
Br–(CH2)6–CO2H
22
2 eq. NaNH2
liq. NH3
23
i) Li NH2
liq. NH3
ii) Br–(CH2)6–CO2H
22
HO2C–(CH2)6–
24
Na–liq. NH3
OH
CO2H
25
O
O
(±) – 16

acetylene to sodiumamide in liq. ammonia).

7-Bromoheptanoic acid (22) was prepared from suberic acid as follows. Suberic acid was heated under reflux with 1.4 equivalents of absolute ethanol in presence of conc. sulfuric acid to afford a 50% yield of hemiester 20, which was subjected to Hunsdiecker reaction in the presence of bromine-mercuric oxide to yield 7-bromoethylheptanoate (21)[44] in 50% yield. Compound 21 on refluxing with 48% hydrobromic acid furnished 7-bromoheptanoic acid (22) in 80% yield.

The alkylation of pent-1-yn-4-ol (23) with 7-bromoheptanoic acid (22) was carried out with excess of lithium-amide in liq. ammonia at -33° for 10 hr to yield 11-hydroxy-8-dodecynoic acid (24) in 75% yield based on the bromoacid used. The IR spectrum of 24 showed a broad band at 3250 cm^{-1} indicating the presence of -OH and -COOH groups. In the ^{1}H-NMR spectrum (Fig.5) the methine proton (-CHOH) appeared at 4.0 ppm as a multiplet while rest of the protons resonated at the expected chemical shifts. The molecular ion peak in its mass spectrum was observed at m/e 212 which was in agreement with the assigned structure.

Having obtained successfully the properly substituted carbon skeleton with the requisite number of carbon atoms, the next concern was to generate the trans double bond from acetylenic group in a stereocontrolled way. Metal ammonia reduction of acetylenic compounds are known to give trans olefins.

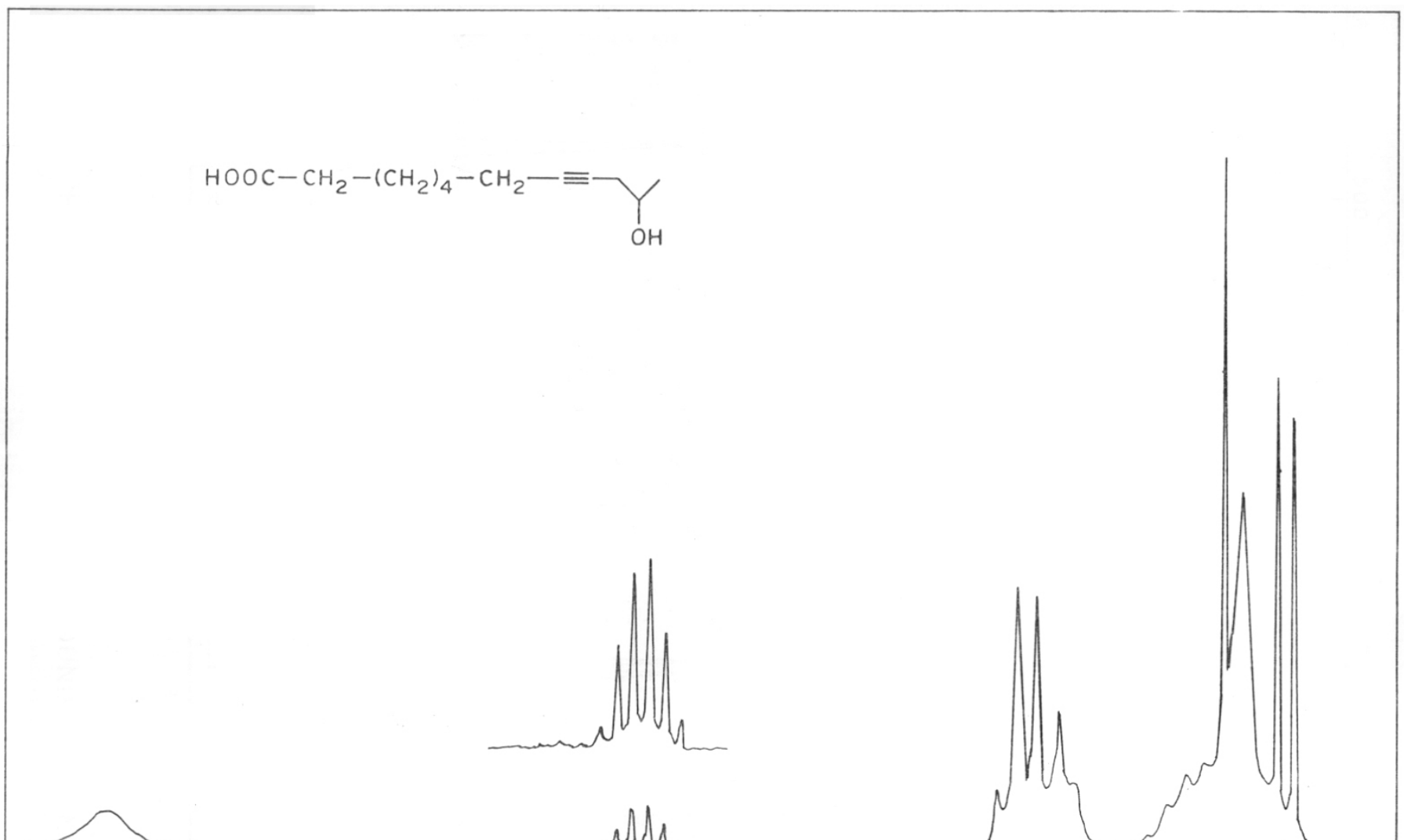


FIG. 5. ^{1}H-NMR SPECTRUM OF COMPOUND (24) IN $CDCl_3$

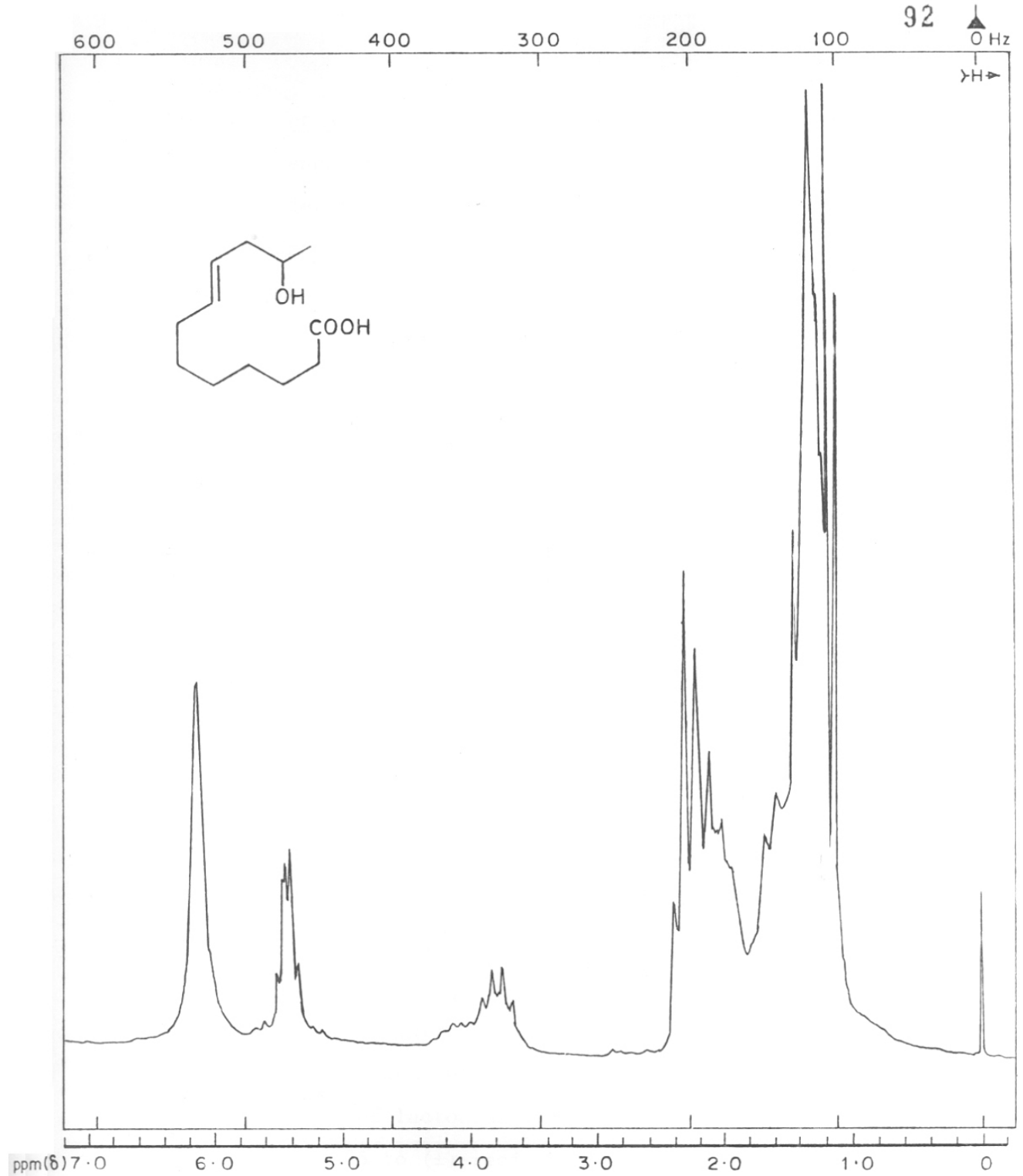


FIG. 6. ^{1}H–NMR SPECTRUM OF COMPOUND (25) IN $CDCl_3$

Mukaiyama et al.[34] had carried out the partial reduction of 24 in presence of lithium metal in liquid ammonia in an autoclave for two days, where it resulted in the formation of (E)-11-hydroxy-8-dodecenamide partially, which was converted to the olefinic acid 25 by alkaline hydrolysis. The formation of the amide may be because of high pressure and longer duration, so if the reaction is carried out at normal pressure and shorter duration,the amide formation can be overcome. Indeed, when the reduction was carried out in presence of metallic sodium in excess of ammonia at -33° at normal pressure for 4 hr, (E)-11-hydroxy-8-dodecenoic acid (25) was isolated in 90% yield without any concomitent formation of amide. In the IR spectrum of 25 the band at 2200 cm^{-1} due to acetylene group had disappeared. The ^{1}H-NMR spectrum (Fig.6) showed a multiplet in the region of 5.4 - 5.7 ppm integrating for two protons was assigned for the olefinic protons and rest of the protons appeared at expected chemical shifts. In the mass spectrum the molecular ion peak was not seen, however the fragment at m/e 196 was due to the loss of water (m-18) besides the fragment at m/e 152 (m-44). Compound 25 was identical in all respects with the reported sample.

Further elaboration of hydroxy acid 25 to (±)-recifeiolide (16) has been carried out by several groups of workers adopting various methods of lactonisation. The conversion of hydroxy acid precursor 25 to (±)-recifeiolide (16) is a well established reaction in literature. The synthesis of 25 would thus constitute the total formal synthesis of (±)-recifeiolide.

EXPERIMENTAL

8-Bromooctanoic acid (12)

Octane-1,8-diol (11.68 g, 0.08 mol) was refluxed with 48% hydrobromic acid (15.5 ml) in toluene for 6 hr. The cooled reaction mixture was diluted with water and the organic layer was washed with 10% aqueous $NaHCO_3$ solution, saturated brine and dried (Na_2SO_4). The solvent was evaporated and the residue was subjected for oxidation without further purification.

The crude 8-bromooctanol was treated with Jones reagent in acetone. The excess of reagent was destroyed by the addition of isopropanol, the reaction mixture was filtered and the solvent was removed. The crude bromooctanoic acid was purified by the acid-base treatment to give pure12 (7.15 g) in 42% yield.

(E)-Pent-2-en-4-yn-1-ol (6)

To a freshly prepared solution of sodium acetylide [obtained by passing acetylene to sodiumamide (prepared from 50.6 g, 2.2 g.atom of sodium)] in liquid ammonia (1.5 lits) was added epichlorohydrin (92.5 g, 1 mol) dropwise over a period of 1.5 hr at -33° and further stirred for 2 hr. The cooling bath was removed after this time and the mixture was stirred for another 3 hr. Then added 75 g of powdered ammonium chloride portionwise and the ammonia was allowed to evaporate. The remaining solid mass was dissolved in water (500 ml) and extracted with ether for 8-10 times. The extracts were dried (Na_2SO_4) and the solvent evaporated. The residue was distilled

at low pressure and collected in a single receiver, which was redistilled at water pump pressure to give 6 (28.5 g) in 35% yield, b.p. 90-91°/40 mm (lit.[25] b.p. 68°/12 mm).

(E)-13-Hydroxy tridec-9-yn-11-enoic acid (13)

To a freshly prepared suspension of lithium amide (prepared from 0.96 g, 0.135 g.atom of lithium) in liquid ammonia (125 ml) were added 6 (5.12 g, 0.0625 mol) in THF (20 ml) over a period of 15 min. and a solution of bromo acid 12 (5.57 g, 0.025 mol) in THF (30 ml) during 25 min. successively. The reaction mixture was further allowed to stir at -33° for 10 hr. Then cooling bath was removed and the ammonia was allowed to evaporate. The residue was neutralised with dil. hydrochloric acid, extracted with chloroform, washed the extracts with water, brine and dried (Na_2SO_4). The residue was purified by column chromatography (silica gel) to give 13 (4.75 g) as a solid in 85% yield (on the basis of bromoacid used) m.p. 65-66°. ^{1}H-NMR (CCl_4); δ 1.1 - 1.9 (m, 10H, 5X $-CH_2$), 2.1 - 2.5 (m, 4H, 2X $-CH_2$), 4.1 (d, 2H, $-CH_2OH$), 5.7 (d, 1H, olefinic), 6.1 (dt, 1H, olefinic). IR (nujol): 3150 cm^{-1} (-OH, COOH), 1690 cm^{-1} (C=O).

Analysis: Calculated for $C_{13}H_{20}O_3$: C, 69.64; H, 8.92; Found: C, 69.68; H, 8.91%.

(E)-13-Oxytridec-9-yn-11-enoic acid (14)

To a solution of 13 (4.48 g, 20 m.mol) in chloroform (225 ml), activated manganesedioxide (40 g) was added and stirred at room temperature for 1.5 hr. The reaction mixture was filtered,

washed with chloroform and concentration of the filtrate gave the aldehyde 14 (2.66 g) in 60% yield as a solid m.p. 51-52°. ^{1}H-NMR ($CDCl_3$): δ 1.1 - 1.8 (m, 10H, 5X $-CH_2$), 2.1 - 2.4 (m, 4H, 2X $-CH_2$), 6.0 - 6.6 (m, 2H, olefinic), 9.5 (dd, 1H, -CHO), 10.0 (broad s, 1H, -COOH). IR (Nujol): 1690 (-C=O), 3200 (broad, -COOH), 2100 (C=C) cm^{-1}.

Analysis: Calculated for $C_{13}H_{18}O_3$: C, 70.27; H, 8.10; Found: C, 70.52; H, 8.08%.

(E)-13-Hydroxyoctadec-9-yn-11-enoic acid (15)

A solution of n-pentylbromide (1.88 g, 12.5 m.mol) in absolute ether (10 ml) was added to magnesium (0.3 g, 12.5 m.mol) in ether (6 ml) over a period of 20 min. at room temperature under N_2 atmosphere while stirring. After 1 hr, a solution of aldehyde 14 (1.11 g, 5 m.mol) in THF (25 ml) was added dropwise and allowed to stir overnight. The mixture was poured into ice-cold aqueous ammonium chloride solution and extracted with ether. The organic layer was washed with water, dried (Na_2SO_4) and evaporated to give 15 (1.10 g) in 75% yield as an oil. ^{1}H-NMR ($CDCl_3$): δ 0.9 (dist. t, 3H, $-CH_3$), 1.1 - 1.8 (m, 18H, 9X $-CH_2$), 2.4 (m, 4H, 2X $-CH_2$), 4.1 (m, 1H, -CHOH), 5.6 - 5.8 (d, 1H, olefinic), 5.9 - 6.1 (dd, 1H, olefinic), 5.9 (broad, 2H, -COOH and -OH). I R (neat): 3300 (broad, COOH, and -OH), 2200 (-C=C-), 1700 (-C=O) cm^{-1}. Mass: M^+ 294.

Analysis: Calculated for $C_{18}H_{30}O_3$: C, 73.48; H, 10.20; Found: C, 73.20; H, 10.22%.

13-Hydroxy-9Z,11E-Octadecadienoic acid (1)

A mixture of the hydroxy acid 15 (0.44 g, 1.5 m.mol) and Lindlar's catalyst (0.15 g) in ethanol (8 ml) containing two drops of quinoline was subjected to hydrogenation at atmospheric pressure. After the absorption of required amount of hydrogen (33.6 ml) the suspension was filtered and washed with ethanol. Ethanol was evaporated from the filtrate. The residue obtained was dissolved in ether, washed with very dil. hydrochloric acid, water, dried (Na_2SO_4) and evaporated to give 1 (0.42 g) in 95% yield as an oil. ^{1}H-NMR ($CDCl_3$): δ 0.9 (dist. t, 3H, $-CH_3$), 1.2 - 1.8 (m, 18H, 9X $-CH_2$), 2.1 - 2.4 (m, 4H, 2X $-CH_2$), 4.1 (m, 1H, -CHOH), 5.5 - 6.3 (m, 6H, 4 olefinic, -OH and -COOH). IR (neat): 3350 (-OH and -COOH), 1700 (C=O) cm^{-1}. Mass: M^+ 296.

Analysis: Calculated for $C_{18}H_{32}O_3$: C, 72.98; H, 10.81; Found: C, 72.90; H, 10.79%.

Ethyl-7-bromoheptanoate (21)

Suberic acid (15 g, 0.086 mol) was refluxed with absolute ethanol (7.1 ml) and conc. sulfuric acid (1.2 ml) for 5 hr. The reaction mixture was poured on ice and extracted with ether. The ethereal extracts were extracted with saturated sodium bicarbonate solution. The aqueous layer was acidified with 1N sulfuric acid, extracted with ether, the ethereal layer washed with water and dried (Na_2SO_4). Evaporation of ether gave the hemiester 20 (8.25 g) in 50% yield.

Hemiester 20 (3.83 g, 0.019 mol) was mixed with red mercuric oxide (4.0 g, 0.019 mol) in CCl_4 (45 ml) under N_2 atmosphere and

refluxed with tungsten lamp. Bromine (1.5 g) in CCl_4 (13 ml) was added dropwise and further refluxed for 2 hr. The reaction mixture was cooled, filtered and the solvent was evaporated. The residue was washed with petroleum ether, by which the insoluble polymers were precipitated. The solvent was evaporated to give the bromo ester 21 (2.25 g) in 50% yield.

7-Bromoheptanoic acid (22)

Bromoester 21 (2.13 g, 9 m.mol) was refluxed with 48% hydrobromic acid (6 ml) for 5 hr. The cooled reaction mixture was diluted with water and extracted with chloroform. Then acid-base extraction method was performed to give pure bromo-acid 22 (1.5 g) in 80% yield. ^{1}H-NMR (CCl_4): δ 1.2 - 2.0 (m, 8H, 4X $-CH_2$), 2.25 (t, 2H, $-CH_2CO-$), 3.3 (t, 2H, $-CH_2Br$), 10.8 (s, 1H, -COOH).

Pent-1-yn-4-ol (23)

To a freshly prepared solution of sodium acetylide [obtained by passing acetylene to a suspension of sodiumamide (prepared from 11.5 g of sodium)] in liquid ammonia (400 ml) was added freshly distilled propylene oxide (36 g, 0.62 mol) during 1 hr. The acetylene flow was maintained for a further 2 hr and then discontinued. The reaction mixture was stirred for 8 hr at -33° and then neutralised by portionwise addition of ammonium chloride (30 g). Afterwards the ammonia was allowed to evaporate overnight and the residue was taken in ether. Evaporation of dried ethereal solution gave a residue, which on distillation gave the

acetylenic alcohol 23 (15 g) in 35.5% yield, b.p. 62°/60 mm (lit.[43] b.p. 74.6°/100 mm).

