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New Stereoselective β-Glycosylation via a Vinyl Oxirane Derived from D-Glucal†

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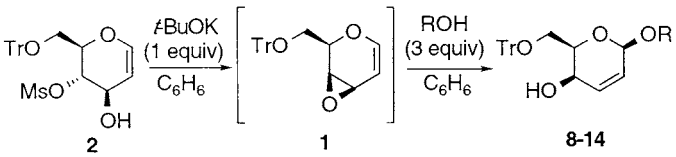
ABSTRACT

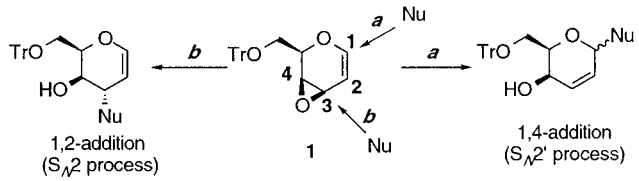


The reaction of the vinyl oxirane 1 derived from D-glucal with a series of O-nucleophiles (alcohols, phenol, and diacetone D-glucose) affords the corresponding 2-unsaturated β-O-glycosides in a completely stereoselective way (syn 1,4-addition pathway). Epoxide 1 is generated in situ by treatment of the corresponding hydroxy mesylate 2 with *t*-BuOK in anhydrous benzene.

2-Unsaturated glycosides (pseudoglycals) are valuable synthetic intermediates, since the unsaturation can be further functionalized for the preparation of structural units present in many natural, biologically active compounds.[1]

In the course of a study aiming to synthesize new glycal donors,[2] we thought it valuable to have epoxide **1** in our hands. Epoxide **1** possesses an intrinsic synthetic interest, due to the fact that it is simultaneously a glycal and a vinyl oxirane (Scheme 1). As a vinyl oxirane, **1** is characterized

Scheme 1. Regiochemistry of Nucleophilic Addition in the Glycal-Derived Vinyl Oxirane **1**



by a double reactivity: (i) at the vinyl terminus, the C(1) of the unsaturated system, through a typical conjugate addition (1,4-addition or S_N2' process, pathway *a*) to yield 2-unsaturated glycosides and (ii) at the allylic oxirane C(3) carbon, through a direct 1,2-addition (or S_N2 process, pathway *b*) to give substituted glycals.[3] The C(1) position of the conjugate system corresponds also in this case to the classic reactive site of any glycal system, as **1** actually is. As a consequence, it appeared to be particularly interesting to check the reactivity of epoxide **1** in the presence of nucleophiles to verify both the regio- and stereoselectivity of the nucleophilic attack.

For the synthesis of epoxide **1**, we needed the ultimate precursor, the hydroxy mesylate **2** with the right stereochemical requirement around C(3) and C(4) (Scheme 2). Compound **2** was prepared in a five-step sequence starting from commercially available tri-*O*-acetyl-D-glucal (**3**), as shown in Scheme 2. Saponification of **3** by means of MeONa/MeOH afforded the D-glucal (**4**),[4] which was treated

† Dedicated to the memory of Professor Serena Catalano.

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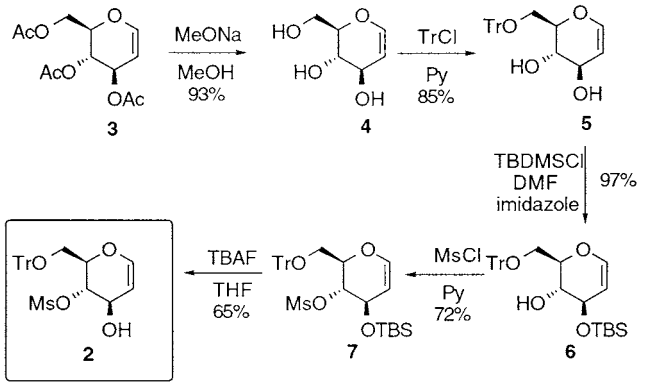
(4) Brimacombe, J. S.; Da'Aboul, I.; Tucker, L. C. N. *Carbohydr. Res.* **1971**, *19*, 276.

