A versatile strategy for the synthesis of *N*-linked glycoamino acids from glycals†‡

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A versatile route for the synthesis of *N*-linked glycoamino acids from readily available glycals is reported. A variety of glycals possessing different carbohydrate templates (mono-, di- and trisaccharide glycals) were shown to undergo a novel iodine catalyzed stereoselective diamination reaction with chloramine-T. Taking advantage of the difference in the reactivity between the anomeric and C2 sulfonamido groups of these diamines **7**, **13**, **15**, **17** and **19**, they could be protected differentially at the C2 and anomeric nitrogen atoms. Thus, chemoselective acetylation of these diamines installed the C2 acetamido group, an essential functionality that plays a crucial role in inducing a β-turn in *N*-linked glycoproteins. Subsequent protection of the anomeric nitrogens of **20a**,**b**,**e** as their Alloc (allyloxycarbonyl) derivatives followed by SmI_2 mediated facile didetosylation afforded **24a–c**. Deprotection of the Alloc group of **24a** and **24c** and coupling of the liberated free amine with a variety of protected amino acids provided *N*-linked glycoamino acids **25** and **27** in high yields. An illustrative synthesis of an *N*-linked glycopeptide **29** is also reported.

Introduction

It has now been well recognized that protein-glycosylation, which is the most complex post-translational modification of proteins, is key to many biological processes such as cell–cell recognition, cell adhesion, cellular differentiation *etc.*[1–4] Significantly, it is the carbohydrate moiety in a glycoprotein that plays a crucial role in protein-folding and transport, inhibiting their proteolysis and improving the biological half-life of proteins.[1–4] Protein glycosylation has also been implicated in various physiological processes including bacterial and viral infection, and hence understanding their structure, stereochemistry and binding ability would enable the development of carbohydrate based therapeutics. However, a major hurdle in this direction is the existence of glycoproteins as a heterogeneous mixture of glycoforms and hence isolation of pure homogeneous glycoproteins/glycopeptides from natural sources has become a formidable task. As a consequence, presently, synthesis (both chemical and enzymatic) of glycoproteins/glycopeptides with a tailored glycosylation pattern seems to be the only solution to obtain well-defined homogeneous materials.[4–6] *N*-Linked glycoproteins **1** (Fig. 1), one among the two forms of protein glycosidation that are naturally found, typically possess a core pentasaccharide moiety which is *always* bound to the side chain of an asparagine amino acid of the protein moiety *via* an *N*-glycosidic linkage. It has also been established that the acetamido group at C2 position and the anomeric β-stereochemistry of **1** are decisive in ensuring a well-defined β-turn in the peptide backbone of *N*-linked glycoproteins.[7]

N-Linked glycopeptides can be readily accessed through a solid phase peptide synthesis where pre-formed glycosyl amino acid building blocks are employed in a step-wise assembly of peptides.[6,8] While this process provides the opportunity for automated synthesis, non-availability of glycosyl amino acid building blocks with complex oligosaccharide side chains, however, is often a matter of

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† This paper is dedicated to Professor Binne Zwanenburg on the occasion of his 73rd birthday.

‡ Electronic supplementary information (ESI) available: Synthesis and detailed characterization of compounds **7c**, **7d**, **13a**, **13b**, **20c**, **20c**, **20d**, **23e**, **24b**, **24d**, **25c**, **25d** and **27c** and copies of ^{1}H and ^{13}C NMR spectra of all compounds. See DOI: 10.1039/b712841j

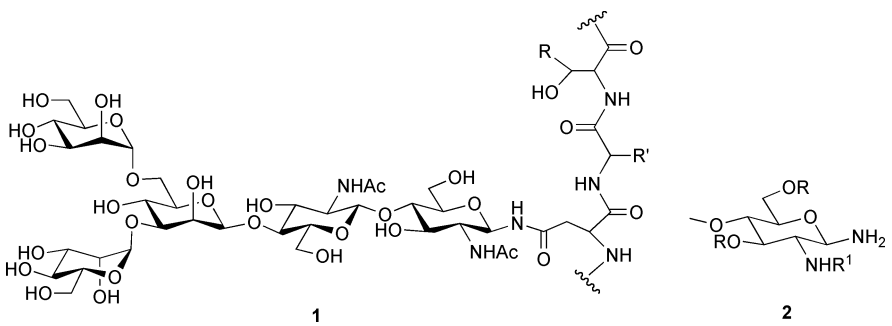


Fig. 1 Examples of an *N*-linked glycoprotein containing the pentasaccharide core **1** and a 2-amino-β-glycosylamine **2**.

concern in this strategy. A convergent approach in which a complex oligosaccharide is directly coupled to a peptide through the anomeric nitrogen provides a very flexible alternative to the former strategy.[9–11] 2-Amino-β-glycosylamines, such as **2** (Fig. 1), serve as the basic carbohydrate building blocks in the convergent synthesis of *N*-linked glycoproteins/glycopeptides. Literature strategies for the synthesis of 2-amino-β-glycosylamines such as Kochetkov's amination and its modification,[12,13] reduction of 2-acetamido glycosyl azides,[10,14] reductive cyclization of δ-hydroxynitriles[15] all rely on the extensive synthetic modifications of D-glucosamine (2-amino-2-deoxy glucose) or its derivatives by way of introducing the second amino functionality at the anomeric position. While 2-amino derivatives of monosaccharides are easily accessible, it is not the case with complex oligosaccharides. Since glycals of mono-, di-, tri- and oligosaccharides are readily available and/or easily prepared, strategies that introduce two amino functionalities on to the double bond of a glycal moiety have significant synthetic advantages. Notable among them are (a) Danishefsky's iodosulfonamidation followed by azidation;[16] (b) Finney's dipolar cycloaddition–photochemical reaction;[17] (c) Nicolaou's synthesis of 2-azido mannosylamine using Burgess reagent;[18] one-pot synthesis of 2-acetamido glycosyl azides by Gin;[19] (e) $Mn(OAc)_3$ catalyzed direct diazidation of glycals.[20] Some of these protocols suffer from drawbacks such as protecting group intolerance, lack of substrate-generality and stereoselectivity, need for special reaction conditions and use of hazardous chemicals such as azides. Recently, we have briefly communicated our research work on a facile and mild *one-pot* stereoselective diamination of a variety of glycals using chloramine-T in presence of iodine as a catalyst and demonstrated the synthetic scope of these diamines with an illustrative synthesis of an *N*-linked glycoamino acid **25a**.[21] Subsequently, we have explored the efficacy of our methodology and successfully realized the stereoselective synthesis of a variety of *N*-linked glycoamino acids including glycosylasparagines in high yields. We have also extended this methodology for a facile synthesis of *N*-Ala-Asp linked glycopeptide. We herein describe a full account of our research findings along with a plausible mechanism for one-pot diamination of glycals.

Results and discussion

Glycal aziridines such as **4** are highly unstable due to the presence of the ring oxygen atom and are opened up immediately in the presence of a nucleophile.[17,22] Our quest for a simple and general synthesis of 2-amino-β-glycosylamines prompted us to take advantage of their instability and hence, we expected that under suitable aziridination conditions and in the presence of an appropriate nitrogen source, the unstable glycal aziridines obtained from glycals **3** could be opened up, in a domino process, by the nucleophilic amino reagent itself, to afford 2-amino glycosylamines such as **5**, directly in one-pot (Fig. 2). After extensive experimentation, we successfully realized our

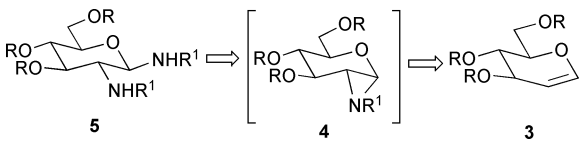
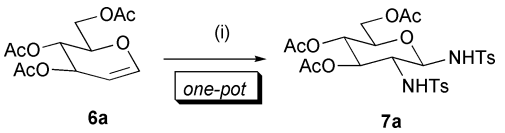


Fig. 2 Retro-synthetic route for diamination of glycals.

hypothesis, when we treated tri-*O*-acetyl-D-glucal **6a** with 15 mol% of iodine and 2.3 eq. of chloramine-T.[23–25] The expected diamine **7a** was obtained in 69% yield as a single diastereomer having the same stereochemistry (β-D-gluco configuration) as in naturally occurring *N*-linked glycoproteins (Scheme 1). The stereochemistry of **7a** was established from detailed ^{1}H-NMR studies.[21]



Scheme 1 Iodine catalyzed reaction of chloramine-T with tri-*O*-acetyl-D-glucal **6a**. *Reagents and conditions*: (i) chloramine-T (2.3 eq.), I_2 (15 mol%), CH_3CN, 0 °C, 14 h, 69%.

A plausible mechanism for the formation of **7a** from **6a** is depicted in Fig. 3. Electrophilic attack of iodine (from the iodine–chloramine-T complex **8**)[23] on to the double bond of **6a**, exclusively from the β-face, might provide the iodonium ion **9**. Anionic opening of the iodonium ion by the nucleophilic nitrogen atom would then lead to intermediate **10**, in which the C2 iodo and anomeric *N*-chloro sulfonamido groups are properly oriented (anti-periplanar) for an aziridine formation **11**, which in fact would very readily be facilitated by the iodide ion present in the medium. S_N2 type anionic ring opening of the aziridine **11** by another molecule of chloramine-T from the β-face would then afford the diamine **7a**. Alternatively, opening of the aziridine ring of **11** by the lone pair of electrons on the ring oxygen atom to afford an oxocarbenium ion followed by nucleophilic attack by another molecule of chloramine-T from the β-face would also afford **7a**. The iodine monochloride (ICl) generated during this reaction would serve as a further source of iodonium ion and hence only a catalytic amount of iodine is required for the reaction. This was further supported from the fact that this reaction also works well with stoichiometric amount ICl.