11-Hydroxy-8-dodecynoic acid (24)

To a freshly prepared suspension of lithium amide (prepared from 0.245 g, 0.035 g.atom of lithium) in liquid ammonia (50 ml) were added 23 (1.47 g, 17.5 m.mol) in THF (5 ml) during 5 min. and the bromoacid 22 (1.46 g, 7 m.mol) in THF (10 ml) over a period of 10 min. successively. The reaction mixture was further stirred at -33° for 10 hr. Then ammonia was allowed to evaporate. The residue was neutralised with dil. HCl, extracted with chloroform, the extracts were washed with water, brine and dried (Na_2SO_4). Evaporation of the solvent gave a residue which was purified by column chromatography (silica gel) to afford 24 (1.11 g) in 75% yield. ^{1}H-NMR ($CDCl_3$): δ 1.25 (d, 3H, $-CH_3$), 1.35 - 1.85 (m, 8H, 4X $-CH_2$), 2.15-2.55 (m, 6H, 3X $-CH_2$), 3.95 (m, 1H, -CHOH), 6.2 (br.s, 2H, OH and -COOH). IR (neat): 3200 (-OH and -COOH), 2200 (-C≡C-), 1700 (-C=O) cm^{-1}. Mass: M^+ 212.

Analysis: Calculated for $C_{12}H_{20}O_3$: C, 67.90; H, 9.43; Found: C, 67.7; H, 9.46%.

(E)-11-Hydroxy-8-dodecenoic acid (25)

Sodium (1.38 g, 0.06 g.atom) was added in small pieces during 45 min. to a stirred mixture of 24 (1.06 g, 5 m.mol) in THF (20 ml) and liquid ammonia (1 lit.) at -33°. The contents were stirred at -33° for an additional 4 hr. Then solid ammonium

chloride was added in portions till the discharge of blue colour and allowed to stand overnight at room temperature. The contents were stirred with water for 30 min. extracted with ether, the ethereal extracts washed with brine, dried (Na_2SO_4) and evaporated to give 25 (0.96 g) in 90% yield as a liquid. ^{1}H-NMR ($CDCl_3$): δ 1.2 (d, 3H, $-CH_3$), 1.3 - 1.8 (m, 8H, 4X $-CH_2$), 1.9 - 2.5 (m, 6H, 3X $-CH_2$), 3.9 (m, 1H, -CHOH), 5.3 - 5.7 (m, 2H, olefinic), 6.98 (br.s, 2H, -OH and -COOH). IR(neat): 3200 (broad, -OH and -COOH), 1705 (-C=O) cm^{-1}. Mass: M^+ 214.

Analysis: Calculated for $C_{12}H_{22}O_3$: C, 67.28; H, 10.28; Found: C, 67.51; H, 10.25%.

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CHAPTER II

PART-B

A METHODOLOGY FOR TWO CARBON HOMOLOGATION

INTRODUCTION

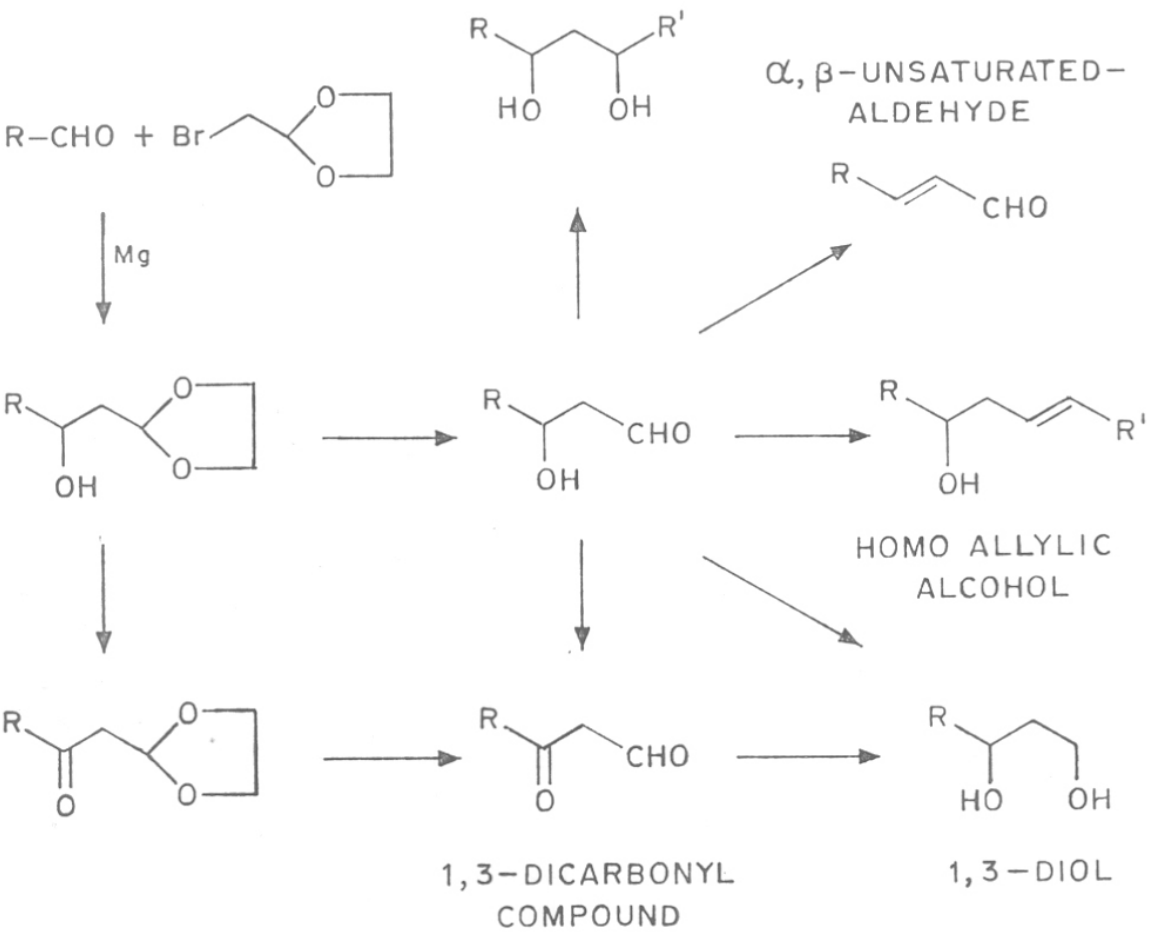
β-Hydroxyaldehydes are versatile intermediates for a variety of compounds such as α,β-unsaturated aldehydes, 1,3-diols, 1,3-dicarbonyl compounds and homoallylic alcohols (Scheme 1). β-Hydroxyaldehydes are better known as aldols and can be prepared by the aldol condensation. Here careful attention to the conditions is necessary, even if the equilibrium favours the formation of the β-hydroxyaldehyde, as aldols readily dehydrate in basic solution to give the conjugated olefinic aldehydes. The convenient way of obtaining β-hydroxyaldehydes is by a Grignard reaction with 2-bromomethyl 1,3-dioxalane (1) on aldehydes.

There are a number of controversial reports on the Grignard reactions of α-halogenoacetals. Wislicenius[1] reported that chloroacetaldehydediethylacetal on treating with metallic sodium furnished ethylvinylether (Scheme 2). Freundler et al.[2] observed the similar type of reaction on bromoacetaldehyde diethylacetal with metals such as sodium, magnesium, zinc.

Hill and Pidgeon[3] reported that the action of metallic sodium on 2-bromomethyl 1,3-dioxalane (1) yielded the sodium salt of hydroxyethyl vinyl ether (2) (Scheme 3).

Kuhn[4] has indicated that the organomagnesium compounds of 2-bromomethyl-2-phenyl-1,3-dioxalane are important from the point of organic synthesis. This work and some other publications have shown contradictory results regarding the composition

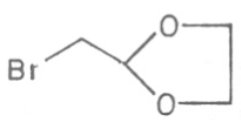
SCHEME–1



SCHEME–2

$$Cl-CH_2-CH(OC_2H_5)_2 + 2\,Na \longrightarrow CH_2=CH\cdot O\cdot CH_2\cdot CH_3$$

SCHEME–3



$$+\,Na \longrightarrow CH_2=CH-OCH_2-CH_2ONa + NaBr$$

2

SCHEME–4

$$Br-CH_2-CH(OR)_2 \xrightarrow[\text{ether}]{Mg} H_2C=CH\cdot OR + Mg(OR)\cdot Br$$

$$+(RO)_2-CH-CH_2-CH_2-CH-(OR)_2$$

of organomagnesium compounds obtained from α-halogenoacetals.

Krause and Williams[5] prepared the organomagnesium compounds of bromoacetal in ether and condensed with β-ionone. Heilbron and Johnson[6] could not reproduce these results neither with magnesium nor with lithium.

Arens and Vandorp[7] showed that it is impossible to prepare normal organometallic compounds from the acetals of bromoacetone and bromoacetaldehyde. Any reactions observed are due to the formation of enol ethers. They further observed that cyclic acetals of bromoacetaldehyde also cannot be used with success.

Wittig and Todt[8] confirmed that the bromoacetal reacts with magnesium in ether and leads to the formation of vinyl ethers and the alcoholates, accompanied by dimers (Scheme 4). Par Cl.Feugeas[9] studied in detail the action of magnesium on halogenoacetals.

PRESENT WORK

A method for β-hydroxyaldehydes has been developed by a Grignard reaction of 2-bromomethyl-1,3-dioxalane (1) with an aldehyde. The resultant Grignard product on deprotection of the ketal group would give a β-hydroxyaldehyde. To show the generality of this method, the Grignard reaction was carried out with butanal, hexanal and decanal and the corresponding β-hydroxyaldehydes 3a, 3b and 3c respectively, where

the aldehyde group is in the protected form were obtained successfully (Scheme 5). The structures of compounds 3a, 3b and 3c were assigned on the basis of their spectral data. In the IR spectra the -OH stretching was seen at 3400 cm^{-1}. In the ^{1}H-NMR spectra of compounds 3a, 3b (Fig.1) and 3c.the protons due to ketal group resonated at 3.90 ppm as multiplet, the methine proton (-OCH-O-) showed a resonance in the region of 5.0 ppm as triplet and rest of the protons appeared at the expected chemical shifts.

This Grignard reaction is very useful in aliphatic chemistry, where a homoallylic alcohol functionality is needed. This functionality is very common in many aliphatic hydroxy unsaturated fatty acids. To show the applicability of this Grignard reaction it was utilised for a two carbon elongation in the efforts made towards the total synthesis of 13-hydroxy-(E)-9-(E)-11-(Z)-15-octadecatrienoic acid (4).

4 was isolated recently from Fukuyuki (Oryza sativa L.) by Kato et al.[10,11,12] along with other oxygenated unsaturated fatty acids (Part A, Fig.1). They acted as self-defensive substances against rice blast disease. These acids inhibit the spore germination and germ tube growth of rice blast fungus. These acids seem to play a role as defensive substances in the rice plant without being affected from the disease.

The efforts made for the synthesis of 4 was shown in the Scheme 6. This route involves mainly (i) utilisation of

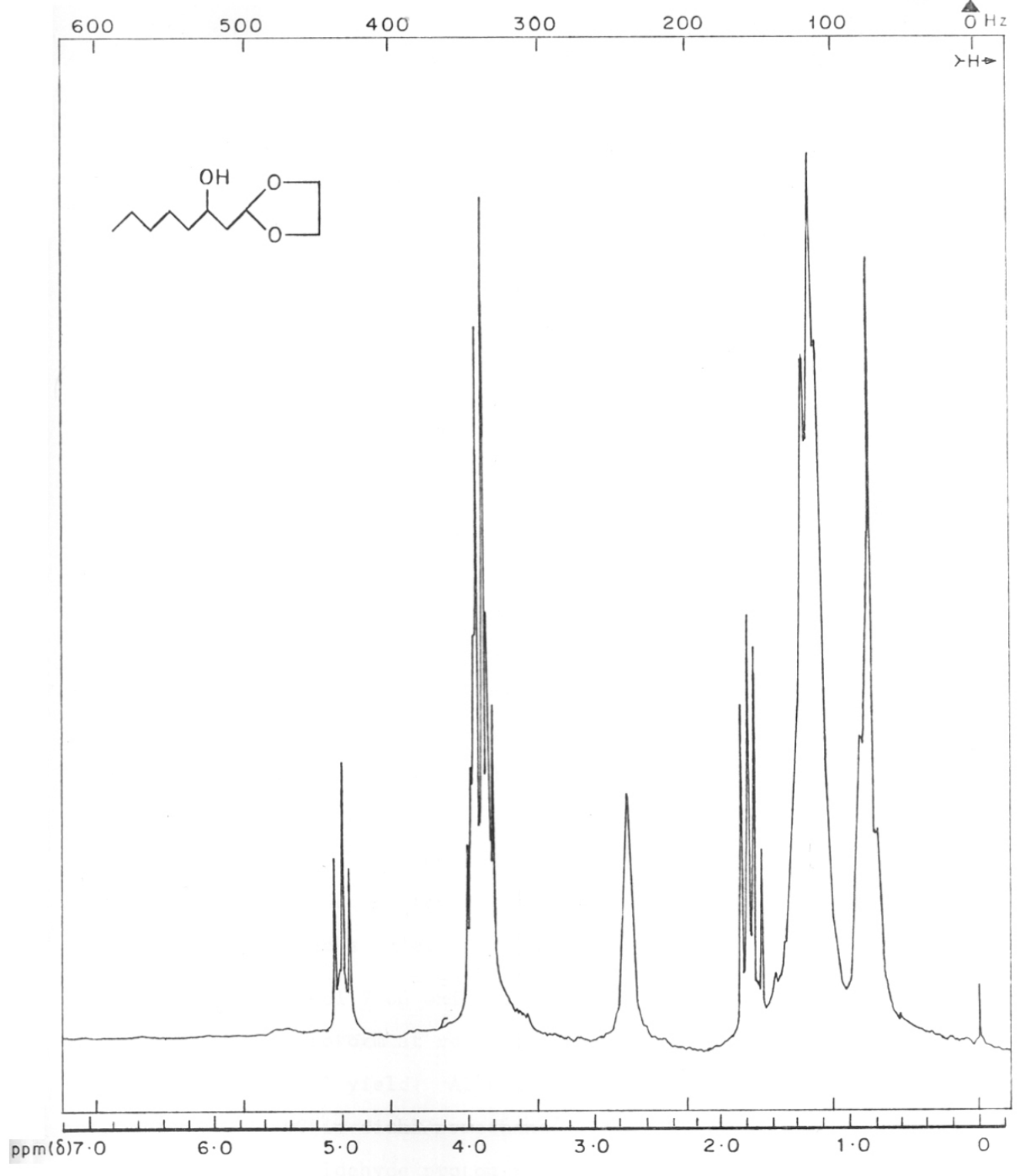


FIG. 1. ^{1}H-NMR SPECTRUM OF COMPOUND (3b) IN $CDCl_3$

(E)-pent-2-ene-4-yn-1-ol (5) for elaborating the carbon skeleton (ii) Grignard reaction by 2-bromomethyl 1,3-dioxalane (1) (iii) removal of THP ether in preference over ethylene ketal group and conversion of $-CH_2OH$ group to -COOH group in neutral conditions.

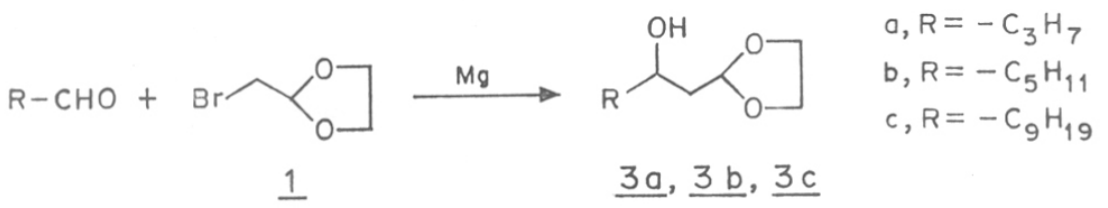
The key synthon (E)-pent-2-ene-4-yn-1-ol (5) was prepared[13] by treating excess of acetylene with epichlorohydrin and sodamide in liq. ammonia at -33° for 3 hr.

Octan-1,8-diol was refluxed with 48% hydrobromic acid in toluene to yield 8-bromo octan-1-ol in 70% yield. The bromo octanol on treatment with dihydropyran in dichloromethane using PTSA as catalyst gave the corresponding THP ether 6 in 90% yield.

Alkylation of 5 with tetrahydropyranyl ether of 8-bromo-octan-1-ol (6) using lithium amide in liq. ammonia as base gave acetylenic alcohol 7 in 70% yield. The IR spectrum of compound 7 showed an absorption at 3340 cm^{-1} for -OH group besides the absorption at 2220 cm^{-1} for the triple bond. In the PMR spectrum, the olefinic protons resonated in the region of δ 5.45 - 6.30 as a multiplet and the tertiary proton of THP showed resonance at δ 4.50 as a broad singlet.

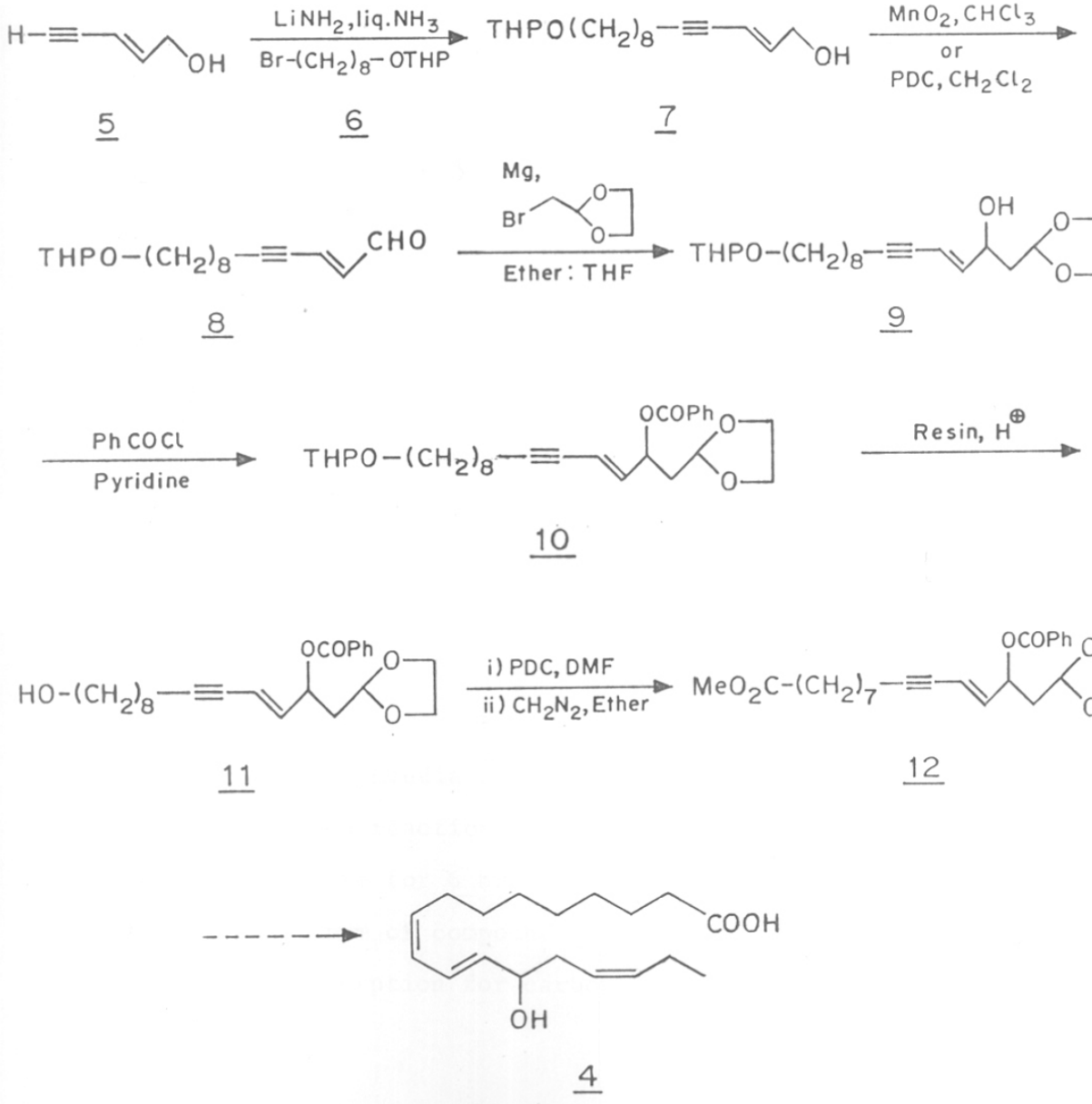
The alcohol 7 on oxidation with activated manganese-dioxide in chloroform at room temperature furnished the aldehyde 8 in 89% yield. Aldehyde 8 was also prepared by oxidation with PDC in dichloromethane. In ^{1}H-NMR spectrum of compound 8 the aldehyde proton resonated at δ 9.50 as a double

SCHEME – 5



1 3a, 3b, 3c

SCHEME – 6



5 6 7 8 9 10 11 12 4

doublet besides the absence of doublet for allylic methylene protons. IR spectrum showed the absorption at 1740 cm^{-1} for carbonyl. The mass spectrum revealed the molecular ion peak at m/e 292 giving further confirmation to the assigned structure.

