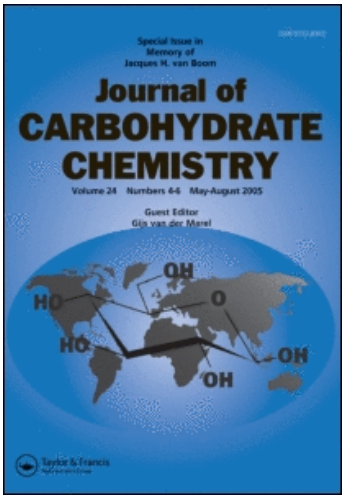

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COMMUNICATION

ACIDIC OPENING OF 4,6-*O*-ORTHOESTERS OF PYRANOSIDES.

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Acid-catalyzed opening of five-membered ring orthoesters of pyranosides are well explored and often used in synthetic pathways.[1] The opening gives the acyl group preferentially on the axial oxygen contrary to most other regioselective methods which give the equatorial ester.[2] Opening of six-membered ring orthoesters are much less investigated. We have made ortho-acetates and -benzoates of different 4,6-diols of glucose and galactose and studied their acid-catalyzed opening. These reactions each gave a high yield mixture of the respective 4- and 6-*O*-mono-esters. With the orthoacetates, the 6-*O*-acetyl derivatives were always in excess, and by treating the 4-*O*-acetyl compounds under conditions that gave base-catalyzed acetyl migration from O-4 to O-6, high overall yields of the 6-*O*-acetates were obtained. With the ortho-benzoates, the ratio between the two products was mainly determined by the protecting groups used at O-2 and -3.

The 4,6-*O*-orthoacetates were made from the 4,6-diols by treatment with trimethyl orthoacetate and a catalytic amount of *p*-toluenesulfonic acid in acetonitrile. The orthoesters were not isolated, but after concentration directly treated

Table 1. Formation and opening of orthoacetates of some pyranosides followed by base-catalyzed acetyl migration[e]

4,6-diol	Yield [a] (%)	Yield [b] (%)	mp[c] (°C)	$[\alpha]_D$[c] ($CHCl_3$)	mp, $[\alpha]_D$(Lit.)[c] (°C), ($CHCl_3$)
Methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside[6]	91	87	57-59	+10°	syrup, +18°[6]
Methyl 2,3-di-*O*-benzoyl-β-D-glucopyranoside[7]	79	76	91	+70°	-
Methyl 2,3-di-*O*-benzyl-β-D-galactopyranoside[6]	90	86	141-143	+8°	-
Methyl 2,3-di-*O*-benzyl-α-D-galactopyranoside[6]	98	90	54-57	+43°	139-141,+13°[6,f]
Methyl 2,3-di-*O*-benzoyl β-D-galactopyranoside[11]	92	87[d]	155-158	+79°	-

a. Total yield of monoacetates

b. Overall yield of 6- *O*-acetates after acetyl migration

c. Data for the 6 -*O*-acetates

d. Acid-catalyzed migration, base catalysis gave the 2-OH compound.[7]

e. Elemental analysis and NMR data for all new compounds were all in agreement with the postulated structure.

f. As can be seen from the data an anomeric mismatch has been made in the earlier publication

with 90 % aqueous trifluoroacetic acid in acetonitrile. This gave a high yield of a mixture of the 4- and 6-*O*-mono-acetates (Table 1). It was not possible to determine the initial ratio between the two products since the opening was immediately followed by acid-catalyzed acetyl migration. Quenching of the reaction after five minutes followed by rapid chromatographic separation on a short silica gel column gave first the pure 6-*O*-acetates in about 60% yield independent of the starting compound, and then the 4-*O*-acetates (22-39%). To increase the yield of the 6-*O*-acetates and make this reaction synthetically useful, the 4-*O*-acetates were dissolved in aqueous pyridine to allow

Table 2. Formation and opening of 4,6-O-orthobenzoates of some pyranosides[a]

4,6-diol		Yield (%)	mp (°C)	$[\alpha]_D$ ($CHCl_3$)	mp, $[\alpha]_D$(Lit.) (°C), ($CHCl_3$)
Methyl 2,3-di-O-benzyl-	4-OBz	60	syrup	-54°	-
α-D-glucopyranoside	6-OBz	22	syrup	+26°	75-77°C, +22°[8]
Methyl 2,3-di-O-benzyl-	4-OBz	67	syrup	-68°	-
β-D-glucopyranoside[9]	6-OBz	27	92-94	+7°	96-98, -9°[9]
Methyl 2,3-di-O-benzyl-	4-OBz	59	syrup	+33°	-
α-D-galactopyranoside	6-OBz	34	90	+83°	-
Methyl 2,3-di-O-benzyl-	4-OBz	48	syrup	+85°	-
β-D-galactopyranoside	6-OBz	32	126	-6°	-
Methyl 2,3-di-O-benzoyl-	4-OBz	34	142-143	+53°	140-142, +55°[10]
α-D-glucopyranoside[10]	6-OBz	55	145-146	+78°	126-133, +141°[10]
Methyl 2,3-di-O-benzoyl-	4-OBz	27	syrup	+47°	-
β-D-glucopyranoside	6-OBz	48	145-146	+71°	144-145, +82°[11]
Methyl 2,3-di-O-benzoyl-	4-OBz	36	151-153	+160°	91-92, +222°[12]
β-D-galactopyranoside	6-OBz	46	144-145	+52°	143-144, +56°[7]

a. Elemental analysis and NMR data for all new compoundsand for those whose data differs substantially from the literature values, were all in agreement with the postulated structure.

