MACROLIDES

A THESIS

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DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

BY

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Dedicated to My Parents

Certified that the work incorporated in the thesis "MACROLIDES" submitted by Mr. G. V. Madhava Sharma was carried out by the candidate under my supervision. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

(A. V. Rama Rao)
Supervisor

CONTENTS

CHAPTER-I

SYNTHESIS OF (±) ZEARALENONE

Synthesis of natural products of biological importance has always fascinated organic chemists. Due to their continuous efforts of last three decades, tremendous amount of developments in the synthesis of complex natural products such as steroids, terpenoids, alkaloids etc have been possible. After the initial discovery of macrocyclic compounds such as civetone and muscone by Ruzicka[1] in 1926, Kerschbaum[2] demonstrated for the first time the presence of lafge ring lactones in exaltolide and ambrettolide. Interest in the large ring lactonic compounds aroused in 1950, when Brockmann and Henkel[3] isolated picromycin, from an Actynomyces culture. Later, this class of natural products termed as "Macrolides" by Woodward[4] in 1957, has attracted worldwide attention owing to its immense physiological and pharmaceutical importance. Thus, a macrolide is defined[5] as a molecule having large ring lactone in its structure. In principle they are considered to be derived from the corresponding hydroxy acids by intramolecular esterification.

Although in the field of antiobiotics several total syntheses of pencillins and cephalosporins and tetracyclines have already been achieved and still being continued because of their medicinal interest, the synthesis of macrolide class of antibiotics, presented an academic challenge to synthetic organic chemists and in past it was largely discarded because of lack of understanding of the complex nature and lack of availability of general methodology. However in recent years due to the profound knowledge of synthetic methods and reagents in this area, numerous elegant syntheses of complex macrolides have appeared. The biological and physiological activities of macrolides are currently under intensive investigation and some of the most important therapeutic agents belong to this class.

Macrolides can be broadly classified[6] as follows:

a) polyoxo macrolides,

b) polyene macrolides,

c) ionophoric macrolides,

d) ansamycins and

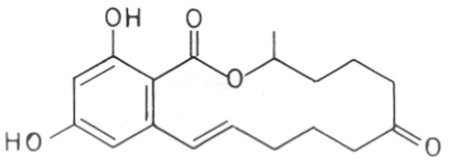
e) other macrolides.

Several lactonic compounds of medium ring size belong to the last group and most of which are isolated either from mould or bacteria e.g. zearalenone, pyrenophorin, curvularin, vermeculin etc.

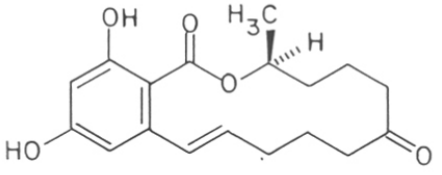
Zearalenone and radicicol are two examples of β-resorcylic acid type of macrolides, which is a rare class of natural products. This present study mainly concerns with the synthesis of zearalenone (1).

Zearalenone (1), a mould metabolite with its striking physiological activity has been isolated from the fungus Gibberela zeae[7] from an infect corn. Urry et al.[8] assigned the structure of zearalenone (1) and (S)-configuration at the C-10' position was established by Kuo et al.[9] .

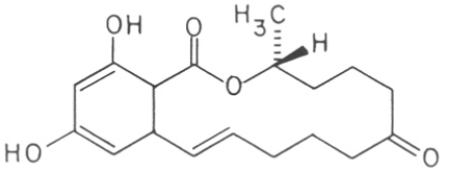
Zearalenone and its derivatives find a number of uses in medicine. It is used as a growth stimulant[10] for animals (stears, sheep and pigs) and oral administration is more effective than any other routes. Mirocha et al.[11] demonstrated that zearalenone produced by the fungus under natural conditions caused marked uterotrophic response in rats, mice and ginuea pigs. This metabolite is associated with hyperestrogenism. In studying the biological activity of zearalenone and its derivatives, it became desirable to determine the effect of absolute configuration on uterotrophic activity. Since the configuration[9] at C-10' in naturally occurring zearalenone has been determined as 'S', Peter and Hurd[12] developed a synthetic sequence to invert the centre to (R)-configuration. The mouse uterotrophic activity data showed that (R)-zearalenone (3) has



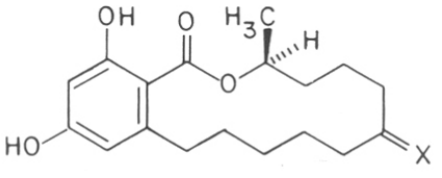
(1) (±)-ZEARALENONE



(2) (S)-ZEARALENONE



(3) (R)-ZEARALENONE



(4) X = O, ZEARALANONE

(5) X = H_2, ZEARALANE

(6) X = H, OH, ZEARALANOL

no activity, but 1:1 mixture of (R) and (S) isomers gave approximately the same response as (S)-zearalenone (2). These results were in agreement with the findings of Hurd and Shah[13] who have demonstrated synthetic (R,S)-zearalenone had about the same activity as (S)-zearalenone (2). This suggests that (R)-zearalenone (3) has a synergistic effect on the uterotrophic activity of (S)-zearalenone. Inflammation in living animals other than human beings is treated[14] by administering an effective dose of (S)-zearalenone (2), zearalanone (4), zearalane (5) and zearalanol (6) (with or without protection of hydroxyl groups). Pregnancy in females is prevented by administering 2, 4 and 6, the last have shown good contraceptive results in humans[15]. 2 and 5 were clinically administered for human cholesterolemia[16] without any undesirable side effects.

Earlier Methods of Synthesis of (±)-Zearalenone

Zearalenone (1) was perhaps the first naturally occurring macrolide to be synthesised. Potent steroid like anabolic and uterotrophic activity of this compound has prompted many groups to develop synthetic routes. For simplicity various synthetic routes have been categorised broadly into two classes: (a) the Wittig approach and (b) the intramolecular alkylation approach.

The Wittig Approach

The synthesis reported by Merck[17,18] and Syntex[19-21] groups involved the construction of aromatic and aliphatic portions independently followed by coupling via a Wittig reaction. The Merck group employed trifluoroacetic anhydride (Scheme-1 and 2) for further cyclisation of the resulting ω-hydroxy acid whereas in Syntex group synthesis cyclisation was effected with sodium t-amyloxide (Scheme-3 and 4). Yields were quite low in both the cases. Peter and Hurd[12] used the former reagent (TFAA) for the synthesis of (R)-zearalenone (3) from (S)-zearalenone (2) obtained by inversion. Another strategy adopted by Syntex group (Scheme-5) made use of the cyclisation of α,ω-diesters with sodium in xylene[21]. However the yield was quite poor.

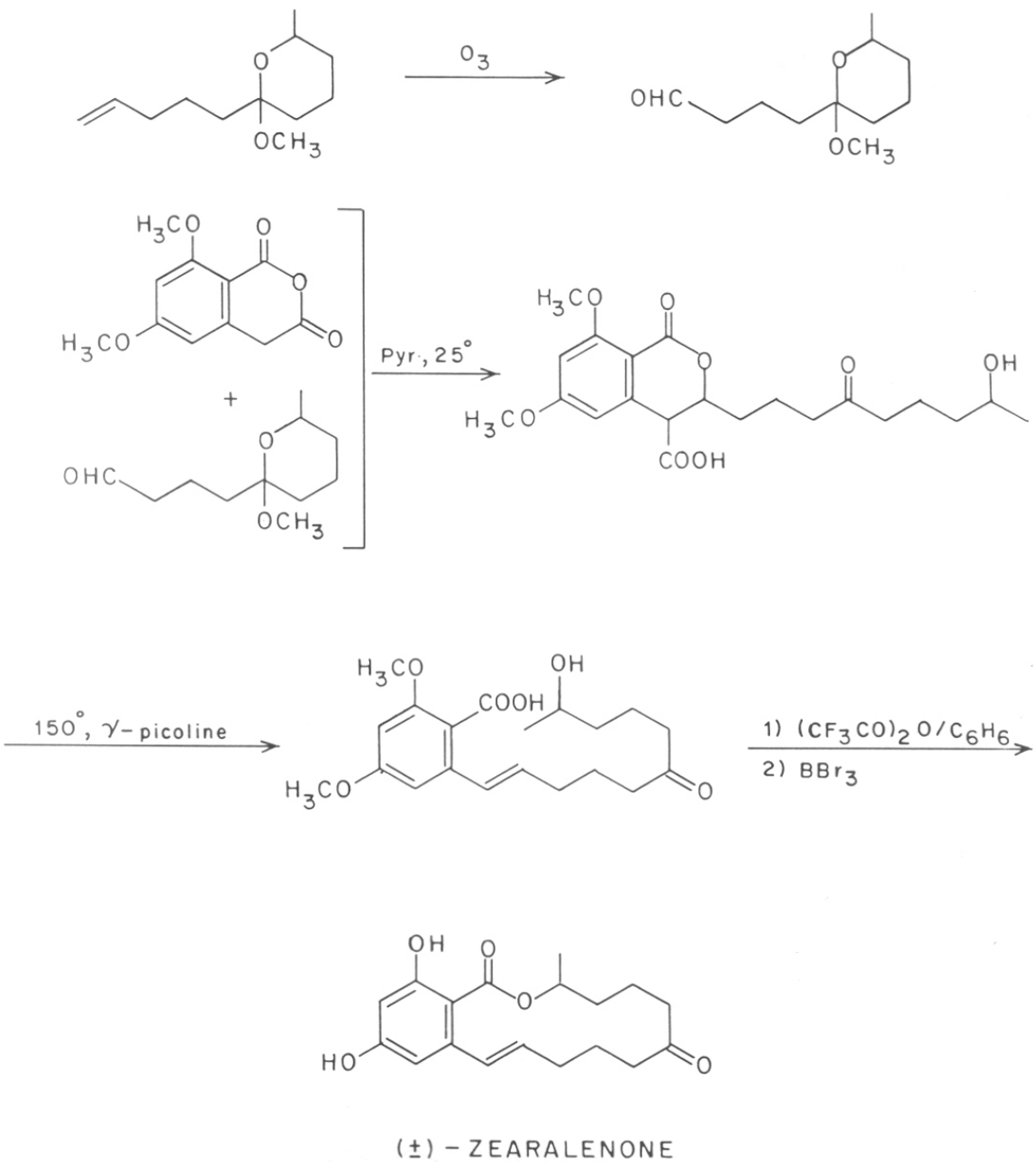
The main disadvantages the Wittig approach suffers from are (a) several steps involved in the preparation of aromatic aldehyde (b) poor selectivity observed during the Wittig reaction and (c) the final cyclisation afforded the lactone in low yield.

The Intramolecular Alkylation Approach

In order to circumvent the aforementioned disadvantages, Tsuji and his coworkers[22] developed a new approach (Scheme-6) where the aliphatic and aromatic portions

Scheme - 1

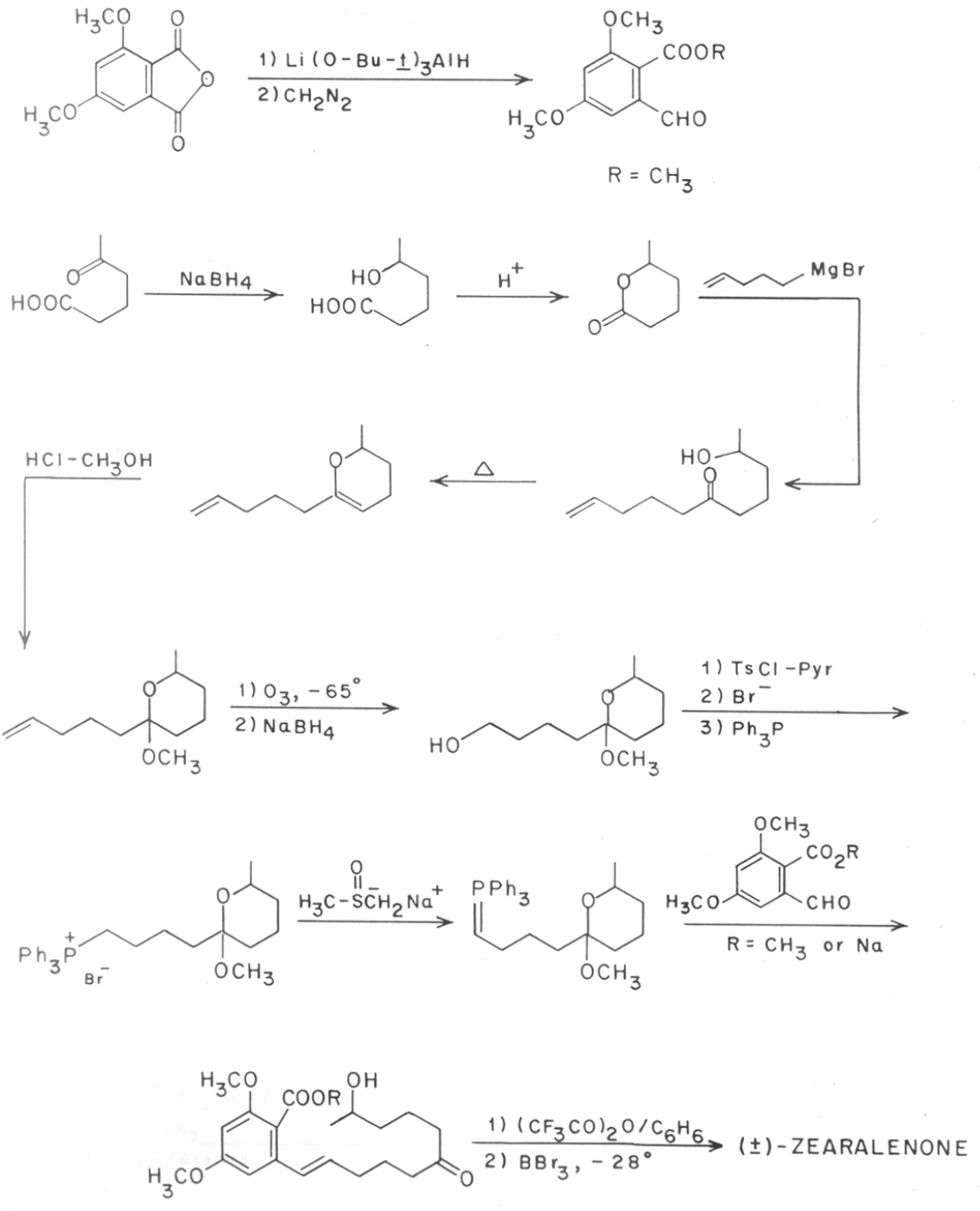
Merck (1967)



(±) - ZEARALENONE

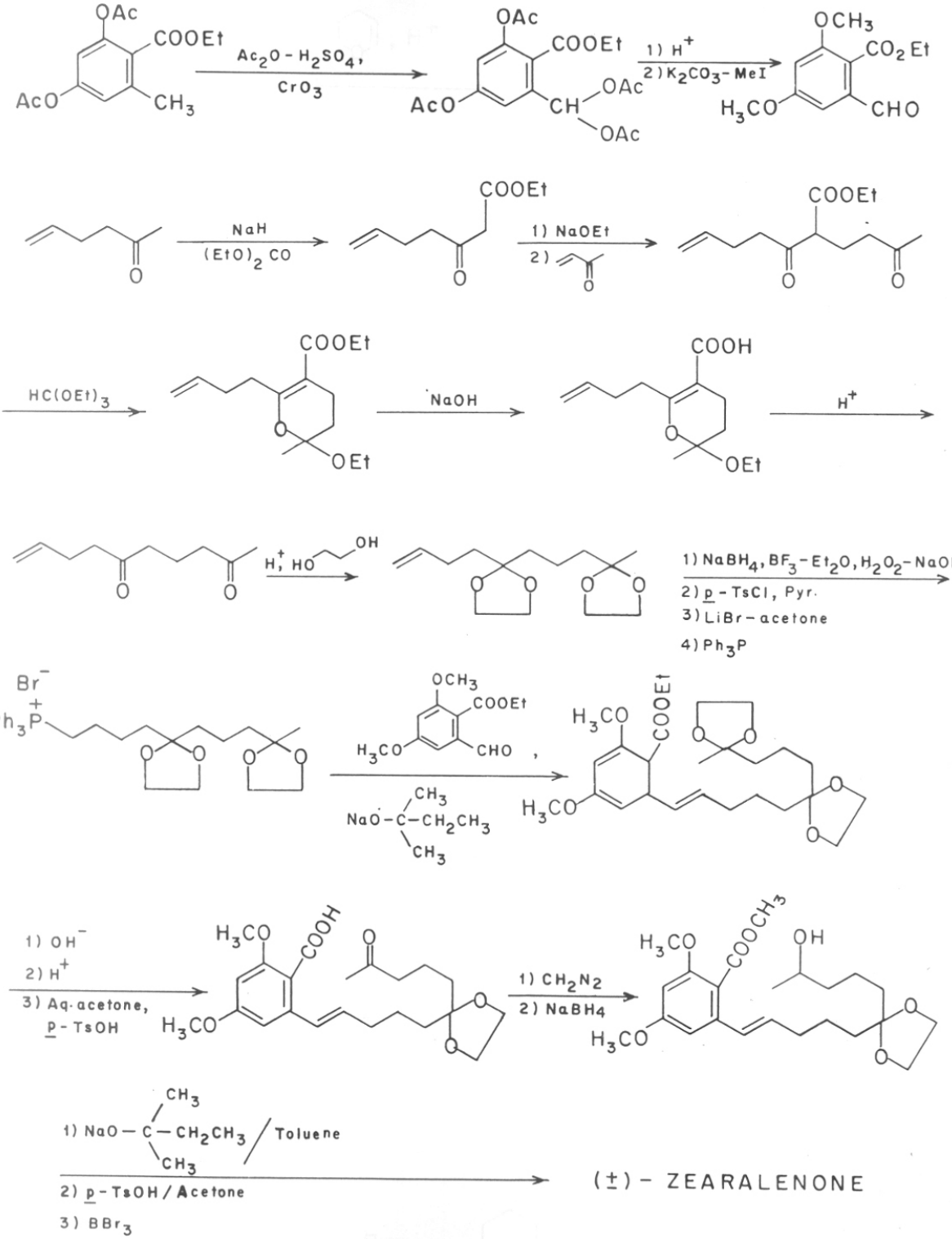
Scheme-2

Merck (1968)



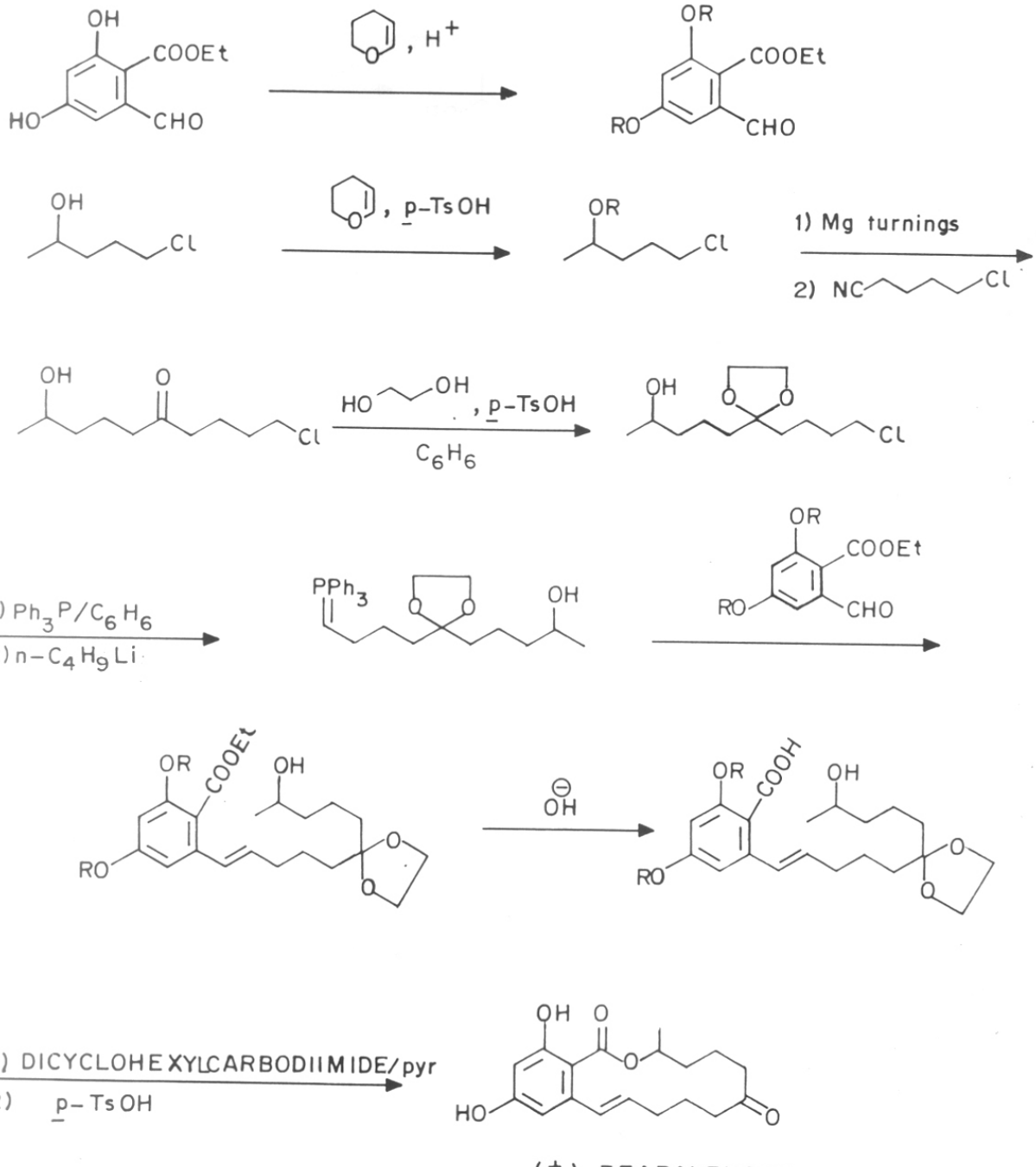
Scheme - 3

Syntex (1968)

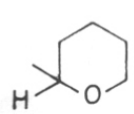


SCHEME- 4

Syntex (1970)

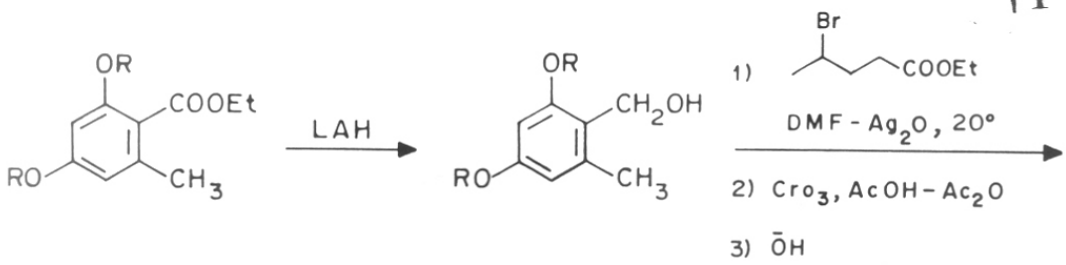


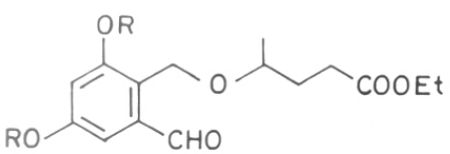
(±)-ZEARALENONE

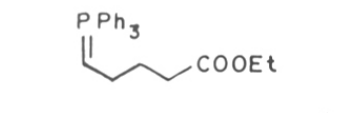
R = 

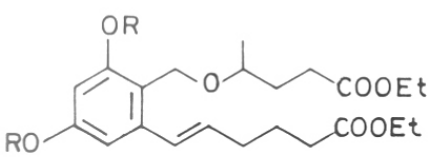
SCHEME – 5

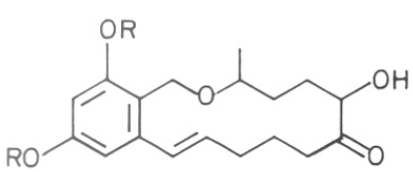
Syntex (1971)

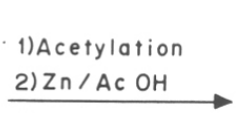


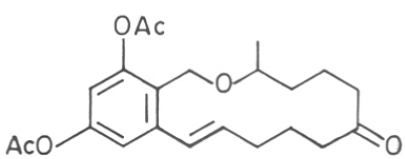


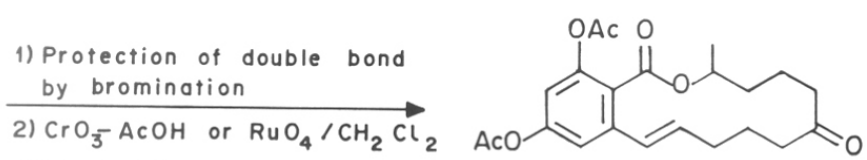


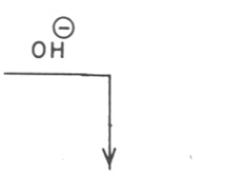


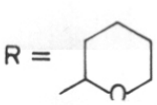






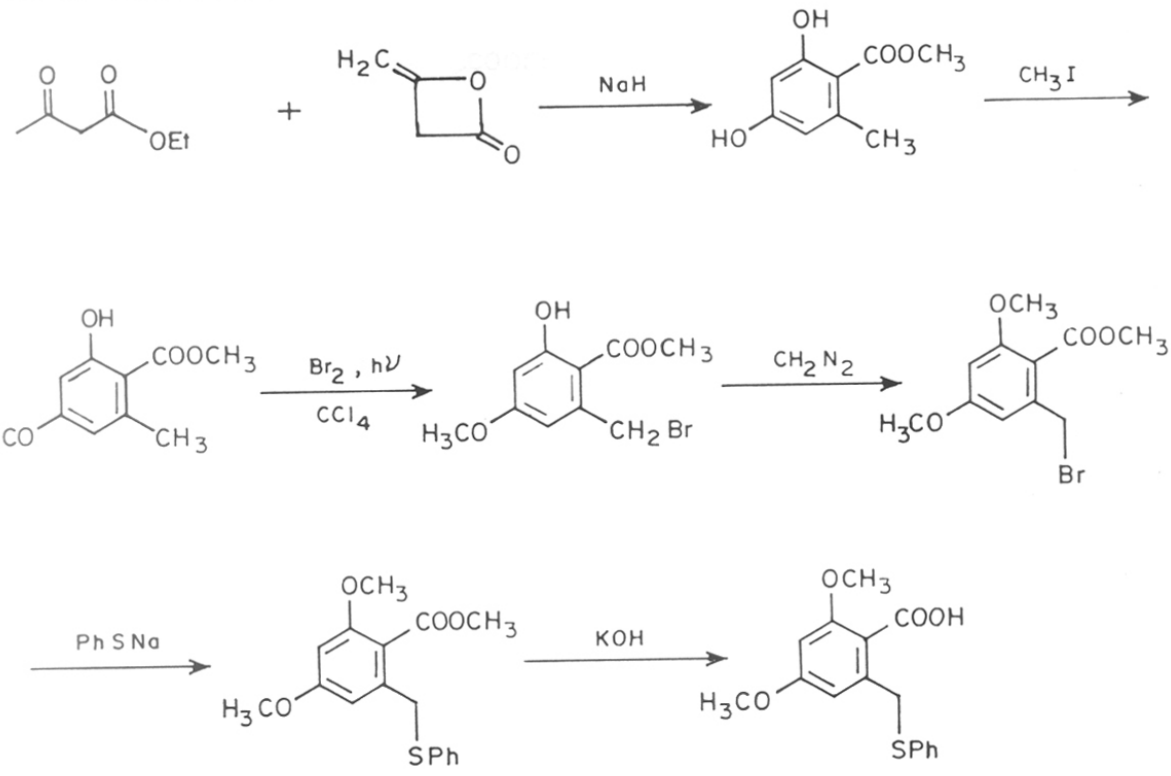




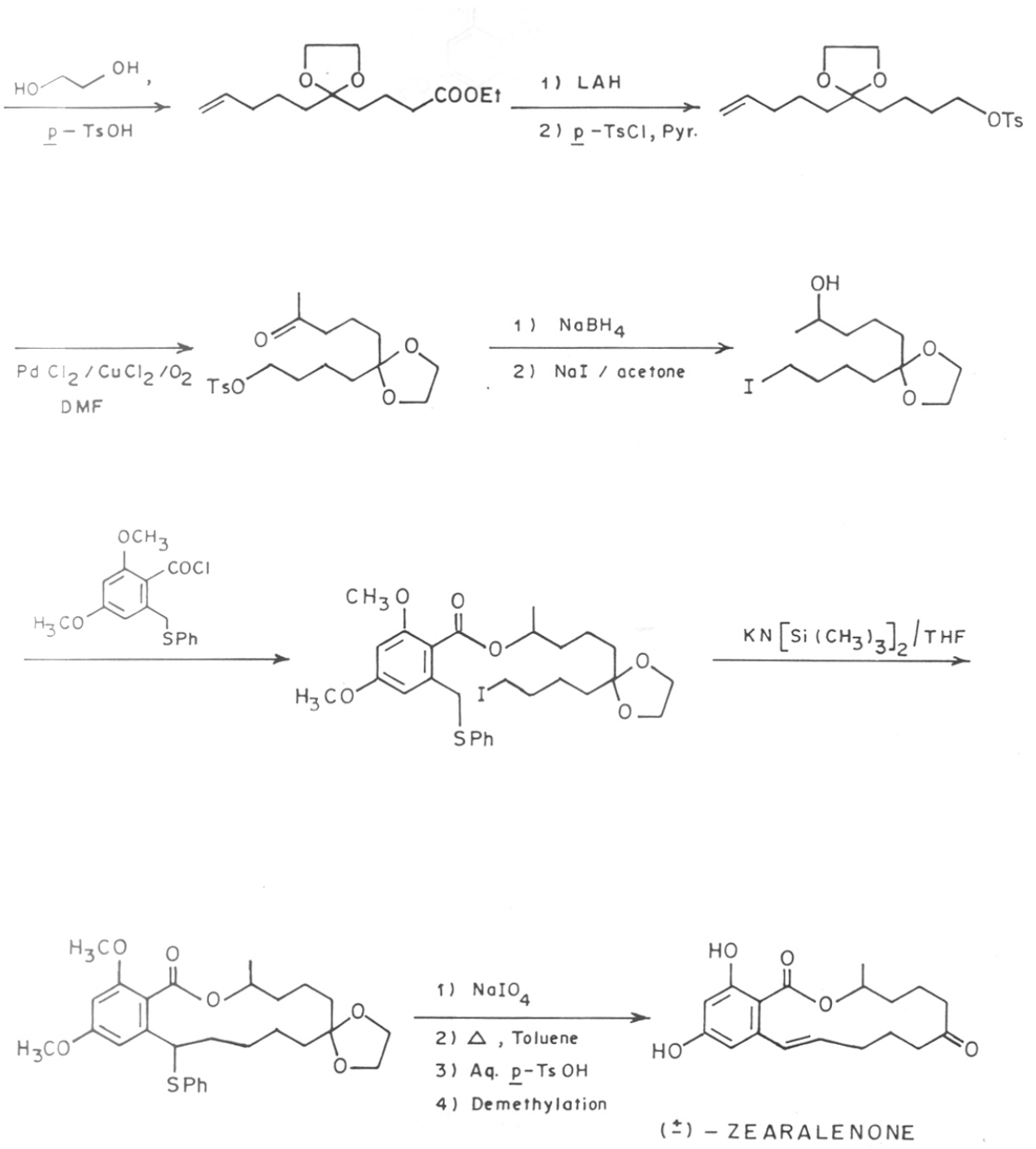


SCHEME – 6.

Tsuji et al (1979)



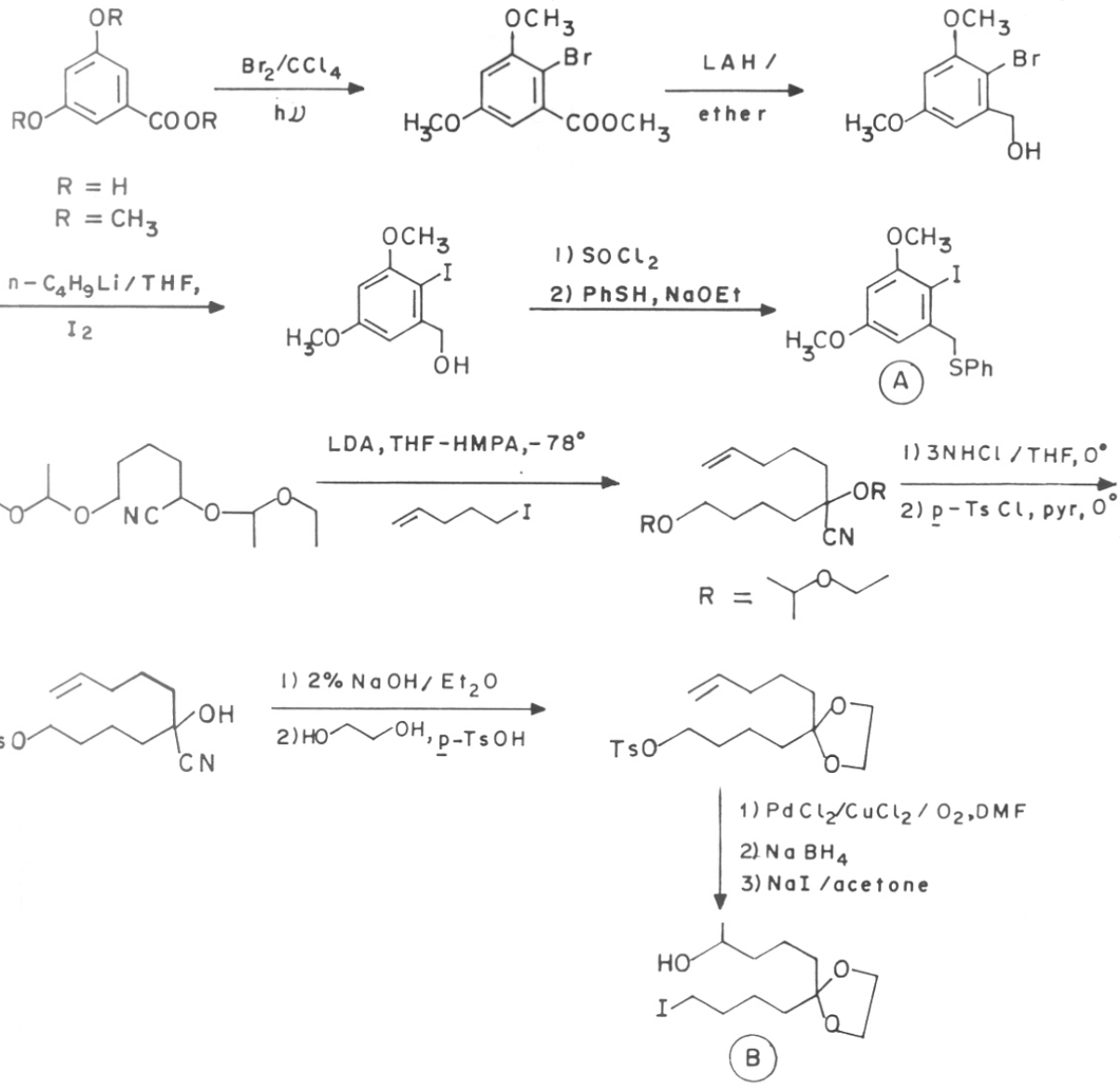
SCHEME – 6. (Contd)



(±) – ZEARALENONE

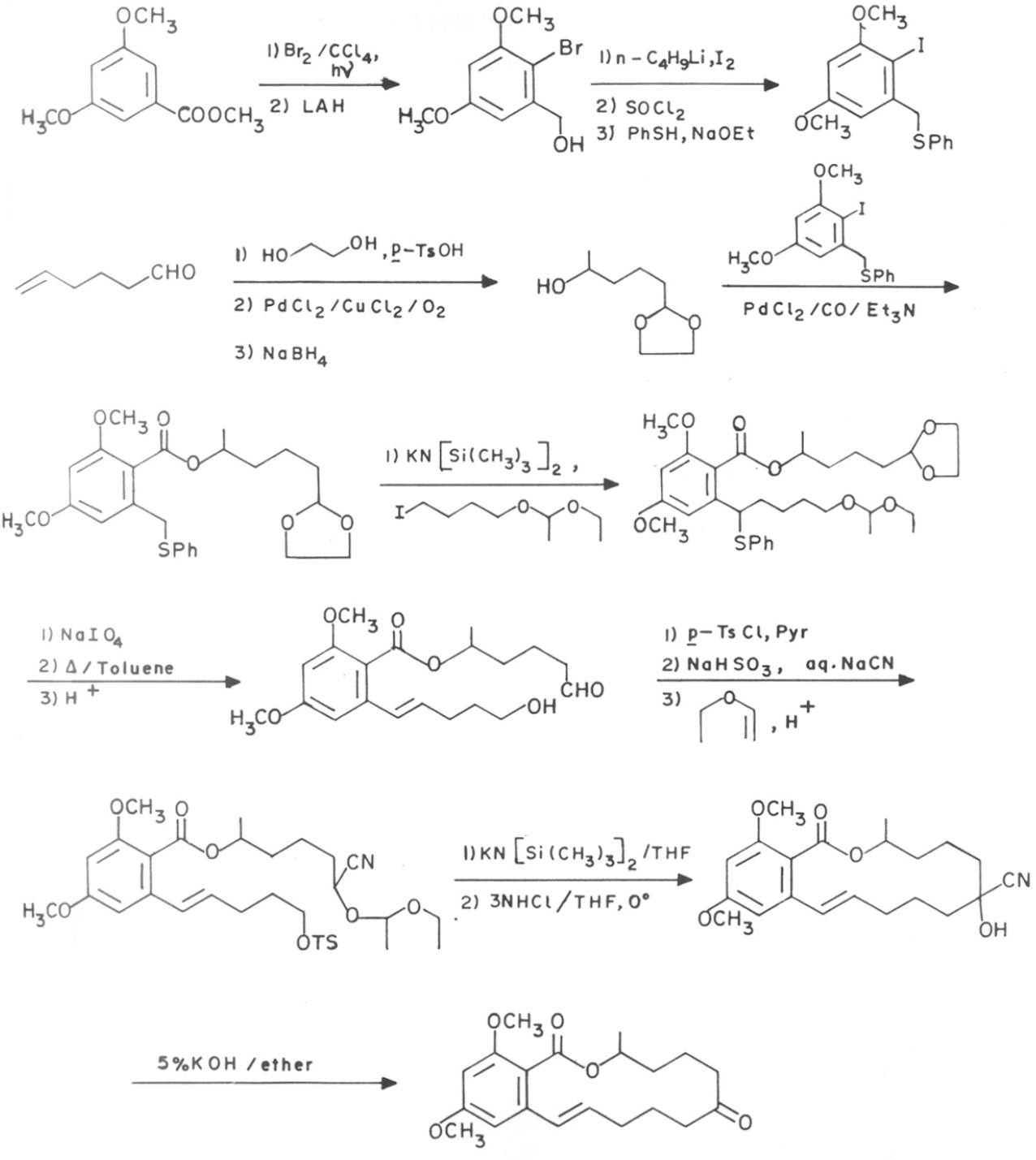
SCHEME–7

Tsuji et al (1980)



SCHEME — 8

Tsuji et al. (1981)



are condensed on esterification followed by an intramolecular C-C bond formation of the ω-halophenylthioacetate for the lactone formation.

In another approach Tsuji *et al.*[23] prepared the ester moiety (Scheme-7) by a palladium catalysed carbonylation of aryliodide in the presence of alcohol, which was smoothly transformed into (±)-zearalenone (1).

Tsuji *et al.*[24] were also responsible for the development of a new strategy (Scheme-8) for the synthesis of (±)-zearalenone. This method featured an intramolecular alkylation of a protected cyanohydrin derivative.

PRESENT WORK

The macrolide structural spectrum is perhaps one of the richest in natural product chemistry. The synthesis of macrolide antibiotics has received due attention by many well known groups worldwide and gaining a momentum due to the recent advancements in this area. A macrolide synthesis unavoidably meets with two major problems. (a) the construction of a medium or large sized lactones and (b) the stereochemical control of numerous chiral centres in the aglycone - along with the attachment of sugar(s). Zearalenone (1), having a wide variety of biological and physiological activities (discussed earlier), attracted several groups to undertake its synthesis and is covered by numerous patents[14-16,20,21]. It has been felt that synthesis of (±)-zearalenone, relatively a simple macrolide, would be a good exercise for entering into the field of macrolides before attempting the synthesis of complex ones.

