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Review

The impact of oxacarbenium ion conformers on the stereochemical outcome of glycosylations

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ABSTRACT

The search for stereoselective glycosylation reactions has occupied synthetic carbohydrate chemists for decades. Traditionally, most attention has been focused on controlling the S_N2-like substitution of anomeric leaving groups as highlighted by Lemieux's in situ anomerization protocol and by the discovery of anomeric triflates as reactive intermediates in the stereoselective formation of β-mannosides. Recently, it has become clear that also S_N1-like reaction pathways can lead to highly selective glycosylation reactions. This review describes some recent examples of stereoselective glycosylations in which oxacarbenium ions are believed to be at the basis of the selectivity. Special attention is paid to the stereodirecting effect of substituents on a pyranosyl ring with an emphasis on the role of the C-5 carboxylate ester in the condensations of mannuronate ester donors.

1. Introduction

The stereoselective construction of glycosidic linkages has long been, and continues to be, one of the main challenges in synthetic carbohydrate chemistry.[1] Whereas 1,2-*trans* glycosidic linkages can be obtained reliably by taking advantage of neighboring group participation of an acyl protective group at the C-2 position in the donor glycoside,[2] a general method for the formation of 1,2-*cis* glycosidic bonds has not been identified.[3,4] As steering of the C-2 function is generally lacking, over the years attention has been focused on tuning other reaction parameters, such as the nature of the anomeric leaving group in the donor glycoside and the corresponding activator system,[5] solvent systems[6] and reaction temperatures.[7] It is becoming increasingly clear that protecting groups or functionalities at positions different from C-2 not only influence the reactivity of the donor[8,9] but can also have a profound effect on the stereochemical outcome of a glycosylation reaction.[10] For example, the anchimeric assistance via a six- or seven-membered ring by acyl protecting groups at O-3[11] and O-4[11b,12] in the donor glycoside is subject of current research.[13] The most striking example of the influence of a non-participating protecting group on the stereochemical outcome is probably the *cis*-directing effect of a 4,6-*O*-acetal function in mannosylation reactions.[14] The group of Crich has shown that 4,6-*O*-benzylidene-protected mannosyl donors preferentially form 1,2-*cis* products, although the formation of 1,2-*cis* mannosidic linkages is disfavored on steric and electronic grounds (vide infra).[15]

In the development of efficient procedures for oligosaccharide synthesis the outcome of a glycosylation reaction is usually interpreted with the aid of a generally accepted nucleophilic displacement mechanism (Scheme 1).[1] Typically, condensation of a suitably protected glycosyl donor and acceptor starts with the activation of the leaving group attached to the C-1 of the donor **I** by a suitable electrophile (E^+). Activated species **II** can then undergo an S_N2-type substitution by an appropriate nucleophile, such as the acceptor. Alternatively, expulsion of the activated leaving group in **II** can produce the oxacarbenium ion **III**. This oxacarbenium ion can be intercepted by the counterion of the activator species (X^-) to give the reactive intermediate **V**, in which the group X is covalently attached to the anomeric center of the glycosyl donor. Depending on the stability of the glycosyl oxacarbenium ion and the nucleofugality of the leaving group X^- an equilibrium will be established between the covalent intermediate **V**, the contact ion pair **IV** and the solvent-separated ion pair **III**. Nucleophilic attack on the reactive intermediate **V** and contact ion pair **IV** proceeds via an S_N2-like mechanism, whereas attack of the solvent-separated ion pair **III** occurs in an S_N1-like fashion. Depending on the many variables operating in a glycosylation reaction, the mechanism can best be regarded as a continuum between S_N2-like and S_N1-like substitution.[16]

In the pursuit of stereoselectivity, most attention has been focused on steering the reaction mechanism to the S_N2-side of the

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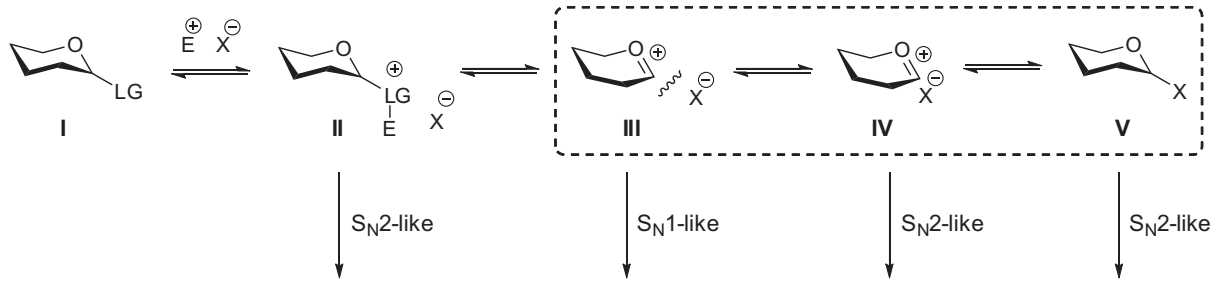


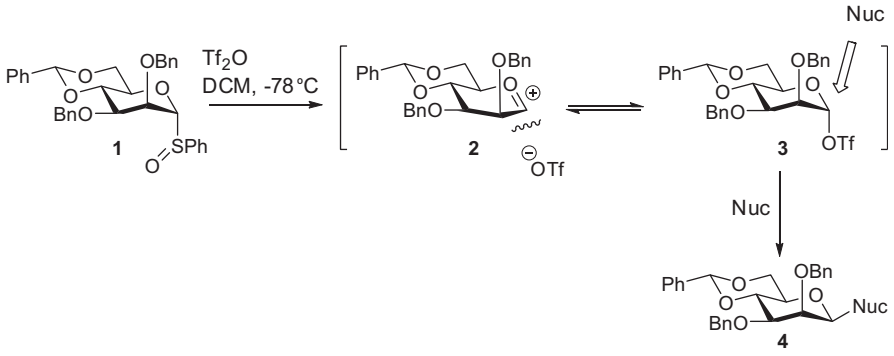
Scheme 1. General glycosylation mechanism.

continuum.[17] In Lemieux's groundbreaking in situ anomerization protocol, for example, the higher reactivity of the β-oriented halide toward direct nucleophilic displacement as compared to the α-anomer is exploited to provide 1,2-*cis* glycosides.[18] It is now well established that the reactivity of a donor glycoside critically depends on the nature and configuration of the substituents on the core of the pyranosyl ring.[8] Electron-withdrawing or conformation restricting groups disfavor the formation of the flattened (solvent-separated) oxacarbenium ion and therefore shift the equilibrium between the ion pair **III** and the covalent intermediate **V** to the side of the latter species. For example, in their seminal work on the synthesis of β-mannosides, Crich and co-workers have shown that activation of a O-4–O-6 benzylidene acetal-containing mannopyranosyl sulfoxide donor **1** with triflic anhydride leads to selective formation of an anomeric α-triflate **3** (see Scheme 2).[14] This reactive intermediate is attacked by the incoming nucleophile in an S_N2-like fashion to provide the β-linked products **4**. The equilibrium between the (solvent-separated) oxacarbenium ion **2** and covalent triflate **3** is shifted to the side of the anomeric triflate because the benzylidene function prevents formation of the flattened mannosyl oxacarbenium ion.[19] In a series of subsequent studies, the groups of Crich and others[20] investigated the mechanistic details behind this remarkable transformation. It is now clear that the stereoselectivity of this type of mannosylation is uniformly high and does not depend on the type of donor mannoside or activation protocol used. Although anomeric triflates have convincingly been demonstrated to be intermediates in this type of mannosylation, α-secondary H/D-kinetic isotope effects revealed that a significant amount of oxacarbenium ion character developed during the S_N2-like displacement of the anomeric leaving group by the incoming nucleophile.[21] The reaction proved to be sensitive to steric effects in the donor mannoside as bulky groups at C-3 and C-2 caused erosion of the β-selectivity.[22] Replacement of the C-2 or C-3 alkoxy function by small groups such as a fluorine or a hydrogen atom also led to diminished selectivities. In this case, the increase in steric interactions between the substituents at C-2 and C-3 when going from the covalent triflate to the oxacarbenium ion intermediate is less than in the case of the 2,3-di-*O*-benzyl benzylidene mannoside. Formation of the oxacarbenium ion is therefore more feasible causing the observed erosion in β-selectivity.[23] Detailed studies on the stereoselectivity of 4,6-*O*-benzylidene mannosides indicate the delicate balance between the reactive intermediates **III–V** and the corresponding S_N1-like and S_N2-like pathways.