Aldehyde 8 was subjected to Grignard reaction where 2,2-ethylenedioxyethylmagnesiumbromide in ether was treated with 8 in tetrahydrofuran at room temperature to give the carbinol 9 in 75% yield, on the basis of the aldehyde used. IR spectrum of compound 9 showed the absence of band for carbonyl, while the absorption for -OH group appeared at 3450 cm^{-1}. In the PMR spectrum, the aldehyde proton disappeared while the protons of ketal group and the methine proton (-CH-O) appeared in the region of δ 3.6 - 4.0 as a multiplet.

Before going for further two carbon homologation it was aimed at the transformation of THP protected primary alcohol group to carboxyl functionality. For the preferential transformation of primary alcohol over secondary alcohol group it was desired to protect the latter as benzoate as it is simple and will not interfere in the depyranalation (acid catalyzed) reaction.

As the compound 9 was found to be unstable for longer durations, it was immediately converted to its benzoate derivative. Thus 9 on reaction with benzoyl chloride in pyridine at room temperature for 6 hr afforded the benzoate 10 in 85% yield. IR spectrum of compound 10 showed the absence of band for -OH while the absorption for carbonyl appeared at 1720 cm^{-1}.

In the ^{1}H-NMR spectrum, aromatic protons showed multiplets in the region of δ 7.20 - 7.50 and δ7.90 - 8.00 and rest of the protons appeared at the expected chemical shift values.

Now it was aimed to deprotect the THP ether in preference over ketal protection. It is well known that acidic resin is very mild catalyst for deprotection of THP ether and it does not touch the ketal protection. So depyranylation of 10 was achieved in 80% yield with acidic resin in methanol at room temperature for overnight to afford the alcohol 11. The PMR spectrum showed the -C$\underline{H}_2$-OH signals at δ 3.65 as a triplet, while the signals due to THP protons disappeared. IR spectrum showed the band for -OH group at 3350 cm^{-1}.

The next task was to convert alcohol function to carboxyl function under neutral conditions as acidic reagents affect the ketal protection, while alkaline agents affect the benzoate group. Thus compound 11 on treatment with excess of PDC in DMF solvent at room temperature for overnight furnished the corresponding acid, which was converted to its methyl ester 12 by treating with ethereal diazomethane. The PMR spectrum (Fig.2) of ester 12 showed the resonance of the methoxyl protons at δ 3.65 as a singlet, while the remaining protons appeared at the expected chemical shifts.

Now the deprotection of ketal function followed by Wittig reaction with propyl bromide and transformation of triple bond to cis-double bond by hydrogenation would give the benzoate of methyl ester of 4. Preliminary experiments to deprotect the

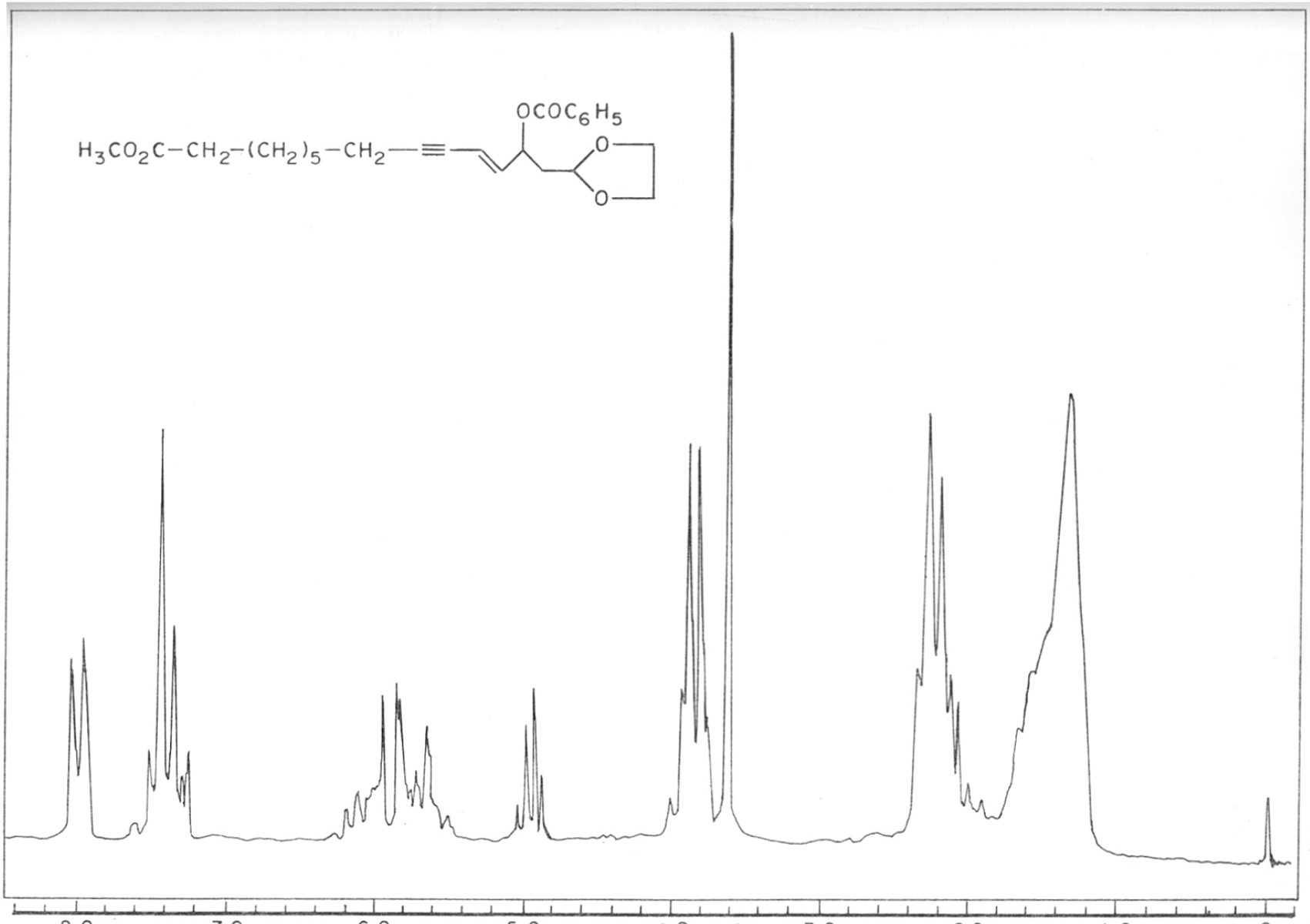


FIG. 2. ^{1}H-NMR SPECTRUM OF COMPOUND (12) IN $CDCl_3$

ketal function with acidic reagents such as PPTS, PTSA, dil.HCl failed to give the desired aldehyde. Thus, further work was abandoned.

EXPERIMENTAL

2-(2-Hydroxypentyl)-1,3-dioxalane (3a)

A solution of 2-bromomethyl-1,3-dioxalane (3.34 g, 20 m.mol) in THF (25 ml) was added to magnesium (0.48 g, 20 m.mol) in ether (3 ml) over a period of 10 min. under N_2 atmosphere, while stirring. After 30 min. a solution of butanal (0.72 g, 10 m.mol) in THF (10 ml) was added dropwise and allowed to stir overnight. The mixture was poured on ice cold aqueous ammonium chloride solution and extracted with ether. The organic layer was washed with water, dried (Na_2SO_4) and evaporated to give 3a (1.12 g) in 70% yield as a liquid. ^{1}H-NMR (CCl_4): δ 0.95 (dist. t, 3H, $-CH_3$), 1.2 - 1.6 (m, 4H, 2X $-CH_2$), 1.75 (m, 2H, $-CH_2$), 2.85 (s, 1H, -OH), 3.5 - 4.0 (m, 5H, -CHOH and $-OCH_2.CH_2O$), 4.95 (t, 1H, OCHO-); IR(neat): 3420 cm^{-1} (-OH).

Analysis: Calculated for $C_8H_{14}O_3$: C, 60.76; H, 8.86; Found: C, 60.65; H, 8.83%.

2-(2-Hydroxyheptyl)-1,3-dioxalane (3b)

This compound was prepared by the Grignard reaction of 2-bromomethyl-1,3-dioxalane (3.34 g, 20 m.mol) and magnesium (0.48 g, 20 m.mol) with hexanal (1.0 g, 10 m.mol) as mentioned above in 68% yield (1.27 g) as a liquid. ^{1}H-NMR ($CDCl_3$): δ 0.95 (dist.t, 3H, $-CH_3$), 1.1 - 1.6 (m, 8H, 4X $-CH_2$), 2.85 (s, 1H, -OH), 3.8 - 4.05 (m, 5H, -CHOH and $-OCH_2CH_2O-$), 5.0 (t, 1H, -OCHO): IR (neat): 3410 cm^{-1} (-OH).

Analysis: Calculated for $C_{10}H_{20}O_3$: C, 63.83; H, 10.64; Found: C, 63.58; H, 10.67%.

2-(2-Hydroxyundecanyl)-1,3-dioxalane (3c)

This was prepared by the Grignard reaction of 2-bromomethyl-1,3-dioxalane (3.34 g, 20 m.mol) and magnesium (0.48 g, 20 m.mol) with decanal (1.56 g, 10 m.mol) in 65% yield (1.58 g). ^{1}H-NMR (CCl_4): δ 0.95 (dist. t, 3H, $-CH_3$), 1.2 - 1.55 (m, 16H, 8X $-CH_2$), 2.75 (s, 1H, -OH), 3.75 - 4.0 (m, 5H, -CHOH and $-OCH_2CH_2O-$), 4.95 (t, 1H, -OCHO-). IR (neat): 3400 cm^{-1} (-OH).

Analysis: Calculated for $C_{14}H_{28}O_3$: C, 68.9; H, 11.5; Found: C, 68.98; H, 11.49%.

8-[Tetrahydro-2H-pyran-2-yl)-oxy]octan-1-ol (6)

Octane-1,8-diol (14.6 g, 0.1 mol) was refluxed with 48% hydrobromic acid (18.5 ml) in toluene as mentioned in the previous part to give 8-bromooctanol (14.63 g) in 70% yield.

8-Bromooctanol (14.63 g, 0.07 mol), dihydropyran (7.64 g, 0.091 mol) and p-toluenesulfonic acid (0.15 g) were stirred in dry dichloromethane (130 ml) at room temperature for 3 hr. The reaction mixture was diluted with dichloromethane, washed with 5% aqueous sodiumbicarbonate and dried (Na_2SO_4). Evaporation of the solvent and chromatographic purification (silica gel) of the residue gave 6 (18.46 g) in 90% yield as a liquid.

(E)-13[(Tetrahydro-2H-pyran-2-yl)-oxy]tridec-2-en-4-yn-1-ol (7)

To a freshly prepared suspension of lithium amide (prepared from 0.97 g, 0.138 g.atom of lithium) in liquid

ammonia (140 ml) were added acetylenic alcohol 5 (5.68 g, 0.0698 mol) in THF (15 ml) during 10 min. and bromide 6 (18.46 g, 0.063 mol) in THF (20 ml) during 15 min. After the addition, the reaction mixture was stirred for further 3 hr at -33° and then quenched by portionwise addition of ammonium chloride (20 g). Then ammonia was allowed to evaporate the residue was dissolved in water and extracted with ether. The ethereal extracts were washed with water, brine and dried (Na_2SO_4). Evaporation of the solvent and chromatographic purification (silica gel) afforded 7 (12.96 g) in 70% yield. ^{1}H-NMR ($CDCl_3$):δ 1.05 - 1.90 (m, 18H, 9X $-CH_2$), 2.10 - 2.50 (m, 2H, $-CH_2$), 3.20 - 4.00 (m, 4H, 2X $-OCH_2$), 4.15 (d, 2H, $-C\underline{H}_2OH$), 4.55 (br.s, 1H, OCHO), 5.45 - 6.32 (m, 2H, olefinic); IR(neat): 2200 (-C$\underline{=}$ C-) and 3340 (-OH) cm^{-1}. Mass: M^+ 294.

Analysis: Calculated for $C_{18}H_{30}O_3$: C, 73.46; H, 10.20; Found: C, 73.40; H, 10.26%.

E-13[(Tetrahydro-2H-pyran-2-yl)-oxy]tridec-2-en-4-4-yn-1-al (8)

To the solution of 7 (11.76 g, 0.04 mol) in chloroform (350 ml), activated manganese dioxide (100 g) was added and stirred at room temperature for 5 hr. The reaction mixture was filtered and concentration of the filtrate gave the aldehyde 8 (10.39 g) in 89% yield as an oil. ^{1}H-NMR ($CDCl_3$);δ 1.26-1.83 (m, 18H, 9X $-CH_2$), 2.46 (dist.t, 2H, $-CH_2$), 3.20 - 3.96 (m, 4H, 2X $-OCH_2$), 4.56 (br.s, 1H, OCHO), 6.23-6.53 (m, 2H, olefinic), 9.50 (dd, 1H, -CHO); IR(neat): 1710 (-C=O) and 2220 (-C$\underline{=}$C-) cm^{-1}. Mass: M^+ 292.

Analysis: Calculated for $C_{18}H_{28}O_3$: C, 73.97; H, 9.60. Found: C, 73.89; H, 9.60%.

(E)-1[(Tetrahydro-2H-pyran-2-yl)oxy]-13-hydroxy-15,15-ethylene-dioxy pentadec-9-yn-11-ene (9)

A solution of 2-bromomethyl-1,3-dioxalane (17.03 g, 0.102 mol) in THF (30 ml) was added to magnesium (2.45 g, 0.102 mol) in absolute ether (10 ml) over a period of 15 min. at room temperature under nitrogen atmosphere while stirring. After 30 min. a solution of aldehyde (8, 10 g, 0.034 mol) in THF (20 ml) was added dropwise and allowed to stir for further 24 hr. The mixture was poured into ice-cold aqueous ammonium chloride solution and extracted with ether. The organic layer was washed with water, dried (Na_2SO_4), evaporated and silica gel chromatographic purification of the resulting residue gave 9 (9.69 g) in 75% yield. ^{1}H-NMR ($CDCl_3$):δ 1.20-1.75 (m, 18H, 9X $-CH_2$), 1.75 - 2.0 (m, 2H, $-CH_2$), 2.25 (m, 2H, $-C\equiv C-CH_2-$), 3.0 (br.s, 1H, -OH), 3.2-4.2 (m, 9H, -CH-O, 4X $-OCH_2-$), 4.55 (br.s, 1H, 3°H), 5.0 (m, 1H, -OCHO-), 5.4-6.2 (m, 2H, olefinic) IR: 2210 cm^{-1} ($-C\equiv C-$) and 3450 cm^{-1} (OH).

(E)-1[(Tetrahydro-2H-pyran-2-yl)oxy]-13-benzoyloxy-15,15-ethylene-dioxy-pentadec-9-yn-11-ene (10)

Benzoyl chloride (4.9 g, 0.035 mol) was added dropwise with stirring at 0° to a solution of the alcohol 9 (9.69 g, 0.0255 mol) in dry pyridine (50 ml) during 15 min. The reaction mixture was allowed to warm to room temperature and stirred for

The reaction mixture was allowed to warm to room temperature and stirred for further 6 hr. It was quenched with ice-cold water and the aqueous layer was extracted with dichloromethane. The organic layer was washed successively with water, aqueous copper sulfate solution and brine, dried (Na_2SO_4) and evaporated the solvent to furnish the benzoate 10 (10.49 g) in 85% yield as a viscous oil. ^{1}H-NMR (CCl_4):δ 1.15 - 1.70 (m, 18H, 9X $-CH_2$), 1.9-2.3 (m, 4H, 2X $-CH_2$), 3.1 - 3.9 (m, 8H, 4X $-OCH_2$), 4.5 (br.s, 1H, 3°H), 4.95 (m, 1H, -OCHO-), 5.4 - 6.2 (m,3H, CHOBz and olefinic), 7.25 - 7.50 (m, 3H, Ar-H), 7.90 - 8.10 (m, 2H, Ar-H); IR: 1720 cm^{-1} (-C=O).

(E)-13-Benzoyloxy-15,15-ethylenedioxy-9-yn-11-en-1-ol (11)

Acidic resin (1 g) was added to solution of benzoate 10 (4.84 g, 10 m.mol) in methanol (30 ml) and stirred at room temperature for 16 hr. Then it was filtered, methanol was removed from the filtrate and residue obtained was purified by silica gel chromatography to afford 11 (3.2 g) in 80% yield as an oil. ^{1}H-NMR ($CDCl_3$):δ 1.15 - 1.70 (m, 12H, 6X $-CH_2$), 1.9 - 2.4 (m, 5H, 2X $-CH_2$- and -OH), 3.65 (t, 2H, $-CH_2OH$), 3.9 (m, 4H, $-OCH_2.CH_2O-$), 4.98 (m, 1H, -OCHO-), 5.50-6.25 (m, 3H, -CHOBz and olefinic), 7.25 - 7.60 (m, 3H, Ar-H), 7.95 - 8.15 (m, 2H,, -Ar-H). IR: 1720 cm^{-1} (C=O), 3350 cm^{-1} (-OH).

Methyl(E)-13-benzoyloxy-15,15-ethylenedioxypentadec-9-yn-11-enoate (12)

To a stirred suspension of pyridinium dichromate (30.0 g, 80 m.mol) in DMF (40 ml) was added a solution of the

alcohol 11 (3.2 g, 8 m.mol) in DMF (10 ml) at room temperature. The reaction mixture was further stirred for 16 hr and then diluted with water (500 ml). It was extracted with ether, the ethereal extracts were washed with water, brine and dried (Na_2SO_4).

Ethereal diazomethane (prepared from N-nitroso-N-methyl urea) was added to the above ethereal solution at 0° and stirred for another 30 min. Evaporation of the solvent and chromatographic purification of the resulting residue furnished the ester 12 (1.71 g) in 50% overall yield. ^{1}H-NMR($CDCl_3$): δ 1.2 - 1.8 (m, 10H, 5X $-CH_2$), 1.95 - 2.40 (m, 6H, 3X $-CH_2$), 3.7 (s, 3H, $-OCH_3$), 3.80 - 3.95 (m, 4H, $OCH_2.CH_2O$), 5.0 (m, 1H, -OCHO-), 5.5 - 6.22 (m, 3H, -CHOBz and olefinic), 7.25 - 7.55 (m, 3H, Ar-H), 7.9 - 8.1 (m, 2H, Ar-H).

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CHAPTER III

SYNTHETIC APPROACHES TOWARDS FREDERICAMYCIN-A

INTRODUCTION

About 20 per cent of the deaths in Western countries are currently ascribed to neoplastic diseases, i.e. those associated with the growth of new abnormal body tissues commonly referred as "Cancer". This disease has engaged the world-wide attention of a variety of research workers.

