Structure-reactivity relationships in glycosylation chemistry

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Chapter 3: Acceptor nucleophilicity – Glycosylation stereoselectivity mapping for all eight diastereomeric pyranosyl donors

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Introduction

Upon activation of a glycosyl donor in a glycosylation reaction, a mixture of different reactive intermediates is formed (***Figure 1***). Depending on the glycosyl donor, the activator, the acceptor (NuH) and external factors, the α-product, the β-product or a mixture thereof can be formed, through a S_N2 mechanism, featuring a covalent reactive intermediate or a S_N1-like mechanism, operating via an oxocarbenium ion intermediate.[1-4] Insight into the "extremes of the mechanistic spectrum" can help to better understand and eventually predict the stereochemical outcome of glycosylation reactions taking place somewhere along the mechanism continuum. The previous Chapter deals with the S_N1 side of the spectrum by determining the influence of the substitution pattern of the sugar ring on the conformational preference and reactivity of the intermediate oxocarbenium ions, using a combination of computational chemistry and glycosylation experiments with C- and D-nucleophiles. This Chapter will focus on the other end of the mechanistic spectrum by investigating the covalent intermediates and the influence of the reactivity of the acceptor on the S_N2 mechanism. For S_N1 reactions and the associated oxocarbenium ions, it is clear that the functional groups on C-2, C-3, C-4 and C-6 heavily influence the outcome,[5-7] with the stereochemistry of C-2 playing an all important role (*this thesis, Chapter 2).* To systematically map the influence of the ring substitution pattern of the donor in S_N2-type glycosylations, in the study of this Chapter all eight diastereomeric pyranosyl thiophenol donors[‡] were used (***Figure 2A***) while the reactive intermediates, formed upon activation were characterised using variable temperature (VT)-NMR. While VT-NMR has been used to detect many covalent species for the usual monosaccharides (predominantly triflates and oxosulfonium triflates)[8-15] the reactive intermediates for the more rare diastereomers have not yet been identified.

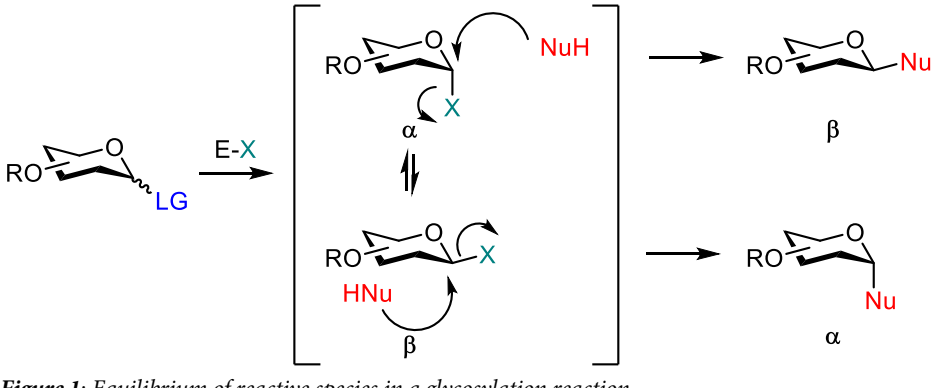


Figure 1*: Equilibrium of reactive species in a glycosylation reaction,*

[‡] For the synthesis of the allose, altrose, gulose, idose and talose donor, see Chapter 2

After establishing of the structure of the species formed upon activation of the eight diastereomeric pyranosyl donors, the effect of the nucleophilicity of the acceptor on the stereoselectivity of the glycosylations was mapped. To this end the well-established set of fluorinated model alcohols (***Figure 2B***) was used. Of these, the most reactive acceptor -ethanol- has been shown to react with relatively stable covalent intermediates (generally the axially oriented α-triflates), while the weaker nucleophiles (such as trifluorethanol) require a more potent electrophile, such as a β-triflate or more dissociated oxocarbenium ion-triflate ion pair.[9, 10, 14, 16-19]

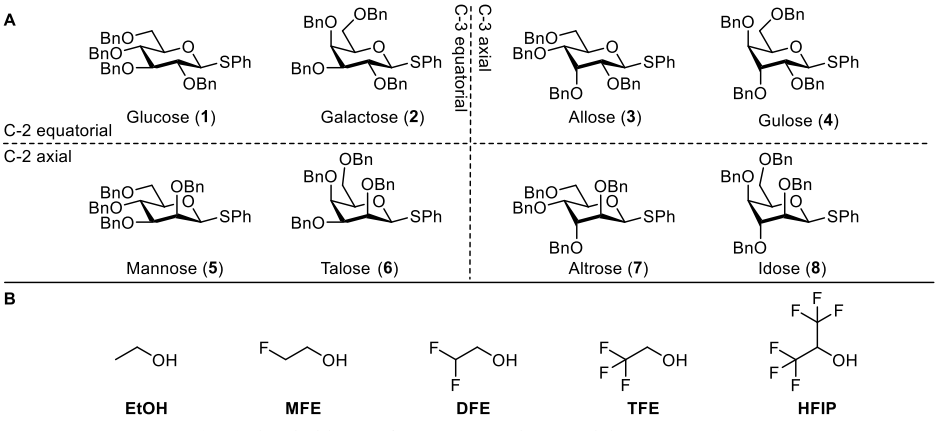


Figure 2: A: *Donors (1-8) divided by configuration and* ***B****: model acceptors (EtOH, MFE, DFE, TFE and HFIP) used in this study.*

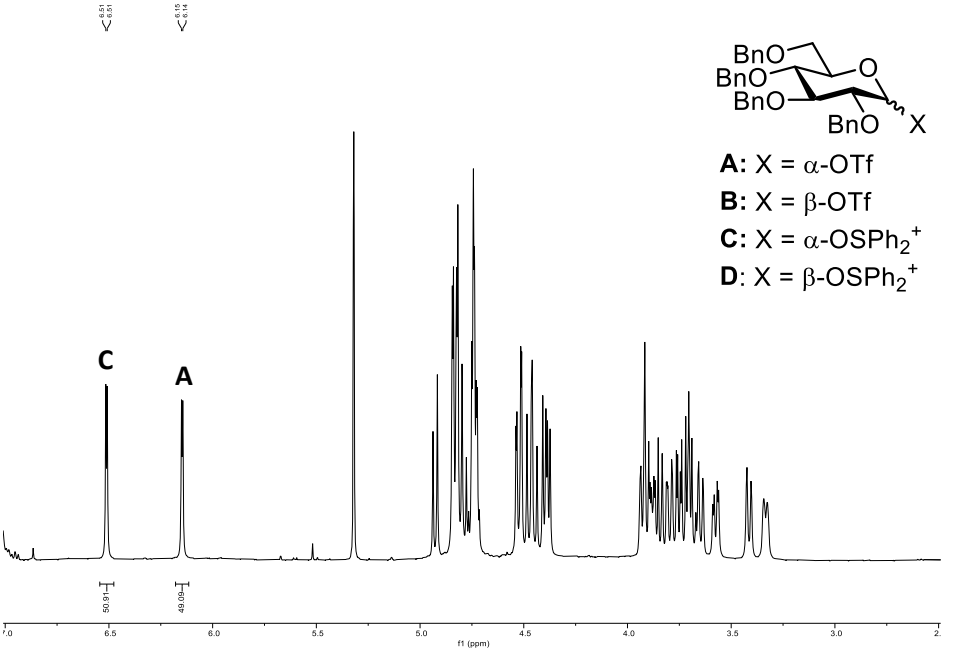
Results and discussion

Characterisation of reactive intermediates

To study the glycosylating properties of the glycosyl donors **1**-**8** their activation and the formation of reactive intermediates was studied by VT-NMR (***Figure* 3**-**6**). To this end, a mixture of the donor (1 eq) and Ph_2SO (1.3 eq) in CD_2Cl_2 (50 mM) was cooled to -80 °C, after which Tf_2O (1.3 eq) added. The reaction mixture was then allowed to warm to -60 °C after which the reactive species were characterized. To aid in the identification some experiments were repeated using 3 eq. Ph_2SO, promoting the formation of sulfoxonium triflate species. The results of the VT-NMR are summarized in ***Table 1***.

When glucose donor **1** was activated, a mixture of two species was formed (***Figure* 3)**, which were identified as the α-triflate (**A**, H-1: 6.15 (d, *J* = 3.1 Hz)), previously reported in literature,[20, 21] and the α-oxosulfonium triflate (**C**, H-1: 6.51 (d, *J* = 3.4 Hz)). Galactose **2** gave three species upon activation: the α-triflate (**A**, H-1: 6.19 (d, *J* = 3.3 Hz)), the α-oxosulfonium triflate (**C**, H-1: 6.43 (d, *J* = 3.5 Hz)) and the β-oxosulfonium triflate (**D**, H-1: 5.50 (d, *J* = 7.9 Hz)), of which the α-triflate has previously been described.[21] Both allose (**3)** and gulose donor (**4**, ***Figure* 4)** gave the α- and β-oxosulfonium triflates upon activation (for allose: **C**, H-1: 6.13 (d, *J* = 3.7 Hz) and **D**, H-1: 5.79 (d, *J* = 7.8 Hz); for gulose: **C**, H-1: 6.21 (d, *J* = 3.6 Hz) and (**D**, H-1: 5.80 (d, *J* = 8.1 Hz)). The latter two donors provide significantly more of the β-oriented covalent species, which can be directly related to the axial C-3-substituent that destabilizes the α-oriented triflate and oxosulfonium triflate through 1,3-diaxial interactions. Activation of mannose donor (**5**, ***Figure* 5)**, led to three species: the α-triflate (**A**, H-1: 6.10 (s)), the α-oxosulfonium triflate (**C**, H-1: 6.44 (s)) and the β-oxosulfonium triflate (**D**, H-1: 5.86 (s)). It has been argued that mannosyl β-triflates cannot be formed because of their instability, that results from the unfavourable orientation with respect to the ring oxygen and the C-2-substituent (the so called Δ2-effect). The formation of the β-oxosulfonium triflate however indicates that a role for these species in the glycosylation manifold should not *a priori* be ruled out. Of note, for a conformationally restricted mannose-type donor a β-oxosulfonium triflate has also been reported.[22] The α-triflate and α-oxosulfonium triflate have previously been characterised for the tetra-*O*-methyl donor.[23, 24] Talose (**6**, ***Figure* 5)**, forms the α-triflate upon activation (**A**, H-1: 6.17 (s)) as well as an α-oxosulfonium triflate (**C**, H-1: 6.28 (s)). No β-oriented species could be identified from the mixture of this active donor. Altrose (**7**, ***Figure* 6)** also gave two α-oriented species upon activation: the α-triflate (**A**, H-1: 5.96 (s)) and the α-oxosulfonium triflate (**C**, H-1: 6.26 (s)). The activation of Idose (**8**, ***Figure* 6)** under the standard conditions led to the formation of a side product, which unfortunately could not be characterized. This may be due to the relatively high reactivity of the idose donor, resulting from the three axial ring substituents.[25] When three equivalents of Ph_2SO were used for the activation the α-triflate (**A**, H-1: 6.17 (s)) as well as the α-oxosulfonium triflate (**C**, H-1: 6.28 (s)) were formed

1H-NMR of activated donor 1



1H-NMR of activated donor 2

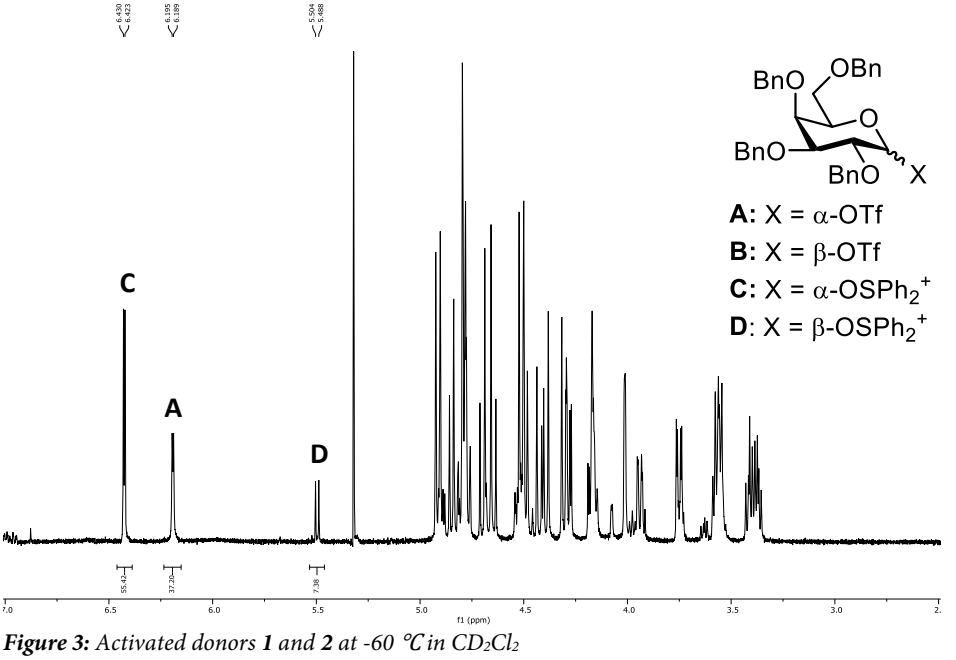
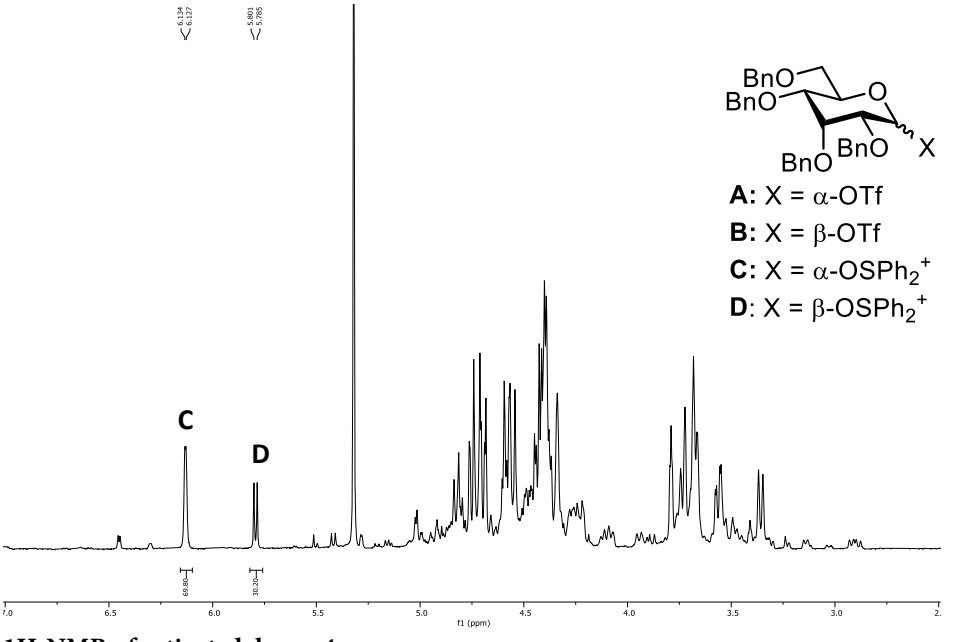


