JOC The Journal of Organic Chemistry

Article

Why is Direct Glycosylation with N-Acetylglucosamine Donors Such a Poor Reaction and What Can Be Done About It?

Mikkel H. S. Marqvorsen, Martin J Pedersen, Michelle R. Rasmussen, Steffan K. Kristensen, Rasmus Dahl-Lassen, and Henrik Helligsø Jensen

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.6b02305 • Publication Date (Web): 05 Dec 2016

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

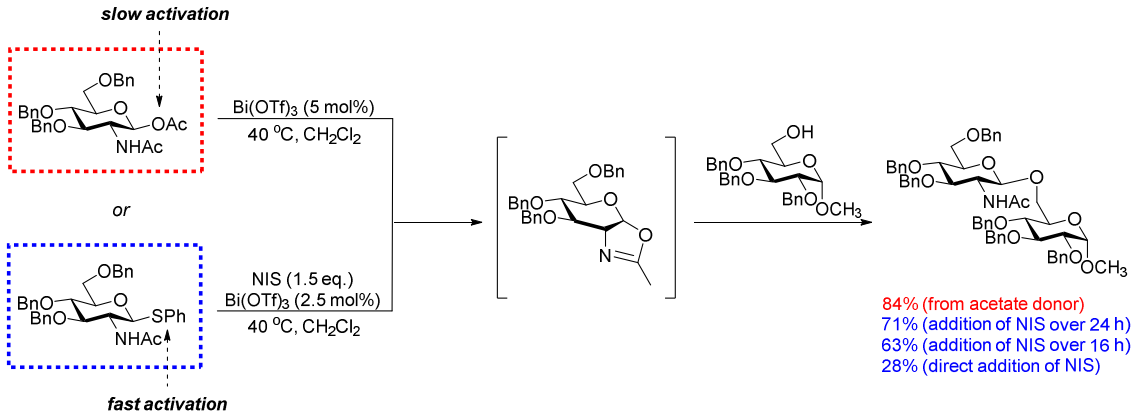
Why is Direct Glycosylation with *N*-Acetylglucosamine Donors Such a Poor Reaction and What Can Be Done About It?

Mikkel H. S. Marqvorsen, Martin J. Pedersen, Michelle R. Rasmussen, Steffan K. Kristensen, Rasmus Dahl-Lassen and Henrik H. Jensen*

Department of Chemistry, Aarhus University, Langelandsgade 140, 8000 Aarhus C, Denmark

hhj@chem.au.dk

Graphical Abstract:



Abstract

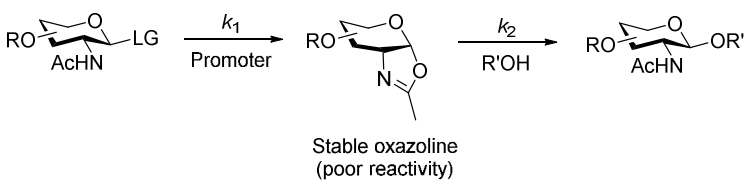
The monosaccharide *N*-acetyl-D-glucosamine (GlcNAc) is an abundant building block in naturally occurring oligosaccharides, but its incorporation by chemical glycosylation is challenging since direct reactions are low-yielding. This issue, generally agreed upon to be caused by an intermediate 1,2-oxazoline, is often bypassed by introducing extra synthetic

steps to avoid the presence of the NHAc functional group during glycosylation. The present paper describes new fundamental mechanistic insights into the inherent challenges of performing direct glycosylation with GlcNAc. These results show that controlling the balance of oxazoline formation and glycosylation is key to achieving acceptable chemical yields. By applying this line of reasoning to direct glycosylation with a traditional thioglycoside donor of GlcNAc, which otherwise affords poor glycosylation yields, one may obtain useful glycosylation results.

Introduction

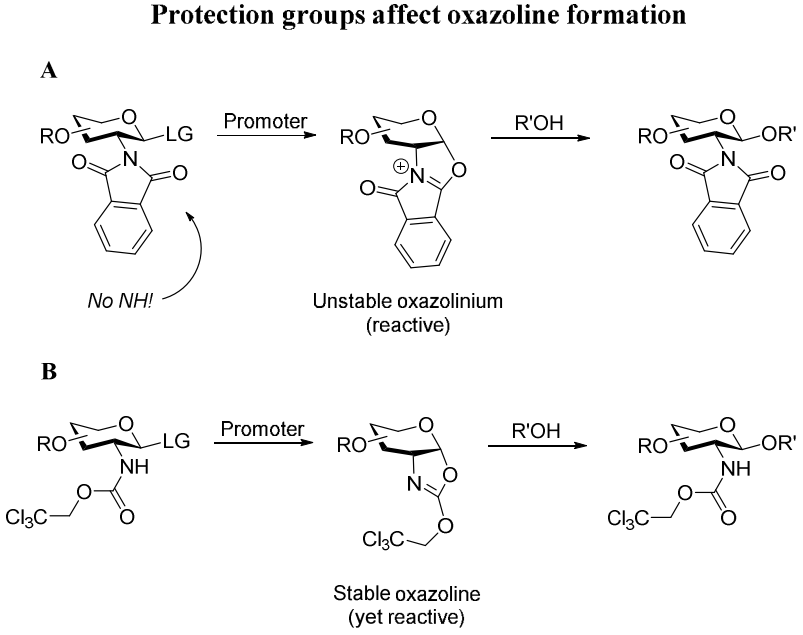
Glycosylation chemistry has become increasingly important since the emergence of glycomics in cellular- and molecular biology as an important field of study.[1] Indeed, the vast majority of functional proteins have been shown to be heavily and diversely glycosylated in vivo. The role of these abundant post-translational modifications in such matters as protein localization, function regulation and stability towards degradation has been probed only superficially even today. Access via synthetic organic chemistry to analytically pure samples of relevant oligosaccharides is required for further in-depth investigation of the roles of such carbohydrates.

N-Acetyl-D-glucosamine (GlcNAc) is the most abundant monosaccharide building block in mammalian glycoconjugates,[2] and their incorporation into synthetic oligosaccharides for biological studies is therefore a necessity. Chemical manipulation of this particular unit is, however, far from trivial due to solubility issues and to the fact that GlcNAc-derivatives function poorly both as glycosyl donors[3,4] and acceptors.[5,6,7] A well-accepted general presumption is that an intermediate oxazoline (Scheme 1)[8,9] is the cause of this poor donor reactivity. Many protecting group strategies prevent the formation of such oxazolines by ensuring the lack of a proton on the nitrogen (e.g. N_3, NAc_2, NPhth). Thus, even if neighbouring group participation is possible during glycosylation, no stable intermediate can be formed (Scheme 2A).



Scheme 1. General scheme for direct glycosylation with GlcNAc with oxazolines as the presumed critical intermediate during the reaction.

Other well studied and high yielding protecting group strategies, however, preserve the NH functionality in the glycosyl donor (e.g. NHTroc and $NHC(O)CH_2Cl$), thus maintaining the possibility of forming the oxazoline (or a derivative thereof, see Scheme 2B). In fact, the existence and stability of such oxazolines has been investigated and established for both NHTroc[10] and $NHC(O)CH_2Cl$[11] protected derivatives of GlcNAc.

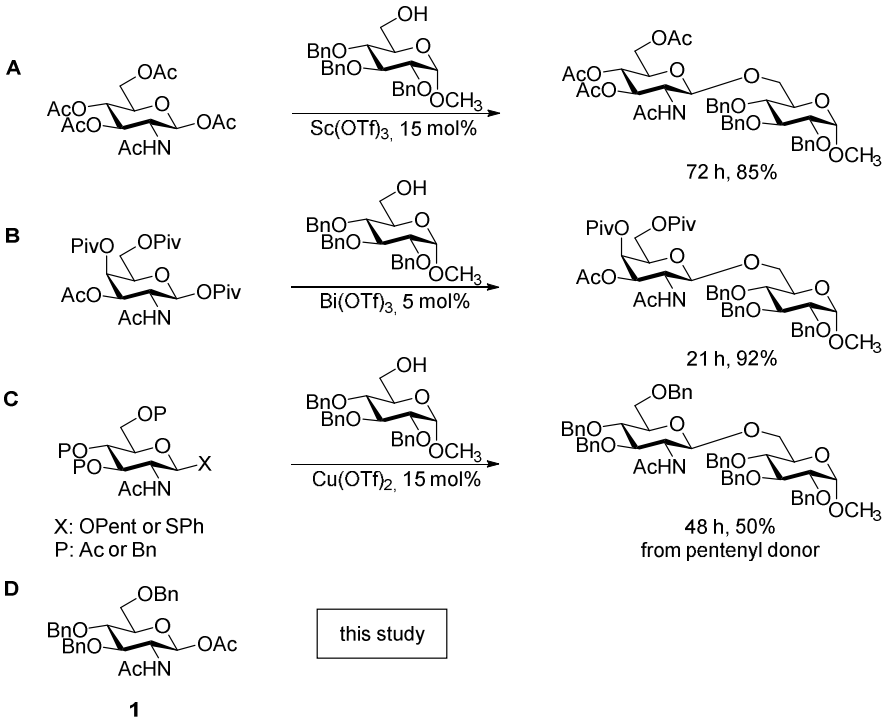


Scheme 2. *N*-protecting groups typically participate in glycosylation through oxazoline/oxazolinium ion formation during glycosylation.

We[12] and others[13,14] have recently addressed the issue of performing direct glycosylation reactions using GlcNAc donors (GlcNAc-ylation) in the presence of the 2-acetamido functionality. Through investigations of the catalytic activation of tetra-*O*-acetyl-β-GlcNAc with various Lewis acidic promotors, we found that the β-anomeric acetyl ester was a suitable leaving group in such systems to give acceptable glycosylation yields (Scheme 3A).[12] Similarly, we have recently demonstrated that β-configured anomeric pivalates (Scheme 3B), which can be readily synthesized from GlcNAc,[15,16] are good donors of *N*-acetyl-D-galactosamine (GalNAc).[17]

In an attempt to increase the reaction rate for GlcNAc-ylation by exchanging the donor functionality to either 1-SPh or 1-*O*-pentenyl, we found the donor fully activated instantly

regardless of the arming/disarming character of the *O*-protecting groups. This system, however, only returned diminished yields of glycosylation products (Scheme 3C).[18]

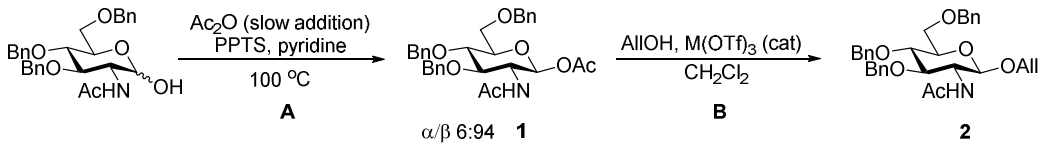


Scheme 3. Overview of previous direct and catalytic GlyNAc-ylation. For references, see: A: ref. 12; B: ref. 17; C: ref. 18.

Given the results listed in Scheme 3, we speculated that balancing the rate of the donor activation (k_1, Scheme 1) with that of the reaction between the oxazoline intermediate and the acceptor alcohol (k_2, Scheme 1) could lead to an improved overall reaction outcome. In this article, we report on the effect of having arming benzyl protection groups on the donor whilst maintaining the slowly activating anomeric β-acetate (donor **1**, Scheme 3D), thereby tuning the reaction rates (small k_1, large k_2) in a way that keeps the oxazoline concentration low in solution. Our studies have led to fundamental insights into the reasons for the disappointing results found with conventional GlcNAc donors.

Results and Discussion

We synthesized donor **1** from commercially available D-GlcNAc using a modified diastereoselective acetylation of 2-acetamido-2-deoxy-3,4,6-tri-*O*-benzyl-D-glucopyranose to give donor **1** with a satisfying crude α/β-ratio of 6:94 (Scheme 4A).[19]



Scheme 4. Formation of donor 1 and glycosylation with allyl alcohol.

In accordance with previous work a range of Lewis acids was screened to establish the behaviour of the newly synthesized donor in chemical glycosylation. The most efficient catalysts with respect to reaction time were $Bi(OTf)_3$, $Fe(OTf)_3$ and TfOH. By using the metal catalyst in combination with the base tri-*tert*-butyl pyrimidine (TTBP)[20] or as their dimethylsulfoxide (DMSO) complexes[21] led to a significant deterioration in overall reaction rate, the magnitude of which for TTBP-added reactions is in contrast to that reported by Beau and co-workers, where only a slight rate decrease with TTBP was observed.[13]

Table 1. Catalytic activation of donor 1 according to Scheme 4B.[a]

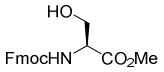
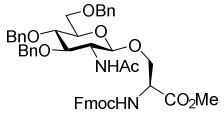
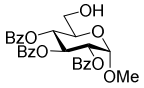
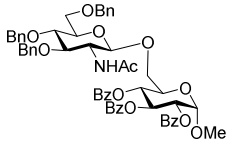
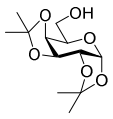
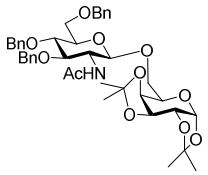
Entry	Catalyst	Loading[b]	Time[c]	Yield[d]
1	$Bi(OTf)_3$	15%	20 min	83%
2	$Bi(OTf)_3$ + TTBP	15%	> 6 h 30 min	87%
3	$Bi(OTf)_3 \cdot 7.8DMSO$	15%	40 min	74%
4	$Bi(OTf)_3 \cdot 7.8DMSO$ + TTBP	15%	4 h 30 min	91%
5[e]	$Fe(OTf)_3$	15%	25 min	88%
6	$Fe(OTf)_3 \cdot 6.2DMSO$	15%	50 min	86%
7	$Fe(OTf)_3 \cdot 6.2DMSO$ + TTBP	15%	5 h 20 min	88%
8	$Cu(OTf)_2$	15%	20 min	74%
9	$Yb(OTf)_3$	15%	35 min	70%
10	$FeCl_3$	15%	45 min	83%
11	$BiCl_3$	15%	4 h	87%
12	$CuCl_2$	15%	6 h	86%
13	TfOH	15%	30 min	82%
14	$Bi(OTf)_3$	5%	40 min	90%
15	$Fe(OTf)_3$	5%	60 min	87%

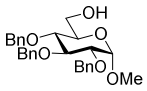
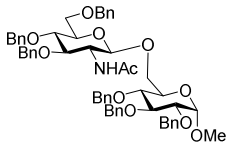
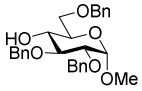
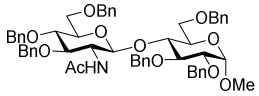
16	$Sc(OTf)_3$	5%	60 min	88%
17	$Cu(OTf)_2$	5%	70 min	86%
18	$Yb(OTf)_3$	5%	115 min	91%
19[f]	$Bi(OTf)_3$	15%	110 min	83%
20[g]	$Bi(OTf)_3$	15%	18 h	73%

[a]All reactions performed in CH_2Cl_2 at reflux with 3 equivalents of allyl alcohol as the acceptor with or without 2 equivalents of TTBP; [b]Catalyst loading relative to donor; [c]Time required for full conversion of donor as determined by TLC analysis; [d]Isolated yield after chromatography; [e]Catalyst added in a glove box due to catalyst hygroscopicity; [f]Tetra-*O*-acetyl β-GlcNAc with benzyl alcohol[12]; [g]1-epimer of donor **1** (**1α**) used.

Going to only 5 mol% catalyst loading still provided a fast turnover and produced allyl glycoside **2** in a useful timespan (Entries 14-18, Table 1). As expected, reaction times were considerably shorter for donor **1** than for its α-anomer (Entry 20, Table 1) and for the corresponding tetra-*O*-acetyl-β-GlcNAc (Entry 19, Table 1), which we had previously reported.

