

## SYNTHESIS AND REACTIONS OF SUGAR CHLOROSULPHATES

Dissertation

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by

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SUMMARY

Partially chlorosulphated derivatives were synthesised for the purpose of examining the reactions of the chlorosulphonyloxy group in the presence of free hydroxyl groups. The behaviour of the chlorosulphonyloxy group was investigated under acidic conditions.

Since sterically favoured chlorosulphonyloxy groups undergo facile replacement by chlorine to form chlorodeoxy sugars, some compounds possessing chlorosulphonyloxy groups which, due to polar and steric effects are not replaced by chloride, were investigated with a view to possible activation of the unfavourable centres towards nucleophilic substitution, thereby making available previously inaccessible chlorodeoxy sugars.

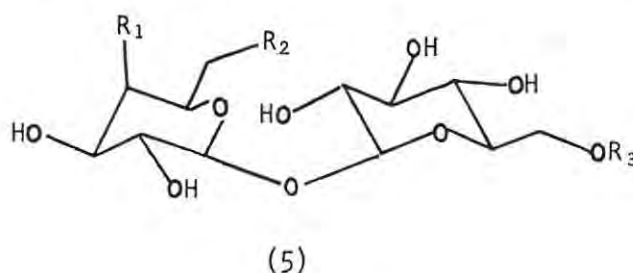
## 1. INTRODUCTION

### Biological significance and synthetic utility of deoxyhalogenated carbohydrates:

Deoxyhalogeno sugars are amongst the most useful and important compounds in carbohydrate chemistry. They are important intermediates in the syntheses of aminodeoxy,<sup>1</sup> deoxy and anhydro sugars. They also serve as intermediates in the introduction of heteroatoms and unsaturation into carbohydrates and related structures.

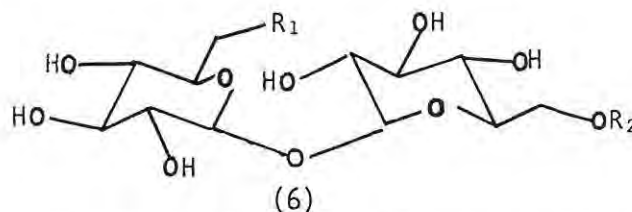
3-Deoxy-3-fluoro-glucose(1) which may be synthesised by treating 1,2:5,6-di-O-isopropylidene- $\alpha$ -D-glucofuranose(2) with diethylaminosulphur trifluoride is of considerable interest as a probe for the normal and abnormal metabolism of glucose and other carbohydrates. The introduction of <sup>14</sup>C into 4-fluoro-4-deoxy-D-glucose(3) permits the understanding of its effects on the metabolism of carbohydrates. Lopes<sup>3</sup> reported an improved synthesis of compound(3) which is amenable to the introduction of <sup>14</sup>C thereby enabling the elucidation of transport parameters of compound(3) and D-glucose(4) in the human erythrocyte.

Although the synthesis<sup>4,5,6</sup> of asymmetric analogues of trehalose has proved difficult, these compounds are of interest in the study of the mechanism of the trehalases and possess other biologically significant properties.



5(a) R<sub>1</sub> = OH; R<sub>2</sub> = OH; R<sub>3</sub> = H  $\alpha$ -D-galactopyranosyl  $\alpha$ -D-glucopyranoside

5(b) R<sub>1</sub> = F; R<sub>2</sub> = OH; R<sub>3</sub> = H 4-fluoro 4-deoxy- $\alpha$ -D-galactopyranosyl  $\alpha$ -D-glucopyranoside



- 6 (a)  $R_1 = F, R_2 = H$  6-fluoro-6-deoxy- $\alpha, \alpha$ -trehalose  
 (b)  $R_1 = I, R_2 = H$  6-iodo-6-deoxy- $\alpha, \alpha$ -trehalose

(5a), (6a) and (6b) are substrates for cockchafer-trehalase. The  $K_m$  of the enzyme is only slightly altered in the (6a) derivative, markedly increased for (5a) while (6b) acted as a competitive inhibitor with respect to  $\alpha, \alpha$ -trehalose. When compound (5b)<sup>2</sup> was assayed for its activity against the trehalase isolated from the flight muscle of the green bottle fly, Lucilia sericata it had about a 30 fold lower affinity for the enzyme than trehalose.

2-Amino-2-deoxy- $\alpha, \alpha$ -trehalose(7) which has been isolated from fermentation of some Streptomyces species shows antibiotic activity which may be due to the inhibition of trehalase. Since insects use trehaloses as storage carbohydrate and rely on trehalase for the release of D-glucose, trehalase inhibitors could have important applications in the insecticide and fungicide fields.

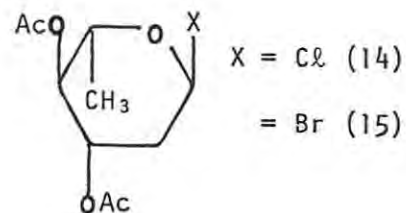
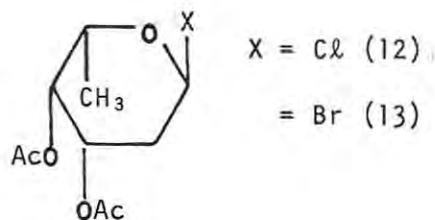
Rao<sup>7</sup> et al., appreciated the problem of the transportation of phosphorylated deoxyfluorotrioses as chemotherapeutic agents into the cancer cell. Since it was thought that secondary deoxyfluorohexoses might gain access to the cancer cell and generate intracellularly 1-fluoro 3-hydroxy-2-propanone 3-phosphate (8) methods were sought for the introduction of fluorine into the 3-or 4-position of the ketohexoses. 5-Deoxy-5-fluoro-L-sorbose(9) which produced striking effects characteristic of the deoxyfluorohexoses, was synthesised.

The inhibition of the synthesis of sialic acid<sup>8</sup> which is responsible for the negative charge on the cell surface may affect the cancer cell. 2-Acetamido-2-deoxy-D-mannose 6-phosphate(10) seems to be an obligatory intermediate in its biosynthetic pathway. Thus substitution of the 6-OH group by F in 2-acetamido 2-deoxy-D-mannose might furnish an effective inhibitor of the specific kinase involved in its formation thus blocking the synthesis of sialic acid.

Since 1-(2-deoxy-2-fluoro- $\beta$ -D-arabinosyl) cytosine or 2'-F-Ara-C has a growth inhibitory effect on a suspension culture of L1210 mouse leukemia, Ritzmann<sup>9</sup> et al., attempted to achieve the direct introduction of a halogeno group into the 2 "up" arabino configuration of a preformed nucleoside.

Chlorination of methyl 3,5-di-O-benzyl-D-ribofuranoside(11) by treatment with carbon tetrachloride and triphenylphosphine yielded methyl 3,5-di-O-benzyl-2-chloro-2-deoxy- $\alpha$ -D-arabinofuranoside(12). The activity of the resulting nucleoside, 1-(2-chloro-2-deoxy- $\beta$ -D-arabinofuranosyl) cytosine hydrochloride or 2'-Cl-Ara-C against the mouse leukemia cells in vitro is of the same order of magnitude as exhibited by 2'-F-Ara-C .

Synthetic anthracyclines having aglycones linked to 3-amino-2,3,6-trideoxy hexopyranoses of the L-lyxo and L-arabino configurations have been shown to possess antibiotic and antineoplastic activity. This suggests that their oxygen analogues, 2,6-dideoxy-L-lyxo- and 2,6-dideoxy-L-arabinohexose when linked to anthracycline aglycones may form glycosides possessing biological activity. The 2,6-dideoxy - L-lyxohexopyranosyl halides(12 and 13) and the 2,6-dideoxy-L-arabinohexopyranosyl halides (14 and 15) could be linked to either anthracycline aglycones or antibiotics.

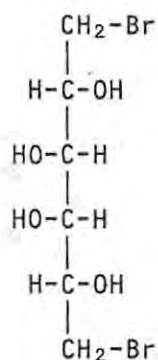


Khadem<sup>10</sup> *et al.*, attempted to synthesise the glycosyl halides (12 and 13) and (14 and 15) from readily available starting material. Treatment of 1,5-anhydro-3,4-di-O-acetyl-1,2,6-trideoxy-L-lyxohex-1-enitol (16) (di-O-acetyl-L-fucal) with hydrogen chloride or hydrogen bromide yielded 3,4-di-O-acetyl-2,6-dideoxy- $\alpha$ -L-lyxohexopyranosyl chloride (12) and bromide (13) while the di-O-acetyl-L-rhamnal (17) afforded 3,4-di-O-acetyl-2,6-dideoxy- $\alpha$ -L-arabinohexopyranosyl chloride (14) and bromide (15) in theoretical yields.

Kovac and Palovick<sup>11</sup> described the conversion of a crystalline methyl 1,2,3-tri-O-acetyl-4-O-methyl- $\beta$ -D-glucopyranuronate (18) by treatment of its p-nitrobenzoate derivative with dichloromethyl methyl ether in the presence of zinc chloride or hydrogen bromide in the presence of glacial acetic acid, into two glycosyl halides which are potential intermediates in the synthesis of 4-O-methyl-D-glucuronic acid containing oligosaccharides. 4-O-Methyl-D-glucuronic acid (19) is a constituent of numerous aldobiouronic acids isolated from depolymerization products of plant polysaccharides. It is abundant in (4-O-methylglucurono)xylans, the main hemicellulose component of hard woods. Although partial hydrolysis of certain polysaccharides yields 4-O-methyl-D-glucuronic acid - aldose type aldobiouronic acids, their preparation is tedious and the substances are rarely obtained in appreciable amounts.

The cytostatic<sup>12</sup> activity of 1,6-dibromo-1,6-dideoxy-D-mannitol (20) was first published in 1963. Several years later the galactitol

isomer (D.B.D.) (21) which was proved to be more active and which inhibited the growth of various transplanted tumours was introduced into clinical practice.



(21)

Previously it was shown that the cytostatic activity of 1,6-di-Q-mesyl-D-mannitol (22) could be significantly increased by methylating the hydroxyl groups at C3 and C4.

Kuszmán<sup>12</sup> investigated the validity of this structure activity relationship in 1,6-dibromo-1,6-dideoxy hexitols of different configurations. The 1,6-dibromo compound having the L-ido configuration showed a high activity.

Reagents used in the synthesis of deoxyhalogenated carbohydrates.

Excellent reviews on deoxyhalogenated carbohydrates have appeared in the literature. Recently Szarek<sup>13</sup> surveyed the synthesis as well as the reactions and synthetic utility of deoxyhalogeno sugars. In this work the direct replacement of hydroxyl groups using reagents such as sulphuryl chloride as well as the use of unsaturated carbohydrate derivatives as precursors for specifically halogenated sugars and the reaction of Q-benzylidene sugars with N-bromosuccinimide was described. An earlier work on deoxyhalogenated carbohydrates was published by Barnett<sup>14</sup>.

Alan H. Haines<sup>15</sup> in his review entitled, "The relative reactivities of hydroxyl groups in carbohydrates", discussed selective halogenation of not only mono- and disaccharides, but also of certain nucleosides using sulphuryl chloride, N,N-dimethyl-(methaniminium) halide derivatives and phosphorus based reagents.

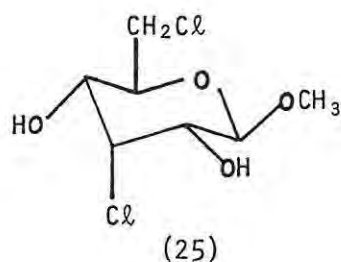
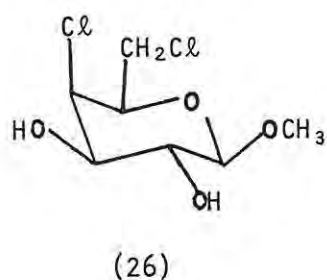
The present review is a continuation of earlier works and covers the literature from 1974-1981. Although it is not intended to be a comprehensive study it does highlight the more important reagents involved in the formation of deoxyhalogenated carbohydrates.

1.1.1 Sulphuryl chloride: The reaction of sulphuryl chloride<sup>13</sup> with carbohydrates containing free hydroxyl groups has been used for the preparation of chlorodeoxy sugars. The chloride ion liberated during the chlorosulphation procedure causes the displacement at certain centres of the chlorosulphonyloxy group depending on whether steric<sup>16</sup> and polar effects are favourable for a nucleophilic bimolecular substitution. Displacement of a sulphonic ester often occurs most readily when this group is situated at a primary centre, whereas displacement at secondary centres on a pyranoid<sup>13</sup> ring is more difficult and often requires the use of high boiling, aprotic solvents of high dielectric constants. A disadvantage of these solvents is that decomposition of the product may occur during the isolation procedure. In a furanoid ring system nucleophilic displacements occur readily, unless the leaving group is exo in a bicyclic system having two fused, five membered rings.

The lack of chloro<sup>17</sup> substitution at C3 on reaction of methyl  $\alpha$ -D-glucopyranoside(23) with sulphuryl chloride has been attributed to the presence of a  $\beta$ -trans-axial methoxyl group at C1. In the case of

methyl  $\beta$ -D-glucopyranoside(24), however, where the methoxyl group at C1 is in an equatorial position, reaction with sulphuryl chloride yielded 3,6-dichloro-3,6-dideoxy methyl  $\beta$ -D-allopyranoside (25) in addition to 4,6-dichloro-4,6-dideoxy methyl  $\beta$ -D-galactopyranoside (26).

The isolation of 3,6-dichloro-3,6-dideoxy methyl  $\beta$ -D-allopyranoside by Szarek<sup>17</sup> et al., provides a facile method for the synthesis of the biologically significant sugar, paratose.

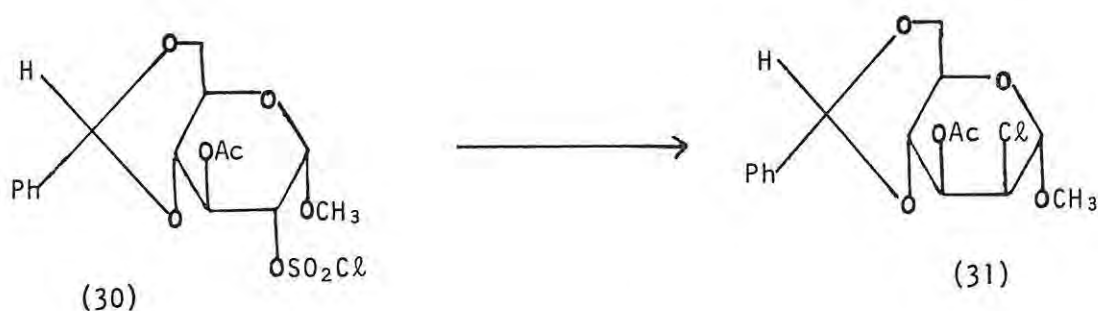


In an earlier study of the reaction of methyl  $\beta$ -D-glucopyranoside with sulphuryl chloride, Jennings<sup>18</sup> and Jones reported the formation of crystalline methyl 6-chloro-6-deoxy- $\beta$ -D-glucopyranoside 2,3,4-trichlorosulphate(27) in a 10% yield and a non crystalline material which was mainly 4,6-dichloro-4,6-dideoxy methyl- $\beta$ -D-galactopyranoside 2,3-dichlorosulphate. Treatment of compound(27) with pyridinium chloride in chloroform for 12 hours at 50°, followed by dechlorosulphation and acid catalysed hydrolysis of the product, yielded 4,6-dichloro-4,6-dideoxy-D-galactose(28) and two minor components whose structures were not elucidated. In this earlier<sup>18</sup> work the formation of a 3,6-dichloro-3,6-dideoxy compound was not explicitly established.

Early attempts at nucleophilic displacements of a 2-chlorosulphonyloxy group on a pyranoid ring were unsuccessful. The inertness of a 2-chlorosulphonyloxy group towards nucleophilic replacement is thought to be due to the presence of a vicinal axial substituent or a  $\beta$ -trans-axial substituent on the pyranoid ring.

Recently, however, Khan<sup>19</sup> et al., succeeded in replacing the 2-chlorosulphonyloxy group in methyl  $\alpha$ -D-glucopyranoside and sucrose derivatives by the chloride ion.

Thus chlorosulphation of methyl 3-O-acetyl-4,6-benzylidene- $\alpha$ -D-glucopyranoside(29) with sulphuryl chloride at  $-75^\circ$  yielded the 2-chlorosulphate (30) in a 60% yield. Reaction of compound(30) with lithium chloride in hexamethylphosphoramide at  $\sim 70^\circ$  for 2.5 hours afforded methyl 3-O-acetyl-4,6-O-benzylidene-2-chloro-2-deoxy- $\alpha$ -D-mannopyranoside (31) in the extremely good yield of 74%.



When the reaction was repeated with lithium bromide, sodium azide, sodium benzoate or sodium chloride as the nucleophile, the 2-hydroxy compound was produced.

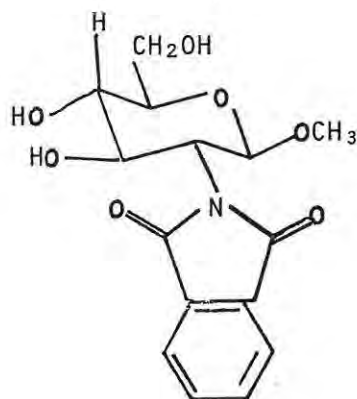
The mechanism involved in the replacement is unclear. The reaction could proceed either via an S<sub>N</sub>2 mechanism or via a cyclic intermediate. However, the inertness of the 2-chlorosulphonyloxy group towards nucleophilic displacement, coupled with the inability of nucleophiles other than chloride to effect replacement at C2 tends to rule out an S<sub>N</sub>2 mechanism. The failure of compound(30) to afford the manno derivative on heating with hexamethylphosphoramide alone seems to rule out the alternative mechanism via a cyclic intermediate. The latter reaction yielded primarily the 2-hydroxy compound.

The above work was extended to sucrose derivatives. Thus 3,4,6,3',

4',6'-hexa-0-acetyl-1-0-benzoyl-sucrose 2-chlorosulphate (32) on reaction with lithium chloride in hexamethylphosphoramide yielded 1-0-benzoyl-2-chloro-2-deoxy-mannosucrose hexa-acetate (33) in a 49% yield in addition to 29% of unreacted starting material, while 3,4,6,3',4',6'-hexa-0-acetyl-sucrose 2,1'-dichlorosulphate (34) on reaction with lithium chloride in hexamethylphosphoramide afforded 2,6,1',6'-tetrachloro-2,6,1',6'-tetradeoxy-mannosucrose tetra-acetate(35) in a 85% yield.

Despite the ease and synthetic flexibility of the chlorosulphation reaction it has not previously been applied to amino sugars. Since reaction of 2-deoxy-2-phthalimido-D-glucose(36) with sulphuryl chloride under standard conditions yielded 6-chloro-2,6-dideoxy-2-phthalimido  $\alpha$ -D-glucopyranosyl chloride 3,4-dichlorosulphate, Bundle<sup>20</sup> investigated the chlorosulphation of methyl 2-deoxy-2-phthalimido- $\beta$ -D-glucopyranoside(37) which afforded the chlorosulphated 6-chloro-6-deoxy glucoside(38). Dechlorosulphation of compound (38) yielded 6-chloro-2,6-dideoxy 2-phthalimido- $\beta$ -D-glucopyranoside(39). Increasing the amount of sulphuryl chloride from 3.5 molar equivalents to 7.7 molar equivalents and allowing the temperature to reach 20° , the reaction, after dechlorosulphation, afforded an optimum 59% yield of methyl 4,6-dichloro-2,4,6-trideoxy-2-phthalimido- $\beta$ -D-galactopyranoside(40). The exclusive formation of compound (40) may be contrasted with the reaction between sulphuryl chloride and methyl  $\beta$ -D-glucopyranoside. In this case both the 4,6-dichloro-galacto- and the 3,6-dichloro- $\alpha$ -allopyranosides were formed.

The absence of the 3,6-dichloro- $\alpha$ -allopyranoside as reported by Bundle<sup>20</sup> even at elevated temperatures, relates to the stereochemistry of C2 phthalimido function.



(37)

The plane of the phthalimido ring system is perpendicular to the mean plane of the pyranose ring hence the carbonyl disposed towards the  $\alpha$ -face of the pyranose ring would render unfavourable the transition state leading to a 3-chloro allopyranoside derivative.

The investigation of the chlorosulphation of methyl 2-deoxy-2-phthalimido- $\beta$ -D-glucopyranoside by Bundle was prompted by the need for a sample of the diamino sugar, 2-acetamido-4-amino-2,4,6-trideoxy-D-glucose(41). This sugar, although previously synthesised by Liav<sup>21</sup> *et al.*, was required as the glycoside, methyl 2-acetamido-4-amino-2,4,6-trideoxy- $\beta$ -D-glucopyranoside(42) to facilitate comparison of  $^{13}\text{C}$  and  $^1\text{H}$  n.m.r. parameters with those of the 2,4-diamino-6-deoxy-hexose which has been identified as a component of pneumococcal C-substance<sup>22,23</sup>.

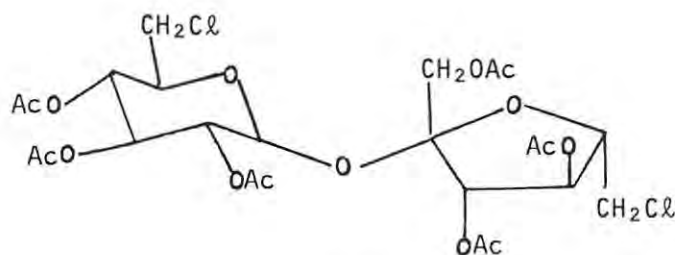
The sulphuryl chloride reagent has also been used with numerous furanose derivatives. Thus<sup>24</sup> reaction of 3-O-benzyl-1,2-O-isopropylidene-6-O-p-tolylsulphonyl- $\alpha$ -D-glucofuranose(43) with sulphuryl chloride yielded 89% of 3-O-benzyl-5-chloro-5-deoxy-1,2-O-isopropylidene-6-O-tolylsulphonyl- $\beta$ -L-idofuranose(44).

Parolis<sup>25</sup> reported the synthesis of 6-chloro-6-deoxy-1,2-O-isopropylidene- $\alpha$ -D-glucofuranose 3,5-dichlorosulphate(45) from the

chlorosulphation at  $-40^{\circ}$  of 1,2-0-isopropylidene- $\alpha$ -D-glucofuranose(46). Compound (45) on heating at  $50^{\circ}$  for  $\pm 16$  hours afforded 5,6-dichloro-5,6-dideoxy-1,2-0-isopropylidene- $\beta$ -L-idofuranose 3-chlorosulphate(47) which on dechlorosulphation yielded 5,6-dichloro-5,6-dideoxy-1,2-0-isopropylidene- $\beta$ -L-idofuranose(48). The L-ido configuration of compounds (44) and (48) is consistent with the inversion of configuration which occurs when a chlorosulphate group is replaced by chloride and was supported by n.m.r. data.

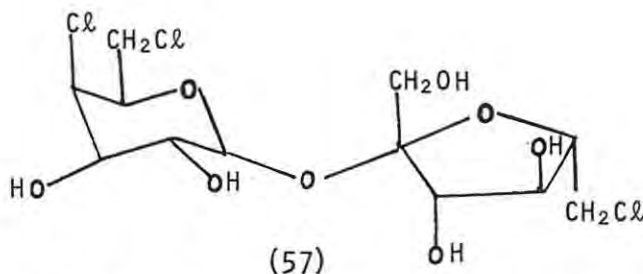
Chlorosulphation<sup>26</sup> of various methyl  $\alpha$ - and  $\beta$ -pentofuranosides with sulphuryl chloride yielded almost exclusively the 5-chloro-5-deoxy derivatives. Small amounts of the trichlorosulphates were isolated in the reaction of the  $\alpha$ -furanosides with sulphuryl chloride. Thus reaction of methyl  $\alpha$ -D-xylofuranoside(49) with sulphuryl chloride afforded methyl 5-chloro-5-deoxy- $\alpha$ -D-xylofuranoside 2,3-dichlorosulphate (53%) (50) and methyl  $\alpha$ -D-xylofuranoside 2,3,5-trichlorosulphate (13%) (51). Dechlorosulphation of compound (50) yielded methyl 5-chloro-5-deoxy- $\alpha$ -D-xylofuranoside(52), while methyl- $\beta$ -D-ribofuranoside(53) afforded methyl 5-chloro-5-deoxy- $\beta$ -D-ribofuranoside 2,3-dichlorosulphate(54) which on dechlorosulphation yielded methyl 5-chloro-5-deoxy- $\beta$ -D-ribofuranoside(55). It appears that the  $\alpha$ -methyl group slightly inhibits the replacement of the 5-chlorosulphonyloxy group by the chloride ion.

It was ascertained by Hough<sup>27</sup> et al., that reaction of sucrose with sulphuryl chloride at  $-78^{\circ}$ , after dechlorosulphation and acetylation yielded 6,6'-dichloro-6,6'-dideoxy-sucrose hexa-acetate (56).



(56)

When the reaction temperature was maintained between  $-5^{\circ}$  and  $-10^{\circ}$  for 16 hours, a crystalline product was isolated in a 30% yield, which was shown by n.m.r. and mass spectrometry to be 4,6-dichloro-4,6-dideoxy- $\alpha$ -D-galactopyranosyl 6-chloro-6-deoxy- $\beta$ -D-fructofuranoside (57) which was isolated as the pentamethanesulphonate and penta-p-nitrobenzoate.

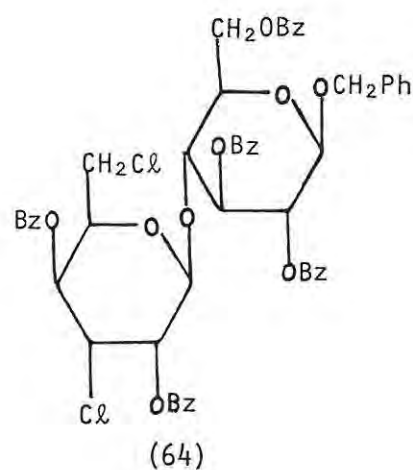
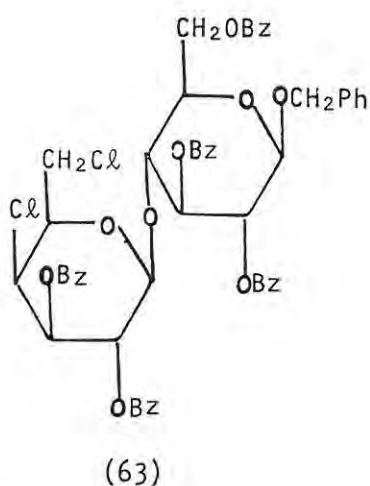


Parolis<sup>28</sup> reported an improved chlorosulphation procedure and the direct isolation and characterization of the "trichloro sucrose penta-chlorosulphate". Chlorosulphation of sucrose was carried out at  $-78^{\circ}$  by the dropwise addition of sulphuryl chloride to a sucrose/pyridine mixture. The reaction was not diluted with chloroform as this led to the formation of a variety of products due to the limited solubility of sucrose in the chloroform/pyridine mixture. In order to enhance the solubility of sucrose, the amount of pyridine was increased but, to avoid the formation of cyclic sulphate, the temperature was rigidly controlled and the ratio of pyridine : sulphuryl chloride was maintained at 1.5 mol - 2 mol : 1 mol.

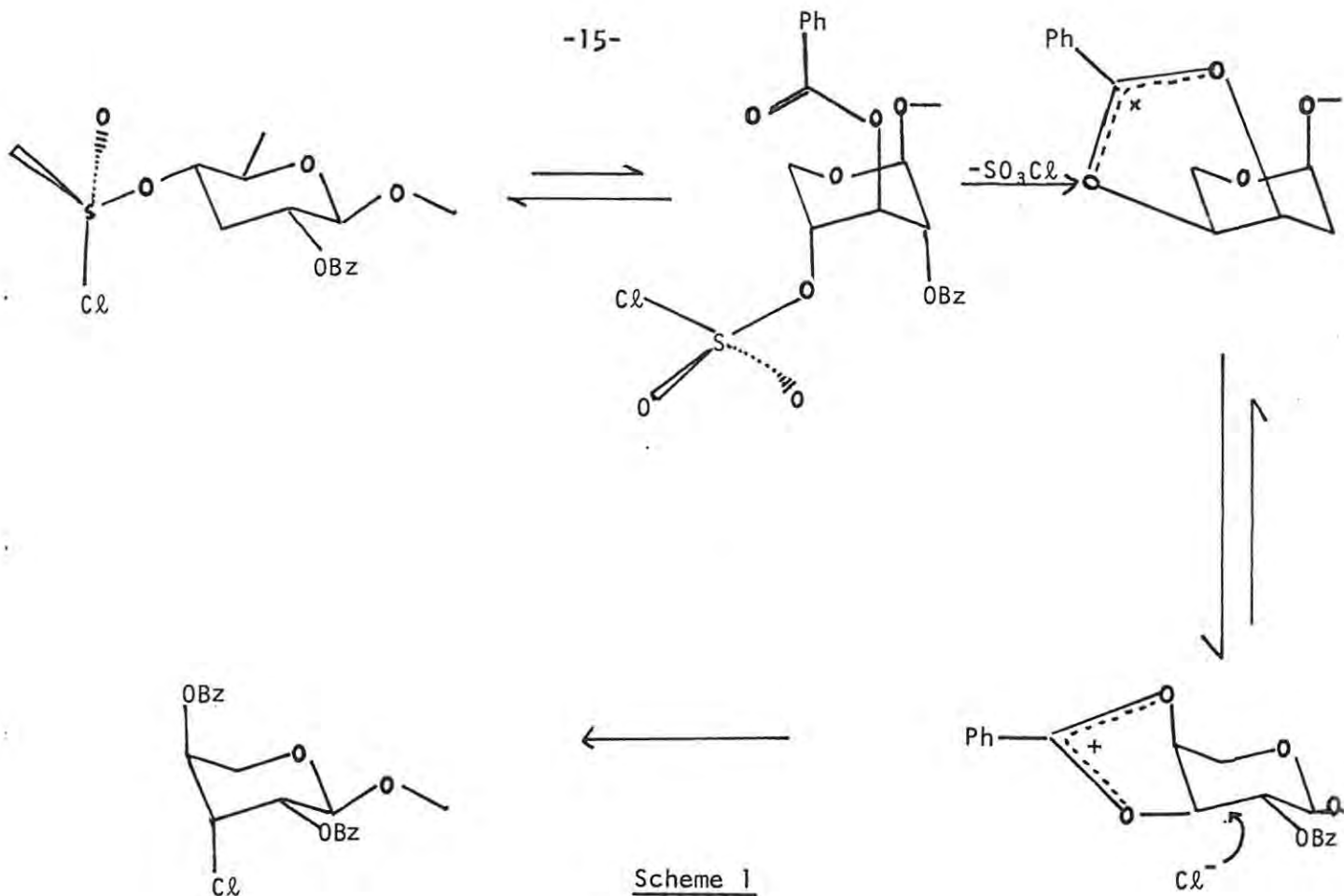
Whereas in the previous report Hough<sup>27</sup> et al., isolated this product after dechlorosulphation followed by column chromatography, the improved reaction procedure<sup>28</sup> led to the direct isolation of 4,6-dichloro-4,6-dideoxy- $\alpha$ -D-galactopyranosyl-6-chloro-6-deoxy- $\beta$ -D-fructofuranoside 2,3,1',3',4'-pentachlorosulphate (58) in a 50% yield. Dechlorosulphation afforded 4,6-dichloro-4,6-dideoxy- $\alpha$ -D-galactopyranosyl-6-chloro-6-deoxy- $\beta$ -D-fructofuranoside (59).

The introduction<sup>29</sup> of chlorine at certain positions of the sucrose molecule has a profound effect on the sweetness of the disaccharide e.g. the 4,6,1',6'-tetrachloro (60) derivative is 200 times sweeter than sucrose.

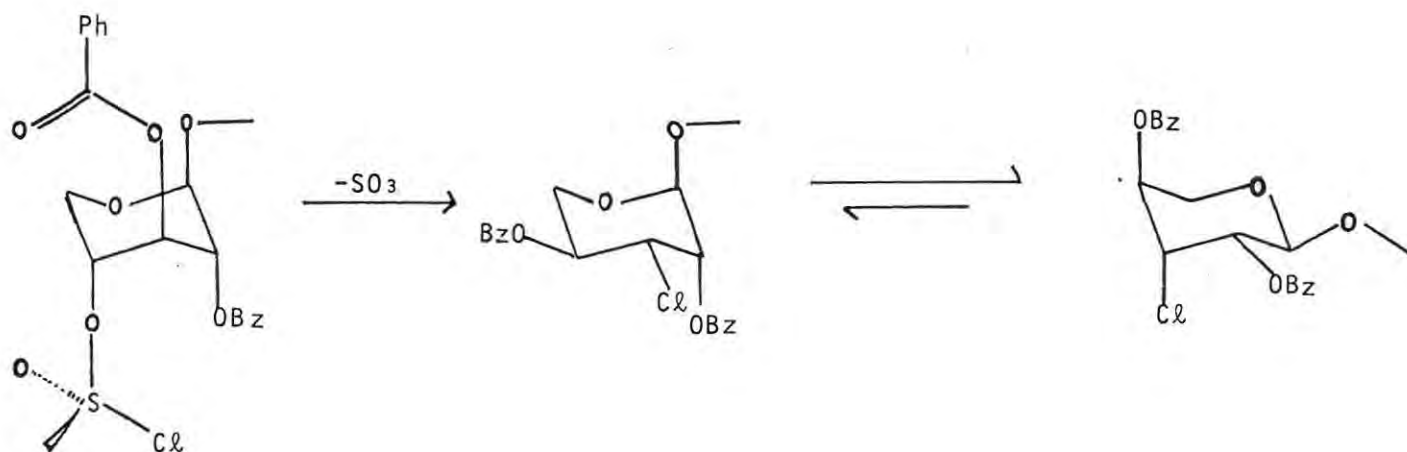
Treatment<sup>30</sup> of benzyl  $\beta$ -cellobioside 2,3,6,2',6'-pentabenzoate (61) with sulphuryl chloride and pyridine at  $-5^\circ$  for 2.5 hours afforded after benzylation benzyl 6'-chloro 6'-deoxy  $\beta$ -cellobioside hexabenzoate (62) while extension of the reaction time afforded the 4',6'-dichloro derivative (50%), benzyl 2,3,6-tri-O-benzoyl-4-O- (2,3-di-O-benzoyl-4,6-dichloro-4,6-dideoxy- $\beta$ -D-galactopyranosyl)  $\beta$ -D-glucofuranoside (63) and the 3',6'-dichloro derivative (4.3%), benzyl 2,3,6-tri-O-benzoyl-4-(2,4-di-O-benzoyl-3,6-dichloro-3,6-dideoxy  $\beta$ -D-gulopyranosyl)- $\beta$ -D-glucofuranoside (64).



The 3',6'-dichloride(64) must arise by neighbouring group participation by the benzoyloxy group at C3' during the loss of the 4-chlorosulphonyloxy group.

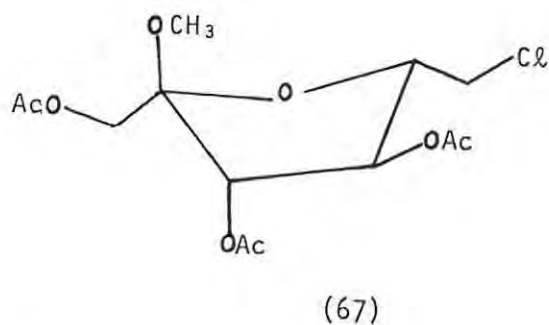
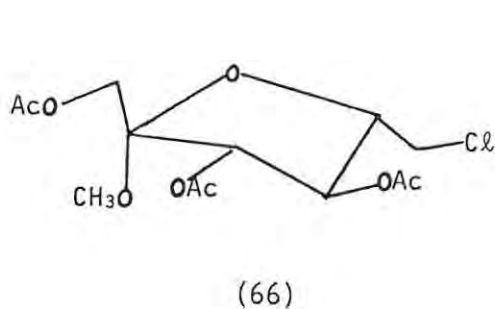
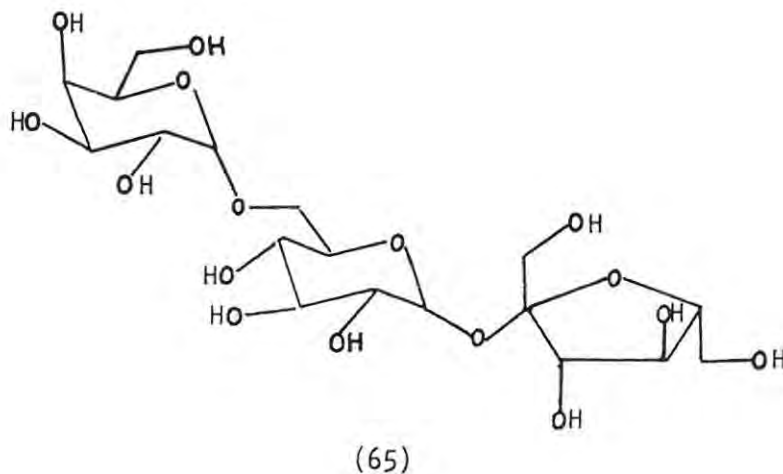


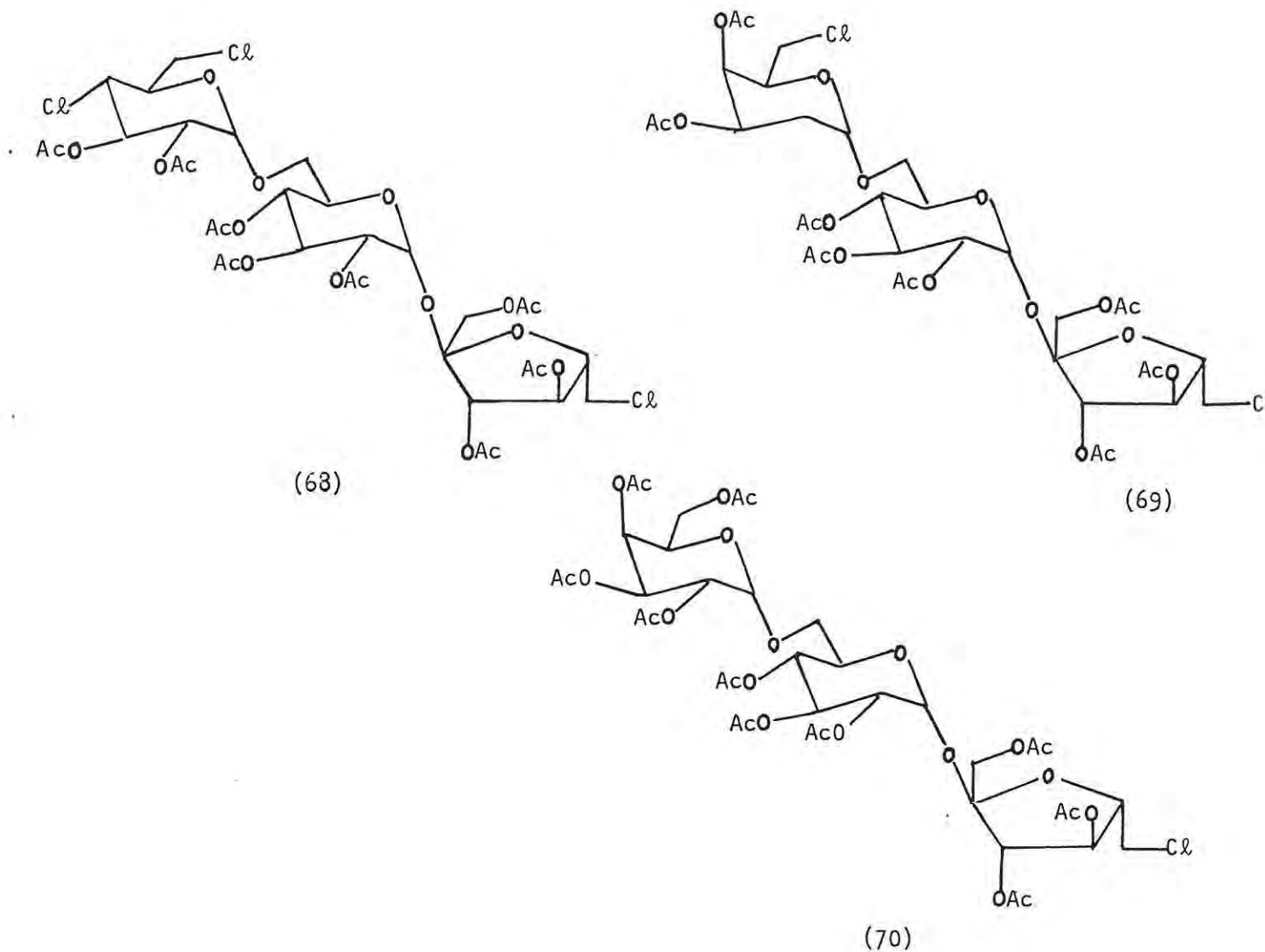
The resulting 3',4'-benzoxonium ion may undergo nucleophilic ring opening by attack of the chloride anion at either C3' or C4' to give respectively the 3',6'-dichloro-gulopyranoside(64) or the 4',6'-dichloro-glucopyranoside. The fact that the 4',6'-dichloro-glucopyranoside was not detected suggests that attack by the chloride anion must take place predominantly at C3' to afford the gulo configuration (Scheme 1). Alternatively it is also



conceivable that the migration of the 3'-benzoyloxy group may be synchronous with the collapse of the chlorosulphonyloxy group and the stereospecific introduction of the chlorine of the chlorosulphonyloxy group (Scheme 2)

Reaction of raffinose<sup>29,31</sup> (65) with sulphurylchloride at -20° for 5 hours yielded after dechlorosulphation and acetylation, one major product, 6'-chloro-6'-deoxy raffinose deca-acetate (70) (43%), and four minor products, methyl 1,3,4-tri-O-acetyl-6-chloro-6-deoxy-β-D-fructofuranoside (66) (6%), methyl 1,3,4-tri-O-acetyl-6-chloro-6-deoxy-α-D-fructofuranoside (67) (5%), the 6,4'',6''-trichloro derivative (68) (10%) and the 6,6''-dichloro derivative (69) (7%).

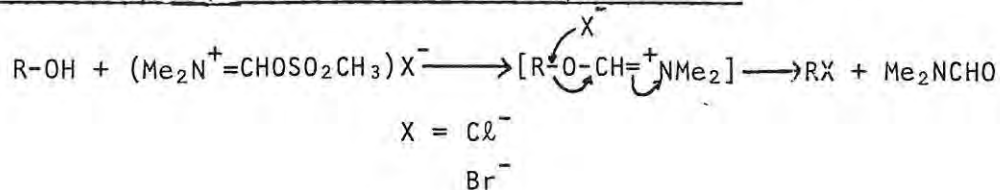




Increasing the reaction time from 5 to 7 hours resulted in an increase to 20% and 13% respectively of compounds (69) and (68). A further extension of the reaction time to 18 hours led to the isolation of the methyl fructofuranosides (66) and (67) in yields of 27% and 24%. The formation of methyl fructofuranosides may be attributed to the cleavage of the glucose-fructose glycosidic bond during chlorination to yield fructofuranosyl chloride which on dechlorosulphation affords the methyl fructofuranosides.

Jennings<sup>32</sup> et al., previously reported that dechlorosulphation of  $\alpha$ -D-xylopyranosyl chloride with methanol yielded the methyl xylopyranosides.

1.1.2 Methanesulphonyl halides/N,N-dimethylformamide



Nucleophilic attack by R-OH (alcohol) on the iminium salt,  $(Me_2N^+=CHOSO_2CH_3)X^-$  derived from mesyl halide - N,N-dimethylformamide occurs to give an intermediate,  $Me_2N^+=CHOR$  which is attacked by chloride/bromide. The rate limiting step in the chlorination/bromination is the formation of the initial iminium salt while the rate of nucleophilic displacement does not affect the overall rate of reaction. Reaction proceeds with the inversion of configuration at chiral centres and only occurs at secondary positions where steric and electronic effects are favourable<sup>16</sup> for an  $S_N2$  reaction.

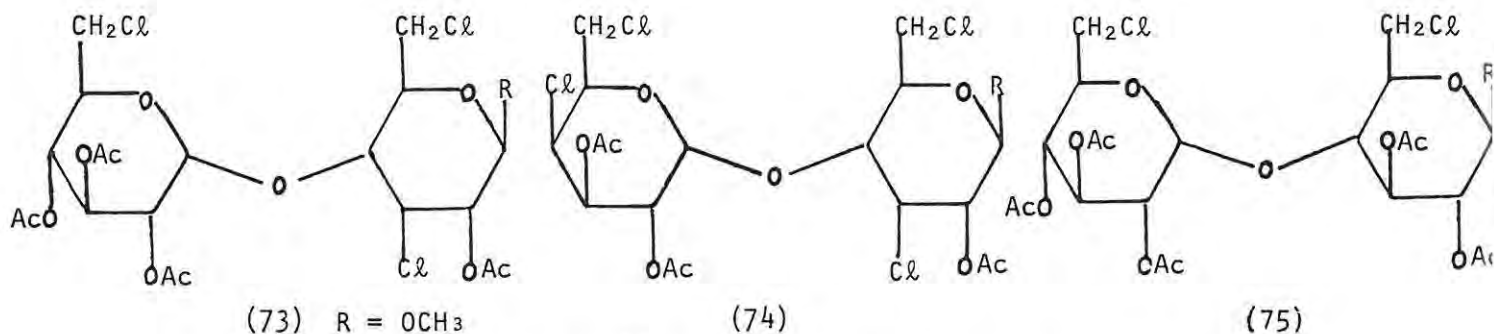
Methanesulphonyl chloride/N,N-dimethylformamide which was previously described as a selective reagent for the replacement of primary hydroxyl groups, effects extensive but selective chlorination of secondary positions especially in disaccharides.