Figure 3: *Activated donors **1** and **2** at -60 ℃ in CD_2Cl_2*

1H-NMR of activated donor 3



1H-NMR of activated donor 4

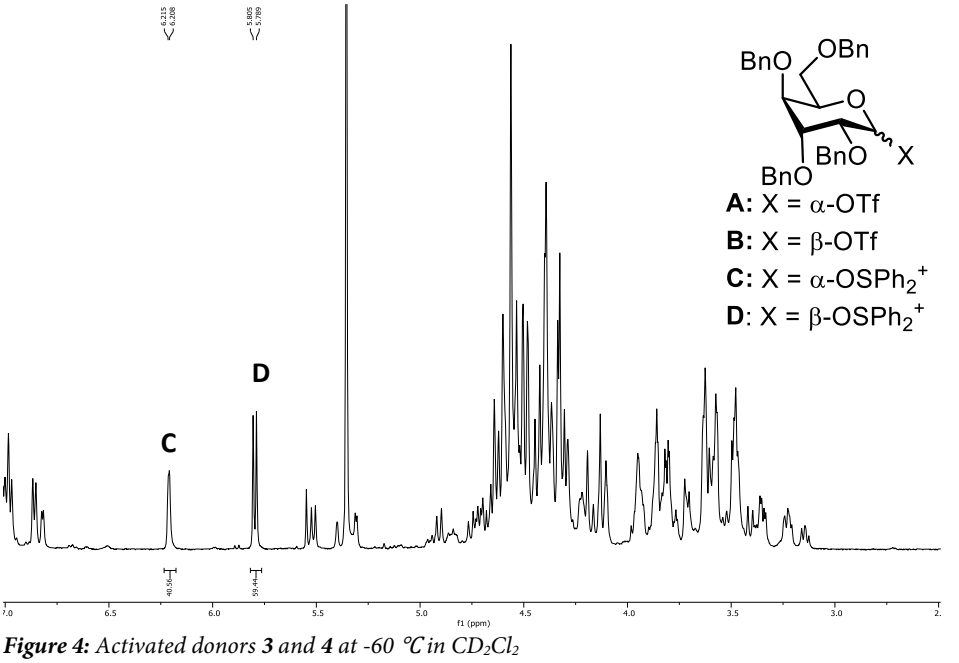
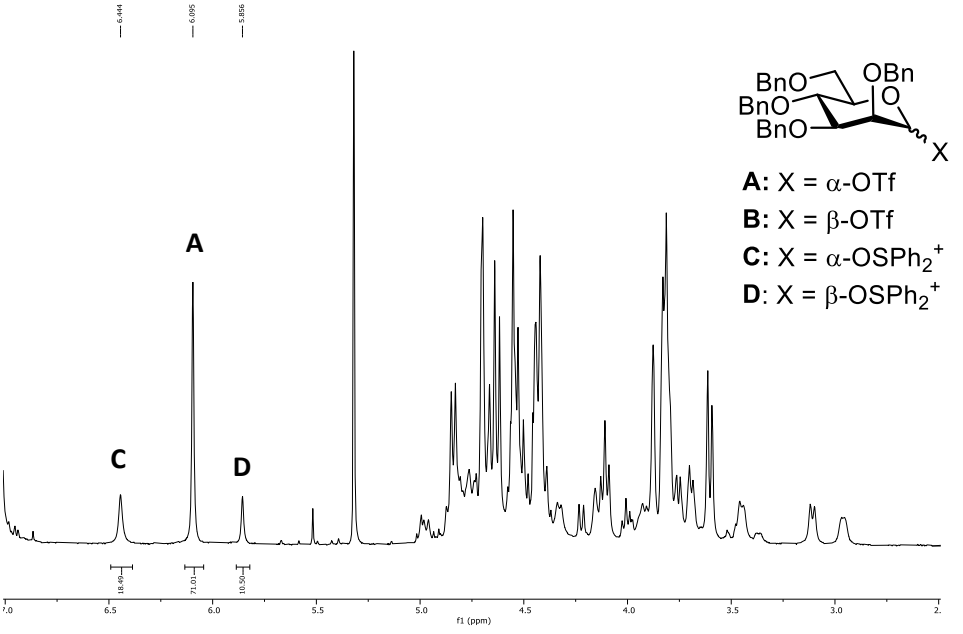


Figure 4: *Activated donors **3** and **4** at -60 ℃ in CD_2Cl_2*

1H-NMR of activated donor 5



1H-NMR of activated donor 6

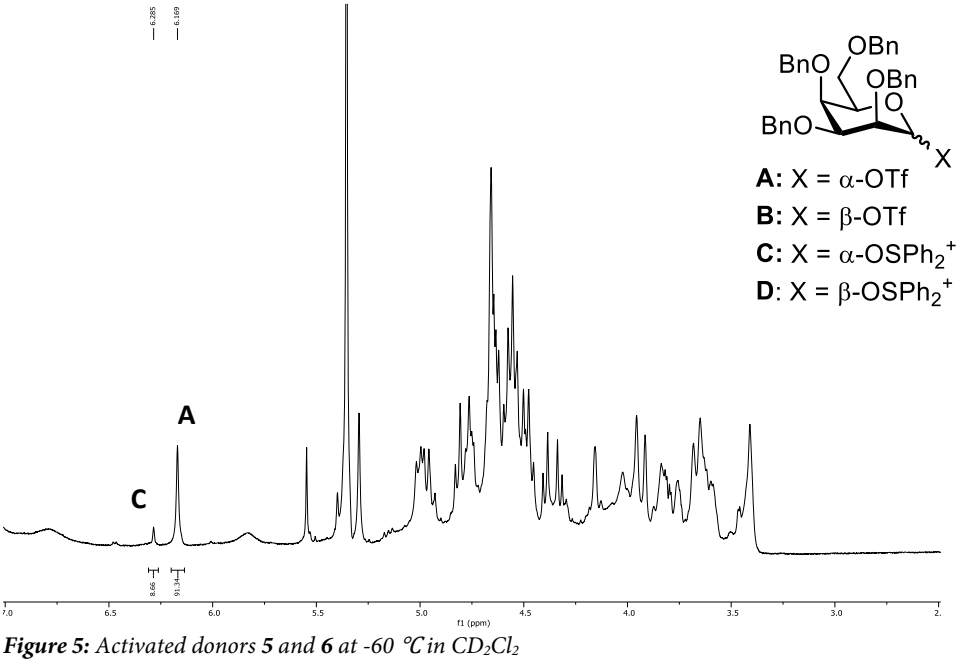
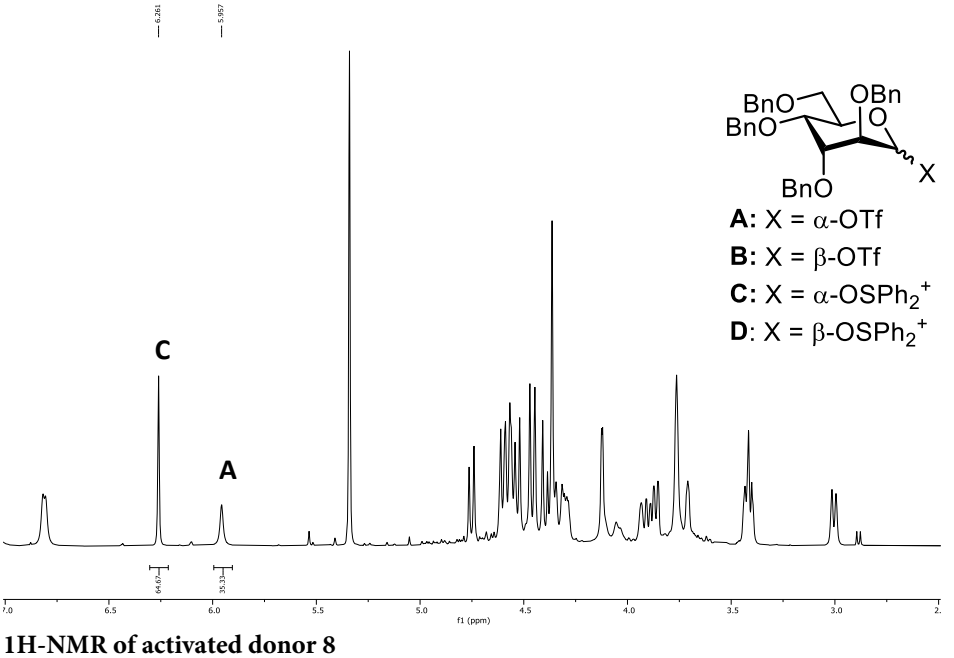


Figure 5: *Activated donors* ***5*** *and* ***6*** *at -60 °C in* CD_2Cl_2

1H-NMR of activated donor 7



1H-NMR of activated donor 8

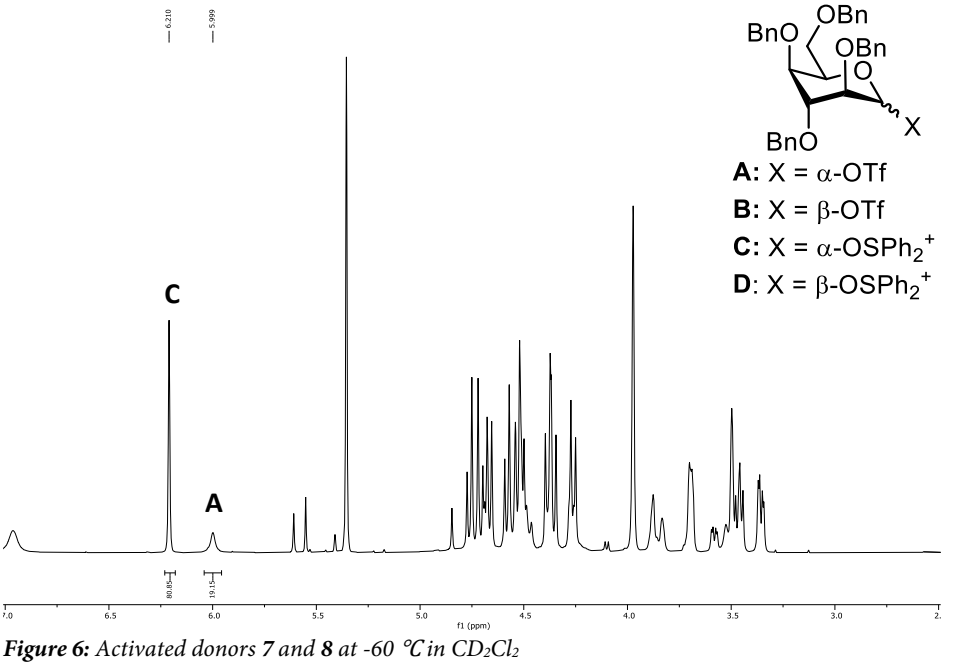


Figure 6: *Activated donors **7** and **8** at -60 °C in CD_2Cl_2*

Table 1: *Reactive species observed with VT-NMR at -60 °C. n.d. = not detected*

Donor	H-1 : δ (multiplicity, J_{H1-H2})				ratio
	α-OTf (A)	β-OTf (B)	α-$OSPh_2^+$ (C)	β-$OSPh_2^+$ (D)	
Glucose (1)	6.15 (d, *J* = 3.1 Hz)	n.d.	6.51 (d, *J* = 3.4 Hz)	n.d.	A:C 49:51
Galactose (2)	6.19 (d, *J* = 3.3 Hz)	n.d.	6.43 (d, *J* = 3.5 Hz)	5.50 (d, *J* = 7.9 Hz)	A:C:D 37:55:7
Allose (3)	n.d.	n.d.	6.13 (d, *J* = 3.7 Hz)	5.79 (d, *J* = 7.8 Hz)	C:D 70:30
Gulose (4)	n.d.	n.d.	6.21 (d, *J* = 3.6 Hz)	5.80 (d, *J* = 8.1 Hz)	C:D 41:59
Mannose (5)	6.10 (s)	n.d.	6.44 (s)	5.86 (s)	A:C:D 71:18:11
Talose (6)	6.17 (s)	n.d.	6.28 (s)	n.d	A:C 91:9
Altrose (7)	5.96 (s)	n.d.	6.26 (s)	n.d	A:C 35:65
Idose (8)[a]	6.00 (s)	n.d.	6.21 (s)	n.d	A:C 19:81

a: 3 eq. of Ph_2SO were used, in VT-NMR with 1.3 eq. Ph_2SO only an yet unidentified decomposition product was found.

Reactions with *O*-nucleophiles

Next, all eight pyranosyl donors were glycosylated with five different acceptors of different nucleophilicity (EtOH, MFE, DFE, TFE and HFIP) to probe the relation between stereoselectivity of the glycosylation reaction and reactivity of the acceptor.[9, 10, 17, 18] The results of these glycosylations are summarized in ***Table 2***, together with the results of the glycosylation of the donors with the S_N1 model nucleophile TES-D (*This thesis, chapter 2*). In Table 2, the donors are organized by configuration of their C-2 and C-3 substituents to highlight the correlation between the orientation of these substituents and the reactivity-stereoselectivity trends. Of note, the selectivity of HFIP, the weakest *O*-nucleophile, differs significantly form the selectivity obtained with TES-D. TES-D gives *cis* selectivity with respect to the C-2-OBn (α when C-2-OBn is equatorial and β when C-2-OBn is axial), while the glycosylations of HFIP selectively provide the α-products, regardless of the stereochemistry of C-2. The differences between the results of the "S_N1 nucleophile" TES-D and HFIP suggest that reactions between a glycosyl donor and a weak *O*-nucleophile follow a different pathway than nucleophilic addition to an oxocarbenium ion. Another clear trend when looking at the stereoselectivity trends going from ethanol (EtOH) to 2,2,2-trifloroethanol (TFE) is observed for the donors having an equatorial C-3-OBn group (*i.e.* glucose, galactose, mannose and talose, **1**, **2**, **5** and **6** respectively): the stereoselectivity observed for these donors gradually changes as a function of acceptor nucleophilicity with the more nucleophilic acceptors giving more β-product and the less nucleophilic acceptors providing more α-product. When the C-3-OBn group is axial (as in the allose, gulose, altrose and idose donors **3**, **4**, **7** and **8**) no clear acceptor reactivity-stereoselectivity relationship was found. A potential mechanistic rationale for these observations is depicted in ***Figure 7***. For the donors with an equatorial C-3-OBn, the α-triflate or α-oxosulfonium triflate are more stable than the β-species, as revealed by the VT-NMR experiments. The α-species can be in equilibrium with the more reactive β-intermediates, that can form, as indicated by the observation of the galactose and mannose β-oxosulfonium triflates. The most reactive acceptors can substitute the α-triflate or α-oxosulfonium triflates to provide the β-product. With gradually decreasing acceptor reactivity, substitution of the more reactive β-intermediates will become more important, leading to the formation of more α-product (***Figure 7A***). In the donors having a C-3-OBn is axial, the difference in stability between the α-species and the β-species is smaller because of the 1,3-diaxial interactions between the α-(oxosulfonium) triflate on C-1 and the OBn-group on C-3.[26] However, in the S_N2-type substitution on the β-species, the trajectory for the incoming nucleophile is also hindered by the C-3-OBn group (***Figure 7B***). Thus, the 'conflicting' steric interactions lead to overall poor stereoselectivity in the glycosylation reactions.

