On the reactivity and selectivity of donor glycosides in glycochemistry and glycobiology

Walvoort, M.T.C.

Chapter 5

Mannopyranosyl Uronic Acid Donor Reactivity

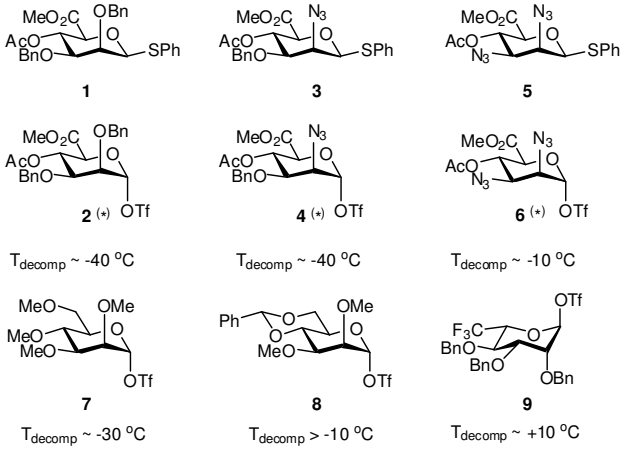
Introduction

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 (relative) 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, and the nature and position of the substituents.[7] Recently, Bols and co-workers have shown that "super-armed" donors can be conceived by forcing the carbohydrate ring substituents in *pseudo*-axial orientations, making the electronegative substituents less deactivating.[8] In general, uronic acid donors, *i.e.* glycosyl pyranosides of which the C-6 is

Partly published in: Walvoort, M. T. C.; de Witte, W.; van Dijk, J.; Dinkelaar, J.; Lodder, G.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *Org. Lett.* **2011**, *13*, 4360-4363

oxidized to a carboxylic acid function, are regarded to be amongst the most unreactive donors by virtue of the electron-withdrawing nature of the appended carboxylic acid ester functionality (F-value$_{COOMe}$ = 0.34; F-value$_{CH2OH}$ = 0.03).[9,10] The previous Chapters deal with the activation and glycosylation behavior of a series of diversely substituted mannuronic acid donors, including mono- and di-azido mannuronic acids.[11] It was 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 remarkable. The latter became apparent in detailed NMR experiments to study the formation of anomeric triflates by the sulfonium ion mediated pre-activation of mannuronic acid donors. 2,3-Di-*O*-benzyl mannuronate donor **1** was rapidly activated using Ph_2SO-Tf_2O at low temperature (-80 ºC) to give mannosyl triflate **2** which could be used as a glycosylating species at the same low temperature (Figure 1).[11a] Analogous results were obtained for the mono- and di-azido mannuronates **3** and **5**, which contain, in addition to the "disarming" C-5 carboxylate, electron-withdrawing azide functionalities at C-2/3 (F-value$_{N3}$ = 0.48).[10] Triflates **4** and **6** were rapidly formed at -80 ºC from their respective donors, and shown to be apt glycosylating species.[11bc,12] 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*-methyl mannosyl triflate **7**,[13] 4,6-*O*-benzylidene-2,3-di-*O*-methyl mannosyl triflate **8**,[13] and 6,6,6-trifluoro mannosyl triflate **9**[14] (F-value$_{CF3}$ = 0.38)[10] are -30 ºC, -10 ºC, and +10 ºC, 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,[15] their relative reactivity with respect to their non-oxidized counterparts was investigated, and is presented in this Chapter.

Figure 1. Previously studied mannuronic acid donors and mannosyl triflates

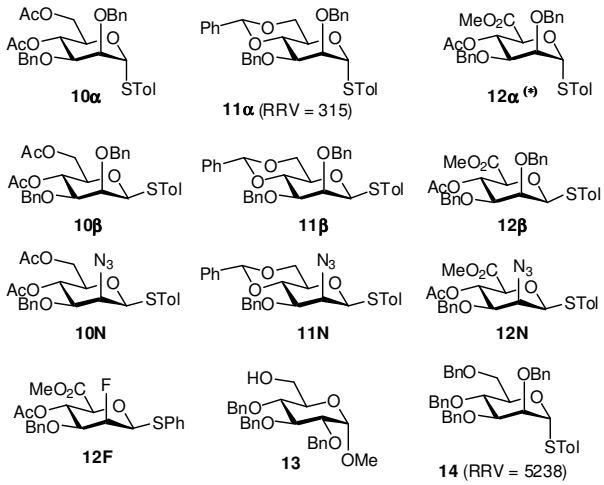


(*) Triflates **2**, **4** and **6** exist as a conformational $^4C_1/^1C_4$ mixture[11]

Results and Discussion

The most extensive donor reactivity study to date has been reported by Wong and co-workers, who quantified the reactivity of more than a hundred *S*-tolyl glycosides.[6] In their experimental set-up, 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,[16,17,18] 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, a set of *S*-tolyl mannosides was selected 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 (**10β**, **11β** and **12β**), three C-2-azido mannosides (**10N**, **11N** and **12N**) and 2,3-diazido- and 2-fluoro mannuronic acid, **5** (Figure 1) and **12F**, respectively. Methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **13** was selected as a model acceptor glycoside. In a general experimental set-up to probe glycosylation efficiency in a competitive manner, every glycosylation reaction employed two donors (**A** and **B**), 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 ºC 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 Tables 1-3.[19,20]

Figure 2. Donors and acceptor used in this study



(*) Donor **12α** exists as a 1:1.5 mixture of $^4C_1$:$^1C_4$ conformers

Table 1. Results of the competing α-thio donors in glycosylation with **13**

Entry	Donor **A**	Donor **B**	Product ratio donor **A** : **B** [a]	Yield (%)
1	**10α**	**11α**	76 : 24	84
2	**10α**	**12α**	97 : 3	55
3	**11α**	**12α**	84 : 16	67

[a] Product ratio was determined by NMR of the disaccharide mixtures. The disaccharides were predominantly obtained as the β-anomers (see Experimental Section)

From the series of reactions using the α-donors (Table 1) it became 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[21] and electronic disarming effect of the benzylidene function in **11α**, which locks the C-6-*O*-substituent in the *tg* conformation,[22] 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**, respectively. Interestingly, for the β-series (Table 2) the reactivity order is changed and mannuronic acid donor **12β** is 7 times more reactive than benzylidene donor **11β**. In this series, diacyl donor **10β** is only twice as reactive as mannuronic acid **12β**. For the 2-azido series an analogous trend is seen (Table 2, entries 4-6). Diacyl donor **10N** is more reactive than mannuronic acid **12N**, which in turn outcompetes benzylidene donor **11N**.

Table 2. Results of the competing β-thio donors in glycosylation with **13**

Entry	Donor **A**	Donor **B**	Product ratio donor **A** : **B** [a]	Yield (%)
1	**10β**	**11β**	88 : 12	99
2	**10β**	**12β**	66 : 33	97
3	**11β**	**12β**	13 : 87	88
4	**10N**	**11N**	89 : 11	60
5	**10N**	**12N**	66 : 33	68
6	**11N**	**12N**	18 : 82	45
7	**12β**	**12N**	99 : 1	99
8	**1**	**12F**	94 : 6	99
9	**3**	**5**	99 : 1	83

[a] Product ratio was determined by NMR of the disaccharide mixtures. The disaccharides were predominantly obtained as the β-anomers (see Experimental Section)

To assess the reactivity of the 2,3-diazido and 2-fluoro mannuronates **5** and **12F**, these donors were competed with **3** and **1** respectively, showing that the azide and fluorine substituent are equally disarming as expected on the basis of their similar *F*-value (0.48 *vs* 0.45). The introduction of two azides leads to a less reactive donor (Table 2, entry 9), in line with expectations.

To verify the unexpectedly high reactivity of the β-mannuronic acid **12β**, this donor was made to compete with α-benzylidene mannoside **11α**, resulting in the predominant formation of the mannuronic acid disaccharide (Table 3, entry 1). 2-Azidomannuronic acid **12N** also outcompeted α-configured **11α**, confirming the high reactivity of the β-anomer (Table 3, entry 2). It was previously established that there is a substantial difference between the reactivity of α- and β-anomeric mannuronic acid donors.[11b,c] For example, donor **3** and **5** (Figure 1) can be readily activated at -80 ºC, whereas their α-configured counterparts require -40 ºC and -10 ºC for complete activation. This reactivity difference was established here in a direct competition experiment of **12α** and **12β** with acceptor **13** (Table 3, entry 3). Since both donors lead to the same product, we determined the ratio of unreacted donors after the reaction, revealing that 9 times more α-donor **12α** than β-donor **12β** remained in the mixture. In a similar experiment involving donors **10α** and **10β**, 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 (Table 3, entry 4).

Table 3. Results of the competing α-thio versus β-thio donors in glycosylation with **13**

Entry	Donor **A**	Donor **B**	Product ratio donor **A** : **B** [a]	Yield (%)
1	**11α**	**12β**	4 : 96	94
2	**11α**	**12N**	20 : 80	18
3	**12α**	**12β**	89 : 11[b]	66
4	**10α**	**10β**	61 : 39[b]	43
5	**12β**	**14**	45 : 55	65

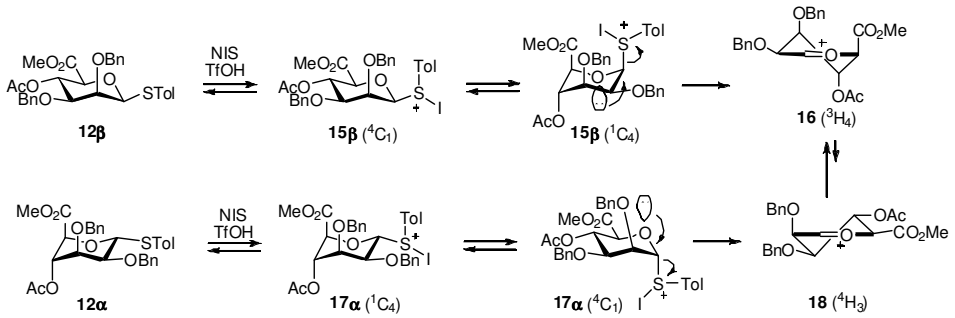
[a] Product ratio was determined by NMR of the disaccharide mixtures. The disaccharides were predominantly obtained as the β-anomers, except for the disaccharide derived from donor **14**; [b] Ratio of recovered donors.

From the results described above it is clear that the β-mannuronic acid donors are reactive glycosyl donors.[23] Wong and co-workers have previously established that donor **11α** has an RRV of 315, on a scale in which the per-*O*-acetylated α-*S*-tolyl mannose donor has a relative reactivity of 1, and perbenzylated α-*S*-tolyl mannoside (**14**) an RRV of 5238.[24] The result recorded in entry 1 of Table 3 (competition between **11α** and **12β**) indicates that the reactivity of mannuronic acid donor **12β** is actually of the same order of magnitude as the reactivity of the "armed" perbenzylated α-mannoside **14**. This was confirmed in an

experiment in which **12β** was made to compete with perbenzylated donor **14** (Table 3, entry 5). The disaccharides formed from donors **12β** and **14** were obtained in a 45 : 55 ratio, revealing the similar reactivity of both donors.

