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Synthesis of α-*N*-Linked Glycopeptides

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A practical synthesis of N^{α}-fluorenylmethoxycarbonyl-N^{γ}-(2,3,4,6-tetra-*O*-acetyl-α-D-glycopyranosyl)-L-asparagine in the *gluco* and *galacto* series has been achieved by using the methodology developed by DeShong and co-workers. The resulting α-*N*-linked glycosyl amino acids were used in a linear approach to the synthesis of glycopeptides featuring the unnatural α-*N*-glycosyl linkage. Activation conditions for both C- and N-terminus elongation in solution have been defined. The main side-reaction encountered was the formation of cyclization by-products (aspartimide) from the activated amino acid during C-terminus elongation. Appropriate condensing agents were identified, which allowed a high yield of dipeptide formation and no epimierization of the glycosyl amino acids. Conditions for sugar deacetylation have also been optimized. Solid-phase synthesis (Fmoc protocol) conditions were explored and PyBROP was found to be the reagent of choice for the activaton of glycosyl amino acids. The synthesis of more complex α-*N*-linked glycopeptides has thus become feasible, which will allow the properties of these neo-glycoconjugates to be studied.

Introduction

The synthesis of neo-glycoconjugates has been attracting considerable attention in recent years.[1] Of these, the analogues of glycopeptides have been particularly investigated owing to the importance of natural glycopeptides and glycoproteins in human health and diseases.[2] Although exceptions have been found,[3] natural *N*-linked glycopeptides present a common core formed by a GlcNAc residue β-linked to the side-chain of an asparagine residue in the peptide chain. Several years ago Imperiali and Woods and coworkers reported one case in which the peptide conformation of an *N*-linked glycopeptide was found to depend on the anomeric configuration of the appended glycan.[4] This result suggested that α-*N*-linked glycopeptides may give new molecules and materials that behave in an unprecedented fashion. New data, however, have been lagging, mostly because of a lack of methods able to secure a viable synthesis of α-*N*-linked glycosylamides. Our laboratory[5] and others[6,7] have been active in this area. We now report on the development of a general approach towards the synthesis of α-*N*-linked glucosyl- and galactosyl-glycopeptides.

In general, glycopeptides can be prepared perhaps more conveniently by using a convergent approach that involves the direct glycosylation of a preformed peptide chain.[8] However, for α-*N*-linked derivatives this approach is precluded by the synthetic difficulties of α-*N*-glycosylation. Rather we have selected a linear approach that makes use of preformed N^{α}-Fmoc-protected N^{γ}-2,3,4,6-tetra-*O*-acetyl-α-D-gluco- or galactopyranosyl-L-asparagine **1** or **2** (Figure 1). We have developed a convenient, high-yielding synthesis of these starting materials based on the technology of DeShong and co-workers,[6] explored their activation in the context of solution-phase peptide synthesis and developed a procedure for solid-phase synthesis. Our results are reported below.

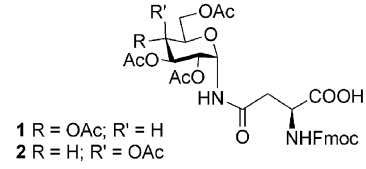

Figure 1. α-*N*-Glycosyl asparagine building blocks for peptide synthesis.

Results and Discussion

A practical synthesis of N^{α}-fluorenylmethoxycarbonyl-N^{γ}-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-L-asparagine (**1**; Scheme 1) was achieved by following the methodology developed by DeShong and co-workers.[6a] Thus, treatment of 2,3,4,6-tetra-*O*-acetyl-β-D-glucosyl azide (**3**) with PPh_3 afforded oxazoline **4**, which was subjected to one-pot acylation with the thiopyridyl ester of *N*-benzyloxycarbonylaspartic acid benzyl ester [Cbz-Asp-(SPy)-OBn, **5**] to yield the fully protected glycosyl amino acid **6** (65%) in an α/β anomeric ratio of ≥9:1, as established by ^{1}H NMR analysis. Hydrogenation of **6** afforded **7** (quantitative yield),

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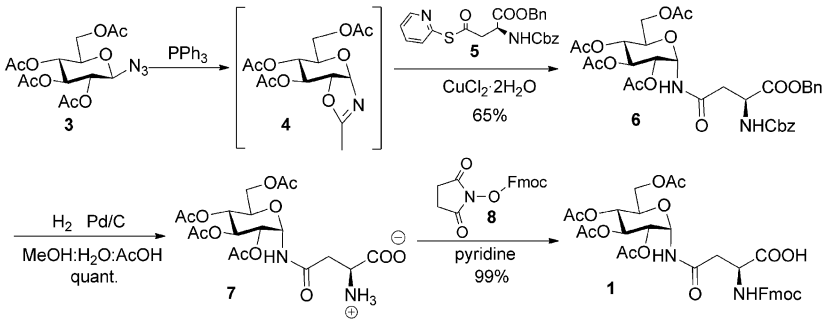


Scheme 1. Synthesis of N^{α}-fluorenylmethoxycarbonyl-N^{γ}-2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl-L-asparagine (**1**). Reagents and conditions: a) 1. PPh_3, nitroethane, 75 °C, 15 h; 2. Cbz-Asp-(SPy)-OBn, $CuCl_2{\cdot}2H_2O$, 30 °C, 24 h, 65% over two steps; b) H_2, Pd/C, MeOH/H_2O/AcOH (25:5:3), 2 h, quantitative; c) Fmoc-OSu, pyridine, 15 h, 99%.

which was transformed into the fluorenylmethoxycarbonyl (Fmoc) derivative by using *N*-(9*H*-fluorenylmethoxycarbonyloxy)succinimide (Fmoc-Osu, **8**) in pyridine (99%).[9] The direct glycosylation of Fmoc-protected Asp [Fmoc-Asp-(SPy)-OR] failed as a result of the instability of this protecting group under the DeShong conditions. The *N*-Fmoc-glucosyl amino acid **1** was crystallized from CH_3CN/H_2O (1:6) to remove the remaining traces of the anomeric β isomer.

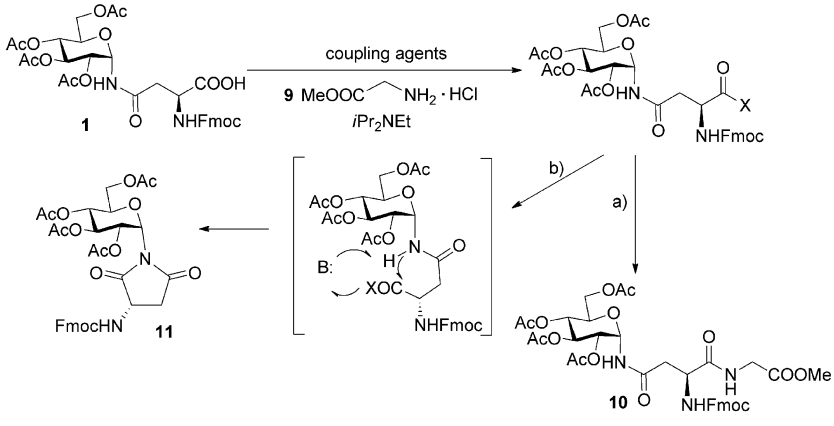
Elongation of the α-*N*-glucosyl asparagine derivative **1** at the C terminus was tested in solution under a variety of coupling conditions with commercially available glycine methyl ester **9** as the coupling partner to afford dipeptide **10** (Scheme 2, Table 1).

These tests showed **1** to be a sluggish substrate, which, upon activation, underwent an easy side-reaction leading to the formation of the *N*-glucosyl aspartimide **11**. For instance, by using EDC/HOBT as activators (Table 1, entry 1), dipeptide **10** was isolated in only 45% yield after 6 h. Analysis of the crude (^{1}H NMR) revealed the presence of 30% aspartimide **11**. Similarly, with HBTU (Table 1, entry 2) **10** and **11** were produced in a ratio of 1:1, as determined by ^{1}H NMR analysis of the crude coupling mixture, and only 40% of **10** was isolated after 6 h. Even larger amounts of cyclization product were obtained by using EDC/HOAT or HATU [*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate]. Aspartimide formation is a well-known side-reaction of asparagine derivatives during peptide synthesis, especially under basic conditions.[10] However, HBTU has been used successfully for the activation of *N*-glycosyl asparagine in the stepwise synthesis of β-*N*-linked glycopeptides.[11] Likewise, although the pentafluorophenyl (PFP) ester of β-glucosyl-*N*-Fmoc-asparagine has been reported as a stable glycosylated building block for peptide synthesis,[12] the corresponding α anomer could not be isolated but cyclized quantitatively to aspartimide **11** during chromatography. In contrast, formation of the PFP ester (with DCC, PFPOH, 1 h, 0 °C) and

Table 1. Elongation of the the C terminus of **1**. Synthesis of α-*N*-glucosyl dipeptide **10**.[a]

Entry	Reagents	Solvent	Reaction time	Yield [%]	
			[h]	**10**[b]	**11**[c]
1	EDC·HCl, HOBt	CH_2Cl_2	6	45	30
2	HBTU	DMF	6	40	44
3	DCC, PFPOH[d]	CH_2Cl_2	5	70	–
4	BOP-Cl	CH_2Cl_2	18	–[e]	–[e]
5	PyBROP	CH_2Cl_2	5	69	–

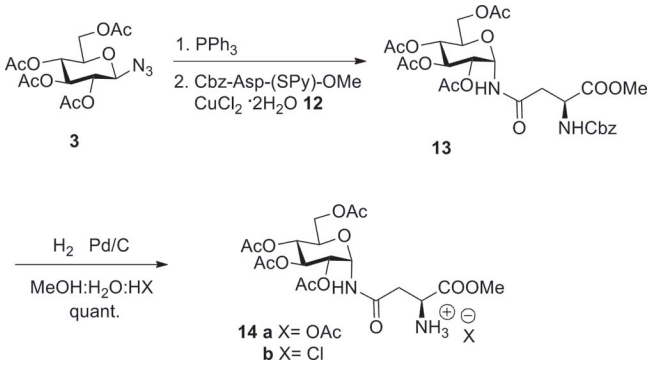
[a] Coupling of Fmoc-protected glucosylasparagine **1** with HCl·Glycine-OMe (**9**). *i*Pr_2NEt was used to release the glycine salt. [b] Isolated yield. [c] ^{1}H NMR analysis of the crude. [d] Followed by in situ addition of **9**. [e] No reaction occurred.



