1. Introduction

Four major classes of macromolecules in biology are DNA, proteins, carbohydrates, and lipids. Among these, carbohydrates allow almost unlimited structural variations. Although carbohydrates can be present without being attached to other molecules, the majority of carbohydrates present in cells are attached to proteins or lipids and the terminology glycoprotein and glycolipid is used to reflect this. Glycoproteins (see Figure 1, 1A and 1B) and glycolipids are major components of the outer surface of mammalian cells. They are fundamental to many important biologically important processes including fertilization, immune defense, viral replication, parasitic infection, cell growth, cell-cell adhesion, degradation of blood clots, and inflammation.

At least in terms of simple tonnage, glycosyl transfer must be accounted one of the most important biochemical reactions. The reaction is formally a nucleophilic substitution at the saturated carbon of the anomeric center and can take place with either retention or inversion of the anomeric configuration. Enzymes whose physiological function is the transfer of glycosyl residues between two oxygen nucleophiles, a nitrogen and an oxygen nucleophile, and even two nitrogen nucleophiles or a nitrogen and a sulfur residue are known. (The natural occurrence of C-glycosyl derivatives also suggests the existence of enzymes that transfer glycosyl residues to carbon nucleophiles.) Enzymes transferring a glycosyl group to water are called glycoside-hydrolases or glycosidases. The realization that certain glycosidase inhibitors might have enormous therapeutic potential in many diseases or protective mechanisms by altering the glycosylation or catabolism of glycoproteins, or by blocking the recognition of specific sugars, has led to a tremendous interest in and demand of these molecules. The most obvious way for the construction of potential enzyme inhibitors is to synthesize derivatives of the substrate of the enzyme. In fact, several monosaccharide derivatives having different substituents at the
anomeric center have been found to inhibit glycosidases (cf. Chapter 3, mechanism-based inhibitors).

Carbohydrate–protein linkages can be imitated by a number of structures. In all these structures, the hydrolytically sensitive C–N or C–O bonds are substituted with stable C–C connections (Figure 1, 1C). A special class of the hybrids of carbohydrates and proteins are the anomeric α-amino acids in which the anomeric center of the sugar and the asymmetric carbon of the amino acid coincide (Figure 1, 1D, cf. Chapter 3.2.).

![Figure 1. Structural units of N- (1A) and O-glycoproteins (1B); C-glycosyl- (1C) and anomeric α-amino acids (1D)]
2. Literature Overview
2.1. Carbenium Ions
2.1.1. Appearance

Tricoordinated carbocations (carbenium ions) may appear as intermediates in transformations such as unimolecular nucleophilic substitutions (path C, Scheme 1), reactions of C=X double bonds with electrophiles (path B) or radicals (path A) provided that the initially formed radical can be oxidized. Path D (bimolecular nucleophilic substitution) represents a competitive route for path C especially in case of strong nucleophiles.

Scheme 1. Reactions involving carbocations as intermediates
2.1.2. Substituted Carbenium Ions: Stability and Reactivity

Variation of stability of carbocations depending on the substituents attached to the positively charged center has been a well-known phenomenon for a long time. According to the nature of the substituent, three main groups are considered. The first group contains the conjugating substituents (C-type), the second includes heteroatoms having lone pairs of electrons (X-type) and the third is the group of electron-withdrawing substituents (Z-type).¹

Conjugating substituents e.g. vinyl, phenyl etc. stabilize carbocations by the delocalization of their π-electrons (to some degree) towards the bond connecting them to the center of the carbenium ion.

### Table 1. Standard enthalpies of formation of substituted methyl cations

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>ΔHᵢ ((R₁R₂R₃C⁺)) [kcal/mol]</th>
<th>Hammett constant for R₁ ((σᵢ+σ_R))</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
<td>261²</td>
<td>0.00</td>
</tr>
<tr>
<td>CH₃</td>
<td>H</td>
<td>H</td>
<td>216</td>
<td>-0.10</td>
</tr>
<tr>
<td>CH₃</td>
<td>CH₃</td>
<td>H</td>
<td>192</td>
<td></td>
</tr>
<tr>
<td>CH₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td>166</td>
<td></td>
</tr>
<tr>
<td>OCH₃</td>
<td>H</td>
<td>H</td>
<td>157</td>
<td>-0.11</td>
</tr>
<tr>
<td>OH</td>
<td>H</td>
<td>H</td>
<td>168</td>
<td>-0.18</td>
</tr>
<tr>
<td>NH₂</td>
<td>H</td>
<td>H</td>
<td>178</td>
<td>-0.36</td>
</tr>
<tr>
<td>OCH₃</td>
<td>CH₃</td>
<td>H</td>
<td>132</td>
<td></td>
</tr>
<tr>
<td>OH</td>
<td>CH₃</td>
<td>H</td>
<td>139</td>
<td></td>
</tr>
<tr>
<td>OH</td>
<td>CH₃</td>
<td>CH₃</td>
<td>119</td>
<td></td>
</tr>
<tr>
<td>CN</td>
<td>H</td>
<td>H</td>
<td>291³</td>
<td>+0.70</td>
</tr>
<tr>
<td>COOR</td>
<td></td>
<td></td>
<td></td>
<td>+0.47</td>
</tr>
<tr>
<td>CONH₂</td>
<td></td>
<td></td>
<td></td>
<td>+0.33</td>
</tr>
</tbody>
</table>
Similarly, heteroatoms stabilize these intermediates by the delocalization of their lone pairs (see Figure 5, page 8). Alkyl groups constitute a special case of X-substitution stabilizing carbenium ions by hyperconjugation. Hyperconjugation is known to be the greatest in case of the methyl substituent.

The higher the number of the C- or X-substituents bound to the positively charged center, the greater is the stability of the carbocation. Standard enthalpies of formation of substituted methyl cations and Hammett substituent constants are collected in Table 1.

Stability of carbocations, however, can be modified in the other direction as well. Thus, appearance of an electron-withdrawing group (Z-type) on the positively charged atom draws along the destabilization of the carbocation (for a review of electronegatively substituted carbocations see ref 6). The evaluation of this effect e.g. by appearance energy measurements, however, is often interfered with the translocation of the positively charged center by means of a hydride shift or neighboring-group participation to reach a state of lower energy, making the characterization of high-energy carbocations extremely difficult. This kind of stabilization of formylmethyl (A), 1-methoxycarbonyl ethyl (B) and carboxamidomethyl (C) cations can be seen in Figure 2.

In case of the cyanomethyl cation, however, no possibility of such charge-translocation exists, thus its $\Delta H_f$ (291 kcal/mol) is determined to be much higher than that of the very unstable methyl cation (261 kcal/mol, Table 1).

On the contrary, the presence of similar stabilization of a carbocationic intermediate by the $\alpha$-CONMe$_2$ group (Figure 3, $X = \text{NMMe}_2$) during solvolyses of mesylates has been reported to be unimportant. They conclude, if carbonyl participation is not important in the “best case” amide systems, it is even more unlikely in the solvolysis of ketones and esters (Figure 3, $X = \text{alkyl, alkoxy}$).
Figure 2. Translocation of the positive charge in destabilized carbocations

Figure 3. Potential stabilization of carbenium ions by carbonyl participation
In the early 80’s, investigating the experimental and theoretical aspects of the interaction of the α-cyano group with carbenium ion centers, Gassman and coworkers proved that in systems lacking a mechanism for extensive charge delocalization into an attached carbon skeleton, conjugative stabilization of the incipient cation by the cyano group almost balances the rate-retarding inductive effect of this function. They arrived at this conclusion during the examination of the solvolytic reactions of various α-cyano substituted sulfonate esters, whose solvolysis rates in comparison with the unsubstituted ones (H/α-CN = (2.7 ± 0.8) x 10^3) were found to contradict the expectations (H/α-CN = 10^9…10^18) calculated from the known H/β-CN ratios (10^3…10^7) using standard extrapolations. (In case of extensive charge delocalization H/α-CN ≈ 10^6). Theoretical bond length and bond order calculations corroborated that α-cyano carbenium ions of general formula A (Figure 4) are significantly stabilized by charge delocalization through resonance structure B, even though this requires a portion of the charge to reside on a divalent nitrogen.

![Figure 4. Resonance structures of α-cyano carbenium ions](image-url)
2.1.3. Glycosylium Ions\textsuperscript{14}

Glycopyranosyl carbenium ions play an important role in the reactions of carbohydrates since their stability is in close relation to the reactivity of the anomeric center towards nucleophilic displacement reactions. The stability of these intermediates can be approximated by that of the tetrahydropyran-2-yl carbenium ions. The standard enthalpies of formation of cyclohexyl\textsuperscript{15} and tetrahydropyran-2-yl\textsuperscript{16} carbenium ions are 171 and 128 kcal/mol, respectively, the lower energy-level of the latter being attributed to the resonance stabilization by the oxygen atom (Figure 5, cf. Chapter 2.1.2.). This suggests that reactions having glycopyranosyl carbenium ion intermediates are also comparatively fast, though they may be somewhat slower than those having tetrahydropyran-2-yl intermediates due to the negative inductive effect of the OH (OR) groups of the sugar ring (cf. Chapter 2.2.).

\begin{center}
\includegraphics[width=0.5\textwidth]{figure5.png}
\end{center}

\textbf{Figure 5. Resonance stabilization of tetrahydropyran-2-yl carbenium ion}

The influence of the ring oxygen on reaction rates can also be demonstrated by an analogy with $\alpha$-chloro ethers. In a series of acyclic $\alpha$-chloro ethers, the presence of the oxygen atom is shown to result in a rate increase of $10^{14}$ for reactions involving an $S_N1$ mechanism and a $10^5$ for reactions involving an $S_N2$ mechanism.\textsuperscript{17}
2.1.4. Glycosyl Donors (Sources of Glycosylium Ions)

The activation of the anomeric hydroxyl group of sugar derivatives for nucleophilic displacement reactions can be achieved in three main ways.18

A.) In the Fischer-Helferich method the cleaving ability of the anomeric hydroxyl group is enhanced by a proton catalyst (Scheme 2, path A).

B.) In the Koenigs-Knorr method and its variants, the anomeric hydroxyl group is exchanged to a halide leaving-group, which is then activated by heavy metal salts. This general principle also includes the use of thioglycosides and 1,2-epoxides as glycosyl donors (Scheme 2, path B).

C.) The trichloroacetimidate method and other types of anomeric oxygen activation include the direct base-catalyzed activation of the anomeric oxygen with trichloroacetonitrile (and related compounds) yielding O-glycosyl trichloroacetimidates, which are highly reactive glycosyl donors under very mild acid-catalysis; and similar approaches via sulfonate, phosphate, acetate and orthoester formation, respectively (Scheme 2, path C).
Scheme 2. Activation of the anomeric hydroxyl group of sugar derivatives\textsuperscript{16}
2.2. Nucleophilic Displacement Reactions at the Anomeric Center of Monosaccharide Derivatives

The reactivity of the anomeric center towards nucleophilic substitution reactions depends mainly on the following factors.

A.) Anomeric configuration of the glycosyl donor

Dependence of the reactivity on the anomeric configuration of the glycosyl donor is well demonstrated, for instance, by the observation that the acetolysis of 3,4,6-tri-O-acetyl-β-D-glucopyranosyl chloride proceeds about 100 times faster than that of its α-anomer.\(^19\) Thus despite the fact that these compounds do not have a strongly participating group at C-2, there is a large rate difference which probably results from the higher initial-state free energy of the β-anomer explained by the operation of the anomeric effect. The same tendency can be observed in the acid-catalyzed hydrolysis of methyl glycosides.\(^{20,21}\)

B.) Adjacent Substituents

The variation of the rate of acid-catalyzed hydrolysis of C-2 substituted methyl glucopyranosides\(^{22-24}\) (Figure 6) suggests that electronic factors at C-2 influence the reactivity of the anomeric center in reactions having similar intermediates, especially unimolecular (cf. Chapter 2.2.1.) nucleophilic displacement reactions, in a great measure.

Quantitative measurements of the anomerization rate of glucopyranosyl halides showed that in general O-acyl protecting groups reduce reactivity at the anomeric center while O-alkyl groups increase it. It depends both on the position of the substituents and on their number.

In his research on pentenyl glycosides, Fraser-Reid later named these two groups of protected glycosyl donors as “disarmed” and
“armed” respectively, however he explains the difference merely in terms of C-2 substituents. Pentenyl glycosides having electron withdrawing acyloxy or halo substituent at C-2 are inert as glycosylating agents (“disarmed”) in comparison with those bearing electron donating alkoxy group at the same position (“armed”). 2-Deoxy derivatives have similar reactivity to the latter group thus they are put among them.

Similar observations were made concerning thioglycosides.

Regarding their mechanisms, the most deeply investigated nucleophilic displacement reactions occurring at the anomeric center of monosaccharide derivatives are the

1.) acid-catalyzed hydrolysis of glycosides, the
2.) nucleophilic displacement reactions of glycosyl halides, and the
3.) anomerization of sugar acetates.

These reactions are extensively reviewed by Capon, who tried to digest an immense number of experimental observations and mechanistic proposals to be able to display a unified approach of reactivity and intermediates.

![Figure 6. Rate of acid-catalyzed hydrolysis of C-2 substituted methyl glucopyranosides](image)

<table>
<thead>
<tr>
<th>R</th>
<th>v_rel</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>1480</td>
</tr>
<tr>
<td>OH</td>
<td>0.708</td>
</tr>
<tr>
<td>NH₃⁺</td>
<td>0.005</td>
</tr>
<tr>
<td>NHCOCH₃</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Figure 6. Rate of acid-catalyzed hydrolysis of C-2 substituted methyl glucopyranosides
Since the reactions which are investigated and discussed in this dissertation are carried out with acetylated sugars this chapter deals mainly with acylated carbohydrate derivatives as well.

2.2.1. Unimolecular Reactions

Reactions at the anomeric center of acylated sugar derivatives proceeding by an S_N1 mechanism may be divided into two classes.

a.) Those going through an „open-ion“ intermediate (e.g. 3A, Figure 7), with no neighboring-group effect; and

b.) those with a „closed-ion“ intermediate (e.g. 3B) and with neighboring-group participation.

![Figure 7. Carbocationic intermediates at the anomeric center](image)

When the leaving group at C-1 and the participating neighboring-group at C-2 are in *trans* relation, there is a possibility of anchimeric assistance i.e. the reaction can go through a „closed-ion“ intermediate like 3B (e.g. reactions of 1,2-*trans* glycopyranosyl chlorides with nucleophiles, anomerization of 1,2-*trans*-glycopyranosyl acetates etc.). If the concentration or the nucleophilicity of the reacting nucleophile is low the initially formed intermediate 3A can be transformed to the „closed-ion“ 3B, thus the product will adopt 1,2-*trans* stereochemistry.
Chapman and Laird suggested that intermediate 3A is stabilized by the delocalization of the charge in an orbital formed by overlap of the vacant p orbital of the sp²-hybridized C-1 with a p orbital of the ring oxygen (cf. Figure 5). This stabilization is maximized by a coplanar arrangement of C-5, O-5, C-1 and C-2, thus reactions of type (a) are considered to go through an intermediate having a half-chair conformation (4B, Scheme 3). The transition of the chair to the half-chair conformation is hindered by the increased opposition of the equatorial substituents on C-2 relative to C-3 and on C-5 relative to C-4 (4B, Scheme 3). The larger the substituent, the greater the hindrance to the formation of the half-chair ion. This conclusion is in agreement with the order of stability of glycosides against acid-catalyzed hydrolysis, which is known to be heptopyranosides > hexopyranosides > 6-deoxy hexopyranosides > pentopyranosides.

Scheme 3. Conversion of the chair to the half-chair conformation of the sugar ring during the acid-catalyzed hydrolysis of glycosides

At the same time, the conversion of the chair to the half-chair conformation is assisted by the recession of the C-2 and C-5 axial substituents away from the C-4 and C-3 axial substituents, respectively (Scheme 3). This effect will be more powerful as the size of these axial substituents increases. Consequently, on comparing methyl D-hexopyranosides which differ only at C-2, C-3 and C-4, it can be
predicted that the order of reactivity, concerning the acid-catalyzed hydrolysis, will be D-idose > D-altrose, D-gulose > D-allose, D-mannose, D-galactose > D-glucose. This sequence agrees well with that found experimentally.\(^{21}\) The same sequence of reactivity has been established in case of the solvolysis of per-O-acetyl-D-glycopyranosyl halides\(^{29-31}\) and of the anomerization of per-O-acetyl-D-glycopyranosyl acetates.\(^{32}\)

The ratios of the rate of solvolysis (in 75 % aqueous acetone and in methanol) of the 1,2-trans-glycopyranosyl halides to those of the corresponding 1,2-cis-halides vary from 20 (\(\delta\Delta G^\ddagger \approx 2\) kcal/mol) for the \(\alpha\)-L-rhamnosyl – 6-deoxy-\(\alpha\)-D-glucosyl pair (A, Figure 8) at 22 °C to 100,000 (\(\delta\Delta G^\ddagger \approx 5\) kcal/mol) for the \(\beta\)-D-glucosyl – \(\alpha\)-D-glucosyl pair (B, Figure 8) at 31.9 °C.\(^{31}\) Since at least 1.5 – 2 kcal/mol of this 5 kcal/mol difference of the free energy of activation is attributable to the difference in free energies of the initial states (cf. Chapter 2.2. A.), the effect of the anchimeric assistance is estimated to about 3 – 3.5 kcal/mol in this case.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure8.png}
\caption{Relative rate of solvolysis of pairs of 1,2-trans and 1,2-cis glycopyranosyl halides}
\end{figure}
Experimental observations show that the effect of variation in the solvent polarity on solvolysis rate is much less for the per-O-acetylated 1,2-trans-glycopyranosyl halides than for the corresponding 1,2-cis-halides. This is consistent with the fact that 1,2-trans-halides undergo solvolysis with neighboring-group participation by the acetoxy group at C-2, where the intermediate carbocation (similar to 3B, Figure 7) and most probably the transition state as well possess the charge in a more dispersed state than intermediate 3A and the transition state of the reaction pathway with no neighboring-group effect.

In order to avoid the complications introduced by a strongly participating group at C-2, Rhind-Tutt and Vernon\textsuperscript{33} studied the methanolysis of tetra-O-methyl-α-D-mannopyranosyl (5A, Scheme 4) and glucopyranosyl chlorides (5F). Since addition of sodium methoxide produced only small increases in rate, they concluded that the mechanism is S\textsubscript{N}1. The glucosyl chloride yielded 94 % ratio of the corresponding β-methyl glycoside (5I), but the mannosyl analog gave only 58 % ratio of the inversion product (5D) the rest being formed by retention of configuration (5E). It was suggested that the products were formed from a specifically oriented ion pair (5B for mannose, 5G for glucose) in which attack from the α-side was prevented by the chloride counterion. With the mannosyl chloride, however, it was also considered that the rate of attack of methanol on the ion pair is reduced by the steric effect of the quasiaxial methoxy group at C-2 therefore much more of the product was formed from the free ion (5C) in which approach from the α-side is possible.

Other nucleophilic displacement reactions at the anomeric center involving ion pair intermediates are: the anomerization of per-O-acetyl-D-glycopyranosyl acetates,\textsuperscript{27} the hydrolysis of per-O-acetyl-D-glycopyranosyl bromides\textsuperscript{31} and the alcoholysis of per-O-acetyl-D-glycopyranosyl bromides by primary alcohols.\textsuperscript{34} Even tetra-O-acetyl-β-D-
glucopyranosyl chloride, when subjected to methanolysis, despite the presence of the neighboring acetoxy group, yields $\alpha$-glycoside lending credit to the existence of an ion pair intermediate.$^{35}$

Scheme 4. Nucleophilic displacement reaction at the anomeric center involving an ion pair intermediate

2.2.2. Bimolecular Reactions

Differentiation between bimolecular reactions and unimolecular reactions involving an ion pair intermediate might not be very easy.

