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Computational and experimental studies of reactive intermediates in glycosylation reactions

Remmerswaal, W.A.

Citation

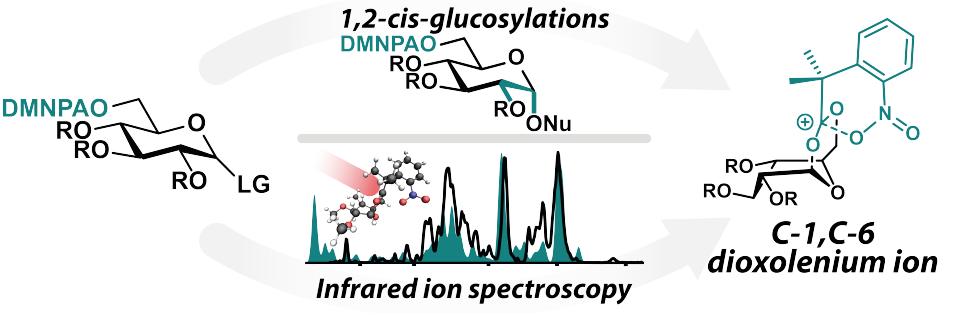
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Chapter 5

Stabilization of Glucosyl Dioxolenium Ions by 'Dual Participation' of the 2,2-Dimethyl-2-(*Ortho*-Nitrophenyl)Acetyl (DMNPA) Protection Group for 1,2-*Cis*-Glucosylation



Abstract | The stereoselective introduction of glycosidic bonds is of paramount importance to oligosaccharide synthesis. Among the various chemical strategies to steer stereoselectivity, participation by either neighboring or distal acyl groups is often used. Recently, the use of the 2,2-dimethyl-2-(*ortho*-nitrophenyl)acetyl (DMNPA) protection group was shown to offer enhanced stereoselective steering compared to other acyl groups. Here, the origin of the stereoselectivity induced by the DMNPA group is investigated through systematic glycosylation reactions and infrared ion spectroscopy (IRIS) combined with techniques such as isotopic labelling of the anomeric center and isomer population analysis. This study indicates that the origin of the stereoselectivity of the glycosylations of the DMNPA-donors does not lie in the direct participation of the nitro moiety, but in the formation of a dioxolenium ion that is strongly stabilized by the nitro group.

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Introduction

The stereoselective introduction of glycosidic bonds remains a major challenge in the chemical synthesis of oligosaccharides. The protecting group pattern on both reaction partners in the glycosylation reaction has a dramatic effect on the stereochemical outcome. Thus, careful selection of the protecting groups can enable one to steer the glycosylation reaction to the desired stereoisomer.[1–4] The use of C-2 acyl protecting groups results in neighboring group participation (NGP) by the formation of a bicyclic C-1,C-2 dioxolenium ion intermediate (Figure 1A), which generally forms 1,2-*trans* glycosidic bonds in a reliable manner.[5,6] This strategy is one of the cornerstones of oligosaccharide synthesis.[7] By definition, however, NGP only allows for the formation of 1,2-*trans* glycosides. In contrast, long-range participation (LRP) of acyl groups from distal positions (*i.e.*, C-3, C-4, and C-6) can enable the introduction of 1,2-*cis* linkages (Figure 1B). The origin and the strength of this stereodirecting effect remains poorly understood and is heavily debated. [8–11] Evidence for the occurrence of LRP comes from the stereoselectivity of glycosylation reactions featuring remote acyl groups on the donor glycosides and the isolation of cyclic orthoesters.[12–25] Dioxolenium ions formed by attack of the remote esters on the anomeric center of activated glycosyl donors have recently been detected in both the gas phase, by infrared ion spectroscopy (IRIS),[26–28] and in solution by NMR experiments.[29–31]

Using a combination of IRIS, density functional theory (DFT) calculations,[32] and model glycosylation experiments,[26] it was recently mapped how the strength of LRP depends on the position of the participating ester groups on the glycosyl donor and on the configuration of the donor glycoside. The strongest LRP was observed for C-3-*O*-acyl mannosyl donors. These donors provide excellent α-selectivity with a range of nucleophiles. DFT calculations have indicated that the bridged intermediate 1,3-dioxolenium ion is significantly more stable than the corresponding oxocarbenium ion. Subsequently, evidence for the existence of this bridged ion in solution was provided using chemical exchange saturation transfer NMR experiments in which a cross peak between the anomeric carbon and a ^{13}C labeled C-3-acyl group was detected.[33] Less prominent LRP effects were observed for other systems such as C-4-acyl galactosides, for which Crich and co-workers have argued that attack on the activated anomeric center of these donors is hampered by the orientation of the C-4-ester. They suggest that this group preferentially takes up a conformation in which the C=O nearly eclipses the C-4,H-4 bond, and that rotation along the C-4-*O*-4 axis is too unfavorable to allow for the formation of a dioxolenium ion.[10] This hypothesis is supported by recent findings in which this rotational barrier is lowered by placing a methyl at C-4, thus creating a quaternary carbon atom. The methylated C-4-*O*-benzoyl group formed a C-4,C-1 dioxolenium ion and was observed by NMR spectroscopy.[34]

Although LRP has also been invoked to account for increased α-selectivity in C-6-acyl glycosyl donors, bridged 1,6-dioxolenium ions have not been observed experimentally. In contrast to the C-1,C-3 and C-1,C-4 dioxolenium ions observed by IRIS for C-3-acyl mannosides and C-4-acyl galactosides, ions generated from C-6-acyl functionalized pyranosides showed ring-opened structures in which the C-6-acyl group attacks C-5 to expel the O-5, forming a C-5,C-6-dioxolenium ion with concomitant generation of the C-1-aldehyde. DFT calculations did not reveal any stabilization of the parent oxocarbenium ions by C-1,C-6-dioxolenium ion formation.

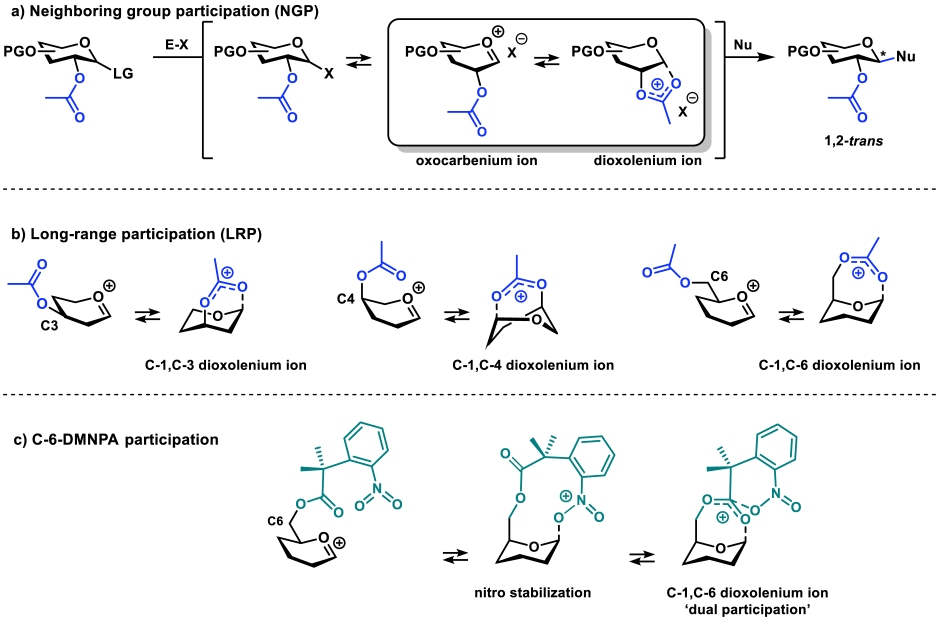


Figure 1. NGP (A) and LRP (B) in glycosylation reactions allow to control the stereoselectivity of glycosylation reactions. Schematic representation of the possible reactive intermediates in NGP and LRP. PG = protection group, E–X = promoter system, Nu = nucleophile. (C) LRP by the DMNPA group, mounted at C-6.

To enhance LRP effects to control the stereoselectivity of glycosylation reactions, the 2,2-dimethyl-2-(*ortho*-nitrophenyl)acetyl (DMNPA) protecting group was recently introduced.[35] This protecting group has been shown to steer the stereoselectivity from various distal positions on differently configured glycosyl donors, consistent with a LRP mechanism.[36] The current hypothesis for the origin of the enhanced LRP effect of the DMNPA is the unique chemical structure that may enable a "dual-participation" mechanism. The intermediate dioxolenium ion can be stabilized through the donation of electron density from the aryl nitro group, which is brought into close proximity of the central carbon atom of the dioxolenium ion by the geminal dimethyl groups through the Thorpe-Ingold effect[37,38] (Figure 1C). This hypothesis is supported by crystal structures that indicate the interaction of the nitro group with the DMNPA carbonyl in the parent donor molecules.

However, little direct experimental evidence is available for the proposed dual-participation mechanism and initial computational studies have shown that stabilization of the intermediate oxocarbenium ion may also take place by direct interaction of the nitro group with the anomeric center. IRIS experiments provide an excellent opportunity to probe the structure of intrinsically labile cations and discriminate dioxolenium and oxocarbenium ions. It has been proposed that the DMNPA group may be used to assist in the formation of α-glucosyl linkages present in many biologically and structurally relevant polysaccharides. Therefore, the possible mechanisms of LRP in DMNPA-functionalized glucosyl donors is studied here. To this end, a set of model glycosylation reactions, employing a set of partially fluorinated alcohol acceptors of gradually increasing nucleophilicity, was combined with the characterization of reactive intermediates by IRIS techniques. Isotope labelling was used to gain additional information on the different isomers of the cations generated upon ionization. An isomer population analysis was performed to probe the structures that were simultaneously present in the gas phase cation mixture.

Altogether, these experiments show that mounting the DMNPA group at the C-3 or C-4 glucosyl alcohols does not affect the stereoselectivity of the glycosylation reactions, but the C-6-DMNPA ester may provide LRP to favor formation of the α-glucosyl products. The C-6-DMNPA group may stabilize the glucosyl oxocarbenium ion through a 'dual participation' mechanism in which the distal ester attacks the anomeric center and the DMNPA nitro group stabilizes the resulting dioxolenium ion. Stabilization of the ionic intermediates can shift the glycosylation reaction mechanism from an S_N2-type substitution on the α-anomeric glucosyl triflate, which leads to the β-linked product, to a mechanism involving the stabilized ionic species that provides the synthetically challenging α-glucosides.

Results and Discussion

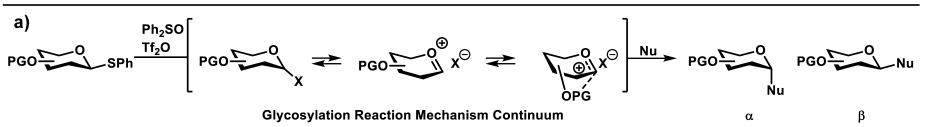
Model glycosylation reactions

To investigate the stereodirecting effect of the DMNPA group, a matrix of model glycosylation reactions was performed in which the stereoselectivity of glycosylations of different glucosyl donors is compared. To this end, the C-3, C-4, and C-6 DMNPA-protected glucosyl donors (**3**, **5**, and **7**, respectively) were synthesized (the synthetic route is depicted in Supplementary scheme S1), alongside their benzoyl counterparts (**2**, **4**, and **6**, respectively) and the benchmark glucosyl donor **1**, bearing solely benzyl ether protecting groups (Table 1). The acceptors used for the model glycosylation reactions consist of a set of model acceptors of systematically increasing nucleophilicity. Glycosylation reactions with these partially fluorinated ethanol derivatives (*i.e.*, hexafluoro-2-propanol, HFIP; 2,2,2-trifluoroethanol, TFE; 2,2-difluoroethanol, DFE; 2-fluoroethanol, MFE; ethanol, EtOH) can be used to probe the effect of acceptor nucleophilicity on the stereoselectivity of the glycosylation reaction.[8] The glycosylation reactions were performed under pre-activation conditions using a slight excess of diphenyl sulfoxide (Ph_2SO) and triflic anhydride (Tf_2O) as an activator system. As previously reported, glycosylation reactions with the per-*O*-benzylated glucose donor exhibit a gradual shift from α- to β-stereoselectivity as the nucleophilicity of the acceptor increases.[39,40] This shift in stereoselectivity can be explained by a shift in the reaction mechanism through which the glycosidic linkages are formed. The weaker nucleophiles require a more electrophilic glycosylating agent, such as a glycosyl oxocarbenium ion-like species, a related contact ion pair, or an equatorial anomeric triflate, while reactive nucleophiles can displace the more stable covalent anomeric axial triflate.

Table 1 summarizes the results of the model glycosylation reactions. All these reactions were performed under the same pre-activation conditions (Tf_2O (1.3 equiv), Ph_2SO (1.3 equiv), 2,4,6-tri-tert-butylpyrimidine (TTBP, 2.5 equiv), DCM (0.05 M), −80 to −60 °C, then add nucleophile (2 equiv) at −80 °C), with excess acceptor and high dilution to minimize the concentration change during the reaction.[38] Previously, it was reported that placing a benzoate on the C-3, C-4, or C-6 of a glucosyl donor had virtually no effect on the stereoselectivity of the glycosylation reactions, compared to the reactions of the per-benzylated glucosyl donor. Installation of the DMNPA group on either C-3 or C-4 did not affect the stereoselectivity trends either. However, a significant shift in stereoselectivity, towards the formation of more α-linked products, was observed when this group is mounted on C-6. Notably, the reactions of 2,2-difluoroethanol and 2,2,2-trifluoroethanol proceeded with excellent selectivity, forming only the α-linked products. As the reactivity of carbohydrate alcohol acceptors roughly corresponds to the reactivity of these model alcohols, this nucleophilicity-stereoselectivity trend indicates that the C-6-DMNPA can be used to construct the challenging α-glucosyl glycosidic linkages in oligosaccharides. The difference in stereoselectivity between the C-6-OBn/Bz donors **1**/**6** and C-6-DMNPA donor **7** is indicative of a shift in the mechanisms of the glycosylation reaction. Specifically, the enhanced selectivity towards a product, with the glycosidic linkage *trans* with respect to the acyl group, may be indicative of a mechanism involving LRP. The absence of enhanced α-selectivity for the *O*-6-benzoate donor demonstrates the LRP enhancing effect of the DMNPA

group. Overall, the stereoselectivity trends in Table 1 indicate that the DMNPA group may enable LRP, but that participation critically depends on the position on the carbohydrate ring.

Table 1. Model glycosylation reactions. The stereoselectivity of the reaction is expressed as α:β and based on ^{1}H-NMR of purified α/β-product mixtures. Blue-colored cells represent α-selectivity, while orange-colored cells represent β-selectivity. The percentage given between brackets represents the yield after purification by column chromatography; Pre-activation based glycosylation conditions: donor **1**-**7** (1 equiv), Tf_2O (1.3 equiv), Ph_2SO (1.3 equiv), TTBP (2.5 equiv), DCM (0.05 M), −80 to −60 °C, then add nucleophile (2 equiv) at −80 °C.



b)

	HO CF3 CF3	HO CF3	HO CHF2	HO CH2F	HO CH3
BnO BnO BnO SPh BnO **1**[a]	>98:2 (41 %)	72:28 (80 %)	48:52 (58 %)	36:64 (75 %)	15:85 (70 %)
BnO BnO BzO SPh BnO **2**[a]	>98:2 (28 %)	76:25 (91 %)	58:42 (97 %)	44:56 (95 %)	40:60 (88 %)
BnO BnO DMNPAO SPh BnO **3**	(- %)[b]	63:37 (66 %)	51:49 (79 %)	41:59 (96 %)	43:57 (100 %)
BnO BzO BnO SPh BnO **4**[a]	>98:2 (19 %)	79:21 (76 %)	48:52 (70 %)	34:66 (82 %)	15:85 (76 %)
BnO DMNPAO BnO SPh BnO **5**	>98:2 (39 %)	80:20 (66 %)	50:50 (77 %)	36:64 (74 %)	24:74 (72 %)
BzO BnO BnO SPh BnO **6**[a]	>98:2 (30 %)	95:5 (82 %)	77:23 (82 %)	35:65 (83 %)	17:83 (94 %)
DMNPAO BnO BnO SPh BnO **7**	>98:2 (34 %)	>98:2 (64 %)	90:10 (67 %)	70:30 (63 %)	40:60 (71 %)

[a] Experimental data of the per-benzyl and benzoate donor glycosylation reactions from Hansen *et al.*[26] [b] Product formation was not observed in crude NMR spectra and the coupled product could not be isolated.

To investigate whether dual participation can play a role in the stabilization of the intermediate glycosyl cations, the structure of the DMNPA-containing glycosyl cations was studied by IRIS. Based on the observed selectivity in the model glycosylation experiments, the methylated (commonly used in IRIS and computational studies to minimize spectral congestion[26,41] and computational cost[26,32], respectively) anomeric sulfoxide derivative of the α-selective glucosyl donor **7**, *i.e.,* glucosyl sulfoxide **8** (Supplementary scheme S2) was prepared. To obtain the glycosyl cations of this donor, the proton adduct was generated by electrospray ionization (ESI+) and isolated in a Bruker AmaZon Speed ion trap.[42] Subsequently, the sulfoxide leaving group was expelled by collision induced dissociation (CID) to generate the glycosyl cation. An IR spectrum of the isolated glycosyl cation was measured using the free-electron laser FELIX[43] in the 600-1900 cm^{-1} range by monitoring the wavelength-dependent IR multiple photon-induced dissociation (IRMPD) yield.[44]

Structural assignment was achieved by comparison of the IR spectra to DFT calculated spectra (B3LYP/6-31++G(d,p)). This combination of functional and basis set has been shown to perform well for predicting vibrational spectra of the type of systems considered here so, for consistency, this approach was continued.[41,45,46] Alternative basis sets and the inclusion of a dispersion correction[45] have been evaluated and only have a minimal effect on the computed vibrational spectra (see Supplementary Figure S4). Higher-level energies were obtained by combining the B3LYP-calculated Gibbs free energy with the electronic energy of an MP2/6-311++G(2d,2p) single point calculation. Candidate geometries of possible conformations were generated using an earlier reported workflow.[47]

The experimental IR spectrum of the glucosyl cation generated from **8** is presented in black in Figure 2, along with the computed spectra of different isomeric cation structures: the ring-opened C-5,C-6-dioxolenium ion with nitro stabilization (**8a**), the nitro-stabilized oxocarbenium ion (**8b**), the C-1,C-6-dioxolenium ion with nitro-stabilization (**8c**), the oxocarbenium ion (**8d**), and the acyl-stabilized oxocarbenium ions (**8e**). Previous work has shown that the most diagnostic peaks for these spectral comparisons are the carbonyl stretch around 1750 cm^{-1}, the oxocarbenium $C=O^+$ stretch around 1600 cm^{-1} and the dioxolenium ion $O\text{-}C^+\text{-}O$ stretch around 1550 cm^{-1}.[26] Unfortunately, both the $O\text{-}C^+\text{-}O$ and $C=O^+$ stretches are obscured by the nitro O-N-O asymmetric stretching in the same region, but, from the generated spectra, it can be concluded that the spectrum corresponding to the dual participation structure **8c** (Figure 2c) matches best, indicating this dioxolenium ion to be favorable. This dual participation structure (**8c**) is, however, unable to account for the characteristic band at 1737 cm^{-1}. This IR frequency points towards the presence of a carbonyl group, that is present in all other isomers considered. The computed C=O stretches of the oxocarbenium with (**8b**) and without (**8e**) nitro stabilization match well with the experiment, suggesting their presence in the ion population. However, the ring-opened structure **8a** and the acyl stabilized oxocarbenium **8e** cannot be definitively excluded, because the former showed a blueshift for the aldehyde stretch. This general mismatch of the experimental C=O stretch with B3LYP-computed frequencies has previously been observed for similar ring-opened structures.[26,48]

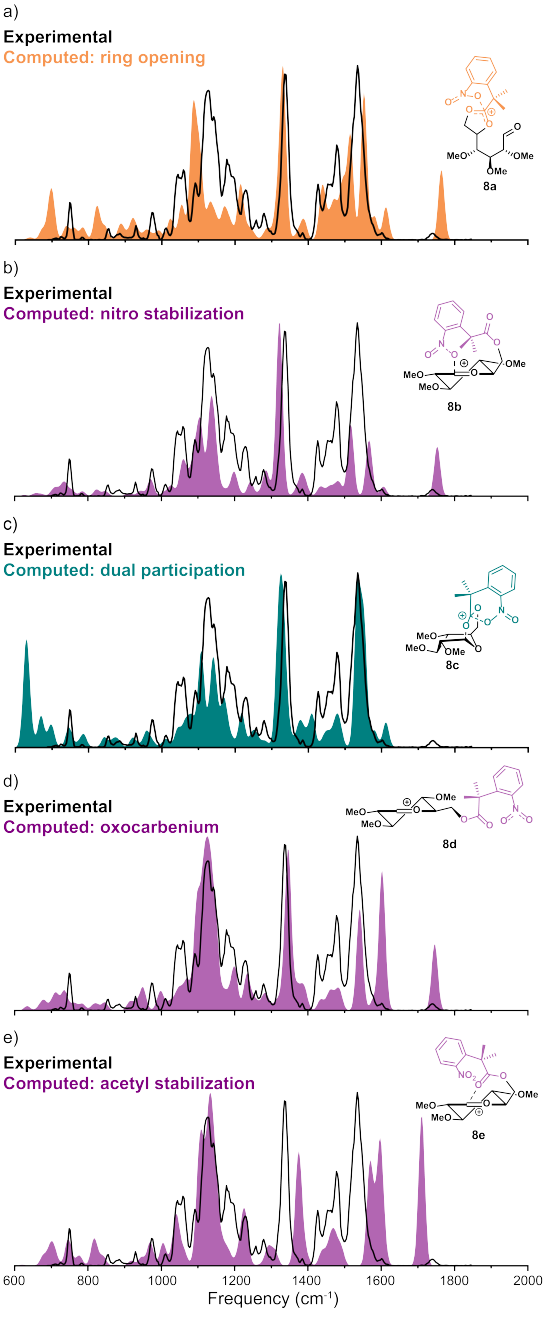


Figure 2. Comparison of the experimental IR spectrum of the glycosyl cation of **8** at m/z 396 (black) to the calculated spectra (filled, colored) of the ring-opened C-5,C-6-dioxolenium ion with nitro-stabilization **8a** (a), the nitro-stabilized oxocarbenium ion **8b** (b), the C-1,C-6-dioxolenium ion with nitro-stabilization **8c** (c), the oxocarbenium ion **8d** (d) and acetyl-stabilized oxocarbenium ion **8e** (e).

