# Nucleophilic Ring Opening Studies on Benzyl Anhydroribopyranosides

**A Thesis**
**Submitted for the Degree of**

**DOCTOR OF PHILOSOPHY**

**By**

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**March 1996**

To my parents,

P. Anantha Kakrannaya

P. Krishnaveni

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DECLARATION

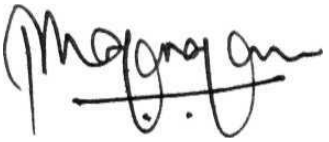
I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad under the supervision of Professor M. Nagarajan.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.

P. K. Vasudeva.

**CERTIFICATE**

This is to certify that the work described in this thesis entitled " **Nucleophilic Ring Opening studies on Benzyl Anhydroribopyranosides** " has been carried out by Mr. P. K. Vasudeva under my supervision and the same has not submitted elsewhere for any degree.



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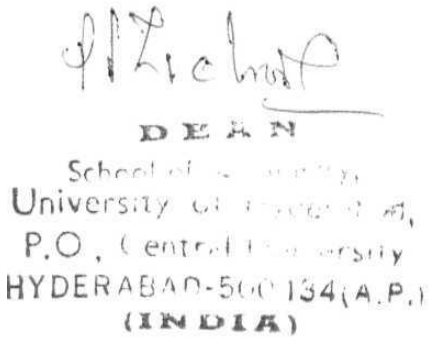

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P. K. Vasudeva.

## ABBREVIATIONS

| | |
|---|---|
| Ac | acetyl |
| Bn | benzyl |
| Bu | butyl |
| Bz | benzoyl |
| COSY | Correlation Spectroscopy |
| DMF | dimethylformamide |
| DMSO | dimethyl sulfoxide |
| Et | ethyl |
| g | gram |
| HMPA | hexamethylphosphoric triamide |
| h | hour(s) |
| LDA | lithium diisopropylamide |
| LAH | lithium aluminum hydride |
| MCPBA | m-chloroperbenzoic acid |
| **Me** | methyl |
| min | minute(s) |
| mmol | millimole(s) |

| | |
|---|---|
| ml | millilitre(s) |
| Ms | methanesulfonyl |
| Nu | nucleophile |
| Ph | phenyl |
| Pr | propyl |
| Py | pyridine |
| rt | room temperature |
| TBDMS | t-butyldimethylsilyl |
| Tf | trifluoromethanesulfonyl |
| THF | tetrahydrofuran |
| TMS | trimethylsilyl |
| Ts | p-toluenesulfonyl |

## ABSTRACT

This thesis deals with the ring opening reactions of benzyl 3,4-anhydro-β-D-ribopyranoside and benzyl 2,3-anhydro-α-D-ribopyranoside. The thesis consists of four sections, namely, introduction, results, discussion and experimental.

The introduction begins with the classification of different sugar epoxides followed by representative examples of ring opening reactions of each class. Reactions of 2,3- and 3,4-anhydrohexopyranosides followed by a detailed survey of alkyl 2,3- and 3,4- anhydroribopyranosides are included to show the versatality of nucleophilic ring opening reactions of epoxides to form simple and rare deoxy sugars. The introduction section concludes with some examples of sugar epoxides as chiral starting materials for the syntheses of biologically active molecules.

Earlier work from our laboratory had shown that benzyl 3,4-anhydro-α-D-ribopyranoside reacted with nucleophiles exclusively at C-3. This result was rationalized based on a repulsive interaction between the entering nucleophile and the electron lone pair on the pyranose oxygen, precluding attack at C-4 and directing it to C-3. To establish the validity of this interpretation, it was thought necessary to study the ring opening reactions of benzyl 3,4-anhydro-β-D-ribopyranoside, wherein the anomeric substituent should now direct opening to C-4 on steric

grounds, overriding the effect of the oxygen lone pair.

Similarly, the nucleophilic ring openings of alkyl 2,3-anhydro-β-D-ribopyranosides have been studied extensively. However, reactions of their a- anomers have not been investigated in detail and that became the objective of our further study. Thus, an examination of the reactions of four possible isomers of alkyl anhydroribopyranosides would be available and this would be expected to provide a better understanding of the various factors that govern nucleophilic ring opening in conformationally mobile sugar epoxides.

Section two presents the results obtained during the course of this research. Benzyl 3,4-anhydro-β-D-ribopyranoside (58) was prepared as reported. Ring opening reactions of 58 with hydride, bromide, iodide, thiophenoxide, azide, methoxide and cyanide were studied with variation of the counter-cation. The regio- and stereochemistry of the ring opened products were established by NMR methods. The results showed that a mixture of products, depending on the type of nucleophile and counter-cation, were obtained due to attack at either epoxide carbon.

Similarly, benzyl 2,3-anhydro-α-D-ribopyranoside (28) was prepared as reported and its nucleophilic ring opening reactions were studied with various nucleophiles. In this case, the results showed a single product irrespective of the nucleophile and its counter-cation, due to attack at C-3. Overall, the a- anomers

showed higher reactivity and selectivity when compared to the corresponding β-anomers.

The results presented above have been rationalized in the third section, discussion. In the case of alkyl anhydropentopyranosides there is a dynamic equilibrium between the two conformers. Therefore, the oxirane ring is susceptible to attack at both places and two products are possible, depending upon which carbon is attacked. The ratio of the two products varies with the structure of the epoxide, the attacking reagent and the reaction conditions. Thus various factors governing the ring opening reactions of anhydropentopyranosides can be conveniently listed as i) electronic factors ii) steric factor and nature of the nucleophile iii) conformational factor and nature of the counter-cation. A detailed discussion of the above factors with examples is included in the discussion section, followed by their application to our systems.

It is clear from our present investigations and earlier reports that the regiochemistry of ring opening of benzyl 2,3-anhydroribopyranosides does not depend upon the anomeric configuration i.e., in both a- and β-anomers ring opening takes place at C-3. In the case of 3,4-anhydroribopyranosides the regiochemistry of the ring opening depends upon the anomeric configuration. Thus, with benzyl 3,4-anhydro-β-D-ribopyranoside the ring opens exclusively at C-3, whereas with benzyl

3,4-anhydro-β-D-ribopyranoside the ring cleaves at both C-3 and C-4 depending upon the nature of the nucleophile and its counter-cation.

In the experimental section, full details of the experimental work performed, are given along with relevent physical and spectroscopic data. The thesis concludes with a bibliography of references pertinet to the work performed.

# Introduction

Carbohydrates have been recognised as naturally occurring organic compounds endowed with a wealth of stereochemical attributes. The thrust of research in this area in recent times has been inspired by biochemical events which have fostered an accelerated effort in synthesis and modification of component sugar units present in oligosaccharides, glycoproteins, proteoglycans, antibiotics and nucleosides.

Carbohydrates are a relatively cheap and replenishable source of chiral carbon compounds, available in a variety of cyclic and acyclic forms, chain lengths and oxidation states. They are endowed with a plethora of functional, stereochemical and conformational features which lend themselves to chemical exploitation. These very features also ensure a measure of regio- and stereocontrol in bond forming reactions that are not easily matched by other classes of organic compounds.

Due to the pioneering efforts of many distinguished carbohydrate chemists, sugars are now recognised as valuable starting materials. Many of the total syntheses of different classes of natural products from sugars have been expertly summarized by Hanessian.[1]

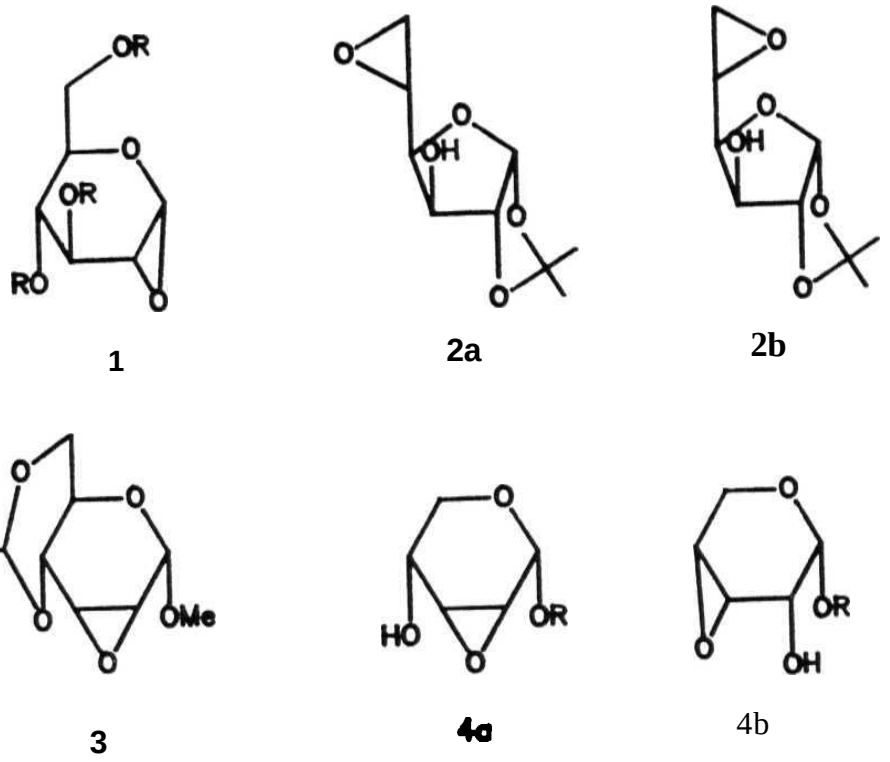
The interest in epoxysugars, as distinct from other anhydro derivatives, lies in this reactive and strained three membered ring. The ring is opened by nucleophilic reagents to give a

product with trans configuration between the hydroxyl group and the substituent group which is derived from the reagent. This reaction has, therefore, provided a versatile method for the preparation of rare sugars from easily accessible ones and for the selective introduction of groups such as O-alkyl, amino and halogen into sugar molecules. Some early and well known examples are the synthesis of glucosamine(2-amino-2-deoxy-D-glucose) in [2] 1939 and chondrosamine (2-amino-2-deoxy-D-galactose) in 1946.[3] In the years following 1946 much attention was also paid to sugar epoxides as intermediates in the preparation of deoxysugars.

Although the preparative aspect of the reactions of sugar epoxides has been studied in great detail, other important factors such as the different proportions in which ring opened products are obtained, have also attracted considerable attention. The chemistry of sugar epoxides has now reached a stage where study of their reactions can reveal much about the electronic, steric and conformational factors which operate in sugar molecules.

In sugar epoxides, four broad structural types can be distinguished, namely (i) 1,2-anhydropyranoses (1), (ii) epoxides with one end of the ring on primary carbon atom (2), (iii) epoxides on a conformationally rigid system (3), (iv) epoxides on a conformationally flexible system (4)(Figure 1).

1,2-Anhydropyranoses, as exemplified by Brigl's anhydride, are extremely reactive and open exclusively at the anomeric

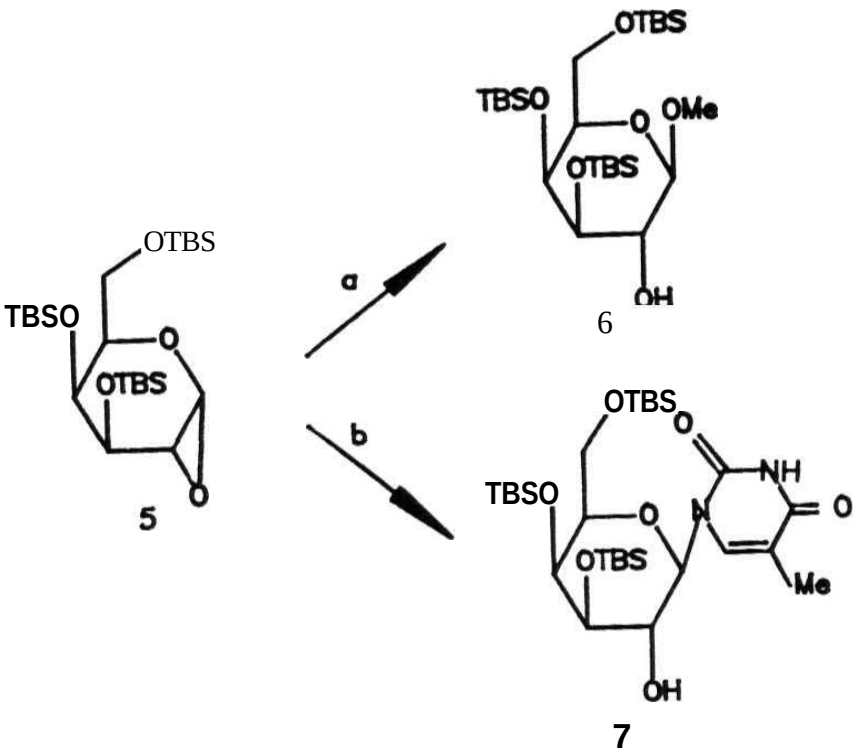



1 2a 2b

3 4a 4b

**Figure 1**

center.[4] Thus, for example, 1,2-anhydro-3,4,6-tri-0-(t-butyldimethylsilyl)-α-D-galactopyranose (5) reacted with anhydrous methanol to give methyl 3,4,6-tri-O-(t-butyldimethylsilyl)-β-D-galactopyranoside (6). The same epoxide (5), when reacted with *bis*-O-(trimethylsilyl) thymine gave 1-[3',4',6'-tri-O-(t-butyldimethylsilyl)-β-D-galactopyranosyl]-5-methyl-2,4-(1H, 3H)- pyrimidnedione (7) (Scheme 1).

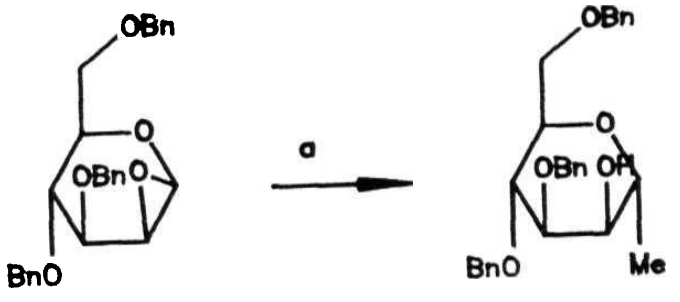



a) MeOH; b) *bis*-O-(trimethylsilyl)thymine.

Scheme 1

1,2-Anhydro-3,4,6-tri-O-benzyl-β-D-mannopyranose (8) reacted with lithium dimethylcuprate to give the corresponding α-D-C-glycoside (9) (Scheme 2).

Recently, Resnati and co-workers reported the reaction of 1,2-anhydro-3,4,6-tri-O-acetyl-α-D-glucopyranose (10) with cholesterol and (S)-citronellol to give the corresponding cholesteryl and citronellyl β-D-glucopyranoside derivatives (Scheme 3).



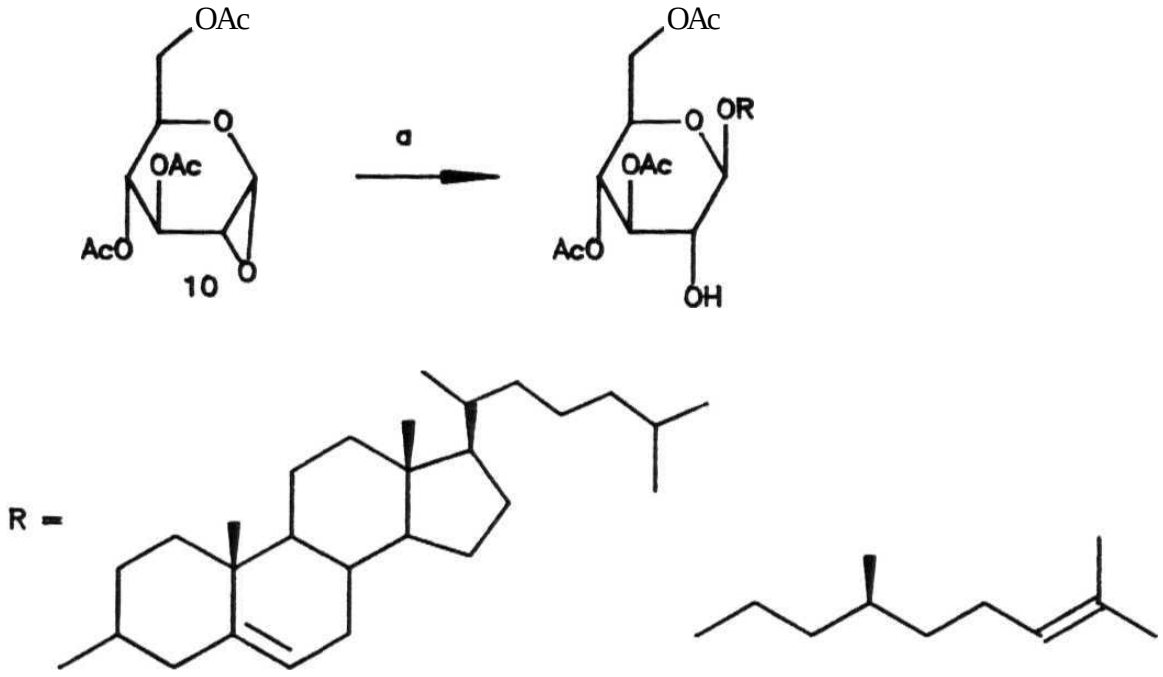

8 9

a) Me CuLi, ether.

**Scheme 2**

Danishefsky has developed a general strategy for oligosaccharide synthesis based upon the reactions of 1,2-anhydropyranosides (Scheme 4). Thus, glycal 11 was converted into the 1,2-epoxide (12) by treating it with dimethyldioxirane which on further reaction with the 3,4-di-O-alkyl-D-glucal gave the disaccharide (13). This sequence can be repeated to obtain the required oligosaccharide. The advantages of this method are considerable. The donor is formed in one easy step from the glycal. The epoxidation is nearly quantitative and is highly stereoselective. (For example, D-glucal and D-galactal give the α-epoxides). Opening of the epoxide by a glycosyl acceptor gives a glycoside corresponding to inversion at the anomeric center of the donor. Finally, each glycosidation gives rise to a unique, free

hydroxyl center at C-2 of the previous donor, which is of great value in the synthesis of branched sugars.

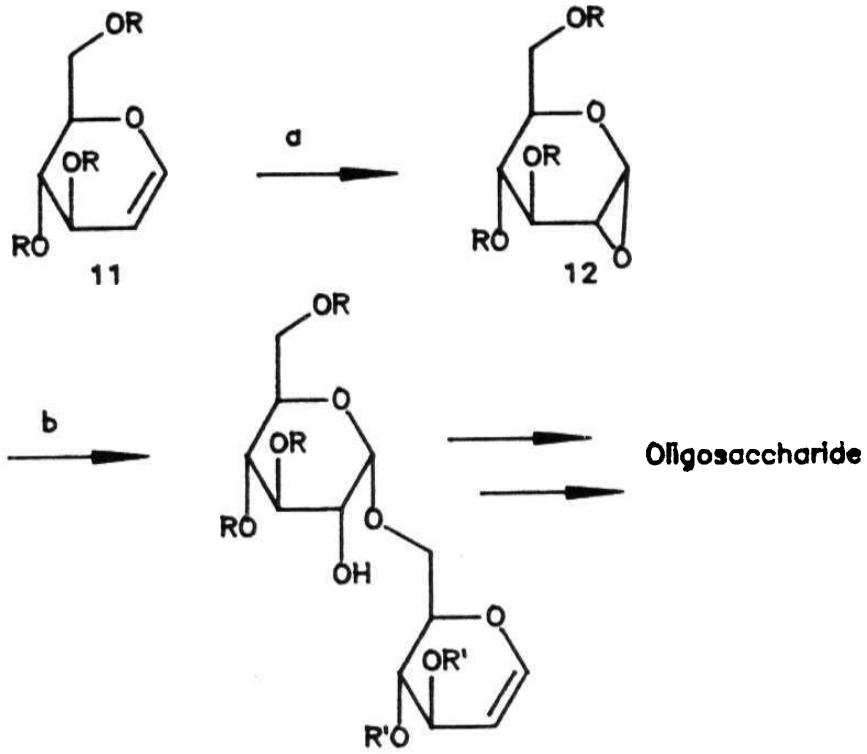



a) R-OH.

Scheme 3

Ring opening of epoxides having one primary carbon occurs regiospecifically at that carbon to give only one product. For example, 5,6-anhydro-1,2-O-isopropylidene-α-D-glycofuranoses 2a and 2b open only at C-6 with a wide range of nucleophiles. Thus, 5,6-anhydro-3-deoxy-3-C-methyl-1,2-O-isopropylidene-α-D-allopyra-

nose (14) reacted with 3-pyridyllithium in ether to give the corresponding 6-deoxy derivative (15) (Scheme 5).

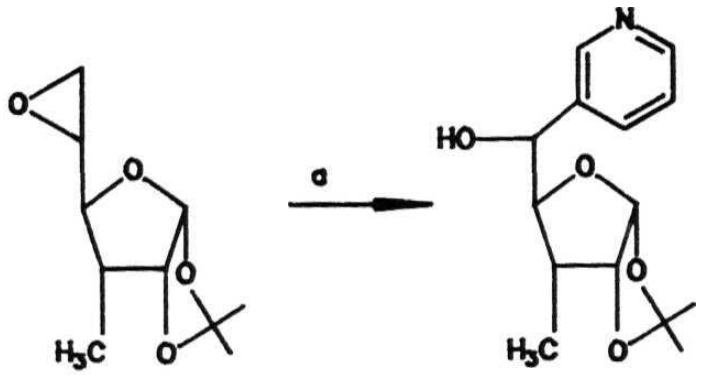



a) dimethyldioxirane; b) 3,4-di-O-alkyl-D-glucal.

Scheme 4

Similarly, 5,6-anhydro-3-O-benzyl-1,2-O-isopropylidene-α-D-glucofuranose (16) reacted with the dianion of 4-pentynol to give

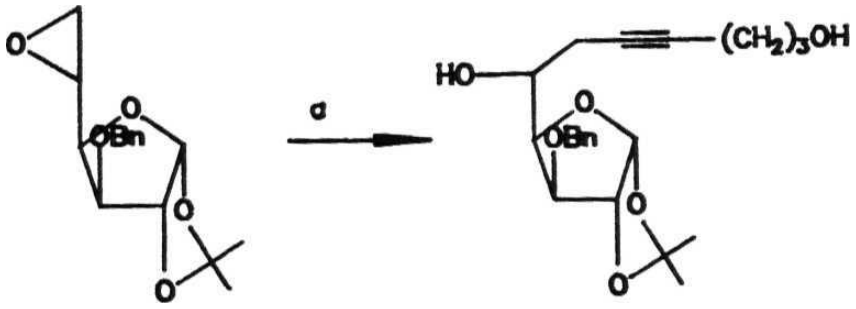
3-O-benzyl-1,2-O-isopropylidene-6-deoxy-6-(5-hydroxy-1-pentynyl)-α-D-glucofuranose (17) (Scheme 6).




**14** **19**

a) 3-pyridyllithium, ether.

Scheme 5



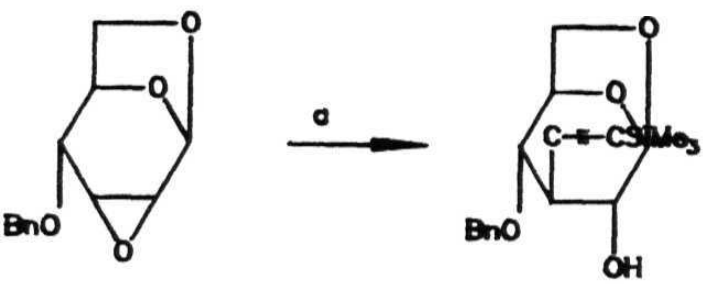

**16** **17**

a) 4-pentynol, n-BuLi.

**Scheme 6**

In conformationally rigid sugar epoxides such as those involving a **4,6-acetal** linkage or **1,6-anhydro** bridge, ring opening leads to one principal product arising from a **trans-diaxial** cleavage.

1,6 : 2,3 **Dianhydro-4-O-benzyl-β-D-allopyranose(18)** reacted with lithium **2-trimethylsilylethynyltrimethylaluminate** in toluene to give **1,6-anhydro-4-O-benzyl-3-deoxy-3-C-(2-trimethylsilyl-**ethynyl)-3-D-glucopyranose (19) in 677. yield (Scheme 7).[7]



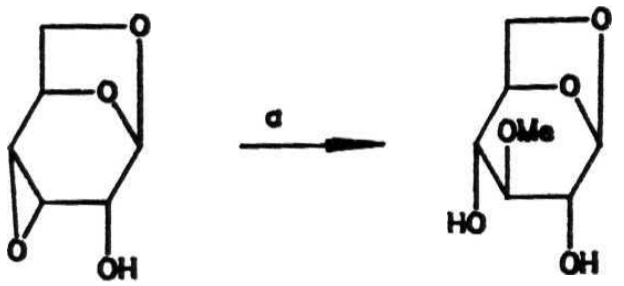

**18** **19**

a) $Me_3SiC{\equiv}CAl(Me)_3Li$.

Scheme 7

Similarly, 1,6 : **3,4-dianhydro-β-D-allopyranose** (20) reacted with sodium methoxide in methanol to give 1,6-anhydro-3-O-methyl -β-D-glucopyranose(21) in 697. yield (Scheme 8).

In the case of methyl **4,6-O-benzylidene-2,3-anhydro-α-D-**allopyranoside (22), nucleophiles attack at C-2 to give the altrose derivatives (Table 1).




**20** **21**

**a) NaOMe, MeOH.**

**Scheme 8**

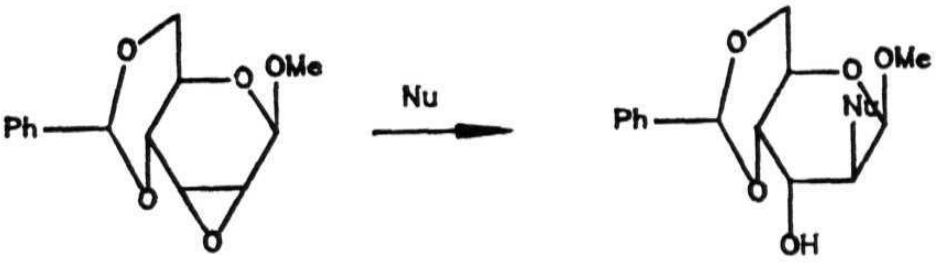
**Table 1**


**22**

| Nucleophiles used | Substitution pattern | Reference |
|---|---|---|
| H, OH, OMe, SMe, $SCH_2Ph$, SPh, $NH_2$, | 2 | 9, 10, 11, 12, 13, 14, 15, |

| | |
|---|---|
| NHMe, $N_3$, Cl, Br, I, $CH_2CO_2Et$, Me. | 16, 17, 18, 19, 20. |

Methyl 4,6-O-benzylidene-2,3-anhydro-β-D-allopyranoside (23) also gave 2-deoxy-2-substituted altrose derivatives (Scheme 9).[21]




**23**

Nu: OMe.

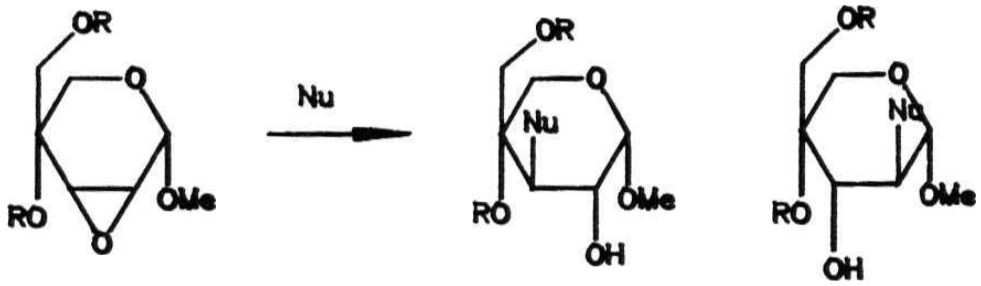
**Scheme 9**

Anhydrohexopyranosides generally adopt a conformation wherein the C-6 carbon is equatorial. While these conformations are not as rigid as the ones discussed earlier, they are not as flexible as those of anhydropentopyranosides. Some reactions of non-rigid anhydrohexopyranosides are now presented.

Reaction of methyl 4,6-di-O-methyl-2,3-anhydro-α-D-allopyranoside with various nucleophiles gave primarily 2-deoxy-2-substituted altroses in most of the cases (Table 2). The

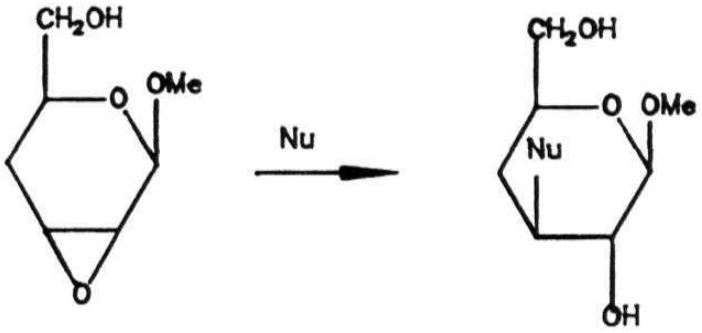
reaction was not as regioselective as in the case of the corresponding rigid sugar epoxides **22** and **23.**

**Table 2**




| R | Nucleophile used | Substitution pattern | Reference |
|---|---|---|---|
| Me | OH, OMe, F, I | 2 | 22, 23, 24, |
| | NMe | 2:3 (1:1) | 25 |
| p-$ClC_6H_4SO_2$ | H | 2:3 (55:27) | 26 |
| p-$H_3CC_6H_4SO_2$ | H | 2:3 (25:4) | 26 |

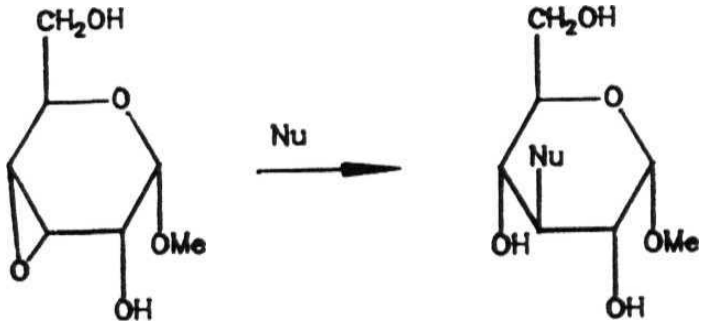
Ethyl or benzyl 2,3-anhydro-4-deoxy-β-DL-*ribo*-hexopyranosides gave 3-substituted DL-*xylo*-hexopyranosides with $NH_3$ and $NHMe_2$ (Scheme 10).[27]




**Nu: $NH_2$, $NMe_2$.**

**Scheme 10**

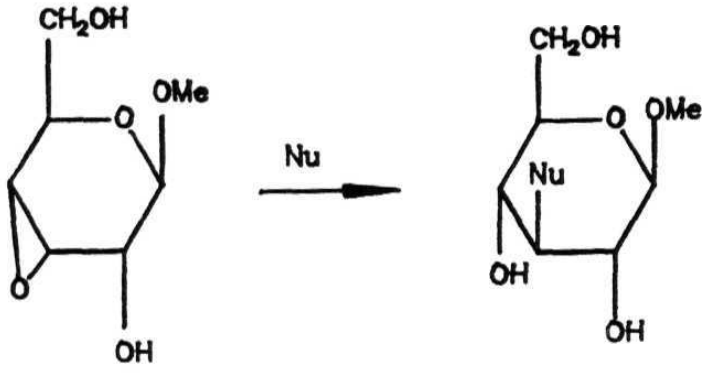
Reaction of methyl 3,4-anhydro-α-D-allopyranoside (24) with nucleophiles gave 3-substituted D-glucose derivative(Scheme 11).[28]




**24** **Nu: OMe**

**Scheme 11**

Methyl 3,4-anhydro-β-D-allopyranoside (25) also furnished a 3-deoxy-3-substituted glucose derivative with $NH_3$(Scheme 12).[21]




Nu: $NH_2$.

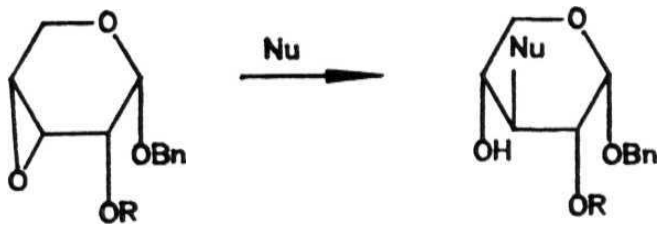
25 **Scheme 12**

In the case of alkyl anhydropentopyranosides there is a dynamic equilibrium between the two conformers. Therefore, the oxirane ring is susceptible to attack at both places and two products are possible, depending upon which carbon atom is attacked by the nucleophile. The ratio of the two products varies with the structure of the epoxide, the attacking reagent and the reaction conditions, and rationalization of the ratios observed provides a subject of enduring interest. In the presentation which follows, 3,4-anhydrosugars are discussed first, followed by 2,3-anhydrosugars.

In the nucleophilic ring opening reactions of benzyl 3,4-anhydro-α-D-ribopyranoside (26) with various nucleophiles, it was observed that reaction occurred exclusively at C-3 [29] (Table 3). The benzyloxy methyl ether of epoxide 26 also reacted in the same

fashion to furnish C-3 substituted derivatives.

