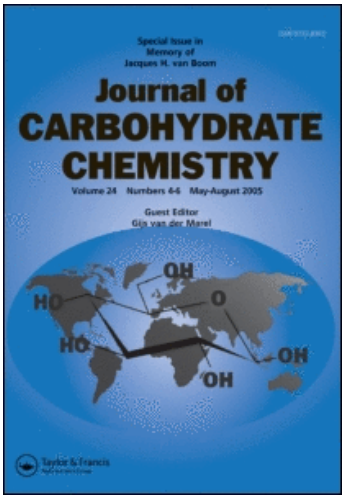

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Neighboring Group Participation in Glycosylation Reactions by 2,6-Disubstituted 2-*O*-Benzoyl groups: A Mechanistic Investigation

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Neighboring Group Participation in Glycosylation Reactions by 2,6-Disubstituted 2-O-Benzoyl groups: A Mechanistic Investigation

Rohan J. Williams, Nathan W. McGill, Jonathan M. White, and Spencer J. Williams

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Variable yields and glycosylation stereoselectivity were obtained for NIS/TfOH-mediated reaction of 4-methoxyphenyl 2,4,6-tetra-*O*-acetyl-β-D-galactopyranoside and thiogalactosides bearing acetyl, benzoyl, 2,6-dimethoxylbenzoyl, 2,4,6-trimethylbenzoyl, or 2,6-dichlorobenzoyl groups at the 2-positions and acetyl at the remainder. X-ray structures of 4-methylphenyl 2,3,4,6-tetra-*O*-(2,4,6-trimethylbenzoyl)-1-thio-β-D-galactopyranoside and 4-methylphenyl 3,4-*O*-isopropylidene-2,6-di-*O*-(2,4,6-trimethylbenzoyl)-1-thio-β-D-galactopyranoside revealed slightly distorted $^4C_1$ chair conformations. Variable temperature NMR revealed that activation of 4-methylphenyl 2,3,4,6-tetra-*O*-(2,4,6-trimethylbenzoyl)-1-thio-β-D-galactopyranoside afforded only dioxolenium ion, whereas 4-methylphenyl 3,4,6-tri-O-acetyl-2-*O*-(2,4,6-trimethylbenzoyl)-1-thio-β-D-galactopyranoside gave a 1:1 mixture of dioxolenium ion and glycosyl triflate. However, the reaction intermediates formed from these deactivated donors do not influence the glycosylation stereoselectivity; instead, it is influenced by steric and electronic interactions at the transition states.

Keywords Glycosylation Reactions; 2,6-Disubstituted 2-O-Benzoyl Groups

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INTRODUCTION

Neighboring group participation is a widely used strategy for stereocontrol in the formation of the glycosidic linkage. The use of 2-*O*-acyl groups on the glycosyl donor as a neighboring group has been employed for more than a century to effect the formation of the 1,2-*trans* linkage.[1] The involvement of the neighboring group is implicit in the observation of 1,2-*trans*-linked products and compelling evidence for the formation of intermediate 1,2-*cis*-dioxolenium ions has been gathered through their isolation in crystalline form,[2] through their spectroscopic observation as reaction intermediates,[3,4] and by computational studies.[5] More recently, other neighboring groups have been employed at the 2-position including 2-picolinyl,[6] 2-O-phosphoryl,[7] and 2-deoxy-2-dibenzylamino[8] groups. Neighboring group participation by groups at more remote sites, namely the 3-, 4-, and 6-positions of a hexopyranose, has been widely invoked in a range of different systems,[9] although a recent mechanistic study provided support only for neighboring group participation from the 3-position.[10] A new twist on the concept of neighboring group participation has been pioneered by Boons et al., who have reported that a (1*S*)-phenyl-2-(phenylsulfanyl)ethyl ester can perform neighboring group participation yielding 1,2-*cis*-α-glycosides through an intermediate sulfonium ion that forms part of a *trans*-decalin-like ring system.[11,12]

Despite the widespread use of neighboring group participation to control the anomeric stereochemistry of glycosylation reactions, there are a range of troublesome side reactions that commonly occur (Fig. 1a). These include transesterification, orthoester formation, and incomplete stereocontrol leading to the formation of significant amounts of 1,2-*cis* products. Transesterification refers to the transfer of the 2-*O*-acyl group from the donor to the acceptor,[13] and the resulting donor-derived intermediates can go on to form 1,2-linked oligosaccharides[14,15] or 2-hydroxyglycosides.[16] Orthoesters are formed from nucleophilic attack by the acceptor alcohol at the central carbon of the dioxolenium ion intermediate. Orthoester formation is more pronounced under basic conditions and in some cases is a function of anomeric stereochemistry of the donor.[17] In many cases the orthoesters can be rearranged by treatment with acid,[18] and orthoesters are frequently used as glycosyl donors in their own right,[18] but in other cases the orthoester cannot be induced to rearrange in a productive fashion.[19] It has been argued that there is a mechanistic link between the formation of orthoesters and transesterification, and computational studies have suggested that in some cases, despite proceeding through a common dioxolenium ion intermediate, these two processes are in fact mechanistically distinct.[20] In some glycosylation reactions, despite the presence of a neighboring vicinal ester group, ineffective stereocontrol is observed.[21,22] An extreme example of this was provided by Kong and coworkers, who reported that 3-*O*-alkyl-2-*O*-benzoyl galactosyl donors provide excellent

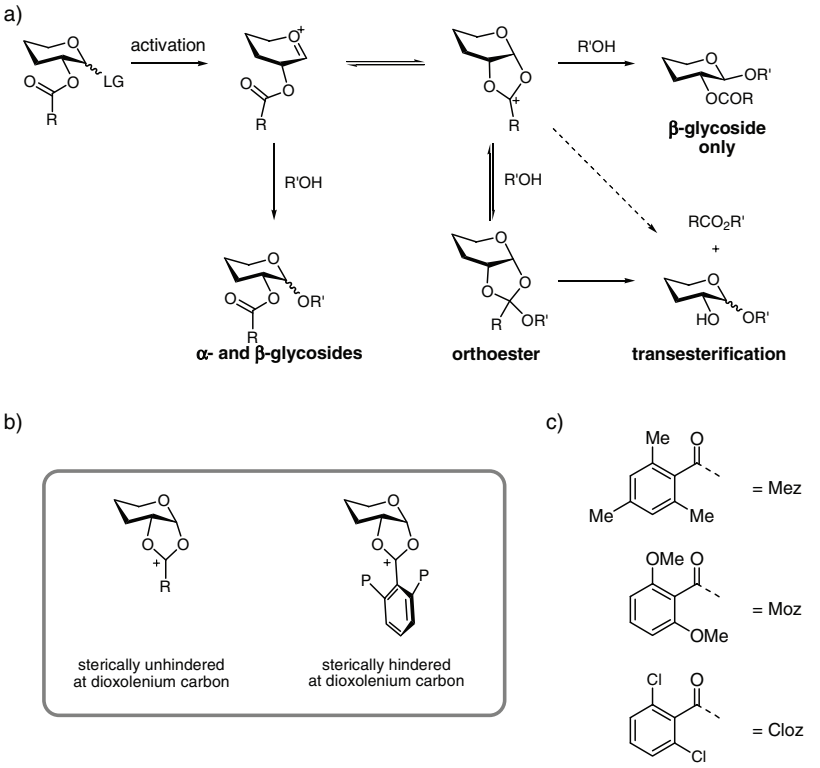


Figure 1: (a) Mechanism of glycosylation with neighboring group participation, and side reactions leading to poor stereoselectivity, orthoester formation, and transesterification. (b) Comparison of dioxolenium ion intermediates arising from standard and 2,6-disubstituted benzoyl groups. (c) Protecting groups investigated in this work: Mez = 2,4,6-trimethylbenzoyl; Moz = 2,6-dimethoxybenzoyl; Cloz = 2,6-dichlorobenzoyl.

cis-α-stereoselectivity.[23] Poor stereocontrol is likely a result of a mismatched pair, where steric and/or electronic factors destabilize the transition state leading to the 1,2-*trans*-glycosidic bond, but not the corresponding transition state leading to the 1,2-*cis*-glycosidic bond. Evidence for this has been corroborated by studies applying the principle of double stereodifferentiation using enantiomeric pairs of glycosyl donors.[24]

We have recently reported studies aimed at the synthesis of the β-D-galactopyranose-1,3-β-D-galactopyranose linkage found within plant arabinogalactan proteins.[25] Significant difficulties were noted in the use of various 2-*O*-acyl groups as neighboring groups including transesterification, orthoester formation, and poor stereoselectivity. Similar problems have been reported by others and appear to be especially pronounced for D-*galacto*-configured glycosyl donors.[21,23,26] In our case these problems were at least partially overcome through the use of a 2,4,6-trimethylbenzoyl (Mez) group, the *ortho* substituents

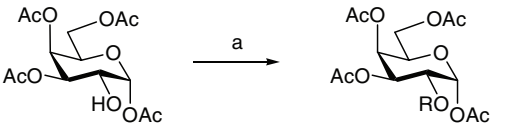
of which were proposed to sterically block the central carbon of the dioxolenium ion intermediate (Fig. 1b).[20,27] However, despite this enticing mechanistic rationale, we found that in at least one case, an orthoester was isolated as the major product using a 2-*O*-Mez protected glycosyl donor.[25] Here we report on a systematic investigation of the outcome of glycosylation reactions of glycosyl donors bearing a range of 2-*O*-acyl groups, and in particular 2,6-disubstituted benzoyl groups (Fig. 1c). We report X-ray structures that provide insight into the ground state structures of two glycosyl donors that give significantly different stereoselectivity in glycosylation reactions. Finally, using low-temperature NMR spectroscopy, we studied the reaction intermediates formed upon activation of the donors, providing mechanistic insight into the variable stereoselectivity seen in glycosylations using these donors.

RESULTS AND DISCUSSION

To systematically explore the effect of different 2-*O*-acyl groups on the outcome of a model glycosylation, we prepared the model donors **1**–**5**. These compounds have a common set of acetyl protecting groups at the 3-, 4-, and 6-positions, but vary in the nature of the acyl group at the 2-position. 1,3,4,6-Tetra-O-acetyl-α-D-galactopyranose **6** was obtained from β-D-galactopyranose penta-acetate by treatment with aqueous CF_3CO_2H according to the procedure of Chittenden.[28] Acylation of **6** with benzoyl (Bz), 2,6-dimethoxylbenzoyl (Moz), 2,4,6-trimethylbenzoyl (Mez), or 2,6-dichlorobenzoyl (Cloz) chlorides afforded the corresponding esters **7**–**10** (Sch. 1). $BF_3.Et_2O$-catalyzed thioglycosylation provided the thioglycosides **2**–**4** in moderate yield, but gave products that were difficult to purify. In practice it proved better to convert **7**–**10** to the glycosyl bromides (with HBr in AcOH), followed by thioglycosylation in the presence of aqueous base with a phase-transfer catalyst, tetrabutylammonium hydrogen sulfate.