To assign the experimental C=O stretch to one of the isomers **8a**, **8b**, **8d**, or **8e**, isotopic labelling was used, where the labeled functional group can be correlated with a specific band in the spectrum by a frequency shift, induced by the change in mass. In the case of compound **8,** the labeled derivative **9** with a ^{13}C-atom at the C-1 position (Supplementary Scheme S2) was synthesized. Figure 3a shows the experimental IR spectra of both the unlabeled (**8**, black) and the labeled (**9**, red) compound. Although variations in intensity are observed, the positions of the IR features are generally conserved after labelling, except for the position of the carbonyl stretch. The redshift of the carbonyl stretch upon labelling indicates that this carbonyl stretch involves the ^{13}C atom, and thus originates from C-1. This stretch must therefore represent the aldehyde found in the ring-opened structure. Further support of this observation is presented in Figure 3b, which shows an overlap of the calculated spectra of the ring-opened structure without labelling (black line) and with labelling (red filled spectrum), showing the same redshift of the carbonyl stretch. None of the other geometries showed a similar frequency shift of bands in this region (Supplementary Figure S1). The labelling thus confirms the presence of the ring-opened conformation and excludes the other oxocarbenium structures, with and without stabilization of the nitro or acetyl group.

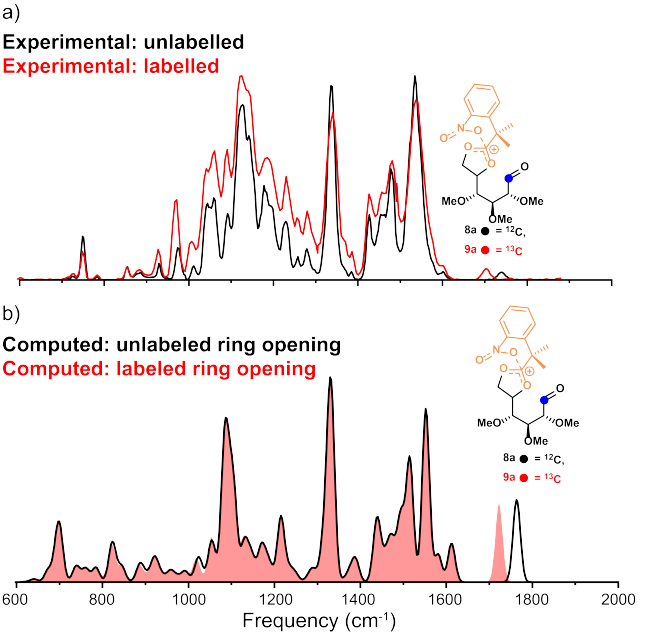


Figure 3. Comparison of the experimental (a) and computational (b) IR spectra of the glycosyl cations of **8** and its ^{13}C-1 labeled analogue **9**.

From the observed intensity of the aldehyde peak it is difficult to assess how much the ring-opened and dual participation dioxolenium ion structures contribute to the ion mixture. To quantify their relative contributions to the total ion population, an isomer population analysis (IPA) was performed.[49–52] In this experiment the IR wavelength is kept fixed while the number of laser pulses irradiating the ions is increased.[52] By monitoring the normalized precursor intensity ($I_{precursor}$ / I_{total}) as a function of the number of pulses, a precursor ion depletion curve is obtained. Only the ions that have a resonant absorption at the selected wavelength absorb IR light and undergo fragmentation, so that convergence to a non-zero plateau is observed when the ion population consists of multiple structures with

unique vibrational bands. The level of the plateau indicates the relative contribution of the absorbing ion to the total population.

Figure 4a displays the results of the IPA for the unlabeled glucosyl cation **8**. The control measurement with the laser at 1125 cm^{-1}, exciting various C-H vibrations present in both the ring-opened and the dual-participation isomers, decayed to 0%, suggesting the absence of background ions (and that all trapped ions have spatial overlap with the laser focus). Tuning the laser to the aldehyde stretch at 1733 cm^{-1} of the ring-opened structure, the normalized precursor intensity converges to 89%, indicating that the 11% that is removed corresponds to the ring-opened isomer and the remaining 89% to the dual-participation isomer. Comparison of the experimental spectrum to a 11:89 mix of the computed spectra of ions **8a** and **8c** shows excellent agreement (Figure 4b), thereby further corroborating the presence of the dual-participating dioxolenium ions. The relative abundance of both structures does not parallel their stability as derived from DFT calculations, which predict the ring-opened structure to be more stable by 40.2 kJ mol^{-1}. The selective depletion of the ring-opened ion **8a** from the ion mixture indicates that the isomers are not in dynamic equilibrium, so it can be argued that the ring-opened structure requires more energy to form. Thus, formation of the dual-participating structure **8c** is kinetically controlled.[53]

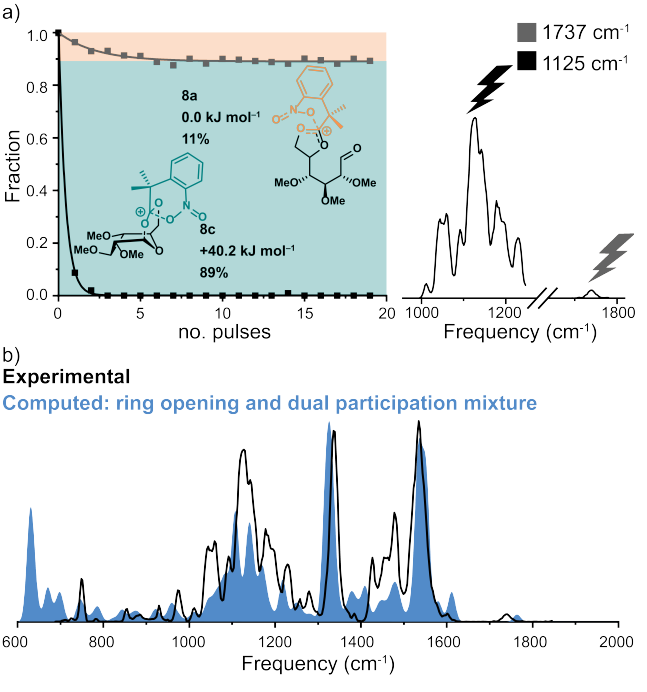


Figure 4. Isomer population analysis of the glycosyl cations of **8** (a) and comparison of the experimental IR spectrum of glycosyl cation of **8** to the 11:89 mix of the computed spectra of structures **8a** and **8c**, respectively (b).

To investigate the kinetic trapping of the dual-participating structure, a second IPA was performed on in-source-generated glycosyl cations that were directly isolated (*i.e.*, not generated using CID). Under the high-pressure conditions in the source region, fragmentation reactions shift towards the thermodynamic product.[54] Indeed, a shift towards the ring-opened structure was observed (11% to 48%, Supplementary Figure S3), thus indicating that the dual-participating structure was kinetically trapped.

The ring-opened structures have never been observed as side products in glycosylation reactions and so the relevance of these gas-phase structures for condensed-phase chemistry is only indirect. The formation of these species in the gas phase at the expense of other isomers, such as oxocarbenium or dioxolenium ions, does provide an indication of the stability of these latter ions. Stable oxocarbenium or dioxolenium ions are less likely to undergo ring opening, and therefore the presence of the ring-opened ions can provide an indirect measure for the relative stability of the oxocarbenium/dioxolenium ions. Here, the observation of dual-participation is of particular interest, because it is the first time that a dioxolenium ion is formed by an *O*-acyl group participating from the 6-position. Earlier, such structures either underwent ring opening[26,27] or showed participation from the 2-[41] or 4-[27] position when other participating groups were present. Thus, it appears that the ability of the DMNPA group to form a dual-participating structure is a necessity for sufficient stabilization to prevent ring opening from occurring.

Overall, the IRIS spectra have indicated the dual participation structure to be the most important glucosyl cation formed upon CID of the C-6-DMNPA glucosyl donors. For the corresponding C-6-benzoate, only the ring-opened C-5,C-6-dioxolenium ion was previously observed,[26] showing that the C-6-DMNPA dual participation leads to a more stable structure. This greater stability of the DMNPA-stabilized dioxolenium ion translates well to the observed shift in stereoselectivity presented in Table 1. The dual participation of the C-6-DMNPA group stabilizes the intermediate ions during the glycosylation reaction, thereby shifting the glycosylation reaction mechanism from the side in which an anomeric α-triflate is displaced in an S_N2-fashion to provide the β-products to the side of the ionic intermediates leading to the formation of the α-products. The DMNPA-group is unable to engage in this dual participation from other positions on the glucose ring, as inferred from the similar stereoselectivity trends of the C-3/C-4-DMNPA and Bz donors. The lack of more effective LRP by the DMNPA compared to the Bz from these latter positions may be accounted for by the steric requirements of the DMNPA-group while forming the bridged dioxolenium ions. The geminal dimethyl group and the quaternary carbon formed by stabilization of the dioxolenium ion by the nitro functionality may be most easily accommodated when the DMNPA group is mounted on the primary alcohol.

Conclusions

In conclusion, the effect of the DMNPA-group on the stereoselectivity of glycosylation reactions was probed. From the series of glycosylation reactions, it became apparent that this group can be mounted at C-6 to direct the glycosylations to provide the challenging α-products. IRIS has provided evidence for the existence of a C-1,C-6-dioxolenium ion in the gas phase. Of note, this is the first glycosyl C-1,C-6-dioxolenium ion that has been observed. Previously, C-6-acetyl and benzoyl glycosyl oxocarbenium ions led to the formation of ring-opened C-5,C-6-dioxolenium ions, indicating that the C-1,C-6-dioxolenium ions were not stable enough. The C-6-DMNPA-derived C-1,C-6-dioxolenium ions can be stabilized by the appended nitro group. The existence of these species in the gas phase indicates that these species may form more readily than the corresponding dioxolenium ions derived from 'typical' acyl groups. A crucial aspect of this study is the isomer population analysis, which quantified the C-1,C-6-dioxolenium ion as the major ion species over the ring-opened C-5,C-6-dioxolenium ion. The unique structure of the DMNPA group enables the dual participation mechanism and may shift the glycosylation reaction mechanism towards the side of the ionic intermediates, providing more of the α-products.

Supporting information

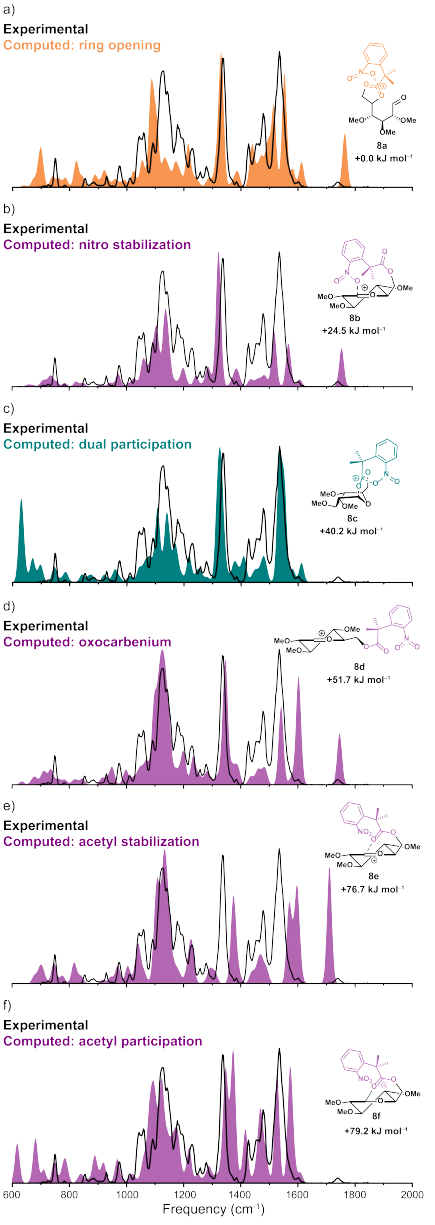
Tandem-MS combined with IR ion spectroscopy

IR spectra of the glucosyl cations were recorded in a quadrupole ion trap mass spectrometer (Bruker, AmaZon Speed ETD, Bremen, Germany) that was coupled to the Free-Electron Laser for Infrared eXperiments (FELIX) beamline. Protonated precursor ions ($[M + H]^+$) and the direct glucosyl cation ($[M\text{-}PhSOH]^+$) were generated from ~10^{-6} M solutions (50:50 acetonitrile:water) containing 2% ammonium acetate. These ions were isolated and in the case of the $[M + H]^+$ ion collisionally activated to yield only the $[M\text{-}PhSOH]^+$ glucosyl cation. After (re)isolation of the glucosyl cation, the ions were irradiated by a single macropulse of FELIX, with a pulse energy of 20-100 mJ and a bandwidth of about ~0.5% of the centre frequency. When the photon-energy is resonant with a vibrational transition of the ions, they undergo IR multi-photon dissociation (IRMPD. By monitoring the fragmentation yield ($\ln[I_{total} / I_{precursor}]$), while scanning the IR wavelength in the 600-1900 cm^{-1} range, an IR spectrum can be reconstructed. The resulting IR spectra are linearly corrected for frequency-dependent variations in laser power and the frequency is calibrated using a grating spectrometer.

Simulation of IR spectra

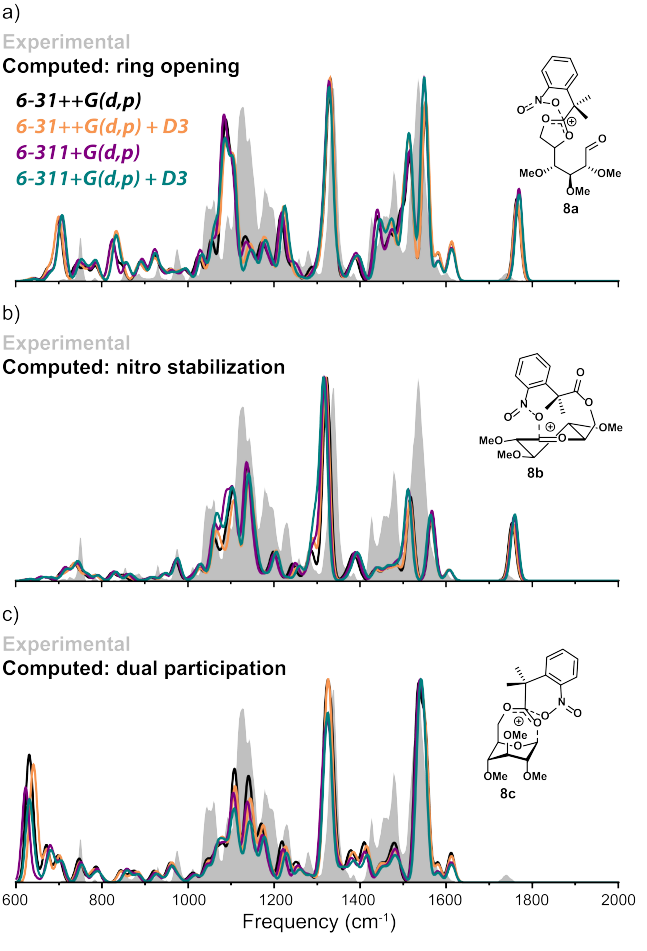
For the conformational search and subsequent geometry optimization and calculation of IR spectra a previously reported workflow has been used.[47] The SMILES code for the oxocarbenium, acetyl participation, dual participation, ether participation and ring-opened ions were used as input for the workflow using the cheminformatics toolbox RDkit.[55] Conformations for the acetyl stabilization and nitro stabilization structures were generated with the oxocarbenium ion conformation search and therefore did not require their own input. The conformational searches were performed using a distance geometry algorithm, yielding 500 random structures, which subsequently were minimized using the MMFF94 classical forcefield.[56] A maximum of 50 conformers were selected based on the root means squared distance between geometries.[57] For these selected conformers a structure optimization and frequency calculation was performed on the semi-empirical PM6 level[58] using the Gaussian 16 package.[59] The remaining conformers were sorted based on their relative energies, which consisted out of an electronic and thermal part. A python script based on atomic distances was used to classify the oxocarbenium, acetyl stabilized and nitro stabilized structures that were obtained from the oxocarbenium conformational search. For each conformer a selection of 2 or 3 structures were reoptimized with the tight command using the B3LYP functional,[60–62] and the 6-31++G(d,p) basis set.[63] Subsequently, a frequency calculation was performed. The frequencies were scaled with a factor of 0.975 and a Gaussian broadening of 20 cm^{-1} was applied. To obtain reliable energies the thermal energy (T=298.15K) of the frequency calculation was combined with the electronic energy of the B3LYP optimized structures, calculated using second order Møller-Plesset perturbation theory and the 6-311++G(2d,2p) basis set.[64]

