Reagent Controlled Synthesis of 1,2-cis-Oligosaccharides

Wang, L.

Chapter 7

Summary and Future Prospects

Summary

The stereoselective synthesis of glycosidic bonds is a very challenge task and there is no general solution for the construction of demanding glycosidic bonds, such as 1,2-*cis* linkages and linkages of 2-deoxy sugars.[1] It is tremendously difficult to design a general glycosylation strategy that can accommodate the varying reactivity of different donor-acceptor glycoside combinations and ensures a fully stereoselective glycosylation process. The introduction of nucleophilic additives to modulate the glycosylation reaction has been an important step forwards in this direction, as this opens the way to match donor and acceptor reactivity.[2] It may enable a glycosylation strategy that employs a single donor type, devoid of any stereodirecting protecting groups and is under full control of the used reagents.[3]

To this end, this Thesis describes a strategy to synthesize 1,2-*cis*-oligosaccharides modulated by

additives, such as dimethylformamide (DMF), triphenylphosphine oxide ($Ph_3P=O$) and *N*-methyl(phenyl)formamide (MPF), using building blocks that carry solely benzyl type protecting groups and are therefore of uniform reactivity. These three additives were used for different classes of donor-acceptor combinations. The additive DMF was mainly used to modulate glycosylations of per-benzylated glucosyl donors and secondary alcohol acceptors. The TMSI-$Ph_3P=O$ condition was used to glycosylate the more reactive primary alcohol acceptors. The MPF additive, which forms less stable anomeric imidinium ion intermediates than DMF, was used for donors that are somewhat less reactive, such as those in the 2-azido-2deoxy series.

Chapter 1 provides an overview of the development of additive mediated glycosylations. Several additives (DMF, phosphine oxides, tetraalkyl ammonium halides) have been well studied on a broad scope of substrates and in a number of applications in oligosaccharide syntheses. Mechanistic studies have provided proof that the intermediate adducts of the additive and glycosyl donor play a key role in the glycosylation mechanism. Notwithstanding the initial successes described in Chapter 1, there still is a great demand to develop new additives and strategies using these reactivity modulators for the selective construction of glycosidic bonds and use assembly of complex and branched oligosaccharides.

Chapter 2 describes an additive controlled glycosylation strategy to assemble branched α-glucans (see Figure 1).[3a] The synthetic strategy builds on the use of DMF and TMSI-$Ph_3P=O$ controlled glycosylation reactions and the use of one single benzyl type protecting group (Bn, PMB, Nap). To illustrate the applicability of the strategy, a linear α-(1,4)-hexasaccharide and a branched α-glucan from *Mycobacterium tuberculosis* were assembled (Figure 1). Encouraged by these results**,** a linear α-(1,3)-glucan from the pathogenic fungus *Aspergillus fumigatus* was assembled in a fully stereoselective manner as described in **Chapter 3**.[3b]

Chapter 4 further explores the methodology for the synthesis of α-(1,2)-glucans. It was observed that DMF-mediated glycosylations proceeded with excellent stereoselectivity to forge α-(1,2)-glucosyl linkages of short oligosaccharides, but the construction of longer kojioligosaccharides was confronted with erosion of stereoselectivity, indicating a limitation of the methodology. Likely, the secondary structure of the larger oligosaccharide acceptors led to the decrease in stereoselectivity. A kojitetrasaccharide and a D-Alanine containing kojibiose glycerol phosphate teichoic acid building block to enable the assembly of *Enterococcus faecalis* LTAs, were synthesized (see Figure 1).

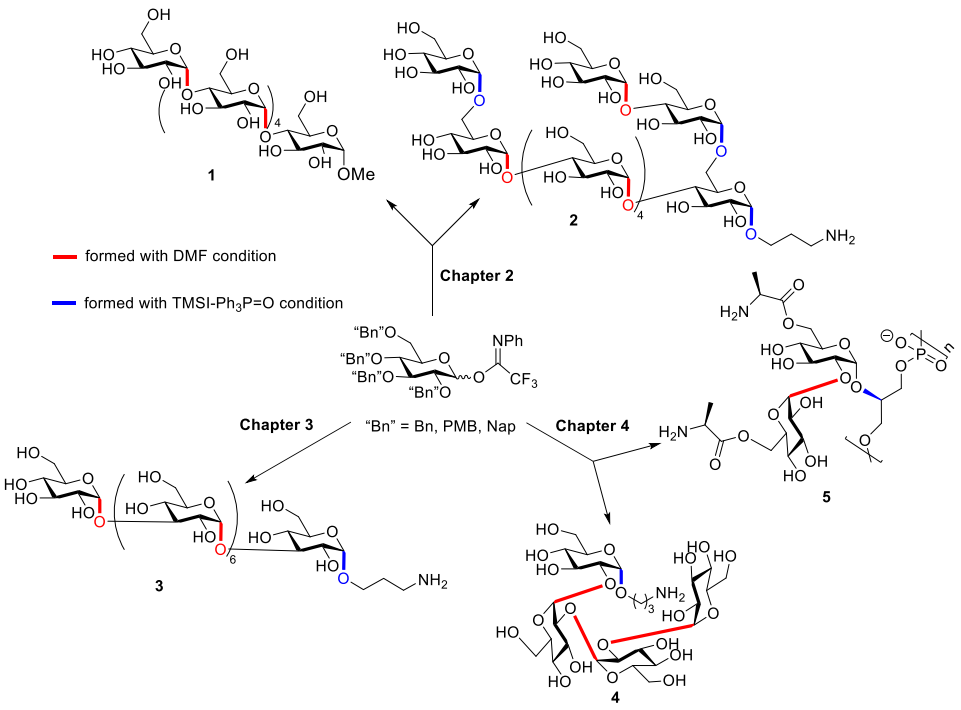


Figure 1. Target molecules assembled in Chapters 2, 3 and 4.

After the successful formation of α-glucosides, the formation of α-galactosides received attention in **Chapter 5** (see Figure 2). The stereoselective construction of the α-(1,4)-galactosides proved especially challenging. After screening different additives, the combination of TMSI-Ph_3P=O at higher temperature proved effective to construct the challenging galactose-α-(1,4)-galactose linkage. It was also shown that the TMSI-Ph_3P=O conditions can be applied to a wider substrate scope.

