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# *Articles*

## Automated, Solid-Phase Synthesis of *C*-Neoglycopeptides: Coupling of Glycosyl Derivatives to Resin-Bound Peptides[1]

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A fully automated solid-phase synthesis of *C*-neoglycopeptides has been developed using a convergent strategy. In this approach, *C*-glycoside derivatives (**3** and **4**) were coupled to resin-bound peptides using a peptide synthesizer. An advantage of the convergent approach is the ability to introduce multiple glycoside units late in the synthesis. The approach presented is highly versatile and efficient and could be used for building *C*-neoglycopeptide libraries. In our study, neoglycopeptides **5** and **6** were obtained from the coupling of *C*-glycoside derivatives (**3** and **4**) to a free amino group of the side chain of short peptides (**2**, $n = 1$ and 3). A similar approach was developed for the synthesis of bivalent neoglycopeptides **8** and **9** in an automated manner. The successful syntheses of *C*-neoglycopeptides **5**, **6**, **8**, and **9** are the first examples of coupling of *C*-glycosyl carboxyl derivatives to the amino groups of the side chains of resin-bound peptides.

As a post-translational process, glycosylation of proteins is responsible for the incorporation of highly branched carbohydrate units onto the side chain of several amino acids of the peptide backbone. The two most common sites involve asparagine and serine/threonine amino acid moieties, resulting in *N*- and *O*-linked glycoproteins. Glycoconjugates (i.e., glycolipids and glycoproteins) play a key role in initiating a diverse range of biological and pathological processes such as cell−cell recognition, fertilization, bacterial/viral infections, inflammation, and tumor metastasis.[2] Unlike protein−protein and nucleotide−protein interactions, carbohydrate-based interactions are weak and are difficult to study. In natural systems, in order to compensate for the weak forces which characterize carbohydrate−protein interactions, it is well recognized that nature employs cooperativity to overcome individual weak ligand−receptor interactions.[3] Model compounds that are based upon carbohydrate conjugate derivatives would be valuable tools in contributing to the understanding of some of these biological and pathological processes. As a long-term goal, mimics of carbohydrate conjugates that are capable of preventing these interactions offer various applications, ranging from antimicrobial agents[4] to antifertility agents.[5]

Over the years, various groups have developed elegant strategies for the synthesis of segments of glycoproteins (i.e., glycopeptides) as glycoconjugate derivatives.[6] Despite several efforts, the synthesis of glycopeptides still remains a challenging area. An important strategy for the synthesis of glycopeptides consists of a solid-phase approach involving glycosylated building blocks. As an alternative to the assembly of building blocks, a convergent solid-phase approach for the synthesis of glycopeptides could prove to be more expedient.[7] The first attempt toward this strategy for the synthesis of *N*-linked glycopeptides was reported by the Affymax group.[7a] A key step in their approach involved the coupling of an unprotected galactosylamine to a pentafluorophenyl carboxyl ester moiety of the resin-bound peptide moiety.

Recently, there has been much emphasis on the synthesis of small molecules as analogues of cell-surface carbohydrate ligands and as probes for obtaining molecular level understanding of carbohydrate−protein interactions.[8] We are developing a flexible and control-oriented model for the synthesis of carbon-linked neoglycopeptides in order to design inhibitors of carbohydrate−protein mediated interactions that involve cell-surface carbohydrates. Our approach is based upon presenting terminal or exposed *C*-glycosides on a peptide/pseudo-peptide template. This would provide controlled, yet broad, structural variation possibilities for displaying *C*-glycoside derivatives (see Figure 1).[9] With ourmodel, it is plausible that the peptide portion of the *C*-linked neoglycopeptides may assist in secondary interactions with adjacent amino acid residues, aiding in overcoming the inherent weakness of carbohydrate−protein interactions. The long-term goal is to assemble combinatorial libraries of *C*-linked neoglycopeptides and screen them for developing inhibitors of cell-surface carbohydrate mediated interactions.[10]

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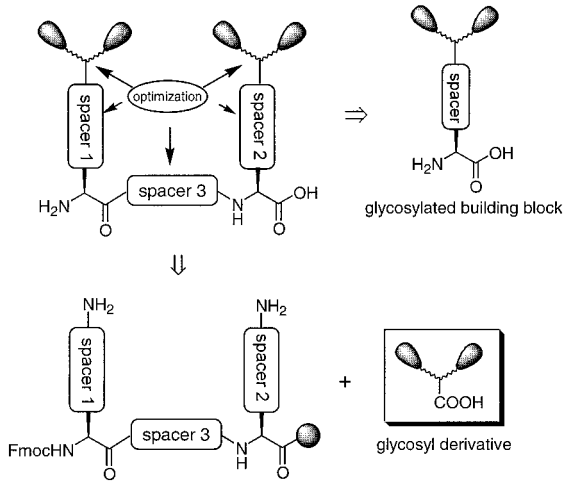