Glucosyl cation spectra



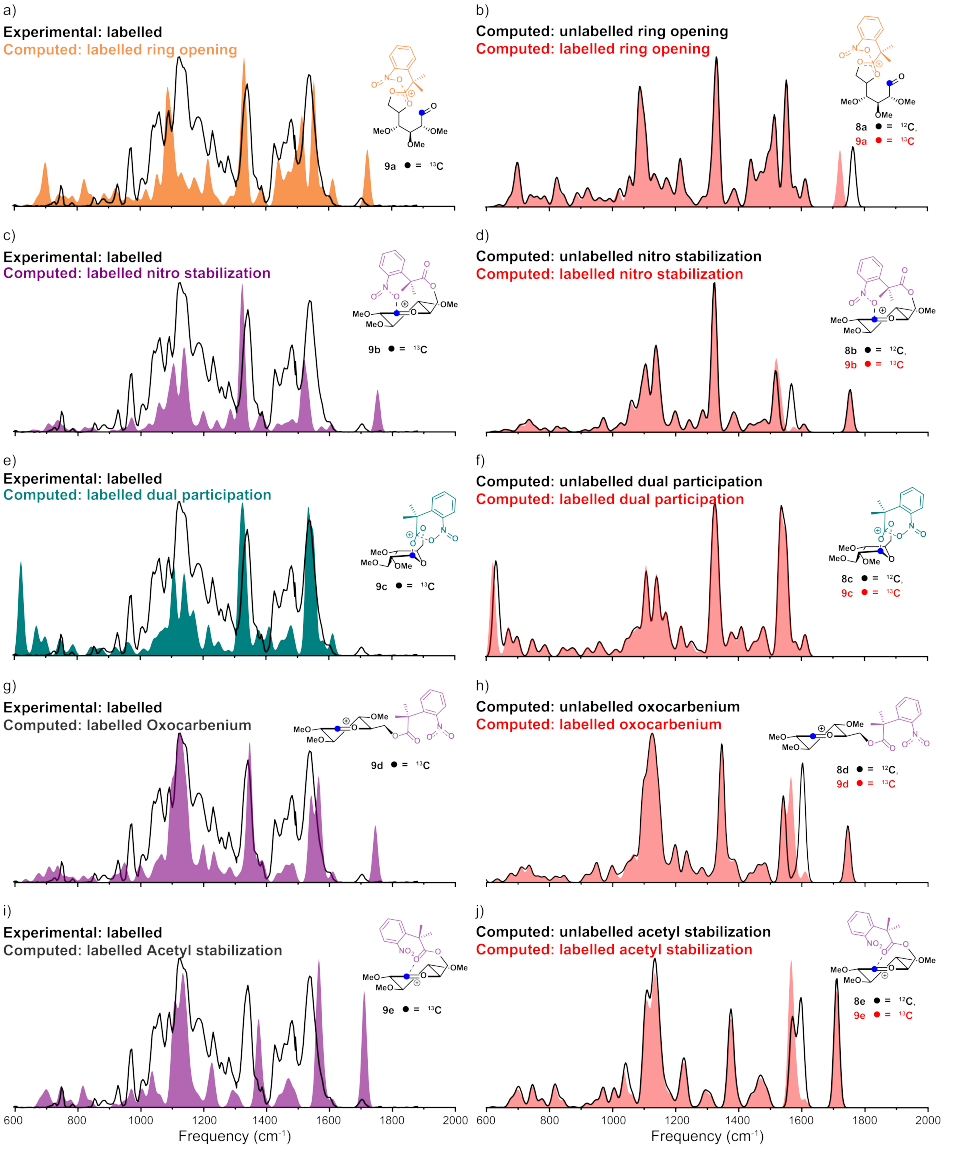
Supplementary Figure S1. Comparison of the experimental IR spectrum of the glycosyl cation of 8 with m/z 396 (black) to the calculated spectra (coloured) of the ring-opened C-5,C-6-dioxolenium ion with nitro-stabilization (a), the nitro-stabilized oxocarbenium ion (b), the C-1,C-6-dioxolenium ion with nitro-stabilization (c), the oxocarbenium ion (d), the acetyl-stabilized oxocarbenium ion (e) and the C-1,C-6-dioxolenium ion without nitro stabilization (f). Relative free energies are given. Exact coordinates of the depicted 3D structures can be found below.

Effect of basis set and dispersion correction on computed vibrational spectra



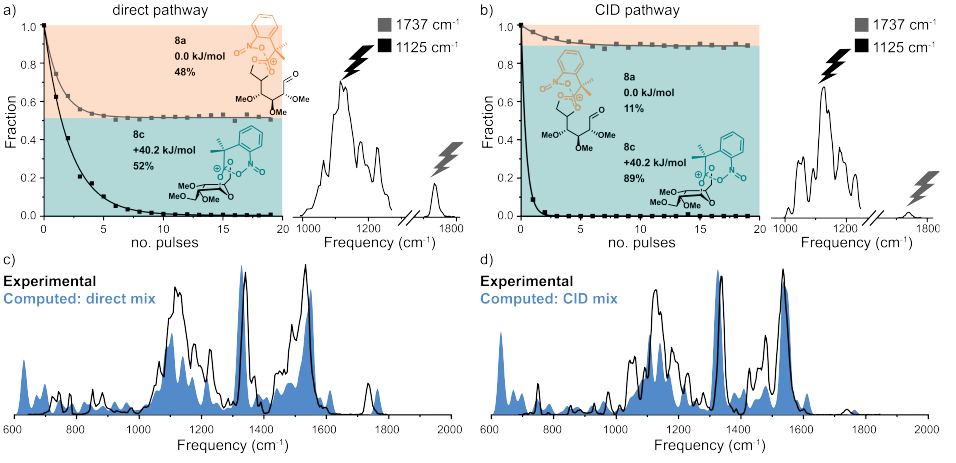
Supplementary Figure S2. The effect of basis set (6-31++G(d,p) vs 6-311+G(d,p)) and adding a dispersion correction (D3)[65]on the B3LYP computed vibrational spectra of the three lowest-energy structures. Experimental IR spectrum of the glycosyl cation of **8** with m/z 396 (gray) and the calculated spectra (coloured) of the ring-opened C-5,C-6-dioxolenium ion with nitro-stabilization (a), the nitro-stabilized oxocarbenium ion (b), the C-1,C-6-dioxolenium ion with nitro-stabilization (c). The B3LYP/6-31++G(d,p) optimized geometry served as starting point for optimization and vibrational analysis using the other methods. For the 6-31++G(d,p) and 6-311+G(d,p) basis sets scaling factors of 0.975 and 0.98 were used, respectively.

Glucosyl cation labelled spectra



Supplementary Figure S3. Left column shows comparison of the experimental IR spectrum of ^{13}C-1 labelled glycosyl cation **9** (black) to the calculated spectra (coloured) and the right column shows comparison of the calculated spectra of both the unlabelled glycosyl cation **8** (black) and the of ^{13}C-1 labelled glycosyl cation **9** (red) of the ring-opened C-5,C-6-dioxolenium ion with nitro-stabilization (a,b), the nitro-stabilized oxocarbenium ion (c,d), the C-1,C-6-dioxolenium ion with nitro-stabilization (e,f), the oxocarbenium ion (g,h) and the acetyl-stabilized oxocarbenium ion (i,j).

Glucosyl cation isomer population analyses (IPA)



Supplementary Figure S4. Top part shows the isomer population analysis of the glycosyl cations of **8** with direct isolation of the glycosyl cation after ESI (a) and with isolation after a CID step (b). Bottom part shows the comparison of the experimental spectrum compared to a mixture of the nitro-stabilized oxocarbenium ion and the C-1,C-6-dioxolenium ion with nitro-stabilization for the direct isolation (c) and with isolation after a CID step (d), where the mixture is made using the experimentally derived populations from a) and b).

Organic Synthesis

General experimental procedures

All chemicals (Acros, Fluka, Merck, and Sigma-Aldrich) were used as received unless stated otherwise. Dichloromethane was stored over activated 4 Å molecular sieves (beads, 8-12 mesh, Sigma-Aldrich). Before use traces of water present in the donor, diphenyl sulfoxide (Ph_2SO) and tri-*tert*-butylpyrimidine (TTBP) were removed by co-evaporation with dry toluene. The acceptors were stored in stock solutions (DCM, 0.5 M) over activated 3 Å molecular sieves (rods, size 1/16 in., Sigma-Aldrich). Trifluoromethanesulfonic anhydride (Tf_2O) was distilled over P_2O_5 and stored at –20 °C under a nitrogen atmosphere. Overnight temperature control was achieved by an FT902 Immersion Cooler (Julabo). Column chromatography was performed on silica gel 60 Å (0.04 – 0.063 mm, Screening Devices B.V.). Size exclusion chromatography was carried out on SephadexTM (LH-20, GE Healthcare Life Sciences) by isocratic elution with DCM:MeOH (1:1, v:v). TLC-analysis was conducted on TLC Silica gel 60 (Kieselgel 60 F254, Merck) with UV detection by (254 nm) and by spraying with 20% sulfuric acid in ethanol followed by charring at ± 150 °C or by spraying with a solution of $(NH_4)_6Mo_7O_{24}{\cdot}H2O$ (25 g/l) and $(NH_4)_4Ce(SO_4)_4{\cdot}2H_2O$ (10 g/l) in 10% sulfuric acid in water followed by charring at ± 250 °C. High-resolution mass spectra were recorded on a Thermo Finnigan LTQ Orbitrap mass spectrometer equipped with an electrospray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10, capillary temperature 275 °C) with resolution R=60.000 at m/z=400 (mass range = 150-4000). ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded on a Bruker AV-400 NMR instrument (400 and 101 MHz respectively), a Bruker AV-500 NMR instrument (500 and 126 MHz respectively), or a Bruker AV-850 NMR instrument (850 and 214 MHz respectively). For samples measured in $CDCl_3$ chemical shifts (δ) are given in ppm relative to tetramethylsilane as an internal standard or the residual signal of the deuterated solvent. Coupling constants (*J*) are given in Hz. To get better resolution of signals with small coupling constants or overlapping signals a gaussian window function (LB ± –1 and GB ± 0.5) was used on the ^{1}H NMR spectrum. All given ^{13}C APT spectra are proton decoupled. NMR peak assignment was made using COSY, HSQC. If necessary additional, HMBC and HMBC-GATED experiments were used to elucidate the structure further. The anomeric product ratios were based on the integration of ^{1}H NMR. If the stereochemistry of the coupled product was not completely clear a deprotection step was used to verify the stereochemistry.

General procedure I: Installation of the DMNPA protecting group.
Based on the protocol by Liu *et al*,[35] a suspension of the glycoside, DMNPAA (1.3 equiv) and 5Å molecular sieves in dry DCM was cooled to −40 °C under inert atmosphere. TMSOTf (2 equiv) was added and the reaction was stirred for 40 minutes. After completion, leftover TMSOTf and leftover DMNPA was quenched with benzylamine (7 equiv). The reaction mixture was diluted with DCM and washed with $NaCHO_3$ and brine. The organic layer was dried with $MgSO_4$, filtered and concentrated *in vacuo*. The resulting residue was purified by silica flash column chromatography.

General procedure II: Synthesis of Phenyl per-*O*-Acetyl-1-thio-β-D-glycopyranoside. To a solution of Ac_2O (7.6 equiv) and a few drops of $HClO_4$ the glycoside (1 equiv) is slowly dissolved portionwise. After all of the glycoside was dissolved, the reaction mixture was stirred for 20 minutes. HBr (33 Wt% in AcOH, 4.4 equiv) was added and the is reaction was stirred until completion. The reaction mixture was diluted with DCM and washed with cold H_2O, and saturated $NaHCO_3$ (aq.). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure, yielding the crude acetobromo-α-D-glycoside. The crude product and thiophenol (1.1 equiv) were dissolved in dry DMF (0.5M). The reaction mixture was cooled to 0 °C, NaH (60% dispersion in mineral oil, 1.1 equiv was added) and the reaction was stirred for 17 h under inert atmosphere. The reaction was cooled to 0 °C, quenched with H_2O and diluted with DCM. The reaction mixture was washed with NaOH (1M), dried over $MgSO_4$ and concentrated *in vacuo*.

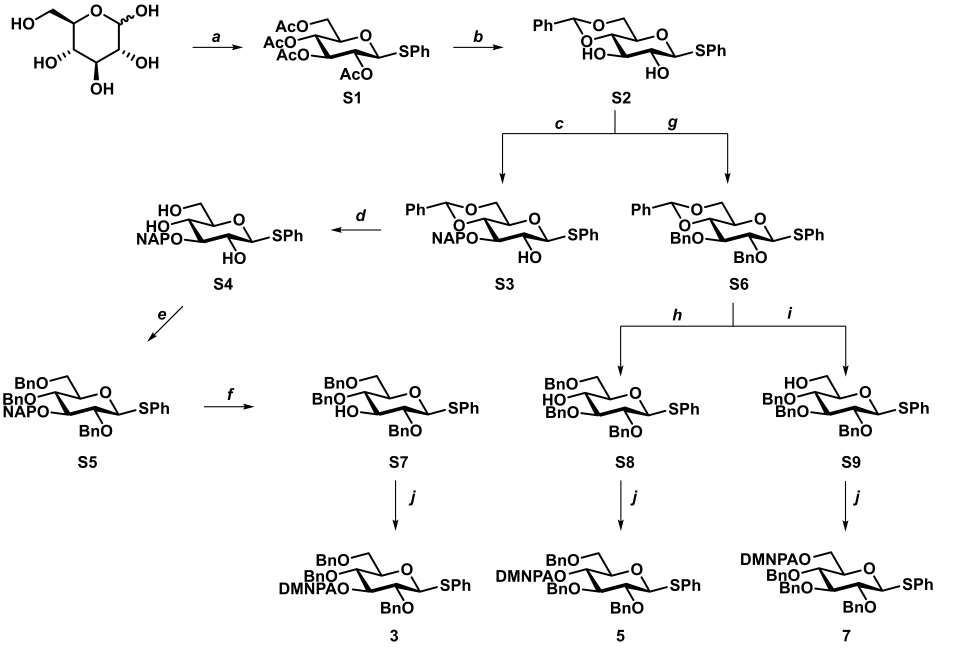
General procedure III: Selective protection of C-6 with a 2-naphthylmethyl ether (NAP) protecting group. Traces of solvent were removed from the glycoside by co-evaporation with toluene, and subsequently dissolved in toluene (0.4 M). Dibutyltin oxide (1.2 equiv) was added, and the resulting suspension was heated with an oil bath and refluxed for 1 h. The reaction mixture was concentrated *in vacuo*, co-evaporated with toluene and dissolved in DMF (0.5 M). 2-(bromomethyl)naphthalene (1.5 equiv) and cesium fluoride (1.5 equiv) were added and it was stirred for 17 h. The reaction mixture was diluted with DCM and washed with saturated $NaHCO_3$ (aq.). The resulting tin paste was filtered from the solution using a Buchner funnel, and the filtrate was dried over $MgSO_4$. It was filtered off, and concentrated *in vacuo*.

General procedure IV: Removal of the naphthylmethyl ether (NAP) protecting group. The 2-naphthylmethyl ether (NAP) protected glycoside was dissolved in DCM:H_2O (9:1, v:v, 0.17M), after which 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (1.5 equiv) was added. The reaction was protected from light and stirred for 1 h. The reaction was quenched by addition of saturated $Na_2S_3O_3$ (aq.) and filtered. The bi-phasic mixture was extracted with DCM. The organic layers were combined and washed with saturated $NaHCO_3$ (aq.), dried over $MgSO_4$, filtered and concentrated *in vacuo*.

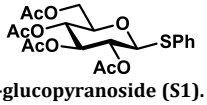
General procedure V: Removal of the benzylidene protecting group. The benzylidene protected glycoside is dissolved in DCM:MeOH (3:7, v:v, 0.05M) of which the acidity is adjusted to pH=2 with *p*-TsOH·H_2O. It was heated to 50 °C with an oil bath and stirred for 17 h. The reaction was neutralized with Et_3N and concentrated *in vacuo*.

General procedure VI: pre-activation Tf_2O/Ph_2SO based *O*-glycosylation. A solution of the donor (100 μmol), Ph_2SO (26 mg, 130 μmol, 1.3 equiv) and TTBP (62 mg, 250 μmol, 2.5 equiv) in DCM (2 mL, 0.05 M) was stirred over activated 3 Å molecular sieves (rods, size 1/16 in., Sigma-Aldrich) for 30 min under an atmosphere of N_2. The solution was cooled to −80 °C and Tf_2O (22 μl, 130 μmol, 1.3 equiv) was slowly added to the reaction mixture. The reaction mixture was allowed to warm to −60 °C in approximately 45 min, followed by cooling to −80 °C and the addition of the acceptor (200 μmol, 2 equiv) in DCM (0.4 mL, 0.5 M). The reaction was allowed to warm up to −60 °C and stirred for an additional 18 h at this temperature until full reaction completion was observed. The reaction was quenched with sat. aq. $NaHCO_3$ at −60 °C and diluted with DCM (5 mL). The resulting solution was washed with H_2O and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography yielded the corresponding *O*-coupled glycoside.

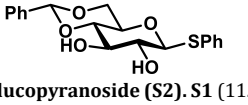
Preparation of the donors 3, 5 and 7



Supplementary scheme S1. Glucoside donor 3,5 and 7 synthesis. *Reagents and conditions:* a) 1. Ac_2O, HCl_4O, HBr; 2. HSPh, NaH, DMF, **S1**: 59%; b) 1. NaOMe, MeOH; 2. benzaldehyde dimethyl acetal, *p*-TsOH·H_2O, acetonitrile, 60 °C, **S2**: 93%; c) 1. Dibutyltin(IV) oxide, toluene, reflux; 2. 2-(bromomethyl)naphthalene, CsF, DMF, **S3**: 60%; d) *p*-TsOH·H_2O, DCM:MeOH, **S4**: quant; e) BnBr, NaH, DMF, 0 °C to rt, **S5**: 88%; f) DDQ, DCM:H_2O, **S7**: quant; g) BnBr, NaH, DMF, 0 °C to rt, **S6**: 93%; h) $NaCNBH_4$, HCl in dioxane, THF, **S8**: 87%; i) $CoCl_2$ in BH_3·THF, **S9**: 89%; j) DMNPAA, TMSOTf, DCM, –40 °C, **3**: 98%, **5**: 94%, **7**: quant.

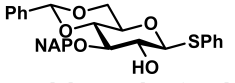


Phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (S1). The title compound was prepared from D-Glucose (50 g, 278 mmol) via general procedure II. Crystallization from boiling EtOH yielded the title compound (63.7 g, 144.6 mmol, 59%) as a white solid. TLC: R_f 0.36, (Pentane:EtOAc, 70:30, v:v); ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC-Gated) δ 7.54 – 7.45 (m, 2H, CH_{arom}), 7.38 – 7.27 (m, 3H, CH_{arom}), 5.23 (t, *J* = 9.3 Hz, 1H, H-4), 5.05 (t, *J* = 9.8 Hz, 1H, H-3), 4.98 (t, *J* = 9.8 Hz, 1H, H-2), 4.71 (d, *J* = 10.1 Hz, 1H, H-1), 4.27 – 4.14 (m, 2H, H-6, H-6), 3.73 (ddd, *J* = 10.1, 5.0, 2.7 Hz, 1H, H-5), 2.12 – 2.06 (m, 6H, 2x CH_3 Ac), 2.02 (s, 3H, CH_3 Ac), 2.00 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, HSQC, HMBC-Gated) δ 170.7, 170.3, 169.5, 169.4 (C=O Ac), 133.3 (CH_{arom}), 131.8 ($C_{q\text{-}arom}$), 129.1, 128.6 (CH_{Arom}), 85.9 (C-1), 75.9 (C-5), 74.1 (C-4), 70.0 (C-2), 68.3 (C-3), 62.3 (C-6), 20.9, 20.9, 20.7, 20.7 (CH_3 Ac); ^{13}C-GATED NMR (101 MHz, $CDCl_3$) δ 85.9 ($J_{H1\text{-}C1}$ = 156 Hz, β); HRMS (ESI) M/Z: [M + Na]$^+$ Calcd for $C_{20}H_{24}O_9NaS^+$ 463.1033; Found 463.1032.