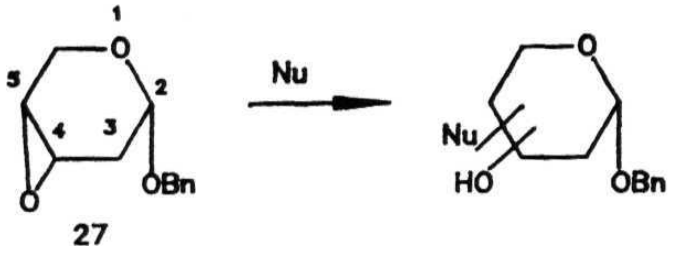
**Table 3**




| R | Nucleophile used | Substitution pattern | Reference |
|---|---|---|---|
| H(26) | C=CH, CN, Br, $N_3$ SPh, H, OMe | 3 | 29 |
| CH OCH Ph | CN, Br, $N_3$ SPh, H, OMe | 3 | 29 |

Crotti and co-workers studied the ring opening reactions of *cis*-2-benzyloxy-4,5-epoxytetrahydropyran (27) with various nucleophiles (Scheme 13).[30]

Thus, epoxide 27 reacted with sodium azide in the presence of ammonium chloride in methanol-water (8:1) at 80 to give C-5



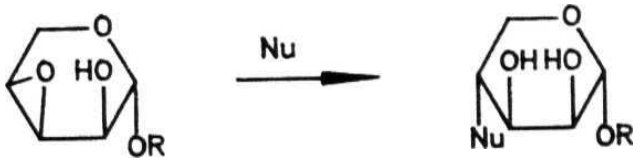

**Nu: $N_3$, $NMe_2$, Cl, H.**

**Scheme 13**

and C-4 substituted azido derivatives in a ratio of 6:94, respectively. Similarly, epoxide 27 reacted with diethylamine in ethanol to furnish C-5 and C-4 substituted amino derivative in a ratio of 24:76, respectively.

Epoxide 27 reacted also with hydrogen chloride in chloroform at room temperature to provide C-5 and C-4 chloro derivatives in a ratio of 5:95 and with LAH in ether at room temperature to yield C-5 and C-4 deoxy derivatives in a ratio of 43:57.

In the β series, it is reported that methyl, ethyl and benzyl 3,4-anhydro-β-ribopyranosides undergo preferential nucleophilic ring opening at C-4, leading to 4-deoxy-4-substituted derivatives (Scheme 14). Thus, reaction of methyl 3,4-anhydro-β-L-ribopyranoside with hydrogen bromide and amines gave



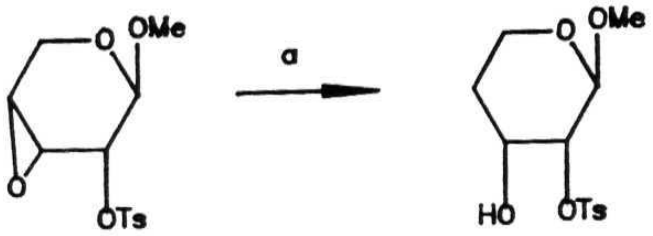

R=CH • Nu: Br, NH NHMe, NHPh.

R=CH CH ; Nu: 0Me(65:19 ratio, 4:3 subs.). Nu: SCH Ph (at -20°)

Scheme 14

mainly 4-substituted lyxopyranosides.[31] Similarly, the corresponding ethyl glycoside on treatment with sodium methoxide furnished the C-4 and C-3 substituted sugars in a ratio of 65:19.[32] The same epoxide reacted with sodium benzyl mercaptide at -20 to give exclusively the 4-lyxo product, while at room temperature and above a small amount of C-3 ring opened product was also seen.[33] Magnusson and co-workers observed that benzyl 3,4-anhydro-β-D-ribopyranoside with lithium bromide in HMPA gave benzyl 4-bromo-4- deoxy-α-L-lyxopyranoside as a minor product, the major product being 2(R)-(benzyloxy)-2,5-dihydrofuran-4-carbox-aldehyde.[34] Finally, Keck showed that benzyl 3,4-anhydro-D-ribopyranosides and hydriodic acid in acetone gave ring opening at C-4.

Reaction of methyl 3,4-anhydro-2-O-(*p*-toluenesulfonyl)-β-D-ribopyranoside with diborane-sodium borohydride proceeded with high regioselectivity to furnish in high yield (90%) the 4-deoxy derivative (Scheme 15 ). Only a trace of a byproduct, presumably the corresponding 3-deoxy derivative, was detected by tlc.




a) $B_2H_6$-$NaBH_4$.

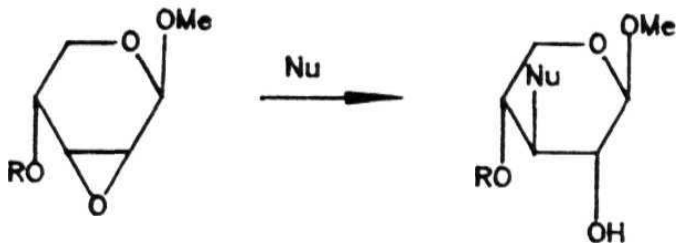
Scheme 15

Nucleophilic ring opening studies of alkyl 2,3-anhydro-β-ribopyranosides showed exclusively C-3 opening with very few exceptions.

Thus, methyl 2,3-anhydro-β-D-ribopyranoside and its 4-O-alkyl derivatives reacted with various nucleophiles as shown in Table 4.

Similarly, benzyl 2,3-anhydro-β-D-ribopyranoside and its 4-0-alkyl derivatives gave the corresponding 3-deoxy-3-substituted xylose derivatives with various nucleophiles (Table 5)

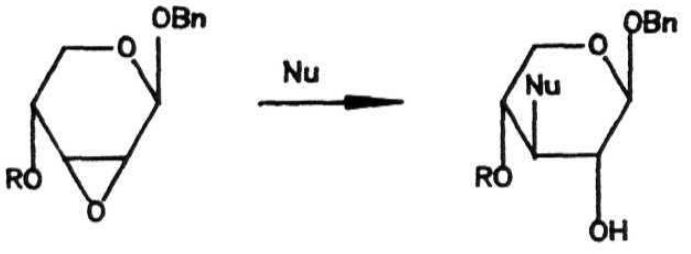
**Table 4**




| R | Nucleophile used | Substitution pattern | Reference |
|---|---|---|---|
| H | H, $OCH_2Ph$, SMe, N NH NHMe(L-series), 3. $NMe_2$, Cl, Ph, C=CPh, HC=CHPh | | 36, 37, 38, 39, 40, 41, 42, 43 |
| | Br | 2:3 (1:9.5) | 44 |
| Me | OH, OMe | 3 | 45 |
| | Br | 2 | 45 |
| | $HC=CMe_2$ | 2:3 (7:93) | 43 |
| $CH_2Ph$ | F, I, Me(L-series) | 3 | 46, 47, 48 |

| | | | |
|---|---|---|---|
| $CH_2$-CH=$CH_2$ | $CH_2$-CH=$CH_2$ | 2:3 (1:1) | 49 |
| *p*-$H_3CC_6H_4SO_2$ | Ph | 3 | 43 |
| | H | 2:3 (1:15) | 26 |

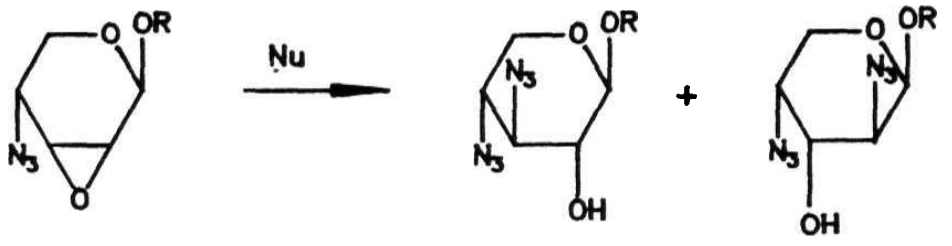
**Table 5**




| R | Nucleophile used | Substitution pattern | Reference |
|---|---|---|---|
| **H** | H, F, Cl(L-series) | 3 | 50, 51, 52 |
| | $NEt_2$ | 3 | 53 |
| Me | OH | 3 | 54 |
| $CH_2Ph$ | $OCH_2Ph$, $N_3$ | 3 | 55, 56 |
| TBDMS | Me | 2 + 3 | 57 |
| (L-series) | C≡CSiMe , | | |

| | | | |
|---|---|---|---|
| | $C\equiv C-(CH_2)_2-OH$ | 3 | 7 |
| | $CH_3(CH_2)_2C(CH_3)=CH_2$ | | |
| | CH=CH | 3 | 7 |
| β-D-xylo -pyranosyl | OH | 3 | 58 |
| 2,3,4,tri-O-benzyl-β-D-xylo -pyranosyl | $OCH_2Ph$ | 3 | 59 |

The reaction of methyl 2,3-anhydro-4-azido-4-deoxy-β-D-ribopyranoside with aqueous potassium hydroxide gave methyl 4-azido-4-deoxy-β-D-xylopyranoside. The corresponding L-isomer was cleaved by methanol-water (2:1) to give methyl 4-azido-4-deoxy-3-O-methyl-β-L-xylopyranoside. Benzyl 2,3-anhydro-4-azido-4-deoxy-β-D-ribopyranoside reacted with ammonia in methanol to give benzyl 2-amino-2-deoxy-4-azido-4-deoxy -β-D-arabinopyranoside and benzyl 3-amino-3-deoxy-4-azido -4-deoxy-β-D-xylopyranoside in a ratio of 3:2, whereas with sodium azide and ammonium chloride in 2-methoxyethanol-water the corresponding 2-azido-2-deoxy substituted arabinoside and 3-azido-3-deoxy substituted xyloside were obtained in a ratio of 3:7 (Scheme 16).[62]



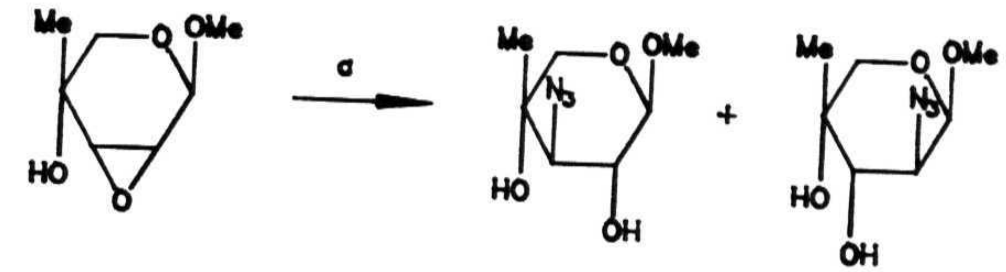

R=$CH_3$; Nu: OH, OMe.

R=$CH_2Ph$; Nu: $NH_2$(3:2 ratio, 2:3 subs.), $N_3$: (3:7 ratio, 2:3 subs.)

Scheme 16

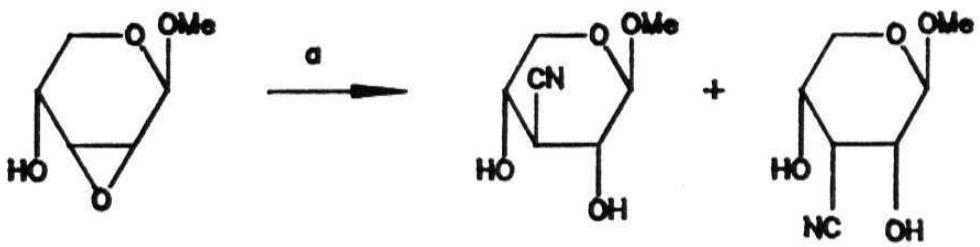
Methyl 4-C-methyl-2,3-anhydro-β-D-ribopyranoside reacted with sodium azide and ammonium chloride in ethanol-water to give methyl 4-C-methyl-3-azido-3-deoxy-β-D-xylopyranoside and methyl 4-C-methyl-2-azido-2-deoxy-3-D-arabinopyranoside in a ratio of 6:1 (Scheme 17).[63]

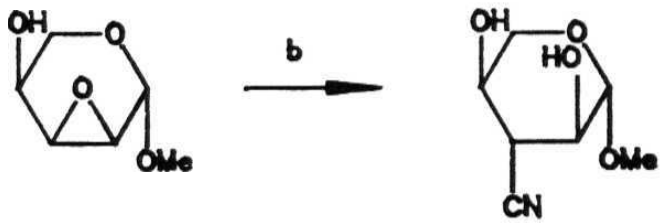
Ring opening of methyl 2,3-anhydro-β-D-ribopyranoside with cyanide ion in an aqueous buffered system (pH 8.5) gave a mixture of methyl 3-cyano-3-deoxy-β-D-xylopyranoside and methyl 3-cyano-3-deoxy-β-D-ribopyranoside, whereas with the corresponding L-isomer, triethylaluminum-hydrogen cyanide reagent gave the corresponding 3-cyano-3-deoxy xylose derivative in 60% yield (Scheme 18).[65]




a) $NaN_3$-$NH_4Cl$/ethanol-water(5:1).

Scheme 17



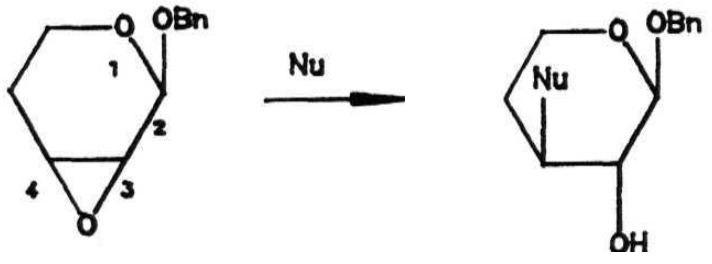




a) CN, pH 8.5; b) Al(Et) -HCN.

Scheme 18

Recently, Crotti and co-workers studied the ring opening of *trans*-2-benzyloxy-3,4-epoxytetrahydropyran with various nucleophiles (Table 6).

**Table 6**




| Nucleophiles used | Substitution pattern | Reference |
|---|---|---|
| $N_3$, SPh, $NEt_2$ $CH_3$, H | 4 | 66 |

Thus, the nucleophilic ring opening of alkyl 2,3-anhydro-β-ribopyranosides and their derivatives have been studied extensively with a variety of nucleophiles.

In the α-series, only a few cleavages have been examined, especially with benzyl 2,3-anhydro-α-D-ribopyranoside (28). Thus,

the reaction of benzyl 2,3-anhydro-α-D-ribopyranoside with trimethylsilyl cyanide gave the C-3 substituted xylose derivative in 59% yield (Scheme 19).[67]


R=CH Ph (28); Nu: CN, Cl, NEt .
R=CH ; Nu: SMe(2:l ratio, 3:2 subs.).
Scheme 19

The epoxide 28 with $Pd(PhCN)_2Cl_2$ in benzene furnished the C-3 substituted xylose derivative in 157. yield.[52] Once again, the same epoxide reacted with N,N-diethyltrimethylsilyl amine-aluminum chloride to give the corresponding C-3 substituted (diethylamino) xylose derivative.[68] Epoxide 28 also reacted with lithium bromide in the presence of N,N,N',N'-tetramethylurea in refluxing toluene to give 2-benzyloxy-2,5-dihydrofuran-4-carboxaldehyde in 21% yield. It was postulated that the bromide attacks at C-3, leading to ring opened product, which rearranges to give the final observed product. Finally, methyl 2,3-anhydro-a-D-ribopyranoside

on treatment with sodium methyl mercaptide gave the C-3 and C-2 substituted sugars in a ratio of 2:1.[36]

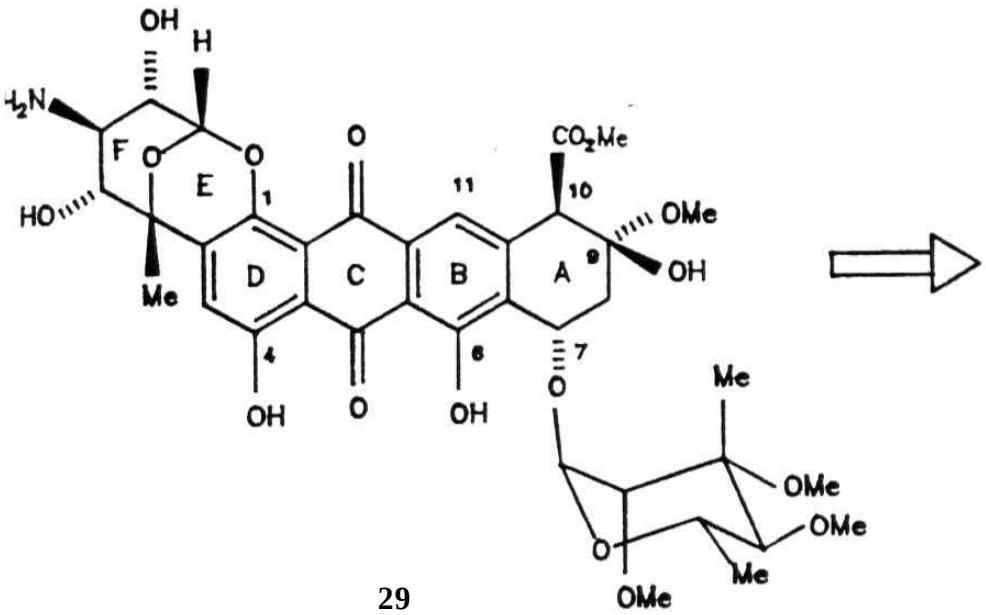
A survey of the above results shows the versatility of nucleophilic ring opening reactions of epoxides to form simple and rare deoxy sugars. Some of them have been used as chiral starting materials for the synthesis of biologically active molecules as can be seen from the following examples.

Thus, the DEF ring of nogalamycin (29), the potent antitumor antibiotic of the anthracycline family was synthesised starting from benzyl 2,3-anhydro-β-D-ribopyranoside (31) (Scheme 20).[53]

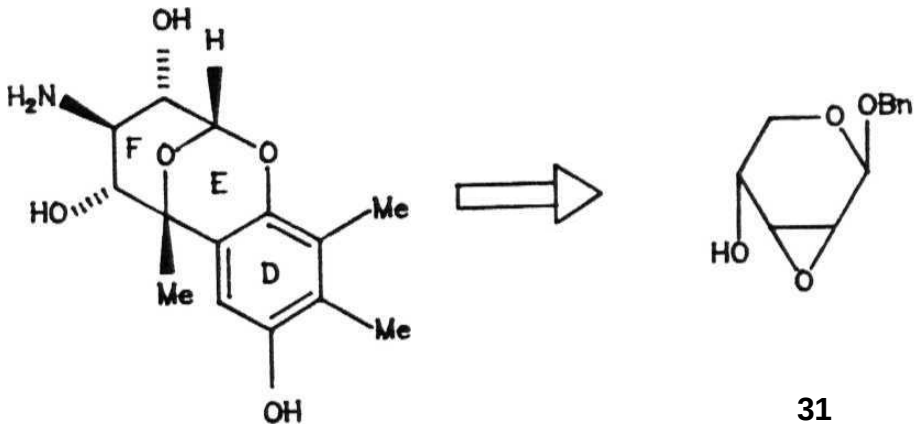
A sophisticated example of a cyclization which involves an enolate carbanion equivalent was carried out with the epoxy -allylsilane (33) derived by a multistep process from benzyl 2,3-anhydro-β-L-ribopyranoside (34).[70] The epoxyallylsilane 34 underwent an intramolecular nucleophilic displacement reaction when the epoxide ring was activated by addition of boron trifluoride etherate to give the highly functionalised 32 in the key step of the synthesis of an enantiomerically pure component of the diterpene taxol (Scheme 21).

Similarly, the intermediate 36, which was used in the synthesis of antimycin A (35), a unique unsymmetrical nine membered dilactone isolated from a number of Streptomyces strains exhibiting both antibiotic and antifungal activity, was synthesised starting from benzyl 2,3-anhydro-α-L-ribopyranoside

(37) (Scheme 22).[71]

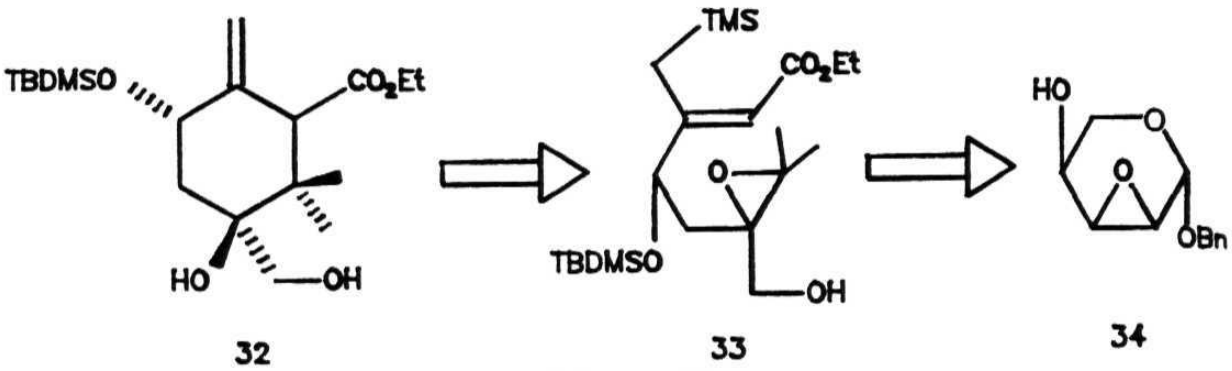



**29**



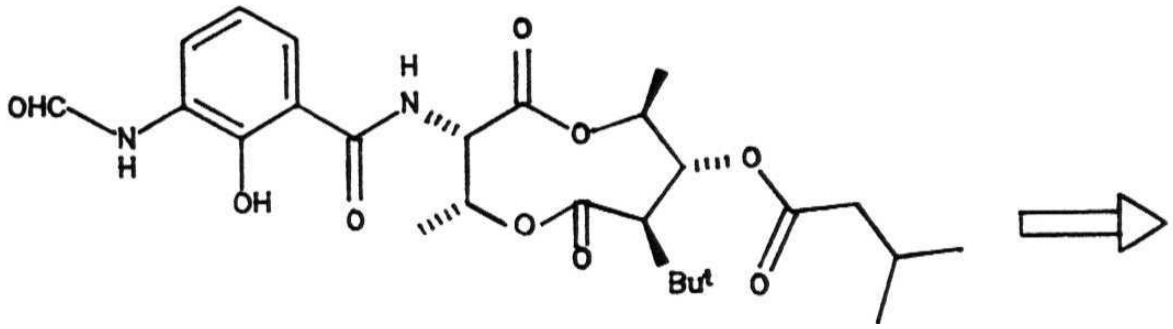

**30** **31**

Scheme 20

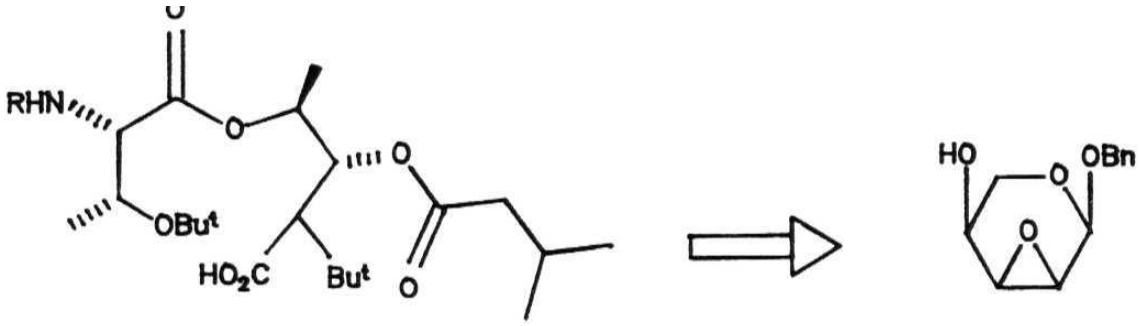



32 33 34

Scheme 21




35



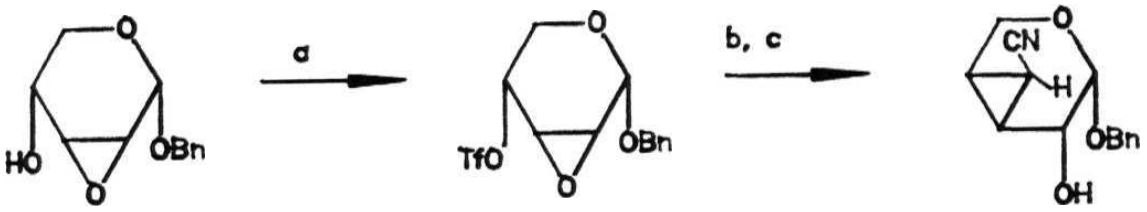

36 37

Scheme 22

Sugar epoxides serve both as a protecting group and as a

reactive site and this dual property has led to their extensive exploitation in carbohydrates synthesis. In this capacity, sugar epoxides have been used in the synthesis of cyclopropanated sugars, polysubstituted chiral butanolides and triquinanes.

Thus, benzyl 2,3-anhydro-α-D-ribopyranoside (28) was converted to its triflate 38, and treated with lithioacetonitrile in presence of HMPA in THF, followed by reaction with lithium diisopropylamide (LDA) to give the cyclopropanated sugar (39) (Scheme 23).



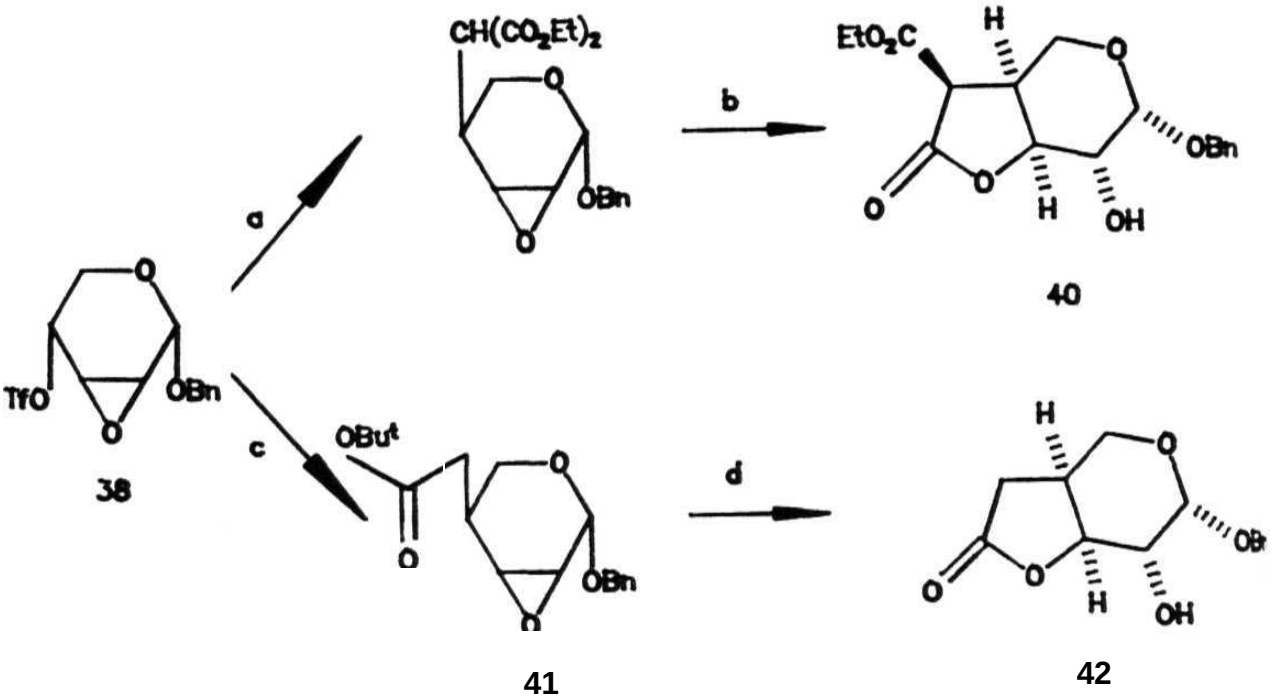

**28** **38** 39

a) $(CF_3SO_2)_2O$, pyridine; b) $LiCH_2CN$, HMPA, THF; c) LDA.

Scheme 23

The triflate 38 on treatment with sodiodiethyl malonate in a mixture of THF and ethanol followed by acidic aqueous work up afforded the tri-substituted γ-butyrolactone (40). Similarly, the triflate 38 reacted with the lithium enolate of tert-butyl acetate in THF-HMPA at -120° to give the ester (41), which on treatment

with trifluoroacetic acid-CH Cl at room temperature furnished the γ-butyrolactone (42) (Scheme 24).

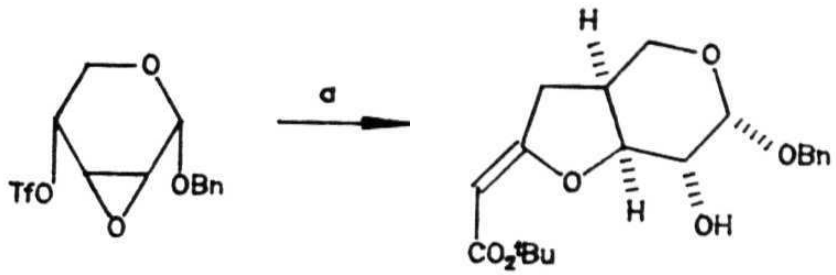



a) $NaCH(CO_2Et)_2$, THF, EtOH, rt; b) acid work-up;
c) LiCH CO $Bu^t$, THF, HMPA, -120°; d) $CF_3COOH$, $CH_2Cl_2$, rt.

Scheme 24

The same triflate 38 was used in a pyranose annulation leading to chiral, highly functionalized a-alkylidene tetrahydrofurans via regio- and stereoselective annulation of a pyranose ring. Thus, triflate 38 when reacted with the dianion of t-butyl acetoacetate in THF at -78° afforded the

Z-tetrahydrofurylidenepyran (43) in 76% yield (Scheme 25).[75]

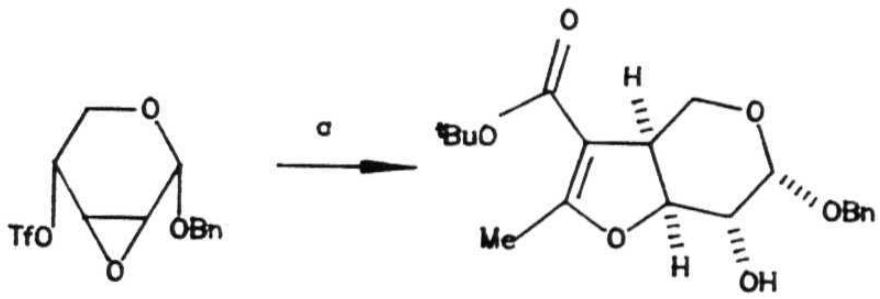



58 43

a) t-butyl acetoacetate, NaH, n-BuLi, THF, -78 .

**Scheme 25**

Once again, the triflate 38 reacted with t-butyl acetoacetate in presence of sodium hydride and 15-crown-5 in THF to give 44 in 85% yield (Scheme 26).[75]



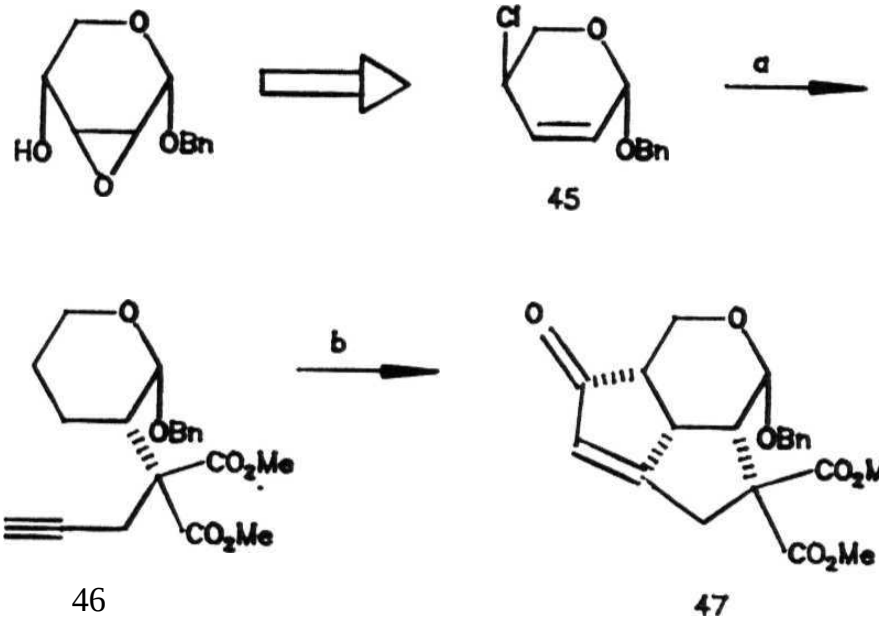

38 44

a) 5 eq. NaH, 15-crown-5, THF, 5 eq. t-butyl acetoacetate 0 - rt.

**Scheme 26**

Olefins derived from anhydroribopyranosides were used in building bis-annulated sugars via the Pausson-Khand reaction bearing the functional code required for angularly fused triquinane synthesis.

