JOC*Note*

An Efficient Stereoselective Dihydroxylation of Glycals using a Bimetallic System, $RuCl_3/CeCl_3/NaIO_4$†

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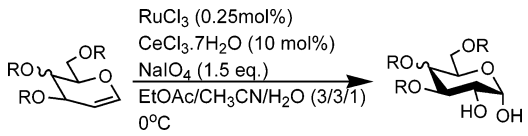


A catalytic dihydroxylation reaction on glycals has been developed using a bimetallic oxidizing system to furnish sugar 1,2-diols in a highly setreoselective manner.

Suitably protected 1,2-dihydroxy carbohydrate derivatives are useful synthetic intermediates in several organic transformations such as in the synthesis of polyhydroxylated chiral natural products,[1] O-glycosides[2] and C-glycosides.[3] They have also used in the O-glycosylations involving intramolecular aglycon delivery.[4] Conventionally, sugar-derived 1,2-diols are prepared using the reaction sequence of conversion of acetobromosugars to the corresponding sugar ortho esters followed by hydrolysis of ortho esters to the sugar 1,2-diols.[5] Although this method has been used widely, use of excess *s*-collidine[6] as solvent during the formation of ortho esters is a serious drawback of this protocol. Other reported methods for the preparation of sugar 1,2-diols include (a) osmium-catalyzed (OsO_4−NMO) dihydroxylation of glycals;[2a,c] (b) conversion of glycals to 1,2-glycal epoxides using dimethyldioxirane followed by hydrolytic opening of 1,2-glycal epoxides;[7] and (c) reaction of glycals with oxone in acetone.[8] There are several drawbacks in the above-mentioned methods, which include the use of very expensive and toxic reagents, difficulties in removing the Osmium salt from the products, use of very unstable epoxidation reagent, and formation of C-2 epimer. Use of oxone for the dihydroxylation of glycals is very convenient but always resulted in formation of a C-2 epimeric mixture as major and minor product in our hands. In view of the importance of 1,2-sugar diols in the synthesis of oligosaccharides and natural products, a strong impetus has been given to develop a mild, less toxic, economically convenient, and user-friendly reaction protocol for their preparation. Recently, we noted a few reports on the oxidative use of $RuCl_3$ in a combination of $NaIO_4$ and a Brønsted or Lewis

SCHEME 1

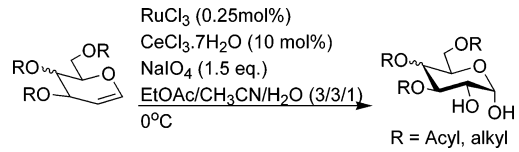
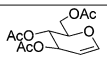
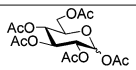
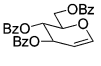
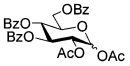
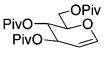
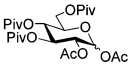
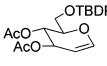
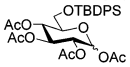
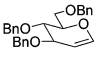
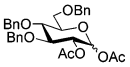
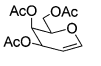
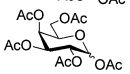
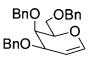
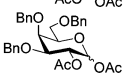
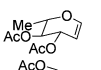
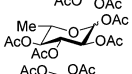
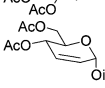
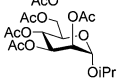
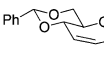
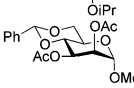
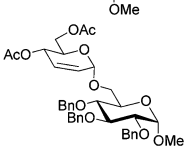
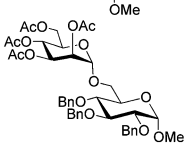
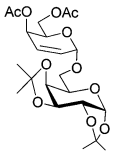
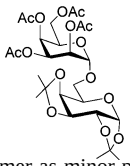


TABLE 1. Stereoselective *cis*-Dihydroxylation of Glycals and Unsaturated Carbohydrate Derivatives using $RuCl_3/CeCl_3{\cdot}7H_2O/NaIO_4$ in $EtOAc/CH_3CN/H_2O$ at 0 °C

Entry	Substrates (a)	Di-*O*-acetates (b)	Time (min)	Yield (%)	α/β	Ref
1			15	88	2.6	11
2			15	85	α	-
3			20	90	2.75	-
4			15	85	1.9	-
5			15	90	1.0	8
6			15	92	1.6	11
7			15	88	0.95	8
8			15	85	9.8	-
9			20	90	--	-
10			20	90	--	12
11			20	85	--	-
12			20	70[a]	--	-

[a] Together with D-gulo-isomer as minor product (~20%).