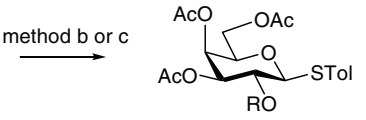
The model glycosyl acceptor **11** was chosen as it represents a challenging substrate to glycosylate, being a secondary alcohol that is sterically hindered and electronically deactivated by the flanking electron-withdrawing protecting groups on the upper and lower faces of the sugar ring. The acceptor **11** was prepared from 4-methoxyphenyl β-D-galactopyranoside[29] in a three-step route involving (a) stannylene-acetal mediated regioselective allylation at O-3, (b) acetylation, and (c) deallylation using $PdCl_2$ (Sch. 2). Much lower yields were obtained when sequential isomerization/hydrolysis with Wilkinson's catalyst/DABCO/aq. HCl or Pd-C/*p*-TsOH was used for the deallylation.

Glycosylation reactions of the acceptor **11** with the donors **1**–**5** were performed using *N*-iodosuccinimide and triflic acid in CH_2Cl_2 (Table 1). The tetra-acetate thioglycoside **1** was a very poor glycosyl donor and provided the disaccharide in only 36% yield but with excellent stereoselectivity (1:35, α:β); 9%



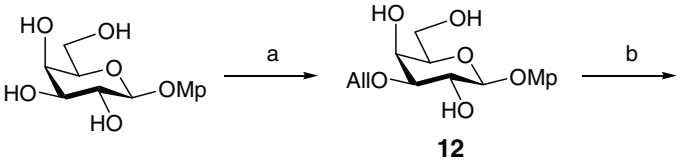
6

7 R = Bz, 93%
8 R = Mez, 100%
9 R = Moz, 100%
10 R = Cloz, 100%



	R	method b	method c
1	Ac	–	–
2	Bz	44%	76%
3	Mez	42%	74%
4	Moz	31%	37%
5	Cloz	0%	66%

Scheme 1: *Reagents and conditions:* (a) RCl, pyr, DMAP; (b) HSTol, F_3BOEt_2, $(CH_2Cl)_2$, 65°C; (c) (i) HBr, AcOH, CH_2Cl_2; (ii) HSTol, Bu_4NHSO_4, CH_2Cl_2, 1 M Na_2CO_3.



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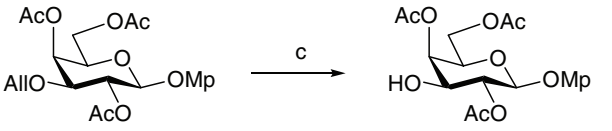
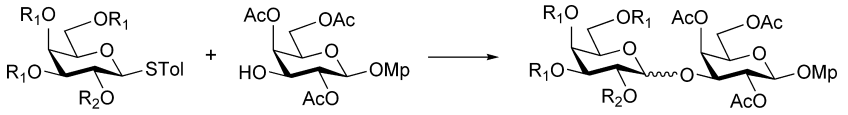


13 **11**

Scheme 2: *Reagents and conditions:* (a) (i) Bu_2SnO, toluene, reflux; (ii) Bu_4NBr, allyl bromide, reflux, 72%; (b) Ac_2O, pyr, 70%; (c) $PdCl_2$, MeOH/toluene (3:1), 69%.

of the transesterification product was also isolated (Table 1, entry 1). The 2-*O*-benzoyl donor **2** provided a somewhat improved yield (44%) and marginally poorer stereoselectivity (1:10, α:β; Table 1, entry 2). In all cases the use of the 2,6-disubstituted benzoates as neighboring groups, glycosyl donors **3**–**5**, provided improved yields, with no transesterification products observed; however, greatly varying stereoselectivity was observed. The mesitoate **3** gave the best yield of disaccharide (66%) but with a poor stereoselectivity (1:2, α:β; Table 1,

Table 1: Outcome of glycosylations of acceptor **11** by the glycosyl donors **1–5, 16** and **19**



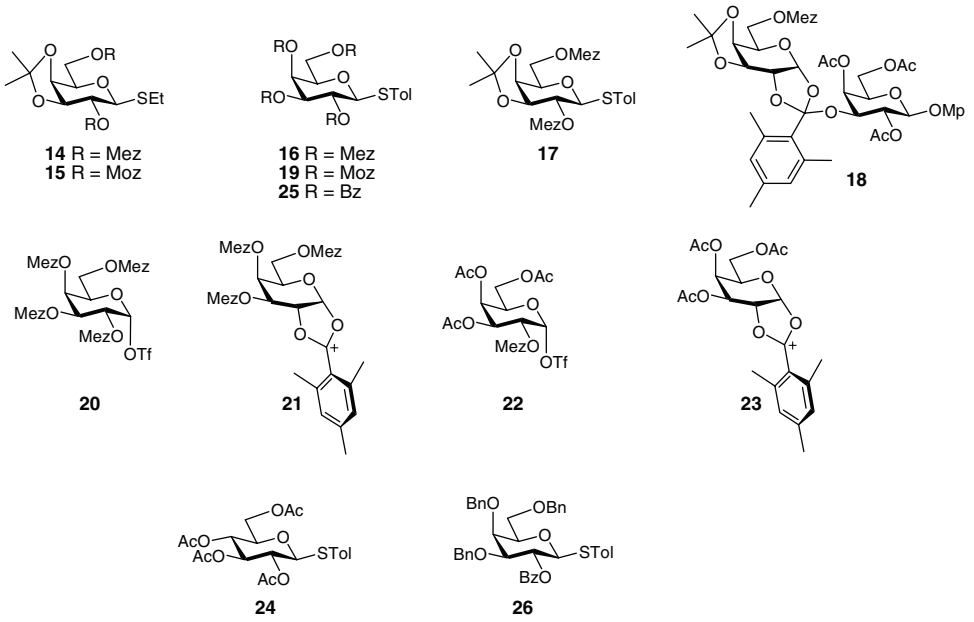
11

Entry	Donor	R_1	R_2	Product	Yield (%)[a]	β/α ratio
1	**1**	Ac	Ac	**27a,b**	36[b]	35:1
2	**2**	Ac	Bz	**28a,b**	44	10:1
3	**3**	Ac	Mez	**29a,b**	66	2:1
4	**4**	Ac	Moz	**30a,b**	56	19:1
5	**5**	Ac	Cloz	**31a,b**	63	1.3/1
6	**16**	Mez	Mez	**32**	57	β only
7	**19**	Moz	Moz	**33**	32	—[c]

[a]*Reagents and conditions*: NIS (2.5 equiv), TfOH (0.25 equiv), 0°C, CH_2Cl_2.
[b]9% of the transesterified product, 4-methoxyphenyl 2,3,4,6-tetra-*O*-acetyl-β-D-galacto pyranoside, was isolated.
[c]The product(s) of the glycosylation could not be adequately purified; after saponification (LiOH in MeOH) of the crude mixture, the β-anomer of the deprotected disaccharide was isolated in the indicated yield.

entry 3); the 2,6-dichlorobenzoate **5** gave a similar yield (63%) and stereoselectivity (1:1.3, α:β; Table 1, entry 4); and the 2,6-dimethoxybenzoate **4** gave a slightly poorer yield (56%) but with excellent stereoselectivity (1:19, α:β; Table 1, entry 5). Two conclusions can be drawn from these results. First, the presence of *ortho* substituents on the benzoyl group affords a significant improvement in yield of the glycosylation reaction, possibly through limiting orthoester formation and transesterification. Second, despite the presence of the ester group at the 2-position, neighboring group participation cannot be guaranteed, with variable stereoselectivity being observed.

The results reported stand in contrast with recently reported work using glycosyl donors bearing more than one 2,6-disubstituted benzoyl group. Whitfield and coworkers have reported that 3,4-di-*O*-isopropylidene thiogalactosides bearing 2,6-dimethoxybenzoyl or 2,6-dimethylbenzoyl groups at the 2- and 6-positions, **14** and **15**, were effective β-selective glycosyl donors for a polymeric PEG-based primary alcohol,[14,20] and we recently showed that a tetramesitoate thiogalactoside **16** provided excellent yields and stereoselectivity in the glycosylation of the alcohol **11** (Scheme 3).[25] However, we observed a significantly different outcome when using the closely related 3,4-di-*O*-isopropylidene-protected thioglycoside **17** in glycosylations of the secondary alcohol **11**. In this case the orthoester **18** was the major product (63%); this orthoester could not be rearranged to a glycoside product.[25]



Scheme 3.

These results suggested that subtle changes in the nature of the protecting groups at remote positions on the glycosyl donor can afford dramatically different outcomes. We were therefore prompted to examine the effect of glycosylations using the synthetically more accessible donors, tetramesitoate **16**[25] and tetra-(2,6-dimethoxybenzoate) **19**. Despite our best efforts, we were unable to prepare the tetra-(2,6-dichlorobenzoate) derivative—it appears that under the forcing conditions required for the installation of four 2,6-dichlorobenzoyl groups, side reactions prevented accumulation of product. Under similar conditions to that used previously, tetramesitoate **16** afforded the disaccharide in 57% yield, with only the β-anomer being observed (Table 1, entry 6); we have reported that after extensive optimization this yield could be improved to 80%.[25] Finally, the tetra-(2,6-dimethoxybenzoate) **19** was a particularly poor glycosyl donor and purification of the products of the reaction was challenging; ultimately a 32% yield of the deprotected β-linked disaccharide was obtained (Table 1, entry 7). These results clearly show that the outcome of these glycosylations depend subtly on the nature of the protecting groups on the carbohydrate, particularly those remote from the anomeric centre. The poor stereoselectivity and lower yields seen for glycosylations with the donors **3**–**5** were unexpected and encouraged us to take a closer look at the underlying chemistry.

We wondered whether the presence of more than one 2,6-disubstituted benzoate ester on the glycosyl donor could lead to steric crowding so that the

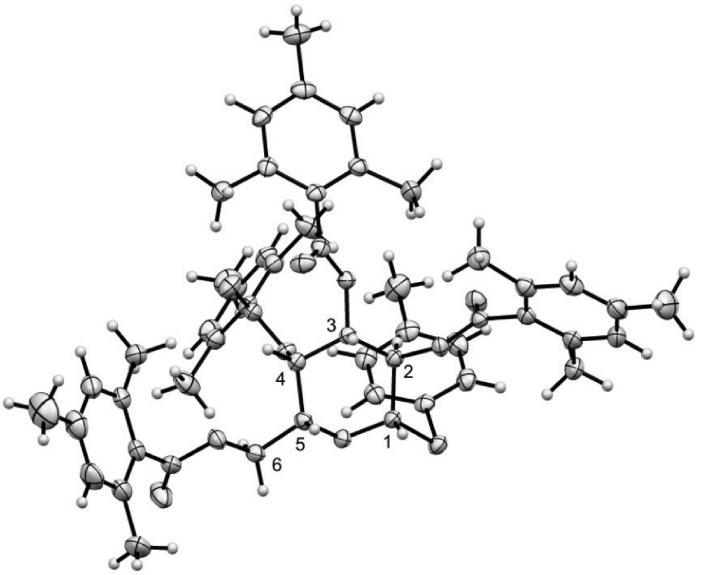


Figure 2: ORTEP diagram of single crystal X-ray structure of tetramesitoate thiogalactoside **16**. Only ring carbons are numbered for clarity. Thermal ellipsoids are at 50% probability.

