Oxacarbenium ion intermediates in the stereoselective synthesis of anionic oligosaccharides

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Chapter 1

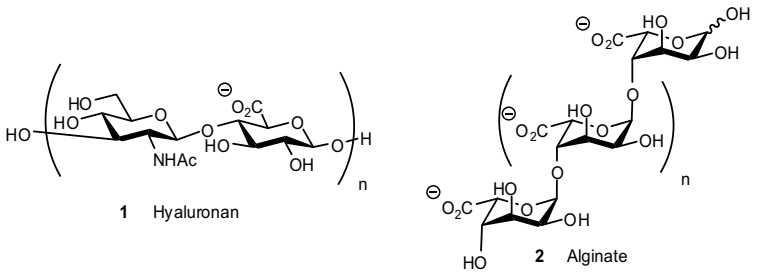
General Introduction: stereoselectivity of reactive intermediates in glycosylation reactions

Introduction

Polysaccharides are nature's most diverse class of biopolymers. This diversity is based on the set of constituting monosaccharide building blocks, which contain a large number of stereocenters and the repeating glycosidic linkages that interconnect the anomeric position of one monosaccharide in the carbohydrate chain with one of the hydroxyls of an adjacent subunit. Moreover the glycosidic bonds can occur in two configurations and the carbohydrate chain can be linear or branched. Next to this, carbohydrates can be covalently attached to proteins (glycoproteins) or lipids (glycolipids). Carbohydrates play a role as structural components and in the storage and transport of energy and are also involved in a broad array of biological processes such as immune defense, fertilization, cell growth and cell-cell adhesion. To elucidate these biological processes the availability of sufficient quantities of pure oligosaccharides and derivatives are indispensable. The isolation of oligosaccharides from natural sources is often hampered by the limited bioavailability and by purification problems to attain homogeneous samples of the target glycoconjugate.

Therefore, synthetic carbohydrate chemistry is the method of choice to supply sufficient amounts of well-defined oligosaccharides. In this thesis, strategies towards synthetically challenging and biologically relevant oligosaccharides are presented. The assembly of hyaluronan oligomers (**1**),[1] having the dimer β-1,3-linked 2-acetamido-2-deoxy-D-glucose-β-(1,4)-D-glucuronic acid as repeating unit and with a glucuronic acid or a glucosamine at the reducing end is described in Chapters 3 and 4, respectively. Chapter 5 presents the synthesis of an alginate trisaccharide (**2**) composed of 1,2-*cis*-linked L-guluronic acid residues[2] (Figure 1). The stereoselectivity of L-gulopyranose, a relatively rare monosaccharide of which little is known regarding its behavior in glycosylation reactions, is explored in this Chapter.

Figure 1



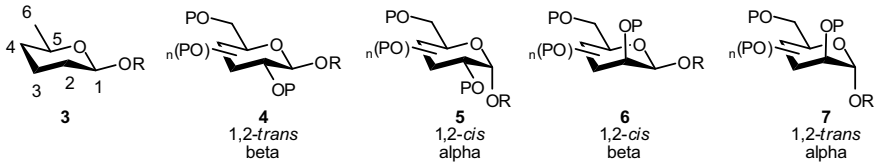
Hyaluronan (**1**) and poly guluronate alginate (**2**).

In addition to the target-orientated synthetic studies described in Chapter 3 to 5, This Thesis addresses some methodological issues. In Chapter 2 the conversion of suitably protected thioglycosides into 1-hydroxy donors is described. In Chapter 6 attention is focused on the stereodirecting effect of the glycosyl C-5 substituent in glycosylation reactions. The stereochemical outcome of glycosylations is surveyed using a set of epimeric D-pyranosides having a C-5 methyl ester, a C-5 benzyloxymethyl or a C-5 methyl substituent. This chapter evaluates mechanistic aspects that play a role in the glycosidic bond forming process and describes the stereoselectivity of possible reactive intermediates.

Stereoselectivity of reactive intermediates in glycosylation reactions

Since the beginning of the 20th century the stereoselective introduction of glycosidic linkages[3] is considered as one of the main challenges in synthetic carbohydrate chemistry. Glycosidic linkages can be divided into two general categories, namely: the 1,2-*trans* and 1,2-*cis* fused glycosides (Figure 2).[4] Despite tremendous progress in the field of synthetic carbohydrate chemistry the completely stereoselective introduction of 1,2-*cis* fused glycosidic bonds still poses a great challenge.

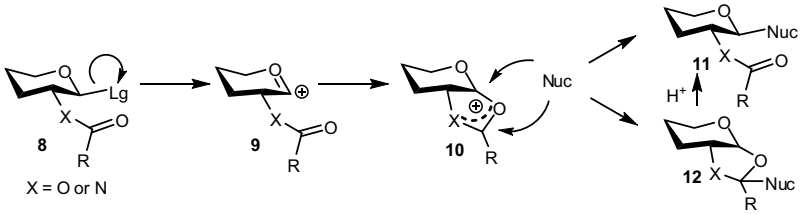
Figure 2



Numbering of D-hexose and nomenclature of the substituents on the anomeric center.

Contrary, the selective introduction of 1,2-*trans* bonds generally represents no problem and can be attained with the aid of an ester or amide function at C-2 in the donor glycoside. Activation of the anomeric centre of a donor glycoside (**8**) leads to attack of the ester (amide) carbonyl on the anomeric center to give acyloxonium ion **10** (Scheme 1), a neighboring group on pyranosides can actively participate in the expulsion of the anomeric leaving group, leading directly to the acyloxonium ion. Subsequent nucleophilic attack in an S_N2 like fashion then leads to the formation of a 1,2-*trans* bond (**11**) (Scheme 1).[5] The glycosylation conditions need to be sufficiently acidic to prevent the formation of orthoester (**12**). Although the formation of a 1,2-*trans* bond by neighboring group participation is considered to be generally applicable, some striking exceptions have been reported in which *trans*/*cis* mixtures and even solely 1,2 *cis* bonds were formed using C-2 acyl donor glycosides. Double stereodifferentiation,[6] in which the donor and acceptor glycoside form a sterically mismatched pair (thereby causing a steric clash in the transition state of the glycosylation) can lead to the formation of anomeric mixtures. The presence of the bulky 4,6-*O*-silylidene group in galactose donors has even led to the isolation of solely 1,2-*cis* linked products irrespectively of the nature of the protective group at C-2.[7]

