Direct formation of β-glycosides of *N*-acetyl glycosamines mediated by rare earth metal triflates†

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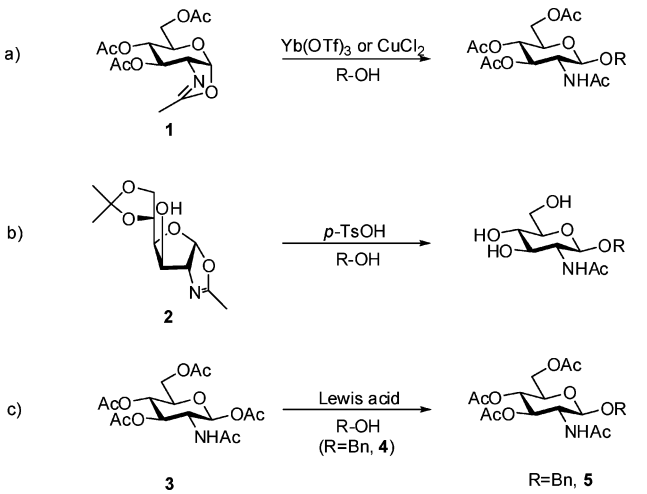
A direct, mild and efficient protocol for the preparation of β-glycosides of *N*-acetyl glucosamine (GlcNAc) and *N*-acetyl galactosamine (GalNAc) has been developed using peracetylated β-GlcNAc and β-GalNAc as donors. All rare Earth metal triflate promoters screened were found to promote glycosylation with $Sc(OTf)_3$ being superior in terms of reaction rate. Simple alcohol glycosylation was found to proceed smoothly in refluxing dichloromethane, whereas higher temperatures under microwave conditions were needed to attain acceptable yields with less reactive, carbohydrate based glycosyl acceptors. The protocol developed was applied to provide the first example of direct chemical formation of a disaccharide using both GlcNAc as a glycosyl donor and acceptor. The α-acetate donor was found to be significantly less reactive than the corresponding β-anomer necessitating higher reaction temperatures under which glycoside anomerisation was found to occur. It was established, that the anomerisation only took place in the presence of both $Sc(OTf)_3$ and acetic acid.

Introduction

The *N*-acetyl glucosamine (GlcNAc) unit is frequently used by Nature as a monosaccharide building block in a range of important oligosaccharides like the core pentasaccharide, nodulation factors, and carbohydrate epitopes.[1] Accordingly, methodology for the efficient preparation of GlcNAc glycosides remains an important component of modern carbohydrate chemistry.[2] Traditionally, the chemical synthesis of the β-GlcNAc glycosidic linkage has most frequently been carried out by using glucosamine-derived donors possessing a temporary protecting group of the 2-amino functionality such as *N*-Troc (*N*-trichloroethoxycarbonyl),[3] *N*-Phth (*N*-phthalimido),[4] *N*,*N*-diacetyl,[5] or azide.[6] Among the less used nitrogen camouflaging groups are *N*-Alloc (*N*-allyloxycarbonyl),[7] *N*-Cbz (*N*-benzyloxycarbonyl),[7] *N*-TCA (*N*-trichloroacetyl),[8] *N*-TCP (tetrachlorophthalimido),[9] *N*-Dts (*N*-dithiasuccinoyl),[10] *N*-DCPhth (*N*-4,5-dichlorophthalimido),[11] *N*-DMM (*N*-dimethylmaleoyl),[12] *N*,*N*-dibenzyl,[13] and *N*-TDG (*N*-thiodiglycoloyl).[14] Although glycosylation generally functions well with donors bearing these protecting groups their drawback is that separate synthetic steps are required for introduction and later interconversion to the biologically relevant 2-acetamido substituent.

To minimise the number of synthetic steps, sugar oxazolines have been explored as potential donors, which directly yield the acetyl function without further manipulations. Traditionally, a range of Lewis acids such as $FeCl_3$,[15] $AlCl_3$,[16] and TMSOTf[2] have been used with some success for glycopyranosyl oxazoline (**1**) activation in chemical GlcNAc-ylation. Recently, stoichiometric cupric salts[17] and $Yb(OTf)_3$ (30 mol%)[18] were established as being useful catalysts for the synthesis of simple glycosides of GlcNAc (Scheme 1a). Bundle and co-workers have furthermore found 5,6-*O*-isopropylidene glucofuranosyl oxazoline (**2**, Scheme 1b) to be a useful donor with *p*-TsOH as the activating agent giving the 2-acetamido glucopyranosides as products.[19]



Scheme 1 Synthesis of GlcNAc β-glycosides. a) from pyranosyl oxazoline,[17,18] b) from furanosyl oxazoline,[19] and c) direct glycosylation from acetate donor, present study.

The use of oxazolines as donors for chemical glycosylation is troubled by their preparation and low shelf stability. We accordingly undertook a study inspired by the above mentioned promising results[18] to search for reaction conditions under which GlcNAc-ylation could be conducted using a stable, storable glycosyl donor.

Rare earth metal triflates have proven to be a highly valuable tool in a wide range of Lewis acid mediated reactions. The advantage of using these metals as catalysts is their high level of acidity in combination with their stability towards moisture.[20]

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This work describes our recent results in using shelf stable and commercially[21] available GlcNAc-acetates (**3**) as glycosyl donors and rare earth metal triflates as Lewis acid promoters, without the need for purification of the oxazoline intermediate. The use of catalytic amounts of rare earth metal triflates is believed to both catalyse oxazoline formation and activation.