Success of our initial results prompted us to investigate the diamination reaction with a variety of glycals possessing different carbohydrate templates. As can be seen from Table 1, in all the cases, the reaction proceeded smoothly affording the corresponding diamines in good to moderate yields. The synthetic advantages of our methodology are: (i) while the literature methodologies of introducing two nitrogen functionalities onto the double bond of glycals are protecting group specific, this reaction does not depend on the nature of the protecting group and works well with both ester as well as ether protected substrates (entries 1–8); (ii) the reaction conditions are mild and do not require special experimentation; (iii) reagents are easily available and non-hazardous; (iv) the reaction can be performed on a large scale without loss in yield. Synthetically more rewarding is the facile transformation of disaccharide glycals **14a–b**,[26] **16**[26] and even a trisaccharide glycal **18**[26] to their corresponding disulfonamides in high yields. Among the various carbohydrates used, the maximum yield (79%) obtained from the diamination of the complex trisaccharide glycal **18** deserves special mention.

In general, while these disulfonamides should prove to be versatile synthetic intermediates in carbohydrate chemistry, their transformation into C2-acetamido-β-glycosylamines, such as **22** (or their stable equivalents), provides the vital glycodomain for the convergent synthesis of *N*-linked glycoamino acids and

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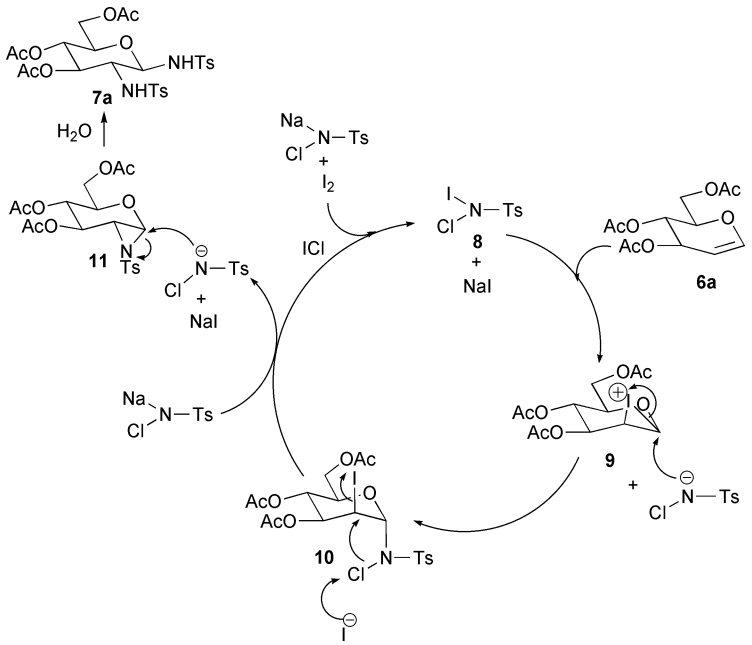
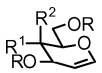
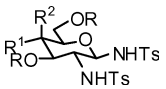
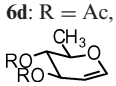
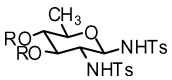
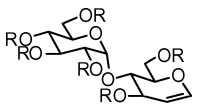
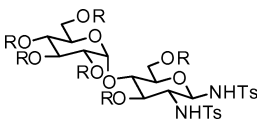
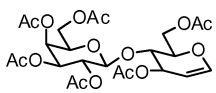
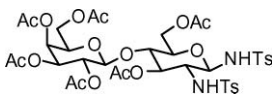
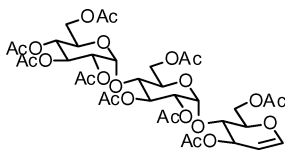
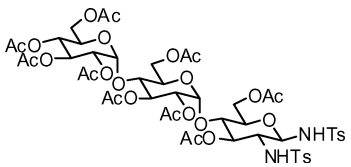


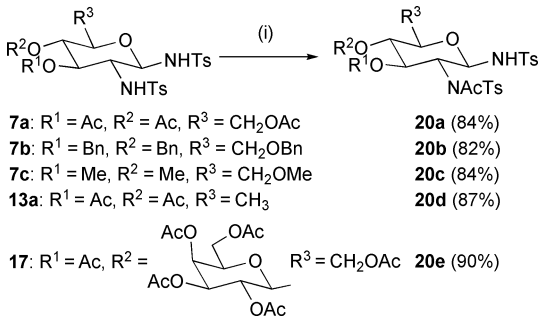
Fig. 3 Proposed mechanism for one-pot diamination of glycals.

Table 1 Iodine catalyzed one-pot disulfonamidation of glycals with chloramine-T[a]

Entry	Starting material	Product	Time/h	Yield (%)[b]
				
1	**6a**: R = Ac, R^1 = OAc, R^2 = H	**7a**	14	69
2	**6b**: R = Bn, R^1 = OBn, R^2 = H	**7b**	13	57
3	**6c**: R = Me, R^1 = OMe, R^2 = H	**7c**	13	60
4	**6d**: R = Ac, R^1 = H, R^2 = OAc	**7d**	72[c]	38[d]
				
5	**12a**: R = Ac[e]	**13a**	14	63
6	**12b**: R = Me[e]	**13b**	14	60
				
7	**14a**: R = Ac[f]	**15a**	96	65[g]
8	**14b**: R = Bn[f]	**15b**	96	51[g,h]
				
9	**16**[f]	**17**	96	71[g]
				
10	**18**[f]	**19**	100	79[g]

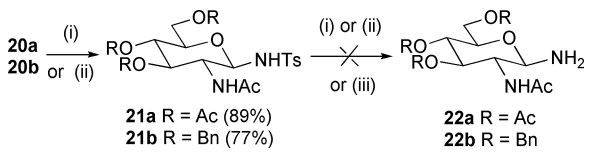
[a] Unless otherwise mentioned, all the reactions were performed at 0 °C using 2.3 eq. of chloramine-T and 15 mol% of iodine in acetonitrile. [b] Isolated yield after column chromatography. [c] The reaction was incomplete. [d] Yield based on recovered starting material; isolated yield 21%. [e] For the synthesis of glycals **12** see ref. 27. [f] For the synthesis of glycals **14**, **16** and **18** see ref. 26. [g] 3.0 eq. of chloramine-T and 20 mol% of iodine were used. [h] Mixture of diastereomers, at 0 °C dr was ~1 : 1 and at −10 °C dr was ~ 4 : 1.

N-linked glycopeptides. For instance, synthesis of **22a** from **7a** requires incorporation of an acetyl group exclusively at the C2 nitrogen followed by didetosylation. When acetylation of **7a** was attempted using acetic anhydride (2 eq.) in presence of DMAP (1 eq.) and pyridine, we were pleasantly surprised to note that acetylation occurred chemoselectively at C2 nitrogen to afford monoacetylated compound **20a** in 84% yield (Scheme 2) and the anomeric nitrogen remained unaffected even with an excess of acetic anhydride (up to 5 eq.) and prolonged reaction time. This was confirmed from the splitting pattern of the H-2 proton in the ^{1}H-NMR spectrum of the product obtained which resonated at δ 4.29 as triplet with $J = 9.0$ Hz due to its coupling with H-1 and H-3. Also, its splitting pattern remained unchanged on exchange with D_2O. On the other hand, the H-2 proton of starting diamine **7a** appeared at δ 3.40 as quartet with $J = 9.0$ Hz due to its coupling with H-1, H-3 and N*H* protons. Even though it may be rationalized that the selective acetylation is due to poor nucleophilicity of the anomeric nitrogen (as compared to the C2 nitrogen) dictated by the electron withdrawing ring oxygen atom, to our knowledge such a selectivity has no precedence. Further, this selective acetylation assumes enormous synthetic significance since an acetamido group at C2 position is an essential functionality of *N*-linked glycopeptides.[7] A variety of other disulfonamides **7b–c**, **13a** and **17** also underwent this selective acetylation to afford the corresponding products **20b–e** in very high yields (Scheme 2)



Scheme 2 Chemoselective acetylation of disulfonamides. *Reagents and conditions*: (i) Ac_2O (2 eq.), DMAP (1 eq.), pyridine, rt, 24 h.

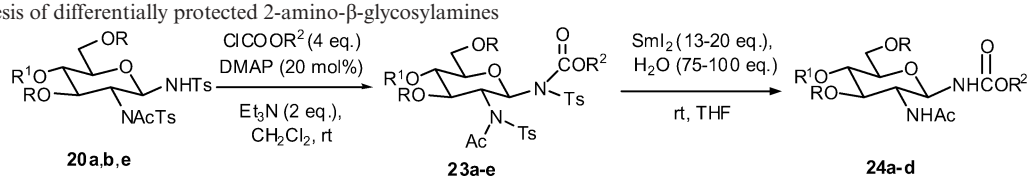
In order to obtain the C2-acetamido-β-glycosylamines **22**, the carbohydrate moieties for *N*-linked glycoamino acids and *N*-linked glycopeptides, didetosylation of compounds **20** was necessary and since they were found to be extremely sensitive to common acidic or basic desulfonating reagents, judicial choice of the reagent was very crucial. Attempted detosylation of **20a** and **20b** with SmI_2 (a mild reagent) in presence of water or HMPA as a co-solvent,[28] afforded **21a** and **21b** respectively wherein the tertiary sulfonamide group at C2 was deprotected while leaving the anomeric sulfonamide group intact (Scheme 3). Subsequent attempts to detosylate **21a** and **21b** using a large excess of the reagent or step-wise detosylation of **20a** and **20b** to obtain **22a** and **22b** were in vain. Consequently, it appeared that protection of the anomeric nitrogen of **20** before detosylation was essential. After several unsuccessful attempts with various reagents, we were finally able to protect the anomeric nitrogen of **20** as their carbamates. Thus, a variety of carbamates **23a–e** were prepared by treating compounds **20a**,**b**,**e** with 4 eq. of alkoxycarbonyl chloride in presence of DMAP and Et_3N (Table 2).

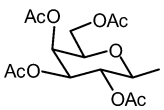


Scheme 3 Attempted synthesis of C2-acetamido glycosylamines. *Reagents and conditions*: (i) SmI_2 (8.5 eq.), H_2O (50 eq.), rt, THF; (ii) SmI_2 (5–8.5 eq.), HMPA (23–46 eq.), rt, THF; (iii) SmI_2–DMPU.

