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On the Generality of Superarmament of Glycosyl Donors

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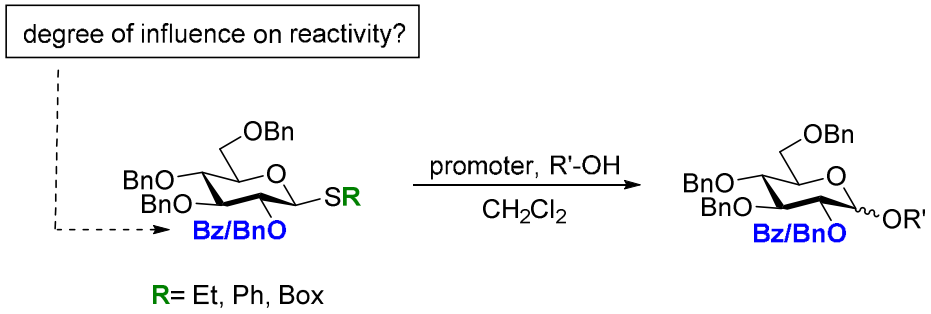

Abstract It was established that 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl protected β-SEt, β-SPh and β-SBox glucosyl donors are not superarmed when using the NIS/TfOH promoter system, but instead have a similar reactivity as the classically armed tetra-*O*-benzyl protected glucosyl counterparts. The β-SBox 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl glucosyl donor, however, was found to be superarmed under DMTST activation. Our studies have shown that the increased reactivity of the β-SBox 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl glucosyl donor with DMTST activation could be a unique case, and that high reactivity for glucosyl donors with the 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl protection pattern is not general as earlier suggested.

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Introduction

Despite the long history of glycosylation chemistry,[1] modern approaches are still highly empirical and no general approach for glycosylation has been established.[2,3] Each glycosidic linkage to be formed can become a unique task of optimizing e.g. glycosyl donor-type, protection group pattern, promoter system, acceptor, solvent and temperature.[4]

Chemoselective activation, reactivity tuning and reactivity measurements of glycosyl donors are ongoing topics in carbohydrate chemistry.[5] The continued interest in glycosyl donor reactivity is a result of the well-established benefit of chemoselective glycosyl donor activation, which has been demonstrated in seminal papers from research groups led by Fraser-Reid,[6] Ley[7] and Wong[8a] respectively using either *O*-pentenyl, seleno- or thioglycosides as donors. Their important contributions have both demonstrated basic chemical behavior of the glycosylation reaction, and shown how this fundamental understanding can be of great benefit for improving the effectiveness of assembling complex oligosaccharide structures. Specifically, Wong and co-workers have impressively measured reactivity values of several hundred glycosyl donors and demonstrated a continuum of reactivity.[8] We have recently further expanded upon this continuum by fine-tuning the reactivity of glycosyl donors by varying the *para*-substituent of benzyl ethers (OMe, H, Cl, CN).[9]

The first chemoselective activation was performed by Fraser-Reid and co-workers using *O*-pentenyl glucosides in a celebrated paper where also the terms *armed* and *disarmed* glycosyl donors were coined.[6] The terms refers to the ease with which the donors were activated, which correlates to their reactivity towards the promoter and their subsequent oxacarbenium ion formation. Later, also the term *superarmed* and *super disarmed* donors have been used in the literature.[12] There has not been given a strict definition of superarmament,[10] but we here suggest the following, which is accordance with initial results by Fraser-Reed and co-workers:

A given aldopyranosyl donor with fixed anomeric stereochemistry is said to be *armed* if it is perbenzylated. An aldopyranosyl donor is termed *disarmed* if it is *i*) peracylated; *ii*) has 1,2-trans stereochemistry;[11] and *iii*) an armed donor of identical stereochemistry and anomeric leaving group can be activated chemoselectively over a mono-deacylated analogue of the donor in question and lead to a successful glycosylation reaction in reasonable yield between the two fragments.

Accordingly, a aldopyranosyl donor is said to be *superarmed* if it can be chemoselectively activated over a mono-debenzylated armed donor of identical stereochemistry and anomeric leaving group and lead to a successful glycosylation reaction between the two fragments where a benzyl ether protecting group has been removed from the armed donor.

The definition given above does not allow for use of the term *superarmed* for donors that are just more reactive than an armed donor or the use of the term disarmed for donor less reactive than and armed donor. The reactivity difference has to be large enough to allow for chemoselective activation and glycosylation. Based on earlier results by Wong[8] and us[9] we believe that a relative reactivity value varying a factor of at least seven-fold is required to allow for a successful glycosylation reaction.

Glycosyl donors that fall into the category of being superarmed have previously been reported by Bols and co-workers, who forced thioglycosides into an axial rich conformation by installing bulky silyl protecting groups.[12] These conformationally superarmed donors were the first to open up for a new unexplored area of reactivity.[13] Later, Demchenko presented the electronically superarmed glycosyl donor possessing a 2-*O*-benzoyl substituent trans to a S-benzoxaloyl (SBox) leaving group, capable of carrying out anchimeric assistance upon activation.[14,15,16,17,18] The

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concept of electronically superarming, defined as being *more reactive,* was expanded and claimed to be general for glycosyl donors of the *O*-pentenyl, *S*-ethyl, *S*-phenyl, *S*-tolyl and *S*-thiazolinyl type using different promoter systems.[19]

In a collaborative effort, Demchenko and Bols have recently combined the chemical features that induces conformational and electronical superarmament, giving highly reactive and stereoselective donors, but a 2-*O*-benzoylated β-1-SPh donor failed to be more reactive under NIS/TfOH activation than the analogous 2-*O*-benzylated donor.[20,21] In addition, work by Wong and co-workers has questioned if the electronically superarmed donor reported by Demchenko and co-workers was even more reactive than a traditionally benzylated, armed donor.[22]

Given the opposing results mentioned above and also results from our own work with the catalytically activated *o*-methoxybenzoate functionalized glycosyl donor,[23] we decided to investigate the electronically superarmed donor system in greater detail. Here, we describe our recent investigations into the generality of superarmament of thioglycoside based glycosyl donors.

