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Regioselective Syntheses of *β*-*N*-Linked Glycoaminoacids and Glycopeptides

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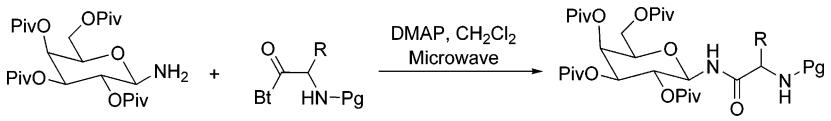

Pg = Cbz, Fmoc

Acylation of tetra-*O*-pivaloyl-*β*-D-galactopyranosylamine **2** by readily available *N*- (Cbz or Fmoc-α-aminoacyl) benzotriazoles under microwave irradiation proceeded diastereoselectively to give *β*-*N*-glycoaminoacids **3a**−**d**, (**3c**+**3c′**) (compound numbers written within brackets represent a racemate or a diastereomeric mixture; compound numbers without brackets represent a single enantiomer) (83−92%), and glycosylated asparagine building block **9** (65%). *N*-Cbz-Protected peptidoylbenzotriazoles **4a**−**c** similarly afforded *β*-*N*-glycodipeptides **5a**−**c** (76−81%). Regiospecific *β*-*N*-linkage formation was established by 1D and 2D NMR techniques for **3b**.

Introduction

The development of novel building blocks opens new possibilities for organic synthesis. Synthetic *N*- and *O*-linked glycopeptides are analogous to those found in naturally occurring carbohydrates linked glycosidically to an α-amino acid of a peptide or a protein. In natural *N*-linked glycoproteins, oligosaccharides are often covalently attached to asparagine side chain via a *β*-*N*-glycosidic linkage,[1−3] while *O*-glycopeptides and proteins are usually attached anomerically to a serine or threonine side chain with an α-*O*-glycosidic linkage[1,3,4] (Figure 1).

The isomer diversity of carbohydrate chains and the roles of nucleic acids and proteins in recording biological information have made glycopeptides and glycoconjugates therapeutic targets and models for biologically relevant systems.[5−7] Glycopeptides are important in biochemical processes ranging from cell growth regulation, immune response, binding of pathogens to intercellular communication, intercellular targeting, cancer cell metastasis, and inflammation.[8−11] Carbohydrate residues are crucial in receptor recognition; antigens are recognized by the immune system in normal tissue,[12] and the isolation and careful structural

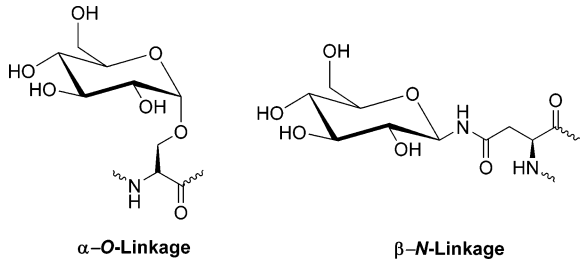

FIGURE 1. α-*O*-Glycosidic and *β*-*N*-glycosidic linkages between carbohydrate and peptides.

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identification of specific carbohydrate antigens overexpressed in cancer cells has inspired carbohydrate-based tumor immunotherapy.[13]

The sugar moieties of glycopeptides define their biological activity, and thus the potential of carbohydrates for the development of new drugs is being explored. Linking peptides to carbohydrates can improve activity and selectivity.[6,14] Protein glycosylation affects pharmacological parameters including the rate of circulation,[15] solubility,[16] proteolytic stability,[17] and immunogenicity.[18] Surfactants combining optically pure, readily available carbohydrates with proteins of agricultural origin are environmentally advantageous. Hydrophilic sugar amino acids linked to lipophilic long chains comprise novel trimodular surfactants.[19] Such potential of glycoaminoacids and glycopeptides has led to the development of chemoenzymatic, convergent, and building block synthetic approaches.[2,14,20−33]

