SYNTHESIS OF BIOLOGICALLY ACTIVE COMPOUNDS

COMPUTERISED

A THESIS
SUBMITTED TO THE
UNIVERSITY OF BOMBAY

FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
(IN CHEMISTRY)

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BY

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AUGUST 1986

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No part of this work has been submitted for a degree or diploma or other academic award. The literature concerning the problem investigated has been surveyed and all the necessary references are given. The experimental work has been carried out entirely by me. In accordance with the usual practice, due acknowledgement has been made wherever the work presented is based on the results of other workers.

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Research Guide

C O N T E N T S

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August 1986

(Anil M. Naik)

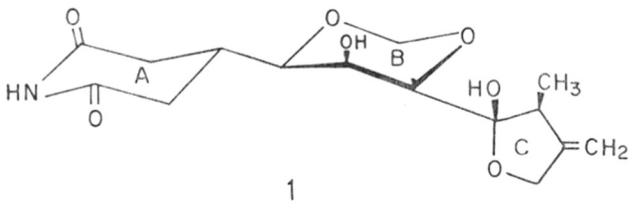
ABSTRACT OF THE
THESIS ENTITLED 'SYNTHESIS OF BIOLOGICALLY ACTIVE COMPOUNDS

This thesis is divided into three chapters.

CHAPTER I - CHEMISTRY OF SESBANIMIDE

In this chapter chemistryof sesbanimide which includes isolation, structure determination, stereochemistry,X-ray crystallography, synthesis and biological activity is discussed.

About 20 percent of the deaths in Western countries are currently ascribed to neoplastic diseases i.e. those diseases which are associated with cancer. This disease being scourge of mankind, has engaged a worldwide attention. As a result, several new natural products of plant as well as microbial origin have been isolated and tested. Sesbanimide (I), isolated from the seeds of Sesbania drummondii and Sesbania punices has been found to be exceptionally potent antitumour agent. It has shown remarkable cytotoxicity against KB cells in vitro and potent inhibiting activity against P-388 murine leukemia in vivo.



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The structure of sesbanimide, in which all the three rings are connected with single bonds was assigned as 1 on the basis of spectroscopic analysis. The relative configuration was established by X-ray crystallographic studies but so far the absolute configuration has not been established.

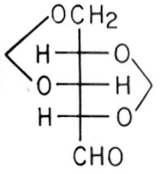
CHAPTER II - SYNTHESIS OF AB RING OF SESBANIMIDE

The absolute configuration of 1 is not known, we therefore proposed to synthesise both the enantiomers which will not only help in determining the absolute configuration but also would help in preparing several new analogues which may prove superior antitumour agents.

This chapter deals with the synthesis of AB ring system of **1**. Analysis of AB ring synstem clearly indicates that carbohydrates can act as a chiral substrate for its synthesis. The chirality for carbon atoms C-7, C-8 and C-9 can be correlated with C-2, C-3 and C-4 carbons of some cheap and abundantly available sugars such as D-sorbitol, D-glucose and D-xylose. Each of these sugars have been employed in the construction of AB ring systems according to schemes 1-3.

Scheme 1

In this approach D-sorbitol was chosen as a starting material and was converted into known 2,4:3,5-di-O-methylene-L-xylose (**2**) and then subjected to the Wittig reaction in the presence of ethoxycarbonylmethylene-triphenylphosphorane to afford the α,β-unsaturated ester (**3**). The Michael reaction of **3** with sodium salt of diethylmalonate followed by deethoxycarbonylation gave the diester (**4**). Compound **4** was treated with ammonia to yield the diamide which on heating formed the glutarimide derivative (**5**). A few problems were encountered in this approach which will be discussed in details.



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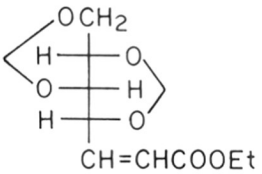

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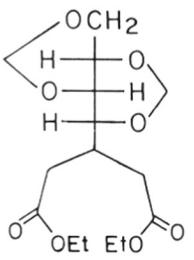

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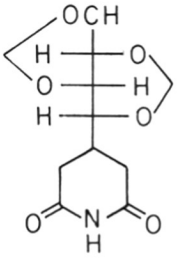

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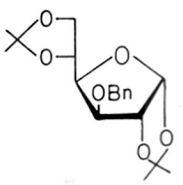
Scheme 2

According to this scheme 3-O-benzyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (**6**) was selected as starting material and was converted into the aldehyde (**7**) by a standard set of reactions. Subsequent Wittig reaction followed by Michael addition and decarboxylation gave the diester (**8**) which was treated with benzylamine in DMF at 170°C to form the N-benzyl glutarimide derivative (**9**). When **9** was treated with ethanedithiol in the presence of zinc chloride, the ring opened to afford the dithiane derivative (**10**) which was treated with dimethoxymethane and toluene-p-sulfonic acid to form the AB ring system (**11**).



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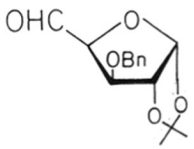

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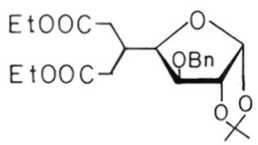

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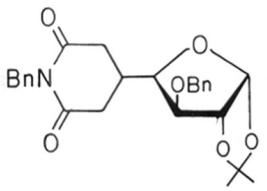

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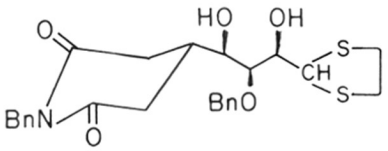

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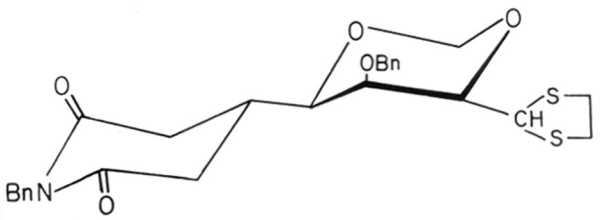

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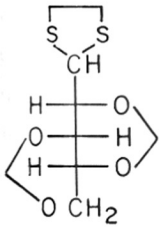
Scheme 3

As indicated earlier that the absolute configuration of sesbanimide (**I**) is not known, therefore, it was thought worthwhile venturing into the synthesis of the other enantiomers which has now been successfully achieved from D-xylose. It is pertinent to note here that one of these two enantiomers will correlate with the natural product.

D-xylose was converted into 2,4:3,5-di-O-methylene-D-xylose dithiane (**12**) in one pot reaction by subsequent treatment with ethanedithiol and 40% aqueous formaldehyde under acidic conditions. Selective acetolysis of 3,5-O-methylene group and consequent hydrolysis afforded the diol (**13**). The hydroxyl groups in **13** were protected as the dibenzyl ether (**14**) and then the dithiane ring was hydrolysed in the presence of mercuricperchlorate to afford the aldehyde. The aldehyde was converted into glutarimide derivative (**15**) by same set of reactions as described earlier.



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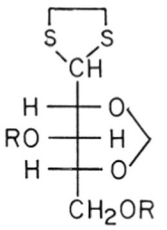
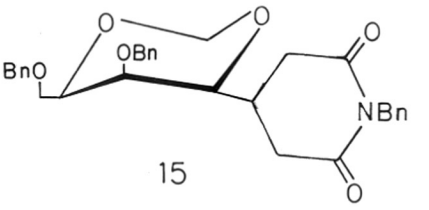


R = H 13
R = Bn 14



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CHAPTER III - SYNTHESIS OF C-RING OF SESBANIMIDE

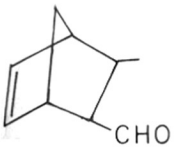
Having successfully achieved the synthesis of AB ring system in both the enantiomeric forms, the construction of ring C was undertaken. In view of the fact that AB ring compounds were rather precious compounds coupled with the fact that no suitable methodology was known for the construction of ring C, reactions in accordance with the proposed schemes were initially attempted on model compounds.

Scheme I

1-Hydroxy-2-hydroxymethylbut-2-ene (**18**) was prepared by the following sequence in which coronaldehyde and cyclopentadiene were allowed to undergo Diels-Alder reaction to give the adduct (**16**). Compound (**16**) was subjected to Cannizzaro reaction in the presence of formaldehyde and sodium hydroxide to afford the compound (**17**) which on Retro-Diels Alder reaction under pyrolytic conditions at 520°C furnished the diol (**18**). In order to convert **18** into monobromide (**19**), **18** was first transformed into its O-benzylidene derivative and then hydrogenolysed in the presence of $LAH\text{-}AlCl_3$ mixture to afford the monoalcohol which was subsequently treated with PBr_3 to afford **19**.

The reaction of the bromide (**19**) with 2-(2-methyl-2-dioxolanyl)ethanal (**22**) was carried out in the the presence of activated zinc in dry THF, the corresponding alcohol (**23**) was isolated in 85% yield and confirmed by PMR spectrum. This clearly indicated that the condensation was occurring at the desired site (secondary carbon). It is recently reported that 3,4-dimethoxybenzyl ether is a superior protecting group as compared to benzyl ether because of the ease with which the former can be cleaved under milder conditions. With this view in mind, the corresponding 3,4-dimethoxybenzyl protected bromide (**20**) was synthesised from **18** by the procedure as described above. Subsequent condensation of **20** with **22** in the presence of zinc proceeded smoothly to afford **24**. Oxidation of secondary alcohol in **24** was effected in the presence of PCC-NaOAc and then the resulting ketone (**27**) was treated with DDQ. Unfortunately, the reaction afforded a complex mixture of products as judged by TLC. This experiment clearly suggested that with DDQ, the ketone (**27**) was undergoing destructive transformation and therefore a more milder condition was warranted. The obvious choice would be to use t-butyldimethylsilyl group as a protecting reagent as it is normally cleaved under extremely mild conditions. Accordingly, 2-chloromethyl-1-t-butyldimethylsilyloxybut-2-ene (**21**) was synthesised by first treating the diol (**18**) with one equivalent of t-butyldimethylsilylchloride-imidazole followed by reaction with tosylchloride-4-(N,N'-dimethylaminopyridine). Treatment of the chloride (**21**) with aldehyde (**22**) under Zaitsev reaction condition gave the product **25** in low yield (15%). The low yield of the desired product was rather surprising, however, further reactions were carried out. This included the oxidation of secondary alcohol and treatment of the ketone (**28**) with 1M solution of tetrabutylammonium fluoride in THF. These reactions resulted in the formation of

the desired lactol (29). The PMR spectrum of **29** in $CDCl_3$ suggested that the compound existed in both closed and open forms. Although the overall synthetic plan worked satisfactorily, the yield of Zaitsev reaction of **21** with **22** could not be improved and therefore an alternative approach was undertaken. Since the compound **23** (prepared earlier with ease) was at hand in substantial amount it was felt worthwhile to explore its utility. Therefore **23** was subjected to the treatment of Li in liquid ammonia which resulted in de-O-benzylyation to give the alcohol (**26**). This alcohol was protected with t-butyldimethylsilyl group to give the key intermediate **25** from which the required lactol (**29**) has already been synthesised. The latter approach gave the alcohol (**25**) in good yields and avoided the tricky condensation of **21** with **22**.



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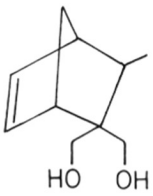

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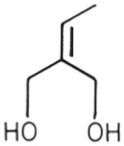

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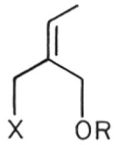

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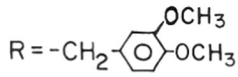
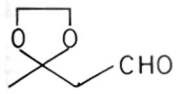


X = Br 20

R = $\overset{|}{\underset{|}{Si}}+$ X = Cl 21



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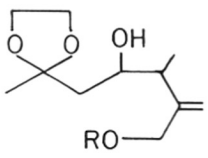
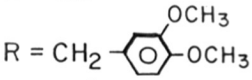


R = Bn 23



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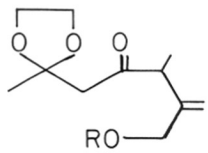
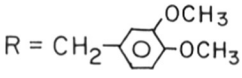
R = $-\overset{|}{\underset{|}{Si}}+$ 25

R = H 26





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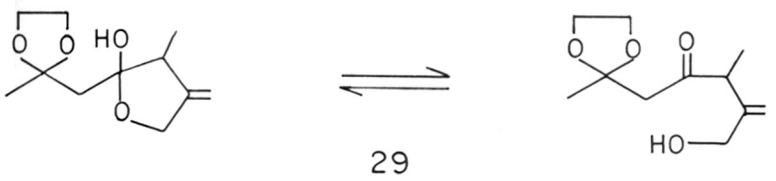
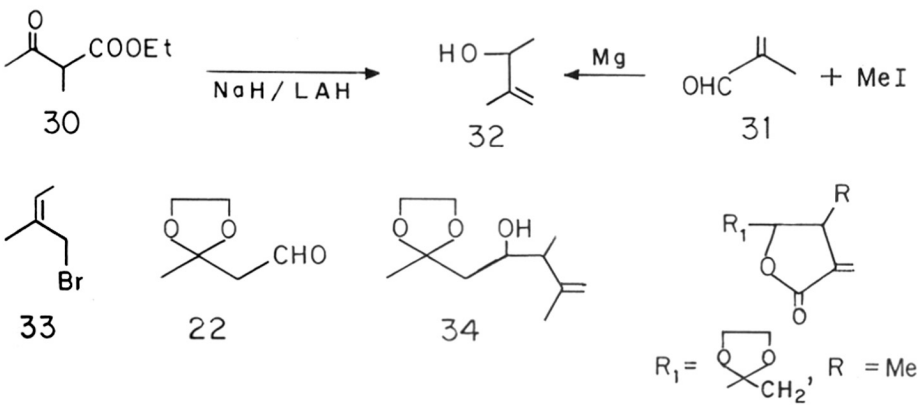
R = $-\overset{|}{\underset{|}{Si}}+$ 28



Scheme 2

The alternate approach towards the construction of C-ring was based on the selenium dioxide oxidation where an allylic methyl could be oxidised to the corresponding allylic alcohol. For example the intermediate **34** could be transformed via the above reaction into the diol derivative (**26**). For this reason the starting material **32** was synthesised from ethyl 2-methyl-4-oxobutanoate (**30**) and NaH-LAH mixture. Later compound **32** was also prepared from **31** and methylmagnesium iodide. Treatment of **32** with PBr_3 led to the formation of bromide (**33**). **33** was then subjected to Zaitsev reaction with the aldehyde (**22**) and the corresponding alcohol (**34**) was obtained in good yield.

Oxidation of the alcohol in the presence of SeO_2-tBuOOH gave the product which was not consistent with the compound **26** prepared earlier. However, based on spectral studies the newly formed product was assigned the structure α-methylenebutylrolactone (**35**). The formation of this product was attributed to the oxidation of allylic methyl group to aldehyde which undergoes cylisation to lactal followed by concomitent oxidation. It is pertinent to point out that α-methylene butyrolactones are versatile intermediates in natural product chemistry and this new methodology can be utilised for different substituted α-methylenebutyrolactones. This α-methylenebutyrolactone (**35**) may be reduced to diol (**26**) which has already been converted to ring C.



CHAPTER I

CHEMISTRY OF SESBANIMIDE

PREAMBLE

About one fifth of the deaths in the Western world are currently ascribed to neoplastic diseases i.e. those diseases which are commonly referred to as cancer. This disease has engaged a worldwide attention. If cancer is detected at an early stage and more importantly localised in humanbeings, then the radiation and surgery certainly have a curative effect. But once it spreads all along to the other organs, the answer then lies in the chemotherapy and/or in combination with surgery and radiation. A large number of anticancer drugs of microbial as well as plant origin are being used in the medicinal practice. Further several other natural products are presently undergoing clinical trials. All these drugs can be broadly classified into four categories namely, (1) alkylating agents (2) anti-metabolites (3) antibiotics (4) miscellaneous compounds.

Recently Powell and coworkers have reported[1] that the extracts from the seeds of Sesbania drummondii has pronounced anticancer activity in experimental systems. Later they isolated the active principles and named the compound as 'Sesbanimide' which revealed a very potent anti-tumour activity.

Isolation[2,3]

Sesbania punicea seeds found in Southern United Sates and South America were ground in a mill to pass through a 50 mesh sieve and then extracted with 70% ethanol and concentrated to give an aqueous residue. Treatment with excess of lead acetate followed by filtration and saturation with hydrogen sulfide gas afforded a suspended solution. This was filtered and extracted with chloroform continuously for 48 h. Removal of chloroform followed by chromatography on silica gel gave Sesbanimide in very small amount,

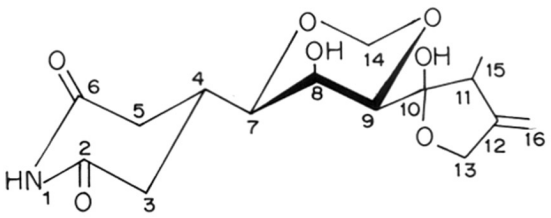
m.p. 155-56°C, $[\alpha]_D$ +54.7° ($CHCl_3$). Similarly sesbanimide and some other analogues of it have been isolated from the seeds of Sesbania drummondii (Rydb.) cory by a similar procedure.

Structural elucidation

On the basis of PMR, ^{13}C NMR, IR and mass spectroscopy of Sesbanimide it was suggested that sesbanimide contains 21 protons and 15 carbon atoms, the correct structure could not be assigned because of the possibilities of several structures emanated from the data. However, single crystal X-ray crystallographic study of sesbanimide was first carried out which suggested its relative structure as **I**. The absolute configuration of sesbanimide however remains to be determined.

Since X-ray afforded the structure of **I**, the interpretation of PMR spectrum was now possible. Equatorial protons of glutarimide ring (H-3', H-5') were located at 2.76 and 2.90 ppm while the axial protons (H-3, H-5) were located at 2.38 and 2.47 ppm. The signals due to axial H-4 proton appeared at 2.63 ppm. Irradiation of this proton signal had effect on a doublet at 3.34 ppm which was then assigned to H-7. By successive irradiation of H-7 and H-8 revealed the signals due to H-9 at 3.58 ppm. A multiplet due to H-11 was observed at 2.60 ppm which showed coupling to methyl group (1.19 ppm) at C-15 and also showed long range coupling with vinylic methylenes H-16, H-16' (4.96, 5.01 ppm). The methylene protons at C-13 were located at 4.47 and 4.55 ppm while remaining methylenedioxy protons H-14, H-14' appeared as two doublets at 4.78 and 5.22 ppm. Similarly all the 15 carbon atoms were assigned in the ^{13}C spectrum by off resonance decoupling experiments. Finally the mass spectrum of sesbanimide revealed a peak at m/z 309.1246 due to the loss of water from the molecular ion

peak $(M-H_2O)^+$.



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Biological activity

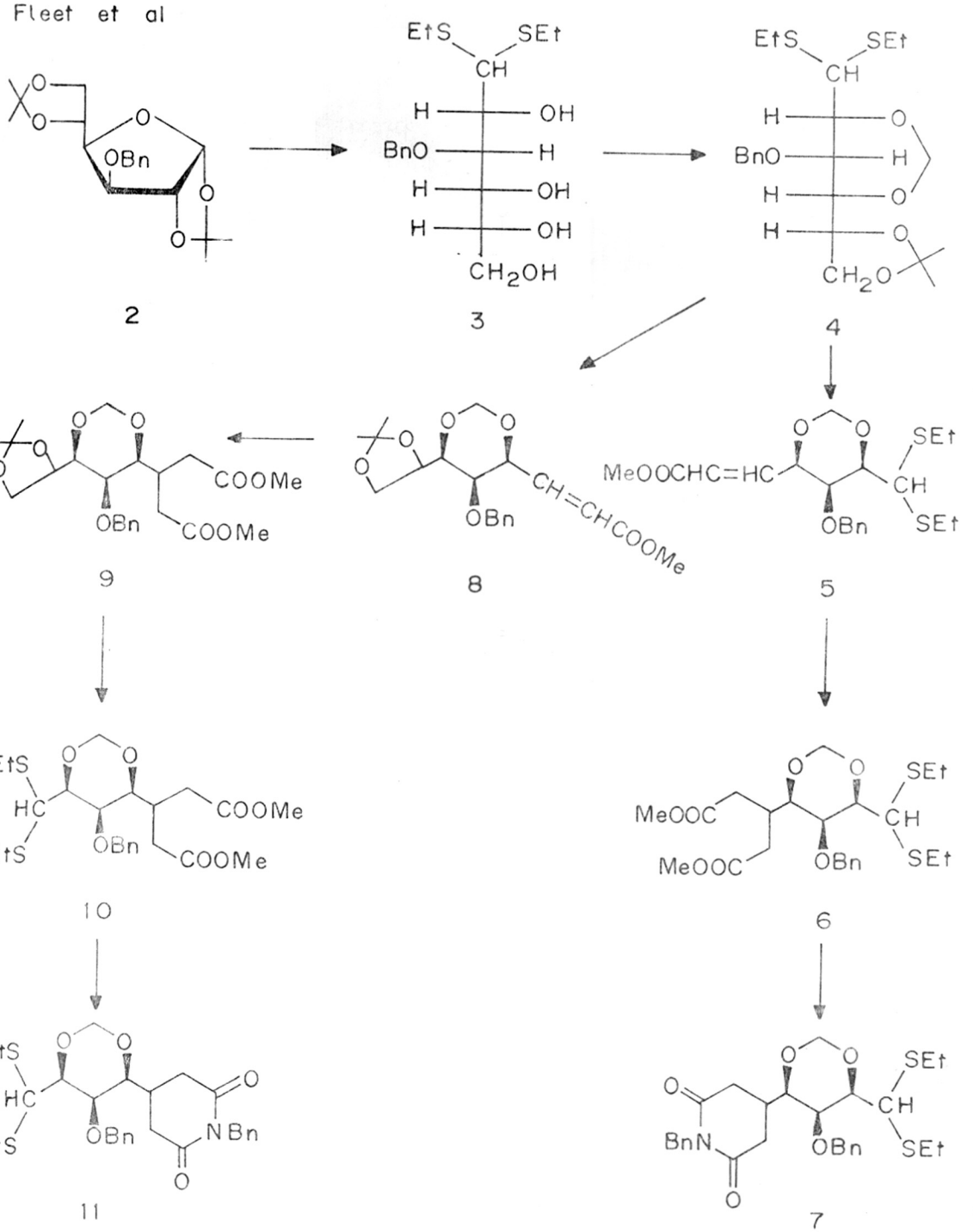
Sesbanimide **1** showed an exceptionally remarkable potent anti-tumour activity in the experimental systems. For example mice with leukemia receiving 0.01 mg of the compound per kilogram of body weight survive 1.7 times longer than their litermates receiving no treatment. It has shown cytotoxicity against KB cells in vitro and inhibitory activity against P-388 murine leukemia in vivo.

Introduction

As indicated earlier that sesbanimide **1** revealed a potent anti-tumour activity in experimental systems which arose interest in this unique molecule. In addition, the novel structural feature of **1**, in which all three rings are linked by single bonds coupled with the fact that no absolute stereochemistry was known, were responsible for the spur of activity towards its total synthesis. When the work was initiated in this laboratory, no synthesis either partial or total was known. However, later several syntheses of AB ring of sesbanimide resulted. Although only one approach for the construction of C-ring on model study (in which the methyl group

SCHEME - I

Fleet et al



at C-15 was absent) has been reported, no properly substituted C-ring has been constructed so far by other laboratories. In this section various reported approaches for the synthesis of sesbanimide will be discussed in details.

Fleet et al. approach[4]

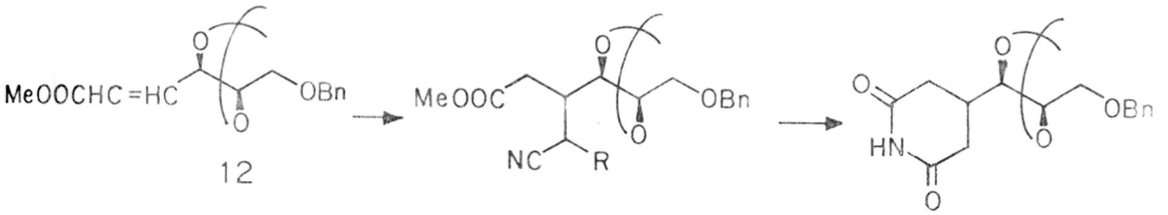
Fleet et al. were the first to report the synthesis of AB rings of sesbanimide in both the enantiomeric forms starting from D-glucose. The known 3-O-benzyl-1,2:5,6-di-O-isopropylidene α -D-glucofuranose was converted into the diethylthioacetal derivative (**3**) by the reaction with ethanethiol and acid. **3** having four hydroxyl groups free was selectively protected as dioxalane at O-5 and O 6 position using acetone $CuSO_4$ and then 1,3-dioxane ring was built at O-3 and O-4 position by using methylene-bromide and sodium hydroxide. It is interesting to note that the compound **4** can be converted to the aldehyde stepwise at both the ends of the molecule thereby making it possible to elaborate the glutarimide ring at each end. This would of course lead to the formation of both the enantiomers of AB ring system.

Thus, 5,6-O-isopropylidene group was selectively cleaved and then subjected to periodate oxidation to generate the aldehyde which underwent Wittig reaction followed by Michael addition with sodium salt of diethylmalonate to give the triester. The triester on deethoxycarbonylation gave the diester (**6**) which on reaction with BnNHLi gave the AB ring system.

The other enantiomer of the AB ring system was synthesised by first hydrolysing the thiol protection followed by successive Wittig

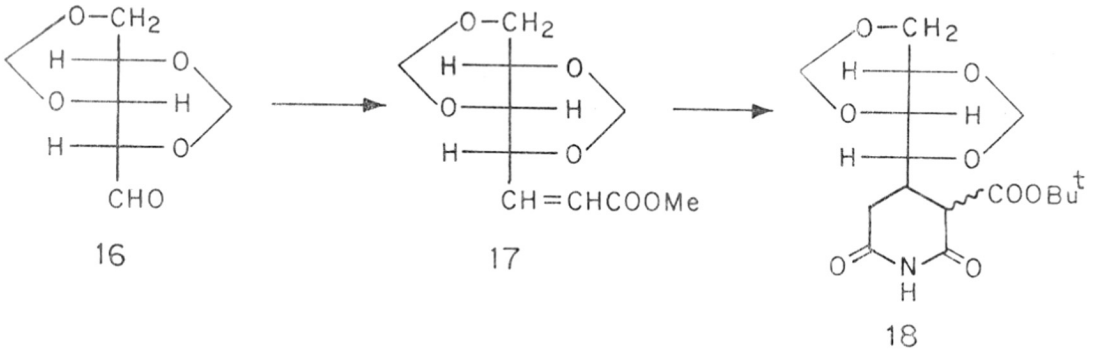
Kiyoshi et al.

SCHEME II



Pandit et al.

SCHEME III



reaction, Michael addition and deethoxycarbonylation to afford the diester (9). The isopropylidene ring was cleaved and the diol was subjected to periodate oxidation followed by protection of the resulting aldehyde as diethylthioacetal diester (10). 10 on reaction with BnNHLi gave the other isomer of AB ring of sesbanimide.

Kiyoshi and Koga approach[5]

These authors reported another strategy for the construction of A-ring of sesbanimide. The α,β-unsaturated ester (12) was treated with lithiated trimethylsilylacetonitrile to afford 1,4-addition product (13). Removal of trimethylsilyl group followed by subsequent treatment with alkaline hydrogen peroxide and potassium tert-butoxide at higher temperature afforded the glutarimide derivative (15).

Pandit et al. approach[6]

In this report, D-sorbitol was used as a starting material and was converted into 2,4:3,5-di-O-methylene-L-xylose (16) by the known procedure. The Wittig reaction of 16 with methoxycarbonylmethylenetriphenylphosphorane afforded the α,β-unsaturated ester (17) which was subjected to Michael addition in the presence of t-butylcarbanomylacetate giving rise to the glutarimide ring derivative (18). The t-butylcarbonyl group was removed by hydrolysis of the ester group followed by decarbonylation. The more susceptible methylene bridge across O-7 and O-9 was opened in the presence of acetic anhydride, acetic acid to give the desired diacetate (19).

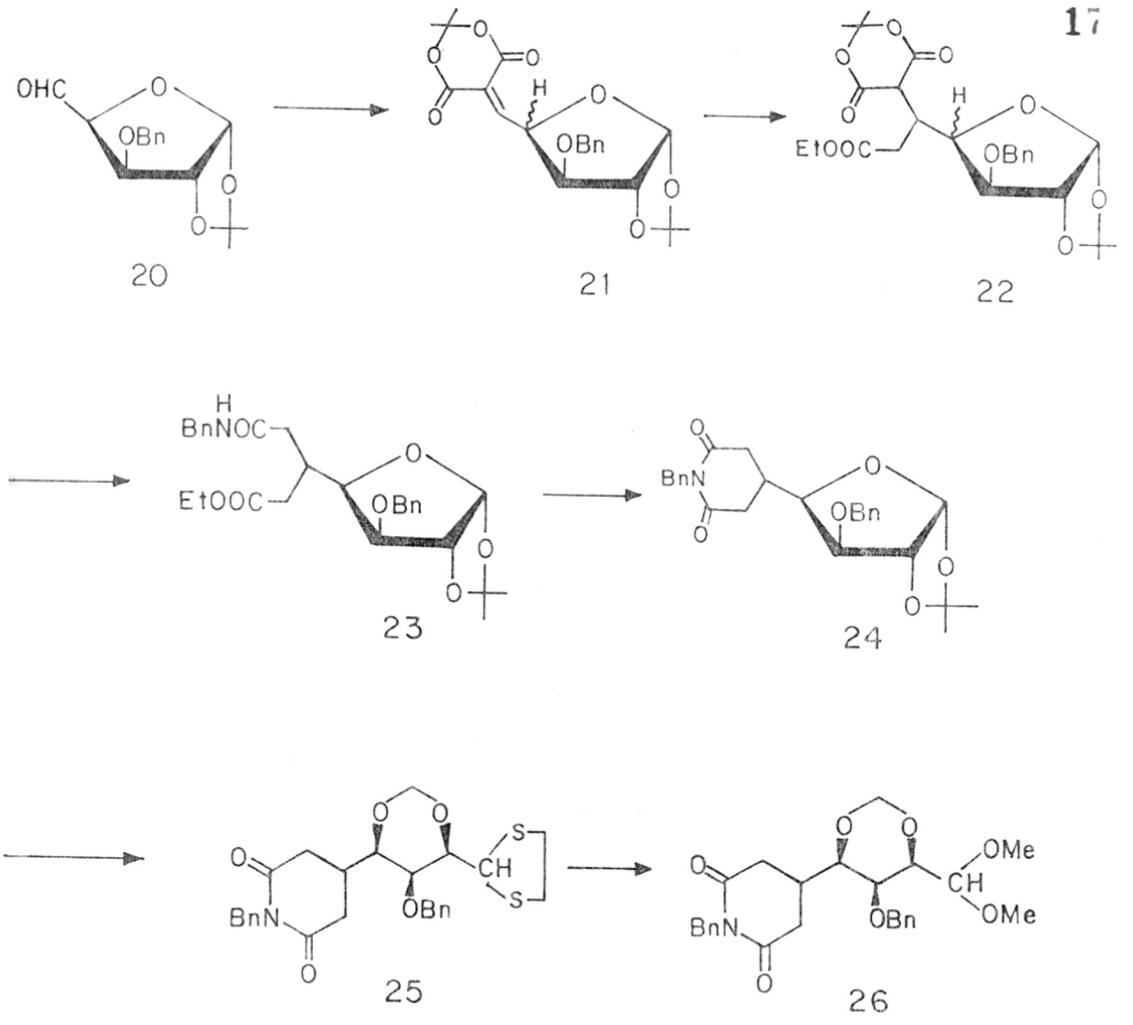
Shibuya approach[7]

This approach involved the use of the known aldehyde (20) which on condensation with Meldrum's acid followed by Michael addition with

Shibuya

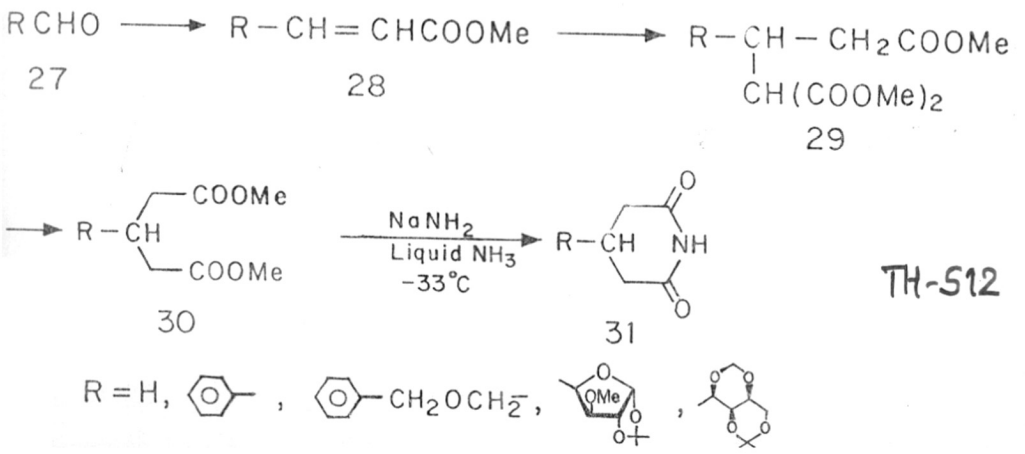
SCHEME IV

547.9:616-006.6(043)
NAI



Kinoshita et.al.

SCHEME V



TH-512

lithioethylacetate afforded the enantiomeric mixture of **22**. Decarboxylative esterification of **22** with p-nitrophenol-copper powder followed by subsequent treatment with benzylamine gave the amide ester (**23**). Hydrolysis and thermal dehydration generated the glutarimide ring derivative (**24**) which on treatment with ethanedithiol and zinc chloride gave the dihydroxy-derivative which was converted into 1,3-dioxane ring by the treatment with paraformaldehyde and toluene-p-sulfonic acid. Hydrolysis of thioacetal with mercuricperchlorate in the presence of methanol-chloroform gave **26**.

Kinoshita et al. approach[8]

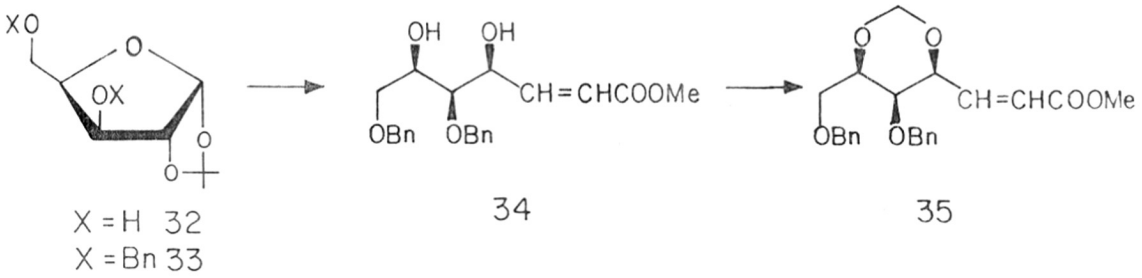
These authors reported a new method of the formation of glutarimide ring from the β-substituted glutaric acid diesters (**30**) by making use of sodiumamide in liquid ammonia at -33°C. A series of β-substituted glutaric acid diesters to the corresponding glutarimide derivatives have been synthesised by this procedure.

Terashima et al. approach[9]

An enantiomeric pair of AB ring system of sesbanimide were synthesised from D and L-xylose. For example, 3,5-di-O-benzyl-D-xylose prepared from D-xylose in four steps, was subjected to Wittig reaction with methoxycarbonylmethylenetriphenylphosphorane and the resulting α,β-unsaturated ester on exposure to trimethylsilyltrifluoromethylsulfonate and dimethoxymethane in the presence of 2,6-lutidine as scavenger, generated the 1,3-dioxane ring (**35**). Its conversion into the diester was followed by the usual technique involving Michael addition, deethoxycarbonylation. The diester (**36**) was converted into corresponding anhydride and then

Terashima et al.

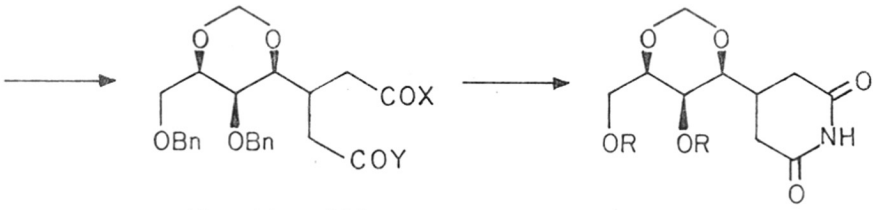
SCHEME VI



X = H 32
X = Bn 33

34

35

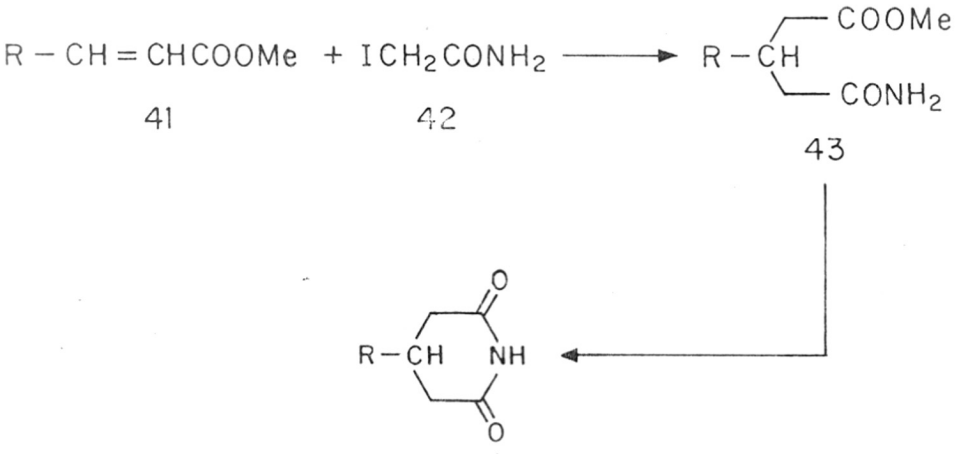


X = Y = OMe 36
X = Y = OH 37
X = OH, Y = NH_2 38

R = Bn 39
R = H 40

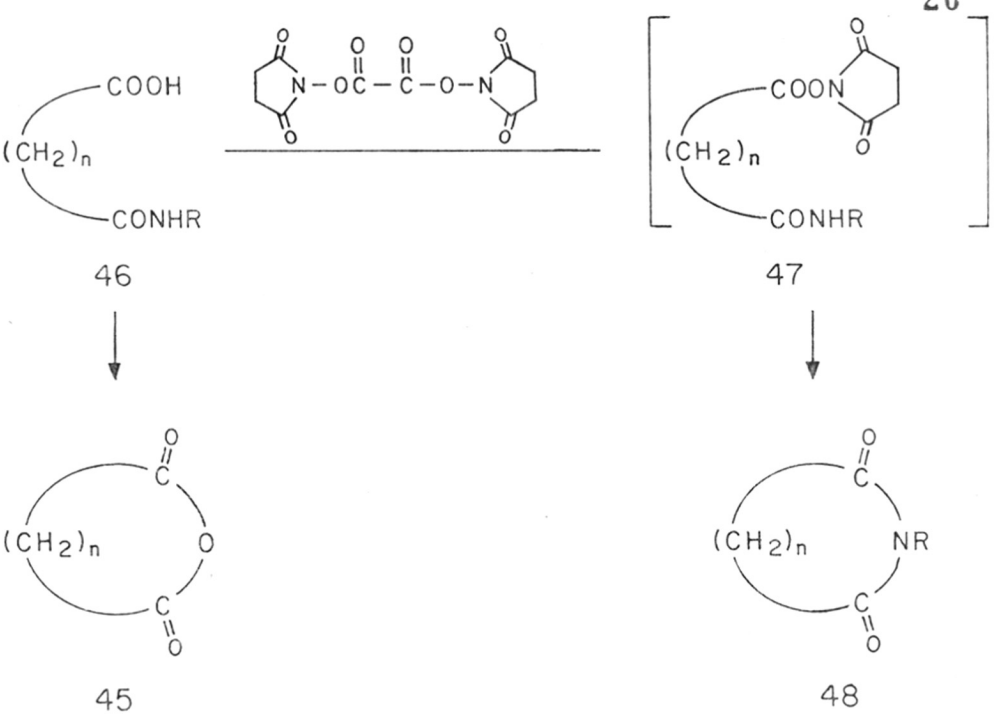
Just et al.

SCHEME VII



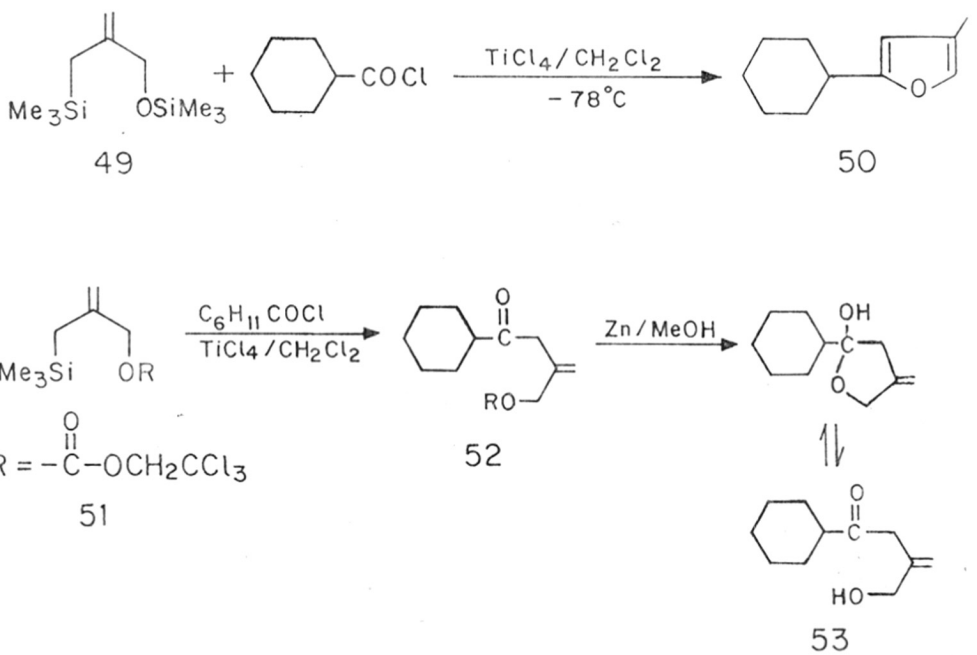
Kometani et al.

SCHEME VIII



Pandit et al.

SCHEME IX



treated with ammonia followed by acetic anhydride and sodiumacetate to form the glutarimide derivative (**39**). The debenzylation of **39** was achieved using Pd-C/H_2 to give the desired compound **40**.

Just et al. approach[10]

A new methodology for the construction of A-ring of sesbanimide reported by Just et al. involves radical reaction of the α,β-unsaturated ester (**41**) with iodoacetamide (**42**) in the presence of tributyltinhydride and tungsten light to give the esteramide (**43**). On heating at 120°C in toluene, **43** gave the A-ring system (**44**) in poor yield (30%).