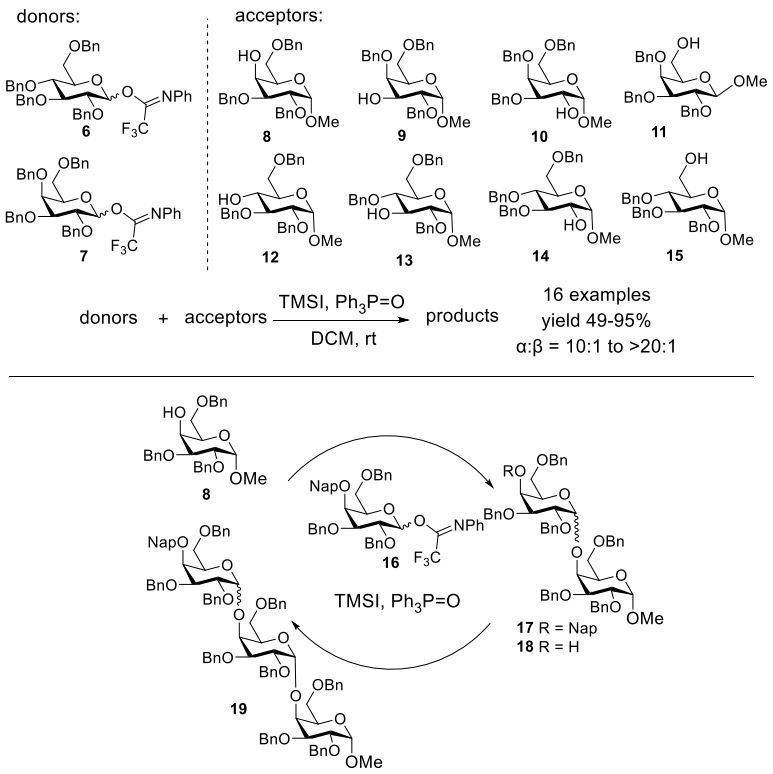


Figure 2. Glycosylations using the TMSI-Ph_3P=O conditions developed in Chapter 5.

A new additive, MPF, was introduced in **Chapter 6** (Figure 3) for the glycosylation 2-azido-2-deoxy building blocks, which are less reactive than their 2-*O*-benzyl counterparts. A linear α-(1,4)-glucosamine tetrasaccharide was assembled to prove the utility of MPF. Next, a linear Pel hexasaccharide was assembled using a [2+2+2] strategy modulated by MPF. The used [galactosazide-α-(1,4)-glucosazide] disaccharide building blocks were synthesized using a 4,6-*O*-DTBS protected galactosyl azide donor.

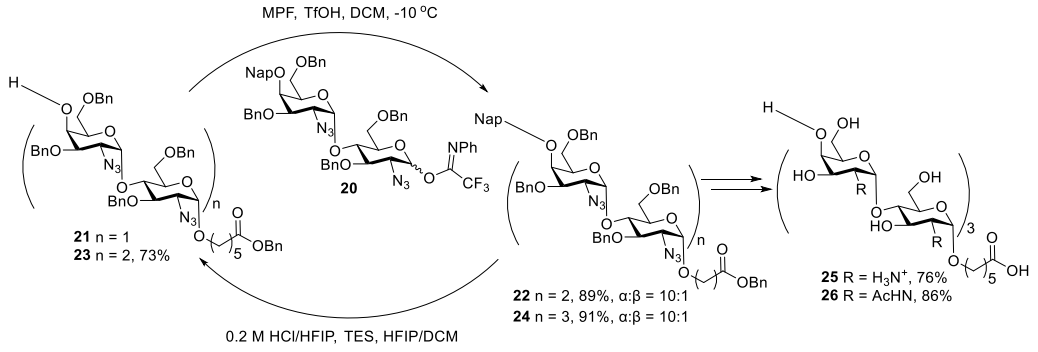
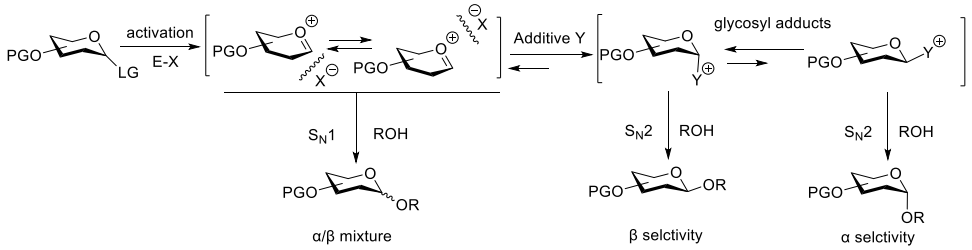


Figure 3. Assembly of Pel fragment.

Future Prospects

In additive-controlled glycosylation reactions, it has been shown that the intermediate adducts of the activated glycosyl donors and additives play a key role in the glycosylation mechanism and the reactivity of the glycosyl adducts is all important for the outcome of the glycosylation reactions.[4] The proposed mechanism for additive controlled glycosylations is depicted in Scheme 1. In this mechanism, the pool of reactive intermediates, initially formed by activation of the parent donor, is trapped by the nucleophilic additive to provide a mixture of α- and β-linked covalent additive-glycosyl donor species. Of these the more reactive β-adduct is displaced more rapidly which can lead to an overall α-selective glycosylation reaction. Judicious tuning of the reactivity of the reactive adducts is important to enable the stereoselective generation the α-linked products. Although spectroscopic evidence has been forwarded for the existence of the covalent additive-glycosyl donor adducts, detailed kinetic studies underpinning the reaction mechanism are missing to date.



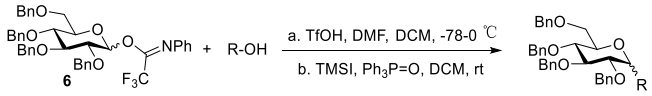
Scheme 1. The proposed reaction mechanism of additive controlled glycosylation reactions.

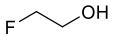
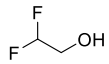
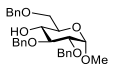
To determine where the reaction mechanism lies along the S_N2-S_N1 continuum and how it shifts with changing donor structure and variation of the additive, kinetic isotope effects (KIE) can be studied. This technique has recently been used for a selection of glycosylation reactions, including the β-mannosylations and α-glucosylations developed by Crich and co-workers using benzylidene protected donors, [1c] the organocatalyzed glycosylations of Jacobsen [5] and the anionic glycosylation reactions of Bennett and co-workers [6]. The evaluation of KIEs (both primary $^{12}C/^{13}C$ and secondary $^{1}H/^{2}H$ effects) in a systematic series of glycosylations in which either the reactivity of the donor, acceptor or additive is gradually changed will provide insight into the origin of the stereoselectivity (or lack thereof) in these glycosylation reactions. This will be instructive in the future development of rationally designed additive controlled glycosylation reactions.

Table 1 shows how the stereoselectivity of a per-*O*-benzylated glucosyl donor developed with gradually changing nucleophilicity of the acceptor (decreasing going from ethanol to monofluorethanol to difluroethanol to trifluoroethanol) for DMF-mediated and TMSI-Ph_3P=O promoted glycosylations. The intermediate glycosyl adduct formed from TMSI-Ph_3P=O is less

reactive than that formed under DMF-modulation. In line with the results described above, the less reactive TMSI-Ph_3P=O conditions always gave a higher α-selectivity than the DMF-mediated conditions but at the expense of a lower yield. The α-selectivity is increasing for both sets of glycosylations from ethanol to trifluoroethanol (entry 1-4, Table 1). This clearly shows the influence of the reactivity of the substrates on the outcome of these glycosylations. Using this set of acceptors to measure KIEs and establish whether and how fast the mechanism changes with changing nucleophilicity will underpin the limitation and substrate scope for the studied additives.

Table 1. The influence of acceptor reactivity in glycosylations of per-*O*-benzylated glucosyl donor.