† C.D.R.I. communication no. 6921.

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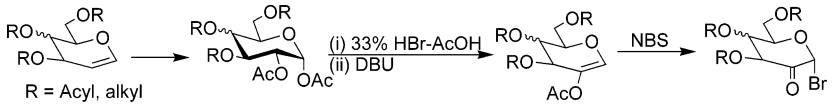
SCHEME 2



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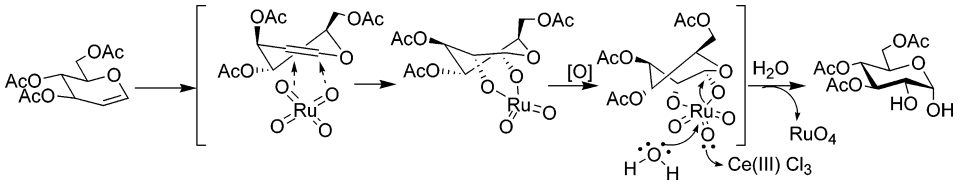

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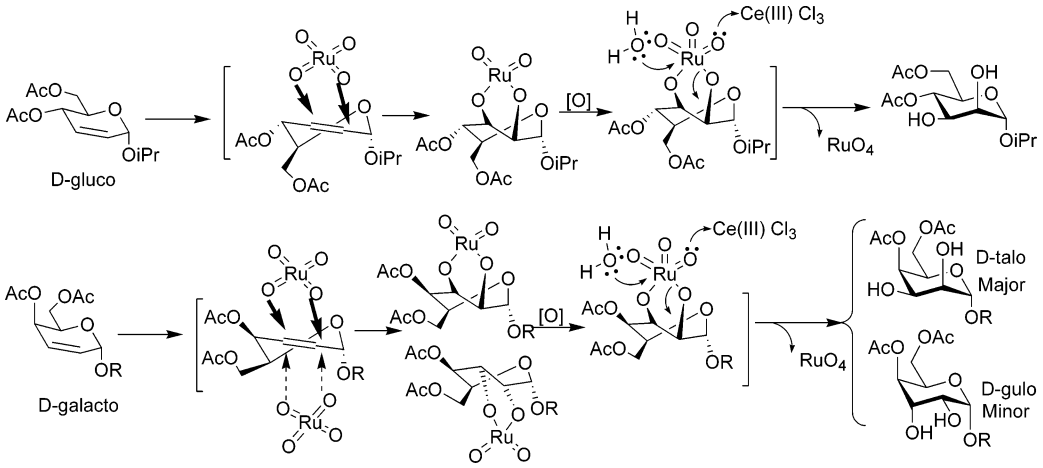

acid in a specific solvent mixture in the preparation of *cis*-1,2-diols from simple alkenes in a highly stereoselective manner.[9] We reasoned that use of $RuCl_3/CeCl_3 \cdot 7H_2O/NaIO_4$, a bimetallic reagent system for the dihydroxylation of glycals, could produce only sugar 1,2-*cis*-diols as it does with the simple alkenes. In this endeavor, we report a highly stereoselective dihydroxylation of glycals toward the formation of 1,2-sugar diols (Scheme 1). This methodology has been further extended for the preparation of disaccharides of uncommon sugars (Table 1, entries 11 and 12).