Competition Experiments and Discussion

We set out to study three (SPh, SEt, SBox) different sets of glucosyl donors (

Figure 1). In each set a traditionally armed tetra-*O*-benzylated donor (**1**, **3** or **5**) was to compete with a donor possessing the electronical superarming protecting group pattern with a 2-*O*-benzoyl group (**2**, **4** or **6**).

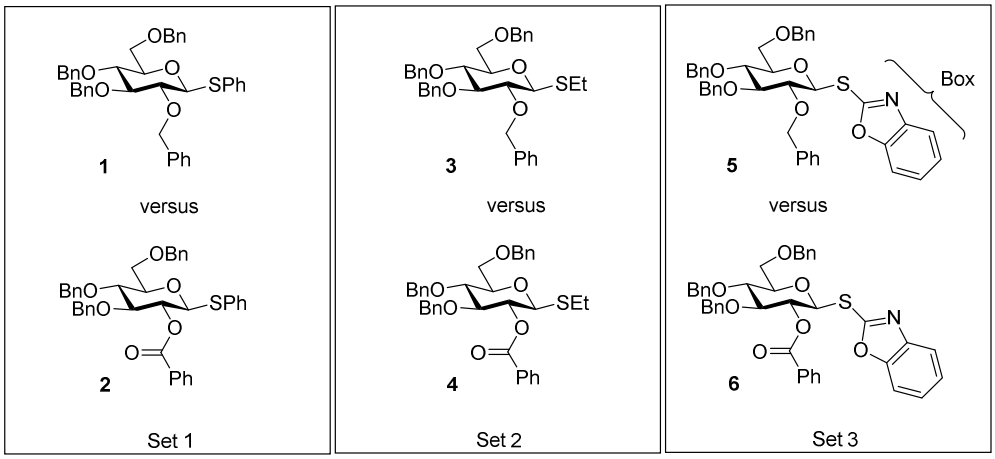

Figure 1.

Prior to the competition experiments, all donors were tested under NIS/TfOH promoted glycosylation conditions[24] using L-menthol as acceptor. All donors (**1-6**) activated easily and gave good and reproducible yields (81-94%). Subsequently, glycosyl donor reactivity was evaluated in competition experiments within each set of donors (

Figure 1). These were performed by mixing the competing donors in a 1.0:1.0 ratio and checking this by ^{13}C-NMR spectroscopy.[25] The mixture was then dissolved and mixed with the acceptor (L-menthol, 5 equiv. or 1 equiv.) and the promoter (always 10 mol% TfOH and NIS in either 1 equiv. or 5-6 equiv., respectively to the equiv. of acceptor). After ended reaction and work-up, a new ^{13}C-NMR spectrum was recorded of the crude reaction mixture and the anomeric signals of the unreacted donors were integrated and compared. The consumption of a donor is hereby a

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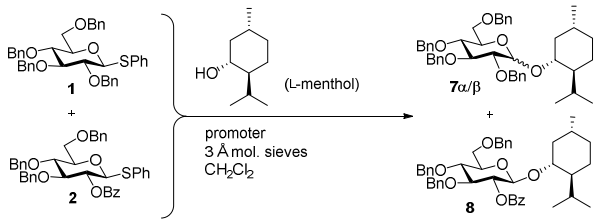
direct result of its reactivity. The smallest integral value after ended reaction consequently results for the most reactive donor. Thus, the smaller the value, the more reactive the donor. All competition experiments were conducted several times and the results were found to be highly reproducible.

Thiophenyl functionalized donors **1** and **2** were competed under five different sets of conditions (Table 1). In Entry 1, the promoter NIS was the limiting factor, while Entry 2 describes the result where the acceptor was the limiting factor. Since more of donor **2** is left unreacted after ended reaction under both sets of conditions, donor **1,** being tetra-*O*-benzylated having an armed protecting group pattern, is clearly the most reactive of the two. This demonstrates that the presence of a 2-*O*-benzoyl group does not generally lead to a more reactive donor, let alone donor superarmament. Performing the competition experiments as described under Entry 2, but at a higher, isothermal temperature (0 °C, Entry 3), did not change the outcome. Next, DMTST was investigated as promoter both in absence (Entry 4) and presence of the sterically hindered base 2,4,6-tri-*tert*butylpyrimidine (TTBP) (Entry 5). In the former case, the reactivity had now turned to become slightly higher for the 2-*O*-benzoyl protected donor (**2**), while the classically armed donor (**1)** was more reactive in the presence of TTBP. We do not characterize the slightly higher reactivity of donor **2** over **1** under DMTST activation as being at the level of superarmed. Lastly, the relative reactivity of the corresponding SEt donors (**3** and **4**) were investigated (Entry 6). The competition experiment resulted in the same finding as for SPh donors **1** and **2,** with the classically armed donor (**3**) being more reactive than the 2-*O*-benzoylated counterpart (**4**).

Table 1. Competition experiments with thioglucoside glycosyl donors



Entry	Promoter system	Acceptor	Temperature/ time	RR[c] 1:2
1	NIS (1 eq.), TfOH (0.1 eq. [a])	5 eq.	-78 to 0 °C/ 4 h	1 : 1.9
2	NIS (5 eq.), TfOH (0.1 eq.[a])	1 eq.	-78 to 0 °C/ 4 h	1 : 2.4
3	NIS (5 eq.), TfOH (0.1 eq. [a])	1 eq.	0 °C/ 2 h	1 : 2.3
4	DMTST (6 eq.)	1 eq.	0 °C/ 2 h	1 : 0.9

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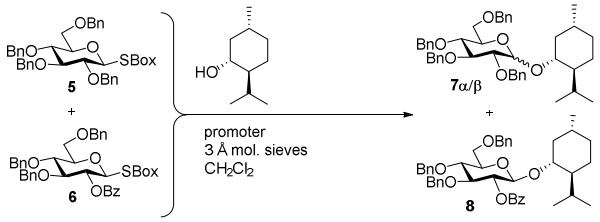
5	DMTST (6 eq.) TTBP (1 eq.)	1 eq.	0 °C/ 2 h	1 : 1.4
6[b]	NIS (1 eq.), TfOH (0.1 eq. [a])	5 eq.	-78 to 0 °C/ 4 h	1 : 2

[a]With respect to the amount of donor. [b]Corresponding SEt donors **3** and **4** were competed against one another. [c]RR: reactivity ratio, (donor **1**)/(donor **2**)[a] and (donor **3**)/(donor **4**)[b]. Ratio refers to the ratio of unreacted donors after glycosylation.

