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On the Reactivity and Selectivity of Galacturonic Acid Lactones

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The reactivity and stereoselectivity of a galacturonic acid 3,6-lactone thioglycosyl donor, previously described as a highly reactive glycosylating agent, has been investigated by using a series of competition experiments and condensation reactions with different thiophilic activator systems. It is revealed that the relative reactivity of the thioglycosides depends on the activator system used and that *p*-nitrophenylsulfenyl triflate shows overall attenuated reactivity differences with respect to the commonly used *N*-iodosuccinimide/triflic acid promoter system. With respect to the stereoselectivity of the studied galacturonic acid 3,6-lactone thioglycosyl donor, it is revealed that a preactivation-based glycosylation system gives rise to α-selective glycosylation, whereas an in situ activation protocol leads to the formation of the β-product with good selectivity. It is hypothesized that these opposing stereoselectivities are the result of different product-forming intermediates. Where preactivation of the donor leads to the formation of an intermediate β-triflate, which is substituted in a concerted fashion to provide the α-product, a $^{3}H_{4}$ oxocarbenium ion like species is substituted in the in situ activation experiment to provide the β-linked product.

Introduction

Galacturonic acid and derivatives thereof are found in various naturally occurring polysaccharides. Due to the synthetic challenge they present and their interesting biological profile, several of these polysaccharides, such as pectin[1] and the zwitterionic polysaccharide Sp1,[2,3] have been the subject of synthetic studies. Selection of the most suitable glycosylation partners depends heavily on the desired stereochemical outcome of the glycosylation reaction, combined with the intrinsic reactivity of both reacting species. Conformational restriction of glycosyl donors has been used to influence both the stereoselectivity and reactivity of the donors at hand.[4] Crich and co-workers have shown that the installation of a 4,6-*O*-benzylidene-type protecting group on a mannosyl donor can give rise to a mannosylating agent that reacts with excellent stereoselectivity to provide β-mannosides.[5] The use of conformationally armed glycosides has been reported by various groups.[6] For instance, Bols and co-workers have shown that placing multiple bulky silyl ethers on the hydroxy groups of a glycosyl donor can lead to a conformational flip of the pyranosyl ring to avoid *gauche* interactions of the bulky protecting groups.[7] This provides "axially rich" donor glycosides, which are significantly more reactive than their non-flipped counterparts. These "super-armed" donors have extended the relative reactivity spectrum beyond the realm of classical armed donors. We have recently introduced galacturonic acid 3,6-lactones as versatile building blocks that can be used effectively in oligosaccharide synthesis.[3,8] The 3,6-lactone bridge forces these galacturonic acids in a $^{1}C_{4}$ chair conformation, which has a major impact on their reactivity, both as a donor and as an acceptor. Because of the $^{1}C_{4}$ conformation, the galactopyranosyl C4-OH group, which is generally regarded as a poor nucleophile,[9] is positioned in an accessible equatorial position and is therefore an apt nucleophile. We have also found that *S*-phenyl galacturonic acid 3,6-lactones, equipped with a nonparticipating C2-benzyl ether, are readily activated at low temperature with the diphenyl sulfoxide (Ph_2SO)/trifluoromethanesulfonic anhydride (Tf_2O) couple,[10] to provide a powerful glycosylating species that reacts with excellent stereoselectivity to provide the α-galacturonic linkage. To put the glycosylation behavior of galacturonic acid 3,6-lactone thioglycoside donors in perspective, we present herein a study of their reactivity and stereoselectivity in comparison with the reactivity of related galactose and galacturonic acid building blocks.

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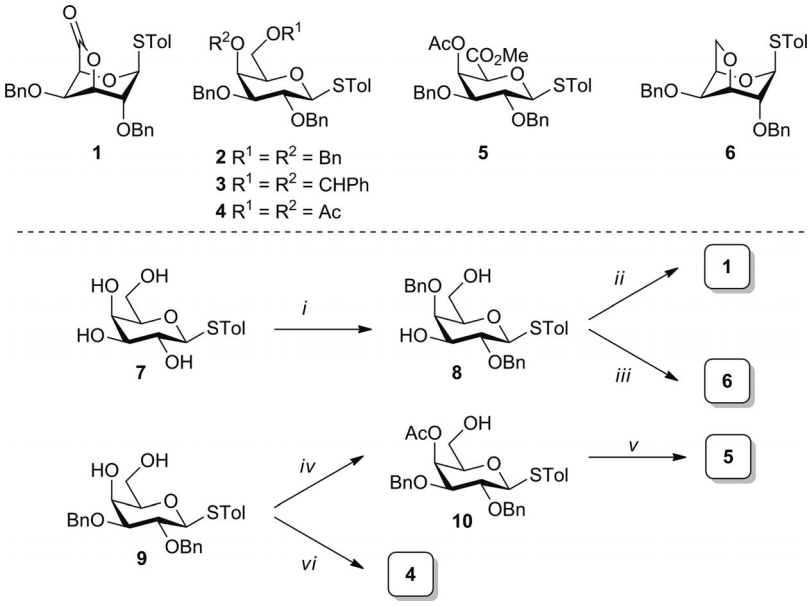
Results and Discussion

The set of building blocks used in this study is depicted in Scheme 1, and includes galacturonic acid 3,6-lactone



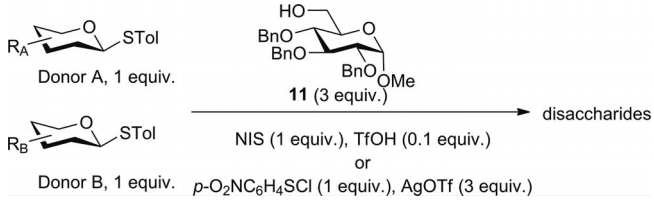
Scheme 1. Syntheses of the studied thiogalactosyl donors. Reagents and conditions: (i) 1. TBDMSCl, imidazole, DMF; 2. BnBr, NaH, DMF, 0 °C; 3. TBAF, THF, (66% over 3 steps); (ii) TEMPO, BAIB, CH_2Cl_2, H_2O, 51%; (iii) 1. TsCl, pyridine; 2. NaH, DMF (40% over 2 steps); (iv) 1. TBDMSCl, pyridine, then Ac_2O; 2. $Et_3N{\cdot}3HF$, THF (86% over 3 steps); (v) 1. TEMPO, BAIB, CH_2Cl_2, H_2O; 2. MeI, K_2CO_3, DMF (45% over 2 steps); (vi) Ac_2O, pyridine (81%).

thioglycoside **1**, perbenzylated thiogalactoside **2**,[11] 4,6-benzylidenethiogalactoside **3**,[11] 4,6-di-*O*-acetylthiogalactoside **4**, galacturonic acid thioglycoside **5**, and 3,6-anhydrothiogalactoside **6**. The latter compound has been included in our study to investigate the influence of the 3,6-bridge, and the resulting conformational flip, on the reactivity of these donors. The synthesis of donors **1**, **4**, **5**, and **6** is depicted in Scheme 1. Galacturonic acid lactone **1** was constructed from tolyl 1-thio-β-D-galactopyranoside **7** by regioselective silylation of the C6-OH and C3-OH groups and subsequent benzylation of the remaining hydroxy groups and desilylation to afford diol **8**. 2,2,6,6-Tetramethylpiperidine-1-oxyl (TEMPO)/[bis(acetoxy)iodo]benzene (BAIB) mediated[12] oxidation and in situ lactone formation yielded lactone **1**. Tosylation of the C6-OH group in diol **8** and treatment of the resulting tosylate with sodium hydride led to the formation of 3,6-anhydrothiogalactoside **6**. From 2,3-di-*O*-benzylthiogalactoside **9**, donors **4** and **5** were accessed through acetylation of both hydroxy functions (→ **4**) or a silylation, acetylation, desilylation, oxidation sequence (→ **5**).