Scheme 2. Optimization of the coupling conditions for **1**: a) peptide coupling; b) aspartimide formation from the activated Asn derivative.

one-pot addition of methyl glycine **9** afforded the required dipeptide in 70% yield after 5 h (Table 1, entry 3). Of the phosphorus-based activating agents tested, bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) gave no reaction in 18 h (Table 1, entry 4). However, by using bromo-tris-pyrrolidinophosphonium hexafluorophosphate (PyBROP), the desired dipeptide **10** was obtained in 69% yield after 5 h with no trace of the competing aspartimide byproduct (Table 1, entry 5). The stereochemical integrity of dipeptide **10** was assessed by ^{1}H and ^{13}C NMR and by HPLC–MS, which showed that no epimerization occurred at either the C_α or the anomeric carbon during the peptide coupling.

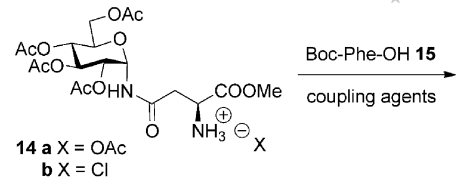
Peptide couplings at the amine terminus were also explored starting from α-*N*-glucosyl asparagine methyl ester **14** (Scheme 3). This was obtained from azide **3**[5a] by treatment with Ph_3P, acylation with the thiopyridyl ester of N^α-Cbz-protected aspartic acid methyl ester [Cbz-Asp(SPy)-OMe, **12**; Scheme 3] and subsequent deprotection by hydrogenation.

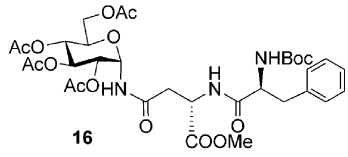


Scheme 3. Synthesis of α-*N*-glucopyranosyl asparagine methyl ester **14**.

The reaction of **14** with *N*-(*tert*-butoxycarbonyl)-L-phenylalanine (Boc-Phe, **15**) to afford dipeptide **16** (Scheme 4) was chosen as a model reaction. From the acetate **14a**, **16** was obtained in 56% yield with EDC/HOBT, in 67% yield with HATU/DIPEA and in 66% yield with PyBROP (Scheme 4). Yields were improved by starting from the hydrochloride salt **14b**, obtained by hydrogenation of **13** in MeOH, to which a stoichiometric amount of acetyl chloride had been added. Coupling of **14b** with **15** with HATU/DIPEA in DMF afforded dipeptide **16** in 87% yield (Scheme 4). No byproducts were observed in these reactions and the spectroscopic data of the dipeptide (^{1}H and ^{13}C NMR) as well as the HPLC–MS analysis showed that a single isomer was obtained.

Once the best coupling conditions had been identified for the elongation of both the carboxy and amine termini of the α-*N*-linked glucopyranosyl derivative, the same protocols were applied to the α-galactosyl amino acid to examine their scope. The DeShong reaction of galactosyl azide **17**[5a] with Ph_3P followed by acylation with Cbz-Asp(SPy)-OBn (**5**) afforded **18** (typically with an α/β ratio of >10:1), which was submitted to hydrogenation and Fmoc protection to

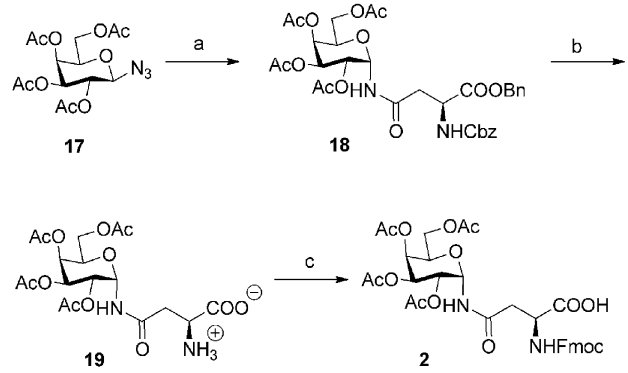




X	Coupl. Ag.	Yield (%)
OAc	EDC/HOBT	56
OAc	HATU	67
OAc	PyBROP	66
Cl	HATU	87

Scheme 4. Elongation of the amine terminus. Synthesis of **16**.

yield **2** (89%, Scheme 5). The remaining traces of the β anomer were removed at this stage by flash chromatography ($CHCl_3$/MeOH from 95:5 to 80:20).

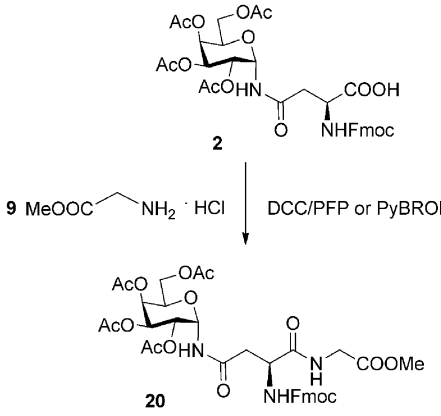


Scheme 5. Synthesis of *N*-fluorenylmethoxycarbonyl-N^γ-2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl-L-asparagine (**1**). Reagents and conditions: a) 1. PPh_3, nitroethane, 75 °C, 15 h; 2. Cbz-Asp-(SPy)-OBn (**5**), $CuCl_2{\cdot}2H_2O$, 30 °C, 24 h, 80% over two steps; b) H_2, Pd/C, MeOH/H_2O/AcOH (25:5:3), 2 h, quantitative; c) Fmoc-OSu (**8**), pyridine, 15 h, 89%.

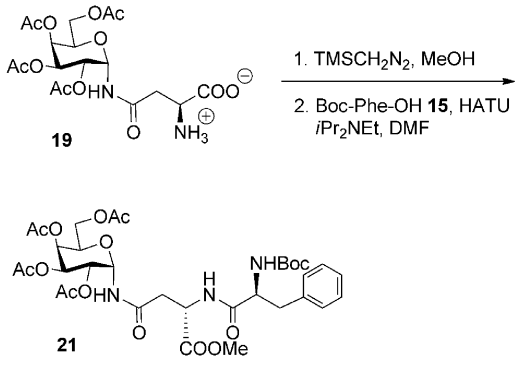
The reaction of **2** with Gly-OMe (**9**) in the presence of PFP and DCC afforded dipeptide **20** in 73% yield, whereas the reaction with PyBROP gave **20** in 62% yield (Scheme 6).

The treatment of **19** with $TMSCH_2N_2$ in MeOH to give the corresponding methyl ester followed by coupling with Boc-phenylalanine (**15**) with HATU afforded **21** in 72% overall yield (Scheme 7).

The spectroscopic (^{1}H and ^{13}C NMR) and chromatographic (HPLC–MS) analyses of both dipeptides **20** and **21** revealed a single isomer. These results confirmed that the coupling conditions optimized for glucose derivative **1** are also suitable for the galactose analogue **2**. The conditions for deacetylation of the sugar moiety were defined by using **23** (Scheme 8) as a tripeptide model. Starting from **2**, coupling (PyBROP) with methylamine hydrochloride afforded

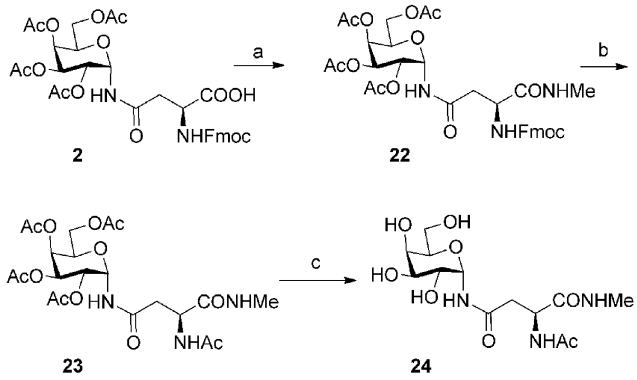


Scheme 6. Coupling in solution of α-*N*-galactopyranosyl asparagine *N*-Fmoc protected with glycine methyl ester.



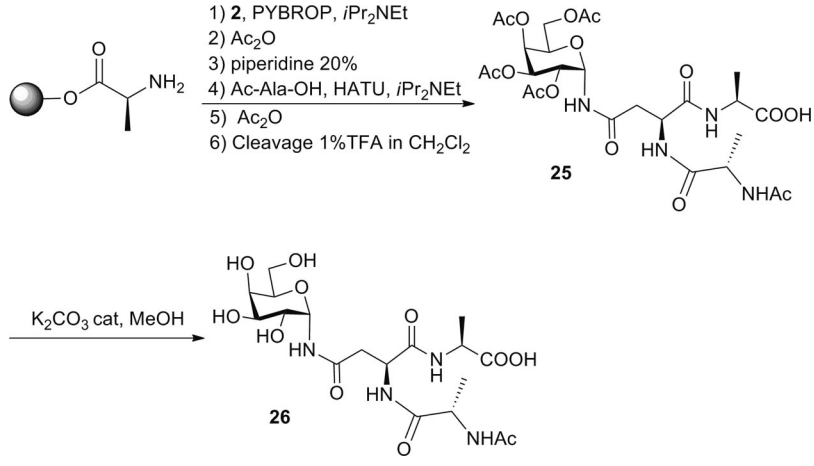
Scheme 7. Coupling in solution of α-*N*-galactopyranosyl asparagine methyl ester with Boc-phenylalanine.

