Reactivity and selectivity in glycosylation reactions

Vorm, S. van der

Chapter 5

The stereoselectivity of 3,4-tethered glucosazide donors

Introduction

Both α- and β-linked glucosamine residues are widespread in naturally occurring carbohydrates.[1–5] While β-glucosamine linkages can be reliably installed using anchimeric assistance of a participating *N*-protecting group, the installation of the α-glucosamine bond commonly hinges on the use of a non-participating *N*-protecting group, where the azide is most commonly employed.[6–8] In chapters 3 and 4, a set of fluorinated model acceptors was introduced to investigate how the stereoselectivity of glycosylations of 4,6-tethered glucosazide donors relates to acceptor nucleophilicity. This approach revealed that the combination of a reactive donor glycoside and a weak nucleophile led to α-selective glycosylation reactions. In the current chapter, the stereoselectivity of glycosylations of a 3,4-tethered glucosazide donor is studied in relation to the nucleophilicity of the acceptor. The reactivity of the donor is assessed using Variable-Temperature NMR (VT-NMR) and competition experiments, followed by a series of glycosylations. The set of partially fluorinated model acceptors and a panel

of carbohydrate acceptors, introduced in the previous chapters, are used to map reactivity-stereoselectivity relationships to provide a basis for α-glucosaminylation reactions. [9–12]

Results and discussion

In an extension of the glucosazide donors described in the previous chapter, the butane diacetal (BDA)[13–15] protected glucosazide donor **1** is glycosylated with the range of acceptors depicted in Figure 1 to investigate how the stereoselectivity of glycosylations of donor **1** depends on the reactivity of these acceptors. Benzylidene glucose donor **2** and benzylidene glucosazide donor **3** serve as a direct comparison for the reactivity and selectivity of donor **1**. The 3,4-*O*-BDA protecting group locks the donor in a *trans*-decalin constellation, conformationally disarming the system, as is also the case for the 4,6-*O*-benzylidene in donors **2** and **3**. Severe conformational changes are prohibited, and the number of possible glycosylation reaction itineraries restricted.[16–18] The difference in electronic properties between the BDA group and the benzylidene acetal can be found in the rotational freedom of the C-6-substituent. In donor **1** the C-6–O-6 bond is not retained in its most electron withdrawing *tg*-conformation, as in donor **2** and **3** (Figure 1C).[18–20] The BDA protected donor **1** is therefore expected to be more reactive than benzylidene glucosazide donor **3**. This has previously been demonstrated in the *manno*-series by Crich and co-workers, who reported highly α-selective mannosylations with BDA-protected mannosyl donors. They related this to the higher reactivity of the BDA donor over the benzylidene donor and therefore a shift in the glycosylation reaction mechanism continuum from the β-selective S_N2-side for the latter donor to the α-selective S_N1-side for the former donor.[21] In contrast, glycosylations of the related 3,4-*O*-BDA-glucosyl donors proceeded with β-selectivity, which they interpreted to arise from an S_N2-type reaction on the relatively stable α-triflate. Collapse into the α-selective oxocarbeniun ion intermediate was prevented by the steric hindrance of the BDA-OMe group with the large C-2-OBn group (See Figure 3).[22] It may be hypothesized that the smaller 2-azido group in donor **1** does not experience this unfavorable steric effect allowing for the easier formation of the oxocarbenium intermediate. On the other hand, Chapter 4 has revealed the azide to promote S_N2-type reactions as a result of its electron withdrawing nature.

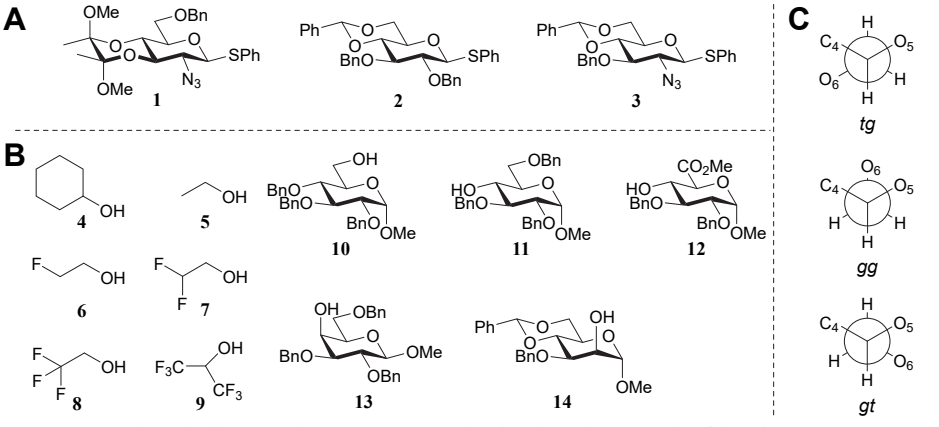
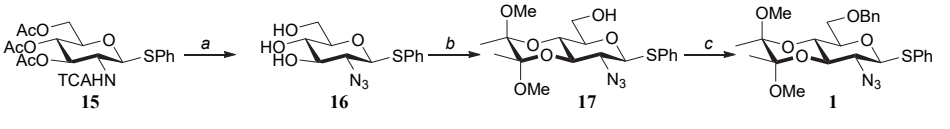


Figure 1. (A) Glycoside donors and (B) acceptors used in the glycosylation study of this chapter. (C) Newman projections of the three staggered rotamer conformations along the C-5–C-6 bond.

Donor **1** is synthesized from acetylated thioglycoside **15** (Scheme 1), by alkaline hydrolysis of the TCA and acetyl groups followed by diazotransfer to give the crude glucosazide **16**. Installation of the BDA and benzyl groups gave donor **1** in good overall yield.

Scheme 1. Synthesis of BDA-donor **1**.



Reagents and conditions: (a) *i*. K_2CO_3, EtOH, H_2O; *ii*. $CuSO_4 \cdot 5H_2O$, imidazole-1-sulfonyl azide hydrochloride[23]; (b) 2,3-butadione, trimethyl orthoformate, CSA, MeOH, 64% (three steps); (c) BnBr, NaH, DMF, 85%.

The activation of donor **1** was studied by VT-NMR.[24] To this end donor **1** was treated with Ph_2SO/Tf_2O in the presence of TTBP in deuterated DCM.[25] Figure 2A displays the spectra of the reaction mixture at a range of temperatures. Interestingly, various species are generated upon activation, the two most predominant of which were assigned as the α-anomeric triflate **18** (labelled ◊, ^{1}H δ = 6.09 ppm, $J_{H\text{-}1\text{–}H\text{-}2}$ = 3.3 Hz, ^{13}C δ = 105.8 ppm) and β-oxosulfonium triflate (labelled *, ^{1}H δ = 5.56 ppm, $J_{H\text{-}1\text{–}H\text{-}2}$ = 7.6 Hz, ^{13}C δ = 103.8 ppm) in a 3:1 ratio. Using either an equimolar amount or an excess of Ph_2SO (5 equivalents), the reaction mixture could be enriched in triflate **18** or

oxosulfonium triflate **19** (Figure 2B depicts the ^{19}F-NMR spectrum of the activation mixture using an excess Ph_2SO, showing full consumption of the anomeric triflate). When the sample (with 1.3 equivalents Ph_2SO) was heated to -50°C the signal of the β-oxosulfonium triflate disappeared irreversibly. Decomposition of the anomeric triflate started around -20°C, similar to the triflates reported in Chapter 4, and no specific product could be identified. The immediate formation of the β-oxosulfonium triflate, and the complete conversion of the anomeric triflate to this species when an excess of Ph_2SO is used, hints at the relatively high reactivity of the donor, in line with the observation made for the two most reactive donors in Chapter 4.

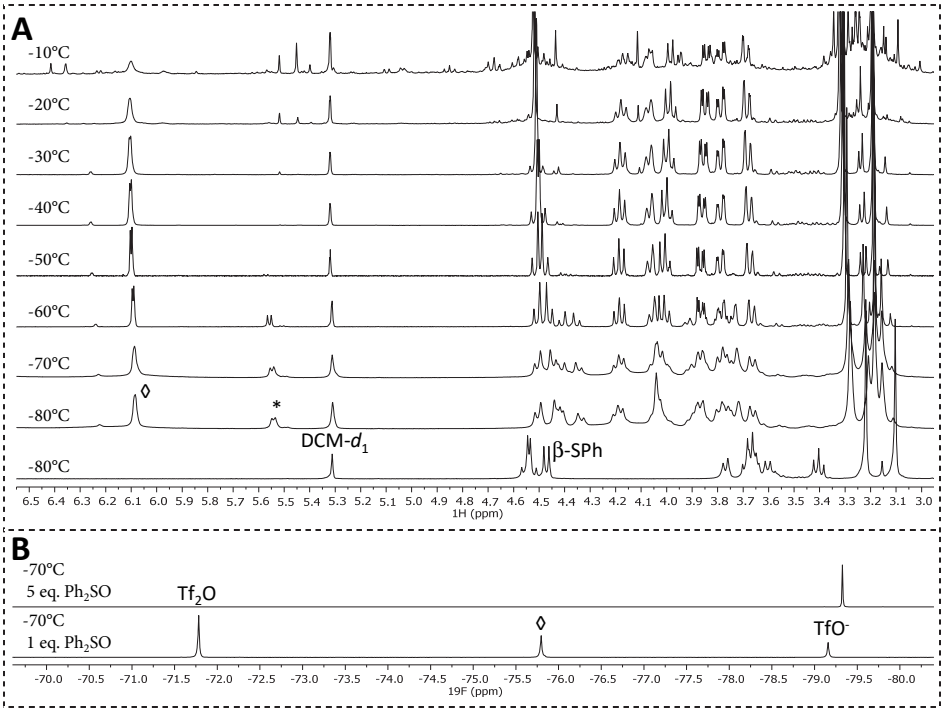
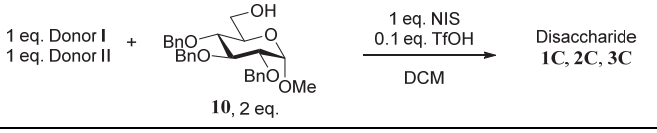


Figure 2. NMR activation study of donor **1**. (A) 1.3 eq. Ph_2SO, 1.3 eq. Tf_2O. The behavior of triflate **18** (◊) and oxosulfonium triflate **19** (*) between -80°C -10°C. (B) ^{19}F-NMR showing triflate **18** (◊) and its absence when 5 eq. Ph_2SO is added.