Considerable efforts have been devoted to the synthesis of *N*-glycoaminoacids and *N*-glycopeptides utilizing solution and solid phase[20−22] methodologies by forming *N*-glycosidic linkages between protected or unprotected glycosylamine and suitably protected and activated amino acid (often aspartic acid) units. Methodologies applicable for both protected and unprotected glycosylamines include (i) coupling with the 3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl (Dhbt)−side chain activated aspartic acid in the presence of DCCI[21] or DIPEA,[21,23] and (ii) utilization of uronium or phosphonium salts: HBTU/DIEA,[22] HBTU/HOBt,[24,25] BOP/HOBt,[25] BOP/DIPEA;[29] however, complications in coupling may arise due to competitive ring closures to form succinimides.[25,26] To minimize undesired side reactions, frequently encountered in the use of in situ coupling reagents, the dually activated asparagine derivative N^{α}-Fmoc-Asp(Cl)-OPft was employed:[27,28] the coupling step in dry solvent (THF) in the presence of *N*-ethylmorpholine gave a glycosylated asparagine building block in 76% yield.[27] However, in solution, N^{α}-Fmoc-Asp(Cl)-OPft is suitable only for coupling with protected glycosylamines,[27,28] which possess sufficient solubility in dry organic solvents. In solid phase methodology, N^{α}-Fmoc-Asp-(Cl)-OPft was utilized for the preparation of unprotected *N*-glycoaminoacid building blocks.[20] Additional routes utilized were DCC/HOBt,[14] isobutyl chloroformate (mixed anhydride method),[14] and EEDQ.[22] Recently, one-bead-one-compound (OBOC) technology pioneered by Lam et al.[30] was applied to the synthesis of glycopeptide libraries.[31−33]

However, the above methodologies can result in anomerization leading to partial, or even predominant, formation of the α-anomeric structures.[14,22,23] The coupling of protected glycosyl amines to Asp-containing peptides may be complicated by competing intramolecular succinimide formation,[25,26] resulting in low yields (25−53%),[14,25] and sometimes requiring reaction times of 7−24 h.[22,29] This has encouraged the search for better methodologies for the syntheses of *β*-*N*-glycoaminoacids and *β*-*N*-glycopeptides.

β-Anomers of the glycoaminoacids are sought since the *β*-*N*-glycosyl linkage is biochemically more common than the α-*N*-linkage;[33] thus *N*-asparagine glycoproteins and glycopeptides are *β*-*N*-linked to an *N*-acetyl glucosamine segment of a chitobiose, as part of a high mannose-containing antennary structure.[2]

Carbohydrates are valuable as enantiomerically pure starting materials in chiral pool syntheses of many chiral natural products and drugs.[34] The polyfunctionality of carbohydrates is useful for binding or coordinating a substrate. Carbohydrate derivatives are efficient auxiliaries for stereodifferentiation in many stereoselective chiral syntheses.[35−42]

We have used *N*-acylbenzotriazoles extensively for *N*-acylation of amines[43] and amides,[43,44] *C*-acylation,[45] and *O*-acylation.[46] Chiral di-, tri-, and tetrapeptides were prepared using (α-Boc-, -Cbz-, and -Fmoc-aminoacyl)benzotriazoles in aqueous acetonitrile in good to high yields from unprotected amino acids, both without (L-Ala, L-Phe, L-Val, L-Leu) and with unprotected (L-Trp, L-Tyr, L-Gln, L-Ser, L-Cys, L-Asn) and protected (N^{ω}-Cbz-L-Lys) side chain functionality.[47] The original chirality was preserved in all cases (>95% as evidenced by NMR and >99% by HPLC).

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SCHEME 1

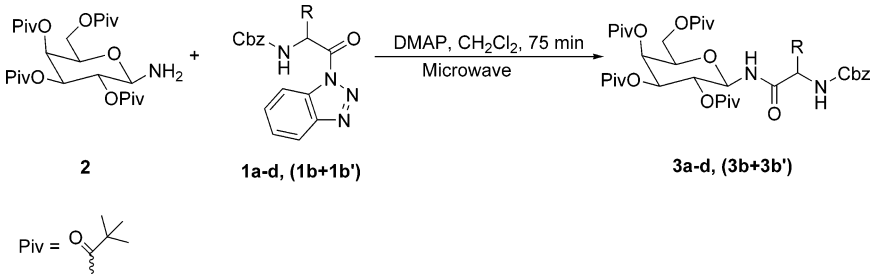

TABLE 1. Preparation of *β*-*N*-Linked Glycoaminoacids 3a−d, (3b+3b′), from Tetra-*O*-pivaloyl-*β*-D-galactopyranosylamine 2 and *N*-(Cbz-α-aminoacyl)benzotriazoles 1a−d, (1a+1b′)

amino acid	product	yield[a] (%)	R.T.[b] (min)
Gly **1a**	Cbz-Gly-*N*-galactopyranose **3a**	87	2.81
L-Phe **1b**	Cbz-L-Phe-*N*-galactopyranose **3b**	92	2.78
L-Trp **1c**	Cbz-L-Trp-*N*-galactopyranose **3c**	82	2.87
L-Met **1d**	Cbz-L-Met-*N*-galactopyranose **3d**	83	2.81
DL−Phe **(1b+1b′)**	Cbz-DL−Phe-*N*-galactopyranose **(3b+3b′)**	87	2.80, 3.25

[a] Isolated yield. [b] For HPLC conditions, refer to the Experimental Section.