Results and discussion

Various Lewis acid catalysts

Early in our study, inspired by the work of Crasto and Jones,[18] we were pleased to find that $Yb(OTf)_3$ (15 mol%) with BnOH (**4**) in refluxing CH_2Cl_2 efficiently catalysed the exclusive formation of benzyl β-glycoside **5** in 75% yield from the stable, commercially available β-peracetylated donor **3** (entry 1, Table 1). This promising result led us to screen for optimal reaction conditions. All Lewis acids tested were capable of promoting glycosylation with isolated yields between 69–88% (entry 1–7, Table 1). Reaction times were typically 20–22 hours but with $Sc(OTf)_3$ and $Cu(OTf)_2$ standing out as significantly more active catalysts resulting in reaction completion after only 4 and 8 hours, respectively (entry 2 and entry 7, Table 1). This confirms the known fact that of this series of catalysts, $Sc(OTf)_3$ is known to have extraordinarily high activity as a Lewis acid.[20]

Also $CuBr_2$ (15 mol%), which had been found by Wittmann and Lennartz[17] to promote oxazoline glycosylation using a stoichiometric amount of Lewis acid gave the expected β-benzyl glycoside (**5**) albeit in only 57% yield (entry 8, Table 1). Interestingly, in contrast to the present results, Wittmann and Lennartz reported that $Cu(OTf)_2$ was not a promoter for the conversion of oxazoline to glycoside.[17]

To shed light on the reaction mechanism an experiment was carried out in refluxing CH_2Cl_2 with $Yb(OTf)_3$ (15 mol%) but leaving out any acceptor alcohol. This led, according to TLC analysis, to the development of a slightly more polar compound, which was found to have the NMR spectral characteristics of the expected oxazoline intermediate.[22] Regardless of the choice of catalyst, performing the reaction in the presence of *e.g.* BnOH (**4**) also showed the development of this more polar compound that eventually disappeared after reaction completion. This strongly indicates that the rare earth metal triflates catalyse both anomeric activation leading to oxazoline formation and later breakdown of this as described by Crasto and Jones.[18]

Table 1 Results of glycosylations according to Scheme 1c conducted with BnOH (4) (3 equiv.)

Entry	T/°C[a]	Solvent	Cat. (15 mol%)	Price/ (€/5 g)[b]	Time	Yield[c]
1	45	CH_2Cl_2	$Yb(OTf)_3$	87.00	22 h	75%
2	45	CH_2Cl_2	$Sc(OTf)_3$	255.30	4 h	81%
3	45	CH_2Cl_2	$Sm(OTf)_3$	101.50	22 h	84%
4	45	CH_2Cl_2	$La(OTf)_3$	74.20	22 h	81%
5	45	CH_2Cl_2	$Dy(OTf)_3$	69.70	20 h	83%
6	45	CH_2Cl_2	$Nd(OTf)_3$	42.50	20 h	88%
7	45	CH_2Cl_2	$Cu(OTf)_2$	83.50	8 h	69%
8	45	CH_2Cl_2	$CuBr_2$	20.90	>24 h	57%
9	45	$ClCH_2CH_2Cl$	$Sc(OTf)_3$	255.30	6 h	69%
10	45	THF	$Sc(OTf)_3$	255.30	>28 h	48%
11	45	$PhCH_3$	$Sc(OTf)_3$	255.30	12 h	54%
12	45	CH_3CN	$Sc(OTf)_3$	255.30	8 h	62%
13	90	$ClCH_2CH_2Cl$	$Sc(OTf)_3$	255.30	90 min	82%
14	90	$ClCH_2CH_2Cl$	none		>30 h	0%

[a] Oil bath temperature. [b] Prices listed on www.sigmaaldrich.com, March 2008. [c] Isolated yield after chromatography.

Due to the superior reactivity of $Sc(OTf)_3$ in spite of it being the most highly priced of the tested catalysts, we continued our screen for the best reaction medium among the standard laboratory solvents (entry 9–12, Table 1). These were found to result in diminished yields compared to when CH_2Cl_2 was used at the same temperature with dichloroethane (DCE) giving the best result (6 hours, 69%, entry 9, Table 1). Both reaction times and yields were the order CH_2Cl_2 > DCE > CH_3CN > $PhCH_3$ > THF.

Heating the reaction mixture to reflux in DCE gave an improved yield of 82% in only 90 min (entry 13, Table 1). The same protocol was investigated leaving out the catalyst showing no product formation after 30 hours demonstrating the necessity of a Lewis acid promoter (entry 14, Table 1).

Various glycosylation reactions

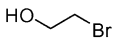
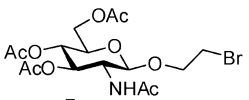
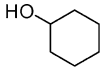
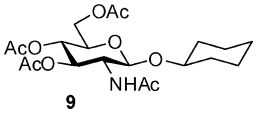
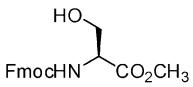
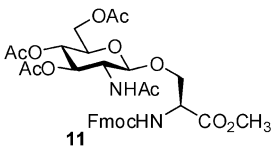
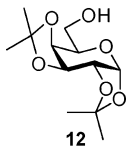
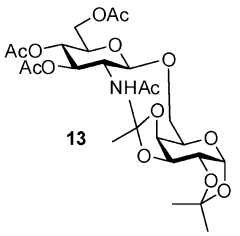
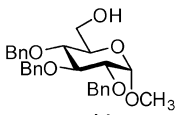
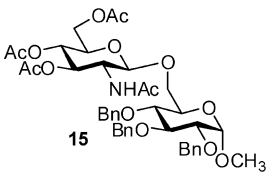
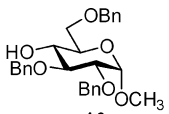
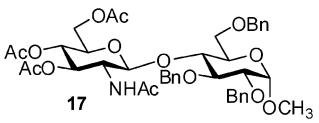
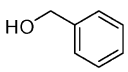
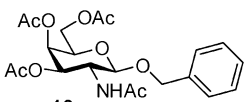
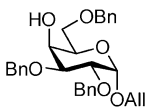
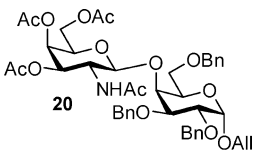
After optimising reaction conditions, the use of various alcohols as potential glycosyl acceptors were explored (Table 2). The electron poor acceptor 2-bromoethanol (**6**,entry 1, Table 2) also yielded the expected β-glycoside (**7**) with a significant prolonged reaction time (27 hours) compared to BnOH (**4**). Glycosylation with cyclohexanol (**8**, entry 2, Table 2) gave the expected β-cyclohexyl glycoside (**9**) in 84% yield but the reaction time had gone from 4 hours with BnOH (**4**) to 48 hours with this more sterically demanding acceptor. The protocol too offered the possibility of preparing a glycoamino acid building block of serine (**11**, 50%, entry 3, Table 2) found in nuclear proteins.[23] It is well-established that carbamate protected serines (**10**) act as poor glycosyl acceptors, a fact that has been ascribed to unfavourable HO: → H–N hydrogen bond formation.[24]