The relative reactivity of the BDA protected glucosazide versus its benzylidene counterpart was evaluated in a set of competition experiments (Table 1). The thioglycosides and acceptor **10** were mixed and made to compete for a limiting amount of NIS. This experiment revealed the BDA donor **1** to be six times more reactive than donor **3** towards NIS and, somewhat surprisingly given the stronger electron withdrawing capacity of the azide, two times more reactive than **2**. Apparently the combined disarming effect of the azide and BDA group, previously found to be semi-disarming,[26,27] is smaller than the disarming effect of the benzylidene group in donor **2**.

Table 1: Activation competition experiments between donors **1**, **2**, and **3**.

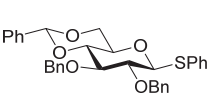
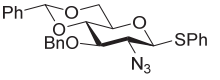
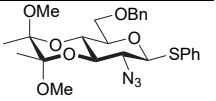
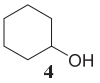
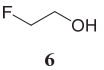
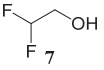
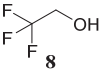
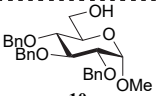
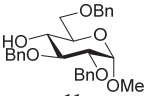
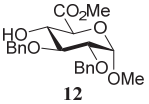
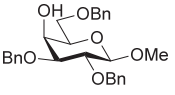
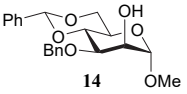


Entry	Donor I	Donor II	Solvent (M)	Product[a] I : II	Recovered donor[a] I : II	Yield[a] %	α : β
1	**1**	**2**	0.1 M DCM	**1C/2C** 2 : 1	1 : 1.4	75%	**1C**; 1 : 6 **2C**; 1 : 1
2	**1**	**3**	0.1 M DCM	**1C/3C** 6 : 1	1 : 10	99%	**1C**; 1 : 6 **3C**; 1 : 3
3	**2**	**3**	0.05 M DCM[b]	**2C/3C** 1 : 0	0 : 1	80%	**1C**; 1.5 : 1

[a]Isolated ratios after size-exclusion chromatography, and yield of the disaccharide fraction. [b]Reference relative reactivity between **2** and **3** (Chapter 4); selectivity increases with dilution.

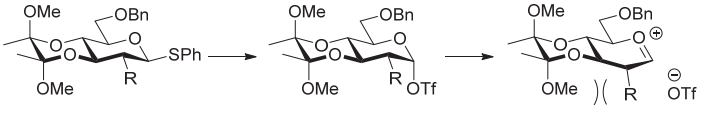
Next, the BDA glucosazide donor **1** was glycosylated with the set of fluorinated model nucleophiles and a selection of carbohydrate acceptors. The results of the glycosylations are listed in Table 2 and compared with the glycosylation results of donors **2** and **3**. The reactions were carried out by preactivating the donor from -78°C to -50°C to remove the contribution of the oxosulfonium triflate on the stereoselectivity of the reaction. Despite the high reactivity observed in the competition and activation experiments, indicating that oxocarbenium ion character readily develops at the anomeric center, the reactions of donor **1** are very β-selective. It is not surprising to find the strong nucleophiles cyclohexanol **4**, ethanol **5** and carbohydrate acceptor **10** to react with full β-selectivity, but the other acceptors, especially trifluoroethanol **8** and axially orientated nucleophiles **13** and **14**, react with unexpected low α-selectivity.

Table 2. Glycosylations of donors **1**-**3** with model acceptors **4**-**9** and carbohydrate acceptors **10**-**14**. Ordered by their overall β- to α-selectivity.

		 **2**	 **3**	 **1**
	Acceptor	Product[a] α:β (yield)[b]	Product α:β (yield)	Product α:β (yield)
A	 **4**	**2A** 71 % 1 : 5.1	**3A** 93 % < 1 : 20	**1A** 87 % < 1 : 20
B	 **5**	**2B** 68 % 1 : 10	**3B** 83 % < 1 : 20	**1B** 90 % < 1 : 20
C	 **6**	**2C** 70 % 1 : 2.8	**3C** 90 % 1 : 6.7	**1C** 97 % 1 : 20
D	 **7**	**2D** 70 % 5 : 1	**3D** 64 % 2.9 : 1	**1D** 84 % 1 : 3.5
E	 **8**	**2E** 64 % > 20 : 1	**3E** 94 % > 20 : 1	**1E** 87 % 2.5 : 1
F	 **9**	**2F** 65 % > 20 : 1	**3F** 53 % > 20 : 1	**1F**[c] 18% > 20 : 1
G	 **10**	**2G** 81 % 1 : 2.7	**3G** 89 % < 1 : 20	**1G** 86 % < 1 : 20
H	 **11**	**2H** 79 % 1 : 1	**3H** 88 % 1 : 7	**1H** 93 % 1 : 15
I	 **12**	**2I** 90 % 5 : 1	**3I** 93 % 1.1 : 1	**1I** 83 % 1.5 : 1
J	 **13**	**2J** 83 % > 20 : 1	**3J** 75 % 9 : 1	**1J** 86 % 1 : 1.8
K	 **14**	**2K** 80 % > 20 : 1	**3K** 74 % 9 : 1	**1K** 93 % 1 : 1.7

[a]Glycosylation results of donors **2** and **3**, are also reported in Chapter 3 and 4 of this thesis, respectively. [b]Ratio and yield of isolated product after column chromatography, anomers were not separated. [c]α,β-Trehalose **24** (neotrehalose) was also isolated as a single anomer in 25% yield.

The high β-selectivity for donor **1** under preactivation conditions is also apparent when compared with the previously reported C-2–OBn analogue.[22] Condensation (See Figure 3) of donor **20** and acceptor **11** provided an anomeric mixture (α/β, 1:4), whereas glycosylation of **1** and **11** led to a much higher β-selectivity (**1H**; α/β, 1:15). This observation is consistent with the scenario drawn in Chapter 4: the 2-azido group promotes an S_N2 pathway (via triflate **18**) due to additional electron-withdrawing from the anomeric center. Although the high β-selectivity appears contradictory to the high reactivity of the donor, it may also be that the BDA glucosazide oxocarbenium ion **22** (as part of a close ion pair) takes up a conformation favoring attack from the β-side.



1: R = N_3
20: R = OBn

18: R = N_3
21: R = OBn

22: R = N_3
23: R = OBn

Figure 3. Reactive species at play in the glycosylation reactions of donors **1** and **20**.

Conclusions

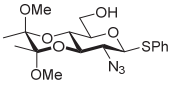
Condensations of butane diacetal (BDA) protected glucosazide donor **1** have been studied using the set of fluorinated model acceptors introduced in Chapters 3 and 4. The BDA protecting group in combination with the 2-azido functionality is highly β-directing in glycosylations without the need for a C-2 participating group. Despite the high β-selectivity, the model acceptors show the anticipated trend of reactivity of the acceptor versus glycosylation stereoselectivity, with less reactive acceptors providing more α-products as was established in Chapters 3 and 4, to provide yet another example of the importance of the reactivity of the acceptor in a glycosylation reaction. The exact underlying mechanism that causes the high β-selectivity has yet to be fully elucidated, but based on precedent, the high β-selective for donor **1** may arise from an S_N2-like substitution of the anomeric α-triflate. How this exactly relates to the high reactivity of the donor remains to be established.

Experimental section

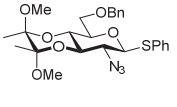
General procedure for Tf_2O/Ph_2SO mediated glycosylations: Donor (0.1 mmol), Ph_2SO (26 mg, 0.13 mmol, 1.3 eq.) and TTBP[29] (62 mg, 0.25 mmol, 2.5 eq.) were coevaporated twice with dry toluene and dissolved in dry DCM (2 mL, 0.05 M donor). Activated 3Å molecular sieves (rods, size 1/16 in.) were added, and the reaction mixture stirred for 1 h at room temperature under a nitrogen atmosphere. The solution was cooled to -78°C and Tf_2O (22 µl, 0.13 mmol, 1.3 eq.) was added. The reaction mixture was allowed to warm to -50°C followed by recooling to -78°C and addition of the acceptor (0.2 mmol, 2 eq.) in DCM (0.4 mL, 0.5 M). The reaction mixture was allowed to warm to -40°C in approximately 90 min and stirred for an additional 0-18 h depending on the acceptor. The reaction was quenched with Et_3N (0.1 mL, 0.72 mmol, 5.5 eq.) at -40 °C and diluted with DCM. The solution was transferred to a separatory funnel and water was added, the layers were separated and the water phase extracted once more with DCM. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silica gel flash column chromatography and when needed, sephadex™ LH-20 size exclusion chromatography yielded the glycosylation product as a mixture of anomers.

General procedure for the NIS/TfOH mediated competition experiments: Donor I (0.1 mmol, 1 eq.), donor II (0.1 mmol, 1 eq.) and acceptor **25** (0.2 mmol, 2 eq.) were together coevaporated with dry toluene (2x). Dry DCM (4 mL, donor concentration 0.1 M), a Teflon stirring bar and 3Å activated molecular sieves (rods, size 1/16 in.) were added and the mixture was stirred under a nitrogen atmosphere for 1 h at room temperature. The mixture was cooled to -40°C and NIS (0.1 mmol, 1 eq.) was added. TfOH (50 µL of a freshly prepared 0.2 M stock solution in dry DCM, 0.1 eq.) was added and the mixture was allowed to warm to 0°C in 3 hours. Et_3N (0.1 mL) was added and the mixture was diluted with EtOAc, washed with sat. aq. NaS_2O_3 and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Size exclusion chromatography (Sephadex LH-20, 1/1 DCM/MeOH) enabled isolation of the disaccharide products and the monosaccharide rests, which were both analysed with NMR spectroscopy. The yield of the disaccharide fraction was determined.

