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One-Pot Conversion of Glycals to *cis*-1,2-Isopropylidene-α-glycosides

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Abstract: Described is a general method for the conversion of glycals to the corresponding 1,2-*cis*-isopropylidene-α-glycosides. Epoxidation of glycals with dimethyldioxirane followed by $ZnCl_2$-catalyzed addition of acetone converted a variety of protected glycals into 1,2-*cis*-isopropylidene-α-glycosides in good yield. The reaction is compatible with a range of protecting groups, including esters, benzyl ethers, and silyl ethers, as well as free hydroxyl groups. This method has been applied to develop a synthesis of protected glucuronic acid **1**, a key intermediate in the synthesis of glycosaminoglycans. Compound **1** was produced in seven steps and 32% overall yield.

Glycals are versatile intermediates in the synthesis of oligosaccharides and other natural products.[1] The challenge of differential protection of carbohydrates is significantly simplified in glycals as only three, rather than five, hydroxyl groups need to be distinguished. Glycals have previously served as starting materials for the synthesis of differentiated glucuronic acid building blocks, important synthons for the modular assembly of glycosaminoglycans (GAGs).[2−4] Syntheses of large GAG structures have not yet involved glycals in the production of glucuronic acid monomers.[5−8]

Differentially protected glucuronic acid **1** (Figure 1) is a key building block in the modular synthesis of heparin.[8,9] The 1,2-isopropylidene group has been shown to lock **1** in the $^1C_4$ conformation, forcing the C4 hydroxyl into an axial position. Glycosylation of this axial hydroxyl group with C2 azido-protected glucosamine trichloroacetimidates resulted in the formation of the glycosidic bond with complete α-selectivity.[9] The nine-step synthesis of **1** previously described relied on the interconversion of the furanose and pyranose forms of the sugar, resulting in a mixture of products and variable yields of the desired compound.[8]

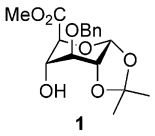

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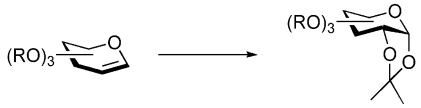
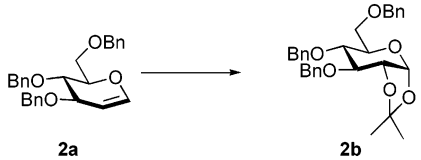
FIGURE 1. Glucuronic acid building block.

SCHEME 1



SCHEME 2



2a **2b**

Direct conversion of a protected glycal to the 1,2-isopropylidene-α-glycoside would avoid the problem of furanose−pyranose conversion and provide more convenient access to **1**. The reaction of glycals, enol ethers, or enol ether epoxides to isopropylidene-protected diols has not been previously described. Several procedures for the direct conversion of aliphatic epoxides to isopropylidenes have been published.[10] These procedures called for the treatment of the epoxide with a Lewis acid (typically $AlCl_3$ or $BF_3{\cdot}Et_2O$) in acetone to effect the ring expansion and were not reported to be diastereoselective.

Glucals are well-known to react readily and selectively to 1,2-anhydroglucoses upon treatment with dimethyldioxirane (DMDO) solution in acetone.[11] We anticipated that addition of an acid catalyst to the reaction mixture after complete epoxidation would bring about the ring-expansion of the anhydrosugar to the 1,2-isopropylidene through the addition of acetone (Scheme 1). The desired α-isomer should be favored by both the anomeric effect and the relatively high strain of the 1,2-*trans*-*β*-acetal.

The proposed reaction was initially developed with use of tribenzyl glucal **2a** as the test substrate (Scheme 2). Epoxidation of **2a** with DMDO is rapid, and the anhydrosugar gives good yields in acid-catalyzed ring opening with alcohols.[11] In this case, after complete epoxidation of the substrate, an acid catalyst was added directly to

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TABLE 1. Reaction Development

activator	DMDO quench	time (h)	yield (%)
0.1 equiv of CSA	no	18	<5
0.1 equiv of $ZnCl_2$	no	4	47
1.0 equiv of $ZnCl_2$	no	20	45
0.1 equiv of $ZnCl_2$	no	20	55
0.025 equiv of $ZnCl_2$	no	18	43
0.1 equiv of $ZnCl_2$	**EVE**	**18**	**67**