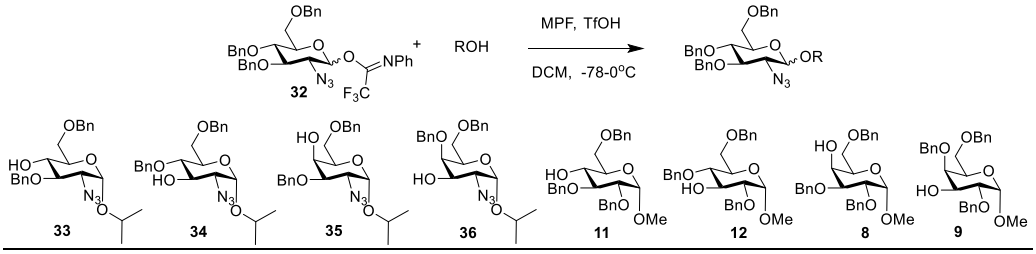


Entry	ROH	Product	Yield %		α:β	
			a	b	a	b
1	ethanol	**27**	quant	quant	2.7:1	4:1
2		**28**	61	42	3.5:1	5.5:1
3		**29**	75	73	6.7:1	15:1
4		**30**	62	80	13:1	18:1
5		**31**	94	61	>20:1	>20:1

In Chapter 6, a new additive, MPF, is preselected for condensations of 2-azido-2-deoxy glucosyl donors. Although this additive was successfully used to assemble an oligo glucosamine and Pel oligosaccharide, Table 2 shows that the substrate scope of this method is quite narrow. The selectivity is significantly better for the C4-OH azidoglucose acceptor **33** and galactose acceptor **35** than their C3-OH counterparts **34** and **36** (entry 1-2 and 3-4, Table 2). A similar trend is revealed for the C4-OH and C3-OH glucose and galactose acceptors (**11** and **12** and **8** and **9**, respectively). Likely this is the result of the reactivity of the MPF imidinium ion, which is too reactive for the C3-OH acceptors, which are more reactive than their C4-OH counterparts. For the more reactive acceptors the less reactive *N*-formylmorfoline (NMF) introduced by Mong and co-workers can be explored.[7] A systematic study in which these additives and DMF are compared side-by-side will inform on the scope and limitations of these additives. It will also be of interest to map how the stereoselectivity of these systems changes with varying protecting group pattern. The use of acyl groups is commonplace to ensure the formation of 1,2-*trans*-

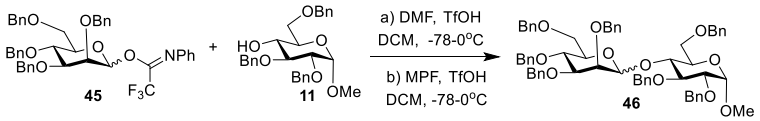
linkages. The electron-withdrawing capacity of these groups will have an effect on the reactivity of neighboring alcohol groups.

Table 2. Glycosylation of 2-azido donor **32** under MPF conditions.



Entry	ROH	product	yield	α:β
1	**33**	**37**	90%	16:1
2	**34**	**38**	78%	8:1
3	**35**	**39**	57%	5:1
4	**36**	**40**	63%,	2:1
5	**11**	**41**	97%	10:1
6	**12**	**42**	92%	3:1
7	**8**	**43**	99%	5:1
8	**9**	**44**	99%	1.2:1

The synthesis of β-mannosides is an extremely challenging task because of the axially oriented substituent at the C2 of the donor. Several successful attempts have been reported to form β-mannosides, including Crich's benzylidene mannose system[8], Demchenko's hydrogen bond guided β-mannosylation strategy,[9] the use of mannuronic acids, and intramolecular aglycon delivery (IAD) systems. An additive controlled glycosylation would offer an even more direct way to construct these challenging linkages. The synthesis of 1,2-*cis*-mannosides is completely different to 1,2-*cis*-glucosides because an equatorial β-glycosic bond needs to be formed instead of an axial α-bond. The glycosylation of per-benzyl mannosyl donor **45** was explored using both DMF and MPF mediated conditions. As shown in Scheme 2, the selectivity of both systems is poor, with the less reactive DMF system performing better than the more reactive MPF one. Therefore, new additives need be found from the "toolbox" by further studying of the relationship of the reactivity of the additives and the stereochemistry of this glycosylation reaction.



a) quant, α:β = 2:1. b) quant, α:β = 5:1.

Scheme 2. Explorative glycosylations of mannosyl donor **45**.

Finally, the scope of the additives, described in this Thesis, should be explored further using various other donor glycosides, including deoxy systems (which can be found on the reactivity side of the spectrum) and glycuronic acids (on the low reactivity side of the spectrum). Relevant examples include fucosylations, rhamnosylations and xylosylations but also C2-deoxy systems such as found in various medically relevant bacterial glycosides and glycoconjugates (*e.g.* doxorubicin, aclarubicin and digitoxin).

Experimental Section

General experimental procedures

All reagents were of commercial grade and used as received. All moisture sensitive reactions were performed under an argon atmosphere. DCM used in the glycosylation reactions was dried with flamed 4Å molecular sieves before being used. Reactions were monitored by TLC analysis with detection by UV (254 nm) and where applicable by spraying with 20% sulfuric acid in EtOH or with a solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4{\cdot}2H_2O$ (10 g/L) in 10% sulfuric acid (aq.) followed by charring at ~150 °C. Column chromatography was carried out using silica gel (0.040-0.063 mm). Size-exclusion chromatography was carried out using Sephadex LH-20. ^1H and ^{13}C spectra were recorded on a Bruker AV 400 and Bruker AV 500 in $CDCl_3$ or D_2O. Chemical shifts (δ) are given in ppm relative to tetramethylsilane as internal standard (^1H NMR in $CDCl_3$) or the residual signal of the deuterated solvent. Coupling constants (*J*) are given in Hz. All ^{13}C spectra are proton decoupled. NMR peak assignments were made using COSY and HSQC experiments, where applicable Clean TOCSY, HMBC and GATED experiments were used to further elucidate the structure. The anomeric product ratios were analyzed through integration of proton NMR signals and HPLC. HPLC analysis was performed over chiralpak AD column (0.46cmΦ×25cm) and eluted with hexane/isopropanol (95/5) mixture at a 1 mL/min flow rate and UV 254nm detector.

Standard procedure

Procedure A for the glycosylation of secondary alcohols:

A mixture of donor (1.0 eq), acceptor (0.7 eq) (donors and acceptors co-evaporated with toluene three times), DMF (16 eq) in dry DCM were stirred over fresh flame-dried molecular sieves 3A under nitrogen. The solution was cooled to -78 °C, after which TfOH (1.0 eq) was added. After 30 min, the reaction was stirred at 0 or -10 °C until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N, filtered and concentrated *in vacuo*. The products were purified by size exclusion and silica gel column chromatography.

Procedure B for the glycosylation of primary alcohols:

A mixture of donor (1.0 eq), acceptor (0.7 eq) (donors and acceptors co-evaporated with toluene three times), $Ph_3P{=}O$ (6

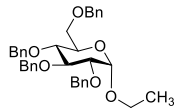
eq) in dry DCM were stirred over fresh flame-dried molecular sieves 3A under nitrogen. Then TMSI (1.0 eq) was added slowly in the mixture. The reaction was stirred at room temperature until TLC-analysis indicated the reaction to be complete. The solution was diluted and the reaction quenched with saturated $Na_2S_2O_3$. The organic phase was washed with water and brine, dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The products were purified by size exclusion and silica gel column chromatography.