**Figure 1.** Model for the presentation of glycoside derivatives on a peptide/pseudo-peptide template.

For designing inhibitors that are based upon *C*-linked neoglycopeptides, initial studies in our group are focused on using α-*C*-galactoside derivatives. α-Galactose is the terminal saccharide of the globotriosylceramide ($Gb_3$) which is present on the cell surface of human endothelial cells. It has been shown that the $Gb_3$ ligand is responsible for the binding of *Escherichia coli* produced verotoxin receptors.[11] The binding subunits of verotoxin are lectins that recognize the galabiose moiety (Galα1*β*4Gal) of glycosphingolipid derivatives. Among several galabiose-based glycosphingolipid derivatives, $Gb_3$ has shown to be one of the effective cell-surface ligands for the binding of verotoxin toxin receptors. The initial carbohydrate ligand−lectin receptor recognition with verotoxin is followed by the endocytosis of the toxic subunit leading to hemorrhagic colitis and hemolytic uremic syndrome in humans. Novel compounds that could interfere with $Gb_3$ glycoconjugate ligand−verotoxin receptor interactions offer new therapeutic approaches to prevent toxin adhesion. Currently, work is in progress to explore various α-galactoside-based *C*-linked neoglycopeptides as possible inhibitors of $Gb_3$ ligand−verotoxin receptor interactions.[12]

The synthesis of a few *C*-linked neoglycopeptides, using solution-phase synthesis of the building blocks followed by building block assembly on solid phase, has been achieved by our group.[9c] In contrast to the synthesis of *O*-glycopeptides, activation of the glycosylated building block prior to the coupling was not required.[6b] Herein, we report a fully automated solid-phase synthesis of *C*-linked neoglycopeptides.[13] An advantage of this approach is an overall increase in efficiency in terms of time, labor, and yields. Another advantage is the ability to introduce multiple saccharide units in the final step before cleavage from the resin. Due to the reasons listed, this approach is adaptable to the future formation of combinatorial libraries. In a convergent approach, coupling of the *C*-glycoside derivative to the resin-bound peptide/pseudo-peptides has been developed using a peptide synthesizer (Schemes 1 and 2).[7] To our knowledge, the synthesis of *C*-neoglycopeptides **5**, **6**, **8**, and **9** demonstrate the first example of the coupling of the carboxyl group of a *C*-glycoside derivative to a resin-bound peptide/pseudo-peptide.