Scheme 1

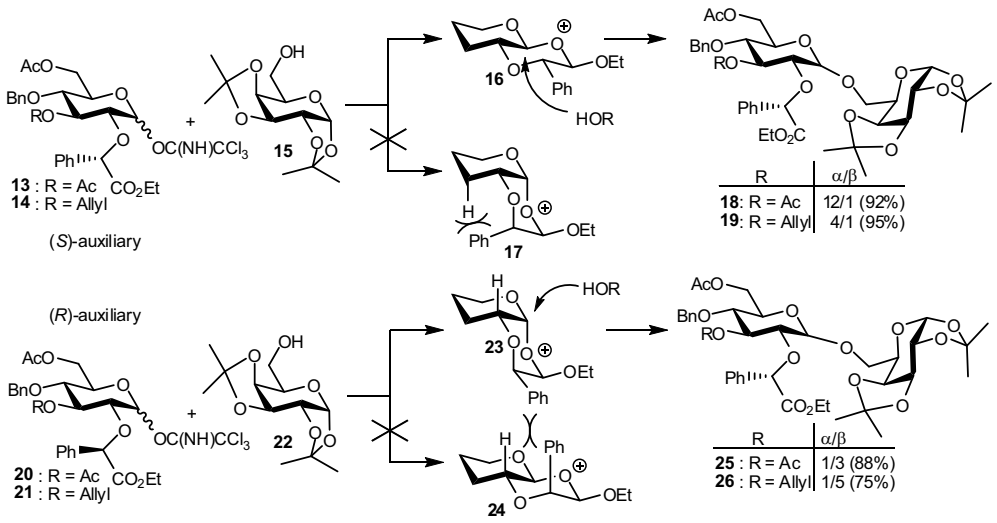


Anchimeric assistance: 1,2-*trans* bond formation directly or via orthoester formation.

An interesting new type of anchimeric assistance that allows the selective introduction of both 1,2-*cis* and 1,2-*trans* glycosidic bond has been developed by Boons and co-workers.[8] Key to their approach is the use of the chiral auxiliaries, (*S*) and (*R*)-(ethoxycarbonyl)benzyl ether on O-2 in **13**, **14** and **20**, **21**, respectively (Scheme 2). Activation of the trichloroacetimidate at the anomeric centre of **13** or **14** (*S* stereoisomer) leads to the formation of the most stable acyloxonium ion **16**. Activation of **20** or **21** (*R*

stereoisomer) leads to **23**. The *S* or *R* configuration of the C2-(ethoxycarbonyl)benzyl ether group determines whether a *trans*- or *cis*-decalin oxonium ion is formed, which is subsequently attacked in an S_N2-like fashion to give either the 1,2-*cis* or 1,2-*trans* glycosidic bond. Good 1,2-*cis* glycosylations have been achieved using this type of anchimeric assistance as depicted in Scheme 2.[8]

Scheme 2

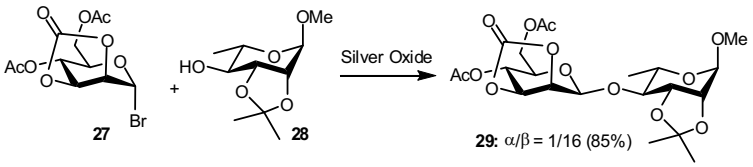


Anchimeric assistance by (*S*) and (*R*)-(ethoxycarbonyl)benzyl ethers. Reagents and conditions: DCM, ROH, -78 °C, TMSOTf.

The presence of ester functionalities at O-3 and O-4 and their possible anchimeric assistance via six- and seven-membered rings respectively, has been associated with the stereoselective outcome of glycosylation reactions.[9] Although the mechanism of these reactions is still under debate,[10] the effect of O-3 acetate functions on the α-selectivity of various glucose,[8,9i] mannose[10,11] and mannuronate ester[12] donors is striking.

Another strategy in controlling the stereoselectivity of glycosylations, entails tuning the nature of the anomeric leaving group in the donor glycoside such that S_N2-like substitutions are favored. Anomeric halides have been shown to undergo an S_N2 reaction under certain conditions. For example, anionic nucleophiles (cyanide, azide, malonate, thiolate, selenoate, or phenolate anions) can directly displace anomeric halides.[13] Another important example of an S_N2 substitution on an anomeric halide is the synthesis of β-mannosides from mannosyl bromides, which are activated by silver salts.[14] The mild activator complexes the anomeric α-bromide **27**, to allow substitution form the opposite face of the mannose core by the incoming alcohol nucleophile **28** (Scheme 3).

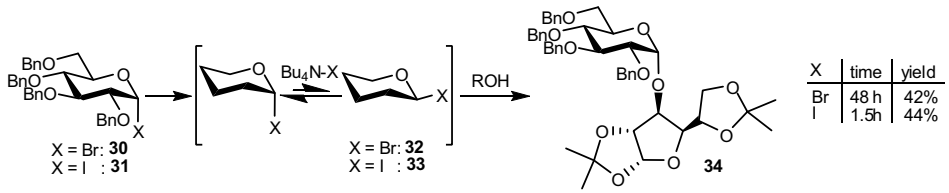
Scheme 3



S_N2 reaction using insoluble silver oxide.[14a] Reagents and conditions: $CHCl_3$, Ag_2O, $CaSO_4$, 1h

In 1975 Lemieux reported that glycosylations of α-glycosyl bromides may proceed with retention to give the 1,2-*cis*-product by the use of tetraethylammonium bromide as additive. The reactivity of the donor as well as the nucleophilicity of the acceptor is of great influence on the success of this procedure. The 1,2-*cis* product formation is explained by S_N2 substitution of the more reactive β-bromide (**32**) that is formed *in situ* by anomerization of the α-bromide (**30**).[15] The rate of the anomerization should be substantially higher than the rate of the nucleophilic attack by the alcohol on the anomeric centre. More recently this method was elaborated with iodine as anomeric halide, facilitating the fast and α-selective glycosylation of glucoside **31** (Scheme 4).[16] The group of Mukaiyama[17] investigated various phosphine oxides as replacement of tetrabutyl ammonium halides to induce α-selective glycosylations. The need of a strong nucleophile to attain a productive glycosylation limits the scope of many of these *in situ* anomerization glycosylation reactions.

Scheme 4

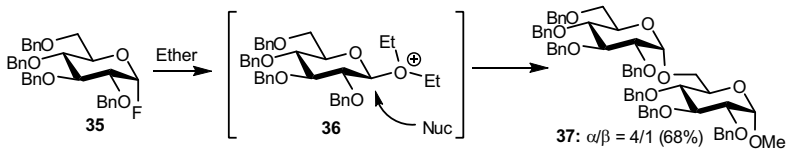


In situ anomerization of glucosyl halides. Reagents and conditions: TBABr (**30**)/TBAI (**31**), DIPEA, Benzene, reflux.