Table 2: *Stereoselectivity of all eight pyranosyl donors with O-nucleophiles and TES-D. Selectivity is given as the α:β ratio in the glycosylation product. Eq = equatorial, Ax = axial n.d. = not determined*

Donor	C-2	C-3	TES-D	HFIP	TFE	DFE	MFE	EtOH
1 Glc	Eq	Eq	**1A** **>98:2** (70%)	**1F** **>98:2** (41%)	**1E** **75:25** (80%)	**1D** **48:52** (58%)	**1C** **36:64** (75%)	**1B** **15:85** (70%)
2 Gal	Eq	Eq	**2A** **>98:2** (86%)	**2F** **>98:2** (33%)	**2E** **87:13** (79%)	**2D** **66:34** (69%)	**2C** **31:69** (84%)	**2B** **17:83** (73%)
3 All	Eq	Ax	**3A** **>98:2** (74%)	**3F** **>98:2** (30%)	**3E** **50:50** (68%)	**3D** **58:42** (60%)	**3C** **55:45** (n.d.)[a]	**3B** **46:54** (45%)
4 Gul	Eq	Ax	**4A** **>98:2** (83%)	**4F** **>98:2** (39%)	**4E** **60:40** (85%)	**4D** **69:31** (83%)	**4C** **83:17** (85%)	**4B** **78:22** (94%)
5 Man	Ax	Eq	**5A** **3:97** (93%)	**5F** **>98:2** (39%)	**5E** **>98:2** (84%)	**5D** **80:20** (65%)	**5C** **60:40** (75%)	**5B** **33:67** (70%)
6 Tal	Ax	Eq	**6A** **<2:98** (51%)	**6F** **>98:2** (14%)	**6E** **90:10** (69%)	**6D** **86:14** (73%)	**6C** **80:20** (74%)	**6B** **68:32** (70%)
7 Alt	Ax	Ax	**7A** **20:80** (55%)	**7F** **>98:2** (16%)	**7E** **85:15** (73%)	**7D** **69:31** (64%)	**7C** **58:42** (60%)	**7B** **75:25** (79%)
8 Ido	Ax	Ax	**8A** **<2:98** (74%)	**8F** **>98:2** (22%)	**8E** **69:31** (66%)	**8D** **55:45** (72%)	**8C** **57:43** (72%)	**8B** **57:43** (76%)

*For reactions with TES-D, see chapter 2. The stereoselectivity of donors **1**, **2** and **5** was previously published.[19] a: an accurate yield can't be determined because of poor separation of the glycosylated product from the hydrolysed donor*

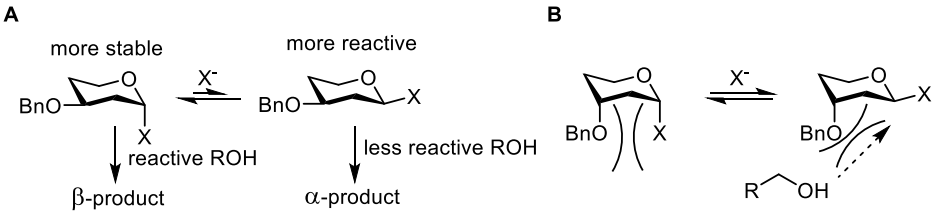


Figure 7: *The impact of the orientation of the C-3-OBn on the acceptor reactivity-stereoselectivity trends. A: For donors having an equatorial C-3-OBn the α-oriented intermediates are more stable, and the β-intermediates are more reactive. The most nucleophilic acceptors can react with the more prevalent former species, while less reactive acceptors need a stronger electrophile. Through a Curtin-Hammett type scenario, the reaction of the poor nucleophiles will shift to the substitution of the β-configured intermediates. B: The axial C-3-OBn destabilizes the α-triflate and oxosulfonium triflate, favoring the formation of the corresponding β-species, but also hinders nucleophilic attack of the incoming nucleophile on the β-species.*

Conclusion

After the investigation of the S_N1 side of the glycosylation as outlined in Chapter 2, the research of this chapter has characterized the covalent reactive species of all eight pyranosyl donors that play a role on the S_N2-side of the glycosylation reaction mechanism continuum. VT-NMR was used to characterise the reactive intermediates. In general, activation of the glycosyl donors leads to the preferential formation of α-triflates and α-oxosulfonium triflates. The galactose and mannose donors do provide a minor amount of the β-oxosulfonium triflate, while activation of the allose and especially the gulose donor, both having an axial C-3-group, leads to the generation of a significant amount of the equatorially oriented oxosulfonium species. Even though only minor amounts of the β-oxosulfonium triflates are formed, the existence of these species indicates that they may play a role in the glycosylation reactions of the different donors. Next, the eight pyranosyl donors were reacted with a set of model acceptors of gradually changing nucleophilicity. From the glycosylation with fluorinated acceptors, it becomes clear that, while S_N1 reactions are typically *1,2-cis* selective as observed by glycosylation with TES-D and supported by CEL-maps of the oxocarbenium ions, glycosylation of (very) weak *O*-nucleophiles always provide the α-product, regardless of the stereochemistry at C-2. This shows that the reactions of weak C/D or O-nucleophiles do not proceed via the same pathway. This discrepancy can be explained by the different nature of the nucleophiles and stereoelectronic effects that play a role in the transition states of the addition reactions to the oxocarbenium ions. The development of a stabilizing anomeric effect may promote the formation of the α-products and H-bonding effects between the nucleophile and donor species will also play a role in shaping the trajectory of the incoming O-nucleophiles. However, the acceptor reactivity-stereoselectivity trends observed here, can also be accounted for

with S_N2-type product forming reaction pathways. For the donors having an equatorially oriented C-3-OBn group, a clear shift from β- to α-selectivity was observed with decreasing nucleophilicity of the acceptor. Through a Curtin-Hammett kinetic scenario, in which the weaker nucleophiles preferentially react with the less available but more reactive intermediates, the acceptor reactivity-stereoselectivity trends can be explained. The donors that carry an axial C-3-OBn group typically provide mixtures of anomers in a ratio that shows no clear correlation with the nucleophilicity of the acceptor. To better understand the stereochemical outcome of the glycosylations studied here, systematic computational studies into the nature of the different transition states as well as kinetic studies, supplemented by the establishment of kinetic isotope effects will prove valuable.

Experimental

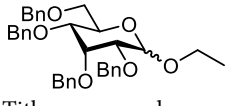
Procedure for VT-NMR experiments of glycosyl donors

A mixture of donor (30 μmol) and Ph_2SO (39 μmol or 90 μmol) was coevaporated with toluene, dissolved in 0.6 mL of CD_2Cl_2 under nitrogen atmosphere and transferred to an oven-dried NMR tube flushed with nitrogen gas and sealed with an NMR tube septum. The magnet was cooled to -80 °C, locked, and shimmed and the sample was measured prior to activation. In a separate cold bath (-80 °C) the sample was treated with Tf_2O (39 μmol) and shaken and recooled 3x. The cold sample was wiped dry and quickly inserted back in the cold magnet. The first ^1H NMR spectrum was immediately recorded. The sample was then reshimmed, and spectra were recorded in 10 °C intervals with at least 5 min of equilibration time for every temperature.

General procedure for Ph_2SO/Tf_2O mediated glycosylations

Donor (0.1 mmol, 1 eq), Ph_2SO (0.13 mmol, 1.3 eq) and TTBP (0.25 mmol, 2.5 eq) were coevaporated twice with toluene, dissolved in 2 mL DCM and stirred for 30 min at RT with 3 Å molecular sieves. The solution was cooled to -80 ^{0}C and Tf_2O (22 μL, 0.13 mmol, 2 eq) was added. The reaction mixture was allowed to warm to −60 ^{0}C and then recooled to −80 ^{0}C, after which the acceptor (0.2 mmol, 2 eq) in DCM (0.4 mL, 0.5 M) was added. The reaction mixture was allowed to warm to −60 ^{0}C for and stirred for 2 hr at that temperature. The reaction was quenched with 2 mL sat aq $NaHCO_3$, and the mixture was diluted with DCM. The solution was transferred to a separatory funnel, water was added, the layers were separated, and the water phase was extracted once more with DCM. The combined organic layers were dried over MgSO4, filtered, and concentrated in vacuo. Purification by silica gel flash column chromatography and/or sephadex LH-20 size-exclusion chromatography yielded the glycosylation product as a mixture of anomers.

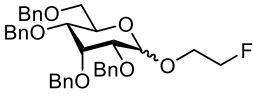
Ethyl-2,3,4,6-tetra-O-benzyl-α,β-D-allopyranoside (3B)



Title compound was prepared according to the general procedure for Ph_2SO/Tf_2O mediated glycosylations with donor **3** and ethanol, yielding compound **3B** (25 mg, 45 μmol, 45%, colourless oil, α:β = 46:54). An analytical amount was separated of both anomers was separated for characterisation. α-anomer: ^1H NMR (400 MHz, $CDCl_3$) δ, 7.35 – 7.15 (m, 20H, CH_{arom}), 4.97 (d, *J* = 12.3 Hz, 1H, C*H*H Bn), 4.92 (d, *J* = 4.0 Hz, 1H, H-1), 4.83 (d, *J* = 12.3 Hz, 1H, CH*H* Bn), 4.64 – 4.56 (m, 3H, C*H*H Bn, CH_2 Bn), 4.52 – 4.45 (m, 2H, C*H*H Bn, CH*H* Bn), 4.37 (d, *J* = 11.6 Hz, 1H, CH*H* Bn), 4.27 (dt, *J* = 10.1, 2.5 Hz, 1H, H-5), 4.18 (t, *J* = 2.8 Hz, 1H, H-3), 3.85 – 3.74 (m, 2H, C*H*H Et, H-6), 3.67 (dd, *J* = 10.5, 2.1 Hz, 1H, H-6), 3.60 – 3.49 (m, 2H, CH*H* Et, H-4), 3.43 (dd, *J* = 4.1, 2.8 Hz, 1H, H-2), 1.28 (t, *J* = 7.1 Hz, 3H, CH_3 Et) ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.7, 139.7, 138.3, 138.2 (C_q), 131.2, 129.5, 128.5, 128.4, 128.4, 128.0, 128.0, 127.9, 127.9, 127.8, 127.8, 127.7, 127.1, 124.9 (CH_{arom}), 97.0 (C-1), 76.7 (C-2), 74.9 (C-4), 73.7, 73.5 (CH_2 Bn), 72.6 (C-3), 71.2, 71.2 (CH_2 Bn), 69.0 (C-6), 66.2 (C-5), 63.9 (CH_2 Et), 15.4 (CH_3 Et); β-anomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.04 (m, 20H, CH_{arom}), 4.93 – 4.84 (m, 3H, 2x C*H*H Bn, H-1), 4.79 (d, *J* = 12.0 Hz, 1H, CH*H* Bn), 4.68 – 4.57 (m, 2H, C*H*H Bn, CH*H* Bn), 4.54 (d, *J* = 12.3 Hz,

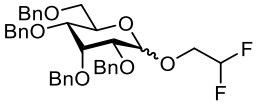
1H, CH*H* Bn), 4.47 (d, *J* = 11.5 Hz, 1H, C*H*H Bn), 4.35 (d, *J* = 11.5 Hz, 1H, CH*H* Bn), 4.10 (t, *J* = 2.6 Hz, 1H, H-3), 4.06 (ddd, *J* = 9.8, 4.8, 1.9 Hz, 1H, H-5), 3.99 (dq, *J* = 9.5, 7.1 Hz, 1H, C*H*H Et), 3.76 (dd, *J* = 10.7, 1.9 Hz, 1H, H-6), 3.70 – 3.55 (m, 2H, CH*H* Et, H-6), 3.45 (dd, *J* = 9.8, 2.5 Hz, 1H, H-4), 3.24 (dd, *J* = 7.9, 2.7 Hz, 1H, H-2), 1.27 (t, *J* = 7.0 Hz, 3H, CH_3 Et) ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.2, 139.0, 138.6, 138.0 (C_q), 128.5, 128.4, 128.4, 128.3, 128.0, 127.9, 127.9, 127.8, 127.7, 127.6, 127.6, 127.4 (CH_{arom}), 101.1 (C-1), 79.1 (C-2), 75.9 (C-4), 74.9 (C-3), 74.5, 73.6, 73.2 (CH_2 Bn), 72.5 (C-5), 71.6 9, CH_2 Bn), 69.6 (C-6), 65.5 (CH_2 Et), 15.6 (CH_3 Et); HRMS: $[M+NH_4]^+$ calcd for $C_{36}H_{40}O_6NH_4$ 586.31631, found 586.31478.