Herein, we demonstrate the efficient and exclusive formation of *β*-*N*-linked glycoaminoacids and glycodipeptides (65−92%) by linking a protected amino sugar moiety to an amino acid or peptide under microwave irradiation.

Results and Discussion

Synthesis of *β*-*N*-Linked Glycoaminoacids 3a−d, (3b+3b′). *β*-*N*-Linked glycoaminoacids **3a**−**d**, (**3b**+**3b′**), were prepared by coupling readily available[47] *N*-(*Z*-α-aminoacyl)benzotriazoles **1a**−**d**, (**1b**+**1b′**), with 2,3,4,6-tetra-*O*-pivaloyl-*β*-D-galactopyranosylamine[35] **2**, a versatile chiral auxiliary utilized for regio- and stereoselective syntheses.[35−42]

Optimally for stereoselective glycosylation, the starting materials **1** and **2** were irradiated at 100 W at 60 °C for 75 min in dry dichloromethane in the presence of 1 equiv of DMAP (Scheme 1 and Table 1). Slow reaction is attributed to the bulky pivaloyl protecting groups. After base work up, column chromatography with ethyl acetate/hexane (1:2) gave glycoaminoacids **3a**−**d**, (**3b**+**3b′**) (82−92%). Pivaloyl groups can be removed without epimerization.[48]

Diastereospecific formation of *β*-*N*-linked building blocks and absence of anomerization was investigated by 1D and 2D NMR analysis (Figures 2−5). Conventional room temperature ^{1}H NMR spectra ($CDCl_3$) for **3a**−**d**, (**3b**+**3b′**), indicated the existence of two species. For example, the proton at amino acid

