SELECTIVE ESTERIFICATION OF CARBOHYDRATES VIA STANNYLENE COMPLEXES

BY

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A thesis submitted in partial fulfilment of the requirements for the Degree of Master of Science in the University of Nairobi.

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DECLARATION

I, JOSEPH M. KERIKO, hereby declare that this thesis is my original work and has not been presented for a degree to any other University.

October 1988

JOSEPH M. KERIKO

This thesis has been submitted for examination with my approval as University Supervisor.

October 1988

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To my parents Wanja and Keriko

and my son Kennedy Keriko

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ABSTRACT

Regioselective esterification and etherification of polyhydroxy compounds have been shown to occur when dibutyltin oxide (DBTO) and bis(tributyltin) oxide (TBTO) are used as O-activating agents. Although the use of DBTO in these reactions was first reported by Wagner in 1974, there is no single mechanism which accounts fully for the observed product distributions in these tin-assisted reactions.

This work has extended the range of carbohydrates to be selectively esterified using tin. Thus, the stannylene complexes of the following sugars were prepared and subsequently reacted with:(i) benzoyl chloride;

-Methyl α-D-glucopyranoside (2)

-Methyl β-D-glucopyranoside (3)

-Methyl α-D-xylopyranoside (11)

-Methyl β-D-xylopyranoside (12)

-α-chloralose (78)

-sucrose and

-levoglucosan (1,6 anhydro β-D-glucopyranoside) (8).

(ii) p-toluene sulphonyl chloride;

-Methyl α-D-glucopyranoside (2)

-Methyl α-D-xylopyranoside (11)

-Methyl β-D-xylopyranoside (12)

(iii) Myristoyl chloride;

-Methyl α-D-glucopyranoside (2)

-Methyl α-D-galactopyranoside (7) and

-Methyl β-D-galactopyranoside (30).

The expected esters, were obtained in good to high yields as indicated below for some of them:

Methyl 2-O-benzoyl-α-D-glucopyranoside (18) from 2 in 70% yield.

Methyl 2-O-Myristoyl-α-D-glucopyranoside (49) from 2 in 81% yield.

Methyl 2-O——tosyl-α-D-glucopyranoside (14) from 2 in 58% yield.

Methyl 2-O-myristoyl-α-D-galactopyranoside (59) from 7 in 76% yield.

Methyl 2-O-benzoyl-α-D-xylopyranoside (71) from 11 in 39% yield.

Methyl 4-O-benzoyl-α-D-xylopyranoside (65) from 11 in 21% yield.

Methyl 4-O-tosyl-α-D-xylopyranoside (84) from 11 in 37% yield.

Methyl 3-O-benzoyl-β-D-xylopyranoside (73) from 12 in 90% yield and

3-O-benzoyl-α-chloralose (99) from 78 in 82% yield.

Based on the results obtained, it is proposed that the tin complex induces selectivity by the way it preferentially forms stable complexes due to intra or intermolecular stabilization by an oxygen

atom. Our proposal makes it possible to predict in advance the positional isomer which would be obtained when various carbohydrates are esterified using this technique.

Some of the above stannylated sugars were also reacted with phenylisocyanate as an electrophile. This electrophile was found to be extremely reactive under the reaction conditions, even at minus 10°C. For this reason, no predominant positional carbamate was consistently obtained and isolated in good yields, and thus no appreciable selectivity was observed in this case.

CHAPTER 1

INTRODUCTION

1.1 THE CARBOHYDRATES:

Carbohydrates is the general name given to polyhydroxy aldehydes, polyhydroxy ketones, or substances that yield such compounds on hydrolysis. They are distributed universally in plants and animals, and make up one of the three major classes of animal food, the other two being proteins and fats.

Carbohydrates are classified as monosaccharides or polysaccharides depending on whether they can be hydrolysed to simpler compounds. Monosaccharides are those that cannot be hydrolysed to simpler compounds and occur naturally as pentoses or hexoses, i.e. five or six-carbon monosaccharides containing a carbonyl group. Among these naturally occuring hexoses is D-glucose (1). D-glucose is the unit of which starch, cellulose and glycogen are made up of, and therefore it is by far the most abundant monosaccharide.

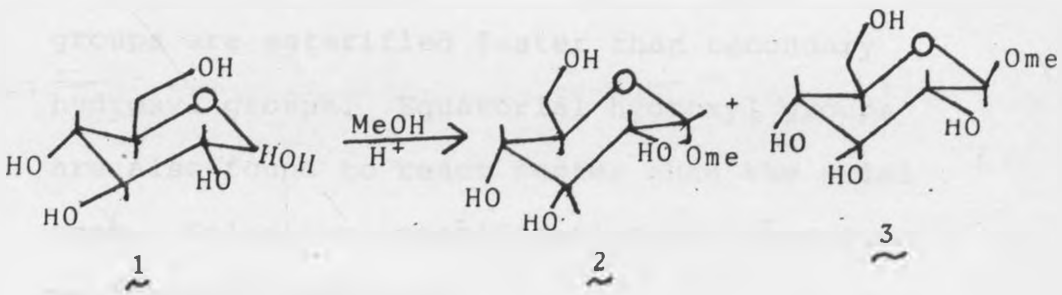
Besides their uses as food, carbohydrates are also used for clothing (cotton and linen, rayon and cellulose acetate), and also for shelter in the form of wood. They have been used as source of energy in the form of wood, charcoal and coal. Glucose syrups are also used as thickening and bodying agents and as preservatives (Shallenberger and Birch 1975).

Combustion of carbohydrates to water and carbon dioxide yields about 16.7K Joules of energy per gram. This could be exploited as a source of energy since the reaction is environmentally non-polluting. The carbon dioxide and water produced during the reaction are taken up by plants again to manufacture more carbohydrates in the presence of sunlight and chlorophyll.

Apart from being an important energy source, carbohydrate derivatives have many other potential uses. Sucrose derivatives of fatty acids for example, being constituted of natural food components, are non-toxic and can be used in pharmaceuticals,cosmetics, food

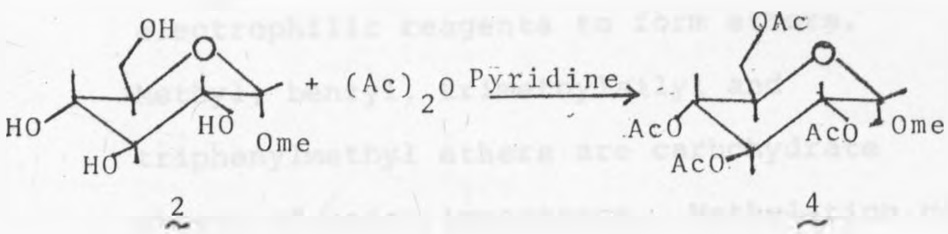
products etc. They also find use as biodegradable detergents (Munavu 1975).

The structure of D-glucose has been elucidated and a host of chemical reactions carried out on it. D-glucose has five hydroxyl groups which have encouraged workers interested in selective reactions to search for ways by which selective reactions on glucose can be performed. It reacts with methanol in the presence of dry hydrogen chloride to form the methyl D-glucosides; methyl α-D-glucopyranoside (2) and the methyl β-D-glucopyranoside (3).



Carbohydrates undergo most of the reactions undergone by alkanols such as esterification, etherification and acetylation. Esterification of carbohydrates yields esters in which all or some of the hydroxyl groups are esterified. For instance,carboxylic acid esters of carbohydrates are prepared by

treating the carbohydrate with the corresponding acid chloride or acid anhydride in the presence of a catalyst as shown in the equation below.



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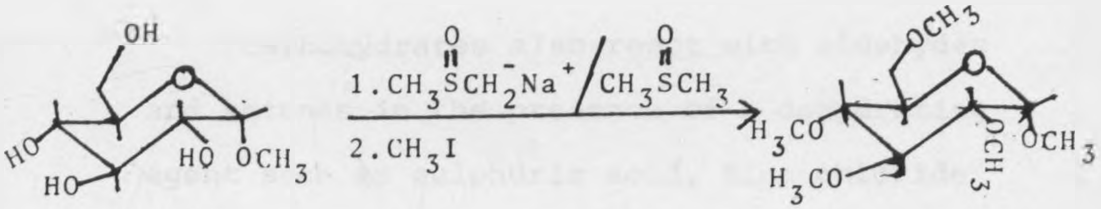
The hydroxyl groups are sterically and conformationally different and therefore their relative reactivities towards esterification are different. In general, primary hydroxyl groups are esterified faster than secondary hydroxyl groups. Equatorial hydroxyl groups are also found to react faster than the axial ones. Selective esterification can therefore be achieved sometimes.

Fatty acid esters of carbohydrates are generally prepared by the transesterification method (Buchanan, Cummerson and Turner 1972). This involves treatment of the carbohydrate with the fatty acid methyl ester in anhydrous dimethylformamide (DMF) at 90-95^{o}C in the presence of solid potassium carbonate catalyst as shown by the equation below.

$$C_{12}H_{22}O_{11} + RCO_2CH_3 \xrightarrow[DMF,80^{\circ}C]{K_2CO_3} C_{12}H_{21}O_{11}COR + CH_3OH$$

Sugars react with other appropriate electrophilic reagents to form ethers. Methyl, benzyl, trimethylsilyl and triphenylmethyl ethers are carbohydrate ethers of major importance. Methylation can be achieved using various procedures. One involves treatment of the sugar with dimsyl sodium in dimethylsulphoxide followed by methyl iodide.



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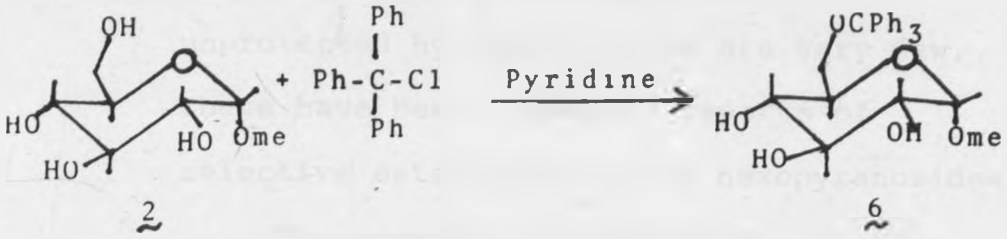
Methyl ethers are stable under mild acidic or basic conditions and for this reason are of great importance in the determination of polysaccharide structure. Benzyl ethers are prepared by treating the sugar with potassium hydroxide and benzyl chloride in an inert solvent. They are also stable under

basic and acidic conditions. Triphenylmethyl-(trityl) ethers are prepared by using triphenylchloromethane in pyridine solvent. In this case the reaction is quite selective and takes place at the primary position only due to the bulkiness of the reagent (McCloskey 1957). Trityl ethers are easily removed by hydrolysis in dilute acids.



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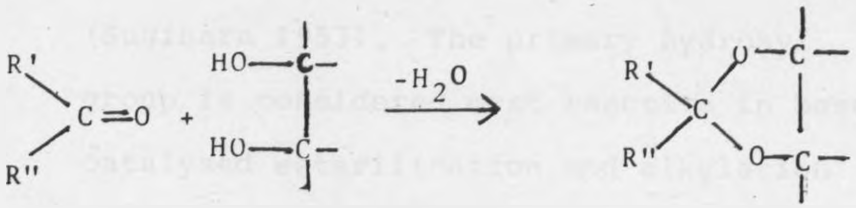
Carbohydrates also react with aldehydes and ketones in the presence of a dehydrating agent such as sulphuric acid, zinc chloride or phosphorus pentoxide to give cyclic acetals (Hough and Mufti 1973) as shown below:



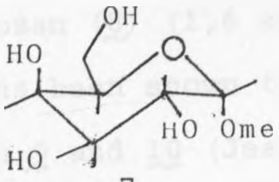
Acetal

1.2 PREFERENTIAL REACTIVITY OF HYDROXYL GROUPS.

As the reactions above show, there are only a few cases in which there is selectivity of the reactions. Considering the importance of the derivatives as possible precursors to antibiotic sugars and other polysaccharides (Umezawa 1974), reports on selective reactions of unprotected hydroxyl groups are very few. There have been, however, reports of selective esterification of hexopyranosides.

The success of a selective reaction in a carbohydrate molecule depends on the differences in the relative reactivities of the different hydroxyl groups. The factors that determine the relative reactivity of various hydroxyl groups are steric, electronic and conformational (Sugihara 1953). The primary hydroxyl group is considered most reactive in base catalysed esterification and alkylation in the case of hexopyranosides. Steric factors make it possible to react this sterically exposed hydroxyl group (at

position 6) cleanly and selectively with bulky electrophilic reagents such as trityl chloride. Using less bulky compounds, several products are obtained though the 6-ether still remains the major product. Thus methyl α-D-glucopyranoside (2) gives the 6-mesylate (20%), the 2-mesylate (2.5%) and the 2,6 dimesylate (10%) when treated with methanesulphonylchloride in pyridine (Chalk, Ball and Long Jr. 1966). This reaction also indicated that the C-2 hydroxyl group is the most reactive secondary hydroxyl group. Even in methyl α-D-galactopyranoside (7), the C-2 hydroxyl group was shown to be the most reactive of the secondary hydroxyl groups.



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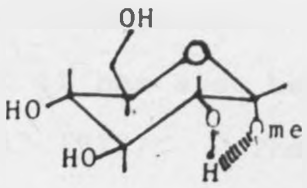
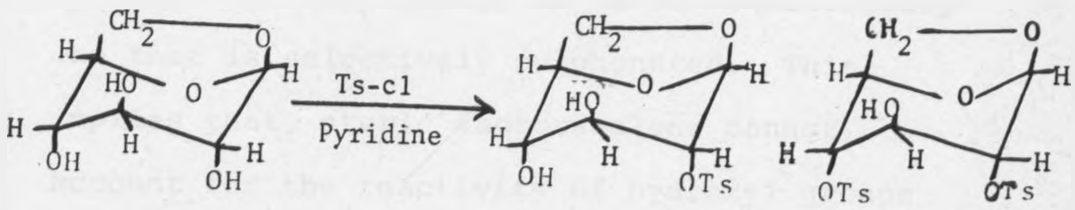
The enhanced reactivity of the C-2 hydroxyl group in methyl α-D-hexopyranosides has been attributed to the formation of an intramolecular hydrogen bond involving the 1-methoxy group as shown in 2a below (Richardson 1967).



2a

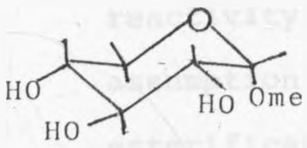
This kind of hydrogen bonding would not be possible in β-hexopyranosides nor when the C-2 hydroxyl group is axial and indeed, the enhanced reactivity of the C-2 hydroxyl group is not observed in these cases (Chalk, Ball and Long Jr. 1966). Recent work shows that the 6-monoester of 2 can be prepared by base catalysed transesterification under solvent free conditions (Bollenback and Parrish 1971).

Carbohydrates for which the primary hydroxyl group is absent are esterified with no selectivity. For example, esterification of Levoglucosan (8) (1,6 anhydro β-D-glucopyranoside) has been shown to yield a mixture of compounds 9 and 10 (Jeanloz, Rapin and Hakomori 1961).



8 9 10

Selective esterification of D-xylopyranosides 11 and 12 has also been reported (Chalk and Ball 1973). The relative reactivities of the hydroxyl groups of methyl α and β-D-xylopyranoside in selective sulphonation reaction with methanesulphonyl chloride in pyridine was determined. It was found that for the α-anomer the order of reactivity is 0-2>0-4>0-3 and for the β-anomer it was found to be 0-4>0-3>0-2.



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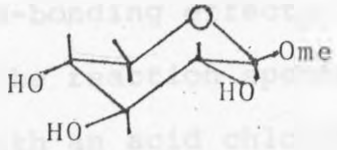

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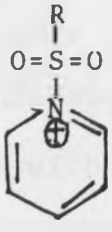
Apart from the nature of the -OH groups, there are many other factors that contribute to the selectivity found in carbohydrates during esterification. Some of them are discussed below.

It is commonly observed that, where there is choice between an axially and an equitorial attached hydroxyl group, it is the equitorially one that is selectively sulphonated. This implies that, steric factors alone cannot account for the reactivity of hydroxyl groups

and therefore other factors play a key role. For example, unimolar p-toluenesulphonylation of 1,4:3,6 diannydro-D-glucitol (Lemieux and McInnes, 1960), gave predominantly 5-p-toluenesulphonate (45%), which is derived by reaction at the sterically hindered endo-hydroxyl group. The exo-2-p-toluenesulphonate was isolated in only 12% yield.

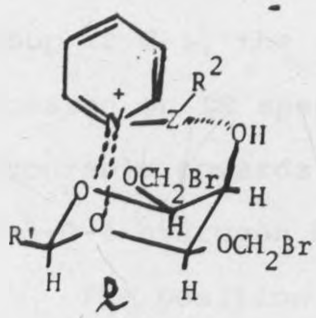
The solvent used also plays a role in selectivity. Polar interactions offer a more-reasonable explanation of the differences in reactivity than H-bonding effects. With the assumption that the reaction species in esterification with an acid chloride in pyridine is an acyl or sulphonyl-pyridinium ion (for example A and B respectively), the selectivity observed was rationalized.

A



B

Interaction of the positively charged nitrogen atom in A and B with the oxygen atoms in the 1,3-dioxane ring promotes reaction with the axial hydroxyl group in Compound D by aiding the favourable alignment of the acyl (or sulphonyl) and hydroxyl functions.



D

Z represents CO or SO_2

The reagent employed also determines the product of the reaction (Jeanloz and Jeanloz 1957). When acid chloride was used for acylation of methyl 4,6-O-benzylidene-α-D-glucopyranoside in equimolar amounts, the 2-ester was the major product, but when carboxylic anhydride was used 3-ester was the major product. In the pyridine, acetic and sulphonic anhydrides favoured the 2-esters. Similar results with methyl 4,6-O-benzylidene-β-D-glucopyranoside showed O-2 and O-3 to be 50% each.

Hydrogen bonding is also responsible for selectivity. For instant, reaction at HO-3 appears to be even greater in the β- than

α-series (Sorkin and Reichstein 1945). Favoured reaction at the equatorial 3-OH in the β-series could be due to its involvement in hydrogen-bonding with the axial oxygen atom on C-4 (Buchanan and Chittenden 1969). Although similar bonding could occur between the equitorial 2-OH group and the oxygen-atom of the equitorial meth group at C-1, the later disposition of groups appeared on IR spectroscopic evidence less favourable towards bonding and therefore cis OH-3-O-4 hydrogen bond is more favourable.

The position occupied by the hydroxyl group on the ring can play an equal or more important part in controlling reactivity than its eq/ax nature, and the type of reaction is also important (Jeanloz 1959). Thus, partial benzoylation of 2-acetamide-1,6-anhydro 2-deoxy-β-D-galactopyranoside (HO-3-ax, HO-4-eq) with benzoyl chloride gave 3- and 4- benzoates in the molar ratio ≃ 4:3 whereas methanesulphonyl chloride mainly yielded the 4-ester. Selective reactivity of the OH groups in 1,6 anhydro-β-D-glucopyranose (HO-2-ax, HO-3-ax, OH-4-ax) toward benzoylation (Cerny, Gut and Pacak) and toluene-sulphonylation (Jeanloz, Rapin and Hakomori 1961)

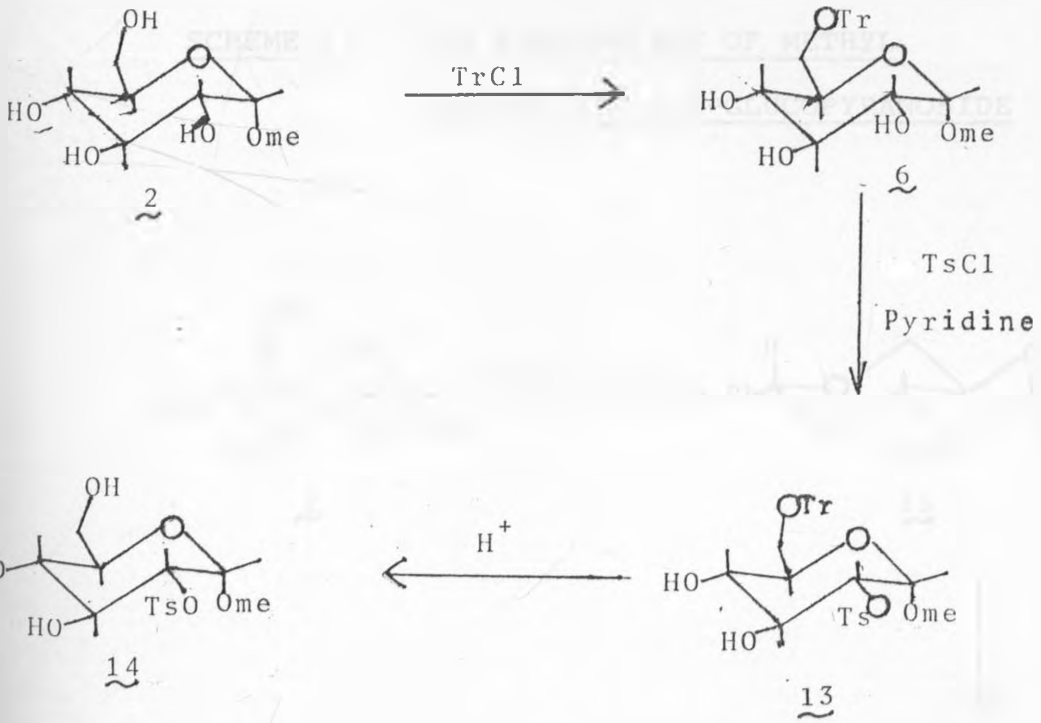
with the respective acid chlorides, HO-2 and HO-4 showed enhanced reactivity over HO-3 and with p-toluenesulphonyl chloride, the order of reactivity of the HO-groups appear to be 2>4>3. The greater reactivity of the HO-2 over HO-3 and HO-4 in the α-gluco seems not to be due to the inductive effect of the anomeric centre (Williams and Richardson 1967). With the α-glucopyranoside, the presence of the cis-OH-2, 1-Ome grouping, favouring intra-molecular hydrogen bonding may be correlated with the enhanced reactivity at 0-2. In the α-manno any activation of HO-2 produced by its proximity to the anomeric centre is apparently counteracted by its sterically unfavourable, axial orientation (Creasey and Guthrie 1972).

1.3 SELECTIVE FUNCTIONALIZATION OF CARBOHYDRATES

In order to prepare pure positional isomers of esters and ethers of carbohydrates, various techniques have been developed which bypass the intrinsic different reactivities of hydroxyl groups. These techniques are used when it is desired to functionalize a given OH group in the presence of a more reactive OH group. Except for the 6-O-monoesters of hexopyranosides, the preparation of any other positional monoester of hexopyranoside requires blocking-deblocking technique. The method involves the protection of the most reactive hydroxyl groups, followed by esterification of the OH groups of interest, and then deprotection. In addition to the steric, electronic and conformational factors, the nature of the reagent, the catalyst, the solvent and the temperature (Munavu 1975) also determine the reactivity of OH groups towards selective functionalization.

The primary hydroxyl group of hexopyranoside is considered more reactive in base catalysed esterification and alkylation reactions. Steric factors makes it possible to react the 6-hydroxyl group cleanly and selectively with bulky electrophilic reagents such as triphenyl methyl chloride as mentioned in section 1.1. The trityl group can serve as a protecting group in the preparation of 2-O-monoester of methyl α-D-glucopyranoside (2) as shown in the following scheme.

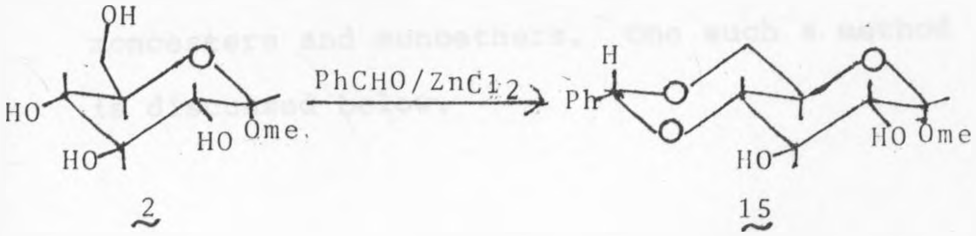
SCHEME 1: PREPARATION OF METHYL 2-O-TOSYL-α-D-GLUCOPYRANOSIDE



The desired reactions are carried out in this blocked state as shown in the scheme above, and after reaction is complete, the blocked groups are deblocked by removal of the blocking reagent. The blocking group has to have properties such that it can be introduced and removed easily without affecting the reacting molecule. Usually the blocking reagents are stable under basic conditions but readily hydrolyzed by dilute acids.

Selective esterification via blocking-deblocking can also be achieved through acetalation. The 2- and 3-monobenzoates of 2 were prepared by the route indicated in Scheme II below.

SCHEME II: THE PREPARATION OF METHYL 2-O-BENZOYL-α-D-GLUCOPYRANOSIDE



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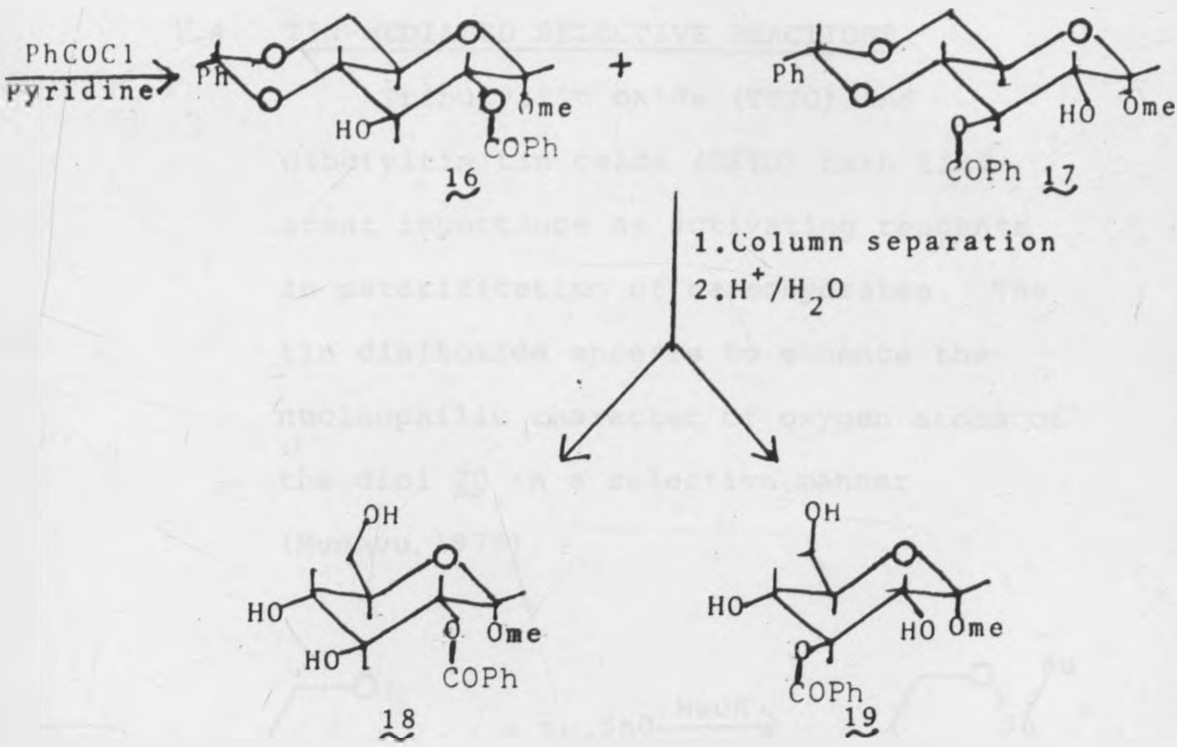
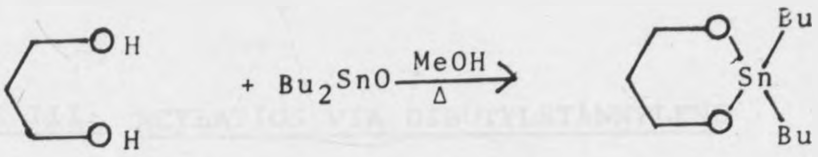


Products 16 and 17 were separated by column chromatography after which they were acid hydrolysed separately to give pure 18 and 19. Due to the many steps involved, the method is tedious and the yields are very low. This resulted in search of new ways which are shorter and which give a high yield of the monoesters and monoethers. One such a method is discussed below.