remote groups may buttress against one another to impede the ability of the acyl group at position 2 to provide anchimeric assistance, or alternatively may distort the pyranose ring conformation and thereby influence the stereoselectivity. We therefore determined the X-ray structures of the tetra-*O*-mesitoyl donor **16** and the 3,4-*O*-isopropylidene protected donor **17** (Figs. 2 and 3). Inspection of these structures reveals no unexpected distortion of the pyranose ring, with both rings being found in approximate $^4C_1$ conformations. In particular, the conformation of **17** is very similar to that seen for ethyl 2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-1-thio-β-D-galactoside,[30] suggesting that the mesitoyl group does not result in significant conformational changes compared to a benzoyl group. In this case and as has been seen elsewhere, the presence of the 3,4-*O*-isopropylidene group in **17** results in only limited flattening of the pyranose ring from a classical $^4C_1$ conformation to a slightly distorted $^4C_1$ conformation.[31] In **17** the *endo* methyl group of the isopropylidene acetal is found 4.6 Å from the anomeric carbon, and has the potential to cause substantial steric repulsion with a nucleophile that approaches from the β-face. In the case of the tetramesitoate **18**, the individual mesitoate groups are well spaced and encapsulate the upper face of the carbohydrate ring, raising the likelihood of significant steric interactions with a glycosyl acceptor approaching from the β-face. However, there is no evidence for antagonistic interactions of the remote mesitoate groups preventing neighboring group participation by the mesitoate at C2. One significant difference seen with mesitoyl groups relative to benzoyl

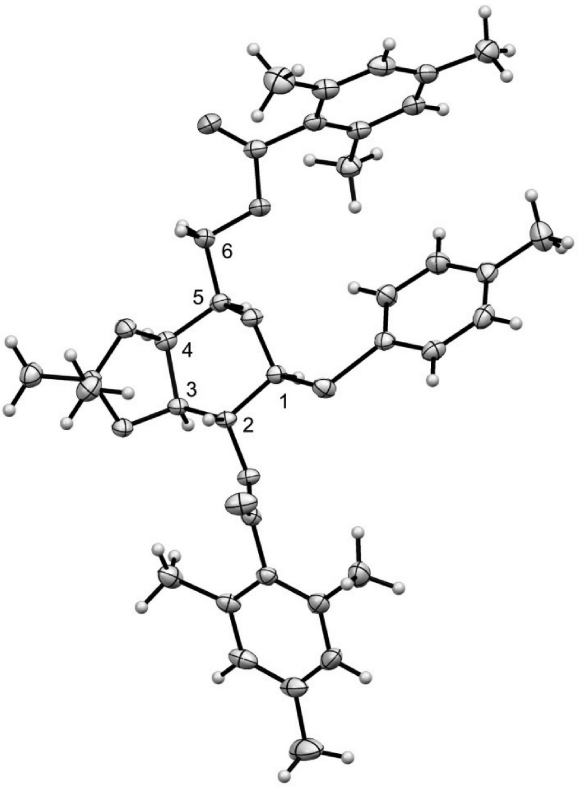


Figure 3: ORTEP diagram of single crystal X-ray structure of isopropylidene thiogalactoside **17**. Only ring carbons are numbered for clarity. Thermal ellipsoids are at 50% probability.

groups is a change in the orientation of the acyl carbonyl group relative to the aromatic ring. For example, in ethyl 2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-1-thio-β-D-galactoside,[30] the torsion angles for O—C(=O)—C_{ipso}—C_{ortho} are close to zero, whereas for **16** or **17**, the corresponding angles fall in the range of 41° to 79°. In particular, the angle for O—C(=O)—C_{ipso}—C_{ortho} for the mesitoyl at C2 is 61° for both **16** and **17**. This may have some impact on the energy of the transition state leading to the formation of a dioxolenium ion intermediate, as discussed later.

We next investigated the nature of the reaction intermediates formed upon activation of the glycosyl donors. In recent years variable temperature NMR has become a valuable ally in the study of intermediates formed in glycosylation reactions.[3,4,11,32] Typically, studies with thioglycosides and sulfoxides have utilized highly soluble activator systems, such as Tf_2O/DTBMP, Tf_2O/benzenesulfinylpiperidine/DTBMP, or TolSOTf/DTBMP, or electrochemical methods. Surprisingly, despite its widespread use as a promoter for glycosylation reactions, we are not aware of any case where NIS/TfOH has been investigated in NMR experiments. Possibly, this is due to the poor solubility

of NIS, especially at low temperatures. However, insight into activation with NIS would be of broad interest as this is a widely used reagent that is readily available. We found that while NIS is poorly soluble in chloroform at low temperature, upon addition of one equivalent of TfOH a homogeneous solution is obtained, presumably composed of iodonium triflate and succinimide (or possibly of protonated NIS with a triflate counterion). Accordingly, we undertook a series of low-temperature NMR experiments in which the thioglycosides **3** or **16** were dissolved in $CDCl_3$ and treated with one equivalent of both NIS and TfOH, in the absence of acceptor alcohol, so as to allow the accumulation of possible reaction intermediates.

Addition of TfOH to a suspension of donor **16** and NIS in $CDCl_3$ at –60°C led immediately to an intensely purple-colored solution. Inspection of the ^1H NMR spectrum revealed that the donor **16** was converted predominantly to a new species characterized by its anomeric proton signal at δ 6.74 ppm (d, $J = 3.5$ Hz). When slowly warmed in 10°C increments, this species remained stable even at –20°C; however, upon warming to –10°C a new set of signals was formed, characterized by a new anomeric signal at δ_H 7.57 ppm (d, $J =$ 7.4 Hz), and δ_C 111.1 ppm assigned to the anomeric carbon of the dioxolenium ion. These data are consistent with the first formed product being the glycosyl triflate **20**, which upon warming is converted to the dioxolenium ion **21** that comprises the major species at 0°C (Fig. 4a). Owing to the nature of the protecting groups, substantial overlap of the anomeric signal of the dioxolenium ion **21** and the aromatic region was observed with the assignment of signals being substantially assisted by the use of ^1H-^1H COSY experiments. The characteristics of these compounds are similar to related dioxolenium ions

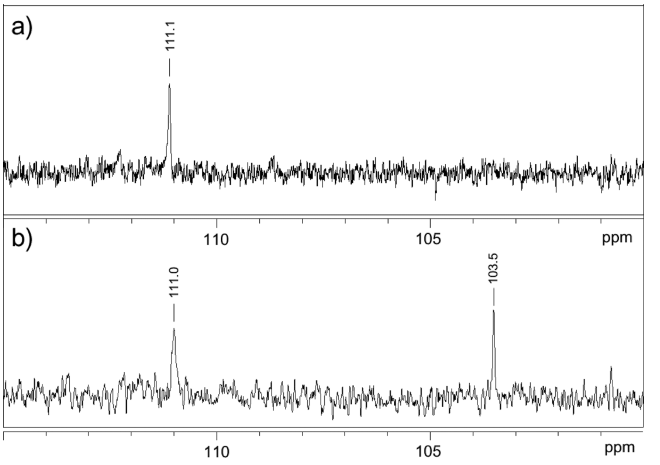


Figure 4: (a) Partial 100-MHz ^{13}C NMR spectrum obtained in $CDCl_3$ upon activation of **16** with NIS/TfOH at –60°C followed by warming to 0°C. (b) Partial 100-MHz ^{13}C NMR spectrum obtained in $CDCl_3$ upon activation of **3** with NIS/TfOH at –60°C followed by warming to 0°C.

reported by Huang and coworkers, who observed δ_C 113.3 and 114.2 ppm for the anomeric carbons, and δ_H 7.35 and δ_H 7.34 ppm for the anomeric protons, of dioxolenium ions formed from **24** and **26**, respectively.[4] On the other hand, Huang and coworkers reported anomeric protons at δ_H 6.57 and 6.21 ppm, and anomeric carbons at δ_C 104.1 and 104.4 ppm, for glycosyl triflates formed from acylated glycosyl donors **24** and **25**, respectively.[4]

When the monomesitoate **3** was activated under the same conditions at –60°C, an approximately 1:1 mixture of two major compounds was formed. One compound was characterized by the presence of signals at δ_H 6.47 ppm (d, $J = 3.5$ Hz) and δ_C 103.5 ppm, which was assigned as the glycosyl triflate **22**. The second compound possessed signals at δ_H 7.64 ppm (d, $J = 8.2$ Hz) and δ_C 111.0 ppm, which was assigned as the dioxolenium ion **23**. In this case upon warming to 0°C the approximately equimolar ratio of **22** and **23** was essentially unchanged (Fig. 4b).

Interpretation of the role of reactive intermediates in glycosylation reactions is complicated by the potential for their facile interconversion with other intermediates, allowing for the operation of a Curtin-Hammett scenario where the product distribution is determined by the relative energetic barriers for product formation, rather than the barriers for their interconversion. In the case of a glycosylation reaction without groups capable of neighboring group participation, two scenarios can be envisioned: an S_N2-like process, such as that seen in the halide-ion catalyzed glycosylations of Lemieux[33] and the β-mannosylation methodology of Crich,[34] wherein either β- or α-configured intermediates are the reactive intermediates, leading to α- or β-configured products, respectively; and an S_N1 process, wherein glycosyl cations are formed, which may react to give products of either α- or β-anomeric stereochemistry. In the case of glycosyl donors capable of neighboring group participation, two main intermediates are likely to be present: the glycosyl cation and the dioxolenium ion intermediate. In some cases, as highlighted by the studies of Huang and coworkers, a glycosyl triflate may also be an important intermediate.[4] It can be expected that reaction with the glycosyl triflate or dioxolenium ion should lead only to β-product, whereas reaction with the glycosyl cation can lead to both α- and β-product, with the energetic barriers to each anomer being nonequal. It is therefore not possible to use product analysis to distinguish between the formation of β-anomer by reaction of an acceptor with a glycosyl cation, an α-triflate, or a dioxolenium ion. Similarly, the formation of an α-anomer may occur through the intermediacy of a glycosyl cation or a β-triflate in the reaction pathway, the latter especially in cases of activated and therefore highly reactive donors.

In our case all preparative glycosylation reactions were performed at 0°C and above. Based on the NMR experiments, for the donor **16** the dioxolenium ion intermediate was the major species present, and the excellent stereoselectivity noted with this donor suggests that the dioxolenium ion simply reacts in

an S_N2-like fashion affording the β-galactoside as the major product. Application of the Curtin-Hammett principle suggests that either the glycosyl cation is not present as an intermediate in this system, or if it is, the barrier for its reaction to give an α-anomer must be high relative to the reaction of the nucleophile with the dioxolenium ion or the β-face of the glycosyl cation. On the other hand, in the case of the donor **3**, poor stereoselectivity is observed, and the α-anomer most likely arises from reaction on the α-face of a glycosyl cation. This suggests that the glycosyl triflate (and possibly the dioxolenium ion) observed in the NMR studies of **3** must be in a facile equilibrium with the glycosyl cation. In the case of the acceptor **11** it seems reasonable to suggest that its hindered nature likely results in a high barrier for an S_N2-like reaction with the glycosyl triflate or dioxolenium ions, thereby allowing for the possibility of reaction with trace amounts of a more reactive glycosyl cation.