We first set out to establish the relative reactivity of the set of donors. To gain more insight into the relative reactivity of glycosyl donors, Ley,[13] Wong,[11] and Bols[14] have determined the reactivity of a wide variety of thioglycosides in a series of competition experiments leading to an extensive relative reactivity value (RRV) scale. We have recently reported a determination of the relative reactivity of mannuronic[15] and glucuronic acid thioglycosyl donors.[16] In contrast to the common perception that the C-5 carboxylic acid ester is a strongly electron-withdrawing ("disarming") substituent, we found that in the β-*manno* series the C-5-carboxylate group (in combination with a 4-*O*-acetyl group) was in fact less disarming than the 4,6-*O*-benzylidene functionality. In the β-*gluco* series the effect of the carboxylate group was more in line with expectations, although the disarming nature proved to be less severe than often presumed. In the vast majority of competition experiments performed to date, thioglycoside donors have been combined with the *N*-iodosuccinimide (NIS)/triflic acid (TfOH) activator system. Therefore, we initially set out to probe the relative reactivity of the set of thiogalactosyl donors **1**–**6** under the aegis of this activator system. However, during the course of our investigation it became apparent that galacturonic acid lactone **1** was inert to this activator, and we therefore also studied the donors in a set of competition experiments by using *para*-nitrophenylsulfenyl triflate (*p*-NO_2PhSOTf),[17] generated from *para*-nitrophenylsulfenyl chloride (*p*-NO_2PhSCl) and silver triflate (AgOTf), as a thiophilic promoter system. We currently have no adequate explanation for the reluctance of donor **1** to react with NIS/TfOH, and note that this result is in contrast with a recent study reported by Furukawa et al.,[18] who investigated glucuronic acid 3,6-lactone donors in combination with this activator; they reported that thiophenyl 2,4-di-*O*-acetylglucuronic acid 3,6-lactone donors are reactive glucuronylating species when activated with NIS/TfOH, and that its 2,4-di-*O*-benzyl counterpart was too reactive to be used as a donor.

Table 1 compiles the results of the competition experiments. In both the NIS/TfOH- and *p*-$O_2NC_6H_4$SOTf-mediated glycosylation, the two donors compete for a limited amount of activator in the presence of excess nucleophile [methyl tri-*O*-benzyl-α-D-glucopyranoside (**11**)].

Table 1. Competitive glycosylation experiments between thioglycosyl donors **1**–**6**.

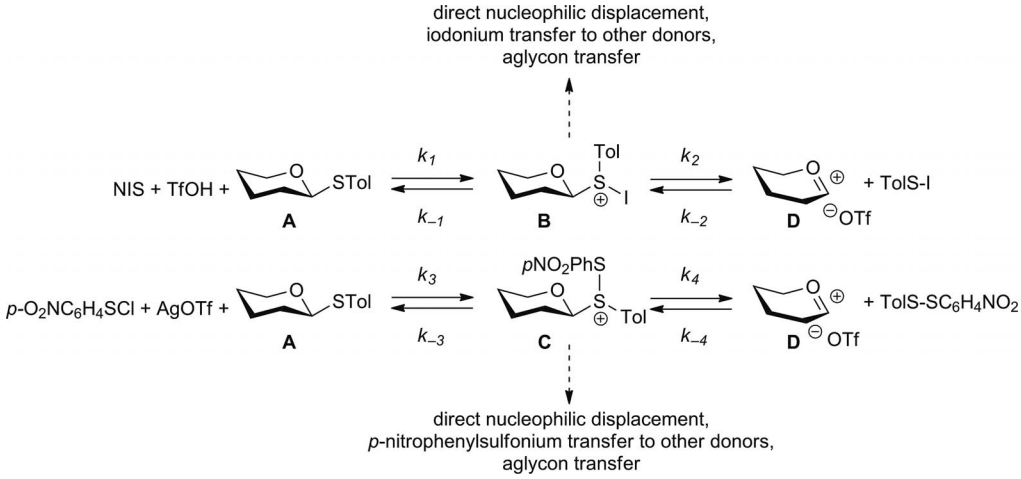


Entry	Donor A	Donor B	Product[a] ratio[b] (donor A/donor B) NIS/TfOH[c]	Yield [%]	p-$O_2NC_6H_4SCl$/AgOTf[c]	Yield [%]
1	**2**	**3**	2.2:1	70	1.8:1	87
2	**4**	**3**	1:5.2	95	1:1.1	85
3	**3**	**5**	16:1	86	4.8:1	80
4	**4**	**5**	11:1	86	1.3:1	81
5	**2**	**6**	1:1.3	quant.	1:1.2	quant.
6	**3**	**6**	1:2.5	99	1:2.2	quant.
7	**1**	**6**	–	–	1:2.4	quant.
8	**1**	**5**	–	–	1: 2.4	78

[a] For structures of the disaccharides, see the Supporting Information. [b] Product ratio was determined by integration of diagnostic ^1H NMR signals of the four possible disaccharides after size-exclusion chromatography. See the Supporting Information for full experimental details. [c] In CH_2Cl_2 at –40 °C to room temp.

From the series of NIS/TfOH-mediated experiments, the following relative reactivities appear. Perbenzylated donor **2** is twice as reactive as benzylidene donor **3** (Table 1, Entry 1); this result is consistent with the relative reactivities determined by Wong and co-workers (**2**: 17000; **3**: 7180).[11] The disarming effect of the 4,6-benzylidene group in **3** is less than the disarming effect of the two acetyl groups in **4**, as revealed in Table 1, Entry 2. Notably, in the *gluco* and *manno* series the 4,6-benzylidene group proved to be more deactivating than two acetyl groups at the C4- and C6-hydroxy moieties. These results can be explained by taking into account that the benzylidene group in galactosyl donor **3** imposes less strain on the pyranosyl ring when adopting a flattened structure to accommodate the developing positive charge at the anomeric center in an oxocarbenium ion or an oxocarbenium ion like intermediate. Furthermore, in the *cis*-decalin system in **3**, the C-6 substituent is positioned in a *gg* position, which is less disarming than the *tg* orientation of the C-6 substituent in the *gluco*- and *manno*-4,6-benzylidene donors.[19] Table 1, Entries 3 and 4 show that the C-5-carboxylic acid ester has a significant disarming effect on the reactivity of the donors studied,[20] and galacturonic acid **5** is the least reactive donor in the NIS/TfOH series. 3,6-Anhydrothiogalactosyl donor **6** is slightly more reactive than perbenzylated thiogalactoside **2** and presents the most reactive donor of the series. This is in line with previous studies on the glycosylation behavior of 3,6-anhydrogalactosyl orthoester donors, which were found to be more reactive than comparable orthoesters of glycosides in a normal conformation.[21] It is also of interest to note that Bols and co-workers have reported that forcing a galactosyl donor into an "axially rich" conformation, by positioning three bulky *tert*-butyldimethylsilyl ethers at C2, C3, and C4, leads to a more reactive donor.[7] A possible explanation for the fact that the reactivity of anhydrothiogalactosyl donor **6** is only marginally higher than the reactivity of perbenzylated thiogalactoside **2** can be that the conformational restriction in **6** prohibits the through-space stabilization of the developing oxocarbenium ion character by the substituents.[22]