1.4 TIN-MEDIATED SELECTIVE REACTIONS

Tributyltin oxide (TBTO) and dibutyltin tin oxide (DBTO) both find great importance as activating reagents in esterification of carbohydrates. The tin dialkoxide appears to enhance the nucleophilic character of oxygen atoms of the diol 20 in a selective manner (Munavu, 1975).



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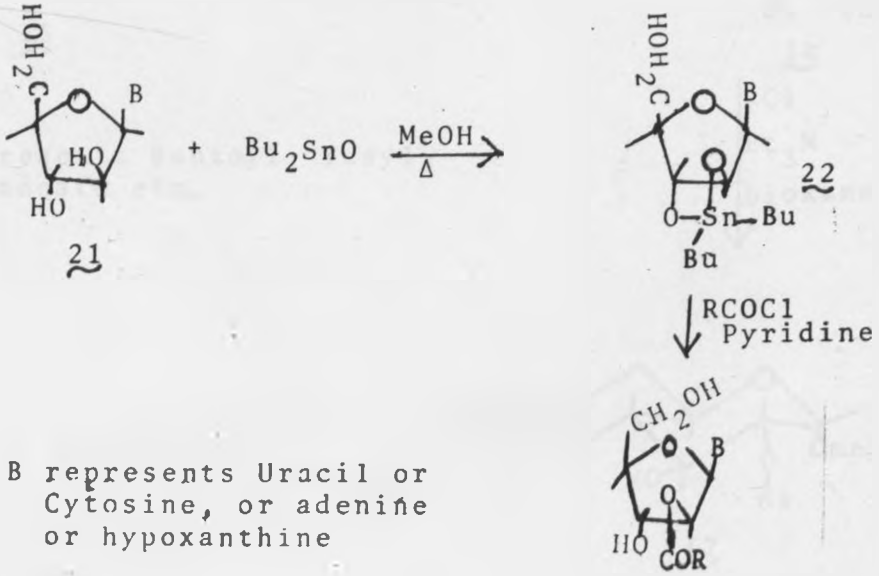
This activating property of the tin oxygen bond was used advantageously to esterify nucleosides 21 (Wagner, Verheyden and Moffat 1974) selectively as shown below:

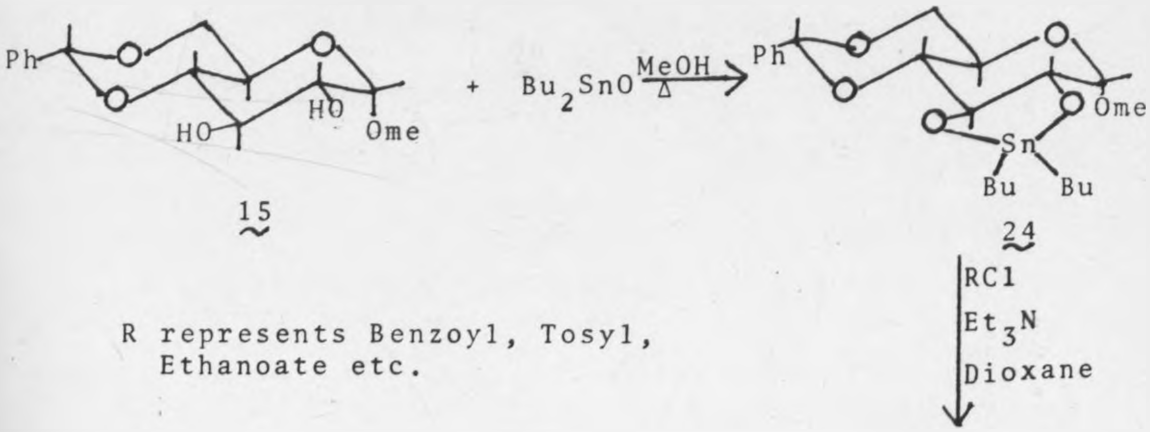


21 22

B represents Uracil or Cytosine, or adenine or hypoxanthine

The above reaction led to the selective formation of 2'(3')-O-acyl nucleosides from which the pure 3'-O-acyl 23 derivative was isolated in good yield by fractional crystallisation. Alkylation of the stannylene complex of other nucleosides gave ethers selectively. This activating property was used in conversion of dialkoxides of carbohydrates into esters as the following reaction scheme shows:

SCHEME III: ACYLATION VIA DIBUTYLSTANNYLENE INTERMEDIARY.



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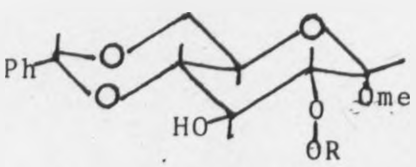
24

R represents Benzoyl, Tosyl, Ethanoate etc.



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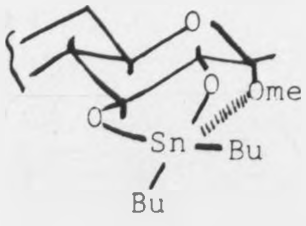
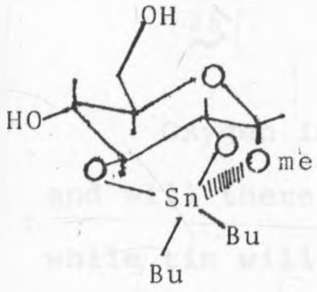
Triethylamine was used as a scavenger of hydrogen chloride and the yields were quite high. The reaction was selective at the 2-position in the case of methyl α-D-glucopyranoside. These results suggest that selectivity at the C-2 is realized only in the cases when the stannylene intermediate is capable of coordination between the α-methoxy group and the tin as shown in structure 24 below:



24

Selective esterification of the unprotected methyl α-D-hexopyranoside was also achieved via the intermediacy of the tin alkoxides (Munavu 1975). Where selective esterification was shown to occur, there was no trace of esterification at the 6-position. This suggests that the dibutylstannylene of methyl α-D-glucopyranoside has structure 25 and not 26.



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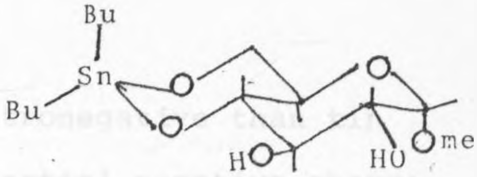
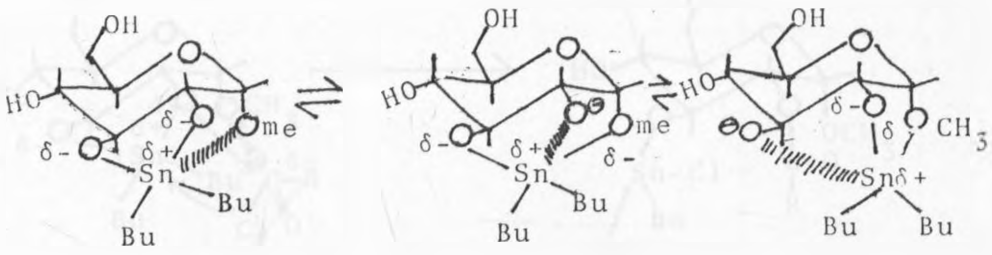


26

This presumed preference for the formation of the 5-membered stannylene ring could be due to the favourable semi-equatorial conformation of the gem-dibutyl groups as compared to the situation in which one of the large butyl group is forced into an unfavourable axial conformation in the case of the 6-membered ring structure 26. The five-membered ring structure may also be favoured because of the additional co-ordination

of the tin with the C-1 methoxy group 25 (Munavu 1975). The tin-glucoside complex is thought to exist in the following equilibria.

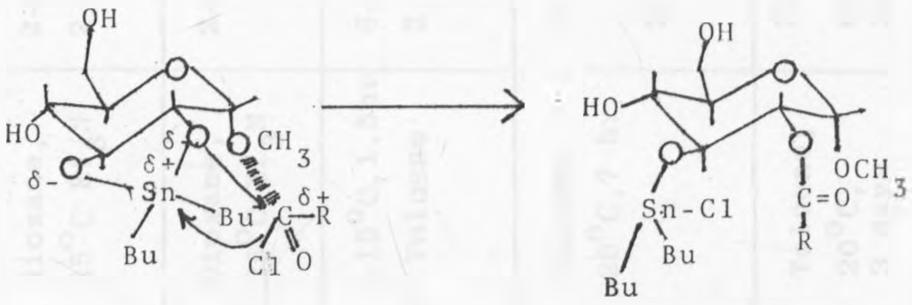


25

Oxygen is more electronegative than tin and will therefore have partial negative charge while tin will have a partial positive charge. The oxygen atom on the methoxy group has a lone pair of electrons that contributes towards partial bond formation with tin. Thus, there is continuous formation and breaking of bonds at C-1 and C-2 as shown above (25).

The acid chloride is thought to approach the C-2 alkoxide oxygen in such a way that the carbonyl group of the acid chloride lies closest to the C-1 methoxy group. The proposed mechanism of the attack is shown in the scheme below.

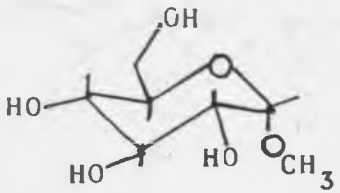
SCHEME IV: MECHANISM OF ATTACK BY THE ELECTROPHILE.



Some of the carbohydrates that have been selectively derivatized using tin alkoxide are shown in Table 1 below:

TABLE 1

SELECTIVE ESTERIFICATION OF CARBOHYDRATES VIA TIN COMPLEXES

CARBOHYDRATE*	TIN COMPOUND	ELECTROPHILE	CONDITIONS	PRODUCT (% YIELD)	REFERENCES
1 Methyl α-D-glucopyranoside  2	Bu_2SnO (1 mole)	PhCOCl	dioxane, 25°C Et_3N	2-benzoate (70%) 2,6-dibenzoate (2%)	Munavu and Szmant 1976
		$CH_3(CH_2)_{12}COCl$	Dioxane, 25°C Et_3N	2-myristate (73%)	"
	$(Bu_3Sn)_2O$ (7.5 mmol)	PhCOCl (15 mmol)	-15°C, 1.5hr Toluene	6-benzoate (73%) 2,6-dibenzoate (20%)	Ogawa and Matsui, 1981
	" (3.75 mmol)	" (7.5 mmol)	Toluene, 20°C, 7 hr	2,3,6-tribenzoate (18.4%) 2,6-dibezoate (81.4%)	"
	$(Bu_3Sn)_2O$ (7.5 mmol)	CH_3-C$_6$H$_4$-SO_2Cl (15 mmol)	Toluene, 20°C, 3 days	2,6-ditosylate (15.9%) 6-Tosylate (40.5%) 2-Tosylate (36.4%)	"

*Note that the amount of carbohydrate was taken as standard and the amount of the other reagents were taken relative to that of the carbohydrate.

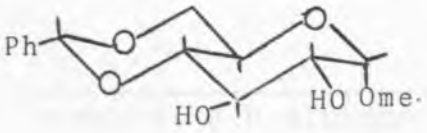
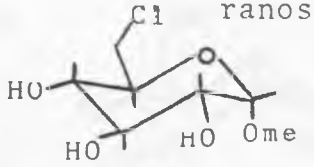
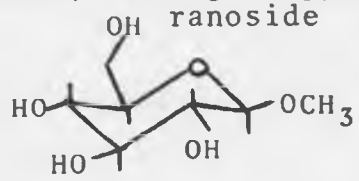
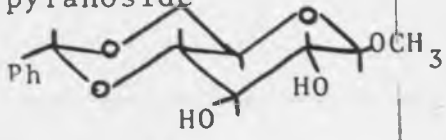
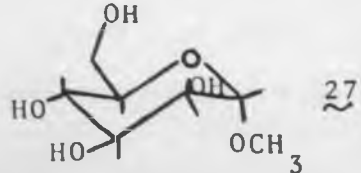
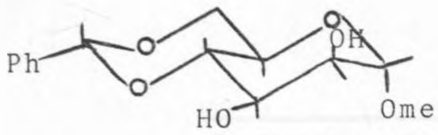
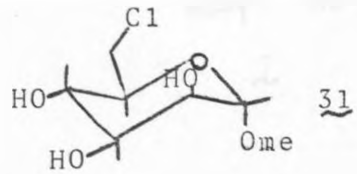
CARBOHYDRATE	TIN COMPOUND	ELECTROPHILE	CONDITIONS	PRODUCT (% YIELD)	REFERENCES
2 Methyl 4,6-o-benzylidene α-D-glucopyranoside.  15	Bu_2SnO (10 mmol)	PhCOCl (10 mmol)	Dioxane, 25°C, 16hrs Et_3N	2-benzoate (86%)	Munavu & Szmant 1976
	" (1 mole)	" (1 mole)	Benzene, 25°C	2-benzoate (80%)	Holzapfel et al. 1984
	" (1 mole)	PhCOCl (0.71 mmol)	Dioxane, benzene N-methylimidazole (1 mole)	3-benzoate (90%)	
	$(Bu_3Sn)_2O$ (1 mole)	PhCOCl (1 mole)	25°C, Benzene, Refluxed, 16 hrs	2-Benzoate (41%) 2,3-dibenzoate (25%)	Holzapfel et al. 1984
	"	PhCOCl (2 mole)	25°C, Benzene	2,3-dibenzoate	"
	$(Bu_3Sn)_2O$ (1 mole)	PhCOCl (1 mole)	Benzene, 25°C, 2hrs	2-benzoate (82%)	Holzapfel et al. 1984
3 Methyl 6-chloro-6-deoxy α-D-glucopyranoside  28	Bu_2SnO (1 mole)	PhCOCl (1 mole)	Benzene, 25°C, 4hrs	2-benzoate (95%)	"

TABLE 1 CONTINUED

CARBOHYDRATE	TIN COMPOUND	ELECTROPHILE	CONDITIONS	PRODUCT (% YIELD)	REFERENCES
	$(Bu_3Sn)_2O$ (0.5 mmol)	PhCOCl (0.94 mmol)	Benzene, 25°C, 4hrs	2-benzoate	Holzapfel et al. 1984
"	" (1 mmol)	PhCOCl (2.9 mmol)	Benzene, 50°C, 20hrs	2,3-dibezoate (90%)	"
4 Methyl β-D-glucopyranoside  3	Bu_2SnO (1 mole)	PhCOCl  $CH_3(CH_2)_{12}COCl$	Dioxane, 25°C Et_3N	6-esters ~80%	Munavu and Szmant 1976
5 Methyl 4,6-o-benzylidene β-D-glucopyranoside  35	Bu_2SnO (1 mole)	PhCOCl	Benzene, 25°C, 16hrs	2-benzoate (85%)	Nashed and Anderson 1976
6  27 6 Methyl α-D-mannopyranoside	Bu_2SnO (1 mole)	PhCOCl (1 mole)	25°C	2- and 3-benzoate (50:50)	Ogawa et al. 1978
	$(Bu_3Sn)_2O$ (3.75 mmol)	PhCOCl (7.5 mmol)	20°C, Toluene 3hrs	3,6-dibezoate (90%)	" (1981)

CARBOHYDRATE	TIN COMPOUND	ELECTROPHILE	CONDITIONS	PRODUCT (% YIELD)	REFERENCES
7. Methyl 4,6-o-benzylidene α-D-mannopyranoside	Bu_2SnO (1 mole)	PhCOCl (1 mole)	1. Benzene, refluxed 16hrs 2. N-Methylimidazole 25%, 2.5hr	3-benzoate (90%)	Holzapfel et al. 1984
 29	Bu_2SnO (1 mole)	PhCOCl (1 mole)	25°C, benzene	3-benzoate (15%) 2-benzoate (85%)	"
	Bu_2SnO	$PhCH_2Br$	Dimethylformamide, 100°C	3-ether (85%)	Nashed and Anderson 1976
		PhCOCl	1. 15°C, Et_3N, Dioxane 20 min 2. 25°C, 1hr	2-benzoate (major) 3-benzoate	"
 31 8. Methyl-6-chloro-6-deoxy α-D-mannopyranoside	Bu_2SnO (1 mole)	PhCOCl (1.2 mmol)	1. Benzene, Reflux 16hr 2. DME, -10°C, 25hr	3-benzoate (90%)	Holzapfel et al. 1981

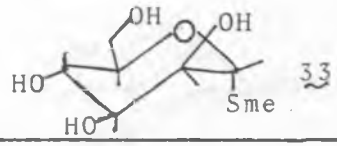
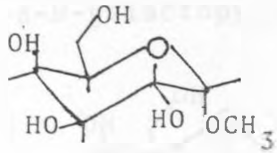
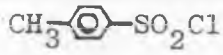
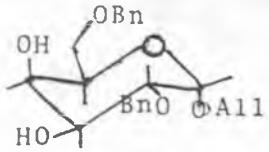
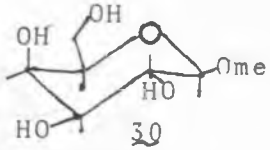
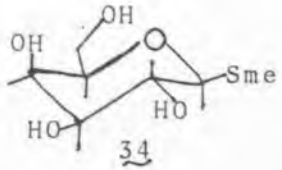
CARBOHYDRATE	TIN COMPOUND	ELECTROPHILE	CONDITIONS	PRODUCT (% YIELD)	REFERENCES
	Bu_2SnO (1 mole)	PhCOCl (2.1 mmol)	Benzene, Reflux; 10hr	2,3-dibenzoate (90%)	Holzapfel et al. 1981
"	"	PhCOCl (1.96 mmol)	Benzene; 25°C; 40min	2,3-dibenzoate (10%) 3-benzoate (60%) 2-benzoate (25%)	"
9 Methyl -1-deoxy-1-thio α-D-mannopyranoside  33	$(Bu_3Sn)_2O$ (3.75 mmol)	PhCOCl (7.5 mmol)	1.Toluene; 2hr; 140°C 2. 25°C, 18hr	2,3,6-tribenzoate (12%) 3,6-dibenzoate (66.4%)	Ogawa and Matsui 1981
10 Methyl α-D-galactopyranoside  7	Bu_2SnO (1 mole)	 (1 mole)	Dioxane; Et_3N; 25°C; 1hr	2-Tosylate (66%)	Munavu and Szmant 1976
	$(Bu_3Sn)_2O$ (3.75 mmol)	PhCOCl (7.5 mmol)	Toluene; 25°C,20hr	6-benzoate (21.9%) 2,3,6-tribenzoate (40%) 2,6-dibenzoate 3,6-dibenzoate (31%, 1:2)	Ogawa and Matsui 1981

TABLE 1 CONTINUED

CARBOHYDRATE	TIN COMPOUND	ELECTROPHILE	CONDITIONS	PRODUCT (% YIELD)	REFERENCES
11 Allyl 2,6 di-O-benzyl-α-D-galactopyranoside  32	Bu_2SnO (2 mole)	PhCOCl (19 mmol)	1.Methanol, Reflux; 1hr 2.Dioxane; Et_3N (19 mmol), 25°C; 1hr	3-benzoate (81%)	Nashed and Anderson 1977
12 Methyl β-D-galacto-pyranoside  30	$(Bu_3Sn)_2O$ (3.75 mmol)	PhCOCl (7.5 mmol)	1. Toluene, 3.5hr; 140°C 2. Toluene, 25°C, 5hr, stir	2,3,6-tribenzoate (4.7%) 3,6-dibenzoate (95%)	Ogawa and Matsui 1981
13 Methyl-1-deoxy-1-thio--β-D-galactopyranoside  34	$(Bu_3Sn)_2O$ (3.75 mmol)	PhCOCl (7.5 mmol)	1. Toluene, 2hr, 140°C 2.Toluene, 18hr, 20°C	3,6-dibenzoate (95.7%) 2,3,6-tribenzoate (2.7%)	Ogawa and Matsui 1981

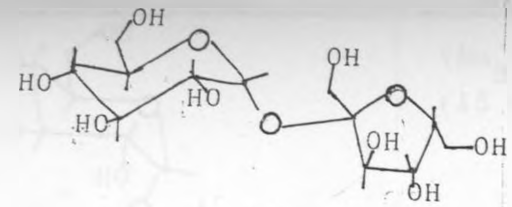
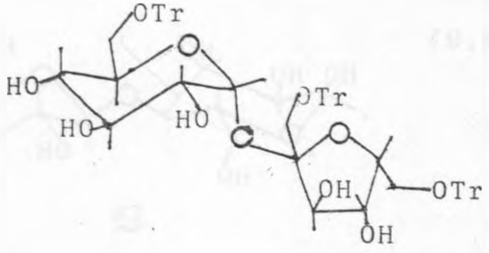
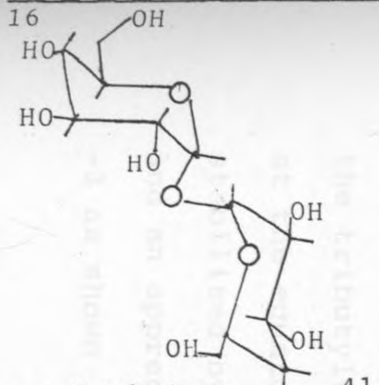
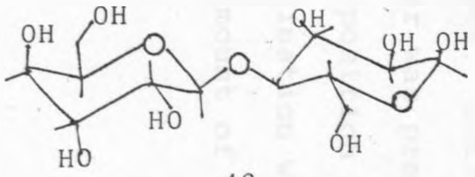
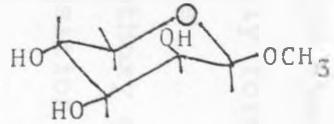
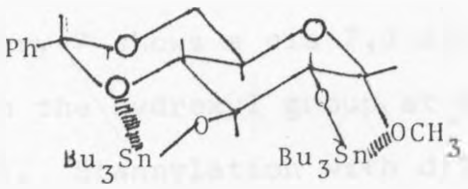
CARBOHYDRATE	TIN COMPOUND	ELECTROPHILE	CONDITIONS	PRODUCT (% YIELD)	REFERENCES
14 Sucrose  36	$(Bu_3Sn)_2O$ (7.5 mmol)	PhCOCl (15 mmol)	1.Toluene, 4hr, 140°C 2.Toluene, 25°C,5hr stirred	2,3,6 1',6'-penta-benzoate (87%)	Ogawa and Matsui 1981
15 6,1',6'-tri-o-trityl sucrose  37	Bu_2SnO (1 mole)	PhCOCl (1 mole)	20°C	3'-benzoate (72%) 2-benzoate (9%)	Nashed et a 1977
	Bu_2SnO (1 mole)	PhCOCl (2 mole)		2,3'-dibenzoate (69%) 2-benzoate (9%)	
	$(Bu_3Sn)_2O$ (0.5 mole)	PhCOCl (1 mole)	20°C	3'-benzoate (62%) 2-benzoate (8%) 2,3'- dibenzoate (12%)	Nashed et al. 1977
	$(Bu_3Sn)_2O$ (1 mole)	PhCOCl (2 mole)	20°C	2,3-dibenzoate (52%)	Nashed et al. 1977

TABLE 1 CONTINUED

CARBOHYDRATE	TIN COMPOUND	ELECTROPHILE	CONDITIONS	PRODUCT (% YIELD)	REFERENCES
16  α-α-Trehalose 41	$(Bu_3Sn)_2O$ (15 mmol)	PhCOCl (30 mmol)	1.Toluene, 24hr, 140°C 2. 20°C, stirred,20hr	2,3,6,2'3',6-hexa-benzoate (73.1%)	Ogawa and Matsui 1981
17 Lactose  42	$(Bu_3Sn)_2O$ (9.5 mmol)	PhCOCl (19.8 mmol)	1.Toluene, 3hr,140°C 2.Toluene, 45°C,2 days stirred	2,6,3',6'-tetra-benzoate (71.9%)	Ogawa and Matsui 1981
18 Methyl-β-D-Arabino-pyranoside  44	Bu_2SnO (0.5 mmol)	PhCOCl (1.22 mmol)	1. Benzene, 16 hr; Reflux 2.25°C, stirred	3-benzoate (91%)	Holzapfel et al. 1984

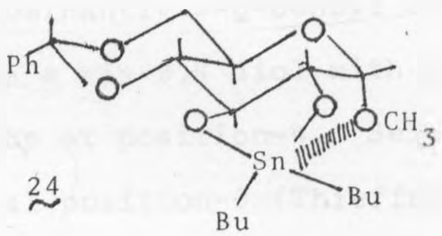
From the table shown above, regioselective acylation of carbohydrates, takes place when dibutyltin oxide (DBTO) and bis(tributyltin) oxide (TBTO) are used as activating agents. In all cases, the incoming electrophile attaches itself to the oxygen atom of the sugar molecule which is directly bonded to the tin atom. However, formation of the stannylene compound seems to favour some regions of the sugar molecule. The regions favoured are those that are most sterically favourable and are stabilized by Intra-Molecular co-ordination with other groups in the sugar molecule.

In trans 2,3 diol (entry 2), bis(tributyltin) oxide was used as an activating agent and position-2 was found to be highly selective compared to position 3 although both positions are equitorial. Benzoylation (using benzoyl chloride) of the stannylene compound gave high yield of the 2-derivative products (82%; Holzapfel et al. 1984). This indicates that, the tributyltin ether was predominantly formed at the equatorial 2-position which was stabilised by co-ordination with 1-methoxy group and an appreciable amount of it at position -3 as shown in 120.



120

The use of dibutyltin oxide also shows similar results and position-2 is more favourable for attack. In this case the five membered stannylene complex was favourably formed across trans 2,3-diol and stabilised by the extra coordination of the tin atom with the 1-methoxy group (Munavu and Szmant 1976).



24

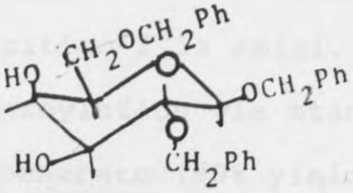
Even the β-anomer shows similar result (entry 5). Here, there is no coordination with the 1-methoxy group but still stannylation with dibutyltin oxide followed by benzoylation gave predominantly 2-O-benzoate (85%, Nashed and Anderson 1976). The two hydroxyl groups are equitorial and are trans to each other but one is regioselectively acylated faster than the

other. The reason behind this is not quite clear. Entry 7 shows a cis 2,3 diol configuration with the hydroxyl group at position-2 being axial. Stannylation with dibutyltin oxide followed by acylation gave the 3-derivative in high yield (90%, Holzapfel et al. 1984). This is expected since the equitorial position-3 is more sterically favourable for attack as compared to the axial position-2.

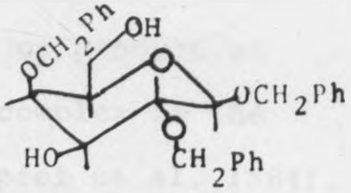
Etherification also shows similar results. Benzyl 2,6-di-O-benzyl-β-D-galactopyranoside (112) was stannylated using dibutyltin oxide followed by etherification using benzyl bromide to give predominantly 3-O-benzyl ether. This example shows a cis-3,4 diol with an axial hydroxyl group at position-4. Selectivity is at the equitorial position-3 (Thieffry, 1981).

In cases where a primary hydroxyl group is involved in the stannylene complex formation, substitution always occurs at that position. This is exemplified by Benzyl 2,4-di-O-benzyl -β-D-galactopyranoside (114) in which stannylation using dibutyltin oxide followed by etherification with benzyl bromide gave 6-O-benzyl ether in high

yield. When dibutyltin oxide is used in the stannylene complex

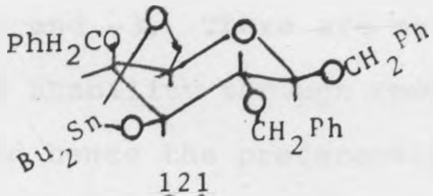


112



114

formation, a seven-membered ring is built which does not appear to suffer more angular strain than one with five or six-membered ring as shown below 121.