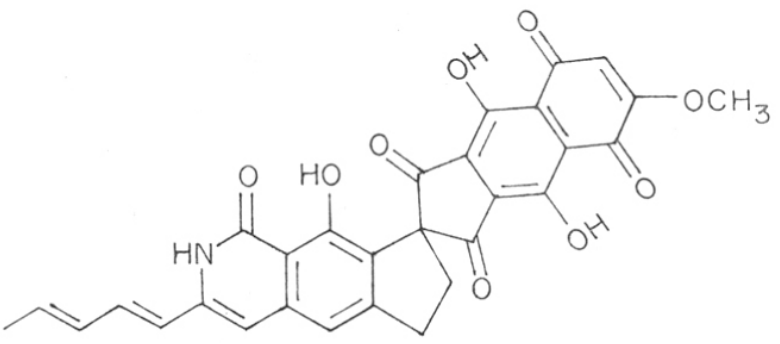
Radiation and surgery have certainly a curative effect as long as it is detected at an early stage and localized[1]. But unfortunately by the time it is detected, the disease often spreads to other organs of the body and then the answer lies in chemotherapy either exclusively or in combination with surgery and radiation.

A large number of anti-cancer drugs are now being used in medicinal practice which have been approved by the National Cancer Institute (USA). Further many are undergoing clinical trials. All these drugs can be broadly classified into (1) alkylating agents, (2) antimetabolites (3) antibiotics and (4) miscellaneous compounds.

To acquire new anticancer agents, a variety of sources have been explored, including synthetic compounds microbial and plant extracts. Among the various compounds which are promising as antitumour agents, natural products, either of plant or microbial origin, are showing much more specificity in their anticancer properties. The antitumour antibiotics may be defined[2]

as microbial products which inhibit the growth of tumour cells and can cause inhibition of experimental tumours. Efforts in recent years have moved towards a systematic exploration of microorganisms. In view of the number of useful materials that have been developed (e.g. mithramycin, mitomycin, bleomycin, daunomycin, adriamycin) the fermentation area still holds considerable interest and promise as a source of new active microbial agents.

During the course of a screening programme for new antitumour antibiotics, Pandey and coworkers[3a] isolated a strain of Sptreptomyces griseus from a soil sample in Frederick, Maryland. Fermentation broths of S. griseus repeatedly showed high in vitro activity against KB and P 388 tumour cell lines and in vivo activity against P 388 tumour cells. A complex of several biologically active compounds was isolated from the broth and the purification of the complex resulted in the isolation of one major and two minor components. The major biologically active component present was named as fredericamycin-A. In vitro fredericamycin A exhibits antibacterial, antifungal and cytotoxic activities[3b]. In vivo it exhibits very good antitumour activity. The structure of fredericamycin-A (1) was established by the combination of spectral analysis and confirmed by X-ray studies[3c] which revealed that the molecule consists of an entirely novel spiroring system, not previously found in the antibiotic structures. The spiro [4,4]nonane system



1

found in fredericamycin-A imposes certain interesting spacial characteristics on the molecule which may have an important role in determining its biological activity.

PRESENT WORK

Fredericamycin-A (1) produced by Streptomyces griseus has been shown to be a potent antitumour agent[3]. Its biological activity and important structural features called for its synthesis.

Compound (1) has entirely novel spiro[4,4]nonane system which was new in antibiotics. Challenging feature in the total synthesis of 1 was to develop a synthetic method for the preparation of spiro [4,4]nonane system. Antithetic analysis

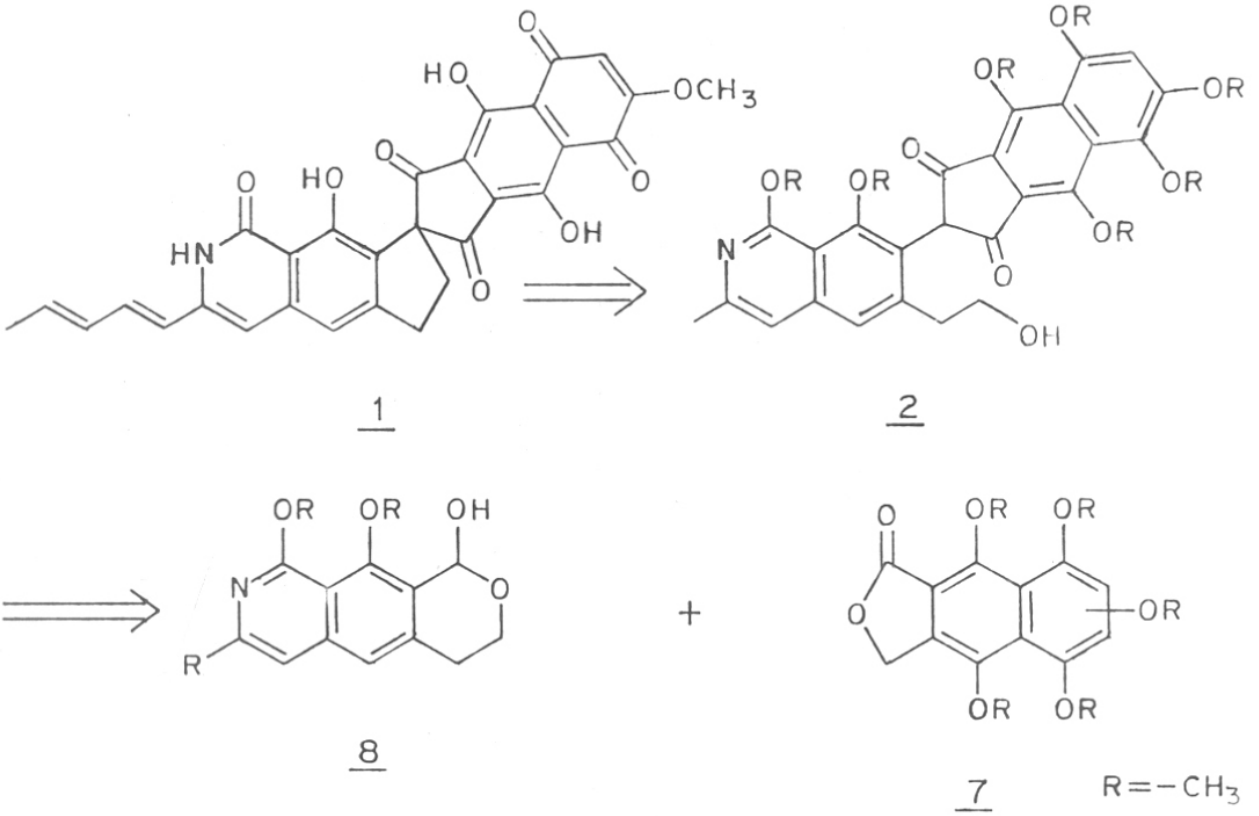
of 1 suggested that such a synthesis could best be achieved first by obtaining 2 (Scheme 1) and then by building the spiro system. Methodology for the synthesis of spiro[4,4]nonane system has recently been developed in these laboratories[4] on a model spiro ring system (3).

This method involved the Dieckman condensation[5] (Scheme 2) of phthalide and 1-hydroxyisochroman (4) in presence of sodium methoxide and the resulting 2(2-hydroxyethylphenyl)-1,3-indandione (5) was treated with toluene p-sulfonic acid (PTSA) to give 5,6-dihydro-12-H-benz[d]inden-[1,2-b] oxepin 12-one (6). 6 on thermolysis underwent rearrangement to give the spiro[4,4]nonane system (3).

Having established a methodology for the synthesis of spiro ring system, studies were directed towards the total synthesis of fredericamycin-A (1). Based on the above strategy the molecule (1) was divided into two key intermediates, 4,5,6,8,9-pentamethoxy-1,3-dihydronaphtho[2,3-C]-furan-1-one (7) and 1-methoxy-6-(2-hydroxyethyl)-7-formyl-8-methoxy isoquinoline (8). As the synthesis of phthalide intermediate 7 was already completed in these laboratories, efforts were made towards the synthesis of isoquinoline intermediate 8.

The challenging structural features present in intermediate 8 could be summarized as follows: (a) Presence of nonsymmetry element (b) presence of array of functionalities and (c) the presence of a hetero atom.

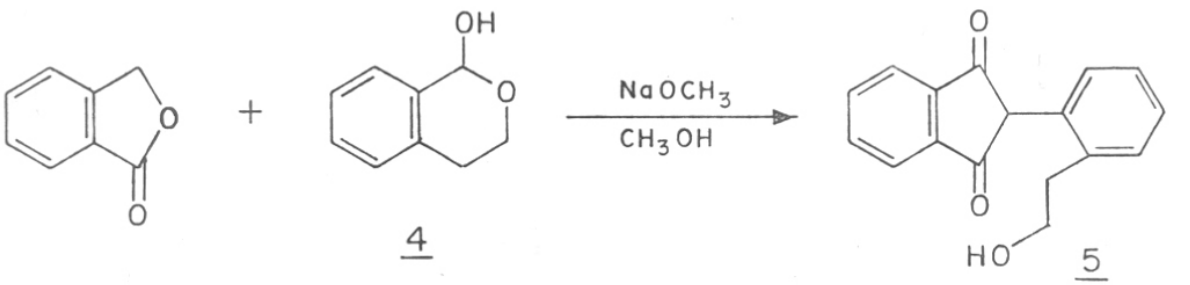
SCHEME – 1



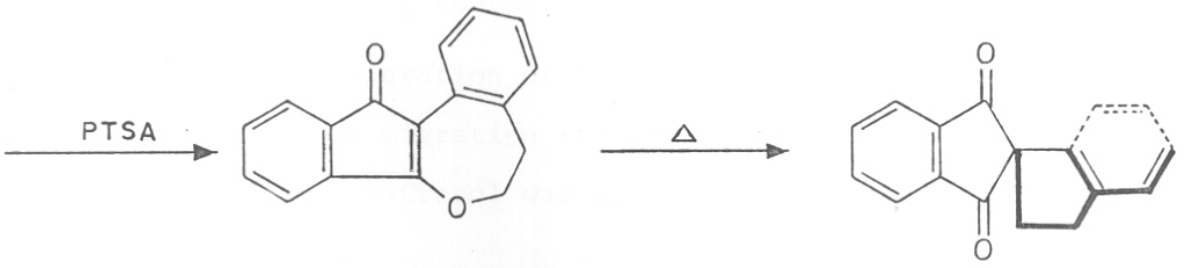
1 2

8 7 R=–CH3

SCHEME–2



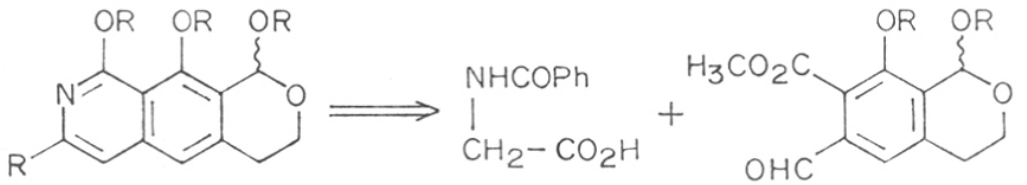
4 5



6 3

First attempted synthesis of the key intermediate 8

There is a report[6] in the literature that isoquinolinone could be synthesised elegantly starting from phthalaldehydic acid (9) and hippuric acid (10). The resulting azlactone 11 could be transformed to isoquinolinone in presence of a base (Scheme 3). Based on this synthesis the retrosynthetic analysis of the key intermediate 8 could be done as follows.



8 12

This analysis clearly suggested that the synthesis of the substituted methylphthalaldate 12 was the key step for the synthesis of 8.

Judicious planning for the synthesis of 12 (Scheme 4) revealed that the substituted indanone 13 would be the suitable intermediate for its synthesis. Although there are a few methods available for the synthesis of indanone derivatives, the one reported[7] by Sakai et al. is probably more suitable for the present synthesis.

The preparation of indanone derivative 13 mainly involved Fries migration and Friedel Craft's cyclization on m-cresol. m-Cresol was treated with 3-chloropropionyl

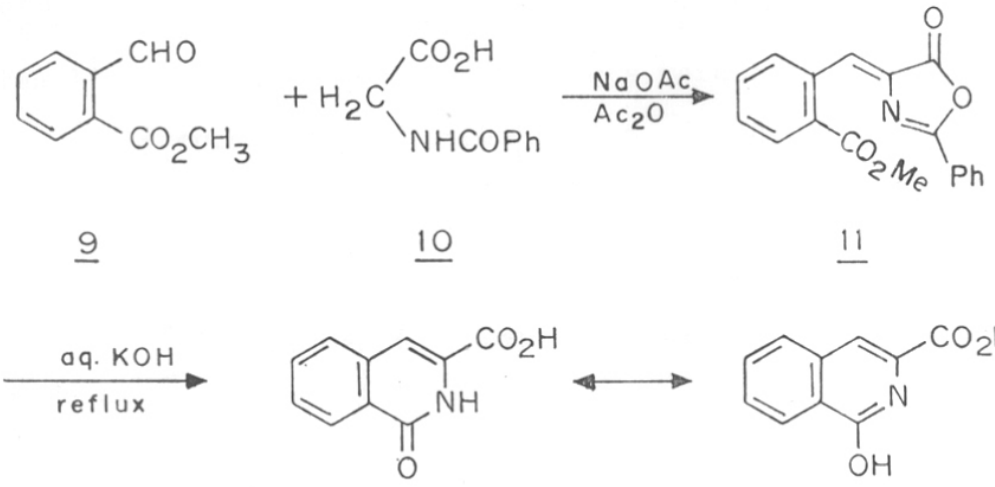
chloride (14) in anhydrous benzene in presence of a drop of conc. sulfuric acid to afford the ester 15 in 70% yield. This ester 15 was heated with excess of anhydrous aluminium chloride to furnish the indanone 13 in 50% yield. In the PMR spectrum of 13, two methylenes appeared as triplets at δ 2.70 and 3.00, whereas two aromatic protons resonated as singlets at δ 6.50 and 6.62. The chelated phenolic hydroxyl group resonated at δ 9.80.

The free hydroxyl in indanone 13 was protected by refluxing with dimethyl sulfate and potassium carbonate in dry acetone to yield 5-methyl-7-methoxy indan-1-one (16). The ^{1}H-NMR spectrum of 16 indicated a singlet for methoxyl group at 3.90 ppm while other protons resonated at expected chemical shifts.

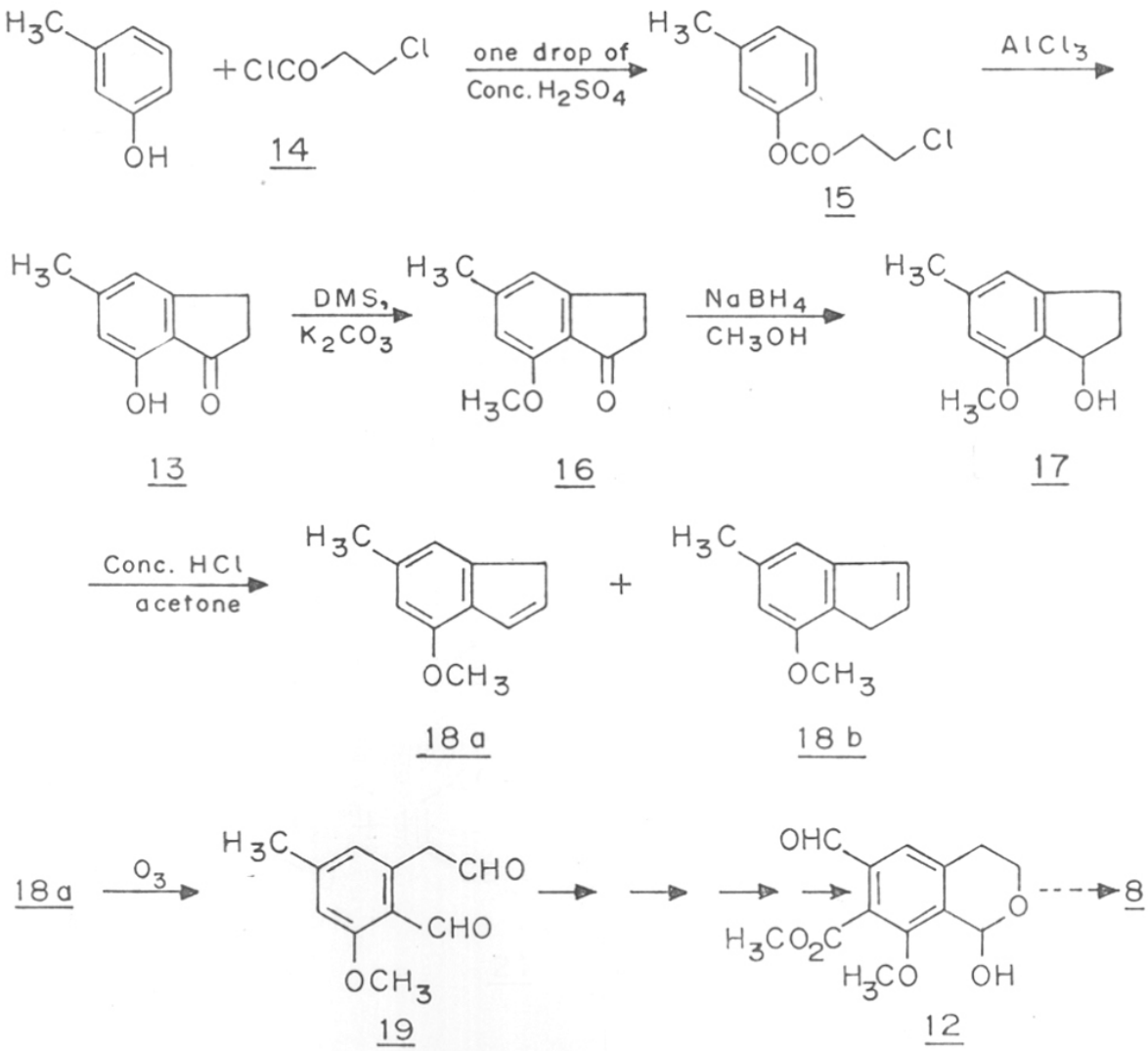
Reduction of the compound 16 with sodium borohydride in methanol underwent smoothly to give the hydroxy indane derivative 17 in 75% yield. In the PMR spectrum of 17, the methine proton at C-1 resonated as multiplet in the region of 5.2 ppm while rest of the protons appeared at the expected chemical shift values.

The hydroxyindane derivative 17 was then subjected to dehydration in presence of a few drops of conc. hydrochloric acid. Although the isolated product from the reaction mixture was homogeneous on TLC, the ^{1}H-NMR spectrum clearly indicated that it was a mixture of two products (18a and 18b), as doubling of the resonances due to methyl group was

SCHEME-3



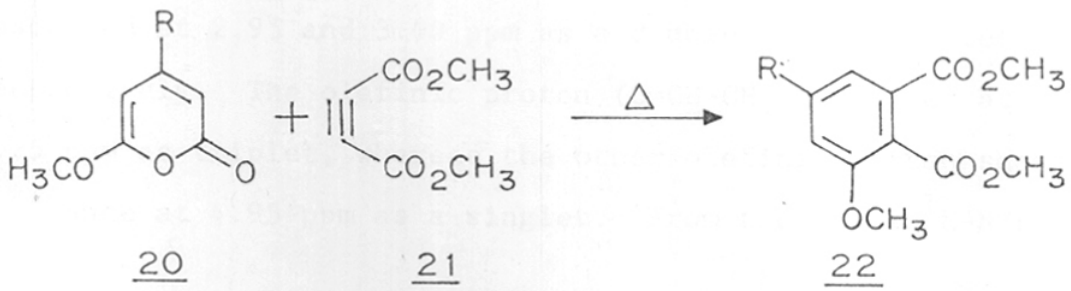
SCHEME-4



clearly revealed. These two products were isomeric, which could only occur by the isomerisation of double bond. There are a few instances in literature[8] where such types of isomerization has been observed.

It was thought of subjecting the indene derivative 18a to ozonolysis to get the corresponding homophthalaldehyde derivative 19 which could be converted to the required phthalaldehydic acid intermediate 12 by further transformations. But this mixture of 18a and 18b was of no use in the present synthesis, because on ozonolysis it would lead to the formation of two isomeric homophthalaldehydic derivatives, whose separation would be tedious and therefore, this scheme was abandoned.