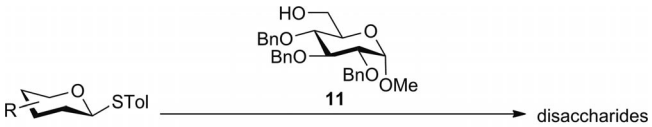
The series of competition reactions with p-$O_2NC_6H_4SCl$/AgOTf reveals the same trends as seen with the NIS/TfOH promoter,[23] albeit with significantly less pronounced reactivity differences. Thus, the reactivity order is 3,6-anhydro donor **6** > perbenzyl donor **2** > benzylidene donor **3** > diacetyl donor **4** > galacturonic acid donor **5**. The competition experiments with the galacturonic acid 3,6-lactone **1** indicate that this donor is less reactive than galacturonic acid **5**, which is in contrast to our perception of the high reactivity of these donors. This finding is also surprising in light of the "axial-rich" nature of this compound as compared to galacturonic acid **5**. The explanation put forward to account for the small increase in reactivity of 3,6-anhydrothiogalactoside **6**, with respect to thiogalactoside **2** (see above), can also be valid here. An explanation that accounts for the downturned reactivity differences found with the p-$O_2NC_6H_4SCl$/AgOTf system and the relatively low reactivity of the lactone donor can also be found in the differences in the rate constants involved in the activation of thioglycosides with the two different activator systems (Scheme 2). In case reversion of the charged thioglycosyl donor (**C** in Scheme 2) into the parent thioglycoside (**A**) and the activator (indicated with rate constant k_{-3}) for the p-$O_2NC_6H_4$-SOTf system is slower than the corresponding reversion with the NIS/TfOH system (species B and rate constant k_{-1}), the overall competition for the activator will be determined less by the relative ease of oxocarbenium ion (**D**) formation (k_2 and k_4).[24] In other words, the first step of the activation – the attack of the anomeric thio group on the electrophile – plays a relatively larger role in the p-$O_2NC_6H_4SOTf$-activated system and leads to the attenuated reactivity differences of the donors studied.



Scheme 2. Possible reaction pathways upon activation of thioglycosides by using p-$O_2NC_6H_4SOTf$ and NIS/TfOH.

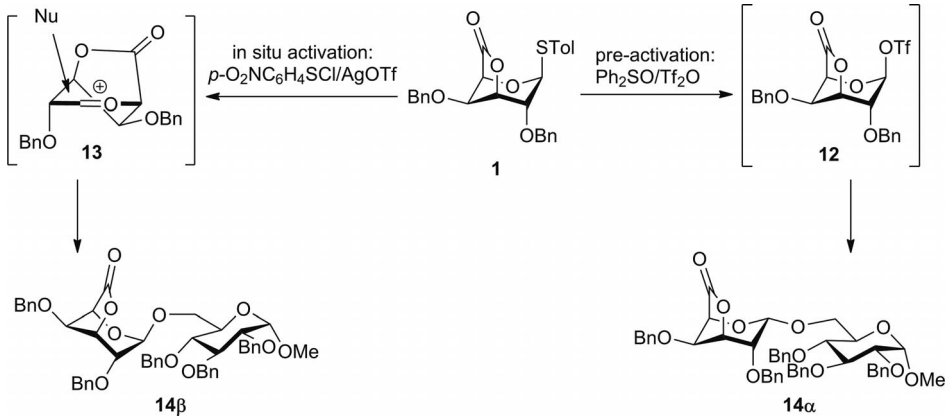
Next, we evaluated the stereoselectivity of the set of donors under the two different activation conditions with glucoside **11** as a nucleophile; Table 2 records the outcomes of these experiments. It is readily apparent from these results that most condensations proceed with very little to no selectivity, the most important exception being the p-$O_2NC_6H_4$-SOTf-mediated condensations of the bridged galacturonic acid lactone **1** and its non-oxidized counterpart 3,6-anhydrothiogalactoside **6**. The condensations of these donors and alcohol **11** proceed with very high (in the case of lactone **1**) or high (for the anhydrogalactoside **6**) stereoselectivity to provide the β-linked disaccharides. The former result stands in sharp contrast to our previous findings that galacturonic acid lactones such as **1** are highly α-selective glycosyl donors by using the Ph_2SO/Tf_2O preactivation protocol. It is now well appreciated that (pre)activation of thioglycosides with electrophiles featuring a triflate counterion can produce intermediate anomeric triflates. These species can be displaced in an S_N2-like process leading to the coupled product with inversion of configuration at the anomeric center (with regard to the intermediate anomeric triflate). We therefore studied the preactivation of donor **1** with the Ph_2SO/Tf_2O couple in a low-temperature NMR experiment. This experiment revealed that, with this activator system, donor **1** was rapidly transformed at –80 °C into β-triflate **12** (see Scheme 3 and Figure 1), which proved to be stable up to –10 °C. Having identified triflate **12** as a possible intermediate in the condensations of the galacturonic acid lactone donors, the contrasting stereochemical outcome of the condensations under Ph_2SO/Tf_2O preactivation and in situ activation with p-$O_2NC_6H_4SCl$ and AgOTf can be rationalized (Scheme 3). Preactivation of donor **1** leads to an intermediate triflate, which is substituted in a concerted fashion to provide the α-linked product. When donor **1** is activated in the presence of a reactive glycosyl acceptor such as **11**, the nucleophile can intercept the intermediate oxocarbenium ion **13**, which will adopt a structure that is close to a $^3H_4$ half chair because of the geometrical constraints imposed by the bridging lactone ring. Nucleophilic attack on this reactive species will occur preferentially from the diastereotopic face leading to the product through a chair-like transition state, i.e., the β-face. Notably, a similar stereochemical result has been reported for the condensation of acceptor **11** with pentenyl 2,4-di-*O*-benzyl-3,6-anhydroglucopyranoside.[25] To examine whether preactivation of 3,6-anhydrogalactopyranoside **6** can also lead to the α-linked disaccharide upon condensation with acceptor **11**, donor **6** was treated with Ph_2SO/Tf_2O at –80 °C, after which glucoside **11** was added. As revealed in Table 2, Entry 6, this condensation protocol indeed led to the predominant formation of the α-linked product, showing that 3,6-anhydrogalactopyranoside **6** and lactone **1** behave in a stereochemical analogous manner.

Table 2. Glycosylations of thioglycosyl donors **1**–**6** and glycosyl acceptor **11** by using different thiophilic activator systems.



Entry	Donor	Product[a] ratio[b] (α/β) and yield [%] NIS/TfOH[c]	p-$O_2NC_6H_4SCl$/AgOTf[c]	Ph_2SO/Tf_2O[d]
1	**1**		0:1 (73)	10:1 (69)
2	**2**	1:1.1 (99)	1:1.6 (quant.)	
3	**3**	1:1.2 (70)	1:1.8 (82)	
4	**4**	1:1.2 (76)	1:1.8 (94)	
5	**5**	1:1.3 (77)	1:3.4 (84)	
6	**6**	1.2:1 (65)	1:5.3 (quant.)	5.2:1 (70)

[a] For structures of the disaccharides, see the Supporting Information. [b] Anomeric ratios were determined by integration of ^1H NMR signals of the disaccharides. [c] In CH_2Cl_2 at –40 °C to room temp. [d] In the presence of 2,4,6-tri-*tert*-butylpyrimidine (TTBP) (2.5 equiv.) in CH_2Cl_2 at –50 °C, then acceptor **11**, warming to room temp.