Procedure C for the glycosylation of secondary alcohols:

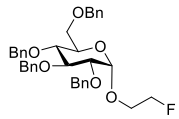
A mixture of donor (1.0 eq), acceptor (0.7 eq) (donors and acceptors co-evaporated with toluene three times), MPF (16 eq) in dry DCM were stirred over fresh flame-dried molecular sieves 3A under nitrogen. The solution was cooled to -78 ℃, after which TfOH (1.0 eq) was added. After 30 min, the reaction was stirred at 0 or -10 ℃ until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N, filtered and concentrated *in vacuo*. The products were purified by size exclusion.

Experimental Procedures and Characterization Data of Products

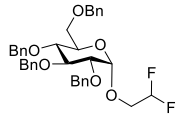
For the synthesis procedure and data of known compounds **6**, **31**, **32**, **33**, **35** see previous Chapter 2 and 6and **27**[10], **44**[11], **46**[12] see references.



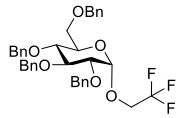
Synthesis of **27**: The reaction was carried out according to the standard procedure A or B. Under condition A, using **6** (70 mg, 0.1 mmol, 0.1 M in DCM), ethanol (11 μL, 0.2 mmol), DMF (124 μL) and TfOH (10 μL, 0.1 mmol). The reaction was stirred at -78-0 ºC until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N, filtered and concentrated *in vacuo*. The product was purified by silica gel column chromatography. Compound **27** (quant, α:β = 2.7:1) was obtained as a colorless syrup. Under condition B, using **6** (80 mg, 0.11 mmol, 0.1 M in DCM), ethanol (13 μL, 0.22 mmol), Ph_3P=O (185 mg, 0.66 mmol) and TMSI (15 μL, 0.11 mmol). The product was purified by silica gel column chromatography. Compound **27** (quant, α:β > 4:1) was obtained as a colorless syrup.



Synthesis of **28**: The reaction was carried out according to the standard procedure A or B. Under condition A, using **6** (70 mg, 0.1 mmol, 0.1 M in DCM), 2-fluoroethanol (11 μL, 0.2 mmol), DMF (124 μL) and TfOH (10 μL, 0.1 mmol). The reaction was stirred at -78-0 ºC until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N, filtered and concentrated *in vacuo*. The product was purified by silica gel column chromatography. Compound **28** (35 mg, 61% yield, α:β = 3.5:1) was obtained as a colorless syrup. Under condition B, using **6** (80 mg, 0.11 mmol, 0.1 M in DCM), 2-fluoroethanol (13 μL, 0.22 mmol), Ph_3P=O (185 mg, 0.66 mmol) and TMSI (15 μL, 0.11 mmol). The product was purified by silica gel column chromatography. Compound **28** (27 mg, 42% yield, α:β > 5.5:1) was obtained as a colorless syrup. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.37-7.11 (m, 20 H, a romatic *H*), 5.00 (d, *J* = 10.8 Hz, 1 H, C*H*H), 4.84-4.77 (m, 4 H), 4.67-4.59 (m, 3 H), 4.55-4.50 (m, 1 H), 4.48-4.44 (m, 2 H), 4.00 (t, *J* = 9.6 Hz, 1 H), 3.90-3.56 (m, 7 H). ^{13}C-APT ($CDCl_3$, 100 MHz,) δ 138.95, 138.32, 137.99 (aromatic *C*), 128.60, 128.53, 128.50, 128.27, 128.08, 128.06, 128.05, 127.84, 127.73 (aromatic *C*H), 97.47, 83.50, 82.08, 81.81, 80.00, 77.68, 75.90, 75.23, 73.58, 73.42, 70.31, 68.48, 67.08 (d, F*C*H$_2$).

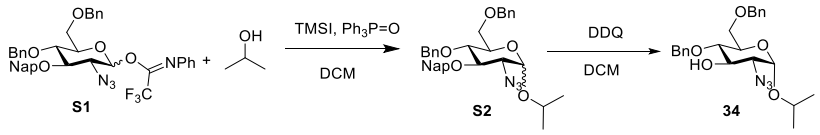


Synthesis of **29**: The reaction was carried out according to the standard procedure A or B. Under condition A, using **6** (70 mg, 0.1 mmol, 0.1 M in DCM), 2-difluoroethanol (11 µL, 0.2 mmol), DMF (124 µL) and TfOH (10 µL, 0.1 mmol). The reaction was stirred at -78-0 ºC until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N, filtered and concentrated *in vacuo*. The product was purified by silica gel column chromatography. Compound **29** (45 mg, 75% yield, α:β = 6.7:1) was obtained as a colorless syrup. Under condition B, using **6** (80 mg, 0.11 mmol, 0.1 M in DCM), 2-difluoroethanol (13 µL, 0.22 mmol), Ph_3P=O (185 mg, 0.66 mmol) and TMSI (15 µL, 0.11 mmol). The product was purified by silica gel column chromatography. Compound **29** (50 mg, 73 % yield, α:β > 15:1) was obtained as a colorless syrup. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.34-7.11 (m, 20 H, aromatic *H*), 6.10-5.81 (m, 1 H, F_2CH), 4.98 (d, *J* = 10.8 Hz, 1 H, C*H*H), 4.84-4.75 (m, 4 H), 4.64-4.58 (m, 2 H), 4.48-4.44 (m, 2 H), 3.96 (t, *J* = 9.2 Hz, 1 H), 3.80-3.56 (m, 7 H). ^{13}C-APT ($CDCl_3$, 100 MHz,) δ 138.80, 138.17, 138.14, 137.85 (aromatic *C*), 128.64, 128.53, 128.51, 128.24, 128.16, 128.03, 127.88, 127.76 (aromatic *C*H), 114.19 (t, F_2CH), 98.09, 81.85, 79.86, 77.46, 75.91, 75.26, 73.61, 73.59, 70.71, 68.31, 67.29 (t, F_2CHCH_2).



Synthesis of **30**: The reaction was carried out according to the standard procedure A or B. Under condition A, using **6** (70 mg, 0.1 mmol, 0.1 M in DCM), 2-trifluoroethanol (11 µL, 0.2 mmol), DMF (124 µL) and TfOH (10 µL, 0.1 mmol). The reaction was stirred at -78-0 ºC until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N, filtered and concentrated *in vacuo*. The product was purified by silica gel column chromatography. Compound **30** (38 mg, 62% yield, α:β = 13:1) was obtained as a colorless syrup. Under condition B, using **6** (80 mg, 0.11 mmol, 0.1 M in DCM), 2-trifluoroethanol (13 µL, 0.11 mmol), Ph_3P=O (185 mg, 0.66 mmol) and TMSI (15 µL, 0.11 mmol). The product was purified by silica gel column chromatography. Compound **30** (56 mg, 80% yield, α:β > 18:1) was obtained as a colorless syrup. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.36-7.11 (m, 20 H, aromatic *H*), 4.98 (d, *J* = 10.8 Hz, 1 H, C*H*H), 4.84-4.77 (m, 4 H), 4.64-4.58 (m, 2 H), 4.48-4.44 (m, 2 H), 3.98 (t, *J* = 9.2 Hz, 1 H), 3.91-3.85 (m, 2 H), 3.77-3.57 (m, 5 H). ^{13}C-APT ($CDCl_3$, 100 MHz,) δ 138.81, 138.15, 137.83 (aromatic *C*), 128.61, 128.52, 128.20, 128.11, 128.05, 128.04, 127.90, 127.76 (aromatic *C*H), 123.76 (q, F_2CH), 97.92, 81.68, 79.76, 75.90, 75.29, 73.61, 73.45, 71.00, 68.21, 64.80 (q, F_2CHCH_2).