A similar series of competition experiments were conducted with the SBox donors **5** and **6** (Table 2). Activation by NIS/TfOH (Entry 1) demonstrated a different behavior for the SBox donors compared to the SPh and SEt donors, in that the 2-*O*-benzoyl analogue of the former donor type is more reactive than the tetra-*O*-benzylated counterparts. Again, the established relative reactivity factor of approximately two does not justify donor **6** being superarmed under NIS/TfOH activation.

Table 2. Competition Experiments with SBox Donors.



Entry	Promoter system	Temperature/ time	RR[b] 5:6
1	NIS (4 eq.), TfOH (40 %[a])	0 °C to rt/ 2.5 h	1: 0.55
2	DMTST (6 eq.)	0 °C/ 2 h	1: 0.1
3	DMTST (6 eq.) TTBP (1 eq.)	0 °C/ 4 h	No reaction
4	TfOH (20 %[a])	0 °C to rt/ 2.5 h	1: 0.7

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5	MeOTf (6 eq.)	0 °C to rt/ 1 h	1: 0.5
6	$Cu(OTf)_2$ (6 eq.)	rt/ 3 h	1:2.5

[a]With respect to the amount of each donor. Acceptor: L-menthol (1 eq.). [b]RR: reactivity ratio, (donor **5)**/(donor **6)**. Ratio refers to the ratio of unreacted donors after glycosylation.

Activation by DMTST[26] of donor **5** and **6** (Entry 2) fully confirms previous reports by Demchenko and co-workers established in their first article on the topic of electronically superarmed donors.[14] The large reactivity difference under DMTST activation being approximately a factor of 10 is expected to merit a classification as superarmed. Chemoselective activation has indeed also been shown by Demchenko and co-workers under this type of activation.[14]

The intriguing difference in reactivity of SBox donors induced by DMTST activation compared to NIS/TfOH activation, led to several speculations into the difference between the two thiophilic promoter systems, which previously has not been thoroughly investigated. Under NIS/TfOH promoted glycosylations with thioglycoside glycosyl donors, NIS is activated by a catalytic amount of TfOH (10 mol%), which remains constant during the reaction since the excess acceptor proton ends up on the nitrogen atom forming the neutral succinimide. In the case of DMTST activation, however, there is no acid present from the beginning of the glycosylation, but excess protons from the acceptor alcohol accumulates as TfOH as the glycosylation proceeds. We therefore speculated whether this increasing amount of acid present under DMTST activation of SBox donors, somehow could be important for the mode of activation of the SBox donors. This donor type could in principle be activated either on the S atom, the more remote N atom or a dynamic combination of the two modes of activation along the course of the reaction..[27]

To a first approximation, according to the hard−soft acid−base (HSAB) principle, the sulfur atom in SBox is a soft Lewis base and should be activated by soft Lewis acids such as iodonium ions and DMTST. Activation could also occur at the harder nitrogen atom of SBox by protonation. One could speculate whether activation at the SBox' sulfur atom would be more inductively influenced by the electron withdrawing effect of the 2-*O*-benzoyl, compared to activation at the more remote nitrogen atom, resulting in a lower rate for thiophilic activation on S compared to N-H+ activation.

To explore the acid dependence of SBox activation by DMTST the acid scavenger TTBP[28] was added to the reaction mixture. While addition of TTBP to the DMTST promoted reaction of SPh donors (**1** and **2**) did not have a pronounced effect (Entry 5, Table 1), activation of SBox in presence of TTBP did not occur at all (Entry 3, Table 2), demonstrating the importance of TfOH for SBox activation. Next, SBox activation with only TfOH was investigated (Entry 4), resulting in a reactivity difference mirroring that found for NIS/TfOH activation of SBox donors, but not to the superarmed level found for DMTST activation. The similar reactivity ratios could indicatethat NIS/TfOH activation of SBox occurs by N-protonation. Demchenko and co-workers, however, have previously studied this reaction and found the disulfide BoxSSBox as a reaction by-product, and of this basis concluded that activation occurs through reaction of S with I+ as generally accepted for thioglycoside activation. The BoxSSBox, however, could in principle also be formed after TfOH activation of the SBox donor generating HSBox followed by oxidation of this by NIS to the disulfide.[27]

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Given the possibility of the nucleofuge HSBox to undergo tautomerisation, as also discussed by Demchenko and co-workers,[27] proposing an exact mechanism for SBox activation with various promoter systems is not trivial. Similarly, it is not clear how different modes of activation influence the degree of armament.

Lastly, to test the influence of other known activators of SBox glycosyl donors we also explored both MeOTf or $Cu(OTf)_2$. The former activator (MeOTf) was found to preferentially activate the 2-*O*-benzoyl donor **6**, but not in a degree near to what can be characterized as superarmed. The latter ($Cu(OTf)_2$) was found to activate the tetra-*O*-benzyl protected donor **5**.

Conclusion

We have investigated whether the presence of a 2-*O*-benzoyl protecting group of a tri-*O*-benzylated glucosyl donor generally leads to superarmament across different donor types (SPh, SEt and SBox) and varying promoter systems. The overall conclusion is, that DMTST and SBox indeed offers a privileged combination of reagents in this study, which results in a reactivity difference large enough between a traditionally armed donor and its 2-*O*-benzoylated counterpart to be synthetically useful. Exchange of a 2-*O*-benzyl group for a 2-*O*-benzoyl does not generally result in superarmament, but does alter the pattern of reactivity, which is a testament to the complexity of glycosyl donor activation and glycosylation. A deeper level of understanding of the mechanisms behind the reaction between the glycosyl donor and promoter could potentially lead to useful tools to make glycosylation chemistry and oligosaccharide synthesis more efficient.