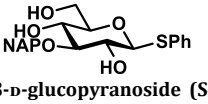


Phenyl 4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside (S2). S1 (11.9 g, 26.9 mmol) was dissolved in MeOH (50 ml, 0.5M). NaOMe in MeOH (25 % Wt, 1.0 ml, 4.37 mmol, 0.16 equiv) was added and the reaction was stirred for 32 hrs. The reaction mixture was acidified to pH=4 using Amberlite H^+, filtered and concentrated *in vacuo*. Traces of MeOH were removed through co-evaporating with toluene, yielding a white solid. The crude product, benzaldehyde dimethyl acetal (4.92 g, 4.85 ml, 32.3 mmol, 1.2 equiv) and *p*-TsOH·H_2O (0.512 g, 2.69 mmol, 0.1 equiv) were dissolved in acetonitrile (50 ml, 0.5M), heated to 60 °C with a water bath and gently concentrated under reduced pressure. After all acetonitrile and formed MeOH were evaporated, the procedure was repeated until TLC indicated full conversion, subsequently the reaction mixture was quenched using Et_3N (0.41 g, 0.56 ml, 4.04 mmol, 0.15 equiv) and concentrated *in vacuo*. Purification by crystallization from boiling acetonitrile

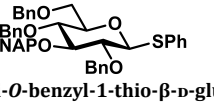
yielded the title compound (9.0 g, 25.0 mmol, 93%) as a white solid. TLC: R_f 0.23, (DCM:MeOH, 90:10, v:v); ^{1}H NMR (400 MHz, CD_3OD, HH-COSY, HSQC, HMBC) δ ^{1}H NMR (400 MHz, MeOD) δ 7.56 – 7.23 (m, 10H, CH_{arom}), 5.55 (s, 1H, C*H*Ph), 4.69 (d, J = 9.8 Hz, 1H, H-1), 4.26 (dd, J = 10.3, 4.7 Hz, 1H, H-6), 3.73 (t, J = 10.0 Hz, 1H, H-6), 3.64 (t, J = 8.7 Hz, 1H, H-3), 3.52 – 3.39 (m, 2H, H-4, H-5), 3.32 – 3.24 (m, 1H, H-2).; ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, HSQC, HMBC) δ 137.7, 132.9 ($C_{q\text{-}arom}$), 132.1, 128.6, 127.6, 127.4, 126.1 (CH_{arom}), 101.5 (CHPh), 88.4 (C-1), 80.5 (C-4), 74.7 (C-3), 73.0 (C-2), 70.3 (C-5), 68.2 (C-6); HRMS (ESI) M/Z: $[M + H]^+$ Calcd for $C_{19}H_{21}O_5S^+$ 361.1104; Found 361.1102.



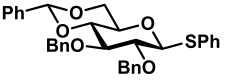
Phenyl 3-*O*-(2-naphthyl)methyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside (S3). The title compound was prepared from **S2** (9.0 g, 25.0 mmol) via general procedure III. Crystallization from boiling EtOAc yielded the title compound (7.5 g, 15.0 mmol, 60%) as a white solid. TLC: R_f 0.55, (pentane:EtOAc, 80:20, v:v); ^{1}H NMR (500 MHz, DMSO-d_6, HH-COSY, HSQC) δ 7.91 – 7.24 (m, 17H, CH_{arom}), 5.97 (d, J = 6.7 Hz, 1H, OH), 5.70 (s, 1H, C*H*Ph), 5.01 – 4.97 (m, 2H, 2x C*H*H Nap), 4.94 (d, J = 9.8 Hz, 1H, H-1), 4.24 (dd, J = 10.0, 4.8 Hz, 1H, H-6), 3.77 – 3.59 (m, 4H, H-3, H-4, H-5, H-6), 3.49 – 3.41 (m, 1H, H-2); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6, HSQC) δ 137.7, 136.7, 133.6, 132.8, 132.4 ($C_{q\text{-}arom}$), 130.4, 129.0, 128.8, 128.1, 127.7, 127.5, 126.9, 126.0, 126.0, 126.0, 125.7 (CH_{arom}), 100.2 (CHPh), 87.4 (C-1), 82.3 (C-3), 80.1 (C-4), 73.7 (CH_2 Nap), 72.6 (C-2), 69.4 (C-5), 67.8 (C-6); HRMS (ESI) M/Z: $[M + NH_4]^+$ Calcd for $C_{30}H_{32}NO_5S^+$ 518.1996; Found 518.1995.



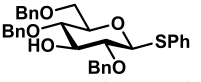
Phenyl 3-*O*-(2-naphthyl)methyl-1-thio-β-D-glucopyranoside (S4). The title compound was synthesized from **S3** (7.5 g, 15.0 mmol) via general procedure V. Flash column chromatography (100:0 → 90:10, DCM:MeOH v:v) yielded the title compound (6.20 g, 15.1 mmol, quant) as a white solid. TLC: R_f 0.30, (DCM:MeOH, 95:5, v:v); ^{1}H NMR (300 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.92 – 7.09 (m, 12H, CH_{arom}), 5.11 (d, J = 11.6 Hz, 1H, C*H*H Nap), 4.97 (d, J = 11.8 Hz, 1H, C*H*H Nap), 4.58 (d, J = 9.5 Hz, 1H, H-1), 3.96 – 3.71 (m, 2H, H-6, H-6), 3.69 – 3.55 (m, 1H, H-4), 3.56 – 3.32 (m, 3H, H-2, H-3, H-5), 3.21 (d, J = 3.5 Hz, 1H, OH-4), 2.79 – 2.56 (m, 2H, OH-2, OH-6); ^{13}C{^{1}H} NMR (80 MHz, $CDCl_3$, HSQC) δ 133.4, 133.1, 132.1 ($C_{q\text{-}arom}$), 129.2, 129.0, 128.5, 128.2, 128.1, 127.8, 127.0, 126.3, 126.1, 126.0, 126.0 (CH_{arom}), 88.5 (C-1), 85.2 (C-3), 79.7 (C-5), 75.0 (CH_2 Nap), 72.7 (C-2), 70.3 (C-4), 62.6 (C-6); HRMS (ESI) M/Z: $[M + NH_4]^+$ Calcd for $C_{23}H_{28}NO_5S^+$ 430.1683; Found 430.1686.



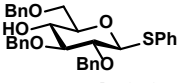
Phenyl 3-*O*-(2-naphthyl)methyl-2,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (S5). S4 (6.19 g, 15.0 mmol) was dissolved in dry DMF (75 ml, 0.2M) and cooled to 0 °C. Under inert atmosphere, NaH (60 Wt % dispersion in mineral oil, 2.70 g, 67.5 mmol, 4.5 equiv) was added portion wise and the reaction mixture was stirred for 10 minutes. Benzyl bromide (6.70 ml, 9.62 g, 56.3 mmol, 3.75 equiv) was added and the reaction was stirred for 5 h while allowing to warm up to RT. Subsequently, the reaction was cooled to 0 °C and quenched with H_2O. The reaction mixture was diluted with H_2O and extracted with DCM. The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (95:5 → 80:20, pentane:EtOAc v:v) yielded the title compound (9.05 g, 13.3 mmol, 88%) as a white solid. TLC: R_f 0.66, (pentane:EtOAc, 80:20, v:v); ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.88 – 7.12 (m, 27H, CH_{arom}), 5.05 (d, J = 11.1 Hz, 1H, C*H*H Bn), 4.99 (d, J = 11.1 Hz, 1H, C*H*H Bn), 4.91 (d, J = 10.3 Hz, 1H, C*H*H Nap), 4.85 (d, J = 10.9 Hz, 1H, C*H*H Bn), 4.75 (d, J = 10.2 Hz, 1H, C*H*H Nap), 4.69 (d, J = 9.7 Hz, 1H, H-1), 4.65 – 4.52 (m, 3H, 3x C*H*H Bn), 3.85 – 3.63 (m, 4H, H-4, H-5, H-6, H-6), 3.60 – 3.47 (m, 2H, H-2, H-3); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, HSQC) δ 138.4, 138.2, 136.0, 134.0,133.4, 133.1 ($C_{q\text{-}arom}$), 132.1, 129.0, 128.6, 128.5, 128.3, 128.3, 128.1, 128.0, 128.0, 127.9, 127.8, 127.7, 127.6, 126.6, 126.2, 126.0, 126.0 (CH_{arom}), 87.6 (C-1), 86.9 (C-4), 81.0 (C-2), 79.2 (C-3), 77.9 (C-5), 76.0 (CH_2 Bn), 75.6 (CH_2 Nap), 75.2, 73.6 (CH_2 Bn), 69.1 (C-6); HRMS (ESI) M/Z: $[M + NH_4]^+$ Calcd for $C_{44}H_{46}NO_5S^+$ 700.3091; Found 700.3088.



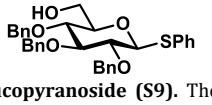
Phenyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside (S6). S2 (5.08 g, 14.0 mmol) was dissolved in dry DMF (100 ml, 0.14M) and cooled to 0 °C. Under inert atmosphere, NaH (60 Wt % dispersion in mineral oil, 1.68 g, 42 mmol, 3 equiv) was added portion wise and the reaction mixture was stirred for 10 minutes. Benzyl bromide (4.2 ml, 35 mmol, 2.5 equiv) was added and the reaction was stirred for 17 h while allowing to warm up to RT. Subsequently, the reaction was cooled to 0 °C and quenched with H_2O. The reaction mixture was diluted with H_2O and extracted with DCM. The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (100:0 → 80:20, pentane:EtOAc v:v) yielded the title compound (7.03 g, 13.0 mmol, 93%) as a white solid. TLC: R_f 0.61, (Pentane:EtOAc, 90:10, v:v); ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.61 – 7.17 (m, 20H, CH_{arom}), 5.59 (s, 1H, C*H*Ph), 4.94 (d, *J* = 11.1 Hz, 1H, C*H*H Bn), 4.89 – 4.73 (m, 4H, H-1, 3x C*H*H Bn), 4.39 (dd, *J* = 10.5, 5.0 Hz, 1H, H-6), 3.88 – 3.76 (m, 2H, H-3, H-6), 3.71 (t, *J* = 9.4 Hz, 1H, H-4), 3.56 – 3.43 (m, 2H, H-2, H-5); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, HSQC) δ 138.4, 138.1, 137.4, 133.2 ($C_{q\text{-}arom}$), 132.5, 129.2, 129.1, 128.6, 128.5, 128.4, 128.4, 128.3, 128.0, 128.0, 127.9, 126.1 (CH_{arom}), 101.3 (CHPh), 88.4 (C-1), 83.1 (C-3), 81.6 (C-4), 80.6 (C-2), 76.1, 75.5 (CH_2 Bn), 70.4 (C-5), 68.8 (C-6); HRMS (ESI) M/Z: $[M + NH_4]^+$ Calcd for $C_{33}H_{36}NO_5S^+$ 558.2309; Found 558.2308.



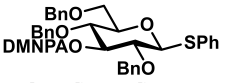
Phenyl 2,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (S7). The title compound was synthesized from **S5** (9.05 g, 12.3 mmol) via general procedure IV. Flash column chromatography (95:5 → 70:30, pentane:EtOAc v:v) yielded the title compound (7,49 g, 13.3 mmol, quant) as a white wax. TLC: R_f 0.52, (pentane:EtOAc, 80:20, v:v); ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC) δ 7.67 – 7.16 (m, 20H, CH_{arom}), 4.94 (d, *J* = 11.0 Hz, 1H, C*H*H Bn), 4.78 (d, *J* = 11.2 Hz, 1H, C*H*H Bn), 4.70 – 4.49 (m, 5H, H-1, 4x C*H*H Bn), 3.83 – 3.67 (m, 3H, H-3, H-6, H-6), 3.58 – 3.43 (m, 2H, H-4, H-5), 3.37 (dd, *J* = 9.7, 8.7 Hz, 1H, H-2), 2.45 (d, *J* = 2.6 Hz, 1H, OH-3); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, HSQC, HMBC) δ 138.3, 138.3, 138.2, 133.9 ($C_{q\text{-}arom}$), 131.9, 129.0, 128.7, 128.6, 128.4, 128.3, 128.2, 128.0, 128.0, 127.8, 127.7, 127.5 (CH_{arom}), 87.1 (C-1), 80.7 (C-2), 78.9 (C-5), 78.7(C-3), 77.4 (C-4), 75.2, 74.7, 73.5 (CH_2 Bn), 69.1 (C-6); HRMS (ESI) M/Z: $[M + NH_4]^+$ Calcd for $C_{33}H_{38}NO_5S^+$ 560.2465; Found 560.2466.



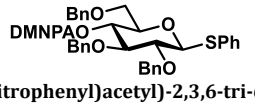
Phenyl 2,3,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (S8). S6 (0.54 g, 1 mmol) was co-evaporated with toluene and dissolved in dry THF (14 ml, 0.1M). $NaCNBH_4$ (0.31 g, 5.0 mmol, 5 equiv) is added under protective atmosphere after which HCl in dioxane (1.3 ml, 5.2 mmol, 4.0M, 5 equiv) is added dropwise. The reaction was stirred for 20 min and subsequently diluted with ice water. The reaction mixute was extracted with DCM and washed with sat. $NaHCO_3$ (aq) and brine. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (100:0 → 80:20, pentane:EtOAc v:v) yielded the title compound (0.47 g, 0.87 mmol, 87%) as a white solid. TLC: R_f 0.56, (pentane:EtOAc, 70:30, v:v); ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC) δ 7.58 – 7.21 (m, 20H, CH_{arom}), 4.93 – 4.86 (m, 2H, 2x C*H*H Bn), 4.80 – 4.70 (m, 2Hz, 2x C*H*H Bn), 4.67 (d, J = 9.4 Hz, 1H, H-1), 4.59 – 4.50 (m, 2H, 2x C*H*H Bn), 3.81 – 3.68 (m, 2H, H-6, H-6), 3.64 (t, J = 9.0 Hz, 1H, H-4), 3.58 – 3.40 (m, 3H, H-2, H-3, H-5), 2.73 (s, 1H, OH); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, HSQC, HMBC) δ 138.5, 138.0, 138.0, 134.2 ($C_{q\text{-}arom}$), 131.9, 129.0, 128.7, 128.6, 128.5, 128.5, 128.3, 128.0, 128.0, 127.8, 127.8, 127.7, 127.6, 127.0 (CH_{arom}), 87.7 (C-1), 86.2 (C-3), 80.5 (C-2), 78.2 (C-5), 75.6, 75.5, 73.7 (CH_2 Bn), 71.6 (C-4), 70.3 (C-6); HRMS (ESI) M/Z: $[M + NH_4]^+$ Calcd for $C_{33}H_{38}NO_5S^+$ 560.2465; Found 560.2466.



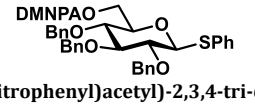
Phenyl 2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (S9). The title compound was prepared from **S6** (0.541 g, 1 mmol) according to literature procedure,[66] yielding the title compound (485 mg, 0.89 mmol, 89%) as a colorless oil. TLC: R_f 0.74, (pentane:EtOAc, 85:15, v:v); ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.53 – 7.20 (m, 21H, CH_{arom}), 4.93 – 4.81 (m, 4H, 4x C*H*H Bn), 4.75 (d, J = 10.3 Hz, 1H, C*H*H Bn), 4.72 (d, J = 9.8 Hz, 1H, H-1), 4.65 (d, J = 11.0 Hz, 1H, C*H*H Bn), 3.86 (dq, J = 12.0, 2.6 Hz, 1H, H-6), 3.76 – 3.64 (m, 2H, , H-3, H-6), 3.58 (t, J = 9.4 Hz, 1H, H-4), 3.48 (dd, J = 9.8, 8.7 Hz, 1H, H-2), 3.38 (ddd, J = 9.7, 4.8, 2.6 Hz, 1H, H-5), 2.17 (t, J = 6.5 Hz, 1H, OH); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, HSQC) δ 138.4, 138.0, 137.9, 133.6 ($C_{q\text{-}arom}$), 131.8, 129.1, 128.6, 128.5, 128.5, 128.3, 128.1, 128.0, 128.0, 127.8, 127.8, 127.7 (CH_{arom}), 87.6 (C-1), 86.6 (C-3), 81.1 (C-2), 79.4 (C-5), 77.6 (C-4), 75.8, 75.6, 75.1 (CH_2 Bn), 62.1 (C-6); HRMS (ESI) M/Z: $[M + NH_4]^+$ Calcd for $C_{33}H_{38}NO_5S^+$ 560.2465; Found 560.2465.



Phenyl 3-*O*-(2,2-dimethyl-2-(*ortho*-nitrophenyl)acetyl)-2,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (3). The title compound was prepared from **S7** (0.81 g, 1.50 mmol) through general procedure I. Flash column chromatography (90:10 → 70:30, pentane:EtOAc v:v) yielded the title compound (1.08 g, 1.47 mmol, 98%) as a yellow oil. TLC: R_f 0.48, (pentane:EtOAc, 80:20, v:v); ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC, HMBC-Gated) δ 7.73 (dd, J = 7.9, 1.4 Hz, 1H, CH_{arom}), 7.56 – 7.42 (m, 4H, CH_{arom}), 7.40 – 7.17 (m, 19H, CH_{arom}), 5.42 (t, J = 7.7 Hz, 1H, H-3), 4.86 (d, J = 8.9 Hz, 1H, H-1), 4.82 (d, J = 10.6 Hz, 1H, C*H*H Bn), 4.65 – 4.55 (m, 2H, 2x C*H*H Bn), 4.50 (d, J = 3.2 Hz, 2H, 2x C*H*H Bn), 4.44 (d, J = 11.3 Hz, 1H, C*H*H Bn), 3.73 – 3.53 (m, 5H, H-2, H-4, H-5, H-6, H-6), 1.60 (s, 3H, CH_3 DMNPA), 1.58 (s, 3H, CH_3 DMNPA); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, HSQC, HMBC, HMBC-Gated) δ 174.3 (C=O DMNPA), 149.1, 138.3, 138.2, 138.0, 137.9, 134.0 ($C_{q\text{-}arom}$), 132.9, 131.9, 129.0, 128.8, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.7, 127.7, 127.6, 127.6, 125.5 (CH_{arom}), 86.7 (C-1), 78.9 (C-2), 78.5 (C-4), 76.0 (C-3), 75.8 (C-5), 73.5, 73.1, 72.4 (CH_2 Bn), 69.2 (C-6), 46.9 (C_q DMNPA), 27.0, 26.9 (CH_3 DMNPA); ^{13}C-GATED NMR (101 MHz, $CDCl_3$) δ 86.7 ($J_{H1\text{-}C1}$ = 158 Hz, β); HRMS (ESI) M/Z: [M + NH_4]$^+$ Calcd for $C_{43}H_{47}N_2O_8S^+$ 751.3048; Found 751.3043.