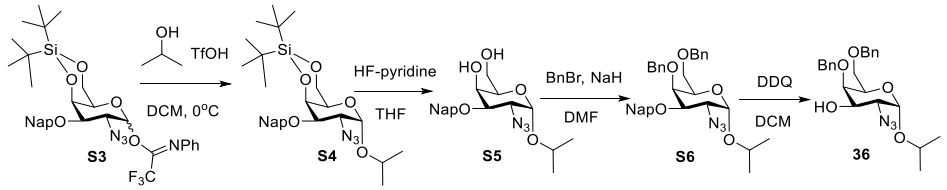
Synthesis of **34**



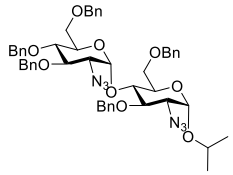
Donor **S1** (1200 mg, 1.7 mmol), isopropanol (265 µL, 3.4 mmol) and Ph_3P=O (2.8 g) were dissolved in DCM, and TMSI (250 µL, 1.7 mmol) was added at room temperature. The reaction was stirred at rt until TLC-analysis showed complete conversion of the donor. The reaction was quenched with Et_3N after completed checking by TLC, filtered and concentrated *in vacuo*. The product was purified by silica gel column chromatography. Compound **S2** was obtained with α:β = 5:1. Next compound **S2** (700 mg, 1.2 mmol) was dissolved in DCM (0.1 M), and then DDQ (300 mg) was added in the solution. The reaction was stirred at rt until TLC-analysis showed complete conversion of the starting material. The reaction was quenched with saturated $Na_2S_2O_3$ after completed checking by TLC, filtered and concentrated *in vacuo*, purified by column chromatography. Compound **34** (660 g, 80% yield) was obtained as colorless syrup. ^{1}H-NMR ($CDCl_3$,

400 MHz) δ 7.36-7.21 (m, 10 H, aromatic *H*), 5.02 (d, *J* = 3.6 Hz, 1 H, H-1a), 4.71 (d, *J* = 11.2 Hz, 1 H, C*H*H), 4.66 (d, *J* = 12.0 Hz, 1 H, CH*H*), 4.56 (d, *J* = 11.2 Hz, 1 H, CH*H*), 4.50 (d, *J* = 12.0 Hz, 1 H, C*H*H), 4.10 (t, *J* = 10.4 Hz, 1 H, H-3a), 3.93-3.84 (m, 2 H, H-5a, H-1º), 3.78 (dd, 1 H, J_1 = 10.8 Hz, J_2 = 3.6 Hz, H-6a_a), 3.65 (dd, 1 H, J_1 = 10.8 Hz, J_2 = 3.6 Hz, H-6a_b), 3.58 (t, 1 H, J_1 = 10.4 Hz, J_2 = 3.6 Hz, H-4a), 3.13 (dd, 1 H, J_1 = 10.4 Hz, J_2 = 3.6 Hz, H-2a), 2.63 (bs, 1 H, O*H*), 1.21 (d, *J* = 8.4 Hz, 3 H, CH_3), 1.20 (d, *J* = 8.4 Hz, 3 H, CH_3). ^{13}C-APT ($CDCl_3$, 100 MHz,) δ 138.12, 137.84 (aromatic *C*), 128.65, 128.47, 128.06, 128.03, 127.86 (aromatic *C*H), 96.41 (C-1a), 78.52 (C-4a), 74.98, 73.62 (*C*H_2), 71.75 (C-3a), 71.00 (C-1º), 70.32 (C-5a), 68.39 (C-6a), 62.78 (C-2a), 23.29 (*C*H_3), 21.59 (*C*H_3).

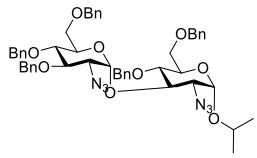
Synthesis of **36**



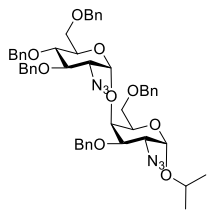
Donor **S3** (855 mg, 1.3 mmol) and isopropanol (150 mg, 2.5 mmol) were dissolved in DCM, cooled to 0 ºC and TfOH (11.5 µL, 0.13 mmol) was added. The reaction was stirred at 0 ºC until TLC-analysis showed complete conversion of the donor. The reaction was quenched with Et_3N after completed checking by TLC, filtered and concentrated *in vacuo*. Compound **S4** (500 mg, 73%) was obtained with full α-selectivity. Then compound **S4** (500 mg, 0.95 mmol) was dissolved in THF. HF-pyridine (10 eq) was added to the solution. After TLC-analysis showed complete consumption of the starting material, the reaction was quenched with saturated $NaHCO_3$. The mixture was diluted with ethyl acetate, washed with H_2O and brine, dried with anhydrous $MgSO_4$, filtered, concentrated *in vacuo*. Crude compound **S5** was dissolved in DMF, and then BnBr (1.5 eq) and NaH (5 eq) were added in the solution. The reaction was stirred at rt until TLC-analysis showed complete conversion of the starting material. The reaction was quenched with ice water after completed checking by TLC, filtered and concentrated *in vacuo,* purified by column chromatography. Compound **S6** (442 mg, 82% yield over two steps) was obtained as colorless syrup. Next compound **S6** (442 mg, 0.78 mmol) was dissolved in DCM, and then DDQ was added in the solution. The reaction was stirred at rt until TLC-analysis showed complete conversion of the starting material. The reaction was quenched with saturated $Na_2S_2O_3$ after completed checking by TLC, filtered and concentrated *in vacuo,* purified by column chromatography. Compound **36** (266 mg, 80%) was obtained as colorless syrup. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.43-7.24 (m, 10 H, aromatic *H*), 5.02 (d, *J* = 3.6 Hz, 1 H, H-1a), 4.90 (d, *J* = 11.6 Hz, 1 H, C*H*H), 4.73 (s, 2 H, PhCH_2), 4.56 (d, *J* = 11.6 Hz, 1 H, CH*H*), 4.00-3.97 (m, 2 H, H-3a, H-4a,), 3.91-3.85 (m, 2 H, H-5a, H-1º), 3.80 (dd, 1 H, J_1 = 10.0 Hz, J_2 = 3.6 Hz, H-2a), 3.74-3.70 (m, 1 H, H-6a_a), 3.56-3.51 (m, 1 H, H-6a_b), 2.07 (bs, 1 H, O*H*), 1.21-1.18 (bt, 6 H, 2 CH_3). ^{13}C-APT ($CDCl_3$, 100 MHz,) δ 137.95, 137.52 (aromatic *C*), 128.53, 128.44, 128.33, 127.97, 127.94, 127.81 (aromatic *C*H), 96.61 (C-1a), 77.39 (C-3a), 74.49 (*C*H_2), 73.41 (C-4a), 72.39 (*C*H_2), 70.74 (C-5a), 70.63 (C-1º), 62.07 (C-6a), 59.61 (C-2a), 23.20 (*C*H_3), 21.44 (*C*H_3). HR-MS: Calculated for $C_{23}H_{29}O_5N_3$ $[M+NH_4]^+$: 445.24455, found: 445.24422.