Thus, olefin 45 was prepared from benzyl 2,3-anhydro-α-D-ribopyranoside in 4 steps in 477. overall yield.[77] Olefin 45 reacted with dimethylpropargyl malonate in presence of a palladium catalyst to give the propargyl derivative 46, which was quantitatively converted into the corresponding hexacarbonyl

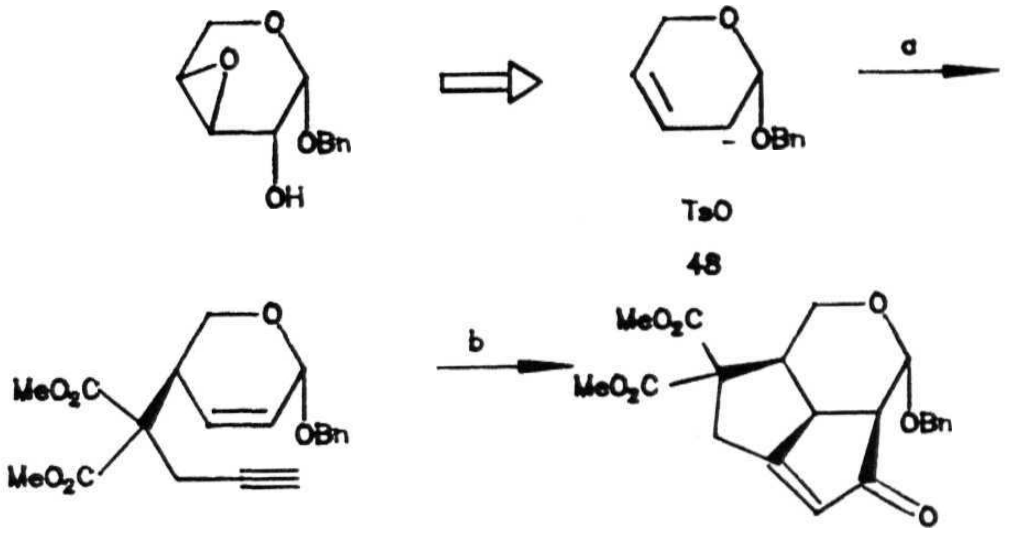



46 47

a) dimethylpropargyl malonate, $Pd(PPh_3)_4$, THF, 0°; b) $Co_2(CO)_8$, benzene, rt, DMSO, 50 .

**Scheme 27**

dicobalt complex, heating of which to 50 for 24h with a catalytic amount of DMSO afforded the polyfunctionalized product 47 (Scheme 27). Similarly, olefin 48 was prepared from benzyl 3,4-anhydro-β-L- arabinopyranoside in 2 steps in 667. overall yield[78] and was converted 50 in an identical manner(Scheme 28).




**49** **50**

a) dimethylpropargyl malonate, Pd(PPh ) , THF, 0 ; b) benzene, rt, DMSO, 50°.

Scheme 28

Nitrate esters of carbohydrates, fluorodeoxy sugars and sulphate esters of carbohydrates were prepared by treating the respective epoxy triflates with corresponding nucleophile. Thus,

benzyl 4-O-trifluoromethanesulfonyl-2,3-anhydro-β-L-ribopyranoside (51) reacted with tetra-n-butyl ammonium nitrate in refluxing acetone to give the corresponding nitrate derivative in 977. yield.[79] Similarly, the same triflate 51 reacted with tetra-n-butylammonium fluoride trihydrate in acetonitrile at room temperature to furnish the corresponding fluoro derivative in *157.* yield.[80] Once again, the same triflate 51 reacted with tetra-n-butylammonium hydrogen sulphate in acetonitrile at room temperature to yield the corresponding sulphate (25%) and cyclic sulphate (597.) (Scheme 29).[81]

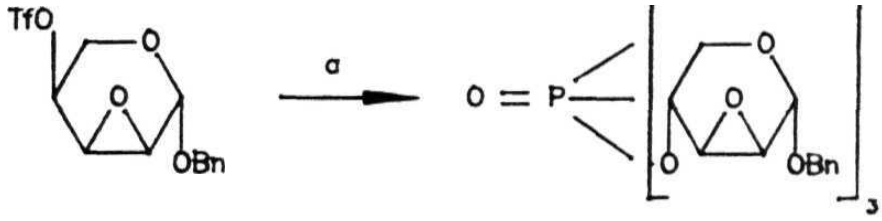

51

Nu: $ONO_2$, F, $OSO_3H$.

Scheme 29

Efficient syntheses of sugar phosphates were also developed by way of displacement reactions of suitably protected monosaccharides with tetra-n-butylammonium dihydrogen phosphate and dibenzyl phosphate. Thus, triflate 51, reacted with

tetra-n-butylammonium dihydrogen phosphate in the presence of 2,4,6-collidine in acetonitrile-THF to give tris-(benzyl 2,3-anhydro-α-D-lyxopyranoside)-4-phosphate (52) in 677. yield (Scheme 30).[82]




51 **52**

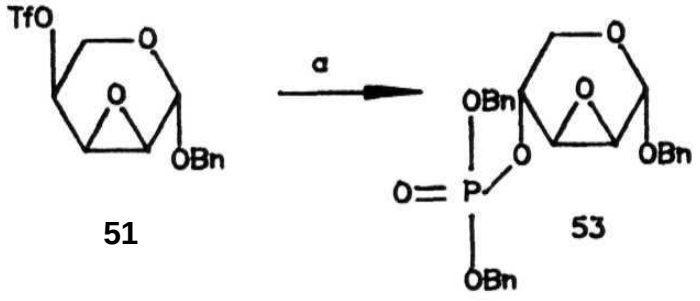
a) n-Bu.N $H_2PO_4$ , CH CN, 2,4,6-collidine, THF.

Scheme 30

Similarly, the same triflate 51 and dibenzyl phosphate/ 2,4,6-collidine in THF gave dibenzyl (benzyl 2,3-anhydro-α-D-lyxopyranoside)-4-phosphate (53) in 517. yield (Scheme 31).[82]

Benzyl 4-O-benzyl-2,3-anhydro-β-L-ribopyranoside (54) reacted with tetrahydropyranyloxypropynyl aluminum to yield the corresponding 3-deoxy-3-substituted derivative, which on further reduction followed by oxidation gave the pyranose annulated δ-lactone 55 (Scheme 32).[83]

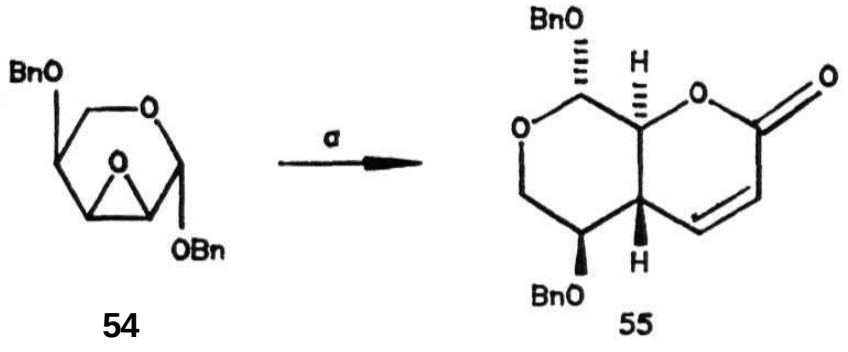
The results summarized in the preceding pages indicate the utility of sugar epoxides as valuable synthetic intermediates.




51 53

a) dibenzyl phosphate, THF, 2,4,6-collidine.

**Scheme 31**




54 55

a) i) (THPOC≡CCH$_2$) Al; ii) reduction; iii) oxidation.

Scheme 32

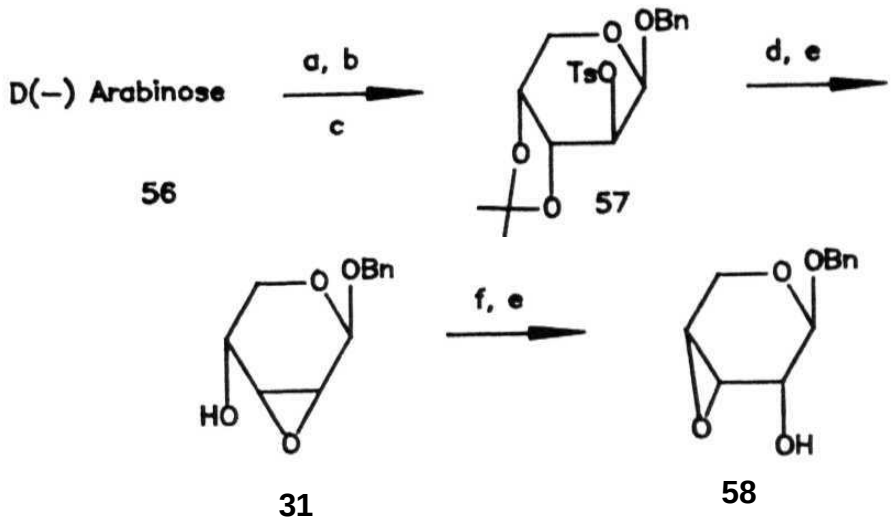
However, a predictable understanding of their reactivity is still lacking. Earlier work from our laboratory had shown that benzyl 3,4- anhydro-α-D-ribopyranoside reacted with nucleophiles exclusively at C-3.[29] This result was rationalized based on a

repulsive interaction between the entering nucleophile and the electron lone pair on the pyranose oxygen, precluding attack at C-4 and directing it to C-3. To establish the validity of this interpretation, it was thought necessary to study the ring opening reactions of benzyl 3,4-anhydro-β-D-ribopyranoside, where the anomeric substituent should now direct opening at C-4 on steric grounds, overriding the effect of the oxygen lone pair.

Similarly, the nucleophilic ring openings of alkyl 2,3-anhydro-β-D-ribopyranosides have been studied extensively. However, reactions of their α- anomers have not been investigated in detail and that became the objective of our further study. Thus, the complete examination of four possible isomers of alkyl anhydroribopyranosides would be completed and this would be expected to provide a better understanding of the various factors that govern nucleophilic ring opening in conformationally mobile sugar epoxides.

# Results

Benzyl 3, 4-anhydro-β-D-ribopyranoside (58) was prepared as reported from D(-) arabinose. (Scheme 33).[34] Thus, commercial D(-) arabinose(56) was treated with benzyl alcohol and dry hydrogen




a) PhCH OH, dry HCl gas; b) acetone, conc.H SO , anhydr.CuSO rt; c) TsCl, pyridine, rt; d) 1N H SO acetone:H O (1:10), reflux ; e) MeONa, MeOH, rt; f)LiBr, 1, 1, 1-trichloro-ethane, reflux.

**Scheme** 33

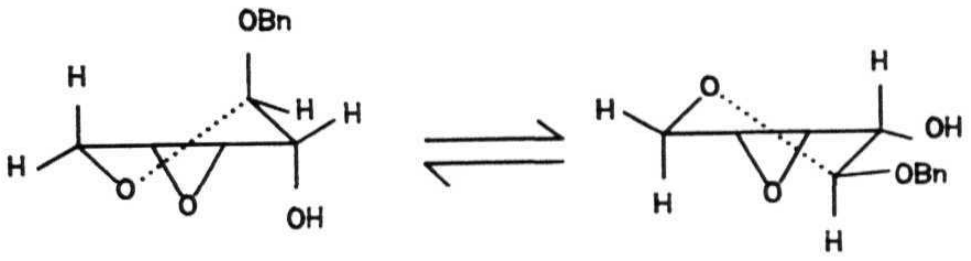
chloride gas to furnish benzyl β-D-arabinopyranoside.[84] Benzyl arabinopyranoside on treatment with acetone, conc.sulphuric acid and anhydrous copper(II) sulphate at room temperature gave the acetonide, which on further treatment with *p*-toluenesulfonyl

chloride in dry pyridine gave benzyl 2-0-p-toluenesulfonyl-3,4-0-isopropylidene-β-D-arabinopyranoside (57). On treatment with 1N sulphuric acid in acetone: water( 1:10) at reflux temperature, 57 gave benzyl 2-O-*p*-toluenesulfonyl-β-D-arabinopyranoside, which was cyclized with sodium methoxide in methanol at room temperature to benzyl 2,3-anhydro-β-D-ribopyranoside(31).[54] Reaction of 31 with lithium bromide in 1,1,1- trichloroethane at reflux temperature gave the 4-bromo lyxose derivative which on further treatment with sodium methoxide in methanol yielded the required epoxide 58. The physical and spectral properties of 58 were in agreement with those reported in the literature.[34]

Sugar epoxides are known to exist as half-chair conformers.[85] In order to determine the major conformer, three methods have been utilised. The most favoured one is to measure vicinal coupling constants, either J _ in 3,4-anhydropyranosides or J _ in 2,3-anhydropyranosides. It was observed that axial-axial couplings show a value ranging from 8-14 Hz, whereas, axial-equatorial and equatorial-equatorial coupling constants lie between 0-8 Hz, thus enabling the assignment of conformation. A second, less accurate method, is to use the chemical shift of the anomeric proton. The axial protons are comparatively shielded with respect to the corresponding equatorial protons. Consequently, the equatorial protons resonate at lower fields than the axial protons.[87] However, this method is of limited value. Finally the

angular dependence of long-range coupling constants over four bonds, as suggested by Barfield [88] and Sternhell [89] has also been employed. If the two protons are equatorial and separated by four bonds in a coplanar W configuration, usually there exists a long-range coupling of the order of 0.5-1.0 Hz, useful for conformational assignment, if detectable. In the case of anhydro sugars, an additional spur to long range coupling lies in the nature of the epoxide ring which acts similar to a double bond in enhancing pseudoallylic coupling, previously found in propylene oxide and indene oxide.

The NMR spectrum of **58** shows a doublet anomeric signal with $J$ coupling constant of 2.2 Hz (in $CDCl_3$). This suggests that **58** preferentially adopts the conformer **58A** as shown in Figure 2.




**58A** **58B**

**Figure 2**

However, the free energy difference between **58A** and **58B** is likely to be small as was shown earlier for the corresponding **α-anomer** by

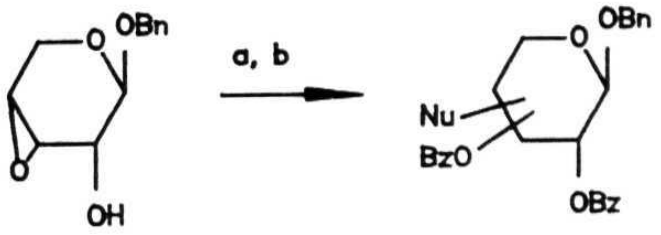
semi-empirical SCFMO calculations.[29] An approximate value of this free energy difference is about 1 Kcal mole , estimated using the observed $J_{1,2}$ coupling constant and the values given by Zamojski for $J_{1,2}$ coupling constants in closely related systems.[91] Therefore, it is reasonable to assume that the product ratios in the nucleophilic ring opening of 58 would be governed by the Curtin-Hammett principle.[92]

As shown in Table 7, nucleophilic ring opening of 58 was carried out with a variety of nucleophiles. The counter-cation was also varied to examine its influence on the course of the reaction. For the purposes of analysis and identification, the crude product mixture was benzoylated and the isomeric dibenzoates were separated and characterized. The regio- and stereochemistry of the ring opened products were established by H COSY experiments and an incisive analysis of the vicinal proton coupling constants, respectively.

Ring opening at C-3 provided benzyl 3-deoxy -3-substituted β-D-xylopyranoside derivatives while cleavage of the C-4 oxygen bond furnished benzyl 4-deoxy-4-substituted-α-L-lyxopyranoside derivatives. NMR data ( Table 8 )clearly showed that in the former family of compounds, both $^{1}C_{4}$ and $^{4}C_{1}$ conformers(Figure 3) are present with no marked preference for either.

This conclusion is readily derived from the fact that $J_{1,2}$ varied from 4.1 to 6.3Hz for these compounds. In the

**Table 7. Ring opening reactions of 58 with different nucleophiles.**




58

a) Nucleophile; b)PhCOCl, pyridine, rt.

| Entry | Nucleophile | Metal counter-cation | Solvent | Yield (%) | Product(%) C-4 | C-3 |
|---|---|---|---|---|---|---|
| 1 | $H(AlH_4^-)$ | $Li^+$ | THF | 78 | 59(07) | 60(93) |
| 2 | $H(BH_4^-)$ | $Na^+$ | EtOH | 60[a] | 59(47) | 60(53) |
| 3 | Br | $Li^+$ | THF | 51[b] | 62(100)[c] | .... |
| 4 | Br | $Mg^{2+}$ | THF | 74 | 64(21) | 65(79) |
| 5 | I | $Li^+$ | THF | 38 | 66(85) | 67(15) |
| 6 | I | $Na^+$ | THF | 72 | 66(96) | 67(04) |
| 7 | I | $Al^{3+}$ | $CH_3CN$ | 50 | 66(60) | 67(40) |
| 8 | I | $Mg^{2+}$ | THF | 72 | 66(19) | 67(81) |
| 9 | I | $Mg^{2+}$ | Benzene | 71 | 66(18) | 67(82) |
| 10 | I | $(n\text{-}Bu)_4N^+$ | THF | | no reaction | |
| 11 | CN | $K^+$ | DMSO | 82[b] | 68(28)[d] | .... |
| | | | | | 69(65)[d] | .... |

| | | | | | |
|---|---|---|---|---|---|
| 12 | OCH | $Na^+$ | THF | | no reaction |
| 13 | C≡CH | $MgBr^+$ | THF | 83[e] | 64(11) 65(89) |
| 14 | $N_3$ | $Na^+$ | DMF | 70 | 71(59) 72(41) |
| 15 | $N_3$ | $Na^+$ | THF | | no reaction |
| 16 | SPh | $Na^+$ | THF | 80 | 73(48) 74(52) |
| 17 | OMe | $Na^+$ | MeOH | 73 | 75(76) 76(24) |
| 18 | OMe | $Mg^{2+}$ | MeOH | 70 | 75(07) 76(93) |
| 19 | OMe | $Na^+$ | THF | | no reaction |

*3.* *b* *c*

26% of epoxy benzoate recovered. yield of diol. 1007. bromodiol 62. 287. of iododiol 68, 657. of cyanodiol 69 and 77. of complex mixture. No product corresponding to ring opening with acetylide anion was observed.

Table 8. Selected H NMR coupling constants of ring opened products

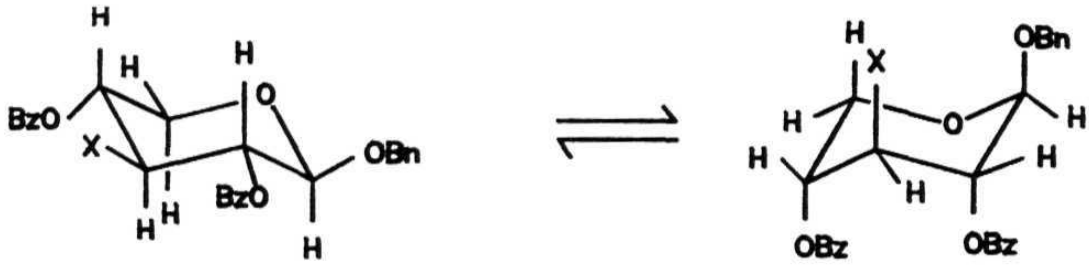
| Compound | Coupling Constants, Hz | | | |
|---|---|---|---|---|
| | $J_{1,2}$ | $J_{3,4}$ | $J_{4,5}$ | $J_{4,5'}$ |
| 59(lyxo) | 2.3 | 11.0<br>4.6 | c | c |
| 60(xylo) | 0 | c | 1.96 | 1.95 |
| 65(xylo) | 5.9 | 8.4 | 4.6 | 7.6 |

| | | | | |
|---|---|---|---|---|
| 66(lyxo) | 1.8 | 11.1 | 5.3 | 11.3 |
| 67(xylo) | 5.7 | 7.6 | c | 7.4 |
| 70(lyxo) | 2.1 | 11.4 | c | c |
| 71(lyxo) | 1.5 | c | 5.5 | 11.2 |
| 72(xylo) | 6.3 | 8.5 | 4.7 | 8.1 |
| 73(lyxo) | 0 | c | c | c |
| 74(xylo) | 2.6 | c | 3.0 | c |
| 75(lyxo) | 2.3 | c | c | c |
| 76(xylo) | 4.2 | 5.6 | 3.5 | 5.4 |

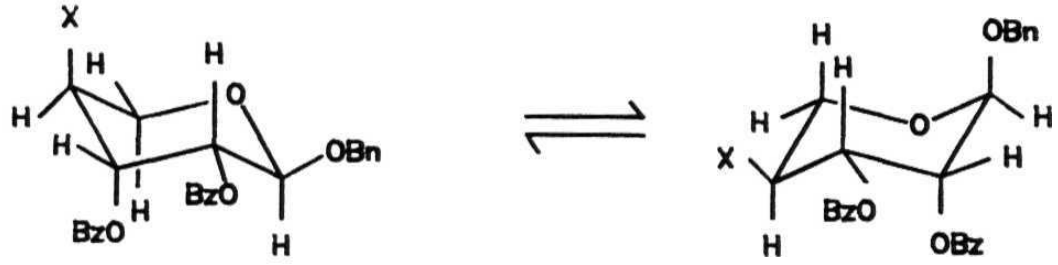
c — complex

α-L-lyxopyranoside series, $J_{1,2}$ varied, with one exception, from 1.5 to 2.3 Hz and $J_{3,4}$ and $J_{4,5}$ between 10.2 to 11.4 Hz and 10.2 to 11.5 Hz, respectively ( of the two protons at C-5, that which resonates at higher field is designated as H-5'). Thus, the $J_{1,2}$ values of the lyxose derivatives show H-1 and H-2 are in a diequatorial orientation. Similarly, large values of that $J_{3,4}$ show that H-3 and H-4 are in a diaxial arrangement. It is obvious that the $^1C_4$ conformer is the major one with the $^4C_1$ conformer being a minor contributor to the conformational equilibrium.

Epoxide 58 reacted with both LAH in THF and NaBH in ethanol giving the ring opened products 59 and 60 (entries 1 and 2). While the ring opening with NaBH was indiscriminate, yielding




$^4C_1$ **3- deoxy 3-subs. -β-D-xylo** $^1C_4$




$^4C_1$ **4-deoxy 4-subs. -α-L-lyxo** $^1C_4$

**Figure 3**

**59** and **60** in almost equal amounts, LAH gave predominantly 60, as a result of hydride attack at C-3.

The H COSY spectrum of 59 was used to assign the regiochemistry of ring opening. In the H COSY spectrum, all the protons except the anomeric proton are expected to show more than one cross peak. Only the doublet signal at 6 5.09 showed a single

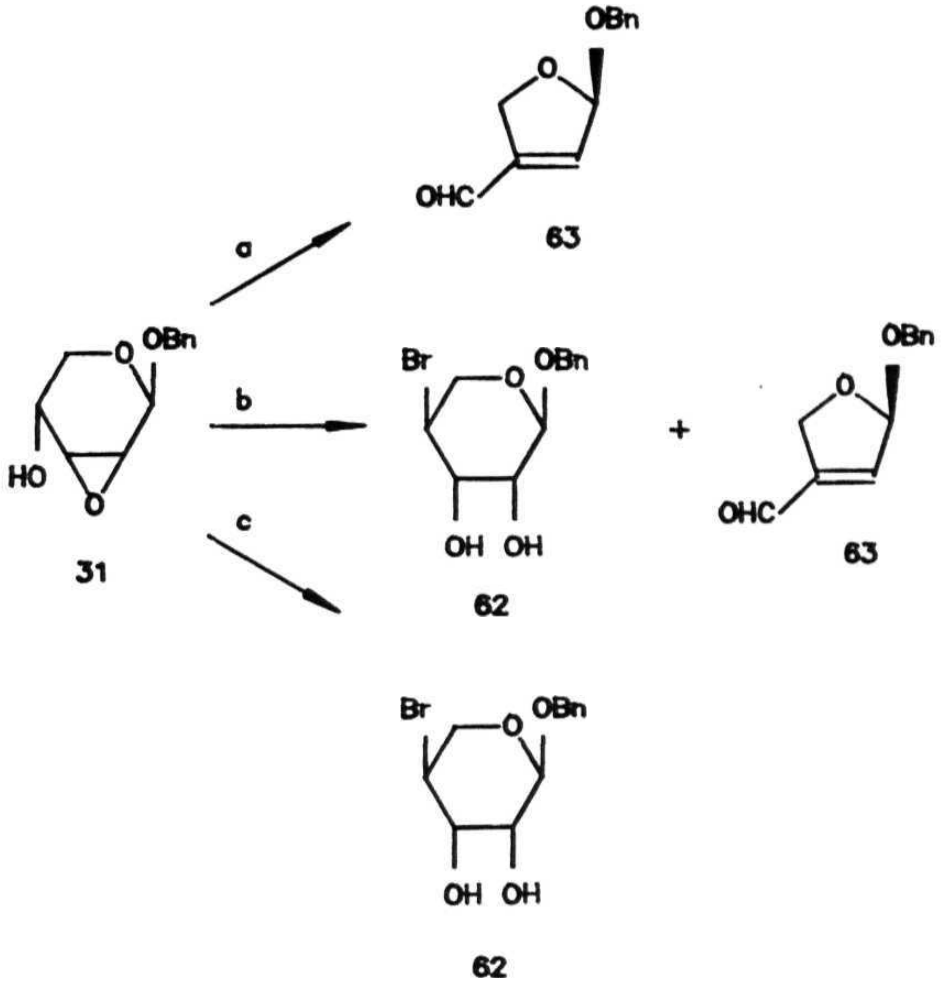
cross peak at *δ* 5.50. Therefore, the doublet signal at *δ* 5.09 was assigned as H-1. The triplet signal at *δ* 5.50 showed two cross peaks at *δ* 5.09 and *δ* 5.66. Thus the triplet signal at *δ* 5.50 was assigned as H-2. A ddd signal at *δ* 5.66 correlated with two cross peaks at *δ* 5.50 and *δ* 2.24. So the ddd signal at *δ* 5.66 was assigned as H-3. The benzylic dd signals at *δ* 4.84, *δ* 4.60 showed cross peaks to one another. The multiplet signal at 5 2.24, integrating for 2 protons showed cross peaks with *δ* 5.66 and *δ* 4.00 and was assigned as H-4 and H-4'. Finally, a multiplet signal at 6 4.00 was assigned as H-5 and H-5'. As the benzoate methine protons are expected to be relatively deshielded compared to the other protons, it is clear that the signals at *δ* 5.66 and 6 5.50, attributable to H-3 and H-2, are the protons indicated above. Therefore, the substituent is located at C-4, fixing the regiochemistry of ring opening. In a similar manner, using the H COSY spectrum of 60, its structure was elucidated as the 3-deoxy derivative, resulting from ring opening at C-3. Thus, the regiochemistry of 59 and 60 were assigned unambiguously.

The stereochemistry of ring opened products was secured by a careful examination of their H NMR spectra, especially the coupling constants between the various protons. Thus, for example, epoxide 58, on reaction with lithium iodide, gave two products 66 and 67 in a 85:15 ratio. That 66 and 67 are products of ring opening at C-4 and C-3, respectively, was clearly established from

their H COSY spectra, as detailed earlier for compounds 59 and 60. To determine the stereochemistry of 66, the coupling constants $J_{1,2}$, $J_{2,3}$, $J_{3,4}$, $J_{4,5}$ and $J_{4,5'}$ were used. $J_{1,2}$ has a value of 1.8 Hz, suggesting a diequatorial arrangement of H-1 and H-2. Both H-2 and H-3 are double doublets with J values of 3.1, 1.8 Hz and 11.1, 3.2 Hz, respectively. Therefore, $J_{2,3}$ is 3.1 Hz and J 11.1 Hz. The latter value immediately leads to the conclusion that both H-3 and H-4 are axially positioned and that H-2 and H-3 bear an equatorial-axial relationship. This is further substantiated by the fact that H-5 appears as an apparent triplet (in reality a double doublet) with $J_{4,5}$ = 11.5 Hz. All these observations can be accounted for satisfactorily only when 49 is an α-L-lyxopyranoside derivative. Since, H-l and H-2 are in a diequatorial arrangement and H-3 and H-4 in a diaxial arrangement this indicates that 66 is in the $^4C_1$ conformation.

Likewise, in compound 67, the coupling constants of significance are J =5.8Hz, J =8.6Hz, J =7.6Hz, J =4.1Hz and $J_{4,5}$=7.4Hz. Once again, these values clearly prove that H-2, H-3 and H-4 are all axially oriented, which is possible only if 67 is of the D-xylo configuration. The large value of J indicates that H-l and H-2 are in a diaxial arrangement. Similarly the value of J also indicates a diaxial arrangement. Thus, 67 is predominantly in the $^4C_1$ conformation with a significant contribution from the $^1C_4$ conformer as well.

It has been reported that lithium bromide reacts with 31 in toluene (Scheme 34 ) in the presence of N,N,N', N'-tetramethylurea




a) LiBr, tetramethylurea, toluene; b) LiBr, HMPA, toluene;
c)LiBr, 1,1,1 trichloroethane.

Scheme 34

to afford 2(R)-(benzyloxy)-2,5-dihydrofuran-4-carboxaldehyde (63) in 347. yield.[34] When HMPA was used instead of tetramethylurea, in addition to aldehyde 63 (25%), benzyl 4-bromo -4-deoxy-α-L-lyxopyranoside (62) (137.) was also obtained. Lyxopyranoside 62 was the exclusively isolated product (49%) when the solvent was 1,1,1-trichloroethane. We find that 58 suffers ring cleavage with anhydrous lithium bromide in THF to form 62 (517.)(entry 3). None of the aldehyde 63 could be detected under these conditions, even on careful examination of the crude product mixture. A marked alteration in regiochemistry occurred when magnesium bromide in THF was employed. The major product 65 (79%) corresponds to bromide attack at C-3 and the minor product 64 (21%) arises from cleavage of the C-4 oxygen bond (entry 4).

With iodide as nucleophile, the regiochemistry of the ring opening of 58 was very much dependent upon the nature of the counter-cation. While lithium iodide in THF gave the C-4 and C-3 ring opened products 66 and 67, respectively, in a 85:15 ratio(entry 5), sodium iodide furnished the same in a 96:4 ratio (entry 6). Aluminum iodide in acetonitrile afforded 66 and 67 with lesser selectivity (3:2)(entry 7). Magnesium iodide reversed the regioselectivity in both THF and benzene. Now 66 and 67 were obtained in a 19:81 ratio (THF)(entry 8) and 18:82 ratio (benzene) (entry 9). Finally, 58 was recovered unchanged on an attempted reaction with tetra-n-butylammonium iodide in THF(entry

10). The chemical yields of the ring opened products are lower when lithium halides are used, perhaps due to competing ring contraction to 2(R)-(benzyloxy)-2,5-dihydrofuran -4-carboxaldehyde (63), followed by its decomposition under the reaction conditions.

When the nucleophile was cyanide, activation of 58 with titanium tetraisopropoxide and tetra-n-butylammonium iodide, as reported by Sharpless, was found necessary.[93] Under these conditions, benzyl 4-deoxy-4-cyano-α-L-lyxopyranoside (69) was obtained as the major product, accompanied by benzyl 4-deoxy-4-iodo-α-L-lyxopyranoside (68) (entry 11). It is interesting to note that 68 is not formed in the experiment with tetra-n-butylammonium iodide reported earlier. Potassium cyanide in 1,3- dimethyl-2-imidazolidone was inactive on attempted reaction with 58, while sodium cyanide in DMF gave a low yield of 69.

Both sodium acetylide and ethynylmagnesium bromide were unsuccessful in attempts to open up 58 with the acetylide anion. While no reaction was observed with sodium acetylide(entry 12), the Grignard reagent functioned as a bromide source and products 64 and 65 were formed in a 11:89 ratio(entry 13). Such halide induced ring openings of epoxides when Grignard reagents are used is well documented.[94] Sodium azide in DMF cleaved 58 to furnish in a 3:2 ratio the C-4 and C-3 opened products 71 and 72, respectively (entry 14). Epoxide 58 was unreactive towards sodium

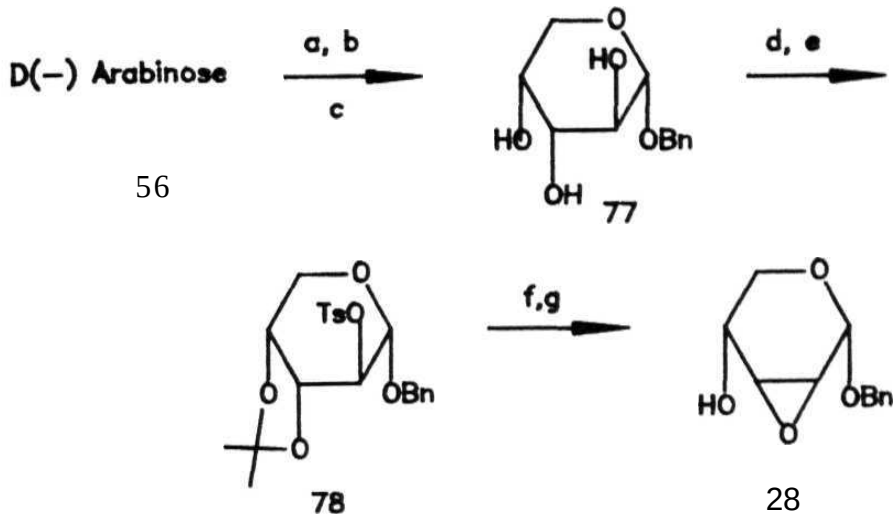
azide in THF even after prolonged reaction times at reflux(entry 15). Similarly, sodium thiophenoxide in THF gave almost equal amounts of 73(487.) and 74(52%)(entry 16).

Finally, when methoxide was employed as a nucleophile, the regiochemistry of the ring opening of 58 again showed a cation dependence. Sodium methoxide in methanol gave as the major product the C-4 ring opened compound 75(767.) versus the C-3 isomer 76(247.)(entry 17). With magnesium methoxide in methanol, the ratio of 75:76 was 7:93(entry 18).Epoxide 58 was inert towards sodium methoxide in THF(entry 19).

Thus, overall, the ratio of ring opened products was mainly dependent upon the counter-cation and the nature of the nucleophile. These results are different from those obtained for the α-epoxide(26). This prompted us to turn our attention to 2,3-anhydroribopyranosides and examine the factors controlling the regiochemistry of ring opening in these compounds.