Experimental Section

General Methods

All reagents were used as purchased without further purification. Importantly, high quality NIS was used (Chempur (004499, *N*-iodosuccinimide/98%+). Dry solvents were taken from a solvent purification system. Glassware used for water-free reactions were dried for 12 h at 120 °C before use. Columns were packed with silica gel 60 (230–400 mesh) as the stationary phase. TLC plates were visualized by 10% H_2SO_4 in EtOH and heating until spots appeared. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a 400 MHz spectrometer with respect to ^{1}H resonances. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal. High-resolution mass spectral (HRMS) data were obtained on an electrospray (ES) mass spectrometer analyzing time-of-flight.

General Procedure for Glycosylations

A mixture of glycosyl donor (0.10 mmol), glycosyl acceptor (0.15 mmol), and freshly activated molecular sieves (3 Å, 100 mg) in CH_2Cl_2 (2 mL) was stirred under argon for 1 h. The solution was cooled to –78 °C using a dry ice/acetone bath. NIS (0.11 mmol) and TfOH (0.1 mL of a 0.1 M solution of TfOH in CH_2Cl_2) were added. Lumps of dry ice were removed

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from the acetone bath and the reaction was slowly allowed to reach 0 °C (approximately 3 hours). Upon completion, the solids were filtered off and the filtrate was washed with aqueous 10% $Na_2S_2O_3$ solution. The organic layer was separated, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to afford the corresponding glycoside. Anomeric ratios were measured by comparison of integral intensities of the anomeric protons and anomeric carbons from ^{1}H-NMR and ^{13}C-NMR spectra of crude reaction mixtures.

Competition Experiments

General Procedure for Competition Experiments with the NIS/TfOH Promoter System

The two glycosyl donors (0.10 mmol each) were dissolved in $CDCl_3$. A ^{13}C NMR spectrum was recorded and the ratios of the donors were checked to be 1.0:1.0 by comparing peak intensities from similar carbon atoms. The solvent was evaporated and (-)-L-menthol (0.5 mmol) and anhydrous CH_2Cl_2 (2 mL) were added. The mixture was stirred with freshly activated molecular sieves (3 Å, 100 mg) for 1 h under inert atmosphere. The solution was cooled to -78 °C and NIS (0.10 mmol) and TfOH (0.1 mL of a 0.1 M solution of TfOH in CH_2Cl_2) were added. Lumps of dry ice were removed from the acetone bath and the reaction mixture was slowly allowed to reach 0 °C over approximately 4 h. At 0 °C the solids were filtered off and the filtrate was washed with aqueous $Na_2S_2O_3$ (10 % in H_2O). The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude mixture was dissolved in $CDCl_3$ and a ^{13}C NMR spectrum was recorded. The unreacted donor ratios were measured by comparison of integral intensities of the anomeric carbons from the ^{13}C NMR spectra of the crude reaction mixtures.

Preparation of DMTST solution[8]

DMSTS was prepared by combining dimethyldisulfide (0.34 mL, 3.0 mmol) and MeOTf (0.26 mL, 3.0 mmol) in dry CH_2Cl_2 (1 mL). The mixture was stirred for 1 h and 0.1 mL was extracted and added to the competition experiment.

General Procedure for Competition Experiments with the DMTST Promoter System

The two glycosyl donors (0.10 mmol each) were dissolved in $CDCl_3$. A ^{13}C NMR spectrum was recorded and the ratios of the donors were checked to be 1.0:1.0. The solvent was

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evaporated and (-)-L-menthol (0.1 mmol) and anhydrous CH_2Cl_2 (2 mL) were added. The mixture was stirred with freshly activated molecular sieves (3 Å, 100 mg) for 1 h under inert atmosphere. The solution was cooled to 0 °C and DMTST (0.6 mmol) was added. The reaction mixture was allowed to stir for 2 h at 0 °C then quenched with one drop of Et_3N. The solid was filtered off and the filtrate was washed with an aqueous solution of NaOH (1 %) and with H_2O (three times). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was dissolved in $CDCl_3$ and a ^{13}C NMR was recorded. The product ratios were measured by comparison of integral intensities of the anomeric carbons from the ^{13}C NMR spectra of the crude reaction mixtures.

General Procedure for Competition Experiments with the DMTST Promoter System and base TTBP

The two glycosyl donors (0.10 mmol each) were dissolved in $CDCl_3$. A ^{13}C NMR spectrum was recorded and the ratios of the donors were checked to be 1.0:1.0. The solvent was evaporated and (-)-L-menthol (0.1 mmol) and anhydrous CH_2Cl_2 (2 mL) were added. The mixture was stirred with freshly activated molecular sieves (3 Å, 100 mg) for 1 h under inert atmosphere. The solution was cooled to 0 °C and TTBP (0.15 mmol) and DMTST (0.6 mmol) were added. The reaction mixture was allowed to stir for 2 h at 0 °C before quenched by one drop of Et_3N. The solid was filtered off and the filtrate was washed with an aqueous solution of NaOH (1 %) and with H_2O (three times). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was dissolved in $CDCl_3$ and a ^{13}C NMR was recorded. The product ratios were measured by comparison of integral intensities of the anomeric carbons from the ^{13}C NMR spectra of the crude reaction mixtures.

General Procedure for Competition Experiments with the MeOTf Promoter System

The two glycosyl donors (0.10 mmol each) were dissolved in $CDCl_3$. A ^{13}C NMR spectrum was recorded and the ratios of the donors were checked to be 1.0:1.0. The solvent was evaporated and (-)-L-menthol (0.1 mmol) and anhydrous CH_2Cl_2 (2 mL) were added. The mixture was stirred with freshly activated molecular sieves (3 Å, 100 mg) for 1 h under inert atmosphere. The solution was cooled to 0 °C and MeOTf (0.6 mmol) was added. The ice bath was removed and the reaction mixture was stirred for 1 h at rt. before Et_3N (0.5 mL) was added. The solid was filtered off and the filtrate was washed with H_2O (three times). The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude mixture

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was dissolved in $CDCl_3$ and a ^{13}C NMR spectrum was recorded. The product ratios were measured by comparison of integral intensities of the anomeric carbons from the ^{13}C NMR spectra of the crude reaction mixtures.