Trichloroacetimidates have also been exploited in S_N2-like substitution reactions. Access to anomerically pure imidates can be achieved by choice of the appropriate base in the reaction of the starting lactol and trichloroacetonitrile. Strong bases, such as DBU, promote the formation of the thermodynamically favored α-imidates, whereas use of a weak base (K_2CO_3) leads to the formation of the kinetic β-imidate. The use of a mild promotor (*e.g.* BF_3•Et_2O) and low temperatures can help the direct displacement of the activated imidate and thus allow an S_N2-like pathway.[18]

Solvents have been exploited to steer the stereoselectivity in glycosylation reactions. Empirically, diethylether, dioxane and tetrahydrofuran have been established to increase α-selectivity.[19] This phenomenon is rationalized by assuming the formation of an equatorially oriented oxonium ion (**36**), which is attacked in an S_N2 type fashion (Scheme 5).[20] It is however not clear why ether derived oxonium ions occupy an equatorial position. It is hypothesized that is due to the reversed anomeric effect, where a cation is favored in an equatorial position rather than in an axial position. However, the reversed anomeric effect is a debated subject.[21] Boons and co-workers[22] have recently demonstrated that thioethers (such as PhSEt or thiophene) can participate in a similar fashion and they provided spectroscopic evidence for the existence of the β-oriented sulfonium ion.

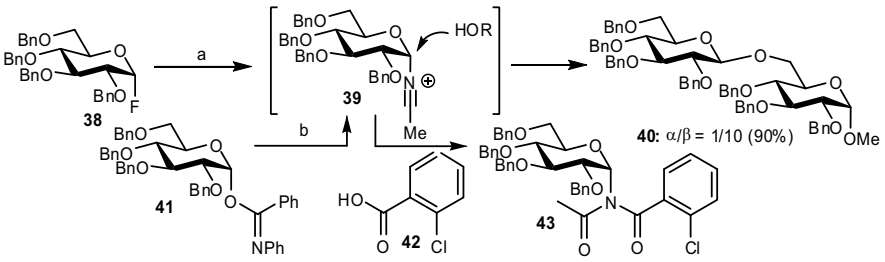
Scheme 5



Ether "assisted" glycosylation. Reagents and conditions: Et_2O, SiF_4, 5 °C.[19a]

Glycosylations using acetonitrile as solvent (or co-solvent) often lead to the predominant formation of β-products.[19a] In this case the axial α-nitrilium ion (**39**) has been invoked to account for the observed selectivity (Scheme 6).[23] This hypothesis has been substantiated by studies in which the nitrilium ion intermediate has been trapped by a nucleophile to provide the axially oriented amide product. For example, Sinaÿ and co-workers demonstrated that nitrilium ion **39** (from 41) can be intercepted by *o*-chlorobenzoic acid (**42**) to give the α-imide adduct **43**.[24] Although many examples can be found in literature where acetonitile has a beneficial effect on the formation of the β-product, exceptions have been noted as well. For example, the group of Schmidt[25] showed that acetonitrile mediated glycosylations of uronic acids resulted in the predominant formation of the α-product.

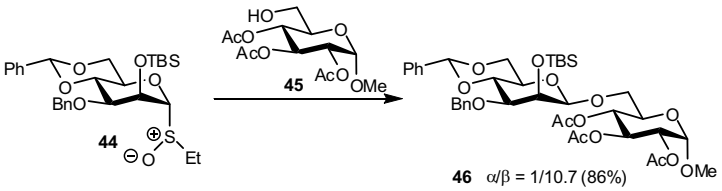
Scheme 6



Schematic representation of acetonitrile assisted glycosylation. Reagents and conditions: a) MeCN, SiF_4, HOR, 0 °C.[19a]; b) MeCN, **42**, rT.[24]

Next to the anomeric leaving group that is installed on a glycoside, the reactivity of the activated species is of prime importance for the stereochemical outcome of a glycosylation. Considerable attention has been devoted to tuning the reactivity of glycosyl donors by varying the nature of the protective groups. Acyl protecting groups reduce the reactivity of glycosyl donors to a larger extent than alkyl protecting groups. On the basis of this tendency the group of Fraser-Reid termed glycosyl donors bearing an O-2 alkyl protecting group as 'armed' and their less reactive O-2 acyl bearing counterparts 'disarmed'.[26] Overtime, the 'armed-disarmed' concept has been elaborated and it is now well established that the nature and position of all substituents on the glycoside core influence the donor reactivity. The reactivity of a broad range of thioglycosides has been determined, leading to the formulation of a relative reactivity scale, which spans over seven orders of magnitude.[27] 4,6-*O*-Acetal groups provide an intermediate level of reactivity ('semi-disarmed'). The group of Crich discovered that mannosyl sulfoxide donors protected with a 4,6-*O* benzylidene acetal (**44**, Scheme 7) are highly 1,2-*cis* selective, showing that acetal protecting groups can also have a decisive effect on the stereochemical outcome of glycosylations.[28] The high selectivity observed in this mannosylation is impressive since formation of the β-mannosidic linkage is disfavored by both the anomeric and the Δ2-effect.[29] Over the years it became apparent that β-selective mannosylations could also be obtained using 4,6-*O*-benzylidene protected mannosides with different anomeric leaving groups and activation protocols.[30]

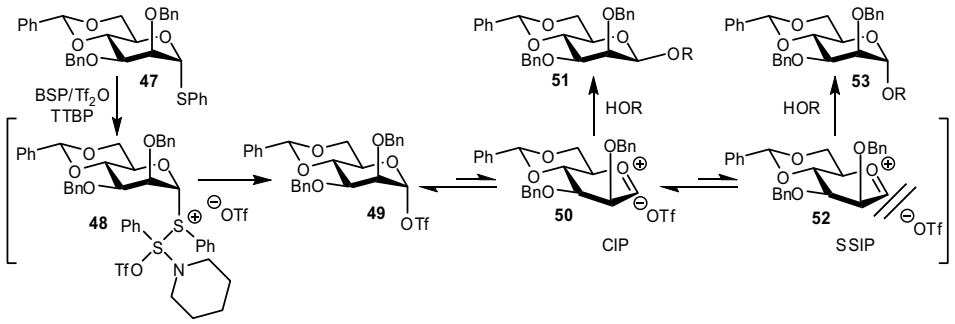
Scheme 7



Glycosylation of 4,6-*O* benzylidene mannose. Reagents and conditions: 2,6-di-tert-butyl-4-methylpyridine (DTBMP), Et_2O/benzene (7/1), -78 °C, then Tf_2O, 5 min, acceptor, -78 °C to rT.

