

SYNTHESIS OF METHYL 2,3,6-TRI-O-BENZYL-  
 $\alpha$ -D-HEXOPYRANOSIDES

## ABSTRACT

A review of methods for synthesizing polysaccharides by condensation and by addition polymerization, led to the conclusion that the latter was the more feasible.

For the synthetic polysaccharide desired for future studies, 1,4-anhydrosugars were required as monomers. A general method for preparing 1,4-anhydroethers was tested on cis-1,4-cyclohexanediol ditosylate, which readily formed the ether on treatment with sodium hydroxide.

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All eight steps were completed in the synthesis of methyl 2,3,6-tri-O-benzyl- $\alpha$ -D-glucopyranoside.

Synthesis of methyl 2,3,6-tri-O-benzyl- $\alpha$ -D-hexopyranosides

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by

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## ABSTRACT

A review of methods for synthesizing polysaccharides by condensation and by addition polymerization, led to the conclusion that the latter was the more feasible.

For the synthetic polysaccharide desired for future studies, 1,4-anhydrosugars were required as monomers. A general method for preparing 1,4-anhydroethers was tested on cis-1,4-cyclohexanediol di-tosylate, which readily formed the ether on treatment with sodium hydroxide.

Hydrolysis of fully methylated mannan was employed to prepare 2,3,6-tri-0-methyl-D-mannose, but the method failed when applied to benzylated mannan. Instead, methyl 6-0-trityl-2,3-0-carbonyl-α-D-mannopyranoside was prepared in a two-step synthesis from the glycoside. In five steps of an eight-step synthesis aimed at producing the tri-0-benzyl glycosides, methyl 6-0-benzoyl-2,3-di-0-benzyl-α-D-galactopyranoside was produced.

All eight steps were completed in the synthesis of methyl 2,3,6-tri-0-benzyl-α-D-glucopyranoside.

The following intermediates were prepared on the route to methyl 2,3,6-tri-0-benzyl-α-D-glucopyranoside: methyl 4,6-0-benzylidene-α-D-glucopyranoside; methyl 4,6-0-benzylidene-2,3-di-0-benzyl-α-D-glucopyranoside; methyl 2,3-di-0-benzyl-α-D-glucopyranoside; methyl 6-0-benzoyl-2,3-di-0-benzyl-α-D-glucopyranoside; methyl 6-0-benzoyl-4-0-(2-tetrahydropyranyl)-2,3-di-0-benzyl-α-D-glucopyranoside; methyl 2,3,6-tri-0-benzyl-4-0-(2-tetrahydropyranyl)-α-D-glucopyranoside.

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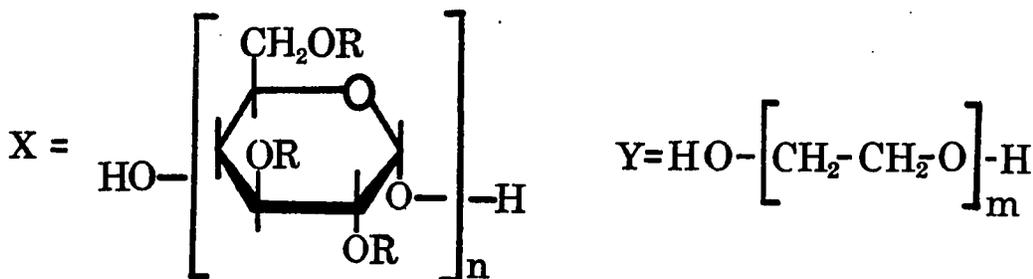
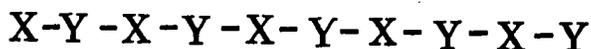
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## INTRODUCTION

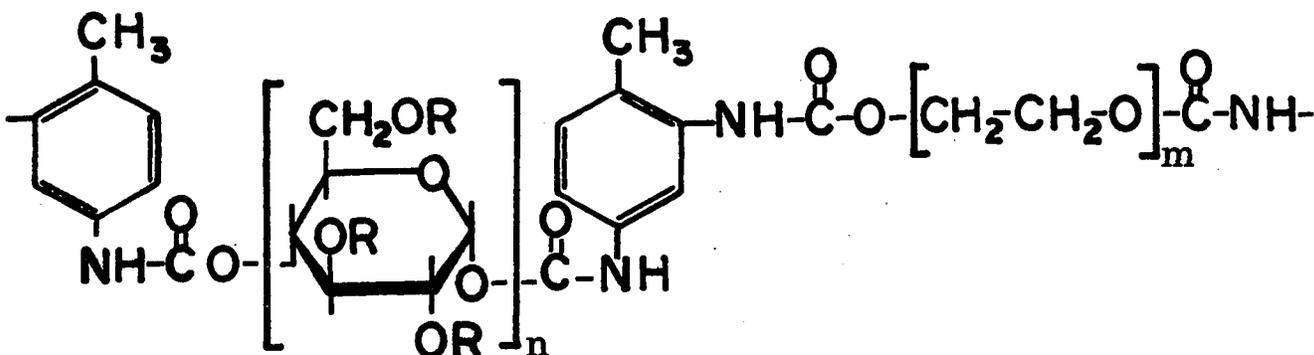
In recent years, increasing interest has developed in the synthesis and study of polymers containing carbohydrate units (1,2). Besides the challenge this complex synthetic problem offers to the organic chemist, the interest lies in the growing importance of such polymers in many branches of science, especially in medicine where they might be used as model substances for the study of physiological processes involving macromolecules.

Although the synthesis of graft polymers of polysaccharides has been a major preoccupation of chemists in this field, none has ever reported attempts to prepare block copolymers in which blocks of polysaccharides (X), would alternate with blocks of some other type (Y):



Hence the properties of such polymers are completely unknown, and, especially since they may prove useful, their synthesis is a worthwhile objective. Accordingly, the synthesis of such polymers is the long range objective of the present work. The general strategy is to prepare linear polysaccharides protected at all but a single hydroxyl group at each end, and to react these polysaccharides with isocyanate-terminated polymers,

probably polyethers:



Earlier experiments in this laboratory (3) were conducted with the purpose of protecting naturally occurring polysaccharides in appropriate positions. This problem proved to be excessively complex because of the inhomogeneity and irregularity of structure of natural polysaccharides, and because of difficulties associated with isolation, and complete structural analysis. Therefore an alternative approach was sought through the synthesis of polysaccharides of predetermined structure, protected in the desired positions.

To this end, the main objective of the present work has been to explore experimental pathways for the synthesis of 1,4-anhydrohexoses suitable for building synthetic stereoregular polysaccharides, protected in the 2,3- and 6-positions. The early section of this thesis will review the methods previously applied in attempts to synthesize stereoregular polysaccharides and will show why the route employing 1,4-anhydrosugars was chosen. Then the chemistry of the synthesis of such sugars, will be reviewed as an introduction to the main experimental work. Since 2,3,6-tri-O-benzyl ethers of monosaccharides appear to be the ideal intermediates for synthesizing 1,4-anhydrosugars, two different approaches were followed

in an effort to simplify the synthesis: a) hydrolysis of polysaccharide ethers linked 1  $\rightarrow$  4, and b) synthesis from monosaccharides. The hydrolysis of fully benzylated polysaccharides proved to be an unpromising route, but the synthetic scheme planned was successfully tested by the synthesis of methyl 2,3,6-tri-O-benzyl- $\alpha$ -D-glucopyranoside, starting from the monosaccharide.

A new method for the formation of internal ethers of six-membered ring compounds was developed in a model experiment. Although this method has not yet been applied to the formation of 1,4-anhydro-sugars, the mild conditions and the relatively easily prepared intermediates employed suggest its applicability in the sugar series.

CHAPTER IChemical Syntheses of PolysaccharidesA - Introduction

Polysaccharides are polymeric materials composed of monomeric sugars tied together by glycosidic linkages. The position of the linkages between sugar units and the configuration at the anomeric carbon atoms differ among different polysaccharides. Polysaccharides, such as cellulose and starch, containing only one kind of polymerized sugar unit (homoglycans), are more abundant in nature than polysaccharides which contain two or more kinds of sugar units (heteroglycans), but the varieties of the latter are more numerous.

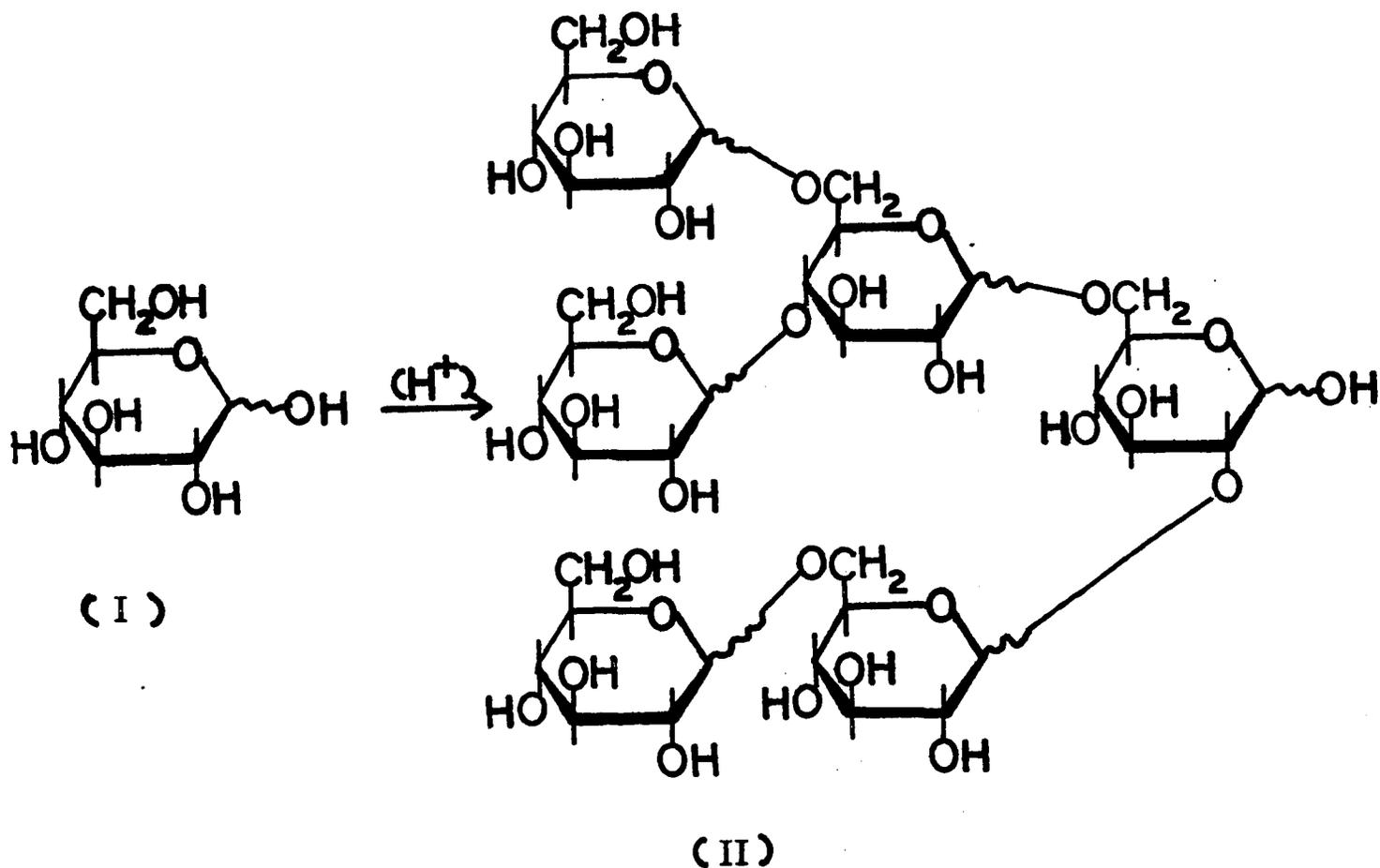
Over the past century the chemical synthesis of specific polysaccharides has attracted the attention of many organic chemists, whose interest has been stimulated primarily by the growing importance of many biopolymers containing carbohydrates. The availability of model polysaccharides of known structure is also considered essential for the solution of many other problems in the organic, physical and biological chemistry of polysaccharides. For example, polysaccharides might provide ideal systems for correlating changes in physical structure with effects on biological activity. Several reviews on this subject have appeared in recent years (1,4). The object of this chapter is to survey the outstanding chemical syntheses of polysaccharides, concentrating on those which yield stereoregular polymers of defined structure. This survey will be confined to only those syntheses which form new glycosidic linkages and will be divided into two parts, dealing with condensation

and addition polymerization, respectively.

B - Condensation polymerization

1) General considerations

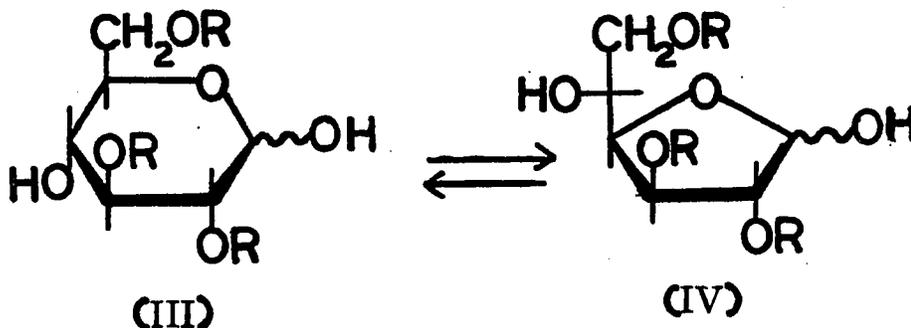
The hydrolysis of cellulose by mineral acids has long been recognized as an equilibrium process, and it therefore seems that condensation polymerization of sugars and their derivatives might be achieved if suitable conditions were chosen to shift the equilibrium towards the polysaccharide. Thus, in early attempts to make synthetic polysaccharides, investigators tried to form new glycosidic linkages by using acid catalysts acting on unsubstituted reducing sugars containing four alcoholic hydroxyl groups and one hemiacetal. The product was a complex mixture of multi-branched polysaccharides, because the positions of the linkages between sugar residues are dependent on the differences of reactivities of the hydroxyl groups which can enter into glycoside formation. D-glucose (I) has been polymerized (5,6) to give highly branched polymers (II).



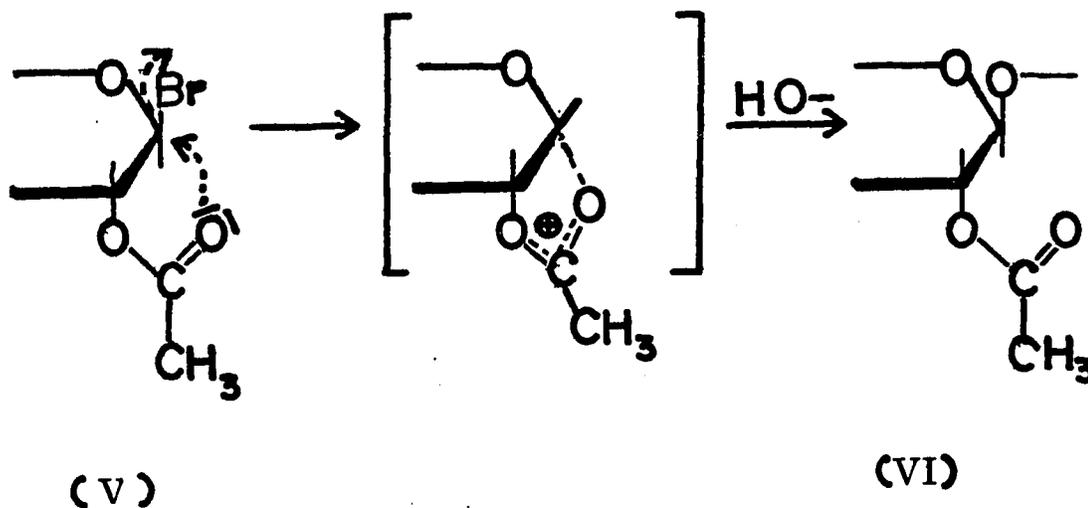
However, a true chemical synthesis of specific oligo- and polysaccharides could not be achieved until suitably protected monosaccharide derivatives were available as starting materials. At first, the methyl group was used for blocking, but it is not easily removed. If free hydroxyl groups were wanted in the final product, new protecting groups had to be used. Acetyl groups proved more satisfactory as

blocking groups, for they are stable under many of the reaction conditions and yet are easily removed by saponification.

A number of modifications of the condensation method have been made, including the use of dehydrating agents (7) (to take up the water formed in the course of the polymerization), anhydrous solvent systems (8) and different acid concentrations (7). Nevertheless, certain difficult problems were encountered with this type of polymerization. One was the interconversion of the pyranose (III) and the furanose (IV) forms of sugars and the consequent random inclusion of sugar residues of different ring size in the polymer.



However, the isomerization of ring forms could be avoided by blocking the hemiacetal hydroxyl groups with suitable substituents, such as halogens (V), so that the glycosidic bond would be formed by direct displacement of the substituent at C-1 (VI):

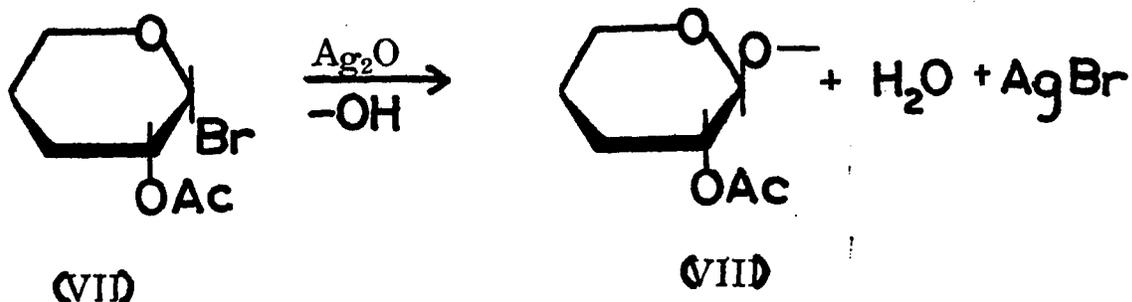


Another problem was the possible formation of two stereoisomeric glycosidic linkages,  $\alpha$ - and  $\beta$ -. Thus, the configuration of the glycosidic bonds in synthetic polyglycoses depended upon the polymerization conditions, and the polymer was not likely to be stereoregular. However, more selective formation of the glycosidic bond might be achieved by the use of two elegant methods: the Koenigs-Knorr reaction and polymerization of sugar ortho-esters.

## 2) Glycosidic bond formation by the Koenigs-Knorr reaction

For the Koenigs-Knorr reaction (9) to be used for synthesizing polysaccharides of definite structure, suitable derivatives of monosaccharides must be employed in which all the hydroxyl groups but one are blocked by some group which later may be easily removed without destroying the linkage formed (10). In contrast to the condensation method discussed previously (in which water is formed), in the Koenigs-Knorr

reaction (VII  $\rightarrow$  VIII) a molecule of hydrogen halide is eliminated from the glycosyl halide (VII) and a hydroxyl group. This reaction proceeds in the presence of silver salts (9) and normally occurs with inversion (11). Thus, since most of the halides used belong to the alpha ( $\alpha$ ) series (VII), the linkage formed in the normal Koenigs-Knorr reaction usually possesses the beta ( $\beta$ ) configuration (VIII):

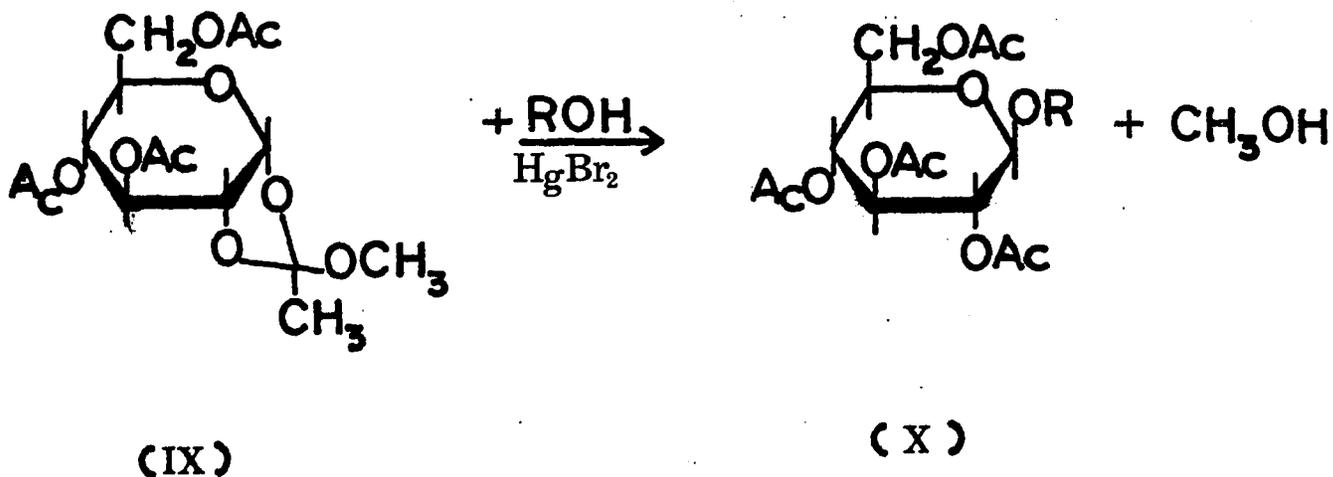


Special care has to be taken to exclude water from the reaction, and to avoid hydrolysis of the glycosyl halide, and desiccants are sometimes used to maintain anhydrous conditions (12). By-products are ortho-esters and anhydrosugars. The poly-glycosides obtained in this reaction generally have a low  $\overline{DP}_n$ : the higher the degree of polymerization of the product the lower its yield (10). The problems connected with this complex reaction have stimulated the development of new glycosylating agents and new glycoside syntheses.