The following reactions, however, exhibit either second-order kinetics and/or a comparatively great negative value of entropy of activation and thus are considered as bimolecular reactions: alcoholysis of tetra-O-acetyl-$\alpha$-D-glucopyranosyl bromide in 2-propanol or cyclohexanol,$^{34}$ reactions of O-acetylglycosyl bromides with secondary amines in acetone$^{28}$, reactions of O-acetylglycosyl bromides with lithium thiophenoxide in 1-pentanol–toluene mixture (19:1 v/v).$^{31}$

Some important glycosylation reactions can also be counted among the members of this group. These reactions include the *in situ*
anomerization procedure, which permits the synthesis of α-linked oligosaccharides in the D-gluco and D-galacto series; the heterogeneous catalyst procedure, by which β-glycosidic linkages can be introduced in the D-manno series and a number of other glycosylation reactions conducted in solvents of low polarity and/or at low temperature like the trichloroacetimidate method using BF$_3$·OEt$_2$ at very low temperatures.

2.2.3. Displacements in C-1 Substituted Pyranoid Sugars

Since the circle of the investigated reactions of this dissertation covers mainly nucleophilic substitutions in C-1 substituted pyranoid sugars it is reasonable to look at the results of similar reactions published so far omitting the reactions of ketoses (C-1 substituent = oxyalkyl), C-1-halo substituted sugar derivatives and 2-deoxy derivatives (KDO and NANA derivatives and similar molecules) because of their different reactivity. Because of the decreased stability of the C-1 substituted glycosylium ions, these reactions, especially in case of cyano substitution, rarely follow an S$_N$1 pathway, instead, furnish the inversion product (Table 2).
<table>
<thead>
<tr>
<th>Starting Sugar</th>
<th>Reaction Conditions</th>
<th>Product(s)</th>
<th>Stereochemistry</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Sugar Structure]</td>
<td>AcOH, Ac₂O AgOAc/Hg(OAc)₂ reflux, 4-8 h</td>
<td>![Product Structure]</td>
<td>inversion</td>
<td>38</td>
</tr>
<tr>
<td>![Sugar Structure]</td>
<td>o-amino-thiophenolate, EtOH</td>
<td>![Product Structure]</td>
<td>inversion</td>
<td>39</td>
</tr>
<tr>
<td>![Sugar Structure]</td>
<td>HS(CH₂)₂NH₂ EtOH</td>
<td>![Product Structure]</td>
<td>inversion</td>
<td>39</td>
</tr>
<tr>
<td>![Sugar Structure]</td>
<td>Bu₄NBr, CCl₄ reflux</td>
<td>![Product Structure] + ![Product Structure]</td>
<td>anomeriz.</td>
<td>40</td>
</tr>
<tr>
<td>![Sugar Structure]</td>
<td>NaN₃, DMSO, r.t.</td>
<td>![Product Structure]</td>
<td>inversion</td>
<td>41</td>
</tr>
<tr>
<td>![Sugar Structure]</td>
<td>NaN₃, DMSO, r.t.</td>
<td>![Product Structure]</td>
<td>inversion</td>
<td>41</td>
</tr>
</tbody>
</table>

Table 2. Nucleophilic displacement reactions at the anomeric center of C-1 substituted pyranoid sugars
<table>
<thead>
<tr>
<th>Starting Sugar</th>
<th>Reaction Conditions</th>
<th>Product(s)</th>
<th>Stereochemistry</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Sugar" /></td>
<td>LiCl, DMSO, r.t.</td>
<td><img src="image2" alt="Product" /></td>
<td>inversion + anomeriz.</td>
<td>41</td>
</tr>
<tr>
<td><img src="image3" alt="Sugar" /></td>
<td>KSCN, CH₃NO₂ 90 °C</td>
<td><img src="image4" alt="Product" /></td>
<td>inversion + anomeriz.</td>
<td>42</td>
</tr>
<tr>
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<td>NaN₃, DMSO, r.t.</td>
<td><img src="image6" alt="Product" /></td>
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<td>41</td>
</tr>
<tr>
<td><img src="image7" alt="Sugar" /></td>
<td>AgOCN, CH₃NO₂ 80 °C</td>
<td><img src="image8" alt="Product" /></td>
<td>retention</td>
<td>43, 44</td>
</tr>
<tr>
<td><img src="image9" alt="Sugar" /></td>
<td>KSCN, CH₃NO₂ 80 °C</td>
<td><img src="image10" alt="Product" /></td>
<td>inversion</td>
<td>43, 44</td>
</tr>
</tbody>
</table>

**Table 2.** Nucleophilic displacement reactions at the anomeric center of C-1 substituted pyranoid sugars (continuation)
2.3. Literature Precedents of the Investigated Reactions

2.3.1. Synthesis of Glycosyl Fluorides

Numerous different reactions have been developed for the synthesis of glycosyl fluoride derivatives starting from several precursors including hemiacetals, glycosyl halides, glycosyl esters, O- and S-glycosides, 1,2-anhydrosugars and glycals; with the application of various fluoride sources such as anhydrous liquid hydrogen fluoride, its solution in pyridine, silver fluoride, silver tetrafluoroborate, tetrabutylammonium fluoride, zinc fluoride (with or without 2,2'-bipyridyl), DAST, 2-fluoro-1-methyl-pyridinium tosylium, iodosotoluol difluoride and 1-aminonito-1,1,2,3,3,3-hexafluoropropane. For reviews of this topic see refs 45-48.

One of the most frequently used glycosyl fluoride syntheses is the Helferich procedure, which involves the reaction of protected glycosyl halides with silver fluoride in anhydrous acetonitrile. Some Helferich-type fluorination reactions are summarized in Table 3. The reaction seems to follow an SN2-type mechanism (maybe with an ion pair intermediate) since the product is always inverted (also with non-participating group at C-2), except with mannose derivatives, whose reactions are admittedly facilitated by neighboring-group participation and yield products of 1,2-trans stereochemistry. These considerations can equally be applied when an SN1 path with solvent participation, with the intermediacy of N-(α-D-glycopyranosyl) acetonitrilium ion, is hypothesized.
<table>
<thead>
<tr>
<th>Starting Sugar</th>
<th>Product</th>
<th>Yield</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Sugar 1" /></td>
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<td>inversion 54 %</td>
<td>49</td>
</tr>
<tr>
<td><img src="image3" alt="Sugar 2" /></td>
<td><img src="image4" alt="Product 2" /></td>
<td>inversion 62 %</td>
<td>50</td>
</tr>
<tr>
<td><img src="image5" alt="Sugar 3" /></td>
<td><img src="image6" alt="Product 3" /></td>
<td>retention sole product as judged by $^{19}$F NMR</td>
<td>50</td>
</tr>
<tr>
<td><img src="image7" alt="Sugar 4" /></td>
<td><img src="image8" alt="Product 4" /></td>
<td>inversion not given</td>
<td>51</td>
</tr>
<tr>
<td><img src="image9" alt="Sugar 5" /></td>
<td><img src="image10" alt="Product 5" /></td>
<td>inversion 73 %</td>
<td>52</td>
</tr>
<tr>
<td><img src="image11" alt="Sugar 6" /></td>
<td><img src="image12" alt="Product 6" /></td>
<td>inversion &gt;75 %</td>
<td>53</td>
</tr>
<tr>
<td><img src="image13" alt="Sugar 7" /></td>
<td><img src="image14" alt="Product 7" /></td>
<td>inversion 69 %</td>
<td>54</td>
</tr>
<tr>
<td><img src="image15" alt="Sugar 8" /></td>
<td><img src="image16" alt="Product 8" /></td>
<td>inversion 77 %</td>
<td>55</td>
</tr>
<tr>
<td><img src="image17" alt="Sugar 9" /></td>
<td><img src="image18" alt="Product 9" /></td>
<td>inversion 82 %</td>
<td>56</td>
</tr>
<tr>
<td><img src="image19" alt="Sugar 10" /></td>
<td><img src="image20" alt="Product 10" /></td>
<td>inversion 61-66 %</td>
<td>57</td>
</tr>
<tr>
<td><img src="image21" alt="Sugar 11" /></td>
<td><img src="image22" alt="Product 11" /></td>
<td>inversion 70 %</td>
<td>58</td>
</tr>
</tbody>
</table>

Table 3. Reactions of some glycopyranosyl halides with silver fluoride in anhydrous acetonitrile
2.3.2. Reactions Having \(N\)-Glycosyl Nitrilium Ion Intermediates

The process now known as the Ritter-reaction was first described in detail in two papers\(^{59,60}\) published in 1948 (for reviews about the Ritter-reaction see refs 61,62). Strongly acidic conditions were used to generate a carbenium ion which underwent nucleophilic attack by a nitrile, and further events led to the \(N\)-substituted amide (Scheme 5).

\[
\begin{align*}
\text{C-} & \text{OH} \\
\text{H}^+ & \text{H}_2\text{O} \\
\text{RCN} & \\
\text{C} & \text{N=}=\text{C} \quad \text{R} \\
\text{H}_2\text{O} & \\
\text{C} & \text{N} \quad \text{C} \quad \text{R} \\
\text{OH} & \\
\end{align*}
\]

Scheme 5. Mechanism of the Ritter reaction

In the carbohydrate field the interaction between acetonitrile, when used as a solvent, and glycosyl oxocarbenium ions formed from different glycosyl donors has first been observed in the late 70’s and early 80’s.\(^{63-66}\) The anomeric configuration of the intermediate glycosyl nitrilium ion, however, was in discordance of opinions of two parties. Pavia et al.\(^{63}\) and Lemieux and Ratcliffe\(^{64}\) favored \(\alpha\)-ions (6\(\alpha\), Figure 9), Sinaÿ and Pougny\(^{65}\) and Schmidt and Rücker\(^ {66}\) have advocated the \(\beta\)-counterpart (6\(\beta\)), because of the so-called reverse anomeric effect\(^ {67}\). Fraser-Reid seemed to choke off the discussion by proving that the anomeric
configuration of the product obtained by Sinaÿ and Pougny was the opposite, and suggesting that the stereochemistry of the reaction of Schmidt and Rücker was controlled by neighboring-group participation instead of glycosyl nitrilium ion intermediates.68

Schmidt still in his recent reviews,37,69 however, makes a stand for the β-nitrilium ions, moreover, he gives the appropriate conditions towards both anomeric nitrilium ion intermediates and a unified approach of glycosylation reaction courses in nitrile- and ether-type solvents, especially for trichloroacetimidate donors (Scheme 6).

![Figure 9. D-Glycopyranosyl nitrilium ion intermediates](image)

In his opinion, the highly α-selective glycosylation with the glycosyl halides of D-glucuronic acid in acetonitrile at −15 °C should be attributed to the sequence of addition of the reagents i.e. addition of catalyst (AgClO₄) prior to the acceptor.66 If it is not so, the fast kinetic α-nitrilium–nitrile conjugate formation providing the β-product precedes formation of the thermodynamically more stable β-nitrilium–nitrile conjugate. Numerous excellent examples of β-selective glycosylations utilizing the intermediacy of α-nitrilium–nitrile conjugates can be found in the two reviews of Schmidt mentioned above, but only two for α-selective ones (including the one mentioned above). Though the presence and the anomeric configuration of β-nitrilium–nitrile conjugates have been
Scheme 6. Glycosylation reaction courses
proved by experimental data\textsuperscript{66} (IR and \textsuperscript{1}H NMR spectroscopy), the question has to be brought on: Why is it so extremely rarely applied?

The \textit{N}-glycosyl nitrilium ion mediated reactions can be classified according to the fate of the nitrilium ion or in other words the character and stereochemistry of the reaction products as follows:

A.) the nitrilium ion reacts with a nucleophile and the nitrile acts as a leaving group (path A, Scheme 7; \textit{β}-selective glycosylation, see above); or

B.) an external nucleophile (mainly water or a carboxylic acid) adds to the carbon atom of the nitrilium ion (path B), the product is an amide in case of water, and a diacyl amide with carboxylic acids; the anomeric configuration of the \textit{N}-glycosyl nitrilium ion can be \textit{α} (no neighboring-group participation)\textsuperscript{64,65,68,70-74} or \textit{β} (neighboring-group participation);\textsuperscript{74-76} or

C.) an intramolecular nucleophilic addition occurs leading to a cyclic product that sometimes opens up to furnish the end-product (path C).\textsuperscript{63,77-80}
Scheme 7. N-Glycosyl nitrilium ion mediated reactions
2.3.3. Transition Metal-Promoted Free-Radical Reactions

Transition metal-promoted generation of C-centered radicals may be started
(a) by an oxidative process, and
(b) a reductive process.

The oxidative method has found numerous applications in the synthesis of a variety of organic molecules. The most frequently employed transition metals are titanium, vanadium, manganese, iron, cobalt, copper and cerium. The radical precursors are mostly enolizable carbonyl compounds (active methylene compounds), enol ethers (especially silyl enol ethers), enolates, enamines, diazo- and azido compounds, organolithium compounds and other carbanionic molecules, organotin compounds and Fischer carbenes. There are some special, but very useful couplings such as the oxidative coupling of aromatic rings, and of allylic and benzylic silanes as well as fragmentations such as the oxidative fragmentation of strained carbocycles.

Very frequently, the fate of a carbon-centered radical, irrespective of the pathway by which it is formed, is to add to a multiple bond, which results in the formation of a new σ-bond. This building strategy has gained special importance in synthetic organic chemistry in the last two decades.

In the field of carbohydrate chemistry, a remarkable synthesis of C-2-branched mono- and disaccharide derivatives has been published recently which employs manganese(III) acetate or cerium(IV)-ammonium nitrate (CAN) for the oxidative generation of malonyl radicals.\textsuperscript{85,86} This synthesis seems to be superior to other approaches\textsuperscript{87-91} leading to C-2-branched carbohydrate derivatives because of the easy availability of the starting materials, the simplicity of the preparation and that it does not involve toxic tin- or mercury compounds.\textsuperscript{88,90}

The first step of the reaction is the generation of malonyl radicals from dimethyl malonate. This electrophilic radical adds to the double
bond of a glycal. The regioselectivity of the addition is controlled by stereoelectronic factors: the MO-coefficient of the HOMO of the double bond is considerably greater at C-2 than at C-1. Because of steric hindrance, the 2,3-trans product is formed predominantly (Scheme 8).

Scheme 8. Addition of oxidatively generated malonyl radicals to glycals

The resulting radical (7, Scheme 8) can either be further oxidized to the cation which is captured by the nucleophilic solvent (1,2-trans product as a result of anchimeric assistance of the ester group of the malonyl substituent at C-2) or converted to the 1-ONO₂ (or 1-OAc)
derivative via a ligand transfer process (the axial stereoselectivity being similar to other reactions involving hexopyranos-1-yl radicals).

The Ce(IV)-mediated process has the advantage of not having side-products probably due to the milder conditions and that the products have more definite stereochemistry. Some representative examples of the Ce(IV)- and Mn(III)-mediated reactions can be seen in Table 4. In the best case (D-galacto configuration), as a result of the additional steric hindrance of the axial 4-OAc, the attack of the malonyl radical occurs with enhanced stereoselectivity, thus only two products are formed: the 1,2-trans methyl glycoside and the 1α-ONO₂ derivative.

<table>
<thead>
<tr>
<th>Starting Sugar</th>
<th>Method*</th>
<th>Yields of the Isolated Products</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><img src="image1" alt="Chemical Structure" /></td>
</tr>
<tr>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>A</td>
<td><img src="image3" alt="Chemical Structure" /></td>
</tr>
<tr>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>52</td>
<td>14</td>
</tr>
<tr>
<td><img src="image7" alt="Chemical Structure" /></td>
<td>(α:β = 16:84)</td>
<td>(α:β = 71:29)</td>
</tr>
<tr>
<td><img src="image8" alt="Chemical Structure" /></td>
<td>B</td>
<td><img src="image9" alt="Chemical Structure" /></td>
</tr>
<tr>
<td><img src="image12" alt="Chemical Structure" /></td>
<td>62</td>
<td>16</td>
</tr>
<tr>
<td><img src="image13" alt="Chemical Structure" /></td>
<td>R: β−OMe</td>
<td>R: α−ONO₂</td>
</tr>
<tr>
<td><img src="image14" alt="Chemical Structure" /></td>
<td>78</td>
<td>8</td>
</tr>
<tr>
<td><img src="image15" alt="Chemical Structure" /></td>
<td>R: β−OMe</td>
<td>R: α−ONO₂</td>
</tr>
</tbody>
</table>

*Method A: 2-4 eq. Mn(OAc)₃•2H₂O, 10 eq. CH₂(COOMe)₂, AcOH, 95 °C
Method B: 3-6 eq. CAN, 10 eq. CH₂(COOMe)₂, MeOH, 0 °C

Table 4. Product distribution in the additions of oxidatively generated malonyl radicals to glycals
3. Results

As part of ongoing projects at the Department of Organic Chemistry in the University of Debrecen, the general aim of my work has been to study some nucleophilic substitutions in C-1 substituted monosaccharide derivatives. Since these projects have also relevance to biologically active carbohydrates, these aspects are briefly described here.

Retaining glycosidases are known to hydrolyze glycosidic bonds with the appearance on the mechanistic pathway of covalent glycosyl-enzyme intermediates which are formed and decomposed via transition states of substantial oxocarbenium ion character. Destabilization of the transition state of decomposition may result in a so-called mechanism-based inactivation of the enzyme by suitably designed molecules. Such a destabilization can be achieved by introducing an electron-withdrawing group (EWG) in the vicinity of the positively charged atoms of the oxocarbenium ion-like intermediate that is to any position marked in Figure 10 (see also Chapter 2.1.2.). To this end several 2-deoxy-2-fluoro mono- and disaccharide derivatives (EWG2 = F) were synthesized and tested against various glycosidases to validate the concept. The 2-fluoro substituents, however, disrupt the most important binding between the enzyme and the 2-OH group. This was overcome by the introduction of a fluorine into the C-5 position (EWG5 = F).