Kometani et al approach[11]

Kometani et al. have shown that the glutarimide ring system of sesbanimide can be generated from the corresponding anhydride derivative (**45**) by three step sequence. The first step involves the reaction of the anhydride with primary amine to give the corresponding acid amide intermediate(**46**). In second step the conversion of the intermediate monoamide to an N-hydroxysuccinimidyl (NHS) ester (**47**) using N,N'-disuccinimidyl-oxalate (DSO) was involved and finally cyclisation of NHS ester was succeeded by heating in trichloromethylene in the presence of 4-(c N,N'-dimethylaminopyridine) to afford **48**.

Pandit et al. approach[12] for the construction of 15-demethyl C-ring.

Pandit et al. describe an approach for the construction of C-ring of sesbanimide as a model study in which the methyl group at C-15 was absent. Initial attempt to react allylsilane (**49**) with cyclohexanecarbonyl-chloride at -78°C in the presence of titaniumtetrachloride as catalyst afforded a furan derivative (**50**). However, the desired β,γ-unsaturated ketone (**52**) formation was later observed when a strong electronegative protecting group such as -$COOCH_2CCl_3$ was employed. Hydrolysis of ester function with zinc and methanol afforded the desired hemiacetal (**53**) in 50% yield.

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CHAPTER II

SYNTHESIS OF AB RING OF SESBANIMIDE

INTRODUCTION

Sesbanimide (I) having a notable anticancer activity coupled with unusual structural features (all the rings are connected by a single C-C bond) distinguish this molecule as a very ineresting target for synthesis. Its synthesis can be considered as an important milestone in order to evaluate the absolute configuration and to study structure-activity relationship. In addition, the methodology which will be developed, would enable to prepare new analogues of sesbanimide. The latter compounds may show activity superior to the parent compound. The most logical method to synthesise I would be to build AB rings first and then to elaborate C-ring on the resulting substrate. This strategy was based on the fact that ring-C, being susceptible to destruction under acid-base conditions, cannot be formed first.

From the examination of the target molecule in question, it can be realised that the compound of the type B having actual or potential aldehyde group at both the ends of the molecule could be an ideal synthon. The compound of the type B is such that one can manoeuver at both the ends of the molecule. The utility of the masked aldehyde group can be exploited to build ring A and C at wherever position one desires.

With this view in mind the first concern therefore was the synthesis of the intermediate of the type B. The structure of the fragment B clearly suggested that carbohydrates would be an ideal starting material and the elements of chirality at C-7, C-8 and C-9 could be correlated with C-2, C-3 and C-4 carbons of several cheaply available sugars such as D-sorbitol, D-glucose and D-xylose. It is gratifying to note that each of these sugars have been successfully utilised in the construction of AB ring system.

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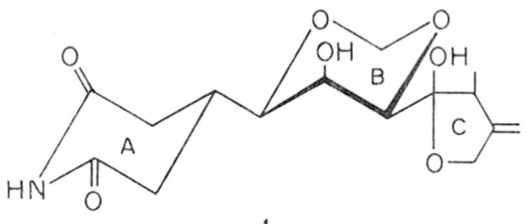

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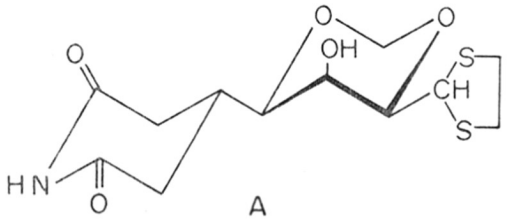
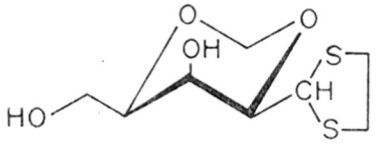


A



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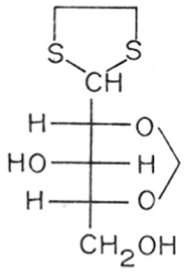
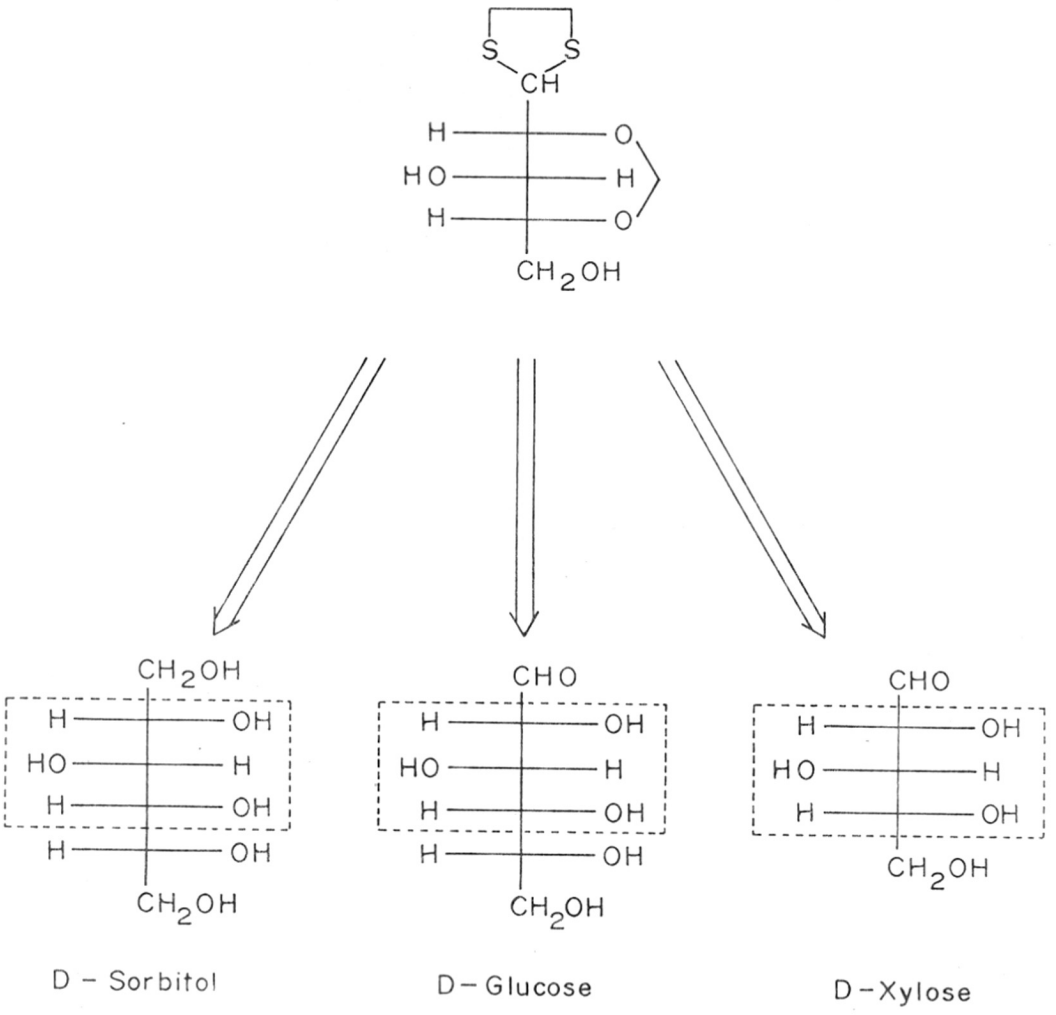


B

SCHEME - II



D - Sorbitol

D - Glucose

D - Xylose

SECTION I

SYNTHESIS OF AB RING FROM D-SORBITOL

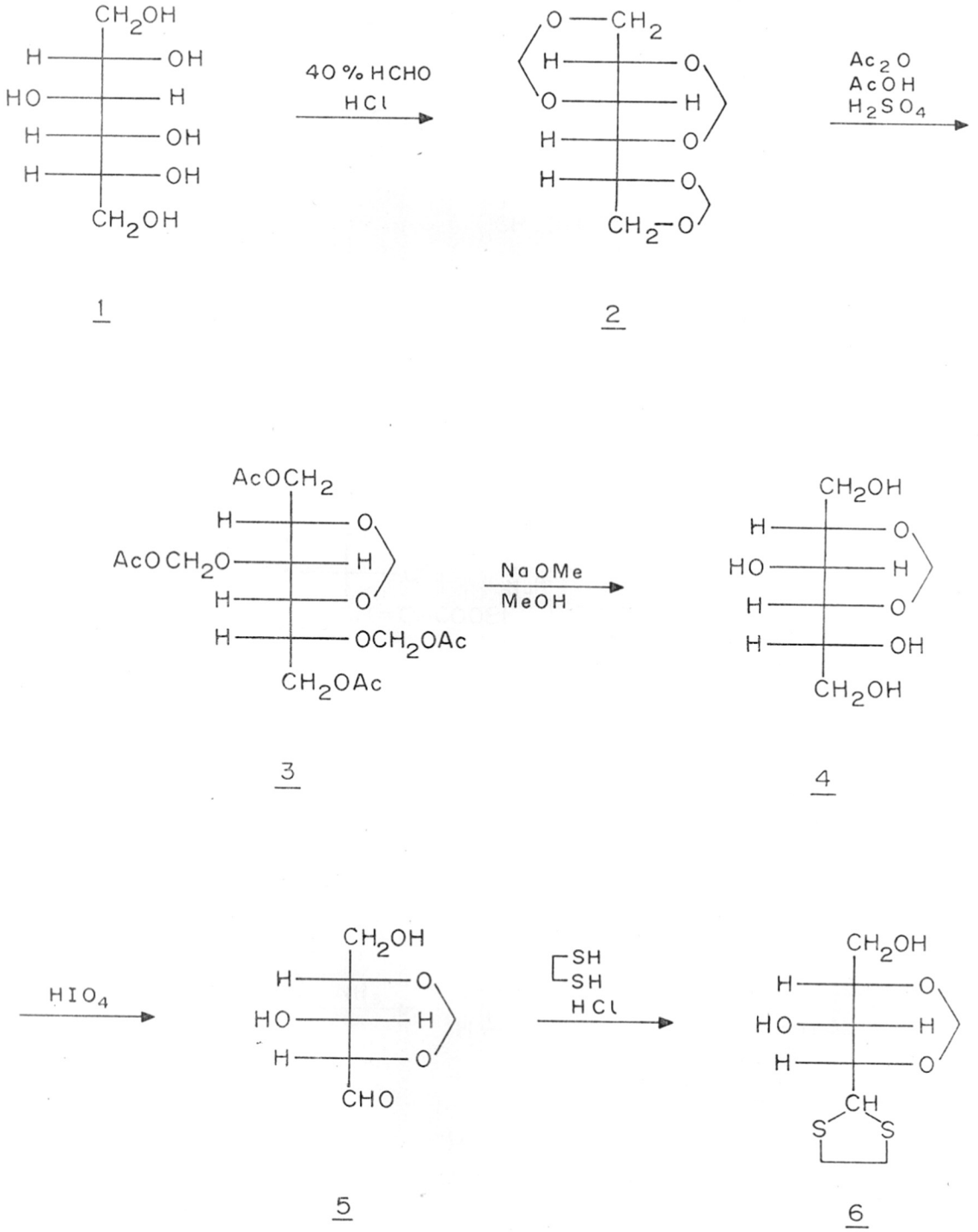
As indicated earlier that the elements of chirality at C-7, C-8, C-9 could be correlated with C-2, C-3 and C-4 of D-sorbitol. In order to evaluate the possibility of using D-sorbitol as a starting material, one has to protect all the hydroxyl groups other than at C-5, C-6. The 5,6-diol can be oxidised and then can be used to build ring-A. In essence, the preparation of compound of the type **5** in which hydroxyls at C-1 and C-3 may or may not be protected is required. Fortunately compound **5** was earlier prepared[1] from D-sorbitol (Scheme 1).

Accordingly D-sorbitol was treated with 40% formaldehyde solution in the presence of concentrated hydrochloric acid to give 1,3:2,4:5,6-tri-O-methylene-D-sorbitol (**2**) in 68% yield.

Acetolysis of **2** in the presence of acetic anhydride, acetic acid and concentrated sulfuric acid selectively cleaved 1,3 and 5,6-O-methylene bridges to give the tetraacetate (**3**) in 52% yield. Subsequent Zamplein deacetylation of **3** followed by periodate oxidation of the resulting tetrol (**4**) gave the required aldehyde (**5**) which was not purified but converted into 1,3-dithialane by the treatment with ethanedithiol and hydrochloric acid in overall 12% yield. The PMR spectrum of **6** corresponded with the assigned structure as signals characteristic of dithiane, O-methylene protons are clearly located. Other protons appeared at the expected chemical shifts.

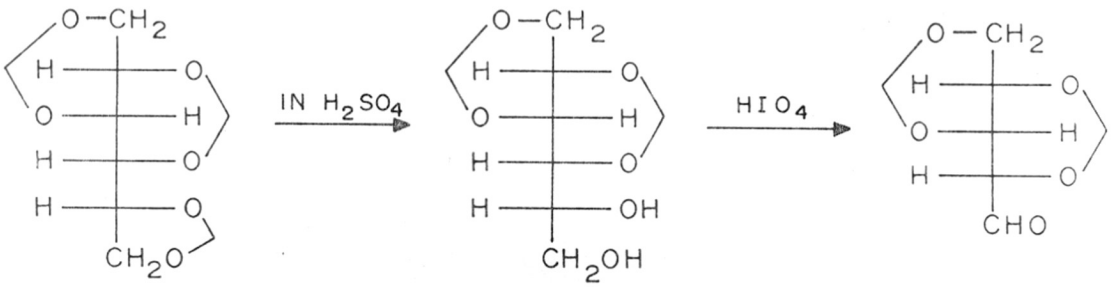
Although this procedure offered the required compound **6**, the periodate oxidation step was far from satisfactory. This reaction invariably produced a mixture of compounds from which the required aldehyde could only be obtained after extensive chromatography. The other major problem

SCHEME – III

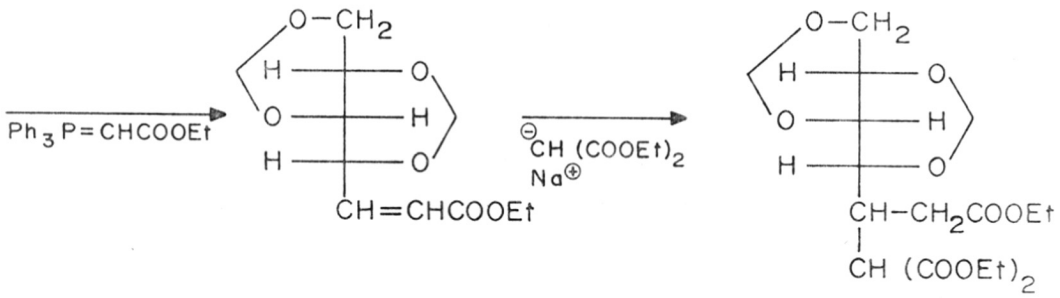


1 2 3 4 5 6

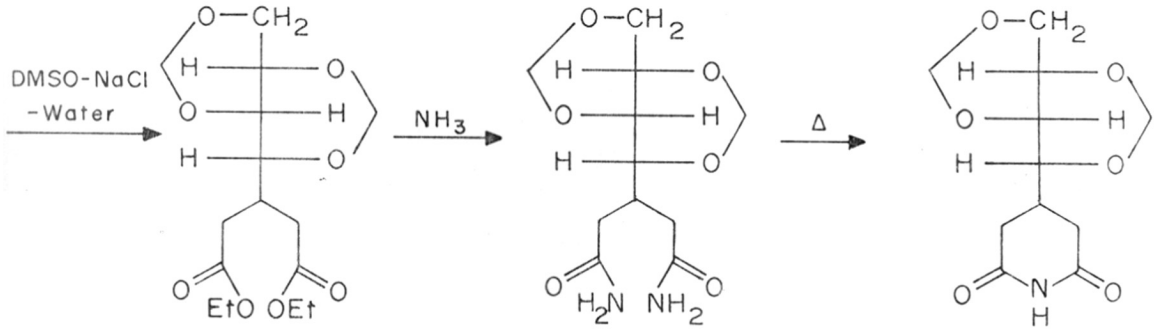
SCHEME - IV



2 7 8



9 10



11 12 13

being the isolation of the aldehyde from the aqueous medium.

With these drawbacks in mind, a modified route for the compound B was investigated (Scheme 2). The strategy for this route was based on the fact that the 5,6-O-methylene group of **2** can be selectively cleaved and then the aldehyde can be generated by the periodate oxidation of the resulting diol. This route would avoid the solubility problem of the aldehyde in aqueous medium as the molecule will be extremely nonpolar. Accordingly, it was observed that one can indeed selectively cleave the 5,6-O-methylene group in **2** in the presence of 1N sulfuric acid under reflux for 10 h in 45% yield. The free diol (**7**) was then oxidized with periodic acid to generate the aldehyde (**8**).

Having successfully synthesised the required intermediate **8**, efforts were directed to the second stage of the plan which involved the construction of ring A. This was accomplished as follows. Subsequent Wittig reaction[2] of **8** with ethoxycarbonylmethylenetriphenylphosphorane gave a mixture of cis and trans α,β-unsaturated esters (**19**) which were separated by column chromatography. The faster moving product was assigned as trans isomer on the basis of PMR spectrum in which the olefinic protons appeared as double doublet at 5.96 and 6.42 ppm with coupling constant of 16 Hz. Other resonances were consistent with product being **9**. The slower moving isomer was cis product because of the coupling constant of 12 Hz between the olefinic protons was observed. Although, the mixture of cis and trans isomer were separated and characterised, later the cis and trans mixture was used as such because in the next step the stereochemistry of the double bond was anyway destroyed.

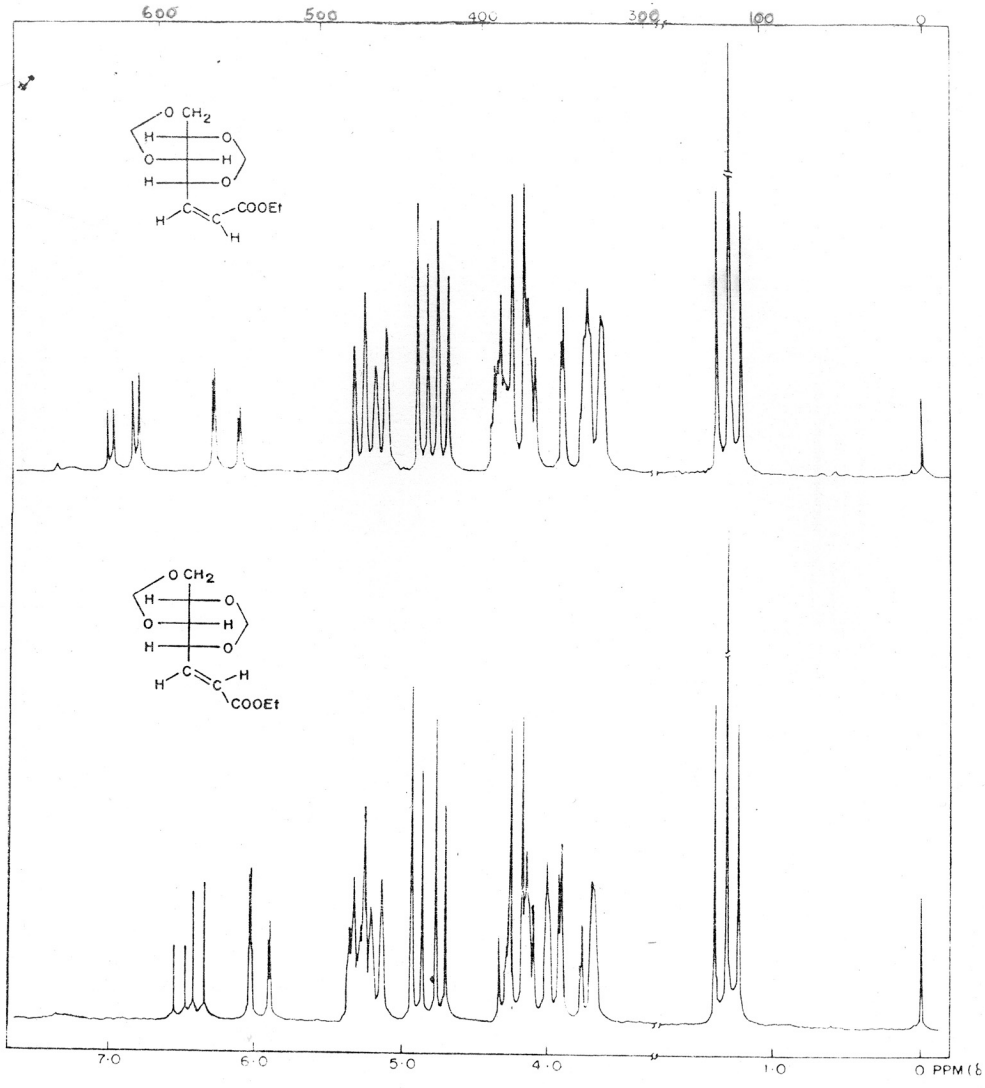


FIG. 1 PMR SPECTRUM OF COMPOUND (9) IN $CDCl_3$

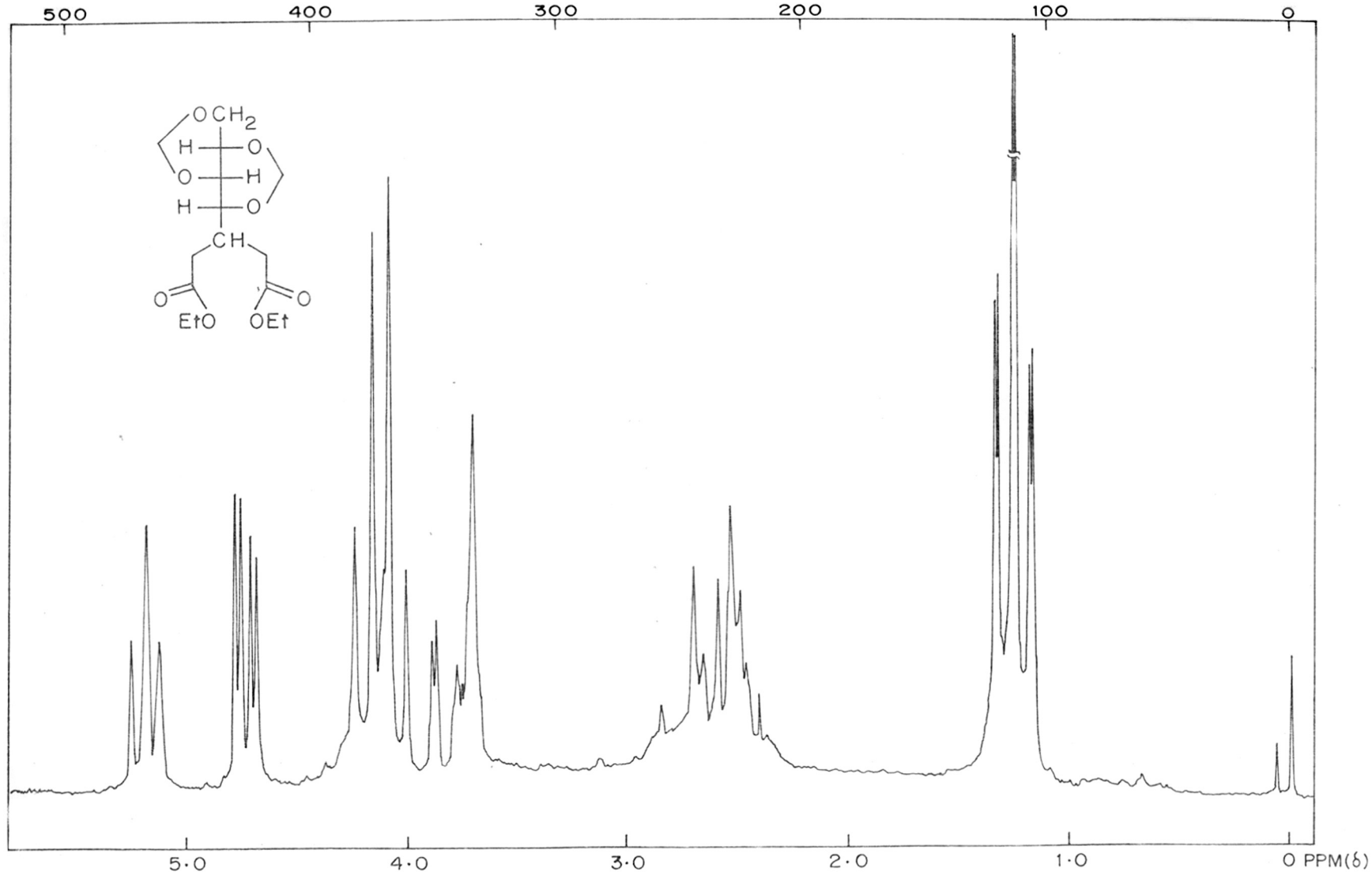


FIG. 2 : PMR SPECTRUM OF COMPOUND (11) IN $CDCl_3$

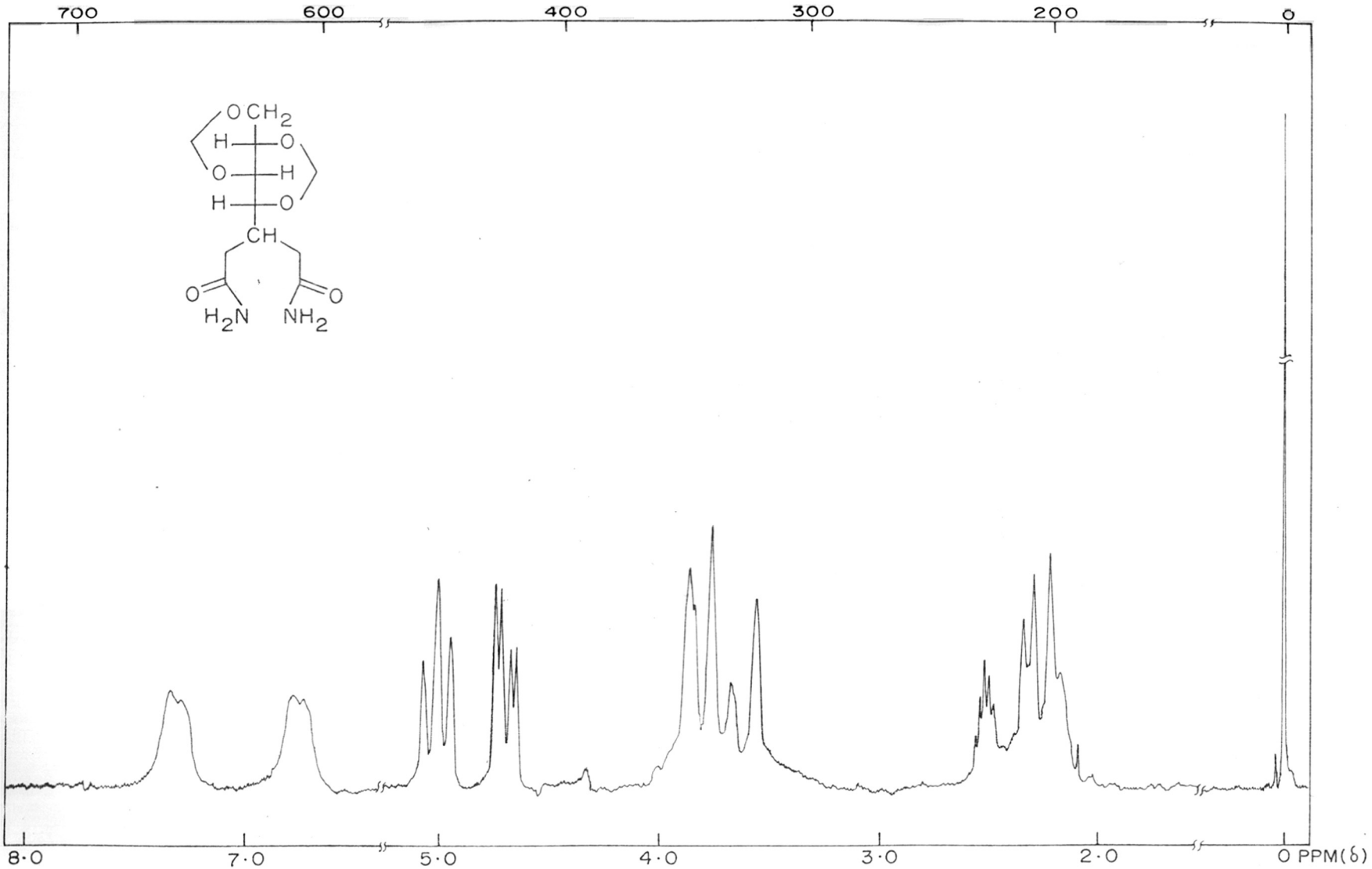


FIG. 3 : PMR SPECTRUM OF COMPOUND (12) IN DMSO-d_6

9 was subjected to Michael reaction[3] in the presence of sodium salt of diethylmalonate to afford the triester (10) which was deethoxycarbonylated[4] in the presence of DMSO-NaCl-H_2O to give the diester (11). In the PMR spectrum of 11 peak characteristic of two carbethoxy groups appeared. In addition four set of doublets for two O-methylene protons appeared in the region 4.7 to 5.3 ppm. When the diester (11) was treated with 25% aqueous methanolic ammonia, the reaction afforded after seven days at room temperature the corresponding diamide (12) in only 10% yield. The appearance of the two broad doublets at 6.73 and 7.28 ppm for amino groups corresponded with the presence of two acetamido groups. These signals were D_2O exchangeable. In addition, the mass spectrum of the diamide revealed the molecular ion peak at 274. Attempts to improve the yield of the diamide under various conditions, such as bubbling ammonia continuously or by using aqueous ammonia solution, however met with failure. The diamide (12) was heated at 250°C under vacuum followed by workup gave a product in 10% yield which was given the structure of cyclic amide (13) on the basis of the mass spectrum which indicated the molecular ion peak at 257.

Inspite of the fact that the above approach involving D-sorbitol as starting material afforded the desired AB ring system of sesbanimide, the overall yield was extremely poor. Critical analysis of the scheme revealed that in the selective hydrolysis of 5,6-O-methylene group, the yield of the resulting dimethylene sorbitol (7) was poor and its isolation involved the removal of substantial amount of water at low temperature. In addition to this, during the Wittig reaction, the α,β-

unsaturated ester **(9)** was always found contaminated with triphenylphosphineoxide because of the close R_f values. Therefore pure α,β-unsaturated ester **(9)** was obtained after extensive chromatography. It is surprising to note that the next two reaction products, namely Michael adduct **(10)** and diester **(11)** were also having R_f values similar to that of α,β-unsaturated ester **(9)**, it made the reactions extremely difficult to monitor. Moreover, the conversion of diester **(11)** to the cyclic amide **(13)** occurred in lessthan 5% yield. With these practical problems, it was decided to explore some other routes where these problems could be circumvented.

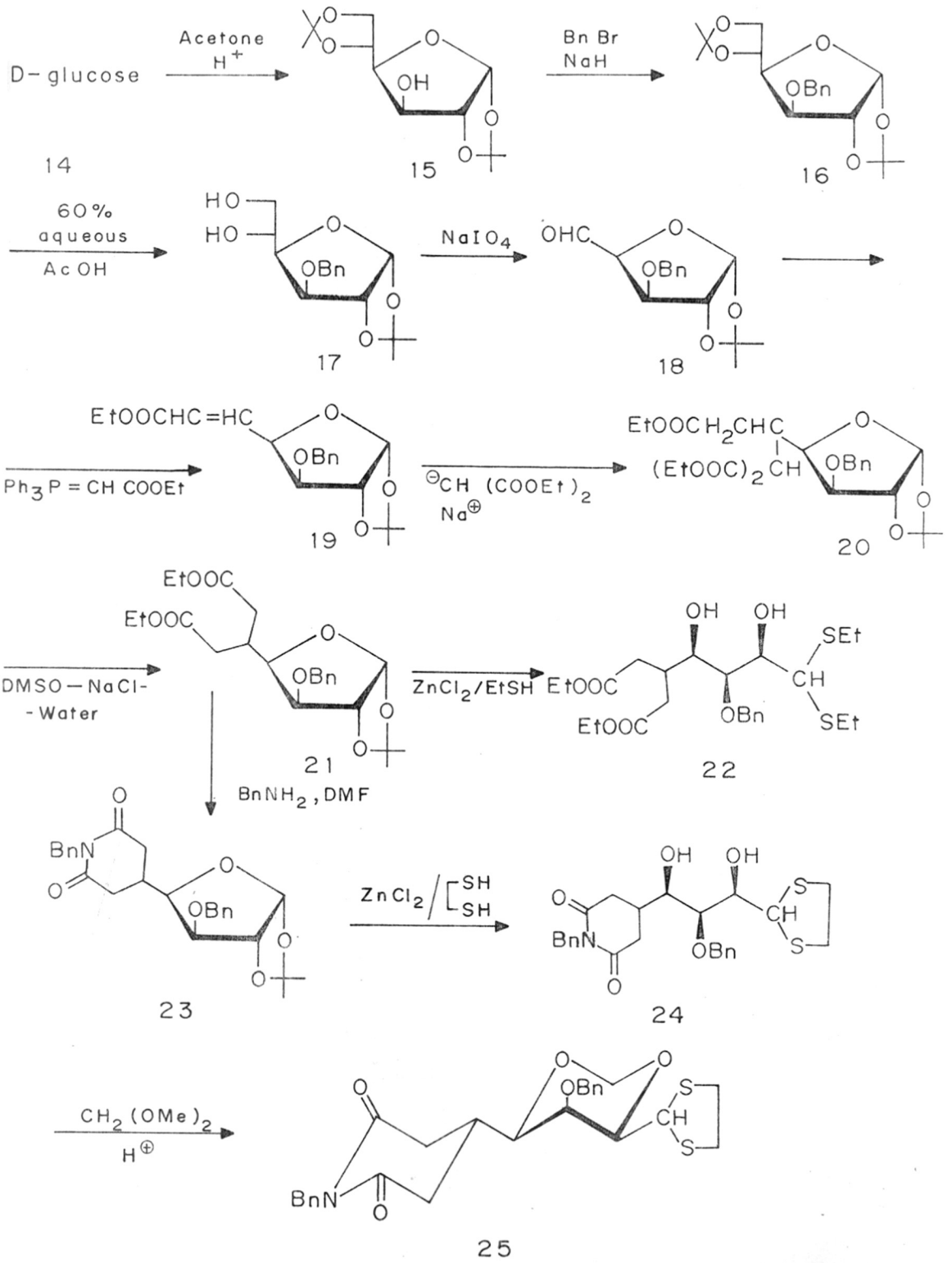
SECTION II

SYNTHESIS OF AB RING FROM D-GLUCOSE

The utility of D-glucose for the synthesis of AB ring system of sesbanimide was explored. The obvious choice was to utilise 3-O-substituted diacetone-D-glucose derivative. Selective hydrolysis of the 5,6-O-isopropylidene group would generate the free 5,6-diol which in turn could be exploited to build ring A by the similar approach as reported in Scheme 2.

In accordance with this strategy, diacetone D-glucose[5] (**15**), prepared from D-glucose in one step was converted into 3-O-benzyl derivative (**16**) by the reaction with benzylbromide and sodium hydride inTHF. Selective hydrolysis of 5,6-O-isopropylidene group was accomplished by using 60% aqueous acetic acid at 35°C for 8 h to afford the diol[6] (**17**) which was subjected to periodate oxidation in aqueous acetonitrile to afford the known aldehyde (**18**). The aldehyde (**18**) was then condensed with ethoxycarbonylmethylenetriphenylphosphorane to give a cis,trans mixture of α,β-unsaturated ester(**19**) in 70% yield. As the R_f values of **19** and triphenylphosphineoxide were quite different, the pure product **19** could be isolated without any difficulty. The PMR spectrum of **19** indicated that it was cis-trans mixture. Since the separation of the mixture was of no interest, it was directly subjected to Michael addition with sodium salt of diethylmalonate which resulted in the formation of triester (**20**) in 91% yield. The loss of olefinic protons in PMR spectrum of compound **20** were clearly observed. Deethoxycarbonylation of the triester (**20**) with sodium chloride in aqueous dimethylsulfoxide at 140°C for 15 h gave the diester (**21**) in 79% yield. In the PMR spectrum of **21**, two doublets corresponding to the two

SCHEME - V


D-glucose
Acetone
H+
Bn Br
NaH
60%
aqueous
AcOH
NaIO4
Ph3P = CH COOEt
⊖CH (COOEt)2
Na⊕
DMSO — NaCl-
- Water
ZnCl2/EtSH
BnNH2, DMF
ZnCl2/SH SH
CH2 (OMe)2
H⊕
14
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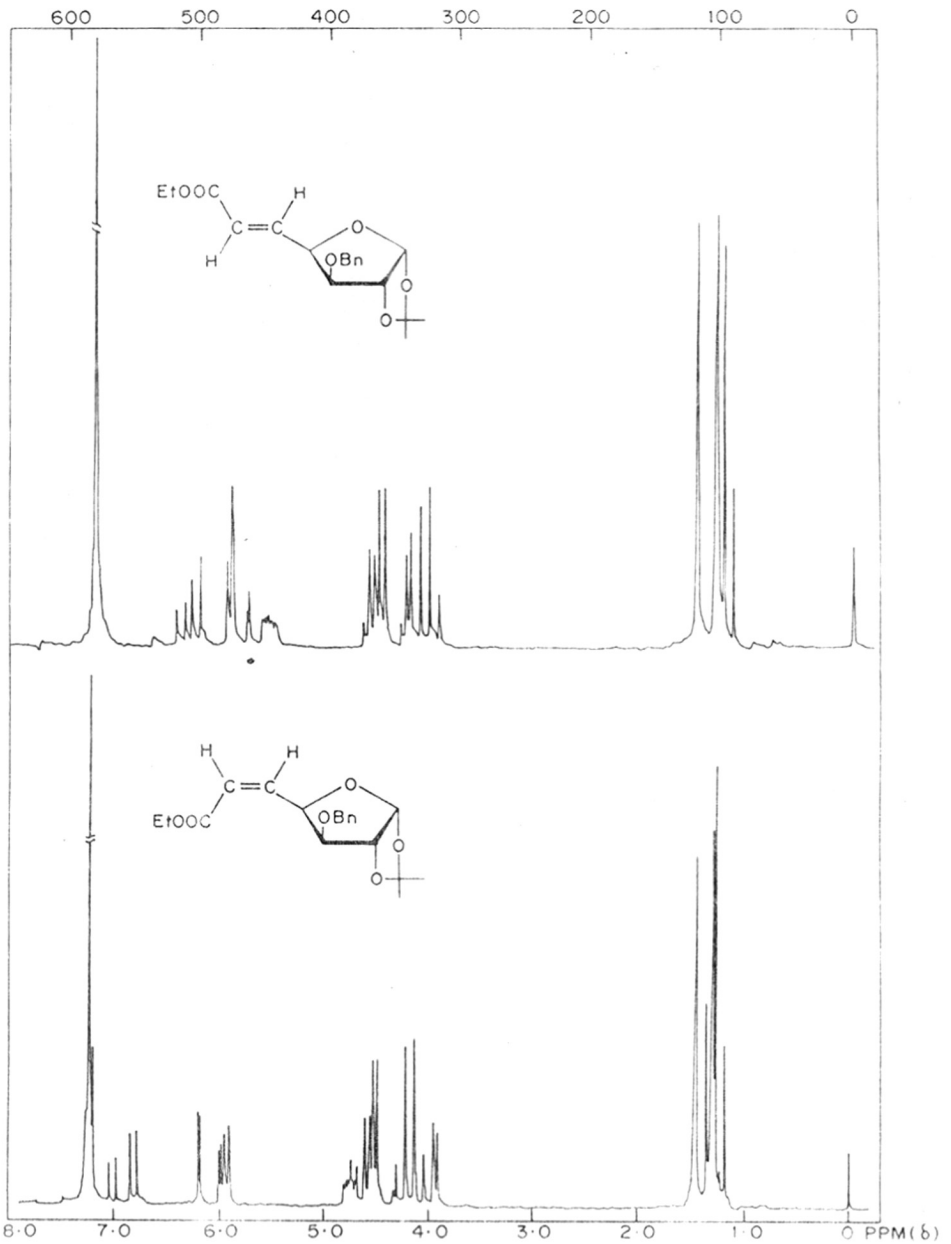


