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Mannopyranosyl Uronic Acid Donor Reactivity

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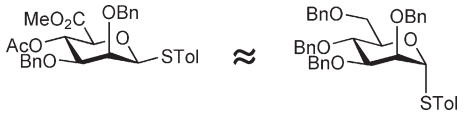
ABSTRACT

Reactivity 

The reactivity of a variety of mannopyranosyl uronic acid donors was assessed in a set of competition experiments, in which two (*S*)-tolyl mannosyl donors were made to compete for a limited amount of promoter (NIS/TfOH). These experiments revealed that the reactivity of mannuronic acid donors is significantly higher than expected based on the electron-withdrawing capacity of the C-5 carboxylic acid ester function. A 4-*O*-acetyl-β-(*S*)-tolyl mannuronic acid donor was found to have similar reactivity as per-*O*-benzyl-α-(*S*)-tolyl mannose.

The substituents on a glycosyl donor have a decisive effect on its reactivity in glycosylation reactions.[1] As first recognized by Paulsen and co-workers, electron-withdrawing groups on the carbohydrate core retard the formation of (partial) positive charge at the anomeric center, thereby slowing down the rate of hydrolysis and/or glycosylation.[2] This observation is formulated in the armed−disarmed concept, introduced by Fraser-Reid, in which benzylated (armed) glycosyl donors can be selectively activated (and coupled) to acylated (disarmed) glycosyl donors.[3] Subsequently the armed−disarmed concept has evolved into a system in which glycosyl donor reactivity is regarded to be a continuum.[4] To gain better insight into the exact reactivity of a glycosyl donor, the groups of Ley[5] and Wong[6] have quantified the reactivity of a large number of thioglycosyl donors and shown that the reactivity of a given donor is a function of the nature of the mono- (or oligo-) saccharide at hand, as well as the nature and position of the substituents. Recently, Bols and co-workers have shown that "super-armed" donors can be conceived by forcing the carbohydrate ring substituents in pseudoaxial orientations, making the electronegative substituents less deactivating.[7] In general, uronic acid donors, being glycosyl pyranosides of which the C-6 is oxidized to a carboxylic acid function, are regarded to be among the most unreactive donors by virtue of the electron-withdrawing nature of the appended carboxylic acid ester function ($F_{COOMe} = 0.34$; $F_{CH_2OH} = 0.03$).[8,9] In our recent

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studies on the use of mannuronic acids in the construction of complex bacterial oligosaccharides,[10−13] we investigated the activation and glycosylation behavior of a series of diversely substituted mannuronic acid donors, including mono- and diazidomannuronic acids. We found that these donors are readily activated to provide glycosylating species, which reacted in a stereoselective manner to provide β-mannosidic linkages. Besides the stereoselectivity of these reactions, the reactivity of the donors studied was also remarkable. The latter became apparent in our NMR experiments to study the formation of anomeric triflates by the sulfonium-ion-mediated preactivation of mannuronic acid donors. 2,3-Di-*O*-benzyl mannuronate donor **1** was rapidly activated using Ph_2SO-Tf_2O at low temperature (−80 °C) to give mannosyl triflate **2**, which could be used as a glycosylating species at the same low temperature (Figure 1).[11] Analogous results were obtained for the mono- and diazidomannuronates **3** and **5**, which contain, in addition to the "disarming" C-5 carboxylate, electron-withdrawing azide functionalities at C-2/3 (F_{N_3} = 0.48).[9]

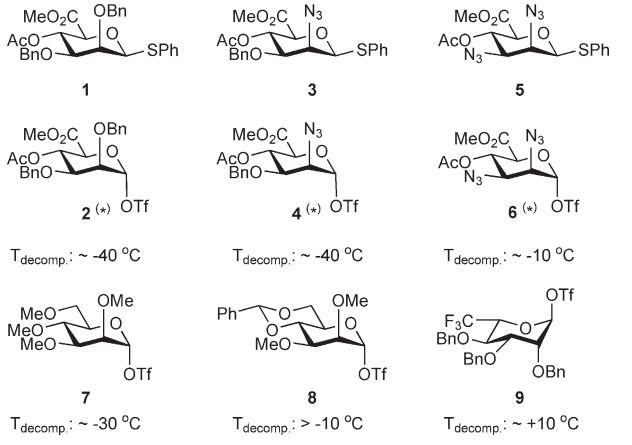

Figure 1. Previously studied mannuronic acid donors and mannosyl triflates. (*) Triflates **2**, **4**, and **6** exist as a conformational $^4C_1/^1C_4$ mixture.[11−13]