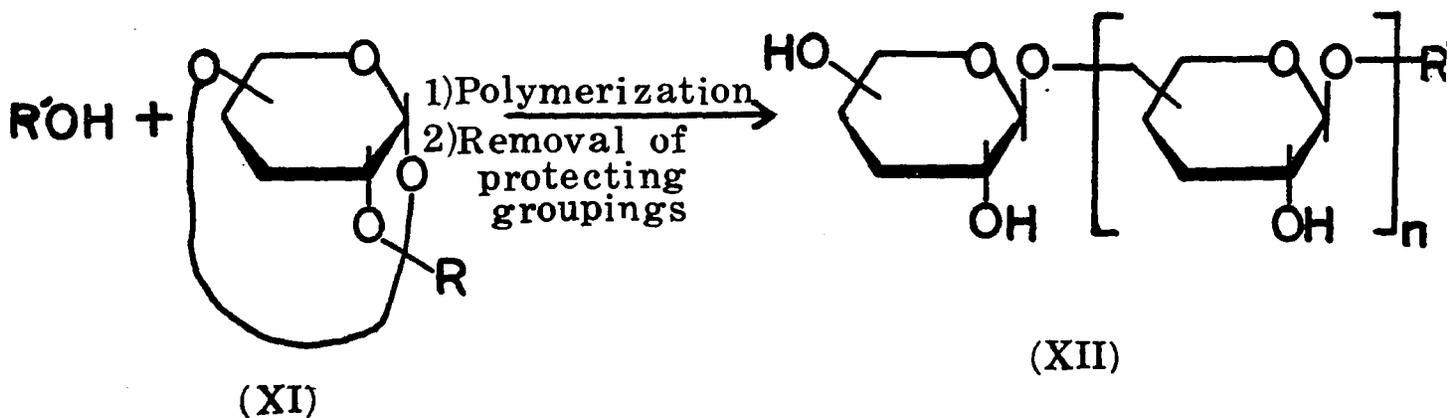
### 3. Polymerization of sugar ortho-esters

In recent years, a new method for the synthesis of glycosides has been developed (13,14). The 1,2-alkyl-orthoacetates of acetylated

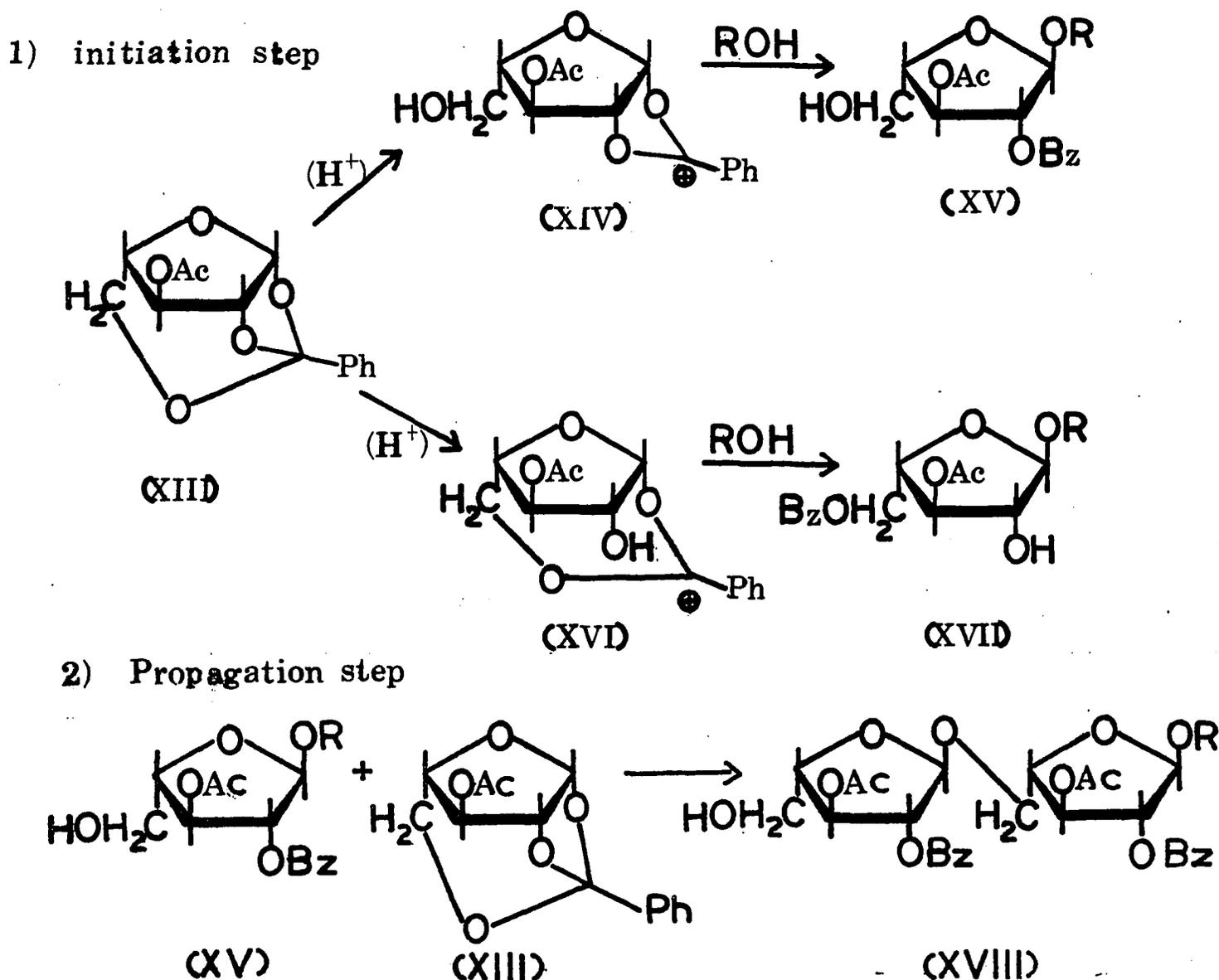
monosaccharides (IX) have been found to react with alcohols, in the presence of catalytic amounts of  $\text{HgBr}_2$  and toluene sulphonic acid, to give the acetylated 1,2-trans-glycosides in good yield.



It has been found that this method of glycosylation is of general application to sugar ortho-esters and possesses the attribute of stereospecificity. After attention had been drawn to this reaction as a possible means for the synthesis of polyglycosides (15) it was successfully used for the preparation of stereoregular polysaccharides, by using the tricyclic ortho-ester  $\beta$ -L-arabinofuranose-1,2,5-ortho-benzoate (16).



The reaction requires an initiator (ROH) which becomes attached to the reducing end of the nascent polysaccharide chain and proceeds according to the scheme (XI  $\rightarrow$  XII). The following mechanism has been proposed (16):



The polymers obtained, arabinans S-1 and S-2, are the first examples reported in the literature of synthetic polysaccharides containing only furanose sugar units. These were obtained in relatively high yields and molecular weights, showing that the polymerization proceeds readily and

that this approach can be used for the synthesis of other polysaccharides.

## C - Addition polymerizations

### 1) General considerations

Addition polymerization of carbohydrates is defined (4) as polymerizing sugar derivatives in a process which gives a glycosidically linked polymer without the evolution of by-products. The molecular formula of the monomeric units is identical with that of the structural units of the polymers (1):



This type of polymerization may be regarded as simpler than the condensation reaction, since in principle it is sufficient to seal the monomer in an evacuated tube with a catalyst and heat it to cause polymerization.

### 2) Polymerization of 1,6-anhydrosugars

#### Polymerization of levoglucosan

Of all the possible polymerizable anhydrosugars, the reaction of levoglucosan, 1,6-anhydro- $\beta$ -D-glucopyranose (XX), has been the most extensively studied. Pictet (17) heated levoglucosan at 240°C in the presence of anhydrous zinc chloride, and obtained products of various degrees of polymerization, from dimeric to octameric, which he described as dextrans. Since levoglucosan is prepared by the pyrolysis of starch and cellulose (17a, 18), Pictet regarded this polymerization as a reversible process.

Despite this modest success, addition polymerizations in the carbohydrate series were subsequently ignored for more than thirty years, until 1959, when Schuerch and co-workers began (19) a series of publications reporting an extensive study of the polymerization of levoglucosan and other anhydrosugars.

In their early experiments, Scheurch and co-workers (19) polymerized unsubstituted levoglucosan in a sealed tube under diminished pressure by heating the monomers at temperatures ranging from 100-130°C and using several types of acid catalysts, with and without solvents. The most satisfactory polymerizations occurred at 115-120°C in the absence of solvents and with 0.02 moles of monochloroacetic acid per mole of monomer as catalyst. In the mechanism proposed for this polymerization, protonation at the oxide oxygen is followed by reaction of the oxonium product (XXI) with another molecule of levoglucosan to yield (XXII) and then the reaction is repeated to form (XXIII):



function, the hydroxyl groups at different positions in the sugar unit might enter into glycosidic linkage during the polymerization, and lead to the formation of highly branched polymers. However, the reactivities of the hydroxyl groups are not identical and do not remain the same during the reaction. Since the primary hydroxyl groups at C-6 are most reactive, the product polymer has a predominance of 1 → 6 linkages. Additional insight into the branched character of the polymer, and therefore the relative reactivities of the hydroxyl groups was obtained by oxidation with sodium meta-periodate (19). A fraction of the polymer consumed 1.44 moles of periodate and formed 0.55 mole of formic acid per anhydro glucose unit. Therefore Schuerch suggested a repeating sequence of twenty units which includes 11 glucose residues containing all three secondary hydroxyl groups (on C<sub>2</sub>, C<sub>3</sub> and C<sub>4</sub>) unsubstituted, and 7 glucose residues with an unsubstituted pair of vicinal hydroxyl groups (C<sub>2</sub>, C<sub>3</sub> or C<sub>3</sub>, C<sub>4</sub>). The remaining two units must be disubstituted on secondary positions or substituted on the C-3 position. The optical rotation of these polymers was  $[\alpha]_D^{20} + 91 \pm 5^\circ$ , indicating that they contained both α and β linkages, with a slight predominance of α-D-glucosidic linkages. Schuerch indicated (19,20) that one of the possible explanations for the lack of stereospecificity was the existence, during the cleavage of the 1,6-oxide bridge, of an intermediate involving the hydroxyl group at C-2. In an effort to study the mechanism of polymerization of 1,6-anhydrohexoses, Schuerch and his co-workers attempted to polymerize several substituted 1,6-anhydrohexoses. Polymerization of 1,6-anhydro-2-O-methyl-β-D-galactopyranose (20) and of other 2,3,4-tri-O-substituted hexoses (21) failed. These results supported the original supposition (19) that

the polymerization probably proceeded via some intermediate related structurally to the 1,2-anhydrosugars. D-galactosan (20) and 1,6-anhydro- $\beta$ -D-mannopyranose (22) were polymerized using conditions similar to those previously used for the polymerization of levoglucosan.

### 3 - Sterically controlled polymerization of 1,6-anhydrosugar derivatives

Although tri-0-methyl levoglucosan at first failed to polymerize in the presence of the several acidic and basic catalysts tested by Schuerch (21), Korshak and co-workers (23) obtained a polymer of high molecular weight by reacting the monomer in the presence of boron tri-fluoride etherate in toluene at room temperature. These results were later confirmed by Schuerch and Tu (24) who found that the polymer obtained by this method possessed a high optical rotation  $[\alpha]_D^{25} + 197^\circ$  to  $199^\circ$ . This result suggested an overwhelming predominance of  $\alpha$ -glucosidic linkages and was an indication of the high stereospecificity governing this polymerization. However these polymers had a  $\overline{DP}_n$  of only about 25. Schuerch and Ruckel (25) then made a systematic study of the polymerization of 1,6-anhydro-2,3,4-tri-0-substituted- $\beta$ -D-glucopyranoses, with the objective of finding suitable synthetic conditions for preparing a linear stereoregular polysaccharide of high molecular weight. Such polymers were obtained from the methyl and ethyl ethers of levoglucosan, the best results being obtained at  $-78^\circ\text{C}$ . Lower temperatures resulted in a remarkable increase in  $\overline{M}_n$ , when methylene dichloride was the solvent and phosphorus pentafluoride the catalyst. The results of these experiments are summarized in Table (I) (25). Various blocking groups which could be easily removed after polymerization were also investigated. Among these only the 2,3,4-tri-0-benzyl-levoglucosan was found to

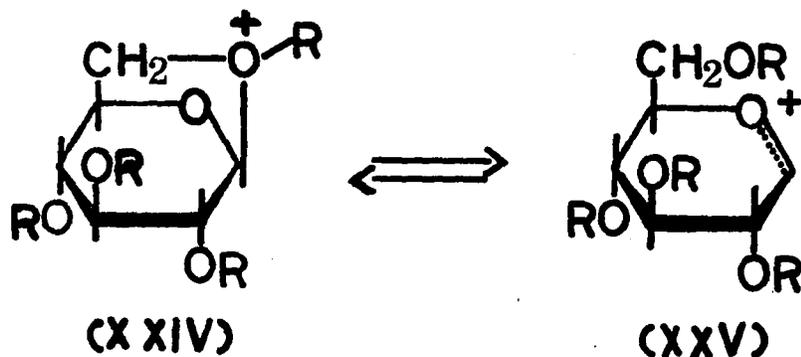
TABLE I

Selected polymerizations of 1,6-anhydro-2,3,4-tri-O-substituted- $\beta$ -D-glucopyranose (25)

Monomer	Catalyst	[Cat.] 100/ [monomer]	Solvent	Monomer solvent ratio (g/100)	Temp. °C	Time hr	% Yield	$\bar{M}_n$	$\bar{DP}_n$	$[\alpha]_D$
Me <sub>3</sub>	BF <sub>3</sub> ·Et <sub>2</sub>	3.6	CH <sub>2</sub> Cl <sub>2</sub>	10	-78°	157	0			
Me <sub>3</sub>	BF <sub>3</sub> ·Et <sub>2</sub>	3.0	CH <sub>2</sub> Cl <sub>2</sub>	10	+25	157	6.0	1,400	8	+183
Me <sub>3</sub>	PF <sub>5</sub>	3.7	CH <sub>2</sub> Cl <sub>2</sub>	10	+17	144	11.1	2,960	14	+141
Me <sub>3</sub>	PF <sub>5</sub>	3.7	CH <sub>2</sub> Cl <sub>2</sub>	10	-28	144	85.3	19,950	98	+202
Me <sub>3</sub>	PF <sub>5</sub>	3.7	CH <sub>2</sub> Cl <sub>2</sub>	10	-78	144	91.9			+196
Me <sub>3</sub>	PF <sub>5</sub>	1.2	CH <sub>2</sub> Cl <sub>2</sub>	10	-78	144	0			
Me <sub>3</sub>	PF <sub>5</sub>	2.5	CH <sub>2</sub> Cl <sub>2</sub>	10	-78	144	30			+202
Me <sub>3</sub>	PF <sub>5</sub>	9.1	CH <sub>2</sub> Cl <sub>2</sub>	10	-78	144	72.5			+195
Me <sub>3</sub>	PF <sub>5</sub>	3.7	CH <sub>2</sub> Cl <sub>2</sub>	10	-78	18	28.9			+199
Me <sub>3</sub>	PF <sub>5</sub>	3.7	CH <sub>2</sub> Cl <sub>2</sub>	10	-78	48	85.6			+208
Me <sub>3</sub>	PF <sub>5</sub>	3.7	CH <sub>2</sub> Cl <sub>2</sub>	10	-78	245	85.5			+198
Et <sub>3</sub>	PF <sub>5</sub>	3.9	CH <sub>2</sub> Cl <sub>2</sub>	10	-78	227	0			
Et <sub>3</sub>	PF <sub>5</sub>	9.5	CH <sub>2</sub> Cl <sub>2</sub>	10	-78	185	5.0			
Et <sub>3</sub>	PF <sub>5</sub>	11.8	CH <sub>2</sub> Cl <sub>2</sub>	10	-78	167	70.0	14,800	60	+181
Et <sub>3</sub>	PF <sub>5</sub>	19.7	CH <sub>2</sub> Cl <sub>2</sub>	10	-78	29	88.6	28,200	114	+198
Et <sub>3</sub>	PF <sub>5</sub>	19.0	CH <sub>2</sub> Cl <sub>2</sub>	20	-78	12	51.0	47,200	192	+178
Et <sub>3</sub>	PF <sub>5</sub>	20.0	CH <sub>2</sub> Cl <sub>2</sub>	20	-78	19	76.5	37,600	152	+184
(CH <sub>2</sub> Ph) <sub>3</sub>	PF <sub>5</sub>	20.2	CH <sub>2</sub> Cl <sub>2</sub>	20	-78	88	90.5	41,800	97	+109

Me <sub>3</sub>	PF <sub>5</sub>	3.7	CH <sub>2</sub> Cl <sub>2</sub>	10	-78	245	85.5			+198
Et <sub>3</sub>	PF <sub>5</sub>	3.9	CH <sub>2</sub> Cl <sub>2</sub>	10	-78	227	0			
Et <sub>3</sub>	PF <sub>5</sub>	9.5	CH <sub>2</sub> Cl <sub>2</sub>	10	-78	185	5.0			
Et <sub>3</sub>	PF <sub>5</sub>	11.8	CH <sub>2</sub> Cl <sub>2</sub>	10	-78	167	70.0	14,800	60	+181
Et <sub>3</sub>	PF <sub>5</sub>	19.7	CH <sub>2</sub> Cl <sub>2</sub>	10	-78	29	88.6	28,200	114	+198
Et <sub>3</sub>	PF <sub>5</sub>	19.0	CH <sub>2</sub> Cl <sub>2</sub>	20	-78	12	51.0	47,200	192	+178
Et <sub>3</sub>	PF <sub>5</sub>	20.0	CH <sub>2</sub> Cl <sub>2</sub>	20	-78	19	76.5	37,600	152	+184
(CH <sub>2</sub> Ph) <sub>3</sub>	PF <sub>5</sub>	20.2	CH <sub>2</sub> Cl <sub>2</sub>	20	-78	88	90.5	41,800	97	+109
(CH <sub>2</sub> Ph) <sub>3</sub>	PF <sub>5</sub>	10.6	CH <sub>2</sub> Cl <sub>2</sub>	20	-78	91	94.5	75,750	178	+113

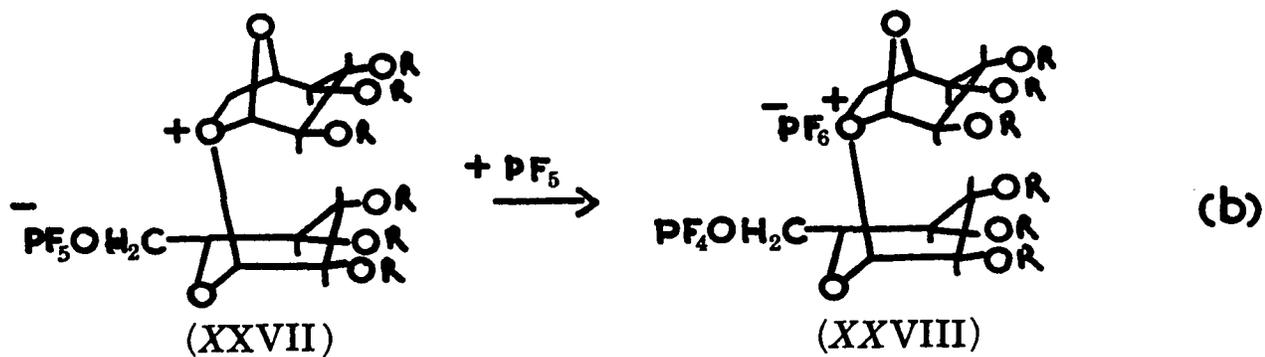
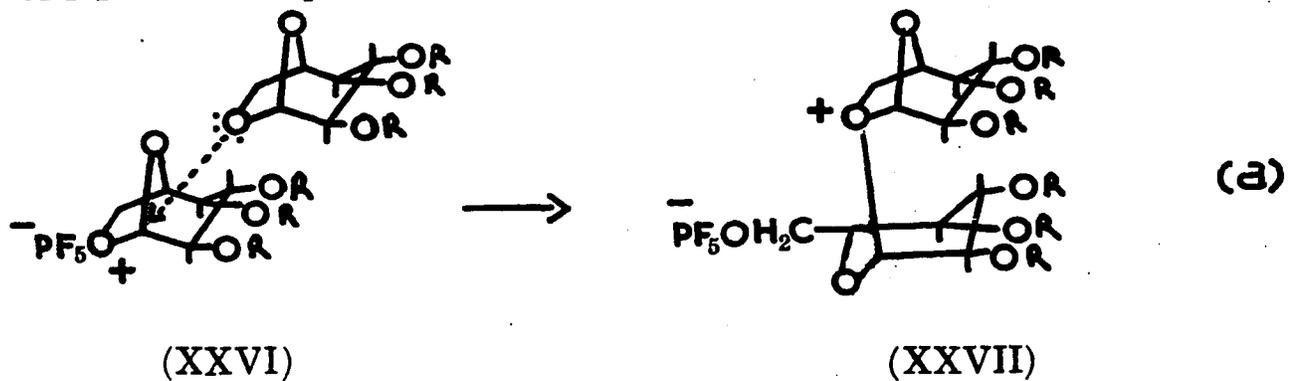
undergo polymerization, and the polysaccharide, poly  $\alpha(1 \rightarrow 6)$ -anhydro-D-glucopyranose, was obtained from the polymer by debenzylolation with sodium in liquid ammonia at  $-78^{\circ}\text{C}$  (26,27). By enzymic analysis (28) this material was found to be 98% linked  $1 \rightarrow 6$ , with 100%  $\alpha$  configuration at C-1. Because  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  catalysed the polymerization of levoglucosan methyl ether at room temperature, but was ineffective at  $-78^{\circ}\text{C}$ , it is probable that no active monomer-catalyst complex was formed (25). Schuerch and Ruckel (25) also discovered a temperature effect in the polymerization catalysed by  $\text{PF}_5$  of the tri-O-methyl ether of levoglucosan. The fact that less regular polymers were obtained at higher temperatures, suggested that the polymerization was probably governed by different mechanisms at low and at high temperature. Later experiments (29) confirmed these observations. Polymerization of tri-O-benzyl levoglucosan at  $0^{\circ}\text{C}$ , with a fixed mole ratio of  $\text{PF}_5$ , yielded a polymer of lower viscosity ( $[\eta]$  0.04) and lower optical rotation ( $[\alpha]_D^{20} + 62.4^{\circ}$ ) than polymerization at  $-78^{\circ}\text{C}$ . At first sight these results appear contradictory when compared with the  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  catalysed polymerization of tri-O-methyl levoglucosan which, at room temperature, yielded a stereoregular polymer of low molecular weight, but did not polymerize at all at  $-78^{\circ}\text{C}$ . However, these results indicate that during the course of polymerization of levoglucosan derivatives, the propagation and termination processes are influenced by the particular Lewis acid and temperature employed. To explain the two types of mechanisms, Schuerch and Zachoval (29) suggested that an oxonium ion (XXIV) and a carbonium (XXV) ion might exist in equilibrium. The former reacting stereospecifically to produce  $\alpha$ -linkages, the latter non-stereospecifically to produce both  $\alpha$ - and  $\beta$ -linkages.



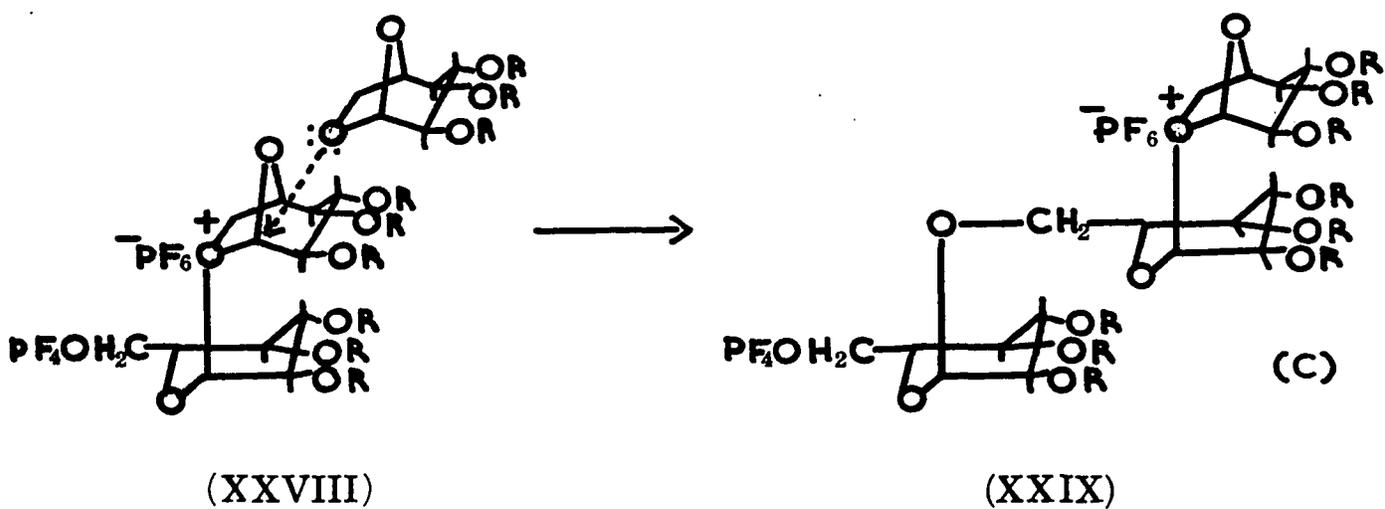
They suggested that  $\text{PF}_5$  and other strong Lewis acids, such as  $\text{SbF}_5$ , might co-ordinate with the oxygen of the 1,6-anhydro ring, to form an oxonium ion (XXIV). This causes stereoregular polymerization at very low temperatures. In contrast, at higher temperatures carbonium ion character (XXV) is induced in the propagating site with concomitant loss of stereoregularity. Boron trifluoride etherate acts as a much weaker acid, inducing no carbonium ion character even at room temperature, and is not sufficiently reactive to cause polymerization at low temperature.

Initiation of the polymerization of tri-O-methyl levoglucosan by means of  $\text{PF}_5$  at low temperatures involves a trialkyl oxonium mechanism (25) according to the following two-step scheme: (a) co-ordination of  $\text{PF}_5$  with the oxide oxygen of levoglucosan gives the salt (XXVI), which undergoes nucleophilic attack on C-1 by the ether oxygen of another anhydro sugar monomer, and yields (XXVII); (b) the abstraction of a fluoride ion by another molecule of  $\text{PF}_5$  (XXVII  $\rightarrow$  XXVIII). During the propagation step (reaction (c)), a growing polymer (XXIX) is produced by a mechanism very similar to reaction (a).