Having failed to get exclusively the required substituted indene 18a, it was thought to prepare the phthalaldehydic acid intermediate by an altogether different route. Based on the report by Kozikowski et al.[9] in which the enol ether of a substituted glutaconic anhydride (20) and an acetylenic derivative 21 undergo Diels-Alder reaction to give the tetrasubstituted benzene derivative 22 (Scheme 5) the present approach was attempted.



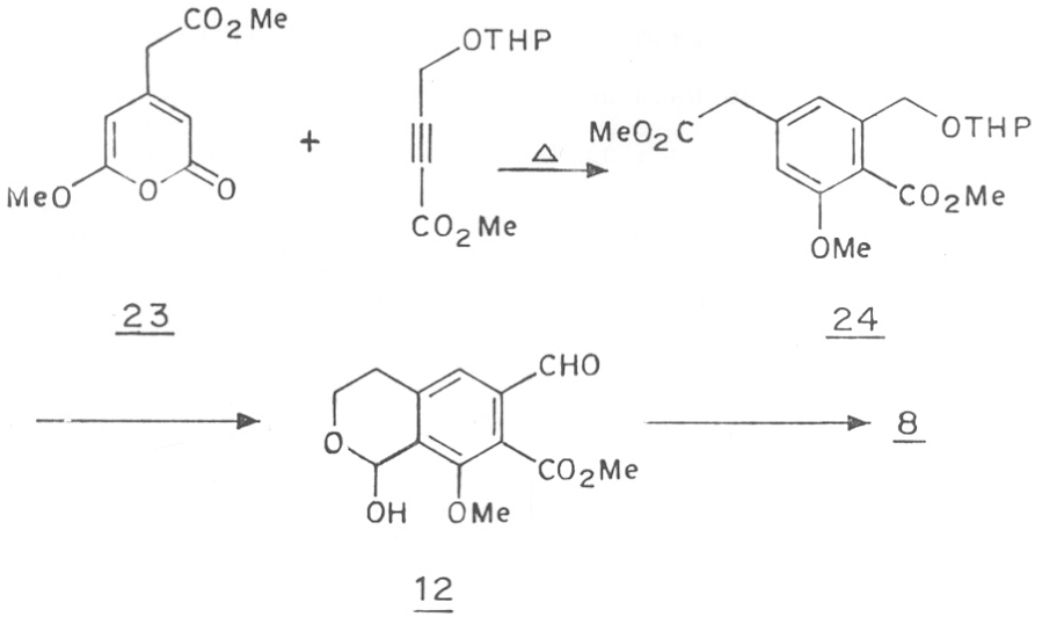
20 21 22

SCHEME-5

From the above reaction it could be suggested that by subjecting the enol ether of a substituted glutaconic-anhydride 23 to the above reaction, the required substituted benzene derivative 24 could be prepared which could lead to the synthesis of 12 (Scheme 6). The synthesis of 23 was attempted from 3-oxoglutaric ester (25) by known procedure[10] (Scheme 7). 25 on treatment with phosphorous pentachloride, followed by 20% hydrochloric acid gave the diacid 26, which was esterified in presence of ethanol and sulfuric acid to give the diester 27. Condensation of 27 with sodium salt of diethylmalonate afforded the tetraester 28, which on decarboxylative hydrolysis with 20% hydrochloric acid furnished the triacid 29. The triacid (29) was then subjected to the treatment with acetic anhydride to afford the corresponding anhydride 30.

The anhydride 30 on treatment with diazomethane in ether surprisingly furnished a mixture of two products. The minor product isolated in 15% yield was the required 23, whose physical and spectral properties coincided with the reported[11] values. The major product isolated in 50% yield was assigned the structure 31 on the basis of its ^{1}H-NMR spectrum. For example the ring methylene and the side chain methylene resonated at 2.95 and 3.00 ppm as a doublet and a singlet respectively. The olefinic proton (C=C<u>H</u>-CH_2) appeared at 5.25 ppm as triplet, whereas the other olefinic proton showed resonance at 4.95 ppm as a singlet. From the above ^{1}H-NMR

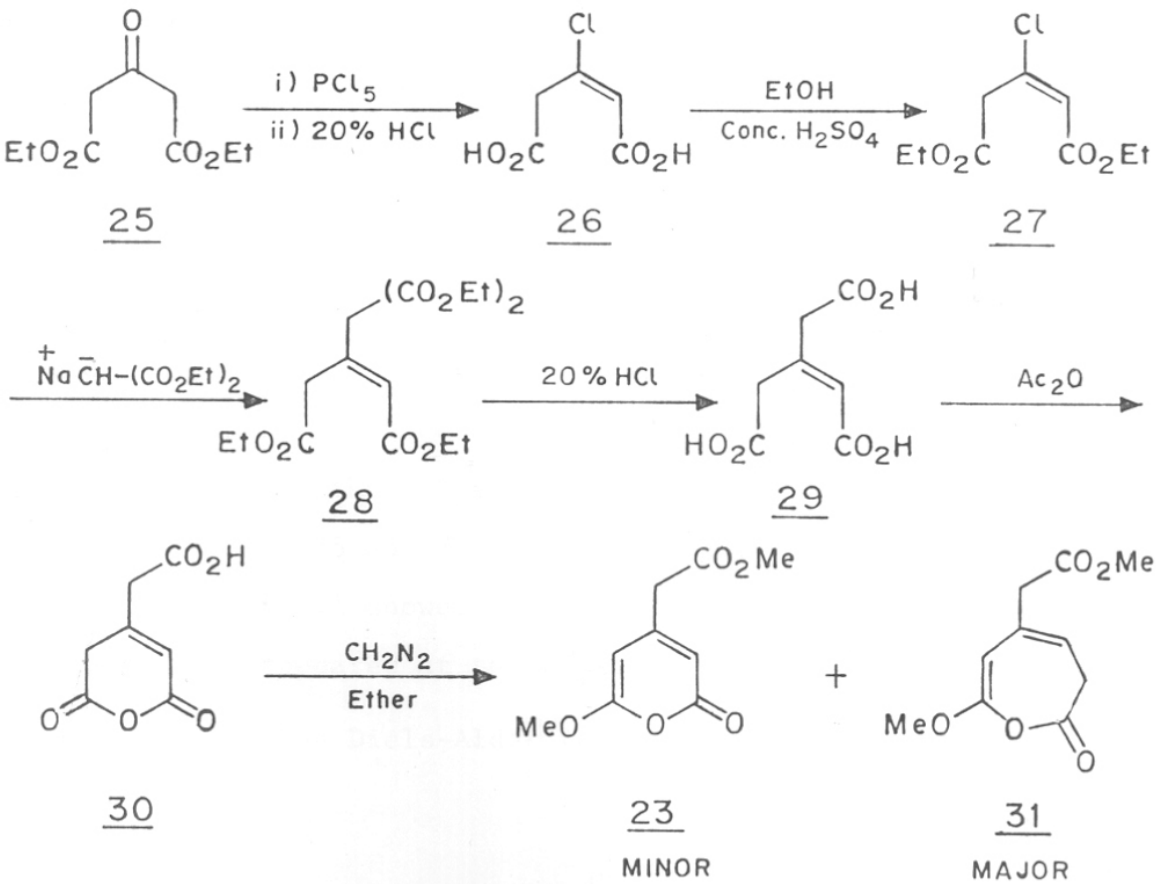
SCHEME – 6



23 24

12

SCHEME – 7



25 26 27

28 29

30 23 MINOR 31 MAJOR

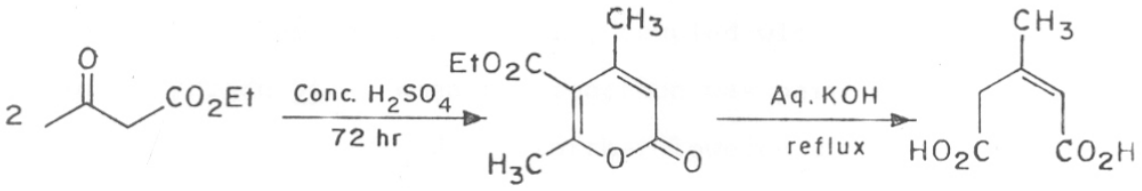
values the given structure 31 looked most feasible, however, judicious structural studies has not been done to confirm the structure. This was due to the little use of the compound 31 in the present synthesis.

Although Jung et al.[11] reported the exclusive formation of 23 from the anhydride 30 and diazomethane, in the author's hand, a mixture of products 23 and 31 were always obtained. In an another study made with analogous anhydride 34 (prepared by the literature procedure[12] as indicated in the scheme 8) with diazomethane a similar mixture of products were obtained.

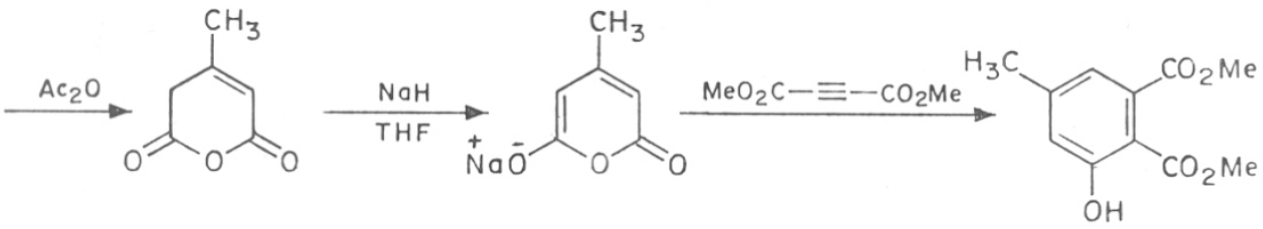
Recently Tamura et al.[13] have shown that substituted glutaconic anhydride could be trapped in an enolate form by treatment with a base which in turn could be used as a potential diene. Thus the anhydride 34 was treated with sodium hydride in THF and the resulting sodium enolate 35 was subjected to Diels-Alder reaction with dimethylacetylene dicarboxylate and the tetrahydropyranyl ether of methyl 4-hydroxy-but-2-ynoate to furnish the corresponding adducts 36 and 37 respectively in about 50% yield (Scheme 8). The structures of 36 and 37 were assigned on the basis of their ^{1}H-NMR spectra. For instance in the PMR spectrum of 37 the two aromatic protons resonated at 6.85 and 7.05 ppm as singlets, the chelated phenolic hydroxyl showed resonance at 11.50 ppm and the rest of the protons appeared at the expected chemical shift values.

Though the Diels-Alder reactions with 34 worked well

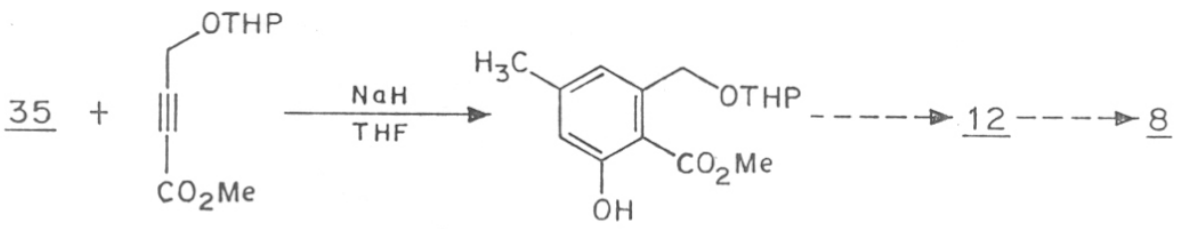
SCHEME-8



32 33



34 35 36



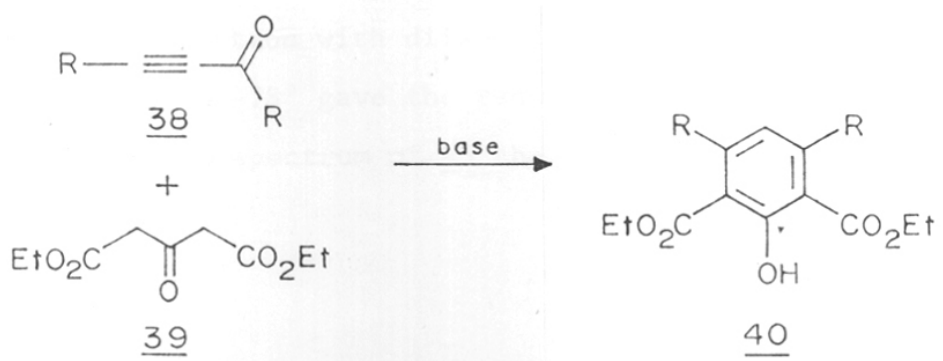
37

in small scale reactions, difficulties were encountered in executing them on larger scale, coupled with the unstability of anhydride 34. When the reaction was performed on a larger scale the yield was further lowered due to certain unexplainable reasons. Since many more steps have to be carried out with 37 before the final product 8 was formed, this route was not further explored.

Regarding the first synthetic approach to the 8 described in the preceding lines, it could be suggested that the failure of the synthetic scheme was attributed to the inability to prepare the properly substituted phthalaldehydic acid intermediate 12. However, this led to think that planning for the synthesis of isoquinoline intermediate 8 has to be conducted by an altogether different route.

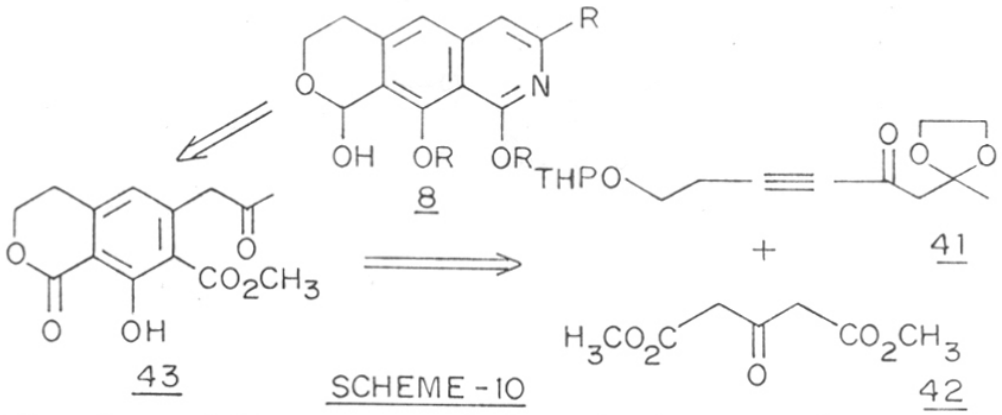
Synthesis of isoquinoline intermediate 8 by an acetylenic approach

It has been demonstrated[14] that ∝-acetylenic ketone (38) when allowed to react with diethyl-1,3-acetonedicarboxylate (39) in presence of a base undergoes Michael addition followed by aldol condensation to give rise to the corresponding



SCHEME - 9

substituted phenol 40. Based on this reaction the following retrosynthetic approach was envisaged (Scheme 10).

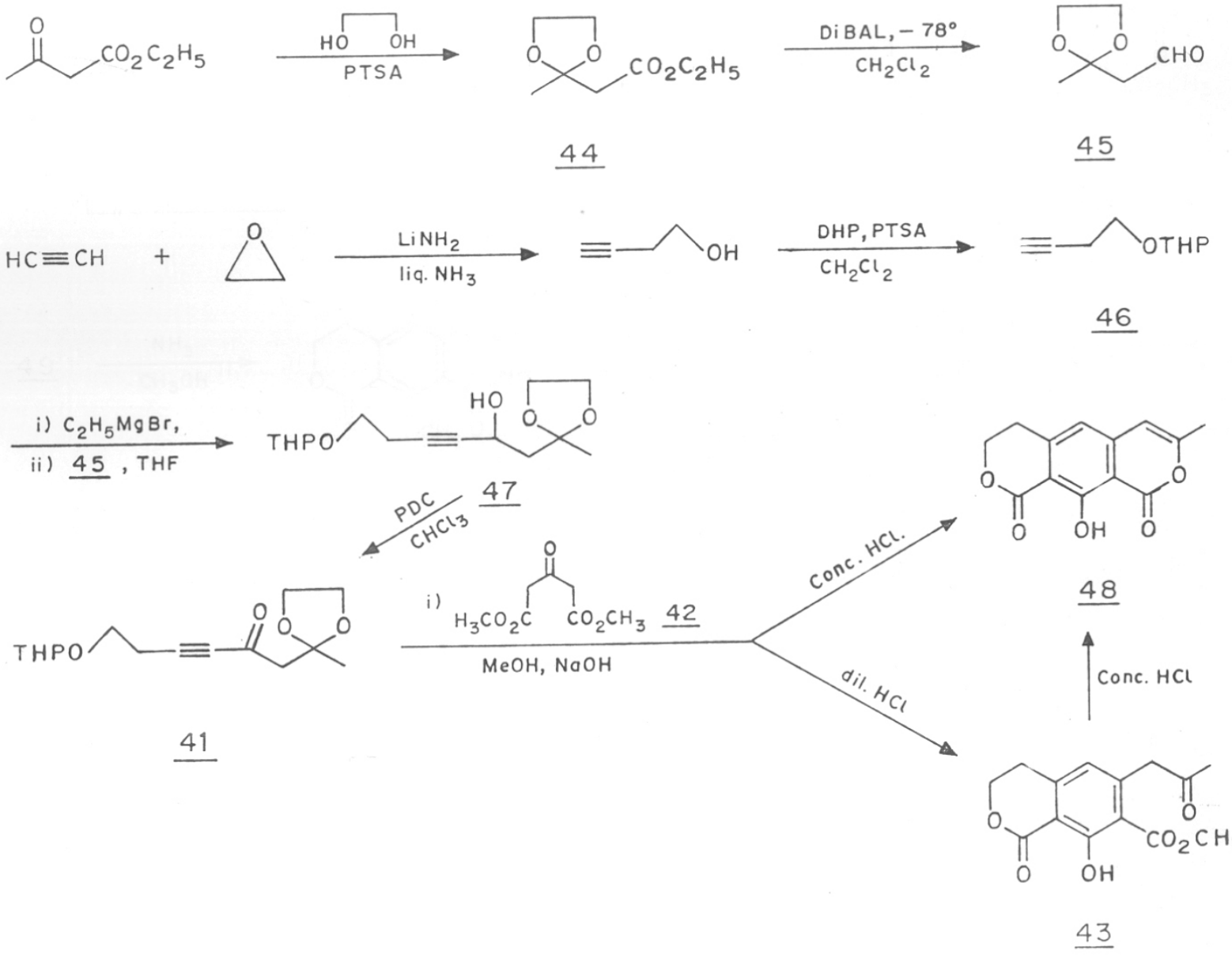


SCHEME-10

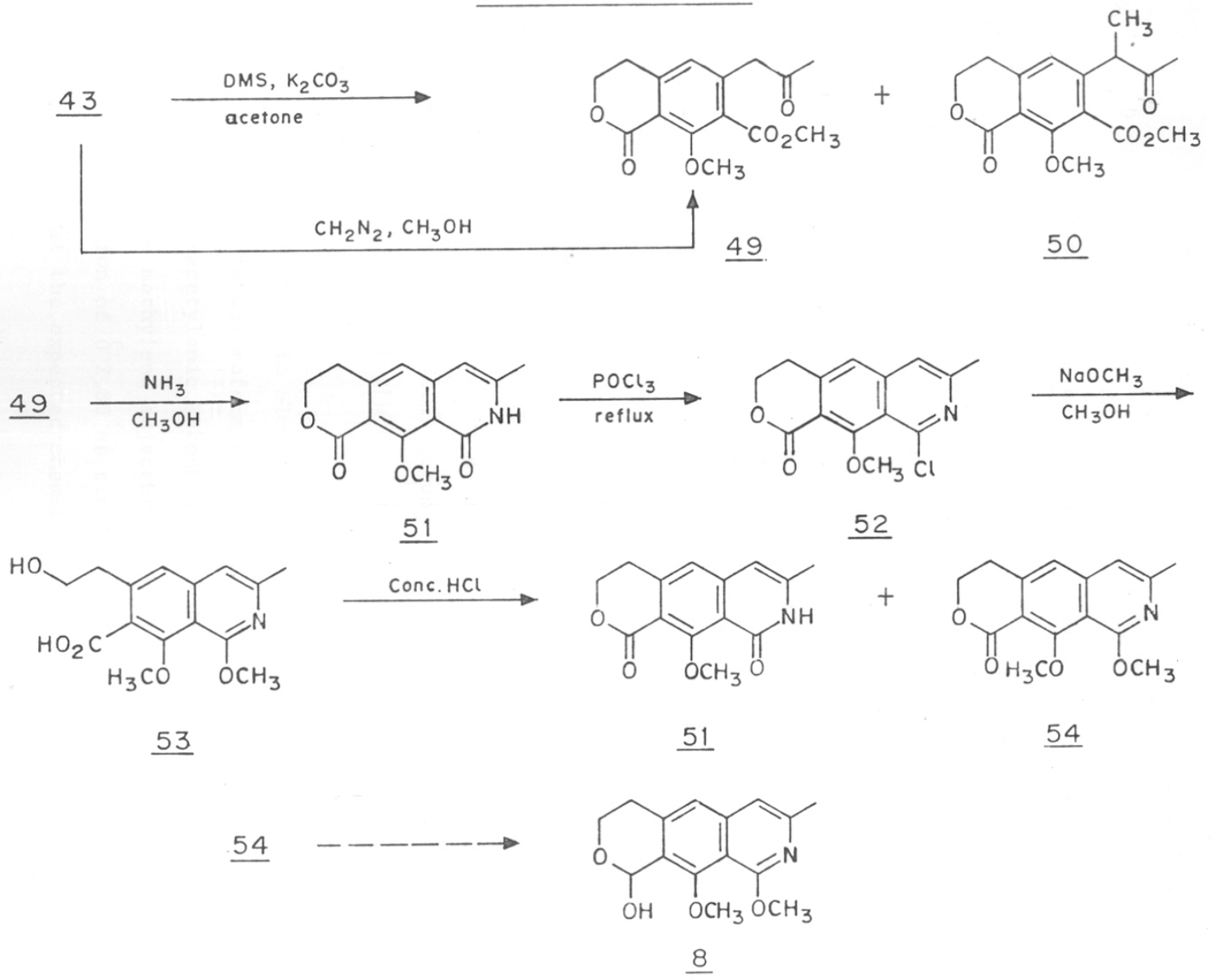
Thus it could be suggested that the key step for successful execution of this scheme was the condensation of 41 and 42 to yield the required intermediate 43. Thus the first concern of the planning was to get the acetylenic ketone 41 in substantial amount and to optimise conditions of the condensation reaction.

