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Trimethylsilylnitrate−Trimethylsilyl Azide: A Novel Reagent System for the Synthesis of 2-Deoxyglycosyl Azides from Glycals. Application in the Synthesis of 2-Deoxy-*β*-*N*-glycopeptides

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Abstract: A novel reagent system comprising Me_3SiN_3 and 20 mol % of Me_3SiONO_2 permits conversion of glycals to 1-azido 2-deoxy sugars in one step in fair to good yields. Galactals offer higher stereoselectivities than do the glucals. Reduction of the azide group with Ph_3P-H_2O to amino functionality followed by coupling with amino acids leads to the synthesis of novel 2-deoxy-*β*-*N*-glycopeptides irrespective of the geometry of initial azido sugars. Using this protocol, a new *γ*-sugar amino acid derivative is also procured.

Glycopeptides play[1,2] an important role in post-translational biological selectivity such as cell growth regulation, intracellular communication, cell adhesion, cell differentiation, and many other cellular events.[3] To understand the precise role of various glycopeptides as well as to modulate their activities, pure glycopeptides need to be procured in sufficient quantity. As a result, synthesis of naturally occurring *O*- and *N*-glycopeptides as well as their modified analogues is an area of intense study.[4] Most of the glycoproteins have the peptide motifs as *β*-linkage at the anomeric carbon, but isolation of nephritogenoside,[5] an α-linked *N*-glycopeptide, has spurred[6] some activity in developing methods for introducing α-linked amino group at the anomeric carbon as well. In this regard, Thiem et al.[7] have recently reported synthesis of a 2-deoxy analogue of nephritogenoside noting the presence of 2-deoxysugars[8] as part of several naturally occurring antibiotics viz. anthracyclins. However, since most of the naturally occurring glycoproteins have *β*-linkage of the peptide motif at the anomeric center, it will also be of interest to develop methods for the synthesis of *β*-linked 2-deoxy-*N*-glycopeptides.

Clearly, one of the first steps toward the stereoselective synthesis of *N*-linked glycopeptides requires methods to stereoselectively introduce an amine functionality or its equivalent at the anomeric center, which will eventually lead to α- or *β*-linked *N*-glycopeptides. The scope of an azido moiety as a good precursor of an amino group has been well explored in carbohydrate chemistry and a number of useful methods have been developed to introduce it on carbohydrate molecules. Leaving groups such as an acetate or a halide moiety (chloride or bromide) at the anomeric center of a carbohydrate molecule have been displaced by an azide group using Me_3SiN_3 or metal azides (lithium, sodium, or silver) as nucleophilic azide sources.[9] This approach has been applied[10] in the synthesis of 2-deoxyglucofuranosyl azides. More recently,[11] an improved method to convert glycosyl iodides into the corresponding glycosyl azides using tetrabutylammonium azide or tetramethylguanidinium azide has also been reported. Introduction of an azido group on to a glycal derivative to obtain 2-deoxy-2-halopyranosyl azides by reacting it with hypervalent iodine reagents such as $PhI(N_3)_2$ or a combination of $PhI(OAc)_2$ and Me_3SiN_3 has been reported by Kirschning et al.[12] Further, the Ferrier type of rearrangement, using Me_3SiN_3 along with a Lewis acid like $Yb(OTf)_3$,[13a] $Sc(OTf)_3$,[13b] and $InBr_3$[13c] has been employed to obtain enopyranosyl azides. In this paper, we wish to report a new, one-step approach toward the synthesis of 2-deoxy-1-azido sugars from glycals and their use in the synthesis of 2-deoxy-*β*-*N*-glycopeptides.

We have been interested[14] in developing newer methodologies for functionalizing 2,3-glycals and their derivatives en route to some useful carbohydrate synthons such