The reported synthesis of (±)-zearalenone by Merck and Syntex[17-21] and Tsuji *et al.*[22-24] have been discussed earlier. All the groups have adopted fundamentally the same strategy in the construction of aromatic and aliphatic segments separately. The earlier groups adopted a Wittig approach whereas the later followed an

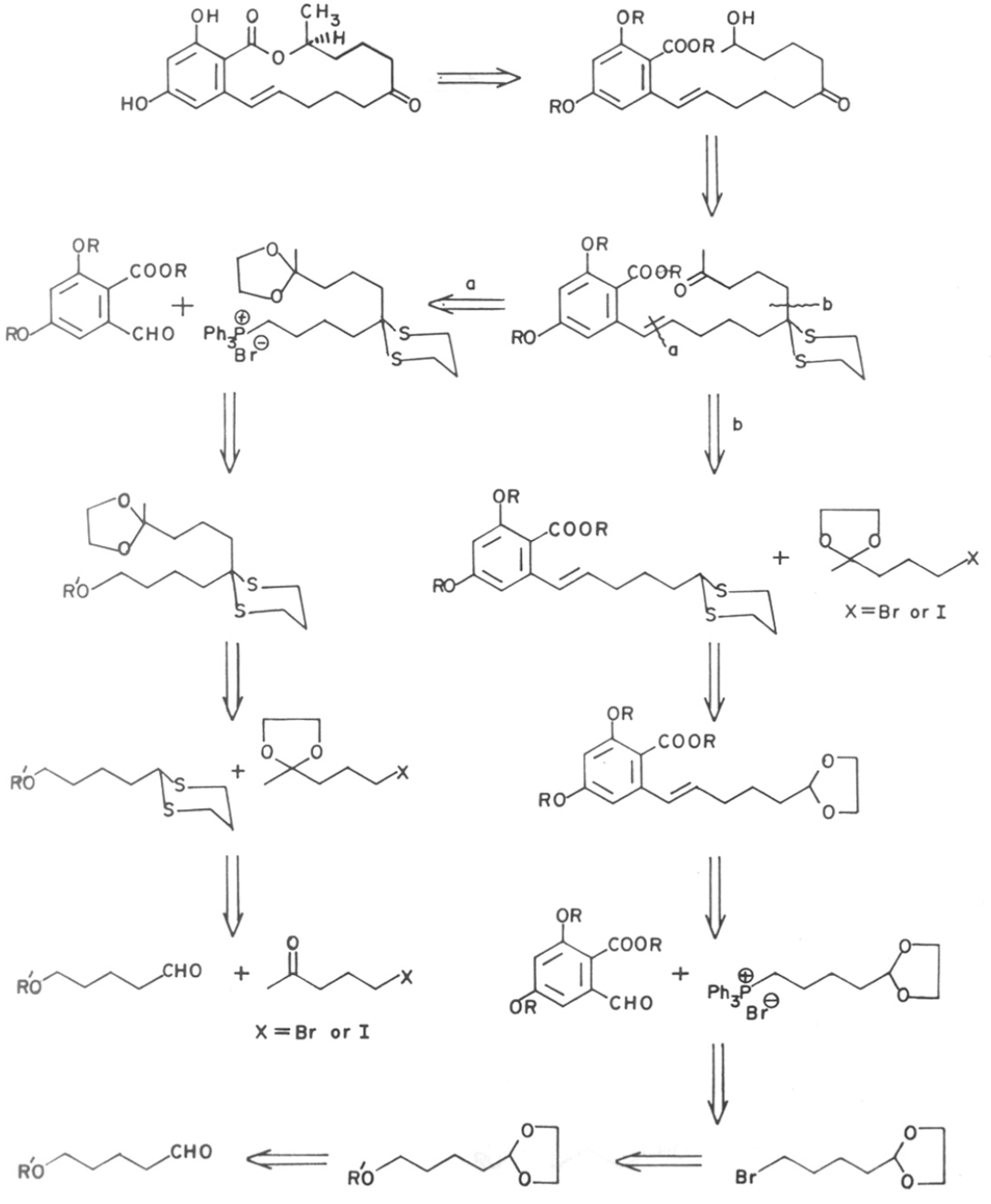
intramolecular alkylation method.

The best possible way of elaborating the synthesis of (±)-zearalenone is to be looked upon in two different approaches, illustrated by the antithetic relationship depicted in Scheme-9 (the Wittig approach) and Scheme-10 (intramolecular alkylation method). However, the disadvantages in the Wittig approach are apparent. Extensive antithetic analysis of the intramolecular alkylation method, depicted in Scheme-10, revealed that (±)-1 can be obtained, without any major constraints being met during the course of going through the sequence of reactions. Therefore, it was felt that (±)-zearalenone can be synthesised by this route, starting from easily accessible organic intermediates.

The synthesis of aromatic part (8) from the ester (21), reported by Hauser[25] was found to be relatively simple and therefore it was duplicated. However, both Merck and Syntex groups have synthesised aliphatics by a tedious route involving numerous steps resulting in low yields. Tsuji *et al.* synthesis of aliphatic moiety involves a palladium catalysed telomerisation of butadiene and its further elaboration. In the present work efforts were directed towards the synthesis of the aliphatic moiety (7) (Scheme-11) by a simple and straightforward method. The main synthetic strategy comprises the choice of protecting

SCHEME – 9

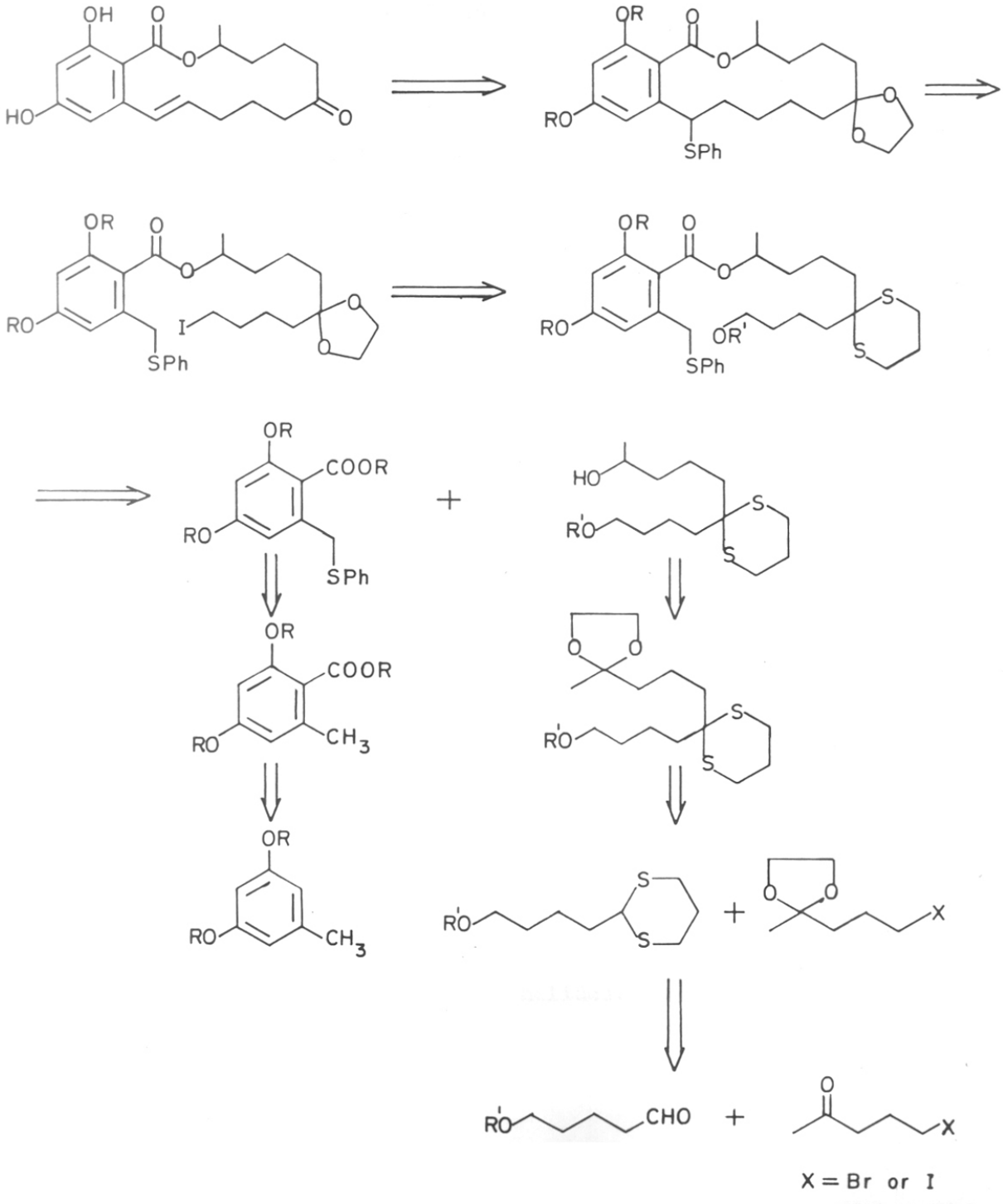
RETROSYNTHESIS OF ZEARALENONE
(WITTIG APPROACH)



SCHEME-10

RETROSYNTHESIS OF ZEARALENONE

(Intramolecular Alkylation Method)



groups for the hydroxyl and two carbonyls and should be such that each may be independently removed without effecting the other. The two ketonic functions of aliphatic moiety present at C-5' and C-9' positions if protected by the same functional group, preferential removal of one over the other for the generation of required function is difficult. Hence, one of these should be protected as an ethyleneketal and the other as a thioketal, the latter of which could be used for C-C bond formation. To achieve this assignment, the lower segment of aliphatic moiety can be looked upon as a thioketal masked hydroxy aldehyde and the upper segment as an ethyleneketal protected bromoketone.

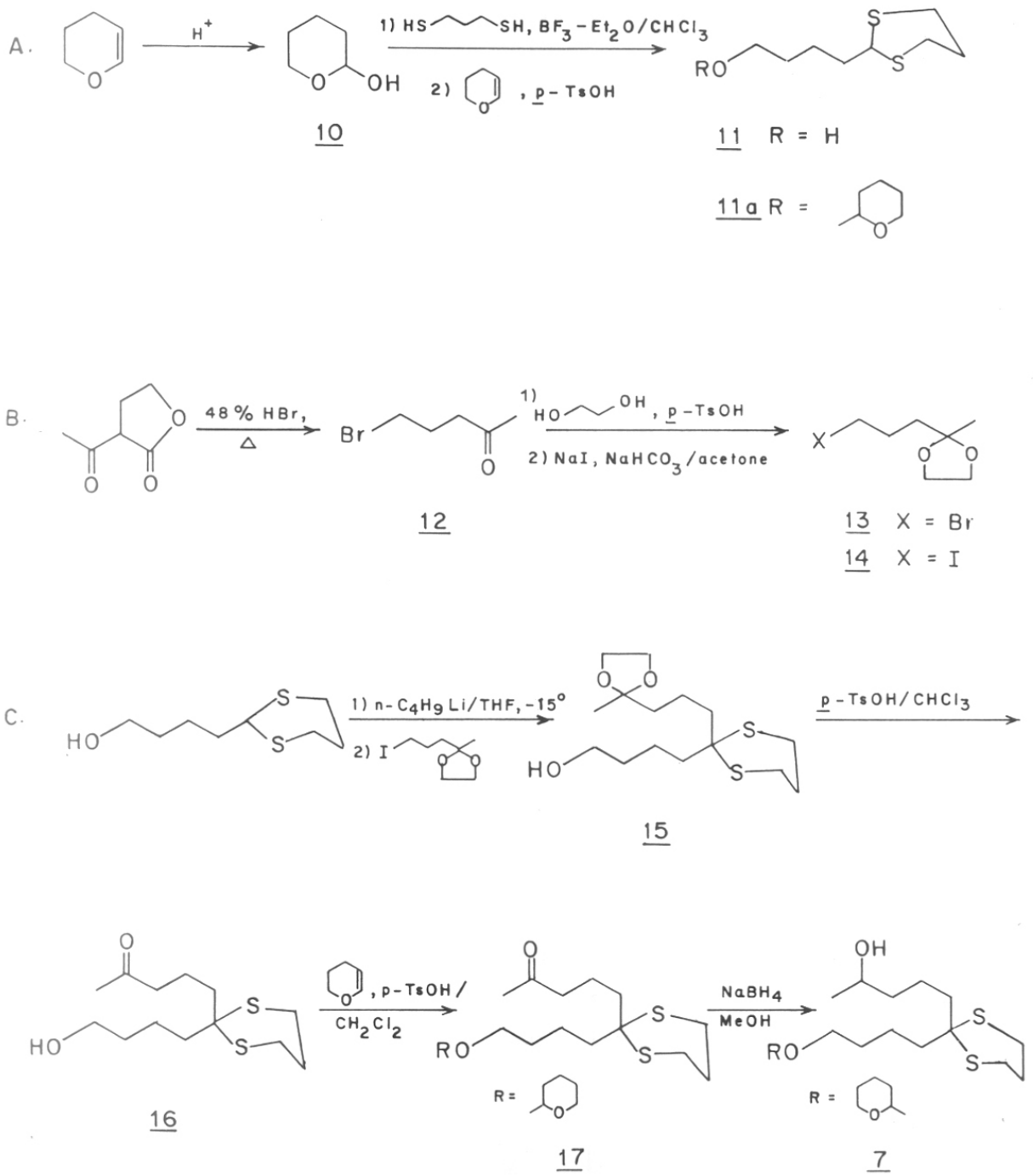
Survey of the literature revealed the use of 2-lithio-1,3-dithianes or 2-lithio-2-substituted-1,3-dithianes as valuable intermediates[26,27] for C-C bond formation. The 'Umpolung'[28] activity of these sulphur stabilised anions have been extensively used in synthetic organic chemistry. The thioketal group in the present synthesis is utilised, both for masking one of the ketonic functions as well as for the C-C bond formation. Therefore, dithiane masking for the construction of aliphatic moiety is a method of preference, due to (a) the ease of preparation of dithianes in good yields (b) their reaction with various elecrophiles (alkyl halides, carbonyl compounds,

epoxides etc.) and (c) conversion to the carbonyl function under mild hydrolytic conditions.

Thus, the strategy in the present synthesis of (±)-zearalenone (1) is (a) synthesis of 2-substituted dithiane (b) C-C bond formation through alkylation of dithiane (c) the generation of required functionalities at desired positions and (d) condensation of aromatic and aliphatic segments, and further elaboration to the intermediate iodide (9).

The synthesis of aliphatic moiety starts from 2,3-dihydropyran, which is an excellent starting material for an aldehyde containing five carbon atoms (Scheme-11). Commercially available 2,3-dihydropyran on treatment with aqueous hydrochloric acid at room temperature afforded the expected 5-hydroxypentanal (10)[29] in 74% yield. The IR spectrum of 10 showed a weak absorption at 1730 cm^{-1} and an intense band at 3300 cm^{-1}, indicating that it exists[30] predominantly in cyclic hemiacetal form as 2-hydroxypyran rather than in the open form as 5-hydroxypentanal. Further confirmation obtained from its formation of 2,4-dinitrophenylhydrazone derivative after a prolonged period of time, which shows that equillibrium shifts slowly to open chain form. 5-Hydroxypentanal (10) on reaction with 1,3-propanedithiol in dry chloroform in the presence of

SCHEME 11


A.
H+
1) HS SH, BF3 – Et2O/CHCl3
2) , p-TsOH
OH
RO
S
S
10
11 R = H
11a R =
B.
48% HBr,
Δ
Br
O
1) HO OH , p-TsOH
2) NaI, NaHCO3/acetone
X
12
13 X = Br
14 X = I
C.
HO
1) n-C4H9Li/THF, -15°
2) I
HO
p-TsOH/CHCl3
15
HO
16
, p-TsOH/
CH2Cl2
RO
R =
17
NaBH4
MeOH
OH
RO
R =
7

borontrifluoride-etherate gave the hydroxy-dithiane (11) in 79% yield. The ^{1}H-NMR spectrum (Fig.1) of 11 in CCl_4 showed two triplets at δ 4.00 and 3.57 assigning for dithiane and -CH_2OH protons respectively. The -SCH_2 protons resonated in the region of δ 2.7 - 2.9 as multiplet. Further, IR spectrum showed a characteristic dithiane band at 915 cm^{-1} and 3200 cm^{-1} for -OH, supporting the structure 11. The hydroxyl group of compound (11) was protected as its THP-ether, on treatment with dihydropyran in presence of p-toluenesulfonic acid (PTSA) to afford 11a in 74% yield. The ^{1}H-NMR spectrum showed the presence of characteristic THP-proton signal. The hydroxy-dithiane (11) or the THP-ether (11a) was further subjected to alkylation to generate carbon skeleton with the properly positioned oxygen functions of aliphatic segment of (±)-zearalenone (1).

2-(3-Bromopropyl)-2-methyl-1,3-dioxolane (13) was prepared from 2-acetyl-γ-butyrolactone by adopting the literature[31] procedure. For example, 2-acetyl-γ-butyrolactone on heating under reflux with 48% hydrobromic acid furnished 5-bromopentan-2-one (12)[31]. Ketalisation[31] of carbonyl function of 12 was achieved by refluxing ethyleneglycol and PTSA in benzene to give the ketal (13) in 81% yield. Compound (13) was identical with the reported sample.

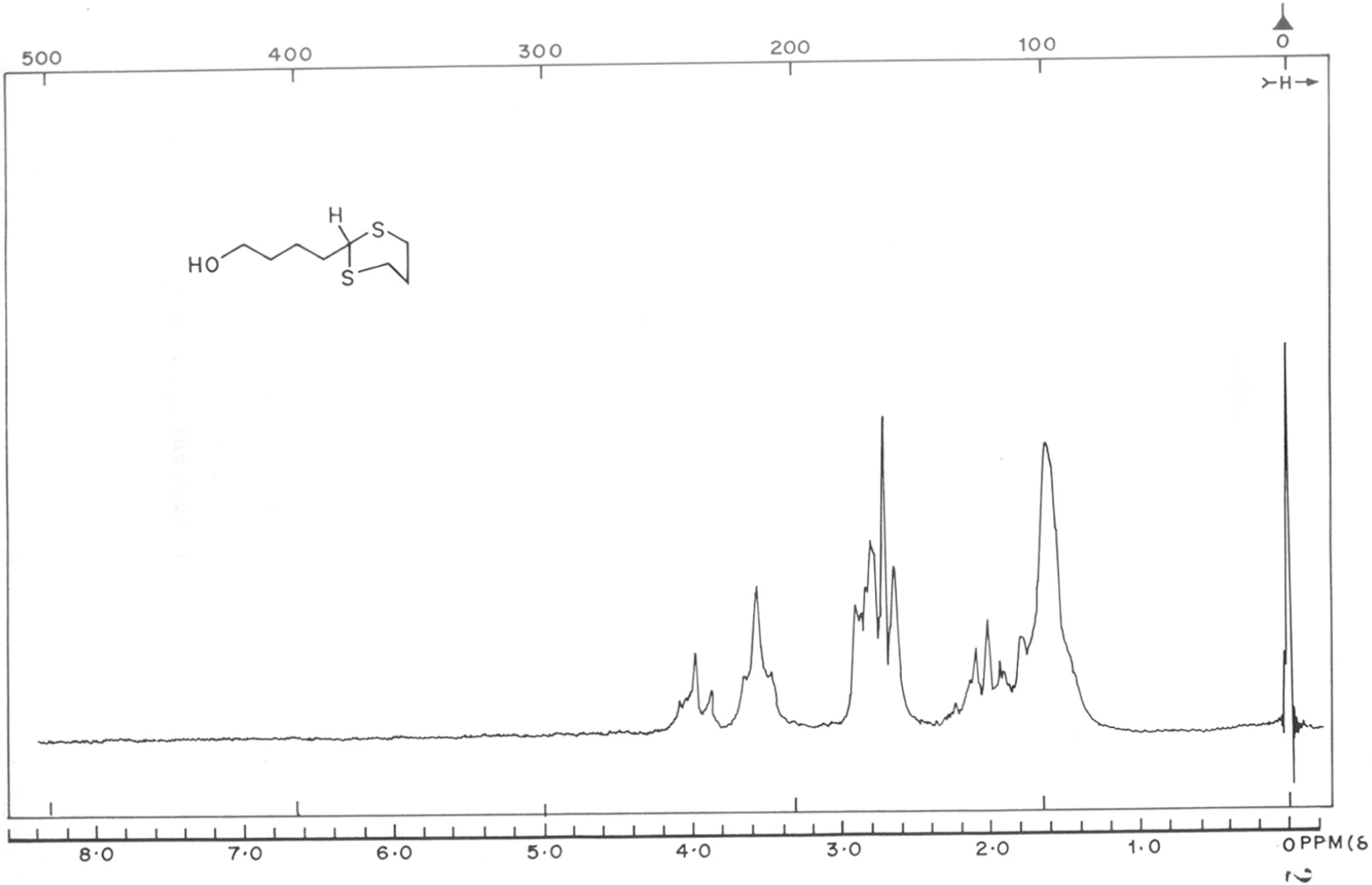


FIG. 1. ^{1}H-NMR SPECTRUM OF COMPOUND (11) IN CCl_4

Metallation of the hydroxydithiane (11) was effected with two molar equivalents of n-BuLi at -15° and its subsequent alkylation with the bromoketal (13) at -15° furnished the alkylated product (15) in poor yields. However, it was felt that the poor yield of the product could be due to the low reactivity of the bromide and the corresponding iodide (14) would be a better alkylating agent. Accordingly the iodide (14) was prepared from the bromide (13) by treatment with sodium iodide in dry acetone at room temperature, under neutral conditions using sodiumbicarbonate, in excellent yields. Compound (14) was found to be unstable for longer periods. The dithiane (11) was metallated with n-BuLi and subsequently subjected to alkylation with a freshly prepared iodide (14), under similar conditions as mentioned above, resulted a mixture of products as judged by TLC. The reaction mixture was subjected to column chromatography on silica gel, to afford two fractions, fraction 'A' and 'B'. The first to be eluted (faster moving on TLC) in fraction 'A' was obtained in 36% yield, anticipated O-alkylated ether. The second fraction (Fraction 'B'), slower moving component on TLC, afforded a compound (49%) which was characterised as the C-alkylated product (15). In the ^{1}H-NMR spectrum (Fig.2) of 15 in CCl_4, the four protons of ketal group

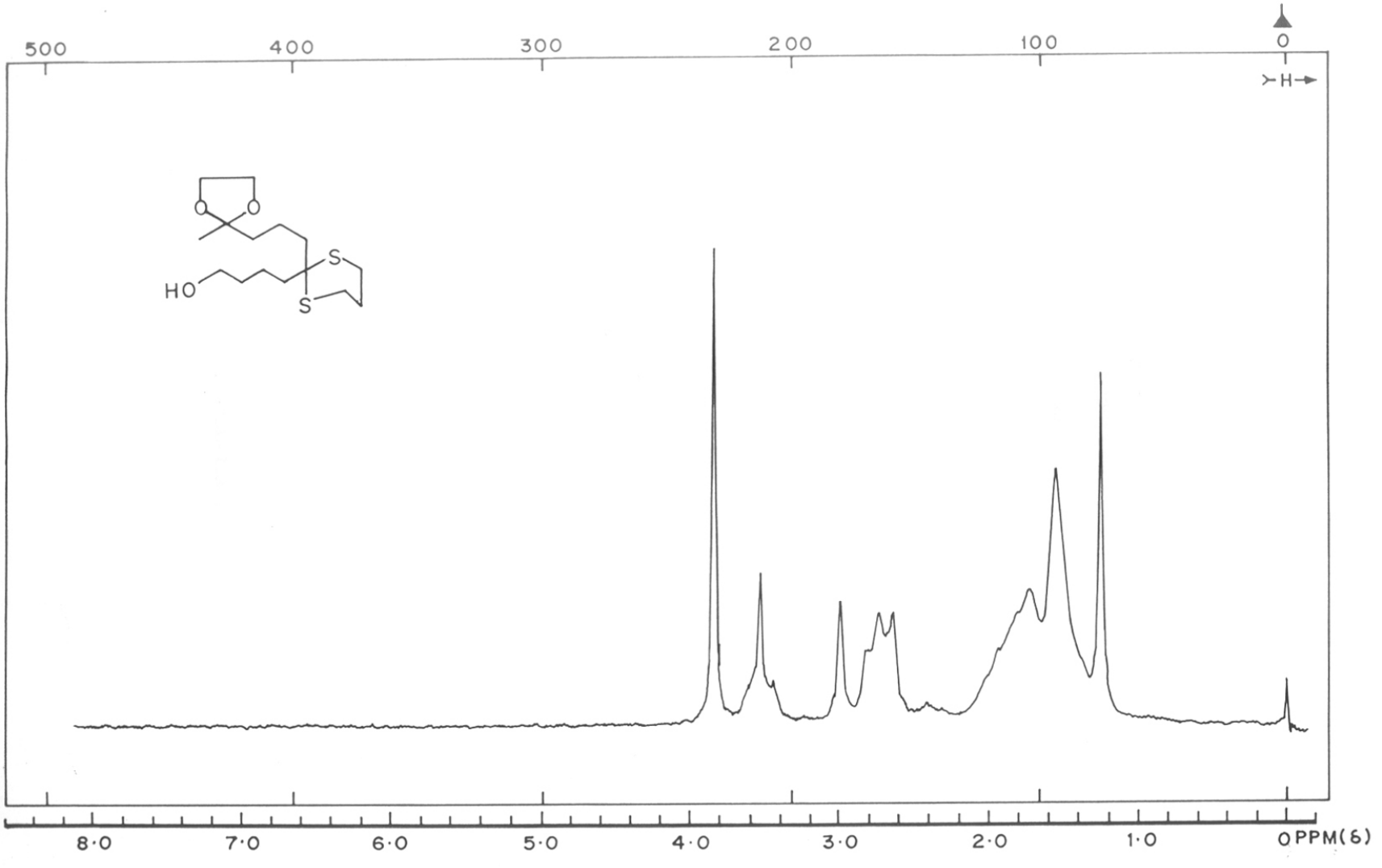


FIG. 2. ^{1}H-NMR SPECTRUM OF COMPOUND (15) IN CCl_4

resonated at δ 3.83 as a singlet, while the triplet at δ 3.50 was accounted for the two protons of $-CH_2OH$. Rest of the protons resonated at the expected chemical shifts. The presence of -OH group was confirmed from the IR spectrum, where the band at 3450 cm^{-1} was observed. The mass spectrum showed the molecular ion peak at m/e 320. The prominent fragment being at m/e 276 (-44) and the fragmentation pattern was in accordance with the assigned structure 15.

A methanolic solution of the alkylated product (15) on treatment with PTSA at room temperature for 20 hr, accomplished the cleavage of ketal protection and furnished a slower moving component on TLC, which was identified as the hydroxy-keto compound (16). In the ^1H-NMR spectrum (Fig.3) of 16 in CCl_4, the acetyl protons resonated at δ 2.05 as a singlet, whereas the triplet at δ 2.43 was assigned to $-COCH_2-$. IR spectrum showed the carbonyl absorption at 1720 cm^{-1} along with 3450 cm^{-1} (OH). The molecular ion peak appeared at m/e 276 in its mass spectrum, besides the fragments at m/e 203 ($m-C_4H_9O$), 191 ($m-C_5H_9O$).

The hydroxy compound (16) on treatment with dihydropyran in dichloromethane containing catalytic amount of PTSA resulted the THP-keto compound (17) in 89%

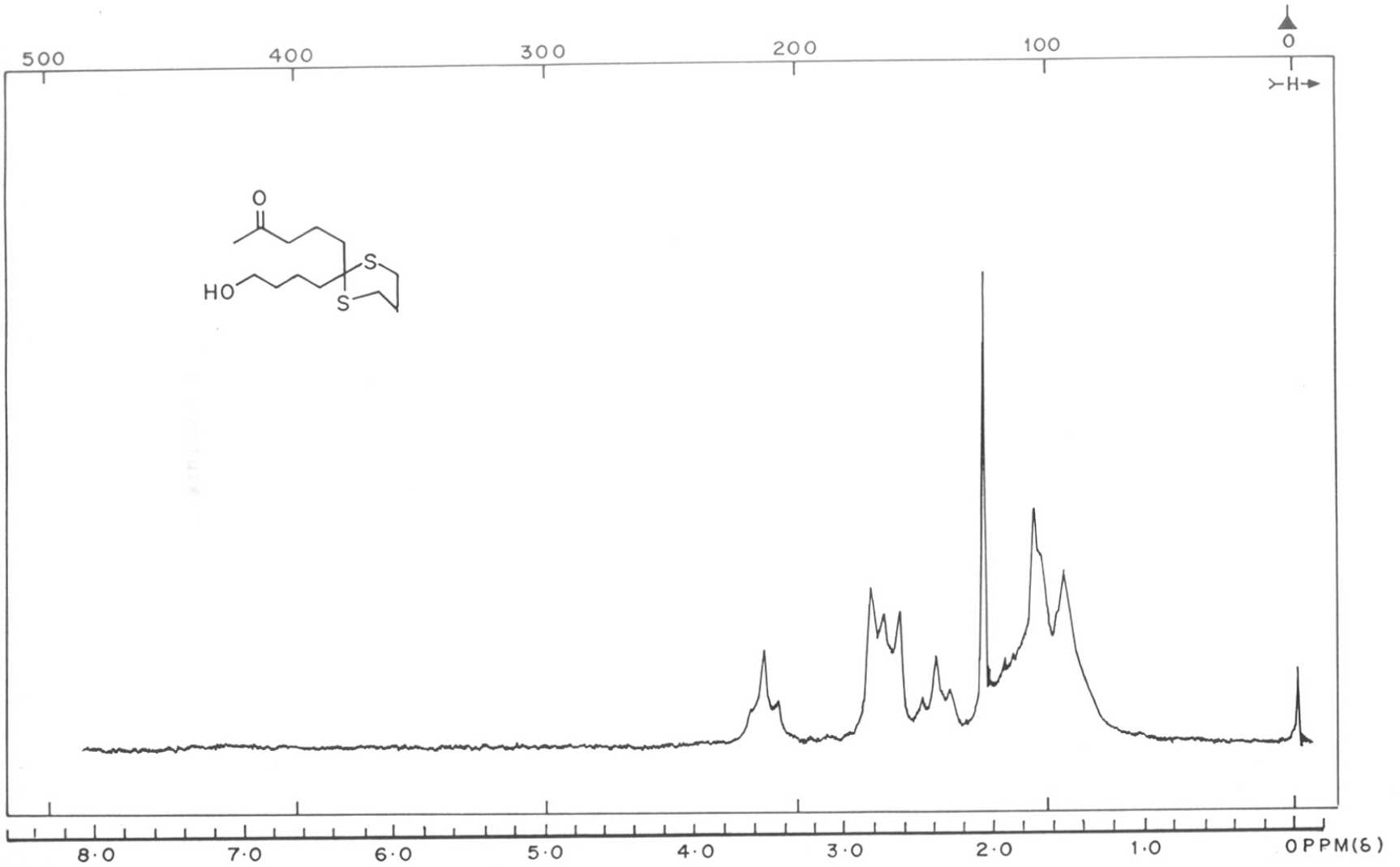


FIG. 3. ^{1}H-NMR SPECTRUM OF COMPOUND (16) IN CCl_4

yield. The ^{1}H-NMR spectrum (Fig.4) of compound (17) in $CDCl_3$ showed the characteristic resonance of THP proton at δ 4.50 as a singlet. Rest of the protons resonated at the expected chemical shifts. IR spectrum showed the absence of absorption for hydroxyl function. Molecular ion peak was observed at m/e 360. Reduction of the carbonyl group of compound (17) was effected with sodium borohydride in methanol resulting in the formation of the hydroxy-THP compound (7) (the aliphatic moiety of zearalenone) in 82% yield. Structure of the resulting alcohol was characterised as 7 on the basis of spectral studies. In the ^{1}H-NMR spectrum (Fig.5) of 7 in CCl_4, the methyl protons resonated at δ 1.16 as a doublet, was the indication of the fact that reduction occurred. The remaining resonances appeared at the expected chemical shifts. Furthermore, in the IR spectrum the band for carbonyl at 1720 cm^{-1} disappeared, whereas the absorption at 3450 cm^{-1} confirmed the presence of -OH. Its mass spectrum showed the molecular ion peak at m/e 362, and further fragmentation was consistent with the assigned structure for 7. The above illustrated sequence of reactions led to the construction of aliphatic carbon skeleton 7, which on condensation and further elaboration will lead to 9.

A survey of literature revealed relatively a simple

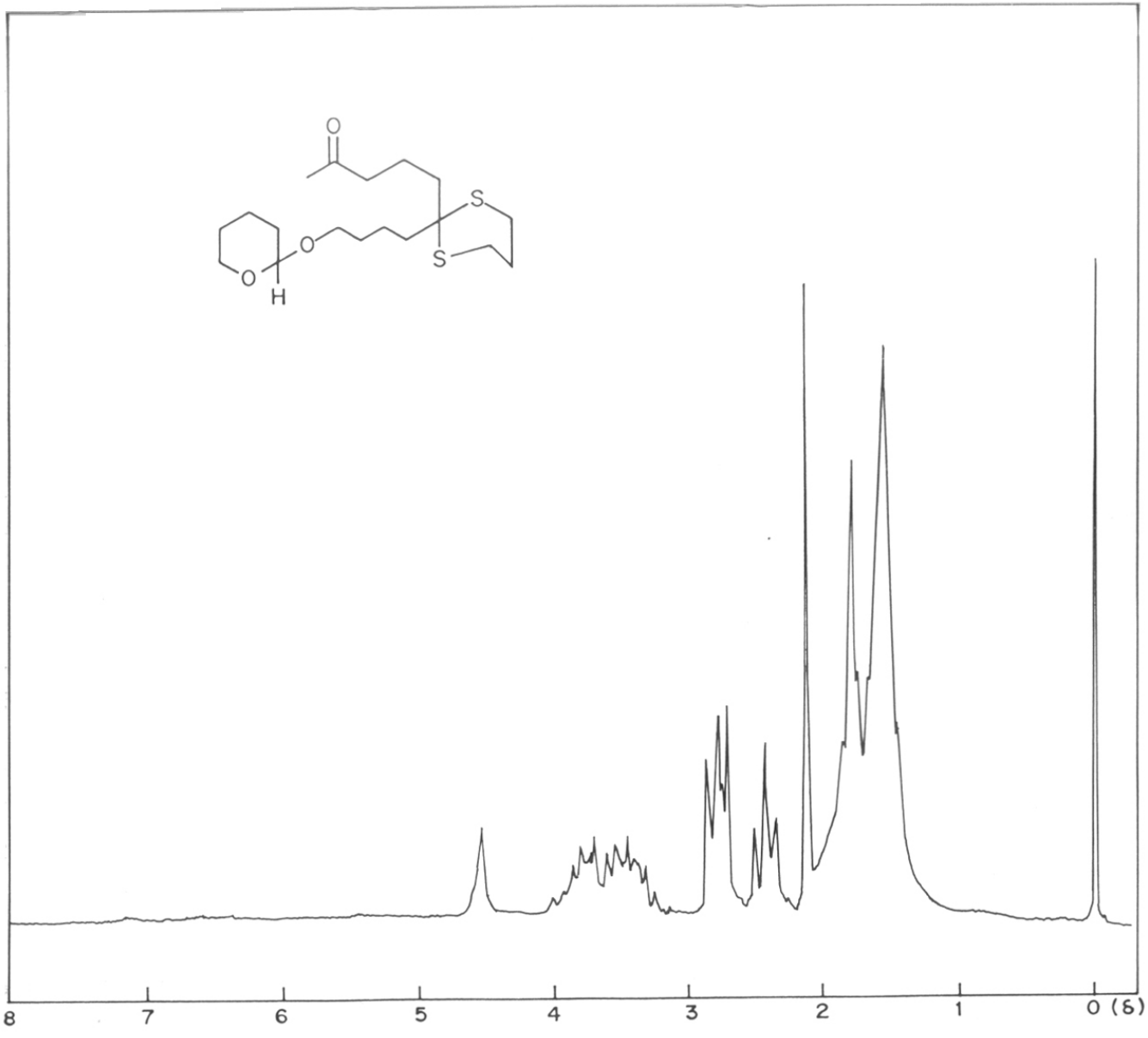


FIG. 4. ^{1}H-NMR SPECTRUM OF COMPOUND (17) IN $CDCl_3$

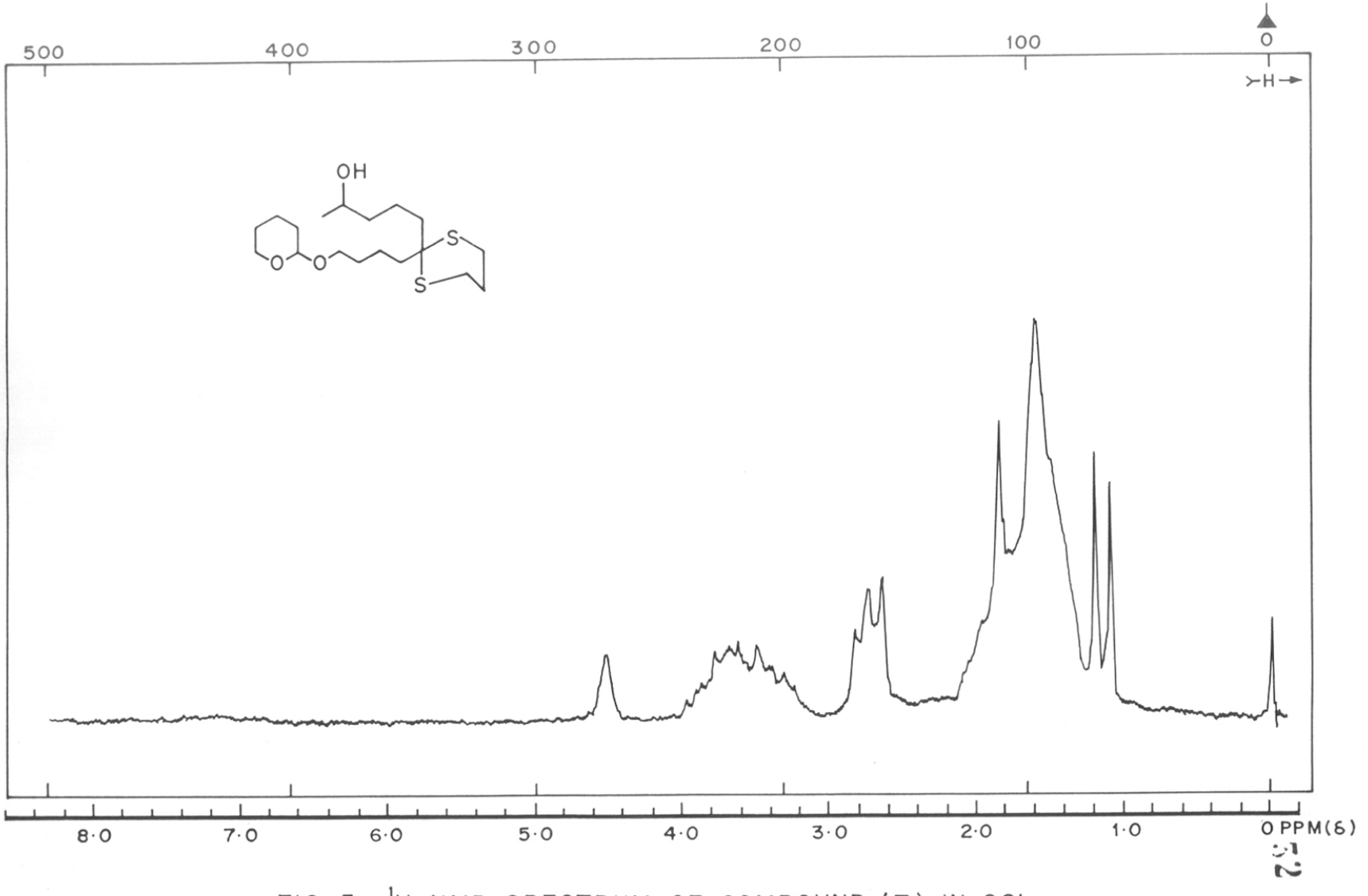
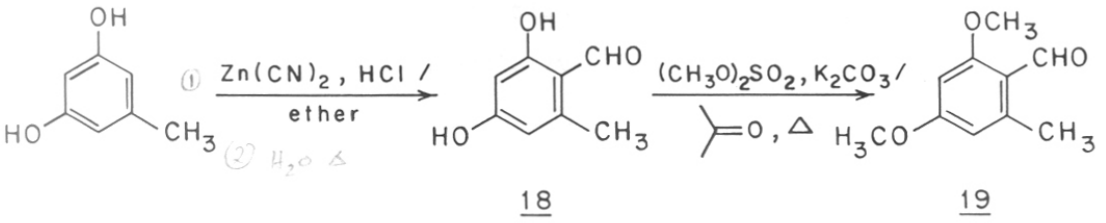


FIG. 5. ^{1}H-NMR SPECTRUM OF COMPOUND (7) IN CCl_4

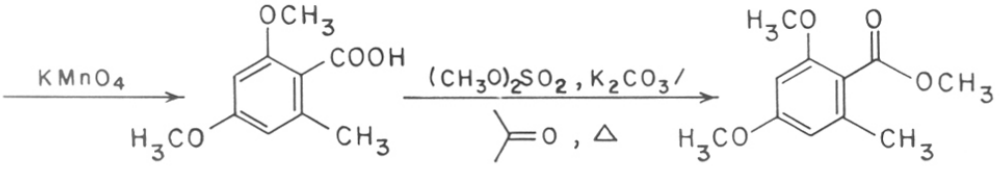
sequence of reactions for the preparation of aromatic moiety (8), hence it was duplicated. The synthesis of 8 starts from orcinol (Scheme-12). Orcinol was subjected to Gattermann formylation[32a] with zinc cyanide in dry ether by bubbling dry HCl gas to furnish the aldehyde (18). Compound (18) on treatment with dimethylsulfate-potassiumcarbonate in refluxing acetone afforded the dimethyl ether (19)[33a]. Oxidation of aldehydic function in 19 with aqueous potassium permanganate in acetone under neutral conditions at 40° resulted in the formation of the acid (20)[33a], which in turn was esterified with dimethyl-sulfate-potassium carbonate in acetone to give the ester (21). Recently Hauser et al.[25] reported conversion of 21 to methyl-2,4-dimethoxy-6-[(phenylthio)methyl] benzoate (8), in a simple and convenient way, which was adopted in the present synthesis. The ester (21) was metallated with LDA at -78°. The dark red anion thus generated was then treated with diphenyldisulphide at -78° to give the benzoate (8) in good yield. Compound (8) was identical with that of the reported[25] sample.

Having synthesised the aliphatic (7) and aromatic (8) moieties successfully, efforts were directed towards the coupling of these two portions together, involving simple and straightforward reactions under mild conditions for giving rise to high yields of products.