121

Regioselectivity is also found to take place even in sugar molecules with three free hydroxyl groups. In entry 3, position-2 is found to be highly selective (95% yield; Holzapfel et al. 1984). All the hydroxyl groups are equitorial, but position-2 seems to be more selective when both tin compounds are employed in the activation process. It seems

the tin complex is formed across tran-2,3 diol in which the extra coordination by the 1-methoxy group enhanced stability of this intermediate compound. In entry 8, there is cis-2,3 diol in which the hydroxyl group at position-2 is axial. The major product of benzoylation via stannylene complex is the 3-benzoate (90% yield; Holzapfel et al. 1984). The equitorial position is preferably functionalised in most of these cases. The use of bis(tributyltin) oxide leads to the formation of tributyltin-ethers at specific region of the sugar molecule. In entry 3, the bis(tin tributyltin-ether is formed preferentially at positions-2 and -3. There are no possibilities of enhanced stability through coordination in entry 18 and hence the preferential functionalization is at postion-3 (91% yield; Holzapfel et al. 1984).

In cases which involve sugars with more than three hydroxyl groups the explanations become more complex. Entry 1 shows a case which involves four free hydroxyl groups. Stannylation followed by benzoylation, gave predominantly 2-ester (70% yield; Munavu and Szmant 1976). This indicates that the tin

complex was formed across trans-3,2 diol and stabilised by co-ordination with 1-methoxy group. When bis(tributyltin) oxide was used, position-6 was functionalised in high yields (73%, Ogawa and Matsui 1981).

Entry 6 is however different, it has one axial and two equitorial hydroxyl groups at positions-2, 3 and 4 respectively plus one primary hydroxyl group. Stannylation using dibutyltin oxide followed by benzoylation using benzoyl chloride, gave -2 and -3 benzoates in equal amounts (50:50; Ogawa and Matsui 1981). Even without the extra enhancement of stability of the tin complex through intra-molecular coordination with 1-methoxy group, the axial position-2 is functionalised faster than the equitorial position-4. When bis-tributyltin oxide is used, 3,6-diester is formed in high yields (90%; Ogawa and Matsui 1981).

Entry 14 has eight-free hydroxyl groups but only position-2 and 3 in addition to the primary hydroxyl groups at positions-6,1' and 6' are preferentially functionalised. The formation of the stannylene complex seems to favour

certain regions of the sugar molecule.
Entry 16 also has eight-free hydroxyl groups but only six are functionalised via its stannylene complex (73.1% yield, Ogawa and Matsui 1984).

1.5 AIM OF THE PROJECT:

From these observations, there is no clear evidence to show why some regions of sugar molecules are more favoured than others, in both the formation of the stannylene compound and the subsequence esterification reacti There seems to be no consistent explanations to the regioselective functionalisation of these tin-assisted reactions. There is some evidence to show that, in addition to selectivity due to enhancement by the tin compound, other factors also prevail.

From the table 1, substitution at position-4 was never observed except in a few cases which are due to the use of excess acylating agent or other factors which are to be investigated in this work. In most cases, position-3 was highly favoured. Substitution of a stannylene involving the primary position always occured at that position. The factors responsible for regioselectivity and non-regioselectivity in most of these cases are not very clear. A few cases are simply explained by steric factors and coordination through hydroxyl groups vicinal to one being considered. This project aims at

trying to investigate some of the factors responsible for these phenomena. In order to do this, we intend to expand this work to involve other sugar molecules that have not been used so far. We hope therefore that, with extra data, the mechanism and the factors responsible for regioselectivity and non-regioselectivity can be explained.

CHAPTER 2

RESULTS AND DISCUSSIONS

2.1 GENERAL

The monosaccharides in Table 2 were found to undergo selective acylation via the intermediary of their stannylene derivatives. The table gives the electrophile used, the conditions of acylation, the products and the percentage yields of the esters formed. However, only dibutyltin oxide (DBTO) was used as the activating agent in this work. Methanol was used as a solvent for stannylation. Benzene was also used to a certain extent especially in cases where azeotropic removal of water was necessary. In this later case, a small amount of methanol (≈10ml) was usually added to accelerate the rate of stannylation. The addition of methanol resulted in the formation of a complex that initiated the stannylation reaction as shown below.

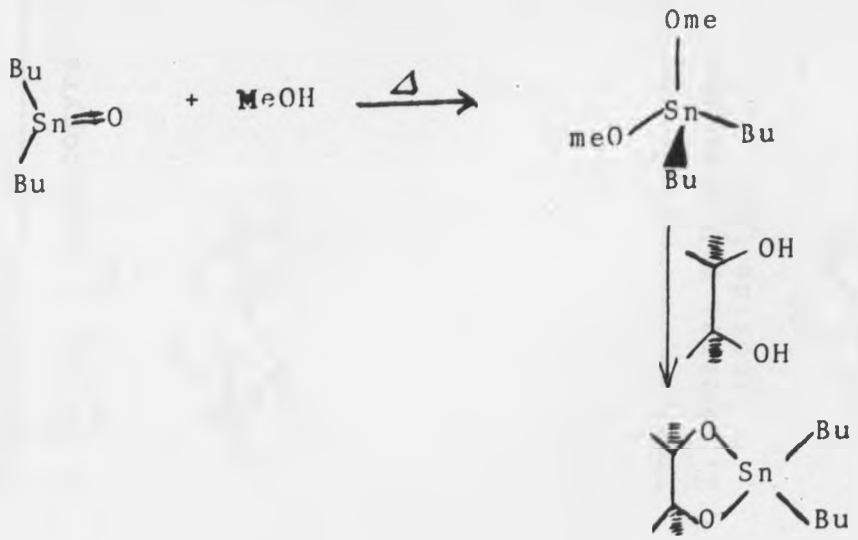
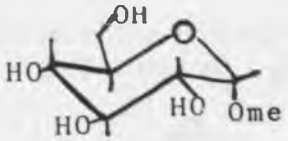
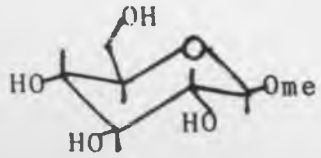
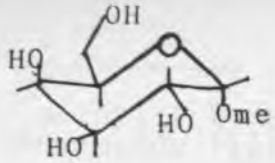
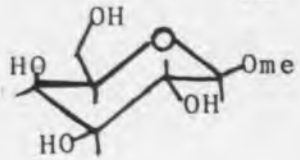
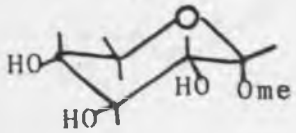


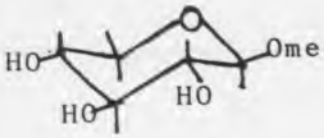
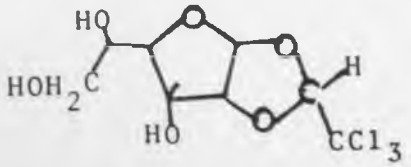
TABLE 2

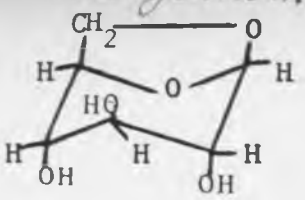
TABLE OF RESULTS

CARBOHYDRATE **	ELECTROPHILE	CONDITIONS	PRODUCTS & YIELDS OF THE ESTERS
1. Methyl α-D-glucopyranoside (2). 	PhCOCl	25°C dioxane Et_3N	2,6 dibenzoate (5% yield)* 2-benzoate (70% yield)
	$CH_3(CH_2)_{12}COCl$	25°C Dioxane Et_3N	2 myristate (81% yield) 6-myristate (19% yield)
	p-TsCl	10°C, dioxane Et_3N	2,6 ditosylate (16% yield) 6-tosylate (26% yield) 2-tosylate (58% yield)
	PhN=C=O	Tetrahydrofuran; -10°C	2,6, dicarbamate (61% yield) 2-carbamate (39% yield)
2. Methyl β-D-glucopyranoside (3). 	PhCOCl	Dioxane; 25°C; Et_3N	One minor diester Two equal major monoesters
	PhN=C=O	Tetrahydrofuran; -10°C	Five products formed Rf 0.71, 0.46, 0.21, 0.14 & 0.09 Not separated.

*Percentage yield (%) refers to percentage selectivity.
**The amount of carbohydrate was taken as standard. The amount of other reagents were taken relative to that of the carbohydrate.

CARBOHYDRATE	ELECTROPHILE	CONDITIONS	PRODUCTS & YIELDS OF THE ESTERS
3. Methyl α-D-galactopyranoside (7). 	MyCOCl	Dioxane; 25°C; Et_3N	2,6-dimyristate (24% yield) 2-myristate (76% yield)
	PhN=C=O	Tetrahydrofuran; -10°C	Four products obtained 1st product - 24% yield 2nd) 3rd) -products - 47% yield 4th product - 30% yield - may be 2-carbamate
4. Methyl β-D-galactopyranoside (30) 	Mycocl.	25°C; Et_3N	Three products formed at Rf 0.50, 0.46 and 0.70 No separation was carried out
	PhN=C=O	-10°C Tetrahydrofuran	Four products were formed at Rf 0.41, 0.30, 0.16 and 0.096
5. Methyl α-D-xylopyranoside (11) 	PhCOCl	Dioxane; 5°C; Et_3N	2,3,4-tribezoate (15% yield) 2,3 dibenzoate (26% yield) 2-benzoate (39% yield) 4-benzoate (21% yield)
	TsCl	25°C; Et_3N	2,3,4-tritosylate(10.6% yield) 2,3 ditosylate (36.8% yield) 2-tosylate (17% yield) 4-tosylate (36.8% yield)

CARBOHYDRATE	ELECTROPHILE	CONDITIONS	PRODUCTS & YIELDS OF THE ESTERS
"	PhN=C=O	-10°C; 1hr; Tetrahydrofuran	2,4-dicarbamate (14% yield) 2-Carbamate (85% yield)
6. Metnyl β-D-xylopyranoside (12). 	PhCOCl	25°C; Dioxane; Et_3N	2,4-dibenzoate (10% yield) 3-benzoate (90% yield)
	TsCl	Dioxane; 25°C; Et_3N	2,4-ditosylate (80% yield) 4-tosylate (20% yield)
	PhN=C=O	Tetrahydrofuran; -10°C; 5hr	2,4-dicarbamate (22.5% yield) 3-carbamate (42.5% yield)
7. α-Chloralose (78). 	PhCOCl	Dioxane; 25°C; Et_3N	One product was isolated pure (82% yield)
	PhN=C=O	Tetrahydrofuran; -10°C; 3 days	3,6 dicarbamate (78% yield). The only one isolated in pure form.

CARBOHYDRATE	ELECTROPHILE	CONDITIONS	PRODUCTS & YIELDS OF THE ESTERS
Levoglucosan.  8	PhCOC1	Dioxane; 25°C; Et_3N; 3 days	Four products observed at Rf 0.11, 0.43, 0.57, 0.75
	Bu_2SnO MyCOC1	Dioxane; 25°C; Et_3N	No separation was done

Benzoylation, tosylation and myristoylation reactions of the sugar molecules shown in Table 2, were carried out at various temperatures in dioxane in the presence of triethylamine. Carbanilation reactions were carried out in tetrahydrofuran at -10°C.

Thin layer chromatography was used to monitor the formation of esters in the reactions. The structures of the products formed were determined using melting point comparisons; IR and NMR spectroscopy; and thin layer chromatography (TLC) behaviours.

Mobility on TLC plate depends on surface adsorption of the compound on the coating. The strength of the adsorption of the hydroxyl groups on the silica gel determines the distance any one product migrates up the plate. The movement of the compound depends on the number of hydroxyl groups attached to that particular compound. It also depends on the nature of the hydroxyl groups, whether primary or secondary, equitorial or axial. Primary hydroxyl groups are more exposed to the silica gel than the secondary hydroxyl groups and therefore the force of attraction between them

and silica gel is greater in the primary hydroxyl groups than the secondary ones. Similarly, the force of attraction between the equitorial hydroxyl groups and silica gel is greater than with axial ones. Thus, a compound possessing primary hydroxyl groups will migrate at a slower rate than the one having only secondary ones.

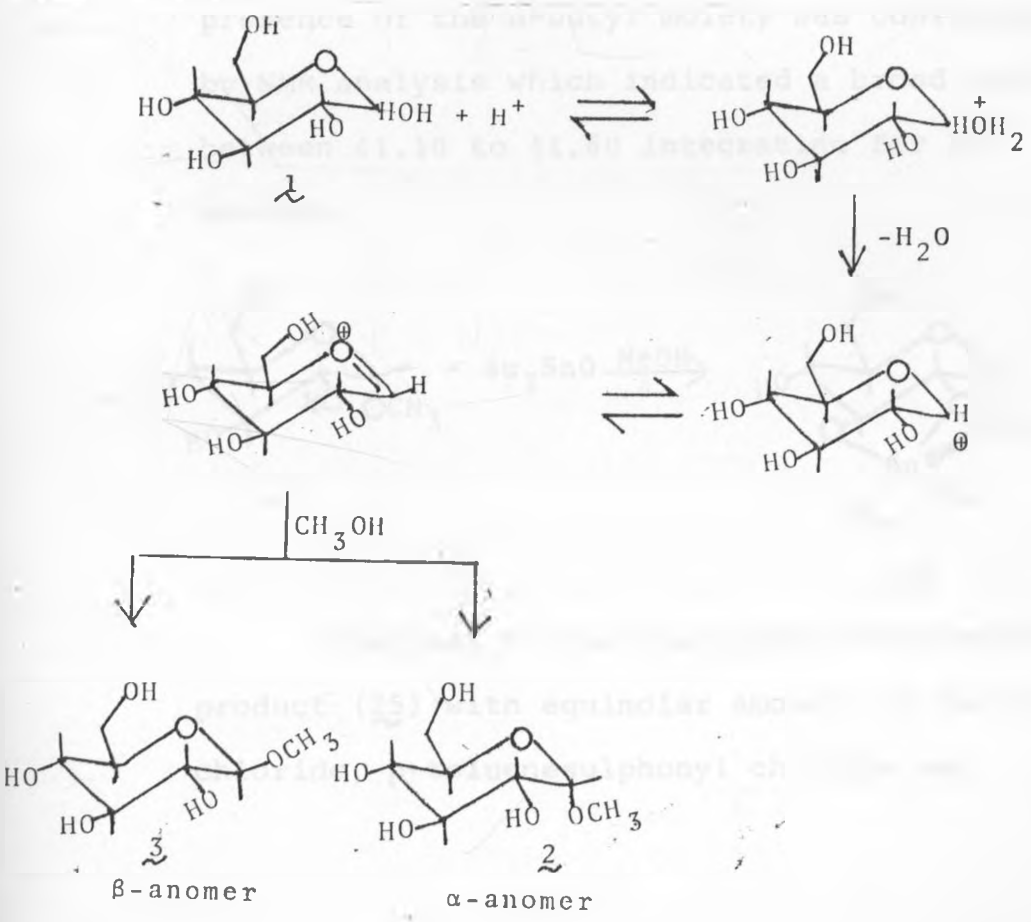
From the results obtained in this work the compounds at the origin of the TLC plate were usually the unreacted starting carbohydrates. These starting materials did not move at all or migrated slowest of all the other compounds in a particular sample. This is because they possessed the greatest number of free hydroxyl groups. From the bottom on a TLC plate, these (unreacted materials) were usually followed by compounds of higher Rf values. These were in most cases, the monoesters such as C2-O, C3-O or C4-O which had two secondary and one free primary hydroxyl groups in case of methyl α-D-glucopyranoside (2), methyl β-D-glucopyranoside (3); methyl α-D-galactopyranoside (7), methyl β-D-galactopyranoside (30) and α-chloralose (78). The C6-O- monoester which had all secondary hydroxyl groups had a slightly higher Rf value. The di- and tri-esters

followed in that order since they have the least number of free hydroxyl groups.
In some cases the C2-O-, C3-O- and C4-O-derivatives on one hand and C6-O-derivative on the other hand were so close together on the TLC plate that their separation was tedious and at times impractical. This is explained by the nature of C6-O- ester. It sometimes migrated slower than expected due to hydrogen bonding which occured between C2-OH group and the C1 methoxy group. The methoxy group has a lone pair of electrons on the oxygen atom and tends to donate it to the C2-OH group and thus increasing the electron density on the hydroxyl group which create a stronger force of attraction between the oxygen and silica gel. This resulted in the C6-O- derivative laging behind and thus a lower Rf value. The C3-O- and C4-O derivatives migrated relatively slower (low Rf) than the C2-O-ester. This was due to the fact that, in addition to the presence of a free primary hydroxyl group in these compounds, there was the effect of electron donation across the C1-methoxy group and the C2-OH group which tended to retard the movement of the compounds up the plate.

2.2 SELECTIVE FUNCTIONALIZATION OF METHYL GLYCOSIDES (α and β-D-glucopyranoside)

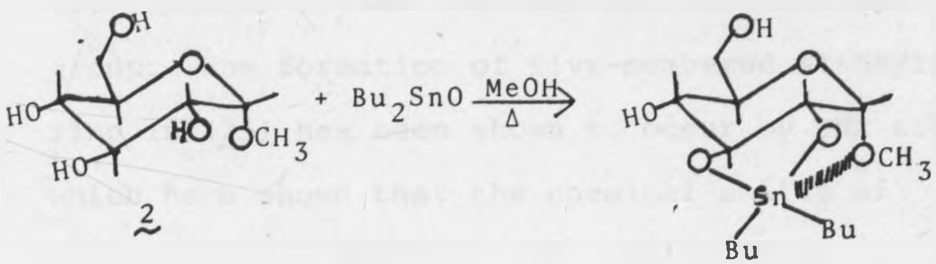
Methyl α-D-glucopyranoside (2) was used as a first substrate for stannylation. The starting glycoside was prepared in 12% yield in this laboratory by the method of Bollenback (1971). The reaction involved treating D-glucose with methanol in the presence of a cation-exchange resin (Amberlite Resin IR 120(H)). The reaction generated methyl α-D-glucopyranoside (2) and methyl β-D-glucopyranoside (3). The mechanism of the reaction is shown in Scheme (V) below.

SCHEME V: MECHANISM OF THE FORMATION OF METHYL α-D-GLUCOPYRANOSIDE (2).



Methyl α-D-glucopyranoside (2) was isolated from the reaction mixture by fractional crystallization from methanol and characterized by mp and mixed mp.

Equimolar quantities of 2 and dibutyltin oxide were refluxed in methanol to give a clear solution which on removal of solvent under reduced pressure, yielded a white solid mass which was recrystallised from benzene to give a white crystalline solid (25) mp 108-120°C (Lit 105-115°C; Munavu and Szmant 1976). The presence of the n-butyl moiety was confirmed by NMR analysis which indicated a broad peak between δ1.10 to δ1.60 integrating for 20 protons.



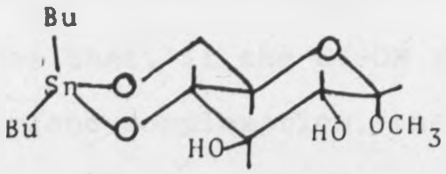
2 25

Treatment of the stannylene intermediate product (25) witn equimolar amounts of benzoyl chloride, p-toluenesulphonyl chloride and

myristoyl chloride in dioxane in the presence of triethylamine gave methyl 2-O-benzoyl α-D-glucopyranoside 48 in 70% yield (mp 169-174°C, Lit 174-175°C; Munavu and Szmant 1976), methyl 2-O-tosyl-α-D-glucopyranoside (14) in 58% yield (mp 108-112°C, Lit 103-104°C, Munavu and Szmant 1976) and methyl 2-O-myristoyl-α-D-glucopyranoside (49) in 81% yield (mp 96-99°C; Lit 94-96°C; Munavu and Szmant 1976) respectively.

The fact that the 2-O-esters were formed in the presence of the more reactive primary C6-OH suggests that the dibutylstannylene of the sugar with the α-configuration has structure 25. In this structure, the stability of the stannylene complex is enhanced by the additional coordination of the tin atom with the C-1 methoxy group. The formation of five-membered stannylene ring in (25) has been shown to occur by NMR studies which have shown that the chemical shifts of the C1-methoxy and C1-H are significantly affected due to the proximity of the tin atom. In the case of structure 25, the more favourable semi-equitorial conformation of the gem-di-O-butyl groups is formed as opposed to the situations

in which one of the bulky groups is forced into an unfavourable axial conformations as in the 6-membered ring structure 26 (Munavu and Szmant 1976).



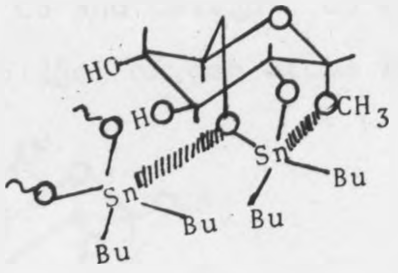
26

There was considerable amount of 6-esters in the three acylation reactions. The C6-myristate and tosylate esters were obtained in 19% and 26% yields respectively. The 2,6-diesters were also obtained in relatively good yields: 2,6-dibenzoate and 2,6-ditosylate were isolated in 5% yield (mp 131-133^{o}C; Lit 139-140^{o}C; Munavu and Szmant 1976) and 26% yield (mp 131-132^{o}C) respectively. The attachment of an acyl group at the 6-position indicates that, the primary hydroxyl group at this position may also be involved in the stannylene complex formation.

During the acylation stage, the incoming electrophile, attacks the oxygen atom of the sugar molecule, that is directly bonded to the tin atom.

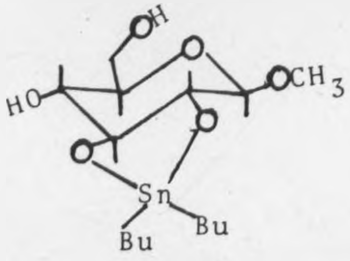
In cases where a primary hydroxyl group is involved in the stannylene complex formation; substitution always occurs at that position. However, our results show that the secondary hydroxyl group at the 2-position is favoured. This indicates that, if the C6-OH is involved in the stannylene complexation, then other factors must contribute to the reluctance of the 6-position to react.

The C6-oxygen atom which would be bound to the tin atom would be less hindered as compared to the C2-oxygen atom and therefore, would tend to form intermolecular bonds with the tin atom of another molecule. This blocks the C6-position leaving position C2 free for attack by the incoming electrophile as shown in 25b, and hence the high yield of 2-derivative obtained in this case at the expense of the C6-derivative.

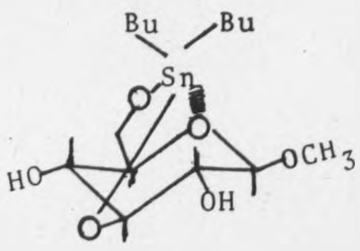


25b

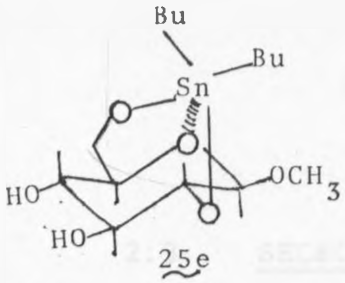
Methyl β-D-glucopyranoside (3) was stannylated next. Equimolar quantities of methyl β-D-glucopyranoside (3) and dibutyltin oxide were refluxed in methanol for one hour to give a clear and homogeneous solution. On removal of methanol under reduced pressure, stannylene derivative of 3 was obtained in 100% yield. The 2-O and 3-O-benzoates were obtained in equal amounts after benzoylation of the stannylene compound with benzoyl chloride in dioxane in the presence of triethylamine. The formation of two equal products in the acylation of β-anomer of glycoside, indicated that, two or more relatively stable stannylene complexes were possible. In this case, there was no enhancement of stability of the tin compound through intramolecular coordination with C1-methoxy group. The stannylene complex is likely to have been formed across C2 and C6(25e), C2 and C3(25c); C3 and C6(25d), C3 and C4(25f) and C4 and C6(25g) oxygen atoms as shown below:



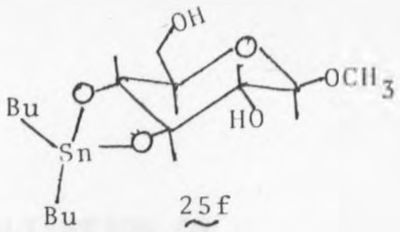
25c



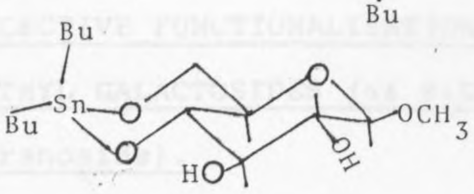
25d



25e



25f



25g

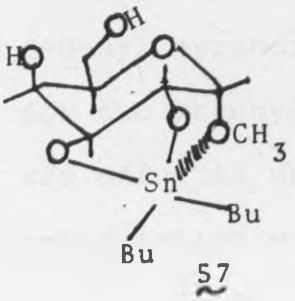
Two important factors that lead to the formation of C2 and C3-O-benzoates exclusively can be drawn from the above listed possible structures of the tin derivatives.

Structures 25d and 25e are more favoured in the formation of stannylene complex of this sugar molecule. The stabilities of these structures is enhanced by intramolecular coordination with the ring oxygen atom in the pyranoside.

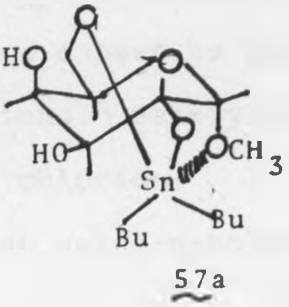
The oxygen atom at C6 position which is bound to the tin atom, is involved in inter-molecular coordination with tin atom of another molecule and thus blocking that position and hence rendering the C2 and C3 oxygen atoms less hindered and more exposed for electrophilic attack. Assuming that structures 25d and 25e are formed at 50:50 ratio, then the two esters would be expected to be formed at the same ratio.

2.3 SELECTIVE FUNCTIONALIZATION OF METHYL GALACTOSIDES (α& β-D-galacto-pyranoside).

When the stannylation and esterification sequence of reactions were repeated with methyl α- and β-D-galactopyranosides 7 and 30, which have similar configuration with the glucosides except at C-4 position; the result agreed reasonably well with our expectations. Myristoylation of methyl α-D-galactopyranoside (7) via its tin derivative, with myristoyl chloride in dioxane in the presence of triethylamine at 25°C for one week, gave methyl 2-O-myristoyl α-D-galactopyranoside (59) in 76% yield. The formation of 2-O-ester in high yield, indicates that the formation of the stannylene derivative proceeded with the formation of structures 57 and 57a whose stabilities are enhanced by intra-molecular coordination with C1-methoxy group.



57



57a

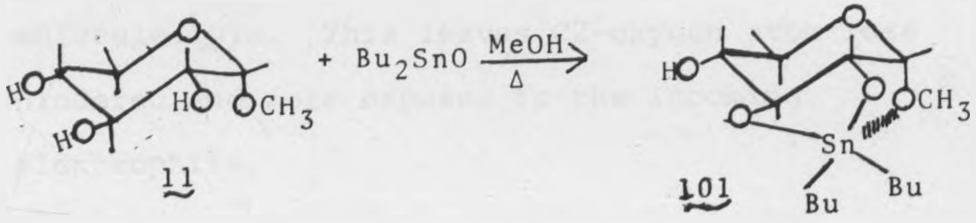
In most of their reactions, galactosides were found to behave like the glucosides. For instance, when a tin compound of methyl β-D-galactopyranoside (61) was myristoylated with myristoyl chloride in dioxane for five days in the presence of triethylamine, three products were revealed by TLC at Rf 0.46, 0.50 and 0.70. This reaction is similar to the acylation of methyl β-D-glucopyranoside (3) via its stannylene complex because, the two starting sugars are quite alike conformationally except at C-4 in which the hydroxyl group is in axial position in the former case.

