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Stereoselective Protection-Free Modification of 3-Keto-saccharides

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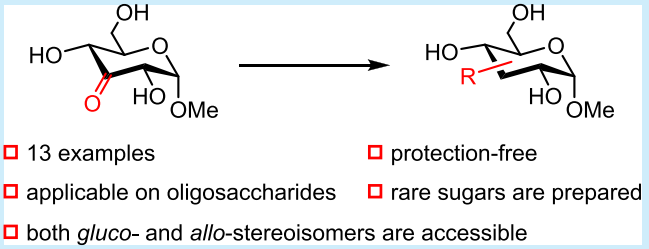
ABSTRACT: Unprotected 3-keto-saccharides have become readily accessible via site-selective oxidation, but their protection-free functionalization is relatively unexplored. Here we show that protecting groups are obsolete in a variety of stereoselective modifications of our model substrate methyl α-glucopyranoside. This allows the preparation of rare sugars and the installation of click handles and reactive groups. To showcase the applicability of the methodology, maltoheptaose has been converted into a chemical probe, and the rare sugar evalose has been synthesized.



Carbohydrates represent the most diverse class of natural products and play a role in many biological processes such as recognition and signal transduction between cells. In addition, carbohydrates form important nutrients for cells. Their diversity is predominantly caused by a large variety of monosaccharides, in particular, in bacteria, in which over 500 different monosaccharides have been discovered, each varying in their configurations and substituents.[1]

In carbohydrate chemistry, most approaches to modify and couple monosaccharides rely heavily on protecting group strategies. In these strategies, all but one hydroxyl group are protected prior to further conversion. The remaining hydroxyl is then either modified to prepare rare monosaccharide building blocks or glycosylated to prepare oligosaccharides.

To reduce the use of protecting groups, site-selective transformations for unprotected carbohydrates are being developed. This field is rapidly expanding, and a broad range of transformations have been reported.[2] This includes catalytic methods to prepare keto-saccharides. Muramatsu demonstrated that organotin compounds mediate the selective oxidation of axial hydroxyl groups in monosaccharides.[3] The Minnaard and Waymouth groups have shown that a broad range of 3-keto-sugars can be prepared with a palladium catalyst.[4−7] The site selectivity of the latter method is independent of the substitution pattern, and this method can even be used on oligosaccharides.[8]

Further functionalization of the unprotected keto-saccharides should allow the straightforward preparation of new carbohydrate building blocks, as demonstrated for GlcNAc,[9] and the introduction of new chemical handles. However, the protection-free functionalization of keto-saccharides is still relatively unexplored because it presents some challenges. First of all, the stereoselectivity of the functionalization reaction should be controlled. Second, the hydroxyl groups of unprotected mono- and oligosaccharides reduce the solubility in aprotic solvents and limit the choice of reagents.

For transformations on protected keto-saccharides, the factors that determine the diastereoselectivity have been well described. These reactions are generally substrate-controlled. Most reactants approach the carbonyl group from the sterically least hindered face, in the case of 3-keto-glucosides, the top face (Figure 1, red arrow). This leads to allo-configured products; that is, the resulting C3−OH is axial.[10−12]

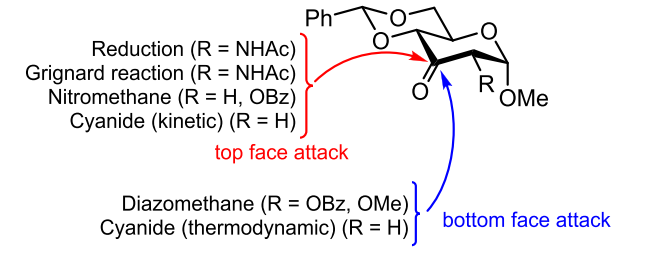


Figure 1. Reported face-selective additions to a keto-saccharide.

Very small, often sp-hybridized nucleophiles or reagents can, however, favor the formation of the gluco-configured product. In these cases, torsional strain prevails over steric effects, as was shown for cyclohexanone,[13] thus favoring attack on the more hindered face. Cyanide is an example of such a small nucleophile, although, in that case, an additional effect plays

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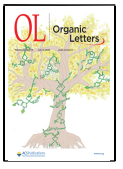
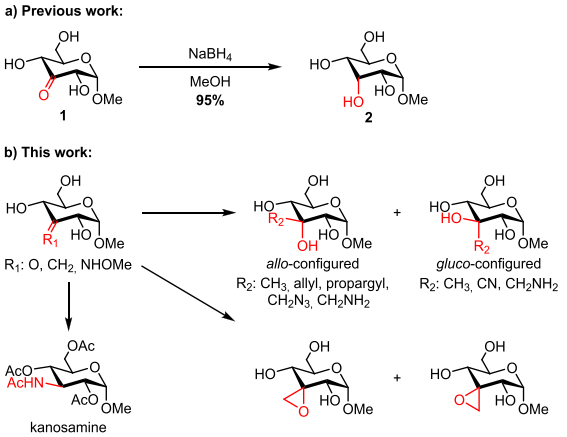


a role. The addition of cyanide is reversible, and the composition of the products can be either kinetically (Figure 1, red arrow) or thermodynamically controlled (Figure 1, blue arrow), depending on the reaction conditions.[14]