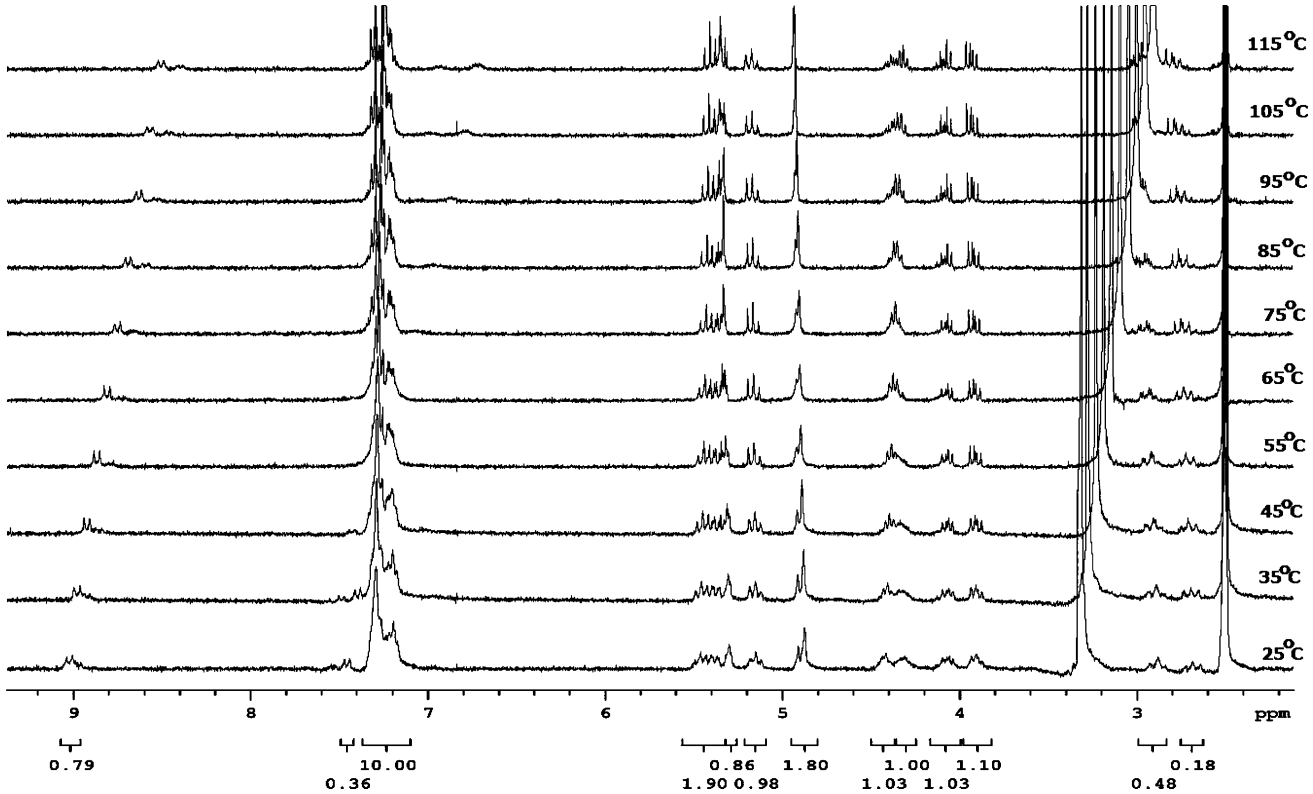

FIGURE 2. Variable temperature experiment for **3b** in DMSO-d_6.

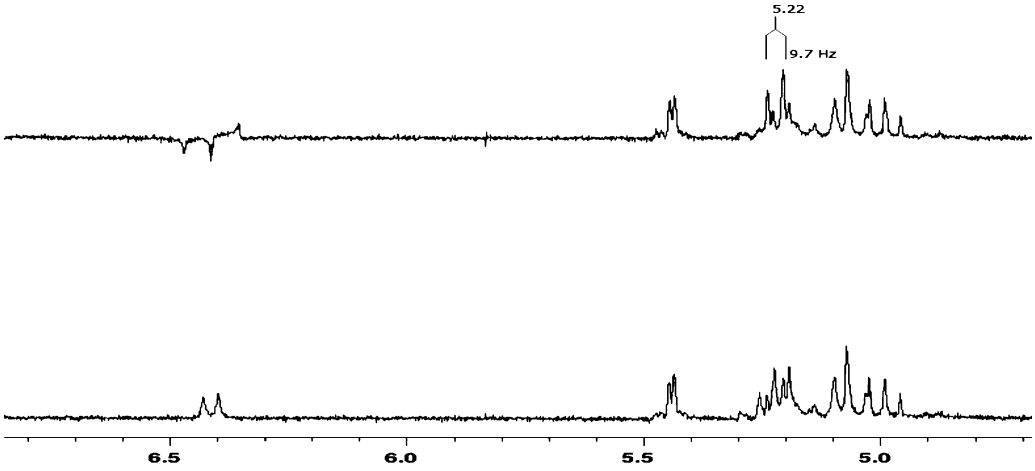

FIGURE 3. Selective decoupling experiment for **3b** in $CDCl_3$ at 20 °C.