![Figure 10. Destabilization of glycopyranosyl oxocarbenium ions](image)

Figure 10. Destabilization of glycopyranosyl oxocarbenium ions
Destabilization of an oxocarbenium ion with the preservation of each binding interaction between the enzyme and the hydroxyl groups of the saccharide can also be achieved by placing an electron-withdrawing group at the anomeric position additionally to a good leaving group. To the best of our knowledge 1-fluoroglycopyranosyl fluorides (EWG1 = F) are the only compounds of this type, which have been subjected to enzymatic evaluation.\textsuperscript{101,102}

Certain C-glycosyl derivatives (EWG1 = CN, COOR, CONH$_2$, CHO, COR etc.) can also result in destabilized glycosyl oxocarbenium ions making the members of this group of compounds potential candidates as new mechanism-based glycosidase inactivators.
3.1. Preparation of C-1 Substituted Glycosyl Fluoride Derivatives

Reactions of per-O-acetylated 1-bromoglycopyranosyl cyanides (8, 10, 12, and 15; Scheme 9 and 10) with silver fluoride in anhydrous acetonitrile were investigated first. In case of the D-galacto\(^{103}\) and D-arabino\(^{103}\) configurated starting materials (8 and 10) the fluoride substitution products, with inversion of configuration around the anomeric center, were the only products (Scheme 9). The crude products of the reactions were practically pure per-O-acetylated 1-fluoroglycopyranosyl cyanides (9 and 11), obtained in 90 and 79 % yield, respectively.\(^{104}\)

\[
\begin{align*}
\text{AgF (2 eq.)} & \quad \text{CH}_3\text{CN} \\
\text{r.t., 2 d} & \quad \text{90 %} \\
\text{8} \quad \text{AgF (2 eq.)} & \quad \text{CH}_3\text{CN} \\
\text{r.t., 2 d} & \quad \text{79 %} \\
\text{10} & \quad \text{9} \\

\text{Scheme 9. Reaction of acetylated 1-bromoglycopyranosyl cyanides (D-galacto and D-arabino) with silver fluoride in acetonitrile}
\end{align*}
\]

In case of the D-gluco\(^{105}\) and D-xylo\(^{103}\) configurated starting materials (12 and 15, Scheme 10) products arising from elimination of the elements of HBr appeared as side products (i.e. the 2-acetoxy-D-glycal derivatives 14 and 17), making the isolation of the desired 1-fluoroglycopyranosyl cyanide derivatives (13 and 16) very difficult. Because of the very similar \(R_f\) value that corresponds to the fluoro and
the unsaturated compounds in each tested eluent systems, the separation of the products by column chromatography was possible only in part, thus the desired products were obtained in very low yield (21 and 11 %, respectively). The side products 14 and 17 could not be isolated in pure state but $^1$H and $^{13}$C NMR analysis of the crude products and the mixed fractions obtained during column chromatography clearly proved that they are identical with those described by Somsák et al.$^{106}$

\[
\begin{align*}
\text{Ratio from } ^1\text{H NMR spectrum of the crude product:} & \quad 1 : 1 \\
\text{Ratio from } ^1\text{H NMR spectrum of the crude product:} & \quad 3 : 1
\end{align*}
\]

Scheme 10. Reaction of acetylated 1-bromoglycopyranosyl cyanides (D-gluco and D-xylo) with silver fluoride in acetonitrile

In order to synthesize the thermodynamically more stable glycosyl fluoride anomers the D-galacto and D-xylo configurated starting materials (8 and 15) were allowed to react with two equivalents of silver tetrafluoroborate in anhydrous toluene at room temperature according to the very mild procedure published by Igarashi and coworkers.$^{107}$ After
the usual aqueous workup and column chromatography 18 and 19 were isolated in 36 and 38 % yield, respectively (Scheme 11).

![Chemical structures of 8, 15, 18, and 19](image)

**Scheme 11.** *Reaction of acetylated 1-bromoglycopyranosyl cyanides (D-galacto and D-xylo) with silver tetrafluoroborate in toluene*

Reaction of 2,3,4,6-tetra-O-acetyl-1-chloro-α-D-galactopyranosyl cyanide (20, Scheme 12) with silver fluoride, employing the same reaction conditions as for the acetylated 1-bromoglycopyranosyl cyanides, was unsuccessful (i.e. no change could be observed by TLC even after several days). Refluxing the reaction mixture for 10 hours (addition of silver fluoride was repeated after 5 h reflux), however, afforded the inversion product 18 as major product in addition to more small-amount side-products, the β-fluoride 9 being present only in traces (1H NMR analysis of the crude product).

Looking for less expensive substitutes of the silver-based reagents, application of zinc fluoride with or without α,α'-bipyridyl was tried but no reaction occurred. In a phase transfer catalyzed system consisting of a benzene solution of 10, 50 % aqueous potassium fluoride solution, and tetrabutylammonium hydrogensulfate slow decomposition could be observed.
Scheme 12. Reaction of 2,3,4,6-tetra-O-acetyl-1-chloro-\(\alpha\)-D-galactopyranosyl cyanide with silver fluoride in acetonitrile

In order to carry out preliminary enzymatic studies deprotection of \(9\) was performed using methanolic ammonia to give 1-fluoro-\(\alpha\)-D-galactopyranosyl cyanide (21) after chromatographic purification (Scheme 13). This proved to be a weak competitive inhibitor of \(E. coli\) \(\beta\)-D-galactosidase (\(K_i = 2\) mM) in an assay carried out as described by Kiss et al.\(^{109}\) No inactivation was observed, probably because the leaving ability of fluorine was so strongly decreased by the presence of the cyano group that formation of a glycosyl-enzyme intermediate (cf. Chapter 3.) became impossible.

Scheme 13. Deacetylation of 2,3,4,6-tetra-O-acetyl-1-fluoro-\(\alpha\)-D-galactopyranosyl cyanide using methanolic ammonia

Structures of the novel per-O-acetylated 1-fluoroglycopyranosyl cyanides (9, 11, 13, 16, 18, 19 and 21) were proved by NMR spectroscopy and elemental analysis (see also Experimental).
In case of the 1-fluoro-hexopyranosyl cyanides (9, 13, 18 and 21) retained sugar configuration and \(^4\)C\(_1\) conformation of the ring was undoubtedly seen from the coupling constants in the \(^1\)H NMR spectra. The presence of the fluorine atom attached to the anomeric center was proved by the characteristic \(^1\)H-\(^19\)F and \(^13\)C-\(^19\)F couplings observed in the signals of H-2 (10.8…20.9 Hz), H-3 and H-5 (~1 Hz, sometimes not seen) H-4 (~3 Hz, only in particular cases, discussed below in detail) and C-1 (220…237 Hz), C-2 (23…31 Hz), CN (42…47 Hz) in the \(^1\)H and \(^13\)C NMR spectra, respectively. Coupling of the fluorine with H-2 were smaller (10.8…14.7 Hz) for 9, 13 and 21, and in keeping with literature values\(^{110}\) indicated the axial H–equatorial F arrangement, while for 18 the value of this coupling (20.9 Hz) agreed well with the trans diaxial positions of the nuclei involved. The anomeric configuration of the fluorine atom was also proved indirectly by the vicinal coupling constant between H-2 and the cyano group in the proton coupled \(^13\)C NMR spectra.\(^{41}\) Its value was 5.1 and 6.1 Hz in case of the \(\beta\)-fluorides 13 and 9 (trans diaxial arrangement of H-2 and the cyano group), respectively and the coupling was not resolved in case of the \(\alpha\)-fluoride 18 (gauche arrangement of H-2 and the cyano group). In case of 21 the value was not determined, though the anomeric configuration is corroborated by the value of \(^5\)J\(_{\text{H-4,F}}\) as discussed below.

Figure 11. Five-bonded couplings observed in the \(^1\)H NMR spectra of 2,3,4,6-tetra-O-acetyl-1-fluoro-\(\alpha\)-glycopyranosyl cyanides
Appearance of $^5J_{H-4,F}$ couplings of $\sim$3 Hz in the $^1$H NMR spectra of 9 and 21 but not of 13 and 18 is in keeping with literature experiences$^{110-113}$ indicating that the fluorine and H-4 are in trans coplanar relationship to the bond which is the midpoint of the coupling pathway (Figure 11). This is a further indirect proof of the anomeric configuration of these 1-fluoroglycopyranosyl cyanide derivatives.

Conformational equilibria of the 1-fluoropentopyranosyl cyanides 11, 16 and 19 lie between those of the corresponding pentopyranosyl fluorides and cyanides (Table 5). This is in accord with the estimated anomeric effect of the cyano group.$^{40}$

Attempted synthesis of C-(2,3,4,6-tetra-O-acetyl-1-fluoro-β-D-galactopyranosyl)formamide (24) by the reaction of the corresponding bromo derivative$^{109}$ (22) with silver fluoride using the same reaction conditions as for the acetylated 1-bromoglycopyranosyl cyanides was unsuccessful. The product which crystallized out during removal of the solvent after the usual workup did not exhibit the characteristic fluoride couplings in its $^1$H NMR spectrum, instead one less exchangeable proton and one more methyl (in the acetyl region) resonance. Later it turned out that the product of the reaction had, at first view strange, structure of 23 (Scheme 14) and was produced in a unique reaction (this reaction will be dealt with in detail in Chapter 4.2.).$^{117}$ Though column chromatography of the mother liquor afforded 3 % of the desired fluoro derivative 24 it was necessary to change the reaction conditions in order to find a suitable procedure for the synthesis of derivatives of this type.

Thus, the reaction was repeated using dimethylsulfoxide as the solvent, but instead of the desired fluorides, an unknown product was obtained in low yield. Later it turned out that the product was originated from the reaction of 22 with the solvent, dimethylsulfoxide.$^{118}$ This reaction will be discussed in detail in Chapter 4.3.
Table 5. Conformational equilibria of 1-fluoropentopyranosyl cyanides\textsuperscript{a} and the related pentopyranosyl fluorides and cyanides

\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
\textbf{Compound} & \textbf{R}^1 & \textbf{R}^2 & \textbf{\textsuperscript{4}C} & \textbf{\textsuperscript{1}C} & \textbf{Solvent} & \textbf{Reference} \\
\hline
\textbf{D-xylo} & F & H & 28 & 72 & CDCl$_3$ & 110 \\
\textbf{16} & H & CN & 76 & 24 & C$_6$D$_6$ & 114 \\
 & & & (85 & 15$^b$ & & \\
\textbf{D-xylo} & H & F & \textasciitilde100 & 67 & CDCl$_3$ & 110 \\
\textbf{19} & CN & H & 55 & 45 & CDCl$_3$ & 115 \\
 & & & (54 & 46$^b$ & & \\
\textbf{D-arabino} & H & F & 94 & 6 & C$_6$D$_6$ & this work \\
\textbf{11} & CN & H & 13 & 87 & C$_6$D$_6$ & 114 \\
 & & & (19 & 81$^b$ & & \\
\hline
\end{tabular}

\textsuperscript{a} Calculated on the basis of $J_{4,5}$ couplings using $J_{4a,5a} = 11.6$ Hz, $J_{4e,5e} = 1.5$ Hz as limiting values for the \textsuperscript{4}C$_1$ and \textsuperscript{1}C$_4$ conformers, respectively.\textsuperscript{116}

\textsuperscript{b} Calculated on the basis of $J_{1,2}$ couplings using $J_{1a,2e} = 1.4$ Hz and $J_{1e,2a} = 6.2$ Hz as limiting values for the corresponding conformers.\textsuperscript{115}
Scheme 14. Reaction of C-(2,3,4,6-tetra-O-acetyl-1-bromo-β-D-galactopyranosyl)formamide with silver fluoride in acetonitrile

The next dipolar-aprotic solvent, which was tried as the reaction medium, was nitromethane. After two days, the corresponding glycosyl fluoride derivatives (24 and 25, Scheme 15) were isolated in addition to the 1-OH derivative 43 26.

Scheme 15. Reaction of C-(2,3,4,6-tetra-O-acetyl-1-bromo-β-D-galactopyranosyl)formamide with silver fluoride in nitromethane

The reaction was repeated using dichloromethane and benzonitrile as solvents. The ratio of the products was determined from the $^1$H NMR spectra of the crude products (Table 6). In case of benzonitrile the corresponding α-benzamide 44 (see Chapter 3.2, Table 12), formed in a solvent-participation reaction similar to the one depicted in Scheme 14, was also obtained in addition to products 24, 25 and 26.
Table 6. Ratio of the products obtained in the reaction of 22 with silver fluoride in different solvents

In order to be able to compare our results in solvents other than acetonitrile with those of the parent compounds, the per-O-acetyl-α-D-glycopyranosyl bromides, and to clarify the effect of acetonitrile on the stereoselectivity of the fluorination reaction introduced by Helferich, we carried out the reaction of D-acetobromoglucose (27) with silver fluoride in acetonitrile, trichloroacetonitrile and nitromethane. The product ratios collected in Table 7 clearly shows the influence of the nitrile-type solvent on the stereochemical outcome of the reaction.

Table 7. Reaction of 27 with silver fluoride in different solvents
3.2. Nitrile Incorporation Reactions

During investigation of the fluorination reaction of C-(2,3,4,6-tetra-O-acetyl-1-bromo-β-D-galactopyranosyl)formamide (22), we have observed an unexpected product. Its formation can be understood by the nucleophilic attack of the acetonitrile, used as solvent, to the glycosyl carbenium ion generated by the fluorinating agent, silver fluoride, from the above-mentioned glycosyl halide (see Scheme 14, Chapter 3.1.).

After determination of the structure of the product (23, Scheme 14) and making a mechanistic proposal for its formation (see Scheme 20, Chapter 4.2.) we continued the examination of this reaction, first by trying the normal Koenigs-Knorr promoter, silver carbonate, and later by conducting the reaction in various nitriles as solvents. Our starting sugars, besides 22, were C-(2,3,4,6-tetra-O-acetyl-1-bromo-β-D-glucopyranosyl)formamide (30) and C-(2,3,4-tri-O-acetyl-1-bromo-α-D-arabinopyranosyl)formamide (31).

The results summarized in Table 8 clearly show the generality of the reaction concerning both the promoter and the nitrile provided that the nitrile is a liquid and thus can be used as the reaction medium. It is noteworthy, that in each investigated nitrile the *axially oriented* amide is the only product and no formation of the *equatorial* isomer is observed.

In order to determine the generality of the latter observation about the stereochemical outcome of the reaction, a number of Koenigs-Knorr promoters were tried instead of silver carbonate (Table 9). From the six employed promoters AgOTf, HgBr₂ and HgI₂ proved to be useful to bring about the reaction without side-reactions; using Hg(CH₃COO)₂, apparently poorly soluble in acetonitrile, only ∼25 % conversion (α:β ratio: ∼2:1) could be achieved even after 2 weeks. The exclusive formation of the *axially oriented* amide, however, did not proved to be independent of the promoter used in the reaction, since in case of mercuric salts (especially mercuric bromide) considerable amount of the *equatorially oriented* amide was present in the reaction mixture.
<table>
<thead>
<tr>
<th>Starting compound</th>
<th>AgX</th>
<th>R-CN</th>
<th>Yield (%)</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="22" /></td>
<td>Ag₂CO₃, AgF, Ag₂CO₃, Ag₂CO₃, Ag₂CO₃, Ag₂CO₃</td>
<td>CH₃, CH₃, CH₂CH₂, CH₂=CH, CH₂=CH-CH₂, CH₃OCH₂</td>
<td>76, 70⁺, 74, 57, 62, 24</td>
<td><img src="image" alt="23" />, <img src="image" alt="22" />, <img src="image" alt="32" />, <img src="image" alt="33" />, <img src="image" alt="34" />, <img src="image" alt="35" /></td>
</tr>
<tr>
<td><img src="image" alt="30" /></td>
<td>AgF, Ag₂CO₃</td>
<td>CH₃, CH₂CH₂</td>
<td>36, 53</td>
<td><img src="image" alt="36" />, <img src="image" alt="37" /></td>
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<tr>
<td><img src="image" alt="31" /></td>
<td>Ag₂CO₃, Ag₂CO₃</td>
<td>CH₃, CH₂=CH</td>
<td>41, 43</td>
<td><img src="image" alt="38" />, <img src="image" alt="39" /></td>
</tr>
</tbody>
</table>

* A small amount of the corresponding C-(2,3,4,6-tetra-O-acetyl-1-fluoro-α-D-galactopyranosyl)formamide (~3 %) was also isolated.

**Table 8.** Preparation of per-O-acetylated N-(1-cyano-D-glycopyranosyl) amides
Reaction of C-(2,3,4,6-tetra-O-acetyl-1-chloro-β-D-galactopyranosyl) formamide (41, not depicted, for preparation of this compound see Experimental) with acetonitrile as solvent in the presence of 1 equiv. of antimony pentachloride (−40 °C → r.t.) furnished a mixture of several products.

![Image of chemical structures]

<table>
<thead>
<tr>
<th>promoter</th>
<th>reaction time</th>
<th>α:β ratio (1H NMR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ag₂CO₃</td>
<td>3 d</td>
<td>100 : 0</td>
</tr>
<tr>
<td>AgOTf</td>
<td>1 min</td>
<td>100 : 0</td>
</tr>
<tr>
<td>HgBr₂</td>
<td>1 h</td>
<td>67 : 33</td>
</tr>
<tr>
<td>HgI₂</td>
<td>1 d</td>
<td>88 : 12</td>
</tr>
<tr>
<td>Hg(NO₃)₂</td>
<td>1 h</td>
<td>_a</td>
</tr>
<tr>
<td>Hg(CH₃COO)₂</td>
<td>14 d</td>
<td>_b</td>
</tr>
<tr>
<td>ZnBr₂</td>
<td>22 d</td>
<td>_a</td>
</tr>
</tbody>
</table>

*a Considerable amount of side-products, overall ratio of the two amides is not more than 50 %

*b Conversion: ~25 %

Table 9. Dependence of the ratio of α- and β-amide on the used promoter

Since all of the experiments carried out so far contained the nitrile as solvent, thus in a very large excess, it was reasonable to try to decrease its amount in order to determine its influence on the ratio of the α- vs. β-amide and to try to extend the procedure for nitriles that cannot be used.
as solvents. From the above promoters only AgOTf and HgBr₂ seemed to be capable (the reaction was either too slow or furnished several side-products with the other promoters, cf. Table 9) to bring about the reaction with smaller amount of nitrile, therefore further experiments were carried out mainly with these two promoters. In the next set of experiments the reactions were conducted in different solvents containing the nitrile only in smaller excess (5 equiv.). In the light of parallel observations concerning solvent-participation reactions of C-(1-bromoglycopyranosyl)formamide derivatives (see Chapter 3.3.), any solvent which could act as a nucleophile, especially alcohols, ketones, esters and sulfoxides, had to be excluded from the investigation.

From the five tested solvents, merely nitromethane turned out to be suitable as reaction medium for the reaction promoted by mercuric bromide (cf. Table 10). Only a small amount of side-products was present in the reaction mixture in addition to the desired amides. The ratio of the β-amide (40) was much higher than in the experiment when acetonitrile was used as solvent (in fact it became the major product of the reaction). The isolation of the β-amide by column chromatography, however, was possible only in 33 % yield. In dichloromethane the reaction was very slow and yielded a mixture of several products. The reaction was very slow in dioxane too, the sole product being the 1-OH derivative 26. A mixture of two products was obtained in HMPT probably resulting from a solvent incorporation reaction, but the products decomposed during column chromatography. In case of benzene, the amount of the crude product after the usual aqueous workup was so small (35 mg from 200 mg starting sugar), that it made the NMR-analysis unavailing.
Table 10. Reactions in different solvents using HgBr₂ promoter

Reactions with silver triflate (1-2 eq.) were conducted in nitromethane-toluene mixture (2:1, V/V) at –50 °C → r.t. excluding moisture and oxygen, in the presence or in the absence of s-collidine (1 eq.). These experiments, however, were impossible to analyze by ¹H NMR because of the small-intensity signals of several different by-products.

Since only HgBr₂ in nitromethane was the only successful promoter-solvent combination to bring about the reaction with small amount of nitrile, we continued our investigations in these conditions.

First, we tried to decrease the amount of the nitrile used for the reaction. Employing 1.5 equiv. acetonitrile, however, the ratio of the side-products exceeded 50 % making the synthesis preparatively useless (Table 11, No. 4). (Though because of the many signals of the side-products the ratio of the two desired amides could not be determined exactly from the ¹H NMR spectrum, the amount of the β-
amide, as compared to that of the $\alpha$-form, was estimated to be even more than in case of 5 equiv. nitrile.) A comparison of product ratios as a function of nitrile-amount can be seen in Table 11 (No. 1-4).