Only a few examples were reported on the ring opening reactions of benzyl 2,3-anhydro-α-D-ribopyranoside, while as mentioned in the introduction, the β- anomer has been well studied. Therefore, we elected to investigate the ring opening reaction of the a- anomer. Benzyl 2,3-anhydro-a-D-ribopyranoside ( 28 ) was prepared from D (-)arabinose as reported (Scheme 35).

Thus, D(-) arabinose was treated with sodium acetate in acetic anhydride to give 1,2,3,4-tetra-O-acetyl-α-D-arabino-




a)$Ac_2O$, NaOAc; b) $PhCH_2OH$, $BF_3.OEt_2$, $CH_2Cl_2$; c)NaOMe(cat), MeOH; d) acetone, 2,2- dimethoxypropane, TsOH(cat.); e)TsCl, pyridine; f)l N $H_2SO_4$ acetone:water(1:10), reflux; g)NaOMe, MeOH.

Scheme 35

pyranose, which on reaction with benzyl alcohol in the presence of boron trifluoride etherate in dichloromethane as solvent, followed by treatment with catalytic amount of sodium methoxide in methanol gave benzyl α-D-arabinopyranoside(60). Arabinoside 77 was reacted with 2,2-dimethoxypropane in the presence of a catalytic amount of p-toluenesulfonic acid in acetone, followed by tosylation in pyridine to furnish benzyl 2-O-p-toluenesulfonyl-3,4-O-isopropylidene-α-D-arabinopyranoside (78). Acetonide 78 on treatment with sulphuric acid in acetone:water (1:10) gave benzyl

2-O-*p*-toluenesulfonyl-α-D-arabinopyranoside which on cyclization with sodium methoxide in methanol gave the required epoxide 28. The spectral properties of 28 agreed well with those reported in the literature.[57]

The H NMR spectrum of 28 shows a singlet anomeric signal (in $CDCl_3$) with $J = 0$ Hz. $J_{1,2}$ could not be measured due to complexity in that region of the spectrum. This suggests that 28 preferentially adopts the conformer 28A as shown in Figure 4.

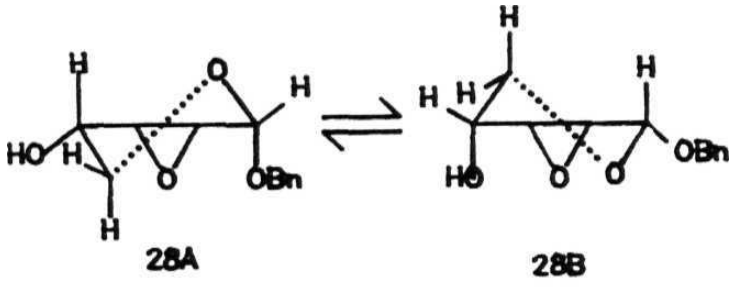
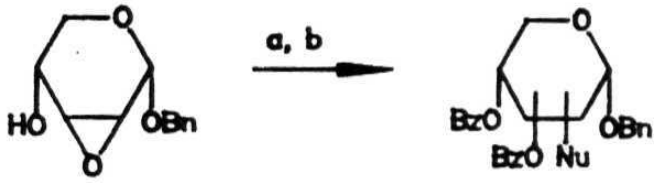



Figure 4

As in the case of 3,4-anhydroribopyranosides, the free energy difference between the two conformers of 28 is likely to be small. It can be assumed that the activation energy required for ring opening will be much larger when compared to the free energy difference between the two conformers.[62] Under these circumstances, the regiochemistry of ring opening would be governed by the Curtin-Hammett principle. i.e., ring opening would

be independent of the position of conformational equilibrium, but depend only upon the activation energies of the reaction involving the two conformers.

Table 9. Ring opening reactions of 28 with different nucleophiles.




28

a) Nucleophile. b) PhCOCl, Pyridine, rt.

| Entry | Nucleophile | Metal Counter-cation | Solvent | Yield(7.) | Site of substitution | Product |
|---|---|---|---|---|---|---|
| 1 | Br | $Mg^{2+}$ | THF | 77 | C-3 | 79 |
| 2 | H | $Li^{+}$ | THF | 78 | C-3 | 80 |
| 3 | CN | $K^{+}$ | DMSO | 70 | C-3 | 81 |
| 4 | $N_3$ | $Na^{+}$ | DMF | 76 | C-3 | 82 |
| 5 | SPh | $Na^{+}$ | THF | 84 | C-3 | 83 |
| 6 | OMe | $Na^{+}$ | MeOH | 83 | C-3 | 85 |
| 7 | OMe | $Mg^{2+}$ | MeOH | 85 | C-3 | 85 |

As shown in Table 9, nucleophilic ring opening of 28 was carried out with a variety of nucleophiles including variation of the counter-cation. It is seen that in all cases, the yields of the ring opened products are very good and within limits of detection, only one product was obtained.

Ring opening at C-3 provided benzyl 3-deoxy-3-substituted α-D-xylopyranoside derivatives. NMR data ( Table 10 )clearly shows

Table 10. Selected H NMR coupling constants of ring opened products.

| Compound | Coupling Constants, Hz | | | |
|---|---|---|---|---|
| | $J_{1,2}$ | $J_{2,3}$ | $J_{4,5}$ | $J_{4,5'}$ |
| 79 | 3.7 | 10.8 | 5.8 | 10.6 |
| 80 | 3.1 | c | c | c |
| 81 | c | c | 5.7 | 10.7 |
| 82 | 3.6 | 10.1 | 5.5 | 10.7 |
| 84 | 3.4 | 10.6 | 6.0 | 10.6 |
| 85 | c | 9.6 | 5.8 | 10.6 |

c = complex

that the $^4C$ conformer is the major one with $^1C$. conformer being a

minor contributor to the conformational equilibrium as J and J, are uniformly high, leading to the conclusion that H-2, H-3. 4,5 H-4 and H-5' are all axially oriented (Figure 5).

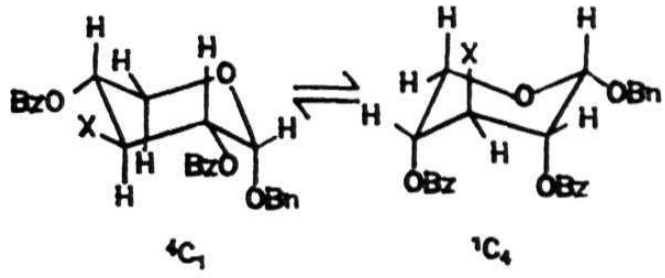



Figure 5

Epoxide 28 reacted with magnesium bromide in THF, giving the ring opened product 79 after benzoylation ( entry 1). Reaction of 28 with LAH at room temperature in THF, after benzoylation, gave 80 (entry 2 ).No C-2 ring opened product was obtained. The ring opening of 28 with cyanide as nucleophile was carried out

93

following the specific conditions of Sharpless. Thus, treatment of 28 with potassium cyanide in dry DMSO in the presence of titanium tetraisopropoxide and tetra-n-butylammonium iodide gave after benzoylation 81, (entry 3 ) in an overall yield of 707..

Epoxide 28 when treated with sodium azide in DMF at 80 yielded a product which was benzoylated to furnish 82 (entry 4 ). The reaction of 28 with sodium thiophenoxide in THF gave 83 after

benzoylation (entry 5) in an overall yield of 837..

Finally, when methoxide (Na counter-cation) was employed as a nucleophile, C-3 ring opened product 85 was obtained after benzoylation (entry 6). With magnesium methoxide, once again the same product 85 was obtained after the usual benzoylation (entry 7). All the above products were thoroughly characterised using the methods detailed earlier for the identification of the ring opened products derived from epoxide 28. Thus, ring opening of epoxide 28 at C-3 provided benzyl 3-deoxy, 3- substituted α-D-xylose derivatives only.

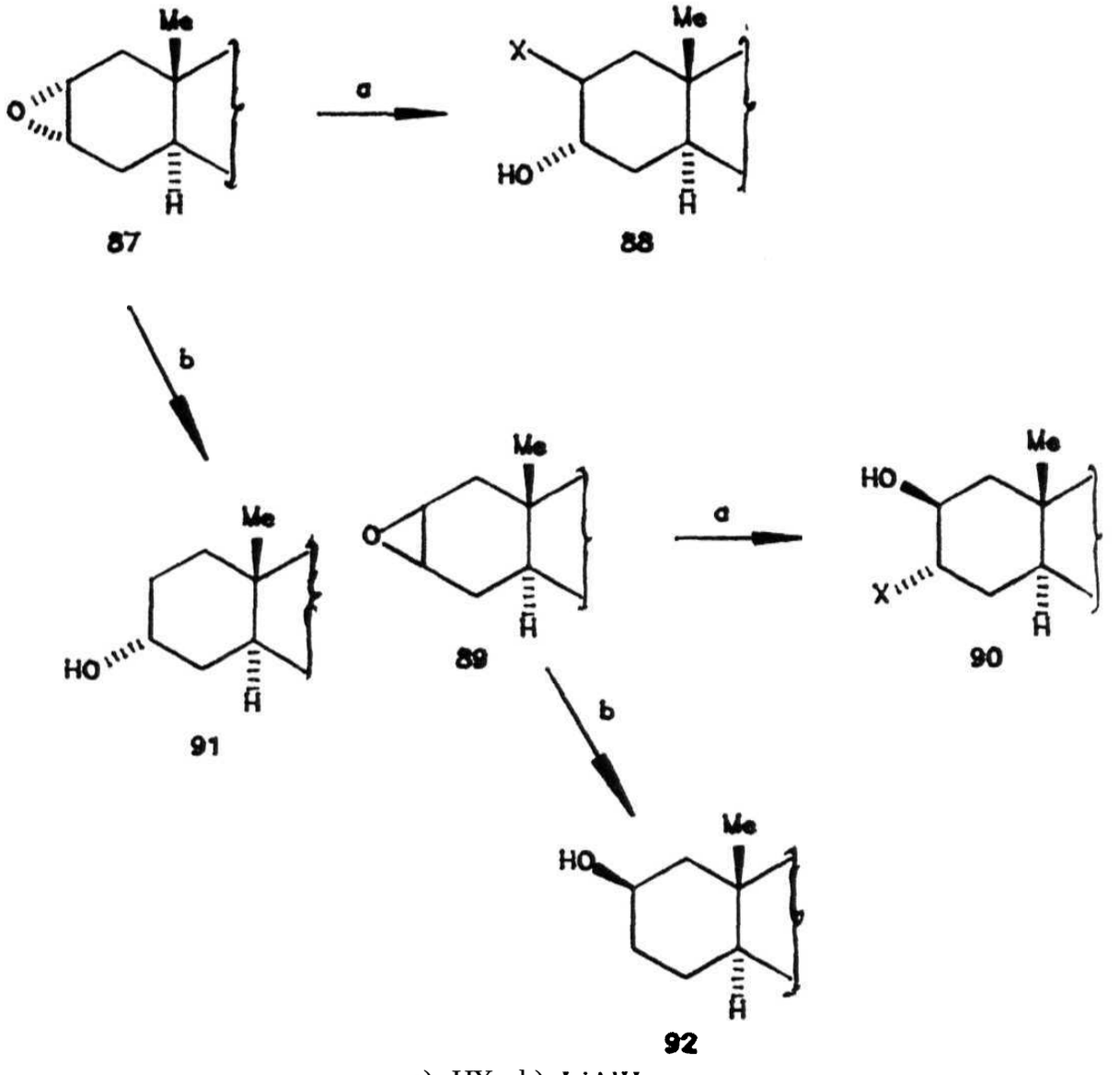
Interestingly, amongst the four possible 2,3- and 3,4-anhydroribopyranosides, we observed good selectivity in the α-series. Also, the a- series was more reactive compared to the corresponding β-series. The relative inertness of the β- series is possibly due to the steric effect of the anomeric group towards axial attack of the nucleophile from the same side.

# Discussion

The regio- and stereochemical features of ring opening of epoxides was first studied by Furst and Plattner. They observed that in rigid steroidal epoxides, the major product was that stereoisomer in which the incoming group and the hydroxyl group were trans-diaxially disposed with respect to one another. The most clear-cut example is the behaviour of 5α-cholestane-2,3-epoxides 87 and 89 towards acids HX, leading invariably to the 2β,3α-isomers 88 and 90, respectively (Scheme 36).[95]

Similarly, LAH in ether yields the 3-α-alcohol 91 and 2β-alcohol 92, respectively.[96] Based on these observations, Furst and Plattner proposed that epoxides preferentially open via axial attack leading to a trans-diaxial product, which is often referred as the Furst-Plattner rule.[97] Angyal studied further mechanistic implications of the rule with a wide variety of substrates including non-rigid systems and discussed the following aspects.
i) The predominance of the diaxial isomer in the reactions of fused, rigid cyclohexene oxide systems; ii) the formation of some of the other, diequatorial, isomer in such systems; and iii) the behaviour of flexible systems.[98]

Figure 6 shows a cyclohexene oxide, rigidly held in its stable half-chair form by fusion to another ring and undergoing reaction with a nucleophile Nu. When Nu attacks the molecule, the most favourable transition state will be anti-parallel, involving




a) HX; b) $LiAlH_4$.

Scheme 36

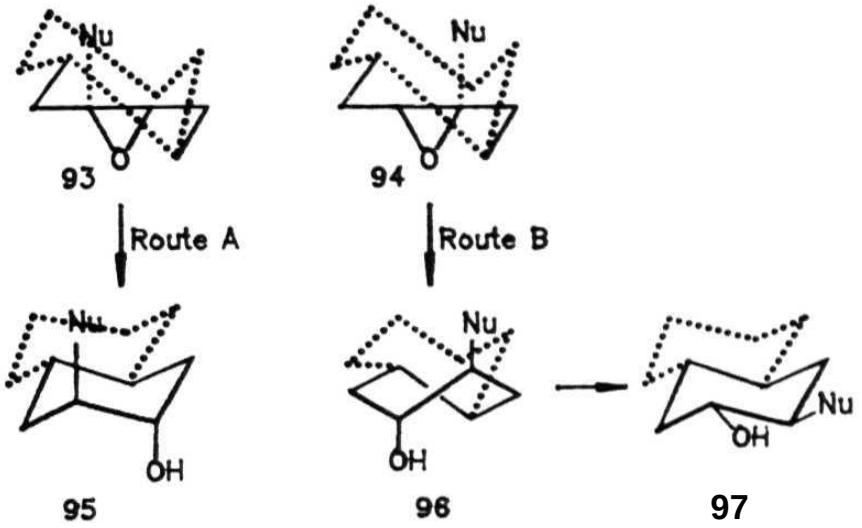



**Figure 6**

the approach of Nu from an axial direction, as in 93 or 94. Route A, in which the transition state is chair like, yielding product 95, will be favoured over route **B,** in which the transition state is boat (or skew) like. Boat conformer 96, the initial product in route **B,** will readily change to the chair conformer 97. Route A represents "diaxial" opening of the epoxide ring and is energetically preferred over route B, the so-called "equatorial" opening. According to Angyal, routes A and B both involve diaxial opening, in contrast to views, expressed by Cookson[99] and by Parker and Issacs who said that when steric or polar factors are also present in the system, the energy difference between the two pathways may be reduced or even reversed, and "exceptions" to the

Furst-Plattner rule may be found. Mechanistically, the Furst-Plattner rule is always obeyed, in the sense that nucleophilic attack always comes from an axial direction, even in examples in which the regioselectivity of the reaction is entirely due to steric or electronic effects.

In the case of flexible cyclohexene epoxides, the situation is more complex, as shown in Figure 7. In route A, the initial diaxial product 99 can undergo conformational change to the

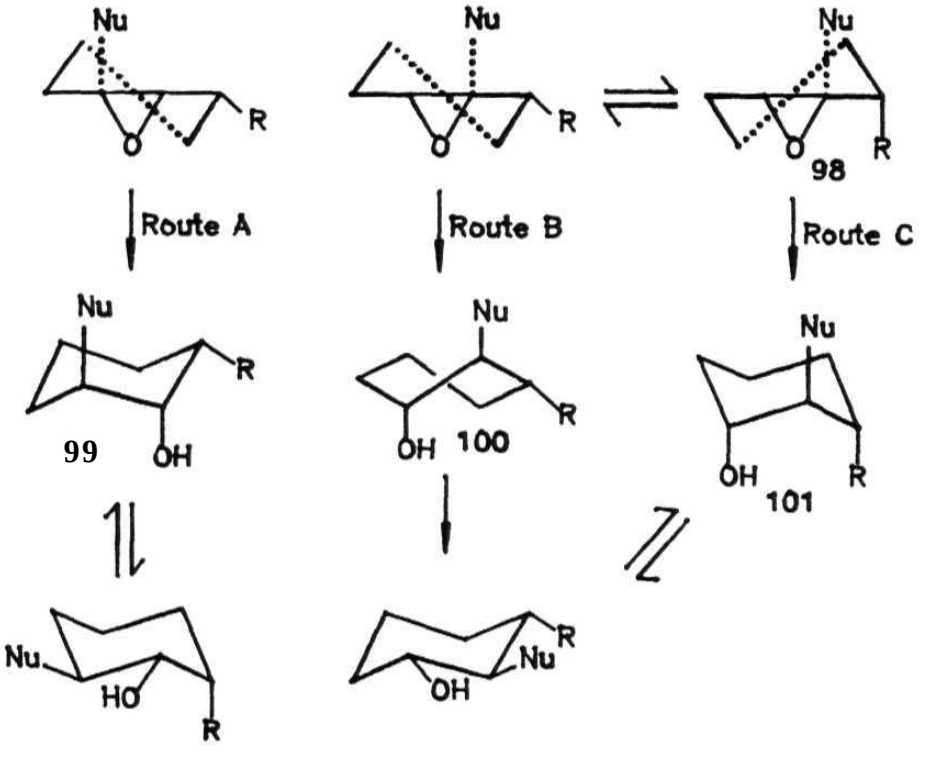



Figure 7

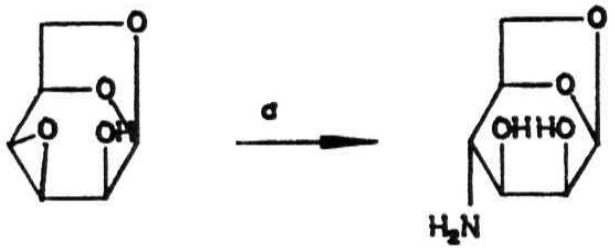
diequatorial form **102.** Furthermore, nucleophile Nu can attack the other carbon atom not only by route **B,** as before, but also by route C, in which the transition state is related to the other half-chair form 98. The initial diaxial product **101** undergoes ring flip to the diequatorial form **103.**

Mills studied the ring opening reactions of rigid sugar epoxides and observed diaxial ring opening, which is similar to that seen in rigid steroidal epoxides. Mills applied the Furst-Plattner rule to account for this behaviour in rigid sugar epoxides. Thus, the talose derivatives **104** and **106** on reaction with ammonia[3] yielded diaxial products **105** and **107,** respectively (Scheme 37). Similarly, the alloside **22** on reaction with aqueous alkali gave **108** (Scheme 38).[102]

In the case of alkyl 2,3- and 3,4-anhydrohexopyranosides, the carbon substituent on C-5 has an interesting effect.

The anhydromannoside **109,** on treatment with hydrogen chloride in acetone, gives a high yield of chlorohydrin **111** (Scheme 39), the isomer expected on polar and conformational grounds. The transition state **110** posseses an equatorial hydroxymethyl group, the anomeric disposition is favourable and there is only a single 1,3-diaxial interaction. In the case of anhydroalloside **112** (Scheme 40), however, the transition state **113** for attack at C-3 has two unfavourable interactions; not only is the anomeric configuration unfavourable, but the C-6

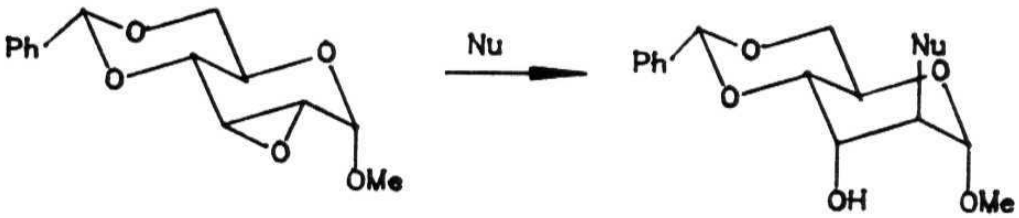

104 105




106 107

a) $NH_3$.

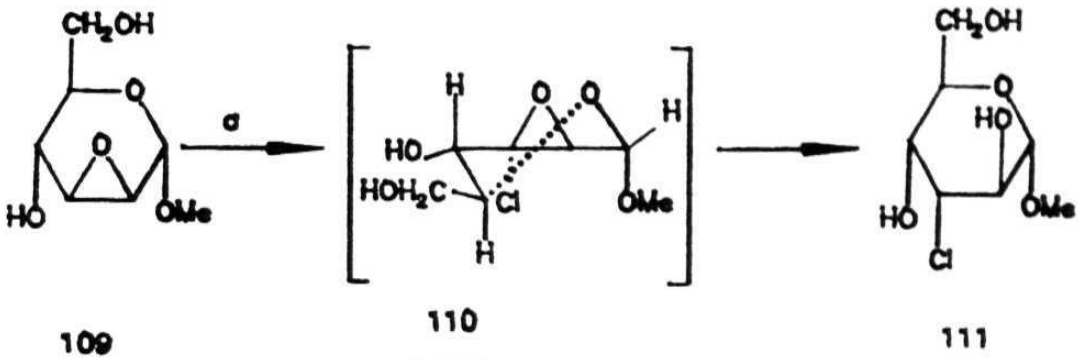
Scheme 37




22 108

Nu: OH.

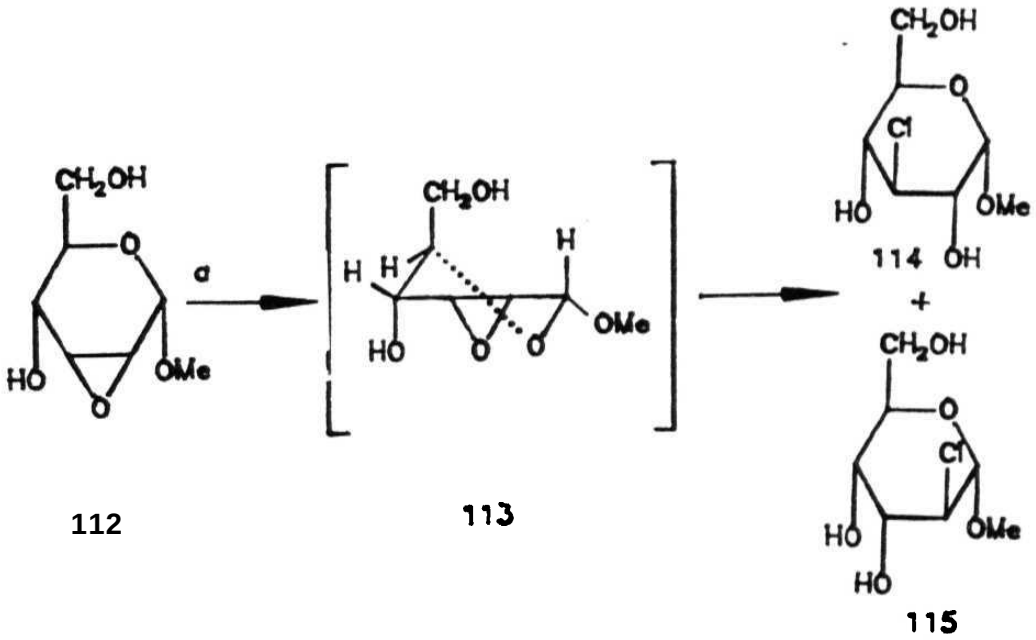
Scheme 38




109 110 111

a) HCl.

Scheme 39



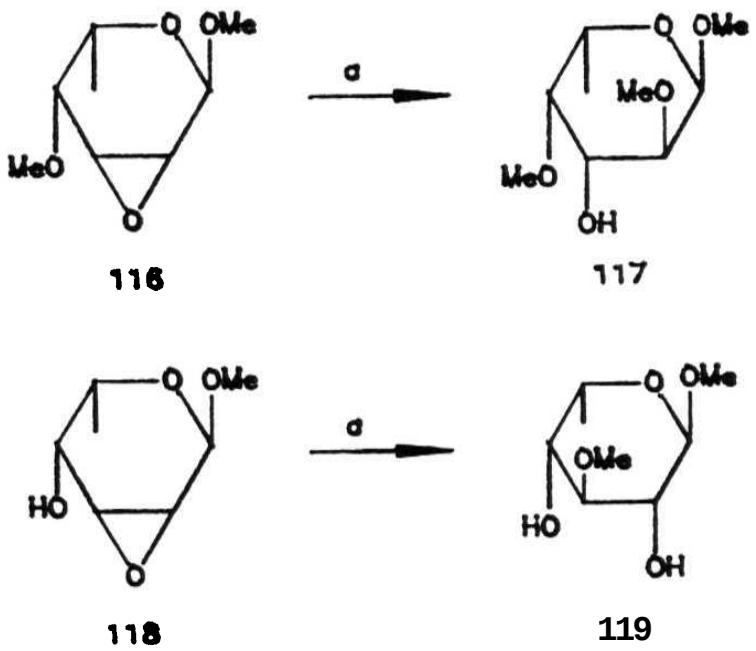

112 113

a) HCl.

Scheme 40

hydroxymethyl group, in an axial orientation, exerts a repulsive steric 1,3-diaxial interaction with the incoming nucleophile. Therefore, both 114 and 115 are formed in comparable amounts.[103]

Charalambus and Percival examined the fission of methyl 2,3- and 3,4- anhydro-6-deoxy-α-L-taloside and their 4- and 2- methyl derivatives with sodium methoxide.[104] Methyl 4-O-methyl -2,3-anhydro-6-deoxy-α-L-taloside(116), when reacted with sodium methoxide, gave the corresponding 2- methoxy derivative (117),



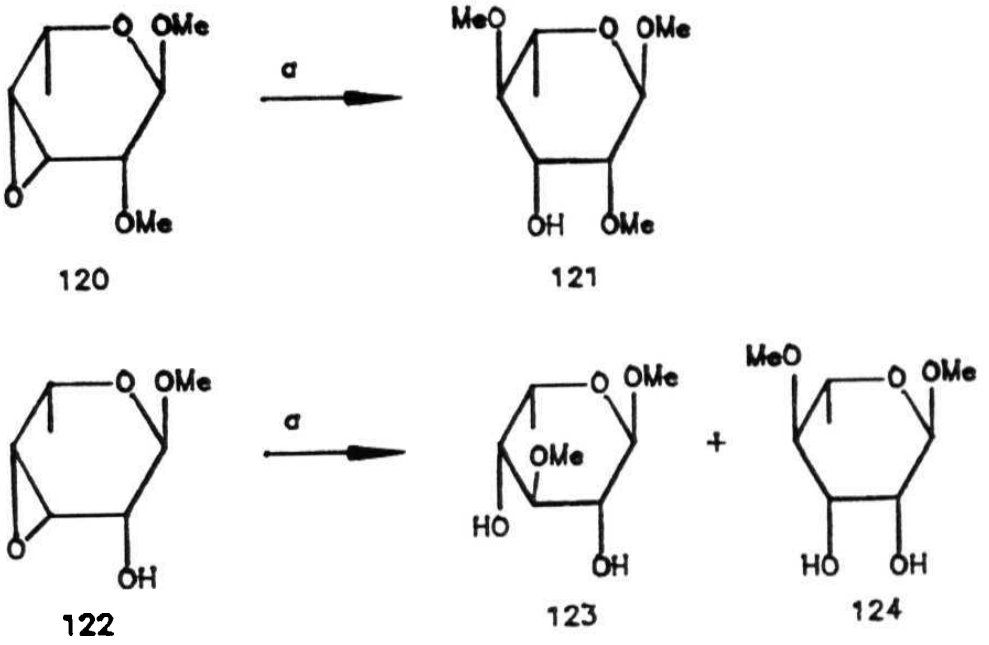

116 117

118 119

a) NaOMe.

Scheme 41

whereas the unmethylated derivative **(118)** gave 3- methoxy derivative (119)(Scheme 41). Similarly, methyl 2-O-methyl -3,4-anhydro-α-L-taloside **(120)** gave the 4-O-methyl derivative **(121),** while unmethylated **(122)** gave 3- and 4- substituted methyl derivatives **123** and **124** in a 2:1 ratio(Scheme 42).




a) NaOMe.

**Scheme 42**

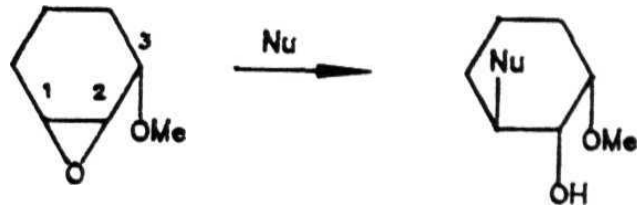
The only reasonable explanation for this variation must involve the free hydroxyl group in **118** and **122** and it was suggested that hydrogen bonding between this group and the

pyranose oxygen was involved in stabilizing one conformation in preference to another.

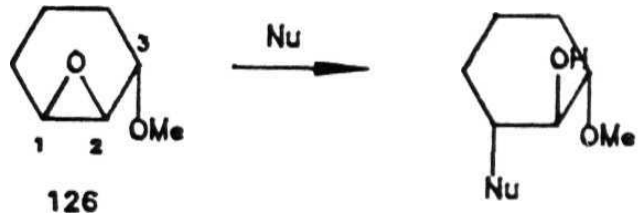
In order to rationalize the results observed in the ring opening of 2,3- and 3,4-anhydropentopyranosides, the explanations offered in the case of cyclohexene oxides can be extended. These include factors such as the role of the pyranose oxygen, anomeric configuration and hydrogen bonding, if any. Thus, overall, the various factors can be conveniently listed as a) electronic factors b) steric factors and nature of the nucleophile c) conformational factors and nature of the counter-cation. A detailed discussion of these factors follows.

**a) Electronic factors:**

Electronic effects are most pronounced when an electron-withdrawing atom or group is located adjacent to the epoxide ring. Thus, 3-methoxycyclohexene oxides **125** and **126** open preferentially at position 1 under nucleophilic attack by hydroxide, methoxide and LAH(Scheme 43). This observation was ascribed to the polar effects of the alkoxy substituent. The electronegative ethereal oxygen, by withdrawing electron density from C-3, imposes a partial positive charge on that carbon atom. A developing positive charge at C-2 would lead to a repulsive interaction between these two centers and hence result in a substantial increase in the energy of activation for attack at C-2, when compared to C-1. Since the repulsive interaction




**125**




**126**

Nu: OH, OMe, H

**Scheme** 43

between the two positively charged centers diminishes as a function of the distance between them, the energy of activation for the path involving **127a** will be less than that for **127b,** and therefore the former will predominate (Figure 8), thus accounting for the results obtained.

Crotti and co-workers studied the ring opening reactions of 3,4-epoxytetrahydropyran **(128)** under non-chelating conditions (Scheme 44).[108] The C-4 selectivity observed in most cases was

**127a** **127b**

**Figure 8**

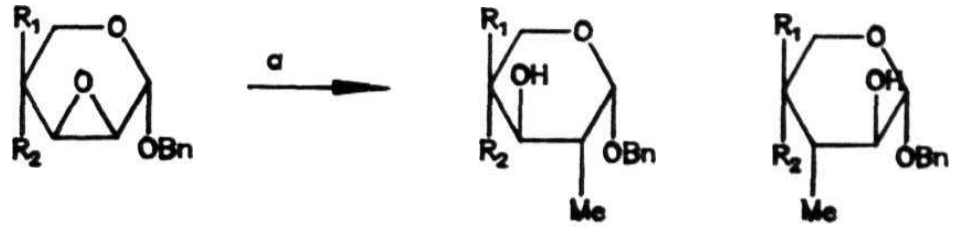

Nu: $NEt_2$, $NMe_2$, $N_3$, Cl, CN, MeO, PhS, Me, H.

Scheme 44

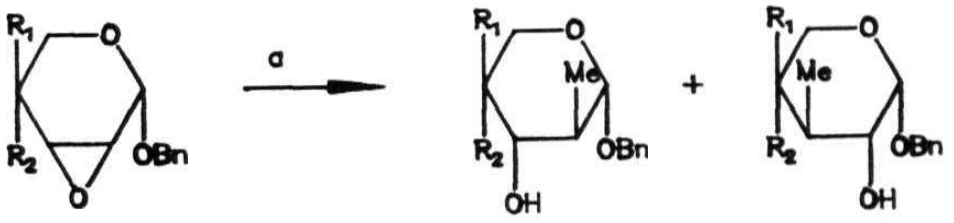
rationalized on the basis of the unfavourable interaction due to the electron-withdrawing inductive effect of the pyranose oxygen and the epoxide ring. A similar rationalization was extended to cts-2-benzyloxy-4,5-epoxytetrahydropyran (27), which also gave C-4 substituted derivatives with various nucleophiles, in most cases.

Magnusson and co-workers, in their study of oxirane ring opening reactions of alkyl 2,3-anhydropentopyranosides with trimethylaluminum, observed ring opening at C-3 as the major

product (Scheme 45) except in one case.[30]




| | C–2 (%) | C–3 (%) |
|---|---|---|
| $R_1$ - OTBDMS, $R_2$ - H | 37 | 11 |
| $R_1$ - H, $R_2$ - OTBDMS | 2 | 56 |




| | C–2 (%) | C–3 (%) |
|---|---|---|
| $R_1$ = H, $R_2$ = OTBDMS | 0 | 38 |
| $R_1$ - OTBDMS, $R_2$ = H | 3 | 39 |

a) $Me_3Al$.