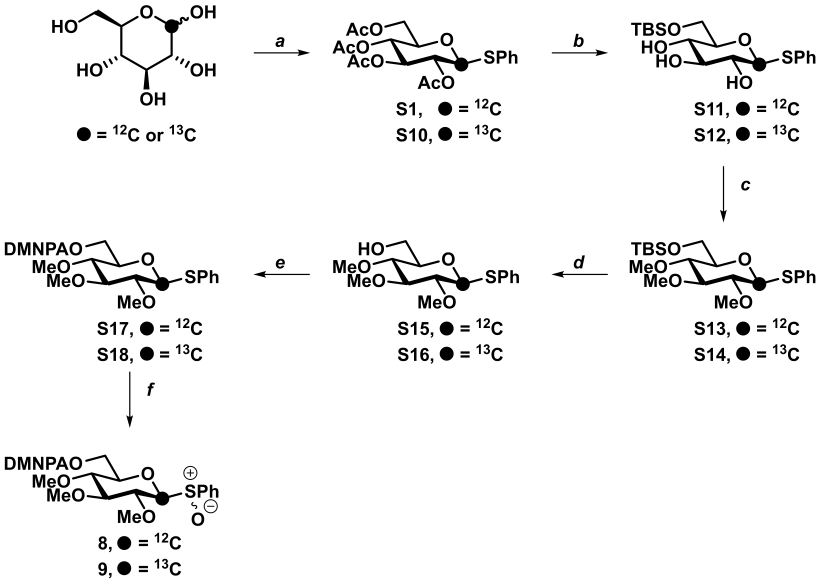


Phenyl 4-*O*-(2,2-dimethyl-2-(*ortho*-nitrophenyl)acetyl)-2,3,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (5). The title compound was prepared from **S8** (0.47 g, 0.87 mmol) through general procedure I. Flash column chromatography (100:0 → 70:30, Pentane:EtOAc v:v) yielded the title compound (600 mg, 0,818 mmol, 94%) as a colorless oil TLC: R_f 0.51, (pentane:EtOAC, 80:20, v:v); ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC) δ 7.79 (dd, J = 8.1, 1.4 Hz, 1H, CH_{arom}), 7.59 – 7.56 (m, 2H, CH_{arom}), 7.53 (ddd, J = 7.9, 7.3, 1.5 Hz, 1H, CH_{arom}), 7.47 (dd, J = 8.1, 1.4 Hz, 1H, CH_{arom}), 7.40 – 7.16 (m, 19H, CH_{arom}), 4.97 (t, J = 9.1 Hz, 1H, H-4), 4.88 – 4.80 (m, 2H, 2x C*H*H Bn), 4.69 (d, J = 9.5 Hz, 1H, H-1), 4.63 (d, J = 11.8 Hz, 1H, C*H*H Bn), 4.59 – 4.50 (m, 4H, 3x C*H*H Bn), 3.81 – 3.76 (m, 1H, H-6), 3.71 – 3.56 (m, 5H, H-2, H-3, H-5, H-6), 1.55 – 1.53 (m, 6H, 2x CH_3 DMNPA); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, HSQC, HMBC) δ 174.6 (C=O DMNPA), 148.9 ($C_{q\text{-}arom}$ DMNPA), 138.7, 138.4, 138.3, 137.8, 134.1 ($C_{q\text{-}arom}$), 133.2, 131.6, 129.1, 128.5, 128.4, 128.4, 128.4, 128.3, 128.1, 128.0, 127.9, 127.6, 127.5, 127.5, 126.9, 125.7 (CH_{arom}), 87.5 (C-1), 83.6 (C-5), 80.8 (C-2), 78.4 (C-3), 75.3, 74.5, 73.5 (CH_2 Bn), 71.5 (C-4), 70.0 (C-6), 46.9 (C_q DMNPA), 27.2, 27.1 (CH_3 DMNPA); HRMS (ESI) M/Z: [M + Na]$^+$ Calcd for $C_{43}H_{43}NNaO_8S^+$ 756.2602; Found 756.2593.

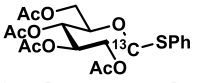


Phenyl 6-*O*-(2,2-dimethyl-2-(*ortho*-nitrophenyl)acetyl)-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (7). The title compound was prepared from **S9** (0.38 g, 0.70 mmol) through general procedure I. Flash column chromatography (100:0 → 70:30, pentane:EtOAc v:v) yielded the title compound (0,51 g, 0,70 mmol, quant) as a colorless oil. TLC: R_f 0.39, (pentane:EtOAc, 80:20, v:v); ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC) δ 7.90 – 7.86 (m, 1H, CH_{arom}), 7.63 – 7.57 (m, 2H, CH_{arom}), 7.56 – 7.53 (m, 2H, CH_{arom}), 7.43 – 7.22 (m, 19H, CH_{arom}), 4.90 – 4.81 (m, 2H, 3x C*H*H Bn), 4.76 (d, J = 10.5 Hz, 1H, C*H*H Bn), 4.71 (d, J = 10.3 Hz, 1H, C*H*H Bn), 4.62 (d, J = 9.8 Hz, 1H, H-1), 4.58 (dd, J = 11.9, 2.0 Hz, 1H, H-6), 4.53 (d, J = 10.6 Hz, 1H, C*H*H Bn), 4.18 (dd, J = 11.9, 5.3 Hz, 1H, H-6), 3.70 (t, J = 8.9 Hz, 1H, H-3), 3.53 (ddd, J = 9.9, 5.3, 2.1 Hz, 1H, H-5), 3.46 – 3.37 (m, 2H, H-2, H-4), 1.70 (s, 3H, CH_3 DMNPA), 1.69 (s, 3H, CH_3 DMNPA); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, HSQC, HMBC) δ 175.1 (C=O DMNPA), 148.8, 139.2 ($C_{q\text{-}arom}$ DMNPA), 138.3, 138.1, 137.7, 133.5 ($C_{q\text{-}arom}$), 133.3, 132.5, 129.0, 128.7, 128.6, 128.6, 128.3, 128.2, 128.1, 128.0, 128.0, 127.9, 127.8, 125.8 (CH_{arom}), 87.4 (C-1), 86.7 (C-3), 80.8 (C-2), 77.9 (C-4), 77.1 (C-5), 76.1, 75.5, 75.2 (CH_2 Bn), 63.6 (C-6), 46.7 (C_q DMNPA), 27.5, 27.4 (CH_3 DMNPA); HRMS (ESI) M/Z: [M + NH_4]$^+$ Calcd for $C_{43}H_{47}N_2O_8S^+$ 751.3048; Found 751.3045.

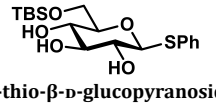
Preparation of donors 8 and 9



Supplementary scheme S2. Glucoside donor **8** and **9** synthesis. a) 1. Ac_2O, HCl_4O, HBr; 2. HSPh, NaH, DMF, **S1**: 59%, **S10:** 31%; b) 1. NaOMe, MeOH; 2. TBDMSCl, Et_3N, MeCN:DMF, **S11**: quant, **S12**: quant; c) MeI, NaH, DMF, 0 °C to rt, **S13**: 76%, **S14**: 80%; d) TBAF, THF, **S15**: 96%, **S16**: 88%; e) DMNPAA, TMSOTf, DCM, –40 °C, **S17**: 62%, **S18**: quant%; f) *m*-CPBA, DCM, –78 °C.

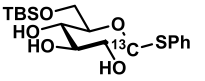


Phenyl 2,3,4,6-tetra-*O*-acetyl-1-^{13}C-thio-β-D-glucopyranoside (S10). The title compound was prepared from D-Glucose-1-^{13}C (1 g, 5.52 mmol) via general procedure II. Flash column chromatography (85:15 → 60:40, Pentane:EtOAc v:v) yielded the title compound (0.75 g, 1.70 mmol, 31%) as a white solid. TLC: R_f 0.64, (pentane:EtOAc, 60:30, v:v); ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC) δ 7.54 – 7.29 (m, 5H, CH_{arom}), 5.23 (td, J = 9.4, 0.9 Hz, 1H (C-3)), 5.05 (dd, J = 10.1, 9.4 Hz, 1H (C-4)), 4.98 (ddd, J = 10.1, 9.2, 5.0 Hz, 1H (C-2)), 4.71 (dd, J = 156.3, 10.1 Hz, 1H (C-1)), 4.27 – 4.15 (m, 2H, H-6, H-6), 3.73 (ddt, J = 10.2, 5.1, 2.6 Hz, 1H, H-5), 2.09 (s, 3H, OAc), 2.08 (s, 3H, OAc), 2.02 (s, 3H, OAc), 1.99 (s, 3H, OAc); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, HSQC, HMBC) δ 170.7, 170.3, 169.5, 169.3 (C=O Ac), 133.2 (CH_{arom}), 131.7 ($C_{q\text{-}arom}$), 129.1, 128.5 (CH_{arom}), 85.8 (C-1), 75.9 (C-5), 74.1 (d, *J* = 3.0 Hz, C-3), 70.1 (d, *J* = 47.4 Hz, C-2), 68.3 (C-4), 62.25 (d, *J* = 4.6 Hz, C-6), 20.8, 20.8, 20.7, 20.7 (OAc); HRMS (ESI) M/Z: $[M + NH_4]^+$ Calcd for $^{13}CC_{19}H_{28}NO_9S^+$ 459.1513; Found 459.1511.

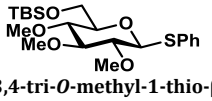


Phenyl 6-*O*-(*tert*-butyldimethylsilyl)-1-thio-β-D-glucopyranoside (S11). S1 (2.16 g, 4.90 mmol) was dissolved in MeOH (10 ml, 0.5M). NaOMe in MeOH (25 % Wt, 0.11 ml, 0.49 mmol, 0.1 equiv) was added and the reaction was stirred for 3 hrs. The reaction mixture was neutralized to pH=7 using Amberlite H^+, filtered and concentrated *in vacuo*. The TBS installation protocol was adopted from Lv *et al* (2019).[67] The crude reaction mixture was suspended in a MeCN:DMF mixture (13.4 ml, 0.4M), and Et_3N (1.23 ml, 0.89 g, 8.83 mmol, 1.8 equiv) was added dissolving all solids. Tert-Butyldimethylsilyl chloride (1.11 g, 7.36 mmol, 1.5 equiv) was added and the reaction was stirred for 45 min. The reaction mixture was directly subjected to flash column chromatography (75:25 → 25:75, pentane:EtOAc v:v), yielding the title compound (1.95 g, 5.04 mmol, quant) as a colorless oil. TLC: R_f 0.37, (DCM:MeOH, 90:10, v:v); ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC) δ 7.61 – 7.11 (m, 5H, CH_{arom}), 4.54 (d, *J* = 9.7 Hz, 1H, H-1), 4.03 – 3.80 (m, 2H, H-6, H-6), 3.58 (t, *J* = 8.8 Hz, 1H, H-3), 3.50 (t, *J* = 9.1 Hz, 1H, H-4), 3.43 – 3.30 (m, 2H, H-2, H-5), 0.90 (s, 9H, C(CH_3)$_3$ TBS), 0.14 – 0.02 (m, 6H, 2x Si(CH_3)$_2$); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, HSQC, HMBC) δ 132.7 ($C_{q\text{-}arom}$), 132.3, 129.1, 129.0, 128.3, 127.9, 125.4

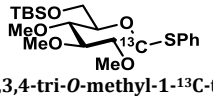
(CH_{arom}), 88.0 (C-1), 79.0 (C-2), 78.0 (C-3), 71.9 (C-5), 71.7 (C-4), 64.2 (C-6), 26.0 (3x C(CH_3)$_3$ TBS), 18.4 (C_q TBS), 5.2 (2x Si(CH_3)$_2$ TBS); HRMS (ESI) M/Z: $[M + NH_4]^+$ Calcd for $C_{18}H_{34}NO_5SSi^+$ 404.1922; Found 404.1923.



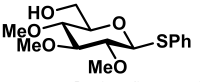
Phenyl 6-*O*-(*tert*-butyldimethylsilyl)-1-^{13}C-thio-β-D-glucopyranoside (S12). S10 (0.72 g, 1.63 mmol) was dissolved in MeOH (3.3 ml, 0.5M). NaOMe in MeOH (25 % Wt, 0.10 ml, 0.49 mmol, 0.3 equiv) was added and the reaction was stirred for 3 hrs. The reaction mixture was neutralized to pH=7 using Amberlite H^+, filtered and concentrated *in vacuo*. The TBS installation protocol was adopted from Lv *et al* (2019).[67] The crude reaction mixture was suspended in a MeCN:DMF mixture (4.4 ml, 0.4M), and Et_3N (0.41 ml, 2.94 mmol, 1.8 equiv) was added dissolving all solids. Tert-Butyldimethylsilyl chloride in toluene (50%, 0.85 ml, 2.45 mmol, 1.5 equiv) was added and the reaction was stirred for 45 min. The reaction mixture was directly subjected to flash column chromatography (75:25 → 25:75, pentane:EtOAc v:v), yielding the title compound (0.95 g, 1.63 mmol, quant) as a white solid. TLC: R_f 0.31, (DCM:MeOH, 90:10, v:v); ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC) δ 7.59 – 7.50 (m, 2H, CH_{arom}), 7.31 – 7.19 (m, 3H, CH_{arom}), 4.63 (dd, *J* = 155.2, 9.7 Hz, 1H, H-2), 3.96 (dd, *J* = 11.1, 2.7 Hz, 1H, H-6), 3.79 (dd, *J* = 11.1, 5.4 Hz, 1H, H-6), 3.64 (t, *J* = 8.4 Hz, 1H, H-4), 3.49 – 3.33 (m, 3H, H-2, H-3, H-5), 0.90 (s, 9H, C(CH_3)$_3$ TBS), 0.08 (s, 3H, $SiCH_3$ TBS), 0.06 (s, 3H, $SiCH_3$ TBS); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, HSQC, HMBC) δ 133.5 ($C_{q\text{-}arom}$), 131.4, 131.4, 128.7, 127.1 (CH_{arom}), 87.5 (C-1), 80.0 (d, *J* = 2.0 Hz, C-3), 78.3 (d, *J* = 2.4 Hz, C-5), 72.1 (d, *J* = 44.6 Hz, C-2), 70.8 (C-4), 63.6 (d, *J* = 4.8 Hz, C-6), 18.2 (*C*(CH_3)$_3$ TBS), –5.4, –5.4 ($SiCH_3$ TBS); HRMS (ESI) M/Z: $[M + Na]^+$ Calcd for $^{13}CC_{17}H_{30}NaO_5SSi^+$ 410.1509; Found 410.1510.



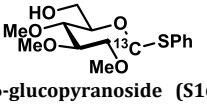
Phenyl 6-*O*-(*tert*-butyldimethylsilyl)-2,3,4-tri-*O*-methyl-1-thio-β-D-glucopyranoside (S13). S11 (1.89 g, 4.90 mmol) was dissolved in dry DMF (24.5 ml, 0.2M) and cooled to 0 °C. Under inert atmosphere, NaH (60 Wt % dispersion in mineral oil, 0.882 g, 22.1 mmol, 4.5 equiv) was added portion wise and the reaction mixture was stirred for 10 minutes. methyl iodide (1.15 ml, 2.61 g, 18.4 mmol, 3.75 equiv) was added and the reaction was stirred for 17 h while allowing to warm up to RT. Subsequently, the reaction was cooled to 0 °C and quenched with H_2O. The reaction mixture was diluted with H_2O and extracted with DCM. The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (100:0 → 80:20, pentane:EtOAc v:v) yielded the title compound (1.61 g, 3.74 mmol, 76%) as a colorless oil. TLC: R_f 0.64, (pentane:EtOAc, 90:10, v:v); ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC) δ 7.60 – 7.50 (m, 2H, CH_{arom}), 7.31 – 7.20 (m, 3H, CH_{arom}), 4.46 (d, J = 9.8 Hz, 1H, H-1), 3.85 (dd, J = 11.3, 1.6 Hz, 1H, H-6), 3.79 (dd, J = 11.3, 3.7 Hz, 1H, H-6), 3.65 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 3.26 – 3.15 (m, 3H, H-3, H-4, H-5), 3.08 – 2.95 (m, 1H, H-2), 0.92 (s, 9H, C(CH_3)$_3$ TBS), 0.10 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, HSQC, HMBC) δ 133.8 ($C_{q\text{-}arom}$), 132.1, 128.9, 127.4 (CH_{arom}), 88.9 (C-3), 87.0 (C-1), 82.3 (C-2), 80.1 (C-5), 79.0 (C-4), 62.2 (C-6), 61.1, 60.8, 60.6 (OCH_3), 26.0 (3x C(CH_3)$_3$ TBS), 18.4 (C_q TBS), –5.0, –5.3 (Si(CH_3)$_2$ TBS); HRMS (ESI) M/Z: $[M + NH_4]^+$ Calcd for $C_{21}H_{40}NO_5SSi^+$ 446.2391; Found 446.2392.



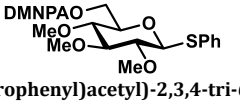
Phenyl 6-*O*-(*tert*-butyldimethylsilyl)-2,3,4-tri-*O*-methyl-1-^{13}C-thio-β-D-glucopyranoside (S14). S12 (0.63 g, 1.63 mmol) was dissolved in dry DMF (15.0 ml, 0.1M) and cooled to 0 °C. Under inert atmosphere, NaH (60 Wt % dispersion in mineral oil, 0.40 g, 10.1 mmol, 6.15 equiv) was added portion wise and the reaction mixture was stirred for 10 minutes. methyl iodide (0.525 ml, 8.39 mmol, 5.15 equiv) was added and the reaction was stirred for 17 h while allowing to warm up to RT. Subsequently, the reaction was cooled to 0 °C and quenched with H_2O. The reaction mixture was diluted with H_2O and extracted with DCM. The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (100:0 → 80:20, pentane:EtOAc v:v) yielded the title compound (0.56 g, 1.31 mmol, 80%) as a white oil. TLC: R_f 0.76, (pentane:EtOAc, 90:10, v:v); ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC) δ 7.61 – 7.19 (m, 5H, CH_{arom}), 4.46 (dd, *J* = 154.5, 9.8 Hz, 1H, H-1), 3.85 (dd, *J* = 11.3, 1.6 Hz, 1H, H-6), 3.79 (dd, *J* = 11.3, 3.4 Hz, 1H, H-6), 3.65 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 3.27 – 3.14 (m, 3H, H-3, H-4, H-5), 3.05 – 2.97 (m, 1H, H-2), 0.92 (s, 9H, C(CH_3)$_3$ TBS), 0.10 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, HSQC, HMBC) δ 133.8 ($C_{q\text{-}arom}$), 132.1, 132.1, 128.8, 127.4 (CH_{arom}), 88.8 (d, *J* = 3.6 Hz, C-3), 87.0 (C-1), 82.3 (d, *J* = 44.0 Hz, C-2), 80.0 (d, *J* = 2.3 Hz, C-5), 78.9 (C-4), 62.2 (d, *J* = 4.8 Hz, C-6), 61.0, 60.8, 60.8, 60.5 (OCH_3), 18.4 (*C*(CH_3)$_3$ TBS), –5.1, –5.3 ($SiCH_3$ TBS); HRMS (ESI) M/Z: $[M + Na]^+$ Calcd for $^{13}CC_{20}H_{36}NaO_5S^+$ 452.1979; Found 452.1977.



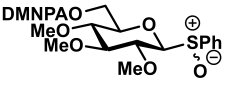
Phenyl 2,3,4-*O*-methyl-1-thio-β-D-glucopyranoside (S15). S13 (1.52 g, 3.55 mmol) was co-evaporated with toluene, and dissolved in THF (10 ml, 0.4M). Tetra-n-butylammonium fluoride in THF (0.1M, 7.11 ml, 7.11 mmol, 2 equiv) was added and the reaction was stirred for 1 h under intert atmosphere. Flash column chromatography (90:10 → 70:30, pentane:EtOAc v:v) yielded the title compound (1.07 g, 3.55 mmol, 96%) as a white solid. TLC: R_f 0.17, (pentane:EtOAc, 80:20, v:v); ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC) δ 7.52 – 7.46 (m, 2H, CH_{arom}), 7.34 – 7.23 (m, 3H, CH_{arom}), 4.55 (d, *J* = 9.9 Hz, 1H, H-2), 3.86 (ddd, *J* = 11.9, 6.1, 2.8 Hz, 1H, H-6), 3.70 (ddd, *J* = 12.0, 7.3, 5.0 Hz, 1H, H-6), 3.66 (s, 3H, OCH_3), 3.62 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 3.28 – 3.21 (m, 2H, H-3, H-5), 3.13 (dd, *J* = 9.8, 8.9 Hz, 1H, H-4), 3.03 (dd, *J* = 9.8, 8.7 Hz, 1H, H-2), 1.94 (t, *J* = 6.7 Hz, 1H, OH-6); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, HSQC, HMBC) δ 133.5 ($C_{q\text{-}arom}$), 132.0, 129.1, 127.8 (CH_{arom}), 88.6 (C-3), 87.2 (C-1), 82.8 (C-2), 79.6 (C-4), 79.2 (C-5), 62.3 (C-6), 61.1, 61.0, 60.7 (OCH_3); HRMS (ESI) M/Z: $[M + NH_4]^+$ Calcd for $C_{15}H_{26}NO_5S^+$ 332.1526; Found 332.1527.