General procedure for the low temperature NMR experiments: A mixture of donor (30 µmol) and Ph_2SO (39 µmol) was coevaporated with dry toluene twice (for the activation of donor 1 also TTBP (75 µmol) was added). Under a nitrogen atmosphere, CD_2Cl_2 (0.6 mL) was added and the mixture transferred to a nitrogen flushed NMR tube and closed with a NMR tube septum. The NMR magnet was cooled to -80°C, locked and shimmed and the sample was measure prior to activation. In a long narrow cold bath (EtOH, -85°C) the sample was treated with Tf_2O (39 µmol), shaken thrice and cooled again after every shake. 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 equilibration time for every temperature.

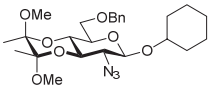


Phenyl 2-azido-2-deoxy-3,4-O-(2,3-dimethoxybutane-2,3-diyl)-1-thio-β-D-glucopyranoside (17). To a solution of crude triol **16** (synthesized as described in Chapter 4) (≤15 mmol) in dry MeOH (100 mL) was added butadione (2.0 mL, 22.5 mmol, 1.5 eq.), trimethyl orthoformate (9.8 mL, 90 mmol, 6 eq.) and CSA (523 mg, 2.25 mmol, 0.15 eq.) and the solution was refluxed overnight. Et_3N was added (1 mL) and the volatiles were removed in vacuo. Crystallization from EtOAc/petroleum ether yielded the tiles compound as a white solid (3.94 g, 9.56 mmol, 64% over three steps). Spectroscopic data were in accord with those previously reported.[30] ^1H NMR ($CDCl_3$, 400 MHz, HH-COSY, HSQC): δ 7.62 – 7.54 (m, 2H, CH_{arom}), 7.41 – 7.34 (m, 3H, CH_{arom}), 4.47 (d, 1H, *J* = 9.9 Hz, H-1), 3.91 (ddd, 1H, *J* = 12.0, 5.6, 2.6 Hz, H-6), 3.81 – 3.70 (m, 2H, H-3, H-6), 3.66 (t, 1H, *J* = 9.7 Hz, H-4), 3.55 (ddd, 1H, *J* = 9.6, 4.5, 2.7 Hz, H-5), 3.43 (t, 1H, *J* = 9.8 Hz, H-2), 3.35 (s, 3H, CH_3 OMe), 3.27 (s, 3H, CH_3 OMe), 2.02 (dd, 1H, *J* = 7.6, 5.9 Hz, 6-OH), 1.35 (s, 3H, CH_3 Me), 1.31 (s, 3H, CH_3 Me); ^{13}C-APT NMR ($CDCl_3$, 101 MHz, HSQC): δ 133.9 (CH_{arom}), 130.7 (C_q SPh), 129.3, 128.9 (CH_{arom}), 100.3, 99.9 (C_q BDA), 86.2 (C-1), 78.2 (C-5), 73.1 (C-3), 65.7 (C-4), 61.5 (C-2), 61.4 (C-6), 48.3, 48.2 (OMe), 17.7, 17.6 (Me).

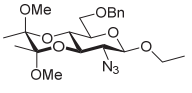


Phenyl 2-azido-6-*O*-benzyl-2-deoxy-3,4-O-(2,3-dimethoxybutane-2,3-diyl)-1-thio-β-D-glucopyranoside (1). Compound **17** was dissolved in DMF (45 mL) and cooled to 0°C. NaH (60% dispersion in mineral oil, 540 mg, 13.5 mmol, 1.5 eq.) and BnBr (1.4 mL, 11.7 mmol, 1.3 eq.) were added and the mixture was stirred at r.t. until complete conversion was observed (TLC). Excess NaH was quenched with MeOH and the solution was reduced in volume under reduced pressure. H_2O was added to the residue and extracted with Et_2O twice and DCM once. Combined organic layers were washed with H_2O and brine, dried with MgSO4, filtered and concentrated in vacuo. Flash column chromatography (1/0 to 9/1 pentane/EtOAc) and subsequently recrystallized (EtOAc, excess petroleum ether) gave the title compound as a white

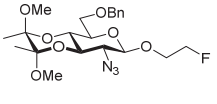
solid in two batches (total yield 3.84 g, 7.66 mmol, 85%). R_f: 0.25 (19/1 pentane/EtOAc). m.p.: 146-149°C.). $[\alpha]_D^{20}$ = +72.2° (*c* = 1.0, $CHCl_3$); IR (thin film): 689, 735, 752, 851, 885, 960, 1032, 1107, 1128, 1265, 1275, 1366, 1375, 1437, 1452, 2110, 2868; ^{1}H NMR ($CDCl_3$, 400 MHz, HH-COSY, HSQC): δ 7.63 – 7.57 (m, 2H, CH_{arom}), 7.36 – 7.27 (m, 5H, CH_{arom}), 7.26 – 7.21 (m, 3H, CH_{arom}), 4.63 (d, 1H, *J* = 11.9 Hz, C*H*H Bn), 4.56 (d, 1H, *J* = 11.9 Hz, CH*H* Bn), 4.41 (d, 1H, *J* = 9.8 Hz, H-1), 3.83 – 3.68 (m, 4H, H-3, H-4, H-6, H-6), 3.66 – 3.60 (m, 1H, H-5), 3.41 (t, 1H, *J* = 9.8 Hz, H-2), 3.32 (s, 3H, CH_3 OMe), 3.17 (s, 3H, CH_3 OMe), 1.32 (s, 3H, CH_3 Me), 1.27 (s, 3H, CH_3 Me); ^{13}C-APT NMR ($CDCl_3$, 101 MHz, HSQC): δ 138.5 (C_q Bn), 134.2 (CH_{arom}), 130.8 (C_q SPh), 129.2, 128.7, 128.4, 127.6, 127.5 (CH_{arom}), 100.3, 99.9 (C_q BDA), 86.1 (C-1), 78.1 (C-5), 73.6 (CH_2 Bn), 73.3 (C-3), 68.3 (C-6), 65.7 (C-4), 61.4 (C-2), 48.3, 48.2 (OMe), 17.8, 17.7 (Me); HRMS: $[M+NH_4]^+$ calcd for $C_{25}H_{35}N_3O_6S$ 519.22718, found 519.22695.



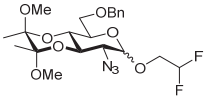
Cyclohexyl 2-azido-6-*O*-benzyl-2-deoxy-3,4-*O*-(2,3-dimethoxybutane-2,3-diyl)-β-D-**glucopyranoside (1A).** Donor **1** and cyclohexanol were condensed using the general procedure for Tf_2O/Ph_2SO mediated glycosylations (for an additional 18 hours at -40°C) and purified by flash column chromatography (1/0 to 9/1 pentane/EtOAc) to yield glycosylation product **1A** (43 mg, 87 µmol, 87%, α:β = <1:20). R_f: 0.6 (9/1 pentane/EtOAc). $[\alpha]_D^{20}$ = +98.6° (*c* = 1.08, $CHCl_3$); IR (thin film): 698, 849, 891, 959, 1047, 1121, 1368, 1452, 2108, 2932; ^{1}H NMR ($CDCl_3$, 400 MHz, HH-COSY, HSQC): δ 7.35 – 7.26 (m, 5H, CH_{arom}), 4.61 (d, 1H, *J* = 12.1 Hz, C*H*H Bn), 4.57 (d, 1H, *J* = 12.1 Hz, CH*H* Bn), 4.41 (d, 1H, *J* = 7.7 Hz, H-1), 3.76 (dd, 1H, *J* = 11.0, 1.6 Hz, H-6), 3.74 – 3.63 (m, 3H, *CH* Cy, H-4, H-6), 3.61 – 3.51 (m, 2H, H-3, H-5), 3.43 (dd, 1H, *J* = 10.4, 7.7 Hz, H-2), 3.30 (s, 3H, CH_3 OMe), 3.18 (s, 3H, CH_3 OMe), 2.02 – 1.87 (m, 2H, CH_2 Cy), 1.82 – 1.71 (m, 2H, CH_2 Cy), 1.58 – 1.37 (m, 3H, CH_2 Cy), 1.33 (s, 3H, CH_3 Me), 1.31 – 1.19 (m, 6H, CH_3 Me, CH_2 Cy); ^{13}C-APT NMR ($CDCl_3$, 101 MHz, HSQC): δ 138.4 (C_q), 128.4, 127.6, 127.6 (CH_{arom}), 101.2 (C-1), 100.0, 99.8 (C_q BDA), 78.3 (CH Cy), 74.0 (C-5), 73.6 (CH_2 Bn), 70.9 (C-3), 68.4 (C-6), 66.5 (C-4), 63.0 (C-2), 48.1, 48.1 (CH_3 OMe), 33.7, 31.8, 25.6, 24.1, 24.0 (CH_2 Cy), 17.7, 17.7 (CH_3 Me); HRMS: $[M+NH_4]^+$ calcd for $C_{25}H_{41}N_4O_7$ 509.29698, found 509.29668.