2-Fluoroethyl-2,3,4,6-tetra-O-benzyl-α,β-D-allopyranoside (3C)



Title compound was prepared according to the general procedure for Ph_2SO/Tf_2O mediated glycosylations with donor **3** and 2-fluoroethanol, yielding compound **3C** (colourless oil, α:β = 55:45, contaminated with hydrolysed donor). Data reported for a 1:1 mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.16 (m, 40H, CH_{arom}), 4.98 – 4.94 (m, 2H, H-1α, C*H*H Bn), 4.93 (d, *J* = 7.9 Hz, 1H, H-1β), 4.90 – 4.86 (m, 2H, 2x C*H*H Bn), 4.84 – 4.77 (m, 2H, 2x CH*H* Bn), 4.66 – 4.58 (m, 6H, 2x CH_2-C*H*HF, 4x C*H*H Bn/CH*H* Bn), 4.56 – 4.44 (m, 7H, 2x CH_2-CH*H*F, 5x C*H*H Bn/CH*H* Bn), 4.38 (d, *J* = 11.6 Hz, 1H, CH*H* Bn), 4.35 (d, *J* = 11.5 Hz, 1H, CH*H* Bn), 4.32 – 4.28 (m, 1H, H-5α), 4.18 (t, *J* = 2.8 Hz, 1H, H-3α), 4.14 – 4.03 (m, 3H, H-3β, H-5β, C*H*H-CH_2F), 3.97 – 3.87 (m, 1H, C*H*H-CH_2F), 3.86 – 3.71 (m, 4H, H-6α, H-6β, 2x CH*H*-CH_2F), 3.70 – 3.64 (m, 2H, H-6α, H-6β), 3.55 (dd, *J* = 9.9, 2.7 Hz, 1H, H-4α), 3.48 – 3.43 (m, 2H, H-2α, H-4β), 3.27 (dd, *J* = 7.9, 2.6 Hz, 1H, H-2β); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.6, 139.1, 138.9, 138.5, 138.2, 138.1, 138.0, 137.9, 137.8, 137.8 (C_q), 128.6, 128.6, 128.6, 128.5, 128.5, 128.5, 128.5, 128.5, 128.4, 128.3, 128.3, 128.1, 128.1, 128.1, 128.1, 128.0, 128.0, 128.0, 128.0, 127.9, 127.9, 127.9, 127.9, 127.8, 127.8, 127.7, 127.7, 127.6, 127.6, 127.5, 127.1 (CH_{arom}), 101.5 (C-1β), 97.6 (C-1α), 83.0 (d, *J* = 169.4 Hz, CH_2-*C*H_2F), 82.9 (d, *J* = 169.4 Hz, , CH_2-*C*H_2F) 78.9 (C-2β), 76.6 (C-2α), 75.7 (C-4β), 74.9 (C-3β), 74.8 (C-4α), 74.5, 73.7, 73.6, 73.6, 73.2 (CH_2 Bn), 72.6, 72.6 (C-3α, C-5β), 71.7, 71.3, 71.2 (CH_2 Bn), 69.4 (C-6β), 68.9 (C-6α, *C*H_2-CH_2F), 67.5 (d, *J* = 20.6 Hz, *C*H_2-CH_2F) 66.4 (C-5α); HRMS: $[M+NH_4]^+$ calcd for $C_{363}H_{39}FO_6NH_4$ 604.30689, found 604.30531.

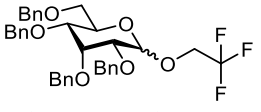
2,2-difluoroethyl-2,3,4,6-tetra-O-benzyl-α,β-D-allopyranoside (3D)



Title compound was prepared according to the general procedure for Ph_2SO/Tf_2O mediated glycosylations with donor **3** and 2,2-difluoroethanol, yielding compound **3D** (36 mg, 60 μmol, 60%, colourless oil, α:β = 58:42) Data reported for a 1:1 mixture: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 6.88 (m, 40H, CH_{arom}), 5.96 (tddd, *J* = 55.6, 7.4, 5.0, 3.6 Hz, 2H, 2x CH_2-C*H*F_2), 4.96 – 4.88 (m, 3H, H-1α, H-1β, C*H*H Bn), 4.86 – 4.76 (m, 3H, 2x C*H*H Bn, CH*H* Bn), 4.62 – 4.53 (m, 6H, 6x C*H*H Bn/CH*H* Bn), 4.52 – 4.44 (m, 4H, 4x C*H*H Bn/CH*H* Bn), 4.38 (d, *J* = 8.4 Hz, 1H, CH*H*Bn), 4.35 (d, *J* = 8.4 Hz, 1H, CH*H*Bn), 4.28 (ddd, *J* = 9.8, 3.4, 2.1 Hz, 1H, H-5α), 4.17 (t, *J* = 2.7 Hz, 1H, H-3α), 4.09 (t, *J* = 2.6 Hz, 1H, H-3β), 4.05 (ddd, *J* = 9.8, 4.5, 2.0 Hz, 1H, H-5β), 4.03 – 3.92 (m,

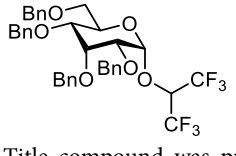
1H, C*H*H-CHF$_2$), 3.90 – 3.71 (m, 5H, H-6α, H-6β, C*H*H-CHF$_2$, 2x CH*H*-CHF$_2$), 3.70 – 3.63 (m, 2H, H-6α, H-6β), 3.55 (dd, *J* = 9.9, 2.7 Hz, 1H, H-4α), 3.47 (dd, *J* = 9.8, 2.5 Hz, 1H, H-4β), 3.44 (dd, *J* = 4.0, 2.8 Hz, 1H, H-2α), 3.26 (dd, *J* = 7.9, 2.6 Hz, 1H, H-2β); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.4, 139.0, 138.6, 138.3, 138.1, 137.9, 137.9 (C_q), 128.6, 128.5, 128.5, 128.5, 128.3, 128.1, 128.1, 128.1, 128.0, 127.9, 127.9, 127.9, 127.9, 127.8, 127.8, 127.7, 127.6, 127.2 (CH_{arom}), 117.3 – 111.7 (m, 2x CH_2-*C*HF$_2$) 101.8 (C-1β), 98.1 (C-1α), 78.8 (C-2β), 76.5 (C-2α), 75.5 (C-4β), 74.7 (C-4α), 74.6 (C-3β), 74.6, 73.7, 73.6, 73.6, 73.2 (CH_2 Bn), 72.6 (C-5β), 72.4 (C-3α), 71.7, 71.5, 71.3 (CH_2 Bn), 69.2 (C-6β), 68.7 (C-6α), 68.9 – 67.4 (m, 2x *C*H$_2$-CHF$_2$), 66.7 (C-5α); HRMS: $[M+NH_4]^+$ calcd for $C_{36}H_{38}F_2O_6NH_4$ 622.29747, found 622.29587.

2,2,2-trifluoroethyl-2,3,4,6-tetra-O-benzyl-α,β-D-allopyranoside (3E)



Title compound was prepared according to the general procedure for Ph_2SO/Tf_2O mediated glycosylations with donor **3** and 2,2,2-trifluoroethanol, yielding compound **3E** (43 mg, 68 µmol, 68%, colourless oil, α:β = 50:50). Data reported for a 1:1 mixture: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.08 (m, 40H, CH_{arom}), 5.04 – 4.97 (m, 3H, H-1α, H-1β, C*H*H Bn), 4.96 – 4.80 (m, 4H, 3x C*H*H Bn, CH*H*Bn), 4.68 – 4.49 (m, 9H, 4x C*H*H Bn, 5x CH*H* Bn), 4.42 (dd, *J* = 13.4, 11.5 Hz, 2H, 2x CH*H* Bn), 4.33 (dt, *J* = 10.4, 2.7 Hz, 1H, H-5α), 4.31 – 4.19 (m, 2H, H-3α, C*H*H-CF$_3$), 4.15 (t, *J* = 2.6 Hz, 1H, H-3β), 4.12 – 4.02 (m, 2H, H-5β, C*H*H-CF$_3$), 4.01 – 3.89 (m, 2H 2x CH*H*-CF$_3$), 3.84 (dd, *J* = 10.6, 3.3 Hz, 1H, H-6α), 3.78 (dd, *J* = 10.8, 2.0 Hz, 1H, H-6β), 3.72 (ddd, *J* = 10.6, 3.3, 2.2 Hz, 2H, H-6α, H-6β), 3.63 (dd, *J* = 9.9, 2.7 Hz, 1H, H-4α), 3.57 – 3.49 (m, 2H, H-2α, H-4β), 3.33 (dd, *J* = 7.9, 2.6 Hz, 1H, H-2β); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.4, 138.9, 138.6, 138.3, 138.1, 138.0, 137.9 (C_q), 128.6, 128.5, 128.5, 128.3, 128.1, 128.0, 128.0, 127.9, 127.9, 127.9, 127.8, 127.8, 127.8, 127.8, 127.7, 127.6, 127.1 (CH_{arom}), 101.6 (C-1β), 97.9 (C-1α), 78.6 (C-2β), 76.7(C-2α), 75.4 (C-4β), 74.7(C-3β), 74.6 (CH_2 Bn), 74.3 (C-4α), 73.7, 73.6, 73.6, 73.2 (CH_2 Bn), 72.7(C-5β), 72.5 (C-3α), 71.7, 71.5, 71.2 (CH_2 Bn), 69.0 (C-6β), 68.6 (C-6α), 67.0 (C-5α), 66.3 (q, *J* = 34.8 Hz, *C*H$_2$-CF$_3$), 65.3 (q, *J* = 34.8 Hz, *C*H$_2$-CF$_3$); HRMS: $[M+NH_4]^+$ calcd for $C_{36}H_{37}F_3O_6NH_4$ 640.28805, found 640.28621.

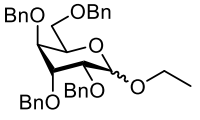
1,1,1,3,3,3-hexafluoro-2-propyl-2,3,4,6-tetra-O-benzyl-α-D-allopyranoside (3F)



Title compound was prepared according to the general procedure for Ph_2SO/Tf_2O mediated glycosylations with donor **3** and 1,1,1,3,3,3-hexafluoropropan-2-ol, yielding compound **3F** (21 mg, 30 µmol, 30%, colourless oil, α:β = >98:2) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.18 (m, 20H, CH_{arom}), 5.22 (d, *J* = 4.0 Hz, 1H, H-1), 4.94 (d, *J* = 12.1 Hz, 1H, C*H*H Bn), 4.80 (d, *J* = 12.0 Hz, 1H, CH*H* Bn), 4.64 (d, *J* = 12.0 Hz, 1H, C*H*H Bn), 4.60 (d, *J* = 12.1 Hz, 1H, C*H*H Bn), 4.55 – 4.44 (m, 4H, C*H*(CF$_3$)$_2$, C*H*H Bn, 2x CH*H* Bn), 4.42 – 4.32 (m, 2H, H-5, CH*H* Bn), 4.18 (t, *J* = 2.6 Hz, 1H, H-3), 3.82 (dd, *J* = 10.7, 2.9 Hz, 1H, H-6), 3.65 (dd, *J* = 10.7, 2.1 Hz, 1H, H-6), 3.61 (dd, *J* = 10.0,

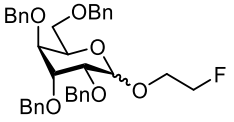
2.6 Hz, 1H, H-4), 3.50 (dd, *J* = 4.1, 2.6 Hz, 1H, H-2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.2, 138.0, 137.9, 137.7 (C_q), 128.6, 128.5, 128.4, 128.4, 128.2, 128.2, 128.1, 128.0, 128.0, 127.9, 127.9, 127.9, 127.9, 127.8, 127.6, 127.2 (CH_{arom}), 99.0 (C-1), 76.5 (C-2), 73.9 (C-4), 73.8, 73.5 (CH_2 Bn), 72.0 (C-3), 71.4, 71.2 (CH_2 Bn), 68.2 (C-6), 67.9 (C-5); HRMS: $[M+NH_4]^+$ calcd for $C_{37}H_{36}F_6O_6$ 708.27543, found 708.27395.

Ethyl-2,3,4,6-tetra-*O*-benzyl-α-D-gulopyranoside (4B)



Title compound was prepared according to the general procedure for Ph_2SO/Tf_2O mediated glycosylations with donor **4** and ethanol, yielding compound **4B** (54 mg, 94 μmol, 94%, colourless oil, α:β = 78:22). Data for the α-anomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.22 (m, 18H, CH_{arom}), 7.14 – 7.08 (m, 2H, CH_{arom}), 4.90 (d, *J* = 3.3 Hz, 1H, H-1), 4.82 (d, *J* = 12.5 Hz, 1H, C*H*H Bn), 4.59 (d, *J* = 9.6 Hz, 1H, C*H*H Bn), 4.56 (d, *J* = 12.5 Hz, 1H, CH*H* Bn), 4.54 – 4.46 (m, 2H, C*H*H Bn, CH*H* Bn), 4.41 (d, *J* = 12.0 Hz, 1H, CH*H* Bn), 4.39 – 4.33 (m, 2H, H-5, C*H*H Bn), 4.29 (d, *J* = 11.9 Hz, 1H, CH*H* Bn), 3.85 – 3.77 (m, 1H, C*H*H Et), 3.77 (td, *J* = 3.6, 2.4 Hz, 2H, H-2, H-3), 3.64 – 3.53 (m, 2H, H-6, CH*H* Et), 3.52 (dd, *J* = 3.5, 1.4 Hz, 1H, H-4), 3.49 (dd, *J* = 9.7, 6.6 Hz, 1H, H-6), 1.29 (t, *J* = 7.1 Hz, 3H, CH_3 Et); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.1, 138.4, 138.1 (C_q), 128.5, 128.5, 128.4, 128.4, 128.3, 128.3, 128.2, 128.0, 128.0, 128.0, 127.9, 127.9, 127.9, 127.8, 127.7, 127.7, 127.7, 127.6, 127.5 (CH_{arom}), 97.0 (C-1), 75.3 (C-4), 73.5 (C-2, C-3), 73.4, 72.9, 72.8, 71.6 (CH_2 Bn), 69.2 (C-6), 65.5 (C-5), 64.0 (CH_2 Et), 15.3 (CH_3 Et); diagnostic peaks for the β-anomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.10 (td, *J* = 6.4, 1.5 Hz, 1H, H-5), 3.97 (dq, *J* = 9.4, 7.1 Hz, 1H, C*H*H Et), 3.73 (t, *J* = 3.5 Hz, 1H), 3.44 (dd, *J* = 3.7, 1.5 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H, CH_3 Et) ^{13}C NMR (126 MHz, $CDCl_3$) δ 100.9 (C-1), 76.4, 75.2, 74.8, 73.6, 72.6, 72.0 (C-5), 69.1 (C-6), 65.2 (CH_2 Et), 15.5 (CH_3 Et); HRMS: $[M+NH_4]^+$ calcd for $C_{36}H_{40}O_6NH_4$ 586.31631, found 586.31510.

