Organic & Biomolecular Chemistry

Accepted Manuscript

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View Article Online
DOI: 10.1039/C8OB03066A

Organic & Biomolecular Chemistry

ARTICLE

Synthesis of lactosamine-based building blocks on a practical scale and investigations of their assembly for the preparation of ^{19}F-labelled LacNAc oligomers

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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The ubiquitous disaccharide *N*-acetyllactosamine (LacNAc type 2, Galβ1,4GlcNAc) is often over-expressed on the surface of cancer cells where it is bound by tumour secreted galectins contributing to cancer-related processes such as metastasis, adhesion, tumour survival, and immune escape. To facilitate NMR investigations into the binding interactions between oligo-LacNAc structures and galectins, which can show both *exo*- and *endo*-binding behaviour, a library of regioselectively ^{19}F-labelled oligo-LacNAc structures was required. Herein, the synthesis on a practical scale of various *N*-protected (Troc, Phth, TFAc) lactosamine donors is reported starting from commercially available lactosamine hydrochloride. Investigations into their glycosylations with lactosamine acceptors to form ^{19}F-containing LacNAc oligomers showed that benzylated acceptors significantly improved the yields over acetylated ones, and that, gratifyingly, the almost untried *N*-trifluoroacetamide (NTFAc) protected donors, already containing the desired ^{19}F-label, were found to be optimal, both considering reaction yields and purification of the glycosylation reactions. The NTFAc group of reducing end acceptors was introduced through *N*-amide transacylation of linker-equipped LacNAc structures. A [2+2] synthetic approach was optimized for the preparation of tetrasaccharide LacNAc/TFAc-dimers and also further expanded to the synthesis of hexasaccharide LacNAc/TFAc-trimer structures.

Introduction

Oligo-*N*-acetyllactosamine and poly-*N*-acetyllactosamine, $[\beta Gal(1\rightarrow4)\beta GlcNAc(1\rightarrow3)]_n$, are ubiquitous constituents of *N*- and *O*-glycans decorating the surface of mammalian cells.[1] These structures are natural ligands for proteins of the galectin family with the binding interaction modulating cell-cell adhesion, inflammatory and immune responses, and a variety of disease associated processes, *e.g.*, tumour development and metastasis.[2] Although all galectins possess similar carbohydrate binding specificities and conserved consensus sequences investigations with various methods, such as crystallography[3] and thermodynamic binding data,[3–5] hemagglutination assays,[5] frontal affinity chromatography (FAC),[6] nuclear magnetic resonance spectroscopy (NMR)[7–10] commonly coupled with molecular dynamics simulations,[7,11,12] and binding experiments with glycan microarrays,[13] have shown that the elongation of the LacNAc type 2 (Galβ1,4GlcNAc) scaffold, the introduction of charges, and its modes of presentation as linear, branched or multivalent oligo-structures, significantly modify the binding affinity of galectins to their *N*-acetyllactosamine-based ligands. Recent reports have suggested that structural[14] and/or dynamics changes[15] not involving the classical contacting residues of the carbohydrate recognition domain (CRD) may play a significant role in the recognition event. In this context, there is no full understanding of the factors that influence the observed binding preferences and binding modes even for simple *N*-acetyllactosamines, linear poly-*N*-acetyllactosamines, and branched ones. Interestingly, depending on the assay set-up, discrepant binding specificities have been proposed. For example, galectin-1 was found to bind both terminal and internal galactose residues of a poly-LacNAc chain (*endo*-binding behaviour)[11] in ^{1}H and ^{13}C NMR studies[16] and FAC experiments.[6] On the opposite, ELISA-type assays with immobilized neoglycoproteins carrying poly-LacNAc chains have shown that galectin-1 does not independently bind to internal LacNAc motifs (*exo*-binding lectin behaviour).[17] Similarly, contrasting reports into the binding preferences of LacNAc oligomers by galectin-9 N-terminal CRD have been presented.[6,18] Further contributing to the poor understanding of the dynamics of glycans recognition by galectins is the lack of libraries of oligo-*N*-acetyllactosamine structures and analogues thereof.[19]

Recently it was shown that the presence of a fluorine probe on carbohydrates, both as deoxy-fluoro compounds[20,21] or fluoroacetamide ($-NHCOCH_xF_y$) containing derivatives,[22–24] can be exploited to follow protein-carbohydrate binding events via ^{19}F NMR spectroscopy. To further investigate this technique in the context of glycan-galectin interactions, we are interested in the design and synthesis of suitable di- and trimeric *N*-

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

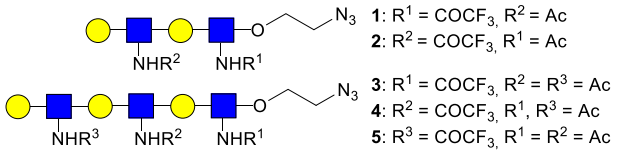

Figure 1: Trifluoroacetamide containing LacNAc/LacNTFAc oligosaccharides **1**–**2** and **3**–**5**.

acetyllactosamines as galectin substrates bearing a trifluoroacetamide group (TFAc) as the fluorine probe on different lactosamine units (Figure 1). The target oligosaccharides are equipped with a 2-azidoethyl spacer to provide a site of attachment for multivalent presentation or, possibly, glycoarray preparation, while the alternate pattern in the disposition of the trifluoroacetamide provides a way to identify single LacNAc units in ^{19}F NMR, with no loss of the binding interaction.[10]

Aside from enzymatic and chemoenzymatic methodologies,[25–27] chemical synthesis of di-, tri-, and tetrameric *N*-acetyllactosamine derivatives has been reported earlier by Alais and Veyrieres,[28,29] Srivastava and Hindsgaul,[30] Nilsson and Norberg,[31] Buskas *et al.*,[32] Severov *et al.*,[33] Pazynina *et al.*,[34] Mong *et al.*,[35] and more recently by Li and co-workers.[36] With the exception of Li and co-workers, most of these syntheses take advantage of a monosaccharide approach from which suitable disaccharide blocks are formed and coupled to obtain oligo-*N*-acetyllactosamine chains. Most recently, the semisynthesis of LacNAc-extended complex-type biantennary oligosaccharides has been described by Maki *et al.*[37] Lactosamine and *N*-acetyllactosamine can be prepared by azidonitration of D-lactal hexaacetate[38] or from an aminophosphonium intermediate as shown by Lafont *et al.*[39] and recently adapted by Li and co-workers.[36] A more efficient route is represented by the Heyns rearrangement of lactulose[40–44] which has been optimised and upscaled to 300 kg batches,[42] making lactosamine hydrochloride an available starting material in oligosaccharide synthesis. Herein we describe the preparation of a set of lactosamine building blocks, starting from lactosamine hydrochloride, including novel trifluoroacetamide-containing donors and acceptors, and their application in the synthesis of trifluoroacetamide containing LacNAc/LacNTFAc tetrasaccharides **1** and **2**. Additionally, the scope is expanded to the synthesis of precursors of the trimeric trifluoroacetamide–containing LacNAc/LacNTFAc structures **3**–**5** (Figure 1).

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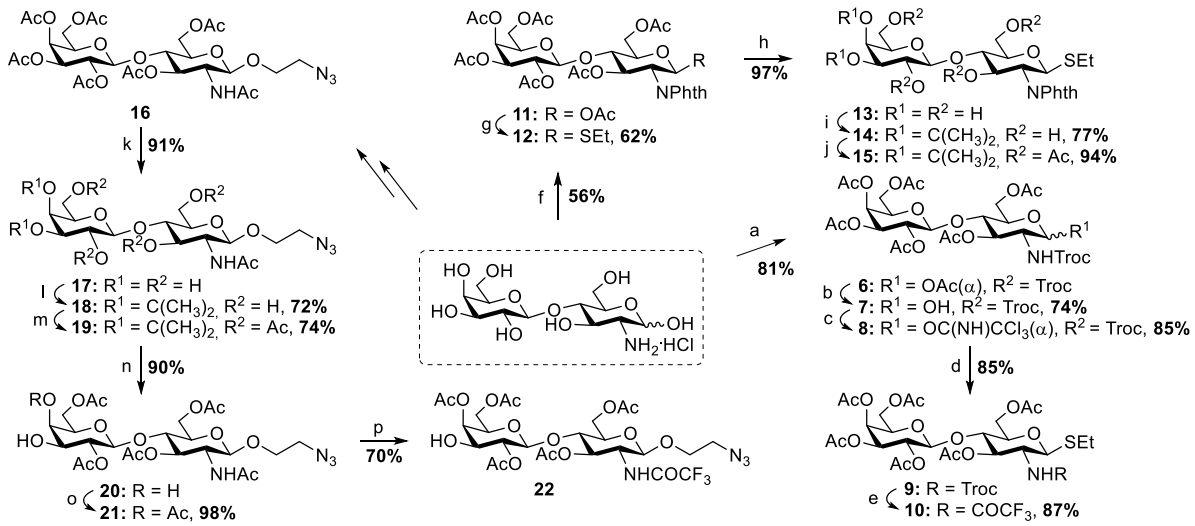
Results and discussion

Synthesis of first generation building blocks from lactosamine hydrochloride

In order to explore the reactivity of different lactosamine derived glycosyl donors and acceptors, 2,2,2-trichloroethoxy carbamate (NHTroc) bearing donors, glycosyl trichloroacetimidate **8** and thioglycoside **9**, trifluoroacetamide (NHTFAc) protected thioglycoside **10**, phthalimide (NPhth) protected thioglycoside **12**, and its corresponding 3',4'-*O*-isopropylidene derivative **15**, were prepared as depicted in Scheme 1. While donors **8**–**12** are fully acetylated, compound **15** allows for the continued elongation to trimeric structures. The NHTFAc group is orthogonal to the NHTroc group but not to the NPhth group, so the latter donor type cannot be used with NHTFAc acceptors for the synthesis of targets **1**–**5**.

We recently reported the synthesis of NHTroc substituted trichloroacetimidate donor **8** starting from lactosamine hydrochloride.[10] Since the introduction of the 2,2,2-trichlorethoxy carbonyl moiety on the lactosamine scaffold followed by peracetylation (Ac_2O, pyridine) yielded almost exclusively the more stable α-acetate **6** (81% yield), the



Scheme 1: Reagents and conditions: (a) i. TrocCl, $NaHCO_3$, H_2O, RT, overnight, ii. Ac_2O, Py, RT, overnight; (b) AcOH-EDA, THF, RT, overnight; (c) Cl_3CCN, DBU, dry CH_2Cl_2, 0 °C, 45 min; (d) EtSH, $BF_3{\cdot}Et_2O$, dry CH_2Cl_2, 0 °C, 1 h, (e) i. Zn, CH_3CN/AcOH, RT, 2 h, ii. TFAA, Et_3N, dry CH_2Cl_2, 0 °C, 3 h; (f) i. MeONa, MeOH, RT, 15 min, ii. Phthalic anhydride, Et_3N, MeOH, 50 °C, 2 h, iii. Ac_2O, Py, RT, overnight; (g) EtSH, $BF_3{\cdot}Et_2O$, TMSOTf, dry CH_2Cl_2, 0 °C → RT, overnight; (h) MeONa, MeOH, pH = 8–9, RT, 7 h; (i) 2,2-DMP, *p*-TsOH, acetone, RT, overnight; (j) Ac_2O, Py, RT, 4 h; (k) MeONa, MeOH, RT, 4 h; (l) 2,2-DMP, *p*-TsOH, 80 °C, overnight; (m) Ac_2O, Py, RT, overnight; (n) 80% *aq.* AcOH, 40 °C, 3 h; (o) i. $CH_3C(OCH_3)_3$, dry CH_3CN, *p*-TsOH, RT, 2 h, ii. 80% *aq.* AcOH, RT, 2 h, (p) i. TFAA, CH_3CN, 135 °C, 3 h, ii. 80% *aq.* AcOH, 40 °C, 2 h.

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	Donor	Acceptor	Promoter	Temperature	Time	Product	Yield
1	**15**	**20**	NIS/TfOH	−10 °C	2 h	Hydrolysis	
2	**15**	**20**	NIS/TfOH	−40 °C → RT	30 min	Hydrolysis	
3	**15**	**20**	NIS/AgOTf	−40 °C → RT	2 h	Complex mixture	
4	**15**	**20**	DMTST	0 °C → RT	2 h	Hydrolysis and 3',4'-*O*-isopropylidene cleavage	
5	**15**	**20**	DMTST/2,4,6-TTBP	0 °C → RT	o/n	**23**, **25**	45%
6	**15**	**21**	DMTST/2,4,6-TTBP	0 °C → RT	o/n	**24**	51%
7	**12**	**21**	DMTST	0 °C → RT	3 h	**26**	30%
8	**10**	**21**	NIS/TfOH	0 °C → RT	2 h	-	-
9	**10**	**21**	NIS/TMSOTf	0 °C	2 h	**27**	40%
10	**9**	**22**	DMTST	0 °C → RT	3 h	**28**	20%
11	**8**	**22**	TMSOTf	0 °C	2 h	**28**	45-56%

Table 1: [2+2] glycosylations tested with acceptors **20**–**22** and donors **8**–**10**, **12**, **15**.

