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SYNTHESIS OF α- AND β-D-MANNOFURANOSIDES via 1-O-ALKYLATION [1]

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Abstract: *α- or, alternatively, β-glycoside and -disaccharide formation with 1-O-metalated mannofuranoses was performed via 1-O-alkylation with triflates. The high stereoselectivity observed is discussed in terms of intra- versus intermolecular complexation of the metal ion.*

Stereoselective formation of the glycosidic bond in disaccharide syntheses is generally achieved by nucleophilic displacement of a readily cleavable group at the anomeric center of the sugar [4]. The direct 1-O-alkylation of furanoses and pyranoses or corresponding metalated derivatives well known with methyl iodide and dimethyl sulfate [5], was recently exploited by us for the chemically and stereochemically highly selective synthesis of α- or β-disaccharides of ribofuranose and glucopyranose [2,3,6,7]. We report here on the development of methods for the highly stereoselective synthesis of α- or, alternatively, β-glycosides and -disaccharides of 2.3 : 5.6-di-O-isopropylidene-D-mannofuranose 1 (Scheme 1).

Specific intra- or intermolecular complexations in 1-O-metalated carbohydrate derivatives may be used in directing the stereoselectivity in 1-O-alkylation reactions. Structure 3 indicates, that the β-anion of 1 displays almost ideal crown ether geometry [8] thus favoring the β-configuration. In our view, this explains the preferred formation of methyl β-glycoside 6a from the sodium salt of 1 with excess methyl iodide in boiling benzene, whereas Kuhn-methylation (CH_3J, Ag_2O in DMF) delivers almost exclusively the α-derivative 5a [9]. Addition of equimolar amounts of NaH to 1 in THF as solvent easily generated the sodium salt of 1 for which we propose structure 3; it reacted with the triflates 4a-c already at or even below room temperature (4b at 10°C) in satisfactory rates with excellent stereochemical results. The β-glycosides 6a, b respectively the β-disaccharide 6c were obtained exclusively.

The importance of intra- versus intermolecular complexation of the metal ion for the stereochemical outcome under these reaction conditions was established by the addition of crown ether (CE). The stereochemistry of the reaction products was reversed. With the sodium salt of 1 and

Scheme 1

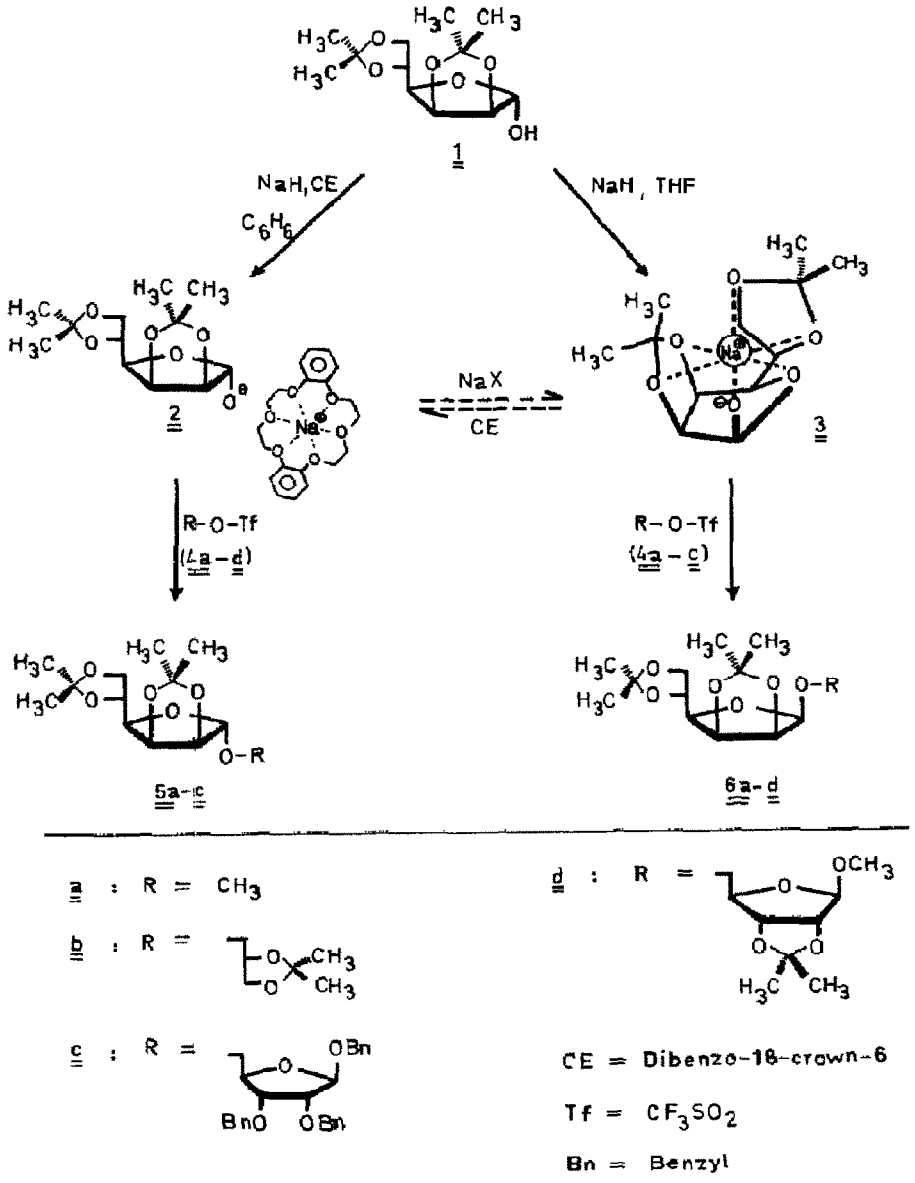
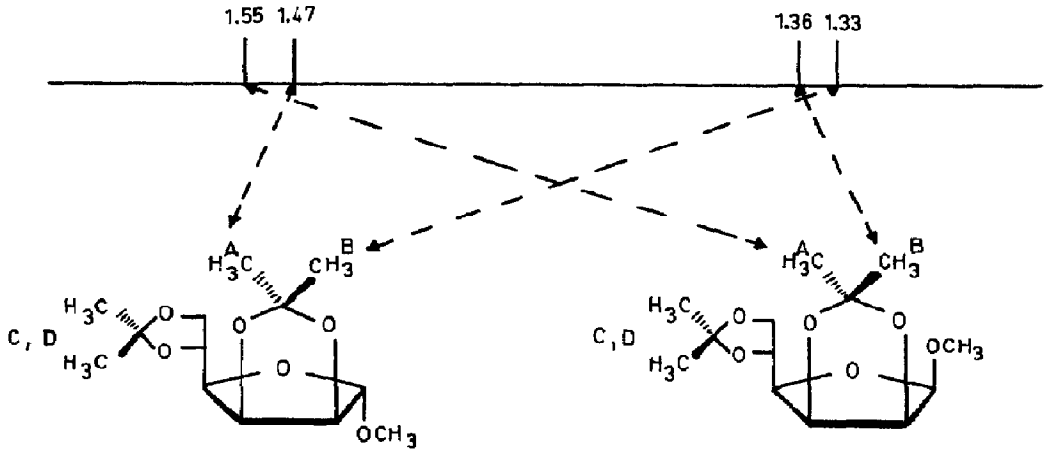