General Procedure for Competition Experiments with the TfOH Promoter System

The two glycosyl donors (0.10 mmol each) were dissolved in $CDCl_3$. A ^{13}C NMR spectrum was recorded and the ratios of the donors were checked to be 1.0:1.0. The solvent was evaporated and (-)-L-menthol (0.1 mmol) and anhydrous CH_2Cl_2 (2 mL) were added. The mixture was stirred with freshly activated molecular sieves (3 Å, 100 mg) for 1 h under inert atmosphere. The solution was cooled to 0 °C and TfOH (0.2 mmol) was added. The ice bath was removed and the reaction mixture was stirred for 1 h at rt. The solid was filtered off and the filtrate was washed with sat. aq. $NaHCO_3$ and H_2O (three times). The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude mixture was dissolved in $CDCl_3$ and a ^{13}C NMR spectrum was recorded. The product ratios were measured by comparison of integral intensities of the anomeric carbons from the ^{13}C NMR spectra of the crude reaction mixtures.

General Procedure for Competition Experiments with the $Cu(OTf)_2$ Promoter System

The two glycosyl donors (0.10 mmol each) were dissolved in $CDCl_3$. A ^{13}C NMR spectrum was recorded and the ratios of the donors were checked to be 1.0:1.0. The solvent was evaporated and (-)-L-menthol (0.1 mmol) and anhydrous CH_2Cl_2 (2 mL) were added. The mixture was stirred with freshly activated molecular sieves (3 Å, 100 mg) for 1 h under inert atmosphere. $Cu(OTf)_2$ (0.60 mmol) was added the green mixture was stirred for 3 h at rt. The solid was filtered off and the filtrate was washed with sat. aq. $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was dissolved in $CDCl_3$ and a ^{13}C NMR spectrum was recorded. The product ratios were measured by comparison of integral intensities of the anomeric carbons from the ^{13}C NMR spectra of the crude reaction mixtures.

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Synthesis of Donors

Phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (1)

Phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (21.8 g, 49.7 mmol, 1 equiv.) was dissolved in MeOH and sodium methoxide solution (25 wt. % in MeOH) was added until a pH-value of approximately 10 was reached. The reaction mixture was stirred for 30 h at rt, then neutralized with DOWEX® Acidic Cation Exchanger Resin in MeOH. The resin was filtered off by suction and the product mixture was concentrated *in vacuo*. The crude product was dissolved in anhydrous DMF (60 mL) and cooled to 0 °C. NaH (60 % (w/w) dispersion in mineral oil, 15.9 g, 397 mmol, 8 equiv.) was added and the mixture was stirred for 10 min prior to dropwise addition of BnBr (35.5 mL, 298 mmol, 6 equiv.). The resulting mixture was stirred for 18 h at rt then quenched by cautiously transferring the mixture into a large volume of H_2O at 0 °C. The aqueous phase was extracted with CH_2Cl_2 (three times) and the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (pentane/EtOAc 4:1) to afford the product (19.9 g, 31.4 mmol, 63 %) as a white solid. R_f 0.66 (pentane/EtOAc 5:1). $[\alpha]_D^{295K}$ +3.2 (*c* 1.0, $CHCl_3$). lit. +3 ($CHCl_3$).[1] M_p (uncorr.) 91.5 – 92.5 °C. lit. 91 – 92 °C.[1] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.57 – 7.52 (m, 2H, Ar*H*), 7.37 – 7.14 (m, 23H, Ar*H*), 4.86 (d, *J* 10.9 Hz, 1H, C*H*HPh), 4.85 (d, *J* 10.2 Hz, 1H, C*H*HPh), 4.81 (d, *J* 10.8 Hz, 1H, CH*H*Ph), 4.79 (d, *J* 10.8 Hz, 1H, C*H*HPh), 4.69 (d, *J* 10.3 Hz, 1H, CH*H*Ph) 4.63 (d, *J* 9.8 Hz, 1H, H1), 4.57 (d, *J* 12.0 Hz, 1H, C*H*HPh), 4.55 (d, *J* 10.8 Hz, 1H, CH*H*Ph), 4.50 (d, *J* 12.0 Hz, 1H, CH*H*Ph) 3.75 (dd, *J* 9.8 Hz, 1H, H6a), 3.72 – 3.64 (m, 2H, H6b, H3/H4), 3.61 (t, *J* 9.2 Hz, 1H, H3/H4) 3.50 – 3.44 (m, 1H, H5), 3.47 (dd, *J* 9.5 Hz, 8.6 Hz, 1H, H2). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 138.4 (Ar*C*), 138.3 (Ar*C*), 138.0 (Ar*C*), 133.8 (Ar*C*), 132.0 – 127.5 (Ar*C*H), 87.5 (C1), 86.8 (C3/C4), 80.6 (C2/C5), 79.1 (C2/C5), 77.8 (C4/C3), 75.9 (*C*H_2Ph), 75.5 (*C*H_2Ph), 75.1 (*C*H_2Ph), 73.5 (*C*H_2Ph), 69.0 (C6). HRMS (ES): calcd. for $C_{40}H_{40}O_5SNa^+$ 655.2494; found 655.2488. Spectral values were in accordance with previously reported data.[2]

Phenyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-thio-β-D-glucoyranoside (2)

Phenyl 3,4,6-tri-*O*-benzyl-1-thio-β-D-glucoyranoside (100 mg, 0.18 mmol, 1 equiv.) was dissolved in anhydrous CH_2Cl_2 (3 mL) and DMAP (9 mg, 0.09 mmol, 0.5 equiv.), Et_3N (0.13 mL, 0.92 mmol, 5 equiv.) and BzCl (0.08 mL, 0.74 mmol, 4 equiv.) were added. The mixture was stirred at rt for 18 h. To quench excess BzCl the mixture was stirred with DMAPA[3] (0. 09 mL, 0.74 mmol, 4 equiv.) for 10 min. The reaction mixture was washed with aq. 1M HCl

