INVESTIGATION OF REACTIONS INVOLVING DESTABILIZED GLYCOSYLIUM ION INTERMEDIATES

Ph.D. dissertation

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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 stabile 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.).

1A

1C

1B

1D

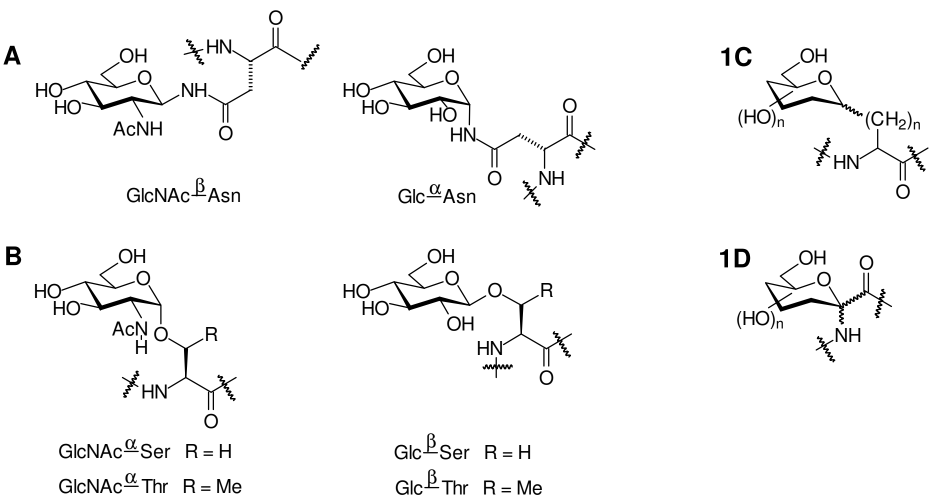


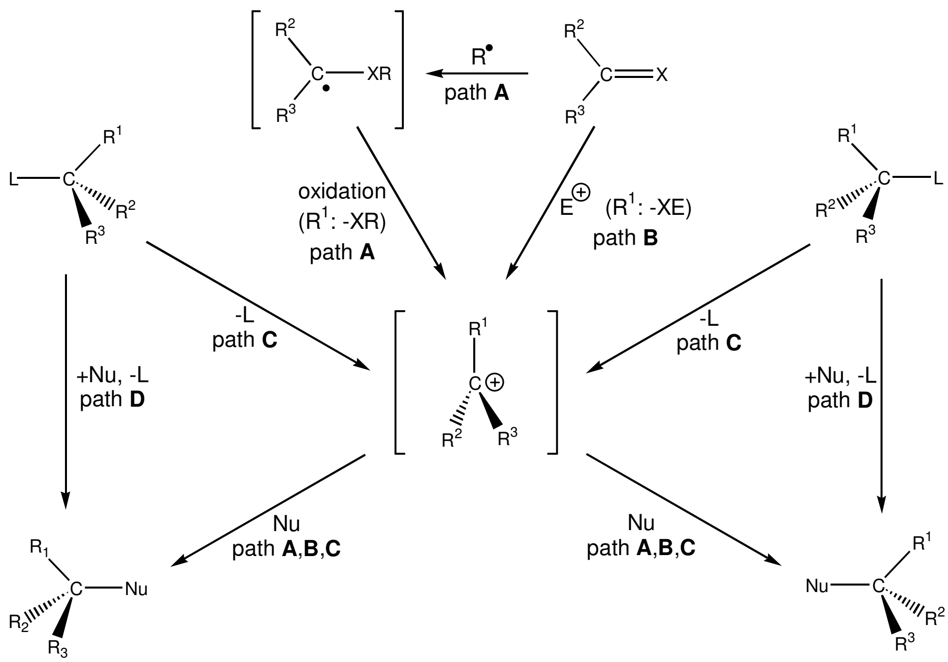
Figure 1. *Structural units of* N- *(**1A**) and* O-g*lycoproteins (**1B**);* C-*glycosyl- (**1C**) and anomeric* α*-amino acids (**1D**)*

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.



E: electrophile, Nu: nucleophile, L: leaving group, X: e.g. O, CR'R''

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.

R_1	**R_2**	**R_3**	**ΔH_f ($R_1R_2R_3C^+$) [kcal/mol]**	**Hammett constant for R_1 ($\sigma_I+\sigma_R$)**
H	H	H	261[2]	0.00
CH_3	H	H	216	- 0.10
CH_3	CH_3	H	192	
CH_3	CH_3	CH_3	166	
OCH_3	H	H	157	- 0.11
OH	H	H	168	- 0.18
NH_2	H	H	178	- 0.36
OCH_3	CH_3	H	132	
OH	CH_3	H	139	
OH	CH_3	CH_3	119	
CN	*H*	*H*	*291*[3]	+ 0.70
COOR				+ 0.47
$CONH_2$				+ 0.33

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

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[4] and Hammett substituent constants[5] 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[7] (**A**), 1-methoxycarbonylethyl[8] (**B**) and carboxamidomethyl[8] (**C**) cations can be seen in Figure 2.

In case of the cyanomethyl cation[3], however, no possibility of such charge-translocation exists, thus its ΔH_f (291 kcal/mol) is determined to be much higher than that of the very unstable methyl cation[2] (261 kcal/mol, Table 1).

On the contrary, the presence of similar stabilization of a carbocationic intermediate by the α-$CONMe_2$ group (Figure 3, X = NMe_2) during solvolyses of mesylates has been reported to be unimportant.[9] 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 = alkyl, alkoxy).

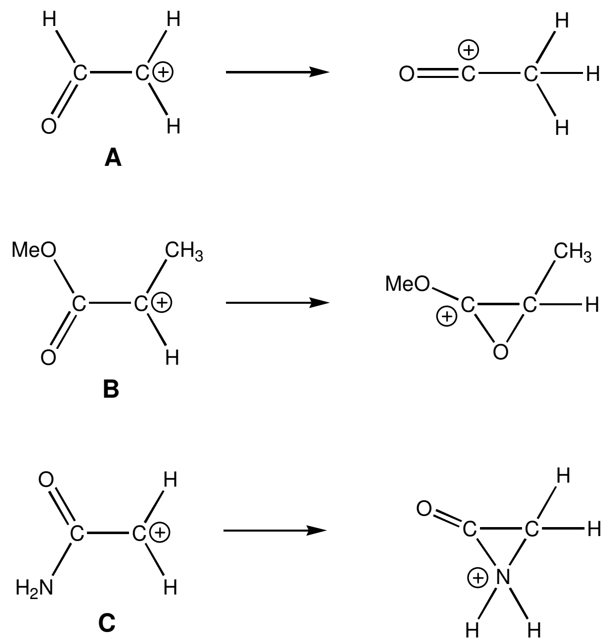


Figure 2. *Translocation of the positive charge in destabilized carbocations*

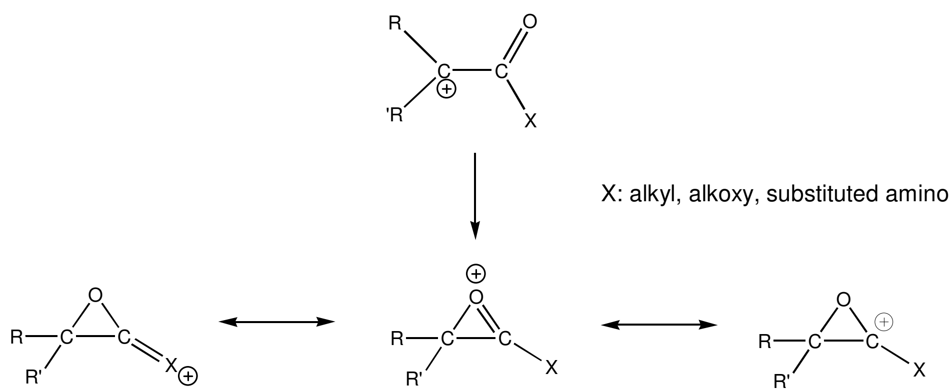


Figure 3. *Potential stabilization of carbenium ions by carbonyl participation*

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[10], conjugative stabilization of the incipient cation by the cyano group almost balances the rate-retarding inductive effect of this function.[11-13] 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 = $(2.7 \pm 0.8) \times 10^3$) were found to contradict the expectations (H/α-CN = $10^9 \ldots 10^{18}$) calculated from the known H/β-CN ratios ($10^3 \ldots 10^7$) using standard extrapolations.[12] (In case of extensive charge delocalization[11] H/α-CN $\approx 10^6$). Theoretical bond length and bond order calculations corroborated[12] 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.

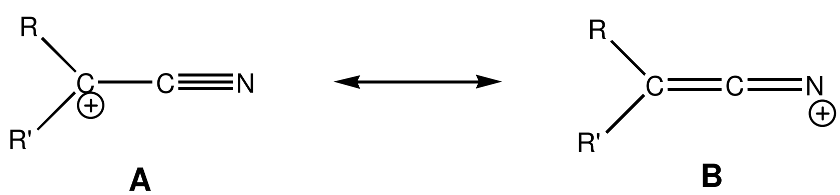


Figure 4. *Resonance structures of α-cyano carbenium ions*

2.1.3. Glycosylium Ions[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[15] and tetrahydropyran-2-yl[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.).

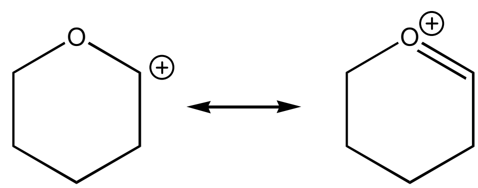


Figure 5. *Resonance stabilization of tetrahydropyran-2-yl carbenium ion*

The influence of the ring oxygen on reaction rates can also be demonstrated by an analogy with α-chloro ethers. In a series of acyclic α-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.[17]

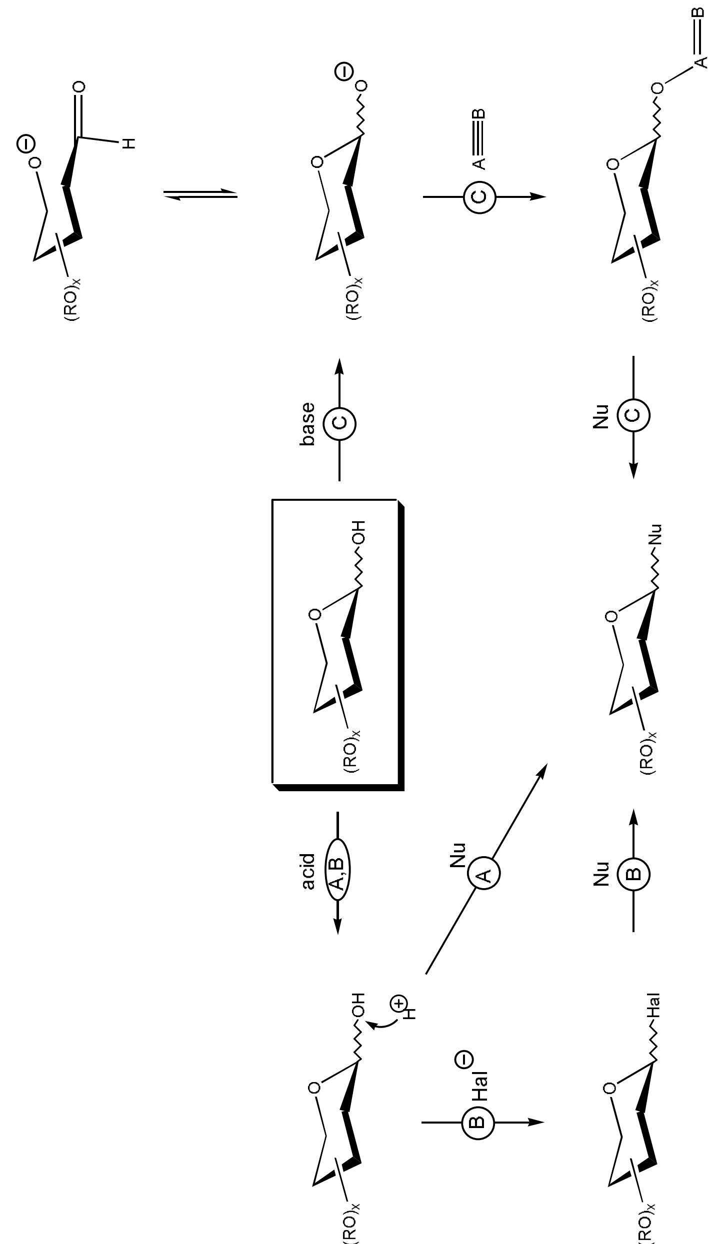
2.1.4. Glycosyl Donors (Sources of Glycosylium Ions)

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*[18]

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] (**2**, 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 glycopyranosyl 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.

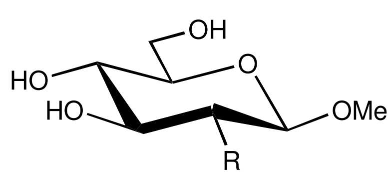
In his research on pentenyl glycosides, Fraser-Reid later named these two groups of protected glycosyl donors as “disarmed” and “armed” respectively, however he explains the difference merely in terms of C-2 substituents.[25] Pentenyl glycosides having electron withdrawing acyloxy or halo substituent 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.[26]

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,[24,27] 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.



2

R	v_{rel}
H	1480
OH	0.708
NH_3^+	0.005
$NHCOCH_3$	4.0

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.

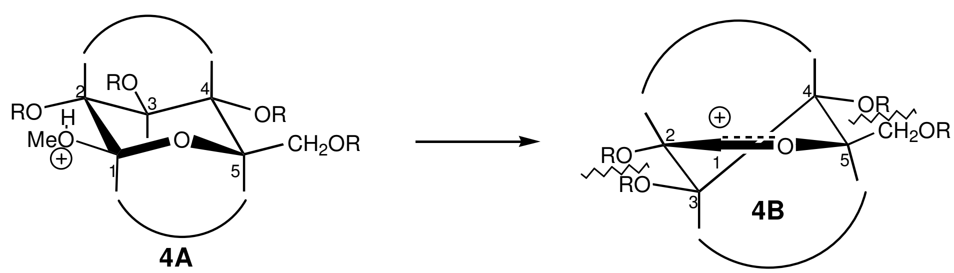
a.) Those going through an „open-ion" intermediate (e.g. **3A**, Figure 7), with no neighboring-group effect; and
b.) those with a „closed-ion" intermediate (e.g. **3B**) and with neighboring-group participation.

3A **3B**

Figure 7. *Carbocationic intermediates at the anomeric center*

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[28] 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 sp^2-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).[27] 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 α-L-rhamnosyl – 6-deoxy-α-D-glucosyl pair (**A**, Figure 8) at 22 °C to 100,000 ($\delta\Delta G^{\ddagger} \approx$ 5 kcal/mol) for the β-D-glucosyl – α-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.

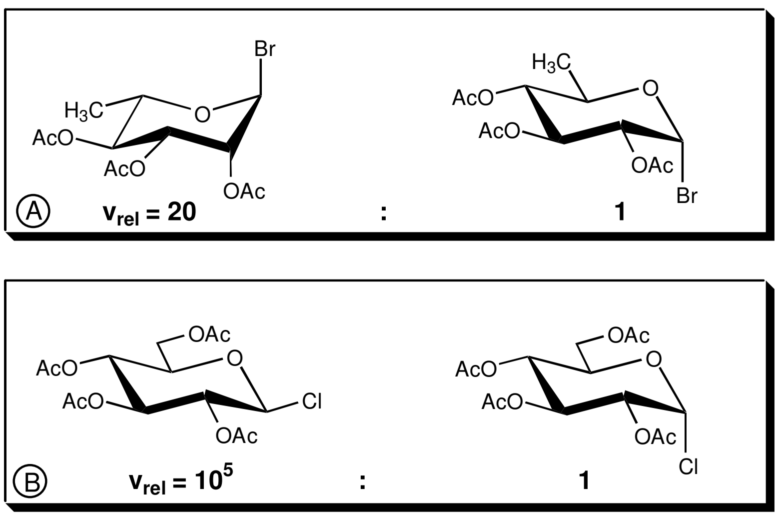
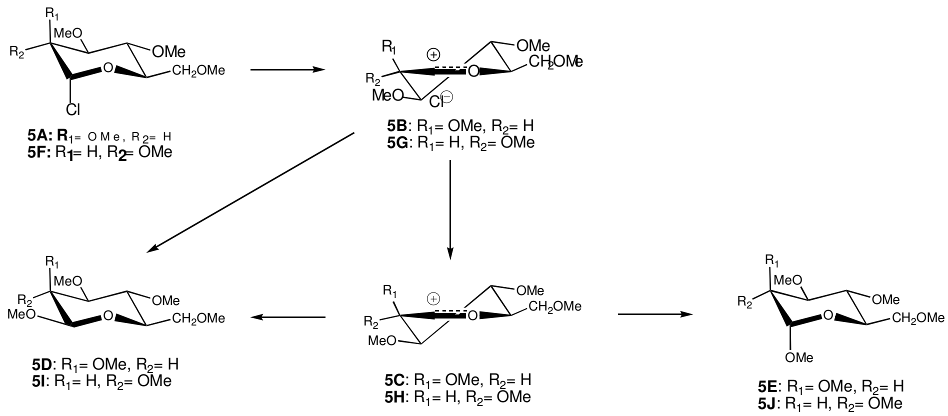


Figure 8. *Relative rate of solvolysis of pairs of 1,2-*trans *and 1,2-*cis *glycopyranosyl halides*

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[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_N1. 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,[27] the hydrolysis of per-*O*-acetyl-D-glycopyranosyl bromides[31] and the alcoholysis of per-*O*-acetyl-D-glycopyranosyl bromides by primary alcohols.[34] Even tetra-*O*-acetyl-β-D-glucopyranosyl chloride, when subjected to methanolysis, despite the presence of the neighboring acetoxy group, yields α-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-α-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[36] and a number of other glycosylation reactions conducted in solvents of low polarity and/or at low temperature like the trichloroacetimidate method using $BF_3{\cdot}OEt_2$ at very low temperatures.[37]

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_N1 pathway, instead, furnish the inversion product (Table 2).