Chelation or electrostatic interactions can also induce the formation of gluco-configured products, as observed in the epoxidation of keto-saccharides with diazomethane. Diazomethane approaches the sterically more hindered bottom face of the α-3-ketoglucoside (Figure 1, blue arrow) because of favorable electrostatic interactions between the zwitterionic diazomethane and the anomeric oxygen atom.[12,15] This effect disappears when the β-anomer is used in the reaction, and the addition is controlled by steric factors (top face attack) again.

We were interested in determining whether transformations on protected keto-sugars would work on unprotected ones as well, *in casu* 3-keto-glucoside (**1**). For example, our group has already shown that **1** is selectively reduced to methyl alloside **2** with sodium borohydride (Scheme 1a).[7] This result prompted

Scheme 1. Overview of Previous and Herein Reported Work

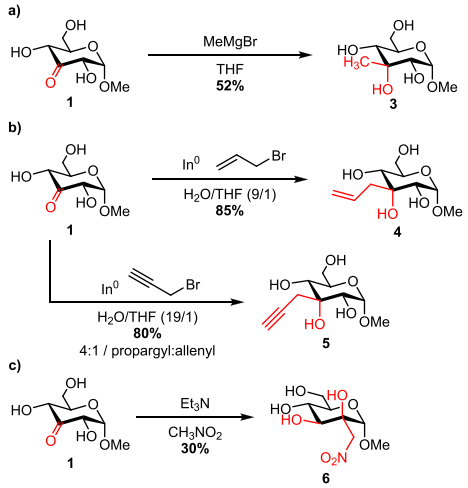


us to investigate what other transformations are compatible with present hydroxyl groups and whether the stereoselectivity of these transformations is still controlled.

Here we show that the ketone functionality of **1** can indeed be converted into many other potentially useful functional groups, including branched-chain sugars and the rare sugar kanosamine (Scheme 1b). This is achieved in a minimum number of steps, with good diastereoselectivity, and without protecting groups. Branched allo-configured products are obtained when **1** is subjected to carbon nucleophiles. Notably, electrostatic interactions in addition reactions can be overcome by performing the reaction in water. Gluco-configured products are prepared either by functionalizing **1** and its corresponding oxime ether with a small reagent or by transformation of the corresponding methylene derivative (*vide infra*).

Methyl branching is found in bacterial monosaccharides;[16] therefore, the direct addition of methylmagnesium bromide to unprotected keto-saccharides was first investigated. The straightforward addition of excess methylmagnesium bromide (5.8 equiv) in THF provided the allo-configured product **3** with high diastereoselectivity (10:1 allo/gluco, Scheme 2a). The presence of large amounts of magnesium salts made purification initially challenging (Table S1). **3** was eventually purified using diol-functionalized silica gel, which removed the

Scheme 2. Grignard Reaction, Indium-Mediated Alkylations, and Nitroaldol Reaction



magnesium salts and provided isomerically pure product in 52% yield.

The direct addition of Grignard reagents is limited to monosaccharides because oligosaccharides are not soluble in THF. Therefore, we explored other carbon nucleophiles that are compatible with protic solvents. Indium-mediated allylation and propargylation under Barbier conditions,[17] which have been used for the chain extensions of aldoses,[18] fulfill this requirement. Under these conditions, the allyl- or propargyl-branched sugar could be obtained from **1** (Scheme 2b). In our hands, both allylation and propargylation proceeded with full allo-stereoselectivity and introduced new handles onto **1** for, for example, click chemistry. **5** remained contaminated with a small amount of the corresponding allenyl product (4:1 propargyl/allenyl).

Next, we attempted to functionalize keto-saccharides via a Henry reaction with nitromethane. Nitroaldol chemistry is also compatible with free hydroxyl groups, and this transformation has been successfully applied on protected keto-saccharides.[11,19] Unexpectedly, the reaction gave a complex mixture without the expected C3 branched product. Instead, the manno-configured C2 branched nitromethyl sugar **6** was isolated as the major product in 30% yield (Scheme 2c). It is likely that under these conditions, **1** isomerizes to its 2-keto regioisomer via keto−enol tautomerism[20] and is then trapped by the nitronate. Protected keto-saccharides are not prone to isomerization under these conditions, hence explaining the differences in the outcome of the reaction.

