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STEREOSELECTIVE GLYCOSIDATIONS OF URONIC ACIDS [1)]

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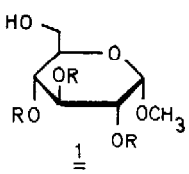
Abstract: *Stereoselective glycosidation and disaccharide formation of uronic acids were performed with silver perchlorate in acetonitrile. The course of the reaction is controlled by intermediate nitrilium acetonitrile conjugates, which are generated in situ.*

D-Glucuronic acid is a building unit of many naturally occurring glycosides and polysaccharides [3)]. However, the α-stereoselective formation of glycosides, di-, and trisaccharides from halogenoses of D-glucopyranuronic acid is not as thoroughly investigated [4,5)] as with D-glucopyranose [6)]. We report on a simple method to obtain the highly stereoselective α-linkage of D-glucopyranuronic acid.

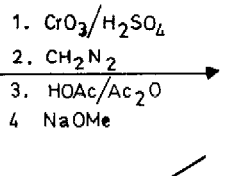
The glucose derivative 1 is conveniently transformed into 2,3,4-tri-O-benzyl-D-glucopyranuronic ester 2 [2,7)]. Treatment with phosphorous tribromide delivers exclusively the α-bromohalogenose 3; whereas reaction with thionyl chloride is dependent on the reaction conditions and leads either to the α-chlorohalogenose 4α or to a mixture of 4α and 4β; this mixture may be separated by crystallization from petroleum ether (b.p. 40-60°C)/benzene (Table 1).

Glycosidations of 3, 4α, and 4β with silver perchlorate in acetonitrile were independent of the starting material, evidencing the existence of a common intermediate, which was generated in situ prior to the addition of the hydrocyclic compound (see general procedure). The stereochemistry of the glycosidation product was highly influenced by the reaction temperature: with methanol the ratio of the anomeric glycosides 5α and 5β was 1:1 at room temperature; only 5α was formed in high chemical yield at -15°C. With 5-unprotected ribose and 2-unprotected arabinose, respectively the α-linked disaccharides 6α and 8α were obtained exclusively at -15°C. 6-Unprotected glucose delivered mainly the α-disaccharide 7α with minor amounts of 7β (α:β≈4:1) under these conditions Different results were obtained in other solvents [2)].

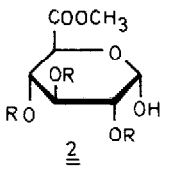
The stereochemical control of the reaction is not effected by neighbouring group participation of the carboxylic ester group [2)]. The common intermediate generated from 3, 4α, 4β exists according to ^{1}H-NMR-data in β-configuration (H-1: δ=6.30 ppm; $J_{1,2}$=8.0 Hz); the methyl ester group shows a normal chemical shift ($COOCH_3$: δ=3.68) and normal IR absorption (ν_{CO}=1748 cm^{-1}). A strong IR absorption at 1640 cm^{-1} is typical for nitrilium acetonitrile conjugates of structure 9 (spectroscopical data from CD_3CN solution); nitrilium salts and conjugates are known to be generated



1

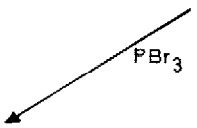


1. CrO_3/H_2SO_4
2. CH_2N_2
3. $HOAc/Ac_2O$
4. NaOMe

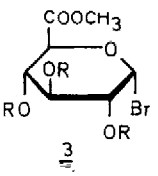


2

R = Benzyl



PBr_3



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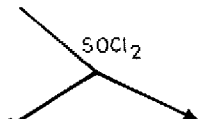
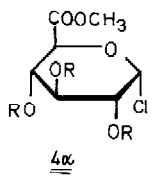
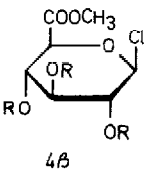


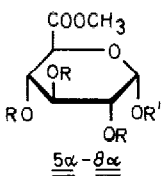
$SOCl_2$



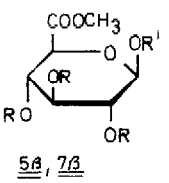
4α



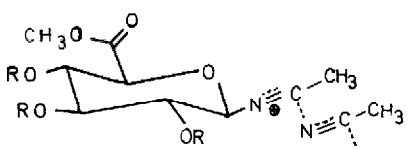
4β



5α - 8α

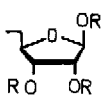


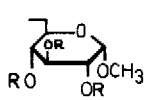
5β, 7β

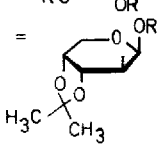


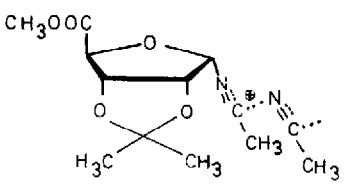
9

5 : R' = CH_3 $25^{\circ}C$: α:β = 1:1
$-15^{\circ}C$: α:β > 19:1 a)