22 in 84% yield. Fmoc deprotection (octanethiol and catalytic DBU)[13] followed by *N*-acetylation (Ac_2O) gave **23** in 62% yield over two steps. Deprotection of the acetyl groups on the carbohydrate moiety to afford **24** was successfully performed with catalytic amounts of K_2CO_3 in MeOH under carefully controlled pH conditions.[14] No epimerization was observed under these conditions by ^1H and ^{13}C NMR or by analysis of the LC–MS chromatograms.



Scheme 8. Synthesis of the glycosyl tripeptide model AcNH-(α-Gal-*N*-)Asn-CONHMe. Reagents and conditions: a) 1. $NH_2Me{\cdot}2HCl$, PyBROP, iPr_2NEt, CH_2Cl_2, 84%; b) 1. octanethiol, cat. DBU, THF; 2. Ac_2O, pyridine, 62% over two steps; c) cat. K_2CO_3, MeOH, 91%.

Finally, conditions for the solid-phase synthesis of the glycopeptides were explored. Both chlorotrityl (CTC) and superacid-sensitive (SASRIN) resins were tested. The resins were loaded with 1 equiv. of Fmoc-Ala and, after protecting group removal, reactions with **2** were attempted using either PFP/DIC or PyBROP. Although PFP/DIC did not afford the expected dipeptide, the reaction proceeded smoothly with PyBROP as the condensing agent (1:1 DMF/CH_2Cl_2, 2 h, 0 °C, 2 h, room temperature). Capping was performed with 1 M acetic anhydride in DMF. The cycle was completed by Fmoc removal under standard conditions (20% piperidine in DMF) and a 77% yield based on **2** was estimated by UV analysis of the solution derived from removal of the Fmoc group. Condensation with AcNH-Ala (HATU), capping with Ac_2O and cleavage (1% TFA in CH_2Cl_2) gave glycopeptide **25** (Scheme 9), which was purified by automated chromatography on a reversed-phase (C-18) column (75% yield based on **2** was obtained both on CTC and on SASRIN). Deprotection of **25** with K_2CO_3 in MeOH (pH 8–9) afforded glycopeptides **26** (Scheme 9) with no trace of racemization or anomerization.



Scheme 9. Solid-phase synthesis of tripeptide **26**.

Conclusions

The α-*N*-glycosyl asparagine building blocks **1** and **2** for use in peptide synthesis have been prepared in good yields and in a form suitably protected for use under solid-phase conditions under the Fmoc protocol. Activation conditions were defined in solution for both C- (DCC/PFP or PyBROP) and N-terminus (HATU) elongation. These conditions led to a good yield of dipeptide formation, no racemization and no formation of cyclization byproducts (aspartimide). Conditions for sugar deprotection (cat. K_2CO_3 in MeOH) were also optimized. Solid-phase synthesis (Fmoc protocol) conditions were explored and PyBROP was found to be the reagent of choice for the activation of the glycosyl amino acids, affording good coupling yields both on CTC and SASRIN supports. With these methodologies in hand, the synthesis of more complex glycopeptides featuring the unnatural α-*N*-glycosyl linkage has become feasible, which will allow the properties of these neo-glycoconjugates to be investigated.

Experimental Section

General: Dichloromethane, methanol and *N*,*N*-diisopropylethylamine (DIPEA) were dried with calcium hydride, THF was distilled from sodium and *N*,*N*-dimethylformamide (DMF) was dried with activated molecular sieves (3 Å). Reactions requiring anhydrous conditions were performed under nitrogen. ^1H and ^{13}C NMR spectra were recorded at 400 MHz with a Bruker AVANCE-400 instrument. Chemical shifts (δ) are expressed in ppm relative to internal Me_4Si as standard. Signals are abbreviated as follows: s, singlet; br. s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Mass spectra were recorded with a Bruker ion-trap Esquire 3000 apparatus (ESI ionization) or a FT-ICR APEX II mass spectrometer and Xmass 4.7 Magnet software (Bruker Daltonics). Thin-layer chromatography (TLC) was carried out with precoated Merck F_{254} silica gel plates. Flash chromatography was carried out with Macherey–Nagel silica gel 60 (230–400 mesh) or with Biotage® SNAP KP-C18-HS cartridges for reversed-phase chromatography. HPLC–MS analyses were performed with an Agilent 1100 instrument with a quaternary pump, diode array detector, autosampler, thermostatted column holder coupled to a Bruker ion-trap Esquire 3000 mass spectrometer equipped with ESI ionization.

H-Ala-2-chlorotrityl and SASRIN resins were purchased from Bachem. Compounds **5** and **12** were prepared from commercially available *N*-benzyloxycarbonyl-L-aspartic acid benzyl ester and *N*-benzyloxycarbonyl-L-aspartic acid methyl ester, respectively, by reaction with triphenylphosphane and 2,2′-dithiodipyridine.[15] Compound **6** has been described previously;[6a] it was prepared by a slight modification of the DeShong protocol, as reported below.

***N*$^{\alpha}$-Benzyloxycarbonyl-*N*$^{\gamma}$-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-L-asparagine Benzyl Ester (6):** 2,3,4,6-Tetra-*O*-acetyl-β-D-glucosyl azide (**3**;[5a] 510 mg, 1.366 mmol, 1 equiv.) and Ph_3P (394 mg, 1.503 mmol, 1.1 equiv.) were dissolved in nitroethane (6 mL) in the presence of ground 3 Å molecular sieves (ca. 1.5 g). The resulting solution was heated at reflux for 15 h under nitrogen and then cooled to room temperature. Cbz-Asp(SPy)-OBn (**5**;[15] 820 mg, 1.82 mmol, 1.3 equiv.) and $CuCl_2 \cdot 2H_2O$ (310 mg, 1.82 mmol, 1.3 equiv.) were added sequentially and the reaction mixture was stirred at 30 °C for 24 h. After completion (TLC, 1:1 hexane/EtOAc) the reaction mixture was diluted with CH_2Cl_2 and filtered through a pad of Celite. The solvent was evaporated and the crude was dissolved in EtOAc and washed with a saturated ammonium chloride solution. The organic phase was dried with sodium sulfate and the solvents evaporated. The crude was purified by flash chromatography (1:1 hexane/EtOAc) to afford **6** (610 mg) in 65% yield. The analytical data were consistent with those reported in the literature.[6a] ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.30–7.35 (m, 10 H, H_{Ar}Cbz, H_{Ar}Bn), 6.57 (br. s, 1 H, Glc-NH-Asn), 5.92 (s, 1 H, 1-H), 5.80 (t, J = 6.2 Hz, 1 H, 3-H), 5.25–5.39 (m, 2 H, 2-H, 4-H), 5.00–5.20 (m, 4 H, CH_2-Cbz, CH_2-Bn), 4.67 (br. s, 1 H, α-H-Asn), 4.24 (dd, J_{gem} = 8.0, $J_{6,5}$ = 4.0 Hz, 1 H, 6-H), 3.97 (dd, J_{gem} = 8.0, $J_{6',5}$ = 1.8 Hz, 1 H, 6′-H), 3.84 (m, 1 H, 5-H), 3.02–2.80 (m, 2 H, CH_2-Asn), 2.04 (s, 3 H, CH_3CO), 2.02 (s, 3 H, CH_3CO), 2.00 (s, 3 H, CH_3CO), 1.96 (s, 3 H, CH_3CO) ppm. MS (ESI): m/z = 709.6 $[M + Na]^+$.

***N*$^{\gamma}$-(2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl)-L-asparagine (7):** Compound **6** (300 mg, 0.437 mmol, 1eq) was dissolved in a mixture of MeOH/H_2O/AcOH (25:5:3, 33 mL) and 10% Pd/C was added. The reaction mixture was stirred under H_2 for 2 h and then was filtered through a pad of Celite and washed with methanol. The solvent was evaporated to afford **7** (228 mg) in quantitative yield. $[\alpha]_D^{20}$ = +62.3 (c = 0.5, MeOH). ^1H NMR (400 MHz, CD_3OD, 25 °C): δ = 5.90 (d, $J_{1,2}$ = 6.0 Hz, 1 H, 1-H), 5.62 (t, $J_{3,2}$ = 9.8 Hz, 1 H, 3-H), 5.10–5.04 (m, 2 H, 2-H, 4-H), 4.29 (dd, J_{gem} = 12.4, $J_{6,5}$ = 3.6 Hz, 1 H, 6-H), 4.05 (dd, J_{gem} = 12.4, $J_{6',5}$ = 1.6 Hz, 1 H, 6′-H), 3.97–3.91 (m, 1 H, 5-H), 3.86–3.83 (br. s, 1 H, α-H-Asn), 3.10–3.01 (m, 1 H, β-CH_2-Asn), 2.89–2.80 (m, 1 H, β-CH_2-Asn), 2.05 (s, 3 H, CH_3CO), 2.04 (s, 3 H, CH_3CO), 2.02 (s, 3 H, CH_3CO), 1.99 (s, 3 H, CH_3CO) ppm. ^{13}C NMR (100 MHz, CD_3OD, 25 °C): δ = 172.6–170.2 (CO), 75.5 (C-1), 71.9 (C-3), 70.7 (C-2), 70.3 (C-4), 70.1 (C-5), 63.5 (C-6), 52.3 (α-C-Asn), 36.7 (β-CH_2-Asn), 21.0, 20.9, 20.8 (4× OAc) ppm. MS (ESI): m/z = 463.4 $[M + H]^+$, 485.6 $[M + Na]^+$.

