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Role of the 4,6-*O*-acetal in the regio- and stereoselective conversion of 2,3-di-*O*-sulfonyl-β-D-galactopyranosides to D-idopyranosides

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ABSTRACT

The recently reported conversion of 2,3-di-*O*-sulfonyl-D-galactopyranosides to D-idopyranosides has provided an efficient route to obtaining orthogonally-protected idopyranoside building blocks with a β-1,2-*cis* glycosidic linkage. In an effort to expand the scope of this process and better understand the regio- and stereoselectivity observed in the key di-inversion step of the method, a small library of 4,6-*O*-acetal protected galactopyranosides has been synthesized and used as substrates in the process, together with a number of substrates that lack the acetal functionality. The results suggest that although the substituent at the acetal center does not contribute to the observed selectivity of the process, the acetal group is indeed required for efficient conversion by reducing the conformational flexibility of the substrate, resulting in enhanced reaction rates at both the O-transsulfonylation and epoxide ring-opening steps.

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1. Introduction

D- and L-idopyranosides are conformationally unique hexopyranosides abundant in nature. For example, they present as D-*ido*-heptopyranosides in the capsular polysaccharide (CPS) structure of *Campylobacter jejuni*,[1] or as the oxidized L-iduronic acids found in glycosaminoglycans (GAGs) such as heparin, heparan, and dermatan sulfates. Idopyranosides can display significant conformational flexibility due to the relative high energy of their $^4C_1$ and $^1C_4$ chair conformations, which results in a lower energy barrier between the chair and twist boat conformations.[2] Since the idopyranosides found in nature are often functionalized with O-substitutions such as partial sulfation in the GAGs (various patterns at all positions) and 7-*O*-phosphoramidation in the *C. jejuni* D-*ido*-heptopyranoside-antigen,[1] accessing orthogonally-protected idopyranoside building blocks are key to streamlining their syntheses in sufficient quantities for biological and pharmacological testing.

Recently, the development of efficient syntheses to obtain antigenic oligosaccharides related to *C. jejuni* CPS has drawn our interest, as this gastrointestinal pathogen also expresses lipopolysaccharides which have structural elements resembling human gangliosides.[3] Upon recovering from *C. jejuni* bacterial infection, some patients develop carbohydrate-specific antibodies against these lipopolysaccharides, leading to the development of Guillain–Barré Syndrome, an acute and severe autoimmune neurological disease resulting from the aforementioned molecular mimicry.[3,4] In an effort to potentially re-direct the immune response away from lipopolysaccharides, we have become interested in chemically synthesizing a carbohydrate-based conjugate vaccine against the unique 6-deoxy-β-D-*ido*-heptopyranoside present in the CPS of *C. jejuni* serotype HS:4 (Fig. 1).[1] Previously, it was shown that subcutaneous inoculation with conjugates containing the CPS extracted from natural sources elicited promising immunological results.[5]

The synthesis of the β-linked *ido*-heptopyranoside present in the *C. jejuni* CPS presents a significant challenge due to the unusual configuration and the β-1,2-*cis*-glycosidic linkage. Recently, our group has published a short, scalable method from D-galactose which could be used to obtain orthogonally protected D-idopyranoside (Scheme 1). The method relies on a di-inversion at C-2 and C-3 of 4,6-*O*-benzylidene-2,3-di-*O*-sulfonyl-β-D-galactopyranosides (**1**–**2**); the conversion proceeds with high regio- and stereoselectivity to give only the desired product (**4**), as detected in the crude ^{1}H NMR.[6] The method was compatible with a series of nucleophiles (MeO^-, $AllO^-$, BnO^-); more importantly, this methodology was also found to be applicable to the synthesis of β-linked idopyranoside-containing oligosaccharides. We also observed that in using the corresponding α-D-galactopyranosides, the conversion proceeds with reduced regio- and stereoselectivity.[6,7] A similar two-step approach using methyl 4,6-*O*-benzylidene-3-*O*-tosyl-β-D-galactopyranoside has also been reported, which upon treatment with base affords the intermediate 2,3-anhydro-gulopyranoside, and subsequent attack with a nucleophile in the presence of microwave irradiation provides the 2-O-substituted idopyranoside.[8]

The acetal protecting group is useful in orthogonal protection strategies, as it can be either fully hydrolyzed, or regioselectively

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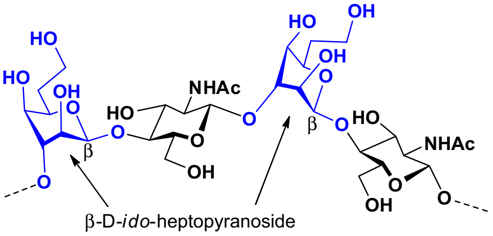


Figure 1. The β-D-*ido*-heptopyranoside present in capsular polysaccharide of *Campylobacter jejuni*.