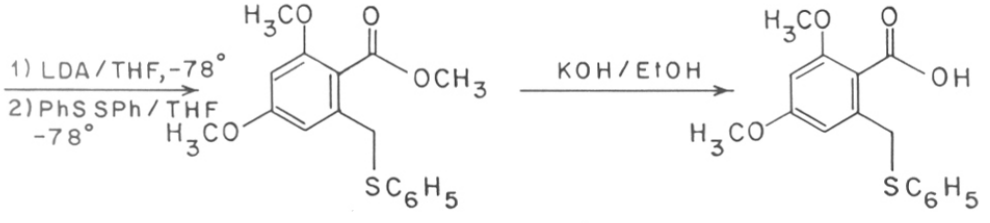
SCHEME-12



18 19



20 21



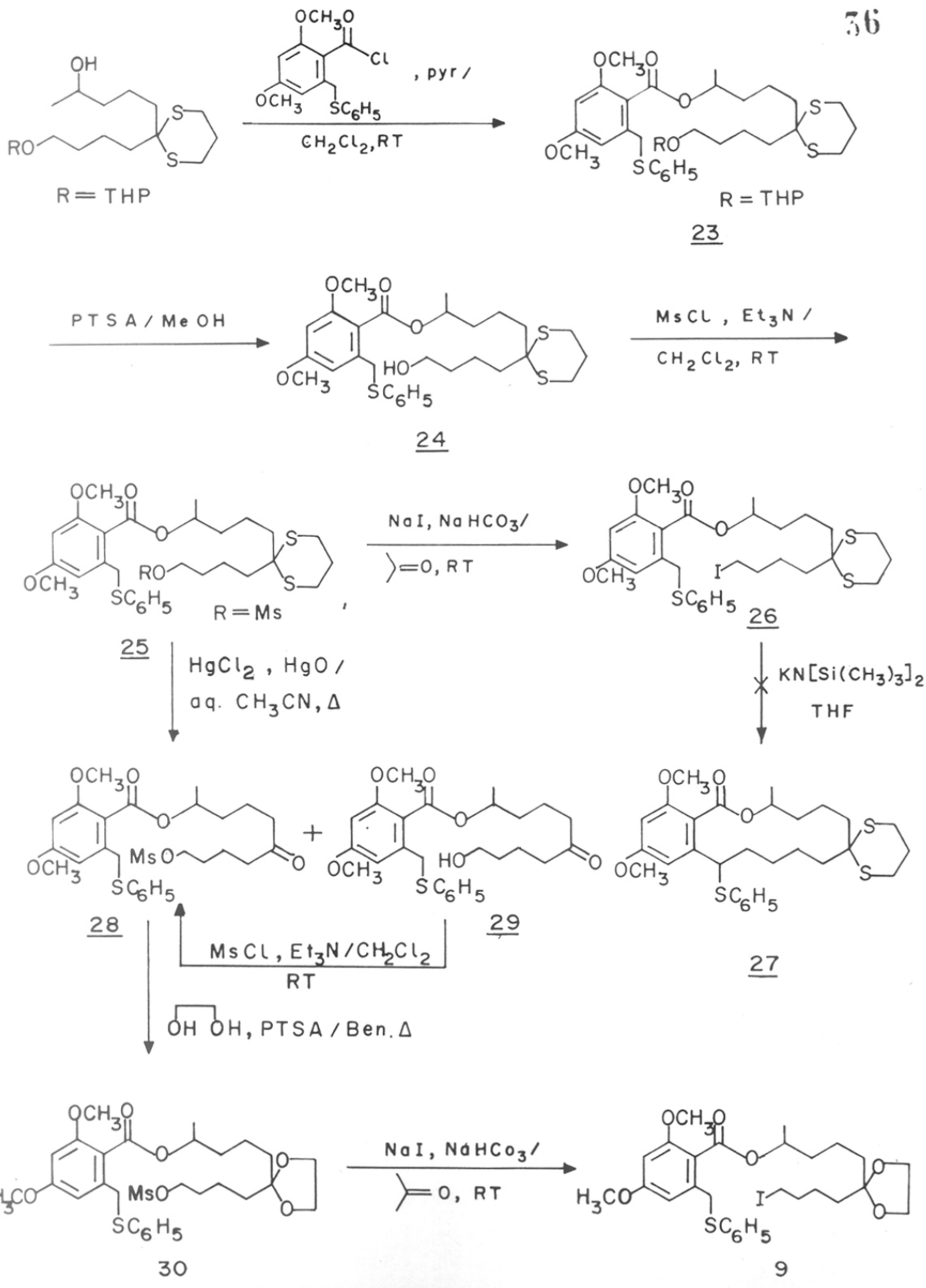
8 22

Hydrolysis of 8 with ethanolic potassium-hydroxide under reflux followed by acidification gave the acid (22) in quantitative yield. The acid (22) was treated with thionylchloride in refluxing benzene for 6 hr, to result the corresponding acid chloride. The acid chloride thus obtained was further used without any purification.

The alcohol (7) (aliphatic segment) in dichloro-methane was treated with freshly prepared acid chloride of 22 (Scheme-13) in the presence of pyridine as base to afford the THP-ester (23) in 59% yield. The structure of compound (23) was assigned from the spectral analysis. In the ^{1}H-NMR spectrum (Fig.6) of 23 in $CDCl_3$, the resonances due to two $-OCH_3$ groups, $-CH_2SPh$ and Ar-H all appeared as singlets at δ 3.68, 3.71, 4.09 and 6.28 respectively, while the $-SC_6\underline{H}_5$ protons appeared as a multiplet at δ 7.0 - 7.2. The remaining protons resonated at the expected chemical shifts. Further confirmation was gleaned from IR spectrum where carbonyl absorption was observed at 1720 cm^{-1}. Mass spectrum showed the molecular ion peak at m/e 648, besides the fragment ion at m/e 564 (m-84).

Depyranylation of the THP=ester (23) was carried on treatment with PTSA in methanol for 6 hr to result the

SCHEME – 13


R = THP
, pyr /
CH2Cl2, RT
23
PTSA / Me OH
24
MsCl , Et3N /
CH2Cl2, RT
NaI, NaHCO3/
=O, RT
R = Ms
25
26
HgCl2 , HgO /
aq. CH3CN, Δ
KN[Si(CH3)3]2/
THF
28
29
27
MsCl, Et3N/CH2Cl2
RT
OH OH, PTSA / Ben. Δ
30
9

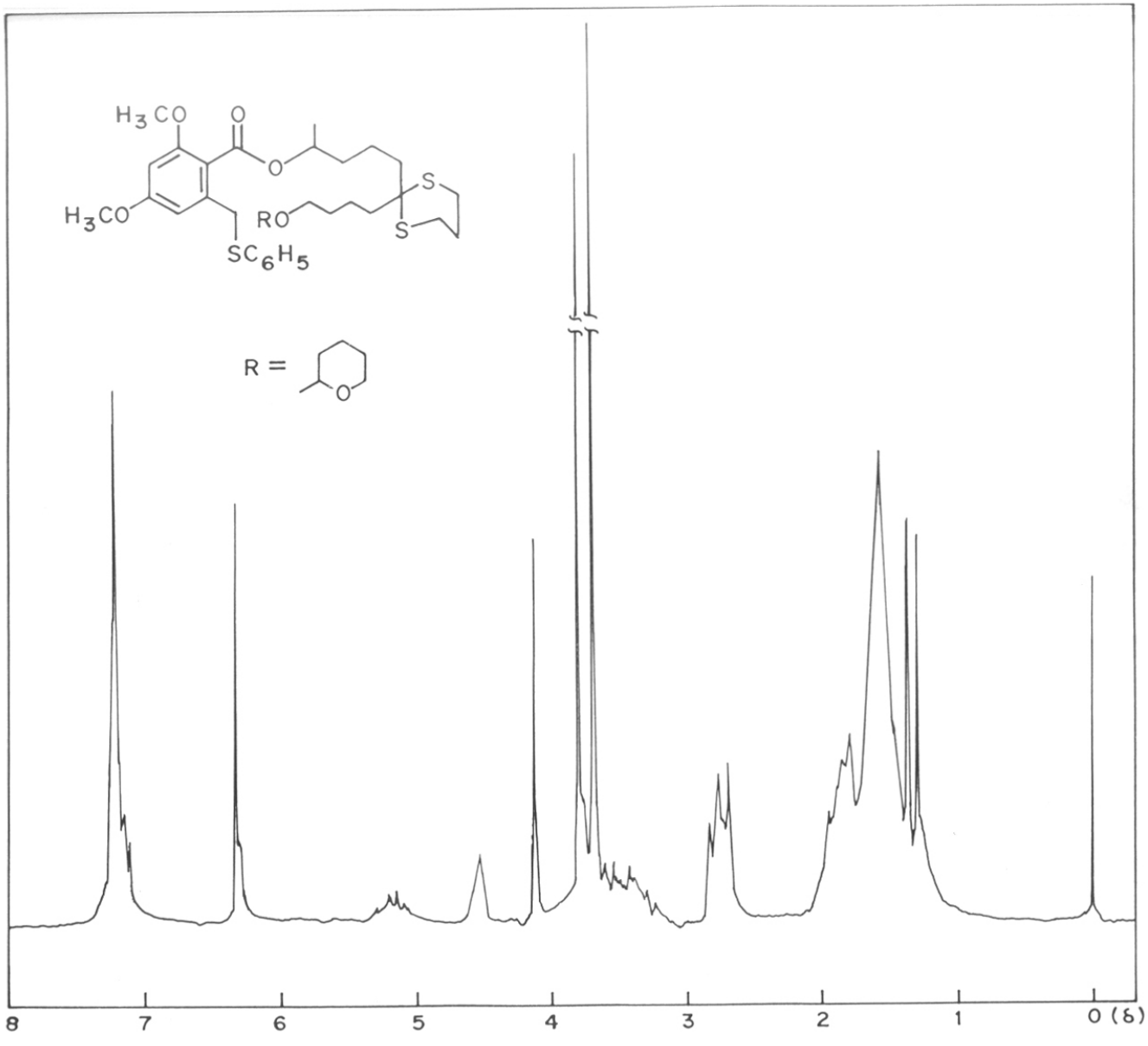


FIG. 6. ^{1}H-NMR SPECTRUM OF COMPOUND (23) IN $CDCl_3$

hydroxy-ester (24) in 74% yield. In the ^{1}H-NMR spectrum (Fig.7) of 24 in $CDCl_3$, the $-C\underline{H}_2OH$ protons resonated at δ 3.60 as a triplet. IR spectrum showed the absorptions at 1720 cm^{-1} and 3450 cm^{-1} for the carbonyl and hydroxyl functions respectively. Molecular ion peak at m/e 564 and further fragmentation pattern was consistent with the assigned structure 24.

The hydroxy-ester (24) was converted to O-mesylate by the conventional procedure. Thus, the compound (24) on reaction with methanesulfonyl chloride in dichloromethane in the presence of triethylamine as base furnished the mesylate (25) in 87% yield. The ^{1}H-NMR spectrum of 25 showed the resonance due to $-SO_2C\underline{H}_3$ at δ 2.96 as a singlet, while the $-SO_3C\underline{H}_2-$ appeared at δ 4.09 as a triplet. IR spectrum showed the absence of band at 3450 cm^{-1} for -OH.

In accordance with the scheme the next aim was to convert the mesylate (25) to the iodide (26) required for the intramolecular alkylation. 25 on reaction with sodium-iodide in dry acetone at room temperature afforded the required iodide (26) as judged by ^{1}H-NMR spectrum. However, attempted cyclisation of 26 to yield the cyclised product (27) was unsuccessful and compound (26) was found to be very much unstable under the reaction conditions. A literature survey revealed the explanation put forward by

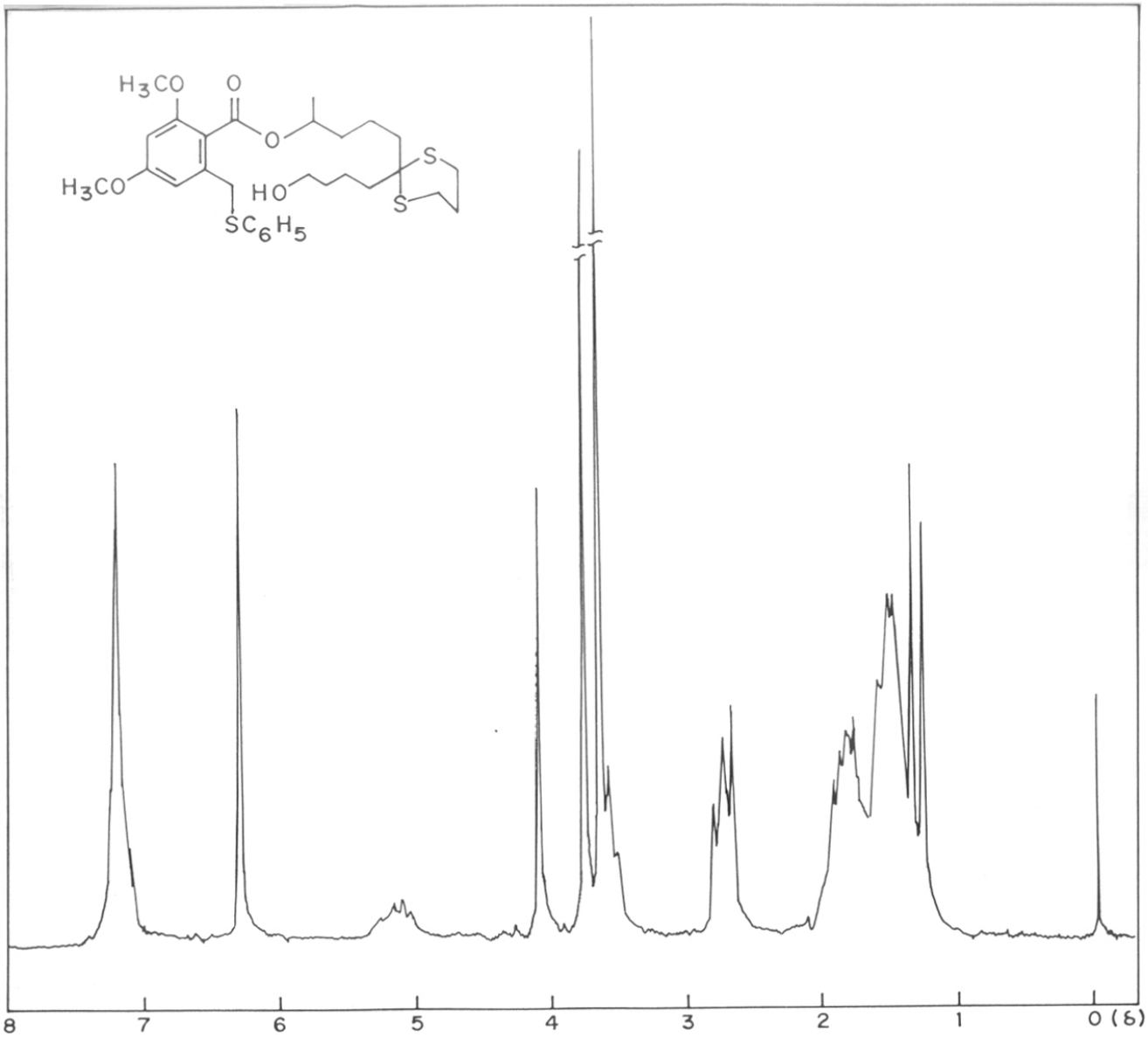


FIG. 7. ^{1}H-NMR SPECTRUM OF COMPOUND (24) IN $CDCl_3$

Corey *et al.*[26a] for the formation of sulphonium bromides (A) by an intramolecular reaction of ω-halodithianes as shown below. Interestingly these sulphonium bromides (A)

were found to undergo internal elimination in the presence of base to provide the assigned structure 'B' cleanly. Similarly difficulties were encountered when the mesylate (C) was converted to the bromide (D) with lithium bromide in

acetone, where a solid material obtained on a slight exposure to heat, probably the compound of type 'E'.

The similar type of six-membered sulfoniumiodide intermediate

was anticipated from the iodide (26), causing the problems during the course of reactions. Thus, it was felt that non-participating carbonyl protective group such as an ethyleneketal would help to overcome the difficulties faced. Therefore, it was decided to replace the thioketal protection by ethylene-ketal followed by further transformations.

Accordingly compound (25) was treated with mercuric chloride-mercuric oxide in refluxing aqueous acetonitrile (80%) to remove[34] the thioketal protection. After one hour no starting material was observed but new spots were seen on TLC. The mixture was separated by column chromatography on silica gel to give two fractions 'A' and 'B'. The major component which was isolated in fraction 'A' (faster moving on TLC) after column chromatography, found to be undoubtedly the mesylate-ketone (28) from its spectral data. The ^{1}H-NMR spectrum (Fig.8) of 28 in $CDCl_3$ showed the resonances due to the $-CH_2-CO-CH_2-$ group at δ 2.2 - 2.5 as a multiplet while the signals due to $-SCH_2-$ were missing. The molecular ion peak was not seen in its mass spectrum, however, a fragment was located at m/e 446 (m-96) due to the loss of mesyl group (96). The slower moving component on TLC was isolated in fraction 'B' in 35% yield. Its IR spectrum showed an absorption at 3450 cm^{-1} indicating the presence of

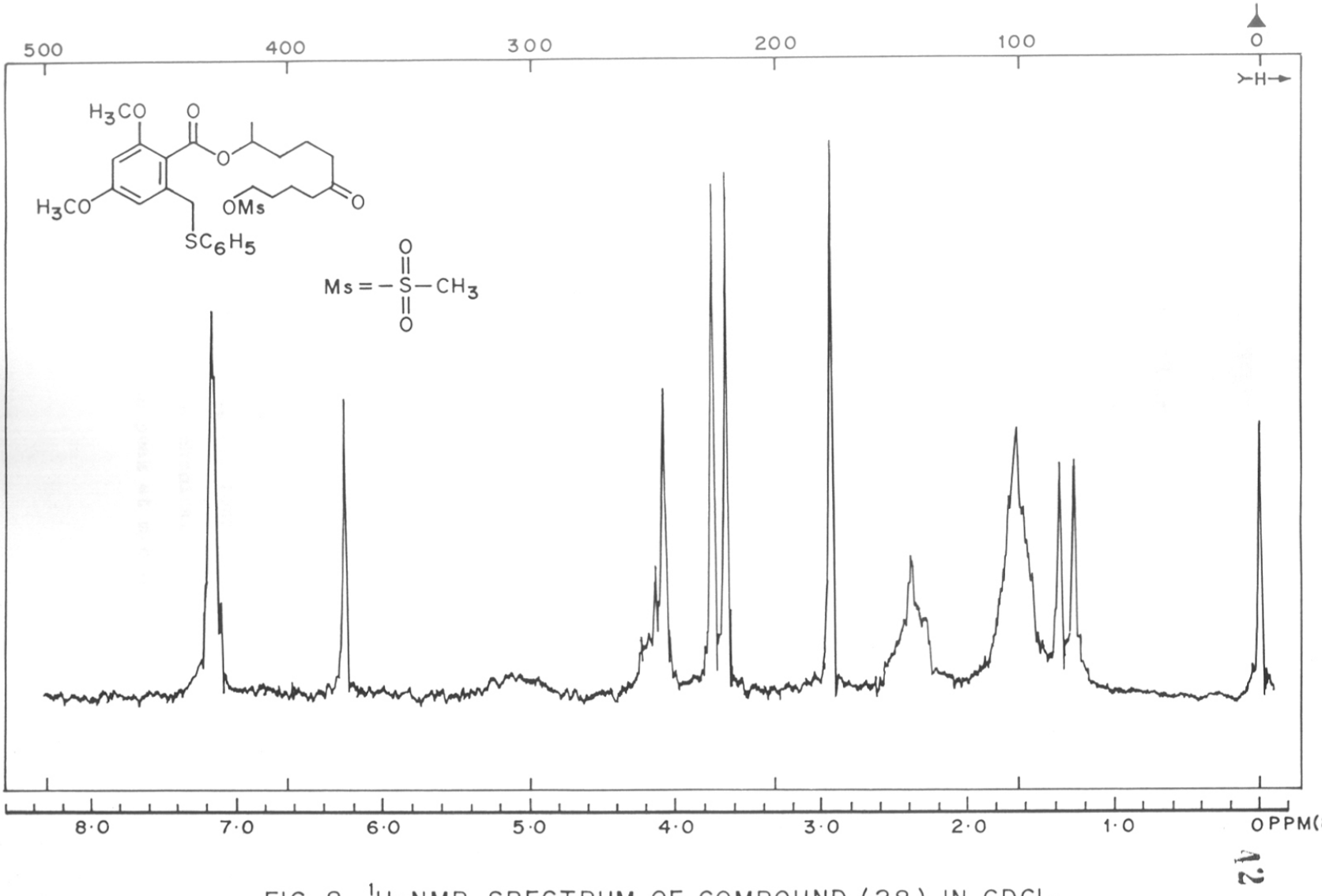


FIG. 8. ^{1}H-NMR SPECTRUM OF COMPOUND (28) IN $CDCl_3$

a -OH group. In the ^{1}H-NMR spectrum of the above compound the signals due to the mesyl group were missing along with $-SCH_2$ signals. It showed the chemical shifts at δ 3.3 triplet and δ 2.0 - 2.3 multiplet which were assigned to $-C\underline{H}_2OH$ and $-C\underline{H}_2COC\underline{H}_2-$ respectively. From the above data the compound was assigned the structure as the hydroxy-keto compound (29). Further evidence for 29 was obtained from its chemical conversion to 28 by conventional O-mesylation by making use of methanesulfonyl chloride in presence of triethylamine. The compound thus obtained was identical with 28 (TLC and spectral data). Hence, the reaction finally not only confirmed the given structure for 29 but also helped in obtaining 28 in excellent yield starting from the mesylate 25, overall in 74% yield.

The ketonic function of 28 was protected on reaction with ethyleneglycol and catalytic amount of PTSA in refluxing benzene to give the mesylate-ketal (30) in 94% yield. The R_f values of both the starting material and the derived ketal were found to be same on TLC (benzene). The structure of the resulting product was indicated by its spectral data. The ^{1}H-NMR spectrum (Fig.9) of compound (30) in $CDCl_3$ showed the characteristic resonance for the ketal group at δ 3.86 as a singlet, integrating for four protons. Remaining protons resonated at the expected chemical shifts. The mass spectrum showed the molecular ion peak at m/e 596 besides the fragmenta-

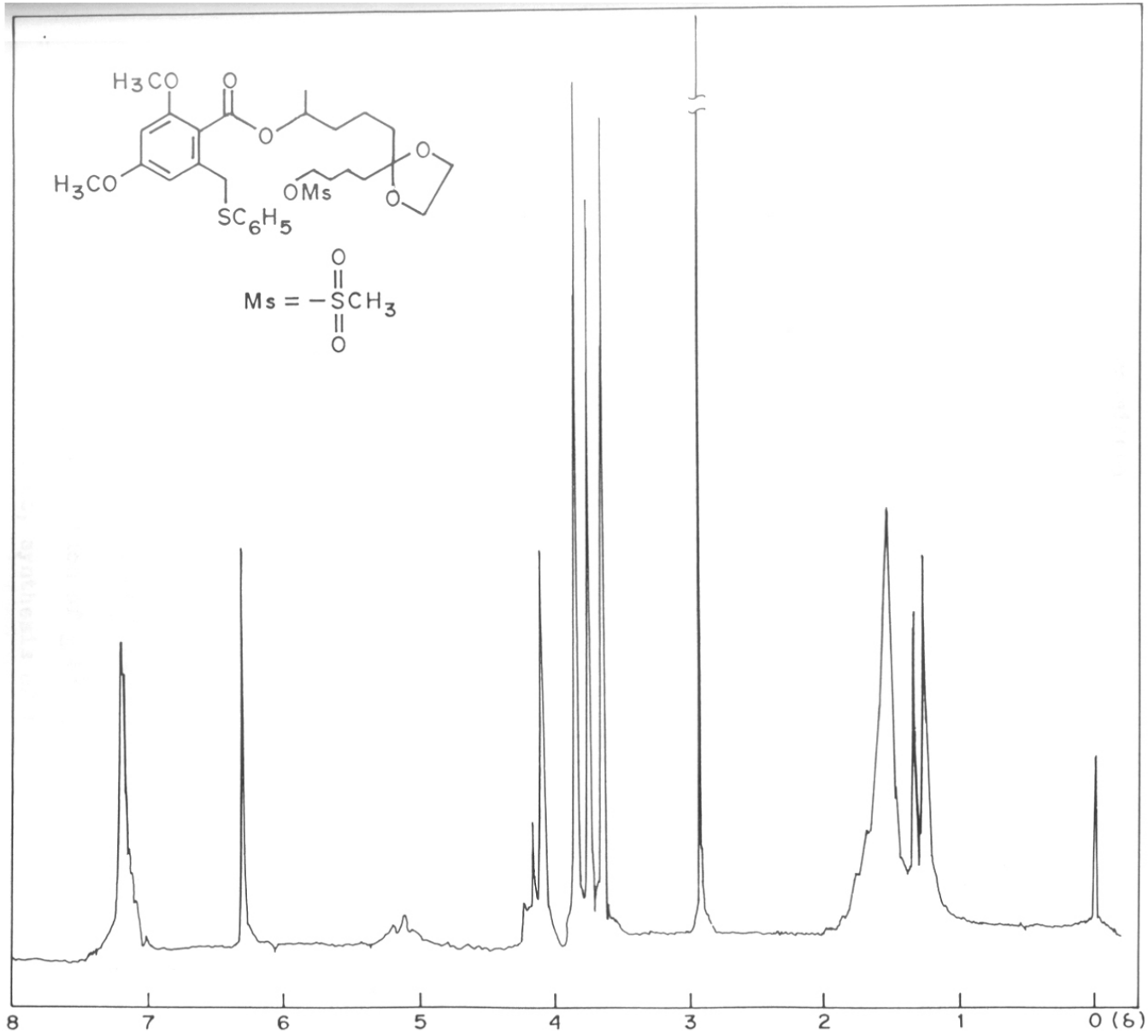


FIG. 9. ^{1}H-NMR SPECTRUM OF COMPOUND (30) IN $CDCl_3$

tion pattern consistent with the assigned structure for 30.

Conversion of the ketal (30) to the corresponding iodide (9) was achieved on reaction with sodiumiodide in acetone under neutral conditions (by using sodiumbicarbonate) in 78% yield. Compound (9) in its ^{1}H-NMR spectrum (Fig.10) in $CDCl_3$ showed a triplet at δ 3.12 for the $-C\underline{H}_2I$ group, while the remaining protons resonating at the expected chemical shifts. IR spectrum showed the ester carbonyl absorption at 1720 cm^{-1}. Analysis of the compound (9) confirmed the molecular formula $C_{28}H_{37}IO_6S$. Furthermore, mass spectrum showed the molecular ion peak at m/e 628, and the other fragment ion peak being at m/e 501 (m-127).

This key intermediate 9 obtained in a simple sequence of reactions, was earlier synthesised by Tsuji et al.[23,24] and successfully elaborated to (±)-zearalenone (1) (Scheme-6 and 7). Iodide (9) on intramolecular alkylation with potassium bis-trimethyl silylamide as base followed by the oxidation ($NaIO_4$) and elimination (heat in xylene) of the thiophenyl group afforded the lactone with trans double bond. Removal of the ketal and demethylation with standard reagents would result in (±)-zearalenone (1).

As further elaboration of 9 to (±)-zearalenone has already been established, synthesis of the key intermediate (9)

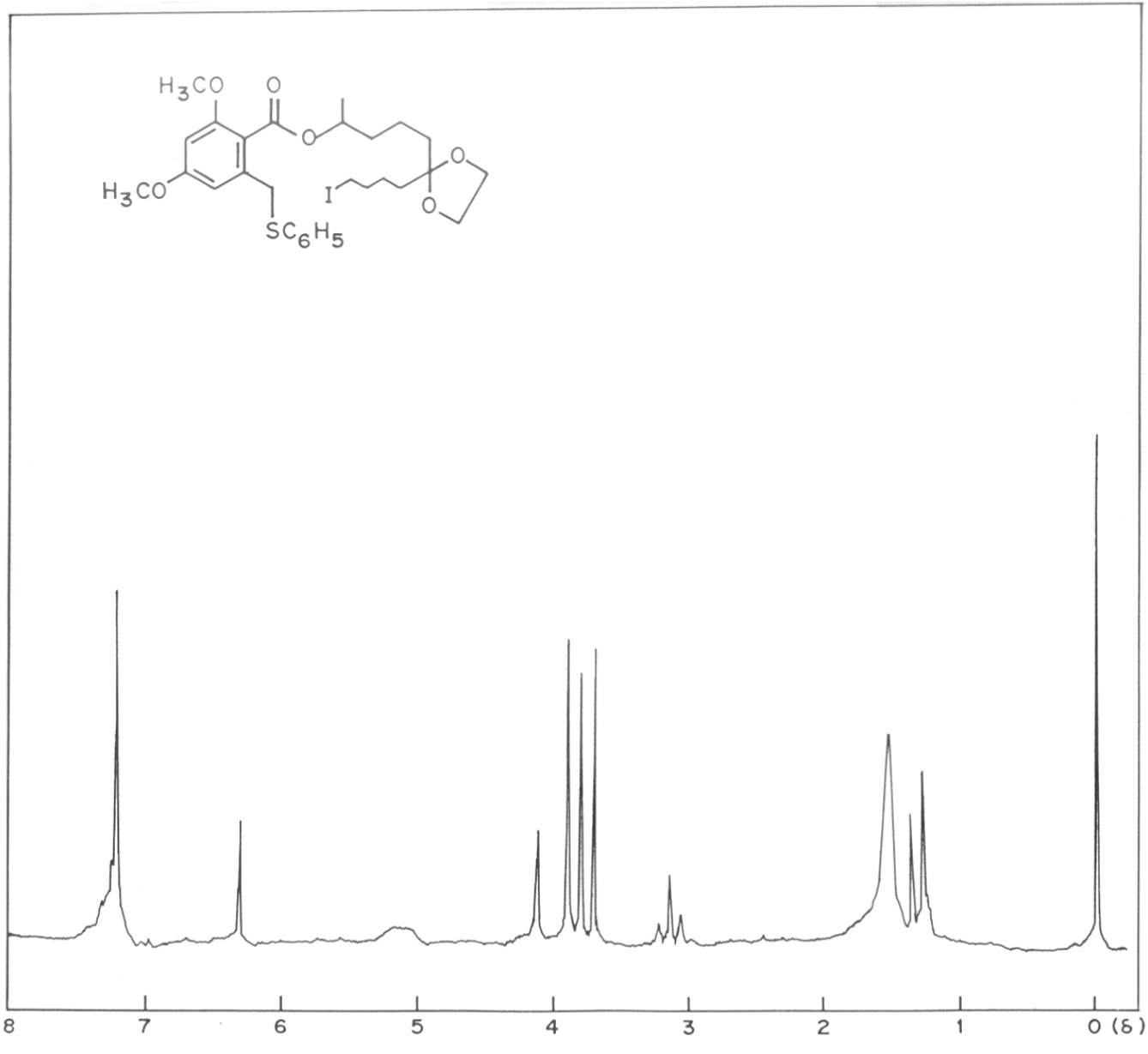


FIG. 10. ^{1}H-NMR SPECTRUM OF COMPOUND (9) IN $CDCl_3$

by the route described above by employing dithiane for the C-C bond formation would formally constitute the total synthesis of (±)-zearalenone (1).

GENERAL REMARKS

Melting points are uncorrected. IR spectra (ν_{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 Bruker WH-90 or Varian FT-80A in $CDCl_3$ or CCl_4 solutions containing TMS as an internal standard with chemical shifts (δ) 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.

All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 50°C.

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

5-Hydroxy pentanal (10):

A mixture of dihydropyran (10 g, 11.7 ml), water (30 ml) and conc. hydrochloric acid (3 ml) was stirred at room temperature until the solution became homogeneous. After 0.5 hr a few drops of phenolphthalein indicator was added and the mixture was neutralised with 20% aqueous sodium hydroxide. Aqueous solution was extracted with ether in cold and subjected to continuous extraction for 12 hr. The combined ethereal extract was dried (Na_2SO_4), evaporated and the residue was distilled under vacuum to afford 5-hydroxypentanal (10, 9 g, 74%) as a colourless viscous oil, b.p. 65-66°/9-10 mm (lit.[29] b.p. 62-66°/10 mm).

2-(4-Hydroxybutyl)-1,3-dithiane (11):

To a stirred solution of 10 (9.5 g, 93 m.mol) and 1,3-propanedithiol (10 g, 93 m.mol) in dry chloroform (40 ml) was added gradually BF_3-etherate (13.2 g, 93 m.mol) during 15 min. at room tempefature. After 7 hr, it was quenched with water and extracted with chloroform. The chloroform layer was successively washed with water, 5% aqueous potassium hydroxide, brine, dried (Na_2SO_4) and concentrated to give a syrupy residue. The residue thus obtained was chromatographed on silica gel (acetone-benzene 1:9) to afford 11 (14 g, 79%)

as a light yellow viscous oil. ^{1}H-NMR (CCl_4): δ 1.3 - 2.1 (m, 8H, 4X $-CH_2-$), 2.64 (s, 1H, -OH; D_2O exchangeable), 2.7 - 2.9 (m, 4H, 2X $-SCH_2-$), 3.57 (t, 2H, $-C\underline{H}_2OH$), 4.00 (t, 1H, $\underline{H}C<^{S}_{S}$); IR (Thin film): 915 cm^{-1} (dithiane) and 3200 cm^{-1} (-OH).

Analysis: Calculated for $C_8H_{16}OS_2$: C, 50.0; H, 8.3; S, 33.3;
Found: C, 49.8; H, 8.1; S, 33.0%.

2-(4-Tetrahydropyranyloxybutyl)-1,3-dithiane (11a):

A mixture of the hydroxy-dithiane (11, 0.960 g, 5 m.mol), dihydropyran (0.63 g, 7.5 m.mol) and p-toluene-sulfonic acid (0.050 g) in dichloromethane was stirred at room temperature for 6 hr. The reaction mixture was diluted with dichloromethane and washed with 5% aqueous sodium bicarbonate. The organic layer was dried (K_2CO_3), evaporated and the residue obtained was chromatographed (silica gel, benzene-pet.ether, 6:4) to afford the THP-derivative (11a, 1.10 g, 80%) as yellow liquid. ^{1}H-NMR (CCl_4): δ 1.2 - 2.1 (m, 14H, 7X $-CH_2-$), 2.6 - 2.9 (m, 4H, 2X $-SCH_2-$), 3.0 - 4.0 (m, 5H, 2X $-OCH_2-$ and $3^{o}\underline{H}$) 4.56 (s, 1H, $H-<^{O}_{O}$); IR: 918 cm^{-1} (dithiane); M^+ 276.

5-Bromopentane-2-one (12):

2-Acetyl-γ-butyrolactone (10 g, 78 m.mol) was added dropwise to a refluxing solution of 48% hydrobromic acid (25 ml)

in water (12 ml) in a flask surmounted with a Dean-Stark apparatus, and the product was collected during the course of reaction in the side arm. The reaction mixture was refluxed for an additional 3 hr. The yellow oily layer so obtained was taken into ether, washed with water and dried (Na_2SO_4). Evaporation of the solvent and distillation of the residue under reduced pressure afforded 5-bromopentane-2-one (12, 9.4 g, 74%) as a light yellow oil, b.p. 79°/21 mm (lit.[31] b.p. 79-81°/21 mm).

2-(3-Bromopropyl)-2-methyl-1,3-dioxolane (13):

5-Bromopentane-2-one (12, 13.5 g, 82 m.mol), ethylene glycol (15.25 g, 246 m.mol) and p-toluenesulfonic acid (0.135 g, 1%) in dry benzene (180 ml) were heated under reflux for 6 hr with the aid of a Dean-Stark water separator. The mixture was cooled, washed with 5% aqueous sodium bicarbonate and dried (K_2CO_3). The solvent was removed and the residue was distilled under reduced pressure to afford 13 (14 g, 81%) as a light yellow oil, b.p. 73°/4 mm (lit.[31], b.p.103-105°/20 mm).

2-(3-Iodopropyl)-2-methyl-1,3-dioxolane (14):

A mixture of 13 (2.8 g, 13.4 m.mol), sodium bicarbonate (3.372 g, 40.2 m.mol) and sodium iodide (4.016 g, 26.7 m.mol) in dry acetone (15 ml) was stirred at room temperature for 4 hr. Acetone was removed, the residue diluted with water and extracted with light petrol. The non-aqueous fraction

was washed with 5% aqueous sodium thiosulphate and filtered through a bed of anhydrous potassium carbonate. Evaporation of the solvent under reduced pressure afforded 14 (3.3 g, 96.5%) as a light yellow oil.

3-[(4-Hydroxybutyl)-1,3-dithian-2-yl]-1-(2-methyl-1,3-dixolan-2-yl)-propane (15):

To a stirred solution of the hydroxy-dithiane (11, 0.960 g, 5 m.mol) in dry THF (5 ml) at -15° was added dropwise n-BuLi (2 molar, 5.5 ml, 11 m.mol in hexane) during 10 min. After 4 hr at -15°, a freshly prepared ketal 14 (2.56 g, 10 m.mol) (reported above) in dry THF (10 ml) was introduced. It was then further stirred at -15° for 2 hr and at 0° for 12 hr. The reaction mixture was quenched with 5% aqueous sodium bicarbonate and extracted with chloroform. The chloroform layer was successively washed with 5% aqueous sodium bicarbonate, water dried (K_2CO_3) and evaporated to give a syrupy liquid. It was subjected to column chromatography on silica gel (acetone-light petrol, 1:9) to furnish two fractions 'A' and 'B'. Fraction 'A' was found to be o-alkylated product. Fraction 'B' containing the title compound (15, 0.78 g, 43%) was collected and concentrated to a colourless oil. ^{1}H-NMR (CCl_4): δ 1.21 (s, 3H, $-CH_3$), 1.3 - 2.0 (m, 14H, 7X $-CH_2-$), 2.5 - 2.8 (m, 4H, 2X $-SCH_2-$), 2.96 (s, 1H, -OH, D_2O exchangeable), 3.50(t, 2H, $-CH_2OH$),

3.83 (s, 4H, $-OCH_2CH_2O-$); IR (Thin film): 915 cm^{-1}, (dithiane), 3450 cm^{-1} (-OH); M^+ 320.

Analysis: Calculated for $C_{15}H_{28}O_3S_2$: C, 56.2; H, 8.75; S, 20.0; Found: C, 56.0; H, 8.75; S, 17.4%.

5-[(4-Hydroxybutyl)-1,3-dithian-2-yl]-pentan-2-one (16):

A methanolic solution of the compound (15, 0.8 g, 25 m.mol) and p-toluenesulfonic acid (0.030 g) was stirred at room temperature for 20 hr. Methanol was removed under reduced pressure and the residue was diluted with water, subsequently extracted with chloroform. The organic layer was washed with water and dried (Na_2SO_4). The solvent was evaporated to give a residue which was chromatographed on a silica gel column (acetone-benzene 0.5:9.5) to furnish 16 (0.560 g, 81%). ^{1}H-NMR (CCl_4): δ 1.2 - 1.9 (m, 12H, 6X $-CH_2-$), 2.05 (s, 3H, $-COCH_3$), 2.43 (t, 2H, $-COCH_2-$) 2.6 - 2.9 (m, 5H, 2X $-SCH_2-$ and -OH), 3.88 (t, 2H, $-CH_2OH$); IR (Thin film): 915 cm^{-1} (dithiane), 1720 cm^{-1} (ketonic carbonyl) and 3450 cm^{-1} (-OH); M^+ 276.

Analysis: Calculated for $C_{13}H_{24}O_2S_2$: C, 56.5; H, 8.7; S, 23.1; Found: C, 56.3; H, 8.2; S, 19.4%.

5-[(4-tetrahydropyranyloxybutyl)-1,3-dithian-2-yl]-pentan-2-one (17):

A mixture of the hydroxy-keto compound (16, 0.6 g,

2.17 m.mol), dihydropyran (0.53 g, 6.3 m.mol) and p-toluene-sulfonic acid (0.020 g) in dichloromethane (10 ml) was stirred at room temperature for 3 hr. It was diluted with dichloromethane (10 ml) and washed with 5% aqueous sodium bicarbonate and dried (K_2CO_3). The residue obtained after solvent removal was purified over a silica-gel column (acetone-light petrol 1:9) to yield 17 (0.70 g, 89%) as yellow oil. ^{1}H-NMR ($CDCl_3$): δ 1.3 - 1.8 (m, 18H, 9X $-CH_2-$), 2.10 (S, 3H, $-COCH_3$), 2.40 (t, 2H, $-COCH_2-$), 2.6 - 2.9 (m, 4H, 2X $-SCH_2$), 3.2 - 3.9 (m, 4H, 2X OCH_2-), 4.5 (S, 1H, H-<O); IR: 1725 cm^{-1} (carbonyl); M^+ 360.

Analysis: Calculated for $C_{18}H_{32}O_3S_2$: C, 60.0; H, 8.9; S, 17.8; Found: C, 60.5; H, 9.0; S, 17.0%.

5-[(4-tetrahydropyranyloxybutyl)-1,3-dithian-2-yl]-pentan-2-ol (7):

To a methanolic solution of the keto compound (17, 3.6 g, 10 m.mol), sodium borohydride (0.74 g, 20 m.mol) was added in two portions and stirred for 8 hr at room temperature. Excess of sodium borohydride was decomposed with water, methanol was removed, the residue was taken up in water and extracted with chloroform. The chloroform layer was washed with water and dried (K_2CO_3). Removal of the solvent and chromatographic purification of the resulting residue (silica gel, acetone-benzene 0.5 :9.5) gave 7 (3.00 g,

82%) as a thick colourless oil. ^{1}H-NMR (CCl_4): δ 1.16 (d, 3H, $-CH_3$), 1.2 - 2.1 (br.m, 20H, 10X $-CH_2-$), 2.6 - 2.8 (m, 4H, 2X $-SCH_2-$), 3.2 - 4.0 (m, 4H, 2X $-OCH_2-$), 4.5 (s, 1H, H- ); IR: 3450 cm^{-1} (OH): M^+ 362.

Analysis: Calculated for $C_{18}H_{34}O_3S_2$: C, 59.6; H, 9.4; S, 17.6; Found: C, 60.2; H, 9.4; S, 17.8%.

2,4-Dihydroxy-6-methyl benzaldehyde (18):

A mixture of orcinol (10 g, 80 m.mol) and zinc cyanide (14 g, 120 m.mol) was taken in dry ether (150 ml). Dry HCl gas was rapidly bubbled through the solution for 3 hr. The supernatant ether layer was decanted and the solid imine complex was repeatedly washed with ether. The solid complex was then digested with water on steambath for 0.5 hr, filtered, washed with water and dried to afford 18 (9.8 g, 80%) as a pale brown solid. Crystallisation from hot water afforded a pale brown crystalline product, m.p. 178° (lit.[32b] m.p. 181-2°).

2,4-Dimethoxy-6-methylbenzaldehyde (19):

Orcinol aldehyde (18, 7.6 g, 50 m.mol), dimethyl sulfate (18.9 g, 150 m.mol) and potassium carbonate (40 g) in dry acetone (80 ml) were heated under reflux for 6 hr. Acetone was removed and cold water was introduced, whereby a solid separated. The separated solid was filtered, washed with water and dried to obtain 19 (7.65 g, 85%), m.p. 62°

(lit.[33a] m.p.64-5°).

2,4-Dimethoxy-6-methyl benzoic acid (20):

To a stirred solution of the aldehyde (19, 7 g, 39 m.mol) in acetone (40 ml) was added 5% aqueous potassium permanganate (500 ml) dropwise at 40-50° during a period of 30 min. After the addition was complete, the reaction mixture was stirred at room temperature for an additional 3 hr. It was filtered and the residue was thoroughly washed with water. The filtrate was concentrated to half its volume, cooled and acidified with conc. hydrochloric acid. The resulting white solid was collected and dried to furnish the acid (20, 4.8 g, 63%), m.p. 140° (lit.[33b] m.p. 142-3°).