When the mechanism of activation as proposed in Scheme 1 is considered, the unexpectedly high reactivity of **12β** may result from the fact that the β-mannuronic acid donor can relatively easily access the $^{3}H_{4}$-oxacarbenium ion **16**.[25,26] This oxacarbenium ion is relatively stable since it positions all 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 *pseudo*-axial positions in the mannosyl oxacarbenium ion,[25] in line with various studies that axial substituents are less disarming than equatorial substituents.[27] They also established that the C-2 substituent has a slight preference for a *pseudo*-equatorial position. It was reported by Codée *et al.* that the C-5 carboxylic acid has a strong preference for a *pseudo*-axial position in an oxacarbenium ion intermediate.[25c, 28] As depicted in Scheme 1, reaction of donor **12β** with NIS and TfOH leads to the reversible formation of "charged" mannoside **15β**. After the mannosyl ring flips to the $^{1}C_{4}$ conformation, the phenylsulfenyl iodide aglycone can be expelled by the ring oxygen lone pair in an antiperiplanar fashion[29] to produce the favorable $^{3}H_{4}$-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 $^{4}C_{1}$ mannoside **17α** leads to the formation of the higher energy $^{4}H_{3}$-oxacarbenium ion **18**, making this a less favorable process than the formation of **16** from **12β**.[30]

Scheme 1. Proposed reaction mechanism for the formation of oxacarbenium ions **16** and **18**



Conclusion

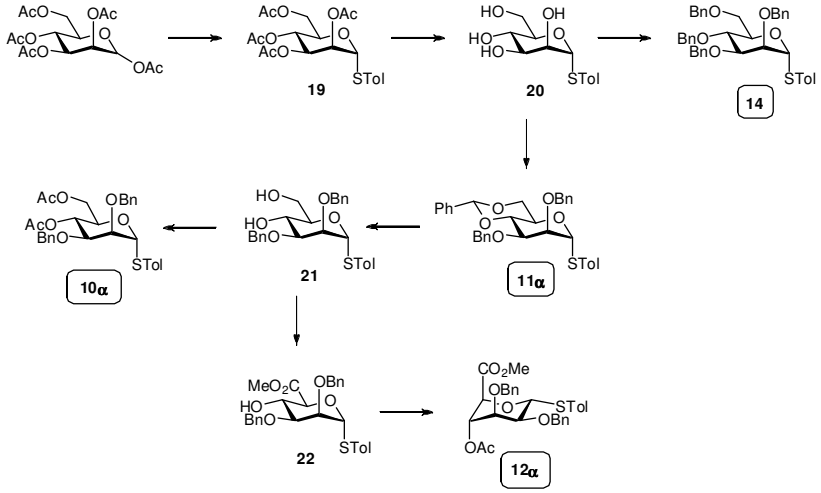
To summarize, the relative reactivities of a series of mannuronic acid donors are determined and it is revealed that β-(*S*)-tolyl mannuronic acids are relatively reactive donors. The high reactivity of these donors contrasts the common perception that uronic acid donors are unreactive glycosylating agents because of the electron-withdrawing nature of the C-5 carboxylic acid ester function. It is postulated that the high reactivity of the β-

mannuronic acids originates from the formation of a relatively favorable $^3H_4$-oxacarbenium ion-like intermediate. The excellent β-selectivity obtained in glycosylations using various mannuronic acid donors can originate (in part) from this oxacarbenium ion, or a species with substantial oxacarbenium ion character. The high reactivity of the β-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.

Experimental Section

General procedure for the NIS/TfOH-mediated competition reaction. In a 25-mL roundbottom flask were donor A (0.1 mmol, 1 eq), donor B (1 eq) and acceptor 13 (3 eq) together co-evaporated with toluene (2x). Freshly distilled DCM (4 mL, donor concentration 0.05 M), a teflon stirrer bar and activated molecular sieves were added and the mixture was stirred under argon for 30 mins at RT. NIS (1 eq) was added and the mixture was cooled to -40 ºC. TfOH (0.1 eq, 0.1 mL of a 0.1 M stock solution in distilled DCM) was added and the mixture was allowed to warm to 0 ºC in ~3 h. Triethylamine (0.1 mL) was added and the mixture was diluted with EtOAc, washed with sat. aq. $Na_2S_2O_3$ (1x) and sat. aq. NaCl (2x), dried over Na_2SO_4 and concentrated *in vacuo*. Elution over a Sephadex column (LH-20, DCM/MeOH, 1/1, v/v) enabled isolation of the disaccharide products and the monosaccharide rests, which were both analysed with NMR spectroscopy. The yield of the disaccharide fraction was determined.

Synthesis of α-donors **10α-12α** and **14**



Tolyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-D-mannopyranoside (19). 1,2,3,4,6-Penta-*O*-acetyl-α/β-D-mannopyranoside (19.5 g, 50 mmol) was dissolved in DCM (250 mL) and *p*-thiocresol (6.21 g, 50 mmol) was added. The mixture was cooled to 0 ºC, followed by the addition of BF_3•Et_2O (12.7 mL, 100 mmol). The mixture was stirred for 72 h at RT, after which time sat. aq. $NaHCO_3$ and solid $NaHCO_3$ were added to neutralize the mixture. The layers were separated and the aqueous layer was extracted with DCM (1x). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, 30% EtOAc in PE) to give the title compound as a yellow oil (Yield: 16.4 g, 37.1 mmol, 74%).The analytical data were in full accord with those reported previously.[6a] TLC: R_f 0.47 (PE/EtOAc, 3/7, v/v).

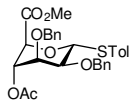
Tolyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside (11α). Compound **19** (16.3 g, 37.0 mmol) was suspended in MeOH (370 mL) and treated with NaOMe (cat.) overnight at RT. The mixture was neutralized using AcOH and concentrated *in vacuo*. The residue was co-evaporated with toluene (3x) to give crude tetra-ol **20**, which was subsequently dissolved in MeCN (370 mL). The resulting solution was cooled to 0 ºC, followed by the addition of $PhCH(OMe)_2$ (5.7 mL, 37.0 mmol) and *p*-TsOH•H_2O (cat.). The mixture was allowed to stir at RT for 72 h, neutralized by the addition of Et_3N and the formed crystals were filtered off to yield the benzylidene-protected intermediate as an off-white solid. ^{1}H NMR ($CDCl_3$, 400 MHz, HH-COSY, HSQC): δ 7.48-7.55 (m, 2H, CH_{arom}), 7.34-7.42 (m, 5H, CH_{arom}), 7.14 (d, 2H, *J* = 8.2 Hz, CH_{arom}), 5.58 (s, 1H, CH Ph), 5.51 (s, 1H, H-1), 4.36 (ddd, 1H, *J* = 4.8, 9.7, 9.8 Hz, H-5), 4.30 (d, 1H, *J* = 3.2 Hz, H-2), 4.23 (dd, 1H, *J* = 4.8, 10.4 Hz, H-3), 4.13 (dd, 1H, *J* = 3.3, 9.5 Hz, H-6), 4.00 (t, 1H, *J* = 9.5 Hz, H-6), 3.83 (t, 1H, *J* = 10.3 Hz, H-4), 2.87 (bs, 1H, 2-OH), 2.78 (bs, 1H, 3-OH), 2.34 (s, 3H, CH_3 STol). A solution of the benzylidene-protected intermediate (7.83 g, 20.9 mmol) in DMF (100 mL) was cooled to 0 ºC, followed by the addition of benzyl bromide (6.0 mL, 50.4 mmol) and NaH (60% dispersion in mineral oil, 1.94 g, 50.4 mmol). The mixture was stirred at RT overnight, after which time the reaction was quenched by the addition of MeOH. The solution was reduced in volume, diluted with Et_2O and washed with H_2O and sat. aq. NaCl. The organic fraction was dried over $MgSO_4$ and concentrated *in vacuo*. Purification using flash column chromatography (silica gel, 10% EtOAc in PE) gave the title compound as a colorless oil (Yield: 10.2 g, 18.4 mmol, 50% over three steps). TLC: R_f 0.40 (PE/EtOAc, 9/1, v/v); $[\alpha]_D^{20}$ +98.0 (*c* 1, DCM); IR (neat, cm^{-1}): 696, 731, 907, 1090, 1373, 1454, 1492; ^{1}H NMR ($CDCl_3$, 400 MHz, HH-COSY, HSQC): δ 7.52 (dd, 2H, *J* = 1.7, 7.7 Hz, CH_{arom}), 7.24-7.41 (m, 15H, CH_{arom}), 7.10 (d, 2H, *J* = 8.0 Hz, CH_{arom}), 5.64 (s, 1H, CH Ph), 5.44 (d, 1H, *J* = 1.2 Hz, H-1), 4.81 (d, 1H, *J* = 12.2 Hz, C*H*H Bn), 4.72 (d, 1H, *J* = 12.6 Hz, C*H*H Bn), 4.69 (d, 1H, *J* = 12.7 Hz, CH*H* Bn), 4.65 (d, 1H, *J* = 12.2 Hz, CH*H* Bn), 4.26-4.34 (m, 2H, H-4, H-5), 4.22 (dd, 1H, *J* = 4.0, 10.2 Hz, H-6), 4.03 (dd, 1H, *J* = 1.3, 3.2 Hz, H-2), 3.97 (dd, 1H, *J* = 3.2, 9.6 Hz, H-3), 3.88 (t, 1H, *J* = 9.9 Hz, H-6), 2.33 (s, 3H, CH_3 STol); ^{13}C-APT NMR ($CDCl_3$, 100 MHz, HSQC): δ 138.3, 137.7, 137.7, 137.5 (C_q), 132.1, 129.8, 128.7, 128.3, 128.1, 128.0, 127.9, 127.7, 127.5, 127.4, 126.0 (CH_{arom}), 101.3 (CH Ph), 87.3 (C-1), 79.0 (C-4), 77.9 (C-2), 76.1 (C-3), 72.9, 72.8 (CH_2 Bn), 68.4 (C-6), 65.3 (C-5), 21.0 (CH_3 STol); ^{13}C-GATED ($CDCl_3$, 100 MHz): δ 87.3 ($J_{C1,H1}$ = 166 Hz, C-1); HRMS: $[M+H]^+$ calcd for $C_{34}H_{35}O_5S$ 555.21997, found 555.22016.

Tolyl 2,3-di-*O*-benzyl-1-thio-α-D-mannopyranoside (21). Compound **11α** (10.2 g, 18.4 mmol) was suspended in MeOH (185 mL) and a catalytic amount of *p*-TsOH•H_2O was added until the acidity of the mixture reached pH<7. The resulting mixture was stirred overnight, followed by the addition of Et_3N until pH>7. The solvent was evaporated and the residue was purified using flash column chromatography (silica gel, 55% EtOAc in PE) to yield the title compound as a yellowish solid (Yield: 8.57 g, 18.4 mmol, >98%). TLC: R_f 0.31 (PE/EtOAc, 2/1, v/v); $[\alpha]_D^{20}$ +51.3 (*c* 0.6, DCM); IR (neat, cm^{-1}): 696, 731, 1018, 1074, 1101, 1454, 1492, 3435; ^{1}H NMR ($CDCl_3$, 400 MHz, HH-COSY, HSQC): δ 7.26-7.38 (m, 12H, CH_{arom}), 7.11 (d, 2H, *J* = 7.9 Hz, CH_{arom}), 5.47 (d, 1H, *J* = 1.4 Hz, H-1), 4.65 (d, 1H, *J* = 12.2 Hz, C*H*H Bn), 4.56 (d, 1H, *J* = 11.7 Hz, C*H*H Bn), 4.54 (d, 1H, *J* = 12.2 Hz, CH*H* Bn), 4.47 (d, 1H, *J* = 11.7 Hz, CH*H* Bn), 4.06-4.15 (m, 2H, H-4, H-5), 3.99 (dd, 1H, *J* = 1.5, 3.0 Hz, H-2), 3.86 (dd, 1H, *J* = 2.8, 11.7 Hz, H-6), 3.81 (dd, 1H, *J* = 4.4, 11.8 Hz, H-6), 3.69 (dd, 1H, *J* = 3.0, 9.1 Hz, H-3), 2.73 (bs, 1H, 4-OH), 2.33 (s, 3H, CH_3 STol), 2.14 (bs, 6-OH); ^{13}C-APT NMR ($CDCl_3$, 100 MHz, HSQC): δ 138.0, 137.6, 137.6 (C_q), 132.4 (CH_{arom}), 129.9 (C_q STol),129.9, 128.5, 128.4, 128.0, 127.9, 127.8 (CH_{arom}), 86.3 (C-1), 79.5 (C-3), 75.3 (C-2), 73.1 (C-4), 72.1, 71.6 (CH_2 Bn), 67.2 (C-5), 62.6 (C-6), 21.1 (CH_3 STol); HRMS: $[M+NH_4]^+$ calcd for $C_{27}H_{34}NO_5S$ 484.21522, found 484.21496.