Methyl  $\beta$ -D-glucopyranoside<sup>33</sup> on reaction with the mesyl chloride/N,N-dimethylformamide reagent at 95° for 90 h, yielded, in addition to 6-chloro-6-deoxy- $\beta$ -D-glucopyranoside (15%), the 4,6- and the 3,6-dichlorides in a ratio of 1 : 2 (15 : 30%). Szarek<sup>17</sup> et al., on reinvestigating the reaction of methyl  $\beta$ -D-glucopyranoside with sulphuryl chloride, reported that the 3,6- and 4,6-dichlorides were produced in yields of 50% and 23% respectively. The advantage of the mesyl chloride/N,N-dimethylformamide reagent over the sulphuryl chloride reagent is that the former allows the isolation of intermediate, chlorinated species at higher temperatures.

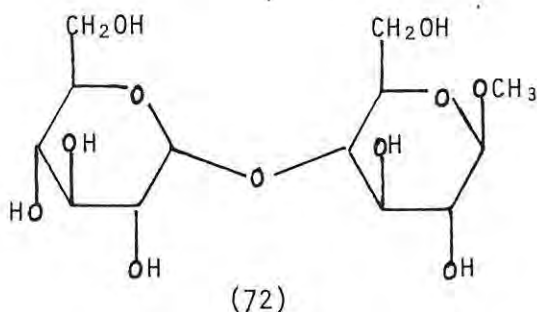
Thus reaction of methyl  $\alpha$ -D-glucopyranoside with mesyl chloride

yielded the 6-chloride (44%) and another compound which, after dechlorosuphation and acetylation proved to be methyl 2,3-di-O-acetyl-4,6-dichloro-4,6-dideoxy- $\alpha$ -D-galactopyranoside (8%) (71).

Treatment of anhydrous methyl  $\beta$ -maltoside (72) with mesyl chloride/N,N-dimethylformamide at 65° for 8 days and subsequent acetylation afforded methyl 2-O-acetyl-3,6-dichloro-3,6-dideoxy-4-O-(2,3,4-tri-O-acetyl-6-chloro-6-deoxy- $\alpha$ -D-glucopyranosyl)- $\beta$ -D-allopyranoside (73) (46%), methyl 2-O-acetyl-3,6-dichloro-3,6-dideoxy-4-O-(2,3-di-O-acetyl-4,6-dichloro-4,6-dideoxy- $\alpha$ -D-galactopyranosyl)- $\beta$ -D-allopyranoside (74) (8%) and methyl 2,3-di-O-acetyl-6-chloro-6-deoxy-4-O-(2,3,4-tri-O-acetyl-6-chloro-6-deoxy- $\alpha$ -D-glucopyranosyl)- $\beta$ -D-glucopyranoside (75) (7-25%).



In  $\beta$ -D-maltoside (72) Edwards<sup>33</sup> *et al.*, observed reaction at C3 but not at



C3' which is hindered by the axial Cl substituent. Subsequent chlorination was observed at C4' although the rate of reaction was much less. Since acylation studies have shown that C3 is the most sterically hindered

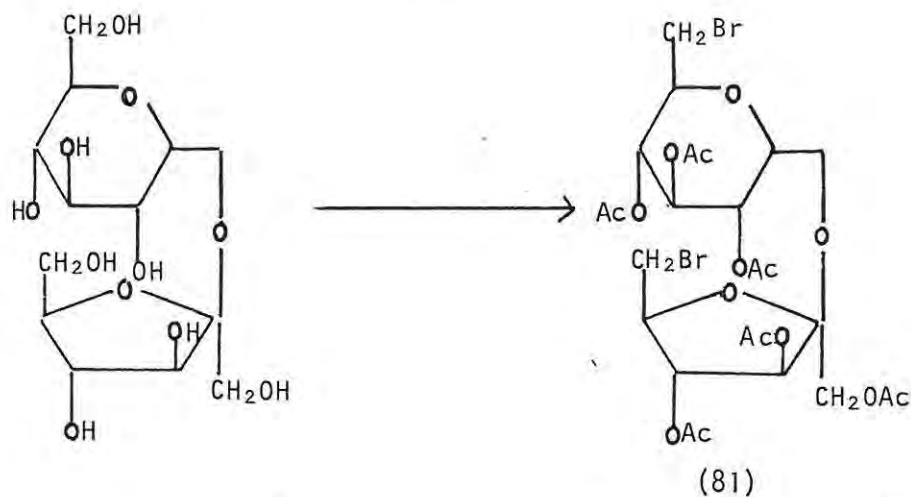
position in the maltoside it is therefore unexpected that an  $S_N2$  transition state should form more readily at this position than at C4'. It has also been noted that nucleophilic displacements occur more readily at C6 than at C6' although the latter is more easily esterified and etherified. This suggests that steric effects, which are very important in acylation reactions, are not so in displacement reactions which are more sensitive to polar effects.

Reaction of benzyl  $\beta$ -cellobioside (76) with the mesyl chloride/N,N-dimethylformamide reagent at 70° for 7 days, afforded after acetylation, benzyl 2,3-di-O-acetyl-6-chloro-6-deoxy-4-O-(2,3-di-O-acetyl-4,6-dichloro-4,6-dideoxy- $\beta$ -D-galactopyranosyl)- $\beta$ -D-glucopyranoside (77) and benzyl 2,3-di-O-acetyl-6-chloro-6-deoxy-4-O-(2,4-di-O-acetyl-3,6-dichloro-3,6-dideoxy- $\beta$ -D-allopyranosyl)- $\beta$ -D-glucopyranoside (78) in a combined yield of 16% and benzyl 2,3-di-O-acetyl-6-chloro-6-deoxy-4-O-(2,3,4-tri-O-acetyl-6-chloro-6-deoxy- $\beta$ -D-glucopyranosyl)- $\beta$ -D-glucopyranoside (25%). Extension of the reaction time to 11 days afforded benzyl 2-O-acetyl-3,6-dichloro-3,6-dideoxy-4-O-(2,4-di-O-acetyl-3,6-dichloro-3,6-dideoxy- $\beta$ -D-allopyranosyl)- $\beta$ -D-allopyranoside (79) (40%), benzyl 2-O-acetyl-3,6-dichloro-3,6-dideoxy-4-O-(2,3-di-O-acetyl-4,6-dichloro-4,6-dideoxy- $\beta$ -D-galactopyranosyl)- $\beta$ -D-allopyranoside (80) (1.4%) and other minor products.

When benzyl  $\beta$ -cellobioside was treated in the usual way with sulphuryl chloride<sup>34</sup> and pyridine, a mixture of the two tetrachlorides (79) and (80) and the two trichlorides (77) and (78) was formed although the overall recovery of the products was only 20%. Replacements in compound (76) are predictable at C3, C3', C4', C6 and C6' while replacement at C3' and C4' will impede further reaction because of the vicinal axial effect. Nevertheless, replacement seems more favourable at C3' and C4' than at C3.

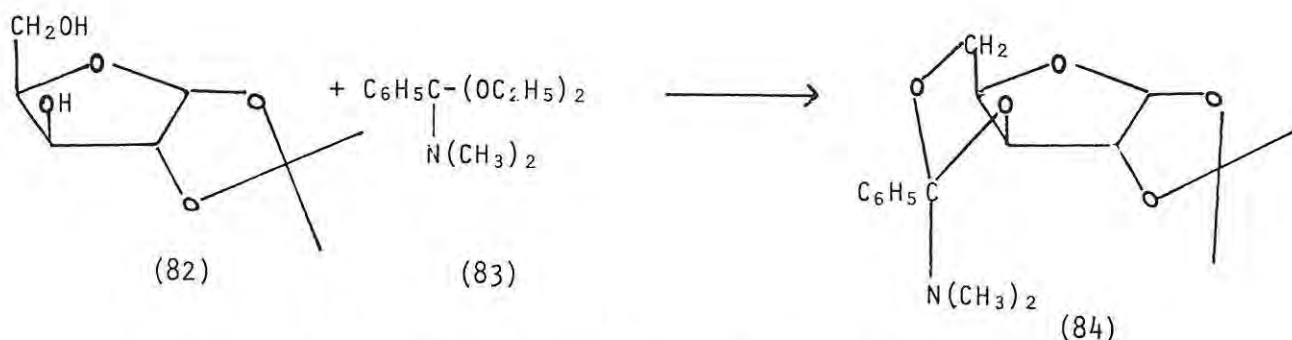
Methanesulphonyl bromide/N,N-dimethylformamide

Treatment of sucrose<sup>35</sup> with methanesulphonyl bromide in N,N-dimethylformamide at -50° for 1.5 hours, then at room temperature for 24 hours and finally at 70° for 4 hours yielded, after work-up and acetylation, the dibromo hexa-acetate (81) in a 24% yield.



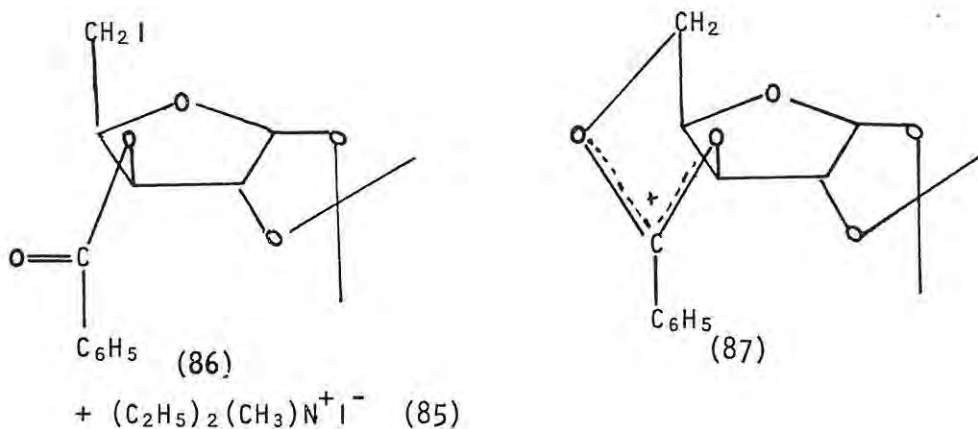
1.1.3 Methyl iodide (or ethyl iodide)

Culberton<sup>36</sup> found that 1,2-O-isopropylidene- $\alpha$ -D-xylofuranose (82) reacted on standing with a dichloromethane solution of N,N-dimethylbenzamide diethyl acetal (83) to give 3,5-O-[ $\alpha$ -(dimethylamino)benzylidene]-1,2-O-isopropylidene- $\alpha$ -D-xylofuranose (84).

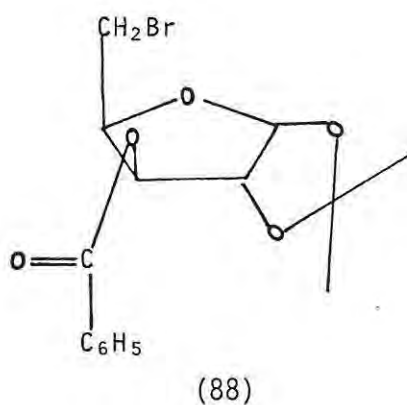


When compound (84) was refluxed with methyl or ethyl iodide a quaternary ammonium iodide salt (85) precipitated while the filtrate yielded a colourless syrup which proved to be 3-O-benzoyl-5-deoxy

- 5-iodo-1,2-0-isopropylidene- $\alpha$ -D-xylofuranose (86).



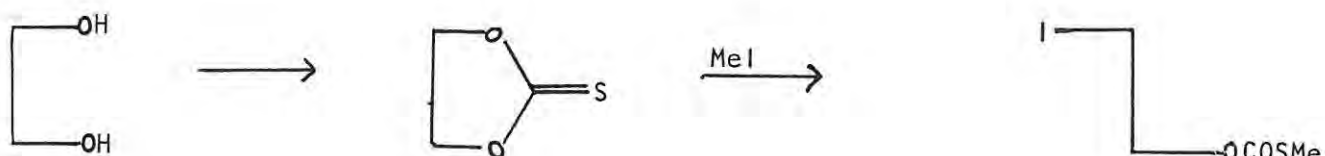
This reaction is thought to proceed via a nucleophilic attack by the halide ion on an acyloxonium ion intermediate (87). Preparation of 3-0-benzoyl-5-bromo 5-deoxy-1,2-0-isopropylidene- $\alpha$ -D-xylofuranose (88) was carried out by refluxing compound (84) in an n-propyl bromide solution or in a chloroform solution containing cyanogen bromide.



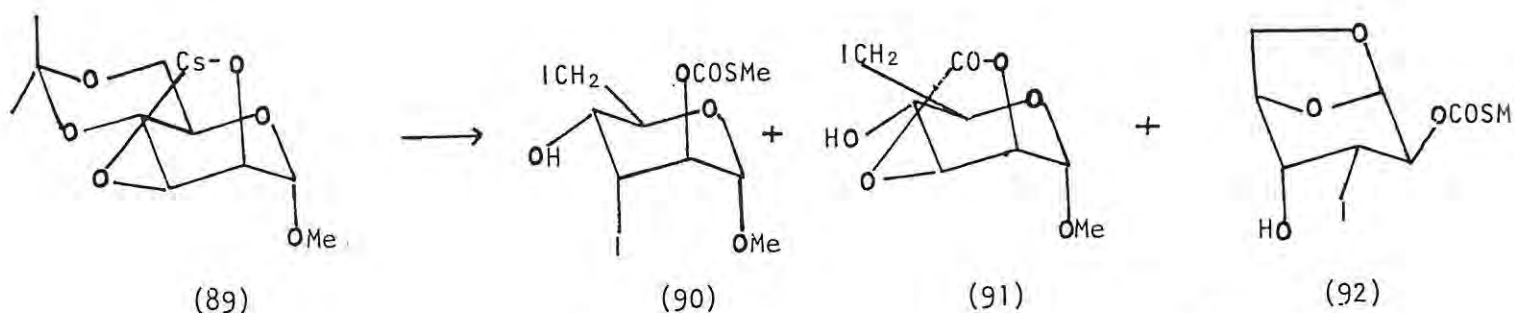
The reaction is possible with any reagent which causes elimination of the dimethylamino moiety and supplies a suitable nucleophile to open the resulting acyloxonium ion intermediate.

In an earlier work, Stick<sup>37</sup> et al., reported the reaction of cyclic

thiocarbonates of 1,2-diols with methyl iodide to form iodo thiocarbonates.



Patroni<sup>38</sup> et al., extended this work to related diols in the carbohydrate field, the compound of choice being the 2,3-0-thiocarbonyl derivative of a protected methyl  $\alpha$ -D-mannopyranoside. Thus treatment of 4,6-0-isopropylidene-2,3-0-thiocarbonyl- $\alpha$ -D-mannoside (89) with methyl iodide at 80° overnight afforded methyl 3,6-dideoxy-3,6-di-iodo-2-0-(methylthio)carbonyl- $\alpha$ -D-altropyranoside (29%) (90), methyl 2,3-0-carbonyl-6-deoxy-6-iodo- $\alpha$ -D-mannopyranoside (14%) (91) and 1,6-anhydro-3-deoxy-3-iodo-2-0-(methylthio)carbonyl- $\beta$ -D-altropyranose (1%) (92).

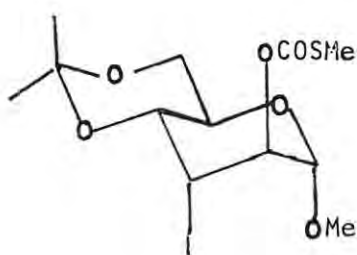


The absence of the 4,6-0-isopropylidene group in all three products indicates the presence of acid in the reaction mixture. Both potassium carbonate and the hindered base, ethyldi-isopropylamine (Hunig's base) were unable to act as an "acid mop" in the presence of methyl iodide.

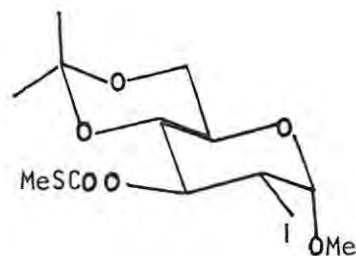
Patroni attempted to maintain neutrality in the presence of methyl iodide by using propylene oxide. However, reaction of compound (89)

with methyl iodide in the presence of propylene oxide yielded methyl 2,3-O-carbonyl-4,6-O-isopropylidene- $\alpha$ -D-mannoside (93) which seemed to suggest that the formation of the iodo thiocarbonate had been suppressed in favour of the thiocarbonate to carbonate conversion.

Reaction of compound (89) with methyl iodide in the presence of the hindered base, N,N,N,N-tetramethylnaphthalene-1,8-diamine (proton sponge), afforded methyl 3-deoxy 3-iodo-4,6-O-isopropylidene-2-O-(methylthio)-carbonyl- $\alpha$ -D-altroside (94) and methyl 2-deoxy-2-iodo-4,6-O-isopropylidene 3-O-(methylthio)-carbonyl- $\alpha$ -D-glucoside (95) in the combined yield of 82%.



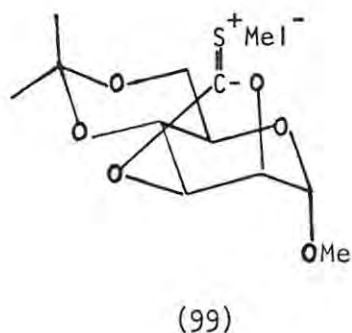
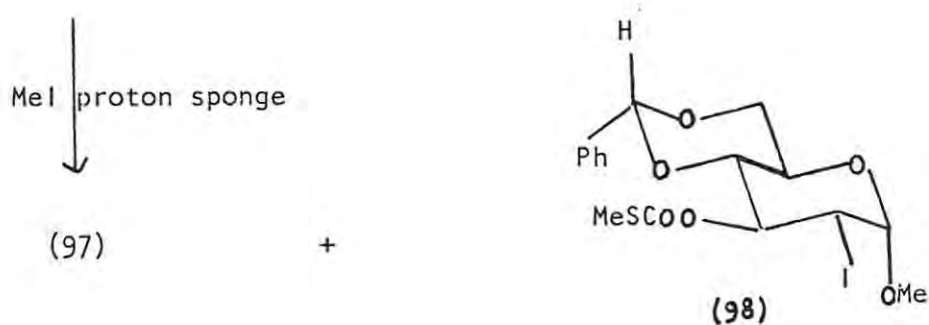
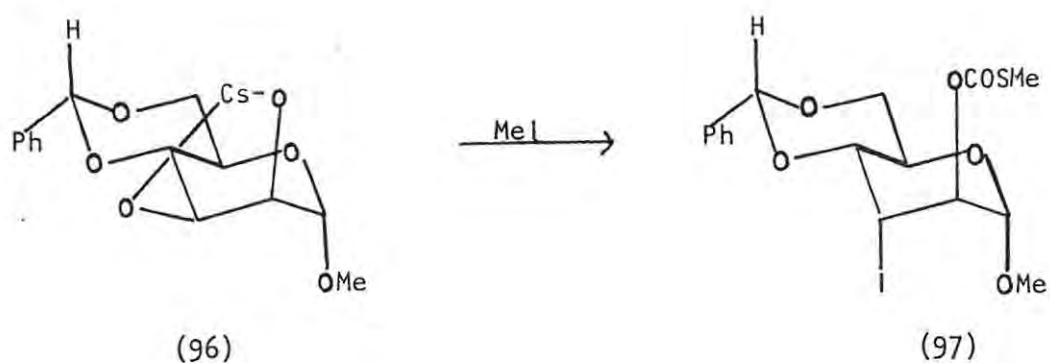
(94)



(95)

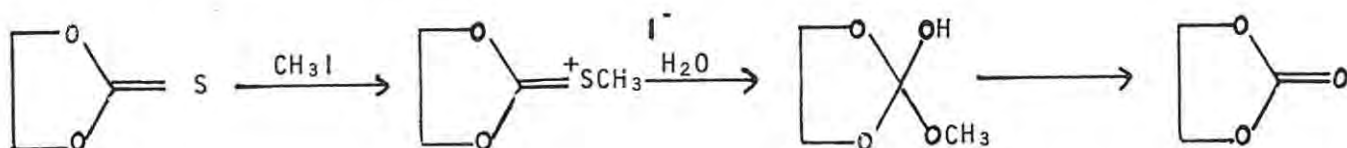
This work was extended to compounds containing a less acid labile 4,6-O-benzylidene group e.g. 4,6-O-benzylidene-2,3-O-thiocarbonyl- $\alpha$ -D-mannoside (96). Reaction of compound (96) with methyl iodide at 80° overnight gave methyl 4,6-benzylidene-3-deoxy-3-iodo 2-O-(methylthio)carbonyl- $\alpha$ -D-altroside (97) (38%) while in the presence of the 'proton sponge', the iodo thiocarbonate (97) and the isomeric methyl 4,6-benzylidene-2-deoxy-2-iodo-3-O-(methylthio)carbonyl- $\alpha$ -D-glucoside (98) were formed in a total yield of 77%, the ratio being 10:1.

The reactions of the thiocarbonates (89) and (96) with methyl iodide/proton sponge to give their respective mixtures of iodo thiocarbonates, may be explained by the intermediacy of the salt (99).

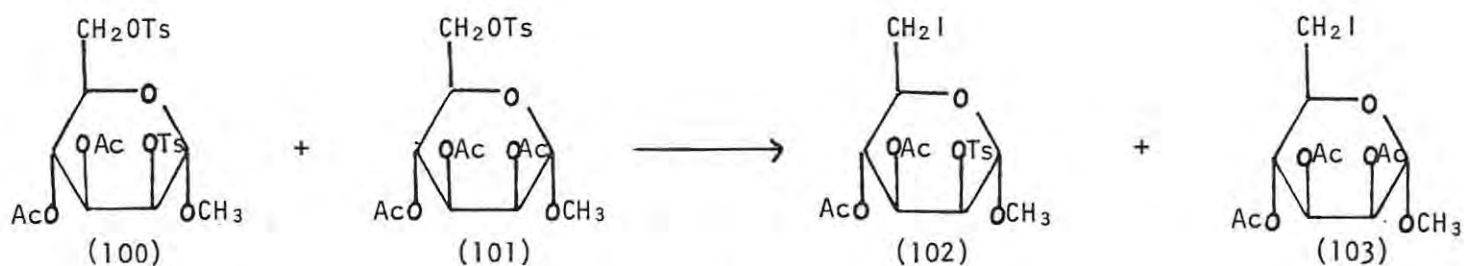


The salt reacts internally to form compounds (94) and (95) showing an inversion of configuration of the carbon bearing the iodine atom. Methyl iodide does not appear to be thermally unstable but an  $\alpha$ -elimination process could generate,  $\text{HI}(\text{CH}_3\text{I} \rightarrow \text{HI} + \text{:CH}_2)$ . The conversion of compound (89) into (90), (91) and (92), relies on the hydrolysis of

methyl iodide for its supply of hydrogen iodide. Compound (90) arises from the combination of the reactions of methyl iodide and hydrogen iodide. Compound (91) requires hydrogen iodide for the introduction of the 6-iodo group. In the anhydro sugar (92) a conformational conversion ( ${}^4C_1-{}^1C_4$ ) is required with a nucleophilic attack by  $\beta$ -O 1 onto the electrophilic C6. The thiocarbonate to carbonate conversion is probably aided by methyl iodide in the following way.



#### 1.1.4 Sodium iodide<sup>39</sup>



Reactions of a mixture of 3,4-di-O-acetyl-2,6-di-O-tosyl methyl  $\alpha$ -D-mannopyranoside (100) and 2,3,4-tri-O-acetyl-6-tosyl methyl  $\alpha$ -D-mannopyranoside (101) with sodium iodide heated under reflux in butanone yielded methyl 2,3,4-tri-O-acetyl-6-iodo-6-deoxy- $\alpha$ -D-mannopyranoside (103) and methyl 3,4-di-O-acetyl-6-iodo-6-deoxy-2-O-p-tolylsulphonyl- $\alpha$ -D-mannopyranoside (102) as a minor product which was easily separated because of its insolubility in ether.

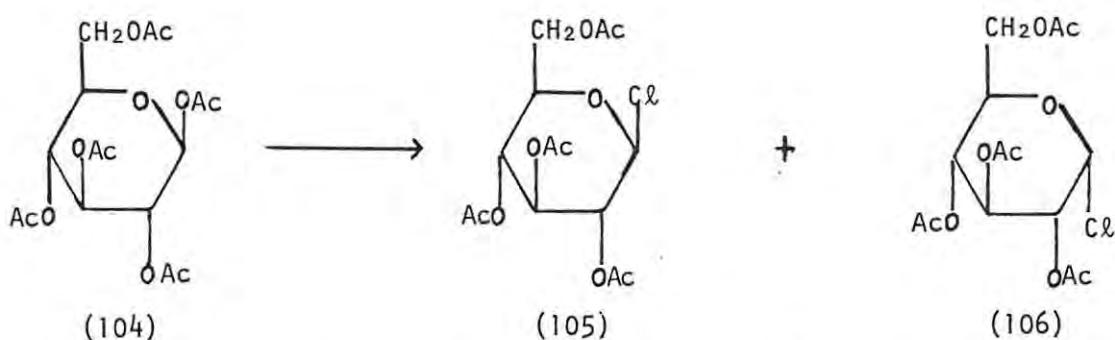
Under these conditions a displacement of primary 6-O-tosyl groups occurs readily but secondary-O-tosyl groups particularly at C2 are inert.

#### 1.1.5 Aluminium chloride, titanium tetrachloride and lithium chloride

Three potential methods of synthesis of hepta-O-acetyl- $\beta$ -cellobiosyl

and lactosyl chlorides were investigated by Dick and Weisleder<sup>40</sup>. These involved the action of aluminium chloride and titanium tetrachloride on octa-0-acetyl- $\beta$ -cellobiose and lactose and thirdly the action of lithium chloride on solutions of hepta-0-acetyl- $\alpha$ -cellobiosyl and lactosyl bromides in hexamethylphosphoramide.

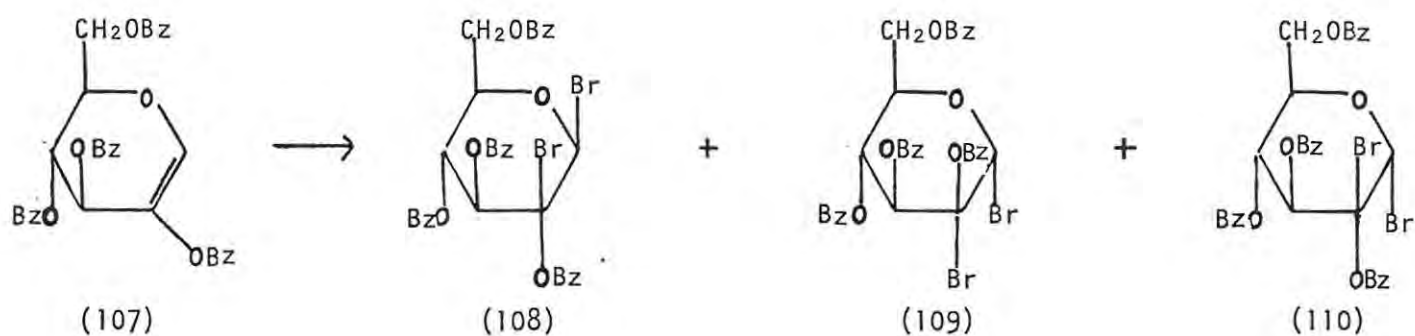
The reaction of 1,2-trans-0-acetyl glucose (104) with either aluminium chloride or titanium tetrachloride produces a mixture of the 1,2-trans-(105) and the 1,2-cis-0-acetyl glycosyl chloride (106).



The cis isomer undergoes displacement with configurational inversion at C1 far more rapidly than does the trans isomer. The rate at which the trans isomer forms are inverted to produce cis isomers, is sufficiently rapid to produce a mixture of isomers unless conditions are adjusted to minimise the length of time newly formed trans products are exposed to secondary chloride ion displacements, or the displacing agent is converted into a product incapable of further interactions. The displacing agent of choice is lithium chloride in hexamethylphosphoramide.

#### 1.1.6 Titanium tetrabromide<sup>41</sup>

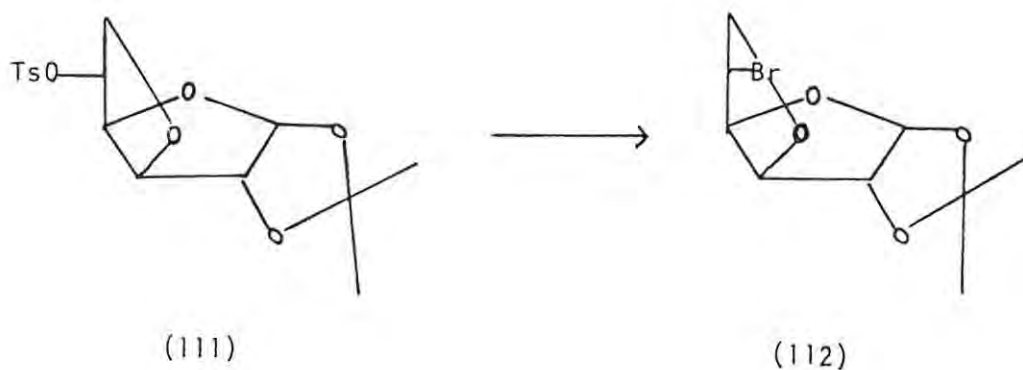
Bromination of 1,5-anhydro-2,3,4,6-tetra-0-benzoyl-D-arabino-hex-1-enitol (107) by reaction with excess bromine in tetrachloromethane yielded a 6:3:1 mixture of the  $\beta$ -D-gluco (108), the  $\alpha$ -D-manno (109) and the  $\alpha$ -D-gluco (110) dibromides.



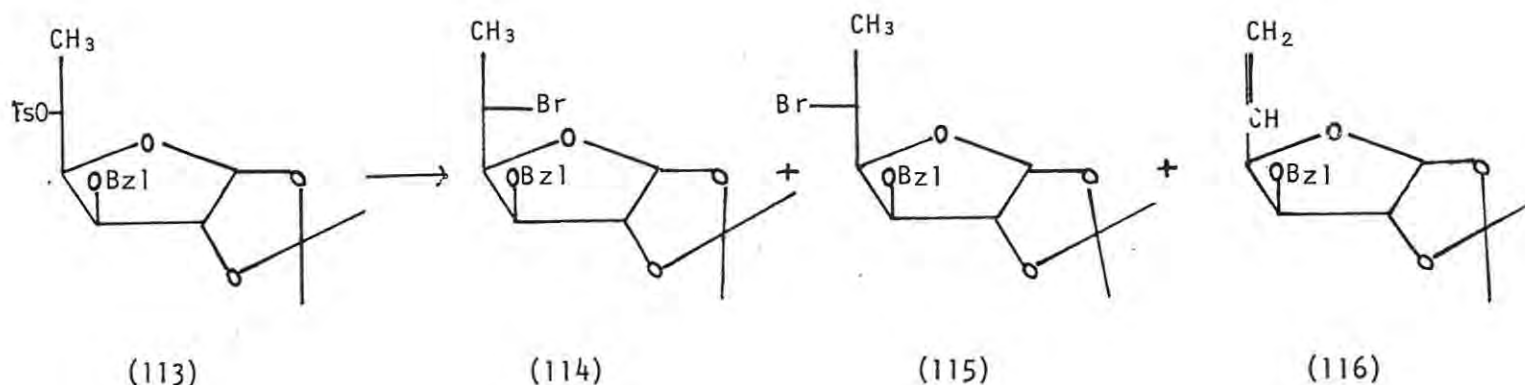
Compound (108) was converted to compound (110) by boiling in tetrachloromethane containing titanium tetrabromide while (109) and (110) remained unchanged when exposed to the same conditions. Facile anomerization of  $\beta$ - $\alpha$  suggested that compound (110) was formed via compound (108) rather than by a trans addition to compound (107). However, on exposure of compound (108) to conditions of bromination no  $\alpha$ -anomer was formed. Even though compound (107) undergoes mainly cis addition of bromine in which attack from above the plane of the pyranose ring is favoured 2:1, ~ 10% of trans addition does occur which affords the  $\alpha$ -isomer (108).

#### 1.1.7 Lithium bromide in N,N-dimethylformamide<sup>42</sup>

Reaction of 3,6-anhydro-1,2-O-isopropylidene-5-O-p-tolylsulphonyl- $\alpha$ -D-glucofuranose (111) with lithium bromide in N,N-dimethylformamide at 130° for 4 hours yielded 3,6-anhydro-5-bromo-5-deoxy-1,2-O-isopropylidene- $\beta$ -L-idofuranose (112) in a 71% yield.

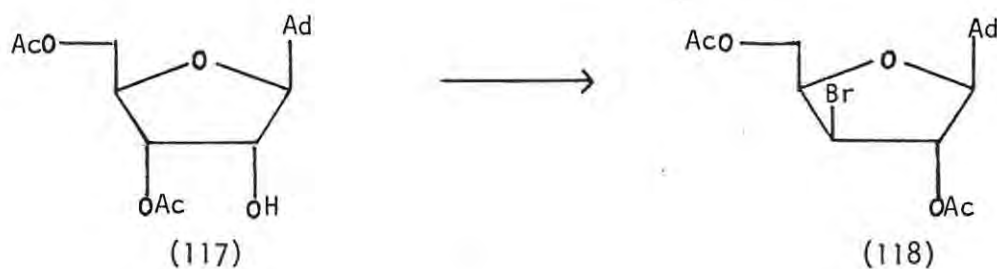


A solution of 3-0-benzyl-6-deoxy-1,2-0-isopropylidene-5-0-p-tolylsulphonyl- $\alpha$ -D-glucofuranose (113) and lithium bromide in N,N-dimethylformamide when heated for 15 hours at 120-130° afforded, after column chromatography, 3-0-benzyl-5-bromo-5,6-dideoxy-1,2-0-isopropylidene- $\beta$ -L-idofuranose (114) (7.8%), 3-0-benzyl-5-bromo-5,6-dideoxy-1,2-0-isopropylidene- $\alpha$ -D-glucofuranose (115) (7.2%) and 3-0-benzyl-5,6-dideoxy-1,2-0-isopropylidene- $\alpha$ -D-xylo-hex-5-enofuranose (116) (2.2%).

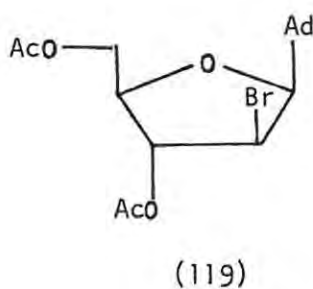


#### 1.1.8 Lithium bromide and phosphorus tribromide<sup>43</sup>

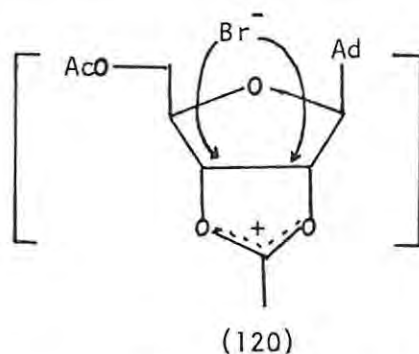
Purine nucleosides containing a 3'-halo 3'-deoxyxylo functionality are versatile intermediates in the preparation of trans  $\beta$ -hydroxy, epoxy, deoxy and unsaturated nucleosides. Reaction of 3',5'-di-0-acetyl adenosine (117) with a large excess of lithium bromide in the presence of boron trifluoride etherate in acetonitrile at room temperature for 24 hours afforded 9-(3-bromo-3-deoxy-2,5-di-0-acetyl- $\beta$ -D-xylofuranosyl) adenine (118) in a 26% yield. This low yield may be attributed to a slowness of the reaction and extensive cleavage of the glycosyl bond.



The yield was increased to 55% when a 1.1 mol eq. of phosphorus tribromide was used instead of lithium bromide. 9-(2-Bromo-2-deoxy-3,5-di-O-acetyl- $\beta$ -D-arabinofuranosyl)adenine occurred as a minor product (119).



The formation of compounds (118) and (119) suggests that the reaction did not proceed via a direct replacement of the hydroxyl group by phosphorus tribromide but via a nucleophilic attack by bromide ion on an acetoxonium ion (120) from the  $\beta$ -face of the sugar at either C3' or C2'.



Attempts to prepare compound (118) by treatment of adenosine with acetic anhydride and phosphorus tribromide in the presence of boron

trifluoroetherate in acetonitrile were unsuccessful since the major product formed was 2',3',5'-tri-0-acetyl adenosine.

#### 1.1.9 Acetyl halides:

Acetyl chloride:<sup>44</sup> Synthesis of 2,2,2-trichloroethyl-2-acetamido-3,6-di-0-acetyl-2-deoxy- $\beta$ -D-glucopyranoside (121) by McLaren<sup>44</sup> et. al., is an extension of the work by Lemieux<sup>45</sup> et al., involving the synthesis of 2,2,2-trichloroethyl-2-acetamido-4,6-benzylidene-2-deoxy- $\beta$ -D-glucoside.

Conflicting results in the literature on the preparation of 2-acetamido-3,4,6-tri-0-acetyl-2-deoxy- $\alpha$ -D-glycosyl chloride (122) from either 2-acetamido-2-deoxy-D-glucose (123) or its tetra-acetate (124) may be attributed to the purity of the acetyl chloride used.

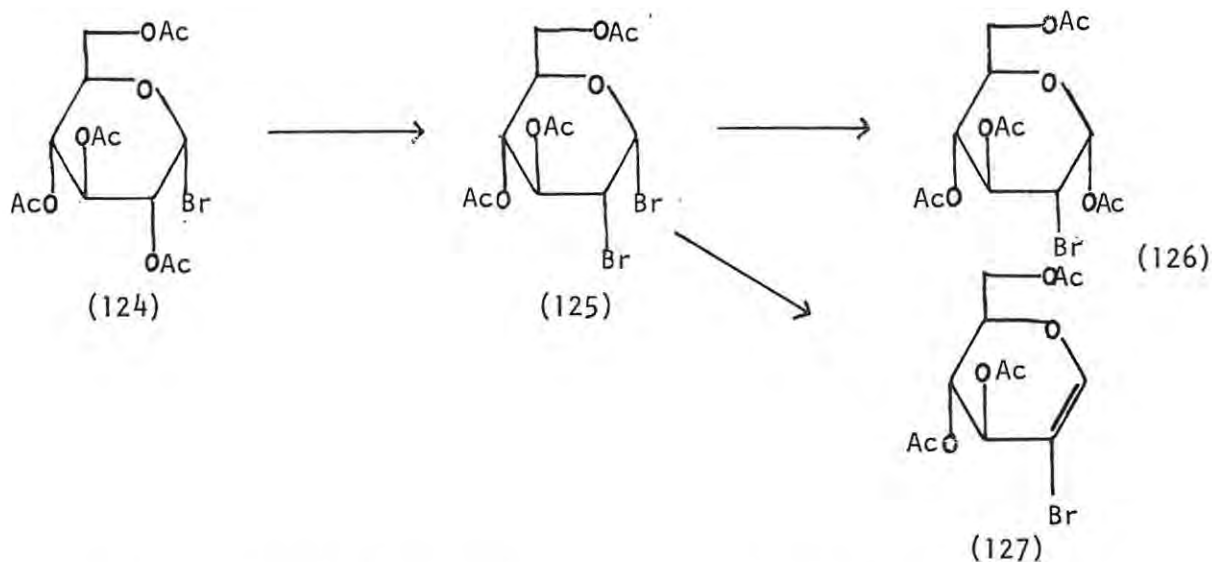
When compound (123) was placed in pure acetyl chloride (distilled and free of hydrogen chloride) no reaction occurred. However, addition of acetic acid after work-up afforded the crystalline compound (122). The success of the acetyl chloride/acetic acid mixture was attributed to the presence of both acetic anhydride and hydrogen chloride and thus  $\text{CH}_3\text{CO}^+$ .

The glycosyl chloride (122) was then transformed into 2,2,2-trichloroethyl-2-acetamido-4,6-0-benzylidene-2-deoxy- $\beta$ -D-glucoside which after sequence acetylation (acetic anhydride/pyridine), acid hydrolysis and selective acetylation with N-acetyl imidazole, afforded the desired aglycone (121), which was required in a programme of research into the synthesis of blood group substances.

#### Acetyl bromide:

Treatment<sup>46</sup> of tetra-0-acetyl- $\alpha$ -D-glucopyranosyl bromide (124) with anhydrous zinc bromide and acetyl bromide afforded tri-0-acetyl-2-bromo-2-deoxy- $\alpha$ -D-glucopyranosyl bromide (125). After 20 hours at room

temperature work-up yielded compound (125) as a major product (28.5%), the  $\alpha$ -1-acetate (126) and the unsaturated compound (127) in a combined yield of 30%.



Attempts to prepare bromodeoxy compounds from acetylated galacto- or mannopyranosyl bromides were unsuccessful while of the pentosyl<sup>47</sup> bromides only the xylopyranosyl bromides gave bromodeoxy derivatives.

Thus only pyranosyl bromides with the substituents at C2, C3 and C4 trans-orientated react with acetyl bromide and zinc bromide. The mechanism for the formation of (125) from (124) is probably the same as that proposed for the reaction of tri-O-acetyl-D-xylopyranosyl bromide with acetyl bromide-zinc bromide and for the reaction of pentosyl<sup>48</sup> bromides with dibromomethyl methyl ether, although this latter reagent is not suitable for the preparation of bromodeoxy hexoses.

#### 1.1.10. Hydrogen bromide

The reaction of per-O-benzyl- $\alpha$ -D-glucopyranosyl bromide with a suitably protected aglycone in the presence of bromide ion which resulted

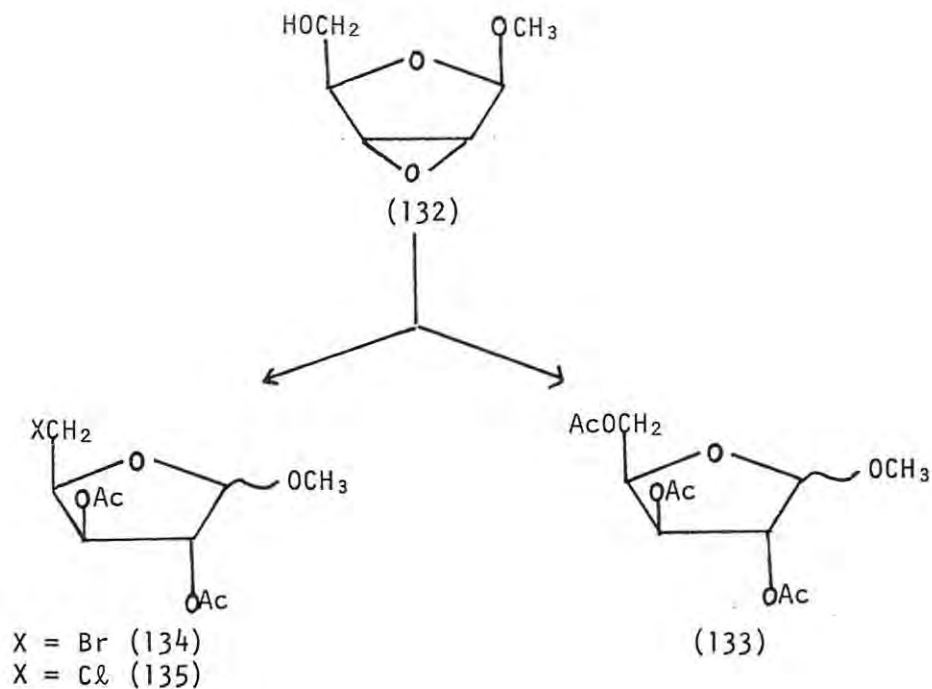
in the synthesis of a new disaccharide prompted James<sup>49</sup> and Stick to investigate methods for the synthesis of tetra-0-benzyl- $\alpha$ -D-galactopyranosyl bromide (128) and tri-0-benzyl- $\alpha$ -L-fucopyranosyl bromide (129). The preparation of the corresponding per-0-benzyl glucopyranoses, which are easily converted into an anomeric mixture of p-nitrobenzoates, was necessary in both cases. Thus reaction of an anomeric mixture at tetra-0-benzyl-1-0-p-nitrobenzoyl-D-galactopyranoses with hydrogen bromide/dichloromethane yielded tetra-0-benzyl-D-galactopyranosyl bromide as an unstable oil.

Similarly (129) was synthesised from tri-0-benzyl-L-fucopyranose via tri-0-benzyl-1-0-p-nitrobenzoyl- $\beta$ -L-fucopyranose.

Pentofuranosyl<sup>50</sup> halides are valuable, synthetic intermediates for the preparation of nucleosides and nucleoside analogues. Preparation of the pentofuranosyl halide, tri-0-(p-nitrobenzoyl)- $\beta$ -D-ribofuranosyl bromide (130) was achieved by reaction of methyl tri-0-(p-nitrobenzoyl)- $\beta$ -D-ribofuranoside with hydrogen bromide/acetic acid, while reaction of methyl tri-0-(p-nitrobenzoyl)- $\beta$ -D-xylofuranoside with hydrogen bromide/dichloromethane, afforded tri-0-(p-nitrobenzoyl)-D-xylofuranosyl bromide (131) which was the first crystalline xylofuranosyl halide.

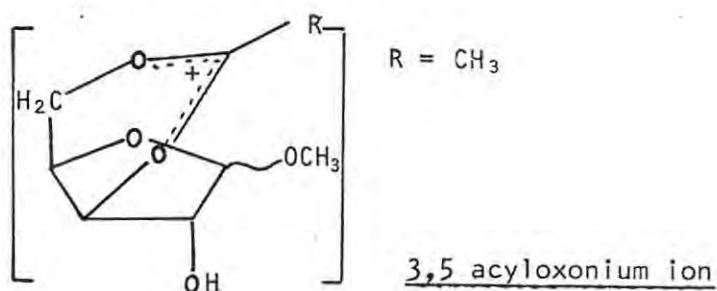
The formation<sup>51</sup> of the 5-bromo/5-chloro 5-deoxy derivatives on reaction of 2,3-anhydro- $\beta$ -D-ribofuranoside (132) with hydrogen bromide/hydrogen chloride and acetic acid-acetic anhydride occurs through the intermediacy of a 3,5 acyloxonium ion. Similar conversions were observed when reagents such as acetyl chloride, acetyl bromide and lithium chloride were used.