Synthesis of **37**: The reaction was carried out according to the standard procedure C. Using **32** (78 mg, 0.12 mmol), **33** (35 mg, 0.08 mmol, 0.1 M in DCM), MPF (156 µL, 1.27 mmol) and TfOH (10 µL, 0.11 mmol). The reaction was stirred at -78-0 ºC until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N, filtered and concentrated *in vacuo*. The products were purified by size exclusion. Compound **37** (65 mg, 90% yield, α:β = 16:1) was obtained as a colorless syrup. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.40-7.10 (m, 25 H, aromatic *H*), 5.67 (d, *J* = 4.0 Hz, 1 H, H-1), 5.05 (d, *J* = 3.6 Hz, 1 H, H-1), 5.00 (d, *J* = 10.4 Hz, 1 H, C*H*H), 4.90-4.86 (m, 3 H), 4.74 (d, *J* = 10.8 Hz, 1 H, C*H*H), 4.55-4.43 (m, 4 H), 4.23 (d, *J* = 12.0 Hz, 1 H, C*H*H), 4.12-4.08 (m, 1 H), 4.07-3.85 (m, 4 H), 3.79 (dd, 1 H, J_1 = 10.8 Hz, J_2 = 3.6 Hz), 3.70-3.62 (m, 3 H), 3.52 (bd, 1 H), 3.36-3.29 (m, 3 H), 1.28-1.24 (m, 6 H, 2 CH_3). ^{13}C-APT ($CDCl_3$, 100 MHz,) δ 138.24, 138.11, 137.96, 137.93, 137.81 (aromatic *C*), 128.57, 128.55, 128.48, 128.45, 128.41, 128.09, 127.97, 127.92, 127.90, 127.83, 127.74, 127.62, 127.37 (aromatic *C*H), 97.71 (C-1), 96.20 (C-1), 80.79, 80.48, 78.10, 75.56, 75.04, 73.38, 73.60, 73.53, 73.46, 71.56, 71.11, 70.12, 69.15, 67.91, 63.59, 63.53, 23.37 (*C*H_3), 21.65 (*C*H_3). HR-MS: Calculated for $C_{50}H_{56}N_6O_9$ $[M+H]^+$: 885.41815, found: 885.41775.

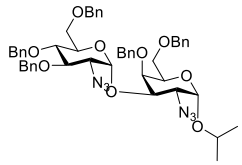


Synthesis of **38**: The reaction was carried out according to the standard procedure C. Using **32** (77 mg, 0.12 mmol), **34** (33 mg, 0.08 mmol, 0.1 M in DCM), DMF (156 µL, 1.27 mmol) and TfOH (10 µL, 0.11 mmol). The reaction was stirred at -78-0 ºC until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N, filtered and concentrated *in vacuo*. The products were purified by size exclusion. Compound **38** (53 mg, 78% yield, α:β = 8:1) was obtained as a colorless syrup. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.38-7.14 (m, 25 H, aromatic *H*), 5.55 (d, *J* = 3.6 Hz, 1 H, H-1), 5.05 (d, *J* = 4.0 Hz, 1 H, H-1), 5.00 (d, *J* = 10.4 Hz, 1 H, C*H*H), 4.98 (d, *J* = 10.8 Hz, 1 H, C*H*H), 4.94-4.86 (m, 2 H), 4.79 (d, *J* = 10.8 Hz, 1 H, C*H*H), 4.69-4.65 (m, 2 H), 4.55-4.42 (m, 4 H), 4.22-4.13 (m, 2 H), 4.05-4.00 (m, 1 H), 3.97-3.74 (m, 7 H), 3.66 (dd, 1 H, J_1 = 10.8 Hz, J_2 = 2.0 Hz), 3.40 (dd, 1 H, J_1 = 10.4 Hz, J_2 = 4.0 Hz), 3.02 (dd, 1 H, J_1 = 10.4 Hz, J_2 = 3.6 Hz), 1.24-1.22 (m, 6 H, 2 CH_3). ^{13}C-APT ($CDCl_3$, 100 MHz,) δ 138.24, 138.07, 138.02, 138.68 (aromatic *C*), 128.55, 128.52, 128.49, 128.46, 128.15, 128.12, 128.08, 127.96, 127.92, 127.83, 127.81, 127.78, 127.44 (aromatic *C*H), 98.77 (C-1), 96.72 (C-1), 80.15, 79.22, 78.28, 75.80, 75.52, 75.02, 74.10, 73.74, 73.73, 71.66, 71.23, 70.37, 68.36, 68.22, 63.54, 61.32, 23.38 (*C*H_3), 21.61 (*C*H_3). HR-MS: Calculated for $C_{50}H_{56}N_6O_9$ $[M+H]^+$: 885.41815, found: 885.41742.

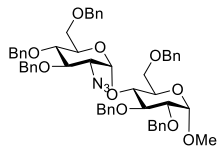


Synthesis of **39**: The reaction was carried out according to the standard procedure C. Using **32** (77 mg, 0.12 mmol), **35** (34 mg, 0.08 mmol, 0.1 M in DCM), DMF (156 µL, 1.27 mmol) and TfOH (10 µL, 0.11 mmol). The reaction was stirred at -78-0 ºC until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N, filtered and concentrated *in vacuo*. The products were purified by size exclusion. Compound **39** (40 mg, 57% yield, α:β = 5:1) was obtained as a colorless syrup. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.40-7.04 (m, 25 H, aromatic *H*), 5.06 (d, *J* = 3.6 Hz, 1 H, H-1), 4.99 (d, *J* = 4.0 Hz, 1 H, H-1), 4.90-4.50 (m, 8 H), 4.42-4.30 (m, 3 H), 4.12-3.86 (m, 7 H), 3.37 (dd, 1 H, J_1 = 10.8 Hz, J_2 = 2.0 Hz), 3.20 (dd, 1 H, J_1 = 10.4 Hz, J_2 = 4.0 Hz), 2.94 (dd, 1 H, J_1 = 10.8 Hz, J_2 = 2.0 Hz), 1.22-1.20 (m, 6 H, 2 CH_3). ^{13}C-APT ($CDCl_3$, 100 MHz,) δ 138.13, 138.11, 137.92, 137.82, 137.60 (aromatic *C*), 128.81, 128.65, 128.55, 128.51, 128.45, 128.40, 128.38, 128.20, 128.17, 128.12, 127.91, 127.85,

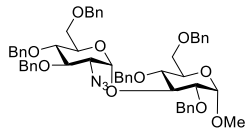
127.80, 127.78, 127.67, 127.18 (aromatic *C*H), 98.91 (C-1), 96.83 (C-1), 80.31, 78.18, 75.82, 75.49, 74.94, 73.71, 73.52, 73.36, 71.97, 71.06, 70.91, 69.18, 67.38, 67.08, 64.15, 59.48, 23.37 (*C*H_3), 21.70 (*C*H_3). HR-MS: Calculated for $C_{50}H_{56}N_6O_9$ $[M+H]^+$: 885.41815, found: 885.41783.