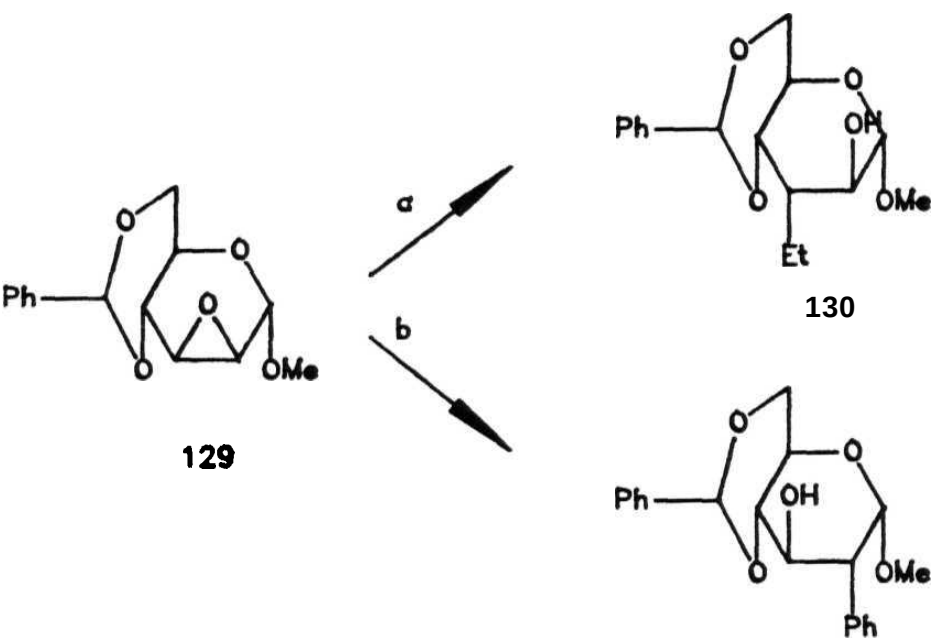
Scheme 45

Once again the same explanation, based on the electron withdrawing character of the anomeric oxygen, destabilizing a

developing positive charge at C-2, was offered and attack at C-3 was accounted for.

**b) Steric factors and nature of the nucleophile.**

Reaction of methyl 2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranoside (129) with diethylmagnesium gave C-3 substituted product **130,** whereas with diphenylmagnesium the C-2 substituted product **131** was formed(Scheme 46). This is probably due to a simple steric effect. The formation of a diaxial product necessitates attack at C-3 and in the case of diphenylmagnesium,




129

130

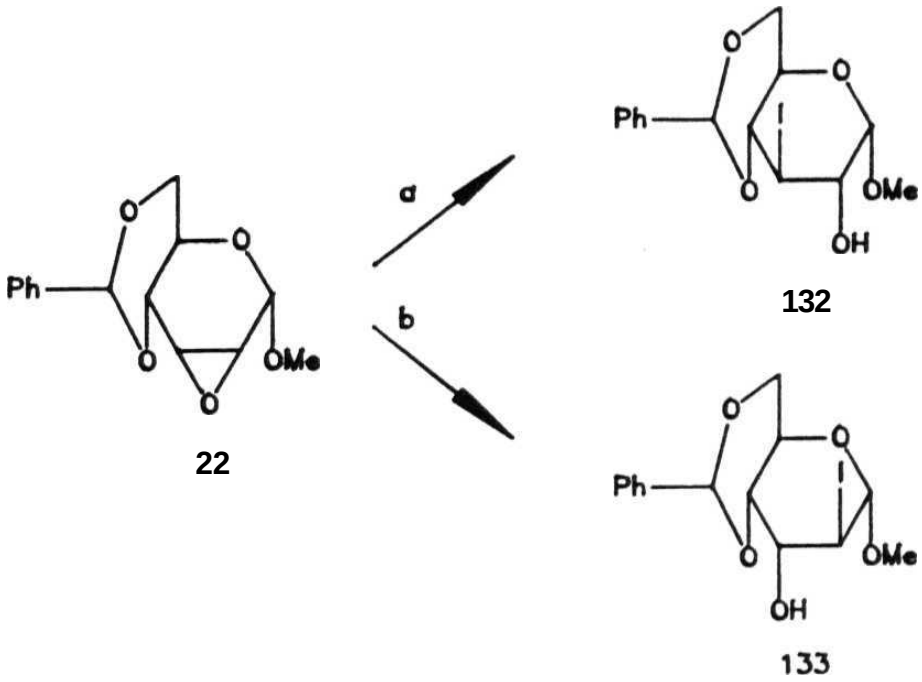
131

a) $(C_2H_5)_2Mg$; b)$(Ph)_2Mg$.

**Scheme 46**

such an attack (presumably by the bulky phenyl anion) may well be subject to steric hindrance by the adjacent bulky benzylidene group as well as repulsive 1,3- diaxial interaction between the phenyl and the anomeric methoxy group.

A somewhat similar observation was made when methyl 2,3-anhydro-4,6-benzylidene-α-D-allopyranoside (22) was reacted with methylmagnesium iodide and ethylmagnesium iodide to give C-3

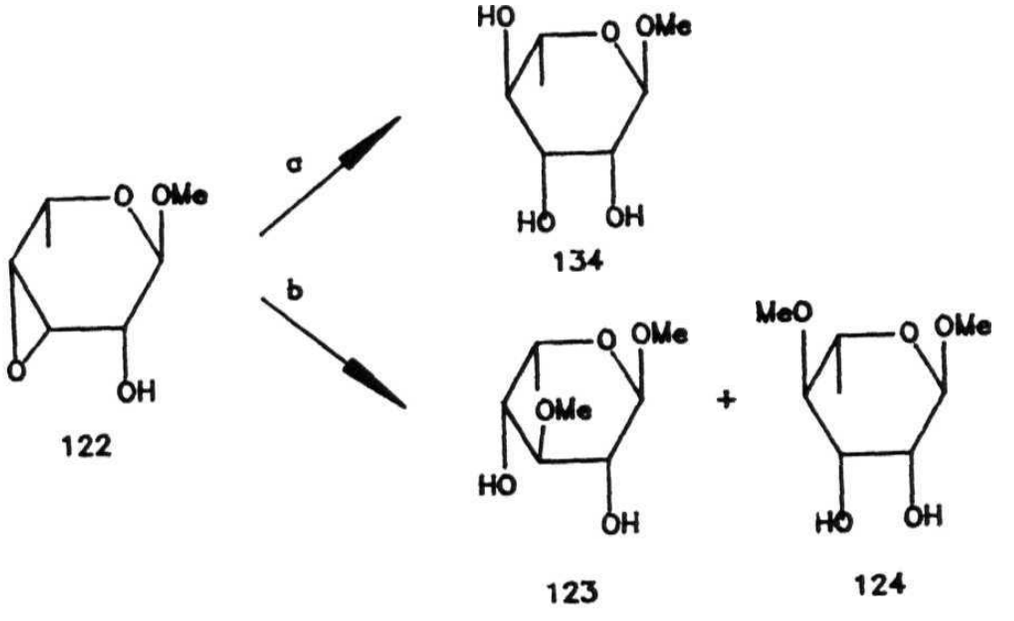



a) MeMgI; b)EtMgI.

Scheme 47

and C-2 substituted iodohydrins 132 and 133, respectively (Scheme 47).[24, 94]

The nature of the nucleophile also determines, to some extent, the regiochemistry of ring opening. Thus, epoxide 122 underwent reaction in aqueous barium hydroxide to give 134, whereas with sodium methoxide 123 and 124 were obtained in ratio of 2:1 (Scheme 48).[104]




a)Ba(OH) ; b)NaOMe.

Scheme 48

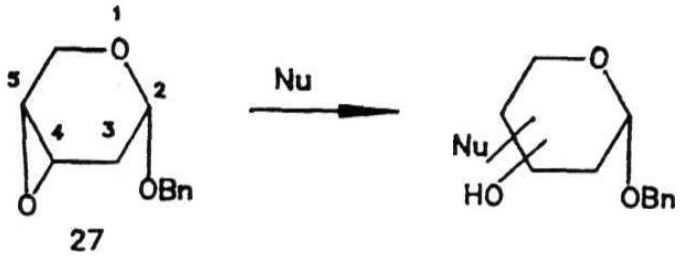
**c) Conformational factors and nature of counter-cation.**

In the case of 2,3- and 3,4-anhydropentopyranosides, the two half-chair forms are freely interconvertible. The regiochemistry of ring opening in these substrates is seldom clear-cut and any nucleophilic attack is governed by the Curtin-Hammett principle, as the activation energy for ring opening of either conformer is much greater than the free energy difference between the conformers.

It has been emphasized that it is the difference in transition state energies which determine the regioselectivity of epoxide ring opening and not the relative proportion of conformers in the ground states. Nevertheless, many of the nonbonded interactions that determine the proportions of ground state conformers are also present in the corresponding transition states. It may be expected, therefore, that in systems lacking steric or polar effects, the regioselectivity can be predicted to a first approximation, from a knowledge of the proportion of conformers in the ground state.

Reactions of *cis*-2-benzyloxy-4,5-epoxytetrahydropyran(27) with nucleophiles under non-chelating conditions preferentially occur at the C-4 carbon(Table 11). This result can be rationalized on the basis of a trans-diaxial opening of the epoxide in accordance with the Furst-Plattner rule, through its more stable conformation 27a (as determined from its NMR spectrum), as well as

**Table 11: Nucleophilic ring opening reactions of the epoxide 27.**




27

| Entry | Reagents | Solvent | C-5 Product[a] | C-4 product |
|---|---|---|---|---|
| 1. | $NaN_3/NH_4Cl$ | MeOH:H 0(8:1) | 6 | 94 |
| 2. | $NaN_3/LiClO_4$ | $CH_3CN$ | 86 | 14 |
| 3. | $Et_2NH$ | EtOH | 24 | 76 |
| 4. | Et NH/$LiClO_4$ | CH CN | 82 | 18 |
| 5. | $LiAlH_4$ | Pentane | 42 | 58 |
| 6. | LiALH /crown | Pentane | 9 | 91 |

C-5 is equivalent to C-4 of epoxide 58 and C-4 equivalent to C-3.

the electronegative effect of the ring oxygen atom, as discussed earlier in (a)(however, the contribution of the anomeric effect in stabilizing conformer 27b was ignored by these authors) (Figure 9).[30]

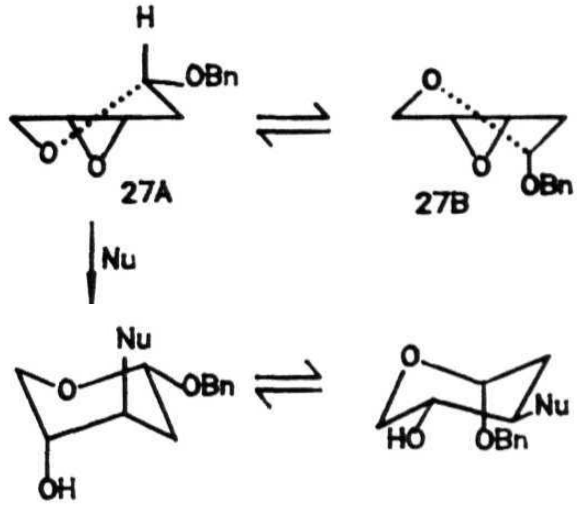



**Figure 9**

Under chelating conditions, a large increase in C-5 selectivity was observed with all nucleophiles. This increase was attributed to the direct intervention of the metal species (Li in this instance) in the opening process by the intermediate

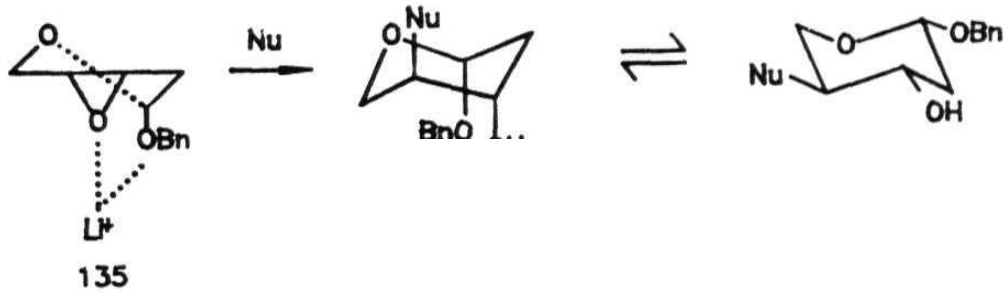


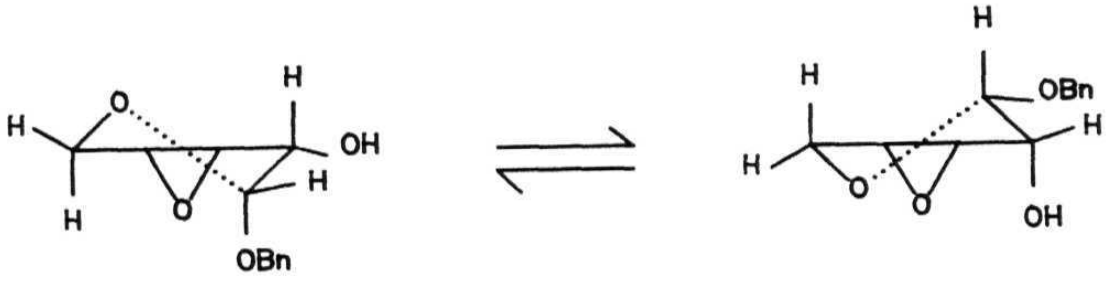

**Figure 10**

formation of a bidentate chelate structure such as 135(Figure 10).

This chelate species is formed by initial complexation of the metal ion with the benzyloxy oxygen of 27 followed by entropically favoured coordination with oxirane oxygen, leading to the bidentate chelate structure **135.** Axial attack of the nucleophile on intermediate **135** would lead to the formation of C-5 products as experimentally observed.

**Background to the present work:**

**In** the case of benzyl 3,4-anhydro-α-D-ribopyranoside (26) it was observed that reaction takes place exclusively at C-3. Between the two possible comformers **26A** and 26B(Figure 11), **26A** is the preferred one due to the anomeric effect. In **26A,** the nucleophile attacks at C-3 as there is a 1,3- diaxial interaction between the incoming nucleophile and pyranose oxygen lone pair for attack at C-4.[29] However, as conformers **26A** and **26B** are not expected to differ significantly in energy, the regiochemistry of ring opening




**26A** **26B**

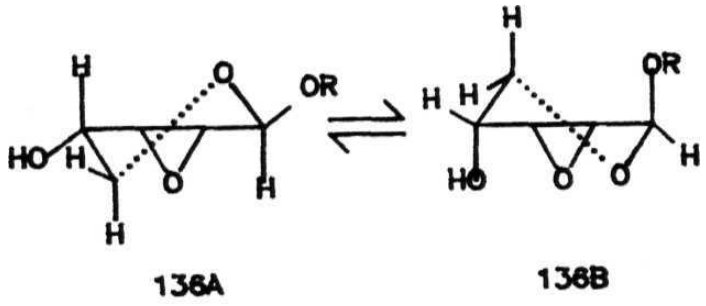
**Figure 11**

preferred in conformer 26B has to be considered as well. In 26B, the nucleophile prefers to attack at C-3 than at C-4 perhaps due to better hydrogen bonding between the hydroxyl group at C-2 and the epoxy oxygen, thereby rendering the C-3 oxygen bond more susceptible to nucleophilic cleavage. Thus in both conformations, attack is favoured at C-3. Therefore, the formation of 3-substituted xylose derivative can be rationalized readily.

As seen in the introduction, ring opening reactions of alkyl 2,3-anhydro-β-D-ribopyranoside (136) have been well studied. In most cases, the ring opens exclusively at C-3 to give C-3 substituted, 3-deoxyxylose derivatives. Newth suggested that the C-4 hydroxyl group adequately explains the formation of xylose derivatives, as conformer 136B (Figure 12) stabilized through a hydrogen bond, reacts preferentially at C-3. This argument is invalidated in basic media, where the hydroxyl group can be deprotonated, thus leading to loss of hydrogen bonding, but is perhaps applicable to non-basic nucleophiles.

Crotti has reported exclusive formation of C-3 substituted products in the absence of hydroxyl group (Table 6). He suggested that the electron withdrawing nature at C-1 destabilises C-2 towards nucleophilc attack, thus directing it to C-3.

Between the two possible conformers 136A and 136B(Figure 12), 136B is the preferred one due to the anomeric effect.[85] This conclusion is also supported by NMR spectral measurements, which




136A 136B

Figure 12

show a singlet anomeric signal in most of the alkyl derivatives, with $J_{2} \simeq 0$ Hz. In conformation 136B, attack can take place either at C-3 or C-2. It was explained that nucleophilic attack on 136B occurs at C-3 than at C-2 as the approach of the nucleophile to the latter position involves a repulsive interaction between the incoming nucleophile and the anomeric alkoxy substituent for C-2 ring opening. Such an interaction is absent for attack at C-3, and in the absence of steric factors, ring opening takes place at C-3.[112] However, as both conformers are not expected to differ significantly in energy, the regiochemistry of ring opening preferred in conformer 136A has to be considered as well. In conformer 136A, there is a 1,3- diaxial interaction between the entering nucleophile and pyranose oxygen lone pair of electrons for attack at C-2. There is no such

repulsive interaction for attack at C-3. Thus, the pyranose oxygen controls the regiochemistry of ring opening directing the attack at C-3. Therefore, the formation of a 3-substituted xylose derivative can be rationalized readily.

Magnusson and co-workers studied the ring opening of 2,3-anhydropentopyranosides. In most cases, mixtures of products were obtained. Formation of the major product in each case was explained as, due to favourable trans-diaxial cleavage (Furst-Plattner rule) as shown in Figure 13.

Thus, various factors are responsible for controlling the regiochemistry in ring opening reactions. In some of the cases surveyed above, 1,3-diaxial interaction between the anomeric group and nucleophile, also between pyranose oxygen and nucleophile were not considered. Keeping all this in view, the following paragraphs present our view of the results detailed in the previous section.

**Present work:**

**a) Reactions of benzyl 3,4-anhydro-β-D-ribopyranoside.**

**A** perusal of the results obtained, as given in the previous section, makes it evident that a number of factors have to be considered to understand the regiochemistry of ring opening of **58**. The more important amongst them are conformational, stereoelectronic factors and the nature of the counter-cation.

All these factors, as applied to epoxide 58, suggest that conformer **58A** with the anomeric substituent in a quasi-axial

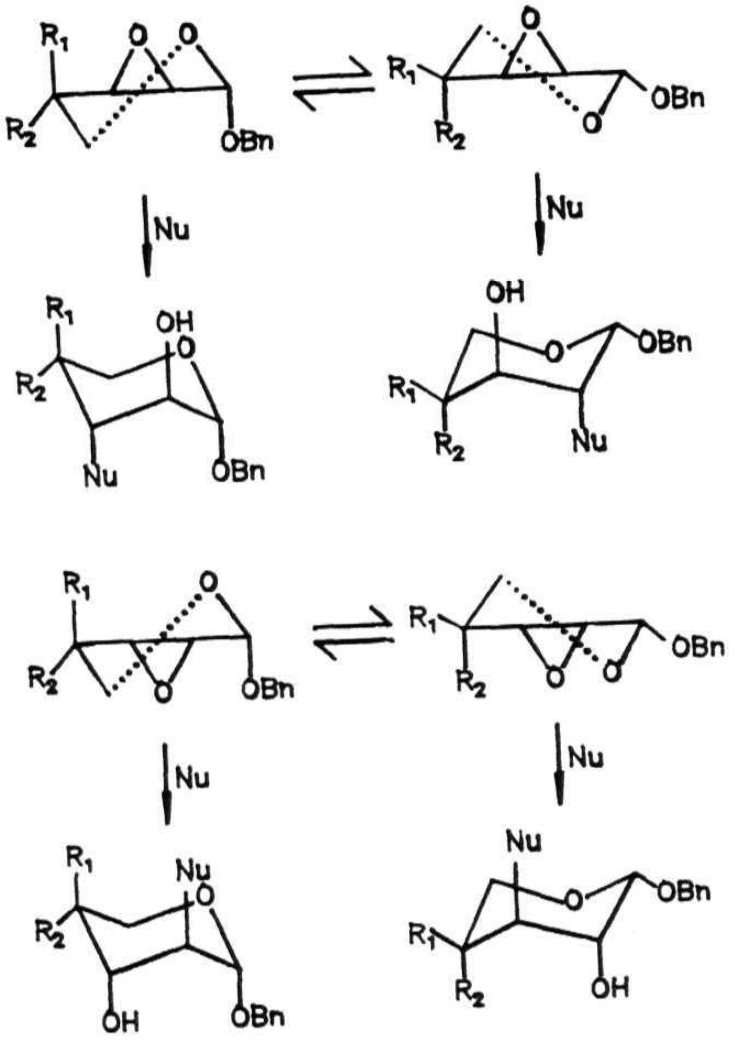
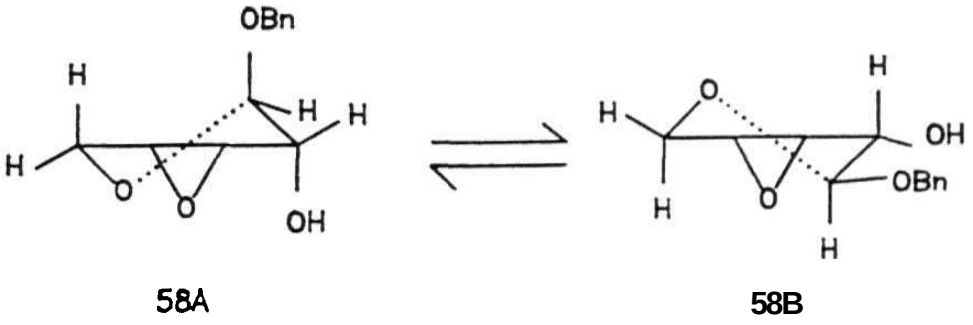



**Figure 13**

position, is likely to lead to a transition state with lower

energy than that obtained from conformer 58B(Figure 2), where the anomeric substituent is quasi-equatorial. Attack by the nucleophile at C-4 of conformer 58A in preference to C-3, leads to a transition state with fewer 1,3 -diaxial interactions and finally results in a 4- substituted 4-deoxy **-α-L-lyxopyranoside**. The alternate conformer 58B, in a similar fashion, would be preferentially cleaved at C-3, as attack at C-4 entails a repulsive 1,3- diaxial interaction between the incoming nucleophile and the lone pair of electrons on the pyranose oxygen. On this basis, it is reasonable to predict that the preferred mode of attack will be at C-4 of the epoxide 58 via conformer **58A.Attack** on conformer 58B, at best a minor pathway, will be preferentially at C-3. As mentioned in the introduction, this is what is seen with methyl, ethyl and benzyl 3,4-**anhydro-β-L-ribopyranosides** in the limited number of examples




**58A** **58B**

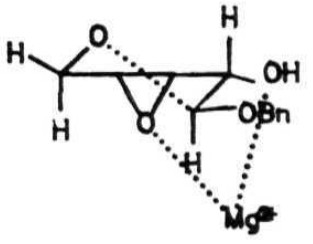
Figure 2

available. The major product results from attack at C-4 and attack at C-3, if any, is minor.

Our results, while largely in agreement with those reported earlier, indicate that ring opening occurs preferentially at C-4 with C-3 as a minor pathway when lithium, sodium, potassium and aluminum are the counter-cations. The exact ratio of C-4 and C-3 ring opened products depends upon the nature of the nucleophile. Thus with sodium thiophenoxide, 487. of C-3 product 74 is obtained. With sodium azide 41%, with sodium methoxide 247., and with sodium iodide 47. C-3 ring opened products 72, 76 and 67 respectively, are formed. This dependence of the regiochemistry of ring cleavage of 58 on the nature of the nucleophile is not readily accountable based upon typical properties of the nucleophile such as its size, charge density or hardness/softness. However,with magnesium salts, the regiochemistry is clear-cut and the major product is now derived from C-3 ring opening.

This could mean that lithium, sodium, potassium and aluminum salts react preferentially through conformer 58A and magnesium salts react through conformer 58B as a major pathway. An alternate explanation for the mode of attack observed with magnesium salts could be that conformer 58A interacts with the magnesium cation and preferentially weakens the C-3- oxygen bond. Consequently, it is easily ruptured by the incoming nucleophile. In order to be an effective regiochemical control element, this

weakening and consequent saving in activation energy should be adequate to compensate for a 1,3- diaxial interaction between the anomeric group and the incoming nucleophile. The driving force for this interaction could be a magnesium chelate such as 137 (Figure 14), which selectively weakens the C-3- oxygen bond.




137

Figure 14

It was observed that there was no change in the ratio of products when the solvent was changed, although the relative conformer population changes from solvent to solvent. Epoxide 58 reacted with magnesium iodide in benzene to give 66 and 67 in a 19:81 ratio, whereas in THF the ratio was 18:82.

An examination of the NMR spectra of epoxide 58 in various solvents showed that the conformation shifts from 58A to 58B on going over from a less polar to a more polar solvent ( Table 12 ). This information is readily apparent from the $J_{2}$ values, which increase with increase in solvent polarity, indicating changes in

**Table 12 NMR spectra of 58 in different solvents**

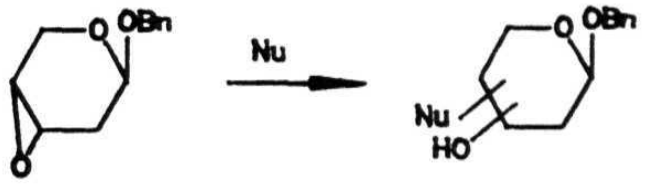
| S. No. | Solvent | $J_{1,2}$ ( Hz ) |
|---|---|---|
| 1. | Dioxan | 3.4 |
| 2. | Benzene | 2.0 |
| 3. | Chloroform | 2.2 |
| 4. | Acetone | 4.0 |
| 5. | DMSO | 4.8 |
| 6. | Water | 3.7 |

the H-1, H-2 dihedral angle and hence conformation. The important conclusion from this is that although the conformer population varies from solvent to solvent, the product ratio remains the same, indicating operation of the Curtin-Hammett principle in a broad sense.

The nature of the counter-cation plays a dominant role in deciding the major product. This is possibly due to chelation of the counter-cation with the one of conformers and weakening of a C-0 bond. To establish this, Crotti extensively studied the epoxide ring opening of various pyranoside derivatives under chelating and non-chelating conditions. In most cases, the regiochemistry of ring opening was reversed (Table 13). The same

observation was found in our case also.

**Table 13: Nucleophilic ring opening reactions of the epoxide 138.**




138

| Entry | Reagents | Solvent | C-5 Product[a] | C-4 product |
|---|---|---|---|---|
| 1. | $NaN_3/NH_4Cl$ | $MeOH:H_2O(8:1)$ | 80 | 20 |
| 2. | $NaN_3/LiClO_4$ | CH CN | 17 | 83 |
| 3. | $Et_2NH$ | EtOH | 37 | 63 |
| 4. | $Et_2NH/LiClO_4$ | CH CN | 11 | 89 |
| 5. | LiAlH | Pentane | 18 | 82 |
| 6. | $LiALH_4$/crown | Pentane | 52 | 48 |

C-5 is equivalent to C-4 of epoxide 58 and C-4 equivalent to C-3.

Crotti has suggested that the role of lithium cation is to chelate and thus, stabilize one conformer in preference to another,

leading to regioselective ring opening. On the contrary, we find that lithium does not exert any influence, but magnesium does. A possible reason for this could be the fact that Crotti's examples have no free hydroxyl group as is present in our substrate.

Aluminum iodide, sodium borohydride, sodium azide and sodium thiophenoxide also give substantial amounts of C-3 derived products. While the presence of aluminum and boron, capable of chelation, is the likely cause for the enhanced formation of C-3 derived products in the first two cases, the results obtained with sodium azide and sodium thiophenoxide cannot be accommodated by this hypothesis. It is worth mentioning that while epoxide 58 does not react with tetra-n-butylammonium iodide alone, the iodo derivative 68 is formed as a minor product when potasium cyanide, tetra-n-butylammonium iodide and titanium tetraisopropoxide are all present. A logical conclusion which can be drawn is that 58 is now activated by titanium tetraisopropoxide and hence suffers cleavage by cyanide as well as iodide. The regiochemistry is different from that seen with magnesium iodide and can be accounted for as reported by Sharpless in his observations on the nucleophilic ring opening of 2,3- epoxy alcohols mediated by titanium tetraisopropoxide.[93] Lithium aluminum hydride appears to be an exception, for though the cation is lithium, the major product is derived from C-3 ring opening. Here, the strong coordination of the aluminum to the hydroxyl group followed by

hydride delivery to the adjacent carbon could account for the regiochemistry observed.

In conclusion, it is clear from our previous work[29] and the present investigation, that the regiochemistry of ring opening of benzyl 3,4- anhydroribopyranosides is critically dependent on the anomeric configuration. When the epoxide ring and the anomeric group are on the same side, the regiochemistry is controlled by a polar repulsive interaction between the incoming nucleophile and the pyranose oxygen lone pair of electrons, directing the attack to C-3. If the epoxide ring and the anomeric substituent are anti to one another, the regiochemistry is now largely controlled by a steric repulsive 1,3- diaxial interaction between the entering nucleophile and the anomeric group, and hence ring opening now occurs at C-4. When a good chelating cation like magnesium is present as the counter-cation, the regiochemistry of ring opening is reversed in favour of C-3, probably due to weakening of the C-3 oxygen bond because of chelation with the metal ion.

**b) Reactions of benzyl 2,3-anhydro-α-D-ribopyranoside.**

As mentioned earlier, (p. 80)the regiochemistry observed in alkyl 2,3-anhydro-β-D-ribopyranosides has been rationalized by considering the repulsive 1,3-interaction between the incoming nucleophile and the pyranose oxygen lone pair of electrons for attack at C-2 and directing the attack to C-3. Thus, the pyranose oxygen controls the regiochemistry, leading to

preferential attack at C-3 for conformer **136A.** For conformer 136B, steric repulsion is adduced as the reason for preferential attack at C-3.

In the case of 2,3-anhydro-α-D-ribopyranosides, no such steric interaction is possible between the incoming nucleophile and anomeric alkoxy substituent. Amongst the two possible conformers **28A** and **28B,** in conformer **28A** (Figure 4), there is a

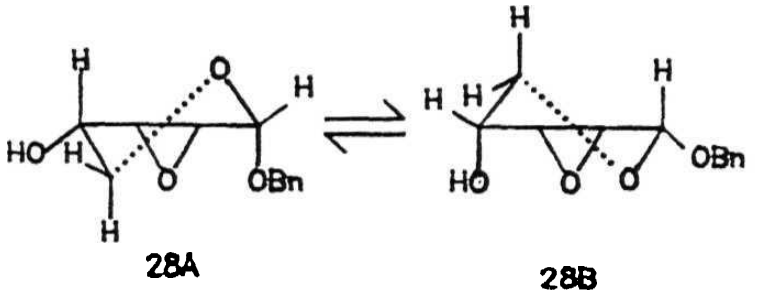



**Figure 4**

repulsive 1,3-interaction between the incoming nucleophile and the pyranose oxygen lone pair of electrons for attack at C-2, therefore directing it to attack at C-3. On the other hand, in conformer **28B,** there is no such repulsive interaction either at C-2 or at C-3. Here, the electron withdrawing character of the anomeric carbon is likely to destabilise a developing positive charge at C-2, and attack at C-3 is anticipated to dominate. The same effect could possibly account for the behaviour of the β-

anomer as well. Thus according to the above reasoning, the observed regioselectivity i.e., preferential attack at C-3 in 28 can be rationalized, especially when other factors of overriding importance, such as steric, are absent.

Recently, Crotti and co-workers, in their study of nucleophilic ring opening of *cis*-2-benzyloxy-3,4-epoxytetra hydropyran **(139)** made a similar observation, i.e., the ring opened at C-4 under both chelating and non-chelating conditions (Table 14).

**Table 14: Nucleophilic ring opening reactions of the epoxide 139.**


**139**

| Entry | Reagents | Solvent | C-4 | C-3 |
|---|---|---|---|---|
| 1. | NaN /$NH_4Cl$ | MeOH:H 0(8:1) | >99 | <1 |
| 2. | $NaN_3/LiClO_4$ | MeCN | >99 | <1 |
| 3. | $NHEt_2$ | EtOH | >99 | <1 |
| 4. | $NHEt_2/LiClO_4$ | MeCN | 77 | 23 |

| | | | | |
|---|---|---|---|---|
| 5. | $Al(Me)_3$ | Pentane | >99 | <1 |
| 6. | Al(Me) /crown | Pentane | >99 | <1 |
| 7. | $LiAlH_4$ | Pentane | 83 | 17 |
| 8. | LiAlH /crown | Pentane | 90 | 10 |

The attack was at C-4 in spite of the absence of hydroxyl group as is present in our case. They have suggested chelation effects of the metal cation as stabilizing one conformer over the other, leading to regioselective ring opening. A second factor mentioned by them is the electron withdrawing nature of the anomeric group, destabilizing nucleophilic attack at C-3 vis-a-vis C-4 and this perhaps is the dominating effect.

In conclusion, it is clear from our present investigation and earlier reports that the regiochemistry of ring opening of benzyl 2,3-anhydroribopyranosides does not depend upon the anomeric configuration. i.e., in both a- and β- anomers ring opening takes place at C-3. In the case of 3.4-anhydroribopyranosides the regiochemistry of the ring opening depends upon the anomeric configuration. Thus, with benzyl 3,4-anhydro-α-D-ribopyranoside the ring opens exclusively at C-3, whereas with benzyl 3,4-anhydro-β-D-ribopyranoside the ring cleaves at both C-3 and C-4 depending upon the nature of the nucleophile and its counter-cation.

