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Stereoselective, Lewis Acid–Catalyzed Glycosylation of Alcohols by Glucose 1,2–Cyclic Sulfites

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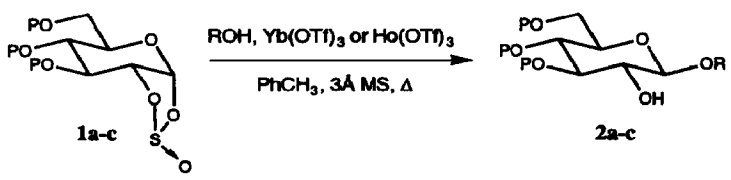
Abstract: *α-D-Glucopyranose-1,2-cyclic sulfites (**1a–c**) have been prepared by reaction of a suitably protected glucose residue and thionyl diimidazole. Reaction of these compounds with alcohols in the presence of $Yb(OTf)_3$ or $Ho(OTf)_3$ stereoselectively affords β-O-glycosides.*

In carbohydrate chemistry, glycosylation remains the most difficult transformation to effect.[1] Very few methods combine both high stereoselectivity and high yield in the formation of the glycosidic bond. Competing S_N1 and S_N2 processes often make it difficult to predict the stereochemical course of a reaction. In addition, many glycosylation conditions require the use of toxic heavy metal salts or suffer from other practical shortcomings. Recently, the usefulness of 1,2–anhydro sugars, generated from the direct epoxidation of glycals with dimethyl dioxirane, as stereoselective glycosyl donors has been demonstrated.[2] These anhydro sugars, however, are not stable, and oxidation with dimethyl dioxirane is operationally difficult on a large scale. It was our goal to find analogs of these epoxides that would be isolable, stable and accessible in large quantities.

In recent years, the use of cyclic sulfates and cyclic sulfites as epoxide equivalents has become increasingly popular due to the availability of enantiomerically pure 1,2–diols via asymmetric dihydroxylation.[3] However, the activation of cyclic sulfites or cyclic sulfates by Lewis acids has not been investigated. We report here a stereoselective glycosylation with glucose 1,2–cyclic sulfites mediated by lanthanide(III) triflates (Scheme 1).

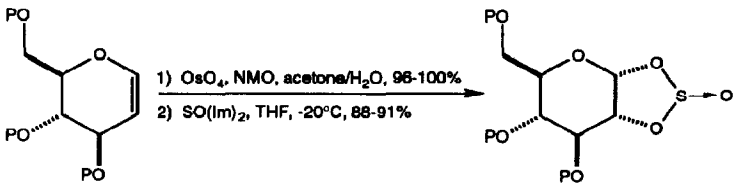
Scheme 1



The synthesis of the title cyclic sulfites was accomplished by thionyl diimidazole addition to an appropriately protected glucose residue,[4,5] which in turn was generated by osmylation of the corresponding glucal (Scheme 2). Osmylation in all cases occurred with greater than 19:1 facial selectivity.[6] Cyclic sulfite formation was completely stereoselective for the 1,2–cis fused product, with a mixture of *endo* and *exo* diastereomers at sulfur. The benzoate–protected cyclic sulfite is a solid and no decomposi-

tion of this compound was detected after two months at room temperature. Acetate– and benzyl–protected cyclic sulfites are oils and are stable for at least two weeks at room temperature.

Scheme 2



Displacement reactions of cyclic sulfites have been limited to those involving reactive nitrogen nucleophiles and such anions as CN^-, Cl^- and benzoate. Addition is effected by heating the cyclic sulfite and nucleophile in a polar, aprotic solvent.[4,7] Similar reactions with weaker oxygen nucleophiles have not been demonstrated, and treatment of our cyclic sulfites with alcohols in acetonitrile or DMF did not produce the desired *O*–glycosides. Reaction of tri-*O*-benzyl cyclic sulfite **1c** with alkoxides led to hydrolysis of the sulfite via initial addition at sulfur as has been previously documented in the case of less reactive, non–glycosyl cyclic sulfites.[2b,7e] We then attempted to activate the glycosyl sulfites with a variety of common Lewis and protic acids, all of which led to either poor reactivity or poor selectivity in the formation of the glycosidic linkage.