On exposure to SmI_2–water, these carbamates **23a–d** underwent a very facile didetosylation affording **24a–d** in high yields (Table 2). It was found that the carbamates of benzyl protected sugars **23b** and **23d** are quite unstable during purification by column chromatography over silica gel, and hence were subjected to didetosylation in the presence of SmI_2–H_2O without purification to obtain **24b** and **24d** respectively in high yields. Unlike the free glycosamines **22** that were reported to be unstable,[11,13,29] the carbamates **24a–d** are quite stable with a long shelf life and thus may serve as their stable synthetic equivalents. Since deprotection of Alloc groups under very mild and neutral conditions is

Table 2 Synthesis of differentially protected 2-amino-β-glycosylamines



Entry	Compd	R	R^1	Product	R^2	Time/h	Yield^a (%)	Compd	Time/h	Yield^a (%)
1	**20a**	Ac	Ac	**23a**	Allyl	9	79	**24a**	1	90
2	**20b**	Bn	Bn	**23b**	Allyl	12	60^b	**24b**	1	78
3	**20e**	Ac		**23c**	Allyl	12	75	**24c**	1	88
4	**20b**	Bn	Bn	**23d**	Et	6	67^b	**24d**	0.5	85
5	**20a**	Ac	Ac	**23e**	Et	6	75	—	—	—^{c}

^{a} Isolated yield after column chromatography. ^{b} Crude yield, without isolation has been taken up to the next step. ^{c} Detosylation reaction not tried.

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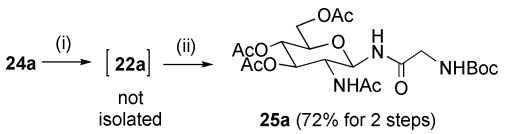
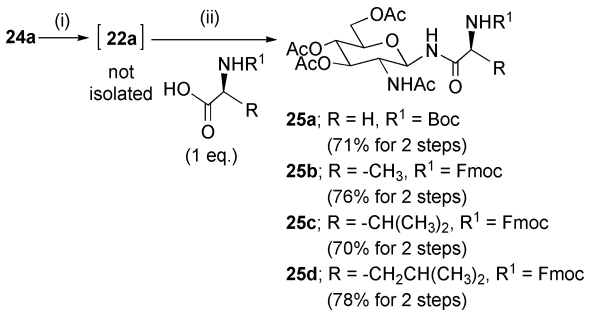
well documented in literature,[13,30] we preferentially attempted the deprotection of Alloc derivatives **24a–c** rather than the ethoxycarbonyl derivative **24d**. Thus, compound **24a** was found to undergo a facile deprotection with a catalytic amount of $Pd[(PPh_3)]_4$ in presence of Et_2NH to afford the free amine **22a** (*vide* TLC) which without isolation was successfully coupled with Boc-glycine in presence of DCC and DMAP to obtain the *N*-linked glycoamino acid **25a** in 72% yield (for two steps) (Scheme 4). Even though the coupling of incipient free amine **22a** with Boc-glycine proceeded smoothly, requirement of an excess of the amino acid (1.5 eq.) posed a serious setback especially during the synthesis of complex *N*-linked glycoamino acids using expensive and/or synthetically precious amino acids. Later, we have identified that use of HOBt as an auxiliary nucleophile in place of DMAP circumvents this problem; the coupling reaction could be efficiently realized with just equimolar amounts of the amino acid and DCC. Using this procedure compound **25a** was obtained from **24a** in almost the same yield as earlier (71% for two steps) (Scheme 5). This two-step (one-pot) synthesis of *N*-linked glycoamino acid from **24a** was successful with a variety of protected amino acids (Fmoc-alanine, Fmoc-valine and Fmoc-leucine), the corresponding *N*-linked glycoamino acids **25b–d** were obtained in high yields (Scheme 5).



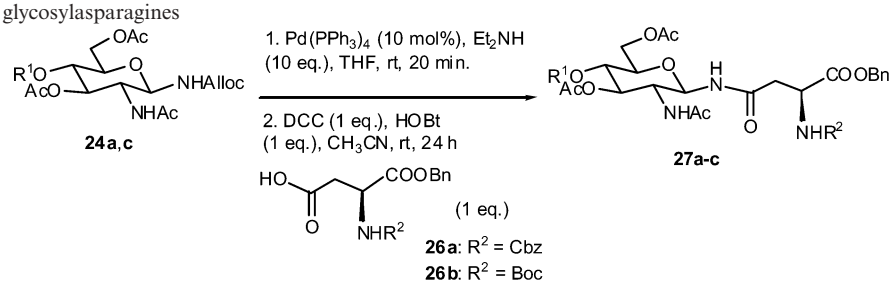
Scheme 4 Deprotection of **24a** and *in situ* DCC–DMAP mediated coupling with Boc-glycine. *Reagents and conditions*: (i) $Pd(PPh_3)_4$ (10 mol%), Et_2NH (10 eq.), rt, THF, 20 min; (ii) DCC (1.8 eq.), DMAP (1.5 eq.), Boc-glycine (1.5 eq.), rt, CH_3CN, 12 h.

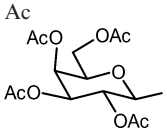
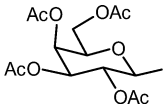


Scheme 5 Deprotection of **24a** and *in situ* DCC–HOBt mediated coupling with protected amino acids. *Reagents and conditions*: (i) $Pd(PPh_3)_4$ (10 mol%), Et_2NH (10 eq.), THF, 20 min; (ii) DCC (1 eq.), HOBt (1 eq.), rt, CH_3CN, 16 h.

Since all the naturally occurring *N*-linked glycoproteins possess carbohydrates that are invariably *N*-linked to the side chain of asparagine, we next attempted and succeeded in synthesizing protected glycosylasparagines using the same strategy as above. Thus, glucosylasparagine **27a** was obtained in 75% yield from **24a** in two steps (Table 3) whose spectral data are identical with the literature values.[31–34] This also establishes that the anomeric β-stereochemistry remained intact through out the entire synthetic sequence. The methodology was also successfully extended to the disaccharide derivative **24c** to obtain the *N*-linked glycoamino acids **27b** and **27c** in good yields (Table 3). It has been observed by us that while with Boc-protected aspartic acid **26b**, only a single diastereomer **27b** with β-anomeric stereochemistry was obtained, Cbz-protected aspartic acid **26a** afforded **27c** as a mixture of anomers in a ratio of 1 : 0.8.[35] Lowering of temperature, however, did not bring about any significant change in the anomeric ratio.

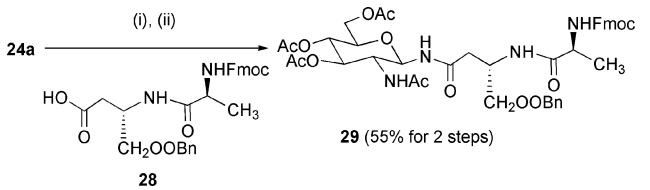
Table 3 Synthesis of glycosylasparagines



Entry	Reactant	R^1	Product	R^2	Yield (%)[a] (for two steps)
1	**24a**	Ac	**27a**	Cbz	75
2	**24c**		**27b**	Boc	64
3	**24c**		**27c**	Cbz	73[b]

[a] Isolated yield after column chromatography. [b] Mixture of diastereomers obtained with $dr \sim 1 : 0.8$.

The efficacy of our methodology was further demonstrated with an illustrative synthesis of an *N*-linked glycopeptide **29**. Thus, Alloc deprotection of **24a** followed by coupling of the liberated free amine with Fmoc-Ala-Asp-OBn **28** afforded **29** in 55% yield (Scheme 6). The success of the reaction clearly favors that the methodology reported in this manuscript could be readily adapted for the synthesis of more complex *N*-linked glycopeptides.



Scheme 6 Synthesis of an *N*-Ala-Asp linked glycopeptide **29**. *Reagents and conditions*: (i) $Pd(PPh_3)_4$ (10 mol%), Et_2NH (10 eq.), THF, rt, 20 min; (ii) **28** (1 eq.), DCC (1 eq.), HOBt (1 eq.), CH_3CN, rt, 24 h.

Conclusions

In conclusion, we have developed a versatile strategy for the synthesis of *N*-linked glycoamino acids from readily available glycals with complete stereocontrol in all steps. Our methodology describes an innovative but yet a simple way of obtaining complex glycosylamines required for subsequent coupling with amino acids/peptides. Synthesis of an *N*-linked glycopeptide **29** illustrates the accessibility of our methodology to such compounds. The simplicity of the methodology coupled with the ready availability of starting materials and stereoselectivity are likely to contribute significantly to the research developments in the area of glycobiology.

Experimental

General

All solvents were purified using standard procedures. Chloramine-T purchased from Aldrich or Fluka Chemicals only was used for consistency of results. Thin layer chromatography (TLC) was performed on Merck silica gel pre-coated on aluminium plates. Flash column chromatography was performed on 230–400 mesh silica gel. Optical rotations were recorded on an Autopol II or Autopol V (Rudolph Research Flanders, New Jersey) instrument. All the rotations were measured at 589 nm (sodium D′ line). Melting points of the compounds are uncorrected. IR spectra were taken within the range 4000–400 cm^{-1} as KBr pellets on a Nicolet (Madison, USA) FT-IR spectrophotometer (Model Protege 460). All the ^1H and ^{13}C NMR spectra were recorded on a 300 M Bruker Spectrospin DPX FT-NMR. Chemical shifts are reported as δ values (ppm) relative to internal standard Me_4Si. Elemental analyses were performed on a Perkin Elmer 2400 series II analyzer. Mass spectra were recorded using Waters Micro Mass Q-TOF instrument.

General procedure for diamination of glycals

To a 0 °C stirred suspension of glycal (1 eq.), chloramine-T (2.3 eq.) in acetonitrile taken in a dried 100 mL round-bottomed flask, was added a catalytic amount of iodine (15 mol%) and the reaction mixture was allowed to stir at 0 °C until the reaction was complete (as indicated by TLC). The reaction mixture was diluted with $CHCl_3$ and stirred for an additional 5 min. It was then transferred into a separatory funnel containing aq. sodium thiosulfate solution and shaken vigorously. The organic layer was separated and the remaining aqueous layer was washed with more $CHCl_3$. The combined organic layer was washed with brine solution and dried over anhydrous sodium sulfate and concentrated. The product was purified by flash chromatography.