It is interesting to compare our results with those of Crich and coworkers[3] and of Huang and coworkers,[4] who studied the intermediates formed upon activation of 2-*O*-acyl glycosyl donors. Crich and coworkers used a range of tri-*O*-benzoyl-D-xylosyl donors and noted that donors derived from this relatively electron-rich sugar (possessing one less electron-withdrawing protecting group than a hexopyranose) readily formed a dioxolenium ion and gave excellent β-stereoselectivity in glycosylation reactions.[3] Huang and coworkers studied the intermediates formed upon activation of the tetraacetate **24**, the tetrabenzoate **25**, and the 2-*O*-benzoyl-3,4,6-tri-O-benzyl-protected galactoside **26** with TolSOTf.[4] Activation of the tetraacetate **24** led to a mixture of glycosyl triflate and dioxolenium ion at low temperature, but upon heating this converted exclusively to the glycosyl triflate. Activation of the tetrabenzoate **25** led to a smooth formation of a glycosyl triflate, with no changes observed at varying temperatures. Finally, activation of the electron-rich donor **26** resulted in clean formation of a dioxolenium ion. When used in a preactivation protocol involving the initial activation of the glycosyl donor prior to addition of the alcohol, all of the glycosyl donors **24**, **25**, and **26** afforded only β-linked products.

Why does subtle variation in the nature of the remote protecting groups in **3** and **16** lead to different pools of activated intermediates and different stereochemical outcomes? The nature of the protecting groups must play a crucial role in determining the stability of the intermediates formed. Ester-protecting groups are electron-withdrawing and destabilize a glycosyl cation, so the formation of a dioxolenium ion or a glycosyl triflate will enable charge dispersal or elimination, respectively. Based on the fact that mesitoates are more electron withdrawing than acetates but more electron donating than benzoates, the stability of the glycosyl cations derived from the donors would follow the series **24** > **25** > **3** > **16**. With regard to the formation of a dioxolenium ion, while a 2,4,6-trimethylphenyl group is electron rich relative to a phenyl or methyl group, its donor properties are complicated by the fact that when oriented orthogonal to the π-system of the dioxolenium ion it will be less able to stabilize

the positive charge, possibly disfavoring the formation of a dioxolenium ion from both **3** and **16**. However, the dioxolenium ion is observed in both cases and so the precise reason for speciation into a glycosyl triflate or dioxolenium ion remains unclear.

For all of the donors investigated by Huang and coworkers, good stereoselectivity is observed irrespective of the existence of the activated intermediate as a glycosyl triflate, a dioxolenium ion, or a mixture of the two, so it seems reasonable to suggest either that (a) glycosyl triflates or dioxolenium ions derived from glycosyl donors bearing 2-*O*-acyl groups can both react in an S_N2-like fashion, or more likely (2) a Curtin-Hammett scenario operates where the reaction intermediates freely interconvert and the product distribution depends on the interactions that occur at the transition states. On this basis we are led to the conclusion that the poor anomeric stereoselectivity observed in glycosylations with the donor **3** arises because of high barriers leading from the dioxolenium ion and/or glycosyl triflate to product, such that equilibration with trace amounts of a glycosyl cation can afford significant amounts of an α-linked product. In our case the poor reactivity of **3** is likely exacerbated by the hindered and deactivated nature of the secondary alcohol acceptor **11**, which results in a mismatched pairing in the transition state leading to the β-product from the dioxolenium ion or glycosyl triflate. This mismatch is less severe in the reactions of the glycosyl cation leading to the α-anomer, which is a likely representative of the pool of reaction intermediates. Finally, on the basis of the X-ray structure for **17**, we ascribe the formation of the orthoester **18** from the glycosyl donor **17** to facile formation of a dioxolenium ion that is hindered from top face attack to give a β-anomer by the *endo* methyl of the isopropylidene group; instead, nucleophilic attack at the orthoester carbon predominates.

One final issue that merits discussion is the effect of the ortho methyl groups on the mesitoyl group in the reaction pathways leading to glycosyl cations and dioxolenium ions. In particular, the X-ray structures reveal that the orientation of the carbonyl group to the aromatic ring for the mesitoyl groups differ significantly to the corresponding orientation in benzoyl groups, owing to the steric interactions preventing coplanarity. DFT calculations by the Whitfield group suggest that for neighboring group participation by monocyclic glycopyranosyl cations there is a transition state to the formation of the dioxolenium ion of rotation of the C2-O2 bond.[35] In contrast, DFT calculations of the corresponding transformation of the bicyclic 2,6-di-*O*-acetyl-3,4-*O*-isopropylidene-D-galactopyranosyl cation revealed that the transition state is conformational interconversion and that nucleophilic attack by the carbonyl group to give the dioxolenium ion was essentially barrierless.[30] The similarity of the crystal structures of **17** and ethyl 2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-1-thio-β-D-galactoside suggests that these two compounds will start from a similar ground state and that they can adopt similar conformations. However, the change in the torsional angle for the aromatic ring and the carbonyl group

should result in a significant alteration in reactivity of this group, which may affect the energy of the transition state between the glycosyl cation to the dioxolenium ion.

These studies reiterate the challenges in defining general glycosylation conditions and that individual solutions to certain challenging glycosylations may require the use of unusual protecting groups and empirical investigation of the effect of changes of remote protecting groups on the reactivity and stereoselectivity of glycosyl donors. On the basis of this work and previous studies, 2,6-disubstituted benzoates have the potential to overcome some side reactions, such as transesterification, in challenging β-galactosylations; however, these groups do not altogether prevent orthoester formation and in some cases provide incomplete anomeric stereocontrol.

EXPERIMENTAL

General experimental details have been provided previously.[36]

4-Methoxyphenyl 3-*O*-allyl-β-D-galactopyranoside (12)

A suspension of 4-methoxyphenyl β-D-galactopyranoside[25] (7.80 g, 27.2 mmol) and Bu_2SnO (8.80 g, 35.4 mmol) in toluene (150 mL) was refluxed for 18 h with azeotropic removal of H_2O. The solvent was evaporated under reduced pressure and the residue was dissolved in THF (100 mL). Bu_4NBr (9.64 mg, 29.9 mmol) and allyl bromide (16.5 g, 136 mmol) were added to the solution, which was refluxed for 2 h. Evaporation of the solvent gave a residue, which was purified by flash chromatography (100% EtOAc) to give **12** (6.37 g, 72%) as colorless crystals, mp 138–139°C, lit.[37] 139–140°C; $[\alpha]_D^{21}$ –13° (c 1.0 in MeOH) lit.[37] $[\alpha]_D^{20}$ –9° (c 1.0 in MeOH); ^{1}H NMR (500 MHz, d_4-MeOH): δ 3.41 (1 H, dd, $J_{2,3} = 10.0$, $J_{3,4} = 3.0$, H3), 3.61 (1 H, m, H5), 3.76 (3 H, s, OCH_3), 3.76–3.81 (2 H, m, H6, 6), 3.86 (1 H, dd, $J_{1,2} = 8.0$, $J_{2,3} = 10.0$, H2), 3.92 (1 H, d, H4), 4.16 (2 H, m, CH_2CHCH_2O), 4.76 (1 H, d, H1), 5.18–6.07 (3 H, m, CH_2CHCH_2O), 6.84–7.09 (4 H, m, Ar); ^{13}C NMR (125 MHz, CD_3OD): δ 56.2 (1 C, O**C**H_3), 62.5, 67.1, 71.6, 76.9, 82.3 (5 C, C2,3,4,5,6), 72.0 (1 C, CH_2CHCH_2O), 104.2 (1 C, C1), 115.6–156.8 (6 C, Ar), 117.6,136.6 (2 C, CH_2CHCH_2O); *m/z* (ESI$^+$) 349.1258 ($C_{16}H_{22}Na\ O_7$ $[M + Na]^+$ requires 349.1258).

4-Methoxyphenyl 2,4,6-tri-*O*-acetyl-3-*O*-allyl-β-D-galactopyranoside (13)

A solution of acetic anhydride (0.30 mL, 3.2 mmol) and allyl ether **12** (105 mg, 0.322 mmol) in pyridine (5 mL) at 0°C was stirred for 2 h. The mixture was diluted with CH_2Cl_2 (20 mL). The organic phase was washed with aq. HCl (1 M, 20 ml), sat. aq. $NaHCO_3$ (20 mL), and brine (10 mL). The organic phase was dried ($MgSO_4$) and evaporated to afford an off-white amorphous solid, which was recrystallized from EtOAc/pet. spirit to afford **13** (101 mg,

70%) as colorless crystals, mp 131–132°C, lit.[38] 130–131°C; $[\alpha]_D^{20}$ +18° (c 1.0 in $CHCl_3$), lit.[38] $[\alpha]_D$ + 24° (c 1.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.07–2.17 (9 H, 3 × s, 3 × Ac), 3.58 (1 H, dd, $J_{2,3}$ = 10.0, $J_{3,4}$ = 3.6, H3), 3.77 (3 H, s, OCH_3), 3.88–4.17 (3 H, m, H5, CH_2CHCH_2O), 4.20 (2 H, m, H6,6), 4.86 (1 H, d, $J_{1,2}$ = 8.0, H1), 5.17–5.28 (2 H, m, CH_2CHCH_2O), 5.34 (1 H, dd, H2), 5.46 (1 H, dd, H4), 6.80–6.98 (4 H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.7–20.9 (3 C, 3 × s, 3 × Ac), 55.6 (1 C, OCH_3), 62.0, 65.9, 70.33, 70.7, 76.6 (5 C, C2,3,4,5,6), 71.1 (1 C, CH_2CHCH_2O), 100.8 (1 C, C1), 114.4–155.6 (6 C, Ar), 117.5–134.0 (2 C, CH_2CHCH_2O), 169.4–170.5 (3 C, 3 × C=O); m/z (ESI^+) 475.1575 ($C_{22}H_{28}NaO_{10}$ $[M + Na]^+$ requires 475.1575).

4-Methoxyphenyl 2,4,6-tri-*O*-acetyl-β-D-galactopyranoside (11)

A suspension of triacetate **13** (998 mg, 2.21 mmol) and $PdCl_2$ (60 mg, 0.34 mmol) in 3:1 MeOH/toluene (25 mL) was stirred at rt for 3.5 h. The mixture was concentrated under reduced pressure and purified by flash chromatography (70% EtOAc/pet. spirits) to afford a residue, which was recrystallized from EtOAc/pet. spirits to afford **11** (628 mg, 69%) as fine colorless needles, mp 134–135°C, lit.[25]; $[\alpha]_D^{22}$ + 2° (c 0.9 in $CHCl_3$) (Found: C, 55.64; H, 5.88. $C_{19}H_{24}O_{10}$ requires C, 55.34; H, 5.87%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.06–2.20 (9 H, 3 × s, 3 × Ac), 2.70 (1 H, d, $J_{3,OH}$ = 6.5, OH), 3.77 (3 H, s, OCH_3), 3.91 (1 H, ddd, $J_{2,3}$ = 10.0, $J_{3,4}$ = 3.5, H3), 3.94 (1 H, ddd, $J_{4,5}$ = 1.0, $J_{5,6}$ = 6.5, $J_{5,6}$ = 6.5, H5), 4.18–4.19 (2 H, m, H6,6), 4.87 (1 H, d, $J_{1,2}$ = 8.0, H1), 5.22 (1 H, dd, H2), 5.37 (1 H, dd, H4), 6.80–6.98 (4 H, m, Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.7–20.9 (3 C, 3 × s, 3 × Ac), 55.7 (1 C, OCH_3), 61.9, 69.5, 71.3, 71.4, 72.6 (5 C, C2,3,4,5,6), 100.5 (1 C, C1), 114.5–155.7 (6 C, Ar), 170.4–171.1 (3 C, 3 × C=O); m/z (ESI^+) 435.1260 ($C_{19}H_{24}NaO_{10}$ $[M + Na]^+$ requires 435.1262).