Ethyl 2-azido-6-*O*-benzyl-2-deoxy-3,4-*O*-(2,3-dimethoxybutane-2,3-diyl)-β-D-glucopyranoside (1B). Donor **1** and ethanol were condensed using the general procedure for Tf_2O/Ph_2SO mediated glycosylations (for an additional 30 min at -40°C) and purified by flash column chromatography (1/0 to 9/1 pentane/EtOAc) to yield glycosylation product **1B** (39.7 mg, 90 µmol, 90%, α:β = <1:20). R_f: 0.48 (9/1 pentane/EtOAc). $[\alpha]_D^{20}$ = +105.2° (*c* = 0.85, $CHCl_3$); IR (thin film): 698, 849, 1047, 1115, 1375, 2108, 2927; ^{1}H NMR ($CDCl_3$, 400 MHz, HH-COSY, HSQC): δ 7.39 – 7.24 (m, 5H, CH_{arom}), 4.61 (d, 1H, *J* = 12.2 Hz, C*H*H Bn), 4.57 (d, 1H, *J* = 12.2 Hz, CH*H* Bn), 4.31 (d, 1H, *J* = 7.7 Hz, H-1), 3.98 (dq, 1H, *J* = 9.5, 7.1 Hz, C*H*H Et), 3.76 (dd, 1H, *J* = 10.9, 1.7 Hz, H-6), 3.71 – 3.64 (m, 2H, H-5, H-6), 3.64 – 3.55 (m, 3H, H-3, H-4, CH*H* Et), 3.46 (dd, 1H, *J* = 10.5, 7.7 Hz, H-2), 3.31 (s, 3H, CH_3 OMe BDA), 3.18 (s, 3H, CH_3 OMe BDA), 1.34 (s, 3H, CH_3 Me BDA), 1.28 (t, 4H, *J* = 7.1 Hz, CH_3 Et), 1.27 (s, 3H, CH_3 Me BDA); ^{13}C-APT NMR ($CDCl_3$, 101 MHz, HSQC): δ 138.2 (C_q), 128.4, 127.6 (CH_{arom}), 102.4 (C-1), 100.1, 99.8 (C_q BDA), 74.0 (C-3/C-4), 73.6 (CH_2 Bn), 71.0 (C-3/C-4), 68.3 (C-6), 66.3 (C-5), 66.0 (CH_2 Et), 62.6 (C-2), 48.2, 48.1 (OMe BDA), 17.7, 17.7 (Me BDA), 15.2 (CH_3 Et); HRMS: $[M+NH_4]^+$ calcd for $C_{21}H_{35}N_4O_7$ 455.25003, found 455.24975.

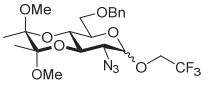


2-Fluoroethyl 2-azido-6-*O*-benzyl-2-deoxy-3,4-*O*-(2,3-dimethoxybutane-2,3-diyl)-β-D-glucopyranoside (1C). Donor **1** and 2-fluoroethanol were condensed using the general procedure for Tf_2O/Ph_2SO mediated glycosylations (for an additional 30 min at -40°C) and purified by flash column chromatography (1/0 to 9/1 pentane/EtOAc) to yield glycosylation product **1C** (44 mg, 97 µmol, 97%, α:β = 1:20). R_f: 0.30 (9/1 pentane/EtOAc). $[\alpha]_D^{20}$ = +96.4° (*c* = 1.10, $CHCl_3$); IR (thin film): 698, 881, 1049, 1113, 1375, 1454, 2110, 2949; ^{1}H NMR ($CDCl_3$, 500 MHz, HH-COSY, HSQC): δ 7.35 – 7.27 (m, 5H, CH_{arom}), 4.71 – 4.62 (m, 1H, C*H*HF), 4.62 – 4.52 (m, 3H, CH*H*F, CH_2 Bn), 4.36 (d, 1H, *J* = 7.7 Hz, H-1), 4.08 (dddd, 1H, *J* = 31.8, 12.2, 4.7, 2.6 Hz, *CH*H-CH_2F), 3.88 (dddd, 2H, *J* = 25.2, 12.1, 6.8, 2.7 Hz, CH*H*-CH_2F), 3.76 (dd, 1H, *J* = 11.0, 1.7 Hz, H-6), 3.72 (t, 1H, *J* = 10.0 Hz, H-4), 3.68 (dd, 1H, *J* = 11.0, 5.3 Hz, H-6), 3.65 – 3.56 (m, 2H, H-3, H-5), 3.50 (dd, 1H, *J* = 10.5, 7.7 Hz, H-2), 3.31 (s, 3H, CH_3 OMe), 3.19 (s, 3H, CH_3 OMe), 1.34 (s, 3H, CH_3 Me), 1.28 (s, 3H, CH_3 Me); ^{13}C-APT NMR ($CDCl_3$, 126 MHz, HSQC): δ 138.2 (C_q), 128.4, 127.7, 127.6 (CH_{arom}), 102.7 (C-1), 100.1, 99.8 (C_q BDA), 82.7 (d, *J* = 169.9 Hz, *C*H_2F), 74.1 (C-5), 73.6 (CH_2 Bn), 71.0 (C-3), 69.0 (d, *J* = 20.3 Hz, *C*H_2-CH_2F), 68.2 (C-6), 66.2 (C-4), 62.6 (C-2), 48.2, 48.2 (OMe), 17.7, 17.7 (Me); HRMS: $[M+NH_4]^+$ calcd for $C_{21}H_{34}FN_4O_7$ 473.24060, found 473.24041.

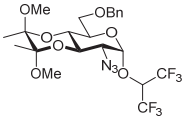


2,2-Difluoroethyl 2-azido-6-*O*-benzyl-2-deoxy-3,4-*O*-(2,3-dimethoxybutane-2,3-diyl)-α/β-D-glucopyranoside (1D). Donor **1** and 2,2-difluoroethanol were condensed using the general procedure for Tf_2O/Ph_2SO mediated glycosylations (for an additional 30 min at -

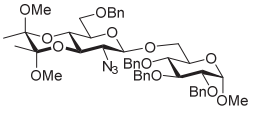
40°C) and purified by flash column chromatography (1/0 to 9/1 pentane/EtOAc) to yield glycosylation product **1D** (40 mg, 84 µmol, 84%, α:β = 1:3.5). R_f: 0.60 (9/1 pentane/EtOAc). IR (thin film): 698, 735, 849, 883, 1030, 1107, 1265, 1373, 1454, 2108, 2926; Data for the β-anomer: ^{1}H NMR ($CDCl_3$, 500 MHz, HH-COSY, HSQC): δ 7.38 – 7.27 (m, 5H, CH_{arom}), 6.10 – 5.82 (m, 1H, C*H*F_2), 4.62 – 4.54 (m, 2H, CH_2 Bn), 4.34 (d, 1H, *J* = 7.7 Hz, H-1), 4.05 – 3.93 (m, 1H, C*H*H-CHF_2), 3.90 – 3.78 (m, 1H, CH*H*-CHF_2,), 3.77 – 3.65 (m, 3H, H-4, H-6, H-6), 3.64 – 3.56 (m, 2H, H-3, H-5), 3.49 (dd, 1H, *J* = 10.5, 7.7 Hz, H-2), 3.30 (s, 3H, CH_3 OMe), 3.19 (s, 3H, CH_3 OMe), 1.34 (s, 3H, CH_3 Me), 1.28 (s, 3H, CH_3 Me); ^{13}C-APT NMR ($CDCl_3$, 126 MHz, HSQC): δ 138.1 (C_q), 128.5, 127.8, 127.6 (CH_{arom}), 114.2 (dd, *J* = 241.8, 240.8 Hz, CHF_2), 102.9 (C-1), 100.1, 99.9 (C_q BDA), 74.2 (C-5), 73.7 (CH_2 Bn), 70.9 (C-3), 68.8 (dd, *J* = 30.3, 28.1 Hz, *C*H_2-CHF_2), 68.1 (C-6), 66.0 (C-4), 62.6 (C-2), 48.2, 48.2 (OMe), 17.7, 17.7 (Me); Diagnostic peaks α-anomer: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.97 (d, 0.3H, *J* = 3.6 Hz, H-1), 4.25 (dd, 0.3H, *J* = 10.8, 9.7 Hz, H-3), 3.39 (dd, 0.3H, *J* = 10.9, 3.6 Hz, H-2), 3.37 (s, 0.9H, CH_3 OMe), 1.35 (s, 0.9H, CH_3 Me), 1.30 (s, 0.9H, CH_3 Me); ^{13}C-APT NMR ($CDCl_3$, 126 MHz, HSQC): δ 137.9, 128.4, 127.7, 127.6, 113.8 (t, *J* = 241.5 Hz), 100.2, 100.1 (C_q BDA), 99.4 (C-1), 73.7 (CH_2 Bn), 70.0 (C-5), 67.7 (C-6), 67.6 (t, *J* = 29.0 Hz, *C*H_2-CHF_2), 67.4 (C-3), 66.3 (C-4), 60.0 (C-2), 48.6, 17.9, 17.8; HRMS: $[M+NH_4]^+$ calcd for $C_{21}H_{33}F_2N_4O_7$ 491.23118, found 491.23061.