Table 2. Glycosylation of various alcohols with donor 1.[a]

Entry	Acceptor	Product	Catalyst[b]	Temp[c]	Time[d]	Yield[e]
1	 **3**	 **8**	5% $Bi(OTf)_3$	Reflux	50 h	80% (16)
2	 **4**	 **9**	5% $Bi(OTf)_3$	Reflux	48 h	90%
3	 **5**	 **10**	5% $Bi(OTf)_3$	Reflux	50 h	71% (22)

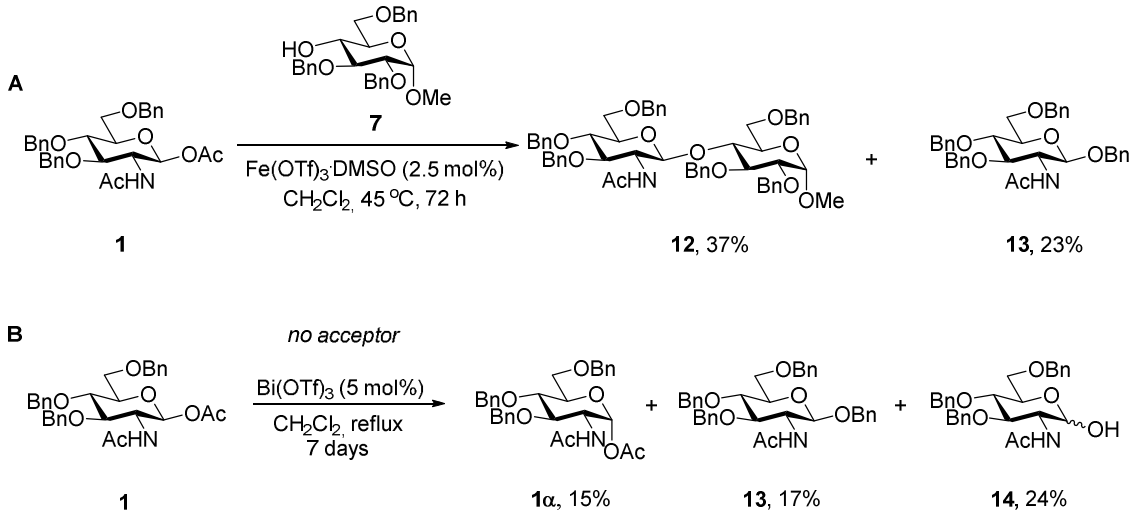
4	**5**	**10**	2.5% $Fe(OTf)_3$ ·6.2DMSO	45 ºC	16 h	87%
5	 **6**	 **11**	5% $Bi(OTf)_3$	Reflux	48 h	84% (16)
6	**6**	**11**	5% $Bi(OTf)_3$	80 ºC[f]	1.5 h	50% (39)
7	**6**	**11**	2.5% $Bi(OTf)_3$	Reflux	43 h	98%
8	**6**	**11**	2.5% $Fe(OTf)_3$ ·6.2DMSO	45 ºC	16 h	88%
9	 **7**	 **12**	2.5% $Bi(OTf)_3$	Reflux	6 days	29% (71)
10	**7**	**12**	2.5% $Fe(OTf)_3$ ·6.2DMSO	45 ºC	72 h	37% (58)

[a]Reactions were conducted in CH_2Cl_2 with donor and acceptor in a 2:1 ratio; [b]Catalyst loading with respect to donor; [c]All reactions were conducted in sealed vials except where marked "Reflux"; [d]No further conversion as determined by TLC analysis; [e]Isolated yield; in brackets re-isolation of acceptor in percent; [f]Reaction carried out under microwave irradiation.

A series of more complex and relevant glycosyl acceptors were explored as substrates to establish the scope of this new glycosylation system. Of the most time-efficient catalysts, we carried on with the easily handled $Bi(OTf)_3$. In addition, we tested $Fe(OTf)_3$·6.2DMSO, which has been reported as a catalyst in similar glycosylation reactions[13] with the advantage of a lower hygroscopicity than $Fe(OTf)_3$ itself.[21] Both excellent glycosylation yields, shorter reaction times and stoichiometry were found with primary acceptor alcohols compared to previous studies (Entries 1-8, Table 2).[12,13] The secondary acceptor **7** (Entries 9 and 10, Table 2) posed more of a challenge, as has often been the case in earlier studies. The yield could be optimised to 37% with re-isolation of most (58%) of the unreacted acceptor. This resulted is an improvement of our earlier findings with the corresponding tetra-*O*-acetylated donor (21% yield, 15 mol% $Sc(OTf)_3$), where four equivalents of glycosyl donor were used.[12] In general,

reactions with challenging acceptors were found to be improved by using less forcing conditions by changing to a milder or less catalyst. This is in accordance with our previous observations for GalNAc-ylation (Scheme 3B).[17]

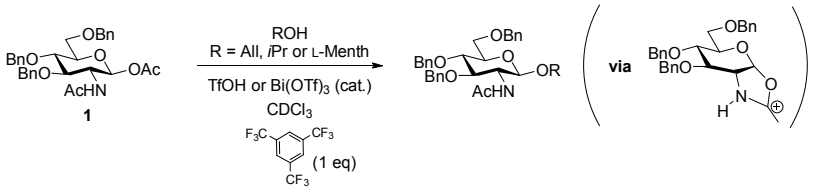
The extended reaction time needed for reaction with the secondary acceptor alcohol **7** resulted in significant amounts of the unexpected benzyl β-glycoside **13** (23%, Scheme 5A), which was also formed in the absence of acceptor (Scheme 5B). This surprising side-reaction will be discussed further below (Scheme 9).



Scheme 5. Reaction of donor **1** over prolonged reaction times with acceptor **5** or in the absence of acceptor.

Detailed reaction monitoring

We considered that a more detailed knowledge about the course of these glycosylation reactions might result in important fundamental insights necessary for future developments in the field. Therefore, representative glycosylation reactions were performed in an NMR-tube at 40 °C with $CDCl_3$ as the solvent and 1,3,5-tris(trifluoromethyl)benzene as internal reference for quantification (Scheme 6).



Scheme 6: Reaction conditions for GlcNAc-ylation monitored by ^{1}H-NMR analysis (see Figure 1 and Figure 2)

Figure 1 and Figure 2 contain normalized integral values as a function of reaction time for selected experiments. Glycosylation with donor **1**, AllOH or *i*PrOH (3 eq.) and 2.5 mol% $Bi(OTf)_3$ at 40 °C both went cleanly, forming product and consuming donor in a synchronous manner across the course of the reaction. A similar result, albeit with a considerably longer reaction time, was obtained under similar conditions using 1 equivalent of the acceptor (-)-L-menthol (Figure 1 and Scheme 7). In none of these reactions did the signals from an oxazolinium species appear integratable in the obtained spectra.

The results changed considerably on going from 2.5 mol% to 15 mol% catalyst (Figure 2). Under these more forcing conditions, (-)-L-menthol consumption and product formation occurred more slowly than the donor activation and oxazolinium ion was in this case observable throughout the reaction to a level corresponding to the catalyst loading. At the 33 min. data point 15% of donor is in actual fact unaccounted for. The same overall observation was made using 15 mol% TfOH as the catalyst.

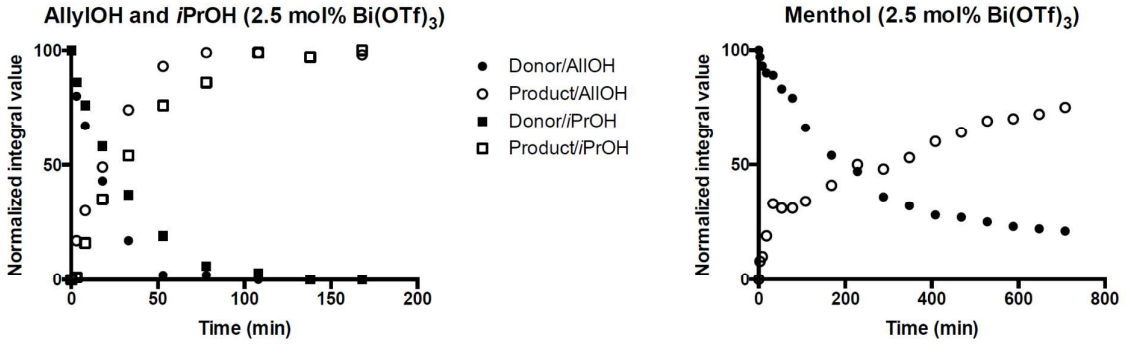


Figure 1. GlcNAc-ylation reaction course according to Scheme 6 by ^{1}H-NMR integrals of donor **1** and product in glycosylation of AllOH or *i*PrOH (2.5 mol% $Bi(OTf)_3$) (left). Closed symbols: Donor; Open symbols: Product. Circles: iPrOH; Squares: AllOH; and (-)-L-menthol (2.5 mol% $Bi(OTf)_3$) (right). The integrals were

normalized according to the internal standard 1,3,5-tris(trifluoromethyl)benzene. Closed symbols: Donor; Open symbols: product.

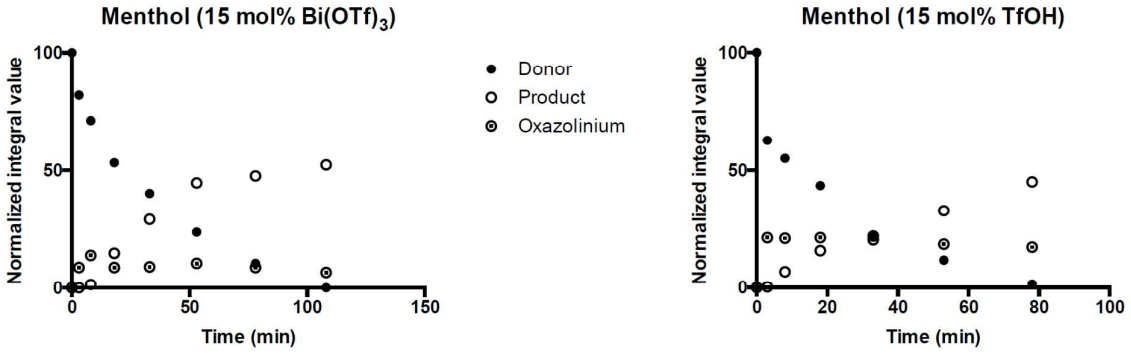
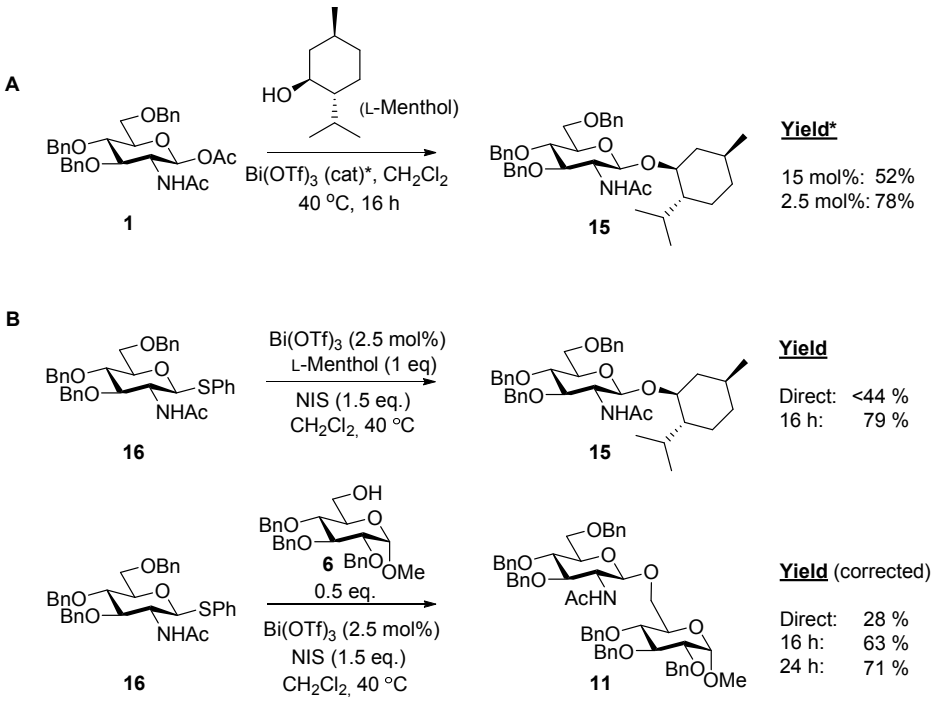


Figure 2 GlcNAc-ylation reaction course according to Scheme 6 by ^{1}H-NMR integrals of donor **1** and product in glycosylation of (-)-L-menthol (15 mol% $Bi(OTf)_3$, left; 15 mol% TfOH, right). Closed symbols: Donor; Open symbols: Product. Dotted symbols: Oxazolinium. The integrals were normalized according to the internal standard 1,3,5-tris(trifluoromethyl)benzene.

Based on these observations, reaction yields might be expected to decrease upon going from low to high catalyst loading. Indeed, with a fixed reaction time of 16 hours, we observed a significantly higher yield of the corresponding reaction using (-)-L-menthol when the catalyst loading was lowered from 15 mol% to 2.5 mol% (Scheme 7A). Yields could also be optimized with acceptors **5** and **6** as shown in Table 2.

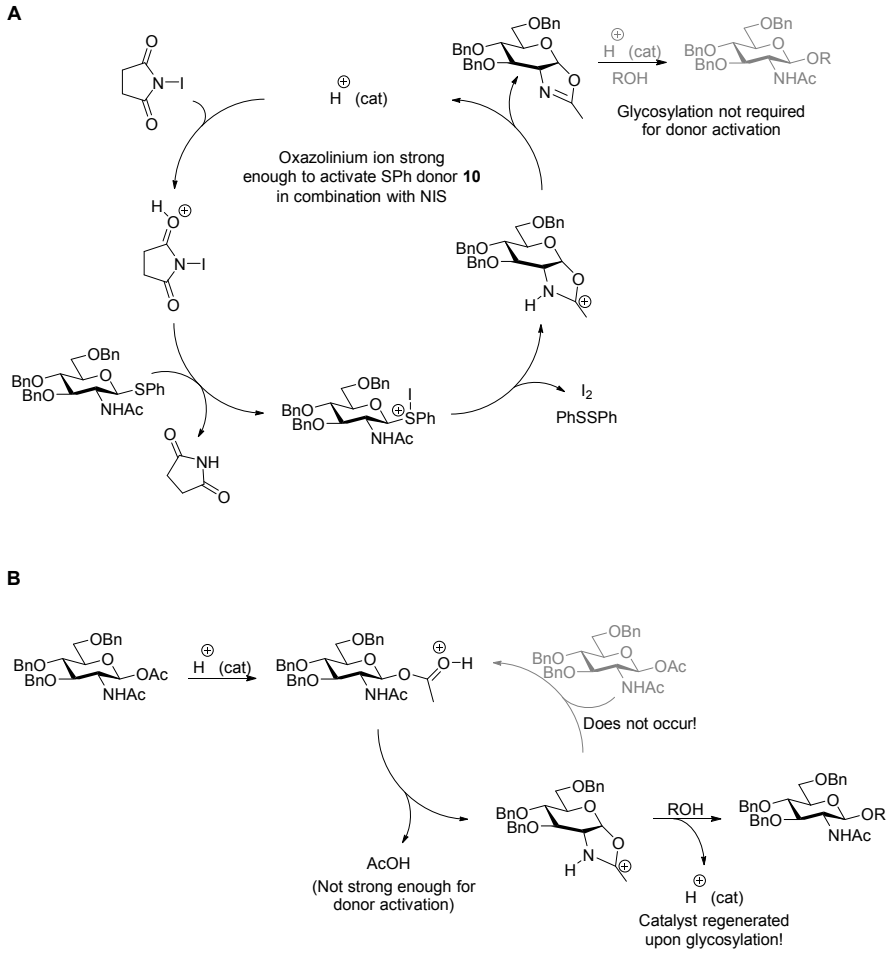


Scheme 7. Isolated yields of A: Reactions corresponding to the ^{1}H-NMR time course experiments with (-)-L-menthol as the acceptor using high (15 mol%) or low (2.5 mol%) catalyst loading. B: Reactions with conventional thioglycoside donor **16** and (-)-L-menthol or **6** as the acceptor adding NIS either directly or over extended periods of time.

