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Communications

A Stereoselective Route from Glycals to Asparagine-Linked N-Protected Glycopeptides

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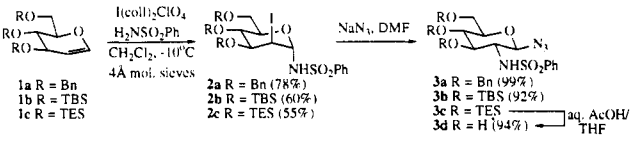
Summary: Iodosulfonamidation of glycals followed by azidolysis produces anomerically pure 1β-azido,2α-sulfonamidohexoses. Reduction of the azides, acylation of the resultant amines with an aspartic acid derivative, and deprotection of the 2-acetylamino function constitutes a completely stereospecific synthesis of asparagine-linked glycopeptide precursors from glycals.

The presence of asparagine-linked polysaccharides is a common feature of many proteins.[1-3] Glycosylation of proteins at certain asparagine (as well as serine and threonine) residues modifies the physical characteristics of the protein, including tertiary structure and protein folding. These modalities can result in altered functional characteristics such as protein–substrate interactions. It has been suggested that in some instances these intermolecular interactions may actually occur at the carbohydrate moieties of glycoproteins.[1c]

We have recently developed an azaglycosylation strategy for the synthesis of 2-acetamido-1-*O*-glycosides from 1,2-glycals (**1a** → **2a**), utilizing 2-iodo-1-*N*-sulfonamides such as **2** as glycosyl donors.[4] This methodology has been demonstrated in the synthesis of allosamidin[5] and sialyl-Lewis X-containing polysaccharides.[6] In this paper we describe the application of this chemistry to the synthesis of glycosylated peptide fragments.

In the course of surveying the reactivity of iodosulfonamides with various heteronucleophiles, we discovered that reaction of **2a–c** with 1 equiv of sodium azide in DMF results in the completely stereoselective migration of the sulfonamide group with installation of azide at the anomeric center, provide **3a–d** in excellent yields (>90%, Scheme I). No exogenous base or excess sodium azide is needed to effect sulfonamide group migration. Moreover, in contrast to our earlier studies with oxygen-centered

Scheme I



nucleophiles,[4-6] there is no requirement of silver salt promoters for displacement of the iodide.

Earlier experiments directed toward the goal systems had explored the possibility of direct introduction of ammonia into iodosulfonamide **2a**. This approach was unsatisfactory, due to low conversion yields (<40%) and due to the stereochemical instability of the resultant glycosylamines under basic conditions. Fortunately, *O*-benzyl-protected glucosyl azide **3a** could be cleanly reduced to the desired glycosylamine with neutral Raney nickel (W-2).[7] However, this glycosylamine proved to be unstable, and condensation with aspartic acid derivatives provided only low yields of glycopeptide product. Furthermore, the glycopeptide linkage which was produced suffered partial

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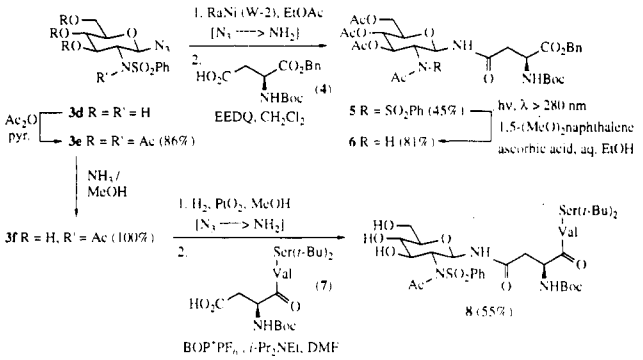
Scheme II



cleavage upon attempted purification (silica gel chromatography) or under mildly basic conditions.

Progress was facilitated when it was found that anomeric azides **3b–c**, bearing silyl ethers as O-protective groups, could be converted to the triol **3d** under mildly acidic conditions,[8] without loss of the azide group. The azide function of acetylated derivative **3e** was then successfully reduced. The resultant glycosylamine was reduced, and the resultant glycosylamine was immediately condensed with **4** to afford the asparagine-linked *N*-(benzenesulfonyl)glucosamine derivative **5** in 45% yield (Scheme II). The mild conditions developed by Yonemitsu for photolytic electron-transfer induced desulfonylation[9] were quite successful for the conversion of **5** to **6**.

Further success was achieved by adapting Lansbury's procedure for coupling unprotected carbohydrate glycosylamines to polypeptides.[3a] Compound **3f** was reduced[10] and coupled with tripeptide **7**, utilizing the mild benzotriazolyloxytris(dimethylamino)phosphonium (BOP) hexafluorophosphate reagent,[11] to afford protected glycopeptide **8** in 55% yield.[12]

In conclusion, we have developed a effective procedure for the conversion of a glycal to a 1β-N-linked asparagine-2α-acetamide equivalent, and the method has been shown to be applicable to the synthesis of a protected glycopeptide precursor. Given the range of enantiomerically pure artificial glycals available via the LACDAC reaction[6,13a] the synthesis of structurally modified glycopeptide congeners for purposes of probing issues of biorecognition is eminently feasible. The extension of this methodology to more complex polysaccharides is planned.

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Supplementary Material Available: Experimental procedures and compound characterization (13 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm addition of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(12) Attempted photodesulfonylation of **8** led to cleavage of the glycopeptide linkage. We suspect that electron-withdrawing protective groups on the carbohydrate (such as acetyl esters) stabilize the glycopeptide in **5** and **6**.

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