Guided by low temperature NMR experiments on the activation of **47**,[31] the group of Crich hypothesized that the observed β-selectivity comes from S_N2 displacement of the intermediate α-anomeric triflate (**49**) or the corresponding contact ion pair (CIP, **50**) (Scheme 8).[32] The interference of the solvent separated ion pair or oxacarbenium ion **52** allowing an S_N1-like displacement is suppressed by the disarming effect of the benzylidene acetal.

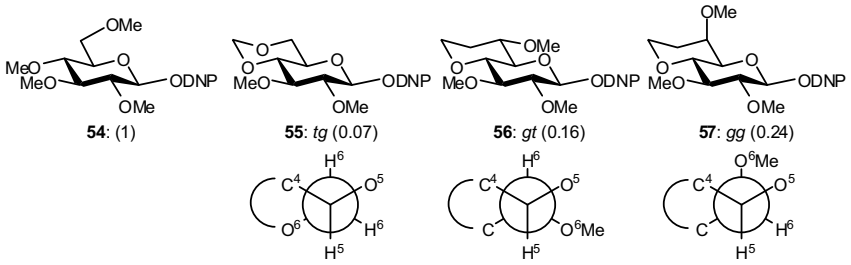
Scheme 8



Proposed intermediates in mannosylation, α-anomeric triflate (**49**) and CIP (**50**).

Kinetic studies of the hydrolysis of methyl glycosides, where formation of the oxacarbenium ion is considered to be the rate-determining step,[33] have shown that the 4,6-*O*-benzylidene acetal disfavors the development of charge at the anomeric center through both torsional and electronical factors. The group of Fraser-Reid demonstrated that cyclic acetals impede flattening of the ring and thereby the formation of the oxacarbenium ion.[26] The electronic factor was established by the group of Bols, who compared the acidic hydrolysis rate of glucosides **54**-**57**, which differ in the orientation of O-6 (Figure 3).[34] Compound **55** with the O-6 substituent positioned trans (*t*) to the pyranosyl ring oxygen (and gauche to C-4, *tg* conformation) hydrolyzed at a lower rate than the glucosides **56** and **57** having a gauche (*g*) orientation with the ring oxygen. It is postulated that this rate difference comes from charge-dipole interactions.[35] The acid stability of **55** is enhanced because the electron withdrawing potency of the O-6 on the ring oxygen is larger in the *tg* conformation (**55**) than in the *gt* (**56**) and *gg* (**57**) conformation.

Figure 3

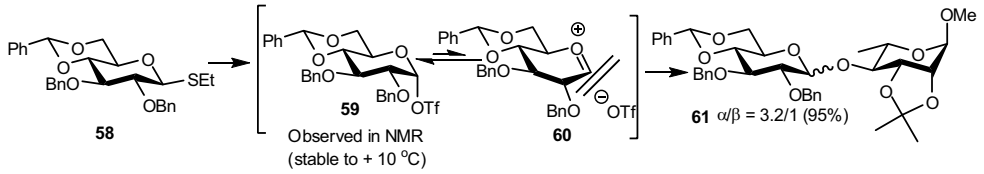


Relative rates of acidic hydrolysis of dinitrophenyl glucosides (relative to glucose **54**). Reagents and conditions: pH 6.5 (0.4M KCl), 37 °C.

Whereas in the mannose case the disarming effect of the 4,6-*O*-benzylidene (as in donor **47**, Scheme 8) allows the S_N2-like substitution of the anomeric α-triflate, the presence of the

4,6-*O*-benzylidene group in the corresponding glucosides leads to the predominant formation of α-linked glucosides (Scheme 9). Low temperature NMR experiments revealed the presence of an α-triflate intermediate (**59**)[36] upon activation of **58**. Obviously formation of α-linked products cannot arise from this species. Therefore, Crich and co-workers reasoned[37] that glycosylations of 4,6-*O*-benzylidene glucose occur through the intermediacy of the solvent separated oxacarbenium ion *via* an S_N1 like mechanism. It was argued that in such a mechanism, the trajectory of the attack on the oxacarbenium ion is dictated by the anomeric effect, which is α-directing.[38] The different behavior of mannoside **47** and glucoside **58** was explained by the steric interactions of the substituents on C2 and C3. Upon flattening of the pyranoside ring to accommodate the positive charge on the oxacarbenium ion, the steric interaction of the C-2 and C-3 substituents will increase, making this an unfavorable process. In glucose this steric interaction is absent and therefore benzylidene glucose more readily adopts the required flattened conformation. As a result the equilibrium between the glucosyl covalent triflate **59** and the solvent separated ion pair **60** is shifted to the side of the ion pair.

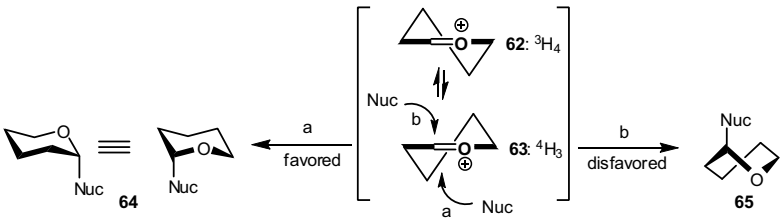
Scheme 9



Glycosylation of **58**. Reagents and conditions: 2,4,6-tri-tert-butylpyrimidine (TTBP), 1-benzenesulfinyl piperidine (BSP), DCM, -60 °C, then Tf_2O, 5 min, acceptor, -60 °C to rT.

Another view on the role of oxacarbenium ions on the stereoselectivity of glycosylations has emerged from studies by Woerpel and co-workers on the mechanism of C-glycosylations. Pyranose oxacarbenium ions can adopt several conformations with the half chair conformations $^4H_3$ **63** and $^3H_4$ **62** being local energy minima.[39] A nucleophile can attack these half-chair conformers following a *pseudo* axial trajectory with a preference for the diastereotopic face that leads to the more favorable chair-like product **64** (Scheme 10).[40] Nucleophilic attack on the oxacarbenium ion half-chair conformers **62** and **63** leads to the α- or the β-product respectively.[41] If there are no prohibitive steric interactions in the transition states leading to the products, the ratio of the α- and β-products mirror the ratio of the half chair oxacarbenium ions. Experimental and computational studies have indicated that the stability of half-chair oxacarbenium ion conformers is affected by the position, the configuration and the nature of the substituents on the pyranose core.[39]