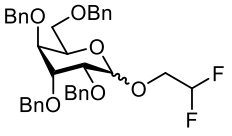
2-fluoroethyl-2,3,4,6-tetra-*O*-benzyl-α-D-gulopyranoside (4C)



Title compound was prepared according to the general procedure for Ph_2SO/Tf_2O mediated glycosylations with donor **4** and 2-fluoroethanol, yielding compound **4C** (50 mg, 85 μmol, 85%, colourless oil, α:β = 83:17). Data for the α-anomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.08 (m, 20H, CH_{arom}), 4.94 (d, *J* = 3.9 Hz, 1H, H-1), 4.83 (d, *J* = 12.4 Hz, 1H, C*H*H Bn), 4.67 (ddd, *J* = 5.3, 4.7, 2.6 Hz, 1H, CH_2-C*H*HF), 4.63 – 4.55 (m, 3H, CH_2-CH*H*F, C*H*H Bn, CH*H* Bn), 4.53 – 4.46 (m, 2H, C*H*H Bn, CH*H* Bn), 4.44 – 4.39 (m, 2H, H-5, CH*H* Bn), 4.37 (d, *J* = 11.9 Hz, 1H, C*H*H Bn), 4.31 (d, *J* = 12.0 Hz, 1H, CH*H* Bn), 3.92 (dddd, *J* = 29.9, 12.3, 4.9, 3.5 Hz, 1H, C*H*H-CH_2F), 3.86 – 3.76 (m, 3H, H-2, H-3, CH*H*-CH_2F), 3.59 – 3.52 (m, 2H, H-4, H-6), 3.48 (dd, *J* = 9.8, 6.5 Hz, 1H, H-6); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.0, 138.4, 138.3, 138.0 (C_q), 128.6, 128.5, 128.5, 128.4, 128.4, 128.4, 128.3, 128.3, 128.2, 128.2, 128.1, 128.1, 128.0, 128.0, 128.0, 127.9, 127.9, 127.8, 127.8, 127.8, 127.7, 127.6, 127.6, 127.5 (CH_{arom}), 97.7 (C-1), 83.1 (d, *J* = 169.0 Hz, CH_2-CH_2F) 75.2

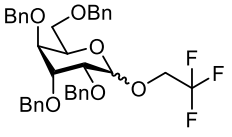
(C-4), 73.5 (C-2/C-3), 73.3, 73.0 (CH_2 Bn), 72.9 (C-2/C-3), 72.9, 71.7 (CH_2 Bn), 69.1 (C-6), 67.5 (d, *J* = 20.6 Hz, *C*H_2-CH_2F), 65.6 (C-5); diagnostic peaks for the β-anomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.88 – 4.85 (m, 2H, H-1, C*H*H Bn), 4.10 (ddd, *J* = 6.3, 5.3, 1.4 Hz, 1H, H-5), 3.74 (t, *J* = 3.4 Hz, 1H), 3.44 (dd, *J* = 3.7, 1.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 101.3 (C-1), 82.8 (d, *J* = 169.3 Hz, CH_2-*C*H_2F), 76.2, 75.0, 74.7, 72.1, 69.0, 68.5 (d, *J* = 20.3 Hz, *C*H_2-CH_2F); HRMS: $[M+NH_4]^+$ calcd for $C_{363}H_{39}FO_6NH_4$ 604.30689, found 604.30571.

2,2-difluoroethyl-2,3,4,6-tetra-*O*-benzyl-α-D-gulopyranoside (4D)



Title compound was prepared according to the general procedure for Ph_2SO/Tf_2O mediated glycosylations with donor **4** and 2,2-difluoroethanol, yielding compound **4D** (50 mg, 83 μmol, 83%, colourless oil, α:β = 69:31) Data for the α-anomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.20 (m, 20H, CH_{arom}), 6.05 (tt, *J* = 55.8, 4.6 Hz, 1H, CH_2-C*H*F_2), 4.89 (d, *J* = 3.9 Hz, 1H, H-1), 4.80 (d, *J* = 12.4 Hz, 1H, C*H*H Bn), 4.56 (s, 2H, CH_2 Bn), 4.50 – 4.45 (m, 2H, C*H*H Bn, C*H*H Bn), 4.42 (d, *J* = 12.0 Hz, 1H, CH*H* Bn), 4.38 – 4.34 (m, 2H, H-5, C*H*H Bn), 4.32 – 4.28 (m, 1H, CH*H* Bn), 3.82 – 3.76 (m, 4H, H-2, H-3, C*H*$_2$-CHF_2), 3.55 – 3.51 (m, 2H, H-4, H-6), 3.45 (dd, *J* = 9.8, 6.1 Hz, 1H, H-6); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.8, 138.2, 138.1, 137.8 (C_q), 128.6, 128.5, 128.5, 128.4, 128.4, 128.2, 128.1, 128.1, 127.8, 127.7 (CH_{arom}), 114.7 (t, *J* = 241.0 Hz, CH_2-*C*HF_2), 98.4 (C-1), 75.1 (C-4), 73.4 (CH_2 Bn), 73.3 (C-3), 73.0, 72.9 (CH_2 Bn), 72.7 (C-5), 71.8 (C-6), 68.2 (t, *J* = 29.1 Hz, *C*H_2-CHF_2), 66.0 (C-5); diagnostic peaks for the β-anomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.90 (d, *J* = 8.1 Hz, 1H, H-1), 4.72 (d, *J* = 12.2 Hz, 1H, C*H*H Bn), 4.15 (td, *J* = 6.4, 1.5 Hz, 1H, H-5), 4.05 (dddd, *J* = 20.0, 11.6, 10.2, 3.3 Hz, 1H, C*H*H-CH_2F), 3.88 (dd, *J* = 4.5, 1.7 Hz, 1H), 3.77 (t, *J* = 3.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 101.7 (C-1), 76.1, 74.9, 74.6, 72.8, 72.7, 72.3, 68.9 – 68.4 (m, *C*H_2-CHF_2); HRMS: $[M+NH_4]^+$ calcd for $C_{36}H_{38}F_2O_6NH_4$ 622.29747, found 622.29587.

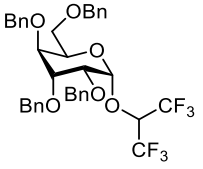
2,2,2-trifluoroethyl-2,3,4,6-tetra-*O*-benzyl-α-D-gulopyranoside (4E)



Title compound was prepared according to the general procedure for Ph_2SO/Tf_2O mediated glycosylations with donor **4** and 2,2,2-trifluoroethanol, yielding compound **4E** (53 mg, 85 μmol, 85%, colourless oil, α:β = 60:40). Data reported for a 1:1 mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 – 6.96 (m, 40H, CH_{arom}), 4.99 (d, *J* = 3.8 Hz, 1H, H-1α), 4.95 (d, *J* = 8.0 Hz, 1H, H-1β), 4.92 – 4.84 (m, 2H, 2x C*H*H Bn), 4.74 (d, *J* = 12.2 Hz, 1H, C*H*H Bn), 4.65 (d, *J* = 12.3 Hz, 1H, C*H*H Bn), 4.62 – 4.39 (m, 11H, H-5α, 3x C*H*H Bn, 7x CH*H* Bn), 4.34 (d, *J* = 2.1 Hz, 1H, CH_2 Bn), 4.23 (dq, *J* = 12.0, 8.7 Hz, 1H, C*H*H-CF_3), 4.14 (td, *J* = 6.4, 1.5 Hz, 1H, H-5β), 4.07 (dq, *J* = 12.4, 9.0 Hz, 1H, C*H*H-CF_3), 4.01 – 3.91 (m, 2H, 2x CH*H*-CF_3), 3.89 (t, *J* = 3.6 Hz, 1H, H-2α), 3.87 – 3.84 (m, 1H, H-3α), 3.77 (t, *J* = 3.5 Hz, 1H, H-3β), 3.66 – 3.57 (m, 5H, H-2β, H-4α, H-6α, 2x H-6β), 3.53 (dd, *J* = 9.8, 6.4 Hz, 1H, H-6α), 3.48 (dd, *J* = 3.8, 1.5 Hz, 1H, H-4β); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.9, 138.7, 138.3, 138.2, 138.2, 137.9, 137.8 (C_q), 128.6, 128.5, 128.5, 128.5, 128.5, 128.5, 128.4,

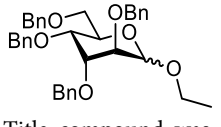
128.4, 128.3, 128.3, 128.2, 128.2, 128.1, 128.0, 128.0, 127.9, 127.8, 127.8, 127.7, 127.5 (CH_{arom}), 125.3, 125.0, 123.1, 122.8 (CH_2-CF_3), 101.5 (C-1β), 97.9 (C-1α), 75.9 (C-2β), 75.4 (C-4α), 74.9 (C-3β), 74.6 (C-4β), 73.6 (CH_2 Bn), 73.6 (C-2α), 73.5, 73.4, 73.1, 73.0 (CH_2 Bn), 72.9 (C-3α), 72.8 (CH_2 Bn), 72.4 (C-5β), 71.8 (CH_2 Bn), 68.9 (C-6α, C-6β), 66.3 (C-5α), 66.2 (q, *J* = 34.8 Hz, *C*H_2-CF_3), 65.2 (q, *J* = 34.7 Hz, *C*H_2-CF_3); HRMS: $[M+NH_4]^+$ calcd for $C_{36}H_{37}F_3O_6NH_4$ 640.28805, found 640.28617

1,1,1,3,3,3-hexafluoro-2-propyl-2,3,4,6-tetra-O-benzyl-α-D-gulopyranoside (4F)



Title compound was prepared according to the general procedure for Ph_2SO/Tf_2O mediated glycosylations with donor **4** and 1,1,1,3,3,3-hexafluoropropan-2-ol, yielding compound **4F** (27 mg, 39 µmol, 39%, colourless oil, α:β = >98:2) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.26 (m, 18H, CH_{arom}), 7.18 – 7.12 (m, 2H, CH_{arom}), 5.19 (d, *J* = 4.0 Hz, 1H, H-1), 4.89 (d, *J* = 11.9 Hz, 1H, C*H*H Bn), 4.65 (d, *J* = 12.1 Hz, 1H, C*H*H Bn), 4.56 – 4.38 (m, 8H, H-5, C*H*$(CF_3)_2$, 2x C*H*H Bn, 4x CH*H* Bn), 3.89 (dd, *J* = 4.0, 3.0 Hz, 1H, H-2), 3.86 – 3.80 (m, 1H, H-3), 3.66 (dd, *J* = 4.1, 1.6 Hz, 1H, H-4), 3.58 – 3.46 (m, 2H, 2x H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.9, 138.2, 137.9, 137.8 (C_q), 128.6, 128.5, 128.3, 128.2, 128.2, 128.0, 127.8, 127.7, 127.7, 127.5 (CH_{arom}), 98.9 (C-1), 75.5 (C-4), 73.4 (CH_2 Bn), 73.3 (C-2), 73.2, 73.2 (CH_2 Bn), 73.0 – 71.9 (m, C-3, *C*H$(CF_3)_2$) 71.6 (CH_2 Bn), 68.5 (C-6), 67.0 (C-5); HRMS: $[M+NH_4]^+$ calcd for $C_{37}H_{36}F_6O_6$ 708.27543, found 708.27274.

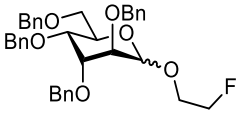
Ethyl-2,3,4,6-tetra-*O*-benzyl-α,β-D-altropyranoside (6B)



Title compound was prepared according to the general procedure for Ph_2SO/Tf_2O mediated glycosylations with donor **6** and ethanol, yielding compound **6B** (45 mg, 79 µmol, 79%, colourless oil, α:β = 75:25). Data for the α-anomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.12 (m, 20H, CH_{arom}), 4.83 (d, *J* = 2.0 Hz, 1H, H-1), 4.64 – 4.57 (m, 3H, 3x C*H*H Bn), 4.53 – 4.47 (m, 4H, C*H*H Bn, 3x CH*H* Bn), 4.44 (d, *J* = 11.8 Hz, 1H, CH*H* Bn), 4.27 (ddd, *J* = 8.0, 4.4, 3.0 Hz, 1H, H-5), 3.87 (dd, *J* = 8.5, 3.3 Hz, 1H, H-4), 3.84 – 3.78 (m, 1H, C*H*H Et), 3.77 (t, *J* = 4.0 Hz, 1H, H-3), 3.74 (dd, *J* = 4.7, 2.0 Hz, 1H, H-2), 3.69 (t, *J* = 3.8 Hz, 2H, 2x H-6), 3.50 – 3.45 (m, 1H, CH*H* Et), 1.22 (t, *J* = 7.1 Hz, 3H, CH_3 Et); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.7, 138.5, 138.3, 138.2 (C_q), 128.5, 128.4, 128.4, 128.4, 128.3, 128.3, 128.0, 127.9, 127.8, 127.8, 127.8, 127.6, 127.5 (CH_{arom}), 99.2 (C-1), 76.0 (C-4), 74.0 (C-3), 73.5 (CH_2 Bn), 72.9 (C-2), 72.7, 72.0, 71.7 (CH_2 Bn), 69.8 (C-6), 68.3 (C-5), 63.4 (CH_2 Et), 15.2 (CH_3 Et); ^{13}C-HMBC-GATED NMR (126 MHz, $CDCl_3$): δ 99.2 ($J_{H1\text{-}C1}$ = 165 Hz, α); diagnostic peaks for the β-anomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.82 – 4.77 (m, 2H, H-1, C*H*H Bn), 4.07 (ddd, *J* = 8.9, 5.9, 2.8 Hz, 1H, H-5), 3.97 (dq, *J* = 9.5, 7.1 Hz, 1H, C*H*H Et), 1.24 (t, *J* = 7.1 Hz, 3H, CH_3 Et); ^{13}C NMR (126 MHz, $CDCl_3$) δ 99.0 (C-1), 75.5, 73.9, 73.8, 73.6, 73.6, 73.4, 72.8, 71.8, 70.4, 65.1 (CH_2 Et), 15.4 (CH_3 Et); ^{13}C-HMBC-GATED NMR

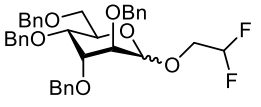
(126 MHz, $CDCl_3$): δ 99.0 ($J_{H1\text{-}C1}$ = 155 Hz, β); HRMS: $[M+NH_4]^+$ calcd for $C_{36}H_{40}O_6NH_4$ 586.31631, found 586.31503.

2-Fluoroethyl-2,3,4,6-tetra-*O*-benzyl-α,β-D-altropyranoside (6C)



Title compound was prepared according to the general procedure for Ph_2SO/Tf_2O mediated glycosylations with donor **6** and 2-fluoroethanol, yielding compound **6C** (35 mg, 60 µmol, 60%, colourless oil, α:β = 58:42). Data reported for a 1:1 mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 – 6.94 (m, 40H, CH_{arom}), 4.93 – 4.90 (m, 2H, H-1α, H-1β), 4.85 (d, *J* = 12.6 Hz, 1H, C*H*H Bn), 4.67 – 4.59 (m, 7H, , 2x CH_2-C*H*HF, 5x C*H*H Bn/CH*H* Bn), 4.59 – 4.49 (m, 9H, 2x CH_2-CH*H*F, 7x C*H*H Bn/CH*H* Bn), 4.46 (d, *J* = 11.8 Hz, 1H, CH*H* Bn), 4.43 (d, *J* = 11.7 Hz, 1H, C*H*H Bn), 4.39 (d, *J* = 11.7 Hz, 1H, CH*H* Bn), 4.31 (dt, *J* = 8.1, 3.8 Hz, 1H, H-5α), 4.18 – 4.06 (m, 2H, H-5β, C*H*H-CH_2F), 4.02 – 3.88 (m, 2H, H-4α, C*H*H-CH_2F), 3.86 – 3.69 (m, 11H, H-2α, H-2β, H-3α, H-3β, H-4β, 2x H-6α, 2x H-6β, 2x CH*H*-CH_2F); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.7, 138.6, 138.4, 138.4, 138.1, 138.1 (C_q), 128.5, 128.5, 128.4, 128.4, 128.3, 128.1, 128.1, 128.0, 127.9, 127.9, 127.9, 127.9, 127.8, 127.8, 127.7, 127.7, 127.6, 127.6 (CH_{arom}), 99.6 (C-1α), 99.5 (C-1β), 83.0 (d, *J* = 168.9 Hz, CH_2-*C*H_2F), 82.9 (d, *J* = 169.1 Hz, CH_2-*C*H_2F), 75.5 (C-2α), 75.1 (C-2β, 73.9 (CH_2 Bn), 73.7 (C-3α), 73.6, 73.5 (CH_2 Bn), 73.4, 73.4 (C-3β, C-4β, C-5β), 72.9 (CH_2 Bn), 72.7 (C-4α), 72.7, 72.0, 71.8, 71.7 (CH_2 Bn), 70.2 (C-6β), 69.7 (C-6α), 68.6 (d, *J* = 19.8 Hz, *C*H_2-CH_2F), 68.4 (C-5α), 66.84 (d, *J* = 20.0 Hz, *C*H_2-CH_2F); ^{13}C-HMBC-GATED NMR (126 MHz, $CDCl_3$): δ 99.6 ($J_{H1\text{-}C1}$ = 168 Hz, α), 99.5 ($J_{H1\text{-}C1}$ = 161 Hz, β); HRMS: $[M+NH_4]^+$ calcd for $C_{363}H_{39}FO_6NH_4$ 604.30689, found 604.30606.