## Initiation step

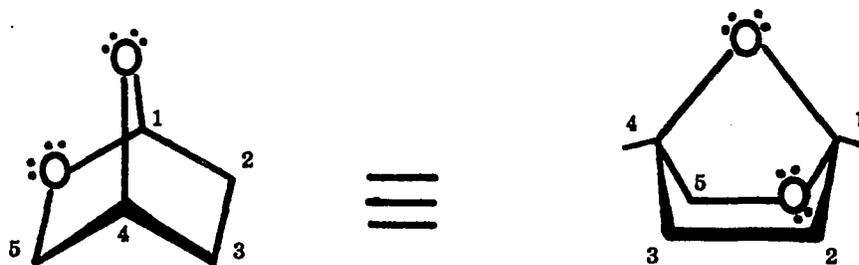


## Propagation step



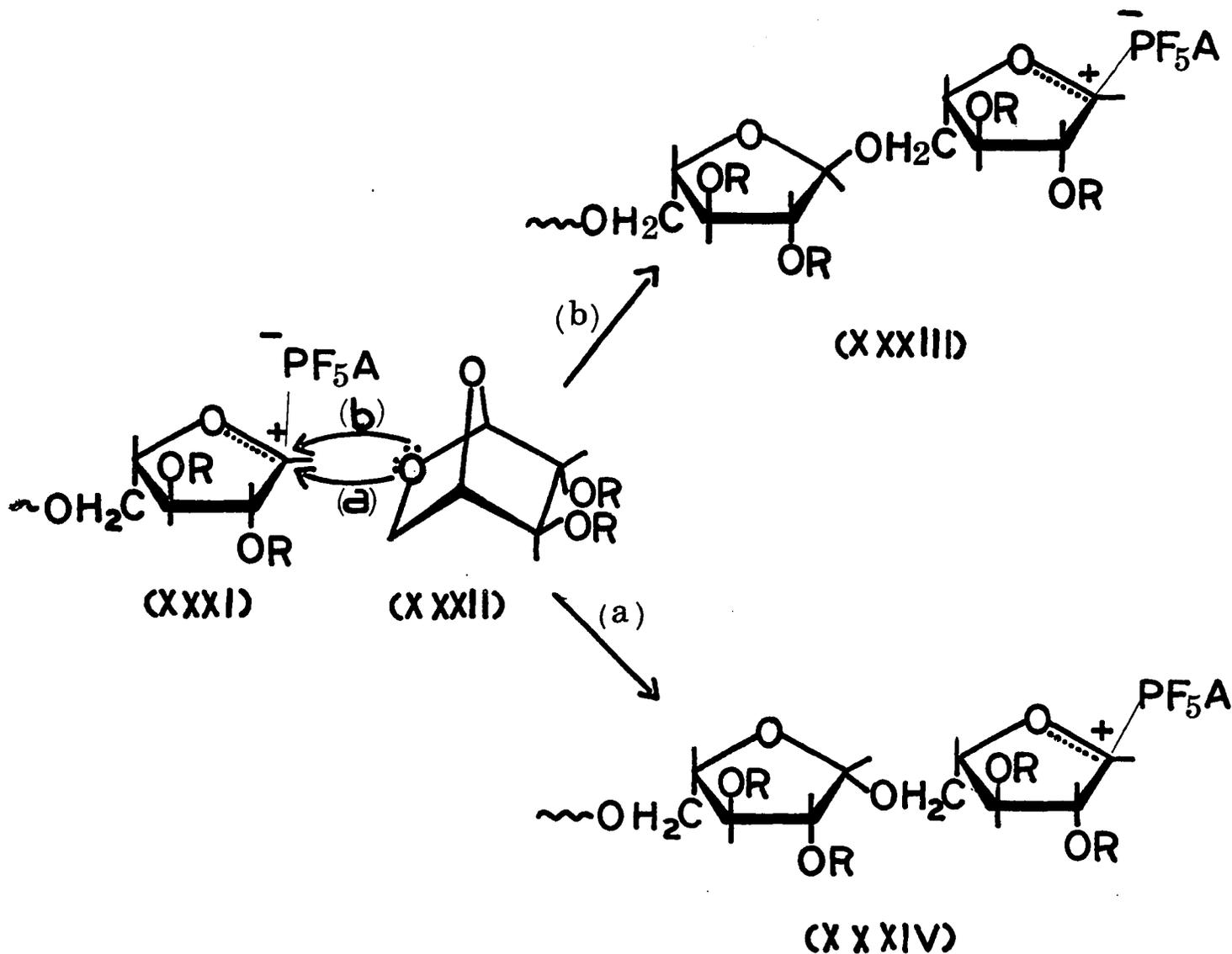
4) - Polymerization of 1,4-anhydrosugars

Addition polymerization of 1,4-anhydrosugar derivatives may be regarded as an alternative method for the chemical synthesis of 1 → 4 linked polysaccharides. Following the successful application of addition polymerization to the stereospecific synthesis of poly(1,6-anhydrosugars), Kops and Schuerch (30) applied the method to the 1,4-anhydrosugars: 1,4-anhydro-2,3,6-tri-O-methyl-D-galactopyranose and 1,4-anhydro-2,3-di-O-methyl-L-arabinopyranose. They treated these anhydrosugars under vacuum with strong Lewis acids, such as PF<sub>5</sub>, and obtained amorphous polymers of moderate molecular weight, the maximum  $\overline{DP}_n$  being approximately 90. Lower temperatures of polymerization gave a higher yield and chain length. However, the 1,4-anhydrosugar monomers did not polymerize at temperatures below -97°C. Varying the temperature of polymerization and polarity of the solvent, or both, caused large variation in the optical rotations of the products. When the polymers were subjected to degradation, chromatographic studies revealed no products arising from C-O bond breakage at the asymmetric C-4 carbon atom. This result indicated that the variations in optical rotations reflected differences in configuration only at the anomeric center. It was therefore suggested that the polymerization might proceed via a carbonium ion which would be considerably stabilized by the neighbouring oxygen in the ring. Because of the particular nature of the 1,4-anhydrohexoses, which include a pyranose and a furanose ring fused together (XXX), the carbonium ion can co-ordinate with either of the ring oxygens in the anhydrosugar.



(XXX)

Since the effective basicities of these oxygens are not greatly different, and since the carbonium ion has equal probability of coordinating with either oxygen, it is not surprising that approximately equal amounts of pyranose and furanose structures have been found in the polymer. The mechanism for incorporating furanose units may be formulated (30):



Since it is suggested that this polymerization proceeds via a carbonium ion mechanism, the nucleophilic attack on C-1 occurs with equal probability through path (a) or path (b), (XXXI  $\rightarrow$  XXXIII) or (XXXI  $\rightarrow$  XXXIV), and causes a random distribution of  $\alpha$  (path a) and  $\beta$  (path b) linkages in the product. However, as indicated by the optical rotation of polymers obtained under different conditions, a thermodynamic control of the type of the glycosidic linkage is possible.

The bulky counter-ion  $[\text{PF}_5\text{A}]^{\ominus}$ , occupying the less hindered side of the furanose ring (XXXI), interacts with the carbonium ion. The strength of this interaction is temperature-dependent and determines whether the nucleophilic attack will proceed by path (a) or path (b).

#### D - Conclusions

From this review, it is concluded that the two methods of synthesis described have different characteristics and therefore different applications. Condensation polymerization, historically the first and more extensively investigated method, yields products of low  $\overline{\text{DPn}}$  with irregular stereochemistry at the anomeric centre and does not easily permit steric control of the glycosidic linkage. Thus, its application is unsuitable for the synthesis of linear polysaccharides with relatively high  $\overline{\text{DPn}}$  and stereoregular glycosidic linkages. Conversely, although addition polymerization is of only relatively recent development, it has the advantage, if appropriate reaction conditions (such as temperature, catalyst, solvent, etc.) are chosen, of yielding products of relatively high  $\overline{\text{DPn}}$  and stereoregular glycosidic linkages in a highly stereospecific reaction. This latter method appears to be the best route for synthesizing the polysaccharides required in the present work. To obtain the desired

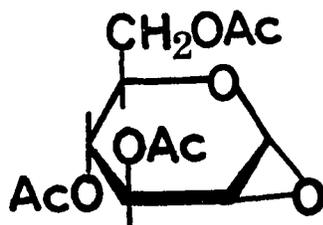
polymers, 1,4-anhydrosugars are required as starting materials.

E - 1,4-anhydrosugars

1) General considerations

Anhydrosugars are formed by intramolecular elimination of a molecule of water from two hydroxyl groups of a monosaccharide molecule. If the hemiacetal hydroxyl group participates in the formation of the anhydro ring, the resultant sugars are termed glycosans, or intramolecular glycosides, and their properties are similar to the glycosides. When aldohexoses are heated with acids, equilibrium mixtures are formed containing one or several anhydrides (31), and 1,6-anhydrohexopyranoses are the predominating glycosans, although other anhydrides are also present. Reviews on glycosans have been published recently (32).

The most common type of glycosan is the 1,6-anhydrohexopyranose, generally prepared by pyrolyzing oligo- and polysaccharides under reduced pressure. Thus 1,6- $\beta$ -D-glucosan (levoglucosan) is made by dry distillation of starch and cellulose (17a, 18, 33). Levoglucosan is also prepared by treating aromatic  $\beta$ -D-glucosides with alkali at 100°C. That this reaction proved (34) not to be applicable to  $\alpha$ -D-glycosides and 2-O-methyl- $\beta$ -D-glycosides, indicated that the formation of 1,6-anhydrosugars probably proceeds via some intermediate involving the corresponding 1,2-anhydride. Another interesting glycosan is the 1,2-anhydro-3,4,6-tri-O-acetyl- $\alpha$ -D-glucopyranose (XXXV), commonly known as Brigl's anhydride, which has a very reactive ethylene oxide ring.

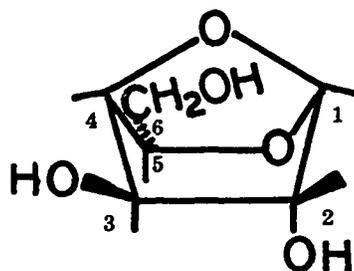


(XXXV)

It reacts easily with hydroxyl groups of alcohols, usually with Walden inversion, to give the glycoside, and consequently is important for the preparation of oligosaccharides (35).

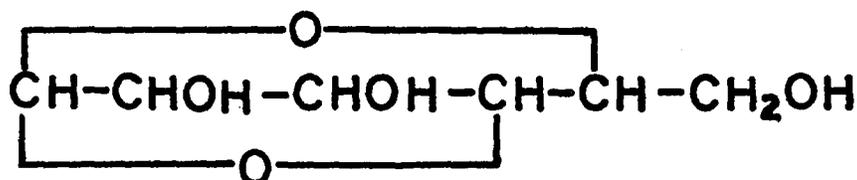
2) - 1,4-anhydro-glycopyranoses

Another type of glycosidic anhydride is the 1,4-anhydro-hexopyranose (or 1,5-anhydrohexofuranose) system, formed by a strained arrangement of two fused five-membered rings. This type possesses both a furanose and a pyranose ring (see (XXX), page 22) and therefore can be termed  $\beta < 1.4 > \alpha < 1.5 >$  glycosans. From steric considerations, the galacto derivative (XXXVI) has been assigned as the most stable (36) of all the diastereomers. It has the least hindered configuration, with the C-6 and O-3 both exo, and with the O-2 atom, though endo, having no hydrogen atom opposed to it on the other ring.



(XXXVI)

Present knowledge suggests that structures assigned to products of previous syntheses of 1,4-anhydrosugars are incorrect. In 1925, Pringsheim (37) heated lichenin at 240°C, and fragmented it to lichosan in 30% yield. Upon standing in aqueous solution for a few days this material repolymerized to a polysaccharide which seemed identical to the original lichenin. The formula ascribed to lichosan by Pringsheim is the 1,4-anhydrohexose (XXXVII).



(XXXVII)

Lichenin was proven later to consist of glucose units linked 1→4 and 1→3 (38), and its  $\frac{1}{2}$ prolysis, like the prolysis of other polysaccharides of similar structure (33,39,40), seems more likely to give the 1,6-anhydride. Therefore the structure originally assigned to lichosan is probably not correct. In 1930, Micheel (41) reacted acetobromorhamose with trimethylamine and obtained a compound to which he assigned the structure of 1,4-anhydro-2,3-di-O-acetyl-rhamnopyranose.

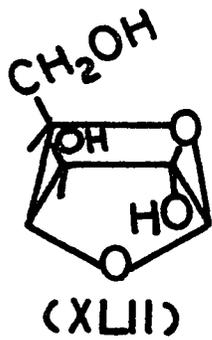
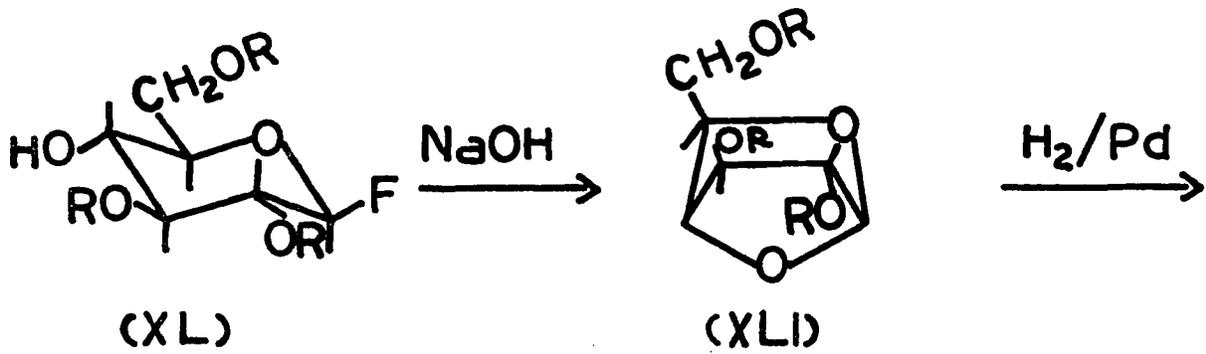
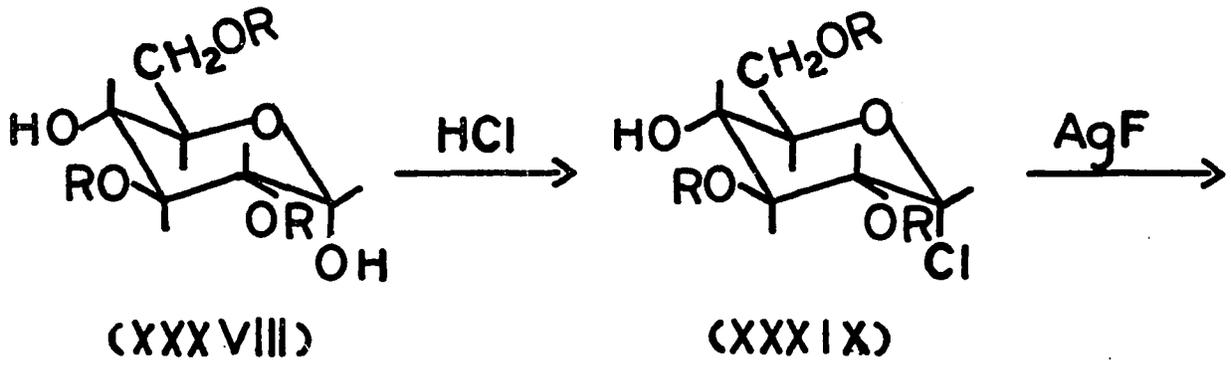
Because of their possible use as intermediates for preparing polysaccharides, the synthesis of 1,4-anhydrosugars has attracted the attention of research workers and anhydrides of this type have been synthesized under forcing conditions from sugars in which all but the hydroxyl groups at C-1 and C-4 were protected. The preparation of 1,4-anhydro-2,3,6-tri-O-methyl-D-glucose from derivatives of 2,3,6-tri-O-methyl-D-glucose gave rise to a

dispute between Freudenberg and Hess on the structure of the products obtained (42-48). By treating 2,3,6-tri-0-methyl-glucosyl chloride with sodium, Freudenberg (43) obtained an anhydride to which he assigned the structure of 1,4-anhydro-2,3,6-tri-0-methyl-D-glucose ( $[\alpha]_D^{20} + 16.5^\circ$  ( $H_2O$ )). This reaction when repeated by Hess and Littmann (45), did not give reproducible results. However, Husemann and Klar have repeated Freudenberg's preparation (49) and have proven that the compound obtained was the 1,4-anhydro-2,3,6-tri-0-methyl-D-glucose. In addition, they devised an alternative synthesis: when 2,3,6-tri-0-methyl-D-glucose mercaptal was treated with silver carbonate at 120-160°C/0.3 torr, it gave an oil displaying the same spectroscopic features as the 1,4-anhydride. In a modification of Freudenberg's method, Husemann and Klar treated a suspension of 2,3,6-tri-0-methyl-D-glucose in absolute ether with gaseous HCl at 0°C and, after neutralization of the solution with sodium oxide in benzene and subsequent evaporation of the solvent, recovered the 1,4-anhydride.

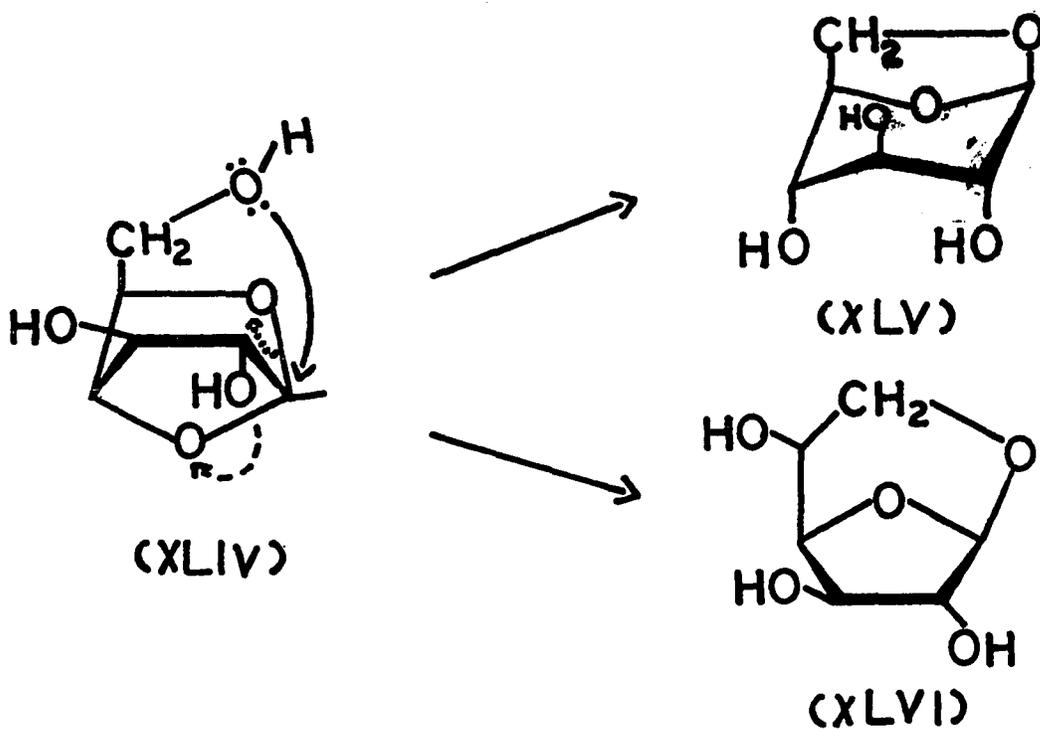
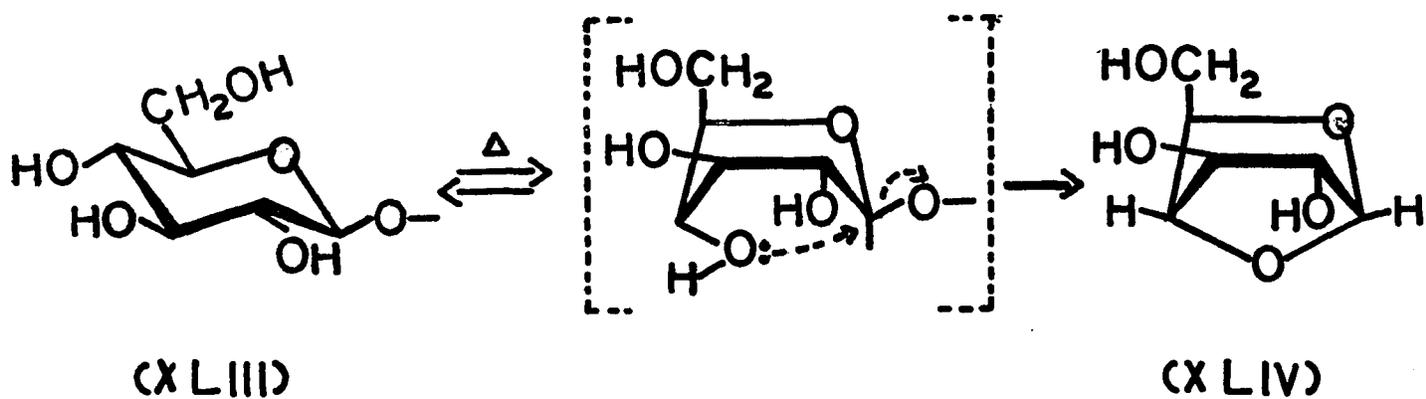
Hess (47,48) believed that the reaction of 2,3,6-tri-0-methyl-4-0-tosyl-D-glucose with alkoxide resulted in inversion on C-5 rather than on C-4 and yielded a 1,4-anhydrosugar with the L-ido configuration ( $[\alpha]_D^{20} + 90.8^\circ$  ( $CHCl_3$ )). Kops and Schuerch (50) repeated the Hess procedure and obtained a sharp-melting crystalline anhydrosugar, which they identified as 1,4-anhydro-2,3,6-tri-0-methyl-D-galactose (m.p. 36-37°C,  $[\alpha]_D^{28} + 86.3^\circ$  ( $CHCl_3$ ) yield 22%) and not 1,4-anhydro-2,3,6-tri-0-methyl-L-idose as claimed by Hess (47). By the same procedure, two 1,4-anhydrosugars were also prepared from the corresponding tosylated D-xylose derivative (50). By inversion of configuration at the asymmetric C-4 atom

the D-xylopyranose gave 1,4-anhydro-2,3-di-O-methyl-L-arabinose, whereas the D-xylofuranose derivative, in which the tosyloxy group is attached to the optically inactive center C-5, gave 1,4-anhydro-2,3-di-O-methyl-D-xylose by internal displacement. The separation of the two anhydrosugars was not successful. Micheel and Kreutzer (51) hydrolysed the disaccharide hept-α-O-benzyl-1-phenyl-α-lactose and obtained 2,3,6-tri-O-benzyl-D-glucose which they converted into 1,4-anhydro-2,3,6-tri-O-benzyl-D-glucose. By debenylation of the latter, they succeeded in making 1,4-anhydro-D-glucose. The anhydride was prepared according to the following sequence of reactions. First 2,3,6-tri-O-benzyl-α-D-glucosyl chloride (XXXIX) was made by treating compound (XXXVIII) with HCl in anhydrous ether, and then was transformed to 2,3,6-tri-O-benzyl-β-D-glucosyl fluoride (XL). Treated with alkali methoxide, (XL) gave 2,3,6-tri-O-benzyl-D-glucosan  $\alpha < 1.4 > \beta < 1.5 >$  (XLI). Subsequently, benzyl groups were removed by catalytic dehydrogenation and the free D-glucosan  $\alpha < 1.4 > \beta < 1.5 >$  (XLII) was finally obtained.