Galactose (**12**) and glucose[25] (**14**) based primary alcohols were furthermore glycosylated in 78% and 85%, respectively (entry 4 and entry 5, Table 2).

Full consumption of acceptor with 4 equivalents of donor (**3**) could not be reached in the case of 4-OH acceptor **16**[26] (entry 6, Table 2). After heating for 72 hours only 21% of the disaccharide **17** could be isolated (64% based on recovered **16**) giving an indication of the scope of the present protocol. In this case adding more donor or catalyst was found not to result in further conversion.

N-Acetyl-galactosamine (GalNAc) has no less biological significance compared to GlcNAc so we were pleased to find $Sc(OTf)_3$ also was an efficient catalyst to bring about galactosylation from the corresponding GalNAc β-acetate donor (4-*epi*-**3**, entry 7, Table 2).[27] The reaction time with BnOH (**4**) as the acceptor was considerably shorter than with the corresponding glucose configured isomer (**3**) as expected, due to the smaller degree of transition state destabilisation exerted by the C-4 axial substituent.[28] It was furthermore possible to galactosylate the hindered secondary galactose based acceptor **19** in 65% yield (83% based on recovered acceptor). The acceptor (**19**) was prepared by benzylidene ring-opening of the known **24** with Et_3SiH–TFA according to Scheme 2. An efficient synthesis of this disaccharide (**20**) being a target sequence for pulmonary pathogens was published recently using Troc-protection of the galactosamine *N*-atom.[29] We believe that

Table 2 $Sc(OTf)_3$ (15 mol%) promoted glycosylation in refluxing CH_2Cl_2

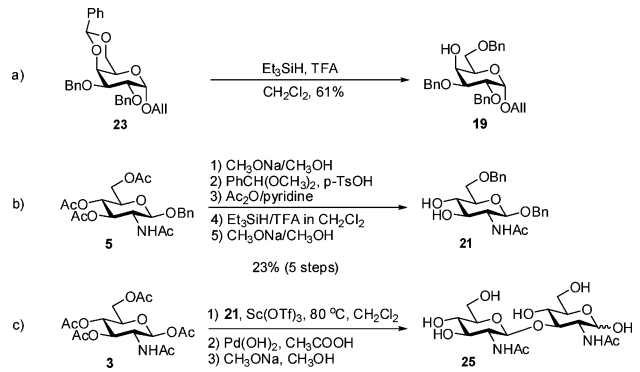
Entry	D[a]	A[b]	Product	(D : A)[c]	Time	Yield[d]
1	**3**	 **6**	 **7**	1 : 3	27 h	67%
2	**3**	 **8**	 **9**	1 : 3	48 h	84%
3	**3**	 **10**	 **11**	1 : 1.5	72 h	50%
4	**3**	 **12**	 **13**	2 : 1	24 h	78%
5	**3**	 **14**	 **15**	4 : 1	72 h	85%
6	**3**	 **16**	 **17**	4 : 1	72 h	21% (64%)
7	4-*epi*-**3**	 **4**	 **18**	1 : 3	2 h	84%
8	4-*epi*-**3**	 **19**	 **20**	4 : 1	72 h	65% (83%)

[a] Donor. [b] Acceptor. [c] Donor : acceptor ratio. [d] Isolated yield after chromatography (yield based on recovered acceptor).

this more direct strategy offers an equally efficient approach to this biologically important disaccharide.

Glycosylation under microwave conditions

Microwave irradiation as a mode of heating is becoming increasingly popular in all aspects of organic chemistry including carbohydrate chemistry.[30–33] Due to the slow reaction rates observed for some of the reactions listed in the above section, we wondered whether microwave irradiation would make the present approach for glycosylation more efficient by lowering the reaction time. Given that microwave reactions are carried out in sealed tubes it is furthermore possible to heat *e.g.* CH_2Cl_2 to temperatures well above the boiling point at atmospheric pressure avoiding the need of higher boiling solvents like DCE. The benefit of this is both the easier later removal of a lower boiling solvent along with



Scheme 2 Synthesis of galactose and *N*-acetyl glucosamine acceptors (a and b), and regioselective glycosylation of 3,4-acceptor (**21**) followed by deprotection to confirm regiochemistry of interglycosidic linkage (c).