As shown by NMR, glycosylation with 15 mol% TfOH or $Bi(OTf)_3$, as compared to 2.5 mol%, clearly resulted in the presence of oxazolinium ion in increased concentrations. Furthermore, separate ^{1}H-NMR experiments indicated that one equivalent of TfOH would convert the acetate donor quantitatively to the oxazolinium species in a few minutes (data not shown), and this species (or the oxazoline) was readily observable as a single spot by TLC analysis. These and the above observations led to the hypothesis that, as a consequence of high catalyst loading, a high concentration of oxazoline during reaction would lead to formation of side-products and diminished yields.

We hereupon turned to a conventional donor type, thioglycoside **16** (Scheme 7B). TLC analysis revealed the fact that with this donor, activation was in all cases complete after a few minutes when introducing 2.5 mol% $Bi(OTf)_3$, acceptor and 1.5 eq. NIS in CH_2Cl_2 at 40 °C. After this time, oxazoline could be observed on TLC analysis for the remaining reaction time. As shown in the above, this is in stark contrast to the acetate **1**, which activates slowly and in

an acceptor-dependent fashion (Scheme 7A). We speculate that the reason for the generally observed poor performance of this donor in 2-acetamido systems is that activation of these thioglycosides is catalytic and acceptor-independent (Scheme 8A). This would lead to an extreme case of the high-catalyst-scenario from above. During activation of the thioglycoside, formation of the relatively acidic oxazolinium species could activate another equivalent of thioglycoside (Scheme 8A). Oxazolinium, however, would not constitute a strong enough acid to activate the less labile acetate donor (Scheme 8B). This donor requires glycosylation of the acceptor to regenerate the acid catalyst for continuation of the activation cycle.



Scheme 8. A: Activation of GlcNAc thioglycosides are acceptor-independent; B: Activation of GlcNAc 1-OAc donors are glycosylation dependent for regeneration of the acid catalyst.

For the above hypothesis to hold true, in accordance with the NMR-studies above, the yields of the glycosylation reactions would be expected to increase if activation of the donor could

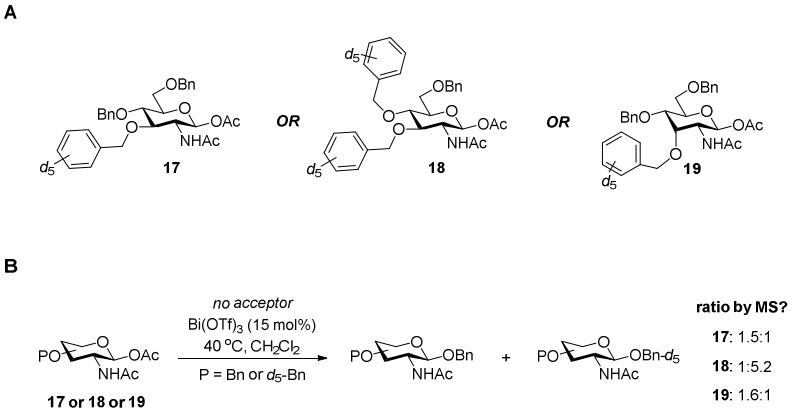
be slowed down. Accordingly, we performed glycosylation reactions under modified conditions as shown in Scheme 7B. To control the activation of the thioglycoside, NIS was added directly to the reaction at the start in one portion or gradually over the 16 hours reaction time via syringe pump. Scheme 7B reveals that slow activation of the thioglycoside **16** does indeed increase the glycosylation yield of 1 equivalent (-)-L-menthol from below 44% to 79%. Furthermore, the reaction became cleaner with slow activation, allowing the isolation of pure product. This trend extends to the carbohydrate-based acceptor **6**; when subjected to similar reaction conditions, the glycosylation yield increased from the rather poor 28% to a more pleasing 63%. Increasing the addition time from 16 hours to 24 hours led to a further enhanced yield of 71%.

Given the above observations, it is interesting to note that when subjected to 2.5 mol% $Bi(OTf)_3$ and 1.5 eq. NIS in CH_2Cl_2 at 40 °C without acceptor, an analogous Troc protected thioglycoside activated immediately, much like the observations we had just made with thioglycoside **16** (data not shown). We attribute the high yields usually obtained with this donor type in spite of this to a higher glycosylation rate (k_2).

Donor degradation

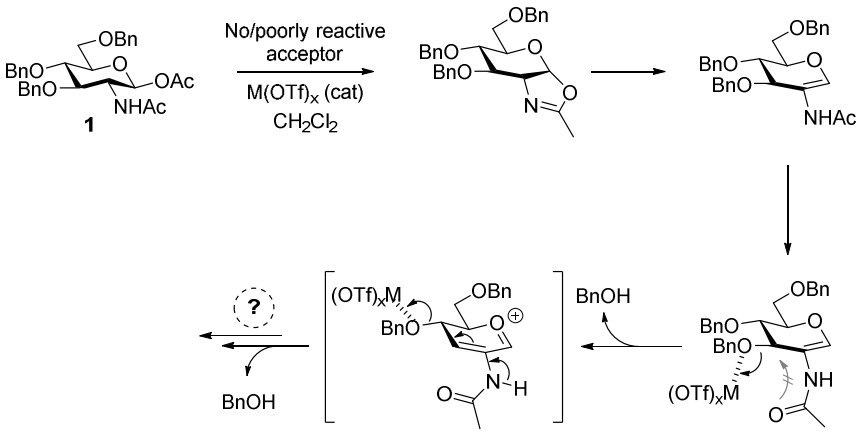
Keen on understanding what becomes of the donor in situations like the one in Figure 2 where the activation (k_1) and glycosylation (k_2) rates are mismatched, we set out to identify some of the donor derived by-products. Under glycosylation conditions with no acceptor present three major products could be identified (Scheme 5B). One dominating side reaction was found to be donor anomerization, which will lower the yield of the overall reaction since **1α** is a less reactive donor (Entry 20, Table 1). Lactol is a commonly formed by-product in glycosylation reactions[22] and could therefore also be expected. More puzzling was the discovery of benzyl glycoside **13** as a major by-product, the same compound as observed in the glycosylation of acceptor **7** in the above (Scheme 5A). As no source of benzyl alcohol had been added, the donor (**1**) must itself have been the source. This should lead to the realization, that in a glycosylation like the one in Scheme 5, not only has 23% of the donor **1** been converted to benzyl glycoside **13**, but another unknown quantity of **1** will have presumably provided the benzyl alcohol, making this a very important donor degradation pathway indeed. In order to investigate the origin of this benzyl alcohol, we synthesized three deuterium-labelled analogues **17**, **18** and **19** (Scheme 9A) including an *allo*-epimer (**19**), and subjected them to glycosylation conditions (Scheme 9B). Each reaction was monitored

using HRMS and the product distributions of non-labelled (light) and labelled (heavy) glycosides were determined for each donor (Scheme 9B).[19]



Scheme 9. A: Deuterium labelled glycosyl donors to study the origin of benzyl alcohol in formation of glycoside **13**. B: Experimental conditions used to study product distributions by HRMS.

Assuming equal ionizability of these mono-, bis- and tris-labelled benzyl glycosides, HRMS indicates the source of the anomeric benzyl group of **13**. We were surprised to find that the combined results indicated that the 3-OBn and the 4-OBn account for roughly 40% of the liberated benzyl alcohol each.[19] We speculate that the Ferrier-type rearrangements reported by Lichtenthaler et al.[23,24] in similar systems might at least partially explain these findings (Scheme 10). Participation of the NHAc was contraindicated by experiments with the *allo*-configured analogue **19**, which yielded the benzyl glycosides in roughly the same ratio as did the corresponding *gluco*-configured **17** (1.6:1 and 1.5:1, respectively).[19]



Scheme 10. Proposed mechanism for the formation of BnOH from donor 1 per analogy to related observations by Lichtenthaler and co-workers.[23,24]

Conclusion

We have shown that donor **1** performs excellently as a glycosyl donor in direct GlcNAc-ylation with primary alcohol acceptors, and that this is an improvement compared to previous donor types investigated in terms of reaction time, catalyst loading and excess of donor used. Compared to existing methodology the glycosylation yield has been significantly improved, but for reactions with a secondary carbohydrate based acceptor yields remain moderate.

More importantly, this study demonstrates the power of balancing the rate of oxazoline formation (k_1, Scheme 1) controlled by e.g. catalyst loading/Lewis acidity and glycosylation (k_2, Scheme 1) influenced by the nature of the acceptor nucleophile. Time course experiments showed a correlation between the synchronous nature of the glycosylation reaction and the success of a direct GlcNAc-ylation. The gained insight led to the controlled activation of a GlcNAc thioglycoside secured by slow addition of NIS to a reaction mixture containing glycosyl donor, acceptor and Lewis acid catalyst. In the case of a carbohydrate based acceptor the yield could be rescued from 28% under conditions with direct addition to 71% with slow addition over 24 hours, approaching the yield obtained with the slowly activating acetate donor function.

We have furthermore found that a significant side-reaction of the glycosyl donor is loss of benzyl alcohol, and that this does not proceed through neighbouring group participation since the analogous AllNAc donor behaved similarly as the GlcNAc donor.

We strongly believe we have shed much needed scientific light upon paramount fundamental issues concerning GlyNAc-derived donors. It is our hope to see these insights kindle a

renewed interest in GlyNAc-chemistry. The question remains whether direct GlyNAc-ylation can indeed be optimized significantly beyond the results disclosed herein.

Experimental Section

General remarks

Air- and moisture sensitive reactions were conducted in flame-dried glassware under an atmosphere of Ar or N_2. Anhydrous solvents were dried over aluminum oxide and dispensed from a solvent purification system. DMF and dioxane were purchased as anhydrous. Solvents were removed under reduced pressure at 40 °C. Flash column chromatography was performed using silica gel (230-400 Mesh) unless otherwise noted. TLC analysis was conducted on silica gel coated aluminum foil (Kieselgel 60 F_{254}) and observed under UV-light or visualized by staining in 10 % H_2SO_4 with orcinol followed by vigorous heating. NMR-spectra were recorded on a 400 spectrometer. Chemical shifts (δ) are reported in ppm relative to the residual signals (^{1}H-NMR: $CDCl_3$, 7.26; CD_3OD, 4.87; DMSO-d_6, 2.50 and ^{13}C-NMR: $CDCl_3$, 77.2; CD_3OD, 49.0; DMSO-d_6, 39.5). ^{1}H- and ^{13}C-NMR spectra were interpreted on the basis of *g*COSY, *g*HMQC and DEPT-135 techniques and where necessary 1D-selective ^{1}H-TOCSY-, proton coupled ^{13}C-, or HMBC-spectra. Mass spectra were recorded on a TOF-Q High Performance MS system. Optical rotations were measured in concentrations reported in g/100mL on a polarimeter and reported in units of deg·cm^2·g^{-1}. Sonication of reactions was carried out in a ultrasonic bath. Microwave experiments were carried out in a Biotage Initiator (external sensor type). Reaction times listed in these cases refer to 'hold time' at the specified temperature.

General procedure for glycosylation

2-Acetamido-1-*O*-acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranose **(1)** (2 eq.) and acceptor (1 eq.) were dissolved in dry CH_2Cl_2 to an acceptor concentration of 0.10 M. Lewis acid (2.5 or 5 mol% with respect to donor according to Table 2.) was added and the reaction mixture stirred at 45 °C. The reaction was monitored by TLC analysis until there was no further indication of reaction development. The reaction mixture was poured into a separation funnel, diluted with CH_2Cl_2 and washed with water. The aqueous layer was extracted twice with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$, filtered, concentrated

under reduced pressure and purified using flash column chromatography which afforded the desired glycoside products (Table 2.).

^{1}H-NMR time course experiments (Figure 1 and Figure 2)

2-Acetamido-1-*O*-acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranose **(1)** (48 mg, 0.09 mmol, 1 eq.), acceptor (3 eq. for AllOH and *i*PrOH, 1 eq. for (-)-L-menthol) and the internal standard 1,3,5-tris(trifluoromethyl)benzene (16.8 µL, 1 eq.) were dissolved in dry $CDCl_3$ (600 µL) and transferred to a NMR-tube. Lewis acid ($Bi(OTf)_3$ or TfOH, 2.5 or 15 mol%) was added whereupon the sample was heated to 40 °C while obtaining ^{1}H-NMR spectra at selected time points (See SI for stacked spectra). Integral values from each spectrum corresponding to baseline separated signals from donor and product (and oxazolinium where relevant) were normalized using the internal standard and plotted against time in Figure 1 and Figure 2 in the main article.

Glycosylation according to Scheme 7A

Two reactions were set up. 2-Acetamido-1-*O*-acetyl-2-deoxy-3,4,6-tri-*O*-benzyl-β-D-glucopyranose (**1**) (48 mg, 0.09 mmol, 1 eq.), (-)-L-menthol (14.1 mg, 0.09 mmol, 1 eq.) and $Bi(OTf)_3$ (2.5 or 15 mol%) were dissolved in dry CH_2Cl_2 (0.6 mL) and heated to 40 °C for 16 hours. The reactions were then evaporated onto Celite® and subjected to flash column chromatography (5→10% EtOAc in toluene) which afforded the desired product **15**.

R_f 0.56 (20% EtOAc in toluene). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 7.36-7.20 (m, 15H, Ar*H*), 5.70 (d, $J_{2,NH}$ 7.9 Hz, 1H, NH), 4.96 (d, $J_{1,2}$ 8.2 Hz, 1H, H1), 4.85 (d, J_{gem} 11.5 Hz, 1H, OC*H*HPh), 4.81 (d, J_{gem} 10.8 Hz, 1H, OC*H*HPh), 4.68 (d, 1H, OCH*H*Ph), 4.64 (d, 1H, OCH*H*Ph), 4.63 (d, J_{gem} 12.9 Hz, 1H, OC*H*HPh), 4.55 (d, 1H, OCH*H*Ph), 4.33 (t, $J_{2,3} = J_{3,4}$ 9,5 Hz, 1H, H3), 3.75 (dd, J_{gem} 11.0, $J_{5,6a}$ 4.1 Hz, 1H, H6a), 3.69 (dd, $J_{5,6b}$ 1.9 Hz, 1H, H6b), 3.63 (t, $J_{3,4} = J_{4,5}$ 9,2 Hz, 1H, H4), 3.52 (ddd, 1H, H5), 3.42 (dt, *J* 4.3 Hz, *J* 10.7 Hz, 1H, C*H*OGlcNAc), 3.15 (dt, 1H, H2), 2.32 (d septet, *J* 2.5 Hz, *J* 7.1 Hz, 1H, C*H*$(CH_3)_2$), 1.93 (dt, *J* 3.9 Hz, *J* 12.2 Hz, 1H) 1.84 (s, 3H, NHC(O)CH_3), 1.68-1-58 (m, 2H), 1.40-1.25 (m, 1H), 1.24-1.14 (m, 1H), 1.06-0.72 (m, 3H), 0.89 (d, *J* 6.8 Hz, 6H, CH_3CHCH_3), 0.80 (d, *J* 7.0 Hz, 3H, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 170.5 (*C*=O), 138.8, 138.4, 138.3, 128.5, 128.4, 128.03, 127.99, 127.8, 127.72, 127.70, 127.6 (Ar), 97.5 (C1), 80.5 (C3), 79.2 (C4), 78.2,

74.81 (C5, O*C*H$_2$Ph), 74.78, 73.76 (O*C*H$_2$Ph), 69.3 (C6), 58.6 (C2), 47.9, 41.0, 34.4, 31.4, 25.1, 23.7 (NHC(O)CH$_3$), 23.1, 22.4 (CH$_3$), 21.2 (CH$_3$), 15.8 (CH$_3$). HRMS(ES): Calcd. for $C_{39}H_{51}NO_6H^+$ 630.3789; found 630.3866.