Both methyl 2,3-di-0-acetyl-5-bromo-5-deoxy- $\alpha/\beta$ -D-xylofuranoside (134) and methyl 2,3-di-0-acetyl-5-chloro-5-deoxy- $\alpha/\beta$ -D-xylofuranoside



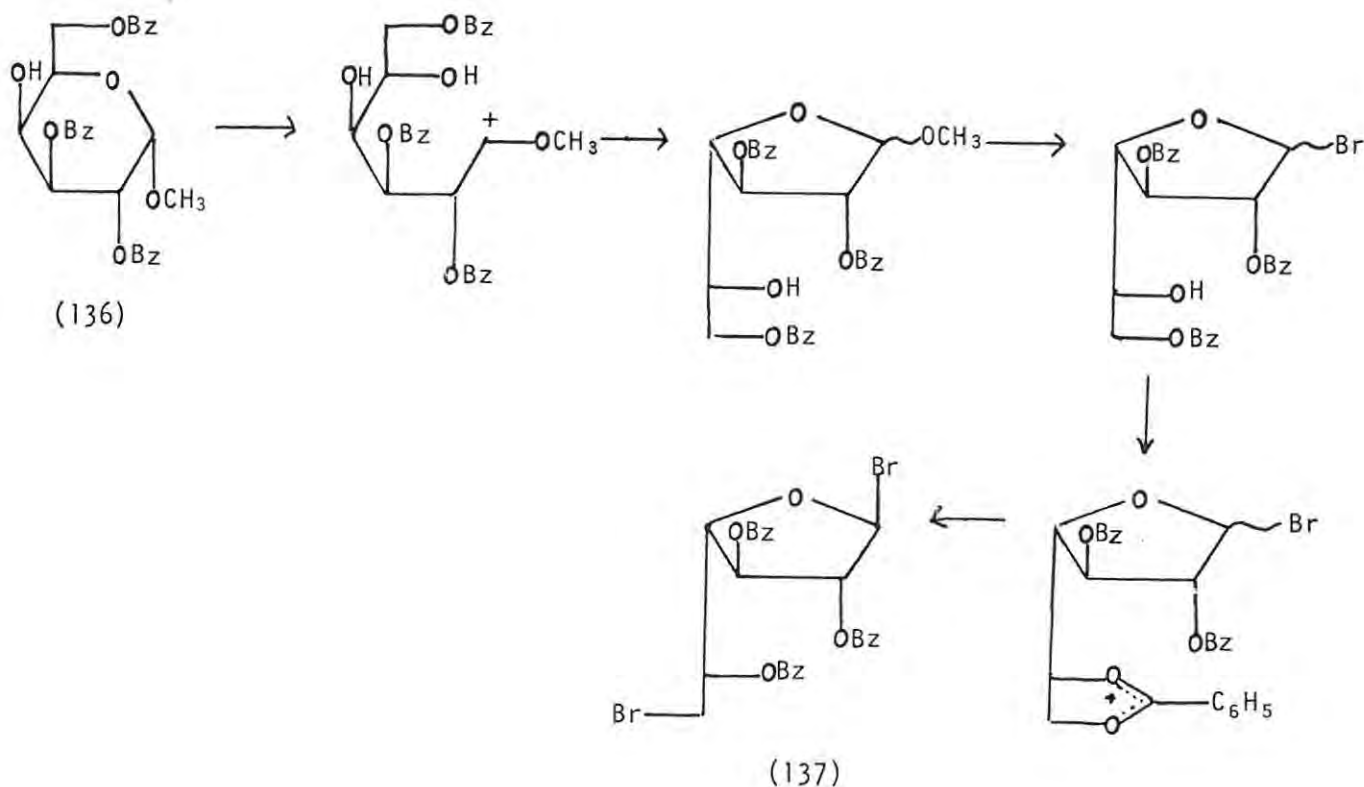
(135) must have been formed by neighbouring group participation of the 5-substituent in the opening of the epoxide ring. All these compounds were isolated as the anomeric mixtures with the  $\beta$ -isomers predominating. Since the starting material contained no  $\alpha$ -isomer, anomerization must occur under these reaction conditions. The ratio of (134)/(135):(133) was partially dependent upon the proportion of acetic acid. Lowering the initial concentration of acetic acid decreased the amount of compound (133) formed. Substitution of acetyl bromide for hydrogen bromide led to the exclusive isolation of compound (134). This, however, did not occur with the chloro derivative as the use of acetyl chloride did not substantially increase the amount of compound (135) formed. This may be attributed to the relative nucleophilicity of the halide ion in

relation to the acetate ion.

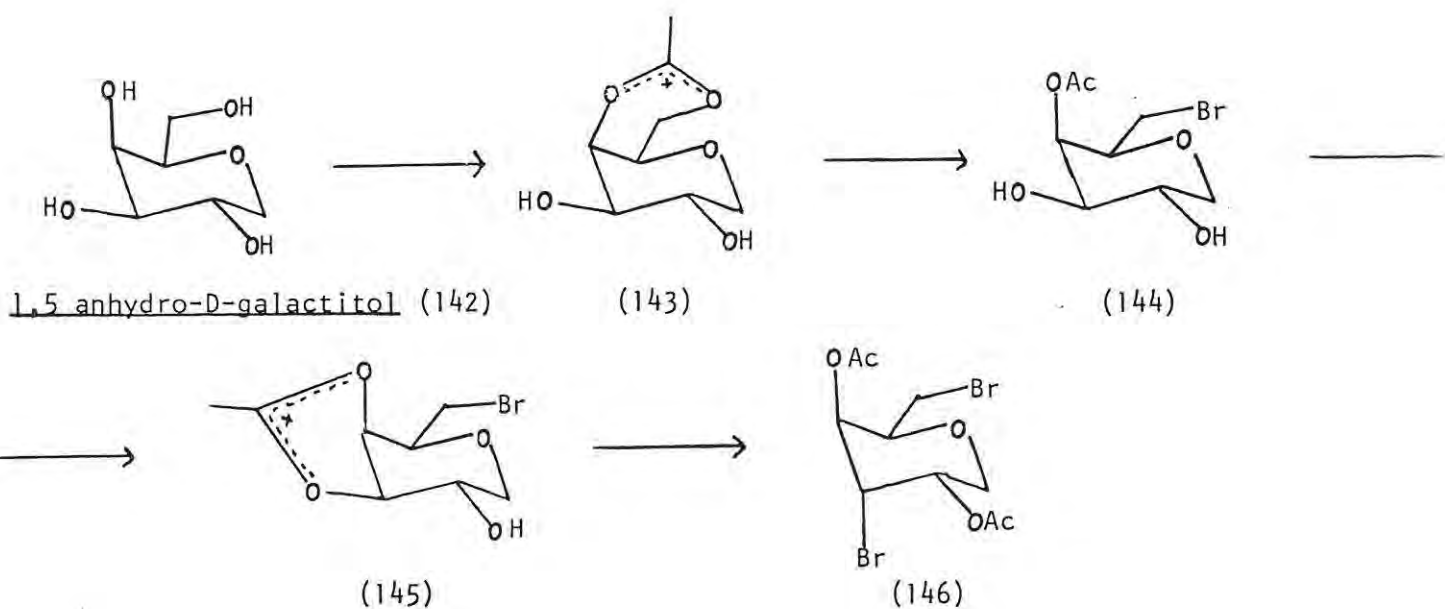
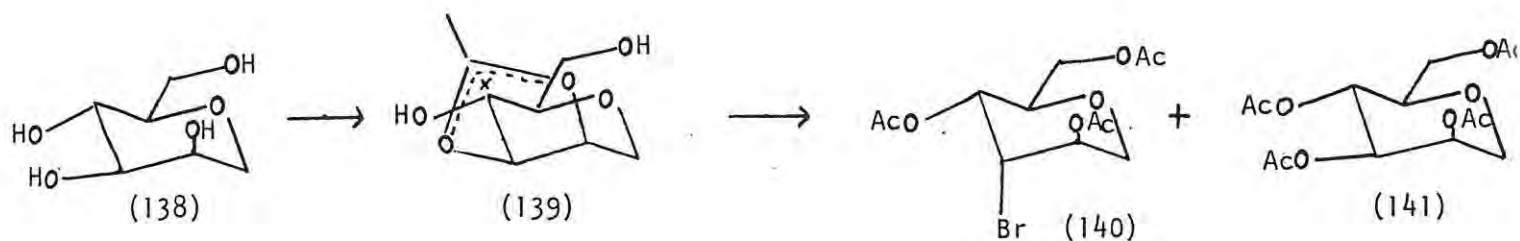


Attempts to synthesise bromodeoxy derivatives of certain sugars by reaction with hydrogen bromide/acetic acid were unsuccessful.

2,4,-Di-O-benzoyl-D-arabinopyranose<sup>52</sup> on reaction with hydrogen bromide/acetic acid afforded the corresponding glycosyl bromide but on further reaction was acetylated to yield the 3-O-acetate. Similar results were obtained when 1,3,5-tri-O-benzoyl- $\alpha$ -D-ribofuranose was treated with hydrogen bromide/acetic acid (HBA) while treatment of methyl 2,3,6-tri-O-benzoyl- $\alpha$ -D-galactopyranoside (136) with HBA for 3 hours at room temperature yielded tri-O-benzoyl-6-bromo-6-deoxy- $\beta$ -D-galactofuranosyl bromide (137).



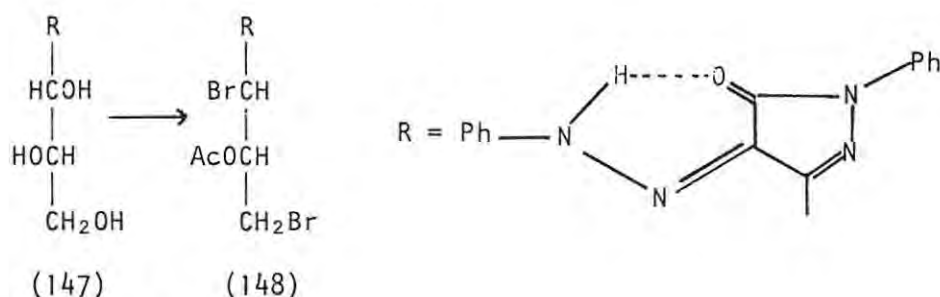
The reaction of diols<sup>53</sup> with HBA probably proceeds via a partial acetylation followed by formation of an acetoxonium ion which reacts with bromide to give a trans-bromo-acetate. Formation of an acetoxonium ion requires a cis diol system, hence a trans compound e.g. 1,5-anhydro-D-glucitol does not yield a bromodeoxy compound but a tetra-acetate. 1,5-Anhydro-D-mannitol (138) does have a cis diol system at C2 and C3 which gives rise to an acetoxonium ion (139). Compound (138) on reaction with HBA for 24 hours at room temperature afforded tri-0-acetyl-3-bromo-3-deoxy-1,5-anhydro-D-altritol (140) (56%) and tetra-0-acetyl-1,5-anhydro-D-mannitol (141) (26%)



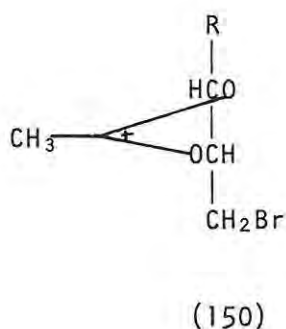
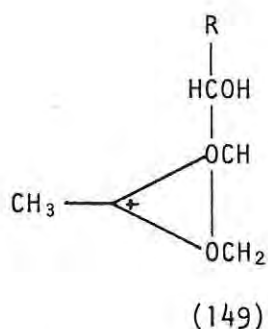
Since both tri-0-acetyl-6-bromo-6-deoxy-1,5-anhydro-D-galactitol and di-0-acetyl-3,6-dibromo-3,6-dideoxy-1,5-anhydro-D-gulitol (146) have a bromo group at C6, the initial step in the reaction with HBA involves partial acetylation and formation of the 4,6 acetoxonium ion (143). Reaction of compound (143) with hydrogen bromide affords compound (144) fully or partially acetylated. The fully acetylated compound will react no further, while the partially acetylated compound (144) may yield the 3,4 acetoxonium ion (145) which will react with bromide to give the trans-diaxial product (146).

The potentiality of bromodeoxy sugars in synthesis, the chemotherapeutic value of bromodeoxy polyols and c-nucleosides drew the attention of El Ashry<sup>54</sup> et al., to the synthesis of bromodeoxy derivatives of some acyclic c-nucleosides.

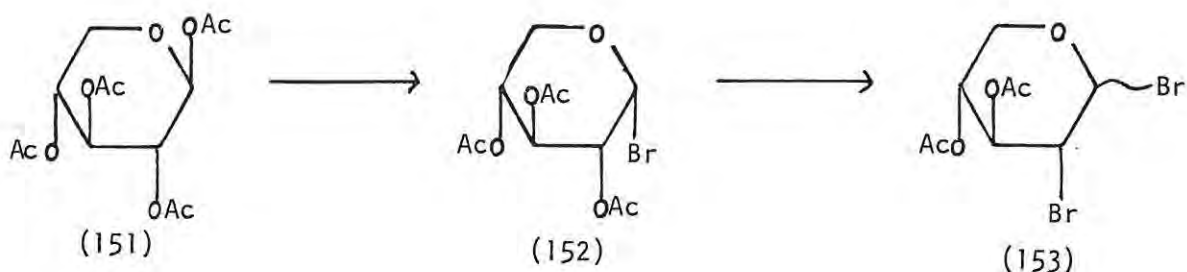
Treatment of 3-(L-threo-glycerol-1-yl)-1-phenyl 4,5-pyrazoledione 4-(phenylhydrazone) (147) with hydrogen bromide/acetic acid yielded 3-(2-0-acetyl-1,3-dibromo-1,3-dideoxy-L-erythro-glycerol-1-yl)-1-phenyl 4,5-pyrazoledione - 4-(phenylhydrazone) (148).



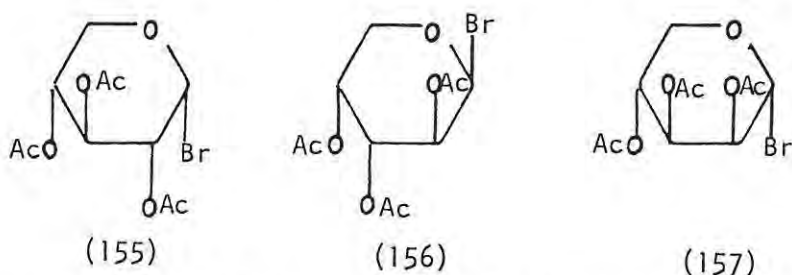
The introduction of bromine into these vicinal diols using hydrogen bromide/acetic acid occurred via a 1,3-dioxolan-2-ylum ion intermediate to give a trans bromo-acetate. Consequently, the bromine atom in (148) may be introduced via the intermediate (150) which is derived from (149) affording the erythro derivative.



1.1.11 Dibromomethyl methyl ether: Treatment<sup>55, 56</sup> of tetra-0-acetyl- $\beta$ -D-xylopyranose (151) with dibromomethyl methyl ether in boiling chloroform in the presence of zinc bromide afforded a glycosyl bromide. When the reaction is maintained at room temperature or at +5° for a week the glycosyl bromide (152) undergoes bromination to yield a dibromo derivative (153).



The fact that the tri-acetates of xylo-, lyxo- and arabinopyranosyl bromides all gave the 2-bromo-D-xylo derivative on treatment with dibromomethyl methyl ether, suggests that reaction proceeds via the acetoxonium ion (154).



This ion may be formed from tri-0-acetyl-xylopyranosyl bromide (155), -arabinopyranosyl bromide (156) or -lyxopyranosyl bromide (159) by inversion of not more than one carbon atom.



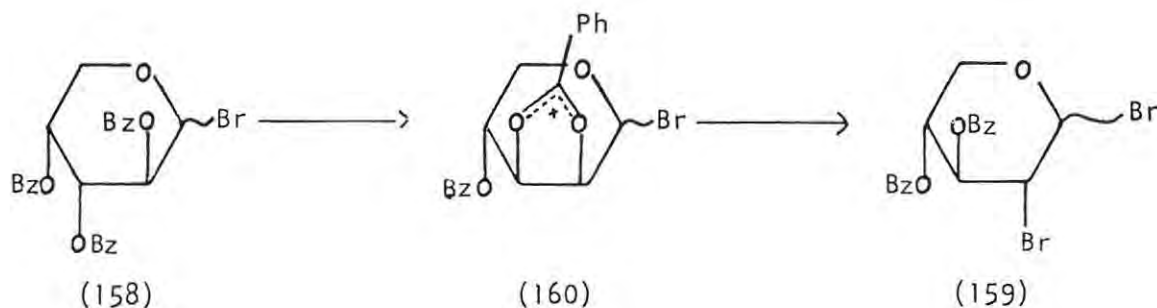
(154)

According to the mechanism proposed by Szabo<sup>57</sup> *et al.*, the attack of  $[\text{BrCH}=\text{OCH}_3]^+$  on an acylated sugar could result in the loss of an O-acetyl group. The acetoxonium ion (154) could arise from compound (155) by the loss of the O-acetyl group at C2 with achimeric assistance from the acetoxy group at C3. Compound (156) could arise from compound (154) by loss of the O-acetyl group at C3. The subsequent attack of bromide at C2 of compound (154) results in a trans opening and formation of the dibromide (153).

Attack of the bromide ion at C2 of compound (154) should afford the 3-bromo-3-deoxy-D-arabinose derivative. Such a product was not isolated presumably because the acetoxonium ion is opened by migration of bromine from C1 to C2 and not attack by bromide ions from solution.

Jennings<sup>58</sup> observed a similar migration of a chloro substituent from C1 to C2 when the chlorosulphates of xylo- and lyxopyranosyl chlorides were treated with aluminium chloride.

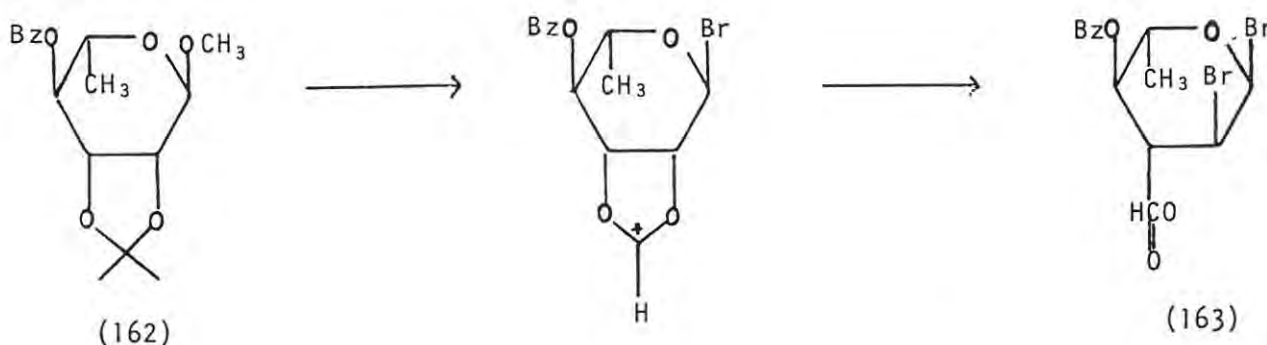
It is assumed that the benzoxonium ion (160) is the intermediate in the conversion of tri-O-benzoyl-D-xylopyranosyl bromide (158) into the bromodeoxy sugar (159).



It might be expected that prolonged reaction of acetylated carbohydrates with dichloromethyl methyl ether would yield 2-chloro-2-deoxy compounds. This, however, did not occur since the reaction of tetra-0-acetyl- $\beta$ -D-xylopyranoside with dichloromethyl methyl ether/zinc chloride afforded tri-0-acetyl- $\alpha$ -D-xylopyranosyl chloride as the final product.

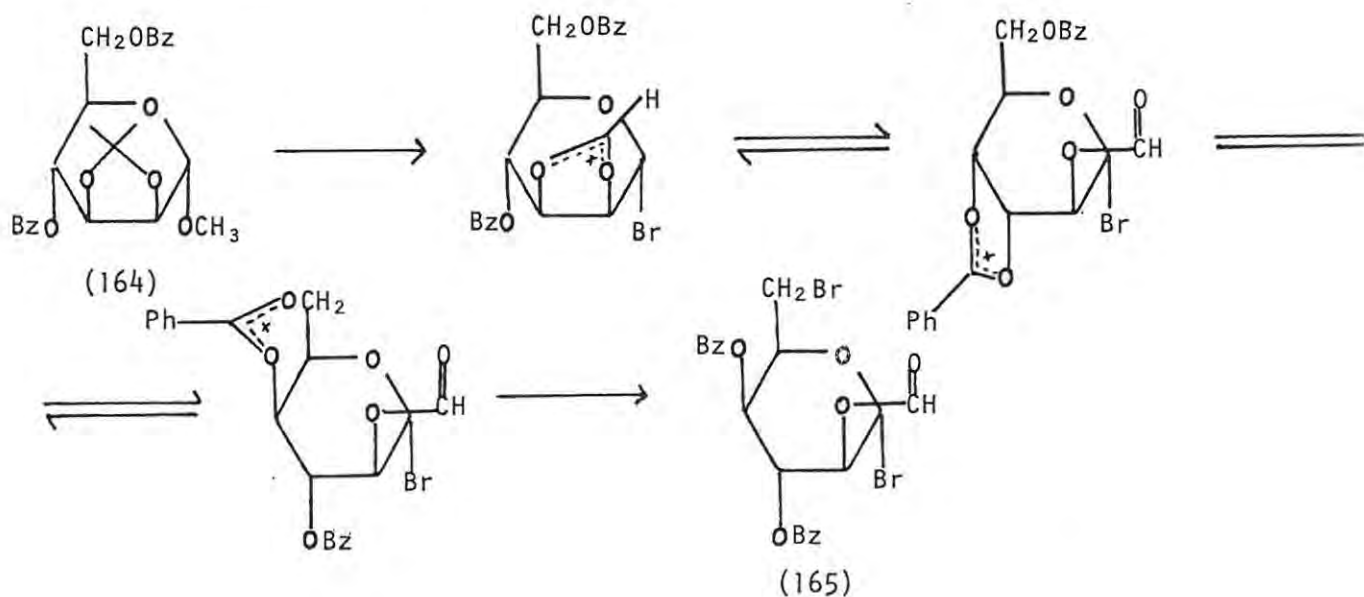
The reaction of 1,2,3,4-tetra-0-acetyl- $\beta$ -D-glucuronate<sup>59</sup> (161) with dichloromethyl methyl ether and a catalytic amount of boron trifluoroetherate afforded the  $\beta$ -chloride, while reaction of compound (161) or an anomeric mixture of the 1-0-acetates with dichloromethyl methyl ether in the presence of catalytic amounts of zinc chloride afforded the  $\alpha$ -chloride.

Bock<sup>60</sup> et al., investigated the effect of dibromomethyl methyl ether on carbohydrates protected with acetal groups e.g. isopropylidene groups. Reaction of methyl 4-0-benzoyl-2,3-isopropylidene- $\alpha$ -L-rhamnopyranoside (162) with dibromomethyl methyl ether afforded the 2-bromo-2-deoxy-L-quinovose derivative (163).

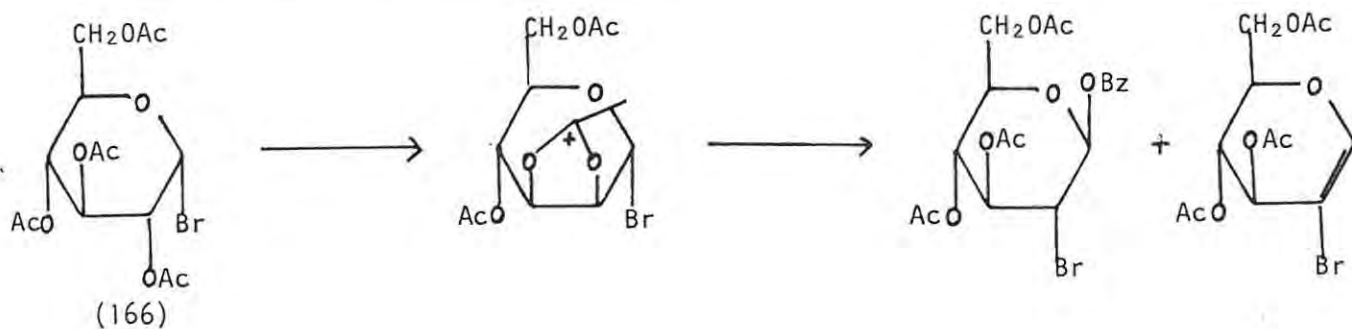


This reaction proceeded via a glycosyl bromide, cleavage of the isopropylidene group, formylation and subsequent formation of the formoxonium ion. In a reaction similar<sup>55</sup> to that of these derivatives the formoxonium ion was opened by migration of bromine from C1 to C2.

Similarly reaction of methyl 4,6-di-O-benzoyl 2,3-O-isopropylidene  $\alpha$ -D-mannopyranoside (164) with dibromomethyl methyl ether afforded a 6-bromo-6-deoxy 2-O-formylidose (165) derivative via acyloxonium-ion rearrangements.



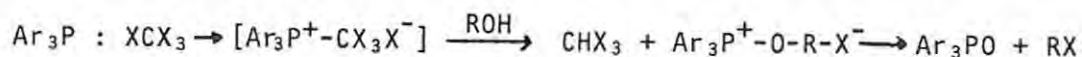
The formoxonium ion is formed in equilibrium with the 3,4 benzoxonium ion and the 4,6 benzoxonium ion. Since benzoxonium ions are far more stable it is not surprising that bromine reacts with the more abundant benzoxonium ion at the primary centre.



Reaction of 2,3,4,6-tetra-0-acetyl- $\alpha$ -D-glucopyranosyl bromide (166) took place via a 2,3 acetoxonium ion having the manno configuration. This ion could have been involved in an equilibria of acetoxonium ions but no 6-bromo-6-deoxy idose derivative was detected. Carbohydrates protected by isopropylidene groups offer a convenient method for the preparation of bromodeoxy sugars having formate protecting groups. Formyl groups may be removed easily and selectively.

#### 1.1.12. Triphenylphosphine<sup>61</sup> and carbon tetrahalides

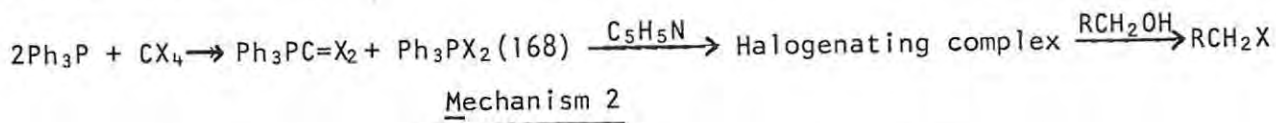
Mixtures of triarylphosphines with carbon tetrahalides are found useful for replacing both primary and secondary hydroxyl groups by halogens. It has been assumed that halogenation with these reagents proceeds via the mechanism (1)



#### Mechanism 1

Pyridine was selected as the medium because of its excellent solvent properties and its volatility. Reaction of methyl  $\alpha$ -D-glucopyranoside in pyridine at 5° with one molar equivalent of triphenylphosphine and carbon tetrachloride yielded 6-chloro-6-deoxy- $\alpha$ -D-glucopyranoside (167) in a 49% yield. The yield was not enhanced by prolonging the reaction time while an increase of the triphenylphosphine to 2 molar equivalents resulted in an almost quantitative yield of compound (167). Similar results were achieved with carbon tetrabromide and carbon tetraiodide. At 65° the halogenation was selective and complete within a few minutes. Thus, it is evident that in pyridine at least, halogenation with these reagents proceeds by a mechanism different from (1). Halogenation

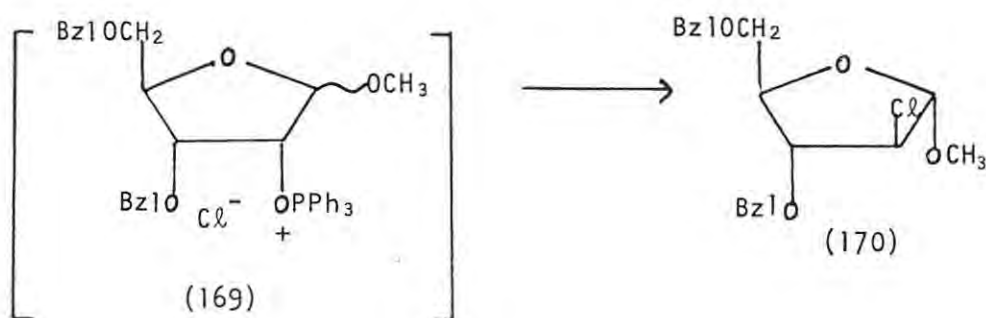
might occur via the initial formation of a triphenylphosphine dihalide (168) ( $X=Cl, Br$  or  $I$ ) to produce a bulky halogenating complex involving the solvent (Mechanism 2).



Reaction of 1,2-O-isopropylidene- $\alpha$ -D-glucofuranose with triphenylphosphine/carbon tetrachloride afforded 6-chloro-6-deoxy-1,2-O-isopropylidene- $\alpha$ -D-glucofuranose while reaction with triphenylphosphine/carbon tetrabromide yielded the 6-bromo-6-deoxy derivative which proved to be a valuable precursor in the synthesis of 5,6-anhydro-1,2-O-isopropylidene- $\alpha$ -D-glucofuranose.

Since 5' haloribonucleosides are useful precursors for the synthesis of nucleotides, anhydronucleotides and deoxynucleotides, the introduction of a halogen atom in the 5' position is important. Crystalline 5' chloroinosine was prepared in a high yield by direct chlorination (method triphenylphosphine/carbon tetrachloride) of inosine. Previous attempts to prepare 5'-chloroinosine by hydrolysis of 5'-chloro 5'-deoxy 2',3'-O-isopropylideneinosine resulted in the formation of a syrup for which no analytical data or physical measurements were given.

Chlorination<sup>62</sup> of an anomeric mixture of methyl 3,5-di-O-benzyl-D-ribofuranoside (predominantly the  $\beta$ -isomer) was achieved by treatment with triphenylphosphine in carbon tetrachloride under reflux for several days.



The ionic intermediate (169) formed almost immediately while subsequent attack by chloride ions at C2 occurred very slowly. The product (170) proved to be  $\alpha$ -anomer despite the fact that the starting material contained predominantly the  $\beta$ -anomer.

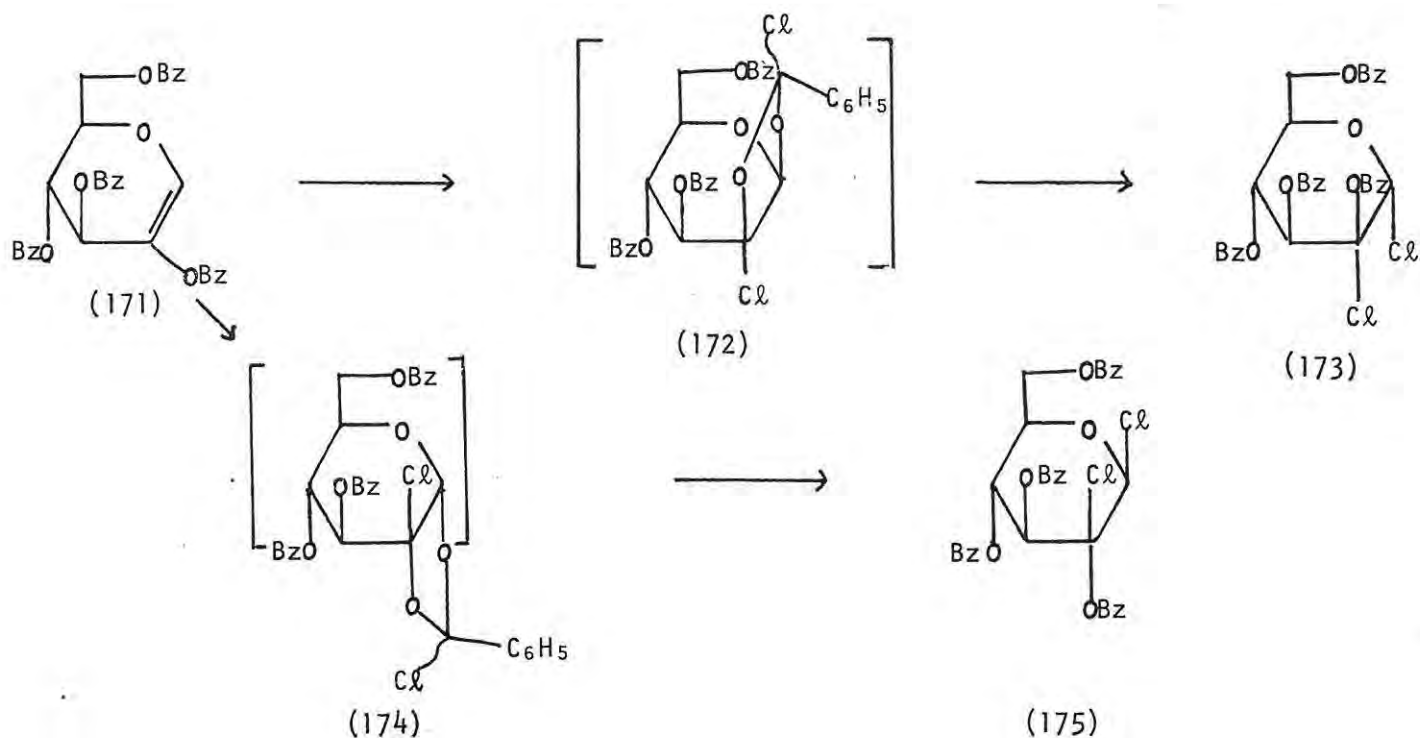
Khan<sup>35</sup> et al., reported the direct synthesis of 6,6'-dichloro-6,6'-dideoxy-sucrose. This compound in addition to its value as a synthetic intermediate is said to have a reversible contraceptive effect on male rats. The selective replacement of primary hydroxyl groups in sugars and certain nucleosides by chlorine has been achieved by the use of triphenylphosphine-N-chloro-succinimide in N,N-dimethylformamide. Treatment of sucrose with this reagent gave a mixture which contained the dichloride as the major carbohydrate product which could be isolated after acetylation and chromatography in a 69% yield. The use of the mesylchloride/N,N-dimethylformamide reagent afforded after acetylation 51% of the dichloride hexa-acetate.

Since the completion of Khan's work two reagents have been reported to effect chlorination at C6 and C6' in sucrose.

- i) Tris(dimethylamino)phosphine<sup>63</sup> - carbon tetrachloride potassium hexafluorophosphine - tetramethylammonium chloride-N,N-dimethylformamide
- ii) Triphenylphosphine<sup>61</sup> - carbon tetrachloride (pyridine)

Reaction of sucrose with triphenylphosphine and carbon tetrachloride in pyridine afforded 6,6'-dichloro-6,6'-dideoxy-sucrose in a high yield thus providing a simple route for the preparation of other sucrose derivatives modified at the 6 and 6' positions.

Results also indicate that the halogenating species might be bulky thus preventing halogenation not only at secondary hydroxyl groups but also at the primary 1' position.



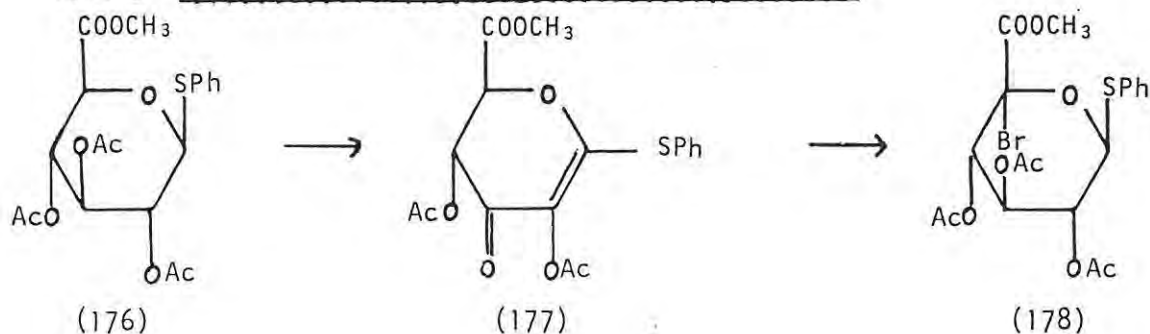
When tetra-O-benzoyl<sup>64</sup> 1-deoxy D-arabino-hex-1-enopyranose (171) was treated with chlorine in carbon tetrachloride at room temperature a crystalline dichloro compound (173) was isolated in a 20% yield.

The material in the mother liquors was almost pure and after chromatography afforded the dichloro compound (175) isomeric with (173).

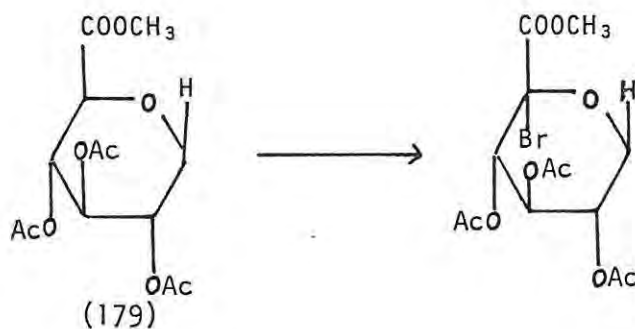
Chlorination of compound (171) at low temperatures yielded the orthoacid chloride (174) which at room temperature rearranged to form compound (175).

The dichloro compound (173) could be formed from (171) by a direct cis addition of chlorine or possibly via the very unstable orthoacid chloride (172).

#### 1.1.13 N-Bromosuccinimide in carbon tetrachloride<sup>65</sup>



When compound (176), methyl(phenyl tri-0-acetyl)l-thio( $\beta$ -D-glucopyranoside)uronate was treated with N-bromosuccinimide in the dark no reaction occurred. The abstraction of H-1 which initiates the formation of the enone (177) and the abstraction of H-5 leading to the formation of the bromo derivative (178) are homolytic processes with the carboxymethyl group providing stabilization of the radical at C5 which is provided at C1 by the phenylthio group. Radical brominations  $\alpha$  to ester carbonyl groups are known and the ring o-atom in the glycoside further assists the process both at C5 and at C1.

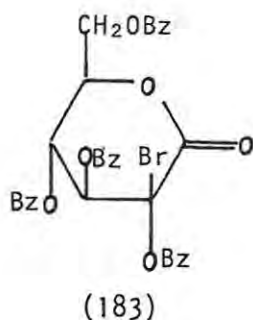


Methyl tri-0-acetyl-2,6-anhydro-L-gulonate (179).

Substitution in the reaction above by the N-bromosuccinimide method occurred with retention of configuration.

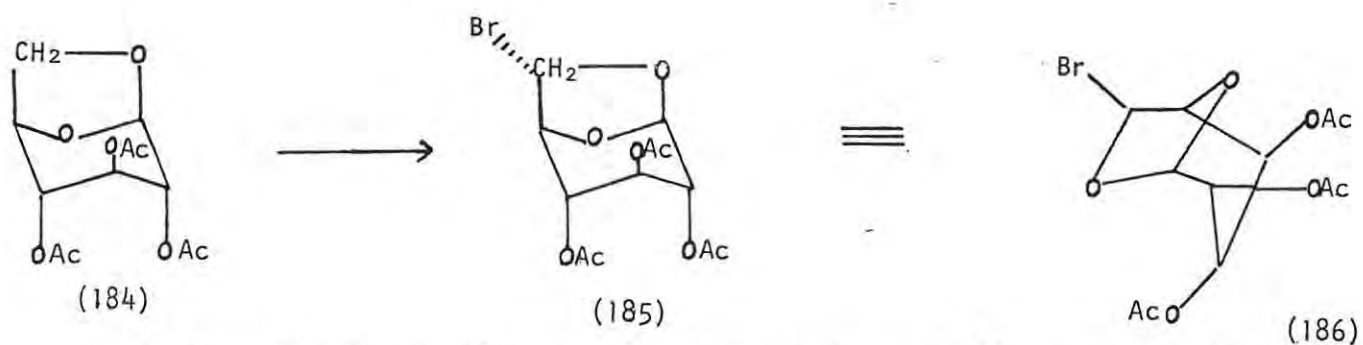
The nature<sup>66</sup> of the substituent bonded to O 1 is critically important in determining whether  $\beta$ -D-glucopyranosyl compounds react with bromine radicals at C1 or C5. Initial abstraction involves the removal of an axial hydrogen atom at C1 or C5. As of yet there has been no report of the specific abstraction of an equatorial proton.

With penta-0-benzoyl- $\alpha$ -D-glucopyranose (180) and penta-0-acetyl- $\alpha$ -D-idopyranose (181) reaction occurred at C5 involving the abstraction of the axial proton. Methyl tetra-0-benzoyl- $\beta$ -D-glucopyranoside (182) yielded the crystalline bromolactone (183) since the methoxy group

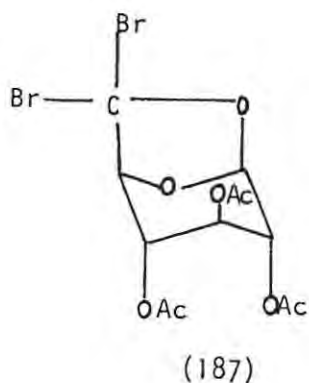


facilitates abstraction at C1 and thus the alkyl group permits O1 to participate in radical stabilization. Because the phenoxy group and particularly the nitrophenoxy group would do this to a lesser extent, phenyl and p-nitrophenyl 2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosides underwent bromination at C5.

D-Glucopyranosyl derivatives e.g. tri-O-acetyl-1,6-anhydro- $\beta$ -D-glucopyranose (184) with an equatorial hydrogen atom at positions adjacent to the ring oxygen, were considered.



If this photobromination was allowed to continue (187) was produced in limited proportions.

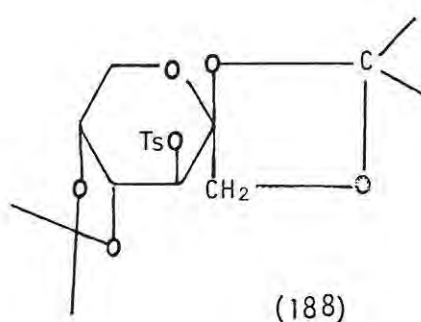
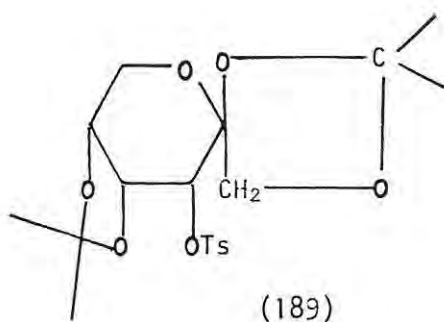


Initial H abstraction probably at the more accessible exo H atom occurred at C6 rather than C1 or C5 where energetically unfavourable removal of the equatorial H atom and formation of non-planar radicals at ring junctions would be involved.

#### 1.1.14 Potassium hydrogen fluoride in methyl cellosolve<sup>7</sup>

The displacement of secondary sulphonic esters of protected sugar derivatives by treatment with tetrabutylammonium fluoride in acetonitrile has the advantage over other methods in the ease of predicting the configuration of the subsequently formed sugar, since only one fluorinated product should result.

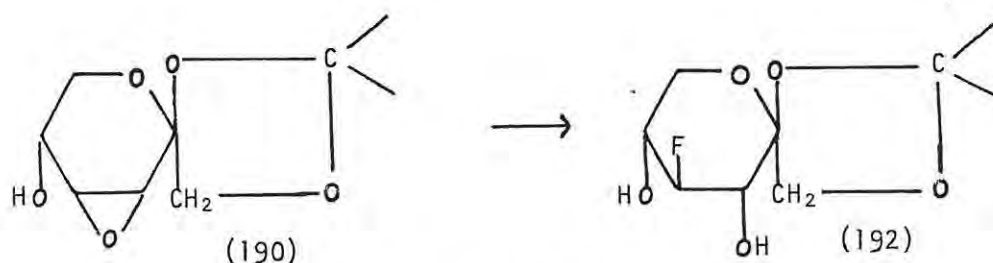
Attempted displacement by Rao<sup>7</sup> et al., of the tosyl group in 1,2:4,5-di-0-isopropylidene-3-0-p-tolylsulphonyl- $\beta$ -D-fructopyranose (188) and 1,2:4,5-di-0-isopropylidene-3-0-p-tolylsulphonyl- $\beta$ -D-psicopyranose (189) even with as powerful a nucleophilic reagent as sodium azide in refluxing N,N-dimethylformamide over long periods failed.



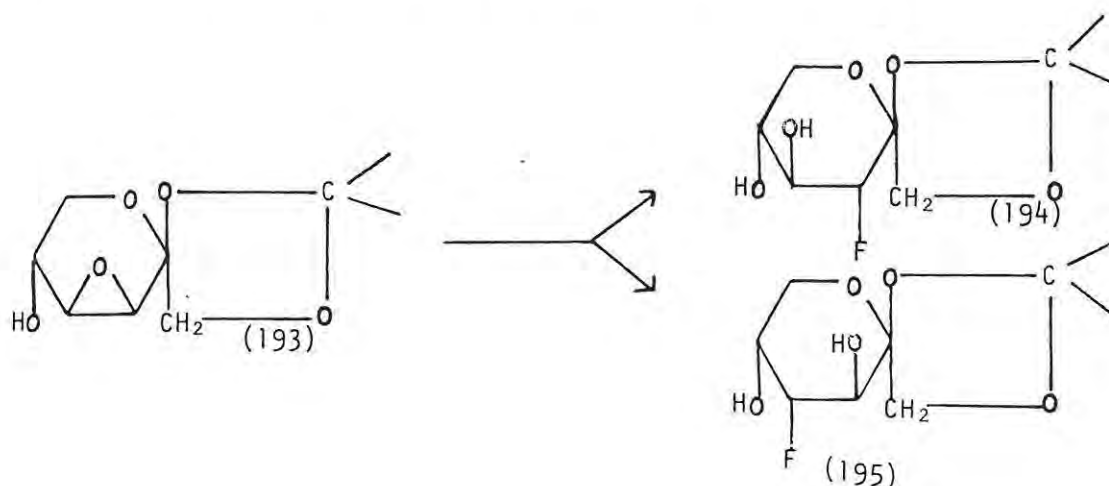
Another method suggested was epoxide cleavage either with hydrogen fluoride at low temperatures or potassium hydrogen fluoride in ethylene glycol at elevated temperatures. Ethylene glycol (boiling) may have deleterious effects on products formed or limit the use of some protective groups.