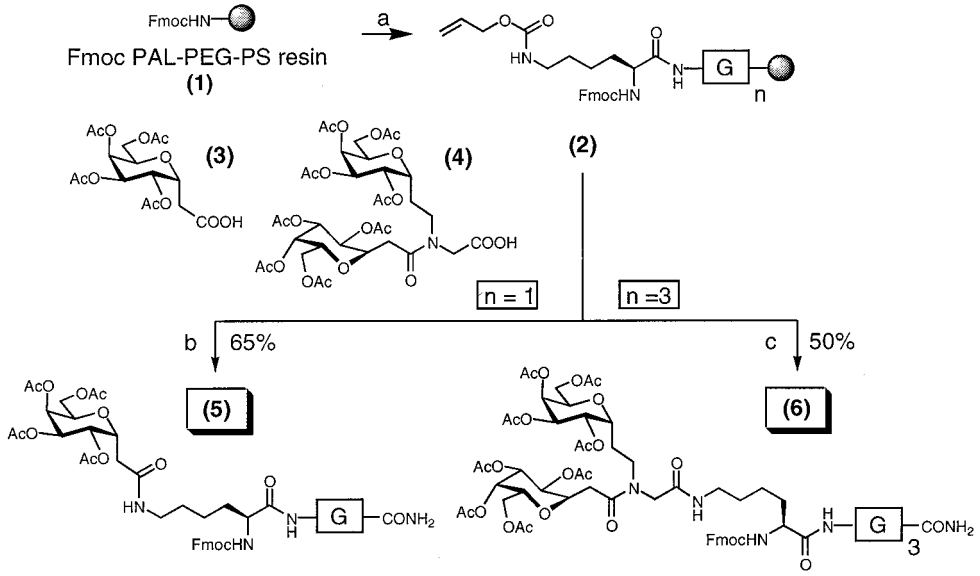
Syntheses of neoglycopeptides (**5**, **6**, **8**, and **9**) were performed utilizing a PerSeptive Biosystems Pioneer peptide synthesis system. Fmoc-PAL-PEG-PS resin[14] (PerSeptive BioSystems, loading 0.16 mmol/g) was treated with 20% piperidine in DMF to remove the Fmoc group. Amino acids were sequentially coupled with the free amino group on the resin using the HATU coupling method (4.0 equiv amino acid, 4.0 equiv HATU, 8.0 equiv DIEA in DMF, 1 h). Coupling was always followed by Fmoc removal with 20% piperidine in DMF, except for the final step in the sequence, in which case the Fmoc protecting group was retained. Following the preparation of the desired amino acid sequence, the alloc protecting group(s), on the side chain of lysine, were removed using 4.0 equiv of $Pd[P(Ph)_3]_4$. A chloroform solution of 5% HOAc and 2.5% *N*-methylmorpholine was used in conjunction with the Pd[0] reagent. The deprotection step was succeeded by a washing step utilizing a solution of 0.5% sodium diethylthiocarbamate and 0.5% DIEA in DMF to scavenge any remaining palladium. The final, on resin, step consisted of coupling the glycoside monomer unit (either **3** or **4**) to the peptide sequence. *C*-Linked glycoside based monomer units **3** and **4** were obtained by solution-phase synthesis.[15] The final step on solid phase was accomplished using standard HATU coupling procedures with coupling times of 16 h. For cases where two glycoside units were being added, two consecutive 16 h couplings were performed. This completes the automated synthesis of the neoglycopeptides (Schemes 1 and 2). Cleavage of the neoglycopeptides from the resin was effected with 95% TFA. Crude neoglycopeptides were purified by reverse-phase HPLC. Overall yields were on the order of 50−65% for the addition of one glycoside unit (compounds **5** and **6**) and 15−20% for the bivalent neoglycopeptides **8** and **9**.

The methodology presented here is highly versatile for the synthesis of *C*-linked neoglycopeptides and for the simultaneous coupling of multiple glycoside units. This has been demonstrated by the coupling of two *C*-glycoside derivatives (**3** and **4**) to different resin-bound peptides via an automated process. Using this convergent approach, it is possible to obtain libraries of a wide variety of *C*-neoglycopeptides. Currently, work is in progress to build a library of bivalent forms of monomeric, α-galactosyl based N-terminal branched amino acid derivative, an inhibitor for the binding of verotoxin to $Gb_3$.[12b]

## Experimental Section

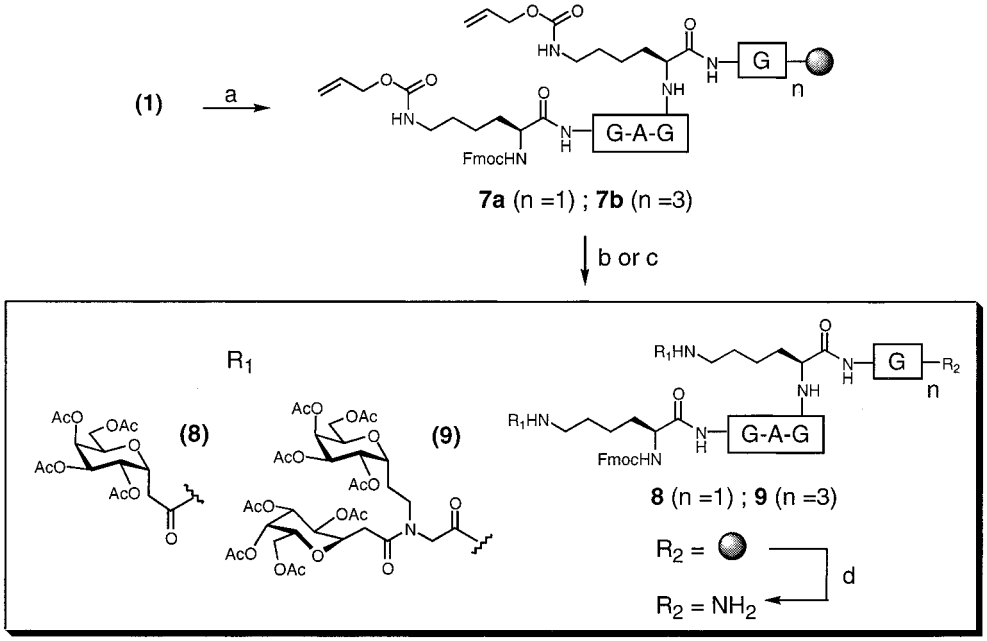
**Neoglycopeptide, 5.** $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.42 (br d, $J$ = 3.7 Hz, 2H), 1.56 (br s, 2H), 1.73−1.84 (m, 2H), 2.02 (s, 3H), 2.05 (s, 6H), 2.13 (s, 3H), 2.44−2.76 (m, 2H), 3.30 (br s, 2H), 3.94−4.06 (m, 3H), 4.18−4.22 (m, 3H), 4.28−4.33 (m, 1H), 4.37−4.46 (m, 2H), 4.70 (t, $J$ = 4.9 Hz, 1H), 5.18 (dd, $J$ = 2.8 Hz, $J$ = 9.0 Hz, 1H), 5.30 (dd, $J$ = 4.8 Hz, $J$ = 8.8 Hz, 1H), 5.40 (br s, 1H), 6.04 (br s, 1H), 6.94−7.06 (m, 3H), 7.28−7.33 (m, 2H), 7.39−7.43 (m, 3H), 7.59 (d, $J$ = 6.9 Hz, 2H), 7.77 (d, $J$ = 7.4 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 21.0, 21.1, 22.4, 28.5, 31.1, 34.2, 39.2, 42.8, 47.4, 54.8, 61.7, 67.5, 67.7, 68.0, 68.3, 69.3, 69.7, 120.5, 125.4, 127.5, 128.3, 141.7, 144.0, 157.3, 170.3,