The NMR data were in accordance with those previously published.[18]

Glycosylation according to Scheme 7B

Two identical reactions were set up in parallel. Phenyl 2-acetamido-2-deoxy-3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside[18] (**16**) (53 mg, 0.09 mmol, 1 eq.), (-)-L-menthol (14.1 mg, 0.09 mmol, 1 eq.) and Bi(OTf)$_3$ (1.5 mg, 2.3 μmol, 2.5 mol%) were dissolved in dry CH_2Cl_2 (0.6 mL) and heated to 40 °C. NIS (30 mg, 0.14 mmol, 1.5 eq.) was added as a solution in dry dioxane (0.5 mL) either directly or over 16 hours via syringe pump (0.52 μL/min). TLC analysis (20% EtOAc in toluene) indicated full conversion of donor after 30 min. with direct addition of NIS. After 16 hours TLC also indicated full conversion of donor with slow addition of NIS. Both reactions were evaporated onto Celite® and subjected to flash column chromatography (0→5→10% EtOAc in toluene) which afforded the desired product **15**.

The glycosylation of methyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (**6**) with phenyl 2-acetamido-2-deoxy-3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (**16**)[18] was carried out like described above with addition of NIS as described in the scheme.

Isolation of donor-derived by-products according to Scheme 5B

2-Acetamido-1-*O*-acetyl-2-deoxy-3,4,6-tri-*O*-benzyl-β-D-glucopyranose (**1**) (86 mg, 0.16 mmol, 1 eq.) and Bi(OTf)$_3$ (5 mg, 8.1 μmol, 5 mol%) were dissolved in dry CH_2Cl_2 (1.1 mL) and heated to 40 °C for 7 days. The resulting mixture was diluted, washed with half saturated $NaHCO_3$ (aq) which was back-extracted thrice with CH_2Cl_2. The combined organics were dried over $MgSO_4$, filtered and evaporated to give a crude which was subjected to flash column chromatography (2:1→1:1→2:3→1:2 pentane:EtOAc, then EtOAc:CH_2Cl_2 9:1) which afforded benzyl 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranoside (**13**) (15.8 mg, 17%), 2-acetamido-1-*O*-acetyl-2-deoxy-3,4,6-tri-*O*-benzyl-α-D-glucopyranose (**1α**) (13.2 mg, 15%) and 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranose (**14**) (18.5 mg, 24%).

2-acetamido-1-*O*-acetyl-2-deoxy-3,4,6-tri-*O*-benzyl-β-D-glucopyranose (1)

2-Acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranose (**12)** (14.3 g, 29.0 mmol, 1 eq.) was dissolved in dry pyridine to a concentration of 0.17 M. Pyridinium *para*-toluenesulfonate (PPTS) (11.0 g, 43.6 mmol, 1.5 eq.) was added and the reaction mixture was heated to 100 °C for 15 minutes under stirring. Ac_2O (8.2 mL, 87 mmol, 3 eq.) was added as a solution in dry pyridine (1.4 M) to the reaction over 15 minutes using syringe pump. The reaction mixture was quenched with CH_3OH (2 mL) and concentrated under reduced pressure to dryness. The resulting crude was dissolved in CH_2Cl_2, washed with 1 M HCl (aq), sat. $NaHCO_3$ (aq), and H_2O. The combined aqueous layers were extracted twice with CH_2Cl_2 which was washed with 1 M HCl (aq), sat. $NaHCO_3$ (aq), and H_2O. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give a crude (16.4 g) with an α/β ratio according to NMR of 7:93. The crude was recrystallized from EtOAc, filtered and washed with cold Et_2O to afford the desired compound **1** (9.85 g, 64%) as a white solid.

R_f 0.28 (EtOAc/toluene 1:1). $[\alpha]_D^{20}$ +28.0 (*c* 1, $CHCl_3$). Lit. +34 (c 0.5, $CHCl_3$).[25a] Mp 148.1-148.8 °C (EtOAc). Lit. 159-162 °C (EtOAc).[25a] ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 7.37-7.27 (m, 13H, Ar*H*), 7.19 (dd, *J* 2.2 Hz, *J* 7.2 Hz, 2H, Ar*H*), 5.69 (d, $J_{1,2}$ 7.8 Hz, 1H, H1), 5.19 (d, $J_{NH,2}$ 8.8 Hz, 1H, NH), 4.80 (d, J_{gem} 11.7 Hz, 1H, OC*H*HPh), 4.76 (d, J_{gem} 10.5 Hz, 1H, OC*H*HPh), 4.65 (d, 1H, OCH*H*Ph), 4.61 (d, J_{gem} 12.0 Hz, 1H, OC*H*HPh), 4.58 (d, 1H, OCH*H*Ph), 4.50 (d, 1H, OCH*H*Ph), 4.03 (dt, $J_{2,3}$ 9,2 Hz, 1H, H2), 3.79 (t, $J_{3,4} = J_{4,5}$ 8.3 Hz, 1H, H4), 3.75-3.72 (m, 2H, H6a, H6b), 3.68 (dd, 1H, H3), 3.66 (td, 1H, $J_{5,6}$ 3.5 Hz, H5), 2.06 (s, 3H, OCOC*H*$_3$), 1.79 (s, 3H, NHCOC*H*$_3$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 170.1, 169.8 (*C*=O), 138.1, 137.9, 137.8 (*ipso*-Ar*C*), 128.5, 128.5, 128.4, 128.2, 128.0, 127.9, 127.9, 127.7 (Ar), 92.8 (C1), 80.7 (C4), 77.5 (C3), 75.6, 74.6, 74.3 (O*C*H$_2$Ph), 73.5 (C5), 68.5 (C6), 53.6 (C2), 23.4 (NHC(O)CH$_3$), 21.1 (OC(O)CH$_3$). HRMS(ES): Calcd. for $C_{31}H_{35}NO_7Na^+$ 556.2306; found 556.2312.

The NMR data were in accordance with those previously published.[11,25]

2-Acetamido-1-*O*-acetyl-2-deoxy-3,4,6-tri-*O*-benzyl-α-D-glucopyranose (1α)

2-Acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranose (**12**) (380 mg, 0.77 mmol, 1 eq.) was dissolved in dry pyridine (3.8 mL) before Ac_2O (220 µL, 2.3 mmol, 3 eq.) was added to the mixture and stirred for 20 h. The reaction mixture was poured into ice-water before extracting with EtOAc and washing with 1 M HCl (aq), sat. $NaHCO_3$ (aq) and brine. The organic layer was dried over $MgSO_4$, filtered, concentrated under reduced pressure and purified by flash column chromatography (EtOAc/CH_2Cl_2 1:5→1:4→1:3) to separate the anomeric mixture and afford the desired compound **1α** (106 mg, 26%) as a colorless amorphous solid, which was recrystallized in EtOAc to afford colorless crystals (59 mg).

R_f (EtOAc/toluene 1:1) 0.19. $[\alpha]_D^{20}$ +94.7 (*c* 1.0, $CHCl_3$). Lit. +149 (*c* 0.29, MeOH).[26] ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 7.40-7.27 (m, 13H, Ar*H*), 7.22-7.19 (m, 2H, Ar*H*), 6.14 (d, $J_{1,2}$ 3.5 Hz, 1H, H1), 4.95-4.88 (m, 1H, N*H*), 4.89 (d, J_{gem} 11.8 Hz, 1H, OC*H*HPh), 4.82 (d, J_{gem} 10.6 Hz, 1H, OC*H*HPh), 4.65 (d, 1H, OCH*H*Ph), 4.64 (d, 1H, J_{gem} 12.1 Hz, OC*H*HPh), 4.59 (d, 1H, OCH*H*Ph), 4.51 (d, 1H, OCH*H*Ph), 4.32 (ddd, $J_{2,NH}$ 8.6 Hz, $J_{2,3}$ 10.7 Hz, 1H, H2), 3.87 (dd, $J_{3,4}$ 8.7 Hz, $J_{4,5}$ 9.7 Hz, 1H, H4), 3.83-3.76 (m, 2H, H5, H6a), 3.71 (dd, 1H, H3), 3.69-3.64 (m, 1H, H6b), 2.07 (s, 3H, OCOCH_3), 1.79 (s, 3H, NHCOCH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 169.9, 169.0 (*C*=O), 138.3, 138.0, 137.8 (ipso-ArC), 128.7, 128.6, 128.5, 128.3, 128.1, 128.0, 127.9, 127.7 (Ar), 91.7 (C1), 79.0 (C3), 77.9 (C4), 75.2, 74.6, 73.6 (O*C*H_2Ph), 73.4 (C5), 68.2 (C6), 51.5 (C2), 23.3 (NHCO*C*H_3), 21.0 (OCO*C*H_3). HRMS(ES): Calcd. for $C_{31}H_{35}NO_7Na^+$ 556.2306; found 556.2309.

Allyl 2-acetamido-2-deoxy-3,4,6-tri-*O*-benzyl-β-D-glucopyranoside (2)

From Allyl 2-acetamido-2-deoxy-β-D-glucopyranoside (**20**):

Allyl 2-acetamido-2-deoxy-β-D-glucopyranoside (12.7 g, 48.6 mmol, 1 eq.) was dissolved in dry DMF (130 mL). 60 % NaH on mineral oil (7.58 g, 190 mmol, 3.9 eq.) was added slowly under vigorous stirring before BnBr (19.1 mL, 160 mmol, 3.3 eq.) was added in small portions over a total of 30 min, after which the mixture was left stirring overnight at room temperature. The mixture was poured onto ice/water and the precipitate was filtered off and the mother liquor extracted with EtOAc (3 x 100 mL). The precipitate and the combined organics were co-evaporated to dryness with toluene and then purified by flash column chromatography (0 → 25% EtOAc in $CHCl_3$) to give the desired product **2** (14.1 g, 54%) as a colorless solid.

From 2-acetamido-1-*O*-acetyl-2-deoxy-3,4,6-tri-*O*-benzyl-β-D-glucopyranose (**1**):

Donor **1** (1 eq.) was dissolved in dry CH_2Cl_2 to a concentration of 0.15 M. Acceptor (3 eq.) and Lewis acid (according to Table 1) were added and the resulting mixture stirred under reflux. The reaction was monitored by TLC analysis and upon completion, the mixture was evaporated onto Celite® and purified by column chromatography to afford the desired allyl glycoside **2** in yields according to Table 1.

R_f (EtOAc/CH_2Cl_2 1:5) 0.26. M_p 144.5-145.9 °C (CH_2Cl_2). Lit. 146.5-149 °C (MeOH).[27] ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 7.35-7.27 (m, 13H, Ar*H*), 7.22-7.19 (m, 2H, Ar*H*), 5.88 (ddt, J_{trans} 16.9 Hz, J_{cis} 10.5 Hz, J_{vic} 5.5 Hz, 1H, CH_2CH=CH_2), 5.56 (d, $J_{NH,2}$ 7.8 Hz, 1H, N*H*), 5.25 (dq, J_{gem}=^4J 1.4 Hz, 1H, CH=C*H*H), 5.16 (dq, 1H, CH=CH*H*), 4.85 (d, $J_{1,2}$ 7.7 Hz, 1H, H1), 4.81 (d, J_{gem} 11.6 Hz, 1H, OC*H*HPh), 4.78 (d, J_{gem} 11.1 Hz, 1H, OC*H*HPh), 4.67 (d, 1H, OCH*H*Ph), 4.61 (d, J_{gem} 12.3 Hz, 1H, OC*H*HPh), 4.59 (d, 1H, OCH*H*Ph), 4.55 (d, 1H, OCH*H*Ph), 4.33 (ddt, J_{gem} 13.0 Hz, 1H, OC*H*HCH=CH_2), 4.11 (dd, $J_{2,3}$ 9.4 Hz, $J_{3,4}$ 8.0 Hz, 1H, H3), 4.07 (ddt, 1H, OCH*H*CH), 3.77 (dd, J_{gem} 10.7 Hz, $J_{5,6a}$ 2.6 Hz, 1H, H6a), 3.72 (dd, $J_{5,6b}$ 4.3 Hz, 1H, H6b), 3.64 (dd, $J_{4,5}$ 9.1 Hz, 1H, H4), 3.60 (ddd, 1H, H5), 3.46 (dt, 1H, H2), 1.85 (s, 3H, NHCOCH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 170.4 (*C*=O), 138.5, 138.2, 138.1 (*ipso*-Ar*C*), 134.1 (CH_2CH=CH_2), 128.3, 128.3, 128.3, 127.9, 127.8, 127.7, 127.6, 127.5 (Ar), 117.0 (CH=CH_2), 99.4 (C1), 80.9 (C4), 78.5 (C3), 74.8, 74.5 (OCH_2Ph), 73.3 (C5), 69.6 (OCH_2CH), 69.0 (C6), 56.3 (C2), 23.5 (NHCOCH_3). LRMS(ES): calcd. for $C_{32}H_{37}NO_6Na^+$ 554.3; found 553.9.

The NMR data were in near-complete accordance with those previously published,[28] although we disagree with a few of the assignments.

_N_-(9-Fluorenylmethoxycarbonyl)-_O_-(2-acetamido-2-deoxy-3,4,6-tri-_O_-benzyl-β-D-glucopyranosyl)-L-serine methyl ester (8)

The general glycosylation procedure was followed using donor **1** (211 mg, 0.40 mmol), $Bi(OTf)_3$ (5 mol%) and *N*-(9-fluorenylmethoxycarbonyl)-L-serine methyl ester **3** (68.4 mg, 0.20 mmol). TLC analysis indicated reaction cessation after 50 hours. Flash column chromatography afforded the desired product **8** (131 mg, 80%) as a clear colorless glass and re-isolated *N*-(9-fluorenylmethoxycarbonyl)-L-serine methyl ester (**3**) (11 mg, 16%).