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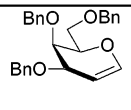
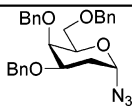
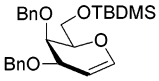
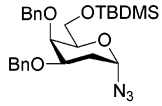
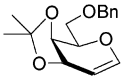
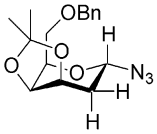
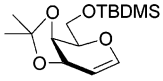
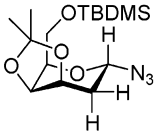
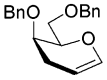
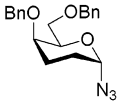
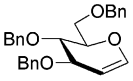
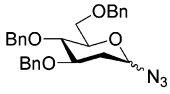
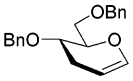
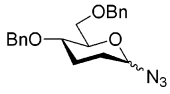
as 1,2-dihydroxy sugars,[14a] 2-acetoxy 1,2-glycals,[14a] 2-amino-*β*-*C*-glycosides,[14b] *N*-acetyl-α-D-lividosaminide,[14c] 2-deoxy-*O*-glycosides,[14d] *C*-2-methyl *O*- and *C*-glycosides and sugar-derived α-methylene-*δ*-valerolactones.[14e] More recently, we have found[14f] that a new reagent system viz. $LaCl_3 \cdot 7H_2O/NaI/PhCH_2OH$ is suitable to hydrate glycals and this methodology was used in synthesizing 1,6-dideoxynojirimycin. A few years ago we developed[15] a new reagent system viz. $Me_3SiONO_2-CrO_3$ to convert olefins into α-nitroketones in one step. The putative intermediate was proposed to be $Me_3SiOCrO_2ONO_2$, which acted as a source of NO_2^+ and $^-OCrO_3SiMe_3$ ions. We therefore presumed that a combination of $Me_3SiONO_2-Me_3SiN_3$ could react with olefins, including glycals, to form the corresponding 2-nitroazides with the loss of $Me_3SiOSiMe_3$. It was expected that from the sugar derived 2-nitroazides the NO_2 group could be reductively removed to obtain 1-azido-2-deoxy sugars which can be further converted to 2-deoxy-*N*-glycopeptides.

In initial experiments, we found that cyclohexene and styrene were unreactive toward this reagent system viz. $Me_3SiONO_2-Me_3SiN_3$ (1:1) but 3,4-dihydro-2*H*-pyran reacted with it to form tetrahydropyran-2-azide in 94% yield. We, therefore, studied the reaction of 3,4,6-tri-*O*-benzyl-D-glucal **1f** (Table 1) with this reagent system and obtained a 2:1 mixture of α and *β* anomers of 1-azido-2-deoxy-3,4,6-tri-*O*-benzyl-D-glucose **4f** in 75% yield. Irrespective of the course of the reaction, the product isolated indicates that eventual addition of the elements of HN_3 viz. H^+ and $^-N_3$ ions to compound **1f** had occurred. Further, glucal **1f** was found to be unreactive toward a freshly made solution (1.2 M) of HN_3 which indicates that the elements of HN_3 were added to it in an indirect manner in its reaction with $Me_3SiONO_2-Me_3SiN_3$. To the best of our knowledge, there is no report in the literature on the addition of HN_3 to olefins. Since the product formed in this reaction did not clearly indicate a role of Me_3SiONO_2, we carried out experiments with less than stoichiometric amounts of Me_3SiONO_2. We subsequently found that 20 mol % of Me_3SiONO_2 (as a solution in CH_3CN) was sufficient to form the 2-deoxy-1-azido sugars from glycals. In these experiments, we had not isolated Me_3SiONO_2, instead its bulk solution was made[16] from $ClSiMe_3$ and $AgNO_3$ and 20 mol % was taken out for each experiment. Galactal derivatives gave better selectivity than the glucal derivatives which gave a mixture of the α and *β*-glycosyl azides (entries **4f**, **4g**). The galactal derivatives **1a**, **1b**, and **1e** (Table 1) gave the corresponding 2-deoxy-1-azido sugars **4a**, **4b**, and **4e** having $^4C_1$ conformation with the azide moiety in α-orientation. However, **1c** and **1d** gave azido sugars **4c** and **4d** which possessed $^1C_4$ conformations.[17] Our results are summarized in Table 1. To the best of our knowledge, this is the first report of converting glycals to 2-deoxy-1-azido sugars in one step, although there are indirect two- or three-step procedures to procure them from glycals via HBr addition followed by further manipulations.[18]

TABLE 1. Conversion of Glycals to 1-Azido Sugars

Entry	Glycal **1a-1g**	1-Azido Sugars **4a-4g**	Time (h)	Yield[a] %
a			12	83
b			5	55
c			6	65[17]
d			6	52[17]
e			10	80
f			14	75[b]
g			11	74[c]

[a] Yields of chromatographically pure compounds. [b] α/β = 2:1. [c] α/β = 1.6:1.

Exposure of 3,4,6-tri-*O*-benzyl-D-glucal **1f** (Scheme 1 where X = H, Y = OBn, R = Bn) to Me_3SiONO_2 (1.1 molar equiv) followed by analysis of the reaction mixture by thin-layer chromatography showed a polar spot compared to the starting material. The reaction mixture was then treated with Me_3SiN_3 followed by aqueous workup to yield 1-azido-2-deoxy sugar **4f** (Scheme 1). If, on the other hand, the reaction was not treated with Me_3SiN_3