***N*$^{\alpha}$-Fluorenylmethoxycarbonyl-*N*$^{\gamma}$-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-L-asparagine (1):** Compound **7** (82 mg, 0.157 mmol, 1 equiv.) and Fmoc-*O*-succinimide (69 mg, 0.204 mmol, 1.3 equiv.) were dissolved in dry pyridine (1.5 mL) under nitrogen. The reaction mixture was stirred at room temperature overnight. After completion (TLC, 85:15 chloroform/methanol and 60:40 chloroform/methanol) the solvent was evaporated, the residue was dissolved in EtOAc and the organic phase was washed with 1 M HCl and dried with Na_2SO_4. The solvent was evaporated under reduced pressure to yield 148 mg of the crude product, which was purified by flash chromatography (95:5 chloroform/methanol) to afford **1** (106 mg) in 99% yield. $[\alpha]_D^{20}$ = +56.3 (c = 0.675, MeOH). ^1H NMR (400 MHz, CD_3OD, 25 °C): δ = 7.79 (d, J = 7.2 Hz, 2 H, 4-H-Fmoc, 5-H-Fmoc), 7.66 (d, J = 7.2 Hz, 2 H, 1-H-Fmoc, 8-H-Fmoc), 7.39 (t, J = 7.2 Hz, 2 H, 3-H-Fmoc, 6-H-Fmoc), 7.31 (t, J = 7.2 Hz, 2-H-Fmoc, 7-H-Fmoc), 5.86 (d, $J_{1,2}$ = 5.6 Hz, 1 H, 1-H), 5.64 (t, $J_{3,2}$ = $J_{3,4}$ = 9.2 Hz, 1 H, 3-H), 5.09–5.02 (m, 2 H, 2-H, 4-H), 4.49 (br. s, 1 H, α-H-Asn), 4.39–4.18 (m, 4 H, 9-H-Fmoc, CH_2-Fmoc, 6-H), 4.01 (dd, J_{gem} = 12.2, $J_{6',5}$ = 1.8 Hz, 1 H, 6′-H), 3.97–3.92 (m, 1 H, 5-H), 2.98–2.76 (m, 2 H, β-CH_2-Asn), 2.16 (s, 3 H, CH_3CO), 2.02 (s, 3 H, CH_3CO), 2.00 (s, 3 H, CH_3CO), 1.98 (s, 3 H, CH_3CO) ppm. ^{13}C NMR (100 MHz, CD_3OD, 25 °C): δ = 172.6–171.4 (CO), 145.4 (C_{quat}Fmoc), 142.7 (C_{quat}Fmoc), 129.0 (C-2-, C-7-Fmoc), 128.4 (C-3-, C-6-Fmoc), 126.4 (C-1-, C-8-Fmoc), 121.0 (C-4-, C-5-Fmoc), 75.4 (C-1), 71.9 (C-3), 70.6 (C-2), 70.1 (C-4), 69.7 (C-5), 68.3 (CH_2-Fmoc), 63.2 (C-6), 50.0 (α-C-Asn), 48.5 (C-9-Fmoc), 39.6 (β-CH_2-Asn), 20.8, 20.7, 20.6 (4× OAc) ppm. FT-ICR MS (ESI): calcd. for $[C_{33}H_{35}O_{14}N_2]^-$ 683.20938; found 683.20968.

N^{α}-Benzyloxycarbonyl-N^{γ}-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-L-asparagine Methyl Ester (13): 2,3,4,6-Tetra-*O*-acetyl-β-D-glucosyl azide (**3**;[5a] 250 mg, 0.670 mmol, 1 equiv.) and Ph_3P (193 mg, 0.737 mmol, 1.1 equiv.) were dissolved in nitroethane (5 mL) in the presence of ground 3 Å molecular sieves (ca. 900 mg). The resulting solution was heated at reflux for 15 h under N_2 and then cooled to room temperature before adding Cbz-Asp(SPy)-OMe (**12**;[15] 325 mg, 0.871 mmol, 1.3 equiv.) and $CuCl_2{\cdot}2H_2O$ (148 mg, 0.871 mmol, 1.3 equiv.). The mixture was stirred at 30 °C for 6 h. After completion (TLC, 1:1 hexane/EtOAc) the reaction mixture was diluted with CH_2Cl_2 and filtered through a pad of Celite. The solvent was evaporated and the crude was dissolved in EtOAc and washed with a saturated ammonium chloride solution. The organic phase was dried with Na_2SO_4 and the solvent removed under reduced pressure. The crude was purified by flash chromatography (1:1 hexane/EtOAc) to afford **13** (143 mg) in 35% yield. $[\alpha]_D^{20}$ = +45.6 (*c* = 0.15, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.36–7.30 (m, 5 H, H_{Ar}-Bn), 6.88 (br. s, 1 H, Glc-NH-Asn), 5.96 (d, *J* = 7.6 Hz, 1 H, NH-Cbz), 5.83 (t, 1 H, 1-H), 5.35 (t, $J_{3,4} = J_{3,2}$ = 9.6 Hz, 1 H, 3-H), 5.18–5.10 (m, 3 H, 2-H, CH_2-Cbz), 5.06 (t, $J_{4,3} = J_{4,5}$ = 9.6 Hz, 1 H, 4-H), 4.64 (br. s, 1 H, α-H-Asn), 4.27 (dd, J_{gem} = 12.0, $J_{6,5}$ = 4.0 Hz, 1 H, 6-H), 4.04 (dd, J_{gem} = 12.0, $J_{6',5}$ = 1.8 Hz, 1 H, 6′-H), 3.90 (m, 1 H, 5-H), 3.75 (s, 3 H, $COOCH_3$), 3.02–2.78 (m, 2 H, CH_2-Asn), 2.06 (s, 3 H, CH_3CO), 2.03 (s, 3 H, CH_3CO), 2.02 (s, 3 H, CH_3CO), 1.98 (s, 3 H, CH_3CO) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 171.4–169.3 (CO), 136.2 (C_{quat}Cbz), 128.7, 128.4, 128.3 (CH-Cbz), 74.5 (C-1), 70.3 (C-3), 68.6 (C-2, C-4), 68.5 (C-5), 67.5 (CH_2-Cbz), 61.9 (C-6), 53.1 ($COOCH_3$), 51.0 (α-C-Asn), 38.6 (β-CH_2-Asn), 20.9, 20.8, 20.6 (4× OAc) ppm. MS (ESI): *m*/*z* = 633.3 $[M + Na]^+$.

N^{γ}-(2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl)-L-asparagine-*O*-methyl Ester Hydrocloride (14b): Compound **13** (35 mg, 0.057 mmol) and acetyl chloride (0.057 mmol, 4 μL) were dissolved in MeOH/H_2O (5:1, 6 mL). Pd/C (10%) was added and the mixture was stirred under hydrogen for 2 h, filtered through a pad of Celite and washed with methanol. The solvent was evaporated to afford **14b** (29 mg) in quantitative yield. $[\alpha]_D^{20}$ = +96.6 (*c* = 1.2, MeOH). ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = 5.85 (d, $J_{1,2}$ = 5.6 Hz, 1 H, 1-H), 5.60 (t, $J_{3,2} = J_{3,4}$ = 9.6 Hz, 1 H, 3-H), 5.09–5.02 (m, 2 H, 2-H, 4-H), 4.37 (br. s, 1 H, α-H-Asn), 4.28 (dd, J_{gem} = 12.0, $J_{6,5}$ = 4.0 Hz, 1 H, 6-H), 4.04 (dd, J_{gem} = 12.0, $J_{6',5}$ = 1.8 Hz, 1 H, 6′-H), 3.94–3.90 (m, 1 H, 5-H), 3.85 (s, 3 H, $COOCH_3$), 3.10–2.97 (m, 2 H, β-CH_2-Asn), 2.12 (s, 3 H, CH_3CO), 2.07 (s, 3 H, CH_3CO), 2.03 (s, 3 H, CH_3CO), 2.01 (s, 3 H, CH_3CO) ppm. ^{13}C NMR (100 MHz, CD_3OD, 25 °C): δ = 172.4–170.0 (CO), 75.3 (C-1), 71.7 (C-3), 70.5 (C-2), 70.1 (C-4), 69.9 (C-5), 63.3 (C-6), 54.1 ($CO-OCH_3$), 50.7 (α-C-Asn), 35.5 (β-CH_2-Asn), 20.8, 20.7, 20.6 (4× OAc) ppm. MS (ESI): *m*/*z* = 499.3 $[M + Na]^+$.