Lanthanide(III) triflates have been shown to be useful as general Lewis acids[8] as well as effective, non–toxic catalysts for glycosylation with 1-*O*-methoxyacetyl sugars.[9] With this in mind, we prepared ytterbium(III) triflate and holmium(III) triflate.[10] These Lewis acids stereoselectively catalyzed *O*–glycosylation of both 1° and 2° alcohols with glycosyl cyclic sulfites **1a–c**. Both Lewis acids catalyzed the reaction with similar yields and selectivities. Holmium(III) triflate gave slightly higher β–selectivity with cyclic sulfites **1a** and **1b** in the case of the 2° alcohol acceptor. We also observed that the stereochemistry at sulfur did not affect the β–selectivity of the reaction. Glycosylation of the *exo*-tri-*O*-benzoyl cyclic sulfite **1a–*exo***, which was separable from the *endo* isomer, and that of a mixture of isomers gave similar ratios of anomers. In all subsequent glycosylations, a mixture of *endo* and *exo* diastereomers of the sulfites was employed. Experimental results are summarized in Table 1.

Investigation of reaction conditions revealed that toluene was the most effective solvent in which to carry out the transformation. All reactions were run at 0.5 M sulfite concentration in toluene, with powdered 3 Å molecular sieves, 20 mole percent of catalyst, and 3 equivalents of acceptor alcohol. Both the exact amount of catalyst and the exact amount of molecular sieves employed proved to be extremely important. It was determined that the optimum amount of catalyst was 0.20 equivalents while the optimum mass of sieves was 1.5 times the mass of the catalyst. These conditions gave high yields and high β–selectivities on both large and small scales.[11]

We observed that tri-*O*-benzyl cyclic sulfite was more reactive than either the tri-*O*-acetyl or the tri-*O*-benzoyl compounds. Glycosylation in the case of the benzyl–protected compound was carried out at 80 °C, while the sulfites with ester protecting groups required a temperature of 100 °C to react. In

Table 1: Glycosylation of alcohols with glucose 1,2–cyclic sulfites.

Donor		Acceptor	Catalyst	Temp(°C)	Time(h)	Yield(%)[a]	2β : 2α[b]
1a:	P = Bz	allyl alcohol	$Yb(OTf)_3$	100	7	86	10 : 1
		benzyl alcohol	$Yb(OTf)_3$	100	4.5	92	11 : 1
		cyclohexanol	$Ho(OTf)_3$	100	1.5	83	8 : 1
1b:	P = Ac	allyl alcohol	$Yb(OTf)_3$	100	1.75	82	9 : 1
		benzyl alcohol	$Yb(OTf)_3$	100	1.5	81	5 : 1
		cyclohexanol	$Ho(OTf)_3$	100	4.5	74	10 : 1
1c:	P = Bn	allyl alcohol	$Yb(OTf)_3$	80	4	71	all β
		benzyl alcohol	$Yb(OTf)_3$	80	2	85	all β
		cyclohexanol	$Yb(OTf)_3$	80	1.5	75	all β

a) Total isolated yield of α plus β. b) Ratios determined by HPLC.

fact, glycosylation of the benzyl–protected sulfite **1a** occurs at temperatures lower than 80 °C, but below this temperature, addition of the alcohol at sulfur becomes more facile than glycosylation. The observed effect of remote electron–withdrawing groups on the reactivity of the glycosyl donor is consistent with the armed/disarmed theory of reactivity.[12]

The mechanism of Lewis acid activation in this case is not readily apparent. It is possible that the lanthanide(III) ion coordinates to the sulfite functionality and activates it for displacement by the alcohol. It is also conceivable that a small amount of triflic acid could be generated, which may activate the sulfite by protonation.[13] To test the latter possibility, triflic acid itself was used as an activator. In catalytic amounts it did not promote glycosylation and in excess, provided a 1:1 ratio of anomers.

Our results indicate that glucose 1,2–cyclic sulfites undergo efficient *O*–glycosylation in an S_N2–like fashion to afford β–glycosides. Furthermore, this is the first demonstration of Lewis acid activation of a cyclic sulfite. This method also stereoselectively provides β–*O*–glucosides with a free 2–hydroxyl differentiated from the 3–, 4– and 6–positions,which we have exploited in the synthesis of an oligosaccharide ligand recognized by the cell adhesion proteins E– and P–selectin.[14] In these studies, we have used glycals as convenient starting materials. However, cis–1,2–cyclic sulfites are available from any 1,2–deprotected carbohydrate.[4,7a,7b] Consequently, our stereoselective glycosylation method should be applicable to a wide range of substrates.