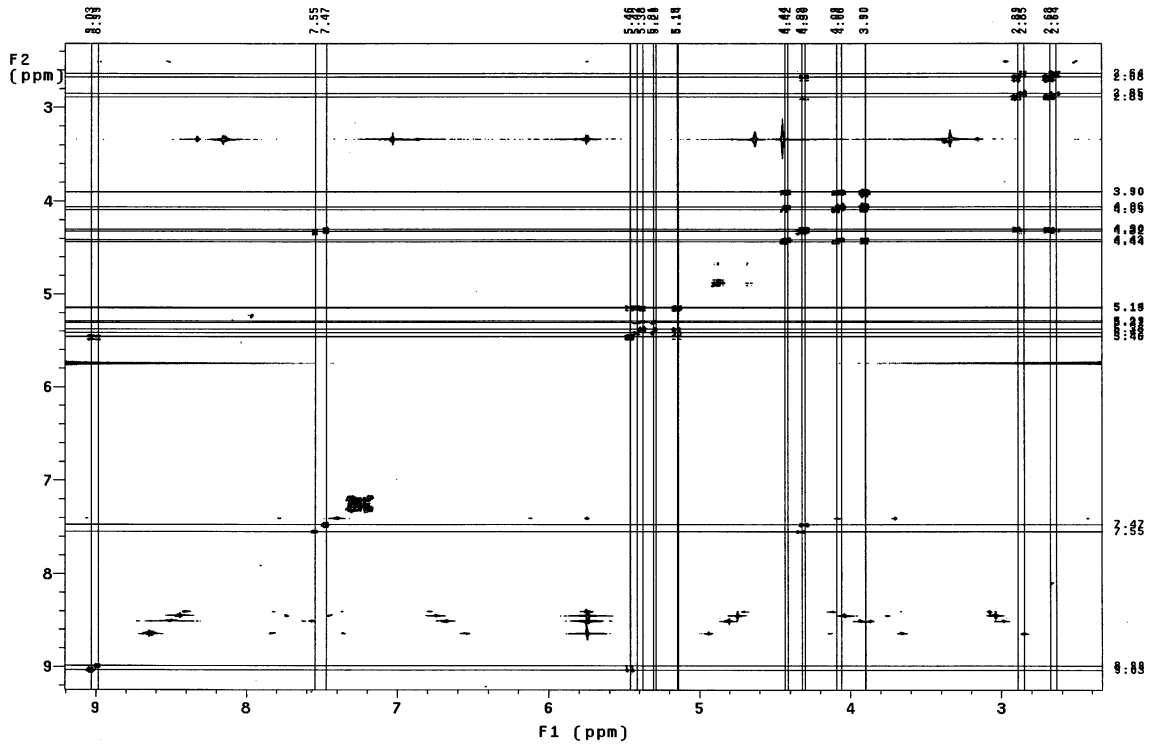

FIGURE 4. $^1H-^1H$ COSY experiment of **3b** in $CDCl_3$ at 20 °C.

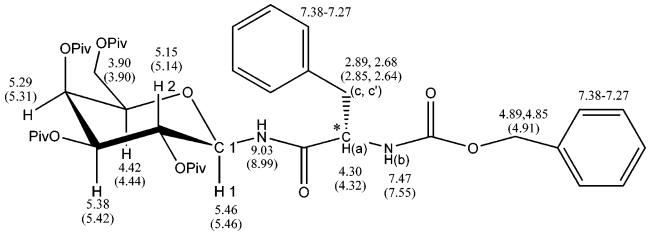

FIGURE 5. Chemical shifts of **3b** for major (no brackets) and minor rotamers (in brackets).

chiral center C*H is displayed for each compound as two sets of quartets with different intensity, which we believe are due to two rotamer species with one conformation preferred. Variable temperature proton spectra (Figure 2) for **3b** (investigated in DMSO-d_6 for better resolution of signals) over the range of 25−115 °C (using 10 °C increments) supported our assumption that the complex peaks obtained at 20 °C were due to restricted rotation at the amide bonds. The two rotameric forms underwent coalescence at 55−65 °C; thus the multiplet

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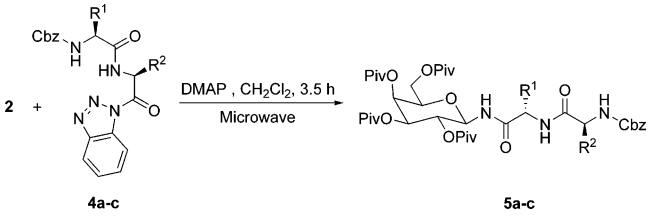
TABLE 2. Preparation of β-*N*-Linked Glycodipeptides 5a−c from Tetra-*O*-pivaloyl-β-D-galactopyranosylamine 2 and *N*-Cbz-dipeptidoylbenzotriazoles 4a−c

4		product	yield[a] (%)
R^1	R^2		
L-Phe **4a**	L-Met **4a**	Cbz-L-Phe-L-Met-*N*-galactopyranose **5a**	76
L-Met **4b**	L-Ala **4b**	Cbz-L-Met-L-Ala-*N*-galactopyranose **5b**	81
L-Met **4c**	L-Trp **4c**	Cbz-L-Met-L-Trp-*N*-galactopyranose **5c**	77

[a] Isolated yield.

SCHEME 2



at 2.64−2.89 ppm coalesced at 65 °C, and the saccharide signals at 3.90−4.42 and 5.26−5.46 ppm coalesced at 55 °C; these changes were reversible in heating−cooling sequences. The high temperature spectra (Figure 2) thus demonstrated the absence of anomerization.

Room temperature ^{1}H NMR spectra of **3a**−**d**, (**3b**+**3b′**), showed that each H1 (anomeric proton) signal from the sugar residue is overlapped by other proton signals resulting in a multiplet at 5.10−5.40 ppm. Therefore, the stereochemistry of the anomeric proton and thus the orientation of the C1−NH glycosidic bond was investigated by selective decoupling experiment and 2D homonuclear correlation COSY for **3b** (Figures 3 and 4).

Selective decoupling of **3b** (in $CDCl_3$) was achieved by irradiation at the appropriate frequency to eliminate coupling of the anomeric proton with the C1NH proton (displayed as doublet at 6.48 ppm; Figure 3). The NH proton in **3b** was selectively decoupled to reveal the coupling constant H1−H2 to be 9.7 Hz, which indicates that H1 and H2 are both axial.

The β-*N*-linked stereochemistry of glycoaminoacid **3b** was confirmed by the homonuclear correlations, COSY (Figure 4). The α-anomeric proton of sugar displays a triplet with $J = 9.5$ Hz, interpreted as equal coupling with the C1NH proton and the adjacent H2 axial proton.

