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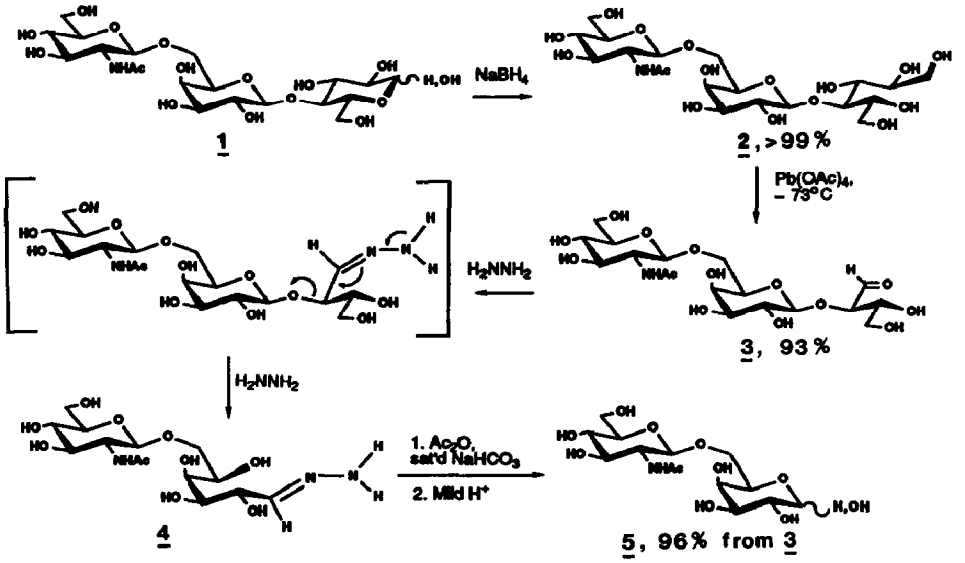
SEQUENTIAL REMOVAL OF MONOSACCHARIDES FROM THE REDUCING END OF OLIGOSACCHARIDES. I. A REACTION BETWEEN HYDRAZINE AND SUGARS HAVING A GLYCOSIDIC SUBSTITUENT ON A CARBON ATOM ADJACENT TO THE CARBONYL GROUP

Brad Bendiak*, Mary Ellen Salyan, and Mario Pantoja
The Biomembrane Institute and University of Washington
201 Elliott Ave. West, Seattle, WA, 98119, USA

Abstract: Hydrazine reacts smoothly with sugars having a glycosidic substituent when the glycosyl moiety is located on a carbon atom adjacent to an aldehyde or keto group, resulting in cleavage of the glycosidic linkage. In excess hydrazine, the released glycoside forms a hydrazone from which the reducing sugar may be recovered in high yields.

Reported herein is a novel cleavage of a glycosidic linkage when the glycosyl moiety is located on a carbon atom adjacent to an aldehyde or keto function.[1] In the development of a methodology for the controlled sequential removal of monosaccharides from the reducing end of oligosaccharides, our objective has been to restrict the chemistry to the reducing monosaccharide in such a way as to first, introduce an aldehyde or keto group adjacent to the glycosidic linkage,[2] and second, cleave the glycosidic bond through reaction with a hydrazino compound, as depicted in the example in Scheme I.

Scheme I

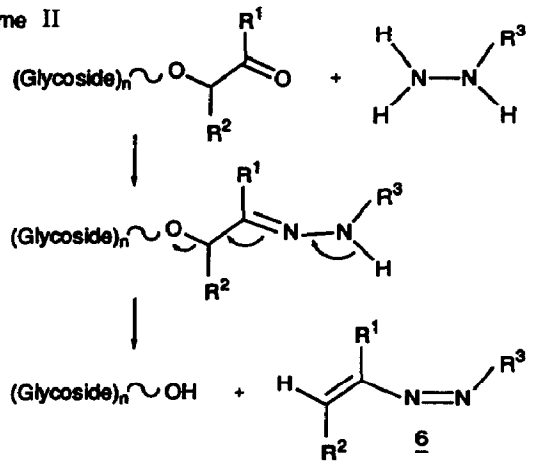


Thus, the trisaccharide 1 (β-D-Glc*p*NAc-[1-6]-β-D-Gal*p*-[1-4]-D-Glc) upon borohydride reduction gave 2 having a 4-substituted D-glucitol residue at the former reducing end.[3] Highly regioselective oxidation with lead tetraacetate at -73°C gave 3, having a 2-substituted D-erythrose at the reducing end.[4] Treatment of 3 with

