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A Method for the Selective Reduction of Carbohydrate 4,6-*O*-Benzylidene Acetals

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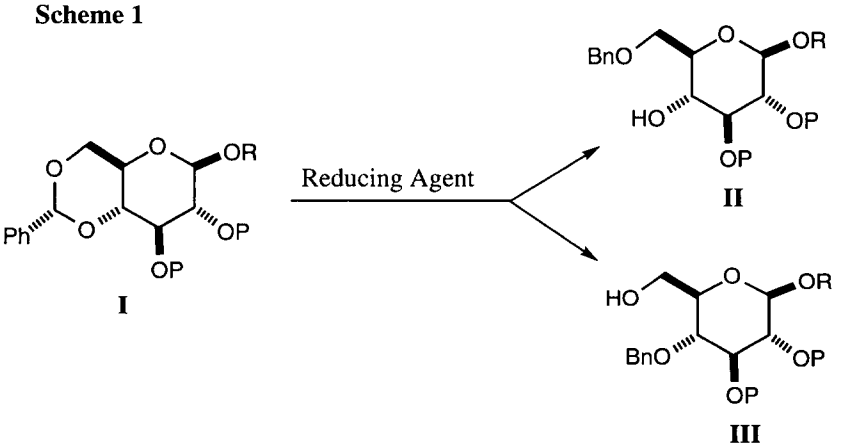
Abstract: Glucose-derived 4,6-*O*-benzylidene acetals can be selectively reduced to the corresponding 6-*O*-benzyl derivatives by the treatment with trifluoroacetic acid and triethylsilane.

Glycobiology is rapidly becoming an important new area for drug discovery.[1] This development is in part due to the numerous advances recently made in the area of oligosaccharide synthesis. These advances include an arsenal of improved methods for the construction of the glycosidic bond.[2] Critical for the success of the glycosidation reactions is the selective manipulation of the sugar hydroxyl groups. This chemistry is needed because in most cases, with the exception of enzyme catalyzed glycosidations,[3] exposure of a unique hydroxyl group is required prior to coupling. Although chemistry for the selective protection of carbohydrates has been extensively studied,[4] there still exists a need for improved methods. One of the most useful and widely utilized methods for differentiating the C-4 hydroxyl of sugars involves the reductive opening of a 4,6-*O*-benzylidene acetal as depicted in Scheme 1. Benzylidene derivatives of carbohydrates can be easily prepared in high yield, and the secondary alcohol products **II** usually predominate. A number of methods exist for the reduction of these acetals including, $LiAlH_4$-$AlCl_3$,[5] $NaCNBH_3$-HCl,[6] and DIBAL[7] as well as others.[8] These methods suffer drawbacks such as an incompatibility with other functionality in the molecule and the need for carefully controlled reaction conditions and rigorously dry reagents and solvent.

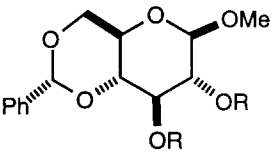
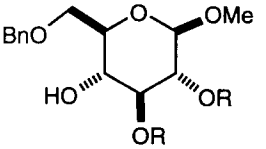
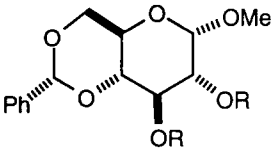
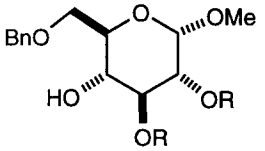
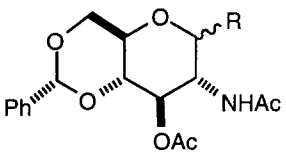
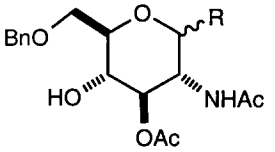
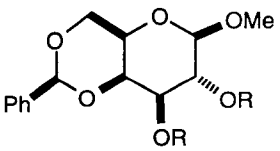
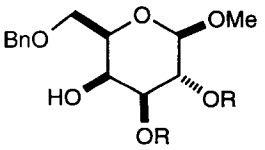
Scheme 1



I **II** **III**

The triethylsilane(TES)—trifluoroacetic acid(TFA) system has been used for the reduction of a number of functional groups including simple acetals and ketals.[9] In this paper we describe the use of this reagent system for selective and high-yielding conversions of 4,6-*O*-benzylidene-protected carbohydrates to the corresponding 6-*O*-benzyl-4-hydroxy derivatives.