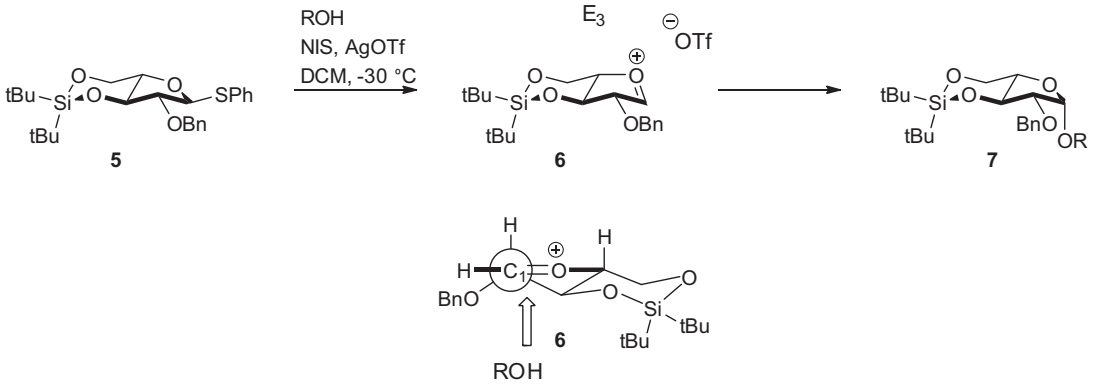
2. Stereoselective S_N1-like mechanisms

The intermediate oxacarbenium ion **III** (Scheme 1) has traditionally been considered to have little stereochemical preference, because it can be attacked from both the α- and β-side. Oxacarbenium ions have been the subject of detailed studies in the fields of computational[24] and analytical[25] chemistry. Recently, several research groups have described highly stereoselective glycosylations, which were postulated to originate from the stereoselective substitution of intermediate oxacarbenium ions. For example, Boons et al. have shown that arabinofuranosyl donors, equipped with a 3,5-silylidene ketal function give rise to highly selective 1,2-*cis* glycosylations. They argued that this selectivity originates from the oxacarbenium ion adopting an E_3 conformation (Scheme 3).[26] Addition of an alcohol nucleophile (ROH) to this oxacarbenium ion (**6**) occurs from the β-face via a staggered transition state, to avoid an eclipsed interaction with the H-2 in **6**.[27]

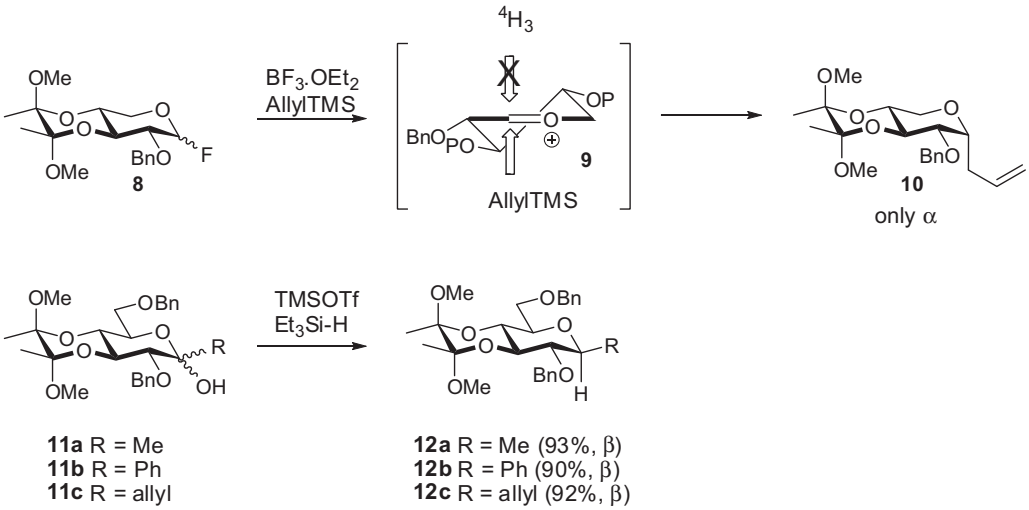
Shuto et al. have shown that conformationally restricted pyranosides can be used to effect the stereoselective formation of *C*-glycosidic bonds.[28] When xylosyl fluoride **8**, protected with a butanedimethylacetal (BDA), was treated with $BF_3{\cdot}OEt_2$ and allyltrimethylsilane the α-linked *C*-allylxyloside **10** was obtained as the sole product (Scheme 4). This selectivity can be explained with conformationally restrained oxacarbenium ion **9** as product forming intermediate. Because of the cyclic BDA acetal, flattening of the pyranosyl ring can only lead to the formation of the $^4H_3$ half chair oxacarbenium ion. Nucleophilic attack on this oxacarbenium ion



Scheme 2. β-Mannosylation via anomeric triflates.



Scheme 3. 1,2-*cis* Glycosylation of conformationally locked arabinofuranoside **5**.