N^{α}-Fluorenylmethoxycarbonyl-N^{γ}-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-L-asparagylglycine Methyl Ester (10): Compound **1** (25 mg, 0.036 mmol, 1 equiv.) and PyBROP (37 mg, 0.080 mmol, 2.2 equiv.) were dissolved in dry CH_2Cl_2 (400 μL) under nitrogen at 0 °C. DIPEA (20 μL, 0.117 mmol, 3.2 equiv.) was added. After 10 min, glycine methyl ester hydrochloride (14 mg, 0.109 mmol, 3 equiv.) and DIPEA (19 μL, 0.109 mmol, 3 equiv.) were added and the reaction mixture was stirred at 0 °C for 2 h and then at room temperature for 3 h. After completion (TLC, 85:15 chloroform/methanol and 30:70 hexane/EtOAc) the solvent was evaporated, the residue was dissolved in EtOAc and the organic phase was washed with 1 M HCl and saturated $NaHCO_3$ and then dried with sodium sulfate. The solvent was evaporated under reduced pressure to yield 33 mg of the crude product, which was purified by flash chromatography (40:60 hexane/EtOAc) to afford **10** (19 mg) in 69% yield. $[\alpha]_D^{20}$ = +66.9 (*c* = 0.9, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.80 (d, *J* = 7.8 Hz, 1 H, Glc-NH-Asn), 7.75 (d, *J* = 7.6 Hz, 2 H, 4-H-, 5-H-Fmoc), 7.58 (d, *J* = 7.2 Hz, 2 H, 1-H-, 8-H-Fmoc), 7.39 (t, *J* = 7.2 Hz, 2 H, 3-H-, 6-H-Fmoc), 7.29 (t, *J* = 7.6 Hz, 2 H, 2-H-, 7-H-Fmoc), 6.57 (d, *J* = 7.2 Hz, 1 H, NH-Fmoc), 5.83 (dd, $J_{1,NH}$ = 7.8, $J_{1,2}$ = 5.6 Hz, 1 H, 1-H), 5.46 (t, $J_{3,2} = J_{3,4}$ = 9.8 Hz, 1 H, 3-H), 5.15–5.05 (m, 2 H, 2-H, 4-H), 4.64 (br. s, 1 H, α-H-Asn), 4.48–4.33 (m, 2 H, CH_2-Fmoc), 4.30–4.18 (m, 2 H, 9-H-Fmoc, 6-H), 4.15–4.03 (m, 2 H, 6′-H, α-H-Gly), 4.00–3.87 (m, 2 H, 5-H, α-H-Gly), 3.72 (s, 3 H, $COOCH_3$), 2.99–2.90 (m, 1 H, β-H-Asn), 2.74–2.66 (m, 1 H, β-H-Asn), 2.05 (s, 3 H, CH_3CO), 2.02 (s, 3 H, CH_3CO), 1.98 (s, 3 H, CH_3CO), 1.96 (s, 3 H, CH_3CO) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 171.5–169.4 (CO), 143.8, 143.7 (C_{quat}Fmoc), 141.4 (C_{quat}Fmoc), 127.9 (C-2-, C-7-Fmoc), 127.2 (C-3-, C-6-Fmoc), 125.2 (C-1-, C-8-Fmoc), 120.2 (C-4-, C-5-Fmoc), 74.5 (C-1), 68.8 (C-3), 68.3 (C-2), 68.2 (C-4, C-5), 67.6 (CH_2-Fmoc), 60.5 (C-6), 52.6 ($COOCH_3$), 51.6 (α-C-Asn), 47.2 (C-9-Fmoc), 41.4 (CH_2-Gly), 37.8 (β-CH_2-Asn), 20.7, 20.6 (4× OAc) ppm. FT-ICR MS (ESI): calcd. for $[C_{36}H_{41}O_{15}N_3Na]^+$ 778.24299; found 778.24140.

(*S*)-1-(2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl)-3-(*N*-fluorenylmethoxycarbonyl)-2,5-dioxopyrrolidine (11): This compound was isolated as a byproduct in some of the coupling reactions leading to **10**, as described in Table 1 (flash chromatography, 40:60 hexane/EtOAc, R_f = 0.37). $[\alpha]_D^{20}$ = +41.2 (*c* = 0.45, CH_2Cl_2). ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = 7.79 (d, *J* = 7.2 Hz, 2 H, 4-H-Fmoc, 5-H-Fmoc), 7.66 (t, *J* = 7.2 Hz, 2 H, 1-H-Fmoc, 8-H-Fmoc), 7.40 (t, *J* = 7.2 Hz, 2 H, 3-H-Fmoc, 6-H-Fmoc), 7.32 (t, *J* = 7.2 Hz, 2-H-Fmoc, 7-H-Fmoc), 6.28 (t, *J* = 9.2 Hz, 1 H, 3-H), 6.05 (d, $J_{1,2}$ = 7.8 Hz, 1 H, 1-H), 5.29 (t, $J_{2,1}$ = 7.8 Hz, 1 H, 2-H), 5.13 (t, *J* = 9.2 Hz, 1 H, 4-H), 4.44–4.28 (m, 3 H, α-H-Asn, 9-H-Fmoc, CH-Fmoc), 4.29–4.17 (m, 3 H, 6-H, 5-H, CH-Fmoc), 4.08–4.02 (m, 1 H, 6′-H), 3.18–3.00 (dd, J_{gem} = 15.6, $J_{\alpha,\beta}$ = 9.2 Hz, 1 H, β-H-Asn), 2.84–2.73 (dd, J_{gem} = 15.6, $J_{\alpha,\beta}$ = 6.4 Hz, 1 H, β-H-Asn), 2.02 (s, 3 H, CH_3CO), 2.01 (s, 3 H, CH_3CO), 2.00 (s, 3 H, CH_3CO), 1.99 (s, 3 H, CH_3CO) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 175.7–169.9 (CO), 143.7, 143.5 (C_{quat}Fmoc), 141.6, 141.5 (C_{quat}Fmoc), 128.1, 128.0 (C-2-, C-7-Fmoc), 127.4 (C-3-, C-6-Fmoc), 125.1 (C-1-, C-8-Fmoc), 120.3 (C-4-, C-5-Fmoc), 74.9 (C-1), 72.9 (C-5), 72.3 (C-3), 68.5 (C-4, C-5), 67.5 (CH_2-Fmoc), 61.9 (C-6), 50.7 (α-C-Asn), 47.3 (C-9-Fmoc), 35.3 (β-CH_2-Asn), 21.9, 20.9, 20.7 (4× OAc) ppm. MS (ESI): *m*/*z* = 689.4 $[M + Na]^+$.

***N*-*tert*-Butoxycarbonyl-L-phenylalanyl-N^{γ}-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-L-asparagine Methyl Ester (16):** Compound **14b** (18 mg, 0.035 mmol, 1 equiv.), Boc-Phe-OH (**15**; 33 mg, 0.123 mmol, 3.5 equiv.) and HATU (47 mg, 0.123 mmol, 3.5 equiv.) were dissolved in dry DMF (400 μL) under nitrogen at 0 °C. DIPEA (28 μL, 0.158 mmol, 4.5 equiv.) was added and the reaction mixture was stirred at 0 °C for 2 h and then at room temperature for 4 h (TLC, 85:15 chloroform/methanol and 30:70 hexane/EtOAc). The solvent was evaporated, the residue was dissolved in EtOAc and the organic phase was washed with 1 M HCl and saturated $NaHCO_3$ and then dried with sodium sulfate. The solvent was evaporated and the crude was purified by flash chromatography (40:60 hexane/EtOAc) to afford **16** (23 mg) in 87% yield. $[\alpha]_D^{20}$ = +51.9 (*c* = 1.35, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.90 (d, $J_{NH,1}$ = 8.6 Hz, 1 H, Glc-NH-Asn), 7.31–7.22 (m, 5 H, CH_{Ar}), 6.77 (d, *J* = 7.2 Hz, 1 H, Asn-NH-Phe), 5.88 (dd, $J_{1,NH}$ = 8.6, $J_{1,2}$ = 5.6 Hz, 1 H, 1-H), 5.58 (t, $J_{3,2} = J_{3,4}$ = 9.6 Hz, 1 H, 3-H), 5.28–5.17 (m, 2 H, NHBoc, 2-H), 5.13 (t, $J_{4,3} = J_{4,5}$ = 9.6 Hz, 1 H, 4-H), 4.98 (br. s, 1 H, α-H-Asn), 4.39–4.25 (m, 2 H, 6-H, α-H-Phe), 4.10–3.98 (m, 2 H, 6′-H, 5-H), 3.73 (s, 3 H, $CO-OCH_3$), 3.14–2.83 (m, 2 H, β-H-Phe), 2.84–2.70 (m, 2 H, β-H-Asn),

2.06 (s, 3 H, CH_3CO), 2.04 (s, 3 H, CH_3CO), 1.97 (s, 3 H, CH_3CO), 1.90 (s, 3 H, CH_3CO), 1.41 (s, 9 H, $COOtBu$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 172.0–169.4 (CO), 156.7 (NHCO), 136.1 ($C_{quat}Ar$), 129.5, 128.9, 127.4 (CH_{Ar}), 80.9 ($C_{quat}tBu$), 74.4 (C-1), 70.5 (C-3), 69.1, 69.0 (C-2, C-5), 68.2 (C-4), 61.8 (C-6), 57.2 (α-C-Phe), 53.0 ($COOCH_3$), 49.7 (α-C-Asn), 39.9 (β-CH_2-Asn), 37.9 (β-CH_2-Phe), 28.6 [$COO(CH_3)_3$], 20.9, 20.8, 20.7, 20.6 (4× OAc) ppm. FT-ICR MS (ESI): calcd. for $[C_{33}H_{45}O_{15}N_3\ Na]^+$ 746.27429; found 746.27414.