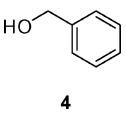
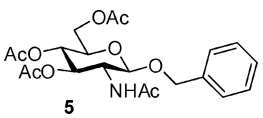
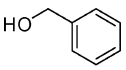
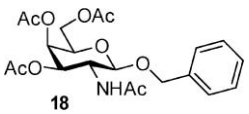
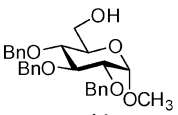
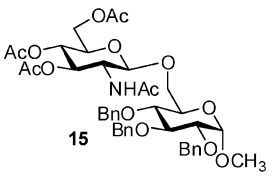
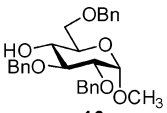
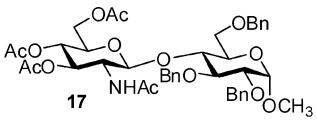
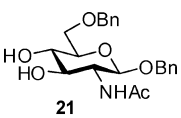
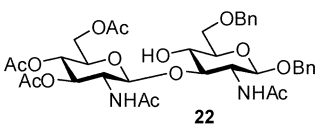
the fact that DCE is less commonly available in comparison to CH_2Cl_2 as a freshly distilled solvent in most chemical laboratories.

We first investigated the GlcNAc- and GalNac-ylation with benzyl alcohol as the acceptor under conditions similar those described above with conventional heating (Table 1, entry 2 and Table 2, entry 7). When heating by microwave irradiation to 80 °C it was yet again observed that galactosylation (5 min, entry 2, Table 3) was faster than glucosylation (20 min, entry 1, Table 3). The reaction time was hence brought down from several hours to minutes while the yield essentially remained the same.

We next decided to explore glycosylation of carbohydrate based alcohols. Primary alcohol **14** could be glycosylated in as little as 3 hours but a slightly lower yield was obtained (entry 3, Table 3). Using microwave heating, a significantly higher level of conversion was obtained with the troublesome secondary alcohol of glucose acceptor **16** (entry 4, Table 3) after 16 hours at 80 °C. Although this cannot be regarded as a high yield it must be kept in mind that only one anomeric product is formed and that no additional steps for protecting group interconversion are required to attain the biologically relevant acetamido function.

Some success in *O*-4 over *O*-3 regioselective galactosylation of β-GlcNAc derivatives has in recent years been reported.[34] Inspired by these results it was decided to investigate whether the present protocol also was able to selectively give a 1→4 linked disaccharide and thereby a di-*N*-acetyl chitobiose derivative. Heating the novel GlcNAc acceptor **21** (Scheme 2) with β-acetate **3** under microwave irradiation in the presence of $Sc(OTf)_3$ (15 mol%), however, was found to selectively produce the 1→3 linked disaccharide in the astonishing yield of 90% (entry 5, Table 3). The regiochemistry of the product was established by the presence of H1′→C3 and H3→C1′ correlations in the HMBC spectrum of the disaccharide (**22**) and confirmed by global deprotection and comparison to known spectral data (Scheme 2c).[35] This, to the best of our knowledge, constitutes the first example of a chemical glycosylation reaction where GlcNAc successfully has been used as both donor and acceptor.

Table 3 $Sc(OTf)_3$ (15 mol%) promoted glycosylation in CH_2Cl_2 under microwave irradiation (80 °C)

Entry	D[a]	A[b]	Product	(D : A)[c]	Time	Yield[d]
1	**3**	 **4**	 **5**	1 : 3	20 min	80%
2	4-*epi*-**3**	 **4**	 **18**	1 : 3	5 min	80%
3	**3**	 **14**	 **15**	2 : 1	3 h	75%
4	**3**	 **16**	 **17**	4 : 1	16 h	43% (68%)
5	**3**	 **21**	 **22**	2 : 1	8 h	90%

[a] Donor. [b] Acceptor. [c] Donor : acceptor ratio. [d] Isolated yield after chromatography (yield based on recovered acceptor).

Glycosylation with α-anomeric acetate

Only β-acetates (**3** and 4-*epi*-**3**) had to this point been explored as the glycosyl donor (Scheme 1c). Despite the fact that this can be easily synthesised[21] on a large scale without the need for chromatographic purification of reaction intermediates, its preparation involves several synthetic steps. We therefore wondered whether an anomeric mixture of acetates being the product of a simple acetylation reaction of D-*N*-acetylglucosamine, could be used with equal success.[36]

Prolonged conventional heating of an α–β-mixture (**3**αβ, α : β = 4.6 : 1) in CH_2Cl_2 with BnOH (**4**)–$Sc(OTf)_3$ according to the standard procedure (entry 2, Table 1) was found only to yield the benzyl glycoside (**5**) according to the proportion of β-donor (**3**). Unreacted donor was accordingly shown to be exclusively the α-anomeric acetate (**3**α) in accordance with the well-known fact that axial donors are less reactive than the corresponding equatorial donors.[37] Changing reaction conditions from conventional reflux to microwave heating at 80 °C in CH_2Cl_2 it was possible to obtain some activation of the α-anomeric acetate but the reaction was still rather sluggish. Full consumption of donor (**3**αβ) was achieved after heating to 110 °C for 5 hours in the presence of benzyl alcohol (**4**) giving a the benzyl glycoside (**5**αβ) in 80% yield. The product, however, was obtained as a 1 : 4 anomeric mixture of glycosides (entry 1, Table 4). This led us to investigate whether glycosylation at this temperature with an α-donor led to an α : β product mixture or rather glycosylation was accordingly slow that anomerisation of the already formed product underwent post-glycosylation anomerisation. The results are listed in Table 4.