This experiment also confirmed the existence of the rotamers postulated above for **3b**. For the major rotamer, coupling occurs between the proton CH(a) at 4.30 ppm, the NH(b) at 7.47 ppm, and the prochiral protons (c,c′) at 2.89 and 2.68 ppm. For the minor rotamer, the corresponding proton at 4.32 ppm coupled with the NH at 7.55 ppm and the prochiral protons at 1.87 and 1.84 ppm (Figure 5).

The detailed NMR study performed for *Z*-L-Phe-β-*N*-galactopyranose **3b** establishes complete retention of original stereochemistry of the anomeric (α) proton from **2** and therefore exclusive formation of β-*N*-linked glycoaminoacids under the conditions utilized in this method.

Synthesis of β-*N*-Linked Glycodipeptides 5a−c. *N*-Cbz-Dipeptidoylbenzotriazoles **4a**−**c** (obtained as reported previously[47]) acylated tetra-*O*-pivaloyl-β-D-galactopyranosylamine **2**

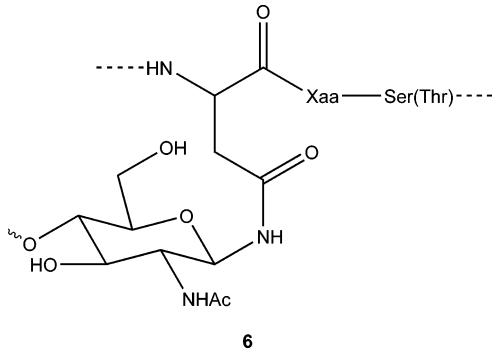


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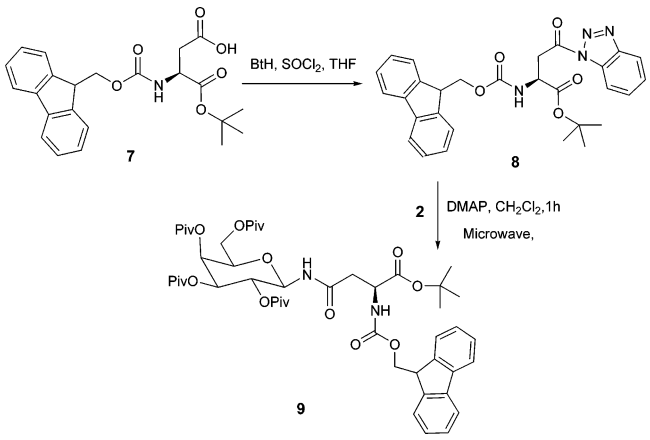
FIGURE 6. Fragment of natural β-*N*-linked asparagine glycoproteins and glycopeptides.

SCHEME 3. Preparation of β-*N*-Linked Piv-Protected Galactopyranosylamine Asparagine Building Block 9



7 8 9

to afford β-*N*-linked glycodipeptides **5a**−**c** (Table 2) under conditions similar to those adopted for the preparation of glycoaminoacids **3a**−**d**, except that complete reaction needed 3.5 h. Base work up (sat. sol. of Na_2CO_3) followed by silica gel chromatography using ethyl acetate/hexane (1:1) as eluent gave glycodipeptides **5a**−**c** (76−81%) (Scheme 2).

Synthesis of β-*N*-Linked Piv-Protected Galactopyranosylamine Asparagine Building Block 9 Using Side Chain Functionality in Asparagines. The *N*-glycoproteins characterized by a β-*N*-glycosidic linkage between *N*-acetylglucosamine and asparagine are especially important in cell biology. Previous syntheses of conjugates of type **6** (Figure 6) have been complicated by isomer formation and side reactions.[42]

The construction of the β-*N*-glycosidic linkage for asparagine glycopeptides by the present method proceeds through coupling of amino sugar **2** to the benzotriazole (Bt)-activated side chain of Fmoc-Asp (Bt)-O^{t}Bu **8**. Our approach to **9** is selective for the β-anomer without side reactions. Fmoc-L-Asp(OH)-α-*O*-*tert*-Bu ester **7** was converted into **8** in 87% yield. The anomeric amino sugar tetra-*O*-pivaloyl-β-D-galactopyranosylamine **2** was acylated by **8** under the conditions described above (in microwave, 1 h) to afford the β-*N*-linked, fully protected, asparagine building block **9**, obtained in 65% yield after chromatographic purification (Scheme 3).