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(x3), sat. aq. $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (pentane/EtOAc 10:1) yielding the product (86 mg, 0.14 mmol, 74%) as a white solid. R_f 0.35 (pentane/EtOAc 5:1). $[\alpha]_D^{295K}$ +28.2 (*c* 1.0, $CHCl_3$), lit. +21.7 (*c* 1.1, $CHCl_3$).[3] M_p (uncorr.) 128.4 – 129.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.09 – 8.03 (m, 2H, Ar*H*), 7.63 – 7.09 (m, 23H, Ar*H*), 5.30 (t, *J* 9.5 Hz, 1H, H2), 4.82 (dd, *J* 10.8 Hz, *J* 10.8 Hz, 2H, C*H*HPh, CH*H*Ph), 4.75 (d, *J* 11.0 Hz, 1H, H1), 4.67 – 4.56 (m, 4H, 2xCH_2Ph), 3.86 (t, *J* 9.3 Hz, 1H, H3), 3.85 – 3.77 (m, 2H, H6a, H6b), 3.76 (t, *J* 8.8 Hz, 1H, H4), 3.67 – 3.60 (m, 1H, H5). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 165.2 (C=O) 138.2 (Ar*C*), 137.9 (Ar*C*), 137.6 (Ar*C*), 137.2 (Ar*C*), 133.2 – 127.6 (Ar*C*H), 86.2 (C1), 84.3 (C3), 79.5 (C5), 77.8 (C4), 75.4 (*C*H_2Ph), 75.1 (*C*H_2Ph), 73.4 (*C*H_2Ph), 72.4 (C2), 68.9 (C6). HRMS (ES): calcd. for $C_{40}H_{38}O_6S$ [M+Na^+] 669.2281; found 669.2288. Spectral values were in accordance with previously reported data.[4]

KSBox salt

K_2CO_3 (5.0 g, 1 equiv.) was added to a stirred solution of HSBox (4.55 g, 1 equiv.) in anhydrous acetone. The mixture was refluxed for at 60 °C for 3 h. The acetone was evaporated off and the KSBox salt (8.9 g) was dried overnight under reduced pressure.

Benzoxazolyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (5)

Phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside (1.57 g, 2.48 mmol, 1 equiv.) was stirred with freshly activated molecular sieves (3 Å, 1.50 g) in anhydrous CH_2Cl_2 (25 mL) for 1 h under inert atmosphere prior to addition of a freshly prepared solution of Br_2 in CH_2Cl_2 (25.2 mL of a 0.118 M solution, 2.98 mmol, 1.2 equiv.). The orange mixture was stirred for 5 min at rt. The solid was filtered off and the filtrate was concentrated *in vacuo*. The crude glucosyl bromide was dissolved in anhydrous acetone (20 mL) and KSBox salt (1.18 g, 6.20 mmol, 2.5 equiv.) and 18-crown-6 ether (72 mg, 0.27 mmol, 0.11 equiv.) were added under inert atmosphere. The reaction mixture was stirred for 16 h at rt. Upon completion, the solid was filtered off and washed with CH_2Cl_2. The filtrate was washed with an 1% NaOH aq. solution and H_2O (three times). The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (toluene/EtOAc 50:1) to afford the product (419 mg, 0.62 mmol, 25 %) as a slightly yellow solid. R_f (EtOAc/pentane 4:1) 0.41. $[\alpha]_D^{295K}$ +6.6 (*c* 1.0, $CHCl_3$), lit. +0.89 (*c* 1.0, $CHCl_3$)[4]. M_p (uncorr.) 95.9 – 96.5 °C, lit. 96 – 97 °C.[6] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.84 – 7.80 (m,

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1H, ArH), 7.61 – 7.34 (m, 23H, ArH), 5.73 (d, *J* 9.4 Hz, 1H, H1), 5.15 (d, *J* 11.0 Hz, 1H, C*H*HPh), 5.12 (d, *J* 10.9 Hz, 1H, CH*H*Ph), 5.09 (d, *J* 10.5 Hz, 1H, C*H*HPh), 5.07 (d, *J* 10.5 Hz, 1H, C*H*HPh) 5.05 (d, *J* 10.5 Hz, 1H, CH*H*Ph), 4.83 (d, *J* 10.9 Hz, 1H, CH*H*Ph), 4.78 (d, *J* 12.0 Hz, 1H, C*H*HPh), 4.65 (d, *J* 12.0 Hz, 1H, CH*H*Ph), 4.07 – 3.94 (m, 5H, H2, H3, H4, H6α, H6β), 3.93 – 3.85 (m, 1H, H5). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 161.5 (*C*=N), 151.7 (Ar*C*-O), 141.7 (Ar*C*-N), 138.2 (Ar*C*), 137.9 (Ar*C*), 137.9 (Ar*C*), 137.4 (Ar*C*), 128.4 – 127.5 (Ar*C*H), 124.3 (Ar*C*H), 124.2 (Ar*C*H), 118.9 (Ar*C*H), 109.9 (Ar*C*H), 86.5, 84.7 (C1), 80.5, 79.6, 77.3, 75.7 (*C*H_2Ph), 75.4 (*C*H_2Ph), 74.9 (*C*H_2Ph), 73.3 (*C*H_2Ph), 68.3 (C6). HRMS (ES): calcd. for $C_{41}H_{39}NO_6SNa^+$ 696.2390; found 696.2399. Spectral values were in accordance with previously reported data.[5]

Benzoxazolyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (6)