Methyl 2,4-dimethoxy-6-methylbenzoate (21):

The acid (20, 4 g, 20 m.mol), dimethyl sulfate (3.8 g, 30 m.mol) and potassium carbonate (30 g) in dry acetone (40 ml) were heated under reflux for 4 hr. Acetone was removed, the resulting residue was diluted with water and extracted with chloroform. The organic layer was washed with water, dried (Na_2SO_4) and evaporated to give the ester (21, 3.42 g, 80%) as a low melting solid, m.p. 40-41° (lit.[35] m.p. 42-43°).

Methyl 2,4-dimethoxy-6[(phenylthio)methyl]-benzoate (8):

The ester (21, 1.05 g, 5 m.mol) in THF (5 ml) was added to a stirred solution of lithium diisopropylamide

[LDA, 5 m.mol: prepared from n-BuLi (0.32 g, 5 m.mol) and diisopropylamine (0.505 g, 5 m.mol)] at -78° under nitrogen. The resulting red solution was introduced dropwise into a solution of diphenyldisulfide (1.09 g, 5 m.mol) in dry THF (20 ml) at -78°. After 10 min. it was quenched with 5% hydrochloric acid (10 ml) and ether (10 ml) at 0°. The two layers were separated followed by repeated extraction of aqueous phase with ether. The combined ethereal layer was washed with water, 5% aqueous sodium hydroxide and water. It was dried (Na_2SO_4) and evaporated to a residue, which was purified by chromatography (silica gel, acetone-light petrol 0.5:9.5) to yield 8 (1 g, 63%) as an oil.

2,4-Dimethoxy-6-[(phenylthio)methyl]-benzoic acid (22):

The benzoate (8, 4.6 g, 15 m.mol) and potassium hydroxide (1.24 g, 22 m.mol) in ethanol (50 ml) was boiled for 4 hr. Ethanol was evaporated and the residue was treated with water. The aqueous solution was extracted with ether and then neutralised with conc. hydrochloric acid at 0° to afford a solid which was filtered, washed with water, dried and crystallised from acetone to get the acid (22, 2.85 g, 63%).

4-[2-(4-Tetrahydropyranyloxybutyl)-1,3-dithian-2-yl]-1-methyl-butyl 2,4-dimethoxy-6-[(phenylthio)methyl]-benzoate (23):

(A) A mixture of the acid(22, 0.286 g, 0.94 m.mol) and

thionyl chloride (0.5 ml, 6.9 m.mol) was heated under reflux in dry benzene (5 ml) for 6 hr. Solvent (3 x 10 ml) was added, codistilled to remove last traces of thionyl chloride and dried to obtain the corresponding acid chloride (0.280 g), which was used without further purification in the later step. IR (Neat): 1790 cm^{-1}.

(B) To the alcohol (7, 0.333 g, 0.92 m.mol) in dichloromethane (5 ml) containing pyridine (0.148 g, 1.87 m.mol) was added dropwise a solution of the above acid chloride (0.280 g) in dichloromethane (5 ml) during 10 min at room temperature. The reaction mixture was allowed to stir overnight and then quenched with 5% aqueous sodium bicarbonate. The aqueous layer was extracted with ether, dried (K_2CO_3) and concentrated. The resulting residue was purified over a short column of silica gel (acetone-benzene 1:9) to give the ester (23, 0.360 g, 59%) as a thick gummy material. ^{1}H-NMR ($CDCl_3$): δ 1.30 (d, 3H, $-CH_3$), 1.4 - 2.0 (m, 20H, 10X $-CH_2-$), 2.6 - 2.9 (m, 4H, 2X $-SCH_2-$), 3.2 - 3.8 (m, 4H, 2X OCH_2-), 3.68 (s, 3H, $-OCH_3$), 3.71 (s, 3H, $-OCH_3$), 4.09 (s, 2H, $-\underline{CH_2}$Ph), 4.50 (br.s, 1H, $\underline{H}-<^{O}_{O}$), 5.0 - 5.3 (m, 1H, $3^{o}H$), 6.28 (s, 2H, Ar-$\underline{H}$), 7.0 - 7.2 (m, 5H, $S-C_6\underline{H}_5$). IR: 1720 cm^{-1} (ester carbonyl); M^+ 648.

Analysis: Calculated for $C_{34}H_{48}O_6S_3$: C, 62.9; H, 7.4; S, 14.8; Found: C, 62.4; H, 7.3; S, 11.2%.

4-[2-(4-Hydroxybutyl)-1,3-dithian-2-yl]-1-methyl-butyl 2,4-dimethoxy-6-[(phenylthio)methyl]benzoate (24):

A methanolic solution of the THP-ester (23, 0.860 g, 1.32 m.mol) containing p-toluenesulfonic acid (0.080 g, 0.5 m.mol) was stirred at room temperature. After 6 hr, methanol was removed under reduced pressure. The residue was treated with water and extracted with dichloromethane. The organic layer was washed with 5% aqueous sodium bicarbonate, water and dried (Na_2SO_4). Evaporation of the solvent and chromatographic purification of the residue over a column of silica gel (acetone-benzene 5:95) afforded the hydroxy-ester (24, 0.550 g, 74%) as a thick gummy material. ^{1}H-NMR ($CDCl_3$): δ 1.23 (d, 3H, $-CH_3$), 1.3 - 2.0 (m, 14H, 7X $-CH_2-$), 2.6 - 2.9 (m, 5H, 2X $-SCH_2-$ and $-O\underline{H}$), 3.60 (t, 2H, $-C\underline{H}_2OH$), 3.70 (s, 3H, $-OCH_3$), 3.80 (s, 3H, $-OCH_3$), 4.10 (s, 2H, $-C\underline{H}_2SPh$), 5.0 - 5.3 (m, 1H, 3^oH), 6.3 (s, 2H, Ar-H), 7.1 - 7.3 (m, 5H, $S-C_6\underline{H}_5$); IR: 1720 cm^{-1} (ester carbonyl) and 3450 cm^{-1} (-OH); M^+ 564.

Analysis: Calculated for $C_{29}H_{40}O_5S_3$: C, 61.7; H, 7.1; S, 17.0; Found: C, 61.3; H, 6.95; S, 13.2%.

4-[2-(4-Methanesulfonyloxybutyl)-1,3-dithiane-2-yl]-1-methyl-butyl 2,4-dimethoxy-6-[(phenylthio)methyl]benzoate(25):

To the hydroxy-ester (24, 0.564 g, 1 m.mol) and triethylamine (0.303 g, 3 m.mol) in dry dichloromethane (10 ml)

was added gradually, methanesulfonyl chloride (0.228 g, 2 m.mol) in dichloromethane (5 ml), in 5 min. at 0°. The contents were then stirred at room temperature for 2 hr. The reaction mixture was decomposed with water and the aqueous layer was extracted with dichloromethane. The combined dichloromethane layer was washed with water, dried (Na_2SO_4) and concentrated to give the required mesylate (25, 0.560 g, 87%) as a dark brown material, which was used without any purification. ^{1}H-NMR ($CDCl_3$): δ 1.31 (d, 3H, $-CH_3$), 1.5 - 2.1 (m, 14H, 7X $-CH_2-$), 2.5 - 2.8 (m, 4H, 2X SCH_2-), 2.96 (s, 3H, $-SO_2CH_3$), 3.60 (s, 3H, $-OCH_3$), 3.73 (s, 3H, $-OCH_3$), 4.09 (t, 2H, $-CH_2SO_3-$), 4.18 (s, 2H, $-CH_2SPh$), 4.8 - 5.2 (m, 1H, 3°H), 6.5 (s, 2H, Ar-H), 6.9 - 7.2 (m, 5H, SPh).

9-Methanesulfonyloxy-1-methyl-5-oxo-nonyl 2,4-dimethoxy-6-[(phenylthio)methyl]benzoate (28):

The mesylate-ester (25, 0.5 g, 0.78 m.mol), mercuric chloride (0.462 g, 1.71 m.mol) and mercuric oxide (0.184 g, 0.85 m.mol) were heated under reflux in 80% aqueous acetonitrile (10 ml) for 1 hr. The reaction mixture was filtered through celite and washed thoroughly with chloroform. The organic layer was washed thoroughly with 5% aqueous ammonium acetate, dried (Na_2SO_4) and the solvent evaporated. The resulting residue was subjected to chromatographic purification (silica gel, acetone-benzene 1:9) to afford two fractions

'A' and 'B'. Fraction 'A' was identified as the mesylate-ketone (28, 0.177 g, 41%), on the basis of its spectral data. ^{1}H-NMR ($CDCl_3$): δ 1.33 (d, 3H, $-CH_3$), 1.5 - 1.8 (m, 8H, 4X $-CH_2-$), 2.2 - 2.5 (m, 4H, $-CH_2COCH_2-$), 2.93 (s, 3H, $-SO_2CH_3$), 3.66 (s, 3H, $-OCH_3$), 3.76 (s, 3H, $-OCH_3$), 4.1 - 4.3 (m, 4H, $-CH_2SPh$ and $-SO_2CH_2-$), 4.8 - 5.3 (m, 1H, 3^{o}H), 6.26 (s, 2H, Ar-H), 7.0 - 7.2 (m, 5H, $S-C_6H_5$); IR: 1720 cm^{-1} (broad). M^+ 446 (m-96).

Analysis: Calculated for $C_{27}H_{36}O_8S_2$: C, 58.6; H, 6.5; S, 11.5; Found: C, 58.8; H, 6.5; S, 12.0%.

Fraction 'B' gave a compound (0.142 g) which was identified as 9-hydroxy-1-methyl-5-oxo-nonyl 2,4-dimethoxy-6-[(phenyl-thio)-methyl]-benzoate (29). ^{1}H-NMR ($CDCl_3$): δ 1.21 (d, 3H, $-CH_3$), 1.3 - 1.5 (m, 8H, 4X $-CH_2-$), 2.0 - 2.3 (m, 4H, $-CH_2COCH_2-$), 2.5 - 2.8 (br.s, 1H, -OH), 3.3 (t, 2H, $-CH_2OH$), 3.42 (s, 3H, $-OCH_3$), 3.54 (s, 3H, $-OCH_3$), 3.81 (s, 2H, $-SCH_2Ph$), 4.5 - 5.0 (m, 1H, 3^{o}H), 6.00 (s, 2H, Ar-H), 6.5 - 7.0 (m, 5H, $S-C_6H_5$); IR: 1720 cm^{-1} (carbonyl) and 3450 cm^{-1} (OH).

Compound (29) was also converted to the mesylate-ketone (28) by following the conventional procedure as described below.

Thus, compound (29, 0.142 g, 0.3 m.mol) was treated with triethylamine (0.909 g, 0.6 m.mol) and methanesulfonyl

chloride (0.684 g, 0.6 m.mol) in dichloromethane to afford compound (28) quantitatively, which was identical in all respects with 28 obtained in Fraction 'A'.

4-[2-(4-Methanesulfonyloxybutyl)-1,3-dioxolan-2-yl]-1-methyl-butyl 2,4-dimethoxy-6[(phenylthio)methyl]benzoate (30):

The keto compound (28, 0.160 g, 0.29 m.mol), ethyleneglycol (0.06 g, 0.87 m.mol) and catalytic amounts of p-toluene sulfonic acid in dry benzene (20 ml) were heated under reflux for 6 hr. The mixture was cooled, washed with 5% aqueous sodium bicarbonate, dried (K_2CO_3) and evaporated to afford the mesylate-ketal (30, 0.160 g, 94%) as a thick gummy material. ^{1}H-NMR ($CDCl_3$): δ 1.34 (d, 3H, $-CH_3$), 1.4 - 1.8 (m, 12H, 6X $-CH_2-$), 2.94 (s, 3H, $-SO_2\underline{CH_3}$), 3.65 (s, 3H, $-OCH_3$), 3.75 (s, 3H, $-OCH_3$), 3.86 (s, 4H, $-OCH_2\underline{CH_2}O-$), 4.0 - 4.2 (m, 4H, $-\underline{CH_2}SPh$ and $-\underline{CH_2}OSO_2-$), 4.8 - 5.3 (m, 1H, 3^oH) 6.2[illegible](s, 2H, Ar-H), 7.0 - 7.2 (m, 5H, $S-C_6\underline{H_5}$); IR: 1720 cm^{-1} (carbonyl). M^+ 596.

Analysis: Calculated for $C_{29}H_{40}O_9S_2$: C, 58.4; H, 6.7; S, 10.7; Found: C, 58.6; H, 7.0; S, 10.4%.

4-[2-(4-Iodobutyl)-1,3-dioxolan-2-yl]-1-methyl-butyl 2,4-dimethoxy-6-[(phenylthio)methyl]benzoate (9):

A mixture of the mesylate-ketal (30, 0.150 g, 0.25 m.mol) sodium iodide (0.075 g, 0.50 m.mol) and sodium bicarbonate (0.063 g, 0.75 m.mol) in dry acetone (5 ml) was stirred at room temperature for 24 hr. Acetone was evaporated, the

residue treated with water and extracted with chloroform. The chloroform layer was washed with brine, dried (K_2CO_3) and evaporated to give the iodide (9, 0.123 g, 78%) as a thick gummy material. ^{1}H-NMR ($CDCl_3$): δ 1.31 (d, 3H, $-CH_3$); 1.4 - 1.6 (m, 12H, 6X $-CH_2-$), 3.12 (t, 2H, $-CH_2I$), 3.68 (s, 3H, $-OCH_3$), 3.75 (s, 3H, $-OCH_3$), 3.81 (s, 4H, $-OCH_2CH_2O-$), 4.10 (s, 2H, $-CH_2SPh$), 4.9 - 5.2 (m, 1H, 3^oH), 6.25 (s, 2H, ArH), 7.0 - 7.3 (m, 5H, $S-C_6H_5$); IR: 1720 cm^{-1} (carbonyl); M^+ 628.

Analysis: Calculated for $C_{28}H_{37}O_6SI$: C, 53.5; H, 5.9; S, 5.0; Found: C, 53.1; H, 6.2; S, 5.7%.

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CHAPTER - II

SYNTHESIS OF (±) RECIFEIOLIDE

INTRODUCTION

The macrolide[1] 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[2,3,4]. These landmark 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 (1) is a naturally occurring 12-membered ring macrolide isolated from the fungus Cephalosporium recifei which grows on malt glucose medium[5]. Vesonder et al.[5]

have assigned the structure of recifeiolide on 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 many well known schools throughout the world and several syntheses have been reported. All the earlier syntheses have been reviewed briefly because detailed studies is beyond the scope of this thesis. In general the construction of carbon skeleton of recifeiolide followed the methods given below.

a) by employing acetylenic precursors

b) by Wittig reaction

c) by utilisation of sulphur stabilised carbanions and d) miscellaneous.

The first total synthesis of recifeiolide as racemate was reported by Corey et al.[6] in 1976. This stereoselective synthesis featured the use of an acetylenic precursor for the creation of trans double bond, besides the double activation method for the final lactonisation (Scheme-1). The THP-protected acetylenic alcohol (3) was

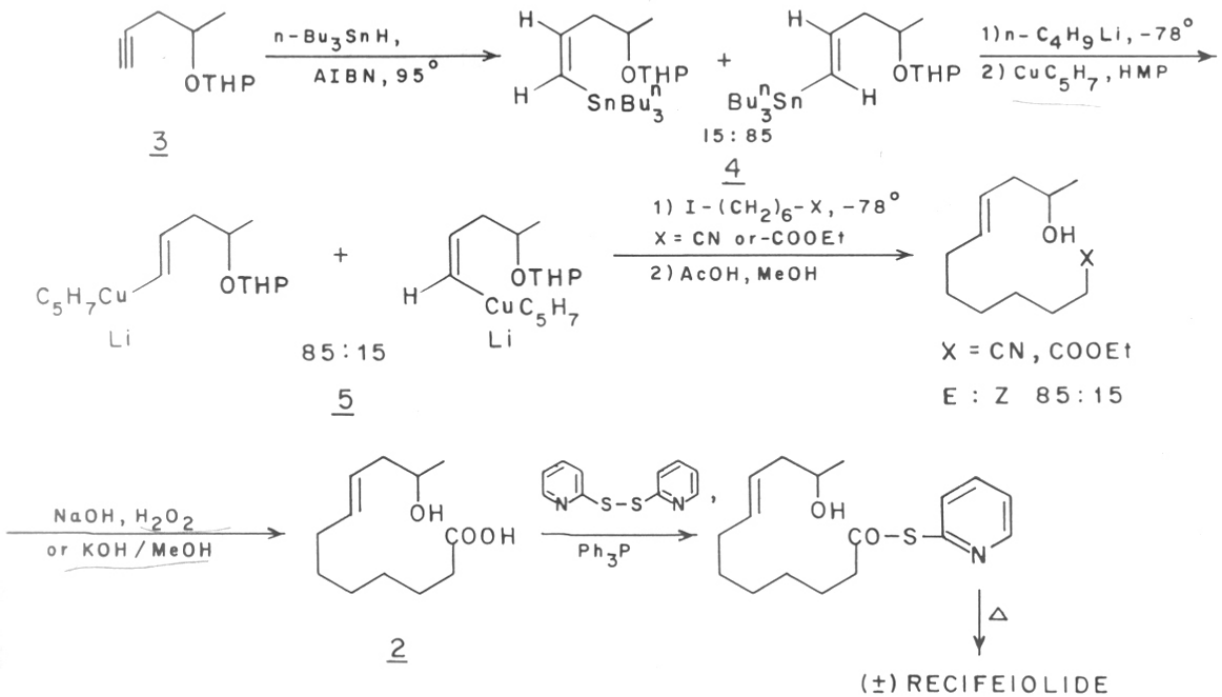
converted to the cuprate (5) *via* a vinyl stannane (4) (E-Z 85:15). The cuprate (5) was transformed into the hydroxy acid (2), which in turn was lactonised to (±)-recifeiolide (1).

The second total synthesis of recifeiolide was due to Gerlach *et al*.[7] in which the 12-membered lactone was prepared in its optically pure form (Scheme-2), starting from (R)-1,3-butanediol (obtained by inversion). The strategy involved in the synthesis was the condensation of the phosphonium salt (7) (a C-4 segment) and the aldehyde (8) (a C-8 segment) to give rise to the hydroxy acid (2). 7 was prepared from (R)-1,3-butanediol through 6, whereas the aldehyde segment 8 was made from 1-methoxy-cyclooctene by ozonolysis. The E-Z isomeric mixture of Wittig product was subjected to photoisomerisation (to E isomer). The E isomer was lactonised with silverperchlorate *via* the thiol ester to (R)-recifeiolide.

Utimoto *et al*.[8] have reported the total synthesis of (R)-recifeiolide in 1977. In this synthesis they have adopted (R)-methyloxirane as the source of chiral centre (Scheme-3). It featured a stereoselective alkenylation of the acetylenic compound via hydroalumination to give the lithium vinylalanate (9). 9 with (R)-methyloxirane gave the basic skeleton (10) with properly substituted

SCHEME-1

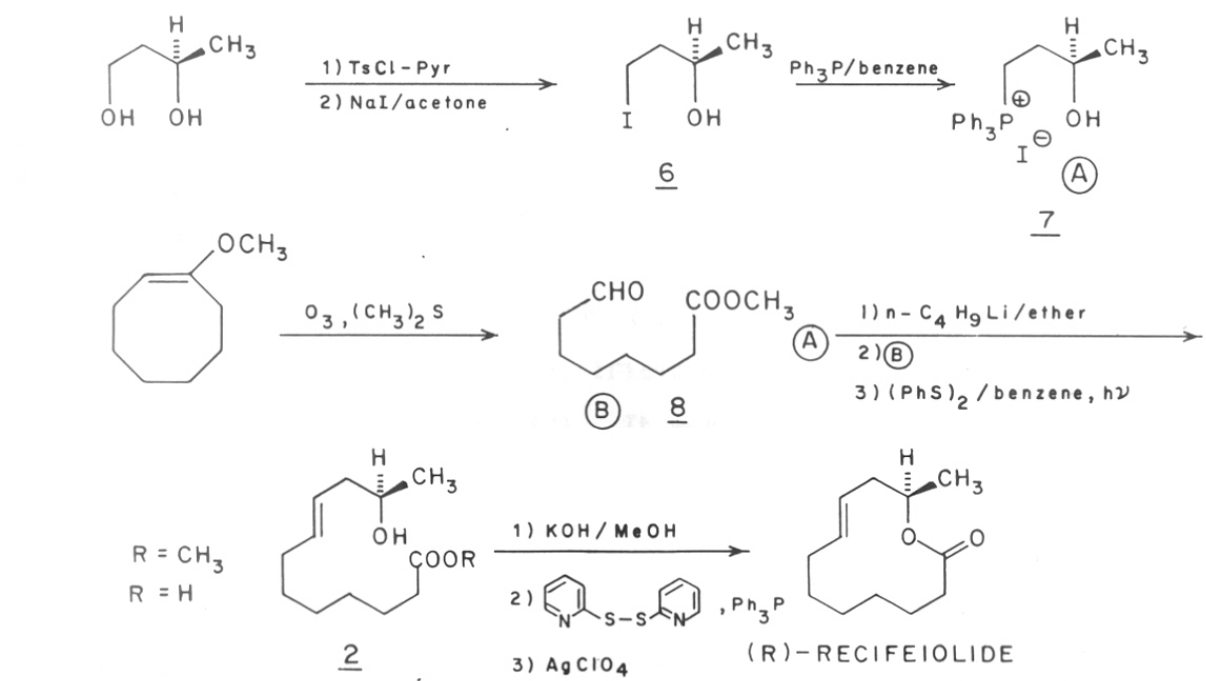
Corey et al (1976)



3 4 5 2

SCHEME-2

Gerlach et al (1976)



6 7 8 2

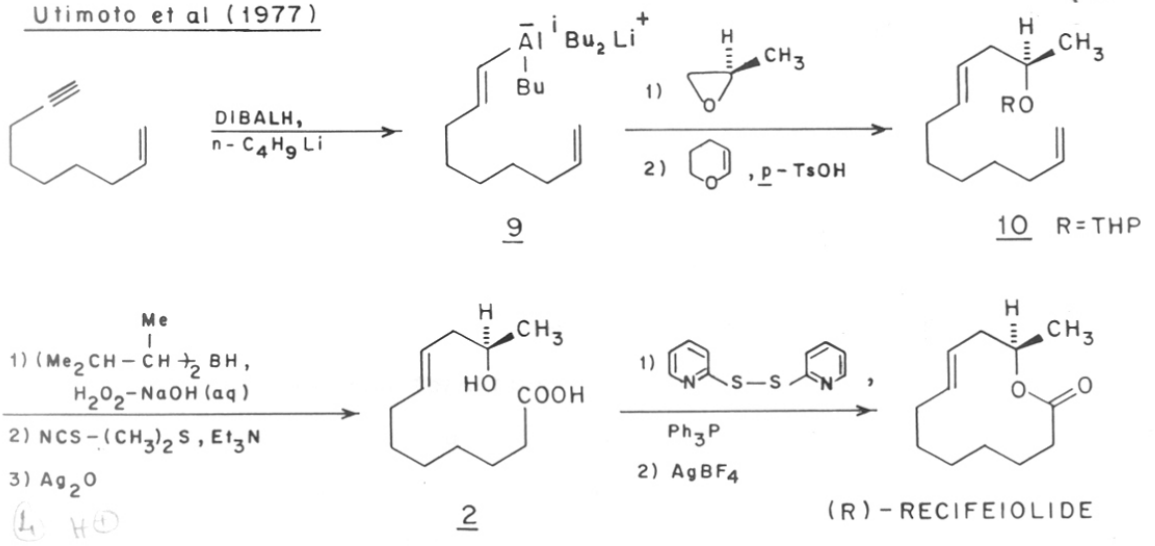
functionalities. It was transformed into the hydroxy acid (2) and subjected to lactonisation by Gerlach[7] method, employing $AgBF_4$ to result (R)-recifeiolide.

Mukaiyama et al.[9] (1977) have reported a total synthesis of (±)recifeiolide (Scheme-4) which featured a new and different lactonisation method developed by his group earlier[4]. This synthesis also utilised an easily available acetylenic alcohol. After the construction of the acid (11), unlike the other two syntheses of Corey and Utimoto, the acetylenic triple bond was transformed into trans double bond with metal-ammonia reduction, to give the hydroxy acid (2). Final lactonisation to (±)-recifeiolide was effected by the utilisation of 1-methyl-2-chloropyridinium iodide.

Tsuji and coworkers[10] have utilised a new synthetic strategy for the construction of hydroxy acid carbon skeleton. This synthesis (Scheme-5) featured a palladium catalysed telomerisation of butadiene with nitroethane to a stereoselective synthesis of hydroxy acid (2). The reaction of butadiene with nitroethane in presence of palladium acetate and triphenyl phosphine gave nitrodiene (12), which on further modifications was transformed into the hydroxy acid (2). It was cyclized to (±)-recifeiolide by adopting Corey's double activation method[2].

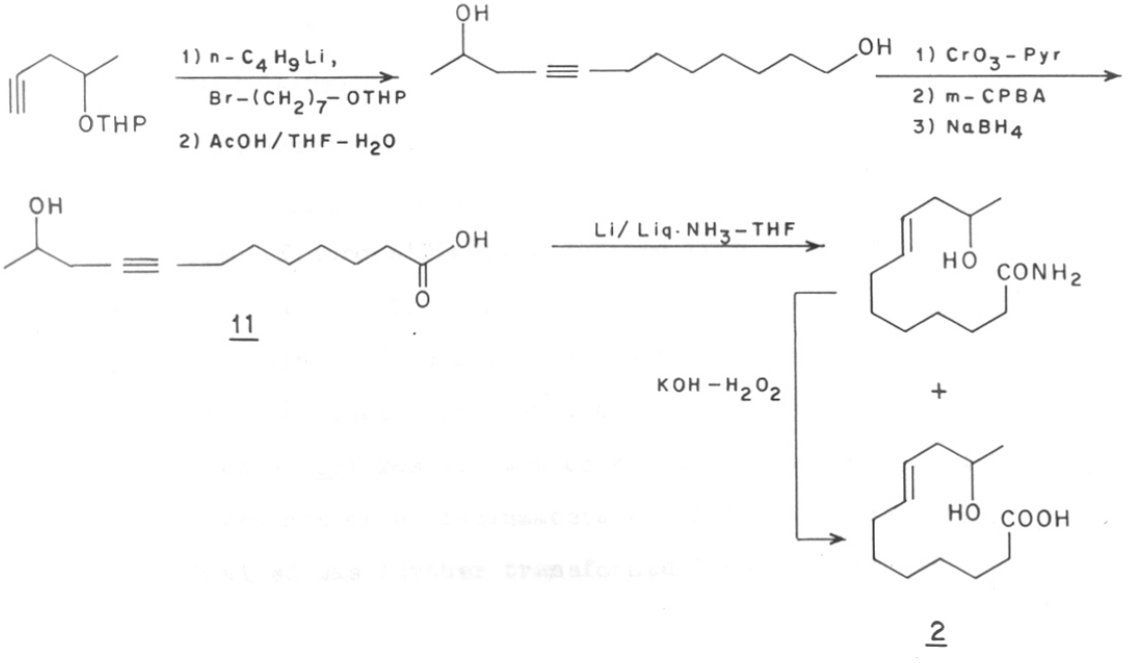
SCHEME-3

Utimoto et al (1977)



SCHEME-4

Mukaiyama et al (1977)

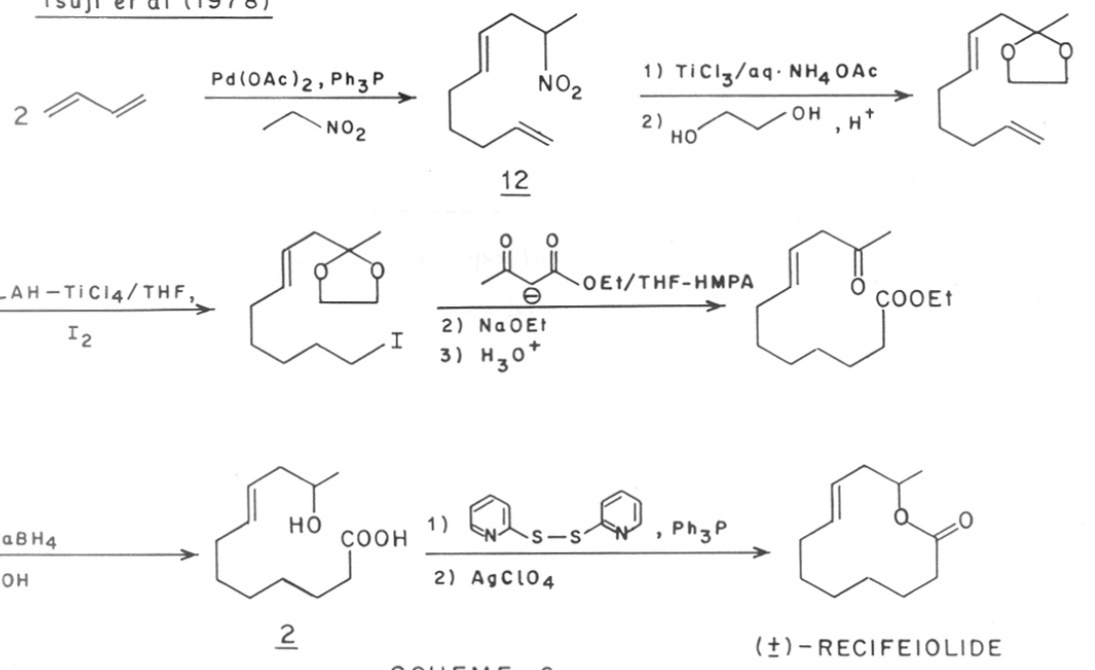


All the syntheses discussed above involved the conventional internal lactonisation of ω-hydroxy acids by different reagents. Tsuji et al.[11] (1978) have differed this approach and built the macrocyclic lactones, involving C-C bond formation based on intramolecular alkylation of carbonium ion generated on ω-halophenylthio-acetates (Scheme-6). The key intermediate (12) obtained by butadiene telomerisation in the earlier method (Scheme-5) was transformed into a ω-iodophenylthioacetate (13) which on intramolecular alkylation with potassium bis-trimethylsilylamide provided the cyclised product (14). 14 on reduction of the thiophenyl group afforded (±)-recifeiolide.

Synthesis of (±)-recifeiolide (Scheme-7) developed by Kumada et al.[12] featured C-C bond formation of alkenylpentafluoro silicates, derived from terminal acetylenes, with allyl halides under the influence of palladium salts. This provides the transformation of terminal acetylenes into stereoselective 1,4-dienes. Thus, the silicate (15) was allowed to react with allylchloride in the presence of palladiumacetate. The 1,4-diene (16) thus obtained was further transformed into the hydroxy acid (2).

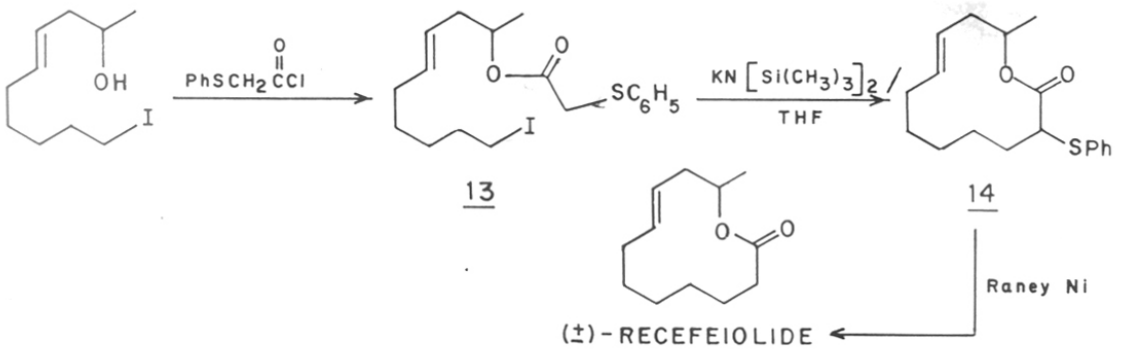
SCHEME-5

Tsuji et al (1978)



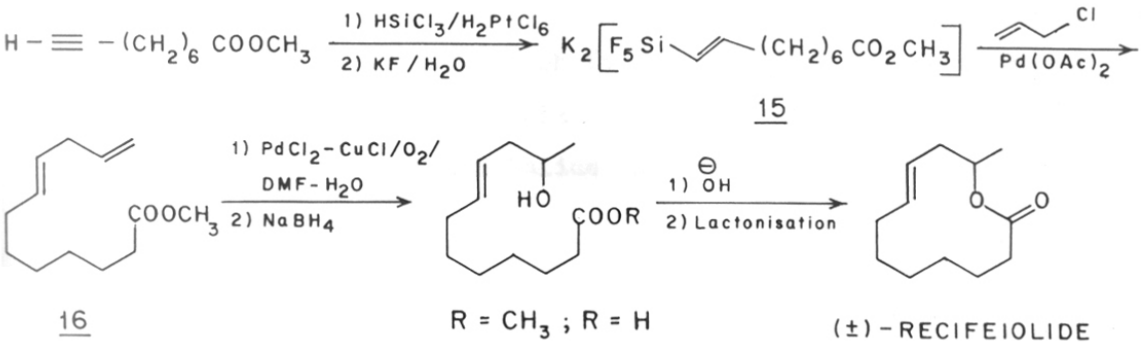
SCHEME-6

Tsuji et al (1978)



SCHEME-7

Kumada et al (1978)



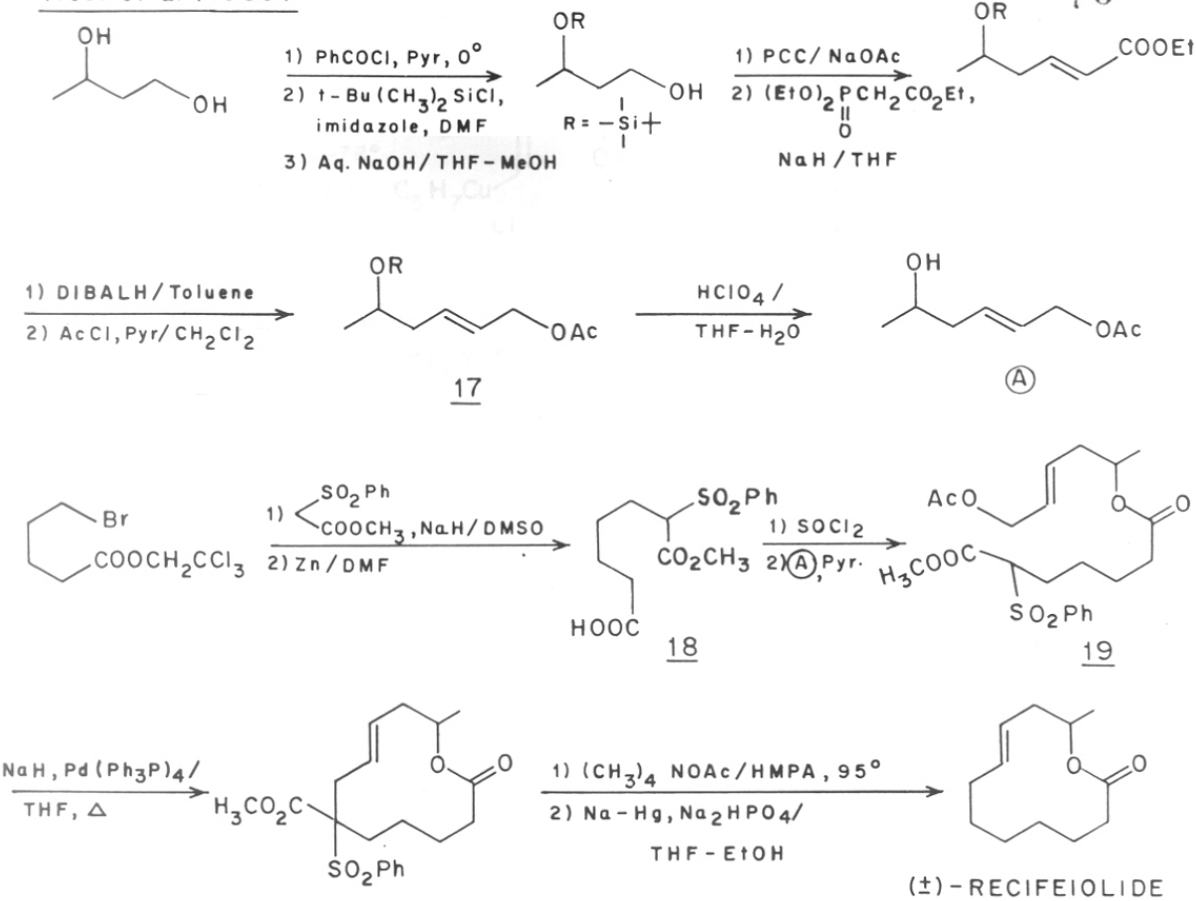
Trost and Verhoeven[13] have reported a different approach for the synthesis of (±)-recifeiolide in 1978, by making use of organo-palladium chemistry. This synthesis (Scheme-8) featured a C-C bond fusion for the lactone formation rather than the conventional lactonisation route. In this method the two segments 17 and 18 were condensed first to the ester 19, which was subjected to the palladium catalysed cyclisation to afford 20, which in turn transformed into (±)-recifeiolide.

Schreiber[14] (1980) developed a synthetic sequence to (±)-recifeiolide (Scheme-9) which featured the generation and usefulness of α-alkoxyhydroperoxides and their fragmentation under the influence of metal catalysis. Thus, the reaction of 21 with propylene oxide in presence of trimethylaluminium gave the keto-alcohol (22). The hydroperoxide (23), obtained from 22 was subsequently treated with ferrous sulphate and copper acetate, to result (±)-recifeiolide.

The synthesis of (±)-recifeiolide reported by Wassermann et al.[15] utilised the substituted oxazoles, where the masked carbonyl function as oxazole was generated under mild conditions of photooxygenation to afford reactive triamides (Scheme-10). Alkylation of 2-alkyl substituted oxazoles (25) with the halide (24) (obtained by Corey[6]

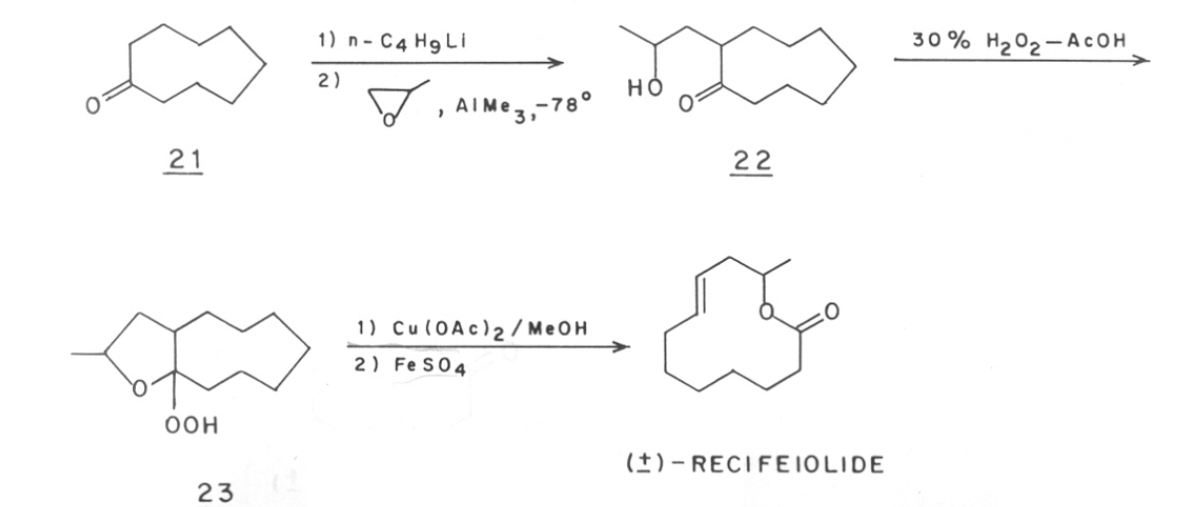
SCHEME - 8

Trost et al (1980)



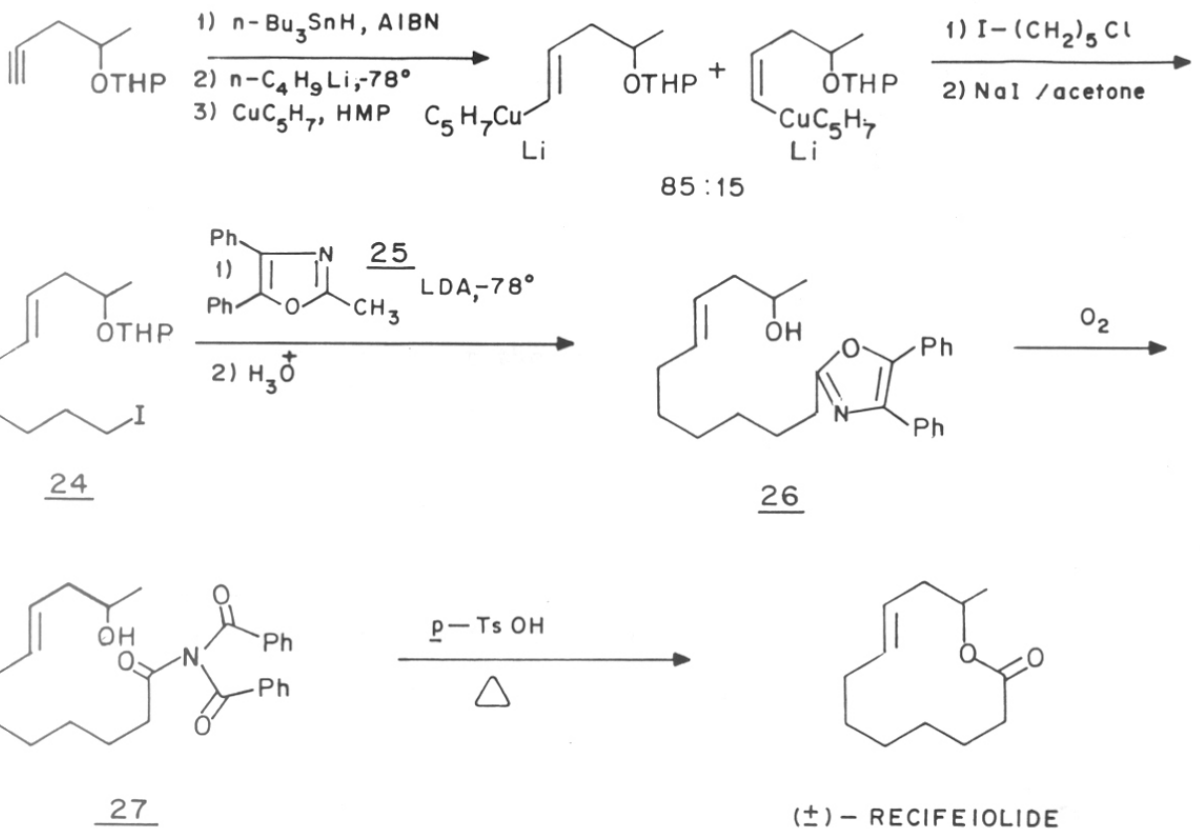
SCHEME - 9

Schreiber (1980)



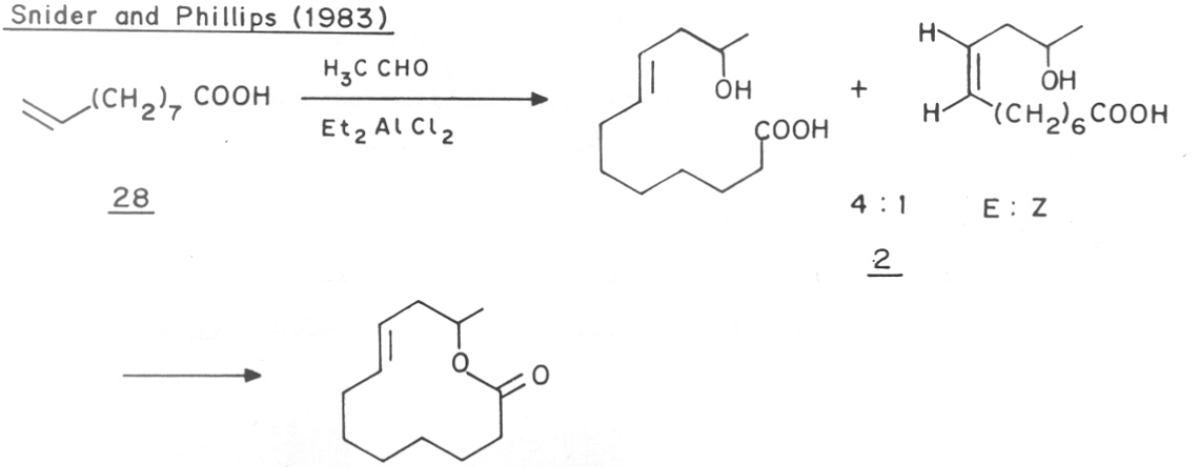
SCHEME – 10

Wasserman et al (1981)



SCHEME – 11

Snider and Phillips (1983)



method) afforded 26, which was photooxygenated to the triamide 27 and finally transformed into (±)-recifeiolide.