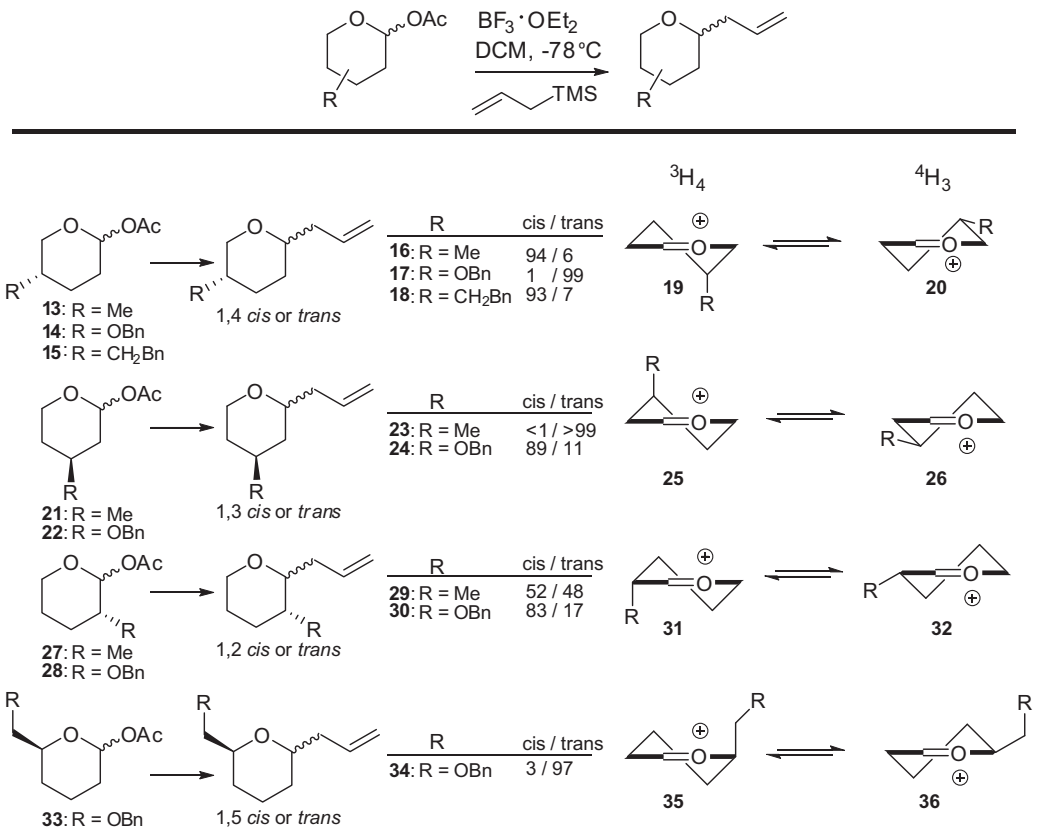


Scheme 4. Stereoselective nucleophilic addition on conformationally restricted pyranosyl oxacarbenium ions.

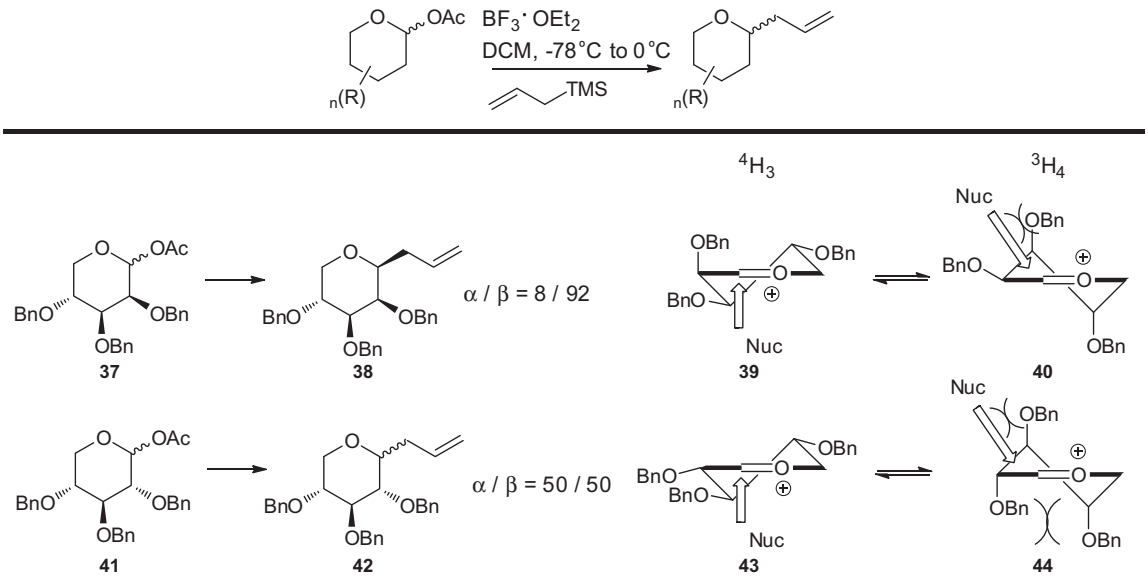
conformer occurs selectively on that diastereotopic face that leads to the chair product as opposed to the twist boat conformer that arises from attack on the other side.[29] Following an analogous approach, the Shuto laboratory showed that ketoglycosides **11a–c** are stereoselectively reduced to provide the β-*C*-glycosidic products **12a–c**.

In a series of elegant studies[30,31] Woerpel and co-workers have investigated the stereodirecting effect of ring substituents on the nucleophilic attack of various *C*-nucleophiles on pyranosyl oxacarbenium ions. Mono-substituted pyranosyl acetates were activated with $BF_3{\cdot}OEt_2$ in the presence of allyltrimethylsilane to provide the allylated pyranosides as summarized in Scheme 5. The stereochemical outcome of the allylations proved to be highly dependent on the nature of the ring substituent at C-3 and C-4. For example, C-4 methyl tetrahydropyran **13** mainly provided the 1,4-*cis* product **16**, whereas the C-4 benzyl ether **14** almost exclusively gave the 1,4-*trans* adduct **17**. Allylation of the C-3 methyl (**21**) and C-3 benzyloxy pyrans (**22**) led to the formation of the 1,3-*trans* (**23**) and 1,3-*cis* (**24**) products, respectively. The C-2 methylated pyran **27** did not show a significant preference for any of the isomers, where allylation of the C-2 benzyloxy pyran **28** displayed a preference for the formation of the 1,2-*cis* product **30**. The C-6 benzyloxymethyl pyran **33** provided the 1,5-*trans* and 1,5-*cis* products **34** in a 97:3 ratio. These results were explained by assuming an equilibrium of oxacarbenium ion half chair conformers as product forming intermediates. To best accommodate the positive anomeric charge the six-membered ring oxacarbenium ions adopt either a $^3H_4$ or a $^4H_3$ half chair conformation. In these conformations, the methyl substituent preferentially takes up a *pseudo*-equatorial position at C-3 or C-4 for steric reasons. The benzyloxy groups on the other hand favor a *pseudo*-axial orientation at these positions to allow stabilization of the electron-depleted anomeric center and reduction of the electron-withdrawing effect.[32] When the C-4 methylated pyran is considered, the $^4H_3$ oxacarbenium ion **20** will be more stable than its $^3H_4$ counterpart **19**. Nucleophilic attack on **20** occurs along a *pseudo*-axial trajectory on the β-face leading to the chair product having a 1,4-*cis*-relationship.[29] The C-4 benzyloxy pyran on the other hand prefers the $^4H_3$ half chair oxacarbenium ion **19**, which is substituted from the α-face. For the C-3 substituted tetrahydropyrans **21** and **22** similar preferences can explain the observed selectivities in **23** and **24**. The benzyloxy substituent at C-2 and the benzyloxymethyl group at C-5 prefer to adopt a *pseudo*-equatorial orientation because of stabilizing hyperconjugative effects of the H-2 in **32** and the minimization of steric interactions in **35**/**36**.

Having determined the preference of each substituent in the pyranose oxacarbenium ion, Woerpel and co-workers investigated the influence of a combination of multiple substituents on the selectivity of the C-glycosylation reaction.[33] The stereodirecting effects of the substituents appended to the pyranose core as revealed in Scheme 5 cannot simply be added to account for the obtained selectivities in **38** and **42** (Scheme 6). Steric interactions between



Scheme 5. Stereochemistry of substitutions of mono-substituted pyranosyl acetates.