# Experimental

Melting points were determined by using a SUPERFIT melting point apparatus and are uncorrected. Optical rotations were measured with an Autopol II automatic polarimeter or JASCO DIP 370 digital polarimeter at 25 . IR spectra were recorded on Perkin-Elmer Model 1310 spectrophotometer or JASCO FT-IR 5300 instrument. Solid samples were prepared as KBr wafers and liquid samples as a film between NaCl plates. $^{1}H$ NMR (200 MHz) and $^{13}C$ NMR (50 MHz) were obtained with a BRUKER AF 200 NMR spectrometer. All spectra were recorded in chloroform-d solution with tetramethylsilane as internal standard unless otherwise stated. Spectral assignments are as follows (1) chemical shift on the $\delta$ scale (TMS = 6 0.00) (2) multiplicity (3) number of hydrogens integrated for by the signal (4) assignment of the signal and (5) coupling constant in hertz (Hz). 2D NMR data were processed using standard software provided with the instrument. Elemental analyses were performed on a Perkin-Elmer 240C CHN analyser.

Analytical TLC was performed on glass plates coated with 250μm and preparative TLC on glass plates coated with 0.1cm Acme silica gel GF and visualised by shining UV light and usually eluted with 2-107. ethyl acetate in hexane, unless otherwise mentioned. All moisture sensitive reactions were carried out under dry nitrogen and all solvents distilled from appropriate drying agents prior to use. After appropriate work-up, the organic

extract was dried over anhydrous magnesium sulphate.

**Benzyl 3,4-anhydro-β-D-ribopyranoside (58)** was prepared in 417. overall yield from benzyl 2,3-anhydro-β-D-ribopyranoside (58) according to ref 34. mp 66-68°; $[\alpha]_D^{25}$ -169.1° (c 0.81, $CHCl_3$) {lit[34] mp 66-68°; $[\alpha]_D^{23}$ -166°(c 0.8, $CDCl_3$)}

IR(KBr) :3440, 3010, 1268, 1100 and 855 $cm^{-1}$.

$^1H$ NMR : *δ* 7.34 (s, 5H, Ar); 4.73, 4.52 (dd, 2H, $OCH_2Ph$, J=11.7); 4.58 (d, 1H, H-1, J=2.2); 4.03 (dd, 1H, H-5, J = 1.43 and 13.3); 3.94 (d, 1H, H-5', J = 13.3); 3.83 (ddd, 1H, H-2, J=2.3, 4.6 and 10.0); 3.52 (t, 1H, H-3, J=4.2); 3.36 (dt, 1H, H-4, J=1.3 and 4.2); 2.52 (dd, 1H, 2-OH, J=8.0 and 10.0).

**General procedure for benzoylation:** Benzoyl chloride (1.1 equiv.) was slowly added to a stirred solution of the alcohol (1 equiv.) in dry pyridine (5 ml) at 0 . The reaction mixture was stirred for 15h at room temperature and then poured into chilled aqueous potassium carbonate (15 ml). After the mixture was stirred for 1h, the product was extracted with dichloromethane (3 x 25 ml). The combined organic phase was washed with aqueous sodium bicarbonate, dried and evaporated. To remove the residual pyridine, toluene (2 x 5 ml) was added and then evaporated from the residue. The crude benzoate was then subjected to chromatographic purification.

**General procedure for debenzoylation:** To a solution of the benzoate (1 equiv.) in dry methanol (5 ml), was added a solution of sodium methoxide (0.1 equiv.) in methanol (0.5 ml). The reaction mixture was stirred at room temperature for 30min. The reaction mixture was neutralized by adding ion-exchange resin (Amberlite-120H ). The resin was filtered off and the methanol removed in vacuo. The residue was then recrystallised from a suitable solvent.

**Reaction of 58 with Lithium aluminum hydride (LAH).** To a stirred solution of LAH (0.009g, 0.225 mmol) in THF (2 ml) was added a solution of epoxy alcohol 58 (0.050g, 0.225 mmol) in THF (2 ml). The resulting mixture was stirred at room temperature for 8h and then quenched by slow addition of saturated aqueous sodium sulphate. The precipitate formed was filtered and the cake was washed with dichloromethane (2 x 5 ml). The combined organic phase was dried and concentrated. The residue was benzoylated and chromatographed to give 59 and 60 in an overall yield of 787.. The fast moving spot was benzyl 4-deoxy-2,3-di-O-benzoyl-β-D-*erythro*-pentopyranoside (59) (0.005g).

$[\alpha]$ :-51.06° (c 0.47, $CHCl_3$).

IR (Neat) :1724, 1452, 1277, 1115 and 710 $cm^{-1}$.

$^1H$ NMR : 6 8.14-7.27 (m, 15H, Ar); 5.66 (ddd, 1H, H-3, J=3.2, 4.6 and 11.0); 5.50 (dd appearing as t, 1H, H-2, J=2.7);

5.09 (d, 1H, H-1, J=2.3); 4.84, 4.60 (dd, 2H, $OCH_2Ph$, J=11.9); 4.14-3.86 (m, 2H, H-5, H-5'); 2.44-2.03 (m, 2H, H-4, H-4').

$^{13}C$ NMR : 165.5, 137.1, 133.3, 133.0, 130.0, 129.9, 129.7, 128.5, 128.4, 127.9, 97.6, 69.5, 69.4, 68.1, 58.9 and 27.2 ppm.

Elemental analysis:

Anal. Calcd for $C_{26}H_{24}O_6$ : C, 72.21; H, 5.59.

Found : C, 72.18; H, 5.62.

The slow moving spot was benzyl 3-deoxy-2,4-di-O-benzoyl-β-D-*erythro*-pentopyranoside (60) (0.071g):

mp :115-117 (ethanol-water).

[α] :-83.33° (c 0.6, CHC1 ).

IR(KBr) : 1718, 1452, 1282, 1086 and 756 cm

$^1H$ NMR : 5 7.99-7.21 (m, 15H, Ar); 5.11-5.07 (m, 2H, H-2, H-4); 4.99 (s, 1H, H-1); 4.81, 4.62 (dd, 2H, OCH Ph, J=12.2); 4.17 (dd, 1H, H-5, J=1.96 and 12.94); 3.92 (dt, 1H, H-5', J=1.95 and 12.74); 2.50-2.40 (m, 2H, H-3 and H-3').

$^{13}C$ NMR : 165.7, 165.4, 133.0, 132.9, 129.9, 129.8, 128.5, 128.2, 128.0, 96.1, 69.4, 67.4, 66.3, 61.4 and 26.9 ppm.

Elemental analysis:

Calcd for $C_{26}H_{24}O_6$ : C, 72.21; H, 5.59.

Found : C, 72.32; H, 5.52.

**Reaction of 58 with Sodium borohydride.** To a stirred solution of sodium borohydride (0.009g, 0.225 mmol) in ethanol (2 ml) was added a solution of epoxy alcohol 58 (0.050g, 0.225 mmol) in ethanol (2 ml). The resulting mixture was refluxed for 24h. The reaction mixture was cooled and ethanol was removed under vacuum. The residue was partitioned between water (5 ml) and chloroform (15 ml). The chloroform layer was separated and the aqueous layer was extracted with chloroform (2 x 15 ml). The combined chloroform extract was dried and concentrated. The residue was benzoylated and chromatographed to give 59 (0.027g), 60 (0.031g) and epoxy benzoate 61 (0.019g). Epoxy benzoate 61 was debenzoylated to give epoxy alcohol 58 (O.Ollg), identical with an authentic sample.

**Reaction of 58 with Lithium bromide.** To a stirred solution of Lithium bromide (0.039g, 0.45 mmol) in THF (2 ml) was added a solution of epoxy alcohol 58 (0.050g, 0.225 mmol) in THF (2 ml). The resulting mixture was refluxed for 2h. The reaction mixture was cooled and THF was removed under vacuum. The residue was partitioned between water (10 ml) and chloroform (20 ml). The chloroform layer was separated and the aqueous layer was extracted with chloroform (2 x 20 ml). The combined chloroform layers were dried and concentrated. The residue was crystallised from toluene to give benzyl 4-bromo-4-deoxy-α-L-lyxopyranoside (62) (0.035g,

517.).

mp 138-140°, $[\alpha]_D^{25}$ -63.1° (c 0.95, $CHCl_3$).
{lit[34] mp 139-141°, $[\alpha]_D^{25}$ +61° (c 0.9, $CHCl_3$)}.

$^1H$ NMR : 6 7.34-7.26 (m, 5H, Ar); 4.95 (s,1H, H-1); 4.76, 4.51 (dd, 2H, $OCH_2Ph$, J=11.9); 4.24-4.16 (m, 1H, H-4); 4.06-3.90(m, 4H, H-2, H-3, H-5, H-5'); 2.63 (d, 1H, 2-OH, J = 3.8); 2.45 (d, 1H, 3-OH, J = 2.8).

$^{13}C$ NMR :136.3, 127.4, 126.8, 98.8, 70.3, 67.9, 62.5 and 49.6ppm.

**Reaction of 58 with Magnesium bromide.** To a stirred mixture of anhydrous magnesium bromide (1.0 mmol) prepared from magnesium (0.024g, 1.0 mg atom) and 1,2-dibromoethane (0.090 ml, 1.0 mmol) in THF (2 ml) was added a solution of epoxy alcohol 58 (0.050g, 0.225 mmol) in THF (2 ml). The resulting mixture was refluxed for 10h. After the mixture was cooled to room temperature, saturated aqueous ammonium chloride was added and the precipitate formed was filtered and the cake was washed with dichloromethane (2 x 10 ml). The combined organic phase was washed with water, dried and concentrated. The residue was benzoylated and chromatographed to give 64 and 65 in an overall yield of 747.. The fast moving spot was benzyl 4-bromo-4-deoxy-2,3-di-O-benzoyl-α-L-lyxopyranoside (64) (0.018g) which was debenzoylated to give 62 (0.009g). The slow moving spot was benzyl 3-bromo-3-deoxy-2, 4-di-O-benzoyl-β-D-xylopyranoside (65) (0.067g).

[α] :-70.27°(c 0.55, $CHCl_3$).

IR(Neat) : 1720, 1455, 1261, 1100 and 730 $cm^{-1}$.

$^1H$ NMR : δ 8.04-7.25 (m, 15H, Ar); 5.51 (dd, 1H, H-2, J=6.5 and 8.2); 5.38 (dt, 1H, H-4, J=8.1 and 4.6); 4.90, 4.66 (dd, 2H, $OCH_2Ph$, J=12.4); 4.71 (d, 1H, H-1, J=5.9); 4.47 (dd, 1H, H-5, J=4.6 and 11.9); 4.35 (t, 1H, H-3, J=8.4); 3.55 (dd, 1H, H-5', J=7.6 and 11.7).

$^{13}C$ NMR : 165.2, 164.8, 136.8, 133.5,133.3, 129.9, 129.3, 129.2, 128.4, 128.3, 127.8, 127.6, 99.5, 72.6, 71.5, 70.2, 62.8 and 47.1 ppm.

Elemental analysis:

Calcd for $C_{26}H_{23}O_6Br$ : C, 61.06; H, 4.53.

Found : C, 60.58; H, 4.60.

**Reaction of 58 with Lithium iodide.** To a stirred solution of lithium iodide (0.060g, 0.45 mmol) in THF (2 ml) was added a solution of epoxy alcohol 58 (0.050g, 0.225 mmol) in THF (2 ml). The resulting mixture was refluxed for 3h. The reaction mixture was cooled and THF was removed under vacuum. The residue was partitioned between water (10 ml) and chloroform (20 ml). The chloroform layer was separated and the aqueous layer was extracted with chloroform (2 x 20 ml). The organic extracts were processed as before. The residue was benzoylated and chromatographed to give 66 and 67 in an overall yield of 387.. The fast moving spot

was benzyl **4-deoxy-4-iodo-2,3-di-O-benzoyl-α-L-lyxopyranoside** (66) (0.042g).

$[\alpha]_D$ :+134.7° (c 0.23, $CHCl_3$).

IR(Neat) : **1720,** 1450, 1260, 1105 and 700 $cm^{-1}$.

$^1H$ NMR : 5 8.06-7.20 **(m,** 15H, **Ar);** 5.74 **(dd,** 1H, H-3, **J=3.2,** and 11.1); 5.58 (dd, 1H, H-2, J=1.8 and 3.1); 5.12 (d, 1H, **H-1,** J=1.8); 4.83, 4.60 (dd, **2H,** $OCH_2$**Ph,** J=11.9); 4.61 (dt, 1H, H-4, **J=5.3** and 11.3); 4.27 (dd appearing as t, 1H, H-5, J=11.5); 4.10 (dd, 1H, **H-5', J=5.1** and 11.3).

$^{13}C$ NMR : 165.1, 136.5, 132.5, 132.3, 129.9, 129.4, 128.8, 128.6, 128.4, 128.2, 128.1, 97.2, 72.3, 70.7, 69.5, 65.5 and 21.8 **ppm.**

Elemental analysis:

**Calcd** for $C_{26}H_{23}O_6I$ : C, 55.92; H, 4.15.

Found : C, 55.85; H, 4.15.

The slow moving spot was benzyl 3-deoxy-3-iodo-2,4-di-0-benzoyl-**β-D-xylopyranoside** (67) (0.007g).

$[\alpha]_D$ : -53.69° (c 0.75, $CHCl_3$).

IR(Neat) : 1730, 1452, 1259, 1107 and 709 $cm^{-1}$.

$^1H$ NMR : 6 8.10-7.27 **(m,** 15H, Ar); 5.55 (dd, 1H, H-2, **J=5.8** and 8.6); 5.41 (dt, 1H, H-4, J=4.1 and 7.6); 4.92, 4.68 (dd, 2H, $OCH_2$**Ph,** J=12.5); 4.73 (d, 1H, H-l, **J=5.76);** 4.50-4.40 **(m,** 2H, H-3, H-5); 3.58 (dd, 1H, **H-5',** J=7.4 and 11.9).

$^{13}C$ NMR : 165.4, 165.2, 133.7, 133.5, 130.1, 128.5, 127.8, 99.4,

73.2, 72.4, 70.2, 63.3 and 23.7 ppm.

Elemental analysis:

Calcd for $C_{26}H_{23}O_6I$ : C, 55.92; H, 4.15.

Found : C, 55.85; H, 4.12.

**Reaction of 58 with Sodium iodide.** To a stirred solution of sodium iodide (0.068g, 0.45 mmol) in THF (2 ml) was added a solution of epoxy alcohol 58 (0.050g, 0.225 mmol) in THF (2 ml). The resulting mixture was refluxed for 40h. Standard work-up gave a residue which was benzoylated and chromatographed to give 66 and 67 in an overall yield of 727.. The ratio of 66 (0.087g) and 67 (0.004g) was 96:4.

**Reaction of 58 with Aluminum iodide.** To a stirred mixture of aluminum iodide, prepared from aluminum powder (0.012g, 0.44 mg atom) and iodine (0.098g, 0.38 mmol) in acetonitrile (2 ml)[113] was added a solution of epoxy alcohol 58 (0.050g, 0.225 mmol) in THF (2 ml). The resulting mixture was refluxed for 30min. The reaction mixture was cooled and a few pieces of ice were added and stirred for 10 min. The aqueous layer was extracted with chloroform (3 x 20 ml) and processed as usual to give, after benzoylation, 66 (0.038g, 607.) and 67 (0.025g, 407.) in an overall chemical yield of 507..

**Reaction of 58 with Magnesium iodide.** a) To a solution of epoxy alcohol 58 (0.050g, 0.225 mmol) in benzene (4 ml) was added a solution (1 ml, 0.45 mmol) of magnesium iodide in ether.[114] The resulting mixture was refluxed for 2h. The reaction mixture was cooled and diluted with dichloromethane (60 ml). The dichloromethane layer was washed with sodium thiosulphate solution (2 x 30 ml), followed by cold water (2 x 30 ml) and dried. The solvent was concentrated under vacuum. The residue was benzoylated and chromatographed to give 66 (0.016g, 187.) and 67 (0.073g, 827.) in an overall yield of 717..

b) A solution of the epoxy alcohol 58 (0.050g, 0.225 mmol) in THF (4 ml) was reacted with a solution of magnesium iodide (1 ml, 0.45 mmol) in ether under identical conditions as the previous one. The resulting residue was benzoylated and chromatographed to give 66 and 67 in an overall yield of 727.. The ratio of 66 (0.017g) and 67 (0.074g) was 19:81.

**Reaction of 58 with Tetra-n-butylammonium iodide.** To a stirred solution of tetra-n-butylammonium iodide (0.082g, 0.22 mmol) in THF (2 ml) was added a solution of epoxy alcohol 58 (0.025g, 0.11 mmol) in THF. The resulting mixture was refluxed for 48h. Tlc showed no formation of any product. The reaction mixture was cooled and the THF was pumped off. The residue was worked up as usual and chromatographed. The purified compound (0.021g) was shown

to be the starting material from its proton NMR spectrum.

**Reaction of 58 with Potassium cyanide.** a)To **a** stirred solution of epoxy alcohol 58 (0.080g, 0.36 mmol) in dry DMSO (5 ml) was added potassium cyanide (0.052g, 0.8 mmol) followed by tetra-n-butylammonium iodide (0.295g, 0.8 mmol). After 5min, titanium tetraisopropoxide (0.285 ml, 0.96 mmol) was slowly injected and the resulting mixture was stirred at room temperature for 72h. Ether (20 ml) followed by 57. sulphuric acid (5 ml) were added and the two phase mixture was stirred till two clear layers were formed (about 1h). The organic phase was separated, washed with water and aqueous sodium bicarbonate, dried and concentrated. The residue was chromatographed with 307. ethyl acetate-hexane as eluent. The purified product contained benzyl 4-iodo-4-deoxy-α-L-lyxopyranoside (68) (0.023g), which on benzoylation gave 66, a complex mixture (0.005g) and benzyl 4-cyano-4-deoxy-α-L-lyxopyranoside (69) (0.053g), which on benzoylation gave benzyl 4-cyano-4-deoxy-2,3-di-O-benzoyl-α-L-lyxo pyranoside (70) (0.074g, 767.).

$[\alpha]_D$ -49.62° (c 0.66, CHC1 ).

IR(Neat) : 2249, 1732, 1273, 1114 and 709 cm .

$^1H$ NMR : 6 8.03-7.26 (m, 15H, Ar); 5.85 (dd, 1H, H-3, J=3.2, and 11.4); 5.63 (t, 1H, H-2, J=2.7); 5.07 (d, 1H, H-1, J=2.1); 4.82, 4.62 (dd, 2H, $OCH_2Ph$, J=11.7); 4.17-4.10 (m,

2H, H-5, H-5'); 3.65-3.51 (m, 1H, H-4).

$^{13}C$ NMR : 165.2, 165.0, 136.3, 133.8, 133.7, 130.0, 129.3, 128.8, 128.6, 128.2, 116.5, 97.2, 70.1, 68.0, 67.7, 59.3 and 29.8 ppm.

Elemental analysis:

Calcd for $C_{27}H_{23}O_6N$ : C, 70.88; H, 5.06; N, 3.06.

Found : C, 70.75; H, 5.09; N, 3.10.

b) To a stirred solution of epoxy alcohol 58 (0.050g, 0.225 mmol) in l,3-dimethyl-2-imidazolidinone (4 ml) was added potassium cyanide (0.033g, 0.5 mmol). On heating to 100° for lh, the solution turned dark brown. The reaction mixture was diluted with ether (10 ml) and treated with *57*, sulphuric acid (3 ml). After stirring for lh, the organic layer was separated. The aqueous layer was extracted with ether (3 x 15 ml) and the combined ether layers were washed with saturated sodium bicarbonate solution (2 x 15 ml), dried and concentrated. The residue was chromatographed. and the purified compound (0.018g) identified as starting material 58 from its NMR spectrum.

c) To a stirred solution of epoxy alcohol 58 (0.025g, 0.112 mmol) in DMF (2 ml) was added potassium cyanide (0.033g, 0.5 mmol). The reaction mixture was maintained at 80 for 2h, then cooled and diluted with chloroform (5 ml). 57. Sulphuric acid (5 ml) was added and the contents were stirred for lh. The organic layer was

separated and the aqueous layer extracted with chloroform (3 x 15 ml). The combined chloroform layer was washed with sodium bicarbonate solution (2 x 15 ml), dried and concentrated. The residue was chromatographed and the purified compound (0.022g)was characterized as recovered 58 from its H NMR spectrum.

**Reaction of 58 with Sodium cyanide.** To a stirred solution of epoxy alcohol 58 (0.10g, 0.45 mmol) in DMF (5 ml) was added sodium cyanide (0.098g, 2 mmol). The reaction mixture was heated to 80° for 16h, when tlc indicated the absence of starting material. The reaction mixture was cooled and the DMF pumped off under vacuum. To the residue was added chloroform (5 ml) and 57. sulphuric acid (5 ml) and the contents stirred for 1h. The organic layer was separated and the aqueous layer was extracted with chloroform (2 x 20 ml). The combined chloroform layer was washed with sodium bicarbonate (2 x 20 ml), dried and concentrated. The residue was benzoylated and chromatographed. The purified product was 70 (0.019g).

**Reaction of 58 with Lithium acetylide.** Acetylene was purified by passing it through a -78° trap, concentrated sulphuric acid trap and sodium hydroxide trap. Acetylene purified as mentioned was allowed to pass through THF (5 ml) at -78° for 10 min. n-BuLi (0.5 ml, 1.2M in hexane, 0.6 mmol) was slowly introduced. After 10

min a solution of 58 (0.10g, 0.45 mmol) in THF (3 ml) was slowly added at -78 and the stirring was continued for 4h. The reaction mixture was allowed to reach room temperature and stirred at that temperature for 10h. Water (1 ml) was added followed by anhydrous potassium carbonate to salt out the organic layer which was then decanted. The pasty residue was washed with dichloromethane (2 x 20 ml) and the combined organic phase was washed with water, dried and concentrated. The residue (0.095g) was starting material as indicated by its proton NMR spectrum.

**Reaction of 58 with Sodium acetylide.** A solution of sodamide in liquid ammonia was prepared by dissolving sodium (0.042g, 1.82 mmol) in liquid ammonia (25 ml) in a 50 ml three necked RB flask. The solution was cooled to -78 and purified acetylene gas was passed through it for 0.5h. The solution was allowed to warm to room temperature over 0.5h. THF (5 ml) was then cautiously added, followed by a solution of the epoxy alcohol 58 (0.10g, 0.45 mmol) in THF (2 ml). The reaction mixture was stirred at room temperature for 48h and then quenched with a saturated solution of ammonium chloride (15 ml) The organic layer was separated and the aqueous layer extracted with dichloromethane (3 x 15 ml). The residue obtained after drying and concentrating the organic layer was chromatographed to give back 58 as identified by its H NMR spectrum.

**Reaction of 58 with Ethynylmagnesium bromide.** To a 0.5 **M** solution of ethynylmagnesium bromide (3 ml, 0.15 mmol) in THF[115] was added a solution of epoxy alcohol 58 (O.lOOg, 0.45 mmol) in THF (2 ml) and the resulting mixture was stirred at room temperature for 48h. The reaction mixture was quenched with saturated ammonium chloride solution (20 ml). The aqueous layer was extracted with chloroform (3 x 40 ml) and worked up as usual. The residue was benzoylated and chromatographed to give 64 and 65 in an overall yield of 837.. The fast moving spot was benzyl 4-bromo-4-deoxy-2,3-di-O-benzoyl-α-L-lyxopyranoside (64) (0.017g) which was debenzoylated to give 62 (0.009g). The slow moving spot was benzyl 3-bromo-3-deoxy-2,4-di-O-benzoyl-β-D-xylopyranoside (67) (0.174g).

Reaction of 58 with Sodium azide. a) To a stirred solution of epoxy alcohol 58 (0.050g, 0.225 mmol) in DMF (3 ml) was added sodium azide (0.033g, 0.5 mmol). The resulting mixture was stirred at 80° for 10h. It was cooled to room temperature and diluted with 1:1 acetone-ether (10 ml) and filtered. The filtrate was washed with water, dried and concentrated. The residue was benzoylated and chromatographed to give 71 and 72 in an overall yield of 70%. The fast moving spot was benzyl 4-azido~4-deoxy-2,3-di-0-benzoyl -α-L-lyxopyranoside (71) (0.044g).

[α] :+114.6° (c 0.41, CHC1 ).

IR(Neat) : 2100, 1720, 1575, 1280 and 700 $cm^{-}$ .

$^1H$ NMR : 5 8.10-7.26 (m, 15H, Ar); 5.67-5.58 (m, 2H, H-2, H-3) 5.02 (d, 1H, H-l, J=1.5); 4.79, 4.59 (dd, 2H, $OCH_2Ph$, J=11.9); 4.29-4.16 (m, 1H, H-4) 3.96 (dd, 1H, H-5, J=5.5 and 11.2); 3.75 (dd appears as triplet, 1H, H-5', J=11.2).

$^{13}C$ NMR : 165.3, 136.5, 133.5, 133.3, 129.8, 129.4, 129.3, 128.6, 128.4, 128.1, 128.0, 96.9, 71.2, 69.7, 69.6, 60.8,and 56.9 ppm.

Elemental analysis:

Calcd for $C_{26}H_{22}N_2O_6$ : C, 65.95; H, 4.89; N, 8.87.

Found : C, 66.0; H, 4.91; N, 8.86.

The slow moving spot was benzyl 3-azido-3-deoxy-2,4-di-0-benzoyl -β-D-xylopyranoside (72) (0.031g):

$[\alpha]_D$ -100.0° (c 0.32, $CHCl_3$).

IR(Neat) : 2100, 1720, 1600, 1450 and 1250 $cm^{-1}$.

$^1H$ NMR : 5 8.07-7.26 (m, 15H, Ar); 5.25 (dd, 1H, H-2, J=6.3 and 8.6); 5.15 (dt, 1H, H-4, J=4.7 and 8.1); 4.88, 4.65 (dd, 2H, $OCH_2Ph$, J=12.5); 4.72 (d, 1H, H-l, J=6.3); 4.38 (dd, 1H, H-5, J=4.7 and 11.8); 4.04 (t, 1H, H-3, J=8.5); 3.54 (dd, 1H, H-5', J=8.1 and 11.8)

$^{13}C$ NMR : 165.4, 165.0, 136.8, 133.6, 133.5, 130.0, 129.9, 129.3, 129.1, 128.6, 128.5, 127.9, 127.8, 99.1, 71.0, 70.2, 62.6 and 62.4 ppm.

Elemental analysis:

Calcd for $C_{26}H_{23}N_3O_6$ : C, 65.95; H, 4.89; N, 8.87.
Found : C, 65.80; H, 4.88; N, 8.82.

b) To a stirred solution of epoxy alcohol 58 (0.025g, 0.112 mmol) in THF (2 ml) was added sodium azide (0.017g, 0.25 mmol). The resulting mixture was refluxed for 30h, when tlc showed no formation of any new product. The mixture was cooled and the THF was pumped off under vacuum. The residue was partitioned between water (5 ml) and chloroform (10 ml) The chloroform layer was separated and the aqueous layer was extracted with chloroform (2 x 10 ml). The combined chloroform extract was dried and concentrated. The residue was chromatographed to give back 58 (0.021g) as indicated from its proton NMR spectrum.

**Reaction of 58 with Sodium thiophenoxide.** **A** 507. suspension of sodium hydride (O.OlOg, 0.225 mmol) was placed in a three necked flask and the mineral oil was removed by washing with dry hexane. THF (2 ml) was added and a solution of thiophenol (0.024g, 0.225 mmol) in THF (1 ml) was added slowly. The resulting mixture was stirred for 30min and then a solution of 58 (0.050g, 0.225 mmol) in THF (2 ml) was slowly added and the stirring was continued for another 24h at room temperature. The reaction mixture was quenched with water (1 ml) and extracted with dichloromethane (2 x 10 ml). The combined organic extracts were washed with water,

sodium bicarbonate, dried and concentrated. The residue was benzoylated and chromatographed to give 73 and 74 in an overall yield of 807.. The fast moving spot was benzyl **4-deoxy-4-(phenylthio)-2,3-di-O-benzoyl-α-L-lyxopyranoside** (73) (0.047g).

$[\alpha]_D$ :+30.76° (c 0.45, $CHCl_3$).

IR(Neat) : 1720, 1455, 1273, 1120 and 710 cm""[1].

$^1H$ NMR : 5 8.10-7.20 (m, 20H, Ar); 5.65-5.59 (m, 2H, H-2, H-3) 5.02 (s, 1H, H-1); 4.75, 4.53 (dd, 2H, $OCH_2Ph$, J=11.9); 4.03-3.82 (m, 3H, H-4, H-5, H-5').

$^{13}C$ NMR : 165.4, 13 6.8, 133.5, 133.4, 133.1, 132.1, 129.8, 129.1,128.5, 128.3, 128.0, 127.9, 97.2, 70.0, 69.8, 69.3, 62.8 and 44.9 ppm.

Elemental analysis:

Calcd for $C_{32}H_{28}O_6S$ : C, 71.09; H, 5.22.

Found : C, 70.95; H, 5.19.

The slow moving spot was benzyl **3-deoxy-3-(phenylthio)-2,4-di-O-benzoyl-β-D-xylopyranoside** (74) (0.049g).

$[\alpha]_D$ : -71.35° (c 0.92, $CHCl_3$).

IR(Neat) : 1722, 1452, 1271, 1111 and 711 cm"[1].

$^1H$ NMR : 5 8.00-7.24 (m, 20H, Ar); 5.34 (dd, 1H, H-2, J=4.1 and 5.5); 5.10 (dt, 1H, H-4, J=5.3 and 3.3); 4.86 (d, 1H, H-l, J=3.8); 4.90, 4.64 (dd, 2H, $OCH_2Ph$, J=12.4); 4.50 (dd, 1H, H-5, J=3.0 and 12.4); 3.75-3.66 (m, 2H, H-3,

H-5').

$^{13}C$ NMR : 165.7, 165.3, 137.1, 133.7, 133.2, 133.1, 130.0, 129.9, 129.7, 129.2, 128.4, 128.3, 128.0, 127.7, 98.3, 71.0, 69.8, 61.0 and 49.0 ppm.

Elemental analysis:

Calcd for $C_{32}H_{28}O_6S$ : C, 71.09; H, 5.22.

Found : C, 71.05; H, 5.25.

**Reaction of 58 with Sodium methoxide.** a) To a solution of sodium methoxide (0.054g, 1.0 mmol) in methanol (2 ml) was added a solution of epoxy alcohol 58 (0.050g, 0.225 mmol) in methanol (2 ml). The resulting mixture was refluxed for 12h. The reaction mixture was cooled and the methanol was removed under vacuum. The residue was partitioned between water (10 ml) and chloroform (20 ml). The chloroform layer was separated and the aqueous layer was extracted with chloroform (2 x 20 ml). The combined chloroform extract was dried and concentrated. The residue was benzoylated and chromatographed to give 75 and 76 in an overall yield of 737.. The fast moving spot was benzyl 3-deoxy-3-methoxy-2,4-di-0-benzoyl -β-D-xylopyranoside (76) (0.018g).

$[\alpha]_D$ :-73.54° (c 0.77, CHC1 ).

IR(Neat) : 1720, 1455, 1260, 1100 and 705 $cm^{-1}$.

$^1H$ NMR : 6 7.97-7.16 (m, 15H, Ar); 5.19 (dd, 1H, H-2, J=4.0 and 4.8); 5.09 (dt, 1H, H-4, J=5.4 and 3.7); 4.72 (d, 1H,

H-1, J=4.2); 4.80, 4.56 (dd, 2H, $OCH_2Ph$, J=12.5); 4.28 (dd, 1H, H-5, J=3.5 and 12.2); 3.69 (dd appearing as t, 1H, H-3, J=5.6); 3.56 (dd, 1H, H-5', J=5.4 and 12.2) 3.49 (s, 3H, $OCH_3$).

$^{13}C$ NMR : 165.7, 165.3, 137.1, 133.2, 129.9, 129.8, 128.4, 127.8, 98.0, 77.8, 70.2, 69.6, 60.3 and 59.1 ppm.

Elemental analysis:

Calcd for $C_{27}H_{26}O_7$ : C, 70.11; H, 5.66.

Found : C, 70.25; H, 5.68.

The slow moving spot was benzyl 4-deoxy-4-methoxy-2,3-di-O-benzoyl-α-L-lyxopyranoside (75) (0.058g).

[α] :+16.56° (c 0.84, CHC1 ).

IR(Neat) : 1728, 1452, 1275, 1111 and 711 cm .

$^1H$ NMR : 5 8.10-7.28 (m, 15H, Ar); 5.74-5.64 (m, 2H, H-2, H-3) 5.03 (d, 1H, H-l, J=2.3); 4.85, 4.63 (dd, 2H, $OCH_2Ph$, J=11.9); 4.09-3.79 (m, 3H, H-4, H-5, H-5'); 3.47 (s, 3H, $OCH_3$).

$^{13}C$ NMR : 165.4, 136.8, 133.3, 133.0, 129.8, 129.7, 128.5, 128.3, 127.9, 97.0, 74.8, 71.6, 70.6, 69.4, 61.1 and 58.9 ppm.

Elemental analysis:

Calcd for $C_{27}H_{26}O_7$ : C, 70.11; H, 5.66.

Found : C, 70.25; H, 5.69.

b) To a stirred suspension of sodium methoxide (0.054g, 1.0 mmol) in THF was added a solution of 58 (0.050g, 0.225 mmol) in THF (3

ml). The resulting mixture was stirred at room temperature for 96h. A tlc test indicated only the presence of starting material. The THF was removed under vacuum and the residue was partitioned between water (10 ml) and chloroform (20 ml). The chloroform layer was separated and the aqueous layer was extracted with chloroform (2 x 20 ml). The combined chloroform extract was dried, concentrated and purified to give back the starting material (0.044g), identified by its H NMR spectrum.