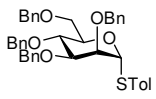
Tolyl 4,6-di-*O*-acetyl-2,3-di-*O*-benzyl-1-thio-α-D-mannopyranoside (10α). Compound **21** (2.80 g, 6.0 mmol) was dissolved in pyridine (30 mL), the resulting solution was cooled to 0 ºC and treated with Ac_2O (2.65 mL, 24 mmol) overnight while allowing the temperature to reach ambient. The reaction was halted by the addition of MeOH (20 mL) and the solvents were evaporated. The residue was taken up in EtOAc and washed with aq. HCl (1M), sat. aq. $NaHCO_3$ and sat. aq. NaCl. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The title compound was obtained by purification using flash column chromatography (silica gel, 20% EtOAc in PE) as a yellowish oil (Yield: 2.87 g,

5.21 mmol, 87%). TLC: R_f 0.50 (PE/EtOAc, 3/1, v/v); $[\alpha]_D^{20}$ +54.3 (*c* 1, DCM); IR (neat, cm^{-1}): 696, 727, 1223, 1367, 1740; ^1H NMR ($CDCl_3$, 400 MHz, HH-COSY, HSQC): δ 7.24-7.36 (m, 12H, CH_{arom}), 7.10 (d, 2H, *J* = 8.0 Hz, CH_{arom}), 5.51 (d, 1H, *J* = 1.5 Hz, H-1), 5.44 (t, 1H, *J* = 9.8 Hz, H-4), 4.69 (d, 1H, *J* = 12.4 Hz, C*H*H Bn), 4.63 (d, 1H, *J* = 12.4 Hz, CH*H* Bn), 4.56 (d, 1H, *J* = 12.2 Hz, C*H*H Bn), 4.45 (d, 1H, *J* = 12.2 Hz, CH*H* Bn), 4.35 (ddd, 1H, *J* = 2.2, 6.0, 8.4 Hz, H-5), 4.24 (dd, 1H, *J* = 6.1, 12.1 Hz, H-6), 4.12 (dd, 1H, *J* = 2.2, 12.1 Hz, H-6), 3.98 (dd, 1H, *J* = 1.9, 2.7 Hz, H-2), 3.78 (dd, 1H, *J* = 3.0, 9.6 Hz, H-3), 2.32 (s, 3H, CH_3 STol), 2.04 (s, 3H, CH_3 Ac), 2.03 (s, 3H, CH_3 Ac); ^{13}C-APT NMR ($CDCl_3$, 100 MHz, HSQC): δ 170.6, 169.6 (C=O Ac), 137.8, 137.7, 137.6 (C_q), 132.0, 129.8 (CH_{arom}), 129.7 (C_q STol), 128.3, 128.2, 127.8, 127.7, 127.6, 127.5 (CH_{arom}), 86.0 (C-1), 76.8 (C-3), 75.3 (C-2), 72.0, 71.6 (CH_2 Bn), 69.7 (C-5), 67.9 (C-4), 62.8 (C-6), 21.0 (CH_3 STol), 20.8, 20.7 (CH_3 Ac); ^{13}C-GATED ($CDCl_3$, 100 MHz): δ 86.0 ($J_{C1,H1}$ = 166 Hz, C-1); HRMS: $[M+NH_4]^+$ calcd for $C_{31}H_{34}NO_7S$ 568.23635, found 568.23638.

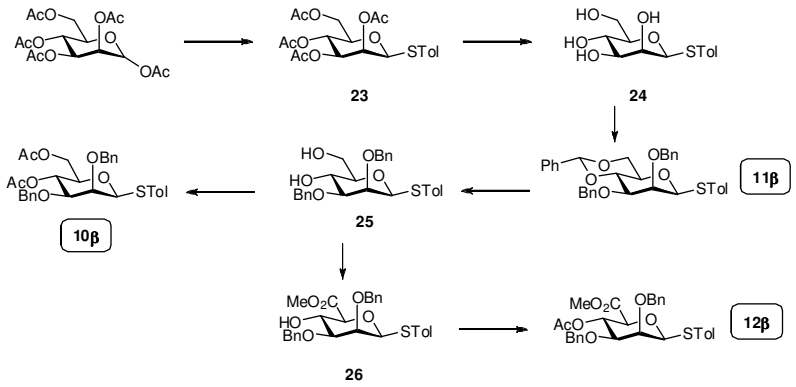
Methyl (tolyl 4-*O*-acetyl-2,3-di-*O*-benzyl-1-thio-α-D-mannopyranosyl uronate) (12α). Compound **21** (5.21 g, 11.18 mmol) was dissolved in DCM/H_2O (110 mL, 2/1, v/v), the mixture was cooled to 0 ºC and treated with TEMPO (0.35 g, 2.24 mmol) and BAIB (8.94 g, 27.94 mmol). The mixture was allowed to warm to RT, followed by the addition of sat. aq. $Na_2S_2O_3$. The layers were separated and the organic fraction was dried over $MgSO_4$ and concentrated *in vacuo*. The uronic acid intermediate was purified using flash column chromatography (silica gel, 30% EtOAc in PE + 1% AcOH) and then dissolved in DMF (46 mL), followed by the addition of MeI (2.30 mL, 37.0 mmol) and K_2CO_3 (7.67 g, 55.5 mmol). The mixture was allowed to stir at RT overnight, diluted with Et_2O and washed with H_2O (2x) and sat. aq. NaCl. The organics were dried over $MgSO_4$, concentrated *in vacuo* and the crude methyl ester **22** was directly dissolved in pyridine (37 mL), the resulting solution was cooled to 0 ºC and treated with Ac_2O (1.39 mL, 14.8 mmol) overnight while allowing the temperature to reach ambient. The reaction was halted by the addition of MeOH (20 mL) and the solvents were evaporated. The residue was taken up in EtOAc and washed with aq. HCl (1M), sat. aq. $NaHCO_3$ and sat. aq. NaCl. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The title compound was obtained by purification using flash column chromatography (silica gel, 25% EtOAc in PE) as an off-white solid (Yield: 3.96 g, 7.19 mmol, 64% over three steps). TLC: R_f 0.26 (PE/EtOAc, 4/1, v/v); $[\alpha]_D^{20}$ +44.0 (*c* 1, DCM); IR (neat, cm^{-1}): 696, 1018, 1026, 1045, 1107, 1121, 1225, 1749; ^1H NMR ($CDCl_3$, 400 MHz, HH-COSY, HSQC): δ 7.46 (d, 2H, *J* = 7.7 Hz, CH_{arom}), 7.23-7.33 (m, 10H, CH_{arom}), 7.10 (d, 2H, *J* = 8.0 Hz, CH_{arom}), 5.71 (d, 1H, *J* = 6.7 Hz, H-1), 5.56 (dd, 1H, *J* = 5.0, 6.1 Hz, H-4), 4.62 (d, 1H, *J* = 11.9 Hz, C*H*H Bn), 4.53-4.57 (m, 3H, CH_2 Bn, H-5), 4.50 (d, 1H, *J* =11.9 Hz, CH*H* Bn), 3.80 (dd, 1H, *J* = 2.8, 6.2 Hz, H-3), 3.75 (d, 1H, *J* = 5.3 Hz, H-2), 3.59 (s, 3H, CH_3 CO_2Me), 2.31 (s, 3H, CH_3 STol), 2.02 (s, 3H, CH_3 Ac); ^{13}C-APT NMR ($CDCl_3$, 100 MHz, HSQC): δ 169.5, 168.3 (C=O Ac, CO_2Me), 137.4, 137.3, 137.2 (C_q), 131.4 (CH_{arom}), 129.6 (C_q STol), 129.5, 128.2, 127.9, 127.7, 127.7 (CH_{arom}), 83.4 (C-1), 73.8 (C-2, C-3), 72.5 (C-5), 72.2 (CH_2 Bn), 69.3 (C-4), 52.2 (CH_3 CO_2Me), 21.0 (CH_3 STol), 20.7 (CH_3 Ac); ^{13}C-GATED ($CDCl_3$, 100 MHz): δ 83.4 ($J_{C1,H1}$ = 163 Hz, C-1); HRMS: $[M+NH_4]^+$ calcd for $C_{30}H_{36}NO_7S$ 554.22070, found 554.22046. NB: the chemical shift of C-1 was deduced from the HSQC cross coupling with H-1 since there was no signal apparent in the ^{13}C-APT spectrum.



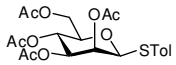
Tolyl 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-mannopyranoside (14). Crude tetra-ol **20** (3.44 g, ~12 mmol) was dissolved in DMF (60 mL) and the solution was cooled to 0 ºC. Benzyl bromide (6.41 mL, 54 mmol) and NaH (60% dispersion in mineral oil, 1.81 g, 54 mmol) were added and the mixture was stirred at RT overnight. The reaction was quenched by the addition of MeOH, the mixture was reduced in volume and taken up in Et_2O. The organic phase was washed with H_2O and sat. aq. NaCl, dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The title compound was purified using flash column chromatography (silica gel, 10% EtOAc in PE) and obtained as a yellowish oil (Yield: 4.91 g, 7.80 mmol, 65%). Spectroscopic data were in accord with those reported previously.[24] TLC: R_f 0.34 (PE/EtOAc, 9/1, v/v).



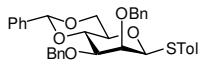
Synthesis of β-donors **10β-12β**



Tolyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-mannopyranoside (23). 1,2,3,4,6-Penta-*O*-acetyl-α/β-D-mannopyranoside (195 g, 500 mmol) was dissolved in AcOH (200 mL) and the resulting mixture was cooled to 0 ºC, followed by the addition of HBr (33 wt% in AcOH, 237 mL, 1.35 mol). The reaction was stirred at RT for 3 h after which time the mixture was poured in ice-water. The crude bromide was extracted using EtOAc (2 x 500 mL) and the combined organic fractions were washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. A solution of the anomeric bromide (~500 mmol) and *p*-thiocresol (65.2 g, 525 mmol) in DMF (1 L) was cooled to 0 ºC and NaH (60% dispersion in mineral oil, 21.0 g, 525 mmol) was added. The mixture was stirred until full consumption of the bromide (R_f 0.53 in PE/EtOAc, 7/3, v/v) was observed using TLC analysis and subsequently quenched by the addition of aq. HCl (0.02 M). The product was extracted with Et_2O and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Crystallization using EtOAc/PE gave the title compound as white crystals (Yield: 186 g, 422 mmol, 84%). The analytical data were in full accord with those reported previously.[31] TLC: R_f 0.50 (toluene/EtOAc, 7/3, v/v).



Tolyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-mannopyranoside (11β). Compound **23** (186 g, 422 mmol) was suspended in MeOH (1.5 L) and NaOMe (cat.) was added. The reaction was allowed to stir overnight at RT, after which time AcOH was added to neutralize the mixture (pH<7) and the solvents were evaporated. The tetra-ol intermediate **24** was crystallized from EtOAc/PE and used directly in the next reaction step (Yield: 111.0 g, 388 mmol, 78%). Compound **24** (28.6 g, 100 mmol) was dissolved in pyridine (500 mL), the resulting solution was cooled to 0 ºC and TMSCl (63.5 mL, 500 mmol) was added. Full consumption of the starting material (R_f 0.35 in MeOH/EtOAc, 1/20, v/v) was indicated by TLC analysis, and Et_2O and H_2O were added. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, concentrated *in vacuo* and co-evaporated with toluene. The per-silylated intermediate was used directly in the next reaction step. The crude intermediate (~100 mmol) was dissolved in dry DCM (500 mL) under an argon atmosphere and the solution was cooled to -80 ºC. $PhCH(OMe)_2$ (10.7 mL, 105 mmol) and TMSOTf (2.7 mL, 15 mmol) were added and the reaction was stirred at -80 ºC, followed by the addition of NaOMe (11.6 g, 215 mmol) and MeOH (20 mL). The mixture was allowed to warm to RT and Amberlite-H^+ was added to neutralize. The solution was filtered off and concentrated *in vacuo*. The benzylidene-intermediate was crystallized from EtOAc (18.1 g, 48.3 mmol) and directly dissolved in DMF (250 mL) and the resulting solution was cooled to 0 ºC, followed by the addition of benzyl bromide (13.8 mL, 116.0 mmol) and NaH (60% dispersion in mineral oil, 3.9 g, 116.0 mmol). The mixture was stirred overnight at RT, after which time MeOH was added to quench the reaction. The mixture was reduced in volume and taken up in Et_2O, the organic phase was washed with H_2O and sat. aq. NaCl, dried over $MgSO_4$ and concentrated *in vacuo*. The title compound was purified using flash column chromatography (silica gel, 15% EtOAc in PE) and obtained as a white solid (Yield: 18.8 g, 33.9 mmol, 34% over three steps). TLC: R_f 0.50 (PE/EtOAc, 7/1, v/v); $[\alpha]_D^{20}$ -34.4 (*c* 1, DCM); IR (neat, cm^{-1}): 696, 733, 1028, 1087, 1456, 1494, 2864; ^1H NMR ($CDCl_3$, 400 MHz, HH-COSY, HSQC): δ 7.44-7.51 (m, 4H, CH_{arom}), 7.22-7.38 (m, 13H, CH_{arom}),