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5. Preparation of cyclic sulfites: Imidazole (8.31 g, 122 mmol) was dissolved in 80 mL anhydrous THF under Ar. This solution was cooled to 0 °C and thionyl chloride (2.22 mL, 30.5 mmol) was added dropwise. This mixture was then diluted with THF (50 mL) and filtered, under inert atmosphere, directly into a solution of 3,4,6-tri-*O*-benzoyl-D-glucopyranose (10.0 g, 20.3 mmol) in 50 mL THF at -20 °C. After stirring at -20 °C for 20 minutes, the reaction mixture was filtered rapidly through a small plug of silica gel. Solvent was evaporated and the product purified by flash column chromatography on florisil (1:3 EtOAc:Hexanes). *Endo*- and *exo*-tri-O-benzoyl-α-D-glucopyranose-1,2-cyclic sulfites were separable. Proton assignments for each isomer were obtained from a ^{1}H COSY experiment. The isomers were differentiated by the downfield chemical shifts of H–3 and H–5 for the *endo* isomer.
6. It is notable that even in the case of acetate–protected glucal, the facial selectivity of the osymylation reaction was very high, which was not the case with dimethyl dioxirane oxidation (see ref. 2b).
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10. Lanthanide(III) triflates were prepared as previously reported (see ref. 8a).
11. Glycosylation procedure: 3,4,6-tri-*O*-benzoyl-α-D-glucopyranose-1,2-cyclic sulfite (9.6 g, 17.8 mmol), $Yb(OTf)_3$ (2.21 g, 3.56 mmol) and powdered 3Å molecular sieves (3.32 g) were placed in anhydrous toluene (35.6 mL) and stirred under Ar for 30 min. Freshly distilled allyl alcohol (3.63 mL, 53.4 mmol) was added and the reaction was heated to 100 °C until TLC indicated complete consumption of starting material (12 h). The reaction mixture was then diluted with 250 mL EtOAc and washed with 1.0 M HCl (2 x 100 mL), saturated $NaHCO_3$ (2 x 100 mL) and saturated NaCl (1 x 100 mL). The combined aqueous washings were extracted with EtOAc (2 x 100 mL), and the organic phases were combined and dried ($MgSO_4$). Filtration and solvent evaporation followed by silica gel chromatography (1:3 EtOAc:Hexanes) afforded the desired product in 76% yield as an 8:1 mixture of anomers.

    3,4,6-tri-*O*-benzoyl-β-D-allylglucopyranoside:
    ^{1}H NMR (300 MHz, $CDCl_3$): δ7.85-8.0 (6H, m, Ph), 7.25-7.55 (9H, m, Ph), 5.91 (1H, m, $-CH_2CH=CH_2$), 5.67 (1H, dd, J = 9.3, 9.3, H–4), 5.59 (1H, dd, J = 9.3, 9.3, H–3), 5.27 (1H, dd, J = 1.2, 7.1, $-CH_2CH=CH_2$ *E*), 5.15 (1H, dd, J = 1.2, 10.1, $-CH_2CH=CH_2$ *Z*), 4.64 (1H, d, J = 7.8, H–1), 4.60 (1H, app. dd, J = 3.3, 12.1, H–6a), 4.48 (1H, app. dd, J = 5.5, 12.1, H–6b), 4.38 (1H, app. dd, J = 5.3, 12.7, $-CH_2CH=CH_2$), 4.18 (1H, app. dd, J = 6.4, 12.7, $-CH_2CH=CH_2$), 4.07 (1H, m, H–5), 3.88 (1H, m, H–2), 3.25 (1H, d, J = 3.5, –OH).
    ^{13}C NMR (62.5 MHz, $CDCl_3$): δ167.5, 166.8, 166.0, 133.8, 133.7, 133.5, 133.4, 130.1, 130.0, 129.5, 128.6, 118.5, 101.9, 75.0, 72.4, 71.8, 70.3, 69.5, 63.1.
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13. It was observed that the reaction mixture was slightly acidic, with a pH between 5 and 6.
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