6 : R' =  $-15^{\circ}C$: α:β > 19:1 a)

7 : R' =  $-15^{\circ}C$: α:β = 4:1

8 : R' =  $-15^{\circ}C$: α:β > 19:1 a)



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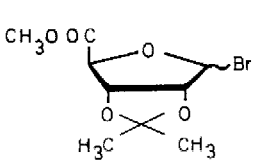
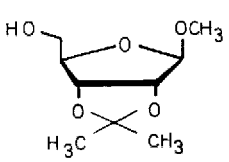


11α, β

+



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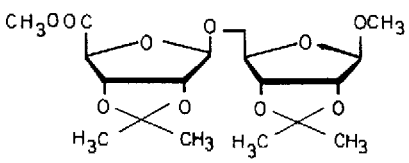

13β (α:β < 1:19)

a) The ß-anomer was not observed by ^{1}H-NMR or thinlayer chromatography.

under these reaction conditions [8]. The reverse anomeric effect [9] favours the β-anomer 9 over the corresponding α-anomer. 9 reacts with alcohols mainly or exclusively to α-glycosides and α-disaccharides presumably via an imidate ester derivative [10].

Table 1: Isolated Glycosides and Disaccharides [a]

Compound	Yield [%] [b]	^{1}H-NMR-data [c] H-1[d]	$J_{1,2}$ [Hz]	rotation $[\alpha]_{578}^{24}$	[°] [e]
2	53	5.15	3.0	8.4 [f]	(c=1.01)
3	77	6.33	4.0	96.4	(c=1.00)
4α	45 } 75	6.00	2.3	78.6	(c=1.00)
4β	30 }	5.25	8.0	9.4	(c=0.746)
5α	96	4.59	3.0	17.6	(c=0.967)
6α	56	4.61	2.8	8.6	(c=1.00)
7α	78	g)	g)	43.8	(c=1.00)
8α	76	5.00	3.0	-84.9	(c=1.10)
13β	80	5.20	0	-88.2	(c=1.06)

a) All compounds gave correct elemental analyses. b) Isolated yields. c) 80 MHz-spectra in $CDCl_3$, internal TMS. d) δ-values. e) In chloroform, f) Mutarotation: final value after 15 min. g) The values could not be obtained from the 80 MHz ^{1}H-NMR-spectrum.

With ribofuranuronic ester, the reverse anomeric effect favours the α-nitrilium derivative 10 [11], therefore the application of this method should lead to highly stereoselective β-glycosidation. As expected, the halogenose mixture 11α/β (α:β≈1:4) yielded exclusively the β-disaccharide 13β using 5-unprotected ribose 12 under identical reaction conditions.

Glycosidations under Koenigs-Knorr conditions [12] with soluble and insoluble catalysts occur frequently under intramolecular participation of substituents, however, α-bond formation with the solvent is usually not observed (well known exception: pyridine) [13,14]. Also, the solvent does not interfere with the stereochemical result in the reactions with silver perchlorate and diethyl ether as investigated by Igarashi et al. [6d,14]. The glycosidations of Schuerch et al. [15] with 1-desoxy-1-sulfonium, -1-ammonium, and 1-phosphonium sugars do not lead to high stereoselectivity in α-disaccharide formation. Possibly this new method for the stereoselective glycosidation and disaccharide formation of uronic acids via nitrilium-acetonitrile-conjugates may have general application [16].

General procedure: To halogenose 3, 4α, 4β, or 11α,β (1 mmole) in 20 ml acetonitrile was added anhydrous silver perchlorate (1.2 mmole) at -15°C. After 40 min the hydroxy compound (2.3 mmole) was added and the mixture stirred for 2 d (secondary hydroxy compounds: 4 d) at -15°C. The reaction mixture was neutralized with anhydrous sodium carbonate, the organic material separated with water/chloroform, the chloroform extract treated with anhydrous sodium sulfate and evaporated to dryness.

Chromatography on silica gel with chloroform/petroleum ether (b.p. 40-60°C)/diethylether = 20:6:1 yields 6α, 7α, 13β and with petroleum ether (b.p. 40-60°C)/ethyl acetate/benzene = 5:1:4 yields

8α. Silica gel filtration with toluene/acetone = 20:1 delivered 5α. Yields and physical data, see Table 1.

References and Footnotes

1) This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

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16) In recent glycosidations in THF/CH_2Cl_2 the observed stereoselectivity was ascribed to the intermediate formation of tetrahydrofuran onium compounds: G. Wulff, U. Schröder, J. Wichelhaus, Carbohydr.Res. 72, 280 (1979).

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