Tetrahedron Letters, Vol. 33, No. 22, pp. 3109-3112, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

THE SYNTHESIS OF 2-AZIDO *C*-GLYCOSYL SUGARS

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Summary: 2-Azido *C*-glycosyl sugars can be prepared by the Lewis acid catalyzed addition of alkyl silanes to the nitrate glycosides of 2-azido sugars. The products are ozonized to the corresponding aldehydes for further elaboration.

Amino sugars are integral components of glycoproteins, a class of natural products with crucial roles in biological recognition phenomena.[1] For example, 2-acetamido α-galactosides linked to serine or threonine are commonly found in *O*-linked glycopeptides such as the blood group and tumor associated antigens.[2,3] *C*-glycosyl derivatives of these sugars can serve as stable analogs for biological recognition studies or as biologically active agents.[4] Efficient methods for the construction of 2-amino *C*-glycosyl compounds are therefore necessary for the generation of more complex carbohydrate analogs such as glycopeptides.

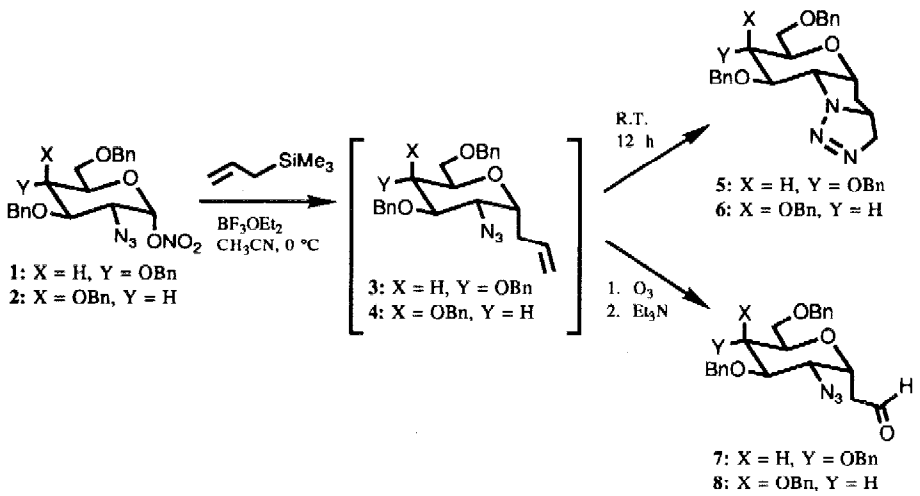
One of the most direct routes to α-linked *C*-glycosyl compounds involves the Lewis acid catalyzed addition of alkyl silanes to activated carbohydrate derivatives.[5] Unfortunately, amino and amido substituents at C-2 are incompatible with these conditions.[6] Previous methods for the synthesis of 2-amino *C*-glycosyl sugars have therefore focussed on opening the pyranose or furanose ring by either a Wittig-type reaction or vinylation reaction followed by cyclization to provide the *C*-glycosyl product.[6-8] Leblanc and coworkers have recently described a different approach involving the hetero [4+2] cycloaddition of azo compounds with C-1 substituted glycals.[9] These methods, however, involve several steps resulting in products that contain amine or amide functionalities which are incompatible with Lewis acidic and anionic conditions and limit subsequent derivatization.

In our efforts to synthesize biologically active *C*-glycosides, we required an efficient method for the preparation of 2-amino α-*C*-glycosyl sugars in which the amine functionality is masked during the synthesis as an unreactive group towards Lewis acids and anionic reagents. Azides are ideal amine equivalents due to their non-nucleophilicity, their stability under acidic and basic conditions, and the ease of reduction to the corresponding amine.[10] Despite the fact that 2-azido sugars have been used extensively in carbohydrate chemistry, *C*-glycosyl derivatives of these compounds have been limited to simple anomeric cyanides.[11] We report herein a method for the synthesis of 2-azido α-*C*-glycosyl compounds by the direct Lewis acid catalyzed addition of alkyl silanes to the nitrate glycosides of 2-azido sugars.

We first investigated the addition reaction of allyltrimethylsilane to compounds **1** and **2** (Scheme I) which were prepared by azidonitration of the corresponding tri-*O*-benzyl glycals.[10b,10c,12] Both compounds **1** and **2** (1 M solution in CH_3CN) were treated with 1.5 equivalents of allyltrimethylsilane and 1.1 equivalents of BF_3OEt_2 at 0 °C for 16 h to afford a 5:1 mixture of α/β *C*-glycosyl propenes **3** and **4**. Both compounds **3** and **4**, however,

react readily at room temperature to afford the unwanted 1,3-dipolar adducts **5** and **6**.[13] Therefore, the crude products **3** and **4** were used without purification after careful extractive workup and were stored at reduced temperatures (< -20 °C). Ozonolysis of compounds **3** and **4** in CH_2Cl_2 at -78 °C followed by reduction with triethylamine provided, after chromatographic purification (10:1 hexanes/ethyl acetate), the stable α-linked aldehydes **7** and **8** in ca. 40 % overall yield from compounds **1** and **2**.[14]