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(17) We thank one of the reviewers, who suggested that we reconfirm the configurations of **4c** and **4d** which, originally, we had perceived to have $^4C_1$ conformations. Accordingly, homonuclear decoupling experiments were performed using the two methylene (H-2) protons in **4c**. Thus, irradiation of the signal for one of the two methylene protons at C-2 (H-2e) at *δ* 2.17−2.23 led to the signal for H-1 to appear as a doublet with J = 8.08 Hz. On the other hand, H-1 appeared as a doublet with J = 5.8 Hz when irradiation of the other C-2 methylene hydrogen (H-2a) at *δ* 1.58−1.65 was performed. This confirms that H-1 and H-2a are diaxially oriented in **4c** and correspondingly the azide group is equatorial. Further, in an NOE experiment, irradiation of the signal for H-1 did not enhance the signals for H-3 and H-5; instead, only the signal for H-2e at *δ* 2.17−2.23, as one would expect, was enhanced. This suggests that H-1 and H-5 have a trans relationship and hence this aspect coupled with the fact that H-1 is axially oriented clearly confirms that **4c** has $^1C_4$ conformation. Likewise, the configuration at H-1 in **4d** and its structure was established.

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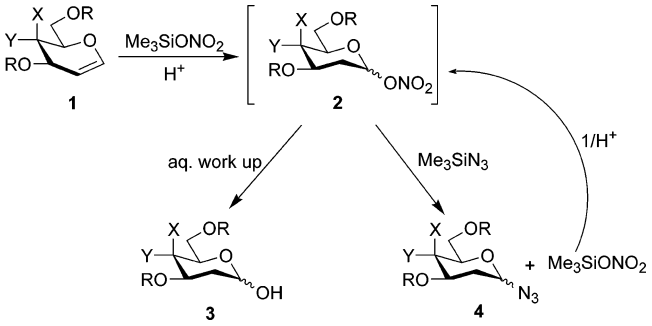
SCHEME 1



and solvent evaporated under vacuum then the product obtained showed in its IR spectrum a strong peak at 1680 cm^{-1} whereas its ^1H NMR spectrum showed peaks of no specific splitting patterns. Mass spectral analysis using electrospray technique (+ ion) suggested the presence of 1-hydroxy sugar derivative **3**; however, the −ve ion detection indicated the presence of a peak at *m*/*z* 479 corresponding to the nitrate ester **2**. Clearly, at this stage the product appears to be a mixture of several components. It is therefore likely that the product of the first reaction is compound **2** which is relatively unstable. Further, if the reaction was first *worked up* with water and the crude product treated with Me_3SiN_3 then the only product isolated after column chromatography was 2-deoxy-3,4,6-tri-*O*-benzyl-D-glucose **3** (Scheme 1). This is not unexpected since it is known[19] that anomeric nitrates are susceptible toward hydrolysis on column chromatography. Further, during workup also the nitrate ester **2** might get hydrolyzed to the hydroxy sugar **3**. We, therefore, presume that while preparing Me_3SiONO_2 from Me_3SiCl and $AgNO_3$ in CH_3CN sufficient amount of H^+ ions (possibly due to dissolved HCl in $ClSiMe_3$) must have been present[20] in the solution which allowed the addition of the elements of HNO_3 to a glycal to form glycosyl nitrate **2** which then subsequently reacts with Me_3SiN_3 to yield the azide **4**. Since Me_3SiONO_2 is recovered back in the reaction of nitrate ester **2** with Me_3SiN_3, only 20 mol % of it is sufficient for the completion of the reaction as the recycled Me_3SiONO_2 again reacts with a glycal to form glycosyl nitrate **2**.

To convert these 2-deoxy-1-azido sugars to the corresponding glycopeptides, we studied their reduction followed by coupling with appropriate amino acids. Reduction of anomeric azides has drawn a lot of attention in recent years,[21] and in this regard, the pioneering work by DeShong[22] has led to the stereoselective formation of α-glycosyl amides via their isoxazoline derivatives by neighboring group participation of the acetyl group at C-2. In all these cases, the in situ generated intermediates were trapped by either a carboxylic acid or its derivative to form the corresponding glycosyl amides. In the present work, however, we have used Ph_3P along with H_2O[23] to reduce the azide functionality and without isolating the free amine it was coupled with an activated amino acid under standard conditions. Interestingly, irrespective of the geometry of the anomeric azide, the geometry of the final coupled product was β at the anomeric center in the four glycopeptides (**5a**−**d**, Scheme 2) that we have synthesized. Thus, the azido sugar **4f** (a mixture of α and β anomers), upon reduction followed by coupling with a monopeptide viz. 1-succinimidyl-*N*-*tert*-butyloxycarbonylglcylglycinate gave exclusively the β-linked glycodipeptide **5d**. It is, however, possible that a small amount of the α-linked glycopeptide may have formed but we could neither isolate the same nor could trace its presence by the NMR spectroscopy of the product isolated by column chromatography. Formation of β-anomeric 1-amino sugars in the cases studied is not unexpected since a somewhat similar observation was reported[24] recently while reducing 1-azidosugars using H_2/Lindlar catalyst where exclusively β-anomeric 1-amino sugars are obtained irrespective of the geometry of the starting anomeric azides. Similarly, NH_4HCO_3 is also known[25] to convert reducing sugars eventually into β-anomeric 1-amino sugars. We believe that this one-step methodology to obtain 2-deoxy-1-azido sugars followed by their conversion to 2-deoxy-*N*-glycopeptides[7,26] will find wide application.