3,4,6-Tri-*O*-acetyl-1,2-dideoxy-1,2-di-(*p*-toluenesulfonamido)-β-D-glucopyranose 7a. Compound **7a** (7.76 g, 69%) was obtained as a white solid from the reaction of tri-*O*-acetyl-D-glucal **6a** (5.00 g, 18.38 mmol) with chloramine-T (11.91 g, 42.27 mmol) and iodine (0.701 g, 2.76 mmol) in CH_3CN (50 mL) in 14 h as per the general procedure. Flash chromatography of the crude reaction mixture was performed with hexane : ethyl acetate (2 : 1). Mp 191–192 °C (from hot benzene); $[\alpha]_D^{28}$ +27.2 (*c* 1.12 in $CHCl_3$) (Found: C, 50.97; H, 5.24; N, 4.78. $C_{26}H_{32}N_2O_{11}S_2$ requires: C, 50.97; H, 5.26; N, 4.57%); ν_{max} (KBr)/cm^{-1} 3286, 2927, 1745, 1599, 1457, 1368, 1329, 1242, 1162, 1091, 1072, 1044; δ_H (300 MHz, $CDCl_3$) 7.82 (2 H, d, *J* 8.2), 7.71 (2 H, d, *J* 8.2), 7.32 (2 H, d, *J* 8.0), 7.29 (2 H, d, *J* 8.0), 6.35 (1 H, d, *J* 7.4, N*H*, exchangeable with D_2O), 5.34 (1 H, d, *J* 8.1, N*H*, exchangeable with D_2O), 4.97–4.87 (2 H, m), 4.67 (1 H, dd, *J* 8.7 and 7.8), 4.14 (1 H, dd, *J* 12.3 and 4.8), 3.96 (1 H, dd, *J* 12.3 and 1.8), 3.67–3.63 (1 H, m), 3.40 (1 H, q, *J* 9.0), 2.43 (3 H, s), 2.42 (3 H, s), 2.06 (3 H, s), 1.97 (3 H, s), 1.48 (3 H, s); δ_C (75 MHz, $CDCl_3$) 171.1, 170.5, 169.4, 143.8, 143.6, 138.2, 137.6, 129.8, 129.4, 127.2, 127.1, 83.6, 72.9, 68.3, 61.7, 56.6, 21.4, 20.6, 20.5, 19.9.

3,4,6-Tri-*O*-benzyl-1,2-dideoxy-1,2-di-(*p*-toluenesulfonamido)-β-D-glucopyranose 7b. Compound **7b** (5.18 g, 57%) was obtained as a white solid from the reaction of tri-*O*-benzyl-D-glucal **6b** (5.00 g, 12.02 mmol) with chloramine-T (7.79 g, 27.65 mmol) and iodine (0.457 g, 1.80 mmol) in CH_3CN (40 mL) in 13 h as per the general procedure. Flash chromatography of the crude reaction mixture was performed with hexane : ethyl acetate (3 : 1). Mp 124 °C (from hot benzene); $[\alpha]_D^{28}$ +18.3 (*c* 2.29 in acetone) (Found: C, 65.18; H, 5.79; N, 4.01. $C_{41}H_{44}N_2O_8S_2$ requires: C, 65.06; H, 5.86; N, 3.70%); ν_{max} (KBr)/cm^{-1} 3266, 2869, 2362, 1456, 1327, 1160, 1090, 1063 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.80 (2 H, d, *J* 8.1), 7.68 (2 H, d, *J* 8.1), 7.29–7.18 (13 H, m), 7.08 (2 H, d, *J* 8.1), 7.04–6.98 (4 H, m), 6.21 (1 H, d, *J* 7.8, N*H*, exchangeable with D_2O), 4.86 (1 H, d, *J* 7.7, N*H*, exchangeable with D_2O), 4.63–4.58 (3 H, m), 4.52 (1 H, d, *J* 11.4), 4.47–4.41 (2 H, m), 4.30 (1 H, d, *J* 12.1), 3.59 (2 H, dd, *J* 9.1 and 8.7), 3.43–3.38 (3 H, m), 3.30 (1 H, ddd, *J* 9.3, 8.7 and 8.4), 2.36 (3 H, s), 2.30 (3 H, s); δ_C (75 MHz, $CDCl_3$) 143.8, 143.6, 139.2, 138.4, 138.2, 137.9, 130.0, 129.7, 129.3, 128.8, 128.7, 128.5, 128.1, 127.9, 127.5, 84.4, 82.5, 78.7, 76.6, 75.5, 75.0, 74.0, 68.7, 58.4, 21.9; HRMS (ESI): $C_{41}H_{44}N_2O_8S_2Na$ $[M + Na]^+$ calcd: 779.2437, found 779.2439.

4-*O*-[2,3,4,6-Tetra-*O*-acetyl-(α-D-glucopyranosyl)]-3,6-di-*O*-acetyl-1,2-dideoxy-1,2-di-(*p*-toluenesulfonamido)-β-D-glucopyranose 15a. In this case 3 eq. of chloramine-T and 20 mol% iodine were used. Compound **15a** (1.00 g, 65%) was obtained as a white solid from the reaction of hexa-*O*-acetyl-D-maltal **14a**[26] (1.00 g, 1.79 mmol) with chloramine-T (1.50 g, 5.34 mmol) and iodine (0.09 g, 0.36 mmol) in CH_3CN (6 mL) in 96 h as per the general

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procedure. Flash chromatography of the crude reaction mixture was performed with hexane : ethyl acetate (1 : 1). Mp 168 °C (from hot benzene); $[\alpha]_D^{28}$ +68.1 (*c* 0.52, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3297, 2926, 1749, 1457, 1333, 1234, 1163, 1088, 1046; δ_H (300 MHz, $CDCl_3$) 7.80 (2 H, d, *J* 7.8), 7.72 (2 H, t, *J* 7.8), 7.30 (4 H, m), 6.19 (1 H, d, *J* 7.5, N*H*, exchangeable with D_2O), 5.30–5.25 (2 H, m), 5.05–4.94 (3 H, m), 4.82 (1 H, dd, *J* 10.2 and 3.6), 4.63 (1 H, t, *J* 8.5), 4.26–4.00 (4 H, m), 3.89–3.81 (2 H, m), 3.60 (1 H, d, *J* 9.6), 3.38 (1 H, q, *J* 9.0), 2.43 (6 H, s), 2.10 (3 H, s), 2.08 (3 H, s), 2.01 (3 H, s), 1.97 (6 H, s), 1.59 (3 H, s); δ_C (75 MHz, $CDCl_3$) 171.5, 170.4, 170.3, 170.2, 169.8, 169.3, 143.9, 143.5, 138.1, 137.4, 129.8, 129.3, 127.1, 95.3, 83.4, 75.1, 73.3, 72.7, 69.8, 69.2, 68.3, 67.8, 62.5, 61.3, 57.0, 21.4, 20.6, 20.5, 20.4, 20.3; HRMS (ESI): $C_{38}H_{49}N_2O_{19}S_2$ [M + H]$^+$ calcd: 901.2371, found 901.2374.

4-*O*-[2,3,4,6-Tetra-*O*-benzyl-(α-D-glucopyranosyl)]-3,6-di-*O*-benzyl-1,2-dideoxy-1,2-di-(*p*-toluenesulfonamido)-β-D-glucopyranose 15b. In this case 3 eq. of chloramine-T and 20 mol% iodine were used. Compound **15b** (0.098 g, 51%) was obtained as a white solid from the reaction of hexa-*O*-benzyl-D-maltal **14a**[26] (0.138 g, 0.163 mmol) with chloramine-T (0.138 g, 0.489 mmol) and iodine (0.008 g, 0.033 mmol) in CH_3CN (3 mL) in 96 h as per the general procedure. Flash chromatography of the crude reaction mixture was performed with hexane : ethyl acetate (2 : 1). Diastereomeric mixtures were obtained in dr = 1 : 1 at 0 °C and dr = 4 : 1 at −10 °C. Mp 42 °C (from hot benzene) for diastereomeric mixture 4 : 1; $[\alpha]_D^{28}$ +18.3 (*c* 0.92 in $CHCl_3$) for diastereomeric mixture 4 : 1; ν_{max} (KBr)/cm^{-1} 3281, 3032, 2917, 2867, 1454, 1331, 1159, 1085; δ_H (300 MHz, $CDCl_3$) 7.73 (2 H, d, *J* 8.3), 7.70 (2 H, d, *J* 8.3), 7.32–7.08 (34 H, m), 6.24 (1 H, d, *J* 9.2, N*H*, exchangeable with D_2O), 5.47 (1 H, d, *J* 8.6, N*H*, exchangeable with D_2O), 4.89–4.23 (14 H, m), 3.92–3.87 (2 H, m), 3.76–3.28 (10 H, m), 2.35 (3 H, s), 2.28 (3 H, s) for major diastereomer; δ_C (75 MHz, $CDCl_3$) 171.5, 143.8, 143.5, 138.9, 138.7, 138.5, 138.4, 138.0, 137.9, 137.6, 130.0, 129.6, 128.8, 128.7, 128.4, 128.2, 128.1, 128.0, 127.9, 127.7, 127.5, 97.7, 83.5, 82.5, 80.0, 77.8, 76.0, 75.4, 73.7, 73.6, 72.6, 72.5, 71.5, 69.8, 68.2, 56.7, 21.8, 21.7 for major diastereomer; HRMS (ESI): $C_{68}H_{72}N_2O_{13}S_2Na$ [M + Na]$^+$ calcd: 211.4374, found 1211.4384.