Scheme 6. Stereochemistry of substitutions of tri-substituted pyranosyl acetates.

the substituents and the incoming nucleophile have an important effect in both the ground state energies of the oxacarbenium ion conformers and the transition states leading to the α- and β-products. Allylation of lyxose acetate **37**, having the *manno* configuration at C-2, C-3 and C-4, yielded mainly the 1,2-*cis* product **38**, corresponding to nucleophilic attack on ion **40** (Scheme 6). This is in line with the results obtained for the mono-substituted tetrahydropyran acetals, even though the incoming nucleophile has a disfavored steric interaction with the C-3 substituent. Xylose acetate **41** reacts in a non-selective manner to afford a 1:1 mixture of anomers (**42**). The favorable orientation of the C-3 and C-4 benzyl ethers in ion **44** 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. These data show that the stereochemical outcome of the glycosylation results from 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.

As part of a program directed toward the synthesis of fragments of naturally occurring anionic polysaccharides, we became interested in the construction of alginate oligomers.[34] Alginates are linear anionic polysaccharides build up from either repeating (1→4)-linked β-D-mannuronic acid monomers, α-L-guluronic acid monomers or (1→4)-linked mannuronic acid–guluronic acid hetero-dimers. The synthesis of fragments of these polymers thus required the repetitive installment of multiple *cis*-glycosidic linkages. At the onset of our synthetic efforts toward guluronic acid oligomers very little was known of glycosylations involving L-gulose and L-guluronic acid. Therefore we investigated the glycosylating properties of a set of L-gulosyl donors (e.g., **45**, **50**, **52** and **55**).[34b]

It soon became apparent that L-gulose donors have an unusually strong preference for the formation of 1,2-*cis* glycosidic linkages (see Table 1). To exclude that double stereodifferentiation[35] is responsible for this selectivity, we also examined D-gulose donor **48**. The identical outcome in the condensations of the L- and D-gulosides **45** and **48** refutes this possibility.[37] It has previously been hypothesized that the anomeric effect can have an important stereodirecting effect in the attack of a nucleophile to a 'flat' oxacarbenium ion, promoting the formation of the more stable α-product.[1a,3a,19d] In gulose, however, the anomeric effect should be largely offset by the 1,3-diaxial interaction of the aglycon and the C-3 substituent.[‡] We therefore dismissed the anomeric effect to be at the basis of the observed selectivity. The sulfonium chemistry used in our glycosylations can lead to the formation of intermediate glycosyl triflates as convincingly demonstrated by Crich and co-workers (*vide supra*).[12b] If a single anomeric triflate of sufficient stability is generated, like in the benzylidene mannopyranoside case, stereoselective S_N2-like displacements can be achieved. In the gulose case, it is conceivable that both α- and β-anomeric triflates exist. Also in this case the anomeric effect, which stabilizes the axial α-triflate, is counterbalanced by steric effects making the α- and β-triflate equally stable. It is thus unlikely that the α-selectivity in the gulosylations arises from the S_N2-like substitution of the β-triflate. When the two likely gulosyl oxacarbenium ion intermediates, the $^3H_4$ conformer **57** and its $^4H_3$ counterpart **58**, are considered it becomes clear that all substituents are favorably positioned in the former half chair and unfavorably in the latter (Scheme 7). The $^3H_4$ conformer **57** will therefore be substantially more stable than its $^4H_3$ congener **58**. In line with the proposal of Woerpel and co-workers, nucleophilic attack on the $^3H_4$ oxacarbenium ion **57** occurs in a *pseudo*-axial fashion on the α-face to provide the 1,2-*cis* chair product. It should be noted that in the two possible transition states from either the $^3H_4$ or the $^4H_3$ half chair, the incoming nucleophile will experience one 1,3-diaxial interaction, making both transitions states comparably favorable on steric grounds.

As outlined in Table 1, the nature of the protecting groups only has a marginal effect on the stereoselectivity of the gulosyl donors. Also the nature of the C-5 substituent does not influence the stereoselectivity significantly. This stands in contrast to the results we obtained in the mannopyranosyl series. Mannopyranosyl donors are generally considered to provide α-selective condensations[15] and the stereoselective construction of the β-mannosidic linkage has indeed been a long-standing challenge. During our synthetic studies toward alginate oligomers we discovered that glycosylations with mannuronate ester donors proceed with excellent selectivity to provide the β-mannuronate products (see e.g., Table 2). This stereochemical outcome can be explained by the S_N2-like substitution of an intermediate α-triflate, which is stabilized with respect to the solvent-separated oxacarbenium ion-triflate ion pair because of the electron-withdrawing effect of the C-5 carboxylate ester (Scheme 8). Alternatively, it is hypothesized that the mannuronate oxacarbenium ion is at the basis of the observed stereoselectivity (Scheme 9). In the most favorable $^3H_4$ oxacarbenium ion **73**, the substituents at C-2, C-3 and C-4 take up their preferred orientation (vide supra). In this constellation the C-5 ester is placed in an axial position, thereby allowing the through-space stabilization of the electron-depleted anomeric center while minimizing its electron-withdrawing effect.[36]

To evaluate the conformational preference for the C-5 carboxylate ester, mono-substituted tetrahydropyran **75** and its benzyloxymethyl counterpart **76** were investigated (Scheme 10). From Table 3 it is clear that the C-5 carboxylate ester containing pyran **75** reacts in a highly 1,5-*cis* fashion when compared to benzyloxymethyl pyran **76**. With the aid of oxacarbenium ion half chair conformers **77** and **78** the stereochemical trends revealed in Table 3 can be explained. The preferential formation of the 1,5-*cis* linked products originates from nucleophilic attack on the $^3H_4$ oxacarbenium ion **77**, in which the carboxylate ester occupies a *pseudo*-axial orientation. When the steric requirements of the nucleophile increase in going from methanol to isopropanol, *tert*-butanol and adamantanol, the 1,5-*cis* preference decreases because of increased 1,3-diaxial interactions with the axial carboxylate ester.

To corroborate the conformational preference of the C-5 carboxylate in **77**/**78** we calculated the relative energies of a series of mono-substituted tetrahydropyran oxacarbenium ions having different substituents at C-5, as summarized in Figure 1.[37] It can be seen that the oxacarbenium ion that positions the carboxylate ester in an axial position is indeed more stable than the half chair oxacarbenium ion having this substituent in an equatorial orientation. For comparison, the trifluoromethyl tetrahydropyran was also evaluated and the calculated energies reveal that for this pyran the equatorial isomer is slightly more stable than its axial counterpart. These results indicate that the preference for the C-5 carboxylate ester to reside in an axial position stems from the through-space stabilization of the positively charged anomeric center rather than from an electron-withdrawing inductive effect.[§] The small difference in stability between the equatorial and axial C-5 CF_3 isomeric oxacarbenium ions became apparent when 1-phenylsulfanyl-5-trifluoromethyltetrahydropyran was coupled with benzyl alcohol to provide an anomeric mixture of 1-benzyloxy-5-trifluoromethyltetrahydropyran (α:β ~ 1:1).[37]