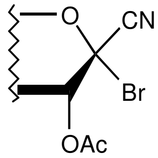
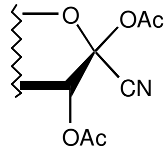
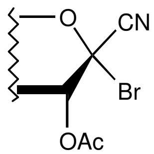
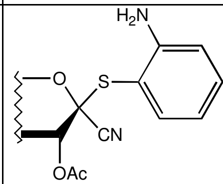
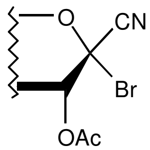
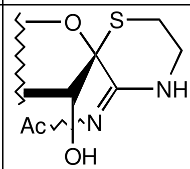
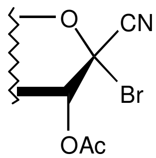
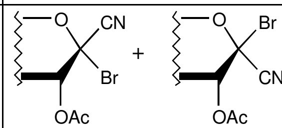
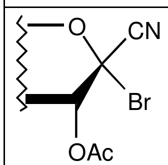
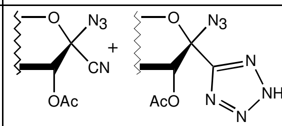
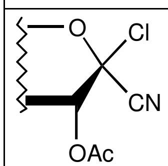
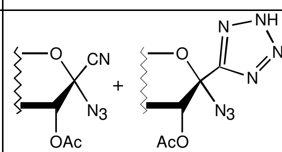
Starting Sugar	Reaction Conditions	Product(s)	Stereo-chemistry	Ref.
	AcOH, Ac_2O AgOAc/$Hg(OAc)_2$ reflux, 4-8 h		inversion	38
	o-amino-thiophenolate, EtOH		inversion	39
	$HS(CH_2)_2NH_2$ EtOH		inversion	39
	Bu_4NBr, CCl_4 reflux	 9 : 1	anomeriz.	40
	NaN_3, DMSO, r.t.		inversion	41
	NaN_3, DMSO, r.t.		inversion	41

Table 2. *Nucleophilic displacement reactions at the anomeric center of C-1 substituted pyranoid sugars*

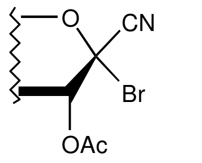
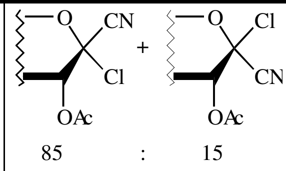
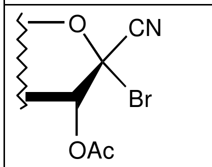
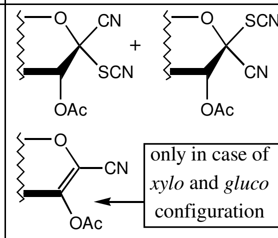
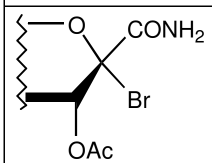
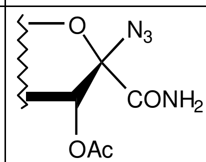
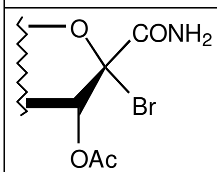
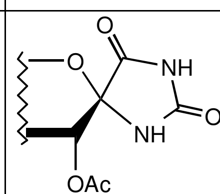
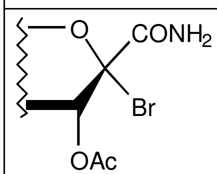
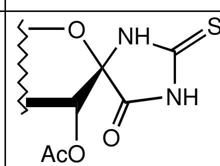
Starting Sugar	Reaction Conditions	Product(s)	Stereo-chemistry	Ref.
	LiCl, DMSO, r.t.		inversion + anomeriz.	41
	KSCN, CH_3NO_2 90 °C		inversion + anomeriz.	42
	NaN_3, DMSO, r.t.		inversion	41
	AgOCN, CH_3NO_2 80 °C		retention	43, 44
	KSCN, CH_3NO_2 80 °C		inversion	43, 44

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 tosylate, iodosotoluol difluoride and 1-amino-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,[49] 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 S_N2-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 S_N1 path with solvent participation, with the intermediacy of *N*-(α-D-glycopyranosyl) acetonitrilium ion, is hypothesized.

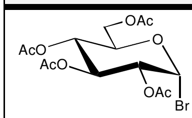
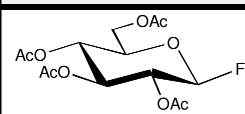
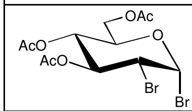
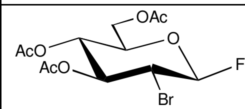
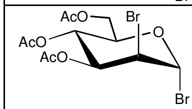
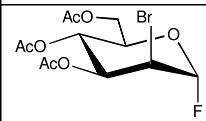
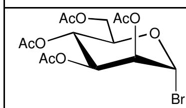
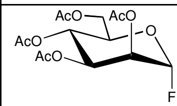
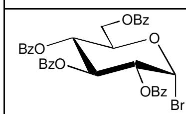
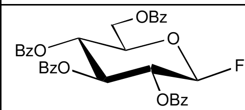
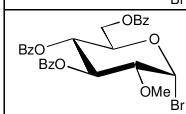
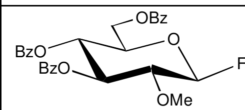
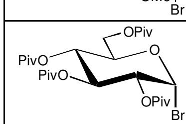
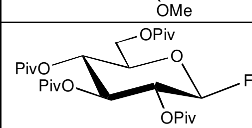
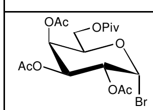
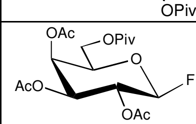
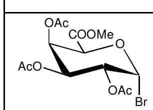
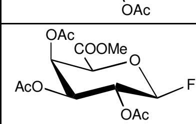
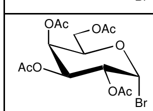
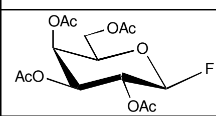
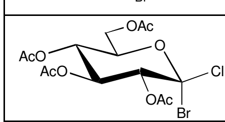
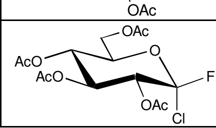
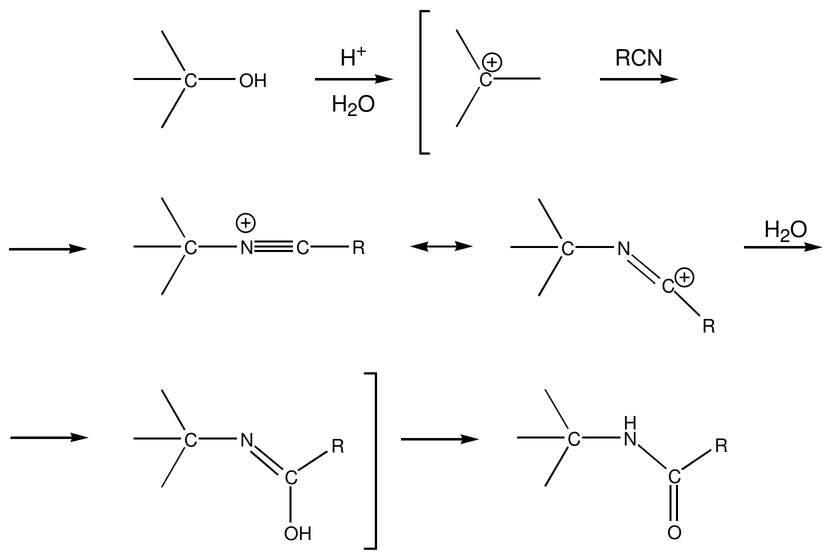
Starting Sugar	Product		Yield[Reference]
		inversion	54 %[49]
		inversion	62 %[50]
		retention	sole product as judged by ^{19}F NMR[50]
		retention	not given[51]
		inversion	73 %[52]
		inversion	>75 %[53]
		inversion	69 %[54]
		inversion	77 %[55]
		inversion	82 %[56]
		inversion	61-66 %[57]
		inversion	70 %[58]

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).



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 α-ions (**6**α, Figure 9), Sinaÿ and Pougny[65] and Schmidt and Rücker[66] have advocated the β-counterpart (**6**β), 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 intermedietes.[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).

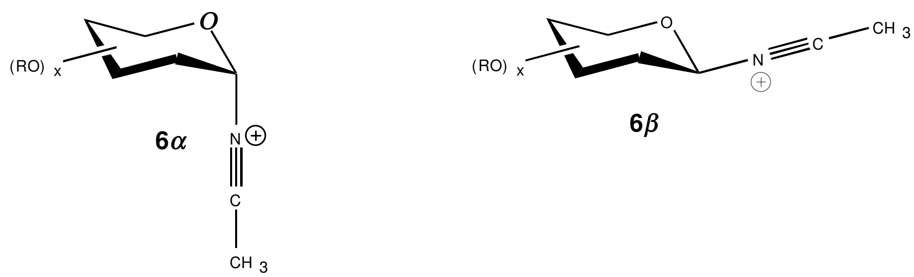
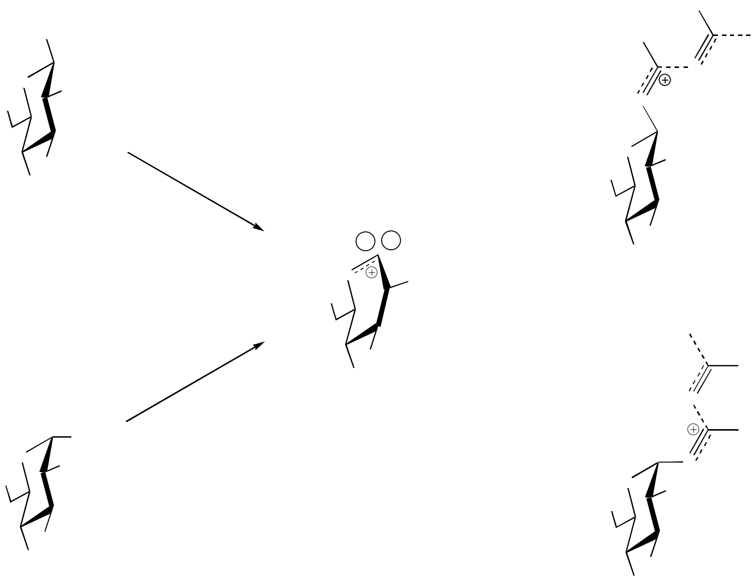


Figure 9. D-*Glycopyranosyl nitrilium ion intermediates*

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 ($AgClO_4$) 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



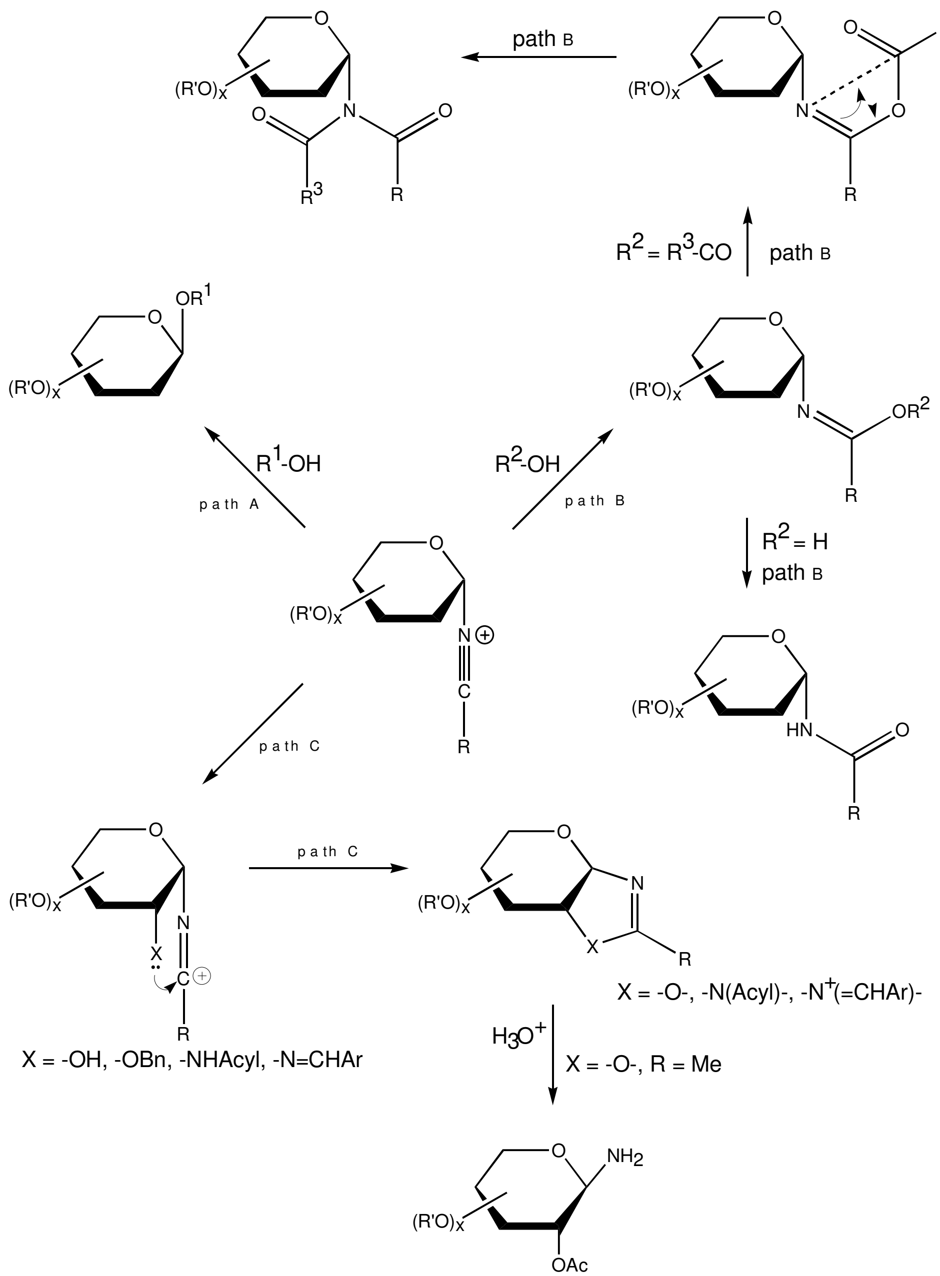
proved by experimental data[66] (IR and ^{1}H NMR spectroscopy), the question has to be brought on: Why is it so extremely rarely applied?

The *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; 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 *N*-glycosyl nitrilium ion can be α (no neighboring-group participation)[64,65,68,70-74] or β (neighboring-group participation);[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**).[63,77-80]



Scheme 7. N-*Glycosyl nitrilium ion mediated reactions*

2.3.3. Transition Metal-Promoted Free-Radical Reactions[81-84]

Transition metal-promoted generation of *C*-centered radicals may be started

(a) by an oxidative process, and

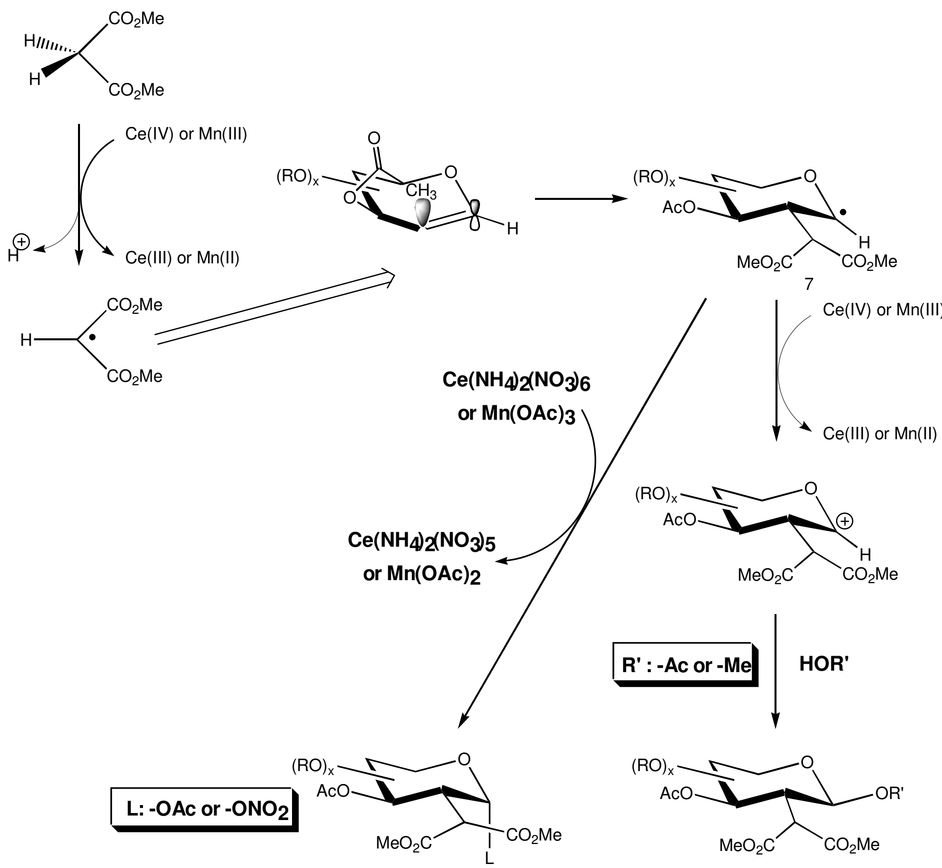
(b) a reductive process.