Snider and Phillips[16] (1983) developed a general synthetic approach for the preparation of homoallylic alcohols by the ene reaction of aldehydes with non-nucleophilic alkenes, under the influence of ethyl aluminium dichloride. Adopting the above strategy, hydroxy acid (2) was prepared (Scheme-11) from the reaction of 28 with acetaldehyde catalysed by ethyl aluminium dichloride.

PRESENT WORK

Recifeiolide (1) is a naturally occurring 12-membered ring lactone, isolated from Cephalosporium racifei. 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 of ring closure. Most of the syntheses adopted the conventional internal lactonisation methods. Various methods have been developed for macrolactonisations such as Corey-Nicolaou double activation method[2], Masamune[3] and Mukaiyama[4] methods etc.

The main structural features present in the synthesis of recifeiolide are the stereoselective introduction of trans double bond and fixation of chiral centre. The best

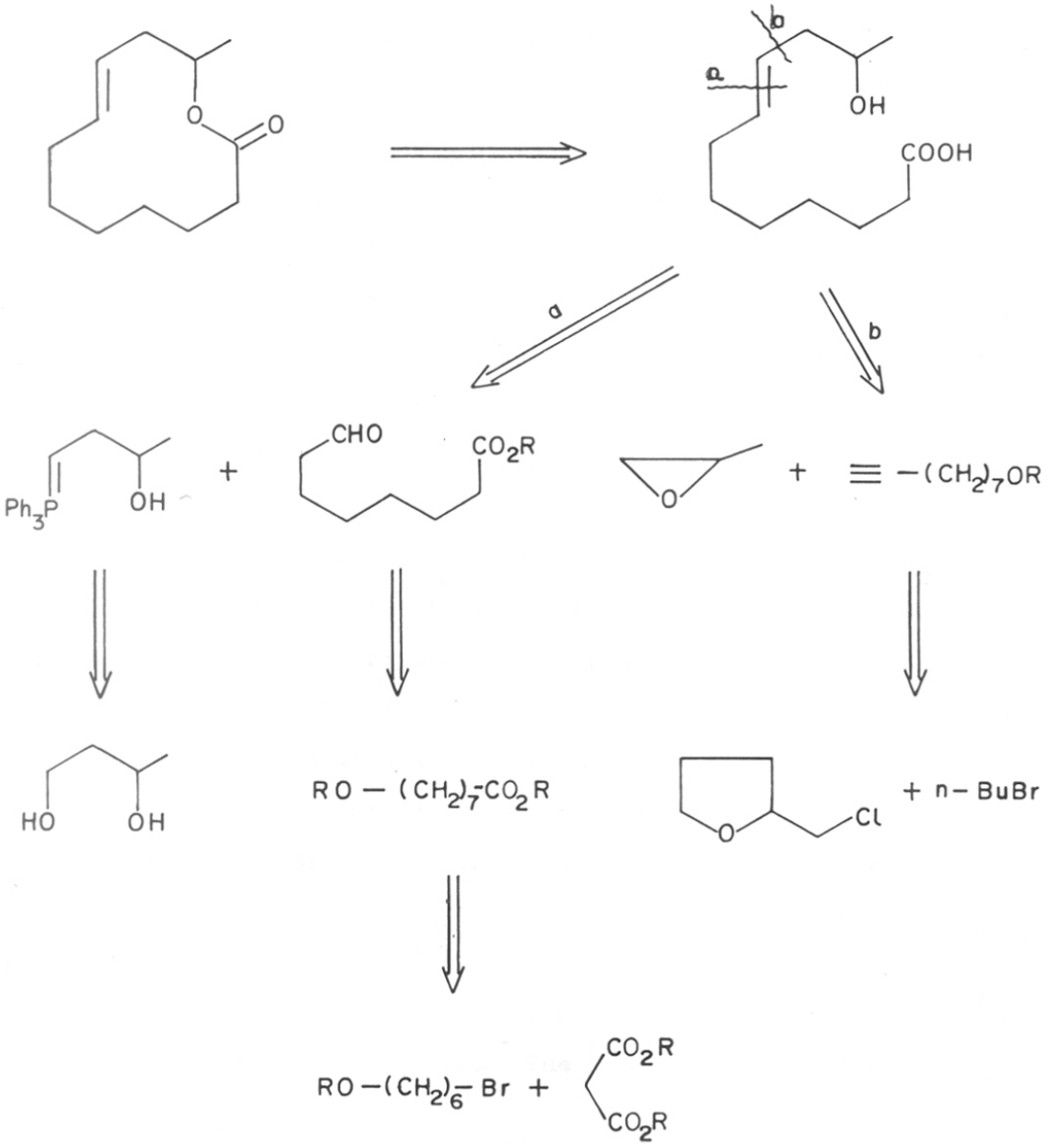
possible way elaborating the synthesis of (±)-1 is illustrated by retro-synthesis indicated in Scheme-12. As depicted in Scheme-12 (path-a), the synthesis of hydroxy acid precursor could be achieved by a Wittig condensation, where the stereoselectivity is not observed during the introduction of double bond. In contrast, the acetylenic precursor in path-b could be made use of not only for the elongation of carbon chain, but for the stereocontrolled introduction of trans double bond also. This chapter is dealt with the synthesis of (±)-recifeiolide in both these different approaches.

The Wittig Approach

In the present work efforts were made towards the synthesis of hydroxy acid (2) by a simple sequence of reactions from easily available chemicals. The synthesis of 2 was further divided into two segments (a) a C-8 aldehyde and (b) a C-4 phosphonium salt. Earlier Gerlach group was the first to report a synthesis of (R)-recifeiolide by making use of a Wittig approach. In their synthesis, the C-4 segment was prepared from optically pure 1,3-butanediol. It was found to be relatively simple and therefore same method was adopted here. Gerlach synthesis of C-8 segment involved ozonolysis of 1-methoxy octene, whereas attempts were made to prepare the C-8 segment in a simple and straight-

SCHEME-12

RETROSYNTHESIS



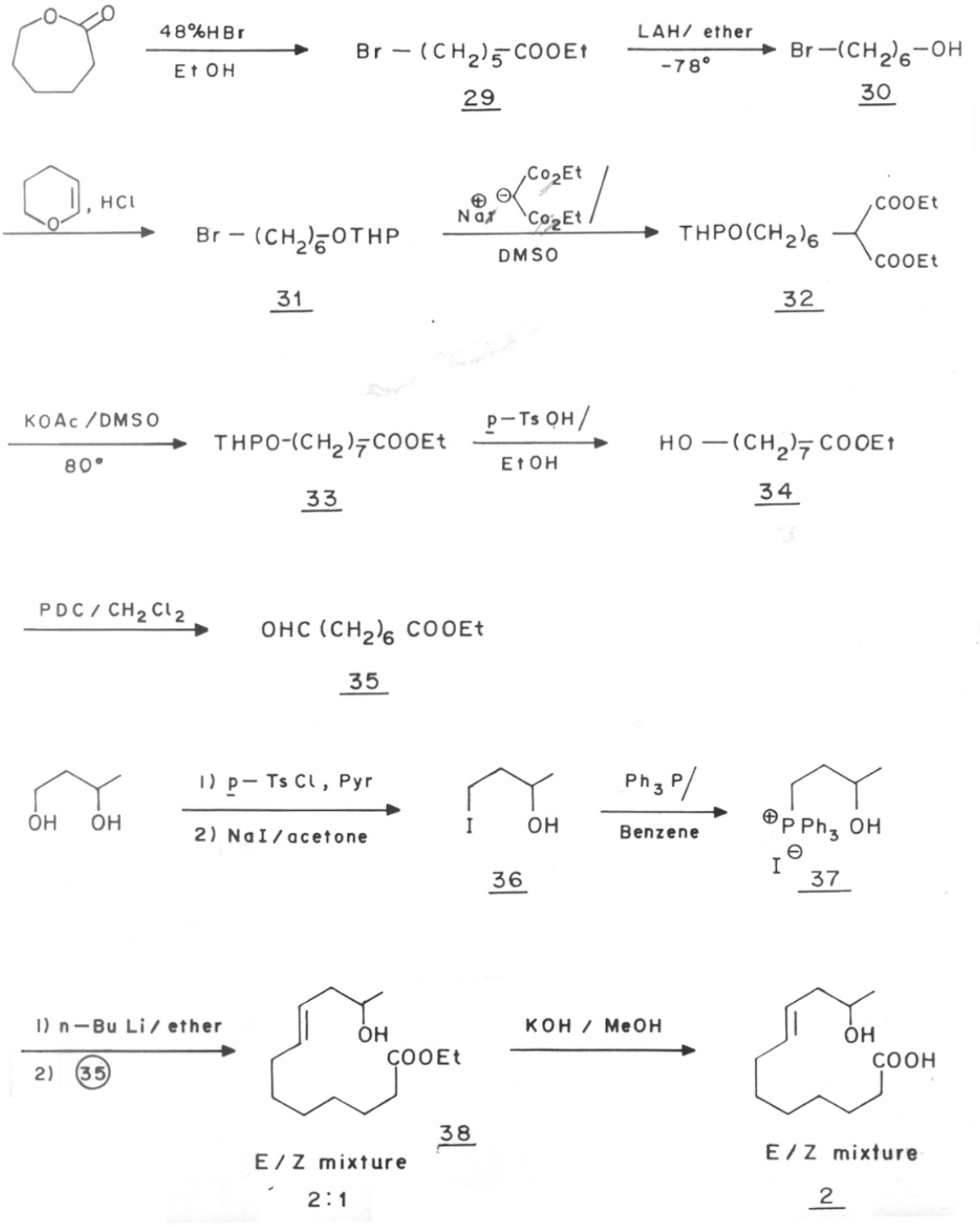
forward way. Thus the major points of interest in the present synthesis are (a) the construction of a C-8 aldehyde, (b) preparation of a C-4 segment as phosphonium salt and (c) the Wittig condensation of C-4 and C-8 segments to afford the hydroxy acid.

In the present synthesis of C-8 aldehyde-ester, caprolactone was chosen as starting material, which provided the six carbon atoms and diethylmalonate as a two carbon synthon. Alkylation and removal of one of the carboethoxy groups would give the requisite number of carbon atoms in the aldehyde segment.

6-Bromohexanol-THP ether (31) was prepared[17] from caprolactone (Scheme-13). Caprolactone on treatment with dry HBr gas in ethanol afforded the bromoester (29), which was subjected to lithiumaluminiumhydride reduction in dry ether at -78° to result in the bromo-alcohol (30) in good yield. Alcoholic function in 30 was protected with dihydropyran in the presence of a few drops of conc. hydrochloric acid to afford the THP-ether (31), which was identical with the reported[18] sample prepared from 1,6-hexanediol. Alkylation of the sodiosalt of diethylmalonate (prepared from diethylmalonate and sodiumethoxide in dry ethanol) in DMSO with the bromide (31) gave the alkylated product (32) in 63% yield. The ^{1}H-NMR spectrum of compound

SCHEME – 13

THE WITTIG APPROACH



32 in CCl_4 showed a singlet at δ 4.4 assigning for the characteristic THP proton. The ester $-OCH_2-$ protons resonated at δ 4.06 as a quadruplicate and the remaining protons were located in the region of δ 1.1 - 1.8 as multiplets. IR spectrum showed the absorption at 1740 cm^{-1} for the ester carbonyl. Mass spectrum gave the molecular ion peak at m/e 344, besides the fragments at m/e 315 (m-29), 299 (m-45), 271 (m-73) and 260 (m-84).

The decarbethoxylation of the alkylated product (32) was attempted under various reported[19] reaction conditions and reagents such as NaCl in DMSO-H_2O, LiBr in DMSO, HMPA-heating, boric acid in DMSO etc. found to be unsuccessful and starting material was recovered. However, decarbethoxylation of 32 was achieved successfully with KOAC-DMSO.

Thus, 32 on heating at 80° with potassium acetate in DMSO under nitrogen atmosphere for 6 hr afforded[20] a compound in 92% yield, which showed the same R_f value on TLC to that of starting material. This compound was characterised as the THP-ester (33) from its spectral data. Compound 33 in its ^1H-NMR spectrum showed the resonance for the newly created methylene adjacent to ester group at δ 2.18 as a distorted triplet, while the remaining protons resonated at the expected chemical shifts. Mass spectrum showed the molecular ion peak at m/e 274 along with

the fragmentation pattern consistent with the assigned structure.

Removal of the THP-group in 33 was achieved with PTSA in ethanol at room temperature to give the hydroxy compound (34) in 85% yield. The ^{1}H-NMR spectrum of 34 in CCl_4 showed a triplet at δ 3.60 for the two protons of $-C\underline{H}_2OH$, while the resonance due to the THP proton disappeared. In IR spectrum the absorption at 3450 cm^{-1} for the hydroxyl functionality was observed.

A solution of the ester (34) in dry dichloromethane was stirred with a suspension of pyridiniumdichromate (PDC) in dichloromethane at room temperature for 6 hr to afford the aldehyde-ester (35) in 75% yield. In the ^{1}H-NMR spectrum of 35, the aldehydic proton resonated at δ 9.75 as a triplet, while the remaining protons appeared at the expected chemical shifts. IR spectrum showed carbonyl absorption at 1720 cm^{-1}.

Having prepared the C-8 segment as the aldehyde-ester (35) (Scheme-13), efforts were directed towards the synthesis of C-4 segment. It was prepared from 1,3-butanediol essentially by the sequence of reactions developed by Gerlach et al.[7]. Thus 1,3-butanediol was converted to monotosylate with p-toluenesulfonyl chloride in pyridine at -25°, which in turn was transformed into the corresponding iodide (36) on treatment with potassiumiodide in acetone at reflux in good yield. Reaction

of the iodide (36) with triphenylphosphine in refluxing benzene furnished the four carbon phosphonium salt (37), which was identical with that of the reported sample.

The Wittig condensation of the two segments 35 and 37 was carried out as reported[7] earlier. The phosphonium salt 37 was treated with n-BuLi in ether at 0°. The phosphorane thus generated was made to react with the aldehyde (35) at 0° for 1 hr to accomplish the Wittig product (38) in 49.4% yield. The ester (38) was obtained as a mixture of E-Z isomers in 2:1 ratio as indicated by the spectral data. Hydrolysis of 38 with ethanolic potassium hydroxide at reflux for 1 hr afforded the hydroxy acid (2) (E-Z mixture 2:1) in 65% yield.

However, the above synthesis has certain drawbacks, such as the formation of 2 as a mixture of E-Z isomers and the tedious workout involved in its separation. This prompted to develop a stereoselective synthesis for (±)-recifeiolide which will be described in the proceeding section.

The Acetylenic Approach

In the earlier part of this chapter the synthesis of the hydroxy-acid (2) (Scheme-13) was discussed, in which it was obtained as a mixture of E-Z isomers (2:1). It was made by a Wittig condensation of C-4 and C-8 segments. Thus,

it could be pointed out that in the earlier approach, the geometrical isomers were invariably formed. Although Gerlach[7] has transformed this mixture of isomers to get major trans product by isomerisations under photolytic conditions, the separation of the resulting mixture involved an extensive chromatography.

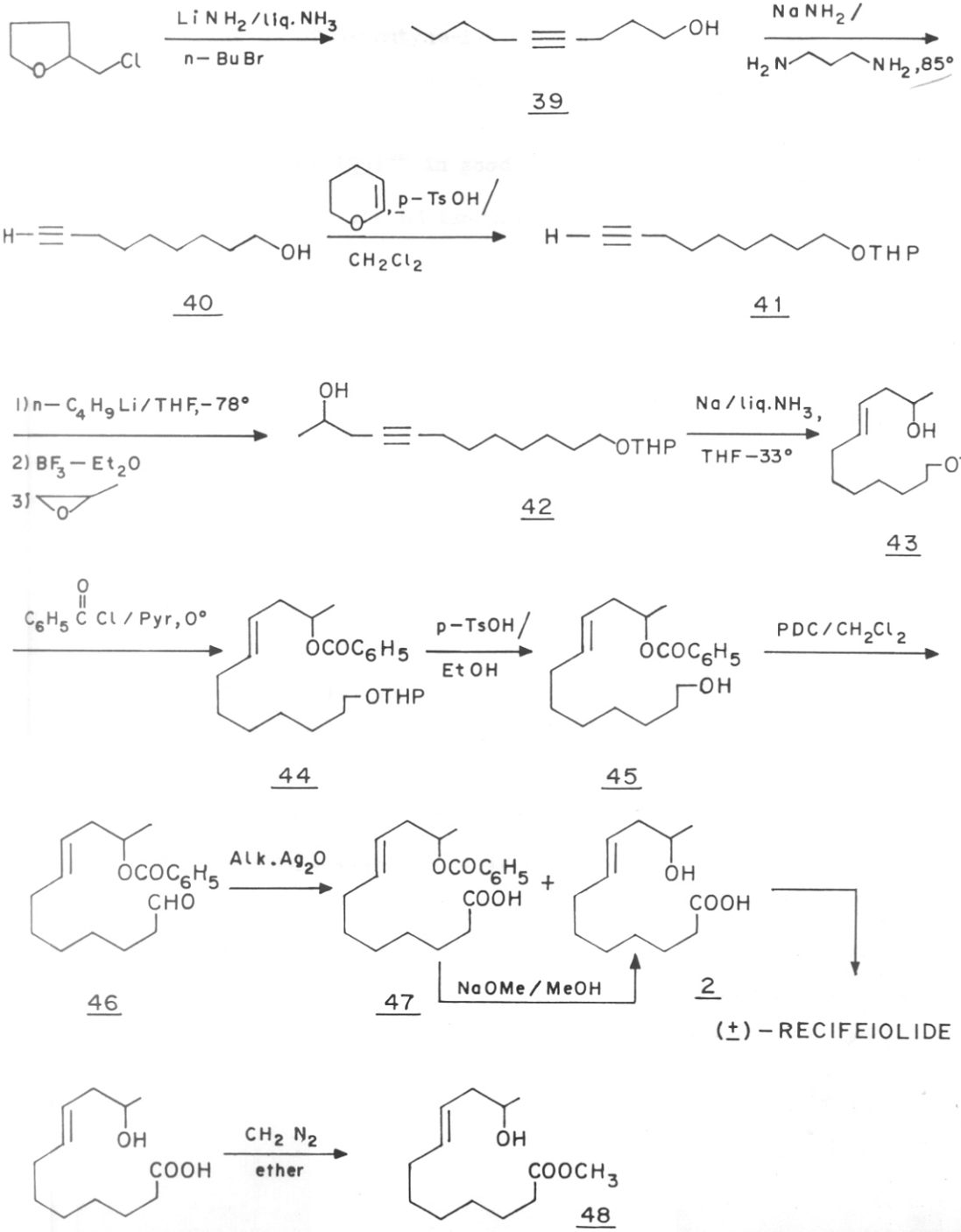
In the present work, efforts were made towards a stereoselective synthesis of 2 as racemate, by making use of an acetylenic precursor (Scheme-14). The simple and stereoselective approach features the "acetylene-zipper" reaction of internal acetylenic alcohol. The terminal triple bond was used both for the C-C bond formation by hydroxyalkylation as well as for the stereoselective introduction of trans double bond.

Thus, the present synthesis features (a) the "acetylene-Zipper reaction (b) the C-C bond formation with a C-3 unit from propylene oxide and (c) the transformation of the triple bond into the trans double bond by a well reviewed metal-ammonia reduction.

Commercially available tetrahydrofurfuryl alcohol was chosen as the starting material for the construction of the hydroxy-acid (2) (Scheme-14). Tetrahydrofurfuryl alcohol on treatment with thionyl chloride in pyridine was converted to the expected tetrahydrofurfurylchloride[21].

SCHEME-14

THE ACETYLENIC APPROACH



Alkylation of 4-pentyne-1-ol (generated *in situ* from the reaction of tetrahydrofurfurylchloride with lithium-amide in liquid ammonia) with n-butylbromide afforded 4-nonyne-1-ol (39)[22] in good yield.

Base catalysed isomerisation of triple bond is a well known reaction[23]. In functionalised acetylenes such as acetylenic alcohols, the successful multi-positional isomerisation[24] of triple bond provides a simple and convenient route to long chain aliphatic compounds, with differentiated remote functionalities. Migration towards the functional group will produce side reactions. But in the case of acetylenic alcohols the quantitative conversion of C-OH to $C-O^-$ would presumably suppress the side reactions. Thus, the migration of triple bonds of internal acetylenic alcohols to the terminus remote from the hydroxyl group is an attractive and novel synthetic tool for C-C bond formation. The isomerisation of internal acetylenic alcohols, the "acetylene-zipper"[24] reaction is carried out in the presence of potassium 3-aminopropylamide (KAPA) in 3-aminopropylamine (APA) (from potassiumhydride in 1,3-diaminopropane) at 0°. This isomerisation can also be caused by the utilisation of metal amides such as potassium amide or sodium amide etc. In contrast to potassiumhydride in APA, the metal amides-APA

system require elevated temperatures and longer durations for the isomerisation of triple bonds. When compared to the alkylamides of monofunctionalised amines, these KAPA or sodium-APA systems are more soluble in excess of diamine such as 1,3-diaminopropane. The higher solvating power of the diamine may be the cause for the high solubility of the base.

Accordingly the internal acetylenic alcohol was subjected to the "acetylene-zipper" reaction by employing sodium amide in 1,3-diaminopropane (APA). Thus, alcohol (39) on treatment with a suspension of sodium amide in APA at 80° for 2 hr afforded the isomerised product, 8-nonyne-1-ol (40)[25] in quantitative yield. The IR spectrum showed an absorption at 2140 cm^{-1} for the terminal triple bond, was a clear indication of the isomerisation. The terminal triple bond proton stretching was seen overlapped at 3450 cm^{-1} along with hydroxyl absorption. In the ^{1}H-NMR spectrum (Fig.1) of compound (40) in CCl_4, the terminal triple bond proton resonated at δ 1.75 as a triplet and the remaining protons gave the signals at the expected chemical shifts. The protection of the alcoholic function in 40 was carried out with dihydropyran in dichloromethane containing catalytic amount of PTSA, to result[25] the THP-derivative 41 in 83% yield. The IR spectrum showed the disappearance of -OH

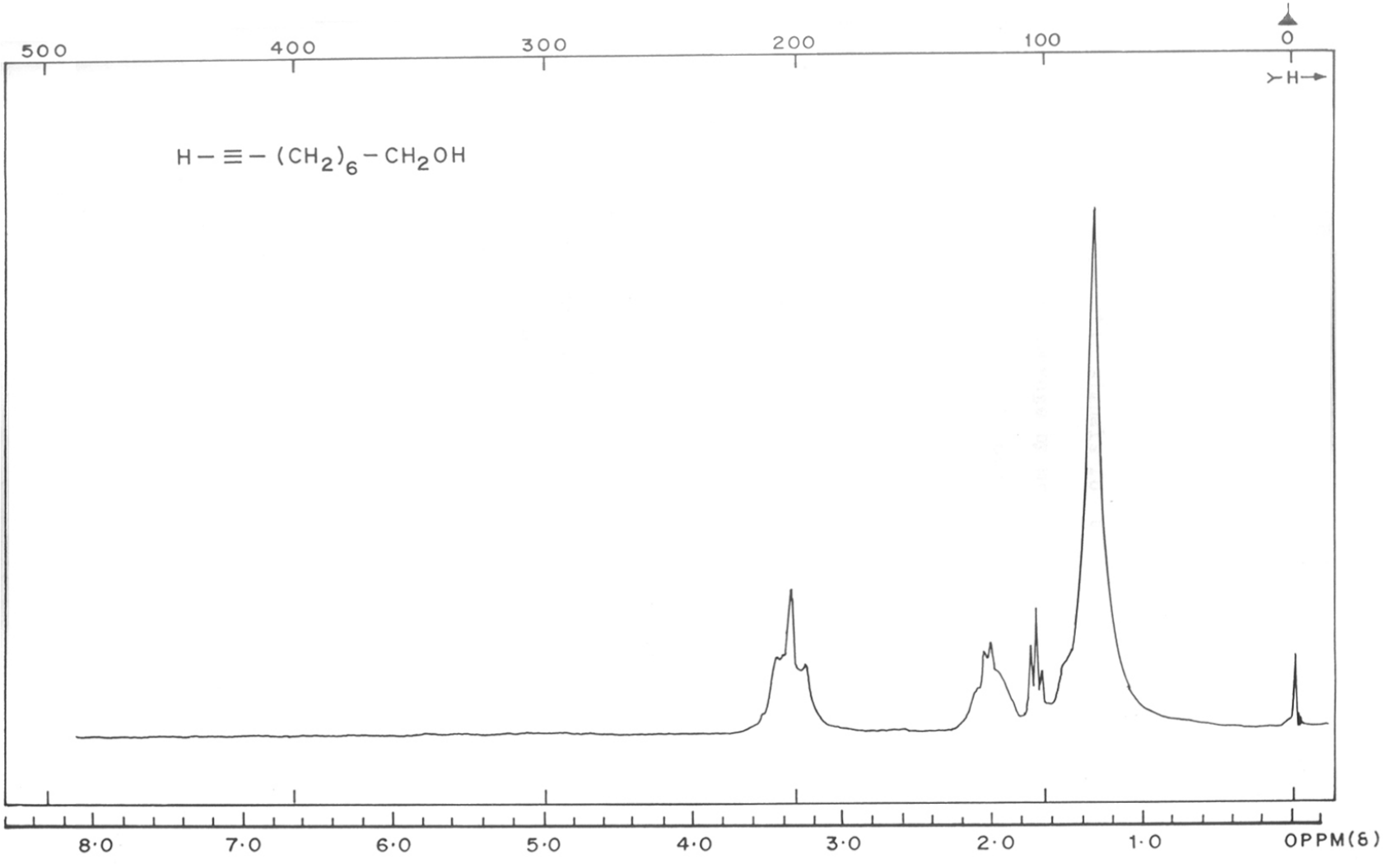


FIG. 1. ^{1}H-NMR SPECTRUM OF COMPOUND (40) IN CCl_4

absorption, while the triple bond proton stretching appeared at 3320 cm^{-1} clearly. The ^{1}H-NMR spectrum showed the characteristic signals for the THP protons.

Oxirane cleavage by metal acetylides is a very useful synthetic tool in organic chemistry. By this method alkynylation[26] of epoxides, by making use of alkynyl boranes, prepared *in situ* provide the β-hydroxyacetylenes in high yields. The same method was adopted in the present synthesis, in which propylene oxide was opened with a functionalised acetylene, where the transformation was a smooth and high yield process. Thus, the THP derivative 41 was sequentially treated with n-BuLi, borontrifluoride-etherate and propylene-oxide at -78° for 1 hr to furnish a mixture of products. The reaction mixture was separated by column chromatography on silica gel into two fractions 'A' and 'B'.

The faster moving component in fraction 'A' was found to be the starting THP-ether 41 (25%). The fraction 'B' obtained in 65% yield was characterised as the hydroxy-alkylated product (42) from its spectral data. In the ^{1}H-NMR spectrum (Fig.2) of compound (42) in $CDCl_3$, the methyl protons resonated at δ 1.20 as a doublet, while the four methylene protons adjacent to triple bond appeared at δ 2.0 - 2.4 as multiplet. The IR spectrum showed the absorption at 3450 cm^{-1} for -OH, besides the absence of bands

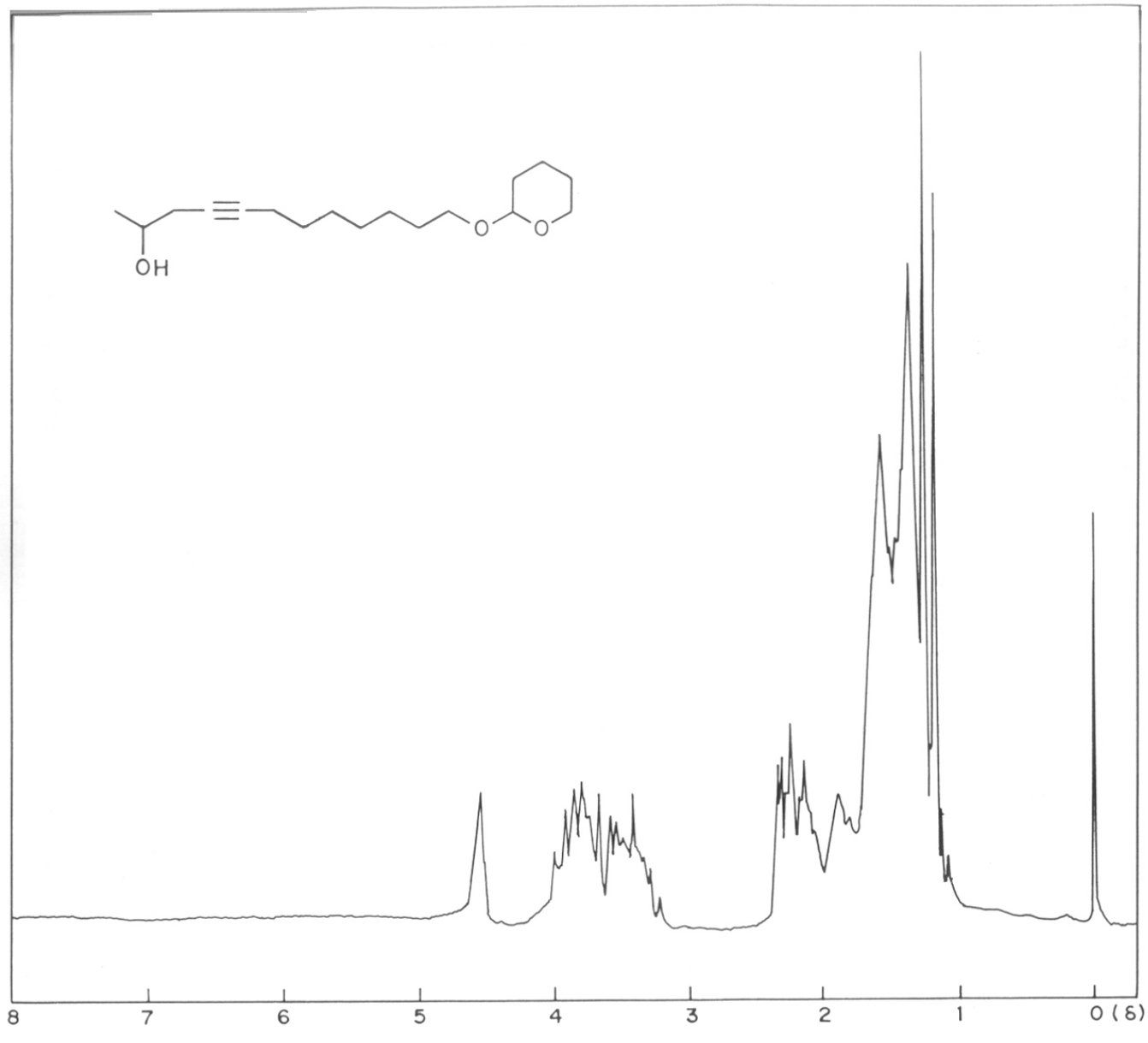


FIG. 2. ^{1}H-NMR SPECTRUM OF COMPOUND (42) IN $CDCl_3$

for terminal triple bond. Mass spectrum showed the molecular ion peak at m/e 282, and further fragmentation pattern was consistent with the assigned structure for compound 42.

Having obtained the carbon skeleton with requisite number of carbon atoms successfully, it was decided to introduce the trans double bond in a stereocontrolled way. Metal ammonia reductions of acetylenic compounds are known[27] to give trans double bond. Thus the acetylenic compound (42) was subjected to reduction with metallic sodium in excess of ammonia, to give the olefin (43) in 90% yield, with high purity of trans geometry. Compound (43) in IR spectrum showed the absorption at 970 cm^{-1} characteristic of trans double bond and no absorption was seen at 730 cm^{-1} for cis double bond, thus indicating the formation of trans olefin. The ^1H-NMR spectrum (Fig.3) of 43 in $CDCl_3$ showed a multiplet in the region of δ 5.3 - 5.6 integrating for two protons, was assigned for the olefinic protons while four protons of methylenes adjacent to the double bond resonated at δ 1.9 - 2.2 as multiplet. The mass spectrum revealed the molecular ion peak at m/e 284, besides the further fragments at m/e 267 (m-17), 225 (m-59) and 201 (m-83). Thus the product obtained was found to be trans exclusively from its spectral data.

On attaining the required geometry in the carbon skeleton, it was aimed at the further transformation of the primary alcoholic group to carboxylic acid function. For the preferential transformation of primary alcohol function over the

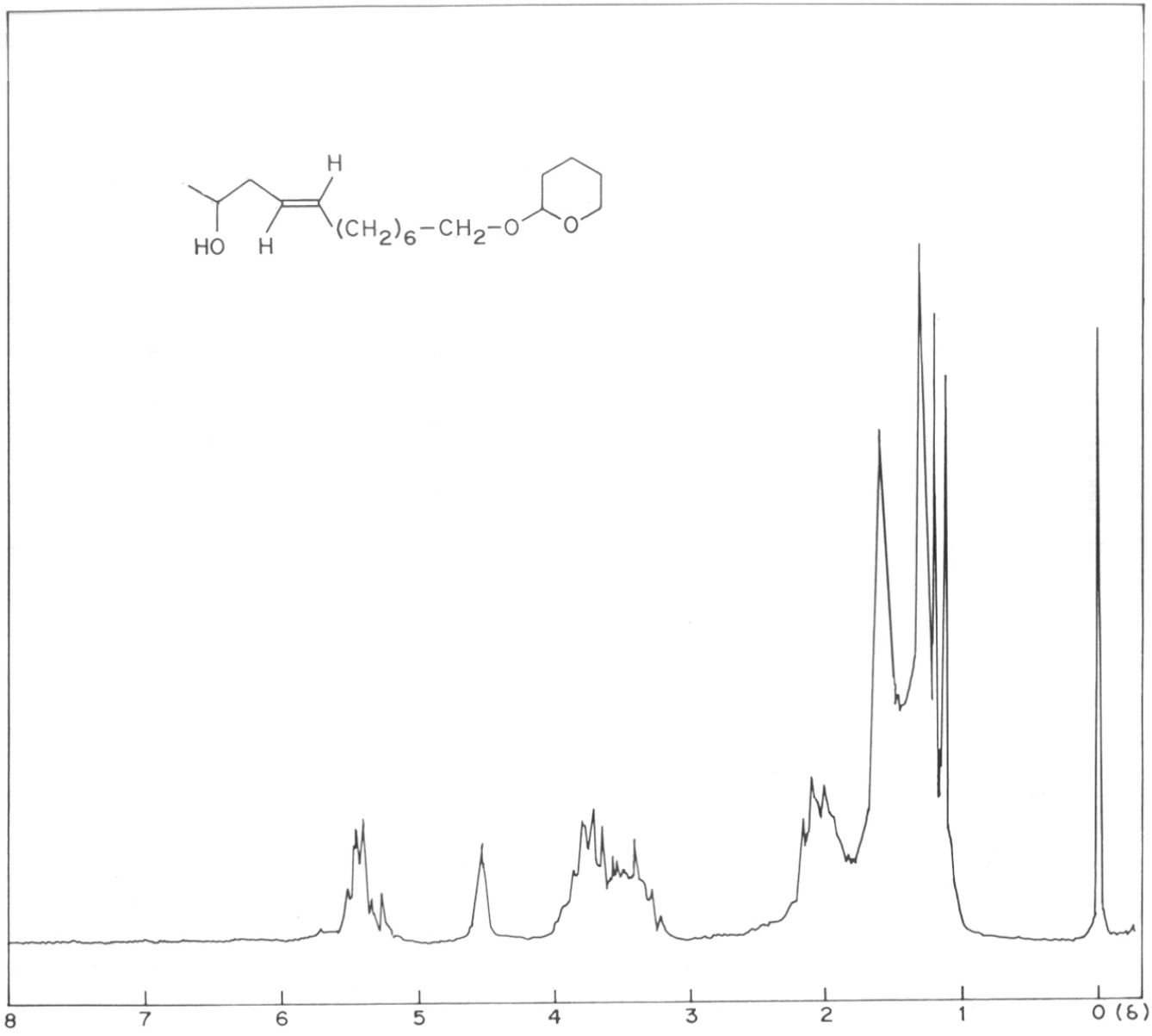


FIG. 3. ^{1}H–NMR SPECTRUM OF COMPOUND (43) IN $CDCl_3$

secondary alcohol, it was decided to protect the secondary alcoholic functionality with a simple and suitable protective group such as benzoate, which would not interfere in the acid hydrolysis of the THP-protection of primary alcohol. Thus, benzoylation of the alcoholic function in compound 43 was carried out with benzoylchloride in pyridine at room temperature to furnish the benzoate (44) in 87% yield. The IR spectrum showed 1740 cm^{-1} stretching for ester carbonyl, besides the absence of absorption for -OH functionality. Further the ^1H-NMR spectrum of 44 in $CDCl_3$ showed the aromatic protons in the region of δ 7.4 - 8.1 as multiplet, while the tertiary proton resonated at δ 5.15 as a quadruplicate. In the mass spectrum the molecular ion peak was located at m/e 388.

The benzoate (44) was subjected to depyranylation by treating with PTSA in ethanol at room temperature to afford the benzoate-alcohol (45) in 85% yield. The IR spectrum showed the absorption at 3400 cm^{-1} and 1740 cm^{-1} for -OH and ester carbonyl respectively. The ^1H-NMR spectrum (Fig.4) of compound (45) in $CDCl_3$ showed the absence of THP protons. The two protons of $-CH_2OH$ group resonated at δ 3.65 as a triplet, while there was no change in the chemical shifts of the remaining protons. The molecular ion peak at m/e 304 was located. Further,

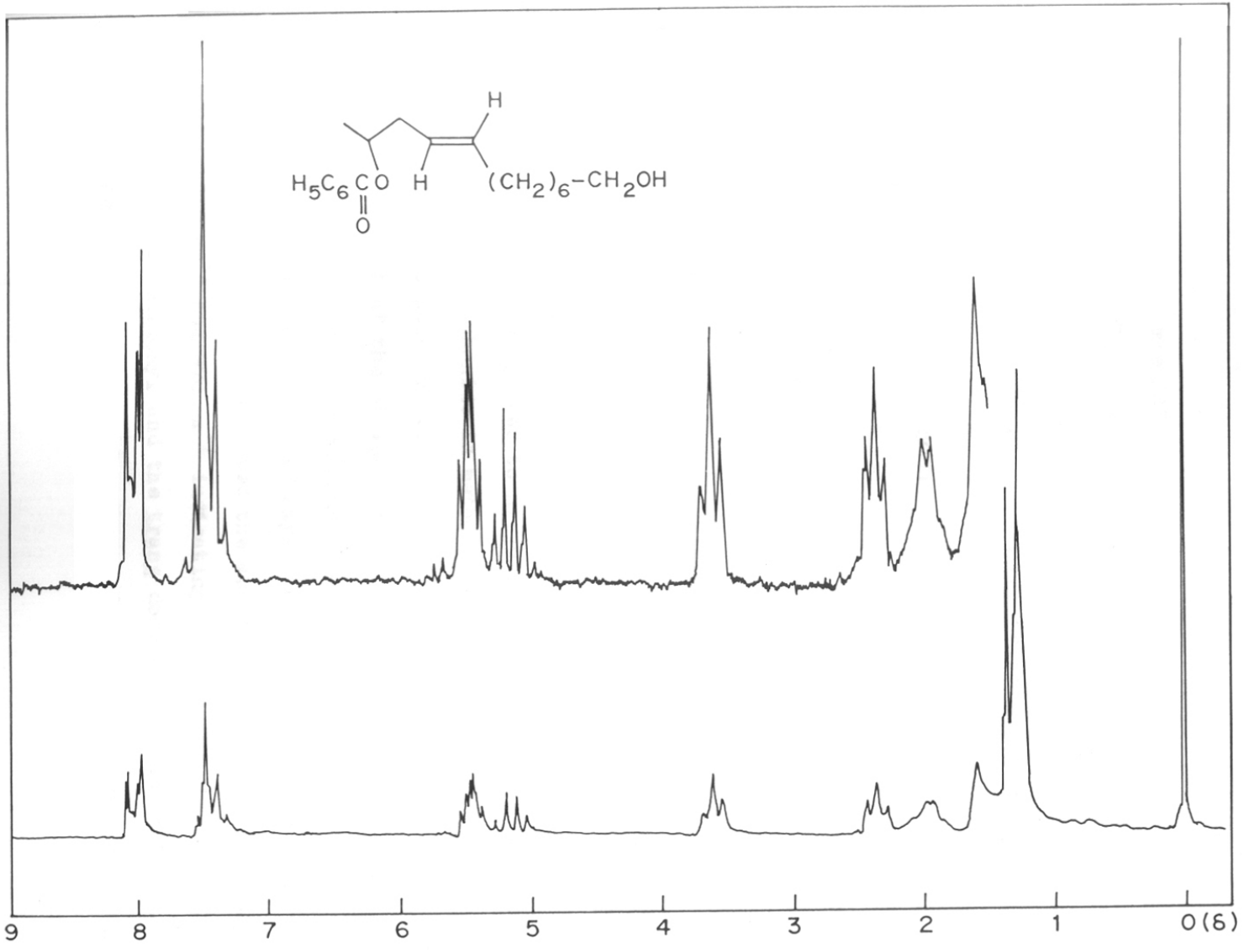


FIG. 4. ^{1}H-NMR SPECTRUM OF COMPOUND (45) IN $CDCl_3$

fragments at m/e 226 (m-78), 199 (m-COC_6H_5), 183 (m-$OCOC_6H_5$) and 163 (m-141) were also seen.