Scheme 3. Rationale for the formation of the dimers **14α** and **14β** by using a preactivation and an in situ activation protocol.

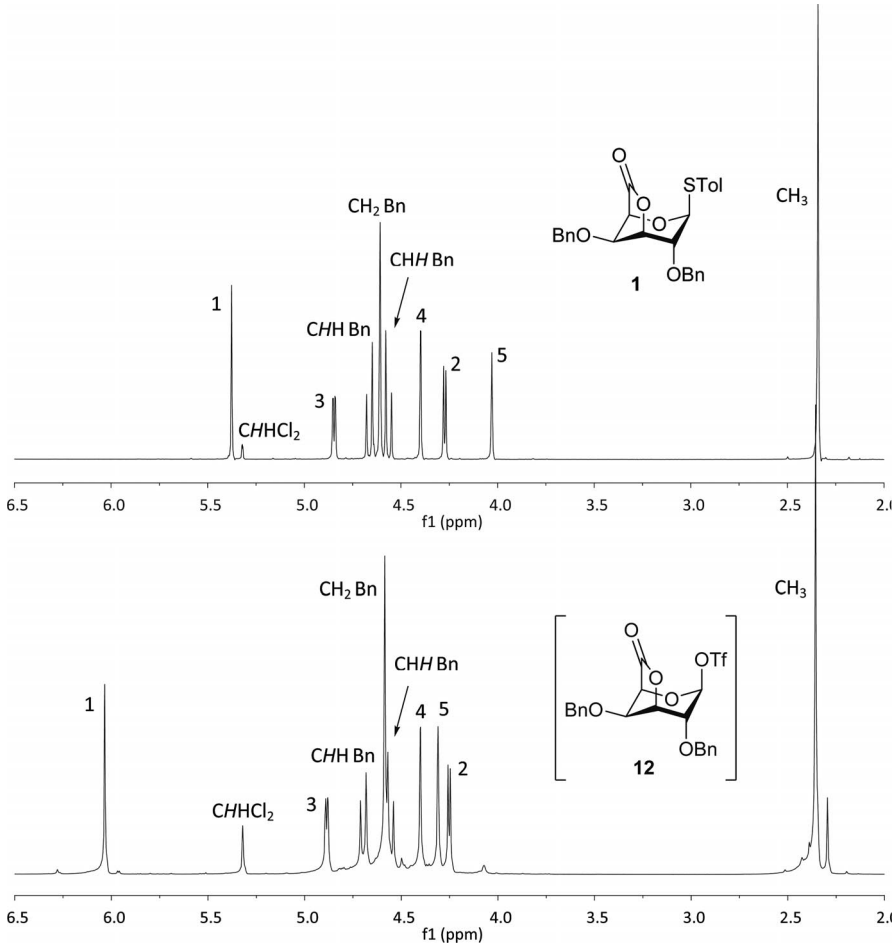


Figure 1. Part of the ^{1}H NMR spectrum of donor **1** obtained before and after treatment with Ph_2SO/Tf_2O in CD_2Cl_2 at –80 °C. The anomeric configuration of **12** was deduced from the $^1J_{C1–H1}$ coupling constant (189 Hz).[26]

Conclusions

We have investigated the reactivity and stereoselectivity of a galacturonic acid 3,6-lactone donor in comparison to a set of galactosyl donors using two different activator systems, NIS/TfOH and *p*-$O_2NC_6H_4SCl$/AgOTf, respectively. The mode of action not only affects the stereoselectivity of the glycosylation reactions reported here, but also has a significant effect on the relative reactivities of the studied galactosyl donors. The use of a *p*-$O_2NC_6H_4SCl$/AgOTf in situ activation protocol leads to attenuated reactivity differences with respect to the NIS/TfOH system. In the establishment of the relative reactivity of galacturonic acid 3,6-lactone donor **1**, only the *p*-$O_2NC_6H_4SCl$/AgOTf could be used, because lactone **1** proved to be completely inert to

activation with NIS/TfOH. By using the former activator, lactone donor **1** proved to be less reactive than the galacturonic acid donor **5**, revealing that, in this case, the relatively axial-rich conformation is not beneficial for reactivity. The use of the different thiophilic activator systems also led to greatly varying stereochemical outcomes. With the bridged lactone and anhydro donors **1** and **6**, both the α- and β-linked products can be selectively accessed depending on the activator system and the timing of the activation. Preactivation of these donors with Ph_2SO/Tf_2O provides α-selective glycosylations, presumably through the intermediacy of an axial β-triflate, whereas the in situ activation protocol with *p*-$O_2NC_6H_4SCl$/AgOTf leads to the corresponding β-products, through a direct substitution of an oxocarbenium ion like intermediate.

Experimental Section

General Procedure for Competitive and Noncompetitive NIS/TfOH-Promoted Glycosylation: The donor(s) (ca. 0.1 mmol, 1 equiv. each) and the acceptor (3 equiv.) were mixed in a round-bottomed flask and coevaporated twice with toluene. Freshly distilled CH_2Cl_2 (donor concentration 0.05 M) and activated molecular sieves (3 Å) were added, and the mixture was stirred under argon at room temperature for 30 min. NIS (1 equiv.) was added, and the mixture was cooled to –40 °C. TfOH (0.1 equiv., 0.1 M stock solution in distilled CH_2Cl_2) was added, and the mixture was warmed to 0 °C in about 3 h. Triethylamine (0.1 mL) was added, and the mixture was diluted with EtOAc, washed with satd. aq. $Na_2S_2O_3$ and brine, dried with Na_2SO_4, and concentrated in vacuo. Size exclusion chromatography on Sephadex LH-20 (CH_2Cl_2/MeOH, 1:1, v/v) enabled isolation of the disaccharide products and recovery of the monosaccharide fraction.

General Procedure for Competitive and Noncompetitive AgOTf/*p*-NO_2PhSCl-Promoted Glycosylation: A suspension of the donor(s) (ca. 0.11 mmol, 1 equiv. each), acceptor **11** (1.5–3 equiv.), silver triflate (72 mg, 0.33 mmol, ca. 3 equiv.), and molecular sieves (3 Å) in anhydrous CH_2Cl_2 (1 mL) was stirred, with the exclusion of light, at room temperature under Ar for 10 min before it was cooled to –40 °C. A solution of *p*-nitrobenzenesulfenyl chloride (95% purity, ca. 0.11 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (0.5 mL) was added dropwise into the above suspension at –40 °C, and the mixture was warmed to 0 °C in about 3 h. Triethylamine (0.2 mL) was added, and the suspension was diluted with CH_2Cl_2 and filtered through Celite. Size exclusion chromatography on Sephadex LH-20 (CH_2Cl_2/MeOH, 1:1, v/v) enabled isolation of the disaccharide products and recovery of a monosaccharide rest fraction.