4-*O*-[2,3,4,6-Tetra-*O*-acetyl-(β-D-galactopyranosyl)]-3,6-di-*O*-acetyl-1,2-dideoxy-1,2-di-(*p*-toluenesulfonamido)-β-D-glucopyranose 17. In this case 3 eq. of chloramine-T and 20 mol% of iodine were used. Compound **17** (6.23 g, 71%) was obtained as a white solid from the reaction of hexa-*O*-acetyl lactal **16**[26] (5.46 g, 9.75 mmol) with chloramine-T (8.24 g, 29.25 mmol) and iodine (0.495 g, 1.95 mmol) in CH_3CN (50 mL) in 96 h as per the general procedure. Flash chromatography of the crude reaction mixture was performed with hexane : ethyl acetate (1 : 1). Mp 107 °C (from hot benzene); $[\alpha]_D^{28}$ +17.7 (*c* 1.21 in $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3479, 3279, 2927, 1751, 1456, 1371, 1338, 1227, 1162, 1048; δ_H (300 MHz, $CDCl_3$) 7.80 (2 H, d, *J* 8.12), 7.71 (2 H, t, *J* 8.1), 7.34 (2 H, t, *J* 7.2), 7.30 (2 H, t, *J* 8.5), 6.36 (1 H, d, *J* 6.9, N*H*, exchangeable with D_2O), 5.32 (1 H, br s), 5.06–4.81 (4 H, m), 4.54 (1 H, dd, *J* 8.4 and 7.9), 4.37 (1 H, d, *J* 7.8), 4.33 (1 H, m), 4.11–3.92 (3 H, m), 3.82–3.80 (1 H, m), 3.65–3.56 (2 H, m), 3.35 (1 H, q, *J* 9.4), 2.44 (6 H, s), 2.11 (3 H, s), 2.10 (3 H, s), 2.04 (3 H, s), 2.03 (3 H, s), 1.95 (3 H, s), 1.57 (3 H, s); δ_C (75 MHz, $CDCl_3$) 171.3, 170.0, 169.1, 144.1, 143.6, 137.3, 129.9, 129.4, 127.2, 100.8, 83.7, 75.7, 73.9, 72.9, 70.8, 70.6, 69.0, 66.6, 61.7, 60.7, 60.7, 56.8, 21.5, 20.5, 20.2; HRMS (ESI): $C_{38}H_{48}N_2O_{19}S_2Na$ [M + Na]$^+$ calcd: 923.2190, found 923.2173.

4-*O*-{[2,3,4,6-Tetra-*O*-acetyl-(α-D-glucopyranosyl)]-2,3,6-tri-*O*-acetyl-(α-D-glucopyranosyl)}-1,2-dideoxy-1,2-di-(*p*-toluenesulfonamido)-β-D-glucopyranose 19. In this case 3 eq. of chloramine-T and 20 mol% of iodine were used. Compound **19** (0.110 g, 79%) was obtained as a white solid from the reaction of nona-*O*-acetyl maltotrial **18**[26] (0.100 g, 0.118 mmol) with chloramine-T (0.100 g, 0.354 mmol) and iodine (0.006 g, 0.024 mmol) in CH_3CN (50 mL) in 100 h as per the general procedure. Flash chromatography of the crude reaction mixture was performed with hexane : ethyl acetate (1 : 1). Mp 108–110 °C (from CH_2Cl_2–hexane); $[\alpha]_D^{28}$ +80.9 (*c* 0.46 in $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3483, 3283, 2959, 1752, 1448, 1375, 1337, 1232, 1162, 1039; δ_H (300 MHz, $CDCl_3$) 7.80 (2 H, d, *J* 7.8), 7.72 (2 H, d, *J* 7.6), 7.34–7.30 (4 H, m), 6.19 (1 H, d, *J* 7.5, -N*H* exchangeable with D_2O), 5.38–5.31 (3 H, m), 5.17–5.07 (2 H, m), 5.04 (1 H, d, *J* 7.9, -N*H* exchangeable with D_2O), 4.99–4.70 (3 H, m), 4.63 (1 H, t, *J* 8.2), 4.46 (1 H, d, *J* 12.2), 4.19–3.80 (9 H, m), 3.65 (1 H, m), 3.36 (1 H, q, *J* 8.5), 2.44 (3 H, s), 2.43 (3 H, s), 2.14 (3 H, s), 2.10 (3 H, s), 2.03 (9 H, s), 2.00 (3 H, s), 1.98 (3 H, s), 1.94 (3 H, s), 1.56 (3 H, s); δ_C (75 MHz, $CDCl_3$) 171.6, 170.5, 170.3, 169.8, 169.6, 169.4, 144.1, 143.6, 138.0, 137.2, 129.9, 129.4, 127.2, 95.6, 95.5, 83.4, 75.2, 73.4, 73.3, 72.3, 71.6, 70.1, 70.0, 69.2, 68.9, 68.4, 67.8, 62.6, 62.0, 61.3, 56.9, 21.5, 20.7, 20.5, 20.4; HRMS (ESI): $C_{50}H_{64}N_2O_{27}S_2Na$ [M + Na]$^+$ calcd: 1211.3036 found 1211.3075.

General procedure for chemoselective acetylation of diamine at C2 nitrogen

To an ice cooled solution of a diamine (1 eq.) in pyridine were added acetic anhydride (2 eq.) and DMAP (1 eq.) and the reaction mixture was allowed to warm to room temperature and stirred for 24 h. The colour of the reaction mixture changed from colourless to dark brown. It was then quenched with 10% HCl solution and extracted with ethyl acetate and washed with water. The organic layers were dried over sodium sulfate and concentrated. The product was purified by flash chromatography.

2-*N*-Acetyl-3,4,6-tri-*O*-acetyl-1,2-dideoxy-1,2-di-(*p*-toluenesulfonamido)-β-D-glucopyranose 20a. Compound **20a** (4.20 g, 84%) was obtained as a white crystalline solid by the acetylation of **7a** (4.68 g, 7.64 mmol) using Ac_2O (1.44 mL, 15.28 mmol) and DMAP (0.932 g, 7.64 mmol) in pyridine (8 mL) as per the general procedure. Flash chromatography of the crude reaction mixture was performed with hexane : ethyl acetate (2 : 1). Mp 121 °C (from benzene–hexane); $[\alpha]_D^{28}$ −23.2 (*c* 1.20 in $CHCl_3$) (Found: C, 51.02; H, 5.22; N, 3.90. $C_{28}H_{34}N_2O_{12}S_2$ requires: C, 51.37; H, 5.23; N, 4.28%); ν_{max} (KBr)/cm^{-1} 3226, 2986, 2928, 1754, 1707, 1597, 1462, 1344, 1234, 1167, 1088, 1058; δ_H (300 MHz, $CDCl_3$) 7.93 (2 H, d, *J* 8.2), 7.77 (2 H, d, *J* 8.2), 7.40 (2 H, d, *J* 8.2), 7.28 (2 H, d, *J* 8.1), 5.80–5.71 (3 H, m), 4.99 (1 H, t, *J* 9.5), 4.29 (1 H, t, *J* 9.0), 4.09 (1 H, dd, *J* 12.3 and 4.3), 3.83 (1 H, dd, *J* 12.3 and 2.00), 3.73–3.68 (1 H, m), 2.45 (3 H, m), 2.42 (3 H, s), 2.07 (3 H, s), 2.04 (3 H, s), 1.98 (3 H, s), 1.79 (3 H, s); δ_C (75 MHz, $CDCl_3$) 170.6, 170.5, 170.0, 169.4, 145.7, 143.7, 137.8, 135.8, 130.2, 129.4, 128.3, 127.3, 81.0, 73.1, 69.7, 69.0, 61.7, 60.9, 25.7, 21.6, 21.5, 20.6, 20.5, 20.4.

4-*O*-[2,3,4,6-Tetra-*O*-acetyl-(β-D-galactopyranosyl)]-2-*N*-acetyl-3,6-di-*O*-acetyl-1,2-dideoxy-1,2-di-(*p*-toluenesulfonamido)-β-D-glucopyranose 20e. Compound **20e** (2.82 g, 90%) was obtained as a white solid by the reaction of **17** (3.00 g, 3.33 mmol) using Ac_2O (0.628 mL, 6.66 mmol) and DMAP (0.406 g, 3.33 mmol) in pyridine (6 mL) as per the general procedure. Flash chromatography of the crude reaction mixture was performed with hexane : ethyl acetate (1 : 1). Mp 90 °C (from CH_2Cl_2–hexane); $[\alpha]_D^{28}$ −12.3 (*c* 0.73 in $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3629, 3258, 2982, 1762, 1598, 1496, 1435, 1371, 1239, 1167, 1059; δ_H (300 MHz, $CDCl_3$) 7.94 (2 H, d, *J* 7.8), 7.75 (2 H, d, *J* 7.8), 7.40 (2 H, d, *J* 7.8), 7.27 (2 H, d, *J* 7.8), 5.76–5.69 (2 H, m), 5.51 (1 H, d, *J* 10.3, N*H*, exchangeable with D_2O), 5.33 (1 H, s), 5.06 (1 H, dd, *J* 9.5 and 8.4), 4.92 (1 H, d, *J* 10.3), 4.44 (1 H, d, *J* 7.5), 4.20–3.94 (5 H, m), 3.86–3.67 (3 H, s), 2.46 (3 H, s), 2.43 (3 H, s), 2.13 (3 H, s), 2.07 (6 H, s), 2.05 (3 H, s), 2.02 (3 H, s), 1.95 (3 H, s), 1.90 (3 H, s); δ_C (75 MHz, $CDCl_3$) 170.4, 170.3, 170.0, 169.7, 168.8, 145.6, 143.6, 137.7, 135.7, 130.1, 129.3, 128.2, 127.2, 100.5, 80.8, 76.8, 73.8, 70.9, 70.5, 69.5, 68.9, 66.5, 61.8, 61.0, 60.7, 25.5, 21.5, 21.4, 20.6, 20.5; HRMS (ESI): $C_{40}H_{51}N_2O_{20}S_2$ [M + H]$^+$ calcd: 943.2477, found 943.2465.

General procedure for SmI_2 mediated detosylation

Procedure A. *Using SmI_2 and HMPA*: Powdered samarium metal (5–10 eq.) was added to a flame dried 100 mL three-necked round bottomed flask and further heated under an argon atmosphere. After cooling under an argon atmosphere, dry THF and CH_2I_2 (5–8.5 eq.) were added to it and the reaction flask was sonicated at room temperature. A deep blue colour was obtained in 5 minutes. After 20 min (1 h for large scale preparation), the reaction flask was taken out and starting compound (1 eq.) was added. No colour change was observed. After 5 minutes HMPA (23–46 eq.) was added dropwise under an argon atmosphere and the colour of the reaction mixture started fading and changed to grey black. After 15 minutes a yellow-brown colour was obtained. After completion of the reaction (as indicated by TLC), the reaction mixture was quenched with saturated NH_4Cl solution and extracted with $CHCl_3$. The combined organic layer was washed with water and dried over sodium sulfate and concentrated. Flash chromatography of the resulting residue provided corresponding detosylated compound.