**Scheme 1.** Coupling of *C*-Glycoside Derivatives (**3** and **4**) to the Resin-Bound Peptide on a Peptide Synthesizer[a]




[a] Standard peptide synthesis: (a) (i) 20% piperidine/DMF, (ii) AAn (4.0 equiv), HATU (4.0 equiv), DIEA (8.0 equiv), DMF, 1 h; (b) (i) $Pd[P(Ph)_3]_4$ (4.0 equiv), 5% HOAc, 2.5% *N*-methylmorpholine, 2 h, (ii) **3** (4.0 equiv), HATU (4.0 equiv), DIEA (8.0 equiv), DMF, 16 h, (iii) 95% TFA; (c) same as step b(i), (ii) **4** (4.0 equiv), HATU (4.0 equiv), DIEA (8.0 equiv), DMF, 16 h, (iii) same as step b(iii).

**Scheme 2.** Automated Solid-Phase Synthesis of *C*-Linked Neoglycopeptide Derivatives[a]




[a] Standard peptide synthesis: (a) (i) 20% piperidine/DMF, (ii) AAn (4.0 equiv), HATU (4.0 equiv), DIEA (8.0 equiv), DMF, 1 h; (b) (i) $Pd[P(Ph)_3]_4$ (8.0 equiv), 5% HOAc, 2.5% *N*-methylmorpholine, 2 h; (ii) **3** (8.0 equiv), HATU (8.0 equiv), DIEA (16.0 equiv), DMF, 16 h; (c) same as step b(i), (ii) **4** (8.0 equiv), HATU (8.0 equiv), DIEA (16.0 equiv), DMF, 32 h; (d) 95% TFA.

170.6, 170.8, 171.6, 171.8, 173.8. LRMS (electrospray, $H_2O$, positive ion mode, *m*/*z*) for $C_{39}H_{48}N_4O_{14}$: 797.2 ($MH^+$).

**Neoglycopeptide, 6.** $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.37 (br s, 2H), 1.47 (br s, 2H), 1.70−1.80 (m, 2H), 1.91 (br s, 2H), 1.99 (s, 3H), 2.03 (s, 6H), 2.06 (s, 3H), 2.08 (s, 6H), 2.12 (s, 3H), 2.16 (s, 3H), 2.54−2.57 (m, 1H), 3.08−3.12 (m, 1H), 3.19−3.26 (m, 2H), 3.50−3.66 (m, 2H), 3.92 (br s, 6H), 4.04−4.35 (m, 13H), 4.86 (br s, 1H), 5.04−5.44 (m, 6H), 6.36 (br s, 1H), 7.02 (br s, 2H), 7.10 (br s, 1H), 7.30 (br s, 2H), 7.40 (t, $J$ = 6.8 Hz, 2H), 7.64−7.58 (m, 2H), 7.70 (br s, 1H), 7.76 (d, $J$ = 7.4 Hz, 2H), 7.86 (br s, 2H). $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 20.9, 21.0, 21.1, 21.2, 22.6, 24.1, 28.8, 31.4, 32.4, 39.1, 42.9, 43.5, 43.8, 45.8, 47.4, 51.4, 56.0, 61.2, 62.8, 67.0, 67.3, 67.4, 67.6, 68.1, 68.2, 68.3, 68.7, 69.1, 71.0, 120.5, 125.5, 127.5, 128.2, 141.6, 144.0, 144.2, 157.4, 169.6, 170.2, 170.3, 170.4, 170.5, 170.6, 170.7, 171.1, 171.2, 171.6, 173.6. LRMS (electrospray, $H_2O$, positive ion mode, *m*/*z*) for $C_{62}H_{83}N_7O_{26}$: 1326.2 ($MH^+$).