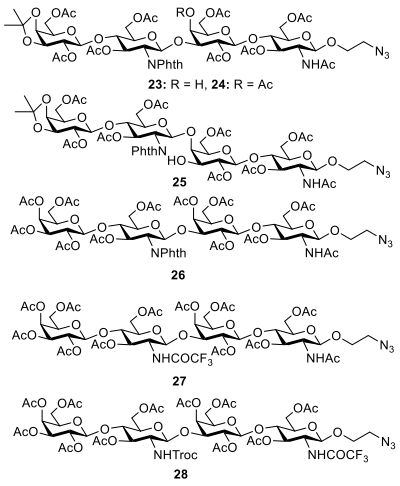

Chart 1: [2+2] glycosylations products

continuing preparation of the corresponding thioglycoside donor **9** by treatment with EtSH and a Lewis acid promoter (*e.g.*, $BF_3{\cdot}Et_2O$ or TMSOTf) proved difficult. For this reason, trichloroacetimidate donor **8** was first prepared by selective anomeric acetate removal (→**7**, 74%) followed by treatment with trichloroacetonitrile and DBU (→**8**, 85%), and subsequently converted to thioglycoside **9** in an 87% yield. From donor **9**, trifluoroacetamide derivative **10** was readily obtained in two steps by cleavage of the carbamate moiety with Zn/AcOH in CH_3CN, followed by reaction with trifluoroacetic anhydride and Et_3N in CH_2Cl_2 (→**10**, 87%). NPhth donors **12** and **15** were both straightforwardly synthesized from lactosamine hydrochloride; reaction with phthalic anhydride in basic conditions, followed by acetylation gave **11** as a separable α/β mixture (α/β = 3:7, 56%). Reaction of the β-anomer of **11** with EtSH and $BF_3{\cdot}Et_2O$ afforded the corresponding thioglycoside **12** in an 85% yield. Further simplifying the synthetic approach, the same reaction was performed on the α/β mixture, requiring the addition of catalytic amounts of TMSOTf to promote the conversion of the α-anomer, globally affording donor **12** in a 62% yield. Compound **12** was then deacetylated under Zemplén conditions (→**13**, 97%) and treated with 2,2-dimethoxypropane and catalytic amounts of *p*-TsOH to give the corresponding 3',4'-*O*-isopropylidene protected derivative **14** as the major product. ^1H and ^{13}C NMR confirmed the formation of the correct dioxolane ring. A quaternary carbon peak appeared at 110.6 ppm corresponding to the formation of a 5-membered ring, and a concurrent down-field shift of the H-3' and H-4' signals was observed in ^1H NMR. Acetylation of **14** gave the desired donor **15** in a 94% yield, on a multi-gram scale. Starting from compound **16**, glycosyl acceptors **20** (3',4'-*O*-diol, NHAc), **21** (3'-OH, NHAc), and **22** (3'-OH, NHTFAc) were prepared as previously reported (Scheme 1).[10] Briefly, lactosamine hydrochloride was peracetylated and converted into its oxazoline derivative prior to the introduction of the 2-azidoethyl linker, yielding compound **16** in an overall 40% yield. Deacetylation (→**17**, 91%) and regioselective introduction of the 3',4'-*O*-isopropylidene gave derivative **18** in a 72% yield. Acetylation (→**19**, 74%) followed by cleavage of the 3',4'-*O*-isopropylidene ring under acidic conditions afforded the corresponding diol (→**20**, 90%). Subsequent 3',4'-*O*-orthoester formation and rearrangement in acidic conditions provided acceptor **21** in a 98% yield over two steps. Secondary amide *N*-transacylation performed with trifluoroacetic anhydride (TFAA) in CH_3CN, followed by mild acidic work-up, afforded the desired trifluoroacetamide derivative (→**22**, 70%). Contrarily to the fast product formation in only five minutes described in the work of Rota *et al.*,[45] the average reaction time on disaccharide **21** was three hours, which was not shortened by microwave heating.

Glycosylations

Performing efficient glycosylation reactions using the synthesised set of building blocks proved difficult (Table 1, Chart 1). Glycosylations of NPhth donor **15** with acceptor **20**, promoted with either NIS/TfOH or NIS/AgOTf, afforded exclusively donor hydrolysis (Entries 1–3), while dimethyl(methylthio)sulfonium triflate (DMTST) activation resulted in the hydrolysis of both the thioglycoside and the acetal moiety of **15** (Entry 4). However, by adding 2,4,6-tri-*tert*-butyl pyrimidine (2,4,6-TTBP) as an acid scavenger, tetrasaccharide **23** was isolated, even though as an inseparable 2:1 mixture with the β(1→4) product **25** (Entry 5). Employing

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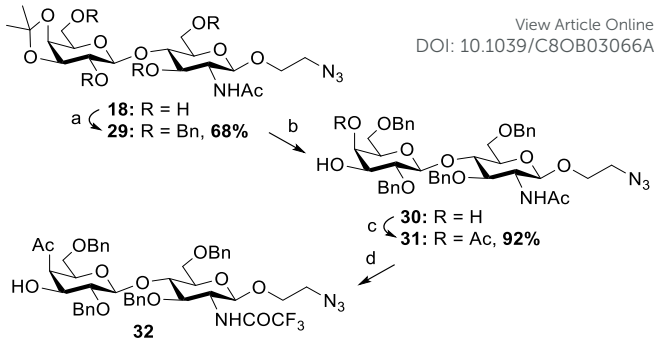
the same glycosylation conditions with 4'–OAc acceptor **21** resulted in the formation of tetrasaccharide **24** in a 51% yield (Entry 6). Nevertheless, as the addition of the acid scavenger substantially slowed the rate of the reaction, thus increasing the number of observed by-products, a non-buffered DMTST–promoted coupling of fully acetylated NPhth donor **12** with acceptor **21** was tested (Entry 7). Unfortunately, the corresponding product **26** was only isolated in 30% yield. Moving to the coupling of NHTFAc donor **10** with acceptor **21**, no reaction was observed with NIS/TfOH as promoting system (Entry 8), while tetrasaccharide **27** was obtained in a 40% yield after activation by NIS/TMSOTf (Entry 9). An even lower product yield was observed in a DMTST–promoted glycosylation of NHTroc protected thioglycoside donor **9** and acceptor **22** (→**28**, 20%, Entry 10), while a TMSOTf–promoted coupling of trichloroacetimidate **8** with acceptor **22** resulted in the formation of tetrasaccharide **28** in variable but acceptable yields (Entry 11). The latter glycosylation was scaled-up and tetrasaccharide **1** was obtained after deprotections, as previously reported.[10]

Synthesis of second generation acceptors and glycosylations

Across all tested couplings, the substantial amounts of recovered unreacted acceptor suggested that compounds **20–22** have low reactivity, not well-matched to the one of the designed donors. Thus, a new set of benzyl ether protected building blocks was synthesized (Scheme 2) and investigated as acceptors. Benzylation (NaH, BnBr) of 3',4'-*O*-isopropylidene precursor **18** was performed at a reaction temperature of −5 °C. By controlling the reaction time and dryness of reagents, the *N*-benzylation byproduct was largely reduced giving compound **29** in a 68% yield on a 2 gram scale. Subsequent 3',4'-*O*-isopropylidene cleavage at 60 °C in 80% *aq.* AcOH (→**30**, 92%), followed by acid catalysed 3',4'-*O*-orthoester formation and its subsequent rearrangement under acidic conditions, afforded acceptor **31** in a 92% yield over two steps. Acetamide *N*-transacylation was carried out at 135 °C with TFAA and in the presence of triethylamine as acid scavenger[45] yielding the corresponding trifluoroacetamide acceptor (→**32**, 58%).



Scheme 2: Reagents and conditions (a) BnBr, NaH (60% dispersion in mineral oil), dry DMF, −5 °C, 3 h; (b) 80% *aq.* AcOH, 60 °C, 2 h; (c) i. $CH_3C(OCH_3)_3$, *p*-TsOH, CH_3CN, RT, 40 min, ii. 80% *aq.* AcOH, RT, 1 h; (d) TFAA, Et_3N, CH_3CN, 135 °C, 2 h.

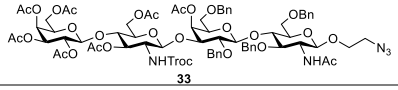
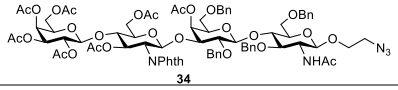
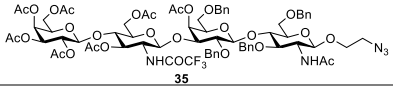
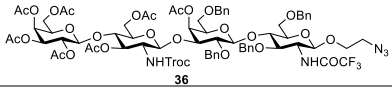
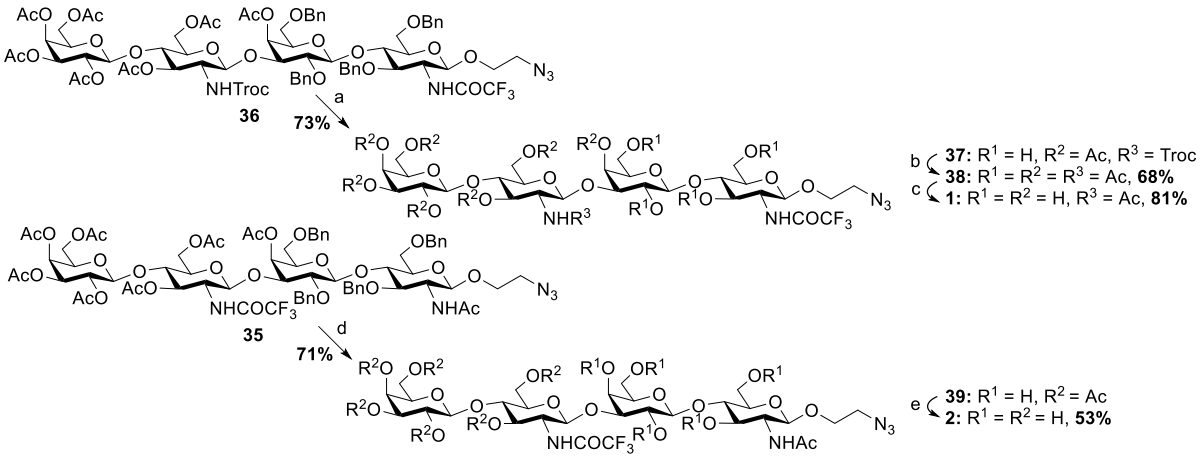
	Donor	Acceptor	Product	Yield
1	9	31	 **33**	87%
2	12	31	 **34**	85%
3	10	31	 **35**	94%
4	9	32	 **36**	78%

Table 2: [2+2] glycosylations with acceptors **31**–**32** and donors **9**–**10**, **12**. General reagents and conditions: NIS, TfOH, −20 °C, dry CH_2Cl_2, 1 h.



Scheme 3: Reagents and conditions (a) $NaBrO_3$, $Na_2S_2O_4$, H_2O, AcOEt, RT, 6 h; (b) i. TBAF (1M in THF), THF, RT, 6 h, ii. Ac_2O, Py, RT, overnight; (c) MeONa, MeOH, pH = 9, RT, overnight; (d) $NaBrO_3$, $Na_2S_2O_4$, H_2O, AcOEt, RT, 6 h; (e) MeONa, MeOH, pH = 9, RT, 7 h.

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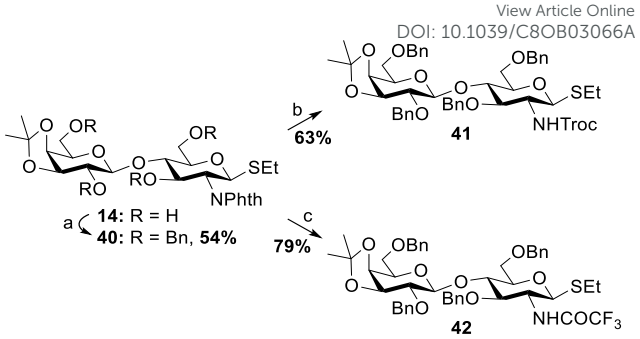
Glycosylations of the acceptors **31** and **32** with donors **9**, **10**, and **12** resulted in high to excellent yields of exclusively β(1→3)-linked tetrasaccharides **34**–**36** (Table 2). The promoting system of choice was NIS/TfOH at −20 °C in CH_2Cl_2. It should be noted that no oxazoline formation was detected for NHTFAc donor **10** and no elimination occurred in case of NPhth donor **12** when the thioglycoside was activated with a stochiometric amount of TfOH (0.8−1 equivalents). NHTFAc protected donors (glucosamine scaffold) were introduced early[46] but have been used less often than carbamate and NPhth protected donors. Regarding NHTFAc donors based on the LacNAc scaffold, only two reports could be found; a LacNAc type 1 (Gal1,3GlcNAc) NHTFAc-protected thioglycoside donor employed in a glycosylation with a lactose-derived acceptor,[47] and, very recently, a LacNAc type 2 NHTFAc-protected imidate donor that was reacted with mannose-based acceptors.[48] In both these reports, the LacNTFAc was produced from monosaccharide precursors and in neither report was a comparison made with other differently *N*-protected donors. Indeed, earlier assessments, considering glycosylation yields, between differently *N*-protected donors have showed the NHTFAc protected donors to be, at the best, equivalent to the other donors.[49] Here, however and most gratifyingly, the lactosamine NHTFAc donor **10** afforded the highest yield and cleanest reaction with benzylated acceptor **31** (Table 2, Entry 3), a characteristic that is reflected on all glycosylations involving NHTFAc protected donors reported in this work (see Table 3, Entry 2 and Table 4, Entry 2). Tetrasaccharides **35** and **36** were selected to study the deprotection of the newly synthesised oligomers in order to allow for the synthesis of compounds **2** and **1**, respectively, as depicted in Scheme 3. Importantly, both protected tetrasaccharides **35** and **36** have already the desired trifluoroacetamide probe installed, thus reducing the number of steps necessary to afford the desired final compounds. Benzyl groups on compound **36** were removed under oxidative conditions[50] by treatment with $NaBrO_3/Na_2S_2O_4$ in AcOEt, thus maintaining the azide functionality and yielding compound **37** in 73% yield. Removal of the Troc carbamate, again without affecting the azide, was performed with TBAF in THF as previously reported by Jacquemard *et al.*[51] and Huang *et al.*,[52] followed by acetylation with Ac_2O in pyridine to give **38** in a 68% yield. Final Zemplén deacetylation gave tetrasaccharide **1** in a 65% yield. Deprotection of **35** proceeded similarly; benzyl groups were first removed under oxidative conditions to give compound **39** (→71%), followed by Zemplén deacetylation affording compound **2** in a 55% yield.



Scheme 4: Reagents and conditions (a) BnBr, TBAI, NaH (60% dispersion in mineral oil), dry DMF, 0 °C → RT, 3 h; (b) i. $H_2N\text{-}NH_2\cdot H_2O$, EtOH, reflux, 6 h, ii. TrocCl, $NaHCO_3$, THF, RT, 3 h; (c) i. $H_2N\text{-}NH_2\cdot H_2O$, EtOH, reflux, 10 h, ii. TFAA, Py, CH_2Cl_2, 0 °C, 1 h.

Expanding the building block library and the strategic assembly to hexasaccharides

To extend the developed methodology to the preparation of larger LacNAc oligomers, a new series of 3',4'-*O*-isopropylidene donors bearing benzyl ether protecting groups instead of acetyl esters was synthesized in order to prevent low yielding [2+4] couplings. Benzylations of the lactosamine scaffold in the presence of the carbamate and NHTFAc as amine protecting groups were deemed not feasible. However, benzylation of NPhth derivatives is possible but care has to be taken to avoid opening of the phthalimide ring.[36] Compound **14** was benzylated with BnBr and NaH in dry DMF giving **40** in a 54% yield on a multi-gram scale (Scheme 4). Compound **40** was then readily converted into its NHTroc protected derivative **41** and NHTFAc analogue **42** by basic cleavage of the phthalimide moiety and treatment with either 2,2,2-trichloroethyl chloroformate in basic conditions (→**41**, 63%) or with trifluoroacetic anhydride in pyridine/CH_2Cl_2 (→**42**, 79%).