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.[85,86] This synthesis seems to be superior to other approaches[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.[88,90]

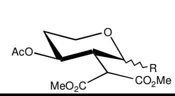
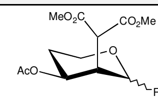
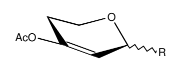
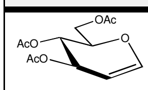
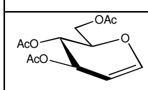
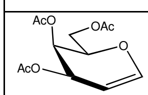
The first step of the reaction is the generation of malonyl radicals from dimethyl malonate. This electrophilic radical adds to the double bond of a glycal. The regioselectivity of the addition is controlled by stereoelectronic factors: the MO-coefficient of the HOMO of the double bond is considerably 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-ONO_2 (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-ONO_2 derivative.

Starting Sugar	Method*	Yields of the Isolated Products			
		 		 	
 	**A** R: –OAc	**52** (α:β = 16:84)		**14** (α:β = 71:29)	**10** (α:β = 10:90)
 	**B**	**62** R: β–OMe	**16** R: α–ONO_2	**14** R: β–OMe	–
 	**B**	**78** R: β–OMe	**8** R: α–ONO_2	–	–

*Method A: 2-4 eq. $Mn(OAc)_3$•$2H_2O$, 10 eq. $CH_2(COOMe)_2$, AcOH, 95 °C
Method B: 3-6 eq. CAN, 10 eq. $CH_2(COOMe)_2$, MeOH, 0 °C

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

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[92] are known to hydrolyze glycosidic bonds with the appearance on the mechanistic pathway of covalent glycosyl-enzyme intermediates[93] 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[94,95] 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-[95-97] and disaccharide derivatives[98] (EWG2 = F) were synthesized and tested against various glycosidases to validate the concept. The 2-fluoro substituents, however, disrupt the most important binding[99] between the enzyme and the 2-OH group. This was overcome by the introduction of a fluorine into the C-5 position[100] (EWG5 = F).

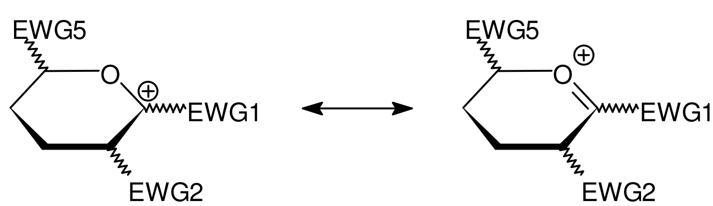


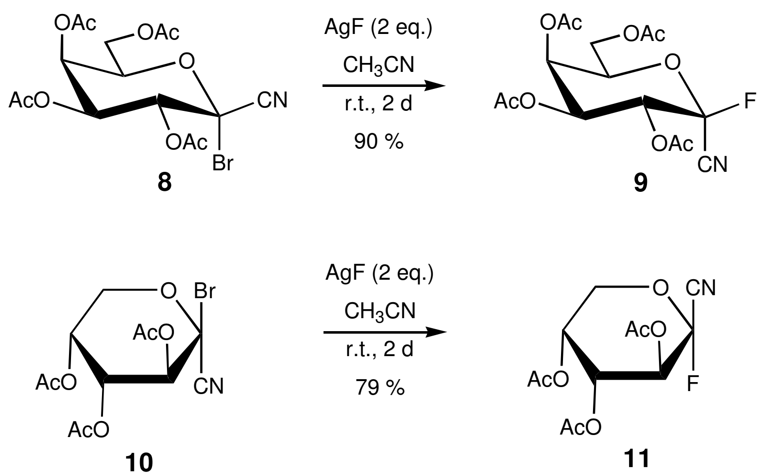
Figure 10. *Destabilization of glycopyranosyl oxocarbenium ions*

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.[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.

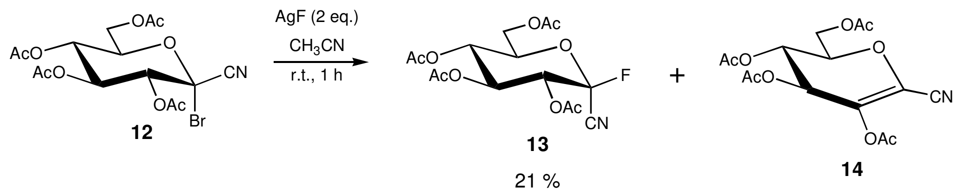
3.1. Preparation of C-1 Substituted Glycosyl Fluoride Derivatives

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]

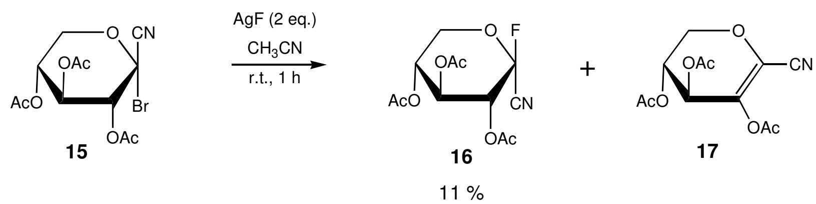


Scheme 9. *Reaction of acetylated 1-bromoglycopyranosyl cyanides (*D-galacto *and* D-arabino*) with silver fluoride in acetonitrile*

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]



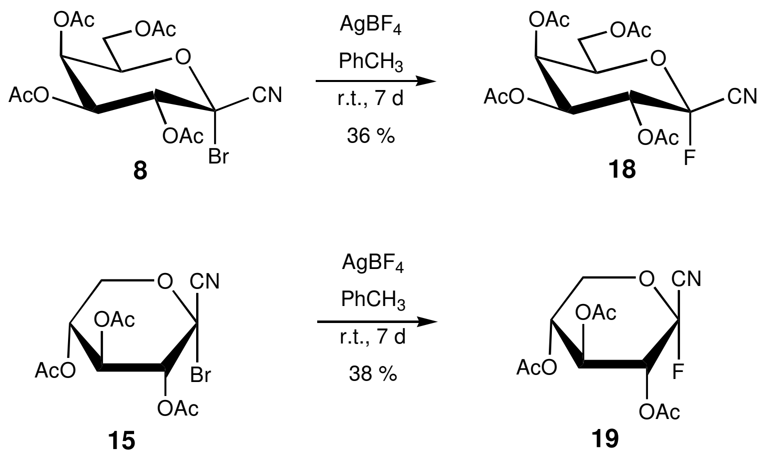
Ratio from ^{1}H NMR spectrum of the crude product: 1 : 1



Ratio from ^{1}H NMR spectrum of the crude product: 3 : 1

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

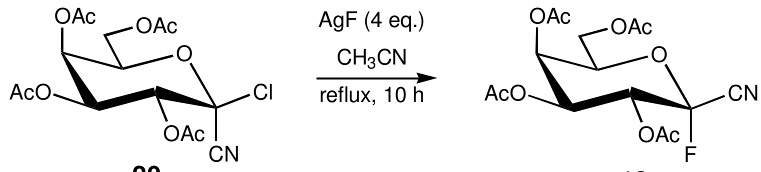
In order to synthesize the thermodynamically more stable glycosyl fluoride anomers the D-*galacto* and D-*xylo* configurated starting materials (**8** and **15**) were allowed to react with two equivalents of silver tetrafluoroborate in anhydrous toluene at room temperature according to the very mild 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).



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

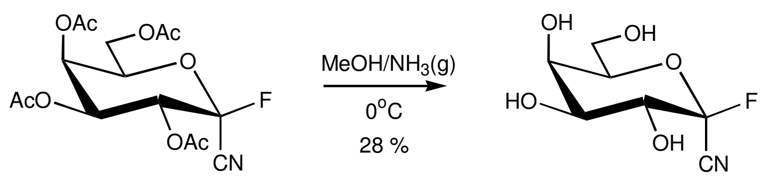
Reaction of 2,3,4,6-tetra-*O*-acetyl-1-chloro-α-D-galactopyranosyl cyanide (**20**, Scheme 12) with silver fluoride, employing the same reaction conditions as for the acetylated 1-bromoglycopyranosyl cyanides, was unsuccessful (i.e. no change could be observed by TLC even after several days). Refluxing 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 (^{1}H 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[108] 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-α-D-galactopyranosyl cyanide with silver fluoride in acetonitrile*

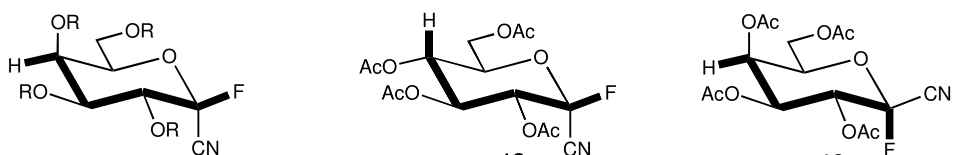
In order to carry out preliminary enzymatic studies deprotection of **9** was performed using methanolic ammonia to give 1-fluoro-*α*-D-galactopyranosyl cyanide (**21**) after chromatographic purification (Scheme 13). This proved to be a weak competitive inhibitor of *E. coli β*-D-galactosidase (K_i = 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-α-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 β-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 α-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 $^{5}J_{H\text{-}4,F}$ as discussed below.



9 (R=Ac) **21** (R=H) J = 3 Hz; **13** J = 0 Hz; **18** J = 0 Hz

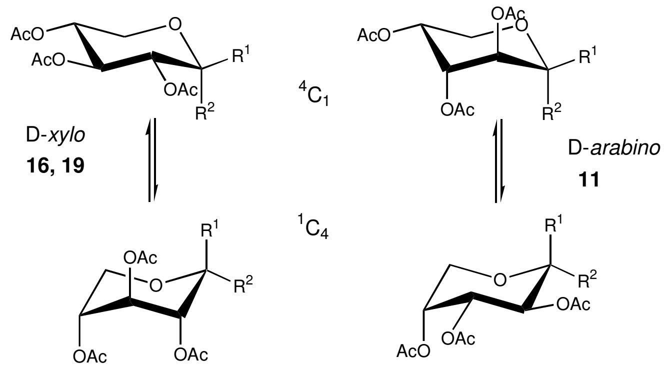
<u>Figure 11.</u> Five-*bonded couplings observed in the ^{1}H NMR spectra of 2,3,4,6-tetra*-O*-acetyl-1-fluoro-*D*-glycopyranosyl cyanides*

Appearance of $^{5}J_{H\text{-}4,\,F}$ couplings of ~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.

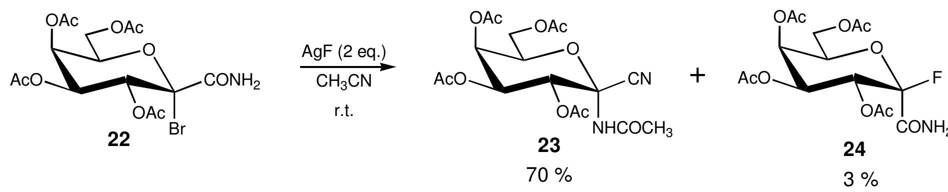


Compound	R^1	R^2	$^4C_1$	$^1C_4$	Solvent	Reference
D-*xylo*	F	H	28	72	$CDCl_3$	110
	H	CN	76	24	C_6D_6	114
			(85	15)[b]		
16	F	CN	33	67	C_6D_6	this work
D-*xylo*	H	F	~100		$CDCl_3$	110
	CN	H	55	45	$CDCl_3$	115
			(54	46)[b]		
19	CN	F	94	6	C_6D_6	this work
D-*arabino*	H	F	65	35	$CDCl_3$	110
	CN	H	13	87	C_6D_6	114
			(19	81)[b]		
11	CN	F	37	63	$CDCl_3$	this work

[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 $^4C_1$ and $^1C_4$ conformers, respectively.[116]

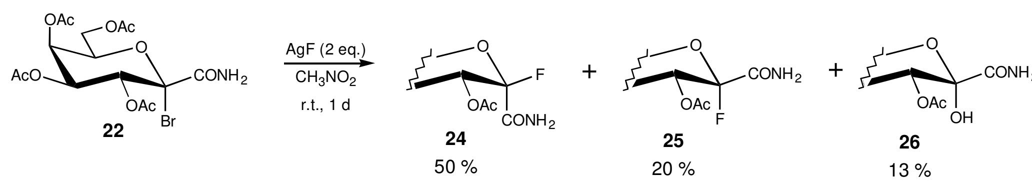
[b] Calculated on the basis of $J_{1,2}$ couplings using $J_{1a,2e}$ = 1.4 Hz and $J_{1e,2a}$ = 6.2 Hz as limiting values for the corresponding conformers.[115]

Table 5. *Conformational equilibria of 1-fluoropentopyranosyl cyanides*[a] *and the related pentopyranosyl fluorides and cyanides*



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*

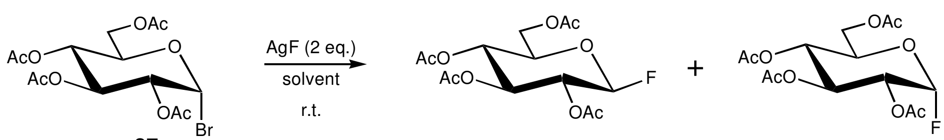
The reaction was repeated using dichloromethane and benzonitrile as solvents. The ratio of the products was determined from the ^{1}H NMR spectra of the crude products (Table 6). In case of benzonitrile the corresponding α-benzamide **44** (see Chapter 3.2, Table 12), formed in a solvent-participation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

Solvent	Ratio of the products (^{1}H NMR) 24	25	26
CH_3NO_2	55	23	22
CH_2Cl_2	52	31	17
PhCN[a]	59[a]	12[a]	12[a]

[a] The remaining ratio (17/100) corresponds to the α-benzamide **44**

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.



27 **28** **29**

Solvent	Ratio of the products (^{1}H NMR) 28	29
CH_3CN	100	0
CCl_3CN	93	7
CH_3NO_2	67	33

Table 7. *Reaction of **27** with silver fluoride in different solvents*

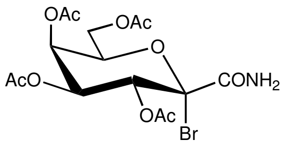
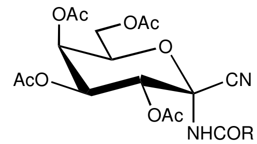
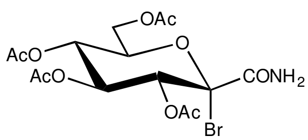
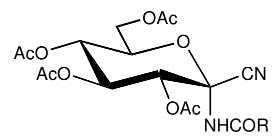
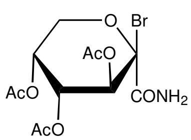
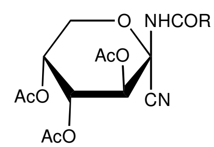
3.2. Nitrile Incorporation Reactions

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[44] (**30**) and *C*-(2,3,4-tri-*O*-acetyl-1-bromo-α-D-arabinopyranosyl)formamide[43] (**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.

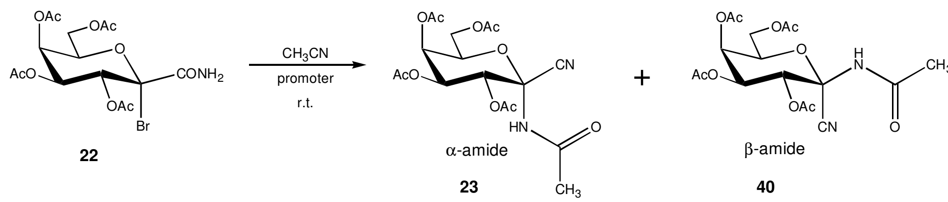
In order to determine the generality of the latter observation about the stereochemical outcome of the reaction, a number of Koenigs-Knorr promoters were tried instead of silver carbonate (Table 9). From the six employed promoters AgOTf, $HgBr_2$ and HgI_2 proved to be useful to bring about the reaction without side-reactions; using $Hg(CH_3COO)_2$, 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.

Starting compound	AgX	*R*-CN	Yield (%)	Product
	Ag_2CO_3	CH_3	76	**23** 
	AgF	CH_3	70[a]	**23**
	Ag_2CO_3	CH_3CH_2	74	**32**
	Ag_2CO_3	CH_2=CH	57	**33**
22	Ag_2CO_3	CH_2=CH-CH_2	62	**34**
	Ag_2CO_3	CH_3OCH_2	24	**35**
	AgF	CH_3	36	**36** 
30	Ag_2CO_3	CH_3CH_2	53	**37**
	Ag_2CO_3	CH_3	41	**38** 
31	Ag_2CO_3	CH_2=CH	43	**39**

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

<u>Table 8.</u> *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.



promoter	reaction time	*α:β* ratio ([1]H NMR)		
Ag_2CO_3	3 d	100	:	0
AgOTf	1 min	100	:	0
$HgBr_2$	1 h	67	:	33
HgI_2	1 d	88	:	12
$Hg(NO_3)_2$	1 h		–[a]	
$Hg(CH_3COO)_2$	14 d		–[b]	
$ZnBr_2$	22 d		–[a]	

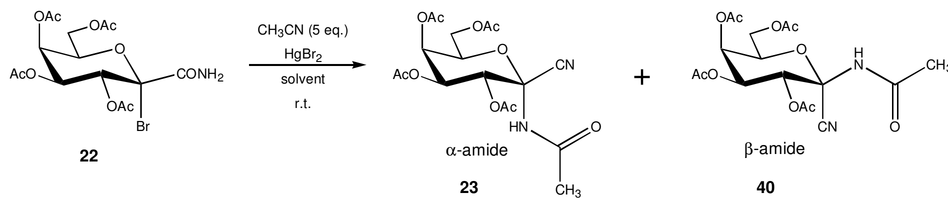
[a] Considerable amount of side-products, overall ratio of the two amides is not more than 50 %

[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 $HgBr_2$ 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.



solvent	reaction time	α:β ratio (^{1}H NMR)
CH_3NO_2	1 d	35 : 65
CH_2Cl_2	14 d	–[a]
dioxane	14 d	–[b,c]
HMPT	1 d	–[a]
PhH	6 d	–[d]

[a] Several side-products
[b] Conversion: < 50 %
[c] Main product: 1-OH derivative **26**
[d] Mass balance: < 20 %

Table 10. *Reactions in different solvents using $HgBr_2$ 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 ^{1}H NMR because of the small-intensity signals of several different by-products.