R_f (Et_2O/CH_2Cl_2 2:5) 0.32. M_p 166.8-167.8 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H 7.74 (d, *J* 7.5 Hz, 2H, Ar*H*), 7.68–7.60 (m, 2H, Ar*H*), 7.38 (t, *J* 7.5 Hz, 2H, Ar*H*), 7.34–7.25 (m, 15H, Ar*H*), 7.21–7.16 (m, 2H, Ar*H*), 5.98 (d, $J_{NHSer,H\alpha}$ 8.2 Hz, 1H, N*H*Ser), 5.50 (d, $J_{NH,2}$ 6.6 Hz, 1H, N*H*), 4.87 (d, $J_{1,2}$ 7.7 Hz, 1H, H1), 4.81 (d, J_{gem} 11.6 Hz, 1H, OC*H*HPh), 4.77 (d, J_{gem} 10.9 Hz, 1H, OC*H*HPh), 4.64 (d, 1H, OCH*H*Ph), 4.59 (d, J_{gem} 12.1 Hz, 1H, OC*H*HPh), 4.57 (d, 1H, OCH*H*Ph), 4.51 (d, 1H, OCH*H*Ph), 4.48–4.40 (m, 2H, Hα, H9), 4.33 (dd, J_{gem} 10.5 Hz , $J_{H\alpha,H\beta}$ 7.5 Hz, 1H, Hβ), 4.29-4.21 (m, 2H, H10), 3.98 (t, $J_{2,3}$ 8.8 Hz, 1H, H3), 3.83 (dd, 1H, J 3.1 Hz, Hβ'), 3.74–3.68 (m, 5H, CH_3, H6), 3.64 (t, $J_{3,4}$ 8.7 Hz, 1H, H4), 3.54 (dt, $J_{4,5}$ 9.2 Hz , $J_{5,6}$ 3.1 Hz, 1H, H5), 3.39 (broad q, 1H, H2), 1.81 (s, 3H, NHC(O)CH_3). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 170.9, 170.5 (*C*=O), 156.3 (NH*C*(O)O), 144.0, 143.8, 141.3 (Ar*C*), 138.4, 138.0 (ipso-Ar*C*), 128.5, 128.4, 128.4, 128.0, 127.8, 127.7, 127.7, 127.1, 125.3, 125.3, 120.0 (Ar), 100.4 (C1), 80.6 (C4), 78.4 (C3), 75.0 (C5), 74.7, 74.6, 73.5 (O*C*H_2Ph), 68.8 (C6), 68.7 (Cβ), 67.1 (C10), 56.5 (C2), 54.5 (Cα), 52.6 (*C*H_3), 47.2 (C9), 23.4 (NHCO*C*H_3). HRMS(ES): Calcd. for $C_{48}H_{50}N_2O_{10}Na^+$ 837.3363; found 837.3381.

Methyl *O*-(2-acetamido-2-deoxy-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (9)

The general glycosylation procedure was followed using donor **1** (213 mg, 0.40 mmol), $Bi(OTf)_3$ (5 mol%) and methyl 2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside **4**[29] (102 mg, 0.20 mmol). TLC analysis indicated reaction cessation after 48 hours. Flash column chromatography afforded the desired disaccharide **9** (178 mg, 90%) as an amorphous solid.

R_f (EtOAc/CH_2Cl_2 1:5) 0.42. M_p 153.0-153.5 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.99–7.95 (m, 2H, Ar*H*), 7.92 (dd, *J* 8.3 Hz, *J* 1.2 Hz, 2H, Ar*H*), 7.82 (dd, *J* 8.4 Hz, *J* 1.3 Hz, 2H, Ar*H*), 7.56–7.26 (m, 22H, Ar*H*), 7.18 (dd, *J* 7.4 Hz, *J* 2.1 Hz, 2H, Ar*H*), 6.13 (t, $J_{2,3} = J_{3,4}$ 9.4 Hz, 1H, H3), 5.95 (d, $J_{NH,2}$ 8.1 Hz, 1H, N*H*), 5.61 (t, $J_{3,4} = J_{4,5}$ 9.8 Hz, 1H, H4), 5.26–5.20 (m, 2H, H1, H2), 4.81 (d, J_{gem} 11.5 Hz, 1H, OC*H*HPh), 4.78 (d, J_{gem} 11.1 Hz, 1H, OC*H*HPh), 4.71 (d, 1H, OC*H*HPh), 4.56 (d, J_{gem} 12.2 Hz, 1H, OC*H*HPh), 4.55 (d, 1H, OCH*H*Ph), 4.50 (d, $J_{1',2'}$ 8.0 Hz, 1H, H1'), 4.50 (d, 1H, OCH*H*Ph), 4.21–4.11 (m, 2H, H5, H6a), 3.88 (dd, $J_{3',4'}$ 9.6 Hz, $J_{2',3'}$ 8.5 Hz, 1H, H3'), 3.81–3.73 (m, 1H, H2'), 3.71 (dd, $J_{6'a,6'b}$ 10.8 Hz, $J_{5',6'a}$ 2.4 Hz, 1H, H6'a), 3.68–3.59 (m, 2H, H6'b, H4'), 3.55 (dd, J_{gem} 11.7 Hz, $J_{5,6b}$ 4.6 Hz, 1H, H6b), 3.49 (ddd, $J_{4',5'}$ 9.3 Hz, $J_{5',6'b}$ 4.7 Hz, 1H, H5'), 3.44 (s, 3H, OCH_3), 1.94 (s, 3H, OC(O)CH_3). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 170.4 (*C*=O), 165.8, 165.7, 165.7 (O*C*(O)Ph), 138.5, 138.3,

138.1 (ipso-Ar*C*, Bz), 133.7, 133.4, 133.1 (ipso-Ar*C*, Bn), 130.0, 129.9, 129.6, 129.3, 129.2, 128.9, 128.6, 128.5, 128.5, 128.4, 128.3, 128.1, 128.0, 127.8, 127.7, 127.6 (Ar), 101.4 (C1'), 97.0 (C1), 81.8 (C4'), 78.4 (C3'), 75.3 (C5'), 74.8 (C4), 73.4, 72.0 (double intensity) (O*C*H_2Ph), 70.8, 69.3, 69.1, 68.5, 67.9 (C6', C6, C5, C3, C2), 56.2 (C2'), 55.6 (O*C*H_3), 23.6 (OC(O)*C*H_3). LRMS(ES): Calcd. for $C_{57}H_{57}NO_{14}Na^+$ 1002.4; found 1001.8.

The NMR data were in accordance with those previously published.[18]

_O_-(2-Acetamido-3,4,6-tri-_O_-benzyl-2-deoxy-β-D-glucopyranosyl)-(1→6)-1,2:3,4-di-_O_-isopropylidene-α-D-galactopyranose (10)

The general glycosylation procedure was followed using donor **1** (150 mg, 0.28 mmol), $Fe(OTf)_3 \cdot 6.2$ DMSO (7 mg, 2.5 mol%) and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**5**) (37 mg, 0.14 mmol). TLC analysis indicated full conversion of acceptor after 16 hours. Flash column chromatography (EtOAc/pentane 1:1→1.5:1) afforded the desired disaccharide **10** (90 mg, 87%) as a clear colorless syrup.

R_f (CH_3OH/CH_2Cl_2 1:10) 0.71. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.36–7.26 (m, 13H, Ar*H*), 7.18 (dd, *J* 7.4Hz , *J* 1.9 Hz, 2H, Ar*H*), 5.55 (d, $J_{NH,2'}$ 7.9 Hz, 1H, N*H*), 5.50 (d, $J_{1,2}$ 5.0 Hz, 1H, H1), 4.80 (d, J_{gem} 11.5 Hz, 1H, OC*H*HPh), 4.78 (d, J_{gem} 10.9 Hz, 1H, OC*H*HPh), 4.69 (d, $J_{1',2'}$ 7.9 Hz, 1H, H1'), 4.68 (d, 1H, OCH*H*Ph), 4.62 (d, J_{gem} 12.1 Hz, 1H, OC*H*HPh), 4.58–4.51 (m, 3H, O*C*H_2Ph, H6a), 4.28 (dd, $J_{2,3}$ 2.4 Hz, 1H, H2), 4.16 (dd, J_{gem} 7.9 Hz, $J_{5,6b}$ 1.8 Hz, 1H, H6b), 4.00 (dd, J_{gem} 11.3 Hz, $J_{5',6'a}$ 3.5 Hz, 1H, H6'a), 3.97–3.90 (m, 2H, H3, H6'b), 3.75–3.61 (m, 5H, H2', H3', H4', H4, H5), 3.54 (dt, $J_{4',5'}$=$J_{5',6'b}$ 9.4 Hz, 1H, H5'), 1.89 (s, 3H, NHC(O)C*H*$_3$), 1.51 (s, 3H, C*C*H_3), 1.42 (s, 3H, CC*H*$_3$), 1.31 (s, 3H, CC*H*$_3$), 1.30 (s, 3H, CC*H*$_3$). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 170.5 (*C*=O), 138.6, 138.3, 138.3 (ipso-Ar*C*), 128.5, 128.4, 128.1, 127.9, 127.8, 127.8, 127.7, 127.6 (Ar), 109.4, 108.7 (*C*$(CH_3)_2$), 101.3 (C1'), 96.4 (C1), 81.4 (C4'), 78.5 (C3'), 75.1, 74.7, 74.5 (O*C*H_2Ph), 73.6, 71.3, 70.8, 70.5, 69.1 (C2, C3, C4, C5', C5), 68.9, 67.9 (C6', C6), 56.2 (C2'), 26.2, 26.1, 25.1, 24.5, 23.7 (NHC(O)*C*H_3, C(*C*H3)$_2$). LRMS(ES): Calcd. for $C_{41}H_{51}NO_{11}Na^+$ 756.3; found 755.9.

The NMR data were in accordance with those previously published.[18]

Methyl *O*-(2-acetamido-2-deoxy-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (11)

The general glycosylation procedure was followed using donor **1** (231 mg, 0.43 mmol), $Bi(OTf)_3$ (2.5 mol%) and methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**6**) (100 mg, 0.22 mmol). TLC analysis indicated reaction cessation after 43 hours. Flash column chromatography (EtOAc/CH_2Cl_2 1:5) afforded the desired disaccharide **11** (198 mg, 98%) as an amorphous solid.

R_f (EtOAc/CH_2Cl_2 1:5) 0.39. M_p 203.7-205.2 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ_H 7.38–7.18 (m, 30H, Ar*H*), 5.43 (d, $J_{NH,2'}$ 7.8 Hz, 1H, NH), 4.98 (d, J_{gem} 10.9 Hz, 1H, OC*H*HPh), 4.84 (d, $J_{1',2'}$ 8.3 Hz, 1H, H1'), 4.84–4.75 (m, 5H, OCH_2Ph), 4.65 (d, J_{gem} 12.2 Hz, 1H, OCH*H*Ph), 4.63 (d, J_{gem} 11.6 Hz, 1H, OCH*H*Ph), 4.60 (d, $J_{1,2}$ 2.9 Hz, 1H, H1), 4.58 (d, J_{gem} 10.3 Hz, 1H, OCH*H*Ph), 4.57 (d, J_{gem} 10.8 Hz, 1H, OCH*H*Ph), 4.56 (d, J_{gem} 12.3 Hz, 1H, OC*H*HPh), 4.51 (d, 1H, OCH*H*Ph), 4.14–4.11 (m, 1H, H4), 4.08 (dd, J_{gem} 10.4 Hz, $J_{5,6a}$ 1.5 Hz, 1H, H6a), 3.98 (t, $J_{2,3}$=$J_{3,4}$ 9.3 Hz, 1H, H3), 3.77–3.54 (m, 7H, H3', H4', H5', H5, H6'a, H6'b, H6b), 3.51 (dd, 1H, H2), 3.44 (dt, $J_{2',3'}$ 9.4 Hz, 1H, H2'), 3.35 (s, 3H, OCH_3), 1.71 (s, 3H, $NHC(O)CH_3$). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C 170.2 (*C*=O), 138.9, 138.6, 138.4, 138.4, 138.3, 138.1 (ipso-Ar), 128.6, 128.6, 128.5, 128.5, 128.4, 128.3, 128.1, 128.0, 128.0, 128.0, 127.9, 127.9, 127.9, 127.8, 127.7, 127.6 (Ar), 99.9 (C1'), 98.2 (C1), 82.2 (C3), 80.3 (C4'), 79.8 (C2), 78.8 (C3'), 77.7, 75.9 (C4, C5'), 75.1, 74.9, 74.7, 74.6, 73.4 (double intensity) (OCH_2Ph), 69.7, 69.2, 67.6 (C5, C6, C6'), 56.9 (C2'), 55.2 (OCH_3), 23.7 ($NHC(O)CH_3$).

LRMS(ES): Calcd. for $C_{57}H_{63}NO_{11}Na^+$ 960.4; found 959.9.

The NMR data were in accordance with those previously published.[18]

Methyl *O*-(2-acetamido-2-deoxy-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (12)

The general glycosylation procedure was followed using donor **1** (150 mg, 0.28 mmol), $Fe(OTf)_3 \cdot 6.2$ DMSO (7 mg, 2.5 mol%) and methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (**7**)[30] (65 mg, 0.14 mmol). TLC analysis indicated reaction cessation after 72 hours. Flash column chromatography (EtOAc/CH_2Cl_2 1:8→1:5) afforded benzyl 2-acetamido-2-deoxy-3,4,6-tri-*O*-benzyl-β-D-glucopyranoside (**13**) (17 mg), a 1:1 mixture of **13** and the desired

disaccharide **12** (36 mg) and the desired disaccharide **12** (27 mg, 21%) as an amorphous solid. Unreacted methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (**7**) was re-isolated (23 mg, 55%). The product was recrystallized from acetone to afford colorless grained crystals. The total corrected yield of the desired product **12**was 37%.

R_f (CH_3OH/CH_2Cl_2 1:10) 0.74. M_p 184.1-185.3 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 7.38-7.26 (m, 15H, Ar*H*), 7.25-7.16 (m, 15H, Ar*H*), 5.00 (d, J_{gem} 11.6 Hz, 1H, OC*H*HPh), 4.84 (d, $J_{NH,2'}$ 8.3 Hz, 1H, NH), 4.80 (d, 1H, J_{gem} 11.7 Hz, OC*H*HPh), 4.78 (d, J_{gem} 11.4 Hz, 1H, OC*H*HPh) 4.75-4.40 (m, 10H, OCH_2Ph, H1, H1'), 4.32 (d, J 12.2 Hz, 1H, OC*H*HPh), 3.91-3.39 (m, 11H, H2, H2', H3, H3', H4, H5, H5', H6a, H6a', H6b, H6b'), 3.35 (s, 3H, O*C*H_3), 3.34-3.30 (m, 1H, H4'), 1.68 (s, 3H, NHC(O)CH_3). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ_C 170.1 (*C*=O), 139.8, 138.7, 138.6, 138.4, 138.3, 138.2 (ipso-Ar), 128.7, 128.6, 128.5, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.1 (Ar), 99.8 (C1'), 98.5 (C1), 81.5 (C3), 80.4 (C4'), 79.4 (C2), 78.9 (C3'), 76.5 (C5'), 75.2 (double intensity) (C5, OCH_2Ph), 74.8, 74.7, 73.7, 73.5, 73.5 (OCH_2Ph), 69.8 (C4), 69.0, 68.4 (C6, C6'), 57.5, 55.4 (C2', O*C*H_3), 23.7 (NHC(O)*C*H_3). HRMS(ES): Calcd. for $C_{57}H_{63}NO_{11}Na^+$ 960.4299; found 960.4310.

Benzyl 2-acetamido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranoside (13)

The general glycosylation procedure was followed using donor **1** (109 mg, 0.20 mmol), $Bi(OTf)_3$ (5 mol%) and benzyl alcohol (22 μL 0.21 mmol). After 3 hours, TLC analysis indicated reaction completion. Flash column chromatography followed by recrystallization from CH_3OH afforded the desired compound **13** as colorless crystals, (100 mg, 84%).