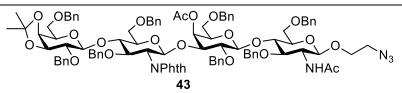
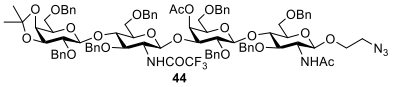
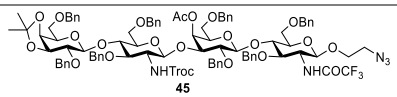
	Donor	Acceptor	Product	Time	Yield
1	40	31	 **43**	90 min	64%
2	42	31	 **44**	20 min	81%
3	41	32	 **45**	1 h	78%

Table 3: [2+2] glycosylations with donors **40**–**42**.General reagents and conditions: NIS, TfOH, −25 °C, dry CH_2Cl_2, 1 h

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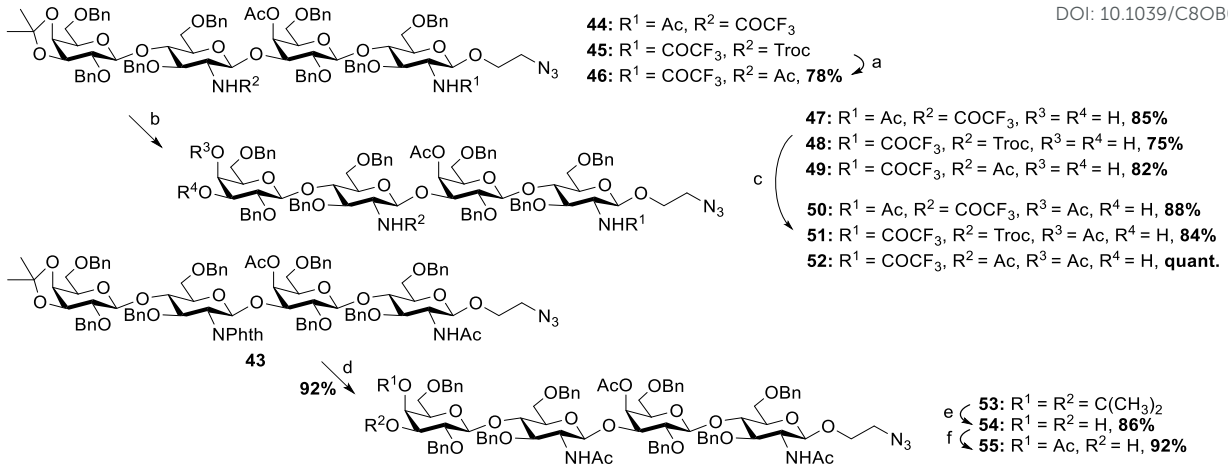
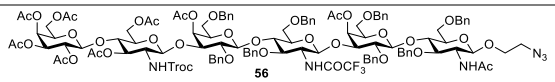
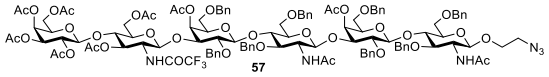
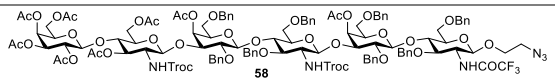
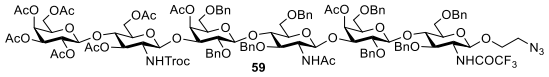
DOI: 10.1039/C8OB03066A



Scheme 5: Reagents and conditions (a) i. TBAF (1M in THF), THF, RT, 8 h, ii. Ac_2O, Py, RT, overnight; (b) 80% *aq.* AcOH, 70 °C, 4–5 h; (c) i. $CH_3C(OCH_3)_3$, *p*-TsOH, CH_3CN, RT, 30 min, ii. 80% *aq.* AcOH, RT, 1 h; (d) i. $H_2N\text{-}NH_2\cdot H_2O$, EtOH, reflux, 8 h, ii. Ac_2O, Py, RT, overnight; (e) 80% *aq.* AcOH, 60 °C, 6 h; (f) i. $CH_3C(OCH_3)_3$, *p*-TsOH, CH_3CN, RT, 30 min, ii. 80% *aq.* AcOH, RT, 1 h.

	Donor	Acceptor	Product	Yield
1	9	50	 **56**	55%
2	10	55	 **57**	80%
3	9	51	 **58**	-
4	9	52	 **59**	58%

The efficiency of the new set of donor building blocks was tested in NIS/TfOH promoted glycosylations with acceptors **31** and **32**. All three glycosylations were completely stereoselective (β-(1→3) linkage formation) with no 3',4'-*O*-isopropylidene cleavage observed during the reaction time, and afforded the desired products in good yields (Table 3), but still lower compared to the corresponding glycosylations with acetylated donors (Table 2). Tetrasaccharides **43**–**45** were then converted into acceptors using the same reaction sequence as before; 3',4'-*O*-isopropylidene removal, 3',4'-*O*-orthoester formation, and its rearrangement in acidic conditions to afford 3'''-OH acceptors **50**, **51**, and **55** (Scheme 5). For compound **43**, an additional step was performed to convert the phthalimide into an acetamide moiety (→**53**, 92%). The NIS/TfOH-promoted coupling of NHTroc thioglycoside **9** with acceptor **50** gave hexasaccharide **56** in a 55% yield (Table 4, Entry 1), while NHTFAc donor **10** gave hexasaccharide **57** in an 80% yield, when coupled with acceptor **55** (Table 4, Entry 2). Again, no oxazoline formation was observed with the NHTFAc-type donor **10**.These yields can be compared with the corresponding [2+2] couplings in Table 2, Entries 4 (78%) and Entry 3 (94%), respectively. NIS/TfOH promoted glycosylation of NHTroc thioglycoside **9** with acceptor **51** did not afford the expected hexasaccharide **58**, but a complex mixture of compounds (Table 4, Entry 3). However, conversion of the Troc moiety of **45** to the corresponding acetamide (→**46**, 78%) allowed the subsequent preparation of acceptor **52** with the same methodology (as depicted in Scheme 5). Coupling of **52** with donor **9** afforded hexasaccharide **59** in 58% yield (Table 4, Entry 4, compare Table 1, Entry 1 (87%)).

Experimental

General methods

Unless noted, chemical reagents and solvents were used without further purification from commercial sources. Lactosamine hydrochloride was purchased from Glycom A/S. Dry solvents as CH_2Cl_2, Et_2O, and THF were obtained from a PureSolv-EN™ solvent purification system (Innovation Technology Inc). Concentration *in vacuo* was performed using a Buchi rotary evaporator. The $^1H/^{13}C/^{19}F$ NMR spectra (δ in ppm, relative to TMS in $CDCl_3$) were recorded with Varian spectrometers (Varian, Palo Alto, CA, USA) (400/101 MHz or 500/125 MHz) at 25 °C. Assignments were aided by $^1H\text{-}^1H$

DOI: 10.1039/C9OB02666A

and ^{1}H-^{13}C correlation experiments. HRMS spectra were recorded on a micromass LCT instrument from Waters and LaserToF LT3 *Plus* MALDI-TOF (DHAP Matrix). LRMS spectra were recorded on a Waters micromass Quattro Micro LC-MS/MS instrument using electrospray ionisation (ESI) in either positive or negative mode. Optical rotations were recorded on a Perkin-Elmer polarimeter (Model 343) at the sodium D-line (589 nm) at 20 °C using a 1 dm cell and are not corrected. Silica gel chromatography was carried out using *Davisil LC60A* (Grace tech., Columbia, MD, USA) SiO_2 (40–63 µm) silica gel. All reactions were monitored by thin-layer chromatography (TLC). TLC was performed on Merck DC-Alufolien plates precoated with silica gel 60 F254. They were visualised with UV-light (254 nm) fluorescence quenching, and/or by charring with an 8% H_2SO_4 dip and/or ninhydrin dip. Deprotected sugars were lyophilised using a freeze-dryer Alpha 1-2 Ldplus (Christ Ltd.), with a pressure of 0.035 mbar and ice condenser temperature −55 °C.

General procedure for [2+2] glycosylation for compounds 33–36

Acceptor (1 eq) and donor (1.2–1.3 eq) were dissolved in dry CH_2Cl_2 (0.018 M) together with 4Å molecular sieves. The mixture was stirred for 1 hour, then NIS (1.5 eq) was added and the mixture was cooled to −20 °C. TfOH (0.5 eq) was then added dropwise and the reaction was stirred for 30 minutes at the same temperature, then quenched with Et_3N, filtered over Celite and evaporated *in vacuo*. Crude was purified by flash column chromatography (see Supplementary Information).

2-Azidoethyl (2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-[3,6-di-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-glucopyranosyl]-(1→3)-(4-*O*-acetyl-2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2-acetamido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (33) R_f = 0.34, Tol/Acetone 7:3; $[\alpha]_D^{20}$ = +2.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.20 (m, 20H, H_{Ar}), 5.72 (d, *J* = 7.4 Hz, 1H, N*H*COCH$_3$), 5.38 – 5.33 (m, 2H, H-4', H-4'''), 5.10 (dd, *J* = 10.4, 7.9 Hz, 1H, H-2'''), 5.02 (d, *J* = 7.7 Hz, 1H, H-1), 4.96 (dd, *J* = 10.4, 3.4 Hz, 1H, H-3'''), 4.92 (d, *J* = 10.9 Hz, 1H, C*H*HPh), 4.86 (d, *J* = 11.7 Hz, 1H, CH*H*Ph), 4.77 – 4.72 (m, 1H, H-3''), 4.67 (dd, *J* = 12.1, 10.2 Hz, 2H, C*H*HPh, CH*H*CCl$_3$), 4.61 – 4.38 (m, 11H, H-1'', H-1''', H-1', CH$_2$Ph, C*H*HCCl$_3$, H-6''a, N*H*COCH$_2$CCl$_3$, CH$_2$Ph), 4.31 (d, *J* = 11.8 Hz, 1H, C*H*HPh), 4.24 – 4.17 (m, 1H, H-3), 4.09 (d, *J* = 6.8 Hz, 2H, H-6a''', H-6b'''), 4.06 – 3.97 (m, 3H, H-6a'', OCH*H*CH$_2$N$_3$, H-4), 3.88 – 3.84 (m, 1H, H-5'''), 3.80 (dd, *J* = 10.9, 3.8 Hz, 1H, H-6a), 3.74 (*a*t, *J* = 9.3 Hz, 1H, H-4''), 3.69 – 3.63 (m, 3H, H-6b, OCH*H*CH$_2$N$_3$, H-3'), 3.61 – 3.54 (m, 2H, H-2'', H-5), 3.53 – 3.42 (m, 4H, OCH$_2$CH*H*N$_3$, H-5'', H-5', H-2'), 3.36 (*a*dt, *J* = 6.9, 3.1 Hz, 2H, H-6a', H-6b'), 3.27 – 3.17 (m, 2H, OCH$_2$CH*H*N$_3$, H-2), 2.14 (s, 3H, OCOCH$_3$), 2.08 (s, 3H, OCOCH$_3$), 2.06 (s, 3H, OCOCH$_3$), 2.05 (s, 3H, OCOCH$_3$), 2.01 (s, 3H, OCOCH$_3$), 1.99 (s, 3H, OCOCH$_3$), 1.97 (s, 3H, OCOCH$_3$), 1.90 (s, 3H, NHCOC*H*$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7 (NH*C*OCH$_3$), 170.6, 170.5, 170.4, 170.23, 170.17, 170.0, 169.3 (7 O*C*OCH$_3$), 154.2 (NH*C*O$_2$CH$_2$CCl$_3$), 138.9, 138.4, 138.2, 138.1 (4 C_{Ar}), 129.2, 128.9, 128.6, 128.5, 128.31, 128.29, 128.2, 128.1, 128.0, 127.82, 127.80, 127.7, 127.1 (20 C_{Ar}), 102.4 (C-1'), 101.4 (C-1'''), 101.1 (C-1''), 99.6 (C-1), 95.7 (CH$_2$*C*Cl$_3$), 80.7 (C-2'), 77.4 (H-3), 76.6 (C-3', H-4), 76.3 (H-4''), 75.2 (CH$_2$Ph), 75.1 (C-5'), 74.4 (CH$_2$Ph, *C*H$_2$CCl$_3$), 73.7 (CH$_2$Ph), 73.6 (CH$_2$Ph), 72.7 (C-5''), 72.6 (C-5), 72.3 (C-3''), 71.1 (C-3'''), 70.9 (C-5'''), 69.8 (C-4'), 69.3 (C-2'''), 68.5 (O*C*H$_2$CH$_2$N$_3$), 68.2 (C-6, C-6'), 66.8 (C-4'''), 61.57 (C-6''), 61.0 (C-6'''), 57.2 (C-2), 56.4 (C-2''), 50.7 (OCH$_2$*C*H$_2$N$_3$), 23.8 (NHCO*C*H$_3$), 20.94, 20.89, 20.84, 20.80, 20.78, 20.76, 20.6 (7 OCO*C*H$_3$); HRMS (ESI$^+$): m/z calcd for $C_{73}H_{88}Cl_3N_5O_{29}$: 1626.4528 [M+Na]$^+$; found 1626.4451.