Method A: Esterification of 1,3,4,6-tetra-*O*-acetyl-α-D-galactopyranose (6)

A mixture of acid chloride (2–4 equiv.), 2-hydroxy tetraacetate **6** (1 equiv.), and DMAP (1 equiv.) in pyridine was stirred at 55°C for 18 h. The reaction was quenched with HCl (3 M) and extracted with CH_2Cl_2. The organic extract was washed with HCl (3 M), sat. aq. $NaHCO_3$, and brine. The organic phase was dried ($MgSO_4$) and evaporated to afford an oil, which was purified by flash chromatography.

Method B: Preparation of β-D-thiogalactosides by Lewis acid-catalyzed thioglycosylation

$BF_3.Et_2O$ (1 equiv.) was added dropwise to a solution of anomeric acetate (1 equiv.) and thiocresol (1.1 equiv.) in dry $(CH_2Cl)_2$ at 0°C. The reaction was

heated to 65°C until TLC indicated consumption of the starting material. The mixture was quenched with H_2O and cooled. The solution was washed with sat. aq. $NaHCO_3$ and brine and the organic phase dried ($MgSO_4$). The solvent was evaporated to give a residue, which was purified by flash chromatography to afford the thiogalactoside.

Method C: Procedure for preparation of β-D-thiogalactosides via α-D-galactosyl bromides

HBr in AcOH (40% vol/vol, 1 mL per 1 g of tetraacetate) was added to a solution of anomeric acetate in CH_2Cl_2 and the solution stirred at rt until TLC indicated consumption of the starting material. The mixture was diluted with ice-cold H_2O and extracted with CH_2Cl_2. The organic extract was washed with H_2O and sat. aq. $NaHCO_3$. The organic phase was dried ($MgSO_4$) and evaporated to afford crude D-galactosyl bromide as a colorless residue. Thiocresol (3 equiv.) was added to a two-phase system containing the crude D-galactosyl bromide (1 equiv.), Bu_4NHSO_4 (1 equiv.), CH_2Cl_2, and aq. 1 M Na_2CO_3 (2 mL per 1 mmol of bromide). After being stirred overnight the mixture was extracted with CH_2Cl_2 and the organic phase washed with sat. aq. $NaHCO_3$, H_2O, and brine. The organic phase was dried ($MgSO_4$) and evaporated to afford a yellow residue, which was purified to yield the thiogalactoside.

1,3,4,6-Tetra-*O*-acetyl-2-*O*-benzoyl-α-D-galactopyranose (7)

According to Method A, benzoyl chloride (2.02 g, 14.4 mmol), **6**[28] (2.50 g, 7.18 mmol), and DMAP (0.09 g, 0.72 mmol) in pyridine (5 mL) and CH_2Cl_2 (25 mL) were stirred for 1 h at rt. Workup gave a white residue, which was recrystallized to afford **7** (3.02 g, 93%) as a white powder; mp 104–105°C (EtOAc/pet. spirit), ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.91–2.14 (12 H, 4 × s, 4 × Ac), 4.08 (1 H, dd, $J_{5,6} = 6.5$, $J_{6,6} = 11.5$, H6), 4.13 (1 H, dd, $J_{5,6} = 7.0$, H6), 4.36 (1 H, ddd, $J_{4,5} = 1.0$, H5), 5.50–5.56 (3 H, m, H2, H3, H4), 6.49 (1 H, d, $J_{1,2} = 3.5$, H1), 7.38–7.92 (5 H, m, Ph); ^{13}C NMR (125.6 MHz, $CDCl_3$): δ 20.41, 20.45, 20.61 (4C, 4 × CH3), 61.08, 66.99, 67.29, 67.41, 68.60 (5C, C2,3,4,5,6), 89.52 (1C, C1), 128.40, 128.77, 129.53, 133.43 (6C, Ar), 165.20, 168.53, 169.95, 170.14 (5C, 5 × C=O); m/z (ESI$^+$) 475.1210 ($C_{21}H_{24}NaO_{11}$ $[M + Na]^+$ requires 475.1211).

1,3,4,6-Tetra-*O*-acetyl-2-*O*-mesitoyl-α-D-galactopyranose (8)

According to Method A, 2,4,6-trimethylbenzoyl chloride (1.05 g, 5.74 mmol), **6** (0.500 g, 1.44 mmol), and DMAP (0.176 g, 1.44 mmol) in pyridine (5 mL) yielded an orange residue upon workup. Flash chromatography (30% EtOAc/pet. spirits) gave **8** (0.71 g) as a white residue; mp 110–113°C (EtOH), ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.01–2.22 (12 H, 4 × s, 4 × Ac), 2.23 (6 H, s, 2 × Ar*C*H$_3$), 2.29 (3 H, s, ArCH$_3$), 4.11 (1 H, dd, $J_{5,6} = 6.5$, $J_{6,6} = 11.5$, H6), 4.15 (1 H, dd, $J_{5,6} = 7.0$, H6), 4.35 (1 H, ddd, $J_{4,5} = 1.0$, H5), 5.42 (1 H, dd, $J_{2,3} = 11.0$,

$J_{3,4}$ = 3.5, H3), 5.55 (1 H, dd, H4), 5.63 (1 H, dd, $J_{1,2}$ = 4.0, H2), 6.56 (1 H, d, H1), 6.85 (2 H, s, Ar); ^{13}C NMR (125.6 MHz, $CDCl_3$): δ 20.44, 20.58, 20.62, 20.74 (4C, 4 × CH_3), 55.82, 55.99 (3C, 3 × *Me*Ar), 61.14, 66.39, 67.51, 68.38 (5C, C2,3,4,5,6), 89.16 (1C, C1), 131.44, 132.16 (6C, Ar), 157.28, 158.24, 160.74, 165.21, 168.63 (5C, 5 × C=O).

1,3,4,6-Tetra-*O*-acetyl-2-*O*-(2,6-dimethoxybenzoyl)-α-D-galactopyranose (9)

According to Method A, 2,6-dimethoxybenzoyl chloride (1.15 g, 5.73 mmol), **6** (0.500 g, 1.44 mmol), and DMAP (0.176 g, 1.44 mmol) yielded an orange residue upon workup. Flash chromatography (50% EtOAc/pet. spirits) afforded **9** (0.74 g) as a white residue; mp 143–145°C (EtOAc/pet. spirit), ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.02–2.20 (12 H, 4 × s, 4 × Ac), 3.77–3.83 (6 H, 2 × s, 2 × OCH_3), 4.11 (1 H, dd, $J_{5,6}$ = 6.5, $J_{6,6}$ = 11.0, H6), 4.14 (1 H, dd, $J_{5,6}$ = 7.0, H6), 4.33 (1 H, ddd, $J_{4,5}$ = 1.0, H5), 5.42 (1 H, dd, $J_{2,3}$ = 11.0, $J_{3,4}$ = 3.0, H3), 5.52 (1 H, dd, H4), 5.65 (1 H, dd, $J_{1,2}$ = 4.0, H2), 6.50 (1 H, d, H1), 6.53 (2 H, m, Ar), 7.29 (1 H, m, Ar); ^{13}C NMR (125.6 MHz, $CDCl_3$): δ 20.37, 20.51, 20.55, 20.67 (4C, 4 × CH_3), 55.77, 55.93 (2C, 2 × *Me*OAr), 61.08, 66.34, 67.46, 68.32 (5C, C2,3,4,5,6), 89.16 (1C, C1), 131.40, 132.13 (6C, Ar), 157.23, 158.17, 160.68, 165.16, 168.57 (5C, 5 × C=O); *m/z* (ESI$^+$) 535.1420 ($C_{23}H_{28}NaO_{13}$ $[M + Na]^+$ requires 535.1422).

1,3,4,6-Tetra-*O*-acetyl-2-*O*-(2,6-dichlorobenzoyl)-α-D-galactopyranose (10)

According to Method A, 2,6-dichlorobenzoyl chloride (3.94 g, 18.8 mmol), **6** (1.64 g, 4.70 mmol), and DMAP (0.574 g, 4.70 mmol) afforded a brown oil upon workup. Flash chromatography (20% EtOAc/toluene) afforded **10** (2.03 g, 83%) as a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.02–2.22 (12 H, 4 × s, 4 × Ac), 4.13 (2 H, m, H6, 6), 4.33 (1 H, ddd, $J_{4,5}$ = 1.0, $J_{5,6}$ = 6.0, $J_{5,6}$ = 7.0, H5), 5.47 (1 H, dd, $J_{2,3}$ = 9.5, $J_{3,4}$ = 3.0, H3), 5.54 (1 H, dd, H4), 5.64 (1 H, dd, $J_{1,2}$ = 3.5, H2), 6.54 (1 H, d, H1), 7.14–7.33 (3 H, m, Ar); ^{13}C NMR (125.6 MHz, $CDCl_3$): δ 20.78, 20.81, 20.99 (4C, 4 × CH_3), 61.20, 67.35, 67.90, 67.91, 68.47 (5C, C2,3,4,5,6), 88.91 (C1), 128.10, 131.51, 131.84, 132.75 (Ar), 168.70, 168.86, 170.10, 170.30, 170.47 (5C, 5 × C=O).

4-Methylphenyl 3,4,6-tri-*O*-acetyl-2-*O*-benzoyl-1-thio-β-D-galactopyranoside (2)

(i) According to Method B, a solution of tetra-acetate **7** (3.02 g, 6.67 mmol), thiocresol (0.828 g, 6.67 mmol), and $BF_3.Et_2O$ (0.819 mL, 6.67 mmol) in $(CH_2Cl)_2$ (10 mL) was stirred for 3.5 h at 65°C. Workup gave a residue, which was recrystallized from EtOAc/pet. spirits affording **2** (1.51 g, 44%) as a white powder, mp 185–187°C, $[\alpha]_D^{20}$ +34° (c 1.1 in $CHCl_3$); ^{1}H NMR (500 MHz,

$CDCl_3$): δ 1.90–2.15 (9 H, 3 × s, 3 × Ac), 2.34 (3 H, s, ArCH_3), 4.00 (1 H, ddd, $J_{4,5} = 1.0$, $J_{5,6} = 6.5$, H5), 4.16 (1 H, dd, $J_{6,6} = 11.0$, H6), 4.23 (1 H, dd, $J_{5,6} = 7.0$, H6), 4.81 (1 H, d, $J_{1,2} = 10.0$, H1), 5.23 (1 H, dd, $J_{2,3} = 10.0$, $J_{3,4} = 3.5$, H3), 5.47 (1 H, dd, H4), 5.49 (1 H, dd, H2), 7.09–7.38 (4 H, m, *Ar*CH_3), 7.38–8.04 (5 H, m, Ph); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.8–21.4 (4 C, 4 × CH_3), 61.9, 67.6, 68.2, 72.9, 74.8 (5 C, C2,3,4,5,6), 87.5 (1 C, C1), 128.8–138.7 (12 C, Ar), 165.4–170.6 (4 C, 4 × C=O); *m*/*z* (ESI^+) 539.1350 ($C_{26}H_{28}NaO_9S$ $[M + Na]^+$ requires 539.1346).