FIG. 4 : PMR SPECTRUM OF COMPOUND (19) IN $CDCl_3$

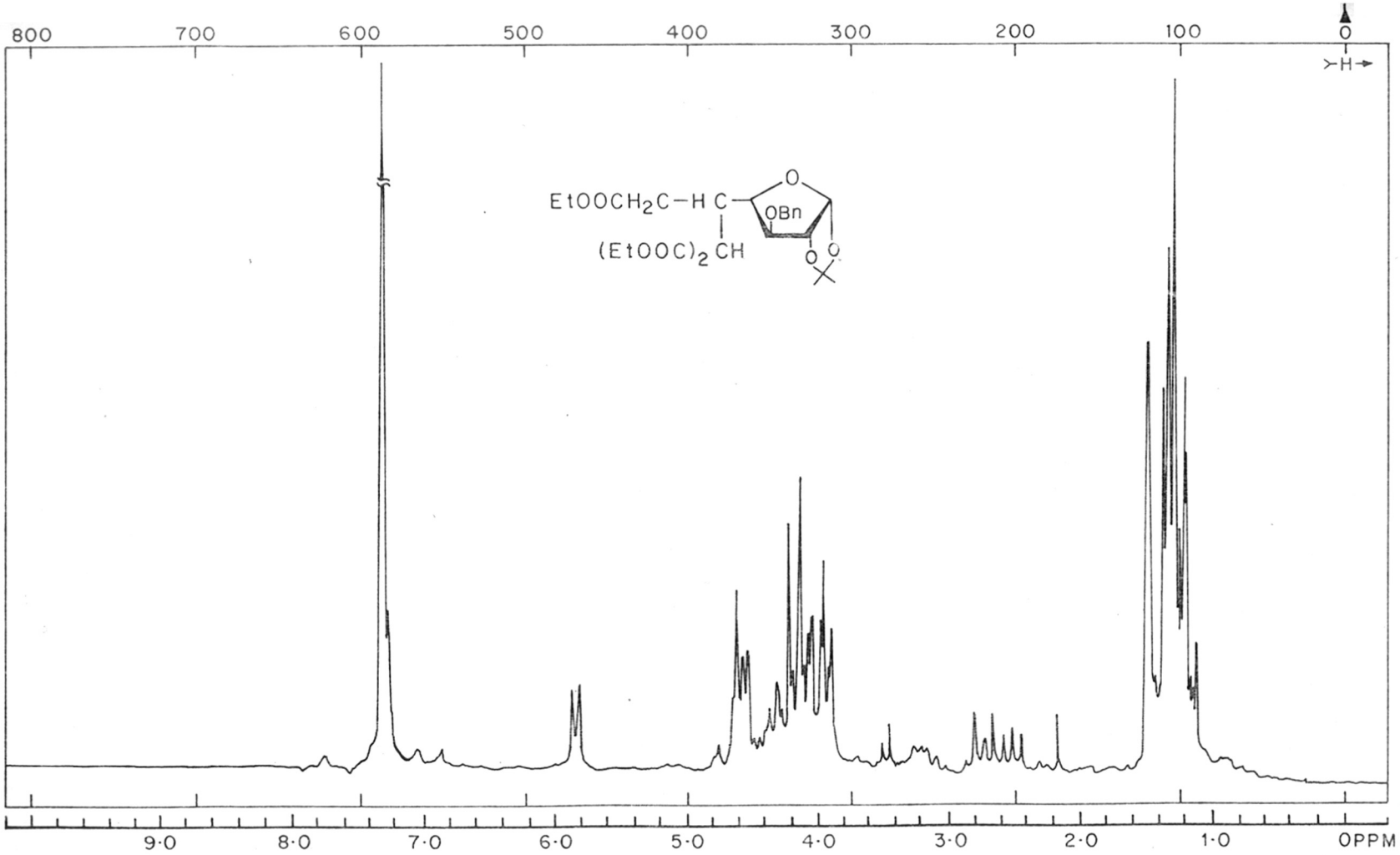


FIG. 5 : PMR SPECTRUM OF COMPOUND (20) IN $CDCl_3$

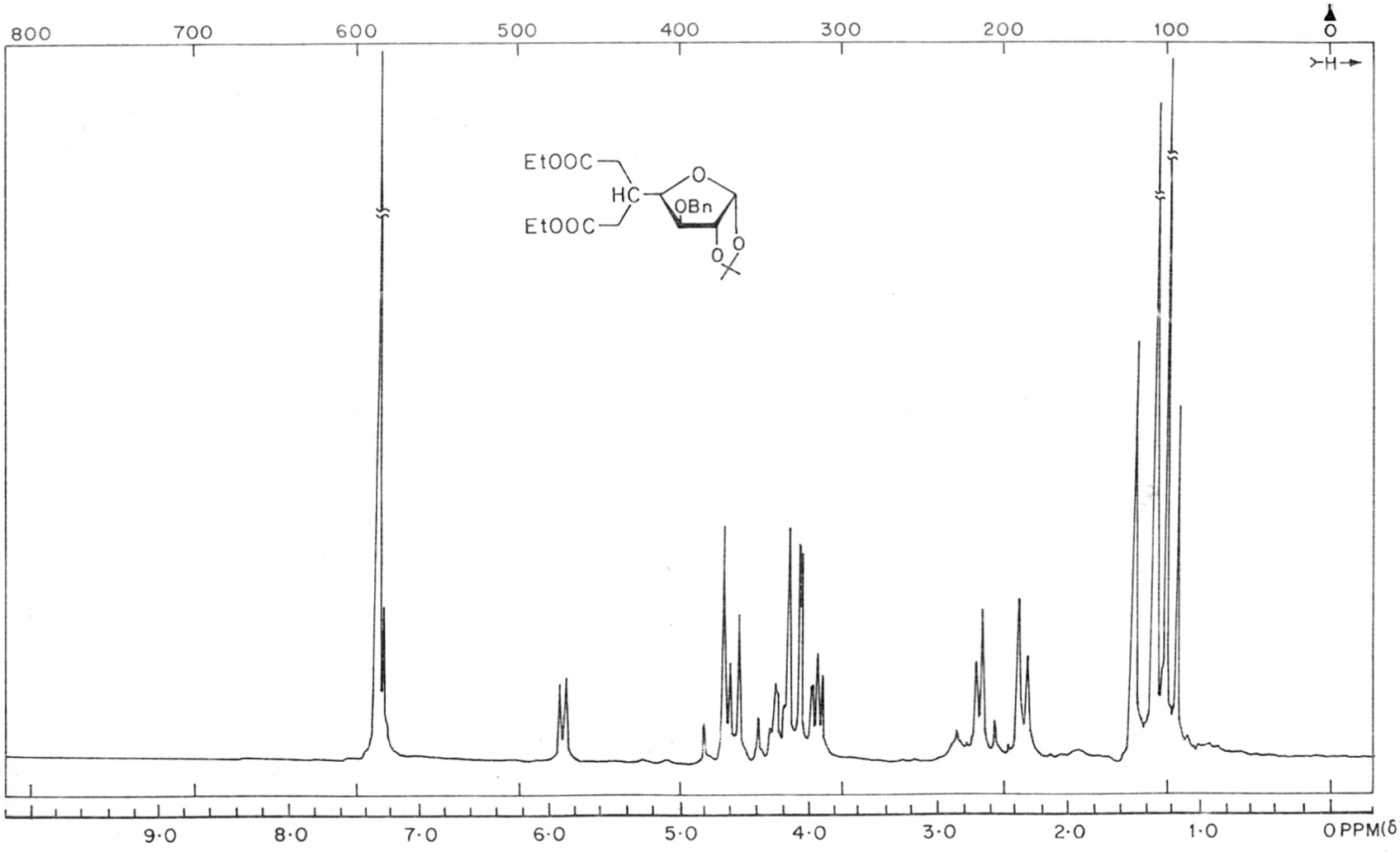


FIG. 6 : PMR SPECTRUM OF COMPOUND (21) IN $CDCl_3$

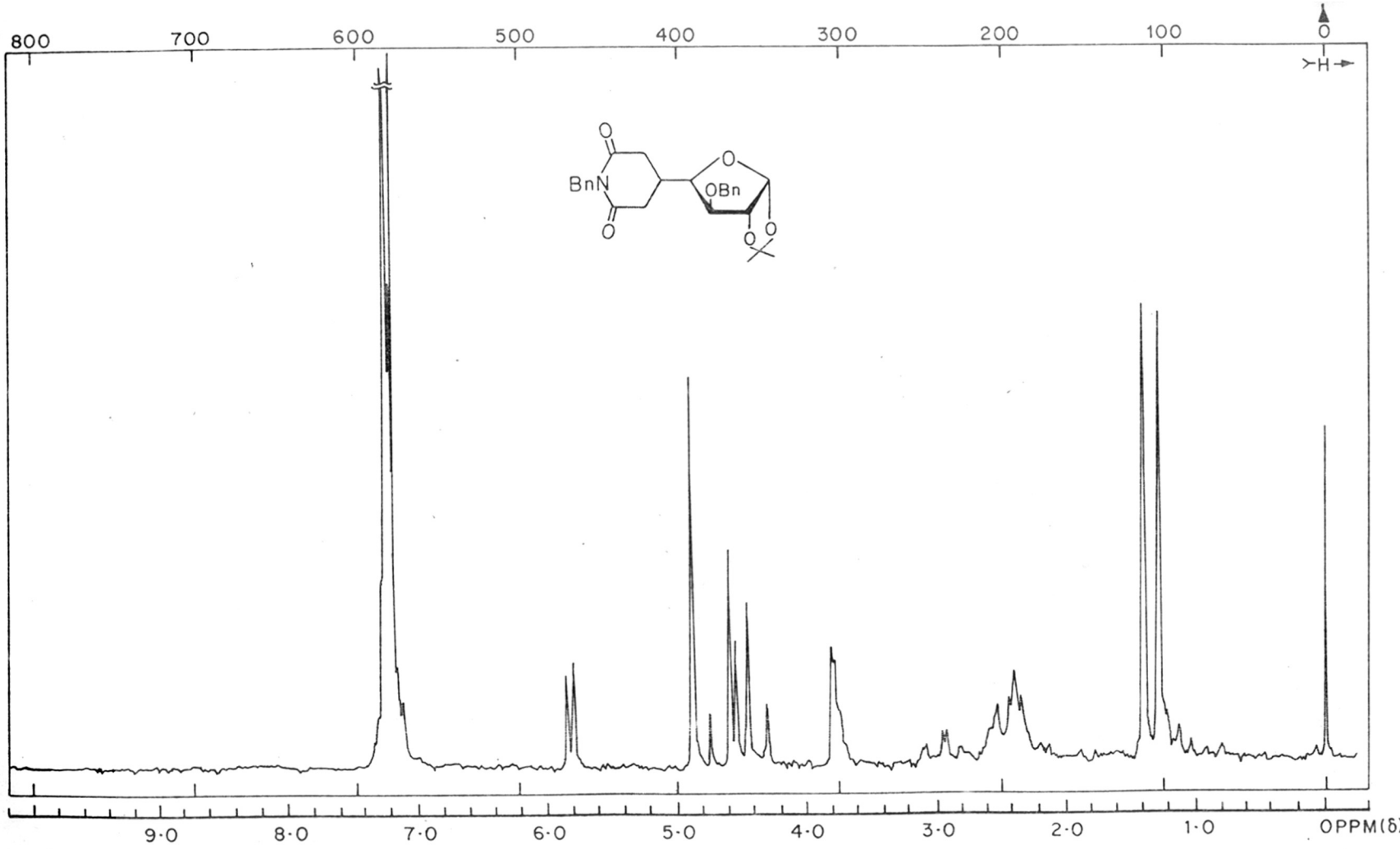


FIG. 7 : PMR SPECTRUM OF COMPOUND (23) IN $CDCl_3$

methylene protons of the side chain were observed at 2.25 and 2.63 ppm. While the remaining protons resonated at the expected chemical shifts.

When the diester (**21**) was treated with ethanethiol in the presence of zinc chloride[7], the ring opened to afford the dithiane derivative (**22**) in 75% yield. Although the PMR spectrum of **22** was complicated because of the overlapping of the signals, the absence of two singlets for the isopropylidene group was clearly observed. However, the microanalysis of the product suggested the assigned structure.

In order to introduce methylene bridge across two free hydroxyl groups, **22** was treated with several reagents such as dibromomethane sodium hydride, 40% aqueous formaldehyde-hydrochloric acid, paraformaldehyde-PTSA-toluene, $CH_2(OMe)_2$-PTSA. However, these reagents failed to give the desired product. In each of these attempts a mixture of product resulted. This could be due to the presence of ester functionalities which may be undergoing lactone formation. Therefore it was decided to convert the diester (**21**) into the cyclic amide.

In the light of the fact that the conversion of diester to cyclic amide with ammonia occurred with poor yield as observed in Scheme 2, it was felt to carry out amide formation with benzylamine. The advantage of having benzyl group was that it could be cleaved at later stages by using milder conditions such as hydrogenolysis. Accordingly the diester and benzylamine were allowed to react in DMF at room temperature, no reaction was observed. Even at reflux temperature, the diester failed to undergo amide formation. However, when the reaction was carried out at 180°C for four days in a sealed tube,

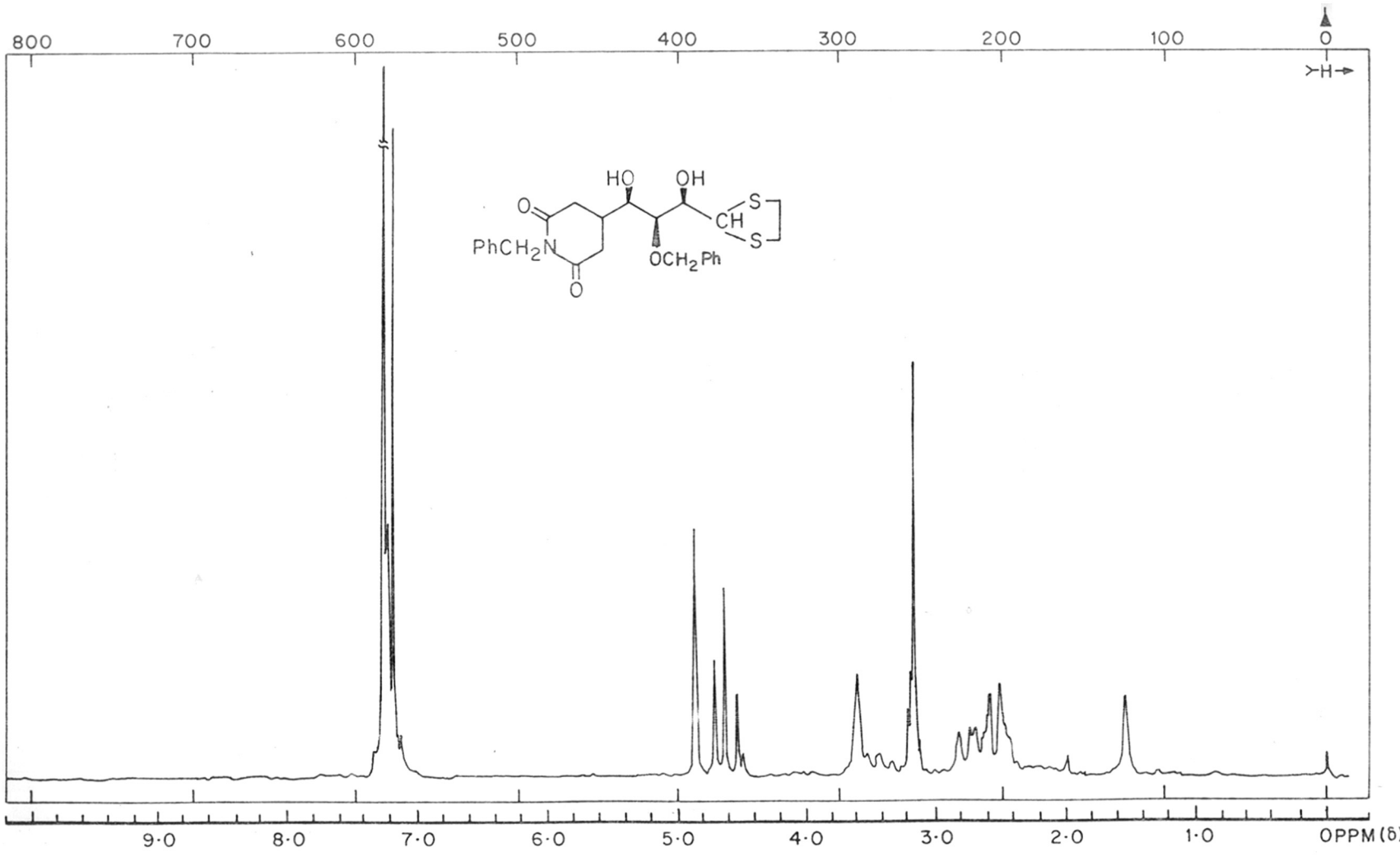


FIG. 8 : PMR SPECTRUM OF COMPOUND (24) IN $CDCl_3$

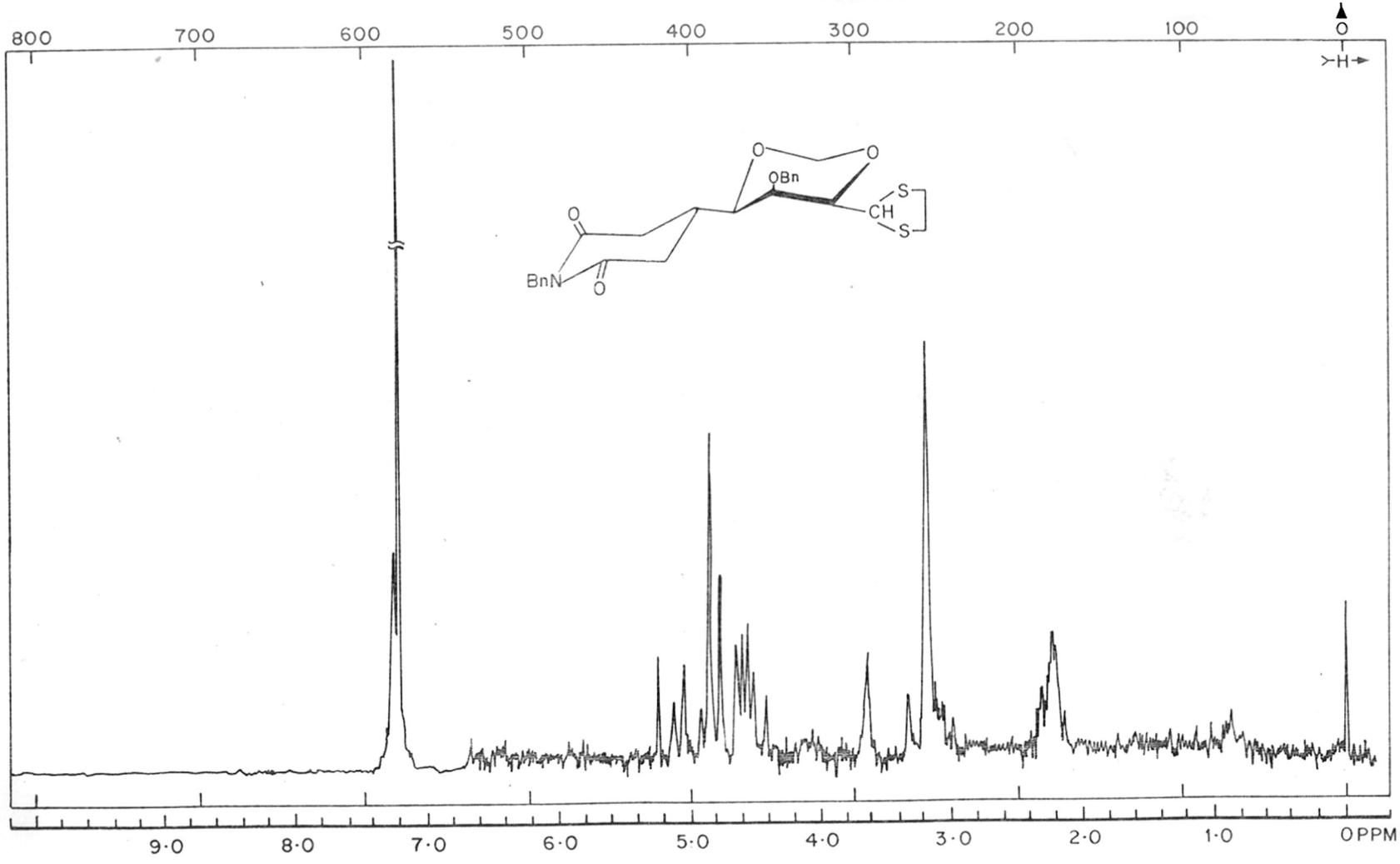


FIG. 9 : PMR SPECTRUM OF COMPOUND (25) IN $CDCl_3$

the desired amide (**23**) was obtained in 80% yield. The PMR spectrum of the amide was amenable to first order analysis and undoubtedly confirmed the assigned structure. For instance, the loss of ethyl groups were seen while the appearance of the two singlets for methylene and aromatic protons of the N-benzyl group were observed at 4.88 and 7.25 ppm respectively. Remaining protons had expected chemical shifts.

The cleavage of the acetonide ring in the presence of ethanedithiol and zinc chloride at 0°C afforded the 1,3-dithialane derivative (**24**) in 80% yield. The PMR spectrum of **24** showed a singlet and a doublet for methylene and methine protons of dithialane at 3.19 and 4.56 ppm respectively. This clearly suggested that 1,3-dithialane group has been incorporated. The 1,3-diol of **24** was then protected with dimethoxymethane in the presence of catalytic amount of toluene p-sulfonic acid to give the O-methylene acetal in 88% yield. In addition to the normal resonances, two additional doublets at 4.62 and 5.14 ppm corresponding to the O-methylene group of the acetal were located in the PMR spectrum of **25** suggesting the assigned structure.

SECTION III

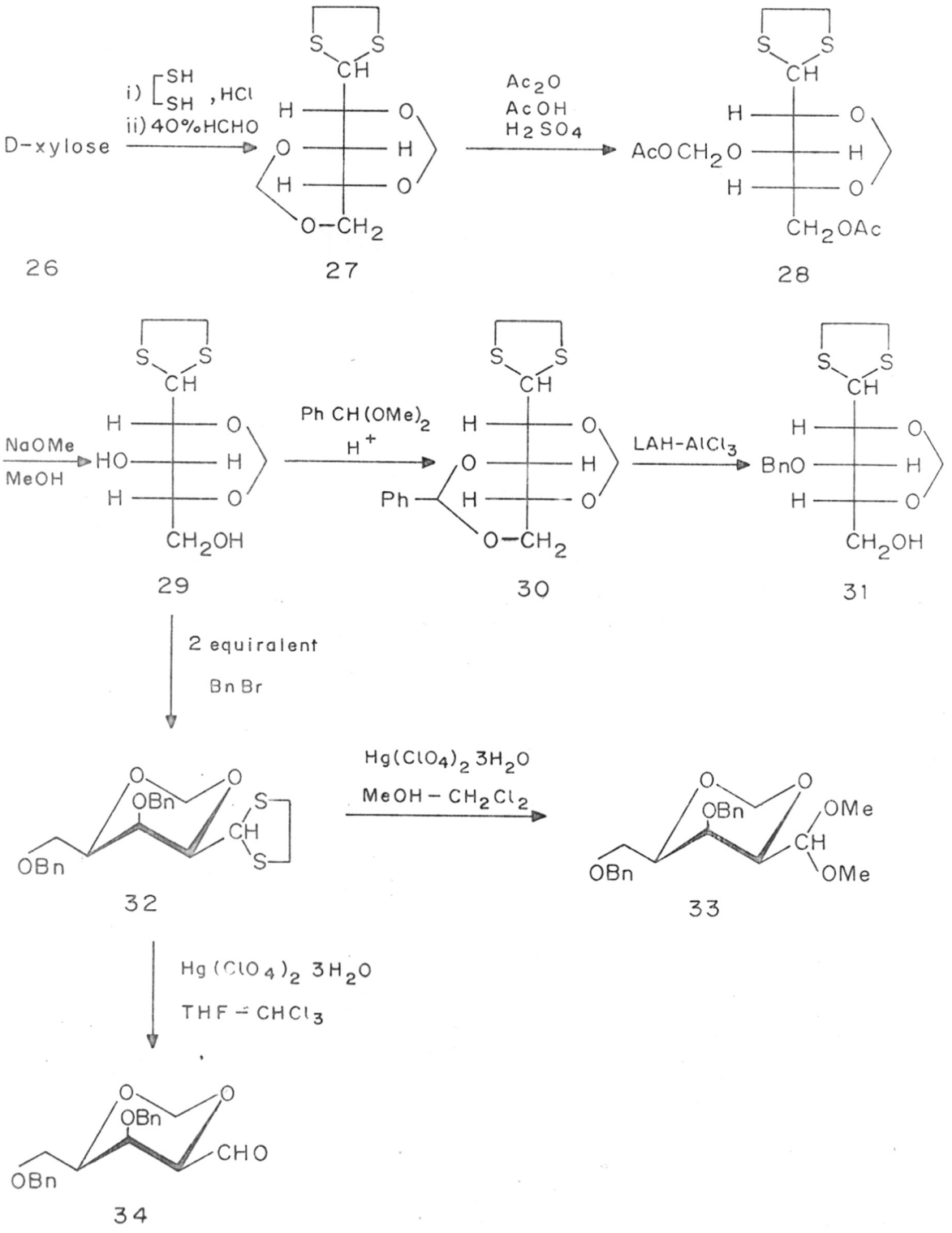
SYNTHESIS OF AB RING FROM D-XYLOSE

Since the absolute configuration of sesbanimide has not been determined so far, the AB ring system synthesised in Section 1 and 2 from D-sorbitol and D-glucose respectively may or may not find correlation with the natural product. Therefore, the synthesis of its enantiomer was undertaken. It may be noted that one of these enantiomers will have all the elements of chirality in perfect correlation with the natural sesbanimide.

The approach indicated in Scheme 3 from D-glucose for the synthesis of AB ring system involved the construction of ring A at C-5 of D-glucose derivative, while the C-1 carbon atom would be made use of for the construction of ring C. If one can reverse this possibility i.e. to build ring A at C-1 then the corresponding enantiomer of AB ring system can be generated. With this view in mind experiments were designed to build ring A at C-1 carbon atom of D-xylose.

D-xylosediethylmercaptan[8], prepared from D-xylose and ethylmercaptan in the presence of concentrated hydrochloric acid, was treated wih aqueous formaldehyde and concentrated hydrochloric acid at 50°C to afford two products as judged by TLC. The slower moving product was assigned the structure 1,2:3,5-di-O-methylene D-xylose on the basis of PMR spectrum and by comparison with the known compound[9] while the faster moving product was the simple formaldehydediethylmercaptan. This reaction clearly indicated that D-xylosediethylmercaptan and aqueous formaldehyde probably undergo trans ketalisation. In an another experiment D-xylosediethylmercaptan was treated with α,α-dimethoxymethane in the presence of toluene p-sulfonic acid, the formation of same two products resulted. The failure to bring about acetalation with formaldehyde

SCHEME - VI

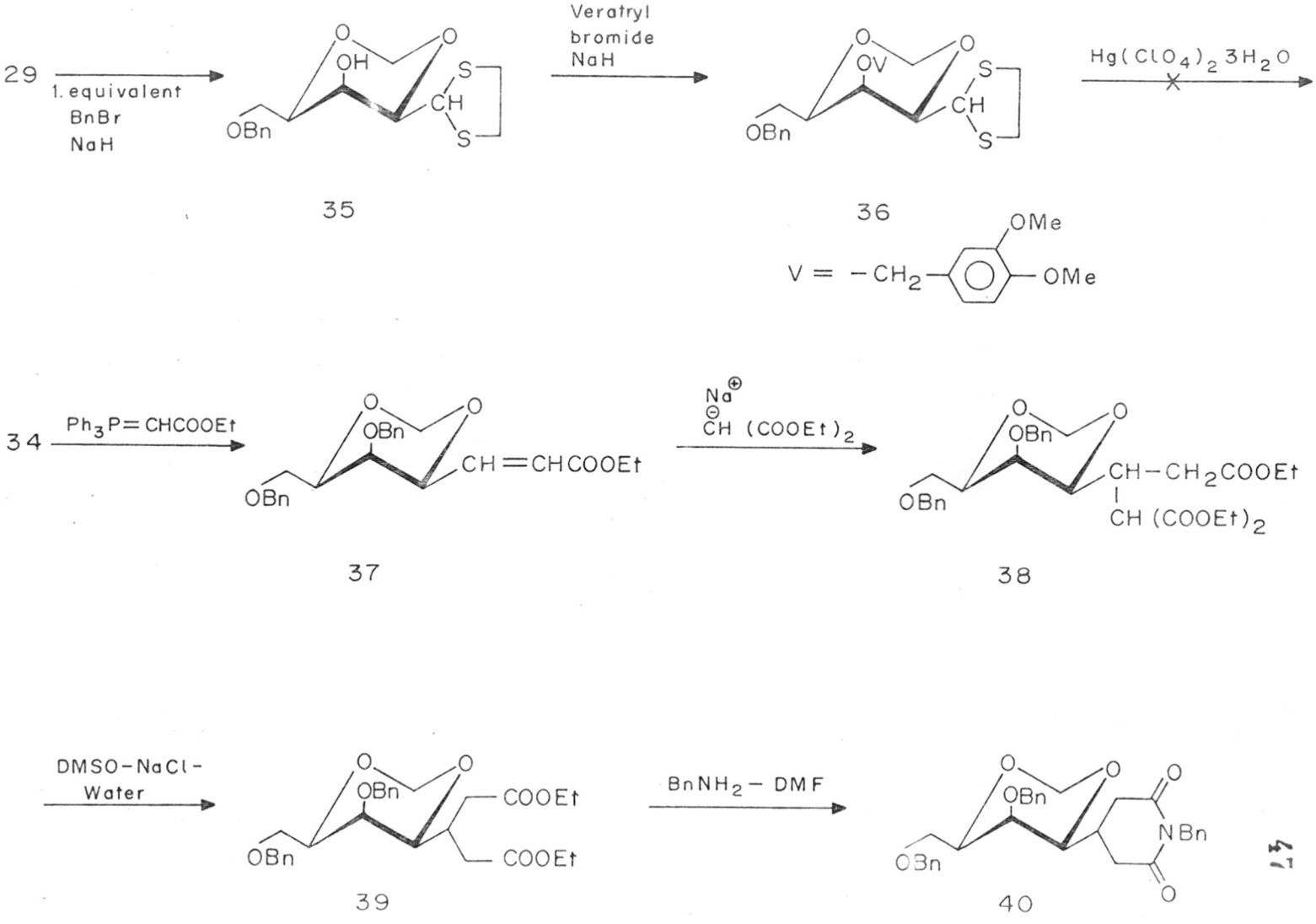


26 27 28

29 30 31

32 33

34


29
1. equivalent
BnBr
NaH
OH
OBn
35
Veratryl
bromide
NaH
OV
36
V = −CH2
OMe
OMe
Hg(ClO4)2 3H2O
34
Ph3P=CHCOOEt
CH=CHCOOEt
37
Na⊕
⊖CH (COOEt)2
CH−CH2COOEt
CH (COOEt)2
38
DMSO−NaCl−
Water
COOEt
COOEt
39
BnNH2 − DMF
NBn
40

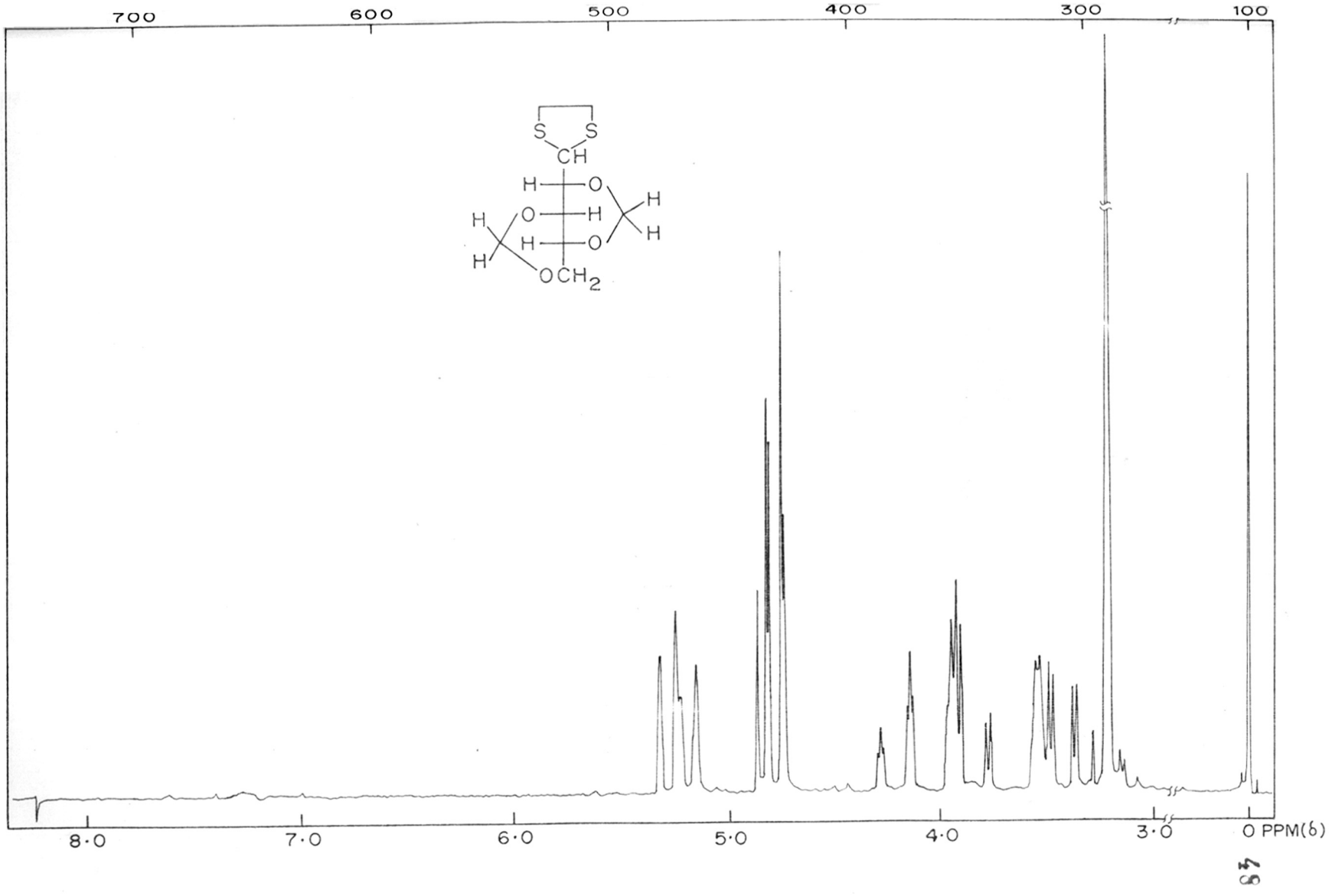


FIG. 10: PMR SPECTRUM OF COMPOUND (27) IN $CDCl_3$

or its derivative was surprising. It was then thought to use cyclic thioacetal as a protective group at C-1 because of the greater stability of cyclic thioacetals in comparison with open chain thioacetal. Accordingly D-xylose was converted into D-xylose 1,3-dithialane by the reaction with ethanedithiol and concentrated hydrochloric acid at 0°C. Its reaction with aqueous formaldehyde and concentrated hydrochloric acid at 50°C resulted in the formation of a solid product which was filtered and assigned the structure as 2,4:3,5-di-O-methylene-D-xylose 1,3-dithialane (**27**). The PMR spectrum of **27** revealed a singlet at 3.17 ppm for two methylene protons of 1,3-dithialane group whereas four doublets at 4.73, 4.75, 5.15 and 5.24 ppm were assigned to the O-methylene ($-OCH_2O-$). The methine proton of 1,3-dithialane group appeared as a doublet at 4.8 ppm. Later studies indicated that the compound **27** could be obtained from D-xylose in one pot by successive treatment with ethanedithiol and 40% aqueous formaldehyde in concentrated hydrochloric acid.

The next stage of the sequence involved the removal of 3,5-O-methylene bridge. There are ample of evidences to suggest that 3,5-O-methylene bridge, being more susceptible to hydrolysis, could be cleaved in preference to 2,4-O-methylene bridge under controlled condition. Compound **27** on treatment with a mixture of acetic acid, acetic anhydride and sulfuric acid after 10 h showed a slower moving spot on TLC. The product isolated in 76% yield was the desired diacetate derivative (**28**) Its PMR spectrum also revealed the assigned structure. For example two doublets for O-methylene protons of acetal group were located at 4.24 and 4.78 ppm. In addition two methyl of the two acetoxy groups

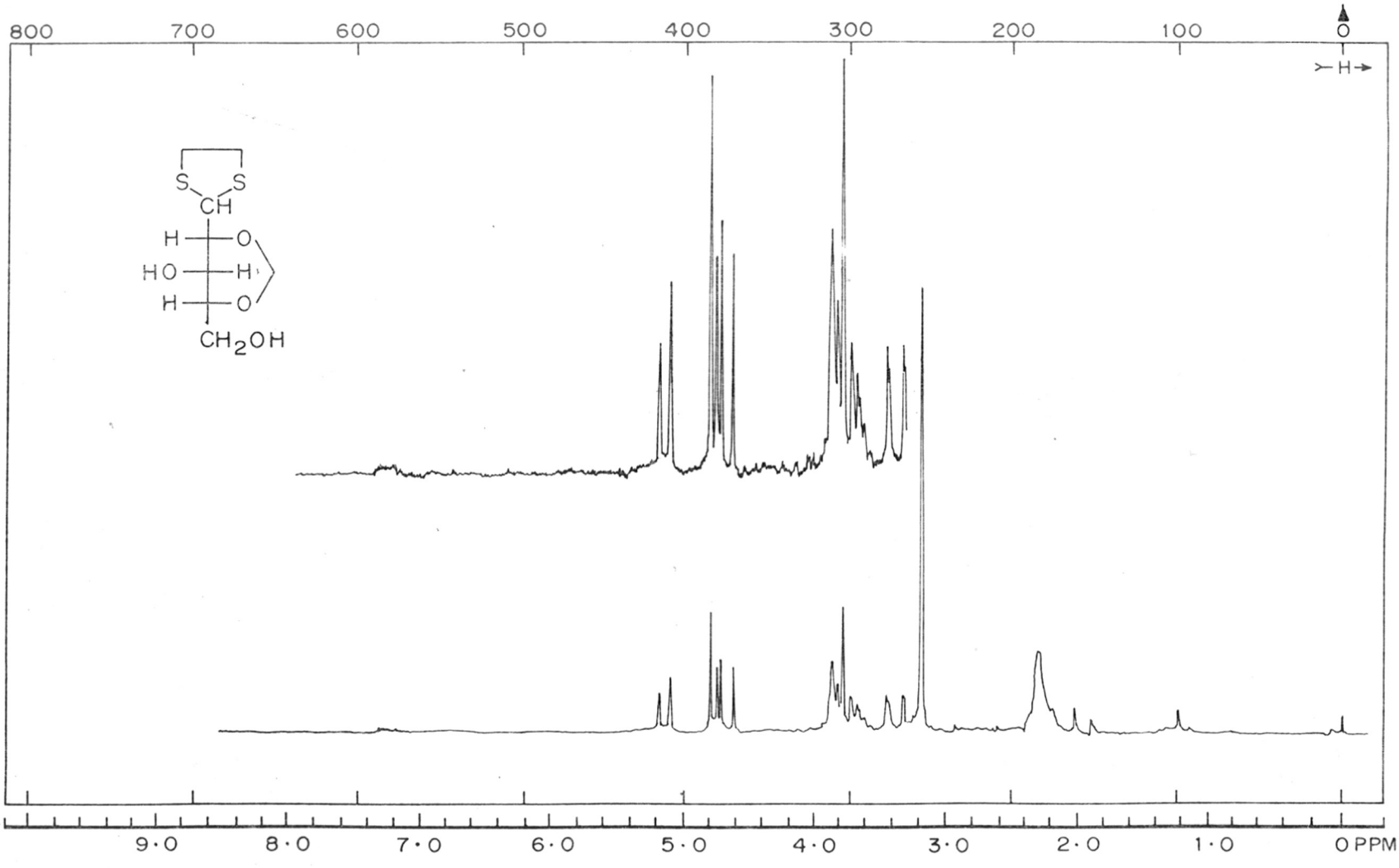


FIG. 11 : PMR SPECTRUM OF COMPOUND (29) IN $CDCl_3$

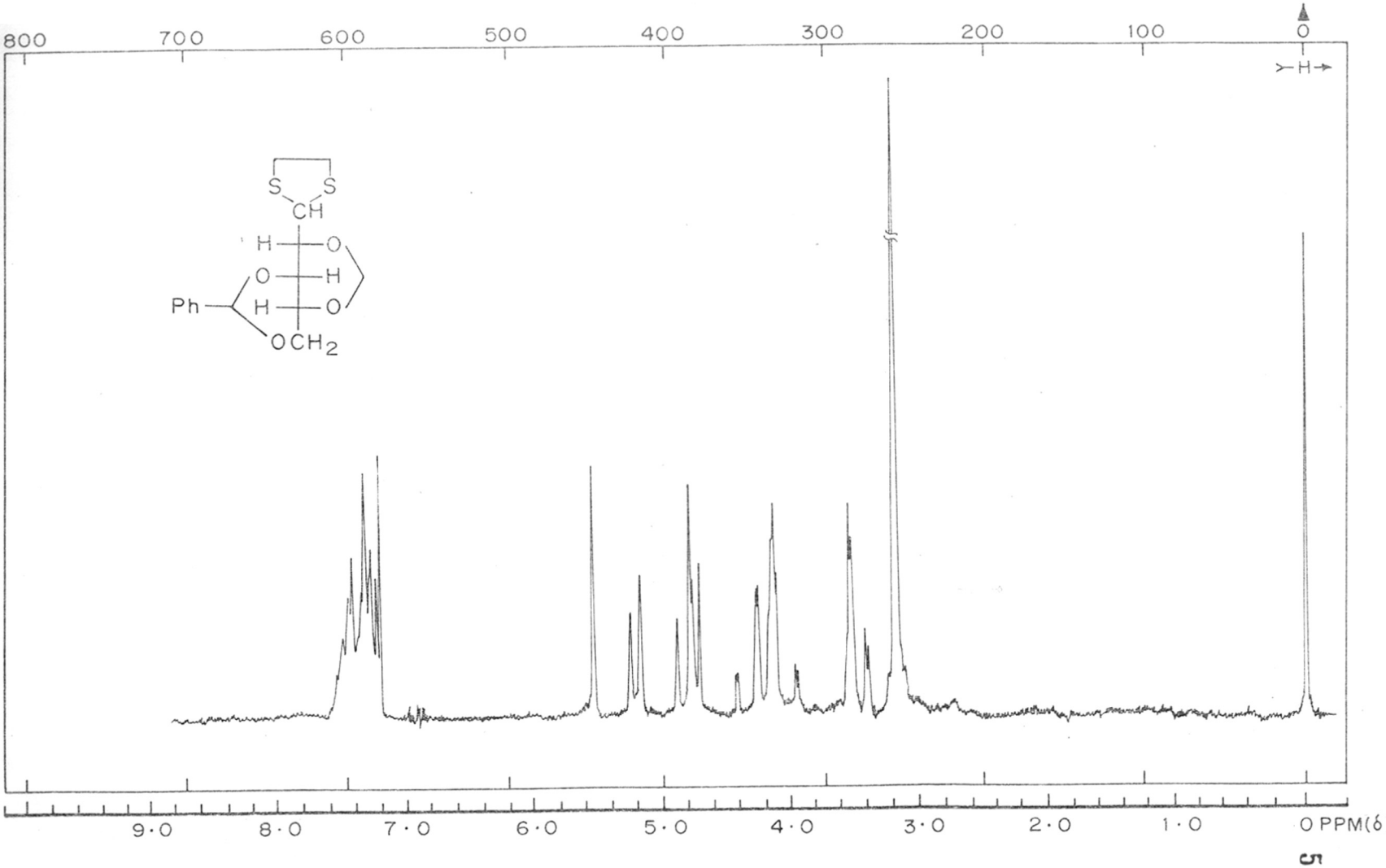


FIG. 12: PMR SPECTRUM OF COMPOUND (30) IN $CDCl_3$

were observed as two singlets at 2.0 ppm. Subsequent hydrolysis of acetyl group in **28** was effected in the presence of methanolic sodium-methoxide to afford **29.** The PMR spectrum of compound **29** was compared with its enantiomer **6** (page) and found to be superimposable. In addition $[\alpha]_D$ of **29** matches with **6** but opposite sign.

The next concern was the hydrolysis of 1,3-dithialane protection in order to generate the aldehyde group which can be used for the building up of the glutarimide ring. Therefore the free hydroxyl groups in **29** were protected as 3,5-O-benzylidene derivative by the treatment with α,α-dimethoxytoluene[10] in the presence of toluene p-sulfonic acid to afford **30,** whose PMR spectrum showed the benzylidene singlet at 5.56 ppm whilst other protons had expected chemical shifts. Deprotection of the thioacetal (**30**) was first attempted with $HgCl_2$-HgO[11] in aqueous acetone under reflux, no reaction was observed as the starting material was recovered. Change of conditions such as the use of high boiling solvents failed to bring any success. Other deprotecting reagents such as $CuCl_2$-CuO[12], NBS[11], Hg $(ClO_4)_2$ $3H_2O$[13], cerric ammonium nitrate[14], DMSO-I_2[15], NCS-$AgNO_3$[11], HBF_4-HgO[16], thallium trinitrate[13] HgO-BF_3 etherate[17] etc. failed to give the desired aldehyde, either the starting material was recovered or the mixture of products were formed as judged on TLC.