2-Azidoethyl (2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-(3,6-di-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-(1→3)-(4-*O*-acetyl-2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2-acetamido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (34) R_f = 0.47, Tol/Acetone 7:3; $[\alpha]_D^{20}$ = +15.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.13 (m, 22H, H_{Ar}), 6.93 (dd, *J* = 6.6, 2.9 Hz, 2H, H_{Ar}), 5.77 (dd, *J* = 10.6, 8.7 Hz, 1H, H-3''), 5.65 (d, *J* = 7.3 Hz, 1H, N*H*COCH$_3$), 5.53 (d, *J* = 8.2 Hz, 1H, H-1''), 5.37 (*a*d, *J* = 3.5 Hz, 1H, H-4'), 5.33 (dd, *J* = 3.5, 1.2 Hz, 1H, H-4'''), 5.13 (dd, *J* = 10.4, 7.9 Hz, 1H, H-2'''), 4.97 (dd, *J* = 10.4, 3.5 Hz, 1H, H-3'''), 4.93 (d, *J* = 7.6 Hz, 1H, H-1), 4.84 (d, *J* = 10.9 Hz, 1H, CH*H*Ph), 4.72 (dd, *J* = 11.9, 2.3 Hz, 1H, H-6''a), 4.56 (d, *J* = 7.9 Hz, 1H, H-1'''), 4.50 (d, *J* = 12.2 Hz, 1H, C*H*HPh), 4.48 – 4.44 (m, 2H, CH*H*Ph, C*H*HPh), 4.35 – 4.22 (m, 4H, H-1' CH*H*Ph, C*H*HPh, CH*H*Ph), 4.13 (dd, *J* = 10.7, 8.4 Hz, 1H, H-2''), 4.10 – 4.02 (m, 5H, H-3, C*H*HPh, H-6'''a, H-6'''b, H-6''b), 3.95 (ddd, *J* = 10.8, 5.2, 3.4 Hz, 1H, OCH*H*CH$_2$N$_3$), 3.92 – 3.83 (m, 3H, H-5''', H-4, H-4''), 3.74 (ddd, *J* = 10.0, 4.2, 2.4 Hz, 1H, H-5''), 3.63 – 3.54 (m, 3H, OC*H*HCH$_2$N$_3$, H-6'a, H-3'), 3.51 (*a*t, *J* = 6.2 Hz, 1H, H-5'), 3.45 – 3.23 (m, 6H, OCH$_2$CH*H*N$_3$, H-6'b, H-6a, H-6b, H-5, H-2'), 3.19 (ddd, *J* = 13.3, 5.2, 3.3 Hz, 1H, OCH$_2$C*H*HN$_3$), 3.11 (dd, *J* = 9.8, 7.6 Hz, 1H, H-2), 2.13 (s, 3H, OCOCH$_3$), 2.09 (s, 3H, OCOCH$_3$), 2.08 (s, 3H, OCOCH$_3$), 2.04 (s, 3H, OCOCH$_3$), 2.00 (s, 3H, OCOCH$_3$), 1.97 (s, 3H, OCOCH$_3$), 1.87 (s, 3H, OCOCH$_3$), 1.85 (s, 3H, NHCOC*H*$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.52 (NH*C*OCH$_3$), 170.46, 170.3, 170.2, 170.1, 169.72, 169.66, 169.1 (7 O*C*OCH$_3$), 138.9 (C_{Ar}), 138.1 (C_{Ar}), 138.0 (C_{Ar}), 137.9 (C_{Ar}), 129.0, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 127.5, 127.1, 126.7, 125.3 (20 C_{Ar}), 102.1 (C-1'), 101.2 (C-1'''), 99.3 (C-1), 98.1 (C-1''), 78.6 (C-2'), 78.5 (C-3'), 77.2 (C-3), 76.7, 76.4 (C-4'', C-4), 74.8 (C-5), 74.4 CH$_2$Ph), 74.2 (CH$_2$Ph), 73.5 (CH$_2$Ph), 73.1 (CH$_2$Ph), 72.4 (C-5'', C-5'), 71.0 (C-4'''), 70.9 (C-3''), 70.6 (C-5'''), 70.1 (C-4'), 69.1 (C-2'''), 68.3, 68.2, 67.7 (C-6', C-6, O*C*H$_2$CH$_2$N$_3$), 66.6 (C-4'''), 61.1 (C-6''), 60.6 (C-6'''), 57.1 (C-2), 55.3 (C-2''), 50.6 (OCH$_2$*C*H$_2$N$_3$), 23.6 (NHCO*C*H$_3$), 20.8, 20.74, 20.65, 20.6, 20.5 (7 OCO*C*H$_3$); HRMS (ESI$^+$): m/z calcd for $C_{78}H_{89}N_5O_{29}$: 1560.5721 [M+H]$^+$; found: 1560.5714.

2-Azidoethyl (2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-(3,6-di-*O*-acetyl-2-deoxy-2-trifluoroacetamido-β-D-glucopyranosyl)-(1→3)-(4-*O*-acetyl-2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2-acetamido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (35) R_f = 0.26, Tol/AcOEt 1:1; $[\alpha]_D^{20}$ = -0.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 – 7.10 (m, 20H, H_{Ar}), 6.22 (d, *J* = 9.5 Hz, 1H, NHCOCF$_3$), 5.74 (d, *J* = 7.4 Hz, 1H, N*H*COCH$_3$), 5.43 – 5.30 (m, 2H, H-4', H-4'''), 5.12 (dd, *J* = 10.5, 7.9 Hz, 1H, H-2'''), 5.02 – 4.96 (m, 2H, H-1, H-3'''), 4.92 – 4.86 (m, 2H, H-3'', C*H*HPh), 4.82 (d, *J* = 11.8 Hz, 1H, CH*H*Ph), 4.71 (d, *J* = 7.8 Hz, 1H, H-1''), 4.68 – 4.62 (m, 2H, C*H*HPh, H-6''a), 4.57 (d, *J* = 11.0 Hz, 1H, CH*H*Ph), 4.53 (d, *J* = 7.9 Hz, 1H, H-1'''), 4.51 – 4.45 (m, 2H, C*H*HPh, CH*H*Ph), 4.44 (d, *J* = 7.8 Hz, 1H, H-1'), 4.40 (d, *J* = 12.1 Hz, 1H, C*H*HPh), 4.31 (d, *J* = 11.9 Hz, 1H, CH*H*Ph), 4.18 (dd, *J* = 9.6, 8.2 Hz, 1H, H-4), 4.14 – 4.08 (m, 2H, H-6'''a,

H-6'''b), 4.06 (dd, *J* = 12.1, 4.4 Hz, 1H, H-6''b), 4.04 – 3.95 (m, 2H, H-3, OCH*H*CH$_2$N$_3$), 3.98 – 3.91 (m, 1H, H-2''), 3.91 – 3.86 (m, 1H, H-5'''), 3.82 (*a*t, *J* = 9.0 Hz, 1H, H-4''), 3.77 (dd, *J* = 10.8, 3.9 Hz, 1H, H-6a), 3.73 – 3.62 (m, 3H, H-3', OC*H*HCH$_2$N$_3$, H-6b), 3.58 (*a*t, *J* = 6.4 Hz, 1H, H-5'), 3.54 – 3.42 (m, 4H, H-2', H-5, H-5'', OCH$_2$CH*H*N$_3$), 3.41 – 3.33 (m, 2H, H-6'a, H-6'b), 3.24 (ddd, *J* = 14.8, 6.2, 3.1 Hz, 1H, OCH$_2$C*H*HN$_3$), 2.15 (s, 3H, OCOCH$_3$), 2.08 (s, 3H, OCOCH$_3$), 2.07 (s, 3H, OCOCH$_3$), 2.06 (s, 3H, OCOCH$_3$), 2.04 (s, 3H, OCOCH$_3$), 2.03 (s, 3H, OCOCH$_3$), 1.98 (s, 3H, OCOCH$_3$), 1.91 (s, 3H, NHCOC*H*$_3$); ^{13}C NMR (126 MHz, CDCl$_3$): δ 170.9, 170.7, 170.53, 170.48, 170.2, 170.14, 170.10, 169.3 (8 *C*OCH$_3$), 157.1 (*a*d, *J* = 37.3 Hz, NH*C*OCF$_3$), 138.9, 138.3, 138.2, 138.1 (4 C$_{Ar}$), 128.7, 128.53, 128.48, 128.31, 128.27, 128.1, 128.04, 127.99, 127.8, 127.7, 127.0 (20 C$_{Ar}$), 115.7 (*a*d, *J* = 287.7 Hz, NHCO*C*F$_3$), 102.4 (C-1'), 101.4 (C-1'''), 100.2 (C-1''), 99.6 (C-1), 80.4 (C-2'), 77.4 (C-4), 76.6 (C-3), 76.3 (C-3'), 75.7 (C-4''), 75.1 (C-5), 75.0 (CH$_2$Ph), 74.3 (CH$_2$Ph), 73.7 (CH$_2$Ph), 73.5 (CH$_2$Ph), 72.9 (C-5''), 72.5 (C-5'), 72.0 (C-3''), 71.0 (C-3'''), 70.9 (C-5'''), 69.8 (C-4'), 69.2 (C-2'''), 68.4 (O*C*H$_2$CH$_2$N$_3$), 68.2 (C-6), 68.1 (C-6'), 66.8 (C-4'''), 61.2 (C-6''), 61.0 (C-6'''), 57.0 (C-2), 54.6 (C-2''), 50.7 (OCH$_2$*C*H$_2$N$_3$), 23.7 (NHCO*C*H$_3$), 20.9, 20.81, 20.79, 20.74, 20.72, 20.63, 20.55 (7 OCO*C*H$_3$); ^{19}F NMR (376 MHz, CDCl$_3$) δ -75.97; HRMS (ESI$^+$): m/z calcd for C$_{72}$H$_{86}$F$_3$N$_5$O$_{28}$: 1548.5309 [M+Na]$^+$; found: 1548.5358.

2-Azidoethyl (2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1⟶4)-[3,6-di-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-glucopyranosyl]-(1⟶3)-(4-*O*-acetyl-2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1⟶4)-3,6-di-*O*-benzyl-2-deoxy-2-trifluoroacetamido-β-D-glucopyranoside (36) R$_f$ = 0.33, Tol/Acetone 8:2; $[\alpha]_D^{20}$= +4.8 (*c* 1.0, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.63 – 7.07 (m, 20H, H$_{Ar}$), 6.74 (d, *J* = 7.6 Hz, 1H, NHCOCF$_3$), 5.38 – 5.32 (m, 2H, H-4', H-4'''), 5.10 (dd, *J* = 10.5, 7.9 Hz, 1H, H-2'''), 4.96 (dd, *J* = 10.5, 3.4 Hz, 1H, H-3'''), 4.90 (d, *J* = 7.1 Hz, 1H, H-1), 4.86 – 4.73 (m, 3H, C*H*HPh, CH*H*CCl$_3$, H-3''), 4.71 – 4.38 (m, 12H, C*H*HCCl$_3$, CH*H*Ph, C*H*HPh, CH$_2$Ph, CH*H*Ph, C*H*HPh, H-6''a, H-1'', H-1''', H-1', N*H*CO$_2$CH$_2$CCl$_3$), 4.31 (d, *J* = 11.8 Hz, 1H, CH*H*Ph), 4.14 – 3.95 (m, 6H, H-6'''a, H-6'''b, H-6''b, OCH*H*CH$_2$N$_3$, H-3, H-4), 3.86 (dd, *J* = 6.8, 1.2 Hz, 1H, H-5'''), 3.84 – 3.77 (m, 1H, H-6a), 3.76 – 3.34 (m, 12H, H-6b, H-3', OC*H*HCH$_2$N$_3$, H-2'', H-2, H-5, H-5', H-2', H-5'', OCH$_2$CH*H*N$_3$, H-6'a, H-6'b), 3.28 (ddd, *J* = 13.2, 5.4, 3.5 Hz, 1H, OCH$_2$C*H*HN$_3$), 2.14 (s, 3H, OCOCH$_3$), 2.08 (s, 3H, OCOCH$_3$), 2.06 (s, 3H, OCOCH$_3$), 2.05 (s, 3H, OCOCH$_3$), 2.02 (m, 6H, 2 OCOCH$_3$), 1.96 (s, 3H, OCOCH$_3$); ^{13}C NMR (126 MHz, CDCl$_3$): δ 170.6, 170.5, 170.4, 170.22, 170.17, 170.0, 169.3 (7 O*C*OCH$_3$), 157.3 (q, *J* = 37.1 Hz, NH*C*OCF$_3$), 154.2 (NH*C*O$_2$CH$_2$CCl$_3$), 138.3, 138.1, 138.0, 137.9 (4 C$_{Ar}$), 128.9, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.9, 127.2 (20 C$_{Ar}$), 115.7 (*a*d, *J* = 288.4 Hz, NHCO*C*F$_3$), 102.8 (C-1'), 101.4 (C-1'''), 101.2 (C-1''), 99.2 (C-1), 95.7 CH$_2$*C*Cl$_3$), 80.5 (C-2'), 76.6 (C-3'), 76.4, 76.3 (C-3, C-4), 76.2 (C-4''), 75.4 (C-5'), 75.3 (CH$_2$Ph), 74.4 (CH$_2$Ph), 74.3 (*C*H$_2$CCl$_3$), 73.7 (CH$_2$Ph), 73.6 (CH$_2$ Ph), 72.8 (C-5), 72.7 (C-5''), 72.2 (C-3''), 71.1 (C-3'''), 70.9 (C-5'''), 69.7 (C-4'), 69.3 (C-2'''), 68.5 (O*C*H$_2$CH$_2$N$_3$), 68.2 (C-6, C-6'), 66.8 (C-4'''), 61.5 (C-6''), 61.0 (C-6'''), 56.4 (C-2''), 55.9 (C-2), 50.7 (OCH$_2$*C*H$_2$N$_3$), 20.94, 20.88, 20.78, 20.75, 20.62, 20.58, 20.52 (7 OCO*C*H$_3$); ^{19}F NMR (376 MHz, CDCl$_3$) δ -75.89; HRMS (ESI$^+$): m/z calcd for C$_{73}$H$_{85}$Cl$_3$F$_3$N$_5$O$_{29}$: 1680.4240 [M+Na]$^+$; found: 1680.5447.

2-Azidoethyl (β-D-galactopyranosyl)-(1⟶4)-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-(1⟶3)-(β-D-galactopyranosyl)-(1⟶4)-(2-deoxy-2-trifluoroacetamido-β-D-glucopyranoside) (1) To a solution of **36** (110 mg, 66 µmol) in AcOEt (880 µL) was added a solution of NaBrO$_3$ (99 mg, 66 µmol) in water (660 µL). Then a solution of Na$_2$S$_2$O$_4$ (108 mg, 0.53 mmol) in water (1.3 mL) was added and the reaction was stirred for 3 hours. The mixture was then quenched with 10% Na$_2$S$_2$O$_3$, extracted with AcOEt, dried over MgSO$_4$, filtered and evaporated under vacuum. Purification by flash column chromatography (CH$_2$Cl$_2$/MeOH, 98:2 → 85:15, v/v) gave **38** (63 mg, 48 µmol, 73%) as a white amorphous solid. To a solution of **38** (25 mg, 18.7 µmol) in dry MeOH (1 mL) was added methanolic sodium methoxide (0.5 M) until pH = 8. The reaction was stirred at RT overnight then quenched with Dowex 50WX8 H$^+$ resin, filtered and concentrated *in vacuo*. The crude residue was purified by Sephadex P-2 size exclusion chromatography (Biogel® P-2, dH$_2$O:*n*-BuOH, 99:1, v/v) to afford **1** (11.5 mg, 12.1 µmol, 70%) as a white amorphous solid. R$_f$ = 0.6, AcOEt/MeOH/AcOH/H$_2$O 4:3:3:1; $[\alpha]_D^{20}$= +10.1 (*c* 0.4, H$_2$O); ^{1}H NMR (500 MHz, D$_2$O): δ 4.72 (m, 2H, H-1, H-1''), 4.51 – 4.46 (m, 2H, H-1''', H-1'), 4.17 (*a*d, *J* = 3.3 Hz, 1H, H-4'), 4.12 – 4.03 (m, 1H, OCH*H*CH$_2$N$_3$), 4.04 – 3.95 (m, 2H, H-6a, H-6b), 3.94 (*a*d, *J* = 3.4 Hz, 1H, H-4'''), 3.91 – 3.71 (m, 16H, H-2'', H-2, H-6'a, H-6'b, H-6'''a, H-6'''b, H-6''a, H-6''b, H-3'', H-3, H-5''', H-5', H-4'', H-4, H-3', OC*H*HCH$_2$N$_3$), 3.68 (dd, *J* = 10.0, 3.4 Hz, 1H, H-3'''), 3.66 – 3.52 (m, 4H, H-5'', H-5, H-2', H-2'''), 3.52 – 3.44 (m, 2H, OCH$_2$C*H*$_2$N$_3$), 2.05 (s, 3H, NHCOC*H*$_3$); ^{13}C NMR (126 MHz, D$_2$O): δ 174.8 (NH*C*OCH$_3$), 159.5 (*a*d, *J* = 37.6 Hz, NH*C*OCF$_3$), 115.7 (*a*d, *J* = 286.3 Hz, NHCO*C*F$_3$), 102.8, 102.9 (C-1', C-1'''), 102.7 (C-1''), 100.2 (C-1), 82.0 (C-3'), 78.2, 78.1 (C-4, C-4''), 75.3 (C-5'''), 74.8 (C-5', C-5''), 74.5 (C-5), 72.4 (C-3'''), 72.1, 71.7 (C-3, C-3'), 70.9, 69.9 (C-2', C-2'''), 68.7 (O*C*H$_2$CH$_2$N$_3$), 68.47 (C-4'''), 68.2 (C-4'), 60.9, 60.9, 59.9, 59.8 (C-6, C-6', C-6'', C-6'''), 55.51 (C-2''), 55.12 (C-2), 50.29 (OCH$_2$*C*H$_2$N$_3$), 22.11 (NHCO*C*H$_3$); ^{19}F NMR (282 MHz, D$_2$O): δ -75.8 (NHCOCF$_3$); HRMS (ESI$^+$): m/z calcd for C$_{30}$H$_{48}$F$_3$N$_5$O$_{21}$: 894.2692 [M+Na]$^+$; found: 894.2648.

