CHAPTER 3

CONVENIENT PREPARATION OF GLYCOSYL BROMIDES

3.1. Introduction

Glycosyl halides are compounds in which the hydroxyl group at the reducing carbon atom of a sugar is replaced by a halogen. The poly-O-acyl-glycosyl halides are important intermediates in Koenigs-Knorr and related glycosidation reactions[61a,64]. Among the glycosyl halides, bromides are the most commonly used due to their reasonable stability and high reactivity. Most of the methods used for the preparation of glycosyl bromides are based on the replacement of an acetoxyl group at the reducing carbon atom by bromine. This can be achieved by treatment with liquid hydrogen bromide[65], hydrogen bromide in glacial acetic acid[66], anhydrous hydrogen bromide in ether[67] or by the recent approach using trimethylsilyl bromide[68]. The operations of acetylation and bromination can be done in a single step by the *in situ* generation of hydrogen bromide in the acetylation medium using red phosphorus and bromine[69]. In one instance, the replacement of 1-hydroxyl group by bromine has been achieved by treatment with triphenylphosphine and N-bromosuccinimide[70]. However, these methods are not always reliable, especially in cases where the sugar

derivative contains acid sensitive functional groups. Therefore, we have been interested in developing a simple and more efficient method for the preparation of glycosyl bromides containing sensitive functional groups.

Phosphorus containing reagents like triphenyl phosphite dibromide[71] and other dihalophosphoranes of this type have been extensively investigated as halogenating agents[72]. Of these, triphenyl phosphite dibromide has been used in carbohydrate chemistry for the replacement of hydroxyl group by bromine[73]. The mechanism of the reactions involving this reagent was studied by conductance measurements[72c]. Later this was reinvestigated with the help of ^{31}P NMR spectroscopy[74]. These studies showed that when one molar equivalent of bromine was added slowly to a chloroform solution of triphenyl phosphite, bromotetraphenoxy phosphorane and phosphorus tribromide were formed. The mechanism suggested involves a series of equilibria and is shown in Scheme 15.

$$(PhO)_3P + Br_2 \longrightarrow (PhO)_3PBr_2$$

$$(PhO)_3P + (PhO)_3PBr_2 \longrightarrow (PhO)_4PBr + (PhO)_2PBr$$

$$(PhO)_2PBr + (PhO)_3PBr_2 \longrightarrow (PhO)_4PBr + PhOPBr_2$$

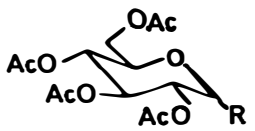
$$PhOPBr_2 + (PhO)_3PBr_2 \longrightarrow (PhO)_4PBr + PBr_3$$

Scheme 15

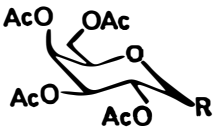
Recently, bromination of aliphatic alcohols bearing acid sensitive functional groups has been achieved using this reagent[75]. A survey of the literature revealed that this reagent has not been utilized for preparing glycosyl bromides. We, therefore, examined the conversion of 1-hydroxy sugars to glycosyl bromides using triphenyl phosphite dibromide.

3.2. Results and discussion

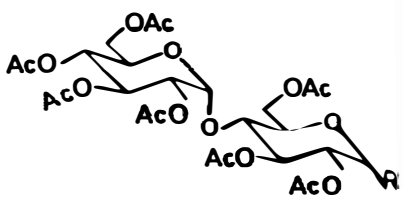
The peracetates (**82a-85a**) of D-glucose, D-galactose, maltose and lactose respectively, were prepared by the conventional procedure involving acetic anhydride in the presence of anhydrous sodium acetate or pyridine as the catalyst[76]. The 1-hydroxy derivatives **82b-85b** (Figure 10) were obtained from the corresponding peracetates by treatment with piperidine[77] in THF at ambient temperature. The products were obtained as mixture of anomers. These compounds were subjected to bromination using an equimolar mixture of triphenyl phosphite and bromine as described in the experimental section. In the presence of one equivalent of pyridine as the base, the reaction was quite rapid as shown in Table 17. The residue obtained after work-up was purified by flash column chromatography and the bromides were isolated in very good yields. The physical constants and NMR spectral data of all these compounds were in excellent agreement with the reported values[78-81].