2.4 SELECTIVE FUNCTIONALIZATION OF METHYL--XYLOSIDES.

The use of dibutyltin oxide (DBTO) in the activation of hydroxyl groups in carbohydrates, was extended to sugar molecules that have not been reported in the literature. Methyl α-D-xylopyranoside (11) and methyl β-D-xylopyranoside (12) were chosen as substrates for the stannylation reactions. Benzoylation was effected using benzoyl chloride; p-tosylation was carried out using p-toluene-

sulphonyl chloride; and myristoylation was carried out using myristoyl chloride. The C-2 and C-3 positions were found to be relatively selective in case of the α-anomer. The β-anomer was found to give one major product of benzoylation.

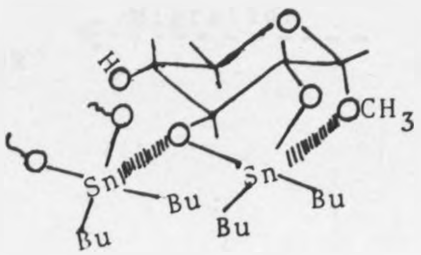
An equimolar mixture of methyl α-D-xylopyranoside (11) and dibutyltin oxide (DBTO) was refluxed in methanol to give the stannylene compound on removal of solvent. The reaction is presumed to proceed as shown below to form 101 as the main structure based on intra-molecular coordination with C1-methoxy group.



11 101

Treatment of 101 with benzoyl chloride in dioxane in the presence of triethylamine gave the 2-O-benzoate in 38.5% yield as a syrup (Lit, syrup, Ferrier et al. 1964) which eventually solidified after storage (mp 60-82°C). Methyl 2,3,4-O-tribenzoyl-

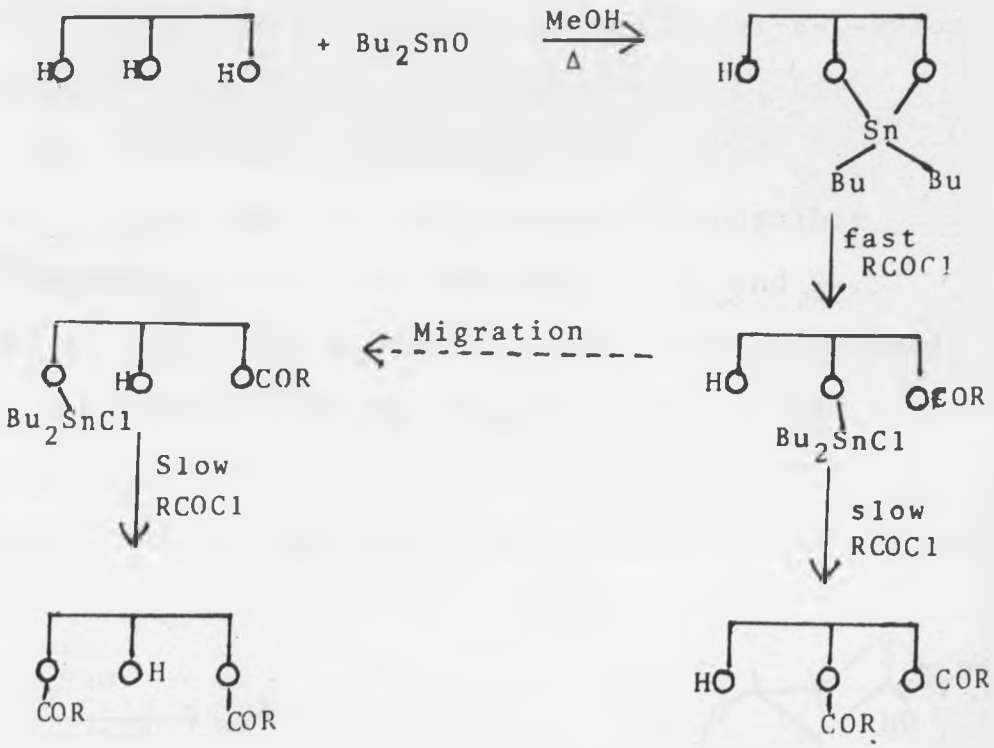
α-D-xylopyranoside (63) was also isolated in 15% yield (mp 109-112°C, Lit 116-118°C; Ferrier et al. 1964); methyl 2,3-O-dibenzoyl-α -D-xylopyranoside (64) was isolated in 26% yield (mp 124-127°C, Lit 128-129°C; Ferrier et al. 1964) and methyl 4-O-benzoyl-α-D- xylopyranoside (65) was isolated in 21% yield (mp 107-110°C). The above results show that the oxygen atoms that are bound to the tin atom at position C-2 and C-3 in 101, are not acylated at the same rate, but that the C2-oxygen is more reactive than the C3-oxygen. The C3-oxygen atom is less hindered than C2-oxygen and therefore, it is involved in intermolecular coordination with tin atom of another stannylene molecule 101a. This leaves C2-oxygen atom less hindered and more exposed to the incoming electrophile.



101a

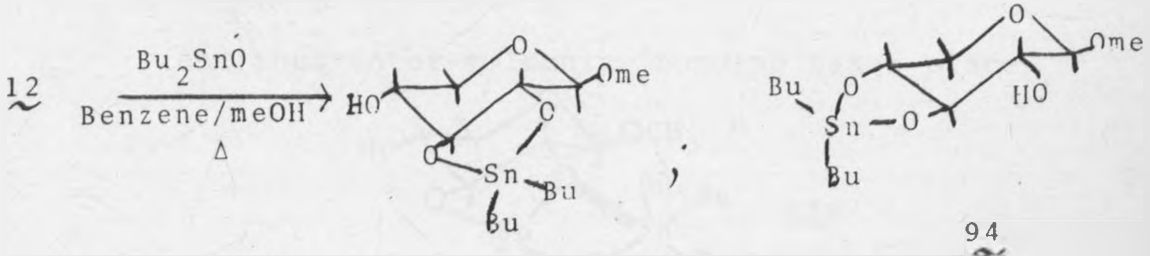
There are possibilities of migration of dibutylchlorostannyl group during esterification (Scheme VI). The migration of the dibutylchlorostannyl group after the first attack by an electrophile is caused by steric effect. The two bulky groups (acyl and dibutylchlorostannyl) tends to repel one another and this leads to the migration of the dibutylchlorostannyl group to the next vacant position. This also explains why 2,4-O-dibenzoate; 4-O-benzoate and tosylates were formed in almost all cases.

Scheme VI: SEQUENCE OF DI-ACYLATION OF METHYL XYLOSIDES.



Methyl β-D-xylopyranoside (12) was next used as the substrate for the stannylation reaction. Dibutyltin oxide was added to a solution of methyl β-D-xylopyranoside (12) in benzene. After 45 min. of reflux with azeotropic removal of water, the organic solvent was removed to give the stannylene compound. On benzoylation with benzoyl chloride in dioxane in the presence of triethylamine, one major product was isolated pure (90% yield). This was methyl 3-O-benzoyl β-D-xylopyranoside (73) (mp 131-135°C, Lit 138-139°C; Ferrier et al. 1964). A small amount of methyl 2,4-di-O-benzoyl-β-D-xylopyranoside was obtained in 10% yield (mp 104-108°C). Tosylation of the stannylene complex with p-toluene-sulfonyl chloride in dioxane gave a high yield of methyl 2,4-O-ditosyl-β-D-xylopyranoside (74) in 80% yield (mp 174-178°C, Lit. 178-179°C, Yotaro Kondo 1982).

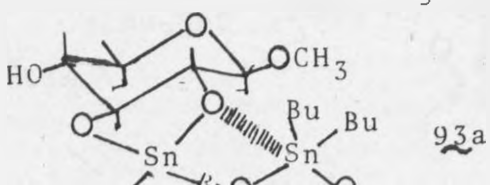
From these results, two equally possible stannylene derivatives were formed; 93 and 94. NMR analysis of the benzoate that formed indicated no substituent-induced chemical shift of the anomeric and C2-H protons but the C3-proton signal shifted downfield (δ5.0 - 5.2).



94

The preferential attack of the electrophile at C3-position is based on steric effect by the neighbouring groups and inter-molecular coordination.

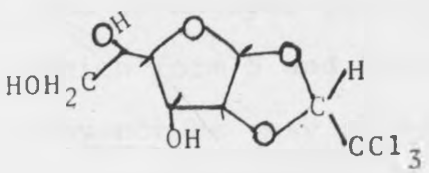
The two tin-bound oxygen atoms at C3 and C2 in 93 are sterically hindered differently. The C3-oxygen atom has a hydroxyl group at C4 closer to it although trans to it. There is a methoxy group at C1 and three hydrogen atoms at C2, C4 and C5 cis to it, while the C2 oxygen has a hydroxyl group at C4 and three hydrogen atoms at C1, C3 and C5 cis to it. This means that C2 oxygen atom is sterically less hindered compared to C3 oxygen and will therefore form intermolecular bonds with tin atom of another molecule thus rendering the sterically hindered position C3 more reactive (93a). Likewise, in structure 94, the tin-bound oxygen at C4 is cis to the hydroxyl group at C2 position as the only bulky group while the tin-bound oxygen at C3 has the C1-methoxy group cis to it. This then implies that, the tin-bound oxygen atom at C4 is less hindered compared to C3 tin-bound oxygen atom and thus inter-molecular bonding takes place



93a

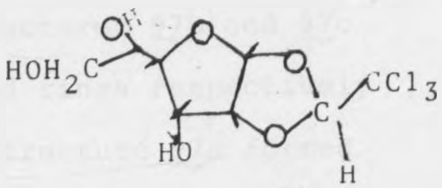
in Section 3.25. Two anomers of chloralose were obtained, α-chloralose (78) and β-chloralose (79). 78 was isolated in 24% yield.

Chloral hydrate + D-glucose $\xrightarrow[12\text{-}15^{\circ}C]{\text{Conc } H_2SO_4}$ α-chloralose (78) + β-chloralose (79) and Dichloralglucos



78

mp 164-167°C

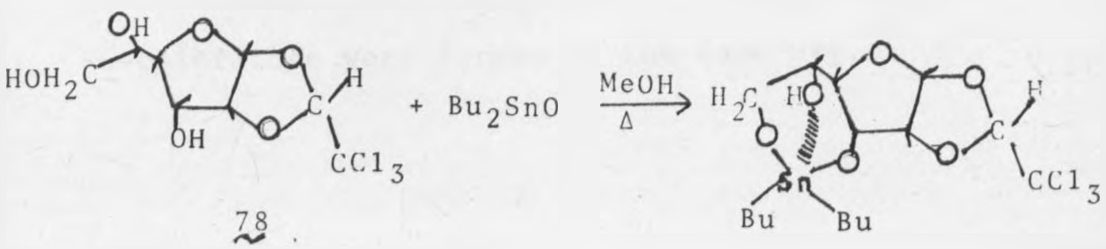


79

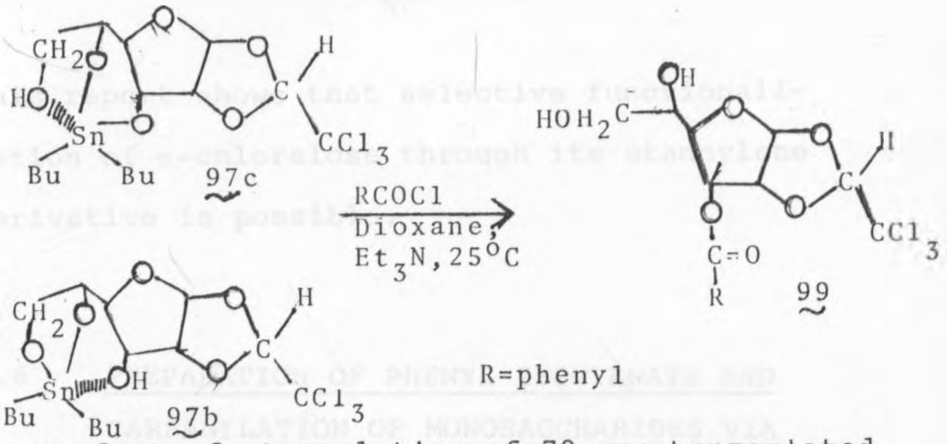
mp 209-212°C

The structure of α-chloralose was confirmed by IR and NMR analysis. IR indicated a characteristic peak at 800 cm^{-1} due to C-Cl str. NMR (DMSO-d_6) indicated the presence of the anomeric proton shown in the compound.

Equimolar quantities of 78 and dibutyltin oxide (DBTO) were refluxed in methanol to give on removal of solvent a white solid.



78



97c

97b

99

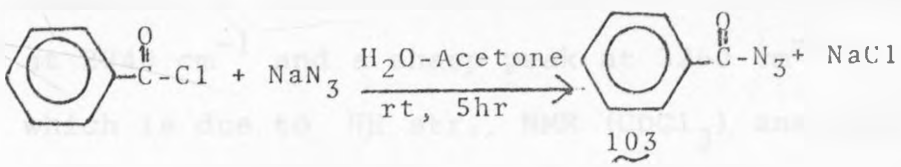
The product of stannylation of 78 was benzoylated with benzoyl chloride in dioxane in the presence of triethylamine to give one major product 3-O-benzoyl α-chloralose (99) in 82% yield.

The three possible stannylene structures of α-chloralose 97a, 97b and 97c are shown. Due to angular strain, structures 97b and 97c which form 5 and 6-membered rings respectively may not be very stable. Structure 97a formed a seven-membered ring which is free from angular strain and therefore relatively stable. The primary hydroxyl groups are very much exposed and relatively sterically less hindered. The tin-bound oxygen at C-6 will then form intermolecular coordination with tin atom of another molecule thus rendering C3 tin-bound oxygen more reactive. This led to the predominant formation of 3-O-benzoate in the benzoylation of α-chloralose via its stannylene intermediate. The corresponding 3-O-tosylate and myristate of α-chloralose were formed in the same way.

This report shows that selective functionalization of α-chloralose through its stannylene derivative is possible.

2.6 PREPARATION OF PHENYL ISOCYANATE AND CARBANILLATION OF MONOSACCHARIDES VIA THEIR STANNYLENE DERIVATIVES.

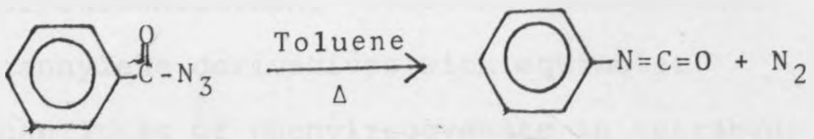
Preparation of urathanes using phenylisocyanates as an electrophile was also carried out. Phenyl isocyanate was prepared via an acid azide (Garfield Powell 1929). Benzoylimide was first prepared by treating benzoyl chloride in dry acetone with a concentrated solution of sodium azide in water. The mixture was stirred for five hours and on extraction with ethyl ether 13% yield of pure sample was obtained. It was recrystallised in benzene-petroleum ether mp 119-122°C (Lit 114-118°C).



103

The resulting product 103 was refluxed for pyrolysis to take place in toluene for 7hrs over an oil bath. The content was then distilled between temperatures 110°C and 120°C to give a dark brownish liquid which crystallised on

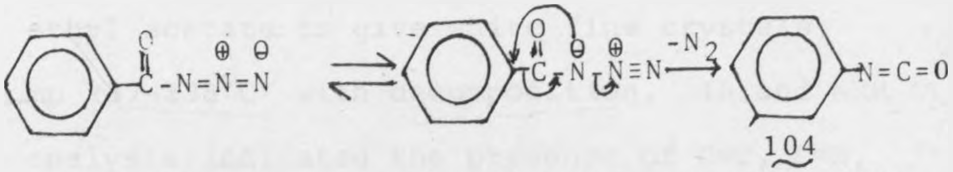
cooling down. The product was phenyl isocyanate (104) which had a lanchrimatory characteristic.



103 104

Benzoylimide underwent Curtius rearrangement (Saunders and Slocombe 1948) to give phenyl-isocyanate in a neutral solvent.

The mechanism of the reaction is shown below:



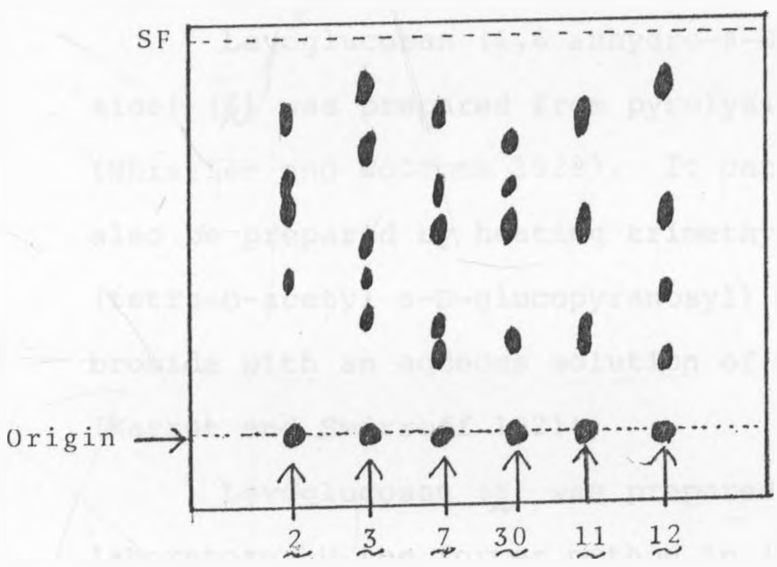
104

The structure of phenylisocyanate (104) was confirmed by IR (Nujol) analysis which indicated a characteristic peak for isocyanates at 2240 cm^{-1} and a sharp peak at 3260 cm^{-1} which is due to NH str. NMR ($CDCl_3$) analysis indicated phenyl protons at δ6,60-7,40 and N-H proton signal at δ8.35(s).

Phenyl isocyanate prepared in this laboratory was used together with some commercial sample which was obtained several months after the laboratory sample had been prepared.

Tin complexes of 2, 3, 7, 30, 11, 12 and 78 were prepared and used as substrates for carbanilation. Treating each of these stannylene derivatives with equimolar quantities of phenylisocyanate in tetrahydrofuran at -10°C gave interesting results. Carbanilation of 25 was so fast that more than three products resulted. Separation gave two pure products only. The first compound to elute from a column of silica gel was probably methyl 2,6-O-diphenyl carbamoyl-α-D-glucopyranoside (54) in 61% yield. The solid mass obtained was recrystallised from ethyl acetate to give white fine crystals, mp 237-238°C with decomposition. IR and NMR analysis indicated the presence of C=C, C=N, C=O and N-H functional groups expected in carbamates. The second compound to be isolated in pure form was assigned methyl 2-O-phenyl carbamoyl α-D-glucopyranoside (55) in 39% yield as a white solid. IR and NMR analysis confirmed this (see Section 3.7). From the results of this reaction, it can be deduced that carbanilation of tin-mediated monosaccharides is not selective.

To support this generalisation, more reactions were carried out with the other selected monosaccharides. In all these, more than three products were obtained which were sometimes very difficult to separate. For instance, carbanilation of 3 via its stannylene derivative gave five products as seen on a TLC plate. TLC analysis of some of these products are shown below.



The solvent used was a mixture of n-hexane and ethyl acetate (1:9).

The carbanilation reactions were so fast that selectivity became very low. However, it is possible that the reaction may be selective at lower temperatures. Those carbamates that we

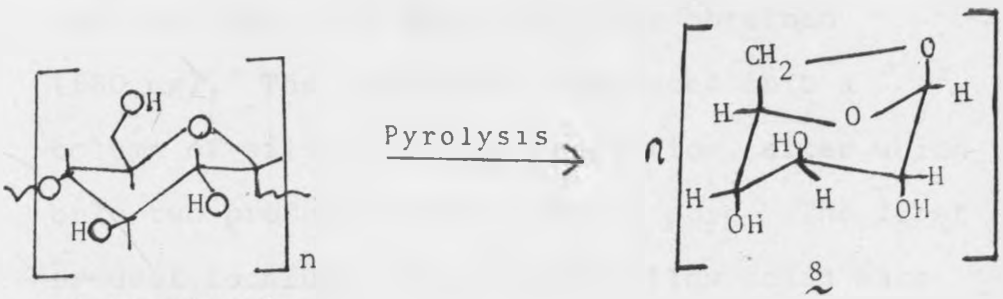
managed to isolate in pure form were analysed. In all the electrophiles used in this work, phenylisocyanate was the most reactive and the least reactive was p-toluenesulphonyl chloride.

2.7 ATTEMPTED PREPARATION AND SELECTIVE FUNCTIONALISATION OF LEVOGLUCOSAN VIA STANNYLENE DERIVATIVE.

Levoglucosan (1,6 anhydro-β-D-glucopyranoside) (8) was prepared from pyrolysis of starch (Whistler and Wolfrom 1929). It can also be prepared by heating trimethyl (tetra-O-acetyl α-D-glucopyranosyl) ammonium bromide with an aqueous solution of barium hydroxide (Karret and Smirroff 1921).

Levoglucosan (8) was prepared in this laboratory by the former method in low yield (1.4% yield). Corn starch was thoroughly dried at 100°C for 24 hours with occassional mixing to accelerate the drying rate. Heating the starch in a round bottomed flask with a large luminous flame, a brownish distillate was collected leaving behind a carbonaceous residue. The dark-brownish syrup was evaporated twice with 100ml acetone and then put into a freezer

after evaporating half amount of the acetone. After a few days a dark-brownish cake formed on the bottom of the flask. This was dissolved in hot methanol and left standing overnight in a freezer after it was decolourised with activated carbon. Colourless crystals of levoglucosan were obtained in 1.4% yield. Mp 172-174°C (Lit 172°C, Whistler and Wolfrom 1929).



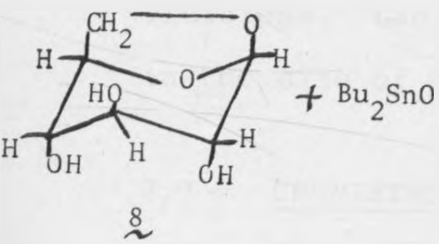
Corn starch

2.8 BENZOYLATION OF 8 VIA STANNYLATION.

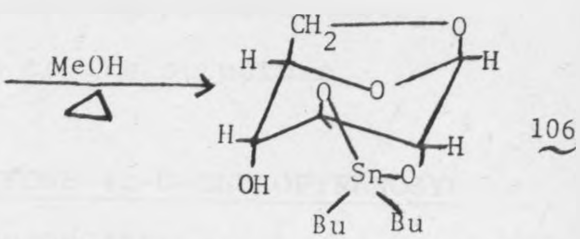
Equimolar quantities of levoglucosan (8) and dibutyltin oxide were refluxed in methanol for 0.5 hr to give a white solid mass on evaporation of solvent (Mp range 152-170°C). To a magnetically stirred solution of stannylated levoglucosan (106) in dioxane, triethylamine was added followed by slow addition of benzoyl chloride at ambient temperature. TLC examination at constant intervals, helped to monitor the

progress of the reaction. One hour after the addition of benzoyl chloride, TLC (ethyl acetate) indicated the presence of four products at Rf 0.11, 0.43, 0.51 and 0.75 plus a lot of starting materials. Three days later; after an increase of temperature from ambient temperature (25°C) to 60°C for 30 minutes, the reaction was stopped, filtered and washed twice with dioxane. On evaporation of the filtrate and washings, a yellow syrup was obtained (560 mg). The syrup was introduced into a column of silica gel for separation, after which only two products were isolated pure. The first product to elute was a light yellow solid mass 24.2mg, mp 115-119°C. This compound was 2,4-O-dibenzoyl-1,6-anhydro ß-D-glucopyranoside (105). This product may have been formed through migration of the dibutyl-chlorostannyl group during the course of benzoylation. The second product to elute was a white solid mass mp 54-56°C. This product may be the 2-O-benzoyl-1,6-anhydro,ß-D-glucopyranoside (107). Selectivity at oxygen(2) and not oxygen(3) may be due to the inductive effect of the anomeric centre which renders the C2-position favourable

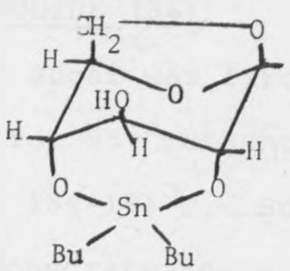
for attack during benzoylation. Ogawa and Matsui (1981) using Bis-tributyltin oxide as the activating reagent, pointed out that, the tributylstannyl group is preferably attached to an equitorial oxygen atom, a situation which was assumed to maximize intramolecular coordination (and therefore stability) at the tin atom. They further mentioned that, both the avoidance of unfavourable gauche-interaction and stabilization by intra-molecular coordination determines the position of preferred stannylation. Assuming that dibutyltin oxide combines with the sugar by attaining the most stable intermediate complex, then, three possible structures 106, 108 and 108a may have been formed, in which the most stable one 108a dominated since it is formed between two cis hydroxyl groups and involves the formation of a six-membered ring which is free from angular strain.



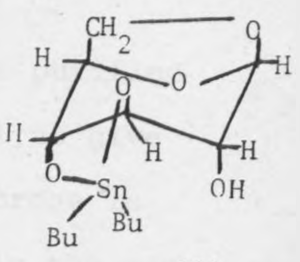
8



106

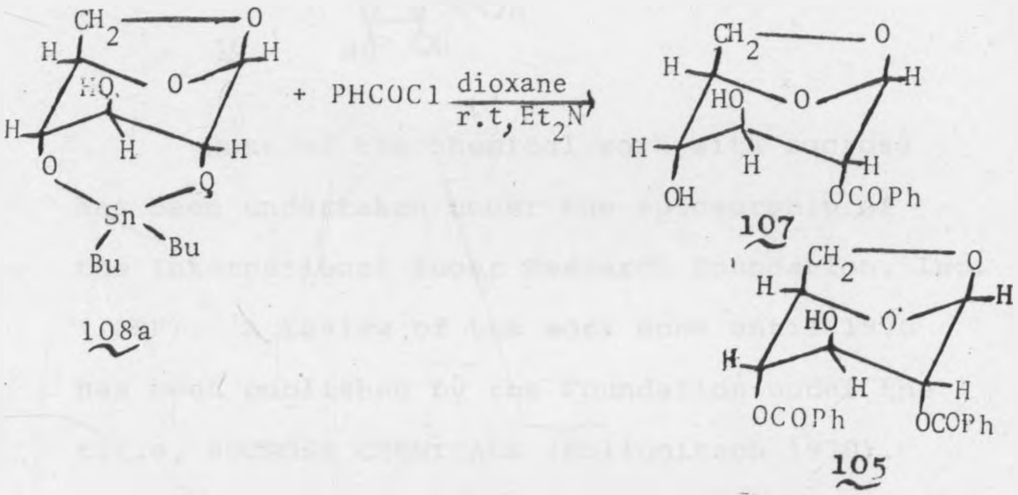


108a



108

2,4-O-dibutylstannylene-1,6-Anhydro β-D-glucopyranoside (108a) was taken as a substrate for benzoylation as described above to give four products from which two products 105 and 107 were isolated in pure form and the other obtained in mixtures.



108a

107

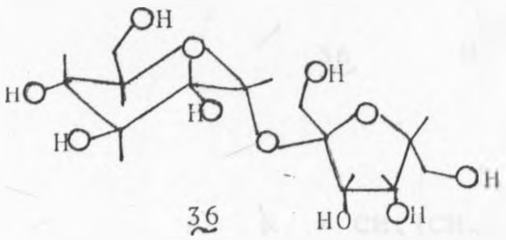
105

No IR nor NMR analysis for these products were done. Several repeated attempts to prepare more levoglucosan for more reactions were fruitless. Lack of dominating product (ester) in the case of 8 is due to its structure.

2.9 CHEMISTRY OF SUCROSE (α-D-GLUCOPYRANOSYL β-D-FRUCTOFURANOSIDE (36).

Commercial cane sugar was first purified by recrystallisation from 95% methanol to give fine crystals mp range 184-191°C. Sucrose is the most abundant carbohydrate found in the sap

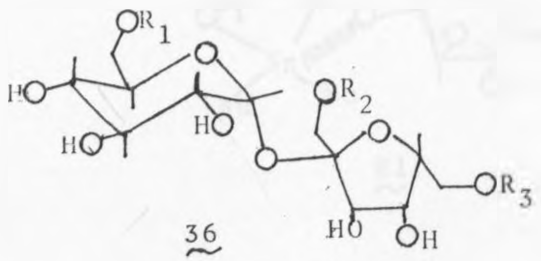
of plants. It is one of the cheapest industrial organic chemicals. The structure of sucrose is shown below, it is a disaccharide made up of a glucose and fructose moieties.