2-Azidoethyl (β-D-galactopyranosyl)-(1⟶4)-(2-deoxy-2-trifluoroacetamido-β-D-glucopyranosyl)-(1⟶3)-(β-D-galactopyranosyl)-(1⟶4)-2-acetamido-2-deoxy-β-D-glucopyranoside (2) To a solution of fully protected tetrasaccharide **35** (100 mg, 65 µmol) in AcOEt (870 µL) was added a solution of NaBrO$_3$ (99 mg, 0.66 mmol) in water (655 µL). Then a solution of Na$_2$S$_2$O$_4$ (90 mg, 0.52 mmol) in water (1.3 mL) was added and the reaction was stirred for 6 hours. The mixture was then quenched with 10% Na$_2$S$_2$O$_3$, extracted with AcOEt, dried over MgSO$_4$, filtered and evaporated. Purification by flash column chromatography (CH$_2$Cl$_2$/MeOH, 98:2 → 85:15) gave **39** (54 mg, 46 µmol, 71%). Compound **39** (50 mg, 43 µmol) was dissolved in dry MeOH (2 mL) and solid MeONa was added until pH = 9. The reaction was stirred for 7 hours then quenched with Dowex 50WX8 H$^+$ resin, filtered and evaporated *in vacuo*. Crude product was purified by size exclusion chromatography (Biogel® P-2, dH$_2$O:*n*-BuOH, 99:1, v/v) to obtain compound **2** (20 mg, 23 µmol, 53%) as a white solid after freeze-dry. R$_f$ = 0.54, AcOEt/MeOH/AcOH/H$_2$O 4:3:3:1; $[\alpha]_D^{20}$= -10.7 (*c* 0.69, H$_2$O); ^{1}H NMR (400 MHz, D$_2$O) δ 4.85 (d, *J* = 7.7 Hz, 1H, H-1), 4.62 (d, *J* = 8.1 Hz, 1H, H-1''), 4.51 (d, *J* = 7.8 Hz, 1H, H-1'''), 4.47 (d, *J* = 7.9 Hz, 1H, H-1'), 4.20 (*a*d, *J* = 3.3 Hz, 1H, H-4'), 4.07 (ddd, *J* = 11.4, 5.5, 3.1 Hz, 1H, OCH*H*CH$_2$N$_3$), 4.01 (dd, *J* = 5.6, 2.3 Hz, 1H, H-6a), 3.98 (dd, *J* = 5.7, 2.1 Hz, 1H, H-6'a), 3.95 (*a*d, *J* = 3.6 Hz, 1H, H-4'''), 3.93 – 3.84 (m, 4H, H-2, H-6b, H-6'b, H-3''), 3.83 – 3.55 (m, 17H, H-2'', H-6''a, H-6''b,

View Article Online DOI: 10.1039/C8OB03066A

H-6'''a, H-6'''b, OC*H*HCH$_2$N$_3$, H-3''', H-5, H-5'', H-5', H-4, H-4'', H-3', H-2', H-2''', H-5''', H-3'), 3.55 – 3.40 (m, 2H, OCH$_2$C*H*$_2$N$_3$), 2.06 (s, 3H, NHCOC*H*$_3$); ^{13}C NMR (126 MHz, D$_2$O) δ 174.6 (NH*C*OCH$_3$), 159.5 (*q*d, *J* = 37.5 Hz, NH*C*OCF$_3$), 115.8 (*q*d, *J* = 286.5 Hz, NHCO*C*F$_3$), 102.9, 102.8 (C-1', C-1'''), 101.9 (C-1), 100.9 (C-1''), 82.4 (C-3'), 78.4 (C-4''), 77.9 (C-4), 75.3, 74.8, 74.7, 74.6 (C-5, C-5', C-5'', C-5'''), 72.5, 72.4, 71.5 (C-3'', C-3''', C-3), 70.9 (C-2'''), 69.8 (C-2'), 68.7 (O*C*H$_2$CH$_2$N$_3$), 68.5 (C-4'''), 68.1 (C-4'), 61.0, 60.9, 60.0, 59.7 (C-6, C-6', C-6'', C-6'''), 55.7 (C-2), 54.9 (C-2''), 50.3 (OCH$_2$*C*H$_2$N$_3$), 22.2 (NHCO*C*H$_3$); ^{19}F NMR (376 MHz, D$_2$O) δ -75.65; HRMS (ESI$^+$): m/z calcd for C$_{30}$H$_{48}$F$_3$N$_5$O$_{21}$: 894.2692 [M+Na]$^+$; found: 894.2648.

General procedure for [2+2] glycosylation for compounds 43–45

Acceptor (1 eq) and donor (1.3–1.4 eq) were dissolved in dry CH_2Cl_2 (0.019 M) together with 4Å molecular sieves. The mixture was stirred for 1 hour, then it was cooled to −30 °C and NIS (1.4 eq) was added followed by TfOH (0.5 eq). The reaction was stirred for 90 minutes at the same temperature, then quenched with Et_3N, filtered over Celite and evaporated *in vacuo*. Crude was purified by flash column chromatography (see Supplementary Information).

2-Azidoethyl (2,6-di-*O*-benzyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-(1⟶4)-(3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-(1⟶3)-(4-*O*-acetyl-2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1⟶4)-2-acetamido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (43) R_f = 0.86, Tol/Acetone 8:2; $[\alpha]_D^{20}$= +27.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.10 (m, 40H, H$_{Ar}$), 6.94 (dd, *J* = 6.6, 2.9 Hz, 2H, H$_{ArNPhth}$), 6.90 – 6.84 (m, 2H, H$_{ArNPhth}$), 5.63 (d, *J* = 7.4 Hz, 1H, N*H*COCH$_3$), 5.41 (*q*d, *J* = 3.6 Hz, 1H, H-4'), 5.29 (d, *J* = 8.3 Hz, 1H, H-1''), 4.88 (d, *J* = 7.6 Hz, 1H, H-1), 4.85 – 4.79 (m, 3H, C*H*HPh, CH*H*Ph, C*H*HPh), 4.75 (d, *J* = 11.7 Hz, 1H, CH*H*Ph), 4.65 (d, *J* = 12.0 Hz, 1H, C*H*HPh), 4.53 (d, *J* = 12.1 Hz, 1H, CH*H*Ph), 4.49 – 4.37 (m, 7H, H-1''', C*H*HPh, CH*H*Ph, C*H*HPh, CH*H*Ph, CH*H*Ph, C*H*HPh), 4.36 – 4.26 (m, 3H, H-3'', CH*H*Ph, C*H*HPh), 4.26 – 4.13 (m, 3H, H-1', CH*H*Ph, H-2''), 4.13 – 4.01 (m, 5H, H-4'', C*H*HPh, H-4''', H-3''', H-3), 3.96 – 3.89 (m, 2H, H-6a, OCH*H*CH$_2$N$_3$), 3.84 (*q*t, *J* = 8.5 Hz, 1H, H-4), 3.82 – 3.78 (m, 1H, H-6b), 3.75 (dd, *J* = 6.4, 2.0 Hz, 1H, H-5'''), 3.65 (dd, *J* = 9.9, 6.5 Hz, 1H, H-6'''a), 3.62 – 3.54 (m, 3H, H-5'', H-6'''b, OC*H*HCH$_2$N$_3$), 3.54 – 3.47 (m, 2H, H-3', H-6a''), 3.47 – 3.28 (m, 7H, OCH$_2$CH*H*N$_3$, H-5', H-2''', H-2', H-6''b, H-6'a, H-6'b), 3.24 – 3.11 (m, 3H, H-5, H-2, OCH$_2$C*H*HN$_3$), 2.01 (s, 3H, OCOCH$_3$), 1.85 (s, 3H, NHCOC*H*$_3$), 1.37 (s, 3H, CH$_3$), 1.33 (s, 3H, CH$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.6 (NH*C*OCH$_3$), 170.1 (O*C*OCH$_3$), 167.6 (2 CO$_{NPhth}$), 139.0, 138.9, 138.8, 138.6, 138.5, 138.4, 138.3, 138.2 (8 C$_{Ar}$), 133.6 (2 C$_{NPhth}$), 131.4 (2 C$_{NPhth}$), 128.50, 128.46, 128.44, 128.39, 128.2, 128.11, 128.08, 128.03, 127.92, 127.87, 127.8, 127.69, 127.67, 127.60, 127.58, 127.5, 127.0, 127.0, 126.6 (40 H$_{Ar}$) 123.1 (2 C$_{NPhth}$), 109.8 (*C*(CH$_3$)$_2$), 102.5 (C-1'''), 102.3 (C-1'), 99.5 (C-1), 99.2 (C-1''), 80.7 (C-2'''), 79.5 (C-3'), 79.3, 78.8, 78.0, 77.4 (C-3''', C-4''', C-3, C-2'), 77.0 (C-3''), 76.4 (C-4), 75.4 (C-5''), 74.9 (C-5), 74.5 (CH$_2$Ph), 74.4 (CH$_2$Ph), 74.2 (CH$_2$Ph), 74.0 (CH$_2$Ph), 73.68 (CH$_2$Ph), 73.65 (CH$_2$Ph), 73.5 (C-4''), 73.3 (CH$_2$Ph), 73.2 (CH$_2$Ph), 72.9 (C-5'), 72.1 (C-5'''), 70.2 (C-4'), 69.2, 68.9, 68.3, 68.0, 67.9 (O*C*H$_2$CH$_2$N$_3$, C-6, C-6', C-6'', C-6'''), 57.0 (C-2), 56.2 (C-2''), 50.7 (OCH$_2$*C*H$_2$N$_3$), 28.1 (CH$_3$), 26.5 (CH$_3$), 23.7 (NHCO*C*H$_3$), 20.9 (OCO*C*H$_3$); HRMS (ESI$^+$): m/z calcd for C$_{97}$H$_{105}$N$_5$O$_{23}$; 1730.7098 [M+Na]$^+$; found: 1730.7119.

2-Azidoethyl (2,6-di-*O*-benzyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-(1⟶4)-(3,6-di-*O*-benzyl-2-deoxy-2-trifluoroacetamido-β-D-glucopyranosyl)-(1⟶3)-(4-*O*-acetyl-2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1⟶4)-2-acetamido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (44) R_f = 0.65, Tol/Acetone 8:2; $[\alpha]_D^{20}$= +5.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.14 (m, 40H, H$_{Ar}$), 6.18 (d, *J* = 7.4 Hz, 1H, NHCOCF$_3$), 5.79 (d, *J* = 7.4 Hz, 1H, N*H*COCH$_3$), 5.42 (*q*d, *J* = 3.5 Hz, 1H, H-4'), 5.01 (d, *J* = 7.6 Hz, 1H, H-1), 4.96 – 4.89 (m, 2H, H-1'', C*H*HPh), 4.82 (m, 2H, C*H*HPh, CH*H*Ph), 4.78 (d, *J* = 11.0 Hz, 1H, CH*H*Ph), 4.73 (d, *J* = 11.7 Hz, 1H, C*H*HPh), 4.63 (d, *J* = 12.1 Hz, 1H, CH*H*Ph), 4.61 – 4.54 (m, 3H, CH$_2$Ph, C*H*HPh), 4.61 – 4.39 (m, 8H, H-1''', H-1', 3 CH$_2$Ph), 4.33 (d, *J* = 11.8 Hz, 1H, CH*H*Ph), 4.20 – 4.16 (m, 1H, H-4), 4.14 (dd, *J* = 5.6, 1.9 Hz, 1H, H-4'''), 4.08 (*q*t, *J* = 6.1 Hz, 1H, H-3'''), 4.06 – 3.96 (m, 3H, H-4'', H-3, OCH*H*CH$_2$N$_3$), 3.88 (dd, *J* = 10.9, 4.3 Hz, 1H, H-6''a), 3.78 – 3.63 (m, 9H, H-3', H-3'', H-5''', H-2'', H-6''b, OC*H*HCH$_2$N$_3$, H-6'''a, H-6'''b, H-6'a), 3.57 (dd, *J* = 9.8, 6.3 Hz, 1H, H-6'b), 3.55 – 3.43 (m, 5H, OCH$_2$CH*H*N$_3$, H-5', H-5, H-5'', H-2'), 3.40 – 3.33 (m, 3H, H-2''', H-6a, H-6b), 3.30 – 3.21 (m, 2H, OCH$_2$C*H*HN$_3$, H-2), 1.99 (s, 3H, OCOC*H*$_3$), 1.92 (s, 3H, NHCOC*H*$_3$), 1.40 (s, 3H, CH$_3$), 1.36 (s, 3H, (CH$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7 (NH*C*OCH$_3$), 170.1 (O*C*OCH$_3$), 157.0 (*q*d, *J* = 36.9 Hz, NH*C*OCF$_3$), 138.9, 138.6, 138.44, 138.42, 138.38, 138.21, 138.19, 138.1 (8 C$_{Ar}$), 128.6 – 127.6 (m, 39 C$_{Ar}$), 127.3 (C$_{Ar}$), 115.7 (*q*d, *J* = 288.7 Hz, NHCO*C*F$_3$), 110.0 (*C*(CH$_3$)$_2$), 102.5 (C-1'), 102.3 (C-1'''), 99.7 (C-1''), 99.6 (C-1), 80.6 (C-2'''), 80.5 (C-2'), 79.4 (C-3'''), 77.6 (C-3''), 77.3 (under $CDCl_3$ peak, C-4), 76.7 (C-3'), 76.6 (C-3), 76.3 (C-4''), 75.5, 75.1, 75.0 (C-5'', C-5, CH$_2$Ph), 74.2 (CH$_2$Ph), 73.8, 73.7, 73.51, 73.47, 73.4, 73.34, 73.30 (6 CH$_2$Ph, C-4'''), 72.7 (C-5'), 72.2 (C-5'''), 69.6 (C-4'), 69.1 (C-6'), 68.4, 68.3, 68.3, 68.1 (C-6'', C-6, C-6''', O*C*H$_2$CH$_2$N$_3$), 56.9 (C-2), 55.7 (C-2''), 50.7 (OCH$_2$*C*H$_2$N$_3$), 28.1 (CH$_3$), 26.5 (CH$_3$), 23.7 (NHCO*C*H$_3$), 20.8 (OCO*C*H$_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.72; HRMS (ESI$^+$): m/z calcd for C$_{91}$H$_{102}$F$_3$N$_5$O$_{22}$: 1696.6861 [M+Na]$^+$; found: 1696.5470.

