A Convergent Strategy for the Critical β-Linked Chitobiosyl-*N*-Glycopeptide Core[1]

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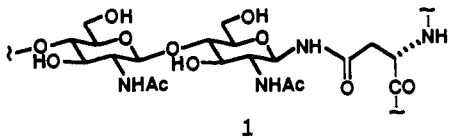
Recent investigations concerning the role of glycoproteins in the mediation of cellular recognition and binding events[2,3] have prompted intensified interest in the chemical syntheses of these structures. The glycoproteins that have been isolated from cell membranes display a diversity of structures, but most share a common core in which a chitobiose residue is attached through a β-N linkage to the carboxamide of asparagine **1**.[4] Heretofore this key linkage has been made most often by Jeanloz's methodology[5,6] in which a glycosyl azide is reduced to the glycosylamine and condensed with aspartic acid and/or aspartoyl-containing peptide under the agency of carbodiimide or another dehydrating agent.[7-9] This method is often complicated by the anomerization of the glycosylamine generating α,β mixtures.[8,10] Glycosyl isothiocyanates, obtainable from the corresponding glycosyl bromides, have also been coupled with aspartic acid to yield amide linkages.[11,12]



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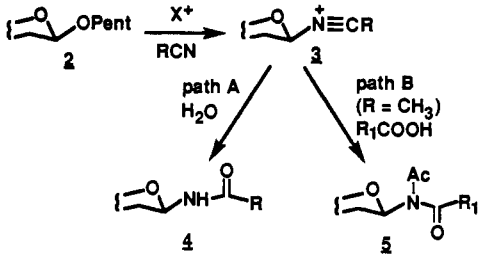
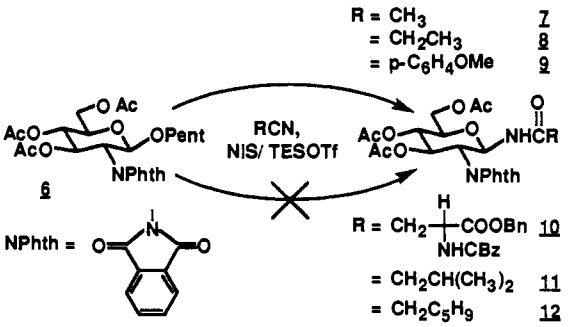
A procedure whereby the peptidyl and glycosyl moieties are linked directly would be advantageous, and indeed such a strategy, arising from our studies on *n*-pentenyl glycosides, has been described for the synthesis of N-α-linked glycopeptides.[13-15] Recently this strategy has been adapted for thioglycosides.[16] In view of the aforementioned ubiquity of substructure **1**, the β-N linkage warranted attention, and in this paper we describe some recent developments in our laboratory.

Scheme I



Scheme II



By analogy with our experiences with the α-anomer[14] we envisaged the intermediacy of a β-nitrilium ion, **3** (Scheme I), which could be trapped directly with water to give the amide **4** (path A), or with a carboxylic acid to give an imidic anhydride intermediate that rearranges spontaneously to the imide **5** (path B). Selective N-deacetylation would then be effected using piperidine as described previously.[13] Both pathways require β-orientation of the ion **3**, and our early investigations[17] have shown that, contrary to previously published reports,[18-22] this orientation is not normally favored. Neighboring-group participation by a C2 substituent was an obvious ploy to obtain the desired β-orientation. However, the use of a C2-*N*-acetyl residue gave complex mixtures. Attention was therefore focused on the phthalimido derivative **6**.

The direct route (e.g., **3** → **4**) would clearly be preferable because of its simplicity. When **6** (Scheme II) was treated with *N*-iodosuccinimide and triethylsilyl triflate in acetonitrile containing 1 equiv of water, amide **7** was obtained in 48% yield accompanied by some hydrolysis product. Similarly, use of propionitrile and *p*-methoxybenzonitrile afforded the corresponding propionamide **8** and benzamide **9** derivatives in 32% and 21% yields, respectively.

To establish the required asparagine linkage we next attempted the coupling of cyanoalanine,[23] but none of the desired product, **10**, was isolated. Likewise, nitriles with branching at the β carbon, such as 3-methyl-*n*-butyronitrile and 2-cyclopentylacetonitrile, failed to give the corresponding glycosyl amide products, **11** and **12**, respectively.