Procedure B. *Using SmI_2 and H_2O*: Powdered samarium metal (5–20 eq.) was added to a flame dried 100 mL three-necked round bottomed flask and further heated under an argon atmosphere. After cooling under an argon atmosphere, dry THF and CH_2I_2 (5–20 eq.) were added to it and the reaction flask was sonicated at room temperature. A deep blue colour was obtained in 5–20 minutes. After 20 min (1 h for large scale preparation), the reaction flask was taken out and starting compound (1 eq.) was added. No colour change was observed. After 5 minutes H_2O (25–100 eq.) was added dropwise under an argon atmosphere and the colour of the reaction mixture started fading and changed to grey black. After 15 minutes a yellow-brown colour was obtained. After 0.5–1 h the reaction was complete (as indicated by TLC). The reaction mixture was quenched with saturated NH_4Cl solution and extracted with $CHCl_3$. The combined organic layer was washed by water and dried over sodium sulfate and concentrated. Flash chromatography of the resulting residue provided corresponding detosylated compound.

2-Acetamido-3,4,6-tri-*O*-acetyl-1,2-dideoxy-1-(*p*-toluenesulfonamido)-β-D-glucopyranose 21a. *Procedure A*: Compound **21a** (0.068 g, 88%) was obtained as a white solid in 30 min from the reaction of **20a** (0.100 g, 0.153 mmol) with 8.5 eq. of SmI_2 (preformed) in dry THF (10 mL) and HMPA (1.22 mL, 7.04 mmol) using general procedure A. Flash chromatography of the crude reaction mixture was performed with hexane : ethyl acetate (1 : 1).

Procedure B: Compound **21a** (0.102 g, 89%) was obtained as a white solid in 25 min. from the reaction of **20a** (0.150 g, 0.23 mmol) with 8.5 eq. of SmI_2 (preformed) in dry THF (10 mL) and degassed water (0.206 g, 11.45 mmol) as per the general procedure B. Flash chromatography of the crude reaction mixture was performed with hexane : ethyl acetate (1 : 1). Mp 160–162 °C (decomp.) (from CH_2Cl_2–hexane); $[\alpha]_D^{28}$ +31.0 (*c* 0.59 in THF); ν_{max} (KBr)/cm^{-1} 3294, 1746, 1658, 1543, 1459, 1377, 1333, 1238, 1157, 1086, 1049; δ_H (300 MHz, $CDCl_3$) 7.76 (2 H, d, *J* 7.8), 7.27 (2 H, d, *J* 7.8), 6.54 (1 H, d, *J* 7.8, N*H*, exchangeable with D_2O), 6.00 (1 H, d, *J* 7.8, N*H*, exchangeable with D_2O), 5.02 (2 H, d, *J* 8.8), 4.72 (1 H, t, *J* 8.7), 4.14–3.97 (3 H, m), 3.65 (1 H, br s), 2.41 (3 H, s), 2.05 (6 H, s), 2.03 (3 H, s), 1.91 (3 H, s); δ_C (75 MHz, $CDCl_3$) 172.4, 171.5, 170.5, 169.3, 143.4, 138.6, 129.3, 127.0, 84.4, 73.0, 72.6, 68.1, 61.9, 53.2, 22.9, 21.5, 20.6; HRMS (ESI): $C_{21}H_{28}N_2O_{10}SNa$ [M + Na]$^+$ calcd: 523.1358, found 523.1362.

2-Acetamido-3,4,6-tri-*O*-benzyl-1,2-dideoxy-1-(*p*-toluenesulfonamido)-β-D-glucopyranose 21b. *Procedure A*: Compound **21b** (0.062 g, yield 77%) was obtained as a white solid in 30 min from the reaction of **20b** (0.100 g, 0.125 mmol) with 5 eq. of SmI_2 (preformed) in dry THF (10 mL) and HMPA (0.500 mL, 2.87 mmol) using general procedure A. Flash chromatography of the crude reaction mixture was performed with hexane : ethyl acetate (1 : 1).

Procedure B: Compound **21b** (0.143 g, 76%) was obtained as a white solid in 30 min from the reaction of **20b** (0.231 g, 0.29 mmol) with 8.5 eq. of SmI_2 (preformed) in dry THF (15 mL) and degassed water (0.261 mL, 14.50 mmol) as per the general procedure B. Flash chromatography of the crude reaction mixture was performed with hexane : ethyl acetate (1 : 1). Mp 160 °C (from CH_2Cl_2–hexane); $[\alpha]_D^{28}$ +11.5 (*c* 0.46 in acetone); ν_{max} (KBr)/cm^{-1} 3242, 3029, 2913, 2868, 1655, 1544, 1454, 1330, 1306, 1155, 1090, 1059; δ_H (300 MHz, $CDCl_3$) 7.74 (2 H, d, *J* 7.8), 7.39–7.14 (17 H, m), 6.62 (1 H, d, *J* 7.2, N*H*, exchangeable with D_2O), 5.00 (1 H, d, *J* 7.5, N*H*, exchangeable with D_2O), 4.80 (2 H, t, *J* 12.3), 4.61–4.42 (4 H, m), 4.31 (1 H, d, *J* 12.3), 3.82 (1 H, q, *J* 9.3), 3.68–3.62 (2 H, m), 3.49–3.38 (3 H, m), 2.33 (3 H, s), 1.71 (3 H, s); δ_C (75 MHz, $CDCl_3$) 172.5, 143.0, 139.0, 138.0, 137.9, 137.8, 129.2, 128.8, 128.5, 128.4, 128.0, 127.6, 127.1, 84.7, 80.8, 78.3, 76.3, 74.9, 74.5, 73.6, 68.4, 53.8, 23.0, 21.4; HRMS (ESI): $C_{36}H_{40}N_2O_7SNa$ [M + Na]$^+$ calcd: 667.2454 found 667.2451.

General procedure for the protection of anomeric nitrogen atom of 20a,b,e as their carbamates

Starting compound (1 eq.) was added to a flame dried 50 mL three-necked round bottomed flask and dissolved in dry CH_2Cl_2 under a N_2 atmosphere. To this, DMAP (20 mol%) and Et_3N (2 eq.) were added and the reaction mixture was cooled in an ice–salt bath. (4 eq.) was injected into the reaction mixture drop-wise.

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After complete addition of alkoxycarbonyl chloride, the reaction mixture was warmed to 30 °C and stirred until the reaction was over (as indicated by TLC). The reaction mixture was quenched with saturated NH_4Cl solution and extracted with $CHCl_3$. The combined organic layers were washed with water and dried over sodium sulfate and concentrated. Flash chromatography of the resulting residue provided corresponding carbamates.

2-*N*-Acetyl-3,4,6-tri-*O*-acetyl-1-*N*-allyloxycarbonyl-1,2-dideoxy-1,2-di-(*p*-toluenesulfonamido)-β-D-glucopyranose 23a. Compound **23a** (2.58 g, 79%) was obtained as a white solid in 9 h from the reaction of **20a** (2.89 g, 4.42 mmol) with DMAP (0.108 g, 0.88 mmol), Et_3N (1.23 mL, 8.84 mmol) and allyloxycarbonyl chloride (1.89 ml, 17.68 mmol) in 10 mL of dry CH_2Cl_2 as per the general procedure described above. Flash chromatography of the crude reaction mixture was performed with hexane : ethyl acetate (3 : 1). Mp 52 °C (from CH_2Cl_2–hexane); $[\alpha]_D^{28}$ −33.4 (*c* 0.64 in $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3029, 2957, 1749, 1708, 1449, 1369, 1235, 1168, 1086, 1054; δ_H (300 MHz, $CDCl_3$) 7.87 (2 H, d, *J* 8.1), 7.76 (2 H, d, *J* 8.1), 7.33 (2 H, d, *J* 8.7), 7.29 (2 H, d, *J* 8.4), 6.76 (1 H, d, *J* 9.3), 5.99 (1 H, t, *J* 9.6), 5.90–5.77 (1 H, m), 5.57 (1 H, t, *J* 9.6), 5.33 (1 H, d, *J* 17.1), 5.23 (1 H, d, *J* 10.5), 5.11 (1 H, t, *J* 9.6), 4.68 (1 H, dd, *J* 13.2 and 5.4), 4.52 (1 H, dd, *J* 13.2 and 5.4), 4.13 (2 H, s), 3.99–3.95 (1 H, m), 2.43 (6 H, s), 2.15 (3 H, s), 2.07 (3 H, s), 2.04 (3 H, s), 2.02 (3 H, s); δ_C (75 MHz, $CDCl_3$) 171.5, 170.4, 169.4, 150.9, 145.3, 144.9, 136.1, 135.8, 130.2, 129.3, 128.6, 128.0, 119, 82.5, 73.9, 70.2, 69.0, 68.1, 62.2, 58.2, 26.1, 21.6, 21.5, 20.7, 20.6; HRMS (ESI): $C_{32}H_{39}N_2O_{14}S_2$ [M + H]$^+$ calcd: 739.1843, found 739.1847.

4-*O*-[2,3,4,6-Tetra-*O*-acetyl-(β-D-galactopyranosyl)]-2-*N*-acetyl-1-*N*-allyloxycarbonyl-3,6-di-*O*-acetyl-1,2-dideoxy-1,2-di-(*p*-toluenesulfonamido)-β-D-glucopyranose 23c. Compound **23c** (1.63 g, 75%) was obtained as a white solid in 12 h from the reaction of **20e** (2.00 g, 2.12 mmol) with DMAP (0.052 g, 0.424 mmol), Et_3N (0.589 mL, 4.24 mmol) and allyloxycarbonyl chloride (0.904 g, 8.48 mmol) in dry CH_2Cl_2 (10 mL) as per the general procedure described above. Flash chromatography of the crude reaction mixture was performed with hexane–ethyl acetate (2 : 1). Mp 79 °C (from CH_2Cl_2–hexane); $[\alpha]_D^{28}$ −27.7 (*c* 0.49 in $CHCl_3$); ν_{max} (KBr)/cm^{-1} 2983, 1747, 1597, 1433, 1370, 1228, 1170, 1063; δ_H (300 MHz, $CDCl_3$) 7.85 (2 H, d, *J* 7.5), 7.77 (2 H, d, *J* 7.5), 7.31 (4 H, m), 6.74 (1 H, d, *J* 9.3), 5.97 (1 H, t, *J* 9.0), 5.80–5.71 (1 H, m), 5.52 (1 H, t, *J* 9.3), 5.36–5.10 (4 H, m), 4.97 (1 H, d, *J* 10.2), 4.64–4.44 (4 H, m), 4.18–4.03 (4 H, m), 3.93–3.79 (2 H, m), 2.44 (6 H, s), 2.16 (3 H, s), 2.13 (3 H, s), 2.09 (9 H, s), 2.06 (3 H, s), 1.97 (3 H, s); δ_C (75 MHz, $CDCl_3$) 171.2, 170.2, 170.1, 170.0, 169.8, 150.6, 145.0, 144.6, 136.1, 135.9, 130.0, 129.2, 128.3, 127.8, 118.7, 100.4, 82.3, 76.7, 74.6, 70.9, 70.6, 69.6, 69.0, 67.7, 66.7, 61.9, 60.8, 58.2, 25.8, 21.4, 20.8, 20.6, 20.4, 20.3; HRMS (ESI): $C_{44}H_{55}N_2O_{22}S_2$ [M + H]$^+$ calcd: 1027.2688, found 1027.2697.