Scheme 2. Synthesis of Hydroxy Mesylate **2**



with TrCl (1 equiv) to give the trityl derivative **5**, O-monoprotected on the less hindered primary hydroxyl. To introduce the mesyl group on the C(4) regioselectively, it was necessary to protect the C(3) position. Actually, due to the decidedly different steric hindrance around the alcoholic functionality on C(3) and C(4), the treatment of **5** with TBDMS−Cl (1 equiv) afforded the mono C(3)-*O*-TBS derivative **6**, which was then treated with MsCl to afford the 3,6-di-O-protected mesylate **7**. The treatment of **7** with TBAF in THF readily deprotects the C(3) position, affording the desired hydroxy mesylate **2**.

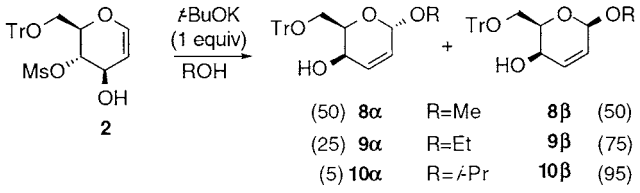
The transformation of compound **2** into epoxide **1** was conducted using *t*-BuOK in anhydrous benzene. We were unable to isolate the epoxide, but conducting the reaction in C_6D_6 showed that compound **1** was formed cleanly within 5 min (^{1}H NMR). This observation led us to leave aside the isolation of epoxide **1** and to utilize a solution of compound **2** in a solvent (benzene, an alcohol, or MeCN, vide infra) in the presence of *t*-BuOK as a source of the epoxide **1**, which is actually formed in situ. In this way, it was possible to check the reactivity of this oxirane system even if it was not effectively isolated.

At first we checked the chemical behavior of **1** in the presence of oxygenated nucleophiles such as alcohols, used as the solvent. In this way, a solution of compound **2** in MeOH in the presence of *t*-BuOK (1 equiv) at room temperature afforded a crude product consisting of an almost 1:1 mixture of anomeric 2-unsaturated methyl α- and *β*-glycosides **8**α and **8***β*, indicating that, in this case, nucleophilic attack had occurred regioselectively in a conjugate fashion (1,4-addition pathway, Scheme 1), with inversion of configuration on C(4) with respect to **2**, but unfortunately devoid of any stereocontrol at the anomeric C(1) carbon (Scheme 3).

Use of more hindered alcohols as the solvent/nucleophile (Scheme 3) led to an increased C(1)-*β*-selectivity. In fact, with EtOH and *i*-PrOH, the corresponding α/*β* ratios were 25:75[5] and 5:95, respectively. The reaction appeared to be interesting to us, because, after all, it turned out to be like a

(5) Ethyl α-glycoside **9**α has been previously described. See: Moufid, N.; Chapleur, Y.; Mayon, P. *J. Chem. Soc., Perkin Trans. 1* **1992**, 991.

Scheme 3. Stereoselectivity of 1,4-Addition of Alcohols (as the solvent/nucleophile) to Compound **2**, in the Presence of *t*-BuOK



new glycosylation procedure. Moreover, to the best of our knowledge, no procedure of this type and no epoxy glycal such as **1** have been described before in literature. Prompted by these considerations, thinking that the presence of the nucleophile as the solvent in the previous protocol, besides not being practical and/or suitable in some cases, undoubtedly had a detrimental effect on the stereoselectivity of the addition reaction, we elaborated a one-pot procedure to make the cyclization process of the hydroxy mesylate **2** independent from the glycosylation process.