When the relative energies of the C-5 carboxylate esters are translated to the mannuronate ester oxacarbenium ions, it becomes clear that the carboxylate ester can take up the most favorable axial orientation in the $^3H_4$ oxacarbenium ion **73**, in line with the preferred orientation of the other ring substituents (Scheme 9). The $^3H_4$ conformer should thus be significantly more stable than its $^4H_3$ counterpart.[**,¶] When a nucleophile attacks the mannuronate ester $^3H_4$ oxacarbenium ion **73** on the β-face, unfavorable 1,3-diaxial interactions will develop with both the C-3 and the C-5 substituent on the pyranose core. Woerpel and co-workers have previously hypothesized that the mannopyranosyl oxacarbenium ion provides

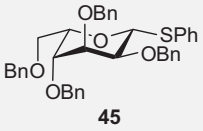
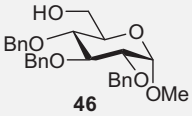
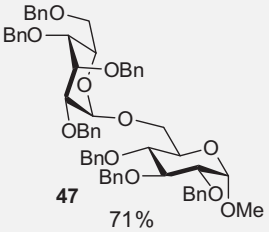
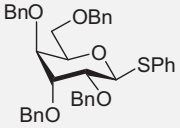
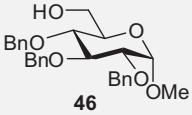
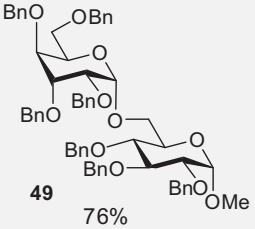
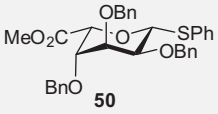
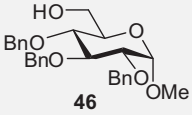
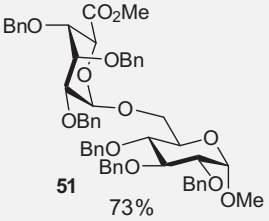
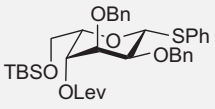
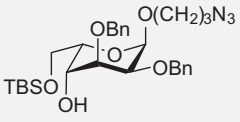
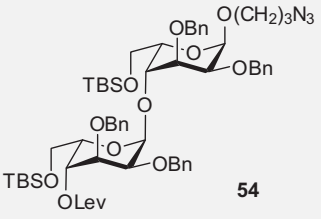
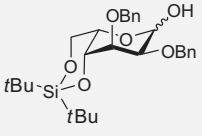
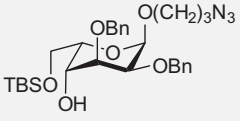
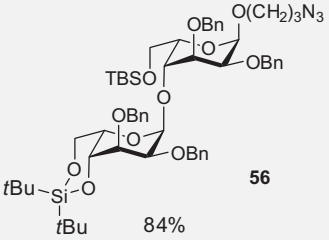
[‡] The proportion of the α-anomer of gulose in aqueous solution is 17%, where glucose exists for 36% and mannose for 66% in the α-form. See: Ref. 44.

[§] The CF_3-group has a σ_p-value of 0.54 and an *F*-value of 0.38. The CO_2Me group has a σ_p-value of 0.45 and an *F*-value of 0.34. See: Ref. 45.

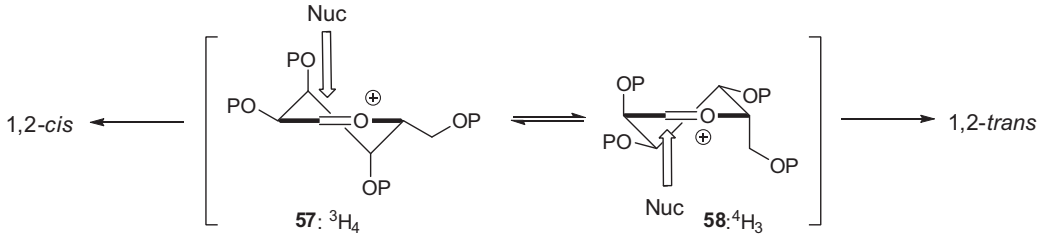
[**] In the L-gulopyranosyl and D-mannupyranosyluronate ester oxacarbenium ion all substituents contribute positively to the stability of one of the two half chair conformers (i.e., the $^3H_4$ half chair), leading to stereoselective glycosylations. Glycosylations of pyranoses with conflicting substituent preferences are in majority less stereoselective. See Ref. 37.

[¶] The mannosyl $^3H_4$ oxacarbenium ion has been calculated to be 6.8 kcal mol^{-1} more stable than its $^4H_3$ counterpart (see Ref. 33). Combining this value with the energies presented in Figure 1, it can be calculated that the mannuronate oxacarbenium ion $^3H_4$ **73** is favored over the $^4H_3$ conformer **74** by ~9 kcal mol^{-1}.

Table 1
Condensations of gulose and guluronic acid donors[a]

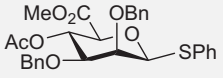
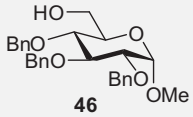
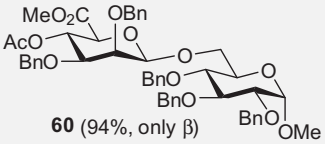
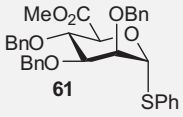
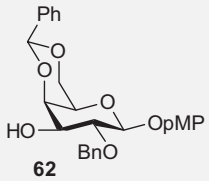
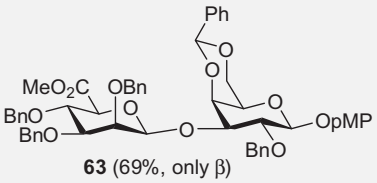
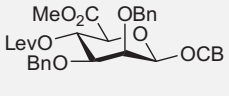
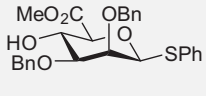
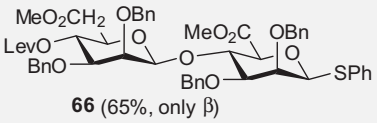
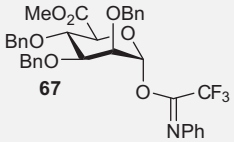
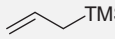
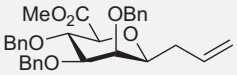
Entry	Donor	Acceptor	Product
1	 **45**	 **46**	 **47** 71% *cis* : *trans* = 13:1
2	 **48**	 **46**	 **49** 76% *cis* : *trans* = 10:1
3	 **50**	 **46**	 **51** 73% *cis* : *trans* = 3:1
4	 **52**	 **53**	 **54** 48% *cis* : *trans* = 6:1
5	 **55**	 **53**	 **56** 84% *cis* : *trans* = 10:1

[a] Reagents: Ph_2SO, Tf_2O, TTBP, DCM.