The preparation of α-acetylenic ketone 41, mainly involved a Grignard reaction between the acetylenic compound 46 and an aldehyde 45. The aldehyde 45 was prepared starting from ethylacetoacetate. Ethylacetoacetate was refluxed with ethyleneglycol in benzene using PTSA as catalyst to afford ethyl-3,3-ethylenedioxybutanoate (44) in 85% yield. Ester 44 on reduction with diisobutylaluminium hydride in dichloromethane at -78° gave the required aldehyde 45 in 75% yield. In the PMR spectrum of 45 the aldehyde proton resonated at

SCHEME-11


CO2C2H5
HO OH
PTSA
CO2C2H5
DiBAL, – 78°
CH2Cl2
CHO
44
45
HC≡CH
+
LiNH2
liq. NH3
OH
DHP, PTSA
CH2Cl2
OTHP
46
i) C2H5MgBr,
ii) 45 , THF
THPO
HO
47
PDC
CHCl3
i)
H3CO2C
CO2CH3
42
MeOH, NaOH
Conc. HCl.
dil. HCl
48
Conc. HCl
CO2CH3
OH
43
41
THPO

SCHEME – 11 (contd.)



9.30 ppm as triplet.

The acetylenic compound 46 was prepared as follows. Ethyleneoxide was opened with lithiumacetylide in liq.ammonia at -33° to give but-3-yn-1-ol. This alcohol on treatment with dihydropyran in dichloromethane using PTSA as catalyst furnished the corresponding THP ether 46 in 90% yield.

After obtaining the acetylenic compound 46, it was subjected to the reaction with the aldehyde 45. For this purpose the acetylenic compound 46 was first treated with ethylmagnesium bromide to get the corresponding acetylene magnesium bromide which was *in situ* treated with the aldehyde 45 in THF to furnish the acetylenic alcohol 47 in 95% yield. In the IR spectrum of 47 the hydroxyl showed the absorption at 3450 cm^{-1}. In the PMR spectrum the characteristic THP tertiary proton resonated at 4.60 ppm as a broad singlet, the protons due to the ketal group appeared at 3.95 ppm as a singlet and rest of the protons appeared at the expected chemical shifts.

The acetylenic alcohol 47 was oxidised with pyridinium-dichromate in chloroform to afford, in 80% yield the corresponding α-acetylenic ketone 41. In PMR spectrum of 41 (Fig.1) the methylene adjacent to the keto group resonated in the region of δ 2.80 as singlet and the remaining protons appeared at the expected chemical shifts.

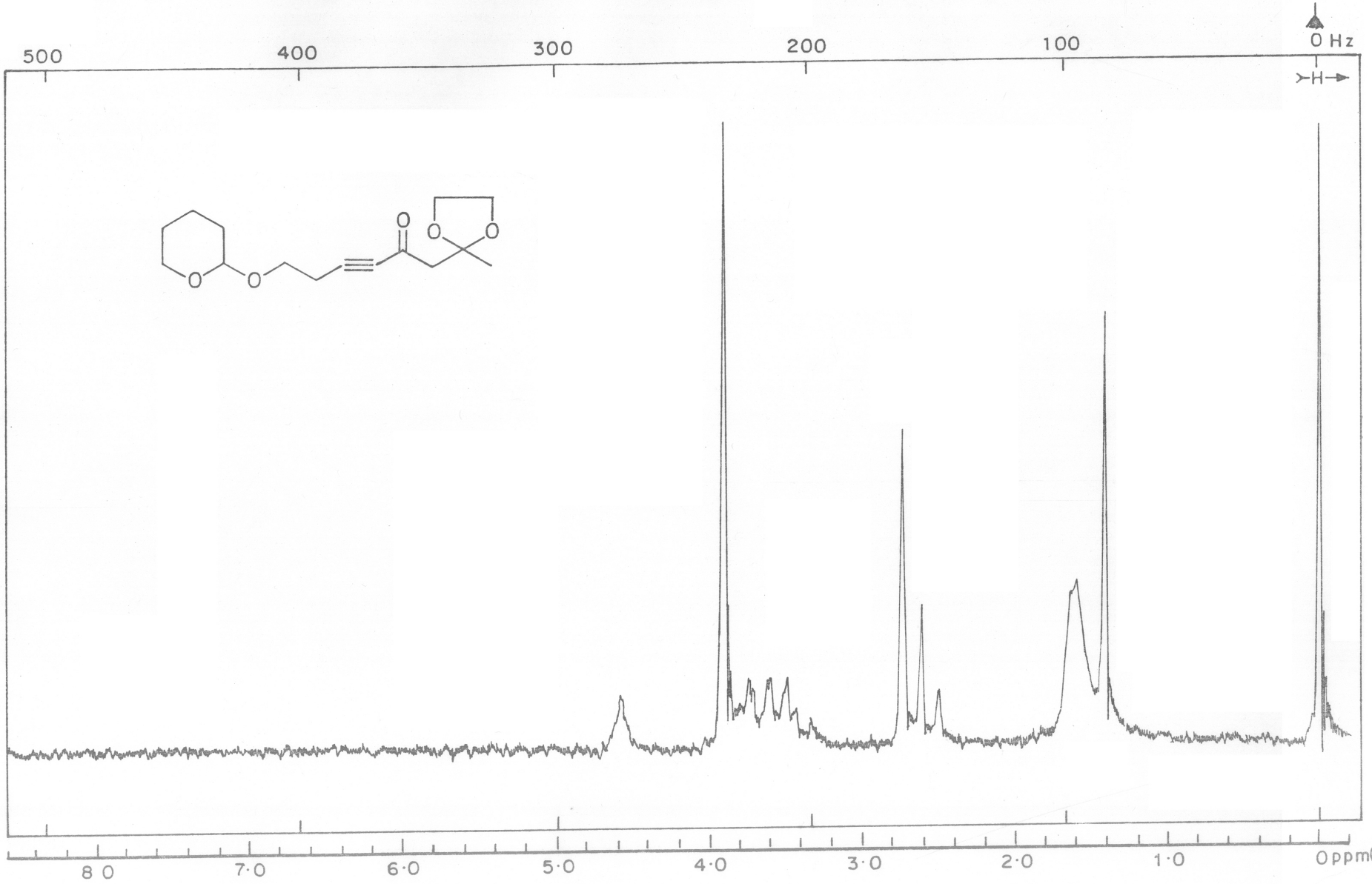


FIG. 1. ^{1}H-NMR SPECTRUM OF COMPOUND (41) IN CCl_4

After obtaining the α-acetylenic ketone 41 the next target was to condense it with dimethyl-1,3-acetone dicarboxylate 42. This was carried out by stirring the mixture of 41 and 42 in the presence of 2N sodiumhydroxide in methanol at room temperature for 36 hr. The reaction mixture was neutralized with conc. hydrochloric acid to afford the dilactone 48 whose structure was given by spectroscopic evidences. For example in the ^{1}H-NMR spectrum of 48 (Fig.2) the two methylenes indicated signals at 3.10 and 4.60 ppm as triplets, the olefinic proton resonated at 6.2 ppm as singlet, the aromatic proton and the chelated phenolic hydroxyl were seen as singlets at 6.70 and 12.85 ppm respectively. In addition, the molecular ion peak at m/e 246 in its mass spectrum gleaned further confirmation to the assigned structure.

It was interesting to note that when the reaction of 41 and 42 was worked up with dilute hydrochloric acid, the formation of monolactone 43 resulted. The structure of the monolactone 43 was given by comparison of its ^{1}H-NMR spectrum (Fig.3) with that of the dilactone 48. For example, the absence of the olefinic proton (δ 6.20) and the appearance of signals due to methylene adjacent to the carbonyl group at 3.8 ppm as singlet clearly indicated the structure assigned. The other protons, however had comparable frequencies in both the compounds. When the

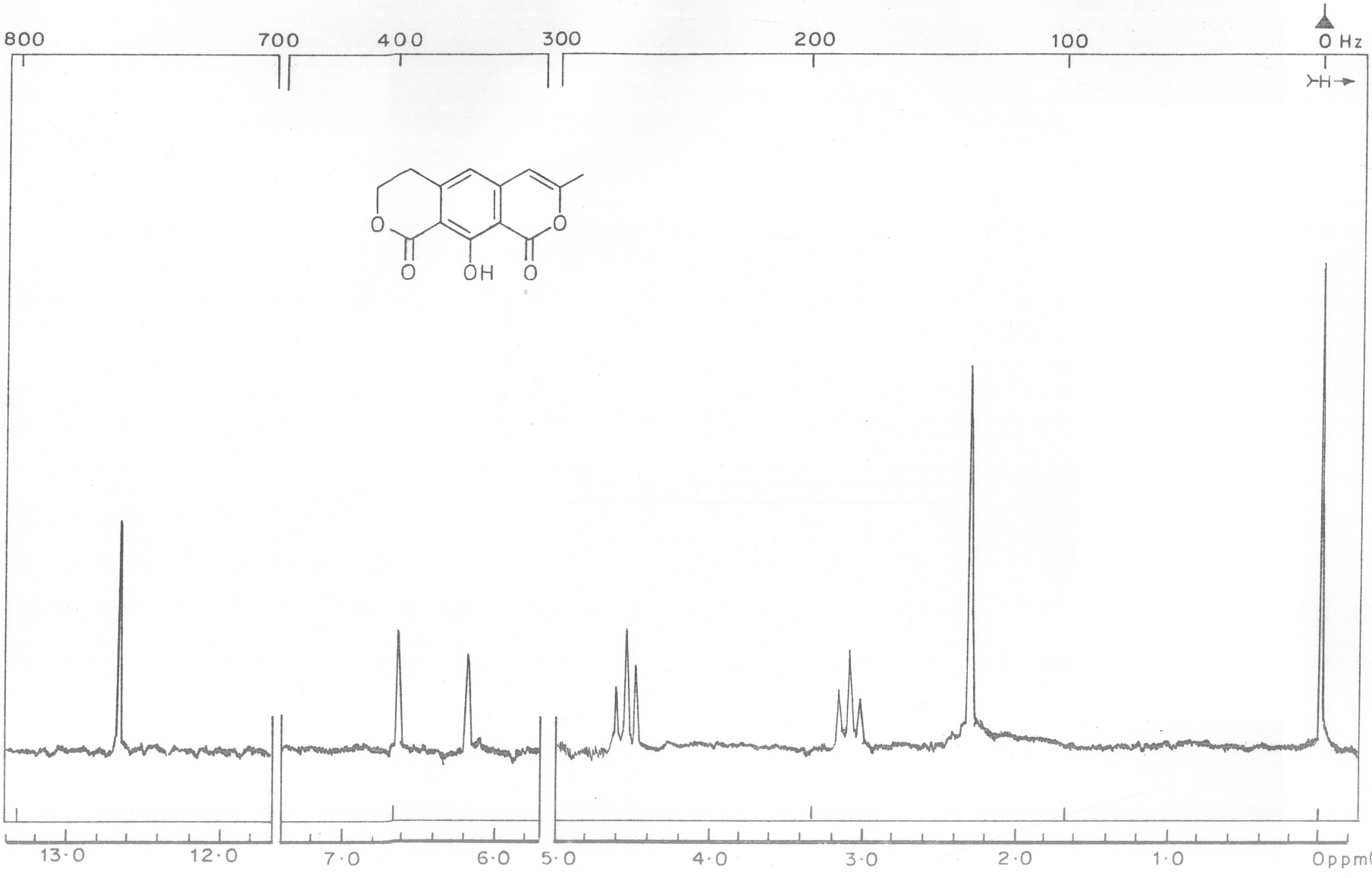


FIG. 2. ^{1}H–NMR SPECTRUM OF COMPOUND (48) IN $CDCl_3$

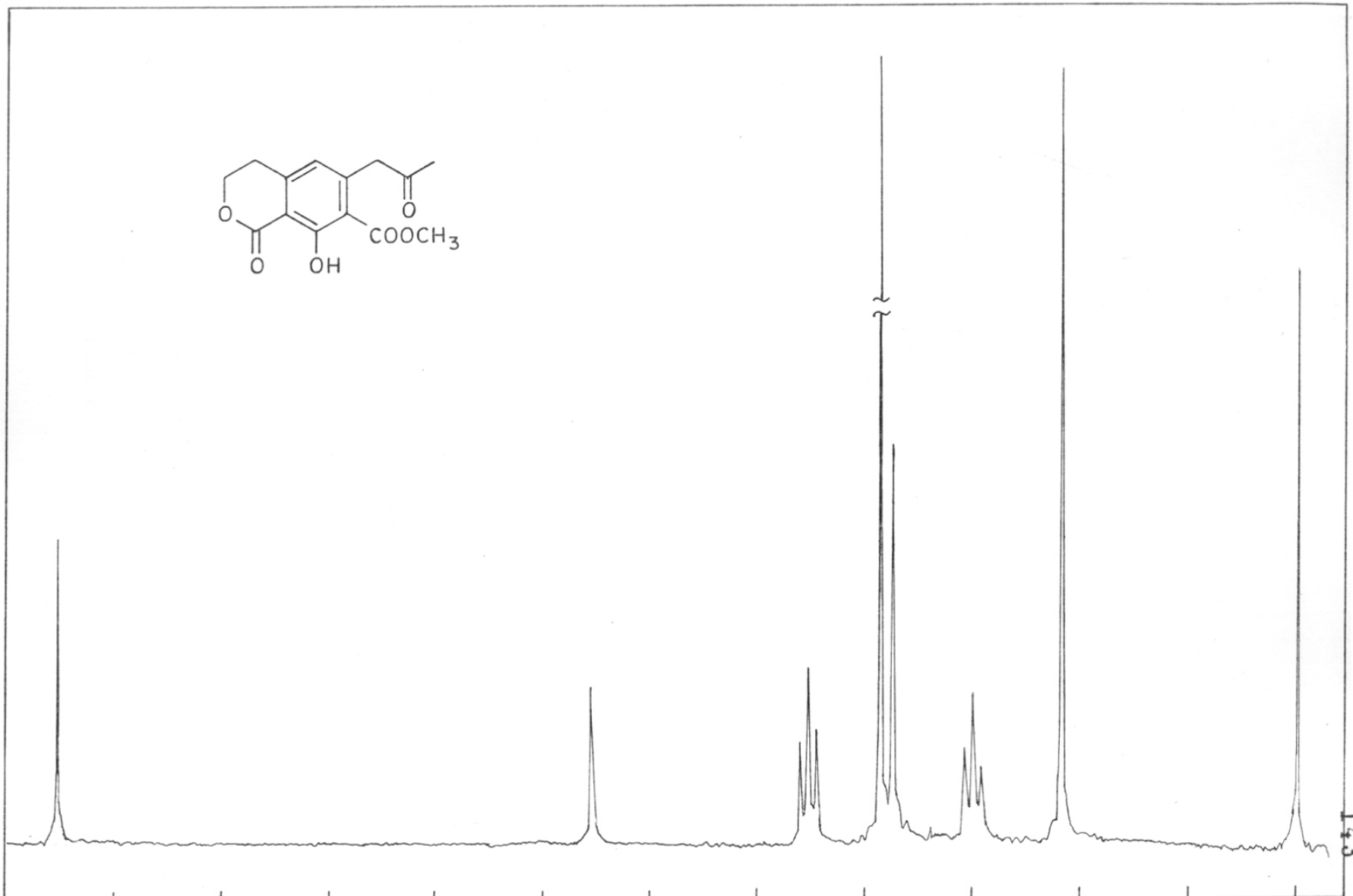


FIG. 3. ^{1}H-NMR SPECTRUM OF COMPOUND (43) IN $CDCl_3$

monolactone 43 was treated with conc. hydrochloric acid, the formation of the dilactone 48 was observed.

After obtaining the carbon framework of the intermediate 8 protection of the phenolic hydroxyl was most desirable before the introduction of 'N' could be ventured. Thus when the dilactone 48 was subjected to O-methylation in presence of DMS and K_2CO_3 in acetone, unfortunately no methylation resulted and the starting material recovered back. Even in the presence of DMF as solvent O-methylation failed to occur. When diazomethane was employed as O-methylating agent, the reaction was not clean but from the ^{1}H-NMR spectrum of the product, it could be inferred that the isocoumarin ring opened along with the formation of methyl ether.

Treatment of the monolactone 43 with dimethylsulfate and potassiumcarbonate in refluxing acetone furnished two products, which were separated and characterised. The minor product isolated in 25% yield was the required product 49, because the ^{1}H-NMR spectrum of 49 indicated peaks characteristic of the given structure. For instance, the loss of phenolic hydroxyl and the appearance to two methoxyl peaks at δ 3.90 and 3.95 were clearly observed. In the ^{1}H-NMR spectrum of major product 50, a doublet due to methyl group (-CH-C$\underline{H}_3$) was shown at 1.30 ppm and a quadruplet of the methine proton (-C$\underline{H}$-CH$_3$) resonated in the region of 3.7 ppm which indicated the structure assigned. It was gratifying to note that when the methylation of 43 was carried out with diazomethane,

a clean reaction occurred and the required O-methyl derivative 49 was obtained in 95% yield.

After obtaining the compound 49 successfully, efforts were directed towards the introduction of 'N' atom. There are several instances in literature[15] where isocoumarins or the corresponding ketoesters on treatment with ammonia furnish the corresponding isoquinolinone derivatives.

Accordingly 49 was treated with ammonia dissolved in methanol at room temperature and the corresponding isoquinolinone 51 was isolated. In the ^{1}H-NMR spectrum of 51 (Fig.4) the loss of benzylic protons were clearly observed and the appearance of an olefinic proton at δ6.20 as singlet was seen, which suggested the structure assigned.

The next aim according to the scheme was to protect the isoquinolinone in the form of its methyl ether 54 to increase its solubility, so that further transformations could be easily carried out. For this, isoquinolinone 51 was heated at reflux with phosphorous-oxychloride and the corresponding 1-chloroderivative 52 was isolated in 65% yield. The structure 52 was confirmed by its spectral data. In the ^{1}H-NMR spectrum (Fig.5) the olefinic proton at 6.20 ppm disappeared, the aromatic protons resonated at 7.25 ppm as a singlet and the remaining protons appeared at the expected chemical shifts. The molecular ion peak at 277 in its mass spectrum was in agreement with the assigned structure.