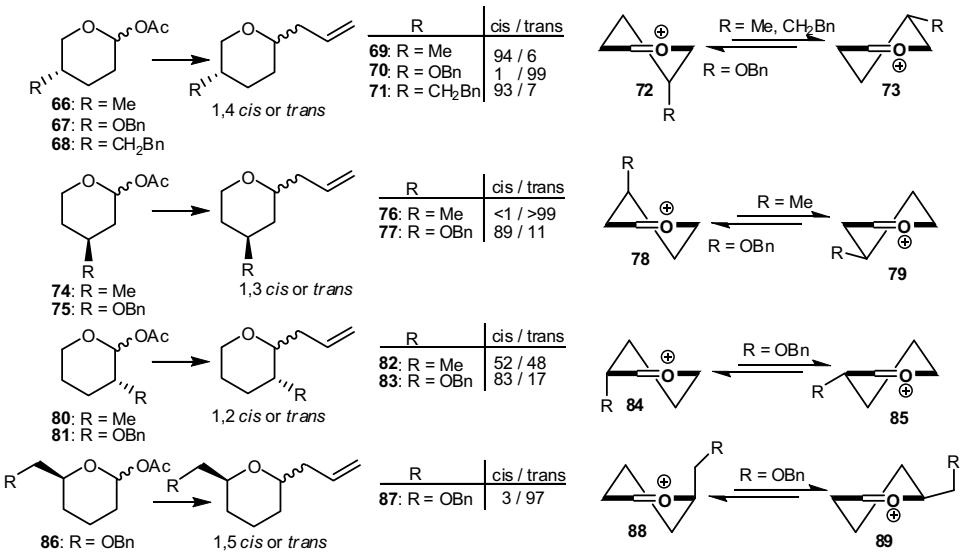
Scheme 10



Oxacarbenium ion conformers and nucleophilic attack on the $^4H_3$ conformer.

Woerpel and co-workers conducted a set of experiments using tetrahydropyran acetals to establish the stabilizing/destabilizing effect of substituents on the 2, 3, 4 and 5 position of the pyranose core. These effects influence the equilibrium between the different conformers ($^3H_4$ and $^4H_3$) and thereby control the stereoselectivity in the nucleophilic substitution of the oxacarbenium ion.[42] Bowen and co-workers reported that electronegative (OH) substituents favor axial positions on C-3 and C-4, as opposed to an equatorial orientation which is favored from a steric point of view.[39] This was experimentally corroborated by the set of allylations depicted in Scheme 11. Allylation of the 4-*O*-benzyl **67** (R = OBn) under the agency of BF_3•OEt_2 and allyltrimethylsilane yielded almost exclusively the 1,4-*trans* product whereas acetal **68** (R = CH_2Bn) mainly provided the 1,4-*cis* product. *C*-Allylation of tetrahydropyrans **74** and **75** also led to the formation of *trans* and *cis* diastereomeric products respectively. The selectivity in these *C*-glycosylations was attributed to the difference in stability of the involved oxacarbenium ion intermediates. Oxacarbenium ion **73** with R = CH_2Bn is favored over its axial counterpart **72** because of unfavorable steric interactions in the latter. Subsitution of **73** along a pseudoaxial trajectory leads to the formation of the 1,4-*cis* product. In the 4-OBn case, the electronic preference of the substituent overrules its steric bias, making the axial conformer **72** (R = OBn) energetically most favorable. Allylation of **72** provides the 1,4-*trans* product. The selectivities of the C3 substituted pyranosides can be explained in an analogous fashion.[43] The preferred axial orientation of the alkoxy substituents has been ascribed to the electrostatic stabilization of the cationic anomeric center by the axially oriented C-3 or C-4 heteroatom. The difference in selectivity of alkyl and ether substituents at the C-2 position is smaller. As depicted in Scheme 11, the C-2 alkyl substituted (**80**) appears to have little effect on the stereochemical outcome, where a C-2 benzyloxy pyran (**81**) provides mainly the 1,2-*cis* product. The preference for C-2 benzyloxy oxacarbenium ion **85** (R = OBn) is thought to evolve from hyperconjugation between the axial C-H bond and the 2p orbital on the electrophilic carbon.[44] The *trans* selectivity of C-5 substituted pyranoside **86** is believed to arise from steric interactions.[45]

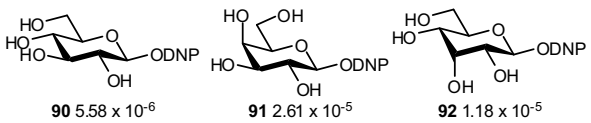
Scheme 11



Nucleophilic adition on 2-, 3-, 4- and 5-substituted tetrahydropyran acetals. Reagents and conditions: DCM, allyltrimethylsilane, -78 °C, BF_3OEt_2.

The stabilizing effect of axially oriented alkoxy substituents at C-3 and C-4 has previously been observed in hydrolysis reactions of different glycosides. The nature and configuration (axial or equatorial) of the substituents on the pyranose ring influences the development of positive charge at the anomeric center and thereby the rate of hydrolysis. As demonstrated by Withers and co-workers, dinitrophenyl (DNP) galactoside **91** and DNP-alloside **92**, both having one axial hydroxyl group, hydrolyze faster than DNP-glucoside **90** (Figure 4).[46,47] Bols and co-workers argue that equatorially placed hydroxyls have a larger electron withdrawing effect on the oxacarbenium ion than their axial counterparts, because of a more unfavorable charge-dipole interaction in the equatorial case.[48,49] They also demonstrated that steric effects are less influential than the electronic effects caused by the orientation of the substituents for the rate of hydrolysis. As depicted in Figure 5, galactosides **97** and **96** hydrolyze faster than glucosides **93** and **94** and the presence of the methyl function has relatively little influence.[50,51]

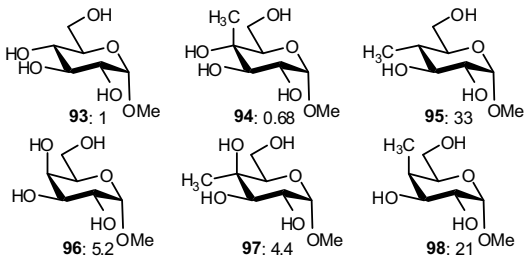
Figure 4



90 5.58 x 10^{-6} **91** 2.61 x 10^{-5} **92** 1.18 x 10^{-5}

Rate constants of spontaneous hydrolysis of dinitrophenyl glycosides in sec^{-1}. Reagents and conditions: pH 6.5 (0.4 M KCl), 37 °C.