Table 1: Yields and optical rotations

	Yields [%] a)	$[\alpha]_{578}^{20}$ [°]		Yields [%] a)	$[\alpha]_{578}^{20}$ [°]
5a	66	+46.0 ($CHCl_3$, C=1.0)	6a	61	-56.0 ($CHCl_3$, C=1.0)
5b	48	+44.3 ($CHCl_3$, C=0.92)	6b	59	-18.4 ($CHCl_3$, C=0.79)
5c	68	+40.0 ($CHCl_3$, C=1.0)	6c	90	-16.6 ($CHCl_3$, C=1.0)
5d	72	+ 2.6 ($CHCl_3$, C=1.0)			

a) Isolated yields; all compounds gave correct elemental analyses.

Scheme 2: Chemical Shift of 2,3-O-Isopropylidene-α- and β-D-mannofuranosides



5a 6a

^{1}H-NMR Data of Compounds 1, 5a-d, 6a-c [a]

Compound	CH_3^A	CH_3^B	$\Delta\delta_{AB}$	CH_3^C [b]	CH_3^D [b]	$\Delta\delta_{CD}$	$J_{1,2}$ [Hz]
1	1.43	1.31	0.12	1.43	1.36	0.07	< 0.2
5a	1.47	1.33	0.14	1.46	1.39	0.07	< 0.2
5b	1.45	1.33	0.12	1.42	1.39	0.03	< 0.2
5c	1.42	1.28	0.14	1.45	1.37	0.08	< 0.2
5d	1.46	1.33	0.13	1.45	1.39	0.06	< 0.2
6a	1.55	1.36	0.19	1.45	1.38	0.07	3.5
6b	1.51	1.34	0.17	1.43	1.40	0.03	b)
6c	1.52	1.35	0.17	1.45	1.38	0.07	3.5

a) $CDCl_3$, internal TMS, δ-values

b) Not assigned

the triflates 4a-d in benzene as solvent and addition of equimolar amounts of dibenzo-18-crown-6 to the reaction mixture we obtained only the α-glycosides 5a-b and the α-disaccharides 5c,d. Therefore we assume that the intramolecularly stabilized α-anion 2 is formed exclusively. Alternatively, this anion reacts preferentially because of solvation and of steric reasons. The effect of metal ion complexation is substantiated by the addition of excess sodium salt to this reaction mixture; again β-glycosidation is favored.

^{1}H-NMR shift data of the 2.3-O-isopropylidene group and the couplings H-1/H-2 ($J_{1,2}$) of the D-mannofuranose are used for the configurational analysis (Scheme 2 and Table 2). The coupling constants $J_{1,2}$ of compounds 5a-d, 6a-c (Table 2) are in accordance with the values obtained for the corresponding methyl 2,3-O-isopropylidene-α- and β-D-lyxofuranosides [10]. Besides, the configuration of the anomeric center can also be derived unambiguously from the chemical shift data of the 2.3-O-isopropylidene group (Scheme 2, Table 2); this method was already applied successfully for O-glycosides of lyxofuranose [10] and ribofuranose [11,12]. The chemical shifts of the methyl groups of the β-anomers 6a-c are at lower field compared with the α-anomers 5a-d; this increased shift to lower field is most prominent for the methyl group with the strongest shift to lower field. Therefore the chemical shift difference for the methyl groups ($\Delta\delta_{AB}$) is always larger for the β-anomers 6a-c than for the α-anomers (5a-d) (Scheme 2, Table 2). This configurational assignment is confirmed by known physical data for 5a and 6a [9]. A similar configuration dependent chemical shift variation is not observed for the 5.6-O-isopropylidene group (see $\Delta\delta_{CD}$ in Table 2).

References and Footnotes

1) O-Alkylation at the anomeric center, part 2. Part 1, see ref. 6. — This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

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8) We are presently investigating the crown ether characteristics of 1 and derivatives: R.R. Schmidt and U. Moering, unpublished results.

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