General Procedure for Ph_2SO/Tf_2O-Promoted Glycosylation: A solution of the donor (ca. 0.11 mmol, 1 equiv.), diphenyl sulfoxide (1.2 equiv.) and tri-*tert*-butylpyrimidine (2.5 equiv.) in CH_2Cl_2 (0.05 M) was stirred in the presence of activated molecular sieves (3 Å) for 30 min. The mixture was cooled to –60 °C before triflic anhydride (1.1 equiv.) was added. The mixture was warmed to –50 °C in 15 min followed by addition of acceptor **11** (2 equiv.) in CH_2Cl_2 (0.15 M). The mixture was warmed to 0 °C in about 3 h, then triethylamine (0.5 mL) was added, and the mixture was diluted with CH_2Cl_2, washed once with satd. aq. $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2. The combined organic fractions were dried ($MgSO_4$), filtered, and concentrated in vacuo. Size exclusion chromatography on Sephadex LH-20 (CH_2Cl_2/MeOH, 1:1, v/v) enabled isolation of the disaccharide products and recovery of a monosaccharide rest fraction.

***p*-Tolyl 2,4-Di-*O*-benzyl-1-thio-β-D-galactopyranosidurono-3,6-lactone (1):** To a vigorously stirred mixture of **8** (5.39 g, 11.5 mmol, 1 equiv.) in CH_2Cl_2/H_2O (54 mL, 2:1, v/v) were added TEMPO (358 mg, 2.3 mmol, 0.2 equiv.) and iodobenzene diacetate (9.28 g, 28.8 mmol, 2.5 equiv.). After complete conversion, the reaction was quenched by the addition of 10% aq. $Na_2S_2O_3$ and satd. aq. $NaHCO_3$. The mixture was extracted twice with EtOAc, and the combined layers were dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography gave **1** (2.72 g, 5.88 mmol, 51%) as an oil. R_f = 0.46 (toluene). $[\alpha]_D^{22}$ = –192 (*c* = 1, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 2952, 1802, 1495, 1455, 1154, 1101, 813, 741, 699, 510 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): δ = 7.40–7.24 (m, 12 H, ArH), 7.11 (d, *J* = 8.0 Hz, 2 H, ArH), 5.34 (s, 1 H, 1-H), 4.80 (dd, *J* = 4.7, 1.3 Hz, 1 H, 3-H), 4.63 (d, *J* = 11.8 Hz, 1 H, CH_2 Bn), 4.58 (2 s, 2 H, CH_2 Bn), 4.53 (d, *J* = 11.8 Hz, 1 H, CH_2 Bn), 4.39 (d, *J* = 1.2 Hz, 1 H, 4-H), 4.25 (d, *J* = 4.7 Hz, 1 H, 2-H), 4.03 (br. s, 1 H, 5-H), 2.32 (s, 3 H, CH_3 Tol) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, HH-COSY, HSQC): δ = 172.7 (C=O), 138.5, 136.6, 136.5 (C_q), 133.3, 129.9, 129.7, 128.7, 128.6, 128.4, 128.2, 127.9, 127.8 (CH_{Ar}), 86.0 (C-1), 78.9 (C-3), 78.4 (C-2), 76.0 (C-4), 72.9, 71.4 (CH_2 Bn), 70.8 (C-5), 21.1 (CH_3 Tol) ppm. HRMS: calcd. for $C_{27}H_{26}O_5SNa$ $[M + Na]^+$ 485.13932; found 485.13905.

***p*-Tolyl 4,6-Di-*O*-acetyl-2,3-di-*O*-benzyl-1-thio-β-D-galactopyranoside (4):** A solution of **9** (4.00 g, 8.57 mmol) in pyridine/Ac_2O (60 mL, 3:1 v/v) was stirred at room temperature overnight. After complete conversion, the reaction was quenched by the addition of MeOH at 0 °C. The mixture was concentrated in vacuo, and the residue was taken up in EtOAc. The organic mixture was washed with 1 M aq. HCl, satd. aq. $NaHCO_3$, and brine, dried with $MgSO_4$, filtered, and concentrated in vacuo to give **4** (3.82 g, 6.94 mmol, 81%). R_f = 0.31 (EtOAc/PE, 1:4). $[\alpha]_D^{22}$ = +25 (*c* = 1, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 2870, 1745, 1494, 1454, 1370, 1229, 1104, 810, 737, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.24 (m, 12 H, ArH), 7.09 (d, *J* = 7.9 Hz, 2 H, ArH), 5.53 (d, *J* = 1.6 Hz, 1 H, 4-H), 4.81–4.69 (m, 3 H, CH_2 Bn), 4.63–4.57 (m, 1 H, 1-H), 4.49 (d, *J* = 11.0 Hz, 1 H, CH_2 Bn), 4.16 (d, *J* = 6.5 Hz, 2 H, 6-H), 3.81–3.74 (m, 1 H, 5-H), 3.68–3.60 (m, 2 H, 2-H, 3-H), 2.32 (s, 3 H, CH_3 Tol), 2.14 (s, 3 H, CH_3 Ac), 2.06 (s, 3 H, CH_3 Ac) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.5, 170.3 (C=O), 138.1, 137.8, 137.4 (C_q), 132.7, 129.5 (CH_{Ar}), 129.4 (C_q), 128.4, 128.3, 128.1, 127.8, 127.8 (CH_{Ar}), 87.9 (C-1), 81.0, 76.5 (C-2, C-3), 75.7 (CH_2 Bn), 74.3 (C-5), 72.0 (CH_2 Bn), 66.5 (C-4), 62.3 (C-6), 21.0 (CH_3 Tol), 20.8, 20.7 (CH_3 Ac) ppm. HRMS: calcd. for $C_{31}H_{34}O_7SNa$ $[M + Na]^+$ 573.19175; found 573.19140.

Methyl (*p*-Tolyl 4-*O*-acetyl-2,3-di-*O*-benzyl-1-thio-β-D-galactopyranoside)uronate (5): To a solution of **10** (1.70 g, 3.35 mmol, 1 equiv.) in CH_2Cl_2/H_2O (24 mL, 2:1, v/v), TEMPO (105 mg, 0.67 mmol, 0.2 equiv.) and BAIB (2.70 g, 8.38 mmol, 2.5 equiv.) were added. The reaction was quenched by the addition of 10% $Na_2S_2O_3$, and the mixture was extracted twice with CH_2Cl_2 and once with EtOAc. The combined extracts were dried with $MgSO_4$, filtered, and concentrated. To a solution of the crude acid in DMF (32 mL) were added K_2CO_3 (2.31 g, 16.75 mmol, 5 equiv.) and MeI (271 μL, 4.36 mmol, 1.3 equiv.). After complete conversion, the mixture was quenched with AcOH (1.9 mL), and the mixture was partitioned between EtOAc and H_2O. The organic layer was washed with satd. aq. $NaHCO_3$ and brine, dried with $MgSO_4$, filtered, and concentrated. Purification by column chromatography (EtOAc/PE, 3:17→1:4) gave **5** (45% over 2 steps). R_f = 0.56