Reaction of 3,4-anhydro-1,2-0-isopropylidene- $\beta$ -D-psicopyranose (190) with potassium hydrogen fluoride in methyl cellosolve was expected to yield 3-deoxy-3-fluoro-1,2-0-isopropylidene- $\beta$ -D-fructopyranose (191) and 4-deoxy-4-fluoro-1,2-0-isopropylidene- $\beta$ -D-sorbopyranose (192).

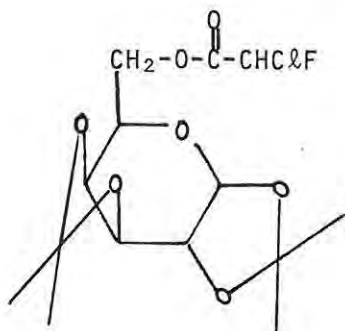
Only one fluorinated derivative was isolated, the yield of which exceeded 80%. This crystalline fluorinated product did not reduce sodium metaperiodate nor did it react with lead tetra-acetate indicating that it had the sorbose configuration and thus proved to be compound (192).



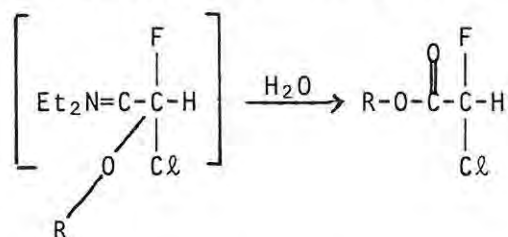
Reaction of 3,4-anhydro-1,2-0-isopropylidene- $\beta$ -D-tagatopyranose (193) with potassium hydrogen fluoride in refluxing methyl cellosolve afforded 40% of an uncharacterised syrup, 25% of unreacted epoxide and 35% of a crystalline material which contained two monofluorinated compounds viz. 3-deoxy-3-fluoro-1,2-0-isopropylidene-D-sorbose (194) and 4-deoxy-4-fluoro-1,2-0-isopropylidene-D-fructose (195).



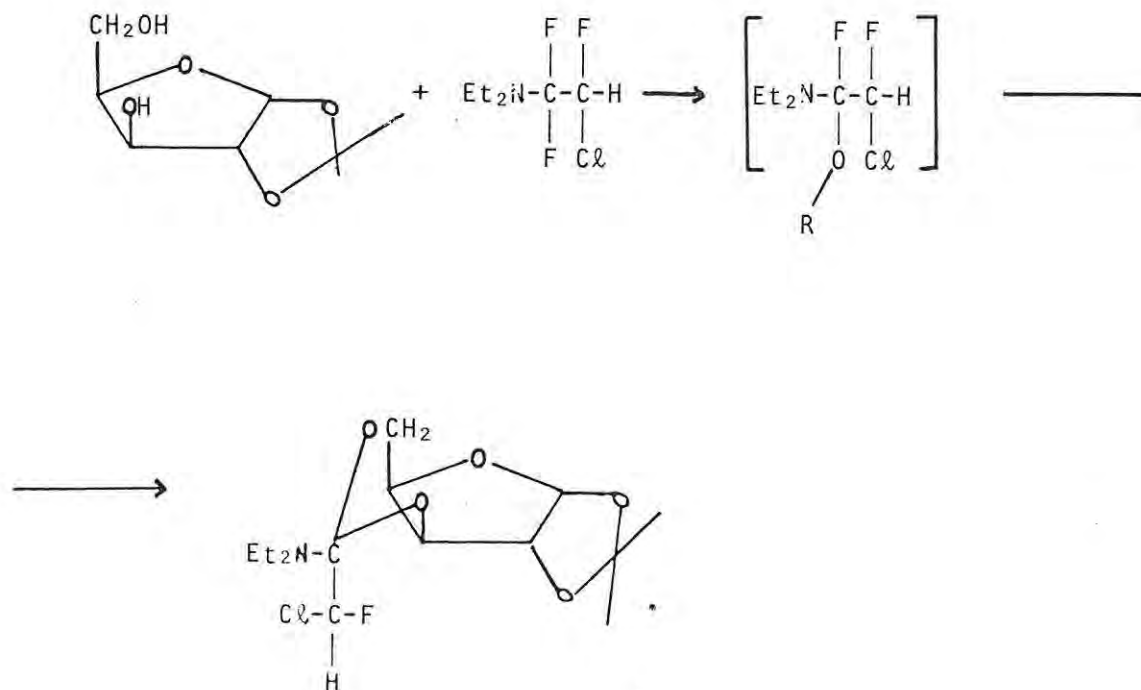
Evelyn<sup>67</sup> and Hall examined the so-called fluoramine reagent, N-(2-chloro-1,1,2-trifluoroethyl) N,N-diethylamine. Although 1,2:3,5-di-O-methylene- $\alpha$ -D-glucofuranose was converted into the corresponding fluoro derivative in a 60% yield, 1,2:3,4-di-O-isopropylidene- $\alpha$ -D-galactopyranose yielded the corresponding chlorofluoroacetate.



C6 is apparently not attacked by the fluoride ion under the reaction conditions employed. The intermediate remains intact and when water is added, hydrolysis occurs to yield the chlorofluoroacetate.



Reaction of the fluoramine reagent with 1,2-O-isopropylidene  $\alpha$ -D-xylofuranose yielded, as the sole product, the cyclic acetal.

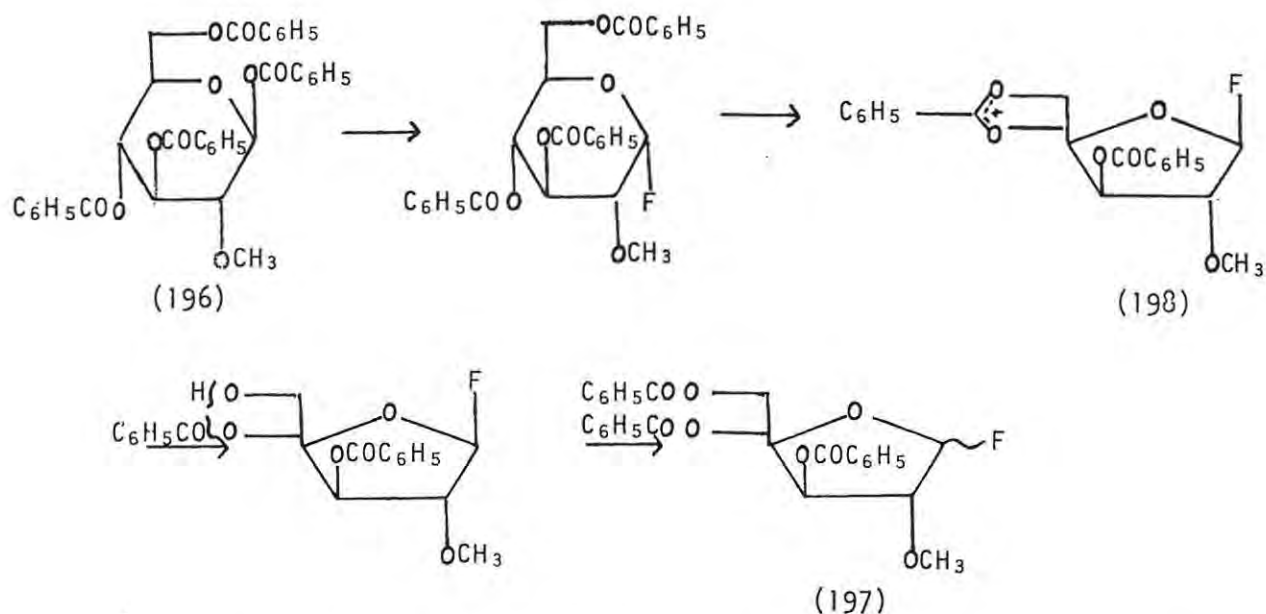


Presumably the reagent was first attacked by 5-OH and the intermediate was trapped, as the cyclic acetal, by further reaction at 3-OH.

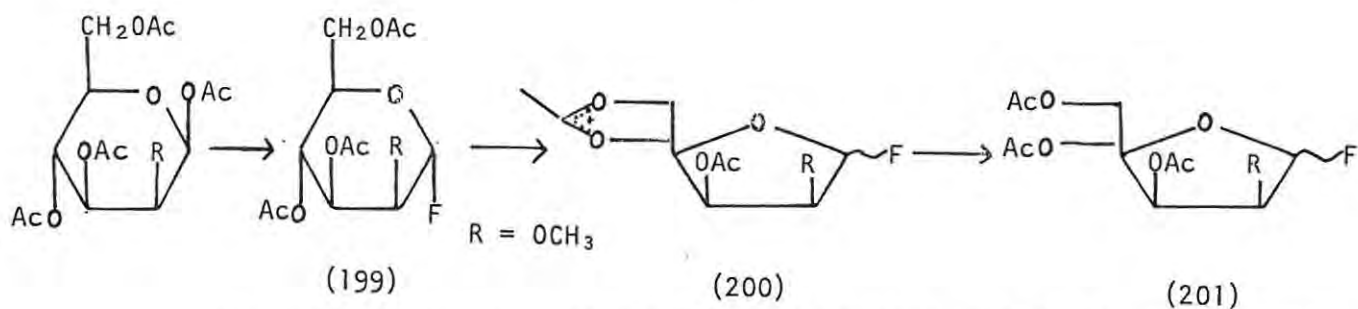
### 1.1.15 Hydrogen fluoride<sup>68,69</sup>

Previous reports on the reaction of tetra-0-benzoyl-2-0-methyl-β-D-glucopyranose (196) with anhydrous hydrogen fluoride at room temperature showed that ring contractions to furanose derivatives took place to a certain<sup>70</sup> extent.

On reinvestigation of the above reaction, Bock<sup>69</sup> et al., found that after 9 days work-up followed by benzoylation gave an anomeric mixture of tri-0-benzoyl-2-0-methyl-D-glucofuranosyl fluoride (197) in a slightly higher yield than when the 24 hour reaction period was used.

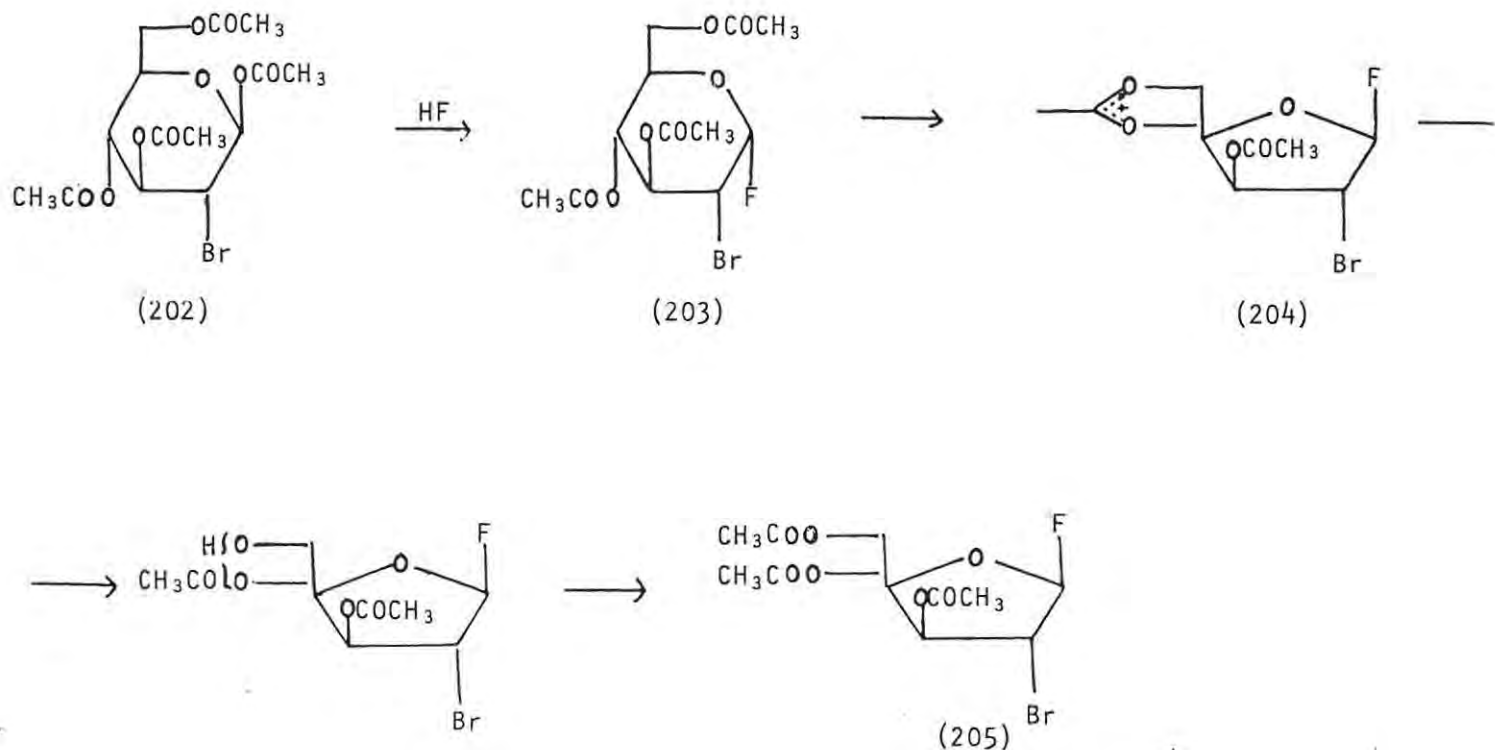


Treatment of tetra-0-acetyl-2-0-methyl-β-D-mannopyranose for 10 minutes with anhydrous hydrogen fluoride at 0° yielded 63% of tri-0-acetyl-2-0-methyl-α-D-mannopyranosyl fluoride (199) which on prolonged reaction at room temperature underwent ring contraction and after 45 hours yielded the acetoxonium ion (200). Work-up and acetylation afforded 40% of tri-0-acetyl-2-0-methyl-β-D-mannofuranosyl fluoride and 11% of the corresponding α-anomer (201).

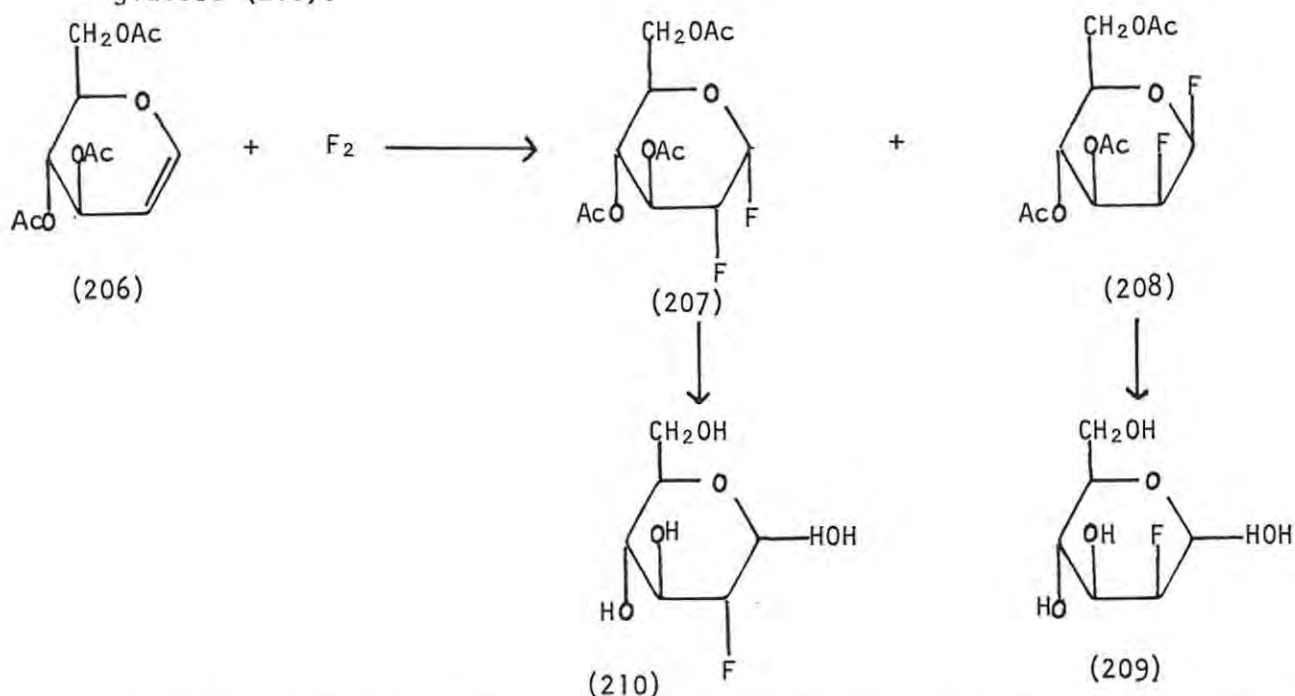


When gluco or manno penta-acetates are treated with hydrogen fluoride inversion at C2 and C3 occurs to yield manno- and altropyranose derivatives respectively. Furanoses are formed to a minor extent. However, in the absence of 2-O-acyl groups as in 2-O-methyl pyranoses, inversion cannot take place and ring contraction predominates leading to the formation of the stable 5,6-dioxolanyium ions (198) and (200).

Brief treatment of tetra-O-acetyl-2-bromo 2-deoxy- $\beta$ -D-glucopyranose (202) afforded tri-O-acetyl-2-bromo-2-deoxy- $\alpha$ -D-glucopyranosyl fluoride (203) which slowly underwent further reaction with hydrogen fluoride and after two weeks at 5° afforded the acetoxonium ion (204). Work-up and acetylation gave the 2-bromo-2-deoxy-furanosyl fluoride (205).



Fluorination with fluorine provides a convenient synthesis of 2-deoxy-2-fluoro-D-glucose (210). Ido<sup>71</sup> *et al.*, described the direct conversion of 3,4,6-tri-O-acetyl-D-glucal (206) to 3,4,6-tri-O-acetyl 2-deoxy-2-fluoro- $\alpha$ -D-glucopyranosyl fluoride (207) and 3,4,6-tri-O-acetyl-2-deoxy-2-fluoro- $\beta$ -D-mannopyranosyl fluoride (208) by reaction with fluorine. Hydrolysis of compound (207) yields 2-deoxy-2-fluoro-D-glucose (210).

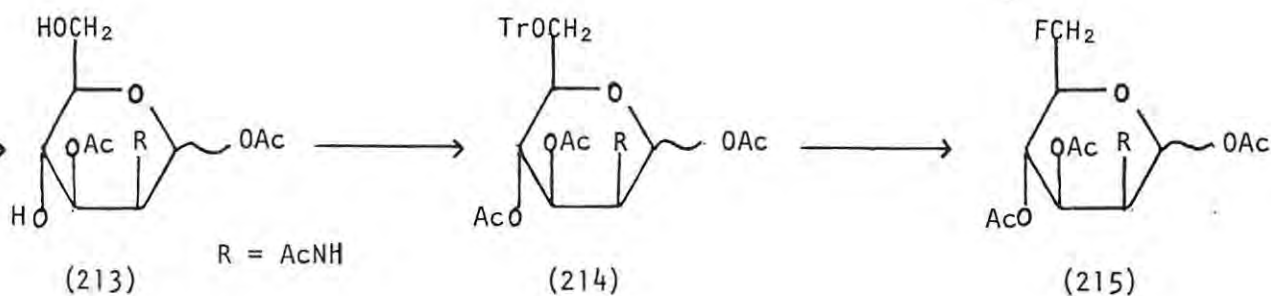
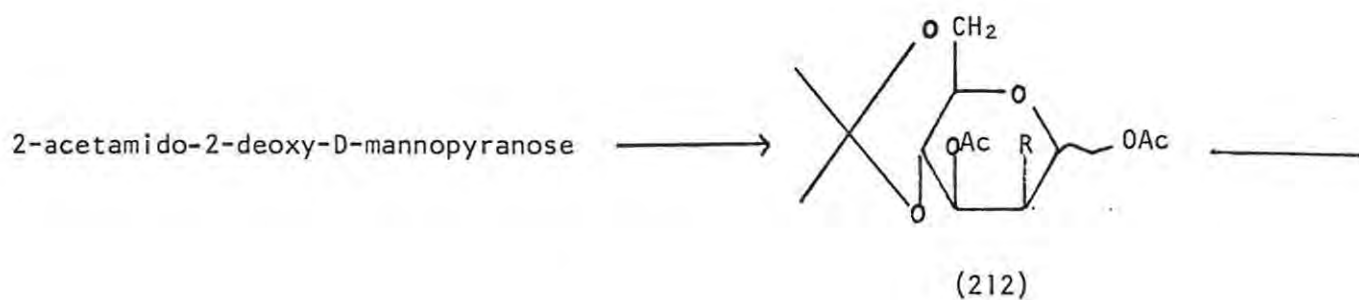


Previously molecular fluorine had a limited value due to extreme chemical reactivity and difficult handling. However, fluorine in an inert gas e.g. helium, allows for electrophilic addition to double bonds and regioselective fluorine substitution at a double bond. 2-Deoxy-2-fluoro-D-glucose had previously been synthesised by fluoride opening of an anhydro sugar and electrophilic fluorination with trifluoromethyl hypofluorite. The starting material in each of these cases was not readily available.

#### 1.1.16 Diethylaminosulphur trifluoride

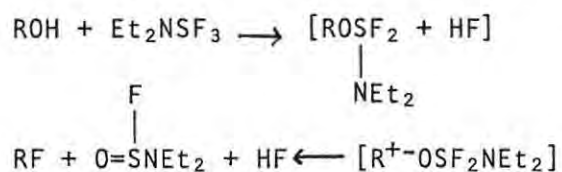
Fluorinated carbohydrates<sup>8</sup> are potential plasma membrane

modifiers and inhibitors. Substitution of the 6-hydroxy by fluorine in 2-acetamido-2-deoxy-D-mannose (211) was achieved by reaction of 2-acetamido-2-deoxy-D-glucose with diethylaminosulphur trifluoride and epimerization. However, when 2-acetamido-2-deoxy-D-mannopyranose (211) was kept in anhydrous pyridine, it epimerized to the D-gluco epimer. To avoid epimerization which might occur during the tritylation procedure due to the presence of pyridine, the anomeric carbon was protected before tritylation.



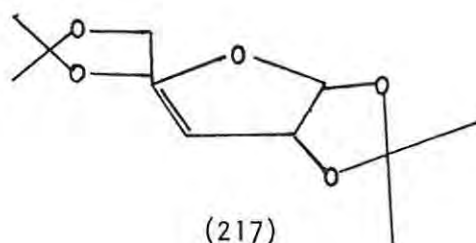
This was accomplished by acetonation followed by acetylation yielding 2-acetamido 1,3-di-O-acetyl-2-deoxy-4,6-O-isopropylidene-D-mannopyranose (212) as an anomeric mixture. Hydrolysis of compound (212) with aqueous acetic acid gave (213) which was subsequently tritylated and fully acetylated to yield 2-acetamido-1,3,4-tri-O-acetyl-2-deoxy-6-O-trityl-D-mannopyranose (214), which when reacted slowly with an excess of diethylaminosulphur trifluoride in diglyme, afforded 2-acetamido-1,3,4-tri-O-acetyl-2,6-dideoxy-6-fluoro-D-mannopyranose (215).

Diethylaminosulphur trifluoride<sup>72</sup> has recently been introduced as a mild and rapid reagent for effecting F for OH conversion with retention of configuration at the reaction centres (Scheme 3).



Scheme 3

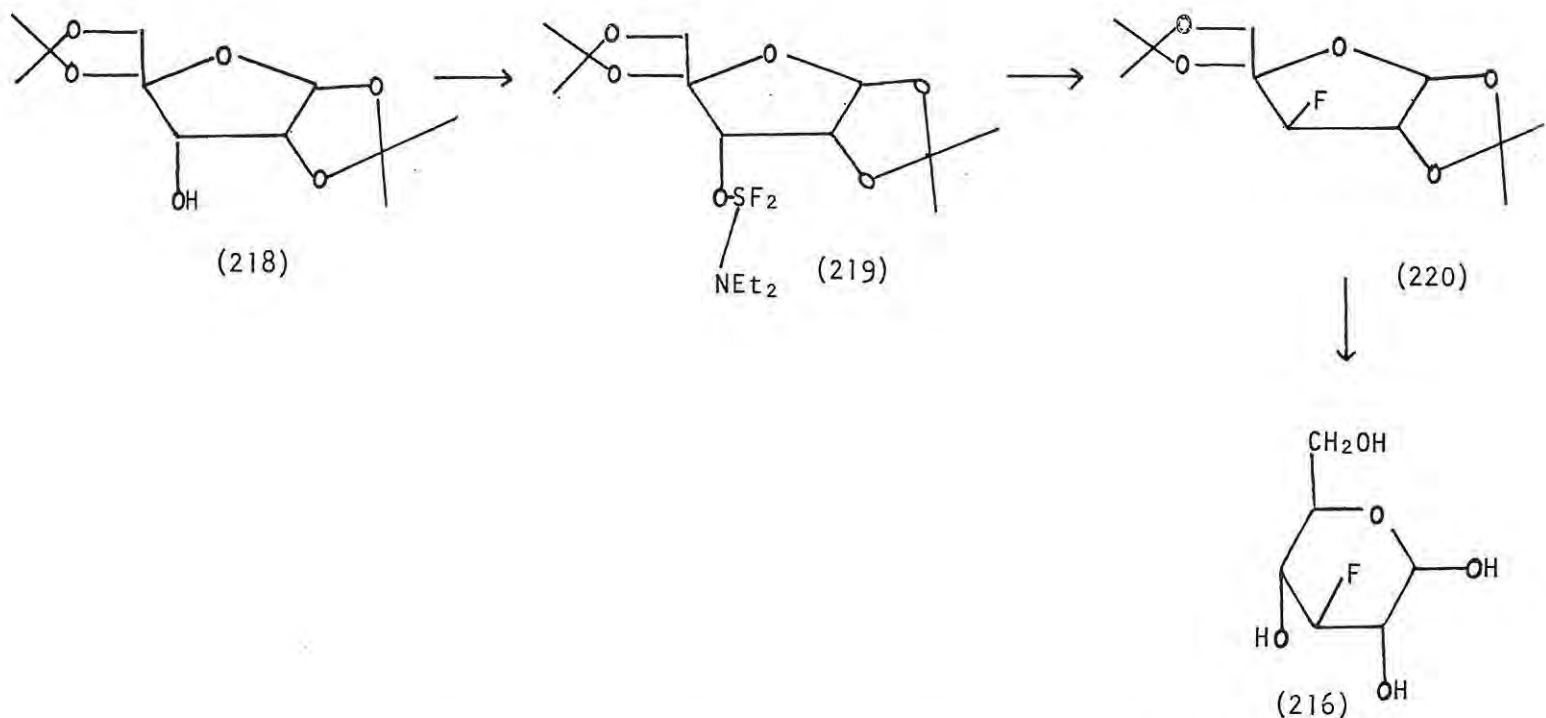
Reaction at 1,2:5,6<sup>73</sup>-di-0-isopropylidene- $\alpha$ -D-glucofuranose with diethylaminosulphur trifluoride/methylene dichloride appeared a simple rapid route for the synthesis of 3-deoxy-3-fluoro-D-glucose (216). However, no reaction occurred and after addition of 2 equivalents of pyridine the olefin (217) was isolated in a 75% yield.



Two further methods were proposed for the synthesis of compound (216).

Since nucleophilic displacement on 1,2:5,6-di-0-isopropylidene 3-tosyl- $\alpha$ -D-allofuranose occurred with inversion of configuration<sup>74</sup> at the 3-position reaction between 1,2:5,6-di-0-isopropylidene- $\alpha$ -D-allofuranose (218) and diethylaminosulphur trifluoride was performed to determine whether the intermediate if formed could undergo nucleophilic displacement to yield the 3-fluoro-gluco derivative. On direct distillation of the reaction mixture 3-deoxy-3-fluoro-1,2:5,6-di-0-

isopropylidene- $\alpha$ -D-glucofuranose (220) was isolated in a 90% yield.



As diethylaminosulphur trifluoride is apparently reacting to give a very good leaving group which is then rapidly displaced by fluoride ion, the alternative of a very good leaving group and an external source of fluoride ion appeared attractive.

The trifluoromethane sulphonate of 1,2:5,6-di-O-isopropylidene- $\alpha$ -D-allofuranose which was refluxed with a 10% excess of cesium fluoride in N,N-dimethyl formamide for 25 minutes afforded compound (220) which on reaction with methylene chloride and excess boron trichloride yielded compound (216).

Thus diethylaminosulphur trifluoride reacts with alcohols to give intermediates rather than transition states which can have reaction pathways other than simple fluorination. The difference in reaction between the two isomeric furanose derivatives could be ascribed to the difference in stability of the two olefins formed by trans-diaxial elimination, (i.e. the  $\Delta^{2,3}$  isomer is a more strained structure than the

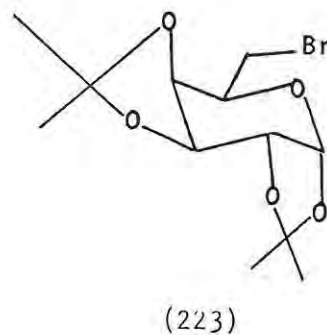
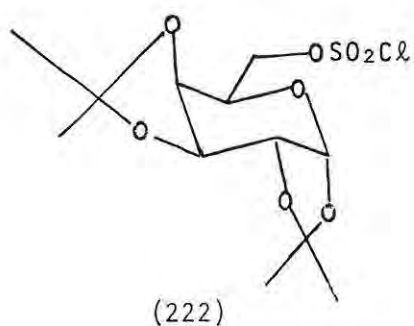
$\Delta^{3,4}$  isomer) or to the steric effects of the 1,2-O-isopropylidene ring blocking the approach of the nucleophile to the  $\alpha$ -face of the ring.

#### 1.1.17 Tetraethylammonium bromide

Displacements<sup>75</sup> of primary and secondary chlorosulphonyloxy groups by bromide proceeded with inversion of configuration and in some instances required the use of aprotic solvents or crown ethers.

Reaction of methyl 4,6-benzylidene- $\beta$ -D-glucopyranoside 2,3,-dichlorosulphate with tetraethylammonium bromide in chloroform afforded 84% of methyl 4,6-benzylidene-3-bromo-3-deoxy- $\beta$ -D-allopyranoside 2-chlorosulphate (221) in 3 hours. Replacing chloroform with N,N-dimethylformamide as solvent the reaction both at 20° and at 0° was completed within 20 minutes. Since N,N-dimethylformamide is sufficiently basic to catalyse hydrolysis and intramolecular cyclization of the chlorosulphonyloxy group, the cyclic sulphate is also formed. The conversion of the glucopyranoside into the allopyranoside (221) by nucleophilic attack of bromide suggests that chlorosulphate displacement proceeds via an  $S_N2$  reaction of sulphonate esters involving carbon-oxygen bond fission.

Reaction of 1,2:3,4-di-O-isopropylidene- $\alpha$ -D-galactopyranose 6-chlorosulphate (222) with bromide in chloroform afforded decomposition products, while in N,N-dimethylformamide reaction with tetraethylammonium bromide for 2 days afforded the 6-bromo-6-deoxy-galactopyranose derivative (223) in a 45% yield.



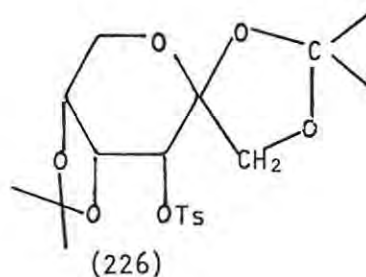
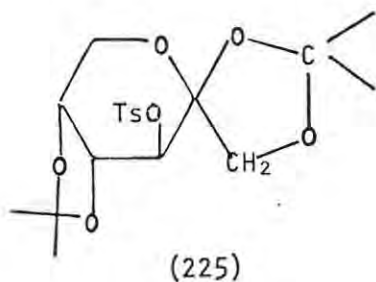
The use of crown ethers as demonstrated by Naidoo<sup>76</sup> and Parolis can improve yields by avoiding solvents e.g. N,N-dimethylformamide which promote side reactions. The particularly convenient displacement to yield 3-bromo-3-deoxy-allose derivatives is the most notable success, allowing efficient and rapid synthesis of paratose.

#### 1.1.18. Tetrabutylammonium halides

2,3:4,5-Di<sup>77</sup>-0-isopropylidene-1-0-methanesulphonyl-β-D-fructopyranose afforded resistance to attack by halide ions. The reaction with the chloride ion was most successful while reaction with tetrabutylammonium fluoride was very slow.

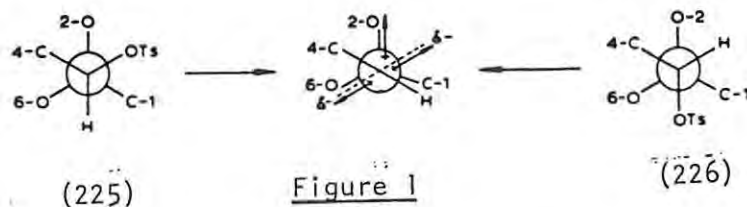
Attempted displacement of the 3-methanesulphonyl, or 3-chlorosulphonyl group of 1,2:4,5-di-0-isopropylidene-β-D-ribohexulopyranose by reaction with tetrabutylammonium fluoride was unsuccessful, even when pyridine was added to minimize acid catalysed decomposition.

Sarel-Imber and Bergmann<sup>78</sup> reported the synthesis of 4-deoxy-4-fluoro 1,2-0-isopropylidene-D-xylohexulopyranose (224); a derivative of the first secondary deoxyfluoroketose. Reaction of a sulphonic ester of a fully protected sugar with potassium fluoride was considered to be reaction method of choice.



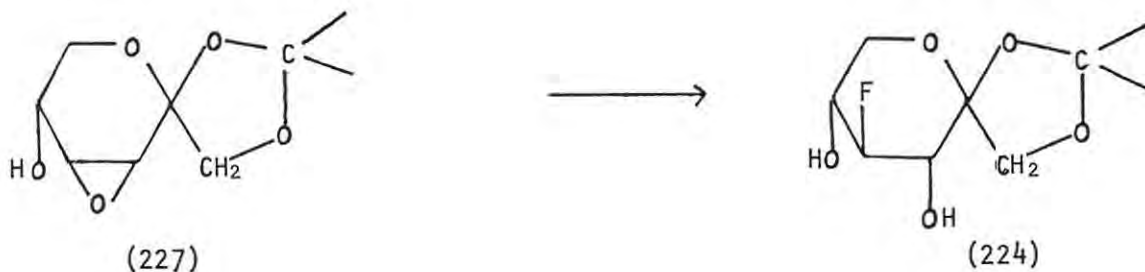
Attempts to replace the tosyl groups in 1,2:4,5-di-O-isopropylidene-3-O-tosyl- $\beta$ -D-fructopyranose (225) and 1,2:4,5-di-O-isopropylidene-3-O-tosyl- $\beta$ -D-hexulopyranose (226) using potassium fluoride or potassium hydrogen fluoride in acetamide at 190°C, N,N-dimethylacetamide or N-methylpyrrolidone at their reflux temperatures, methyl sulphoxide at 100° or tetrabutylammonium fluoride in acetonitrile first at 50°; then at boiling temperature for several days, failed.

The resistance of the sulphonyloxy group in compounds (225) and (226) towards fluoride displacement may be explained by the interaction of the permanent dipoles about the anomeric group with those formed during the development of the transition state viewed along C2 - C3 bonds (Figure 1).

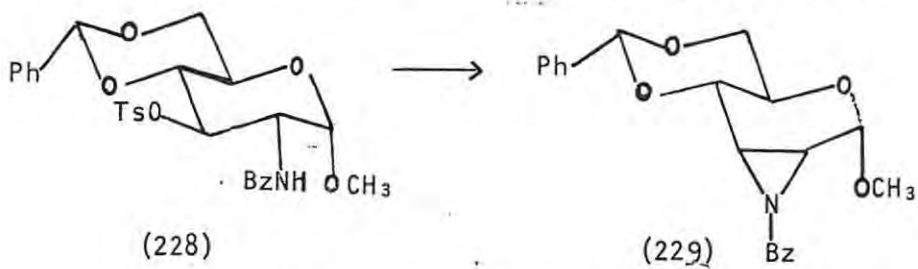


Bergman<sup>78</sup> et al., decided on a different synthetic approach based on the fact that sugar toluene-p-sulphonates containing a vicinal trans-hydroxyl group react with fluoride via epoxide formation.

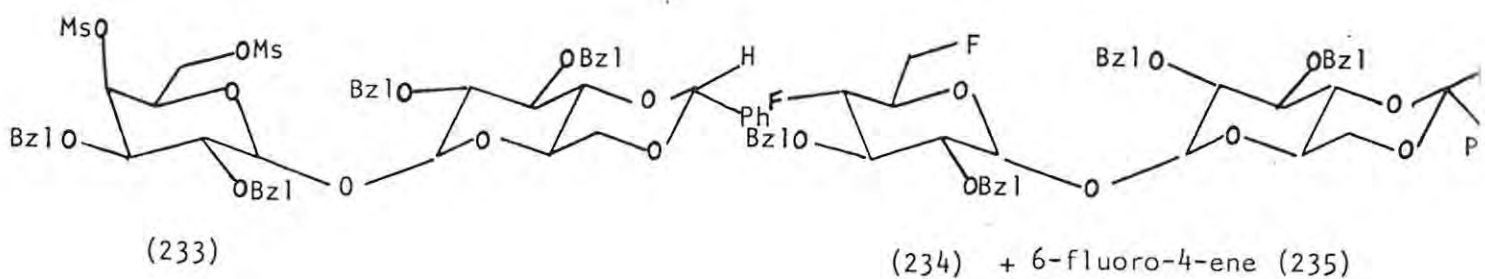
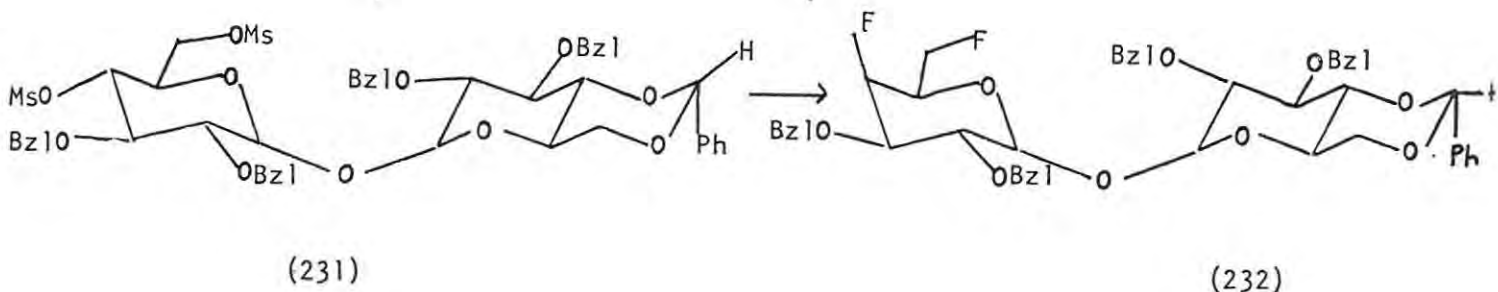
When 1,2-O-isopropylidene 3-O-tosyl  $\beta$ -D-fructopyranose was heated with potassium fluoride in N,N-dimethylacetamide it gave the known 3,4-anhydro-1,2-O-isopropylidene-D-ribohexulopyranose (227) which proved to be resistant to nucleophilic attack. When compound (227) was heated with tetrabutylammonium fluoride in acetonitrile for 3 days, ~ 50% of the epoxide reacted to give 4-deoxy-4-fluoro-1,2-O-isopropylidene- $\beta$ -D-xylohexulopyranose (224).



Hough<sup>79</sup> et al., investigated the reaction of methyl 2-benzamido-4,6-benzylidene-2-deoxy-3-O-tosyl- $\alpha$ -D-glucopyranoside (228) with the fluoride anion. Participation by the neighbouring N-benzoyl group was expected to occur thereby enhancing displacement of the sulphonate to yield methyl 3-benzamido-4,6-benzylidene-2,3-dideoxy 2-fluoro- $\alpha$ -D-altropyranoside (230) (35%).

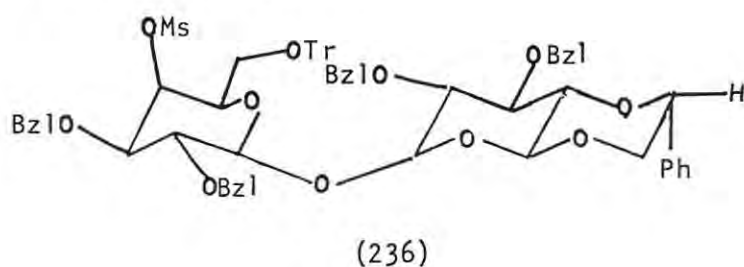


Displacement by fluoride occurs via the N-benzoyl epimine (229) involving N rather than O participation from the benzamido group. The N participation must be due to the high basicity of the fluoride anion.



Reaction of 2,3-di-O-benzyl<sup>BzO</sup> 4,6-di-O-mesyl- $\alpha$ -D-glucopyranosyl 2,3-di-O-benzyl-4,6-benzylidene- $\alpha$ -D-glucopyranoside (231) with tetrabutylammonium fluoride in acetonitrile for 4 days yielded 71% of the difluoride (232). The synthesis of the difluoride (234) from (233), 2,3-di-O-benzyl-4,6-di-O-mesyl- $\alpha$ -D-galactopyranosyl 2,3-di-O-benzyl 4,6-benzylidene- $\alpha$ -D-glucopyranoside proved difficult. Elimination reactions are more competitive in the galacto series because of the anti-periplanar relationship between the 4-sulphonyloxy group and the two vicinal protons at 3 and 5 positions. There is resistance of 6-sulphonyloxy group of the galactopyranosides towards nucleophilic displacement compared to the corresponding glucosides. Initial displacement of the 6-mesyloxy followed by both displacement at C4 with inversion of configuration and elimination afforded the 6-fluoroene (235).

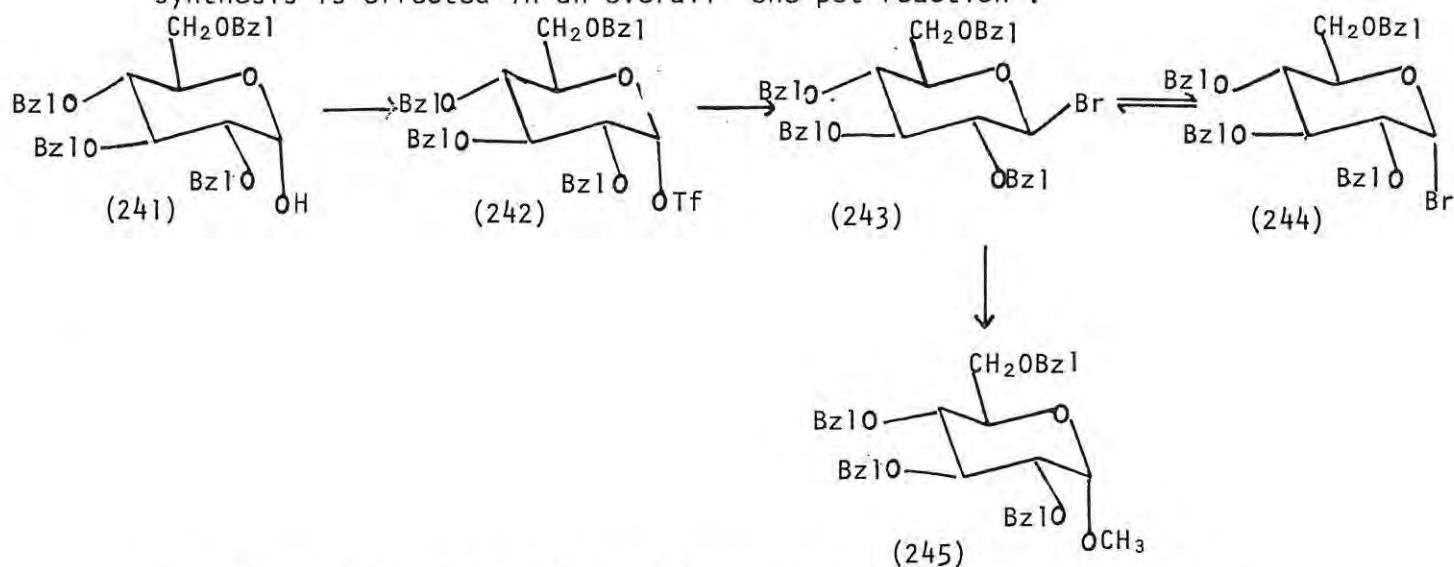
4-deoxy-4-fluoro- $\alpha,\alpha$ -trehalose was synthesised from the axial 4-sulphonate (236).



6-deoxy<sup>4</sup>-6-fluoro- $\alpha,\alpha$ -trehalose (237) was synthesised via 2,3,4,6,2',3'-hexa-O-benzyl- $\alpha,\alpha$ -trehalose (238). Treatment of 2,3,4,6-tetra-O-benzyl- $\alpha$ -D-glucopyranosyl 2,3-di-O-benzyl-6-O-toluene-p-sulphonyl- $\alpha$ -D-glucopyranoside (239) with tetrabutylammonium fluoride gave 48% of 2,3,4,6-tetra-O-benzyl- $\alpha$ -D-glucopyranosyl 2,3-di-O-benzyl-6-deoxy-6-fluoro- $\alpha$ -D-glucopyranoside (240) together with 35% of compound (238) arising from sulphonic acid cleavage. A similar side reaction was encountered in the conversion of 2,3,2',3'-tetra-O-benzyl-4,6,4',6'-tetra-O-mesyl- $\alpha,\alpha$ -trehalose into the 6,6'-difluoro derivative.

Asymmetric derivatives of the symmetrical disaccharide  $\alpha,\alpha$ -trehalose are of interest in the study of the mechanism of action of the trehalases which are a wide spread group of highly specific glycosidases.

The reaction<sup>81</sup> of aldose derivatives containing a free anomeric hydroxyl group with trifluoromethanesulphonic anhydride or methanesulphonic anhydride in the presence of halide ions and collidine affords glycosyl halides. If alcohol is introduced glycoside synthesis is effected in an overall "one pot reaction".