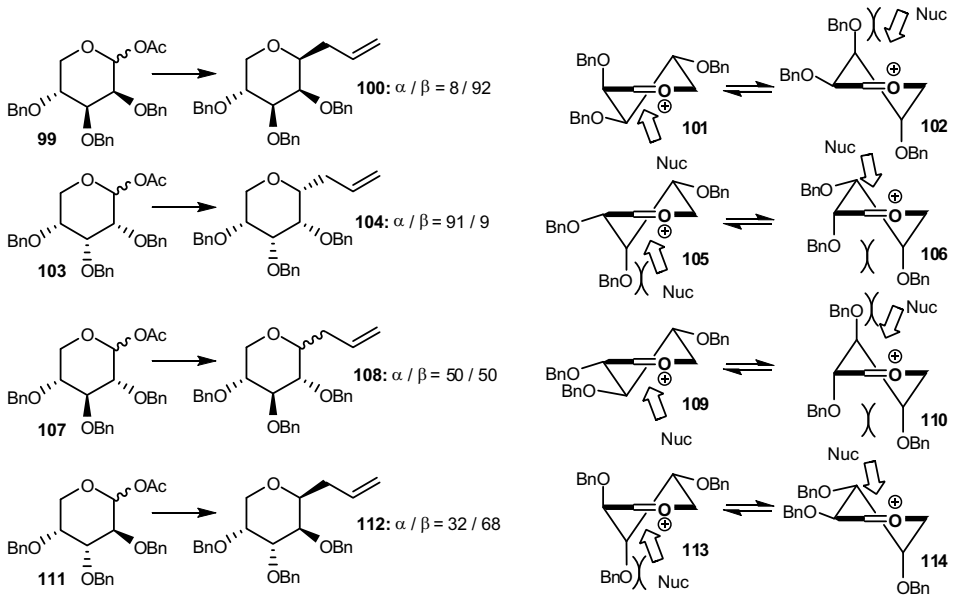
Figure 5



Relative rates of acid hydrolysis (glucose = 1). Reagents and conditions: 2 M HCl, 74 °C.

Having determined the preference of each substituent on the pyranose oxacarbenium ion, Woerpel and co-workers[45] investigated the effect of multiple substituents on the stereoselectivity of the *C*-glycosylation reaction. The stereodirecting contributions of the substituents revealed in Scheme 11 can not simply be added to account for the selectivities obtained in systems with multiple substituents. Steric interactions between the substituents and the incoming nucleophile effect both the ground state energies of the oxacarbenium ion conformers and the transition states leading to the α- and β-products. Four pentoses were examined for their stereopreference in a glycosylation with allyl trimethylsilane, as depicted in Scheme 12.[44] Lyxose acetate **99**, having the D-*manno* configuration at C-2, C-3 and C-4, yielded mainly the 1,2-*cis* product, corresponding to nucleophilic attack on an oxacarbenium ion in the $^3H_4$ conformer (**101**). This is in line with the results obtained with the acetals depicted in Scheme 11, even though the incoming nucleophile has an unfavorable steric interaction with the C-3 substituent. Ribose acetate donor **103** mainly provided the all *cis* product (**104**), originating from ion **105**. Conformer **105** is energetically more favored than its congener **106**, because the latter places only the C4 substituent in its most favorable orientation and suffers from a 1,3-diaxial interaction between the C-2 and C-4 functionality. Xylose acetate **107** reacts in a non selective manner to afford a 1/1 mixture of anomers (**108**). The favorable orientation of the C-3 and C-4 benzyl ethers in ion **110**, is offset by the destabilizing steric interaction between the C-2 and C-4 substituents and the 1,3-diaxial interaction of the incoming nucleophile with the group at C-3. The *cis*-preference of arabino acetate **111** is ascribed to the negative interaction of the nucleophile with C-3 in ion **113** in addition to the disfavored position of the C-2 and C-3 substituent in this conformer. These results show that the stereochemical outcome of the glycosylations is the result of both the stability of the oxacarbenium ion, which depends on a combination of steric and electronic substituent effects, and the steric interactions of the incoming nucleophile with the oxacarbenium ion.

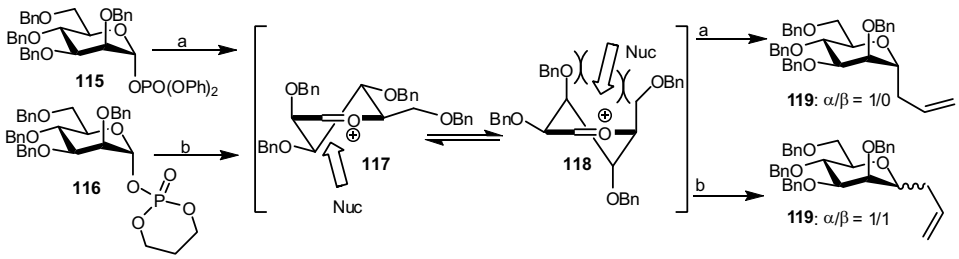
Scheme 12



Nucleophilic adition on 2-, 3-, 4- and 5-substituted tetrahydropyran acetals. Reagents and conditions: DCM, allyltrimethylsilane, -78 °C, BF_3OEt_2.

The 1,2-*cis*-selectivity of lyxose acetate **99** stands in contrast to the 1,2-*trans*-selectivity regularly obtained in *O*- or *C*-glycosylations using mannose donors, which only differs from **99** in the substituent on C5. For example, the group of Seeberger[52] reported that the allylation of phosphate donor **115** proceeds with complete α-selectivity (Scheme 13). A notable difference between this *C*-allylation and the condensation studies by Woerpel described above is the relatively high temperature (0 °C) at which the mannosylation using **115** was performed. Singh and Vankayalapati[53] conduct the experiments with mannosylphosphate **116** at -78 °C, and obtained a 1:1 mixture of anomers (Scheme 13).

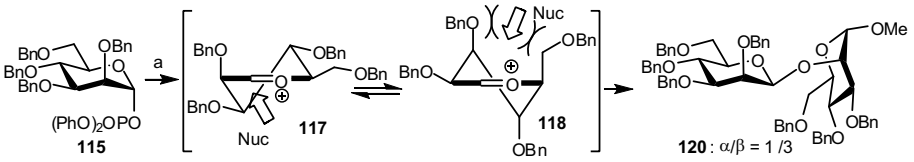
Scheme 13



C-Glycosylations using mannosyl phosphates. Reagents and conditions: a) DCM, allyltrimethylsilane, 0 °C, TMSOTf; b) DCM, allyltrimethylsilane, -78 °C, TMSOTf.