(EtOAc/PE, 3:7). $[\alpha]_D^{22}$ = +25 (*c* = 5, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 1746, 1371, 1265, 1227, 1101, 1061, 1028, 810, 731, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.56 (dd, *J* = 8.1 Hz, 2 H, ArH), 7.39 (d, *J* = 7.0 Hz, 2 H, ArH), 7.36–7.22 (m, 8 H, ArH), 7.08 (d, *J* = 8.0 Hz, 2 H, ArH), 5.80 (s, 1 H, 4-H), 4.73 (m, 3 H, CH_2 Bn), 4.58 (d, *J* = 8.9 Hz, 1 H, 1-H), 4.47 (d, *J* = 11.1 Hz, 1 H, CH_2 Bn), 4.11 (s, 1 H, 5-H), 3.72 (s, 3 H, CH_3 OMe), 3.66 (s, 1 H, 3-H), 3.64 (s, 1 H, 2-H), 2.29 (s, 3 H, CH_3 Tol), 2.07 (s, 3 H, CH_3 OAc) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.6, 166.9 (C=O), 137.9, 137.7, 137.1 (C_q), 133.0, 129.3 (CH_{Ar}), 128.9 (C_q), 128.2, 128.1, 127.9, 127.6, 127.5 (CH_{Ar}), 87.5 (C-1), 80.3 (C-3), 75.8 (C-2), 75.4 (CH_2 Bn), 75.2 (C-5), 71.7 (CH_2 Bn), 67.4 (C-4), 52.3 (CH_3 OMe), 20.8 (CH_3 Tol), 20.5 (CH_3 OAc) ppm. HRMS: calcd. for $C_{30}H_{32}O_7SNa$ $[M + Na]^+$ 559.17610; found 559.17566.

***p*-Tolyl 3,6-Anhydro-2,4-di-*O*-benzyl-β-D-galactopyranoside (6):** To a solution of **8** (3.9 g, 8.25 mmol, 1 equiv.) in pyridine (41 mL) was added tosyl chloride (1.75 g, 9.08 mmol, 1.1 equiv.) at 0 °C. The mixture was stirred under argon at room temperature for 3 d, then the reaction was quenched by the addition of MeOH (3.3 mL), and the mixture was partitioned between EtOAc and aq. 1 M HCl solution. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with satd. aq. $NaHCO_3$ solution, H_2O, and brine, dried with $MgSO_4$, filtered, and concentrated. The crude product was dissolved in DMF (100 mL), and NaH (60% in mineral oil, 300 mg, 12.4 mmol, 1.5 equiv.) was added at 0 °C. The mixture was stirred at room temperature overnight, then partitioned between H_2O and diethyl ether and the aqueous layer was extracted. The combined organic layers were washed with satd. aq. $NaHCO_3$ solution, H_2O, and brine, dried with $MgSO_4$, filtered, and concentrated. Flash column chromatography (EtOAc/PE, 1:19→1:4) afforded **6** (1.6 g, 3.5 mmol, 40% over 2 steps). R_f = 0.6 (EtOAc/PE, 3:7, v/v). $[\alpha]_D^{22}$ = –21 (*c* = 1, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 2938, 1494, 1455, 1069, 805, 738, 698, 632, 536 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.27 (m, 10 H, ArH), 7.27–7.22 (m, 2 H, ArH), 7.09 (d, *J* = 8.0 Hz, 2 H, ArH), 5.28 (s, 1 H, 1-H), 4.84 (d, *J* = 9.6 Hz, 1 H, 6-H), 4.62–4.52 (m, 3 H, CH_2 Bn), 4.46–4.43 (m, 2 H, 3-H, CH_2 Bn), 4.37 (br. s, 1 H, 5-H), 4.28 (d, *J* = 1.7 Hz, 1 H, 4-H), 4.10 (d, *J* = 5.9 Hz, 1 H, 2-H), 3.96 (dd, *J* = 9.6, 2.7 Hz, 1 H, 6-H), 2.31 (s, 3 H, CH_3 Tol) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.6, 137.3, 137.1, 132.3 (C_q), 131.1, 129.7, 129.7, 128.4, 128.4, 127.9, 127.8, 127.7, 127.6, 125.2 (CH_{Ar}), 84.9 (C-1), 82.1 (C-2), 77.9 (C-4), 77.6 (C-3), 76.9 (C-5), 72.4, 71.1 (CH_2 Bn), 69.9 (C-6), 21.0 (CH_3 STol) ppm. HRMS: calcd. for $C_{27}H_{28}O_4SNa$ $[M + Na]^+$ 471.16005; found 471.15984.

***p*-Tolyl 2,4-Di-*O*-benzyl-1-thio-β-D-galactopyranoside (8):** To a mixture of **7** (7.3 g, 25.4 mmol, 1 equiv.) in DMF (130 mL) were added imidazole (6.1 g, 88.9 mmol, 3.5 equiv.) and TBSCl (11.5 g, 76.2 mmol, 3 equiv.). After stirring for 2 h, TLC analysis showed complete consumption of the starting material. The reaction was quenched by the addition of MeOH (3 mL) and partitioned between H_2O and EtOAc. The aqueous layer was extracted, and the combined organic phases were washed with aq. 1 M HCl, satd. aq. $NaHCO_3$, and brine, dried with $MgSO_4$, filtered, and concentrated. The crude product was dissolved in DMF (130 mL), and benzyl bromide (9.1 mL, 76.2 mmol, 3 equiv.) and NaH (60% in mineral oil, 3.11 g, 76.2 mmol, 3 equiv.) were added at 0 °C. After stirring at ambient temperature overnight, the reaction was quenched by the addition of MeOH at 0 °C, and the mixture was taken up in Et_2O, washed with 5% aq. LiCl and brine. After drying with $MgSO_4$, filtration, and concentration under reduced pressure, the residue was dissolved in THF (34 mL) and treated with TBAF (1 M in THF, 102 mL, 101.6 mmol, 4 equiv.). The mixture was stirred for 3 h and subsequently partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc, and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. Purification by flash column chromatography (EtOAc/PE, 3:7→1:1) afforded **8** (7.9 g, 16.9 mmol, 66% over 3 steps). R_f = 0.2 (EtOAc/PE, 3:7). $[\alpha]_D^{22}$ = +2 (*c* = 1, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3420, 2868, 1494, 1454, 1358, 1055, 866, 809, 734, 697, 530 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 8.1 Hz, 2 H, ArH), 7.40–7.26 (m, 10 H, ArH), 7.05 (d, *J* = 8.0 Hz, 2 H, ArH), 4.92 (d, *J* = 10.9 Hz, 1 H, CH_2 Bn), 4.76 (d, *J* = 11.6 Hz, 1 H, CH_2 Bn), 4.66–4.60 (m, 2 H, CH_2 Bn), 4.58–4.51 (m, 1 H, 1-H), 3.84 (dd, *J* = 11.3, 7.3 Hz, 1 H, 6-H), 3.75 (s, 1 H, 4-H), 3.69–3.65 (m, 2 H, 2-H, 3-H), 3.59–3.50 (m, 1 H, 6-H), 3.44 (dd, *J* = 6.8, 5.4 Hz, 1 H, 5-H), 2.43 (s, 1 H, OH), 2.31 (s, 3 H, CH_3 STol), 2.05 (s, 1 H, OH) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.1 (C_q), 138.0 (C_q), 137.4 (C_q), 132.7, 131.9 (CH_{Ar}), 129.9 (C_q), 129.7, 128.5, 128.4, 128.2, 128.2, 128.0, 128.0, 127.9, 127.6 (CH_{Ar}), 87.5 (C-1), 78.9 (C-5), 78.2 (C-2), 75.8, 75.7 (C-3, C-4), 75.2, 74.7 (CH_2 Bn), 62.1 (C-6), 21.0 (CH_3 Tol) ppm. HRMS: calcd. for $C_{27}H_{30}O_5SNa$ $[M + Na]^+$ 489.17062; found 489.17017.