Table 1

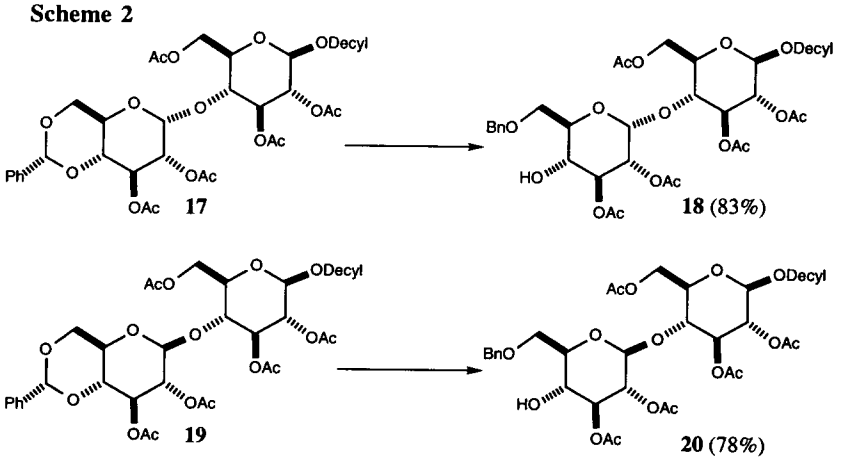
Acetal	Product (%yield)
 **1 R = Ac** **3 R = Bn**	 **2 R = Ac (95%)** **4 R = Bn (80%)**
 **5 R = Ac** **7 R = Bn**	 **6 R = Ac (98%)** **8 R = Bn (81%)**
 **9 R = β-OMe** **11 R = α-OMe**	 **10 R = β-OMe (94%)** **12 R = α-OMe (92%)**
 **13 R = Ac** **15 R = Bn**	 **14 R = Ac (No Reaction)** **16 R = Bn (No Reaction)**

The first substrate examined was the simple monosaccharide methyl β-D-glucoside, varying the protecting groups at C-2 and C-3 (acetate or benzyl) and the configuration at C-1 (α or β). The results are shown in Table 1. Treatment of **1** with 5 equivalents of TES and 5 equivalents of TFA in dichloromethane afforded the C-4 alcohol **2** in 95% yield. In this and subsequent reactions, none of the primary alcohol could be detected. Both benzyl and acetate protecting groups are tolerated, although the acetate-protected compounds reacted faster and more cleanly. The configuration of the anomeric center had no effect on the reaction. It is important to note that the methyl glycoside was not reduced during the reaction although such reductions have been observed under similar conditions (i.e., TES-BF_3OEt_2).[10]

Other sugars were then explored. The *N*-acetyl glucosamine derivatives **9** and **11** worked equally well, affording the secondary alcohols in over 90% yield. Interestingly, there was no reaction when the galactose compounds **13** or **15** were subjected to the standard conditions. In an attempt to increase the reactivity of the acetal, the *para*-methoxyphenyl analog was prepared. Although the starting material was rapidly consumed upon exposure to TFA/TES, mostly hydrolysis products were produced.

In order to explore whether disaccharides would be acceptable substrates, compounds **17** and **19** were synthesized by standard methods. The reduction of these acetals was slow and the rate of hydrolysis became competitive. Sucessful results were achieved however by concentrating the starting material from toluene prior to reduction. The addition of three equivalents of trifluoroacetic anhydride also seemed to improve the results. In this manner, the 4'-OH products **18** and **20** were produced in 83% and 78% yield, respectively.

Scheme 2



A typical procedure is as follows: Trifluoroacetic acid (0.53 mL, 6.8 mmol) was added dropwise to a solution of compound **1** (0.5 g, 1.37 mmol) and triethylsilane (1.09 mL, 6.8 mmol) in dichloromethane (5 mL) at 0°C.[11] When the addition was complete (5 min), the reaction was warmed to room temperature until starting material was consumed (~2 to 4 hours). The mixture was diluted with ethyl acetate and washed with aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered and concentrated. The product was purified by flash chromatography (30% EtOAc/hexanes) to afford the alcohol **2** as a colorless syrup (0.475 g, 95%).

In summary, a mild and selective method for the reduction of 4,6-*O*-benzylidene acetals of glucosides has been established. The TFA/TES reagent system affords the 6-*O*-benzyl products in good yields under easily controlled reaction conditions.

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11) The trifluoroacetic acid, triethylsilane and anhydrous dichloromethane was used as received from the supplier (Aldrich Chemical Co.) without purification.

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