In the modified protocol, *t*-BuOK (1 equiv) was added to a solution of compound **2** in anhydrous benzene at room temperature (Scheme in Table 1). The formation in situ of epoxide **1** was followed by TLC (disappearance of the starting material), and MeOH (the glycosyl acceptor, 3 equiv) was rapidly added to afford the 2-unsaturated methyl *β*-glycoside **8***β* as practically the only reaction product (the corresponding α-anomer **8**α was less than 3%, ^{1}H NMR) (Table 1, entry 1). Glycosyl acceptors other than MeOH were utilized in coupling with glycal-derived vinyl oxirane **1** under the same protocol. The results obtained indicate that primary (EtOH and BnOH), secondary (*i*-PrOH), and even tertiary alcohols (*t*-BuOH) and phenol are glycosylated to afford a good yield of the corresponding *β*-glycosides **9**−**13***β* in a completely stereoselective way (the corresponding α-anomers were absent, ^{1}H NMR) (Table 1, entries 2−6).[1a,c,6−8] The use of diacetone D-glucose (**15**) as the glycosyl acceptor demonstrated that our protocol is also useful for the

(6) The structures of glycosides **8**−**14** have been demonstrated by comparison of their ^{1}H and ^{13}C NMR spectra with previously reported data for the same compound, as in the case of **9**α (see ref 5), and/or closely related compounds (α and *β*-anomers). See: (a) Wieczorek, E.; Thiem, J. *J. Carbohydr. Chem.* **1998**, *17*, 785. (b) Nguefack, J.-F.; Bolitt, V.; Sinou, D. *J. Org. Chem.* **1997**, *62*, 1341. (c) Baer, H. H.; Hanna, Z. S. *Can. J. Chem.* **1981**, *59*, 889.

(7) A confirmation of the assigned *β*-glycosidic structure of **8**−**14***β* was obtained by hydrogenation (Pd/C, AcOEt) of the *O*-ethyl derivatives **9***β* and **9**α to the corresponding saturated compounds **9***β*-H and **9**α-H, respectively. The ^{1}H NMR spectrum of **9***β*-H shows the anomeric H-1 proton (*δ* 4.50) as a doublet of doublets (J = 8.6, 2.1 Hz), whereas **9**α-H shows the same proton (*δ* 4.89) as a broad singlet ($W_{1/2}$ = 6.5 Hz) to indicate its axial (**9***β*-H) and equatorial orientations (**9**α-H). See: Chini, M.; Crotti, P.; Gardelli, C.; Macchia, F. *J. Org. Chem.* **1994**, *59*, 4131 and references therein.

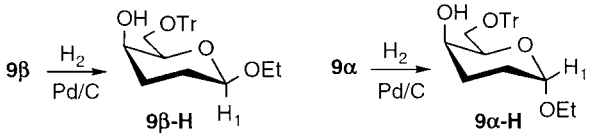
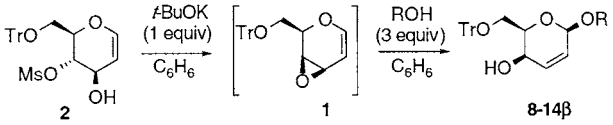
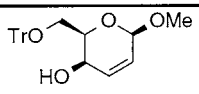
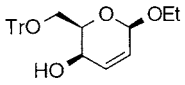
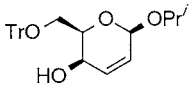
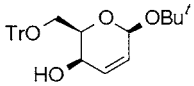
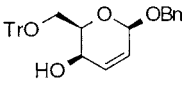
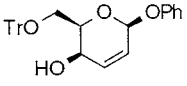
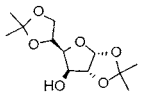
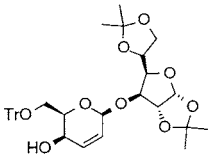


Table 1. Glycosylation of the in Situ-Formed Epoxide **1** with Alcohols and Phenol



entry	glycosyl acceptor	time (h)	product[a]	yield (%)
1	MeOH	0.5	 **8β**	92
2	EtOH	0.5	 **9β**	85
3	*i*-PrOH	2	 **10β**	91
4	*t*-BuOH	2	 **11β**	78
5	BnOH	3	 **12β**	91
6	PhOH	3	 **13β**	89
7	 **15**	2	 **14β**	76

[a] The corresponding α-anomer was absent (less than 3% appeared only in the case of entry 1).