2-Azidoethyl (2,6-di-*O*-benzyl-3,4-*O*-isopropylidene-β-D-galactopyranosyl)-(1⟶4)-[3,6-di-*O*-benzyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-glucopyranosyl]-(1⟶3)-(4-*O*-acetyl-2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1⟶4)-3,6-di-*O*-benzyl-2-deoxy-2-trifluoroacetamido-β-D-glucopyranoside (45) R_f = 0.46, Tol/Acetone 9:1; $[\alpha]_D^{20}$= +5.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.21 (m, 40H, H$_{Ar}$), 6.72 (d, *J* = 7.6 Hz, 1H, NHCOCF$_3$), 5.43 (*q*d, *J* = 3.6 Hz, 1H, H-4'), 4.90 (d, *J* = 7.0 Hz, 1H, H-1), 4.87 – 4.77 (m, 4H, CH*H*Ph, C*H*HPh, CH*H*Ph, N*H*CO$_2$CH$_2$CCl$_3$), 4.74 – 4.28 (m, 20H, H-1'', H-1''', H-1', CH*H*CCl$_3$, 8 CH*H*Ph), 4.13 (dd, *J* = 5.5, 2.0 Hz, 1H, H-4'''), 4.10 – 3.93 (m, 5H, H-3, H-3''', H-4, H-4'', OC*H*HCH$_2$N$_3$), 3.82 (*q*td, *J* = 10.4, 9.8, 4.3 Hz, 1H, H-6''a), 3.79 – 3.76 (m, 1H, H-6''b), 3.73 (ddd, *J* = 12.9, 5.3, 2.0 Hz, 1H, H-5'''), 3.70 – 3.60 (m, 5H, OCH*H*CH$_2$N$_3$, H-6a, H-6b, H-6'''a, H-3'), 3.59 – 3.49 (m, 5H, H-2, H-6'''b, H-5', H-5, H-2'), 3.49 – 3.34 (m, 7H, OCH$_2$C*H*HN$_3$, H-2'', H-6'a, H-6'b, H-5'', H-3'', H-2'''), 3.28 (ddd, *J* = 13.2, 5.4, 3.5 Hz, 1H, OCH$_2$CH*H*N$_3$), 2.02 (s, 3H, OCOCH$_3$), 1.41 (s, 3H, CH$_3$), 1.36 (s, 3H, CH$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0 (O*C*OCH$_3$), 157.1 (*q*d, *J* = 37.2 Hz, NH*C*OCF$_3$), 153.9 (NH*C*O$_2$CH$_2$CCl$_3$), 138.8, 138.7, 138.5, 138.12, 138.06, 138.0 (8 C$_{Ar}$), 128.7, 128.6, 128.53, 128.47, 128.43, 128.41, 128.37, 128.33, 128.30, 128.2, 128.1, 128.04, 127.99, 127.9, 127.8, 127.68, 127.67, 127.63, 127.56, 127.2 (40 C$_{Ar}$), 115.6 (*q*d, *J* = 288.6 Hz, NHCO*C*F$_3$), 109.9 (*C*(CH$_3$)$_2$), 102.9 (C-1'), 102.2 (C-1'''), 101.2 (C-1''), 99.2 (C-1), 95.8 (CH$_2$*C*Cl$_3$), 80.7 (C-2'''), 80.4 (C-2'), 79.5 (C-3'''), 79.2 (C-3''), 77.4 (C-

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DOI: 10.1039/C8OB03060A

3'), 76.4, 76.3 (C-3, C-4, C-4''), 75.5, 75.4 (C-5, C-5''), 75.0, 74.33, 74.25, 73.8, 73.5, 73.4, 73.3 (8 CH_2Ph, $\underline{C}H_2CCl_3$, C-4'''), 73.1 (C-5'), 72.1 (C-5'''), 69.8 (C-4'), 69.1 (C-6'''), 68.5 (O$\underline{C}H_2CH_2N_3$), 68.3, 68.2 (C-6, C-6', C-6''), 57.0 (C-2''), 55.8 (C-2), 50.7 (OCH$_2\underline{C}H_2N_3$), 28.1 (CH_3), 26.5 (CH_3), 20.8 (OCO$\underline{C}H_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.88; HRMS (ESI$^+$): m/z calcd for $C_{92}H_{101}Cl_3F_3N_5O_{23}$: 1828.5797 [M+Na]$^+$; found 1828.4799.

General procedure for the formation of acceptors 50–52 and 55 via 3',4'-*O*-isopropylidene cleavage, orthoester formation, and rearrangement sequence:

Fully protected tetrasaccharide (1 eq) was stirred in *aq.* 80% AcOH (0.02 M) for 4-5 hours at 60–70 °C. After dilution with toluene the solvents were removed and crude was purified by column chromatography to afford the corresponding diol derivative. Diol (1 eq) was then dissolved in CH_3CN (0.05 M) and reacted with $CH_3C(OCH_3)_3$ (3 eq) and *p*-TsOH (0.1-0.5 eq). After 30 minutes the reaction was quenched with Et_3N and concentrated to dryness. Crude orthoester product was then dissolved in *aq.* 80% AcOH (0.05 M) and stirred for 1 hour at RT. After solvent removal, crude was purified by flash column chromatography (see Supplementary Information).

2-Azidoethyl (4-*O*-acetyl-2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-(3,6-di-*O*-benzyl-2-deoxy-2-trifluoroacetamido-β-D-glucopyranosyl)-(1→3)-(4-*O*-acetyl-2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2-acetamido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (50) R_f = 0.53, Tol/Acetone 8:2; $[\alpha]_D^{20}$ = -2.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.20 (m, 40H, H_{Ar}), 6.26 (d, *J* = 8.2 Hz, 1H, NHCOCF$_3$), 5.76 (d, *J* = 7.4 Hz, 1H, N$\underline{H}$COCH$_3$), 5.42 (*a*d, *J* = 3.6 Hz, 1H, H-4'), 5.35 (dd, *J* = 3.5, 1.1 Hz, 1H, H-4'''), 5.00 (d, *J* = 7.8 Hz, 1H, H-1), 4.97 (d, *J* = 7.1 Hz, 1H, H-1'), 4.91 (d, *J* = 11.1 Hz, 1H, C$\underline{H}$HPh), 4.85 (d, *J* = 11.3 Hz, 1H, CH$\underline{H}$Ph), 4.88 – 4.71 (m, 2H, CH$\underline{H}$Ph, C$\underline{H}$HPh), 4.69 (d, *J* = 11.3 Hz, 1H, CH$\underline{H}$Ph), 4.64 (d, *J* = 12.1 Hz, 1H, C$\underline{H}$HPh), 4.60 – 4.26 (m, 12H, H-1''', H-1', CH_2Ph, CH_2Ph, CH_2Ph, CH_2Ph, CH_2Ph), 4.18 (dd, *J* = 9.5, 8.2 Hz, 1H, H-3), 4.05 (*a*t, *J* = 8.2 Hz, 1H, H-4''), 4.03 – 3.96 (m, 2H, OCH$\underline{H}$CH$_2$N$_3$, H-4), 3.84 (dd, *J* = 10.9, 4.3 Hz, 1H, H-6''a), 3.79 – 3.62 (m, 8H, H-6''b, H-6a, H-6b, H-3''', H-3', H-3'', H-2'', OC$\underline{H}$HCH$_2$N$_3$), 3.60 – 3.55 (m, 1H, H-5'''), 3.55 – 3.43 (m, 5H, H-5', H-5, H-5'', H-2', OCH$_2$CH$\underline{H}$N$_3$), 3.43 – 3.40 (m, 1H, H-2'''), 3.37 (m, 2H, H-6'a, H-6'b), 3.33 (m, 2H, H-6'''a, H-6'''b), 3.25 3.28 – 3.21 (m, 2H, OCH$_2$C$\underline{H}$HN$_3$, H-2), 2.02 (s, 3H, OCOCH$_3$), 1.99 (s, 3H, OCOCH$_3$), 1.91 (s, 3H, NHCOC$\underline{H}_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 170.6, 169.9 (3 $\underline{C}$OCH$_3$), 156.9 (*a*d, *J* = 36.8 Hz, NH$\underline{C}$OCF$_3$), 138.8, 138.4, 138.12, 138.08, 138.07, 138.06, 137.9, 137.7 (8 C_{Ar}), 129.02, 128.96, 128.59, 128.58, 128.56, 128.41, 128.38, 128.37, 128.35, 128.22, 128.17, 128.14, 128.09, 128.0, 127.87, 127.85, 127.81, 127.75, 127.7, 127.64, 127.55, 127.2 (40 C_{Ar}), 115.6 (*a*d, *J* = 288.6 Hz, NHCO$\underline{C}$F$_3$), 102.8 (C-1'''), 102.4 (C-1'), 99.5 (C-1), 99.4 (C-1''), 80.3 (C-2'), 79.9 (C-2'''), 77.3 (C-3), 77.2 (C-3''), 76.7 (C-3'), 76.4 (C-4), 76.2 (C-4''), 75.4 (C-5''), 75.1 (CH_2Ph), 74.93, 74.86 (CH_2Ph, C-5'), 74.1, 73.6, 73.46, 73.45, 73.24, 73.19 (6 CH_2Ph), 72.6 (C-5'), 72.3 (C-3'''), 72.1 (C-5'''), 69.54 (C-4'''), 69.47 (C-4'), 68.3 (O$\underline{C}$H$_2$CH$_2$N$_3$), 68.1, 68.0 (C-6, C-6', C-6''), 67.3 (C-6'''), 56.8 (C-2), 55.5 (C-2''), 50.6 (OCH$_2\underline{C}$H$_2$N$_3$), 23.6 (NHCO$\underline{C}$H$_3$), 20.7 (OCO$\underline{C}$H$_3$), 20.6 (OCO$\underline{C}$H$_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.72 (NHCOCF$_3$); HRMS (ESI$^+$): m/z calcd for $C_{90}H_{100}F_3N_5O_{23}$; 1698.6659 [M+Na]$^+$; found 1698.6711.

2-Azidoethyl (4-*O*-acetyl-2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-[3,6-di-*O*-benzyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-glucopyranosyl]-(1→3)-(4-*O*-acetyl-2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-trifluoroacetamido-β-D-glucopyranoside (51) R_f = 0.75. Tol/Acetone 7:3; $[\alpha]_D^{20}$ = +1.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.17 (m, 40H, H_{Ar}), 6.74 (d, *J* = 7.6 Hz, 1H, N$\underline{H}$COCF$_3$), 5.45 (*a*d, *J* = 3.6 Hz, 1H, H-4'), 5.35 (*a*d, *J* = 3.5 Hz, 1H, H-4'''), 4.90 (d, *J* = 7.1 Hz, 1H, H-1), 4.89 – 4.80 (m, 3H, C$\underline{H}$HPh, CH$\underline{H}$Ph, CH$\underline{H}$CCl$_3$), 4.78 (d, *J* = 7.9 Hz, 1H, H-1''), 4.73 – 4.38 (m, 16H, 6 CH_2Ph, C$\underline{H}$HCl$_3$, H-1''', H-1', N$\underline{H}$CO$_2$CH$_2$CCl$_3$), 4.34 (d, *J* = 11.7 Hz, 1H, CH$\underline{H}$Ph), 4.24 (d, *J* = 11.9 Hz, 1H, C$\underline{H}$HPh), 4.08 (*a*t, *J* = 8.1 Hz, 1H, H-4), 4.04 – 3.96 (m, 3H, H-3, H-4'', OCH$\underline{H}$CH$_2$N$_3$), 3.82 (dd, *J* = 11.0, 4.4 Hz, 1H, H-6''a), 3.80 – 3.74 (m, 2H, H-6''b, H-6a), 3.71 – 3.60 (m, 4H, H-6b, OC$\underline{H}$HCH$_2$N$_3$, H-3''', H-3'), 3.59 – 3.51 (m, 6H, H-2, H-5''', H-5', H-5, H-3'', H-2'), 3.47 – 3.40 (m, 5H, OCH$_2$CH$\underline{H}$N$_3$, H-2'', H-6'a, H-5'', H-2'''), 3.40 – 3.34 (m, 1H, H-6'b), 3.33 – 3.25 (m, 3H, OCH$_2$C$\underline{H}$HN$_3$, H-6'''a, H-6'''b), 2.03 – 2.00 (m, 6H, 2 OCOCH$_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.90 (O$\underline{C}$OCH$_3$), 169.87 (O$\underline{C}$OCH$_3$), 157.1 (*a*d, *J* = 37.3 Hz, NH$\underline{C}$OCF$_3$), 153.8 (NH$\underline{C}$O$_2$CH$_2$Cl$_3$), 138.61, 138.60, 138.23, 138.16, 138.0, 137.91, 137.88, 137.8 (8 C_{Ar}), 129.0, 128.6, 128.54, 128.48, 128.43, 128.39, 128.38, 128.36, 128.3, 128.0, 127.92, 127.89, 127.87, 127.84, 127.81, 127.75, 127.71, 127.69, 127.65, 127.57, 127.4 (40 C_{Ar}), 115.6 (*a*d, *J* = 288.2 Hz, NHCO$\underline{C}$F$_3$), 102.7 (C-1'), 102.5 (C-1'''), 100.9 (C-1''), 99.0 (C-1), 95.6 ($CH_2\underline{C}Cl_3$), 80.2 (C-2'), 80.1 (C-2'''), 79.2 (C-3''), 77.7 (C-3'), 76.3, 76.2 (C-3, C-4, C-4''), 75.3, 75.2 (C-5, C-5''), 75.11, 74.12, 73.6, 73.4, 73.3, 73.2 (8 CH_2Ph, $\underline{C}H_2CCl_3$), 72.9 (C-5'), 72.4 (C-3'''), 72.0 (C-5'''), 69.6 (C-4'), 69.6 (C-4'''), 68.3 (O$\underline{C}$H$_2$CH$_2$N$_3$), 68.1, 68.0 (C-6, C-6', C-6''), 67.3 (C-6'''), 57.0 (C-2''), 55.7 (C-2), 50.6 (OCH$_2\underline{C}$H$_2$N$_3$), 20.74 (OCO$\underline{C}$H$_3$), 20.68 (OCO$\underline{C}$H$_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.89 (NHCOCF$_3$); HRMS (ESI$^+$): m/z calcd for $C_{91}H_{99}Cl_3F_3N_5O_{24}$: 1830.5595 [M+Na]$^+$; found: 1830.5514.