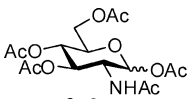
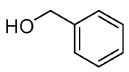
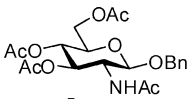
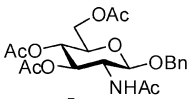
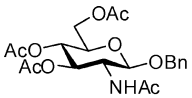
Since we expected that the rare earth metal triflate was responsible for the anomerisation we were surprised that treatment of benzyl glycoside **5** (entry 2, Table 4) with $Sc(OTf)_3$ resulted in complete isolation of starting material in its β-anomeric form. Heating benzyl glycoside **5** with a stoichiometric amount of acetic acid leaving out the $Sc(OTf)_3$ under otherwise identical conditions also showed lack of anomerisation (entry 3, Table 4). These observations could indicate that the glycoside (**5**) was anomerically stable under the reaction conditions and that the α-glycoside product (entry 1, Table 4) in some way originated from using the α-acetate donor **3**α. As a final control experiment the benzyl glycoside was treated with both $Sc(OTf)_3$ and acetic acid and these conditions indeed did show anomerisation to occur (entry 4, Table 4). This can only mean that a powerful Lewis acid like triflic acid forms from the reaction of $Sc(OTf)_3$ with acetic acid, which is capable of catalysing post-glycosylation anomerisation. This, hence, only becomes relevant due to the more forcing conditions required to activate the α-acetate donor (**3**α).

Conclusion

The results presented in this article demonstrate that scandium triflate efficiently catalyses the activation of β-GlcNAc and β-GalNAc tetraacetates in the presence of a variety of glycosyl acceptors resulting in the exclusive formation of the β-glycoside. The donor substrates are shelf stable and have the benefit of directly producing 2-acetamido substituent circumventing the use of traditional phthalimido- or Troc protecting groups.

For slowly reacting alcohols, microwave irradiation was found to significantly diminish reaction time and in certain cases result in higher acceptor turnover. α-Acetates were found to have poor glycosyl donor properties and the reaction conditions needed to bring about full conversion resulted in product anomerisation catalysed by both $Sc(OTf)_3$ and the acetic acid formed during the reaction.

Table 4 Reaction conducted in CH_2Cl_2 under microwave irradiation (110 °C) for 5 hours

Entry	D[a]	A[b]	$Sc(OTf)_3$	AcOH	α : β product ratio[c]
1	 **3**αβ	 **4** (3 equiv.)	15 mol%	none	21 : 79
2	 **5**	none	15 mol%	none	0 : 100
3	 **5**	none	none	1 equiv.	0 : 100
4	 **5**	none	15 mol%	1 equiv.	28 : 72

[a] Donor; [b] Acceptor. [c] α : β product ratio of benzyl glucoside (5αβ) as determined by NMR analysis of the crude reaction mixture.

We believe that this protocol offers a convenient approach for the synthesis of β-glycosides of GlcNAc and GalNAc that will be of high value to carbohydrate chemistry.

Experimental section

General methods

All reagents except otherwise stated were used as purchased without further purification. Solvents were dried according to standard procedures. Columns for flash chromatography were packed with silica gel (60 Å). TLC plates (Kieselgel 60 F_{254}) were visualised by use of a "Ce-Mol" solution (Ce(IV)sulfate (10 g) and ammonium molybdate (15 g) dissolved in 10% H_2SO_4 (1 L)) and heated until coloured spots appeared. ^{1}H and ^{13}C NMR experiments were recorded on a Varian Mercury 400 NMR instrument and assigned using DEPT-135, *g*HMQC, and *g*COSY-experiments. Mass spectral analyses were carried out as electrospray experiments on a Micromass LC-TOF instrument. Optical rotation was measured on a PE-314 polarimeter. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Melting points were measured on a Büchi B-540.

Microwave experiments were carried out on in a Biotage Initiator (Biotage, Sweden). Reaction times listed refer to 'hold time' at the specified temperature.

General procedure for the synthesis of benzyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside (5) with various catalysts and solvents

Donor **3** (200 mg, 0.51 mmol) and catalyst (0.081 mmol) were dissolved in dry solvent (2.5 mL) and benzyl alcohol (**4**) (0.17 mL, 1.6 mmol) was added. The mixture was heated to reflux with condenser under an atmosphere of nitrogen until TLC analysis indicated that the reaction gave no further conversion. The reaction mixture was worked up by diluting with CH_2Cl_2 and washing the organic layer with water, followed by extraction with CH_2Cl_2. When MeCN or THF were used as solvent, the combined organic extracts were washed with brine. The mixture was then dried over anhydrous $MgSO_4$ and purified by column chromatography (pentane–EtOAc 1 : 1 → EtOAc) to give the benzyl glycoside **5** as white crystals in varying yields as listed in Table 1. R_f (EtOAc): 0.58. Mp (uncorr.): 165–167 °C. LRMS(ES+): calcd. for $C_{21}H_{27}NO_9Na$: 460.2, found: 460.2. Spectral data was in accordance with previously reported results.[38]

General procedure for the coupling of 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose to various alcohols

Glycosyl acceptor was added to a dry solution of donor **3** and catalyst (0.15 eq.). The mixture was heated to reflux with condenser under nitrogen, until TLC analysis indicated that the reaction gave no further conversion. The reaction mixture was worked up by diluting with CH_2Cl_2 and washing with water, followed by extraction with CH_2Cl_2. The combined organic extracts were then dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo*, and purified by flash column chromatography on silica using an appropriate eluent.