Recent studies on the mechanism of pyrolysis of cellulosic materials (52-54) have indicated that 1,4-anhydrosugar derivatives might also be prepared by this route. Several mechanisms have been suggested to account for the transformation of cellulose into levoglucosan (40). One of these (52,53) presumes the formation of the intermediate 1,4-anhydride (XLIV), which is subsequently rearranged to 1,6-anhydro-β-D-glucopyranose (XLV) or 1,6-anhydro-β-D-glucofuranose (XLVI), according to whether the C-6 hydroxyl group attacks the 1,4 or the 1,5 ring of the intermediate compound. Therefore, 1,4-anhydro compounds can be formed



when the hydroxyl group at C-6 is blocked. For example 1,4-anhydro-2,3,6-tri-O-methyl- $\alpha$ -D-glucopyranose has been obtained by pyrolysis of tri-O-methyl cellulose (54).



## CHAPTER II

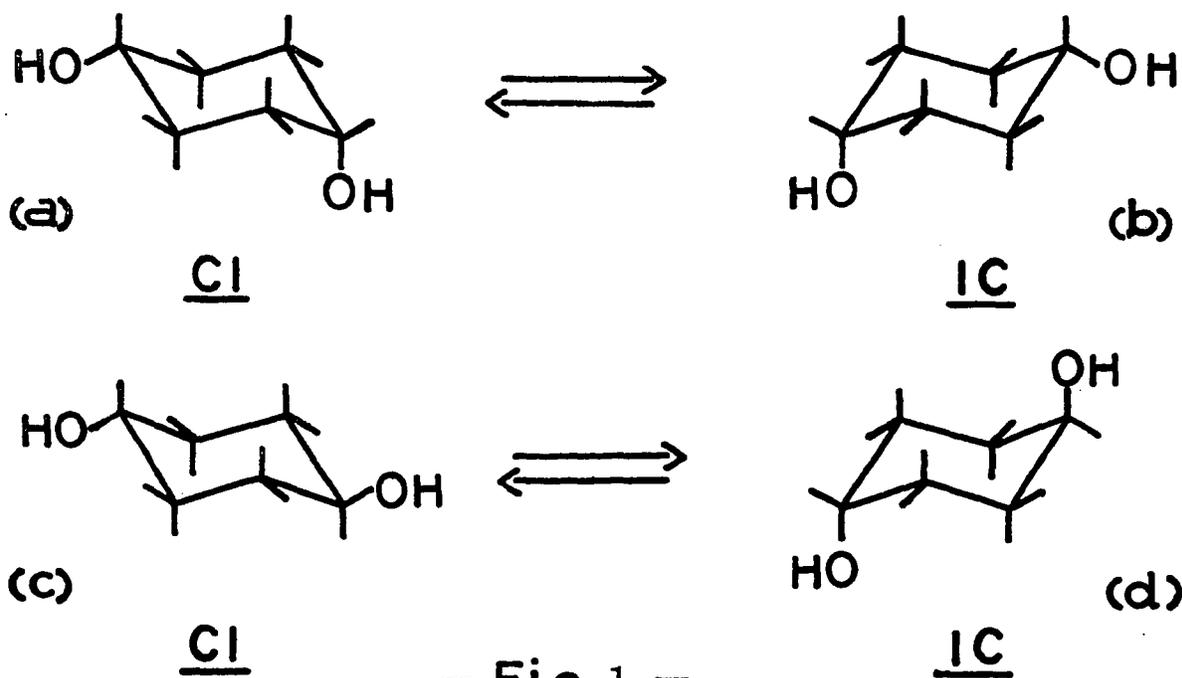
The preparation of 1,4-anhydro ethersA - Discussion

When leaving groups from sugar derivatives possessing the appropriate steric configuration undergo internal displacement, 1,4-anhydro-sugars are formed (49). However, yields are low because there are two competing reactions: 1) hydrolysis at the site of the leaving group, and 2) the formation of condensation oligosaccharides (10). The synthesis of suitable starting materials is a further disadvantage, for they are often obtainable only by laborious and tedious reaction sequences (51). In this part of the research we have explored a method by which internal ethers of relatively easily prepared 1,4-derivatives of six-membered cyclic compounds might be formed under rather mild conditions and therefore might be applicable to the sugar series. To this end 1,4-cyclohexanediol was adopted as a model, because it displays a structure similar to hexopyranose sugars having the C-1 and C-4 hydroxyl groups free.

The formation of 1,4-anhydro-cyclohexanediol by dehydration of a mixture of cis- and trans-1,4-cyclohexanediol isomers, by heating the mixture at 200-240°C over activated alumina, is reported in the literature (55). However the drastic conditions employed in that reaction suggest that such a procedure is not applicable in the sugar series.

NMR spectroscopy proved to be a valuable tool for determining the percentage of cis- and trans-isomers in 1,4-cyclohexanediol. Both cis- and trans-1,4-cyclohexane diols in solution form equilibrium mixtures of conformers of which the two chair configurations IC and CI are dominant.

In solution, cis-1,4-cyclohexanediol can exist in an equilibrium mixture of the two conformers (a) and (b), one the mirror image of the other, which both possess one hydroxyl group equatorial and one axial. Because they are equally stable, and the energy barrier between the two is not high, the rate of exchange between (a) and (b) is expected to be relatively high. However, although a solution of trans-1,4-cyclohexanediol also contains an equilibrium mixture of two conformers (c) and (d), they are not mirror images (one having both its hydroxyl groups equatorial and the other both axial). At room temperature the equilibrium between (c) and (d) is shifted toward (c), which is by far the more abundant because its conformation is more stable.

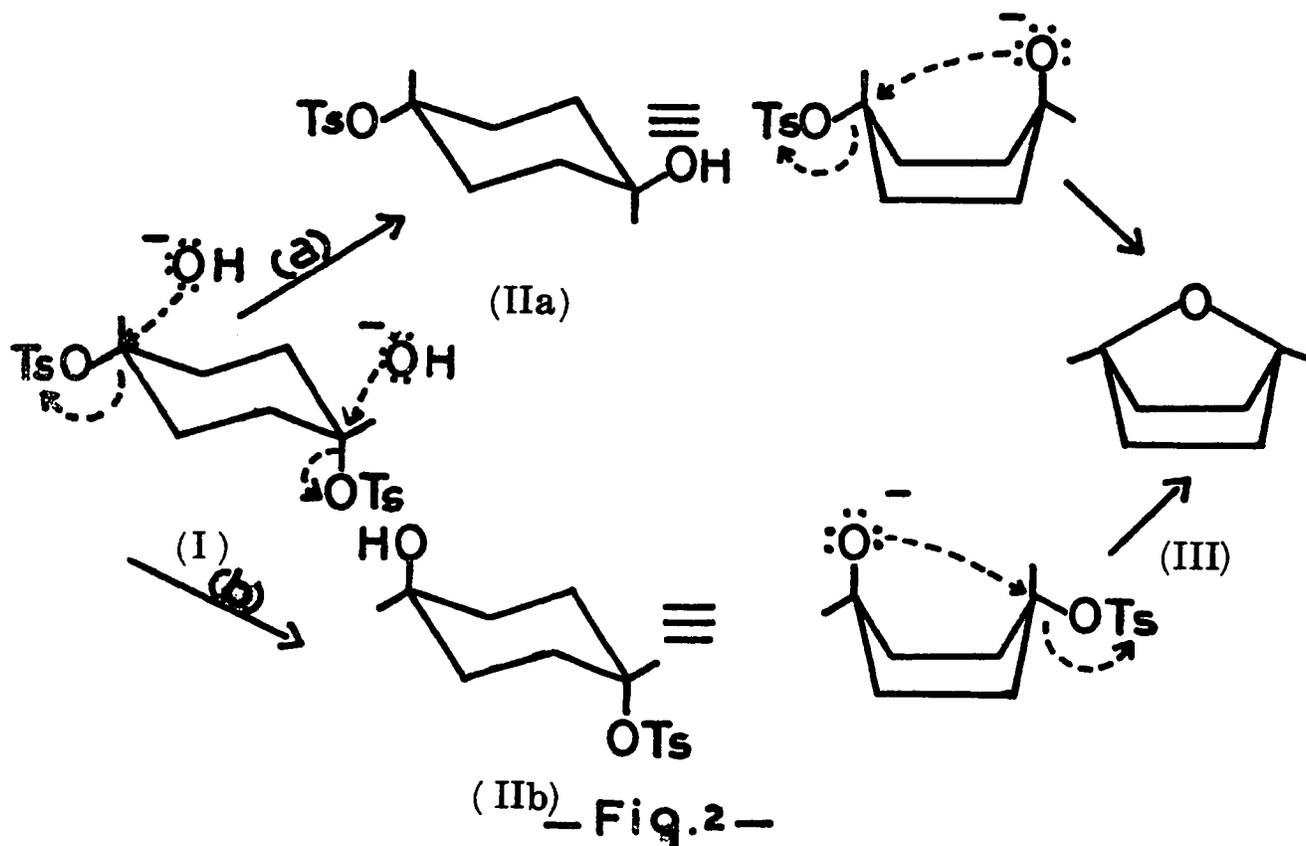


- Fig. 1 -

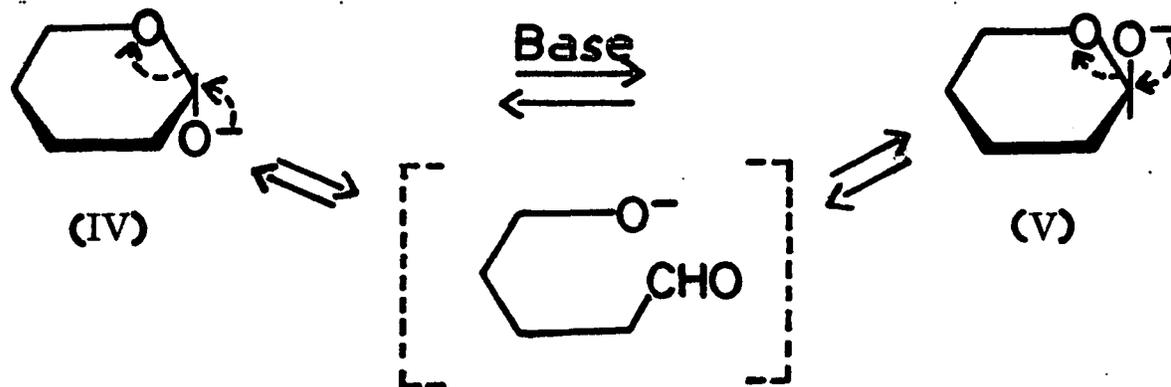
The NMR spectra displayed by the two 1,4-cyclohexanediols in DMSO- $d_6$  reflect the differences in their equilibria. Trans-1,4-cyclohexanediol, frozen by strong hydrogen bonds with solvent molecules into the more stable diequatorial configuration (c), displays two patterns of signals at  $\delta_{\tau} 8.25$  and

at 8.85 $\tau$ , respectively for the equatorial and axial protons of the cyclohexane ring, and a doublet for the hydroxyl group protons at 5.53 $\tau$ . In contrast, because of the rapid interconversion in cis-1,4-cyclohexandiol, the cyclohexane ring protons are not differentiated and display a single pattern at 8.50 $\tau$  which is about the average of the signals due to equatorial and axial protons. The hydroxyl group protons display only one doublet 5.68 $\tau$  instead of two as would be expected if the compound were not in rapid equilibrium. Since the spectra of the cis- and trans-1,4-cyclohexanediols are not overlapping, an evaluation of the percentage of the two isomers in a mixture can be made by integrating the signals of the hydroxyl group protons.

The reaction for producing the epoxide bridge is founded on the assumption that when cis-1,4-cyclohexanediol-di-tosylate (I) is treated with base, the statistical probability that the base attack will be contemporaneous on the two tosyloxy groups is slight; consequently only one tosyl is likely to be hydrolysed to form the monotosylate (IIa, IIb) intermediate with inversion. In basic solution the tosyloxy group of compound (II) undergoes internal displacement and forms the internal ether bridge. If the axial tosyl is hydrolysed, the reaction will proceed by path (a), but if the equatorial is hydrolysed first the reaction will proceed by path (b).



These theoretical considerations of the possibility of a selective hydrolysis followed by internal displacement in 1,4-di-O-tosyl-cyclohexanediol were substantiated by the successful preparation of 1,4-epoxycyclohexane by the path outlined. It is worth noting that although this reaction occurs with double inversion, first hydrolysis and then internal elimination, the product (III) will have the same conformation whichever the path. This conclusion will also hold for the sugar series in which, because of the existence of the equilibrium between the anions (IV) and (V), this reaction can take place whether the two tosyloxy groups in the starting material are cis- or trans-.



Thus, the method is of considerable utility, because 1,4-di-O-tosyl hexopyranoses, with the hydroxyl groups at C-2, C-3 and C-6 protected, are relatively easily prepared. The products will give inversion of configuration at the asymmetric atom C-4.

#### B - Experimental

Evaporations were done under reduced pressure, at approximately 40°C in a rotatory evaporator.

IR spectra were measured on a Unicam SP-200G spectrometer in  $\text{CCl}_4$  solution, KBr pellets, or as films on NaCl discs.

NMR spectra were measured on AT-60 or HA-100 Varian spectrometers; TMS was used as internal reference.

#### 1) - Cis- and trans-1,4-cyclohexanediol diacetate

Commercial 1,4-cyclohexanediol, distilled under vacuum (b.p. 128°/5 mm), crystallized on standing into a hard, white solid, which was a mixture composed of 40% of the cis and 60% of the trans-isomers, as found by NMR spectroscopy (DMSO- $d_6$  as solvent). Ten grams of this mixture was refluxed with 20 ml of acetyl chloride in

50 ml of benzene for 4 hrs and the resulting diacetate isomers (15.6 g, 88% yield) were separated on a silica gel column with ethyl acetate as eluant. The trans-isomer (8.3 g) was the first fraction eluted and it was recrystallized from a small volume of absolute EtOH, m.p. 102-103°C (literature, 105° (56), 101-102° (55)). The second fraction was the cis-diacetate (5.6 g) and it was crystallized first from absolute ethanol and then recrystallized from a small volume of acetone, m.p., 37-38° (literature, 38° (56), 33-34° (55)).

2) - Cis- and trans-1,4-cyclohexanediol

In a solution of 100 ml of MeOH to which had been added 0.5 g of metallic sodium, 5.0 g of the trans-diacetate was dissolved. The compound was completely hydrolyzed after 20 min as determined on a TLC plate, with EtOAc as eluant. Solid CO<sub>2</sub> was added to the solution until it was neutral and then it was evaporated to dryness under reduced pressure. The resulting white material was dissolved in about 50 ml of water, and cation exchange resin Amberlite IR-120-H was added to this solution until evolution of CO<sub>2</sub> ceased. At this point the resin was filtered off and washed, and the filtrate and washings collected together were evaporated to dryness. The resulting material was dissolved in acetone (50 ml) and, after drying over anhydrous MgSO<sub>4</sub>, was concentrated to small volume. This solution, left overnight in the cold room, yielded white crystals which, after drying under vacuum at 60° and recrystallizing three times from acetone, melted at 141-142.5° (literature 143° (56), 142° (55)). Cis-1,4-cyclohexanediol diacetate was hydrolyzed in a similar manner, and the product was also recrystallized from acetone. It melted at 102-103° (literature, 104.5° (56), 107° (55)).

3) Cis- and trans-1,4-cyclohexanediol di-tosylate

A solution of 2.0 g of cis-1,4-cyclohexanediol in 10 ml of dry

pyridine was tosylated with *p*-toluene-sulphonyl chloride according to a standard procedure (57). On working up the reaction products, 5.3 g (yield 72%) of cis-1,4-cyclohexanediol di-tosylate was obtained. After recrystallization from a mixture of chloroform and pet. ether (b.p. 60-120°), the product melted at 96.5-97°C (literature 98-99° (57)).

The trans-1,4-cyclohexanediol (2.0 g) was tosylated in a similar manner and gave 5.7 g (yield 78%) of trans-1,4-cyclohexanediol di-tosylate, which after recrystallization from hot MeOH melted at 155-156°C (literature 159° (57) with decomposition).

4) - 1,4-epoxycyclohexane (7-oxabicyclo [2.2.1] heptane)

To a stirred solution of 2.0 g of cis-1,4-cyclohexanediol-di-tosylate in 20 ml of dioxane, was added 10 ml of 2N NaOH. The solution was kept under constant stirring at a temperature of 60-70°C for 6 hrs, and then was treated with an excess of cation exchange resin Amberlite IR-120-H. The solution, slightly acid because of the presence of *p*-toluene-sulphonic acid, was then extracted three times with CHCl<sub>3</sub>. From the extracts, after drying over MgSO<sub>4</sub>, chloroform and dioxane were evaporated off under reduced pressure. The oily residue was distilled (b.p. 119-121°C/760 mm), to give a product (0.28 g 61% yield) shown by G.L.C. to be pure and displaying an NMR spectrum (no solvent): 5.55τ (doublets of doublet 2H, J' = 5 cps and J'' = 3 cps), 8.60τ (multiplet, 8H) and an IR spectrum identical to that of 1,4-epoxycyclohexane prepared by another route (55) (literature, b.p. 120.1° (55) and 117-118° (58)).

## CHAPTER III

Preparation of hexopyranoses having a free hydroxyl group at C-4A - Introduction

Sugar derivatives possessing a free hydroxyl group at C-4 and the hydroxyl groups at C-2, C-3 and C-6 conveniently protected are required as intermediates on the route to 1,4-anhydrosugars, and their synthesis is a rather complex task. As we have seen in the previous review of the chemistry of 1,4-anhydrosugars, there has been much difficulty in synthesizing such intermediates, and monosaccharides with the hydroxyl groups at C-1 and C-4 free have been prepared by hydrolysis of alkylated oligo- and polysaccharides linked 1 → 4. The synthesis of 1,4-anhydrides of glucose and galactose derivatives (the two major components of polysaccharides) has been reported in the literature (42-51).

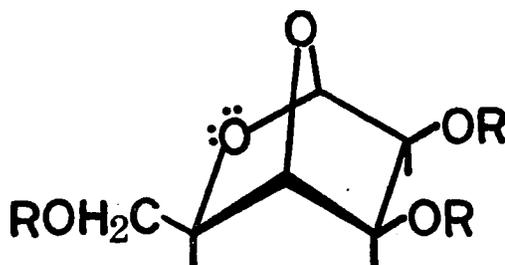
One of the major objectives of this research has been to explore synthetic routes to new classes of 1,4-anhydrosugars and initially the manno- series was adopted for its favourable steric conformation. Two different approaches were followed in an effort to simplify the synthesis: a) hydrolysis of polysaccharide ethers linked 1 → 4, and b) synthesis from monosaccharides.

B - Hydrolysis of polysaccharide ethers linked 1 → 4

Mannan A from ivory nuts (Phytelephas macrocarpa) was chosen for the hydrolysis study. In contrast with mannan B, which is insoluble in aqueous sodium hydroxide and has an average chain length of 39-40, mannan A is soluble and has  $\overline{DP}_n$  of 10-13 (59,60). Methylation studies (60,61) have indicated that both varieties of mannan are composed mainly of chains of  $\beta$ -1,4-anhydro-D-mannopyranose residues; on hydrolysis, fully

methylated mannan A gives (along with lesser quantities of other methyl ethers) 81.8% yield of 2,3,6-tri-O-methyl-D-mannose. This result suggested that other 2,3,6-tri-O-substituted ethers of mannose might be similarly obtained in high yield.

The particular advantage of mannose derivatives in the execution of the subsequent plan is that it has a favourable steric conformation: by inversion at the asymmetric centre C-4, it yields the 1,4-anhydride of D-talose (I), with all its etherified hydroxyl groups equatorial and consequently rather stable.



(I)

1) - Preparation of 2,3,6-tri-O-alkyl-D-mannose

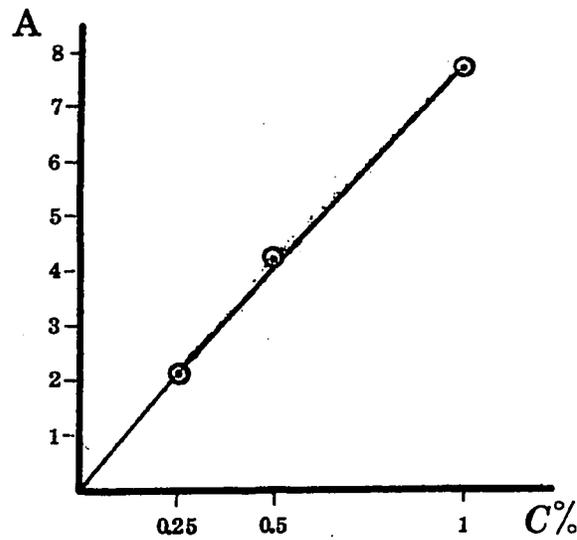
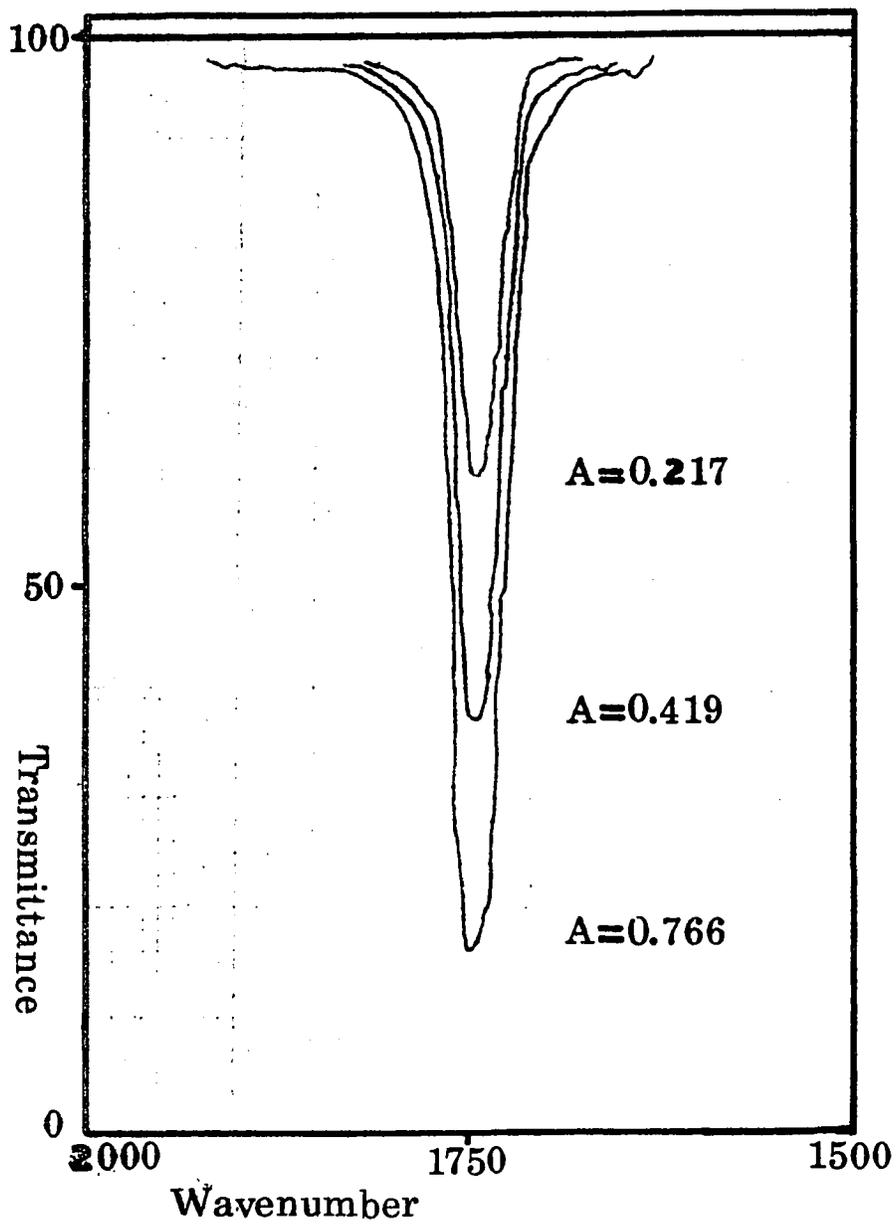
Discussion

Mannan was extracted from ivory nut shavings by means of cold aqueous sodium hydroxide and purified by two precipitations, as the copper complex, with Fehling's solution (62). Owing to the insolubility of mannan in most organic solvents the methylated polysaccharide could be prepared conveniently only by simultaneous deacetylation and methylation of the acetylated mannan. The latter was made by a modification (63) of the Carson and Maclay method (64) in which mannan is first dispersed as a smooth paste in formamide in order to keep the polysaccharide in a reactive swollen

state during the esterification, and subsequently acetylated with pyridine and acetic anhydride. The quantitative estimation of the acetyl content in acetylated mannan, after alkylation reactions, was determined from the infrared spectrum of the reaction products.