Since only $HgBr_2$ 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 ^{1}H NMR spectrum, the amount of the β-

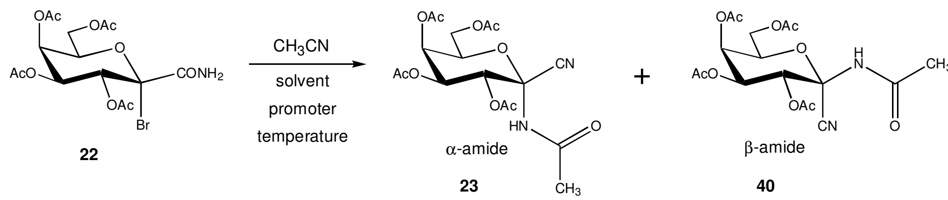
amide, as compared to that of the α-form, was estimated to be even more than in case of 5 equiv. nitrile.) A comparison of product ratios as a function of nitrile-amount can be seen in Table 11 (No. 1-4).

In the next set of experiments, we tried promoter-combinations containing mercuric bromide in order that we may increase the ratio of the β-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 α- and β-amides towards the preference of the α-amide (Table 11, Exp. 6 and 7). Using $ZnBr_2$ together with $HgBr_2$, on the other hand, facilitated an increased ratio of the β-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 β-amide increases at lower temperatures, while at higher temperatures, formation of the α-amide becomes predominant (Table 11, No. 10-13).

The question was arisen, whether the ratio of the two anomeric 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 ^{o}C: no anomerization
3.) 1 day at 100 ^{o}C: no anomerization

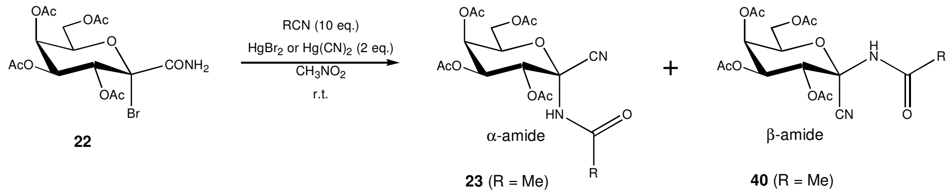


Exp. No.	solvent	promoter	CH_3CN (eq.)	Temp. (°C)	α:β ratio ([1]H NMR)
1	CH_3CN	$HgBr_2$	as solvent	25	67:33
2	CH_3NO_2	$HgBr_2$	10	25	36:64
3	CH_3NO_2	$HgBr_2$	5	25	35:65
4	CH_3NO_2	$HgBr_2$	1.5	25	–[a]
5	CH_3NO_2	$HgBr_2$	5	25	35:65
6	CH_3NO_2	$HgBr_2/Hg(CN)_2$	5	25	89:11
7	CH_3NO_2	$Hg(CN)_2$	5	25	90:10
8	CH_3NO_2	$HgBr_2/ZnBr_2$	5	25	19:81
9	CH_3NO_2	$HgCl_2$	5	25	–[b]
10	CH_3CN	$HgBr_2$	as solvent	-30	57:43
11	CH_3CN	$HgBr_2$	as solvent	25	67:33
12	CH_3NO_2	$HgBr_2$	5	25	35:65
13	CH_3NO_2	$HgBr_2$	5	50	83:17

[a] Several by products, see text [b] Main product: 1-Cl derivative, see text

Table 11. *Reaction of **22** with acetonitrile in different conditions*

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.



23 (R = Me) **40** (R = Me)
42 (R = t-Bu) **43** (R = t-Bu)
44 (R = Ph) **45** (R = Ph)

	α:β ratio (^{1}H NMR)	
R	$HgBr_2$	$Hg(CN)_2$
$-CH_3$	36:64	90:10[a]
$-C(CH_3)_3$	22:78	84:16
-Ph	~1:1[b]	100:0

[a] With 5 eq. CH_3CN [b] More complex mixture

Table 12. *Reactions carried out with different nitriles*

Comparing the experiments with acetonitrile and with pivalonitrile (t-butylcyanide) shows that the sterically demanding pivalonitrile is less capable of attacking from the α-side, thus a higher ratio of β-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 α-amides (**23**, **42** and **44**).

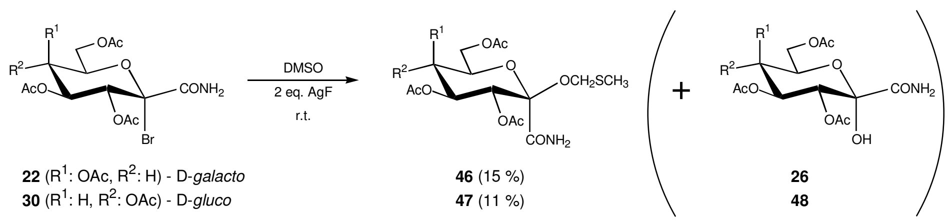
Structures of the novel per-*O*-acetylated *N*-acyl-1-cyanoglycosylamines (**23**, **32**-**40**, **42**-**45**) were proved by NMR spectroscopy and elemental analysis (see also Experimental).

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 –$CONH_2$ group. The presence of extra signals in the ^{1}H- and ^{13}C 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 ^{1}H-coupled ^{13}C NMR spectrum) unlike that of acetyls, 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.[118] The yields are very low, the major products being the 1-OH derivatives **26** and **48**[44] (Scheme 16).



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 (^{1}H NMR analysis).

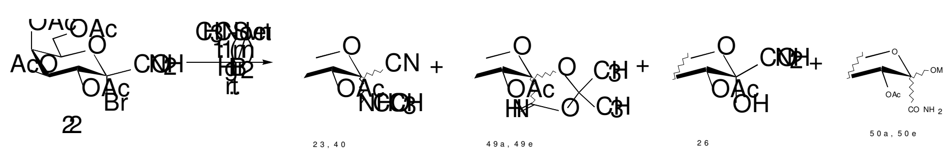
Substitution of silver fluoride by silver carbonate or silver oxide resulted in the exclusive formation of the corresponding 1-OH derivatives.

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 $^4C_1$ 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 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 $J_{H-2, CONH2}$ 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).



Solvents	Ratio of products (from ^{1}H NMR, crude product)			
	23, 40	**49a, 49e**	**26**	**50a, 50e**
CH_3CN, MeOH	0	–	–	100
CH_3CN, DMSO	0	–	100	–
CH_3CN, $(CH_3)_2CO$	several side-products			

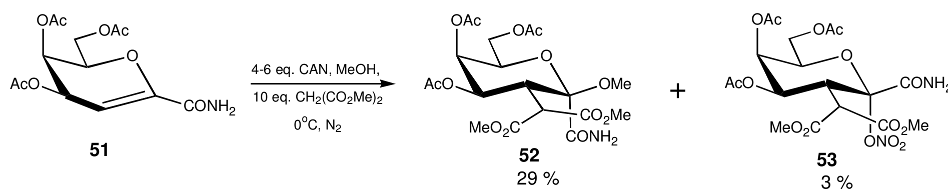
Table 13. *Reaction of **22** with mixtures of nucleophilic solvents in the presence of HgBr$_2$*

3.4. Cerium(IV)-ammonium Nitrate Mediated Addition of Malonyl Radical to C-1 Substituted Glycals[119]

Since a new synthesis of C-1 substituted glycal derivatives under aprotic conditions was worked out in our laboratory,[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.[85,86] Since they obtained the best results (least complicated product mixtures) in the D-*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_3N-containing eluent, neutralized silica gel, neutral Al_2O_3) failed because of decomposition or the inadequate R_f difference of the products on the used adsorbent.

The reaction of the carbamoyl-substituted glycal derivative **51**[109] was investigated first. Thus, in the presence of 4-6 equiv. $Ce(NH_4)_2(NO_3)_6$ 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*

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 1α-OH derivative (**54**, Figure 12) appeared among the products in a non-negligible ratio (10-50 %).

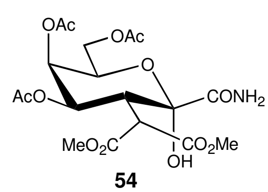
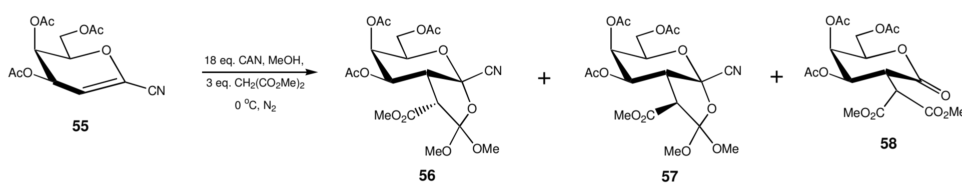


Figure 12. *Hydrolysis product obtained in the reaction of **51** with dimethyl malonate in the presence of "moist CAN"*

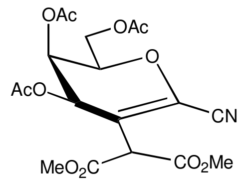
The cyano-substituted D-galactal **55**[120] was the second glycal derivative to be investigated. This could also be transformed to the 2-*C* substituted sugar, but the products were completely different from those appeared so far in this type of reaction. In two of the three products, there were one 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.



Reaction Time [h]	Ratio of products (^{1}H NMR)		
	56	57	58
0.5	68	25	7
1	54	38	8
2	20	38	42
4[a]	–	26	55
8[b]	–	11	61
24[c]	–	–	–

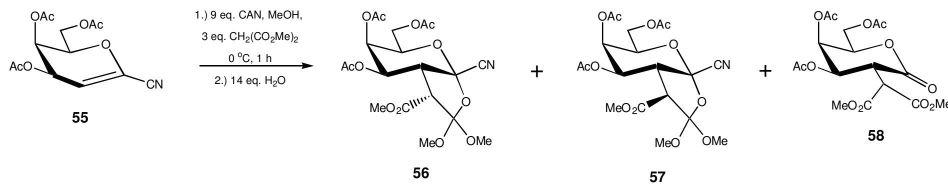
[a] 19 % of an unknown product [b] 28 % of the unknown product
[c] Complete decomposition

Table 14. *Dependence of product ratio on reaction time*



59

Figure 13. *Elimination product obtained in the reaction of **55** with dimethyl malonate in the presence of CAN*



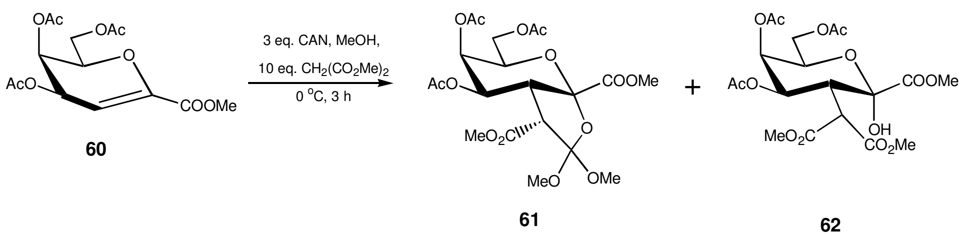
Reaction Time[a] [min]	Ratio of products (^1H NMR)		
	56	**57**	**58**
0	50	37	13
1[b]	11	26	26
30[c]	–	18	31
270[d]	–	–	72

[a] After addition of water [b] 37 % of an unknown intermediate
[c] 51 % of the unknown intermediate
[d] 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_2O 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 $^4C_1$ conformation of their ring was seen from the coupling pattern of their ^{1}H 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, -C**H**(OMe)$_2$) in the ^{1}H NMR spectra while 5 new carbons characteristic of this residue in the ^{13}C 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 exchangable 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]

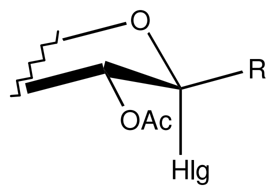
4. Discussion

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-*gluco* and D-*galacto* configuration (with non-participating group at C-2 as well) and retained (*axial* fluoride) in case of D-*manno* 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.

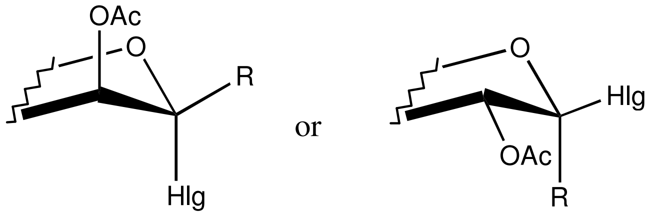
In case of the unsubstituted (see Table 3, Chapter 2.3.1.) and the carbamoyl-substituted (see Chapter 3.2.) 1,2-*cis* glycopyranosyl halides the stereochemistry of the product is probably governed by the fast stereoselective formation of an α-nitrilium–nitrile conjugate (cf. Chapter 2.3.2.). In the first 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 (**6**α, 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

R	Stereochemistry of the glycosyl fluoride	
	Solvent: CH_3CN	**Solvent: CH_3NO_2**
–H	1,2-*trans* (*equatorial*)	mixed
–$CONH_2$	Solvent incorporation	mixed
–CN	1,2-*trans* (*equatorial*)	–

Table 16. *Reaction of 1,2-cis glycosyl halides with silver fluoride in nitromethane and acetonitrile*

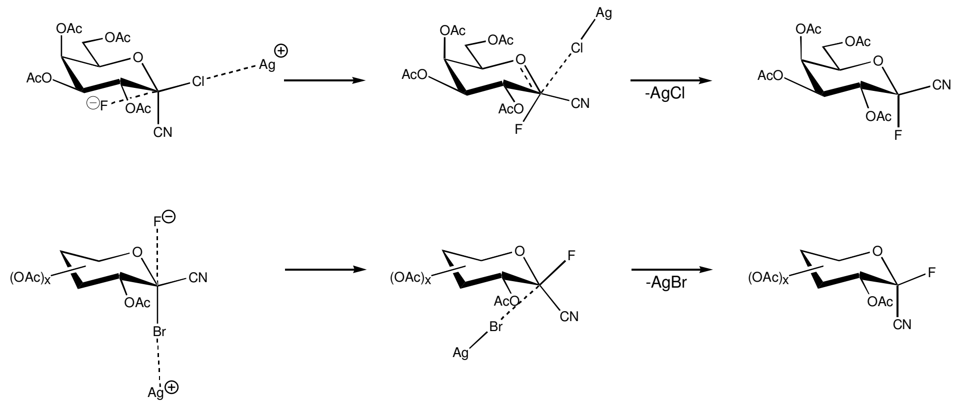


Starting material: 1,2-trans glycosyl halide

R	Stereochemistry of the glycosyl fluoride	
	Solvent: CH_3CN	Solvent: CH_3NO_2
–H	1,2-*trans* (*axial)*	–
$–CONH_2$	–	–
–CN	1,2-*cis* (*axial*)	–

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 S_N2 or S_N2-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 CH_3CN*

The appearance of the unsaturated compounds **14** and **17** in the reaction mixtures obtained with D-*gluco* and D-*xylo* configurated starting materials but not with the D-*galacto* and D-*arabino* 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-*gluco* (**12**) and D-*xylo* (**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-*galacto* (**8**) and D-*arabino* (**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 occured 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]

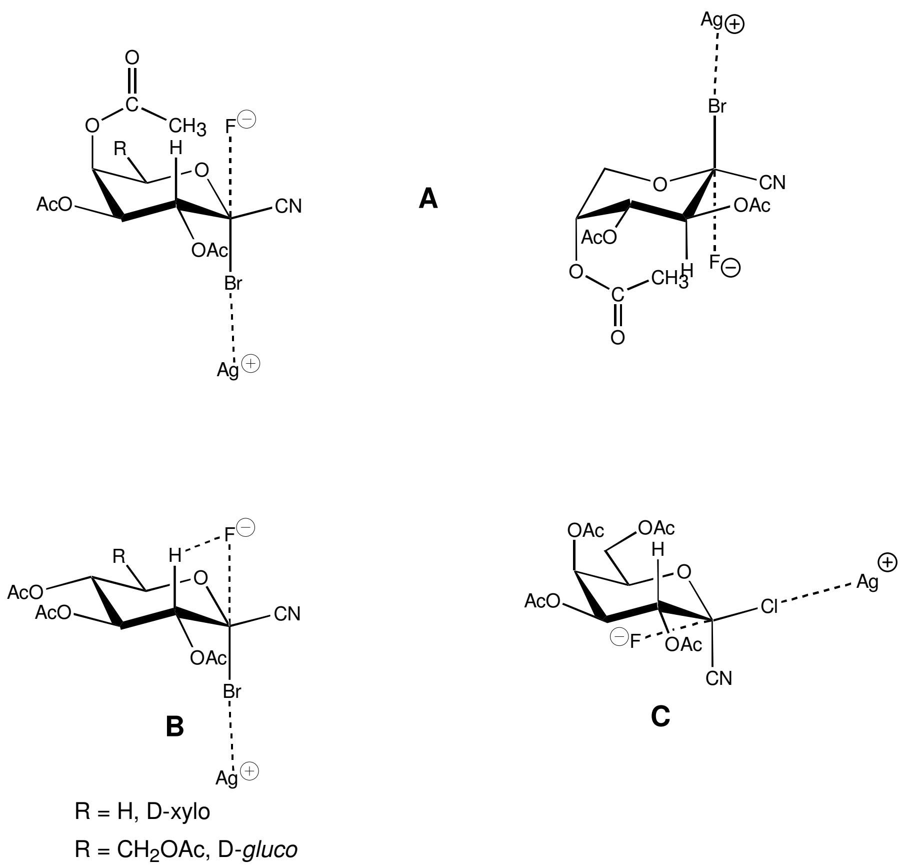


Figure 14. *Transition states corresponding to different configurations of the starting sugar*