Allyl *O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzyl-α-D-galactopyranoside (20)

Dry toluene was removed under reduced pressure from a round bottomed flask containing a stirrer bar, β-D-*N*-acetyl-galactosamine tetraacetate (4-*epi*-**3**) (133 mg, 0.34 mmol) and galactose acceptor **19** (84 mg, 0.17 mmol). When dry, the mixture was dissolved in CH_2Cl_2 (1.0 mL) and $Sc(OTf)_3$ (13 mg, 0.026 mmol) was added before the mixture was heated to reflux under an atmosphere of nitrogen. After 24 h another portion of donor (67 mg, 0.17 mmol) and $Sc(OTf)_3$ (13 mg, 0.026 mmol) were added. After a total of 67 h no further reaction was observed by TLC analysis (EtOAc–pentane 2 : 1). The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with $NaHCO_3$ (sat. aq.), dried ($MgSO_4$) and purified by column chromatography (EtOAc–pentane 1 : 4 → 2 : 1). This gave un-reacted acceptor (18 mg) and the desired disaccharide (91 mg, 65%, 83% rcv.) as a colourless oil. R_f(EtOAc–pentane 1 : 1) 0.12. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.43–7.25 (m, 15H, Ar*H*), 5.97–5.87 (m, 1H, C*H*=CH$_2$), 5.53 (d, 1H, $J_{NH,2}$ 8.4 Hz, N*H*), 5.31 (b d, J_{vic} 17.2 Hz, CH=C*H*H), 5.26 (d, 1H, *J* 3.2 Hz, H4′), 5.20 (b d, 1H, J_{vic} 10.4 Hz, CH=CH*H*), 4.91 (d, 1H, $J_{1,2}$ 3.6 Hz, H1), 4.87 (d, 1H, J_{gem} 10.4 Hz, PhC*H*H), 4.70–4.55 (m, 7H, PhCH*H*, PhC*H*$_2$, PhC*H*$_2$, H1′, H3′), 4.23–3.96 (m, 8H, C*H*$_2$CH=CH$_2$, H2′, H6′a, H6′b, H3, H4, H5), 3.81 (dd, 1H, $J_{2,3}$ 10.0 Hz, H2), 3.77 (t, 1H, *J* 7.6 Hz, H5′), 3.71 (dd, 1H, $J_{5,6a}$ 6.0 Hz, $J_{6a,6b}$ 10.0 Hz), 3.64 (dd, 1H, $J_{5,6b}$ 6.4 Hz, H6b), 2.15, 1.99, 1.95, 1.55 (C(O)C*H*$_3$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.7, 170.6, 170.2 (*C*O), 138.6, 138.4, 138.0, 129.2, 128.9, 128.7, 128.6, 128.1, 128.0, 127.8, 127.7 (Ar), 134.0 (*C*H=CH$_2$), 118.4 (CH=*C*H$_2$), 103.4 (C1′), 95.7 (C1), 78.1, 77.9, 77.7 (C2, C3, C4), 74.9, 73.6, 73.0 (Ph*C*H$_2$), 72.3 (C3′), 71.1 (C5′), 69.8 (C6), 69.4 (C5), 68.6 (*C*H$_2$CH=CH$_2$), 66.7 (C4′), 61.5 (C6′), 50.7 (C2′), 23.2, 21.0, 20.9, 20.9 (C(O)*C*H$_3$). $[\alpha]_D^{21}$ 24.8 (*c* 1.0, $CHCl_3$), HRMS(ES+): calcd. for $C_{44}H_{53}NO_{14}Na$: 842.3364; found: 842.3370.

Benzyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-galactopyranoside (18)

Benzyl alcohol (**4**) (88 μL, 0.85 mmol) and $Sc(OTf)_3$ (21 mg, 0.042 mmol) were added to β-D-*N*-acetyl-galactosamine tetraacetate (4-*epi*-**3**) (110 mg, 0.28 mmol) in CH_2Cl_2 (0.84 mL). The reaction mixture was heated to reflux on an oil bath (2 h) or 80 °C under microwave conditions (5 min) before the reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with $NaHCO_3$ (sat. aq.), dried ($MgSO_4$), concentrated, and purified by column chromatography (EtOAc–pentane 1 : 1 → EtOAc). This gave the benzyl galactoside **18** as a white powder (104 mg, 84%, oil bath) (99 mg, 80%, microwave). R_f(EtOAc) 0.37. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.33–7.25 (m, 5H, Ar*H*), 5.73 (d, 1H, $J_{2,NH}$ 8.4 Hz, N*H*), 5.32 (d, 1H, $J_{3,4}$ 3.2 Hz, H4), 5.20 (dd, 1H, $J_{2,3}$ 11.2 Hz, H3), 4.87 (d, 1H, J_{gem} 12.0 Hz, PhC*H*HO), 4.65 (d, 1H, $J_{1,2}$ 8.4 Hz, H1), 4.58 (d, 1H, PhCH*H*O), 4.19–4.00 (m, 3H, H5, H6a, H6b), 3.90–3.87 (m, 1H, H2), 2.11, 2.03, 1.94, 1.85 (s, 12H, C(O)C*H*$_3$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.7, 170.6, 170.5 (*C*O), 137.3, 128.7, 128.4, 128.2 (Ar), 100.0 (C1), 70.9 (double intensity), 70.2, 67.1, 61.8 (C3, C4, C5, C6, O*C*H$_2$Ph), 51.5 (C2), 23.6, 20.9 (triple intensity, C(O)*C*H$_3$). $[\alpha]_D^{21}$ −50.2 (*c* 1.0, $CHCl_3$) (lit.: $[\alpha]_D^{23}$ −55

(c 1.0, $CHCl_3$).[39] HRMS(ES+): calcd. for $C_{21}H_{27}NO_9Na$: 460.1584; found: 460.1580.