A linear relationship is set by the Lambert-Beer law between the radiation transmitted through a solution, expressed as absorbance, and the concentration of a component in that solution. The absorbance  $\underline{A}$  is defined as  $\underline{A} = \log \frac{I_0}{I}$ , where  $I_0$  is the total energy incident and  $I$  the energy transmitted by the solution. When the absorbances  $\underline{A}$  of a characteristic infrared or other absorption band, measured at different concentrations, are plotted versus the concentrations, a straight line is obtained if that compound follows the Lambert-Beer law. Quantitative determination of a specific component in a mixture may be accomplished by comparing the intensity of a unique infrared absorption (it does not overlap with absorptions of other components of the mixture) with the intensity of the same band from the pure component at known concentrations.

As we regard partly alkylated acetyl mannan as a mixture of acetyl and alkyl mannan, we have applied this technique to the products of the acetyl mannan alkylation reaction. From their infrared spectra we have been able to determine the degree of acetyl content after alkylation. A working curve for acetyl mannan was constructed (see Fig. 1), with the  $\text{C=O}$  stretching absorption band ( $1750 \text{ cm}^{-1}$ ) being chosen as a unique band. The absorbance,  $\underline{A}$ , of this band measured in chloroform at different concentrations of acetylated polysaccharide was plotted versus the concentrations. A nearly straight line was obtained. Using this curve,



- Fig. 1 -

the percentage of acetyl groups still present in the polysaccharide was measured, permitting estimation of the degree of alkyl substitution.

Methylation was performed in two stages: first with sodium hydroxide and methyl sulphate to a methoxyl content of 23%, and subsequently with methyl iodide in a solution of dimethyl sulphoxide containing sodium hydride.

By the end of the second reaction the carbonyl absorption band at  $1750\text{ cm}^{-1}$  in the infrared spectrum of the polysaccharide had disappeared. The methoxyl content was 41% which is lower than the theoretical (45.5%), but this can be explained by the presence in the polysaccharide chain of some di-methylated units at occasional sites of branching. The methylated mannan was hydrolyzed successively with 90% formic acid and with dilute sulphuric acid and the product mixture of methylated sugars was separated on a cellulose column. The largest fraction eluted (-OMe 41.3%) was identified as 2,3,6-tri-O-methyl-D-mannose by converting it to its 1,4-di-O-p-nitrobenzoate derivative.

By NMR spectroscopy it was found that 2,3,6-tri-O-methyl-D-mannose was a mixture of the  $\alpha$ - and  $\beta$ -anomers in the ratio of 3:1, respectively. In fact, although in the spectra of the two compounds the signals due to the methoxyl and ring protons are overlapping, separate signals are given by the C-1 protons ( $\delta$ ) ( $\alpha$  and  $\beta$ ), the  $\alpha$  at lower field (4.68 $\tau$ ) and the  $\beta$  at higher (5.28 $\tau$ ). The anomeric proton appears at lower field since the carbon to which it is attached bears two electron withdrawing oxygen atoms. The assignment of the two lines is in accord with the observation that, in a ring compound, an axially oriented hydrogen ( $H_B$ ) is more shielded than an equatorially oriented hydrogen ( $H_A$ ) and therefore

resonates at higher magnetic field. By integrating the areas of the signals due to these two protons the ratio of the two anomers in equilibrium could be determined. Fully benzylated mannan was prepared in a similar way, and then hydrolysis was attempted. With the intention of breaking the polysaccharide chain to a sufficient extent to create hydrophilic groups which would then permit a total hydrolysis in aqueous acid, hydrolysis in mixtures of dioxane and mineral acids as well as in 90% formic acid were attempted, but proved ineffective. Hydrolysis in rather concentrated sulphuric acid produced a completely uncontrollable chain rupture and oxidation. These attempts were not completely negative, but the results obtained indicated that the fully benzylated mannan was extremely resistant to acid hydrolysis (at least under the conditions tested), presumably because of its hydrophobic character. This route to 2,3,6-tri-O-benzyl-D-mannose was considered unpromising, and was abandoned.

## 2) - Experimental

After methylation reactions the methoxyl content in mannan was determined on samples ranging from 20-33 mg. The analytical technique used (66) was a modification of the classical Zeisel method. Apparatus and procedure followed are described in (67).

Paper chromatography was done by the descending method on Whatman No. 1 filter paper with the following solvent systems (V/V):  
A) Butan-1-ol-ethanol-water (4:1:5, top layer); B) Butan-2-one saturated with water; C) Ethyl acetate-pyridine-water (10:4:3). Sugars were located on chromatograms either by u) spraying with p-anisidine hydrochloride, or w) with silver nitrate and alkali.

Solutions were concentrated under reduced pressure at a bath

temperature of about 40°C.

IR spectra were measured on a Unicam SP-200G spectrometer in  $\text{CCl}_4$  solution or as films on NaCl discs as required.

NMR spectra were measured on an HA-100 Varian Spectrometer using TMS as internal reference. Chemical shifts are reported in  $\tau$  units.

a) - Extraction and purification of mannan

Mannan was extracted from ivory nut shavings and purified according to a method described by Rao et al. (62). Only mannan A was used in our experiments.

b) - Acetylated mannan

Mannan was acetylated essentially by the procedure used by Schlubach and Reppenning (63), modified as follows: five grams of dry polysaccharide was uniformly dispersed in 100 ml of formamide by vigorous stirring at room temperature. To the resulting stiff paste, 50 ml of acetic anhydride and 25 ml of dry pyridine were added slowly with stirring and slight cooling. After stirring 5 hours at room temperature the mixture was heated to 40-45°C for 30 min, then cooled down again to room temperature, and kept for 24-28 hours. The solution was then slowly poured into 500 ml of stirred ice water, and the resulting precipitate was washed free of acid with water and then dried. The brownish-white product was dissolved in acetone (50-60 ml) and decolorized by boiling with charcoal and filtering. Then the solution was reduced to a small volume, and acetyl mannan was recovered by pouring the acetone solution into ice water. The precipitated polysaccharide was filtered off and then dried under vacuum at 40-45°C. The product (8.6 g, yield 91%) did not absorb infrared radiation in the range of 3400-3600  $\text{cm}^{-1}$ .

c) - Methylated mannan

In an adaptation of Haworth's method, the acetylated mannan (3.0 g) was dissolved in acetone (75 ml) and, in a nitrogen atmosphere, 20% w/v aqueous sodium hydroxide (20 ml) and methyl sulphate (5 ml) were added slowly and simultaneously to the stirred solution. The solution was stirred at room temperature, and after 2 hours the addition of sodium hydroxide (20 ml) and methyl sulphate (5 ml) was repeated. Then stirring was continued for a further 16 hours at room temperature, and the resulting solution was finally heated in a water-bath to destroy residual methyl sulphate and remove the by-product methanol. Water (ca:40 ml) was added to the mixture, and the partly methylated polysaccharide was extracted with chloroform (2 x 50 ml). The combined chloroform extract was washed with water until the washings were neutral and, after drying over anhydrous  $MgSO_4$ , was concentrated under reduced pressure to a syrup (-OMe 23%, calculated for methylated hexosan 45.5%). After suspending the partly methylated material (4.0 g) in 70 ml of dry dimethyl sulphoxide (distilled over  $CaH_2$  and stored over a molecular sieve), it was brought into solution, by heating at  $60^\circ C$  after which it was then cooled to room temperature. Thirty milliliters of base (3.0 g of NaH + 30 ml of DMSO, prepared separately according to a standard procedure (68)) was added, and the mixture was stirred for 5 hours to complete the formation of alkoxide. Then, while the temperature was kept at about  $10^\circ C$  by cooling with a bath of ice water, methyl iodide (10 ml) was added. Heat was produced by the reaction until it was complete. The resulting clear solution was dialysed (for 48 hours) and, after its volume was concentrated to about 100 ml, it was extracted with chloroform (2 x 50 ml).

The combined chloroform extract was washed with water and then decolorized with charcoal. After evaporation of the solvent, the syrupy residue was freeze-dried (yield 1.5 g, 70%, -OMe 41%). The infrared spectrum of this material had no absorption bands at  $1750\text{ cm}^{-1}$  or in the range  $3400\text{--}3600\text{ cm}^{-1}$ .

d) 2,3,6-tri-O-methyl-D-mannose

Methylated mannan (1.5 g) was dissolved in 90% formic acid (50 ml), and kept for 5 hours at the temperature of a boiling water bath. Formic acid was then removed by evaporation under reduced pressure, and the resulting syrup was taken up in 0.25 M sulphuric acid (50 ml) and heated at  $100^{\circ}\text{C}$  for a further 18 hours, when the optical rotation reached a constant value. This solution was then neutralized with anion exchange resin Dowex IX-8 in its bicarbonate form, concentrated to a syrup and finally freeze-dried (yield 1.40 g, 85%). Paper chromatography of the hydrolysate (solvents (A) and (B)) showed that the mixture contained a major component and small impurities of higher mobility.

The syrupy hydrolysate (1.4 g) was fractionated on a column (60 x 2.5 cm) packed with cellulose. Solvent (B) was used as eluent (69), and recovery from the column was 96.5%. Two fractions, a and b, were eluted: by paper chromatography (solvent A) fraction a (0.326 g) was found to contain two compounds; fraction b (1.025 g) was a pure compound. For further purification, fraction a was dissolved in water (10 ml) and the mixture was extracted continuously with chloroform. The component with greater solubility in chloroform was extracted first. This compound was not analysed further, but it is presumed to be tetra-O-methyl mannose. The second component extracted exhibited the same mobility as fraction b.

on a paper chromatogram (solvent B). This compound and fraction b were therefore combined (1.203 g, -OMe, 41.3%, calculated for tri-O-methyl hexoses-OMe, 41.9%). A portion of this compound was converted into and identified as the 1,4-di-O-p-nitrobenzoate-2,3,6-tri-O-methyl-D-mannose (70), which melted at 184-185°C (literature (71) m.p. 187-188°C and (62) m.p. 189-190). The optical rotation displayed by the 2,3,6-tri-O-methyl-D-mannose was  $[\alpha]_D^{20} - 6^\circ$  ( $c$  2.2, H<sub>2</sub>O) (literature:  $[\alpha]_D - 5^\circ$  ( $c$  2.0, H<sub>2</sub>O) (71), and  $[\alpha]_D^{30} - 9^\circ$  ( $c$  1.0, H<sub>2</sub>O) (62)).

NMR data (in CDCl<sub>3</sub>): 4.68 (doublet  $J_{a,e} = 2.5$  cps, H<sub>1</sub>α), 5.28 (doublet  $J_{a,e} = 2.5$ , H<sub>1</sub>β) 6-6.5 (multiplets, ring H's), 6.52 (singlet, 6 H of -OCH<sub>3</sub>) and 6.61 (singlet, 3 H of -OCH<sub>3</sub>). From its NMR spectrum it was determined that in solution 2,3,6-tri-O-methyl-D-mannose forms a mixture of the α- and β- anomers, in the approximate ratio of 3:1.

e) Benzylated mannan

Acetyl mannan (3.0 g), prepared as described above (see p. 44) was dissolved in benzyl chloride (50 ml) and, after addition of powdered potassium hydroxide (15 g), was stirred under nitrogen at 60-70°C for 3 hours. The mixture was brought to room temperature, benzene (50 ml) and water (50 ml) were added. After shaking, the organic layer was separated and washed with water, until the washings were neutral. It was dried over anhydrous MgSO<sub>4</sub>, and concentrated under reduced pressure to a small volume. Since condensation by-products (such as benzyl ether) were formed during the reaction, these last were distilled off under high vacuum. The resulting syrupy residue (3.1 g), after decolorizing with charcoal and drying in vacuum, still had 10-15% of acetyl groups (as measured from its infrared spectrum.)

To a DMSO solution (50 ml) of the alkoxide of the partly benzylated mannan, generated as described above (see page 45), benzyl chloride (5 ml) was added. After 15 min, evolution of heat ceased, and the reaction was complete. The products were worked up as described for the methylated mannan (see pages 45-46). The syrupy product (yield 3.2g, 74%) had no infrared absorption bands at  $1850\text{ cm}^{-1}$  and  $3400\text{-}3600\text{ cm}^{-1}$ , but had strong aromatic absorption bands ( $690\text{-}735\text{ cm}^{-1}$ ,  $1450$  and  $1500\text{ cm}^{-1}$ ).

f) - Attempted hydrolysis of benzylated mannan

Benzylated mannan (1.0 g) was dissolved in dioxane (50 ml) and 0.25 M sulphuric acid (50 ml) was added, whereupon the polysaccharide separated from the solution and formed a suspension which was stirred vigorously overnight at the temperature of a bath of boiling water. After removal of the sulphuric acid by means of an excess of anion exchange resin (Dowex 1X-8 in its bicarbonate form) and evaporation of the solvent, the resulting syrupy material was decolorized over charcoal and finally dried (yield, 0.9 g). Thin-layer chromatography (chloroform as solvent) and paper chromatography (solvent C) indicated that only a small fraction of this compound had undergone hydrolysis and yielded several compounds. The hydrolysis was repeated by successively using 1.0 M sulphuric acid and 0.5 M hydrochloric acid in dioxane solutions and by following the same procedure as above, but the modification was no more successful than the original experiment. In another attempt, the benzylated polysaccharide (1.0 g) was dispersed in 90% formic acid (50 ml) with partial solution, and then was stirred vigorously for 16-18 hours at refluxing temperature. After evaporation of the formic acid under reduced pressure, the syrupy

residue was dissolved in dioxane (20 ml) and taken up in 0.5 M sulphuric acid (20 ml). Again, upon addition of the mineral acid, the polysaccharide separated from the solution. This indicated that the hydrolysis in formic acid had not generated hydrophilic groups to an extent sufficient to permit subsequent hydrolysis in aqueous acid.

A dispersion of benzylated polysaccharide (500 mg) in 70% sulphuric acid (20 ml) was stirred vigorously while being heated at 40-45°C for two hours. The hydrolysis products were worked up as described for the previous hydrolysates. Thin-layer chromatography (solvent chloroform) and paper chromatography (solvent C) showed a large number of spots, but no effort was made to identify them, since the primary purpose of obtaining benzylated mannose in good yield had apparently not been achieved.

#### C - Synthesis of methyl 2,3,6-tri-O-benzyl- $\alpha$ -D-hexopyranosides

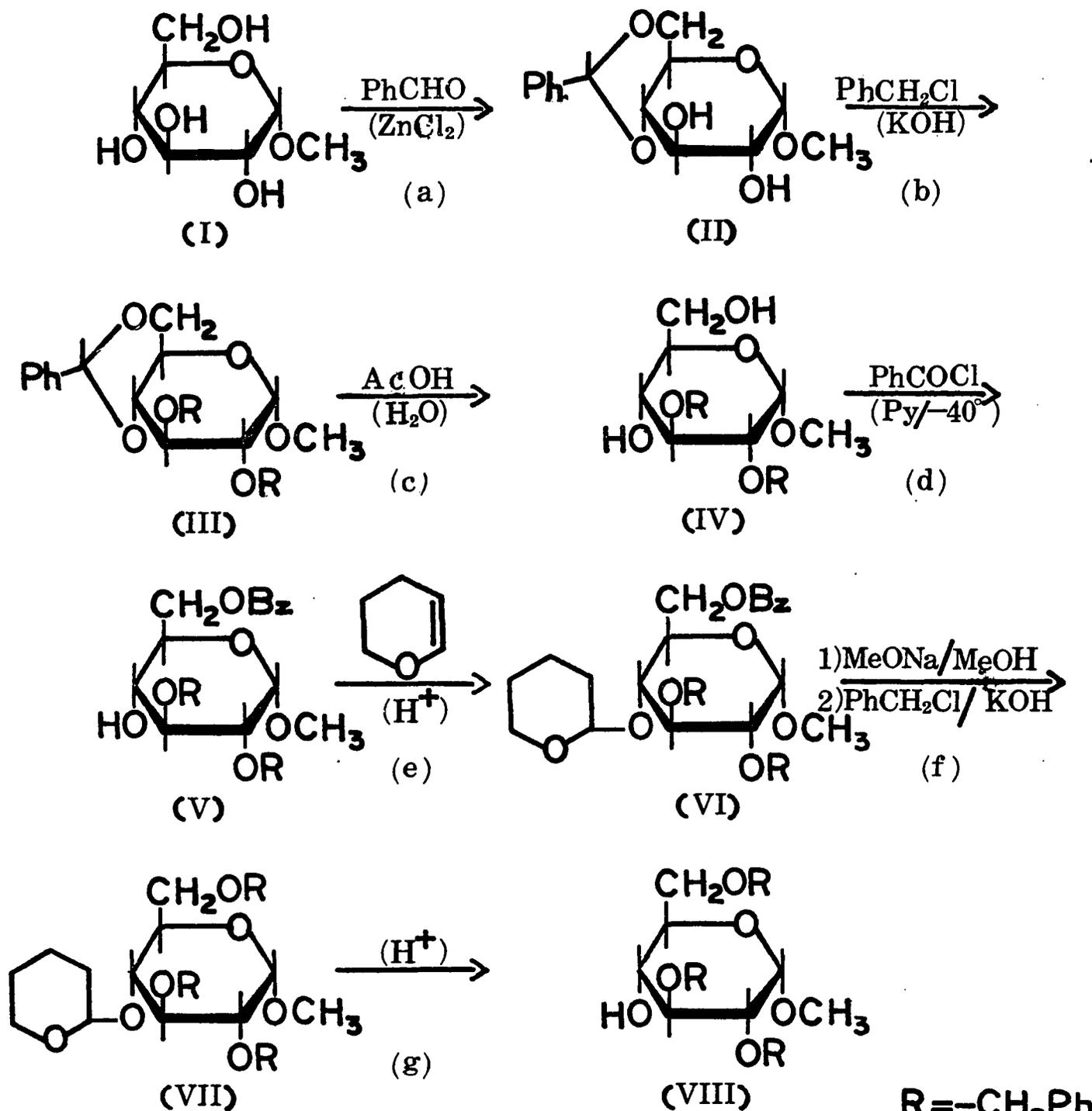
##### 1) - General considerations

Benzyl ethers of monosaccharides appear the ideal intermediates for synthesizing 1,4-anhydrosugars, because the benzyl group, besides being quite stable under acid and alkaline conditions, has the advantage of being easily removed by catalytic hydrogenolysis once the synthesis has been completed. However, since the hydrolysis of benzylated polysaccharides proved to be an unpromising route to the 2,3,6-tri-O-benzyl-D-hexopyranoses, investigation of a synthetic pathway was undertaken.

Besides one hydroxyl in its hemiacetal group, the polyhydroxylated molecule of a hexose possesses two other types of hydroxyl groups with different reactivities (72). Of the two, the primary hydroxyl at C-6 is more reactive than the secondary hydroxyls at C-2, C-3 and C-4. These differences were exploited in the two synthetic schemes planned for the

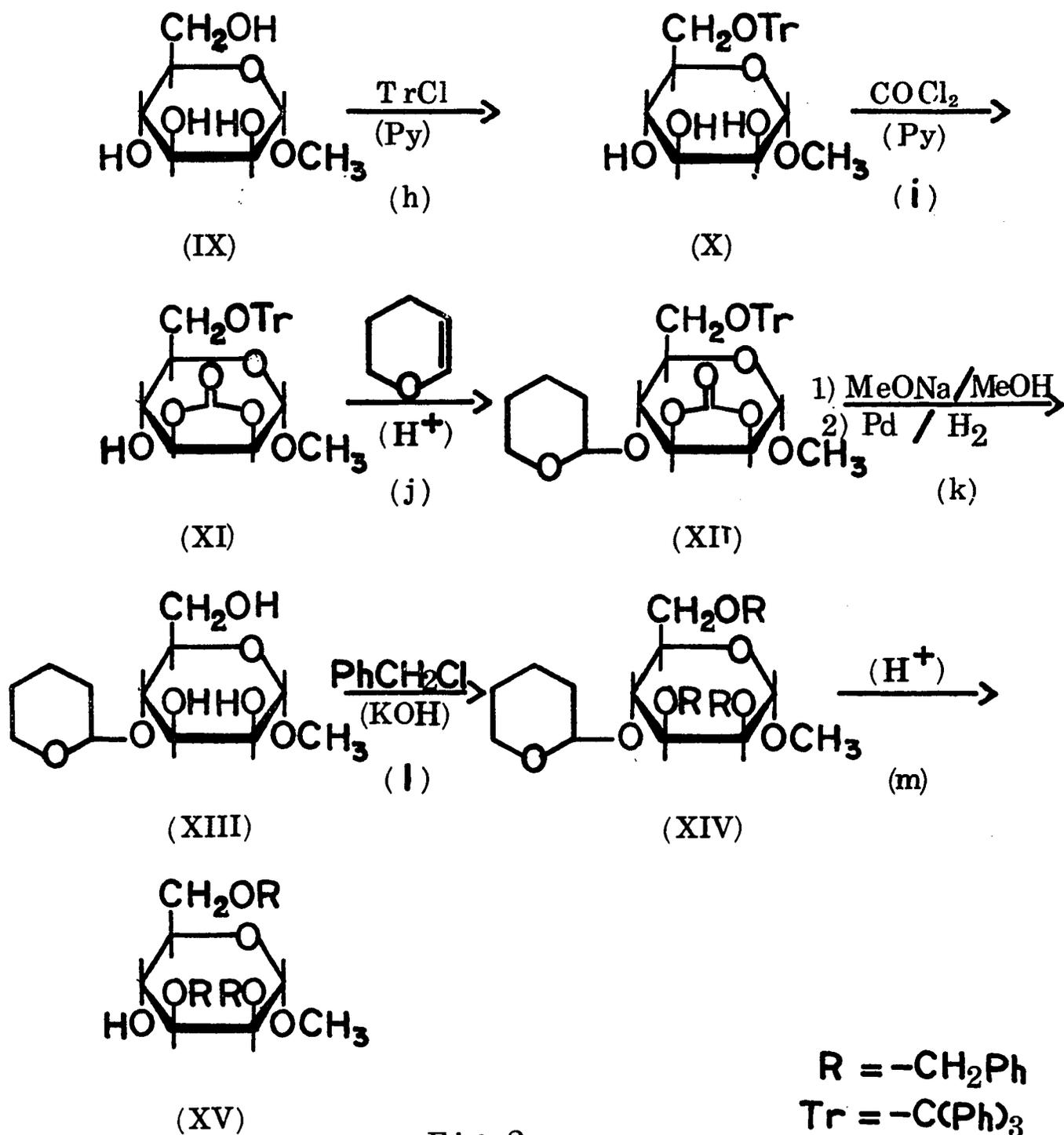
preparation of partly benzylated sugars. Both schemes, as summarized in Figures 1 and 2, contain an intermediate step in which the hydroxyl group at C-6 is subjected to selective acylation or etherification.