2-Azidoethyl (4-*O*-acetyl-2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-(2-acetamido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-(4-*O*-acetyl-2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-trifluoroacetamido-β-D-glucopyranoside (52) R_f = 0.43, Tol/Acetone 7:3; $[\alpha]_D^{20}$ = +3.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.21 (m, 40H, H_{Ar}), 6.82 (d, *J* = 7.6 Hz, 1H, NHCOCF$_3$), 5.41 (*a*d, *J* = 3.5 Hz, 1H, H-4'), 5.35 (*a*d, *J* = 3.5 Hz, 1H, H-4'''), 5.26 (d, *J* = 7.8 Hz, 1H, N$\underline{H}$COCH$_3$), 5.06 (d, *J* = 7.5 Hz, 1H, H-1''), 4.91 – 4.84 (m, 3H, H-1, CH_2Ph), 4.83 – 4.76 (m, 2H, CH_2Ph), 4.70 – 4.60 (m, 3H, CH_2Ph, CH$\underline{H}$Ph), 4.59 – 4.52 (m, 3H, C$\underline{H}$HPh, CH_2Ph), 4.51 (d, *J* = 7.8 Hz, 1H, H-1'''), 4.48 – 4.38 (m, 5H, H-1', 2 CH_2Ph), 4.34 (d, *J* = 11.7 Hz, 1H, CH$\underline{H}$Ph), 4.28 (d, *J* = 12.1 Hz, 1H, C$\underline{H}$HPh), 4.11 – 3.94 (m, 5H, H-3'', H-3, H-4, H-4'', OCH$\underline{H}$CH$_2$N$_3$), 3.86 – 3.75 (m, 3H, H-6''a, H-6''b, H-6a), 3.71 (dd, *J* = 10.6, 3.5 Hz, 1H, H-6b), 3.68 – 3.50 (m, 9H, OC$\underline{H}$HCH$_2$N$_3$, H-2, H-6b, H-3''', H-3', H-5''', H-5', H-5'', H-2'), 3.47 – 3.39 (m, 3H, OCH$_2$CH$\underline{H}$N$_3$, H-6'a, H-2'''), 3.39 – 3.33 (m, 4H, H-2'', H-6'b, H-6'''a, H-6'''b), 3.29 (m, 1H, OCH$_2$C$\underline{H}$HN$_3$), 2.01 (s, 6H, 2 OCOCH$_3$), 1.52 (s, 3H, NHCOC$\underline{H}_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 170.2, 170.0 (3 $\underline{C}$OCH$_3$), 157.1 (*a*d, *J* = 37.2 Hz, NH$\underline{C}$OCF$_3$), 138.9, 138.7, 138.3, 138.1, 137.99, 137.95, 137.9, 137.8 (8 C_{Ar}), 128.6, 128.43, 128.41, 128.36, 128.24, 128.22, 128.20, 128.12, 128.08, 127.9, 127.8, 127.71, 127.69, 127.63, 127.55, 127.5, 127.2 (40 C_{Ar}), 115.6 (*a*d, *J* = 288.6 Hz,

NHCO$\underline{C}$F$_3$), 102.8 (C-1'), 102.5 (C-1'''), 100.2 (C-1''), 99.0 (C-1), 80.0 (C-2'''), 79.5 (C-2'), 78.8 (C-3'), 78.0 (C-3''), 76.4, 76.3, 76.1 (C-3, C-4, C-4''), 75.3 (C-5), 75.09 (C-5''), 75.06 (CH$_2$Ph), 75.0 (CH$_2$Ph), 73.9 (CH$_2$Ph), 73.6 (2 CH$_2$Ph), 73.4 (CH$_2$Ph), 73.3 (CH$_2$Ph), 73.2 (CH$_2$Ph), 73.0 (C-5'), 72.3 (C-3'''), 72.0 (C-5'''), 69.54 (C-4'''), 69.46 (C-4'), 68.6 (C-6'), 68.3 (O$\underline{C}$H$_2$CH$_2$N$_3$, C-6), 68.2 (C-6''), 67.4 (C-6'''), 56.6 (C-2''), 55.4 (C-2), 50.6 (OCH$_2\underline{C}$H$_2$N$_3$), 23.2 (NHCO$\underline{C}$H$_3$), 20.8 (2 OCO$\underline{C}$H$_3$); HRMS (ESI$^+$): m/z calcd for $C_{90}H_{100}F_3N_5O_{23}$; 1698.6654 [M+Na]$^+$; found 1698.4514.

2-Azidoethyl (4-*O*-acetyl-2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-(2-acetamido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-(4-*O*-acetyl-2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2-acetamido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (55) R$_f$ = 0.23, cHex/Acetone 7:3; $[\alpha]_D^{20}$= +4.9 (*c* 1.0, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.38 – 7.18 (m, 40H, H$_{Ar}$), 5.74 (d, *J* = 7.4 Hz, 1H, N$\underline{H}$COCH$_3$), 5.41 (*a*d, *J* = 3.5 Hz, 1H, H-4'), 5.34 (dd, *J* = 3.5, 1.0 Hz, 1H, H-4'''), 5.22 (d, *J* = 7.9 Hz, 1H, N$\underline{H}$COCH$_3$''), 5.03 – 4.98 (m, 2H, H-1, H-1''), 4.91 (d, *J* = 11.1 Hz, 1H, C$\underline{H}$HPh), 4.88 – 4.84 (m, 2H, CH$\underline{H}$Ph, C$\underline{H}$HPh), 4.81 (d, *J* = 11.6 Hz, 1H, CH$\underline{H}$Ph), 4.68 – 4.60 (m, 3H, 2 CH$_2$Ph, C$\underline{H}$HPh), 4.59 – 4.52 (m, 2H, CH$_2$Ph), 4.50 (d, *J* = 7.8 Hz, 1H, H-1'''), 4.47 – 4.36 (m, 5H, H-1', 2 CH$_2$Ph), 4.31 (d, *J* = 11.9 Hz, 1H, CH$\underline{H}$Ph), 4.26 (d, *J* = 12.0 Hz, 1H, C$\underline{H}$HPh), 4.19 (dd, *J* = 9.5, 8.1 Hz, 1H, H-3), 4.06 – 3.95 (m, 4H, H-3'', H-4, H-4'', OC$\underline{H}$HCH$_2$N$_3$), 3.83 (dd, *J* = 10.8, 4.0 Hz, 1H, H-6a), 3.79 – 3.73 (m, 2H, H-6b, H-6''a), 3.69 – 3.60 (m, 4H, H-6''b, OCH$\underline{H}$CH$_2$N$_3$, H-3''', H-3'), 3.58 – 3.48 (m, 4H, H-5''', H-5', H-5'', H-2'), 3.48 – 3.30 (m, 7H, OCH$_2$C$\underline{H}$HN$_3$, H-2'', H-6'''a, H-6'''b, H-6'a, H-6'b, H-2'''), 3.28 – 3.21 (m, 2H, H-2, OCH$_2$CH$\underline{H}$N$_3$), 2.01 – 1.97 (m, 6H, 2 OCOCH$_3$), 1.89 (s, 3H, NHCOC$\underline{H}_3$), 1.49 (s, 3H, NHCOC$\underline{H}_3$); ^{13}C NMR (126 MHz, CDCl$_3$) δ 170.8 (O$\underline{C}$OCH$_3$), 170.6 (NH$\underline{C}$OCH$_3$), 170.2 (NH$\underline{C}$OCH$_3$), 169.9 (O$\underline{C}$OCH$_3$), 138.9, 138.8, 138.4, 138.2, 138.1, 137.8 (8 C$_{Ar}$), 128.6 – 127.0 (m, 40 C$_{Ar}$), 102.5 (C-1'''), 102.4 (C-1'), 100.3 (C-1''), 99.5 (C-1), 80.0 (C-2'''), 79.7 (C-2'), 78.8 (C-3'), 78.1 (C-4''), 77.4 (under CDCl$_3$ peak, C-3''), 76.6 (C-3), 76.2 (C-4), 75.11, 75.06, 75.0, 74.9 (2 CH$_2$Ph, C-5'', C-5), 74.1 (CH$_2$Ph), 73.6, 73.4, 73.3, 73.2 (5 CH$_2$Ph), 72.8 (C-5'), 72.3 (C-3'''), 72.0 (C-5'''), 69.6 (C-4', C-4'''), 68.6 (C-6'), 68.3, 68.2 (C-6, C-6'', O$\underline{C}$H$_2$CH$_2$N$_3$), 67.4 (C-6'''), 56.7 (C-2, C-2''), 50.6 (OCH$_2\underline{C}$H$_2$N$_3$), 23.6 (NHCO$\underline{C}$H$_3$), 23.1 (NHCO$\underline{C}$H$_3$), 20.8 (OCO$\underline{C}$H$_3$), 20.7 (OCO$\underline{C}$H$_3$); HRMS (ESI$^+$): m/z calcd for $C_{90}H_{103}N_5O_{23}$: 1644.6942 [M+Na]$^+$; found: 1644.7008.

General procedure for [2+4] glycosylation for compounds 56, 57, 59
Acceptor (1 eq) and donor (1.5 eq) were dissolved in dry CH$_2$Cl$_2$ (0.015 M) together with 4Å molecular sieves. The mixture was stirred for 1 hour, then the mixture was cooled to −20 °C and NIS (1.5 eq) was added followed by TfOH (0.8 eq). The reaction was stirred for 1 hour at the same temperature, then quenched with Et$_3$N, filtered over Celite and evaporated *in vacuo*. Crude was purified by flash column chromatography (see Supplementary Information).

2-Azidoethyl (2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-[3,6-di-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-glucopyranoside]-(1→3)-(4-*O*-acetyl-2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-(3,6-di-*O*-benzyl-2-deoxy-2-trifluoroacetamido-β-D-glucopyranosyl)-(1→3)-(4-*O*-acetyl-2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2-acetamido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (56) R$_f$ = 0.31, cHex/Acetone 1:1; $[\alpha]_D^{20}$= +3.8 (*c* 1.0, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.35 – 7.20 (m, 40H, H$_{Ar}$), 6.32 (d, *J* = 8.3 Hz, 1H, NHCOCF$_3$), 5.80 (d, *J* = 7.4 Hz, 1H, N$\underline{H}$COCH$_3$), 5.39 (*a*d, *J* = 3.6 Hz, 1H, H-4'), 5.37 (br, 1H, H-4'''), 5.36 – 5.34 (m, 1H, H-4'''''), 5.10 (dd, *J* = 10.4, 7.9 Hz, 1H, H-2'''''), 5.01 – 4.88 (m, 4H, H-3''''', CH$\underline{H}$Ph, H-1, H-1''), 4.86 – 4.73 (m, 5H, H-3''', C$\underline{H}$HPh, CH$_2$Ph, N$\underline{H}$CO$_2$CH$_2$CCl$_3$), 4.68 (m, 2H, CH$\underline{H}$CCl$_3$, C$\underline{H}$HPh), 4.63 – 4.53 (m, 7H, H-6'''a, C$\underline{H}$HCl$_3$, CH$_2$Ph, CH$_2$Ph , H-1''', C$\underline{H}$HPh), 4.52 – 4.39 (m, 7H, H-1''''', H-1''', C$\underline{H}$HPh, 2 CH$_2$Ph), 4.41 – 4.33 (m, 2H, C$\underline{H}$HPh, H-1'), 4.33 – 4.27 (m, 2H, CH$_2$Ph), 4.16 (dd, *J* = 9.6, 8.2 Hz, 1H, H-3), 4.12 – 4.09 (m, 2H, H-6''''a, H-6''''b), 4.08 – 3.96 (m, 4H, H-6'''b, OC$\underline{H}$HCH$_2$N$_3$, H-4'', H-4), 3.88 (dd, *J* = 6.8, 1.3 Hz, 2H, H-5'''''), 3.82 – 3.56 (m, 12H, H-2'', H-2'''', H-6''a, H-6''b, H-6a, H-6b, OCH$\underline{H}$CH$_2$N$_3$, H-5'''', H-3'', H-3', H-3''', H-4''''), 3.54 – 3.42 (m, 6H, H-5''', H-5', H-5, H-2', H-2''', OCH$_2$C$\underline{H}$HN$_3$), 3.41 – 3.31 (m, 5H, H-6'''a, H-6'''b, H-6'a, H-6'b, H-5''), 3.27 – 3.20 (m, 2H, H-2, OCH$_2$CH$\underline{H}$N$_3$), 2.15 (s, 3H, OCOCH$_3$), 2.09 (s, 3H, OCOCH$_3$), 2.08 (s, 3H, OCOCH$_3$), 2.06 (s, 3H, OCOCH$_3$), 2.03 (s, 3H, OCOCH$_3$), 2.02 (s, 3H, OCOCH$_3$), 1.99 – 1.96 (m, 6H, 2 OCOCH$_3$), 1.91 (s, 3H, NHCOC$\underline{H}_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 170.7, 170.54, 170.45, 170.4, 170.2, 170.1, 170.0, 169.9, 169.2 (9 COCH$_3$), 156.9 (*a*d, *J* = 36.9 Hz, NH$\underline{C}$OCF$_3$), 154.1 (NH$\underline{C}$O$_2$CH$_2$CCl$_3$), 138.8, 138.4, 138.3, 138.12, 138.07, 138.0, 137.9, 137.8 (8 C$_{Ar}$), 128.7, 128.4, 128.4 – 128.2, 128.19, 128.18, 128.15, 128.1, 128.0, 127.87, 127.85, 127.8, 127.71, 127.65, 127.6, 127.5, 127.2, 127.1 (40 C$_{Ar}$), 115.6 (*a*d, *J* = 288.7 Hz, NHCO$\underline{C}$F$_3$), 102.4 (C-1'''), 102.3 (C-1'), 101.2 (C-1''''), 101.0 (C-1'''), 99.5 (C-1), 99.3 (C-1''), 95.6 (CH$_2\underline{C}$Cl$_3$), 80.3 (C-2', C-2'''), 77.3 (C-3), 76.7 (C-4''', C-3''', C-3'), 76.4 (C-4), 76.1 (C-3''), 75.8 (C-4''), 75.3 (C-5''), 75.1, 74.9, 74.8, 74.3, 74.1, 73.7, 73.51, 73.48, 73.3, 73.2 (8 CH$_2$Ph, C-5, $\underline{C}$H$_2$CCl$_3$), 72.5 (C-5', C-5''', C-5''''), 72.3 (C-3''''), 71.0 (C-3'''''), 70.7 (C-5'''''), 69.7, 69.5 (C-4', C-4'''), 69.2 (C-2'''''), 68.2, 68.1, 68.0, 67.8 (C-6'', C-6, C-6', C-6''', O$\underline{C}$H$_2$CH$_2$N$_3$), 66.66 (C-4'''''), 61.4 (C-6''''), 60.9 (C-6'''''), 56.8 (C-2), 56.3 (C-2''''), 55.8 (C-2''), 50.6 (OCH$_2\underline{C}$H$_2$N$_3$), 23.5 (NHCO$\underline{C}$H$_3$), 20.79, 20.77, 20.7, 20.63, 20.61, 20.5 (8 OCOCH$_3$); ^{19}F NMR (376 MHz, CDCl$_3$) δ -75.69 (NHCOCF$_3$); HRMS (ESI$^+$): m/z calcd for $C_{117}H_{134}Cl_3F_3N_6O_{40}$: 2447.7546 [M+Na]$^+$; found: 2447.8903.