In a first set of experiments, tri-*O*-acetyl-D-glucal was treated with $RuCl_3/CeCl_3 \cdot 7H_2O/NaIO_4$ in $EtOAc/CH_3CN/H_2O$ at 0 °C, varying the quantity of $CeCl_3 \cdot 7H_2O$ and $NaIO_4$. It was observed that treatment of tri-*O*-acetyl-D-glucal with a combination of $RuCl_3/CeCl_3 \cdot 7H_2O/NaIO_4$ in a mixed solvent at 0 °C can furnish 3,4,6-tri-*O*-acetyl-D-glucose-1,2-diol in 15 min. A series of differentially protected glycals was transformed into 1,2-diols following the similar reaction condition. An anomeric mixture of sugar 1,2-diols was isolated, which were further acetylated for the structural confirmation of the products. From the spectral analysis, it was found that the stereochemistry at C-2 is equatorial in every case. In another set of experiments, a variety of 2,3-unsaturated mono- and disaccharides were also reacted with reagent combination toward the formation of 2,3-unprotected mono- and disaccharides. Exclusive formation of *cis*-diol was observed depending on the stereochemistry of the substituents present in the substrates. As expected, no trace of the formation of other epimer was observed in TLC and spectral analysis. Under these reaction conditions, common protecting groups used in the protection of carbohydrates (e.g., benzylidene, isopropylidene, TBDPS, acetyl, benzyl, benzoyl, pivaloyl, etc.) were quite stable. This stereoselective dihydroxylation has been applied to the preparation of disaccharides containing mannose, talose, and gulose using a reaction sequence consisting of Ferrier rearrangement followed by *cis*-dihydroxylation. Additionally, sugar 1,2-di-*O*-acetates thus obtained can be further converted to 2-acetoxy glycals by anomeric bromination using 33% HBr−AcOH and subsequent elimination of HBr on treatment with DBU. Synthesis of ulosyl bromides for their use in the glycosylation can also be prepared from the 2-acetoxy glycal or enol acetate by treatment with *N*-bromosuccinimide as reported by Lichtenthaler et al.[10] (Scheme 2).

The plausible mechanism for the formation of exclusively single epimeric *cis*-diol can be explained by considering the *syn*-addition of the RuO_4 to the olefinic bond from the less sterically hindered site and hydrolysis of the Ru-complex activated by $CeCl_3$ (Schemes 3 and 4).

In summary, a mild, stereoselective protocol for the *cis*-dihydroxylation of glycals and unsaturated sugar derivatives has been developed using an economically convenient, less toxic bimetallic catalyst system. The reaction is very fast and yields are excellent. The reaction protocol has been further extended toward the formation of 2-acetoxy glycal derivatives and unusual disaccharides.

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Experimental Section

General Reaction Protocol for *cis*-Dihydroxylation of Glycal or 2,3-Unsaturated Glycoside. A mixture of $NaIO_4$ (300 mg, 1.4 mmol) and $CeCl_3 \cdot 7H_2O$ (38 mg, 0.1 mmol) in H_2O (2 mL) was stirred at room temperature for a few minutes. The reaction mixture was cooled to 0 °C, and to the cooled reaction mixture were added EtOAc (3 mL), CH_3CN (6 mL), and $RuCl_3 \cdot H_2O$ (5.2 mg, 0.025 mmol) successively. After the mixture stirred for 2.0 min, a solution of substrate (1.0 mmol) in EtOAc (3 mL) was added, and the resulting heterogeneous mixture was stirred until the full consumption of the starting material (Table 1). After completion of the reaction (TLC), the reaction mixture was diluted with EtOAc (25 mL). The organic layer was washed with aqueous $NaHCO_3$ and water, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified over SiO_2 using hexanes−EtOAc as eluant. Acetylation of the diol was carried out conventionally using acetic anhydride and pyridine, and the product was characterized by spectroscopic and analytical techniques. Spectral data of compounds **1b**, **5b**, **6b**, **7b**, and **10b** are reported in the cited references. Spectral data for all compounds are reported in Supporting Information.

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Supporting Information Available: General experimental methods, ^1H NMR and ^{13}C NMR spectral data and spectra of all products, and 2D HSQC, HMBC, and COSY spectra of compounds **9b**, **11b**, and **12b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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