hydrazine cleaved the glycosidic linkage, giving the disaccharide product derived from the nonreducing portion of the molecule, which reacted further to form the hydrazone **4**. Cleavage of the hydrazone was achieved by *N*-acetylation, followed by mild acid hydrolysis of the resultant acetohydrazide derivative[5] giving the reducing disaccharide, **5**, in 96% yield from **3**.

A key step in the reaction series is the reaction between a hydrazino compound and sugars having a glycosidic substituent on a carbon atom adjacent to the carbonyl group, shown more generally in Scheme II. Our evidence indicates that the reaction proceeds via generation of an azoethylene derivative **6**, which is susceptible to further rearrangements depending on the nature of the R groups.[6] Mechanistically similar reactions have been reported in the elimination of a 2-*O*-acetyl group from acyclic, peracetylated phenylhydrazones of monosaccharides, to give phenylazoethylene derivatives,[7] and in the reaction of hydrazine with α,β-epoxy ketones to give allylic alcohols.[8]

Scheme II



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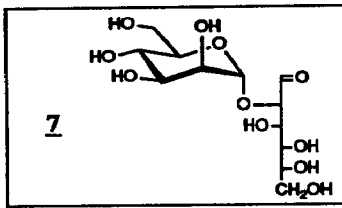
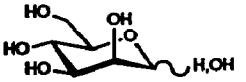
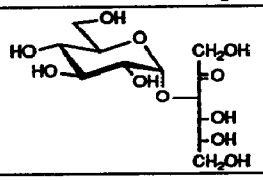
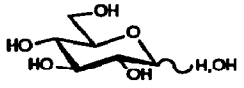
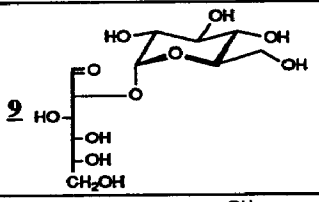
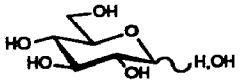
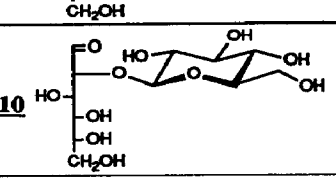
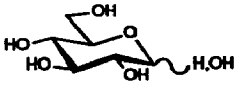
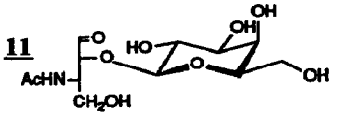
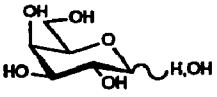
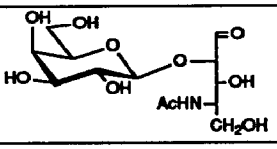
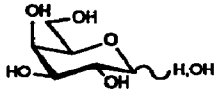
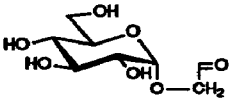
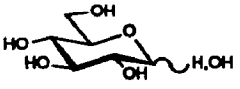
To assess the generality of this reaction, several compounds were either obtained or prepared, having a glycosidic substituent on a carbon adjacent to an aldehyde or keto group.[9] The compounds 2-*O*-α-D-mannopyranosyl-D-mannose (**7**), 3-*O*-α-D-glucopyranosyl-D-fructose (**8**), 2-*O*-α-D-glucopyranosyl-D-glucose (**9**), and 2-*O*-β-D-glucopyranosyl-D-glucose (**10**) were obtained commercially. The compounds 3-acetamido-3-deoxy-2-*O*-(β-D-galactopyranosyl)-L-threose (**11**), 4-acetamido-4-deoxy-2-*O*-(β-D-galactopyranosyl)-L-xylose (**12**), and 2-*O*-α-D-glucopyranosyl-glycolaldehyde (**13**) were prepared by lead tetraacetate oxidation[2] of 2-acetamido-2-deoxy-3-*O*-(β-D-galactopyranosyl)-D-galactitol (for **11**), 2-acetamido-2-deoxy-4-*O*-(β-D-galactopyranosyl)-D-glucitol (for **12**), and 6-*O*-α-D-glucopyranosyl-D-glucitol (for **13**).