Discouraged by the failure to deprotect 1,3-dithialane, it was decided to changethe protective group at C-3 and C-5 and therefore the compound **30** was subjected to hydrogenolysis[18] in the presence of LAH-$AlCl_3$ to give a free primary hydroxyl derivative (**31**). The

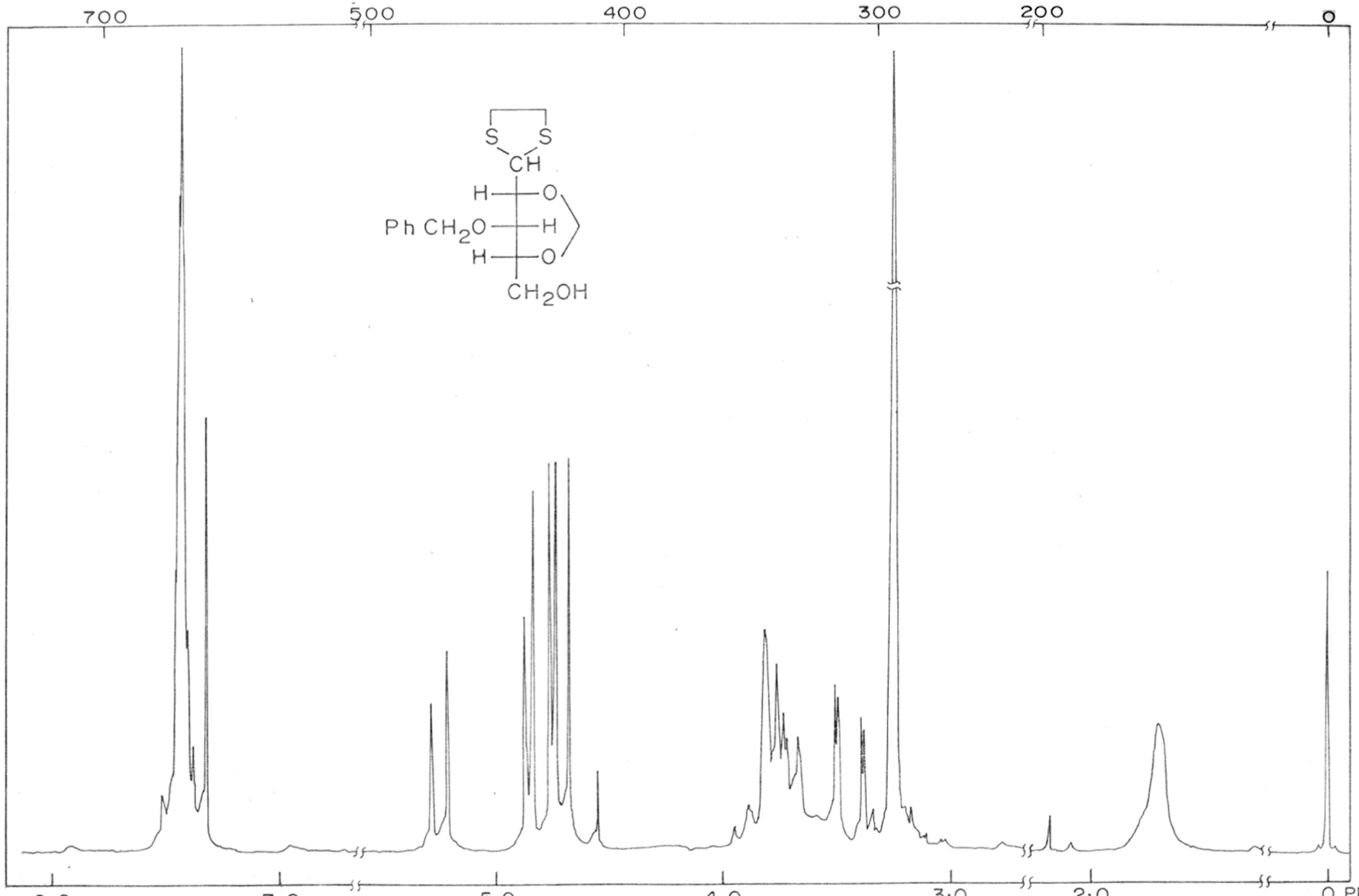


FIG. 13: PMR SPECTRUM OF COMPOUND (31) IN $CDCl_3$

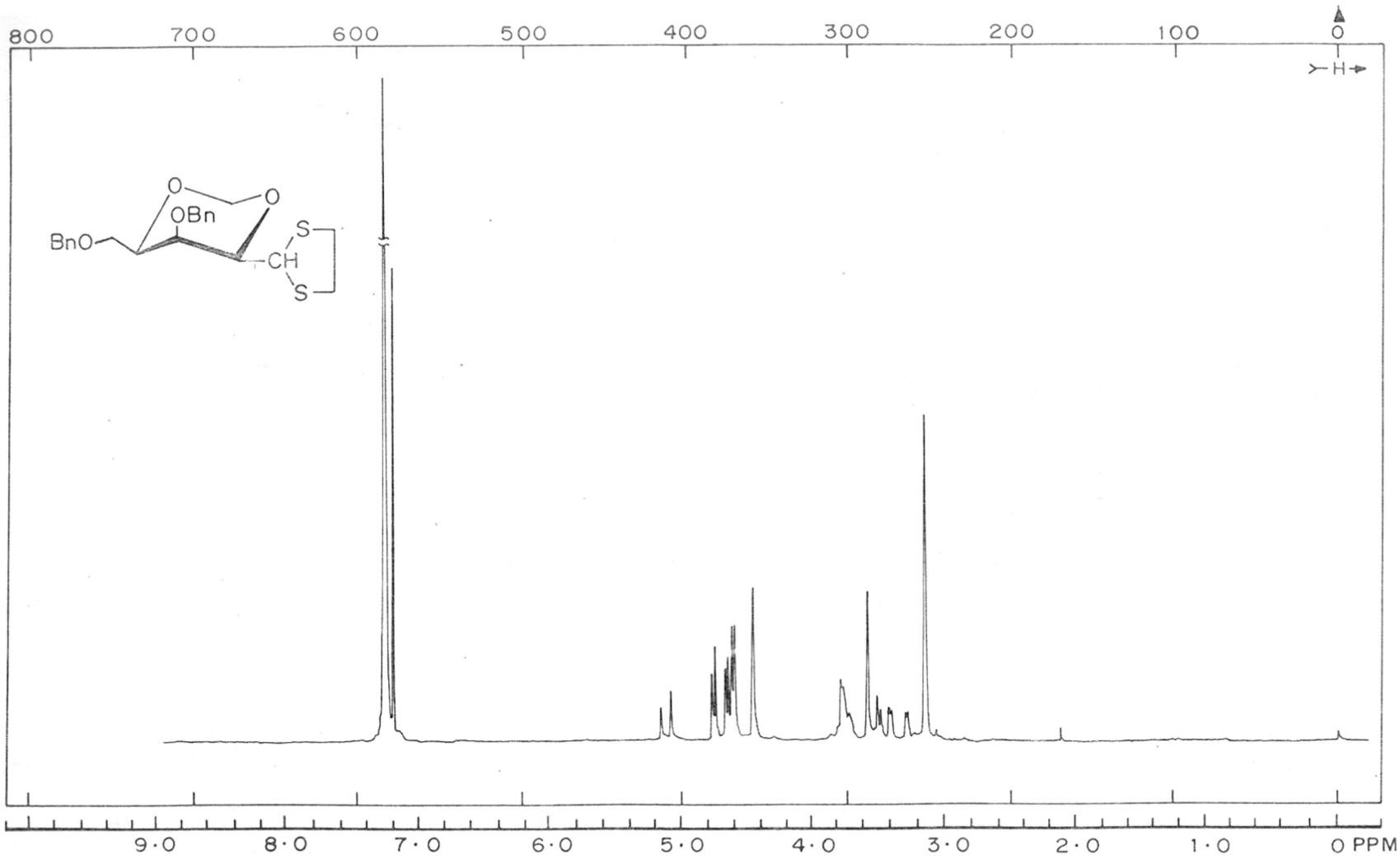


FIG. 14: PMR SPECTRUM OF COMPOUND (32) IN $CDCl_3$

structure of **31** was confirmed by the PMR spectrum in which a double doublet due to benzylic methylene appeared at 4.71 ppm. In the aromatic region a multiplet corresponding to aromatic protons was also observed. Other protons revealed resonances in agreement with the assigned structure. To confirm that the primary hydroxyl group was indeed free, its PMR spectrum was recorded in DMSO-d_6 which revealed a D_2O exchangeable triplet at 4.90 ppm. This experiment undoubtedly confirmed the assigned structure. Had the secondary hydroxyl been free a D_2O exchangeable doublet would have resulted around the same region. All the attempts to cleave the 1,3-dithialane protective group from compound **31** failed under various conditions as described above. This failure could be attributed to the presence of free hydroxyl group.

Therefore, in an another approach both the free hydroxyls present in **29** were protected as di-O-benzylether (**32**) by treatment with benzylbromide and sodium hydride. The PMR spectrum of dibenzyl derivative (**32**) showed peaks corresponding to two benzyl groups in the region of 4.5 ppm and in addition the aromatic protons at 7.3 ppm were integrated for 10 protons. Other peaks were properly assigned to the remaining protons. When compound **32** was treated with mercuric perchlorate in methanol:methylene chloride mixture, after 12 h the formation of a single product was realised which was isolated and assigned as 3,5-di-O-benzyl-2,4-O-methylene-D-xylose dimethylacetal (**33**) on the basis of the spectral analysis. For example, a singlet corresponding to the dithialane group was absent, while the two methoxyl singlets revealed at 3.25 and 3.44 ppm. In addition resonances due to two benzylic

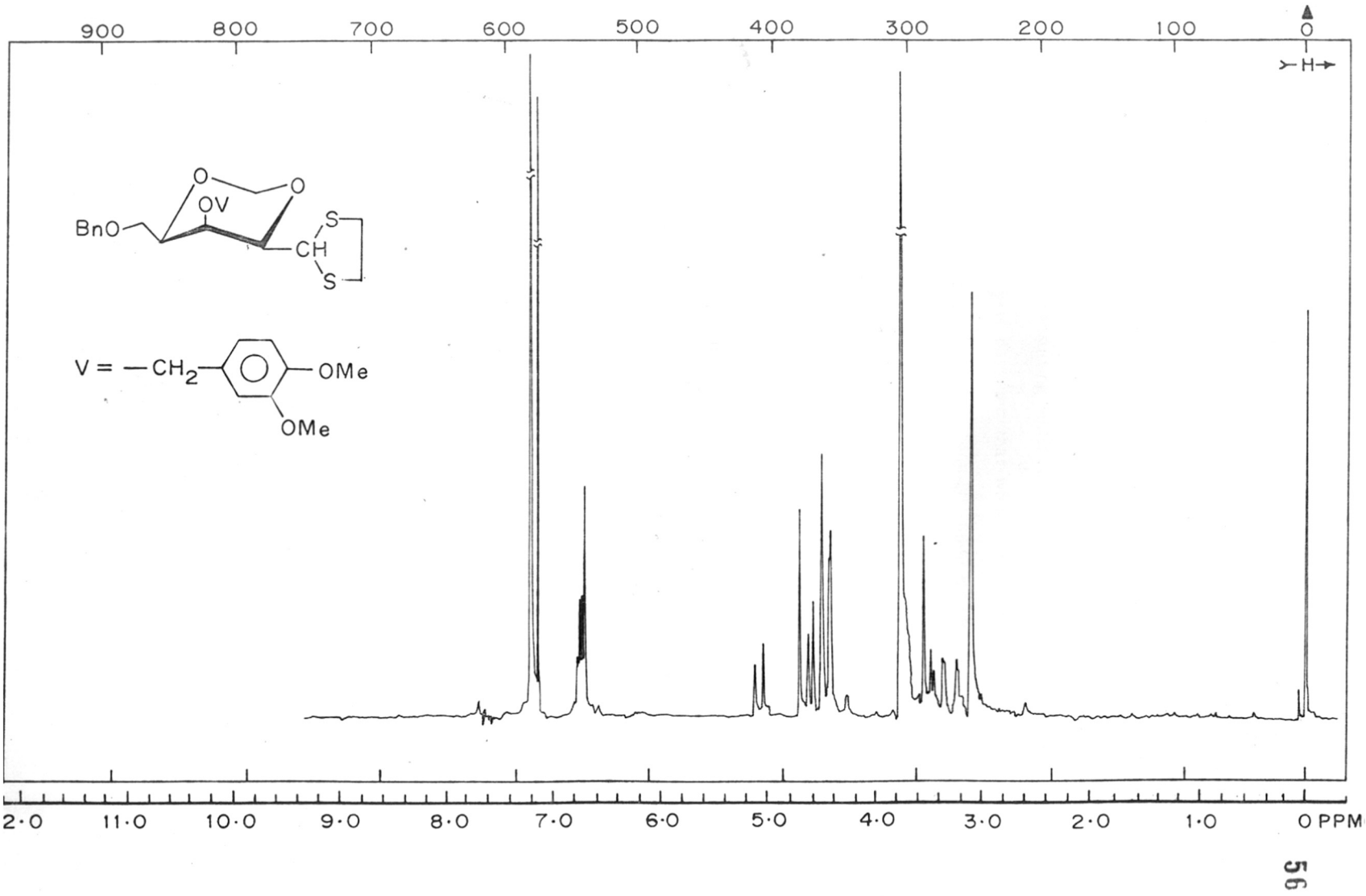


FIG. 15: PMR SPECTRUM OF COMPOUND (36) IN $CDCl_3$

protons appeared at 4.44 and 4.54 ppm. A doublet at 4.56 ppm was assigned to H-1, whereas two set of doublets at 4.69 and 5.13 ppm corresponded to O-methylene group. The formation of dimethylacetal could be envisaged due to the presence of methanol. In the presence of acidic conditions the resulting aldehyde has undergone dimethyl acetal formation. Later it was observed that when THF was utilised as solvent in place of methanol the corresponding aldehyde (**34**) was exclusively formed within 24 h. Its characterisation was done by the PMR spectrum in which a doublet at 9.19 ppm corresponding to aldehyde proton was observed.

Having successfully done the dethioacetalization of **32** with mercuric perchlorate, efforts were then directed to carry out similar reaction on the compound **36** in which the secondary and primary hydroxyl groups are protected by different substituents. This was necessary because after the formation of glutarimide ring a generation of free primary hydroxyl group will be required for the construction of ring C while keeping the hydroxyl group at C-3 protected. Therefore experiments were designed where the diol (**29**) was converted into the monobenzylether (**35**) by the reaction with one molar equivalent of benzyl bromide and sodiumhydride. The PMR spectrum of **35** revealed a singlet at 4.50 ppm for the benzylic proton. Other protons showed chemical shifts consistent with the assigned structure. When the PMR spectrum of **35** was scanned in DMSO-d_6 a doublet was observed at 4.84 ppm which was D_2O-exchangeable. This confirmed that the secondary hydroxyl group was free.

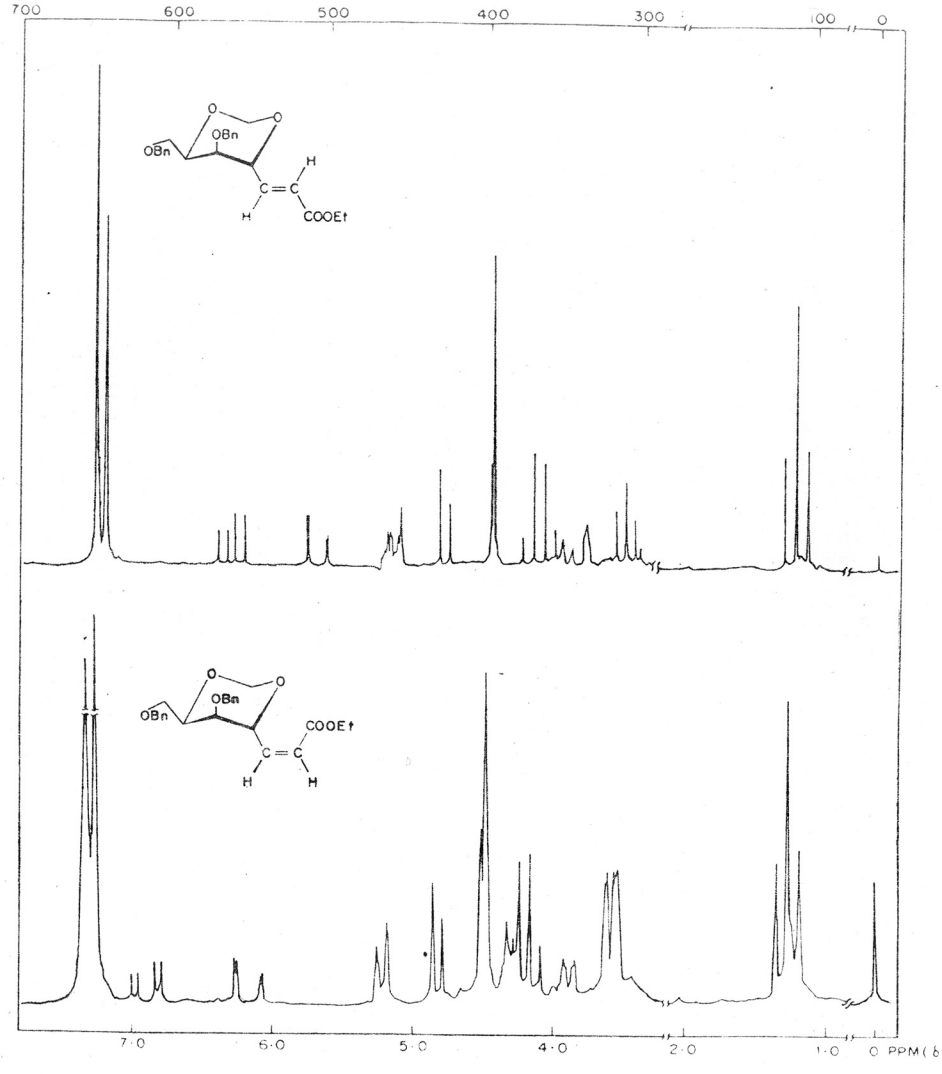


FIG 16: PMR SPECTRUM OF COMPOUND (3.7) IN $CDCl_3$.

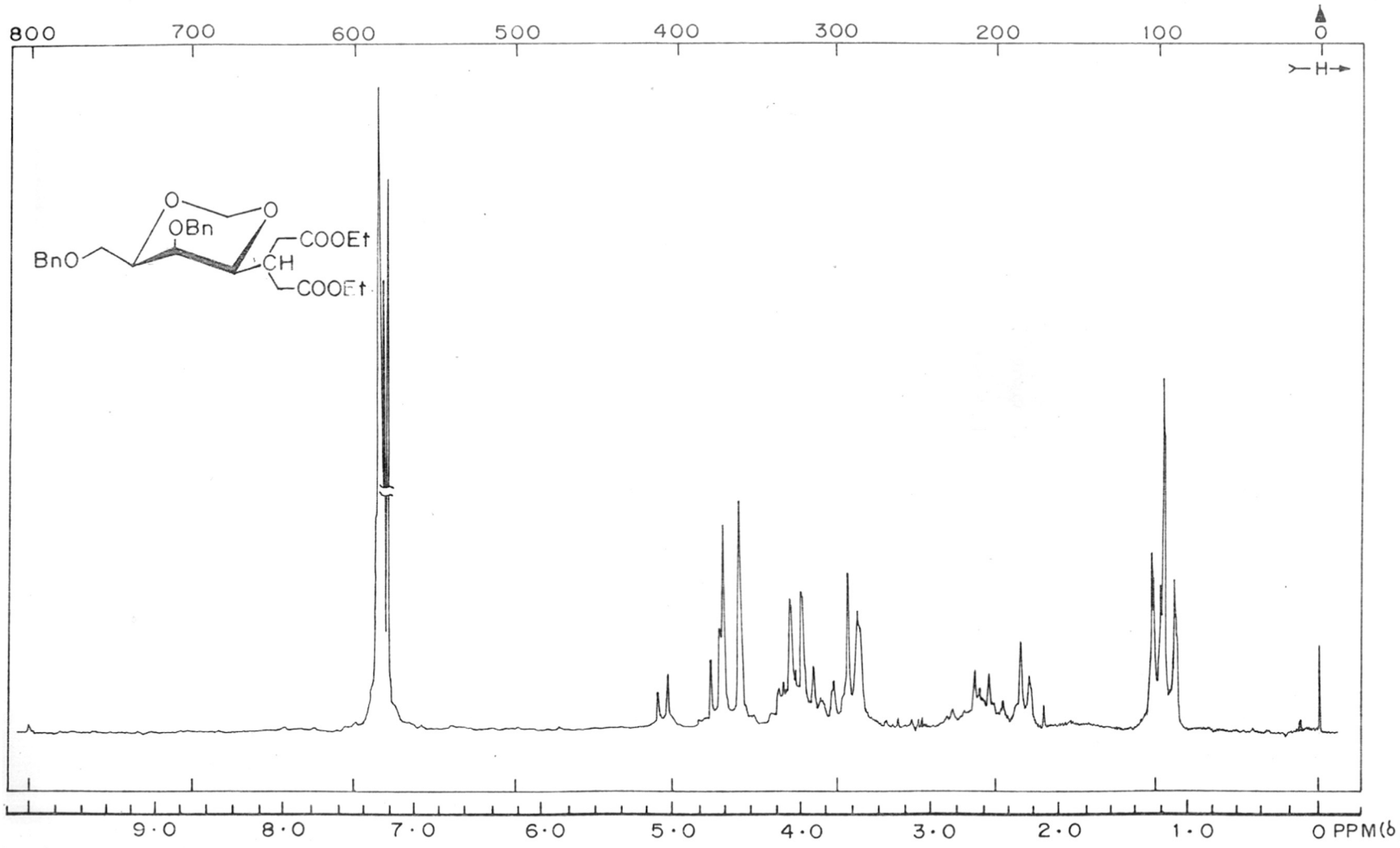


FIG. 17: PMR SPECTRUM OF COMPOUND (39) IN $CDCl_3$

It is known in literature that 3,5-dimethoxy-O-benzyl group and O-benzyl group can be selectively deprotected in presence of each other under different conditions. For example 3,4-dimethoxy O-benzyl group can be removed with DDQ keeping the O-benzyl group intact[19]. Similarly O-benzyl group can be deprotected with Raney Ni while 3,4-dimethoxy-O-benzyl group remains unaffected[20]. Advantage of this behaviour was exploited in the present situation and therefore the free hydroxyl group at C-3 was protected as 3,4-dimethoxy-O-benzyl ether (**36**) by the reaction with 3,4-dimethoxybenzyl bromide and sodium-hydride. The presence of 3,4-dimethoxy-O-benzyl group in **36** was confirmed by PMR spectrum when a singlet corresponding to methoxyl group was observed at 3.83 ppm (integrating for 6 protons). Treatment of **36** with mercuricperchlorate in THF-$CHCl_3$ mixture was carried out, surprisingly the reaction showed a number of spots on TLC. By changing solvent system of the reaction (methanol-methylene chloride), no success was realised. Failure to effect the hydrolysis of 3,4-dimethoxy O-benzyl substituted dithialane may be attributed to susceptibility of 3,4-dimethoxy-O-benzyl group to undergo decomposition under the given condition.

Although it was most desirable to introduce different substituents at C-3 and C-5 of the D-xylose derivative (**29**) so that one can cleave one protective group at the expense of other, all the attempts resulted in failure. Therefore, it was decided to rely on the earlier approach where both the hydroxyl groups were protected with O-benzyl group. Accordingly the aldehyde (**34**) was subjected to the reaction

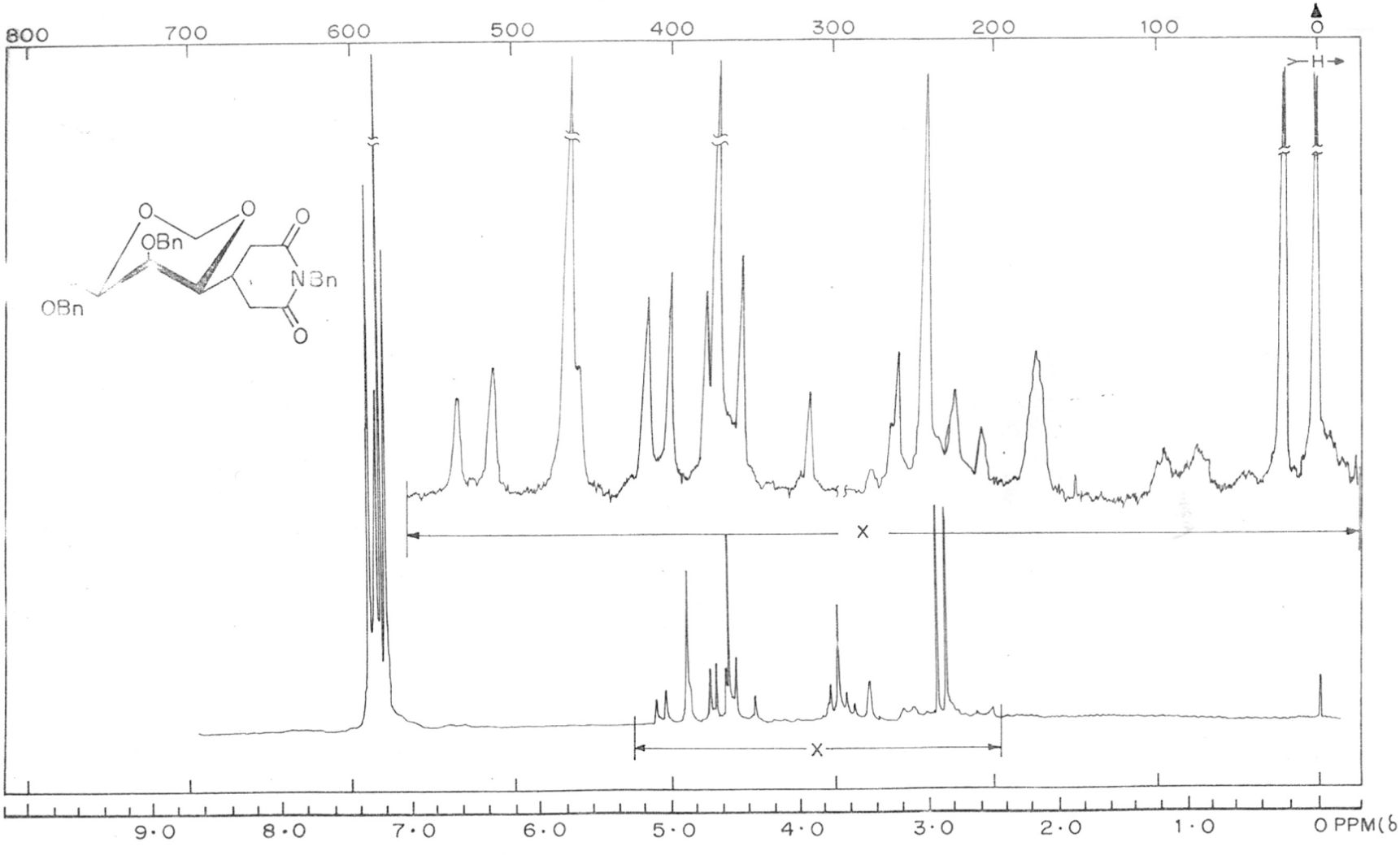


FIG. 18: PMR SPECTRUM OF COMPOUND (40) IN $CDCl_3$

with ethoxycarbonylmethylenetriphenylphosphorane in benzene under reflux to give the α,β-unsaturated ester (**37**) whose PMR spectrum indicated that it was cis, trans mixture. However, the mixture was subjected to Michael addition with sodium salt of diethylmalonate which afforded the triester (**38**) in 79% yield. The PMR spectrum was in agreement with the assigned structure **38**. The triester was then decarbethoxylated in the presence of DMSO-sodiumchloride-water at 160°C to give the diester (**39**). The compound **39** was then treated with benzylamine in DMF at 170°C for 5 days in a sealed tube to give rise to N-benzyl-protected glutarimide derivative (**40**) in 87% yield. The PMR spectrum of **40** revealed the benzylic methylene corresponding to two O-benzyl and N-benzyl substituent in the region of 4.0 - 5.0 ppm. In addition two set of doublets for methylene protons of glutarimide ring were revealed at 2.80 and 2.95 ppm, whereas a multiplet for the methine proton of glutarimide ring was observed in the region 3.0 - 3.2 ppm. Other protons were assigned resonances in accordance with the expected chemical shifts.

GENERAL REMARKS

B.p. and m.p. are uncorrected.

All solvents and reagents were purified and dried by standard techniques. All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 45°C.

All columns used for column chromatography were dry packed with silica gel (60-120 mesh) procured from Acme Synthetic Chemicals.

Identification of the compound was done by spraying the TLC plates with 2% α -naphthol solution in ethanol containing 5% sulfuric acid and/or with 5% cerric sulphate solution and then heating the TLC plate in an oven at 120°C for 5 minutes.

^{1}H-NMR spectra were obtained on a Varian T-60 or JNM-PMX-60 or Varian FT-80A or Brucker WH-90 spectrometer in $CDCl_3$ solutions (unless otherwise stated) containing tetramethylsilane (TMS) as an internal standard with chemical shifts (δ) expressed in ppm downfield from TMS. The following abbreviations have been used while presenting the data: s - singlet, d - doublet, t - triplet, q - quartet, m - multiplet.

IR spectra (ν_{max} in cm^{-1}) were recorded in nujol or neat (liq. film) on a Perkin-Elmer Model 683 spectrometer with sodium chloride optics.

Mass spectra were run on AEI MS - 30 double beam mass spectrometer or CEC 21-110B mass spectrometer using ionisation potential of 70 eV and a direct inlet system.

Optical rotations were measured on JASCO DIP-181 polarimeter using sodium lamp (λ_{max} 589 nm) as the source at 25°C.

Analytical GLC has been carried out on Hewlett Packard Gas Chromatograph model 5793 using the following columns: (i) OV-101 5%, 6 ft. x 1/8" (ii) FFAP 5%, 6 ft.x 1/8". Nitrogen was used as carrier gas, with F/D detector with flow rate of 30 ml/min.

EXPERIMENTAL

1,3:2,4:5,6-tri-O-methylene-D-sorbitol (2)

The solution of D-sorbitol (200 g) in a mixture of 40% aqueous formaldehyde (300 ml) and concentrated hydrochloric acid (200 ml) was maintained at 50°C. After 4 days the mixture was cooled to 5°C and the solid separated was filtered to yield 1,3:2,4:5,6-tri-O-methylene D-sorbitol (162 g, 68%) which was crystallised from 50% ethanol m.p. 214°C [lit.[1] m.p. 212-216°C].

3,5-di-O-acetoxymethyl-1,6-di-O-acetyl-2,4-O-methylene-D-sorbitol (3).

To the rapidly stirred mixture of acetic anhydride (175 ml), glacial acetic acid (75 ml) and concentrated sulfuric acid (2.5 ml) at 0°C was added dry, powdered tri-O-methylene-D-sorbitol (80 g). After 15 minutes the solution was poured into 3 lit. of vigorously stirred ice and water. The product 3,5-di-O-acetoxymethyl-1,6-di-O-acetyl-2,4-O-methylene-D-sorbitol separated was filtered after 2 h, washed with water and dried to give the title compound (80 g, 52%). It was crystallised from 12 parts ethanol m.p. 111°C (lit.[1] m.p. 111-12°C).

2,4-O-methylene-D-sorbitol (4)

To the solution of 10 g of acetate derivative (**3**) in 100 ml of chloroform at 0°C, 10 ml of 0.2N sodium methoxide in methanol was added. Then the reaction mixture was allowed to stand for 18 h at 5°C. Solid separated from the reaction mixture was filtered to give 2,4-O-methylene-D-sorbitol (4.6 g, quantitative). It was crystallised from ethanol m.p. 164°C (lit.[1] m.p. 163-64°C).

2,4-O-methylene-L-xylose (5)

To a solution of 2,4-O-methylene-D-sorbitol (5 g) in water (50 ml) at 5°C, 0.616M aqueous periodic acid (50 ml, 1.20 molecular equivalents) was added. The reaction mixture was allowed to stand at 25°C for 18 h. Then cold saturated barium hydroxide solution was added in slight excess and the precipitated barium iodate and periodate were filtered. The filtrate was concentrated in vacuo to give crude 2,4-O-methylene-L-xylose as syrup.

2,4-O-methylene-L-xylose-1,3-dithialane (6)

To the stirred solution of crude 2,4-O-methylene-L-xylose (1.62 g, 0.01 moles) in concentrated hydrochloric acid at 0°C was added ethanedithiol(1.8 ml, 0.02 moles). After 6 h, the reaction mixture was diluted with methanol. The acid was neutralised with lead carbonate. Inorganic material was filtered. The methanol was evaporated. The crude product was purified by column chromatography over silica gel (5% acetone in chloroform) to give the title compound (300 mg, 12.5%), m.p. 125°C, $[\alpha]_D$ -2.0 ($CHCl_3$). PMR($CDCl_3$): δ 2.25 (bs, 2H, OH, D_2O exchangeable), 3.19 (s, 4H, -S-CH_2CH_2-S-), 3.31- 3.94 (m, 5H), 4.69 (d, 1H, J = 9.45 Hz, ), 4.77, 5.10 (2 d, 2H, J = 6.3 Hz, OCH_2O). Mass: 238 (M^+).

Analysis: Calculated for $C_8H_{14}S_2O_4$: C, 40.34; H, 5.92; S, 26.89. Found: C,40.12; H, 6.03; S, 26.71%.

1,3:2,4-di-O-methylene-D-sorbitol(7)

Tri-O-methylene-D-sorbitol(**2**) (50 g) was boiled under stirring with 1N sulfuric acid (400 ml). After 10 h the solution was neutralised with barium carbonate. Inorganic material was filtered and washed with water. Filtrate was evaporated to dryness under reduced pressure

to give a crude product which was crystallised from chloroform to give title compound (**7**) (21 g, 44.5%) m.p.[1]173°C.

Aldehydo 2,4:3,5-di-O-methylene-L-xylose monohydrate

A solution of 1,3:2,4-di-O-methylene-D-sorbitol (30 g, 0.14 moles) in water (200 ml) was cooled to 5°C and periodic acid (37 g, 0.16 moles) in water (150 ml) was slowly added. The reaction mixture was kept at 5°C for 24 h. The product separated was filtered, washed with cold water and dried (14.5 g, 52%) m.p.175-80°C.

Aldehydo 2,4:3,5-di-O-methylene-L-xylose (8)

The sample of aldehydo-2,4:3,5-di-O-methylene-L-xylose monohydratae was sublimed in vacuum at 140-5°C to give the compound **8** m.p.[1] 189-92°C.

Ethyl (4R, 5S, 6R)-4,6:5,7-di-O-methylenehept-2-enoate (9)

To the solution of compound **8** (19.2 g, 0.1 moles) in benzene (75 ml) was added ethoxycarbonylmethylenetriphenylphosphorane (38.2g, 0.11 moles). The reaction mixture was refluxed for 4-5 h, the solvent was evaporated and the crude product was purified by column chromatography over silica gel (10% ethylacetate in pet.ether) to give the title compound (18 g, 74%) (mixture of E/Z isomers). PMR ($CDCl_3$) Z isomer: 1.30 (t, 3H, J = 7 Hz, $OCH_2\underline{CH_3}$), 3.55 - 4.44 (m, 5H), 4.20 (q, 2H, J = 7 Hz, $O\underline{CH_2}CH_3$) 4.73, 4.89, 5.18, 5.30 (4 d, 4H, J= 6 Hz, -O $\underline{CH_2}$O-), 6.22 (dd, 1H, J_1 = 2 Hz, J_2 = 16 Hz, CH=$\underline{CH}$ COOEt), 6.93 (dd, 1H, J_1 = 4 Hz, J_2 = 16 Hz, -$\underline{CH}$=CH COOEt).

Analysis: Calculated for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60; Found: C, 54.33; H, 6.67%.

PMR ($CDCl_3$) E isomer: 1.30 (t, 3H, J = 7 Hz, $OCH_2\underline{CH_3}$), 3.62 - 4.26 (m, 4H), 4.20 (q, 2H, J = 7 Hz, $OC\underline{H_2}CH_3$), 4.73, 4.89, 5.18, 5.30 (4d, 4H, J = 6 Hz, $-OC\underline{H_2}O-$), 5.28 (m, 1H, -CH- CH=CHCOOEt), 5.96 (dd, 1H, J_1 = 2 Hz, J_2 = 12 Hz, -CH=CH COOEt), 6.42 (dd, 1H, J_1 = 6 Hz, J_2 = 12 Hz, -CH=CH COOEt).

Analysis: Calculated for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 53.96; H, 6.71%.

Ethyl (4R, 5S, 6R)-2-carbethoxy-3-carbethoxymethyl-4,6:5,7-di-O-methylene heptanoate (10)

To the solution of diethylmalonate (17.6 g, 0.11 moles) in dry dimethoxyethane (25 ml) was added sodium (2.8 g 0.12 moles) in small pieces. Reaction mixture was refluxed. After 2 h the reaction mixture was cooled to room temperature and compound **9** (24.4 g, 0.1 moles) in dry dimethoxyethane (25 ml) was added. After 24 h, the reaction mixture was diluted with water and extracted with chloroform. Chloroform layer was washed with water, dried over anhydrous sodium sulfate and evaporated to give the title compound **10** (22.2 g, 55%). PMR ($CDCl_3$): 1.24, 1.26 (2t, 9H, J = 7 Hz, 3 X $OCH_2\underline{CH_3}$), 2.44 - 4.33 (m, 15H), 4.71 - 5.15 (m, 4H, 2X $OC\underline{H_2}O$).

Analysis: Calculated for $C_{18}H_{28}O_{10}$: C, 53.46; H, 6.98. Found: C, 53.71; H, 6.92%.

Ethyl (4R, 5S, 6R) 3-carbethoxymethyl-4,6:5,7-di-O-methylene heptanoate (11)

A mixture of compound **10** (4.04 g, 0.01 mole), sodium chloride (1.16 g, 0.02 mole), water (0.18 ml, 0.01 mole) and DMSO (15 ml) was heated at 140-50°C. After 8 h, the reaction mixture was diluted with water and extracted with methylene chloride (3 x 100 ml). Combined

methylene chloride layer was washed with water (8 x 100 ml), dried over anhydrous sodium sulfate and evaporated. The crude product was purified by column chromatography over silica gel (10% ethyl acetate in pet.ether) (yield 1.1 g, 33%). PMR ($CDCl_3$): 1.24, 1.26 (2t, 6H, J = 7 Hz, 2X $OCH_2\underline{CH_3}$), 2.30 - 3.00 (m, 5H, $\underline{CH}(\underline{CH_2}COOEt)_2$), 3.46 - 4.08 (m, 5H), 4.11 (q, 4H, J = 7 Hz, 2X $OCH_2\underline{CH_3}$), 4.71, 4.75, 5.16, 5.22 (4d, 4H, J = 6 Hz, 2X $-OCH_2O-$).

Analysis: Calculated for $C_{15}H_{24}O_8$: C, 54.21; H, 7.28. Found: C, 53.97; H, 7.17%.

(4R, 5S, 6R)-3-carbamidomethyl-4,6:5,7-di-O-methylene heptamide (12)

To the solution of compound **11** (500 mg) in methanol (1 ml), 25% aqueous ammonia solution (1 ml) was added. The reaction mixture was kept at room temperature. After 7 days, methanol and water were evaporated under reduced pressure. The crude product was purified by column chromatography over silica gel (20% acetone in chloroform) to get the title compound **12** (40 mg, 10%) m.p. 255°C. Mass: 274 (M^+). PMR ($CDCl_3$): 2.06 - 2.6 (m, 5H, $\underline{CH}$ $(\underline{CH_2}CONH_2)_2$) 3.24 - 4.0 (m, 6H), 4.6, 4.68, 4.96, 5.04 (4d, 4H, J = 6 Hz, $-OCH_2O-$), 6.73 (bd, 2H, J = 6 Hz, $-NH_2$ exchangeable with D_2O), 7.28 (bd, 2H, J = 5 Hz, $-NH_2$ exchangeable with D_2O).

Analysis: Calculated for $C_{11}H_{18}N_2O_6$: C, 48.17; H, 6.62; N, 10.21. Found: C, 48.01; H, 6.53; N, 10.39%.

4-[(1R,2S,3R) 1,3:2,4-di-O-methylenebutanyl]-glutarimide (13)

The diamide **(12)** (40 mg) was taken in a round bottom flask and heated at 250°C under 5 mm vacuum. After 0.5 h, the flask was

cooled and the crude product was purified by column chromatography over silica gel (10% methanol in chloroform) to get the desired cyclic amide (**13**) (4 mg, 10%) m.p. 248-49°C. Mass: 257 (M^+).

Analysis: Calculated for $C_{11}H_{15}NO_6$: C, 51.36; H, 5.88; N, 5.45. Found:C, 51.31; H, 5.82; N, 5.61%.

EXPERIMENTAL

1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (15)

To the vigorously stirred mixture of anhydrous powdered D-glucose (200 g) in acetone (4 lit.) at 0°C was added sulfuric acid (96%, 160 ml) in 20 portions at 10-15 min. intervals while maintaining the temperature at 5-10°C. After the addition of sulfuric acid the temperature was allowed to rise to room temperature and stirring was continued for 5 h. The solution was cooled again to 0°C and 50% sodium hydroxide solution (245 g of sodium hydroxide in 300 ml water) was added with stirring to near neutrality. A small amount of solid sodium-bicarbonate was added to maintain the solution near neutrality. After standing overnight, the salts were removed by filtration and the acetone solution was concentrated under reduced pressure to a thick syrup. The mixture was dissolved in chloroform and the chloroform solution was washed with water, dried over anhydrous sodium sulfate and concentrated to a small volume. The di-O-isopropylidene-α-D-glucofuranose was crystallised from the solution by the addition of pet.ether (121 g, 42%) m.p.[5] 110°C.

3-O-benzyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (16).

In a two necked flask under nitrogen atmosphere, 50% sodium hydride (5.3 g, 0.11 mole) was placed. It was washed two times with dry hexane, dried under vacuum and dry THF (25 ml) was added. To this suspension under stirring, a solution of diacetonoid glucose **(15)** (26 g, 0.1 mole) in dry THF (100 ml) was slowly added. The reaction mixture was stirred at room temperature. After 1 h, benzyl bromide (13 ml, 0.11 mole) and tetrabutylammoniumiodide (100 mg) were added. After

10 h reaction mixture was diluted with water and extracted with methylene chloride. Organic layer was washed with water, dried over anhydrous sodium sulfate and evaporated to give compound **16** (33 g, 94%).PMR($CDCl_3$) δ 1.25 (s, 3H, C-C<u>H</u>$_3$), 1.31 (s, 3H, C-C<u>H</u>$_3$), 1.38 (s, 3H, C-C<u>H</u>$_3$), 1.44 (s, 3H, C-C<u>H</u>$_3$), 3.94 - 4.50 (m, 5H, H-2, H-3, H-4, H-5, H-6), 4.63 (s, 2H, OC<u>H</u>$_2$Ph), 5.81 (d, 1H, J=3.15 Hz, H-1), 7.25 (s, 5H, aromatic).