Scheme (A) applies to the gluco- series:



- Fig. 1 -

Scheme (B) applies to the manno- series:



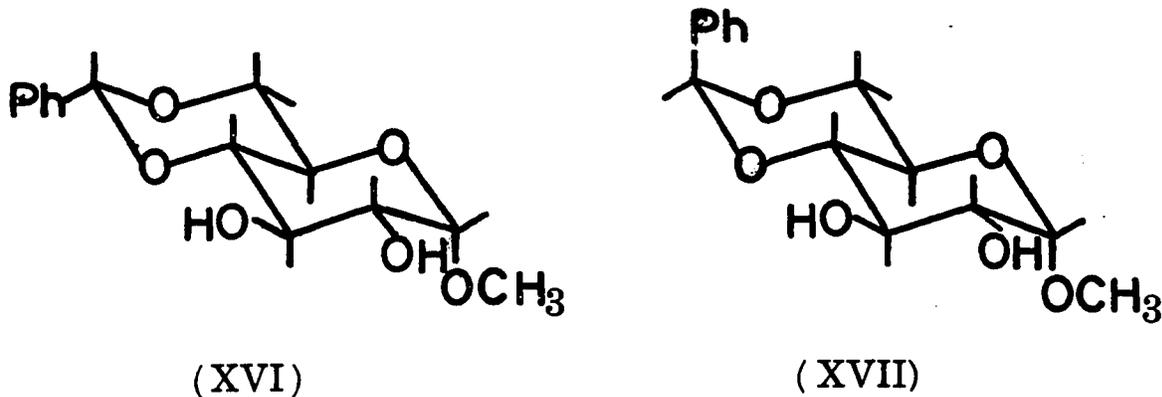
- Fig. 2 -

2) Discussion of the synthetic scheme (A)

The essential traits of the synthetic scheme (Fig. 1) that we have applied in the gluco-, galacto- and manno- series may be summarized as follows:

Although the commercially available methyl  $\alpha$ -D-glucopyranoside was used as starting material in the gluco- series, in the others, the methyl  $\alpha$ -D-glycosides were prepared by the action of hydrogen chloride and anhydrous alcohol upon the appropriate monosaccharides. This procedure, substantially the Fisher method (73), forms a mixture of glycosides. However, optimum conditions (74) were selected to direct the process towards predominant formation of the product required. In the glycosylation of D-galactose (reaction conditions: conc. 1.25 g/100 ml, 4% HCl, reflux temperature) long reaction times were needed (30 to 40 hours) to produce the  $\alpha$ -D-pyranoside in a 20-25% yield; after remethylation of the mother liquor, an overall yield of 40-42% was obtained. Methyl  $\alpha$ -D-mannoside (reaction conditions: conc. 5.5 g/100 ml, 3% HCl, reflux temperature) was produced in 35-40% yield in shorter reaction times (16-18 hours). Through the action of benzaldehyde in the presence of fused zinc chloride the benzylidene group was introduced into the molecule of the glycoside, and the following intermediates were prepared: methyl 4,6-O-benzylidene- $\alpha$ -D-glucopyranoside, methyl 4,6-O-benzylidene- $\alpha$ -D-galactopyranoside, methyl 4,6-O-benzylidene- $\alpha$ -D-mannopyranoside and methyl 4,6:2,3-di-O-benzylidene- $\alpha$ -D-mannopyranoside. During the formation of the cyclic acetals (1,3-dioxane derivatives) a new asymmetric centre was introduced into the molecule and consequently the formation of diastereoisomers was theoretically possible. If the 1,3-dioxane ring assumes the chair conformation the two

diastereoisomers could have the phenyl substituent either equatorial (XVI) or axial (XVII) at the acetal carbon atom



In order to explain the occurrence of only one stable isomer of methyl 4,6-benzylidene- $\beta$ -D-glucopyranoside, Angyal (75) assigned a chair conformation to the 1,3-dioxane ring of the cyclic acetal, with the substituent at the acetal carbon atom in the equatorial position (XVI).

We found that the benzylidene derivatives gave NMR spectra with a single signal (4.38-4.48 $\tau$ ) for the proton at the acetal carbon atom (Table I), confirming that, in the acetal-forming reaction, only the thermodynamically more stable diastereoisomer was formed. In a study of the configuration at the asymmetric carbon atom of the benzylidene group it has been determined (76) that the diastereoisomer formed was the one bearing the phenyl substituent in equatorial position.

TABLE I

Chemical shifts of the proton at the acetal carbon atom of benzylidene derivatives

	$\tau$ (a)
Methyl 4,6- <u>O</u> -benzylidene- $\alpha$ - <u>D</u> -glucoside	4.42
Methyl 4,6- <u>O</u> -benzylidene- $\alpha$ - <u>D</u> -galactoside	4.48
Methyl 4,6- <u>O</u> -benzylidene- $\alpha$ - <u>D</u> -mannoside	4.38
Methyl 2,3:4,6-di- <u>O</u> -benzylidene- $\alpha$ - <u>D</u> -mannoside	4.40 / 3.75 (b)

(a) The values of the chemical shifts reported in the literature (76) for the same proton are in the range 4.45-4.56 $\tau$

(b) Proton of the five-membered ring acetal

The reaction conditions which produced the 4,6-O-benzylidene in the gluco- and galacto- series led to the predominant formation of the 4,6:2,3-di-O-benzylidene derivatives when employed in the manno-series. In order to make the 4,6-O-benzylidene derivative predominate in the manno-series, molecular sieves were used as catalyst in place of zinc chloride.

The utility of these intermediates is that the O-benzylidene group, stable in alkaline conditions, permits benzylation of the unprotected hydroxyl groups at C-2 and C-3, and is thereafter easily removed by acid hydrolysis. Accordingly, the mono-O-benzylidene derivatives were benzylated with powdered potassium hydroxide and benzyl chloride to 4,6-O-benzylidene-2,3-di-O-benzyl- $\alpha$ -D-glycopyranosides (step b, Fig. 1). By the end of the benzylation reaction the absorption band at 3400-3600  $\text{cm}^{-1}$

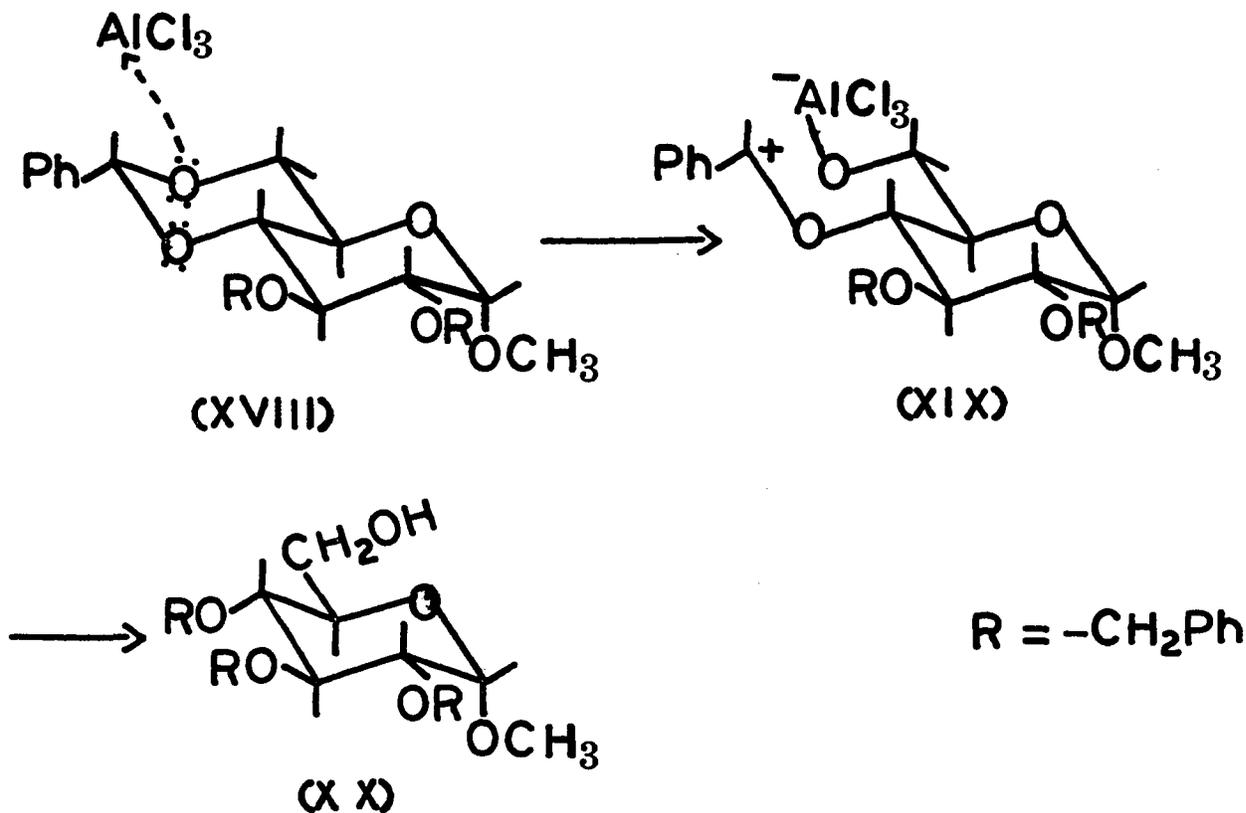
(-OH str.), had disappeared from the infrared spectra of the products. The NMR spectra of the benzylation reaction products, indicated that 10 aromatic protons and 4 methylene protons had been introduced into the molecule. Since methyl 4,6-O-benzylidene-2,3-O-benzyl- $\alpha$ -D-mannoside could not be obtained pure and crystallization could not be induced, this synthesis for the manno- series was halted at this point.

Attempted preparation of methyl 2,3,6-tri-O-benzyl- $\alpha$ -D-galactopyranoside by hydrogenolysis of the acetal ring of benzylidene derivatives with  $\text{LiAlH}_4/\text{AlCl}_3$

In the sugar series the reductive cleavage with  $\text{LiAlH}_4/\text{AlCl}_3$  of the O-benzylidene 1,3-dioxane ring to ethers and its possible synthetic applications, has recently been investigated (77). Hydrogenolysis of methyl 4,6-O-benzylidene derivatives of  $\alpha$ -glucoside,  $\alpha$ -galactoside and  $\alpha$ -mannoside has been reported to yield the respective 6-O-benzyl and 4-O-benzyl derivatives in various ratios (77). These results have suggested the possibility that methyl 2,3,6-tri-O-benzyl- $\alpha$ -D-glycopyranosides might be prepared directly by hydrogenolysis of the 4,6-O-benzylidene-2,3-di-O-benzyl derivatives with  $\text{LiAlH}_4/\text{AlCl}_3$ . Although polar effects have been found to predominate (78), in the mechanism proposed for this reduction, steric factors can also play an important role. In the bicyclic system of the methyl 4,6-O-benzylidene-2,3-di-O-benzyl- $\alpha$ -D-glucopyranoside, the 1,3-dioxane ring has a trans-junction (XVIII).

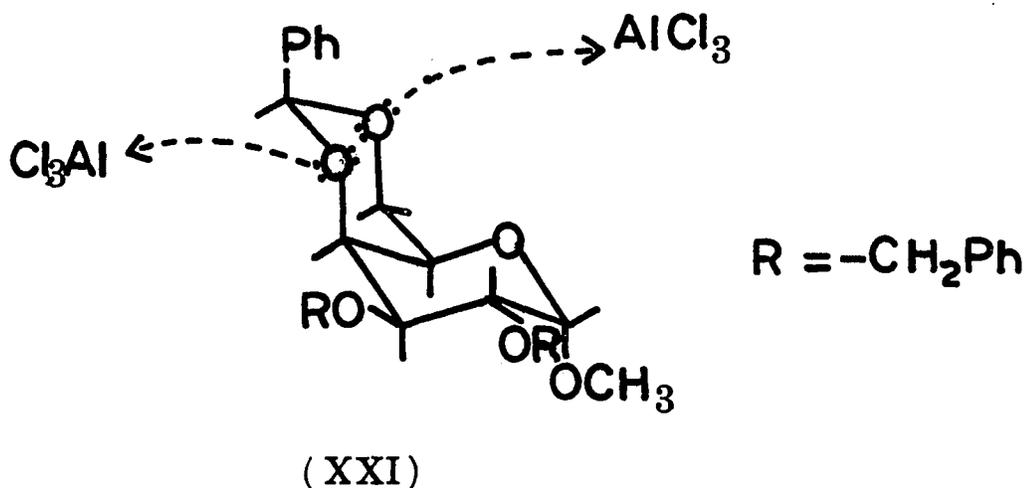
Due to the steric hindrance of the bulky benzyl group at C-3, the attack of aluminium chloride, with subsequent carbonium ion formation, can take place more easily at the oxygen on the less hindered side of the benzylidene ring (XIX). Experimentally, the reduction of this

compound has been found (77) to give predominantly the 4-O-benzyl derivative (XX).



However, inspection of the methyl 4,6-O-benzylidene-2,3-di-O-benzyl- $\alpha$ -D-galactopyranoside molecule (XXI), in which the two rings have a cis-junction, suggests that it has less steric impediment due to the benzyl group at C-3. Consequently attack might be expected on either side of the 1,3-dioxane ring. Accordingly, we reduced compound (XXI) under the same conditions used by Bhattacharjee and Gorin (77), and expected to obtain at least some of the 6-O-benzyl compound. The syrupy product of the reduction gave a major spot, accompanied by some impurities, on the thin layer chromatographic plate. This compound was found to absorb infrared radiation

at  $3500\text{ cm}^{-1}$ ; its NMR spectrum displayed a multiplet due to 15 aromatic protons, and no signal for the benzylidene acetal proton. Thus, reduction of the benzylidene ring has occurred, and the reduction product was a tri-O-benzyl compound. It was then acetylated, and in the NMR spectrum of the acetylated compound the signals due to two protons were shifted to lower field, from 6.38 to 5.95 $\tau$ . The reduction product was methylated and, after hydrogenation of the benzyl groups, identified as methyl 6-O-methyl- $\alpha$ -D-galactopyranoside.



Thus, the product of the first reduction had been methyl 2,3,4-tri-O-benzyl- $\alpha$ -D-galactopyranoside. Therefore, in spite of the seemingly higher accessibility of the benzylidene ring in galactose derivatives (XXI), the substituent at C-3 (in this case a benzyl group) still appears to exert effective steric hindrance, and inhibits the attack of  $\text{AlCl}_3$  on that side.

The benzylidene residue from methyl 4,6-O-benzylidene-2,3-di-O-benzyl- $\alpha$ -D-glycosides was removed by hydrolysis with acetic acid (step c, Fig. 1). Effective removal was indicated by the infrared spectrum of the products, which absorb in the range  $3400\text{--}3600\text{ cm}^{-1}$ , and by their NMR spectra which give a pattern of signals due to 10 aromatic protons and 3 methoxyl protons, but no signals for protons at the acetal carbon atom in the

benzylidene ring (4.4 - 4.5 $\mu$ ). The following compounds were prepared: methyl 2,3-di-0-benzyl- $\alpha$ -D-glucopyranoside and methyl 2,3,di-0-benzyl- $\alpha$ -D-galactopyranoside.

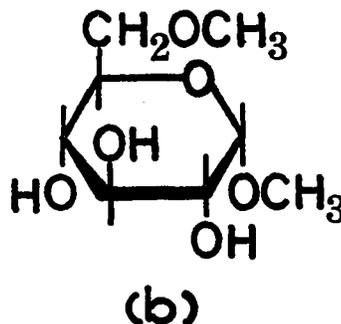
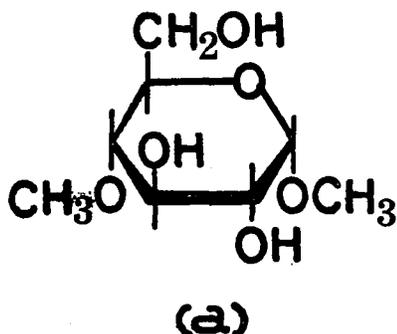
In a polyhydroxylate monosaccharide molecule the different reactivities (72) of the various hydroxyl groups extend beyond the obvious difference between primary and secondary. A variation has also been observed among the secondary hydroxyl groups themselves (72). This difference seems to result from their relative spatial arrangement, although neighboring groups may also play an important role. By selective benzylation at low temperatures, Williams and Richardson (79) were able to obtain the 2,3,6-tri-0-benzoates of some glycopyranosides. From the selectivity of benzylation at the various hydroxyl groups these authors concluded that the group at C-4 is the least reactive of the secondary hydroxyls. The model of methyl 2,3,di-0-benzyl- $\alpha$ -D-glycopyranosides indicates that two hydroxyl groups are unprotected: the primary at C-6, and the secondary at C-4. Previous results suggest the speculation that the difference in reactivity between the hydroxyl groups at C-4 and C-6 is such as to permit selective benzylation at the hydroxyl group at C-6 in the methyl 2,3-di-0-benzyl- $\alpha$ -D-glycopyranosides. In our experiments on selective benzylation the conditions of Williams (79) were employed (1,1 molar equivalent of benzoyl chloride in pyridine, at  $-40^{\circ}\text{C}$ ), (step d, Fig. 1). Crystalline products were obtained from methyl glucoside and galactoside derivatives. In the infrared spectrum, these compounds showed a strong absorption band at  $1705\text{ cm}^{-1}$  (C=O stretching vibration) and a rather sharp band at  $3500\text{ cm}^{-1}$  (-OH stretching vibration). On measuring

the spectrum at increasing dilutions in  $\text{CCl}_4$ , the intensity of the absorption at  $3500 \text{ cm}^{-1}$  was found to decrease while the intensity of a band at  $3600 \text{ cm}^{-1}$  increased.

"Free" hydroxyl groups (as observed in dilute solutions in non-polar solvents) display narrow bands in the  $3650\text{-}3600 \text{ cm}^{-1}$  region. On hydrogen bonding, such bands are consistently shifted towards lower wavenumbers, and a large increase in their intensity and width is also observed (80). From the study of the  $\text{-OH}$  stretching vibration band, information can often be obtained regarding the formation of hydrogen bonds and their type. We can divide the hydrogen bonds formed by an hydroxylated compound into two types: intermolecular and intramolecular. If by dilution in a non-polar solvent we attenuate the effect of the first type, in the infrared spectrum of a monohydroxylated compound, in which the intramolecular type is missing, the  $\text{-OH}$  stretching vibration will appear as the sharp band of a "free" hydroxyl group at  $3600 \text{ cm}^{-1}$ .

In the NMR spectrum, these compounds displayed a pattern of signals due to 15 aromatic H's and the signals due to 2H are shifted to lower field. These spectroscopic results, together with the elementary analysis, indicated that the products of the benzoylation reaction (step d, Fig. 1), were the methyl mono-O-benzoyl-2,3-di-O-benzyl- $\alpha$ -D-glycopyranosides. However, additional information was required to establish the position of the free hydroxyl group in these last compounds. A portion of the methyl mono-O-benzoyl-2,3-di-O-benzyl- $\alpha$ -D-glucopyranoside was methylated until the  $\text{-OH}$  absorption band disappeared from the infrared spectrum. After methanolysis to remove the benzoyl group, and catalytic hydrogenolysis to remove the benzyl groups, the methylation products were analysed by

paper chromatography and by G.L.C. (81). The chromatographic analysis revealed a single component (XXII) which was either (a) or (b):

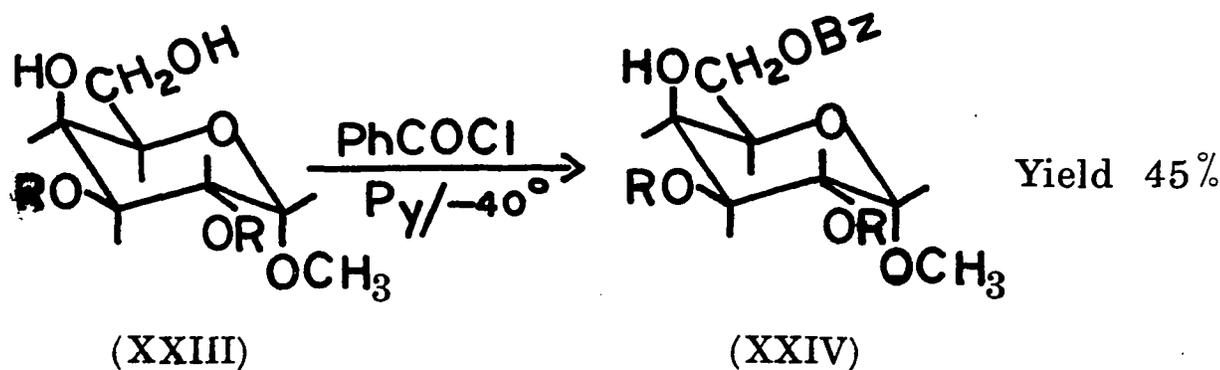
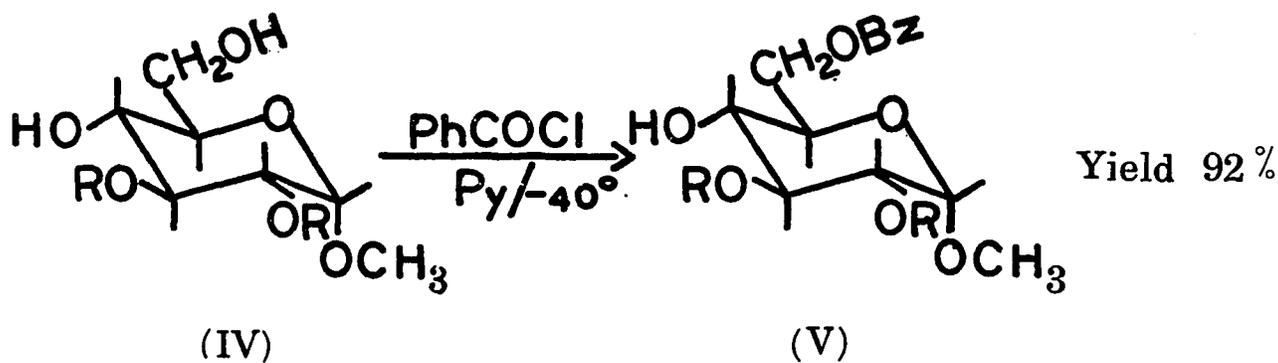


On oxidation with periodic acid, (b) would yield formic acid and (a) would not. (Periodic acid oxidizes vicinal hydroxyl groups to dialdehydes; but, when more than two vicinal hydroxyl groups are present the oxidation continues through this portion of the molecule to produce formic acid from secondary hydroxyl groups, and formaldehyde from primary (82).) When the compound (XXII) was treated with periodic acid, and the reaction was followed by NMR spectroscopy, it was observed that (XXII) underwent oxidation, but no formation of formic acid or formaldehyde was observed. Thus the structure of (XXII) must be (a).

From the shift of the C-4 in the  $^{13}\text{C}$  NMR spectrum of this compound, it was possible to assign the methoxyl group as linked to this carbon atom (83).

Thus, the compound was formulated as the methyl 4-O-methyl- $\alpha$ -D-glucopyranoside,  $[\alpha]_{\text{D}}^{21} + 154.5^{\circ}$  (c 3.21,  $\text{H}_2\text{O}$ ) (literature (84)  $[\alpha]_{\text{D}}^{25} + 154.7^{\circ}$  (c 1.0,  $\text{H}_2\text{O}$ )). Hence, the product of benzylation must have been methyl 6-O-benzoyl-2,3-di-O-benzyl- $\alpha$ -D-glucopyranoside (V), and therefore under the conditions chosen, the benzylation proceeds selectively at C-6.

The selective benzylation of methyl 2,3-di-O-benzyl- $\alpha$ -D-galactopyranoside was found in an analogous way to yield the methyl 6-O-benzoyl-2,3-di-O-benzyl- $\alpha$ -D-galactopyranoside. The glucoside derivative (IV) gave a yield of 92% of 6-O-benzoate (V), whereas the equivalent galactoside derivative (XXIII) gave a yield of 45% of (XXIV). The low yield of the latter is partly due to the formation of the 4,6-di-O-benzoate derivative, as revealed by the NMR spectrum of the products. As equatorial hydroxyl groups of cyclohexane derivatives have been reported (85) to be acylated more readily than the axial, it might be expected that the same assumption could apply to the hydroxyl at C-4 of hexopyranoside derivatives. The yields of the two benzylation reactions seem to suggest that in forming the ester, the axial hydroxyl at C-4 of compound (XXIII) is acylated more readily than the equatorial hydroxyl of compound (IV).



If the previous assumption is valid, it could be speculated from these results that during benzylation of compounds (IV) and (XXIII), steric effects probably act on the hydroxyls at C-4 in such a way as apparently to invert the relative reactivities of the two hydroxyl groups. No further experiments were performed to confirm this supposition.

By selective benzylation of the hydroxyl groups at C-6 of compound (IV) and (XXIII) we completed the preparation of hexopyranosides having the hydroxyl groups at C-2, C-3 and C-6 protected, and the hydroxyl group at C-4 free. However, the benzoyl group, readily hydrolyzed in basic media, is not an effective protecting group in the preparation of 1,4-anhydro-sugars. Therefore it was replaced with a benzyl group according to the series of reactions represented in Fig. 1 as steps e, f, g. Methyl 6-O-benzoyl- $\alpha$ -D-glucopyranoside (V) reacted under mild acid catalysis with one molar equivalent of dihydropyran to yield the 2-tetrahydropyranyl derivative (VI) (step e, Fig. 1). This protecting group was chosen because, in addition to being stable in basic media, it can be readily cleaved by the action of mild aqueous acid with regeneration of the hydroxyl group (86).