Phenyl 2-*O*-benzoyl-3,4,6-tri-*O*-benzyl-1-thio-β-D-glucoyranoside (700 mg, 1.08 mmol, 1 equiv.) was stirred with freshly activated molecular sieves (3 Å, 500 mg) in anhydrous CH_2Cl_2 (15 mL) for 1 h under inert atmosphere prior to addition of a freshly prepared solution of Br_2 in CH_2Cl_2 (9.1 mL of a 0.118 M solution, 2.98 mmol, 1.2 equiv.). The reaction mixture was stirred for 5 min at rt. The solid was filtered off and the filtrate was concentrated *in vacuo*. The crude glucosyl bromide **16** was dissolved in anhydrous acetone (20 mL) and KSBox salt (1.18 g, 6.20 mmol, 2.5 equiv.) and 18-crown-6 ether (72 mg, 0.27 mmol, 0.11 equiv.) were added under inert atmosphere. The reaction mixture was stirred for 16 h at rt. Upon completion, the solid was filtered off and washed with CH_2Cl_2. The filtrate was washed with an 1% NaOH aq. solution and H_2O (three times). The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (pentane/EtOAc 10:1) to afford the product (586 mg, 0.85 mmol, 79%) as a white solid. R_f(EtOAc/pentane 4:1) 0.30. $[\alpha]_D^{295K}$ +66.8 (*c* 1.0, $CHCl_3$), lit. +106.7 (*c* 1, $CHCl_3$).[6] M_p (uncorr.) 96.2 – 98.0 °C, lit. 96 – 97 °C.[6] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.12 (d, *J* 7.4 Hz, 2H, Ar*H*), 7.72 (d, *J* 7.6 Hz, 1H, Ar*H*), 7.61 (t, *J* 7.4 Hz, 1H, Ar*H*), 7.51 – 7.25 (m, 20H, Ar*H*), 5.95 (d, *J* 10.3 Hz, 1H, H1), 5.68 (dd, *J* 10.1 Hz, 9.0 Hz, 1H, H2), 4.99 (d, *J* 10.9 Hz, 1H, C*H*HPh), 4.93 (d, *J* 11.1 Hz, 1H, C*H*HPh), 4.85 (d, *J* 11.1 Hz, 1H CH*H*Ph), 4.76 (d, *J* 10.9 Hz, 1H, CH*H*Ph), 4.75 (d, *J* 12.0 Hz, 2H, C*H*HPh), 4.62 (d, *J* 12.0 Hz, 1H, CH*H*Ph), 4.14 (t, *J* 8.8 Hz, 1H, H3), 4.07 (t, *J* 9.1 Hz, 1H, H4), 3.98 – 3.90 (m, 3H, H5, H6α, H6β). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 165.4 (*C*=O), 162.0 (*C*=N), 152.0 (Ar*C*-O), 141.7 (Ar*C*-N), 138.1 (Ar*C*), 137.7 (Ar*C*), 133.5 (Ar*C*), 130.0 (Ar*C*H), 129.3 (Ar*C*),

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128.6 - 127.8 (Ar*C*H), 124.5 (Ar*C*H), 124.4 (Ar*C*H), 118.9 (Ar*C*H), 110.2 (Ar*C*H), 84.0 (H1), 84.0 (H3), 80.2 (H5), 77.5 (H4), 75.5 (*C*H_2Ph), 75.2 (*C*H_2Ph), 73.6 (*C*H_2Ph), 72.5 (H2), 68.5 (H6). HRMS (ES): calcd. for $C_{41}H_{37}NO_7SNa^+$ 710.2183; found 710.2190. Spectral values were in accordance with previously reported data.[6]

L-Menthyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (7α)

Appearance: Colorless oil. R_f 0.38 (pentane/EtOAc, 5:1). $[\alpha]_D^{295K}$ +31 (*c* 1.0, $CHCl_3$), lit. +31.3 (*c* 1.1, $CHCl_3$).[7] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.37 - 7.23 (m, 18H, Ar*H*), 7.15 - 7.11 (m, 2H, Ar*H*), 5.02 (d, *J* 3.6 Hz, 1H, H1), 4.98 (d, *J* 10.9 Hz, 1H, C*H*HPh), 4.84 (d, *J* 10.7 Hz, 1H, C*H*HPh), 4.82 (d, *J* 10.9 Hz, 1H, CH*H*Ph), 4.72 (d, *J* 11.8 Hz, 1H, C*H*HPh), 4.68 (d, *J* 12.3 Hz, 1H, CH*H*Ph), 4.64 (d, *J* 12.3 Hz, 1H, C*H*HPh), 4.47 (d, *J* 12.1 Hz, 1H, CH*H*Ph), 4.45 (d, *J* 10.7 Hz, 1H, CH*H*Ph), 4.02 (t, *J* 9.5 Hz, H3), 4.00 – 3.93 (m, 1H, H5), 3.75 (dd, *J* 10.5, 3.7 Hz, 1H, H6α), 3.64 (t, *J* 9.4 Hz, 1H, H4), 3.64 (dd, *J* 10.5, 1.6 Hz, 1H, H6β), 3.55 (dd, *J* 19.8, 3.6 Hz, 1H, H2), 3.35 (dt, *J* 10.6, 4.3 Hz, 1H, OC*H*), 2.42 (dsep, *J* 6.9, 1.9 Hz, 1H, C*H*$(CH_3)_2$), 2.16 – 2.08 (m, 1H), 1.65 - 1.57 (m, 2H), 1.40 – 1.25 (m, 2H), 1.08 – 0.75 (m, 3H), 0.86 (d, *J* 6.4 Hz, 3H, CH_3), 0.83 (d, *J* 7.1 Hz, 3H, CH_3), 0.71 (d, *J* 6.9 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 138.9 (Ar*C*), 138.4 (Ar*C*), 138.3 (Ar*C*), 138.0 (Ar*C*), 128.5 - 127.5 (Ar*C*H), 98.6 (C1), 82.0 (C3), 81.0 (O*C*H), 80.5 (C2), 78.1 (C4), 75.5 (*C*H_2Ph), 75.1 (*C*H_2Ph), 73.5 (*C*H_2Ph), 73.2 (*C*H_2Ph), 70.3 (C5), 68.6 (C6), 48.8, 43.1 (*C*H_2), 34.3 (*C*H_2), 31.7, 24.6 (*C*H$(CH_3)_2$), 22.9 (*C*H_2), 22.3 (*C*H_3), 21.1 (*C*H_3), 16.1 (*C*H_3). HRMS (ES): Calcd. for $C_{44}H_{54}O_6NH_4^+$ 696.4259; found 696.4273. Spectral values were in accordance with previously reported data.[7]

L-Menthyl 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside (7β)