Analysis: Calculated for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48. Found: C, 65.30; H, 7.38%.

3-<u>O</u>-benzyl-1,2-<u>O</u>-isopropylidene-α-<u>D</u>-glucofuranose (17)

The solution of compound **16** (30 g) in 60% aqueous acetic acid (120 ml) was stirred at 35°C. After 7 h, the hydrolysate was concentrated under reduced pressure to a syrup. This syrup was dissolved in chloroform, washed subsequently with dilute sodiumbicarbonate solution, water, dried over anhydrous sodium sulfate and evaporated to give a syrupy compound **17** (25 g, 95%) $[\alpha]^6_D$ -48.4 ($CHCl_3$). PMR ($CDCl_3$):δ 1.25 (s, 3H, C-C<u>H</u>$_3$),1.44 (s, 3H, C-C<u>H</u>$_3$), 3.06 (bs, 2H, OH exchangeable with D_2O), 3.56 - 4.69(m, 6H), 5.81 (d, 1H, J = 3.15 Hz, H-1), 7.25 (s, 5H, aromatic).

Analysis: Calculated for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 61.78; H, 7.18%.

3-<u>O</u>-benzyl-1,2-<u>O</u>-isopropylidene- α -<u>D</u>-xylopentodialdo-1,4-furanose (18)

To the solution of compound **17** (31 g, 0.1 mole) in 60% aqueous acetonitrile (100 ml) at 0°C, sodium periodate(23.5 g, 0.11 mole) was slowly added. After 3 h, it was diluted with water and extracted with methylene chloride. Organic layer was washed with water, dried over anhydrous sodium sulfate and evaporated to give the desired aldehyde **(18)**[6] (25.5 g, 92%). PMR ($CDCl_3$):1.33,1.44(2s, 6H, C-C<u>H</u>$_3$), 4.25 - 4.69 (m, 5H, H-2, H-3, H-4, O-C<u>H</u>$_2$Ph), 6.03 (d, 1H, J = 3.15 Hz, H-1), 7.25

(s, 5H, aromatic), 9.62 (d, 1H, CHCHO).

Analysis: Calculated for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.89; H, 6.43%.

6-Carbethoxy-3-O-benzyl-1,2-O-isopropylidene 5,6-di-deoxy-α-D-xylohexo-5-enofuranose (19)

To the stirred solution of aldehyde **(18)** (27.7 g, 0.1 mole) in benzene (100 ml) was added ethoxycarbonylmethylenetriphenylphosphorane (38.3 g, 0.11 mole). The reaction mixture was refluxed. After 4 h, benzene was removed. The crude product was purified by column chromatography over silica gel (20% ethylacetate in pet.ether) to yield the compound **19** (E/Z isomers 3:2) (30 g, 86.2%) as yellow oil. PMR ($CDCl_3$): (Z isomer): δ 1.22 (t,3H, J=6.3 Hz, $-OCH_2CH_3$), 1.25 (s, 3H, $C-CH_3$), 1.44 (s, 3H, $C-CH_3$), 3.94 (d, 1H, J=3.15 Hz, H-2), 4.19 (q, 2H, J=6.3 Hz, OCH_2CH_3), 4.49 (dd, 2H, J_1=12.6 Hz, J_2=15.75 Hz, OCH_2Ph), 4.57 (d,1H, J=3.15 Hz, H-3), 4.75 (m, 1H, H-4), 5.93(d, 1H,J=3.15 Hz, H-1), 6.09 (dd, 1H, J = 15.75 Hz, CH=CHCOOEt), 6.93 (dd, 1H, J_1=15.75 Hz J_2 = 6.3 Hz, CH=CH COOEt), 7.25 (s, 5H, aromatic).

Analysis: Calculated for $C_{19}H_{24}O_6$:C, 65.50; H, 6.94. Found: C, 65.43; H, 6.90%.

PMR ($CDCl_3$): (E isomer): δ 1.22 (t, 3H, J = 6.3 Hz, $-OCH_2CH_3$), 1.26 (s,3H, $C-CH_3$), 1.50 (s, 3H,$C-CH_3$), 4.09(q, 2H, J = 6.3 Hz, $-OCH_2CH_3$), 4.25 (d, 1H, J = 3.15 Hz,H-2), 4.49 (dd, 2H, J_1 = 12.6 Hz, J_2 = 15.75Hz, OCH_2Ph), 4.57 (d, 1H, J = 3.15 Hz, H-3),5.56 (m, 1H, H-4), 5.86 (dd, 1H,J_1= 12.6 Hz, -CH=CH COOEt), 5.94 (d, 1H, J = 3.15 Hz, H-1), 6.34 (dd, 1H, J_1 = 12.6 Hz, J_2 = 6.3 Hz, -CH=CH COOEt), 7.18 (s, 5H, aromatic).

Analysis: Calculated for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.58; H, 6.87%.

(5 RS)-6,6-dicarbethoxy-5-ethoxycarbonylmethylene-3-O-benzyl-1,2-O-isopropylidene-5,6-di-deoxy-α-D-xylohexofuranose (20)

To the stirred solution of diethylmalonate (15.2 g, 0.098 mole) in dry dimethoxyethane (100ml) was added sodium (2.25 g, 0.098 mole). The reaction mixture was refluxed till all sodium dissolved. Then it was cooled to room temperature and compound **19** (30 g, 0.086 mole) in dry dimethoxyethane (50 ml) was added dropwise. The reaction mixture was then stirred at 40°C. After 10 h, it was diluted with water and immediately extracted with chloroform. Chloroform layer was washed with water, dried over anhydrous sodium sulfate and evaporated to give the triester (**20**) as viscous oil (40g, 91.3%). PMR ($CDCl_3$): δ 1.0 (t, 9H, J = 6.3 Hz, O-$CH_2\underline{CH_3}$),1.06 (s, 3H, -C-$\underline{CH_3}$), 1.19(s, 3H, C-$\underline{CH_3}$), 2.31 (m, 2H, -CH-$\underline{CH_2}$COOEt), 2.94 (m, 1H, $\underline{CH}CH_2$COOEt), 3.56 - 4.4 (m, 11H,H-2, H-3, H-4,4X-O$\underline{CH_2}$-), 5.56 (d, 1H, J = 3.15 Hz, H-1), 7.06 (s, 5H,aromatic).

Analysis: Calculated for $C_{26}H_{36}O_{10}$: C, 61.40; H, 7.14. Found: C, 61.35; H, 7.11%.

6-Carbethoxy-5-ethoxycarbonylmethylene-3-O-benzyl-1,2-isopropylidene-5,6-di-deoxy-α-D-xylohexofuranose (21)

A mixture of triester (**20**) (40 g, 0.079 mole), sodium chloride (9.26 g, 0.16 mole), water (2.9 ml, 0.16 mole) in DMSO (160 ml) was heated at 140-50°C for 15 h. Then the reaction mixture was diluted with water and extracted with chloroform (2 x 250 ml). The combined organic layer was washed withwater(8 x 200 ml), dried over anhydrous sodium sulfate and evaporated to yield the diester (**21**) (27 g, 78.6%) as a pale yellow oil.

PMR ($CDCl_3$): δ 1.10 (t, 6H, J = 6.3 Hz, $OCH_2\underline{CH_3}$), 1.22 (s, 3H, C-CH_3), 1.46 (s, 3H, C-CH_3),2.25 (d, 2H, J= 6.3 Hz, -$\underline{CH_2}$COOEt), 2.63 (d, 2H, J= 3.15 Hz, $\underline{CH_2}$COOEt), 2.63 (m, 1H, $\underline{CH}(CH_2COOEt)_2$), 3.87 (d,1H, J = 3.15 Hz, H-2), 4.06 (q, 4H, J = 6.3 Hz, O-$\underline{CH_2}CH_3$), 4.19 (m, 1H, H-4), 4.5 (dd, 2H, J_1 = 12.6 Hz, J_2 = 22.05 Hz, OCH_2Ph), 4.56 (d, 1H, J = 3.15 Hz, H-3), 5.87 (d, 1H, J = 3.15 Hz, H-1), 7.25 (s, 5H, aromatic).

Analysis: Calculated for $C_{23}H_{32}O_8$: C, 63.28; H, 7.39. Found: C, 63.40; H, 7.31%.

Ethyl (4R,5S,6R)-5-benzyloxy-3-carbethoxymethyl 7,7-diethylmercapto-4,5-dihydroxyheptanoate (22)

To the stirred solution of compound **21** (4.36 g, 0.01 mole) and ethylmercaptan (3.25 ml, 0.044 mole) in methylenechloride at 0°C was added zinc chloride (25 mg). After 8 h, solid sodiumbicarbonate was added, reaction mixture was filtered and concentrated to give the crude product which was purified by column chromatography over silica gel (30% ethylacetate in pet.ether) to give **22** (3.8 g, 75%). PMR ($CDCl_3$): δ 1.25 (t, 12H, 4 X $CH_2\underline{CH_3}$), 1.56 (s, 2H, OH, exchangeable with D_2O), 2-3 (m, 9H), 4.13 (q, 4H, J = 6.3 Hz, $O\underline{CH_2}CH_3$), 3.94 - 4.06 (m, 3H, 2 X $\underline{CH}$OH, $\underline{CH}$-SEt), 4.44 (t, 1H, J = 4.73 Hz, $\underline{CH}OCH_2$Ph), 4.81 (s, 2H, -$O\underline{CH_2}$Ph), 7.31 (s, 5H, aromatic).

Analysis: Calculated for $C_{24}H_{28}S_2O_7$: C,57.37; H, 7.57; S,12.75. Found: C, 57.71; H, 7.44; S, 12.83%.

N-benzyl-4-[(1R,2S,3R,4R)-2-benzyloxy-3,4-O-isopropylidene-1,4-furanosyl]-glutarimide (23)

A mixture of diester (**21**) (4.36 g, 0.01 mole), benzylamine

(1.17g, 0.011 mole) and DMF (10 ml) were heated in a sealed tube at 180°C for 4 days. Then DMF and excess of benzylamine was removed under reduced pressure. The crude product was purified by column chromatography over silica gel (20% ethylacetate in pet. ether) to yield the compound **23** (3.6 g, 77.7%) m.p. 101°C, $[\alpha]_D$ -55.0 ($CHCl_3$). PMR ($CDCl_3$): δ 1.25 (s, 3H, C-C<u>H</u>$_3$), 1.44 (s, 3H, C-C<u>H</u>$_3$), 2.44 (m, 4H, 2X CHC<u>H</u>$_2$CO), 2.94 (m, 1H, C<u>H</u>CH$_2$CO), 3.80 (m, 2H, H-2, H-4), 4.5 (dd, 2H, J_1 = 12.6 Hz, J_2 = 22.05 Hz, OC<u>H</u>$_2$Ph), 4.56 (d, 1H, J = 3.15 Hz, H-3), 4.88 (s, 2H, N-C<u>H</u>$_2$Ph), 5.81 (d, 1H, J = 3.15 Hz, H-1), 7.25 (bs, 10H, aromatic). Mass: 451 (M^+).

Analysis: Calculated for $C_{26}H_{29}NO_6$: C, 69.16; H, 6.47; N, 3.10.Found: C,69.04; H, 6.41; N,3.12%.

N-benzyl-4-[(1R,2S,3R)-2-benzyloxy-1,3-dihydroxybutanal 1,3-dithialane] glutarimide (24)

To the stirred solution of compound **23** (4.51 g, 0.01 mole) and ethanedithiol (2.0 ml, 0.024 mole) in methylene chloride at 0°C was added zinc chloride (10 mg). After 10 h, solid sodiumbicarbonate was added, reaction mixture was filtered and concentrated to give the crude product which was purified by column chromatography over silica gel (30% ethylacetate in pet.ether) to give **24** (3.9 g, 80%), $[\alpha]_D$ -10.2° ($CHCl_3$). PMR ($CDCl_3$): δ 1.56 (bs, 2H, OH, exchangeable with D_2O),2.38 -2.88 (m, 7H), 3.19 (s, 4H, -S-C<u>H</u>$_2$C<u>H</u>$_2$S-), 3.31 - 3.69 (m, 3H), 4.56 (d, 1H, J = 7.9 Hz, ), 4.69 (q, 2H, J = 11 Hz, N-C<u>H</u>$_2$Ph), 4.88 (s, 2H, OC<u>H</u>$_2$Ph), 7.31 (s, 10H, aromatic).

Analysis: Calculated for $C_{25}H_{29}NS_2O_5$: C, 61.59; H,6.00; N, 2.87; S, 13.14. Found:C, 61.82; H,5.92; N, 2.83; S, 13.02%.

N-benzyl-4-[(1R,2S ,3R)-2-benzyloxy 1,3-O-methylene butanal 1,3-dithialane]-glutarimide (25)

To the stirred solution of the diol **(24)** (2.43 g, 5 m.mole) and dimethoxymethane (0.455 g, 6 m.mole) in dry acetonitrile (5 ml) at 0°C was added p-toluene sulfonic acid (5 mg). After 2 h, solid sodiumbicarbonate was added to the reaction mixture. It was filtered and acetonitrile was removed. Purification by column chromatography over silica gel (20% ehylacetate in pet.ether) afforded the desired dioxane (25) (2.2 g, 88%) m.p. 197-98°C. $[\alpha]_D$ -38.8°($CHCl_3$). PMR ($CDCl_3$): δ 2.13 - 2.57(m, 4H), 3.15 (m, 1H),3.19 -3.25 (bs, 4H, SCH_2CH_2S), 3.30 (m,1H), 3.71 (bs, 1H), 4.55 ,-4.88 (2d, 1H, J = 11.7 Hz, NCH_2Ph), 4.62 and 5.14 (2d, 1H, J = 6.3 Hz, OCH_2O), 4.75 (d, 1H, J = 11.25 Hz, $CH\begin{matrix}S\\S\end{matrix}$) 7.18 - 7.37 (m, 10H, aromatic).

Analysis: Calculated for $C_{26}H_{29}NS_2O_5$: C, 62.51; H, 5.85; N, 2.80; S, 12.83. Found:C, 62.62; H, 5.79; N,2.86; S, 12.93%.

2,4:3,5-di-O-methylene-D-xylose 1,3-dithialane (27)

To a stirred solution of D-xylose (100 g, 0.67 mole), concentrated hydrochloric acid (100 ml) at 0°C was added dropwise ethanedithiol (67.38 g, 0.71 mole). After 7 h, at 0°C, 40% aqueous formaldehyde solution (150 ml, 2 mole) was introduced. The resulting mixture was heated at 50°C for 48 h. The solid separated was filtered, washed with water and crystallised from methanol to give **27** (116 g, 70%) m.p. 210°C, $[\alpha]_D$ +12° ($CHCl_3$). PMR ($CDCl_3$): δ 3.17 (s, 4H, $-SCH_2CH_2S-$), 3.4 (dd, 1H, J_1 = 4 Hz, J_2 = 10 Hz), 3.51 (bd, 1H), 3.82 (dd, 1H, J_1 = 2Hz, J_2 = 12 Hz), 3.91 (bd, 1H, J = 2 Hz), 4.18 (dt, 1H, J = 12 Hz), 4.73, 4.75, 5.15, 5.24 (4d, 4H, J = 6 Hz, 2X $-OCH_2O$), 4.8 (d, 1H, J = 4 Hz, $-CH-S-CH_2CH_2S$). Mass: 250 (M^+).

Analysis: Calculated for $C_9H_{14}S_2O_4$: C, 43.20; H, 5.64; S, 25.64. Found: C, 42.98; H, 5.62; S, 25.76%.

3-C-hydroxymethyl-2,4-O-methylene-D-xylose 1,3-dithialane-5-diacetate (28)

To a vigorously stirred mixture of acetic anhydride (440 ml), acetic acid (180 ml), concentrated sulfuric acid (6 ml) was slowly added the compound **27** (100 g) at room temperature. After 10 h, it was poured over crushed ice with stirring. The solid separated was filtered, washed with cold water, recrystallised from methanol to yield **28** (107 g, 76%) m.p. 124°C $[\alpha]_D$ +13.2 ($CHCl_3$). PMR ($CDCl_3$): δ 2.11 (s, 3H, $OCOCH_3$), 2.15 (s, 3H, $OCOCH_3$), 3.22 (m, 4H, $-SCH_2CH_2S-$), 3.38 (dd, 1H, J = 10 Hz, $-CHCHOCH_2COCH_3$), 3.89 (m, 3H, $CHCH_2OAc$), 4.24 (d, 2H, J = 7 Hz, $-CHCHS-$), 4.24, 4.78 (2d, 2H, J = 7 Hz, $-OCH_2O-$), 4.75 (d, 1H, J = 7 Hz, $CH\langle^{S}_{S}$), 5.42 (dd, 2H, J_1 = 6 Hz, J_2 = 8 Hz, OCH_2OAc).

Analysis: Calculated for $C_{13}H_{20}S_2O_7$: C, 44.31; H, 5.68; S, 18.18. Found: C, 44.37; H, 5.79; S, 18.06%.

2,4-O-methylene-D-xylose 1,3-dithialane (29)

To a solution of diacetate (**28**) (1.4 g, 4 m.mole) in chloroform (10 ml) at 0°C was added 0.2M sodiummethoxide in methanol (1.5 ml) It was stored at 5°C for 18 h. Then the reaction mixture was neutralised with concentrated hydrochloric acid (to pH 6). The solid was filtered and chloroform layer was dried over anhydrous sodium sulfate and concentrated to afford the diol (0.95 g, quantitative) m.p. 125°C, $[\alpha]_D$ +2.0 ($CHCl_3$). PMR ($CDCl_3$): δ 2.25 (bs, 2H, OH, exchangeable with D_2O), 3.19 (s, 4H, $-SCH_2CH_2S-$), 3.31 -3.94 (m, 5H), 4.69 (d, 1H, J = 9.45 Hz, ), 4.77, 5.10 (2d, 2H, J = 6.3 Hz, $-OCH_2O-$). Mass: 238 (M^+).

Analysis: Calculated for $C_8H_{14}S_2O_4$: C, 40.34; H, 5.92; S, 26.89. Found: C, 40.25; H, 5.87; S, 27.04%.

3,5-O-benzylidene-2,4-O-methylene-D-xylose 1,3-dithialane (30)

To a stirred solution of the diol (**29**) (2.1 g, 8.8 m.mole) and toluene-p-sulfonic acid (5 mg) in dry acetonitrile (5 ml) under nitrogen atmosphere, was added α,α-dimethoxytoluene (1.4 ml, 9.0 m.mole) at room temperature. After 24 h, the product started separating, it was cooled to 0°C and filtered and recrystallised from methanol to yield the compound **30** (2.1 g, 75%) m.p. 239°C. PMR ($CDCl_3$): δ 3.19 (s, 4H, $-SCH_2CH_2S-$), 3.44 - 4.5 (m, 5H), 4.81 (d, 1H, J = 9.45 Hz, ), 4.75, 5.25 (2d, 2H, J = 6.3 Hz, $-OCH_2O-$), 5.56 (s, 1H,  Ph), 7.19 - 7.63 (m, 5H, aromatic).

Analysis: Calculated for $C_{15}H_{18}S_2O_4$: C, 55.21; H, 5.56; S, 19.63. Found: C, 54.97; H, 5.51; S, 19.58%.

3-O-benzyl-2,4-O-methylene-D-xylose 1,3-dithialane (31)

To a suspension of aluminium chloride (3 g, 0.026 mole) in dry ether (30 ml) at 0°C was added slowly LAH (250 mg, 0.0065 mole). After 0.5 h, the compound **30** (4.35 g, 0.013 mole) in dry methylene chloride (30 ml) was introduced. The reaction mixture was refluxed for 24 h when TLC indicated completion of reaction. The reaction was cooled to 0°C and then slowly decomposed with 20% aqueous sodium hydroxide solution. Aqueous layer was extracted repeatedly with ether. Ether layer was dried over anhydrous sodium sulfate and concentrated to give the product which was recrystallised from benzene to afford **31** (3.2 g, 73%) m.p. 141°C. PMR ($CDCl_3$): δ 1.68 (bs, 1H, -OH, exchangeable with D_2O), 3.22 (s, 4H, -SC<u>H</u>$_2$C<u>H</u>$_2$S-), 3.44 (dd, 1H, J_1 = 10 Hz, -OC<u>H</u>CHS-), 3.58 - 3.95 (m, 4H), 4.71 (dd, 2H, J_1 = 12 Hz, J_2 = 18 Hz, -OC<u>H</u>$_2$Ph), 4.82 (d, 1H, J = 10 Hz, ), 4.78, 5.22 (2d, 2H, J = 6 Hz, -OC<u>H</u>$_2$O-), 7.44 (m, 5H, aromatic).

Analysis: Calculated for $C_{15}H_{20}S_2O_4$: C, 54.87; H, 6.14; S, 19.51. Found: C, 54.53; H, 6.13; S, 19.32%.

3,5-di-O-benzyl-2,4-O-methylene-D-xylose 1,3-dithialane (32)

In a two-necked flask under nitrogen atmosphere, 50% sodium hydride (1.15 g, 0.024 mole) was placed. It was washed two times with dry hexane, dried under vacuum and dry THF (5 ml) was added. Then to this suspension under stirring, solution of diol (**29**) (2.38 g, 0.01 mole) in dry THF (15 ml) was slowly added. The reaction mixture was stirred at room temperature. After 1 h, benzyl bromide (3.8 ml, 0.022 mole)

was added slowly. After 10 h, the reaction mixture was diluted with water and extracted with chloroform. Organic layer was washed with water, dried over anhydrous sodium sulfate and evaporated to give dibenzyl derivative **(32)** (4 g, 96%) m.p. 81°C $[\alpha]_D$ -1.52° ($CHCl_3$). PMR ($CDCl_3$): δ 3.13 (s, 4H, -SCH_2CH_2S-),3.25 - 3.81 (m, 5H), 4.44 (s, 2H, OCH_2Ph), 4.56 (d, 2H, OCH_2Ph), 4.69 (d, 1H, J = 9.45 Hz, ), 4.7, 5.13 (2d, 2H, J = 6.3 Hz, -OCH_2O-), 7.3 (s, 10H, aromatic).

Analysis: Calculated for $C_{22}H_{26}S_2O_4$: C, 63.15; H, 6.26; S, 15.31. Found:C, 63.07; H, 6.20; S, 15.34%.

3,5-di-O-benzyl-2,4-O-methylene-D-xylose dimethyl acetal (33)

To a solution of dithiane **(32)** (4.18 g, 0.01 mole) in methylene chloride (100 ml) was dropwise added a solution of mercuric perchlorate (18.12 g, 0.04 mole) in dry methanol (50 ml). After 12 h, at 25°C, white fine precipitate was filtered off and the filtrate was immediately poured into ice water, then extracted with methylenechloride. Organic layer was washed with 1N aqueous KI solution, water, brine, dried over anhydrous sodium sulfate and evaporated to give the desired compound **33** (3.4 g, 87%) as yellow syrup. PMR ($CDCl_3$): δ 3.25 (s, 3H,OCH_3), 3.44 (s, 3H, OCH_3), 3.44 - 4.0 (m, 5H), 4.44 (bs, 2H, OCH_2Ph), 4.56 (bs, 2H, OCH_2Ph), 4.56 (d, 1H, J = 7.8 Hz, $CH(OMe)_2$), 4.75, 5.13 (2d, 2H, J = 6.3 Hz, -OCH_2O-), 7.25 (s, 10H, aromatic).

Analysis: Calculated for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27. Found: C, 68.17; H, 7.20%.

3,5-di-O-benzyl-2,4-O-methylene-D-xylose (34)

To a solution of dithiane **(32)** (4.18 g, 0.01 mole) in chloroform (100 ml) was dropwise added a solution of mercuric perchlorate (18.12 g,

0.04 mole) in dry THF (50 ml). After 24h, at 25°C, white fine precipitate was filtered off and the filtrate was immediately poured into ice water, then extracted with chloroform. Chloroform layer was washed with 1N aqueous KI solution, water, brine, dried over anhydrous sodium sulfate and evaporated to give the aldehyde (**34**) (2.9 g, 88.4%) as yellow syrup.

5-O-benzyl-2,4-O-methylene-D-xylose 1,3-dithialane (35)

In a two-necked flask under nitrogen atmosphere, 50% sodium hydride (575 mg, 0.012 mole) was placed. It was washed two times with dry hexane, dried under vacuum and dry THF (5 ml) was added. Then to this suspension under stirring, solution of the diol (**29**) (2.38g, 0.01 mole) in dry THF (15 ml) was slowly added. The reaction mixture was stirred at room temperature. After 1 h, benzylbromide (1.9 ml, 0.011 mole) was added slowly. After 10 h, reaction mixture was diluted with water and extracted with chloroform. Chloroform layer was washed with water, brine, dried over anhydrous sodium sulfate and evaporated to give monobenzyl derivative (**35**) (2.3 g, 71%), m.p. 101-2°C $[\alpha]_D$ -2.22 ($CHCl_3$). PMR ($CDCl_3$): δ 2.13 (bs, 1H, OH, exchangeable with D_2O), 3.13 (s, 4H, $-SCH_2CH_2S-$), 3.25 - 3.88 (m, 5H), 4.5 (s, 2H, OCH_2Ph), 4.6 (d, 1H, J = 9.45 Hz, ), 4.69, 5.07 (2d, 2H, J = 6.3 Hz, OCH_2O), 7.25 (s, 5H, aromatic).

Analysis: Calculated for $C_{15}H_{20}S_2O_4$: C, 54.87; H, 6.14; S, 19.51. Found: C, 54.95; H, 6.01; S, 19.75%.

5-O-benzyl-3-O-(3,4-dimethoxybenzyl)-2,4-O-methylene-D-xylose-1,3-dithialane (36)

In a two-necked flask under nitrogen atmosphere, 50% sodium

hydride (0.5 g, 0.011 mole) was placed. It was washed with dry hexane, dried under vacuum and dry THF (2 ml) was added. Then to this suspension under stirring solution of compound **35** (3.28 g, 0.01 mole) in THF (3 ml) was slowly added. The reaction mixture was stirred at room temperature. After 1 h, dimethoxybenzylbromide (2.54 g, 0.011mole) in THF (2 ml) was added slowly. After 10 h, the reaction mixture was diluted with water and extracted with chloroform. Chloroform layer was washed with water, dried over anhydrous sodium sulfate and evaporated to give compound **36** which was crystallised from methanol (3.9 g, 82%), m.p. 115°C $[\alpha]_D$ -9.84 ($CHCl_3$). PMR ($CDCl_3$): δ 3.15 (s, 4H, -SCH_2CH_2S-), 3.23 - 3.68 (m, 5H), 3.83 (s, 6H, 2X OCH_3), 4.5 (q, 2H, J = 11.3 Hz,OCH_2DMB), 4.55 (s, 2H, OCH_2Ph), 4.65 (d, 1H, J = 11.3 Hz, ), 4.73, 5.10 (2d, 2H, J = 7.66 Hz, OCH_2O-), 6.68 - 6.83 (m, 3H, aromatic), 7.25 (s, 5H, aromatic).

Analysis: Calculated for $C_{24}H_{30}S_2O_6$: C, 60.24; H, 6.32; S, 13.39. Found: C, 60.11; H, 6.37; S, 13.30%.

Ethyl (4R, 5S, 6R) 5,7-dibenzyloxy 4,6-O-methylenehept-2-enoate (37)

To the stirred solution of aldehyde (**34**) (3.42 g, 0.01 mole) in benzene (15 ml) was added carbethoxymethylenetriphenylphosphorane (3.82 g, 0.011 mole). The reaction mixture was refluxed. After 3 h, benzene was removed. The crude product was purified by column chromatography over silica gel (20% ethylacetate in pet.ether) afforded the E and Z isomer of the title compound **37** (3.5 g, 84%) (E/Z isomers 7:3).

PMR ($CDCl_3$): (Z isomer): δ 1.29 (t, 3H, J = 7 Hz, OCH_2CH_3), 3.28 -

4.71 (m, 9H), 4.22 (q, 2H, J = 7 Hz, -OC<u>H</u>$_2$CH$_3$), 4.76, 5.11 (2d, 2H, J = 6 Hz, -OC<u>H</u>$_2$O-), 6.15 (dd, 1H, J_1 = 16 Hz, J_2 = 2 Hz, CH=C<u>H</u> COOEt), 6.89 (dd, 1H, J_1 = 4 Hz, J_2 = 16 Hz, C<u>H</u>=CHCOOEt), 7.26 (s, 5H, aromatic) 7.3 (s, 5H, aromatic).

Analysis: Calculated for $C_{24}H_{28}O_6$: C, 69.88; H, 6.84. Found: C, 69.71; H, 6.89%.

PMR ($CDCl_3$): (E isomer): δ 1.22 (t, 3H, J = 7 Hz, -OCH$_2$C<u>H</u>$_3$), 3.26 - 3.95 (m, 4H), 4.09 (q, 2H, J = 7 Hz, OC<u>H</u>$_2$CH$_3$), 4.42 (s, 4H, 2X OC<u>H</u>$_2$Ph 4.82, 5.22 (2d, 2H, J = 6 Hz, OC<u>H</u>$_2$O). 5.15 (m, 1H, C<u>H</u>-CH=CH COOEt), 5.64 (dd, 1H, J_1 = 12 Hz, J_2 = 2 Hz, CH=C<u>H</u> COOEt), 6.24 (dd, 1H, J_1 = 6 Hz, J_2 = 12 Hz, C<u>H</u>=CH COOEt), 7.26, 7.3 (2s, 10H, aromatic).

Analysis:Calculated for $C_{24}H_{28}O_6$: C, 69.88; H, 6.84. Found: C, 69.62; H, 6.79%.

Ethyl (4R,5S,6R)-2-carbethoxy-3-carbethoxymethyl 5,7-dibenzyloxy-4,6-O-methylene heptanoate (38)

To the stirred solution of diethylmalonate (1.7 g, 0.012 mole) in dry dimethoxyethane (20 ml) was added sodium (260 mg, 0.012 mole). The reaction mixture was refluxed till sodium dissolved. Then it was cooled to room temperature and compound **37** (4.12 g, 0.01 mole) in dry dimethoxyethane (10 ml) was added dropwise. Reaction mixture was then stirred at 40°C. After 15 h, it was diluted with 1% aqueous hydrochloric acid and immediately extracted with chloroform. Chloroform layer was washed with water, brine, dried over anhydrous sodium sulfate and evaporated to give the triester **38** as yellow oil (4.5 g, 79%).

PMR ($CDCl_3$): δ 1.07 - 1.38 (3t, 9H, 3X OCH$_2$C<u>H</u>$_3$), 2.06 - 2.38 (m, 2H), 2.5 (t, 1H, C<u>H</u>-CH$_2$COOEt), 3.05 - 4.31 (m, 12H), 4.5 (s, 2H, OC<u>H</u>$_2$Ph), 4.63 (s, 2H, OC<u>H</u>$_2$Ph), 4.80, 5.06 (2d, 2H, OC<u>H</u>$_2$O), 7.25 (s, 10H, aromatic).

Analysis: Calculated for $C_{31}H_{40}O_{10}$: C, 65.02; H, 7.04.

Found: C, 65.11; H, 6.93%.

Ethyl (4R,5S,6R)-3-carbethoxymethyl-5,7-dibenzyloxy-4,6-O-methylene heptanoate (39)

A mixture of triester **(38)** (4.5 g, 7.9 m.mole), sodium chloride (0.928 g, 16 m.mole) water (0.29 ml,16 m.mole) and DMSO (20 ml) was heated at 160°C for 3 h. Then the reaction mixture was diluted with water and extracted with methylene chloride (2 X 100 ml). Combined methylene chloride layer was washed with water (8 x 100 ml), brine, dried over anhydrous sodium sulfate and evaporated to yield diester **(39)** (3.5 g, 87%) as yellow oil $[\alpha]_D$ -8.4° ($CHCl_3$). PMR ($CDCl_3$): δ 1.19,1.20 (2t, 6H, $OCH_2\underline{CH_3}$), 2.19 - 2.81 (m, 5H, $\underline{CH}\underline{CH_2}COOEt$), 3.44 -4.25 (m, 9H), 4.5 (s, 2H, OCH_2Ph), 4.6 (s, 2H, OCH_2Ph), 4.63, 5.06 (2d, 2H, J = 6.3 Hz, OCH_2O), 7.2 - 7.38 (m, 10H, aromatic).

Analysis: Calculated for $C_{28}H_{36}O_8$: C, 67.18; H, 7.25. Found: C, 67.11; H, 7.22%.

N-benzyl-4-[(1R,2S,3R)-2',4'-dibenzyloxy-1',3'-O-methylenebutanyl]-glutarimide (40)

A solution of diester **(39)** (1 g,2 m.mole), benzylamine (234mg, 2.2 m.mole) and DMF (2 ml) was heated in the sealed tube at 170°C for 5 days. Then the DMF and excess of benzylamine was removed under reduced pressure. The crude product was purified by column chromatography over silica gel (20% ethylacetate in pet.ether) to yield the glutarimide **(40)** (900 mg, 87.3%) $[\alpha]_D$ +34.9 ($CHCl_3$). PMR ($CDCl_3$): δ2.80, 2.95 (2d,4H,J = 5.5 Hz, $CHCH_2CO$), 3.06-3.19 (m, 1H, $\underline{CH}CH_2CO$), 3.38 - 3.81 (m, 5H), 4.56 (s, 2H, NCH_2Ph), 4.63, 5.10 (2d, 2H, J = 6.3 Hz, OCH_2O), 4.88 (s, 2H, OCH_2Ph), 4.44,4.80 (2d, J = 11.1 Hz, OCH_2Ph),

7.15 - 7.4 (m, 15H, aromatic).

Analysis: Calculated for $C_{31}H_{33}NO_6$: C, 72.21; H, 6.45; N,2.72. Found:C, 72.16; H, 6.41; N,2.72%.

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CHAPTER III

SYNTHESIS OF C-RING OF SESBANIMIDE

INTRODUCTION

In sesbanimide, all the three rings are joined by single bonds. Ring C, systematically named as 2'-hydroxy-3'-methyl-4'-methylene tetrahydrofuran is coupled to AB ring system at C-10. Spectral studies have indicated that ring C exist in equilibrium with open and closed forms and the ratio of these forms is solvent dependent. The C-ring of sesbanimide is a unique character because such type of systems have not been encountered in any natural products so far. It is noteworthy to point out that this ring C of sesbanimide is extremely vulnerable to dehydration and rearrangement to form the corresponding 3,4-dimethylfuran derivative in presence of traces of acidic or basic impurities Therefore there is no doubt that the synthesis of ring C of sesbanimide is a challenging task and no methodology has been reported so far to construct such type of ring.

In the retrosynthetic analysis of sesbanimide (page) the bond disconnection for ring C has been carried out between C-10 and C-11 which resulted in the formation of two segments X and Y. The synthesis of segment X (AB ring synthon) has already been carried out in both the enantiomeric forms starting from carbohydrate precursors. This has been discussed in Chapter II. Therefore this chapter deals with the construction of ring C at the carbon atom C-10 of AB ring synthon.

The most logical method to build ring C would involve the condensation of organometallic reagent (Segment Y) with the aldehyde

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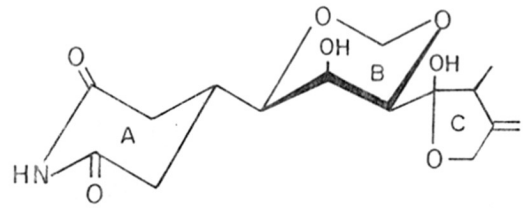

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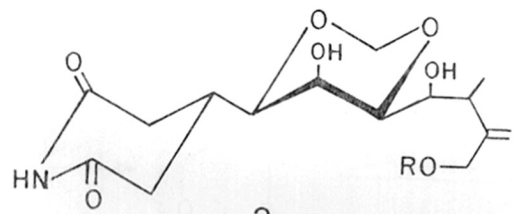

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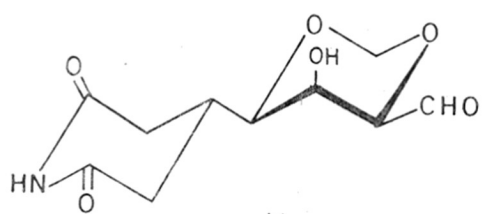
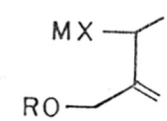
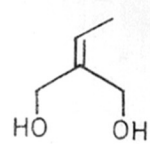


X

+



Y



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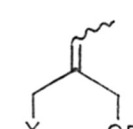

3

X = Cl or Br

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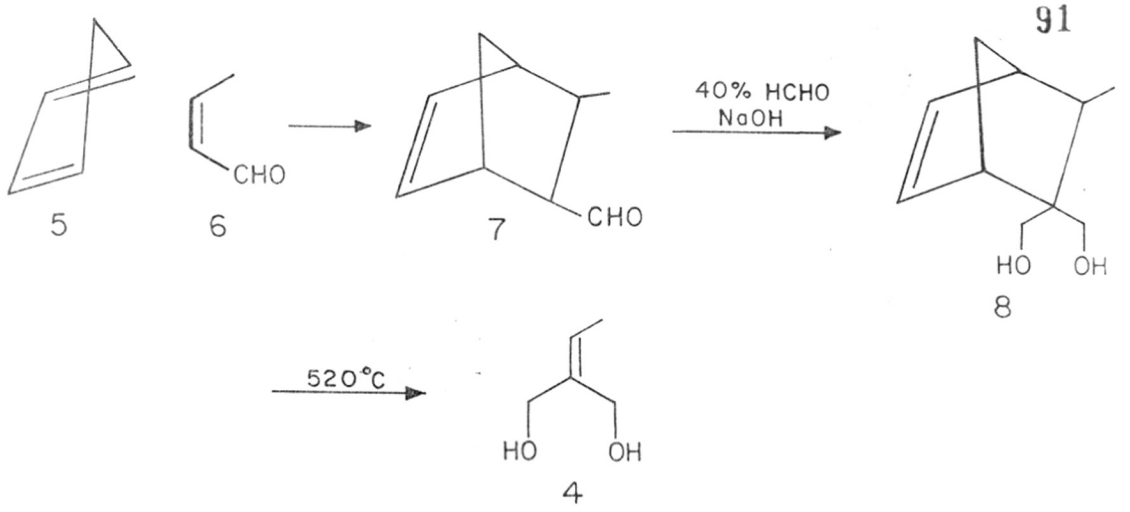

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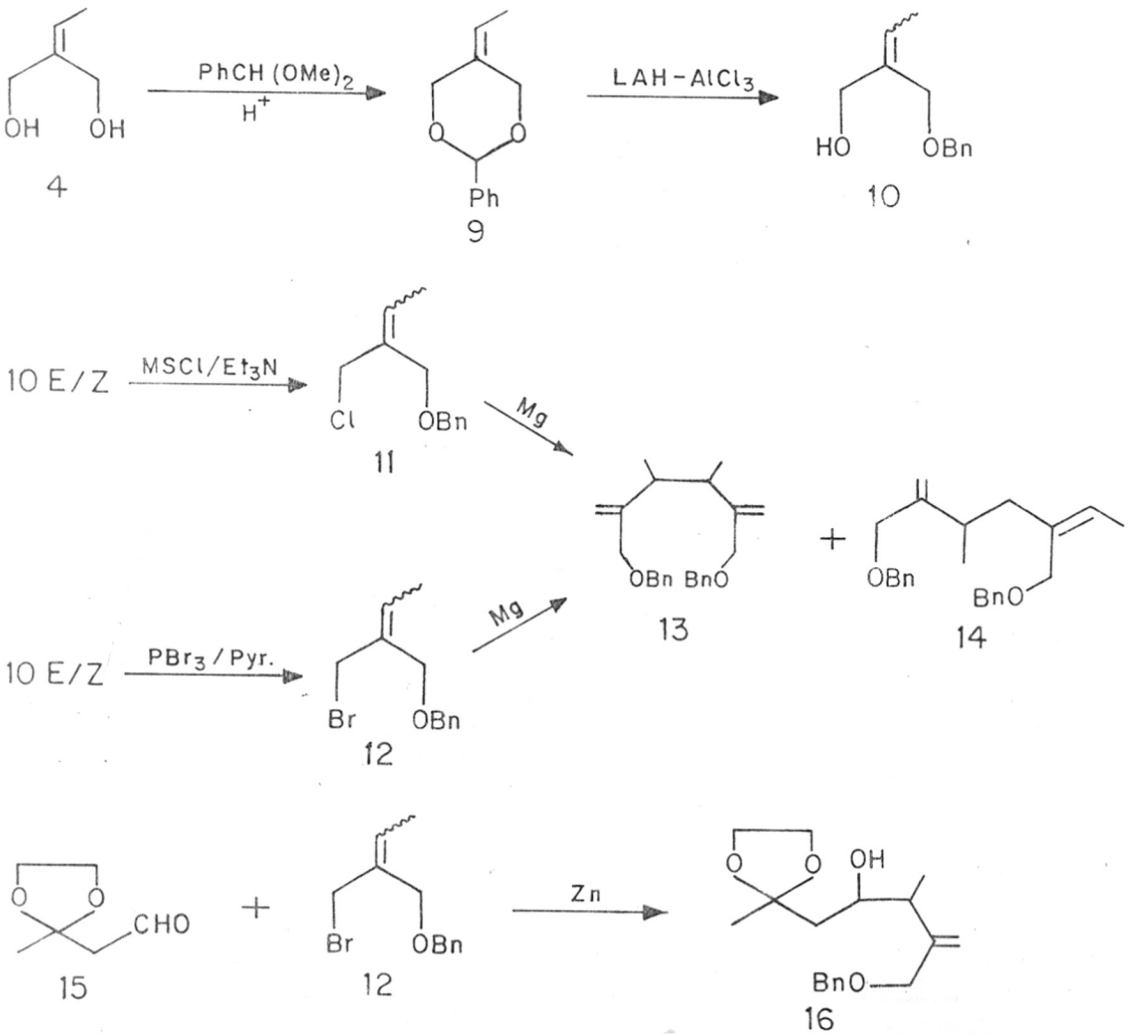


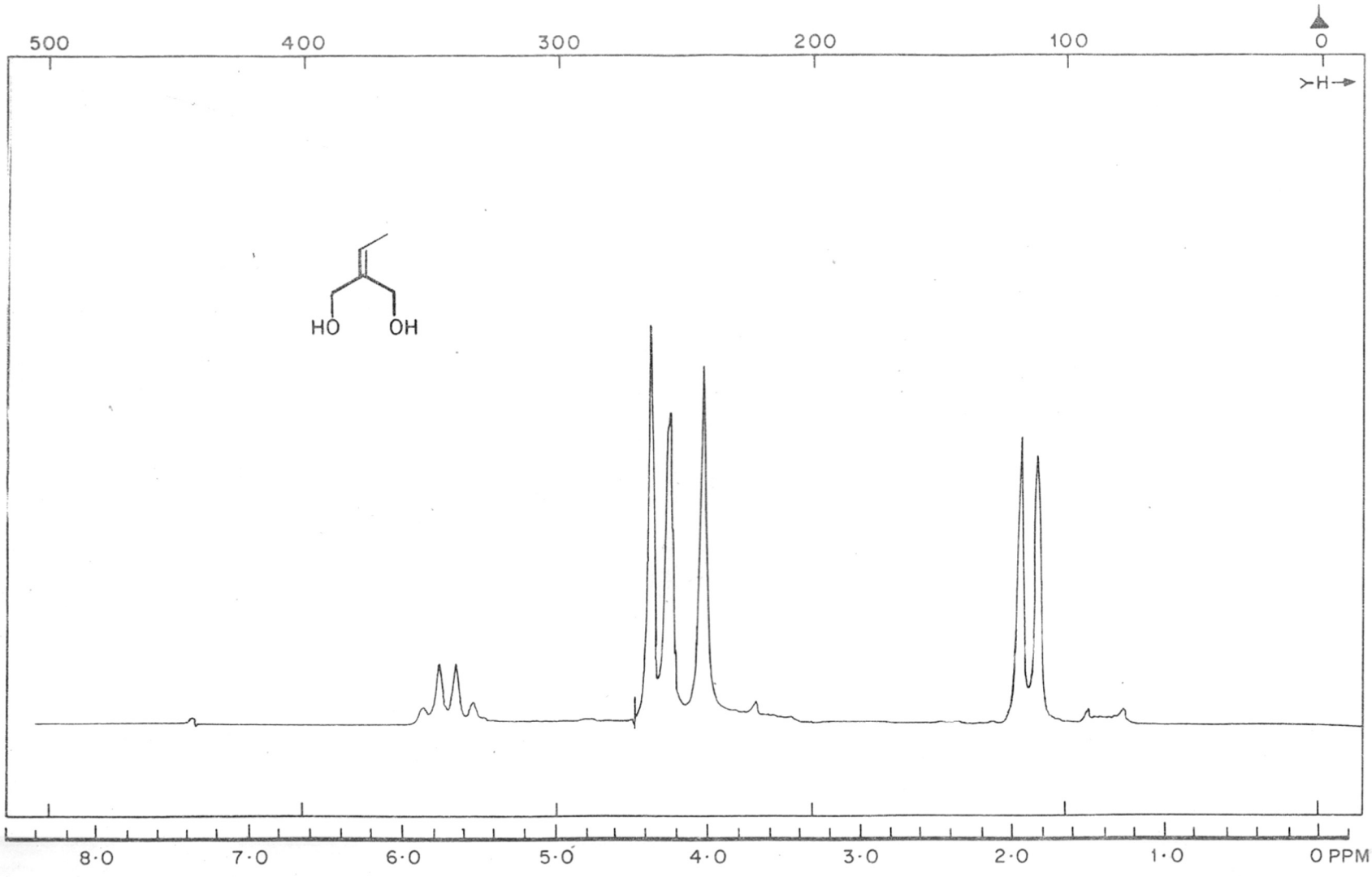


FIG. 1 : PMR SPECTRUM OF COMPOUND (4) IN $CDCl_3$

(segment X) followed by subsequent reactions. The organometallic reagent (segment Y) could be realised from the halide derivative (**3**), the latter derivative in turn may be obtained from the corresponding diol intermediate (**4**). Thus the diol (**4**) was prepared by a modified synthetic route (Scheme 1) in which the crotonaldehyde and cyclopentadiene were allowed to undergo Diels-Alder reaction[1] at 100°C to afford the adduct (**7**) in 52% yield. When the aldehyde (**7**) was treated with 40% formaldehyde solution and sodium hydroxide, two reactions occurred simultaniously. In the first instance hydroxymethylation of **7** on carbon atom alpha to aldehyde gave the product which subsequently underwent cross Canizzaro reaction with formaldehyde to afford 2,2-bis (hydroxymethyl)-3-methyl-bicyclo[2.2.1]hept-5-ene (**8**)[2] in 76% yield. The melting point of **8** was in agreement with that of reported compound. Retro Diels-Alder reaction of **8** was effected by pyrolysis at 520°C to give the corresponding 1-hydroxy-2-hydroxymethyl but-2-ene (**4**) in 83% yield.