Following hydrazine treatment and release of the hydrazone group,[5] the results (Table 1) demonstrate that cleavage of the glycosidic bond proceeds whether the glycoside is of α or β configuration, and whether the glycoside is adjacent to an aldehyde or keto function. In addition, the released sugars that were examined did not undergo epimerization at C-2 or enolization reactions under the mild conditions of the hydrazine treatment. The facile conditions of the reaction, combined with the high rates of lead tetraacetate oxidation of alditols as compared to glycopyranosides at low temperatures, should enable the reaction series to be applied to a variety of structures.

Table 1: Reaction of hydrazine with compounds having a glycosidic substituent on a carbon atom adjacent to a carbonyl group. Yields are those of the reducing monosaccharide product derived from the glycon, following release of the hydrazone group.

Starting compound	Product from glycon	% Yield
 **7**		88
 **8**		98
 **9**		95
 **10**		97
 **11**		99
 **12**		93
 **13**		82

Acknowledgements: This work was supported by funds from the Biomembrane Institute.

References and Notes

1. Presented at the 21st meeting of the Society for Complex Carbohydrates, Nashville, Tennessee, Abstr. 1.14 and 1.15, Nov 11-14, 1992; Bendiak, B. and Pantoja, M. Glycobiology, **1992**, *2*, 460; Bendiak, B., Glycobiology, **1992**, *2*, 460.

2. The highest yielding, and most generally applicable procedure for introduction of an aldehyde or keto function further down the chain of the reducing monosaccharide involved reduction with $NaBH_4$, followed by highly regioselective oxidation of the resultant

alditol with lead tetraacetate (Scheme I) or periodic acid. Lead tetraacetate has been used in this context in the preparation of 2-*O*-glycosyl-glycerols [(a) Charlson, A.J., and Perlin, A.S. Can. J. Chem., **1956**, *34*, 1200-1208. (b) Charlson, A.J., Gorin, P.A.J., and Perlin, A.S. Can. J. Chem., **1956**, *34*, 1811-1818. (c) Charlson, A.J., Gorin, P.A.J., and Perlin, A.S. Can. J. Chem., **1957**, *35*, 365-373. (d) Gorin, P.A.J. and Perlin, A.S. Can. J. Chem., **1958**, *36*, 999-1003. (e) Charlson, A.J., Gorin, P.A.J. and Perlin, A.S. Methods Carbohydr. Chem., **1962**, *1*, 419-426. Modified conditions typically employed herein were, A: 50 mM $Pb(OAc)_4$ (in > 20-fold molar excess) in 1:1 (vol/vol) DMSO:glacial acetic acid, -30 to -60°C, for 1 h or B: 0.5 mmol $Pb(OAc)_4$ (in > 20-fold molar excess) added to a solution of 1.0 mL water, 3.2 mL glacial acetic acid, and 12.3 mL acetone at -73°C, with stirring for 1 h. Comparative rates of oxidation of alditols as compared to their respective α- and β-*O*-methyl glycopyranosides under these conditions are extremely high; preliminary data at -60°C under the conditions in A, above, indicate numbers well above 10^3 for the 2-acetamido-2-deoxy-D-gluco and 2-acetamido-2-deoxy-D-galacto series. Other attempted reactions to introduce a carbonyl group adjacent to the glycosidic linkage, which gave lower yields, were "descent of the series" reactions [(a) Fletcher, H.G., Jr., Diehl, H.W. and Hudson, C.S. J. Am. Chem. Soc., **1950**, *72*, 4546. (b) Whistler, R.L. and Schweiger, R. J. Am. Chem. Soc., **1959**, *81*, 5190-5193. (c) Whistler, R.L. and Yagi, K. J. Org. Chem., **1961**, *26*, 1050-1052. (d) Weygand, F., and Löwenfeld, R. Chem. Ber., **1950**, *83*, 559-563)], Amadori rearrangements [(a) Kuhn, R. and Weygand, F. Ber., **1937**, *70*, 769-772. (b) Micheel, F. and Schleppinghoff, B. Chem. Ber., **1956**, *89*, 1702-1708. (c) reviewed by Paulsen, H. and Pflughaupt, K.-W. (In "The Carbohydrates, Chemistry and Biochemistry"; Pigman, W. and Horton, D., Eds.; Academic Press: New York, **1980**; Vol. IB, p881-927)], and arylosazone formation followed by deprotection [reviewed by Mester, L. and El Khadem, H.S. (In "The Carbohydrates, Chemistry and Biochemistry"; Pigman, W. and Horton, D., Eds.; Academic Press: New York, **1980**; Vol. IB, p929-988)]. However, these reactions may be applicable, perhaps even preferable, in specific situations.