Oxidation of 45 with pyridinium-dichromate (PDC) in dry dichloromethane at room temperature afforded the benzoate-aldehyde (46) in 67% yield. IR spectrum showed the absence of hydroxy function. In the ^{1}H-NMR spectrum of compound (46), the aldehydic proton resonated at δ 9.75 as a triplet, while the rest of the signals appeared at the expected values. The molecular ion peak in the mass spectrum appeared at m/e 302.

Aldehyde (46) was subjected to further oxidation with alkaline silver oxide to give a mixture of two products on TLC. Anticipating one of them as the benzoate acid (47) and the other as hydroxy acid (2), the crude reaction mixture was subjected to hydrolysis with catalytic amount of sodium methoxide in methanol to give a single slower moving compound on TLC; which had the identical R_f value with that of the slower moving component of the reaction mixture. The compound thus obtained in 75% yield was characterised as the hydroxy-acid (2) from the spectral data. IR spectrum showed the absorptions at 3450-3200 cm^{-1}, 1710 cm^{-1} and 970 cm^{-1} indicating the -OH and -OH of -COOH, the acid carbonyl and the trans double bond respectively. The ^{1}H-NMR spectrum of compound (2) showed a broad multiplet

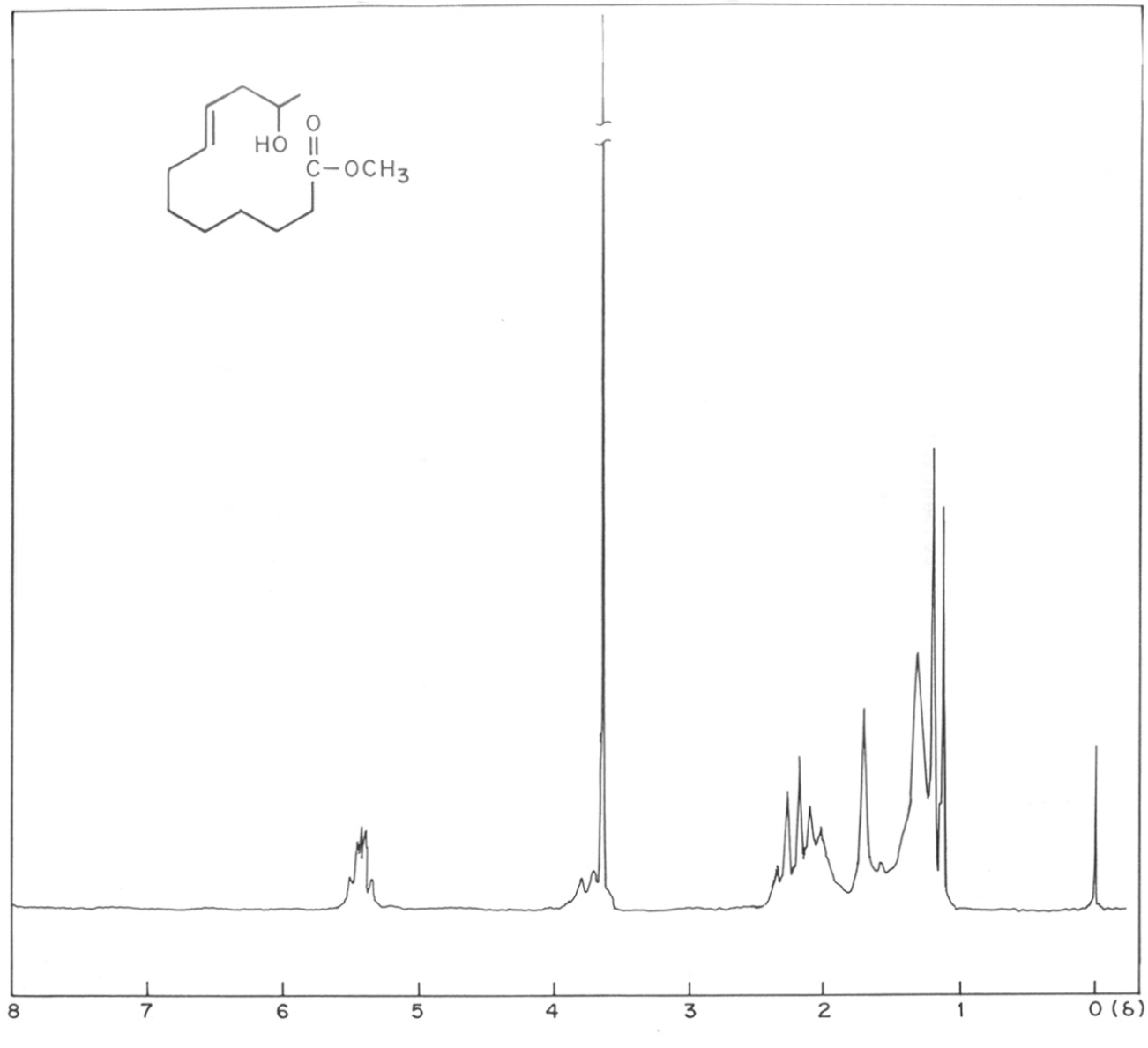


FIG. 5. ^{1}H-NMR SPECTRUM OF COMPOUND (48) IN $CDCl_3$

in the region of δ 5.0 - 5.5 integrating for four protons and was assigned for two olefinic protons and two -OH protons (-OH and -COO<u>H</u>). Further this region underwent D_2O exchange giving rise to a clear multiplet integrating for two protons. The methyl protons reappeared as a doublet at δ 1.16 while the six protons of three methylenes (-C<u>H</u>$_2$COOH, -C<u>H</u>$_2$-CH=CH-C<u>H</u>$_2$) resonated in the region of δ 1.8 - 2.4 as a multiplet. In the mass spectrum 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 (<u>2</u>) was identical in all respects with the reported sample. The hydroxy acid (<u>2</u>) was converted to its methyl ester (<u>48</u>), on treatment with ethereal diazomethane. The ^{1}H-NMR spectrum (Fig.5) of <u>48</u> in $CDCl_3$ showed a resonance of the methoxyl protons at δ 3.65 as a singlet, while rest of the protons resonated at their expected chemical shifts. The IR spectrum showed the -OH absorption at 3450 cm^{-1}, while the ester carbonyl at 1740 cm^{-1}.

Further elaboration of hydroxy acid (<u>2</u>) to (±)-recifeiolide (<u>1</u>) has been carried out by many groups adopting various methods of lactonisations. The conversion of hydroxyacid precursor <u>2</u> to (±)-recifeiolide (<u>1</u>) is a well established reaction in literature. The synthesis of <u>2</u> would thus constitute the total synthesis of (±)-recifeiolide.

EXPERIMENTAL

Ethyl 6-bromohexanoate (29)

To a well stirred solution of caprolactone (22.8 g, 0.2 mol) in dry ethanol (350 ml) dry HBr gas was bubbled for 4 hr. The reaction mixture was then diluted with water and extracted with chloroform. The chloroform layer was washed with water, 5% aqueous sodium bicarbonate, dried (Na_2SO_4) and concentrated to get a residue, which was distilled under vacuum to get the ester (29, 35.6 g, 80%), as a yellow liquid, b.p. 140-5°/10 mm (lit.[28] 117-20°/4 mm).

6-Bromohexanol (30)

The ester (29, 22.3 g, 0.1 mole) in dry ether (50 ml) was introduced dropwise, to a stirred suspension of LAH (3.8 g, 0.1 mole) in ether (50 ml) at -75° under nitrogen during 30 min. After 3 hr, the mixture was quenched with 2N sulfuric acid and extracted with ether. Ethereal layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent and distillation of the resulting residue under reduced pressure afforded 30 (12 g, 66%) as a colourless liquid, b.p. 120-5°/10 mm (lit.[29] b.p. 105-6°/5 mm).

6-Bromo-1-[(tetrahydro-2H-pyran-2-yl)oxy]-hexane (31)

Dihydropyran (7 g, 0.083 mole), the bromo alcohol (30, 10 g, 0.055 mol) and conc. HCl (3 ml) were stirred at

room temperature for 5 hr. The reaction mixture was then diluted with ether and washed with 5% aqueous sodium bicarbonate, dried (K_2CO_3) and evaporated. The resulting residue was passed through a short column (silica gel, hexane) to afford the THP derivative (31, 11 g, 75%) as yellow liquid.

Ethyl 2-carbethoxy-8-[(tetrahydro-2H-pyran-2-yl)oxy]-octanoate (32)

A solution of diethylmalonate (16 g, 0.12 mol) in dry ethanol (50 ml) was added dropwise to a freshly prepared sodium ethoxide solution(from 8.1 g, 0.12 mol of sodium and 50 ml ethanol) during a period of 15 min. at room temperature. The contents were stirred for an additional 1 hr during which a white crystalline solid separated. Ethanol was removed completely under reduced pressure to give the sodio salt of diethylmalonate.

The above sodio salt (7.5 g, 0.05 mol) in dry DMSO (70 ml) was treated with the bromo-THP (31, 10 g, 0.37 mol) at room temperature. After 12 hr, the reaction mixture was decomposed with water and extracted with hexane. The hexane layer was washed with water and dried (Na_2SO_4). Solvent removal gave a residue which was distilled under vacuum to produce the pure diester (32, 8.1 g, 63%) b.p. 195-200°/10 mm, (lit.[30] b.p. 183-85°/7 mm). ^{1}H-NMR (CCl_4): δ 1.1-1.8

(m, 22H, 8X-CH_2- and 2X-CH_3); 3.0 - 3.7 (m, 5H, 2X-OCH_2- and 3°H), 4.06 (q, 4H, 2X -OCH_2CH_3), 4.40 (s, 1H, H-<^O_O); IR: 1740 cm^{-1} (carbonyl); M^+ 344.

Analysis: Calculated for $C_{18}H_{32}O_6$: C, 62.7; H, 9.3; Found: C, 62.3; H, 9.1%.

Ethyl 8-[(tetrahydro-2H-pyran-2-yl)oxy]-octanoate (33)

A mixture of the diester (32, 3.44 g, 10 m.mol) and potassium acetate (1.47 g, 15 m.mol) in dry DMSO (25 ml) under nitrogen was heated at 80° for 6 hr. It was cooled, diluted with water and extracted with hexane. The hexane layer was washed with water, brine, dried (Na_2SO_4) and evaporated to give the mono ester (33, 2.5 g, 92%) as colourless liquid. ^{1}H-NMR (CCl_4): δ 1.0 - 1.7 (m, 19H, 8X -CH_2- and -CH_3), 2.18 (dist. t, 2H, -CH_2CO_2R), 3.0 - 3.7 (m, 4H, 2X -OCH_2-) 3.9 (q, 2H, -OCH_2CH_3), 4.38 (s, 1H, H-<^O_O); IR: 1740 cm^{-1} (ester carbonyl); M^+ 272.

Analysis: Calculated for $C_{15}H_{28}O_4$: C, 66.1; H, 10.2; Found: C, 65.8; H, 10.0%.

Ethyl 8-hydroxy octanoate (34)

A solution of the ester (33, 2 g, 7.3 m.mol) in ethanol (20 ml) containing p-toluenesulfonic acid (0.100 g) was stirred at room temperature for 12 hr. Ethanol was removed, diluted with water and extracted with chloroform. The chloroform layer was washed with water, dried (Na_2SO_4)

and evaporated to yield the hydroxy-ester (34, 1.17 g, 85%). ^{1}H-NMR (CCl_4): δ 1.1 - 1.7 (m, 13H, 5X-CH_2- and -CH_3), 2.25 (t, 2H, -CH_2COOR), 3.6 (t, 2H, -CH_2OH), 4.05 (q, 2H, -O$CH_2$$CH_3$); IR: 1740 cm^{-1} (ester carbonyl) and 3450 cm^{-1} (OH); m/e 157 (m-31).

Analysis: Calculated for $C_{10}H_{20}O_3$: C, 63.8; H, 10.6; Found: C, 64.1; H, 10.6%.

Ethyl 8-oxo-octanoate (35)

A suspension of pyridinium dichromate (3.0 g, 8 m.mol) in dry dichloromethane was treated with a solution of the alcohol (34, 1 g, 5.3 m.mol) in dichloromethane (15 ml). After being stirred for 6 hr, the reaction mixture was filtered and the residue was thoroughly washed with dry ether. The filtrate was passed through a short column (silica gel, benzene) to afford the aldehyde (35, 0.740 g, 75%). ^{1}H-NMR ($CDCl_3$): 1.1 - 1.5 (m, 11H, 4X-CH_2- and -CH_3), 1.5 - 1.8 (m, 2H, CH_2CHO), 2.1 - 2.4 (m, 2H, -CH_2CO_2R), 4.1 (q, 2H, -O$CH_2$$CH_3$), 9.75 (t, 1H, -CHO); IR: 1720 cm^{-1} (broad); m/e 157 (m-29).

Analysis: Calculated for $C_{10}H_{18}O_3$: C, 64.5; H, 9.6; Found: C, 64.2; H, 9.6%.

(±)-1-Iodobutan-3-ol (36)

To a solution of 1,3-butanediol (10 g, 0.11 mol) in pyridine (10 ml) at -25^o was slowly added, a solution of p-toluene sulfonylchloride (23 g, 0.12 mol) in pyridine

(50 ml) during 30 min. The solution was dissolved in benzene, washed sequentially with 2N sulfuric acid, 2N potassium hydroxide, water, dried (Na_2SO_4) and evaporated to result the tosylate (22 g, 81%) as a thick oil.

A mixture of the above crude tosylate (22 g, 0.09 mol) and potassium iodide (72 g, 0.43 mole) in acetone (150 ml) was heated under reflux for 1 hr. Acetone was removed, the residue extracted with ether and then washed successively with 2N potassium hydroxide and water. It was dried (Na_2SO_4) and concentrated to give the iodide (36, 13.5 g, 75%) as an oil b.p. 34-35°/0.3 mm (lit.[7] b.p. 33-36°/0.01 Torr.).

(±)-(3-Hydroxybut-1-yl)-triphenylphosphonium iodide (37)

A mixture of the iodide (36, 4 g, 20 m.mol), triphenyl phosphine (5.8 g, 22 m.mol) in benzene (20 ml) was heated under reflux for 20 hr. The solid separated was filtered, dried and recrystallised from methanol-ethyl acetate (1:1) to give 37 (6 g, 65%) as prisms, m.p. 219-220° (decomp.) (lit.[7] m.p. 219-221°/decomp.).

(±)-Ethyl-11-hydroxy-8-dodecenoate (38)

To a stirred suspension of the phosphonium salt (37, 0.6 g, 1.29 m.mol) in dry ether (5 ml) was added dropwise n-BuLi (0.083 g, 1.3 m.mol) during 5 min. at 0°. After 20 min. a solution of the aldehyde (35, 0.186 g, 1 m.mol) in ether (3 ml) was introduced. The contents were allowed to

stir for 1 hr, after which it was quenched with water (4 ml). Ether was decanted and the white residue was extracted with ether. The combined organic layer was dried (Na_2SO_4) and evaporated. The resulting residue was purified by chromatography (silica gel, ethyl acetate-cyclohexane 1:1) to afford the ester (38, 0.119 g, 49.4%) as a mixture of E-Z isomers. ^{1}H-NMR ($CDCl_3$):δ 1.0 - 1.8 (m, 14H, 7X-CH_2-), 1.9 - 2.3 (m, 7H, 3X-CH_2- and -OH), 3.5 and 3.53 (2 unresolvable sextets with ratio, ca. 2:1, 1H), 4.10 (q, 2H, -OCH_2-), 5.2 - 5.5 (m, 2H, olefinic). IR: 730 cm^{-1} (cis), 975 cm^{-1} (trans), 1740 cm^{-1} (ester carbonyl), 3440 cm^{-1} (OH); M^+ 242.

(±)-11-Hydroxy-8-dodecenoic acid (2)

The ester (38, 0.08 g, 0.33 m.mol) was boiled with an ethanolic solution (2 ml) of potassium hydroxide for 1 hr. Ethanol was evaporated, the residue was diluted with water and washed with ether. The aqueous layer was neutralised with dil. HCl and extracted with ether. The ethereal layer was washed with water, dried (Na_2SO_4) and evaporated to afford the hydroxy-acid (2, 0.045 g, 65%) as a mixture of (E-Z) isomers. ^{1}H-NMR ($CDCl_3$):δ 1.16 and 1.25 (d, 3H, -CH_3), 1.2 - 1.7 (m, 8H, 4X-CH_2-), 1.9 - 2.4 (m, 6H, -$\underline{H}_2$COOH and -$\underline{H}_2$-CH=CH-$\underline{H}_2$-), 3.73, 3.8 (2 unresolvable sextets with ratio, ca. 2:1, 1H), 5.2 - 5.5 (m, 4H, olefinic, -O$\underline{H}$ and CO$\underline{O}$H, D_2O exchangeable). IR: 730 cm^{-1} (cis), 970 cm^{-1} (trans),

1720 cm^{-1} (acid carbonyl), 3200-3400 cm^{-1} (OH and -CO-OH) m/e 196 (m-18).

4-Nonyne-1-ol (39)

To a freshly prepared suspension of lithium amide (prepared from 2.1 g, 0.3 mole of lithium) in liquid ammonia (150 ml) was added 2-chloromethyl tetrahydrofuran (12 g, 0.1 mole) over a period of 10 min. The reaction mixture was stirred for 3 hr at -33° at the end of which a solution of n-butylbromide (13.7 g, 0.1 mole) in THF (20 ml) was added and allowed for an additional 30 min. Ammonia was allowed to evaporate and quenched the reaction with 20% aqueous ammonium chloride. It was extracted with ether, washed with brine and dried (Na_2SO_4). Evaporation of the solvent and distillation of the resulting residue under reduced pressure gave 39 (8.4 g, 60%), b.p. 110-15°/10 mm (lit.[22] b.p. 102-105°/9 mm).

8-Nonyne-1-ol (40)

A suspension of sodium amide (1.17 g, 30 m.mol) in 1,3-diaminopropane (16 ml) was heated at 80° for 25 min. It was cooled to room temperature and 39 (1.40 g, 10 m.mol) was added to the stirred suspension during 15 min. The reaction mixture was heated at 80° for 2 hr. It was cooled, ice-cold water (150 ml) was added and extracted with ether. The organic layer was washed with water, 5% hydrochloric acid,

brine and dried (Na_2SO_4). The solvent was removed and the residue was distilled under vacuum to afford 40 (1.2 g, 85%), b.p. 100-102°/3 mm (lit.[25] b.p. 68-69°/0.5 mm). ^{1}H-NMR (CCl_4): δ 1.1 - 1.5 (m, 10H, 5X-CH_2-), 1.75 (t, 1H, -C≡C$\underline{H}$), 2.06 (dist. t, 2H, -C≡C-C$\underline{H}_2$), 3.46 (t, 3H, -C$\underline{H}_2$-OH and O$\underline{H}$); IR: 2140 cm^{-1} (C≡C) and 3450 cm^{-1} (OH and C≡C$\underline{H}$).

1-[(Tetrahydro-2H-pyran-2-yl)oxy]-8-nonyne (41):

A mixture of alcohol (40, 1.2 g, 8.6 m.mol), dihydropyran (1 ml, 15 m.mol) and p-toluenesulfonic acid (0.05 g) was stirred in dry dichloromethane (15 ml) at room temperature for 8 hr. The reaction mixture was diluted with dichloromethane, washed with 5% aqueous sodium bicarbonate and dried (K_2CO_3). Evaporation of the solvent and chromatographic purification (silica gel, benzene) of the residue yielded 41 (1.6 g, 83%) as pale yellow oil (lit.[25] b.p. 73-74°/0.3 mm).

1-[(Tetrahydro-2H-pyran-2-yl)oxy]-dodec-8-yn-11-ol (42)

To a stirred solution of 41 (1.12 g, 5 m.mol) in dry THF (5 ml), while maintaining the temperature at -78°, a hexane solution of n-BuLi (0.320 g, 5 m.mol), BF_3-etherate (0.7 ml) and propylene oxide (0.690 ml, 0.57 g, 10 m.mol) were added sequentially at 10 min. interval. The contents were allowed to stand at -78° for further 1 hr. It was quenched with aqueous ammonium chloride and extracted with

dichloromethane. Organic layer was washed with brine, dried (K_2CO_3) and solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, acetone-light petrol, 1:9) to afford two fractions 'A' and 'B'. Fraction 'A' was found to contain the starting material 41 (25%). Fraction 'B' gave the required product 42 (0.920 g, 65%) as a colourless oil. ^{1}H-NMR ($CDCl_3$): δ 1.20 (d, 3H, $-CH_3$), 1.3 - 1.9 (m, 16H, 8X $-CH_2-$), 2.0 - 2.4 (m, 4H, $-CH_2-C\equiv C-$), 3.2 - 4.0 (m, 5H, 2X $-OCH_2-$ and 3°H), 4.55 (s, 1H, H-^O_O); IR: 3450 cm^{-1} (OH); M^+ 282.

Analysis: Calculated for $C_{17}H_{30}O_3$: C, 72.2; H, 10.6; Found: C, 72.5; H, 10.5%.

(E)-1-[(Tetrahydro-2H-pyran-2-yl)oxy]-dodec-8-en-11-ol (43):

Sodium (0.5 g) was added in small portions during 45 min. to a stirred mixture of 42 (1 g, 3.54 m.mol) in THF (5 ml) and liquid ammonia (800 ml) at -33° and the contents were left for an additional 4 hr. Solid ammonium chloride was added in portions till the discharge of blue colour. After the evaporation of ammonia, the contents were stirred with water for 30 min. extracted with ether and washed with brine. Ethereal layer was dried (Na_2SO_4) and solvent was removed under reduced pressure to give the olefin (43, 0.9 g, 90%) as a colourless liquid. ^{1}H-NMR ($CDCl_3$): δ 1.15 (d, 3H, $-CH_3$), 1.2 - 1.7 (m, 16H, 8X $-CH_2-$), 1.9 - 2.2 (m, 5H, $H_2CCH_2-CH=CHCH_2$ and -OH), 3.2 - 4.0 (m, 5H, 2X $-OCH_2-$ and 3°H), 4.60 (s, 1H,

H-<O>O), 5.3 - 5.6 (m, 2H, olefinic); IR: 970 cm^{-1} (trans, double bond), 3440 cm^{-1} (OH); M^+ 284.

Analysis: Calculated for $C_{17}H_{32}O_3$: C, 71.8; H, 11.2; Found: C, 71.5; H, 11.3%.

(E)-11-Benzoyloxy-1-[(tetrahydro-2H-pyran-2-yl)oxy]-8-dodecene (44):

Benzoyl chloride (0.5 g, 3.57 m.mol) was added dropwise with stirring at 0°C to a solution of the alcohol (43, 0.670 g, 2.35 m.mol) in dry pyridine (10 ml) during 10 min. After being stirred at 0° for 15 min. the reaction was allowed to reach room temperature and left for 6 hr. It was quenched with ice-cold water and extracted the aqueous layer with dichloromethane. The organic layer was washed sequentially with water, 5% hydrochloric acid, 5% aqueous sodium bicarbonate and brine, dried (Na_2SO_4) and evaporated the solvent to furnish the benzoate (44, 0.8 g, 87%) as an oil. ^{1}H-NMR ($CDCl_3$): δ 1.1 - 1.7 (m, 19H, 8X-CH_2- and -CH_3), 1.8 - 2.1 (m, 2H, -CH=CHCH_2), 2.35 (t, 2H, OR-CH_2), 3.2 - 3.9 (m, 4H, 2X -OCH_2-), 4.53 (s, 1H, H-<O>O), 5.15 (q, 1H, 3°H), 5.2 - 5.5 (m, 2H, olefinic), 7.4 - 7.6 (m, 3H, Ar-H), 7.9 - 8.1 (m, 2H, Ar-H); IR: 970 cm^{-1} (trans double bond) and 1740 cm^{-1} (ester carbonyl); M^+ 388.

Analysis: Calculated for $C_{24}H_{36}O_4$: C, 74.2; H, 9.2; Found: C, 74.0; H, 9.3%.

(E)-11-Benzoyloxy-dodec-8-en-1-ol (45)

A solution of the benzoate (44, 0.8 g, 2 m.mol) in ethanol (10 ml) containing p-toluenesulfonic acid (0.020 g) was stirred at room temperature for 48 hr. Ethanol was removed, the residue was treated with water and extracted with dichloromethane. After washing with water, the organic layer was dried (Na_2SO_4) and evaporated to give the alcohol (45, 0.530 g, 85%) as a colourless oil. ^{1}H-NMR ($CDCl_3$): δ 1.2 - 1.6 (m, 13H, 5X-CH_2- and -CH_3), 1.8 - 2.1 (m, 3H, -CH=CHC$\underline{H}_2$- and -O$\underline{H}$), 2.35 (t, 2H, $\underset{OR}{\diagdown}C\underline{H}_2$-), 3.65 (t, 2H, -$C\underline{H}_2$OH), 5.15 (q, 1H, 3°H), 5.3 - 5.5 (m, 2H, olefinic), 7.3 - 7.6 (m, 3H, Ar-H), 7.9 - 8.1 (m, 2H, Ar-H); IR: 975 cm^{-1} (trans double bond), 1740 cm^{-1} (ester carbonyl) and 3400 cm^{-1} (OH); M^+ 304.

Analysis: Calculated for $C_{19}H_{28}O_3$: C, 75.0; H, 9.2; Found: C, 75.1; H, 9.3%.

(E)-11-Benzoyloxy-8-dodecenal (46):

To a stirred suspension of pyridinium dichromate (0.8 g, 2 m.mol) in dichloromethane (20 ml) was added a solution of the alcohol (45, 0.3 g, 0.98 m.mol) in dichloromethane (10 ml) at room temperature. After a period of 6 hr the contents were treated with ether and reaction mixture was filtered. The combined filtrate was passed through a short column of silica gel to afford 46 (0.2 g, 67%) as pale

yellow oil. ^{1}H-NMR ($CDCl_3$): 1.1 - 1.6 (m, 13H, 5X-CH_2- and -CH_3), 1.7 - 2.1 (m, 2H; CH=CHC$\underline{H}_2$), 2.40 (t, 2H, $\underline{CH}_2$), 5.15 (q, 1H, 3°H), 5.3 - 5.5 (m, 2H, olefinic), 7.3 - 7.5 (m, 3H, Ar-H), 7.9 - 8.1 (m, 2H, Ar-H), 9.75 (t, 1H, -C$\underline{H}$O); IR: 970 cm^{-1} and 1720 - 1730 cm^{-1}; M^+ 302.

Analysis: Calculated for $C_{15}H_{26}O_3$: C, 75.4; H, 8.6; Found: C, 75.2; H, 8.7%.

(E)-(±)-11-Hydroxy-8-dodecenoic acid (2)

To a solution of the aldehyde (46, 0.150 g, 0.5 m.mol) in ethanol (5 ml) was added sequentially a solution of silver nitrate (0.040 g, 0.23 m.mol) in water (3 ml) followed by aqueous potassium hydroxide (5 ml, 70%) dropwise. The reaction mixture was stirred for 4 hr at room temperature and filtered. The filtrate was washed with ether, neutralised with dilute hydrochloric acid and extracted with ether. Organic layer was washed with water, dried (Na_2SO_4) and evaporated to result a mixture of acids 47 and 2.

A solution of the above crude reaction mixture was stirred with catalytic amount of sodium methoxide in dry methanol at room temperature for 12 hr. Methanol was removed and the residue was treated with water. Aqueous layer was washed with ether and neutralised with dil.hydrochloric acid. It was extracted with ether; organic layer was washed with water, dried (Na_2SO_4) and evaporated to furnish

the hydroxy-acid (2, 0.080 g, 75%). ^{1}H-NMR ($CDCl_3$): δ 1.16 (d, 3H, $-CH_3$), 1.2 - 1.6 (m, 8H, 4X $-CH_2$), 1.8 - 2.4 (m, 6H, $-\underline{CH}_2-CH=CH-\underline{CH}_2-$ and $-\underline{CH}_2COOH$), 3.6 - 3.9 (m, 1H, 3°H), 5.0 - 5.5 (m, 4H, olefinic and $-O\underline{H}$ and $-COO\underline{H}$, D_2O exchangeable; IR: 970 cm^{-1} and 1710 cm^{-1} (carbonyl), 3200 - 3450 cm^{-1} (OH and $-COO\underline{H}$); M^+ 196 (m-18).

Analysis: Calculated for $C_{12}H_{22}O_3$: C, 67.2; H, 10.2; Found: C, 67.6; H, 10.1%.

(±)-Methyl-(E)-11-hydroxy-8-dodecenoate (48)

An ethereal solution of the hydroxy acid (2, 0.070 g) was treated with ethereal diazomethane at 0° and allowed for 30 min. Ether and excess of diazomethane were removed to afford the methyl ester (48) in quantitative yield; ^{1}H-NMR ($CDCl_3$): δ1.16 (d, 3H, $-CH_3$), 1.2 - 1.5 (m, 8H, 4X$-CH_2-$), 1.70 (br.s, 1H, -OH, D_2O exchangeable), 1.9 - 2.4 (m, 6H, $-\underline{CH}_2CH=CH\underline{CH}_2-$ and $-\underline{CH}_2COOCH_3$), 3.65 (s, 3H, $-OCH_3$), 3.6 - 3.8 (m, 1H, 3°H), 5.3 - 5.5 (m, 2H, olefinic); IR: 970 cm^{-1} (olefinic), 1740 cm^{-1} (ester carbonyl) and 3450 cm^{-1} (OH); m/e 210 (m-18).

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CHAPTER – III

PREPARATION OF METHYL [2-CHLORO-3-METHOXY-5-(2-METHYL-6-OXO-2,4-HEXADIENYL) PHENYL] METHYL CARBAMATE : A KEY INTERMEDIATE IN THE SYNTHESIS OF MAYTANSINOIDS

It is known that about 20% of the population in Western countries die of neoplastic diseases commonly known as 'cancer'. This has attracted the attention of research workers throughout the world in recent years. Radiation and surgery have certainly a curative effect as long as it is detected at an early stage and localised. 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 anticancer drugs are now being used and further many are under clinical trials. Many drugs now available for the treatment of certain types of cancer are often toxic. These can be broadly classified as (1) alkylating agents (2) antimetabolites (3) antibiotics and (4) miscellaneous compounds.

Although a large number of synthetic compounds have been made and they are subjected to extensive biological screening, the results so far obtained have not been encouraging. The reason seems to be that due to high reactivity of these compounds with many cell constituents, they reduce therapeutic indices. Increasing stress is therefore being laid on natural products which might act as prototypes for synthetic chemist by building more effective and less toxic compounds. Various

natural products, either of plant or microbial origin have been found to be promising anticancer agents, showing much more specificity in their properties.

The antitumour activity of certain plant materials has been known for many centuries. Plant preparations were prescribed, for what is thought to be 'cancer' as early as 1500 B.C. Even now in many countries plant extracts are in use as remedies for cancer[1].

For the last 20 years several groups are engaged in the isolation and structure elucidation of plant derived tumour inhibitors. The results are promising and have yielded many novel types of growth inhibiting compounds. Many of the compounds possess structures and chemical properties, which suggest that they may act by selective alkylation of growth regulatory macromolecules. This approach may finally result in synthesising safe and clinically useful chemotherapeutic agents.

For many years African witch doctors have been using a plant extract for treating cancer. In the course of continuing search for tumour inhibitors from plant sources, Kupchan *et al.*[2] have isolated maytansine (1), the active principle of an alcoholic extract of *Maytenus ovatus*. Maytansine (1) is a novel anti-leukemic ansa macrolide. It has a large ring lactam and has been included

in the class of ansa macrolides along with rifamycins, streptovaricins etc. These compounds contain an aliphatic ansa bridge - a bridge connecting two non-adjacent positions of an aromatic nucleus, for which the term 'ansamycin' has been suggested by Prelog*.

Maytansine (1) is present in very minute quantities in plant sources. Its structure was determined by Kupchan et al.[2] by X-ray crystallography and the absolute configurations[2] are 3S, 4S, 5S, 6R, 7S, 9S, 10R and 2's. The ansamycin antibiotics and their derivatives aroused considerable interest as antiviral, antimicrobial agents and inhibitors of RNA tumour virus reverse transcriptases.

Maytansine is an exceptionally interesting anti-leukemic ansa macrolide producing antitumour activity at the level of μg/Kg animal body weight. The potent antileukemic activity of maytansine stimulated interest in the chemistry and biological properties of related compounds. It also shows significant inhibitory activity against the L-120 mouse leukemia, Lewis lung carcinoma and B-16 melanocarcinoma murine tumour system.

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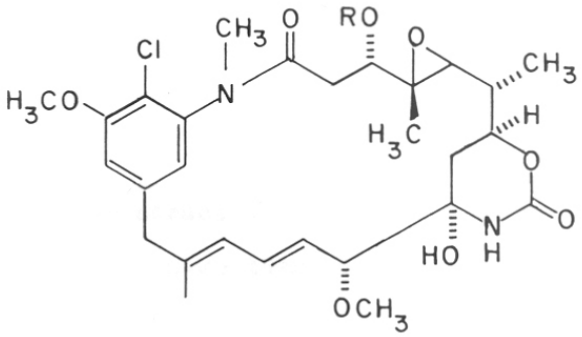
*The term ansa was originally proposed by Lütting-haus[3] for compounds of this type, usually meta and para bridged benzenes.

The biological activity of maytansine (1) has prompted in the isolation of several maytansinoids (a group of structurally related ansa macrolides isolated from Maytenus and Colubrina sps.) from different plant species. Kupchan and coworkers[4] (1972) have isolated two new maytansinoids, maytanprine (2) and maytanbutine (3) from the plant Maytenus buchananii (Loes). They showed antileukemic activity against P-388 lymphocytic leukemia over a 50-100 fold dosage range at the μg/Kg level. In the year 1974, the efforts of the same workers[5], resulted in the isolation of four more maytansinoids from Maytenus buchananii (Loes) R. Wilczeck. Maytanvaline (4) is a highly antileukemic maytanside ester. The other three being maysine (7), normaysine (8) and maysenine (9), are the first reported maytansides lacking antileukemic activity and show 1/10,000 the cytotoxicity of the maytanside ester. In the year 1975, Kupchan et al.[6] isolated two more new maytansinoids from Putterlickia verrucosa Szyszyl (Celastraceae), which are maytanacine (5) and maytansinol (6). Maytanacine (5) exhibits potent antileukemic activity and is the first reported maytanside ester which does not bear amino acid residue at C-3, whereas maytansinol (6) is the parent alcohol of the potent maytanside ester, lacks antileukemic activity and shows 1/100,000 the cytotoxicity of maytanacine (5).



1. MAYTANSINE — R = $-C(=O)CH(CH_3)N(CH_3)-C(=O)-CH_3$

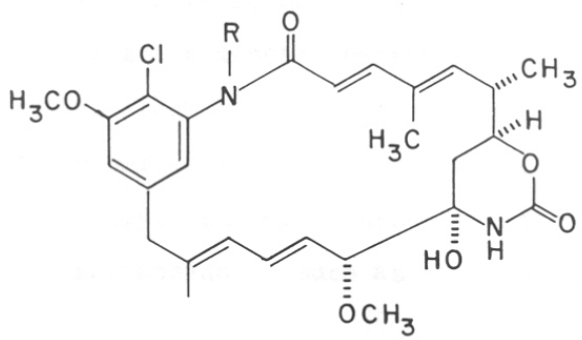
2. MAYTANPRINE — R = $-C(=O)CH(CH_3)N(CH_3)-C(=O)-CH(CH_3)_2$

3. MAYTANBUTINE — R = $-C(=O)CH(CH_3)N(CH_3)-C(=O)-CH(CH_3)_2$

4. MAYTANVALINE — R = $-C(=O)CH(CH_3)NC(=O)CH_2CH(CH_3)_2$

5. MAYTANACINE — R = $-C(=O)CH_3$

6. MAYTANSINOL — R = H



7. MAYSINE — R = CH_3 ; 4,5-EPOXIDE

8. NORMAYSINE — R = H ; 4,5-EPOXIDE

9. MAYSENINE — R = CH_3

Some structural requirements for the antileukemic activity also have been noticed. From the studies[7] it was noticed that the presence of ester group is necessary for the potent activity. Thus, 1 to 5 are active. The activity of 1 to 5 also shows that variations in the ester group and the replacement by simple alkyl ester as in maytanacine (5) is not accompanied by marked changes. The lack of biological activity of the maytansides 6 to 9 further confirm that the ester group at C-3 appears to be necessary for potent antitubulin and antileukemic activity. The ester function in the active maytansides may play a key role in the formation of highly selective molecular complexes with growth regulatory biological macromolecules. The carbinolamide and the epoxide function are necessary for the selective alkylation of growth regulatory biological macromolecules. Thus, the maytansine ethyl ether, in which the carbinolamide moiety is blocked by etherification, shows no antileukemic activity.

The biological activities of these structurally interesting maytansinoid group of natural products, which are available in minute quantities (10^{-4} % or less) in their respective plant sources, has prompted many synthetic organic chemists to develop synthetic routes to the naturally occurring maytansinoids. Recently total synthesis of several maytansinoids such as maytansine[8], maysine[9], N-methyl

maysenine[10] and maytansinol[11] have been reported. Several synthetic sequences appeared for the construction of various parts of maytansinoids. As the scope of this chapter is confined to the synthesis of dienal portion, the earlier attempts towards the synthesis of aromatic portion will be reviewed briefly.

Four synthetic approaches were reported simultaneously for the aromatic segment of maytansinoids in 1977. Meyers and coworkers[12] prepared the key intermediate, the bromide (12) (Scheme-1) starting from methylvanillate. In this synthesis monomethylation of the amine (10) to the corresponding N-methyl derivative (11) was achieved by Kadin[13] method, where 10 was first converted to the corresponding trifluoroacetamide and then to 11 with sodiumhydride-methyliodide.

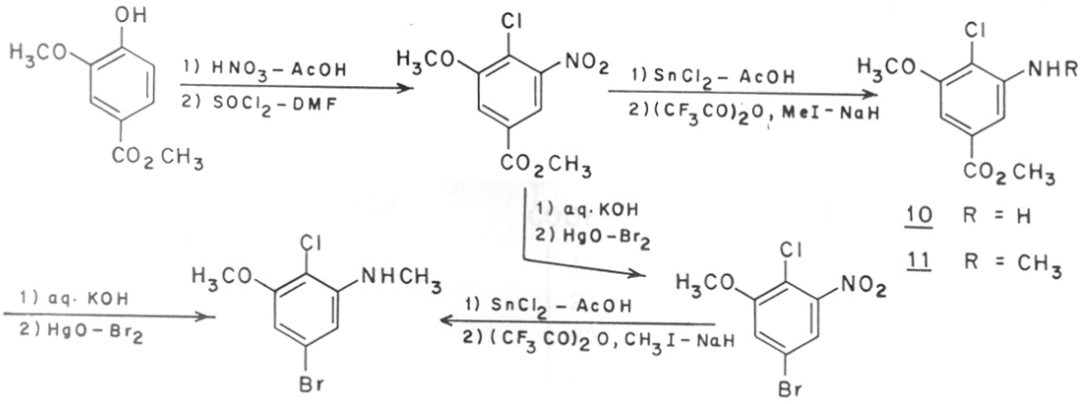
The synthesis of the substituted benzylbromide (13) (Scheme-2) reported by Ganem and Foy[14] was achieved starting from 5-methylcyclohexan-1,3-dione.

The ester (15) (Scheme-3) was synthesised by Corey et al.[15], starting from the enone-ester (14), which could be easily obtained by the Birch reduction of gallic acid.