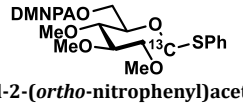
Phenyl 2,3,4-tri-*O*-methyl-1-^{13}C-thio-β-D-glucopyranoside (S16). S14 (0.53 g, 1.23 mmol) was co-evaporated with toluene, and dissolved in THF (3,5 ml, 0.35M). Tetra-n-butylammonium fluoride in THF (0.1M, 2.47 ml, 2.47 mmol, 2 equiv) was added and the reaction was stirred for 1 h under intert atmosphere. Flash column chromatography (80:20 → 60:40, pentane:EtOAc v:v) yielded the title compound (0.34 g, 1.08 mmol, 88%) as a white solid. TLC: R_f 0.27, (pentane:EtOAc, 70:30, v:v); ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC) δ 7.6 – 7.2 (m, 5H, CH_{arom}), 4.5 (dd, *J* = 156.3, 9.8 Hz, 1H, H-1), 3.9 – 3.6 (m, 8H, H-6, H-6, 2x OMe), 3.5 (s, 3H, OMe), 3.3 – 3.2 (m, 2H, H-3, H-5), 3.1 (dd, *J* = 9.8, 9.0 Hz, 1H, H-4), 3.0 (ddd, *J* = 9.8, 8.7, 5.3 Hz, 1H, H-2), 2.1 (s, 1H, OH-6); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, HSQC, HMBC) δ 133.5 ($C_{q\text{-}arom}$), 131.9, 129.1, 127.7 (CH_{arom}), 88.6 (d, *J* = 3.7 Hz, C-3), 87.1 (C-1), 82.7 (d, *J* = 44.1 Hz, C-2), 79.5 (C-4), 79.2 (d, *J* = 2.2 Hz, C-5), 62.2 (d, *J* = 4.4 Hz, C-6), 61.1 (CH_3), 60.1 (d, *J* = 1.7 Hz, CH_3), 60.7 (CH_3); HRMS (ESI) M/Z: $[M + Na]^+$ Calcd for $^{13}CC_{14}H_{22}NaO_5S^+$ 338.1114; Found 338.1111.



Phenyl 6-*O*-(2,2-dimethyl-2-(*ortho*-nitrophenyl)acetyl)-2,3,4-tri-*O*-methyl-1-thio-β-D-glucopyranoside (S17). The title compound was prepared from **S15** (0.15 g, 0.48 mmol) through general procedure I. Flash column chromatography (90:10 → 70:30, pentane:EtOAc v:v) yielded the title compound (0,15 g, 0,30 mmol, 62%) as a colorless oil. TLC: R_f 0.55, (pentane:EtOAc, 70:30, v:v); ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC) δ 8.06 (dd, *J* = 8.0, 1.3 Hz, 1H, CH_{arom}), 7.80 – 7.69 (m, 2H, CH_{arom}), 7.69 – 7.60 (m, 2H, CH_{arom}), 7.56 (ddd, *J* = 8.1, 6.7, 2.0 Hz, 1H, CH_{arom}), 7.43 – 7.34 (m, 3H, CH_{arom}), 4.67 – 4.55 (m, 2H, H-1, H-6), 4.27 (dd, *J* = 11.8, 5.8 Hz, 1H), 3.78 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.62 (s, 3H, OCH_3), 3.53 (ddd, *J* = 9.9, 5.9, 2.1 Hz, 1H, H-5), 3.36 (t, *J* = 8.8 Hz, 1H, H-3), 3.15 – 3.05 (m, 2H, H-2, H-4), 1.85 – 1.79 (m, 6H, 2x CH_3 DMNPA); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, HSQC, HMBC) δ 175.2 (C=O DMNPA), 148.8, 139.3, 133.4 ($C_{q\text{-}arom}$), 133.3, 132.4, 128.9, 128.2, 127.9, 127.7, 125.8 (CH_{arom}), 88.6 (C-3), 87.0 (C-1), 82.4 (C-2), 79.8 (C-4), 76.9 (C-5), 63.9 (C-6), 61.1, 60.9, 60.6 (OCH_3), 46.7 (C_q DMNPA), 27.5, 27.4 (CH_3 DMNPA); HRMS (ESI) M/Z: $[M + NH_4]^+$ Calcd for $C_{25}H_{35}N_2O_8S^+$ 523.2109; Found 523.2110.

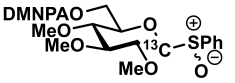


Phenyl 6-*O*-(2,2-dimethyl-2-(*ortho*-nitrophenyl)acetyl)-2,3,4-tri-*O*-methyl-1-sulphoxide-β-D-glucopyranoside (8). A solution of **S17** (15 mg, 0.030 mmol) in DCM (0.6 mL) was cooled to –78 °C under inert atmosphere and then *m*-CPBA (8.0 mg, 0.033 mmol) was added. The reaction was stirred for three hours, diluted with DCM (15 mL) and washed with 10% aq. $Na_2S_2O_3$ solution, sat. aq. $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered, concentrated *in vacuo*. The crude product (15 mg) was used directly for IRMPD experiments. HRMS (ESI) M/Z: $[M + Na]^+$ Calcd for $C_{25}H_{31}NNaO_9S^+$, 544.1617; Found 544.1606.



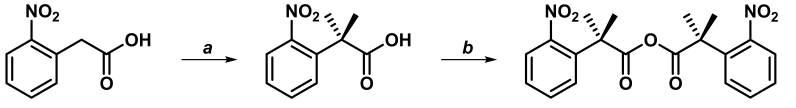
Phenyl 6-*O*-(2,2-dimethyl-2-(*ortho*-nitrophenyl)acetyl)-2,3,4-tri-*O*-methyl-1-^{13}C-thio-β-D-glucopyranoside (S18). The title compound was prepared from **S16** (0.075 g, 0.239 mmol) through general

procedure I. Flash column chromatography (90:10 → 70:30, pentane:EtOAc v:v) yielded the title compound (0.134 g, 0.27 mmol, quant) as a colorless oil. TLC: R_f 0.48, (pentane:EtOAc, 70:30, v:v); ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC) δ 7.92 (dd, *J* = 8.1, 1.4 Hz, 1H, CH_{arom}), 7.65 – 7.56 (m, 2H, CH_{arom}), 7.55 – 7.47 (m, 2H, CH_{arom}), 7.41 (ddd, *J* = 8.1, 6.9, 1.8 Hz, 1H, CH_{arom}), 7.29 – 7.21 (m, 3H, CH_{arom}), 4.48 (dd, *J* = 11.8, 2.1 Hz, 1H, H-6), 4.45 (dd, *J* = 155.4, 9.8 Hz, 1H, H-1), 4.13 (dd, *J* = 11.8, 5.9 Hz, 1H, H-6), 3.63 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3), 3.39 (ddt, *J* = 10.3, 5.8, 2.3 Hz, 1H, H-5), 3.21 (td, *J* = 8.8, 1.0 Hz, 1H, H-3), 2.96 (ddd, *J* = 10.0, 8.8, 5.0 Hz, 2H, H-2), 1.69 – 1.65 (m, 6H, 2x CH_3 DMNPA); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, HSQC, HMBC) δ 175.2 (C=O DMNPA), 139.3, 133.4 ($C_{q\text{-}arom}$), 133.3, 132.4, 132.4, 128.9, 128.2, 127.9, 127.7, 125.8 (CH_{arom}), 88.6 (d, *J* = 3.7 Hz, C-3), 87.0 (C-1), 82.4 (d, *J* = 44.7 Hz, C-2), 79.8 (C-4), 76.9 (C-5), 63.9 (d, *J* = 4.6 Hz, C-6), 61.1 (OCH_3), 60.9 (d, *J* = 1.7 Hz, OCH_3), 60.6 (OCH_3), 46.7 (C_q DMNPA), 27.5, 27.4 (CH_3 DMNPA); HRMS (ESI) M/Z: [M + NH_4]$^+$ Calcd for $^{13}CC_{24}H_{35}N_2O_8S^+$ 524.2142; Found 524.2141.



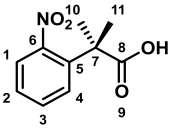
Phenyl 6-*O*-(2,2-dimethyl-2-(*ortho*-nitrophenyl)acetyl)-2,3,4-tri-*O*-methyl-1-^{13}C-sulphoxide-β-D-glucopyrano-side (9). A solution of **S18** (15 mg, 0.030 mmol) in DCM (0.6 mL) was cooled to –78 °C under inert atmosphere and then *m*-CPBA (8.0 mg, 0.033 mmol) was added. The reaction was stirred for three hours, diluted with DCM (15 mL) and washed with 10% aq. $Na_2S_2O_3$ solution, sat. aq. $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered, concentrated *in vacuo*. The crude product (15 mg) was used directly for IRMPD experiments. HRMS (ESI) M/Z: [M + Na]$^+$ Calcd for $C_{24}{}^{13}CH_{31}NNaO_9S^+$, 545.1651; Found 545.1645.

Preparation of DMNPAA reagent

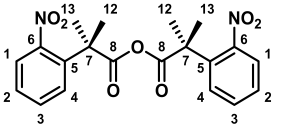


S19 **S20**

Supplementary scheme S3. DMNPAA reagent **S20** synthesis. a) 1. $SOCl_2$, MeOH, 0 °C to rt; 2. MeI, NaH, DMF, 0 °C to rt; 3. MeOH, NaOH,reflux, **S19**: 47%; b) DCC, CH_2Cl_2, **S20**: 74%.

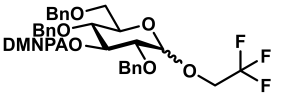


2-methyl-2-(2-nitrophenyl)propanoic acid (S19). The title compound was prepared according to literature procedure,[35] (12.7 g, 60.7 mmol, 47%) as a yellow solid. TLC: R_f 0.61, (DCM:MeOH, 95:5, v:v); ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC) δ 7.97 (dt, J = 8.2, 0.9 Hz, 1H, CH_{arom}-1), 7.62 (dd, J = 4.7, 0.9 Hz, 2H, CH_{arom}-3,4), 7.46 – 7.38 (m, 1H, CH_{arom}-2), 1.70 (s, 6H, 2x CH_3); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, HSQC) δ 181.9 (C=O), 148.4 (C_q-6), 138.9 (C_q-5), 133.5 (C-3), 128.3 (C-4), 128.1 (C-2), 125.9 (C-1), 46.5 (C_q-7), 27.2 (C-10, C-11); HRMS (ESI) M/Z: [M + NH_4]$^+$ Calcd for $C_{10}H_{15}N_2O_4^+$ 227.1026; Found 227.1025.

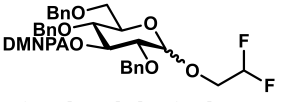


2-methyl-2-(2-nitrophenyl)propanoic anhydride (S20). The DMNPA reagent was prepared from **S19** (12.7 g, 60.7 mmol) according to literature procedure,[35] yielding the title compound (9.0 g, 30.4 mmol, 74%) as yellow crystals. TLC: R_f 0.39, (pentane:EtOAc, 70:30, v:v); ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC) δ 7.75 (dd, J = 8.1, 1.5 Hz, 1H, H-1), 7.55 (ddd, J = 8.0, 7.3, 1.5 Hz, 1H, H-3), 7.45 (dd, J = 8.1, 1.4 Hz, 1H, H-4), 7.34 (ddd, J = 8.1, 7.3, 1.4 Hz, 1H, H-2), 1.59 (s, 6H, 2x CH_3); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, HSQC, HMBC) δ 169.3 (C=O), 147.6 (C-6), 137.7 (C-5), 133.7 (C-3), 128.2 (C-4), 128.0 (C-2), 125.8 (C-1), 47.4 (C-7), 26.2 (C-13, C-12); HRMS (ESI) M/Z: [M + NH_4]$^+$ Calcd for $C_{20}H_{24}N_3O_7^+$ 418.1609; Found 418.1606.

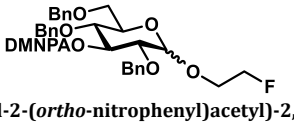
Model glycosylation reactions



2,2,2-Trifluoroethyl 3-*O*-(2,2-dimethyl-2-(*ortho*-nitrophenyl)acetyl)-2,4,6-tri-*O*-benzyl-ᴅ-glucopyranoside (S21). The title compound was prepared according to general procedure VI, using **3** as the donor and 2,2,2-trifluoroethanol as the acceptor. Flash column chromatography (100:0 → 85:15, pentane:EtOAc v:v) yielded the title compound (52 mg, 0.066 mmol, 66%, α:β; 63:37) as a colorless oil. TLC: R_f 0.38, (85:15, pentane:EtOAc, v:v); ^{1}H NMR (850 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC, HMBC-Gated) δ 7.83 – 7.12 (m, 50H), 5.53 (t, *J* = 9.5 Hz, 1H, H-3, α), 5.25 (dd, *J* = 8.1, 6.1 Hz, 1H, H-3 β), 4.84 (d, *J* = 11.4 Hz, 1H, C*H*H Bn βz), 4.70 (dd, *J* = 11.9, 4.8 Hz, 2H), 4.68 (d, *J* = 5.7 Hz, 1H, H-1 β), 4.62 (d, *J* = 3.6 Hz, 1H, H-1 α), 4.61 (d, *J* = 11.0 Hz, 2H), 4.54 – 4.49 (m, 2H), 4.48 (d, *J* = 12.1 Hz, 1H), 4.42 (d, *J* = 12.1 Hz, 1H), 4.38 – 4.33 (m, 3H), 4.19 (dq, *J* = 12.0, 8.7 Hz, 1H, C*H*HCF$_3$ β), 3.85 (dd, *J* = 9.9, 8.1 Hz, 1H, H-4 β), 3.83 – 3.78 (m, 2H), 3.75 (dq, *J* = 12.4, 8.7 Hz, 1H, CH*H*CF$_3$ α), 3.71 (ddd, *J* = 9.9, 3.8, 2.4 Hz, 1H, CH*H*CF$_3$ β), 3.70 – 3.65 (m, 2H), 3.65 – 3.60 (m, 2H), 3.57 – 3.53 (m, 2H), 3.50 (dd, *J* = 9.8, 3.6 Hz, 1H, H-2 α), 1.65 (s, 3H, CH_3 DMNPA α), 1.63 (s, 2H, CH_3 DMNPA β), 1.62 (s, 3H, CH_3 DMNPA α), 1.58 (s, 2H, CH_3 DMNPA β); ^{13}C{^{1}H} NMR (214 MHz, $CDCl_3$, HSQC, HMBC, HMBC-Gated) δ 174.5 (C=O DMNPA β), 174.3 (C=O DMNPA α), 149.1, 149.0, 145.7, 138.3, 138.3, 138.2, 138.0, 138.0, 138.0, 137.9, 137.7, 132.8, 131.2, 129.4, 128.9, 128.5, 128.5, 128.5, 128.4, 128.3, 128.3, 128.1, 128.0, 128.0, 128.0, 128.0, 127.9, 127.8, 127.8, 127.8, 127.7, 127.6, 127.6, 127.5, 125.6, 125.4, 124.9, 123.8 (q, *J* = 277.9 Hz, CF_3), 123.6 (q, *J* = 278.5 Hz, CF_3), 101.4 (C-1 β), 97.5 (C-1 α), 78.7 (C-2 β), 78.2 (C-2 α), 76.1 (C-3 β), 75.6, 75.2 (C-4 β), 73.8 (C-3 α), 73.6, 73.5, 73.5, 73.2, 73.0, 70.5, 68.6 (C-6 β), 68.1 (C-6 α), 65.4, 65.2, 65.2, 65.0, 65.0, 64.9, 64.8, 64.7, 47.1 (C_q DMNPA α), 46.8 (C_q DMNPA β), 27.1 (CH_3 DMNPA α), 26.9 (CH_3 DMNPA β), 26.8 (CH_3 DMNPA α), 26.7 (CH_3 DMNPA β); ^{13}C-GATED NMR (214 MHz, $CDCl_3$) δ 101.4 ($J_{H1\text{-}C1}$ = 166 Hz, β) 97.5 ($J_{H1\text{-}C1}$ = 169 Hz, α); HRMS (ESI) M/Z: $[M + NH_4]^+$ Calcd for $C_{39}H_{44}F_3N_2O_9^+$ 741.2993; Found 741.2982.

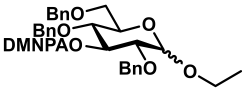


2,2-Difluoroethyl 3-*O*-(2,2-dimethyl-2-(*ortho*-nitrophenyl)acetyl)-2,4,6-tri-*O*-benzyl-ᴅ-glucopyranoside (S22). The title compound was prepared according to general procedure VI, using **3** as the donor and 2,2-difluoroethanol as the acceptor. Flash column chromatography (100:0 → 80:20, pentane:EtOAc v:v) yielded the title compound (56 mg, 0.079 mmol, 79%, α:β; 51:49) as a colorless oil. TLC: R_f 0.35, (85:15, pentane:EtOAc, v:v); ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC, HMBC-Gated) δ 7.81 – 7.09 (m, 55H), 5.88 (tt, *J* = 55.6, 4.3 Hz, 1H, CHF_2 β), 5.82 (tdd, *J* = 55.5, 5.1, 3.2 Hz, 1H, CHF_2 α), 5.52 (t, *J* = 9.6 Hz, 1H, H-3 α), 5.27 (dd, *J* = 8.3, 7.2 Hz, 1H, H-3 β), 4.83 (d, *J* = 11.6 Hz, 1H), 4.71 (d, *J* = 12.4 Hz, 1H), 4.66 (d, *J* = 11.7 Hz, 1H), 4.63 – 4.55 (m, 4H, H-1 α, H-1 β, C*H*H Bn, C*H*H Bn), 4.55 – 4.45 (m, 3H), 4.42 (d, *J* = 12.1 Hz, 1H), 4.40 – 4.30 (m, 3H), 4.02 – 3.88 (m, 1H, C*H*HCHF$_2$), 3.83 (ddd, *J* = 10.1, 3.5, 2.1 Hz, 1H, H-5 β), 3.76 (dd, *J* = 9.6, 8.3 Hz, 1H, H-4 β), 3.72 – 3.44 (m, 11H), 1.65 (s, 3H), 1.63 – 1.61 (m, 6H), 1.58 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, HSQC, HMBC, HMBC-Gated) δ 174.4 (C=O), 174.3 (C=O), 149.2, 149.0, 145.7, 138.3, 138.3, 138.3, 138.0, 137.9, 137.7, 132.9, 132.7, 131.2, 129.4, 128.9, 128.7, 128.5, 128.5, 128.4, 128.3, 128.3, 128.1, 128.0, 128.0, 127.9, 127.9, 127.8, 127.8, 127.7, 127.6, 127.6, 127.5, 127.4, 125.5, 125.4, 124.9, 114.2 (t, *J* = 240.9 Hz, CHF_2 α), 114.1 (t, *J* = 241.2 Hz CHF_2 β), 102.5 (C-1 β), 97.5 (C-1 α), 79.3, 78.3, 76.1 (C-3 β), 75.7 (C-4 β), 75.5, 74.1 (C-3 α), 73.9, 70.2 (C-5 β), 68.7, 68.4, 68.3, 68.1, 67.8, 67.6, 67.3, 67.0, 47.1 (C_q DMNPA), 46.9 (C_q DMNPA), 27.1 (CH_3 DMNPA), 27.0 (CH_3 DMNPA), 26.8 (CH_3 DMNPA), 26.8 (CH_3 DMNPA); ^{13}C-GATED NMR (101 MHz, $CDCl_3$) δ 102.5 ($J_{H1\text{-}C1}$ = 164 Hz, β), 97.5 ($J_{H1\text{-}C1}$ = 170 Hz, α); HRMS (ESI) M/Z: $[M + NH_4]^+$ Calcd for $C_{39}H_{45}F_2N_2O_9^+$ 723.3088; Found 723.3084.