**Reaction of 58 with Magnesium methoxide.** a)To a stirred suspension of magnesium methoxide (1.0 mmol) prepared from magnesium (0.024g, 1.0 mg atom) and methanol (2 ml) was added a solution of epoxy alcohol 58 (0.050g, 0.225 mmol) in methanol (2 ml). The resulting mixture was refluxed for 12h, then cooled and concentrated. The residue was partitioned between 57. hydrochloric acid (20 ml) and chloroform (20 ml) and worked up as usual. The residue was benzoylated and chromatographed to give **75** and 76 in an overall yield of 707.. The ratio of **75:76** was 7:93.

b) To a stirred suspension of magnesium methoxide (0.040g, 0.46 mmol) in THF was added a solution of epoxy alcohol 58 (0.050g, 0.225 mmol) in THF (3 ml). The resulting mixture was refluxed for 24h. Routine work-up gave back 58 (0.028g) characterized by its H NMR spectrum.

**Benzyl 2,3-anhydro-α-D-ribopyranoside (28)** was prepared in 717. overall yield from benzyl oc-D-arabinopyranoside (77) according to ref 57.

mp 66-67°; $[\alpha]_D^{25}$ +137.9° (c 1.035,EtOAc)

{lit[57] mp 96-97°; $[\alpha]_D^{20}$ +134° (c 0.98,EtOAc)}.

IR(KBr) :3429, 1452, 1064, 904 and 873 $cm^{-1}$.

$^1H$ NMR : 5 7.39-7.26 (m, 5H, Ar); 4.94 (s, 1H, H-1); 4.83, 4.61 (dd, 2H, $OCH_2Ph$, J=11.6); 4.16-4.00 (m, 1H, H-4,); 3.61-3.49 (m, 4H, H-2, H-3, H-5, H-5'); 1.88 (d, 1H, 4-OH, J=10.4).

Elemental analysis:

Calcd. for $C_{12}H_{14}O_4$ : C, 64.85; H, 6.35.

Found. : C, 64.92; H, 6.38.

Reaction of 28 with Magnesium bromide. To a stirred mixture of anhydrous magnesium bromide (1.0 mmol) prepared from magnesium (0.024g, 1.0 mg atom) and 1,2-dibromoethane (0.090 ml, 1.0 mmol) in THF (2 ml) was added a solution of epoxy alcohol 28 (0.050g, 0.225 mmol) in THF (2 ml). The resulting mixture was refluxed for 6h. After the mixture was cooled to room temperature, saturated aqueous ammonium chloride was added and the precipitate formed was filtered off and the cake was washed with dichloromethane (2 x 10 ml). The combined organic phase was washed with water, dried and concentrated. The residue was benzoylated and chromatographed to

give 3-bromo-3-deoxy-2, 4-di-O-benzoyl-α-D-xylopyranoside (79) (0.089g, 77%).

mp : 156-158° (ethanol).

$[\alpha]_D$ :+83.47°(c 0.345, $CHCl_3$).

IR(KBr) : 1728, 1452, 1263, 1107 and 707 $cm^{-1}$.

$^1H$ NMR : *6* 8.13-7.16 (m, 15H, Ar); 5.42 (dt, 1H, H-4, J=5.8 and 10.6); 5.29 (dd, 1H, H-2, J=3.9 and 10.8); 5.19 (d, 1H, H-1, J=3.7); 4.79, 4.54 (dd, 2H, $OCH_2Ph$, J=12.4); 4.71 (dd appearing as t, 1H, H-3, J=10.7); 4.06 (dd, 1H, H-5, J=5.8 and 10.7); 3.82 (dd appearing as t, 1H, H-5', J=10.6).

$^{13}C$ NMR : 165.3, 165.2, 136.7, 133.4, 130.0, 129.9, 129.3, 128.4, 128.0, 127.7, 95.2, 73.5, 72.1, 69.8, 60.1,and 48.5 ppm.

Elemental analysis:

Calcd for $C_{26}H_{23}O_6Br$ : C, 61.06; H, 4.53.

Found : C, 61.12; H, 4.58.

**Reaction** of 28 **with LAH.** To a stirred solution of LAH (0.009g, 0.225 mmol) in THF (2 ml) was added a solution of epoxy alcohol 28 (0.05g, 0.225 mmol) in THF (2 ml). The resulting mixture was stirred at room temperature for 5h and then saturated aqueous sodium sulphate was slowly added. The precipitate formed was filtered off and the cake was washed with dichloromethane (2 x 5 ml). The combined organic phase was dried and concentrated. The

residue was benzoylated and chromatographed to give benzyl 3-deoxy-2,4-di-O-benzoyl-α-D-*erythro*-pentopyranoside (80) (0.076g, 787.).

mp :68-70° (ethanol-water).

$[\alpha]_D$ :+77.87° (c 0.33, $CHCl_3$).

IR(KBr) : 1728, 1452, 1278, 1109 and 709 $cm^{-1}$.

$^1H$ NMR : 5 8.04-7.25 (m, 15H, Ar); 5.33-5.13 (m, 2H, H-2, H-4); 5.09 (d, 1H, H-1, J=3.1); 4.86, 4.61 (dd, 2H, $OCH_2Ph$, J=12.4); 3.97-3.80 (m, 2H, H-5, H-5'); 2.51-2.30 (m, 2H, H-3, H-3').

$^{13}C$ NMR : 165.6, 165.5, 137.4, 133.1, 129.8, 129.7, 128.3, 127.7, 127.6, 94.3, 69.4, 68.6, 66.8, 60.4 and 29.6 ppm.

Elemental analysis:

Calcd for $C_{26}H_{24}O_6$ : C, 72.21; H, 5.59.

Found : C, 72.12; H, 5.49.

**Reaction of 28 with Potassium cyanide.** To a stirred solution of epoxy alcohol 28 (0.050g, 0.225 mmol) in dry DMSO (3 ml) was added potassium cyanide (0.033g, 0.5 mmol) followed by tetra-n-butylammonium iodide (0.185g, 0.5 mmol). After 5min, titanium tetraisopropoxide (0.179 ml, 0.60 mmol) was slowly injected and the resulting mixture was stirred at room temperature for 72h. Ether (10 ml) followed by 57. sulphuric acid (3 ml) were added and the two phase mixture was stirred till two clear layers

were formed (about 1h). The organic phase was separated, washed with water and aqueous sodium bicarbonate, dried and concentrated. The residue was benzoylated and the resulting material was chromatographed to give benzyl 3-cyano-3-deoxy-2,4-di-0-benzoyl-α-D-xylopyranoside (81) (0.072g, 707.).

mp : 142-144 (ethanol-water).

$[\alpha]_D$ :+94.10° (c 0.39, $CHCl_3$).

IR(KBr) : 2251, 1728, 1452, 1176 and 709 $cm^{-1}$.

$^1H$ NMR : 5 8.15-7.16 (m, 15H, Ar); 5.46-5.25 (m, 3H, H-1, H-2, H-4); 4.79, 4.56 (dd, 2H, $OCH_2Ph$, J=11.9); 4.08 (dd, 1H, H-5, J=5.7 and 10.7); 3.80 (dd appearing as t, 1H, H-3, J=10.8); 3.73 (dd appearing as t, 1H, H-5', J=10.7).

$^{13}C$ NMR : 165.1, 164.9, 136.4, 133.7, 129.9, 128.5, 128.1, 127.7, 116.5, 92.9, 69.9, 69.1, 67.5, 59.0 and 33.8 ppm.

Elemental analysis:

Calcd for $C_{27}H_{23}O_6N$ : C, 70.88; H, 5.06; N, 3.06.

Found : C, 71.01; H, 4.78; N, 3.26.

Reaction of 28 with Sodium azide. To a stirred solution of epoxy alcohol 28 (0.050g, 0.225 mmol) in DMF (3 ml) was added sodium azide (0.033g, 0.5 mmol). The resulting mixture was stirred at 80 for 10h. It was cooled to room temperature and diluted with 1:1 acetone-ether (10 ml) and filtered. The filtrate was washed with water, dried and concentrated. The residue was benzoylated and

chromatographed to give benzyl 3-azido-3-deoxy-2,4-di-O-benzoyl -α-D-xylopyranoside (82) (0.081g, 767.).

mp :126-128° (ethanol-water).

$[\alpha]_D$ :+76.75° (c 0.37, $CHCl_3$).

IR(KBr) : 2112, 1726, 1601, 1259 and 709 $cm^{-1}$.

$^1H$ NMR : 5 8.15-7.20 (m, 15H, Ar); 5.25 (d, 1H, H-1, J=3.6); 5.13 (dt, 1H, H-4, J=5.5 and 10.5); 5.00 (dd, 1H, H-2, J=3.8 and 10.1); 4.79, 4.54 (dd, 2H, $OCH_2Ph$, J=11.9); 4.42 (dd appearing as t, 1H, H-3, J=10.1); 4.05 (dd, 1H, H-5, J=5.5 and 10.8); 3.81 (dd appearing as t, 1H, H-5', J=10.7).

$^{13}C$ NMR : 165.4, 165.3, 136.7, 133.5, 129.9, 129.8, 129.2, 128.5, 128.4, 128.0, 127.7, 94.6, 72.2, 70.5, 69.9, 61.3 and 58.8 ppm.

Elemental analysis:

Calcd for $C_{26}H_{23}N_3O_6$ : C, 65.95; H, 4.89; N, 8.87.

Found : C, 66.02; H, 4.95; N, 8.92.

Reaction of 28 with Sodium thiophenoxide. A *507.* suspension of sodium hydride (O.OlOg, 0.225 mmol) was placed in a three necked flask and the mineral oil was removed by washing with dry hexane. THF (2 ml) was added and a solution of thiophenol (0.024g, 0.225 mmol) in THF (1 ml) was added slowly. The resulting mixture was stirred for 30 min and then a solution of 28 (0.050 g, 0.225 mmol)

in THF (2 ml) was slowly added and the stirring was continued for another 6h at room temperature. The reaction mixture was quenched with water (1 ml) and extracted with dichloromethane (2 x 10 ml). The combined organic extracts were washed with water, sodium bicarbonate, dried and concentrated. The residue was benzoylated and chromatographed to give benzyl 3-deoxy-3-(phenylthio)-2,4-di-O-benzoyl-α-D-xylopyranoside (83) (0.102g, 847.).

IR(Neat) : 1724, 1452, 1263, 1107 and 711 cm$^{-1}$.

$^1$H NMR 5 8.02-7.11 (m, 20H, Ar); 5.20-5.10 (m, 2H, H-1, H-4); 4.97 (dd, 1H, H-2, J=3.6 and 11.0); 4.78, 4.53 (dd, 2H, OC*H* Ph, J=12.1); 4.04-3.83 (m, 3H, H-3, H-5, H-5').

Oxidation of 83 with m-Chloroperbenzoic acid (MCPBA). To a stirred solution of 83 (0.102g, 0.19 mmol) in dichloromethane (10 ml) at 0° was added a solution of MCPBA (0.093g, 0.57 mmol) in dichloromethane (6 ml). The resulting mixture was stirred overnight at 8-9°. The reaction mixture was stirred at room temperature for 2h after adding 207. aqueous sodium sulphite (10 ml) and the separated organic phase was successively washed with aqueous sodium bicarbonate and water , dried and concentrated. The residue was chromatographed to give benzyl 3-deoxy-3-(phenylsulfonyl)-2,4-di-O-benzoyl-α-D-xylopyranoside (84) (0.074g, 687.).

mp : 118-120° (ethanol-water).

$[\alpha]_D$ : +67.10° (c 0.38, CHCl$_3$).

IR(KBr) : 1726, 1452, 1309, 1259, 1147 and 706 $cm^{-1}$.

$^{1}H$ NMR : 5 7.95-7.12 (m, 20H, Ar); 5.63 (dt, 1H, H-4, J=5.9 and 9.7); 5.43 (dd, 1H, H-2, J=3.2 and 10.6); 5.18 (d, 1H, H-1, J=3.4); 4.75, 4.49 (dd, 2H, $OCH_2Ph$, J=11.9); 4.33 (dd appearing as t, 1H, H-3, J=10.5); 4.04 (dd, 1H, H-5, J=6.0 and 10.8); 3.81 (dd appearing as t, 1H, H-5', J=10.6).

$^{13}C$ NMR : 164.8, 139.2, 136.5, 133.7, 133.4, 130.0, 129.9, 129.2, 128.5, 128.3, 128.0, 127.7, 93.9, 69.9, 67.6, 65.2, 63.9 and 58.8 ppm.

Elemental analysis:

Calcd for $C_{22}H_{20}O_6S$ : C, 67.12; H, 4.92.

Found : C, 67.25; H, 4.94.

**Reaction of 28 with Sodium methoxide.** a) To a solution of sodium methoxide (0.054g, 1.0 mmol) in methanol (2 ml) was added a solution of epoxy alcohol 28 (0.050g, 0.225 mmol) in methanol (2 ml). The resulting mixture was refluxed for 8h. The reaction mixture was cooled and the methanol was removed under vacuum. The residue was partitioned between water (10 ml) and chloroform (20 ml). The chloroform layer was separated and the aqueous layer was extracted with chloroform (2 x 20 ml). The combined chloroform extract was dried and concentrated. The residue was benzoylated and chromatographed to give 85 (0.059g) and 86 (0.021g). The fast

moving spot was benzyl 3-deoxy-3-methoxy-2,4-di-O-benzoyl-α-D-xylopyranoside (85) (0.059g).

mp : 108-110° (ethanol).

$[\alpha]_D$ :+77.41°(c 0.31, $CHCl_3$).

IR(KBr) : 1726, 1452, 1273, 1113 and 707 $cm^{-1}$.

$^1H$ NMR : 6 8.11-7.18 (m, 15H, Ar); 5.29-5.16 (m, 2H, H-1, H-4); 5.09 (dd, 1H, H-2, J=3.9 and 9.6); 4.78, 4.52 (dd, 2H, $OCH_2Ph$, J=12.1); 4.11 (t, 1H, H-3, J=9.4); 4.01 (dd, 1H, H-5, J=5.8 and 10.7); 3.79 (t, 1H, H-5', J=10.6).

$^{13}C$ NMR : 165.6, 165.5, 137.1, 133.2, 129.8, 129.7, 128.4, 127.8, 127.7, 95.6, 78.3, 73.2, 71.7, 69.7, 60.6 and 59.2 ppm.

Elemental analysis:

Calcd for $C_{27}H_{26}O_7$ : C, 70.11; H, 5.66.

Found : C, 70.23; H, 5.70.

The slow moving spot was benzyl 2,3-anhydro-4-O-benzoyl-α-D-ribopyranoside (86).

mp : 106-108° (ethanol-water).

$[\alpha]_D$ :+169.45°(c 0.37, CHC1 ).

IR(KBr) :1730, 1452, 1269, 1113, 916 and 835 cm .

$^1H$ NMR : 5 8.06-7.24 (m, 10H, Ar); 5.43 (dd, 1H, H-4, J=6.1 and 9.7); 5.04 (d, 1H, H-l, J=2.9); 4.85, 4.64 (dd, 2H, OCH Ph, J=12.1); 3.93 (t, 1H, H-5, J=10.2); 3.72-3.63(m, 2H, H-5' and H-3); 3.54 (t, 1H, H-2, J=3.5).

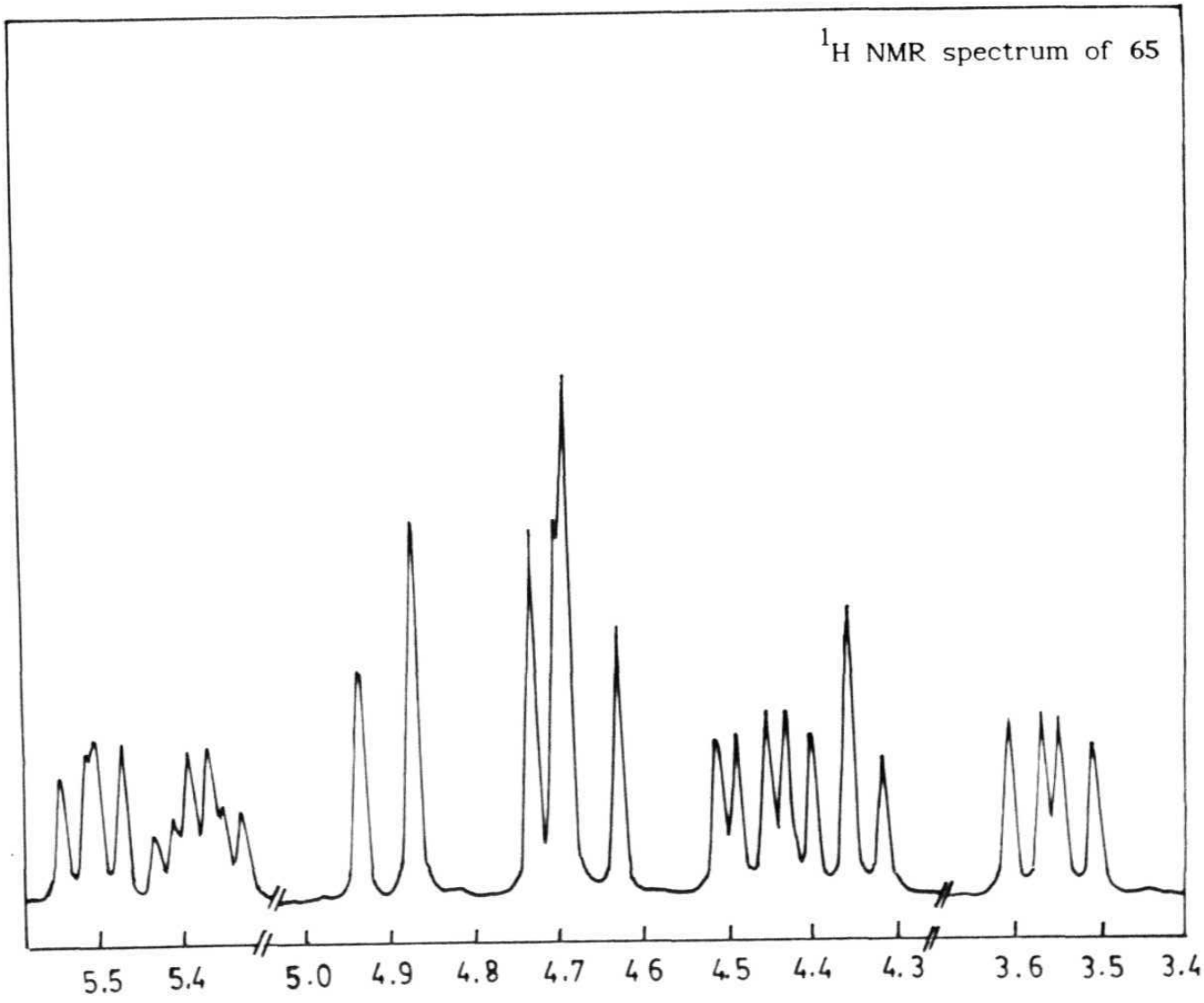
Elemental analysis:

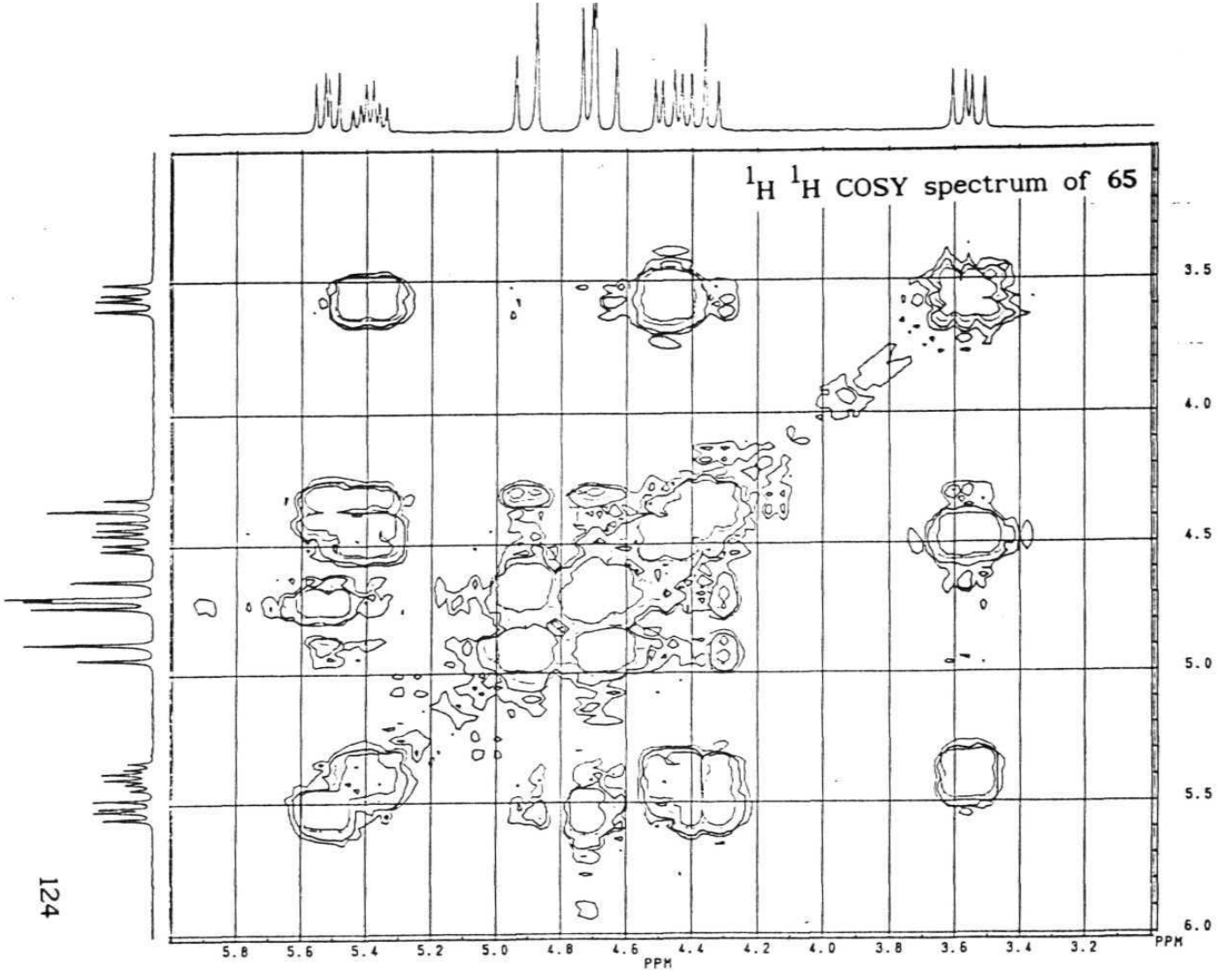
| | |
|---|---|
| Calcd for $C_{19}H_{18}O_5$ | : C, 69.92; H, 5.55. |
| Found | : C, 70.00; H, 5.58. |

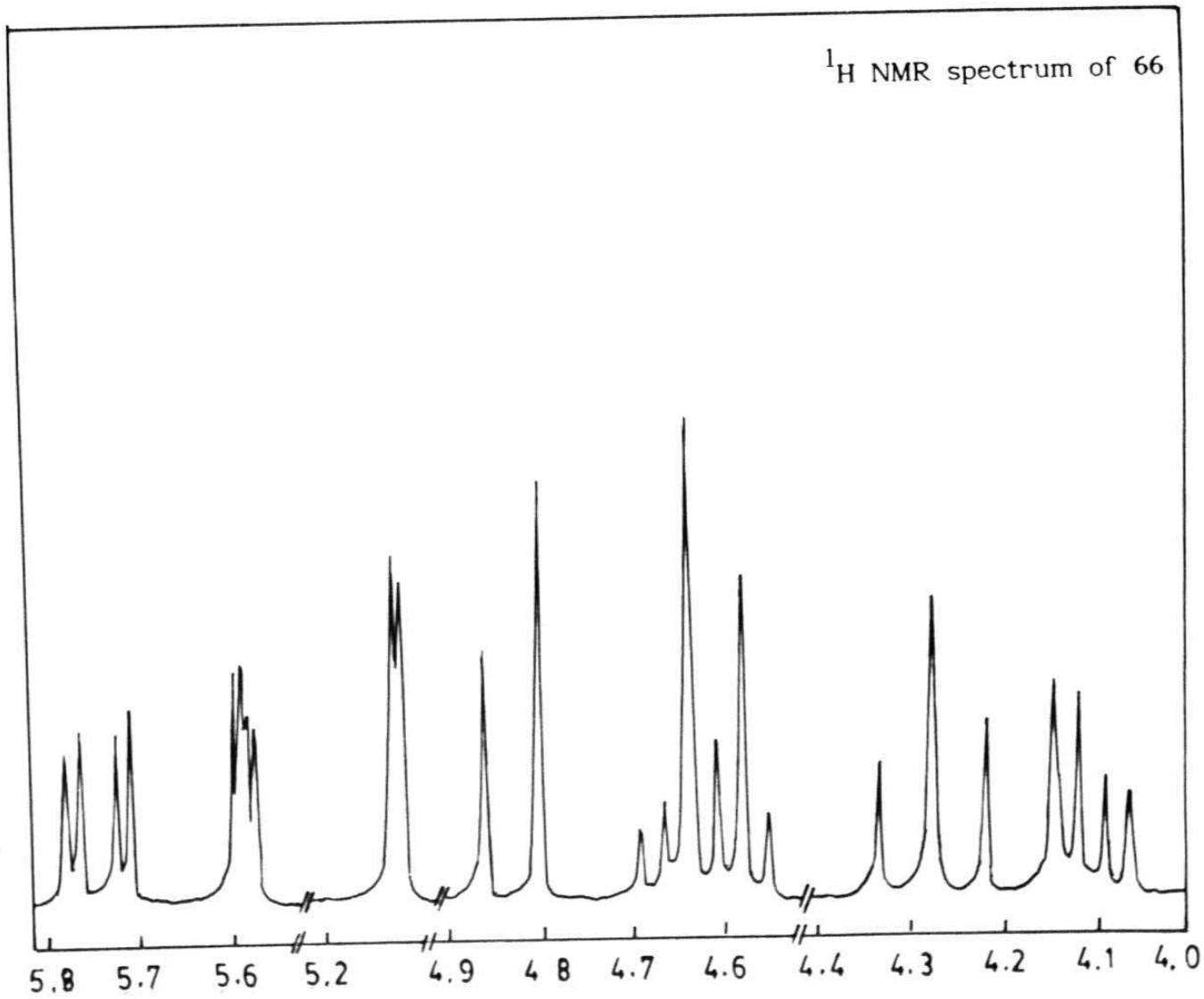
b) To a solution of sodium methoxide (0.054g, 1.0 mmol) in methanol (2 ml) was added a solution of epoxy alcohol 28 (0.050g, 0.225 mmol) in methanol (2 ml). The resulting mixture was refluxed for 12h. The reaction mixture was cooled and methanol was removed under vacuum. The residue was partitioned between water (10 ml) and chloroform (20 ml) and worked up as usual. The residue was benzoylated and chromatographed to give benzyl 3-methoxy-3-deoxy-2,4-di-O-benzoyl-α-D-xylopyranoside (85) (0.087g, 837.).

**Reaction of 28 with Magnesium methoxide.** To a stirred suspension of magnesium methoxide (1.0 mmol) prepared from magnesium (0.024g, 1.0 mg atom) and methanol (2 ml) was added a solution of epoxy alcohol 28 (0.050g, 0.225 mmol) in methanol (2 ml). The resulting mixture was refluxed for 7h. The reaction mixture was cooled and concentrated. The residue was partitioned between *57.* hydrochloric acid (20 ml) and chloroform (20 ml) and worked up as usual. The residue was benzoylated and chromatographed to give 85 (0.089g, 857.).