In the same year, Götschi et al.[16] reported the first synthesis of the dienal (17) (Scheme-4). In this synthesis ethylvanillate was transformed into the N-methyl-

SCHEME-1

Meyers and Kane (1977)



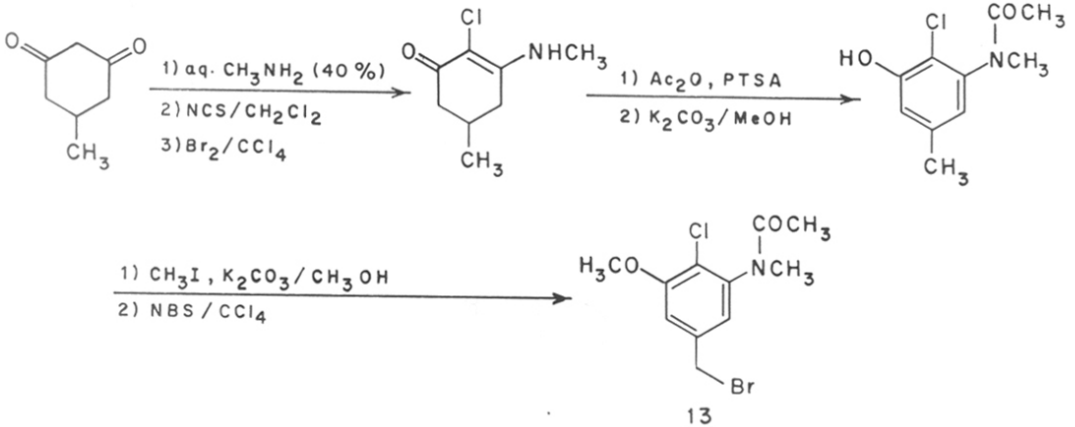
10 R = H

11 R = CH_3

12

SCHEME-2

Ganem and Foy (1977)



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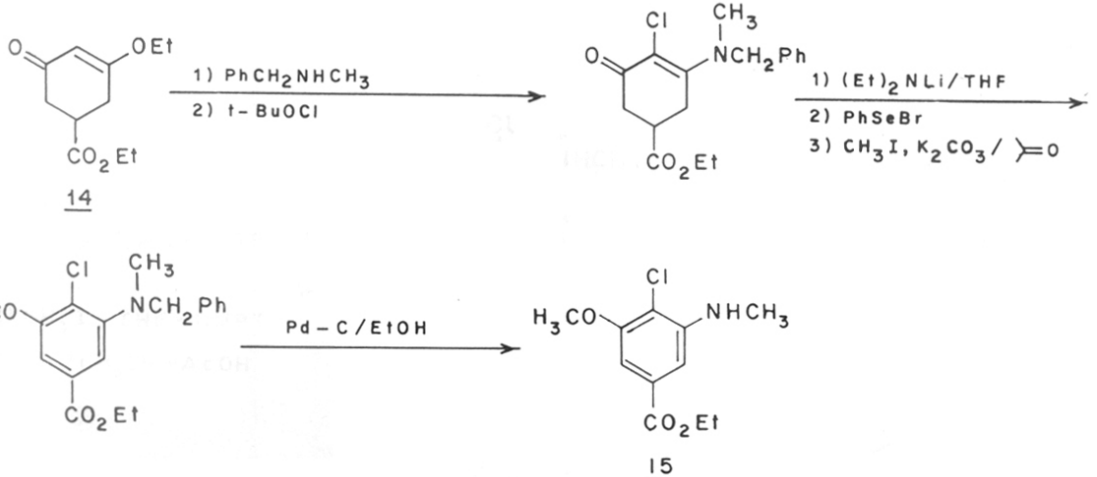
SCHEME-3

Corey et al (1977)



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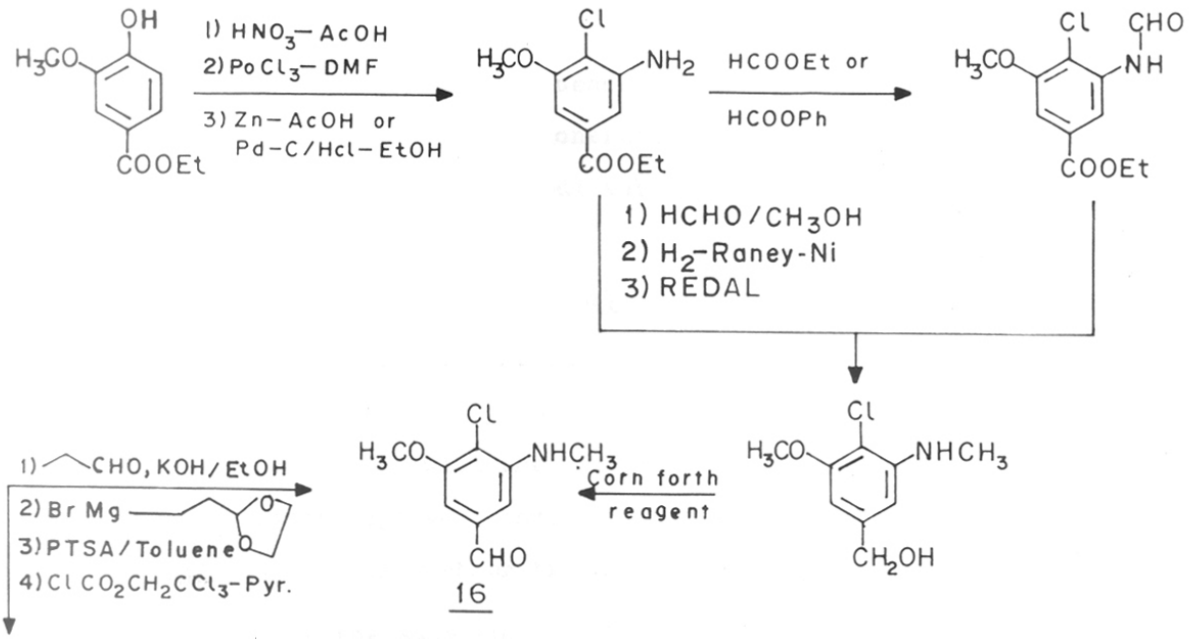
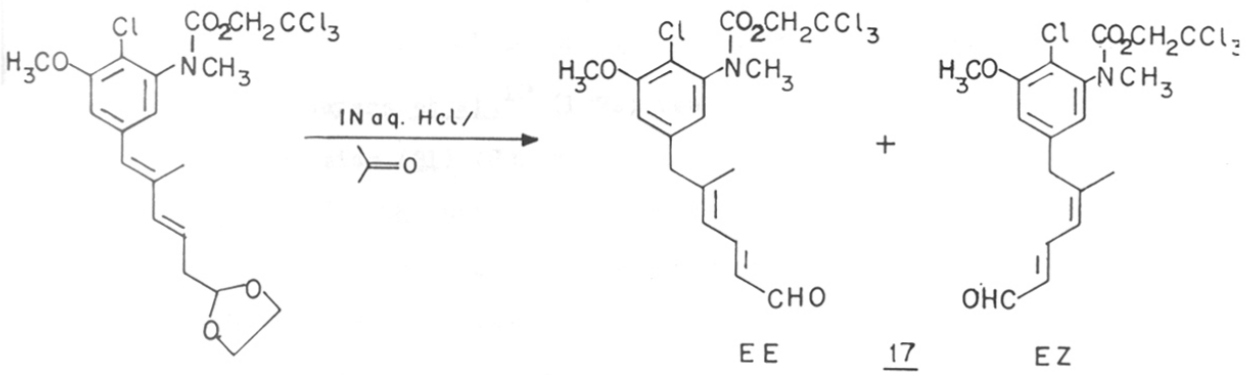
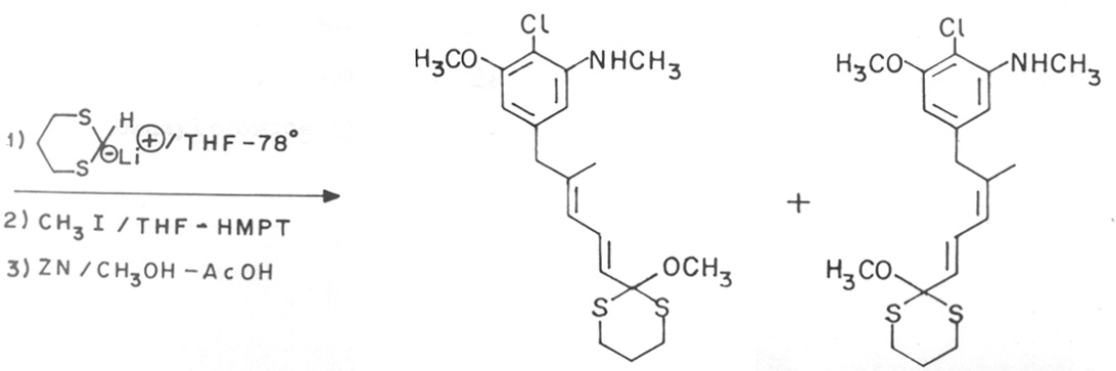
SCHEME-4

Götschi et al







benzaldehyde (16) by a sequence of reactions. This aldehyde on condensation with propionaldehyde and further Grignard with 2-(2-bromoethyl)-1,3-dioxolane led to the formation of 17, after acid treatment.

Corey et al.[17] reported a synthesis of the dienal (23) (Scheme-5) in 1978. The ester (18) reported[15] earlier was converted to the benzyliodide (19). This was subjected to the condensation with the allylcuprate (20) to furnish 21. The alcohol (21) was converted to the α,β-unsaturated aldehyde (22), which was further transformed into 23.

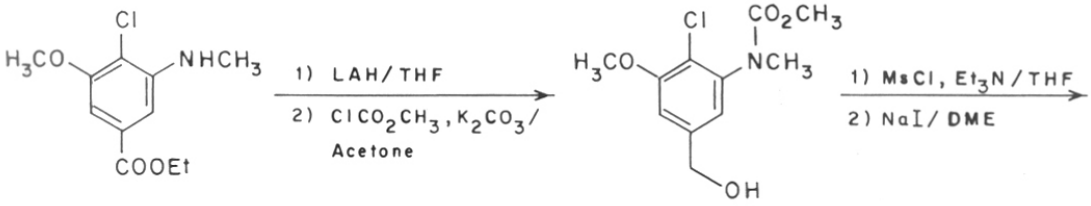
In the same year (1978), Meyers et al.[18] reported a synthesis of dienal (27) (Scheme-6), through the phosphonate reagent (25). The ester (24)[12] was converted to 25 and condensed with the dialdehyde (26) to yield 27, on acid hydrolysis.

Meyers et al.[19] (1979) reported a synthesis of the dienylbromide (31) (Scheme-7), starting from the bromide (28)[12]. The bromide (28) was transformed into 29 and then condensed with the mesylate (30) in the presence of a copper reagent (Scheme-7) to give 31.

Pak-Tsun Ho[20] reported a synthesis of the allylphosphonate reagent (38) starting from 6-amino-m-cresol (32) (Scheme-8). Compound (32) was transformed into the substituted benzylbromide (33) by a sequence of reactions and condensed

SCHEME - 5

Corey et al (1978)



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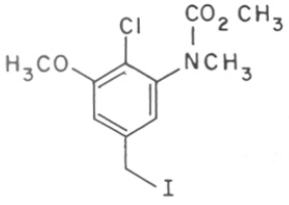

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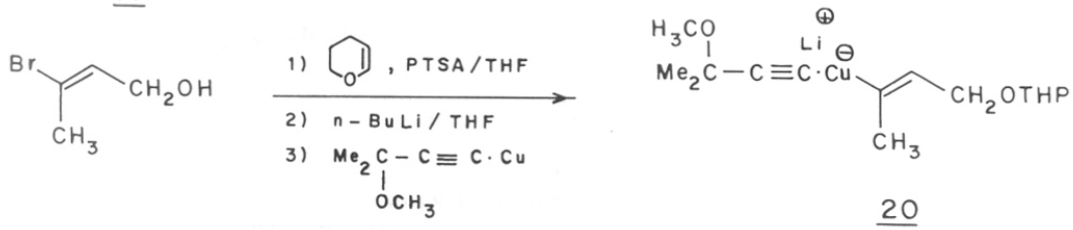

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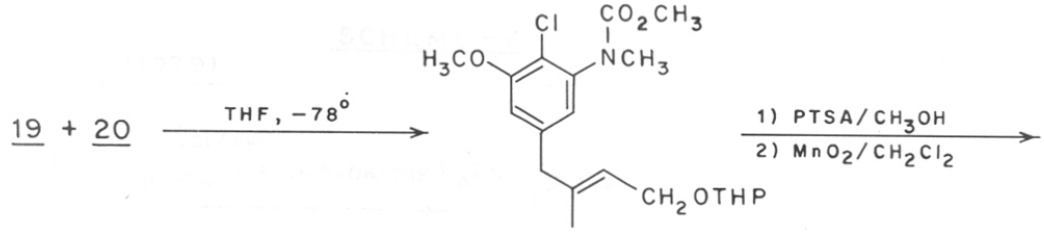
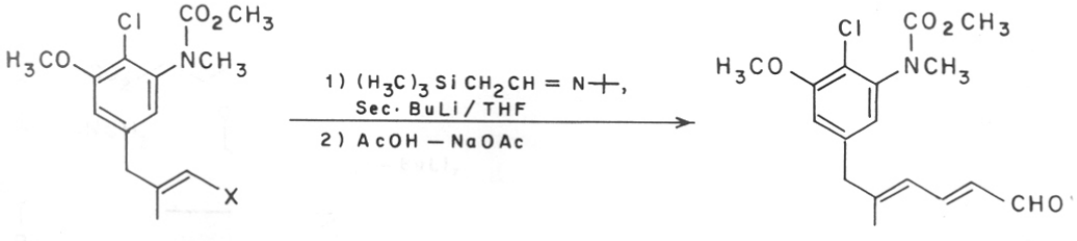




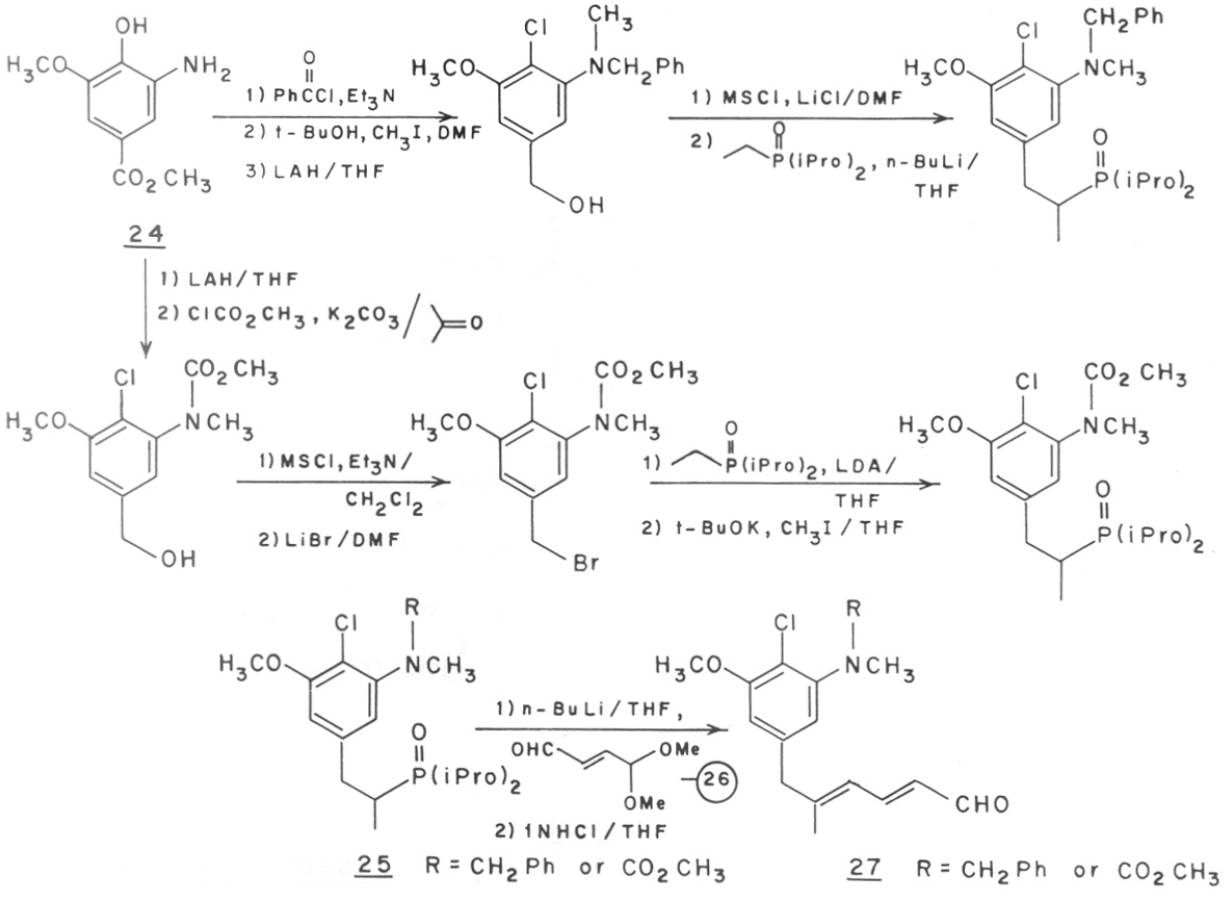
21 X = CH_2OH

22 X = CHO

23

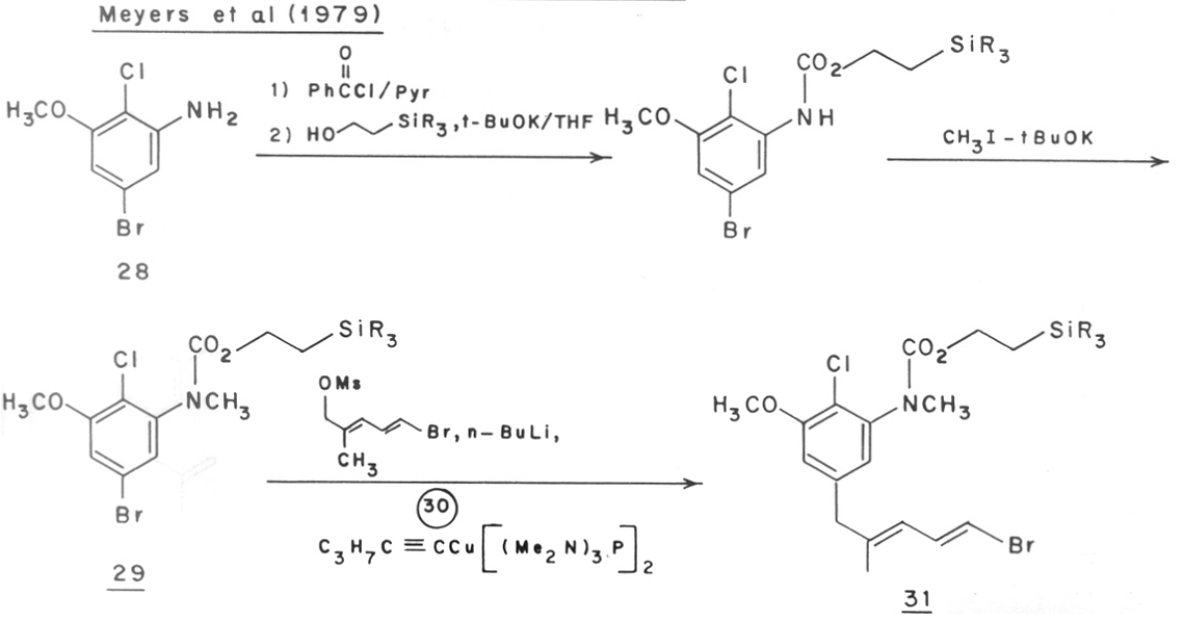
SCHEME-6

Meyers et al (1978)



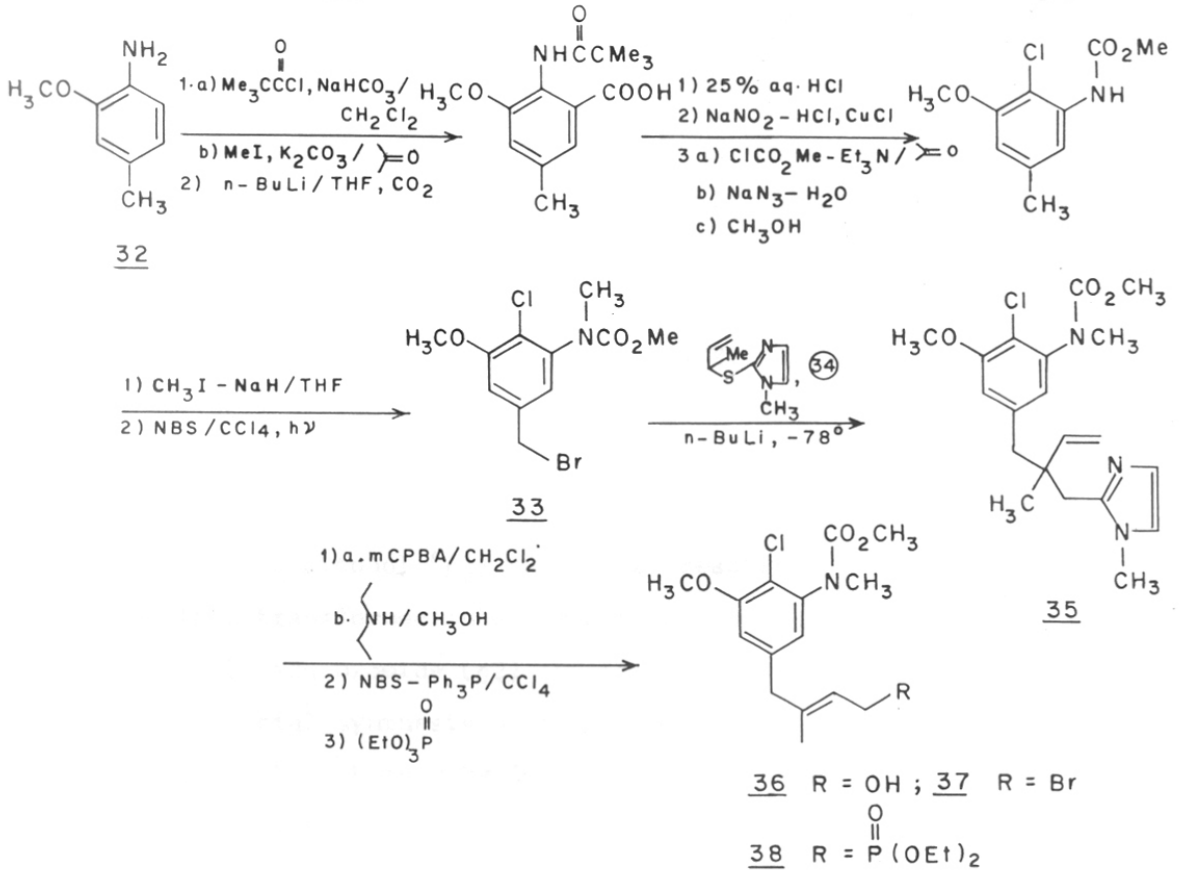
SCHEME-7

Meyers et al (1979)



SCHEME-8

Pak-Tsun HO (1980)



32

33

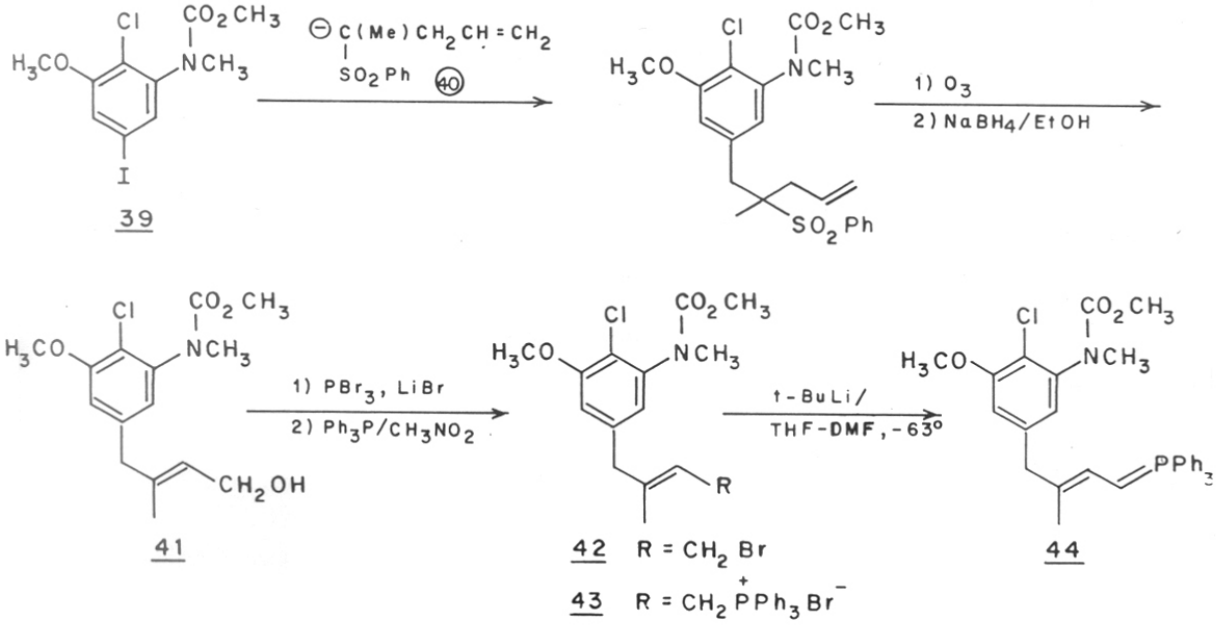
35

36 R = OH ; 37 R = Br

38 R = P(=O)(OEt)2

SCHEME-9

Isobe et al (1982)



39

41

42 R = CH_2Br

43 R = $CH_2\overset{+}{P}Ph_3Br^-$

44

with the reagent (34) to afford 35. 35 on further transformations gave the α,β-unsaturated phosphonate reagent (38), through an allyl alcohol (36) and allyl halide (37).

Isobe et al.[11] in the year 1982, reported a synthesis of α,β-unsaturated phosphorane (44) (scheme-9) starting from the known aromatic iodide (39), reported by Götschi et al.[21]. 39 was condensed with the sulfone (40) to give the α,β-unsaturated alcohol (41) on further reactions. Alcohol (41) was then transformed into the phosphorane (44) via the corresponding bromide (42) and the phosphonium salt (43).

Total synthesis of different maytansinoids are successfully achieved by Corey et al.[8], Meyers et al.[9] and Isobe et al.[10].

PRESENT WORK

The maytansinoids are a group of structurally related ansa macrolides isolated from *maytenus* sps. The potent antileukemic activity of maytansine and related maytanside esters stimulated interest in the chemistry and biological properties of related compounds. Recent findings showed maytansine (1) to be antitubulin, antimitotic and antileukemic and the agent is under toxicological investigations in preparation for clinical trials. The biological activity of these molecules attracted the world-wide attention. The isolated yields of these maytansinoids from their respective natural sources were found to be very minute in the order of 10^{-4} % or still less. The activity of the molecule in combination with the high costs involved in their isolation has sparked many groups to initiate synthetic sequences aimed at the total synthesis of naturally occurring maytansinoids.

A number of approaches made in the synthesis of various parts of maytansine (1) have been reported. For convenient reasons the molecule was divided by Meyers *et al.*[12] into four zones: (a) the Northern zone (b) the Southern zone (c) the Eastern zone and (d) the Western zone, which was adopted here.

The so-called Western zone is a tetrasubstituted

aromatic compound commonly found in all the maytansinoids. An unusual assemblage of three different heterosubstituents *viz*. -OMe, Cl and NH_2 are present on vicinal carbons. The synthesis of Western zone thus features the gathering of proper substituents, selection of a protective group for the amine function in addition to a suitable functional group for linkage to the Southern zone. For the preparation of western zone, including southern zone several synthetic approaches are reported.

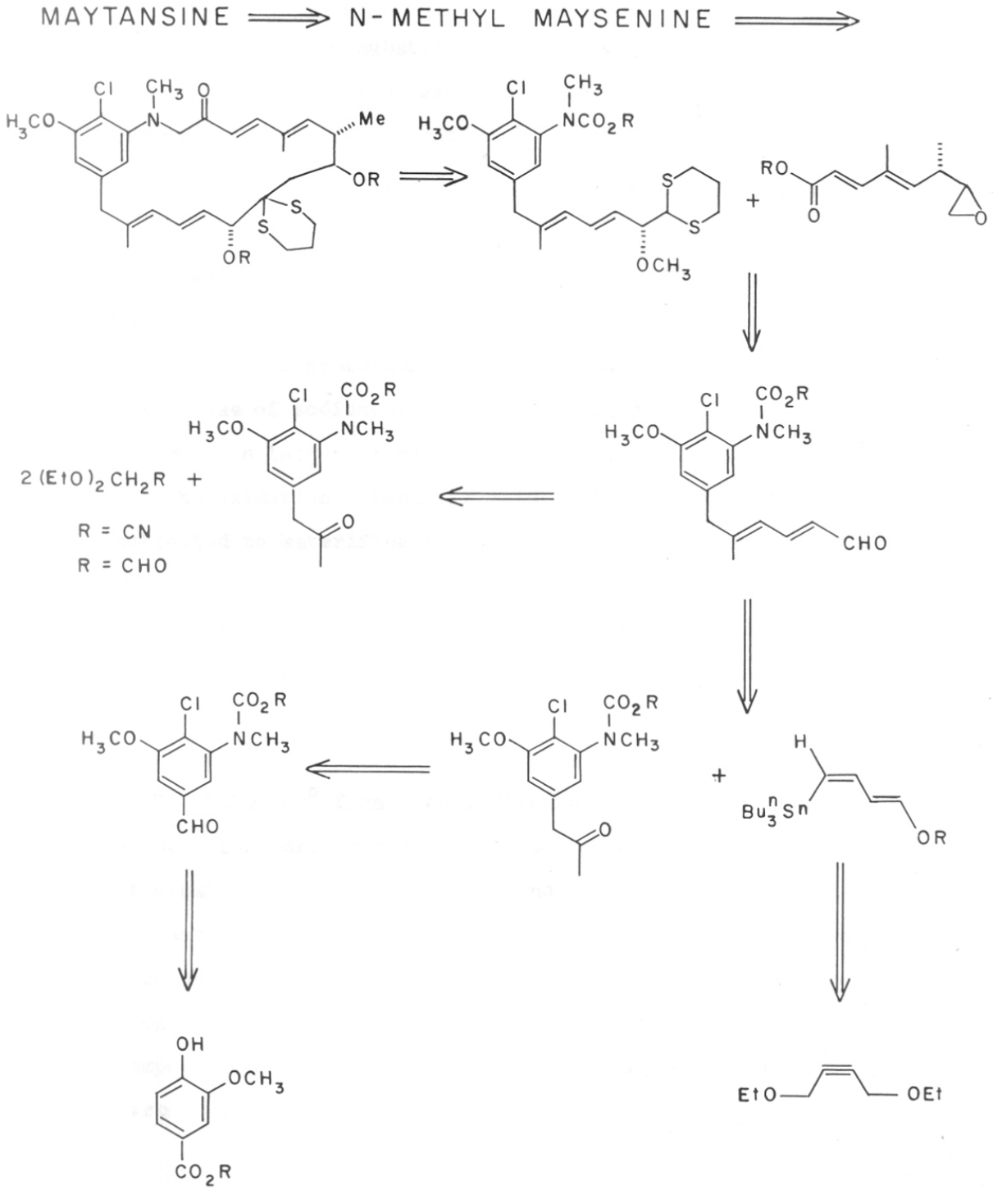
During the present investigation, it was felt that the Western zone together with the Southern zone constitute the key intermediate dienal (45), which is a common fragment in all the maytansinoid antitumor agents. The development of this intermediate by a simple route will allow for further elaboration to different types of maytansinoids.

From the retrosynthesis study (Scheme-10) of maytansine and N-methyl maysenine, it was felt that such a goal could be achieved from the intermediate ketone by a Wittig or suitable reaction. In the present work the ketone was prepared in a simple sequence of reactions and transformed into the dienal by a sequential two carbon homologation or by a four carbon homologation.

Thus, the strategy involved in the present synthesis of the dienal fragment is (a) the preparation of Western zone

SCHEME 10

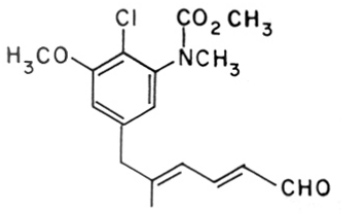
(RETRO SYNTHESIS)



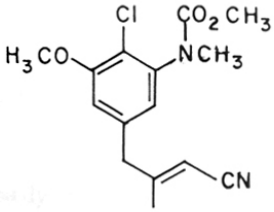
with appropriately substituted aromatic ring (b) the protection of the amino group (c) the conversion to the ketone and further elaboration.

Thus, the present synthesis involves a simple and convenient route for the preparation of the ketone (58) and dienal (45) (Scheme-11) starting from vanilline. Commercially available vanilline was oxidised to vanillic acid (48)[22] or preferably by a modified procedure[23], by making use of sodiumchlorite and sulfamic acid. The only drawback in latter procedure was the high dilution required for the oxidation. Vanillic acid (48), thus obtained was subjected to esterification on treatment with methanol and sulfuric acid to afford the known methylvanillate (49) in quantitative yield. Nitration of methylvanillate (49) was carried in glacial acetic acid with conc. nitric acid at 0° to result the yellow nitro compound (50). Compound (50) on reaction with thionyl chloride in dry dimethylformamide (DMF) at 80-100° furnished a mixture of compounds. The crude chloroform extract was passed through a dry column of alumina to remove the unreacted starting material and sulphur formed during the course of reaction. The chloro compound (51) thus obtained was crystallised from methanol (60% yield). Alternatively 51 was prepared from the nitro compound (50) on treatment with a triphenylphosphine - carbontetrachloride complex in dry DMF at 95-100° for 4 hr,

SCHEME – II



45



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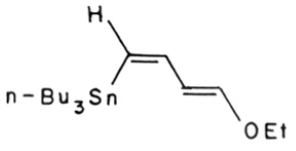

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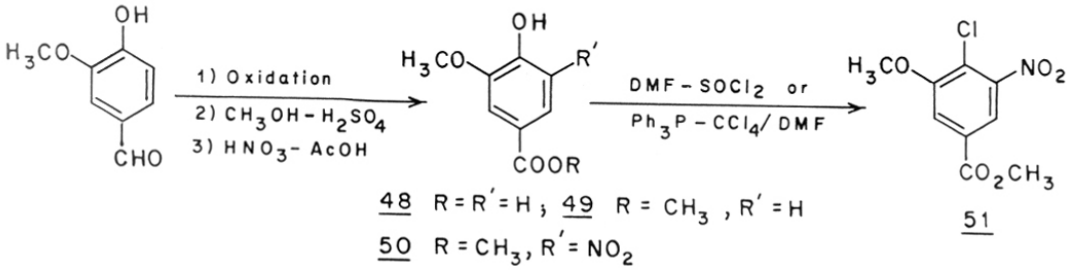
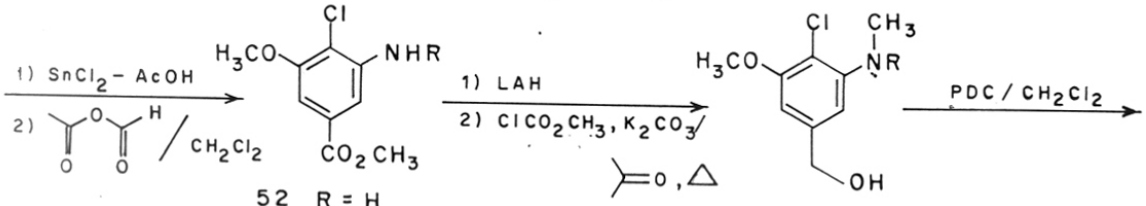


48 R = R′ = H; 49 R = CH_3, R′ = H

50 R = CH_3, R′ = NO_2

51

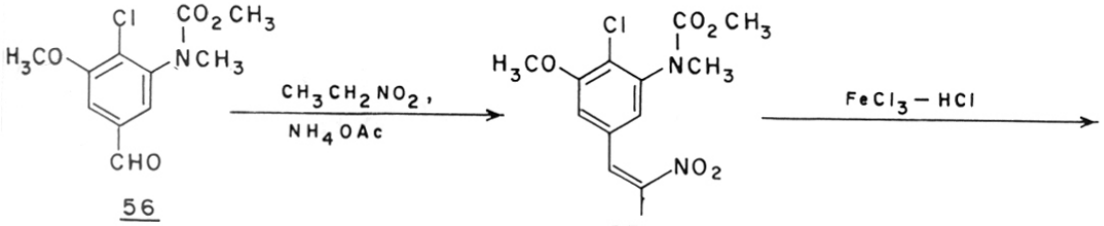


52 R = H

53 R = CHO

54 R = H

55 R = CO_2CH_3



56

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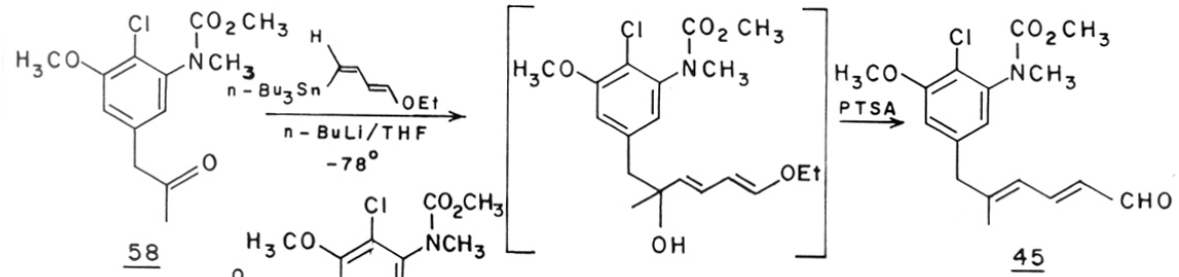

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45

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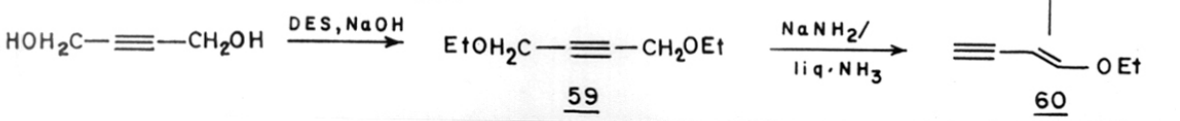

59

47

60

in 25% yield. The ready formation of this aromatic segment (51) provides a key intermediate in the Western zone of the molecule, where the requisite substituents are present at the positions mentioned earlier.

Having prepared 51, it was further transformed into the ketone (58) by a sequence of reactions discussed below. Reduction of the nitro compound (51) in methanol by employing stannous chloride-acetic acid at room temperature resulted the amino compound (52) in 79% yield. Compound (52) can also be conveniently made by catalytic hydrogenation of 51 by using palladium-carbon as catalyst. However, hydrogenation often fails due to the poisoning of the catalyst by traces of sulphur compounds left in the previous thionyl chloride reaction. Compound (52) was thus obtained as pale yellow needles, m.p. 88-89°. This product was reported earlier by Meyers and Kane[12] as a low melting solid.

In the earlier synthesis reported by Meyers et al.[12] the N-methylation was achieved by the adoption of Kadin[13] procedure. In the present work it was carried out in two steps: (a) formylation and (b) lithium aluminium hydride (LAH) reduction, during which both the formyl and ester groups were reduced. Thus, reaction of the amine (52) in dichloromethane with acetic-formic anhydride at room temperature for 1 hr resulted in the formation of N-formylamino derivative (53)

in quantitative yield. In the ^{1}H-NMR spectrum of 53 the formyl and -NH protons resonated as singlets at δ 8.68 and 8.53 respectively, while rest of the signals appeared at the expected chemical shifts. IR spectrum showed the absorptions at 1710 cm^{-1} (carbonyl) and 3400 cm^{-1} (NH).

The formylamino derivative thus obtained was subjected to reduction of both the ester and formyl groups. Thus, reaction of 53 with an excess of LAH at room temperature for 20 hr gave the amino alcohol (54) in 79% yield. The ^{1}H-NMR spectrum (Fig.1) of 54 in $CDCl_3$ showed the N-methyl and benzylic protons at δ 2.87 and 4.60 as singlets respectively, while the remaining protons signals appeared at their expected chemical shifts.