The α-products obtained in the condensations of **115** and **116** can be explained by attack on oxacarbenium ion **117**, which has minimal steric interactions with the incoming nucleophile. Although $^3H_4$ conformer **118** places the C-2, C-3 and C-4 substituents in the most favorable positions, this oxacarbenium ion suffers from 1,3-diaxial interactions of C-3 with C-5. In addition, the incoming nucleophile is hindered by both the C-3 and C-5 substituent. These steric interactions make the transition state for **118** to the β-product unfavorable, and product formation therefore arises (in part) from the higher ground state energy oxacarbenium ion **117**, following a Curtin-Hammett kinetic scenario.[54] Seeberger and co-workers also condensed mannose donor **115** with alcohol an *O*-nucleophile, yielding mainly the β-product (Scheme 14).[53] This indicates that both the temperature and the reactivity of the nucleophile have a large effect on the selectivity of the reaction.[55]

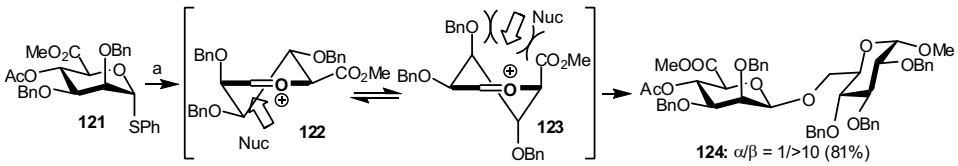
Scheme 14



Glycosylations on mannose by Seeberger and co-workers.[53] Reagents and conditions: DCM, Nucleophile, -78 °C, TMSOTf.

van den Bos *et al.* showed mannuronate esters donor **121** are highly β-selective (Scheme 15).[12] This selectivity can be the result of S_N2 type substitution of an α-anomeric triflate, in analogy to the condensations of benzylidene mannosides.[28] Alternatively, the β-selectivity of **121** may arise from $^3H_4$ oxacarbenium ion **123**, in which the C-5 ester occupies an axial position (Scheme 17). As such the ester should have a stabilizing effect on the positive charge at the anomeric center, similar to the effect of the axial C-3 and C-4 heteroatoms in the studies performed by Woepel and co-workers.[43]

Scheme 15

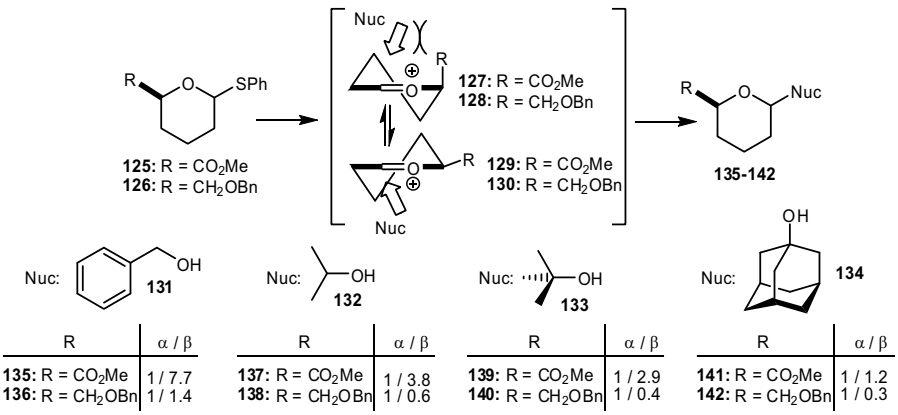


Glycosylation with mannuronate ester **121**. Reagents and conditions: a) TTBP, DCM, -60 °C, then Tf_2O, -45 °C 15 min., Acceptor, to rT.

To investigate the effect of the C-5 carboxylate on the selectivity of mannuronate esters, the "stripped" thioglycosides **125** and **126**, having only a substituent at C-5, were investigated.[56] As can be seen in Scheme 16, all condensations of C-5-carboxylate **125**

provided substantially more of the 1,5-*cis* product than its benzyloxymethyl counterpart **126**. The β-selectivity of **125** can be accounted for by considering oxacarbenium ions **127** and **128** as product forming intermediates. In **127** the axial position of the C-5 carboxylate ester minimizes the electron withdrawing nature of the substituent and allows for electron donation of the carboxylate carbonyl into the oxacarbenium ion. Similarly in mannuronate ester **121** the effect of the carboxylic ester works in concert with the other substituents on the ring favoring the formation of the $^{3}H_{4}$ half chair **123** over the $^{4}H_{3}$ conformer **122**, giving rise to the high β-selectivity of the manuronate esters (Scheme 15). The additional stabilization that the uronate ester provides in the $^{4}H_{3}$ half chair **123** as compared to its non-oxidized counterpart **118** prevents a Curtin-Hammett scenario to take place.

Scheme 16



R	α / β
135: R = CO_2Me	1 / 7.7
136: R = CH_2OBn	1 / 1.4

R	α / β
137: R = CO_2Me	1 / 3.8
138: R = CH_2OBn	1 / 0.6

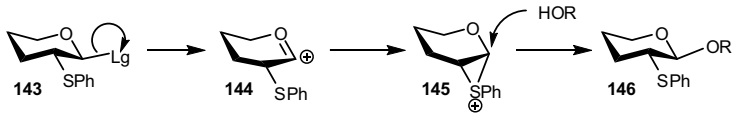
R	α / β
139: R = CO_2Me	1 / 2.9
140: R = CH_2OBn	1 / 0.4

R	α / β
141: R = CO_2Me	1 / 1.2
142: R = CH_2OBn	1 / 0.3

Oxacarbenium ions of "stripped" uronate ester and its benzyloxymethyl counterpart. Reagents and conditions: TTBP, DCM, -78 °C, then Tf_2O 5 min, then acceptor, -78 °C, 15 min.

The stereodirecting effect of other functional groups has also been explained by attack of the nucleophile on the more stable oxacarbenium ion conformer. 2-Deoxy-2-thio, iodonium and selenium glycosides are known to yield 1,2-*trans* glycosidic linkages with good to excellent selectivity. This selectivity was long thought to arise from an episulfonium (or the corresponding selenonium / iodonium) ion **145** which is displaced in an S_N2 type fashion by the incoming nucleophile (Scheme 17).[57] However, computational[58] and experimental[59] data suggest that the oxacarbenium ion **144** is more stable than the episulfonium ion **145**. Product formation can therefore also arise from nucleophilic attack on the oxacarbenium ion rather than the episulfonium species. The preference for an oxacarbenium ion conformer with an axial C-2 substituent (see for example **151/152** in Scheme 18) is thought to arise from the stabilizing hyperconjugative interaction between σ C–SPh and π* C–O of the oxacarbenium ion.[60]