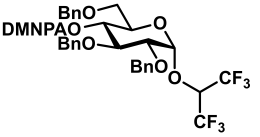


f2-Fluoroethyl 3-*O*-(2,2-dimethyl-2-(*ortho*-nitrophenyl)acetyl)-2,4,6-tri-*O*-benzyl-ᴅ-glucoyranoside (S23). The title compound was prepared according to general procedure VI, using **3** as the donor and 2-Fluoroethanol as the acceptor. Flash column chromatography (100:0 → 80:20, pentane:EtOAc v:v) yielded the title compound (66 mg, 0.096 mmol, 96%, α:β; 41:59) as a colorless oil. TLC: R_f 0.30, (85:15, pentane:EtOAc, v:v); ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC, HMBC-Gated) δ 7.78 – 7.12 (m, 51H), 5.57 (t, *J* = 9.5 Hz, 1H, H-3 α), 5.30 (t, *J* = 8.3 Hz, 1H, H-3 β), 4.92 (d, *J* = 11.5 Hz, 1H), 4.69 (d, *J* = 12.4 Hz, 1H), 4.65 (d, *J* = 3.5 Hz, 1H, H-1 α), 4.64 – 4.58 (m, 3H), 4.56 (d, *J* = 7.2 Hz, 1H, H-1 β), 4.55 – 4.31 (m, 9H), 4.05 (dddd, *J* = 32.3, 12.0, 4.8, 2.5 Hz, 1H, C*H*HCHF$_2$ β), 3.89 (ddd, *J* = 10.1, 3.4, 2.1 Hz, 1H, H-5 β), 3.81 – 3.41 (m, 11H), 1.65 (s, 2H), 1.62 (d, *J* = 1.8 Hz, 6H), 1.57 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, HSQC, HMBC, HMBC-Gated) δ 174.3 (C=O β), 174.3 (C=O α), 149.2, 149.1, 145.6, 138.5, 138.3, 138.3, 138.3, 138.1, 138.0, 137.8, 132.8, 132.6, 131.1, 129.4, 128.9, 128.7,

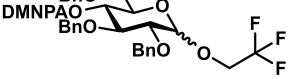
128.5, 128.5, 128.4, 128.4, 128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 127.9, 127.9, 127.8, 127.8, 127.8, 127.7, 127.7, 127.6, 127.6, 127.6, 127.5, 127.4, 127.3, 125.4, 125.3, 124.8, 102.7 (C-1 β), 97.0 (C-1 α), 82.61 (d, *J* = 169.8 Hz, CHF_2 β), 82.52 (d, *J* = 169.9 Hz, CHF_2 α), 79.6, 78.3, 76.1 (C-3 β), 75.9, 75.7, 74.2, 74.1 (C-3 α), 73.6, 73.5, 73.5, 73.2, 72.9, 69.7 (C-5 β), 68.8, 68.5, 68.4, 68.3, 67.2, 67.0, 47.1 (C_q DMNPA α), 46.9 (C_q DMNPA β), 27.0 (CH_3 DMNPA α), 26.9 (CH_3 DMNPA β), 26.8 (CH_3 DMNPA α), 26.7 (CH_3 DMNPA β); ^{13}C-GATED NMR (101 MHz, $CDCl_3$) δ 102.7 ($J_{H1\text{-}C1}$ = 161 Hz, β), 97.0 ($J_{H1\text{-}C1}$ = 169 Hz, α); HRMS (ESI) M/Z: $[M + NH_4]^+$ Calcd for $C_{39}H_{46}FN_2O_9^+$ 705.3182; Found 705.3182.



Ethyl 3-*O*-(2,2-dimethyl-2-(*ortho*-nitrophenyl)acetyl)-2,4,6-tri-*O*-benzyl-D-glucopyranoside (S24). The title compound was prepared according to general procedure VI, using **3** as the donor and ethanol as the acceptor. Flash column chromatography (100:0 → 80:20, pentane:EtOAc v:v) yielded the title compound (69 mg, quant, α:β; 43:57) as a colorless oil. TLC: R_f 0.35, (85:15, pentane:EtOAc, v:v); ^{1}H NMR (400 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC, HMBC-Gated) δ 7.77 – 7.12 (m, 42H), 5.57 (t, *J* = 9.5 Hz, 1H, H-3 α), 5.31 (t, *J* = 8.6 Hz, 1H, H-3 β), 4.95 (d, *J* = 11.6 Hz, 1H), 4.68 (d, *J* = 12.5 Hz, 1H), 4.63 – 4.58 (m, 1H), 4.59 (d, *J* = 3.3 Hz, 1H, H-1 α), 4.57 – 4.51 (m, 3H), 4.50 (d, *J* = 7.5 Hz, 1H, H-1 β), 4.44 (d, *J* = 12.1 Hz, 1H), 4.40 – 4.31 (m, 3H), 3.95 (dq, *J* = 9.5, 7.1 Hz, 1H, C*H*HCH_3 β), 3.84 (ddd, *J* = 10.1, 3.5, 2.1 Hz, 1H, H-5 β), 3.71 – 3.48 (m, 8H), 3.45 (dd, *J* = 9.9, 3.5 Hz, 1H, H-2 α), 3.39 (dd, *J* = 8.6, 7.3 Hz, 1H, H-2 β), 3.30 (dq, *J* = 9.8, 7.1 Hz, 1H, C*H*HCH_3 α), 1.65 (s, 3H, CH_3 DMNPA α), 1.62 (s, 3H, CH_3 DMNPA α), 1.61 (s, 3H, CH_3 DMNPA β), 1.56 (s, 3H, CH_3 DMNPA β) 1.22 – 1.14 (m, 6H, CH_2CH_3 α, CH_2CH_3 β); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, HSQC, HMBC, HMBC-Gated) δ 174.3 (C=O α), 174.2 (C=O β), 149.2, 149.1, 145.6, 138.7, 138.4, 138.3, 138.2, 138.2, 138.1, 138.0, 137.8, 102.9 (C-1 β), 96.4 (C-1 α), 79.9 (C-2 β), 78.4 (C-2 α), 76.2 (C-3 β), 76.1, 76.0, 74.4 (C-3 α), 74.4, 73.6, 73.5, 73.4, 73.3, 73.3, 72.8, 69.5 (C-5 β), 68.9, 68.5, 65.4 (CH_2 Et β), 63.5 (CH_2 Et α), 47.2 (C_q DMNPA β), 47.0 (C_q DMNPA α), 27.0, 26.9, 26.7, 15.3 (CH_3 Et β), 15.0 (CH_3 Et β); ^{13}C-GATED NMR (101 MHz, $CDCl_3$) δ 102.9 ($J_{H1\text{-}C1}$ = 160 Hz, β), 96.4 ($J_{H1\text{-}C1}$ = 169 Hz, α); HRMS (ESI) M/Z: $[M + NH_4]^+$ Calcd for $C_{39}H_{47}N_2O_9^+$ 687.3276; Found 687.3277.

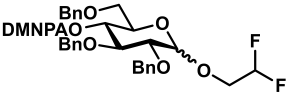


1,1,1,3,3,3-Hexafluoro-2-propyl 4-*O*-(2,2-dimethyl-2-(*ortho*-nitrophenyl)acetyl)-2,3,6-tri-*O*-benzyl-α-D-gluco-pyranoside (S25). The title compound was prepared according to general procedure VI, using **5** as the donor and 1,1,1,3,3,3-hexafluoro-2-propanol as the acceptor. Flash column chromatography (100:0 → 85:15, pentane:EtOAc v:v) yielded the title compound (31 mg, 39 mmol, 39%, α:β; >98:2) as a colorless oil. TLC: R_f 0.32, (pentane:EtOAc, 85:15, v:v); ^{1}H NMR (850 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC, HMBC-Gated) δ 7.86 – 7.16 (m, 39H), 5.19 (d, *J* = 3.7 Hz, 1H, H-1), 5.15 (dd, *J* = 10.2, 8.9 Hz, 1H, H-4), 4.95 (d, *J* = 11.4 Hz, 1H, C*H* Bn), 4.65 (d, *J* = 11.8 Hz, 1H, C*H* Bn), 4.62 (d, *J* = 11.4 Hz, 1H, C*H* Bn), 4.59 – 4.54 (m, 2H, CH*H* Bn, CH*H* Bn), 4.52 (d, *J* = 11.8 Hz, 1H, CH*H* Bn), 3.94 (ddd, *J* = 10.3, 4.9, 2.2 Hz, 1H, H-5), 3.91 (t, *J* = 9.3 Hz, 1H, H-3), 3.71 (dd, *J* = 9.6, 3.6 Hz, 1H, H-2), 3.69 – 3.61 (m, 2H, H-6, H-6), 1.57 (s, 3H, CH_3 DMNPA), 1.53 (s, 3H, CH_3 DMNPA); ^{13}C{^{1}H} NMR (214 MHz, $CDCl_3$, HSQC, HMBC, HMBC-Gated) δ 174.3 (C=O), 148.8, 145.7, 138.7, 138.4, 138.3, 137.3, 133.3, 131.2, 129.4, 128.6, 128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 128.0, 127.6, 127.3, 126.9, 125.7, 124.9, 98.5 (C-1), 78.7 (C-2), 77.8 (C-3), 74.4 (CH_2 Bn), 73.6 (CH_2 Bn), 73.3 (CH_2 Bn), 72.4 (p, *J* = 32.8 Hz, $CH(CF_3)_2$), 70.9 (C-5), 70.2 (C-4), 68.3 (C-6), 47.0 (C_q DMNPA), 27.4 (CH_3 DMNPA), 27.2 (CH_3 DMNPA); ^{13}C-GATED NMR (214 MHz, $CDCl_3$) δ 98.5 ($J_{H1\text{-}C1}$ = 172 Hz, β); HRMS (ESI) M/Z: $[M + NH_4]^+$ Calcd for $C_{40}H_{43}F_6N_2O_9^+$ 809.2867; Found 809.2863.

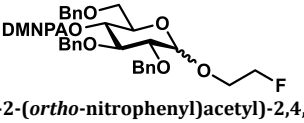


2,2,2-Trifluoroethyl 4-*O*-(2,2-dimethyl-2-(*ortho*-nitrophenyl)acetyl)-2,3,6-tri-*O*-benzyl-D-glucopyranoside (S26). The title compound was prepared according to general procedure VI, using **5** as the donor and 2,2,2-trifluoroethanol as the acceptor. Flash column chromatography (100:0 → 85:15, pentane:EtOAc v:v) yielded the title compound (72 mg, 0.066 mmol, 66%, α:β; 80:20) as a colorless oil. TLC: R_f 0.45, (pentane:EtOAc, 80:20, v:v); ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC, HMBC-Gated) δ 7.86 – 7.18 (m, 36H), 5.05 (dd, *J* = 10.2, 9.2 Hz, 1H, H-4 α), 5.00 – 4.91 (m, 1H), 4.88 (d, *J* = 2.9 Hz, 0.25H), 4.86 (d, *J* = 3.5 Hz, 1H, H-1 α), 4.69 – 4.61 (m, 2H), 4.59 – 4.45 (m, 4H, H-1 β), 4.20 (dq, *J* = 12.5, 8.8 Hz, 0.25H, C*H*HCF_3), 4.01 – 3.75 (m, 4H), 3.73 – 3.53 (m, 4H), 1.57 (s, 3H, CH_3 DMNPA α), 1.54 (s, 0.75H, CH_3 DMNPA β), 1.52 (s, 3H, CH_3 DMNPA α), 1.52 (s, 0.75H, CH_3 DMNPA β); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, HSQC, HMBC, HMBC-Gated) δ 174.5 (C=O β),

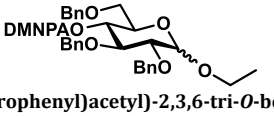
174.4 (C=O α), 148.8, 145.9, 138.7, 138.6, 138.5, 138.4, 138.4, 138.3, 137.8, 133.3, 131.2, 129.4, 128.6, 128.5, 128.5, 128.4, 128.4, 128.3, 128.3, 128.2, 128.1, 128.0, 128.0, 127.9, 127.6, 127.3, 127.0, 124.9, 123.9 (q, *J* = 278.8 Hz, CF_3 β), 122.8, 120.6, 103.3 (C-1 β), 97.1 (C-1 α), 81.2 (C-3 β), 81.1 (C-2 β), 79.6 (C-2 α), 78.4 (C-3 αf), 74.7, 74.4, 74.0, 73.6, 73.1, 71.1 (C-4 β), 70.8 (C-4 α), 70.0, 69.6 (C-6 β), 68.8 (C-6 α), 66.1, 65.8, 64.43 (q, *J* = 34.8 Hz, CH_2CF_3), 47.0 (C_q DMNPA α), 46.9 (C_q DMNPA β), 27.3 (CH_3 DMNPA α), 27.2 (CH_3 DMNPA β), 27.1 (CH_3 DMNPA α), 27.1 (CH_3 DMNPA β); ^{13}C-GATED NMR (126 MHz, $CDCl_3$) δ 103.3 ($J_{H1\text{-}C1}$ = 161 Hz, β), 97.1 ($J_{H1\text{-}C1}$ = 172 Hz, α); HRMS (ESI) M/Z: $[M + NH_4]^+$ Calcd for $C_{39}H_{44}F_3N_2O_9^+$ 741.2993; Found 741.2994.



2,2-Difluoroethyl 4-*O*-(2,2-dimethyl-2-(*ortho*-nitrophenyl)acetyl)-2,3,6-tri-*O*-benzyl-D-glucopyranoside (S27). The title compound was prepared according to general procedure VI, using **5** as the donor and 2,2-difluoroethanol as the acceptor. Flash column chromatography (95:5 → 80:20, pentane:EtOAc v:v) yielded the title compound (54 mg, 0.077 mmol, 77%, α:β; 50:50) as a colorless oil. TLC: R_f 0.36, (pentane:EtOAc, 80:20, v:v); ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC, HMBC-Gated) δ 7.93 – 7.17 (m, 55H), 5.99 (tdd, *J* = 55.4, 4.9, 3.6 Hz, 1H, CHF_2 α), 5.95 (dddd, *J* = 56.1, 54.8, 5.4, 2.9 Hz, 1H, CHF_2 β), 5.03 (dd, *J* = 10.2, 9.2 Hz, 1H, H-4 α), 4.98 – 4.91 (m, 2H), 4.89 – 4.82 (m, 2H), 4.77 (d, *J* = 3.6 Hz, 1H, H-1 α), 4.69 – 4.47 (m, 9H), 4.45 (d, *J* = 7.5 Hz, 1H, H-1 β), 4.01 (dddd, *J* = 20.7, 11.8, 10.4, 2.9 Hz, 1H, C*H*HCHF$_2$ β), 3.90 (t, *J* = 9.4 Hz, 1H, H-3 α), 3.87 – 3.66 (m, 6H), 3.66 – 3.51 (m, 6H), 1.56 (s, 3H, CH_3 DMNPA), 1.54 (s, 3H, CH_3 DMNPA), 1.52 (s, 6H, CH_3 DMNPA, CH_3 DMNPA); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, HSQC, HMBC, HMBC-Gated) δ 174.5 (C=O α), 174.5 (C=O β), 148.8, 145.8, 138.6, 138.5, 138.4, 138.4, 138.3, 138.0, 137.8, 133.3, 131.2, 129.4, 128.6, 128.5, 128.5, 128.4, 128.3, 128.3, 128.3, 128.2, 128.2, 128.0, 128.0, 127.9, 127.9, 127.7, 127.6, 127.4, 127.3, 127.0, 127.0, 125.7, 124.9, 114.2 (dd, *J* = 242.2, 239.8 Hz, CHF_2 β), 114.1 (t, *J* = 241.2 Hz, CHF_2 α), 103.8 (C-1 β), 97.6 (C-1 α), 81.4 (C-2 α), 81.4 (C-2 β), 79.8, 78.6, 74.7, 74.4, 74.2, 73.9, 73.5, 73.3, 71.2 (C-4 β), 70.9 (C-4 α), 69.7, 69.6, 68.9, 68.9, 68.7, 68.7, 68.5, 67.7, 67.4, 67.2, 47.0 (C_q DMNPA), 46.9 (C_q DMNPA), 27.3 (CH_3 DMNPA), 27.2 (CH_3 DMNPA), 27.1 (CH_3 DMNPA, CH_3 DMNPA); ^{13}C-GATED NMR (126 MHz, $CDCl_3$) δ 103.8 ($J_{H1\text{-}C1}$ = 160 Hz, β), 97.6 ($J_{H1\text{-}C1}$ = 170 Hz, α); HRMS (ESI) M/Z: $[M + NH_4]^+$ Calcd for $C_{39}H_{45}F_2N_2O_9^+$ 723.3088; Found 723.3087.

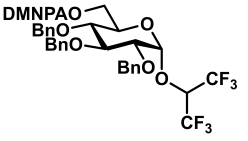


2-Fluoroethyl 4-*O*-(2,2-dimethyl-2-(*ortho*-nitrophenyl)acetyl)-2,4,6-tri-*O*-benzyl-D-glucopyranoside (S28). The title compound was prepared according to general procedure VI, using **5** as the donor and 2-Fluoroethanol as the acceptor. Flash column chromatography (90:10 → 75:25, pentane:EtOAc v:v) yielded the title compound (51 mg, 0.074 mmol, 75%, α:β; 36:64) as a colorless oil. TLC: R_f 0.25, (pentane:EtOAc, 80:20, v:v); ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC, HMBC-Gated) δ 7.85 – 7.20 (m, 38H), 5.06 (dd, *J* = 10.2, 9.2 Hz, 0.56H, H-4 α), 4.99 (d, *J* = 11.5 Hz, 1H), 4.98 – 4.90 (m, 2H), 4.88 (d, *J* = 11.4 Hz, 1H), 4.83 (d, *J* = 3.6 Hz, 0.56H, H-1 α), 4.73 – 4.48 (m, 8H), 4.48 (d, *J* = 7.5 Hz, 1H, H-1 β), 4.11 (dddd, *J* = 33.8, 12.2, 4.5, 2.4 Hz, 1H, CH_2F β), 3.95 (t, *J* = 9.4 Hz, 0.56H, H-3 α), 3.94 – 3.79 (m, 2H), 3.81 – 3.53 (m, 7H), 1.57 (s, 1.68H, CH_3 DMNPA α), 1.55 (s, 3H, CH_3 DMNPA β), 1.53 (s, 4.68H, CH_3 DMNPA α, CH_3 DMNPA β); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, HSQC, HMBC, HMBC-Gated) δ 174.5 (C=O β), 174.5 (C=O α), 148.8, 145.7, 138.8, 138.7, 138.5, 138.5, 138.4, 138.2, 138.0, 133.2, 131.2, 129.4, 128.6, 128.6, 128.5, 128.5, 128.5, 128.4, 128.4, 128.3, 128.3, 128.3, 128.2, 128.1, 128.1, 128.0, 128.0, 128.0, 127.9, 127.9, 127.8, 127.6, 127.5, 127.4, 127.2, 127.1, 126.9, 125.7, 124.9, 103.5 (C-1 β), 96.9 (C-1 α), 82.7 (d, *J* = 169.8 Hz, CH_2F β), 82.6 (d, *J* = 169.7 Hz, CH_2F α), 81.5 (C-3 β), 81.4 (C-2 β), 79.9 (C-2 α), 78.7 (C-3 α), 77.4, 77.2, 76.9, 74.6, 74.3, 74.2, 73.8, 73.5, 73.5, 73.1 (C-4 β), 71.3 (C-4 α), 71.1, 69.8, 69.3, 69.0, 68.9 (d, *J* = 19.9 Hz, CH_2CH_2F β), 67.2 (d, *J* = 20.1 Hz, CH_2CH_2F α), 47.0 (C_q DMNPA α), 46.9 (C_q DMNPA β), 27.3 (CH_3 DMNPA α), 27.2 (CH_3 DMNPA β), 27.1 (CH_3 DMNPA α), 27.1 (CH_3 DMNPA β); ^{13}C-GATED NMR (126 MHz, $CDCl_3$) δ 103.5 ($J_{H1\text{-}C1}$ = 160 Hz, β), 96.9 ($J_{H1\text{-}C1}$ = 171zz Hz, α); HRMS (ESI) M/Z: $[M + NH_4]^+$ Calcd for $C_{39}H_{46}FN_2O_9^+$ 705.3182; Found 705.3181.