Compound **4** has been prepared earlier by Weiss and Bensa[3] by pyrolysis of 11,11-bis(hydroxymethyl)-12-methyl-9,10-dihydro-9,10 ethanoanthracene, the latter being obtained by sequential Diels-Alder reaction[4] of anthracene with crotonaldehyde followed by the reaction with formaldehyde and sodium hydroxide[3]. The PMR spectrum of **4** was consistent with its structure. For example a doublet corresponding to vinylic methyl was observed at 1.87 ppm. A broad singlet at 3.97 ppm which was D_2O exchangeable was assigned to the two hydroxyl protons while singlet at 4.20 and 4.33 ppm were due to two methylenes. A quartet in the downfield region of 5.70 ppm was due to the olefinic protons.

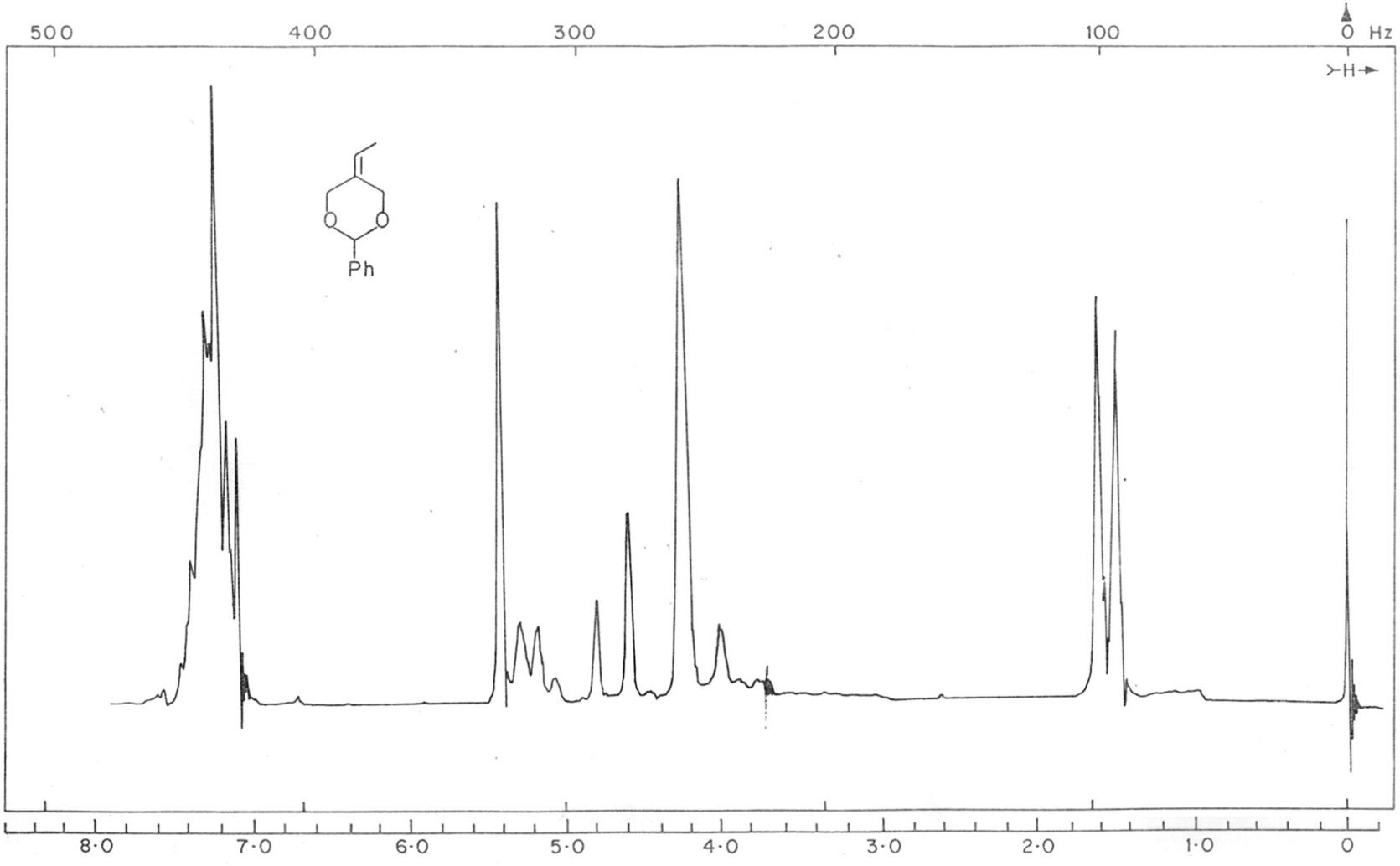


FIG. 2 : PMR SPECTRUM OF COMPOUND (9) IN CCl_4

The next step involved the conversion of diol (**4**) into its substituted monobromo derivative (**3**). The classical method would be to effect monobromination of diol (**4**) followed by the protection of the free hydroxyl group. Therefore monobromination of diol (**4**) was attempted by treating **4** wih 48% aqueous hydrobromic acid in refluxing toluene. A faster moving product was obtained whose PMR spectrum showed that it was 1-bromo-2-bromomethylbut-2-ene (dibromide). For example, two singlets due to methylene protons showed downfield shift (4.03, 4.07 ppm) as compared with the corresponding chemical shift of the methylene of the diol (**4**). Had it been a monobromo derivative only one of the singlets would have shown downfield shift. Remaining protons revealed at the expected chemical shifts. In order to avoid the formation of the dibromo compound in the above reaction, it was thought of carrying out the same reaction by the liquid liquid extraction in hexane, by adopting the procedure reported by Maurer et al.[5] for the conversion of octanediol to the corresponding monobromo derivative. This was based on the fact that once the monobromide is formed it could have more solubility in hexane and therefore could be trapped in hexane layer. However, the compound isolated in hexane fraction was none other than the dibromide. This suggested that the monobromide formed in the reaction still has considerable affinity for water and chooses to remain in aqueous layer which obviously resulted in the formation of dibromide.

Due to the inability to bring about direct monobromination of the diol (**4**), the sequence was reversed i.e. to selectively protect

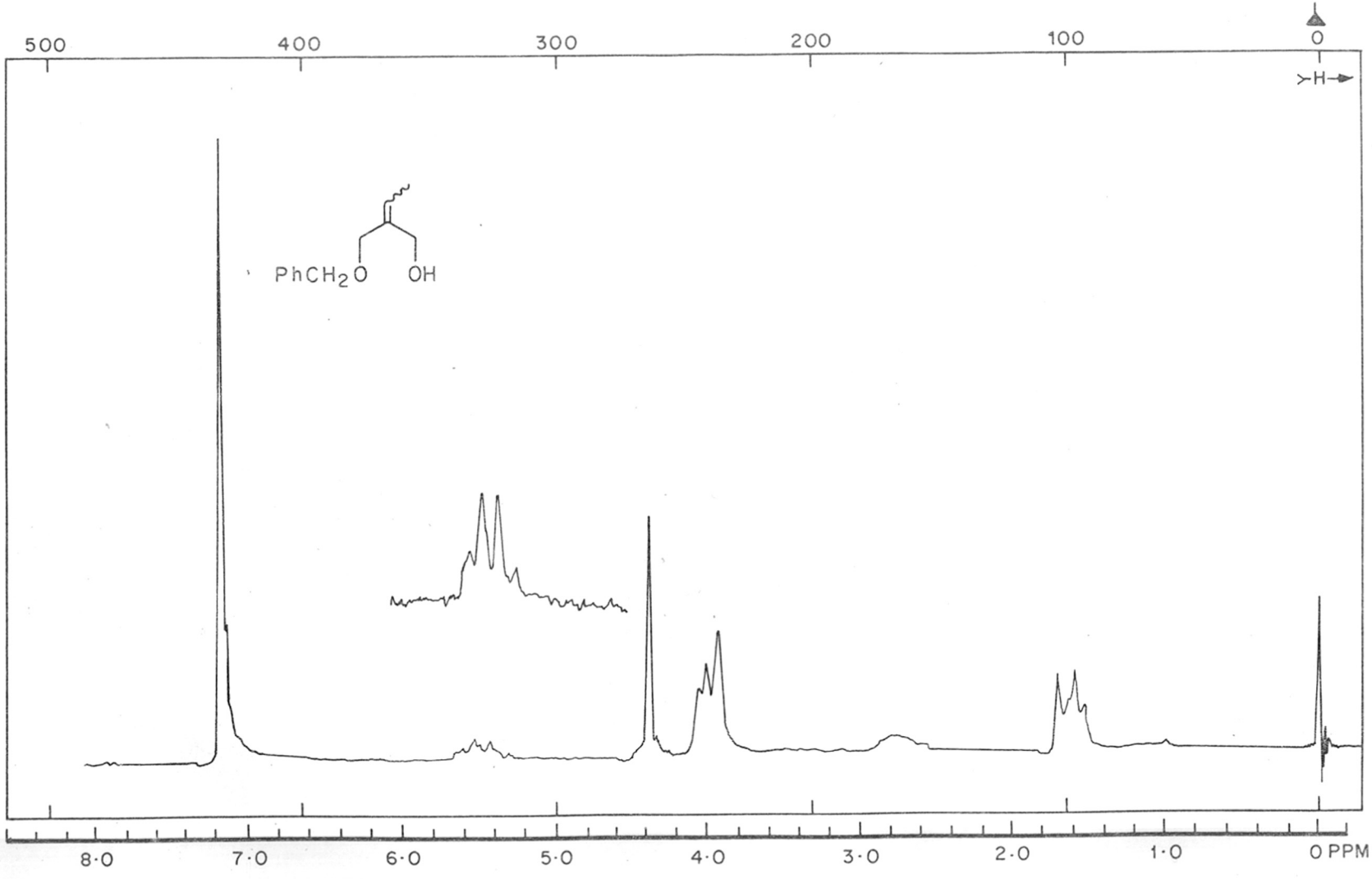


FIG. 3 : PMR SPECTRUM OF COMPOUND (10) IN $CDCl_3$

4 as benzyl ether and then to attempt the monobromination. The diol on treatment with one molar equivalent of benzylbromide-sodium-hydride afforded the monobenzyl ether (**10**) in 55% yield. The structure of this monobenzyl ether was confirmed by the PMR spectrum in which two doublets were observed for the vinylic methyl at 1.60 and 1.63 ppm which clearly indicated that the product was a mixture of E and Z isomers. The presence of a singlet for benzylic protons was observed at4.40 ppm, while other protons were assigned. This reaction also afforded considerable amount of faster moving dibenzylether. Considering low yield of the monobenzylether (**10**) an alternative approach, based on selective hydrogenolysis of benzylidene derivative to the monobenzyl-ether was adopted (Scheme 2). Therefore the diol (**4**) was converted into the benzylidene drivative (**9**) by treatment with α,α-dimethoxytoluene in acetonitrile containing catalytic amount of toluene p-sulfonic acid at room temperature. The expected benzylidene derivative (**9**) isolated in 92% yield indicated in its PMR spectrum the presence of a benzylidene proton at 5.43 ppm as a singlet. In addition a doublet for vinylic methyl and a quartet for the olefinic proton were observed at 1.53 and 5.27 ppm respectively. One of the ring methylenes appeared as a AB quartet at 4.40 ppm while the second methylene resonated as a singlet at 4.27 ppm. Aromatic protons appeared as a multiplet at 7.27 ppm. These PMR values of **9** demonstrated the assigned structure.

Hydrogenolysis[6] of **9** in a mixture of LAH and $AlCl_3$ in ether gave mono-O-benzylether **10** in 89% yield. It is pertinent to mention that the overall yield of monobenzylderivative **10** by a two step process

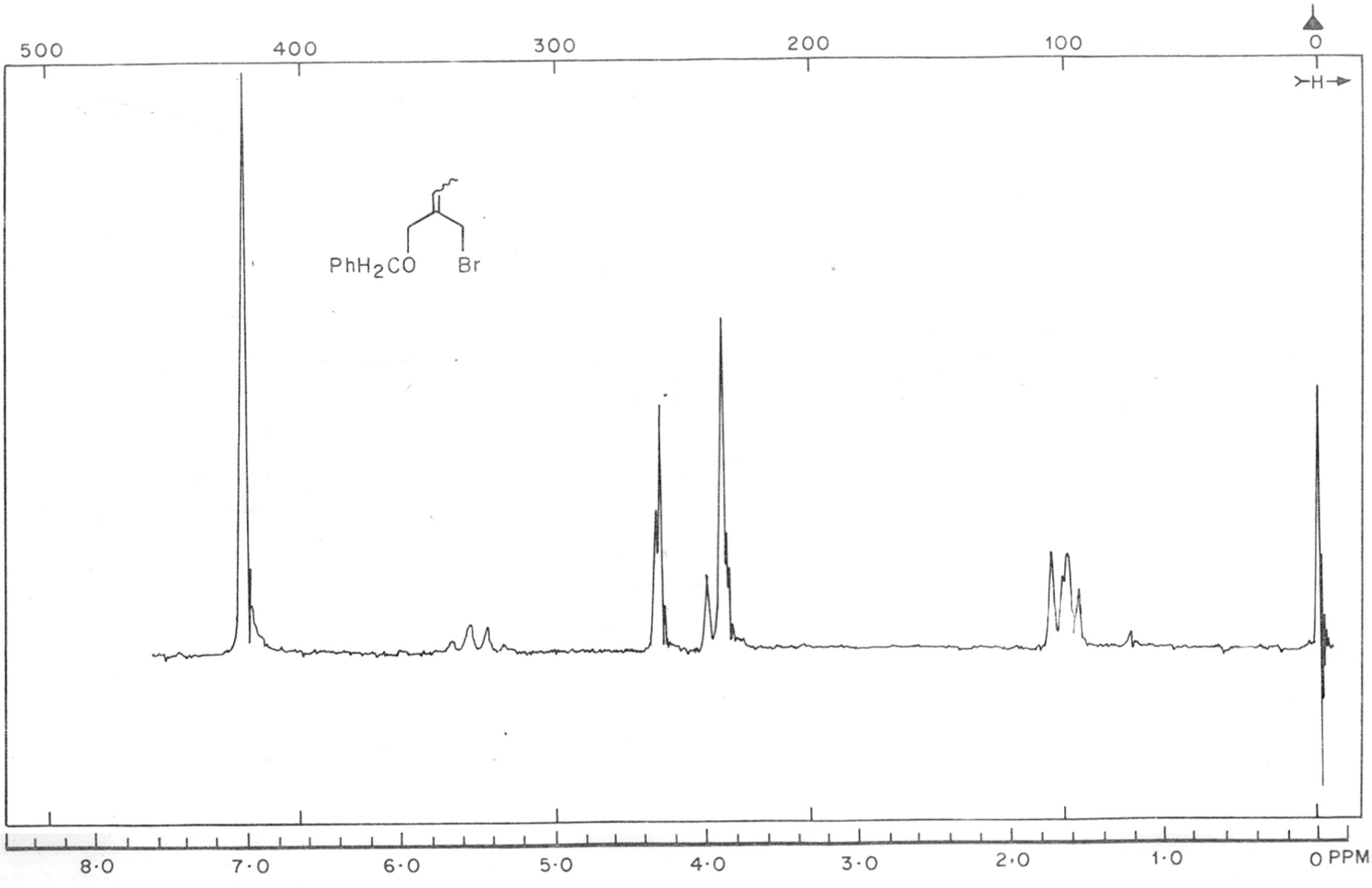


FIG. 4 : PMR SPECTRUM OF COMPOUND (12) IN CCl_4

was better than the earlier method. Although this reaction afforded a mixture of E and Z isomers, they were not separated because geometrical stereochemistry was of no consequence at the later stages of the synthesis. Therefore further reactions were carried out on the E/Z mixture. The alcohol (**10**) was then treated with mesylchloride in the presence of triethylamine and methylenechloride, the resulting product was not the expected mesylate but the required chloride (**11**) obtained in 94% yield. The structure of the chloride (**11**) was clearly suggested by the PMR spectrum where the expected signals due to methyl of mesylate group was absent. The mass spectrum of the chloride revealed the molecular ion peak at m/z 210. The formation of the chloride (**11**) in the above reaction was attributed to the fact that the mesylate intermediate being allylic underwent displacement with chloride ion under the reaction conditions.

Having prepared the required substituted halide, the next programme involved its condensation with the AB ring system of sesbanimide. In order to establish the methodology for the construction of ring C by using the halide (**11**) it was felt essential to explore this reaction with model compound. In addition, the AB ring synthon being precious material, could not be employed for investigative study. For model studies, 2-(2-methyl-2-dioxolanyl)ethanal (**15**) was chosen and was prepared by the literature procedure[7]. Ethylacetoacetate was treated with ethyleneglycol in the presence of an acid with an azeotropic removal of water to get ethyl 2-(2-methyl-2-dioxolanyl)acetate. Subsequent treatment with DIBAL at -78°C afforded the required aldehyde (**15**).

In order to prepare Grignard reagent, **11** was treated with magnesium in ether at 0°C, unfortunately the reaction failed to initiate. However, at ambient temperature, magnesium was found to react and after 0.5 h the aldehyde was introduced. From this reaction two products were isolated in the ratio of 4:1, the PMR spectrum of them indicated that they were not the required product, since signals due to the aldehyde **(15)** were completely absent. Careful analysis of PMR spectrum revealed that the faster moving minor product was the dimer **(14)**. In the PMR spectrum, two doublets due to the methyl group were observed at 1.00 and 1.60 ppm. The downfield shift of one of the methyl groups was due to its vinylic nature. A multiplet around 2.2 ppm integrating for three protons was assigned to the methine and the methylene protons ($-C\underline{H}_2C\underline{H}CH_3$), whereas methylenes ($-C\underline{H}_2OBn$) appeared as a multiplet at 3.8 ppm. Moreover, benzylic protons appeared as two broad singlets at 4.30 and 4.37 ppm. The resonances due to exomethylene protons ($=\!\!\begin{smallmatrix}H\\H\end{smallmatrix}$) appeared as multiplet at 4.9 ppm and the vinylic proton ($-C\underline{H}CH_3$) was located at 5.3 ppm as a multiplet. The aromatic protons appeared as a singlet at 7.1 ppm. These PMR data clearly indicated the dimeric structure as **14**. The slower moving product isolated as a major one was given the structure **13** on the basis of PMR spectrum. Since the dimer **(13)** had a centre of symmetry only resonances due to the one half were observed. For example, a multiplet at 0.95 and 2.2 ppm corresponded with the methyl and the methine protons ($C\underline{H}C\underline{H}_3$). A multiplet, AB quartet appeared at3.8 and 4.28 ppm were assigned to methylene and benzylic protons, while two multiplets at around 4.8 ppm corresponded with the exomethylene protons. The aromatic

protons appeared as a singlet at 7.25 ppm. Reaction of activated[8] or nonactivated magnesium and other metals such as lithium with halide (11) also afforded the same mixture of dimers.

In view of the fact that the chloride (11) failed to form the Grignard reagent at 0°C and that at elevated temperatures it underwent dimerisation, it was thought worthwhile exploring the formation of Grignard reagent with corresponding bromo compound (12) at lower temperatures. Therefore, the alcohol (10) was treated with PBr_3 and pyridine[9] in dry ether at 0°C to give the bromide (12) in 90% yield. Its structure was proved by comparison of its PMR spectrum with that of the chloride (11). The bromide (12) indeed reacted with magnessium at 0°C and the resulting mixture was treated with aldehyde (15). The products isolated after the workup corresponded with the two dimers obtained earlier.

Examination of this reaction suggested that this methodology in which organometallic reagent was formed first and then allowed to react with the aldehyde was not particularly suitable. This was because of the susceptibility of the organometallic reagent to undergo dimerisation. Therefore, what was required was a method in which the formation of organometallic reagent immediately precedes condensation with the aldehyde. The most obvious choice was to use organometallic reagent prepared from the bromide (12) and activated zinc dust[10] in accordance with the Zaitsev[11] reaction. It is indeed gratifying to note that the reaction of the aldehyde (15) with the bromide (12) in the presence of activated zinc dust and catalytic amount of iodine at room temperature

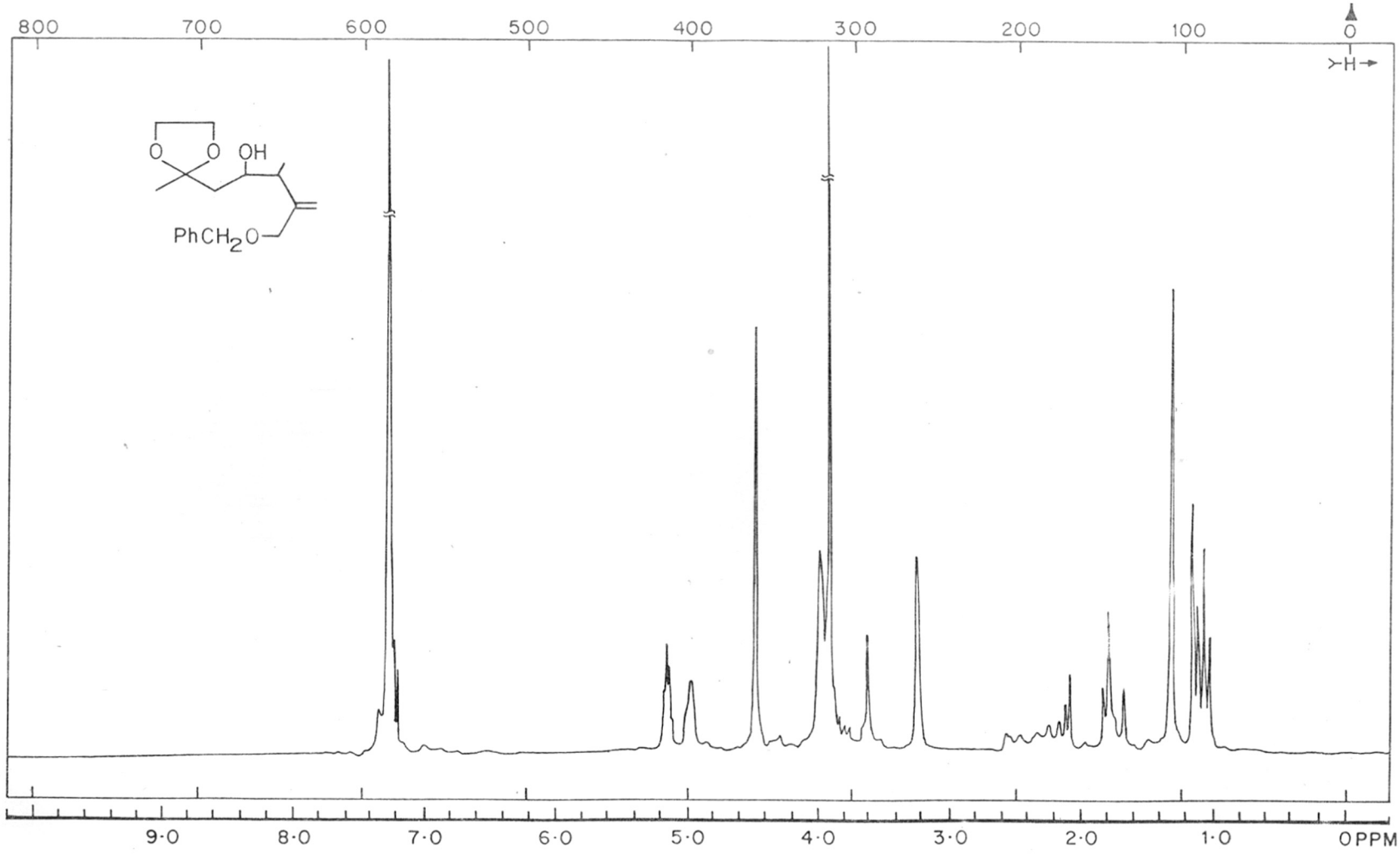
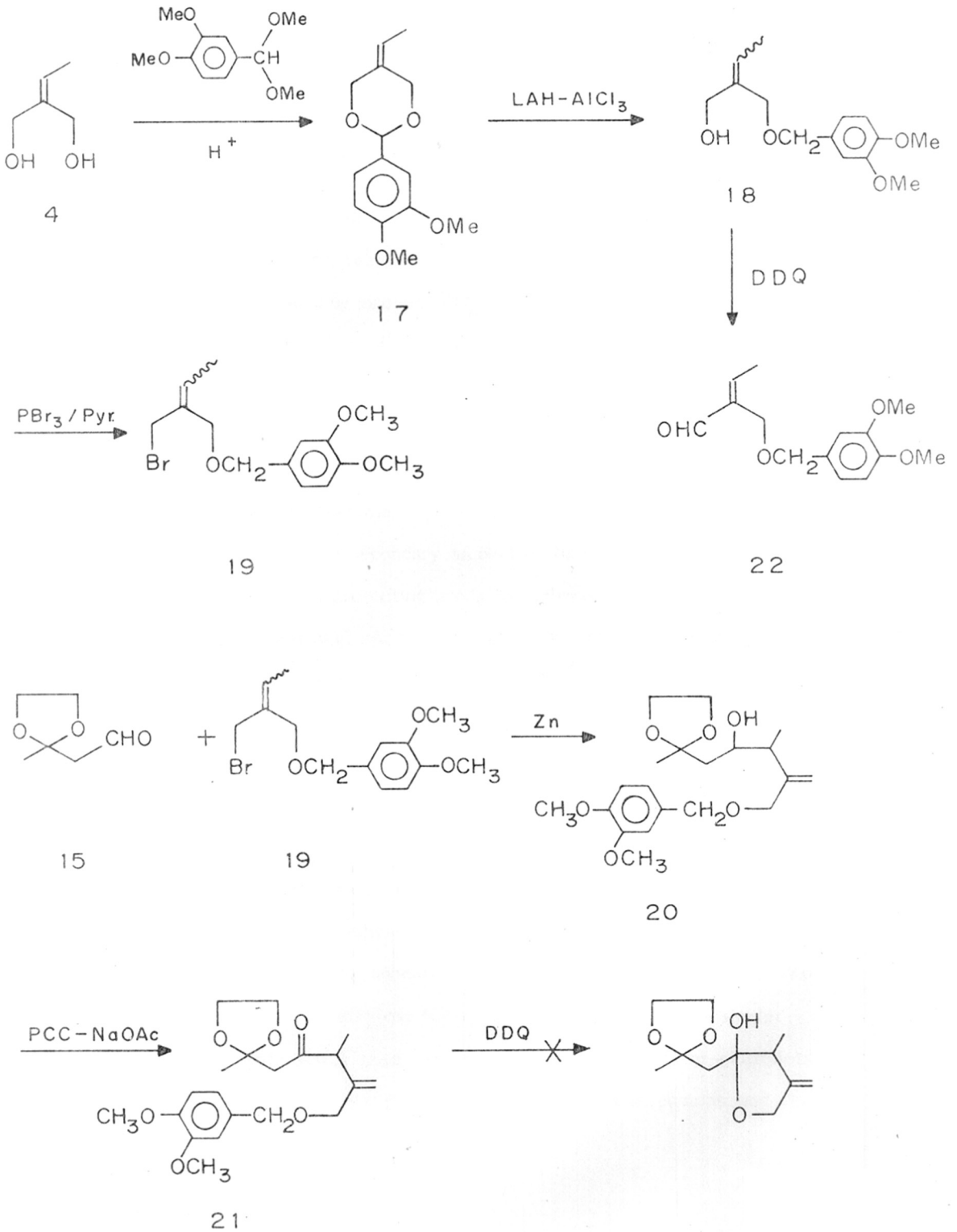


FIG. 5 : PMR SPECTRUM OF COMPOUND (16) IN $CDCl_3$

in dry THF afforded the required alcohol (**16**) and no dimeric products of halide was detected. The PMR spectrum of **16** indicated that the product was diasteriomeric mixture as two doublets corresponding to methyl group at C-3' was observed at 1.06 and 1.13 ppm. A singlet for methyl at C-2, a multiplet for methine (H-3') and a methylene protons of C-1' around 2.0 ppm were observed. A singlet due to hydroxyl group appeared at 3.25 ppm whereas methine (H-2') and methylene protons ($C\underline{H}_2OBn$) appeared as multiplet around 4.0 ppm. Two singlets for ethylene ketal ($OC\underline{H}_2C\underline{H}_2O$-) and benzylic protons were observed at 3.94 and 4.50 ppm. Two multiplets at 4.9 and 5.1 ppm for exomethylene protons were observed while the aromatic protons appeared at 7.31 ppm as a singlet. This reaction clearly indicated that the condensation reported above was occurring at the desired site i.e. secondary carbon. There are ample of evidences where such reactions have been observed.

Recent report by Yonemitsu et al.[12] have shown that 3,4-dimethoxy-O-benzyl ether can be oxidatively cleaved in presence of double bond and the benzyl ether. Since in the present synthesis, at later stages of the synthetic scheme the benzyl protection would have to be removed, it was thought worthwhile carrying the above condensation with 3,4-dimethoxy-O-benzyl protected bromide (**19**). The latter compound was prepared (Scheme 3) by a procedure similar to the one adopted for the benzyl protected bromide (**12**). For example, the diol (**4**) was converted into the corresponding 3,4-dimethoxy-O-benzylidene derivative (**17**) by the treatment with 3,4-dimethoxybenzaldehyde dimethylacetal and toluene-p-sulfonic acid in dry acetonitrile. The PMR spectrum

SCHEME – IV


MeO
OMe
MeO
CH
OMe
H+
OH
OH
4
17
LAH-AlCl3
OH
OCH2
OMe
OMe
18
DDQ
PBr3 / Pyr.
Br
OCH2
OCH3
OCH3
19
OHC
OCH2
OMe
OMe
22
CHO
15
+
Br
OCH2
OCH3
OCH3
19
Zn
OH
CH3O
CH2O
OCH3
20
PCC – NaOAc
CH3O
CH2O
OCH3
21
DDQ
OH

was identical with the product **9** except for the additional singlet at 3.70 ppm for the two methoxyl groups whereas in the aromatic region the presence of multiplet for three protons were recorded.

Hydrogenolysis of **17** with LAH and $AlCl_3$ gave the mixture of E/Z isomers of the alcohol (**18**) in 82% yield confirmed by its PMR spectrum. Subsequent reaction with PBr_3 and pyridine at 0°C gave rise to the corresponding bromide (**19**) which was identified by its PMR spectrum. Condensation of the aldehyde (**15**) with the bromide (**19**) in the presence of activated zinc dust and catalytic amount of iodine gave the alcohol (**20**) in 75% yield. The resonances in the PMR spectrum of **20** were consistent with the assigned structure.

Having obtained the required intermediate **20,** the next concern was the oxidation of the secondary alcohol in **20** followed by the removal of dimethoxy-O-benzyl protecting group which would result in the formation of desired C-ring. Accordingly **20** was treated with pyridinium chlorochromate and sodium acetate[13] in methylene chloride at room temperature and after 24 h the expected ketone (**21**) was isolated in 67% yields. The formation of the ketone destroyed the asymmetric centre in **20** and led to the formation of the single product. In the PMR spectrum of **21,** two C-methyl groups were located at 1.18 and 1.33 ppm. Two quartets appeared at 2.81 and 3.44 ppm were assigned to methine (H-3') and methylene protons at C-1' respectively. A multiplet integrating for 8 protons appeared at 3.9 ppm corresponded with two methoxyl group and a methylene ($\underline{CH}_2OCH_2Ar$) protons while a singlet for benzylic protons was localized at 4.44 ppm. Two sets of multiplets at 5.05 and 5.2 ppm were given to the exomethylene protons and the

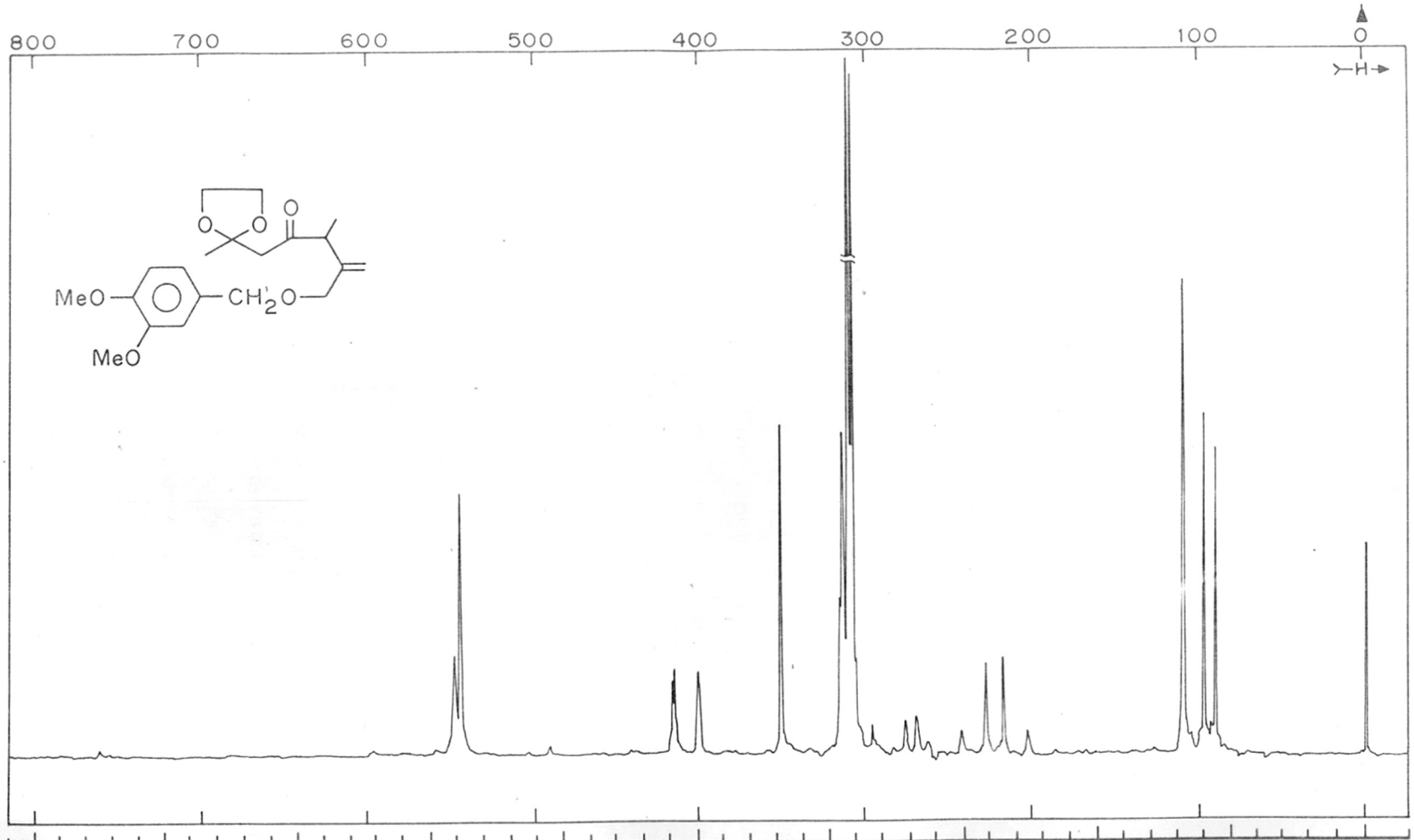


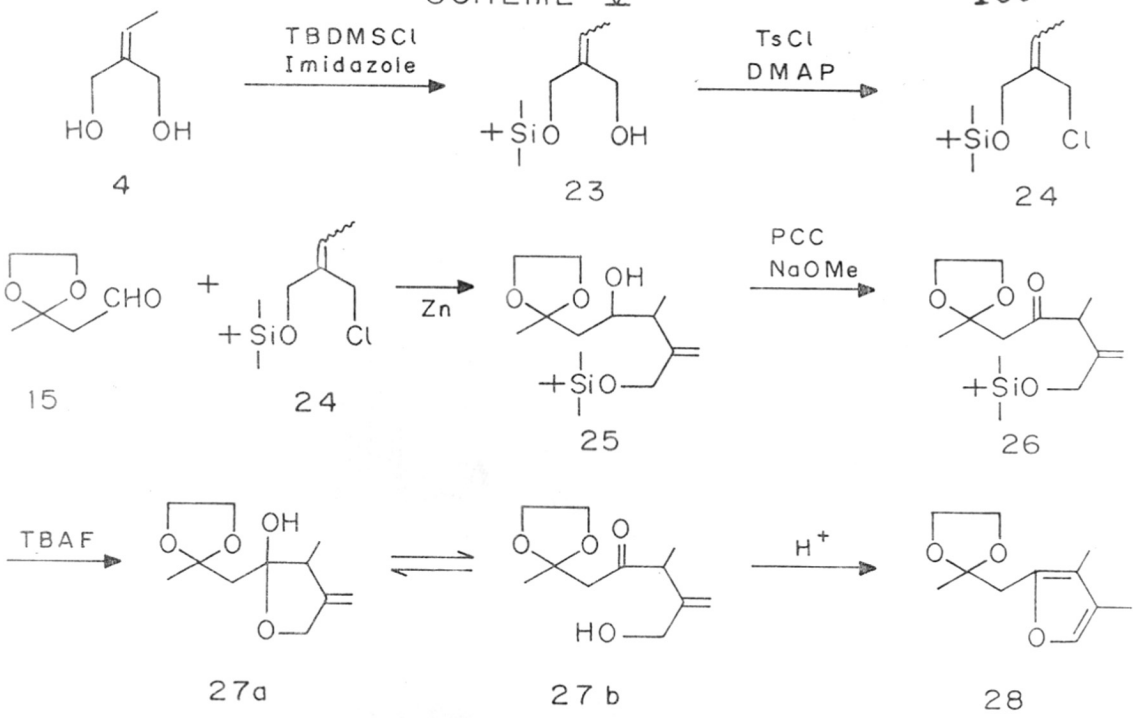
FIG. 6 : PMR SPECTRUM OF COMPOUND (21) IN $CDCl_3$

multiplet at 6.30 ppm corresponded to aromatic protons.