2,2,2-trifluoroethyl 2-azido-6-*O*-benzyl-2-deoxy-3,4-*O*-(2,3-dimethoxybutane-2,3-diyl)-α/β-D-glucopyranoside (1E). Donor **1** and 2,2,2-trifluoroethanol were condensed using the general procedure for Tf_2O/Ph_2SO mediated glycosylations (for an additional 30 min at -40°C) and purified by flash column chromatography (1/0 to 9/1 pentane/EtOAc) to yield glycosylation product **1E** (43 mg, 87 µmol, 87%, α:β = 2.5:1). R_f: 0.35 9/1 (pentane/EtOAc). IR (thin film): 673, 737, 851, 885, 972, 1030, 1111, 1279, 1377, 2108, 2949; Data for the α-anomer: ^{1}H NMR ($CDCl_3$, 400 MHz, HH-COSY, HSQC, HMBC): δ 7.38 – 7.24 (m, 5H, CH_{arom}), 5.01 (d, 1H, *J* = 3.6 Hz, H-1), 4.60 – 4.55 (m, 2H, CH_2 Bn), 4.28 (dd, 1H, *J* = 10.9, 9.5 Hz, H-3), 4.01 – 3.91 (m, 3H, C*H*$_2$$CF_3$, H-5), 3.89 – 3.82 (m, 1H, H-4), 3.78 – 3.66 (m, 2H, H-6, H-6), 3.41 – 3.35 (m, 4H, CH_3 OMe, H-2), 3.19 (s, 3H, CH_3 OMe), 1.35 (s, 3H, CH_3 Me), 1.30 (s, 3H, CH_3 Me); ^{13}C-APT NMR ($CDCl_3$, 101 MHz, HSQC, HMBC): δ 137.9 (C_q), 128.4, 127.8, 127.6 (CH_{arom}), 123.5 (q, *J* = 278.4 Hz, CF_3), 100.2, 100.1 (C_q BDA), 99.3 (C-1), 73.7 (CH_2 Bn), 70.3 (C-5), 67.6 (C-6), 67.2 (C-3), 66.2 (C-4), 65.1 (q, *J* = 35.3 Hz, *C*$H_2$$CF_3$), 59.8 (C-2), 48.6, 48.2 (OMe), 17.8, 17.8 (Me); Diagnostic peaks β-anomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.38 (d, 0.38H, *J* = 7.6 Hz, H-1), 4.16 (dq, 0.38H, *J* = 12.5, 8.7 Hz, C*H*H-CF_3), 3.65 – 3.56 (m, 2H, H-3, H-5), 3.50 (dd, 0.38H, *J* = 10.5, 7.6 Hz, H-2), 3.30 (s, 1.14H), 1.34 (s, 1.14H), 1.28 (s, 1.14H); ^{13}C-APT NMR ($CDCl_3$, 101 MHz): δ 102.4 (C-1), 100.2, 99.9, 74.4, 70.7, 68.0, 66.5, 66.0 (q, *J* = 35.1 Hz), 62.6, 48.2, 48.2, 17.7, 17.6; HRMS: $[M+NH_4]^+$ calcd for $C_{21}H_{32}F_3N_4O_7$ 509.22176, found 509.22116.

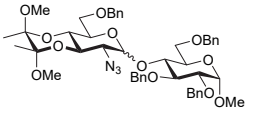


1,1,1,3,3,3-Hexafluoro-2-propyl 2-azido-6-*O*-benzyl-2-deoxy-3,4-*O*-(2,3-dimethoxybutane-2,3-diyl)-α-D-glucopyranoside (1F). Donor **1** and hexafluoro-*iso*-propanol were condensed using the general procedure for Tf_2O/Ph_2SO mediated glycosylations (for an additional 120 hours at -40°C) and purified by flash column chromatography (1/0 to 9/1 pentane/EtOAc) to yield glycosylation product **1F** (10 mg, 18 µmol, 18%, α:β = >20:1). R_f: 0.7 (9/1 pentane/EtOAc). $[\alpha]_D^{23}$ = +182.1° (*c* = 0.52, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, HH-COSY, HSQC, HMBC): δ 7.36 – 7.28 (m, 5H, CH_{arom}), 5.17 (d, 1H, *J* = 3.9 Hz, H-1), 4.58 (d, 1H, *J* = 12.0 Hz, C*H*H Bn), 4.54 (d, 1H, *J* = 12.0 Hz, CH*H* Bn), 4.44 (hept, 1H, *J* = 5.8 Hz, C*H* HFIP), 4.23 (dd, 1H, *J* = 11.1, 9.6 Hz, H-3), 4.02 (ddd, 1H, *J* = 10.0, 3.5, 2.0 Hz, H-5), 3.92 (t, 1H, *J* = 9.9 Hz, H-4), 3.78 (dd, 1H, *J* = 11.2, 3.5 Hz, H-6), 3.64 (dd, 1H, *J* = 11.1, 2.0 Hz, H-6), 3.46 (dd, 1H, *J* = 11.0, 3.9 Hz, H-2), 3.38 (s, 3H, CH_3 OMe), 3.20 (s, 3H, CH_3 OMe), 1.36 (s, 3H, CH_3 Me), 1.31 (s, 3H, CH_3 Me); ^{13}C-APT NMR ($CDCl_3$, 101 MHz, HSQC, HMBC): δ 137.8 (C_q Bn), 128.5, 127.8, 127.6 (CH_{arom} Bn), 101.1 (C-1), 100.3, 100.2 (C_q BDA), 73.8 (CH_2 Bn), 73.3 (CH HFIP), 71.3 (C-5), 67.2 (C-6), 66.9 (C-3), 65.9 (C-4), 59.8 (C-2), 48.8, 48.3 (OMe), 17.8, 17.8 (Me); HRMS: $[M+NH_4]^+$ calcd for $C_{22}H_{31}F_6N_4O_7$ 577.20914, found 577.20899.

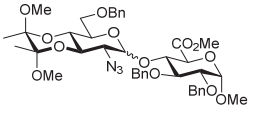


Methyl 6-*O*-(2-azido-6-*O*-benzyl-2-deoxy-3,4-*O*-(2,3-dimethoxybutane-2,3-diyl)-β-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (1G). Donor **1** and acceptor **10** were condensed using the general procedure for Tf_2O/Ph_2SO mediated glycosylations (for an additional 18 hours at -40°C) and purified by flash column chromatography (19/1 to 3/1 pentane/EtOAc) to yield glycosylation product **1G** (74 mg, 86 µmol, 86%, α:β = <1:20). R_f: 0.41 (4/1 pentane/EtOAc). $[\alpha]_D^{20}$ = +54.9° (*c* = 1.85, $CHCl_3$); IR (thin film): 696, 735, 849, 962, 1107, 1134, 1369, 1454, 2108, 2907; ^{1}H NMR ($CDCl_3$, 400 MHz, HH-COSY, HSQC, HMBC): δ 7.38 – 7.24 (m, 20H, CH_{arom}), 4.98 (d, 1H, *J* = 10.9 Hz, C*H*H Bn), 4.92 (d, 1H, *J* = 11.1 Hz, C*H*H Bn), 4.84 – 4.76 (m, 2H, CH*H* Bn, C*H*H Bn), 4.66 (d, 1H, *J* = 11.0 Hz, CH*H* Bn), 4.65 (d, 1H, *J* = 12.1 Hz, CH*H* Bn), 4.62 (d, 1H, *J* = 3.5 Hz, H-1), 4.58 (d, 1H, *J* = 12.1 Hz, C*H*H Bn), 4.53 (d, 1H, *J* = 12.2 Hz, CH*H* Bn), 4.20 (d, 1H, *J* = 7.7 Hz, H-1'), 4.12 (dd, 1H, *J* = 10.9, 1.6 Hz, H-6), 4.00 (t, 1H, *J* = 9.3 Hz, H-3), 3.83 – 3.77 (m, 1H, H-5), 3.76 – 3.63 (m, 4H, H-4', H-6, H-6', H-6'), 3.63 – 3.52 (m, 4H, H-2, H-3',

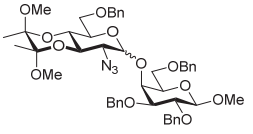
H-4, H-5'), 3.50 (dd, 1H, *J* = 10.3, 7.7 Hz, H-2'), 3.38 (s, 3H, CH_3 OMe), 3.30 (s, 3H, CH_3 OMe BDA), 3.16 (s, 3H, CH_3 OMe BDA), 1.33 (s, 3H, CH_3 Me), 1.26 (s, 3H, CH_3 Me); ^{13}C-APT NMR ($CDCl_3$, 101 MHz, HSQC, HMBC): δ 138.8, 138.5, 138.3, 138.2 (C_q), 128.5, 128.5, 128.5, 128.4, 128.2, 128.2, 128.1, 128.0, 127.8, 127.8, 127.6, 127.6, 127.5 (CH_{arom}), 102.7 (C-1'), 100.1, 99.8 (C_q BDA), 98.2 (C-1), 82.2 (C-3), 79.9 (C-2), 77.7 (C-4), 75.8, 74.9 (CH_2 Bn), 74.3 (C-5), 73.6, 73.5 (CH_2 Bn), 71.3 (C-3'), 69.8 (C-5), 68.6 (C-6), 68.3 (C-6'), 66.2 (C-4'), 62.8 (C-2'), 55.3 (CH_3 OMe), 48.1, 48.1 (CH_3 OMe BDA), 17.7, 17.6 (CH_3 Me BDA); HRMS: $[M+NH_4]^+$ calcd for $C_{47}H_{61}N_4O_{12}$ 873.42805, found 873.42812.