In the next set of experiments, we tried promoter-combinations containing mercuric bromide in order that we may increase the ratio of the $\beta$-amide. An interesting effect of Hg(CN)$_2$ as a promoter or co-promoter was observed when used in nitromethane with 5 equiv. acetonitrile. Namely, application of Hg(CN)$_2$ either alone or together with HgBr$_2$ resulted in a dramatic change in the ratio of the $\alpha$- and $\beta$-amides towards the preference of the $\alpha$-amide (Table 11, Exp. 6 and 7). Using ZnBr$_2$ together with HgBr$_2$, on the other hand, facilitated an increased ratio of the $\beta$-amide, though making the reaction extremely sluggish (No. 8). In case of HgCl$_2$, the chloro-substituted product (41) was obtained as the major product (~70 % ratio) in addition to a smaller amount of the desired amides (23 and 40) and the 1-OH derivative 26 (No. 9).

The temperature-dependence of the reaction was also tested conducting the reaction in acetonitrile and in nitromethane (containing 5 equiv. acetonitrile) the promoter being HgBr$_2$ in both cases. It is clearly seen from the experiments that the ratio of the $\beta$-amide increases at lower temperatures, while at higher temperatures, formation of the $\alpha$-amide becomes predominant (Table 11, No. 10-13).

The question was arisen, whether the ratio of the two anomic amides was influenced by a concurrent anomerization under the reaction conditions. Thus, pure 40 was stirred under normal reaction conditions i.e. in nitromethane with 2 eq. of the promoter. Two independent experiments were started, one with mercuric bromide and another with mercuric cyanide. The anomerizations were attempted at three different temperatures. The experiments showed that 40 was totally inert under the normal reaction conditions even at elevated temperatures.

1.) 3 days at room temperature: no anomerization
2.) 7 days at 40-45 °C: no anomerization
3.) 1 day at 100 °C: no anomerization
The best two procedures that permit high ratios of the α- and the β-amide, respectively, were tested with three different nitriles to explore the influence of steric and/or electronic factors of the nitrile on the ratio of the corresponding α- and β-amides.

Table 11. Reaction of 22 with acetonitrile in different conditions

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>solvent</th>
<th>promoter</th>
<th>CH₃CN (eq.)</th>
<th>Temp. (°C)</th>
<th>α:β ratio (¹H NMR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃CN</td>
<td>HgBr₂</td>
<td>as solvent</td>
<td>25</td>
<td>67:33</td>
</tr>
<tr>
<td>2</td>
<td>CH₃NO₂</td>
<td>HgBr₂</td>
<td>10</td>
<td>25</td>
<td>36:64</td>
</tr>
<tr>
<td>3</td>
<td>CH₃NO₂</td>
<td>HgBr₂</td>
<td>5</td>
<td>25</td>
<td>35:65</td>
</tr>
<tr>
<td>4</td>
<td>CH₃NO₂</td>
<td>HgBr₂</td>
<td>1.5</td>
<td>25</td>
<td>_a</td>
</tr>
<tr>
<td>5</td>
<td>CH₃NO₂</td>
<td>HgBr₂</td>
<td>5</td>
<td>25</td>
<td>35:65</td>
</tr>
<tr>
<td>6</td>
<td>CH₃NO₂</td>
<td>HgBr₂/Hg(CN)₂</td>
<td>5</td>
<td>25</td>
<td>89:11</td>
</tr>
<tr>
<td>7</td>
<td>CH₃NO₂</td>
<td>Hg(CN)₂</td>
<td>5</td>
<td>25</td>
<td>90:10</td>
</tr>
<tr>
<td>8</td>
<td>CH₃NO₂</td>
<td>HgBr₂/ZnBr₂</td>
<td>5</td>
<td>25</td>
<td>19:81</td>
</tr>
<tr>
<td>9</td>
<td>CH₃NO₂</td>
<td>HgCl₂</td>
<td>5</td>
<td>25</td>
<td>_b</td>
</tr>
<tr>
<td>10</td>
<td>CH₃CN</td>
<td>HgBr₂</td>
<td>as solvent</td>
<td>-30</td>
<td>57:43</td>
</tr>
<tr>
<td>11</td>
<td>CH₃CN</td>
<td>HgBr₂</td>
<td>as solvent</td>
<td>25</td>
<td>67:33</td>
</tr>
<tr>
<td>12</td>
<td>CH₃NO₂</td>
<td>HgBr₂</td>
<td>5</td>
<td>25</td>
<td>35:65</td>
</tr>
<tr>
<td>13</td>
<td>CH₃NO₂</td>
<td>HgBr₂</td>
<td>5</td>
<td>50</td>
<td>83:17</td>
</tr>
</tbody>
</table>

a Several by products, see text  b Main product: 1-Cl derivative, see text
Comparing the experiments with acetonitrile and with pivalonitrile (t-butylnitrile) shows that the sterically demanding pivalonitrile is less capable of attacking from the \( \alpha \)-side, thus a higher ratio of \( \beta \)-amide is obtained (Table 12). In case of benzonitrile, HgBr\(_2\) gave an unclear reaction compared to the other nitrile-type nucleophiles.

Reactions promoted by Hg(CN)\(_2\) resulted in a stereoselective formation of the corresponding \( \alpha \)-amides (23, 42 and 44).

Structures of the novel per-O-acetylated \( N \)-acyl-1-cyanoglycosyl-\( \beta \)-aminoles (23, 32-40, 42-45) were proved by NMR spectroscopy and elemental analysis (see also Experimental).

In case of the hexopyranose derivatives retained sugar configuration and \( 4C_1 \) conformation of the ring was undoubtedly seen from the coupling constants in the \( {^1}H \) NMR spectra.

The absence of signal for the anomeric proton in \( {^1}H \)- and the type of signal for C-1 (quaternary) in \( J \)-modulated \( {^{13}}C \) NMR spectra showed the presence of two substituents at the anomeric center of these compounds. The presence of only one exchangeable proton disclosed...
the presence of an intact –CONH₂ group. The presence of extra signals in the ¹H- and ¹³C NMR spectra corresponding to the side chain of the nitrile used for the reaction and of one more peak in the carbonyl region, having a coupling pattern (in ¹H-coupled ¹³C NMR spectrum) unlike that of acetyl groups, proved the presence of the –NHCOR group at the anomeric center. The other C-1 substituent, the cyano group exhibited its characteristic signal between 111 and 116 ppm in each cases.
3.3. Pummerer-type Rearrangement Leading to Methylthiomethyl Glycosides

During investigation of the fluorination reactions of C-(1-bromoglycopyranosyl)formamides, it was found that, in the presence of silver fluoride, 22 and 30 was converted, in a solvent-participation reaction (for mechanism see Chapter 4.3.), to the corresponding methylthiomethyl glycoside 46 and 47, respectively. The yields are very low, the major products being the 1-OH derivatives 26 and 48 (Scheme 16).

\[
\begin{align*}
22 & \text{ (R}_1: \text{OAc, R}_2: \text{H) - D-galacto} \\
30 & \text{ (R}_1: \text{H, R}_2: \text{OAc) - D-gluco}
\end{align*}
\]

Scheme 16. Reaction of C-(1-bromoglycopyranosyl)formamide derivatives with DMSO in the presence of silver fluoride

If the aqueous workup was carried out using diethylether the 1-OH derivatives (26 and 48) remained in the aqueous phase thus simplifying the isolation of 46 and 47, while employing ethyl acetate these derivatives predominated in the crude products (1H NMR analysis).

Substitution of silver fluoride by silver carbonate or silver oxide resulted in the exclusive formation of the corresponding 1-OH derivatives.

Structures of the novel per-O-acetylated methylthiomethyl glycosides (46 and 47) were proved by NMR spectroscopy and elemental analysis (see also Experimental).

Retained sugar configuration and \(^4\)C\(_1\) conformation of the ring was undoubtedly seen from the coupling constants in the \(^1\)H NMR spectra.
The absence of signal for the anomeric proton in $^1$H- and the type of signal for C-1 (quaternary) in J-modulated $^{13}$C NMR spectra showed the presence of two substituents at the anomeric center of these compounds. The two exchangeable protons and the five carbonyl signals suggested the presence of an intact –CONH$_2$ group. The presence of extra signals in the $^1$H- and $^{13}$C NMR spectra corresponding to the methylthiomethoxy moiety (see Table 23) proved the presence of this group at the anomeric center. The anomeric configuration was determined by the value of $J_{H-2, CONH_2}$ and showed that the carbamoyl group is axially oriented in both molecules.

Since reactions of C-(1-bromoglycopyranosyl)formamide derivatives with other nucleophilic solvents (e.g. alcohols, ketones) were also investigated in our laboratory (see Chapter 4.3.), we decided to start a series of experiments in order that we may compare the nucleophilicity of these nucleophilic solvents. Thus, 22 was stirred in a 1:1 (n/n) mixture of different pairs of solvents, selected from the group of acetonitrile, acetone, dimethyl sulfoxide and methyl alcohol, using HgBr$_2$ as the promoter. Results are summarized in Table 13 (49a, 50a and 49e, 50e denote the products arising from the axial and equatorial attack of the nucleophiles, respectively).

<table>
<thead>
<tr>
<th>Solvents</th>
<th>Ratio of products (from $^1$H NMR, crude product)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_3$CN, MeOH</td>
<td>0 49a 49e</td>
</tr>
<tr>
<td>CH$_3$CN, DMSO</td>
<td>0 49e 50e</td>
</tr>
<tr>
<td>CH$_3$CN, (CH$_3$)$_2$CO</td>
<td>several side-products</td>
</tr>
</tbody>
</table>

Table 13. Reaction of 22 with mixtures of nucleophilic solvents in the presence of HgBr$_2$
3.4. Cerium(IV)-ammonium Nitrate Mediated Addition of Malonyl Radical to C-1 Substituted Glycals

Since a new synthesis of C-1 substituted glycal derivatives under aprotic conditions was worked out in our laboratory,\textsuperscript{106,109,120} it seemed reasonable to try to employ these novel glycal derivatives for the investigation of reactions involving glycopyranosyl carbenium ion intermediates as well. We have chosen the cerium(IV)-ammonium nitrate (CAN) mediated radical addition since we had a collaboration with Prof. Linker from the University of Stuttgart who was the first to use this procedure in the carbohydrate field.\textsuperscript{85,86} Since they obtained the best results (least complicated product mixtures) in the D-\textit{galacto} configuration (cf. Chapter 2.3.3.) we started our investigations with substituted D-galactal analogs. The addition of dimethyl malonate to each investigated C-1 substituted D-galactal (51, 55 and 60) proceeded smoothly and resulted novel C-2 branched monosaccharide derivatives. Because of their hydrolytic instability (especially during column chromatography) the isolation of these products was usually not possible in a completely pure form. Thus, characterization of the products, except some cases, was accomplished merely by NMR spectroscopy. It is because of the same reason that the yields of isolation are always low, though the mass of the crude product, in most of the cases, was close to the theoretical yield. Attempts to isolate the products by modified chromatographic methods (Et\textsubscript{3}N-containing eluent, neutralized silica gel, neutral Al\textsubscript{2}O\textsubscript{3}) failed because of decomposition or the inadequate R\textsubscript{f} difference of the products on the used adsorbent.

The reaction of the carbamoyl-substituted glycal derivative 51\textsuperscript{109} was investigated first. Thus, in the presence of 4-6 equiv. Ce(NH\textsubscript{4})\textsubscript{2}(NO\textsubscript{3})\textsubscript{6} in degassed dry methanol containing 10 equiv. dimethyl malonate, we observed complete disappearance of the starting sugar after 2-4 hours. The products, which had similar structures as in the case of the unsubstituted glycals, however, were isolated only in much lower yields (Scheme 17).
During the trials aimed to improve the yields of the products, we found that the ratio of the two products depends on the reaction time. While faster addition of CAN (shorter reaction time) resulted in a higher ratio (around 50%) of the 1-ONO$_2$ derivative (53), in case of slower addition (longer reaction time) the reaction mixture contained only small amount of this compound (around 10%). In order to be able to draw sound conclusions from this observation, we started reactions with the parent compound, 3,4,6-tri-O-acetyl-D-galactal as well. These latter experiments showed that the product ratio obtained with D-galactal is independent of the reaction time (or at least it is nearly constant when exposed to the same changes of reaction time).

![Scheme 17. Reaction of 51 with dimethyl malonate in the presence of CAN](image1)

The other observation during the investigation of this reaction is connected to the water-content of the reactants (especially CAN). When, accidentally, we used a little bit moist CAN, the 1$\alpha$-OH derivative (54, Figure 12) appeared among the products in a non-negligible ratio (10-50%).

![Figure 12. Hydrolysis product obtained in the reaction of 51 with dimethyl malonate in the presence of “moist CAN”](image2)
The cyano-substituted D-galactal $55^{120}$ was the second glycal derivative to be investigated. This could also be transformed to the 2-C substituted sugar, but the products were completely different from those appeared so far in this type of reaction. In two of the three products, there were one less signal in the carbonyl region and one more at about 120 ppm. Their $^{13}$C NMR spectra were almost identical. The third product also contained the malonyl residue but there was no C-1 (in its "normal place") and cyano group in the molecule and there was one more carbonyl resonance. The first two turned out to be a diastereomeric pair of two orthoesters, the third has at first view strange structure of $58$. In case of $55$ as well, the product ratio depends on the reaction time. During the investigation of this dependence, we were able to isolate a fourth product occasionally present in the reaction mixture ($59$ in 0-15 % ratio, Figure 13). A collection of experiments showing the influence of the employed reaction time can be found in Table 14.

<table>
<thead>
<tr>
<th>Reaction Time [h]</th>
<th>Ratio of products ($^1$H NMR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>56</td>
</tr>
<tr>
<td>0.5</td>
<td>68</td>
</tr>
<tr>
<td>1</td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>4$^a$</td>
<td>-</td>
</tr>
<tr>
<td>8$^b$</td>
<td>-</td>
</tr>
<tr>
<td>24$^c$</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$ 19 % of an unknown product  
$^b$ 28 % of the unknown product  
$^c$ Complete decomposition

Table 14, *Dependence of product ratio on reaction time*
Figure 13. Elimination product obtained in the reaction of 55 with dimethyl malonate in the presence of CAN

<table>
<thead>
<tr>
<th>Reaction Time&lt;sup&gt;a&lt;/sup&gt; [min]</th>
<th>Ratio of products (&lt;sup&gt;1&lt;/sup&gt;H NMR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>56</td>
</tr>
<tr>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>11</td>
</tr>
<tr>
<td>30&lt;sup&gt;c&lt;/sup&gt;</td>
<td>–</td>
</tr>
<tr>
<td>270&lt;sup&gt;d&lt;/sup&gt;</td>
<td>–</td>
</tr>
</tbody>
</table>

<sup>a</sup> After addition of water  <sup>b</sup> 37 % of an unknown intermediate  
<sup>c</sup> 51 % of the unknown intermediate  
<sup>d</sup> 28 % of another product having similar signals to 58

Table 15. In situ hydrolysis of orthoesters 56 and 57

Since the lactone (58) seems to be formed from the orthoesters in longer reactions (cf. Table 14) and that its formation can only be imagined by hydrolysis (see Chapter 4.4. for mechanism; methanol and especially CAN may contain traces of water), we decided to start experiments to bring about this hydrolysis by the addition of water to the reaction mixture. Indeed, the addition of 14 equiv. H<sub>2</sub>O after complete
disappearance of the starting sugar (55) resulted in a rapid hydrolysis of the orthoesters 56 and 57. The former hydrolyzed much faster but after 4.5 hours 57 was also absent from the reaction mixture, which contained only 58 (Table 15).

Reaction of the methoxycarbonyl substituted d-galactal (60, for preparation see Experimental) proceeded similarly to the cyano substituted one i.e. with formation of orthoesters, but only one of the orthoesters (61) was isolated along with the 1-OH derivative 62 (Scheme 18).

Scheme 18. Reaction of 60 with dimethyl malonate in the presence of CAN

The structures of the novel C-2 malonyl substituted sugar derivatives (52-54, 56-59, 61 and 62) were proved by NMR spectroscopy. Except 59, the d-galacto configuration of the sugars and the 4C1 conformation of their ring was seen from the coupling pattern of their 1H NMR spectra. The presence of the malonyl group at C-2 was proved by the appearance of two new singlets (each 3H, -OMe) and one new doublet (1H, -CH(OMe)2) in the 1H NMR spectra while 5 new carbons characteristic of this residue in the 13C NMR spectra (in case of orthoesters 56, 57 and 61 the one new carbonyl resonance and the 4 additional new signals at around 50 ppm is in agreement with the structures of these molecules and discloses that they are simple methyl glycosides). The value of the chemical shifts of H-2 and C-2 also corroborates the presence of a carbon substituent at this position.
In case of the 1-OH derivatives 54 and 62, the presence of the hydroxyl group was shown by the one new exchangeable signal in their $^{1}$H NMR spectra.

The NMR spectra of the unsaturated derivative 59 is in keeping with the presence of the double bond, the malonyl residue and the cyano group. The absence of the signal of H-2 and the appearance of H-7 as a singlet corroborates the suggested structure.

The anomeric configuration of the molecules was proved by the vicinal coupling constant of H-2 and the substituent at C-1 (CONH$_2$, CN or COOMe) in the $^{1}$H coupled $^{13}$C NMR spectra.$^{41}$
4. Discussion
4.1. Synthesis of Glycosyl Fluoride Derivatives

We used Helferich’s procedure for the preparation of glycosyl fluoride derivatives. The starting materials of this reaction are the protected glycosyl chlorides and bromides. The substitution is carried out in acetonitrile as solvent and uses silver fluoride as the fluoride source, which is an electrophilic promoter as well. In case of the literature examples of reactions of unsubstituted sugars collected in Table 3 the anomeric configuration of the product is inverted (equatorial fluoride) in case of D-glucose and D-galactose configuration (with non-participating group at C-2 as well) and retained (axial fluoride) in case of D-mannose configuration (participating group at C-2).

Since, to the best of our knowledge, there is no general explanation of Helferich’s widely used fluorination procedure and that the behavior of the per-O-acetyl-1-halo-D-glycopyranosyl cyanides seems to be different from that of the unsubstituted glycosyl halides under these conditions, we decided to try to digest all the experimental data in hand and give an overall view of this reaction. The stereochemical outcome of this reaction obtained with various glycosyl halide derivatives in acetonitrile (common solvent in the Helferich’s procedure) and in nitromethane is summarized in Table 16 and 17.

In case of the unsubstituted (see Table 3, Chapter 2.3.1.) and the carbamoyl-substituted (see Chapter 3.2.) 1,2-cis glycopyranosyl halides the stereochemistry of the product is probably governed by the fast stereoselective formation of an α-nitrilium–nitrile conjugate (cf. Chapter 2.3.2.). In the first case, it restricts the attack of the fluoride (β-fluoride) and in the second, it determines the place of the N-acyl residue in the product (cf. Scheme 20, Chapter 4.2.). In both instances, the first step of the reaction is the formation of an “open” glycopyranosyl carbenium ion similar to 3A (Figure 7, Chapter 2.2.1.), which is then attacked by the solvent acetonitrile resulting in an α-glycosyl nitrilium ion intermediate (6α, Figure 9, Chapter 2.3.2.). This role of the nitrile-type solvent is
corroborated by the observation that if these reactions are conducted in nitromethane (another dipolar-aprotic solvent, having similar dielectric constant as acetonitrile) the product will be a mixture of the two anomeric glycosyl fluoride derivatives (α:β ratio ≈ 1:2, see also Table 6 and 7 in Chapter 3.1.). When neighboring-group participation is favored by a 1,2-trans arrangement of the 2-OAc and the leaving group (halogen), however, a “closed-ion” intermediate is formed (see 3B, Figure 7, Chapter 2.2.1) and the product will certainly adopt 1,2-trans stereochemistry (see the two examples with D-manno configuration in Table 3, Chapter 2.3.1.).