N^{α}-Benzyloxycarbonyl-N^{γ}-(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)-L-asparagine Benzyl Ester (18): 2,3,4,6-Tetra-*O*-acetyl-β-D-galactosyl azide (**17**;[5a] 402 mg, 1.077 mmol, 1 equiv.) and Ph_3P (311 mg, 1.185 mmol, 1.1 equiv.) were dissolved in nitroethane (6 mL) in the presence of ground 3 Å molecular sieves (ca. 1.2 g). The resulting solution was heated at reflux for 15 h under nitrogen and then cooled to room temperature. Cbz-Asp(SPy)-OBn (**5**;[15] 630 mg, 1.400 mmol, 1.3 equiv.) and $CuCl_2{\cdot}2H_2O$ (239 mg, 1.400 mmol, 1.3 equiv.) were added sequentially and the reaction mixture was stirred at 30 °C for 24 h. After completion (TLC, 1:1 hexane/EtOAc) the reaction mixture was diluted with CH_2Cl_2 and filtered through a pad of Celite. The solvent was evaporated and the crude was dissolved in EtOAc and washed with a saturated ammonium chloride solution. The organic phase was dried with sodium sulfate and the solvents evaporated. The crude was purified by flash chromatography (1:1 hexane/EtOAc) to afford **18** (592 mg) in 80% yield. $[\alpha]_D^{20}$ = +65.4 (*c* = 1, MeOH). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.32–7.28 (m, 10 H, H_{Ar}Cbz, H_{Ar}Bn), 7.14 (br. s, 1 H, Gal-NH-Asn), 6.01 (d, *J* = 7.6 Hz, 1 H, NH-Cbz), 5.91 (dd, $J_{1,NH}$ = 7.6, $J_{1,2}$ = 5.2 Hz, 1 H, 1-H), 5.41–5.30 (m, 2 H, 2-H, 4-H), 5.25 (dd, $J_{3,4}$ = 3.2, $J_{3,2}$ = 11.0 Hz, 1 H, 3-H), 5.18–5.05 (m, 4 H, CH_2-Cbz, CH_2-Bn), 4.69 (br. s, 1 H, α-H-Asn), 4.11–3.98 (m, 3 H, 5-H, 6-H), 3.05–2.81 (m, 2 H, CH_2-Asn), 2.13 (s, 3 H, CH_3CO), 2.04 (s, 3 H, CH_3CO), 2.01 (s, 3 H, CH_3CO), 1.96 (s, 3 H, CH_3CO) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 170.8–169.6 (CO), 156.5 (NHCO), 136.1 (C_{quat}Bn), 135.3 (C_{quat}Cbz), 142.7 (CH-Bn, CH-Cbz), 74.8 (C-1), 68.0 (C-3, C-4, C-5), 67.6 (CH_2-Cbz), 67.2 (C-2), 66.2 (CH_2-Cbz), 61.7 (C-6), 51.2 (α-C-Asn), 38.5 (β-CH_2-Asn), 21.3, 20.7 (4× OAc) ppm. MS (ESI): *m*/*z* = 709.4 $[M + Na]^+$.

N^{γ}-(2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl)-L-asparagine (19): Compound **18** (250 mg, 0.364 mmol) was dissolved in 15 mL of a mixture of MeOH/H_2O/AcOH (25:5:3) and 10% Pd/C was added. The reaction mixture was stirred under hydrogen for 2 h, then filtered through a pad of Celite and washed with methanol. The solvent was evaporated to afford **19** (190 mg) in quantitative yield. $[\alpha]_D^{20}$ = +91.7 (*c* = 2.25, MeOH). ^1H NMR (400 MHz, CD_3OD, 25 °C): δ = 5.93 (d, $J_{1,2}$ = 5.2 Hz, 1 H, 1-H), 5.53–5.45 (m, 2 H, 3-H, 4-H), 5.26 (dd, $J_{2,1}$ = 5.2, $J_{2,3}$ = 10.8 Hz, 1 H, 2-H), 4.21–4.05 (m, 2 H, 5-H, 6-H), 4.04–4.00 (m, 1 H, 6′-H), 3.92 (br. s, 1 H, α-H-Asn), 3.12–3.03 (m, 1 H, β-CH_2-Asn), 2.93–2.82 (m, 1 H, β-CH_2-Asn), 2.15 (s, 3 H, CH_3CO), 2.05 (s, 3 H, CH_3CO), 2.01 (s, 3 H, CH_3CO), 1.97 (s, 3 H, CH_3CO) ppm. ^{13}C NMR (100 MHz, CD_3OD, 25 °C): δ = 173.8–171.7 (CO), 75.7 (C-1), 68.8 (C-3, C-4, C-5), 67.8 (C-2), 62.6 (C-6), 52.6 (α-C-Asn), 36.5 (β-CH_2-Asn), 20.8, 20.7, 20.6 (4× OAc) ppm. MS (ESI): *m*/*z* = 463.0 $[M + H]^+$, 485.1 $[M + Na]^+$.

N^{α}-Fluorenylmethoxycarbonyl-N^{γ}-(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)-L-asparagine (2): Compound **19** (190 mg, 0.364 mmol, 1 equiv.) and Fmoc-*O*-succinimide (135 mg, 0.400 mmol, 1.1 equiv.) were dissolved in dry pyridine (1.8 mL) under nitrogen. The reaction mixture was stirred at room temperature overnight. After completion of the reaction (TLC, 8:2 chloroform/methanol and, 6:4 chloroform/methanol) the solvent was evaporated, the residue was dissolved in EtOAc and the organic phase was washed with 1 M HCl and then dried with sodium sulfate. The solvent was evaporated under reduced pressure to yield 318 mg of the crude product, which was purified by flash chromatography (95:5 chloroform/methanol) to afford **2** (222 mg) in 89% yield. $[\alpha]_D^{20}$ = +72.6 (*c* = 0.5, MeOH). ^1H NMR (400 MHz, CD_3OD, 25 °C): δ = 7.80 (d, *J* = 7.6 Hz, 2 H, 4-H-, 5-H-Fmoc), 7.66 (d, *J* = 7.0 Hz, 2 H, 1-H-, 8-H-Fmoc), 7.40 (t, *J* = 7.6 Hz, 2 H, 3-H-, 6-H-Fmoc), 7.32 (t, *J* = 7.0 Hz, 2 H, 2-H-, 7-H-Fmoc), 5.90 (d, $J_{1,2}$ = 5.2 Hz, 1 H, 1-H), 5.53–5.48 (m, 1 H, 3-H), 5.50–5.43 (m, 1 H, 4-H), 5.26 (dd, $J_{2,1}$ = 5.2, $J_{2,3}$ = 10.8 Hz, 1 H, 2-H), 4.61 (br. s, 1 H, α-H-Asn), 4.42–4.21 (m, 3 H, 9-H-Fmoc, CH_2-Fmoc), 4.17–4.07 (m, 2 H, 5-H, 6-H), 4.03–3.96 (m, 1 H, 6′-H), 2.94 (dd, J_{gem} = 15.4, $J_{\alpha,\beta}$ = 5.2 Hz, 1 H, β-H-Asn), 2.80 (dd, J_{gem} = 15.4, $J_{\alpha,\beta}$ = 6.8 Hz, 1 H, β-H-Asn), 2.14 (s, 3 H, CH_3CO), 2.02 (s, 3 H, CH_3CO), 1.98 (s, 3 H, CH_3CO), 1.95 (s, 3 H, CH_3CO) ppm. ^{13}C NMR (100 MHz, CD_3OD, 25 °C): δ = 173.6–171.7 (CO), 158.5 (NHCO), 145.4 (C_{quat}Fmoc), 145.3 (C_{quat}Fmoc), 142.7 (C_{quat}Fmoc), 129.0 (C_2-, C_7-Fmoc), 128.3 (C-3-, C-6-Fmoc), 126.4, 126.3 (C-1-, C-8-Fmoc), 121.1 (C-4-, C-5-Fmoc), 75.6 (C-1), 69.1 (C-3), 69.1 (C-4), 68.7 (C-5), 68.3 (CH_2-Fmoc), 67.7 (C-2), 62.6 (C-6), 52.3 (α-C-Asn), 48.5 (C-9-Fmoc), 38.9 (β-CH_2-Asn), 20.7, 20.6 (4× OAc) ppm. FT-ICR MS (ESI): calcd. for $[C_{33}H_{35}O_{14}N_2]^-$ 683.20938; found 683.20959.

N^{α}-Fluorenylmethoxycarbonyl-N^{γ}-(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)-L-asparagylglycine Methyl Ester (20): Compound **2** (35 mg, 0.051 mmol, 1 equiv.) and PyBROP (52 mg, 0.112 mmol, 2.2 equiv.) were dissolved in dry CH_2Cl_2 (400 μL) under nitrogen at 0 °C. DIPEA (20 μL, 0.112 mmol, 2.2 equiv.) was added. After 10 min, glycine methyl ester hydrochloride (19 mg, 0.153 mmol, 3 equiv.) and DIPEA (27 μL, 0.153 mmol, 3 equiv.) were added and the reaction mixture was stirred at 0 °C for 2 h and then at room temperature for 5 h. After completion (TLC, 85:15 chloroform/methanol and 30:70 hexane/EtOAc) the solvent was evaporated, the residue was dissolved in EtOAc and the organic phase was washed with 1 M HCl and saturated $NaHCO_3$ and then dried with sodium sulfate. The solvent was evaporated and the crude was purified by flash chromatography (40:60 hexane/EtOAc) to afford **20** (24 mg) in 62% yield. $[\alpha]_D^{20}$ = +55.1 (*c* = 0.5, MeOH). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.75 (d, *J* = 7.2 Hz, 2 H, 4-H-, 5-H-Fmoc), 7.59 (d, *J* = 7.6 Hz, 2 H, 1-H-, 8-H-Fmoc), 7.39 (t, *J* = 7.6 Hz, 2 H, 3-H-, 6-H-Fmoc), 7.35 (br. s, 1 H, Gal-NH-Asn), 7.30 (t, *J* = 7.2 Hz, 2 H, 2-H-, 7-H-Fmoc), 7.23 (br. s, 1 H, NH-Gly), 6.41 (d, *J* = 7.4 Hz, 1 H, NH-Fmoc), 5.87 (dd, $J_{1,NH}$ = 7.4, $J_{1,2}$ = 5.2 Hz, 1 H, 1-H), 5.41 (d, $J_{4,5}$ = $J_{4,3}$ = 3.2 Hz, 1 H, 4-H), 5.36 (dd, $J_{2,3}$ = 10.8 Hz, 1 H, 2-H), 5.27 (m, 1 H, 3-H), 4.63 (br. s, 1 H, α-H-Asn), 4.50–4.37 (m, 2 H, CH_2-Fmoc), 4.26–4.18 (m, 2 H, 9-H-Fmoc, 5-H), 4.11 (dd, J_{gem} = 11.4, $J_{6,5}$ = 6.6 Hz, 1 H, 6-H), 4.08–3.97 (m, 3 H, 6′-H, α-CH_2-Gly), 3.73 (s, 3 H, $COOCH_3$), 3.00–2.89 (m, 1 H, β-H-Asn), 2.70–2.65 (m, 1 H, β-H-Asn), 2.15 (s, 3 H, CH_3CO), 2.04 (s, 3 H, CH_3CO), 2.02 (s, 3 H, CH_3CO), 1.99 (s, 3 H, CH_3CO) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 172.0–169.7 (CO), 143.8 (C_{quat}Fmoc), 141.5 (C_{quat}Fmoc), 128.0 (C-2-, C-7-Fmoc), 127.3 (C-3-, C-6-Fmoc), 125.3 (C-1-, C-8-Fmoc), 120.3 (C-4-, C-5-Fmoc), 75.1 (C-1), 67.7 (C-2, C-3), 67.2 (C-4), 67.2 (CH_2-Fmoc), 66.2 (C-5), 61.7 (C-6), 52.7 ($COOCH_3$), 51.9 (α-C-Asn), 47.3 (C-9-Fmoc), 41.5 (CH_2-Gly), 38.2 (β-CH_2-Asn), 20.9, 20.8 (4× OAc) ppm. FT-ICR MS (ESI): calcd. for $[C_{36}H_{41}O_{15}N_3\ Na]^+$ 778.24299; found 778.24179.