(ii) According to Method **C**, treatment of tetra-acetate **7** (0.579 g, 1.28 mmol) with HBr in AcOH (0.58 mL) for 1 h gave the intermediate bromide (0.61 g) as a white residue. Treatment of the residue (0.61 g, 1.28 mmol) with thiocresol (0.48 g, 3.84 mmol), Bu_4NHSO_4 (0.43 g, 1.28 mmol), and 1 M $NaHCO_3$ (2.60 mL) gave a residue, which was recrystallized from EtOH to afford **2** (0.51 g, 76% over the two steps) as a white powder.

4-Methylphenyl 3,4,6-tri-O-acetyl-2-O-mesitoyl-1-thio-β-D-galactopyranoside (3)

(i) According to Method B, a solution of tetra-acetate **8** (1.29 g, 2.61 mmol), thiocresol (0.32 g, 2.61 mmol), and $BF_3.Et_2O$ (0.32 mL, 2.61 mmol) in $(CH_2Cl)_2$ (5 mL) was stirred for 5.5 h at 65°C. Workup gave a residue, which was recrystallized from EtOH to yield **3** (0.62 g, 42%) as white needles, mp 147°C, $[\alpha]_D^{19} + 10^\circ$ (c 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.99–2.16 (9 H, 3 × s, 3 × Ac), 2.29–2.36 (12 H, s, ArCH_3), 3.93 (1 H, ddd, $J_{4,5} = 1.0$, $J_{5,6} = 6.5$, $J_{5,6} = 6.5$, H5), 4.14 (1 H, dd, $J_{6,6} = 11.5$, H6), 4.22 (1 H, dd, H6), 4.71 (1 H, d, $J_{1,2} = 10.0$, H1), 5.07 (1 H, dd, $J_{2,3} = 10.0$, $J_{3,4} = 3.5$, H3), 5.46 (1 H, dd, H4), 5.54 (1 H, dd, H2), 6.86 (2 H, s, C_6H_2), 7.11 (2 H, m, C_6H_4), 7.44 (2 H, m, C_6H_4); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.5–21.4 (7 C, 7 × CH_3), 61.8, 67.3, 67.6, 72.8, 74.3 (5 C, C2,3,4,5,6), 87.1 (1 C, C1), 128.8–140.0 (12 C, Ar), 168.7–170.6 (4 C, 4 × C=O); *m*/*z* (ESI^+) 581.1819 ($C_{29}H_{34}NaO_9S$ $[M + Na]^+$ requires 581.1816).

(ii) According to Method C, treatment of tetra-acetate **8** (0.42 g, 0.84 mmol) with HBr in AcOH (0.42 mL) for 45 min gave the intermediate bromide (0.44 g) as a yellow oil. Treatment of the crude bromide (0.44 g, 0.84 mmol) with thiocresol (3.12 g, 2.52 mmol), Bu_4NHSO_4 (2.85 g, 0.84 mmol), and 1 M $NaHCO_3$ (1.70 mL) gave a residue, which was recrystallized from EtOH to afford **3** (0.31 g, 74% over the two steps) as a white powder.

4-Methylphenyl 3,4,6-tri-O-acetyl-2-O-(2,6-dimethoxybenzoyl)-1-thio-β-D- galactopyranoside (4)

(i) According to Method B, a solution of tetra-acetate **9** (1.6 g, 3.8 mmol), thiocresol (0.47 g, 3.8 mmol), and $BF_3.Et_2O$ (0.47 mL, 3.8 mmol) in $(CH_2Cl)_2$ (5 mL) was stirred for 4 h at 65°C. Workup gave a residue, which was recrystallized from EtOH, affording **4** (0.58 g, 31%) as a white powder, mp 159–160°C, $[\alpha]_D^{20} -1^\circ$ (c 1.1 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.02–2.12 (9 H, 3 × s,

3 × Ac), 2.35 (3 H, s, ArCH_3), 3.81 (6 H, s, 2 × OCH_3), 3.93 (1 H, ddd, $J_{4,5}$ = 1.0, $J_{5,6}$ = 6.5, $J_{5,6}$ = 6.5, H5), 4.13 (1 H, dd, $J_{6,6}$ = 11.0, H6), 4.21 (1 H, dd, H6), 4.71 (1 H, d, $J_{1,2}$ = 10.0, H1), 5.11 (1 H, dd, $J_{2,3}$ = 10.0, $J_{3,4}$ = 3.5, H3), 5.39 (1 H, dd, H2), 5.41 (1 H, dd, H4), 6.56 (2 H, m, Ar), 7.12 (2 H, m, Ar), 7.33 (1 H, m, Ar), 7.49 (2 H, m, Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.9–21.4 (4 C, 4 × CH_3), 56.2 (1 C, OCH_3), 61.9, 67.6, 67.7, 72.6, 74.5 (5 C, C2,3,4,5,6), 86.3 (1 C, C1), 104.3, 112.6–138.7 (12 C, Ar), 157.8–170.7 (4 C, 4 × C=O); *m/z* (ESI^+) 599.1558 ($C_{28}H_{32}NaO_{11}S$ $[M + Na]^+$ requires 599.1558).

(ii) According to Method C, treatment of **9** (0.77 g, 1.5 mmol) with HBr in AcOH (1.50 mL) for 45 min gave the intermediate bromide (0.81 g) as a yellow oil. Treatment of the crude bromide (0.81 g, 1.5 mmol) with thiocresol (0.56 g, 4.5 mmol), Bu_4NHSO_4 (0.51 g, 1.5 mmol), and 1 M $NaHCO_3$ (3.0 mL) gave a residue, which was recrystallized from EtOH to afford **4** (0.15 g, 17% over the two steps) as white needles.

4-Methylphenyl 3,4,6-tri-*O*-acetyl-2-*O*-(2,6-dichlorobenzoyl)-1-thio-β-D- galactopyranoside (5)

According to Method C, treatment of tetra-acetate **10** (1.1 g, 2.2 mmol) with HBr in AcOH (2.2 mL) for 5 h gave the intermediate bromide (1.2 g) as a white residue. Treatment of the crude bromide (1.2 g, 2.2 mmol) with thiocresol (0.81 g, 6.5 mmol), Bu_4NHSO_4 (0.74 g, 2.2 mmol), and 1 M $NaHCO_3$ (4.30 mL) gave a residue, which was purified by flash chromatography (15% EtOAc/toluene) to afford **5** (1.27 g, 66% over two steps) as a colorless oil. $[\alpha]_D^{20}$ +37° (c 0.9 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.00–2.13 (9 H, 3 × s, 3 × Ac), 2.36 (3 H, s, ArCH_3), 3.95 (1 H, ddd, $J_{4,5}$ = 1.0, $J_{5,6}$ = 7.0, $J_{5,6}$ = 7.0, H5), 4.15 (1 H, dd, $J_{6,6}$ = 11.5, H6), 4.23 (1 H, dd, H6), 4.74 (1 H, d, $J_{1,2}$ = 10.0, H1), 5.13 (1 H, dd, $J_{2,3}$ = 9.5, $J_{3,4}$ = 3.0, H3), 5.46 (1 H, dd, H4), 5.49 (1 H, dd, H2), 7.14 (2 H, m, *Ar*CH_3), 7.24–7.35 (3 H, m, C_6H_3), 7.49 (2 H, m, *Ar*CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.9–21.7 (5 C, 5 × CH_3), 61.8, 67.3, 69.1, 72.5, 74.4 (5 C, C2,3,4,5,6), 86.3 (1 C, C1), 125.5–133.8 (12 C, Ar), 163.2–170.6 (4 C, 4 × C=O); *m/z* (ESI^+) 607.0567 ($C_{26}H_{26}NaO_9S$ $[M + Na]^+$ requires 607.0567).

4-Methylphenyl 2,3,4,6-tetra-*O*-(2,6-dimethoxybenzoyl)-1-thio-β-D-galactopyranoside (19)

A mixture of 2,6-dimethoxybenzoyl chloride (2.80 g, 14.0 mmol), 4-methylphenyl 1-thio-β-D-galactopyranoside[39] (0.40 g, 1.4 mmol), and DMAP (0.17 g, 1.4 mmol) in pyridine (12 mL) was stirred at 80°C for 2 d. The mixture was quenched with H_2O (50 mL) and cooled to rt. The mixture was then diluted with CH_2Cl_2 (50 mL) and washed with aq. HCl (3 M, 3 × 50 mL), sat. aq. $NaHCO_3$ (1 × 50 mL), and brine (1 × 50 mL). The organic phase was dried ($MgSO_4$) and evaporated to afford a viscous oil, which was purified by flash chromatography (EtOAc/pet. spirits 40%) yielding **19** (0.95 g, 72%) as a colorless glass; $[\alpha]_D^{19}$ –72° (c 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.19 (3 H, s, ArCH_3), 3.54–3.82 (24 H, 4 × s, 4 × Ar(OCH_3)$_2$), 4.19 (1 H, ddd, $J_{4,5}$ =

1.0, $J_{5,6} = 7.0$, $J_{5,6} = 7.0$, H5), 4.49 (1 H, dd, $J_{6,6} = 11.5$, H6), 4.49 (1 H, dd, H6), 4.81 (1 H, d, $J_{1,2} = 10.0$, H1), 5.51 (1 H, dd, $J_{2,3} = 10.0$, H2), 5.71 (1 H, dd, $J_{3,4} = 3.0$, H3), 6.00 (1 H, d, H4), 6.44–7.32 (12 H, 4 × C_6H_3), 6.72–7.42 (4 H, m, C_6H_4); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.1 (1 C, Ar*C*H_3), 55.6–56.0 (8 C, 8 × OCH_3), 63.3, 68.0, 68.3, 72.4, 75.3 (5 C, C2,3,4,5,6), 86.1 (1 C, C1), 103.4–140.4 (30 C, Ar), 163.6–166.2 (4 C, 4 × C=O); *m/z* (ESI$^+$) 965.2663 ($C_{49}H_{50}NaO_{17}S$ $[M + Na]^+$ requires 965.2661).

Method D: NIS/TfOH promoted glycosylation of 11 with thioglycosides

TfOH (0.25 equiv.) was added to thiogalactoside donor (1.1–1.2 equiv.), acceptor **11** (1 equiv.), NIS (2.5 equiv.), and freshly activated 4 Å molecular sieves in dry CH_2Cl_2 at 0°C. When TLC indicated complete consumption of the donor, the reaction was quenched with sat. aq. $NaHCO_3$ and 0.5 M sodium thiosulfate solution. The mixture was filtered and extracted with CH_2Cl_2 and the organic extract was washed with sat. aq. $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$) and evaporated to give a crude residue, which was purified by flash chromatography.