Synthesis of **40**: The reaction was carried out according to the standard procedure C. Using **32** (77 mg, 0.12 mmol), **36** (33 mg, 0.08 mmol, 0.1 M in DCM), DMF (156 µL, 1.27 mmol) and TfOH (10 µL, 0.11 mmol). The reaction was stirred at -78-0 ºC until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N, filtered and concentrated *in vacuo*. The products were purified by size exclusion. Compound **40** (44 mg, 63% yield, α:β = 2:1) was obtained as a colorless syrup. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.38-7.10 (m, 25 H, aromatic *H*), 5.18 (d, *J* = 3.6 Hz, 1 H, H-1), 5.07-5.04 (m, 2 H), 4.84-4.75 (m, 3 H), 4.66 (d, *J* = 12.0 Hz, 1 H, C*H*H), 4.60-4.43 (m, 5 H), 4.17-4.02 (m), 3.95-3.78 (m), 3.73-3.47 (m), 1.21-1.19 (m, 6 H, 2 C*H*$_3$). ^{13}C-APT ($CDCl_3$, 100 MHz,) δ 138.71, 138.21, 138.02, 137.94, 137.92 (aromatic *C*), 128.56, 128.53, 128.50, 128.42, 128.22, 128.05, 127.93, 127.86, 127.80, 127.74 (aromatic *C*H), 96.69 (C-1), 96.54 (C-1), 80.58, 78.24, 75.62, 75.37, 75.19, 75.07, 74.96, 73.81, 73.62, 73.56, 71.62, 70.73, 69.48, 68.51, 68.19, 63.98, 59.09, 23.35 (*C*H_3), 21.54 (*C*H_3). HR-MS: Calculated for $C_{50}H_{56}N_6O_9$ $[M+H]^+$: 885.41815, found: 885.41763.

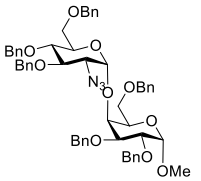


Synthesis of **41**: The reaction was carried out according to the standard procedure C. Using **32** (63 mg, 0.1 mmol), **11** (30 mg, 0.06 mmol, 0.1 M in DCM), MPF (127 µL, 1.0 mmol) and TfOH (10 µL, 0.1 mmol). The reaction was stirred at -78-0 ºC until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N, filtered and concentrated *in vacuo*. The products were purified by size exclusion. Compound **41** (60 mg, 97% yield, α:β = 10:1) was obtained as a colorless syrup. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.36-7.09 (m, 30 H, aromatic *H*), 5.74 (d, *J* = 4.0 Hz, 1 H, H-1), 5.11 (d, *J* = 10.8 Hz, 1 H, 1 C*H*H), 4.87-4.84 (m, 3 H), 4.77-4.73 (m, 2 H), 4.64-4.60 (m, 2 H), 4.50-4.43 (m, 4 H), 4.24 (d, *J* = 12.4 Hz, 1 H, C*H*H), 4.08 (t, *J* = 9.2 Hz, 1 H, C*H*H), 3.94-3.63 (m, 8 H), 3.58 (dd, 1 H, J_1 = 9.2 Hz, J_2 = 3.6 Hz), 3.51 (dd, 1 H, J_1 = 10.8 Hz, J_2 = 2.0 Hz), 3.38 (s, 3 H, OC*H*$_3$), 3.33-3.27 (m, 2 H). ^{13}C-APT ($CDCl_3$, 100 MHz,) δ 138.77, 138.26, 138.18, 138.08, 138.05, 137.87 (aromatic *C*), 128.62, 128.57, 128.46, 128.42, 128.31, 128.12, 127.94, 127.88, 127.83, 127.69, 127.61, 127.58, 127.37 (aromatic *C*H), 97.87 (C-1), 97.83 (C-1), 82.12, 80.59, 80.25, 78.17, 75.47, 75.14, 75.05, 73.64, 73.43, 73.32, 71.50, 69.57, 69.37, 67.92, 63.41, 55.43 (*C*H_3). HR-MS: Calculated for $C_{55}H_{59}N_3O_{10}$ $[M+NH_4]^+$: 939.45387, found: 939.45366.

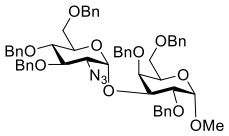


Synthesis of **42**: The reaction was carried out according to the standard procedure C. Using **32** (63 mg, 0.1 mmol), **12** (30 mg, 0.06 mmol, 0.1 M in DCM), MPF (127 µL, 1.0 mmol) and TfOH (10 µL, 0.1 mmol). The reaction was stirred at -78-0 ºC until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N, filtered and concentrated *in vacuo*. The products were purified by size exclusion. Compound **42** (55 mg, 92% yield, α:β = 3:1) was obtained as a colorless syrup. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.36-7.09 (m, 30 H, aromatic *H*), 5.74 (d, *J* = 4.0 Hz, 1 H, H-1), 5.11 (d, *J* = 10.8 Hz, 1 H, 1 C*H*H), 4.87-4.84 (m, 3 H), 4.77-4.73 (m, 2 H), 4.64-4.60 (m, 2 H), 4.50-4.43 (m, 4 H), 4.24 (d, *J* = 12.4 Hz, 1 H, C*H*H), 4.08 (t, *J* = 9.2 Hz, 1 H, C*H*H), 3.94-3.63 (m, 8 H), 3.58 (dd, 1 H, J_1 = 9.2 Hz, J_2 = 3.6 Hz), 3.51 (dd, 1 H, J_1 = 10.8 Hz, J_2 = 2.0 Hz), 3.38 (s, 3 H, OC*H*$_3$), 3.33-3.27 (m, 2 H). ^{13}C-APT ($CDCl_3$, 100

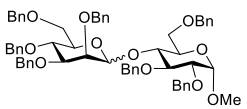
MHz,) δ 138.77, 138.26, 138.18, 138.08, 138.05, 137.87 (aromatic *C*), 128.62, 128.57, 128.46, 128.42, 128.31, 128.12, 127.94, 127.88, 127.83, 127.69, 127.61, 127.58, 127.37 (aromatic *C*H), 97.87 (C-1), 97.83 (C-1), 82.12, 80.59, 80.25, 78.17, 75.47, 75.14, 75.05, 73.64, 73.43, 73.32, 71.50, 69.57, 69.37, 67.92, 63.41, 55.43 (*C*H_3). HR-MS: Calculated for $C_{55}H_{59}N_3O_{10}$ $[M+NH_4]^+$: 939.45387, found: 939.45374.