Conclusion

The present coupling of *N*-(α-protected aminoacyl)benzotriazoles and *N*-Cbz-protected dipeptidoylbenzotriazoles with

2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine **2** provides selectively the β-anomers of β-*N*-linked glycoaminoacids and glycopeptides, with the purity and yield significantly increased over previous approaches. Stereochemistry was confirmed by NMR study including $^1H-^1H$ COSY, selective decoupling, and variable temperature experiments. The protocol described should be suitable for the synthesis of other β-*N*-linked glycopeptides.

Experimental Section

General Procedure for the Preparation of Glycoaminoacids 3a−d, (3b+3b′), under Microwave Irradiation. A dried heavy-walled Pyrex tube containing a small stir bar was charged with *N*-(*Z*-α-aminoacyl)benzotriazole **1** (1.0 mmol), 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine **2** (1 mmol), DMAP (1 mmol), and CH_2Cl_2 (1 mL). The reaction mixture was exposed to microwave irradiation (100 W) for 75 min at a temperature of 60 °C. After the irradiation, the reaction mixture was allowed to cool through an inbuilt system in the instrument until the temperature had fallen below 30 °C. The reaction mixture obtained was diluted with EtOAc (20 mL), and the organic layer was washed with sat. Na_2CO_3 solution (3 × 15 mL), sat. NaCl solution (20 mL), and dried over $MgSO_4$. After evaporation of the solvent, the residue was subjected to silica gel column chromatography using EtOAc/hexanes (1:2) as an eluent, affording the desired glycoaminoacids **3a**−**d**, (**3b**+**3b′**).

***N*$^\alpha$-Carbobenzyloxy-*N*$^\delta$-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)glycine, Cbz-Gly-*N*-galactopyranose, 3a:** Colorless solid (87%), $[\alpha]^{23}_D = +13.5$ (*c* 2.03, CH_2Cl_2); mp 76−77 °C; ^1H NMR ($CDCl_3$) δ 1.08−1.1.14 (m, 17H), 1.17 (s, 9H), 1.27 (s, 10H), 3.82 (dd, *J* = 17.2, 5.7 Hz, 1H), 3.91 (d, *J* = 5.8 Hz, 1H), 3.94−4.05 (m, 1H), 4.06−4.17 (m, 2H), 5.06−5.23 (m, 1H), 5.15 (s, 2H), 5.23−5.36 (m, 3H), 5.47 (d, *J* = 3.2 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 1H), 7.30−7.42 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 26.9, 27.0, 27.0, 27.2, 38.7, 38.7, 39.0, 39.0, 44.4, 60.7, 66.6, 67.4, 68.1, 70.7, 72.8, 78.5, 128.2, 128.3, 128.6, 135.9, 156.2, 169.2, 176.7, 176.9, 177.8, 178.7. Anal. Calcd for $C_{36}H_{54}N_2O_{12}$: C, 61.17; H, 7.72; N, 3.96. Found: C, 61.03; H, 7.87; N, 4.06.

General Procedure for the Preparation of Glycodipeptides 5a−c under Microwave Irradiation. A dried heavy-walled Pyrex tube containing a small stir bar was charged with *N*$^\alpha$-Cbz-protected dipeptidoylbenzotriazoles **4** (1.0 mmol), 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine **2** (1 mmol), DMAP (1 mmol), and CH_2Cl_2 (0.5 mL). The reaction mixture was exposed to microwave irradiation (100 W) for 3 h and 30 min at a temperature of 60 °C. After irradiation, the reaction mixture was allowed to cool down through an inbuilt system in the instrument until the temperature had fallen below 30 °C. The reaction mixture was diluted with EtOAc (20 mL), and the solution was washed with sat. Na_2CO_3 solution (3 × 15 mL), sat. NaCl solution (20 mL), and dried over $MgSO_4$. After the evaporation of the solvent, the residue was subjected to silica gel column chromatography using EtOAc/hexanes (1:1) as eluent, affording the desired glycodipeptides **5a**−**c**.