R_f (EtOAc/CH_2Cl_2 1:5) 0.41. M_p 156.2-157.7 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ_H 7.37–7.26 (m, 18H, Ar*H*), 7.20 (dd, *J* 7.4 Hz, *J* 2.0 Hz, 2H, Ar*H*), 5.45 (d, $J_{NH,2}$ 7.7 Hz, 1H, N*H*), 4.89 (d, J_{gem} 12.0 Hz, 1H, OC*H*HPh), 4.83 (d, $J_{1,2}$ 7.7 Hz, 1H, H1), 4.80 (d, J_{gem} 11.5 Hz, 1H, OC*H*HPh), 4.78 (d, 1H, J_{gem} 10.9 Hz, OC*H*HPh), 4.65 (d, 1H, OCH*H*Ph), 4.63 (d, J_{gem} 12.1 Hz, 1H, OCH*H*Ph), 4.59 (d, 1H, OCH*H*Ph), 4.57 (d, 1H, OCH*H*Ph), 4.55 (d, 1H, OCH*H*Ph), 4.04 (dd, $J_{2,3}$ 9.5 Hz, $J_{3,4}$ 8.2 Hz, 1H, H3), 3.79 (dd, J_{gem} 10.7 Hz, $J_{5,6a}$ 2.8 Hz, 1H, H6a), 3.74 (dd, $J_{5,6b}$ 4.3 Hz, 1H, H6b), 3.67 (dd, $J_{4,5}$ 9.1Hz, 1H, H4), 3.60 (ddd, 1H, H5), 3.55 (dt, 1H, H2), 1.81 (s, 3H, NHC(O)CH_3). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ_C 170.3 (*C*=O), 138.5, 138.3, 138.2, 137.7 (ipso-ArC), 128.5, 128.5, 128.5, 128.1, 128.0, 127.9, 127.9, 127.8, 127.7 (Ar),

99.4 (C1), 80.5 (C3), 78.6 (C4), 75.0 (C5), 74.6, 74.5, 73.6, 70.8 (O*C*H$_2$Ph), 69.2 (C6), 56.5 (C2), 23.6 (NHC(O)*C*H$_3$). LRMS(ES): Calcd. for $C_{36}H_{39}NO_6Na^+$ 604.3; found 604.1.

The data were in accordance with the previously published values.[31]

2-Acetamido-1-*O*-acetyl-4,6-di-*O*-benzyl-2-deoxy-3-*O*-(2,3,4,5,6-pentadeuteriobenzyl)-β-D-glucopyranose (17)

In a glove box as previously described, allyl 2-acetamido-4,6-di-*O*-benzyl-2-deoxy-3-*O*-(2,3,4,5,6-pentadeuteriobenzyl)-β-D-glucopyranoside (**21**) (329 mg, 0.61 mmol, 1 eq.) was dissolved in dry dioxane (1.7 mL). Pd(dba)$_2$ (17.6 mg, 31 µmol, 5 mol%), P(*t*Bu)$_3$ (6.2 mg, 31 µmol, 5 mol%) and COgen (CAS: 1072315-89-9) (7.4 mg, 31 µmol, 5 mol%) were mixed separately in dry dioxane (0.3 mL) and subsequently added to the solution containing the allyl glycoside. The reaction vessel was sealed, removed from the glove box and heated to 80 °C. After 24 hours of heating, a crude ^{1}H-NMR spectrum indicated full conversion. The mixture was concentrated to dryness and the resulting residue was re-dissolved in a 1:9 mixture of 1M HCl (aq) and acetone (5 mL total volume) and heated to 55 °C for 6 hours. The mixture was co-evaporated with toluene to dryness and taken up in dry pyridine (3.7 mL). The resulting mixture pyridinium *p*-toluenesulfonate (225 mg, 0.90 mmol, 1.5 eq.) was added before heated to 100 °C. A mixture of Ac_2O (172 µL, 1.8 mmol, 3 eq.) in dry pyridine (7.5 mL) was added by syringe pump over 15 min, whereupon the reaction mixture was concentrated to dryness and purified by flash column chromatography (10→40% EtOAc in toluene). This afforded the desired compound **17** (120 mg, 40%) as a white solid.

R_f 0.28 (EtOAc/toluene 1:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 7.36-7.25 (m, 8H, Ar*H*), 7.22-7.16 (m, 2H, Ar*H*), 5.69 (d, $J_{1,2}$ 7.9 Hz, 1H, H1), 5.39 (d, $J_{NH,2}$ 9.1 Hz, 1H, NH), 4.82 (d, J_{gem} 11.7 Hz, 1H, OC*H*HPh), 4.77 (d, J_{gem} 10.9 Hz, 1H, OC*H*HPh), 4.67 (d, 1H, OCH*H*Ph), 4.61 (d, J_{gem} 12.1 Hz, 1H, OC*H*HPh), 4.57 (d, 1H, OCH*H*Ph), 4.50 (d, 1H, OCH*H*Ph), 4.03 (dt, $J_{1,2}$=$J_{2,3}$ 9.2 Hz 1H, H2), 3.79 (dd, $J_{3,4}$ 8.4 Hz, $J_{4,5}$ 8.6 Hz, 1H, H4), 3.74 (d, $J_{5,6}$ 3.4 Hz, 2H, H6), 3.70 (dd, 1H, H3), 3.66 (td, 1H, H5), 2.06 (s, 3H, OC(O)C*H*$_3$), 1.81 (s, 3H, NHC(O)C*H*$_3$). ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 170.2, 169.9 (*C*=O), 138.03, 138.00, 137.9 (*ipso*-Ar*C*), 128.6, 128.5, 128.1, 127.99, 127.96, 127.8 (Ar), 92.9 (C1), 80.7 (C4), 77.6 (C3), 75.7, 74.7, 74.3 (O*C*H$_2$Ph), 73.6 (C5), 68.6 (C6), 53.7 (C2), 23.4 (NHC(O)*C*H$_3$), 21.1 (OC(O)*C*H$_3$). HRMS(ES): Calcd. for $C_{31}H_{30}D_5NO_7Na^+$ 561.2620; found 561.2626.

The NMR data were in agreement with those of the unlabeled congener.

2-Acetamido-1-*O*-acetyl-6-*O*-benzyl-2-deoxy-3,4-di-*O*-(2,3,4,5,6-pentadeuteriobenzyl)-β-D-glucopyranose (18)

In a glove box as previously described, allyl 2-acetamido-6-*O*-benzyl-2-deoxy-3,4-di-*O*-(2,3,4,5,6-pentadeuteriobenzyl)-β-D-glucopyranoside **22** (219 mg, 0.40 mmol, 1 eq.) was dissolved in dry dioxane (0.8 mL). $Pd(dba)_2$ (11.6 mg, 20 µmol, 5 mol%), $P(tBu)_3$ (4.1 mg, 20 µmol, 5 mol%) and COgen (CAS: 1072315-89-9) (4.9 mg, 20 µmol, 5 mol%) were mixed separately in dry dioxane (0.3 mL) and subsequently added to the solution containing the allyl glycoside. The reaction vessel was sealed, removed from the glove box and heated to 80 °C. After 29 hours of heating, a crude ^{1}H-NMR spectrum indicated full conversion. The mixture was reduced to dryness and the resulting residue was redissolved in a 1:9 mixture of 1M HCl (aq) and acetone (5 mL total volume) and heated to 55 °C for 6 hours. The mixture was coevaporated with toluene to dryness and redissolved in dry pyridine (2.4 mL). The resulting mixture was added pyridinium *p*-toluenesulfonate (152 mg, 0.60 mmol, 1.5 eq.) and heated to 100 °C. A mixture of Ac_2O (114 µL, 1.2 mmol, 3 eq.) in dry pyridine (0.85 mL) was added by syringe pump over 15 min, whereupon the mixture was evaporated to dryness and purified by flash column chromatography (10→40% EtOAc in toluene) which afforded the desired compound **18** (47.5 mg, 24%) as a white solid.

R_f 0.28 (EtOAc/toluene 1:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 7.39-7.25 (m, 5H, Ar*H*) 5.69 (d, $J_{1,2}$ 7.9 Hz, 1H, H1), 5.28 (d, $J_{NH,2}$ 9.1 Hz, 1H, NH), 4.82 (d, J_{gem} 11.7 Hz, 1H, OC*H*HPh), 4.77 (d, J_{gem} 10.9 Hz, 1H, OC*H*HPh), 4.66 (d, 1H, OCH*H*Ph), 4.61 (d, J_{gem} 12.1 Hz, 1H, OC*H*HPh), 4.58 (d, 1H, OCH*H*Ph), 4.50 (d, 1H, OCH*H*Ph), 4.04 (dt, $J_{1,2}$=$J_{2,3}$ 9.2 Hz 1H, H2), 3.79 (dd, $J_{3,4}$ 8.4 Hz, $J_{4,5}$ 8.5 Hz, 1H, H4), 3.74 (d, $J_{5,6}$ 3.5 Hz, 2H, H6), 3.69 (dd, 1H, H3), 3.66 (td, 1H, H5), 2.05 (s, 3H, OC(O)CH_3), 1.79 (s, 3H, NHC(O)CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 170.1, 169.9 (*C*=O), 138.0, 137.7 (*ipso*-Ar*C*), 128.5, 128.0, 127.5 (Ar), 92.9 (C1), 80.5 (C4), 77.6 (C3), 75.7, 74.6, 74.2 (O*C*H_2Ph), 73.6 (C5), 68.6 (C6), 53.7 (C2), 23.5 (NHC(O)*C*H_3), 21.2 (OC(O)*C*H_3). HRMS(ES): Calcd. for $C_{31}H_{25}D_{10}NO_7Na^+$ 566.2933; found 566.2944.

The NMR data were in agreement with those of the unlabeled congener.

2-Acetamido-1-*O*-acetyl-4,6-di-*O*-benzyl-2-deoxy-3-*O*-(2,3,4,5,6-pentadeuteriobenzyl)-β-D-allopyranose (19)

(1,5-Cyclooctadiene)bis(methyldiphenylphosphine)iridium(I) hexafluorophosphate (3 mg, 3 μmol, 3 mol%) was dissolved in dry THF (2 mL), bubbled through with H_2 for 15 min. and then degassed with a flow of argon under sonication for 10 min. Allyl 2-acetamido-4,6-di-*O*-benzyl-2-deoxy-3-*O*-(2,3,4,5,6-pentadeuteriobenzyl)-β-D-allopyranoside (**24**) (61.7 mg, 0.12 mmol, 1 eq.) was dissolved in dry THF (3 mL) and added to the catalyst containing solution. The resulting yellow solution was stirred under an atmosphere of argon at room temperature. After 24 hours, a crude ^{1}H-NMR spectrum indicated incomplete conversion. Another 3 mg catalyst was activated in a separate vial and transferred to the reaction mixture. After three days, the mixture was diluted with acetone (9 mL) and a 1 M solution hydrochloric acid and heated to reflux for two hours. TLC analysis indicated full conversion, and the mixture was co-evaporated with toluene to dryness. The resulting crude was re-dissolved in dry pyridine (0.5 mL), added pyridinium *p*-toluenesulfonate (45 mg, 0.18 mmol, 1.5 eq.) and heated to 100 °C. A solution of Ac_2O (33 μL, 0.35 mmol, 3 eq.) in dry pyridine (0.25 mL) was added by means of syringe pump during the course of 10 min. and the resulting mixture was left overnight at room temperature. After 16 hours, the excess Ac_2O was quenched with MeOH (0.5 mL). The mixture was evaporated to dryness under reduced pressure, re-dissolved in $CHCl_3$ and washed with 1 M HCl (aq) followed by sat. aq. $NaHCO_3$, in both cases extracting thrice with $CHCl_3$. The combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. Purification by repeated flash column chromatography (30% EtOAc in toluene, then 10% EtOAc in CH_2Cl_2) afforded the desired compound **19** (19.5 mg, 31%) as a white solid.

R_f (30% EtOAc in toluene) 0.35. ^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 7.38-7.23 (m, 10H, Ar*H*), 5.83 (d, $J_{1,2}$ 8.1 Hz, 1H, H1), 5.74 (d, $J_{NH,2}$ 9.6 Hz, 1H, N*H*), 4.91 (d, J_{gem} 11.8 Hz, 1H, OC*H*HPh), 4.64 (d, J_{gem} 11.4 Hz, 1H, OC*H*HPh), 4.63 (d, J_{gem} 12.1 Hz, 1H, OCH*H*Ph), 4.55 (d, 1H, OC*H*HPh), 4.50 (d, 1H, OCH*H*Ph), 4.47 (d, 1H, OCH*H*Ph), 4.21-4.11 (m, 2H, H2, H5), 4.02 (t, $J_{2,3}$=$J_{3,4}$ 2.7 Hz, 1H, H3), 3.79 (dd, $J_{4,5}$ 8.9 Hz, 1H, H4), 3.73 (d, $J_{5,6}$ 3.3 Hz, 2H, H3), 2.05 (s, 3H, OC(O)CH_3), 1.71 (s, 3H, NHC(O)CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 170.1, 169.9 (*C*=O), 138.13, 138.09, 137.7 (*ipso*-Ar*C*), 128.7, 128.5, 128.2, 128.1, 128.0, 127.8 (Ar), 92.4 (C1), 75.8 (C4), 74.8 (C3), 74.5 (OCH_2Ph), 74.0 (C5), 73.7, 72.8 (O*C*H_2Ph), 68.9 (C6), 51.1 (C2), 23.2 (NHC(O)*C*H_3), 21.2 (OC(O)*C*H_3). HRMS(ES): Calcd. for $C_{31}H_{30}D_5NO_7Na^+$ 561.2620; found 561.2622.

Allyl 2-acetamido-2-deoxy-β-D-glucopyranoside (20)

N-Acetyl-D-glucosamine (10.0 g, 45.1 mmol, 1 eq.) was dissolved in a mixture of dry pyridine (25 mL) and dry CH_2Cl_2 (50 mL) in a pre-dried flask under an atmosphere of nitrogen. The mixture was left stirring overnight at room temperature. The mixture was cooled to -10 °C and pivaloyl chloride (17 mL, 138 mmol, 3 eq.) was added. The mixture was allowed to reach room temperature and was left stirring for 2 days before acetic anhydride (21.3 mL, 226 mmol, 5 eq.) was added and the mixture stirred for another 3 hours. The reaction mixture was then washed several times with hydrochloric acid (1 M) until the aqueous phase stayed acidic according to pH paper test. The combined organic layers were then washed with water and brine before dried over Na_2SO_4 and filtered. The mixture was concentrated to give a crude mixture, which was used in the next step without further purification.

The crude mixture was dissolved in dry CH_2Cl_2 and triflic acid (1.80 mL, 20.3 mmol, 45 mol%) was added using a glass syringe. AllOH (9.2 mL, 135 mmol, 3 eq.) was added and the reaction mixture heated to 40 °C overnight before washed with water and aq. $NaHCO_3$. The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude glycoside mixture was re-dissolved in dry methanol, and sodium (1.5 g, 65.2 mmol, 1.4 eq.) was added. The reaction mixture was heated to 50 °C for 24 hours and then concentrated onto Celite® and purified before purified by flash column chromatography (water/*i*-propanol/EtOAc 1:4:16) to give the desired compound **20** (8.15 g, 69%) as a colorless solid.

M_p: 161.4-162.8 °C. Lit. 160-163 °C.[32] ^{1}H-NMR (400 MHz, CD_3OD): δ_H 5.89 (ddt, J_{trans} 17.3 Hz, J_{cis} 10.6 Hz, J_{vic} 5.3 Hz, 1H, C*H*=CH_2), 5.27 (dd, J_{gem} 1.7 Hz, 1H, CH=C*H*H), 5.13 (dd, 1H, CH=CH*H*), 4.44 (d, $J_{1,2}$ 8.4 Hz, 1H, H1), 4.34 (dd, J_{gem} 13.3 Hz, 1H, OC*H*HCH), 4.07 (dd, 1H, OCH*H*CH), 3.88 (dd, J_{gem} 11.9 Hz, $J_{5,6a}$ 2.1 Hz, 1H, H6a), 3.72 – 3.63 (m, 2H, H2, H6b), 3.45 (dd, *J* 10.2 Hz, *J* 8.6 Hz, 1H, H3), 3.38 – 3.21 (m, 3H, H4, H5, NH), 1.97 (s, 3H, NHCOC*H*$_3$). ^{13}C-NMR (100 MHz, CD_3OD) δ_C 173.8 (*C*=O), 135.6 (CH_2*C*H=CH_2), 116.9 (CH=*C*H_2), 101.9 (C1), 78.0 (C5), 76.1 (C3), 72.2 (C4), 70.7 (O*C*H_2CH), 62.8 (C6), 57.3 (C2), 22.9 (NHCO*C*H_3). HRMS (ES): Calcd. for $C_{11}H_{19}O_6NH^+$ 262.1285; found 262.1290.

