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Metal Trifluoromethanesulfonate-Catalyzed Regioselective Borane-Reductive Ring Opening of Benzylidene Acetals: A Concise Synthesis of 1,4-Dideoxy-1,4-imino-L-xylitol

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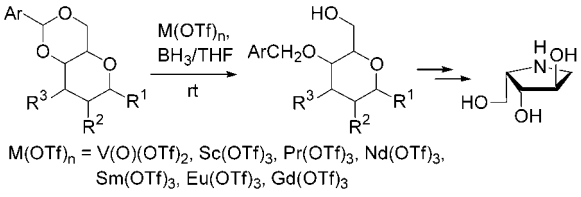
ABSTRACT



A highly regioselective borane-reductive ring opening of the 4,6-*O*-benzylidene-D-hexopyranosides to the corresponding 6-alcohols in excellent yields at room temperature via various metal trifluoromethanesulfonates as catalysts is described here. Its application in the synthesis of 1,4-dideoxy-1,4-imino-L-xylitol is also highlighted.

Regioselective protection of individual hydroxyl groups in a carbohydrate molecule is a prominent problem frequently encountered during the synthesis of biologically potent oligosaccharides and glycoconjugates, as well as natural products.[1] Substituted and unsubstituted benzylidene acetals are mainly used for 4,6-*O*-protection of hexopyranosides because these not only are easy to install but also can be regioselectively cleaved at will, with appropriate choice of reaction conditions, to establish orthogonal protecting group patterns.[2] Some effective reagents to cleave the 4,6-*O*-benzylidene acetals to provide the corresponding 6-*O*-benzyl ethers have been reported.[3] For the preparation of the 4-*O*-benzyl derivatives, $LiAlH_4/AlCl_3$[4] or DIBAL[5] are generally used to revert the regioselectivity of ring opening. However, these reagents lack chemoselectivity, especially with those

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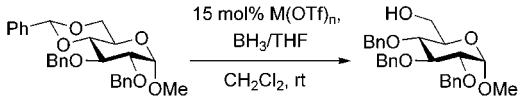
substrates bearing base-sensitive functional groups. Alternatively, a combination of reducing reagents ($NaCNBH_3$, Et_3SiH, and BH_3) with Lewis acids ($AlCl_3$, $BF_3{\cdot}OEt_2$, TMSCl, $PhBCl_2$, and Bu_2BOTf) are also described in the literature.[3a,b,e,f,6] Since these traditional Lewis acids are extremely moisture-sensitive and often have to be used in stoichiometric amounts in the reactions, there is a need to search for new catalysts that are applicable to a wide range of substrates.

Metal(III) trifluoromethanesulfonates (M = lanthanide elements, Sc, In, and Bi) and oxavanadium(IV) trifluoromethanesulfonate [$V(O)(OTf)_2$] are water-stable, reusable, and valuable Lewis acids that have been used as efficient catalysts in a variety of reactions.[7−13] To the best of our knowledge to date, these metal trifluoromethanesulfonates have not been employed in conjunction with a reducing agent. We have explored herein their catalytic activities in the BH_3-reductive cleavage of benzylidene acetals.

Methyl 4,6-*O*-benzylidene-2,3-di-*O*-benzyl-α-D-glucopyranoside **1** was selected as the model compound for our studies. Treatment of **1** with $BH_3{\cdot}THF$ in the presence of 15 mol % $M(OTf)_n$ gave the corresponding 6-alcohol **2** in excellent yields. The reaction conditions and results are illustrated in Table 1. Initially (entry 1), when the benzylidene acetal ring was opened at 0 °C, it took a prolonged time for completion and a small amount of acetal-hydrolyzed product was also detected along with the expected product **2** (87%), whereas conducting the same transformation at ambient temperature resulted in formation of **2** (94%) in much shorter reaction time. Interestingly, all $M(OTf)_n$ were appropriate as catalysts to carry out the bond cleavages at room temperature in ca. 3−5 h (entries 2−8).