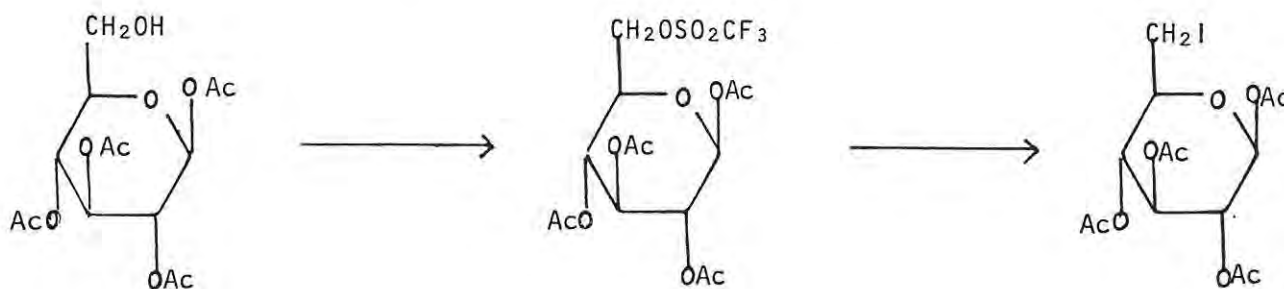
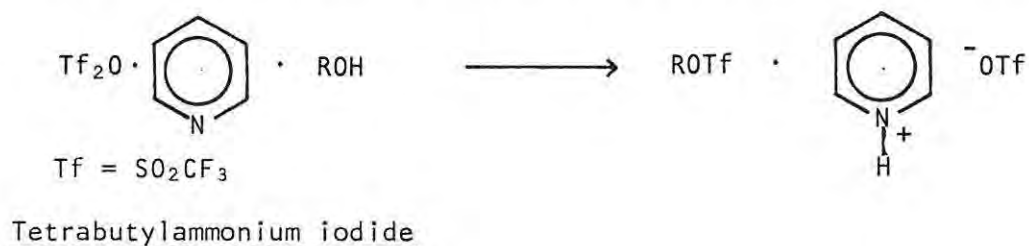


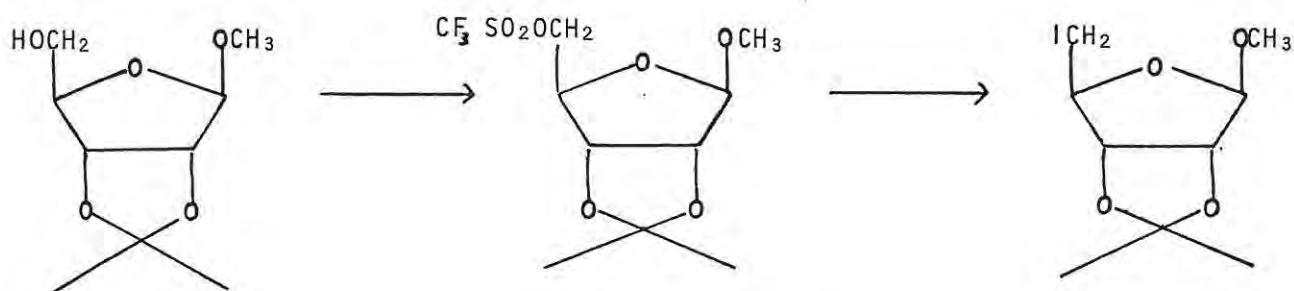
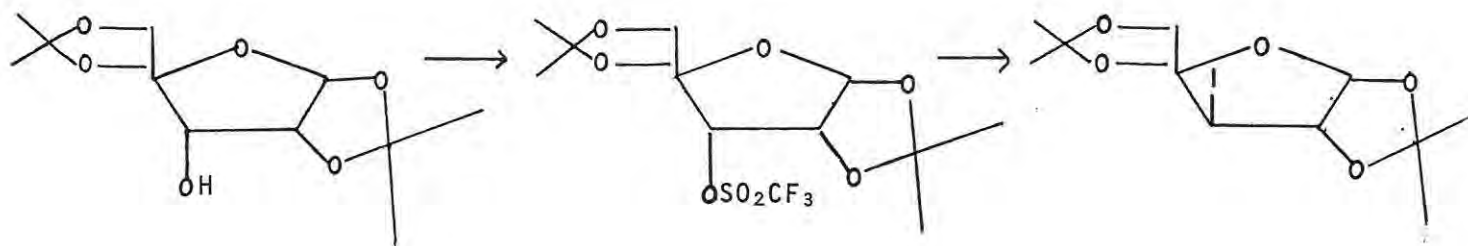
The aldose (241) 2,3,4,6-tetra-O-benzyl- $\alpha$ -D-glucopyranose may be converted into the glycoside (245) through the successive intermediacy of the 1-triflate (242) and the glycosyl bromides (243) and (244). Advantages of the "one pot reaction" are in the diminution of the number of steps involved and the ability to prepare glycosyl halides bearing acid-labile protecting groups since acidic conditions are not employed in the triflation-bromination process. Due to the presence of excess bromide ion in the medium compounds (243) and (244) are in equilibrium permitting glycoside formation to take place under kinetic control i.e. (243) reacts more rapidly with alcohol favouring the formation of the  $\alpha$ -glycosides.

Carbohydrates<sup>82,83</sup> containing a triflate group react with tetrabutylammonium halides (chloride, bromide and iodide) to yield deoxyhalogeno sugars. This method has the following advantages over the other displacement reactions.

- i) It is mild and convenient.
- ii) There are no molecular rearrangements and lack of reactivity at secondary carbon atoms.
- iii) Competing elimination reactions seldom occur.
- iv) Destructively vigorous conditions are not present.

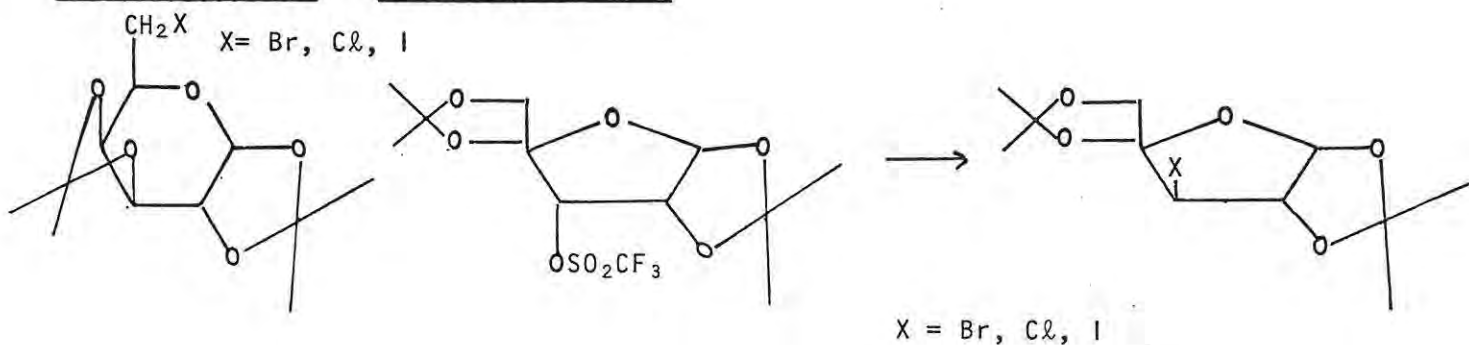
The triflyl group is displaced with ease and the enhanced nucleophilicity of the halide ion in the form of its tetrabutylammonium salt facilitates the introduction of halogens at both secondary and primary positions. General procedure for triflate synthesis involves the reaction of a dichloromethane solution of each partially protected carbohydrate with triflic anhydride in the presence of pyridine.



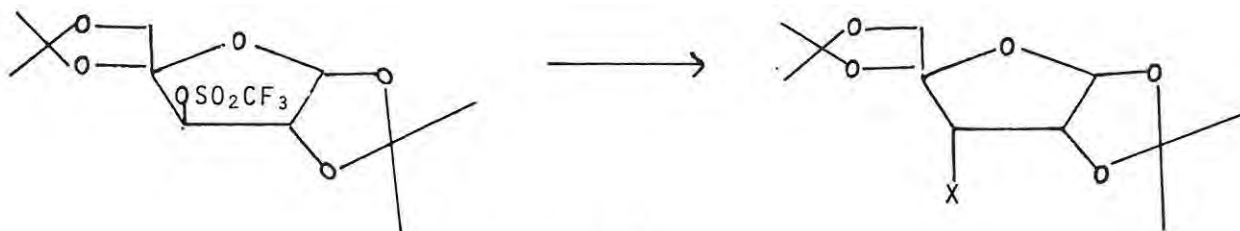


Displacement of the triflate group by Cl and Br using tetrabutylammonium chloride and bromide was investigated

Primary Triflate:      Secondary Triflate:

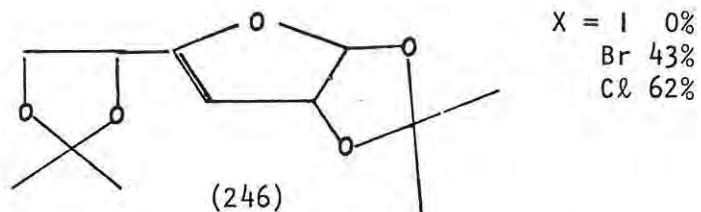


Secondary Triflate: (where substitution is known to be difficult)



X = I    55%  
 Br    42%  
 Cl    22%

Displacement on the more hindered triflate using more basic bromide and chloride ions resulted in elimination competing with substitution to yield to compound (246).



It was necessary to add sodium bicarbonate to the reaction mixtures in which elimination was taking place, otherwise acid liberated caused complete product decomposition. Triflate formation and reactions which may occur in the presence of ketal and ester protecting groups are not accompanied by rearrangement. Elimination reactions are rare and completely avoided with iodide as nucleophile.

2. EXPERIMENTAL

2.1. General procedures

Thin-layer chromatography (T.l.c.) was performed on glass plates with Kieselgel G (Merck) as adsorbent. The plates were developed with the following solvent systems:

|         |                         |         |                        |
|---------|-------------------------|---------|------------------------|
| Solvent | ether : petroleum ether | Solvent | ether : methanol       |
| 1       | 2 : 8                   | 9       | 9 : 1                  |
| 2       | 3 : 7                   | 10      | 7 : 3                  |
| 3       | 4 : 6                   | Solvent | chloroform             |
| 4       | 5 : 5                   | 11      | 10                     |
| 5       | 6 : 4                   | Solvent | ethyl acetate          |
| 6       | 7 : 3                   | 12      | 10                     |
| 7       | 8 : 2                   | Solvent | ethyl acetate:methanol |
| Solvent | ether                   | 13      | 9 : 1                  |
| 8       | 10                      |         |                        |

The developed plates were visualized with the following spray reagents: a 10% v/v sulphuric acid in ethanol (followed by charring on a hot plate at  $\approx 150^\circ$ ), b<sup>84</sup> butanol-pyridine-aniline (8:2:1).

Dry column chromatography was performed on Kieselgel 60 (Merck) (70-230 mesh ASTM) using a 1-2% loading and fractions (10-15 ml) were collected automatically and monitored by t.l.c.

Melting points (mp) were determined with a Gallenkamp melting point apparatus and are uncorrected.

Optical rotations were measured in chloroform solution (unless otherwise stated) with a Perkin-Elmer 141 automatic polarimeter.

Infra-red (i.r.) spectra were recorded on a Beckman IR 8 spectrophotometer using chloroform as solvent.

Nuclear magnetic resonance (n.m.r.) spectra were recorded on a Perkin-Elmer R-12 spectrometer at 60 MHz using chloroform as solvent with tetramethylsilane (t.m.s.) as the internal standard. Wherever possible n.m.r. assignments were confirmed by decoupling experiments.

Mass spectra were determined with an A.E.I. MS-30 spectrometer at 70eV. Unless otherwise stated concentration of solutions was carried out under reduced pressure at room temperature in a Büchi Rotavapour outfit. The term "petroleum ether" refers to the fraction of boiling point 40-60°, unless otherwise stated.

#### 2.1.2. General chlorosulphation work-up procedure<sup>85</sup>

The reaction mixture was diluted with chloroform and poured into chilled 10% sulphuric acid (equal volume) in a separating flask. The chloroform layer was separated, washed sequentially with water, a saturated sodium bicarbonate solution and finally water (2X), dried (sodium sulphate) and concentrated under reduced pressure at 30° to yield the product.

#### 2.2.1. Methyl 4,6-dichloro-4,6-dideoxy- $\alpha$ -D-galactopyranoside 2,3-dichlorosulphate (1)

Methyl  $\alpha$ -D-glucopyranoside (10 g) was treated with sulphuryl chloride (18 ml) and pyridine (20 ml) in chloroform (40 ml) as previously reported<sup>86</sup> to afford methyl 4,6-dichloro-4,6-dideoxy- $\alpha$ -D-galactopyranoside 2,3-dichlorosulphate 1 as a pale yellow syrup in a 92.8% yield. The syrup had an  $[\alpha]_D^{26} + 116.6^\circ$  (c, 1.4); lit<sup>86</sup>  $[\alpha]_D + 115^\circ$  (c, 1.2 chloroform).

#### 2.2.2. Methyl 4,6-dichloro-4,6-dideoxy- $\alpha$ -D-galactopyranoside (2)

Compound 1 (20.4 g) in methanol was catalytically dechlorosulphated with sodium iodide (10% in methanol) as previously reported<sup>86</sup> to yield

methyl 4,6-dichloro-4,6-dideoxy- $\alpha$ -D-galactopyranoside 2 as a white, crystalline powder (7.0 g, 64.0%), which was recrystallized from chloroform-petroleum ether and had mp 156-156.5°,  $[\alpha]_D^{24} + 155.2^\circ$  (c, 1.3); lit<sup>86</sup> mp 158° and  $[\alpha]_D + 179^\circ$  (c, 2.0 water).

2.2.3. Partial chlorosulphation of methyl 4,6-dichloro-4,6-dideoxy- $\alpha$ -D-galactopyranoside (2)

To a solution of compound 2 (5 g) in chloroform (100 ml) and pyridine (11 ml) at -15° was added sulphuryl chloride (3 ml in 25 ml chloroform) dropwise with stirring over a period of 1.5 hours. Work-up as described above afforded a syrupy, crystalline mass (5.9 g) which contained (t.l.c., solvent 4, spray a) 5 compounds,  $R_f$  0.77, 0.50, 0.34, 0.58 and 0.06 respectively.

The mixture (5.9 g) was separated by column chromatography (solvent 1) to afford the following compounds containing chlorosulphate groups:

Compound 3 was obtained as a chromatographically, homogeneous compound (0.9 g, 12.7%),  $R_f$  0.50 (solvent 4, spray a) and gave a positive reaction with spray b. Recrystallization from ether-petroleum ether afforded white crystals, mp 131-133°,  $[\alpha]_D^{24} + 174.4^\circ$  (c, 1.3) and  $\lambda_{max}$  2.84 (OH), 7.06 and 8.24  $\mu$ m (OSO<sub>2</sub>Cl). Parolis<sup>87</sup> et al., reported mp 132-133°,  $[\alpha]_D + 180^\circ$  (c 0.3, chloroform) and  $\lambda_{max}$  2.90 (OH), 7.06 and 8.35  $\mu$ m (OSO<sub>2</sub>Cl) for methyl 4,6-dichloro-4,6-dideoxy- $\alpha$ -D-galactopyranoside 3-chlorosulphate.

Anal. Calc. for C<sub>7</sub>H<sub>11</sub>O<sub>6</sub>SCl<sub>3</sub>: C, 25.5; H, 3.3 Found: C, 25.6; H, 3.3.

Compound 4 was obtained as a chromatographically, homogeneous compound (0.5 g, 6.3%),  $R_f$  0.34 (solvent 4, spray a) which gave a positive reaction with spray b and was recrystallized from ether-petroleum ether to afford white needles, mp 128-129°,  $[\alpha]_D^{21} + 160^\circ$

( $c$  1.2) and  $\lambda_{\max}$  2.84 (OH), 7.33 and 8.28  $\mu\text{m}$  (OSO<sub>2</sub>Cl). Compound 4 was shown to be methyl 4,6-dichloro-4,6-dideoxy- $\alpha$ -D-galactopyranoside 2-chlorosulphate.

Anal: Calc. for C<sub>7</sub>H<sub>11</sub>O<sub>6</sub>SCl<sub>3</sub>: C, 25.5; H, 3.3 Found: C, 25.5; H, 3.3

2.2.4. Methyl 3-O-acetyl-4,6-dichloro-4,6-dideoxy- $\alpha$ -D-galactopyranoside(5)

To a cooled solution (0°) of compound 2 (2 g) in chloroform (40 ml) was added dropwise with stirring acetylating mixture, (pyridine 1.4 g and acetic anhydride 0.9 g in 10 ml chloroform) over a period of 1 hour. The reaction mixture was maintained at 0° for a further 2 hours and then stirred at room temperature for 20 hours. The addition of acetylating mixture and stirring of the reaction mixture was repeated twice as described above, after which the mixture was diluted with chloroform, washed successively with water, 10% sulphuric acid, twice again with water, dried (sodium sulphate) and concentrated to yield a syrupy, crystalline mass (1.8 g). T.l.c. (solvent 11 spray a) showed spots at R<sub>f</sub> 0.69 (corresponding to the di-acetate) and R<sub>f</sub> 0.35 (corresponding to the 3- and 2-O-acetates 5 and 6) in the approximate ratio of 1:20. Recrystallization of the mixture from ether-petroleum ether afforded pure methyl 3-O-acetyl-4,6-dichloro-4,6-dideoxy- $\alpha$ -D-galactopyranoside 5 (0.8 g, 31.7%), mp 116-117°,  $[\alpha]_D^{19} + 221.1^\circ$  ( $c$ , 1.4) and  $\lambda_{\max}$  2.83 (OH) and 5.77  $\mu\text{m}$  (OAc); lit<sup>87</sup> mp 117-118° and  $[\alpha]_D + 210.5^\circ$  ( $c$  1.1, chloroform).

2.2.5. Chlorosulphation of a mixture of methyl 3-O-acetyl- and 2-O-acetyl-4,6-dichloro-4,6-dideoxy- $\alpha$ -D-galactopyranosides (5) and (6)

To a cooled solution (-15°) of a mixture of compounds 5 and 6 in chloroform (80 ml) and pyridine (3.8 ml) was added dropwise with stirring sulphuryl chloride (1.8 ml in chloroform 40 ml) over a

period of 1 hour. The mixture was maintained at 0° for a further 2 hours after which a further addition of sulphuryl chloride (1.8 ml) was carried out as above. T.l.c. (solvent 4, spray a) showed that the mixture contained two compounds, R<sub>f</sub> 0.86 and 0.75 both showing a positive reaction with spray b. Work-up as described above afforded a yellow syrup (4.8 g, 84.7%). Separation of the syrup by column chromatography on silica gel using solvents 1 and 2 afforded the following fractions.

Fraction i, a chromatographically, homogeneous syrup (2.9 g, 52.9%), R<sub>f</sub> 0.90 (solvent 4, spray a),  $[\alpha]_D^{24} + 147.4^\circ$  (c, 1.2) and  $\lambda_{\max}$  5.74 (OAc), 7.05 and 8.27  $\mu\text{m}$  (OSO<sub>2</sub>Cl) was shown to be methyl 3-O-acetyl-4,6-dichloro-4,6-dideoxy- $\alpha$ -D-galactopyranoside 2-chlorosulphate 7.

Anal: Calc. for C<sub>9</sub>H<sub>13</sub>O<sub>7</sub>SCl<sub>3</sub>: C, 29.1; H, 3.5 Found: C, 28.4; H, 3.7

Fraction ii, a chromatographically, homogeneous syrup (1.1 g, 20.6%), R<sub>f</sub> 0.53 (solvent 4, spray a),  $[\alpha]_D^{20} + 150.9^\circ$  (c, 1.2) and  $\lambda_{\max}$  5.89 (OAc), 7.49 and 8.30  $\mu\text{m}$  (OSO<sub>2</sub>Cl) proved to be methyl 2-O-acetyl-4,6-dichloro-4,6-dideoxy- $\alpha$ -D-galactopyranoside 3-chlorosulphate 8.

(Parolis<sup>87</sup> et al., reported  $[\alpha]_D + 142.2^\circ$  (c 1.1, chloroform)).

Anal: Calc. for C<sub>9</sub>H<sub>13</sub>O<sub>7</sub>SCl<sub>3</sub>: C, 29.1; H, 3.5 Found: C, 28.8; H, 3.5

2.2.6. Methyl 3-O-acetyl-4,6-dichloro-4,6-dideoxy- $\alpha$ -D-galactopyranoside 2-chlorosulphate (7).

Compound 4 (200 mg) in chloroform (5 ml) at -5° was treated with a 50:1 mixture of acetic anhydride and sulphuric acid (0.65 ml). After 30 minutes at -5° the mixture was poured into ice water and extracted twice with chloroform. The combined chloroform extracts were washed sequentially with water, saturated sodium bicarbonate solution (5X) and water (2X). The chloroform solution was dried (sodium sulphate) and concentrated to afford 7 as a syrup (180 mg,

86.1%),  $[\alpha]_D^{22} + 145.6^\circ$  (c, 1.2) and  $R_f$  0.90 (solvent 4, sprays a and b).

2.2.7. Methyl 2-O-acetyl-4,6-dichloro-4,6-dideoxy- $\alpha$ -D-galactopyranoside 3-chlorosulphate (8)

Reaction of compound 3 (200 mg) with a 50:1 mixture of acetic anhydride and sulphuric acid (1.1 ml) as described above afforded compound 8 as a pale yellow syrup (190 mg, 90.9%),  $[\alpha]_D^{22} + 151.7^\circ$  (c, 1.2) and  $R_f$  0.53 (solvent 4, sprays a and b).

(Parolis<sup>87</sup> et al., reported  $[\alpha]_D + 142.2^\circ$  (c, 1.1, chloroform) and a yield of 79%).

2.2.8. Methyl 2-O-acetyl-4,6-dichloro-4,6-dideoxy- $\alpha$ -D-galactopyranoside (6)

Triphenylphosphine (190 mg) was added to a solution of compound 8 (200 mg) in chloroform (5 ml) and the solution was stirred at room temperature for 1 hour. The mixture was diluted with chloroform, washed with water, dried (sodium sulphate) and concentrated to afford a syrupy, crystalline mass which was separated by dry column chromatography on silica gel using solvent 6 to afford compound 6 as a chromatographically, homogeneous syrup (130 mg, 88.4%),  $R_f$  0.15 (solvent 4, spray a),  $[\alpha]_D^{20} + 164.5^\circ$  (c, 1.4) and  $\lambda_{max}$  2.70 (OH) and 5.78  $\mu m$  (OAc). The syrup gave a negative reaction with spray b.

Anal: Calc. for  $C_9H_{14}O_5Cl_2$ : C, 40.5; H, 5.3 Found: C, 39.7; H, 5.2

(Parolis<sup>87</sup> et al., reported that dechlorosulphation of compound 8 with sodium iodide afforded a syrup (94%),  $[\alpha]_D + 174.7^\circ$  and  $\lambda_{max}$  2.88 (OH) and 5.75  $\mu m$  (OAc).

2.2.9. Reaction of 7 with lithium chloride

Compound 7 (150 mg) and lithium chloride (45 mg) in hexamethylphosphoramide (2 ml) were heated at 60-70° with stirring for 4 hours. The mixture was poured into ice water and extracted with

chloroform (3X). The combined chloroform extracts were dried (sodium sulphate) and concentrated to afford a crystalline residue which was shown by t.l.c. ( $R_f$  0.42, solvent 4, spray a) to be a single compound which gave a negative reaction with spray b.

Recrystallization of the residue from ether-petroleum ether afforded needle crystals, mp 112-114°,  $[\alpha]_D^{22} + 212.5^\circ$ ,  $\lambda_{\max}$  2.84 (OH) and 5.78  $\mu\text{m}$  (OAc) and mixed mp 113-115° with methyl 3-0-acetyl-4,6-dichloro-4,6-dideoxy- $\alpha$ -D-galactopyranoside 5.

#### 2.2.10. Reaction of (8) with lithium chloride

Reaction of 8 (100 mg) with lithium chloride in hexamethylphosphoramide as described above afforded a yellow syrup. T.l.c. (solvent 4, spray a) of the syrup showed a single spot,  $R_f$  0.15 which gave a negative reaction with spray b and corresponded (t.l.c.) to methyl 2-0-acetyl-4,6-dichloro-4,6-dideoxy- $\alpha$ -D-galactopyranoside 6 ( $R_f$  0.15, solvent 4).

#### 2.3.1. 6-Chloro-6-deoxy-1,2-0-isopropylidene- $\alpha$ -D-glucofuranose 3,5-dichlorosulphate (9)

Reaction of 1,2-0-isopropylidene- $\alpha$ -D-glucofuranose (10 g) with sulphuryl chloride and pyridine as previously reported<sup>25</sup> afforded 6-chloro-6-deoxy-1,2-0-isopropylidene- $\alpha$ -D-glucofuranose 3,5-dichlorosulphate 9 (15.2 g, 84.2%), mp 56-57° and  $[\alpha]_D^{20} - 41.1^\circ$  (c, 1.5); lit<sup>25</sup> mp 56-57.5°, and  $[\alpha]_D - 41.1^\circ$ .

#### 2.3.2. 6-Chloro-6-deoxy-1,2-0-isopropylidene- $\alpha$ -D-glucofuranose (10)

Compound 9 (10 g) in methanol was treated with sodium iodide in acetone-methanol (1:1) according to the method of Lawton<sup>88</sup> et al., to give a crystalline product (4 g, 70.5%) which was shown by t.l.c. (solvent 4, spray a) to be a single compound,  $R_f$  0.34 which gave a negative reaction with spray b and was recrystallized from ether-

petroleum ether, mp 77-79° and  $[\alpha]_D^{22} - 10.4^\circ$  ( $c$ , 1.2); lit<sup>25</sup> mp 78-79° and  $[\alpha]_D - 11.8^\circ$ .

2.3.3. Partial chlorosulphation of 6-chloro-6-deoxy-1,2-0-isopropylidene- $\alpha$ -D-glucofuranose (10)

To compound 10 (5 g) in chloroform (250 ml) and pyridine (3.8 ml) was added sulphuryl chloride (2.6 ml in chloroform 50 ml) dropwise with stirring over a period of 2 hours. After a further addition of sulphuryl chloride (2.6 ml) as described above the mixture was maintained at -10° for 17 hours. Work-up as described above afforded a yellow, syrupy liquid (2.8 g) which contained two major compounds  $R_f$  0.63 11 and  $R_f$  0.28 12 (solvent 4, sprays a and b) and trace amounts of a third component,  $R_f$  0.04 which was indistinguishable from the starting material 10.

The mixture (2.8 g) was separated by column chromatography (solvent 1) to afford the following compounds containing chlorosulphate groups:

Compound 11 was obtained as a chromatographically, homogeneous, crystalline compound (860 mg, 11.9%), which when recrystallized from ether-petroleum ether afforded white crystals, mp 90-92°,  $[\alpha]_D^{19} - 33.2^\circ$  ( $c$ , 1.3) and  $\lambda_{max}$  2.82 (OH), 7.77 and 8.40  $\mu m$  (OSO<sub>2</sub>Cl) and was shown to be 6-chloro-6-deoxy-1,2-0-isopropylidene- $\alpha$ -D-glucofuranose 3-chlorosulphate 11.

Anal: Calc. for C<sub>9</sub>H<sub>14</sub>O<sub>7</sub>SCl<sub>2</sub>. C, 32.1; H, 4.2 Found: C, 32.0; H, 4.2.

Compound 12 was isolated as a chromatographically, homogeneous, crystalline compound (500 mg, 6.9%), which recrystallized as fluffy, white crystals from ether-petroleum ether, mp 88-89°,  $[\alpha]_D^{19} - 19.4^\circ$  ( $c$ , 1.1) and  $\lambda_{max}$  2.82 (OH), 7.77 and 8.40  $\mu m$  (OSO<sub>2</sub>Cl). This compound proved to be 6-chloro-6-deoxy-1,2-0-isopropylidene- $\alpha$ -D-glucofuranose 5-chlorosulphate 12.

Anal: Calc. for C<sub>9</sub>H<sub>14</sub>O<sub>7</sub>SCl<sub>2</sub>. C, 32.1; H, 4.2 Found: C, 32.1; H, 4.2.

2.3.4. 3-0-Acetyl-6-chloro-6-deoxy-1,2-0-isopropylidene- $\alpha$ -D-glucofuranose 5-chlorosulphate (13)

Compound 12 (100 mg) in chloroform (2 ml) at  $-15^{\circ}$  was reacted with a 50:1 mixture of acetic anhydride and sulphuric acid (1 ml). T.l.c. showed the presence of a single compound,  $R_f$  0.81 (solvent 7, spray a) which gave a positive reaction with spray b. Work-up as described above afforded a crystalline compound 13, (105 mg, 92.9%) which was recrystallized from ether-petroleum ether, mp  $103-104^{\circ}$  (decomp.), softens at  $98^{\circ}$ ,  $[\alpha]_D^{18} - 44.6^{\circ}$  (c, 1.2) and  $\lambda_{max}$  5.80 (OAc), 7.77 and  $8.38 \mu m$  (OSO<sub>2</sub>Cl).

2.3.5. 5-0-Acetyl-6-chloro 6-deoxy-1,2-0-isopropylidene- $\alpha$ -D-glucofuranose 3-chlorosulphate (14)

Compound 11 (100 mg) in chloroform (2 ml) at  $-15^{\circ}$  was treated with a 50:1 mixture of acetic anhydride and sulphuric acid (1 ml). T.l.c. showed that the mixture contained a single compound,  $R_f$  0.80 (solvent 5, sprays a and b). Work-up as described above afforded a crystalline compound (102 mg, 90.3%) which was recrystallized from ether-petroleum ether, mp  $81.5^{\circ}-82.5^{\circ}$ ,  $[\alpha]_D^{18} - 35.7^{\circ}$  (c, 1.1) and  $\lambda_{max}$  5.75 (OAc), 7.77 and  $8.28 \mu m$  (OSO<sub>2</sub>Cl) and proved to be 5-0-acetyl-6-chloro-6-deoxy-1,2-0-isopropylidene- $\alpha$ -D-glucofuranose 3-chlorosulphate 14.

Anal: Calc. for C<sub>11</sub>H<sub>16</sub>O<sub>8</sub>SCl<sub>2</sub>: C, 34.8; H, 4.2 Found: C, 35.1; H, 4.3.

2.3.6. Chlorosulphation of 3-0-acetyl-1,2-0-isopropylidene- $\alpha$ -D-glucofuranose.

3-0-Acetyl-1,2-0-isopropylidene- $\alpha$ -D-glucofuranose (2 g) in chloroform (20 ml) and pyridine (7.4 ml) at  $-15^{\circ}$  was reacted with sulphuryl chloride (5 ml in chloroform 20 ml). The mixture which was maintained at  $-15^{\circ}$  for 1 hour,  $0^{\circ}$  for 3 hours and then at room

temperature for 17 hours, was shown to contain a single compound,  $R_f$  0.79 (solvent 7, sprays a and b). The reaction mixture when processed in the usual way afforded a crystalline product, which was recrystallized from ether (2.9 g, 69.3%), mp 100-102° (decomp), softens at 95°,  $[\alpha]_D^{19} - 43.5^\circ$  (c, 1.2) and  $\lambda_{max}$  5.80 (OAc) 7.77 and 8.38  $\mu\text{m}$  (OSO<sub>2</sub>Cl). This compound proved to be 3-0-acetyl-6-chloro 6-deoxy-1,2-0-isopropylidene- $\alpha$ -D-glucofuranose 5-chlorosulphate 13.

Anal: Calc. for C<sub>11</sub>H<sub>16</sub>O<sub>8</sub>SCl<sub>2</sub>: C, 34.8; H, 4.2 Found: C, 34.7; H, 4.3.

2.4.1. 5,6-Dichloro-5,6-dideoxy-1,2-0-isopropylidene- $\beta$ -L-idofuranose 3-chlorosulphate (15)

To a solution of 1,2-0-isopropylidene- $\alpha$ -D-glucofuranose (5 g) in chloroform (50 ml) and pyridine (12.4 ml) at -15° was added dropwise with stirring sulphuryl chloride (8.3 ml in chloroform 30 ml) over a period of 1 hour. The mixture which was maintained at -15° for 2 hours, 0° for 5 hours and then at room temperature for 16 hours was shown to contain one major compound,  $R_f$  0.58 (solvent 3, sprays a and b) which corresponded to 6-chloro-6-deoxy-1,2-0-isopropylidene- $\alpha$ -D-glucofuranose 3,5-dichlorosulphate.

The mixture was then heated under reflux at 50° for 16 hours, after which work-up as described above afforded a clear syrup which crystallized on standing (6.4 g, 79.2%). Recrystallization from acetone-petroleum ether yielded needle-like crystals and t.l.c. (solvent 3, spray a) indicated the presence of a single compound 15. mp 71-73°,  $[\alpha]_D^{20} + 8.1^\circ$  (c, 1.5) and  $\lambda_{max}$  7.28 and 8.43  $\mu\text{m}$  (OSO<sub>2</sub>Cl) which proved to be 5,6-dichloro-5,6-dideoxy-1,2-isopropylidene- $\beta$ -L-idofuranose 3-chlorosulphate 15.

2.4.2. Reaction of 5,6-dichloro-5,6-dideoxy-1,2-O-isopropylidene-  
β-L-idofuranose 3-chlorosulphate with lithium chloride in  
hexamethylphosphoramide

Compound 15 (5 g) was added to a mixture of lithium chloride (5 g) and hexamethylphosphoramide (25 ml) and stirred at 60° for 0.5 hours. After a further 1 hour at room temperature the mixture was poured into a saturated sodium bicarbonate solution and extracted with ether (3X). The combined ether extracts were washed with water, dried (sodium sulphate) and concentrated to afford a yellowish syrup (1.2 g), which was shown to contain (t.l.c.) 3 compounds (solvent 2, spray a), R<sub>f</sub> 0.67, R<sub>f</sub> 0.62 (corresponding to compound 15) and 0.12 (corresponding to the dechlorosulphated derivative).

Dechlorosulphation of (1.7 g) of the above mixture with sodium iodide as previously described afforded an orange syrup (1.1 g) which contained two compounds, R<sub>f</sub> 0.75 and R<sub>f</sub> 0.12 (solvent 2, spray a) in the approximate ratio of 1:1. Both compounds gave a negative reaction with spray b.

The mixture (1.1 g) was separated by chromatography on silica gel using solvents 1, 2 and 4 to afford the following fractions:

Fraction i, a chromatographically, homogeneous compound (250 mg, 29.2%), R<sub>f</sub> 0.73 (solvent 2, spray a) which was recrystallized from ether-petroleum ether, mp 54-55°,  $[\alpha]_D^{18} + 58.6^\circ$  (c, 1.1) and was shown to be 3,5,6-trichloro-3,5,6-trideoxy-1,2-O-isopropylidene-β-L-talofuranose 16.

Anal: Calc. for C<sub>9</sub>H<sub>13</sub>O<sub>3</sub>Cl<sub>3</sub>: C, 39.2; H, 4.7 Found: C, 39.8; H, 4.8

Cl 38.32

Cl 41.41

Fraction ii, which was isolated as a crystalline product (600 mg) was recrystallized from ether-petroleum ether and had mp 108-110°,

$[\alpha]_D^{18} - 17.3^\circ$  ( $c$ , 1.5) and  $\lambda_{\max} 2.84$  (OH) proved to be 5,6-dichloro-5,6-dideoxy-1,2-0-isopropylidene- $\beta$ -L-idofuranose 17; lit<sup>88</sup> mp 112-114° and  $[\alpha]_D - 18.7^\circ$ .

2.5.1. 1,2:5,6-Di-0-isopropylidene- $\alpha$ -D-glucofuranose 3-chlorosulphate  
(18)

1,2:5,6-Di-0-isopropylidene- $\alpha$ -D-glucofuranose (5 g) was reacted with sulphuryl chloride and pyridine as previously described<sup>86</sup> to afford 1,2:5,6-di-0-isopropylidene- $\alpha$ -D-glucofuranose 3-chlorosulphate 18 (5.5 g, 80.1%), mp 91-93°, softens at 90°, and  $[\alpha]_D^{19} - 54.8^\circ$  ( $c$ , 1.4); lit<sup>86</sup> mp 92° and  $[\alpha]_D - 40^\circ$ .

Anal: Calc. for  $C_{12}H_{19}O_8SCl$ : C, 40.2; H, 5.3 Found: C, 40.3; H, 5.4.

2.5.2. Reaction of 1,2:5,6-di-0-isopropylidene- $\alpha$ -D-glucofuranose  
3-chlorosulphate (18) with lithium chloride in  
hexamethylphosphoramide

Compound 18 (3 g) and lithium chloride in hexamethylphosphoramide (10 ml) were heated at 50-60° with stirring for 30 minutes. The mixture was worked up as described above to afford a white solid (1.3 g, 63.7%) which was shown to contain one major compound  $R_f$  0.70 (solvent 9, spray a). Recrystallization from chloroform-petroleum ether afforded fluffy, white crystals mp 160-161° (not depressed on admixture with authentic 1,2-0-isopropylidene- $\alpha$ -D-glucofuranose) and chromatographically identical to 1,2-0-isopropylidene- $\alpha$ -D-glucofuranose ( $R_f$  0.70, solvent 9, spray a).

2.6.1. Methyl 4,6-benzylidene- $\alpha$ -D-glucofuranoside (20)

Methyl  $\alpha$ -D-glucofuranoside (9.7 g) on reaction with  $\alpha, \alpha$ -dimethoxytoluene and p-toluenesulphonic acid in N,N-dimethylformamide as previously described<sup>89</sup> afforded methyl 4,6-benzylidene- $\alpha$ -D-

glucopyranoside (9 g, 63.8%), mp 162-164° and  $[\alpha]_D^{20} + 95.4^\circ$  ( $c$ , 1.3); lit<sup>89</sup> mp 167-168.5° and  $[\alpha]_D + 105^\circ$  ( $c$ , 1.1, chloroform).

2.6.2. Partial chlorosulphation of methyl 4,6-benzylidene- $\alpha$ -D-glucopyranoside (20)

To a solution of compound 20 (4 g) in chloroform (40 ml) and pyridine (7.0 ml) at -5° was added dropwise with stirring sulphuryl chloride (4 ml in chloroform 20 ml) over a period of 2.25 hours. After 3 hours at 0°, t.l.c. (solvent 4, spray a) showed that the mixture contained 4 compounds at  $R_f$  0.88, 0.66 (corresponding to the dichlorosulphate) 0.30, all giving a positive reaction with spray b and 0.08 (indistinguishable from the starting material 20).

The mixture on work-up afforded a crystalline mass (2.97 g) which when separated on a column of silica gel using solvents 3, 4 and 7 afforded the following fractions:

Fraction i, was isolated as a chromatographically, pure compound (500 mg, 9.3%),  $R_f$  0.81 (solvent 4, sprays a and b), was recrystallized from ether-petroleum ether and had mp 104-106°,  $[\alpha]_D^{20} + 86.1^\circ$  ( $c$ , 1.1),  $\lambda_{max}$  2.84 (OH), 7.77 and 8.38  $\mu$ m (OSO<sub>2</sub>Cl) and proved to be methyl 4,6-benzylidene- $\alpha$ -D-glucopyranoside 2-chlorosulphate 21.

Anal: Calc. for C<sub>14</sub>H<sub>17</sub>O<sub>8</sub>SCl: C, 44.2; H, 4.5 Found: C, 44.3; H, 4.5.

Fraction ii, was obtained as a chromatographically, homogeneous compound (650 mg, 12.1%),  $R_f$  0.26 (solvent 4, sprays a and b) was recrystallized from ether-petroleum ether, had mp 99-102° (decomp),  $[\alpha]_D^{21} + 78.4^\circ$  ( $c$ , 1.0),  $\lambda_{max}$  2.80 (OH), 7.37 and 8.28  $\mu$ m (OSO<sub>2</sub>Cl) and was shown to be methyl 4,6-benzylidene- $\alpha$ -D-glucopyranoside 3-chlorosulphate 22.

Anal: Calc. for C<sub>14</sub>H<sub>17</sub>O<sub>8</sub>SCl: C, 44.2; H, 4.5 Found: C, 44.2; H, 4.5.

2.6.3. Methyl 4,6-benzylidene- $\alpha$ -D-glucofuranoside 2,3-dichlorosulphate (23)

Methyl 4,6-benzylidene- $\alpha$ -D-glucofuranoside (100 mg) was reacted with sulphuryl chloride and pyridine as previously described<sup>86</sup> to afford methyl 4,6-benzylidene- $\alpha$ -D-glucofuranoside 2,3-dichlorosulphate 23 (155 mg, 91.7%), mp 131-133° and  $[\alpha]_D^{24} + 37.9^\circ$  (c, 1.1); lit<sup>86</sup> mp 133-136° and  $[\alpha]_D + 41.5^\circ$  (c, 1.5, chloroform).

Anal: Calc. for C<sub>14</sub>H<sub>16</sub>O<sub>10</sub>S<sub>2</sub>Cl<sub>2</sub>: C, 35.1; H, 3.3 Found: C, 35.0; H, 3.3.

2.6.4. Reaction of methyl 4,6-benzylidene- $\alpha$ -D-glucofuranoside 2,3-dichlorosulphate with lithium chloride in N,N-dimethylformamide

Compound 23 (100 mg) and lithium chloride (100 mg) in N,N-dimethylformamide were stirred at 60-80° for 2 hours and then at room temperature overnight. The mixture was shown (t.l.c.) to contain two compounds (solvent 5, spray a) R<sub>f</sub> 0.33 (corresponding to the cyclic sulphate derivative) and R<sub>f</sub> 0.21 (corresponding to the dechlorosulphated derivative) in the approximate ratio of 1:1. Both products gave a negative reaction with spray b.

2.6.5. Methyl 4,6-benzylidene- $\alpha$ -D-glucofuranoside 2,3-sulphate (24)

Compound 23 (150 mg) was dissolved in pyridine (3 ml) and maintained at 0° for 28 hours. T.l.c. (solvent 4, spray a) showed that the mixture contained a single compound, R<sub>f</sub> 0.44 which gave a negative reaction with spray b. Work-up as previously described afforded a syrup (65 mg, 63.1%) which crystallized on standing, mp 106-108° (decomp); lit<sup>86</sup> mp 103-106°.

Anal: Calc. for C<sub>14</sub>H<sub>16</sub>O<sub>7</sub>S: C, 48.8; H, 4.7 Found: C, 48.9; H, 4.8.

2.6.6. Reaction of methyl 4,6-benzylidene- $\alpha$ -D-glucofuranoside 2,3-sulphate with lithium chloride in hexamethylphosphoramide

100 mgm of lithium chloride in hexamethylphosphoramide (1 ml) was

added to compound 24 (100 mg) with stirring at 60-80° for 2 hours. After 17 hours at room temperature the mixture was shown (t.l.c.) to contain a single compound,  $R_f$  0.44 (solvent 5, spray a) which gave a negative reaction with spray b and corresponded to the cyclic sulphate 24 ( $R_f$  0.39, solvent 5, spray a).

2.6.7. Reaction of methyl 4,6-benzylidene- $\alpha$ -D-glucofuranoside 2,3-dichlorosulphate (23) with trifluoroacetic acid

Compound 23 (2 g) was stirred at room temperature in a mixture of trifluoroacetic acid (18 ml) and water (2 ml) for  $\pm 10$  minutes as previously reported<sup>90</sup>. T.l.c. (solvent 3, sprays a and b) showed that the mixture contained one major compound,  $R_f$  0.16 and a trace amount of a compound,  $R_f$  0.90 which was indistinguishable from the starting material 23. The trifluoroacetic acid-water mixture was removed under reduced pressure by co-distillation with toluene to afford a crystalline product (1.5 g, 92.0%) which was recrystallized from ether-petroleum ether and proved to be methyl- $\alpha$ -D-glucofuranoside 2,3-dichlorosulphate 25, mp 116-117°,  $[\alpha]_D^{20} + 91.5^\circ$  (c, 1.5) and  $\lambda_{max}$  2.79 (OH), 7.12 and 8.48  $\mu$ m (OSO<sub>2</sub>Cl).

Anal: Calc. for C<sub>7</sub>H<sub>12</sub>O<sub>9</sub>S<sub>2</sub>Cl<sub>2</sub>: C, 21.5; H, 3.1 Found: C, 21.7; H, 3.1.

2.6.8. Methyl 4,6-di-O-acetyl- $\alpha$ -D-glucofuranoside 2,3-dichlorosulphate (26)

Compound 25 (400 mg) in acetic anhydride (10 ml) at -10° was treated with a 50:1 mixture of acetic anhydride and sulphuric acid (2.2 ml). After 20 minutes at 0° the mixture was poured into an ice-sodium bicarbonate mixture and worked up as described above to afford a crystalline compound 26 (450 mg, 92.6%) which was recrystallized from ether-petroleum ether and had mp 117-118°, softens at 112°,  $[\alpha]_D^{15} + 5.1^\circ$  (c, 0.9) and  $\lambda_{max}$  5.80 (OAc), 7.60 and 8.30  $\mu$ m (OSO<sub>2</sub>Cl).

Anal: Calc. for C<sub>11</sub>H<sub>16</sub>O<sub>12</sub>S<sub>2</sub>Cl<sub>2</sub>: C, 27.8; H, 3.4 Found: C, 28.2; H, 3.4.

2.6.9. Direct synthesis of methyl 4,6-di-O-acetyl- $\alpha$ -D-glucopyranoside 2,3-dichlorosulphate (26) from methyl 4,6-benzylidene- $\alpha$ -D-glucopyranoside 2,3-dichlorosulphate (23)

Compound 23 (500 mg) was dissolved with stirring at room temperature in a mixture of trifluoroacetic acid (4.5 ml) and water (0.5 ml). After 10 minutes t.l.c. indicated the presence of a single compound,  $R_f$  0.30 (solvent 4, spray a and b) which corresponded to compound 25. The mixture at 0° was treated with a 50:1 mixture of acetic anhydride and sulphuric acid (4 ml) and after 20 minutes at 0° was poured into an ice-sodium bicarbonate mixture and worked up as described above to afford a yellow syrup 26 which crystallized from ether-petroleum ether (450 mg, 90.9%), mp 117-118° and  $\lambda_{max}$  5.80 (OAc), 7.60 and 8.30  $\mu$ m (OSO<sub>2</sub>Cl).