The NMR data were in accordance with those previously published.[33]

Allyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-(2,3,4,5,6-pentadeuteriobenzyl)-β-D-glucopyranoside (21)

Allyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside[34] (500 mg, 1.4 mmol, 1 eq.) was dissolved in dry DMF (5 mL). The temperature of the resulting solution was buffered with a water bath at ambient temperature prior to the addition of 60% NaH on mineral oil (74 mg, 1.9 mmol, 1.3 eq.). After gas evolution had ceased, 2,3,4,5,6-pentadeuteriobenzyl bromide[35] (0.2 mL, 1.6 mmol, 1.1 eq.) was added in four portions over ten minutes and the mixture was stirred at room temperature. After 4 hours, TLC analysis (40% EtOAc in toluene) indicated full conversion. The mixture was diluted with $CHCl_3$ and poured onto a 1:1 mixture of sat. aqueous $NaHCO_3$ and brine. This was extracted 5 times with $CHCl_3$ and the combined organic layers were dried over $MgSO_4$, filtered and concentrated to dryness in vacuo overnight. Recrystallization from MeOH yielded the desired compound **21** (479 mg, 75%) as a white cotton-like solid.

R_f (2% MeOH in $CHCl_3$) 0.26. $[\alpha]_D^{298K}$ -13.6 (*c* 0.25, $CHCl_3$). M_p 263.9-264.6 °C. ^{1}H-NMR (10% CD_3OD in $CDCl_3$): δ_H 7.42-7.19 (m, 5H, Ar*H*), 5.81-5.65 (m, 1H, OCH_2CH=CH_2), 5.46 (s, 1H, PhC*H*), 5.14 (d, J_{trans} 17.1 Hz, 1H, OCH_2CH=C*H*H), 5.05 (d, J_{cis} 10.1 Hz, 1H, OCH_2CH=CH*H*), 4.75 (d, J_{gem} 11.8 Hz, 1H, OC*H*HPh), 4.65 (d, $J_{1,2}$ 8.2 Hz, 1H, H1), 4.53 (d, 1H, OCH*H*Ph), 4.27-4.14 (m, 2H, H6a, OC*H*HCHCH_2), 4.00-3.84 (m, 2H, H3, OCH*H*CHCH_2), 3.68 (t, J_{gem}=$J_{5,6b}$ 9.2 Hz, 1H, H6b), 3.59 (t, $J_{3,4}$=$J_{4,5}$ 9.3 Hz, 1H, H4), 3.49 (t, $J_{1,2}$=$J_{2,3}$ 9.0 Hz, 1H, H2), 3.42-3.29 (m, 1H, H5), 1.78 (s, 3H, NHC(O)CH_3). ^{13}C-NMR (10 % CD_3OD in $CDCl_3$): δ_C 171.5 (*C*=O), 138.0, 137.1 (Ar), 133.6 (OCH_2CH=CH_2), 128.9, 128.2, 125.9 (Ar), 117.2 (OCH_2CH=*C*H_2), 101.1 (PhCH), 100.1 (C1), 82.2 (C4), 77.3 (C3), 74.1 (O*C*H_2Ph), 70.1 (O*C*H_2CH=CH_2), 68.6 (C6), 65.9 (C5), 56.2 (C2), 22.7 (NHC(O)*C*H_3). HRMS(ES): Calcd. for $C_{25}H_{24}D_5NO_6H^+$ 445.2381; found 445.2388.

Allyl 2-acetamido-6-*O*-benzyl-2-deoxy-3-*O*-(2,3,4,5,6-pentadeuteriobenzyl)-β-D-glucopyranoside (22)

Allyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-(2,3,4,5,6-pentadeuteriobenzyl)-β-D-glucopyranoside **21** (479 mg, 1.1 mmol, 1 eq.) was suspended in dry CH_2Cl_2 (12 mL) and cooled to 0 °C. Et_3SiH (0.34 mL, 2.2 mmol, 2 eq.) was added via syringe followed by the dropwise addition of freshly distilled $BF_3{\cdot}OEt_2$ (0.40 mL, 3.2 mmol, 3 eq.). The reaction

mixture was stirred at 0 °C for 6 hours, whereupon TLC analysis (4% MeOH in $CHCl_3$) indicated full conversion. The reaction was quenched with sat. aq. $NaHCO_3$. Brine was added and the resulting mixture was extracted 5 times with $CHCl_3$. The combined organic layers were dried over $MgSO_4$ and evaporated onto Celite®. Flash column chromatography (10→20% EtOAc in CH_2Cl_2) afforded the desired compound **22** (362 mg, 75%) as a white solid.

R_f (40% EtOAc in toluene) 0.26. $[\alpha]_D^{301K}$ -19.4 (*c* 1, $CHCl_3$). M_p 137.5-138.6 °C. ^{1}H-NMR ($CDCl_3$): δ_H 7.31-7.18 (m, 5H, Ar*H*), 5.84-5.73 (m, 1H, OCH_2CH=CH_2), 5.17 (dd, J_{trans} 17.2 Hz, J_{gem} 1.6 Hz, 1H, OCH_2CH=C*H*H), 5.07 (dd, J_{cis} 10.4 Hz, 1H, OCH_2CH=CH*H*), 4.73 (d, J_{gem} 11.7 Hz, 1H, OC*H*HPh), 4.66 (d, $J_{1,2}$ 8.3 Hz, 1H, H1), 4.63 (d, 1H, OCH*H*Ph), 4.52 (d, J_{gem} 12.0 Hz, 1H, OC*H*HPh), 4.48 (d, 1H, OCH*H*Ph), 4.23 (dd, J_{gem} 13.1 Hz, J_{vic} 5.1 Hz, 2H, OC*H*HCH=CH_2), 3.98 (dd, 2H, OCH*H*CH=CH_2), 4.00-3.83 (dd, *J* 8.8 Hz, *J* 10.1 Hz, 1H, H3), 3.70 (dd, J_{gem} 10.4 Hz, $J_{5,6a}$ 3.9 Hz, 1H, H6a), 3.64 (dd, $J_{5,6b}$ 5.3 Hz, 1H, H6b), 3.61-3.49 (m, 2H, H2, H4), 3.48-3.40 (m, 1H, H5), 1.82 (s, 3H, NHC(O)C*H*$_3$). ^{13}C-NMR ($CDCl_3$): δ_C 170.8 (*C*=O), 138.4, 137.9 (Ar), 134.0 (OCH_2CH=CH_2), 128.4, 127.69, 127.65 (Ar), 117.2 (OCH_2CH=CH_2), 99.5 (C1), 80.8 (C3), 74.3 (C5), 73.7, 73.5 (OCH_2Ph), 72.3 (C4), 70.4 (C6), 69.7 (OCH_2CH=CH_2), 55.9 (C2), 23.5 (NHC(O)CH_3). HRMS(ES): Calcd. for $C_{25}H_{26}D_5NO_6H^+$ 447.2538; found 447.2548.

Allyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-(2,3,4,5,6-pentadeuteriobenzyl)-β-D-allopyranoside (23)

Allyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-allopyranoside[36] (500 mg, 1.4 mmol, 1 eq.) was dissolved in dry DMF (5 mL). The temperature of the resulting solution was buffered with a water bath at ambient temperature prior to the addition of 60% NaH on mineral oil (74 mg, 1.9 mmol, 1.3 eq.). After gas evolution had ceased, 2,3,4,5,6-pentadeuteriobenzyl bromide[35] (0.2 mL, 1.6 mmol, 1.1 eq.) was added in four portions over ten minutes and the mixture was stirred at room temperature. After 16 hours, TLC analysis (40% EtOAc in toluene) indicated incomplete conversion. Another 0.65 eq. of NaH and 0.55 eq. of 2,3,4,5,6-pentadeuteriobenzyl bromide was added. After three hours, TLC analysis indicated full conversion. The mixture was diluted with $CHCl_3$ and poured onto a 1:1 mixture of sat. aq. $NaHCO_3$ and brine. This was extracted 2 times with $CHCl_3$ and the combined

organic layers were dried over $MgSO_4$, filtered and concentrated to dryness in vacuo overnight. The resulting residue was re-dissolved in $CHCl_3$ and evaporated onto Celite®. Flash column chromatography (20→30% EtOAc in toluene) afforded the desired product **23** (403 mg, 63%) as a flocculent white solid.

R_f (40% EtOAc in toluene) 0.41. $[\alpha]_D^{296K}$ -112.8 (*c* 1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): δ_H 7.54-7.46 (m, 2H, Ar*H*), 7.42-7.46 (m, 3H, Ar*H*), 5.85 (dddd, J_{trans} 17.2 Hz, J_{cis} 10.6 Hz, J_{vic} 5.9 Hz, J_{vic} 4.9 Hz, 1H, OCH_2CHCH_2), 5.79-5.71 (m, 1H, NH), 5.53 (s, 1H, PhC*H*), 5.27 (dq, 1H, OCH_2CH=C*H*H), 5.16 (dq, 1H, OCH_2CH=CH*H*), 5.02 (d, J_{gem} 11.7 Hz, 1H, OC*H*HPh), 4.65 (d, $J_{1,2}$ 8.6 Hz, 1H, H1), 4.54 (d, 1H, OCH*H*Ph), 4.39 (dd, J_{gem} 10.4 Hz, $J_{5,6a}$ 5.1 Hz, H6a), 4.33 (ddt, 1H, OC*H*HCH=CH_2), 4.17 (dt, $J_{2,3}$ 3.1 Hz, 1H, H2), 4.13-4.05 (m, 2H, H3, H5), 4.03 (ddt, 1H, OCH*H*CH=CH_2), 3.80 (t, J_{gem}=$J_{5,6b}$ 10.4 Hz, 1H, H6b), 3.73 (dd, $J_{3,4}$ 2.0 Hz, $J_{4,5}$ 9.5 Hz, 1H, H4), 1.85 (s, 3H, NHC(O)CH_3). ^{13}C-NMR ($CDCl_3$): δ_C 169.4 (*C*=O), 138.1, 137.5, (Ar), 133.9 (OCH_2CHCH_2), 129.2, 128.4, 126.2 (Ar), 117.1 (OCH_2CHCH_2), 102.1 (Ph*C*H), 99.7 (C1), 80.2 (C4), 75.9 (C3), 74.7 (OCH_2Ph), 69.9 (OCH_2CHCH_2), 69.3 (C6), 63.8 (C5), 52.0 (C2), 23.3 (NHC(O)*C*H_3). HRMS(ES): Calcd. for $C_{25}H_{24}D_5NO_6H^+$ 445.2381; found 445.2390.

Allyl 2-acetamido-4-*O*-benzyl-2-deoxy-3-*O*-(2,3,4,5,6-pentadeuteriobenzyl)-β-D-allopyranoside (24)

Allyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-(2,3,4,5,6-pentadeuteriobenzyl)-β-D-allopyranoside **23** (400 mg, 0.90 mmol, 1 eq.) was dissolved in dry CH_2Cl_2 (11 mL) and cooled to -78 °C prior to the addition of Et_3SiH (0.47 mL, 2.9 mmol, 3.3 eq.) and $PhBCl_2$ (0.34 mL, 2.6 mmol, 2.9 eq.), both via syringe. After 80 min., TLC analysis (40% EtOAc in toluene) indicated full conversion. The reaction was quenched with Et_3N (2 mL) and MeOH (2 mL) before heating to room temperature. The mixture was washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated in vacuo to yield a crude, which was purified by flash column chromatography (50→100% EtOAc in toluene), affording the desired compound **24** (68.5 mg, 17%) as a white solid.

R_f (50% EtOAc in toluene) 0.35. $[\alpha]_D^{298K}$ -72.8 (*c* 1, $CHCl_3$). M_p 147.9-148.7 °C. ^{1}H-NMR ($CDCl_3$): δ_H 7.41-7.28 (m, 5H, Ar*H*), 5.92-5.77 (m, 2H, OCH_2CH=CH_2, N*H*), 5.24 (d, J_{trans} 17.2 Hz, 1H, OCH_2CH=C*H*H), 5.15 (d, J_{cis} 10.4 Hz, 1H, OCH_2CH=CH*H*), 4.91 (d, J_{gem} 11.7 Hz, 1H, OC*H*HPh), 4.71 (d, J_{gem} 11.5 Hz, 1H, OC*H*HPh), 4.67 (d, $J_{1,2}$ 7.4 Hz, 1H, H1), 4.61

(d, 1H, OCH*H*Ph), 4.51 (d, 1H, OCH*H*Ph), 4.28 (d, J_{gem} 13.3 Hz, 1H, OC*H*HCH=CH_2), 4.13 (s, 1H, H3), 4.10-3.95 (m, 3H, OCH*H*CH=CH_2, H2, H5), 3.87 (d, J_{gem} 12.1 Hz, H6a), 3.79-3.71 (m, 1H, H6b), 3.68 (d, $J_{4,5}$ 10.1 Hz, 1H, H4), 2.20-2.12 (m, 1H, OH), 1.79 (s, 3H, NHC(O)CH_3). ^{13}C-NMR ($CDCl_3$): δ_C 169.8 (*C*=O), 138.3, 137.6 (Ar), 134.0 (OCH_2*C*H=CH_2), 128.7, 128.2, 128.1 (Ar), 117.2 (OCH_2CH=*C*H_2), 99.3 (C1), 76.2 (C4), 74.7 (C3), 74.4 (O*C*H_2Ph), 73.9 (C5), 72.7 (O*C*H_2Ph), 69.8 (O*C*H_2CH=CH_2), 62.6 (C6), 51.6 (C2), 23.4 (NHC(O)*C*H_3). HRMS(ES): Calcd. for $C_{25}H_{26}D_5NO_6H^+$ 447.2538; found 447.2544.

Allyl 2-acetamido-4,6-di-*O*-benzyl-2-deoxy-3-*O*-(2,3,4,5,6-pentadeuteriobenzyl)-β-D-glucopyranoside (25)

Allyl 2-acetamido-6-*O*-benzyl-2-deoxy-3-*O*-(2,3,4,5,6-pentadeuteriobenzyl)-β-D-glucopyranoside (**22**) (362 mg, 0.81 mmol, 1 eq.) was dissolved in dry DMF (4 mL). The temperature of the resulting solution was buffered with a water bath at ambient temperature prior to the addition of 60% NaH on mineral oil (42 mg, 1.1 mmol, 1.3 eq.). After gas evolution had ceased, benzyl bromide (0.1 mL, 0.89 mmol, 1.1 eq.) was added in two portions over 15 min. and the resulting mixture was stirred at room temperature for 16 hours after which TLC analysis (40% EtOAc in CH_2Cl_2) indicated full conversion. The reaction was quenched with sat. aq. $NaHCO_3$. Brine was added and the resulting mixture was extracted 5 times with $CHCl_3$. The combined organic layers were dried over $MgSO_4$ and evaporated onto Celite®. Flash column chromatography (10→30% EtOAc in $CHCl_3$) afforded the desired compound **25** (329 mg, 76%) as a white solid.