2-Acetamido-3,4,6-tri-*O*-acetyl-1-*N*-allyloxycarbonyl-2-deoxy-β-D-glucopyranosylamine 24a. Compound **24a** (0.105 g, 90%) was obtained as a white solid in 1 h from the reaction **23a** (0.200 g, 0.27 mmol) with 13 eq. of SmI_2 (preformed) in dry THF (20 mL) and degassed water (0.366 mL, 20.32 mmol) using general procedure B for detosylation as described above. Flash chromatography of the crude reaction mixture was performed with hexane : ethyl acetate (1 : 1). Mp 164 °C (decomp.) (from CH_2Cl_2–hexane); $[\alpha]_D^{28}$ −9.3 (*c* 0.59 in $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3325, 3268, 2925, 1749, 1709, 1655, 1542, 1224, 1046; δ_H (300 MHz, $CDCl_3$) 6.23 (1 H, d, *J* 8.7, N*H*, exchangeable with D_2O), 5.99 (1 H, br d, N*H*, exchangeable with D_2O), 5.94–5.81 (1 H, m), 5.27 (1 H, d, *J* 17.1), 5.20 (1 H, d, *J* 10.5), 5.16–5.02 (2 H, m), 4.86 (1 H, t, *J* 9.3), 4.56 (2 H, d, *J* 5.4), 4.30 (1 H, dd, *J* 12.3 and 3.9), 4.19–4.07 (2 H, m), 3.74 (1 H, br d), 2.09 (3 H, s), 2.07 (3 H, s), 2.04 (3 H, s), 1.96 (3 H, s); δ_C (75 MHz, $CDCl_3$) 171.5, 170.7, 169.3, 155.8, 132.2, 117.7, 82.2, 73.1, 68.0, 65.9, 61.8, 52.7, 23.0, 20.6, 20.5; HRMS (ESI): $C_{18}H_{27}N_2O_{10}$ [M + H]$^+$ calcd: 431.1666, found 431.1667.

4-*O*-[2,3,4,6-Tetra-*O*-acetyl-(β-D-galactopyranosyl)]-2-acetamido-3,6-di-*O*-acetyl-1-*N*-allyloxycarbonyl-2-deoxy-β-D-glucopyranosylamine 24c. Compound **24c** (0.123 g, 88%) was obtained as a white solid in 1 h from the reaction **23c** (0.200 g, 0.195 mmol) with 17 eq. of SmI_2 (preformed) in dry THF (20 mL) and degassed water (0.351 mL, 19.50 mmol) using general procedure B for detosylation as described above. Flash chromatography of the crude reaction mixture was performed with hexane : ethyl acetate (1 : 2). Mp 94 °C (from CH_2Cl_2–hexane); $[\alpha]_D^{28}$ +5.4 (*c* 0.58 in $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3369, 2927, 1747, 1540, 1370, 1227, 1048; δ_H (300 MHz, $CDCl_3$) 6.17 (1 H, d, *J* 7.4, N*H*, exchangeable with D_2O), 6.02 (1 H, d, *J* 7.8, N*H*, exchangeable with D_2O), 5.92–5.81 (1 H, m), 5.33 (2 H, d, *J* 17.0), 5.22 (1 H, dd, *J* 10.4 and 8.7), 5.14–4.95 (3 H, m), 4.79 (1 H, t, *J* 8.0), 4.56–4.41 (4 H, m), 4.15–3.96 (4 H, m), 3.89–3.67 (3 H, m), 2.15 (3 H, s), 2.12 (3 H, s), 2.10 (3 H, s), 2.06 (6 H, s), 1.97 (3 H, s), 1.96 (3 H, s); δ_C (75 MHz, $CDCl_3$) 171.8, 171.4, 170.3, 170.2, 170.0, 169.1, 155.6, 132.2, 117.7, 101.0, 82.3, 75.7, 73.9, 73.1, 70.8, 70.6, 69.0, 66.6, 65.9, 62.0, 60.8, 53.1, 22.9, 20.7, 20.5; HRMS (ESI): $C_{30}H_{43}N_2O_{18}$ [M + H]$^+$ calcd: 719.2511, found 719.2523.

General procedure for synthesis of *N*-linked glycoamino acids 25a–d, 27a–c and an *N*-linked glycopeptide 29

Procedure A using DCC–DMAP: Starting compound (1 eq.) was added to a flame dried 50 mL three-necked round bottomed flask and dissolved in dry THF under an argon atmosphere. To this, $Pd(PPh_3)_4$ (10 mol%) was added followed by drop-wise addition of Et_2NH (10 eq.). The reaction mixture was allowed to stir at room temperature. After completion of the reaction (20 minutes, as indicated by TLC), the THF was evaporated completely. The residue was then dissolved in dry CH_2Cl_2 and transferred drop-wise to a suspension of protected amino acid (1.5 eq.), DCC (1.8 eq.) and DMAP (1.5 eq.) in dry CH_2Cl_2 that was pre-stirred for 2 h. The reaction mixture was then allowed to stir at 30 °C for 12 h, after which it was filtered and the residue was washed with more CH_2Cl_2. The organic layer was washed with 5% $NaHCO_3$, saturated NH_4Cl, dried over sodium sulfate and concentrated. Flash chromatography of the resulting residue provided the corresponding *N*-linked glycoamino acids.

Procedure B using DCC–HOBt: Starting compound (1 eq.) was added to a flame dried 50 mL three-necked round bottomed flask and dissolved in dry THF under an argon atmosphere. To this, $Pd(PPh_3)_4$ (10 mol%) was added followed by drop-wise addition of Et_2NH (10 eq.). The reaction mixture was allowed to stir at room temperature. After completion of the reaction (20 minutes, as indicated by TLC), the THF was evaporated completely. The residue was then dissolved in dry CH_3CN and transferred drop-wise to a suspension of protected amino acid (1 eq.), DCC (1 eq.)

and 1-hydroxybenzotriazole (HOBt) (1 eq.) in dry CH_3CN that was pre-stirred for 2 h. The reaction mixture was then allowed to stir at 30 °C for 12–24 h, after which it was filtered and the residue was washed with CH_2Cl_2. The organic layer was washed with 5% $NaHCO_3$, saturated NH_4Cl, dried over sodium sulfate and concentrated. Flash chromatography of the resulting residue provided the corresponding *N*-linked glycoamino acids.

2-Acetamido-3,4,6-tri-*O*-acetyl-1-*N*-[*N*-*tert*-butyloxycarbonyl-L-glycyl]-2-deoxy-β-D-glucopyranosylamine 25a. *Procedure A*: Compound **25a** (0.167 g, 72%) was obtained as a white solid in 12 h from the reaction of **24a** (0.198 g, 0.460 mmol) with $Pd(PPh_3)_4$ (0.058 g, 0.05 mmol), Et_2NH (0.477 mL, 4.60 mmol), *N*-Boc-glycine (0.184 g, 0.690 mmol), DCC (0.171 g, 0.830 mmol) and DMAP (0.084 g, 0.69 mmol) in dry CH_2Cl_2 (6 mL) as per the general procedure A. Flash chromatography of the crude reaction mixture was performed with ethyl acetate. Mp 85 °C (from ethyl acetate–hexane); $[\alpha]_D^{28}$ +3.4 (*c* 0.24 in $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3319, 2976, 2359, 1747, 1665, 1533, 1376, 1241, 1169, 1047; δ_H (300 MHz, $CDCl_3$) 7.46 (1 H, d, *J* 7.6, N*H*, exchangeable with D_2O), 6.26 (1 H, d, *J* 8.3, N*H*, exchangeable with D_2O), 5.16–5.09 (4 H, m), 4.28 (1 H, dd, *J* 12.3 and 4.2), 4.21–4.13 (1 H, m), 4.08 (1 H, dd, *J* 12.3 and 1.8), 3.81–3.80 (3 H, m), 2.09 (3 H, s), 2.06 (3 H, s), 2.04 (3 H, s), 1.94 (3 H, s), 1.46 (9 H, s); δ_C (75 MHz, $CDCl_3$): 172.0, 171.6, 170.7, 170.7, 169.3, 155.7, 80.0, 73.5, 72.8, 67.9, 61.8, 53.1, 44.1, 28.3, 22.9, 20.7, 20.6, 20.5; HRMS (ESI): $C_{21}H_{34}N_3O_{11}$ [M + H]$^+$ calcd: 504.2193, found 504.2204.

Procedure B: Compound **25a** (0.164 g, 71%) was obtained in 16 h from the reaction of **24a** (0.198 g, 0.46 mmol) with $Pd(PPh_3)_4$ (0.053 g, 0.046 mmol), Et_2NH (0.477 mL, 4.60 mmol), *N*-Boc-glycine (0.080 g, 0.460 mmol), DCC (0.095 g, 0.460 mmol) and HOBt (0.062 g, 0.460 mmol) in dry CH_3CN (10 mL) as per the general procedure B.