2.7.1. Methyl 4,6-benzylidene- $\alpha$ -D-galactopyranoside (27)

Methyl  $\alpha$ -D-galactopyranoside (20 g) when reacted with zinc chloride and benzaldehyde as previously reported<sup>91</sup> afforded methyl 4,6-benzylidene- $\alpha$ -D-galactopyranoside (18.7 g, 61.7%) mp 160-162°; lit<sup>91</sup> mp 169-170°.

2.7.2. Methyl 4,6-benzylidene- $\alpha$ -D-galactopyranoside 2,3-dichlorosulphate (28)

To a solution of compound 27 (2.5 g) in chloroform (30 ml) and pyridine (1.4 ml) at 0° was added dropwise with stirring sulphuryl chloride (0.9 ml in chloroform 20 ml) over a period of 30 minutes. After 2 hours at 0° work-up as described above afforded a crystalline mass (2 g, 47.2%), which when recrystallized from ether-petroleum ether was shown to contain a single compound 28,  $R_f$  0.67 (solvent 6, sprays a and b), mp 141.5-143°,  $[\alpha]_D^{19} + 160.7^\circ$  (c, 1.6) and  $\lambda_{max}$  7.30 and 8.48  $\mu$ m (OSO<sub>2</sub>Cl).

Anal: Calc. for C<sub>14</sub>H<sub>16</sub>O<sub>10</sub>S<sub>2</sub>Cl<sub>2</sub>: C, 35.1; H, 3.3 Found: C, 35.0; H, 3.5.

2.7.3. Reaction of methyl 4,6-benzylidene- $\alpha$ -D-galactopyranoside 2,3-dichlorosulphate with trifluoroacetic acid

Compound 28 (200 mg) was stirred at room temperature in a mixture of trifluoroacetic acid (1.8 ml) and water (0.2 ml) for  $\pm 10$  minutes. Work-up as described above afforded a crystalline mass which was shown by t.l.c. (solvent 6, sprays a and b) to contain two compounds,  $R_f$  0.54 (corresponding to the starting material) and  $R_f$  0.40. Recrystallization from chloroform-petroleum ether afforded a chromatographically, homogeneous compound 29 (150 mg, 92.0%),  $R_f$  0.40 (solvent 6, sprays a and b) which proved to be methyl- $\alpha$ -D-galactopyranoside 2,3-dichlorosulphate 29, mp 118-120°,  $[\alpha]_D^{15} + 369.8^\circ$  (c, 1.2) and  $\lambda_{\max}$  2.80 (OH), 7.22 and 8.38  $\mu\text{m}$  (OSO<sub>2</sub>Cl).

Anal: Calc. for C<sub>7</sub>H<sub>12</sub>O<sub>10</sub>S<sub>2</sub>Cl<sub>2</sub>: C, 21.5; H, 3.1 Found: C, 21.6; H, 3.1.

2.7.4. Direct synthesis of methyl 4,6-di-O-acetyl- $\alpha$ -D-galactopyranoside 2,3-dichlorosulphate (30) from methyl 4,6-benzylidene- $\alpha$ -D-galactopyranoside 2,3-dichlorosulphate (28)

Compound 28 (500 mg) was stirred at room temperature in a mixture of trifluoroacetic acid (4.5 ml) and water (0.5 ml) for  $\pm 10$  minutes. T.l.c. (solvent 6, sprays a and b) at this stage indicated the presence of a single compound,  $R_f$  0.42 (corresponding to 29). The mixture was cooled (-5°) and was treated with a 50:1 mixture of acetic anhydride and sulphuric acid (4 ml) and after 20 minutes at -5° was worked up as described above to afford a pale yellow syrup which crystallized on standing. Recrystallization from ether-petroleum ether afforded a chromatographically homogeneous compound (470 mg, 94.8%) which proved to be methyl 4,6-di-O-acetyl- $\alpha$ -D-galactopyranoside 2,3-dichlorosulphate 30, mp 108-110°,  $[\alpha]_D^{15} + 202.6^\circ$  (c, 3.0) and  $\lambda_{\max}$  5.77 (OAc) and 7.33  $\mu\text{m}$  (OSO<sub>2</sub>Cl).

Anal: Calc. for  $C_{11}H_{16}O_{12}S_2Cl_2$ : C, 27.9; H, 3.4 Found: C, 28.2; H, 3.6.

2.8.1. Methyl 4,6-benzylidene- $\alpha$ -D-mannopyranoside (31)

Methyl  $\alpha$ -D-mannopyranoside (9.7 g) was reacted with  $\alpha,\alpha$ -dimethoxytoluene and p-toluenesulphonic acid in N,N-dimethylformamide as previously reported<sup>89</sup> in the preparation of methyl 4,6-benzylidene- $\alpha$ -D-glucopyranoside 20. The mixture contained 3 compounds (solvent 8, spray a),  $R_f$  0.98, 0.59 and 0.11 (corresponding to the starting material). Recrystallization of the mixture from methanol-water afforded what appeared to be a single compound (1 g), mp 149-150°, which proved to be a mixture of the exo and endo isomers of methyl 2,3:4,6-di-benzylidene- $\alpha$ -D-mannopyranoside 32. The mother liquors were then concentrated, dissolved in chloroform, decolourized (charcoal) and dried (sodium sulphate). Recrystallization from hot benzene afforded a chromatographically homogeneous compound,  $R_f$  0.59 (solvent 8, spray a) which was shown to be methyl 4,6-benzylidene- $\alpha$ -D-mannopyranoside 31 (9 g, 63.8%), mp 143.5-145° and  $[\alpha]_D^{19} + 31.1^\circ$  (c, 1.2 methanol); lit<sup>38</sup> mp 141-143°, and yield 51%.

2.8.2. Reaction of methyl 4,6-benzylidene- $\alpha$ -D-mannopyranoside with sulphuryl chloride and pyridine at 0°

To a solution of compound 31 (1 g) in chloroform (20 ml) and pyridine (0.2 ml) at 0° was added dropwise with stirring sulphuryl chloride (0.1 ml in chloroform 2 ml) over a period of 15 minutes. After 30 minutes at 0° the addition of sulphuryl chloride and pyridine as described above was repeated (4X) at regular intervals. The mixture when worked up as described above afforded a crystalline mass (540 mg) which on recrystallization from chloroform-petroleum ether was shown to contain what appeared to be a single compound,  $R_f$  0.94 (solvent 4, spray a) which gave a negative reaction with spray b and had mp 150-151° and proved to be a mixture of the exo and endo isomers of methyl 2,3:4,6-

di-benzylidene- $\alpha$ -D-mannopyranoside 32.

2.8.3. Synthesis of methyl 4,6-benzylidene- $\alpha$ -D-mannopyranoside replacing p-toluenesulphonic acid with sulphuryl chloride as catalyst.

Methyl  $\alpha$ -D-mannopyranoside (970 mg) was dissolved with heating ( $\pm 70^\circ$ ) in  $\alpha,\alpha$ -dimethoxytoluene (760 mg) and N,N-dimethylformamide (4 ml). Sulphuryl chloride (4 drops) was added to the cooled mixture ( $0^\circ$ ) which was then stirred at room temperature for 5 hours after which t.l.c. (solvent 8, spray a) indicated the presence of 3 compounds,  $R_f$  0.96, 0.60 and 0.13 (corresponding to the starting material) in the approximate ratio of 4:5:1. After removal of N,N-dimethylformamide, the residue was dissolved in chloroform and the solution was washed successively with a saturated sodium bicarbonate solution, water (2X), dried (sodium sulphate) and concentrated to yield a syrupy, crystalline mass (730 mg). Recrystallization first from chloroform-petroleum ether afforded 130 mg of methyl 4,6-benzylidene- $\alpha$ -D-mannopyranoside 31,  $R_f$  0.60 (solvent 8, spray a) and mp  $138-141^\circ$ .

Recrystallization of the residue from chloroform-petroleum ether yielded 100 mgm of a mixture of the exo and endo isomers of methyl 2,3:4,6-di-benzylidene- $\alpha$ -D-mannopyranoside 32,  $R_f$  0.96 (solvent 8, spray a) and mp  $150-151^\circ$ .

2.9.1. Methyl 4,6-benzylidene- $\alpha$ -D-mannopyranoside 2,3-dichlorosulphate (33)

To a solution of compound 31 (500 mg) in chloroform (5 ml) and pyridine (0.8 ml) at  $-15^\circ$  was added sulphuryl chloride (0.5 ml) dropwise with stirring over a period of 20 minutes. Work-up as described above afforded a crystalline mass (800 mg, 94.5%) which when recrystallized from ether-petroleum ether was shown (t.l.c.) to contain a single compound 33,  $R_f$  0.87 (solvent 4, sprays a and b), mp  $103-105^\circ$

(decomp),  $[\alpha]_D^{22} - 28.5^\circ$  ( $c$ , 1.4) and  $\lambda_{\max}$  7.30 and 8.48  $\mu\text{m}$  (OSO<sub>2</sub>Cl).

Compound 33 proved to be methyl 4,6-benzylidene- $\alpha$ -D-mannopyranoside 2,3-dichlorosulphate.

Anal: Calc. for C<sub>14</sub>H<sub>16</sub>O<sub>10</sub>S<sub>2</sub>Cl<sub>2</sub> C, 35.0; H, 3.5 Found: C, 35.0; H, 3.5.

2.9.2. Reaction of methyl 4,6-benzylidene- $\alpha$ -D-mannopyranoside 2,3-dichlorosulphate with trifluoroacetic acid

Compound 33 (100 mg) was stirred at room temperature in a mixture of trifluoroacetic acid (0.9 ml) and water (0.1 ml). After 20 minutes the mixture was shown to contain a single compound,  $R_f$  0.19 (solvent 4, sprays a and b), whereupon work-up as usual afforded a syrup (60 mg, 73.6%) which was shown to be methyl  $\alpha$ -D-mannopyranoside 2,3-dichlorosulphate 34,  $\lambda_{\max}$  2.84 (OH) 7.77 and 8.38  $\mu\text{m}$  (OSO<sub>2</sub>Cl).

2.9.3. Direct synthesis of methyl 4,6-di-O-acetyl- $\alpha$ -D-mannopyranoside 2,3-dichlorosulphate (35) from methyl 4,6-benzylidene- $\alpha$ -D-mannopyranoside 2,3-dichlorosulphate (33)

Compound 33 (900 mg) was stirred at room temperature in a mixture of trifluoroacetic acid (9 ml) and water (1 ml). After 10 minutes the mixture was shown to contain a single compound,  $R_f$  0.21 (solvent 4, sprays a and b) which corresponded to methyl  $\alpha$ -D-mannopyranoside, 2,3-dichlorosulphate. The mixture was cooled (-16°) and treated with a 50:1 mixture of acetic anhydride and sulphuric acid (10 ml) and worked up as usual to afford a crystalline compound (400 mg, 44.8%).

Recrystallization from ether-petroleum ether afforded 35, mp 118-119° (decomp), softens at 111°,  $[\alpha]_D^{15} + 9.0^\circ$  ( $c$ , 1.1) and  $\lambda_{\max}$  5.80 (OAc), 7.37 and 8.38  $\mu\text{m}$  (OSO<sub>2</sub>Cl). T.l.c. (solvent 4, spray a) indicated the presence of a single compound,  $R_f$  0.28 which gave a positive reaction with spray b was shown to be methyl 4,6-di-O-acetyl- $\alpha$ -D-mannopyranoside 2,3-dichlorosulphate 35.

Anal: Calc. for  $C_{11}H_{16}O_{12}S_2Cl_2$ . C, 27.9; H, 3.4 Found: C, 28.0; H, 3.3.

2.9.4. Partial acetylation of methyl 4,6-benzylidene- $\alpha$ -D-mannopyranoside

Methyl 4,6-benzylidene- $\alpha$ -D-mannopyranoside (2 g) in pyridine/toluene at  $-5^\circ$  when treated with acetic anhydride/pyridine as previously reported yielded<sup>92</sup> a mixture after which dry column chromatography using solvent 8 afforded the following compounds:

- i) Methyl 2,3-di-0-acetyl-4,6-benzylidene- $\alpha$ -D-mannopyranoside 36 which was obtained as a syrup (250 mg),  $R_f$  0.90 (solvent 4, spray a)
- ii) Methyl 2-0-acetyl-4,6-benzylidene- $\alpha$ -D-mannopyranoside 37 which was obtained as a yellow syrup (200 mg, 8.7%),  $R_f$  0.36 (solvent 3, spray a)
- iii) Methyl 3-0-acetyl-4,6-benzylidene- $\alpha$ -D-mannopyranoside 38, which was isolated as a syrup (800 mg, 34.8%),  $R_f$  0.52 (solvent 3, spray a); lit<sup>92</sup> yield 30%.

2.9.5. Chlorosulphation of methyl 3-0-acetyl-4,6-benzylidene- $\alpha$ -D-mannopyranoside (38)

To a solution of compound 38 (400 mg) in chloroform (8 ml) and pyridine (2 ml) at  $-10^\circ$  was added dropwise with stirring sulphuryl chloride (1.2 ml). After 20 minutes at  $-10^\circ$  work-up in the usual way afforded a pale yellow syrup (400 mg, 88.3%) which was shown to contain a single compound 39,  $R_f$  0.80 (solvent 4, spray a) which gave a positive reaction with spray b,  $[\alpha]_D^{18} + 7.7^\circ$  (c, 1.3) and  $\lambda_{max}$  5.70 (OAc), 7.40 and 8.38  $\mu m$  (OSO<sub>2</sub>Cl). Compound 39 proved to be methyl 3-0-acetyl-4,6-benzylidene- $\alpha$ -D-mannopyranoside 2-chlorosulphate.

2.9.6. Chlorosulphation of methyl 2-0-acetyl-4,6-benzylidene- $\alpha$ -D-mannopyranoside (37)

Compound 37 (200 mg) was reacted with sulphuryl chloride and pyridine as described above to afford a pale yellow syrup (220 mg, 84.6%) which was shown to contain a single compound 40,  $R_f$  0.72 (solvent 4, sprays a and b),  $[\alpha]_D^{15} + 58.9^\circ$  (c, 2.8) and  $\lambda_{max}$  5.70 (OAc), 7.40 and 8.38  $\mu m$  (OSO<sub>2</sub>Cl). Compound 40 was shown to be methyl 2-0-acetyl-4,6-benzylidene- $\alpha$ -D-mannopyranoside 3-chlorosulphate.

2.9.7. Reaction of compound (40) with lithium chloride

Compound 40 (20 mg) and lithium chloride (20 mg) in hexamethylphosphoramide (0.2 ml) were heated at 70-80° with stirring for 1 hour. The mixture was shown to contain a single compound,  $R_f$  0.35 (solvent 3, spray a) which gave a negative reaction with spray b and corresponded (t.l.c.) to methyl 2-0-acetyl-4,6-benzylidene- $\alpha$ -D-mannopyranoside 37 ( $R_f$  0.36, solvent 3, spray a).

2.9.8. Reaction of compound (39) with lithium chloride

Reaction of compound 39 (20 mg) with lithium chloride in hexamethylphosphoramide as described above afforded a pale yellow syrup. T.l.c. (solvent 3, spray a) showed that the syrup contained one compound,  $R_f$  0.49 which gave a negative reaction with spray b and corresponded (t.l.c.) to methyl 3-0-acetyl-4,6-benzylidene- $\alpha$ -D-mannopyranoside 38 ( $R_f$  0.51, solvent 3, spray a).

2.10.1. Methyl 4,6-0-isopropylidene- $\alpha$ -D-mannopyranoside (41)

Methyl  $\alpha$ -D-mannopyranoside (5.8 g) on reaction with isopropenyl methyl ether and p-toluenesulphonic acid in N,N-dimethylformamide as previously described<sup>93</sup> afforded after column chromatography, methyl 4,6-

Q-isopropylidene- $\alpha$ -D-mannopyranoside as a crystalline solid which when recrystallized from ethyl acetate-hexane yielded fluffy, white crystals (5.5 g, 79.7%), mp 96-97° and  $[\alpha]_D^{23} + 61.1^\circ$  (c, 1.3, methanol); lit<sup>93</sup> mp 98-99°.

2.10.2. Methyl 4,6-0-isopropylidene- $\alpha$ -D-mannopyranoside 2,3-dichlorosulphate (42)

To a solution of compound 41 (100 g) in chloroform (1 ml) and pyridine (0.08 ml) at -10° was added dropwise with stirring sulphuryl chloride (0.05 ml). After 5 hours at -10° work-up in the usual manner afforded a crystalline mass (180 mg, 97.8%) which was shown to contain (t.l.c.) a single compound  $R_f$  0.79 (solvent 4, sprays a and b). Recrystallization from ether-petroleum ether afforded compound 42 which proved to be methyl 4,6-0-isopropylidene- $\alpha$ -D-mannopyranoside 2,3-dichlorosulphate, mp 48-50°,  $[\alpha]_D^{19} - 22.3^\circ$  (c, 1.3) and  $\lambda_{max}$  7.25 and 8.38  $\mu$ m (OSO<sub>2</sub>Cl).

Anal: Calc. for C<sub>10</sub>H<sub>16</sub>O<sub>10</sub>S<sub>2</sub>Cl<sub>2</sub>. C, 27.9; H, 3.7 Found: C, 25.2, H, 3.6.

2.10.3. Reaction of methyl 4,6-0-isopropylidene- $\alpha$ -D-mannopyranoside 2,3-dichlorosulphate with trifluoroacetic acid

Compound 42 (180 mg) was stirred at room temperature in a mixture of trifluoroacetic acid (0.9 ml) and water (0.1 ml) for  $\pm$ 20 minutes. The mixture was worked up as usual to afford a clear, colourless syrup (140 mg, 85.9%) which contained a single compound,  $R_f$  0.21 (solvent 4, sprays a and b) and corresponds (t.l.c.) to methyl  $\alpha$ -D-mannopyranoside 2,3-dichlorosulphate 34.

2.11.1. 5-Chloro-5-deoxy-1,2-0-isopropylidene- $\alpha$ -D-xylofuranose 3-chlorosulphate (43)

To a cooled (-15°) solution of 1,2-0-isopropylidene- $\alpha$ -D-

xylofuranose (5 g) in chloroform (35 ml) and pyridine (15 ml) was added sulphuryl chloride (7 ml diluted with 15 ml chloroform) as described above over 1.25 hours. After 2 hours at  $-15^{\circ}$  and 2 hours at room temperature the product was isolated in the usual manner to yield a white solid (6.7 g, 83.2%) which was shown to contain a single compound 43,  $R_f$  0.88 (solvent 4, sprays a and b) and on recrystallization from ether-petroleum ether afforded white crystals, mp  $98.5-100^{\circ}$  and  $[\alpha]_D^{22} - 72^{\circ}$  (c, 1.3); lit<sup>94</sup> mp  $96.5-97.5^{\circ}$  and  $[\alpha]_D - 76.3^{\circ}$  (c, 1.76, chloroform).

2.11.2. 5-Chloro-5-deoxy-1,2-O-isopropylidene- $\alpha$ -D-xylofuranose (44)

Compound 43 (790 mg) was dechlorosulphated with sodium iodide as previously described<sup>94</sup> to afford a crystalline mass which was shown (t.l.c.) to contain a single compound 44,  $R_f$  0.48 (solvent 4, spray a) giving a negative reaction with spray b. Recrystallization from ether-petroleum ether afforded white crystals (480 mg, 89.4%), mp  $97-98^{\circ}$ ,  $[\alpha]_D^{19} - 36.7^{\circ}$  (c, 1.2) and  $\lambda_{max}$  2.84  $\mu$ m (OH). Compound 44 proved to be 5-chloro-5-deoxy-1,2-O-isopropylidene- $\alpha$ -D-xylofuranose. lit<sup>94</sup> mp  $98-99^{\circ}$  and  $[\alpha]_D - 40.07^{\circ}$  (c, 1.33, chloroform).

2.11.3. Reaction of 5-chloro-5-deoxy-1,2-O-isopropylidene- $\alpha$ -D-xylofuranose 3-chlorosulphate (i) with hexamethylphosphoramide

To compound 43 (5 mg) at room temperature was added hexamethylphosphoramide (0.5 ml). After 30 minutes t.l.c. showed that the mixture contained one major compound,  $R_f$  0.32 (solvent 4, spray a) which corresponded to the dechlorosulphated product 44 and trace amounts of a compound,  $R_f$  0.77, indistinguishable from the starting material.

(ii) with lithium chloride in hexamethylphosphoramide followed by reaction with acetic anhydride and pyridine.

Compound 43 (200 mg) and lithium chloride (277 mg) in hexamethylphosphoramide (2 ml) were heated at 60-70° with stirring for 0.75 hours. T.l.c. (solvent 2, spray a) indicated the presence of two compounds,  $R_f$  0.98 (corresponded to the starting material) and  $R_f$  0.51 (corresponded to the dechlorosulphated compound 44) in the approximate ratio of 1:1. The latter compound when reacted with acetic anhydride and pyridine afforded a single compound 45,  $R_f$  0.78 (solvent 4, spray a). Compound 45 proved to be 3-0-acetyl-5-chloro 5-deoxy-1,2-0-isopropylidene- $\alpha$ -D-xylofuranose.

2.11.4. Acetylation of 5-chloro-5-deoxy-1,2-0-isopropylidene- $\alpha$ -D-xylofuranose

Compound 44 (150 mg) was reacted with acetic anhydride and pyridine as described above to afford 3-0-acetyl-5-chloro 5-deoxy-1,2-0-isopropylidene- $\alpha$ -D-xylofuranose 45 (170 mg, 94.0%).

2.11.5. Reaction of 5-chloro 5-deoxy-1,2-0-isopropylidene- $\alpha$ -D-xylofuranose 3-chlorosulphate (43) with trifluoroacetic acid

Compound 43 (5 g) in a mixture of trifluoroacetic acid (45 ml) and water (5 ml) at room temperature was stirred for 30 minutes, whereupon t.l.c. (solvent 3, spray a) indicated the presence of one major compound,  $R_f$  0.17 and a trace of a compound,  $R_f$  0.81 (corresponding to the starting material), both giving a positive reaction with spray b. Work-up in the usual manner yielded a crystalline mass (4.35 g 92.0%) which when recrystallized from ether-petroleum ether afforded a chromatographically, pure compound 46,  $R_f$  0.50 (solvent 4, sprays a and b), mp 78-80°,  $[\alpha]_D^{23} - 20.4^\circ$  (c, 1.4)

and  $\lambda_{\max}$  2.94 (OH), broad peak, 7.12 and 8.48  $\mu\text{m}$  ( $\text{OSO}_2\text{Cl}$ ). Compound 46 was shown to be 5-chloro-5-deoxy-D-xylofuranose 3-chlorosulphate.

Anal: Calc. for  $\text{C}_5\text{H}_8\text{O}_6\text{SCl}_2$  C, 22.5; H, 3.0 Found: C, 22.6; H, 3.2.

2.11.6. Acetylation of 5-chloro-5-deoxy-D-xylofuranose 3-chlorosulphate (46)

Compound 46 (3.3 g) in acetic anhydride (25 ml) at  $-15^\circ$  was treated with a 50:1 mixture of acetic anhydride and sulphuric acid (35 ml) as described above over 5 hours. T.l.c. (solvent 3, spray a) revealed the presence of a single compound,  $R_f$  0.54 which gave a positive reaction with spray b. The mixture was poured into an ice-saturated sodium bicarbonate mixture and worked up as before to afford a crystalline compound 47 (1.6 g, 36.1%) which was recrystallized from ether-petroleum ether, mp  $81.5^\circ$ - $82^\circ$ , softens at  $78^\circ$ ,  $[\alpha]_D^{19} - 105^\circ$  (c, 1.2) and  $\lambda_{\max}$  5.86 (OAc) and 7.77  $\mu\text{m}$  ( $\text{OSO}_2\text{Cl}$ ) and proved to be 1,2-di-O-acetyl-5-chloro-5-deoxy- $\beta$ -D-xylofuranose 3-chlorosulphate 47.

Anal: Calc. for  $\text{C}_9\text{H}_{12}\text{O}_8\text{SCl}_2$  C, 30.8; H, 3.4 Found: C, 30.6; H, 3.5.

2.11.7. Reaction of 1,2-di-O-acetyl-5-chloro-5-deoxy- $\beta$ -D-xylofuranose 3-chlorosulphate (47) with lithium chloride in hexamethylphosphoramide

Compound 47 (1.6 g) and lithium chloride (1.5 g) in hexamethylphosphoramide (5 ml) were heated at  $60$ - $70^\circ$  with stirring for 20 minutes. T.l.c. (solvent 3, spray a) indicated the presence of one major compound ( $\sim 80\%$ ),  $R_f$  0.58 which gave a negative reaction with spray b and four minor compounds with  $R_f$ 's 0.44, 0.34, 0.22 and 0.18 respectively. The mixture was diluted with a saturated solution of sodium bicarbonate and extracted with ether (3X). The combined ether extracts were washed with water, dried (sodium sulphate) and concentrated

to yield a syrupy crystalline mass (860 mg). The syrup was separated by chromatography on silica gel using solvent 1 to afford:

Compound 48, a chromatographically pure compound (300 mg, 21.9%),  $R_f$  0.64 (solvent 4, spray a) giving a negative reaction with spray b was recrystallized from ether-petroleum ether, mp 71-73°,  $[\alpha]_D^{21} - 43.2^\circ$  (c, 1.5) and  $\lambda_{max}$  5.90  $\mu$ m (OAc). Compound 48 was shown to be 1,2-di-0-acetyl-3,5-dichloro-3,5-dideoxy- $\beta$ -D-ribofuranose.

Anal: Calc. for  $C_9H_{12}O_5Cl_2$  C, 39.9; H, 4.4 Found: C, 39.9; H, 4.4  
Cl, 25.93 Cl, 26.35

2.12.1. 3,5-Di-0-benzoyl-1,2-0-isopropylidene- $\alpha$ -D-xylofuranose (49)

To a cooled (0°) solution of 1,2-0-isopropylidene- $\alpha$ -D-xylofuranose in pyridine (7 ml) was added dropwise with stirring, benzoyl chloride (4 ml diluted in 5 ml chloroform). The mixture which was shown to contain a single compound,  $R_f$  0.77 (solvent 4, spray a) was then poured into a mixture of chloroform and 10% sulphuric acid (cooled). The chloroform layer was separated, washed with a saturated sodium bicarbonate solution, water, dried (sodium sulphate) and concentrated to yield a pale yellow syrup 49 (4.1 g, 96.9%),  $[\alpha]_D^{27} - 38.7^\circ$  (c, 1.4) and  $\lambda_{max}$  5.78 (OBz).

Anal: Calc. for  $C_{22}H_{22}O_7$  C, 66.3; H, 5.5 Found: C, 67.3; H, 5.3.

2.12.2. Reaction of 3,5-di-0-benzoyl-1,2-0-isopropylidene- $\alpha$ -D-xylofuranose with trifluoroacetic acid

Compound 49 (1 g) was stirred at room temperature in a mixture of trifluoroacetic acid (9 ml) and water (1 ml) for  $\pm$ 30 minutes. Work-up as usual afforded a cloudy syrup (700 mg, 77.9%) which contained a compound 50,  $R_f$  0.82 (solvent 8, spray a),  $[\alpha]_D^{17} + 7.3^\circ$  (c, 1.2, methanol) and  $\lambda_{max}$  3.04 (OH), broad peak, and 5.90  $\mu$ m (OBz). Compound 50 proved to be 3,5-di-0-benzoyl-D-xylofuranose.

Anal: Calc. for  $C_{19}H_{18}O_7$  C, 63.7; H, 5.0 Found: C, 63.1; H, 5.1.

2.12.3. Chlorosulphation of 3,5-di-O-benzoyl-D-xylofuranose (50)

To a cooled ( $-15^\circ$ ) solution of compound 50 (500 mg) in chloroform (6 ml) and pyridine (0.5 ml) was added sulphuryl chloride (0.3 ml diluted in 3 ml chloroform) as described over 10 minutes. After 20 minutes at  $-15^\circ$  work-up as usual afforded a yellow syrup (410 mg, 61.9%) which was shown to be a mixture of two compounds having  $R_f$  values of 0.87 and 0.81 (solvent 4, sprays a and b),  $[\alpha]_D^{17} + 23.7^\circ$  (c, 1.1) and  $\lambda_{max}$  5.80 (OBz), 7.02 and 8.28  $\mu$ m (OSO<sub>2</sub>Cl). The mixture proved to be 3,5-di-O-benzoyl- $\alpha/\beta$ -D-xylofuranosyl chloride 2-chlorosulphate 51.

2.12.4. Reaction of the mixture (51) with sodium iodide/anhydrous methanol

Mixture 51 (300 mg) in anhydrous methanol (5 ml) at room temperature was treated with 10% sodium iodide/anhydrous methanol (4 drops). After 1 hour the mixture was shown to contain two compounds,  $R_f$  0.35 and 0.29 (solvent 4, spray a) both giving a negative reaction with spray b. Work-up as described above afforded a yellow syrup (160 mg, 70.2%),  $[\alpha]_D^{20} + 25.8^\circ$  (c, 1.6) and  $\lambda_{max}$  2.94 (OH) and 5.88  $\mu$ m (OBz). The mixture proved to be methyl 3,5-di-O-benzoyl- $\alpha/\beta$ -D-xylofuranosides 52.

2.12.5. Reaction of the mixture (52) with sulphuryl chloride and pyridine

Mixture 52 (160 mg) in chloroform (5 ml) and pyridine (0.1 ml) at  $0^\circ$  was reacted with sulphuryl chloride (0.06 ml). T.l.c. (solvent 4, spray a) showed the presence of two compounds,  $R_f$  0.61 and 0.56 both giving a positive reaction with spray b. Work-up as before afforded a yellow syrup (110 mg, 52.1%),  $[\alpha]_D^{17} + 46.1^\circ$  (c, 2.0) and  $\lambda_{max}$  5.84 (OBz) and 7.24  $\mu$ m (OSO<sub>2</sub>Cl) which was shown to be a mixture

of methyl 3,5-di-0-benzoyl- $\alpha/\beta$ -D-xylofuranoside 2-chlorosulphate 53.

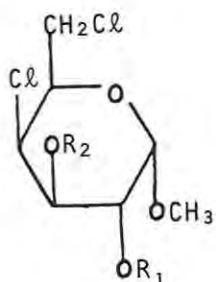
2.12.6. Reaction of the mixture (53) with lithium chloride in hexamethylphosphoramide

Mixture 53 (50 mg) and lithium chloride (50 mg) in hexamethylphosphoramide (0.5 ml) were heated at 60-70° with stirring for 1 hour. T.l.c. (solvent 4, spray a) showed the presence of two compounds,  $R_f$  0.33 and 0.28 both giving a negative reaction with spray b and corresponding to the mixture 52.

DISCUSSION

The reaction of carbohydrates with sulphuryl chloride and pyridine is a convenient and effective procedure for the preparation of chlorodeoxy sugars. The chloride ion liberated during the chlorosulphation procedure causes displacement of the chlorosulphonyloxy group at certain centres, depending on whether steric<sup>16</sup> and polar effects are favourable for a nucleophilic bimolecular substitution. Recently<sup>75</sup> the displacement of a 3-chlorosulphonyloxy group by bromide with inversion of configuration has been reported, while the replacement of the chloro group of primary and secondary chlorosulphonyloxy groups by azide has been described by Naidoo<sup>94</sup> et al. With the exception of the above reactions and the reaction of chlorosulphate esters with base, little is known about the reactions of carbohydrate chlorosulphates.

It was therefore decided to synthesise partially and fully chlorosulphated sugars and to examine some of their reactions under acidic conditions, since under basic conditions epoxidation, cyclization and hydrolysis reactions occur. Since Khan<sup>19</sup> succeeded in replacing the 2-chlorosulphonyloxy group of methyl 3-O-acetyl-4,6-benzylidene- $\alpha$ -D-glucopyranoside 2-chlorosulphate by chloride, acetylation of the partially chlorosulphated derivatives was undertaken with a view to possible activation of secondary centres, which are normally resistant towards nucleophilic displacement by chloride.



- (3) R<sub>1</sub> = H, R<sub>2</sub> = SO<sub>2</sub>Cl
- (4) R<sub>1</sub> = SO<sub>2</sub>Cl, R<sub>2</sub> = H
- (5) R<sub>1</sub> = H, R<sub>2</sub> = Ac
- (6) R<sub>1</sub> = Ac, R<sub>2</sub> = H
- (7) R<sub>1</sub> = SO<sub>2</sub>Cl, R<sub>2</sub> = Ac
- (8) R<sub>1</sub> = Ac, R<sub>2</sub> = SO<sub>2</sub>Cl

Table 1 - Chemical shifts ( $\tau$ -values) and first-order coupling constants (Hz) for compounds 3, 4, 5, 6, 7 and 8

| Compound          | <u>3</u>     | <u>4</u> | <u>4*</u>     | <u>5</u>          | <u>5*</u>     | <u>6</u> | <u>7</u>     | <u>8</u>     |
|-------------------|--------------|----------|---------------|-------------------|---------------|----------|--------------|--------------|
| H-1               | 5.02(d)      | 4.79(d)  | 4.21-4.91(cm) | 5.12(d)           | 4.52-5.13     | 5.13(d)  | 4.33-4.97(m) | 4.62-4.75(m) |
| H-2               | 5.58-5.98    | 5.02(q)  |               | 6.02(q)           |               | 4.96(q)  |              | 4.96(q)      |
| H-3               | 4.86(q)      | 5.58(q)  |               | 4.82(q)           |               | 5.82(q)  |              | 4.62-4.75(m) |
| H-4               | 5.20(dd)     | 5.30(dd) | 5.09(dd)      | 5.40(dd)          | 5.28(dd)      | 5.47(dd) | 5.21(dd)     | 5.21(dd)     |
| H-5               | 5.58-5.98(m) | 5.69(cm) | 5.59(cm)      | 5.41(cm)          | 5.55-5.95(cm) | 5.67(cm) | 5.67(cm)     | 5.80(cm)     |
| H-6               | 6.31(d)      | 6.59(d)  | 6.28(d)       | 6.37(d)           | 6.31(d)       | 6.39(d)  | 6.31(d)      | 6.38(d)      |
| H-6'              |              |          |               |                   |               |          |              |              |
| OH                | 7.76(s)      | 7.50(s)  |               | $\approx$ 7.73(s) |               | 7.78(s)  |              |              |
| OCH <sub>3</sub>  | 6.45(s)      | 6.46(s)  | 6.41(s)       | 6.49(s)           | 6.50(s)       | 6.62(s)  | 6.46(s)      | 6.61(s)      |
| OAc               |              |          |               | 7.85(s)           | 7.86(s)       | 7.92(s)  | 7.82(s)      | 7.95(s)      |
| NH                |              |          | 1.28(s)       |                   | 1.10(s)       |          |              |              |
| J <sub>1,2</sub>  | 4.0          | 4.0      | 4.0           | 4.0               |               | 3.3      |              | 2.7          |
| J <sub>2,3</sub>  | 9.3          | 9.3      | 9.3           | 10.7              |               | 10.7     |              |              |
| J <sub>3,4</sub>  | 4.0          | 4.0      | 4.0           | 4.0               | 4.0           | 4.7      | 4.0          | 3.3          |
| J <sub>4,5</sub>  | 1.3          | 1.3      | 1.3           | 1.3               | 1.3           | 1.3      | 1.3          | 1.3          |
| J <sub>5,6</sub>  |              |          |               |                   |               |          |              |              |
| J <sub>5,6'</sub> |              |          |               |                   |               |          |              |              |
| J <sub>6,6'</sub> |              |          |               |                   |               |          |              |              |

Key: d = doublet; dd = double doublet; s = singlet; m = multiplet; cm = complex multiplet; q = quartet

\* with shift reagent, trichloroacetyl isocyanate

Partial chlorosulphation of methyl 4,6-dichloro-4,6-dideoxy- $\alpha$ -D-galactopyranoside at  $-15^{\circ}$  afforded, after column chromatography, the 3-chlorosulphate 3 (12.7%), the mp and the optical rotation of which were consistent with that reported by Parolis<sup>87</sup> et al., and the 2-chlorosulphate 4 (6.3%). Attempts to increase these low yields by further addition of sulphuryl chloride and pyridine resulted in an increased formation of the dichlorosulphate and cyclic sulphate derivatives. The latter derivative was also formed as a result of heat generated during dry column chromatography of the mixture.

In the n.m.r. spectrum of 3 (Table 1), the resonance due to H-3 appeared at a low field ( $\tau$  4.86), due to the deshielding effect of the chlorosulphonyloxy group at C3 and partly overlapped with the H-1 doublet. The resonances due to H-5 and H-2 occurred as a complex multiplet and were not discernable.

The infra-red spectrum of 4 showed the presence of both hydroxyl and chlorosulphonyloxy groups. The n.m.r. spectrum of 4 (Table 1) revealed the presence of a doublet due to H-1, a quartet for H-2 shifted downfield due to the chlorosulphonyloxy group at C2. H-3 occurred as a quartet overlapping with H-5. Addition of trichloroacetyl isocyanate resulted in the appearance of a broad singlet at  $\tau$  1.28, due to the NH of the resulting carbamate, while H-3 was strongly deshielded and appeared together with H-1 and H-2 as a complex multiplet at  $\tau$  4.21-4.91.

Treatment of compounds 3 and 4 in chloroform with a 50:1 mixture of acetic anhydride and sulphuric acid afforded methyl 2-0-acetyl-4,6-dichloro-4,6-dideoxy- $\alpha$ -D-galactopyranoside 3-chlorosulphate 8 and methyl 3-0-acetyl-4,6-dichloro-4,6-dideoxy- $\alpha$ -D-

-galactopyranoside 2-chlorosulphate 7 respectively. The infra-red spectra of compounds 7 and 8 showed the presence of both acetyl and chlorosulphonyloxy groups.

The mass spectral fragmentation pathways (Table II) for compounds 3, 4, 7 and 8 are depicted in Scheme A. Route 1 is a general fragmentation pathway for all four compounds, while a fragmentation pathway peculiar to 4 and 7, which appeared to be initiated by the cleavage of the C1-C2 bond with the formation of an ion at  $m/e$  (M-99), is depicted in Route 2. The latter route confirms presence of a chlorosulphonyloxy group at C2 in both 4 and 7.

The mass spectrum of compound 7 (Table II, Scheme A) gave rise to a high intensity peak at  $m/e$  133 in association with its isotopic counterpart at  $m/e$  135 in the ratio of 3:1, indicating the presence of a single chlorine atom, while in compounds 3 and 8 a high intensity peak occurred at  $m/e$  117 associated with a peak at  $m/e$  119 in a 3:1 ratio, indicating this to be a fragment bearing a single chlorine atom. These fragments confirmed the difference in the position of chlorosulphonyloxy groups at C2 and C3 in compounds 3 and 8 and 4 and 7.

Because of the low yields of the monochlorosulphates 3 and 4 achieved, the alternative route of partial acetylation of methyl 4,6-dichloro-4,6-dideoxy- $\alpha$ -D-galactopyranoside followed by chlorosulphation of the mono-acetates was investigated, in order to achieve increased yields of compounds 7 and 8.

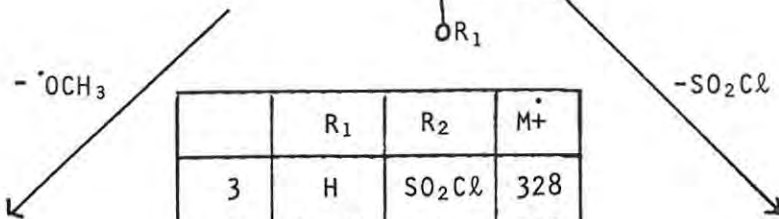
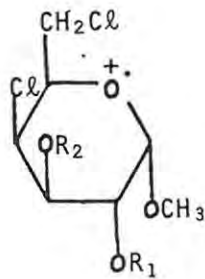
Methyl 4,6-dichloro-4,6-dideoxy- $\alpha$ -D-galactopyranoside in chloroform at 0°, when treated with a mixture of acetic anhydride and pyridine as described by Parolis<sup>87</sup> et al., afforded after

column chromatography to remove traces of the di-acetate, a syrupy

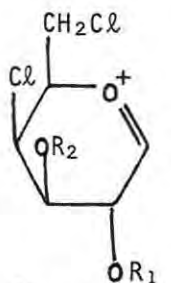
Table 11 Relative intensities in the mass spectra of compounds  
3, 4, 7 and 8

| Compound   | <u>3</u>             | <u>4</u> | <u>7</u> | <u>8</u> |
|------------|----------------------|----------|----------|----------|
| $m/e$      | Relative intensity % |          |          |          |
| (M-31)     | 339                  |          |          | 0.75     |
| (M-31)     | 297                  | 0.67     | 0.19     |          |
| (M-31)-18  | 279                  | 0.18     | 0.12     | 6.31     |
| (M-99)     | 271                  |          | 2.37     |          |
| (M-99)     | 229                  |          | 0.16     |          |
| (M-31)-116 | 223                  |          |          | 3.34     |
| (M-99)-60  | 211                  |          | 33.52    |          |
|            | 181                  | 2.11     |          |          |
| (M-159)-36 | 175                  |          | 63.09    |          |
| (M-99)-60  | 169                  |          | 15.84    |          |
|            | 152                  | 2.24     |          | 6.29     |
|            | 133                  |          | 2.82     | 70.81    |
|            | 117                  | 100      |          | 44.48    |
|            | 83                   |          | 100      |          |
|            | 60                   |          | 100      |          |
|            | 43                   |          |          | 100      |

crystalline mass, which appeared to be a chromatographically pure compound, but proved to be a mixture of methyl 3-0-acetyl-4,6-dichloro-4,6-dideoxy- $\alpha$ -D-galactopyranoside 5 and methyl 2-0-acetyl-4,6-dichloro-4,6-dideoxy- $\alpha$ -D-galactopyranoside 6. Although the mono-acetates 5 and 6 possessed very similar  $R_f$  values, fractional crystallization of the mixture afforded compound 5 as needles, with mp and optical rotation consistent with those reported by Parolis<sup>87</sup> et al. Compound 6 could not be isolated at this stage.

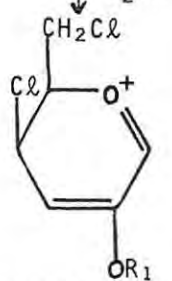


|   | R <sub>1</sub>     | R <sub>2</sub>     | M <sup>+</sup> |
|---|--------------------|--------------------|----------------|
| 3 | H                  | SO <sub>2</sub> Cl | 328            |
| 4 | SO <sub>2</sub> Cl | H                  | 328            |
| 7 | SO <sub>2</sub> Cl | Ac                 | 370            |
| 8 | Ac                 | SO <sub>2</sub> Cl | 370            |

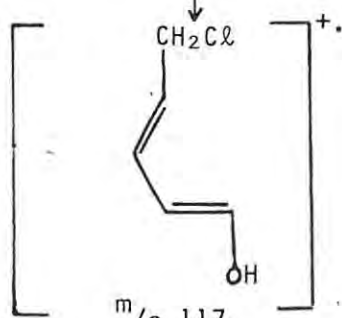
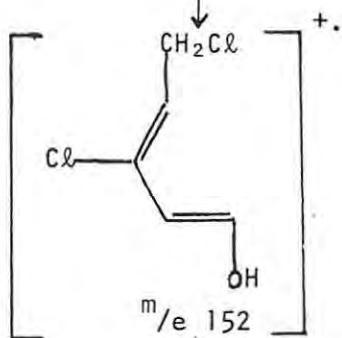


$m/e$  (M-31)

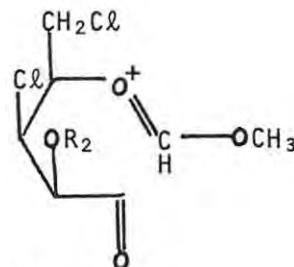
$-R_2OH$



$m/e$  (M-31) - 116, 18 or 60

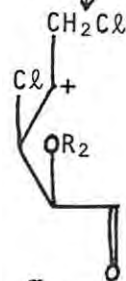


Route 1



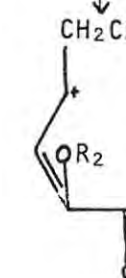
$m/e$  (M-99)

$-HCOOCH_3$



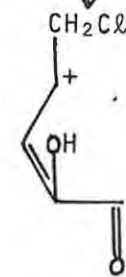
$m/e$  (M-99) - 60

$-HCl$



(M-159) - 36

$-CH_2=C=O$  from 7



$m/e$  133

Route 2

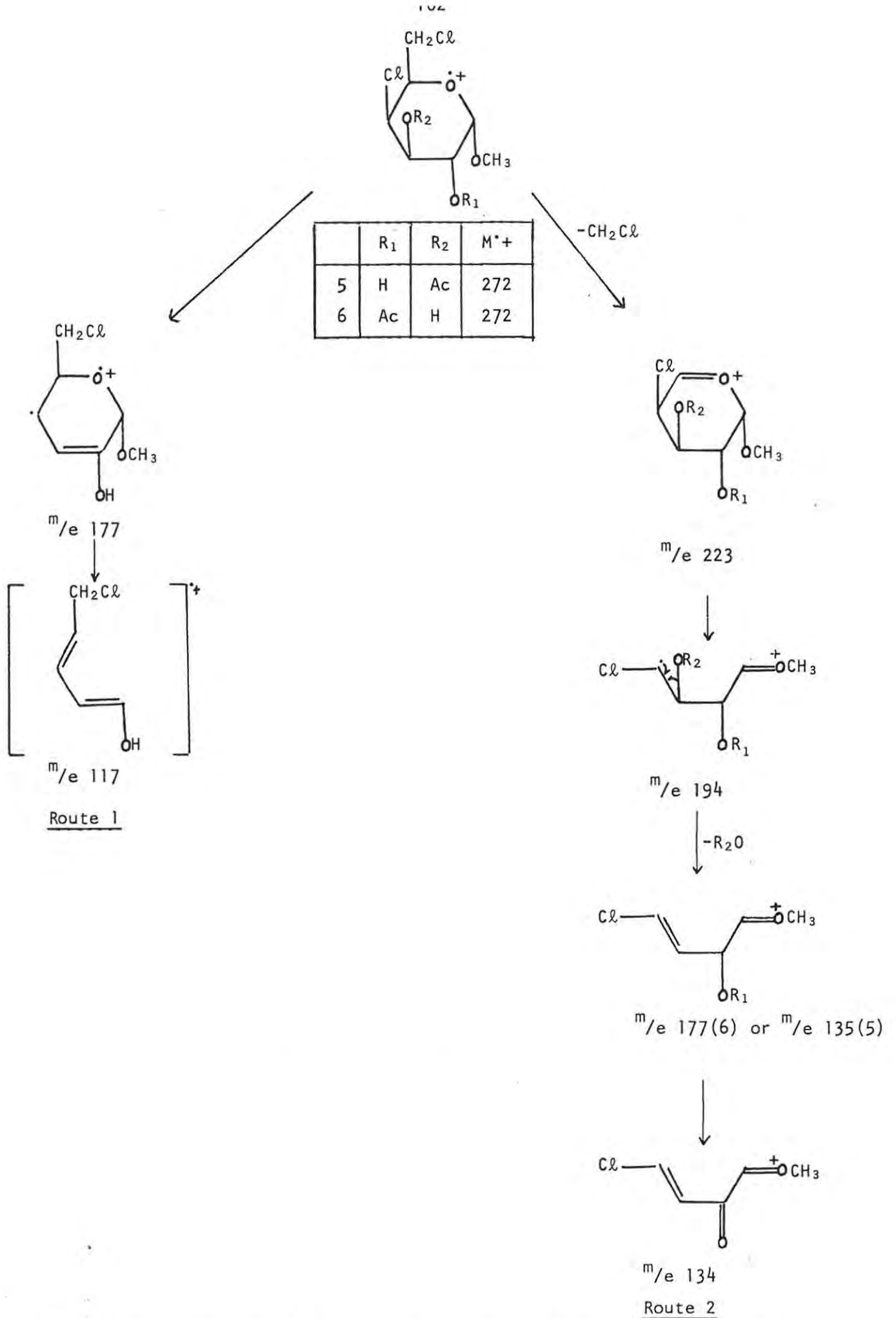
Scheme A - Mass spectral fragmentation pathways for compounds 3, 4, 7 and 8

In the n.m.r. spectrum of compound 5 (Table I) the resonance due to H-3 appeared as a quartet further downfield than that of the H-1 doublet, due to the deshielding effect of the acetyl group at C3. H-2 occurred as a quartet overlapping with H-5, while the signal due to the hydroxyl occurred as a broad singlet at  $\tau$  7.73, partially obscured by the acetate signal at  $\tau$  7.85. Addition of trichloroacetyl isocyanate resulted in the appearance of a broad 1-proton singlet at  $\tau$  1.10 due to the NH of the resulting carbamate and the deshielding of H-2 which appeared as part of a complex multiplet at  $\tau$  4.52-5.13.

