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Equatorial Anomeric Triflates from Mannuronic Acid Esters

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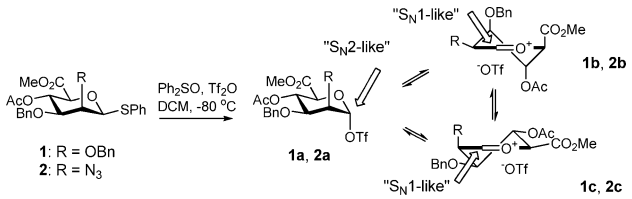
The stereoselective construction of 1,2-*cis* glycosidic bonds continues to be one of the largest challenges in synthetic carbohydrate chemistry. Because the glycosidic bond forming process can proceed via different (S_N1- and S_N2-like) reaction pathways and through the intermediacy of different reactive species (e.g., anomeric triflates, oxacarbenium ions), it is exceedingly difficult to identify and control the exact reaction pathway. In the course of our research toward the construction of anionic oligosaccharides, we have recently reported that condensations of 1-thio mannuronate ester donors proceed with excellent 1,2-*cis* selectivity to provide β-linked products.[1] On the one hand, this selectivity can be explained by invoking an axial α-anomeric triflate (**1a**, Scheme 1) as a product forming intermediate, which is substituted in an S_N2-like manner. The axial anomeric triflate is preferentially formed following the dictates of the anomeric effect.[2,3] On the other hand, an oxacarbenium ion intermediate may be formed that preferentially adopts the $^3H_4$ half-chair conformation **1b**. In this half-chair the C-5 carboxylate occupies a pseudoaxial position to allow a through space stabilization of the positive charge at the anomeric center.[1c] The other ring substituents are also in their most favorable orientation: the C-3 and C-4 substituents are positioned axially, and the C-2 functionality is positioned equatorially.[4] The incoming nucleophile attacks this half chair along a pseudoaxial trajectory on the β-face of the molecule to produce a 1,2-*cis* linkage. The alternative $^4H_3$ half-chair **1c**, which would lead to the α-linked product, is strongly disfavored due to misplacement of all ring substituents.

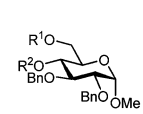
Scheme 1. Intermediates in the Glycosylation of Donors **1** and **2**

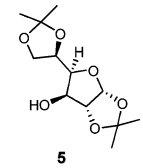


To gain more insight into the mechanism underlying the exceptional 1,2-*cis* selectivity, we set out to study the behavior in glycosylations of 1-thio mannosaziduronate donor **2**, bearing an electron-withdrawing azide functionality at C-2. Its natural equivalent, mannosaminuronic acid, is found in various (bacterial) polysaccharides,[5] in which it generally is β-linked. First, the stereoselectivity of donor **2** was assessed in three condensation reactions with acceptors **3**, **4** and **5** using the Ph_2SO-Tf_2O activator system.[6] The primary acceptor **3** gave disaccharide **6** in high yield and excellent selectivity (Table 1). Also the secondary acceptors **4** and **5** were coupled with high β-selectivity, with acceptor **5** being superior in yield and selectivity. These results are comparable in stereoselectivity to those obtained for 2-*O*-Bn mannuronate donor **1**.[1]

Table 1. Results from the Glycosylation of Donor **2**

Acceptor	Product	Yield (α:β)
3	**6**	90% (1:7)
4	**7**	53% (1:4)
5	**8**	85% (0:1)





Next, we set out to identify possible reactive intermediates formed upon activation of uronate **2** by low-temperature NMR spectroscopy. A mixture of β-thiodonor **2** and Ph_2SO (1.3 equiv) in DCM-d_2 (0.05 M) at −80 °C was treated with Tf_2O (1.3 equiv), and a ^1H NMR spectrum was recorded. The donor was instantaneously consumed to yield the spectrum shown in Figure 1, displaying two distinct sets of signals. When the reaction mixture was warmed to −40 °C, the two resonance sets coalesced to one averaged set of signals (see Supporting Information). Upon cooling to −80 °C, the two resonance sets appeared again, indicating a dynamic equilibrium of two species. Above −40 °C decomposition was observed. Using 2D COSY and HSQC measurements all pyranosyl peaks were assigned as reported in Figure 1.

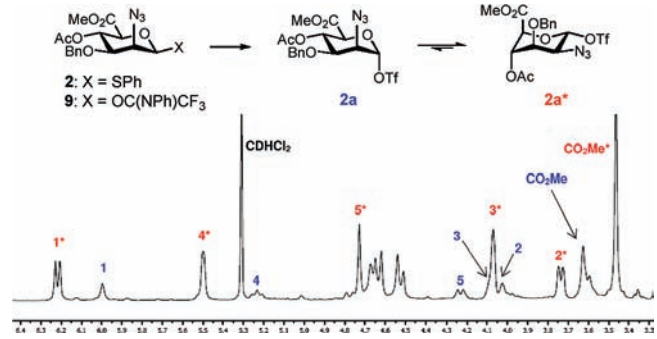


Figure 1. Part of the ^1H NMR spectrum obtained after activation of mannuronic acid esters **2** and **9** at −80 °C.

