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An Improved Method for the Synthesis of Anhydroalditols

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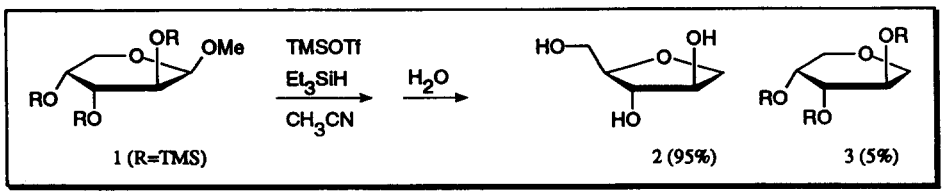
Abstract: An improved synthesis of anhydroalditols through reductive cleavage of acetylated carbohydrates is reported. The procedure appears to have generality. Ring rearrangements, which complicate some other reported procedures for the preparation of anhydroalditols, were not observed. The acetate protecting groups used were stable under the reaction conditions employed.

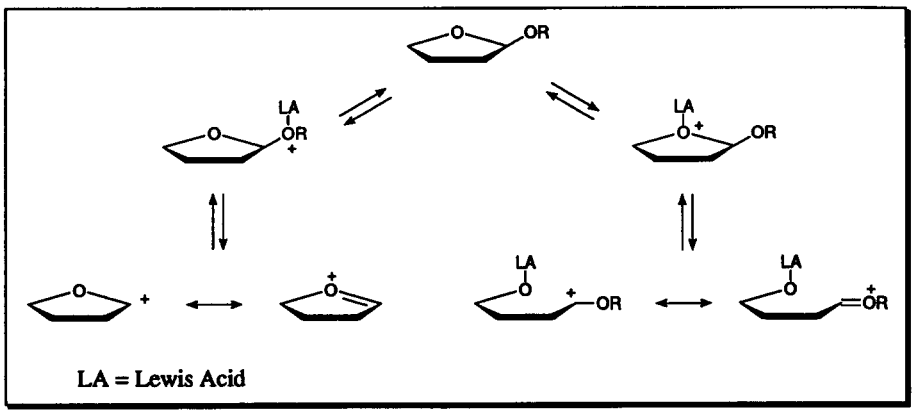
Methodologies for the deoxygenation of the anomeric hydroxyl group of carbohydrates to produce anhydroalditols are of interest, not only in carbohydrate and complex carbohydrate chemistry,[1,2] but also in the synthesis of new families of modified nucleosides that are isomeric with their natural counterparts.[3-7] A variety of methods have been developed for the synthesis of anhydroalditols including acid-catalyzed dehydration of acylic alditols,[8,9] catalytic hydrogenation of glycals[10] and thioglycosides,[11] reduction of glycosyl halides,[12-15] and reductive cleavage of appropriate carbohydrate precursors.[1,2,16-19] The reductive cleavage of methyl glycosides involves the generation of an incipient carbonium-oxonium ion at the anomeric position. This cation can be reductively trapped with trialkylsilanes (ionic hydrogenation).[20] The overall methodology has been reported to be efficient with silyl protecting groups despite problems of deprotection and ring contraction in certain cases (Scheme 1).[2]



Scheme 1

Our work using the foregoing reductive demethoxylation methodology of Bennek and Gray[2] originally developed for analytical work has met with mixed success when carried out on a preparative scale. In addition, the observed deprotection and ring contraction with silyl protecting groups bring into question the stability of these groups under the reaction conditions and also indicate that an acyclic intermediate is being formed in these cases (Scheme 2, only partial structures are shown). The use of a methyl acetal (e.g. as

shown in Scheme 1) stabilizes this acyclic carbocation, slows the reaction and allows for ring rearrangement. An acetate group at the anomeric position and the presence of another at the neighboring center would allow more efficient departure of the anomeric leaving group complex and subsequent stabilization of the resulting cyclic carbonium-oxonium ion. This communication reports on an efficient procedure for the reductive cleavage of anomeric acetates in carbohydrate molecules without rearrangement which provides an improved method for the synthesis of anhydroalditols.