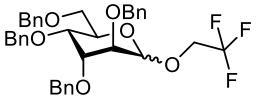
2,2-difluoroethyl-2,3,4,6-tetra-*O*-benzyl-α,β-D-altropyranoside (6D)



Title compound was prepared according to the general procedure for Ph_2SO/Tf_2O mediated glycosylations with donor **6** and 2,2-difluoroethanol, yielding compound **6D** (39 mg, 64 µmol, 64%, colourless oil, α:β = 69:31) Data for the α-anomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 6.98 (m, 20H, CH_{arom}), 5.91 (dddd, *J* = 56.1, 55.2, 5.2, 3.3 Hz, 1H, CH_2-C*H*F_2), 4.85 (d, *J* = 1.4 Hz, 1H, H-1), 4.63 – 4.50 (m, 4H, 4x C*H*H Bn/ CH*H* Bn), 4.50 – 4.37 (m, 4H, 4x C*H*H Bn/ CH*H* Bn), 4.26 (dt, *J* = 8.8, 3.7 Hz, 1H, H-5), 3.91 – 3.83 (m, 2H, H-4, C*H*H-CHF_2), 3.77 – 3.74 (m, 2H, H-2, H-3), 3.70 – 3.64 (m, 3H, 2x H-6, CH*H*-CHF_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.5, 138.5, 138.3, 138.3, 137.9 (C_q), 128.6, 128.5, 128.4, 128.4, 128.0, 127.9, 127.9, 127.8 (CH_{arom}), 117.0 – 112.1 (m, CH_2-*C*HF_2) 100.1 (C-1), 75.4, 73.6 (C-2, C-3), 73.6, 72.8 (CH_2 Bn), 72.6 (C-4), 72.2, 71.8 (CH_2 Bn), 69.6 (C-6), 68.6 (C-5), 67.1 (dd, *J* = 29.6, 27.2 Hz, *C*H_2-CHF_2); ^{13}C-HMBC-GATED NMR (126 MHz, $CDCl_3$): δ 100.1 ($J_{H1\text{-}C1}$ = 168 Hz, α); diagnostic peaks for the β-anomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.98 (dddd, *J* = 56.3, 55.0, 5.5, 3.0 Hz, 1H, CH_2-C*H*F_2), 4.90 (d, *J* = 1.4 Hz, 1H, H-1), 4.81 (d, *J* = 12.5 Hz, 1H, C*H*H Bn), 4.10 (ddd, *J* = 9.4, 5.8, 2.5 Hz, 1H, H-5), 4.08 – 4.00 (m, 1H, C*H*H-CHF_2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 99.9 (C-1), 74.9, 73.9, 73.8, 73.5, 73.2, 73.0, 71.9,

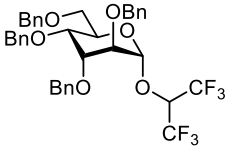
70.0 (C-6); ^{13}C-HMBC-GATED NMR (126 MHz, $CDCl_3$): δ 99.9 ($J_{H1\text{-}C1}$ = 160 Hz, β); HRMS: $[M+NH_4]^+$ calcd for $C_{36}H_{38}F_2O_6NH_4$ 622.29747, found 622.29581.

2,2,2-trifluoroethyl-2,3,4,6-tetra-*O*-benzyl-α,β-D-altropyranoside (6E)



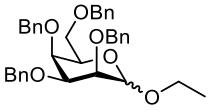
Title compound was prepared according to the general procedure for Ph_2SO/Tf_2O mediated glycosylations with donor **6** and 2,2,2-trifluoroethanol, yielding compound **6E** (46 mg, 73 µmol, 73%, colourless oil, α:β = 85:15). Data for the α-anomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.25 (m, 20H, CH_{arom}), 4.94 (s, 1H, H-1), 4.67 – 4.59 (m, 3H, 3x C*H*H Bn), 4.58 – 4.50 (m, 4H, C*H*H Bn, 3x CH*H* Bn), 4.47 (d, *J* = 11.8 Hz, 1H, CH*H* Bn), 4.30 (ddd, *J* = 8.9, 4.3, 2.8 Hz, 1H, H-5), 4.06 (dq, *J* = 12.3, 9.0 Hz, 1H, C*H*H-CF_3), 3.95 – 3.86 (m, 2H, H-4, CH*H*-CF_3), 3.83 – 3.79 (m, 2H, H-2, H-3), 3.76 – 3.70 (m, 2H, 2x H-6); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.4, 138.3, 138.3, 137.8 (C_q), 128.6, 128.4, 128.4, 128.1, 128.0, 127.9, 127.8, 127.8, 127.7 (CH_{arom}), 124.1 (q, *J* = 278.3 Hz, CH_2-CF_3), 99.7 (C-1), 75.1 (C-2/C-3), 73.6 (CH_2 Bn), 73.6 (C-2/C-3), 72.8 (CH_2 Bn), 72.5 (C-4), 72.2, 71.8 (CH_2 Bn), 69.4 (C-6), 68.7 (C-5), 64.36 (q, *J* = 34.5 Hz, *C*H_2-CF_3); ^{13}C-HMBC-GATED NMR (126 MHz, $CDCl_3$): δ 99.7 ($J_{H1\text{-}C1}$ = 169 Hz, α); diagnostic peaks for the β-anomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.96 (d, *J* = 1.4 Hz, 1H, H-1), 4.82 (d, *J* = 12.5 Hz, 1H, C*H*H Bn), 4.42 (d, *J* = 11.7 Hz, 1H, CH*H* Bn), 4.24 (dq, *J* = 12.4, 8.9 Hz, 1H, C*H*H-CF_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 99.6 (C-1), 74.6, 73.8, 73.8, 73.7, 73.6, 73.1, 73.0, 72.0, 70.0 (C-6); ^{13}C-HMBC-GATED NMR (126 MHz, $CDCl_3$): δ 99.7 ($J_{H1\text{-}C1}$ = 162 Hz, β); HRMS: $[M+NH_4]^+$ calcd for $C_{36}H_{37}F_3O_6NH_4$ 640.28805, found 640.28612

1,1,1,3,3,3-hexafluoro-2-propyl-2,3,4,6-tetra-O-benzyl-α-D-altropyranoside (6F)



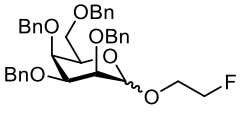
Title compound was prepared according to the general procedure for Ph_2SO/Tf_2O mediated glycosylations with donor **6** and 1,1,1,3,3,3-hexafluoropropan-2-ol, yielding compound **6F** (11 mg, 16 µmol, 16%, colourless oil, α:β = >98:2) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 18H, CH_{arom}), 7.21 (ddt, *J* = 8.4, 5.3, 2.2 Hz, 2H, CH_{arom}), 5.05 (s, 1H, H-1), 4.64 (d, *J* = 12.1 Hz, 1H, C*H*H Bn), 4.58 – 4.49 (m, 4H, C*H*$(CF_3)_2$, 3x C*H*H Bn), 4.48 – 4.39 (m, 3H, 3x CH*H* Bn), 4.35 – 4.29 (m, 2H, H-5, CH*H* Bn), 3.96 (dd, *J* = 9.4, 3.1 Hz, 1H, H-4), 3.80 (dd, *J* = 4.3, 1.6 Hz, 1H, H-2), 3.78 – 3.73 (m, 2H, H-3, H-6), 3.66 (dd, *J* = 10.9, 2.3 Hz, 1H, H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2 (C_q), 130.5, 128.9, 128.7, 128.6, 128.5, 128.5, 128.5, 128.4, 128.4, 128.4, 128.3, 128.2, 128.2, 128.0, 128.0, 128.0, 127.9, 127.9, 127.9, 127.7 (CH_{arom}), 100.7 (C-1), 74.3 (C-2), 73.6 (CH_2 Bn), 73.1 (C-3), 72.9, 72.3, 72.0 (CH_2 Bn), 72.0 (C-4), 69.1 (C-5), 69.0 (C-6); ^{13}C-HMBC-GATED NMR (101 MHz, $CDCl_3$): δ 100.7 ($J_{H1\text{-}C1}$ = 173 Hz, α); HRMS: $[M+NH_4]^+$ calcd for $C_{37}H_{36}F_6O_6$ 708.27543, found 708.27387.

Ethyl-2,3,4,6-tetra-*O*-benzyl-α,β-D-talopyranoside (7B)



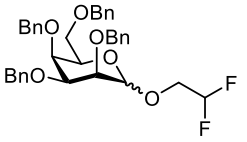
Title compound was prepared according to the general procedure for Ph_2SO/Tf_2O mediated glycosylations with donor **7** and ethanol, yielding compound **7B** (40 mg, 70 µmol, 70%, colourless oil, α:β = 68:32) Data for the α-anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.23 (m, 20H, CH_{arom}), 5.04 – 4.99 (m, 2H, H-1, C*H*H Bn), 4.92 (d, *J* = 12.6 Hz, 1H, C*H*H Bn), 4.85 – 4.76 (m, 2H, 2x CH*H* Bn), 4.62 – 4.57 (m, 3H, C*H*H Bn, CH_2 Bn), 4.54 – 4.51 (m, 1H, CH*H* Bn), 4.02 (td, *J* = 6.3, 1.9 Hz, 1H, H-5), 3.96 (p, *J* = 1.4 Hz, 1H, H-3), 3.83 – 3.72 (m, 5H, H-2, H-4, 2x H-6, C*H*H Et), 3.50 (dq, *J* = 9.8, 6.9 Hz, 1H, CH*H* Et), 1.21 (t, *J* = 7.1 Hz, 3H, CH_3 Et); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.2, 138.9, 138.6, 138.4 (C_q), 128.5, 128.4, 128.4, 128.3, 128.3, 128.2, 128.1, 127.9, 127.2 (CH_{arom}), 99.0 (C-1), 77.6, 74.6 (C-2, C-4), 73.8, 73.7 (CH_2 Bn), 73.5 (C-3), 73.2, 71.3 (CH_2 Bn), 70.8 (C-5), 69.6 (C-6), 63.2 (CH_2 Et), 15.1 (CH_3 Et); ^{13}C-HMBC-GATED NMR (101 MHz, $CDCl_3$): δ 99.0 ($J_{H1\text{-}C1}$ = 169 Hz, α); diagnostic peaks for the β-anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.45 (d, *J* = 12.2 Hz, 1H, CH*H* Bn), 4.42 (d, *J* = 1.3 Hz, 1H, H-1), 4.08 (dt, *J* = 9.3, 7.1 Hz, 1H, C*H*H Et), 3.93 (dt, *J* = 3.1, 1.2 Hz, 1H), 3.59 (td, *J* = 5.4, 4.7, 2.2 Hz, 1H, H-5), 3.44 (t, *J* = 3.1 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H, CH_3 Et); ^{13}C NMR (101 MHz, $CDCl_3$) δ 102.4 (C-1), 79.0, 75.3, 74.8, 74.6, 72.6, 70.8, 69.8 (C-6), 64.9 (CH_2 Et), 15.3 (CH_3 Et); ^{13}C-HMBC-GATED NMR (101 MHz, $CDCl_3$): δ 102.4 ($J_{H1\text{-}C1}$ = 154 Hz, β) HRMS: $[M+NH_4]^+$ calcd for $C_{36}H_{40}O_6NH_4$ 586.31631, found 586.31493.

2-fluoroethyl-2,3,4,6-tetra-*O*-benzyl-α,β-D-talopyranoside (7C)



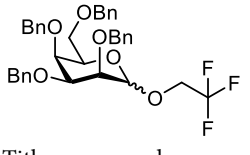
Title compound was prepared according to the general procedure for Ph_2SO/Tf_2O mediated glycosylations with donor **7** and 2-fluoroethanol, yielding compound **7C** (43 mg, 74 µmol, 74%, colourless oil, α:β = 80:20) Data for the α-anomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 6.98 (m, 20H, CH_{arom}), 5.01 (d, *J* = 1.8 Hz, 1H, H-1), 4.96 (d, *J* = 11.9 Hz, 1H, C*H*H Bn), 4.86 (d, *J* = 12.5 Hz, 1H, C*H*H Bn), 4.78 – 4.70 (m, 2H, 2x CH*H* Bn), 4.57 – 4.51 (m, 4H, C*H*H Bn, CH_2 Bn, CH_2-C*H*HF), 4.49 – 4.44 (m, 2H, CH*H* Bn, CH_2-CH*H*F), 3.98 (td, *J* = 6.2, 1.9 Hz, 1H, H-5), 3.91 (dt, *J* = 2.7, 1.4 Hz, 1H, H-3), 3.89 – 3.79 (m, 2H, H-2, C*H*H-CH_2F), 3.79 – 3.76 (m, 1H, H-4), 3.75 – 3.62 (m, 3H, 2x H-6, CH*H*-CH_2F); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.1, 138.7, 138.4, 138.3 (C_q), 128.5, 128.4, 128.4, 128.4, 128.3, 128.3, 128.2, 128.2, 128.1, 128.1, 128.0, 127.9, 127.8, 127.8, 127.7, 127.6, 127.6, 127.5, 127.4, 127.3, 127.2, 127.2 (CH_{arom}), 99.5 (C-1), 82.6 (d, *J* = 169.6 Hz, CH_2-*C*H_2F), 77.4 (C-4), 74.3 (C-2), 73.8, 73.6 (CH_2 Bn), 73.3 (C-3), 73.3, 71.3 (CH_2 Bn), 70.9 (C-5), 69.6 (C-6), 66.6 (d, *J* = 19.7 Hz, *C*H_2-CH_2F); ^{13}C-HMBC-GATED NMR (126 MHz, $CDCl_3$): δ 99.5 ($J_{H1\text{-}C1}$ = 170 Hz, α); diagnostic peaks for the β-anomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.06 (d, *J* = 12.8 Hz, 1H, C*H*H Bn), 4.16 – 4.02 (m, 1H, C*H*H-CF_2), 3.55 (t, *J* = 5.7 Hz, 1H), 3.39 (t, *J* = 3.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 102.1 (C-1), 83.0 (d, *J* = 169.0 Hz, CH_2-*C*H_2F), 81.4, 79.2, 75.3, 74.4, 72.4, 68.21 (d, *J* = 19.8 Hz, *C*H_2-CH_2F); HRMS: $[M+NH_4]^+$ calcd for $C_{363}H_{39}FO_6NH_4$ 604.30689, found 604.30540.