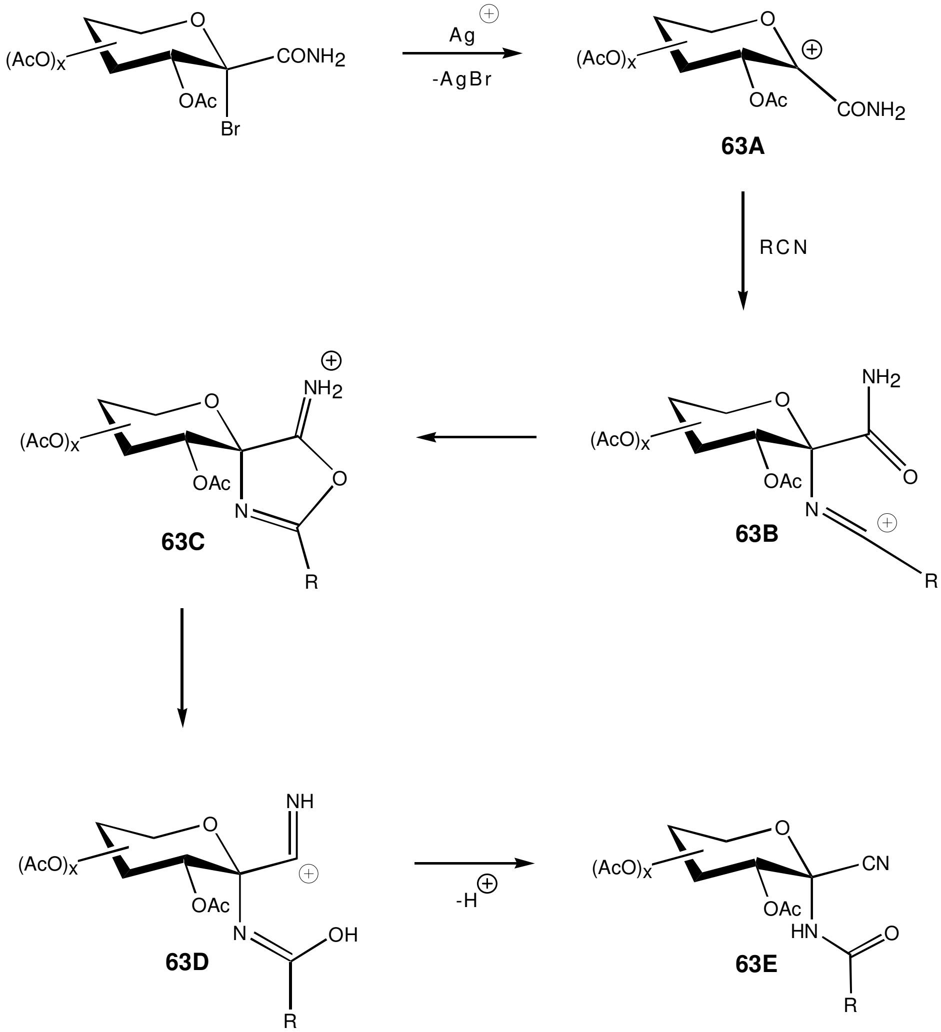
4.2. Nitrile Incorporation Reactions

The reaction which we discovered during the investigation of the fluorination reactions of the fully acetylated *C*-(1-bromoglycopyranosyl)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*-glycosylnitrilium 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** $\rightarrow$ **63E** reaction sequence, has already been observed by Jochims and Glocker.[122]

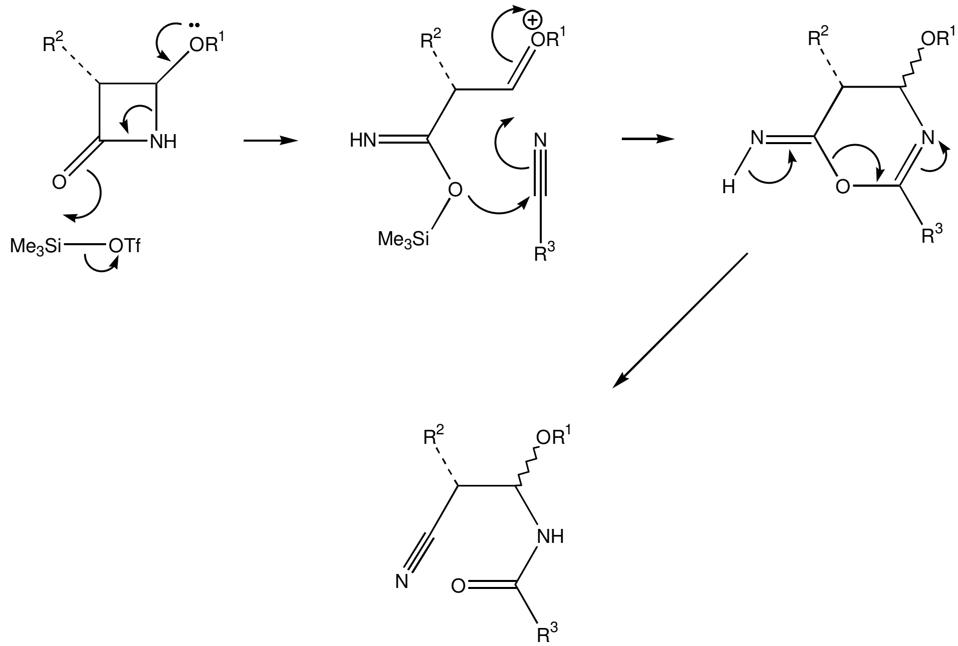
The cleavage of the β-lactam ring discovered by Kita and coworkers[123,124] (Scheme 21) constitutes a completely similar reaction sequence to the one observed by us, though with one more carbon between the two reacting sites of the molecule.

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.).

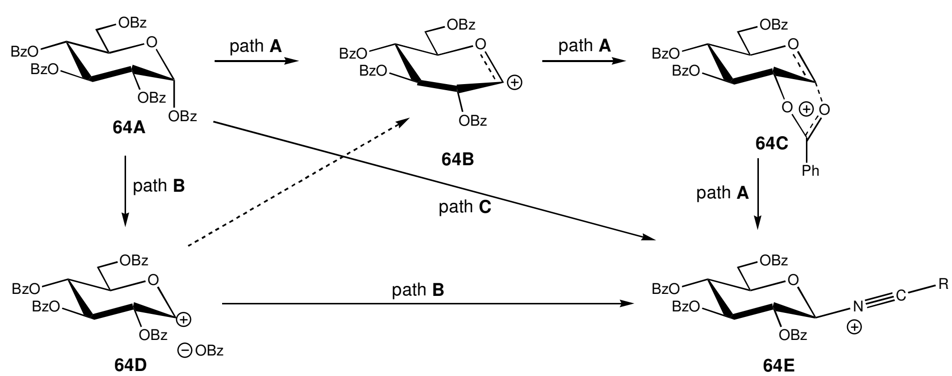


Scheme 20. *Proposed mechanism for the reaction of* C*-(per-*O*-acetyl-1-bromo-*D*-glycopyranosyl)formamides with nitriles*

Formation of β-amide from penta-*O*-benzoyl-α-D-glucopyranose **64A** (1 equiv. $AcNHCH_2CN$, CH_2Cl_2, $SnCl_4$) 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

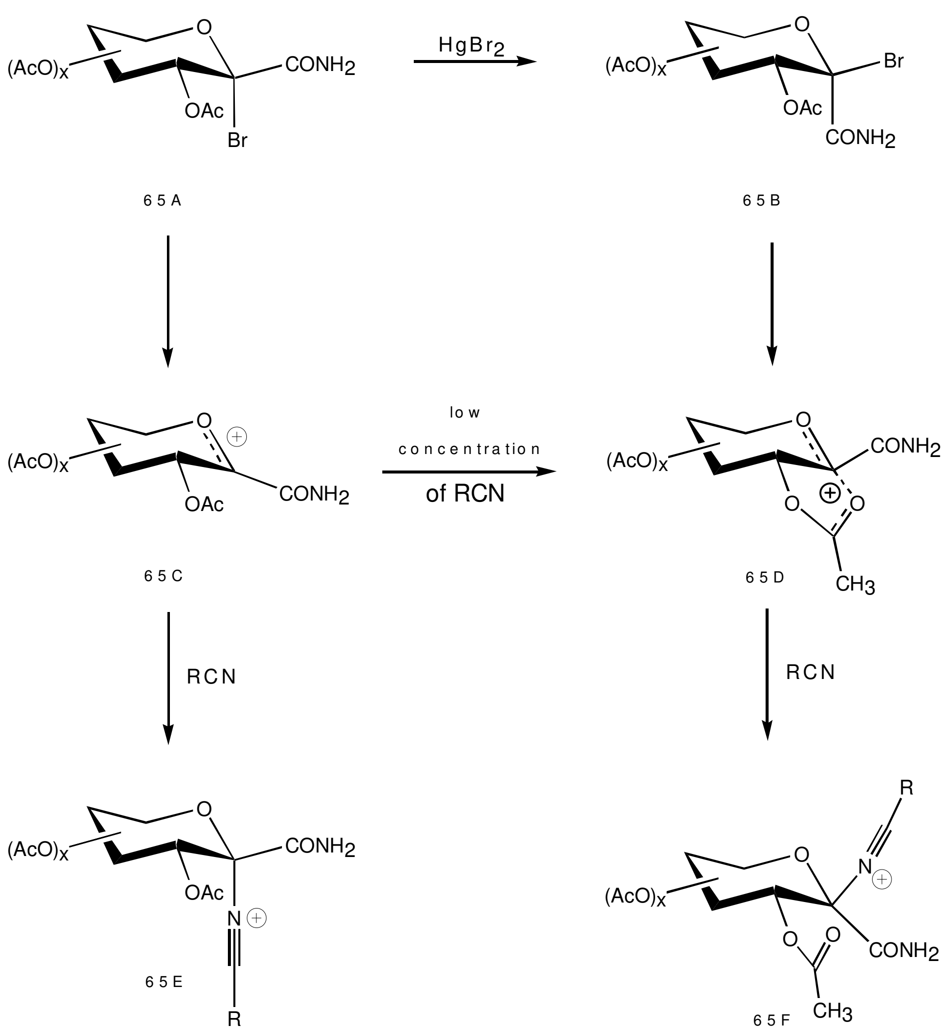


Scheme 21. *Cleavage of the β-lactam ring observed by Kita et al.*



Scheme 22. *Possible pathways for the reaction of penta-O-benzoyl-α-D-glucopyranose with acetamido acetonitrile in CH_2Cl_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.



<u>Scheme 23.</u> *Possible pathways explaining the formation of β-amide using $HgBr_2$ promoter*

The non-negligible ratio (33 %) of β-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_2CO_3) to a synchronous S_N2-type ($HgBr_2$) push-pull pathway. The other possible explanation supposes the anomerization of the starting α-bromide by $HgBr_2$. The resulting β-bromide would react with neighboring-group participation to yield the β-amide (**65A** • **65B** • **65D** • **65F**, Scheme 23).

Decreasing the amount of the nitrile increases the ratio of the β-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.

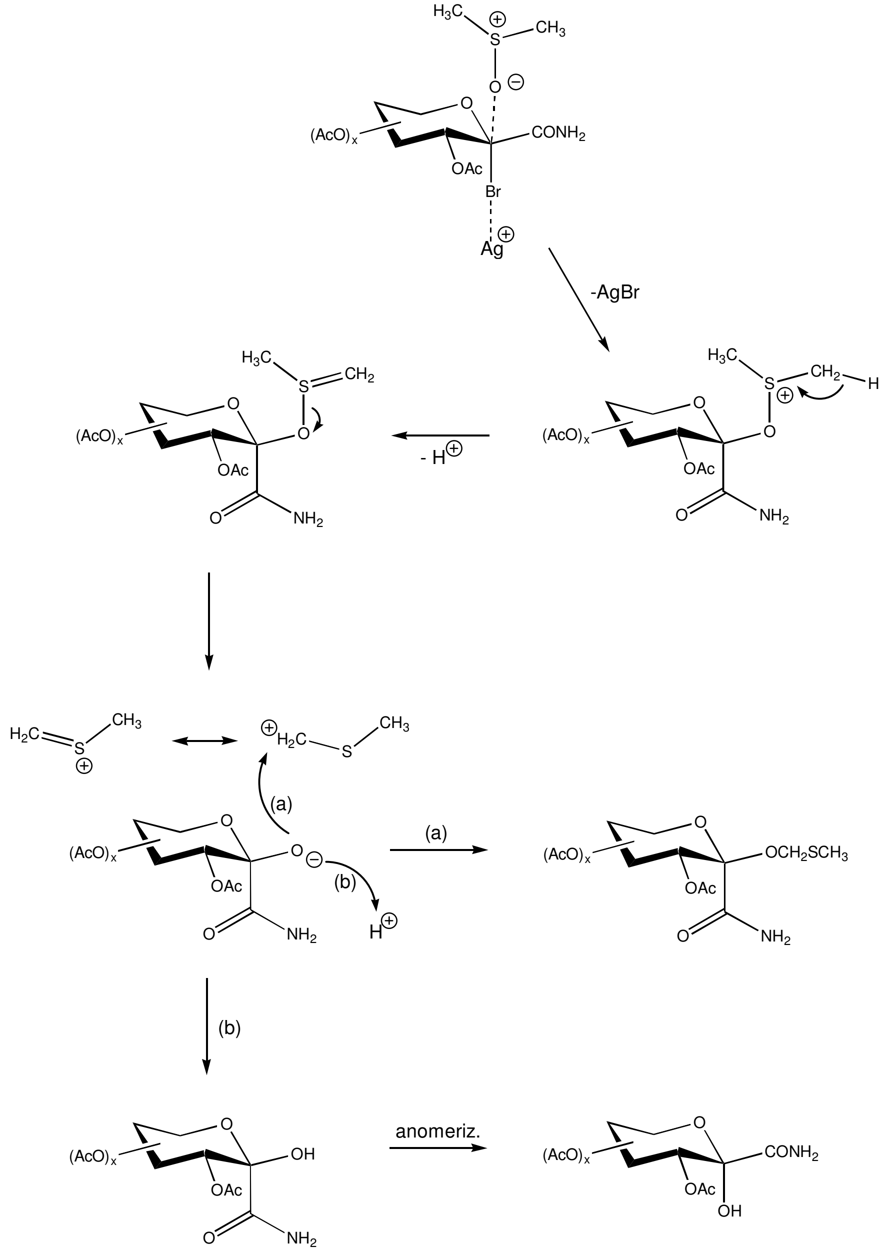
4.3. Other Solvent Participation Reactions of the Fully Acetylated *C*-(1-Bromoglycopyranosyl)formamides

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.[125] The stereoselective formation of the β-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.

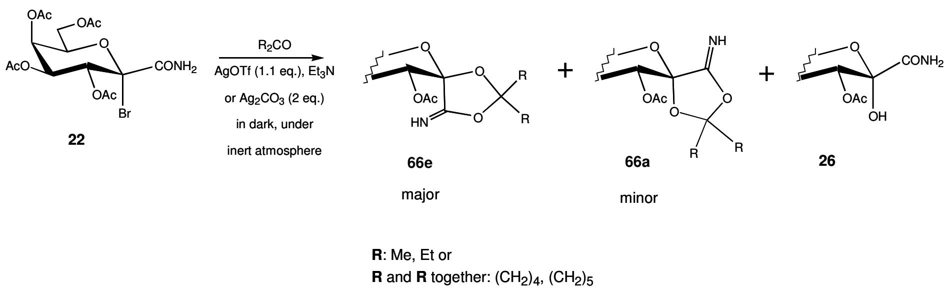
Similar solvent incorporation reaction was observed by L. Kovács and K. Czifrák in our laboratory with ketones. Thus **22**, when stirred in various symmetric ketones in the presence of a suitable promoter, were converted to the spiro-iminodioxolane derivatives **66e** and **66a** (Scheme 25).[118,126] 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** • **67B**, Scheme 26), to the best of our knowledge, has not yet been observed.

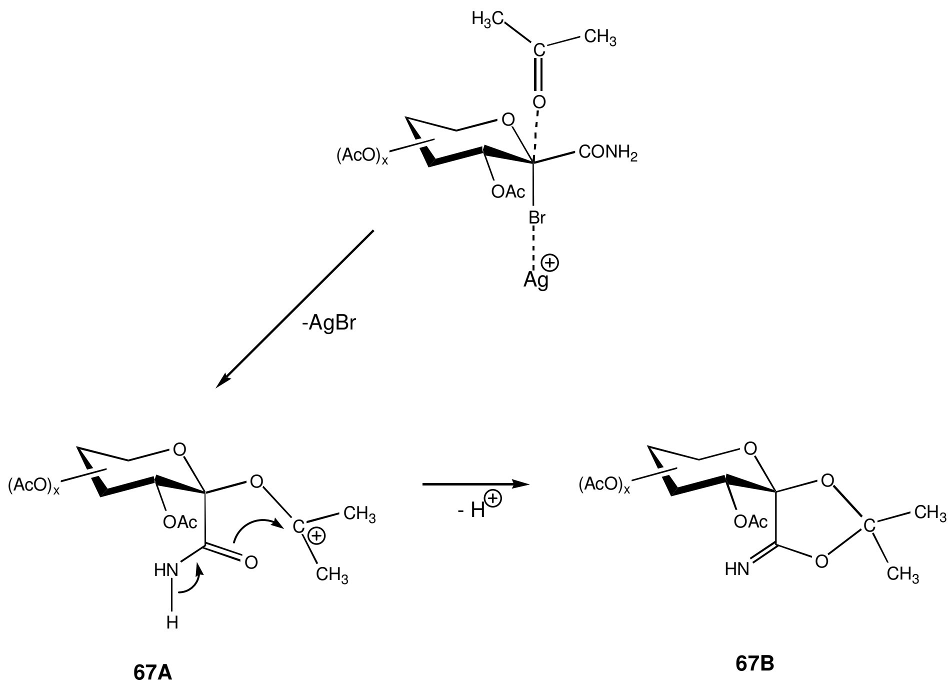
S_N2-type incorporation of acetone has also been observed recently by Fairbanks' group in glycosylation reactions (see Scheme 27).