We have further utilized the present methodology in synthesizing a 2-deoxy sugar derived γ-amino acid ester **8** as shown in Scheme 3. Thus, 6-*O*-TBDMS-protected 3,4-di-*O*-benzyl-D-galactal **1b** was converted into α-1-azido-2-deoxy sugar **4b** in 55% yield by using Me_3SiONO_2−Me_3SiN_3 reagent system. Reduction of the azide **4b** with Ph_3P−H_2O gave the corresponding β-amino sugar derivative whose acetylation gave *N*-acetylamino sugar **6** in 70% yield. Deprotection of −OTBDMS group using *n*-Bu_4NF followed by oxidation with NaOCl−TEMPO[9b,11] gave the desired amino acid which was characterized as the corresponding methyl ester **8**. In view of the importance[27] of sugar amino acids in the synthesis of modified peptidomimetics, we believe that the sugar amino acid derivative **8** will be useful.

In summary, we have developed a new reagent system to convert glycals into 1-azido-2-deoxy sugars. The utility of these azido sugars in the synthesis of 2-deoxy-β-*N*-glycopeptides and a sugar amino acid has been demonstrated. We expect that the new reagent system Me_3SiN_3−Me_3SiONO_2, as well as the methodology of formation of 2-deoxy-β-*N*-glycopeptides and the sugar-derived γ-amino acid will find use in further studies.

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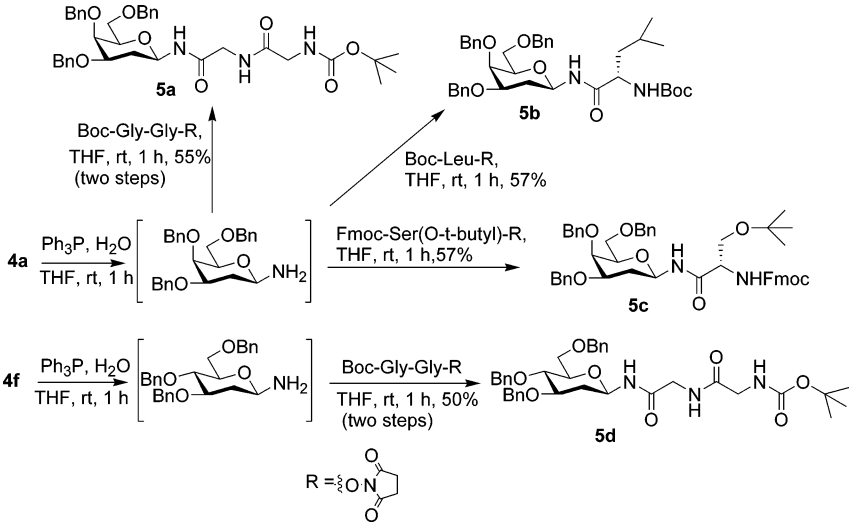
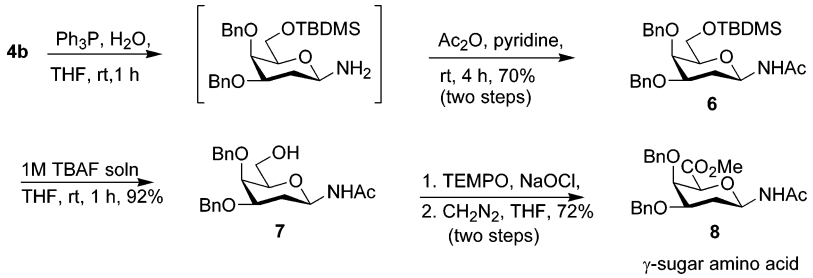
SCHEME 2



SCHEME 3



Experimental Section:

General Procedure for the Synthesis of 2-Deoxy Glycopyranosyl Azide. To a stirred solution of Me_3SiONO_2[16] (~20 mol %) in freshly distilled dry CH_3CN (2 mL) at 0 °C was added TMS−N_3 (37 μL, 0.288 mmol). A solution of a glycal (0.240 mmol) in CH_3CN (2 mL) was then added dropwise to the reaction mixture. The cooling bath was removed and stirring continued for a period as indicated in Table 1. The reaction mixture was then extracted with diethyl ether (2 × 20 mL) followed by usual workup to give a residue which was purified by column chromatography to give an azido sugar.

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Supporting Information Available: Experimental procedures and spectral data for compounds **4a**−**g**, **5a**−**d**, and **6**−**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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