Triflates **4** and **6** were rapidly formed at −80 °C from their respective donors and shown to be apt glycosylating species.[12−14] In addition, the decomposition temperatures of triflates **2**, **4**, and **6** proved to be unexpectedly low, as indicated in Figure 1. For comparison, the decomposition temperatures of per-*O*-methylmannosyl triflate **7**,[15] 4,6-*O*-benzylidene-2,3-di-*O*-methylmannosyl trilfate **8**,[15] and 6,6,6-trifluoromannosyl triflate **9**[16] (F_{CF_3} = 0.38)[9] are −30, −10, and +10 °C, respectively. Thus, the reactivity of the mannuronate donors and the stability of the intermediate triflates do not match the expectations. To gain more insight into the reactivity of mannopyranosyl uronic acid donors, we set out to investigate their relative reactivity with respect to their non-oxidized counterparts. We here report the results of this study.[17]

The most extensive donor reactivity study to date has been reported by Wong and co-workers, who quantified the reactivity of more than 100 (*S*)-tolyl glycosides.[6] In their experimental setup, relative reactivity values (RRVs) were established in competition experiments in which two donors were forced to compete for a limited amount of NIS/TfOH as the stoichiometric promoter in the presence of excess acceptor (MeOH). Although the kinetics of halonium-mediated thioglycoside activation are complex and not fully understood,[18−20] it is generally assumed that formation of an intermediate with oxacarbenium ion character from the charged thioglycoside is the rate-determining step in these reactions. To establish the relative donor reactivity of a series of mannopyranosyl uronic acids and mannopyranoside reference donors, we chose to use (*S*)-tolyl mannosides in combination with the NIS/TfOH promoter system, staying close to the system devised by Wong and co-workers.[6] The donors used in this study are depicted in Figure 2 and include a set of α-configured mannosides (**10α**, **11α**, and **12α**), a set of the analogous β-configured donors (**10*β***, **11*β***, and **12*β***), three C-2-azido mannosides (**10N**, **11N**, and **12N**), and 2,3-diazido- and 2-fluoromannuronic acid, **5** and **12F**, respectively. We employed methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **13** as a model acceptor glycoside. In our experiments, we used two donors, NIS, a catalytic amount of TfOH, and the acceptor in a molar ratio of 1:1:1:0.1:3. All condensations were performed under standardized conditions (0.05 M of donor in methylene chloride, −40 °C to rt). The crude product mixtures were purified by size exclusion chromatography to isolate the disaccharide fraction, and the relative ratios of the formed disaccharides were determined by NMR spectroscopy. The results of the competition experiments are summarized in Table 1.

From the series of reactions using the α-donors (entries 1−3), it becomes apparent that the 4,6-di-*O*-acetyl donor **10α** is the most reactive of the three α-donors surveyed, followed by the 4,6-benzylidene mannoside **11α**, with the mannuronic acid **12α** being the least reactive. Apparently, the combined torsional and electronic disarming effect of

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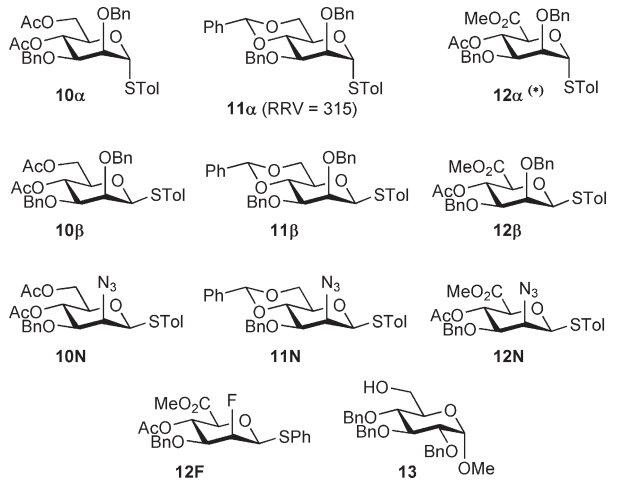

Figure 2. Donors and acceptor used in this study. (*) Donor **12α** exists as a 1:1.5 $^4C_1/^1C_4$ conformer mixture (see Supporting Information).