36

Most of the chemical work with sucrose has been undertaken under the sponsorship of the International Sugar Research Foundation, Inc. (ISRF). A review of the work done until 1970 has been published by the Foundation under the title, SUCROSE CHEMICALS (Kollonitsch 1970).

The isolation, purification and structure determination of sucrose (Pictet 1930, Kirk-Othmer 1969, Levi and Purves 1949) constitute the earliest and most thorough work done with this molecule. Pure sucrose monoesters have been prepared in the past(Munavu 1975). From the general view point that primary hydroxyl groups are more reactive than secondary ones, the isolated sucrose monoesters were assumed to be one of the following three monoesters or a mixture of all three.



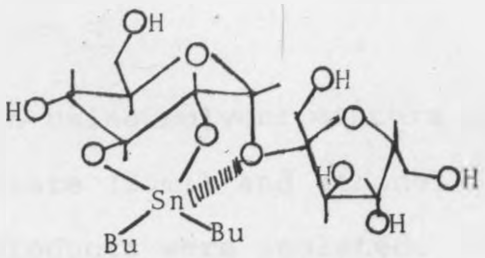
36

a. $R_1 = CH_3(CH_2)_{12}CO-$, $R_2=R_3=H$

b. $R_2 = CH_3(CH_2)_{12}CO-$, $R_1=R_3=H$

c. $R_3 = CH_3(CH_2)_{12}CO-$, $R_1=R_2=H$

These are some of the results obtained by direct myristoylation of sucrose. Our aim was to try to functionalise the less reactive secondary hydroxyl groups in the presence of more reactive primary hydroxyl groups. This was carried out using dibutyltin oxide as the activating reagent. Sucrose 36, has an α-anomeric form at the D-glucose moiety and hence by reacting it with dibutyltin oxide, we expected to get the stannylene intermediate product 81, which on acylation should show selectivity at C-2 position.

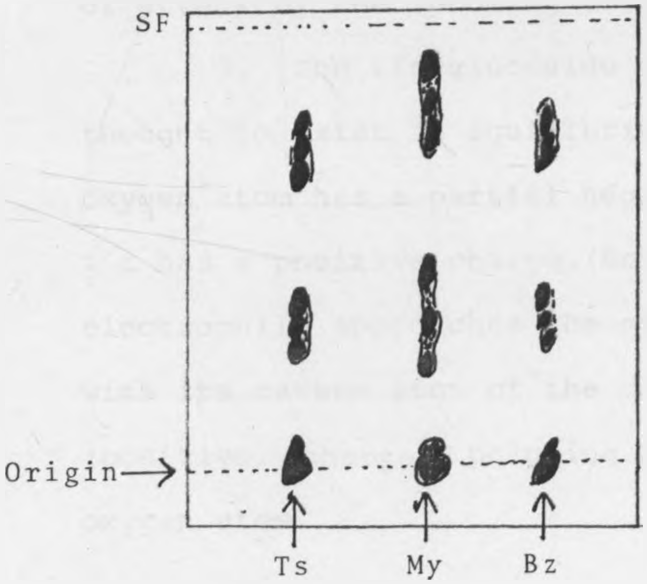


81

The reaction above was effected by refluxing equimolar quantities of 36 and dibutyltinoxide in methanol. On removal of solvent under diminished pressure a white solid mass 100% yield 81 was obtained mp range 176-190^{o}C with decomposition (Lit mp 150-170^{o}C with decomposition; Munavu 1975). Triethylamine was added to a solution of 81 in dioxane followed by slow addition of equimolar amount of benzoyl chloride. The reaction progress was monitored by TLC [solvent mixture of, methanol (10ml), acetone (10ml), water (2ml) and chloroform (58ml)] at constant intervals. Four days later, the reaction was stopped and two streaks each carrying three products were clearly seen on TLC plate plus a lot of unreacted materials at the origin. On removal of solvent under reduced pressure, a brownish syrup was obtained. The syrup was introduced on a column of silica gel for

separation using solvent mixture of (benzene (20ml), ethyl acetate (20ml) and ethanol (10ml) but no pure products were isolated. This was due to the closeness of the products in every streak.

Myristoylation and tosylation of 81 using myristoyl chloride and p-toluenesulphonyl chloride respectively resulted into too much of myristic and p-toluenesulphonic acids plus a lot of unreacted materials. The appearance of the TLC plate of the three acylations is shown below. The results of this section indicated no selectivity of acylation of sucrose via the stannylene derivative.



Ts - Tosylates)
)
My - Myristates) of
)sucr
Bz - Benzoate)

SF - Solvent Front

2.10 SUMMARY AND CONCLUSIONS

1. From the observations made throughout this work, it can be concluded that dibutyltin oxide (DBTO) is suitable as an activating agent in selective functionalization of polyhydroxy compounds. In most of the reaction carried out, the incoming electrophile was attached to the oxygen atom of the sugar molecule that was bound to the tin atom of dibutyltin oxide.

2. Several factors are responsible for the preferential attack of the electrophile on a particular tin-bound oxygen of the sugar molecule. Before the electrophile is introduced, the stannylene molecules align themselves in the most stable form hence determining the position of attack by the incoming electrophile.

3. The tin-glucoside complexes are thought to exist in equilibrium and always the oxygen atom has a partial negative charge while tin has a positive charge (Scheme IV). The electrophile approaches the stannylene complex with its carbon atom of the carbonyl center (positively charged) pointing at the tin-bound oxygen atom.

The position of attack will therefore be determined by the steric effect of the neighbouring groups around this particular tin-bound oxygen atom. Bigger clusters of atoms around this oxygen atom will prevent the approaching electrophile from reaching it.

CHAPTER 3

EXPERIMENTAL

3.1 GENERAL

All melting points were determined using a Gallenkamp Melting point apparatus and are uncorrected. TLC plates were coated with silica gel mixed with water in the ratio 1:1 (by weight) using a B.T.L. Mobile Coating apparatus. The plates were activated by putting them in an oven at 100^{o}C for one hour. Detection was effected by charring the plates with 50% sulphuric acid or a solvent mixture of 85 ml methanol, 25ml glacial acetic acid, 5 ml concentrated sulphuric acid and one ml anisaldehyde. IR spectra were recorded as KBr pellets or with nujol on a Perkin-Elmer 598 Spectrometer. NMR spectra were recorded on a Perkin-Elmer R-12 spectrometer and chemical shifts are given in δ units relative to TMS.

Evaporation of solvents was done using a rotatory vacuum evaporator and crystallization was done using various

solvents. The columns for column chromatography were made by adding 30gm of silica gel for each 1 gm of sample to be separated. Solvents were obtained from BDH Chemicals and Aldrich Chemicals Company. Some chemicals were obtained from Eastman Organic Chemicals. Sugar were obtained from Pfanstiehl Laboratories (U.S.). Percentage yields here refers to percentage selectivity of electrophiles.

3.2 PREPARATION OF METHYL α-D-GLUCOPYRANOSIDE (2)

Methyl α-D-glucopyranoside (2) was prepared in 12% yield by the method of Bollenback (1971). A mixture of anhydrous D-glucose (150g) and dry methanol (200 ml) were refluxed in the presence of a cation exchange resin - Amberlite IR-120H (46g) for one and half hours. Needle-like crystals from ethanol were obtained, mp 159-167°C (Lit 167-169°C, Wolform 1963).

IR (KBr pellets) show a wide peak between 2800 cm^{-1} and 2960 cm^{-1} due to the methyl group. NMR (DMSO-d_6) indicated a sharp peak at δ3.20 due to the methoxy group and a peak at δ4.55 due to the anomeric hydrogen proton.

3.3 METHY 2,3-O-DIBUTYLSTANNYLENE -α-D-GLUCOPYRANOSIDE (25).

Dibutyltin oxide (3.13g, 12.5 mmol) was added to a solution of methyl α-D-glucopyranoside (2), (2.43g, 12.5 mmol) in dry methanol (150 ml), in a round-bottomed flask fitted with a reflux condenser. The resulting cloudy solution was refluxed on a heating mantle until it became homogeneous and clear (60 min). The clear solution was filtered and the solvent removed under reduced pressure to give a white solid, 4.60g (83% yield) mp 108-120°C (Lit 105-115°C; Munavu and Szmant 1976). IR spectrum (KBr pellets) showed a peak at 2830 cm^{-1} due to the CH str of the butyl groups. NMR ($CDCl_3$) shows a broad peak between δ1.10 and 1.60 due to the methyl group from the tin butyl system. There is a peak at δ4.60 due to the anomeric hydrogen proton.

3.4 BENZOYLATION OF METHYL 2,3-O-DIBUTYLSTANNY-LENE-α-D-GLUCOPYRANOSIDE (25).

To a magnetically stirred cloudy solution of methyl 2,3-O-dibutylstannylene-α-D-glucopyranoside (25) (2.13g, 5mmol) in dioxane (100 ml), triethylamine (0.77 ml, 5.5 mmol) was added at

room temperature followed by slow addition of benzoyl chloride (0.66 ml, 5.5 mmol). TLC (ethyl acetate) examination after one hour revealed three compounds, one at the origin and the other two at Rf 0.79 and 0.39. The cloudy solution became clear and a precipitate started forming 7 minutes later. The reaction was stopped after 24 hours, filtered and the solvent removed from the filtrate to give a light brownish syrup. The syrup was fractionated on a column of silica gel using ethyl acetate as eluant. The first compound to elute from the column was methyl 2,6-di-O-benzoyl-α-D-glucopyranoside (47) 50 mg (5% yield) as a white solid. It was recrystallised from a mixture of ethyl acetate and petroleum ether (1:1) to give white crystals mp 131-133°C (Lit[3] 139-140°C ; Munavu and Szmant 1976). IR (KBr pellets) indicated two characteristic aromatic CH str peaks at 3160 cm^{-1} and 3050 cm^{-1}, C=O str peak at 1680 cm^{-1} and an aromatic C=C str peak at 1590 cm^{-1} and 1575 cm^{-1}. NMR indicated two sets of aromatic protons at δ7.10 (quartet) and δ7.50 (multiplet). An anomeric proton peak at δ4.50 (singlet), and a peak at δ2.85 (singlet) due to the methoxy group protons.

The second compound to elute from the column was methyl 2-O-benzoyl-α-D-glucopyranoside (18); 700mg (70% yield). This was recrystallised from ethyl acetate and petroleum ether to give white fine crystals mp 169-174°C (Lit 174-175°C, Munavu and Szmant 1976). IR spectrum (KBr pellets) shows a shoulder at 3060 cm^{-1} due to the aromatic CH str. Another peak is also found at 1690 cm^{-1} due to the carbonyl (C=O str) of the benzoyl group. A C=C str at 1590 cm^{-1} and 1579 cm^{-1} due to the phenyl group is also observed. NMR (acetone -d_6) analysis indicated phenyl protons at δ7.10 and δ7.50. Anomeric proton at δ4.40; a peak at δ2.80 due to the methoxy group protons and at δ2.25 (singlet) due to a free hydroxyl proton.

3.5 MYRISTOYLATION OF METHYL 2,3-O-DIBUTYL-STANNYLENE-α-D-GLUCOPYRANOSIDE (25).

To a magnetically stirred cloudy solution of methyl 2,3-O-dibutylstannylene-α-D-glucopyranoside (25) (4.25g, 10 mmol) in dioxane (100 ml), triethylamine (1.54 ml, 11 mmol) was added at room temperature followed by slow addition of myristoyl chloride (2.71g, 11 mmol) in dioxane

(10 ml). One hour later, TLC examination (ethyl acetate, silica gel) indicated the presence of three compounds, one at the origin and the other two at Rf 0.59 and 0.90. The reaction was allowed to continue for 16 hours after which it was stopped since TLC (ethyl acetate) indicated no further changes in the products distribution. The reactants were filtered and the solvent removed from the filtrate under reduced pressure to give a light-brownish syrup. The syrup was fractionated on a column of silica gel and using ethyl acetate as eluant, the first few fractions collected contained myristic acid, 38 mg, mp 52-54°C (Lit 58.2°C).

The first product to elute from the column was methyl 2-O-myristoyl-α-D-glucopyranoside (49), 85 mg (81% yield) as white fine crystals from ethyl acetate-petroleum ether (1:1), mp 96-99°C (Lit 94-96°C; Munavu and Szmant 1976). IR spectrum (KBr pellet) shows a single sharp peak at 1700 cm^{-1} which is due to the C=O str of the myristoyl group, plus a broad band at 2825 cm^{-1} due to the myristoyl group CH str. NMR (acetone-d_6) analysis

indicated a peak at δ4.40 (doublet) due to the anomeric proton, a peak at δ2.85 (singlet) due to the methoxy group, other peaks between δ1.60 and δ0.81 are seen due to the methylene protons of myristoyl group.

The second compound to elute was methyl 6-O-myristoyl-α-D-glucopyranoside (50) 20 mg (19% yield) as white crystals when recrystallised from ethyl acetate-petroleum ether (1:1), mp 78-79°C (Lit 83-85°C; Munavu and Szmant 1976). NMR (acetone-d_6) shows a peak at δ4.10 due to the anomeric proton, a singlet at δ2.80 due to the methoxyl group ($-OCH_3$), peaks at δ1.50 (quartet) and δ0.72 due to CH_2-groups and $-CH_3$ group respectively of the myristoyl group.

3.6 TOSYLATION OF METHYL 2,3-O-DIBUTYLSTANNYLENE-α-D-GLUCOPYRANOSIDE (25).

To a magnetically stirred cloudy solution of methyl 2,3-O-dibutylstannylene-α-D-glucopyranoside (25) (3.53g, 8.3 mmol) in dioxane (150 ml), triethylamine (1.5 ml) was added followed by slow addition of p-Toluenesulphonyl

chloride (1.58g, 8.3 mmol) in dioxane (10 ml) at 10°C. The progress of reaction was monitored by TLC examination. After one hour, two compounds could be seen at Rf 0.90 and 0.50. After twenty four hours TLC revealed three compounds at Rf 0.90, 0.53 and 0.50. The reaction was stopped, filtered and washed twice with 10 ml of dioxane. The filtrate and the washings were mixed and the solvent removed under reduced pressure to give a light-yellow syrup. The syrup was fractionated on a column of silica gel and separation was effected using ethyl acetate as eluant.

The first compound to elute was methyl 2,6-O-ditosyl-α-D-glucopyranoside (51) (60 mg, 16% yield) as a dark brown syrup. The second compound to elute was methyl 6-O-tosyl-α-D-glucopyranoside (52) 110 mg (26% yield) as white fine crystals from ethyl acetate mp 131-132°C. IR (KBr) analysis shows a broad band at 3250 cm^{-1} due to OH str, a shoulder at 3020 cm^{-1} due to CH str, a band at 2890 cm^{-1} due to CH str. There is also a band at 1585 cm^{-1} due to C=C str and a characteristic band at 1320 cm^{-1} due to S=O str of the sulfone group. NMR (acetone-d_6) analysis

shows peaks at δ7.0 and 7.2 (doublet) due to the aromatic protons, a peak at δ4.15 due to the anomeric proton, methoxy protons are seen at δ2.70 (singlet), other C-H protons are seen at δ1.90 and δ1.50 (triplet) due to CH_2 protons.

The third compound to elute was methyl 2-O-tosyl-α-D-glucopyranoside (14) 220 mg (58% yield) as white fine crystals from ethyl acetate, mp 108-112°C (Lit 103-104°C; Munavu and Szmants 1976). IR (KBr) analysis indicate the presence of OH str by a shoulder at 3480 cm^{-1} and a broad band at 3250 cm^{-1}. A peak at 2890 cm^{-1} reveals the presence of CH str, a peak at 1585 cm^{-1} due C=C str is also seen. A sharp peak at 1320 cm^{-1} due to S=O str is observed. NMR (acetone-d_6) analysis shows the aromatic protons at δ7.35 (doublet) and 6.95 (doublet), anomeric proton is shown by a peak at δ4.00 (doublet), methoxy protons are shown by the peak at δ2.72. The spectrum also shows a peak at δ2.38 which is due to hydroxy protons (singlet). This shows that there is a free primary hydroxyl group

in the compound. Another peak at δ1.50 (doublet) is due to methylene protons.

3.7 CARBANILATION OF METHYL 2,3-O-DIBUTYL-STANNYLENE-α-D-GLUCOPYRANOSIDE (25).

To a magnetically stirred cloudy solution of methyl 2,3-O-dibutylstannylene-α-D-glucopyranoside (25) (4.25g, 10 mmol) in tetrahydrofuran (70 ml) at -10°C, a solution of phenylisocyanate (1.1 ml, 10 mmol) in tetrahydrofuran (10 ml) was added slowly for 60 minutes. TLC (ethyl acetate) examination half-way during the addition of phenylisocyanate solution revealed the presence of two products at Rf 0.40 and 0.67 plus some starting materials. The product distribution did not change even after 24 hours except it intensified on addition of all the phenylisocyanate.

The reaction was stopped, filtered and the solvent from the filtrate was removed under reduced pressure to give a brownish syrup, 3.48g. The syrup was fractionated on a column of silica gel using ethyl acetate as eluant. The first compound to elute was methyl 2,6-O-diphenyl carbonyl α-D-glucopyranoside

(54) 103.7 mg (61% yield), as a white solid which recrystallized from ethyl acetate, mp 237-238°C with decomposition. IR (KBr) analysis shows a peak at 1590 cm^{-1} due to C=C str band, a characteristic peak for carbamates at 1925 cm^{-1} due to C=N str. Another peak at 1690 cm^{-1} due to C=O str is also observed. There was another peak at 1285 cm^{-1} due to C-N str. NMR (DMSO-d_6) analysis shows peaks at δ8.46 (doublet) due to N-H proton, a peak at δ7.32 due to phenyl protons, another at δ3.61 (singlet) due to the anomeric proton. A sharp peak at δ3.19 (singlet) due to the methoxy protons and the methylene protons at δ2.30 (multiplet).

The second compound to elute was methyl 2-O-phenyl carbamoyl-α-D-glucopyranoside (55) 67.4 mg (39% yield) as a white solid which recrystallised from ethyl acetate, mp 236-239°C. IR (KBr) analysis shows the following bands as expected; a shoulder at 3040 cm^{-1} due to C-H str band, a shoulder at 1690 cm^{-1} due to C=O str band and a sharp peak at 1585 cm^{-1} due to C= C str from the phenyl ring. There is also a peak at 1930 cm^{-1} which is due to C=N str band. NMR (DMSO-d_6) analysis shows peaks at

δ8.50 due to N-H proton, at δ7.30 (multiplet) due to aromatic protons. A peak at δ4.20 due to the anomeric proton is seen. The methoxy protons are indicated by a peak at δ3.20 (singlet). The melting point of the mixtures of (54) and (55) was found to be 204-210°C which shows the two compounds to be different.

3.8 STANNYLATION OF METHYL β-D-GLUCOPYRANOSIDE (3).

Dibutyltin oxide (3.125g, 12.5 mmol) was added to a solution of methyl β-D-glucopyranoside (3) (2.43g, 12.5 mmol) in methanol (75 ml) and the resulting cloudy solution brought to reflux. When the solution became clear and homogeneous (one hour), it was stopped, filtered and the solvent removed under reduced pressure to give a white solid, 5.50g (100% yield) mp 123-136°C. IR (KBr) analysis shows a broad band between 3400 cm^{-1} and 3200 cm^{-1} due to OH str bands and another one between 2900 cm^{-1} and 2800 cm^{-1} due to CH str band.

3.9 BENZOYLATION OF METHYL β-D-GLUCOPYRANOSIDE TIN DERIVATIVE (56).

To a magnetically stirred cloudy solution of methyl β-D-glucopyranoside tin complex (56) (2.13 gm, 5 mmol) in dioxane (75 ml), triethylamine (1.45 ml) was added followed by slow addition of benzoyl chloride (0.58 ml, 5 mmol) in dioxane (10 ml) at ambient temperature. After one hour the solution became clear and a white precipitate started forming. TLC (ethyl acetate, silica gel) indicated two major products close together at Rf 0.53 and a minor product at Rf 0,75 and a substantial amount of starting materials.

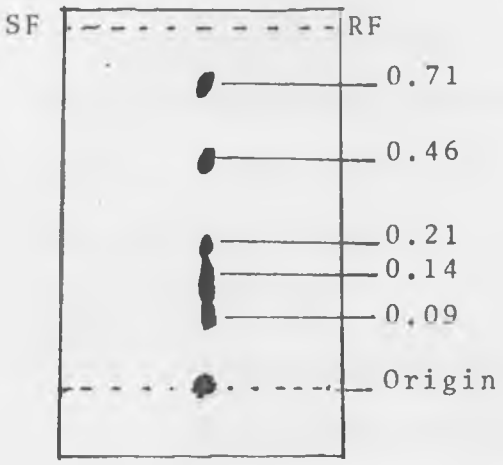
0.5 hrs later, the content was filtered and washed with dioxane (10 ml). The filtrate and the washings were evaporated in vacuo to give a yellow syrup. TLC (ethyl acetate) examination of the syrup indicated two major products and a minor product. No separation was carried out.

3.10 CARBANILATION OF METHYL β-D-GLUCOPYRANOSIDE TIN DERIVATIVE (56).

To a magnetically stirred cloudy solution of methyl β-D-glucopyranoside-tin derivative

(56) (4.25g, 10 mmol) in tetrahydrofuran (75 ml) at -10°C, phenylisocyanate (1.12 ml, 10 mmol) in tetrahydrofuran (20 ml) was added slowly for thirty minutes. The reaction was monitored by constant TLC examination. After all the isocyanate was added TLC (ethylacetate:n-hexane, 9:1) indicated the presence of four compounds at Rfs 0.71, 0.21, 0.09 and 0.14 plus a lot of starting materials. TLC fifteen minutes later indicated five compounds with the new product at Rf 0.46. The reaction was stopped, filtered and from the filtrate, the solvent was removed under reduced pressure to give a light brown syrup, 5.75g.

It was rather difficult to separate the many products. Using n-hexane the first two compounds were removed in very small amounts. Using ethyl acetate the other three compounds with the major one at Rf 0.14 were removed as mixtures. TLC (n-hexane, ethyl acetate 1:9) of the syrup appeared as shown below.



Solvent used was a mixture of n-hexane and ethyl acetate 1:9.

3.11 STANNYLATION OF METHYL α-D-GALACTOPYRANOSIDE (7).

In a round-bottomed flask containing benzene (120 ml), equimolar quantities of methyl α-D-galactopyranoside (7) (3.88g, 20 mmol) and dibutyltinoxide (4.98g, 20 mmol) were introduced and the resulting solution refluxed in a Dean-Stark apparatus. About 10 ml of methanol was added to catalyse the reaction and in twenty minutes the solution became clear and homogeneous. The reaction was stopped, filtered and the solvent from the filtrate removed in vacuo to give a white solid, mass 8.80g (100% yield) mp 78-88°C (Lit[3] 75-85°C ; Munavu and Szmant 1976) of methyl 2,3-O-dibutylstannylene

-α-D-galactopyranoside (57). IR (KBr) analysis shows a broad band between 3540 cm^{-1} and 3200 cm^{-1} due to OH str and another at 2950 cm^{-1} due to the CH str of the butyl moiety.

3.12 MYRISTOYLATION OF METHYL 2,3-O-DIBUTYL-STANNYLENE-α-D-GALACTOPYRANODISE (57).

To a magnetically stirred cloudy solution of methyl 2,3-O-dibutylstannylene-α-D-galactopyranoside (57) (4.25g, 10 mmol) in dioxane (70 ml), triethylamine (1.54 ml) was added followed by slow addition of myristoyl chloride (2.71g, 10 mmol) in dioxane (10 ml) at room temperature. TLC (ethyl acetate) examination after one hour revealed two products and too much of unreacted materials seen at the origin. After one week most of the materials had reacted, and only two products were seen. The reaction was stopped, filtered and washed once with 10 ml of dioxane. From the mixture of the filtrate and washings, the solvent was removed under reduced pressure to give a light brown syrup.

The syrup was fractionated on a column of silica gel and ethyl acetate as eluant. The first compound to elute was methyl

2,6-O-dimyristoyl-α-D-galactopyranoside (58), 52.6 mg (24% yield). This was recrystallised from ethyl acetate and petroleum ether (1:1) to give a white solid, mp 43-44°C.

The second compound to elute was methyl 2-O-myristoyl-α-D-galactopyranoside (59) 166.4 mg (76% yield). This was recrystallised from ethyl acetate and petroleum ether (1:1) to give a white solid, mp 128-134°C. IR(KBr) analysis shows a sharp band between 2900 cm^{-1}-2960 cm^{-1} and at 2865 cm^{-1} due to the myristoyl moiety CH str bands. A peak at 1680 cm^{-1} is seen due to C=O str band.

3.13 CARBANILATION OF METHYL 2,3-O-DIBUTYL-STANNYLENE-α-D-GALACTOPYRANOSIDE (57).

Phenyl isocyanate (1.2 ml, 10 mmol) in tetrahydrofuran (10 ml) was added slowly to a magnetically stirred cloudy solution of methyl 2,3-O-dibutylstannylene-α-D-galactopyranoside (57) (4.25g, 10 mmol) in tetrahydrofuran (50 ml) at -10°C. A white precipitate started to form immediately after all the phenylisocyanate was added. TLC (ethyl acetate) examination after all the phenyl isocyanate was added indicated the presence of four products and no unreacted

materials. TLC five hours later indicated no much changes in the products distribution at Rf 0.71, 0.411, 0.385, and 0.178 (major). After stirring for an additional one hour, the reactants were filtered and washed twice with 10 ml of tetrahydrofuran. Evaporation of the filtrate and washings in vacuo left a brown syrup, 4.26 gm. The syrup was fractionated on a column of silica gel and using n-hexane, the first product was removed as a white solid, (110 mg; 24% yield). Using ethyl acetate as eluant the second and third compounds were eluted as mixtures in form of brownish thick syrup 210 mg (47% yield).

The fourth and the major product was removed as white crystals form ethyl acetate (130 mg; 30% yield) of methyl 2-O-phenyl carbamoyl-α-D-galactopyranoside (60).

3.14 STANNYLATION OF METHYL β-D-GALACTOPYRANOSIDE (30).

Equimolar quantities of methyl β-D-galactopyranoside (30) (1.94g, 10 mmol) and dibutyltin oxide (2.49g, 10 mmol) were put into around bottom flask containing dry methanol (70 ml). The resulting cloudy solution

was refluxed until it became clear and homogeneous ($1\frac{1}{2}$ hrs), after which it was stopped and the content filtered. The solvent was removed in vacuo to give a white solid 4.39g (100% yield) mp 134-142°C (Lit 135-145°C; Munavu and Szmant 1976) of methyl 2,3-O-dibutylstannylene-β-D-galactopyranoside (61). IR (KBr) analysis indicates a peak at 3510 cm^{-1} due to free OH str, a peak at 2950 cm^{-1} due to CH str of dibutyl tin moiety.

3.15 MYRISTOYLATION OF METHYL 2,3-O-DIBUTYL-STANNYLENE-β-D-GALACTOPYRANOSIDE (61).

Triethylamine (1.54 ml) was added into a solution of methyl 2,3-O-dibutylstannylene--β-D-galactopyranoside (61) (4.25g, 10 mmol) in dioxane (100 ml), followed by slow addition of myristoyl chloride (2.71g, 10 mmol) in dioxane (10 ml). The resulting cloudy solution was magnetically stirred. TLC (ethyl acetate) examination after one hour revealed the presence of two equal products close together at Rf 0.50 and 0.46, in addition to unreacted materials at the origin. TLC after five days indicated that most of the unreacted materials had disappeared and a new product at Rf 0.70

had formed. The reaction was stopped, filtered and washed once with dioxane (10 ml). Evaporation of solvent from the filtrate and washings gave a light brown syrup, 4.16g.