Chlorosulphation of a mixture of methyl 3-0-acetyl-(5) and 2-0-acetyl-(6)-4,6-dichloro-4,6-dideoxy- $\alpha$ -D-galactopyranoside afforded a mixture of compounds 7 (52.9%) and 8 (20.6%), whose  $R_f$  values were sufficiently different to allow for their separation by column chromatography. The optical rotations and  $R_f$  values compared with those reported from the acetylation of compounds 3 and 4.

The n.m.r. spectrum of compound 7 (Table I) showed that H-2 and H-3 were deshielded by the electron withdrawing effects of the chlorosulphonyloxy and acetyl groups at C2 and C3, so that they overlapped with H-1 and were not discernable, while in 8, H-1 and H-3 occurred as an overlapping multiplet due to the deshielding effect of the chlorosulphonyloxy group at C3. H-2 appeared as a deshielded quartet due to the presence of the acetyl group at C2.

Treatment of compound 8 with sodium iodide at room temperature removed not only the chlorosulphonyloxy but also the acetyl group to afford methyl 4,6-dichloro-4,6-dideoxy- $\alpha$ -D-galactopyranoside.



Scheme B - Mass spectral fragmentation pathways for compounds 5 and 6

Dechlorosulphation of 8 was achieved with triphenylphosphine in 1-chloroform which afforded after column chromatography the 2-0-acetyl derivative 6 as a pale yellow syrup (88.4%). The infra-red spectrum of 6 showed the presence of hydroxyl and acetyl groups.

In the n.m.r. spectrum of 6 (Table I), H-2 appeared as a quartet overlapping with H-1 due to the deshielding effect of the acetyl group at C2, while H-3 appeared as a quartet overlapping with H-5.

Table III Relative intensities of peaks in the mass spectra of  
5 and 6

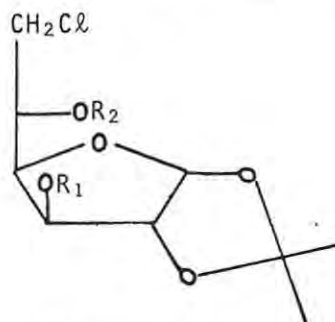
| Compound                 |     | <u>5</u>             | <u>6</u> |
|--------------------------|-----|----------------------|----------|
| $m/e$                    |     | Relative intensity % |          |
| (M-31)                   | 241 | 0.16                 | 0.43     |
| (M-31)-R <sub>2</sub> OH | 223 |                      | 1.44     |
|                          | 194 |                      | 0.38     |
| (M-31)-R <sub>2</sub> OH | 181 | 1.89                 |          |
|                          | 177 | 5.96                 | 0.49     |
|                          | 152 | 2.99                 | 0.83     |
|                          | 134 |                      | 7.07     |
|                          | 117 | 70.78                | 2.52     |
|                          | 43  | 100                  | 100      |

The mass spectral data for compounds 5 and 6 is given in Table III. The presence of peaks at  $m/e$  181 in 5 and  $m/e$  223 in 6 as depicted in Route 1, Scheme A, indicates the difference in the functional groups at C2 and C3. A further fragmentation pathway for 6 is shown in Route 2, Scheme B. The absence of prominent peaks at  $m/e$  194 and  $m/e$  135 in the mass spectrum of 5 confirmed that this

pathway was not applicable to 5. The peak at  $m/e$  177 in compound 5 is depicted in Route 1, Scheme B since its presence cannot be explained via Route 2, Scheme B as for 6. Loss of methyl formate from the peak at  $m/e$  177 produces a prominent  $m/e$  117 peak in 5. This peak is not of major significance in 6.

The galacto configuration<sup>95</sup> for compounds 3, 4, 5, 6, 7 and 8 was clearly evident by the presence of H-4 as a narrow double doublet with  $J_{4,5} = 1.3$  Hz, while H-6,6' occurring as a doublet appeared to be coupled only to H-5, which occurred as a broad triplet with additional narrow splitting by virtue of its coupling with H-4. The occurrence of H-5 as a triplet and H-6,6' as a doublet, suggests the presence of a deceptively simple ABX subsystem<sup>96</sup>. The elemental analyses of compounds 3, 4, 6, 7 and 8 were in accord with the expected structures.

The 2- and 3-chlorosulphonyloxy groups are under normal conditions inert towards nucleophilic displacement. However, since Khan<sup>19</sup> succeeded in replacing the 2-chlorosulphonyloxy group of methyl 3-0-acetyl-4,6-benzylidene- $\alpha$ -D-glucopyranoside 2-chlorosulphate with chloride, it was hoped that the adjacent acetyl group in compounds 7 and 8 would facilitate similar replacement reactions. However, reaction of compounds 7 and 8 with lithium chloride in hexamethylphosphoramide afforded the 3-0-acetyl (5) and 2-0-acetyl derivatives (6) respectively.



- (11)  $R_1 = SO_2Cl, R_2 = H$   
 (12)  $R_1 = H, R_2 = SO_2Cl$   
 (13)  $R_1 = Ac, R_2 = SO_2Cl$   
 (14)  $R_1 = SO_2Cl, R_2 = Ac$

Partial chlorosulphation of 6-chloro-6-deoxy-1,2-0-isopropylidene- $\alpha$ -D-glucofuranose at 0° afforded 6-chloro-6-deoxy-1,2-0-isopropylidene  $\alpha$ -D-glucofuranose 3-chlorosulphate 11 (11.9%) and 6-chloro-6-deoxy-1,2-0-isopropylidene- $\alpha$ -D-glucofuranose 5-chlorosulphate 12 (6.9%). Although the yield of 12 was lower than that of 11, it was ascertained that isomerization of the exocyclic to the endocyclic chlorosulphate derivative did not occur during the reaction. The infra-red spectra of 11 and 12 revealed the presence of both hydroxyl and chlorosulphonyloxy absorbance peaks.

Table IV - Chemical shifts ( $\tau$ -values) and first-order coupling constants (Hz) for compounds 11-14

| Compound                         | <u>11</u> | <u>11</u> *   | <u>12</u>    | <u>12</u> *  | <u>13</u>    | <u>14</u>    |
|----------------------------------|-----------|---------------|--------------|--------------|--------------|--------------|
| H-1                              | 3.92(d)   | 3.99(d)       | 3.98(d)      | 4.01(d)      | 4.02(d)      | 3.95(d)      |
| H-2                              | 5.00(d)   | 5.09(d)       | 5.39(d)      | 5.20(d)      | 5.34(d)      | 5.03(d)      |
| H-3                              | 4.54(d)   | 4.69(d)       | 5.31-5.62(m) | 4.34-4.64(m) | 4.64(d)      | 4.67(d)      |
| H-4                              | 5.68(q)   | 5.28(dd)      |              | 5.28(dd)     | 5.32(dd)     | 5.27(dd)     |
| H-5                              | 5.72(q)   | 4.71-5.01(cm) | 4.38-4.71(m) | 4.34-4.64(m) | 4.44-4.74(m) | 4.58-4.95(m) |
| H-6                              | 5.99(dd)  | 5.87(dd)      | 5.75(dd)     | 5.72(dd)     | 5.75(dd)     | 5.91(dd)     |
| H-6'                             | 6.24(dd)  | 6.20(dd)      | 6.07(dd)     | 6.04(dd)     | 6.04(dd)     | 6.20(dd)     |
| OH                               | 7.44(d)   |               | 7.56(s)      |              |              |              |
| OCH <sub>3</sub>                 |           |               |              |              |              |              |
| OAc                              |           |               |              |              | 7.86(s)      | 7.90(s)      |
| NH                               |           | 1.43(s)       |              | 1.38(s)      |              |              |
| C(CH <sub>3</sub> ) <sub>2</sub> | 8.44(s)   | 8.53(s)       | 8.48(s)      | 8.44(s)      | 8.44(s)      | 8.44(s)      |
|                                  | 8.62(s)   | 8.82(s)       | 8.66(s)      | 8.64(s)      | 8.67(s)      | 8.63(s)      |
| J <sub>1,2</sub>                 | 4.0       | 4.0           | 2.7          | 3.3          | 3.3          | 4.0          |
| J <sub>2,3</sub>                 |           |               |              |              |              |              |
| J <sub>3,4</sub>                 | 2.7       | 2.7           |              | 3.3          | 3.3          | 2.7          |
| J <sub>4,5</sub>                 | 8.0       | 9.3           |              | 9.3          | 7.3          | 9.3          |
| J <sub>5,6</sub>                 | 2.7       | 2.7           | 2.7          | 3.3          | 3.3          | 2.7          |
| J <sub>5,6'</sub>                | 4.0       | 2.7           | 4.0          | 3.3          | 4.0          | 2.7          |
| J <sub>6,6'</sub>                | 12.0      | 13.3          | 13.3         | 13.3         | 12.7         | 12.0         |

Key: d = doublet; dd = double doublet; s = singlet; m = multiplet; cm = complex multiplet

\* with shift reagent, trichloroacetyl isocyanate

The n.m.r. spectrum of 11 (Table IV) showed H-1, H-2 and H-3 as doublets with H-3 occurring further downfield than in the n.m.r. spectrum of 1,2-0-isopropylidene- $\alpha$ -D-glucofuranose due to the electron withdrawing effects of the chlorosulphonyloxy group at C3. H-4 and H-5 appeared as overlapping quartets, while the signals due to H-6 and H-6' gave rise to a pair of overlapping double doublets. The signal due to the hydroxyl appeared as a doublet at  $\tau$  7.44, while in compound 12 the hydroxyl at C3 appeared as a singlet. The splitting of the hydroxyl signal in 11 is possibly due to the effect of H-5.

Addition of trichloroacetyl isocyanate resulted in the appearance of a singlet at  $\tau$  1.43 due to the NH group of the resulting carbamate, and H-6 and H-6' as clearly defined double doublets due to the deshielding of H-5, which confirmed that the free hydroxyl in 11 was located at C5.

In the n.m.r. of 12 (Table IV), H-5 occurred as a low intensity complex multiplet shifted downfield due to the electron withdrawing chlorosulphonyloxy group at C5, which also caused H-6 and H-6' to be deshielded and thus to overlap the H-3 and H-4 resonances.

Addition of trichloroacetyl isocyanate resulted in H-3 being strongly deshielded and appearing as a quartet overlapping with H-5, while H-4, H-6 and H-6' now became clearly discernable double doublets.

Reaction of compounds 11 and 12 at  $-15^\circ$  with a 50:1 mixture of acetic anhydride and sulphuric acid afforded the 3-0-acetyl 13 (92.9%) and 5-0-acetyl 14 (90.3%) derivatives respectively.

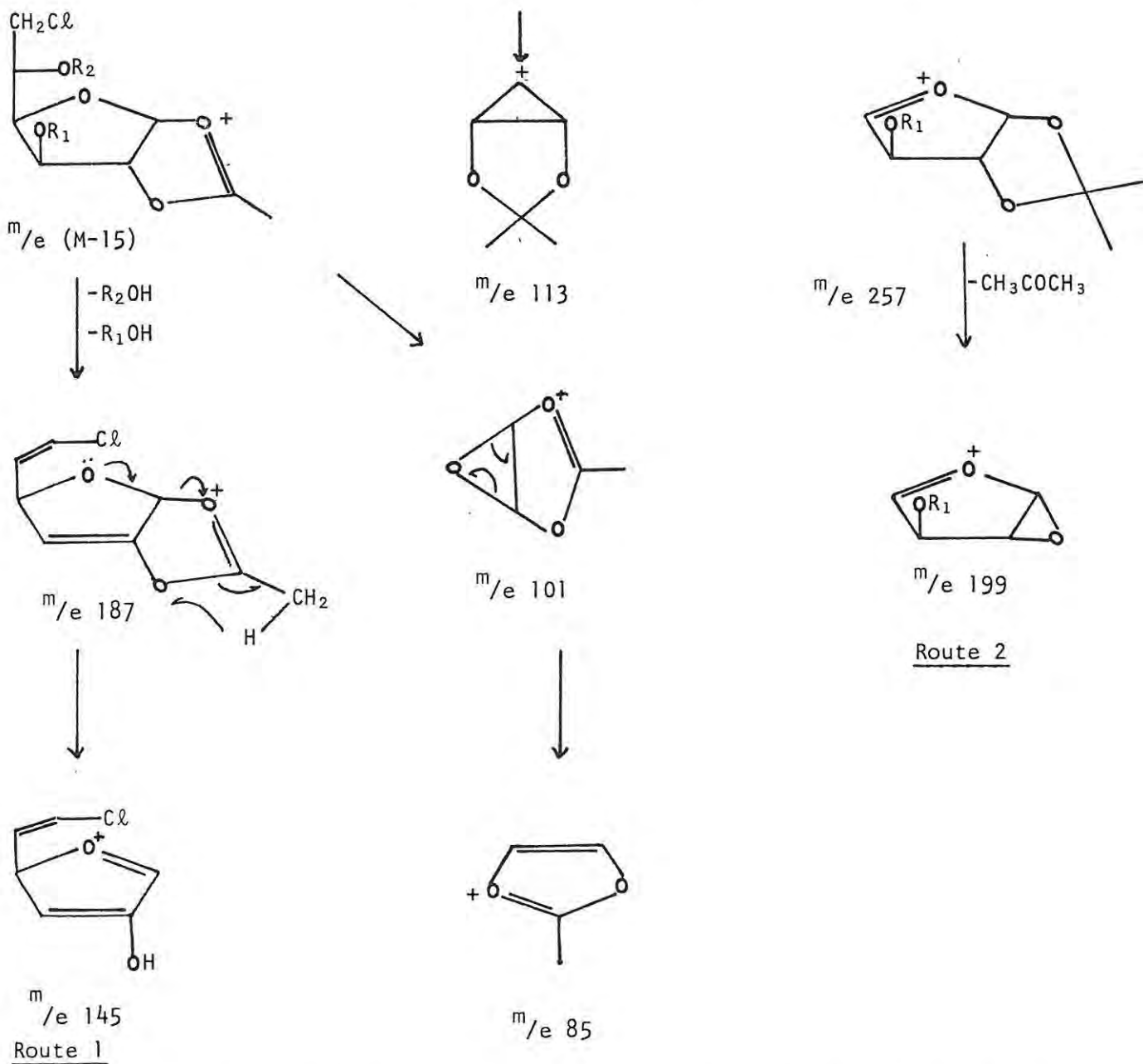
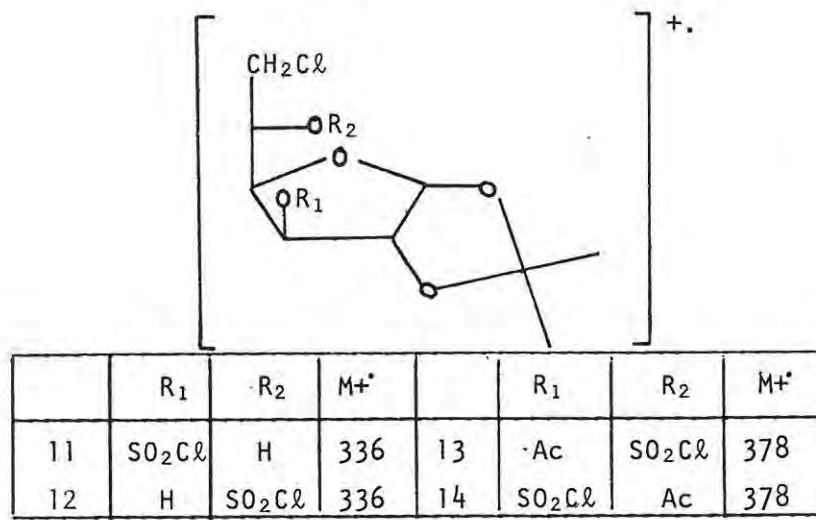
The n.m.r. spectra of 13 and 14 (Table IV) were, as expected, similar to the spectra of 11\* and 12\*. In compound 13 the resonance due to H-4 appeared as a double doublet overlapping with H-2, while in

compound 14 the double doublet of H-4 does not overlap with H-2, since H-2 was deshielded to a greater extent than in 13, probably due to the stronger electron withdrawing effects of the chlorosulphonyloxy group at C3 in 14, as compared to the acetyl group in 13.

Table V - Relative intensities of peaks in the mass spectra of compounds 11, 12, 13 and 14.

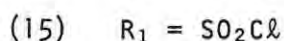
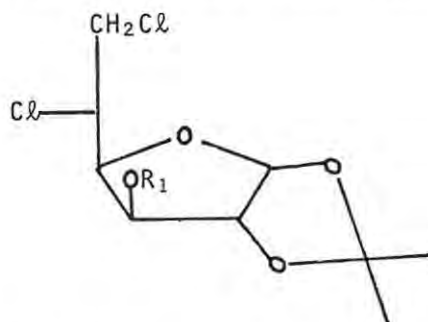
| Compound   | <u>11</u>            | <u>12</u> | <u>13</u> | <u>14</u> |
|------------|----------------------|-----------|-----------|-----------|
| $m/e$      | Relative intensity % |           |           |           |
| 363 (M-15) |                      |           | 3.16      | 1.50      |
| 321 (M-15) | 5.00                 | 2.38      |           |           |
| 257        | 4.20                 |           |           | 0.05      |
| 199        | 0.80                 |           |           | 1.58      |
| 187        | 1.26                 | 5.63      | 13.33     | 0.21      |
| 145        | 0.50                 | 5.63      | 6.33      | 0.19      |
| 113        | 15.85                | 1.41      |           | 4.45      |
| 101        |                      | 2.23      | 5.32      |           |
| 85         | 42.02                | 9.45      | 4.47      | 2.24      |
| 43         | 100                  | 100       | 100       | 100       |

The mass spectral fragmentation pathways for compounds 11, 12, 13 and 14 are typical of mono-isopropylidene hexoses<sup>97</sup> and are shown in Scheme C (Table V). Compounds 12 and 14 exhibited fragments at  $m/e$  337 (M+1) and  $m/e$  379 (M+1) respectively. Although the molecular ions of compounds 11 and 13 were absent, the mass spectra showed (M-15) peaks in association with their isotopic counterparts (M-15+2, M-15+4) in the ratio of 9:6:1 confirming the presence of two chlorine atoms in both 11 and 13. The presence of ions  $m/e$  257 and  $m/e$  199 only in the mass spectra of 11 and 14 is added confirmation of the presence of a chlorosulphonyloxy group at C3 in these two compounds.



Scheme C - Mass spectral fragmentation pathways for compounds 11, 12, 13 and 14

The chlorosulphation of 3-0-acetyl-1,2-0-isopropylidene- $\alpha$ -D-glucofuranose to afford 3-0-acetyl-1,2-0-isopropylidene- $\alpha$ -D-glucofuranose 5-chlorosulphate offered additional confirmation of the structure of compound 13.



1,2-0-Isopropylidene- $\alpha$ -D-glucofuranose when treated with sulphuryl chloride and pyridine, firstly at low temperatures and then at 50°, yielded 5,6-dichloro-5,6-dideoxy- $\beta$ -L-idofuranose 3-chlorosulphate 15 as a crystalline compound. This compound was synthesised in order to attempt the replacement of the chlorosulphonyloxy group at C3 by chloride. Parolis<sup>25</sup> isolated 5,6-dichloro-5,6-dideoxy-1,2-0-isopropylidene- $\beta$ -L-idofuranose 3-chlorosulphate as a syrup contaminated with 6-chloro-6-deoxy-1,2-0-isopropylidene- $\alpha$ -D-glucofuranose 3,5-dichlorosulphate.

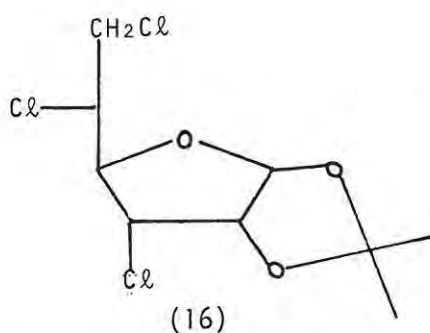
The infra-red spectrum of 15 showed the characteristic peaks for the chlorosulphonyloxy group.

In the n.m.r. spectrum of 15 (Table VI), H-1, H-2 and H-3 occurred as doublets, H-3 resonating at a lower field than usual due to the strong electron withdrawing chlorosulphonyloxy group at C3, while H-4 appeared as a double doublet. H-5 appeared as a complex multiplet and H-6 and H-6' as not easily discernable double doublets.

Table IV - Chemical shifts ( $\tau$ -values) and first order coupling constants (Hz) for compounds 15 and 16

| Compound                         | <u>15</u>    | <u>16</u>    |
|----------------------------------|--------------|--------------|
| H-1                              | 3.83(d)      | 4.07(d)      |
| H-2                              | 4.94(d)      | 5.22(dd)     |
| H-3                              | 4.58(d)      | 5.32(dd)     |
| H-4                              | 5.19(dd)     | 5.92(dd)     |
| H-5                              | 5.41-5.63(m) | 5.56-5.98(m) |
| H-6                              | 5.92(dd)     | 5.98-6.22(m) |
| H-6'                             | 6.16(dd)     |              |
| C(CH <sub>3</sub> ) <sub>2</sub> | 8.43(s)      | 8.40(s)      |
|                                  | 8.61(s)      | 8.59(s)      |
| J <sub>1,2</sub>                 | 4.0          | 3.3          |
| J <sub>2,3</sub>                 |              | 4.0          |
| J <sub>3,4</sub>                 | 3.3          | 9.3          |
| J <sub>4,5</sub>                 | 5.3          | 4.0          |
| J <sub>5,6</sub>                 | 5.3          | 6.7          |
| J <sub>5,6'</sub>                | 6.7          | 8.0          |
| J <sub>6,6'</sub>                | 12.0         |              |

Key: d = doublet; dd = double doublet; s = singlet and m = multiplet.



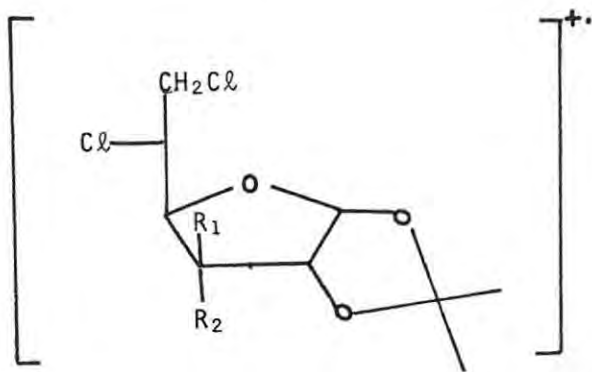
Reaction of compound 15 with lithium chloride in hexamethylphosphoramide at 60° afforded a black, syrupy mixture containing 3 compounds, the dechlorosulphated derivative, compound 15 and another compound, which although possessing a very similar R<sub>f</sub> value to 15 gave a negative reaction

with spray b. The mixture was dechlorosulphated in order to allow for chromatographic separation of the latter compound which proved to be 3,5,6-trichloro-3,5,6-trideoxy-1,2-0-isopropylidene- $\beta$ -L-talofuranose 16.

Infra-red spectral data showing the absence of chlorosulphonyloxy and hydroxyl groups and the elemental analysis indicating the presence of three chlorine atoms confirmed that replacement of the 3-chlorosulphonyloxy group by chloride had been successful. The n.m.r. spectrum of 16 (Table VI) showed H-1 as a doublet, H-2, H-3 and H-4 as double doublets, while H-5 appeared as a complex multiplet overlapping with H-4. The appearance of H-2 as a double doublet in 16 compared to a doublet in 15, indicated that nucleophilic replacement of the chlorosulphonyloxy group at C3 by chloride had occurred with inversion to afford the  $\beta$ -L-talo derivative.

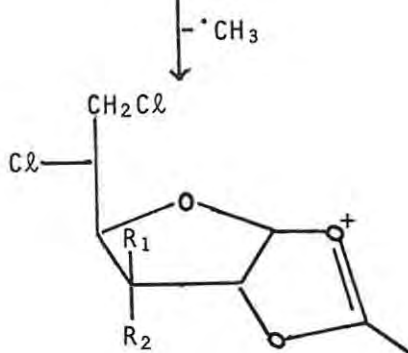
The mass spectral fragmentation pathways for 15 and 16 are depicted in Scheme D. The mass spectra of the isopropylidene derivatives 11, 12, 13 and 14 contained a peak at  $m/e$  187 in a 3:1 ratio with a peak at  $m/e$  189 confirming the presence of a chlorine atom, while in 15 and 16 the peak at  $m/e$  181 in association with its isotopic counterparts at  $m/e$  183 and  $m/e$  185, in the ratio of 9:6:1 confirmed this to be a fragment bearing two chlorine atoms. Route 2, Scheme C, a pathway applicable to 11, 14 and 15 only appeared to be initiated by cleavage of the C4 - C5 bond with the formation of a peak at  $m/e$  257 ( $m/e$  259, 3:1) confirming the presence of a 3-chlorosulphonyloxy group in all three compounds.

Reaction of 1,2:5,6-di-0-isopropylidene- $\alpha$ -D-glucofuranose with sulphuryl chloride and pyridine afforded 1,2:5,6-di-0-isopropylidene- $\alpha$ -D-glucofuranose 3-chlorosulphate 18, the mp and optical rotation of which were consistent with that reported by Jennings<sup>86</sup> and Jones.



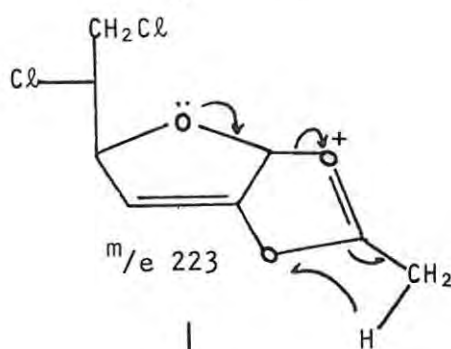
|    | R <sub>1</sub>      | R <sub>2</sub> | M <sup>+</sup> |
|----|---------------------|----------------|----------------|
| 15 | OSO <sub>2</sub> Cl | H              | 354            |
| 16 | H                   | Cl             | 274            |

Scheme C, Route 2

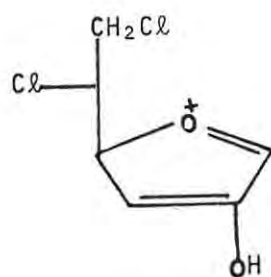


<sup>m</sup>/<sub>e</sub> (M-15)

-R<sub>1</sub>H or R<sub>2</sub>H



<sup>m</sup>/<sub>e</sub> 223

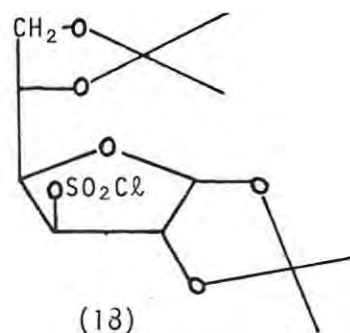


<sup>m</sup>/<sub>e</sub> 181

Scheme D - Mass spectral fragmentation pathways for compounds 15 and 16

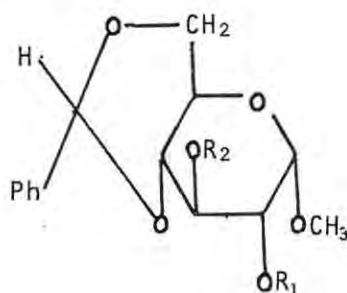
Table VII - Relative intensities of the peaks in the mass spectra of compounds 15 and 16

| Compound   | <u>15</u>            | <u>16</u> |
|------------|----------------------|-----------|
| $m/e$      | Relative intensity % |           |
| 339 (M-15) | 3.16                 |           |
| 259 (M-15) |                      | 3.15      |
| 257        | 3.55                 |           |
| 223        | 0.56                 |           |
| 199        | 0.89                 |           |
| 181        | 31.61                | 8.41      |
| 43         | 100                  | 100       |



Attempted replacement of the chlorosulphonyloxy group at C3 by reaction with lithium chloride and hexamethylphosphoramide was unsuccessful. 1,2-O-Isopropylidene- $\alpha$ -D-glucofuranose was the only product isolated.

A similar result was reported by Naidoo<sup>94</sup> who observed the formation of 1,2:5,6-di-O-isopropylidene- $\alpha$ -D-glucofuranose and 1,2-O-isopropylidene- $\alpha$ -D-glucofuranose, when 1,2:5,6-di-O-isopropylidene- $\alpha$ -D-glucofuranose 3-azidosulphate was treated with potassium azide in the presence of 18-crown-6-ether.



- (20)  $R_1 = H, R_2 = H$   
 (21)  $R_1 = SO_2Cl, R_2 = H$   
 (22)  $R_1 = H, R_2 = SO_2Cl$   
 (23)  $R_1 = SO_2Cl, R_2 = SO_2Cl$

Partial chlorosulphation of methyl 4,6-benzylidene- $\alpha$ -D-glucopyranoside at  $-5^\circ$  afforded after column chromatography, methyl 4,6-benzylidene- $\alpha$ -D-glucopyranoside 2-chlorosulphate 21 (9.3%) and 3-chlorosulphate 22 (12.1%). Khan<sup>98</sup> prepared methyl 4,6-benzylidene  $\alpha$ -D-glucopyranoside 2-chlorosulphate as the 3-O-acetyl derivative in a 60% yield. The dichlorosulphate derivative 23 although formed during this reaction was not isolated. The low yields of compounds 21 and 22 may be attributed to the small amounts of sulphuryl chloride and pyridine used in order to minimize dichlorosulphate formation. The infra-red spectrum of 21 revealed absorbances due to chlorosulphonyloxy and hydroxyl groups.

The n.m.r. spectrum of 21 (Table VII) contained a doublet for H-1, a quartet for H-2, deshielded due to the electron withdrawing effects of the chlorosulphonyloxy group at C2, while H-3, H-4, H-5, H-6 and H-6' overlapped appearing as a complex multiplet. The signal due to the hydroxyl group appeared as a broad singlet at  $\tau$  6.96. The addition of trichloroacetyl isocyanate resulted in a broad singlet at  $\tau$  1.31 due to the NH of the resulting carbamate complex, while H-3 was strongly

deshielded and appeared as a triplet centred at  $\tau$  4.39 and overlapped with the 1-proton singlet of the benzylidene group.

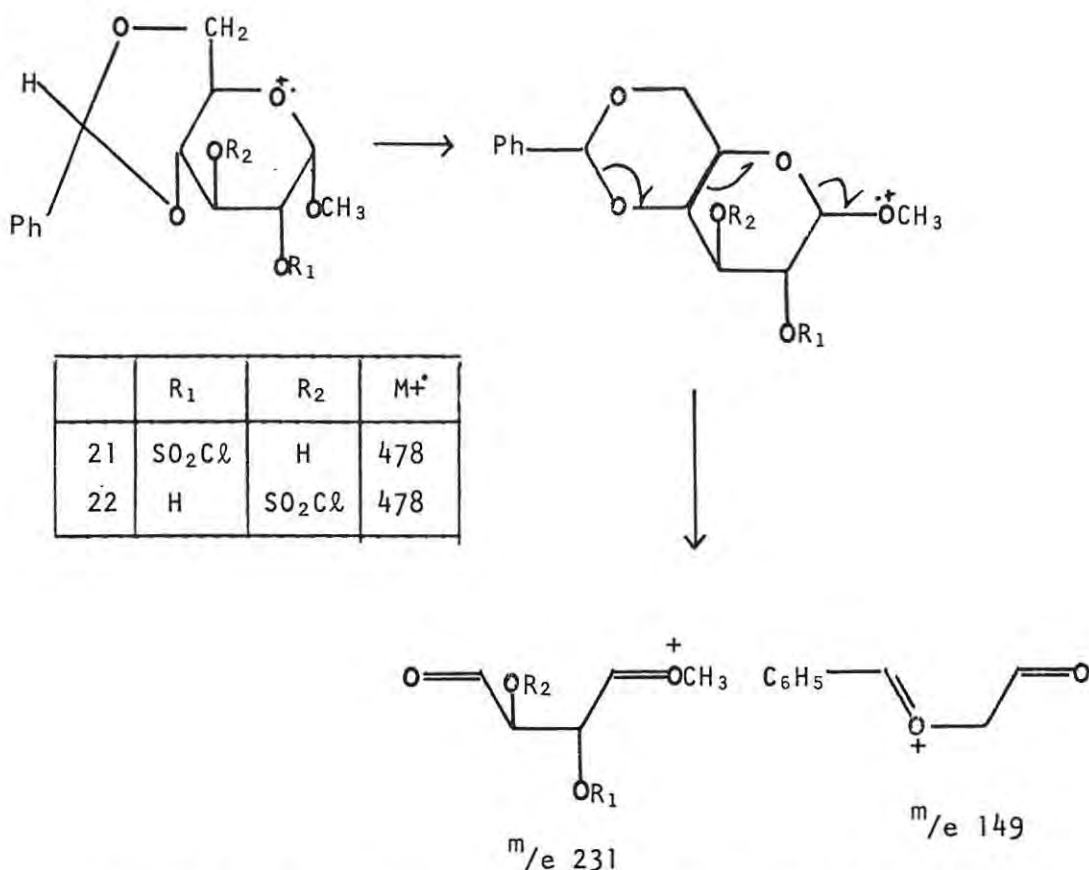
Table VIII - Chemical shifts ( $\tau$ -values) and first-order coupling constants (Hz) for compounds 21 and 22

| Compound         | <u>21</u>      | <u>21*</u>     | <u>22</u>      |
|------------------|----------------|----------------|----------------|
| H-1              | 4.91(d)        | 4.76(d)        | 4.99(d)        |
| H-2              | 5.27(q)        | 5.02(q)        | 5.98(q)        |
| H-3              | 5.57-6.47(cm)  | 4.24(t)        | 4.74(t)        |
| H-4              |                | 5.47-6.27(m)   | 5.76(t)        |
| H-5              |                |                | 5.84-6.29(m)   |
| H-6              |                |                |                |
| H-6'             |                |                |                |
| OH               | 6.96(s)        |                |                |
| PhCH             | 4.50(s)        | 4.39(s)        | 4.18(s)        |
| aromatic protons | 2.28-2.67(m)5H | 2.28-2.68(m)5H | 2.10-2.67(m)5H |
| NH               |                | 1.31(s)        |                |
| OCH <sub>3</sub> | 8.80(s)        | 6.46(s)        | 6.47(s)        |
| J <sub>1,2</sub> | 4.0            | 4.0            | 3.3            |
| J <sub>2,3</sub> | 9.3            | 9.3            | 9.3            |
| J <sub>3,4</sub> |                | 9.3            | 9.3            |
| J <sub>4,5</sub> |                |                | 8.7            |

Key: d = doublet; dd = double doublet; s = singlet;  
 m = multiplet; cm = complex multiplet  
 \* with shift reagent, trichloroacetyl isocyanate

The infra-red spectrum of 22 was similar to that of 21, while the n.m.r. spectrum in deuterio-acetone showed H-3 as a triplet overlapping with the H-1 doublet due to the deshielding effect of the chlorosulphonyloxy group at C3. Addition of trichloroacetyl isocyanate resulted in the appearance of a broad singlet at  $\tau$  -0.16 due to the NH of the resulting carbamate complex. However, decomposition of the product during the

n.m.r. experiment prevented the acquisition of further information.



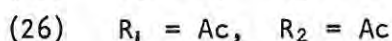
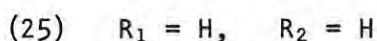
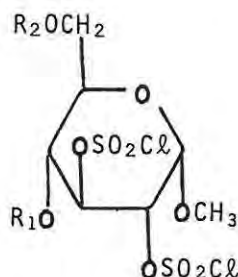
Scheme E - Mass spectral fragmentation pathways of compounds 21 and 22

Table IX - Relative intensities of the peaks in the mass spectra of compounds 21 and 22

| Compound | <u>21</u>            | <u>22</u> |
|----------|----------------------|-----------|
| $m/e$    | Relative intensity % |           |
| 231      | 5.62                 | 0.45      |
| 149      | 9.40                 | 0.89      |
| 105      | 100                  | 100       |

Fragmentation of compounds 21 and 22 proceeded via h-fracture<sup>97</sup> as depicted in Scheme E. In the mass spectra of both compounds a

peak at  $m/e$  231 in association with its isotopic counterpart at  $m/e$  233 in a 3:1 ratio confirmed the presence of a chlorine atom, while the elemental analyses of both compounds were in accord with the expected structures.



Methyl 4,6-benzylidene- $\alpha$ -D-glucopyranoside when reacted with sulphuryl chloride and pyridine as previously described<sup>86</sup> afforded methyl 4,6-benzylidene- $\alpha$ -D-glucopyranoside 2,3-dichlorosulphate 23. Reaction of 23 with lithium chloride in N,N-dimethylformamide at 60-80° afforded the cyclic sulphate and dechlorosulphated derivatives in a 1:1 ratio, while no reaction occurred on treatment of methyl 4,6-benzylidene- $\alpha$ -D-glucopyranoside 2,3-sulphate with lithium chloride in hexamethylphosphoramide.

Reaction of methyl 4,6-benzylidene- $\alpha$ -D-glucopyranoside 2,3-dichlorosulphate with trifluoroacetic acid afforded the starting material, after work-up as described by Christensen and Goodman<sup>90</sup>. Since t.l.c. had indicated that the reaction had gone to completion, readdition of the benzylidene group must have occurred during the work-up in the presence of trifluoroacetic acid at the slightly elevated temperature employed. In order to avoid this readdition the trifluoroacetic acid was removed at 30° under reduced pressure, by co-distillation with toluene to afford methyl  $\alpha$ -D-glucopyranoside 2,3-dichlorosulphate 25. The infra-

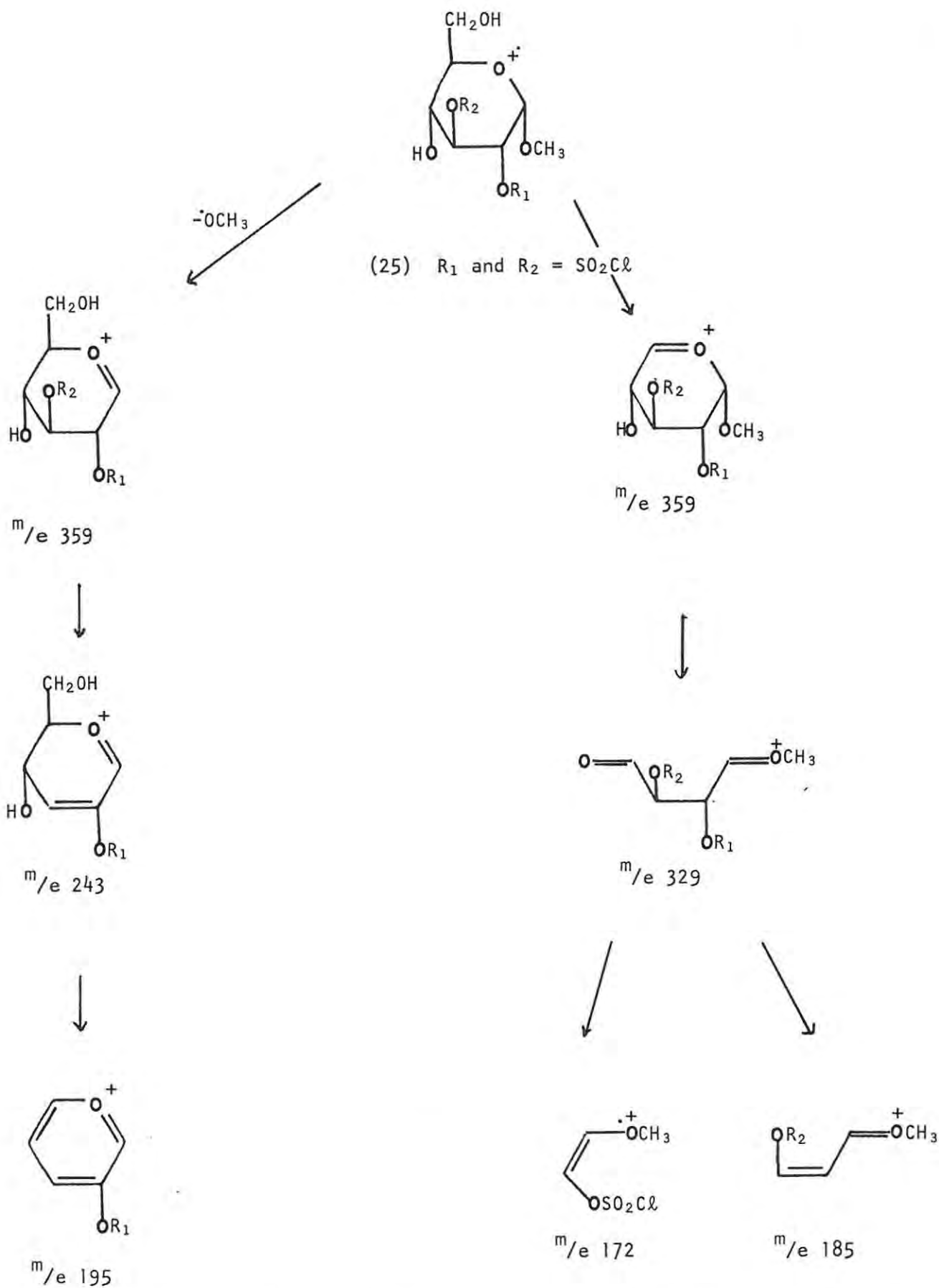
red spectrum of 25 revealed the presence of hydroxyl and chlorosulphonyloxy absorbance peaks.

Table X - Chemical shifts ( $\tau$ -values) and first-order coupling constants (Hz) for compounds 25 and 26

| Compound          | <u>25</u>     | <u>26</u>          |
|-------------------|---------------|--------------------|
| H-1               | 4.75(d)       | 4.69(d)            |
| H-2               | 5.12(q)       | 5.08(q)            |
| H-3               | 4.81(q)       | 4.41-4.89(m)       |
| H-4               | 5.98(t)       |                    |
| H-5               | 5.87-6.65(cm) | 5.44-6.09(m)       |
| H-6               |               | 5.59(dd)           |
| H-6'              |               | 5.88(dd)           |
| OH                |               |                    |
| OCH <sub>3</sub>  | 6.46(s)       | 6.44(s)            |
| OAc               |               | 7.83(s)<br>7.88(s) |
| J <sub>1,2</sub>  | 3.3           | 3.3                |
| J <sub>2,3</sub>  | 10.0          | 10.0               |
| J <sub>3,4</sub>  | 5.3           |                    |
| J <sub>4,5</sub>  | 5.3           |                    |
| J <sub>5,6</sub>  |               | 5.3                |
| J <sub>5,6'</sub> |               | 2.7                |
| J <sub>6,6'</sub> |               | 12.7               |

Key: d = doublet; dd = double doublet, t = triplet,  
q = quartet; s = singlet; m = multiplet;  
cm = complex multiplet

In the n.m.r. spectrum of compound 25 (Table X), H-1 appeared as a doublet, and H-2 and H-3 as quartets deshielded due to the presence of the chlorosulphonyloxy groups at C2 and C3. H-4 appeared as a triplet while H-5, H-6 and H-6' were seen as a complex multiplet and not assigned. The mass spectral data for compound 25 is given in Table XI and the possible fragmentation pathways are shown in Scheme F.