Table 1. $M(OTf)_n$-Catalyzed BH_3-Reductive Ring Opening of the 4,6-*O*-Benzylidene Acetal **1** at O6



1 **2**

entry	$M(OTf)_n$	*T* (°C)	*t* (h)	yield (%)
1	$V(O)(OTf)_2$	0	27	87
2	$V(O)(OTf)_2$	rt	3	94
3	$Sc(OTf)_3$	rt	5	93
4	$Pr(OTf)_3$	rt	5	91
5	$Nd(OTf)_3$	rt	4	94
6	$Sm(OTf)_3$	rt	3.5	92
7	$Eu(OTf)_3$	rt	3	87
8	$Gd(OTf)_3$	rt	3	88

On the basis of our new findings, the applications of $V(O)(OTf)_2$[9d] in a variety of 4,6-*O*-benzylidene-D-hexopyranosides are studied further (Table 2). To test the compatibility of different protecting groups, the D-*gluco* derivatives **3** and **5** were examined (entries 1 and 2), and the alcohols **4** and **6** were isolated in 83% and 92% yields, respectively. The reactions worked equally well with the β-D-gluco- (entries 3−5), α-D-galacto- (entries 6 and 7), and α-D-mannopyranosyl sugars (entry 8). It is evident from the above results that the electron-donating protecting groups in the substrate speed up the reaction while electron-withdrawing groups slow it down. Obviously, the reaction rate is concerned with the nucleophilicity of the 6-oxygen atom for the Lewis acid catalyst. Finally, to extend this reaction in the D-glucosamine derivative **19**,[14] the corresponding 6-alcohol **20** was successfully obtained in 84% yield (entry 9). Its absolute configuration was determined through the X-ray single-crystal analysis (see Supporting Information).

Iminosugars, which are polyhydroxylated nitrogen-containing heterocycles, have been attracting the interest of

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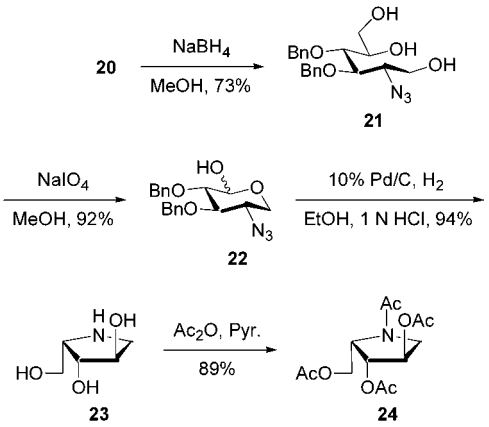
Table 2. Borane-Reductive Ring Opening of Various 4,6-*O*-Benzylidene-D-hexopyranosides at Room Temperature in the Presence of 15 Mol % $V(O)(OTf)_2$ as Catalyst

entry	acetal	t (h)	product	yield (%)
1	**3** : R = H	12	**4** : R = H	83
2	**5** : R = Bz	16	**6** : R = Bz	92
3	**7** : R = Bn	3	**8** : R = Bn	86
4	**9** : R = Bz	7.5	**10** : R = Bz	90
5	**11**	1	**12**	86
6	**13** : R = Bn	3	**14** : R = Bn	88
7	**15** : R = Bz	18	**16** : R = Bz	74
8	**17**	3	**18**	91
9	**19**	3	**20**	90

synthetic chemists as a result of their potent glycosidase inhibition, antiviral activities, and anticancer properties.[15] As a part of our ongoing research program to synthesize the biologically important and rare L-form sugars,[16] we proceeded to prepare 1,4-dideoxy-1,4-imino-L-xylitol **23**,[17] a potential inhibitor of glycosidases.

With the key synthon **20** in hand, the synthesis of **23** was efficiently carried out in three steps (Scheme 1). Reduction

Scheme 1



of **20** with sodium borohydride led to the triol **21** (73%), which was subjected to $NaIO_4$ oxidative cleavage of carbon−carbon single bond between the vicinal hydroxyl groups to furnish the cyclic hemiacetal **22** (92%). Further reduction of **22** under hydrogenation conditions afforded the target molecule **23** in 94% yield. Comparison of our data of its peracetylated derivative **24** with the literature report[17f] revealed identity with respect to ^1H and ^{13}C spectra.

In conclusion, we have successfully developed a $M(OTf)_n$-catalyzed regioselective BH_3-reductive ring opening of the 4,6-*O*-benzylidene-D-hexopyranosides to the corresponding 6-alcohols in excellent yields at room temperature and applied the key synthon **20** to synthesize 1,4-dideoxy-1,4-imino-L-xylitol **23** in three straightforward steps. This representative example demonstrates the inherent synthetic potential of this methodology. The efforts to prepare other biologically important iminocyclitols are currently underway.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds and X-ray structural information for compound **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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