Appearance: White solid. R_f 0.47 (pentane/EtOAc, 5:1). $[\alpha]_D^{295K}$ -16 (*c* 1.0, $CHCl_3$), lit. -17.2 (*c* 1.05, $CHCl_3$).[8] ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.57 – 7.53 (m, 1H, Ar*H*), 7.43 – 7.23 (m, 19H, Ar*H*), 5.01 (d, *J* 10.6 Hz, 1H, C*H*HPh), 4.98 (d, *J* 10.8 Hz, 1H, C*H*HPh), 4.88 (d, *J* 10.8 Hz, 1H, C*H*HPh), 4.85 (d, *J* 11.0 Hz, 1H, CH*H*Ph), 4.74 (d, *J* 10.9 Hz, 1H, CH*H*Ph), 4.67 (d, *J* 12.0 Hz, 1H, C*H*HPh), 4.64 (d, *J* 10.4 Hz, 1H, CH*H*Ph), 4.60 (d, *J* 12.2 Hz, 1H, CH*H*Ph), 4.53 (d, *J* 7.8 Hz, 1H, H1), 3.75 (d, *J* 3.2 Hz, 2H, H6α, H6β), 3.70 (t, *J* 8.5 Hz, H3/H4), 3.65 (t, *J* 9.0 Hz, H4/H3), 3.56 (td, *J* 10.7, 4.2 Hz, 1H, OC*H*), 3.50 – 3.44 (m, 1H, H5), 3.47 (t, *J* 8.2 Hz, 1H, H2), 2.46 – 2.35 (m, 1H, C*H*$(CH_3)_2$), 2.20 (d, *J* 12.1 Hz, 1H), 1.72 (m, 2H), 1.46

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– 1.28 (m, 2H), 1.11 – 0.92 (m, 3H), 0.98 (d, *J* 7.1 Hz, 3H, C*H*$_3$), 0.96 (d, *J* 6.6 Hz, 3H, C*H*$_3$), 0.88 (d, *J* 6.9 Hz, 3H, C*H*$_3$). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 138.9 (Ar*C*), 138.6 (Ar*C*), 138.4 (Ar*C*), 138.3 (Ar*C*), 129.1 – 127.2 (Ar*C*H), 100.8 (C1), 85.0 (C3/C4), 82.3 (C5/C2), 78.0 (C4/C3), 77.8 (O*C*H), 75.7 (*C*H_2Ph), 75.1 (*C*H_2Ph), 74.9 (*C*H_2Ph), 74.9 (C2/C5), 73.7 (*C*H_2Ph), 69.4 (C6), 48.2, 41.0 (*C*H_2), 34.5 (*C*H_2), 31.5, 25.3 (*C*H(CH_3)$_2$), 23.3 (*C*H_2), 22.3 (*C*H_3), 21.2 (*C*H_3), 16.0 (*C*H_3). Spectral values were in accordance with previously reported data.[8]

L-Menthyl 3,4,6-tri-*O*-benzyl-2-*O*-benzoyl-β-D-glucopyranoside (8)

Appearance: White solid. R_f 0.50 (pentane/EtOAc, 4:1). $[\alpha]_D^{295K}$ -17 (*c* 1.0, $CHCl_3$). M_p (uncorr.) 68.0 – 70.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.95 -7.92 (m, 2H, Ar*H*), 7.51 – 7.39 (m, 1H, Ar*H*), 7.34 (t, *J* 7.7 Hz, 2H, Ar*H*), 7.28 – 7.13 (m, 10H, Ar*H*), 7.09 – 7.01 (m, 5H, Ar*H*), 5.14 (t, *J* 8.5 Hz, 1H, H2), 4.76 (d, *J* 10.6 Hz, 1H, C*H*HPh), 4.66 (d, *J* 11.0 Hz, 1H, C*H*HPh), 4.58 (d, *J* 10.6 Hz, 1H, CH*H*Ph), 4.56 (d, *J* 12.1 Hz, 1H, C*H*HPh), 4.55 (d, *J* 10.8 Hz, 1H, CH*H*Ph), 4.49 (d, *J* 12.5 Hz, 1H, CH*H*Ph), 4.48 (d, *J* 8.3 Hz, 1H, H1), 3.72 (t, *J* 9.0 Hz, 1H, H3), 3.70 – 3.62 (m, 3H, H4, H6α, H6β), 3.47 – 3.40 (m, 1H, H5), 3.31 (td, *J* 10.8, 4.1 Hz, 1H, OC*H*), 2.23 (dsep, *J* 6.9, 2.5 Hz, 1H, C*H*(CH_3)$_2$), 1.82 – 1.75 (m, 1H), 1.52 – 1.41 (m, 2H), 1.24 – 1.11 (m, 2H), 1.10 - 1.00 (m, 1H), 0.89 - 0.78 (m, 1H), 0.77 (d, *J* 7.1 Hz, 3H, C*H*$_3$), 0.69 (d, *J* 6.8 Hz, 3H, C*H*$_3$), 0.64 (d, *J* 6.6 Hz, 3H, C*H*$_3$), 0.60 - 0.47 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 165.3 (*C*=O), 138.5 (Ar*C*), 138.2 (Ar*C*), 138.1 (Ar*C*), 133.0 (Ar*C*H), 130.4 (Ar*C*), 129.9 (Ar*C*H), 129.2 (Ar*C*H), 128.6 - 127.3 (Ar*C*H), 99.3 (C1), 83.1 (C3), 78.8 (O*C*H), 78.3 (C4), 75.4 (C5), 75.2 (*C*H_2Ph), 74.9 (*C*H_2Ph), 74.2 (C2), 73.9 (*C*H_2Ph), 69.3 (C6), 47.5, 41.1 (*C*H_2), 34.3 (*C*H_2), 31.4, 25.1, 23.1 (*C*H(CH_3)$_2$), 22.2 (*C*H_3), 21.1 (*C*H_3), 15.9 (*C*H_3). HRMS (ES) Calcd. for $C_{44}H_{52}O_7NH_4^+$ 710.4071 found; 710.4062.

Associated content

Supporting Information

The Supporting Information is available free of charge on the publications website: Glycosylation results under a non-competitive setting and ^{1}H and ^{13}C spectra of compounds.

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