R_f (40% EtOAc in toluene) 0.37. ^{1}H-NMR ($CDCl_3$): δ_H 7.40-7.17 (m, 10H, Ar*H*), 5.94-5.82 (m, 1H, OCH_2C*H*=CH_2), 5.64 (d, $J_{NH,2}$ 7.7 Hz, 1H, N*H*), 5.26 (dq, J_{trans} 17.2 Hz, J_{gem}=^4J 1.6 Hz, 1H, OCH_2CH=C*H*H), 5.16 (dd, J_{cis} 10.4 Hz, 1H, OCH_2CH=CH*H*), 4.84 (d, $J_{1,2}$ 7.7 Hz, 1H, H1), 4.82 (d, J_{gem} 11.5 Hz, 1H, OC*H*HPh), 4.78 (d, J_{gem} 11.0 Hz, 1H, OC*H*HPh), 4.67 (d, 1H, OCH*H*Ph), 4.62 (d, J_{gem} 12.2 Hz, 1H, OC*H*HPh), 4.58 (d, 1H, OCH*H*Ph), 4.55 (d, 1H, OCH*H*Ph), 4.33 (ddt, J_{gem} 12.9 Hz, 1H, OC*H*HCH=CH_2), 4.14-4.03 (m, 2H, H3, OCH*H*CH=CH_2), 3.77 (dd, J_{gem} 10.7 Hz, $J_{5,6a}$ 2.5 Hz, 1H, H6a), 3.72 (dd, $J_{5,6b}$ 4.4 Hz, 1H, H6b), 3.65 (dd, $J_{4,5}$ 9.1 Hz, $J_{3,4}$ 8.0 Hz, 1H, H4), 3.59 (ddd, 1H, H5), 3.47 (dt, 1H, H2), 1.85 (s, 3H, NHCOCH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 170.4 (*C*=O), 138.4, 138.3, 138.1 (*ipso*-Ar*C*), 134.1 (OCH_2*C*H=CH_2), 128.53, 128.46, 128.0, 127.9, 127.7 (Ar), 117.5

(OCH$_2$CH=*C*H$_2$), 99.1 (C1), 80.3 (C4), 78.6 (C3), 74.8, 74.62, 74.56 (O*C*H$_2$Ph), 73.6 (C5), 69.9 (O*C*H$_2$CH=CH$_2$), 69.1 (C6), 56.9 (C2), 23.7 (NHCO*C*H$_3$). HRMS(ES): Calcd. for $C_{32}H_{32}D_5NO_6H^+$ 537.3007; found 537.3010.

Allyl 2-acetamido-6-*O*-benzyl-2-deoxy-3,4-di-*O*-(2,3,4,5,6-pentadeuteriobenzyl)-β-D-glucopyranoside (26)

Allyl 2-acetamido-6-*O*-benzyl-2-deoxy-3-*O*-(2,3,4,5,6-pentadeuteriobenzyl)-β-D-glucopyranoside **22** (265 mg, 0.59 mmol, 1 eq.) was dissolved in dry DMF (2.7 mL). The temperature of the resulting solution was buffered with a water bath at ambient temperature prior to the addition of 60% NaH on mineral oil (31 mg, 0.8 mmol, 1.3 eq.). After gas evolution had ceased, 2,3,4,5,6-pentadeuteriobenzyl bromide[35] (0.08 mL, 0.64 mmol, 1.1 eq.) was added and the resulting mixture was stirred at room temperature overnight. After 16 hours TLC analysis (40% EtOAc in CH_2Cl_2) indicated only half conversion. Another 0.65 eq. of NaH and 0.55 eq. of 2,3,4,5,6-pentadeuteriobenzyl bromide were added, and after 1.5 hours at room temperature TLC analysis indicated full conversion. The reaction was quenched with sat. aq. $NaHCO_3$. Brine was added and the resulting mixture was extracted 5 times with $CHCl_3$. The combined organic layers were dried over $MgSO_4$ and evaporated onto Celite®. Flash column chromatography (10→20% EtOAc in $CHCl_3$) afforded the desired compound **26** (219 mg, 68%) as a white solid.

R_f (20% EtOAc in $CHCl_3$) 0.39. ^{1}H-NMR ($CDCl_3$): δ_H 7.36-7.25 (m, 5H, Ar*H*), 5.94-5.82 (m, 1H, OCH$_2$C*H*=CH$_2$), 5.72 (d, $J_{NH,2}$ 7.3 Hz, 1H, N*H*), 5.25 (dq, J_{trans} 17.3 Hz, J_{gem}=^4J 1.6 Hz, 1H, OCH$_2$CH=C*H*H), 5.16 (dd, J_{cis} 10.4 Hz, 1H, OCH$_2$CH=CH*H*), 4.83 (d, $J_{1,2}$ 7.7 Hz, 1H, H1), 4.82 (d, J_{gem} 11.5 Hz, 1H, OC*H*HPh), 4.78 (d, J_{gem} 11.0 Hz, 1H, OC*H*HPh), 4.67 (d, 1H, OCH*H*Ph), 4.62 (d, J_{gem} 12.2 Hz, 1H, OC*H*HPh), 4.58 (d, 1H, OCH*H*Ph), 4.55 (d, 1H, OCH*H*Ph), 4.33 (dd, J_{gem} 13.0 Hz, J_{vic} 5.2 Hz, 1H, OC*H*HCH=CH$_2$), 4.13-4.03 (m, 2H, H3, OCH*H*CH=CH$_2$), 3.76 (dd, J_{gem} 10.7 Hz, $J_{5,6a}$ 2.6 Hz, 1H, H6a), 3.72 (dd, $J_{5,6b}$ 4.3 Hz, 1H, H6b), 3.65 (dd, $J_{4,5}$ 9.1 Hz, $J_{3,4}$ 8.1 Hz, 1H, H4), 3.59 (ddd, 1H, H5), 3.49 (dt, 1H, H2), 1.85 (s, 3H, NHC(O)C*H*$_3$). ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 170.4 (*C*=O), 138.3, 138.2, 137.9 (*ipso*-Ar*C*), 134.1 (OCH$_2$*C*H=CH$_2$), 128.4, 127.9, 127.7 (Ar), 117.4 (OCH$_2$CH=*C*H$_2$), 99.1 (C1), 80.4 (C4), 78.6 (C3), 74.8, 74.5(2C) (O*C*H$_2$Ph), 73.5 (C5), 69.9 (O*C*H$_2$CH=CH$_2$), 69.1 (C6), 56.8 (C2), 23.7 (NHC(O)*C*H$_3$). HRMS(ES): Calcd. for $C_{32}H_{27}D_{10}NO_6H^+$ 542.3321; found 542.3328.

Allyl 2-acetamido-4,6-di-*O*-benzyl-2-deoxy-3-*O*-(2,3,4,5,6-pentadeuteriobenzyl)-β-D-allopyranoside (27)

Allyl 2-acetamido-4-*O*-benzyl-2-deoxy-3-*O*-(2,3,4,5,6-pentadeuteriobenzyl)-β-D-allopyranoside **24** (65 mg, 0.15 mmol, 1 eq.) was dissolved in dry DMF (0.66 mL). The temperature of the resulting solution was buffered with a water bath at ambient temperature prior to the addition of 60% NaH on mineral oil (8 mg, 0.19 mmol, 1.3 eq.). After gas evolution had ceased, benzyl bromide (19 μL, 0.16 mmol, 1.1 eq.) was added and the resulting mixture was stirred at room temperature overnight. After 16 hours TLC analysis (40% EtOAc in toluene) indicated less than full conversion. Another 0.65 eq. of NaH and 0.55 eq. of BnBr was added, and after one hour TLC analysis indicated full conversion. The reaction was quenched with sat. aq. $NaHCO_3$. Brine was added and the resulting mixture was extracted 5 times with $CHCl_3$. The combined organic layers were dried over $MgSO_4$ and concentrated onto Celite®. Flash column chromatography (20% EtOAc in toluene) afforded the desired compound **27** (57.8 mg, 78%) as a white solid.

R_f (20% EtOAc in toluene) 0.23. $[\alpha]_D^{298K}$ -51.4 (*c* 1, $CHCl_3$). M_p 116.1-117.2 °C. ^{1}H-NMR ($CDCl_3$): δ_H 7.37-7.26 (m, 10H, Ar*H*), 6.26-6.07 (bs, 1H, N*H*), 5.90-5.79 (m, 1H, OCH_2CH=CH_2), 5.26 (dd, J_{trans} 17.2 Hz, J_{gem} 1.4 Hz, 1H, OCH_2CH=C*H*H), 5.14 (dd, J_{cis} 10.4 Hz, 1H, OCH_2CH=CH*H*), 4.78 (d, J_{gem} 11.7 Hz, 1H, OC*H*HPh), 4.68 (d, $J_{1,2}$ 6.2 Hz, 1H, H1), 4.68 (d, J_{gem} 11.3 Hz, 1H, OC*H*HPh), 4.59 (d, 1H, OCH*H*Ph), 4.58 (d, J_{gem} 12.1 Hz, 1H, OC*H*HPh), 4.53 (d, 1H, OCH*H*Ph), 4.51 (d, 1H, OCH*H*Ph), 4.27 (ddt, J_{gem} 13.1 Hz, J_{vic} 4.9 Hz, 1H, OC*H*HCH=CH_2), 4.21-4.11 (m, 1H, H2), 4.14 (dt, $J_{4,5}$ 6.7 Hz, $J_{5,6}$ 4.8 Hz, 1H, H5), 4.08 (t, $J_{2,3}$=$J_{3,4}$ 3.0 Hz, 1H, H3), 4.00 (dd, J_{vic} 5.8 Hz, 1H, OCH*H*CH=CH_2), 3.78 (dd, 1H, H4), 3.73 (dd, J_{gem} 10.5 Hz, 1H, H6a), 3.67 (dd, 1H, H6b), 1.80 (s, 3H, NHC(O)CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 169.9 (*C*=O), 138.3, 137.9 (*ipso*-Ar*C*), 134.1 (OCH_2*C*H=CH_2), 128.6, 128.5, 128.10, 128.08, 127.84, 127.77 (Ar), 117.0 (OCH_2CH=*C*H_2), 99.3 (C1), 76.2 (C4), 74.1 (C5), 73.5, 72.8 (O*C*H_2Ph), 69.8 (C6), 69.3 (O*C*H_2CH=CH_2), 51.2 (C2), 23.5 (NHC(O)*C*H_3). HRMS(ES): Calcd. for $C_{32}H_{32}D_5NO_6H^+$ 537.3007; found 537.3014.

Supporting Information

^{1}H and ^{13}C NMR spectra of products and representative stacked 1H NMR spectra (Figure 1 and Figure 2). Synthesis of 1 and detailed screening results for its acetylation. Further details of the synthesis of deuterium labelled compounds 17, 18 and 19 and MS analysis data of their degradation according to Scheme 9.

References

[1] Hart, G. W.; Copeland, R. J. *Cell* **2010**, *143*, 672–676.
[2] Werz, D. B.; Ranzinger, R.; Hergel, S.; Adibekian, A.; von der Lieth, C.-W.; Seeberger, P. H. *ACS Chem. Biol.* **2010**, *2*, 685–691.
[3] Enugala, R.; Carvalho, L. C. R.; Pires, M. J. D.; Marques, M. M. B. *Chem. Asian J.* **2012**, *7*, 2482–2501.
[4] Bongat, A. F. G.; Demchenko, A. V. *Carbohydr. Res.* **2007**, *342*, 374–406.
[5] Crich, D.; Dudkin, V. *J. Am. Chem. Soc.* **2001**, *123*, 6819–6825.
[6] Liao, L.; Auzanneau, F.-I. *Org. Lett.* **2003**, *5*, 2607–2610.
[7] Liao, L.; Auzanneau, F.-I. *J. Org. Chem.* **2005**, *70*, 6265–6273.
[8] In this article we choose to represent oxazolines and their derivatives as a $^{4}H_{5}$ halfchair conformation. The actual conformation is debated, but evidence suggests that the sp^{2} NCO-motif in the oxazoline ring enforces a change to either this or the twist boat (See references 9 and 10). Both of these are very different from the parent $^{4}C_{1}$ chair and this, we feel, is an important point to consider in these systems.
[9] Srivastava, V. K. *Carbohydr. Res.* **1982**, *103*, 286–292.
[10] Pertel, S. S.; Kononov, L. O.; Zinin, A. I.; Chirva, V. J.; Kakayan, E. S. *Carbohydr. Res.* **2012**, *356*, 172–179.
[11] Kiso, M.; Anderson, L. *Carbohydr. Res.* **1985**, *136*, 309–323.
[12] Christensen, H.; Christiansen, M. S.; Petersen, J.; Jensen, H. H. *Org. Biomol. Chem.* **2008**, *6*, 3276–3283.
[13] Stévenin, A.; Boyer, F.-D.; Beau, J.-M. *Eur. J. Org. Chem.* **2012**, 1699–1702.
[14] Mandal, S.; Sharma, N.; Mukhopadhyay, B. *Synlett*, **2009**, 3111–3114.
[15] Ljekvakovic, D.; Tomic, S.; Tomasic, J. *Carbohydr. Res.* **1988**, *182*, 197-205.
[16] Feng, J.; Ling, C.-C. *Carbohydr. Res.* **2010**, *345*, 2450–2457.
[17] Rasmussen, M. R.; Marqvorsen, M. H. S.; Kristensen, S. K.; Jensen, H. H. *J. Org. Chem.* **2014**, *79*, 11011–11019.
[18] Krag, J.; Christiansen, M. S.; Petersen, J. G.; Jensen, H. H. *Carbohydr. Res.* **2010**, *345*, 872–879.
[19] For details, see Supporting Information.
[20] Crich, D.; Smith, M.; Yao, Q.; Picione, J. *Synlett*, **2001**, 323-326.
[21] Antoniotti, S.; Duñach, E. *Chem. Commun.* **2008**, 993-995.
[22] Christensen, H. M.; Oscarson, S.; Jensen, H. H. *Carbohydr. Res.* **2015**, *408*, 51–95.
[23] Jarglis, P.; Lichtenthaler, F. W. *Tetrahedron Lett.* **1982**, *23*, 3781-3784.
[24] Lichtenthaler, F. W.; Rönninger, S.; Jarglis, P. *Liebigs Ann. Chem.* **1989**, 1153-1161.
[25] Inch, T. D.; Fletcher, H. G. *J. Org. Chem.*, **1966**, *31*, 1810–1815.
[26] Harrison, R.; Fletcher, H. G. *J. Org. Chem.* **1965**, *30*, 2317–2321.
[27] Nashed, M. A.; Slife, C. W.; Kiso, M.; Anderson, L. *Carbohydr. Res.* **1980**, *82*, 237–252.
[28] Oda, Y.; Midorikawa, M.; Yamanoi, T. *Heterocycles*, **2015**, *90*, 198-215.
[29] Zhang, F.; Zhang, W.; Zhang, Y.; Curran, D. P.; Liu, G. *J. Org. Chem.* **2009**, *74*, 2594–2597.
[30] Dasgupta, F.; Anderson, L. *Carbohydr. Res.* **1990**, *202*, 239–255.
[31] Liu, J.; Gin, D.Y., *J. Am. Chem. Soc.*, **2002**, *124*, 9789–9797.
[32] Sasaki, K.; Nishida, Y.; Kambara, M.; Uzawa, H.; Takahashi, T.; Suzuki, T.; Suzuki, Y.; Kobayashi, K. *Bioorg. Med. Chem.* **2004**, *12*, 1367–1375.
[33] Lin, Y. A.; Chalker, J. M.; Davis, B. G. *J. Am. Chem. Soc.* **2010**, *132*, 16805-16811.
[34] Aguilera, B.; Jiménez-Barbero, J.; Fernández-Mayoralas, A. *Carbohydr. Res.* **1998**, *308*, 19-27.
[35] Hartz, N.; Prakash, G. K. S.; Olah, G. A. *J. Am. Chem. Soc.* **1993**, *115*, 901-905.
[36] Blattner, R.; Furneaux, R. H.; Kemmitt, T.; Tyler, P. C.; Ferrier, R. J.; Tidén, A.-K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3411-3421.