![Starting material: 1,2-cis glycosyl halide](image)

<table>
<thead>
<tr>
<th>R</th>
<th>Stereochemistry of the glycosyl fluoride</th>
<th>Solvent: CH₃CN</th>
<th>Solvent: CH₃NO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>–H</td>
<td>1,2-trans (equatorial)</td>
<td>mixed</td>
<td></td>
</tr>
<tr>
<td>–CONH₂</td>
<td>Solvent incorporation</td>
<td>mixed</td>
<td></td>
</tr>
<tr>
<td>–CN</td>
<td>1,2-trans (equatorial)</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

Table 16. Reaction of 1,2-cis glycosyl halides with silver fluoride in nitromethane and acetonitrile
Starting material: 1,2-trans glycosyl halide

<table>
<thead>
<tr>
<th>R</th>
<th>Solvent: CH₃CN</th>
<th>Solvent: CH₃NO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>–H</td>
<td>1,2-trans (axial)</td>
<td>–</td>
</tr>
<tr>
<td>–CONH₂</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>–CN</td>
<td>1,2-cis (axial)</td>
<td>–</td>
</tr>
</tbody>
</table>

Table 17. Reaction of 1,2-trans glycosyl halides with silver fluoride in nitromethane and acetonitrile

The universality of configurational inversion around the reaction center in case of 1,2-cis and of 1,2-trans 1-cyanoglycopyranosyl halides, suggests an Sₐ2 or Sₐ2-type mechanism. A unimolecular reaction pathway similar to the one described so far is interfered with the much lower stability of the corresponding 1-cyanoglycopyranosyl carbenium ion. Therefore, the carbenium ion itself does not appear as an intermediate of the reaction, instead a synchronous push-pull mechanism seems to be the most probable in which the reaction proceeds through a transition state in which the C-1–halogen bond is weakened but not broken by complexation with a silver ion and more or less synchronously an attack of the fluoride ion takes place (Scheme 19).
**Scheme 19. Proposed mechanism for the reaction of per-O-acetyl-1-halo-D-glycopyranosyl cyanides with AgF in CH₃CN**

The appearance of the unsaturated compounds 14 and 17 in the reaction mixtures obtained with D-glucos and D-xylos configurated starting materials but not with the D-galactos and D-arabinos ones can also be explained within the framework of this mechanistic proposal as follows. The attack of the fluoride ion can reach both C-1 and H-2 in those configurations where the 4-OAc group is equatorial (Figure 14; B, D-glucos (12) and D-xylos (15) compounds) to produce parallelly the substitution (13 and 16) and elimination (14 and 17) products. In configurations with an axial 4-OAc group, the above centers are sterically more hindered (A, D-galactos (8) and D-arabinos (10) compounds), therefore, no elimination occurs and the substitution is significantly slower (cf. the rate of S_N2-type reactions of mannose derivatives, Chapter 2.2.2.). Displacement of the equatorial chlorine in 20 requires an even more crowded transition state (C) and, accordingly, this reaction can only be performed with prolonged heating. If the reaction went through a glycosylium ion intermediate, preferential formation of the β-fluoride should have occurred as a result of a neighboring group participation reaction. Elimination is disfavored by the non-coplanar arrangement of H-2 and the chlorine.
This mechanistic proposal is also in keeping with the fact that hydrogen bromide elimination was observed only in two cases. If the reactions proceeded through carbocationic intermediates the unsaturated compounds of type 14 and 17 should have appeared in each instance, since it had been shown that silver triflate catalyzed elimination of hydrogen bromide could be achieved from each investigated 1-bromoglycosyl cyanide.106

The outcome of experiments with silver tetrafluoroborate producing axial fluorides is in agreement with literature experiences.107,121

![Diagram of transition states](image)

**Figure 14.** Transition states corresponding to different configurations of the starting sugar
4.2. Nitrile Incorporation Reactions

The reaction which we discovered during the investigation of the fluorination reactions of the fully acetylated C-(1-bromoglyco-pyranosyl)formamides (see Scheme 14, Chapter 3.1.) was without precedent (or at least we thought so at the time when we observed it), thus we had the task of exploring the mechanism and explain the formation of the unexpected product 23. It became clear soon, that the first step of the reaction is analogous to the first step of the well-known Ritter reaction i.e. the acetonitrile attacks the glycosylium ion (63A, Scheme 20). The fate of the resulting N-glycosynitrilium ion (63B) turned out to be similar to path C of Scheme 7 (Chapter 2.3.2.), since the carbonyl oxygen of the adjacent carboxamido group acts as a nucleophile to form the cyclic intermediate 63C. Tautomeric ring opening of this intermediate and subsequent tautomerization of 63D furnish the product 63E.

Dehydration of amides by nitrilium salts, the intermolecular form of the 63A → 63E reaction sequence, has already been observed by Jochims and Glocker.122

The cleavage of the β-lactam ring discovered by Kita and coworkers123,124 (Scheme 21) constitutes a completely similar reaction sequence to the one observed by us, though with one more carbon between the two reacting sites of the molecule.

The stereoselectivity of the reaction is in agreement with the earlier observations concerning reactions going through N-glycopyranosyl nitrilium ion intermediates (see Chapter 2.3.2.), since the intramolecular nucleophile (the carboxamido group), being always in place, reacts instantaneously with the kinetic α-nitrilium ion (or α-nitrilium–nitrile conjugate) to give the α-amide. Neighboring-group participation and therefore formation of β-nitrilium ion (or β-nitrilium–nitrile conjugate) is not expectable, since the leaving group and the potential participating group are not in trans relationship (see Chapter 2.2.1.).
Scheme 20. Proposed mechanism for the reaction of C-(per-O-acetyl-1-bromo-D-glycopyranosyl)formamides with nitriles

Formation of β-amide from penta-O-benzoyl-α-D-glucopyranose 64A (1 equiv. AcNHCH2CN, CH2Cl2, SnCl4) reported by Elías et al. seems to contradict the rule for neighboring-group participation, it is more likely, however, that the reaction adopts an S_N2 or S_N2-type pathway (Scheme
Scheme 21. Cleavage of the β-lactam ring observed by Kita et al.

Scheme 22. Possible pathways for the reaction of penta-O-benzoyl-α-D-glucopyranose with acetamido acetonitrile in CH$_2$Cl$_2$
22, path B or C) instead of neighboring-group participation (path A), since the existence of intermediate 64B of path A is hardly feasible in a poorly solvating medium such as dichloromethane.

Scheme 23. Possible pathways explaining the formation of β-amide using HgBr₂ promoter
The non-negligible ratio (33%) of \( \beta \)-amide (40) in the product mixture when using HgBr\(_2\) in acetonitrile may be explained by two different interpretations. One of them assumes the lower affinity of mercury bromide towards bromine as compared to that of silver carbonate. This would result in a shift of the reaction mechanism from an \( S_N1 \) (Ag\(_2\)CO\(_3\)) to a synchronous \( S_N2 \)-type (HgBr\(_2\)) push-pull pathway. The other possible explanation supposes the anomerization of the starting \( \alpha \)-bromide by HgBr\(_2\). The resulting \( \beta \)-bromide would react with neighboring-group participation to yield the \( \beta \)-amide (65A → 65B → 65D → 65F, Scheme 23).

Decreasing the amount of the nitrile increases the ratio of the \( \beta \)-amide as well. This experience can also be explained by the latter proposal since if the concentration of the nitrile decreases, the probability of the 65C → 65D step and thus the ratio of 65F vs. 65E increases.
4.3. Other Solvent Participation Reactions of the Fully Acetylated C-(1-
Bromoglycopyranosyl)formamides

The products obtained in the reaction of the acetyl protected C-(1-
bromoglycopyranosyl)formamides 22 and 30 with silver fluoride in
dimethylsulfoxide (see Scheme 16, Chapter 3.3.) can be rationalized by
a Pummerer-type rearrangement reported to occur between sulfoxides
and various electron-deficient carbon centers.\textsuperscript{125} The stereoselective
formation of the $\beta$-methylthiomethyl glycosides (46 and 47) observed in
both cases is probably due to the higher nucleophilicity of dimethyl
sulfoxide. Thus, the departure of bromide by complexation with silver
fluoride and attack of DMSO occurs, more or less, synchronously
(Scheme 24). We cannot explain, however, why silver fluoride is the only
promoter that facilitates the formation of the methylthiomethyl
glycosides.

Similar solvent incorporation reaction was observed by L. Kovács and
K. Czifrák in our laboratory with ketones. Thus 22, when stirred in
various symmetric ketones in the presence of a suitable promoter, were
converted to the spiro-iminodioxolane derivatives 66e and 66a (Scheme
25).\textsuperscript{118,126} The product originated from an upside attack by the ketone
(66e) was found to be the major product in all cases. Both spiro-
dioxolane derivatives could be isolated in pure form by column
chromatography, the overall yield of them being between 45 and 75 %.

The stereoselectivity of this reaction can probably be accounted for
similar reasons as the reaction with dimethylsulfoxide. The reaction with
ketones is unique, however, since reaction of the carbamoyl group with
acetonium ions or similar carbocations originated from ketones
(transformation similar to 67A $\rightarrow$ 67B, Scheme 26), to the best of our
knowledge, has not yet been observed.

$S_n$2-type incorporation of acetone has also been observed recently
by Fairbanks’ group in glycosylation reactions (see Scheme 27).
Scheme 24. Proposed mechanism for the reaction of acetylated C-(1-bromoglycopyranosyl)formamides with DMSO using AgF
Scheme 25. Reaction of C-(2,3,4,6-tetra-O-acetyl-1-bromogalactopyranosyl)formamide with ketones in the presence of AgOTf or Ag₂CO₃

Scheme 26. Proposed mechanism for the reaction of acetylated C-(1-bromoglycopyranosyl)formamides with acetone using Ag₂CO₃ promoter
Scheme 27. Incorporation of the solvent acetone in a glycosylation reaction with phenyl 2,3,4,6-tetra-O-benzyl-thiogluco-pyranoside
4.4. Cerium(IV)-ammonium Nitrate Mediated Radical Additions

From the three investigated glycal analogs, only the carbamoyl substituted 2-D-galactal furnished products similar to the ones obtained with the acetylated 2-D-galactal itself. The ratio of the products was, however, markedly different from that of the parent compound and depended on the reaction time unlike in case of 2-D-galactal. The higher ratio of the 1-ONO$_2$ derivative (53) in the reaction mixture when using short reaction times is probably the result of slower oxidation of the anomeric radical 68E (due to the higher energy-level of the electro-negatively substituted carbenium ion, cf. Chapter 2.1.2.), thus making the ligand transfer process more probable. The more crowded tertiary nitrate-ester, on the other hand, is probably more susceptible to solvolysis than the secondary one formed from 3,4,6-tri-O-acetyl-D-galactal. The oxidation potential of the employed D-galactal derivatives can be evaluated by cyclovoltametric measurements in order to approximate the ease of oxidation of the individual substituted glycosyl radicals. The values obtained with these derivatives are listed in Table 18.$^{127}$

<table>
<thead>
<tr>
<th>R</th>
<th>H</th>
<th>CONH$_2$</th>
<th>CN</th>
<th>COOMe</th>
</tr>
</thead>
<tbody>
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<td>1.96</td>
<td>&gt; 2.8</td>
<td>&gt; 2.8</td>
</tr>
</tbody>
</table>

Table 18. Cyclovoltametric values for R-substituted triacetyl D-galactals

In the case of the other two glycal derivatives (55 and 60) the oxidation of the anomeric radical is even less probable because of the uncommonly high energy-level of the carbenium ion that would result. One of the proposable pathways involves a radical cyclization–oxidation reaction sequence ($68E \rightarrow 68I \rightarrow 68G$, Scheme 28) the other assumes the electronic assistance of the neighboring malonyl residue in the "otherwise unaccomplishable" oxidation step ($68E \rightarrow 68G$). The former,
however, brings on the question, why the ligand transfer process does not compete and vice versa, why the ring closure does not compete in case of 51. The latter, on the other hand, questions why methanol does not act similarly to produce the methyl glycoside in one step.

Scheme 28. Possible reaction pathways in the CAN-mediated addition of dimethyl malonate to substituted D-galactals
Formation of the elimination product 59 in case of the cyano substituted D-galactal can be rationalized by one or both of the two pathways depicted in Scheme 28 (68E → 68K → 68J or 68E → 68J). Formation of similar elimination products cannot be excluded in the other two cases, moreover characteristic signals that may correspond to analogous molecules are seen in the ¹H NMR spectra of the crude products obtained with 51 and 60 as well.

Hydrolytic processes responsible for the formation of 54, 58 and 62 can be imagined by the Lewis-acid catalyzed substitution of –OMe (of the orthoesters) and the –ONO₂ groups (at the anomeric center) by water molecule (68F → 68C, 68D → 68B), but the existence of concurrent ligand transfer processes resulting the same products cannot either be excluded (68E → 68B).
5. Experimental

General Methods: Melting points were measured on a Kofler hot-stage and are uncorrected. Optical rotations were determined with a Perkin-Elmer 241 polarimeter at room temperature. NMR spectra were recorded with a Bruker WP 200 SY (1H, 200 MHz; 13C, 50 MHz), Bruker AM 360 (1H, 360 MHz; 13C, 90 MHz) or Avance DRX 500 (1H, 500 MHz; 13C, 125 MHz) spectrometer, with tetramethylsilane as an internal standard (1H) except for D₂O solutions that were calibrated to the value of the SR parameter (both 1H and 13C). The other 13C spectra were calibrated to the peaks of the deuterated solvent. TLC was performed on DC-Alurolle, Kieselgel 60 F254 (Merck), the plates were visualized by gentle heating. For column chromatography Kieselgel 60 (Merck) was used. Organic solutions were dried over anhydrous MgSO₄ and concentrated in vacuo at 40-50°C (water bath).

5.1. Syntheses of Starting Materials

C-(2,3,4,6-Tetra-O-acetyl-1-chloro-β-D-galactopyranosyl)formamide (41): 443 mg 2,3,4,6-tetra-O-acetyl-1-chloro-β-D-galactopyranosyl cyanide was dissolved in 4 ml cold (0 °C) AcOH which had previously been saturated with dry gaseous HCl. The solution was allowed to warm up to room temperature and to stand until TLC showed complete disappearance of the starting sugar (2 h). The reaction mixture was diluted with EtOAc and extracted with chilled water, satd. aq. NaHCO₃ solution and brine. Drying and concentration resulted a syrup, which was triturated with diethylether and evaporated to dryness. Crystallization from diethylether afforded title compound 41 (413 mg, 89 %).

1H NMR (360 MHz, CDCl₃): δ = 1.99, 2.08, 2.11, 2.18 (4s, 12H, OAc), 4.17 (dd, J = 11.6, 5.8 Hz, 1H, H-6'), 4.30 (dd, J = 11.6, 6.8 Hz, 1H, H-6), 4.58 (ddd, J = 6.8, 5.8, 1.5 Hz, 1H, H-5), 5.34 (dd, J = 10.4, 3.2 Hz, 1H, H-3), 5.55 (dd, J = 3.2, 1.5 Hz, 1H, H-4), 5.68 (d, J = 10.4 Hz, 1H, H-2), 6.47, 6.57 (2s, 2H, NH).
$^{13}$C NMR (90 MHz, CDCl$_3$): $\delta = 20.40$, 20.50, 20.58, 20.65 (COCH$_3$), 96.86 (C-1), 66.54, 66.86, 68.67, 71.90 (C-2,3,4,5), 60.90 (C-6), 166.68 (CONH$_2$, $J = 2.5$ Hz), 169.41, 169.76, 169.87, 170.52 (COCH$_3$).

*Methyl C-(3,4,6-tri-O-acetyl-2-deoxy-D-lyxo-hex-1-enopyranosyl)formate (60):* C-(3,4,6-tri-O-acetyl-2-deoxy-D-lyxo-hex-1-enopyranosyl)carb-aldehyde\textsuperscript{128} (100 mg, 0.33 mmol) was dissolved in 3 ml dry MeOH containing 0.06 ml (3 equiv.) dry AcOH. To this solution 290 mg (10 equiv.) activated MnO$_2$ and 50 mg NaCN (dried, 3 equiv.) was added and the mixture was stirred vigorously at 25 °C for 5 hours (TLC: complete). The suspension was diluted with 25 ml EtOAc and transferred to a separating funnel which contained 15 ml of an aqueous Na$_2$CO$_3$ solution (10 % (m/V)). After extraction the aqueous phase was washed with 2x15 ml EtOAc. The combined organic phase was extracted with aqueous Na$_2$CO$_3$ solution (10 % (m/V)), cc. NaCl solution (aqueous) dried and concentrated. Crude product: 84 mg (76 %) colorless syrupy 60. Its NMR data were identical with those published by Banaszek et al.\textsuperscript{129}
5.2. Synthesis of C-1 Substituted Glycosyl Fluoride Derivatives

**General procedure A** for the reaction of 1-chloro- \((20)^{41}\) and 1-bromoglycopyranosyl cyanides \((8, 10, 12\) and \(15)^{103,105}\) with silver fluoride: To a solution of a halo-cyanide (1 mmol) in dry acetonitrile (16 ml) dry silver fluoride (2 mmol) was added (the addition of the same amount of AgF was repeated in the case of \(20\) after 5 hours) and the suspension was stirred at room temperature (heated at reflux for 10 h in the case of \(20\)) in the dark. After the reaction had been completed (TLC) the mixture was diluted with chloroform (100 ml), filtered on Celite, and concentrated. Flash chromatography of the resulting syrup on a short silica-column (to remove silver salts) afforded a colorless or yellowish syrup.

**General procedure B** for the reaction of 1-bromoglycopyranosyl cyanides \((8\) and \(15\)) with silver tetrafluoroborate: To a solution of freshly dried silver tetrafluoroborate (2 mmol) in dry toluene (15 ml) a bromo-cyanide (1 mmol) dissolved in the same solvent (5 ml) was added at once when a white tar precipitated. The mixture was stirred at room temperature in the dark until the substrate was no more seen on TLC. The suspension was diluted with chloroform (50 ml), then filtered on Celite, and the filtrate was extracted with 1 M aqueous Na$_2$S$_2$O$_3$ solution (3 x 15 ml) and water (3 x 5 ml). The crude product was obtained by concentration of the dried organic layer.

**2,3,4,6-Tetra-O-acetyl-1-fluoro-\(\alpha\)-D-galactopyranosyl cyanide** \((9)\).

Prepared from \(8\) (1.81 g, 4.15 mmol) according to general procedure A: reaction time 2 d. Crude product: practically pure \(9\) (1.40 g, 90 %) which was crystallized from EtOH. Mp 87-88 °C; \([\alpha]_D^0 +80\) (c=1.2, CHCl$_3$). Anal.: Calcd for C$_{15}$H$_{18}$NO$_9$F (375.31): C, 48.01; H, 4.83; N, 3.73; F, 5.06. Found: C, 48.58; H, 4.99; N, 3.51; F, 5.21.

$^1$H and $^{13}$C NMR spectroscopic data are given in Table 19 and 20, respectively.
2,3,4-Tri-O-acetyl-1-fluoro-β-D-arabinopyranosyl cyanide (11).
Prepared from 10 (2.32 g, 6.37 mmol) according to general procedure A: reaction time 2 d. Crude product: practically pure 11 (1.52 g, 79 %) which was crystallized from EtOH. Mp 156-157 °C; [α]D +63 (c=1.2, CHCl3). Anal.: Calcd for C12H14NO7F (303.24): C, 47.53; H, 4.65; N, 4.62; F, 6.26. Found: C, 48.08; H, 4.80; N, 4.47; F, 6.28. 
1H and 13C NMR spectroscopic data are given in Table 19 and 20, respectively.