4-Methoxyphenyl 2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl-(1→3)-2,4,6-tri-O-acetyl-β-D-galactopyranoside (27a) and 4-Methoxyphenyl 2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl-(1→3)-2,4,6-tri-O-acetyl-β-D-galactopyranoside (27b)

According to Method D, thiogalactoside donor **1** (250 mg, 0.550 mmol) and acceptor **11** (210 mg, 0.509 mmol) gave, after flash chromatography (50% EtOAc/pet. spirits), the transesterified product 4-methoxyphenyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (32 mg, 9%) as white crystals, which was identified by comparison to authentic material. Next to elute was the α-linked disaccharide **27a** (4 mg, 1%) as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.96–2.18 (21 H, 7 × s, 7 × Ac), 3.78 (3 H, s, OCH_3), 3.93 (1 H, ddd, $J_{4,5} = 1.0$, $J_{5,6} = 6.0$, $J_{5,6} = 6.5$, H5^A), 3.95–4.24 (5 H, m, (H6,6)^A, (H3,6,6)^B), 4.93 (1 H, ddd, $J_{4,5} = 1.0$, $J_{5,6} = 6.0$, $J_{5,6} = 6.0$, H5^B), 4.84 (1 H, d, $J_{1,2} = 7.5$, H1^B), 5.17 (1 H, dd, $J_{2,3} = 10.5$, $J_{3,4} = 3.5$, H3^A), 5.18 (1 H, dd, $J_{1,2} = 3.5$, $J_{2,3} = 10.0$, H2^A), 5.28 (1 H, d, $J_{1,2} = 3.5$, H1^A), 5.41 (1 H, dd, $J_{4,5} = 1.0$, H4^B), 5.47 (1 H, dd, H4^A), 5.49 (1 H, dd, $J_{2,3} = 10.5$, H2^B), 6.81–6.95 (4 H, m, Ar). Last to elute was the β-linked disaccharide **27b** (144 mg, 35%) as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.98–2.18 (21 H, 7 × s, 7 × Ac), 3.78 (3 H, s, OCH_3), 3.88 (1 H, ddd, $J_{4,5} = 1.0$, $J_{5,6} = 6.0$, $J_{5,6} = 6.5$, H5^A), 3.92 (1 H, dd, $J_{2,3} = 10.0$, $J_{3,4} = 3.0$, H3^B), 3.94 (1 H, ddd, $J_{4,5} = 1.0$, $J_{5,6} = 6.0$, $J_{5,6} = 6.5$, H5^B), 4.11–4.22 (4 H, m, (H6,6)^A, (H6,6)^B), 4.60 (1 H, d, $J_{1,2} = 7.5$, H1^A), 4.82 (1 H, d, $J_{1,2} = 8.0$, H1^B), 4.95 (1 H, dd, $J_{2,3} = 10.5$, $J_{3,4} = 3.5$, H3^A), 5.12 (1 H, dd, H2^B), 5.36 (1 H, dd, H4^B), 5.44 (1 H, dd, H2^A), 5.48 (1 H, dd, H4^A), 6.81 (2 H,

m, Ar), 6.94 (2 H, m, Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.8–20.1 (7 C, 7 × Ac), 55.9 (1 C, OCH_3), 61.2, 62.4, 67.0, 68.8, 69.0, 70.9, 71.1, 71.8, 76.1 (10 C, $(C2,3,4,5,6)^A$, $(C2,3,4,5,6)^B$), 100.8, 101.4 (2 C, $C1^A$,1^B), 114.8–155.9 (6 C, Ar), 169.2–170.7 (7 C, 7 × C=O); *m/z* (ESI^+) 765.2213 ($C_{33}H_{42}NaO_{19}$ $[M + Na]^+$ requires 765.2213).

4-Methoxyphenyl 3,4,6-tri-*O*-acetyl-2-*O*-benzoyl-α-D-galactopyranosyl-(1→3)-2,4,6-tri-*O*-acetyl-β-D-galactopyranoside (28a) and 4-Methoxyphenyl 3,4,6-tri-*O*-acetyl-2-*O*-benzoyl-β-D-galactopyranosyl-(1→3)-2,4,6-tri-*O*-acetyl-β-D-galactopyranoside (28b)

According to Method D, thiogalactoside donor **2** (290 mg, 0.561 mmol) and acceptor **11** (210 mg, 0.509 mmol) gave, after flash chromatography (50%–60% EtOAc/pet. spirits), the α-linked disaccharide **28a** (16 mg, 4%) as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.44–2.19 (18 H, 6 × s, 6 × Ac), 3.77 (3 H, s, OCH_3), 3.88 (1 H, ddd, $J_{4,5} = 1.0$, $J_{5,6} = 6.5$, $J_{5,6} = 6.5$, $H5^B$), 3.97 (1 H, dd, $J_{2,3} = 10.0$, $J_{3,4} = 3.0$, $H3^B$), 4.03–4.25 (4 H, m, $(H6,6)^A$, $(H6,6)^B$) 4.34 (1 H, ddd, $J_{4,5} = 1.5$, $J_{5,6} = 6.5$, $J_{5,6} = 6.5$, $H5^A$), 4.82 (1 H, d, $J_{1,2} = 7.5$, $H1^B$), 5.38 (1 H, dd, $J_{2,3} = 10.5$, $J_{3,4} = 3.0$, $H3^A$), 5.39 (1 H, dd, $H4^B$), 5.44 (1 H, d, $J_{1,2} = 3.5$, $H1^A$), 5.46–5.50 (2 H, m, $H2^A$, $H2^B$), 6.80–6.94 (4 H, m, Ar), 7.45–8.07 (5 H, m, Ph). Next to elute was the β-linked disaccharide **28b** (0.16 g, 40%) as a colorless oil, $[\alpha]_D^{20}$ +37° (c 1.1 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.58–2.18 (18 H, 6 × s, 6 × Ac), 3.74 (3 H, s, OCH_3), 3.87 (1 H, dd, $J_{2,3} = 10.0$, $J_{3,4} = 4.0$, $H3^B$), 3.89 (1 H, ddd, $J_{4,5} = 0.5$, $J_{5,6} = 6.0$, $J_{5,6} = 6.0$, $H5^B$), 3.96 (1 H, ddd, $J_{4,5} = 1.0$, $J_{5,6} = 6.0$, $J_{5,6} = 6.0$, $H5^A$), 4.10–4.21 (4 H, m, $(H6,6)^A$,$(H6,6)^B$), 4.72 (1 H, d, $J_{1,2} = 7.5$, $H1^A$), 4.74 (1 H, d, $J_{1,2} = 7.5$, $H1^B$), 5.18 (1 H, dd, $J_{2,3} = 10.5$, $J_{3,4}$ 3.0, $H3^A$), 5.35 (1 H, dd, $H2^B$), 5.41 (1 H, dd, $H4^B$), 5.42 (1 H, dd, $H2^A$), 5.48 (1 H, dd, $H4^A$), 6.74–6.86 (4 H, m, Ar), 7.44–7.98 (5 H, m, Ph); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.4–21.0 (6 C, 6 × Ac), 55.7 (1 C, OCH_3), 61.2, 62.7, 67.1, 68.8, 69.6, 70.4, 70.9, 71.2, 71.9 (10 C, $(C2,3,4,5,6)^A$, $(C2,3,4,5,6)^B$), 100.9, 101.7 (2 C, $C1^A$,$C1^B$), 114.6–155.8 (12 C, Ar), 164.9–170.7, 170.8 (7 C, 7 × C=O); *m/z* (ESI^+) 827.2369 ($C_{38}H_{44}NaO_{19}$ $[M + Na]^+$ requires 827.2369).

4-Methoxyphenyl 3,4,6-tri-*O*-acetyl-2-*O*-mesitoyl-α-D-galactopyranosyl-(1→3)-2,4,6-tri-*O*-acetyl-β-D-galactopyranoside (29a) and 4-Methoxyphenyl 3,4,6-tri-*O*-acetyl-2-*O*-mesitoyl-β-D-galactopyranosyl-(1→3)-2,4,6-tri-*O*-acetyl-β-D-galactopyranoside (29b)

According to Method D, thiogalactoside donor **3** (310 mg, 0.561 mmol) and acceptor **11** (210 mg, 0.509 mmol) gave, after flash chromatography (40%–50% EtOAc/pet. spirits), the α-linked disaccharide **29a** (93 mg, 22%) as a colorless

oil, which was crystallized from EtOH to afford white needles, mp 203–205°C, ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.59–2.19 (18 H, 6 × s, 6 × Ac), 2.28–2.35 (9 H, s, ArCH_3), 3.78 (3 H, s, OCH_3), 3.88 (1 H, ddd, $J_{4,5} = 0.5$, $J_{5,6} = 6.5$, $J_{5,6} = 7.0$, H5^A), 3.94 (1 H, dd, $J_{2,3} = 10.0$, $J_{3,4} = 3.5$, H3^B), 4.06–4.24 (4 H, m, (H6,6)^A, (H6,6)^B), 4.30 (1 H, ddd, $J_{4,5} = 0.5$, $J_{5,6} = 6.5$, $J_{5,6} = 7.0$, H5^B), 4.82 (1 H, d, $J_{1,2} = 8.0$, H1^B), 5.23 (1 H, dd, $J_{2,3} = 11.0$, $J_{3,4} = 3.5$, H3^A), 5.33 (1 H, d, $J_{1,2} = 3.0$, H1^A), 5.40 (1 H, dd, H4^B), 5.45 (1 H, dd, H2^B), 5.54 (1 H, dd, H4^A), 5.67 (1 H, dd, H2^A), 6.81–6.94 (6 H, m, Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.4–21.3 (6 C, 6 × Ac), 55.9 (1 C, OCH_3), 61.8, 61.9, 64.5, 66.5, 67.1, 68.0, 68.3, 69.7, 71.3, 72.7 (10 C, (C2,3,4,5,6)^A, (C2,3,4,5,6)^B), 93.6, 101.2 (2 C, C1^A,C1^B), 114.8–156.0 (12 C, Ar), 168.2–170.6 (7 C, 7 × C=O); *m/z* (ESI$^+$) 869.2843 ($C_{41}H_{50}NaO_{19}$ [M + Na]$^+$ requires 869.2839). Next to elute was the β-linked disaccharide **29b** (190 mg, 44%) as a colorless oil, which was crystallized from EtOH to afford white needles, mp 173–174°C, $[\alpha]_D^{20}$ +36° (c 1.0 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.64–2.22 (18 H, 6 × s, 6 × Ac), 2.26 (6 H, s, 2 × $C_6H_2CH_3$), 2.28 (3 H, s, $C_6H_2CH_3$), 3.76 (3 H, s, OCH_3), 3.92 (1 H, ddd, $J_{4,5} = 1.0$, $J_{5,6} = 7.0$, $J_{5,6} = 7.0$, H5^A), 3.95 (1 H, ddd, $J_{4,5} = 1.0$, $J_{5,6} = 6.0$, $J_{5,6} = 6.5$, H5^B), 4.05 (1 H, dd, $J_{2,3} = 10.0$, $J_{3,4} = 3.0$, H3^B), 4.11–4.27 (4 H, m, (H6,6)^A, (H6,6)^B), 4.71 (1 H, d, $J_{1,2} = 8.0$, H1^A), 4.79 (1 H, d, $J_{1,2} = 8.0$, H1^B), 5.03 (1 H, dd, $J_{2,3} = 10.5$, $J_{3,4} = 3.0$, H3^A), 5.42 (1 H, dd, H4^B), 5.48 (1 H, dd, H4^A), 5.37–5.42 (2 H, m, H2^A, H2^B), 6.78–6.89 (6 H, m, Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.2–21.4 (6 C, 6 × Ac), 55.9 (1 C, OCH_3), 61.2, 62.4, 66.9, 69.1, 69.6, 71.0, 71.1, 71.3, 72.0, 75.3 (10 C, (C2,3,4,5,6)^A,(C2,3,4,5,6)^B), 101.5, 101.1 (2 C, C1^A,C1^B), 114.7–155.8 (12 C, Ar), 168.2–170.7 (7 C, 7 × C=O); *m/z* (ESI$^+$) 869.2844 ($C_{41}H_{50}NaO_{19}$ [M + Na]$^+$ requires 869.2839).