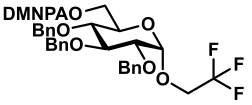


Ethyl 4-*O*-(2,2-dimethyl-2-(*ortho*-nitrophenyl)acetyl)-2,3,6-tri-*O*-benzyl-D-glucopyranoside (S29). The title compound was prepared according to general procedure VI, using **5** as the donor and ethanol as the acceptor. Flash column chromatography (95:5 → 80:20, pentane:EtOAc v:v) yielded the title compound (48 mg, 0.072 mmol, 72%, α:β; 26:74) as a colorless oil. TLC: R_f 0.45, (pentane:EtOAc, 80:20, v:v); ^{1}H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC, HMBC-Gated) δ 7.84 – 7.17 (m, 35H), 5.04 (dd, *J* = 10.2, 9.1 Hz, 0.31H, H-4 α), 4.99 (d, *J* = 11.5 Hz, 0.31H, C*H*H Bn α), 4.95 – 4.88 (m, 2H), 4.85 (d, *J* = 11.4 Hz, 1H), 4.78 (d, *J* = 3.6 Hz, 0.31H, H-

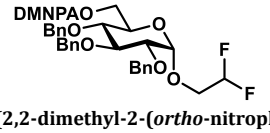
1 α), 4.69 – 4.50 (m, 5H), 4.47 (d, *J* = 11.4 Hz, 1H), 4.42 (d, *J* = 7.6 Hz, 1H, H-1 β), 4.01 (dq, *J* = 9.6, 7.1 Hz, 1H, C*H*HCH$_3$ β), 3.93 (t, *J* = 9.4 Hz, 0.31H, H-3 α), 3.85 (ddd, *J* = 10.2, 5.8, 2.1 Hz, 0.31H, H-5 α), 3.81 – 3.47 (m, 8H), 1.56 (s, 0.93H, CH$_3$ DMNPA α), 1.53 (s, 3H, CH$_3$ DMNPA β), 1.52 (s, 0.93H, CH$_3$ DMNPA α), 1.51 (s, 3H, CH$_3$ DMNPA β), 1.31 – 1.24 (m, 5H, CH$_2$CH$_3$ α, CH$_2$CH$_3$ β); ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$, HSQC, HMBC, HMBC-Gated) δ 174.5 (C=O β), 174.5 (C=O β), 148.9, 145.7, 138.9, 138.7, 138.6, 138.6, 138.5, 138.5, 138.4, 138.1, 133.1, 131.1, 129.4, 128.5, 128.5, 128.5, 128.4, 128.4, 128.3, 128.2, 128.2, 128.2, 128.0, 128.0, 127.9, 127.7, 127.5, 127.4, 127.3, 127.1, 126.9, 125.6, 124.9, 103.2 (C-1 β), 96.1 (C-1 α), 81.6, 81.6, 80.0 (C-2 α), 78.9 (C-3 α), 74.5, 74.3, 74.2, 73.7, 73.6, 73.5, 73.0, 71.5 (C-4 β), 71.4 (C-4 α), 69.9 (C-6 β), 69.1 (C-5 α), 69.1 (C-6 α), 65.7 (CH$_2$ Et β), 63.5 (CH$_2$ Et α), 47.0 (C$_q$ DMNPA α), 46.9 (C$_q$ DMNPA β), 27.3 (CH$_3$ DMNPA α), 27.2 (CH$_3$ DMNPA β), 27.1 (CH$_3$ DMNPA α), 27.1 (CH$_3$ DMNPA β), 15.4 (CH$_3$ Et α), 15.0 (CH$_3$ Et β); ^{13}C-GATED NMR (126 MHz, CDCl$_3$) δ 103.2 ($J_{H1\text{-}C1}$ = 159 Hz, β), 96.1 ($J_{H1\text{-}C1}$ = 167 Hz, α); HRMS (ESI) M/Z: [M + NH$_4$]$^+$ Calcd for $C_{39}H_{47}N_2O_9^+$ 687.3276; Found 687.3277.



1,1,1,3,3,3-Hexafluoro-2-propyl 6-*O*-(2,2-dimethyl-2-(*ortho*-nitrophenyl)acetyl)-2,3,4-tri-*O*-benzyl-α-D-gluco-pyranoside (S30). The title compound was prepared according to general procedure VI, using **7** as the donor and 1,1,1,3,3,3-hexafluoro-2-propanol as the acceptor. Flash column chromatography (100:0 → 90:10, pentane:EtOAc v:v) yielded the title compound (27 mg, 0.034 mmol, 0.034, 34%, α:β; >98:2) as a colorless oil. TLC: R_f 0.48, (80:20, pentane:EtOAc, v:v); ^{1}H NMR (500 MHz, CDCl$_3$, HH-COSY, HSQC, HMBC, HMBC-Gated) δ 7.94 – 7.20 (m, 45H), 5.10 (d, *J* = 3.8 Hz, 1H, H-1 α), 4.94 (d, *J* = 10.7 Hz, 1H), 4.83 – 4.76 (m, 2H), 4.73 – 4.63 (m, 2H), 4.40 (dd, *J* = 11.9, 1.9 Hz, 1H, H-6), 4.32 (hept, *J* = 5.9 Hz, 1H, CH(CF$_3$)$_2$), 4.14 (dd, *J* = 12.0, 5.7 Hz, 1H, H-6), 3.98 – 3.85 (m, 2H, H-3, H-5), 3.53 (dd, *J* = 9.8, 3.8 Hz, 1H, H-2), 3.30 (dd, *J* = 10.2, 9.1 Hz, 1H, H-4), 1.68 (s, 3H, CH$_3$ DMNPA), 1.66 (s, 3H, CH$_3$ DMNPA); ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$, HSQC, HMBC, HMBC-Gated) δ 175.0 (C=O DMNPA), 148.4, 145.7, 139.4, 138.4, 137.6, 137.5, 133.6, 131.2, 129.4, 128.7, 128.6, 128.6, 128.2, 128.2, 128.2, 128.1, 128.1, 128.1, 128.0, 127.9, 125.7, 124.9, 98.6 (C-1), 81.0 (C-3), 79.0 (C-2), 77.5 (C-4), 76.0, 75.5, 73.4, 72.7 – 71.5 (m, CH(CF$_3$)$_2$), 70.4 (C-5), 63.5 (C-6), 46.7 (C$_q$ DMNPA), 27.5 (CH$_3$ DMNPA), 27.5 (CH$_3$ DMNPA); ^{13}C-GATED NMR (126 MHz, CDCl$_3$) δ 98.6 ($J_{H1\text{-}C1}$ = 171 Hz, α); HRMS (ESI) M/Z: [M + NH$_4$]$^+$ Calcd for $C_{40}H_{43}F_6N_2O_9^+$ 809.2867; Found 809.2866.

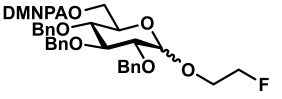


2,2,2-Trifluoroethyl 6-*O*-(2,2-dimethyl-2-(*ortho*-nitrophenyl)acetyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (S31). The title compound was prepared according to general procedure VI, using **7** as the donor and 2,2,2-trifluoroethanol as the acceptor. Flash column chromatography (100:0 → 90:10, pentane:EtOAc v:v) yielded the title compound (46 mg, 0.064 mmol, 64%, α:β; >98:2) as a colorless oil. TLC: R_f 0.40, (80:20, pentane:EtOAc, v:v); ^{1}H NMR (500 MHz, CDCl$_3$, HH-COSY, HSQC, HMBC, HMBC-Gated) δ 7.93 – 7.22 (m, 27H), 4.95 (d, *J* = 10.7 Hz, 1H), 4.82 – 4.73 (m, 3H), 4.75 (d, *J* = 3.5 Hz, 1H, H-1), 4.63 (d, *J* = 11.9 Hz, 1H), 4.47 (d, *J* = 10.6 Hz, 1H), 4.43 (dd, *J* = 11.8, 2.0 Hz, 1H, H-6), 4.09 (dd, *J* = 11.8, 6.0 Hz, 1H, H-6), 3.95 (t, *J* = 9.3 Hz, 1H, H-3), 3.75 (ddd, *J* = 10.2, 5.9, 1.9 Hz, 1H, H-5), 3.68 (q, *J* = 8.7 Hz, 2H, CH$_2$CF$_3$), 3.48 (dd, *J* = 9.6, 3.7 Hz, 1H, H-2), 3.28 (dd, *J* = 10.2, 8.9 Hz, 1H, H-4), 1.67 (s, 3H, CH$_3$ DMNPA), 1.66 (s, 3H, CH$_3$ DMNPA); ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$, HSQC, HMBC, HMBC-Gated) δ 175.0 (C=O DMNPA), 148.5, 145.8, 139.3, 138.6, 138.0, 137.7, 133.5, 131.2, 129.4, 128.6, 128.6, 128.6, 128.2, 128.1, 128.1, 128.0, 127.8, 125.7, 124.9, 124.3 (q, *J* = 277.6 Hz, CF$_3$), 97.2 (C-1), 81.4 (C-3), 79.7 (C-2), 77.7 (C-4), 76.0, 75.3, 73.3, 69.5, 63.7 (C-6), 64.21 (q, *J* = 34.9 Hz), 46.6 (C$_q$ DMNPA), 27.4 (CH$_3$ DMNPA, CH$_3$ DMNPA); ^{13}C-GATED NMR (126 MHz, CDCl$_3$) δ 97.2 ($J_{H1\text{-}C1}$ = 171 Hz, α); HRMS (ESI) M/Z: [M + NH$_4$]$^+$ Calcd for $C_{39}H_{44}F_3N_2O_9^+$ 741.2993; Found 741.2989.

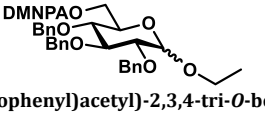


2,2-Difluoroethyl 6-*O*-(2,2-dimethyl-2-(*ortho*-nitrophenyl)acetyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (S32). The title compound was prepared according to general procedure VI, using **7** as the donor and 2,2-difluoroethanol as the acceptor. Flash column chromatography (95:5 → 85:15, pentane:EtOAc v:v) yielded the title compound (47 mg, 0.067 mmol, 67%, α:β; 90:10) as a colorless oil. TLC: R_f 0.31, (80:20, pentane:EtOAc, v:v); ^{1}H NMR (400 MHz, CDCl$_3$, HH-COSY, HSQC, HMBC, HMBC-Gated) δ 7.94 – 7.21 (m, 31H), 6.04 – 5.79 (m, 0.11H, CHCF$_2$ β), 5.85 (tt, *J* = 55.6, 4.4 Hz, 1H, CHCF$_2$ α), 4.95 (d, *J* = 10.7 Hz, 1H), 4.93 – 4.86 (m,

0.11H), 4.82 – 4.74 (m, 3H), 4.68 (d, *J* = 3.7 Hz, 1H, H-1 α), 4.62 (d, *J* = 11.9 Hz, 1H), 4.47 (d, *J* = 10.5 Hz, 1H), 4.43 (dd, *J* = 11.8, 2.0 Hz, 1H, H-6 α), 4.08 (dd, *J* = 11.8, 6.1 Hz, 1H, H-6 α), 4.00 (dd, *J* = 11.8, 6.1 Hz, 0.11H, H-6 β), 3.97 – 3.93 (t, *J* = 9.5, 1H, H-3 α), 3.78 (ddd, *J* = 10.1, 6.1, 1.9 Hz, 1H, H-5 α), 3.66 – 3.59 (m, 0.12H), 3.57 – 3.49 (m, 2H, CH_2CHF_2 α), 3.46 (dd, *J* = 9.7, 3.6 Hz, 1H, H-2 α), 3.37 (dd, *J* = 9.2, 7.8 Hz, 0.11H, H-2 β), 3.28 (dd, *J* = 10.1, 8.9 Hz, 1H, H-4 α), 1.67 (s, 3H, CH_3 DMNPA α), 1.66 (s, 3H, CH_3 DMNPA); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, HSQC, HMBC, HMBC-Gated) δ 175.0 (C=O α), 174.9 (C=O β), 148.5, 145.7, 139.2, 138.6, 138.4, 138.3, 138.0, 137.7, 137.7, 133.5, 131.2, 129.4, 128.6, 128.6, 128.5, 128.5, 128.3, 128.2, 128.2, 128.1, 128.1, 128.1, 128.0, 127.9, 127.8, 125.8, 124.9, 114.05 (t, *J* = 241.3 Hz, CHF_2), 103.8 (C-1 β), 97.4 (C-1 α), 84.3 (C-3 β), 82.1 (C-2 β), 81.6 (C-3 α), 79.8 (C-2 α), 77.9 (C-4 α), 77.8 (C-4 β), 76.0, 75.9, 75.3, 75.1, 75.0, 73.4, 73.1 (C-5 β), 69.3 (C-5 α), 66.9 (t, *J* = 28.9 Hz, CH_2CHF_2), 63.8 (C-6 α), 63.4 (C-6 β), 46.7 (C_q DMNPA β), 46.6 (C_q DMNPA α), 27.5 (CH_3 DMNPA β), 27.4 (CH_3 DMNPA α, CH_3 DMNPA α), 27.1 (CH_3 DMNPA β); ^{13}C-GATED NMR (126 MHz, $CDCl_3$) δ 103.8 ($J_{H1\text{-}C1}$ = 160 Hz, β), 97.4 ($J_{H1\text{-}C1}$ = 168 Hz, α); HRMS (ESI) M/Z: $[M + NH_4]^+$ Calcd for $C_{39}H_{45}F_2N_2O_9^+$ 723.3088; Found 723.3085.



2-Fluoroethyl 6-*O*-(2,2-dimethyl-2-(*ortho*-nitrophenyl)acetyl)-2,3,4-tri-*O*-benzyl-D-glucopyranoside (S33). The title compound was prepared according to general procedure VI, using **7** as the donor and 2-Fluoroethanol as the acceptor. Flash column chromatography (90:10 → 75:25, pentane:EtOAc v:v) yielded the title compound (43 mg, 0.063, 63% mmol, α:β; 70:30) as a colorless oil. TLC: R_f 0.24, (80:20, pentane:EtOAc, v:v); ^1H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC, HMBC-Gated) δ 7.95 – 7.18 (m, 44H), 4.99 – 4.89 (m, 2H), 4.82 – 4.74 (m, 4H), 4.73 (d, *J* = 3.6 Hz, 1H, H-1 α), 4.69 (d, *J* = 10.9 Hz, 0.55H, C*H*H Bn β), 4.67 – 4.43 (m, 8H), 4.42 (d, *J* = 7.8 Hz, 0.45H, H-1 β), 4.11 (dd, *J* = 11.8, 5.5 Hz, 1H, H-6 α), 4.04 (dd, *J* = 11.7, 5.7 Hz, 1H, H-6 βffzgff), 4.01 – 3.91 (m, 2H), 3.87 – 3.73 (m, 2H), 3.70 – 3.53 (m, 3H), 3.50 – 3.43 (m, 2H), 3.38 (dd, *J* = 9.2, 7.8 Hz, 0.45H, H-2 β), 3.34 – 3.26 (m, 2H), 1.68 (s, 1.35H, CH_3 DMNPA β), 1.67 (s, 1.35H, CH_3 DMNPA β), 1.67 (s, 3H, CH_3 DMNPA α), 1.66 (s, 3H, CH_3 DMNPA α); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, HSQC, HMBC, HMBC-Gated) δ 175.0 (C=O α), 175.0 (C=O β), 148.7, 148.6, 145.7, 139.3, 139.3, 138.7, 138.5, 138.5, 138.4, 138.2, 137.9, 137.8, 133.4, 133.3, 131.2, 129.4, 128.6, 128.6, 128.5, 128.5, 128.5, 128.4, 128.4, 128.2, 128.2, 128.2, 128.1, 128.1, 128.1, 128.0, 128.0, 128.0, 127.8, 127.8, 127.8, 125.7, 125.7, 124.9, 103.5 (C-1 β), 96.9 (C-1 α), 84.4 (C-3 β), 82.7 (d, *J* = 169.6 Hz, CH_2F β), 82.2 (C-2 β), 82.4 (d, *J* = 169.9 Hz, CH_2F α), 81.8 (C-3 α), 80.0 (C-2 α), 78.0 (C-4 α), 77.9 (C-4 β), 75.9, 75.9, 75.3, 75.1, 74.9, 73.2, 72.9 (C-5 β), 68.9 (C-5 α), 68.7 (d, *J* = 20.0 Hz, CH_2CH_2F β), 66.7 (d, *J* = 20.4 Hz, CH_2CH_2F α), 63.8 (C-6 α), 63.5 (C-6 β), 46.7 (C_q DMNPA α, C_q DMNPA β), 27.4 (CH_3 DMNPA β), 27.4 (CH_3 DMNPA β), 27.4 (CH_3 DMNPA α, CH_3 DMNPA β); ^{13}C-GATED NMR (126 MHz, $CDCl_3$) δ 103.5 ($J_{H1\text{-}C1}$ = 158 Hz, β), 96.9 ($J_{H1\text{-}C1}$ = 168 Hz, α); HRMS (ESI) M/Z: $[M + NH_4]^+$ Calcd for $C_{39}H_{46}FN_2O_9^+$ 705.3182; Found 705.3179.



Ethyl 6-*O*-(2,2-dimethyl-2-(*ortho*-nitrophenyl)acetyl)-2,3,4-tri-*O*-benzyl-D-glucopyranoside (S34). The title compound was prepared according to general procedure VI, using **7** as the donor and ethanol as the acceptor. Flash column chromatography (100:0 → 80:20, pentane:EtOAc v:v) yielded the title compound (52 mg, 0.078 mmol, 78%, α:β; 60:40) as a colorless oil. TLC: R_f 0.44, (80:20, pentane:EtOAc, v:v); ^1H NMR (500 MHz, $CDCl_3$, HH-COSY, HSQC, HMBC, HMBC-Gated) δ7.7 – 7.2 (m, 95H), 5.0 (d, *J* = 10.7 Hz, 1H), 5.0 – 4.7 (m, 12H), 4.7 (d, *J* = 3.6 Hz, 1H, H-1 α), 4.7 – 4.4 (m, 7H), 4.4 (d, *J* = 7.8 Hz, 1H, H-1 β), 4.1 (dd, *J* = 11.8, 5.7 Hz, 1H, H-6 α), 4.0 (dd, *J* = 11.7, 6.1 Hz, 1H, H-6 β), 4.0 (d, *J* = 9.2 Hz, 1H, H-3 α), 3.9 – 3.8 (m, 2H), 3.6 (t, *J* = 9.1 Hz, 1H, H-3 β), 3.6 – 3.2 (m, 9H), 1.7 (s, 3H, CH_3 DMNPA α), 1.7 (s, 3H, CH_3 DMNPA β), 1.7 (s, 3H, CH_3 DMNPA α), 1.7 (s, 3H, CH_3 DMNPA β), 1.2 (t, *J* = 7.2 Hz, 3H, CH_3 Et β), 1.1 (t, *J* = 7.1 Hz, 3H, CH_3 Et α); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$, HSQC, HMBC, HMBC-Gated) δ 175.1 (C=O β), 175.0 (C=O α), 145.7, 139.4, 139.3, 139.2, 138.8, 138.6, 138.6, 138.3, 138.3, 138.1, 137.9, 137.9, 137.7, 133.5, 131.2, 129.4, 129.0, 128.6, 128.6, 128.6, 128.6, 128.5, 128.5, 128.5, 128.2, 128.2, 128.2, 128.2, 128.1, 128.1, 128.0, 127.9, 127.8, 127.8, 127.8, 125.8, 125.7, 124.9, 103.3 (C-1 β), 96.2 (C-1 α), 84.6 (C-3 β), 82.4 (C-2 β), 82.0 (C-3 α), 80.1 (C-2 α), 78.3, 78.2, 75.9, 75.9, 75.3, 75.1, 74.9, 73.2, 72.9, 68.8, 65.5 (C-6 β), 63.9 (CH_2 α), 63.8 (CH_2 β), 63.1 (C-6 α), 46.7 (C_q DMNPA α), 46.7 (C_q DMNPA β), 27.4 (CH_3 DMNPA α), 27.4 (CH_3 DMNPA α, CH_3 DMNPA β), 27.4 (CH_3 DMNPA β), 15.5, 15.0; ^{13}C-GATED NMR (126 MHz, $CDCl_3$) δ 103.3 ($J_{H1\text{-}C1}$ = 157 Hz, β), 96.2 ($J_{H1\text{-}C1}$ = 167 Hz, α); HRMS (ESI) M/Z: $[M + NH_4]^+$ Calcd for $C_{39}H_{47}N_2O_9^+$ 687.3276; Found 687.3278.

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