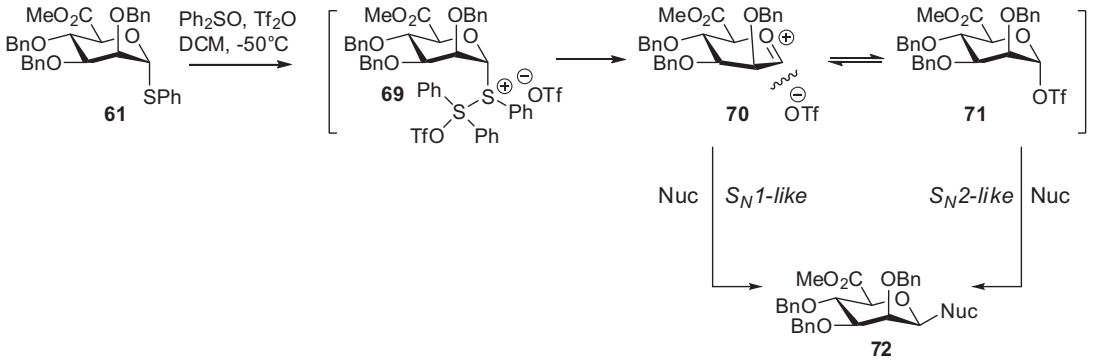


Scheme 7. Nucleophilic attack on the gulopyranosyl oxacarbenium ion.

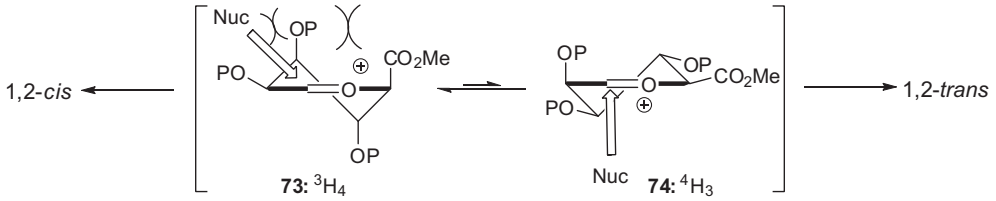
Table 2
β-Mannosylations using various mannosyl uronate donors and acceptors

Entry	Donor	Acceptor	Product
1[a]	 **59**	 **46**	 **60** (94%, only β)
2[a]	 **61**	 **62**	 **63** (69%, only β)
3[b]	 **64**	 **65**	 **66** (65%, only β)
4[c]	 **67**		 **68** (74%, only β)

[a] Reagents: Ph_2SO, Tf_2O, TTBP.
[b] Conditions: Ph_2SO, Tf_2O, DTBMP.
[c] TMSOTf (cat).



Scheme 8. Mechanism behind the β-selectivity in condensations of mannuronate ester donors.

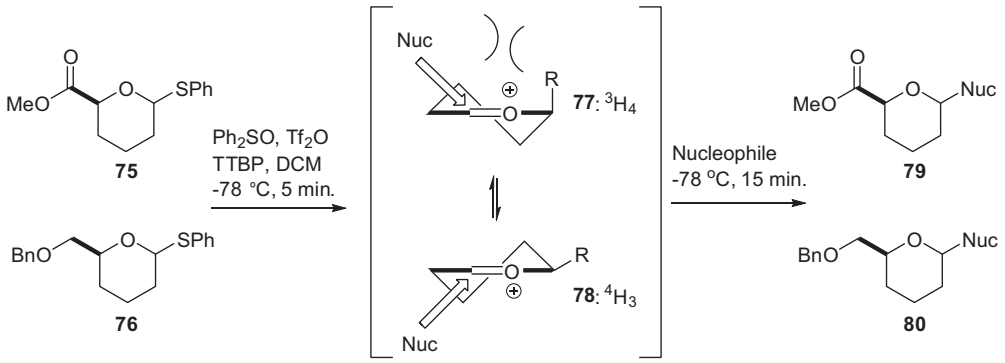


Scheme 9. Nucleophilic attack on the mannuronate ester oxacarbenium ion.

α-selective condensations because these steric interactions are large enough to prevent nucleophilic attack on the β-face of the $^3H_4$ oxacarbenium ion.[33] A Curtin–Hammett kinetic scenario, in which product formation arising from the higher ground state energy $^4H_3$ oxacarbenium ion was forwarded to account for the formation of the α-product. The extra stabilization by the axial C-5 ester in oxacarbenium ion **73** can prevent such a Curtin–Hammett scheme to occur. Furthermore, the reduced size of the methyl ester as compared to the benzyloxymethylene group leads to less steric hindrance of the former group with the incoming nucleophile.[‖]

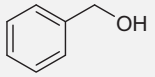
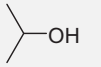
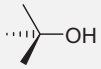
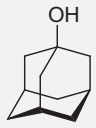
With the objective to exclude the formation of the $^3H_4$ oxacarbenium ion and thereby induce nucleophilic attack on the other half

[‖] The *A*-values for the methyl ester and CH_2OH are 1.2 kcal mol^{-1} and 1.8 kcal mol^{-1}, respectively. See: Ref. 46.



Scheme 10. Substitutions on mono-functionalized tetrahydropyrans **75** and **76**.

Table 3
Condensations of **75** and **76**

Entry	Nucleophile	Product, α:β (yield)	
1		**79a**, 1: 7.7 (67%)	**80a**, 1: 1.4 (82%)
2		**79b**, 1: 3.8 (48%)	**80b**, 1: 0.60 (61%)
3		**79c**, 1: 2.9 (52%)	**80c**, 1: 0.38 (60%)
4		**79d**, 1: 1.2 (52%)	**80d**, 1: 0.33 (74%)

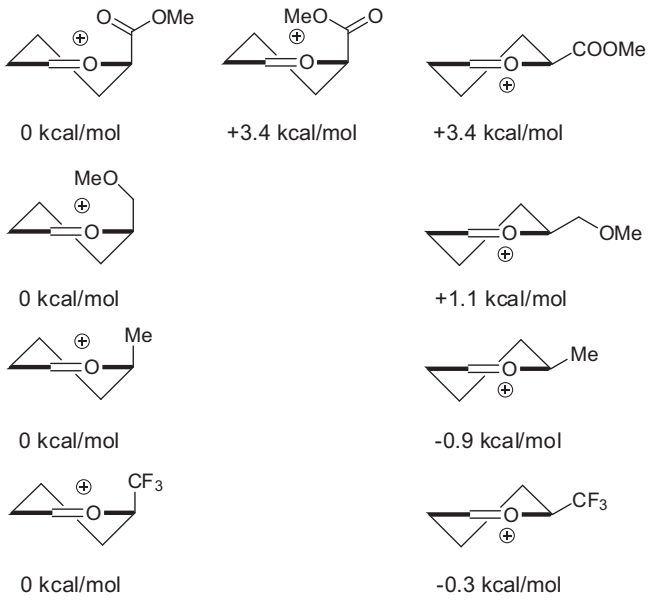
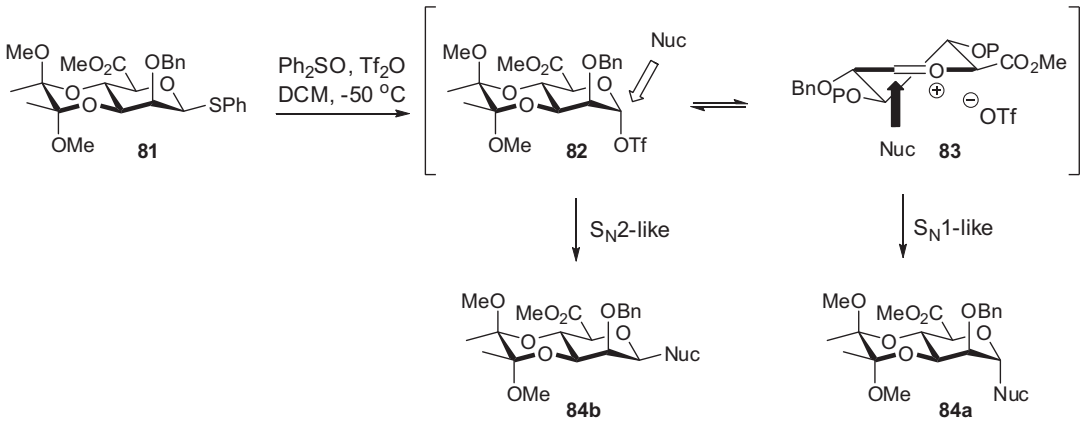