In light of the failure to couple cyanoalanine, we turned our attention to the indirect route, path B. When aspartic acid derivative **13**[24] (Scheme III) was reacted with **6** in acetonitrile

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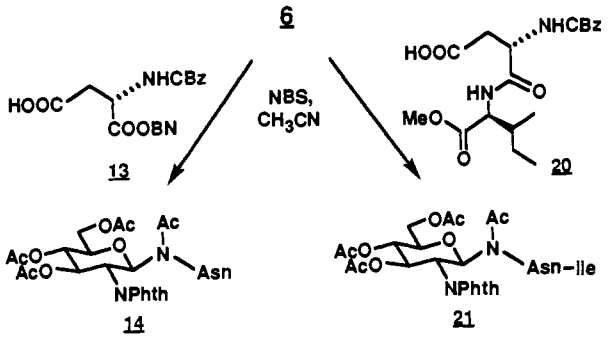
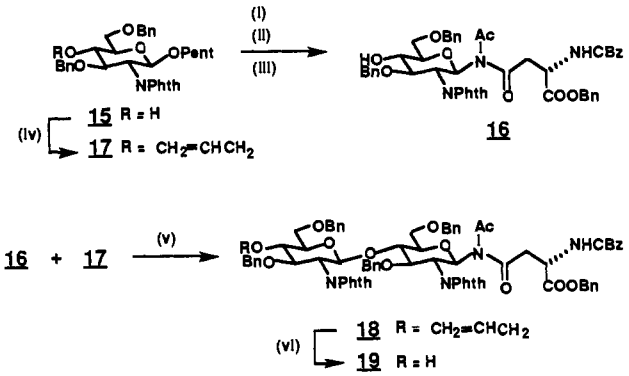
Scheme III



Scheme IV[a]



[a] (i) $(ClCH_2CO)_2O$, pyr. (ii) **13**, NBS, CH_3CN, 3 Å molecular sieves. (iii) Thiourea, $NaHCO_3$, EtOH. (iv) Allylbromide, NaH, DMF. (v) NIS, triethylsilyl triflate. (vi) $PdCl_2$, AcONa, AcOH.

using NBS as promoter, the β-asparagine-linked product **14** was generated in 48% isolated yield. The yield is attenuated somewhat by the competing reaction of oxocarbenium ion directly with the carboxylate to generate the glycosyl ester that was isolated in 18% yield.

The glycopeptide core skeleton **19** was established according to Scheme IV. In order to extend the oligosaccharide chain at the C4 position, we required the 3,6-di-*O*-benzyl glycoside **15** which was prepared from **6** according to standard procedures.[25] Glycoside **15** was protected at C4 as the chloroacetate and coupled readily with **13** to give the asparagine-linked product in 52% yield. Deprotection of the chloroacetate with thiourea gave **16** (75%), followed by coupling with the 4-*O*-allyl protected derivative **17** under the agency of NIS/triethylsilyl triflate, gave the asparagine-linked disaccharide derivative **18** in 62% yield. *It is noteworthy that, under the coupling conditions, the NIS/triethylsilyl triflate did not affect the allyloxy group at C4 of the glycosyl donor.* The latter was conveniently removed with $PdCl_2$ under mild conditions[26] to give **19** in 67% yield.

In a most significant development we have found that dipeptides can be similarly coupled. Thus, pentenyl glycoside **6** was coupled with aspartyl isoleucine derivative **20**[27,28] (Scheme III) to give the β glycosylamide **21** in 40% yield. This intriguing result extends the utility of pentenyl coupling beyond single amino acids and raises the prospect for the wholesale attachment of polypeptide to carbohydrate.

Thus, this technique allows the facile introduction of β-N linkages from pentenyl glycosides and bypasses the multistep approaches that are commonly utilized. Continuing investigations into the pentenyl-mediated coupling of glycopeptides to larger carbohydrate components will be reported in subsequent publications.

Supplementary Material Available: Experimental details of the preparation of compounds **6–9** and **13–21** (13 pages). Ordering information is given on any current masthead page.

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