4-Methoxyphenyl 3,4,6-tri-*O*-acetyl-2-*O*-(2,6-dimethoxybenzoyl)-α-D-galactopyranosyl-(1→3)-2,4,6-tri-*O*-acetyl-β-D-galactopyranoside (30a) and 4-Methoxyphenyl 3,4,6-tri-*O*-acetyl-2-*O*-(2,6-dimethoxybenzoyl)-β-D-galactopyranosyl-(1→3)-2,4,6-tri-*O*-acetyl-β-D-galactopyranoside (30b)

According to Method D, thiogalactoside donor **4** (320 mg, 0.561 mmol) and acceptor **11** (206 mg, 0.506 mmol) gave, after flash chromatography (60% EtOAc/pet. spirits), the α-linked disaccharide **30a** (12 mg, 2%) as a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.01–2.19 (18 H, 6 × s, 6 × Ac), 3.78 (3 H, s, OCH_3), 3.84 (6 H, s, 2 × OCH_3), 4.10–4.21 (5 H, m, (H5,6,6)^A, (H2,3)^B), 4.36 (2 H, m, (H6,6)^B), 4.53 (1 H, ddd, $J_{4,5} = 0.5$, $J_{5,6} = 6.0$, $J_{5,6} = 6.0$, H5^B), 4.91 (1 H, d, $J_{1,2} = 8.5$, H1^B), 5.02 (1 H, dd, $J_{2,3} = 10.0$, $J_{3,4} = 3.0$, H3^A), 5.44 (1 H, dd, $J_{1,2} = 3.5$, H2^A), 5.47 (1 H, d, H1^A), 5.50 (1 H, dd, H4^A), 5.62 (1 H, dd, $J_{3,4} = 3.0$, H4^B), 6.82–6.96 (4 H, m, Ar), 7.33 (3 H, m, C_6H_4). Next to elute was

the β-linked disaccharide **30b** (230 mg, 54%) as a colorless oil, $[\alpha]_D^{20}$ +39° (c 1.1 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.01–2.21 (18 H, 6 × s, 6 × Ac), 3.76 (3 H, s, OCH_3), 3.81 (6 H, s, 2 × OCH_3), 3.88 (1 H, ddd, $J_{4,5} = 0.5$, $J_{5,6} = 6.5$, $J_{5,6} = 7.0$, H5^A), 3.96 (1 H, dd, $J_{2,3}$ 1 = 0.0, $J_{3,4} = 3.0$, H3^B), 4.11–4.24 (5 H, m, (H6,6)^A, (H5,6,6)^B), 4.71 (1 H, d, $J_{1,2} = 8.0$, H1^A), 4.75 (1 H, d, $J_{1,2} = 8.0$, H1^B), 5.04 (1 H, dd, $J_{2,3} = 10.5$, $J_{3,4} = 3.5$, H3^A), 5.36 (1 H, dd, H2^B), 5.37 (1 H, dd, H2^A), 5.38 (1 H, dd, H4^A), 5.49 (1 H, dd, $J_{3,4} = 3.0$, H4^B), 6.87 (2 H, m, C_6H_4), 6.77–6.90 (4 H, m, Ar), 6.87 (3 H, m, C_6H_4); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.8–21.0 (6 C, 6 × Ac), 55.9, 56.1, 56.6 (3 C, OCH_3), 61.3, 62.4, 67.1, 68.2, 69.1, 69.4, 70.8, 71.0, 71.5, 71.9 (10 C, (C2,3,4,5,6)^A, (C2,3,4,5,6)^B), 101.2, 101.5 (2 C, C1^A,1^B), 114.7–158.4 (12 C, Ar), 164.4–170.7 (7 C, 7 × C=O); m/z (ESI$^+$) 887.2582 ($C_{40}H_{48}NaO_{21}$ [M + Na]$^+$ requires 887.2580).

4-Methoxyphenyl 3,4,6-tri-*O*-acetyl-2-*O*-(2,6-dichlorobenzoyl)-α-D-galactopyranosyl-(1→3)-2,4,6-tri-*O*-acetyl-β-D-galactopyranoside (31a) and 4-Methoxyphenyl 3,4,6-tri-*O*-acetyl-2-*O*-(2,6-dichlorobenzoyl)-β-D-galactopyranosyl-(1→3)-2,4,6-tri-*O*-acetyl-β-D-galactopyranoside (31b)

According to Method D, thiogalactoside donor **5** (320 g, 0.561 mmol) and acceptor **11** (210 g, 0.509 mmol) gave, after flash chromatography (30% EtOAc/pet. spirits), the α-linked disaccharide **31a** (120 mg, 27%) as a colorless oil, $[\alpha]_D^{23}$ +73° (c 1.1 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.88–2.18 (18 H, 6 × s, 6 × Ac), 3.78 (3 H, s, OCH_3), 3.87 (1 H, ddd, $J_{4,5} = 1.0$, $J_{5,6} = 7.0$, $J_{5,6} = 7.0$, H5^A), 3.93 (1 H, dd, $J_{2,3} = 10.0$, $J_{3,4} = 3.5$, H3^B), 4.01–4.13 (4 H, m, (H6,6)^A, (H6,6)^B), 4.21 (1 H, ddd, $J_{4,5} = 1.0$, $J_{5,6} = 6.5$, $J_{5,6} = 6.5$, H5^B), 4.22 (1 H, dd, $J_{1,2} = 8.0$, H2^B), 4.80 (1 H, d, H1^B), 5.30 (1 H, d, H1^A), 5.38 (1 H, dd, $J_{3,4} = 3.5$, H4^A), 5.45 (1 H, dd, $J_{2,3} = 10.0$, H3^A), 5.51 (1 H, dd, H4^B), 5.58 (1 H, dd, H2^A), 6.81–6.94 (4 H, m, C_6H_4), 7.32–7.40 (3 H, m, C_6H_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.3–21.1 (6 C, 6 × Ac), 55.9 (1 C, OCH_3), 61.1, 62.1, 66.7, 67.6, 67.7, 68.0, 69.1, 70.5, 71.5, 71.8 (10 C, (C2,3,4,5,6)^A, (C2,3,4,5,6)^B), 97.0, 101.2 (2 C, C1^A,1^B), 114.8–156.0 (12 C, Ar), 169.4–170.7 (7 C, 7 × C=O); m/z (ESI$^+$) 895.1592 ($C_{38}H_{42}NaCl_2O_{19}$ [M + Na]$^+$ requires 895.1597). Next to elute was the β-linked disaccharide **31b** (160 mg, 36%) as a colorless oil, $[\alpha]_D^{24}$ +25° (c 1.1 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.79–2.23 (18 H, 6 × s, 6 × Ac), 3.76 (3 H, s, OCH_3), 3.91–4.27 (7 H, m, (H5,6,6)^A, (H2,3,5,6,6)^B), 4.76 (1 H, d, $J_{1,2} = 8.0$, H1^B), 5.30 (1 H, d, $J_{1,2} = 8.0$, H1^A), 5.37 (1 H, dd, $J_{2,3} = 10.0$, H2^A), 5.42 (1 H, dd, $J_{4,5} = 1.0$, H4^B), 5.46 (1 H, dd, $J_{3,4} = 3.5$, H3^A), 5.48 (1 H, dd, $J_{4,5} = 1.0$, H4^A), 6.78–6.90 (4 H, m, Ar), 7.31–7.38 (3 H, m, C_6H_4); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.7–21.2 (6 C, 6 × Ac), 55.9 (1 C, OCH_3), 61.1, 62.3, 62.6, 67.0, 69.2, 70.7, 70.8, 71.1, 72.0, 76.0 (10 C, (C2,3,4,5,6)^A, (C2,3,4,5,6)^B), 100.8,

101.2 (2 C, $C1^A$,$C1^B$), 114.7–154.7 (12 C, Ar), 169.5–170.9 (7 C, 7 × C=O); *m/z* (ESI^+) 895.1591 ($C_{38}H_{42}NaCl_2O_{19}$ $[M + Na]^+$ requires 895.1597).

Variable Temperature NMR Studies: Representative Procedure

To a suspension of the thioglycoside **3** (10 mg, 0.023 mmol) and NIS (5.7 mg, 0.025 mmol) in $CDCl_3$ (1 mL) in a 5-mm NMR tube at –78°C was added TfOH (2.2 μL, 0.025 mmol), and the mixture dissolved by gentle vortexing. The glycosyl triflate **22** (anomeric δ_H: 6.47 ppm [d, $J = 3.5$ Hz]; anomeric δ_C: 103.5 ppm) and dioxolenium ion **23** (anomeric δ_H: 7.64 ppm [d, $J = 8.2$ Hz]; anomeric δ_C: 111.0 ppm) were instantly formed. The mixture of **22** and **23** was allowed to warm at 10 °C/10 min with monitoring by 400 MHz 1H and 100 MHz ^{13}C NMR spectroscopies.

Crystallography

Intensity data were collected with an Oxford Diffraction Sapphire CCD diffractometer using Cu-Ka radiation (graphite crystal monochromator λ = 1.54184); the temperature during data collection was maintained at 130.0(1) K using an Oxford Cryosystems cooling device.

Crystal data for 16

$C_{53}H_{58}O_9S$, $M = 871.05$, $T = 130.0(2)$ K, $\lambda = 1.5418$, Orthorhombic, space group $P2_12_12_1$ $a = 15.0642(2)$, $b = 15.4036(2)$, $c = 19.9343(2)$ Å, $V = 4625.6(1)$ $Å^3$, $Z = 4$, $D_c = 1.251$ mg/M^{-3} μ(Cu-Kα) 1.082 mm^{-1}, F(000) = 1856, crystal size 0.5 × 0.4 × 0.35 mm. 17327 reflections measured, 8226 independent reflections ($R_{int} = 0.0253$), the final R was 0.0352 [$I > 2\sigma(I)$] and $wR(F^2)$ was 0.0882 (all data).

Crystal data for 17

$C_{36}H_{42}O_7S$, $M = 618.76$, $T = 130.0(2)$ K, $\lambda = 1.5418$, Monoclinic, space group $P2_1$ $a = 16.9919(3)$, $b = 6.0300(1)$, $c = 18.2773(3)$ Å, $\beta = 117.288(2)°$, $V = 1664.30(5)$ $Å^3$, $Z = 2$, $D_c = 1.235$ mg/M^{-3} μ(Cu-Kα) 1.245 mm^{-1}, F(000) = 660, crystal size 0.45 × 0.4 × 0.3 mm. 9405 reflections measured, 5270 independent reflections ($R_{int} = 0.0202$), the final R was 0.0332 [$I > 2\sigma(I)$] and $wR(F^2)$ was 0.0923 (all data).

Supporting information

NMR spectra for compounds **2–5**, **7–10**, **19**, **27–29**, **31**; representative variable temperature NMR spectra; and coordinates for the crystal structures are available online. Crystallographic data files for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre

as files CCDC-784498 and CCDC-784499 and are available on request from http://www.ccdc.cam.ac.uk/. (these details will be added upon acceptance)

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