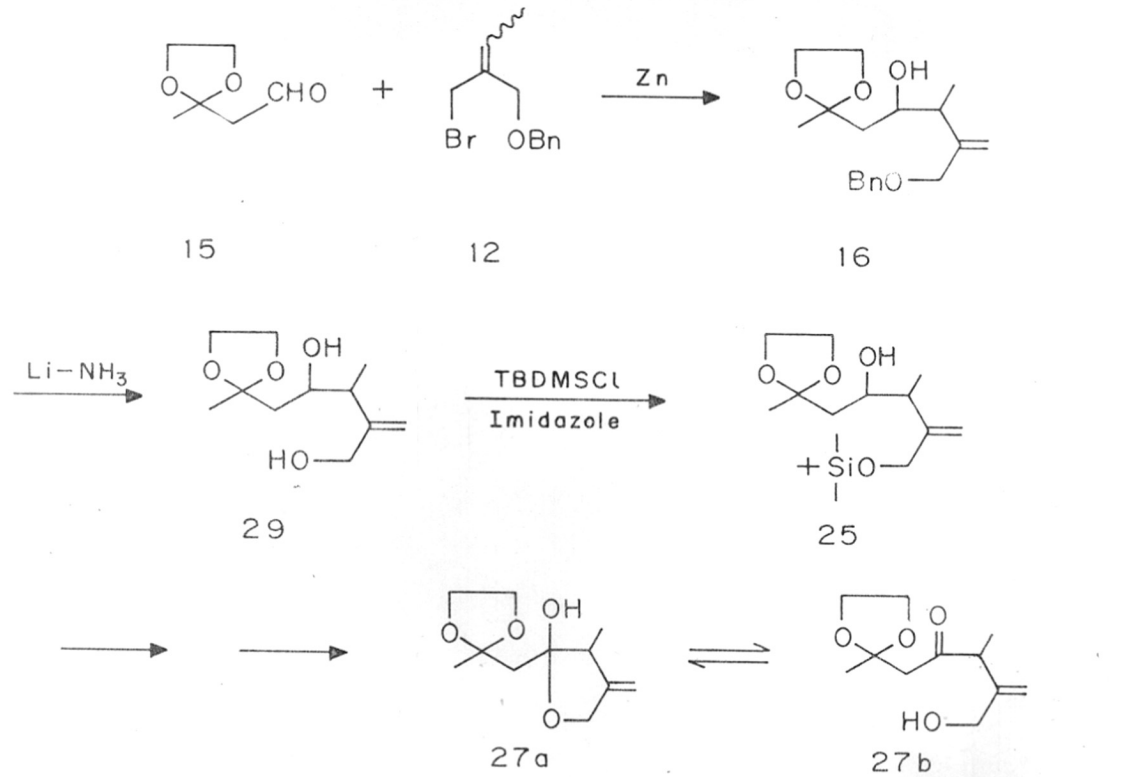
Having established the structure of **21** unambiguously, the compound **21** was then treated with DDQ in aqueous methylenechloride at room temperature in order to remove 3,4-dimethoxy-O-benzyl group. Surprisingly a mixture of product resulted which could not be separated by chromatography. The reaction was then attempted at 0°C, however, it failed to bring about any change as similar mixture of products resulted as judged by TLC. The formation of a complex mixture may be attributed to the following reason. In the presence of DDQ, **21** underwent cleavage generating the alcohol and the alcohol being allylic, underwent further oxidation in the presence of DDQ. In order to prove this suggestion, a small experiment was carried out on **18** with DDQ. It was observed that the allylic alcohol in **18** was getting oxidized so fast that the product isolated was found to contain 3,4-dimethoxy-O-benzyl group. The structure of the product was assigned **22.** When the reaction was continued for a long time then TLC indicated the formation of number of spots due to the overoxidation.

After the advent of silylethers as a protective group, silyloxy derivatives are finding importance in synthetic organic chemistry for the selective protection of hydroxyl groups. The ease with which the silyloxy protecting group can be introduced and more importantly the ease with which they can be removed are one of the factors for their selection in number of syntheses reported. Therefore, in the present synthesis (Scheme 4) the strategy would involve the preparation of monosilyloxy derivative of the diol **(4)** and subsequent conversion into the halide derivative. Thus the diol **(4)** was treated with one equivalent

SCHEME-V



SCHEME-VI



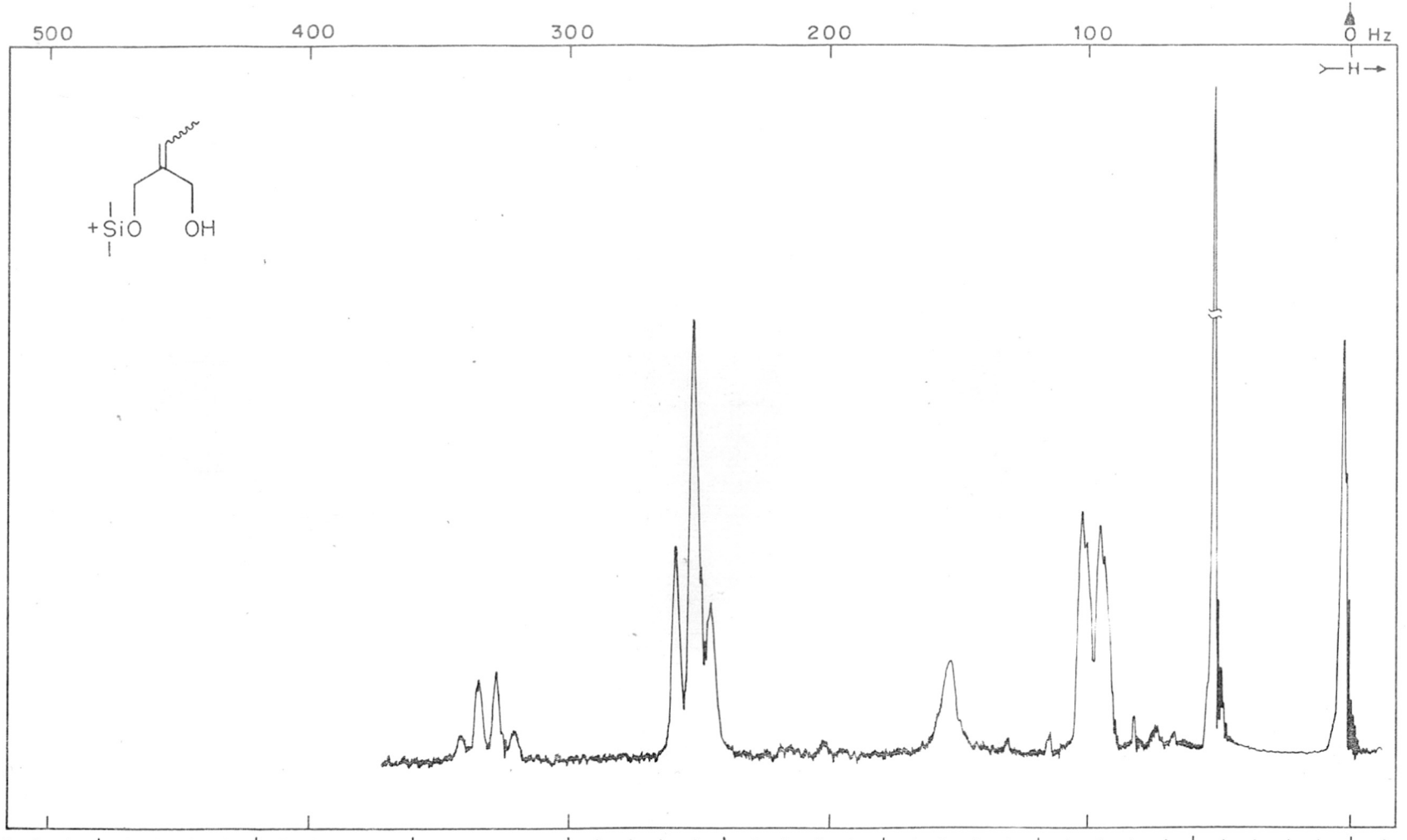


FIG. 7 : PMR SPECTRUM OF COMPOUND (23) IN $CDCl_3$

of tert-butyldimethylsilylchloride and imidazole[14] to afford the monosilyloxyderivative (**23**) whose structure was confirmed by the PMR spectrum which showed the presence of t-butyldimethylsilyloxy group as two singlets were observed below 1.0 ppm. The resonances due to vinylic methyl, methylenes and vinylic protons were also observed. A D_2O exchangeable broad singlet at 2.5 ppm indicated that one hydroxyl was free. From this reaction negligible amount of disilyloxy derivative was also obtained but not fully characterised.

Treatment of the monosilyloxy derivative (**23**) with tosylchloride 4-(N,N'-dimethylaminopyridine)[15] in methylene chloride afforded the corresponding chloro compound (**24**) in 75% yield. When the PMR spectrum of this chloride was compared with that of monosilyloxyderivative (**24**), not much difference was observed. However, the broad singlet due to the OH group has clearly disappeared. Condensation of the monochloride (**24**) with the aldehyde (**15**) was carried out according to the procedure described earlier, followed by chromatographic separation gave the desired alcohol (**25**) in only 15% yield. In the PMR spectrum of **25**, the presence of two multiplets at 4.8 and 5.2 ppm for the exomethylene protons indicated that the condensation has occurred at the secondary carbon. Other peaks were consistent with the assigned structure.

Oxidation of the secondary alcohol in **25** was effected by the treatment with pyridinium chlorochromate and sodiumacetate in methylene chloride at room temperature to give the ketone (**26**) in 75% yield. The structure of **26** was based on the PMR spectrum where a downfield shift of resonances due to the methine (H-3') and methylene

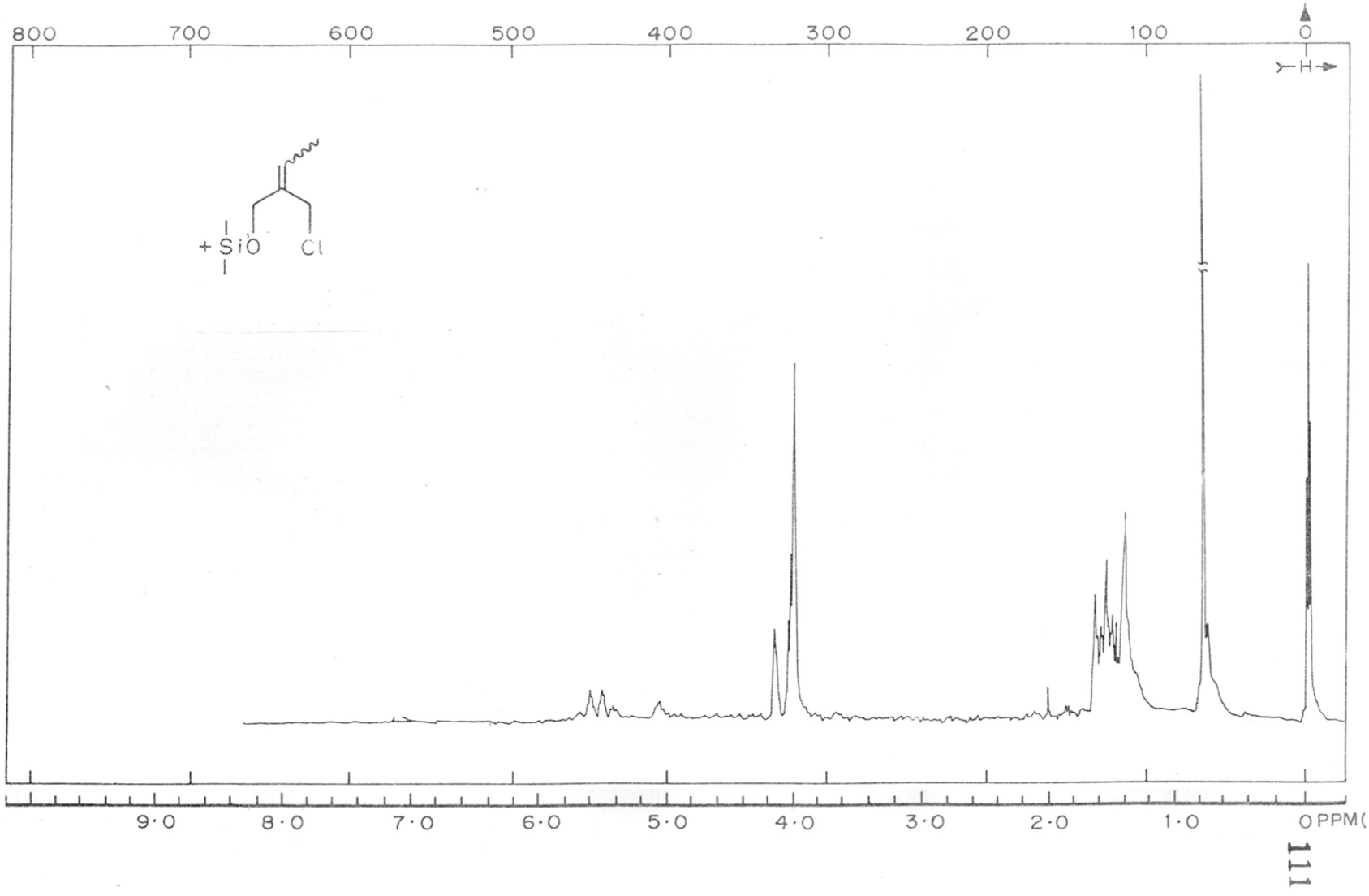


FIG. 8 : PMR SPECTRUM OF COMPOUND (24) IN $CDCl_3$

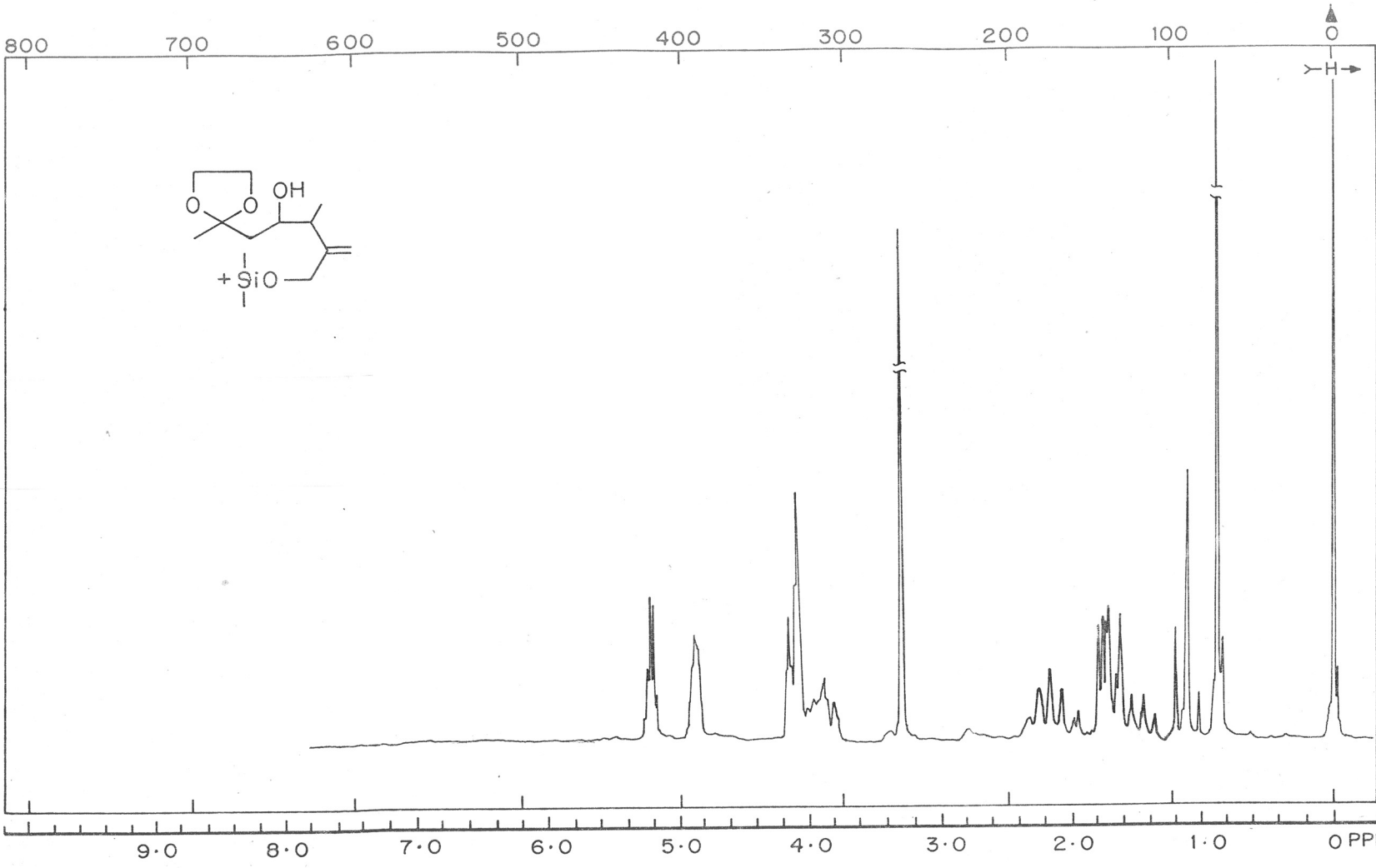


FIG. 9 : PMR SPECTRUM OF COMPOUND (25) IN $CDCl_3$

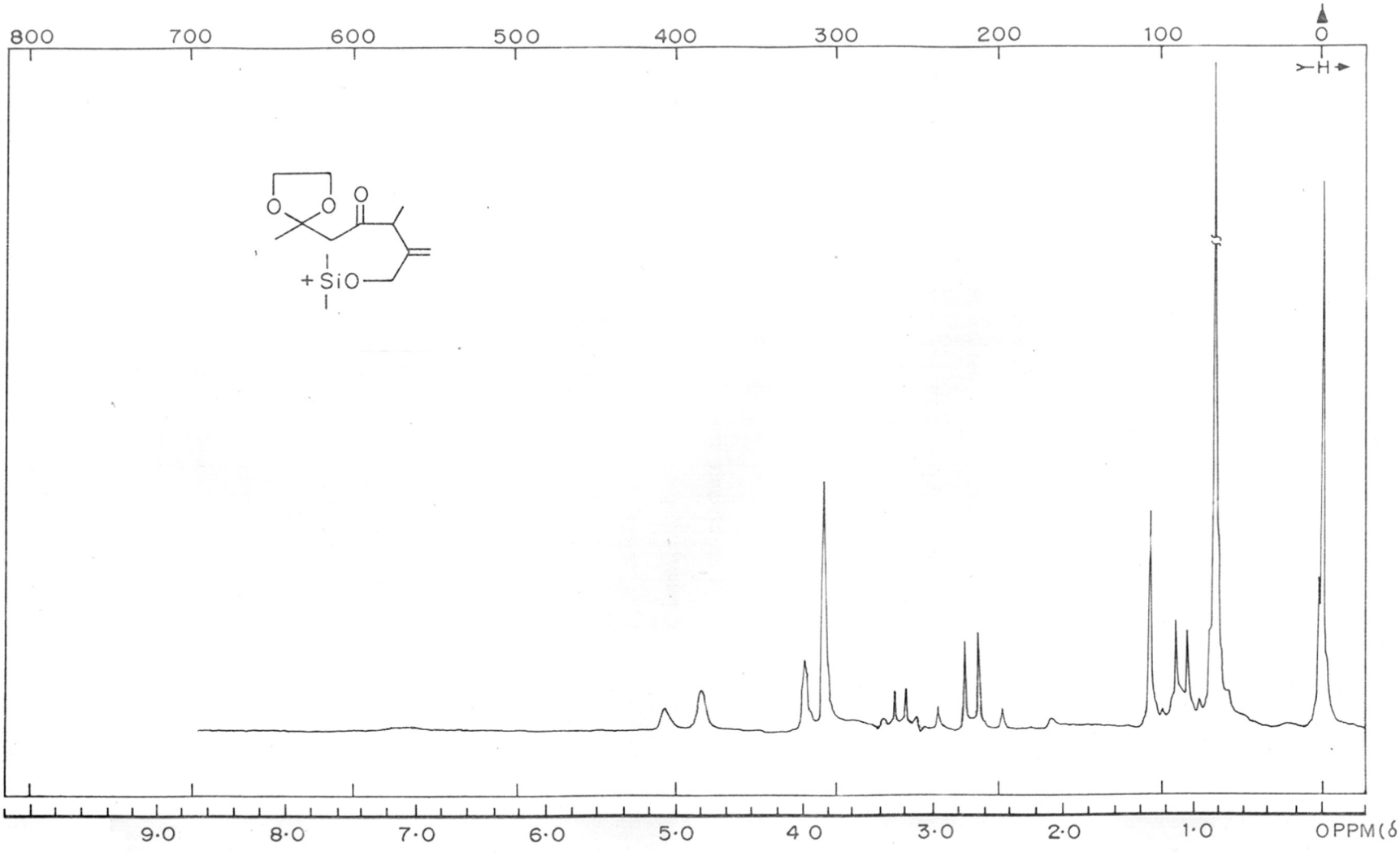


FIG. 10: PMR SPECTRUM OF COMPOUND (26) IN $CDCl_3$

protons on C-1' was observed suggesting these protons were adjacent to the ketone group. Other protons had expected chemical shifts. Cleavage of the t-butyldimethylsilyl group was achieved by treating the compound **26** with one molar solution of tetrabutylammoniumfluoride[14] in THF. The resulting product was confirmed as the required compound **27** on the basis of its PMR spectrum which showed that the compound **27** in $CDCl_3$ solution existed in open (**27b**) as well as closed (**27a**) forms in 1:4 ratio. Although the PMR spectrum at first instance showed a complicated pattern, careful analysis indicated that the product also was a diasteriomeric mixture in the closed form. The methyl group at C-3 showed three doublets in the region of 0.83 to 1.31 ppm corresponding to an open form and two diasteriomeric forms. Similarly methyl group at C-2' showed three singlets at 1.46, 1.50 and 1.53 ppm while methylene proton on C-1 showed a multiplet at 2.0 ppm (closed form). A multiplet at 2.3 ppm was assigned to the methine proton (H-3) (closed form). In addition a broad singlet observed at 2.81 ppm was due to the methylene protons on C-1' of the open form, a quadruplate at 3.56 ppm was assigned to the methine proton of the open form. Two singlets observed around 4.0 ppm corresponded with methylene protons of ethylene ketal group for both open and closed forms. Two set of multiplets appeared at 4.56 and 4.88 ppm are assigned for the methylene protons on C-5 and exomethylene protons of the closed form respectively whereas two set of multiplets at 5.1 and 5.3 ppm for the exomethylene protons of the open form. Based on the above PMR analysis the structure of the product **27** was confirmed. The final proof of **27** was gleaned from its mass spectrum in which the molecular

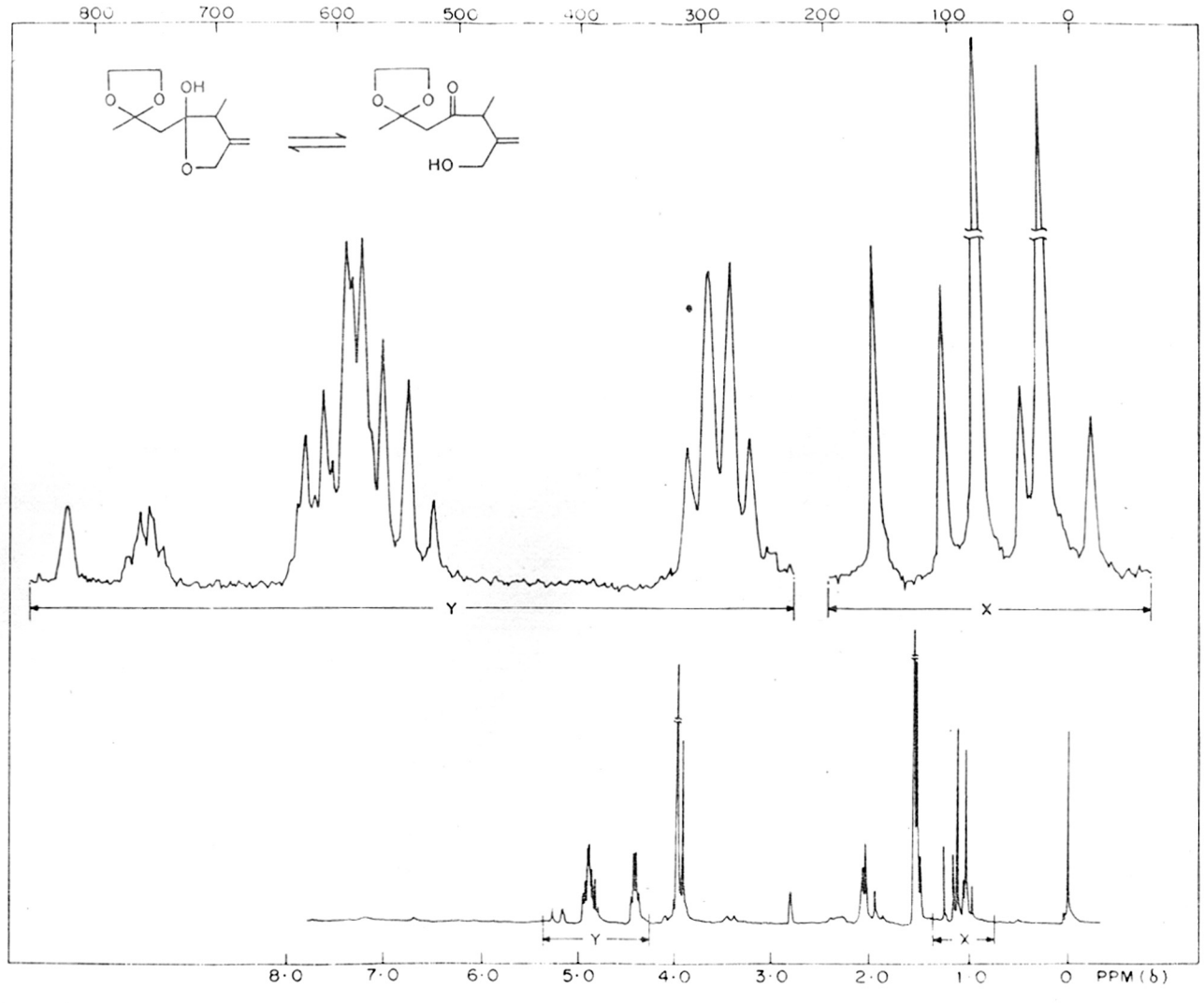


FIG 11 PMR SPECTRUM OF COMPOUND (27a & 27b)

IN $CDCl_3$

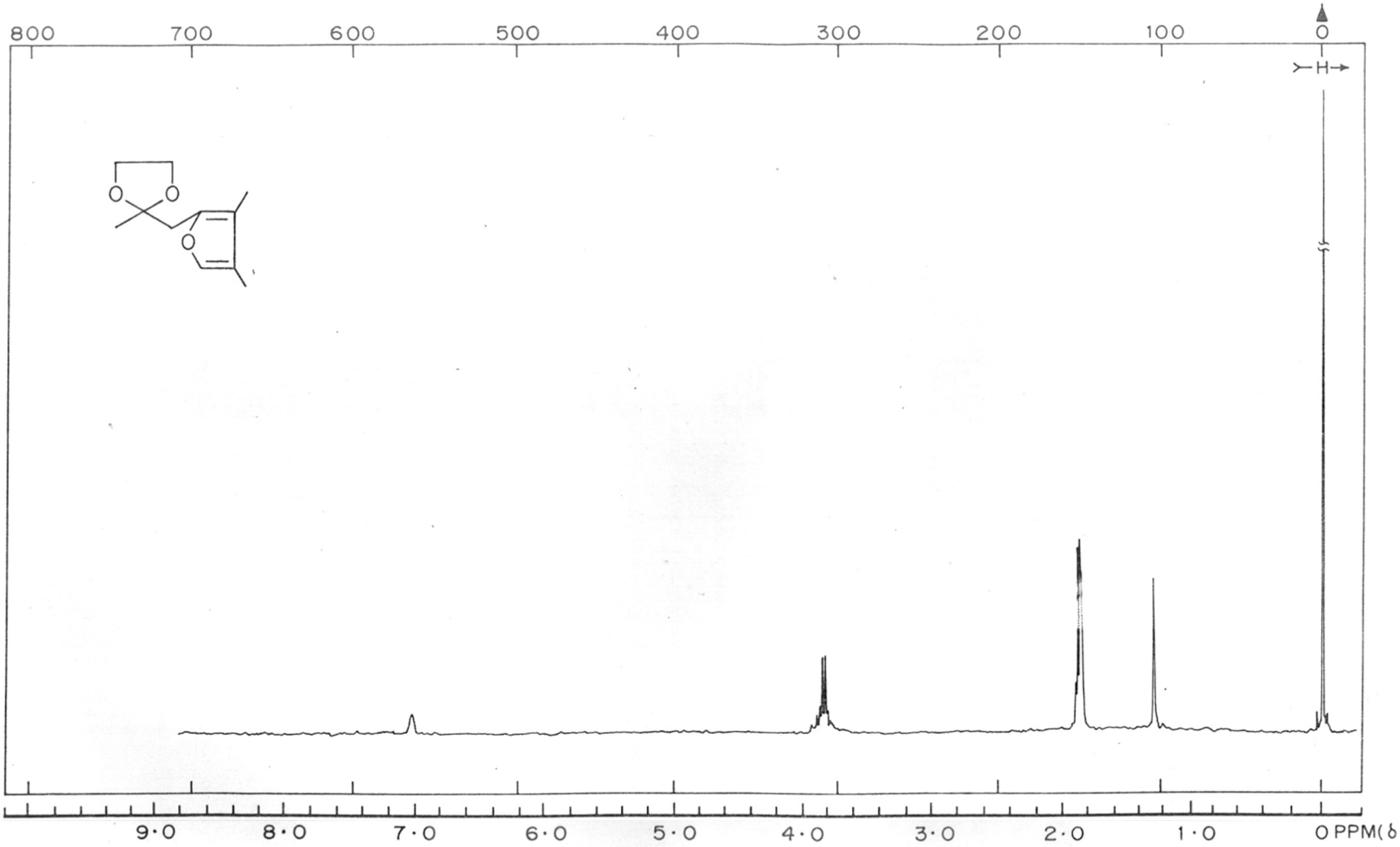


FIG. 12: PMR SPECTRUM OF COMPOUND (28) IN $CDCl_3$

ion peak was observed at m/z 214 corresponding to C-ring system (**27**).

It is interesting to note that the above mentioned PMR spectrum was scanned in a purified $CDCl_3$ solvent. However, when the spectrum was scanned from a commercial $CDCl_3$ (Fluka), the corresponding formation of 3,4-dimethylfuran derivative (**28**) was observed whose PMR spectrum revealed three singlets corresponding to three methyl groups, multiplet at 3.88 ppm for ethylene ketal protons and a singlet at 7.06 ppm for the aromatic proton. This observation suggested that the C-ring of sesbanimide was extremely labile under acidic condition and small amount of acid present in commercial $CDCl_3$ was substantial to force the dehydration and rearrangement to occur.

Although the above synthetic scheme afforded the desired ring-C (**27**), the overall yield of the product was far from satisfactory. In particular, the condensation reaction of the silyloxychloride derivative (**24**) with the aldehyde (**15**) could be considered as the only step where the yield was extremely low and therefore modification of this step was required.

As it has been earlier reported in this Section that the condensation of 2-benzyloxymethylcrotylbromide (**12**) with the aldehyde (**15**) under the Zaitsev reaction condition worked very well to afford the desired alcohol (**16**) in good yield. The utility of this product was probed as follows (Scheme 5).

16 was treated with lithium in liquid ammonia[16] which resulted in the removal of benzyl group to give rise to the diol (**29**) in 90% yield. The reaction was found to be clean and the structure of the diol (**29**) was demonstrated by its PMR spectrum which was amenable

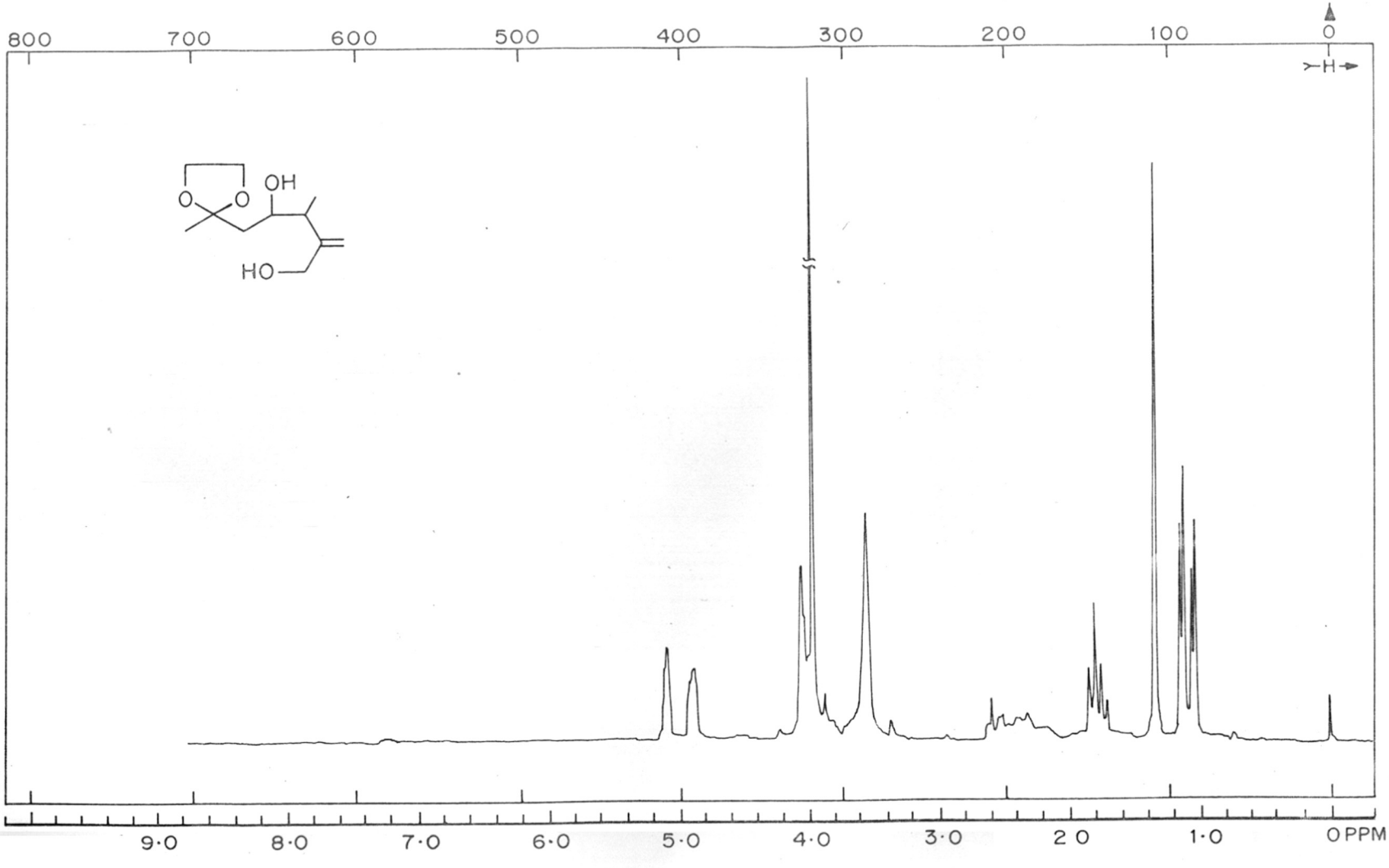


FIG. 13: PMR SPECTRUM OF COMPOUND (29) IN $CDCl_3$

to first order analysis. Most of the signals were correctly assigned. The loss of benzyl group was clearly indicated by the absence of the resonances due to benzylic methylene and aromatic protons.

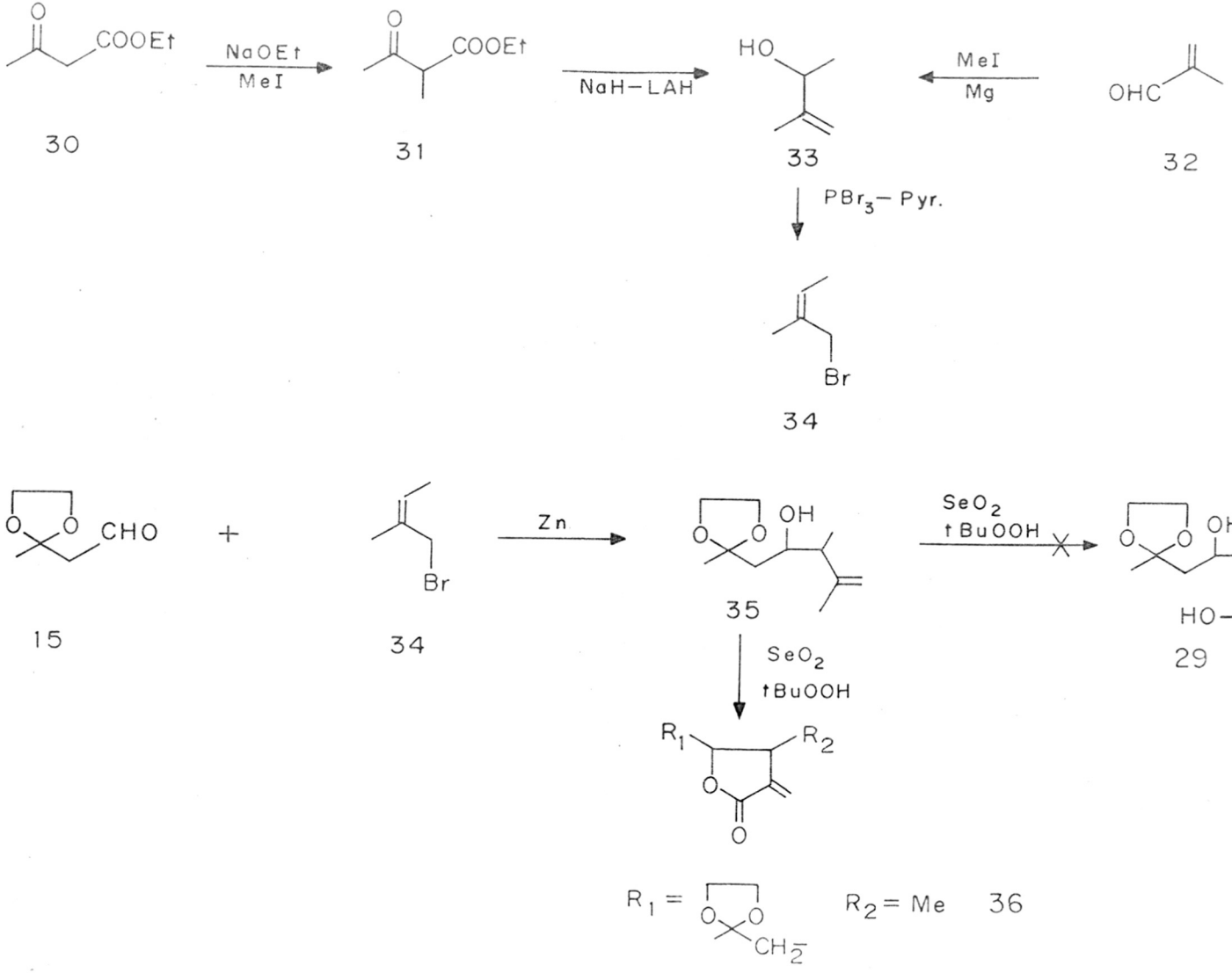
Subsequent treatment of the diol (**29**) with t-butyldimethylsilylchloride and imidazole afforded the monosilyl derivative (**25**) in which the silyloxy group was present at primary hydroxyl group. The PMR spectrum of this was identical in all respects with product prepared earlier. The overall yield of **25** by the above mentioned route was 75%.

In an alternate approach towards the construction of ring-C, the utility of the oxidation of the allylic methyl under Sharpless condition[17] was explored. The stategy here involved the preparation of an intermediate of the type **35** which on selenium dioxide oxidation would generate the corresponding diol (**29**), the latter product could be extended to ring-C by the procedure reported earlier.

In accordance with this scheme (Scheme 6), the synthesis of 3-methylbut-3-ene-2-ol (**33**) was undertaken. This compound was synthesised from ethyl 2-methyl-3-oxobutanoate (**31**). Treatment of **31** with sodium hydride followed by reaction with lithiumaluminium hydride[18] gave the required product **33** in overall 67% yield. The physical and spectroscopic data corresponded very well with the data reported in the literature. The literature procedure[19] for the preparation of **33** involved the Grignard reaction of methylmagnesium iodide with methylprop-2-en-1-al (**32**) in 65% yield. The former procedure developed in this laboratory for **33** was found to be straightforward and superior with respect to cost and overall yield. Subsequently the alcohol (**33**) was converted into the bromide (**34**) in 60% yield by treatment with PBr_3 and pyridine in ether at -33°C. The boiling point and PMR spectral data of **34** coincided with the authentic sample[20].

The bromide (**34**) was then condensed with the aldehyde (**15**) in the presence of the activated zinc dust and catalytic amount of iodine at room temperature, the resulting product obtained in 75% yield was assigned the structure **35** as its PMR spectrum revealed two doublets for diasteriomers at 1.0 and 1.10 ppm for the C-3' methyl group. A singlet for methyl at C-2 was observed at 1.35 ppm whereas two

SCHEME - VII


COOEt
NaOEt
MeI
COOEt
NaH–LAH
HO
MeI
Mg
OHC
30
31
33
32
PBr3– Pyr.
Br
34
CHO
+
Br
Zn
OH
SeO2
tBuOOH
OH
HO
15
34
35
29
SeO2
tBuOOH
R1
R2
O
O
R1 =
R2 = Me
36
CH2

set of multiplets corresponding to methylene on C-1' and methine (H-3') protons were recorded in the region of 1.6 - 2.3 ppm. A D_2O exchangeable singlet for the hydroxyl group revealed at 3.15 ppm whereas a singlet for methylene protons of the ketal functionality at 3.95 ppm. Resonances due to exomethylene protons appeared around 4.8 ppm. Based on these values of the PMR spectrum the structure was confirmed as **35.**

The next step involved the oxidation of the allylic methyl of **35** in the presence of SeO_2-t-BuOOH in methylenechloride at room temperature (Sharpless condition). The product isolated from the reaction was undoubtedly not the required compound **29,** however, the structure suggested for this compound was α-methylene-γ-butyrolactone derivative (**36**). The PMR spectrum was consistent with this structure. For example, a methyl at C-3 showed a doublet at 1.31 ppm while a singlet due to methyl on C-2' was observed at 1.38 ppm. The methylene (on C-1) and methine (H-3) protons appeared as a multiplet around 1.9 ppm. Moreover singlet for the ethylene ketal and a multiplet for H-2 were observed around 4.0 ppm, whereas two set of multiplets for exomethylene protons were located at 4.9 and 5.05 ppm. The IR spectrum of **36** showed the absorption at 1770 cm^{-1} which clearly indicated that γ-lactone moiety was present. The mass spectrum of **36** revealed a peak at m/z 198 to $M^+ - CH_3$.