2-Acetamido-3,4,6-tri-*O*-acetyl-1-*N*-[*N*-(fluorenylmethoxycarbonyl-L-alanyl]-2-deoxy-β-D-glucopyranosylamine 25b. Compound **25b** (0.281 g, 76%) was obtained as an off white solid in 16 h from the reaction of **24a** (0.250 g, 0.581 mmol) with $Pd(PPh_3)_4$ (0.067 g, 0.058 mmol), Et_2NH (0.603 mL, 5.81 mmol), Fmoc-alanine (0.181 g, 0.581 mmol), DCC (0.119 g, 0.581 mmol) and HOBt (0.078 g, 0.581 mmol) in dry CH_3CN (15 mL) as per the general procedure B. Flash chromatography of the crude reaction mixture was performed with hexane : ethyl acetate (1 : 2). Mp 204–206 °C (from CH_2Cl_2–hexane); $[\alpha]_D^{28}$ −5.02 (*c* 0.55 in $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3306, 1748, 1670, 1541, 1374, 1236, 1044; δ_H (300 M, $CDCl_3$) 7.76 (2 H, d, *J* 7.3), 7.60 (2 H, d, *J* 7.0), 7.44 (1 H, d, *J* 8.4, N*H*, exchangeable with D_2O), 7.40 (2 H, t, *J* 7.5), 7.31 (2 H, t, *J* 7.5), 6.11 (1 H, d, *J* 7.8, N*H*, exchangeable with D_2O), 5.42 (1 H, d, *J* 6.9, N*H*, exchangeable with D_2O), 5.12–5.04 (3 H, m), 4.39–4.05 (7 H, m), 3.77 (1 H, br s), 2.06 (6 H, s), 2.04 (3 H, s), 1.90 (3 H, s), 1.38 (3 H, d, *J* 6.1); δ_C (75 MHz, $CDCl_3$) 173.4, 172.2, 171.7, 170.6, 169.2, 155.7, 143.8, 141.3, 127.7, 127.0, 125.2, 125.1, 119.9, 80.2, 73.6, 72.8, 67.9, 67.1, 61.7, 53.5, 50.7, 47.1, 23.0, 20.7, 20.5, 18.3; HRMS (ESI): $C_{32}H_{38}N_3O_{11}$ [M + H]$^+$ calcd: 640.2506, found 640.2535.

2-Acetamido-3,4,6-tri-*O*-acetyl-1-*N*-[1-benzyl-*N*-(benzyloxy)-carbonyl-L-aspart-4-oyl]-2-deoxy-β-D-glucopyranosylamine 27a. Compound **27a** (0.167 g, 75%) was obtained as a white solid in 24 h from the reaction of **24a** (0.140 g, 0.325 mmol) with $Pd(PPh_3)_4$ (0.037 g, 0.032 mmol), Et_2NH (0.337 mL, 3.25 mmol), 1-benzyl *N*-(benzyloxycarbonyl)-L-aspartate **26a** (0.116 g, 0.325 mmol), DCC (0.044 g, 0.325 mmol) and HOBt (0.067 g, 0.325 mmol) in dry CH_3CN (10 mL) as per the general procedure B. Flash chromatography of the crude reaction mixture was performed with hexane : ethyl acetate (1 : 3). Mp 222–224 °C (from ethyl acetate–hexane) {lit. mp 213–215 °C,[31] 225 °C,[32] 214–215 °C[33] and 213–217 °C[34]}; $[\alpha]_D^{28}$ +6.3 (*c* 0.58 in $CHCl_3$) {lit. $[\alpha]_D$ +9 (*c* 1 in $CHCl_3$),[31] +7 (*c* 1 in $CHCl_3$),[32] +10 (*c* 0.5 in $CHCl_3$)[33] and +12 (*c* 0.5 in $CHCl_3$)[34]} (Found: C, 57.81; H, 5.78; N, 6.06. $C_{33}H_{39}N_3O_{13}$ requires: C, 57.80; H, 5.73; N, 6.13%); ν_{max} (KBr)/cm^{-1} 3307, 1743, 1697, 1661, 1546, 1376, 1229; δ_H (300 MHz, $CDCl_3$) 7.36–7.33 (10 H, m), 7.17 (1 H, d, *J* 7.8, N*H*, exchangeable with D_2O), 6.02 (1 H, d, *J* 8.7, N*H*, exchangeable with D_2O), 5.78 (1 H, d, *J* 7.9, N*H*, exchangeable with D_2O), 5.23–5.07 (5 H, m), 5.01–4.90 (2 H, m), 4.68–4.65 (1 H, m), 4.27 (1 H, dd, *J* 12.5 and 4.2), 4.08–4.00 (2 H, m), 3.72–3.70 (1 H, m), 2.86 (1 H, dd, *J* 16.5 and 4.5), 2.70 (1 H, dd, *J* 16.0 and 4.5), 2.07 (3 H, s), 2.06 (3 H, s), 2.05 (3 H, s), 1.82 (3 H, s); δ_C (75 MHz, $CDCl_3$) 172.4, 171.7, 170.9, 170.7, 169.2, 156.1, 136.1, 135.5, 128.5, 128.3, 128.1, 128.0, 80.1, 73.5, 72.7, 67.7, 67.2, 67.0, 61.7, 53.1, 50.6, 37.7, 22.8, 20.7, 20.6, 20.5; HRMS (ESI): $C_{33}H_{40}N_3O_{13}$ [M + H]$^+$ calcd: 686.2561 found 686.2554.

2-Acetamido-3,6-di-*O*-acetyl-*N*-[1-benzyl-*N*-(*tert*-butyloxycarbonyl)-L-aspart-4-oyl]-2-deoxy-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-glucopyranosylamine 27b. Compound **27b** (0.084 g, 64%) was obtained as a white solid in 24 h from the reaction of **24d** (0.100 g, 0.139 mmol) with $Pd(PPh_3)_4$ (0.016 g, 0.014 mmol), Et_2NH (0.144 mL, 1.39 mmol), 1-benzyl *N*-(*tert*-butyloxycarbonyl)-L-aspartate **26b** (0.045 g, 0.139 mmol), DCC (0.029 g, 0.139 mmol) and HOBt (0.019 g, 0.139 mmol) in dry CH_3CN (10 mL) as per the general procedure B. Flash chromatography of the crude reaction mixture was performed with hexane : ethyl acetate (1 : 4). Mp 92 °C (from ethyl acetate–hexane); $[\alpha]_D^{28}$ +9.7 (*c* 0.52 in $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3365, 2978, 2933, 1750, 1666, 1545, 1374, 1226, 1169, 1055; δ_H (300 MHz, $CDCl_3$) 7.36–7.34 (5 H, m), 7.12 (1 H, d, *J* 7.8, N*H*, exchangeable with D_2O), 5.82 (1 H, d, *J* 7.8, N*H*, exchangeable with D_2O), 5.75 (1 H, d, *J* 9.1, N*H*, exchangeable with D_2O), 5.36 (1 H, br s), 5.25–5.07 (3 H, m), 4.99–4.93 (2 H, m), 4.88 (1 H, t, *J* 9.1), 4.57–4.55 (1 H, m), 4.47 (1 H, d, *J* 7.8), 4.40 (1 H, d, *J* 11.6), 4.14–3.94 (4 H, m), 3.87 (1 H, t, *J* 6.8), 3.76 (1 H, t, *J* 9.2), 3.64 (1 H, m), 2.84 (1 H, dd, *J* 16.3 and 3.7), 2.65 (1 H, dd, *J* 16.1 and 3.8), 2.16 (3 H, s), 2.12 (3 H, s), 2.10 (3 H, s), 2.06 (6 H, s), 1.98 (3 H, s), 1.84 (3 H, s), 1.42 (9 H, s); δ_C (75 MHz, $CDCl_3$) 172.6, 171.6, 171.3, 171.1, 170.3, 170.0, 169.2, 155.5, 135.6, 128.4, 128.3, 128.0, 101.0, 80.0, 75.6, 74.3, 72.9, 70.8, 70.6, 68.9, 67.0, 66.5, 62.0, 60.8, 53.3, 50.0, 37.7, 28.2, 22.9, 20.8, 20.6; HRMS (ESI): $C_{42}H_{58}N_3O_{21}$ [M + H]$^+$ calcd: 940.3563, found 940.3600.

2-Acetamido-3,4,6-tri-*O*-acetyl-1-*N*-{1-benzyl-2-*N*-[*N*-(fluorenylmethoxycarbonyl-L-alanyl)]-L-aspart-4-oyl}-2-deoxy-β-D-glucopyranosylamine 29. Compound **29** (0.179 g, 55%) was obtained as a white solid in 24 h from the reaction of **24a** (0.166 g, 0.386 mmol) with $Pd(PPh_3)_4$ (0.044 g, 0.036 mmol), Et_2NH (0.401 mL, 3.86 mmol), Fmoc-Ala-Asp-OBn **28** (0.199 g, 0.386 mmol), DCC (0.079 g, 0.386 mmol) and HOBt (0.052 g, 0.386 mmol) in dry CH_3CN (10 mL) as per the general procedure B. Flash chromatography of the crude reaction mixture was

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performed with hexane : ethyl acetate (1 : 4). Mp 228–230 °C (from DMSO–H_2O); $[\alpha]_D^{28}$ +7.3 (*c* 0.11 in $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3307, 1746, 1665, 1538, 1449, 1375, 1236, 1044; δ_H (300 MHz, $CDCl_3$) 7.78 (2 H, d, *J* 7.9), 7.63 (2 H, br s), 7.44–7.28 (10 H, m), 5.88 (1 H, d, *J* 7.9, N*H*, exchangeable with D_2O), 5.61 (1 H, d, *J* 5.8, N*H*, exchangeable with D_2O), 5.18–4.89 (7 H, m), 4.42–4.24 (5 H, m), 4.13–4.04 (2 H, m), 3.65 (1 H, d, *J* 8.3), 2.90 (1 H, dd, *J* 16.4 and 4.3), 2.73 (1 H, dd, *J* 16.3 and 3.3), 2.07 (3 H, s), 2.06 (6 H, s), 1.86 (3 H, s), 1.38 (3 H, d, *J* 6.0); δ_C (75 MHz, DMSO-d_6) 172.6, 170.9, 170.0, 169.6, 169.5, 169.3, 155.6, 143.9, 143.8, 140.7, 135.9, 128.3, 127.9, 127.6, 127.1, 125.3, 120.1, 78.0, 73.3, 72.3, 68.3, 66.0, 65.6, 61.8, 52.2, 49.8, 48.3, 46.6, 36.7, 22.6, 20.5, 20.4, 20.3, 18.2; HRMS (ESI): $C_{43}H_{49}N_4O_{14}$ $[M + H]^+$ calcd: 845.3245, found 845.3257.

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