7.06 (d, 2H, *J* = 7.9 Hz, CH_{arom}), 5.57 (s, 1H, CH Ph), 5.08 (d, 1H, *J* = 11.1 Hz, C*H*H Bn), 4.85 (d, 1H, *J* = 12.3 Hz, C*H*H Bn), 4.83 (d, 1H, *J* = 11.1 Hz, CH*H* Bn), 4.74 (s, 1H, H-1), 4.69 (d, 1H, *J* = 12.3 Hz, CH*H* Bn), 4.27 (t, 1H, *J* = 9.6 Hz, H-4), 4.25 (dd, 1H, *J* = 5.3, 10.2 Hz, H-6), 4.12 (d, 1H, *J* = 2.1 Hz, H-2), 3.89 (t, 1H, *J* = 10.3 Hz, H-6), 3.67 (dd, 1H, *J* = 2.9, 9.8 Hz, H-3), 3.32 (ddd, 1H, *J* = 4.9, 9.7, 9.7 Hz, H-5), 2.28 (s, 3H, CH_3 STol); ^{13}C-APT NMR ($CDCl_3$, 100 MHz, HSQC): δ 138.2, 137.8, 137.4 (C_q), 131.5 (CH_{arom}), 131.1 (C_q STol), 129.6, 128.7, 128.5, 128.2, 128.0, 127.6, 127.5, 127.4, 125.9 (CH_{arom}), 101.2 (CH Ph), 89.2 (C-1), 79.7 (C-3), 78.8, 78.5 (C-2, C-4), 75.7, 73.0 (CH_2 Bn), 71.4 (C-5), 68.3 (C-6), 20.9 (CH_3 STol); ^{13}C-GATED ($CDCl_3$, 100 MHz): δ 89.2($J_{C1,H1}$ = 154 Hz, C-1); HRMS: $[M+NH_4]^+$ calcd for $C_{34}H_{38}NO_5S$ 572.24652, found 572.24605.

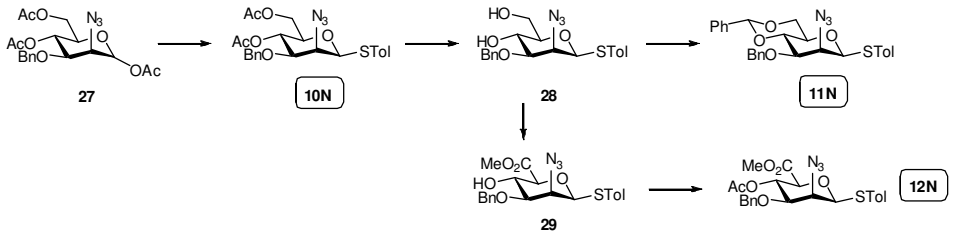
Tolyl 2,3-di-*O*-benzyl-1-thio-β-D-mannopyranoside (25). Compound **11β** (13.7 g, 24.7 mmol) was suspended in MeOH (250 mL) and *p*-TsOH•H_2O (cat.) was added until the mixture was acidic. The reaction was allowed to stir overnight at RT and subsequently quenched by the addition of Et_3N (until pH>7). The solvents were evaporated and the title compound was obtained by flash column chromatography (silica gel, 45% EtOAc in PE) as a yellowish glass (Yield: 11.0 g, 23.5 mmol, 95%). TLC: R_f 0.37 (PE/EtOAc, 1/1, v/v); $[\alpha]_D^{20}$ -62.1 (*c* 1, DCM); IR (neat, cm^{-1}): 696, 733, 1026, 1067, 1121, 3352; ^{1}H NMR ($CDCl_3$, 400 MHz, HH-COSY, HSQC): δ 7.43 (d, 2H, *J* = 7.6 Hz, CH_{arom}), 7.25-7.36 (m, 10H, CH_{arom}), 7.07 (d, 2H, *J* = 8.0 Hz, CH_{arom}), 4.94 (d, 1H, *J* = 11.3 Hz, C*H*H Bn), 4.79 (d, 1H, *J* = 11.3 Hz, CH*H* Bn), 4.72 (s, 1H, H-1), 4.68 (d, 1H, *J* = 11.8 Hz, C*H*H Bn), 4.56 (d, 1H, *J* = 13.1 Hz, CH*H* Bn), 4.10 (d, 1H, *J* = 2.5 Hz, H-2), 4.03 (t, 1H, *J* = 9.5 Hz, H-4), 3.85 (dd, 1H, *J* = 3.0, 11.8 Hz, H-6), 3.77 (dd, 1H, *J* = 5.4, 11.8 Hz, H-6), 3.41 (dd, 1H, *J* = 2.6, 9.5 Hz, H-3), 3.27 (ddd, 1H, *J* = 3.6, 5.3, 9.2 Hz, H-5), 3.03 (bs, 1H, OH), 2.64 (bs, 1H, OH), 2.29 (s, 3H, CH_3 STol); ^{13}C-APT NMR ($CDCl_3$, 100 MHz, HSQC): δ 137.9, 137.5 (C_q), 131.3 (CH_{arom}), 131.1 (C_q STol), 129.7, 128.6, 128.3, 128.2, 128.0, 127.7 (CH_{arom}), 88.2 (C-1), 83.5 (C-3), 80.0 (C-5), 76.6 (C-2), 75.1, 72.1 (CH_2 Bn), 67.4 (C-4), 62.9 (C-6), 21.0 (CH_3 STol); HRMS: $[M+NH_4]^+$ calcd for $C_{27}H_{34}NO_5S$ 484.21522, found 484.21504.

Tolyl 4,6-di-*O*-acetyl-2,3-di-*O*-benzyl-1-thio-β-D-mannopyranoside (10β). A solution of compound **25** (2.33 g, 5 mmol) in pyridine (25 mL) was cooled to 0 ºC, followed by the addition of Ac_2O (2.21 mL, 20 mmol). The resulting reaction was allowed to stir overnight at RT, followed by the addition of MeOH to quench. The solvents were evaporated, the residue was diluted with EtOAc and washed with aq. HCl (1 M), sat. aq. $NaHCO_3$ and sat. aq. NaCl. The organic phase was dried over $MgSO_4$, concentrated *in vacuo* and purified using flash column chromatography (silica gel, 20% EtOAc in PE). The title compound was obtained as a yellowish oil (Yield: 1.34 g, 3.13 mmol, 63%). TLC: R_f 0.53 (PE/EtOAc, 3/1, v/v); $[\alpha]_D^{20}$ -76.4 (*c* 1, DCM); IR (neat, cm^{-1}): 696, 735, 1055, 1231, 1366, 1742; ^{1}H NMR ($CDCl_3$, 400 MHz, HH-COSY, HSQC): δ 7.44 (d, 2H, *J* = 7.2 Hz, CH_{arom}), 7.40 (d, 2H, *J* = 8.1 Hz, CH_{arom}), 7.20-7.35 (m, 8H, CH_{arom}), 7.05 (d, 2H, *J* = 8.0 Hz, CH_{arom}), 5.41 (t, 1H, *J* = 9.8 Hz, H-4), 4.99 (d, 1H, *J* = 11.5 Hz, C*H*H Bn), 4.79 (d, 1H, *J* = 11.5 Hz, CH*H* Bn), 4.65 (s, 1H, H-1), 4.63 (d, 1H, *J* = 12.2 Hz, C*H*H Bn), 4.49 (d, 1H, *J* = 12.2 Hz, CH*H* Bn), 4.22 (dd, 1H, *J* = 6.9, 12.0 Hz, H-6), 4.11-4.16 (m, 2H, H-2, H-6), 3.55 (dd, 1H, *J* = 2.7, 9.6 Hz, H-3), 3.49-3.54 (m, 1H, H-5), 2.28 (s, 3H, CH_3 STol), 2.01 (s, 3H, CH_3 Ac), 1.97 (s, 3H, CH_3 Ac); ^{13}C-APT NMR ($CDCl_3$, 100 MHz, HSQC): δ 170.3, 169.4 (C=O Ac), 137.6, 137.3, 137.2 (C_q), 131.2 (CH_{arom}), 131.1 (C_q STol), 129.3, 128.1, 128.0, 127.8, 127.6, 127.3, 127.2 (CH_{arom}), 87.8 (C-1), 80.7 (C-3), 76.3, 76.1 (C-2, C-5), 74.6, 71.9 (CH_2 Bn), 67.9 (C-4), 63.1 (C-6), 20.8, 20.5, 20.4 (CH_3 STol, Ac); ^{13}C-GATED ($CDCl_3$, 100 MHz): δ 87.8 ($J_{C1,H1}$= 152 Hz, C-1); HRMS: $[M+NH_4]^+$ calcd for $C_{31}H_{38}NO_7S$ 568.23635, found 568.23621.

Methyl (tolyl 4-*O*-acetyl-2,3-di-*O*-benzyl-1-thio-β-D-mannopyranosyl uronate) (12β). Diol **25** (2.33 g, 5.0 mmol) was dissolved in DCM (34 mL) and H_2O (15 mL) was added. The emulsion was cooled to 0 ºC, followed by the addition of TEMPO (0.16 g, 1.0 mmol) and BAIB (4.0 g, 12.5 mmol). The mixture was stirred vigorously and allowed to reach RT, after which time the reaction was quenched by the addition of sat. aq. $Na_2S_2O_3$. The mixture was diluted with DCM and H_2O and the layers were separated. The organic phase was dried over $MgSO_4$, concentrated *in vacuo* and purified using flash column chromatography (silica gel, 25% EtOAc in PE +1% AcOH). The uronic acid intermediate was dissolved in DMF (12 mL) and MeI (0.6 mL, 2.42 mmol) and K_2CO_3 (2.0 g, 14.5 mmol) were subsequently added. The resulting suspension was stirred overnight at RT, diluted with Et_2O and washed with H_2O. The organic

layer was washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated *in vacuo*, The crude methyl uronate **26** was directly dissolved in pyridine (10 mL), the solution was cooled to 0 ºC and treated with Ac_2O (0.46 mL, 4.13 mmol). The mixture was stirred overnight at RT, after which time the reaction was quenched by the addition of MeOH. The solvents were evaporated and the residue was diluted with EtOAc, washed with HCl (1 M), sat. aq. $NaHCO_3$ and sat. aq. NaCl, dried over $MgSO_4$ and concentrated *in vacuo*. The title compound was acquired by flash column chromatography (silica gel, 25% EtOAc in PE) as an off-white solid (Yield: 0.94 g, 1.75 mmol, 35% over three steps). TLC: R_f 0.63 (PE/EtOAc, 3/2, v/v); $[\alpha]_D^{20}$ -86.8 (*c* 1, DCM); IR (neat, cm^{-1}): 694, 729, 1236, 1736, 1749; ^{1}H NMR ($CDCl_3$, 400 MHz, HH-COSY, HSQC): δ 7.46 (d, 2H, *J* = 7.2 Hz, CH_{arom}), 7.38 (d, 2H, *J* = 8.1 Hz, CH_{arom}), 7.28-7.37 (m, 8H, CH_{arom}), 7.09 (d, 2H, *J* = 8.0 Hz, CH_{arom}), 5.60 (t, 1H, *J* = 9.6 Hz, H-4), 5.01 (d, 1H, *J* = 11.6 Hz, C*H*H Bn), 4.85 (d, 1H, *J* = 11.6 Hz, CH*H* Bn), 4.70 (s, 1H, H-1), 4.66 (d, 1H, *J* = 12.2 Hz, C*H*H Bn), 4.56 (d, 1H, *J* = 12.2 Hz, CH*H* Bn), 4.14 (d, 1H, *J* = 2.2 Hz, H-2), 3.84 (d, 1H, *J* = 9.6 Hz, H-5), 3.73 (s, 3H, CH_3 CO_2Me), 3.58 (dd, 1H, *J* = 2.8, 9.7 Hz, H-3), 2.32 (s, 3H, CH_3 STol), 2.00 (s, 3H, CH_3 Ac); ^{13}C-APT NMR ($CDCl_3$, 100 MHz, HSQC): δ 169.5, 167.6 (C=O Ac, CO_2Me), 137.7, 137.6, 137.5 (C_q), 131.7 (CH_{arom}), 131.0 (C_q STol), 129.7, 128.4, 128.1, 127.8, 127.6, 127.5 (CH_{arom}), 88.9 (C-1), 80.3 (C-3), 77.0 (C-5), 76.2 (C-2), 74.8, 72.4 (CH_2 Bn), 68.7 (C-4), 52.5 (CH_3 CO_2Me), 21.0, 20.7 (CH_3 STol, Ac); ^{13}C-GATED ($CDCl_3$, 100 MHz): δ 88.9 ($J_{C1,H1}$ = 152 Hz, C-1); HRMS: $[M+NH_4]^+$ calcd for $C_{30}H_{36}NO_7S$ 554.22070, found 554.22070.