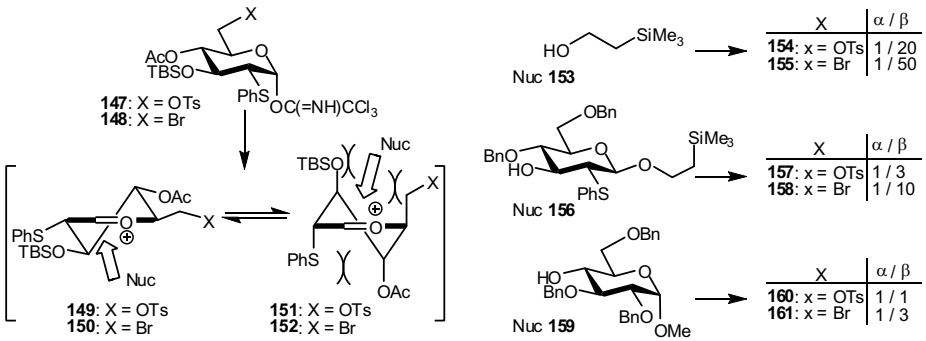
Scheme 17



Episulfonium ion in an S_n2 reaction pathway

Roush and co-workers reported that the condensation of donor **147** and **148** with primary alcohol **153** proceeded with high β-selectivity to provide **154** and **155** (Scheme 18). [61,62] With increasing bulk of the acceptor the *trans*-selectivity decreased (**154** to **157** to **160**). The $^4H_3$ and $^3H_4$ oxacarbenium ions **149**-**152** were invoked as product forming intermediates, of which **151** and **152** should be the most stable, but also the most sterically congested. The higher selectivity of 6-Br (**148**) versus 6-*O*-tosyl (**147**) was argued to result from the difference in inductive effect of the substituents.[63]

Scheme 18

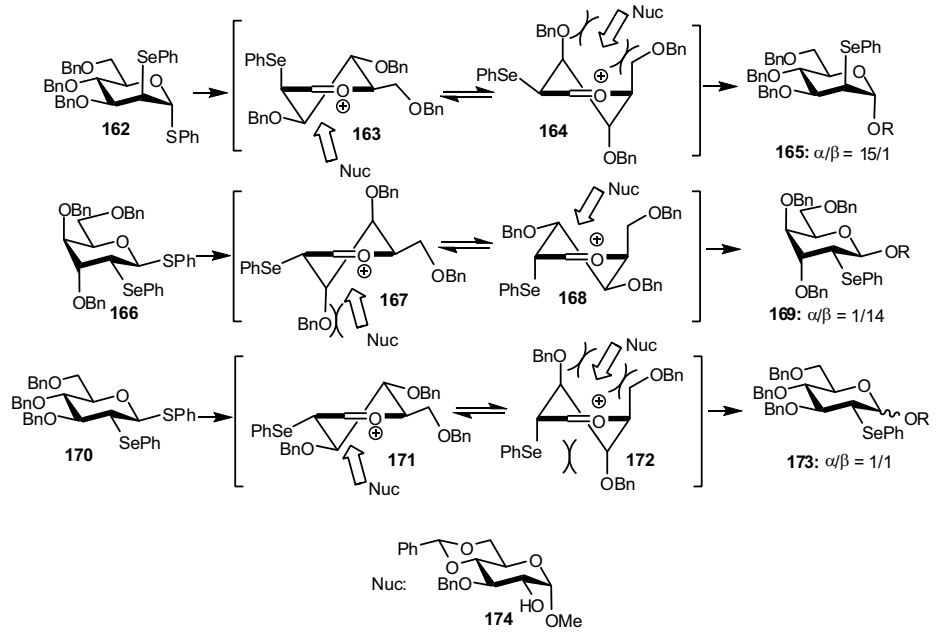


Glycosylations of C-2-SPh glucosides. Reagents and conditions: DCM, ROH, -78 °C, TMSOTf.

Castillón also reported that hyperconjugative stabilization by the C-2 phenylselenyl group is of decisive effect on the stereoselectivity of glycosylations of 2-deoxy-2-phenylselenyl thioglycosides.[60] In the coupling of mannoside **162** and guloside **166** with glucopyranoside **174**, disaccharides **165** and **169** were obtained with excellent α- and β-selectivity, respectively (Scheme 19). The 2-deoxy-2-phenylselenyl glucoside **170** provided a 1:1 mixture of diastereomers (**173**). The stereochemical outcomes of the condensations were rationalized to arise from the intermediate oxacarbenium ions involved.[64] The mannosyl $^4H_3$ ion **163** places the phenylselenyl group in a favorable axial position, and does not suffer from any sterically demanding interactions. Nucleophilic attack on this ion leads to the formation of the α-product **165**. Similarly, nucleophilic attack on gulose oxacarbenium ion **168** with an axial C2-SePh, is favored over the pathway involving ion **167**, leading to the selective formation of β-disaccharide **169**. The axial SePh halfchair conformer in the glucose case (*i.e.* ion **172**) on the other hand experiences two 1,3-diaxial interactions in the

ground state of the oxacarbenium ion. The nucleophillic attack on this oxacarbenium ion leads to two additional 1,3-diaxial interactions of the nucleophile and the substituents on C-3 and C-5. Thus, in this case product formation also arises from the oxacarbenium ion having its C-2 phenylselenyl group in an equatorial position, and an anomeric mixture is formed.

Scheme 19



Oxacarbenium ions with 1-3 diaxial interactions. Reagents and conditions: toluene/dioxane (1:3), acceptor (**174**), NIS, 0 °C, TfOH.

To conclude, the mechanism of glycosylation reactions is highly complex and can follow several pathways involving various reactive intermediates. Over the years, different strategies have been devised for stereoselective glycosylations, exploiting the reactivity of particular reactive species. For example, anomeric halides and triflates have been used in stereoselective S_N2 like condensations and stereoselective S_N1 type glycosylations have been achieved building on the stereopreference of the intermediate oxacarbenium ions. Nonetheless the stereoselective installation of a *cis*-glycosidic bond still presents a challenge and requires the careful tuning of reaction parameters, including the protecting group pattern, leaving group, activator, solvent and temperature. The reliability with which a *trans* glycosidic linkage can be installed, has not yet been realized for the construction of the *cis* glycosidic bond. Mechanistic studies on the formation of the glycosidic bond are a valuable approach to tune the stereochemistry of glycosylations.

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[63] These results can also arise from through space stabilization of the positive charge at the anomeric center by the bromine/tosyl, which is possible when the C-5 substituent is in an axial orientation.
[64] It should be noted that dioxane, known to effect the stereochemical outcome of glycosylation reactions, was used as solvent in these studies.