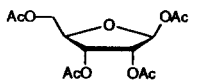
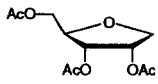
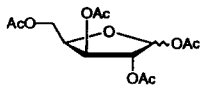
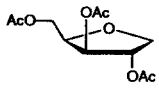
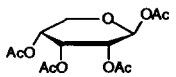
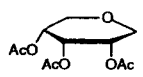
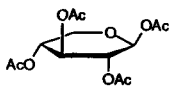
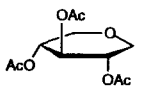
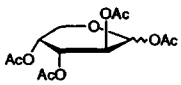
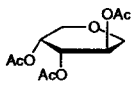
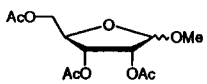
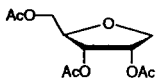
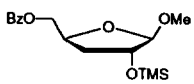
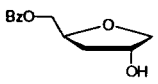
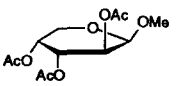
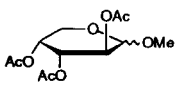
Scheme 2

The results of our studies are summarized in Table 1. Because carbohydrate precursors are most commonly available either as β-anomers or as anomeric α,β-mixtures, the compounds chosen for this study included largely these substrates. In each example, the carbohydrate precursor (10 mmol) was allowed to react at room temperature with trimethylsilyl triflate (20 mmol) and triethylsilane (30 mmol) in acetonitrile (5-10 mL) for 24 h and the reaction was then worked up. Structural identification of the products, which are known compounds,[2,3,21-23] was carried out by ^{1}H and ^{13}C NMR data (including DEPT data).[24] The procedure can best be exemplified by examining the case of 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose. This compound in acetonitrile was converted almost quantitatively to 2,3,5-tri-O-acetyl-1,4-anhydro-D-ribitol by treatment with TMS triflate and triethylsilane (Table 1, Entry 1). The xylofuranose tetraacetate (α:β ratio 1:1, Table 1, Entry 2) was converted in 88% isolated yield to the corresponding anhydroalditol. Ribopyranose acetate (Entry 3) gave an 84% isolated yield of desired product. There was no evidence of ring rearrangement. The xylopyranose and the arabinopyranose tetraacetates (Entries 4 and 5, respectively) gave similar results. In stark contrast, the corresponding 2,3,5-tri-O-acetyl-1-O-methylglycoside (Entry 6) gave variable yields in the range of 40%. The yields were even more variable in the methylacetal case (Entry 7) where the neighboring group was a trimethylsilyloxy. Also, the trimethylsilyl protected O-methyl glycoside related to Entry 6 gave similar, and, in most experiments, lower yields. Finally, while the arabinopyranose tetraacetate (Entry 5) gave excellent yields of the deoxygenated product, its 1-methylacetal derivative (Entry

8) did not deoxygenate but underwent epimerization to the α,β mixture of the starting compound presumably through an acyclic carbonium-oxonium ion intermediate stabilized by the methoxy group (see Scheme 2).

In summary, deoxygenation reactions involving the anomeric hydroxyl group can best be carried out by reductive deacetylation using TMS triflate and triethylsilane in acetonitrile at room temperature. The presence of an adjacent participating acetate group further facilitates the deoxygenation process through stabilization of the cyclic carbonium-oxonium ion. Ring rearrangements did not complicate these conversions.

Table 1. Representative Examples of Substrates and Products in Carbohydrate Anomeric Deoxygenations Leading to Anhydroalditols

Entry	Carbohydrate	Product	%Yield
1			94
2			88
3			84
4			80
5			85
6			40
7			30
8			80

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24. Spectral data for 2,3,5-tri-O-acetyl-1,4-anhydro-D-ribitol (Entry 1 in Table 1): ^{1}H NMR ($CDCl_3$) δ 2.09 (s, 3H), 2.10 (s, 3H), 2.11 (s, 3H), 3.88 (dd, 1H, J=3.9, 10.3 Hz), 4.15 (m, 2H), 4.24 (dd, 1H, J=5.1, 10.3 Hz), 4.34 (m, 1H), 5.13 (dd, 1H, J=5.5, 6.6 Hz), 5.37 (dt, 1H, J=4.0, 5.3 Hz). ^{13}C NMR ($CDCl_3$) δ 20.5, 20.6, 20.8, 63.5 (-CH_2-), 70.8 (-CH_2-), 71.1, 71.7, 78.0, 169.8, 169.9, 170.6.

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