2-Azidoethyl (2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-(3,6-di-*O*-acetyl-2-deoxy-2-trifluoroacetamido-β-D-glucopyranosyl)-(1→3)-(4-*O*-acetyl-2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-(2-acetamido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-(4-*O*-acetyl-2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-2-acetamido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranoside (57) R$_f$ = 0.40, cHex/Acetone 1:1; $[\alpha]_D^{20}$= +5.4 (*c* 1.0, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.46 – 7.10 (m, 40H, H$_{Ar}$), 6.18 (d, *J* = 9.6 Hz, 1H, NHCOCF$_3$), 5.72 (d, *J* = 7.4 Hz, 1H, N$\underline{H}$COCH$_3$), 5.40 – 5.34 (m, 3H, H-4''''', H-4', H-4'''), 5.17 (d, *J* = 7.9 Hz, 1H, N$\underline{H}$COCH$_3$), 5.12 (dd, *J* = 10.4, 7.9 Hz, 1H, H-2'''''), 5.01 – 4.95 (m, 3H, H-1, H-1'', H-3'''''), 4.92 (d, *J* = 11.1 Hz, 1H, C$\underline{H}$HPh), 4.90 – 4.80 (m, 4H, H-3''', CH$\underline{H}$Ph, CH$_2$Ph), 4.72 – 4.61 (m, 4H, H-1''', CH$_2$Ph, H-6'''a), 4.60 – 4.36 (m, 11H, H-1''', H-1''''', H-1', 4 CH$_2$Ph), 4.32 (d, *J* = 11.9 Hz, 1H, C$\underline{H}$HPh), 4.28 (d, *J* = 11.9 Hz, 1H, CH$\underline{H}$Ph), 4.19 (dd, *J* = 9.4, 8.1 Hz, 1H, H-3''), 4.12 – 4.09 (m, 2H, H-6''''a, H-6''''b), 4.09 – 3.90 (m, 6H, H-6'''b, OCH$\underline{H}$CH$_2$N$_3$, H-4, H-3, H-4'', H-2''''), 3.90 – 3.86 (m, 1H, H-5'''''), 3.84 – 3.74 (m, 3H, H-6a, H-6''a, H-4''''), 3.74 – 3.63 (m, 4H, H-6b, H-6''b, H-3''', OC$\underline{H}$HCH$_2$N$_3$), 3.62 – 3.58 (m, 2H, H-5''', H-3'), 3.58 – 3.41 (m, 6H, H-5', H-5, H-5'', H-2', H-2''', OCH$_2$CH$\underline{H}$N$_3$), 3.41 – 3.29 (m, 5H, H-2, H-6'a, H-6'b, H-6'''a, H-6'''b), 3.24 (m, 2H, H-2'',

OCH_2CHHN_3), 2.15 (s, 3H, $OCOCH_3$), 2.09 – 2.06 (m, 9H, 3 $OCOCH_3$), 2.04 (s, 3H, $OCOCH_3$), 2.03 (s, 3H, $OCOCH_3$), 1.98 (s, 6H, 2 $OCOCH_3$), 1.89 (s, 3H, $NHCOCH_3$), 1.49 (s, 3H, $NHCOCH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 170.5, 170.40, 170.36, 170.12, 170.06, 170.01, 169.95, 169.9, 169.2 (10 $COCH_3$), 157.0 (q, J = 37.3 Hz, $NHCOCF_3$), 138.9, 138.8, 138.7, 138.4, 138.13, 138.05, 138.0, 137.9 (8 C_{Ar}), 128.6, 128.4, 128.32, 128.30, 128.12, 128.08, 128.06, 128.0, 127.9, 127.81, 127.77, 127.64, 127.61, 127.57, 127.5, 127.4, 127.0, 126.8 (40 C_{Ar}), 115.5 (*a*d, J = 288.3 Hz, $NHCOCF_3$), 102.4 (C-1'), 102.22 (C-1'''), 101.2 (C-1''''), 100.4 (C-1), 100.1 (C-1''''), 99.5 (C-1''), 80.2 (C-2'''), 79.7 (C-2'), 78.8 (C-3'), 78.0 (C-4''), 77.2 (C-3''), 76.6 (C-3), 76.1 (C-3'''), 75.9 (C-4), 75.6 (C-4''''), 75.1, 75.0, 74.9 (CH_2Ph, CH_2Ph, H-5'', H-5), 74.0 (CH_2Ph), 73.53, 73.49, 73.3, 73.2 (5 CH_2Ph), 72.8, 72.7 (C-5', C-5'''), 72.3 (C-5''''), 71.9 (C-3''''), 70.9 (C-3'''''), 70.8 (C-5'''''), 69.7 (C-4', C-4'''), 69.1 (C-2'''''), 68.5 (C-6'), 68.3 ($OCH_2CH_2N_3$), 68.2, 68.0, 67.9 (C-6, C-6'', C-6'''), 66.6 (C-4'''''), 61.1 (C-6''''), 60.9 (C-6'''''), 56.7 (C-2''), 56.4 (C-2), 54.5 (C-2''''), 50.6 ($OCH_2CH_2N_3$), 23.6 ($NHCOCH_3$), 23.1 ($NHCOCH_3$), 20.79, 20.75, 20.63, 20.59, 20.5 (8 $OCOCH_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.95 ($NHCOCF_3$); HRMS (ESI^+): m/z calcd for $C_{116}H_{135}F_3N_6O_{39}$: 2315.8609 $[M+Na]^+$; found: 2315.8827.

2-Azidoethyl (2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-[3,6-di-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-glucopyranoside]-(1→3)-(4-*O*-acetyl-2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-(2-acetamido-3,6-di-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)-(1→3)-(4-*O*-acetyl-2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-3,6-di-*O*-benzyl-2-deoxy-2-trifluoroacetamido-β-D-glucopyranoside (59) R_f = 0.20, Tol/Acetone 8:2; $[\alpha]_D^{20}$ = +6.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.16 (m, 40H, H_{Ar}), 6.81 (d, *J* = 7.7 Hz, 1H, $NHCOCF_3$), 5.40 – 5.33 (m, 3H, H-4'''', H-4', H-4'''), 5.25 (d, *J* = 8.0 Hz, 1H, $NHCOCH_3$), 5.11 (dd, *J* = 10.4, 7.9 Hz, 1H, H-2'''''), 5.03 (d, *J* = 7.9 Hz, 1H, H-1''), 4.97 (dd, *J* = 10.4, 3.4 Hz, 1H, H-3''''), 4.91 – 4.84 (m, 3H, H-1, CH_2Ph), 4.83 – 4.76 (m, 2H, CH_2Ph), 4.75 – 4.63 (m, 4H, H-3'''', CH_2Ph, $CHHCCl_3$), 4.61 – 4.36 (m, 15H, H-6''''a, $CHHCCl_3$, 4 CH_2Ph, H-1'''', H-1''''', H-1''', H-1', $NHCO_2CH_2CCl_3$), 4.35 – 4.27 (m, 2H, CH_2Ph), 4.13 – 4.08 (m, 2H, H-6''''a, H-6''''b), 4.08 – 3.95 (m, 6H, H-6''''b, $OCHHCH_2N_3$, H-3, H-4, H-4'', H-3''), 3.87 (*a*t, *J* = 6.9 Hz, 1H, H-5'''''), 3.83 – 3.48 (m, 14H, H-2, H-2'''', H-6''a, H-6''b, H-6a, H-6b, $OCHHCH_2N_3$, H-5'''', H-5''', H-5, H-4''', H-3''', H-3', H-2'), 3.49 – 3.38 (m, 5H, CH_2CHHN_3, H-6'a, H-5', H-5'', H-2'''), 3.38 – 3.25 (m, 5H, H-2'', OCH_2CHHN_3, H-6'''a, H-6'''b, H-6'b), 2.15 (s, 3H, $OCOCH_3$), 2.09 – 2.05 (m, 12H, 4 $OCOCH_3$), 2.02 (s, 3H, $OCOCH_3$), 2.01 (s, 3H, $OCOCH_3$), 2.00 (s, 3H, $OCOCH_3$), 1.98 (s, 3H, $NHCOCH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 170.4, 170.3, 170.1, 170.03, 169.99, 169.2, 169.94, 169.93 (9 $COCH_3$), 156.7 (*a*d, *J* = 37.4 Hz, $NHCOCF_3$), 154.1 ($NHCO_2CH_2CCl_3$), 138.8, 138.6, 138.4, 138.3, 138.0, 137.92, 137.89 (8 C_{Ar}), 128.7, 128.4, 128.3, 128.22, 128.18, 128.1, 127.9, 127.81, 127.79, 127.73, 127.66, 127.6, 127.54, 127.47, 127.1, 127.0 (40 C_{Ar}), 115.6 (*a*d, *J* = 286.9 Hz, $NHCOCF_3$), 102.8 (C-1'), 102.1 (C-1'''), 101.2 (C-1''''), 101.0 (C-1''''), 100.3 (C-1''), 99.0 (C-1), 95.6 (CH_2CCl_3), 80.6 (C-2'''), 79.4 (C-2'), 77.9 (C-3'), 77.2 (C-3''), 76.3, 76.1, 76.0 (C-3''', C-4'''', C-4'', C-4, C-3), 75.3, 75.0 (C-5, C-5'', CH_2Ph, CH_2Ph), 74.3 (CH_2CCl_3), 73.9, 73.6, 73.5, 73.33, 73.26 (6 CH_2Ph), 73.0, 72.5, 72.3 (C-5'''', C-5''', C-5'), 72.1 (C-3''''), 71.0 (C-3'''''), 70.7 (C-5'''''), 69.7, 69.4 (C-4', C-4'''), 69.1 (C-3'''''), 68.6 (C-6'), 68.3 (C-6'', C-6, $OCH_2CH_2N_3$), 67.9 (C-6'''), 66.6 (C-4'''''), 61.5 (C-6''''), 61.4 (C-6'''''), 56.7 (C-2''), 56.2 (C-2''''), 55.4 (C-2), 50.6 ($OCH_2CH_2N_3$), 23.1 ($NHCOCH_3$), 20.8, 20.74, 20.73, 20.69, 20.65, 20.63, 20.61, 20.5 (8 $OCOCH_3$); ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.88 ($NHCOCF_3$); HRMS (ESI^+): m/z calcd for $C_{117}H_{134}Cl_3F_3N_6O_{40}$: 2447.7546 $[M+Na]^+$; found: 2447.6873.

Conclusions

The synthesis of several diverse lactosamine based building blocks from lactosamine hydrochloride was successfully developed. A set of disaccharide blocks bearing different amine protecting groups (Troc, Phth, TFAc, Ac) was prepared either as 2-azidoethyl equipped glycosyl acceptors, or as versatile thioglycoside donors. The availability of a library of lactosamine based building blocks, all synthesised on a multi-gram scale, opens the possibility for glycosylation reactivity testing and constitutes an essential synthetic toolbox for the preparation of similar structures, *e.g.* various lactosamine containing *N*-glycan fragments. Particularly, the work presents a successful example of the use of trifluoroacetamide bearing glycosyl donors in the build-up of LacNAc oligosaccharides, with the best glycosylation yields (>80%) always obtained for this type of glycosyl donor. The reactions with trifluoroacetamide donors were always completely stereoselective (1,2-*trans* linkage) and no oxazoline formation was observed. The strategic assembly of the synthesised set of glycosyl donors and acceptors puts emphasis on the need to tune acceptor reactivity. The developed high yielding methodologies for [2+2] glycosylations were applied to the synthesis of the desired NHTFAc containing tetrasaccharides **1** and **2** and the work on [2+4] glycosylations demonstrates the possibility of further syntheses of larger LacNAc oligosaccharides in an efficient way. The presence of a 2-deoxy-2-trifluoroacetamide tag on the prepared structures constitutes an important tool to allow for future ^{19}F NMR interaction studies with LacNAc binding lectins, *e.g.* galectins, to further the knowledge into the characteristics of the binding interaction, both from a structural and dynamics point-of-view.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We gratefully acknowledge financial support from European Commission's GLYCOPHARM ITN project (contract no. 317297) and Science Foundation Ireland (Grant no. 13/IA/1959).

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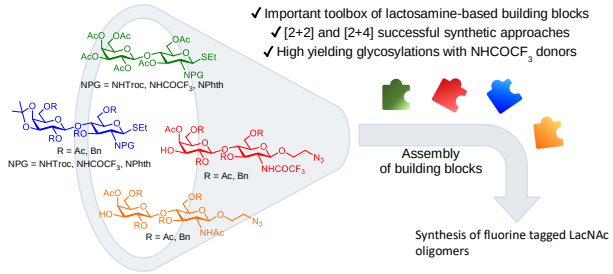

The synthesis of ^{19}F containing LacNAc oligomers through the strategic assembly of a small library of LacNAc/NTFAc disaccharide building blocks