Because the 2-tetrahydropyranyl group resembles a glycopyranoside, compound (VI) is like a 1,4-linked disaccharide molecule in structure. Since a new asymmetric centre was generated at the cyclic acetal carbon atom, during the 2-tetrahydropyranyl ether formation, the existence of diastereoisomers was possible. In the NMR spectrum of compound (VI), the proton at C-2 on the tetrahydropyranyl group appears at low magnetic field denoting its anomeric character. Because the signals of this proton overlap with others, it was not possible to make assignments for the  $\alpha$  and  $\beta$  types of protons, and the abundance of the diastereoisomers could not be determined by integration.

As the tetrahydropyranyl group was to be removed subsequently, the identification and separation of the diastereoisomers was not undertaken.

The benzoyl group from methyl 6-O-benzoyl-4-O-(2-tetrahydropyranyl)-2,3-di-O-benzyl- $\alpha$ -D-glucopyranoside (VI) was removed by methanolysis (step f-1, fig. 1). Effective removal was indicated by the infrared spectrum of the products, which did not show  $\text{>C} = \text{O}$  stretching absorption, while a rather sharp band appeared at  $3500 \text{ cm}^{-1}$ , and by the NMR spectrum which displayed a pattern of signals due to 10 aromatic H. The hydrolysis products were subsequently benzylated with powdered KOH and benzyl chloride, (step f-2, fig. 1). On chromatographic analysis the products of this reaction proved to be a mixture of several compounds, which were separated on a silica gel column. The NMR spectra of the different fractions indicated the presence in the mixture of benzyl-(2-tetrahydropyranyl) ether and of tetra-O-benzyl-glucoside, in addition to the desired product (VII). On examining the benzylation products we can see that the tetrahydropyranyl group was partly cleaved during the course of the benzylation reaction. Although tetrahydropyranyl ethers are considered stable to base (86), the results of this reaction seem to indicate that tetrahydropyranyl ethers of sugar derivatives, under the alkaline conditions employed, are not stable and therefore these groups, under such conditions, no longer provide effective protection. Therefore, in order to bring about the benzylation of the hydroxyl group at C-6 without cleaving the protecting group at C-4, two benzylation procedures, employing milder conditions, were explored: a) benzylation with benzyl bromide and pyridine; and b) benzylation with benzyl bromide and silver oxide. These procedures are analogous to other ether forming reactions employed in the

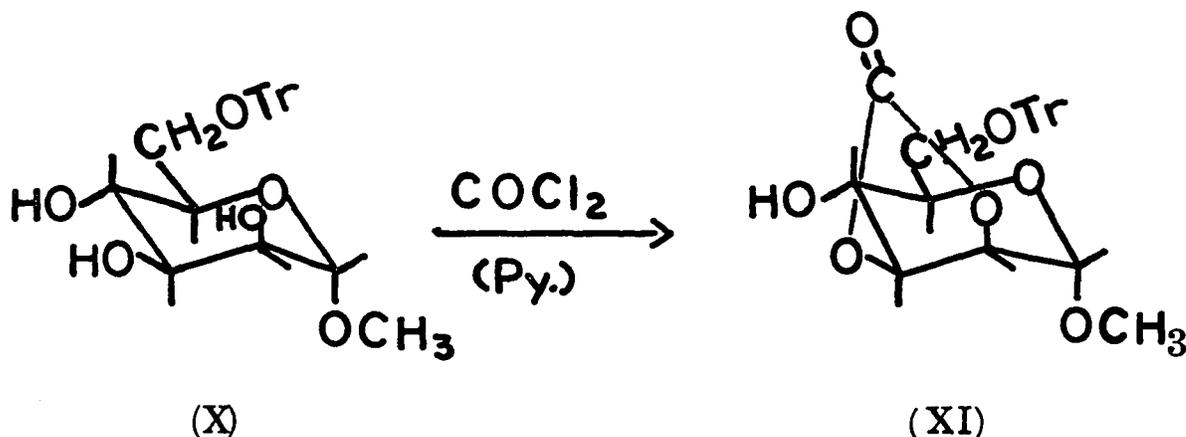
sugar series. In a preliminary experiment conducted on methyl alcohol, only procedure b) gave positive results and yielded benzyl methyl ether. The same benzylation procedure was attempted with diacetone fructose, a monosaccharide molecule containing acid-labile groups. However, as shown by the NMR spectrum of the products, benzylation of this compound caused the complete cleavage of the acetal groups. Since these benzylating procedures were unpromising, they were abandoned. Instead, the methyl 4-O-(2-tetrahydropyranyl)-2,3,6-tri-O-benzyl- $\alpha$ -D-glucopyranoside (VII) obtained by fractionation, was hydrolyzed in acetone with hydrochloric acid (step g, fig. 1). The hydrolysis product absorbed infrared radiation at  $3500\text{ cm}^{-1}$ . Its NMR spectrum displays a signal due to a hydroxyl group proton (shifts to higher field on heating the sample), and a pattern of signals due to 15 aromatic protons. After methylating a portion of this compound, it was subjected to catalytic hydrogenolysis to remove the benzyl groups. The methylated compound was identical to an authentic sample of methyl 4-O-methyl- $\alpha$ -D-glucopyranoside and therefore the hydrolysis product was identified as methyl 2,3,6-tri-O-benzyl- $\alpha$ -D-glucopyranoside (VIII).

### 3) - Discussion of the synthetic scheme (B)

Difficulties were encountered in applying synthetic scheme (A) to the manno- series; frequently the products could not be crystallized, and the isolation and purification of the syrupy materials was not always possible. Therefore an alternative synthetic scheme (scheme B, fig. 2), was planned. The objective was to reduce the number of intermediate steps and to obtain crystallizable products. Again the crucial step is the selective etherification of the hydroxyl group at C-6, based upon the difference in

reactivity between primary and secondary hydroxyl groups. Tritylation (triphenyl methyl ether formation) is a highly selective reaction in the sugar series, since the bulky trityl group yields almost exclusively the methyl 6-O-trityl derivatives, when proper conditions are chosen. Thus, methyl  $\alpha$ -D-mannopyranoside was tritylated in pyridine using 0.9 molar equivalents of triphenyl methyl chloride (step h, fig. 2). We employed slightly less than a molar equivalent of this reagent, since a molar excess of triphenyl methyl chloride brings about the formation of triphenyl carbinol, which is not easily separated from the desired compound. Although this precaution was taken, the tritylation products still contained triphenyl carbinol, revealed as a yellow spot on the thin layer chromatography plate. The tritylated mannoside was isolated as a syrup after column chromatography and its NMR spectrum showed 15 aromatic protons. It absorbed infrared radiation at the characteristic wave numbers of aromatic compounds. Although the product was not crystalline, this evidence suggests that it was the methyl 6-O-trityl- $\alpha$ -D-mannopyranoside.

From its molecular model this compound appeared to have three unprotected hydroxyl groups (at C-2, C-3 and C-4) with a steric configuration favorable to the formation of a cyclic carbonate. However, as we have previously found, the hydroxyl group at C-2 appears to be more reactive than the one at C-4, thus favoring formation of the 2,3-O-cyclic carbonate (XI).



Accordingly, methyl 6-0-trityl- $\alpha$ -D-mannopyranoside was reacted with phosgene in pyridine (step i, fig. 2), and yielded a hard crystalline compound, which absorbed infrared radiation at  $1820\text{ cm}^{-1}$  ( $\text{>C} = \text{O}$ ), and at  $3500\text{ cm}^{-1}$  ( $-\text{OH}$ ). Its NMR spectrum displayed a pattern of signals due to 15 aromatic protons. These results, together with the elementary analysis, are consistent with the formation of a cyclic carbonate. This compound had the same m.p. as that of an authentic sample (87) of methyl 6-0-trityl-2,3-0-carbonyl- $\alpha$ -D-mannopyranoside, and therefore was finally identified as such.

The preparation of compound (XI) completes the synthesis of a mannoside molecule in which the hydroxyl groups at C-6, C-3 and C-2 are protected, while the hydroxyl at C-4 is free. However, compound (XI) is not a suitable intermediate for preparing 1,4-anhydrosugars, for the protecting groups are easily removed by the action of acid (trityl) and base (carbonate), and therefore their replacement with benzyl groups is required, as indicated in steps i, k, l, m of fig. 2. This sequence of reactions is in essence very similar to the procedure employed successfully in scheme (A) for replacing benzoyl with benzyl groups in the glucopyranoside derivative (V).

#### 4) - Experimental

Solutions were concentrated under reduced pressure at a bath temperature of about  $40^{\circ}\text{C}$ .

NMR spectra were measured on T-60 and HA-100 Varian Spectrometers using TMS as internal reference. Chemical shifts are reported in  $\tau$  units.

IR spectra were measured on a Unicam SP-200G Spectrometer, in KBr pellets,  $\text{CCl}_4$  solutions or as films on NaCl discs, as required. Spectra of dilute solutions in  $\text{CCl}_4$ , were measured using WF spectroil cells, transparent to IR

radiation, and having a light path of 1 cm.

Melting points were taken between glass slides on a Fisher-Johns apparatus and were uncorrected.

Optical rotations were determined in a 3 ml tube at the temperature of  $20 \pm 1^\circ\text{C}$ , by a Carl Zeiss Photoelectric Precision Polarimeter 0.005°.

Petroleum ether b.p.  $60-80^\circ\text{C}$  was used throughout.

a) - Methyl  $\alpha$ -D-galactopyranoside (XXV)

Fifty grams of D-galactose was added to dry methanol (4000 ml) containing 4% of hydrogen chloride, and the system was refluxed for 32-36 hours, while anhydrous conditions were maintained. By adding  $\text{PbCO}_3$  in small portions, the reaction mixture was brought to neutrality and, after removal of the precipitate by filtration, the methanolic solution was concentrated to small volume (200-300 ml) by evaporation under reduced pressure. Left for 24 hours in the cold room, this solution gave a precipitate which was purified by recrystallization first from absolute ethanol (100ml) and then from a mixture of absolute ethanol and ethyl acetate (3:1; 2 x 150 ml). After drying in a vacuum oven at  $60-65^\circ\text{C}$  for 48 hours, the crystalline methyl  $\alpha$ -D-galactoside (XXV) (yield 12 g, 22%) melted at  $113-114^\circ\text{C}$ ,  $[\alpha]_D + 188.2^\circ$  ( $c$  3.2,  $\text{H}_2\text{O}$ ) (literature m.p.  $114-116^\circ\text{C}$ ,  $[\alpha]_D + 192.7$  ( $\text{H}_2\text{O}$ ) (88), and m.p.  $114-115^\circ\text{C}$ ,  $[\alpha]_D^{20} 196.6^\circ$  ( $c$  2.0,  $\text{H}_2\text{O}$ ) (89)). On a paper chromatogram (solvent: EtOAc-AcOH  $\text{HCOOH-H}_2\text{O}$ , 18:3:1:4), this compound showed different mobility from that of the reducing sugar. The mother liquor was treated again for a further 72 hours under similar conditions, and by working up the reaction products as described above, an additional 9.5 g of methyl  $\alpha$ -D-galactoside (XXV) was obtained (overall yield 40%).

b) - Methyl  $\alpha$ -D-mannopyranoside

A solution of D-mannose (50 g) in dry methanol (900 ml) containing 3% of hydrogen chloride, was refluxed for 16-18 hours. The reaction mixture was then neutralized by adding  $\text{PbCO}_3$  and, after removal of the precipitate ( $\text{PbCl}_2$ ) by filtration, was evaporated under vacuum to a small volume (150-250 ml). Left in the cold room overnight, the syrupy methanolic solution gave a fine precipitate of methyl  $\alpha$ -D-mannopyranoside which was purified by recrystallization from hot isopropyl alcohol (2 x 200 ml).

Yield 27 g (50%), m.p. 189-190°,  $[\alpha]_D + 78.5^\circ$  (c 2.5,  $\text{H}_2\text{O}$ ) (literature: m.p. 193-194°C and  $[\alpha]_D + 79.2$  ( $\text{H}_2\text{O}$ ) (90)). On a paper chromatogram (solvent: EtOAc-AcOH-HCOOH- $\text{H}_2\text{O}$ ; 18:3:1:4) the product had a different mobility from that of the reducing sugar.

c) - Methyl 4,6-O-benzylidene- $\alpha$ -D-glucoside (II)

Thirty grams of dry methyl  $\alpha$ -D-glucopyranoside (I) was added to benzaldehyde (300 ml) containing 15-20 g of fused zinc chloride, and the mixture was shaken at room temperature for 6 hours. The resulting viscous solution was slowly poured into a flask containing ice water (1000 ml) and petroleum ether (500 ml), maintained under vigorous stirring, and a precipitate formed in the petroleum ether layer. This mixture was left standing in the cold room for 4 hours, and then the crude precipitate was separated by filtration, washed with ice water, and finally dried in vacuo at 60-65°C. The product, still containing benzaldehyde, was purified by recrystallization, first from a mixture of petroleum ether and chloroform (1:10; 2 x 100 ml) and then from a mixture of petroleum ether and absolute ethanol (2:1; 2 x 200 ml). The resulting crystals of methyl 4,6-O-benzylidene- $\alpha$ -D-glucoside, were obtained in a yield of 35 g (76%), m.p. 161-161.5°C,

$[\alpha]_D + 142.3^\circ$  ( $c$  2.5,  $\text{CHCl}_3$ ) (literature m.p.  $161-162^\circ\text{C}$   $[\alpha]_D 143^\circ$  ( $\text{CHCl}_3$ ) (91)). NMR data (in  $\text{CDCl}_3$ ): 2.60 (multiplet, 5 aromatic H), 4.42 (singlet, H at the acetal carbon atom), 5.07 (doublet  $J = 2.5$  cps, anomeric H), 6.55 (singlet, anomeric  $-\text{OCH}_3$ ). The IR spectrum of this compound displays the characteristic aromatic absorption bands ( $650-750$ ,  $1500$ ,  $3050\text{ cm}^{-1}$ ), and the OH stretching vibration band ( $3400-3600\text{ cm}^{-1}$ )

d) - Methyl 4,6-O-benzylidene- $\alpha$ -D-galactoside (XXVII)

Twenty grams of methyl  $\alpha$ -D-galactopyranoside (XXV) was reacted with benzaldehyde under the same conditions as used for methyl  $\alpha$ -D-glucopyranoside. The crude precipitate, obtained by working up the reaction products, was recrystallized from a mixture of petroleum ether and absolute ethanol (2:1; 2 x 100 ml). The yield of methyl 4,6-O-benzylidene- $\alpha$ -D-galactoside was 9.2g (30%), m.p.  $169-170^\circ\text{C}$  and  $[\alpha]_D + 142^\circ$  ( $c$  3.2,  $\text{CHCl}_3$ ) (literature: m.p.  $169-170^\circ\text{C}$ ,  $[\alpha]_D + 144^\circ$  ( $\text{CHCl}_3$ ) (92)). NMR data (in  $\text{CDCl}_3$ ): 2.60 (multiplet, 5 aromatic H), 4.48 (singlet, H at the acetal carbon atom), 5.12 (doublet  $J_{1,2} = 1.0$  cps, anomeric H) and 6.57 (singlet, anomeric  $-\text{OCH}_3$ ). This compound absorbs infrared radiation in the range  $3400-3600\text{ cm}^{-1}$  and its spectrum displays the characteristic aromatic absorption bands.

e) - Methyl 2,3:4,6-di-O-benzylidene- $\alpha$ -D-mannoside

Twenty grams of methyl  $\alpha$ -D-mannopyranoside (XXVI) was reacted with benzaldehyde, with zinc chloride as catalyst, under the same conditions as for methyl  $\alpha$ -D-glucoside and methyl  $\alpha$ -D-galactoside. The crude crystalline product migrated as two spots on the TLC plate ( $\text{CHCl}_3$  solvent), a major one and a small impurity of lower mobility. It was recrystallized from a mixture of petroleum ether and chloroform (1:5, 3 x 100 ml) to yield 24.7 g (65%) of methyl 2,3:4,6-di-O-benzylidene- $\alpha$ -D-mannoside, m.p.  $175-176^\circ\text{C}$  (literature m.p.  $175-178^\circ\text{C}$  (93)).

Its IR spectrum did not show any absorption band in the range 3400-3600  $\text{cm}^{-1}$  (no "free" -OH groups).

NMR spectrum (in  $\text{CDCl}_3$ ): 2.61 (multiplet, 10 aromatic H), 3.75 (singlet, H at the benzylidene acetal carbon atom), 4.40 (singlet, H at the benzylidene acetal carbon atom), 5.02 (singlet, anomeric H) and 6.61 (singlet, anomeric  $-\text{OCH}_3$ ).

f) - Methyl 4,6-O-benzylidene- $\alpha$ -D-mannoside (XXVIII)

Twenty grams of methyl  $\alpha$ -D-mannopyranoside was reacted with benzaldehyde (300 ml), with molecular sieves as desiccant. After the reaction mixture had been shaken at room temperature for 26-28 hours, the resulting syrupy solution was poured slowly into a stirred suspension of ice water (600 ml) and petroleum ether (300 ml). The crude precipitate, which formed in the petroleum ether layer was filtered and washed with ice water, then dried and recrystallized first from a mixture of petroleum ether and absolute ethanol (2:1; 100 ml) and finally from hot water (2 x 50 ml). The crystalline methyl 4,6-O-benzylidene- $\alpha$ -D-mannopyranoside (yield 14.5 g., 48%) melted at 145-146°C (literature: m.p. 146-147°C (93)), and absorbed infrared radiation in the range 3600-3400  $\text{cm}^{-1}$ . NMR data (in  $\text{CDCl}_3$ ): 2.5 (multiplet, 5 aromatic H), 4.38 (singlet, H at the benzylidene acetal carbon atom), 5.18 (singlet, anomeric H) and 6.54 (singlet anomeric  $-\text{OCH}_3$ ).

g) - Methyl 4,6-O-benzylidene-2,3-di-O-benzyl- $\alpha$ -D-glucoside (III)

Ten grams of dry and finely powdered methyl 4,6-O-benzylidene- $\alpha$ -D-glucopyranoside (II) was added to a stirred suspension of powdered potassium hydroxide (10 g) in benzyl chloride (100 ml). The system was stirred under nitrogen at room temperature for 2 1/2 hours, and then for a further 1/2 hour at 40°C. After dilution with chloroform, the reaction mixture was washed with

water (100 ml) until washings were neutral (4 times), then the chloroform solution was dried over anhydrous  $\text{MgSO}_4$ , and the solvent and excess benzyl chloride were evaporated at  $70^\circ\text{C}$  under reduced pressure. The crude material, which crystallized on cooling, was recrystallized first from a mixture of petroleum ether and ethyl acetate (1:3; 2 x 50 ml) and then from methanol (50 ml). After drying overnight in vacuo at  $40\text{--}45^\circ\text{C}$  the yield of methyl 4,6-O-benzylidene-2,3-di-O-benzyl- $\alpha$ -D-glucoside was 12.3 g (78%), m.p.  $97\text{--}97.5^\circ\text{C}$ ,  $[\alpha]_D + 22.3$  ( $c$  2.5 acetone) (literature: m.p.  $99^\circ\text{C}$  and  $[\alpha]_D + 23.5^\circ$  ( $c$  1.0, acetone) (94)). This compound does not absorb infrared radiation in the range  $3400\text{--}3600\text{ cm}^{-1}$  (no "free" -OH groups). NMR data (in  $\text{CDCl}_3$ ): 2.62 (multiplet, 15 aromatic H), 4.42 (singlet, acetal H), 6.55 (singlet, anomeric  $-\text{OCH}_3$ ).

h) - Methyl 4,6-O-benzylidene-2,3-di-O-benzyl- $\alpha$ -D-galactoside (XXI)

Five grams of methyl 4,6-O-benzylidene- $\alpha$ -D-galactopyranoside (XXVII) was benzylated under the reaction conditions described for the glucoside derivative. After recrystallization from a mixture of petroleum ether and chloroform (1:5; 3 x 50 ml), the yield of methyl 4,6-O-benzylidene-2,3-di-O-benzyl- $\alpha$ -D-galactoside was 7 g (89%) m.p.  $176\text{--}177^\circ\text{C}$ . The infrared spectrum of this compound had no absorption bands in the range  $3600\text{--}3400\text{ cm}^{-1}$  (no "free" -OH groups). NMR data (in  $\text{CDCl}_3$ ): 2.61 (multiplet, 15 aromatic H), 4.46 (singlet, acetal H), 5.14 (singlet, anomeric H), and 6.53 (singlet, anomeric  $-\text{OCH}_3$ ). Elemental analysis: calc. for  $\text{C}_{28}\text{H}_{30}\text{O}_6$ , C 72.8%, H 6.5%; found C 72.4%, H 6.6%.

i) - Methyl 4,6-O-benzylidene-2,3-di-O-benzyl- $\alpha$ -D-mannoside

Five grams of methyl 4,6-O-benzylidene- $\alpha$ -D-mannopyranoside (XXVIII)

was benzylated according to the procedure described previously for the equivalent glucoside derivative. On the TLC plate (chloroform solvent), the syrupy products gave three spots, all of different mobility from that of the starting material. After introducing the mixture into a silica gel column, it was eluted with chloroform, and three fractions were collected. However, thin layer chromatography ( $\text{CHCl}_3$  solvent) indicated that a good separation had not been achieved. The IR spectra of the second and third fractions eluted, had absorption bands in the range  $3400\text{-}3600\text{ cm}^{-1}$ , while the first fraction did not absorb in that range. Fractions 2 and 3, probably partly reacted materials, were not further analysed. NMR data (in  $\text{CDCl}_3$ ) of fraction I, which was presumably methyl 4,6-O-benzylidene-2,3-di-O-benzyl- $\alpha$ -D-mannoside: 2.65 (multiplet, 15 aromatic H), 4.38 (singlet, acetal H), and 6.72 (singlet, anomeric  $-\text{OCH}_3$ ). Crystallization of this compound from a mixture of petroleum ether and chloroform, from methanol, and from ethyl acetate was attempted without success.

j) - Reduction of methyl 4,6-O-benzylidene-2,3-di-O-benzyl- $\alpha$ -D-galactoside to methyl 2,3,4-tri-O-benzyl- $\alpha$ -D-galactoside

Five hundred milligrams of methyl 4,6-O-benzylidene-2,3-di-O-benzyl- $\alpha$ -D-galactoside (XXI) was reduced with  $\text{LiAlH}_4/\text{AlCl}_3$  according to the procedure described by Bhattacharjee and Gorin (71). The following reaction conditions were selected: 1.2 molar equivalents of reducing agent, reflux temperature for three hours and the yield of the syrupy reduction products was 0.4 g (80%). On the TLC plate ( $\text{CHCl}_3$  solvent) this crude material migrated as two spots of about the same intensity, one of which having the same mobility as the starting material. The mixture placed on a silica gel column, was eluted with  $\text{CHCl}_3$  as two pure fractions (A) and (B),

and the recovery from the column was 85%. On the TLC plate ( $\text{CHCl}_3$  solvent), the first fraction eluted (A) had the same mobility as the starting material and was not further analysed. Fraction (B) (170 mg), eluted second, absorbed infrared radiation at  $3500\text{ cm}^{-1}$ . On dilution this band shifted to  $3600\text{ cm}^{-1}$ , and its NMR spectrum displayed a pattern of signals at  $2.63\tau$  due to 15 aromatic H, but no signal at  $4.46\tau$ .