Synthesis of the 2-azido-2-deoxy mannose derivatives **10N-12N**

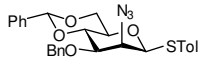


Tolyl 4,6-di-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy-1-thio-β-D-mannopyranoside (10N). 1,4,6-Tri-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy-α/β-D-mannopyranoside **27**[11b] (9.33 g, 22.1 mmol) was dissolved in dry DCE (110 mL), followed by the addition of *p*-thiocresol (3.02 g, 24.3 mmol) and BF_3•Et_2O (5.49 mL, 44.2 mmol). The resulting mixture was stirred at 35 ºC for 2 h, after which time the mixture was diluted with EtOAc and quenched by the addition of sat. aq. $NaHCO_3$. The organic layer was isolated, dried over $MgSO_4$ and concentrated *in vacuo*. Purification using flash column chromatography (silica gel, 25% EtOAc in PE) yielded the title compound as a yellowish solid (Yield: 4.34 g, 9.0 mmol, 41%), next to the α-fused product (Yield: 2.56 g, 5.3 mmol, 24%). TLC: R_f 0.43 (PE/EtOAc, 2/1, v/v); $[\alpha]_D^{20}$-15.1 (*c* 1, DCM); IR (neat, cm^{-1}): 1045, 1086, 1231, 1368, 1744, 2106; ^{1}H NMR ($CDCl_3$, 400 MHz, HH-COSY, HSQC): δ 7.40 (d, 2H, *J* = 8.1 Hz, CH_{arom}), 7.27-7.35 (m, 5H, CH_{arom}), 7.10 (d, 2H, *J* = 8.0 Hz, CH_{arom}), 5.27 (t, 1H, *J* = 9.8 Hz, H-4), 4.71 (d, 1H, *J* = 12.2 Hz, C*H*H Bn), 4.66 (d, 1H, *J* = 1.1 Hz, H-1), 4.57 (d, 1H, *J* = 12.2 Hz, CH*H* Bn), 4.09, 4.21 (m, 3H, H-2, H-6), 3.71 (dd, 1H, *J* = 3.8, 9.5 Hz, H-3), 3.48 (ddd, 1H, *J* = 2.8, 6.5, 6.5 Hz, H-5), 2.33 (s, 3H, CH_3 STol), 2.06 (s, 3H, CH_3 Ac), 2.00 (s, 3H, CH_3 Ac); ^{13}C-APT NMR ($CDCl_3$, 100 MHz, HSQC): δ 170.6, 169.4 (C=O Ac), 138.1, 136.9 (C_q), 132.0 (CH_{arom}), 130.1 (C_q STol), 129.7, 128.5, 128.1, 127.7 (CH_{arom}), 86.1 (C-1), 79.6 (C-3), 76.4 (C-5), 72.1 (CH_2 Bn), 67.4 (C-4), 62.9 (C-2), 62.8 (C-6), 21.0 (CH_3 STol), 20.7, 20.7 (CH_3 Ac); ^{13}C-GATED ($CDCl_3$, 100 MHz): δ 86.1 ($J_{C1,H1}$ = 154 Hz, C-1); HRMS: $[M+NH_4]^+$ calcd for $C_{24}H_{31}N_4O_6S$ 503.19588, found 503.19563.

Tolyl 2-azido-3-*O*-benzyl-2-deoxy-1-thio-β-D-mannopyranoside (28). Compound **10N** (1.50 g, 3.10 mmol) was dissolved in MeOH/DCM (30 mL, 1/1, v/v) and treated with NaOMe (40 mg, 0.74 mmol) for 2 days. The mixture was neutralized by the addition of Amberlite-H^+, filtrated and concentrated *in vacuo*. Purification using flash column chromatography (silica gel, 66% EtOAc in PE) yielded compound **28** as a colorless oil (Yield: 1.22 g, 3.05 mmol, 98%). TLC: R_f 0.35 (PE/EtOAc, 1/1, v/v); $[\alpha]_D^{20}$ -37.3 (*c* 1, DCM); IR (neat, cm^{-1}): 698, 737, 808, 1016, 1069, 1267, 2104, 3343; ^{1}H NMR ($CDCl_3$, 400 MHz, HH-COSY, HSQC): δ 7.27-7.39 (m, 7H, CH_{arom}), 7.10 (d, 2H, *J* = 8.0 Hz, CH_{arom}), 4.77 (d, 1H, *J* = 11.6 Hz, C*H*H Bn), 4.70 (s, 1H, H-1), 4.64 (d, 1H, *J* = 11.6 Hz, CH*H* Bn), 4.13 (d, 1H, *J* = 3.4 Hz, H-2), 3.95 (t,

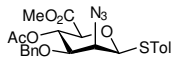
1H, *J* = 9.4 Hz, H-4), 3.86 (dd, 1H, *J* = 3.3, 12.0 Hz, H-6), 3.78 (dd, 1H, *J* = 5.0, 12.1 Hz, H-6), 3.58 (dd, 1H, *J* = 3.6, 9.2 Hz, H-3), 3.26 (ddd, 1H, *J* = 4.0, 4.9, 4.9, H-5), 2.85 (bs, 2H, 4-OH, 6-OH), 2.32 (s, 3H, CH_3 STol); ^{13}C-APT NMR ($CDCl_3$, 100 MHz, HSQC): δ 137.4, 137.1 (C_q), 131.0 (CH_{arom}), 130.0 (C_q STol), 129.5, 128.2, 127.7, 127.6 (CH_{arom}), 85.4 (C-1), 81.9 (C-3), 79.7 (C-5), 72.3 (CH_2 Bn), 66.1 (C-4), 62.9 (C-2), 61.6 (C-6), 20.7 (CH_3 STol); ^{13}C-GATED ($CDCl_3$, 100 MHz): δ 85.4 ($J_{C1,H1}$ = 154 Hz, C-1); HRMS: $[M+Na]^+$ calcd for $C_{20}H_{23}N_3O_4SNa$ 424.13015, found 424.12954.

Tolyl 2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-1-thio-β-D-mannopyranoside (11N). Compound **28**



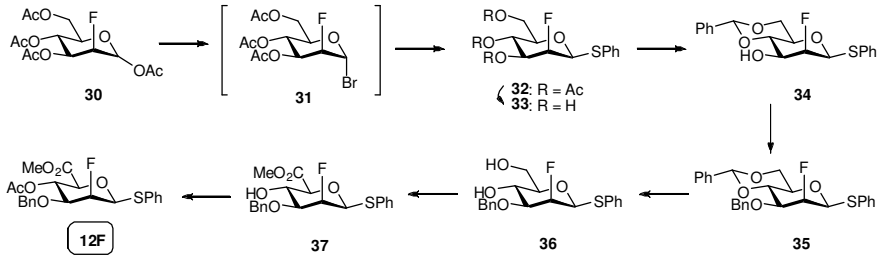
(0.79 g, 2.0 mmol) was dissolved in MeCN (10 mL), followed by the addition of $PhCH(OMe)_2$ (0.32 mL, 2.2 mmol) and *p*-TsOH•H_2O (37 mg, 0.2 mmol). The resulting solution was stirred for 2 days. The mixture was neutralized with Et_3N, diluted with EtOAc and washed with H_2O (3x). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The title compound was obtained by crystallization from EtOAc/PE as white fluffy crystals (Yield: 0.77 g, 1.6 mmol, 81%). TLC: R_f 0.85 (PE/EtOAc, 2/1, v/v); $[\alpha]_D^{20}$ +7.4 (*c* 1, DCM); IR (neat, cm^{-1}): 696, 733, 1069, 1086, 1098, 1269, 2102; ^{1}H NMR ($CDCl_3$, 400 MHz, HH-COSY, HSQC): δ 7.43-7.50 (m, 2H, CH_{arom}), 7.25-7.41 (m, 10H, CH_{arom}), 7.11 (d, 2H, *J* = 8.0 Hz, CH_{arom}), 5.60 (s, 1H, CH Ph), 4.89 (d, 1H, *J* = 12.3 Hz, C*H*H Bn), 4.75 (d, 1H, *J* = 11.9 Hz, CH*H* Bn), 4.74 (d, 1H, *J* = 1.4 Hz, H-1), 4.27 (dd, 1H, *J* = 4.9, 10.5 Hz, H-6), 4.20 (dd, 1H, *J* = 1.2, 3.6 Hz, H-2), 4.15 (t, 1H, *J* = 9.5 Hz, H-4), 3.87 (t, 1H, *J* = 10.3 Hz, H-6) 3.83 (dd, 1H, *J* = 3.7, 9.6 Hz, H-3), 3.33 (ddd, 1H, *J* = 4.9, 9.8, 9.8 Hz, H-5), 2.33 (s, 3H, CH_3 STol); ^{13}C-APT NMR ($CDCl_3$, 100 MHz, HSQC): δ 138.2, 137.6, 137.2 (C_q), 132.1 (CH_{arom}), 130.0 (C_q STol), 129.8, 128.9, 128.4, 128.2, 127.9, 127.5, 125.9 (CH_{arom}), 101.4 (CH Ph), 87.1 (C-1), 78.4, 78.3 (C-3, C-4), 73.1 (CH_2 Bn), 71.4 (C-5), 68.2 (C-6), 64.7 (C-2), 21.1 (CH_3 STol); ^{13}C-GATED ($CDCl_3$, 100 MHz): δ 87.1 ($J_{C1,H1}$= 156 Hz, C-1); HRMS: $[M+NH_4]^+$ calcd for $C_{27}H_{31}N_4O_4S$ 507.20605, found 507.20552.