Scheme F - Mass spectral fragmentation pathways for compounds 25, 29 and 34

Table XI - Relative intensities of the peaks in the mass spectra of compounds 25, 29 and 34

| Compound | <u>25</u>            | <u>29</u> | <u>34</u> |
|----------|----------------------|-----------|-----------|
| $m/e$    | Relative intensity % |           |           |
| 359      | 0.15                 | 0.63      | 3.34      |
| 329      | 5.43                 | 1.41      | 5.61      |
| 243      | 6.32                 | 4.73      | 8.42      |
| 195      | 0.80                 | 1.41      | 4.21      |
| 185      | 13.35                | 25.10     | 44.78     |
| 172      | 4.47                 | 8.42      | 22.39     |
| 73       |                      | 100       | 100       |
| 48       | 100                  |           |           |

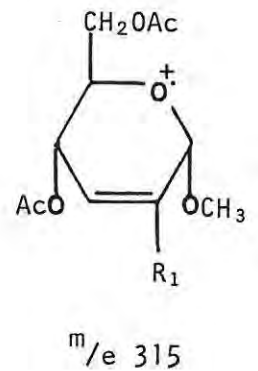
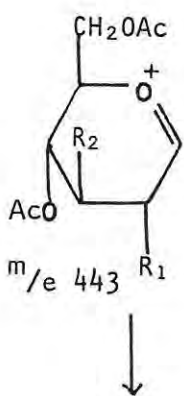
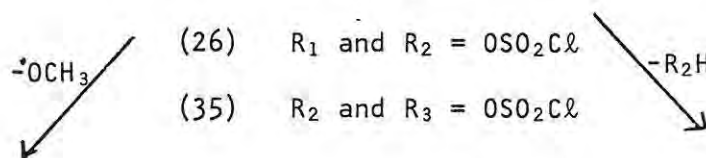
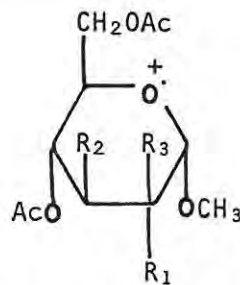
Acetylation of compound 25 in acetic anhydride at  $-10^{\circ}$  afforded methyl 4,6-di-0-acetyl- $\alpha$ -D-glucopyranoside 2,3-dichlorosulphate 26 as a pure, crystalline product. Because of the readdition of the benzylidene group which occurred to a small extent, even during the modified work-up procedure, direct synthesis of compound 26 from 23 was undertaken by addition of the acetylating mixture to the trifluoroacetic acid-methyl 4,6-benzylidene- $\alpha$ -D-glucopyranoside 2,3-dichlorosulphate reaction mixture after removal of the benzylidene group was complete (t.l.c.). The reaction mixture was then poured onto ice and subsequently extracted with chloroform. The infra-red spectrum of compound 26 revealed characteristic absorbance peaks for chlorosulphonyloxy and acetyl groups.

In the n.m.r. spectrum of 26 (Table X), H-1 appeared as a doublet, H-2 a quartet and H-6 and H-6' as double doublets. Due to the electron withdrawing effects of the chlorosulphonyloxy and acetyl groups at C3 and C4, the signals due to H-3 and H-4 were deshielded and overlapped with the H-1 signal. H-6 and H-6' were shifted downfield due to the

acetyl group at C6, thus overlapping with H-5.

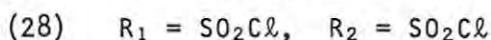
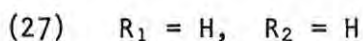
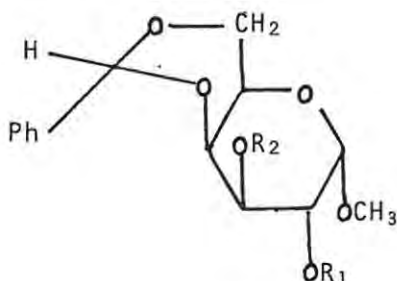
Table XII - Relative intensities of the peaks in the mass spectra of compounds 26 and 35

| Compound | <u>26</u>            | <u>35</u> |
|----------|----------------------|-----------|
| $m/e$    | Relative intensity % |           |
| 443      | 0.18                 | 0.30      |
| 315      | 0.94                 | 2.16      |
| 195      | 2.11                 | 3.55      |
| 43       | 100                  | 100       |



Scheme G - Mass spectral fragmentation pathways for compounds 26 and 35

The mass spectra of both 26 and 35 (Table XII, Scheme G) showed peaks at  $m/e$  315 and  $m/e$  195 in association with their isotopic counterparts at  $m/e$  317 and  $m/e$  197 respectively, in the ratio of 3:1 confirming the presence of one chlorine atom in each fragment.



Reaction of methyl 4,6-benzylidene- $\alpha$ -D-galactopyranoside with sulphuryl chloride and pyridine at  $0^\circ$  afforded methyl 4,6-benzylidene- $\alpha$ -D-galactopyranoside 2,3-dichlorosulphate 28. The monochlorosulphated derivatives were not isolable, even at lower temperatures. The infrared spectrum of compound 28 indicated the presence of absorbance peaks characteristic for the chlorosulphonyloxy group.

Because of the chlorosulphonyloxy groups at C2 and C3 the signals due to H-2 and H-3 were shifted downfield coalescing with H-1 to form a high intensity broad singlet (Table XIII). A characteristic<sup>95</sup> narrow double doublet for H-4 with  $J_{4,5} = 1.3$  Hz, confirmed the galacto configuration, while the signals due to H-5, H-6 and H-6' appeared as a complex multiplet and were not assigned.

Mass spectral fragmentation of 28<sup>97</sup> and 33 (methyl 4,6-benzylidene- $\alpha$ -D-mannopyranoside 2,3-dichlorosulphate) proceeded via h-fracture. Peaks at  $m/e$  213 and  $m/e$  185 in association with their isotopic counterparts at  $m/e$  215 and  $m/e$  187 respectively in the ratio of 3:1 confirmed these to be fragments bearing a chlorine atom.

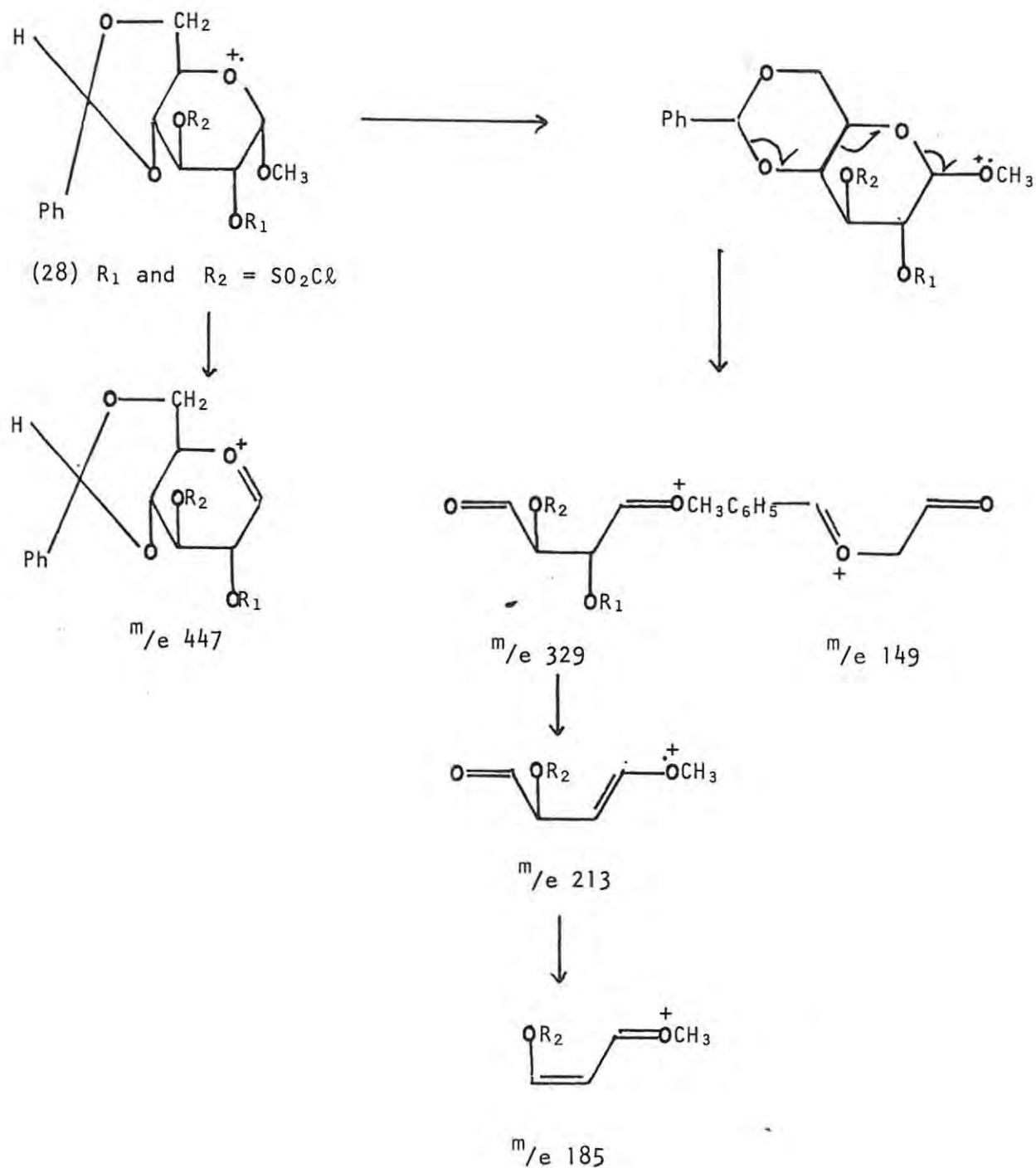
Table XIII - Chemical shifts ( $\tau$ -values) and first-order coupling constants (Hz) for compounds 28, 29 and 30

| Compound          | <u>28</u>        | <u>29</u>     | <u>29*</u>    | <u>30</u>            |
|-------------------|------------------|---------------|---------------|----------------------|
| H-1               |                  |               | 3.91 (d)      | 4.11 (d)             |
| H-2               | 4.62-4.79 (s)    | 4.49-4.68 (m) | 4.23 (dd)     | 4.89 (dd)            |
| H-3               |                  |               | 4.20 (dd)     | 4.59 (dd)            |
| H-4               | 5.82 (dd)        | 5.18-5.33     | 4.46-4.67     | $\approx$ 4.77 (d)   |
| H-5               | 5.22-5.62 (m)    |               |               | 5.52-5.98 (m)        |
| H-6               | 5.92-6.47 (m)    | 6.04-6.22 (m) | 5.14-5.83 (m) | 5.66 (dd)            |
| H-6'              |                  |               |               | 5.89 (dd)            |
| OH                |                  | 6.81 (s)      |               |                      |
| PhCH              | 4.41 (s)         |               |               |                      |
| aromatic protons  | 2.32-2.78 (m) 5H |               |               |                      |
| NH                |                  |               |               |                      |
| OCH <sub>3</sub>  | 6.54 (s)         | 6.49 (s)      | 6.37 (s)      | 6.43 (s)             |
| OAc               |                  |               |               | 7.76 (s)<br>7.91 (s) |
| J <sub>1,2</sub>  |                  |               | 3.3           | 3.3                  |
| J <sub>2,3</sub>  |                  |               | 10.7          | 10.7                 |
| J <sub>3,4</sub>  | 6.0              |               | 3.3           | 4.0                  |
| J <sub>4,5</sub>  | 1.3              | 1.3           | 1.3           |                      |
| J <sub>5,6</sub>  |                  | 4.7           |               | 3.3                  |
| J <sub>5,6'</sub> |                  | 7.3           |               | 2.7                  |
| J <sub>6,6'</sub> |                  |               |               | 7.3                  |

Key: d = doublet; dd = double doublet; s = singlet; m = multiplet

cm = complex multiplet

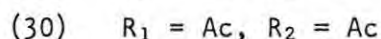
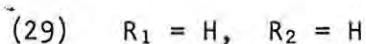
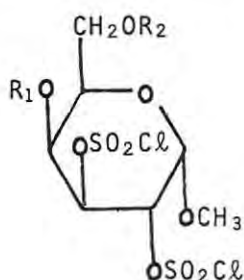
\* with shift reagent, trichloroacetyl isocyanate.



Scheme H - Mass spectral fragmentation pathways of compounds 28 and 33

Table XIV - Relative intensities of the peaks in the mass spectra of compounds 28 and 33

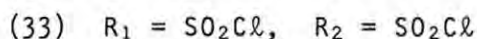
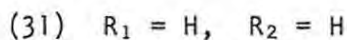
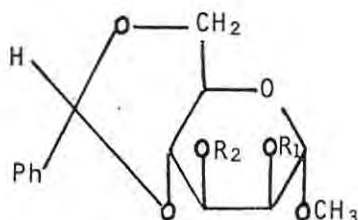
| Compound | <u>28</u>            | <u>33</u> |
|----------|----------------------|-----------|
| m/e      | Relative intensity % |           |
| 447      | 0.25                 | 1.68      |
| 329      | 1.06                 | 6.30      |
| 213      | 1.99                 | 9.43      |
| 185      | 1.88                 | 6.30      |
| 149      | 1.68                 | 8.62      |
| 105      | 100                  | 100       |



Methyl  $\alpha$ -D-galactopyranoside 2,3-dichlorosulphate 29 was isolated as a pure, crystalline product after reaction of compound 28 with trifluoroacetic acid as described for the gluco isomer. The infra-red spectrum of 29 showed absorbance peaks for hydroxyl and chlorosulphonyloxy groups.

In the n.m.r. spectrum of compound 29 (Table XIII), the deshielding effects of the electron withdrawing chlorosulphonyloxy groups at C2 and C3 caused the signals due to H-2 and H-3 to overlap with H-1. The signal due to the two hydroxyl groups occurred as a broad 2-proton singlet at  $\tau$  6.81. On addition of trichloroacetyl isocyanate H-4 and the methylene protons were deshielded, confirming the location of the hydroxyl groups at C4 and C6.

Mass spectral fragmentation of 29 occurred in exactly the same manner as depicted for the gluco isomer 25 in Scheme F. The spectrum gave rise to peaks at  $m/e$  243, 185 and 172 in association with peaks at  $m/e$  245, 187 and 174 respectively in a 3:1 ratio confirming these to be fragments bearing single chlorine atoms. Methyl 4,6-di-O-acetyl- $\alpha$ -D-galactopyranoside 2,3-dichlorosulphate 30 was synthesised directly from methyl 4,6-benzylidene- $\alpha$ -D-galactopyranoside 2,3-dichlorosulphate 28 according to the procedure described for the gluco isomer. The infra-red spectrum of 30 revealed absorbances due to acetyl and chlorosulphonyloxy groups, while in the n.m.r. spectrum (Table XIII), H-2, H-3, H-4, H-6 and H-6' were deshielded due to the electron withdrawing effects of the chlorosulphonyloxy and acetyl groups respectively.



Reaction of methyl  $\alpha$ -D-mannopyranoside in N,N-dimethylformamide with  $\alpha,\alpha$ -dimethoxytoluene and p-toluenesulphonic acid as catalyst, as proposed by Evans<sup>89</sup> et al., for the gluco isomer yielded a mixture containing 3 compounds. Recrystallization of the mixture from methanol-water afforded a crystalline product which proved to be a mixture of the exo and endo isomers of 2,3:4,6-di-O-benzylidene- $\alpha$ -D-mannopyranoside. Thereafter, recrystallization of the residue from hot benzene afforded pure methyl 4,6-benzylidene- $\alpha$ -D-mannopyranoside 31 in

a 64% yield. Recently, Patroni<sup>38</sup> et al., reported the synthesis of methyl 4,6-benzylidene- $\alpha$ -D-mannopyranoside in a 51% yield, by reaction of methyl  $\alpha$ -D-mannopyranoside in N,N-dimethylformamide with pyridinium p-toluenesulphonate and  $\alpha,\alpha$ -dimethoxytoluene. Previously<sup>99</sup> the maximum yield reported using the formic acid procedure, was 32%.

Reaction of compound 31 with sulphuryl chloride and pyridine at 0° afforded a crystalline compound in a 50% yield, which proved to be a mixture of the exo and endo isomers of 2,3:4,6-di-O-benzylidene- $\alpha$ -D-mannopyranoside. The above reaction prompted us to investigate the use of sulphuryl chloride as a catalyst in the synthesis of the benzylidene derivatives of methyl  $\alpha$ -D-mannopyranoside. Although the reaction afforded the di- and mono-benzylidene derivatives, the yields achieved were inferior to those obtained using p-toluenesulphonic acid as catalyst. Reduction of the temperature to -15° during the reaction of compound 31 with sulphuryl chloride and pyridine made possible the isolation of the dichlorosulphate 33. The infra-red spectrum of 33 showed characteristic absorbance peaks for the chlorosulphonyloxy group, while the elemental analysis agreed with the expected structure. The coupling constants<sup>98</sup> ( $J_{1,2} = 2.7$ ,  $J_{2,3} = 4.0$ ,  $J_{3,4} = 8.7$  and  $J_{4,5} = 8.7$ ) were in agreement with the <sup>4</sup>C<sub>1</sub> conformation and the  $\alpha$ -manno configuration for compound 33 (Table XV). H-2 and H-3 appeared as quartets deshielded due to the chlorosulphonyloxy groups at C2 and C3, while H-1 occurred as a doublet and H-4 a quartet. The mass spectral fragmentation of 33 is as depicted for the galacto isomer in Scheme H.

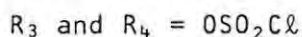
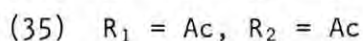
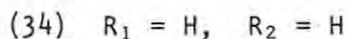
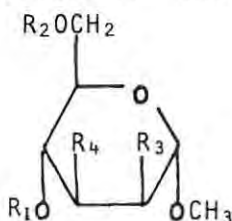


Table XV - Chemical shifts ( $\tau$ -values) and first-order coupling constants (Hz) for compounds 33, 34, 35 and 39

| Compound          | <u>33</u>      | <u>34</u>     | <u>34*</u>   | <u>35</u>    | <u>39</u>      |
|-------------------|----------------|---------------|--------------|--------------|----------------|
| H-1               | 4.70(d)        | 4.88(d)       | 4.79(d)      | 4.80(d)      | 4.93(d)        |
| H-2               | 4.93(q)        | 4.82(dd)      | 4.39-4.83(m) | 4.83(q)      | 4.71(dd)       |
| H-3               | 4.61(q)        | 4.68(q)       |              | 4.59(q)      | 4.51(dd)       |
| H-4               | 5.76(t)        | 5.76(t)       |              | 4.59(t)      |                |
| H-5               |                | 5.54-6.63(cm) | 5.30-5.91(m) | 5.60-6.07(m) | 5.45-6.39(m)   |
| H-6               | 5.58-6.29(cm)  | 5.91(dd)      |              |              |                |
| H-6'              |                | 6.16(dd)      |              |              |                |
| OH                |                | 6.81(s)2(OH)  |              |              |                |
| PhCH              | 4.37(s)        |               |              |              | 4.33(s)        |
| aromatic protons  | 2.19-2.73(s)5H |               |              |              | 2.39-2.65(m)5H |
| NH                |                |               | 1.29(s)2(H)  |              |                |
| OCH <sub>3</sub>  | 6.52(s)        | 6.48(s)       | 6.40(s)      | 6.43(s)      | 6.58(s)        |
| OAc               |                |               |              | 7.84(s)2(Ac) | 7.89(s)        |
| J <sub>1,2</sub>  | 2.7            | 1.3           | 1.3          | 1.3          | 2.0            |
| J <sub>2,3</sub>  | 4.0            | 5.3           |              | 4.7          | 3.3            |
| J <sub>3,4</sub>  | 8.7            | 9.3           |              | 10.0         |                |
| J <sub>4,5</sub>  | 8.7            | 9.3           |              | 10.0         | 6.7            |
| J <sub>5,6</sub>  |                | 3.3           |              |              |                |
| J <sub>5,6'</sub> |                | 4.0           |              |              |                |
| J <sub>6,6'</sub> |                | 10.7          |              |              |                |

Key: d = doublet; dd = double doublet; s = singlet; m = multiplet, cm = complex multiplet

\* with shift reagent, trichloroacetyl isocyanate

Reaction of compound 33 with trifluoroacetic acid as described above afforded methyl  $\alpha$ -D-mannopyranoside 2,3-dichlorosulphate 34 as a colourless syrup. The infra-red spectrum of 34 revealed absorbances due to hydroxyl and chlorosulphonyloxy groups.

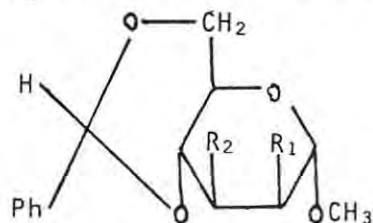
In the n.m.r. spectrum of compound 34 (Table XV), H-1 appeared as a doublet

overlapping with the double doublet H-2, while H-3 occurred as a double doublet. Both H-2 and H-3 were deshielded due to the chlorosulphonyloxy groups. H-4 occurred as a triplet and H-6 and H-6' as overlapping double doublets, while the signal due to the two hydroxyl groups was seen as a high intensity singlet at  $\tau$  6.81. The first order coupling constants were in agreement with the  $^4C_1$  conformation and the  $\alpha$ -manno configuration of 34. Addition of trichloroacetyl isocyanate to the n.m.r. solution of 34 in deuterio-acetone caused the appearance of a broad 2-proton singlet, while marked deshielding of H-4 revealed that one of the carbamate groups was located at C4. The methylene protons were also deshielded showing that the other carbamate group was located at C6.

The major fragmentation pattern for 34 is as depicted for the gluco isomer in Scheme F. Peaks situated at  $m/e$  243, 185 and 172 in a 3:1 ratio with peaks at  $m/e$  245, 187 and 174 confirmed the presence of single chlorine atoms.

Direct synthesis of methyl 4,6-di-O-acetyl- $\alpha$ -D-mannopyranoside 2,3-dichlorosulphate 35 from methyl 4,6-benzylidene- $\alpha$ -D-mannopyranoside 2,3-dichlorosulphate 33 was carried out as described for the gluco 26 and galacto 30 compounds.

The mass spectral fragmentation pathways of compound 35 are as depicted in Scheme G for the gluco compound.



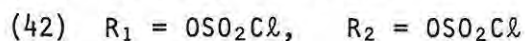
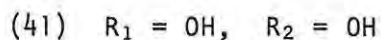
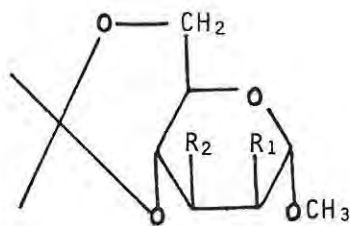
- (37)  $R_1 = \text{OAc}, R_2 = \text{OH}$   
 (38)  $R_1 = \text{OH}, R_2 = \text{OAc}$   
 (39)  $R_1 = \text{OSO}_2\text{Cl}, R_2 = \text{OAc}$   
 (40)  $R_1 = \text{OAc}, R_2 = \text{OSO}_2\text{Cl}$

Partial<sup>92</sup> acetylation of methyl 4,6-benzylidene- $\alpha$ -D-mannopyranoside afforded after column chromatography in addition to the di-0-acetate, methyl 2-0-acetyl- (37) and methyl 3-0-acetyl- (38) 4,6-benzylidene- $\alpha$ -D-mannopyranoside in low yields.

Chlorosulphation of compounds 37 and 38 at  $-10^\circ$  afforded methyl 2-0-acetyl-4,6-benzylidene- $\alpha$ -D-mannopyranoside 3-chlorosulphate 40 and methyl 3-0-acetyl-4,6-benzylidene- $\alpha$ -D-mannopyranoside 2-chlorosulphate 39 as extremely unstable compounds. Because of their instability satisfactory elemental analyses could not be obtained for 39 and 40. The infra-red spectra of 39 and 40 revealed the characteristic absorbance peaks for chlorosulphonyloxy and acetyl groups.

In the n.m.r. spectrum of 39 (Table XV), H-2 and H-3 appeared as double doublets both shifted downfield due to the chlorosulphonyloxy and acetyl groups at C2 and C3 respectively. H-1 occurred as a doublet, while H-4, H-5, H-6 and H-6' were seen as a complex multiplet and not assigned.

The presence of peaks at  $m/e$  273 and  $m/e$  149, the former existing in a 3:1 relationship with a peak at  $m/e$  275 confirming this to be a fragment with one chlorine atom, established that mass spectral fragmentation of 39 and 40 proceeded via h-fracture<sup>97</sup>. Both compounds exhibited molecular ions at  $m/e$  422 in association with their isotopic counterparts at  $m/e$  424 in a ratio of 3:1, confirming the presence of a chlorine atom in both compounds. It was hoped as with compounds 7 and 8, that the acetyl groups adjacent to the chlorosulphonyloxy groups at C2 and C3 in 39 and 40 respectively might activate these normally inert centres towards nucleophilic displacement by chloride. However, reaction of compounds 39 and 40 with lithium chloride in hexamethylphosphoramide afforded the 3-0-acetyl 38 and 2-0-acetyl 37 derivatives respectively.



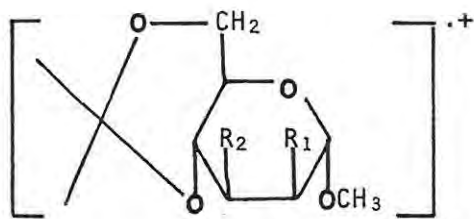
Reaction of 4,6-0-isopropylidene- $\alpha$ -D-mannopyranoside 41 at  $-10^\circ$  with sulphuryl chloride and pyridine afforded, methyl 4,6-0-isopropylidene- $\alpha$ -D-mannopyranoside 2,3-dichlorosulphate 42 which was recrystallized with difficulty from ether-petroleum ether. The infra-red spectrum of 42 showed the characteristic absorbance peaks for the chlorosulphonyloxy group, while in the n.m.r. spectrum (Table XVI), H-1 appeared as a doublet, H-2 and H-3 as double doublets shifted downfield due to the chlorosulphonyloxy groups at C2 and C3. H-4 occurred as a triplet and H-6 and H-6' as overlapping double doublets.

The mass spectrum of compound 42 (Table XVIII, Scheme 1) showed peaks at  $m/e$  243 and  $m/e$  195 in a 3:1 ratio with their isotopic counterparts at  $m/e$  245 and  $m/e$  197 respectively, indicating the presence of one chlorine atom. Reaction of 42 with trifluoroacetic acid as described by Christensen and Goodman<sup>90</sup> afforded after column chromatography, a clear colourless syrup which proved to be methyl  $\alpha$ -D-mannopyranoside 2,3-dichlorosulphate 34. It was not necessary to use the modified work-up procedure for the isopropylidene acetals as readdition of the isopropylidene group did not occur. However, these reactions do not go to completion and it is therefore necessary to employ either recrystallization or column chromatography in order to isolate the pure product.

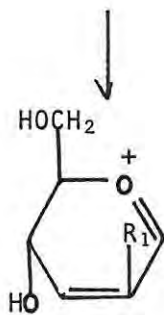
Table XVI - Chemical shifts ( $\tau$ -values) and first-order coupling constants (Hz) for compound 42

| Compound                         | <u>42</u>          |
|----------------------------------|--------------------|
| H-1                              | 4.86(d)            |
| H-2                              | 4.82(dd)           |
| H-3                              | 4.67(q)            |
| H-4                              | 5.77(t)            |
| H-5                              | 5.52-6.30(m)       |
| H-6                              | 5.92(dd)           |
| H-6'                             | 6.17(dd)           |
| OCH <sub>3</sub>                 | 6.48(s)            |
| C(CH <sub>3</sub> ) <sub>2</sub> | 5.44(s)<br>5.57(s) |
| J <sub>1,2</sub>                 | 1.3                |
| J <sub>2,3</sub>                 | 4.0                |
| J <sub>3,4</sub>                 | 9.3                |
| J <sub>4,5</sub>                 | 9.3                |
| J <sub>5,6</sub>                 | 2.3                |
| J <sub>5,6'</sub>                | 2.7                |
| J <sub>6,6'</sub>                | 9.3                |

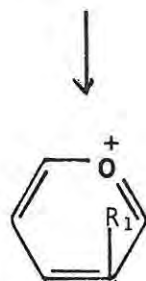
Key: d = doublet;  
 dd = double doublet;  
 s = singlet;  
 m = multiplet;  
 q = quartet;  
 t = triplet;



$R_1$  and  $R_2 = OSO_2Cl$



$m/e$  243

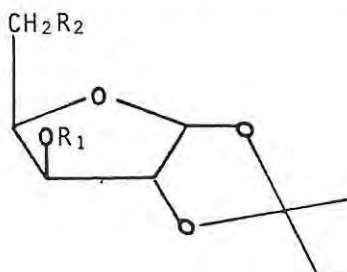


$m/e$  195

Table XVIII - Relative intensities of peaks in the mass spectrum of 42

| Compound | <u>42</u>            |
|----------|----------------------|
| $m/e$    | Relative Intensity % |
| 243      | 0.63                 |
| 195      | 0.98                 |
| 113      | 100                  |

Scheme I - Mass spectral fragmentation pathways of compound 42



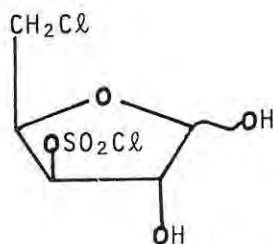
(43)  $R_1 = SO_2Cl$ ,  $R_2 = Cl$

(44)  $R_1 = H$ ,  $R_2 = Cl$

(45)  $R_1 = Ac$ ,  $R_2 = Cl$

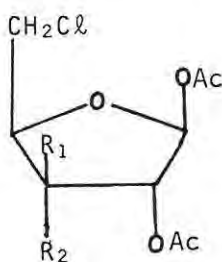
5-Chloro-5-deoxy-1,2-0-isopropylidene- $\alpha$ -D-xylofuranose 3-chlorosulphate 43<sup>94</sup> was synthesised by reaction of 1,2-0-isopropylidene- $\alpha$ -D-xylofuranose at  $-15^\circ$  with sulphuryl chloride and pyridine.

Reaction of 43 with lithium chloride in hexamethylphosphoramide at  $60^\circ$  afforded two compounds, one corresponding to 43, the other to the dechlorosulphated derivative. Isolation and acetylation of the latter product afforded a compound which corresponded to the 3-0-acetyl-5-chloro-5-deoxy-1,2-0-isopropylidene- $\alpha$ -D-xylofuranose 45, synthesised by acetylation of compound 44, confirming that on reaction of compound 43 with lithium chloride in hexamethylphosphoramide, dechlorosulphation had occurred.



(46)

Treatment of compound 43 with trifluoroacetic acid afforded a chromatographically homogeneous compound 46<sup>90</sup> which proved to be 5-chloro-5-deoxy- $\alpha/\beta$ -D-xylofuranose 3-chlorosulphate. The infra-red spectrum of 46 revealed the characteristic absorbance peaks for hydroxyl and chlorosulphonyloxy groups, while the elemental analysis was in accord with the expected structure.



(47)  $R_1 = \text{OSO}_2\text{Cl}$ ,  $R_2 = \text{H}$

(48)  $R_1 = \text{H}$ ,  $R_2 = \text{Cl}$

Acetylation of 46 in chloroform as solvent afforded two compounds possessing very similar  $R_f$  values, presumed to be the  $\alpha$  and  $\beta$  acetates. When compound 46 was acetylated in acetic anhydride a single compound 47, which showed a negative optical rotation was obtained. Compound 47 was assigned the structure 1,2-di-0-acetyl-5-chloro-5-deoxy- $\beta$ -D-xylofuranose 3-chlorosulphate on the basis of negative optical rotation and the appearance of H-1 as a singlet in its n.m.r. spectrum. Tetra-0-acetyl- $\beta$ -D-xylofuranose has a negative rotation, while a positive optical rotation has been reported for the  $\alpha$ -anomer<sup>100</sup>.

Magnani<sup>101</sup> et al., reported H-1 a singlet for the  $\beta$ - and a doublet for the  $\alpha$ -anomer of tetra-0-acetyl-D-xylofuranose.

The n.m.r. spectrum of 47 (Table XVII), showed H-1 a singlet, H-2 a singlet and H-3 a doublet, all deshielded as a result of the acetyl and chlorosulphonyloxy groups respectively. The infra-red spectrum of 47 showed absorbance peaks for acetyl and chlorosulphonyloxy groups.

Table XVII - Chemical shifts ( $\tau$ -values) and first-order coupling constants (Hz) for compounds 47 and 48

| Compound   | <u>47</u>    | <u>48</u>    |
|------------|--------------|--------------|
| H-1        | 3.86(s)      | 3.86(s)      |
| H-2        | 4.36(s)      | 4.63(d)      |
| H-3        | 4.58(d)      | 5.51(d)      |
| H-4        | 5.06-5.46(m) | 5.29-5.76(m) |
| H-5        | 6.11-6.51    | 6.13-6.30    |
| H-5'       |              |              |
| OAc        | 7.82(s)      | 7.89(s)      |
| OAc        | 7.87(s)      | 7.99(s)      |
| $J_{1,2}$  | 4.7          | 4.0          |
| $J_{2,3}$  |              |              |
| $J_{3,4}$  |              |              |
| $J_{4,5}$  |              |              |
| $J_{4,5'}$ |              |              |
| $J_{5,5'}$ |              |              |

Key: d = doublet; s = singlet; m = multiplet

Since nucleophilic displacement of the chlorosulphonyloxy group at C3 in compound 43 was unsuccessful, compound 47 was synthesised with a view to possible activation of the 3-chlorosulphonyloxy group by the electron withdrawing effects of the acetyl groups at C1 and C2, towards nucleophilic displacement by chloride.

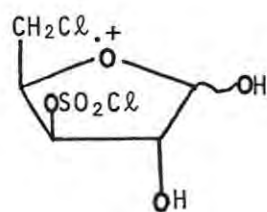
Reaction of compound 47 with lithium chloride in hexamethylphosphoramide afforded after column chromatography, 1,2-di-0-acetyl-3,5-dichloro-3,5-dideoxy- $\beta$ -D-ribofuranose 48. The infra-red spectrum of 48, showing an absence of hydroxyl and chlorosulphonyloxy groups and the elemental analysis indicating the presence of two chlorine atoms, confirmed the replacement of the 3-chlorosulphonyloxy group by chloride.

In the n.m.r. spectrum of 48 (Table XVII), the H-1 singlet was similarly deshielded as in 47 due to the acetyl group at C1. H-3 appeared as a doublet and was not deshielded to the same extent as in 47, due to the presence of the chloro group instead of the chlorosulphonyloxy group at C3, resulting in an overlap of H-3 with H-4. The appearance of H-2 as a singlet in 47 and a doublet in 48 suggested that nucleophilic replacement of the chlorosulphonyloxy group at C3 by chloride had occurred with inversion of configuration.

The mass spectral fragmentation patterns for compounds 46, 47 and 48 are depicted in Scheme J. In all three spectra a peak occurred at  $m/e$  133 in a 3:1 relationship with a peak at  $m/e$  135 confirming this to be a fragment bearing a single chlorine atom.

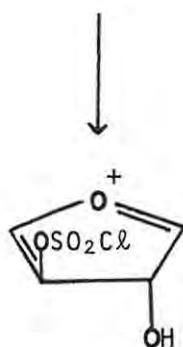
Table XIX - Relative intensities of the peaks in the mass spectra of compounds 46, 47 and 48

| Compound | <u>46</u>            | Compound  | <u>47</u>            | Compound  | <u>48</u>            |
|----------|----------------------|-----------|----------------------|-----------|----------------------|
| $m/e$    | Relative Intensity % | $m/e$     | Relative Intensity % | $m/e$     | Relative Intensity % |
| 199      | 1.19                 | (M-59)291 | 1.06                 | (M-59)211 | 1.78                 |
|          |                      | 175       | 0.94                 | 175       | 2.82                 |
| 133      | 9.44                 | 133       | 5.30                 | 133       | 4.84                 |
| 64       | 100                  | 43        | 100                  | 43        | 100                  |

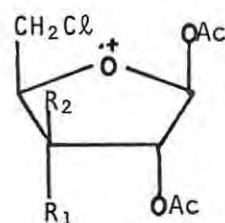


$m/e$  266

(46)

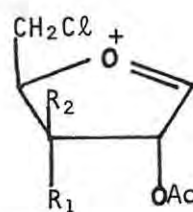
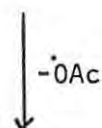


$m/e$  199

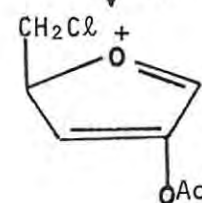
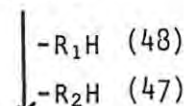


$R_1 = H, R_2 = OSO_2Cl$  (47)

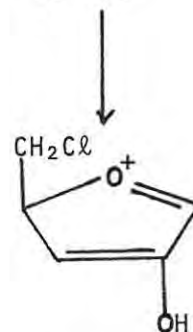
$R_1 = Cl, R_2 = H$  (48)



$m/e$  (M-59)

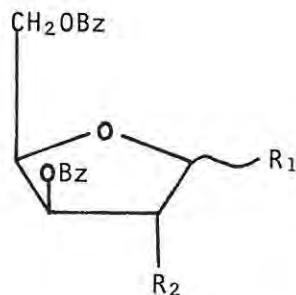


$m/e$  175



$m/e$  133

Scheme J - Mass spectral fragmentation pathways of compounds 46, 47 and 48



- (50)  $R_1 = \text{OH}, R_2 = \text{OH}$   
 (51)  $R_1 = \text{Cl}, R_2 = \text{OSO}_2\text{Cl}$   
 (52)  $R_1 = \text{OCH}_3, R_2 = \text{OH}$   
 (53)  $R_1 = \text{OCH}_3, R_2 = \text{OSO}_2\text{Cl}$

3,5-Di-0-benzoyl-1,2-0-isopropylidene- $\alpha$ -D-xylofuranose 49 which was obtained by reaction of 1,2-0-isopropylidene- $\alpha$ -D-xylofuranose with benzoyl chloride and pyridine, when reacted with trifluoroacetic acid yielded 3,5-di-0-benzoyl-D-xylofuranose 50 as a cloudy syrup. The infra-red spectrum of 50 showed absorbance peaks for hydroxyl and benzoyl groups, while the elemental analyses of both 49 and 50 were in accord with the expected structures.

The n.m.r. spectrum of 49 (Table XX), showed H-1 a doublet and H-3 a doublet shifted downfield due to the electron withdrawing effects of the benzoyl group at C3. Due to the benzoyl group at C5, the H-5,5' signal was deshielded so that it overlapped with those of H-2 and H-4 and these signals were not assigned.

Reaction of 50 with sulphuryl chloride and pyridine at  $-15^\circ$  afforded a yellow syrup which proved to be a mixture of the  $\alpha$ - and  $\beta$ -isomers of 3,5-di-0-benzoyl-D-xylofuranosyl chloride 2-chlorosulphate 51 in the approximate ratio of 5:2. The infra-red spectrum of 51 showed the characteristic absorbance peaks for chlorosulphonyloxy and benzoyl groups.

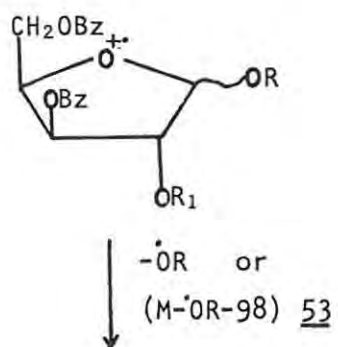
Table XX - Chemical shifts ( $\tau$ -values) and first-order coupling constants (Hz) for 49.

| Compound                         | <u>49</u>                    |
|----------------------------------|------------------------------|
| H-1                              | 3.84(d)                      |
| H-2                              | see below                    |
| H-3                              | 4.30(d)                      |
| H-4<br>H-5<br>H-5'               | 5.14-5.66(m)<br>includes H-2 |
| aromatic protons                 | 1.64-2.66(m)                 |
| C(CH <sub>3</sub> ) <sub>2</sub> | 8.41(s)                      |
|                                  | 8.64(s)                      |
| J <sub>1,2</sub>                 | 4.0                          |
| J <sub>2,3</sub>                 | 2.7                          |

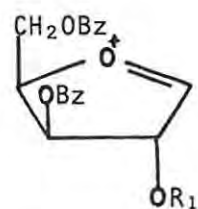
Key: d = doublet; s = singlet;  
m = multiplet

Treatment of the mixture 51 with sodium iodide/anhydrous methanol afforded a mixture of methyl 3,5-di-O-benzoyl- $\alpha/\beta$ -D-xylofuranose in the approximate ratio of 2:1, while the infra-red spectrum revealed the presence of hydroxyl and benzoyl absorbance peaks.

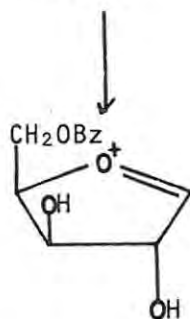
The mixture 52 was chlorosulphated to afford methyl 3,5-di-O-benzoyl- $\alpha/\beta$ -D-xylofuranose 2-chlorosulphate (2:1), with a view to replacing the chlorosulphonyloxy group at C2 with chloride by reaction with lithium chloride in hexamethylphosphoramide. It was hoped that the benzoyl group at C3 might enhance the activity of the normally inert C2 centre towards nucleophilic replacement. The reaction, however, yielded the dechlorosulphated mixture 52.



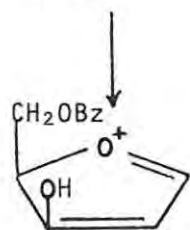
|    | R               | R <sub>1</sub>     | M <sup>+</sup> |
|----|-----------------|--------------------|----------------|
| 50 | H               | H                  | 358            |
| 52 | CH <sub>3</sub> | H                  | 372            |
| 53 | CH <sub>3</sub> | SO <sub>2</sub> Cl | 470            |



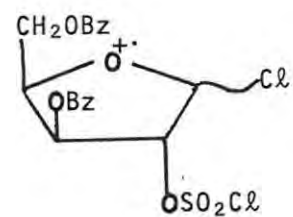
$m/e$  341



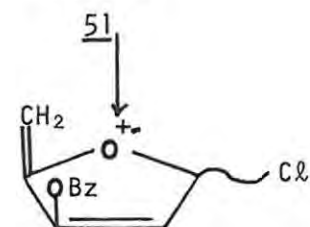
$m/e$  237



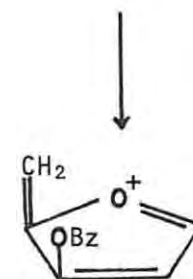
$m/e$  219



$m/e$  474



$m/e$  236



$m/e$  201

Scheme K - Mass spectral fragmentation pathways for compounds 50, 51, 52 and 53

Table XXI - Relative intensities of the peaks in the mass spectra of 50, 51, 52 and 53

| Mixture | <u>50</u>            | <u>52</u> | <u>53</u> | Mixture | <u>51</u>            |
|---------|----------------------|-----------|-----------|---------|----------------------|
| $m/e$   | Relative intensity % |           |           | $m/e$   | Relative intensity % |
| 341     | 1.12                 | 0.38      | 0.06      | 236     | 0.16                 |
| 237     | 0.38                 | 1.26      | 0.10      | 201     | 0.11                 |
| 219     | 2.37                 | 0.13      | 0.06      | 122     | 37.44                |
| 122     | 22.4                 | 10.59     | 9.38      | 105     | 100                  |
| 105     | 100                  | 100       | 100       | 77      | 29.86                |
| 77      | 100                  | 56.30     | 37.35     |         |                      |

The mass spectrum of 51 revealed a peak at  $m/e$  236 in a 3:1 ratio with its isotopic counterpart at  $m/e$  238 confirming the presence of a chlorine atom, while the mass spectra of 50, 51, 52 and 53 all gave rise to prominent peaks at  $m/e$  77, 105 and 122 indicating the presence of benzoyl groups.

The replacement of the 3-chlorosulphonyloxy group of 5,6-dichloro-5,6-dideoxy-1,2-O-isopropylidene- $\beta$ -L-idofuranose by chloride with inversion of configuration confirmed that nucleophilic displacement reactions in furanoid rings generally occur quite readily. The isolation of the dechlorosulphated product as well, during this reaction, shows that hydrolysis is a competing reaction. In the reaction of 1,2-O-isopropylidene- $\alpha$ -D-xylofuranose 3-chlorosulphate (43) with lithium chloride in hexamethylphosphoramide, the hydrolysis predominated as only the dechlorosulphated product was formed. Replacement of the isopropylidene group in (43) with acetyl groups, followed by reaction of the product with lithium chloride, gave the 3-chloro derivative, suggesting that the adjacent acetyl group had activated the 3-

chlorosulphonyloxy group towards nucleophilic displacement. This activation was not, however, noted with a 2-chlorosulphonyloxy group in a furanoid ring, since methyl 3,5-di-0-benzoyl- $\alpha/\beta$ -xylofuranosides 2-chlorosulphate afforded only the dechlorosulphated products.

The inertness of the C2 chlorosulphonyloxy and some C3 chlorosulphonyloxy groups on a pyranoid ring may be demonstrated again by the lack of substitution of the chlorosulphonyloxy groups in methyl 3-0-acetyl-4,6-benzylidene- $\alpha$ -D-mannopyranoside 2-chlorosulphate, methyl 2-0-acetyl-4,6-benzylidene- $\alpha$ -D-mannopyranoside 3-chlorosulphate, methyl 3-0-acetyl-4,6-dichloro-4,6-dideoxy- $\alpha$ -D-galactopyranoside 2-chlorosulphate, methyl 2-0-acetyl-4,6-dichloro-4,6-dideoxy- $\alpha$ -D-galactopyranoside 3-chlorosulphate and methyl 4,6-benzylidene- $\alpha$ -D-glucopyranoside 2,3-dichlorosulphate. In the latter compound, reaction afforded the cyclic sulphate, while in former compounds hydrolysis occurred.

The above work suggests that the replacement of a 2-chlorosulphonyloxy group on a pyranoid system by chloride is not a general reaction. Regretably Khan's<sup>19</sup> successes in replacing the 2-chlorosulphonyloxy groups in methyl 3-0-acetyl-4,6-benzylidene- $\alpha$ -D-glucopyranoside 2-chlorosulphate, 3, 4, 6, 3', 4', 6'-hexa-0-acetyl-sucrose 2,1'-dichlorosulphate, 3, 4, 6, 3', 4', 6'-hexa-0-acetyl-1'-0-benzoyl-sucrose 2-chlorosulphate, and 3, 4, 3', 4'-tetra-0-acetyl-6, 6'-dichloro-6,6'-dideoxysucrose 2,1'-dichlorosulphate by chloride should therefore be viewed as isolated cases.

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