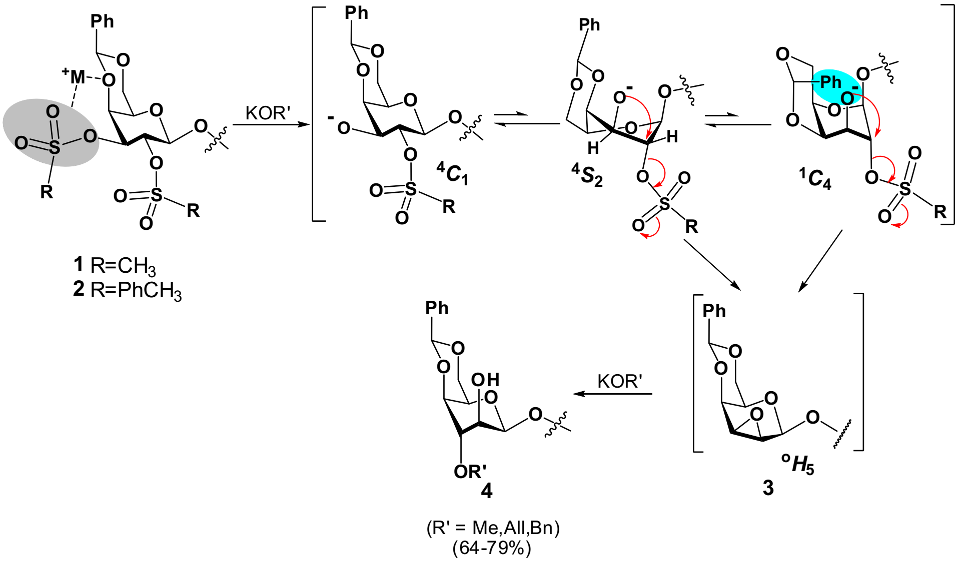
opened under reductive conditions by using a combination of hydride agent (such as $LiAlH_4$, $NaBH_3CN$, DIBAL-H, silane, and borane) and Lewis acid (TMSOTf, $AlCl_3$, $BF_3{\cdot}Et_2O$, metal triflate, etc.).[9–11] Applying the Hanessian–Hullar reaction conditions[12] or using substituted benzylidenes and other related acetals could offer further flexibility in orthogonal deprotections for our total synthesis of *C. jejuni ido*-heptopyranoside analogs.

We also probed the mechanism of the regio- and stereoselective di-inversion step of the 2,3-di-*O*-sulfonates and found that alkali cations play an important role in preferentially activating sulfonates that have a *cis*-oriented neighboring oxygen, leading to an O-transsulfonylation as a result of S–O bond scission. The alkali cation could coordinate with either the more electron rich oxygen of the S=O or the slightly less electron rich oxygen of the S–O.[13] After the 3-O-transsulfonylation step, a negatively charged 3-oxide is generated, which nucleophilically substitutes the C-2 sulfonate by attacking the backside of the stereocenter, resulting in an inversion of C-2 configuration. However, this step is not straightforward, as the molecule adopts predominantly the $^4C_1$ chair conformation, causing both C-2 and C-3 substituents to occupy a *trans*-diequatorial orientation; the formation of the 2,3-epoxide is not possible from such conformation. In order for the intramolecular S_N2 nucleophilic substitution to occur, the molecule needs to switch to another conformation so that the two substituents at C-2 and C-3 can achieve a *trans*-diaxial or pseudo-*trans*-diaxial orientation. This can be realized through conversion to the $^4S_2$ or $^1C_4$ conformation. In this work, we set out to probe the influence of conformational flexibility on the conversion of 4,6-*O*-benzylidene protected galactopyranoside systems to idopyranosides.

2. Results and discussion

Conformational flexibility of the substrates greatly affects the conversion of 4,6-*O*-acetal protected galactopyranosides to the corresponding idopyranosides. As discussed above, it is beneficial to have a more flexible substrate so that the ring-flip can occur to facilitate epoxide formation; however, for steps involving the O-desulfonylation and epoxide opening, a less conformationally flexible substrate should be favored, as this facilitates the intermolecular nucleophilic attacks. In 4,6-*O*-benzylidene protected β-galactopyranosides the $^4C_1$ chair is most stable, as in the $^4S_2$ or $^1C_4$ conformers more substituents will be forced to occupy an axial or pseudo-axial position, resulting in higher energy conformations. Through examination of a molecular model, we also observed that the phenyl group of the acetal may play a significant role in controlling the conformational flexibility; for example, if the pyranoside adopts a $^4C_1$ chair, the most stable conformation of the molecule should occur when the six-membered acetal ring also adopts a chair conformation placing the phenyl group in an equatorial position. However, when a ring-flip of the pyranoside to the $^1C_4$ chair occurs, if the six-membered acetal ring also flips to the opposite chair, this would place the phenyl ring in close proximity to the C-3 substituent, thus increasing unfavorable steric interactions; the introduction of additional substituents on the phenyl ring, especially at the *m*- and *o*-positions, would increase the steric hindrance further, thus decreasing the conformational flexibility. Thus, the *o*-, *m*-, and *p*-methoxybenzylidene protected galactopyranosides (**5**–**7**) and a *p*-nitrobenzylidene protected analog (**8**) were synthesized and compared to the less sterically hindered ethylidene analog (**9**), as well as the highly flexible methylidene analog (**10**) (Fig. 2). The placement of the electron-withdrawing nitro group on the phenyl ring could also affect the electron density of the acetal O-4 and O-6 centers compared to the other electron-donating methoxybenzylidene analogs; this could influence the alkali-coordination, thus affecting the reaction rate of the O-transsulfonylation step.

In order to synthesize the desired acetal derivatives **5**–**8**, the respective dimethyl acetal reagents **12**–**15** were synthesized from their corresponding aldehyde in near quantitative yields using the method described by Johnsson et al.[14] Camphorsulfonic acid (CSA)-catalyzed transacetalations of compounds **12**–**15** with methyl β-D-galactopyranoside (**11**) afforded the corresponding



Scheme 1. Key step involving the di-inversion of C-2 and C-3 in the regio- and stereoselective conversion of D-galactopyranosides to D-idopyranosides.

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