The anomeric H-1 signal at 6.00 ppm was a singlet as expected for a *manno* H-1. The H-1* doublet at 6.22 ppm however displayed a coupling constant of $^3J_{H1-H2} = 8.8$ Hz indicating a *trans*-diaxial relationship between H-1* and H-2*. In mannosyl pyranosides such a large coupling constant is caused by a change in conformation from the $^4C_1$ to the $^1C_4$ chair. This ring flip was supported by the coupling constants of the other ring protons. The chemical shifts of the two anomeric signals H-1 and H-1* are both indicative of an anomeric triflate.[7] Strikingly, this suggests that activation of

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mannosazide uronate **2** leads to a conformational mixture of anomeric triflates in which the $^1C_4$ chair product **2a***, which accommodates the anomeric triflate in the equatorial position, is predominantly formed (**2a***:**2a** = 3:1).

To confirm that the spectrum displayed in Figure 1 indeed belongs to a conformational mixture of α-anomeric triflates, *N*-(phenyl)trifluoroacetimidate **9** was activated in a low-temperature NMR experiment. When donor **9** was treated with an equimolar amount of TfOH in DCM-d_2 at −80 °C, the imidate was immediately consumed and the resulting spectrum matched the one shown in Figure 1. Activation of 1-thio mannuronate **2** and imidate **9** thus lead to an identical mixture of anomeric α-triflates in which the equatorial triflate **2a*** prevails.[8]

Whereas axial anomeric triflates have been frequently characterized by NMR studies,[9] equatorial anomeric triflates have up to now never been spectroscopically detected. Nonetheless, they have been invoked as product forming intermediates during glycosylation.[10,11] With electron-withdrawing substituents at the anomeric center, pyranosyl ring inversion has been observed before, but always to profit from the stabilizing anomeric effect.[2,3] Since the preference for an electronegative substituent to reside in an axial anomeric position is more pronounced in mannosides than in other glycosides,[3] the finding that mannosaziduronic acid ester preferentially forms the equatorial triflate **2a*** is highly unexpected. In addition to the lack of anomeric stabilization, this structure also places three of the five substituents in a sterically disfavored axial position.

We rationalize this atypical behavior by taking into account that this species carries a significant amount of positive charge on its anomeric carbon atom; the presence of the anomeric triflate, the C-5 ester, and the C-2 azide together render the anomeric center of the mannosyl core electron-deficient. Consequently, the structure of the equatorial triflate **2a*** approximates the structure of the corresponding oxacarbenium ion **2b**. In analogy to the $^3H_4$ half-chair **2b**, the $^1C_4$ triflate **2a*** places the C-5 methyl uronate as well as C-3 and C-4 substituents in a *pseudo*-axial position to stabilize the partially electron-positive anomeric center.[12] Notably, this stabilizing effect is strong enough to overrule both the anomeric effect and the unfavorable 1,3-diaxial interactions. The preferential flip of the electron-deficient mannuronate core to the $^1C_4$ chair conformation thus supports the model we proposed for the lower ground-state energy of the $^3H_4$ half-chair mannuronate oxacarbenium ion.[1b]

To endorse the postulation that the developing positive charge at C-1 is the driving force for the inversion of chair conformation, mannuronate lactone **10** was synthesized. As in the mannuronate oxacarbenium ion, the C-1 of the lactone is sp^2-hybridized and carries a partial positive charge. Analysis by NMR spectroscopy revealed that lactone **10** adopts a flattened $^1C_4$ chair at room temperature, as depicted in Figure 2. X-ray crystallography corroborated this structure (Figure 2).

The existence of the conformational mixture of α-anomeric triflates provides support for a glycosylation pathway having both S_N1- and S_N2-character. Substitution of the triflate is accompanied by the development of significant oxacarbenium ion character at the anomeric center. To accommodate this (partial) positive charge, the mannuronates **1** and **2** adopt a conformation approaching the $^3H_4$ half chair, as illustrated by the asymmetric exploded transition state **11** (Figure 2).[13] The (stereo)electronic effects stabilizing this conformation are already apparent in the neutral triflate **2a*** and lactone **10** and will become more important with increasing positive charge at C-1. In this glycosylation scenario, the amount of S_N1- and S_N2-like character is determined by the reactivity of the incoming nucleophile. Thus, both the anomeric triflate and the formation of the $^3H_4$ oxacarbenium ion contribute to the excellent β-selectivity observed in the condensation of mannuronates **1** and **2**.

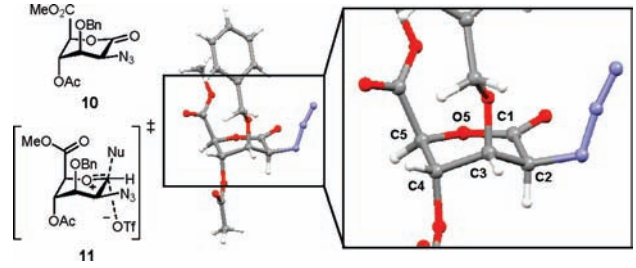

Figure 2. X-ray crystallographic structure of lactone **10** and proposed transition state **11**.

In conclusion, activation of mannosyl methyl uronates leads to the predominant formation of equatorial mannosyl triflates. This finding contrasts with conventional wisdom that the anomeric effect is of decisive influence on both the conformation of glycosides and their behavior in glycosylations.

Acknowledgment. This work was supported by Top Institute Pharma and The Netherlands Organization of Scientific Research (NWO, veni grant). The authors thank C. Erkelens and F. Lefeber for their assistance with executing the NMR experiments.

Supporting Information Available: Spectroscopic data of the reported compounds, low-temperature NMR spectra and X-ray crystallographic data of **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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