Methyl (tolyl 4-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy-1-thio-β-D-mannopyranosyl uronate) (12N). Compound



28 (0.89 g, 2.23 mmol) was dissolved in DCM/H_2O (15 mL, 2/1, v/v), the mixture was cooled to 0 ºC and treated with TEMPO (70 mg, 0.45 mmol) and BAIB (1.80 g, 5.58 mmol) for 2 h. Sat. aq. $Na_2S_2O_3$ was added, the mixture was diluted with EtOAc and the organic phase was washed with H_2O (2x) and sat. aq. NaCl (1x), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was then dissolved in dry DMF (15 mL), followed by the addition of MeI (0.42 mL, 6.69 mmol) and K_2CO_3 (0.93 g, 6.69 mmol). The mixture was allowed to stir at RT for 1.5 h, diluted with EtOAc and washed with H_2O (2x) and sat. aq. NaCl. The organics were dried over $MgSO_4$, concentrated *in vacuo* and the methyl uronate **29** was isolated using flash column chromatography (silica gel, 25% EtOAc in PE). Spectroscopic data are reported for compound **29**: ^{1}H NMR ($CDCl_3$, 400 MHz, HH-COSY, HSQC): δ 7.28-7.43 (m, 7H, CH_{arom}), 7.11 (d, 2H, *J* = 8.0 Hz, CH_{arom}), 4.81 (d, 1H, *J* = 12.3 Hz, C*H*H Bn), 4.78 (d, 1H, *J* = 12.4 Hz, CH*H* Bn), 4.67 (s, 1H, H-1), 4.23 (t, 1H, *J* = 9.4 Hz, H-4), 4.12 (d, 1H, *J* = 3.3 Hz, H-2), 3.81 (s, 3H, CH_3 CO_2Me), 3.72 (d, 1H, *J* = 9.7 Hz, H-5), 3.62 (dd, 1H, *J* = 3.7, 9.2 Hz, H-3), 3.19 (bs, 1H, 4-OH), 2.33 (s, 3H, CH_3 STol); ^{13}C-APT NMR ($CDCl_3$, 100 MHz, HSQC): δ 169.2 (C=O CO_2Me), 138.2, 137.3 (C_q), 132.1 (CH_{arom}), 129.9 (C_q STol), 129.8, 128.6, 128.1, 127.8 (CH_{arom}), 86.9 (C-1), 81.1 (C-3), 87.0 (C-5), 73.0 (CH_2 Bn), 68.1 (C-4), 63.0 (C-2), 52.7 (CH_3 CO_2Me), 21.0 (CH_3 STol); ^{13}C-GATED ($CDCl_3$, 100 MHz): δ 86.9 ($J_{C1,H1}$ = 155 Hz, C-1). Compound **29** (0.66 g, 1.5 mmol) was treated with pyridine/Ac_2O (8 mL, 3/1, v/v) for 1.5 h. The mixture was diluted with EtOAc, washed with H_2O (3x), dried over $MgSO_4$ and concentrated *in vacuo* to yield the title compound as a white amorphous solid (Yield: 0.72 g, 1.5 mmol, 67% over three steps). TLC: R_f 0.55 (PE/EtOAc, 2/1, v/v); $[\alpha]_D^{20}$ -34.8 (*c* 1, DCM); IR (neat, cm^{-1}): 731, 1051, 1088, 1225, 1747, 2106; ^{1}H NMR ($CDCl_3$, 400 MHz, HH-COSY, HSQC): δ 7.30-7.40 (m, 7H, CH_{arom}), 7.11 (d, 2H, *J* = 8.0 Hz, CH_{arom}), 5.43 (t, 1H, *J* = 9.7 Hz, H-4), 4.72 (d, 1H, *J* = 12.2 Hz, C*H*H Bn), 4.67 (s, 1H, H-1), 4.64 (d, 1H, *J* = 12.2 Hz, CH*H* Bn), 4.18 (d, 1H, *J* = 3.2 Hz, H-2), 3.79 (d, 1H, *J* = 9.9 Hz, H-5), 3.74-3.77 (m, 1H, H-3), 3.73 (s, 3H, CH_3 CO_2Me), 2.33 (s, 3H, CH_3 STol), 2.01 (s, 3H, CH_3 Ac); ^{13}C-APT NMR ($CDCl_3$, 100 MHz, HSQC): δ 169.3, 167.2 (C=O Ac, CO_2Me), 138.3, 136.9 (C_q), 132.2, 129.8 (CH_{arom}), 129.8 (C_q STol), 128.6, 128.2, 127.8 (CH_{arom}), 86.7 (C-1), 79.0 (C-3), 76.9 (C-5), 72.5 (CH_2 Bn), 68.2 (C-4), 63.0 (C-2), 52.7 (CH_3 CO_2Me), 21.1 (CH_3 STol), 20.6 (CH_3 Ac); ^{13}C-GATED ($CDCl_3$, 100 MHz): δ 86.7 ($J_{C1,H1}$ = 155 Hz, C-1); HRMS: $[M+NH_4]^+$ calcd for $C_{23}H_{29}N_4O_6S$ 489.18023, found 489.17981.

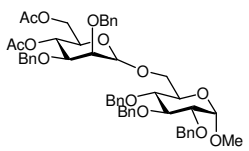
Synthesis of the 2-deoxy-2-fluoro mannuronate **12F**



Phenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-1-thio-β-D-mannopyranoside (32). A solution of compound **30**[32] (5.64 g, 16.1 mmol) in DCM (10.7 mL) was cooled to 0 ºC and HBr (33 wt% in AcOH, 14.5 mL, 80.5 mmol) was added. The resulting mixture was stirred at RT for 5 h, after which time the mixture was poured into ice-water. EtOAc was added and the organic phase was washed with sat. aq. $NaHCO_3$ and sat. aq. NaCl, dried over $MgSO_4$ and concentrated *in vacuo*. The crude bromide **31** was used in the next reaction step without further purification. TLC: R_f 0.64 (PE/EtOAc, 7/3, v/v). Bromide **31** (~9.0 mmol) was dissolved in DMF (18 mL) and PhSH (0.97 mL, 9.53 mmol) was added. The mixture was cooled to 0 ºC, followed by the addition of NaH (60% dispersion in mineral oil, 0.32 g, 9.53 mmol). The reaction was stirred overnight at RT, after which time aq. HCl (0.02 M) was added. The mixture was diluted with Et_2O and H_2O, the organic phase was washed with sat. aq. NaCl (3x), dried over $MgSO_4$ and concentrated *in vacuo*. Purification using flash column chromatography (silica gel, 33% EtOAc in PE) yielded the title compound as a colored oil (Yield: 2.53 g, 6.31 mmol, 70% over two steps). TLC: R_f 0.17 (PE/EtOAc, 3/1, v/v); $[\alpha]_D^{20}$ -110.0 (*c* 0.74, DCM); IR (neat, cm^{-1}): 1051, 1221, 1368, 1740; ^{1}H NMR ($CDCl_3$, 400 MHz, HH-COSY, HSQC): δ 7.51-7.57 (m, 2H, CH_{arom}), 7.29-7.35 (m, 3H, CH_{arom}), 5.38 (t, 1H, *J* = 10.0 Hz, H-4), 5.08 (dd, 1H, *J* = 2.5, 49.8 Hz, H-2), 4.99 (ddd, 1H, *J* = 2.7, 9.9, 27.6 Hz, H-3), 4.87 (d, 1H, *J* = 26.6 Hz, H-1), 4.28 (dd, 1H, *J* = 6.0, 12.2 Hz, H-6), 4.18 (dd, 1H, *J* = 2.3, 12.2 Hz, H-6), 3.71 (ddd, 1H, *J* = 2.5, 6.3, 6.5 Hz, H-5), 2.12 (s, 3H, CH_3 Ac), 2.09 (s, 3H, CH_3 Ac), 2.05 (s, 3H, CH_3 Ac); ^{13}C-APT NMR ($CDCl_3$, 100 MHz, HSQC): δ 170.6, 170.2, 169.3 (C=O Ac), 133.1 (C_q), 131.9, 129.1, 128.1 (CH_{arom}), 88.9 (d, *J* = 186 Hz, C-2), 85.2 (d, *J* = 18 Hz, C-1), 76.2 (C-5), 72.3 (d, *J* = 18 Hz, C-3), 65.5 (C-4), 62.5 (C-6), 20.7, 20.6, 20.6 (CH_3 Ac); ^{13}C-GATED ($CDCl_3$, 100 MHz): δ 85.2 ($J_{C1,H1}$ = 151 Hz, C-1); HRMS: $[M+Na]^+$ calcd for $C_{18}H_{21}FO_7SNa$ 423.08842, found 423.08802.

Methyl (phenyl 4-*O*-acetyl-3-*O*-benzyl-2-deoxy-2-fluoro-1-thio-β-D-mannopyranosyl uronate) (12F). Compound **32** (2.53 g, 6.31 mmol) was suspended in MeOH and treated with NaOMe (30 mg, 0.63 mmol) at RT overnight. The reaction was quenched by the addition of Amberlite-H^+ till pH~7 and the solvents were evaporated. Crude triol **33** (~5.2 mmol) was then dissolved in DMF (50 mL), followed by the addition of $PhCH(OMe)_2$ (1.17 mL, 7.77 mmol) and *p*-TsOH•H_2O (cat.) and the resulting solution was stirred at RT overnight. The reaction was neutralized by the addition of Et_3N and the mixture was reduced in volume. The residue was taken up in Et_2O/EtOAc and washed with H_2O (2x) and sat. aq. NaCl. The organic phase was dried over $MgSO_4$, concentrated *in vacuo* and the benzylidene-protected intermediate **34** was obtained by crystallization (EtOAc/PE). A solution of compound **34** (~3.53 mmol) in DMF (18 mL) was cooled to 0 ºC and subsequently benzyl bromide (0.84 mL, 7.05 mmol) and NaH (60% dispersion in mineral oil, 0.28 g, 7.05 mmol) were added. The reaction was stirred at RT for 4 h, followed by the addition of MeOH. The mixture was reduced in volume and the residue was dissolved in EtOAc and washed with H_2O (2x) and sat. aq. NaCl. The organic phase was dried over $MgSO_4$, concentrated *in vacuo* and purified using flash column chromatography (silica gel, 20% EtOAc in PE) to yield compound **35** as a white solid (Yield: 1.51 g, 3.34 mmol, 53% over three steps). Spectroscopic data are reported for compound **35**: TLC: R_f 0.63 (PE/EtOAc, 4/1, v/v); ^{1}H NMR ($CDCl_3$, 400 MHz, HH-COSY, HSQC): δ 7.46-7.51 (m, 4H, CH_{arom}), 7.26-7.41 (m, 11H, CH_{arom}), 5.64 (s, 1H, CH Ph), 5.02 (dd, 1H, *J* = 2.7, 48.5 Hz, H-2), 4.87 (d, 1H, *J* = 12.9 Hz, C*H*H Bn), 4.85 (d, 1H, *J* = 27.9 Hz, H-1), 4.78 (d, 1H, *J* = 12.3 Hz, CH*H* Bn), 4.35 (dd, 1H, *J* = 4.9, 10.6 Hz, H-6), 4.19 (dt, 1H, *J* = 1.5, 9.8 Hz, H-4), 3.92 (t, 1H, *J* = 10.3 Hz, H-6), 3.70 (ddd, 1H, *J* = 2.7, 9.9, 26.0 Hz, H-3), 3.45 (ddd, 1H, *J* = 5.0, 9.7, 9.7 Hz, H-5); ^{13}C-APT NMR ($CDCl_3$, 100 MHz, HSQC): δ 137.5, 137.2 (C_q), 133.5 (C_q SPh), 131.5, 129.1, 129.0,