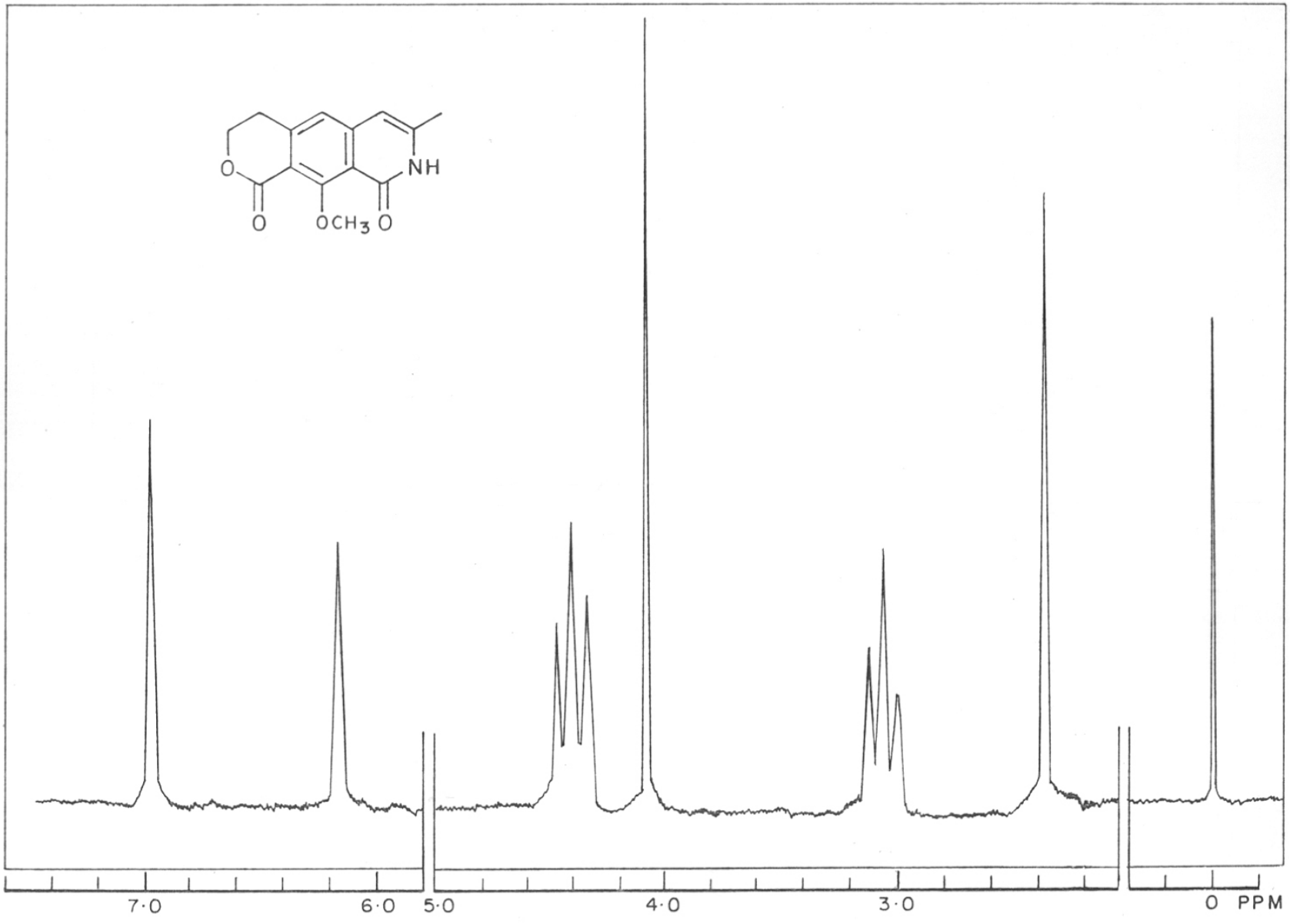


FIG. 4. ^{1}H–NMR SPECTRUM OF COMPOUND (51) IN $CDCl_3$

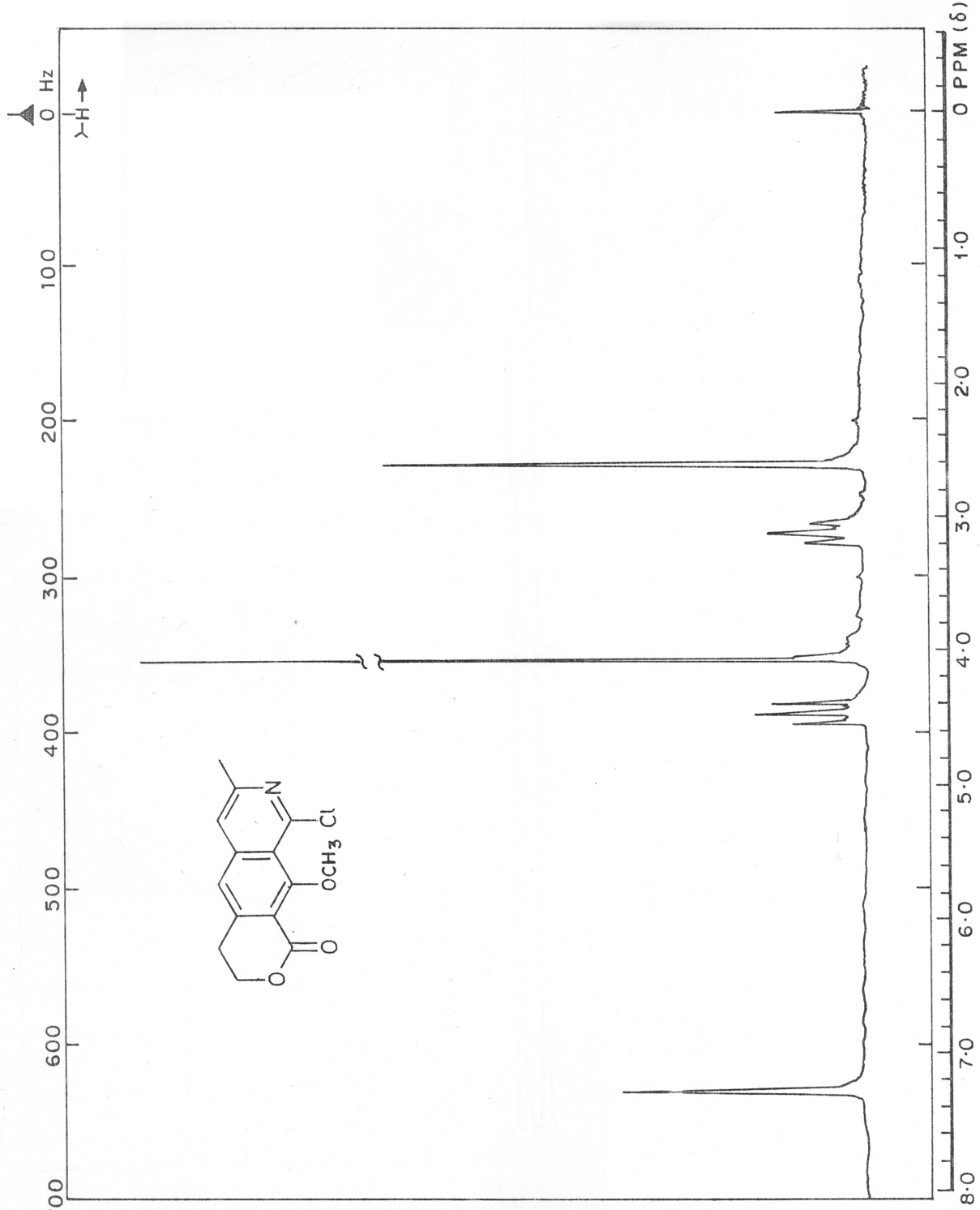


FIG. 5. ^{1}H-NMR SPECTRUM OF COMPOUND (52) IN $CDCl_3$

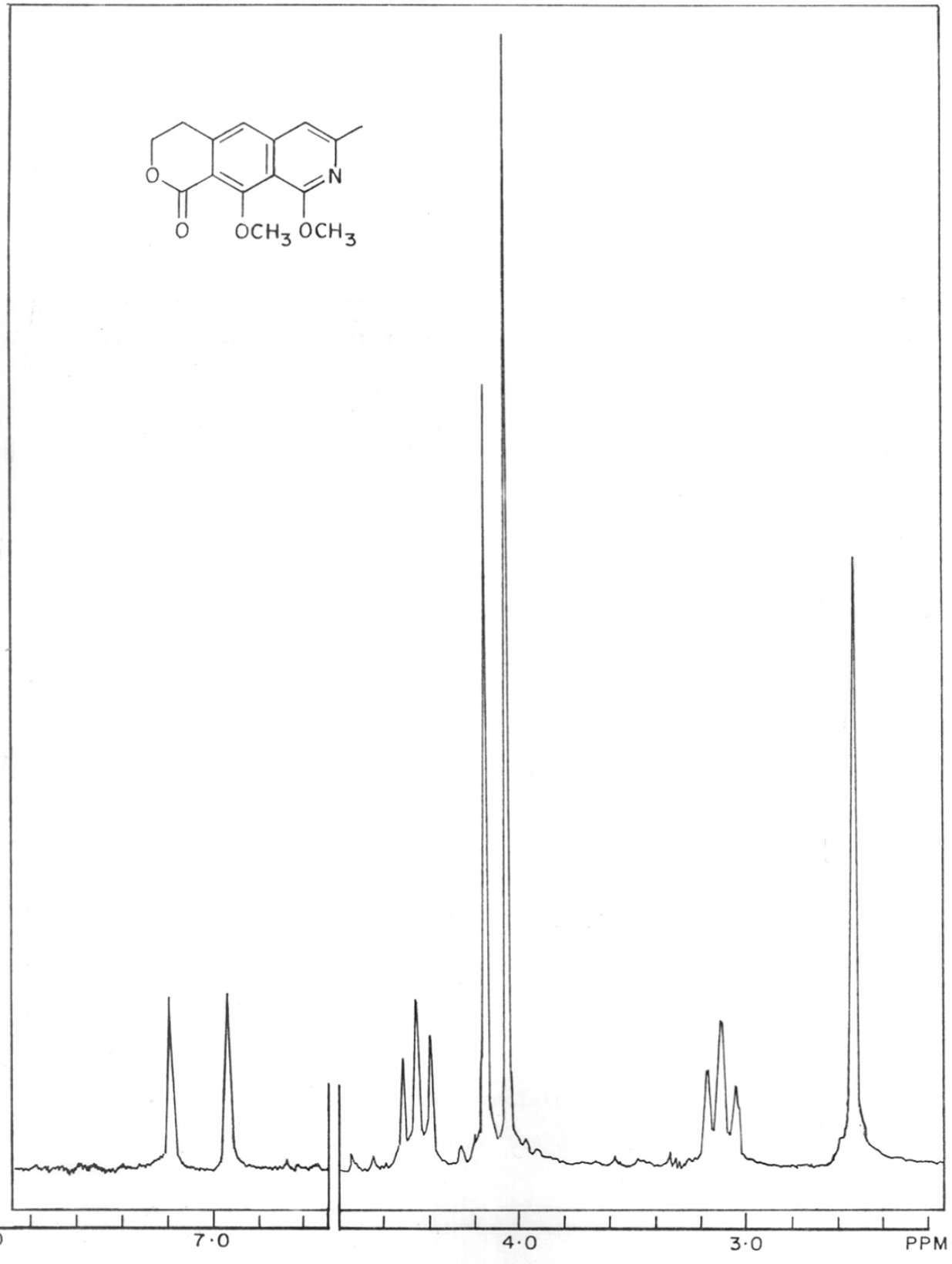


FIG. 6. ^{1}H-NMR SPECTRUM OF COMPOUND (54) IN $CDCl_3$

The chloroderivative 52 was then treated with sodium methoxide in methanol to give a product 53, whose ^{1}H-NMR spectrum revealed two methoxy signals at 4.05 and 4.15 ppm which indicated that the displacement of chloride with methoxyl had occurred. The upfield shift of the two methylenes (2.95 and 3.90 ppm) as compared with the methylenes of the parent compound 52 suggested that the δ-lactone ring had opened to give the hydroxy acid 53.

In order to convert the hydroxy acid 53 into δ-lactone, the compound 53 was treated with conc. hydrochloric acid. TLC indicated two products, which were separated by column chromatography. The major product isolated (60%) was the required product 54, in whose ^{1}H-NMR spectrum (Fig.6), the methylene signals appeared at 3.10 and 4.45 ppm. In addition, two singlets due to two methoxyl groups at 4.00 and 4.10 ppm were also seen, thus indicating the introduction of another methoxyl group.

The minor product 51 was confirmed by comparison of its spectral data with the sample obtained earlier. This compound 51 was the result of the hydrolysis of the methoxy group at C-1 in 53.

The quantity of 54 obtained is not sufficient for its conversion to the intermediate 8. The preparation of substantial amount of 54 and its conversion to 8 is in progress.

EXPERIMENTAL

3-Chloropropionyl chloride (14)

Dry hydrogenchloride gas was passed to a solution of freshly distilled acrylic acid (36 g, 0.5 mol) in ether (250 ml) till the required amount of gas (18.3 g) was absorbed. Then ether was evaporated to give 3-chloropropionic acid.

Thionyl chloride (43.8 ml) was added to the above halo acid during 30 min. at 45° while stirring. Then it was refluxed for 1.5 hr and the excess of thionylchloride was distilled off. The remaining residue was distilled to afford 14 (38.1 g) in an overall yield of 60% b.p. 142-144°.

7-Hydroxy-5-methyl indan-1-one (13)

A mixture of 3-chloropropionyl chloride (34.9 g, 0.275 mol) m-cresol (27 g, 0.25 mol) and a drop of conc. H_2SO_4 in dry benzene (100 ml) was stirred at 20° until the evolution of HCl ceased. The mixture was heated slowly and then finally refluxed for 1 hr. The reaction mixture was cooled and the unreacted m-cresol was extracted several times with 5% aqueous NaOH. The organic layer was dried and evaporated to give the ester 15 (34.7 g) in 70% yield.

Ester 15 (34.7 g, 0.174 mol) and aluminium chloride (115 g, 0.87 mol) were mixed with an efficient stirring. The mixture was heated at 90-100° for 1 hr. Then the temperature was raised gradually to 160° over a period of 2 hr and maintained

at this temperature for one additional hr. It was then finally heated at 180° for 1 hr. The cooled reaction mixture was decomposed by the addition of a mixture of ice and conc.HCl (50 ml). It was extracted with ethylacetate, the extracts were washed with water, brine and dried. Evaporation of the solvent and chromatographic purification (silica gel) of the resulting residue afforded the indanone 13 (14.17 g) in 50% yield as a solid. ^{1}H-NMR (CCl_4): δ 2.3 (s, 3H, $-CH_3$), 2.7 (t, 2H, $-CH_2$), 3.0 (t, 2H, $-CH_2$), 6.4 (s, 1H, Ar-H), 6.6 (s, 1H, Ar-H), 8.9 (s, 1H,-OH).

5-Methyl-7-methoxyindan-1-one (16)

Indanone 13 (6.48 g, 40 m.mol) was refluxed with dimethyl sulfate (6.5 g, 52 m.mol) and anhyd. potassium carbonate (11g, 80 m.mol) in acetone (80 ml) for 4 hr. Then acetone was distilled off and ice cold water was added to the residue. It was extracted with ether, ethereal extracts were washed with water, brine, dried and evaporated to give 16 (6.68 g) in 95% yield.

1-Hydroxy-5-methyl-7-methoxy indane (17)

A solution of sodiumborohydride (0.76 g, 20 m.mol) in methanol (10 ml) was added to a stirred solution of indanone 16 (3.52 g, 20 m.mol) in methanol (20 ml) at 0° during 10 min. The reaction mixture was then stirred at room temperature for 2 hr and methanol was removed under reduced pressure. Water was added to the residue and extracted with ethylacetate. Dried

ethylacetate layer was evaporated to afford the alcohol 17 (2.67 g) in 75% yield. ^{1}H-NMR (CCl_4): δ 1.95 - 2.15 (m, 2H, $-CH_2$), 2.25 (s, 3H, $-CH_3$), 2.8 (t, 2H, $-CH_2$), 3.8 (s, 3H, $-OCH_3$), 5.25 (dist.t, 1H, -CHOH), 6.3 (s, 1H, Ar-H), 6.5 (s, 1H, Ar-H).

Dehydration of hydroxy indane 17

Conc. hydrochloric acid (3 drops) was added to a stirred solution of hydroxy indane 17 (1.78 g, 10 m.mol) in acetone (15 ml) at room temperature and it was further stirred for 30 min. Acetone was distilled off and the residue was diluted with water. It was extracted with ether and dried. Evaporation of ether and chromatographic purification (silica gel) of the resulting residue furnished a mixture of 18a and 18b (1.92 g) in 80% yield. ^{1}H-NMR of isomeric mixture (CCl_4): δ 2.18 and 2.25 (s, 3H, Ar-CH_3), 2.50 - 3.20 (m, 2H, $-CH_2$), 3.70 (br.s, 3H, $-OCH_3$), 5.85 - 6.90 (m, 4H, 2X Ar-H and olefinic).

Diethyl-3-chloroglutaconate (27)

Diethyl-3-oxoglutarate (50.5 g, 0.25 mol) was added dropwise with stirring over 10 min. to PCl_5 (85.0 g, 0.408 mol) and then heated to 65° for 30 min. The red solution was poured over ice (300 g) and stirred for 30 min. The mixture was extracted with ether and concentrated. The residue was boiled with 20% HCl for 3 hr and the clear solution was evaporated to give 26 as a crystalline solid (25.2 g), in 70% yield.

The above solid was mixed with absolute ethanol (58 ml, 0.99 mol), dry benzene (100 ml) and conc. sulfuric acid (7 ml).

The resulting solution was refluxed for 8 hr and then poured into water. The benzene layer was separated and the aqueous layer was extracted with ether. The combined extracts were washed with saturated $NaHCO_3$ solution, water and dried (Na_2SO_4). Evaporation of the solvent and distillation of the remaining residue afforded the ester 27 (33 g) in 85% yield. b.p. 115-117°/5 mm. (lit.[10] b.p. 135-140°/11 mm). ^{1}H-NMR (CCl_4): δ 1.3 (t, 6H, 2X $-CH_3$), 3.4 and 3.98 (s, 2H, $-CH_2$), 4.15 (q, 4H, 2X $-CH_2$), 6.05 and 6.10 (s, 1H, olefinic).

3-Carboxymethyl glutaconic acid (29)

The compound 27 (33 g, 0.149 mol) was added to a cold and stirred suspension of sodiomalonate (0.178 mol) in absolute ethanol. After the reaction subsided, it was refluxed for 1 hr. and then ethanol was removed. Water was added to the residue and extracted with ether. Dried ethereal extracts were evaporated and distillation of the resulting residue furnished the tetraethyl ester 28 (25.5 g) in 50% yield. b.p. 160-162°/1 mm (lit.[10] 220-222/12 mm). ^{1}H-NMR (CCl_4): δ 1.25 (t, 12H, 4X $-CH_3$), 3.47 (s, 2H, $-CH_2$), 3.72 (s, 1H, -CH), 3.85 - 4.40 (m, 8H, 4X $-CH_2$), 5.90 and 5.95 (s, 1H, olefinic).

A mixture of 28 (25.5 g, 0.074 mol) and 20% hydrochloric acid (30 ml) was boiled with continuous stirring at such a rate that the alcohol was removed as fast as it was formed, but without undue removal of water. When the calculated amount of ethanol was distilled out, the solution was evaporated to dryness under reduced pressure to give the triacid 29 (11.2 g) in 80%

yield. ^{1}H-NMR (TFA): δ 3.45 (s, 2H, $-CH_2$), 3.95 (s, 2H, $-CH_2$), 6.05 (s, 1H, olefinic).