A portion of fraction (B), methyl 2,3,4-tri-O-benzyl- $\alpha$ -D-galactoside (60 mg), dissolved in dry pyridine (100 ml), was acetylated with acetic anhydride (5 ml). The solution, cooled to  $0^\circ\text{C}$  during the addition of  $\text{Ac}_2\text{O}$ , was shaken at room temperature for 18-20 hours and then poured slowly into stirred ice water (300 ml). A syrupy precipitate formed, which was filtered off, washed with ice water, dried in the air, and then redissolved in chloroform. After drying the solution over anhydrous  $\text{MgSO}_4$ , chloroform was evaporated under vacuum and the resulting syrup was left under mechanical vacuum for 48 hours. This material (pure on the TLC plate) gave on its infrared spectrum a strong absorption band at  $1720\text{ cm}^{-1}$  ( $>\text{C}=\text{O}$  stretching vibration), but no band in the range  $3400\text{-}3600\text{ cm}^{-1}$ . NMR data (in  $\text{CDCl}_3$ ): 2.65 (multiplet, 15 aromatic H), 6.65 (singlet, anomeric  $-\text{OCH}_3$ ) and 8.05 (singlet, 3H of  $-\text{COCH}_3$ ), the signals due to two protons were shifted from  $6.38\tau$  in the spectrum of the reduced compound to  $5.95\tau$  in the spectrum of its acetylation product.

Another portion of fraction (B) (100 mg) was methylated by shaking in the dark with silver oxide (0.25 g) and methyl iodide and with a molecular sieve as a drying agent. After filtration of the molecular sieve and of the solid material, the solvent was evaporated under reduced pressure and then the resulting syrupy compound was dissolved in methanol and then hydrogenolysed

with palladium black as catalyst. After filtration of the catalyst, the methanol was partly evaporated under reduced pressure, and the solution, left in the cold, gave a precipitate. Yield of methyl 6-O-methyl- $\alpha$ -D-galactoside, after recrystallization from methanol (5 ml), 36 mg (80%), m.p. 135-135.5°C,  $[\alpha]_D + 164^\circ$  (C 1.2, H<sub>2</sub>O) (literature: m.p. 137-138°C,  $[\alpha]_D + 165^\circ$  (C 1.0, H<sub>2</sub>O) (95)).

k) - Methyl 2,3-di-O-benzyl- $\alpha$ -D-glucopyranoside (IV)

Ten grams of methyl 4,6,O-benzylidene-2,3,di-O-benzyl- $\alpha$ -D-gluco-pyranoside (III) was dissolved in glacial (99.8%) acetic acid (50-60 ml). This solution, maintained under continuous stirring in an open flask, was boiled for 30 minutes, while water (5 ml) was added dropwise. After cooling to room temperature, the reaction mixture was diluted with chloroform (30-40 ml) and then washed with a 10% aqueous solution of K<sub>2</sub>CO<sub>3</sub> (2 x 100 ml). From the resulting neutral solution, after drying over anhydrous MgSO<sub>4</sub>, chloroform and residual benzaldehyde were removed by evaporation under reduced pressure. The crude crystalline material which formed on cooling was recrystallized from a mixture of petroleum ether and chloroform (1:10; 3 x 30-40 ml) and the yield of white fine precipitate of methyl 2,3-di-O-benzyl- $\alpha$ -D-gluco-pyranoside was, after drying, 6.5 g (80%), m.p. 73-74°C,  $[\alpha]_D + 85.2^\circ$  (C 2.5, acetone) (literature: m.p. 75-76°C (96), and m.p. 79-80°C,  $[\alpha]_D 88.7^\circ$  (C 1.0, acetone) (94)). Elemental analysis: calc. for C<sub>21</sub>H<sub>26</sub>O<sub>6</sub>, C 67.4% and H 7.0%, found C 67.3% and H 6.9%. The hydrolysis product absorbed infrared radiation in the range 3400-3600 cm<sup>-1</sup>. NMR data (in CDCl<sub>3</sub>) 2.65 (multiplet, 10 aromatic H) and 6.58 (singlet, anomeric -OCH<sub>2</sub>). No signal was recorded at 4.42 $\tau$  for the proton at the benzylidene acetal carbon atom.

l) - Methyl 2,3-di-O-benzyl- $\alpha$ -D-galactoside (XXIII)

Three grams of methyl 4,6-O-benzylidene-2,3-di-O-benzyl- $\alpha$ -D-galactopyranoside (XXI) was dissolved in glacial acetic acid (30 ml) and hydrolyzed according to the procedure described previously for the glucoside derivative (III). Crystallization of the syrupy product (yield 2.24 g, 92%) was unsuccessfully attempted from a mixture of petroleum ether and chloroform (1:10), from methanol and water (5:1) and from ethanol. Left standing the compound started to crystallize after 5 months. The syrupy methyl 2,3-di-O-benzyl- $\alpha$ -D-galactoside migrated as a single spot on the TLC plate (solvent benzene:methanol/5:1), and its infrared spectrum had a large absorption band in the range 3400-3600  $\text{cm}^{-1}$  ("free" -OH groups). This compound exhibited an optical rotation of  $[\alpha]_D + 43.5^\circ$  (c 3.58,  $\text{CHCl}_3$ ). NMR data (in  $\text{CDCl}_3$ ): 2.62 (multiplet, 10 aromatic H) and 6.61 (singlet, anomeric -OCH<sub>3</sub>), but no signal was detected at 4.46  $\tau$ .

m) - Methyl 6-O-benzoyl-2,3-di-O-benzyl- $\alpha$ -D-glucopyranoside (V)

Five grams of dry methyl 2,3-di-O-benzyl- $\alpha$ -D-glucopyranoside (IV) was dissolved in dry pyridine (25 ml) and, after cooling to  $-40^\circ\text{C}$ , benzyl chloride (1.7 ml, 1.1 molar equivs.) was added in two portions to the solution. The reaction mixture, kept at  $-35^\circ$  to  $-40^\circ\text{C}$ , was stirred for three hours, while maintaining dry conditions, and then left standing overnight at  $-20^\circ\text{C}$ . A few drops of water were added to decompose unreacted benzoyl chloride. The reaction mixture was then diluted with  $\text{CH}_2\text{Cl}_2$  (25 ml), washed with a 1.0 N  $\text{H}_2\text{SO}_4$  solution (2 x 50 ml), and dried over anhydrous  $\text{MgSO}_4$ . Finally, the solvent was evaporated under reduced pressure. Traces of pyridine were removed from the syrupy material (yield 9.19 g, 92%) by dissolving it in ethyl

acetate (25 ml) and then evaporating under reduced pressure (3 times). Upon standing in the cold the syrup yielded methyl 6-O-benzoyl-2,3-di-O-benzyl- $\alpha$ -D-glucopyranoside (V) which, after recrystallization from a mixture of petroleum ether and ethyl acetate (3:1; 3 x 20-30 ml) and drying under vacuum at 40-45°C, melted at 78.5-79.5°C,  $[\alpha]_D + 23.5^\circ$  (c 3.5, CHCl<sub>3</sub>). Elemental analysis: calc. for C<sub>28</sub>H<sub>30</sub>O<sub>7</sub>, C 70.4% and H 6.4; found C 69.9% and H 6.4%. IR spectrum: sharp absorption band at 3500 cm<sup>-1</sup> which, on dilution on CCl<sub>4</sub> shifts to 3600 cm<sup>-1</sup> (no hydrogen bonded -OH group). NMR data (in CDCl<sub>3</sub>): 1.82 (doublets of doublet  $J_{1,2} = 7.5$  cps,  $J_{1,3} = 2$  cps, 2H ortho to the carboxyl in the benzoyl group), 2.54 (multiplet, 13 aromatic H) 6.54 (singlet, anomeric -OCH<sub>3</sub>). The signals of two protons, at 6.35 $\tau$  in the spectrum of methyl 2,3-di-O-benzyl- $\alpha$ -D-glucoside, were shifted to 5.37 $\tau$ .

A portion of this crystalline material (V) (2.0 g) was methylated by shaking it at room temperature for 24 hours with silver oxide (1 g) and methyl iodide, and with a molecular sieve as a drying agent. After removal of the molecular sieve and the solid material by filtration, and evaporation of the solvent, the residual syrupy material still absorbed IR radiation at 3500 cm<sup>-1</sup>, and therefore was methylated again under the same conditions. The disappearance of the absorption band at 3500 cm<sup>-1</sup> in the IR spectrum indicated that the methylation had gone to completion. The methylated compound (yield 1.24 g, 60%) was then dissolved in methanol (20 ml) and sodium methoxide (0.20 g) was added to the solution. After one hour the methanolic solution was neutralized by adding of solid CO<sub>2</sub> and then diluted with CHCl<sub>3</sub> and washed with water (2 x 30 ml). The organic layer was first dried over anhydrous MgSO<sub>4</sub>, and then evaporated under reduced pressure. To

the resulting syrupy material, dissolved in methanol (20-30 ml), palladium black (100 mg) was added and then hydrogen was bubbled for two hours into the stirred solution. After filtering off the catalyst, methanol was evaporated under reduced pressure and the resulting syrup was then redissolved into water (20 ml) and washed with ethyl ether (2 x 20 ml) in order to remove the aromatic material still present (i.e. methyl benzoate). The water was evaporated off and, after freeze drying, the yield of the syrupy methyl 4-O-methyl- $\alpha$ -D-glucopyranoside (XXII) was 356 mg (overall 41.2%). Compound (XXII), analyzed by GLC as its TMS derivative (81), gave a single peak. On paper chromatogram (solvent: EtOAc-AcOH-HCOOH-H<sub>2</sub>O, 18:3:1:4), it migrated as a single spot, and its infrared spectrum had no aromatic absorption bands. Proton magnetic resonance data (in D<sub>2</sub>O): 5.12 (doublet  $J_{1,2} = 3.2$  cps anomeric H), 6.35 (singlet, methoxyl H) and 6.58 (singlet, anomeric -OCH<sub>3</sub>). A few milligrams of NaIO<sub>4</sub> were introduced into the NMR tube and, after the sample had been left at room temperature overnight, a second spectrum indicated that oxidation had taken place, but no signals due to formic acid or formaldehyde were detected. Compound (XXII) exhibited an optical rotation of  $[\alpha]_D + 154.4^\circ$  (C 3.21, H<sub>2</sub>O) (literature:  $[\alpha]_D + 154.7^\circ$  (C 1.0, H<sub>2</sub>O) (84)).

n) - Methyl 6-O-benzoyl-2,3-di-O-benzyl- $\alpha$ -D-galactopyranoside (XXIV)

Three grams of methyl 2,3-di-O-benzyl- $\alpha$ -D-galactopyranoside (XXIII) was dissolved in dry pyridine (25 ml) and benzoylated under the conditions described above for compound (IV). The syrupy product (yield 3.56 g) gave two spots of about the same intensity on the TLC plate (benzene:methanol/9:1). They both had different mobilities from that of the starting material. The NMR spectrum of the mixture (in CDCl<sub>3</sub>) had two singlets for the anomeric -OCH<sub>3</sub>'s, and it was determined by integration that each component was present in a ratio of about 50±10% in the mixture, which was then placed on a silica

gel column and eluted with chloroform. Fraction (A) (150 g), eluted first, had no infrared absorption bands in the range  $3400-3600\text{ cm}^{-1}$  (no "free" hydroxyl groups) and was assigned as the di-benzoate product. Fraction (B), eluted second, (yield 1.62 g., 42.3%) was methyl 6-O-benzoyl-2,3-di-O-benzyl- $\alpha$ -D-galactoside, and absorbed infrared radiation at  $3500\text{ cm}^{-1}$  (on dilution shifted to  $3580\text{ cm}^{-1}$ ) and  $1730\text{ cm}^{-1}$ .

NMR data (in  $\text{CDCl}_3$ ): 1.83 (doublets of doublet:  $J_{1,2} = 7.5\text{ cps}$ ,  $J_{1,3} = 1.5\text{ cps}$ , 2H ortho to the carboxyl in the benzoyl group), 2.54 (multiplet, 13 aromatic H) and 6.53 (singlet, anomeric  $-\text{OCH}_3$ ). The signals of two protons at  $6.17\tau$  in the spectrum of compound (XXIII), were shifted to  $5.37\tau$ .

Compound (XXIV) after recrystallization from a mixture of petroleum ether and chloroform (5:1 ; 3 x 20 ml), melted at  $89-90^\circ\text{C}$ ,  $[\alpha]_D + 32.6^\circ$  ( $C$  3.33,  $\text{CHCl}_3$ ). Elemental analysis: calc. for  $\text{C}_{28}\text{H}_{30}\text{O}_7$ , C 70.4% and H 6.4%; found C 70.9% and H 6.3%. A portion of compound (XXIV) (0.218 g) was methylated, hydrolysed and finally catalytically hydrogenolysed according to the procedure described for compound (V). The syrupy methylated material proved to be pure on chromatographic analysis (GLC and paper) and to be oxidized by periodic acid without yielding formic acid or formaldehyde. The yield of methyl 4-O-methyl- $\alpha$ -D-galactopyranoside was 71 mg (overall 75%),  $[\alpha]_D + 167.5^\circ$  ( $C$  2.26,  $\text{H}_2\text{O}$ ).

o) - Methyl 6-O-benzoyl-4-O-(2- tetrahydropyranyl)-2,3-di-O-benzyl- $\alpha$ -D-glucoside (VI)

Two grams of methyl 6-O-benzoyl-2,3-di-O-benzyl- $\alpha$ -D-glucopyranoside (V) was dissolved in dry chloroform (25 ml) and, after adding 5 molar equivalents of dihydropyran (2 ml), gaseous HCl was bubbled into the solution. Then the reaction mixture was shaken at room temperature

for 30 minutes and, after refluxing for a further 5 minutes, was neutralized by shaking in a separatory funnel with a 10% aqueous solution of  $\text{NaHCO}_3$  (30 ml). The organic layer was washed with water (30 ml) and then dried over anhydrous  $\text{MgSO}_4$ . Chloroform and excess dihydropyran were evaporated under reduced pressure and the oily residue (yield 2.20g, 93%) was crystallized from a mixture of petroleum ether and chloroform (20:1 ; 2 x 20 ml). The crystalline methyl 6-O-benzoyl-4-O-(2-tetrahydropyranyl)-2,3-di-O-benzyl- $\alpha$ -D-glucoside, after drying under vacuum, melted at 72-74°C and its infrared spectrum displayed a strong absorption band in the range 2800-3000  $\text{cm}^{-1}$ , but no bands in the range 3400-3600  $\text{cm}^{-1}$ . NMR data (in  $\text{CDCl}_3$ ): 1.76 (doublets of doublet, 2H ortho to the carboxyl in the benzoyl group), 2.48 (multiplet, 13 aromatic H), 6.36 (singlet, anomeric -OCH<sub>3</sub>) and 8.20-8.55 (multiplets, 6 pyran ring H).

p) - Methyl 2,3,6-tri-O-benzyl-4-O-(2-tetrahydropyranyl)- $\alpha$ -D-glucoside (VII)

Two grams of methyl 6-O-benzoyl-4-O-(2-tetrahydropyranyl)-2,3-di-O-benzyl- $\alpha$ -D-glucopyranoside (VI), dissolved in methanol (20-30 ml), was hydrolysed according to the procedure described above for methyl 6-O-benzoyl-4-O-methyl-2,3-di-O-benzyl- $\alpha$ -D-glucoside. Traces of methyl benzoate from the syrupy product (yield 1.2 g, 80%) were removed by washing it with water (3 x 30 ml) and then evaporating under reduced pressure. After freeze drying, the absorption band at 3500-3600  $\text{cm}^{-1}$  and the disappearance of the band at 1720  $\text{cm}^{-1}$  in the infrared spectrum of the products indicated successful hydrolysis of compound (VI). NMR data (in  $\text{CDCl}_3$ ): 2.55 (singlet, 10 aromatic H) and 6.50 (singlet, anomeric -OCH<sub>3</sub>). The hydrolysis product (pure on the TLC plate) dissolved in benzyl chloride (25-30 ml) after addition of powdered potassium hydroxide (1 g), was benzylated as described above for

compound (II). The syrupy benzylation product migrated on the TLC plate ( $\text{CHCl}_3$ , solvent) as three spots and when it was placed on a silica gel column, chloroform eluted three pure fractions (A, B, C). The oily (A) fraction (0.15 g) eluted first was benzyl-(2- tetrahydropyranyl) ether. NMR data (in  $\text{CDCl}_3$ ): 2.65 (multiplet, 5 aromatic H), 8.80 (multiplets, 6 tetrahydropyranyl ring H). The syrupy (B) fraction (0.45 g) eluted second, was methyl 2,3,4,6-tetra-O-benzyl- $\alpha$ -D-glucoside. NMR data (in  $\text{CDCl}_3$ ): 2.55 (multiplet, 20 aromatic H) and 6.50 (singlet, anomeric  $-\text{OCH}_3$ ). The syrupy (C) fraction (yield 0.8 g, 55%), eluted last, did not absorb infrared radiation in the range  $3400\text{--}3600\text{ cm}^{-1}$ , and from its NMR spectrum (in  $\text{CDCl}_3$ ) was assigned as methyl 2,3,6-tri-O-benzyl-4-O-(2- tetrahydropyranyl)- $\alpha$ -D-glucoside (VII): 2.55 (multiplet, 15 aromatic H), 6.50 (singlet, anomeric  $-\text{OCH}_3$ ) and 8.30 (multiplets, 6 pyranosyl ring H).

q) - Methyl 2,3,6-tri-O-benzyl- $\alpha$ -D-glucopyranoside (VIII)

Eight hundred milligrams of methyl 2,3,6-tri-O-benzyl-4-O-(2- tetrahydropyranyl)- $\alpha$ -D-glucoside (VII) was dissolved in acetone (20 ml), and, after adding 0.5N HCl solution (5 ml), was shaken at room temperature for 1 hour and then heated at  $40\text{--}50^\circ\text{C}$  for a further 5 minutes. After diluting with  $\text{CH}_2\text{Cl}_2$  (20 ml), the reaction mixture was first shaken with a 10% aqueous solution of  $\text{NaHCO}_3$  (2 x 20 ml) and then washed with water (2 x 20 ml). The organic layer was dried over anhydrous  $\text{MgSO}_4$ , and finally the solvent was evaporated under reduced pressure. The syrupy methyl 2,3,6-tri-O-benzyl- $\alpha$ -D-glucoside (yield 0.55 g, 81%), absorbed infrared radiation at  $3500\text{ cm}^{-1}$  ("free" hydroxyl group) and migrated on the TLC plate ( $\text{CHCl}_3$  solvent) as a single spot. Crystallization of compound (VIII) was attempted from a mixture of petroleum ether and chloroform (1:10) and from methanol, but was

not successful. NMR data (in  $\text{CDCl}_3$ ): 2.60 (multiplet, 15 aromatic H), 6.55 (singlet, anomeric  $-\text{OCH}_3$ ), and 7.40 (H, hydroxyl group). This last signal was shifted to higher field when the temperature of the sample was increased.

A fraction of compound (VIII) (150 mg) was methylated with  $\text{Ag}_2\text{O}$  and  $\text{CH}_3\text{I}$  and then hydrogenolysed with palladium black as catalyst as described above for compound (V). The methylated compound (40 mg) had the same retention time on G.L.C., and on paper chromatography (EtOAc-AcOH-HCOOH- $\text{H}_2\text{O}$ , 18:3:1:4) showed the same mobility, as methyl 4-O-methyl- $\alpha$ -D-glucopyranoside (XXII).

r) - Methyl 6-O-trityl- $\alpha$ -D-mannopyranoside (X)

Ten grams of methyl  $\alpha$ -D-mannopyranoside was dissolved in dry pyridine (50 ml), triphenyl chloride (12.9 g, 0.9 molar equivalents) was added, and the solution was kept for 4 hours at the temperature of a boiling water bath. On being slowly poured into stirred ice-water (2000 ml) the reaction mixture gave a white precipitate. The mixture was left standing overnight in the cold room, and then the precipitate was filtered off, washed thoroughly with ice-water, and finally dried under vacuum at 40-45°C (yield 18 g, 80%). On the TLC plate (ethylacetate solvent, 2,4-dinitrophenylhydrazine spray) the tritylation product migrated as two spots:  $R_f$  0.74 (yellow) and  $R_f$  0.45 (brown), indicating the presence in the products of triphenyl carbinol. Therefore the mixture (5.0 g) was introduced into a silica gel column and eluted with chloroform and methanol (10:1) as methyl 6-O-trityl- $\alpha$ -D-mannopyranoside. Its infrared spectrum displayed the characteristic aromatic absorption bands. NMR data (in  $\text{CDCl}_3$ ): 2.35

(multiplet, 15 aromatic H), 4.95 (singlet, anomeric H) and 6.30 (singlet, anomeric  $-\text{OCH}_3$ ).

s)-Methyl 6-O-trityl-2,3-O-carbonyl- $\alpha$ -D-mannoside (XI)

A solution of five grams of methyl 6-O-trityl- $\alpha$ -D-mannopyranoside (X) dissolved in dry pyridine (50 ml) was cooled to  $-20^\circ\text{C}$ . With constant stirring, a solution of phosgene (12.5%) in benzene (18 ml) was added dropwise over the course of 30 minutes. The reaction mixture was kept for 1 hour at  $-20^\circ\text{C}$  and for a further 1/2 hour at room temperature. It was then diluted with  $\text{CHCl}_3$  (20-30 ml) and washed with a saturated aqueous solution of  $\text{NaHCO}_3$  (2 x 50 ml). After drying the organic layer over anhydrous  $\text{MgSO}_4$ , chloroform and pyridine were removed by evaporation under reduced pressure and the syrupy product was crystallized from a mixture of petroleum ether and ethyl ether (1:10; 3 x 50 ml). Yield of methyl 6-O-trityl-2,3-O-carbonyl- $\alpha$ -D-mannoside, 3.5 g (66%) m.p.  $170-171^\circ\text{C}$ ,  $[\alpha]_D + 7.0^\circ$  (c 3.33,  $\text{CHCl}_3$ ). Elemental analysis: calc. for  $\text{C}_{27}\text{H}_{26}\text{O}_7$  C 70.1% and H 5.7%; found C 70.1% and H 5.6%. IR data:  $1820\text{ cm}^{-1}$  ( $\text{C}=\text{O}$  stretching) and  $3400-3500\text{ cm}^{-1}$  ( $-\text{OH}$  stretching). NMR data (in  $\text{DMSO}-d_6$ ): 2.35 (multiplet, 15 aromatic H), 3.9 (doublet  $J = 6.5$  cps, hydroxyl H at C-4) 4.58 (singlet, anomeric H) and 6.20 (singlet, anomeric  $-\text{OCH}_3$ ).

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## CLAIMS TO ORIGINAL RESEARCH

A general method for the formation of 1,4-internal ethers of six-membered ring compounds was conceived and tested on cis-1,4-cyclohexanediol di-tosylate, which readily formed the ether on treatment with sodium hydroxide.

An eight-step synthetic scheme was devised and executed for producing methyl 2,3,6-tri-0-benzyl- $\alpha$ -D-glycopyranosides.

Reduction of the 1,3-dioxane ring in methyl 4,6-0-benzylidene-2,3-di-0-benzyl- $\alpha$ -D-galactopyranoside, with  $\text{LiAlH}_4/\text{AlCl}_3$ , was found to yield methyl 2,3,4-tri-0-benzyl- $\alpha$ -D-galactopyranoside, in spite of the seemingly high accessibility of the benzylidene ring.

By selective benzylation of the hydroxyl group at C-6 in methyl 2,3-di-0-benzyl- $\alpha$ -D-glucopyranoside and methyl 2,3-di-0-benzyl- $\alpha$ -D-galactopyranoside, it was found that the hydroxyl group at C-4 of the latter is more readily acylated, although axially oriented.

(2-tetrahydropyranyl) ethers of sugars were found to not be stable under strong alkaline conditions, and therefore to not provide, under such conditions, an effective protection for hydroxyl groups.

Fully benzylated mannan was found to be resistant to acid hydrolysis.

The following new compounds were prepared:

methyl 6-0-benzoyl-2,3-di-0-benzyl- $\alpha$ -D-glucopyranoside;  
methyl 6-0-benzoyl-2,3-di-0-benzyl- $\alpha$ -D-galactopyranoside;  
methyl 4-0-methyl- $\alpha$ -D-galactopyranoside; methyl 6-0-benzoyl-4-0-(2-tetrahydropyranyl)-2,3-di-0-benzyl- $\alpha$ -D-glucopyranoside; methyl 2,3,6-tri-0-benzyl- $\alpha$ -D-glucopyranoside.