Attempted separation using ethyl acetate was not successful. Most of the fractions collected contained mixtures and very few contained pure products. The second and third products were too close together for precise separation.

3.16 CARBANILATION OF METHYL 2,3-O-DIBUTYL-STANNYLENE-β-D-GALACTOPYRANOSIDE (61).

To a solution of stannylated methyl β-D-galactopyranoside (61) (4.25 gm, 10 mmol) in 100 ml tetrahydrofuran at -10°C, phenylisocyanate (1.2 ml, 10 mmol) in 10 ml tetrahydrofuran was added slowly with vigorous stirring using a magnetic stirrer immediately a few drops were added, a white fine precipitate started to form. TLC (ethyl acetate) indicated a compound at Rf 0.41 and a lot of starting materials. After all the phenylisocyanate was added, TLC revealed three more products at Rf 0.30, 0.16, and 0.096. In all these compounds no major product was isolated.

3.17 METHYL 2,3-O-DIBUTYLSTANNYLENE -α-D-XYLOPYRANASIDE (101)

To a solution of methyl α-D-Xylopyranoside (11) (1.64gm, 10 mmol). In methanol (200 ml), dibutyltin oxide (2.48gm, 10 mmol) was added and the resulting cloudy solution was refluxed. The solution became homogeneous and clear after one and half hours. The solvent was removed in vacuo under diminished pressure to give a white solid 3.79 gm (93% yield) mp 129-134°C.

3.18 BENZOYLATION OF METHYL 2,3-O-DIBUTYL-STANNYLENE-α-D-XYLOPYRANOSIDE (101)

To a magnetically stirred cloudy solution of methyl 2,3-O-dibutylstannylene-α-D-xylopyranoside (101) (1.98 gm, 5 mmol) in dioxane (100 ml), triethylamine (0.77 ml) was added followed by slow addition of benzoyl chloride (0.66 ml, 5 mmol) in 10 ml of dioxane at 5°C for 20 min. After all the benzoyl chloride was added the temperature was increased slowly to room temperature (23°C). TLC (ethyl acetate, silica gel) examination indicated three products at Rf 0.69, 0.47 and 0.38 plus too much of the starting materials. The reaction was stopped

after 24 hours, filtered and washed twice with 10 ml of dioxane. Solvent from the filtrate was removed in vacuo to give a light brown syrup.

The syrup was fractionated on a column of silica gel and using ethyl acetate as eluant, the first compound which was eluted was methyl 2,3,4-O-tribenzoyl-α-D-xylopyranoside (63) (130 mg, 15% yield); white glassy crystals from ethyl acetate mp 109-112°C (Lit 116-118°C; Ferrier J. 1964). IR (KBr) spectrum indicates the presence of a strong band at 3040 cm^{-1} due to CH str of the phenyl group. A strong absorption band at 1680 cm^{-1} due to C=O str is also seen. There is also a sharp peak at 1590 cm^{-1} due to C=C str from the phenyl group. NMR (DMSO-d_6) shows the aromatic protons at δ7.4, an anomeric proton at δ4.35, methoxy protons at δ3.20, methylene protons at around δ1.50.

The second compound to elute was methyl 2,3-O-dibenzoyl-α-D-xylopyranoside (64), 210 mg (26% yield) as white crystals from ethyl acetate and petroleum ether (1:1) mp 124-127°C (Lit 128-129°C; Ferrier J. 1964). IR (KBr) analysis shows a strong band at 1700 cm^{-1} due to the

C=O str, a sharp peak at 1590 cm^{-1} due to C=C str is also seen. A broad band at 3104 cm^{-1} due to the aromatic CH str. NMR (Acetone-d_6) shows peaks at δ7.5 and 7.0 due to the aromatic protons. A peak at δ4.31 (singlet) is also seen which is due to the anomeric proton. Other peaks that appear are those of hydroxyl groups between δ3.60-3.00. A sharp singlet at δ2.80 due to the methoxy protons is seen. There is also a peak at δ1.45 which is due to the methylene protons.

The third compound to elute was methyl 2-O-benzoyl-α-D-xylopyranoside (71), 330 mg (38.5% yield) a colourless syrup (Lit. obtained as a syrup in 5% yield, Ferrier J. 1964).

The fourth compound to elute was methyl 4-O-benzoyl-α-D-xylopyranoside (65), 170 mg (21% yield) white crystals from ethyl acetate and petroleum ether (1:1) mp 107-110°C. IR (KBr) analysis shows peaks at 3490 cm^{-1} due to OH str, at 2900 cm^{-1} due to CH str, at 1700 cm^{-1} due to C=O str and at 1580 cm^{-1} due to C=C str. NMR ($CDCl_3$) analysis shows the aromatic protons between δ7.51 and 8.0 (multiplet) a peak at δ4.75 (doublet) due to the anomeric proton, a sharp singlet at δ3.44 due to the methoxy protons.

3.19 CARBANILATION OF METHYL 2,3-O-DIBUTYL-STANNYLENE-α-D-XYLOPYRANOSIDE (101).

To a magnetically stirred solution of methyl 2,3-O-dibutylstannylene-α-D-xylopyranoside (101), (390 mg, 1 mmol) in tetrahydrofuran (50 ml), phenylisocyanate (0.11 ml, 1 mmol) in tetrahydrofuran (10 ml) was added slowly at -10°C for a period of one hour. After the addition of phenylisocyanate was complete, TLC examination (ethyl acetate 80%, n-Hexane 20%) indicated two products at Rf = 0.60 and 0.36. The reaction was stopped, filtered and washed twice with 10 ml of tetrahydrofuran to give a very fine white ppt and a clear filtrate. Removal of solvent under reduced pressure left behind a light brown syrup, 340 mg.

The syrup was fractionated on a column of silica gel and separation was effected by the use of ethyl acetate as eluant. The first compound to elute was most probably methyl 2,4-O-diphenylcarbamoyl-α-D-xylopyranoside (66) 11.8mg (14% yield). A white solid recrystallised from ethyl acetate, mp 235-238°C. IR spectrum (KBr pellets) shows a shoulder

at 3100 cm^{-1} due to CH str of the phenyl group. A shoulder at 1695 cm^{-1} due to C=O str band and a sharp peak at 1585 cm^{-1} due to C=C str of the phenyl ring. NMR (DMSO-d_6) shows a peak at δ8.6 due to the NH proton, a peak between δ7.3-7.5 due to the aromatic protons, a peak at δ3.4 (singlet) due to methoxy proton, a peak at δ2.5 (doublet) due to methylene protons (CH_2).

The second compound to elute was methyl 2-O-phenylcarbamoyl-α-D-xylopyranoside (67), 72.8 mg (85% yield) white crystals from ethyl acetate 128-134°C. IR spectrum (KBr pellets) shows a band at 1680 cm^{-1} which is due to the C=O str band and another sharp peak at 1590 cm^{-1} due to the C=C str of the phenyl ring. NMR (Acetone-d_6) shows a peak at δ8.1 due to NH proton, a peak between δ6.4-7.15 (multiplet) due to the aromatic protons. There also appears a peak at δ4.20 (multiplet) which is due to CH (anomeric) proton. A peak at δ2.8 (singlet) due to methoxy protons. There is also a peak at δ1.55 (doublet) due to CH_2 protons.

3.20 TOSYLATION OF METHYL 2,3-O-DIBUTYL-STANNYLENE-α-D-XYLOPYRANOSIDE (101).

To a magnetically stirred cloudy solution of methyl 2,3-O-dibutylstannylene-α-D-xylopyranoside (101) (1.98g, 5 mmol) in dioxane (120 ml) triethylamine (0.77 ml) was added followed by slow addition of p-toluene sulphonyl chloride (950 mg, 5 mmol) in dioxane (30 ml) at room temperature (25°C). The progress of the reaction was followed by constant use of TLC. Twenty four hours later, the cloudiness disappeared and a white precipitate started to form twenty six hours later. TLC (ethyl acetate) indicated three products at Rf 0.77, 0.46 (major) and 0.34 and a lot of unreacted materials. The reaction was stopped twenty hours later after TLC indicated no much changes in the products distributions and intensities. A dark brown syrup (150 mg) was obtained on removal of solvent under reduced pressure.

The syrup was fractionated on a column of silica gel and using ethyl acetate as eluant, the first compound to elute was methyl 2,3,4-O-tritosyl-α-D-xylopyranoside (68) (20 mg; 10.6% yield) a light brownish thick

syrup (Lit. not crystallised, Yotaro Kondo 1982).

The second compound to elute was methyl 2,3-O-ditosyl-α-D-xylopyranoside (69) (70 mg; 36.8% yield) a white solid mass recrystallised from ethyl acetate and petroleum ether (1:1) mp 142-145°C (Lit 168-169°C; Yotaro Kondo 1982). IR (KBr) analysis shows a peaks at 3400 cm^{-1} due to CH str of the xylose moiety. A broad band at 3160 cm^{-1} due to aromatic CH str. A band at 2900 cm^{-1} which is due to CH str from the methyl group of the p-toluene sulphonyl group. A sharp peak at 1585 cm^{-1} is also seen due to C=C str. Another characteristic sharp peak is seen at 1350 cm^{-1} due to S=O str (antisymmetric sulfone). NMR (DMSO-d_6) analysis indicates the presence of aromatic protons at δ7.70 (multiplet). Anomeric proton is indicated by a peak at δ4.30 (doublet). The methoxy protons are indicated by the peak at δ2.98 (singlet). Methylene protons are indicated by a peak at δ2.35.

The third compound to elute was methyl 2-O-tosyl-α-D-xylopyranoside (70) (30 mg;

17% yield) white crystals from ethyl acetate and petroleum ether (1:1) mp 124-127°C (Lit 135-136°C Yotaro Kondo 1982; Buchanan and Fletcher 1966).

The fourth compound to elute was a colourless syrup that solidified on standing, mass (70 mg; 36.8% yield). The solid was dissolved in hot ethyl acetate and gave colourless crystals on standing, mp 54-58°C of methyl 4-O-tosyl-α-D-xylopyranoside (84) (Lit 57-58°C Buchanan and Fletcher 1966; Yotaro Kondo 1982).

3.21 METHYL 2,3-O-DIBUTYLSTANNYLENE--β-D-XYLOPYRANOSIDE (93).

To a solution of methyl β-D-xylopyranoside (12) (1.64 gm, 10 mmol) in benzene (150 ml), dibutyltin oxide (2.48 gm, 10 mmol) was added and the resulting milky solution was refluxed. Methanol (5 ml) was added to catalyse the reaction. When the solution became clear and homogeneous (45 min) the reaction was stopped and the solvent removed in vacuo to give a white crystalline solid (3.31 gm; 83.8% yield) mp 130-136°C of methyl 2,3-O-dibutylstannylene--β-D-xylopyranoside (93).

3.22 BENZOYLATION OF METHYL 2,3-O-DIBUTYL-STANNYLENE-β-D-XYLOPYRANOSIDE (93).

To a magnetically stirred cloudy solution of methyl 2,3-O-dibutylstannylene-β-D-xylopyranoside (93) (1.98 gm, 5 mmol) in dioxane (50 mls), triethylamine (0.77 ml, 5 mmol) was added followed by slow addition of benzoyl chloride (0.66 mls, 5 mmol) in dioxane (10 ml) for 30 min. at room temperature (23°C). On addition of benzoyl chloride, the cloudiness disappeared and a white precipitate started forming. TLC examination (ethyl acetate, silica gel) after one hour revealed two compounds at Rf 0.63 and 0.50 plus a lot of starting materials. TLC examination after twenty hours indicated no much changes in the products distribution. The reaction was then stopped, filtered and washed twice with 10 mls of dioxane. The washings and the filtrate were mixed and the solvent removed under reduced pressure to give a white solid. The solid was fractionated on a column of silica gel and using ethyl acetate as eluant, the first compound to elute was a white crystalline solid from

ethyl acetate and petroleum ether (1:1) of methyl 2,4-O-dibenzoyl-β-D-xylopyranoside (72) (80 mg; 10% yield) mp 104-108°C. IR (KBr) shows the presence of a C=O str band at 1670 cm^{-1} and a C=C str band at 1580 cm^{-1} due to the introduced benzoyl group.

The second compound to elute was a white crystalline solid from ethyl acetate petroleum ether (1:1) of methyl 3-O-benzoyl -β-D-xylopyranoside (73) 711.5 mg (90% yield) mp 131-135°C recrystallised from ethyl acetate and petroleum ether. (Lit. 138-139°C, Ferrier 1964). IR (KBr) shows a broad band between 3200 cm^{-1} and 3040 cm^{-1} due to CH str from the phenyl group. A sharp peak at 1700 cm^{-1} is also observed which is due to C=O str, another band at 1590 cm^{-1} is also observed which is due to C=C str band of the phenyl ring. NMR ($CDCl_3$) shows a peak between δ8.0-8.2 (multiplet) and δ7.4-7.55 (multiplet) due to the aromatic protons. A peak at δ5.10 (multiplet) due to hydroxyl proton is observed. Peaks between δ4.45-4.00 due to anomeric proton and C2-H also

appears. A singlet peak at δ3.56 due to methoxy group is also seen.

3.23 TOSYLATION OF METHYL 2,3-O-DIBUTYL-STANNYLENE-β-D-XYLOPYRANOSIDE (93).

To a cloudy solution of methyl 2,3,O-dibutylstannylene-β-D-xylopyranoside (93) (0.98g, 2.5 mmol) in dioxane (50 ml) in a round bottom flask fitted with a magnetic stirrer, triethylamine (0.38 ml) was added followed by slow addition of p-toluenesulphonyl chloride (0.48g, 2.5 mmol) in dioxane (10 ml) at 23°C for 15 min. The progress of the reaction was monitored by TLC (ethyl acetate). One hour after all the p-toluenesulphonyl chloride was added, TLC examination indicated too much of the starting materials and no product had formed. The solution became clear after twenty hours and a white precipitate started forming after another twenty eight hours. TLC indicated two products at Rf 0.70 and 0.44. The reaction was stopped after seventy-two hours, filtered and washed twice with 10 ml of dioxane. The washings were mixed with the filtrate and

using a vacuum evaporator the solvent was removed to give a light yellow syrup.

The syrup was fractionated on a column of silica gel and separation was effected by use of ethyl acetate as eluant. The first compound to elute was methyl 2,4-O-ditosyl--β-D-xylopyranoside (74) (105 mg; 80% yield) as white crystals from ethyl acetate and petroleum ether (1:1) mp 174-178°C (Lit 178-179°C, Yataro Kondo 1982). IR (KBr) analysis show a broad band between 3600 cm^{-1} due to the hydroxyl group of the sugar moiety. A broad band between 2800 cm^{-1} and 2940 cm^{-1} is also observed which is due to the CH str bands of the methyl and the sugar molecule. A sharp peak at 1585 cm^{-1} is also appearing which is due to C=C str of the phenyl group. A sharp peak at 1315 cm^{-1} due to S=O str band is seen. NMR (DMSO-d_6) indicates peaks at δ7.4-7.8 due to the aromatic protons of the tosyl moiety. A peak found at δ5.10 is present which is due to the anomeric proton of the sugar moiety. A peak at δ3.35.5 (singlet) is present which is due to the methoxy protons. A peak for the methylene protons is present at δ2.38.(doublet).

The second compound to elute was methyl -4-O-tosyl β-D-xylopyranoside (75) (30mg, 20% yield), mp 122-125°C recrystallised from ethyl acetate petroleum ether (1:1) (Lit mp 128-129°C; Yotaro Kondo 1982).

3.24 CARBANILATION OF METHYL β-D-XYLOPYRANOSIDE (12) VIA TIN DERIVATIVE.

Into a three-neck round bottomed flask containing 20 ml of tetrahydrofuran, stannylated methyl β-D-xylopyranoside (93) (395 mg, 1 mmol) was added. The resulting solution was stirred vigorously at -10°C. Phenylisocyanate (0.11 ml, 1 mmol) in tetrahydrofuran (10 ml) was then added slowly for 30 min. The progress of the reaction was followed by constant TLC examination with ethyl acetate as eluant. Immediate spoting after all the isocyanate had been added indicated three products at Rf 0.79, 0.47 (minor) and 0.36 (major) plus some starting materials at the origin. The reaction was stopped five hours after, filtered and solvent removed in vacuo from the filtrate to give a light-brownish syrup 380 mg.

The syrup was fractionated on a column of silica gel, and using ethyl acetate as eluant, the first compound to elute, methyl 2,4-O-diphenylcarbamoyl-β-D-xylopyranoside (76), was obtained as colourless fine crystals (90 mg; 22.5% yield) recrystallised from ethyl acetate, mp 230-239°C. The second compound to elute was a light-brownish syrup (140 mg; 35% yield) but was not pure. The third compound to elute was methyl 3-O-phenylcarbamoyl--β-D-xylopyranoside (77) (170 mg; 42.5% yield) recrystallised from ethyl acetate, colourless crystals mp 154-156°C (Lit 147-149°C; Ferrier R.J. 1964). IR (KBr) analysis shows a sharp peak at 3300 cm^{-1} which is due to NH str, a shoulder at 3500 cm^{-1} is seen which is due to OH str. A sharp peak at 1685 cm^{-1} due to C=O str is also seen, a peak at 1580 cm^{-1} due C=C str. NMR (acetone-d_6) shows the following peaks, at δ8.15 which is due to NH proton, δ6.7-7.1 (multiplet) which is due to the aromatic protons. At δ3.85 (multiplet) which is due to the anomeric proton. At δ2.85 (singlet) due to the methoxy protons. There is also a peak at δ1.49 which is due to the methylene (CH_2-) protons.

(KBr pellet) indicates a broad band at 3300 cm^{-1} due to OH str, a peak at 2900 cm^{-1} due to CH str of the α-chloralose molecule. A characteristic peak at 800 cm^{-1} is seen which is due to C-Cl str. NMR analysis (DMSO-d_6) indicates a peak at δ5.70 (singlet) due to the anomeric proton, (proton attached to the carbon next to oxygen atoms and the carbon attached to the three chlorine atoms). Another peak at δ6.10. (triplet), a sharp peak at δ4.30, (S) is due to anomeric proton; and a peak for CH_2 protons is observed at δ2.45.

3.26 DI-O-BUTYLSTANNYLENE α-CHLORALOSE (97)

Into a three-neck round bottom flask containing 200 ml of benzene, α-chloralose (78) (3.11g, 10 mmol) was put in followed by the addition of dibutyltin oxide (2.48g, 10 mmol). The content was refluxed with azeotropic removal of water. After the solution became clear and homogeneous (48 hours), the solvent was removed under diminished pressure to give a white solid mass (7.47g;100% yield) mp 148-170°C. IR analysis (KBr pellets), indicates a broad peak at 2860-2980 cm^{-1} due to the introduced dibutyl group.

3.27 BENZOYLATION OF DI-O-BUTYLSTANNYLENE α-CHLORALOSE (97).

To a magnetically stirred cloudy solution of di-O-butylstannylene α-chloralose (97) (5.4g, 10 mmol) in dioxane (50 ml), triethylamine (1.54 ml) was added followed by slow addition of benzoyl chloride (1.32 ml, 10 mmol) in dioxane (10 ml) at room temperature. The reactant became clear even before all the benzoyl chloride was added. A white precipitate started to form immediately. TLC (ethyl acetate, silica gel) examination after half-hour revealed no product formed, only too much of the starting materials was seen at the origin. Three days after; TLC indicated only one product at Rf 0.58 and a little bit of the starting materials. The reaction was stopped, filtered and solvent removed under reduced pressure to give a white solid. The solid was fractionated on a column of silica gel and separation was effected by using ethyl acetate as eluant. The major product of benzoyl α-chloralose (99) (173 mg,82% yield) was obtained. It was recrystallised from ethyl acetate to give white crystals mp 234-236^{o}C. TLC examination of this

product using various solvents shows it to be homogeneous. IR spectrum (KBr pellet) shows peaks at 3405 cm^{-1} due to OH str, and 2910 cm^{-1} due to CH str. A sharp band at 1675 cm^{-1} due to C=O str of the benzoyl group. A sharp peak at 1595 cm^{-1} due to C=C str. A sharp characteristic peak at 800 cm^{-1} due to CCl str. NMR (DMSO-d_6) analysis shows a peak between δ7.50 and 7.85 due to the phenyl protons and another at δ5.72 due to anomeric proton and δ6.10 due to α-chloralose moeity from hydroxyl protons.

3.28 CARBANILATION OF DI-Q-BUTYLSTANNYLENE α-CHLORALOSE (97).

To a magnetically stirred cloudy solution of α-chloralose-tin compound (668mg, 1.24 mmol) in tetrahydrofuran (30 ml) at -10°C, phenyl isocyanate (0.15 ml, 1.24 mmol) was added slowly for 45 min. A white precipitate formed immediately the isocyanate was added. TLC examination indicated two compounds at Rf 0.62 (major) 0.18 (minor). The reaction was allowed to continue for three days after which TLC (ethyl acetate 80%, n-hexane 20%) indicated the

same product distributions with very little of the starting materials. The reaction was stopped, filtered and solvent removed in vacuo to give a white solid 690 mg. This was all fractionated on a column of silica gel and separation was effected by first passing petroleum ether followed by ethyl acetate and finally methanol.

The first compound to elute was 3,6-O-diphenyl carbamoyl-α-chloralose (80), white needle crystals from ethyl acetate Rf 0.620 (87.6mg; 78% yield) mp 231-233°C. IR (KBr pellets) analysis indicates a broad band between 3260 cm^{-1} and 3320 cm^{-1} due to OH str and NH str, a band at 3040 cm^{-1} due to the aromatic CH str. A peak at 1910 cm^{-1} due to C=N str is seen. A sharp peak at 1700 cm^{-1} due to C=O str and at 1650 cm^{-1} and 1580 cm^{-1} due to C=C aromatic. A sharp peak at 770 cm^{-1} and 825 cm^{-1} due to C-Cl str. NMR (DMSO d_6) analysis shows peak at the following regions; a peak at δ8.20 due to NH proton, aromatic protons are indicated by peaks between δ7.2 and 6.8 (multiplet)

a sharp peak at δ2.85 (singlet) due to OH proton and another peak at δ1.5-1.72, due to methylene protons.

3.29 STANNYLATION OF SUCROSE (36)

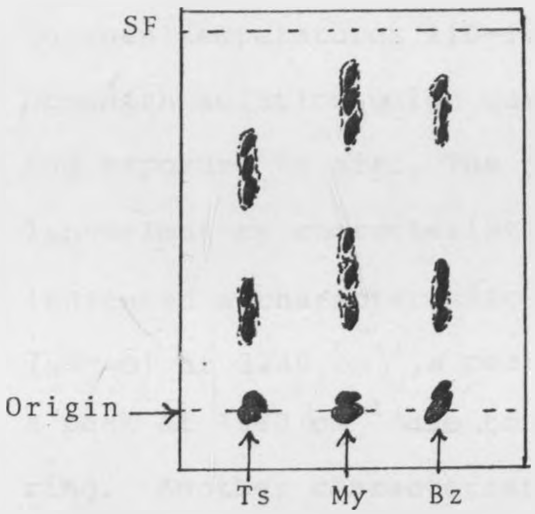
To a solution of sucrose (36) (3.42g, 10 mmol) in methanol (100 ml), dibutyltin oxide (2.48g, 10 mmol) was added in a round bottom flask to form a milky solution. The content was brought to reflux. The heating was stopped when the solution became clear and homogeneous (60 min). The clear solution was filtered and the solvent from the filtrate removed under reduced pressure to give a white solid mass 6.14g (100% yield) mp range 176-190°C with decomposition of 2,3-O-dibutylstannylene-α-D-glucopyranosyl -β-D-fractofuranoside (81).

Sucrose:- Commercial cane sugar was recrystallised from 95% pure ethanol to give fine crystals mp range 184-191°C.

3.30 BENZOYLATION OF SUCROSE VIA IT'S DIBUTYLSTANNYLENE DERIVATIVE (81)

To a magnetically stirred cloudy solution of stannylated sucrose (81) (5.73g), 10 mmol) in dioxane (75 ml), triethylamine (1.54 ml, 10 mmol) was added followed by slow addition of benzoyl chloride (13.2 ml, 10 mmol) at room temperature. The reaction's progress was monitored by TLC examination at constant interval. TLC [methanol (10 ml), acetone (10 ml), water (2 ml) and chloroform (58 ml)] examination four days after, indicated the presence of two distinct streaks at Rf 0.38 and 0.31 - each streak seemed to be made up of three compounds. This also revealed a lot of unreacted materials at the origin. The white precipitate that formed was filtered and solvent from filtrate was removed under diminished pressure to give a brownish syrup mass 3.52g. The syrup was fractionated on a column of silica gel and using solvent mixture [Benzene (20 ml), Ethyl acetate (20 ml) and Ethanol (10 ml)], it was not possible to obtain pure compounds. All fractions obtained contained mixtures. This was due to closeness of the compounds.

Myristoylation and tosylation of sucrose resulted into too much of myristic acid and p-toluene sulphonic acid respectively. In addition to this, too much of the unreacted materials resulted. The TLC examination of the three attempted acylation of sucrose appeared as shown below.



Ts-Tosylates)
My-Myristates) of
Bz-Benzoate) sucrose
SF-Solvent Front

3.31 PREPARATION OF PHENYLISOCYANATE (104)

Phenylisocyanate was prepared in this laboratory via an acid azide (Forster, M. O 1909). Benzoylimide was prepared by the interaction of benzoyl chloride (1.405g, 10 mmol) in dry acetone (75 ml) and sodium azide (0.65g, 10 mmol) in water (75 ml). The mixture of the two solutions was stirred continuously for 5 hours. On separation and extraction with ether, this gave benzoyl azide in a state of purity (184mg) recrystallised from

benzene-petroleum ether mp 119-122°C. (Lit 114-118°C; Forster et al. 1909).

3.32 PYROLYSIS OF BENZOYLIMIDE

The benzoylimide prepared above was refluxed with dry toluene (30 ml) for seven hour over an oil bath. The product was then distilled between temperatures 110-120°C to give a dark brownish solution which gave crystals on cooling, and exposure to air. The crystals formed had a lanchrimatory characteristics. IR analysis (Nujol) indicated a characteristic peak for isocyanates (N=C=O) at 2240 cm^{-1}, a peak at 3260 due to NH str, a peak at 1580 cm^{-1} due to C=C of the phenyl ring. Another characteristic peak at 1290 cm^{-1} due to N-C str is seen.

NMR ($CDCl_3$) analysis indicates a complex multiplet at δ = 6.60-7.40 due to the phenyl protons and also a peak at δ = 8.35 (singlet) due to NH proton.

3.33 ATTEMPTED PREPARATION OF LEVOGLUCOSAN (1,6 ANHYDRO β-D-GLUCOPYRANOSIDE) (8)

Levoglucosan (8) (1,6 anhydro β-D-glucopyranoside) can be prepared by pyrolysis of starch (Wolform et al.1963). It

was first described and characterised as its acetate and benzoate. Levoglucosan; an anhydride of D-glucose, can also be prepared by heating trimethyl (tetra-O-acetyl α-D-glucopyranosyl) ammonium bromide with an aqueous solution of barium hydroxide (Karret and Smirnoff 1921) 1,6-Anhydro β-D-glucopyranoside (8) was prepared in this laboratory in low yield by pyrolysis of corn starch. Corn starch from Corn Product Cooperation (C.P.C.) Kenya (Ltd) was thoroughly dried at 100°C for 24 hours with occassional mixing to accelerate the process. A 500 ml round bottomed flask was attached through a 60° curved glass connected to a litre of suction flask. An apparatus with all ground-glass was used. The suction flask was cooled in an ice and water bath.

The round-bottomed flask was half-way filled with dried corn starch (120g). It was then directly heated caustiously and continously using a large luminous flame. The distillate was collected in the receiver until no more appeared to collect (2½ hours) leaving a carbonaceous residue, approximately 18.4g. The dark-brown syrup was evaporated twice with 100 ml of acetone under diminished pressure.