2,3,4,6-Tetra-O-acetyl-1-fluoro-α-D-glucopyranosyl cyanide (13).
Prepared from 12 (1.46 g, 3.35 mmol) according to general procedure A: reaction time 1 h. Crude product: 1.11 g, identified as a mixture of 13 and 14 in ~1:1 ratio by 1H NMR. Column chromatography (eluent: EtOAc-hexanes 1:4 → 1:1) afforded pure 13 (266 mg, 21 %) as a colorless syrup. [α]D +57 (c=1.5, CHCl3). Anal.: Calcd for C15H18NO9F (375.31): C, 48.01; H, 4.83; N, 3.73; F, 5.06. Found: C, 49.18; H, 5.11; N, 3.36; F, 5.49. 
1H and 13C NMR spectroscopic data are given in Table 19 and 20, respectively.

2,3,4-Tri-O-acetyl-1-fluoro-α-D-xylopyranosyl cyanide (16).
Prepared from 15 (0.50 g, 1.37 mmol) according to general procedure A: reaction time 1 h. Crude product: 220 mg, identified as a mixture of 16 and 17 in ~3:1 ratio by 1H NMR. Column chromatography (eluent: EtOAc-hexanes 1:4 → 1:1) afforded pure 16 (47 mg, 11 %) which was crystallized from Et2O-hexanes. Mp 119-121 °C; [α]D -23 (c=1.5, CHCl3). Anal.: Calcd for C12H14NO7F (303.24): C, 47.53; H, 4.65; N, 4.62; F, 6.26. Found: C, 47.78; H, 4.57; N, 4.59; F, 6.15. 
1H and 13C NMR spectroscopic data are given in Table 19 and 20, respectively.
2,3,4,6-Tetra-O-acetyl-1-fluoro-β-D-galactopyranosyl cyanide (18).
Prepared from 8 (0.32 g, 0.73 mmol) according to general procedure B: reaction time 1 week. Crude product: 164 mg. Column chromatography (eluent: EtOAc-hexanes 1:3 → 1:1) afforded pure 18 (99 mg, 36 %) as a colorless syrup. \([\alpha]_D +71\) (c=1.1, CHCl₃). Anal.: Calcd for C₁₅H₁₈NO₉F (375.31): C, 48.01; H, 4.83; N, 3.73; F, 5.06. Found: C, 47.88; H, 4.71; N, 3.59; F, 5.15.

1H and 13C NMR spectroscopic data are given in Table 19 and 20, respectively.

2,3,4-Tri-O-acetyl-1-fluoro-β-D-xylopyranosyl cyanide (19).
Prepared from 15 (0.32 g, 0.88 mmol) according to general procedure B: reaction time 1 week. Crude product: 240 mg. Column chromatography (eluent: EtOAc-hexanes 1:3 → 1:1) afforded pure 19 (101 mg, 38 %) as a colorless syrup, which was crystallized from CH₂Cl₂-Et₂O. Mp 164-165 °C; \([\alpha]_D +23\) (c=1.1, CHCl₃). Anal.: Calcd for C₁₂H₁₄NO₇F (303.24): C, 47.53; H, 4.65; N, 4.62; F, 6.26. Found: C, 47.78; H, 4.78; N, 4.49; F, 6.39.

1H and 13C NMR spectroscopic data are given in Table 19 and 20, respectively.

1-Fluoro-α-D-galactopyranosyl cyanide (21).
Prepared from 9 (375 mg, 1.00 mmol) with saturated methanolic ammonia (10 ml) at 0 °C. After 30 min the solution was concentrated, and subjected to column chromatography (eluent: chloroform-methanol 9 : 1) to give pure 21 (59 mg, 28 %) as a colorless syrup. \([\alpha]_D +97\) (c=0.3, H₂O). Anal.: Calcd for C₇H₁₀NO₅F (207.16): C, 40.59; H, 4.87; N, 6.76. Found: C, 40.38; H, 4.75; N, 6.57.

1H and 13C NMR spectroscopic data are given in Table 19 and 20, respectively.
Table 19

$^1$H NMR data of the 1-fluoroglycopyranosyl cyanides measured at 200 MHz

<table>
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<tr>
<th>Compound (solvent)</th>
<th>H-2 $J_{2,3}$ $J_{F,2}$</th>
<th>H-3 $J_{3,4}$ $J_{F,3}$</th>
<th>H-4 $J_{4,5}$ $J_{F,4}$</th>
<th>H-5 $J_{5,6}$ / $J_{5,6'}$</th>
<th>H-6/H-6' $J_{5,5'}$</th>
<th>CH$_3$</th>
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</thead>
<tbody>
<tr>
<td>9$^c$ (CDCl$_3$)</td>
<td>5.50 10.9 12.1</td>
<td>5.17 3.2 0.7</td>
<td>5.52 1.2 3.0</td>
<td>4.39 5.9/6.8 0.8</td>
<td>4.27/4.21 11.5</td>
<td>2.01 2.09 2.19 2.20</td>
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<tr>
<td>11$^b$ (CDCl$_3$)</td>
<td>5.44 8.3 8.5</td>
<td>5.21 3.3 2.2</td>
<td>5.34 5.2/2.7</td>
<td>—</td>
<td>4.23/4.06 12.9</td>
<td>2.06 2.12 2.20</td>
</tr>
<tr>
<td>13 (C$_6$D$_6$)</td>
<td>5.42 9.0 10.8</td>
<td>5.26 8.5 ∼1</td>
<td>5.51 10.0</td>
<td>3.88 4.0/2.0</td>
<td>4.11/3.78 12.8</td>
<td>1.47 1.58 1.58 1.61</td>
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<tr>
<td>16 (C$_6$D$_6$)</td>
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<td>5.26 5.2 3.3/4.5</td>
<td>—</td>
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<tr>
<td>18 (CDCl$_3$)</td>
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<td>4.46 7.0/5.9</td>
<td>4.20/4.15 12.4</td>
<td>2.00 2.08 2.20 2.21</td>
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<td>19 (C$_6$D$_6$)</td>
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<td>5.44 8.6 6.2/11.0</td>
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<td>3.42/3.13 11.3</td>
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<tr>
<td>21$^c$ (D$_2$O)</td>
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<td>3.86 n.d.$^d$</td>
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$^a$ Applies for the pentose derivatives 11, 16 and 19. $^b$ 500 MHz. 
$^c$ 360 MHz. $^d$ Cannot be determined.
Table 20

$^{13}$C NMR data for the 1-fluoroglycopyranosyl cyanides measured in CDCl$_3$ at 50.3 MHz ($\delta$ [ppm], $J$ [Hz])

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<td>J$_{C,F}$</td>
<td>J$_{C,F}$</td>
<td>J$_{C,F}$</td>
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<td>66.95</td>
<td>71.64</td>
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<td>111.66</td>
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<td>21$^b$</td>
<td>110.20</td>
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<td>70.17</td>
<td>73.37</td>
<td>80.43</td>
<td>63.18</td>
<td>115.37</td>
<td>47</td>
<td>n.d.$^c$</td>
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</table>

$^a$ Measured at 125 MHz. $^b$ Measured in D$_2$O at 90 MHz. $^c$ Not determined
C-(2,3,4,6-tetra-O-acetyl-1-fluoro-α-D-galactopyranosyl)formamide (24) and C-(2,3,4,6-tetra-O-acetyl-1-fluoro-β-D-galactopyranosyl)formamide (25).

In 8 ml dried nitromethane, 400 mg 22 (0.881 mmol) was dissolved and activated molecular sieves were added. The solution was stirred for overnight and AgF was added (224 mg, 1.76 mmol) in one portion. After 1 day, the TLC showed complete conversion (eluent: ethylacetate–hexanes 3:1, V/V). Thus, the reaction mixture was diluted with ethylacetate, filtered through Celite and concentrated. Column chromatography of the resulting syrup (eluent: ethylacetate–hexanes 1:1 → 3:1, V/V) afforded 173 mg 24 (50 %), 69 mg 25 (20 %) and 45 mg 26 (13 %).

24: 
$^1$H NMR (360 MHz, CDCl$_3$): $\delta$ = 1.98, 2.05, 2.10, 2.19 (4s, 12H, OAc), 4.14 (dd, $J$ = 11.5, 6.5 Hz, 1H, H-6$'$), 4.19 (dd, $J$ = 11.5, 6.5 Hz, 1H, H-6), 4.88 (ddd, $J$ = 6.5, 6.5, 1.6 Hz, 1H, H-5), 5.53 (dd, $J$ = 16.6, 10.6 Hz, 1H, H-2), 5.54 (ddd, $J$ = 3.5, 2.8, 1.5 Hz, 1H, H-4), 5.77 (dd, $J$ = 10.6, 3.5 Hz, 1H, H-3), 6.53, 6.56 (2s, 2H, NH). $^{13}$C NMR (90 MHz, CDCl$_3$): $\delta$ = 20.43, 20.48 (COCH$_3$), 107.24 (d, $J$ = 229 Hz, C-1), 68.68 (d, $J$ = 27 Hz, C-2), 61.25 (C-6), 167.59 (CONH$_2$, $J$ = 32 Hz), 169.41, 169.76, 169.87, 170.52 (COCH$_3$).

25: 
$^1$H NMR (200 MHz, CDCl$_3$): $\delta$ = 2.03, 2.05, 2.09, 2.10 (4s, 12H, OAc), 4.24 (d, $J$ = 2.9 Hz, 2H, H-6,6$'$), 4.57 (dddd, $J$ = 10.0, 2.9, 2.9, 2.9 Hz, 1H, H-5), 5.32 (dd, $J$ = 10.0, 8.8 Hz, 1H, H-4), 5.64 (dd, $J$ = 8.8, 7.3 Hz, 1H, H-3), 5.35 (dd, $J$ = 12.0, 7.3 Hz, 1H, H-2), 6.64, 6.73 (2s, 2H, NH).
5.3. Synthesis of N-Acyl-1-Cyano-Glycosylamine Derivatives

**General procedure A for the preparation of per-O-acetyl-N-acyl-1-cyano-b-glycopyranosylamines 23, 32-39:**

An acetylated C-(1-bromo-b-glycopyranosyl)formamide\(^{43,44,109}\) (22, 30, 31) (0.25 mmol) was dissolved in a nitrile (RCN) (1 ml), distilled from \(\text{P}_2\text{O}_5\), and silver carbonate (0.069 g, 0.25 mmol) was added in one portion. The mixture was stirred at room temperature in the dark until complete disappearance of the starting material (TLC ethyl acetate–hexane 3 : 1) (2-3 days). It was then diluted with acetone (9 ml), filtered through a Celite pad, the filter cake was washed with acetone (3 ml), and the filtrate was concentrated under diminished pressure at 40 ºC (bath temperature). The residue was purified on a short silica gel column to eliminate very polar contaminations and silver salts (eluent: ethyl acetate–chloroform 1 : 3) to give pure products 23, 32-39.

**General procedure B for the reaction of C-(2,3,4,6-tetra-O-acetyl-1-bromo-\(\beta\)-D-glycopyranosyl)formamides 22 and 30 with silver fluoride:**

To a solution of a bromosugar (1 mmol) in dry acetonitrile (16 ml) dry silver fluoride (2 mmol) was added and the suspension was stirred at room temperature in the dark. After the reaction had been completed (TLC) the mixture was diluted with chloroform (100 ml), filtered on Celite, and concentrated. The residue was purified by silica gel column chromatography (eluent: ethyl acetate–chloroform 1 : 3).

**General procedure C for the preparation of per-O-acetyl-N-acyl-1-cyano-\(\alpha\)-D-galactopyranosylamines 42 and 44:**

C-(2,3,4,6-Tetra-O-acetyl-1-bromo-\(\beta\)-D-galactopyranosyl)formamide (22) (500 mg, 1.10 mmol) was dissolved in a mixture of dry nitromethane (4.7 ml) and a nitrile (10 equiv.), and stirred with freshly activated molecular sieves overnight. Mercury cyanide (500 mg, 1.98 mmol) was added in one portion. The mixture was stirred at room temperature until complete disappearance of the starting material (TLC ethyl acetate–
hexane 3 : 1) (2-3 days). It was then diluted with chloroform, filtered through a Celite pad, and the filtrate was concentrated under diminished pressure (in case of benzonitrile co-evaporation with water was used for the final removal of the nitrile). The residue was dissolved in chloroform and washed several times with 1 M KBr solution in order to remove mercury salts. The products were purified by column chromatography (eluent: ethyl acetate–hexanes 1:1 → 3:1) to give pure products 42 and 44.

**General procedure D for the preparation of per-O-acetyl-N-acyl-1-cyano-β-D-galactopyranosylamines 40, 43, 45:**

C-(2,3,4,6-Tetra-O-acetyl-1-bromo-β-D-galactopyranosyl)formamide (22) (500 mg, 1.10 mmol) was dissolved in a mixture of dry nitromethane (4.7 ml) and a nitrile (10 equiv.), and stirred with freshly activated molecular sieves overnight. Mercury bromide (500 mg, 1.39 mmol) was added in one portion. The mixture was stirred at room temperature until complete disappearance of the starting material (TLC ethyl acetate–hexane 3 : 1) (2-3 days). It was then diluted with chloroform, filtered through a Celite pad, and the filtrate was concentrated under diminished pressure. The residue was dissolved in chloroform and washed several times with 1 M KBr solution in order to remove mercury salts. The products were purified by column chromatography (eluent: ethyl acetate–hexanes 1:1 → 3:1) to give pure products.

**N-Acetyl-2,3,4,6-tetra-O-acetyl-1-cyano-α-D-galactopyranosylamine** (23).

Prepared from 22 (511 mg, 1.12 mmol) in acetonitrile according to general procedure A: reaction time 2 d. Crude product: 498 mg yellowish syrup, which was crystallized from EtOAc to afford white crystals (353 mg, 76 %). Mp 155-156 °C; [α]₀ +49 (c=1.15, CHCl₃). Anal.: Calcd for C₁₇H₂₂N₂O₁₀ (414.364): C, 49.28; H, 5.35; N, 6.76. Found: C, 48.27; H, 5.43; N, 6.35.
1H and 13C NMR spectroscopic data are given in Table 21 and 22, respectively.

N-Propanoyl-2,3,4,6-tetra-O-acetyl-1-cyano-α-D-galactopyranosyl-amine (32).
Prepared from 22 (50 mg, 0.11 mmol) in propionitrile according to general procedure A: reaction time 2 d. Crude product: 35 mg colorless syrup, practically pure 32 (74 %), which was crystallized twice from CH2Cl2 – Et2O to afford white crystals (15 mg). Mp 186-187 °C; [α]D +55 (c=0.91, CHCl3). Anal.: Calcd for C18H24N2O10 (428.391): C, 50.47; H, 5.65; N, 6.54. Found: C, 50.41; H, 5.93; N, 6.67.

N-Propanoyl-2,3,4,6-tetra-O-acetyl-1-cyano-α-D-galactopyranosyl-amine (33).
Prepared from 22 (50 mg, 0.11 mmol) in acrylonitrile according to general procedure A: reaction time 2 d. Crude product: 27 mg yellowish syrup, practically pure 33 (57 %), which was crystallized from CH2Cl2 – Et2O to afford white crystals (10 mg). Mp 158-160 °C; [α]D +61 (c=0.80, CHCl3). Anal.: Calcd for C18H22N2O10 (426.375): C, 50.70; H, 5.20; N, 6.57. Found: C, 49.93; H, 5.12; N, 6.39.

1H and 13C NMR spectroscopic data are given in Table 21 and 22, respectively.

N-(3'-Butenoyl)-2,3,4,6-tetra-O-acetyl-1-cyano-α-D-galactopyranosyl-amine (34).
Prepared from 22 (100 mg, 0.22 mmol) in allylcyanide according to general procedure A: reaction time 2 d. Crude product: 311 mg colorless syrupy liquid (probably containing allylcyanide). Column chromatography (eluent: EtOAc-hexanes 1:1 → 3:1) of the liquid afforded 92 mg syrup, which was subjected to column chromatography again to yield pure 34 (60 mg, 62 %). White crystalline material (29 mg) was obtained by crystallization of the syrup from CH2Cl2 – Et2O. Mp 149-150 °C; [α]D +57
N-Methoxyacetyl-2,3,4,6-tetra-O-acetyl-1-cyano-α-D-galactopyranosylamine (35).
Prepared from 22 (100 mg, 0.22 mmol) in methoxyacetonitrile according to general procedure A: reaction time 2 d. Crude product: 51 mg yellowish syrup. Column chromatography (eluent: EtOAc-hexanes 1:1 → 3:1) afforded 19 mg pure 35 as a colorless syrup (24 %). White crystalline material was obtained by crystallization of the syrup together with another crop of pure 35 from CH₂Cl₂ – Et₂O. Mp 149-151 °C; [α]D +29 (c=1.22, CHCl₃). Anal.: Calcd for C₁₉H₂₄N₂O₁₀ (440.401): C, 51.82; H, 5.49; N, 6.36. Found: C, 51.34; H, 5.43; N, 6.55.

1H and 13C NMR spectroscopic data are given in Table 21 and 22, respectively.

N-Propanoyl-2,3,4,6-tetra-O-acetyl-1-cyano-α-D-glucopyranosylamine (37).
Prepared from 30 (314 mg, 0.69 mmol) in propionitrile according to general procedure A: reaction time 3 d. Crude product: 290 mg yellowish syrup. Column chromatography (eluent: EtOAc-hexanes 1:1 → 3:1) of the crude product yielded 157 mg pure 37 (53 %) as a colorless syrup. Crystallization from EtOAc afforded white crystals. Mp 187-189 °C; [α]D +25 (c=0.61, CHCl₃). Anal.: Calcd for C₁₈H₂₄N₂O₁₀ (444.390): C, 48.65; H, 5.44; N, 6.30. Found: C, 50.00; H, 5.70; N, 6.47.

1H and 13C NMR spectroscopic data are given in Table 21 and 22, respectively.

N-Acetyl-2,3,4-tri-O-acetyl-1-cyano-β-D-arabinopyranosylamine (38).
Prepared from 31 (140 mg, 0.36 mmol) in acetonitrile according to general procedure A: reaction time 2 d. Crude product: 101 mg yellowish
syrup. Column chromatography (eluent: EtOAc-hexanes 1:1 → 3:1) of the crude product yielded 52 mg pure 38 (41 %) as a colorless syrup, which was crystallized from CH₂Cl₂ – Et₂O to afford white crystals (43 mg). Mp 170-172 °C; [α]D -29 (c=1.07, CHCl₃). Anal.: Calcd for C₁₇H₂₂N₂O₁₀ (342.301): C, 49.12; H, 5.30; N, 8.18. Found: C, 50.10; H, 5.57; N, 8.33.

N-Propenoyl-2,3,4-tri-O-acetyl-1-cyano-β-D-arabinopyranosylamine (39).
Prepared from 31 (308 mg, 0.81 mmol) in acrylonitrile according to general procedure A: reaction time 2 d. Crude product: 251 mg yellowish syrup. Column chromatography (eluent: EtOAc-hexanes 1:1 → 3:1) of the crude product yielded 120 mg pure 39 (43 %) as a colorless syrup. [α]D -29 (c=1.06, CHCl₃).

1H and 13C NMR spectroscopic data are given in Table 21 and 22, respectively.