***p*-Tolyl 4-*O*-Acetyl-2,3-di-*O*-benzyl-1-thio-β-D-galactopyranoside (10):** To a solution of **9** (1.74 g, 3.72 mmol, 1 equiv.) in pyridine (20 mL) was added TBDMSCl (673 mg, 4.46 mmol, 1.2 equiv.), and the reaction mixture was stirred at room temperature overnight. Ac_2O (5 mL) was added, and the reaction mixture was stirred overnight again. The reaction was quenched by the addition of MeOH (10 mL), and the solvent was removed under reduced pressure. The crude material was coevaporated with toluene and dissolved in THF (20 mL). TEA·3HF (4.85 mL, 29.8 mmol, 8 equiv.) was added, and the reaction mixture was stirred at 70 °C for 1 h. The reaction mixture was allowed to cool to room temperature and partitioned between EtOAc and satd. aq. $NaHCO_3$. The aqueous phase was extracted with EtOAc, and the combined organic layers were washed with satd. aq. $NaHCO_3$ and brine. After drying with $MgSO_4$, filtration, and concentration, the crude mixture was purified by column chromatography (EtOAc/PE, 1:4→2:3) to yield **10** (1.64 g, 3.21 mmol, 86% over 3 steps). R_f = 0.21 (EtOAc/PE, 3:7). $[\alpha]_D^{22}$ = +17 (*c* = 1, CH_2Cl_2). IR (neat): $\tilde{\nu}$ = 3462, 2870, 1741, 1494, 1454, 1369, 1232, 1090, 734, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC): δ = 7.50–7.22 (m, 12 H, ArH), 7.08 (d, *J* = 8.0 Hz, 2 H, ArH), 5.46 (d, *J* = 2.6 Hz, 1 H, 4-H), 4.81–4.70 (m, 2 H, CH_2 Bn), 4.67 (d, *J* = 11.2 Hz, 1 H, CH_2 Bn), 4.61 (d, *J* = 9.0 Hz, 1 H, 1-H), 4.50 (d, *J* = 11.2 Hz, 1 H, CH_2 Bn), 3.74–3.61 (m, 3 H, 6-H, 2-H, 3-H), 3.57 (t, *J* = 6.4 Hz, 1 H, 5-H), 3.50 (dd, *J* = 11.2, 6.2 Hz, 1 H, 6-H), 2.67 (s, 1 H, OH), 2.30 (s, 3 H, CH_3 Tol), 2.13 (s, 3 H, CH_3 Ac) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, HH-COSY, HSQC): δ = 171.2 (C=O), 138.0, 137.7, 137.3 (C_q), 132.4, 129.5 (CH_{Ar}), 129.3 (C_q), 128.3, 128.2, 128.0, 127.9, 127.8, 127.7 (CH_{Ar}), 87.7 (C-1), 80.8 (C-3), 77.1 (C-5), 76.7 (C-2), 75.6, 71.8 (CH_2 Bn), 67.0 (C-4), 60.8 (C-6), 21.0 (CH_3 Ac), 20.7 (CH_3 STol) ppm. HRMS: calcd. for $C_{29}H_{32}O_6SNa$ $[M + Na]^+$ 531.18118; found 531.18093.

Methyl *O*-(2,4-Di-*O*-benzyl-β-D-galactopyranosylurono-3,6-lactone)-(1→6)-2,3,4-tri-*O*-benzyl-α-glucopyranoside (14β): Prepared according to the procedure described for AgOTf/*p*-$NO_2C_6H_4SCl$-promoted glycosylation by using donor **1** (49 mg, 109 μmol) and acceptor **11** (77 mg, 165 μmol, 1.5 equiv.). The β-coupled product was obtained in 73% yield (64 mg, 79 μmol), whereas its α-configured epimer was observed in trace amounts only. R_f = 0.7 (EtOAc/PE, 3:7, v/v). IR (neat): $\tilde{\nu}$ = 2919, 1800, 1498, 1454, 1362, 1058, 1028, 927, 736, 696, 531, 458, 354 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.16 (m, 25 H, ArH), 4.96 (d, *J* = 10.8 Hz, 1 H, CH_2 Bn), 4.89–4.83 (m, 2 H, 1′-H, CH_2 Bn), 4.80–4.74 (m, 2 H, CH_2 Bn), 4.73 (dd, *J* = 4.6, 1.3 Hz, 1 H, 3′-H), 4.65 (d, *J* = 12.1 Hz,

1 H, CH_2 Bn), 4.58–4.49 (m, 5 H, 1-H, CH_2 Bn), 4.42 (d, J = 11.8 Hz, 1 H, CH_2 Bn), 4.33 (d, J = 0.9 Hz, 1 H, 4′-H), 4.03–3.95 (m, 3 H, 3-H, 2′-H, 5′-H), 3.91 (dd, J = 11.1, 1.9 Hz, 1 H, 6-H), 3.83–3.77 (m, 1 H, 5-H), 3.53–3.43 (m, 2 H, 2-H, 6-H), 3.35 (s, 3 H, CH_3 OMe), 3.27 (dd, J = 10.0, 9.0 Hz, 1 H, 4-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.8 (C=O), 138.6, 138.1, 136.8, 136.7 (C_q), 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5 (CH_{Ar}), 100.3 (C-1′), 97.7 (C-1), 81.8 (C-3), 79.9 (C-2), 78.6 (C-3′), 78.3 (C-4), 77.2 (C-2′), 75.9 (C-4′), 75.7, 74.5, 73.3, 72.8, 71.2 (CH_2 Bn), 70.6 (C-5′), 69.7 (C-5), 67.6 (C-6), 55.0 (CH_3 OMe) ppm. ^{13}C-HMBC NMR (100 MHz, $CDCl_3$): δ = 100.3 ($J_{C1'\beta,H1'\beta}$ = 172.8 Hz, C-1′), 97.7 ($J_{C1\beta,H1\beta}$ = 167.8 Hz, C-1) ppm. HRMS: calcd. for $C_{48}H_{50}O_{11}Na$ $[M + Na]^+$ 825.32453; found 825.32458.