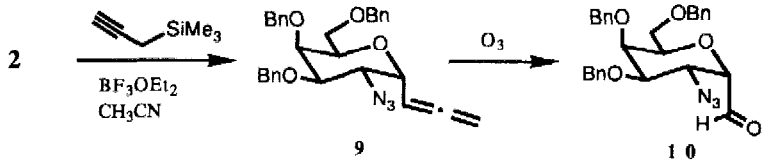
Scheme I



Alternatively, aldehydes **7** and **8** can be generated by a similar reaction sequence starting with the corresponding acetate glycosides of compounds **1** and **2** which were prepared by reaction of the nitrate sugars with 3 equivalents of NaOAc in acetic acid at 100 °C for 8 h. In this case, however, the less reactive acetate derivatives required 3 equivalents of BF_3OEt_2 and a reaction time of 48 h at 0 °C. When methyl 2-azido-2-deoxy-(3,4,6-tri-*O*-benzyl)-β-D-glucopyranoside was reacted with allyltrimethylsilane in the presence of a variety of Lewis acids (BF_3OEt_2, TMSOTf, $TiCl_4$, $SnCl_4$) no reaction was observed. Therefore, unlike the methyl glycosides of 2-alkoxy sugars, the methyl glycosides of 2-azido sugars are unreactive under the normal conditions for Lewis acid catalyzed *C*-glycosylation reactions.

Compound **2** (1 M solution in CH_3CN) can also be reacted with 1.5 equivalents of propargyltrimethylsilane and 1.1 equivalents of BF_3OEt_2 at 0 °C to room temperature over a 10 h period to afford the corresponding α-*C*-glycosyl allene **9** in 65 % yield (Scheme II).[15,16] Unlike the allyl derivatives **3** and **4**, the allene **9** is sufficiently stable at room temperature to be purified by silica gel chromatography (7:1 pentane/ether). Compound **9** decomposes to several products, however, after two weeks at 0 °C and should therefore be stored at reduced temperatures. Ozonolysis of compound **9** in CH_2Cl_2 at -78 °C provides quantitatively the sensitive aldehyde **10**.[17] Compound **10** readily undergoes β-elimination of the azide upon exposure to silica gel at room temperature and must be used without further purification.

Scheme II



In summary, we have described an efficient method for the preparation of 2-azido *C*-glycosyl sugars. Aldehydes **8** and **10** have been used as substrates for aldol condensations and Wittig reactions, respectively, and can be further derivatized to afford a variety of electrophilic substrates. Reductive acetylation of the 2-azido *C*-glycosyl products can be effected with thiolacetic acid[18] to provide the corresponding 2-acetamido analogs of the naturally occurring sugars.[19] We are currently investigating the utility of these compounds in the synthesis of stable analogs of complex oligosaccharides.

Acknowledgement.

The authors thank the American Cancer Society for a Junior Faculty Award (M. B.), Eli Lilly for a Junior Investigator Award (M. B.) and an ACS Medicinal Chemistry Fellowship (C. B.) and AT&T Bell Laboratories for a GRPW grant (C. B.). This research was supported by National Institute of Health award # R29 GM43037-02.

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12. The azidonitration procedure used for the synthesis of compounds **1** and **2** is a modified version of that described by Schmidt and coworkers (refs. 10b and 10c). A solution of the 3,4,6-tri-*O*-benzyl glycal in acetonitrile (0.1 M) was cooled to -23 °C and treated with 1.6 equivalents of NaN_3 and 3 equivalents of cerium ammonium nitrate (CAN). The suspension was stirred for 2.5 h and then poured into ice water and diluted with ether. The organic layer was separated, washed with water and brine and dried over $MgSO_4$. The crude product was purified by silica gel chromatography eluting with 15:1 hexanes/ethyl acetate.
13. The intramolecular 1,3-dipolar addition is complete after 12 h at room temperature. Dipolar adducts were characterized by NMR, IR and mass spectrometry without assignment of the stereochemistry of the bridgehead carbon atom.
14. The β-linked aldehyde was not isolated but can be easily separated from the α-linked isomer by silica gel chromatography.
15. The acetate glycoside can also be used as a substrate for the synthesis of allene **9** in which case the reaction is started at 0 °C with 1.5 equivalents of propargyltrimethylsilane. The reaction is warmed to room temperature over a 12 h period, another 1.0 equivalents of propargyltrimethylsilane are added and then the reaction is continued for another 12 h. In this case, however, only ca. 50 % of the acetate glycoside reacts and the yield of compound **9** is significantly lower.
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(Received in USA 19 February 1992)