3-Carboxymethylglutaconic anhydride (30)

A mixture of 29 (1.88 g, 10 m.mol) and acetic anhydride (2.85 ml, 30 m.mol) was heated at 80° for 30 min. and then the solution was evaporated to dryness to give 30 as a solid.

Treatment of 30 with diazomethane

The above solid was dissolved in anhydrous THF (10 ml), cooled to 0° and ethereal diazomethane (prepared from N-nitroso-N-methylurea) was added. It was further stirred at 0° for 30 min. The solvent was evaporated and chromatographic separation (silica gel) of the resulting residue gave a mixture of 23 (0.24 g) and 31 (1.02 g) in an overall yield of 65%. ^{1}H-NMR of 23 (CCl_4): δ 3.3 (s, 2H, $-CH_2$), 3.70 (s, 3H, $-OCH_3$), 3.95 (s, 3H, $-OCH_3$), 5.25 (br.s, 1H, olefinic), 5.65 (br.s, 1H, olefinic). ^{1}H-NMR of 31 (CCl_4): δ 2.95 (d, 2H, $-CH_2$), 3.0 (s, 2H, $-CH_2$), 3.55 (s, 3H, $-OCH_3$), 3.60 (s, 3H, $-OCH_3$), 4.95 (s, 1H, olefinic), 5.25 (t, 1H, olefinic).

Ethyl isodehydroacetate (32)

Ethylacetoacetate (65 g, 0.5 mol) was added dropwise with stirring to ice-cooled conc. H_2SO_4 (66.5 ml, 1.25 mol) over a period of 1 hr at such a rate that the temperature was maintained at 10° - 15°. The orange solution was allowed to stand at 25° for 72 hr, poured into ice and extracted with ether. The ether layer was washed with 10% Na_2CO_3 solution,

dried (Na_2SO_4) and evaporated to give an orange liquid. Distillation afforded 32 (44 g) in 45% yield. b.p. 118-122°/2 mm (lit.[11] b.p. 85-95°/0.02 mm). ^{1}H-NMR (CCl_4): δ 1.3 (t, 3H, $-CH_3$), 2.08 (s, 3H, $-CH_3$), 2.25 (s, 3H, $-CH_3$), 4.03 (q, 2H, $-OCH_2$), 5.6 (br.s, 1H, olefinic).

3-Methylglutaconic acid (33)

A mixture of 32 (19.6 g, 0.1 mol) and KOH (39.2 g, 0.7 mol) in 200 ml of water was refluxed for 2 hr. The mixture was cooled, extracted with ether, the aqueous layer was acidified with conc. hydrochloric acid and re-extracted with ether. The second organic extract was dried (Na_2SO_4) and evaporated to give 33 (12.2 g) in 85% yield as an off-white solid m.p. 115-116°. ^{1}H-NMR of E/Z isomers (acetone-d_6): δ 2.00 and 2.28 (s, 3H, $-CH_3$), 3.25 and 3.85 (s, 2H, $-CH_2$), 5.90 (br.s, 1H, olefinic), 7.82 (br.s, 2H, 2X -COOH).

5,6-Dihydro-4-methyl-2H-pyran-2,6-dione (34)

A mixture of 33 (7.2 g, 0.05 mol) and acetic anhydride (1.18 ml, 0.125 mol) was heated at 80° for 30 min. the solution was cooled and evaporated under reduced pressure. The resulting oil was distilled to give 34 (5.02 g) as a colourless crystalline solid, m.p. 85-87°; ^{1}H-NMR ($CDCl_3$): δ 2.0 (m, 3H, $-CH_3$), 3.45 (m, 2H, $-CH_2$), 6.05 (m, 1H, olefinic).

Dimethyl-3-hydroxy-5-methylphthalate (36)

A solution of 34 (0.25 g, 2 m.mol) in THF (2 ml) was added to a suspension of sodium hydride (0.12 g, 5 m.mol) in

THF (3 ml) at 0°. Dimethyl acetylene dicarboxylate (0.31 g, 2.2 m.mol) in THF (4 ml) was added to the resulting sodioanion of 34 and it was stirred at room temperature for further 8 hr. It was poured into ice, extracted with ether, acidified with acetic acid, and reextracted with ether. The second organic extract was dried (Na_2SO_4) and evaporated to give 36 (0.22 g) in 50% yield. ^{1}H-NMR (CCl_4): δ 2.5 (s, 3H, $-CH_3$), 4.1 (s, 3H, $-OCH_3$), 4.2 (s, 3H, $-OCH_3$), 7.1 (br.s, 1H, Ar-H), 7.25 (br.s, 1H, Ar-H), 11.15 (s, 1H, -OH).

2-Carbomethoxy-3-[(tetrahydro-2H-pyran-2-yl)-oxy] methyl-5-methylphenol (37)

A solution of tetrahydropyranyl ether of methyl-4-hydroxy -2-butynoate (0.435 g, 2.2 m.mol) in THF (3 ml) was added to the sodioanion of 34 (2 m.mol) in THF (6 ml) obtained as mentioned above. It was further stirred at 60° for 6 hr. Then the usual work up furnished 37 (0.275 g) in 50% yield. ^{1}H-NMR (CCl_4): δ 1.3 - 1.7 (m, 6H, 3X $-CH_2$), 2.35 (s, 3H, $-CH_3$), 3.4 - 3.8 (m, 2H, $-OCH_2$), 4.0 (s, 3H, $-OCH_3$), 4.75 (br.s, 2H, benzylic), 4.85 (br.s, 1H, -OCHO), 6.8 (br.s, 1H, Ar-H), 7.0 (br.s, 1H, Ar-H), 11.6 (s, 1H,OH).

Ethyl-3,3-ethylenedioxybutanoate (44)

A mixture of freshly distilled ethylacetoacetate (65 g, 0.5 mol), ethyleneglycol (62 g, 1 mol) and p-toluenesulfonic acid (1 g) in anhyd. benzene (250 ml) was heated under reflux for 8 hr. A Dean-Stark trap was used to remove water generated

during the reaction. When the reaction was complete the mixture was washed with 5% aqueous $NaHCO_3$ and dried over Na_2SO_4. The liquid residue after removal of solvent was distilled to give 44 (74 g) in 84.8% yield. b.p. 102°/15 mm (lit.[14] b.p. 110°/20 mm); ^{1}H-NMR (CCl_4): δ 1.30 (t, 3H, $-CH_3$), 1.46 (s, 3H, $-CH_3$), 2.58 (s, 2H, $-CH_2$), 3.95 (s, 4H, $OCH_2.CH_2O$), 4.12 (q, 2H, OCH_2).

3,3-Ethylenedioxybutanal (45)

To a rapidly mechanically stirred solution of 44 (74 g, 0.42 mol) in dry dichloromethane at -78° was added diisobutylaluminium hydride (75 g, 0.525 mol) over a period of 15 min. under N_2. After the addition of hydride was complete, the mixture was stirred for another hr at -78° and then poured into a flask (3 lit.) containing distilled water (750 ml). The mixture was stirred mechanically for 15 min. and then 4N HCl (300 ml) was added at 5 min. intervals in four equal portions. The mixture was vigorously stirred mechanically after each addition. The organic layer was separated and dried (Na_2SO_4). The liquid obtained after removal of solvent was distilled to give 45 (41.8 g) in 75% yield. b.p. 76-77°/20 mm (lit.[14] 70-72°/16 mm). ^{1}H-NMR(CCl_4): δ 1.40 (s, 3H, $-CH_3$), 2.68 (d, 2H, $-CH_2$), 4.00 (s, 4H, OCH_2-CH_2O), 9.80 (t, 1H, CHO).

4-[(Tetrahydro-2H-pyran-2-yl)-oxy]-1-butyne (46)

To a solution of lithiumacetylide [obtained by

passing acetylene to lithium amide (prepared from 3.5 g, 0.5 g.atom of lithium)] in liq. ammonia (500 ml), ethylene-oxide (24 g,0.54 mol) was added in five equal portions at 1 hr intervals at -33°. The reaction mixture was stirred at -33° for further 12 hr and then ammonia was allowed to evaporate. The residue was treated with saturated NH_4Cl solution, extracted with ether and ethereal extracts were dried (Na_2SO_4). The liquid obtained after the removal of solvent was distilled to give but-3-yn-1-ol (24.5 g) in 70% yield. b.p. 56-58°/30 mm (lit. b.p. 34°/10 mm).

A mixture of but-3-yn-1-ol (21 g, 0.3 mol), dihydro-pyran (33.6 g, 0.4 mol) and p-toluene sulfonic acid (0.15 g) was stirred in dry dichloromethane (200 ml) at room temperature for 6 hr. Usual work up and distillation of the crude product gave 46 in 90% yield b.p. 60-63°/2 mm. ^{1}H-NMR (CCl_4): δ 1.5 (m, 6H, 3X $-CH_2$), 1.8 (t, 1H, $-C\equiv CH$), 2.10-2.49 (m, 2H, $-CH_2$), 3.1-3.6 (m, 4H, 2X OCH_2), 4.39 (s, 1H, OCHO).

1-[(Tetrahydro-2H-pyran-2-yl)-oxy]-7,7-ethylenedioxy-oct-3-yn-5-ol (47)

To a solution of ethyl magnesium bromide [prepared from ethylbromide (21.9 g, 0.201 mol) and magnesium (4.8 g, 0.2 mol)] in THF (60 ml) was added 46 (30.8 g, 0.2 mol) in THF (50 ml) over a period of 20 min. The reaction mixture was heated under reflux for 5 hr, then cooled to 0° and was added aldehyde 45 (26 g, 0.2 mol) in THF (40 ml) during 20 min.

The reaction mixture was further stirred at room temp. for overnight. Aqueous NH_4Cl solution (26 g) was added, the aq. layer was extracted with ethylacetate and the combined organic extracts were dried (Na_2SO_4). The residue, after removal of the solvent was passed through a short silica gel column to afford pure 47 (53.9 g) in 95% yield. IR (neat): 3440 cm^{-1}(-OH). ^{1}H-NMR(CCl_4): δ 1.33 (s, 3H, CH_3), 1.40 - 1.75 (m, 6H, 3X $-CH_2$), 1.98 (d, 2H, $-CH_2$), 2.48 (dt, 2H, $C\equiv C-CH_2$), 2.90 (d, 1H, -OH), 3.25 - 3.90 (m, 4H, 2X OCH_2), 3.95 (s, 4H, OCH_2-CH_2O), 4.25 - 4.55 (m, 1H, -CHOH), 4.60 (br.s, 1H, OCHO).

Analysis: Calculated for $C_{15}H_{24}O_5$: C, 63.38; H, 8.45; Found: C, 63.27; H, 8.43%.

1-[(Tetrahydro-2H-pyran-2-yl)-oxy]-7,7-ethylenedioxy oct-3-yn-5-one (41)

To a stirred suspension of pyridinium dichromate (150 g, 0.4 mol) in chloroform (300 ml) was added a solution of alcohol 47 (28.4 g, 0.1 mol) in chloroform (50 ml) at room temperature. After stirring for 48 hr, it was filtered through celite. Evaporation of the solvent and chromatographic purification (silica gel) of the residue gave pure 41 (22.5 g) in 80% yield. IR (neat): 1660, 1730 (C=O), 2200 cm^{-1} ($-C\equiv C-$). ^{1}H-NMR (CCl_4): δ1.40 (s, 3H, $-CH_3$), 1.5 - 1.8 (m, 6H, 3X $-CH_2$), 1.6 (t, 2H, $-C\equiv C-CH_2$), 2.8 (s, 2H, $CO-CH_2$), 3.2 - 3.9 (m, 4H, 2X OCH_2), 3.95 (s, 4H, $OCH_2.CH_2O-$), 4.6 (br.s, 1H, OCHO).

Dimethylacetone-1,3-dicarboxylate (42)

Citric acid (52.5 g, 0.27 mol) was added to a stirred sulfuric acid (150 ml) portionwise during 1 hr at room temperature. After the addition, the reaction mixture was heated at 60° for 4 hr. Then absolute methanol (188.5 ml) was added dropwise while maintaining the temperature at 30°. The reaction mixture was further stirred at 30° for 2 hr. Then a mixture of chloroform (82 ml) and ice pieces (200 g) was added and stirred. The organic layer was separated, the aqueous layer extracted with $CHCl_3$ and the combined organic extracts were dried (Na_2SO_4). The liquid obtained after the removal of solvent was distilled to give 42 (38.5 g) in 82% yield. b.p. 110-112°/5 mm.

Lactone of 3-methyl-6-(2-hydroxyethyl)-7-carboxy-8-hydroxy isocoumarin (48)

To a mixture of 41 (2.82 g, 10 m.mol) and 42 (1.74 g, 10 m.mol) in methanol (25 ml) was added 2N sodium hydroxide (30 ml) dropwise and the reaction mixture was stirred at room temperature for 36 hr. Methanol was then removed under reduced pressure, conc.HCl (15 ml) was added to the residue and stirred for 1 hr. It was extracted with chloroform, the organic extracts were dried (Na_2SO_4) and evaporated. Chromatographic purification (silica gel, chloroform) gave 48 (0.54 g) in 22% yield. ^{1}H-NMR ($CDCl_3$): δ 2.3 (s, 3H, $-CH_3$), 3.1 (t, 2H, $-CH_2$), 4.60 (t, 2H, $-CH_2O$), 6.20 (s, 1H, olefinic), 6.70 (s, 1H, Ar-H), 12.85 (s, 1H, -OH). Mass: M^+ 246.

6-(2-oxopropyl)-7-carbomethoxy-8-hydroxy-3,4-dihydro-isocoumarin (43)

To a mixture of 41 (5.64 g, 0.02 mol) and 42 (3.48 g, 0.02 mol) in methanol (40 ml) was added 2N sodium hydroxide (55 ml) dropwise and the reaction mixture was stirred at room temperature for 36 hr. Methanol was evaporated, the residue was treated with dil. HCl and extracted with $CHCl_3$. The chloroform extracts were dried (Na_2SO_4) and evaporated. Chromatographic purification (silica gel) of the resulting residue gave 43 (1.39 g) in 25% yield. ^{1}H-NMR ($CDCl_3$): δ 2.10 (s, 3H, $-COCH_3$), 3.0 (t, 2H, $-CH_2$), 3.80 (s, 2H, $-CH_2CO$), 3.90 (s, 3H, $-OCH_3$), 4.6 (t, 2H, $-OCH_2$), 6.6 (s, 1H, Ar-H), 11.6 (s, 1H, -OH).

Treatment of 43 with dimethylsulfate and potassium carbonate

A mixture of 43 (0.83 g, 3 m.mol), dimethylsulfate (0.75 g, 6 m.mol) and potassium carbonate (1.24 g, 9 m.mol) in acetone (20 ml) was heated under reflux for 5 hr. Acetone was removed and cold water was added. The aqueous layer was extracted with chloroform and the combined organic layer was dried (Na_2SO_4). Removal of solvent and chromatographic separation (silica gel) of the resulting residue furnished two products, the corresponding methyl ether 49 (0.22 g) in 25% yield and 6-(1-methyl-2-oxopropyl)-7-carbomethoxy-8-methoxy-3,4-dihydroisocoumarin (50, 0.55 g) in 60% yield. ^{1}H-NMR of 49 ($CDCl_3$): δ 2.22 (s, 3H, $-COCH_3$), 3.00 (t, 2H,

$-CH_2$),3.75 (s, 2H, $-CH_2CO-$), 3.90 (s, 3H, $-OCH_3$), 3.95 (s, 3H, $-OCH_3$), 4.47 (t, 2H, $-OCH_2$), 6.88 (s, 1H, Ar-H). ^{1}H-NMR of 50 ($CDCl_3$): δ 1.30 (d, 3H, $-CH-CH_3$), 2.05 (s, 3H, $-COCH_3$), 2.96 (t, 2H, $-CH_2$), 3.70 (q, 1H, -CH), 3.88 (s, 6H, 2X $-OCH_3$), 4.42 (t, 2H, $-OCH_2$), 6.8 (s, 1H, Ar-H).

6-(2-Oxopropyl)-7-carbomethoxy-8-methoxy-3,4-dihydroisocoumarin (49)

A solution of diazomethane, prepared from N-nitroso-N-methyl urea (1.5 g, 15 m.mol) in ether (20 ml) was added to an ice-cooled solution of 43 (0.83 g, 3 m.mol) in ether (20 ml). The mixture was stirred for 30 min. and evaporated under reduced pressure. Chromatographic purification (silica gel) of the resulting residue afforded 49 (0.83 g) in 95% yield.

Lactone of 3-methyl-6-(2-hydroxyethyl)-7-carboxy-8-methoxy-1-(2H)-isoquinolone (51)

A solution of ammonia in methanol (8 ml) was added to 49 (0.58 g, 2 m.mol) at 1 hr intervals in four equal portions and the reaction mixture was stirred overnight. Methanol was evaporated and the residue was crystallised from methanol to give 51 (0.41 g) in 80% yield. ^{1}H-NMR ($CDCl_3$): δ 2.45 (s, 3H, $-CH_3$), 3.05 (t, 2H, $-CH_2$), 4.1 (s, 3H, $-OCH_3$), 4.5 (t, 2H, $-OCH_2$), 6.2 (s, 1H, olefinic) 7.0 (s, 1H, Ar-H).

Lactone of 1-chloro-3-methyl-6-(2-hydroxyethyl)-7-carboxy-8-methoxyisoquinoline (52)

A mixture of 51 (0.41 g, 1.58 m.mol) and $POCl_3$ (4 ml) was refluxed for 2 hr, the reaction mixture poured on crushed

ice, allowed to stand overnight and made alkaline with solid $NaHCO_3$. It was extracted with chloroform, the combined organic layer was dried (Na_2SO_4) and evaporated. The residue was chromatographed to give pure 52 (0.285 g) in 65% yield. IR (Nujol): 1720 cm^{-1} (-C=O); ^{1}H-NMR ($CDCl_3$): δ 2.6 (s, 3H, $-CH_3$), 3.1 (t, 2H, $-CH_2$), 4.0 (s, 3H, $-OCH_3$), 4.5 (t, 2H, $-OCH_2$), 7.25 (s, 2H, Ar-H). Mass: M^+ 277.

Analysis: Calculated for $C_{14}H_{12}ClNO_3$: C, 60.54; H, 4.32; N, 5.04. Found: C, 60.81; H, 4.31; N, 5.12%.

1-Methoxy-3-methyl-6-(2-hydroxyethyl)-7-carboxy-8-methoxy-isoquinoline (53)

To a solution of sodium methoxide (prepared from 46 m.gm, 2 m.mol of sodium) in methanol (4 ml) was added 52 (0.27 g, 1 m.mol) and refluxed for 6 hr. Methanol was removed and the residue was treated with dil.HCl. It was extracted with ethylacetate, the combined organic layer was dried and evaporated to give 53 (0.25 g) in 85% yield. ^{1}H-NMR (acetone-d_6): δ 2.48 (s, 3H, $-CH_3$), 2.95 (t, 2H, $-CH_2$), 3.2 (br.s, 2H, -OH, and -COOH), 3.90 (t, 2H, $-OCH_2$), 3.92 (s, 3H, $-OCH_3$), 4.05 (s, 3H, $-OCH_3$), 7.08 (s, 1H, Ar-H), 7.45 (s, 1H, Ar-H).

Treatment of 53 with conc. HCl

Conc. hydrochloric acid (0.5 ml) was added to a solution of 53 (0.11 g, 0.37 m.mol) in methanol (5 ml) and stirred for 12 hr. Methanol was evaporated, the residue was diluted with water and extracted with chloroform. The combined organic

layer was dried (Na_2SO_4) and evaporated. The resulting residue, on chromatographic separation (silica gel) afforded two products, 51 (25 mg) in 25% yield and the lactone of 1-methoxy-3-methyl-6-(2-hydroxyethyl)-7-carboxy-8-methoxy-isoquinoline (54, 60 mg) in 60% yield. ^{1}H-NMR ($CDCl_3$): δ 2.55 (s, 3H, $-CH_3$), 3.10 (t, 2H, $-CH_2$), 4.00 (s, 3H, $-OCH_3$), 4.10 (s, 3H, $-OCH_3$), 4.45 (t, 2H, $-OCH_2$), 6.95 (s, 1H, Ar-H), 7.15 (s, 1H, Ar-H).

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