Methyl *O*-(2,4-Di-*O*-benzyl-α-D-galactopyranosylurono-3,6-lactone)-(1→6)-2,3,4-tri-*O*-benzyl-α-glucopyranoside (14α): Prepared according to the procedure described for Ph_2SO/Tf_2O-promoted glycosylation by using donor **1** (46 mg, 100 μmol, 1 equiv.) and acceptor **11** (93 mg, 0.2 mmol, 2 equiv.). This gave a 10:1 α/β mixture (55 mg, 69 μmol, 69%). IR (neat): $\tilde{\nu}$ = 694, 734, 979, 1026, 1141, 1203, 1355, 1436, 1759 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ (α-coupled product) = 3.22 (s, 3 H, CH_3 OMe), 3.42 (dd, J = 10.0, 3.5 Hz, 1 H, 2-H), 3.54 (t, J = 9.5 Hz, 1 H, 4-H), 3.68 (d, J = 11.0 Hz, 1 H, 6-H), 3.73 (d, J = 9.5 Hz, 1 H, 5-H), 3.97 (t, J = 9.5 Hz, 1 H, 3-H), 4.00 (br. s, 1 H, 2′-H), 4.11 (s, 1 H, 5′-H), 4.19 (dd, J = 11.0, 3.5 Hz, 1 H, 6-H), 4.44 (s, 1 H, 4′-H), 4.54 (s, 1 H, 1-H), 4.55 (s, 2 H, CH_2Ph), 4.57 (d, J = 12.5 Hz, 1 H, CH*H*Ph), 4.62 (d, J = 12.0 Hz, 1 H, CH*H*Ph), 4.65 (d, J = 10.0 Hz, 1 H, CH*H*Ph), 4.69 (d, J = 5.0 Hz, 1 H, 3′-H), 4.76 (d, J = 10.5 Hz, 1 H, C*H*HPh), 4.79 (d, J = 12.0 Hz, 1 H, C*H*HPh), 4.83 (d, J = 11.0 Hz, 1 H, CH*H*Ph), 4.89 (s, 1 H, 1′-H), 4.90 (d, J = 12.5 Hz, 1 H, C*H*HPh), 4.96 (d, J = 11.0 Hz, 1 H, C*H*HPh), 7.24–7.65 (m, 25 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.1 (CH_3 OMe), 68.5 (C-6), 69.8 (C-5), 71.9 (C-5′), 71.6 (CH_2 Bn), 73.3 (CH_2 Bn), 74.2 (CH_2 Bn), 74.4 (C-2′), 75.1 (CH_2 Bn), 76.0 (C-4′), 77.7 (C-4), 79.9 (C-2), 80.2 (C-3′), 81.7 (C-3), 98.0 (C-1), 98.8 (C-1′), 124.7–130.9 (CH_{Ar}), 136.7 (C_q Bn), 137.5 (C_q Bn), 138.0 (C_q Bn), 138.1 (C_q Bn), 138.7 (C_q Bn), 171.6 (C=O lactone) ppm. ^{13}C-GATED NMR (125 MHz, $CDCl_3$): 98.0 ($J_{C1,H1}$ = 161 Hz, C-1), 102.4 ($J_{C1',H1'}$ = 163 Hz, C-1′). MS (ESI): m/z = 825.3 $[M + Na]^+$.

2,4-*O*-Dibenzyl-β-D-galacturonic Acid 3,6-Lactone Triflate (12): Uronic acid lactone donor **1** (13 mg, 30 μmol, 1 equiv.) and Ph_2SO (8 mg, 39 μmol, 1.3 equiv.) were coevaporated with toluene (2×). The residue was dissolved in CD_2Cl_2 (0.6 mL) and transferred to an NMR tube under argon. The NMR probe was cooled to –80 °C, and the sample was locked and shimmed. In an acetone/dry ice bath (–80 °C) the sample was treated with Tf_2O (39 μmol, 1.3 equiv.), shaken thrice and placed back into the NMR magnet. The stability of the observed anomeric triflate **12** was checked by repeatedly allowing the temperature to rise by 10 °C and recording the ^1H NMR spectrum. The triflate was stable up to –10 °C. ^1H NMR (400 MHz, CD_2Cl_2, T = 193 K): δ = 6.06 (s, 1 H, 1-H), 4.91 (d, J = 4.5 Hz, 1 H, 3-H), 4.69 (d, J = 11.4 Hz, 1 H, CH_2 Bn), 4.61–4.50 (m, 3 H, CH_2 Bn), 4.40 (s, 1 H, 4-H), 4.35 (s, 1 H, 5-H), 4.27 (d, J = 4.6 Hz, 1 H, 2-H) ppm. ^{13}C NMR (100 MHz, CD_2Cl_2, HH-COSY, HSQC, T = 193 K): δ = 170.4 (C=O), 104.2 (C-1), 77.5 (C-3), 75.1 (C-2), 73.4 (C-4), 73.1, 71.1 (CH_2 Bn), 71.0 (C-5) ppm. ^{13}C-GATED NMR (125 MHz, $CDCl_3$): δ = 104.2 ($J_{C1,H1}$ = 189 Hz).

Supporting Information (see footnote on the first page of this article): Experimental procedures for the glycosylations and 1D and 2D NMR spectra.

Acknowledgment

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[1] For examples of syntheses of pectin fragments and for the use of uronic acids in synthesis in general, see: J. D. C. Codée, A. E. Christina, M. T. C. Walvoort, H. S. Overkleeft, G. A. van der Marel, *Top. Curr. Chem.* **2011**, *301*, 253–289.
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[22] When 3,6-anhydrothiogalactoside **6** is regarded as a deoxy sugar, the anhydro bridge does not seem to contribute favorably to the reactivity of the donor. For comparison: Wong and co-workers[11] have established that perbenzylated fucose (RRV 72000) is four times as reactive as the corresponding perbenzylated galactosyl donor.

[23] The RRVs in the *p*-$NO_2C_6H_4SCl$/AgOTf glycosylations do not show a quantitative correlation throughout the series, and therefore our analysis is limited to the trends observed in this series.

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[26] The $^1J_{C1,H1}$ coupling constant for an equatorial anomeric proton is generally larger (by approximately 10 Hz) than that of the corresponding axial anomeric proton. In analogy to the coupling constant obtained for 4,6-*O*-benzylidene-2,3-*O*-methyl-α-D-mannosyl triflate ($^1J_{C1,H1}$ = 185 Hz), having an equatorially oriented anomeric proton (D. Crich, S. Sun, *J. Am. Chem. Soc.* **1997**, *119*, 11217–11223), and the $^1J_{C1,H1}$ coupling constant in methyl (4-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy mannopyranosyl uronosyl) triflate, having an axially oriented proton when adopting a $^1C_4$ conformation ($^1J_{C1,H1}$ = 177 Hz) (M. T. C. Walvoort, G. Lodder, J. Mazurek, H. S. Overkleeft, J. D. C. Codée, G. A. van der Marel, *J. Am. Chem. Soc.* **2009**, *131*, 12080–12081), the large value for the $^1J_{C1,H1}$ coupling constant in **12** is indicative of an axial triflate.

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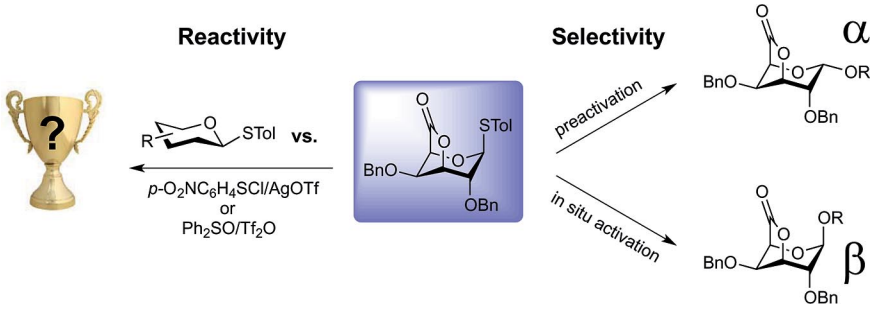
Glycosylation Reactivity and Selectivity



The reactivity and stereoselectivity of a galacturonic acid 3,6-lactone thioglycosyl donor has been investigated by using thiophilic activator systems. The reactivity of the thioglycosides depend on the activator system used. The stereoselectivity arises from preactivation of the glycosylation system, giving rise to α-selective glycosylation, whereas in situ activation gives the β-product.

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On the Reactivity and Selectivity of Galacturonic Acid Lactones

Keywords: Lactones / Glycosides / Glycosylation / Chemoselectivity / Diastereoselectivity