2,2-difluoroethyl-2,3,4,6-tetra-*O*-benzyl-α,β-D-talopyranoside (7D)



Title compound was prepared according to the general procedure for Ph_2SO/Tf_2O mediated glycosylations with donor **7** and 2,2-fluoroethanol, yielding compound **7D** (44 mg, 73 µmol, 73%, colourless oil, α:β = 86:14) Data for the α-anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 6.98 (m, 20H, CH_{arom}), 5.88 (tdd, *J* = 55.4, 4.8, 3.5 Hz, 1H, CH_2-C*H*F_2), 4.99 (d, *J* = 1.9 Hz, 1H, H-1), 4.95 (d, *J* = 11.9 Hz, 1H, C*H*H Bn), 4.85 (d, *J* = 12.4 Hz, 1H, C*H*H Bn), 4.77 – 4.67 (m, 2H, 2x CH*H* Bn), 4.55 – 4.43 (m, 4H, 2x CH_2 Bn), 3.95 (td, *J* = 6.1, 1.9 Hz, 1H, H-5), 3.89 (p, *J* = 1.4 Hz, 1H, H-3), 3.82 – 3.72 (m, 4H, H-2, H-3, H-6, C*H*H-CHF_2), 3.72 – 3.64 (m, 2H, H-6, CH*H*-CHF_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.0, 138.6, 138.3, 138.2 (C_q), 128.5, 128.5, 128.3, 128.2, 128.2, 128.2, 127.9, 127.8, 127.7, 127.6, 127.5, 127.3 (CH_{arom}), 114.1 (t, *J* = 240.9 Hz, CH_2-CHF_2) 100.1 (C-1), 77.1, 74.0 (C-2, C-3), 73.8, 73.6, 73.4 (CH_2 Bn), 73.2 (C-4), 71.4 (C-5), 71.4 (CH_2 Bn), 69.5 (C-6), 66.9 (t, *J* = 28.1 Hz, *C*H_2-CHF_2); ^{13}C-HMBC-GATED NMR (101 MHz, $CDCl_3$): δ 100.1 ($J_{H1\text{-}C1}$ = 171 Hz, α); diagnostic peaks for the β-anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 – 5.78 (m, 1H, CH_2-C*H*F_2), 4.45 – 4.42 (m, 2H, H-1, CH*H* Bn), 4.39 (d, *J* = 12.2 Hz, 1H), 4.07 (dddd, *J* = 23.5, 11.8, 9.3, 2.7 Hz, 1H, C*H*H-CHF_2), 3.56 (dt, *J* = 6.9, 3.5 Hz, 1H), 3.39 (t, *J* = 3.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 102.1 (C-1), 75.5, 74.6, 74.2, 72.3, 70.8; ^{13}C-HMBC-GATED NMR (101 MHz, $CDCl_3$): δ 102.1 ($J_{H1\text{-}C1}$ = 156 Hz, β); HRMS: $[M+NH_4]^+$ calcd for $C_{36}H_{38}F_2O_6NH_4$ 622.29747, found 622.29554.

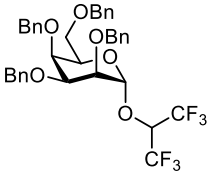
2,2,2-trifluoroethyl-2,3,4,6-tetra-*O*-benzyl-α,β-D-talopyranoside (7E)



Title compound was prepared according to the general procedure for Ph_2SO/Tf_2O mediated glycosylations with donor **7** and 2,2,2-fluoroethanol, yielding compound **7E** (43 mg, 43 µmol, 43%, colourless oil, α:β = 90:10) Data for the α-anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 6.96 (m, 20H, CH_{arom}), 5.04 (d, *J* = 1.9 Hz, 1H, H-1), 4.95 (d, *J* = 11.8 Hz, 1H, C*H*H Bn), 4.85 (d, *J* = 12.4 Hz, 1H, C*H*H Bn), 4.77 – 4.69 (m, 2H, 2x CH*H* Bn), 4.55 – 4.50 (m, 3H, C*H*H Bn, CH_2 Bn), 4.47 (d, *J* = 11.9 Hz, 1H, CH*H* Bn), 4.01 – 3.90 (m, 3H, H-3, H-5, C*H*H-CF_3), 3.88 – 3.78 (m, 2H, H-2, CH*H*-CF_3), 3.76 – 3.66 (m, 3H, H-4, 2x H-6); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.9, 138.4, 138.2, 138.2 (C_q), 128.5, 128.5, 128.5, 128.4, 128.3, 128.2, 128.2, 128.2, 127.9, 127.8, 127.7, 127.7, 127.5, 127.4, 127.3 (CH_{arom}), 99.7 (C-1), 76.9 (c-4), 73.8(C-2, CH_2 Bn), 73.6, 73.5(CH_2 Bn), 73.0(C-3), 71.6 (C-5), 71.4 (CH_2 Bn), 69.4 (C-6), 64.2 (q, *J* = 34.8 Hz, *C*H_2-CF_3); ^{13}C-HMBC-GATED NMR (101 MHz, $CDCl_3$): δ 99.7 ($J_{H1\text{-}C1}$ = 172 Hz, α); diagnostic peaks for the β-anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38 (d, *J* = 12.1 Hz, 1H, CH*H* Bn), 4.21 (dq, *J* = 12.4, 8.9 Hz, 1H, C*H*H-CF_3), 3.57 (dt, *J* = 6.5, 3.2 Hz, 1H), 3.42 – 3.38 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 75.6, 70.9, 69.5, a cross-peak for (H-1, C-1) is visible at (4.50, 101.4) in the HSQC spectrum; ^{13}C-

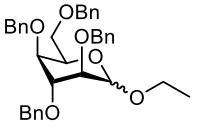
HMBC-GATED NMR (101 MHz, $CDCl_3$): δ 101.4 ($J_{H1\text{-}C1}$ = 157 Hz, β); HRMS: $[M+NH_4]^+$ calcd for $C_{36}H_{37}F_3O_6NH_4$ 640.28805, found 640.28619.

1,1,1,3,3,3-hexafluoro-2-propyl-2,3,4,6-tetra-O-benzyl-α-D-talopyranoside (7F)



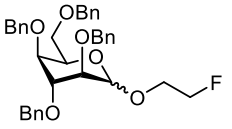
Title compound was prepared according to the general procedure for Ph_2SO/Tf_2O mediated glycosylations with donor **7** and 1,1,1,3,3,3-hexafluoropropan-2-ol, yielding compound **7F** (10 mg, 14 µmol, 14%, colourless oil, α:β = >98:2) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.20 (m, 20H, CH_{arom}), 5.22 (d, *J* = 1.7 Hz, 1H, H-1), 4.96 (d, *J* = 11.8 Hz, 1H, C*H*H Bn), 4.81 (d, *J* = 12.4 Hz, 1H, C*H*H Bn), 4.76 – 4.70 (m, 2H, 2x CH*H* Bn), 4.54 (s, 2H, CH_2 Bn), 4.52 – 4.44 (m, 3H, C*H*$(CF_3)_2$), 4.03 (td, *J* = 6.2, 1.8 Hz, 1H, H-5), 3.95 (p, *J* = 1.4 Hz, 1H, H-4), 3.85 (dt, *J* = 3.0, 1.3 Hz, 1H, H-2), 3.74 – 3.65 (m, 3H, H-3, 2x H-6); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.8, 138.2, 138.0, 138.0 (C_q), 128.6, 128.5, 128.5, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 127.4 (CH_{arom}), 101.2 (C-1), 76.5 (C-3), 73.8, 73.7, 73.6 (CH_2 Bn), 73.4 (C-2), 72.6 (C-4), 72.4 (C-5), 71.5 (CH_2 Bn), 69.0 (C-6); ^{13}C-HMBC-GATED NMR (126 MHz, $CDCl_3$): δ 101.2 ($J_{H1\text{-}C1}$ = 175 Hz, α); HRMS: $[M+NH_4]^+$ calcd for $C_{37}H_{36}F_6O_6$ 708.27543, found 708.27354.

Ethyl-2,3,4,6-tetra-*O*-benzyl-α,β-D-idopyranoside (8B)



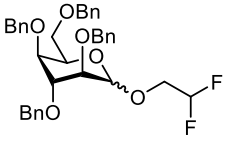
Title compound was prepared according to the general procedure for Ph_2SO/Tf_2O mediated glycosylations with donor **8** and ethanol, yielding compound **8B** (44 mg, 76 µmol, 76%, colourless oil, α:β = 57:43). Data reported for a 1:1 mixture: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.13 (m, 40H, CH_{arom}), 4.85 (d, *J* = 5.4 Hz, 1H, H-1α), 4.79 (d, *J* = 11.5 Hz, 1H, C*H*H Bn), 4.77 – 4.70 (m, 3H, H-1β, C*H*H Bn, C*H*H Bn), 4.68 – 4.60 (m, 5H, 5x C*H*H Bn/CH*H* Bn), 4.58 – 4.46 (m, 8H, 8x C*H*H Bn/CH*H* Bn), 4.21 (dt, *J* = 7.0, 4.6 Hz, 1H, H-5α), 4.13 (dt, *J* = 7.4, 4.8 Hz, 1H, H-5β), 3.97 (dq, *J* = 9.5, 7.0 Hz, 1H, C*H*H Et), 3.91 – 3.84 (m, 2H, C*H*H Et, H-6β), 3.83 – 3.77 (m, 3H), 3.77 – 3.72 (m, 1H, H-6α), 3.71 – 3.65 (m, 2H), 3.60 – 3.51 (m, 2H), 3.51 – 3.44 (m, 3H), 1.23 (t, *J* = 7.1 Hz, 6H, 2x CH_3 Et); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.7, 138.5, 138.3, 138.3, 138.3 (C_q), 128.5, 128.5, 128.4, 128.2, 128.1, 128.1, 128.1, 128.0, 128.0, 127.9, 127.9, 127.8, 127.8, 127.8, 127.7, 127.7 (CH_{arom}), 100.1 (C-1α), 98.9 (C-1β), 80.1, 79.2, 77.8, 75.8, 75.6, 74.3, 74.1 (C-5β), 73.9, 73.8, 73.7, 73.5, 73.4, 73.2, 72.7, 70.0 (C-5α), 69.9 (C-6β), 68.4 (C-6α), 64.4, 64.3 (2x CH_2 Et), 15.4, 15.1 (2x CH_3 Et); ^{13}C-HMBC-GATED NMR (101 MHz, $CDCl_3$): δ 100.1 ($J_{H1\text{-}C1}$ = 165 Hz, α), 98.9 ($J_{H1\text{-}C1}$ = 161 Hz, β); HRMS: $[M+NH_4]^+$ calcd for $C_{36}H_{40}O_6NH_4$ 586.31631, found 586.31458.

2-fluoroethy-2,3,4,6-tetra-*O*-benzyl-α,β-D-idopyranoside (8C)



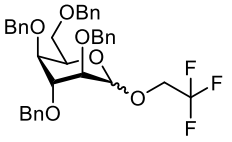
Title compound was prepared according to the general procedure for Ph_2SO/Tf_2O mediated glycosylations with donor **8** and 2-fluoroethanol, yielding compound **8C** (42 mg, 72 μmol, 72%, colourless oil, α:β = 57:43). Data reported for a 1:1 mixture: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 6.84 (m, 40H, CH_{arom}), 4.95 (d, *J* = 5.0 Hz, 1H, H-1α), 4.87 – 4.78 (m, 5H, H-1β, 4x C*H*H Bn/CH*H* Bn), 4.76 – 4.61 (m, 8H, 6x C*H*H Bn/CH*H* Bn, 2x CH_2-C*H*HF), 4.61 – 4.47 (m, 8H, 6x C*H*H Bn/CH*H* Bn, 2x CH_2-CH*H*F), 4.26 (dt, *J* = 7.1, 4.4 Hz, 1H, H-5α), 4.22 – 4.08 (m, 2H, H-5β, C*H*H-CH_2F), 4.07 – 3.95 (m, 1H, C*H*H-CH_2F), 3.92 (dd, *J* = 10.1, 7.8 Hz, 1H, H-6β), 3.88 – 3.75 (m, 6H,, H-3α, H-3β, H-6α, H-6β, 2x CH*H*-CH_2F), 3.76 – 3.67 (m, 2H, H-4α, H-6β), 3.63 – 3.54 (m, 2H, H-2α, H-2β), 3.54 (dd, *J* = 5.4, 3.9 Hz, 1H, H-4β); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.7, 138.5, 138.4, 138.3, 138.3, 138.2, 138.2 (C_q), 128.5, 128.5, 128.4, 128.3, 128.2, 128.2, 128.1, 128.0, 127.9, 127.9, 127.9, 127.9, 127.8, 127.8, 127.7, 127.7, 127.7 (CH_{arom}), 100.8 (C-1α), 99.7 (C-1α), 83.0 (d, *J* = 169.0 Hz, CH_2-*C*H_2F), 82.8 (d, *J* = 169.4 Hz, CH_2-*C*H_2F), 79.4 (C-2β), 78.8 (C-3β), 77.5 (C-4α), 75.9 (C-2α), 75.2 (C-3α, C-4β), 74.2 (C-5β), 74.1, 73.8, 73.7, 73.6, 73.5, 73.4, 73.2, 72.7 (CH_2 Bn), 69.9 (C-5α), 69.7 (C-6β), 68.6 (C-6α), 68.0 (d, *J* = 19.8 Hz, *C*H_2-CH_2F), 67.5 (d, *J* = 19.9 Hz, *C*H_2-CH_2F); ^{13}C-HMBC-GATED NMR (101 MHz, $CDCl_3$): δ 100.8 ($J_{H1\text{-}C1}$ = 167 Hz, α), 99.7 ($J_{H1\text{-}C1}$ = 162 Hz, β); HRMS: $[M+NH_4]^+$ calcd for $C_{363}H_{39}FO_6NH_4$ 604.30689, found 604.30571.