The amino alcohol (54) on reaction with methyl chloroformate and anhydrous potassium carbonate in acetone at reflux temperature for 12 hr and subsequent isolation and mild hydrolysis of the crude product with methanolic sodium hydroxide at room temperature for 2 hr afforded the urethane derivative (55) in 87% yield. In the ^{1}H-NMR spectrum (Fig.2) of compound (55) in $CDCl_3$, the methoxyl protons resonated at δ 3.93 as a singlet while the resonance due to the N-methyl protons shifted slightly downfield (δ 2.93) and rest of the signals appeared at their expected chemical shifts. IR spectrum showed the absorptions at 1740 cm^{-1} and 3450 cm^{-1}

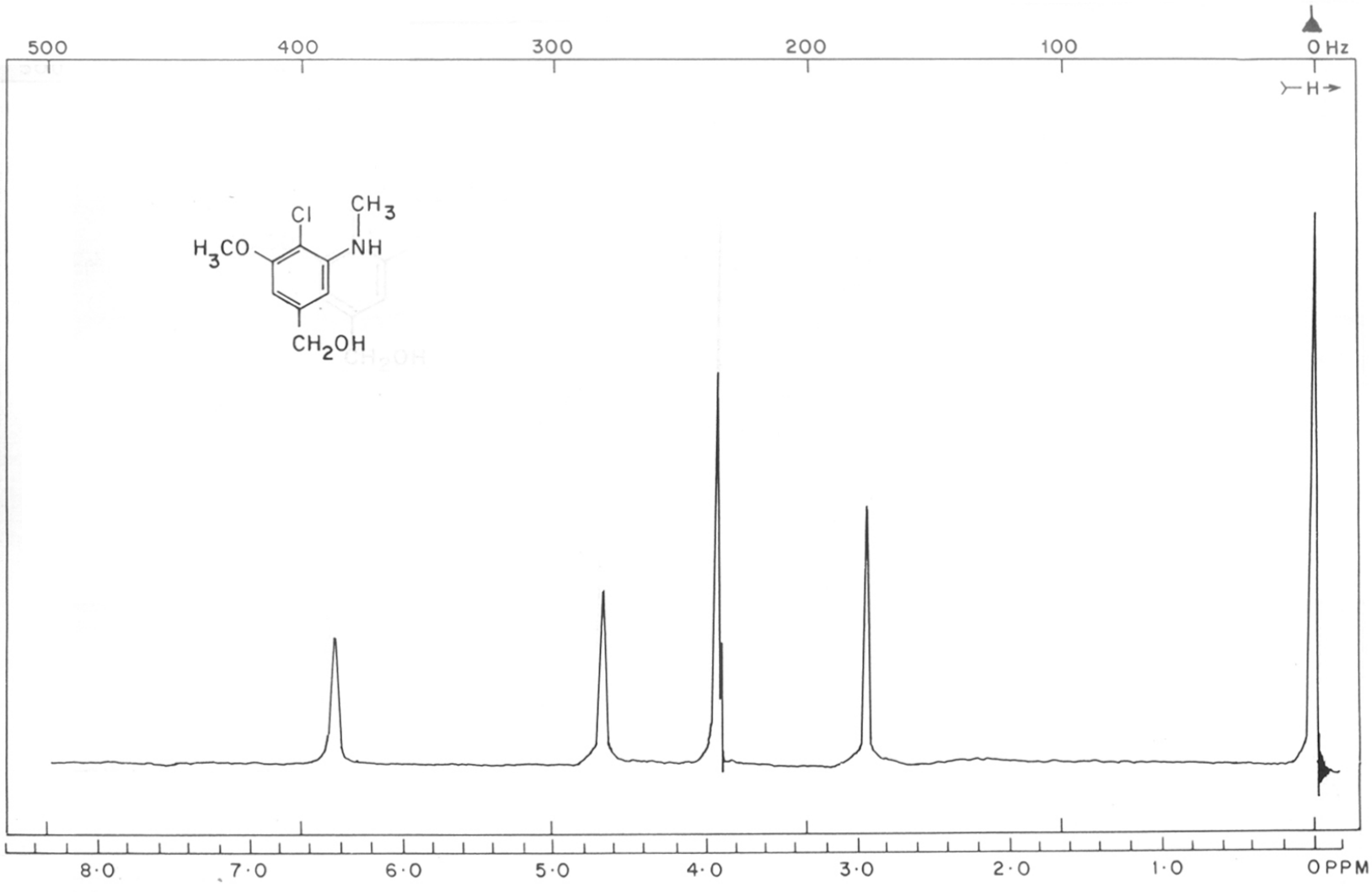

FIG. 1 ^{1}H NMR SPECTRUM OF COMPOUND (54) IN $CDCl_3$

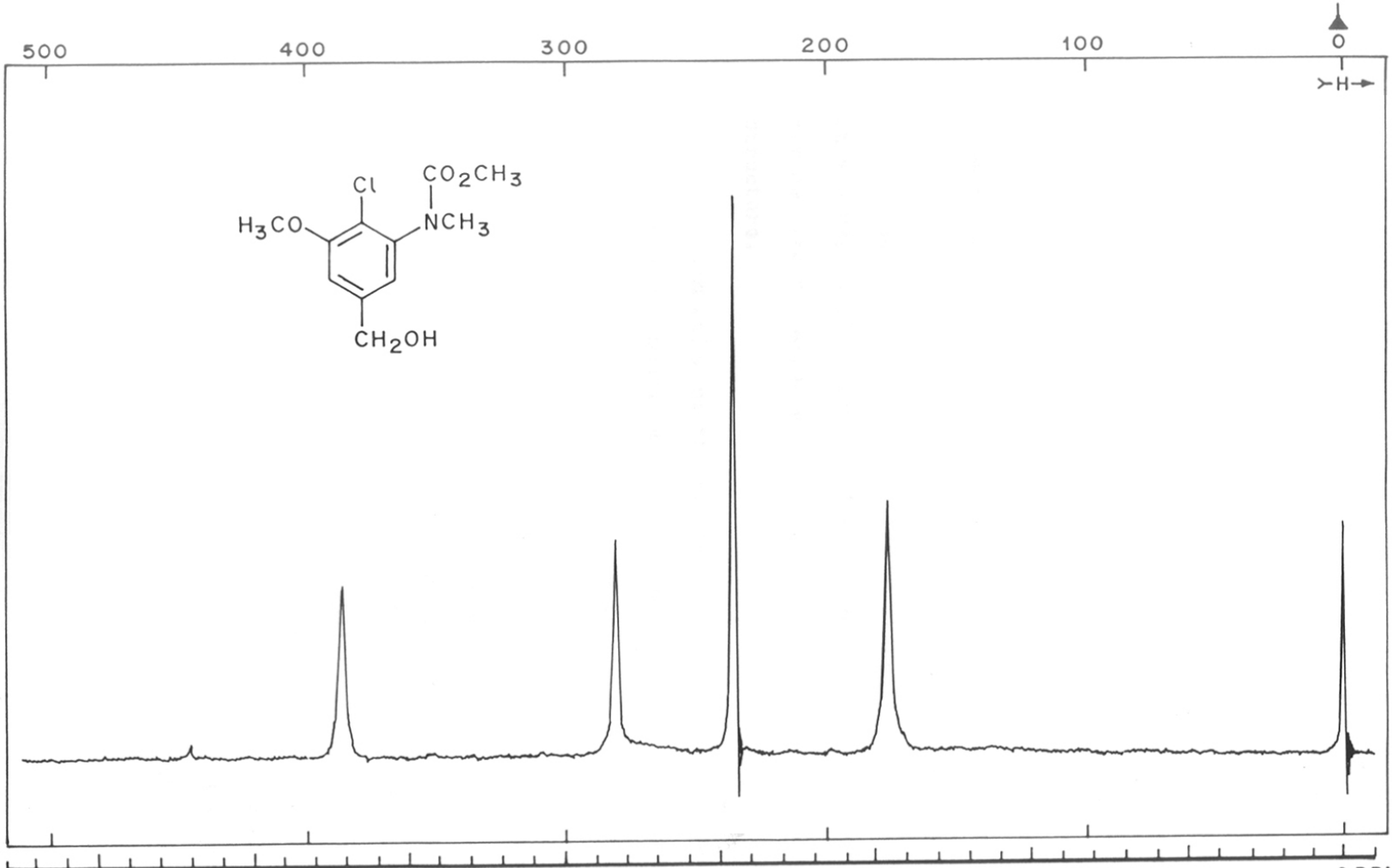

FIG. 2. ^{1}H-NMR SPECTRUM OF COMPOUND (55) IN $CDCl_3$

for carbonyl and -OH functions respectively.

Oxidation of the urethane (55) in dry dichloromethane was carried out with chromiumtrioxide and pyridine at room temperature for 1 hr to afford the aldehyde (56) in 75% yield. In the ^{1}H-NMR spectrum of 56, the formyl proton resonated at δ 9.50 as a singlet, while the remaining proton signals appeared at the expected chemical shifts. The IR spectrum showed the absence of -OH absorption. The molecular ion peak was not seen in themass spectrum, however, there was a fragment at m/e 222 (m-35) which was due to the loss of chlorine. Further fragmentation was in consistence with the assigned structure.

Condensation of the aldehyde (56) with nitroethane in presence of ammoniumacetate at reflux for 30 min. afforded the nitro compound (57) in good yield. It was then reduced with iron powder-hydrochloric acid in ethanol to afford the desired ketone (58) in 61% yield. In the ^{1}H-NMR spectrum (Fig.3) of 58 in CCl_4 the acetyl protons resonated at δ2.16 as a singlet while the benzylic protons were located at δ 3.66 along with $-OCH_3$ protons. The remaining protons resonated at the expected values of chemical shifts. In the mass spectrum the molecular ion peak was seen at m/e 285 and further fragmentation pattern was in accordance with the assigned structure for 58. The acquisition of the ketone (58) furnishes the aromatic precursor which can be utilised

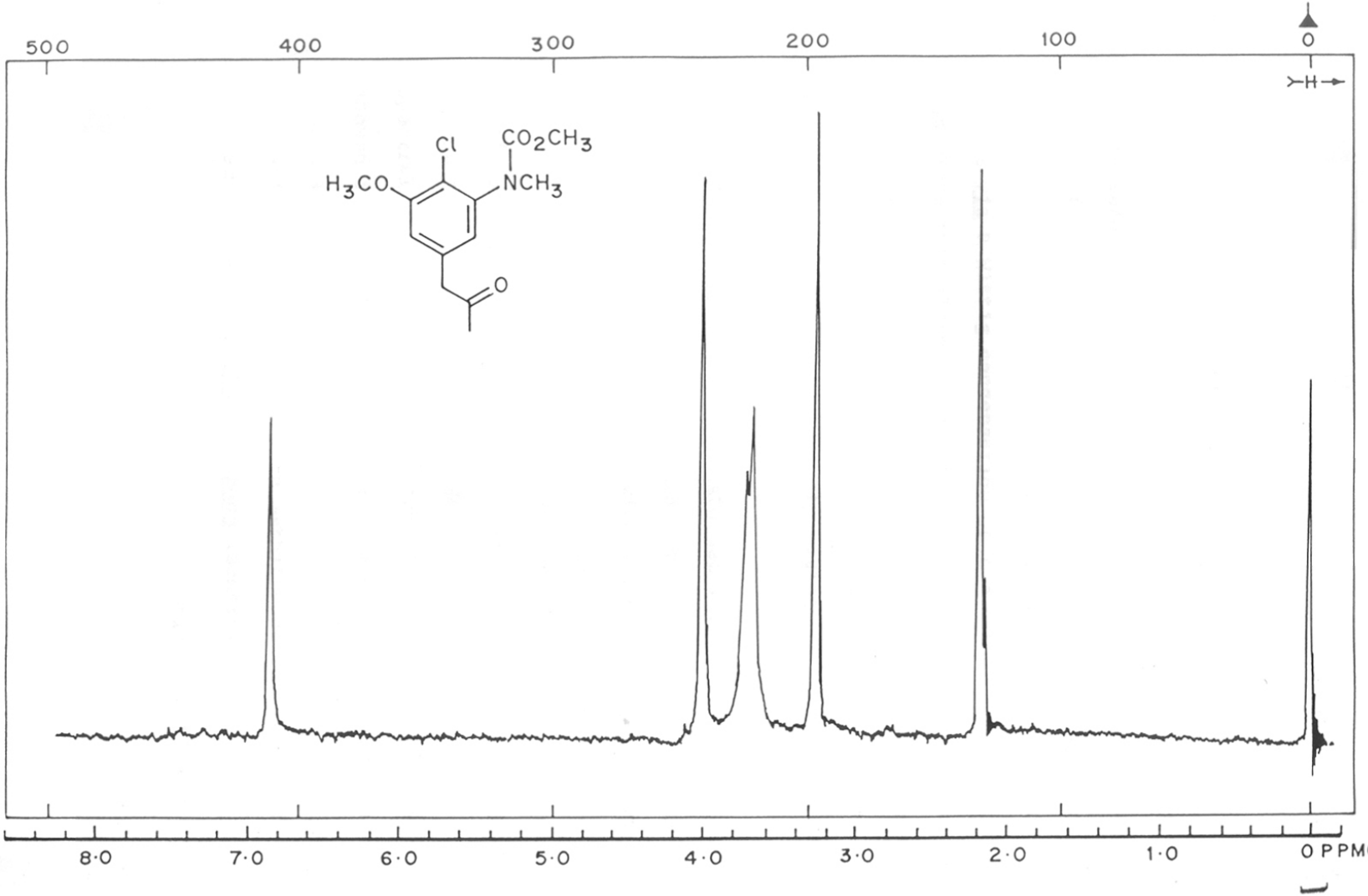

FIG. 3. ^{1}H-NMR SPECTRUM OF COMPOUND (58) IN CCl_4

in coupling to the Southern zone.

Having prepared the key intermediate 58 successfully, efforts were directed towards the elaboration to the dienal fragment (45) of the maytansinoids. To achieve this goal it was looked in two different ways (Scheme-10). The first one was via a Wittig condensation of the ketone (58) with diethylcyanomethylphosphonate and further elaboration into the dienal (45), by homologation adopting the above sequence of reactions. In the second approach, it was aimed to prepare 45 with four carbon elongation, by making use of a four carbon stannane reagent (47).

The ketone (58) was transformed into (46) by a Wittig reaction. Thus, diethylcyanomethylphosphonate prepared by a known[24] procedure, was treated with sodiummethoxide in dry methanol at room temperature. The anion thus generated was then treated with a solution of the ketone (58) in methanol at 0^{o} for 1.5 hr to afford the α,β-unsaturated nitrile (46) in 75% yield. The structure of 46 was characterised from its spectral data. The ^{1}H-NMR spectrum (Fig.4) of 46 in $CDCl_3$ showed it to be a mixture of E-Z isomers (2:1). The vinylic proton appeared at δ 4.95, 5.15 as a singlet for E and Z respectively, while the vinylic methyl appeared at δ 1.75, 1.95 as doublets for cis and trans isomers.

The IR spectrum showed the absorptions at 1725 cm^{-1}

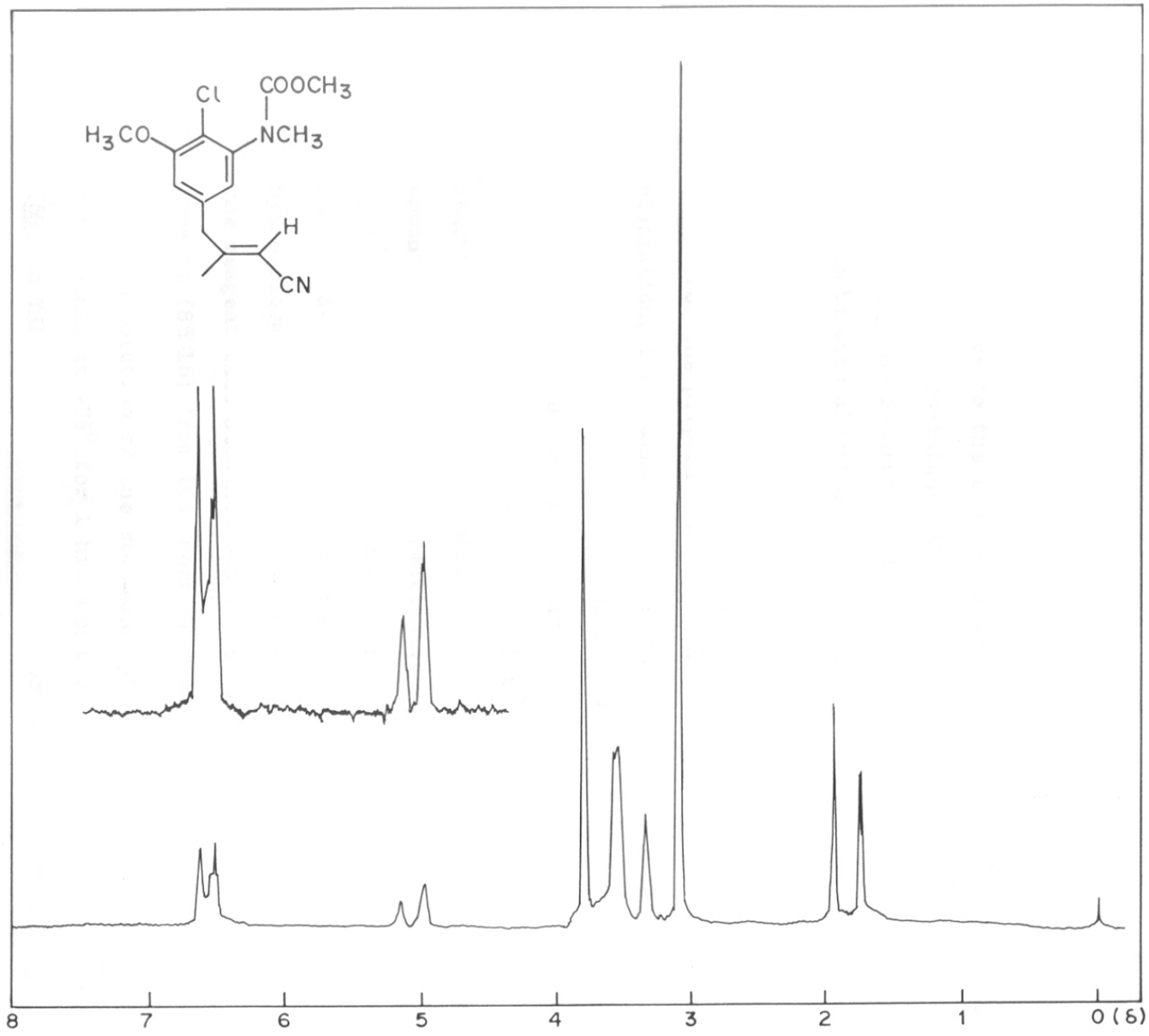

FIG. 4. ^{1}H-NMR SPECTRUM OF COMPOUND (46) IN $CDCl_3$

and 2240 cm^{-1} for the carbonyl and nitrile functionalities respectively. Molecular ion peak in its mass spectrum was not seen, however, the fragment ion observed at m/e 273 (m-35) was due to the loss of chlorine, besides the further fragmentation consistent with the assigned structure. The nitrile (46) on reduction with DIBAL would result the α,β-unsaturated aldehyde, which could be elaborated to 45. However, this work has been temporarily suspended in view of non-availability of DIBAL.

For the preparation of the dienal (45) by a four carbon elongation, the stannane reagent was prepared by a known[25] procedure. Thus, but-2-yn-1,4-diol on treatment with diethyl-sulfate in aqueous sodiumhydroxide at room temperature was converted into the corresponding diethyl ether (59)[26]. Reaction of 59 with a freshly prepared sodium amide in liquid ammonia resulted in the formation of the acetylenic compound (60)[27]. 60 was treated[25] with a freshly prepared tributyl-tinhydride [from bis(tributyl tin) oxide and polymethyl-hydrosiloxane][28] to afford the stannane (47) in good yield. The reagent thus obtained was found to be a mixture of E-Z isomers (85:15) from its spectral data.

A solution of the stannane (47) in dry THF was treated[25] with n-BuLi at -78° for 1 hr. and was reacted with the ketone (58) in THF at -78° for 3 hr. The resulted crude product was isolated and subsequently subjected to hydrolysis with PTSA

in THF at room temperature for 2 hr to furnish 45. From the spectral studies it was found to be a mixture of both the starting material (58) and the dienal (45) (GC). The ^{1}H-NMR spectrum of the product thus obtained showed a resonance for aldehydic proton at δ 9.76 as a doublet, was the indication of the formation of dienal (45). However, all attempts towards the separation of this mixture into pure 45 were unsuccessful. Inspite of the fact that the 45 was formed, but could not be obtained in a pure form. Hence the route was abandoned.

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

Vanillic acid (48)

Method I: A mixture of potassium hydroxide (420 g, 7.5 mol) and water (50 g) was heated on a sand bath at 125°, with vigorous stirring. The mixture gelled and the temperature raised to 150°. Vanillin (152 g, 1 mol.) was added in small portions during a period of 30 min. so as to maintain a constant temperature at 150°. At the end of the addition the mixture became pasty and temperature rose to 190° and stirring continued for an additional 10 min. It was left for cooling, dissolved in water (2 l.), acidified with conc. hydrochloric acid to give a solid, which was filtered, washed and dried to yield 48 (145 g, 86%) as white solid, m.p. 208-209° (lit.[22] m.p. 209-10°).

Method II: To a solution of vanillin (6.25 g, 0.05 mol) and sulphamic acid (6.5 g, 0.067 mol) in water (1 l.), a solution of sodium chlorite (5.4 g, 0.060 mol) in water (80 ml) was added at room temperature over a period of 25 min. The contents of the reaction mixture were stirred for 1 hr. The precipitate separated was filtered and washed with water to afford 48 (4.9 g, 70%) as white solid, m.p. 208°.

Methyl vanillate (49)

The acid (48, 130 g, 0.77 mol) and conc. sulfuric acid

(15 ml) in dry methanol (2.6 l.) were heated under reflux for 48 hr. The mixture was concentrated to about 500 ml and poured over ice-cold water. The oily layer thus separated was extracted with chloroform washed with water and dried (Na_2SO_4). Evaporation of the solvent gave an oil, which crystallised on addition of hexane into colourless needles of the ester (49, 117 g, 83%), m.p. 62° (lit.[29] m.p.63-64°).

Methyl 4-hydroxy-3-methoxy-5-nitrobenzoate (50)

To a stirred and cooled (0-5°) solution of the ester (49, 100 g, 0.54 mol) in glacial acetic acid (500 ml) was added slowly a solution of conc. nitric acid (55 g, sp.gr. 1.42) in glacial acetic acid (50 ml) over a period of 2 hr. The contents of the flask were allowed to reach slowly to room temperature and stirred for an additional 4 hr during which the nitro compound separated as a yellow solid. Ice-cold water (1000 ml) was added to the reaction and the light yellow solid was collected and washed with water to give 50 (104 g, 84%), m.p. 153° (lit.[12] m.p. 154-55°). ^{1}H-NMR ($CDCl_3$)δ 3.95 (s, 3H, $-OCH_3$), 4.02 (s, 3H, $-OCH_3$), 7.73 (d, 1H, Ar-H), 8.40 (d, 1H, Ar-H).

Methyl 4-chloro-3-methoxy-5-nitrobenzoate (51)

Method I: Thionyl chloride (150 ml) was added dropwise to DMF (150 ml), during 30 min. at 0°. After being stirred for 30 min. the resulting complex was treated with the nitro

compound (50, 25 g, 0.11 mol) in portions over 15 min. at 0°. The reaction mixture was heated at 80° for 2 hr and further at 100° for 8 hr. It was cooled, poured over ice-water (600ml) and stirred for 2 hr. The dark gummy product was extracted with chloroform and washed with water, dried. The chloroform extract was passed through a column of alumina (chloroform as eluent) to give the crude product (~25-30 g) along with sulfur (~10 g). It was dissolved in hot methanol (400 ml) and filtered to remove sulfur, the filtrate was concentrated to yield crystalline chloro compound (51, 16.2 g, 60%), m.p. 103° (lit.[12] m.p. 103-4°).

Method II: A solution of triphenylphosphine (0.340 g, 0.001 mol) in carbon tetrachloride (3.5 ml) was heated under reflux for 3 hr, followed by evaporation of the solvent. The dried complex was stirred with 50 (0.227 g, 0.001 mol) in DMF (3 ml) at 95-100° for 4 hr. DMF was removed under vacuum, the residue was taken up in chloroform, washed with water and dried (Na_2SO_4). Evaporation of the solvent and chromatographic purification (alumina, benzene) of the resulting residue gave the chloro compound (51, 0.06 g, 25%) as colourless needles, m.p. 103°.

Methyl 3-amino-4-chloro-5-methoxy benzoate (52):

To a suspension of 51 (24.5 g, 0.1 mol) in methanol (400 ml) and glacial acetic acid (100 ml), powdered stannous

chloride (120 g, 0.64 mol) was added and the contents were stirred at room temperature for 12 hr. It was concentrated under reduced pressure; the thick viscous liquid was dissolved in chloroform (500 ml), cooled and made alkaline with ammonium hydroxide (250 ml) while stirring. The white precipitate of stannic hydroxide was filtered through celite. The filtrate was washed with water, dried (Na_2SO_4) and concentrated to furnish the amino compound (52, 17 g, 79%) as pale yellow solid. Recrystallisation from methanol afforded pale yellow needles, m.p. 88-89° (lit.[12] m.p. low melting solid).

Methyl 4-chloro-3-formylamino-5-methoxybenzoate (53)

A solution of acetic-formic anhydride (13.2 g, 0.15 mol) in dichloromethane (50 ml) was added dropwise, to a stirred solution of the amine (52, 15 g, 0.07 mol) in dichloromethane (150 ml), over a period of 30 min. at room temperature. After 30 min. it was further diluted with dichloromethane (300 ml), washed with water, 5% aqueous sodium bicarbonate and water. The organic phase dried (Na_2SO_4) and evaporated to give 53 (15.5 g, 92%) as white crystalline compound. Trituration with hexane followed by drying the solid gave pure 53, m.p. 157-158°. ^{1}H-NMR (acetone d_6):δ 3.88 (s, 3H, $-OCH_3$), 3.96 (s, 3H, OCH_3), 7.38 (br.s, 2H, ArH), 8.53 (s, 1H, -NH), 8.68 (s, 1H, -NCHO);

IR($CHCl_3$): 1710 cm^{-1} (carbonyl), 3400 cm^{-1} (NH); M^+ 243.

4-Chloro-3-methoxy-5-(methylamino)benzyl alcohol (54)

To a stirred and cooled suspension of LAH (4.24 g, 0.11 mol) in THF (50 ml) under nitrogen, a solution of the ester (53, 12 g, 0.05 mol) in THF (150 ml) was added over a period of 30 min. Then the contents were stirred at room temperature for 20 hr. The reaction was quenched by the addition of water (4 ml), 3N sodium hydroxide (4 ml) and water (12 ml) and filtered. The residue was washed with ethyl acetate and the filtrate was evaporated to give a thick yellow oil. Chromatographic purification (silica gel, benzene) of the crude product furnished the amino-alcohol (54, 7.8 g, 79%) as colourless needles, m.p. 83-84° (lit.[17] b.p. 145-150°/0.1 mm); ^{1}H-NMR ($CDCl_3$): δ 2.87 (s, 3H, $-NCH_3$), 3.84 (s, 3H, $-OCH_3$), 4.60 (s, 2H, $-CH_2Ar$), 6.32 (s, 2H, Ar-H); IR (Nujol): 3240 cm^{-1} (OH), 3400 cm^{-1} (-NH).

Methyl [2-chloro-5-hydroxymethyl-3-methoxyphenyl]methyl carbamate (55)

A mixture of the alcohol (54, 7 g, 0.035 mol), methyl chloroformate (13 g, 0.14 mol) and potassium carbonate (28 g, 0.20 mol) was heated under reflux in dry acetone (80 ml) for 12 hr. The contents were cooled, acetone was removed, the residue was treated with water and stirred for

30 min. The thick oily compound separated was extracted with ether. Evaporation of ether gave an oil, which was hydrolysed with 4% methanolic sodium hydroxide (70 ml) at room temperature for 2 hr. Methanol was removed, the residue was treated with water and extracted with ether. The organic layer was washed with water, dried (Na_2SO_4) and concentrated to yield the urethane derivative (55, 7.8 g, 87%) as a low melting solid, m.p. 86-89°. ^{1}H-NMR ($CDCl_3$):δ 2.93 (s, 3H, $-NC\underline{H}_3$), 3.93 (s, 6H, $-OCH_3$), 4.70 (s, 2H, $-C\underline{H}_2Ar$), 6.46 (br.s, 2H, Ar-H); IR (Nujol): 1740 cm^{-1} (ester carbonyl), 3450 (OH); M^+ 259.

Analysis: Calculated for $C_{11}H_{14}ClNO_4$: C, 50.9; H, 5.4; N, 5.4; Cl, 13.5; Found: C, 50.5; H, 5.6; N, 4.9; Cl, 12.7%.

Methyl [2-chloro-5-formyl-3-methoxyphenyl]methyl carbamate (56)

To a cooled (0°) and stirred suspension of chromium trioxide (13.8 g, 0.14 mol) in pyridine (22 g, 0.28 mol) and dichloromethane (100 ml) was added a solution of the alcohol (55, 6 g, 0.023 mol) in dichloromethane (20 ml) in one portion. After 1 hr, the reaction mixture was decanted, the residual complex was washed with ether. The combined organic extract was washed successively with 5% aqueous sodium hydroxide, 5% hydrochloric acid, 5% aqueous sodium bicarbonate and water. It was dried (Na_2SO_4) and evaporated to a residue, which was filtered

through a short column of silica gel (benzene) to give the aldehyde (56, 4.46 g, 75%) as colourless solid, m.p. 95-100°. ^{1}H-NMR ($CDCl_3$):δ 3.3 (s, 3H, NCH_3), 3.76 (s, 3H, $-OCH_3$), 4.10 (s, 3H, $-OCH_3$), 7.56 (s, 2H, Ar-H), 9.50 (s, 1H, -CHO); IR (Nujol): 1725 cm^{-1} (carbonyls); m/e 222 (m-35).

Analysis: Calculated for $C_{11}H_{12}ClNO_4$: C, 51.3; H, 4.6; N, 5.4; Cl, 13.6; Found: C, 51.7; H, 4.9; N, 5.1; Cl, 13.4%.

Methyl[2-chloro-3-methoxy-5-(2-nitro-1-propenyl)phenyl]methyl carbamate (57)

A solution of the aldehyde (56, 4 g, 0.01 mol) and ammonium acetate (1.44 g, 0.018 mol) in nitroethane (50 ml) was heated under reflux for 30 min. The reaction mixture was cooled to room temperature, diluted with dichloromethane (50 ml) and further cooled to -78°. The precipitated solid was filtered, washed with ice-cold dichloromethane (50 ml). The combined filtrate was evaporated and the residue was crystallised from ether to afford 57 (4.20 g, 86%) as yellow solid, m.p. 105-9°. ^{1}H-NMR ($CDCl_3$):δ 2.43 (s, 3H, $=C(CH_3)$), 3.13 (s, 3H, NCH_3), 3.6 (br.s, 4H, $-OCH_3$ and $>=<H$), 3.9 (s, 3H, $-OCH_3$), 6.83 (s, 2H, Ar-H); IR (Nujol): 1340 cm^{-1} and 1510 cm^{-1} ($C-NO_2$), 1730 cm^{-1} (carbonyl); m/e 279 (m-35).

Analysis: Calculated for $C_{13}H_{15}ClN_2O_5$: C, 49.6;

H, 4.7; Cl, 11.1; N, 8.9; Found: C, 49.3; H, 5.0; Cl, 11.0; N, 8.8%.

Methyl [2-chloro-3-methoxy-5-(2-oxopropanyl)phenyl]methyl carbamate (58)

Iron powder (3.38 g), ferric chloride (0.132 g) was added in one portion, to a solution of the compound (57, 2.7 g, 0.008 mol) in ethanol (22.6 ml) and water (58.4 ml), under vigorous stirring. Conc. hydrochloric acid (2.2 ml) was then added in dropwise manner. The reaction mixture was heated at reflux for 4 hr. It was cooled, filtered and the residue was washed sequentially with methanol (45 ml) and hot water (45 ml). The filtrate was evaporated under vacuum to 80 ml, treated with water and made alkaline with solid sodium carbonate. The aqueous phase was extracted with ether. The ethereal layer was washed with water, dried (Na_2SO_4) and evaporated to get a residue which was chromatographically purified (silica gel, benzene) to furnish the ketone (58, 1.5 g, 61%) as a low melting solid. ^{1}H-NMR (CCl_4):δ 2.16 (s, 3H, $-COCH_3$), 3.23 (s, 3H, NCH_3), 3.66 (s, 5H, $-COCH_2-$ and $-OCH_3$), 4.00 (s, 3H, $-OCH_3$), 6.83 (s, 2H, Ar-H); IR: 1710-1740 cm^{-1} (broad, carbonyls); M^+ 285.

Methyl[2-chloro-3-methoxy-5-(3-cyano-2-methyl-2-propenyl) phenyl]methyl carbamate (46)

To a freshly prepared sodium methoxide [prepared from

sodium (0.025 g, 1 g.atom) in methanol (2 ml)] solution in methanol under nitrogen, a solution of diethyl cyanomethyl phosphonate (0.132 g, 0.75 m.mol) in methanol (2 ml) was added at room temperature. After 15 min. it was cooled (0^{o}) and stirred with the ketone (58, 0.142 g, 0.5 m.mol) in methanol (2 ml) for 1.5 hr. The reaction was quenched with water and extracted with ether. The organic layer was washed with water, dried (Na_2SO_4) and evaporated to give α,β-unsaturated nitrile (46, 0.115 g, 75%) as an oil. ^{1}H-NMR ($CDCl_3$): δ 1.75, 1.95 (d, 3H, $\overset{CH_3}{\diagdown}$, ratio ca. 1:2), 3.05 (s, 3H, NCH_3), 3.3, 3.5 (s, 2H, $ArCH_2$- ratio ca. 1:2), 3.60 (s, 3H, $-OCH_3$), 3.75 (s, 3H, $-OCH_3$), 4.95, 5.15 (d, 1H, vinylic, ratio ca. 2:1), 6.5, 6.65 (s, 2H, Ar-H, ratio ca. 2:1); IR: 1725 cm^{-1} (ester carbonyl), 2240 cm^{-1} (nitrile); m/e 273 (m-35).

1,4-Diethoxy-2-butyne (59)

To a solution of butyne-1,4-diol (17.2 g, 0.2 mol) in water (32 ml), sodium hydroxide (20 g, 0.5 mol) and diethylsulfate (77 g, 0.5 mol) were added in turn during 1.5 hr, while maintaining the temperature at 35-40^{o}. After the complete addition, the reaction mixture was heated at 90^{o} for 3 hr. It was cooled to room temperature, ice-cold water was added and extracted with ether. The unwashed ethereal layer was dried (Na_2SO_4), solvent was removed and

the residue was distilled under vacuum to afford 59 (21.5 g, 75%), b.p. 85-90°/20 mm (lit.[26] b.p. 76°/12 mm).

1-Ethoxy-but-1-en-3-yne (60)

To a freshly prepared suspension of sodium amide (9.7 g, 0.25 mol) in liquid ammonia (150 ml), was added 59 (14.4 g, 0.1 mol). After being stirred for 1 hr, ether (25 ml) was added and ammonia was allowed to evaporate. The reaction mixture was treated with ice-cold water and extracted with ether. The unwashed ethereal layer was dried (Na_2SO_4), evaporated and the resulting residue was distilled under reduced pressure to afford 60 (7.7 g, 81%), b.p. 32-33°/10 mm (lit.[27] b.p. 32°/10 mm).

1-Tri-n-butylstannyl-4-ethoxybutadiene (47)

A mixture of 60 (0.960 g, 10 m.mol) freshly prepared tri-n-butyl tinhydride [2.90 g, 10 m.mol; prepared from bis(tri-n-butyl tinoxide and polymethyl hydrosiloxane)] and azobisisobutyronitrile (AIBN) was heated at 90° for 10 hr. The reaction mixture was distilled under vacuum to give the stannane (47, 2.31 g, 60%) as a thick oil, b.p. 80-85°/0.03 mm (lit.[25] 120-130°/0.3 mm).

Methyl[2-chloro-3-methoxy-5-(2-methyl-6-oxo-2,4-hexadienyl) phenyl] methyl carbamate (45)

To a stirred solution of the stannane (47, 0.650 g, 1.68 m.mol) in dry THF (7 ml) at -78° under nitrogen was

added n-BuLi (0.112 g, 1.75 m.mol; in hexane) over 5 min. After 1 hr, the ketone (58, 0.436 g, 1.53 m.mol) in THF (5 ml) was added and left at -78° for 3 hr. The reaction was quenched with 5% aqueous sodium bicarbonate and extracted with ether. The organic layer was washed with water, dried (Na_2SO_4) and evaporated to an oily compound. The above crude product, thus obtained was stirred with PTSA (ca.60 mg) in THF (5 ml) at room temperature for 2 hr. Solvent was evaporated and the residue was taken up in ether. Ethereal layer was washed with 5% aqueous sodium bicarbonate, dried (Na_2SO_4) and evaporated under reduced pressure. The resulting residue was purified chromatographically (silica gel, acetone-benzene 5:95) to afford the dienal (45) as a mixture along with the starting material (58).

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SUMMARY

S U M M A R Y

Synthesis of macrolides, the large ring lactone molecules, has attracted the attention of organic chemists during the recent years due to their biological and physiological activities. This thesis describes convenient syntheses of two important macrolides, zearalenone and recifeiolide and a simple synthesis of methyl[2-chloro-3-methoxy-5(2-methyl-6-oxo-2,4-hexadienyl)phenyl] methyl carbamate, a key intermediate in the synthesis of maytansinoids.

CHAPTER I - SYNTHESIS OF (±)ZEARALENONE

(±)Zearalenone (1), a mould metabolite of pathogenic fungi, Gibberela zeae, was isolated by Urry et al. Due to its potent steroid like anabolic and uterotrophic activity several synthetic pathways have been developed. The methods developed by Merck and Syntex groups utilised a Wittig approach, while the Tsuji's method involved an intramolecular alkylation for C-C bond formation.

In the present method the key intermediate (2) was synthesised by a simple and straightforward method starting from easily accessible materials. The strategy involves the preparation of aliphatic (3) and aromatic (4) portions separately and condensing 3 and 4 to get 2 on further elaboration.

Aliphatic moiety 3 has been prepared starting from 2,3-dihydropyran. Thus, 5-hydroxy pentanal prepared from dihydropyran was converted into the dithiane derivative (5) by treatment with 1,3-propanedithiol.

Metallation of the hydroxydithiane (5) with 2 molar equivalents of n-BuLi followed by alkylation with 2-(3-iodopropyl)

2-methyl-1,3-dioxolane prepared by known procedure afforded the desired alkylated product (6). 6 on subsequent treatment with PTSA/MeOH furnished 7. The alcoholic function in compound (7) was protected by treatment with dihydropyran to give 8, which was then reduced with $NaBH_4$ in methanol to 3.

For the construction of aromatic moiety (4), orcinol was formylated and converted to 2,4-dimethoxy-6-methyl benzaldehyde, which on oxidation with $KMnO_4$ followed by esterification afforded the ester (4a). Treatment of 4a with LDA and diphenyldisulfide resulted in the formation of 4b, after hydrolysis with ethanolic potassium hydroxide.

The condensation of 3 and 4b was carried in the presence of pyridine in dichloromethane to afford 9, which on mild hydrolysis provided the hydroxy ester (10). The alcohol (10) was transformed into the corresponding iodide (12) via its mesylate (11).

However, the attempted alkylation of 12 with potassium

bis-trimethylsilylamide was found to be unsuccessful. It is likely that ω-bromodithiane derivatives undergo intramolecular alkylation to form sulfonium bromides (A) which may undergo elimination under basic conditions to give compounds of type (B).

In view of the above difficulty, it was felt that the protection of the carbonyl group as ethylene ketal would solve the problem. Consequently, the mesylate (11) was subjected to desulfurisation with mercuric chloride-mercuric oxide in aqueous acetonitrile to afford the ketone (13). Subsequent ketalisation of 13 with ethyleneglycol to (14) followed by treatment with sodium iodide - sodium bicarbonate in acetone furnished 2.

Since the intramolecular alkylation of the iodide (2) with potassium bis-trimethyl silyl amide and further elaboration to (±)zearalenone (1) is well established in literature, the synthesis of 2 constitutes the total synthesis of (±)zearalenone.

CHAPTER II - SYNTHESIS OF (±)RECIFEIOLIDE

Recifeiolide (1) (11-hydroxy-trans-8-dodecenoic acid lactone) has been isolated from a fungus Cephalosporium recifei by Vesonder et al.

Present work describes a convenient synthesis of the hydroxy-acid (2), the key intermediate in the synthesis of 1, through two different approaches: (a) the Wittig approach and (b) the acetylenic approach.

(a) The Wittig Approach

The main strategy in this work was to synthesise a C-8 segment (3) (the aldehyde-ester) and a C-4 segment (4) (the phosphonium salt) separately and condensing them by a Wittig reaction to give 2, which can be lactonised to (±)1.

The C-8 segment was prepared from easily available caprolactone. Thus, 6-bromo-1-(tetrahydropyranyloxy)-hexane, obtained from caprolactone, was treated with sodio salt of diethylmalonate in DMSO to afford the diester (5). Treatment of 5 with potassium acetate in DMSO and mild hydrolysis of the resultant product gave the ester 6. Oxidation of 6 with PDC resulted in the formation of the required C-8 moiety (3).

Compound 4 was prepared according to Gerlach method. Thus, 1,3-butanediol was converted to its monotosylate with p-toluenesulfonyl chloride in pyridine, which on further treatment with potassium iodide in acetone and refluxing with triphenyl phosphine in benzene furnished 4. The Wittig

condensation of 3 and 4 was effected with n-BuLi to afford the ester 7, which on saponification with methanolic potassium hydroxide gave the hydroxy-acid (2) as a mixture of E-Z isomers (2:1).

(b) The Acetylenic Approach

The above synthesis did not provide cleanely the desired isomer of 2. To solve this problem, a stereo-selective route to (±)recifeiolide was developed by making use of an acetylenic precursor.

Alkylation of 4-pentyne-1-ol, generated in situ from tetrahydrofurfuryl chloride (with lithium in liq. ammonia) with n-butylbromide afforded the acetylenic alcohol 8. Compound 8 on "acetylene-zipper" reaction with $NaNH_2$ in 1,3-diaminopropane and subsequent reaction of the resultant product with dihydropyran gave 9.

Compound (9) on sequential treatment with n-BuLi, BF_3-Et_2O and methyloxirane furnished 10. The triple bond in 10 was reduced with sodium in liquid ammonia to give the olefin 11. For the preferential further transformation on the primary alcoholic function, the secondary alcohol group was protected as its benzoate (12), with benzoyl chloride in pyridine and then subjected to depyranylation to obtain the alcohol 13.

Sequential oxidation of 13 with PDC in dichloromethane, alkaline silver oxide in ethanol afforded a mixture of acids 14 and 2. Hydrolysis of this mixture with sodium methoxide in methanol and neutralisation resulted the hydroxy-acid (2), with a trans double bond. Since the lactonisation of 2 has been reported by many groups, the synthesis of 2 constitutes the total synthesis of (±)recifeiolide (1).

CHAPTER III - PREPARATION OF METHYL[2-CHLORO-3-METHOXY-5-(2-METHYL)-6-OXO-2,4-HEXADIENYL)PHENYL]-METHYL CARBAMATE: A KEY INTERMEDIATE IN THE SYNTHESIS OF MAYTANSINOIDS.

Maytansinoids are clinically very important molecules. Maytansine (1) isolated from the plant *Maytenus ovatus* is an exceptionally interesting ansa macrolide. Its anti-tumour activity and effectiveness as anti-cancer drug has prompted many organic chemists to develop simple methods for the synthesis of 1.

In the present work, efforts were made to synthesise the dienal 2, the western zone together with southern zone, a key intermediate for the synthesis of maytansinoids. To achieve this goal, an intermediate ketone (3) was prepared which could be transformed into 2 by a sequential two carbon homologation or by a four carbon homologation.

The ketone (3) was prepared starting from vanilline. Thus, vanilline on oxidation followed by esterification ($MeOH-H_2SO_4$) gave methyl vanillate. It was nitrated with nitric acid-acetic acid at 0^oC and further converted to methyl 4-chloro-5-methoxy-3-nitro benzoate on refluxing with $DMF-SOCl_2$. Reduction of the nitro compound with stannous chloride-acetic acid in methanol and subsequent reaction with acetic-formic anhydride in dichloromethane afforded methyl 4-chloro-3-formylamino-5-methoxy benzoate. The formylamino derivative was subjected to LAH reduction to give the alcohol (4). The reaction of 4 with methyl chloroformate-potassium carbonate in refluxing acetone followed by hydrolysis (NaOH/MeOH) of the resulting product furnished the urethane derivative 5.

Oxidation of 5 with PDC in dichloromethane and subsequent condensation with nitroethane in the presence of ammonium acetate followed by reductive hydrolysis with iron powder, ferric chloride and conc. HCl afforded the ketone (3).

The four carbon stannane reagent (8) was made by a known procedure from but-2-yne-1,4-diol. Treatment of 8 with n-BuLi followed by the reaction with 3 in THF and subsequent hydrolysis (PTSA) gave a product, which was found to be a mixture of both the starting material (3) and the dienal (2). However, all attempts towards separation of this mixture were unsuccessful. Hence, an attempt was made to synthesise 2 from 3 by a two carbon homologation. Thus, the reaction of 3 with diethyl cyanomethyl phosphonate in the presence of sodium methoxide in methanol gave the α,β-unsaturated nitrile (6) as a mixture of E-Z isomers (2:1). The reduction

of 6 with DIBALH would result 7, which could be elaborated to 2. However due to the non-availability of DIBALH this work has been temporarily suspended.

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