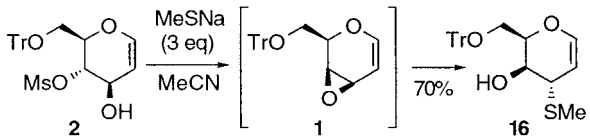
construction of a disaccharide (Table 1, entry 7). After 2 h at room temperature, the corresponding *β*-linked disaccharide **14***β* was obtained. It is to be noted that the acid-labile protecting groups present in **15** are not affected by the reaction conditions at all.

The new *β*-O-glycosylation method described here, when an alcohol is utilized as the glycosyl acceptor, is apparently closely related to the Ferrier rearrangement of glycals,[9] because in both cases 2-unsaturated glycosides are obtained. However, the two procedures show evident and important differences. First of all, the Ferrier rearrangement commonly leads to products mostly deriving from an α-glycosylation process (the corresponding *β*-glycosides may be present only as minor components, 10−20%),[6c,9] while in the present case, a complete *β*-glycosylation occurs. Second, but not less important, the Ferrier rearrangement requires the presence of a Lewis acid, while in our protocol, smoothly basic or practically neutral conditions are used (basic conditions are necessary only in order to generate the epoxide from the precursor, the hydroxy mesylate **2**). Actually, this can make the difference between the two protocols, considering that protecting groups possibly present on the glycosyl donor and/or acceptor could be differently sensitive to acid and alkaline conditions.

Finally, the present glycosylation procedure allows the preparation of 2-unsaturated *β*-glycosides such as **8**−**14***β*, possessing a galacto configuration on C(4), starting from the cheap and easily available tri-*O*-acetyl-D-glucal (**3**). On the contrary, following the Ferrier rearrangement, the same C(4) configuration could be obtained only by starting from the decidedly more expensive tri-*O*-acetyl-D-galactal.[10]

To check preliminarily the stereo- and regioselectivity of the reaction of epoxide **1** with a stronger nucleophile than the alcohols so far utilized, a solution of compound **2** in MeCN was treated with MeSNa (3 equiv) (Scheme 4). A

Scheme 4. Stereo- and Regioselectivity of the Addition of MeSNa to Compound **2**



clear reaction occurred exclusively affording, in a completely regio- and stereoselective way, the trans methylthio alcohol **16** deriving from a direct attack of the nucleophile at the allylic C(3) oxirane carbon of the intermediate epoxide **1** through an anti 1,2-addition pathway (S_N2 process, pathway *b*, Scheme 1). This result demonstrates that glycoside formation is not inevitable and that the character of the nucleophile is important.

Studies are under way in order to evaluate (i) the more general validity of the method of glycosylation so far developed, (ii) the regio- and stereochemical behavior of nucleophiles other than alcohols and MeSNa at the moment preliminarily studied, and (iii) the reactivity of the other vinyl oxirane stereoisomer of epoxide **1**.

(8) In principle, a S_N2' process can occur by either a syn or anti pathway. The completely stereoselective *β*-glycosylation observed in the reaction of epoxide **1** with alcohols (3 equiv) in anhydrous benzene may be rationalized by admitting an attack of the nucleophile (ROH) in a syn orientation relative to the leaving group (oxirane C(3)−O bond). A coordination between the oxirane oxygen and the nucleophilic alcohol through the proton could be responsible for the complete *β*-stereoselectivity observed (for an example of an exclusive syn S_N2' process in a cyclic allylic system, see: Stork, G.; Kreft, A. F., III. *J. Am. Chem. Soc.* **1977**, *99*, 3850). It is to be noted that a syn S_N2' process with ROH in vinyl oxirane systems has been previously reported only by means of a Pd(0)-catalyzed protocol (see: Larock, R. C.; Lee, N. H. *J. Org. Chem.* **1991**, *56*, 6253). For a recent report on the ring opening of vinyl oxiranes with alcohols, see: Fagnou, K.; Lautens, M. *Org. Lett.* **2000**, *2*, 2319 and references therein

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Supporting Information Available: Experimental details and spectral and analytical data for all reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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