Reaction of C-(2,3,4,6-tetra-O-acetyl-1-bromo-β-D-galactopyranosyl) formamide 22 with silver fluoride according to general procedure B: From 620 mg 22 (1.37 mmol), reaction time: 1 d. Crude product: 567 mg yellowish syrup. Column chromatography (eluent: EtOAc-hexanes 1:1 → 3:1) afforded colorless syrup 23 (381 mg, 70 %) and 24 (16 mg, 3 %).

Reaction of C-(2,3,4,6-tetra-O-acetyl-1-bromo-β-D-glucopyranosyl) formamide (30) with silver fluoride according to general procedure B: From 599 mg 30 (1.32 mmol), reaction time: 1 d. Crude product: 336 mg yellowish syrup. Column chromatography (eluent: EtOAc-hexanes 1:1 → 3:1) afforded colorless syrup N-Acetyl-2,3,4,6-tetra-O-acetyl-1-cyano-α-D-glucopyranosylamine 36 (196 mg, 36 %). Mp 179-181 °C; [α]D +57 (c=1.01, acetone). Anal.: Calcd for C₁₇H₂₂N₂O₁₀ (414.364): C, 49.28; H, 5.35; N, 6.76. Found: C, 48.52; H, 5.60; N, 6.70.

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$^1$H and $^{13}$C NMR spectroscopic data are given in Table 21 and 22, respectively.

Reaction of C-(2,3,4,6-tetra-O-acetyl-1-bromo-β-D-galactopyranosyl) formamide (22) with pivalonitrile according to general procedure C: From 500 mg 22 (1.10 mmol), reaction time: 3 d. Crude product: 458 mg yellowish syrup. Column chromatography afforded 43 (299 mg, 60 %) and 42 (32 mg, 6 %).

42: Colorless syrup; $[\alpha]_D^\circ +59$ (c=1.06, CHCl$_3$). Anal.: Calcd for C$_{20}$H$_{28}$N$_2$O$_{10}$ (456.444): C, 52.63; H, 6.18; N, 6.14. Found: C, 52.49; H, 5.95; N, 5.81.

43: Colorless syrup; identical with the substance obtained by procedure D.

Reaction of C-(2,3,4,6-tetra-O-acetyl-1-bromo-β-D-galactopyranosyl) formamide (22) with benzonitrile according to general procedure C: From 500 mg 22 (1.10 mmol), reaction time: 3 d. Crude product: 468 mg yellowish syrup. Column chromatography afforded 44 (323 mg, 64 %) as a colorless syrup.

44: $[\alpha]_D^\circ +66$ (c=1.00, CHCl$_3$). Anal.: Calcd for C$_{22}$H$_{24}$N$_2$O$_{10}$ (476.433): C, 55.46; H, 5.08; N, 5.88. Found: C, 55.11; H, 4.89; N, 5.52.

Reaction of C-(2,3,4,6-tetra-O-acetyl-1-bromo-β-D-galactopyranosyl) formamide (22) with acetonitrile according to general procedure D: From 500 mg 22 (1.10 mmol), reaction time: 2 d. Crude product: 392 mg yellowish syrup. Column chromatography afforded 40 (149 mg, 33 %), 26 (85 mg, 20 %) and 23 (66 mg, 15 %).

40: White crystals, Mp 161-163 °C. Anal.: Calcd for C$_{17}$H$_{22}$N$_2$O$_{10}$ (414.364): C, 49.28; H, 5.35; N, 6.76. Found: C, 48.77; H, 5.23; N, 6.00.

Reaction of C-(2,3,4,6-tetra-O-acetyl-1-bromo-β-D-galactopyranosyl) formamide (22) with pivalonitrile according to general procedure D: From 500 mg 22 (1.10 mmol), reaction time: 3 d. Crude product: 468 mg
yellowish syrup. Column chromatography afforded 43 (161 mg, 32 %), 26 (87 mg, 20 %) and 42 (62 mg, 12 %).

43: White crystals, Mp 158-160 °C. Anal.: Calcd for C_{20}H_{28}N_{2}O_{10} (456.444): C, 52.63; H, 6.18; N, 6.14. Found: C, 52.60; H, 5.90; N, 5.72.

Reaction of C-(2,3,4,6-tetra-O-acetyl-1-bromo-β-D-galactopyranosyl) formamide (22) with benzonitrile according to general procedure D:
From 500 mg 22 (1.10 mmol), reaction time: 3 d. Crude product: 266 mg yellowish syrup. Column chromatography afforded 45 (161 mg, 32 %), 26 (87 mg, 20 %) and 44 (62 mg, 12 %).

45: White crystals, Mp 159-162 °C. Anal.: Calcd for C_{22}H_{24}N_{2}O_{10} (476.433): C, 55.46; H, 5.08; N, 5.88. Found: C, 55.20; H, 4.95; N, 5.41.
Table 21

$^1$H NMR data for N-(1-cyano-D-glycopyranosyl)amides 23 and 32-35 measured in CDCl$_3$ at 360 MHz referenced to internal Me$_4$Si ($\delta$ [ppm], J [Hz])

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$^a$ Integral: 6H $^b$ At 200 MHz.
Table 21 (continuation)

$^1$H NMR data for N-(1-cyano-D-glycopyranosyl)amides 36-40 measured in CDCl$_3$ at 200 MHz referenced to internal Me$_4$Si ($\delta$ [ppm], $J$ [Hz])

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$^a$ Assignments for H-4 and H-5 are tentative. $^b$ Assignment for H-3 is tentative. $^c$ Assignment for H-6 is tentative.
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<td>doublet</td>
<td></td>
<td>2.06&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
<td>2.16</td>
<td></td>
</tr>
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<td></td>
<td></td>
<td>2.21</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Applies for the pentose derivatives 38 and 39.  
<sup>b</sup> In (CD<sub>3</sub>)<sub>2</sub>CO.  
<sup>c</sup> Integral: 6H
**Table 21 (continuation)**

$^1$H NMR data for $N$-(1-cyano-$d$-glycopyranosyl)amides 42-45 measured in CDCl$_3$ at 360 MHz referenced to internal Me$_4$Si ($\delta$ [ppm], $J$ [Hz])

<table>
<thead>
<tr>
<th>Compound</th>
<th>H-2</th>
<th>H-3</th>
<th>H-4</th>
<th>H-5</th>
<th>H-6/H-6’</th>
<th>NH</th>
<th>CH$_3$</th>
<th>Others</th>
</tr>
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<tbody>
<tr>
<td>42</td>
<td>5.75</td>
<td>5.12</td>
<td>5.40</td>
<td>4.02–4.21</td>
<td>multiplet</td>
<td>6.52</td>
<td>2.00</td>
<td>1.28 (s, 9H) t-butyl</td>
</tr>
<tr>
<td></td>
<td>10.5</td>
<td>3.2</td>
<td>–</td>
<td></td>
<td></td>
<td>2.04</td>
<td>2.17</td>
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<td>43</td>
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<td>5.46</td>
<td>5.54</td>
<td>4.43</td>
<td>4.20/4.16</td>
<td>7.14</td>
<td>2.02</td>
<td>1.20 (s, 9H) t-butyl</td>
</tr>
<tr>
<td></td>
<td>10.3</td>
<td>3.2</td>
<td>1.0</td>
<td>6.8/6.8</td>
<td>11.3</td>
<td>2.05</td>
<td>2.18</td>
<td>2.21</td>
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<tr>
<td>44</td>
<td>5.85</td>
<td>5.37</td>
<td>5.45</td>
<td>4.32</td>
<td>4.22/4.10</td>
<td>7.14</td>
<td>1.97</td>
<td>7.53 (t, 2H) 7.63 (t, 1H) 7.90 (d, 2H) phenyl</td>
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<tr>
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<td>10.4</td>
<td>3.2</td>
<td>1.2</td>
<td>6.7/6.7</td>
<td>11.0</td>
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<td>45</td>
<td>5.33</td>
<td>5.52</td>
<td>5.58</td>
<td>4.52</td>
<td>4.19/4.22</td>
<td>7.88</td>
<td>2.04</td>
<td>7.48 (t, 2H) 7.58 (t, 1H) 7.81 (d, 2H) phenyl</td>
</tr>
<tr>
<td></td>
<td>10.4</td>
<td>3.0</td>
<td>1.2</td>
<td>6.7/6.7</td>
<td>11.0</td>
<td>2.06</td>
<td>2.17</td>
<td>2.24</td>
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Table 22

$^{13}$C NMR data for N-(1-cyano-D-glycopyranosyl)amides 23 and 32-35 in CDCl$_3$ at 90 MHz referenced to solvent residual signal ($\delta$ [ppm], J [Hz])

<table>
<thead>
<tr>
<th>Compound</th>
<th>C-1</th>
<th>C-2,3,4,5</th>
<th>C-6</th>
<th>CN ($J_{H2,CN}/J_{NH,CN}$)</th>
<th>C=O</th>
<th>CH$_3$</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>77.71</td>
<td>67.71</td>
<td>67.29</td>
<td>67.50</td>
<td>67.74</td>
<td>60.57</td>
<td>114.75 ($\sim3/\sim3$)</td>
</tr>
<tr>
<td>32$^b$</td>
<td>77.67</td>
<td>67.71</td>
<td>67.39</td>
<td>67.63</td>
<td>60.64</td>
<td>114.78 ($\sim3/\sim3$)</td>
<td>168.13</td>
</tr>
<tr>
<td>33</td>
<td>78.17</td>
<td>67.71</td>
<td>67.61</td>
<td>67.74</td>
<td>68.08</td>
<td>60.64</td>
<td>114.47 ($\sim3/\sim3$)</td>
</tr>
<tr>
<td>34</td>
<td>77.98</td>
<td>66.59</td>
<td>67.62</td>
<td>67.74</td>
<td>68.05</td>
<td>60.66</td>
<td>114.45 ($\sim3/\sim3$)</td>
</tr>
<tr>
<td>35</td>
<td>77.81</td>
<td>66.42</td>
<td>67.55</td>
<td>67.85</td>
<td>68.10</td>
<td>60.52</td>
<td>114.13 ($\sim3/\sim3$)</td>
</tr>
</tbody>
</table>

$^a$ Signal of higher intensity $^b$ At 50 MHz.
Table 22 (continuation)

$^{13}$C NMR data for $N$-(1-cyano-D-glycopyranosyl)amides 36-40 in CDCl$_3$ at 90 MHz referenced to solvent residual signal ($\delta$ [ppm], $J$ [Hz])

<table>
<thead>
<tr>
<th>Compound</th>
<th>C-1</th>
<th>C-2,3,4,5</th>
<th>C-6</th>
<th>CN ($J_{H2,CN}/J_{NH,CN}$)</th>
<th>C=O</th>
<th>CH$_3$</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>36$^{ab}$</td>
<td>78.13</td>
<td>68.54</td>
<td>69.26</td>
<td>71.11</td>
<td>71.46</td>
<td>61.83</td>
<td>115.91 (~3/~3)</td>
</tr>
<tr>
<td>37$^a$</td>
<td>76.05</td>
<td>66.88</td>
<td>68.19</td>
<td>69.79</td>
<td>70.13</td>
<td>60.58</td>
<td>114.09 (~3/~3)</td>
</tr>
<tr>
<td>38</td>
<td>78.05</td>
<td>66.77</td>
<td>66.94</td>
<td>67.90</td>
<td></td>
<td>61.58</td>
<td>114.71 (~3/~3)</td>
</tr>
<tr>
<td>39$^a$</td>
<td>78.14</td>
<td>66.67</td>
<td>66.91</td>
<td>67.71</td>
<td></td>
<td>61.65</td>
<td>114.55 (~3/~3)</td>
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<td>40</td>
<td>79.86</td>
<td>66.13</td>
<td>68.53$^c$</td>
<td>71.23</td>
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<td>60.20</td>
<td>111.86</td>
</tr>
</tbody>
</table>

$^a$ At 50 MHz.  $^b$ In (CD$_3$)$_2$CO.  $^c$ Signal of higher intensity.
Table 22 (continuation)

$^{13}$C NMR data for N-(1-cyano-D-glycopyranosyl)amides 42-45
in CDCl$_3$ at 90 MHz referenced to solvent residual signal (δ [ppm], J [Hz])

<table>
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<tr>
<th>Compound</th>
<th>C-1</th>
<th>C-2,3,4,5</th>
<th>C-6</th>
<th>CN $^a$</th>
<th>C=O</th>
<th>CH$_3$</th>
<th>Others</th>
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<tr>
<td>42</td>
<td>77.88</td>
<td>66.40</td>
<td>60.60</td>
<td>114.52</td>
<td>167.63</td>
<td>20.24</td>
<td>26.95,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>67.57</td>
<td></td>
<td>(~3/~3)</td>
<td>169.65</td>
<td>20.32</td>
<td>20.32,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>67.77$^a$</td>
<td></td>
<td></td>
<td>169.95</td>
<td>20.81</td>
<td>39.54,</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>170.29</td>
<td>20.84</td>
<td>t-butyl</td>
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<td></td>
<td>177.82</td>
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<td></td>
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<tr>
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<td>66.16</td>
<td>60.09</td>
<td>112.01</td>
<td>169.09</td>
<td>20.32</td>
<td>39.01,</td>
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<td>(5.5/7.6)</td>
<td>169.73</td>
<td>20.48$^a$</td>
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<td>170.11</td>
<td>20.61</td>
<td>t-butyl</td>
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<td>177.38</td>
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<td>45</td>
<td>80.60</td>
<td>66.21</td>
<td>60.16</td>
<td>111.93</td>
<td>165.44</td>
<td>20.27</td>
<td>127.26$^a$</td>
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<td>68.44</td>
<td></td>
<td>(5.5/7.3)</td>
<td>169.06</td>
<td>20.36</td>
<td>128.75$^a$</td>
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<td>172.65</td>
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<td>phenyl</td>
</tr>
</tbody>
</table>

$^a$ Signal of higher intensity
5.4. Synthesis of Methylthiomethyl Glycoside Derivatives

**General procedure for the preparation of the methylthiomethyl glycosides 46 and 47:**

A C-(2,3,4,6-tetra-O-acetyl-1-bromo-d-glycopyranosyl)formamide\(^{44,109}\) (22, 30) was dissolved in dry dimethylsulfoxide (4 ml/mmol sugar) and silver fluoride (2 equiv.) was added in one portion. The mixture was stirred at room temperature in the dark until complete disappearance of the starting material (TLC ethyl acetate–hexane 3 : 1) (5 – 30 minutes). It was then diluted with water (10 ml), extracted with diethylether (5 x 10 ml). The organic phase was washed with chilled water (2 x 5 ml) and dried with anhydrous MgSO\(_4\). After filtering the drying agent off, the filtrate was concentrated under diminished pressure at 40 °C (bath temperature), to give pure products 46 and 47, respectively.

*Methylthiomethyl 2,3,4,6-tetra-O-acetyl-1-carbamoyl-\(\beta\)-D-galactopyranoside* (46).

Prepared from 22 (111 mg, 0.24 mmol) according to general procedure: reaction time 5 min. Crude product: 17 mg (15 %) practically pure 46 as a colorless syrup, which was crystallized from CH\(_2\)Cl\(_2\) – Et\(_2\)O to afford white crystals. Mp 155-156 °C; \([\alpha]_D^0 +29\) (c=1.07, CHCl\(_3\)). Anal.: Calcd for C\(_{17}\)H\(_{25}\)NO\(_{11}\)S (451.447): C, 45.23; H, 5.58; N, 3.10. Found: C, 46.31; H, 5.93; N, 3.46.

\(^1\)H and \(^{13}\)C NMR spectroscopic data are given in Table 23.

*Methylthiomethyl 2,3,4,6-tetra-O-acetyl-1-carbamoyl-\(\beta\)-D-glucopyranoside* (47).

Prepared from 30 (288 mg, 0.63 mmol) according to general procedure: reaction time 30 min. Crude product: 31 mg (11 %) practically pure 47 (colorless syrup). \([\alpha]_D^0 +21\) (c=1.03, CHCl\(_3\)). Anal.: Calcd for C\(_{17}\)H\(_{25}\)NO\(_{11}\)S (451.447): C, 45.23; H, 5.58; N, 3.10. Found: C, 46.12; H, 5.91; N, 3.33.

\(^1\)H and \(^{13}\)C NMR spectroscopic data are given in Table 23.
Table 23

$^1$H and $^{13}$C NMR data for methylthiomethyl glycosides 46 and 47 measured in CDCl$_3$ referenced to internal Me$_4$Si ($\delta$ [ppm], $J$ [Hz])

<table>
<thead>
<tr>
<th>Compound</th>
<th>H-2</th>
<th>H-3</th>
<th>H-4</th>
<th>H-5</th>
<th>H-6/H-6’</th>
<th>NH$_2$</th>
<th>CH$_3$</th>
<th>Others</th>
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<td>$J_{2,3}$</td>
<td>$J_{3,4}$</td>
<td>$J_{4,5}$</td>
<td>$J_{5,6}/J_{5,6’}$</td>
<td>$J_{6,6’}$</td>
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</tr>
<tr>
<td>C-1</td>
<td>C-2,3,4,5</td>
<td>C-6</td>
<td>C=O</td>
<td>CH$_3$</td>
<td>Others</td>
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<tr>
<td>46</td>
<td>5.40</td>
<td>5.82</td>
<td>5.47</td>
<td>4.83</td>
<td>4.04</td>
<td>5.69</td>
<td>1.91</td>
<td>4.77 (d),</td>
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<td>3.2</td>
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<td>doublet</td>
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<td>1.97</td>
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<td>97.46</td>
<td>66.22, 67.32, 69.81, 71.45</td>
<td>61.25</td>
<td>168.99$^b$</td>
<td>169.81$^b$</td>
<td>170.32</td>
<td>20.71$^b$</td>
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<td>1.97</td>
<td>4.78 (d)</td>
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<td>96.98</td>
<td>67.66, 69.43, 71.77, 71.78</td>
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<td>168.76</td>
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<td>OCH$_2$S</td>
</tr>
</tbody>
</table>

$^a$ Integral: 6H $^b$ Signal of higher intensity
5.5. Synthesis of C-2 Branched Monosaccharide Derivatives

**General procedure A** for the reaction of C-1 substituted D-galactal derivatives (51, 55 and 60) with dimethyl malonate: To a solution of a D-galactal (1 mmol) in a mixture of dry, degassed MeOH (6 ml) and dimethyl malonate (10 mmol, 1.1 ml) was added dropwise a solution of 2-6 mmol CAN (1.1-3.3 g) in the same MeOH (4 ml/g CAN) at 0 °C with stirring (2-6 h). After the reaction had been completed (TLC) the mixture was diluted with ethylacetate, extracted with chilled water and satd. aq. NaHCO₃ solution, dried and concentrated (finally under high vacuum at 60-80 °C to remove the excess of dimethyl malonate).

**General procedure B** for the reaction of C-1 substituted D-galactal derivatives (51, 55 and 60) with dimethyl malonate: A solution of 9-18 mmol CAN (5.0-10.0 g) in dry MeOH (11-22 ml) was degassed using vacuum at 0 °C. A substituted D-galactal (1 mmol) was suspended in the solution, and dimethyl malonate (4 mmol, 0.45 ml) was added at once with stirring. After the reaction had been completed (TLC, 5-30 min) the mixture was diluted with ethylacetate, extracted with chilled water and satd. aq. NaHCO₃ solution, dried and concentrated (finally under high vacuum at 60-80 °C to remove the excess of dimethyl malonate).