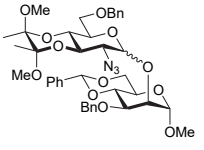
Methyl 4-*O*-(2-azido-6-*O*-benzyl-2-deoxy-3,4-*O*-(2,3-dimethoxybutane-2,3-diyl)-α/β-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (1H). Donor **1** and acceptor **11** were condensed using the general procedure for Tf_2O/Ph_2SO mediated glycosylations (for an additional 18 hours at -40°C) and purified by flash column chromatography (19/1 to 4/1 pentane/EtOAc) to yield glycosylation product **1H** (80 mg, 93 µmol, 93%, α:β = 1:15). R_f: 0.51 (4/1 pentane/EtOAc). IR (thin film): 696, 737, 1045, 1109, 1134, 1368, 1454, 1497, 2108, 2900; Data for the β-anomer: ^{1}H NMR ($CDCl_3$, 400 MHz, HH-COSY, HSQC, HMBC): δ 7.37 – 7.19 (m, 20H, CH_{arom}), 5.00 (d, 1H, *J* = 11.4 Hz, C*H*H Bn), 4.80 (d, 1H, *J* = 11.4 Hz, CH*H* Bn), 4.74 (d, 1H, *J* = 12.2 Hz, C*H*H Bn), 4.62 (d, 1H, *J* = 12.0 Hz, C*H*H Bn), 4.58 (d, 1H, *J* = 12.1 Hz, CH*H* Bn), 4.57 (d, 1H, *J* = 3.8 Hz, H-1), 4.52 (d, 1H, *J* = 12.1 Hz, CH*H* Bn), 4.48 (d, 1H, *J* = 12.4 Hz, C*H*H Bn), 4.35 (d, 1H, *J* = 7.8 Hz, H-1'), 4.33 (d, 1H, *J* = 12.2 Hz, CH*H* Bn), 4.00 – 3.94 (m, 1H, H-4), 3.91 (t, 1H, *J* = 9.1 Hz, H-3), 3.87 (dd, 1H, *J* = 10.8, 3.3 Hz, H-6), 3.81 – 3.76 (m, 1H, H-5), 3.71 (dd, 1H, *J* = 10.8, 1.6 Hz, H-6), 3.68 (t, 1H, *J* = 9.6 Hz, H-4'), 3.63 (dd, 1H, *J* = 11.1, 1.4 Hz, H-6'), 3.55 (t, 1H, *J* = 10.0 Hz, H-3'), 3.48 – 3.35 (m, 7H, CH_3 OMe, H-2, H-2', H-5', H-6'), 3.32 (s, 3H, CH_3 OMe BDA), 3.17 (s, 3H, CH_3 OMe BDA), 1.33 (s, 3H, CH_3 Me BDA), 1.26 (s, 3H, CH_3 Me BDA); ^{13}C-APT NMR ($CDCl_3$, 101 MHz, HSQC, HMBC): δ 139.5, 138.6, 138.3, 137.9 (C_q), 128.6, 128.5, 128.4, 128.4, 128.3, 128.2, 128.2, 128.1, 127.8, 127.8, 127.8, 127.8, 127.6, 127.5, 127.4, 127.3, 127.1 (CH_{arom}), 101.3 (C-1'), 100.1, 99.8 (C_q BDA), 98.4 (C-1), 80.3 (C-3), 79.1 (C-2), 76.7 (C-4), 75.4 (CH_2 Bn), 74.3 (C-5'), 73.7, 73.5 (CH_2 Bn), 71.6 (C-3'), 69.8 (C-5), 68.4 (C-6), 68.1 (C-6'), 66.2 (C-4'), 63.5 (C-2'), 55.3 (OMe), 48.2, 48.1 (OMe BDA), 17.7, 17.6 (Me BDA); Diagnostic peaks α-anomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.72 (d, 0.1H, *J* = 4.1 Hz, H-1'), 5.09 (d, 0.1H, *J* = 10.5 Hz, C*H*H Bn), 4.84 (d, 0.1H, *J* = 10.5 Hz, CH*H* Bn), 4.17 – 4.11 (m, 0.1H), 4.06 (d, 0.1H, *J* = 9.1 Hz); ^{13}C-APT NMR ($CDCl_3$, 101 MHz): δ 100.0 (C_q BDA), 98.6 (C-1'), 97.7 (C-1), 82.0, 80.6, 75.1, 74.2, 73.3, 70.2, 60.0, 55.4, 48.6; HRMS: $[M+NH_4]^+$ calcd for $C_{47}H_{61}N_4O_{12}$ 873.42805, found 873.42783.



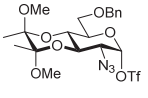
Methyl (Methyl 4-*O*-[2-azido-6-*O*-benzyl-2-deoxy-3,4-*O*-(2,3-dimethoxybutane-2,3-diyl)-α/β-D-glucopyranosyl]-2,3-di-*O*-benzyl-α-D-glucopyranosyl uronate) (1I). Donor **1** and acceptor **12** were condensed using the general procedure for Tf_2O/Ph_2SO mediated glycosylations (for an additional 18 hours at -40°C) and purified by flash column chromatography (19/1 to 4/1 pentane/EtOAc) to yield glycosylation product **1I** (66 mg, 83 µmol, 83%, α:β = 1.5:1). R_f: 0.44 and 0.47 (4/1 pentane/EtOAc). IR (thin film): 698, 735, 1043, 1107, 1454, 1749, 2108, 2949; Reported as a 1 : 0.7 mixture of anomers: ^{1}H NMR ($CDCl_3$, 400 MHz, HH-COSY, HSQC, HMBC): δ 7.34 – 7.21 (m, 31H), 5.58 (d, 1H, *J* = 3.8 Hz, H-1'$_\alpha$), 5.05 – 4.98 (m, 1.7H, C*H*H Bn $_\alpha$, C*H*H Bn$_\beta$), 4.85 (d, 1H, *J* = 10.5 Hz, CH*H* Bn$_\alpha$), 4.82 – 4.71 (m, 2.4H, C*H*H Bn$_\alpha$, CH*H* Bn$_\beta$, C*H*H Bn$_\beta$), 4.62 – 4.53 (m, 4.4H, C*H*H Bn$_\alpha$, CH*H* Bn$_\alpha$ CH*H* Bn$_\beta$, H-1$_\alpha$, H-1$_\beta$), 4.50 (d, 1H, *J* = 12.0 Hz, CH*H* Bn$_\alpha$), 4.43 (d, 0.7H, *J* = 12.2 Hz, C*H*H Bn$_\beta$), 4.38 (d, 0.7H, *J* = 7.8 Hz, H-1'$_\beta$), 4.34 (d, 0.7H, *J* = 12.1 Hz, CH*H* Bn$_\beta$), 4.23 (d, 0.7H, *J* = 9.8 Hz, H-5$_\beta$), 4.18 (d, 1H, *J* = 9.4 Hz, H-5$_\alpha$), 4.13 (dd, 1H, *J* = 10.9, 9.7 Hz, H-3'$_\alpha$), 4.08 – 4.00 (m, 2.7H, H-3$_\alpha$, H-4$_\alpha$, H-4$_\beta$), 3.93 (t, 0.7H, *J* = 9.1 Hz, H-3$_\beta$), 3.83 (t, 1H, *J* = 10.0 Hz, H-4'$_\alpha$), 3.81 (s, 2.1H, CH_3 CO_2Me_β), 3.73 – 3.67 (m, 4.7H, CH_3 CO_2Me_α, H-4'$_\beta$, H-6'$_\alpha$), 3.61 – 3.44 (m, 6.5H, H-2$_\alpha$, H-2$_\beta$, H-3'$_\beta$, H-5'$_\alpha$, H-5'$_\beta$, H-6'$_\alpha$, H-6'$_\beta$, H-6'$_\beta$), 3.41 – 3.36 (m, 5.8H, CH_3 OMe$_\alpha$, CH_3 OMe$_\beta$, H-2'$_\beta$), 3.35 (s, 3H, CH_3 OMe BDA$_\alpha$), 3.30 – 3.26 (m, 3.1H, CH_3 OMe BDA$_\beta$, H-2'), 3.16 (s, 2.1H, CH_3 OMe BDA$_\beta$), 3.15 (s, 3H, CH_3 OMe BDA$_\alpha$), 1.32 (s, 5.1H, CH_3 Me BDA$_\alpha$, CH_3 Me BDA$_\beta$), 1.25 (s, 2.1H, CH_3 Me BDA$_\beta$), 1.23 (s, 3H, CH_3 Me BDA$_\alpha$); ^{13}C-APT NMR ($CDCl_3$, 101 MHz, HSQC, HMBC): δ 170.1, 169.9 (C=O), 139.3, 138.5, 138.4, 138.1, 138.1, 137.8 (C_q), 128.6, 128.5, 128.5, 128.4, 128.3, 128.3, 128.2, 128.2, 128.0, 128.0, 128.0, 127.8, 127.7, 127.7, 127.6, 127.6, 127.6, 127.5, 127.4, 127.4, 127.2 (CH_{arom}), 102.1 (C-1'$_\beta$), 100.1, 99.8, 99.8 (C_q BDA), 98.9 (C-1$_\beta$), 98.6 (C-1$_\alpha$), 98.3 (C-1'$_\alpha$), 81.3 (C-3$_\alpha$), 79.8 (C-3$_\beta$), 79.6 (C-2$_\alpha$), 79.0 (C-4$_\beta$), 78.6 (C-2$_\beta$), 75.5, 75.4 (CH_2 Bn), 74.9 (C-4$_\alpha$), 74.4 (C-5'$_\beta$), 73.9, 73.8, 73.7, 73.5 (CH_2 Bn), 71.3 (C-3'$_\beta$), 70.1 (C-5$_\alpha$), 70.0 (C-5'$_\alpha$), 69.9 (C-5$_\beta$), 68.0 (C-6'$_\beta$), 67.4 (C-3'$_\alpha$), 67.3 (C-6'$_\alpha$), 66.0 (C-4'$_\beta$), 65.8 (C-4'$_\alpha$), 63.4 (C-2'$_\alpha$), 60.1 (C-2'$_\beta$), 55.9, 55.8 (OMe), 52.7, 52.7 (CO_2 Me), 48.4, 48.2, 48.1, 48.1 (OMe BDA), 17.9, 17.7, 17.7, 17.6 (Me BDA); HRMS: $[M+NH_4]^+$ calcd for $C_{41}H_{55}N_4O_{13}$ 811.37601, found 811.37610.