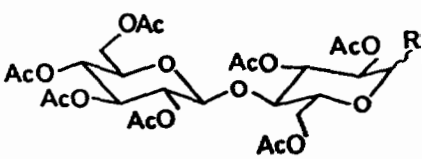
82a-82c



83a-83c



84a-84c



85a-85c

82a, 84a, 85a R = β-OAc

83a R = α-OAc

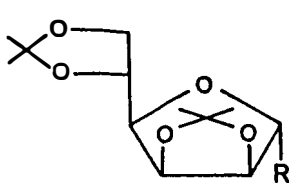
82b-85b R = OH

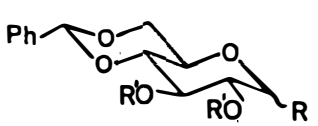
82c-85c R = α-Br

Figure 10

Since the reaction was quite facile with simple sugars, our investigations were extended to sugars containing sensitive functionalities

(Figure 11). Di-O-isopropylidene mannofuranose (**86a**) was prepared from D-mannose by treatment with acetone in the presence of sulphuric acid as the catalyst[82]. The reaction of **86a** with triphenyl phosphite dibromide proceeded smoothly as it was evident from TLC. But the yield of the product isolated after purification of the residue by flash column chromatography was only 50%. This may be attributed to the instability of the bromide. The ^{1}H NMR spectrum of the compound showed a singlet at δ 6.2 due to the anomeric proton. A doublet was observed at δ 5.03 corresponding to H2 and the rest of the ring protons appeared as a multiplet centered at δ 4.20. Resonances due to the isopropylidene protons (>C(C$\underline{H}_3$)$_2$) were observed as overlapping singlets around δ 1.30.





86a R = OH

86b R = Br

87a R = OH , R' = H

87b R = β - OAc , R' = Ac

87c R = OH , R' = Ac

87d R = α - Br , R' = Ac

Figure 11

Table 17 Preparation of glycosyl bromides using $(PhO)_3PBr_2$

Entry	Substrate	Reaction period (min)	Product	mp (°C)	[α]D (deg)	Yield (%)	Ref.
1	2,3,4,6-tetra-O-acetyl-D-gulcopyranose (**82b**)	5	**82c**	86-88	+140.8 (c 1.0, CH_2Cl_2)	89	78
2	2,3,4,6-tetra-O-acetyl-D-galactopyranose (**83b**)	10	**83c**	85	+140.0 (c 1.73, $CHCl_3$)	90	79
3	2,3,6;2',3',4',6'-hepta-O-acetyl maltose (**84b**)	45	**84c**	111	+172.4 (c 1.0, $CHCl_3$)	75	80
4	2,3,6;2',3',4',6'-hepta-O-acetyl lactose (**85b**)	60	**85c**	140	+116.4 (c 0.5, $CHCl_3$)	82	81
5	2,3;5,6-di-O-isopropylidene mannofuranose (**86a**)	5	**86b**	unstable	-	50	70
6	4,6-O-benzylidene-2,3-di-O-acetyl-D-glucopyranose (**87c**)	5	**87d**	121	+117.2 (c 0.1, CH_2Cl_2)	85	-

For the synthesis of 4,6-O-benzylidene-2,3-di-O-acetyl-D-gluco-pyranose (**87c**), D-glucose was converted to the 4,6-O-benzylidene derivative **87a** by treatment with benzaldehyde in the presence of anhydrous zinc chloride as the catalyst[63]. This partially protected sugar was acetylated using acetic anhydride-sodium acetate to get the triacetyl derivative **87b**, $[\alpha]_D$ -51.4° (c 0.32, CH_2Cl_2). The structure of the compound was confirmed by its ^1H NMR spectrum. It revealed a singlet at δ 7.3 due to the aromatic protons, and another singlet at δ 5.5 due to the benzylidene (>C<u>H</u>Ph) proton. Resonances due to the acetyl protons (-O-CO-C<u>H</u>$_3$) were visible at δ 2.0. The IR spectrum showed characteristic carbonyl absorptions at 1730 cm^{-1}. Treatment of **87b** with one equivalent of piperidine, in THF medium, resulted in the selective removal of the anomeric acetyl group to give the product **87c** in 92% yield, as a syrup. Bromination of this compound as in the previous cases furnished the α-bromo sugar **87d** as colourless needle shaped crystals (85%) after purification. Further recrystallization from hexane-ether mixture gave crystals with mp 121°C and $[\alpha]_D$ +117.2° (c 0.1, CH_2Cl_2). The structure of the compound was confirmed by its ^1H NMR spectrum which showed a doublet at δ 6.35 due to the anomeric proton with J = 4.4 Hz, establishing its β-configuration. The signal due to the benzylidene proton (>C<u>H</u>Ph) was visible at δ 5.2. The signals at δ 2.0 and 1.94 were attributed to the acetyl (-O-CO-C<u>H</u>$_3$) protons. Further, its IR spectrum showed carbonyl absorption at 1750 cm^{-1}.

These results clearly demonstrate that sugar derivatives can be converted to glycosyl bromides very conveniently and efficiently, using triphenyl phosphite dibromide.