***N*-*tert*-Butoxycarbonyl-L-phenylalanyl-N^{γ}-(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)-L-asparagine Methyl Ester (21):** Compound **19** (19 mg, 0.036 mmol, 1 equiv.) was dissolved in dry methanol

(400 μL) under nitrogen. A 2 M (trimethylsilyl)diazomethane solution in diethyl ether (91 μL, 0.182 mmol, 5 equiv.) was added dropwise. After completion of the reaction (TLC, 6:4 chloroform/methanol and 7:3 chloroform/methanol) the solvent was evaporated. Boc-Phe-OH (**15**; 29 mg, 0.109 mmol, 3 equiv.) and PyBROP (51 mg, 0.109 mmol, 3 equiv.) were added to the crude and the mixture was dissolved in dry CH_2Cl_2 (350 μL). DIPEA (25 μL, 0.145 mmol, 4 equiv.) was added under nitrogen at 0 °C and the reaction mixture was stirred at 0 °C for 2 h and then at room temperature for 5 h (TLC, 85:15 chloroform/methanol and 30:70 hexane/EtOAc). The solvent was evaporated, the residue was dissolved in EtOAc and the organic phase was washed with 1 M HCl and saturated $NaHCO_3$ and then dried with sodium sulfate. The solvent was evaporated and the crude was purified by flash chromatography (40:60 hexane/EtOAc) to afford **21** (19 mg) in 72% yield. $[\alpha]_D^{20}$ = +51.7 (*c* = 0.6, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.76 (d, $J_{NH,1}$ = 8.8 Hz, 1 H, Gal-NH-Asn), 7.31–7.16 (m, 5 H, CH_{Ar}), 6.71 (d, *J* = 8.0 Hz, 1 H, Asn-NH-Phe), 5.92 (dd, $J_{1,NH}$ = 8.8, $J_{1,2}$ = 5.2 Hz, 1 H, 1-H), 5.59–5.51 (m, 1 H, 3 H), 5.41 (dd, $J_{2,1}$ = 5.2, $J_{2,3}$ = 11.0 Hz, 1 H, 2-H), 5.35 (m, 1 H, 4-H), 5.18 (d, *J* = 4.0 Hz, 1 H, NHBoc), 4.91 (br. s, 1 H, α-H-Asn), 4.26–4.18 (m, 2 H, 5-H, α-H-Phe), 4.15–4.00 (m, 2 H, 6-H), 3.72 (s, 3 H, $COOCH_3$), 3.11–2.92 (m, 2 H, β-CH_2-Phe), 2.84–2.67 (m, 2 H, β-CH_2-Asn), 2.15 (s, 3 H, CH_3CO), 2.01 (s, 3 H, CH_3CO), 1.99 (s, 3 H, CH_3CO), 1.96 (s, 3 H, CH_3CO), 1.41 (s, 9 H, $COOtBu$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 171.8–169.7 (CO), 136.1 (C_{quat}Ar), 129.3, 128.9, 127.4 (CH_{Ar}), 80.8 ($C_{quat}tBu$), 74.8 (C-1), 67.9 (C-4), 67.8 (C-5), 67.4 (C-3), 66.7 (C-2), 61.5 (C-6), 57.1 (α-C-Phe), 53.0 ($COOCH_3$), 49.7 (α-C-Asn), 40.0 (β-CH_2-Asn), 37.9 (β-CH_2-Phe), 28.5 [$COO(CH_3)_3$], 20.9, 20.8, 20.7 (4× OAc) ppm. FT-ICR MS (ESI): calcd. for $[C_{33}H_{45}O_{15}N_3\ Na]^+$ 746.27429; found 746.27378.

N^{α}-Fluorenylmethoxycarbonyl-N^{γ}-(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)-L-asparagine-*N*-methylamide (22): Compound **2** (102 mg, 0.149 mmol, 1 equiv.), *N*-methylamine hydrochloride (30 mg, 0.447 mmol, 3 equiv.) and PyBROP (167 mg, 0.357 mmol, 2.4 equiv.) were dissolved in dry CH_2Cl_2 (1.5 mL) under nitrogen at 0 °C. DIPEA (140 μL, 0.804 mmol, 5.4 equiv.) was added and the reaction mixture was stirred at 0 °C for 2 h and then at room temperature for 4 h (TLC, 8:2 chloroform/methanol and 1:9 hexane/EtOAc). The solvent was evaporated, the residue was dissolved in EtOAc and the organic phase was washed with 1 M HCl and saturated $NaHCO_3$ and then dried with sodium sulfate. The solvent was evaporated and the crude was purified by flash chromatography (1:9 hexane/EtOAc) to afford **22** (87 mg) in 84% yield. $[\alpha]_D^{20}$ = +52.8 (*c* = 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.75 (d, *J* = 7.2 Hz, 2 H, 4-H-, 5-H-Fmoc), 7.72 (br. s, 1 H, Gal-NH-Asn), 7.57 (d, *J* = 7.6 Hz, 2 H, 1-H-, 8-H-Fmoc), 7.39 (t, *J* = 7.6 Hz, 2 H, 3-H-, 6-H-Fmoc), 7.30 (t, *J* = 7.2 Hz, 2 H, 2-H-, 7-H-Fmoc), 6.84 (br. s, 1 H, NHMe), 6.47 (br. s, 1 H, NH-Fmoc), 5.89 (dd, $J_{1,NH}$ = 7.6, $J_{1,2}$ = 4.4 Hz, 1 H, 1-H), 5.41 (br. s, 1 H, 4-H), 5.36–5.28 (m, 2 H, 2-H, 3-H), 4.56 (br. s, 1 H, α-H-Asn), 4.52–4.38 (m, 2 H, CH_2-Fmoc), 4.22–4.15 (m, 2 H, 9-H-Fmoc, 5-H), 4.12–4.00 (m, 2 H, 6-H), 3.00–2.91 (m, 1 H, β-CH_2-Asn), 2.79 (s, 3 H, $NHCH_3$), 2.70–2.63 (m, 2 H, β-CH_2-Asn), 2.14 (s, 3 H, CH_3CO), 2.00 (s, 3 H, CH_3CO), 1.99 (s, 3 H, CH_3CO), 1.96 (s, 3 H, CH_3CO) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 171.6–169.8 (CO), 143.8, 143.7 (C_{quat}Fmoc), 141.6, 141.5 (C_{quat}Fmoc), 128.0 (C-2-, C-7-Fmoc), 127.3 (C-3-, C-6-Fmoc), 125.2 (C-1-, C-8-Fmoc), 120.3 (C-4-, C-5-Fmoc), 75.0 (C-1), 67.8, 67.4 (C-2, C-3, C-4), 67.6 (CH_2-Fmoc), 66.3 (C-5), 61.6 (C-6), 52.0 (α-C-Asn), 47.3 (C-9-Fmoc), 38.0 (β-CH_2-Asn), 26.8 ($NHCH_3$), 20.8 (4× OAc) ppm. MS (ESI): *m*/*z* = 720.4 $[M + Na]^+$.