Methyl 4-*O*-(2-azido-6-*O*-benzyl-2-deoxy-3,4-*O*-(2,3-dimethoxybutane-2,3-diyl)-α/β-D-glucopyranosyl)-2,3,6-tri-*O*-benzyl-β-D-galactopyranoside (1J). Donor **1** and acceptor **13** were condensed using the general procedure for Tf_2O/Ph_2SO mediated glycosylations (for an additional 18 hours at -40°C) and purified by flash column chromatography (19/1 to 4/1 pentane/EtOAc) to yield glycosylation product **1J** (74 mg, 86 µmol, 86%, α:β = 1:1.7). R_f: 0.48 and 0.54 (4/1 pentane/EtOAc). IR (thin film): 696, 737, 1034, 1109, 1368, 1454, 2108, 2930; Reported as a 1 : 1.5 mixture of anomers: ^{1}H NMR ($CDCl_3$, 400 MHz, HH-COSY, HSQC, HMBC): δ 7.42 – 7.19 (m, 50H, CH_{arom}), 4.99 (d, 1H, *J* = 3.9 Hz, H-1'$_α$), 4.90 (d, 1H, *J* = 10.9 Hz, C*H*H Bn$_α$), 4.90 – 4.83 (m, 3H, 2xC*H*H Bn$_β$), 4.79 (d, 1H, *J* = 10.9 Hz, CH*H* Bn$_α$), 4.75 – 4.71 (m, 4H, CH*H* Bn$_β$, C*H*H Bn$_α$, H-1'$_β$), 4.66 (d, 1.5H, *J* = 12.2 Hz, CH*H* Bn$_β$), 4.62 (d, 1H, *J* = 12.5 Hz, CH*H* Bn$_α$), 4.53 (s, 2H, CH_2 Bn$_α$), 4.49 (s, 3H, CH_2 Bn$_β$), 4.48 – 4.40 (m, 4H, CH_2 Bn$_β$, C*H*H Bn$_α$), 4.32 (d, 1H, *J* = 12.2 Hz, CH*H* Bn$_α$), 4.28 (d, 1.5H, *J* = 7.8 Hz, H-1$_β$), 4.27 – 4.21 (m, 2H, H-3'$_α$, H-5'$_α$), 4.23 (d, 1H, *J* = 7.6 Hz, H-1$_α$), 4.14 (d, 1H, *J* = 3.0 Hz, H-4$_α$), 4.09 (d, 1.5H, *J* = 2.6 Hz, H-4$_β$), 3.98 – 3.87 (m, 3.5H, H-2$_β$, H-4'$_α$, H-6$_α$), 3.82 (dd, 1.5H, *J* = 10.5, 4.7 Hz, H-6'$_β$), 3.75 – 3.55 (m, 14H, CH_3 OMe$_β$, H-2$_α$, H-4'$_β$, H-5'$_β$, H-6'$_β$, H-6$_α$, H-6$_β$, H-6$_β$), 3.54 – 3.40 (m, 11H, CH_3 OMe$_α$, H-2'$_β$, H-3$_β$, H-3'$_β$, H-5$_α$, H-5$_β$, H-6'$_α$), 3.40 – 3.33 (m, 5H, CH_3 OMe BDA$_α$, H-2'$_α$, H-3$_α$), 3.31 (s, 4.5H, CH_3 OMe BDA$_β$), 3.18 – 3.10 (m, 8.5H, CH_3 OMe BDA$_{α,β}$, H-6'$_α$), 1.34 (s, 3H, CH_3 Me BDA$_α$), 1.34 (s, 4.5H, CH_3 Me BDA$_β$), 1.29 (s, 3H, CH_3 Me BDA$_α$), 1.27 (s, 4.5H, CH_3 Me BDA$_β$); ^{13}C-APT NMR ($CDCl_3$, 101 MHz, HSQC, HMBC): δ 138.9, 138.8, 138.6, 138.5, 138.5, 138.3, 138.2, 137.6 (C_q), 128.6, 128.4, 128.4, 128.4, 128.3, 128.3, 128.2, 128.2, 128.2, 128.1, 127.6, 127.6, 127.6, 127.6, 127.5, 127.5, 127.5, 127.5, 127.3, 127.2 (CH_{arom}), 105.3 (C-1$_α$), 105.1 (C-1$_β$), 102.5 (C-1'$_β$), 100.1, 100.0, 99.9, 99.8 (C_q BDA), 99.4 (C-1'$_α$), 81.3 (C-3$_β$), 80.2 (C-3$_α$), 79.5 (C-2$_β$) , 79.0 (C-2$_α$), 75.2, 75.0 (CH_2 Bn), 74.1 (C-4$_α$), 73.9 (C-5'$_β$), 73.9 (C-5$_β$), 73.7 (CH_2 Bn), 73.6 (C-4$_β$), 73.6, 73.6, 73.5, 73.4 (CH_2 Bn), 73.0 (C-5$_α$), 72.9 (CH_2 Bn), 70.7 (C-3'$_β$), 70.3 (C-6'$_β$), 69.5 (C-5'$_α$), 68.5 (C-6$_β$), 68.0 (C-3'$_α$), 67.2, 67.1 (C-6$_α$, C-6'$_α$), 66.2 (C-4'$_β$), 66.0 (C-4'$_α$), 62.7 (C-2'$_β$), 60.9 (C-2'$_α$), 57.3, 57.2 (OMe), 48.7, 48.2, 48.1, 48.1 (OMe BDA), 17.9, 17.9, 17.7, 17.7 (Me BDA); HRMS: $[M+NH_4]^+$ calcd for $C_{47}H_{61}N_4O_{12}$ 873.42805, found 873.42801.

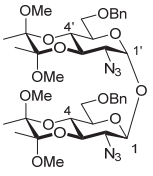


Methyl 2-*O*-(2-azido-6-*O*-benzyl-2-deoxy-3,4-*O*-(2,3-dimethoxybutane-2,3-diyl)-α/β-D-glucopyranosyl)-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (1K). Donor **1** and acceptor **14** were condensed using the general procedure for Tf_2O/Ph_2SO mediated glycosylations (for an additional 18 hours at -40°C) and purified by flash column chromatography (19/1 to 4/1 pentane/EtOAc) to yield glycosylation product **1K** (71 mg, 93 µmol, 93%, α:β = 1:1.7). R_f: 0.45 (4/1 pentane/EtOAc).IR (thin film): 698, 1038, 1109, 1126, 1375, 1454, 2110, 2912; Data for the β-anomer: ^{1}H NMR ($CDCl_3$, 400 MHz, HH-COSY, HSQC, HMBC): δ 7.52 – 7.47 (m, 2H, CH_{arom}), 7.40 – 7.32 (m, 3H, CH_{arom}), 7.30 – 7.19 (m, 10H, CH_{arom}), 5.60 (s, 1H, C*H*Ph), 4.86 – 4.78 (m, 2H, C*H*H Bn, H-1), 4.64 (d, 1H, *J* = 12.5 Hz, CH*H* Bn), 4.54 (d, 1H, *J* = 12.0 Hz, C*H*H Bn), 4.49 (d, 1H, *J* = 11.9 Hz, CH*H* Bn), 4.41 (d, 1H, *J* = 7.3 Hz, H-1'), 4.29 (dd, 1H, *J* = 3.3, 1.5 Hz, H-2), 4.24 (dd, 1H, *J* = 10.0, 4.6 Hz, H-6), 4.16 (t, 1H, *J* = 9.7 Hz, H-4), 3.93 (dd, 1H, *J* = 10.1, 3.4 Hz, H-3), 3.86 (t, 1H, *J* = 10.2 Hz, H-6), 3.82 – 3.61 (m, 6H, H-2', H-4', H-5, H-5', H-6', H-6'), 3.57 (dd, 1H, *J* = 10.8, 7.9 Hz, H-3'), 3.37 (s, 3H, CH_3 OMe), 3.30 (s, 3H, CH_3 OMe BDA), 3.18 (s, 3H, CH_3 OMe BDA), 1.34 (s, 3H, CH_3 Me BDA), 1.28 (s, 3H, CH_3 Me BDA); ^{13}C-APT NMR ($CDCl_3$, 101 MHz, HSQC, HMBC): δ 138.5, 138.1, 137.8 (C_q), 128.4, 128.3, 128.2, 127.8, 127.6, 127.4, 127.3, 126.2, 126.2 (CH_{arom}), 101.6 (CHPh), 101.4 (C-1'), 100.0, 99.8 (C_q BDA), 99.3 (C-1), 78.1 (C-4), 74.7 (C-2), 74.4 (C-5'), 73.8 (CH_2 Bn), 73.7 (C-3), 71.0 (CH_2 Bn), 70.5 (C-3'), 68.9, 68.8 (C-6, C-6'), 66.4 (C-4'), 64.2 (C-5), 63.0 (C-2'), 55.0 (OMe), 48.1 (OMe BDA), 17.7, 17.7 (Me BDA); Data for the α-anomer: ^{1}H NMR ($CDCl_3$, 400 MHz, HH-COSY, HSQC, HMBC): δ 7.51 – 7.43 (m, 2H, CH_{arom}), 7.40 – 7.23 (m, 13H, CH_{arom}), 5.62 (s, 1H, C*H*Ph), 5.35 (d, 1H, *J* = 3.8 Hz, H-1'), 4.88 (d, 1H, *J* = 12.4 Hz, C*H*H Bn), 4.75 (d, 1H, *J* = 1.3 Hz, H-1), 4.69 (d, 1H, *J* = 12.4 Hz, CH*H* Bn), 4.57 (s, 2H, CH_2 Bn), 4.32 (dd, 1H, *J* = 10.9, 9.6 Hz, H-3'), 4.30 – 4.22 (m, 2H, H-4, H-6), 4.10 (dd, 1H, *J* = 3.0, 1.7 Hz, H-2), 4.03 (ddd, *J* = 10.2, 5.0, 1.7 Hz, 1H, H-5'), 3.96 (dd, 1H, *J* = 9.9, 3.1 Hz, H-3), 3.85 (t, 1H, *J* = 10.2 Hz, H-6), 3.80 – 3.66 (m, 4H, H-4', H-5, H-6', H-6'), 3.42 (s, 3H, CH_3 OMe BDA), 3.25 – 3.17 (m, 7H, CH_3 OMe BDA, CH_3 OMe, H-2'), 1.36 (s, 3H, CH_3 Me BDA), 1.32 (s, 3H, CH_3 Me BDA); ^{13}C-APT NMR ($CDCl_3$, 101 MHz, HSQC, HMBC): δ 138.8, 138.0, 137.8 (C_q), 128.9, 128.8, 128.3, 128.2, 127.7, 127.7, 127.6, 127.4, 126.2 (CH_{arom}), 101.6 (CHPh), 100.9 (C-1), 100.2 (C-1'), 100.1, 100.0 (C_q BDA), 79.5 (C-4), 76.1 (C-2), 75.5 (C-3), 73.7, 73.1 (CH_2 Bn), 70.0 (C-5'), 69.0 (C-6), 68.2 (C-6'), 66.9 (C-4'), 66.5 (C-3'), 63.9 (C-5), 60.1 (C-2'), 54.8 (OMe), 48.7, 48.2 (OMe BDA), 17.9, 17.8 (Me BDA); HRMS: $[M+NH_4]^+$ calcd for $C_{40}H_{53}N_4O_{12}$ 781.36545, found 781.36550.