2,2-difluoroethy-2,3,4,6-tetra-*O*-benzyl-α,β-D-idopyranoside (8D)



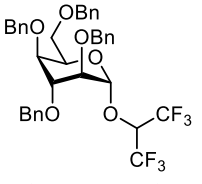
Title compound was prepared according to the general procedure for Ph_2SO/Tf_2O mediated glycosylations with donor **8** and 2,2-difluoroethanol, yielding compound **8D** (44 mg, 72 μmol, 72%, colourless oil, α:β = 55:45) Data reported for a 1:1 mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.06 (m, 40H, CH_{arom}), 6.11 – 5.84 (m, 2H, 2x CH_2-C*H*F_2), 4.93 (d, *J* = 4.7 Hz, 1H, H-1α), 4.82 (d, *J* = 2.4 Hz, 1H, H-1β), 4.80 – 4.45 (m, 16H, 8x CH_2 Bn), 4.24 (dt, *J* = 7.2, 4.2 Hz, 1H, H-5α), 4.14 (ddd, *J* = 8.1, 4.8, 3.4 Hz, 1H, H-5β), 4.12 – 4.02 (m, 1H, C*H*H-CHF_2), 3.99 – 3.85 (m, 2H, H-6β, C*H*H-CHF_2), 3.85 – 3.83 (m, 1H, H-3α), 3.82 – 3.72 (m, 5H, H-3β, H-6α, H-6β, 2x CH*H*-CHF_2), 3.70 – 3.67 (m, 2H, H-4α, H-6α), 3.58 – 3.54 (m, 2H, H-2αβ), 3.51 (dd, *J* = 5.0, 3.6 Hz, 1H, H-4β); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.5, 138.4, 138.1, 138.1, 138.0, 138.0 (C_q), 128.5, 128.5, 128.5, 128.4, 128.3, 128.2, 128.2, 128.1, 128.0, 128.0, 127.9, 127.9, 127.8, 127.8, 127.8, 127.7 (CH_{arom}), 116.8 – 112.1 (m, 2x CH_2-*C*HF_2) 101.4 (C-1α), 100.0 (C-1β), 78.9 (C-2α), 78.5 (C-3α), 77.3 (C-4α), 75.4 (C-2β), 74.9 (C-3β), 74.7 (C-4β), 74.3 (C-5β), 74.0, 73.8, 73.8, 73.5, 73.5, 73.4, 73.1, 72.6 (CH_2 Bn), 69.9 (C-6β), 69.5 (C-6α), 68.6 (C-5α); ^{13}C-HMBC-GATED NMR (101 MHz, $CDCl_3$): δ 101.4 ($J_{H1\text{-}C1}$ = 168 Hz, α), 100.0 ($J_{H1\text{-}C1}$ = 162 Hz, β); HRMS: $[M+NH_4]^+$ calcd for $C_{36}H_{38}F_2O_6NH_4$ 622.29747, found 622.29604.

2,2,2-trifluoroethy-2,3,4,6-tetra-*O*-benzyl-α,β-D-idopyranoside (8E)



Title compound was prepared according to the general procedure for Ph_2SO/Tf_2O mediated glycosylations with donor **8** and 2,2,2-trifluoroethanol, yielding compound **8E** (41 mg, 66 µmol, 66%, α:β = 69:31) Data for the α-anomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.24 (m, 20H, CH_{arom}), 4.99 (d, *J* = 4.6 Hz, 1H, H-1), 4.79 (dd, *J* = 11.5, 10.0 Hz, 2H, CH_2 Bn), 4.71 – 4.60 (m, 3H, 3x C*H*H Bn), 4.59 – 4.51 (m, 3H, 3x CH*H* Bn), 4.23 (dt, *J* = 7.1, 4.2 Hz, 1H, H-5), 4.13 – 4.05 (m, 1H, C*H*H-CF_3), 3.98 – 3.89 (m, 1H, CH*H*-CF_3), 3.84 (dd, *J* = 7.2, 5.7 Hz, 1H, H-3), 3.78 – 3.73 (m, 1H, H-6), 3.70 – 3.65 (m, 2H, H-4, H-6), 3.59 (dd, *J* = 7.2, 4.7 Hz, 1H, H-2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.4, 138.1, 138.1, 138.0 (C_q), 128.6, 128.5, 128.5, 128.5, 128.3, 128.1, 128.0, 128.0, 127.9, 127.9, 127.7 (CH_{arom}), 101.0 (C-1), 78.4, 78.3 (C-2, C-3), 77.2 (C-4), 74.0, 73.8, 73.5, 73.2 (CH_2 Bn), 70.0 (C-5), 68.6 (C-6), 64.6 (q, *J* = 34.5 Hz, *C*H-CF_3); ^{13}C-HMBC-GATED NMR (126 MHz, $CDCl_3$): δ 101.0 ($J_{H1\text{-}C1}$ = 169 Hz, α); diagnostic peaks for the β-anomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.89 (d, *J* = 2.5 Hz, 1H, H-1), 3.51 (dd, *J* = 5.2, 3.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 99.7 (C-1), 74.4, 73.6, 72.7, 69.4 (C-6), 68.2 – 67.3 (m, 2x *C*H_2-CHF_2); ^{13}C-HMBC-GATED NMR (126 MHz, $CDCl_3$): δ 99.7 ($J_{H1\text{-}C1}$ = 163 Hz, β); HRMS: $[M+NH_4]^+$ calcd for $C_{36}H_{37}F_3O_6NH_4$ 640.28805, found 640.28690.

1,1,1,3,3,3-hexafluoro-2-propyl-2,3,4,6-tetra-O-benzyl-α-D-idopyranoside (8F)



Title compound was prepared according to the general procedure for Ph_2SO/Tf_2O mediated glycosylations with donor **8** and 1,1,1,3,3,3-hexafluoropropan-2-ol, yielding compound **8F** (15 mg, 22 µmol, 22%, colourless oil, α:β = >98:2) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.20 (m, 20H, CH_{arom}), 5.16 (d, *J* = 4.2 Hz, 1H, H-1), 4.76 (t, *J* = 11.4 Hz, 2H, CH_2 Bn), 4.67 (d, *J* = 11.7 Hz, 1H, C*H*H Bn), 4.65 – 4.59 (m, 2H, C*H*(CF_3)$_2$, C*H*H Bn), 4.57 (d, *J* = 11.5 Hz, 1H, CH*H* Bn), 4.54 (d, *J* = 11.8 Hz, 1H, CH*H* Bn), 4.52 (d, *J* = 3.1 Hz, 2H, CH_2 Bn), 4.26 (td, *J* = 6.2, 3.6 Hz, 1H, H-5), 3.81 (dd, *J* = 7.1, 5.1 Hz, 1H, H-3), 3.72 – 3.68 (m, 3H, H-4, 2x H-6), 3.65 (dd, *J* = 7.1, 4.2 Hz, 1H, H-2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.3, 138.1, 138.1, 137.6 (C_q), 129.6, 129.3, 128.9, 128.7, 128.6, 128.6, 128.6, 128.5, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.8, 127.8, 127.7, 127.7 (CH_{arom}), 101.6 (C-1), 78.1 (C-3), 77.6 (C-2), 73.8, 73.8, 73.6, 73.3 (CH_2 Bn), 70.1 (C-5), 68.2 (C-6), a cross-peak for (H-4, C-4) is visible at (3.70, 76.2) in the HSQC spectrum; ^{13}C-HMBC-GATED NMR (126 MHz, $CDCl_3$): δ 101.6 ($J_{H1\text{-}C1}$ = 173 Hz, α); HRMS: $[M+NH_4]^+$ calcd for $C_{37}H_{36}F_6O_6$ 708.27543, found 708.27396.

References

1. Adero, P. O.; Amarasekara, H.; Wen, P.; Bohé, L.; Crich, D., The Experimental Evidence in Support of Glycosylation Mechanisms at the SN1–SN2 Interface. *Chemical Reviews* **2018,** *118* (17), 8242-8284.
2. Crich, D., Mechanism of a Chemical Glycosylation Reaction. *Accounts of Chemical Research* **2010,** *43* (8), 1144-1153.
3. Bohé, L.; Crich, D., A propos of glycosyl cations and the mechanism of chemical glycosylation. *Comptes Rendus Chimie* **2011,** *14* (1), 3-16.
4. Andreana, P. R.; Crich, D., Guidelines for O-Glycoside Formation from First Principles. *ACS Central Science* **2021,** *7* (9), 1454-1462.
5. Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A., Stereochemical Reversal of Nucleophilic Substitution Reactions Depending upon Substituent: Reactions of Heteroatom-Substituted Six-Membered-Ring Oxocarbenium Ions through Pseudoaxial Conformers. *Journal of the American Chemical Society* **2000,** *122* (1), 168-169.
6. Chamberland, S.; Ziller, J. W.; Woerpel, K. A., Structural Evidence that Alkoxy Substituents Adopt Electronically Preferred Pseudoaxial Orientations in Six-Membered Ring Dioxocarbenium Ions. *Journal of the American Chemical Society* **2005,** *127* (15), 5322-5323.
7. Yang, M. T.; Woerpel, K. A., The Effect of Electrostatic Interactions on Conformational Equilibria of Multiply Substituted Tetrahydropyran Oxocarbenium Ions. *The Journal of Organic Chemistry* **2009,** *74* (2), 545-553.
8. Frihed, T. G.; Bols, M.; Pedersen, C. M., Mechanisms of Glycosylation Reactions Studied by Low-Temperature Nuclear Magnetic Resonance. *Chemical Reviews* **2015,** *115* (11), 4963-5013.
9. Hagen, B.; Ali, S.; Overkleeft, H. S.; van der Marel, G. A.; Codée, J. D. C., Mapping the Reactivity and Selectivity of 2-Azidofucosyl Donors for the Assembly of N-Acetylfucosamine-Containing Bacterial Oligosaccharides. *The Journal of Organic Chemistry* **2017,** *82* (2), 848-868.
10. van der Vorm, S.; Overkleeft, H. S.; van der Marel, G. A.; Codée, J. D. C., Stereoselectivity of Conformationally Restricted Glucosazide Donors. *The Journal of Organic Chemistry* **2017,** *82* (9), 4793-4811.
11. Walvoort, M. T. C.; Moggré, G.-J.; Lodder, G.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A., Stereoselective Synthesis of 2,3-Diamino-2,3-dideoxy-β-d-mannopyranosyl Uronates. *The Journal of Organic Chemistry* **2011,** *76* (18), 7301-7315.
12. Walvoort, M. T. C.; Lodder, G.; Mazurek, J.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A., Equatorial Anomeric Triflates from Mannuronic Acid Esters. *Journal of the American Chemical Society* **2009,** *131* (34), 12080-12081.
13. Walvoort, M. T. C.; Lodder, G.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A., Mannosazide Methyl Uronate Donors. Glycosylating Properties and Use

in the Construction of β-ManNAcA-Containing Oligosaccharides. *The Journal of Organic Chemistry* **2010,** *75* (23), 7990-8002.

14. Hansen, T.; Ofman, T. P.; Vlaming, J. G. C.; Gagarinov, I. A.; van Beek, J.; Goté, T. A.; Tichem, J. M.; Ruijgrok, G.; Overkleeft, H. S.; Filippov, D. V.; van der Marel, G. A.; Codée, J. D. C., Reactivity–Stereoselectivity Mapping for the Assembly of Mycobacterium marinum Lipooligosaccharides. *Angewandte Chemie International Edition* **2021,** *60* (2), 937-945.

15. Qiao, Y.; Ge, W.; Jia, L.; Hou, X.; Wang, Y.; Pedersen, C. M., Glycosylation intermediates studied using low temperature 1H- and 19F-DOSY NMR: new insight into the activation of trichloroacetimidates. *Chemical Communications* **2016,** *52* (76), 11418-11421.

16. Beaver, M. G.; Woerpel, K. A., Erosion of Stereochemical Control with Increasing Nucleophilicity: O-Glycosylation at the Diffusion Limit. *The Journal of Organic Chemistry* **2010,** *75* (4), 1107-1118.

17. van der Vorm, S.; Hansen, T.; Overkleeft, H. S.; van der Marel, G. A.; Codée, J. D. C., The influence of acceptor nucleophilicity on the glycosylation reaction mechanism. *Chemical Science* **2017,** *8* (3), 1867-1875.

18. van der Vorm, S.; Hansen, T.; van Hengst, J. M. A.; Overkleeft, H. S.; van der Marel, G. A.; Codée, J. D. C., Acceptor reactivity in glycosylation reactions. *Chemical Society Reviews* **2019,** *48* (17), 4688-4706.

19. Hansen, T.; Elferink, H.; van Hengst, J. M. A.; Houthuijs, K. J.; Remmerswaal, W. A.; Kromm, A.; Berden, G.; van der Vorm, S.; Rijs, A. M.; Overkleeft, H. S.; Filippov, D. V.; Rutjes, F. P. J. T.; van der Marel, G. A.; Martens, J.; Oomens, J.; Codée, J. D. C.; Boltje, T. J., Characterization of glycosyl dioxolenium ions and their role in glycosylation reactions. *Nature Communications* **2020,** *11* (1), 2664.

20. Rencurosi, A.; Lay, L.; Russo, G.; Caneva, E.; Poletti, L., NMR evidence for the participation of triflated ionic liquids in glycosylation reaction mechanisms. *Carbohydrate Research* **2006,** *341* (7), 903-908.

21. Nokami, T.; Shibuya, A.; Tsuyama, H.; Suga, S.; Bowers, A. A.; Crich, D.; Yoshida, J.-i., Electrochemical Generation of Glycosyl Triflate Pools. *Journal of the American Chemical Society* **2007,** *129* (35), 10922-10928.

22. Frihed, T. G.; Walvoort, M. T. C.; Codée, J. D. C.; van der Marel, G. A.; Bols, M.; Pedersen, C. M., Influence of O6 in Mannosylations Using Benzylidene Protected Donors: Stereoelectronic or Conformational Effects? *The Journal of Organic Chemistry* **2013,** *78* (6), 2191-2205.

23. Crich, D.; Sun, S., Are Glycosyl Triflates Intermediates in the Sulfoxide Glycosylation Method? A Chemical and 1H, 13C, and 19F NMR Spectroscopic Investigation. *Journal of the American Chemical Society* **1997,** *119* (46), 11217-11223.

24. Garcia, B. A.; Gin, D. Y., Dehydrative Glycosylation with Activated Diphenyl Sulfonium Reagents. Scope, Mode of C(1)-Hemiacetal Activation, and Detection of

Reactive Glycosyl Intermediates. *Journal of the American Chemical Society* **2000,** *122* (18), 4269-4279.

25. Pedersen, C. M.; Nordstrøm, L. U.; Bols, M., "Super Armed" Glycosyl Donors: Conformational Arming of Thioglycosides by Silylation. *Journal of the American Chemical Society* **2007,** *129* (29), 9222-9235.

26. Santana, A. G.; Montalvillo-Jiménez, L.; Díaz-Casado, L.; Corzana, F.; Merino, P.; Cañada, F. J.; Jiménez-Osés, G.; Jiménez-Barbero, J.; Gómez, A. M.; Asensio, J. L., Dissecting the Essential Role of Anomeric β-Triflates in Glycosylation Reactions. *Journal of the American Chemical Society* **2020,** *142* (28), 12501-12514.