the benzylidene function in **11α**, which locks the C-6-*O*-substituent in the *tg* conformation,[21] renders this mannoside less reactive than mannosyl donor **10α**, having two electron-withdrawing acyl functions. The strong electron-withdrawing effect of the C-5 carboxylic acid ester in **12α** makes the mannuronate donor approximately 30 and 5 times less reactive than donor **10α** and **11α**. Interestingly, for the β-series (entries 4−6), the reactivity order is changed and mannuronic acid donor **12*β*** is 7 times more reactive than benzylidene donor **11*β***. In this series, diacyl donor **10*β*** is only twice as reactive as mannuronic acid **12*β***. For the 2-azido series, an analogous trend is seen (entries 7−9). Diacyl donor **10N** is more reactive than mannuronic acid **12N**, which in turn outcompetes benzylidene donor **11N**. To assess the reactivity of the 2,3-diazido- and 2-fluoromannuronates **5** and **12F**, these donors were competed with **3** and **1**, respectively, showing that the azide and fluorine substituents are equally disarming, as expected on the basis of their similar *F* values (0.48 vs 0.45). The introduction of two azides leads to a less reactive donor (entry 12), in line with expectations.

To verify the unexpectedly high reactivity of the β-mannuronic acid **12*β***, this donor competed with α-benzylidene mannoside **11α** and led to the predominant formation of the mannuronic acid disaccharide (entry 13). 2-Azidomannuronic acid **12N** also outcompeted α-configured **11α**, confirming the high reactivity of the β-anomer (entry 14). We have previously established that there is a substantial difference between the reactivity of α- and β-anomeric mannuronic acid donors.[12,13] For example, donors **3** and **5** (Figure 1) can be readily activated at −80 °C, whereas their α-configured counterparts require −40 and −10 °C for complete activation. This

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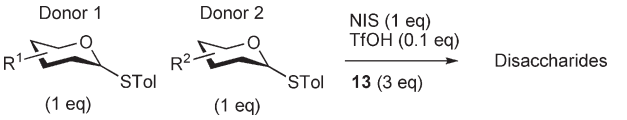
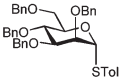
Table 1. Competing Donors in Glycosylation of **13**



entry	donor 1	donor 2	product ratio[a] donor 1:2	yield[c]
1	**10α**	**11α**	76:24	84%
2	**10α**	**12α**	97:3	55%
3	**11α**	**12α**	84:16	67%
4	**10β**	**11β**	88:12	99%
5	**10β**	**12β**	66:33	97%
6	**11β**	**12β**	13:87	88%
7	**10N**	**11N**	89:11	60%
8	**10N**	**12N**	66:33	68%
9	**11N**	**12N**	18:82	45%
10	**12β**	**12N**	99:1	99%
11[b]	**1**	**12F**	94:6	99%
12[b]	**3**	**5**	99:1	83%
13	**11α**	**12β**	4:96	94%
14	**11α**	**12N**	20:80	18%
15	**12β**	 **14** (RRV = 5000)	45:55	65%

[a] Product ratio was determined by NMR of the disaccharide mixtures. The disaccharides were obtained predominantly as β-anomers (see Supporting Information), except for the disaccharide derived from **14**. [b] (*S*)-Phenyl donors were used. [c] Combined yield of disaccharides.

reactivity difference was established here in a direct competition experiment in which **12α** and **12*β*** competed for activator. Since both donors lead to the same product, we determined the ratio of unreacted donor after the reaction, revealing that 9 times more α-donor **12α** than β-donor **12*β*** remained in the mixture. In a similar experiment involving donors **10α** and **10*β***, the reactivity difference between the anomers of the "non-oxidized" mannosyl donor **10** was shown to be smaller: after the coupling reaction, the unreacted α- and β-donors were recovered in a 61:39 ratio.

From the results described above, it is clear that the β-mannuronic acid donors are reactive glycosyl donors. Wong and co-workers have previously established that donor **11α** has a RRV of 315, on a scale in which the per-*O*-acetylated α-(*S*)-tolyl mannose donor has a relative reactivity of 1 and the most reactive perbenzylated α-(*S*)-tolyl mannoside (**14**) a RRV of 5000.[6] The result recorded in entry 13 of Table 1 indicates that the reactivity of mannuronic acid donor **12*β*** is actually of the same order of magnitude as the reactivity of the "armed" perbenzylated α-mannoside. This was confirmed in an experiment in which **12*β*** was made to compete with perbenzylated donor **14** (entry 15). The disaccharides formed from donors **12*β*** and **14**[22] were obtained in a 45:55 ratio, revealing the similar reactivity of both donors. We hypothesize that the unexpectedly high reactivity of **12*β*** results from the