**Neoglycopeptide, 8.** $^1H$ NMR (400 MHz, $CD_3OD$): $\delta$ 1.36 (d, $J$ = 7.0 Hz, 3H), 1.37−1.49 (m, 4H), 1.53−1.56 (m, 4H), 1.72−1.88 (m, 4H), 2.01 (s, 3H), 2.02 (s, 9H), 2.03 (s, 3H), 2.05 (s, 3H), 2.11 (s, 3H), 2.12 (s, 3H), 2.40−2.75 (m, 4H), 3.16−3.27 (m, 4H), 3.75−4.48 (m, 18H), 4.64−4.72 (m, 2H), 5.04−5.42 (m, 6H), 7.34 (t, $J$ = 7.4 Hz, 2H), 7.42 (t, $J$ = 7.4 Hz, 2H), 7.69 (d, $J$ = 7.4 Hz, 2H), 7.82 (d, $J$ = 7.4 Hz, 2H). $^{13}C$ NMR (100 MHz, $CD_3OD$): $\delta$ 16.3, 19.5,

19.6, 19.7, 19.9, 23.2, 28.8, 29.0, 30.9, 31.2, 34.0, 39.2, 42.3, 42.8, 42.9, 47.4, 50.3, 54.2, 56.0, 61.5, 67.0, 67.9, 68.0, 68.3, 69.1, 70.4, 71.5, 120.0, 125.2, 125.3, 127.2, 127.9, 141.6, 144.2, 157.8, 170.3, 170.5, 170.9, 171.2, 173.3, 173.6, 174.9. LRMS (electrospray, $H_2O$, positive ion mode, *m*/*z*) for $C_{68}H_{91}N_9O_{28}$: 1482.6 ($MH^+$), 741.9 ($MH^+/2$).

**Neoglycopeptide, 9.** $^1$H NMR (400 MHz, $CD_3OD$): $\delta$ 1.36 (d, $J$ = 6.4 Hz, 3H), 1.40−1.41 (m, 4H), 1.55−1.63 (m, 4H), 1.72−1.85 (m, 4H), 2.01−2.13 (m, 52H), 2.47−2.98 (m, 4H), 3.21 (br s, 4H), 3.37−3.76 (m, 4H), 3.88−4.45 (m, 34H), 4.72−4.98 (m, 2H), 5.08−5.43 (m, 12H), 7.34 (t, $J$ = 7.4 Hz, 2H), 7.42 (t, $J$ = 7.4 Hz, 2H), 7.69 (d, $J$ = 7.4 Hz, 2H), 7.83 (d, $J$ = 7.4 Hz, 2H). LRMS (electrospray, $H_2O$, positive ion mode, *m*/*z*) for $C_{108}H_{147}N_{13}O_{50}$: 2426.3 ($MH^+$), 1214.6 ($MH^+/2$), 809.9 ($MH^+/3$).

**Supporting Information Available.** $^1$H NMR, $^{13}$C NMR, and LRMS spectra for compounds **5**, **6**, **8**, and **9** (23 pages). Ordering information is given on any current masthead page.

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(14) Abbreviations: Fmoc-PAL-PEG-PS, fluorenylmethoxycarbonyl-5-(4′-aminomethyl-3′,5′-dimethoxyphenoxyvaleric acid-poly(ethylene glycol) polystyrene; DMF, *N*,*N*-dimethylformamide; HATU, *N*-[(dimethylamino)-1*H*-1,2,3-traizolo[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide; DIEA, diisopropylethylamine; TFA, trifluoroacetic acid.

(15) See reference 9a, for the solution-phase synthesis of *C*-linked glycoside based monomeric units **3** and **4**.


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