N^{α}-Acetyl-N^{γ}-(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)-L-asparagine-*N*-methylamide (23): Compound **22** (65 mg, 0.093 mmol, 1 equiv.) was dissolved in dry THF (800 μL) under nitrogen. Octanethiol (29 μL, 0.158 mmol, 10 equiv.) and DBU were added sequentially and the reaction mixture was stirred for 1 h (TLC, 9:1 chloroform/methanol and 1:9 hexane/EtOAc). The solvent was evaporated. The residue was washed thoroughly with a mixture of cold diethyl ether and pentane (1:1). The crude solid was then dissolved in Ac_2O (500 μL) and pyridine (15 μL) was added. The reaction mixture was stirred for 3 h (TLC, 90:10 chloroform/methanol), the solvent was evaporated and the reaction mixture was purified by flash chromatography (95:5 chloroform/methanol) to afford **23** (32 mg) in 62% yield over the two steps. $[\alpha]_D^{20}$ = +84.2 (*c* = 0.7, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.28 (d, *J* = 8.6 Hz, 1 H, Gal-NH-Asn), 7.58 (d, *J* = 7.6 Hz, 1 H, NHAc), 7.29 (d, *J* = 4.8 Hz, 1 H, NHMe), 5.89 (dd, $J_{1,NH}$ = 8.6, $J_{1,2}$ = 5.2 Hz, 1 H, 1-H), 5.39 (m, 1 H, 4-H), 5.34–5.27 (m, 2 H, 2-H, 3-H), 4.83 (br. s, 1 H, α-H-Asn), 4.22–4.18 (m, 1 H, 5-H), 4.12–4.01 (m, 2 H, 6-H), 2.84 (dd, J_{gem} = 15.4, $J_{\alpha,\beta}$ = 5.4 Hz, 1 H, β-H-Asn), 2.79 (d, $J_{Me,NH}$ = 4.8 Hz, 3 H, CH_3N), 2.63 (dd, J_{gem} = 15.4, $J_{\alpha,\beta}$ = 6.8 Hz, 1 H, β-H-Asn), 2.14 (s, 3 H, CH_3CO), 2.04 (s, 3 H, CH_3CO), 2.02 (s, 3 H, CH_3CO), 2.00 (s, 3 H, CH_3CO), 1.98 (s, 3 H, NHAc) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 172.5–169.9 (CO), 74.7 (C-1), 67.7 (C-2, C-3), 67.5 (C-4), 66.5 (C-5), 61.7 (C-6), 50.5 (α-C-Asn), 37.9 (β-CH_2-Asn), 26.5 ($NHCH_3$), 23.2 ($CONHCH_3$), 20.8, 20.7 (4× OAc) ppm. MS (ESI): *m*/*z* = 540.4 $[M + Na]^+$.

N^{α}-Acetyl-N^{γ}-(α-D-galactopyranosyl)-L-asparagine-*N*-methylamide (24): Compound **23** (13 mg, 0.025 mmol, 1 equiv.) was dissolved in dry methanol (250 μL) and a catalytic amount of K_2CO_3 (0.095 equiv., pH 8–9) was added. The reaction mixture was stirred for 2 h (TLC, 6:4 chloroform/methanol and 8:2 chloroform/methanol). IRA H^+ 120 was added to neutral pH. The mixture was filtered and washed with methanol. The solvent was evaporated to afford **24** (8 mg) in 91% yield. $[\alpha]_D^{20}$ = +43.9 (*c* = 0.15, MeOH). ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = 5.55 (d, $J_{1,2}$ = 5.4 Hz, 1 H, 1-H), 4.69 (t, *J* = 6.4 Hz, 1 H, α-H-Asn), 3.98 (dd, $J_{2,3}$ = 10, $J_{2,1}$ = 5.4 Hz, 1 H, 2-H), 3.87 (d, $J_{4,5}$ = $J_{4,3}$ = 3.2 Hz, 1 H, 4-H), 3.74 (dd, $J_{3,2}$ = 10, $J_{3,4}$ = 3.2 Hz, 1 H, 3-H), 3.70–3.61 (m, 3 H, 5-H, 6-H), 2.82–2.72 (m, 5 H, β-CH_2-Asn, $NHCH_3$), 1.99 (s, 3 H, NHAc) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 173.9–173.5 (CO), 78.5 (C-1), 73.7 (C-5), 71.5 (C-3), 70.7 (C-4), 68.4 (C-2), 62.9 (C-6), 51.8 (α-C-Asn), 38.6 (β-CH_2-Asn), 26.7 ($NHCH_3$), 22.8 ($CONHCH_3$) ppm. FT-ICR MS (ESI): calcd. for $[C_{33}H_{45}O_{15}N_3Na]^+$ 372.13774; found 372.13771.

N^{α}-(L-*N*-Acetylalanyl)-N^{γ}-(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)-L-asparagyl-L-alanine (25): H-Ala-2-chlorotrityl resin (90 mg, loading 0.5–0.9 mmol/g) was swollen in DMF. Then the resin was suspended in a solution of DMF/CH_2Cl_2 (1:1, 400 μL) and compound **2** (25 mg, 0.036 mmol) and PyBROP (34 mg, 0.072 mmol) were added. DIPEA (37 μL, 0.216 mmol) was added at 0 °C. The reaction mixture was shaken at 0 °C for 2 h and then at room temperature for 2 h. Capping was performed with a solution of 1 M Ac_2O in DMF (800 μL). After Fmoc removal under standard conditions (20% piperidine in DMF), the yield of coupling was estimated by measuring the UV absorption at 301 nm (ε = 7800) of the solution derived from deprotection (77% based on **2**). Condensation with Ac-Ala-OH (24 mg, 0.18 mmol), HATU (68 mg, 0.18 mmol) and DIPEA (31 μL, 0.18 mmol) was performed in a solution of DMF/CH_2Cl_2 (1:1, 400 μL) for 2 h. Capping with Ac_2O and cleavage (1% TFA in CH_2Cl_2) gave **25**, which was purified by automated chromatography on a reversed-phase C-18 column (CH_3CN/H_2O 0→80%; t_r = 6 min) to afford 18 mg (75%

yield). $[\alpha]_D^{20}$ = +46.3 (*c* = 0.4, MeOH). ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = 5.83 (d, $J_{1,2}$ = 5.6 Hz, 1 H, 1-H), 5.49 (dd, $J_{3,2}$ = 11.0, $J_{3,4}$ = 3.4 Hz, 1 H, 3-H), 5.42 (d, $J_{4,3}$ = 3.4 Hz, 1 H, 4-H), 5.23 (dd, $J_{2,3}$ = 11.0, $J_{2,1}$ = 5.6 Hz, 1 H, 2-H), 4.73 (t, *J* = 6.0 Hz, 1 H, α-H-Asn), 4.38–4.31 (m, 1 H, α-H-Ala), 4.29–4.20 (m, 1 H, α-H-Ala), 4.16–4.08 (m, 2 H, 5-H, 6-H), 4.04–3.96 (m, 1 H, 6′-H), 2.89–2.73 (m, 2 H, β-CH_2-Asn), 2.14 (s, 3 H, CH_3CO), 2.04 (s, 3 H, CH_3CO), 1.99 (s, 3 H, NHAc), 1.98 (s, 3 H, CH_3CO), 1.96 (s, 3 H, CH_3CO) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 175.8–171.7 (CO), 75.8 (C-1), 69.1 (C-4, C-3), 68.6 (C-5), 67.8 (C-2), 62.6 (C-6), 51.3 (α-C-Asn), 51.2 (α-C-Ala), 49.4 (α-C-Ala), 38.0 (β-CH_2-Asn), 22.6 ($NHCH_3$), 20.6 (4 × OAc), 17.8 (CH_3), 17.7 (CH_3) ppm. MS (ESI): *m*/*z* = 647.3 $[M + H]^+$.

***N*$^{\alpha}$-(L-*N*-Acetylalanyl)-*N*$^{\gamma}$-(α-D-galactopyranosyl)-L-asparagyl-L-alanine (26):** Compound **25** (8 mg, 0.012 mmol, 1 equiv.) was dissolved in dry methanol (250 μL) and K_2CO_3 (0.7 equiv.) was added. The reaction mixture was stirred for 3 h (TLC, 6:4 chloroform/methanol and 8:2 chloroform/methanol). The reaction was neutralized by adding 0.035 M HCl solution (250 μL, 0.7 equiv.). The solvent was evaporated and the compound was purified by preparative HPLC (C-18 reversed phase, 100:0 to 60:40 H_2O/CH_3CN in 14 min; t_r = 7 min) to afford **26** (5 mg) in 84% yield. $[\alpha]_D^{20}$ = +40.4 (*c* = 0.15, MeOH). ^{1}H NMR (400 MHz, D_2O, 25 °C): δ = 5.55 (d, $J_{1,2}$ = 5.6 Hz, 1 H, 1-H), 4.70 (dd, *J* = 5.6, *J* = 8.0 Hz, 1 H, α-H-Asn), 4.23 (m, 2 H, α-H-Ala), 4.00 (dd, $J_{2,3}$ = 10.6, $J_{2,1}$ = 5.6 Hz, 1 H, 2-H), 3.93 (d, $J_{4,3}$ = 3.4 Hz, 1 H, 4-H), 3.80 (dd, $J_{3,2}$ = 10.6, $J_{3,4}$ = 3.4 Hz, 1 H, 3-H), 3.73–3.68 (m, 1 H, 6-H), 3.66–3.62 (m, 1 H, 6′-H), 2.91 (dd, J_{gem} = 16.0, $J_{\alpha,\beta}$ = 5.6 Hz, 1 H, β-H-Asn), 2.82 (dd, J_{gem} = 16.0, $J_{\alpha,\beta}$ = 8.0 Hz, 1 H, β-H-Asn), 1.99 (s, 3 H, NHAc), 1.33 (dd, *J* = 8.8 Hz, 6 H, CH_3Ala) ppm. ^{13}C NMR (300 MHz, D_2O, 25 °C): δ = 174.4–172.2 (CO), 77.7 (C-1), 72.6 (C-5), 70.1 (C-3), 69.6 (C-4), 67.0 (C-2), 61.8 (C-6), 61.4 (α-C-Asn), 50.9 (α-C-Ala), 50.6 (α-C-Ala), 37.2 (β-CH_2-Asn), 22.4 ($NHCH_3$), 17.6 (CH_3), 17.3 (CH_3) ppm. FT-ICR MS (ESI): calcd. for $[C_{18}H_{29}O_{11}N_4]^-$ 477.18383; found 477.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of all the new compounds.

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