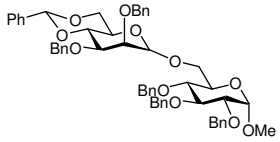
128.5, 128.2, 128.0, 127.9, 126.0 (CH_{arom}), 101.6 (CH Ph), 90.5 (d, *J* = 186 Hz, C-2), 86.4 (d, *J* = 19 Hz, C-1), 77.9 (C-4), 76.3 (d, *J* = 17 Hz, C-3), 72.7 (CH_2 Bn), 71.3 (C-5), 68.3 (C-6); ^{13}C-GATED ($CDCl_3$, 100 MHz): δ 86.4 ($J_{C1,H1}$ = 155 Hz, C-1). Compound **35** (1.46 g, 3.22 mmol) was suspended in MeOH and *p*-TsOH•H_2O was added until the mixture was acidic (pH<5). The reaction was allowed to stir overnight, after which time Et_3N was added to quench to reaction. The solvents were evaporated and compound **36** was purified using flash column chromatography (silica gel, 30% PE in EtOAc) and obtained as a colored oil (Yield: 0.98 g, 2.67 mmol, 83%). Spectroscopic data are reported for compound **36**: TLC: R_f 0.25 (PE/EtOAc, 1/1, v/v); ^{1}H NMR ($CDCl_3$/MeOD, 400 MHz, HH-COSY, HSQC): δ 7.47 (d, 2H, *J* = 8.0 Hz, CH_{arom}), 7.26-7.41 (m, 8H, CH_{arom}), 4.99 (dd, 1H, *J* = 2.3, 49.7 Hz, H-2), 4.85 (d, 1H, *J* = 27.6 Hz, H-1), 4.80 (d, 1H, *J* = 12.4 Hz, C*H*H Bn), 4.71 (d, 1H, *J* = 11.7 Hz, CH*H* Bn), 3.96 (t, 1H, *J* = 9.6 Hz, H-4), 3.90 (dd, 1H, *J* = 2.8, 12.3 Hz, H-6), 3.81 (dd, 1H, *J* = 4.7, 12.3 Hz, H-6), 3.42-3.53 (m, 1H, H-3), 3.32-3.39 (m, 1H, H-5); ^{13}C-APT NMR ($CDCl_3$, 100 MHz, HSQC): δ 137.2 (C_q), 133.5 (C_q SPh), 130.7, 129.0, 128.4, 128.0, 127.8, 127.6 (CH_{arom}), 88.8 (d, *J* = 184 Hz, C-2), 85.0 (d, *J* = 18 Hz, C-1), 80.2 (d, *J* = 18 Hz, C-3), 80.2 (C-5), 71.9 (CH_2 Bn), 65.9 (C-4), 61.7 (C-6); HRMS: $[M+NH_4]^+$ calcd for $C_{19}H_{25}FNO_4S$ 382.14828, found 382.14863. Diol **36** (0.98 g, 2.67 mmol) was dissolved in EtOAc (18 mL) and H_2O (8 mL) was added. The mixture was cooled to 0 ºC, followed by the addition of TEMPO (80 mg, 0.53 mmol) and BAIB (2.15 g, 6.68 mmol). The mixture was allowed to stir at RT for 5 h, after which time sat. aq. $Na_2S_2O_3$ was added. The organic phase was separated and washed with sat. aq. NaCl, dried over $MgSO_4$ and concentrated *in vacuo*. The crude uronic acid was then dissolved in DMF (13 mL) and treated with MeI (0.5 mL, 8.0 mmol) and K_2CO_3 (1.11 g, 8.0 mmol) at RT overnight. The mixture was diluted with EtOAc and H_2O, the organic layer was washed with H_2O and sat. aq. NaCl, dried over $MgSO_4$ and concentrated *in vacuo*. Purification using flash column chromatography (silica gel, 40% EtOAc in PE) afforded the methyl ester intermediate **37** as a yellow oil. Spectroscopic data are reported for compound **37**: ^{1}H NMR ($CDCl_3$, 400 MHz, HH-COSY, HSQC): δ 7.45-7.51 (m, 2H, CH_{arom}), 7.24-7.35 (m, 8H, CH_{arom}), 4.94 (dd, 1H, *J* = 2.6, 49.3 Hz, H-2), 4.76 (d, 1H, *J* = 12.0 Hz, C*H*H Bn), 4.75 (d, 1H, *J* = 27.0 Hz, H-1), 4.70 (d, 1H, *J* = 12.0 Hz, CH*H* Bn), 4.23 (t, 1H, *J* = 9.6 Hz, H-4), 3.81 (d, 1H, *J* = 9.7 Hz, H-5), 3.78 (s, 3H, CH_3 CO_2Me), 3.46 (ddd, 1H, *J* = 2.6, 9.5, 27.8 Hz, H-3), 3.38 (bs, 1H, 4-OH); ^{13}C-APT NMR ($CDCl_3$, 100 MHz, HSQC): δ 168.8 (C=O CO_2Me), 137.2 (C_q), 133.4 (C_q SPh), 131.1, 129.0, 128.4, 127.9, 127.7 (CH_{arom}), 88.4 (d, *J* = 186 Hz, C-2), 85.8 (d, *J* = 18 Hz, C-1), 79.0 (d, *J* = 18 Hz, C-3), 77.9 (C-5), 72.0 (CH_2 Bn), 67.6 (C-4), 52.7 (CH_3 CO_2Me); ^{13}C-GATED ($CDCl_3$, 100 MHz): δ 85.8 ($J_{C1,H1}$ = 152 Hz, C-1). Methyl uronate **37** (0.99 g, 2.52 mmol) was dissolved in pyridine (25 mL) and treated with Ac_2O (0.47 mL, 5.0 mmol) at RT overnight. The reaction was quenched by the addition of MeOH, the solvents were evaporated and the residue was dissolved in EtOAc and washed with H_2O and sat. aq. NaCl. The organic phase was dried over $MgSO_4$, concentrated *in vacuo* and purified using flash column chromatography (silica gel, 40% EtOAc in PE) to yield the title compound as an off-white solid (Yield: 1.03 g, 2.37 mmol, 89% over three steps). TLC: R_f 0.69 (PE/EtOAc, 1/1, v/v); $[\alpha]_D^{20}$ -118.0 (*c* 1, DCM); IR (neat, cm^{-1}): 692, 741, 1059, 1227, 1748; ^{1}H NMR ($CDCl_3$, 400 MHz, HH-COSY, HSQC): δ 7.44-7.48 (m, 2H, CH_{arom}), 7.24-7.33 (m, 8H, CH_{arom}), 5.46 (t, 1H, *J* = 9.9 Hz, H-4), 5.06 (dd, 1H, *J* = 2.5, 49.1 Hz, H-2), 4.86 (d, 1H, *J* = 26.6 Hz, H-1), 4.74 (d, 1H, *J* = 12.3 Hz, C*H*H Bn), 4.61 (d, 1H, *J* = 12.3 Hz, CH*H* Bn), 3.94 (d, 1H, *J* = 9.9 Hz, H-5), 3.69 (ddd, 1H, *J* = 2.7, 9.8, 27.1 Hz, H-3), 3.68 (s, 3H, CH_3 CO_2Me), 1.99 (s, 3H, CH_3 Ac); ^{13}C-APT NMR ($CDCl_3$, 100 MHz, HSQC): δ 169.3, 167.0 (C=O Ac, CO_2Me), 137.0 (C_q), 133.1 (C_q SPh), 131.2, 128.9, 128.3, 127.8, 127.4 (CH_{arom}), 88.2 (d, *J* = 186 Hz, C-2), 85.5 (d, *J* = 18 Hz, C-1), 77.1 (d, *J* = 18 Hz, C-3), 76.2 (C-5), 71.7 (CH_2 Bn), 67.6 (C-4), 52.5 (CH_3 CO_2Me), 20.4 (CH_3 Ac); ^{13}C-GATED ($CDCl_3$, 100 MHz): δ 85.5 ($J_{C1,H1}$= 154 Hz, C-1); HRMS: $[M+NH_4]^+$ calcd for $C_{20}H_{27}FNO_4S$ 396.16393, found 396.16399.

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(4,6-di-*O*-acetyl-2,3-di-*O*-benzyl-α/β-D-mannopyranosyl)-α-D-glucopyranoside (38). 

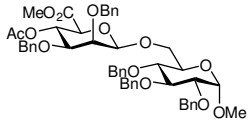
Disaccharide **38** was produced as an anomeric mixutre (α : β = 1 : 3). TLC: R_f α 0.60, β 0.23 (PE/EtOAc, 2/1, v/v); IR (neat, cm^{-1}): 696, 733, 1028, 1047, 1238, 1742; Spectroscopic data are reported for the major isomer (β): ^{1}H NMR ($CDCl_3$, 400 MHz, HH-COSY, HSQC): δ 7.15-7.42 (m, 25H, CH_{arom}), 5.33 (t, 1H, *J* = 9.7 Hz, H-4'), 5.02 (d, 1H, *J* = 10.9 Hz, C*H*H Bn), 4.89 (d, 1H, *J* = 12.6 Hz, C*H*H Bn), 4.74-4.86 (m, 4H, CH_2 Bn), 4.67 (d, 1H, *J* = 12.2 Hz, CH*H* Bn), 4.58 (d, 1H, *J* = 3.4 Hz, H-1), 4.51 (d, 1H, *J* = 11.3 Hz, CH*H* Bn), 4.48 (d, 1H, *J* = 12.0 Hz, C*H*H Bn), 4.31 (d, 1H, *J* = 12.3 Hz, CH*H* Bn), 4.22 (dd, 1H, *J* = 5.8, 12.1 Hz, H-6'), 4.11-4.17 (m, 3H, H-1', H-6, H-6'), 4.02 (t, 1H,

J = 9.3 Hz, H-3), 3.77-3.84 (m, 1H, H-5), 3.72 (d, 1H, *J* = 2.8 Hz, H-2'), 3.51 (dd, 1H, *J* = 3.5, 9.7 Hz, H-2), 3.43-3.47 (m, 2H, H-5', H-6), 3.42 (t, 1H, *J* = 9.6 Hz, H-4), 3.34-3.36 (m, 1H, H-3'), 3.33 (s, 3H, OMe), 2.02 (s, 3H, CH_3 Ac), 2.01 (s, 3H, CH_3 Ac); ^{13}C-APT NMR ($CDCl_3$, 100 MHz, HSQC): δ 170.9, 169.6 (C=O Ac), 138.7, 138.3, 138.2, 137.9, 137.7 (C_q), 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 127.6, 127.4, 127.3, 127.2 (CH_{arom}), 101.4 (C-1'), 97.7 (C-1), 82.0 (C-3), 79.7 (C-2), 78.8 (C-3'), 77.6 (C-4), 75.7, 74.7, 73.5, 73.3 (CH_2 Bn), 72.8 (C-2'), 72.5 (C-5'), 71.2 (CH_2 Bn), 69.6 (C-5), 68.4 (C-6), 68.2 (C-4'), 63.2 (C-6'), 55.0 (OMe), 20.9, 20.8 (CH_3 Ac); ^{13}C-GATED ($CDCl_3$, 100 MHz): δ 101.4 ($J_{C1,H1}$ = 152 Hz, C-1'), 97.7 ($J_{C1,H1}$ = 167 Hz, C-1); HRMS: $[M+Na]^+$ calcd for $C_{52}H_{58}O_{13}Na$ 913.37696, found 913.37718.

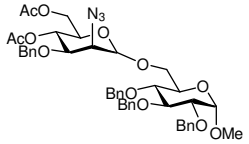
Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α/β-D-mannopyranosyl)-α-D-glucopyranoside (39). Disaccharide **39** was produced as an anomeric mixutre (α : β = 1 : 8.3). Spectroscopic data were in accord with those reported previously.[33]



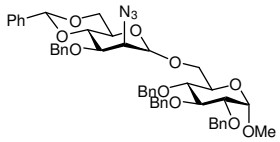
Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(methyl 4-*O*-acetyl-2,3-di-*O*-benzyl-β-D-mannopyranosyl uronate)-α-D-glucopyranoside (40). Disaccharide **40** was produced as the purely β-fused product. Spectroscopic data were in accord with those reported previously.[34]



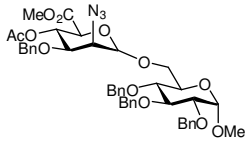
Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(4,6-di-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy-α/β-D-mannopyranosyl)-α-D-glucopyranoside (41). Disaccharide **41** was produced as an anomeric mixture (α : β = 1 : 5.9). Spectroscopic data were in accord with those reported previously.[35]



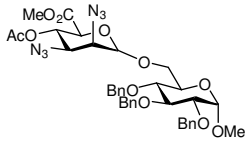
Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2-azido-3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-α/β-D-mannopyranosyl)-α-D-glucopyranoside (42). Disaccharide **42** was produced as an anomeric mixture (α : β = 1 : 3). Spectroscopic data were in accord with those reported previously.[36]

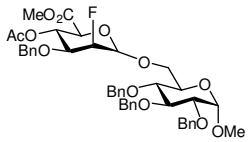


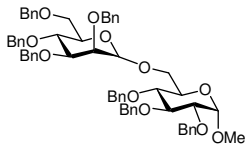
Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(methyl 4-*O*-acetyl-2-azido-3-*O*-benzyl-2-deoxy-α/β-D-mannopyranosyl uronate)-α-D-glucopyranoside (43). Disaccharide **43** was produced as an anomeric mixture (α : β = 1 : 7). Spectroscopic data were in accord with those reported previously.[11a]



Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(methyl 4-*O*-acetyl-2,3-diazido-2,3-dideoxy-α/β-D-mannopyranosyl uronate)-α-D-glucopyranoside (44). Disaccharide **44** was produced as an anomeric mixture (α : β = 1 : 5.5). Spectroscopic data were in accord with those reported previously.[11c]



Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(methyl 4-*O*-acetyl-3-*O*-benzyl-2-deoxy-2-fluoro-α/β-D-mannopyranosyl uronate)-α-D-glucopyranoside (45). 
Disaccharide **45** was produced as an anomeric mixture (α : β = 1 : 5). TLC: R_f α 0.43, β 0.25 (PE/EtOAc, 2/1 , v/v); IR (neat, cm^{-1}): 738.7, 1028, 1051, 1094, 1229, 1751, 2924; Spectroscopic data are reported for the major isomer (β): ^{1}H NMR ($CDCl_3$, 400 MHz, HH-COSY, HSQC): δ 7.28-7.40 (m, 20H, CH_{arom}), 5.39 (t, 1H, *J* = 9.6 Hz, H-4'), 4.99 (d, 1H, *J* = 10.8 Hz, C*H*H Bn), 4.86 (d, 1H, *J* = 11.5 Hz, C*H*H Bn), 4.75-4.83 (m, 2H, CH_2 Bn), 4.52-4.72 (m, 6H, CH_2 Bn, H-1, H-2'), 4.16 (d, 1H, *J* = 17.0 Hz, H-1'), 4.09 (dd, 1H, *J* = 1.8, 10.8 Hz, H-6), 3.99 (t, 1H, *J* = 9.2 Hz, H-3), 3.75-3.81 (m, 2H, H-5, H-5'), 3.70 (s, 3H, CH_3 CO_2Me), 3.39-3.56 (m, 4H, H-2, H-3', H-4, H-6), 3.32 (s, 3H, OMe), 2.04 (s, 3H, CH_3 Ac); ^{13}C-APT NMR ($CDCl_3$, 100 MHz, HSQC): δ 169.3, 167.3 (C=O Ac, CO_2Me), 138.7, 138.4, 138.0, 137.2 (C_q), 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6 (CH_{arom}), 98.8 (d, *J* = 16 Hz, C-1'), 97.8 (C-1), 86.1 (d, *J* = 190 Hz, C-2'), 82.1 (C-3), 79.8 (C-2), 77.4 (C-4), 76.1 (d, *J* = 17 Hz, C-3'), 75.7, 74.6, 73.4 (CH_2 Bn), 73.2 (C-5'), 71.7 (CH_2 Bn), 69.6 (C-5), 68.7 (C-6), 68.3 (C-4'), 55.1 (OMe), 52.7 (CH_3 CO_2Me), 20.7 (CH_3 Ac); ^{13}C-GATED ($CDCl_3$, 100 MHz): δ 98.8 ($J_{C1,H1}$= 156 Hz, C-1'), 97.8 ($J_{C1,H1}$= 162 Hz, C-1); HRMS: $[M+Na]^+$ calcd for $C_{44}H_{49}FO_{12}Na$ 811.31003, found 811.31011.

Methyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-mannopyranosyl)-α-D-glucopyranoside (46). 
Disaccharide **46** was produced as an anomeric mixture (α : β = 1 : 2). The analytical data of the title compound have been reported previously.[25c]

Footnotes and References

[1] a) *Comprehensive Glycoscience*, J. P. Kamerling Ed.; Elsevier, Oxford, **2007**; Vol. 1; b) *The Organic Chemistry of Sugars*, D.E. Levy, P. Fügedi Eds.; CRC Press, Boca Raton, **2006**.

[2] Paulsen, H.; Richter, A.; Sinnwell, V.; Stenzel, W. *Carbohydr. Res.* **1978**, *64*, 339-364.

[3] a) Mootoo, D. R.; Konradson, P.; Ududong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583-5584; b) Fraser-Reid, B.; Wu, Z.; Ududong, U.; Ottoson, H. *J. Org. Chem.* **1990**, *55*, 6068-6070.

[4] a) Codée, J. D. C.; Litjens, R. E. J. N.; van den Bos, L. J.; Overkleeft, H. S.; van der Marel, G. A. *Chem. Soc. Rev.* **2005**, *34*, 769-782; b) Wang, Y.; Ye, X.-S.; Zhang, L.-H. *Org. Biomol. Chem.* **2007**, *5*, 2189-2200.

[5] Douglas, N. L.; Ley, S. V.; Lücking, U.; Warriner, S. L. *J. Chem. Soc.-Perkin Trans. 1* **1998**, 51-65.

[6] a) Zhang, Z. Y.; Ollmann, I. R.; Ye, X. S.; Wischna, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734-753; b) Koeller, K. M.; Wong, C.-H. *Chem. Rev.* **2000**, *100*, 4465-4493; c) Ritter, T. K.; Mong, K. K. T.; Liu, H. T.; Nakatani, T.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4657-4660; d) Lee, J.-C.; Greenberg, W. A.; Wong, C.-H. *Nat. Prot.* **2006**, *1*, 3143-3152.

[7] Hsu, Y.; Lu, X.-A.; Zulueta, M. M. L.; Tsai, C.-M.; Lin, K.-I.; Hung, S.-C.; Wong, C.-H. *J. Am. Chem. Soc.* **2012**, *134*, 4549-4552.

[8] a) Pedersen, C. M.; Nordstrøm, L. U.; Bols, M. *J. Am. Chem. Soc.* **2007**, *129*, 9222-9235; b) Pedersen, C. M.; Marinescu, L. G.; Bols, M. *Chem. Commun.* **2008**, 2465-2467; c) Pedersen, C. M.; Marinescu, L. G.; Bols, M. *C. R. Chimie* **2011**, *14*, 17-43.

[9] a) van den Bos, L. J.; Codée, J. D. C.; Litjens, R. E. J. N.; Dinkelaar, J.; Overkleeft, H. S.; van der Marel, G. A. *Eur. J. Org. Chem.* **2007**, 3963-3976; b) Codée, J. D. C.; Christina, A. E.; Walvoort, M. T. C.; Overkleeft, H. S.; van der Marel, G. A. *Topics Curr. Chem.* **2011**, vol. 301, p. 253-289.

[10] Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165-195.

[11] a) Walvoort, M. T. C.; Lodder, G.; Mazurek, J.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *J. Am. Chem. Soc.* **2009**, *131*, 12080-12081; b) Walvoort, M. T. C.; Lodder, G.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *J. Org. Chem.* **2010**, *75*, 7990-8002; c) Walvoort, M. T. C.; Moggré, G.-J.; Lodder, G.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *J. Org. Chem.* **2011**, *76*, 7301-7315.

[12] The anomeric triflates can act as product-forming intermediates or serve as a reservoir for oxacarbenium ion intermediates.

[13] Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1998**, *120*, 435-436.
[14] Crich, D.; Vinogradova, O. *J. Am. Chem. Soc.* **2007**, *129*, 11756-11765.
[15] To date, the relative donor reactivity of pyranosyl uronic acids has not been quantified. For a study on the relative rates of anomerization of glucopyranosyl uronic acids and glucopyranosides, see: Pilgrim, W.; Murphy, P. V. *J. Org. Chem.* **2010**, *75*, 6747-6755.
[16] The activation of thioglycosides using NIS-TfOH can involve activation by iodonium triflate, the generated sulfenyliodide and iodide, and can proceed through direct activation of the promoter or *via* halonium transfer or aglycone transfer. See references 17 and 18.
[17] Ravindranathan Kartha, K. P.; Cura, P.; Aloui M.; Readman, K.; Rutherford, T. J.; Field, R. A. *Tetrahedron: Asymm.* **2000**, *11*, 581-593.
[18] Fraser-Reid, B.; Christóbal López, J.; Gómez, A. M.; Uriel C. *Eur. J. Org. Chem.* **2004**, 1387-1395.
[19] Other examples of using a similar experimental set-up for competition reactions are reported: a) Premathilake, H. D.; Mydock, L. K.; Demchenko, A. V. *J. Org. Chem.* **2010**, *75*, 1095-1100; b) Ranade, S. C.; Kaeothip, S.; Demchenko, A. V. *Org. Lett.* **2010**, *12*, 5628-5631; c) Uriel, C.; Gomez, A. M.; López, J. C.; Fraser-Reid, B. *J. Carb. Chem.* **2005**, *24*, 665-675; d) Zeng, Y.; Wang, Z.; Whitfield, D.; Huang, X. *J. Org. Chem.* **2008**, *73*, 7952-7962.
[20] Also competition experiments between different acceptors have been reported: Crich, D.; Dudkin, V. *J. Am. Chem. Soc.* **2001**, *123*, 6819-6825. See for relative reactivities of different aglycones: Lahmann, M.; Oscarson, S. *Can. J. Chem.* **2002**, *80*, 889-893.
[21] Fraser-Reid, B.; Wu, Z.; Andrews, C. W.; Skowronski, E. *J. Am. Chem. Soc.* **1991**, *113*, 1435-1437.
[22] a) Jensen, H. H.; Nordstrøm, M.; Bols, M. *J. Am. Chem. Soc.* **2004**, *126*, 9205-9213; b) Crich, D. *Acc. Chem. Res.* **2010**, *43*, 1144-1153.
[23] When donor **12β** was competed with its glucuronic acid counterpart, only the disaccharide from **12β** was observed.
[24] Ye, X.-S.; Wong, C.-H. *J. Org. Chem.* **2000**, *65*, 2410-2431.
[25] a) Lucero, C. G.; Woerpel, K. A. *J. Org. Chem.* **2006**, *71*, 2641-2647; b) Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 168-169; c) Dinkelaar, J.; de Jong, A.-R.; van Meer, R.; Somers, M.; Lodder, G.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *J. Org. Chem.* **2009**, *74*, 4982-4991.
[26] For recent reviews on oxacarbenium ions, see: a) Walvoort, M. T. C.; Dinkelaar, J.; van den Bos, L. J.; Lodder, G.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *Carbohydr. Res.* **2010**, *345*, 1252-1263; b) Smith, D. M.; Woerpel, K. A. *Org. Biomol. Chem.* **2006**, *4*, 1195-1201; c) Horenstein, N. A. *Adv. Phys. Org. Chem.* **2006**, *41*, 275-314; d) Bohé, L.; Crich, D. *C. R. Chimie* **2011**, *14*, 3-16; d) Whitfield, D. M. *Advances in Carbohydr. Chem. Biochem.* **2009**, *62*, 83-159.
[27] See for example: Jensen, H. H.; Bols, M. *Acc. Chem. Res.* **2006**, *39*, 259-265, and references therein.
[28] Codée, J. D. C.; van den Bos, L. J.; de Jong, A.-R.; Dinkelaar, J.; Lodder, G.; Overkleeft, H. S.; van der Marel, G. A. *J. Org. Chem.* **2009**, *74*, 38-47.
[29] a) Deslongchamps, P. *Stereoelectronic effects in Organic Chemistry*, Pergamon, New York, **1983**; b) Deslongchamps, P. *Pure Appl. Chem.* **1993**, *65*, 1161-1178.
[30] 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 **12β** can be caused by the destabilizing Δ2-effect present in **12β**. Taken together, ground state energy differences can not alone account for the larger difference in reactivity between **12β** and **12α** compared to the reactivity difference between **10α** and **10β**.
[31] Yu, H. N.; Furukawa, J.-i.; Ikeda, T.; Wong, C.-H. *Org. Lett.* **2004**, *6*, 723-726.
[32] Benito, D.; Matheu, M. I.; Morère, A.; Díaz, Y.; Castillón, S. *Tetrahedron* **2008**, *64*, 10906-10911.
[33] Baek, J. Y.; Choi, T. J.; Jeon, H. B.; Kim, K. S. *Angew. Chem. Int. Ed.* **2006**, *45*, 7436-7440.
[34] van den Bos, L. J.; Dinkelaar, J.; Overkleeft, H. S.; van der Marel, G. A. *J. Am. Chem. Soc.* **2006**, *128*, 13066-13067.
[35] van den Bos, L. J.; Duivenvoorden, B. A.; de Koning, M. C.; Filippov, D. V.; Overkleeft, H. S.; van der Marel, G. A. *Eur. J. Org. Chem.* **2007**, 116-124.
[36] Litjens, R. E. J. N.; van den Bos, L. J.; Codée, J. D. C.; van den Berg, R. J. B. H. N.; Overkleeft, H. S.; van der Marel, G. A. *Eur. J. Org. Chem.* **2005**, 918-924.