***N*$^\alpha$-Carbobenzyloxy-*N*$^\delta$-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)-L-phenylalanine-L-methionine, Cbz-L-Phe-L-Met-*N*-galactopyranose, 5a:** Colorless solid (76%), mp 106−107 °C, $[\alpha]^{23}_D = +11.0$ (*c* 1.90, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.05−1.12 (m, 11H), 1.12−1.19 (m, 15H), 1.22 (s, 6H), 1.26 (s, 4H), 1.60−1.90 (m, 3H), 2.00 (s, 2H), 2.12−2.24 (m, 1H), 2.32−2.44 (m, 1H), 3.00−3.19 (m, 2H), 3.96 (dt, *J* = 9.9, 6.3 Hz, 1H), 4.01−4.21 (m, 2H), 4.32 (q, *J* = 7.2 Hz, 0.6H), 4.44 (q, *J* = 6.4 Hz, 0.4H), 4.49−4.60 (m, 1H), 5.01−5.10 (m, 1H), 5.10−5.20 (m, 2H), 5.20−5.31 (m, 2H), 5.37−5.48 (m, 2H), 6.45 (d, *J* = 8.5 Hz, 0.6H), 6.70 (d, *J* = 7.4 Hz, 0.4H), 7.10 (d, *J* = 9.1 Hz, 0.4H), 7.14−7.38 (m, 10.6H); ^{13}C NMR ($CDCl_3$) δ 15.1, 15.1, 26.9, 27.0, 27.1, 29.8, 29.9, 30.8, 31.0, 37.9, 38.7, 38.8, 39.0, 39.0, 52.1, 57.1, 60.6, 60.6, 66.6, 67.3, 67.9, 70.9, 71.1, 72.6, 72.7, 78.4, 78.5, 127.2, 128.1, 128.2, 128.2, 128.3, 128.5, 128.5, 128.8, 129.1, 129.2, 135.8, 135.9, 136.2, 156.2, 170.9, 171.0, 171.3, 176.7, 177.0, 177.8, 178.2. Anal. Calcd for $C_{48}H_{69}N_3O_{13}S$: C, 62.11; H, 7.51; N, 4.53. Found: C, 62.20; H, 7.64; N, 4.43.

***N*$^\alpha$-(Fluoren-9-ylmethoxycarbonyl)-*N*$^\delta$-(2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosyl)-L-asparagine, 9:** A dried heavy-walled Pyrex tube containing a small stir bar was charged with (*S*)-4-benzotriazol-1-yl-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-4-oxobutyric acid *tert*-butyl ester (0.3 mmol) **8**, 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine **2** (0.2 mmol), DMAP (0.05 mmol), and CH_2Cl_2 (1 mL). The reaction mixture was exposed to microwave irradiation (100 W) for 1 h at a temperature of 60 °C. After irradiation, the reaction mixture was allowed to cool down through an inbuilt system in the instrument until the temperature had fallen below 30 °C. The reaction mixture was diluted with EtOAc (20 mL), and the solution was washed with sat. Na_2CO_3 solution (3 × 15 mL), sat. NaCl solution (1 × 20 mL), and dried over $MgSO_4$. After evaporation of solvent, the residue was subjected to silica gel column chromatography using EtOAc/hexanes (1:6) as an eluent to afford the **9** in 65% yield: colorless solid, mp 86−87 °C, $[\alpha]^{23}_D = +5.4$ (*c* 1.88, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.09−1.15 (m, 9H), 1.15−1.21 (m, 18H), 1.23−1.29 (m, 9H), 1.42−1.48 (m, 9H), 2.48−2.64 (m, 1H), 2.90−3.05 (m, 1H), 3.92−4.22 (m, 3H), 4.23−4.40 (m, 1H), 4.40−4.47 (m, 1H), 4.48−4.60 (m, 1H), 5.00−5.32 (m, 3H), 5.43 (d, *J* = 3.0 Hz, 0.1H), 5.46 (d, *J* = 3.0 Hz, 0.9H), 5.94 (t, *J* = 9.1 Hz, 1H), 7.28−7.46 (m, 5H), 7.59 (d, *J* = 7.3 Hz, 1H), 7.62−7.70 (m, 1H), 7.77 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 26.8, 26.9, 27.0, 27.1, 27.9, 36.5, 38.6, 38.7, 38.7, 38.9, 39.0, 47.0, 47.1, 51.2, 60.3, 60.6, 61.1, 66.6, 67.0, 67.4, 67.5, 67.9, 68.3, 69.7, 70.8, 71.2, 71.5, 72.4, 72.6, 78.6, 78.8, 81.8, 82.1, 85.4, 120.0, 125.0, 125.1, 127.0, 127.7, 141.2, 143.6, 143.7, 156.1, 171.0, 171.1, 176.6, 176.7, 176.8, 176.9, 177.2, 177.7, 177.8, 178.5. Anal. Calcd for $C_{49}H_{68}N_2O_{14}$: C, 64.74; H, 7.54; N, 3.08. Found: C, 64.37; H, 7.82; N, 2.92.

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Supporting Information Available: Compound characterization data for **3a**−**d**, (**3b**+**3b′**), **4c**, **5a**−**c**, **8**, and **9** are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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