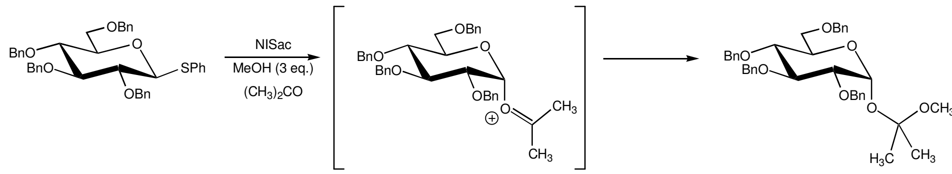
Scheme 24. *Proposed mechanism for the reaction of acetylated* C*-(1-bromoglycopyranosyl)formamides with DMSO using AgF*



Scheme 25. *Reaction of* C*-(2,3,4,6-tetra-*O*-acetyl-1-bromogalacto-pyranosyl)formamide with ketones in the presence of AgOTf or* Ag_2CO_3



Scheme 26. *Proposed mechanism for the reaction of acetylated* C*-(1-bromoglycopyranosyl)formamides with acetone using* Ag_2CO_3 *promoter*



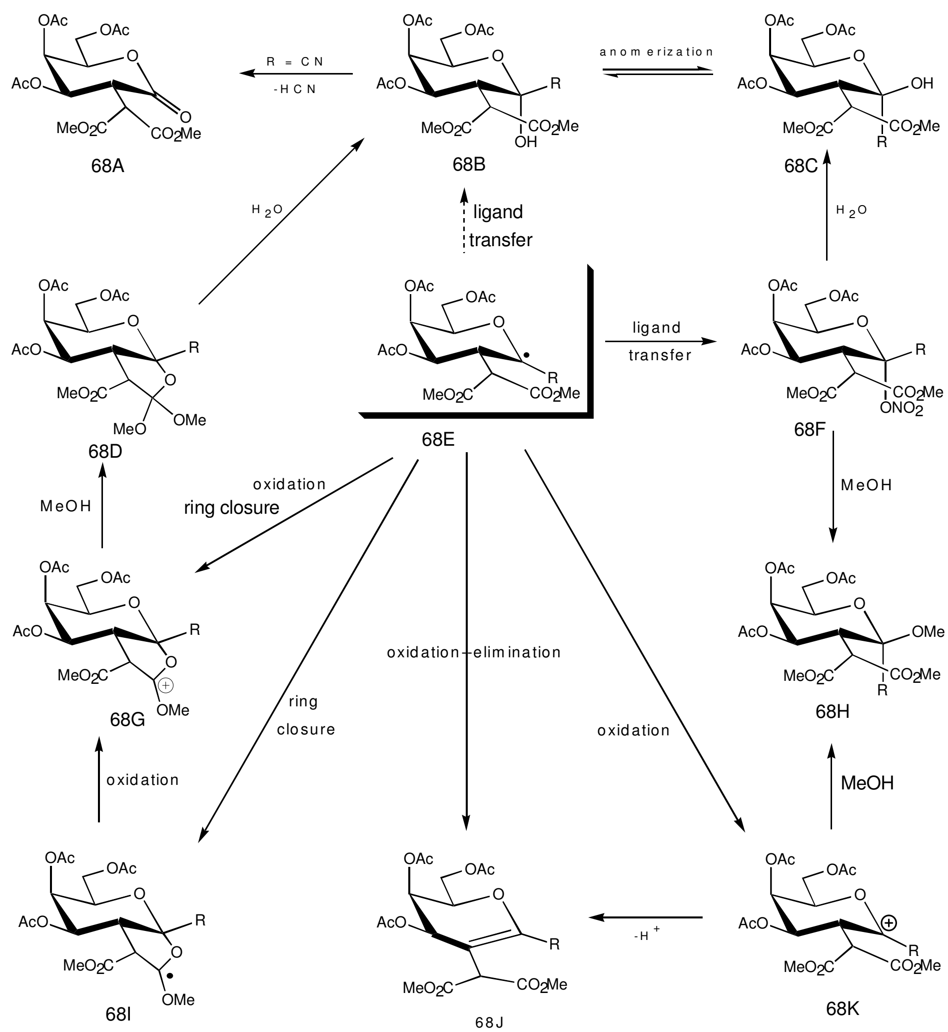
Scheme 27. *Incorporation of the solvent acetone in a glycosylation reaction with phenyl 2,3,4,6-tetra-*O*-benzyl-thioglucopyranoside*

From the three investigated glycal analogs, only the carbamoyl substituted D-galactal furnished products similar to the ones obtained with the acetylated 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 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 electronegatively 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]

R	H	$CONH_2$	CN	COOMe
U [V]	1.86	1.96	> 2.8	> 2.8

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 • 68I • 68G**, Scheme 28) the other assumes the electronic assistance of the neighboring malonyl residue in the "otherwise unaccomplishable" oxidation step (**68E • 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 ^{1}H 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 $–ONO_2$ 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 (^{1}H, 200 MHz; ^{13}C, 50 MHz), Bruker AM 360 (^{1}H, 360 MHz; ^{13}C, 90 MHz) or Avance DRX 500 (^{1}H, 500 MHz; ^{13}C, 125 MHz) spectrometer, with tetramethylsilane as an internal standard (^{1}H) except for D_2O solutions that were calibrated to the value of the SR parameter (both ^{1}H and ^{13}C). The other ^{13}C spectra were calibrated to the peaks of the deuterated solvent. TLC was performed on DC-Alurolle, Kieselgel 60 F_{254} (Merck), the plates were visualized by gentle heating. For column chromatography Kieselgel 60 (Merck) was used. Organic solutions were dried over anhydrous $MgSO_4$ 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[41] 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. $NaHCO_3$ 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 %).

^{1}H NMR (360 MHz, $CDCl_3$): 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, $CDCl_3$): δ = 20.40, 20.50, 20.58, 20.65 (CO**CH_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 (**CO**CH_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)carbaldehyde[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_2CO_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_2CO_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.[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), than filtered on Celite, and the filtrate was extracted with 1 M aqueous $Na_2S_2O_3$ 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-α-*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; $[\alpha]_D$ +80 (c=1.2, $CHCl_3$). Anal.: Calcd for $C_{15}H_{18}NO_9F$ (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; $[\alpha]_D$ +63 (c=1.2, $CHCl_3$). Anal.: Calcd for $C_{12}H_{14}NO_7F$ (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.
^{1}H and ^{13}C 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 ^{1}H NMR. Column chromatography (eluent: EtOAc-hexanes 1:4 • 1:1) afforded pure **13** (266 mg, 21 %) as a colorless syrup. $[\alpha]_D$ +57 (c=1.5, $CHCl_3$). Anal.: Calcd for $C_{15}H_{18}NO_9F$ (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.
^{1}H and ^{13}C 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 ^{1}H NMR. Column chromatography (eluent: EtOAc-hexanes 1:4 • 1:1) afforded pure **16** (47 mg, 11 %) which was crystallized from Et_2O-hexanes. Mp 119-121 °C; $[\alpha]_D$ -23 (c=1.5, $CHCl_3$). Anal.: Calcd for $C_{12}H_{14}NO_7F$ (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.
^{1}H and ^{13}C 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, $CHCl_3$). Anal.: Calcd for $C_{15}H_{18}NO_9F$ (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.

^{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*-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 CH_2Cl_2-Et_2O. Mp 164-165 °C; $[\alpha]_D$ +23 (c=1.1, $CHCl_3$). Anal.: Calcd for $C_{12}H_{14}NO_7F$ (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.

^{1}H and ^{13}C 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, H_2O). Anal.: Calcd for $C_7H_{10}NO_5F$ (207.16): C, 40.59; H, 4.87; N, 6.76. Found: C, 40.38; H, 4.75; N, 6.57.

^{1}H and ^{13}C 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

Compound (solvent)	H-2 $J_{2,3}$ $J_{F,2}$	H-3 $J_{3,4}$ $J_{F,3}$	H-4 $J_{4,5}$ ($J_{4,5}$ /$J_{4,5'}$ [a]) $J_{F,4}$	H-5 $J_{5,6}$ /$J_{5,6'}$ $J_{F,5}$	H-6/H-6' (H-5/H-5'[a]) $J_{6,6'}$ ($J_{5,5'}$[a])	CH_3
9[c] ($CDCl_3$)	5.50 *10.9* *12.1*	5.17 *3.2* *0.7*	5.52 *1.2* *3.0*	4.39 *5.9/6.8* *0.8*	4.27/4.21 *11.5*	2.01 2.09 2.19 2.20
11[b] ($CDCl_3$)	5.44 *8.3* *8.5*	5.21 *3.3*	5.34 *5.2/2.7* *2.2*	—	4.23/4.06 *12.9*	2.06 2.12 2.20
13 (C_6D_6)	5.42 *9.0* *10.8*	5.26 *8.5* *~1*	5.51 *10.0*	3.88 *4.0/2.0*	4.11/3.78 *12.8*	1.47 1.58 1.58 1.61
16 (C_6D_6)	5.35 *5.4* *6.9*	5.26 *5.2*	4.64 *3.3/4.5*	—	3.74/3.45 *13.0*	1.53 1.54 1.56
18 ($CDCl_3$)	5.66 *10.6* *20.9*	5.25 *3.2*	5.54 *1.3*	4.46 *7.0/5.9*	4.20/4.15 *12.4*	2.00 2.08 2.20 2.21
19 (C_6D_6)	5.29 *9.7* *20.7*	5.44 *8.6*	4.78 *6.2/11.0*	—	3.42/3.13 *11.3*	1.46 1.56 1.59
21[c] (D_2O)	3.95 *10.4* *14.7*	3.85 *3.1*	4.07 *0.8* *3.3*	4.12 *4.6/7.2* *1.0*	3.86 *n.d.*[d] *n.d.*[d]	—

[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 (δ [ppm], *J* [Hz])

<table>
<tr><th>Com-
pound</th><th>C-1
J_{C,F}</th><th>C-2
J_{C,F}</th><th>C-3
J_{C,F}</th><th>C-4</th><th>C-5</th><th>C-6</th><th>CN
J_{C,F}
J_{CN,H-2}</th><th>CO</th><th>CH₃</th></tr>
<tr><td>9</td><td>104.10
220</td><td>68.07
26</td><td>68.84
8.5</td><td colspan="2">65.63
72.98</td><td>60.43</td><td>111.23
46
6.1</td><td>168.52
169.32
169.60
170.01</td><td>20.22
20.34</td></tr>
<tr><td>11[a]</td><td>103.71
224</td><td>67.95
30</td><td>67.52
5</td><td>64.90</td><td>63.57</td><td>—</td><td>111.56
44
3.9</td><td>168.32
169.29
169.59</td><td>20.34
20.36
20.54</td></tr>
<tr><td>13[a]</td><td>103.35
221</td><td>70.67
31</td><td colspan="3">66.27
70.58
73.47</td><td>60.52</td><td>111.16
45
5.1</td><td>168.27
169.00
169.31
170.16</td><td>20.25
20.31
20.44</td></tr>
<tr><td>16</td><td>102.96
225</td><td>67.19
33</td><td colspan="2">65.47
66.86</td><td>62.49</td><td>—</td><td>111.83
42
n.d.[c]</td><td>168.22
168.78
169.48</td><td>20.38
20.46
20.63</td></tr>
<tr><td>18</td><td>102.00
235</td><td>67.18
23</td><td colspan="3">66.46
66.95
71.64</td><td>60.48</td><td>111.66
42
<2</td><td>168.69
169.38
169.58
169.99</td><td>20.36</td></tr>
<tr><td>19</td><td>102.27
237</td><td>70.41
26</td><td colspan="2">67.00
68.78</td><td>62.08</td><td>—</td><td>111.75
43
<2</td><td>168.64
169.36
169.46</td><td>20.09
20.35</td></tr>
<tr><td>21[b]</td><td>110.20
212</td><td>73.50
23</td><td colspan="3">70.17
73.37
80.43</td><td>63.18</td><td>115.37
47
n.d.[c]</td><td>—</td><td>—</td></tr>
</table>

[a] Measured at 125 MHz. [b] Measured in D_2O 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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 20.43, 20.48 (CO**CH_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 (**CO**CH_3).

25: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 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).

General procedure A *for the preparation of per-*O*-acetyl-*N*-acyl-1-cyano-*D*-glycopyranosylamines* ***23, 32-39***:
An acetylated *C*-(1-bromo-D-glycopyranosyl)formamide[43,44,109] (**22, 30, 31**) (0.25 mmol) was dissolved in a nitrile (RCN) (1 ml), distilled from P_2O_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-β-*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-α-*D*-galactopyranosylamines* ***42*** *and* ***44***:
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 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; $[\alpha]_D$ +49 (c=1.15, $CHCl_3$). Anal.: Calcd for $C_{17}H_{22}N_2O_{10}$ (414.364): C, 49.28; H, 5.35; N, 6.76. Found: C, 48.27; H, 5.43; N, 6.35.

^{1}H and ^{13}C 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 CH_2Cl_2 – Et_2O to afford white crystals (15 mg). Mp 186-187 °C; $[\alpha]_D$ +55 (c=0.91, $CHCl_3$). Anal.: Calcd for $C_{18}H_{24}N_2O_{10}$ (428.391): C, 50.47; H, 5.65; N, 6.54. Found: C, 50.41; H, 5.93; N, 6.67.

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

N-*Propenoyl-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 CH_2Cl_2 – Et_2O to afford white crystals (10 mg). Mp 158-160 °C; $[\alpha]_D$ +61 (c=0.80, $CHCl_3$). Anal.: Calcd for $C_{18}H_{22}N_2O_{10}$ (426.375): C, 50.70; H, 5.20; N, 6.57. Found: C, 49.93; H, 5.12; N, 6.39.

^{1}H and ^{13}C 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 CH_2Cl_2 – Et_2O. Mp 149-150 °C; $[\alpha]_D$ +57

(c=0.88, $CHCl_3$). Anal.: Calcd for $C_{19}H_{24}N_2O_{10}$ (440.401): C, 51.82; H, 5.49; N, 6.36. Found: C, 51.34; H, 5.43; N, 6.55.
^{1}H and ^{13}C NMR spectroscopic data are given in Table 21 and 22, respectively.

N-*Methoxyacetyl-2,3,4,6-tetra-*O*-acetyl-1-cyano-α-D-galactopyranosyl-amine* (**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 CH_2Cl_2 – Et_2O. Mp 149-151 °C; $[\alpha]_D$ +29 (c=1.22, $CHCl_3$). Anal.: Calcd for $C_{18}H_{24}N_2O_{11}$ (444.390): C, 48.65; H, 5.44; N, 6.30. Found: C, 50.00; H, 5.70; N, 6.47.
^{1}H and ^{13}C 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; $[\alpha]_D$ +25 (c=0.61, $CHCl_3$). Anal.: Calcd for $C_{18}H_{24}N_2O_{10}$ (428.391): C, 50.47; H, 5.65; N, 6.54. Found: C, 50.03; H, 5.52; N, 6.23.
^{1}H and ^{13}C 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 CH_2Cl_2 – Et_2O to afford white crystals (43 mg). Mp 170-172 °C; $[\alpha]_D$ -29 (c=1.07, $CHCl_3$). Anal.: Calcd for $C_{17}H_{22}N_2O_{10}$ (342.301): C, 49.12; H, 5.30; N, 8.18. Found: C, 50.10; H, 5.57; N, 8.33.
^{1}H and ^{13}C NMR spectroscopic data are given in Table 21 and 22, respectively.