Figure 1. Calculated relative energies (MP3) of C-5 substituted pyranosyl oxacarbenium ions.

chair conformer, the glycosylation behavior of conformationally restricted mannuronate donor **81** was investigated (Scheme 11).[38] Glycosylations with BDA-protected mannopyranosyl donors were previously reported to occur with high α-selectivity.[11c] Using low-temperature NMR spectroscopy the activation of thiomannuronate **81** was followed and the single intermediate that was formed upon activation of **81** was tentatively assigned to be the α-triflate **82**. Upon treatment of this species with a variety of glycosyl acceptors the α-disaccharides **90–92** were predominantly formed (see Table 4). Obviously the α-linked disaccharide products can not arise from direct S_N2-like displacement of the observed anomeric α-triflate **82**. They can however arise from the oxacarbenium ion intermediate **83** which can only access the $^4H_3$ half chair conformation because of the conformational restriction imposed by the BDA acetal. In the condensation of mannuronate **81** and primary alcohol **46** a substantial amount of β-linked disaccharide was also formed. Formation of this product can be explained by the direct S_N2-like displacement of anomeric triflate **82**, because of the relatively high nucleophilicity of the acceptor alcohol involved. Crich and co-workers previously reported that the condensation of this acceptor with the 'non-oxidized' BDA-protected mannopyranosyl donor provided only the α-linked disaccharide,[11c] indicating that the C-5 carboxylate provides some extra stabilization to the anomeric triflate. For less reactive glycosyl acceptors **83** and **84** the conformational restriction of the BDA acetal[8a,39]in combination with the electron-withdrawing effect of the C-5 carboxylic ester in **81** apparently can not prevent the anomeric triflate from dissociating into the oxacarbenium ion. Glycosylation takes place through the latter species.

To gain further insight into the factors underlying the selectivity of the mannuronate ester donors the glycosylation behavior of mannosaziduronic acid ester **93** was studied.[40] We have previously noted that the substitution of the C-2 *O*-benzyl group in 2,3-di-*O*-benzyl-4,6-benzylidene mannopyranosyl thiodonors for a C-2 azide functionality led to a decreased β-selectivity for this type of donor.[41] In the case of the mannuronate donor **93**, introduction of the C-2 azide did not have an adverse effect on the selectivity and disaccharides **94**, **96**, and **98** were obtained in high yield from **93** and acceptors **46**, **95** and **97**, respectively (see Table 5).

In studying the activation process of donor **93**, low-temperature NMR measurements revealed that treatment of β-thiodonor **93** with Ph_2SO and Tf_2O in CD_2Cl_2 led to a mixture of two anomeric triflates (see Fig. 2). These two mannuronate triflates were in dynamic equilibrium because the two resonance sets observed at −80 °C coalesced upon warming of the NMR probe to −40 °C. When cooled back to −80 °C the two distinct sets of peaks reappeared. Similar NMR spectra were obtained when the activation of *N*-(phenyl)trifluoroacetimidate donor **99** with a stoichiometric amount of TfOH was studied. The two anomeric triflates observed at −80 °C were determined to be α-mannosyl triflate **100**, having a $^4C_1$ conformation and its $^1C_4$ counterpart **101**. Interestingly the $^1C_4$ conformer **101**, having the anomeric triflate in the equatorial position, prevailed in the reaction mixture ($^1C_4$:$^4C_1$ = 3:1). It is of interest that we obtained a similar result in the activation of mannuronate **59** under identical conditions, and noted that methyl (4-acetyl-2,3-*O*-benzyl-1-trifluoromethylsulfonyl-α-mannopyranosyluronate) exists as a 1.4:1 mixture of $^1C_4$:$^4C_1$ chairs at −80 °C.



Scheme 11. Mechanism of glycosylation of conformationally restricted mannuronate ester **81**.

Table 4
Glycosylation of mannuronates **81** and **85**

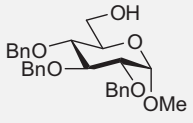
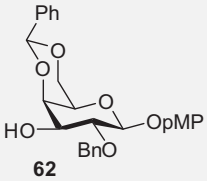
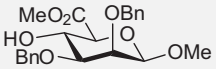
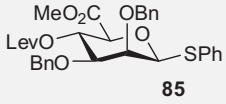
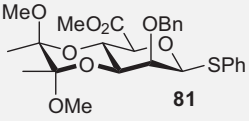
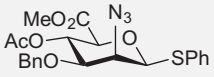
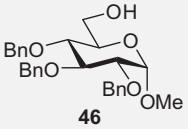
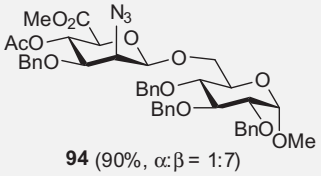
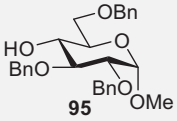
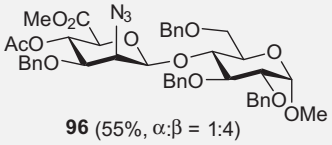
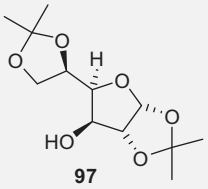
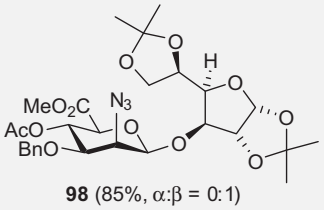
Ph_2SO, Tf_2O, TTBP, DCM −60 °C to rt Yield (α:β)	 **46**	 **62**	 **86**
 **85**	87, 93% (0:1)	88, 73% (0:1)	89, 55% (0:1)
 **81**	90, 56% (2:1)	91, 56% (1:0)	92, 49% (3:1)

Table 5
Glycosylations of mannosaziduronic acid ester **93**[a]

Entry	Donor	Acceptor	Product
1	 **93**	 **46**	 **94** (90%, α:β = 1:7)
2	**93**	 **95**	 **96** (55%, α:β = 1:4)
3	**93**	 **97**	 **98** (85%, α:β = 0:1)

[a] Reagents: Ph_2SO, Tf_2O, TTBP.