Trifluoromethanesulfonyl 2-azido-6-*O*-benzyl-2-deoxy-3,4-*O*-(2,3-dimethoxybutane-2,3-diyl)-α-D-glucopyranoside (18). ^{1}H NMR (CD_2Cl_2, *T* = 243 K, 500 MHz, HH-COSY, HSQC): δ 6.10 (d, 1H, *J* = 3.3 Hz, H-1), 4.52 (d, 1H, *J* = 11.5 Hz, C*H*H Bn), 4.48 (d, 1H, *J* = 11.3 Hz, CH*H* Bn), 4.19 (t, 1H, *J* = 10.2 Hz, H-3), 4.07 (d, 1H, *J* = 10.4 Hz, H-5), 4.01 (t, 1H, *J* = 9.9 Hz, H-4), 3.87 (dd, 1H, *J* = 10.8, 3.5 Hz, H-2), 3.79 (dd, 1H, *J* = 11.1, 2.3 Hz, H-6), 3.67 (d, 1H, *J* = 11.1 Hz, H-6), 3.30 (s, 3H, CH_3 OMe), 3.19 (s, 3H, CH_3 OMe),

1.30 (s, 3H, CH_3 Me), 1.25 (s, 3H, CH_3 Me); ^{13}C-APT NMR (CD_2Cl2, 126 MHz, HSQC): δ 105.8 (C-1), 99.8, 99.6 (C_q BDA), 73.2 (C-5), 72.9 (CH_2 Bn), 67.5 (C-3), 65.9 (C-6), 63.6 (C-4), 58.6 (C-2), 48.3, 48.1 (OMe), 17.3, 17.2 (Me).



1-(2-azido-6-*O*-benzyl-2-deoxy-3,4-*O*-[2,3-dimethoxybutane-2,3-diyl]-α-D-glucopyranosyl)-2-azido-6-*O*-benzyl-2-deoxy-3,4-*O*-[2,3-dimethoxybutane-2,3-diyl]-β-D-glucopyranoside (24). IR (thin film): 698, 737, 883, 1032, 1107, 1134, 1263, 1279, 1375, 1454, 2108, 2926, 2947, 2994;^{1}H NMR ($CDCl_3$, 400 MHz, HH-COSY, HSQC): δ 7.36 – 7.21 (m, 10H, CH_{arom}), 5.20 (d, 1H, *J* = 3.6 Hz, H-1'), 4.53 – 4.46 (m, 2H, CH_2 Bn), 4.44 – 4.38 (m, 2H, C*H*H Bn, H-1), 4.35 – 4.28 (m, 2H, CH*H* Bn, H-3'), 4.23 (dt, 1H, *J* = 10.7, 2.4 Hz, H-5'), 3.93 (t, 1H, *J* = 10.0 Hz, H-4'), 3.74 – 3.52 (m, 8H, H-2, H-3, H-4, H-5, 2xH-6, 2xH-6'), 3.39 (dd, 1H, *J* = 7.3, 3.5 Hz, H-2'), 3.37 (s, 3H, CH_3 OMe), 3.32 (s, 3H, CH_3 OMe), 3.21 (s, 3H, CH_3 OMe), 3.16 (s, 3H, CH_3 OMe), 1.35 (s, 3H, CH_3 Me), 1.34 (s, 3H, CH_3 Me), 1.29 (s, 3H, CH_3 Me), 1.28 (s, 3H, CH_3 Me); ^{13}C-APT NMR ($CDCl_3$, 101 MHz, HSQC): δ 138.3, 138.2 (C_q Bn), 128.5, 128.3, 127.7, 127.6 (CH_{arom}), 102.0 (C-1), 100.3, 100.2, 100.0, 99.9 (C_q BDA), 99.8 (C-1'), 74.4 (C-5), 73.6, 73.5 (CH_2 Bn), 71.6 (C-3), 70.6 (C-5'), 68.3 (C-6), 67.5 (C-3'), 67.4 (C-6'), 66.0 (C-4'), 65.9 (C-4), 63.3 (C-2), 60.1 (C-2'), 48.7, 48.2, 48.2, 48.2 (OMe), 17.9, 17.8, 17.8, 17.7 (Me); HRMS: $[M+NH_4]^+$ calcd for $C_{38}H_{56}N_6O_{13}$ 818.39306, found 818.39310.

References and footnotes

(1) Griffiths, A. J.; Davies, D. B. *Carbohydr. Polym.* **1991**, *14* (4), 339–365.
(2) Griffiths, A. J.; Davies, D. B. *Carbohydr. Polym.* **1991**, *14* (3), 241–279.
(3) Demchenko, A. V. *Handbook of Chemical Glycosylation: Advances in Stereoselectivity and Therapeutic Relevance*; Wiley-VCH Verlag GmbH & Co. KGaA, 2008.
(4) Boltje, T. J.; Buskas, T.; Boons, G.-J. *Nat. Chem.* **2009**, *1* (8), 611–622.
(5) Varki, A. *Glycobiology* **1993**, *3* (2), 97–130.
(6) Bongat, A. F. G.; Demchenko, A. V. *Carbohydr. Res.* **2007**, *342* (3–4), 374–406.
(7) Nigudkar, S. S.; Demchenko, A. V. *Chem. Sci.* **2015**, *6* (5), 2687–2704.
(8) Enugala, R.; Carvalho, L. C. R.; Dias Pires, M. J.; Marques, M. M. B. *Chem. – Asian J.* **2012**, *7* (11), 2482–2501.
(9) Manabe, S.; Ito, Y. *Chem. Rec.* **2014**, *14* (3), 502–515.
(10) Benakli, K.; Zha, C.; Kerns, R. J. *J. Am. Chem. Soc.* **2001**, *123* (38), 9461–9462.
(11) Boysen, M.; Gemma, E.; Lahmann, M.; Oscarson, S. *Chem. Commun.* **2005**, *0* (24), 3044–3046.
(12) Geng, Y.; Zhang, L.-H.; Ye, X.-S. *Tetrahedron* **2008**, *64* (22), 4949–4958.
(13) Hense, A.; Ley, S. V.; Osborn, H. M. I.; Owen, D. R.; Poisson, J.-F.; Warriner, S. L.; Wesson, K. E. *J. Chem. Soc. [Perkin 1]* **1997**, *0* (14), 2023–2032.
(14) Montchamp, J.-L.; Tian, F.; Hart, M. E.; Frost, J. W. *J. Org. Chem.* **1996**, *61* (11), 3897–3899.
(15) Douglas, N. L.; Ley, S. V.; Osborn, H. M. I.; Owen, D. R.; Priepke, H. W. M.; Warriner, S. L. *Synlett* **1996**, *1996* (08), 793–795.
(16) Fraser-Reid, B.; Wu, Z.; Andrews, C. W.; Skowronski, E.; Bowen, J. P. *J. Am. Chem. Soc.* **1991**, *113* (4), 1434–1435.
(17) Andrews, C. W.; Rodebaugh, R.; Fraser-Reid, B. *J. Org. Chem.* **1996**, *61* (16), 5280–5289.
(18) Jensen, H. H.; Nordstrøm, L. U.; Bols, M. *J. Am. Chem. Soc.* **2004**, *126* (30), 9205–9213.
(19) Frihed, T. G.; Walvoort, M. T. C.; Codée, J. D. C.; van der Marel, G. A.; Bols, M.; Pedersen, C. M. *J. Org. Chem.* **2013**, *78* (6), 2191–2205.
(20) Moumé-Pymbock, M.; Furukawa, T.; Mondal, S.; Crich, D. *J. Am. Chem. Soc.* **2013**, *135* (38), 14249–14255.
(21) Crich, D.; Cai, W.; Dai, Z. *J. Org. Chem.* **2000**, *65* (5), 1291–1297.
(22) Crich, D.; Subramanian, V.; Hutton, T. K. *Tetrahedron* **2007**, *63* (23), 5042–5049.
(23) Goddard-Borger, E. D.; Stick, R. V. *Org. Lett.* **2007**, *9* (19), 3797–3800.
(24) Frihed, T. G.; Bols, M.; Pedersen, C. M. *Chem. Rev.* **2015**, *115* (11), 4963–5013.
(25) Codée, J. D. C.; Litjens, R. E. J. N.; den Heeten, R.; Overkleeft, H. S.; van Boom, J. H.; van der Marel, G. A. *Org. Lett.* **2003**, *5* (9), 1519–1522.
(26) Douglas, N. L.; Ley, S. V.; Lücking, U.; Warriner, S. L. *J. Chem. Soc. [Perkin 1]* **1998**, No. 1, 51–66.
(27) Boons, G.-J.; Grice, P.; Leslie, R.; Ley, S. V.; Yeung, L. L. *Tetrahedron Lett.* **1993**, *34* (52), 8523–8526.

(29) Crich, D.; Smith, M.; Yao, Q.; Picione, J. *Synthesis* **2001**, *2001* (02), 0323–0326.
(30) Subramanian, V.; Moumé-Pymbock, M.; Hu, T.; Crich, D. *J. Org. Chem.* **2011**, *76* (10), 3691–3709.