Synthesis of **43**: The reaction was carried out according to the standard procedure C. Using **32** (63 mg, 0.1 mmol), **8** (30 mg, 0.06 mmol, 0.1 M in DCM), MPF (127 μL, 1.0 mmol) and TfOH (10 μL, 0.1 mmol). The reaction was stirred at -78-0 ºC until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N, filtered and concentrated *in vacuo*. The products were purified by size exclusion. Compound **43** (61 mg, 99% yield, α:β = 5:1) was obtained as a colorless syrup. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.38-7.11 (m, 30 H, aromatic *H*), 4.94 (d, *J* = 3.6 Hz, 1 H, H-1), 4.88-4.68 (m, 9 H), 4.56-4.41 (m, 4 H), 4.25-4.15 (m, 3 H), 3.93-3.83 (m, 5 H), 3.78-3.73 (m, 1 H), 3.57-3.51 (m, 1 H), 3.38-3.34 (m, 4 H), 3.28 (dd, 1 H, J_1 = 10.8 Hz, J_2 = 2.0 Hz), 3.02 (dd, 1 H, J_1 = 10.8 Hz, J_2 = 2.0 Hz). ^{13}C-APT ($CDCl_3$, 100 MHz,) δ 138.79, 138.44, 138.26, 138.20, 137.96, 137.67 (aromatic *C*), 128.61, 128.57, 128.47, 128.45, 128.40, 128.18, 128.13, 128.10, 127.91, 127.86, 127.80, 127.77, 127.59, 127.54 (aromatic *C*H), 98.71 (C-1), 98.61 (C-1), 80.53, 78.24, 77.39, 75.48, 75.32, 74.98, 74.89, 73.69, 73.43, 73.28, 70.79, 68.96, 67.52, 67.36, 64.19, 55.51 (*C*H_3). HR-MS: Calculated for $C_{55}H_{59}N_3O_{10}$ $[M+NH_4]^+$: 939.45387, found: 939.45353.



Synthesis of **44**: The reaction was carried out according to the standard procedure C. Using **32** (63 mg, 0.1 mmol), **9** (30 mg, 0.06 mmol, 0.1 M in DCM), MPF (127 μL, 1.0 mmol) and TfOH (10 μL, 0.1 mmol). The reaction was stirred at -78-0 ºC until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N, filtered and concentrated *in vacuo*. The products were purified by size exclusion. Compound **44** (61 mg, 99% yield, α:β = 1.2:1) was obtained as a colorless syrup. HR-MS: Calculated for $C_{55}H_{59}N_3O_{10}$ $[M+NH_4]^+$: 939.45387, found: 939.45379.



Synthesis of **46**: The reaction was carried out according to the standard procedure A and C. Under condition A, using **45** (106 mg, 0.15 mmol, 0.1 M in DCM), **9** (45 mg, 0.1 mmol), DMF (189 μL, 2.4 mmol) and TfOH (13 μL, 1.59 mmol). The reaction was stirred at -78-0 ºC until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N, filtered and concentrated *in vacuo*. The products were purified by size exclusion. Compound **46** (67 mg, quent, α:β = 2:1) was obtained as a colorless syrup. Under condition C, using **45** (106 mg, 0.15 mmol, 0.1 M in DCM), **9** (45 mg, 0.1 mmol), MPFF (189 μL, 2.4 mmol) and TfOH (13 μL, 1.59 mmol). The reaction was stirred at -78-0 ºC until TLC-analysis showed complete conversion of the acceptor. The reaction was quenched with Et_3N, filtered and concentrated *in vacuo*. The products were purified by size exclusion. Compound **46** (67 mg, quent, α:β = 5:1) was obtained as a colorless syrup.

References

[1] a) S. S. Nigudkar and A. V. Demchenko, *Chem. Sci.* **2015**, *6*, 2687-2704; b) in *Handbook of Chemical Glycosylation: Advances in Stereoselectivity and Therapeutic Relevance*, pp. I-XXI; c) M. Huang, G. E. Garrett, N. Birlirakis, L. Bohé, D. A. Pratt and D. Crich, *Nat. Chem.* **2012**, *4*, 663.

[2] a) S. K. Mulani, W.-C. Hung, A. B. Ingle, K.-S. Shiau and K.-K. T. Mong, *Org. Biomol. Chem.* **2014**, *12*, 1184-1197;

b) H. Yao, M. D. Vu and X.-W. Liu, *Carbohydr. Res.* **2019**, *473*, 72-81.

[3] a) L. Wang, H. S. Overkleeft, G. A. van der Marel and J. D. C. Codée, *J. Am. Chem. Soc.* **2018**, *140*, 4632-4638; b) L. Wang, H. S. Overkleeft, G. A. van der Marel and J. D. C. Codée, *Eur. J. Org. Chem.* **2019**, *2019*, 1994-2003.

[4] a) A. C. West and C. Schuerch, *J. Am. Chem. Soc.* **1973**, *95*, 1333-1335; b) B. A. Garcia and D. Y. Gin, *J. Am. Chem. Soc.* **2000**, *122*, 4269-4279; c) S. N. Lam and J. Gervay-Hague, *Org. Lett.* **2002**, *4*, 2039-2042; d) R. U. Lemieux, K. B. Hendriks, R. V. Stick and K. James, *J. Am. Chem. Soc.* **1975**, *97*, 4056-4062; e) K. Yohei and M. Teruaki, *Chem. Lett.* **2004**, *33*, 874-875; f) M. Teruaki and K. Yohei, *Chem. Lett.* **2004**, *33*, 10-11; g) S.-R. Lu, Y.-H. Lai, J.-H. Chen, C.-Y. Liu and K.-K. T. Mong, *Angew. Chem. Int. Ed. Engl.* **2011**, *123*, 7453-7458.

[5] Y. Park, K. C. Harper, N. Kuhl, E. E. Kwan, R. Y. Liu and E. N. Jacobsen, *Science* **2017**, *355*, 162-166.

[6] M.-H. Zhuo, D. J. Wilbur, E. E. Kwan and C. S. Bennett, *J. Am. Chem. Soc.* **2019**, *141*, 16743-16754.

[7] A. B. Ingle, C.-S. Chao, W.-C. Hung and K.-K. T. Mong, *Org. Lett.* **2013**, *15*, 5290-5293.

[8] a) D. Crich, H. Li, Q. Yao, D. J. Wink, R. D. Sommer and A. L. Rheingold, *J. Am. Chem. Soc.* **2001**, *123*, 5826-5828; b) D. Crich and M. Smith, *J. Am. Chem. Soc.* **2002**, *124*, 8867-8869; c) D. Crich, A. Banerjee and Q. Yao, *J. Am. Chem. Soc.* **2004**, *126*, 14930-14934; d) D. Crich, W. Li and H. Li, *J. Am. Chem. Soc.* **2004**, *126*, 15081-15086.

[9] J. P. Yasomanee and A. V. Demchenko, *J. Am. Chem. Soc.* **2012**, *134*, 20097-20102.

[10] X. Liu, B. Zhang, X. Gu, G. Chen, L. Chen, X. Wang, B. Xiong, Q.-D. You, Y.-L. Chen and J. Shen, *Carbohydr. Res.* **2014**, *398*, 45-49.

[11] T. Tsuda, S. Nakamura and S. Hashimoto, *Tetrahedron* **2004**, *60*, 10711-10737.

[12] L. Sun, X. Wu, D.-C. Xiong and X.-S. Ye, *Angew. Chem. Int. Ed. Engl.* **2016**, *55*, 8041-8044.