The formation of the lactone **36** may be attributed to the overoxidation of the initially formed aldehyde intermediate which underwent cyclisation with the available hydroxyl to give the lactol. The lactol then gets oxidised to the corresponding γ-lactone under the reaction conditions. Although, this reaction sequence did not

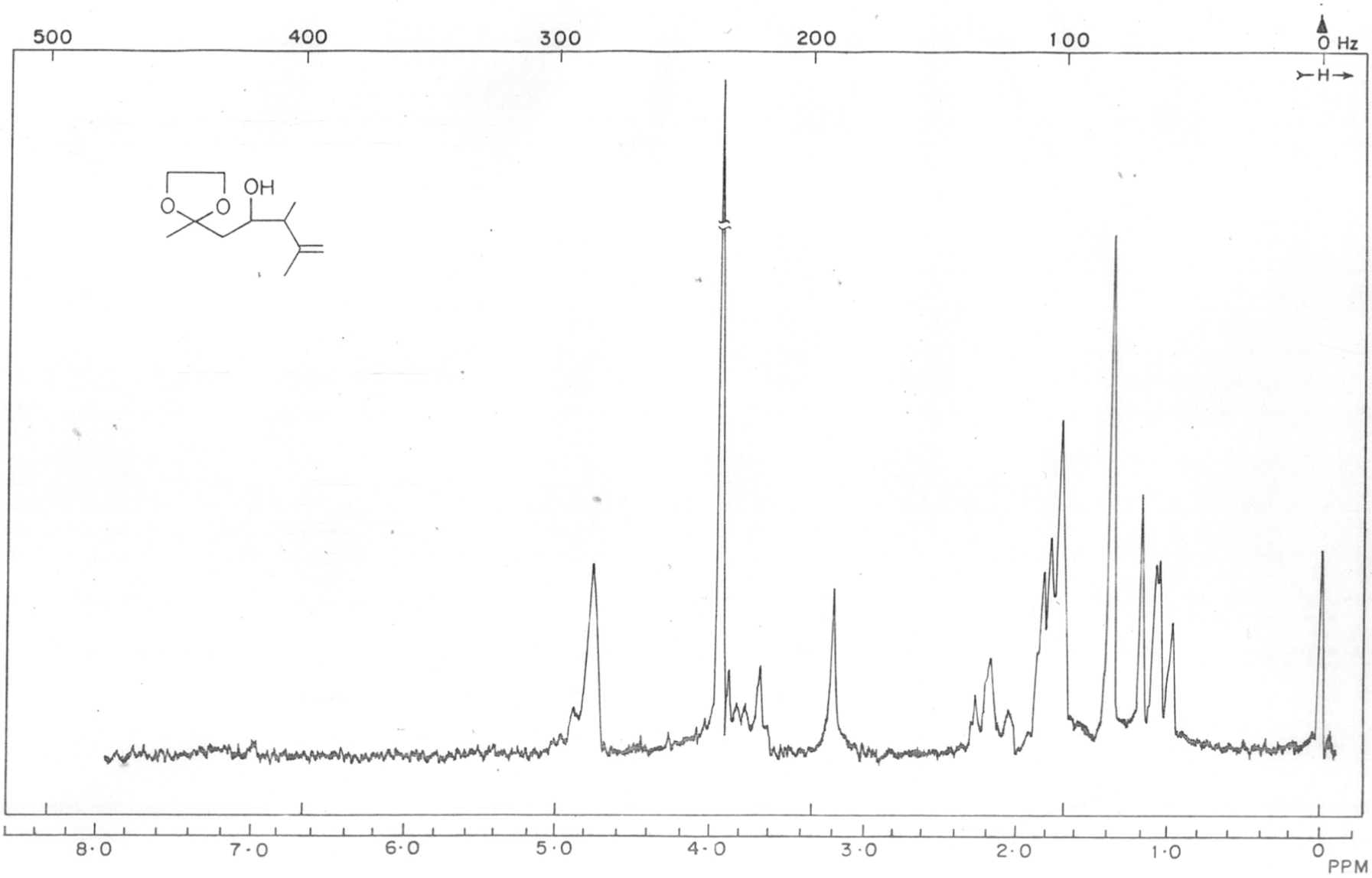


FIG. 14: PMR SPECTRUM OF COMPOUND (35) IN $CDCl_3$

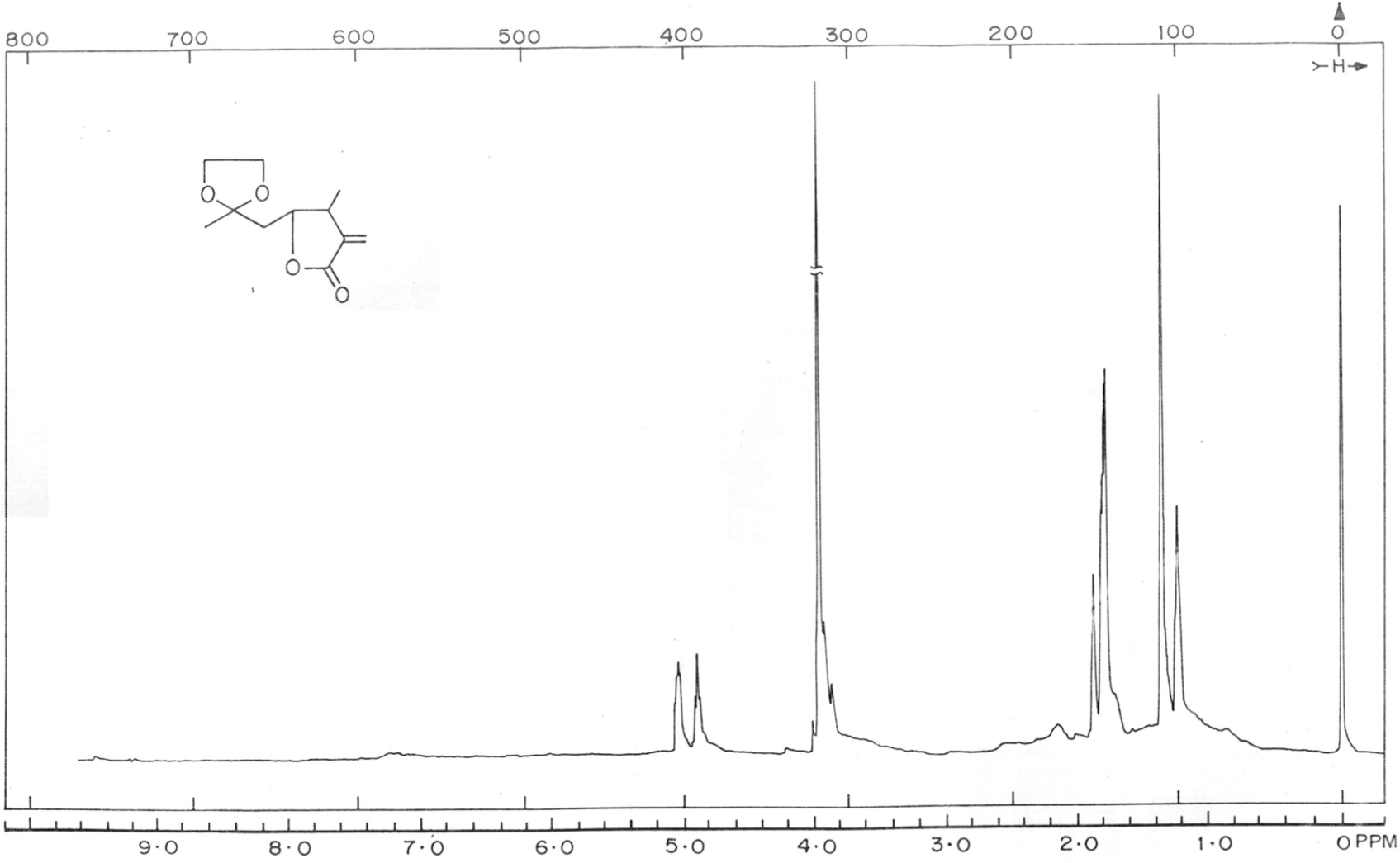


FIG. 15 : PMR SPECTRUM OF COMPOUND (36) IN $CDCl_3$

afford the required diol system (**29**) which would be suitable for the formation of C-ring of sesbanimide, nevertheless this methodology constituted a new procedure for the formation of α-methylene-γ-butyrolactone. It is indeed possible to synthesise number of differently substituted γ-butyrolactones by changing substituents (R_1 and R_2) of the starting materials. The utility[21] of α-methylenebutyrolactones inheriting various biological activities is well known in natural product chemistry.

It is pertinent to mention here that one can convert α-methylene-butyrolactone (**36**) to the corresponding diol system (**29**) by reduction with DIBAL or LAH which in turn could be used for the construction of C-ring as demonstrated earlier. Work in this regard is being pursued in this laboratory.

The project on the total synthesis of sesbanimide was conceived in this group in late 1983. A project of this nature was first felt to be a formidable task and that it would not come to a successful end with various odds and one may have to visualise in an Indian laboratory with day today problems. Due to careful planning and pursuation at each stage against various odds the synthesis of rings A,B and C were accomplished, paricularly worthworthy was a new developed methodology for the substituted lactol ring. What therefore remains to be achieved is the coupling of the ring AB with C. At this juncture it was realised that the total synthesis of sesbanimide involves long planning and can be achieved only by a relay team. Thus the investigator, being first to start this work, has done his job to the extent possible and passed on to the next person to complete his task. This thesis, therefore, constitutes an account of the path traversed by the first runner of the game.

EXPERIMENTAL

Bicyclo[2.2.1]hept-5-ene-2-formyl-3-methyl (7)

Cyclopentadiene (**5**) (104 g, 0.64 mole) (prepared from dicyclopentadiene by heating it at 160°C) was directly collected into the stirred solution of crotonaldehyde (**6**) (100 g,0.7 mole) at 0°C. After complete addition the reaction mixture was heated at 95-100°C. After 6 h, the unreacted crotonaldehyde was distilled under reduced pressure at about 60°C. The residue was fractionally distilled under vacuum to get the desired product **7** (110 g, 51.4%), b.p.[1] 67-70°C/12 mm

2-methyl-3,3-bis(hydroxymethyl)-bicyclo[2.2.1]hept-5-ene (8)

A mixture of 40% aqueous formaldehyde solution (120 g) in ethanol (222 ml), compound **7** (80 g) and 1,4-diaminobenzene (50 mg) was slowly added to the 50% aqueous sodiumhydroxide solution (56 g) at 10°C during about 30 min. After complete addition the reaction mixture was heated at 50-60°C for 1 h. Then it was cooled, and acidified with hydrochloric acid. Ethanol was removed under reduced pressure. Oily layer was separated from the aqueous layer. Aqueous layer was extracted with chloroform. Combined organic layer was dried over anhydrous sodium sulfate and evaporated. The crude product was distilled under reduced pressure to get compound **8** b.p. 135-40°C/3 mm. It was crystallised from pet. ether. Yield 74 g (75.5%) m.p.[2] 69-71°C.

1-Hydroxy-2-hydroxymethylbut-2-ene (4)

The solution of compound **8** (100 g) in benzene (500 ml) was passed under nitrogen flow over the silica column packed with porcelein beads at 520°C at the rate of 1 ml/min. The vapours of the product were allowed to pass through a condenser at the bottom of the column

and collected as a liquid in the receiving flask kept in an ice bath. After completion of pyrolysis, benzene was removed. Crude product was dissolved in water (50 ml). The water layer was extracted with pet.ether (4 x 50 ml) to remove the dicyclopentadiene. The water was evaporated under reduced pressure. The crude product was distilled to get the compound **4** (50 g, 83%) b.p. 110-13°C/2-3 mm. PMR ($CDCl_3$): δ 1.87 (d, 3H, J = 6 Hz, $CHC\underline{H}_3$), 3.97 (s, 2H, OH, exchangeable with D_2O), 4.2 (s, 2H, $C\underline{H}_2OH$), 4.33 (s, 2H, $C\underline{H}_2OH$), 5.7 (q, 1H, J = 6 Hz, $C\underline{H}CH_3$).

Analysis: Calculated for $C_5H_{10}O_2$: C, 58.80; H, 9.87. Found: C, 59.01; H, 9.78%.

1-Bromo-2-bromomethylbut-2-ene

The solution of diol (**4**) (1 g), toluene (5 ml), 48% aqueous hydrobromic acid (2 ml) was refluxed. After 2 h, the reaction mixture was diluted with water. Toluene layer was washed with sodiumbicarbonate solution, water, dried over anhydrous sodium sulfate and evaporated to yield the dibromo compound (1.9 g, 83.3%). PMR ($CDCl_3$): δ 1.73 (d, 3H, J = 7 Hz, $CHC\underline{H}_3$), 4.03 (s, 2H, $C\underline{H}_2Br$), 4.07 (s, 2H, $-C\underline{H}_2Br$), 5.73 (q, 1H, J = 7 Hz, $C\underline{H}CH_3$).

5-exomethylmethylene-2-phenyl 1,3-dioxane (9)

To the stirred solution of diol (**4**) (10.2 g, 0.1 mole), toluene-p-sulfonic acid (5 mg) in dry acetonitrile (25 ml) under nitrogen atmosphere was added α,α-dimethoxytoluene (16 g, 0.11 mole) at room temperature. After 24 h, solid sodium bicarbonate (2 g) was added to the stirred reaction mixture. After 2 h, the reaction mixture was filtered and concentrated to get the crude product. It was dissolved in chloroform and washed with 5% sodiumbisulfite solution, water, dried over anhydrous sodiumsulfate and evaporated to yield the desired compound **9** (17 g,

89.5%). PMR (CCl_4): δ 1.53 (d, 3H, J = 7 Hz, $CHC\underline{H}_3$), 4.27 (s, 2H, $OC\underline{H}_2$), 4.4 (dd, 2H, J_1 = 12 Hz, J_2 = 36 Hz, $OC\underline{H}_2$-), 5.27 (q, 1H, J = 7 Hz, $C\underline{H}CH_3$), 5.43 (s, 1H, -$C\underline{H}$Ph), 7.27 (m, 5H, aromatic).

Analysis: Calculated for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.82; H, 7.45%.

1-Benzyloxy-2-hydroxymethylbut-2-ene (10)

To a suspension of aluminium chloride (26.6 g, 0.2 mole) in dry ether (50 ml) at 0°C was added slowly LAH (1.9 g, 0.05 mole). After 0.5 h, the compound **9** (19.0 g, 0.1 mole) in dry ether (25 ml) was introduced. The reaction mixture was stirred at 0°C. After 5 h it was carefully decomposed with 20% aqueous sodium hydroxide solution. Aqueous layer was extracted repeatedly with ether. Ether layer was dried over anhydrous sodium sulfate and concentrated to give the desired compound **10** (17.09 g, 89%). PMR ($CDCl_3$): δ 1.6, 1.67 (2d, 3H, J = 7 Hz, $CHC\underline{H}_3$), 2.8 (bs, 1H, OH, exchangeable with D_2O), 3.93 (m, 4H, -$C\underline{H}_2O$-), 4.4 (s, 2H, $OC\underline{H}_2$Ph), 5.5 (q, 1H, J = 7 Hz, $C\underline{H}CH_3$), 7.17 (s, 5H, aromatic).

Analysis: Calculated for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.89; H, 8.44%.

1-Benzyloxy-2-chloromethylbut-2-ene (11)

To the stirred solution of alcohol (**10**) (1.92 g, 0.01 mole), triethylamine (4.3 ml, 0.03 mole) in dry methylenechloride (10 ml) at 0°C, methanesulfonylchloride (1.2 ml, 0.015 mole) was added dropwise. The reaction mixture was then stirred at room temperature. After 24 h, it was diluted with water and extracted with methylenechloride. Organic layer was washed with water, 1% hydrochloric acid, water,

brine, dried over anhydrous sodium sulfate and evaporated to give the crude compound (**11**) which was distilled at 160°C/5 mm to give the chloride (**11**) (2 g, 94%). PMR (CCl_4): δ 1.53, 1.63 (2d, 3H, J = 6 Hz, $CHC\underline{H}_3$), 3.73 (m, 4H, $C\underline{H}_2O$), 4.1 (bs,2H, $OC\underline{H}_2Ph$), 5.23 (bq, 1H, $C\underline{H}CH_3$), 6.67 (s, 5H,aromatic). Mass: 210 (M^+).

Analysis: Calculated for $C_{12}H_{15}ClO$: C, 68.57; H, 7.11; Cl, 16.82. Found: C, 68.80; H, 7.16; Cl, 16.66%.

1-Benzyloxy-2-bromomethylbut-2-ene (12)

To the stirred solution of compound **10** (1.92 g, 0.01 mole), pyridine (0.8 ml,0.01 mole) in dry ether (10 ml) at 0°C, PBr_3 (0.5 ml, 0.0053 mole) was added dropwise. The reaction mixture was stirred at 0°C. After 3 h, the reaction mixture was diluted with water and extracted with ether. Ether layer was washed with 1% hydrochloric acid, water, brine, dried over anhydrous sodium sulfate and evaporated. The crude product was distilled under reduced pressure to give the bromide (**12**) (2.3 g, 90.2%), b.p. 140°C/5 mm. PMR (CCl_4): δ 1.65, 1.7 (2d, 3H, J = 6 Hz,$CHC\underline{H}_3$), 3.9 (m, 4H, $C\underline{H}_2O$), 4.3, 4.33 (2s,2H, $OC\underline{H}_2Ph$), 5.5(m, 1H, $C\underline{H}CH_3$), 7.0 (s, 5H, aromatic).

Analysis: Calculated for $C_{12}H_{15}BrO$: C, 56.47; H, 5.88; Br, 31.37. Found:C, 56.21; H, 5.95; Br, 31.13%.

Ethyl 2-(2-methyl-2-dioxolanyl) acetate

A mixture of 130 g (1 mole) of freshly distilled ethylaceto-acetate, 124 g (2 mole) of ethyleneglycol and 2 g of toluene-p-sulfonic acid in 400 ml benzene was heated under reflux in an oil bath for 8 h. A Dean Stark trap was used to remove water generated during the reaction. When the reaction was complete the mixture was washed

once with 5% aqueous sodiumbicarbonate solution and dried over anhydrous sodium sulfate. The liquid residue after removal of solvent was distilled, b.p. 110°C/20 mm to give the title compound (150 g, 86%). PMR (CCl_4):δ 1.32 (t, 3H, J = 7Hz, $CH_2\underline{CH_3}$), 1.45 (s, 3H, -$\underline{CH_3}$), 2.62 (s, 2H, $\underline{CH_2}CO$), 3.95 (s,4H, $O\underline{CH_2}\underline{CH_2}O$), 4.15 (q, 2H, J = 7 Hz, $\underline{CH_2}CH_3$).

2-(2-methyl-2-dioxolanyl) ethanal (15)

In a 1 lit. three-necked round bottom flask with three way stopcock, mechanical stirrer and an addition funnel was placed ethyl 2-(2-methyl-2-dioxolanyl) acetate (25 g, 0.14 mole) in 150 ml dry methylene chloride. It was cooled to -78°C (acetone-liquid nitrogen). Dibal (25 g 0.175 mole, 125 ml 20% solution in hexane) was introduced into addition funnel by a syringe and it was added to reaction mixture slowly in about 15 min. Then it was stirred at the same temperature for 1.25h. The reaction mixture was poured into 250 ml distilled water under vigorous stirring. The solvent was separated and evaporated to give about 15 g of crude product. It was purified by distillation (b.p. 70-75°C/16 mm) to get 8 g pure aldehyde. PMR (CCl_4): δ 1.40 (s, 3H, -$\underline{CH_3}$), 2.67 (d, 2H, J = 3 Hz, $-CH_2-$), 4.0 (s, 4H,-O-$\underline{CH_2}\underline{CH_2}$O),9.75 (t, 1H, J = 3 Hz, $C\underline{H}O$).

2-methyl-2-[4'-benzyloxymethyl-2'-hydroxy-3'-methylpent-4'-enyl]1,3-dioxalane (16)

To the stirred solution of aldehyde (15) (1.30 g, 0.01 mole), activated zinc dust (0.82 g,0.012 mole), iodine (5 mg) in dry THF (4 ml) under nitrogen atmosphere was slowly added the bromide (12) (2.81 g, 0.011 mole) in dry THF (4 ml) at room temperature. The reaction mixture was stirred at room temperature for 15 h. Then it was diluted

with saturated ammonium chloride solution and extracted with methylene chloride. Methylene chloride layer was washed with water, dried over anhydrous sodium sulfate and evaporated to give **16** (2.6 g, 85%). PMR ($CDCl_3$): δ 1.06, 1.13 (2d, 3H, J = 6.3 Hz, $CHC\underline{H}_3$, diasteriomers), 1.31 (s, 3H, $-\overset{|}{\underset{|}{C}}-C\underline{H}_3$), 1.63 - 2.63 (m, 3H, $C\underline{H}CH_3$, $-C\underline{H}_2CHOH$), 3.25 (s, 1H, -OH, exchangeable with D_2O), 3.80 (m, 1H, $C\underline{H}OH$), 3.94 (s, 4H, $OC\underline{H}_2C\underline{H}_2O$), 4.0 (s, 2H, $-OC\underline{H}_2\overset{|}{C}=$), 4.5 (s,2H, $OC\underline{H}_2Ph$), 5.06 (m, 2H, $=\!\!<^{H}_{H}$), 7.31 (s, 5H, aromatic).

Analysis: Calculated for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.48; H, 8.59%.

5-exomethylmethylene-3,4-dimethoxyphenyl-1,3-dioxane (17)

To the stirred solution of diol (**4**) (10.2 g, 0.1 mole), toluene-p-sulfonic acid (5 mg) in dry acetonitrile (25 ml) under nitrogen atmosphere was added 3,4-dimethoxybenzaldehyde dimethylacetal (23.3 g, 0.11 mole) at room temperature. After 24 h, solid sodiumbicarbonate (2 g) was added to the stirred reaction mixture. After 2 h, the reaction mixture was filtered and concentrated to get the crude product. It was then dissolved in chloroform and washed twice with 5% sodiumbisulfite solution, water, dried over anhydrous sodiumsulfate and evaporated to yield the desired product (**17**) (23 g, 92%). PMR (CCl_4):δ1.6 (d, 3H, J = 7 Hz, $CHC\underline{H}_3$), 3.7 (s, 6H, 2x $OC\underline{H}_3$), 4.27 (s,2H, $-C\underline{H}_2O$),4.46 (dd, 2H, J_1 = 12 Hz, J_2 = 34 Hz, $C\underline{H}_2O$), 5.27 (m, 1H, $C\underline{H}CH_3$), 5.33 (s, 2H, $C\underline{H}Ar$), 6.76 (m,3H, aromatic).

1-(3,4-dimethoxybenzyloxy)-2-hydroxymethylbut-2-ene (18)

To a suspension of aluminium chloride (26.6 g, 0.2 mole) in dry ether (50 ml) at 0°C was added slowly LAH (1.9 g, 0.05 mole).

After 0.5 h,the compound **17**(25 g, 0.1 mole) in dry ether (50 ml) was introduced. The reaction mixture was stirred at 0°C. After 1.5 h, it was carefully decomposed with 20% aqueous sodiumhydroxide solution. Aqueous layer was extracted repeatedly with ether. Ether layer was dried over anhydrous sodium sulfate and evaporated to give the compound **18** (21.2 g, 84%). PMR ($CDCl_3$): δ 1.6, 1.63 (2d, 3H, J = 7 Hz, $CHC\underline{H}_3$), 3.73 (s, 6H, 2X $OC\underline{H}_3$), 3.8 - 4.5 (m, 4H, $=\overset{1}{C}\text{-}C\underline{H}_2O$), 4.33 (s,2H, $OC\underline{H}_2Ar$), 5.53(m, lH, $C\underline{H}CH_3$), 6.67, 6.73 (2s, 3H, aromatic).

Analysis: Calculated for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.45; H, 7.87%.

l-(3,4-dimethoxybenzyloxy)-2-bromomethylbut-2-ene (19)

To the stirred solution of compound **18** (2.52 g, 0.01 mole), pyridine (0.8 ml, 0.01 mole) in dry ether (10 ml) at 0°C, PBr_3 (0.5 ml, 0.0053 mole) was added dropwise. The reaction mixture was stirred at 0°C. After 3 h, the reaction mixture was diluted with water, extracted with ether. Ether layer was washed with water, brine, dried over anhydrous sodium sulfate and evaporated to give the bromide **(19)** (2.6 g, 82.5%). PMR (CCl_4): δ 1.53, 1.7 (2d, 3H, J = 7 Hz, $CHC\underline{H}_3$), 3.73 (s, 6H, 2X $OC\underline{H}_3$), 3.9, 3.95, 4.05, 4.26, 4.33 (5s, 6H, 2X $OC\underline{H}_2$-), 5.66 (m,lH, $C\underline{H}CH_3$), 6.6, 6.68 (2s, 3H, aromatic).

Analysis: Calculated for $C_{14}H_{19}BrO_3$: C, 53.33; H, 6.03; Br,25.40 Found: C, 53.52; H, 6.14; Br, 24.97%.

2-methyl-2-[4'-(3",4"-dimethoxybenzyloxymethyl)-2'-hydroxy-3'-methyl pent-4'-enyl] l,3-dioxalane (20)

To the stirred solution of aldehyde **(15)**(1.30 g, 0.01 mole), activated zinc dust (0.82 g, 0.012 mole), iodine (5 mg) in dry THF (4 ml) under nitrogen atmosphere was slowly added bromide **(19)** (3.46 g,

0.011 mole) in dry THF (4 ml) at room temperature. The reaction mixture was stirred at room temperature for 12 h. Then it was diluted with saturated ammonium chloride solution and extracted with methylene chloride. Methylene chloride layer was washed with water, dried over anhydrous sodium sulfate and evaporated to give **20** (2.7 g, 75%). PMR ($CDCl_3$): δ 1.06, 1.13 (2d, 3H, J = 6.3 Hz, $CHC\underline{H}_3$ diasteriomers), 1.31 (s, 3H, $-\underset{|}{\overset{|}{C}}-C\underline{H}_3$), 1.56 -2.38 (m, 3H, $C\underline{H}CH_3$, $C\underline{H}_2CHOH$), 3.44 (bs, 1H, OH, exchangeable with D_2O), 3.75 - 4.06 (m, 12H, 2X $OC\underline{H}_3$, $-OCH_2CH_2O-$, $C\underline{H}_2C=$), 4.44 (s, 2H, $OC\underline{H}_2Ar$), 4.89 - 5.19 (m, 2H, $=\!\!<^{H}_{H}$), 6.25 - 6.44 (m, 3H, aromatic).

Analysis: Calculated for $C_{20}H_{30}O_6$: C, 65.55; H, 8.25. Found: C, 65.48; H, 8.32%.

2-methyl-2-[4'-(3",4"-dimethoxybenzyloxymethyl)-3'-methyl-2'-oxopent-4'-enyl] 1,3-dioxalane (21)

To the stirred solution of alcohol (**20**) (2 g, 5.5 m.mole), anhydrous sodium acetate (100 mg) in dry methylene chloride (20 ml), pyridinium chlorochromate (PCC) (1.76 g, 8.2 m.mole) was slowly added. After stirring at room temperature for 15 h, the reaction mixture was diluted with water and extracted with methylene chloride. Methylene chloride layer was washed with water, dried over anhydrous sodium sulfate and evaporated to give the crude product which was purified by column chromatography over silica gel (10% ethyl acetate in pet.ether) to get the ketone (**21**) (1.3 g, 67%). PMR ($CDCl_3$): δ 1.18 (d, 3H, J = 6.3 Hz, $CHC\underline{H}_3$), 1.38 (s, 3H, $-\underset{|}{\overset{|}{C}}-C\underline{H}_3$), 2.81 (dd, 2H, J_1 = 14.2 Hz, J_2 = 25.2 Hz, $C\underline{H}_2CO$), 3.44 (q, 1H, J = 6.3 Hz, $C\underline{H}CH_3$), 3.75 - 4.06 (m, 12H, 2X $OC\underline{H}_3$, $OC\underline{H}_2C\underline{H}_2O$, $C\underline{H}_2C=$), 4.44 (s, 2H, $OC\underline{H}_2Ar$), 5.0 - 5.30

(m, 2H, $=\!\!<^{H}_{H}$), 6.75 - 6.9 (m, 3H, aromatic).

Analysis: Calculated for $C_{20}H_{28}O_6$: C, 65.91; H, 7.74. Found: C, 65.99; H, 7.67%.

2-Hydroxymethyl-1-t-butyldimethylsilyloxybut-2-ene (23)

To the cooled solution (0°C) of diol (**4**) (10.2 g, 0.1 mole), imidazole (13.6 g, 0.2 mole) in dry THF (50 ml) under stirring in nitrogen atmosphere was dropwise added t-butyldimethylchlorosilane (15.0 g, 0.1 mole) in dry THF (15 ml). Reaction mixture was then allowed to come to room temperature. After 10 h, the reaction mixture was diluted with water and extracted with methylene chloride. Methylene chloride layer was washed with water, dried over anhydrous sodium sulfate and evaporated to give the crude product as a mixture of mono and disilyl compounds which was purified by column chromatography over silica gel (10% ethylacetate in pet.ether) to yield the desired compound **23** (12.6 g, 58%). PMR ($CDCl_3$):δ 0.0 (s,3H, $Si(C\underline{H}_3)_2$), 0.8 (s, 9H, $-SiC(C\underline{H}_3)_3$), 1.57, 1.60 (2d, 3H, J = 7 Hz, $CHC\underline{H}_3$), 2.5 (bs, 1H, -OH, exchangeable with D_2O), 4.1 (m, 4H, $2X{=}CHC\underline{H}_2$), 5.47 (bq, 1H, J = 7 Hz, $C\underline{H}CH_3$).

2-Chloromethyl-1-t-butyldimethylsilyloxybut-2-ene (24)

The solution of alcohol (**23**) (868 mg, 4 m.mole), tosylchloride (912 mg, 4.8 m.mole), dimethylaminopyridine (536 mg,4.4 m.mole) in dry methylene chloride (5 ml) was stirred at 30°C for 15 h. After completion of reaction the solid sodiumbicarbonate was added to the reaction mixture. After stirring for 0.5 h, it was filtered. Methylene-chloride was evaporated. The crude product was purified by column chromatography over silica gel (5% ethylacetate in pet. ether) to give the chloro-compound (**24**) (700 mg, 75%). PMR ($CDCl_3$): 0.0 (s, 6H,

$Si(C\underline{H}_3)_2$), 0.7 (s, 9H, -Si-C($C\underline{H}_3$)$_3$), 1.37 (m, 3H, CHC$\underline{H}_3$), 3.43 (m, 4H, =C-C$\underline{H}_2$-),4.7 (bq, 1H, C$\underline{H}$CH$_3$).

2-Methyl-2-[4'-t-butyldimethylsilyloxymethyl-2'-hydroxy-3'-methylpent-4'-enyl] 1,3-dioxalane (25)

To the solution of the aldehyde (**15**) (325 mg, 2.5 m.mole), activated zinc dust (187 mg, 2.75 m.mole), iodine (10 mg) and dry THF (5 ml) under stirring and in nitrogen atmosphere was added the solution of chlorocompound (**24**) (642 mg, 2.74 m.mole) in dry THF (1 ml). The reaction mixture was stirred for 10 h. Then it was diluted with saturated ammonium chloride solution and extracted with methylene chloride. Methylene chloride layer was washed with water, dried over anhydrous sodium sulfate and evaporated to give the crude product which was purified by column chromatography over silica gel (10% ethylacetate in pet.ether) to get compound **25** (125 mg, 15%). PMR ($CDCl_3$): δ 0.0 (s,6H, -Si($C\underline{H}_3$)$_2$), 0.86 (s, 9H, -SiC($C\underline{H}_3$)$_3$), 1.0 (d, 3H, J = 7 Hz, CHC$\underline{H}_3$), 1.27 (s,3H, -C-C$\underline{H}_3$), 1.7 (m, 2H, C$\underline{H}_2$CHOH),2.0 (m, 1H, C$\underline{H}$CH$_3$),3.0 (bs,1H, OH, exchangeable with D_2O),3.57 (m, 1H, C$\underline{H}$OH), 3.9 (s, 4H, OC$\underline{H}_2$C$\underline{H}_2$O), 4.0 (m, 2H, C$\underline{H}_2$OSi), 4.87 (m, 2H, =C$\underline{H}_2$).

2-Methyl-2-[4'-t-butyldimethylsilyloxymethyl-3'-methyl-2'-oxopent-4'-enyl] 1,3-dioxalane (26)

To the stirred solution of compound **25** (3.30 g, 0.01 mole), anhydrous sodium acetatae (100 mg) in methylenechloride (25 ml), pyridinium chlorochromate (PCC) (3.25 g,0.015 mole) was slowly added. After stirring at room temperature for 15 h, the reaction mixture was diluted with water and extracted wih methylenechloride. Methylene chloride layer was washed with water, dried over anhydrous sodium sulfate and evaporated. The crude product was purified by column chromatography over silica gel to afford the ketone (**26**) (2.5 g,75%).

PMR ($CDCl_3$): δ 0.0 (s, 6H, $Si(C\underline{H}_3)_2$), 0.8 (s, 9H, $-SiC(C\underline{H}_3)_3$), 1.06 (d, 3H, J = 6.3 Hz, $CHC\underline{H}_3$), 1.38 (s, 3H, $C-C\underline{H}_3$), 2.69 (dd, 2H, J_1 = 14.18 Hz, J_2 = 23.6 Hz, $C\underline{H}_2CO$), 3.25 (m, 1H, $C\underline{H}CH_3$), 3.88 (s, 4H, $OC\underline{H}_2C\underline{H}_2O$),4.0 (bs, 2H, $C\underline{H}_2OSi$), 4.94 (m, 2H, $=\!\!<^{H}_{H}$).

2-Hydroxy-2-[2'-methyl-2'-dioxalanylmethyl]-3-methyl-4-methylene terahydrofuran (27a)

2-methyl-2-[4'-hydroxymethyl-3'-methyl 2'-oxopent-4'-enyl] 1,3-dioxalane (27b)

To the stirred solution of ketone (**26**) (1.25 g, 3.8 m.mole) in dry THF (5 ml) at 0°C was added 1M solution of tetrabutylammonium fluoride (7.65 ml, 7.6 m.mole). After 2 h, at 0°C the reaction mixture was diluted with water and extracted with ether. Ether layer was washed with water, dried over anhydrous sodiumsulfate and evaporated. The crude product was purified by column chromatography over neutral alumina column (20% ethylacetate in pet.ether) to afford the desired compound **27** (650 mg, 80%). PMR ($CDCl_3$): δ 1.02, 1.06, 1.18 (3d, 3H, $CHC\underline{H}_3$, mixture of diasteriomers + open form), 1.46, 1.50, 1.53 (3s, 3H, $-C(CH_3)-C\underline{H}_3$,2-diasteriomers + open form), 2.38 (m,1H, $C\underline{H}CH_3$ closed form), 2.81 (s, $C\underline{H}_2CHOH$ open form), 3.56 (m, $C\underline{H}CH_3$, open form), 3.94, 4.0 (2s, 4H, $-OC\underline{H}_2C\underline{H}_2O-$ each for closed and open form), 4.56 (dd, 2H, $OC\underline{H}_2C=$ closed form), 4.88 (m, 2H, $=\!\!<^{H}_{H}$ closed form),5.19 (d, $=\!\!<^{H}_{H}$ open form). Mass: 214 (M^+).

Analysis: Calculated for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.71; H, 8.43%.

2-methyl-2-[2'-hydroxy-4'-hydroxymethyl-3'-methylpent-4'-enyl] 1,3-dioxalane (29)

To the stirred and cooled (-76°C) solution of liquid ammonia

(200 ml) was added lithium metal (125 mg, 5 g.atom). After stirring for 30 minutes at -76°C the compound **(27)** (1.1 g, 3.6 m.mole) in dry THF (1 ml) was added to the reaction mixture. After 2 h, at -76°C the reaction mixture was quenched by adding solid ammonium chloride. The ammonia was evaporated. The residue was extracted with hot chloroform. Chloroform layer was dried over anhydrous sodium sulfate and evaporated to give the diol **(29)** (700 mg, 90%). PMR ($CDCl_3$): δ1.06, 1.09 (2d, 3H, J = 6.3 Hz, $CHC\underline{H}_3$, diasteriomers), 1.3 (s, 3H, $-\overset{\overset{O}{\|}}{\underset{|}{C}}-C\underline{H}_3$), 1.69 - 2.69 (m, 3H, $C\underline{H}CH_3$, $C\underline{H}_2CHOH$), 3.56 (s, 2H, -OH, exchangeable with D_2O),3.94 (s, 4H, $-OC\underline{H}_2C\underline{H}_2O-$), 3.88 (m, 1H, $C\underline{H}OH$), 4.06 (s, 2H, $OC\underline{H}_2\overset{|}{C}=$), 5.0 (m, 2H, $=\!\!<^{H}_{H}$).

Analysis: Calculated for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.20; H, 9.24%.

2-methyl-2-[4'-t-butyldimethylsilyloxymethyl-2'-hydroxy-3'-methylpent-4-enyl] 1,3-dioxalane (25)

To the stirred solution of the diol **(29)** (2.16 g, 0.01 mole), imidazole (1.36 g, 0.02 mole) in dry THF (5 ml) under nitrogen atmosphere was added t-butyldimethylchlorosilane (1.7 g, 0.011 mole). The solution was stirred at room temperature. After 10 h, it was diluted with water and extracted with methylene chloride. Methylene chloride layer was washed with water, dried over anhydrous sodiumsulfate and evaporated to give **25** (3.30 g, quantitative). PMR ($CDCl_3$): δ 0.0 (s, 6H, $Si(C\underline{H}_3)_2$), 0.86 (s, 9H, $-Si-C(C\underline{H}_3)_3$), 1.0 (d, 3H, J = 7 Hz, $CHC\underline{H}_3$), 1.27 (s, 3H, $-\overset{|}{\underset{|}{C}}-C\underline{H}_3$), 1.7 (m, 2H, $C\underline{H}_2CHOH$), 2.0 (m, 1H, $C\underline{H}CH_3$), 3.0(bs, 1H, -OH, exchangeable with D_2O); 3.57 (m, 1H,$C\underline{H}OH$), 3.9 (s, 4H, $-OC\underline{H}_2C\underline{H}_2O-$), 4.0 (m, 2H, $C\underline{H}_2O\overset{|}{\underset{|}{Si}}+$), 4.87 (m, 2H,$=\!\!<^{H}_{H}$).

EXPERIMENTAL

Ethyl 2-methyl-3-oxobutanoate (31)

In 1 lit. three-necked round bottom flask, equipped with a stirrer and reflux condenser was placed ethanol (250 ml). Sodium (10.6 g, 0.46 mole) was slowly added and the solution was refluxed till all sodium dissolved. Then ethylacetoacetate (60 g, 0.46 mole) was slowly added. After refluxing 1 h, the reaction mixture was cooled to 0°C and methyliodide (29 ml, 0.46 mole) was slowly added. After stirring for 4 h at room temperature, ethanol was evaporated and the reaction mixture was diluted with water and extracted with ether. Ether layer was washed with water, dried over anhydrous sodium sulfate and evaporated. The crude product was distilled to get (56 g, 85%) of ethyl 2-methyl-3-oxobutanoate.

3-Hydroxy-2-methylbut-1-ene (33) from 30

50% Sodium hydride (11.6 g, 0.24 mole) was placed in a three-necked 1 lit. flask equipped with stirrer and reflux condenser. It was washed with dry hexane, then dried under vacuum and dry ether (200 ml) was added in the flask. After cooling it to 0°C, compound **31** (35 g, 0.24 mole) in dry ether (100 ml) was slowly added. The stirring was continued at room temperature. After 2 h the flask was cooled to 0°C and LAH (9.5 g, 0.25 mole) was slowly added in portions during 1 h. Then the reaction mixture was allowed to come to room temperature. After 15 h it was worked up by the slow addition of water at 0°C and the ether layer was separated. The residue was washed with ether. The combined ether layer was dried over anhydrous sodium sulfate and evaporated. The crude product was purified by distillation at 116-17°C to give the desired alcohol **(33)** (14 g, 67%).

3-Hydroxy-2-methylbut-1-ene (33) from 32

To the suspension of magnesium (2.6 g, 0.11 mole) in dry ether (25 ml) was slowly added methyl iodide (15.6 g, 0.11 mole). The solution was stirred at room temperature. After 2 h, compound **32** (7 g, 0.1 mole) in dry ether (10 ml) was slowly introduced in the reaction mixture. After stirring for 5 h the reaction mixture was decomposed by addition of saturated ammonium chloride solution and extracted with ether. Ether layer was dried over anhydrous sodium sulfate and evaporated. The crude product was distilled at 116-17°C to give the desired alcohol (**33**) (6.5 g, 76%).

1-Bromo-2-methylbut-2-ene (34)

To the solution of alcohol (**33**) (8.6 g, 0.1 mole), pyridine (8 ml, 0.1 mole) in dry ether (40 ml) at -30°C was slowly added PBr_3 (3.1 ml, 0.033 mole) in dry ether (15 ml). The reaction was continued for 2 h at -33°C and then the reaction mixture was diluted with water and extracted with ether. Ether layer was washed with water, dried over anhydrous sodium sulfate and evaporated to give the crude product which on distillation gave the desired bromide (**34**) (9.2 g, 62%) $b.p._{270}$ 92-5°C. PMR (CCl_4): δ 1.5 - 2.0 (m, 6H, 2X $C\underline{H}_3$), 3.95 (s, 2H, $C\underline{H}_2Br$), 5.6 (q, 1H, J = 6.0 Hz, $C\underline{H}CH_3$).

Analysis: Calculated for C_5H_9Br: C, 40.26; H, 6.04; Br,53.69. Found:C, 40.21; H, 6.07; Br, 53.83%.

2-Methyl-2-[3'-methyl-4'-methyl-2'-oxopent-4-enyl]1,3-dioxalane (35)

To the stirred solution of aldehyde (**15**) (6.5 g, 0.05 mole), activated zinc dust (3.6 g, 0.054 mole), iodine (100 mg) in dry THF (30 ml) under nitrogen atmosphere was slowly added the bromide (**34**)

(8.2 g, 0.055 mole) in dry THF (10 ml) at room temperature. The reaction mixture was stirred at room temperature for 15 h. Then it was diluted with saturated ammonium chloride solution and extracted with methylene chloride. Methylene chloride layer was washed with water, dried over anhydrous sodium sulfate and evaporated to give the alcohol (**35**) (7.5 g, 75%). PMR ($CDCl_3$):δ 1.0, 1.1 (2d, 3H, J = 7.5 Hz, CH-C$\underline{H}_3$, diasteriomers), 1.35 (s, 3H, -$\underset{|}{\overset{|}{C}}$-C$\underline{H}_3$), 1.45 - 1.9 (m, 2H, -C$\underline{H}_2$-), 2.0 - 2.3 (m, 1H, C$\underline{H}$-$CH_3$), 3.15 (s, 1H, OH, exchangeable with D_2O), 3.6 - 3.8 (m, 1H, C$\underline{H}$OH), 3.95 (s, 4H, OC$\underline{H}_2$ C$\underline{H}_2$O) 4.8 (m, 2H, = $\overset{H}{\underset{H}{}}$).

Analysis: Calculated for $C_{11}H_{20}O_3$: C, 65.97; H,10.07. Found: C, 66.21; H, 9.93%.

2-[2'-methyl-2'-dioxalanylmethyl]-3-methyl-4-methylene-5'-oxotetrahydrofuran (36)

In a 25 ml two-necked round bottom flask was placed selenium dioxide (1.65 g, 0.015 mole), methylene chloride (8 ml) and 90% t-butylhydroperoxide (2 ml, 0.02 mole). The mixture was stirred at room temperature. After 0.5 h, the alcohol (**35**) (2 g, 0.01 mole) in methylene-chloride (2 ml) was slowly added. After stirring for 15 h at room temperature the reaction mixture was diluted with water and extracted with methylene chloride. The methylene chloride layer was washed with water, dried over anhydrous sodium sulfate and evaporated to give the crude product which was purified by column chromatography over silica gel (10% ethylacetate in pet.ether) to give the desired compound **36** (1.3 g, 61%). PMR ($CDCl_3$): δ 1.31 (d, 3H, J = 9.45 Hz, CHC$\underline{H}_3$), 1.38 (s, 3H, -$\underset{|}{\overset{|}{C}}$-C$\underline{H}_3$), 1.69 -1.94 (m, 2H, -$CH_2$-), 2.0 - 2.3 (m, 1H, C$\underline{H}$$CH_3$).

3.75 - 4.06 (m, 5H, $-OC\underline{H}_2C\underline{H}_2O-$, $-C\underline{H}O$), 4.90 (m, 2H, $=\overset{H}{\underset{H}{}}$). IR (liq.film): 1770 cm^{-1} (lactone).

Analysis: Calculated for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.34; H, 7.53%.

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