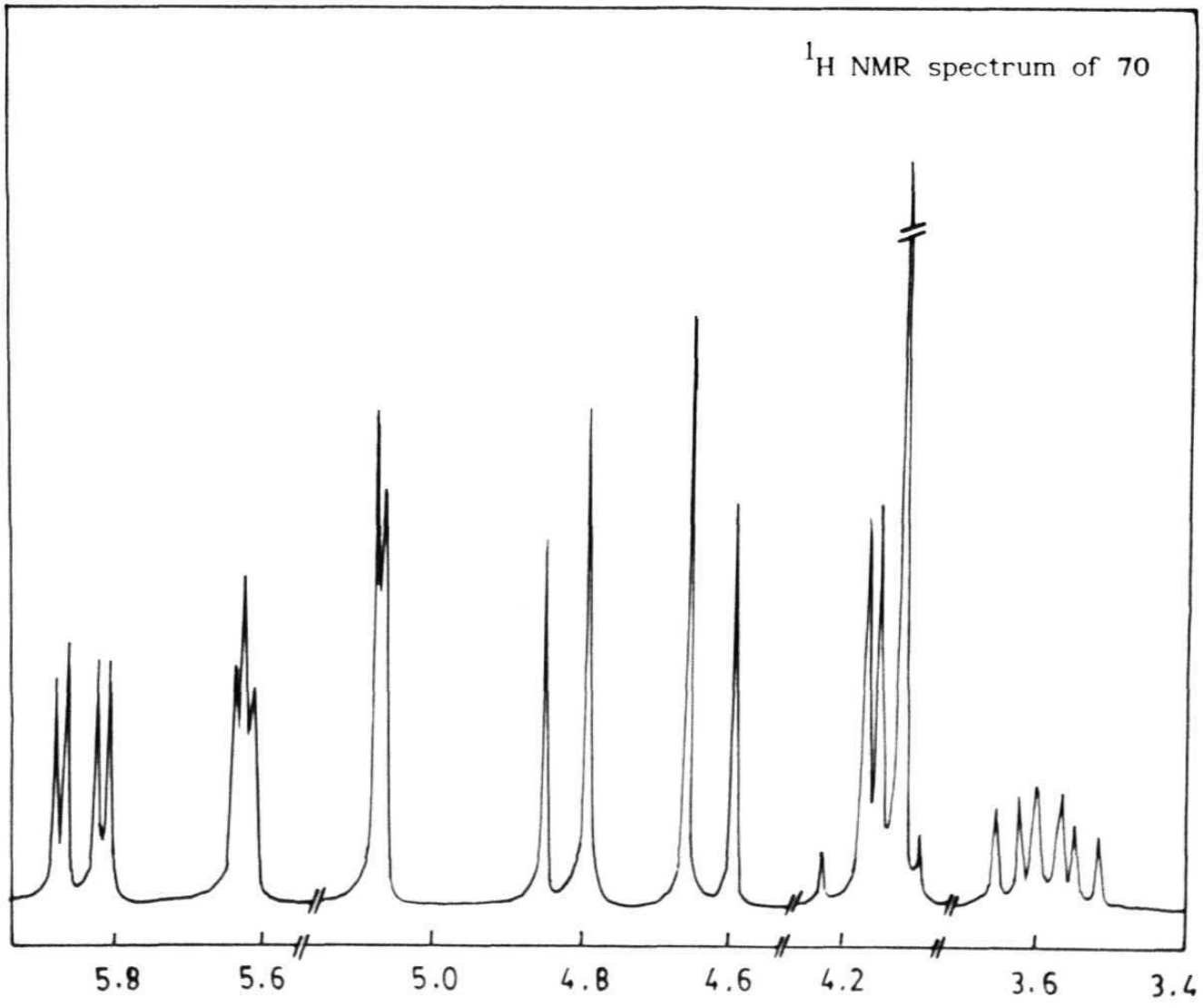
# Spectra

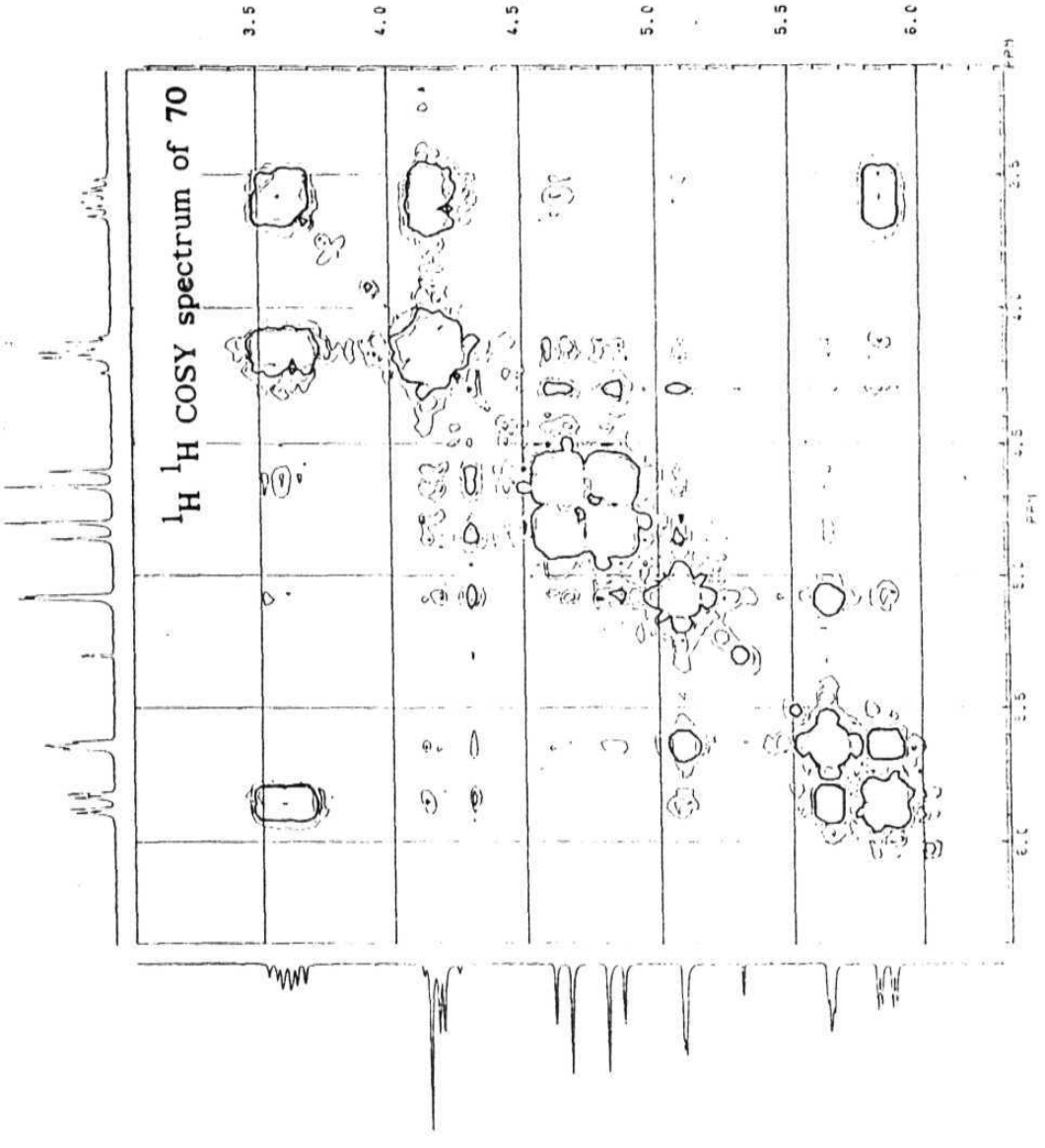

$^1$H NMR spectrum of 65
5.5
5.4
5.0
4.9
4.8
4.7
4.6
4.5
4.4
4.3
3.6
3.5
3.4

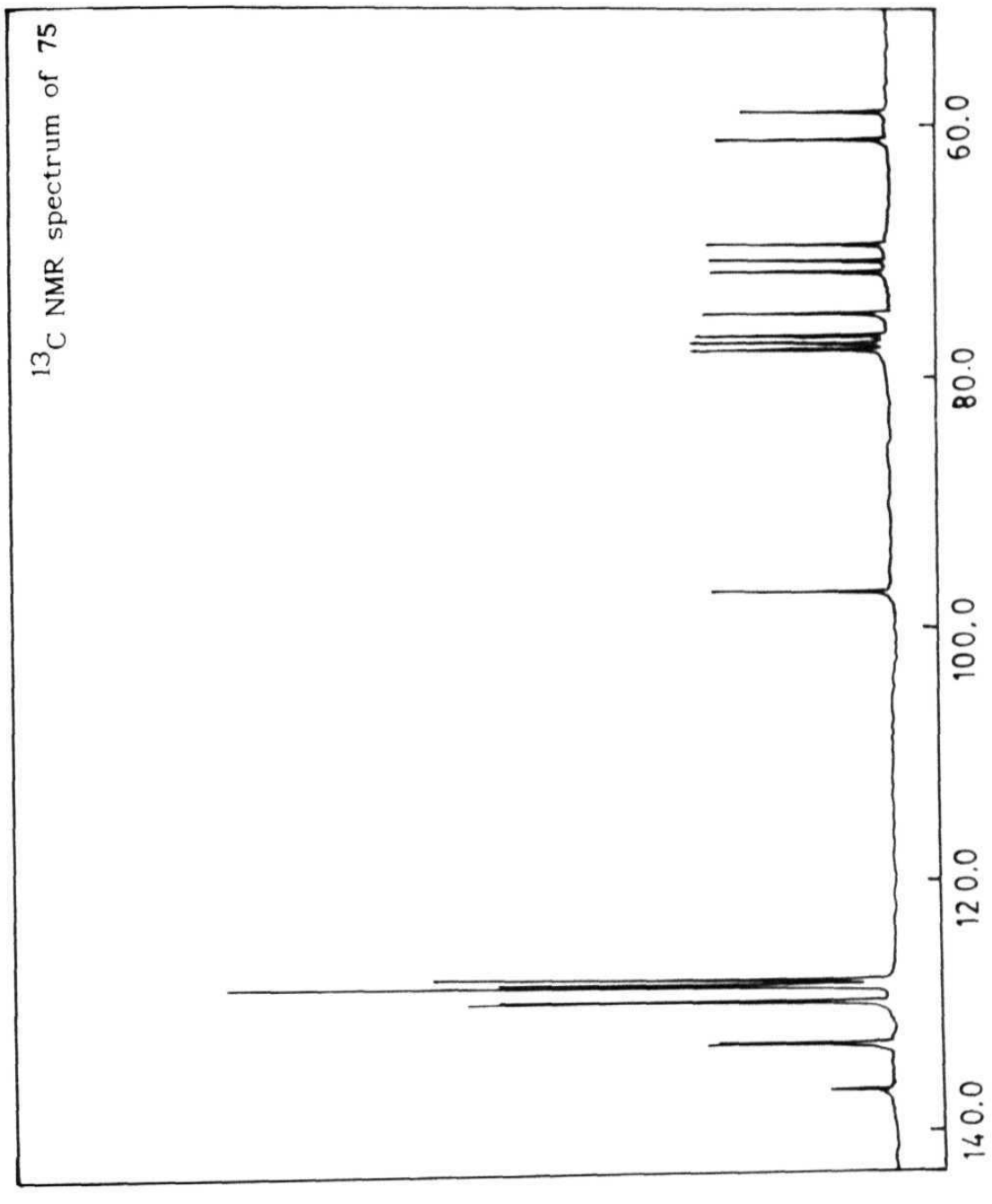

$^1$H $^1$H COSY spectrum of 65
3.5
4.0
4.5
5.0
5.5
6.0
5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2
PPM
PPM

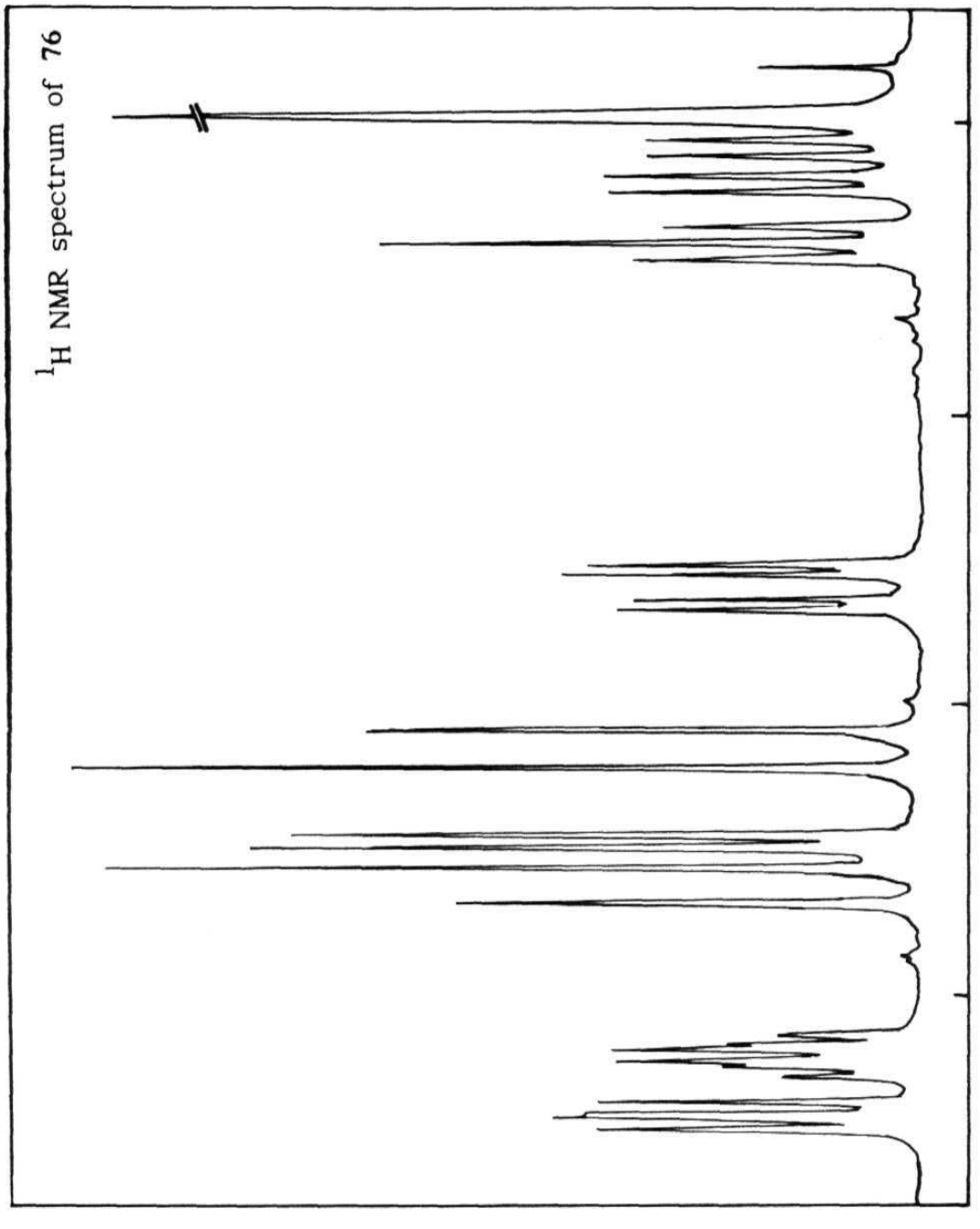

$^1$H NMR spectrum of 66
5.8
5.7
5.6
5.2
4.9
4.8
4.7
4.6
4.4
4.3
4.2
4.1
4.0

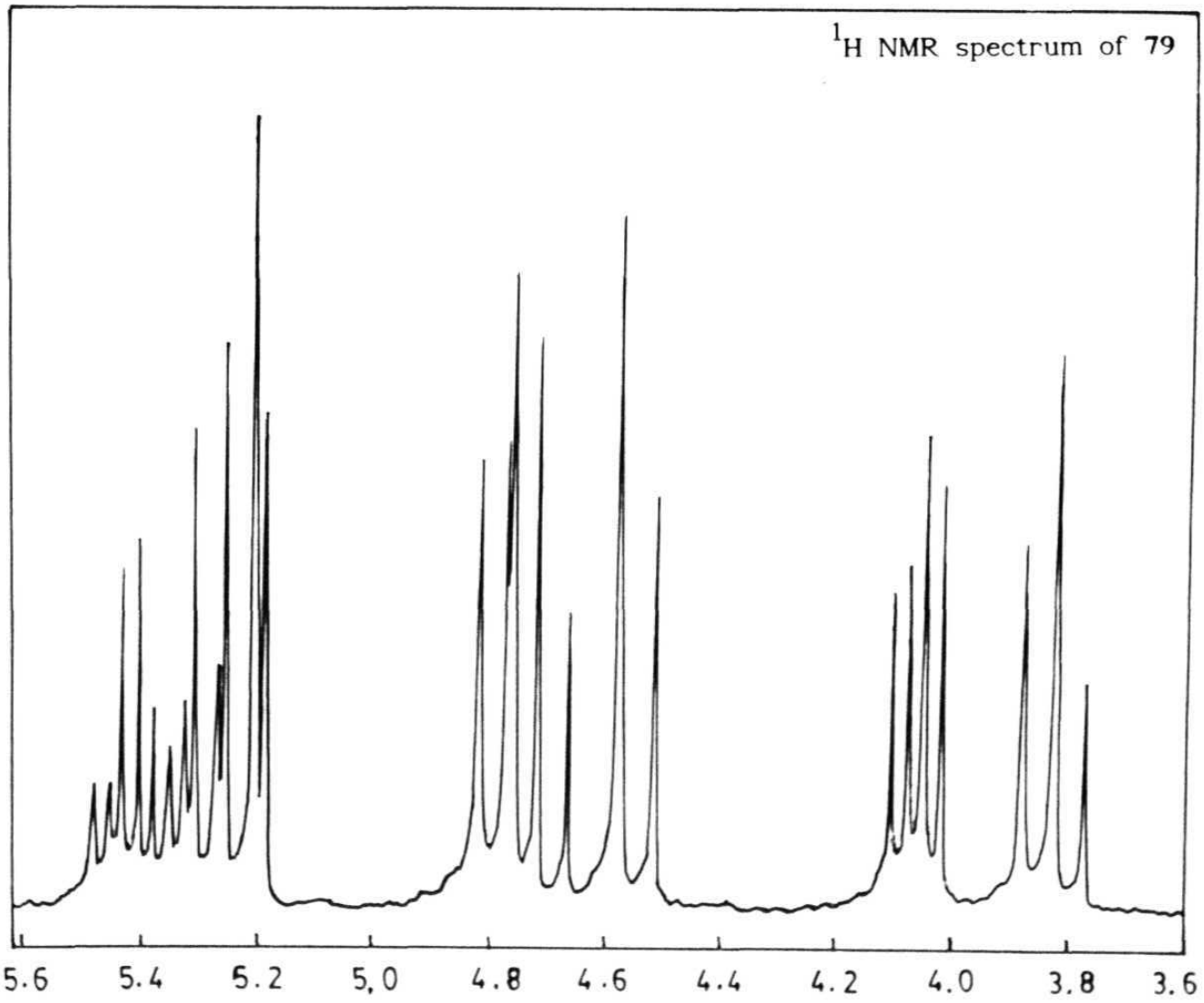
$^1H$ $^1H$ COSY spectrum of 67
3.0
3.5
4.0
4.5
5.0
5.5
6.0
PPM

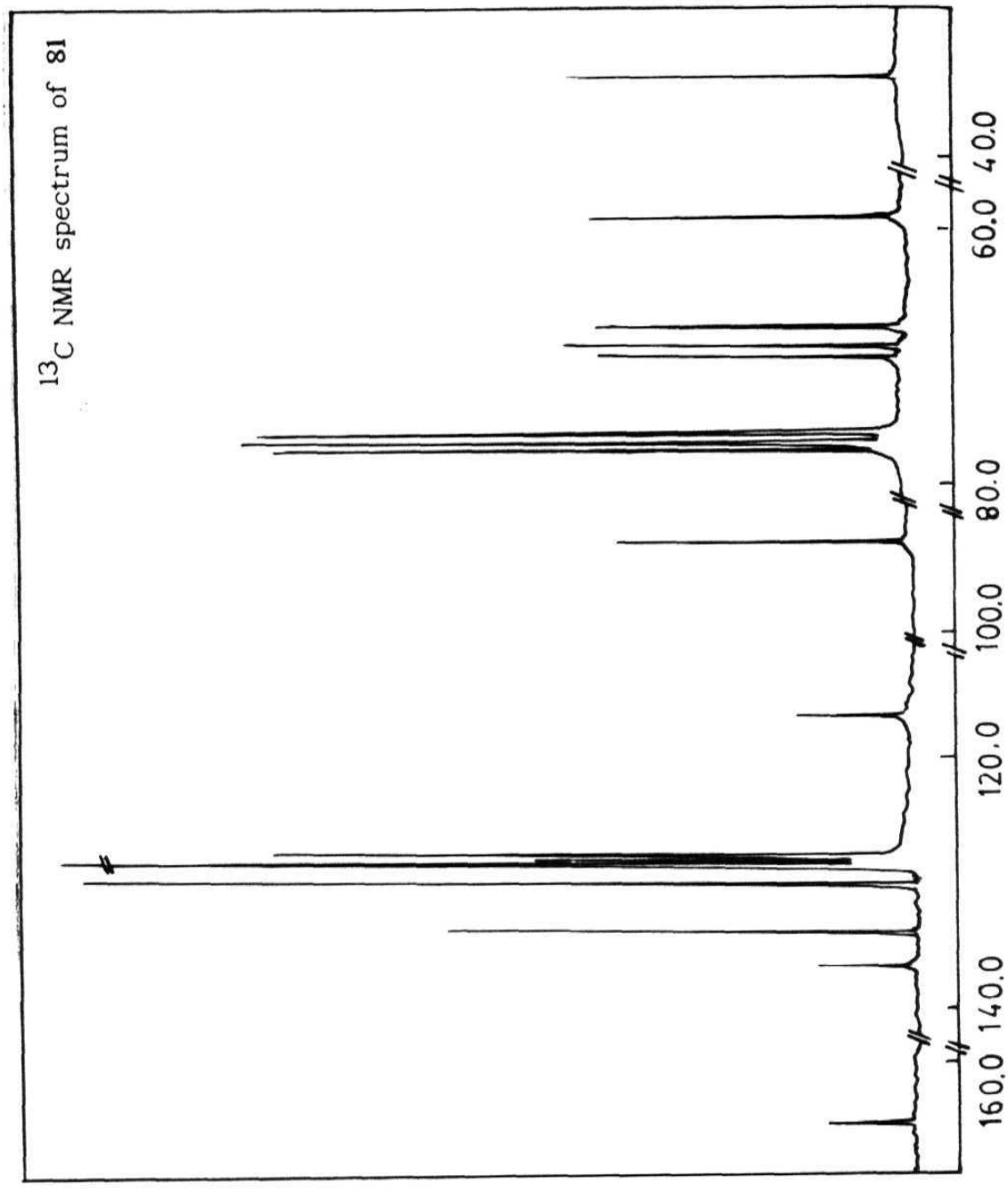

$^1$H NMR spectrum of 70
5.8
5.6
5.0
4.8
4.6
4.2
3.6
3.4

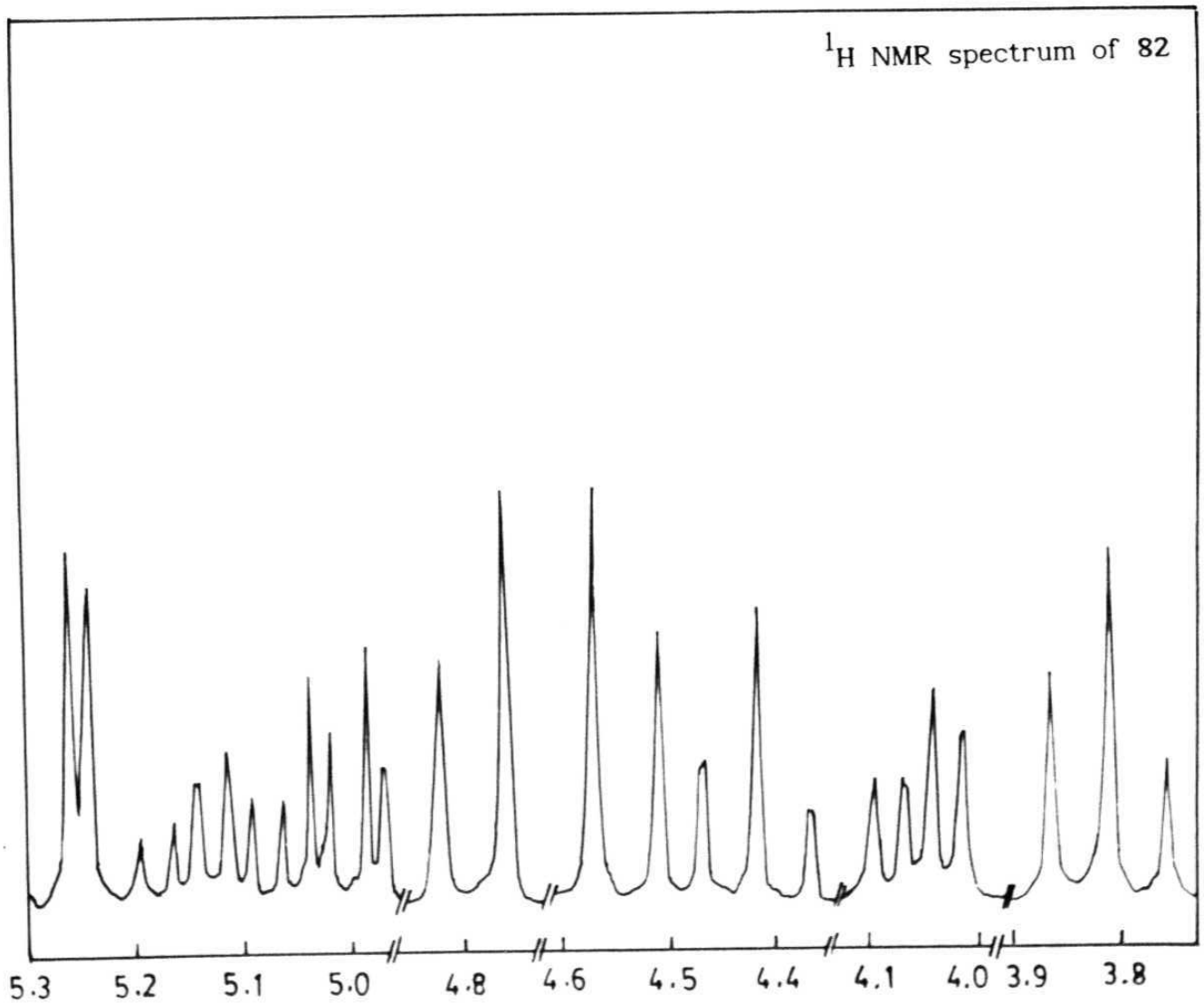

$^1H$ $^1H$ COSY spectrum of 70
3.5
4.0
4.5
5.0
5.5
6.0
PPM

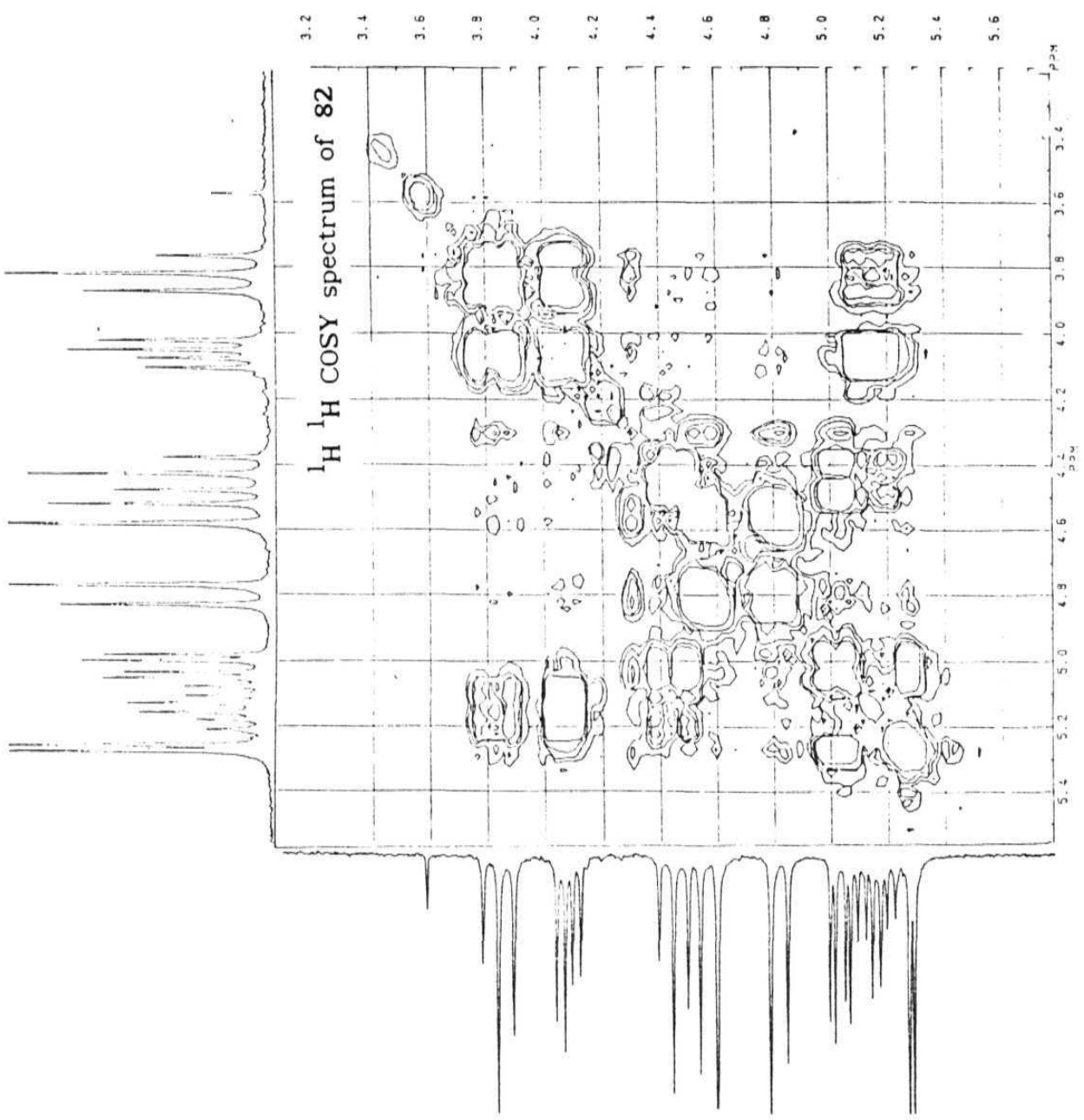

$^{13}C$ NMR spectrum of 75
140.0
120.0
100.0
80.0
60.0

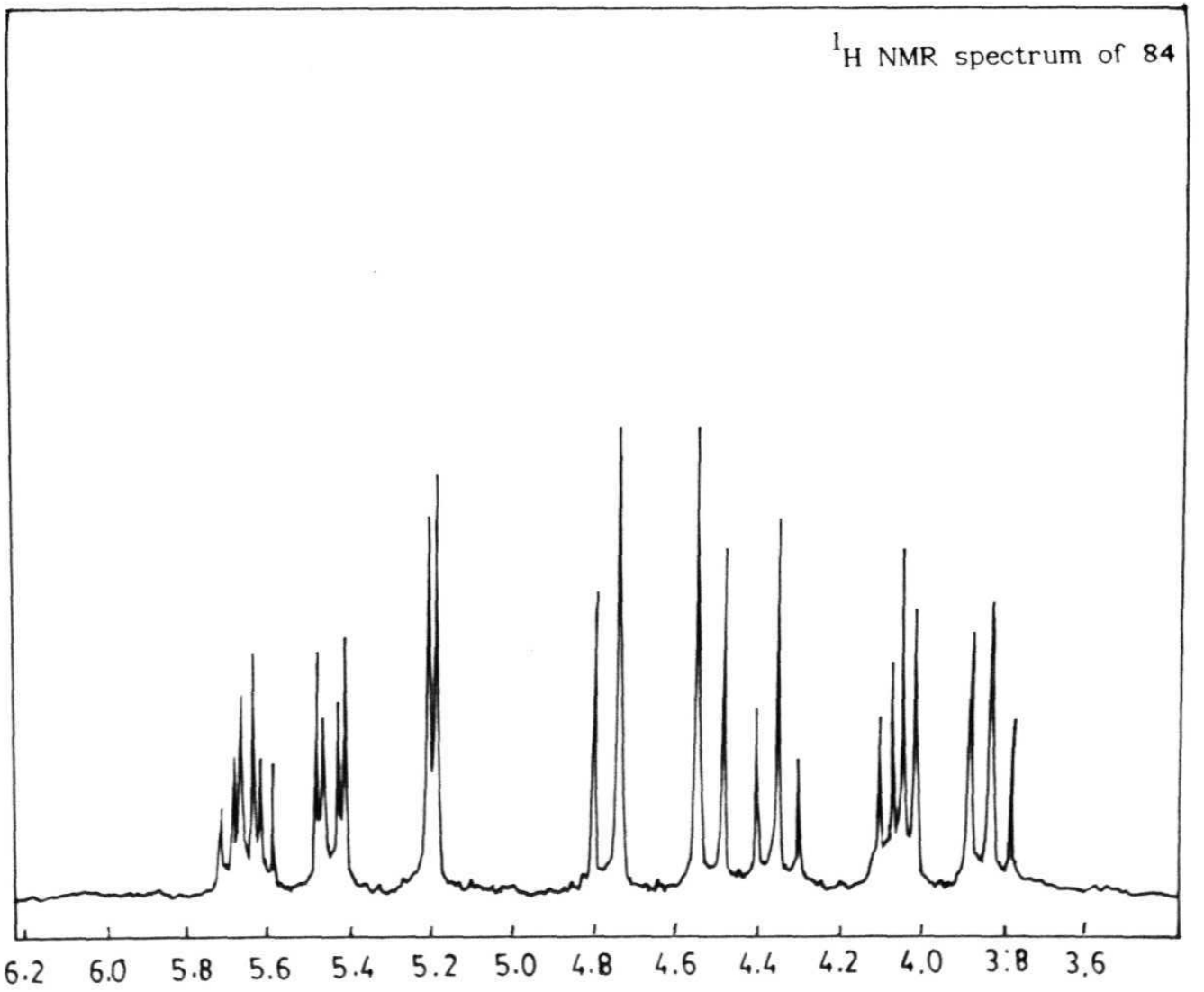

$^1$H NMR spectrum of 76
5.0
4.5
4.0
3.5

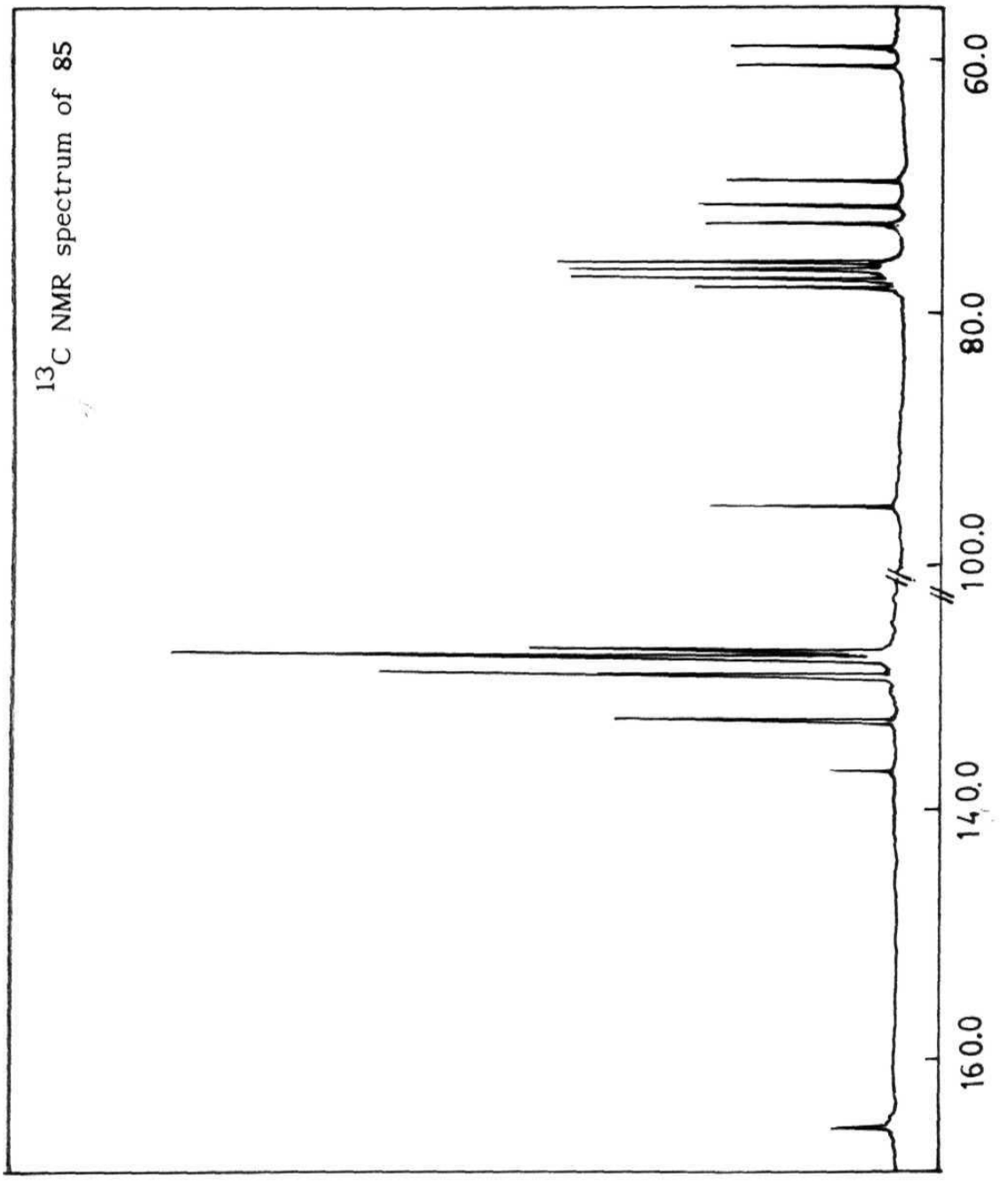

$^1$H NMR spectrum of 79
5.6
5.4
5.2
5,0
4.8
4.6
4.4
4.2
4.0
3.8
3.6


$^{13}C$ NMR spectrum of 81
160.0
140.0
120.0
100.0
80.0
60.0
40.0


$^1$H NMR spectrum of 82
5.3
5.2
5.1
5.0
4.8
4.6
4.5
4.4
4.1
4.0
3.9
3.8


$^1H$ $^1H$ COSY spectrum of 82
3.2
3.4
3.6
3.8
4.0
4.2
4.4
4.6
4.8
5.0
5.2
5.4
5.6
PPM


$^1$H NMR spectrum of 84
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6


$^{13}$C NMR spectrum of 85
160.0
140.0
100.0
80.0
60.0

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## CURRICULAM VITAE

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2 Ring Opening Reactions of Benzyl 2,3-Anhydro-a-D-Ribopyranoside, Vasudeva, P. K.; Nagarajan, M. *Tetrahedron.* **(1996,** *52,* 0000 )