Benzyl 2-acetamido-6-*O*-benzyl-2-deoxy-β-D-glucopyranoside (21)

Donor **3** (4.92 g, 12.6 mmol) and benzyl alcohol (**4**) (4.0 mL, 0.0378 mol) were coupled according to the general procedure with $Sc(OTf)_3$ (0.933 g, 0.188 mmol) as catalyst in dry CH_2Cl_2 (50 mL). After 4 h TLC analysis indicated no further reaction. The reaction mixture was worked up as described in the general procedure and purified by column chromatography (pentane–EtOAc 1 : 1 → EtOAc) to give benzyl glycoside **5** (4.31 g, 78%). This (4.31 g, 9.86 mmol) was dissolved in dry CH_3OH (25 mL) under a N_2-atmosphere. With a syringe, a catalytic amount of a freshly prepared $NaOCH_3$ solution was transferred to the reaction mixture. When no further reaction was observed by TLC analysis (EtOAc–CH_3OH 9 : 1), Amberlite (IR-120H$^+$) was added. The reaction mixture was stirred for 10 min before Amberlite was filtered off and the resulting mixture concentrated under vacuum to give the crude triol. This was then dissolved in dry CH_3CN (80 mL) before benzaldehyde dimethyl acetal (1.6 mL, 10.6 mmol) and PTSA (68 mg, 0.36 mmol) were added. The heterogeneous reaction mixture was stirred at ambient temperature for 1 h and then heated to 50 °C for 30 min. The solid was filtered off, washed with Et_2O and dissolved in dry pyridine–acetic anhydride (1 : 1, 40 mL) with 4-DMAP (25 mg, 0.21 mmol) and stirred at ambient temperature overnight. The reaction mixture was quenched with H_2O (ice bath), the aqueous phase extracted 4 times with CH_2Cl_2, dried over $MgSO_4$, and concentrated under vacuum to give crude benzyl 2-acetamido-2-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside, which was sufficiently pure for further reaction (1.843 g, 42%, 3 steps). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.43–7.25 (m, 10H, Ar-*H*), 5.52 (s, 1H, PhC*H*O$_2$), 5.32 (b s, 1H, N*H*), 5.16 (t, $J_{3,4} = J_{2,3}$ 9.8 Hz, H3), 4.93 (d, 1H, J_{gem} 12.2 Hz, PhC*H*H), 4.60 (d, 1H, PhCH*H*), 4.53 (d, 1H, $J_{1,2}$ 8.8 Hz, H1), 4.39 (dd, 1H, $J_{5,6a}$ 5.4 Hz, $J_{6a,6b}$ 10.2 Hz, H6a), 4.15 (m, 1H, H2), 3.84 (t, 1H, H6b), 3.73 (t, 1H, H4), 3.48 (ddd, 1H, H5), 2.06, 1.82 (s, 6H, C(O)C*H*$_3$). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 171.5, 170.3 (*C*O), 137.2, 129.4, 128.7, 128.5, 128.2, 128.1, 126.4 (Ar), 101.6, 100.9 (Ph*C*HO$_2$, C1), 78.8, 72.1, 71.0, 68.9, 66.8 (C3, C4, C5, C6, Ph*C*H$_2$O1), 54.7 (C2), 23.5, 21.1 (C(O)*C*H$_3$).

To a stirred solution of crude benzyl 2-acetamido-2-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside (1.840 g, 4.17 mmol) in dry CH_2Cl_2 (5 mL) and triethylsilane (3.3 mL, 20.9 mmol) at 0 °C under an atmosphere of N_2 was added TFA (1.6 mL, 20.9 mmol) over 5 min. The reaction mixture was stirred on an ice bath for 15 min. and then at ambient temperature for 30 min. The mixture was transferred to a separation funnel containing $NaHCO_3$ (25 mL, sat. aq. Caution: development of CO_2). The aqueous phase was extracted three times with CH_2Cl_2 (25 mL) and the combined organic layers dried over $MgSO_4$ and concentrated under vacuum. The product was purified by column chromatography (EtOAc–pentane 3 : 1 → EtOAc–CH_3OH 10 : 1) to give the desired dibenzyl glucoside (0.991 g 54%) as a colourless powder. R_f(EtOAc) 0.26. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.32–7.27 (m, 10H, Ar*H*), 6.46 (d, 1H, $J_{NH,2}$ 9.2 Hz, N*H*Ac), 5.08 (t, 1H, $J_{2,3} = J_{3,4}$ 9.2 Hz, H3), 4.83 (d, 1H, J 12.4 Hz, PhC*H*HO1), 4.60–4.54 (m, 4H, H-1, PhC*H*HO1, PhC*H*$_2$O6), 3.99 (q, 1H, H2), 3.86 (b s, 1H, O*H*), 3.81 (m, 1H, H6a), 3.72 (dd, 1H, $J_{6a,6b}$ 11.2 Hz, $J_{5,6b}$ 5.2 Hz, H6b), 3.66 (t, 1H, H4), 6.59–3.55 (m, 1H, H5), 2.00, 1.83 (s, 6H, C(O)C*H*$_3$). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 172.2, 170.7 (*C*O), 138.1, 137.6, 128.7, 128.6, 128.1, 128.0, 127.9 (Ar), 100.1 (C1), 75.9, 74.8, 73.9, 70.6, 70.5, 70.4 (C3, C4, C5, C6, Ph*C*H$_2$O1, Ph*C*H$_2$O6), 54.2 (C2), 23.4, 21.2 (C(O)*C*H$_3$).