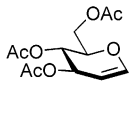
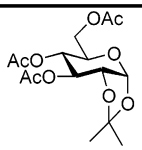
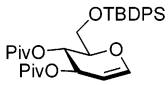
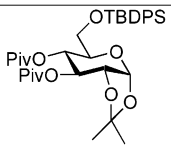
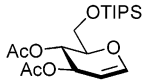
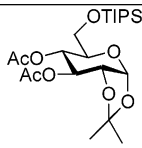
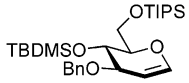
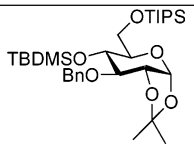
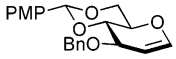
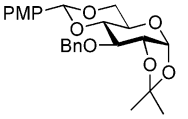
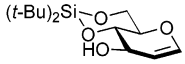
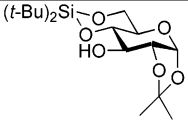
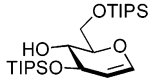
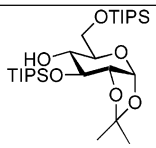
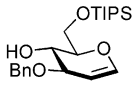
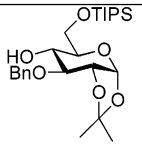
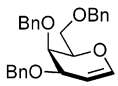
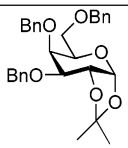
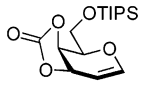
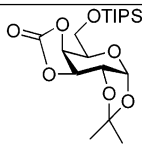
the reaction mixture to effect the addition of acetone to the anhydrosugar. Camphorsulfonic acid (CSA), a protic acid, gave only trace amounts of product while the remainder of the material decomposed. The Lewis acid $ZnCl_2$ afforded the product **2b** in significantly higher yields and the reaction was optimized for time and equivalents of $ZnCl_2$ (Table 1). The yield of this reaction was further improved by quenching the excess oxidant before addition of the acid, either by evaporation of the solvent followed by dissolution of the residue in anhydrous acetone or by addition of ethyl vinyl ether (EVE) to react the remaining DMDO. Both procedures worked equally well in initial trials; addition of EVE was selected due to the ease of the procedure. Conversion of **2a** to **2b** by epoxidation with DMDO, followed by addition of EVE to quench the remaining oxidant and subsequent reaction with 0.1 equiv of $ZnCl_2$ for 18 h yielded 67% of the desired product. Other Lewis acids ($AlCl_3$, $SnCl_4$, and $BF_3 \cdot Et_2O$) gave results similar to those with $ZnCl_2$.

Next, the substrate scope and protecting group compatibility of the reaction was explored (Table 2). Differentially protected glucals (entries 4, 5, 6, 9, and 10) and tribenzyl galactal (entry 11) reacted smoothly; ester, silyl ether, and benzyl groups were tolerated. Glycals with unprotected secondary hydroxyl groups (entries 9 and 10) were also readily converted into the desired products in good yield. Deactivated tri-*O*-acetyl-D-glucal **3a** gave a low yield of isopropylidene **3b** due to its poor reactivity with DMDO.[1] The conversion of glycals containing cyclic protecting groups (entries 7, 8, and 12) also proceeded in poor yield. While epoxidation appeared complete, treatment with $ZnCl_2$ did not afford the isopropylidene in significant quantities.

With this new transformation in hand, a short synthesis of the glucuronic acid building block methyl 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucopyranosiduronate (**1**) was developed (Scheme 3). Glycal **10a** can be produced in three steps from commercially available **3a** via a previously reported route in 67% overall yield.[4] Epoxidation of **10a** with DMDO followed by reaction with $ZnCl_2$ produced **10b**; the crude product mixture was carried on without purification. Treatment of this mixture with tetrabutylammonium fluoride cleaved the silyl ether to reveal the primary hydroxyl group. The crude product was reacted with bleach and catalytic 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) to selectively oxidize the C6-hydroxyl to the carboxylic acid. The crude acid was methylated with use of methyl iodide and $KHCO_3$ in DMF. Purification via flash silica gel column chromatography gave **1** in 48% yield.

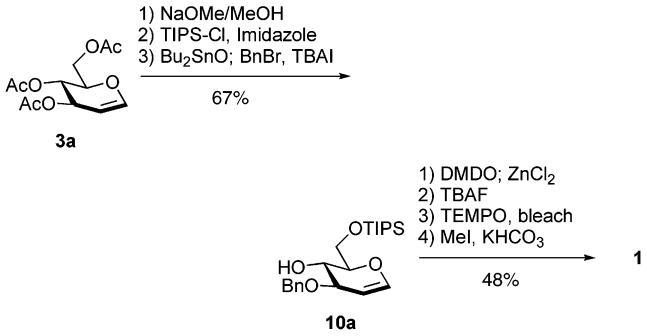
Reported herein is a general methodology for the conversion of differentiated glycals to the corresponding 1,2-*cis*-isopropylidienes via a one-pot procedure. The reaction described is easily executed and tolerates a

TABLE 2. Substrate Scope[b]

Entry	Substrate (a)	Product (b)	Yield (%)
3			20
4			60
5			75
6			75
7			22[a]
8			18
9			70
10			73
11			78
12			N.D.

[a] The product isolated was a 6:1 mixture of compounds, likely diastereomers from epimerization of the benzylidene acetal. [b] PMP = *p*-methoxyphenyl, Piv = pivoalyl (trimethylacetyl).

SCHEME 3



variety of useful protecting groups, including silyl ethers, benzyl ethers, esters, and free hydroxyls. Glycals containing cyclic protecting groups, such as acetals and internal carbonates, are not useful substrates, as their epoxides do not add acetone readily. This new methodology was applied to the synthesis of glucuronic acid derivative **1**, a useful building block in the assembly of glycosaminoglycans, such as heparin. The synthesis of **1** was achieved in seven steps and 32% overall yield.

Experimental Section

Conversion of Glycals to 1,2-*cis*-Isopropylidenes (General Procedure). Glycal (0.1 mmol) was dried by coevaporation with toluene and dissolved in CH_2Cl_2 (250 μL) under N_2. The solution was cooled to 0 °C and DMDO (1.5 mL, ~0.08 M in acetone) was added. The reaction mixture was stirred for 10 min, ethyl vinyl ether (10 μL, 0.1 mol) was added, and the reaction mixture was stirred for an additional 10 min. Zinc(II) chloride (20 μL, 0.5 M in Et_2O) was added, and the reaction mixture was allowed to warm to room temperature and stirred for 18 h. The reaction mixture was poured into water (50 mL) and the aqueous phase extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Products were purified via flash silica gel column chromatography (between 10:1 and 20:1 hexanes:ethyl acetate).

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Supporting Information Available: Experimental procedures and characterization data for all compounds not previously reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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