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. $[\alpha]_D$ -29 (c=1.06, $CHCl_3$).
^{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 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 syrupy **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 syrupy *N*-Acetyl-2,3,4,6-tetra-*O*-acetyl-1-cyano-*α*-D-glucopyranosylamine **36** (196 mg, 36 %). Mp 179-181 °C; $[\alpha]_D$

+57 (c=1.01, acetone). Anal.: Calcd for $C_{17}H_{22}N_2O_{10}$ (414.364): C, 49.28; H, 5.35; N, 6.76. Found: C, 48.52; H, 5.60; N, 6.70.
^{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; $[\alpha]_D$ +59 (c=1.06, $CHCl_3$). Anal.: Calcd for $C_{20}H_{28}N_2O_{10}$ (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: $[\alpha]_D$ +66 (c=1.00, $CHCl_3$). Anal.: Calcd for $C_{22}H_{24}N_2O_{10}$ (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 $C_{17}H_{22}N_2O_{10}$ (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 $C_{20}H_{28}N_2O_{10}$ (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 $C_{22}H_{24}N_2O_{10}$ (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_4Si (δ [ppm], J [Hz])

Com-pound	H-2 $J_{2,3}$	H-3 $J_{3,4}$	H-4 $J_{4,5}$	H-5 $J_{5,6}/J_{5,6'}$	H-6/H-6' $J_{6,6'}$	NH	CH_3	Others
23	5.75 *10.7*	5.30 *3.4*	5.27 *<1*	4.26 *6.0/6.0*	4.09 *multiplet*	7.90	1.99 2.03 2.19[a] 2.20	—
32[b]	5.76 *10.6*	5.30 *3.4*	5.38 *<1*	4.26 *6.6/6.6*	4.10 *multiplet*	7.68	1.99 2.03 2.17 2.20	1.21 (t), 2.42 (q) ethyl
33	5.78 *10.6*	5.25 *2.8*	5.39 *<1*	4.23 *6.6/6.6*	4.18/4.09 *10.7*	7.20	1.99 2.02 2.16 2.20	5.86 (d), 6.29 (dd), 6.51 (d) vinyl
34	5.38 *3.1*	5.35-5.40 *multiplet*		4.00-4.20 *multiplet*		6.85	2.00 2.03 2.16 2.20	3.19 (d), 5.14 (m), 5.99 (m) allyl
35	5.78 *10.9*	5.11 *3.2*	5.41 *<1*	4.22-4.05 *multiplet*		7.34	2.01 2.03 2.17 2.21	3.49 (s) OMe 3.97 (d), 4.04 (d) **CH_2**OMe

[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_4Si (δ [ppm], *J* [Hz])

Compound	H-2 $J_{2,3}$	H-3 $J_{3,4}$	H-4 $J_{4,5}$ or $J_{4,5}/J_{4,5'}$[a]	H-5 $J_{5,6}/J_{5,6'}$ or H-5/H-5'[a] $J_{5,5'}$[a]	H-6/H-6' $J_{6,6'}$	NH	CH_3	Others
36[b]	5.52 *10.0*	5.16 *8.7*	5.42 *10.0*	4.13 *4.5/2.4*	4.31/4.02 *12.3*	8.72	1.96 1.99 2.02 2.10 2.11	—
37	5.57 *9.8*	5.16 *9.4*	5.31 *8.7*	3.96 *4.4/2.2*	4.29/4.06 *12.5*	6.97	2.03[c] 2.11 2.16	1.21 (t), 2.42 (q) ethyl
38	5.69 *9.6*	5.34 *3.6*	5.30 *1.6/2.5*	4.06/3.85 *13.5*	—	8.53	1.96 2.08 2.13[c]	—
39	5.77 *8.8*	5.28 *3.5*	5.24 *2.6/2.6*	3.95	—	6.90	2.06 2.17 2.18	5.86 (dd), 6.29 (dd), 6.51 (dd) vinyl
40	5.22 *10.5*	5.41 *3.1*	5.53 *1.3*	4.44 *6.8/6.8*	4.17 *doublet*	7.21	2.01 2.06[c] 2.16 2.21	—

[a] Applies for the pentose derivatives **38** and **39**. [b] In $(CD_3)_2CO$. [c] 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_4Si (δ [ppm], *J* [Hz])

Com-pound	H-2 $J_{2,3}$	H-3 $J_{3,4}$	H-4 $J_{4,5}$	H-5 $J_{5,6}/J_{5,6'}$	H-6/H-6' $J_{6,6'}$	NH	CH_3	Others
42	5.75 *10.5*	5.12 *3.2*	5.40 –	4.02–4.21 *multiplet*		6.52	2.00 2.04 2.17 2.21	1.28 (s, 9H) t-butyl
43	5.18 *10.3*	5.46 *3.2*	5.54 *1.0*	4.43 *6.8/6.8*	4.20/4.16 *11.3*	7.14	2.02 2.05 2.18 2.21	1.20 (s, 9H) t-butyl
44	5.85 *10.4*	5.37 3.2	5.45 *1.2*	4.32 *6.7/6.7*	4.22/4.10 *11.0*	7.14	1.97 1.99 2.18 2.22	7.53 (t, 2H) 7.63 (t, 1H) 7.90 (d, 2H) phenyl
45	5.33 *10.4*	5.52 *3.0*	5.58 *1.2*	4.52 *6.7/6.7*	4.19/4.22 *11.0*	7.88	2.04 2.06 2.17 2.24	7.48 (t, 2H) 7.58 (t, 1H) 7.81 (d, 2H) phenyl

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 (δ [ppm], J [Hz])

Compound	C-1	C-2,3,4,5	C-6	CN ($J_{H-2,CN}$/$J_{NH,CN}$)	C=O	CH_3	Others
23	77.71	66.71 67.29 67.50 67.74	60.57	114.75 (~3/~3)	168.17 169.74 170.03 170.28 171.24	20.34[a] 20.46[a] 22.94	—
32[b]	77.67	66.71 67.39 67.63	60.64	114.78 (~3/~3)	168.13 169.73 170.02 170.27 174.54	20.31[a] 20.41[a]	8.91, 28.86 ethyl
33	78.17	66.71 67.61 67.74 68.08	60.64	114.47 (~3/~3)	165.25 167.99 169.99 170.08 170.35	20.40[a] 20.49[a]	128.79, 130.20 vinyl
34	77.98	66.59 67.62 67.74 68.05	60.66	114.45 (~3/~3)	167.76 167.79 169.90 170.05 170.34	20.33 20.44 20.53[a]	40.99, 120.46, 129.95 allyl
35	77.81	66.42 67.55 67.85 68.10	60.52	114.13 (~3/~3)	167.71 169.34 169.87 170.06 170.33	20.40 20.44 20.56[a]	59.27 OMe 71.61 **CH_2**OMe

[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 (δ [ppm], J [Hz])

Com-pound	C-1	C-2,3,4,5	C-6	CN ($J_{H-2,CN}$/$J_{NH,CN}$)	C=O	CH_3	Others
36[a,b]	78.13	68.54 69.26 71.11 71.46	61.83	115.91 (~3/~3)	168.95 169.78 170.22 170.45 170.68	20.27 20.38 20.44 20.50 22.90	—
37[a]	76.05	66.88 68.19 69.79 70.13	60.58	114.09 (~3/~3)	167.60 168.72 169.83 170.29 173.40	19.90 20.02 20.07 20.24	8.45, 28.70 ethyl
38	78.05	66.77 66.94 67.90	61.58	114.71 (~3/~3)	168.21 169.76 170.07 170.88	20.39 20.51 20.74 23.04	—
39[a]	78.14	66.67 66.91 67.71	61.65	114.55 (~3/~3)	165.56 168.33 169.64 170.05	20.31 20.41 20.67	128.91, 129.73 vinyl
40	79.86	66.13 68.53[c] 71.23	60.20	111.86	169.07 169.26 169.61 170.09 171.66	20.17 20.27 20.36 20.52 23.10	

[a] At 50 MHz. [b] In $(CD_3)_2CO$. [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])

Com-pound	C-1	C-2,3,4,5	C-6	CN ($J_{H\text{-}2,CN}$/$J_{NH,CN}$)	C=O	CH_3	Others
42	77.88	66.40 67.57 67.77[a]	60.60	114.52 (~3/~3)	167.63 169.65 169.95 170.29 177.82	20.24 20.32 20.81 20.84	26.95, 39.54 t-butyl
43	80.34	66.16 68.43 68.91 71.30	60.09	112.01 (5.5/7.6)	169.09 169.73 170.11 172.34 177.38	20.32 20.48[a] 20.61	39.01 26.90 t-butyl
45	80.60	66.21 68.44 69.14 71.40	60.16	111.93 (5.5/7.3)	165.44 169.06 169.63 170.05 172.65	20.27 20.36 20.42 20.69	127.26[a] 128.75[a] 131.52 132.84 phenyl

[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 ºC (bath temperature), to give pure products **46** and **47**, respectively.

Methylthiomethyl 2,3,4,6-tetra-O-acetyl-1-carbamoyl-β-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_2Cl_2 – Et_2O to afford white crystals. Mp 155-156 °C; $[\alpha]_D$ +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-β-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). $[\alpha]_D$ +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_4Si (δ [ppm], *J* [Hz])

Compound	H-2 $J_{2,3}$	H-3 $J_{3,4}$	H-4 $J_{4,5}$	H-5 $J_{5,6}/J_{5,6'}$	H-6/H-6' $J_{6,6'}$	NH_2	CH_3	Others
	C-1	C-2,3,4,5			C-6	C=O	CH_3	Others
46	5.40 *10.5*	5.82 *3.2*	5.47 *1.2*	4.83 *6.6/6.6*	4.04 *doublet*	5.69 6.69	1.91 1.97 2.02 2.11[a]	4.77 (d), 4.86 (d) OCH_2S
	97.46	66.22, 67.32, 69.81, 71.45			61.25	168.99[b] 169.81[b] 170.32	20.71[b]	14.91 SMe 67.82 OCH_2S
47	5.23 *8.9*	5.82 *9.1*	5.15 *9.8*	4.55 *1.1/3.1*	4.08/4.18 *12.9*	5.98 6.71	1.93 1.97 2.00 2.02 2.11	4.72 (d), 4.78 (d) OCH_2S
	96.98	67.66, 69.43, 71.77, 71.78			61.65	168.76 169.35 169.68 169.78 170.59	20.64[b] 20.73	14.82 SMe 67.95 OCH_2S

[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. $NaHCO_3$ 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. $NaHCO_3$ 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 ^{1}H NMR. Column chromatography afforded partially pure **53** (19 mg, 3 %), **52** (153 mg, 26 %) and **54** (17 mg, 3 %) as colorless syrups. ^{1}H and ^{13}C 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_4Si (δ [ppm], *J* [Hz])

Cpd	H-2 $J_{2,3}$	H-3 $J_{3,4}$	H-4 $J_{4,5}$	H-5 $J_{5,6}/J_{5,6'}$	H-6/H-6' $J_{6,6'}$	H-7 $J_{2,7}$	CH_3	OMe	Others
52	3.44 *11.7*	5.94 *3.2*	5.42 *1.1*	4.47 *6.5/6.5*	4.06/4.10 *11.0*	3.54 *4.2*	1.88 2.01 2.13	3.47 3.67 3.72	5.84 6.57 $CONH_2$
53	3.35 *12.1*	5.68 *2.6*	5.54 *1.1*	4.34 *4.7/7.9*	3.96/4.51 *11.6*	4.44 *2.1*	1.90 2.03 2.17	3.72 3.77	5.99 6.79 $CONH_2$
56	3.07 *9.2*	5.68 *3.7*	5.46 –	4.09-4.19 (m)		3.69 *6.8*	1.97 2.08 2.16	3.43 3.48 3.70	
57	3.31 *9.8*	5.00 *2.9*	5.37 *1.5*	4.31 *7.0/6.1*	4.18/4.22 *11.5*	3.22 *2.6*	2.05 2.07 2.19	3.43 3.44 3.80	
58	3.40 *10.5*	5.35 *3.0*	5.64 *1.2*	4.85 *6.8/6.8*	4.22/4.26 *11.6*	4.05 *3.7*	2.00 2.08 2.16	3.78 3.80	
59	–	6.01 *4.2* *1.0*[a]	5.50 *1.7*	4.51 *6.4/6.4*	4.20/4.24 *11.6*	4.48 –	1.92 2.08 2.12	3.76 3.77	
61	3.29 *9.2*	5.76 *3.7*	5.47 –	4.08-4.20 (m)		3.54 *7.4*	1.96 2.07 2.11	3.33 3.43 3.67 3.87	
62	3.57 *11.9*	5.68 *2.6*	5.46 –	4.41 *6.5/6.5*	4.04/4.12 *11.1*	3.26 *3.5*	2.05 2.07 2.19	3.43 3.44 3.80	4.34 OH

[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 (δ [ppm], J [Hz])

Cpd	C-1	C-2,3,4,5	C-6	C-7, OMe	C=O	CH_3	Others
52	102.11	40.50 65.72 67.44 71.50	61.11	46.43 52.62 52.78	167.67 168.70 169.16 169.84 170.90	20.36 20.59 20.63	166.66 $CONH_2$ (*J*=6.4 Hz)
53	98.60	37.42 66.27 69.62 70.78	61.81	48.55 49.48 52.35 52.74	167.40 168.99 169.30 170.02 170.45	20.46 20.57 20.66	169.65 $CONH_2$ (singlet)
56	97.14	44.33 63.78 66.29 69.65	61.30	47.54 49.84 51.67 52.37	165.44 169.26 169.86 170.28	20.39 20.51 20.59	119.69 O**C**$(OMe)_2$ 116.21 CN (*J*=3.2 Hz)
57	97.22	44.49 64.11 70.10 70.86	61.13	50.39 51.63 52.73 53.16	167.56 169.91 170.18 170.27	20.56 20.58 20.66	119.76 O**C**$(OMe)_2$ 115.95 CN
58	See C=O	42.06 64.66 68.57 74.07	61.08	50.05 52.83 53.12	167.83 167.86 168.14 169.50 169.56 170.14	20.31 20.41 20.50	

Table 25 (continuation)

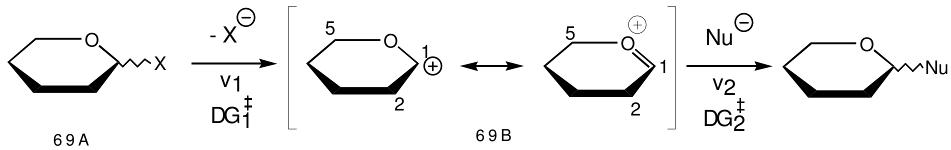
^{13}C NMR data for C-2 branched sugar derivatives (**52**-**54**, **56**-**59**, **61**, **62**) measured in $CDCl_3$ at 90 MHz referenced to solvent residual signal (δ [ppm], J [Hz])

59	130.61	118.11 61.90 65.58 74.37	61.06	51.81 52.86 52.97	166.07 166.66 168.84 169.71 170.20	19.88 20.27 20.50	111.79 CN
61	102.52	40.34 64.16 67.30 69.14	61.55	48.05 49.32 51.22 52.00 53.24	166.37 167.44 169.33 169.98 170.29	20.46[a] 20.58	
62	96.66	39.83 66.69 68.33 68.54	61.59	49.14 52.41 52.60 53.98	167.40 168.30 168.71 169.30 170.26 170.42	20.39 20.62[a]	

[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).



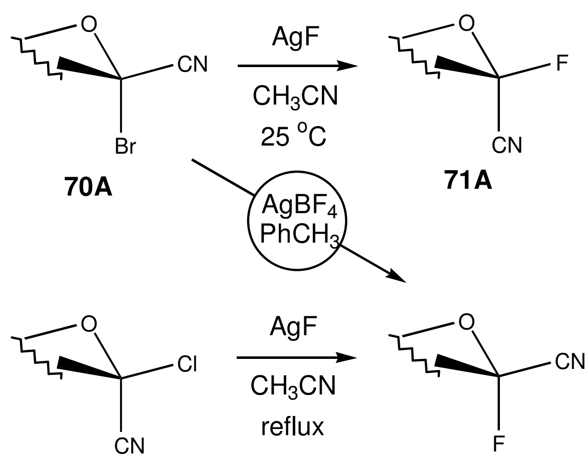
x : leaving group

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 ($\Delta G_1^{\ddagger}$), 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 donors[25,26]).

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.



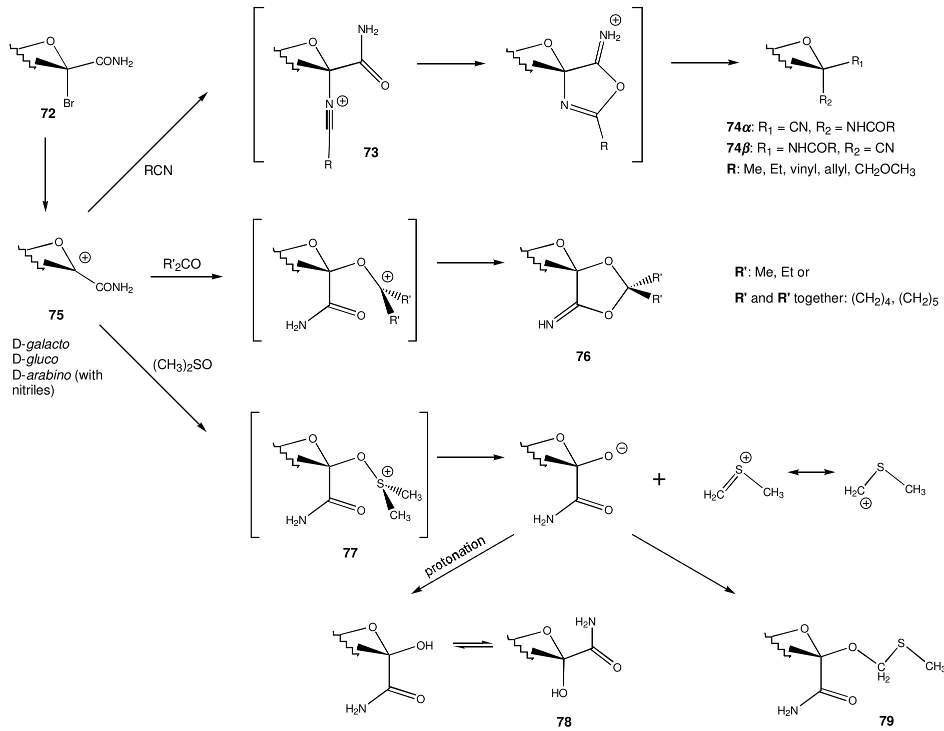
Scheme 30. *Reaction of 1-cyanoglycopyranosyl halides with silver fluoride under Helferich conditions*

The presence of the less strongly electron withdrawing carbamoyl group (–$CONH_2$), 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** • **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 glycosylium 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-α-D-glycopyranosyl-amines (**74**α, 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 α-glycosyl-nitrilium ions (**73**).[68,124] This reaction may form a basis for an effective and stereoselective synthesis leading to novel derivatives of anomeric α-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**β) 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.