Purified 3-*O*-acetyl monosaccharide (980 mg, 2.21 mmol) was then dissolved in dry CH_3OH under an N_2-atmosphere. With a syringe a catalytic amount of a freshly prepared $NaOCH_3$ solution was transferred to the reaction mixture. After 10 minutes of stirring, the reaction mixture consisted of a white solid. CH_3OH (enough to dissolve the solid) and Amberlite (IR-120H$^+$) were added, and after stirring the Amberlite was filtered of and the resulting mixture was concentrated under reduced pressure to give the desired product in quantitative yield as a white powder (23% over 5 steps). R_f(EtOAc–CH_3OH 6 : 1) 0.44. Mp (uncorr.) 175–178 °C (EtOAc–CH_3OH).[40] ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 7.72 (d, 1H, $J_{NH,2}$ 9.2 Hz, N*H*), 7.34–7.23 (m, 10 H, Ar*H*), 5.11 (b s, 1H, O*H*), 4.97 (b s, 1H, O*H*), 4.73 (d, 1H, J_{gem} 12.6 Hz, PhC*H*HO1), 4.53 (s, 2H, PhC*H*$_2$O6), 4.49 (d, 1H, PhCH*H*O1), 4.38 (d, 1H, $J_{1,2}$ 8.4 Hz, H1), 3.76 (d, 1H, $J_{6a,6b}$ 10.8 Hz, H6a), 3.52 (dd, 1H, $J_{5,6b}$ 6.0 Hz, H6b), 3.50 (q, 1H, H2), 3.32–3.27 (under H_2O, H3, H5), 3.10 (t, 1H, $J_{3,4} = J_{4,5}$ 9.0 Hz, H4), 1.79 (s, 3H, COC*H*$_3$); ^{1}H-NMR (DMSO-d_6 + drop of D_2O, 400 MHz) δ 7.34–7.23 (m, 10H, Ar*H*), 4.70 (d, 1H, J_{gem} 12.0 Hz, PhC*H*HO1), 4.50 (s, 2H, PhC*H*$_2$O6), 4.45 (d, 1H, PhCH*H*O1), 4.36 (d, 1H, $J_{1,2}$ 8.4 Hz, H1), 3.80–3.68 (under DHO signal, 1H, H6a), 3.53 (dd, 1H, $J_{5,6b}$ 6.0 Hz, $J_{6a,6b}$ 10.8 Hz, H6b), 3.49 (t, 1H, H2), 3.31–3.24 (m, 2H, H3, H5), 3.10 (t, 1H, J 9.2 Hz, H4), 1.79 (s, 3H, C(O)C*H*$_3$). ^{13}C-NMR (DMSO-d_6, 100 MHz): δ 170.6 (*C*O), 139.2, 138.5, 128.9, 128.1, 127.9 (Ar), 101.3 (C1), 76.1, 74.5 (C3, C5), 73.0 (Ph*C*H$_2$O6), 71.1 (C4), 70.4 (Ph*C*H$_2$O1), 70.2 (C6), 55.9 (C2), 23.5 (C(O)*C*H$_3$). $[\alpha]_D^{22}$ −33.6 (c 1.0, CH_3OH). HRMS(ES+): calcd. for $C_{22}H_{27}NO_6Na$, 427.1736; found, 427.1727.

Benzyl *O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-2-acetamido-6-*O*-benzyl-2-deoxy-β-D-glucopyranoside (22)

Donor **3** (310 mg, 0.80 mmol) and 3,4-acceptor **21** (160 mg, 0.40 mmol) were dissolved in CH_2Cl_2 (2 mL) before $Sc(OTf)_3$ (59 mg, 0.12 mmol) was added. The reaction mixture was heated to 80 °C under microwave irradiation for 8 h before it was cooled and poured into a separation funnel containing AcOEt (20 mL) and $NaHCO_3$ (sat. aq. 20 mL). The aqueous layer further was extracted with AcOEt (2 × 20 mL) before the combined organic extracts were washed with H_2O (10 mL) and reduced to half the volume under reduced pressure. The remaining solution was cooled in a refrigerator for 2 h before the precipitate was isolated by vacuum filtration. This gave disaccharide **22** as a colourless powder (275 mg, 90%). ^{1}H-NMR (DMSO-d_6, 400 MHz): δ 7.75 (d, 1H, $J_{NH,2}$ 8.8 Hz, H2/H2′), 7.70 (d, 1H, $J_{NH,2}$ 8.8 Hz, H2′/H2), 7.34–7.25 (m, 10H, Ar*H*), 5.26 (t, 1H, $J_{2',3'} = J_{3',4'}$ 9.8 Hz, H3′), 4.82 (d, 1H, $J_{1',2'}$ 8.8 Hz, H1′), 4.81 (t, 1H, H4′), 4.74 (d, 1H, J_{gem} 12.4 Hz, PhC*H*HO1), 4.53 (s, 2H, PhC*H*$_2$O6), 4.50 (d, 1H, PhCH*H*O1), 4.44 (d, 1H, $J_{1,2}$ 8.0 Hz, H1), 4.41 (b s, 1H, O*H*), 4.16 (dd, 1H, $J_{5',6'a}$ 5.4 Hz, $J_{6'a,6'b}$ 12.0 Hz, H6′a), 4.03 (dd, 1H, $J_{5',6'b}$ 2.6 Hz, H6′b), 3.83–3.78 (m, 1H, H5′), 3.75 (b d, 1H, $J_{6a,6b}$ 9.6 Hz, H6a), 3.65 (t, 1H, 9.2 Hz, H3), 3.60–3.52 (m, 3H, H2, H6b, H2′), 3.37–3.33 (m, 1H, H5), 3.24 (t, 1H, H4), 1.97, 1.95, 1.90, 1.83, 1.73 (s,

15H, C(O)CH_3). ^{13}C-NMR (DMSO-d_6, 100 MHz): δ 170.7, 170.3, 170.1, 170.0, 170.0 (*C*O), 139.3, 138.6, 128.9, 128.8, 128.1, 128.0, 128.0, 127.9 (Ar), 101.1 (C1), 100.8 (C1′), 83.5 (C3), 75.8 (C4), 73.0 (Ph*C*H$_2$O6), 72.7 (C3′), 71.2 (C5′), 70.4 (Ph*C*H$_2$O1), 70.1 (C6), 69.5, 69.5 (C2′, C4′), 62.7 (C6′), 54.5, 54.4 (C2, C2′), 23.9, 23.4 (NHC(O)*C*H$_3$), 21.1, 21.1, 21.1 (OC(O)*C*H$_3$). $[\alpha]_D^{21}$ −8.5 (*c* 1.0, CH_3CO_2H). HRMS(ES+): calcd. for $C_{36}H_{46}N_2O_{14}Na$: 753.2847; found: 753.2853.

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