*Reaction of C-(3,4,6-tri-O-acetyl-2-deoxy-D-lyxo-hex-1-enopyranosyl) formamide (51) with dimethyl malonate according to general procedure A*: From 387 mg 51 (1.23 mmol), reaction time: 3 h. Crude product: 498 mg yellowish syrup identified as a mixture of 52, 53 and 54 in 80:14:6 ratio by ¹H NMR. Column chromatography afforded partially pure 53 (19 mg, 3 %), 52 (153 mg, 26 %) and 54 (17 mg, 3 %) as colorless syrups. ¹H and ¹³C NMR spectroscopic data are given in Table 24 and 25.

*Reaction of 3,4,6-tri-O-acetyl-2-deoxy-D-lyxo-hex-1-enopyranosyl cyanide (55) with dimethyl malonate according to general procedure B*: From 311 mg 55 (1.05 mmol), reaction time: 2 h. Crude product: 423 mg
yellowish syrup identified as a mixture of 56, 57, 58 and 59 in 53:28:9:10 ratio by $^1$H NMR. Column chromatography afforded partially pure 56 (90 mg, 19 %), 57 (21 mg, 4 %), 59 (19 mg, 4 %) and 58 (9 mg, 2 %) as colorless syrups. $^1$H and $^{13}$C NMR spectroscopic data are given in Table 24 and 25.

Reaction of methyl C-(3,4,6-tri-O-acetyl-2-deoxy-D-lyxo-hex-1-enopyranosyl) formate (60) with dimethyl malonate according to general procedure A: From 223 mg 60 (0.67 mmol), reaction time: 3 h. Crude product: 301 mg yellowish syrup. Column chromatography afforded partially pure 61 (96 mg, 30 %) and 62 (28 mg, 9 %) as colorless syrups. $^1$H and $^{13}$C NMR spectroscopic data are given in Table 24 and 25.
Table 24

$^1$H NMR data for C-2 branched sugar derivatives (52-54, 56-59, 61, 62) measured in CDCl$_3$ at 360 MHz referenced to internal Me$_4$Si ($\delta$ [ppm], $J$ [Hz])

<table>
<thead>
<tr>
<th>Cpd</th>
<th>H-2</th>
<th>H-3</th>
<th>H-4</th>
<th>H-5</th>
<th>H-6/H-6'</th>
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<th>Others</th>
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$^a$ $J_{3,5}$
Table 25

$^{13}$C NMR data for C-2 branched sugar derivatives (52-54, 56-59, 61, 62) measured in CDCl$_3$ at 90 MHz referenced to solvent residual signal ($\delta$ [ppm], J [Hz])

<table>
<thead>
<tr>
<th>Cp d</th>
<th>C-1</th>
<th>C-2,3,4, 5</th>
<th>C-6</th>
<th>C-7, OMe</th>
<th>C=O</th>
<th>CH$_3$</th>
<th>Others</th>
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<td>46.43</td>
<td>167.67</td>
<td>20.36</td>
<td>166.66 CONH$_2$ (J=6.4 Hz)</td>
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<td>52.62</td>
<td>168.70</td>
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Table 25 (continuation)

$^{13}$C NMR data for C-2 branched sugar derivatives (52-54, 56-59, 61, 62) measured in CDCl$_3$ at 90 MHz referenced to solvent residual signal ($\delta$ [ppm], $J$ [Hz])

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<td>20.27</td>
<td>20.58</td>
<td>20.62$^a$</td>
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$^a$ Signal of higher intensity
6. Summary

Nucleophilic substitutions are one of the most important reactions occurring at the anomeric center of carbohydrate derivatives. In the transition state of unimolecular substitutions, the anomeric center has a positive charge and the intermediate is called glycosyl carbenium ion (69B, Scheme 29).

Scheme 29. Unimolecular nucleophilic substitutions at the anomeric center

Nucleophilic substitutions, employing various nucleophiles, can provide easy routes for the synthesis of O-, N-, S- and C-glycosyl derivatives. Glycosyl donors can be of different reactivity depending on the leaving ability of the X-group ($\Delta G_1$), but in case of a given nucleophile (Nu) it is probably reasonable to consider the rate of the second step ($v_2$) to be independent of any factors except the energy-level of the intermediate glycosyl carbenium ion. The energy-level of this intermediate is influenced mainly by the electron withdrawing or donating character of the substituents close to the anomeric center (i.e. at C-1, C-2 and C-5). A special case of this influence include the type and number of O-protecting groups of the saccharide (cf. “armed” and “disarmed” glycosyl donors25,26).

This dissertation examines the influence of the C-1 substituents on the reactivity of C-1 substituted glycosyl donors and on the outcome of their reactions. Each of the investigated substituents (CN, CONH$_2$, COOMe) are Z-type (electron withdrawing), the investigated reactions
are the following. Fluoro-substitution, reaction with nitriles (Ritter), solvent incorporation reactions with other nucleophilic solvents and the addition of oxidatively generated malonyl radicals to glycals in methanol.

The reaction of per-O-acetyl-1-cyanoglycopyranosyl halides with silver fluoride in acetonitrile was investigated first (Helferich conditions). Contrary to the behavior of the unsubstituted glycosyl halides known from the literature, irrespective of the anomeric configuration of the starting glycosyl halide, inversion product was obtained in each case (Scheme 30). We explained this difference by the change in the strength of the C-1–halogen bond and the stability of the glycosyl carbenium ion that necessitates a push-pull pathway and excludes the intermediacy of a glycosylium ion.

Scheme 30. Reaction of 1-cyanoglycopyranosyl halides with silver fluoride under Helferich conditions

The presence of the less strongly electron withdrawing carbamoyl group (–CONH₂), however, did not alter the fluoro-substitution reaction. Thus, despite the fact that the reaction had to be carried out in a solvent
other than acetonitrile, it went similarly to that of the unsubstituted analogs and gave a mixture of the two anomeric fluorides.

In the D-gluco and D-xylo configuration, we have attempted and successfully accomplished the preparation of the thermodynamically more stable glycosyl fluoride derivatives directly from the more easily available glycosyl bromide derivatives ($70A \rightarrow 71B$, retention product). We used the method published by Irishawa et al.\(^{107}\) The method employs silver tetrafluoroborate which is believed to anomerize the glycosyl fluorides.\(^{121}\)

The glycosylum ion ($75$, Scheme 31), which is formed from the carbamoyl-substituted glycosyl bromides ($72$), was found to react with various types of nucleophilic solvents. In two instances, the presence of the carbamoyl oxygen is probably essential for the reaction. The reaction with nitriles furnishes $N$-acyl-1-cyano-$\alpha$-D-glycopyranosyl-aminines ($74\alpha$, in three sugar configurations and with five different nitriles, yield: 41-76 %), the reaction with ketones gives spiro-iminodioxolane type carbohydrate derivatives ($76$). This latter reaction is studied in our laboratory by László Kovács and Katalin Czifrák.

The stereoselectivity of the former reaction, in the presence of a silver-salt promoter, is probably controlled by the fast kinetic formation and intramolecular dehydration of $\alpha$-glycosyl-nitrilium ions ($73$).\(^{68,124}\) This reaction may form a basis for an effective and stereoselective synthesis leading to novel derivatives of anomeric $\alpha$-aminoacids. We have systematically examined the reaction by applying different promoters, changing the structure and the excess of the nitrile and variation of temperature in order to determine its scope and limitations. It was found that in the presence of HgBr$_2$ the reaction could be carried out using 5-10 equiv. nitrile without considerable amount of side-products. The stereoselectivity of the reaction is, however, changed in these conditions and the other anomeric amide ($74\beta$) becomes the major product.
Scheme 31. Reaction of 1-carbamoylglycopyranosyl halides with different nucleophilic solvents in the presence of an electrophilic promoter.

The upside attack seems to be favored in the ketone incorporation reaction, since the spiro-iminodioxolane (76) is found to be the major product in this reaction.

The carbamoyl group does not participate in the reaction with dimethyl sulfoxide; the sulfur-centered cation (77) formed in the first step is stabilized by the well-known Pummerer-type rearrangement. The main products of these reactions are the 1-OH derivatives (78), the methylthiomethyl-glycosides (79) are isolated in 11 and 15 % yield in D-gluco and D-galacto configuration, respectively. The reaction is stereoselective since only β-glycosides are formed.
The last investigated reaction seems to be extraneous to the reactions examined so far. This reaction is published by Linker et al. who describe a method for the generation of malonyl radicals by an oxidative pathway and the addition of these free radicals to D-glycals (Scheme 32, R' = H). The reaction is carried out in methanol the oxidizing agent being CAN. The main product is the methyl glycoside substituted with a malonyl side-chain at the C-2 position.

We have accomplished the reaction with three different C-1 substituted D-galactals (80, R' = CN, CONH₂, COOMe), but our products were similar only in one case (R' = CONH₂). In the other two cases (R' = CN, COOMe), orthoesters (86) are obtained as the major products of the reaction. This anomalous behavior was explained by the stronger electron withdrawing character of these latter groups as compared to the carbamoyl group. The oxidation of the stable capto-dative free radical (82, R' = CN, COOMe) yielding the destabilized glycosylium ion (84) is probably much slower than in case of the unsubstituted or the carbamoyl-substituted derivatives because of the increased free-energy difference between the radical (82) and the carbocation (84) mentioned above.

The longer half-life and perhaps the more appropriate energy-level of the SOMO of this radical may favor free-radical cyclization (82 → 83, R' = CN, COOMe). Another possibility that the unusually low energy-level of the LUMO of the glycosylium ion facilitates the intramolecular carbonyl addition (84 → 85).

It can be concluded from the outcome of the reactions dealt with in this dissertation that the electron withdrawing character of the substituent at C-1 can considerably influence nucleophilic substitutions and other reactions supposing the intermediacy of glycosylium ions.
Scheme 32. Reaction of substituted D-galactals with oxidatively generated malonyl radicals

The three investigated substituents can be classified according to their behavior in these reactions as follows. The carbamoyl group is placed in the first class. It has no or little influence on the reactions because of its electron withdrawing character; on the other hand, it can
specifically change the way of certain reactions due to its nucleophilic oxygen. These latter reactions are very weakly investigated up to now. The other class contains the cyano group and the ester group. These substituents, because of their strongly electron withdrawing character, cause substantial differences in the chemical behavior which is seen in (a) the decreased reactivity and (b) manifestation of other reaction mechanisms.
7. Összefoglalás (Summary in Hungarian)

A szénhidrátok anomer centrumán lejátszódó reakciók egyik nagy csoportját alkotják a nukleofil szubsztitúciós reakciók. Az ilyen típusú reakciók átmeneti állapotában az anomer centrum pozitív töltéstöbbletet hordoz; unimolekuláris folyamatok esetén a köztterméket glikozil-karbéniumionnak nevezzük (1. ábra, 69B).

<diagram/>

**1. ábra**

Ezek az átalakítások a nukleofil (Nu) minőségétől függően igen változatos O-, N-, S- és C-glikozil származékok előállítására lehetnek alkalmasak. A glikozilcsoportot szolgáltató glikozil donorok különböző reaktivitásúak lehetnek (attól függően, hogy az X távozócsoporthoz mennyire könnyen távolítható el a molekuláról: ΔG₁‡), de adott nukleofil (Nu) esetén a második reakciólepés sebessége (v₂) – jó közelítéssel – csak az intermedier glikozil-karbéniumion energiaszintjétől függ. A fenti glikozil karbéniumion energiaszintjét befolyásoló tényezők között találjuk a szénhidrátszármazékon megtalálható O-védcsoportok számát és minőségét (ld. „armed” és „disarmed” glikozil donorok25,26) és a pozitív töltésű atomok környezetében (esetünkben a C-1, C-2 és C-5 atomokon) elhelyezkedő egyéb szubsztituensek elektronvonzó ill. elektronküldő sajátosságát.

Jelen dolgozat témája az anomer centrum (C-1) szubsztituenseinek az intermedier glikoziliumion stabilitására és ezáltal magukra a vizsgált reakciókra való hatásának tanulmányozása. Az általam vizsgált szubsztituensek mindegyike (CN, CONH₂ és COOMe) Z-típusú, vagyis elektronvonzó szubsztituens. A vizsgált reakciók: fluorszubsztitúció,
reakció nitrilekkel (Ritter), egyéb nukleofil-oldószer beépüléses reakciók és egy malonilgyök-addíciós (részben ionos lefutású) reakció.

Elsőként per-O-acetil-1-ciano-glikopiranozil halogenidek reakcióját tanulmányoztuk AgF-al acetonitrilben (Helferich körülmények). A szubsztituálatlan származékok irodalomból ismeretes viselkedésétől eltérően a kiindulási glikozil-halogenid anomerkonfigurációjától függetlenül mindig inverziós fluor sulphármazékot kaptunk (2. ábra). A reakció lefutásában tapasztalt eltérést a kiindulási glikozil halogenidek C-1–halogén kötéserőségében illetve a köztitermékként feltételezett glikozil karbéniumion stabilitásában fellelhető különbséggel értelmeztük. A cianocsoporttal szubsztituált származékoktól eltérően a kevésbé elektronvonzó amidcsoport (–CONH₂) jelenléte nem változtatta meg a fluorosubsztitúció lefutását, így az – bár az acetonitril beépülése miatt a reakciót más oldószerben kellett elvégezni – a szubsztituálatlan származékokéhoz hasonlóan ment végbe.

![2. ábra](image-url)
Irodalmi módszer\textsuperscript{107} alkalmazásával (AgBF$_4$-al, toluolban) sikerült a glikozil-bromidokból előállítani a termodinamikailag stabillabb glikozil-fluorid származékokat (retenciós termék), képződésüket azzal az irodalmi ténnyel magyaráztuk, hogy az AgBF$_4$ képes anomerizálni a glikozil-fluoridokat.\textsuperscript{121}

Az amidszubsztituált glikozil bromidokból (72) képződő glikozil karbéniumion (75) többféle – nukleofil jellegű – oldósszerrel is reaktiába lépett. Ezek közül két esetben – minden valószínűség szerint – az amidcsoport karbonil oxigénjével való stabilizálódás ill. további átalakulás lehetősége miatt megy végbe a reakció: a nitrilekkel való reakció $N$-acil-1-ciano-$\alpha$-D-glikopiranozilaminokat (74$\alpha$) eredményez (három különböző cukorkonfigurációban és ötféle nitrillel 41-76 %-os hozammal), a ketonokkal való – Kovács László és Czifrák Katalin által tanulmányozott – reakció spiro-iminodioxolán típusú szénhidrát-származékokat (76) szolgáltat (két különböző cukorkonfigurációban és ötféle szimmetrikus ketonnal 45-75 %-os hozammal). Az előbbi reakció sztereoselektivitását – Ag-só promotor jelenlétében – az $\alpha$-glikozil-nitriliumionok (73) irodalomból ismeretes gyors képződése és $\alpha$-amidokká (74$\alpha$) való intramolekuláris hidratációja (ami egyszerre a karbamoil csoport dehidratációját is jelenti) szabja meg. A reakció az anomer $\alpha$-aminosavak újabb származékainak jó hozamú, sztereoselektív előállításának alapja lehet. A reakciókörülmények szisztematikus változtatásával megvizsgáltuk a reakció alkalmazhatósági körét a promotor, a nitrilmennyiség és minőség valamint a hőmérséklet függvényében, és azt találtuk, hogy HgBr$_2$ promotor alkalmazásával a reakció 5-10 ekv. nitrillel is elvégezhető anélkül, hogy számtettevő mennyiségben keletkeznek melléktermékek. Ilyen körülmények között azonban a reakció sztereoselektivitása megváltozik, és az Ag-sókkal kapott termék anomerpárja (74$\beta$) lesz a reakció főterméke, amely oszlopkromatográfia segítségével izolálható.
A ketonbeépülési reakcióban a felső oldali támadás a kedvezményezett, így az ábrán látható spiro-iminodioxolán (76) származék lesz a reakció főterméke.


A vizsgált reakciók sorába látszólag nem illik bele az először Linker és munkatársai által szubsztituált glikálszármazékokon (4. ábra, 80, R’ = H) alkalmazott malonilgyök-addíció.85,86 A reakcióban a malonilgyök cérium-ammónium-nitrát (CAN) segítségével oxidatív úton keletkezik, főterméként az általuk vizsgált összes glikállal a C-2 helyzetben malonilrész tartalmazó metilglikozidot (81) kapták (a reakció oldószere metanol). A fenti reakciót három különböző, C-1 helyzetben elektronvonzó csoporttal szubsztituált glikálszármazékkal elvégezve csak egy esetben (80, R’ = CONH₂) tapasztaltunk a szubsztituált glikáll alakú 1-OH mentes termékeket. A másik két esetben (80, R’ = CN, COOMe) a reakció főtermékeként ortoészterek (86) keletkeztek. Ezt az eltérő viselkedést a C-1 szubsztituens elektronvonzó képességének erősödésével magyaráztuk. A reakció intermediáriukban fellépő stabilis kapto-datív gyök (82) és a belőle oxidációval keletkező – az erősen elektronvonzó szubsztituens jelenléte miatt – destabilizált glikozíliumion (84) közötti energiakülönbség miatt lelassul a gyök karbokationná való oxidációja, ugyanakkor – a gyök hosszabb élettartama és esetleg SOMO-energiája alacsony gyökös gyűrűzáráshoz alkalmas volta miatt – ciklizáció következhet be. Másik lehetőség, hogy a képződő glikozíliumion (84) különösen alacsony LUMO-energiája esetén a karbonilcsoportra való intramolekuláris addíció.

Az elvégzett kísérletekből kitűnik, hogy a C-1 szubsztituens sajátsága valóban jelentős hatással lehet az anomercentrum nukleofil
szubsztitúciós reakcióira és más, glikoziliumion köztterméket feltételező reakcióira.

A megvizsgált három szubsztituens, a tanulmányozott reakciókban mutatott viselkedésük alapján két csoportra oszthatjuk. Az egyik csoportba az amidcsoport (–CONH₂) kerül, amely elektronvonzó sajátsága révén nem, vagy csak kis mértékben változtatja meg a glikoziliumion reaktivitását, ugyanakkor karbonilcsoportja révén specifikus hatást gyakorol egyes reakciók kimenetelére. A másik csoportba a cianocsoport és az észtercsoport tartozik; ezek a szubsztituensek erősen elektronvonzó tulajdonságuk révén alapvető reaktivitási különbséget eredményeznek, amely részben a csökkent reakciókészségben, részben pedig más reakcióutak kedvezményezésében nyilvánul meg.

3. ábra
\[ R' = \text{H or CONH}_2 \]
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Ezen értekezést a Debreceni Egyetem TTK Kémia Doktori Iskola „Szénhidráltartalmú természetes anyagok kémiája” című K/5 programja keretében készítettem a Debreceni Egyetem TTK doktori (Ph.D.) fokozatának elnyerése céljából.


Gyóllai Viktor
jelölt


Dr. Somsák László
egyetemi docens
témavezető
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INVESTIGATION OF REACTIONS INVOLVING
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doktori (Ph.D.) értekezés

GYÖLLAI VIKTOR

Témavezetők: Prof. Dr. Somsák László

Debreceni Egyetem, Szerves Kémiai Tanszék
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Értekezés a doktori (Ph.D.) fokozat megszerzése érdekében a kémia tudományágban

Írta: Gyóllai Viktor
okleveles vegyész; kémia tanár; angol-magyar szakfordító

Készült a Debreceni Egyetem TTK Kémia Doktori Iskolája (K/5 alprogramja) keretében

Témavezető: Dr. Somsák László

A doktori szigorlati bizottság:

elnök: Dr. ...........................................................
tagok: Dr. ...........................................................


Az értekezés bírálói:

Dr. ........................................................... ..............................
Dr. ........................................................... ..............................
Dr. ........................................................... ..............................

A bírálóbizottság:

elnök: Dr. ........................................................... ..............................
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