The thick syrup was mixed with minimum quantity of acetone (17 ml) to give a thin liquid. The liquid was then nucleated by scratching the sides of the container and then put in a fridge for five days. Dark-brown thick cake formed on the bottom of the flask. It was washed with three portions of acetone (10 ml) sucked dry and dissolved in hot methanol with the addition of activated carbon. The suspension was filtered while hot and allowed to crystallise in a fridge. After one day, colourless crystals of lavoglucosan (8) 1.72gm (1.4% yield) mp 172-174°C. (Lit 172°C; Wolform et al. 1963) were obtained.

3.34 STANNYLATION OF LEVOGLUCOSAN (8)

Equimolar quantities of levoglucosan (8) (162 mg, 1 mmol) and dibutyltin oxide (245 mg, 1 mmol) in methanol (50 ml) were refluxed for 30 min when it became clear and homogeneous. It was then filtered and solvent removed under reduced pressure to give a white solid mass 0.40g (400 mg) mp 152-170°C.

3.35 BENZOYLATION OF LEVOGLUCOSAN (8) VIA TIN DERIVATIVE.

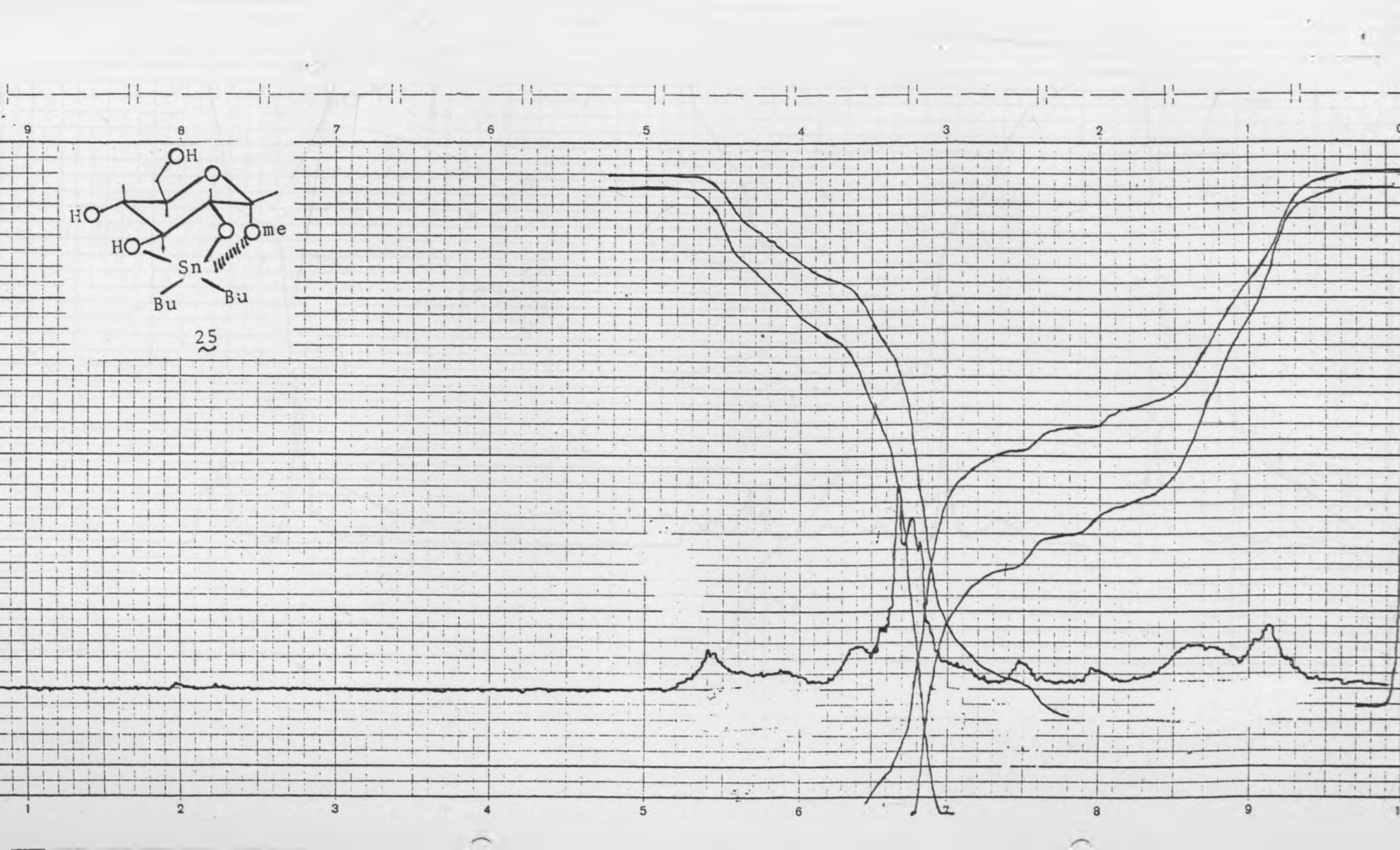
Triethylamine (0.77 ml) was added into a magnetically stirred solution of stannylated levoglucosan (8) (194.5 mg, 0.5 mmol) in dioxane (50 ml) followed by slow addition of benzoyl chloride (0.066 ml, 0.5 mmol) at ambient temperature. The reaction was closely monitored by TLC examination at regular intervals. Using ethyl acetate as solvent four compounds were observed at Rf 0.11, 0.43, 0.57 and 0.75 plus a lot of starting materials. After three days; the temperature was increased from room temperature to 60°C for 30 minutes to accelerate the reaction. After this, it was found that, most of the unreacted material had reacted. The reaction was then stopped, filtered and washed twice with dioxane (10 ml). The solvent was removed under diminished pressure from the filtrate and washings, to give a yellow syrup 560 mg. The yellow syrup was introduced into a column of silica gel for separation. Using ethyl acetate as eluant, the first compound to elute was a light yellow solid mass 24.2 mg of 1,6 anhydro-4-O-benzoyl-β-D-glucopyranose, mp 115-119°C

(Lit mp 123-126^{o}C; Jeanloz, Annette, Rapin and Hakomori 1961).

The second compound to elute was a white solid mp 54-56^{o}C. No analysis was carried out for these compounds. Most of the other products were eluted in mixtures. Myristoylation of levoglucosan via the stannylated derivative was also done but separation was not successful.

A P P E N D I X A

CHEMICAL SPECTRA::



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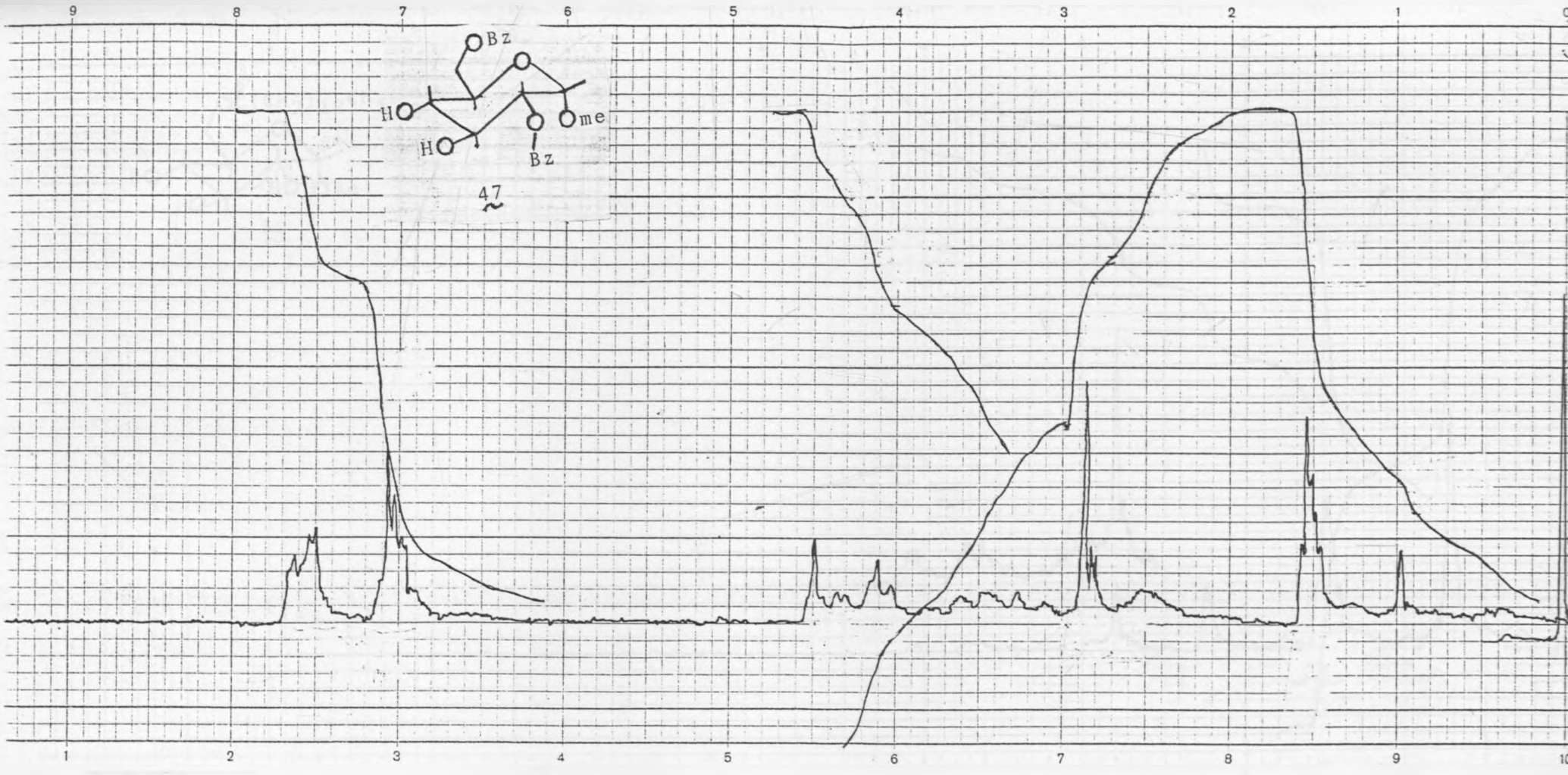

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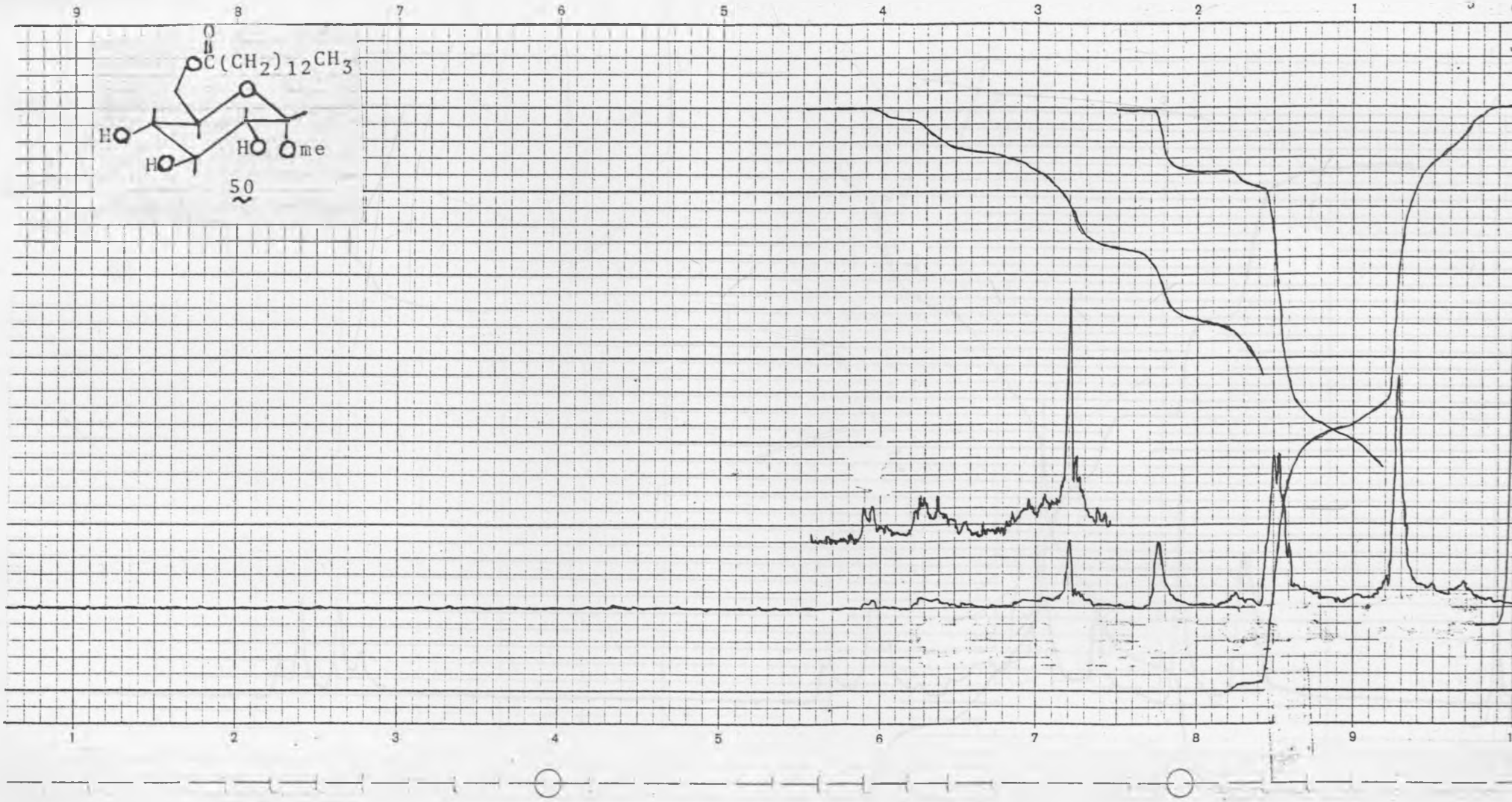
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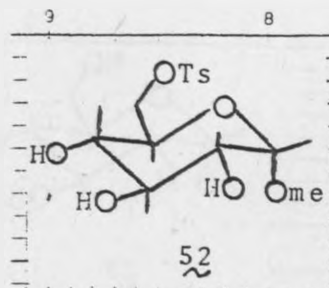

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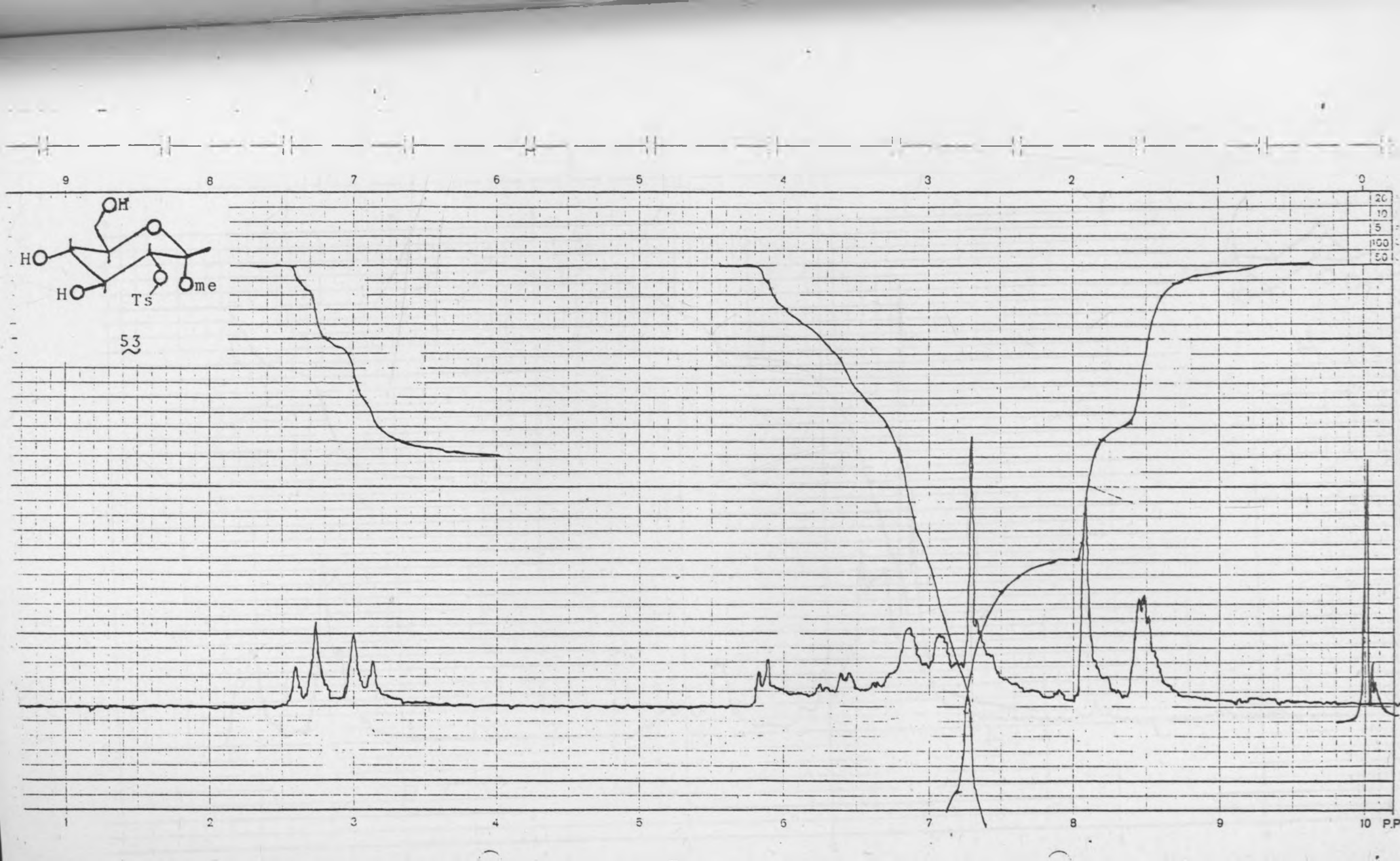
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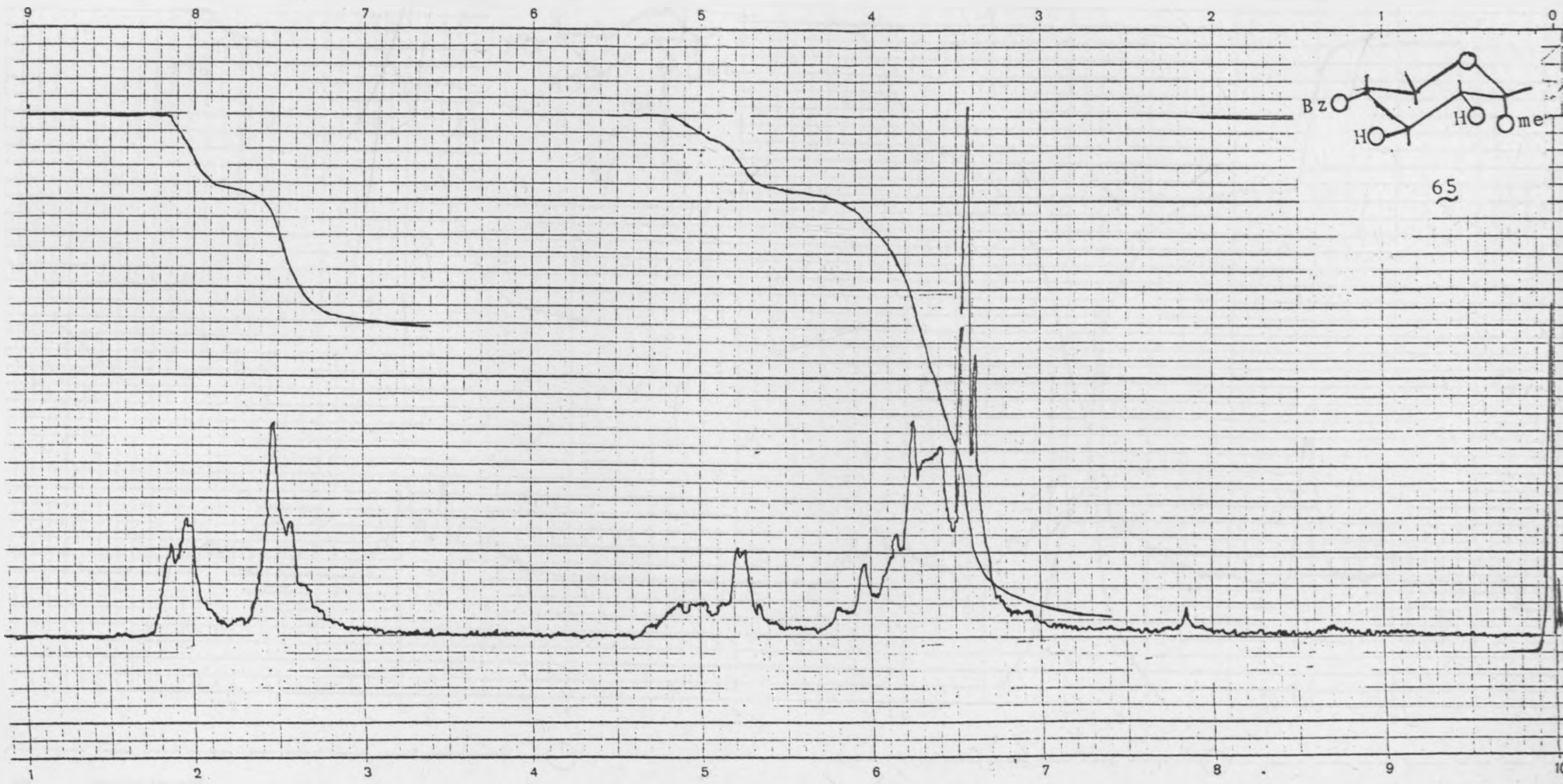
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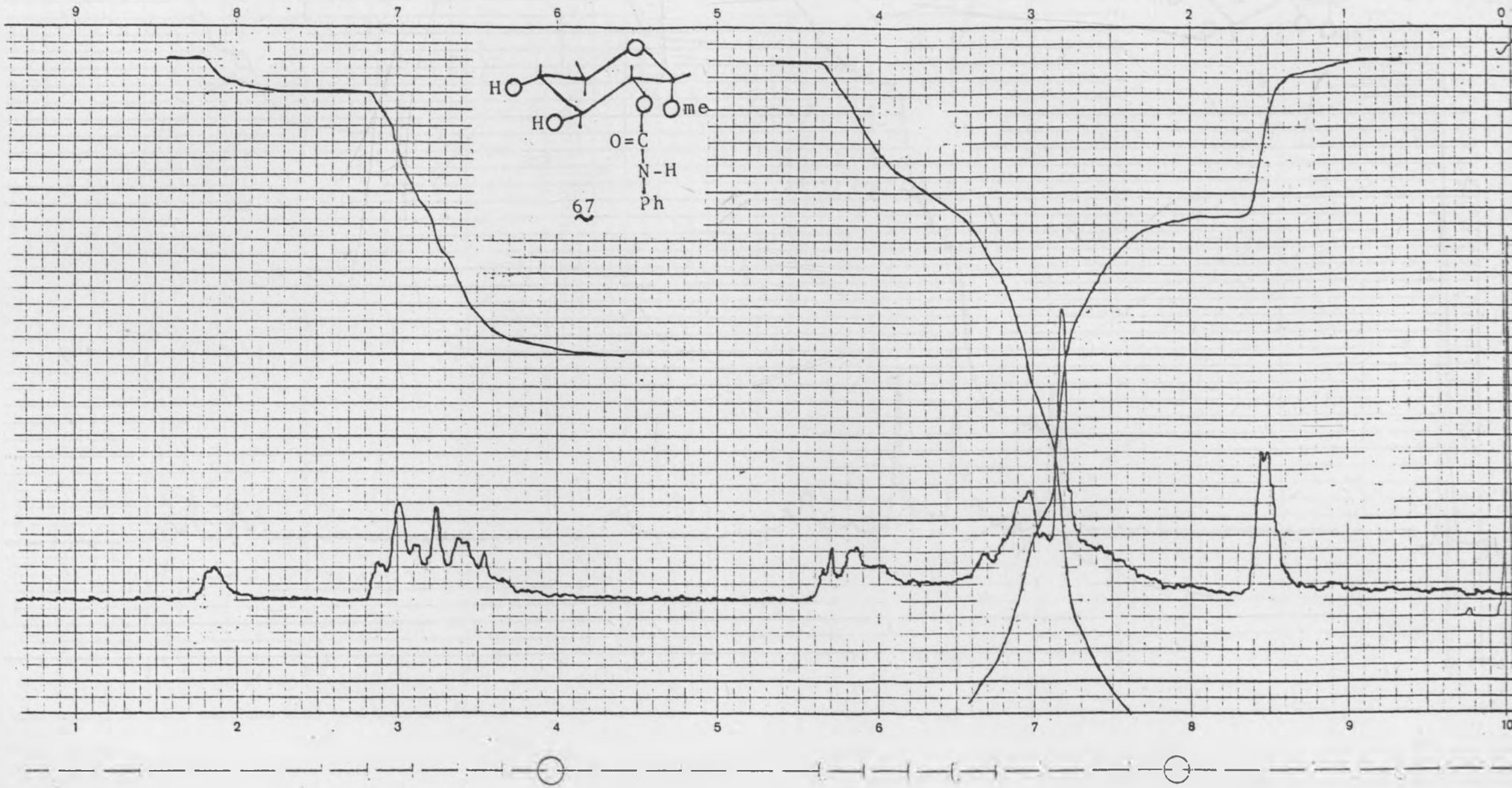

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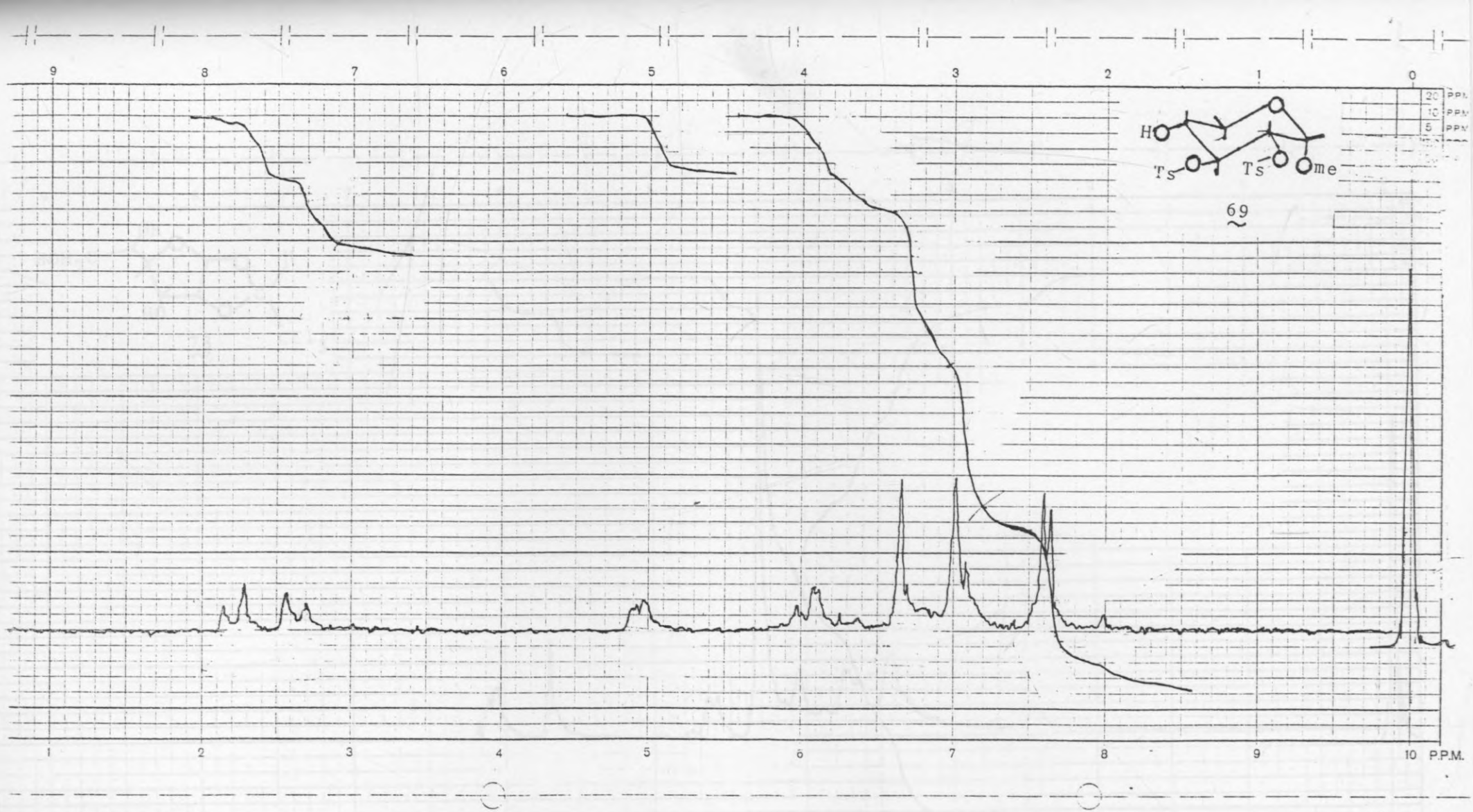