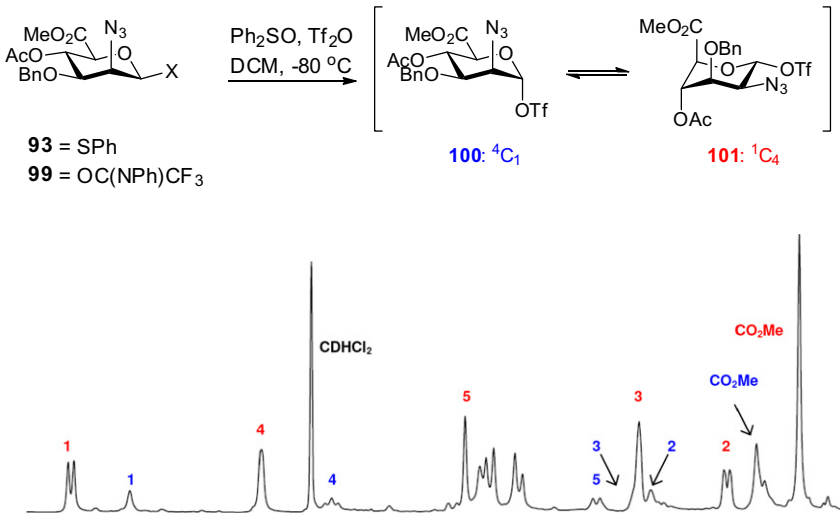
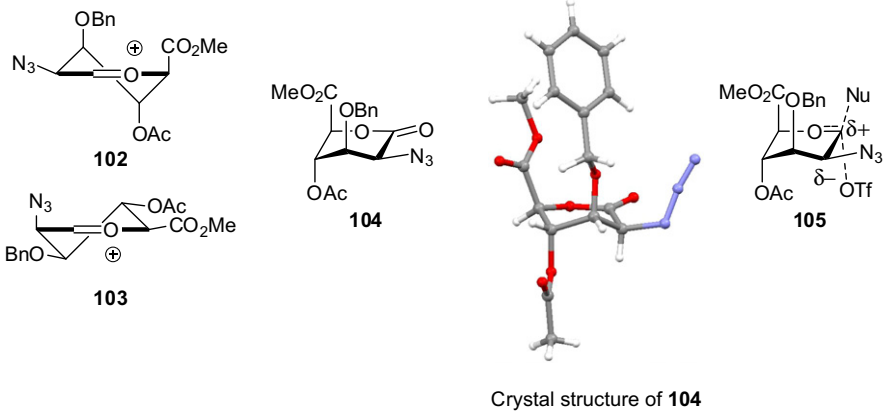


Figure 2. Part of the ^{1}H NMR spectrum obtained after activation of donors **93** and **99** at −80 °C.

Considering the lack of anomeric stabilization and the destabilizing 1,3-diaxial interactions in the $^{1}C_4$ species, the preferential formation of equatorial triflate **101** was highly unexpected. The unusual conformational flip from the $^{4}C_1$ to the $^{1}C_4$ conformation can be rationalized by considering the half chair oxacarbenium ion structures **102** and **103** (Scheme 12). As for mannuronate ester **73**, the $^{3}H_4$ conformer **102** places all substituents in the most favorable position to accommodate the positive charge at the anomeric center. The presence of the electron-withdrawing triflate at C-1 and the methyl ester at C-5 render the anomeric center of the mannuronate triflate so electron-depleted that the structure of the covalent triflate approaches the conformation of the oxacarbenium ion half chair **102**.

To further the hypothesis that the lack of electron-density at C-1 is the driving force for the ring inversion, the mannosazide methyl ester lactone **104** was synthesized. The C-1 of this lactone carries a significant positive charge and is sp^2 hybridized. NMR and X-ray crystallography revealed that lactone **104** indeed adopts an inverted conformation approaching the $^{3}H_4$ half chair at room temperature (Scheme 12), providing support for the above-mentioned hypothesis. The fact that 6,6,6-trifluoro-α-rhamnosyl triflate, bearing a strongly electron-withdrawing CF_3 functionality at C-5,[††] exists in the regular $^{4}C_1$ conformation[42] indicates that not only the electron-withdrawing effect of the C-5 substituent causes the pyranosyl ring of the mannuronate triflates to flip. Rather, the extra stabilization that the C-5 carboxylate ester provides to the electron depleted anomeric center when occupying an axial position in the $^{1}C_4$ chair is at the basis of the ring flip.

The existence of triflates **100** and **101** (Fig. 2) has significant bearing on the mechanism through which glycosylations of mannuronate ester donors proceed and provides evidence for both an S_N2-like and S_N1-like reaction pathway. On one hand, the identification of the α-triflates lends support to an S_N2-like mechanism. On the other hand, the stereoelectronic effects responsible for the conformational flip of the mannopyranosyl chair point to an S_N1-like pathway. These stereoelectronic effects which stabilize the structure of the neutral anomeric triflate **101** and lactone **104** will become even more important when positive charge develops at the anomeric center upon substitution of the anomeric triflate. The glycosylations of mannuronate esters most probably occur through an asymmetric exploded transition state, such as **105**, following an S_N2-like pathway with significant S_N1 (oxacarbenium ion) character as depicted in Scheme 12. The nature of the nucleophile determines the place in this S_N1–S_N2 continuum.[43] The anomeric triflate and the formation of the $^{3}H_4$ oxacarbenium ion both contribute to the excellent β-selectivities observed in the condensations of mannuronate ester donors.



Scheme 12. Structure of oxacarbenium ions **102** and **103** and lactone **104**.

3. Summary and conclusion

En route to the synthesis of alginate oligosaccharides we found that the formation of 1,2-*cis* L-gulosidic and 1,2-*cis* D-mannuronic ester linkages proceeds with unexpected high stereoselectivity. Commonly, a reaction mechanism involving either S_N2-like substitution of an anomeric leaving group, such as a triflate, or selective attack at C-1 directed by the anomeric effect is employed to account for the formation of 1,2-*cis* glycosides. Because the stereoselective formation of the 1,2-*cis* L-gulosidic linkages is difficult to reconcile with such a reaction mechanism, we have postulated that the intermediate gulosyl oxacarbenium ion is at the basis of the observed selectivity. In line with kinetic studies on the hydrolysis of glycosidic bonds,[9e,31e] computational data and in particular mechanistic studies on the influence of oxacarbenium ion conformers on the stereochemical outcome of C-glycosylations by the group of Woerpel, it can be reasoned that activation of L-gulopyranosyl donors leads to the preferential formation of the $^3H_4$ oxacarbenium ion. An incoming nucleophile selectively attacks this ion on the diastereotopic face that leads to the chair product, which explains the observed α-selectivity. The selective formation of 1,2-*cis* D-mannuronic ester linkages also fits this mechanism, in which the C-5 carboxylate ester preferentially occupies a *pseudo*-axial orientation in a half chair oxacarbenium ion. However, the glycosylations of mannurate esters can also occur via an S_N2-like attack on the α-triflate. Low-temperature NMR studies on mannosaziduronic acid ester triflates guided us to the point of view that glycosylations of mannuronate esters most probably occur through an asymmetric exploded transition state, following an S_N2-like pathway with significant oxacarbenium ion character, the extent of which is determined by the nature of the nucleophile. The anomeric α-triflate and the preferential formation of the $^3H_4$ oxacarbenium ion work in concert in the formation of the 1,2-*cis* mannuronic ester linkages. In conclusion, not only the anomeric effect, but also oxacarbenium ion conformers, their stability and their stereochemical preference in reacting with nucleophiles are to be considered as contributing factors in the interpretation of the stereochemical outcome of glycosylation reactions that proceed through intermediates which display significant oxacarbenium ion character.

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