base-catalyzed acetyl migration to give about 90% extra of 6-O-acetate at equilibrium.[3] The time to reach the equilibrium was drastically diminished (from several hours down to about 15 minutes) if a catalytic amount of triethylamine was added. Altogether this reaction sequence represents a convenient and high-yielding method for regioselective acetylation of the primary hydroxyl groups in 4,6-diols of pyranosides (Table 1). If the separation of the two regioisomers is difficult, it can be of advantage to make the acetyl migration directly on the mixture of the 4- and 6-O-

Table 3. Opening of orthobenzoates of methyl 2,3-di-*O*-X-α-D-glucopyranoside[a]

X		Yield (%)	mp (°C)	$[\alpha]_D$ ($CHCl_3$)	mp, $[\alpha]_D$(Lit.) (°C), ($CHCl_3$)
p-methoxy-benzyl[b]	4-OBz	67	syrup	-65°	-
	6-OBz	23	syrup	+28°	-
p-nitro-benzyl[c]	4-OBz	66	syrup	-40°	-
	6-OBz	22	syrup	+52°	-
p-nitro-benzoyl[13]	4-OBz	30	syrup	-65°	-
	6-OBz	61	179-184	181°	-

a. Elemental analysis and NMR data for all new compounds were all in agreement with the postulated structure.

b. Syrup, $[\alpha]_D$= +8°

c. Syrup, $[\alpha]_D$= +58°

acetates before chromatography.[4] This works equally well, but diminishes the overall yield of the 6-*O*-acetate with about 10 % due to the equilibrium in the migration step.

The formation and opening of 4,6-*O*-orthobenzoates were performed in the same way as with the orthoacetates. Once more, a high yield of a mixture of the two possible benzoates was obtained (Table 2).

Since benzoates are less prone to undergo acyl migration than acetates,[2a] the ratio between the two products in these reactions should tell us more about the initial opening ratio. Also, experiments with pure 4-*O*-benzoate derivatives treated under the conditions used for the orthoester openings did not give any acyl migration. As can be seen from Table 2, different ratios of products were obtained from different diols. The effect of different configuration at C-1 (α - β) or at C-4 (glucose - galactose) was small and irregular, but the choice of protecting groups at O-2 and-3 played an important role. All derivatives with benzoates as protecting groups gave the 6-*O*-benzoate in excess, whereas those with benzyl groups gave predominantly the 4-*O*-benzoate (Table 2).

The opening to the 6-*O*-benzoate was found to be more sensitive to hydrolysis. Experiments performed under less controlled conditions giving more hydrolysis always lowered the yields of the 6-*O*-benzoyl compound (10-15%), while the yields of the 4-*O*-benzoyl derivative were constant within experimental error (< 4%).

To further investigate the role of the protecting groups in these openings, different substituents were introduced into the phenyl ring of the protecting groups. The *p*-nitro- and the *p*-methoxy-derivatives were chosen but no effect due to these substituents compared to the parent compounds could be noticed (Table 3, compare Table 2).

EXPERIMENTAL

General methods – These were the same as those earlier reported[5], except that the NMR-spectra were obtained with a JEOL GSX 270 spectrometer. All optical rotations were measured at room temperature.

General procedure for the formation of 6-O-acetates - The 4,6-diol (150 mg) and *p*-toluenesulfonic acid (15 mg) were dissolved in acetonitrile (15 mL) and trimethyl orthoacetate (150 μL) was added. After five min the mixture was concentrated and the residue dissolved in acetonitrile (15 mL), aqueous trifluoroacetic acid (90%, 150μL) was added and after five min dilution with toluene and concentration gave a residue that was purified on a silica gel column (75 g, toluene/ ethyl acetate,1:1) to give the 6-*O*-acetate and the 4-*O*-acetate. The 4-*O*-acetate was dissolved in pyridine:water and triethylamine (30μL) was added. When TLC showed no further acyl migration the mixture was concentrated and purified on a silica gel column to yield the 6-*O*-acetate.

General procedure for the formation and opening of 4,6-O-orthobenzoates - The 4,6-diol (150 mg) and *p*-toluenesulfonic acid (15 mg) were dissolved in acetonitrile (15 mL) and triethyl orthobenzoate (150μL) was added. After five min aqueous trifluoroacetic acid (90%, 150 μL) was added and after additional ten min dilution with toluene, concentration, and purification on a silica gel column (75 g , toluene/ ethylacetate, 3:1) yielded the 4-*O*-benzoate and the 6-*O*-benzoate.

Preparation of starting material - All the 4,6-diols were prepared by acid hydrolysis of the parent 4,6-*O*-benzylidene derivatives, which were made by standard procedures from the methyl glycosides.

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