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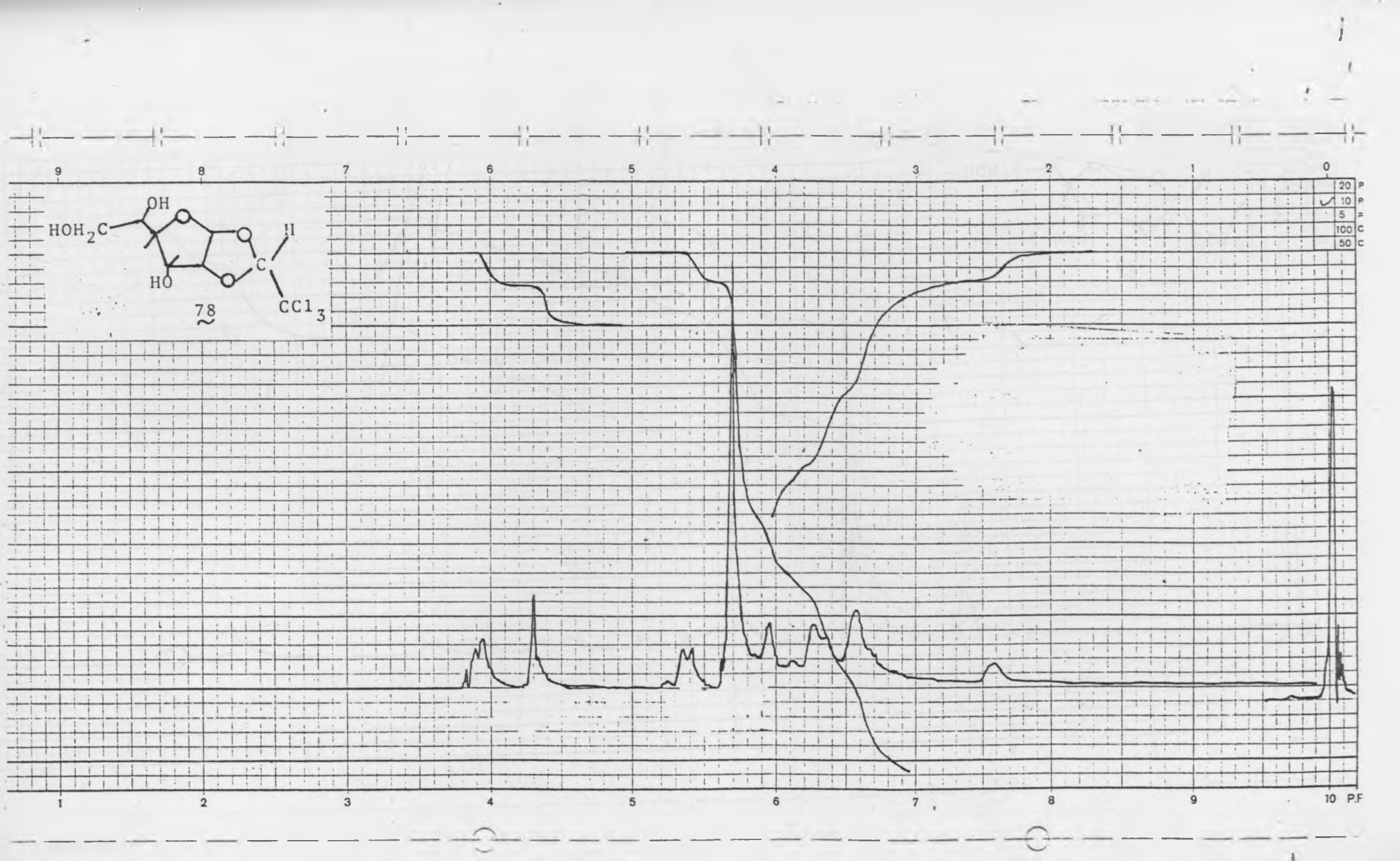
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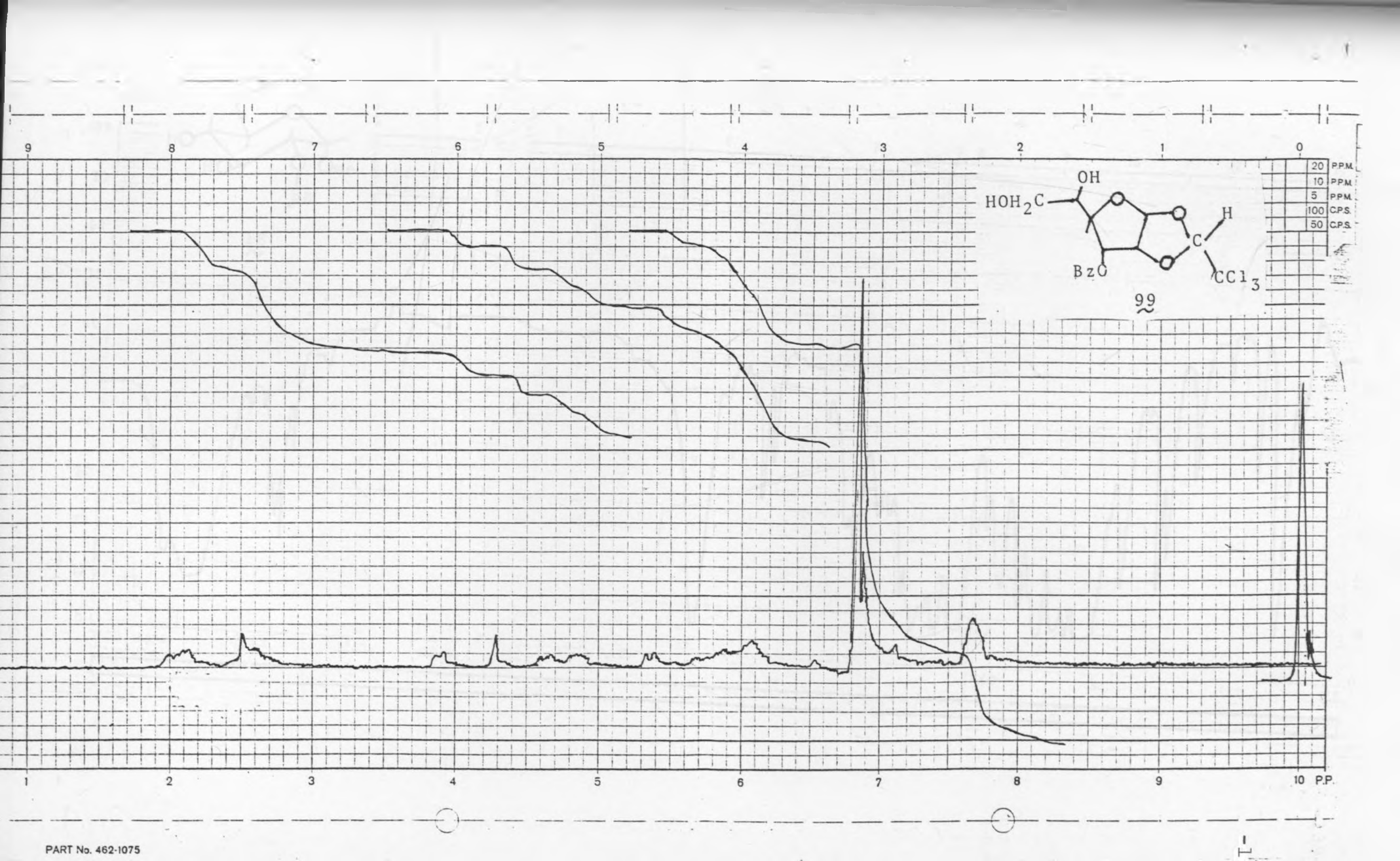

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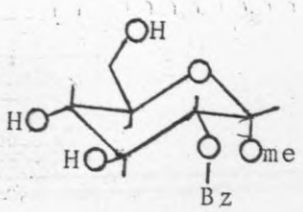

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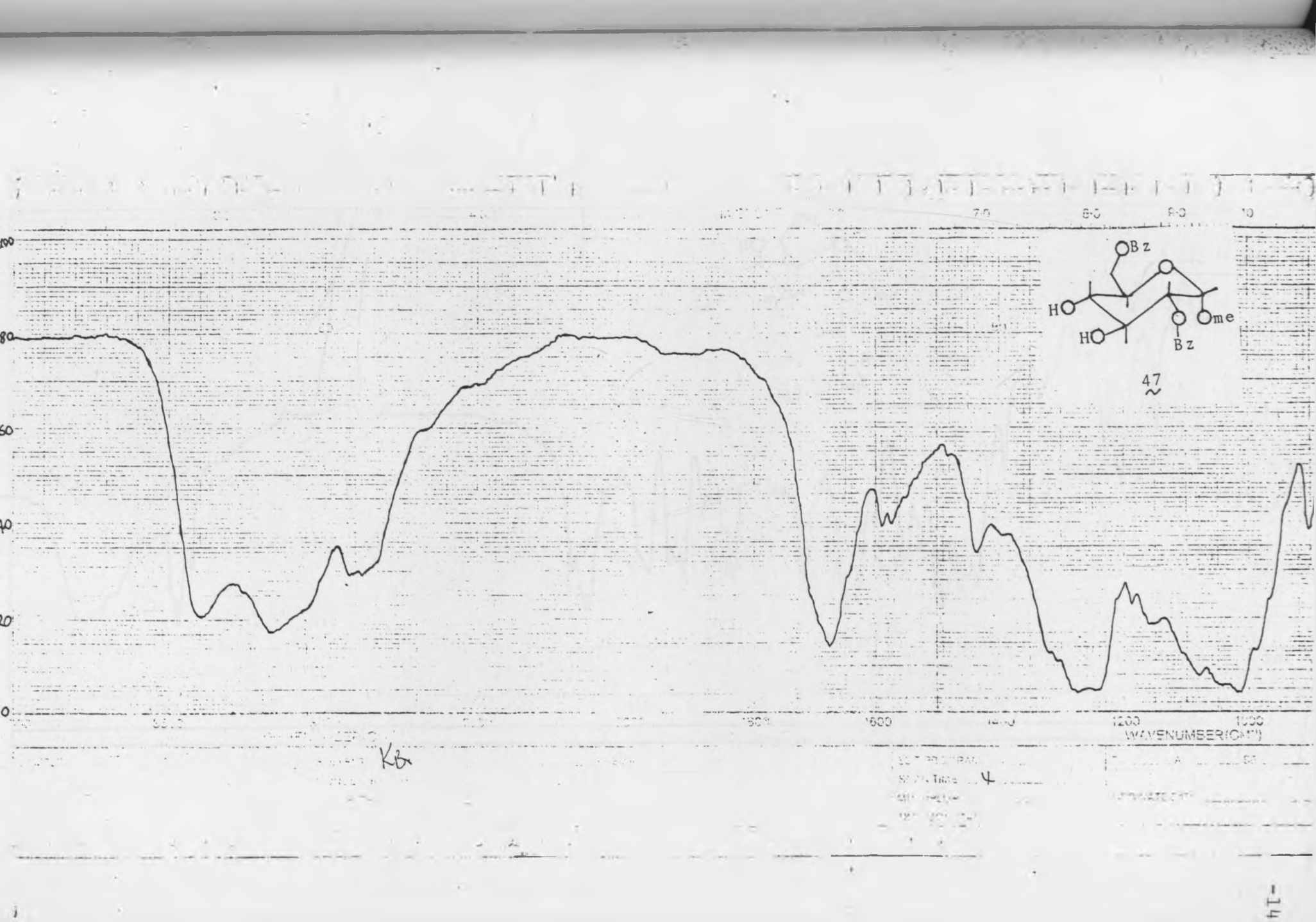
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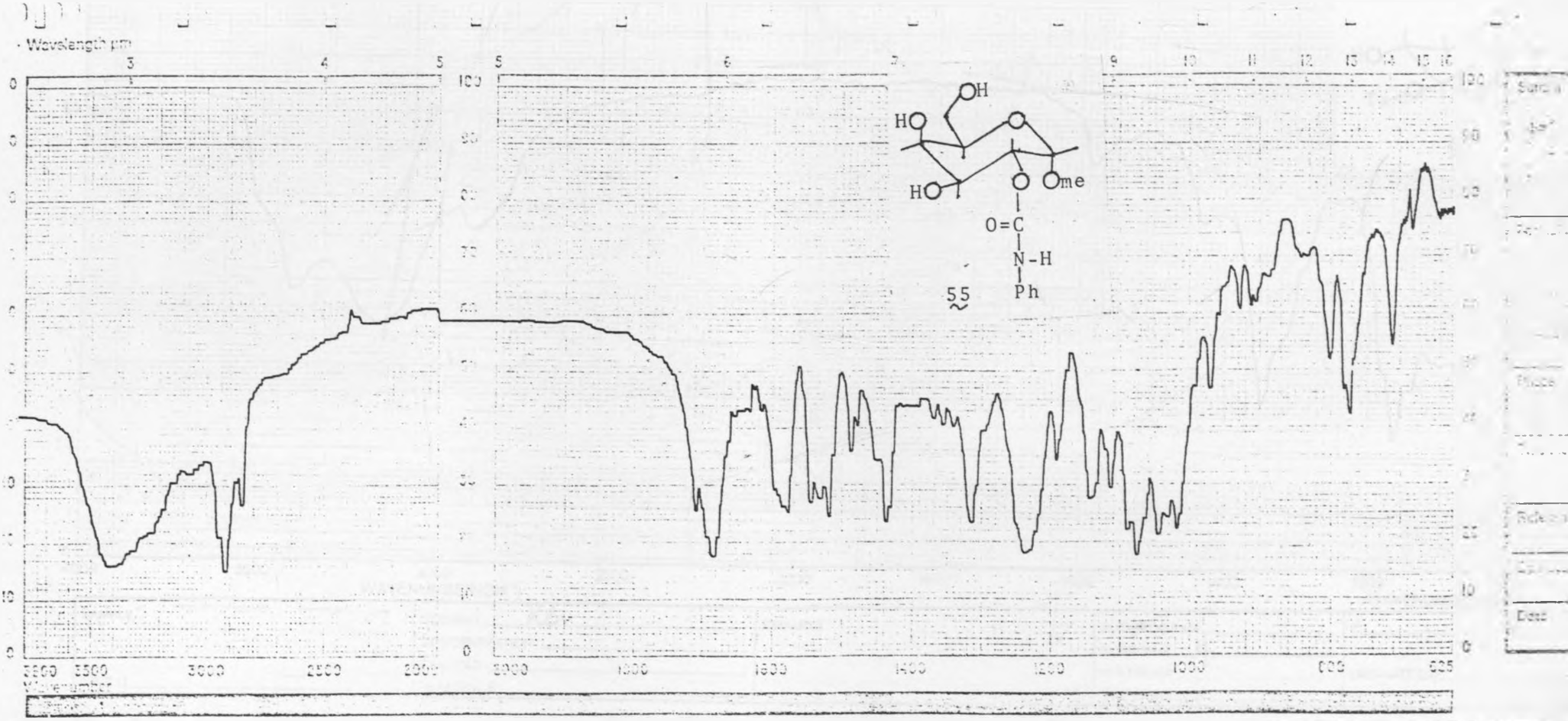
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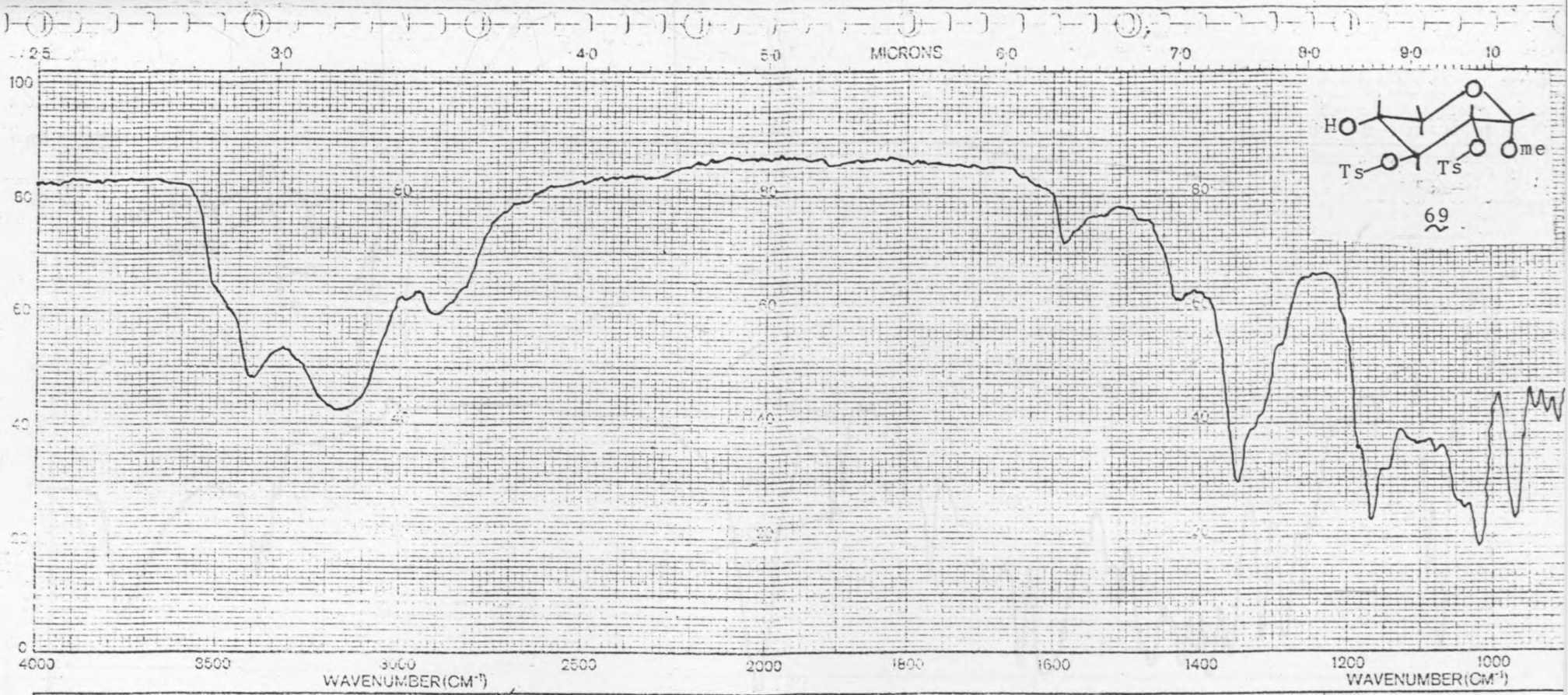

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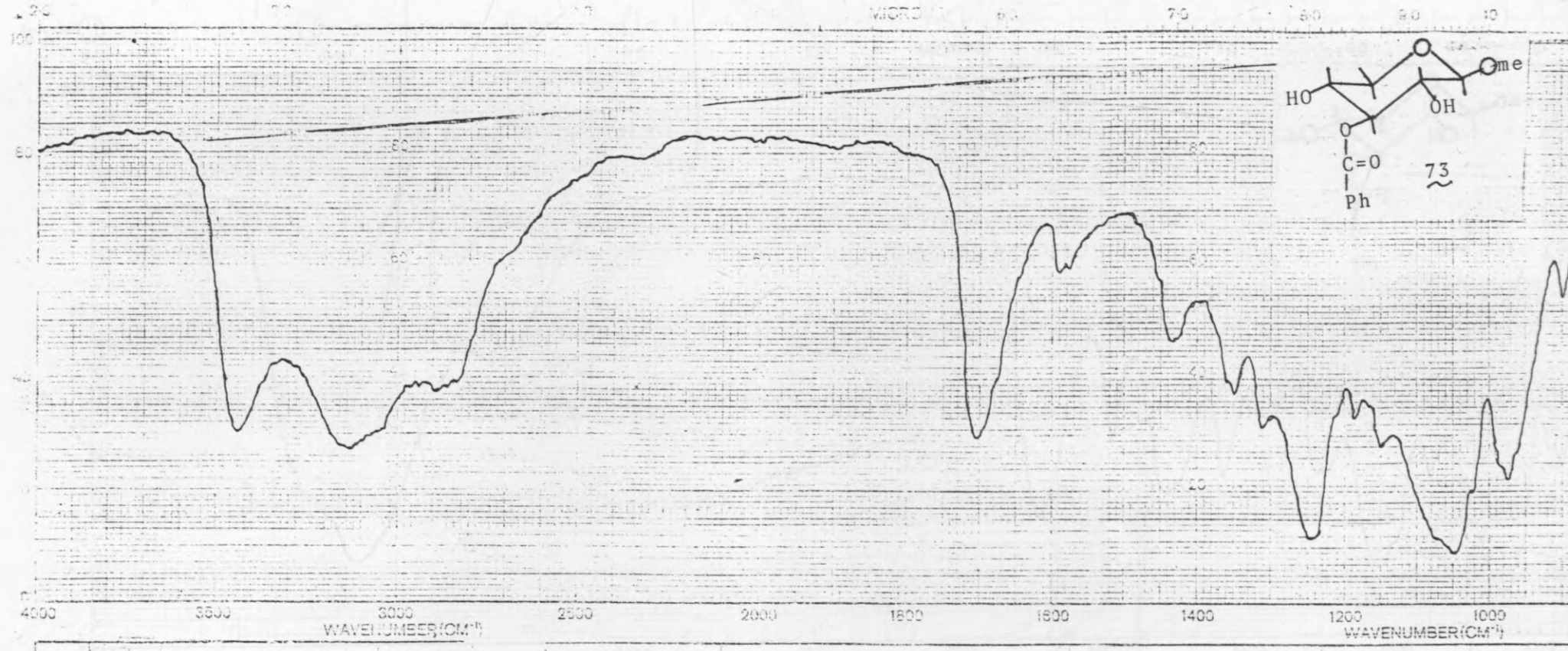

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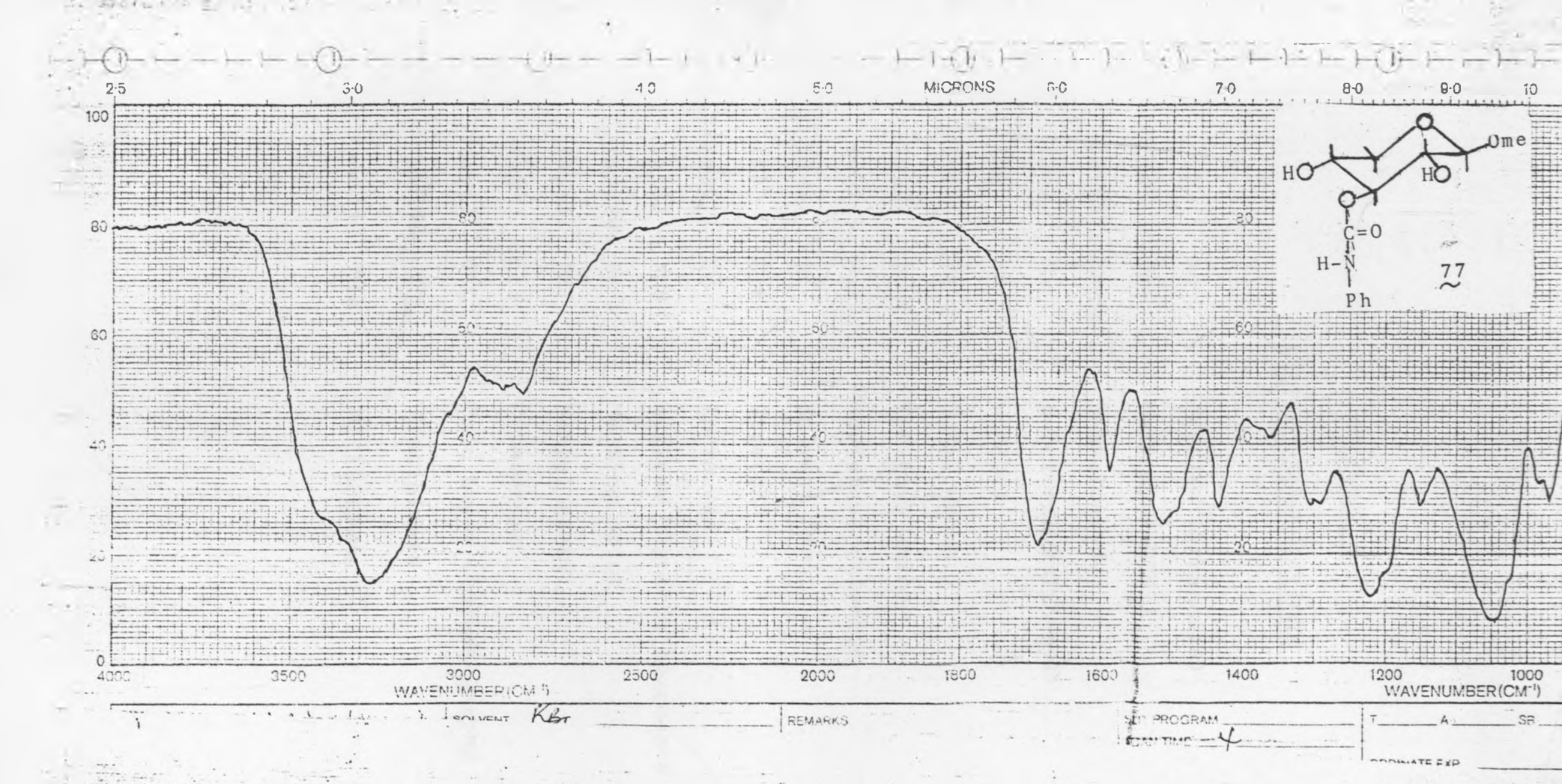
	CELL PATH		MULTIPLIER	ORDINATE EXP	
			TIME CONSTANT		


2·5
3·0
4·0
5·0
MICRONS
6·0
7·0
8·0
9·0
10
100
80
60
40
20
0
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
WAVENUMBER(CM⁻¹)
WAVENUMBER(CM⁻¹)
HO
HO
Ome
C=O
H-N
Ph
77
SOLVENT KBr
REMARKS

APPENDIX B

LIST OF ABBREVIATIONS

(i)	Ac	Acetate (Ethanoate)
(ii)	Ome	Methoxy ($-OCH_3$)
(iii)	phCHO	Benzaldehyde
(iv)	Ts	p-Toluene sulphonyl
(v)	BZ	Benzoyl
(vi)	Bu	Butyl group
(vii)	Et_3N	Triethyl amine
(viii)	MyCOCl	Myristoyl chloride
(ix)	SF	Solvent Front
(x)	Str	Stretch
(xi)	IR	Infra red
(xii)	NMR	Nuclear Magnetic Resonance
(xiii)	Mp	Melting point
(xiv)	Bn	Benzyl group
(xv)	Lit	Literature
(xvi)	TLC	Thin Layer Chromatography
(xvii)	PPt	Precipitate
(xviii)	Mls	Milliliters

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