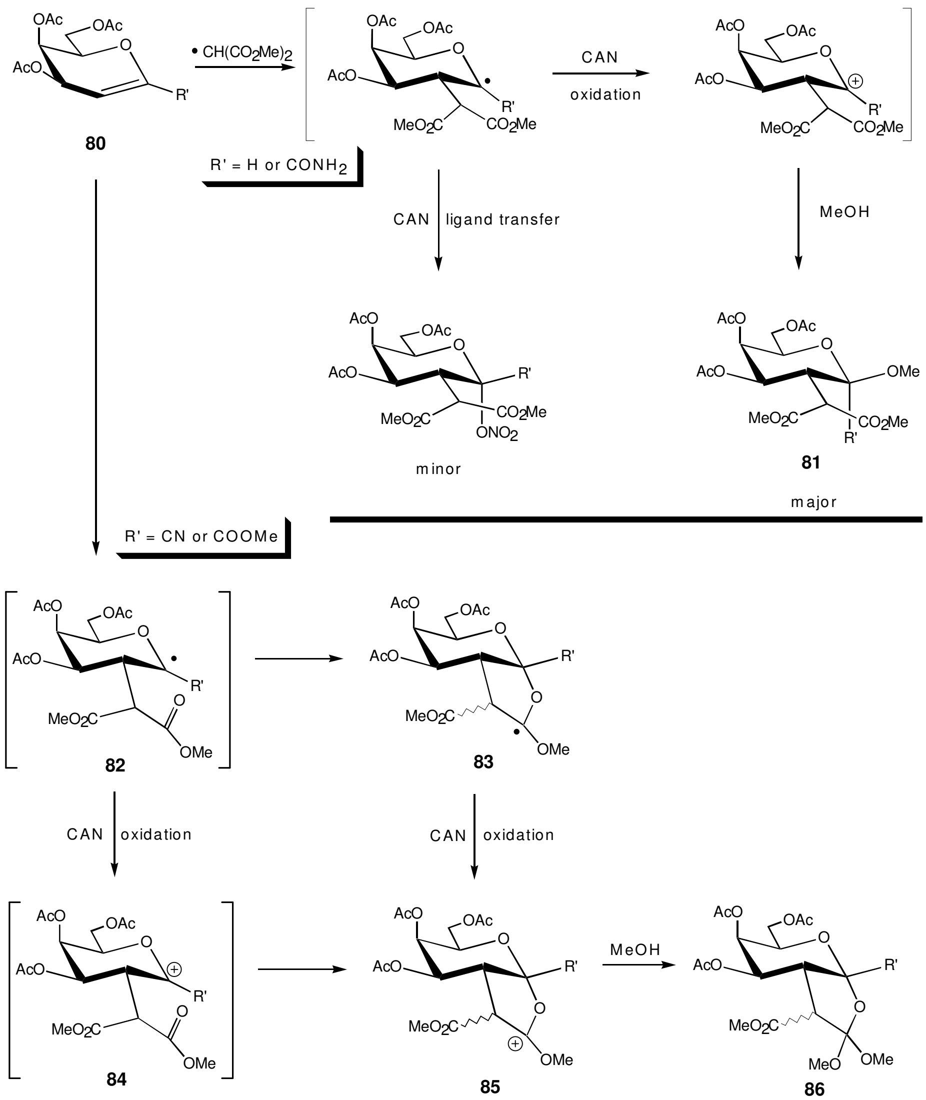
The carbamoyl group does not participate in the reaction with dimethyl sulfoxide; the sulfur-centered cation (**77**) formed in the first step is stabilized by the well-known Pummerer-type rearrangement. The main products of these reactions are the 1-OH derivatives (**78**), the methylthiomethyl-glycosides (**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).[85,86] The reaction is carried out in methanol the oxidizing agent being CAN. The main product is the methyl glycoside (**81**) 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, $CONH_2$, COOMe), but our products were similar only in one case (R' = $CONH_2$). 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 stabile 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.

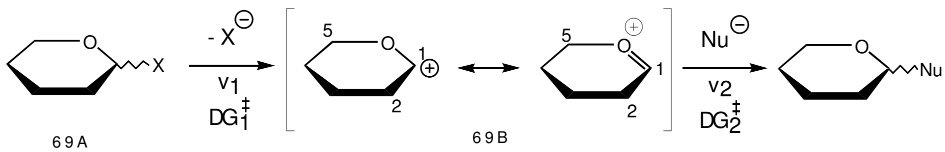


Scheme 32. *Reaction of substituted D-galactals with oxidatively generated malonyl radicals*

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 köztiterméket glikozil-karbéniumionnak nevezzük (1. ábra, **69B**).



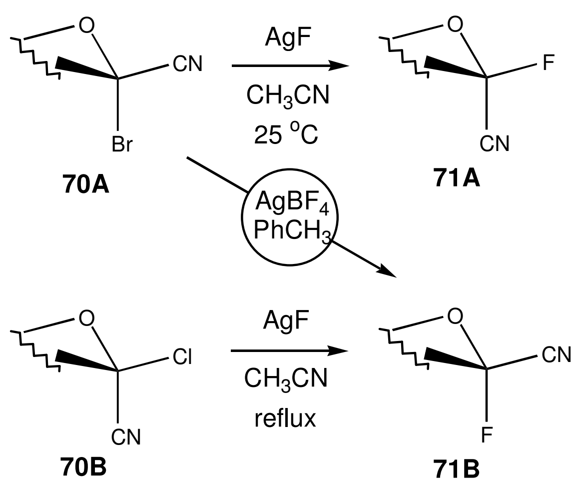
X : távozócsoport

1. ábra

Ezek az átalakítások a nukleofil (Nu) minõségétõl függõen igen változatos *O*-, *N*-, *S*- és *C*-glikozil származékok elõállítására lehetnek alkalmasak. A glikozilcsoportot szolgáltató glikozil donorok különbözõ reaktivitásúak lehetnek (attól függõen, hogy az X távozócsoport mennyire könnyen távolítható el a molekuláról: $\Delta G_1^{\ddagger}$), de adott nukleofil (Nu) esetén a második reakciólépés sebessége (v_2) – jó közelítéssel – csak az intermedier glikozil-karbéniumion energiaszintjétõl függ. A fenti glikozil karbéniumion energiaszintjét befolyásoló tényezõk között találjuk a szénhidrátszármazékon megtalálható *O*-védõcsoportok számát és minõségét (ld. „armed" és „disarmed" glikozil donorok[25,26]) és a pozitív töltésû atomok környezetében (esetünkben a C-1, C-2 és C-5 atomokon) elhelyezkedõ egyéb szubsztituensek elektronvonzó ill. elektronküldõ sajátosságát.

Jelen dolgozat témája az anomer centrum (C-1) szubsztituenseinek az intermedier glikozíliumion stabilitására és ezáltal magukra a vizsgált reakciókra való hatásának tanulmányozása. Az általam vizsgált szubsztituensek mindegyike (CN, $CONH_2$ 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.

Elsõként per-*O*-acetil-1-ciano-glikopiranozil halogenidek reakcióját tanulmányoztuk AgF-al acetonitrilben (Helferich körülmények). A szubsztituálatlan származékok irodalomból ismeretes viselkedésétõl eltérõen a kiindulási glikozil-halogenid anomerkonfigurációjától függetlenül mindig inverziós fluorszármazékot kaptunk (2. ábra). A reakció lefutásában tapasztalt eltérést a kiindulási glikozil halogenidek C-1–halogén kötéserõsségében illetve a köztitermékként feltételezett glikozil karbéniumion stabilitásában fellelhetõ különbséggel értelmeztük. A cianocsoporttal szubsztituált származékoktól eltérõen a kevésbé elektronvonzó amidcsoport (–$CONH_2$) jelenléte nem változtatta meg a fluorszubsztitúció lefutását, így az – bár az acetonitril beépülése miatt a reakciót más oldószerben kellett elvégezni – a szubsztituálatlan származékokéhoz hasonlóan ment végbe.



2. ábra

Irodalmi módszer[107] alkalmazásával ($AgBF_4$-al, toluolban) sikerült a **70A** glikozil-bromidokból előállítani a termodinamikailag stabilabb **71B** glikozil-fluorid származékokat (retenciós termék), képződésüket azzal az irodalmi ténnyel magyaráztuk, hogy az $AgBF_4$ képes anomerizálni a glikozil-fluoridokat.[121]

Az amidszubsztituált glikozil bromidokból (**72**) képződő glikozil karbéniumion (**75**) többféle – nukleofil jellegű – oldószerrel is reakcióba 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-α-D-glikopiranozilaminokat (**74**α) 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 sztereoszelektivitását – Ag-só promotor jelenlétében – az α-glikozil-nitríliumionok (**73**) irodalomból ismeretes gyors képződése és α-amidokká (**74**α) való intramolekuláris hidratációja (ami egyszerre a karbamoil csoport dehidratációját is jelenti) szabja meg. A reakció az anomer α-aminosavak újabb származékainak jó hozamú, sztereoszelektív 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 számottevő mennyiségben keletkeznének melléktermékek. Ilyen körülmények között azonban a reakció sztereoszelektivitása megváltozik, és az Ag-sókkal kapott termék anomerpárja (**74**β) lesz a reakció főterméke, amely oszlopkromatográfia segítségével izolálható.

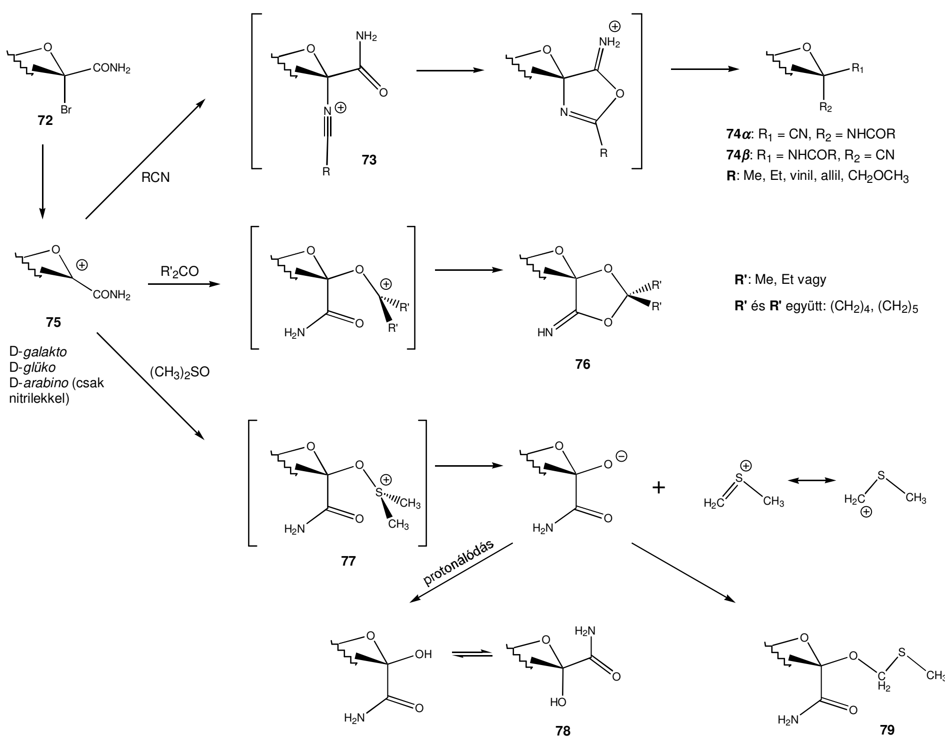
A ketonbeépülési reakcióban a felsõ oldali támadás a kedvezményezett, így az ábrán látható spiro-iminodioxolán (**76**) származék lesz a reakció fõterméke.

A dimetil-szulfoxiddal való reakcióban az amidcsoport nem vesz részt, a reakció elsõ lépésében keletkezõ kation a jól ismert Pummerer átrendezõdéssel stabilizálódik. A reakció fõterméke az 1-OH származék (**78**), a metiltiometil-glikozidok (**79**) D-*glüko* és D-*galakto* konfiguráció esetén rendre 11 ill. 15 %-al izolálhatók. A reakció sztereoszelektív, csak β-glikozidok képzõdnek.

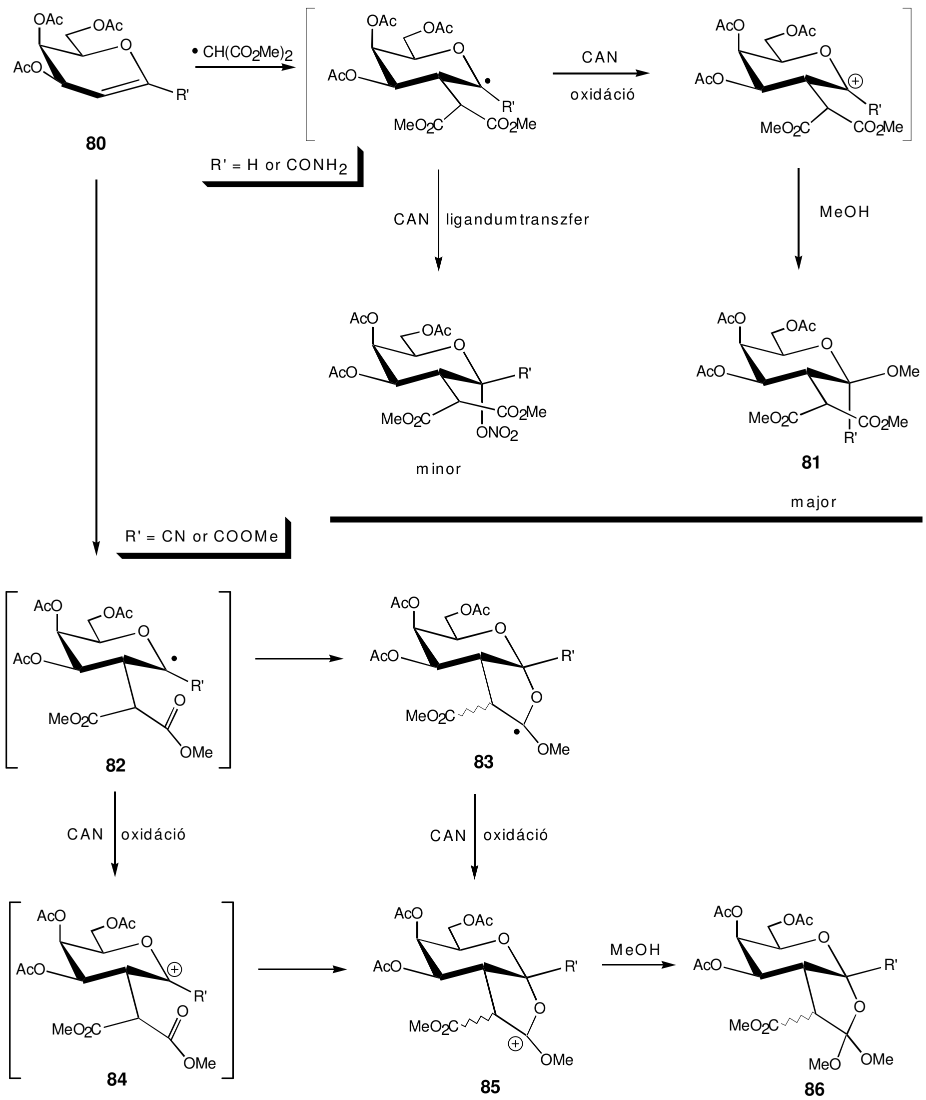
A vizsgált reakciók sorába látszólag nem illik bele az elõször Linker és munkatársai által szubsztituálatlan glikálszármazékokon (4. ábra, **80**, R' = H) alkalmazott malonilgyök-addíció.[85,86] A reakcióban a malonilgyök cérium-ammónium-nitrát (CAN) segítségével oxidatív úton keletkezik, fõtermékként az általuk vizsgált összes glikállal a C-2 helyzetben malonilrészt tartalmazó metilglikozidot (**81**) kapták (a reakció oldószere metanol). A fenti reakciót három különbözõ, C-1 helyzetben elektronvonzó csoporttal szubsztituált glikálszármazékkal elvégezve csak egy esetben (**80**, R' = $CONH_2$) tapasztaltunk a szubsztituálatlan analogonok esetén kapotthoz hasonló termékösszetételt. A másik két esetben (**80**, R′ = CN, COOMe) a reakció fõtermékeként ortoészterek (**86**) keletkeztek. Ezt az eltérõ viselkedést a C-1 szubsztituens elektronvonzó képességének erõsödésével magyaráztuk. A reakció intermediereként fellépõ stabilis kapto-datív gyök (**82**) és a belõle oxidációval keletkezõ – az erõsen elektronvonzó szubsztituens jelenléte miatt – destabilizált glikozíliumion (**84**) közötti energiakülönbség miatt lelassul a gyök karbokationná való oxidációja, ugyanakkor – a gyök hosszabb élettartama és esetleg SOMO-energiaszintjének gyökös gyûrûzáráshoz alkalmas volta miatt – ciklizáció következhet be. Másik lehetõség, hogy a képzõdõ glikozíliumion (**84**) különösen alacsony LUMO-energiaszintje teszi lehetõvé a karbonilcsoportra való intramolekuláris addíciót.

Az elvégzett kísérletekbõl kitûnik, hogy a C-1 szubsztituens sajátsága valóban jelentõs hatással lehet az anomercentrum nukleofil szubsztitúciós reakcióira és más, glikozíliumion köztiterméket feltételező reakciókra.

A megvizsgált három szubsztituenst, a tanulmányozott reakciókban mutatott viselkedésük alapján két csoportra oszthatjuk. Az egyik csoportba az amidcsoport (–$CONH_2$) kerül, amely elektronvonzó sajátsága révén nem, vagy csak kis mértékben változtatja meg a glikozíliumion 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 reaktivitásbeli különbséget eredményeznek, amely részben a csökkent reakciókészségben, részben pedig más reakcióutak kedvezményezésében nyilvánul meg.



3. ábra


80
• CH(CO2Me)2
R' = H or CONH2
CAN
oxidáció
CAN
ligandumtranszfer
MeOH
minor
81
major
R' = CN or COOMe
82
83
CAN
oxidáció
CAN
oxidáció
84
85
MeOH
86

4. ábra

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