3. Typical conditions for reduction; 1 M $NaBH_4$ (in > 10-fold molar excess), room temperature, 24 h. Quantitation was performed with the anthrone reagent (Spiro, R.G. Methods Enzymol., **1966**, *8*, 3-26), and for the aldehyde before and after reduction by the method of Park, J.T. and Johnson, M.J., J. Biol. Chem., **1949**, *181*, 149-151.
4. Oxidation was performed under conditions described in B, above.[2]
5. Hydrazine treatment was typically carried out using anhydrous hydrazine (in large molar excess), at 50-70°C for 24 h, under argon; for deprotection of the hydrazone, *N*-acetylation with acetic anhydride in saturated $NaHCO_3$, followed by mild acid treatment (50 mM H_2SO_4, 35°C, 1 h; see Bendiak, B. and Cumming, D.A. Carbohydr. Res., **1985**, *144*, 1-12). We have synthesized the *N'*-(glycopyranosyl)acetohydrazide derivatives of all D-hexoses, D-pentoses, 2-acetamido-2-deoxy-D-glucose and 2-acetamido-2-deoxy-D-galactose, all of which are quantitatively hydrolyzed under the above conditions.
6. R^1 and R^2 may be H or other portions of monosaccharides having hydroxyl and/or *N*-acetamido substitutions. Where R^3 was one of several aryl groups that were examined, the elimination of the glycosidic substituent occurred readily, but the released glycoside reacted more rapidly with the arylhydrazine to form the well-known arylosazone derivatives (Fischer, E. Ber., **1884**, *17*, 579-584, reviewed by Mester, L. and El Khadem, H.S.[2]). Therefore, most arylhydrazines are not useful in accomplishing this overall reaction series, because the next reducing monosaccharide is modified at C-2 in high yields.
7. (a) Wolfrom, M.L., Fraenkel, G., Lineback, D.R. and Komitsky, F., Jr. J. Org. Chem., **1964**, *29*, 457-461.
   (b) El Khadem, H., Wolfrom, M.L., El Shafei, Z.M. and El Ashry, S.H. Carbohydr. Res., **1967**, *4*, 225-229.
8. Wharton, P.S. and Bohlen, D.H. J. Org. Chem., **1961**, *26*, 3615-3616.
9. All new compounds were fully characterized by ^{1}H-NMR (500 MHz), MS, and high resolution MS. Structures 3 and 11-13 were also characterized after reduction, as were their respective alditols or ethylene glycol after isolation following acid hydrolysis and high-performance liquid chromatography.

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