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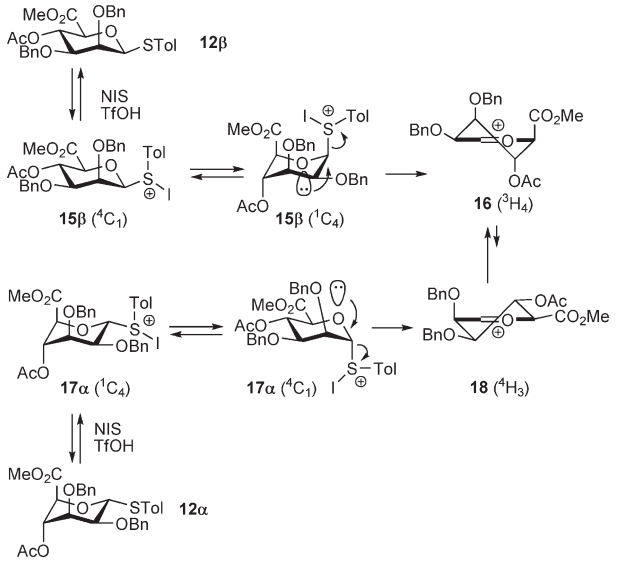
Scheme 1. Proposed Reaction Mechanism for the Formation of Oxacarbenium Ions **16** and **18**



fact that the β-mannuronic acid donor can relatively easily access the $^3H_4$-oxacarbenium ion **16** (Scheme 1).[23,24] This oxacarbenium ion is relatively stable because it positions all of its substituents in favorable orientations on the mannosyl half-chair. Woerpel and co-workers have shown that the substituents at C-3 and C-4 prefer to occupy pseudoaxial positions in the mannosyl oxacarbenium ion,[23] in line with various studies that axial substituents are less disarming than equatorial substituents.[25] They also established that the C-2 substituent has a slight preference for a pseudoequatorial position. We have reported that the C-5 carboxylic acid has a strong preference for a pseudoaxial position in an oxacarbenium ion intermediate.[10b,23c] As depicted in Scheme 1, reaction of donor **12*β*** with NIS and TfOH leads to the reversible formation of "charged" mannoside **15*β***. The phenylsulfenyl iodide aglycone can be expelled by the ring oxygen lone pair in an antiperiplanar fashion,[26] after the mannosyl ring flips to the $^1C_4$ conformation, to produce the favorable $^3H_4$-oxacarbenium ion **16**. Benzylidene donor **11** cannot access this favorable oxacarbenium ion conformation and is therefore less reactive. The lower reactivity of the α-anomer **12α** can also be accounted for using the oxacarbenium ion conformers **16** and **18**. After reaction of α-anomer **12α** with NIS/TfOH, the antiperiplanar expulsion of the charged aglycone from $^4C_1$ mannoside **17α** leads to the formation of the higher energy $^4H_3$-oxacarbenium ion **18**, making this a less favorable process than the formation of **16** from **12*β***.[27]

In conclusion, we have determined the relative reactivities of a series of mannuronic acid donors, and it is revealed that β-(*S*)-tolyl mannuronic acids are relatively reactive donors. The high reactivity of these donors contrasts the common perception that uronic acid donors are unreactive glycosylating agents because of the electron-withdrawing nature of the C-5 carboxylic acid ester function. It is postulated that the high reactivity of the mannuronic acids originates from the formation of a relatively favorable $^3H_4$-oxacarbenium ion-like intermediate. We have previously hypothesized that the β-selectivity, obtained in glycosylations using various mannuronic acid donors, originates (in part) from this oxacarbenium ion or a species with substantial oxacarbenium ion character. The high reactivity of the mannuronic acid donors lends support to this mechanism. The relatively high reactivity of the mannuronic acid donors opens the way to combine these donors in armed−disarmed coupling strategies using non-oxidized thioglycosides as the less reactive coupling partner. The investigation of the relative reactivity of other pyranosyl uronic acids will be reported in due course.

Acknowledgment. This work was supported by The Netherlands Organization of Scientific Research (NWO) and Top Institute Pharma (TIP).

Supporting Information Available. Experimental procedures for the synthesis of the donors and competition experiments. ^1H and ^{13}C spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) Differences in ground state energy also contribute to the reactivity difference between the α- and β-anomers. In D-mannopyranosides, the stabilizing anomeric effect is often at the basis of the higher stability and lower reactivity of the α-anomer with respect to its β-isomer. However, donor **12α**, predominantly occupying a $^1C_4$ conformation, does not benefit from a stabilizing anomeric effect. A difference in ground state energy of **12α** and **12*β*** can be caused by the destabilizing Δ2 effect present in **12*β***. Taken together, ground state energy differences can not alone account for the larger difference in reactivity between **12*β*** and **12α** compared to the reactivity difference between **10α** and **10*β***.