Finally, we decided to react ketone **1** with diazomethane.[21,22] Even though diazomethane decomposes in protic solvents, nucleophilic addition to ketones has enabled the epoxidation of protected ketosaccharides. Subjecting **1** dissolved in ethanol to an ether solution of diazomethane afforded the epoxide as an epimeric mixture. Electrostatic interactions play a key role in the stereoselectivity of the diazomethane addition (*vide supra.*).[12,15] We found that the polarity of the solvent had a pronounced effect on the stereochemical outcome of the reaction (Table S3). The use of a biphasic mixture of water and diethyl ether resulted in the almost exclusive formation of allo-configured epoxide **7** (33:1 allo/gluco) in quantitative yield (Scheme 3a). Apparently, water induces attack from the least hindered face, presumably by disrupting the electrostatic interactions. As such, the face

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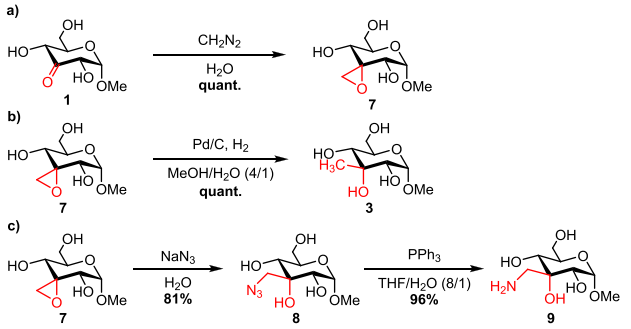
Scheme 3. Epoxidation of 1 with Diazomethane and Further Modification of 7



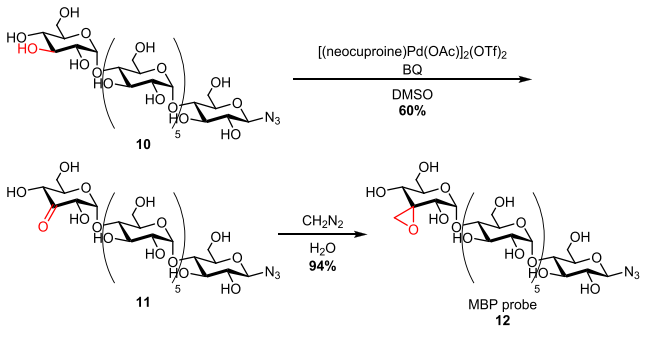
selectivities in protected and unprotected α-glucosides are opposite (Figure 1).

The straightforward preparation of epoxide **7** with diazomethane allowed further modification. The hydrogenolysis of **7** provided an alternative route to **3** (Scheme 3b). The addition of methylmagnesium bromide provides **3** in one step and in 52% yield (*vide supra*), whereas the method with diazomethane and hydrogenolysis does not require purification and is quantitative.

The epoxide moiety in **7** also enabled the introduction of ligation handles. Ring opening with sodium azide yielded azidomethyl-branched sugar **8** (Scheme 3c), which may be used in bioorthogonal reactions. Staudinger reduction of the azido group produced aminomethyl-branched alloside **9**. This amino group is a handle for further chemistry as well because it lends itself for selective amide formation under Schotten–Baumann conditions. The transformations in Scheme 3 are high yielding and require little purification, and hence the epoxidation with diazomethane is the method of choice for introducng new handles or branching onto keto-saccharides with allo-stereochemistry.

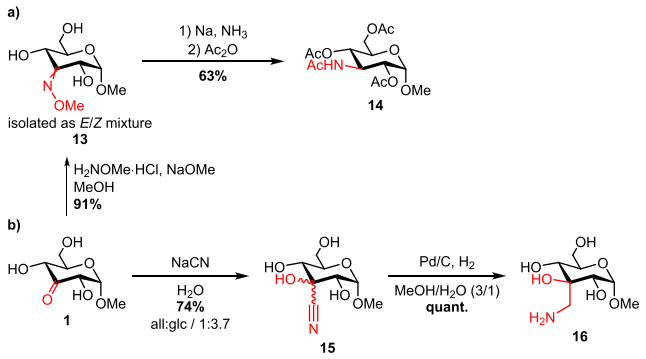
To demonstrate the versatility of the epoxide formation with diazomethane, oligosaccharide **10** was converted into a chemical probe for the promiscuous maltose-binding protein (MBP) from *E. coli*.[23] Keto-maltoheptaosyl azide (**11**), prepared by site-selective oxidation,[8] was successfully reacted with diazomethane in good yield and with good selectivity (Scheme 4). Incubating MBP, possessing two surface-exposed cysteines, with probe **12** and the subsequent visualization of the probe adducts by clicking a fluorophore onto the azide gave a pronounced fluorescence signal. The signal disappeared when MBP was denatured or when maltopentaose was added as a competitor, indicating that **12** labeled MBP in an affinity-based manner (Figure S2).

Scheme 4. Oxidation of β-D-Maltoheptoasyl Azide and Subsequent Epoxide Formation



Because the interaction between proteins and carbohydrates depends on the stereochemistry, we next focused on gluco-configured products. The synthesis of kanosamine from oxime ether **13** via a dissolving metal reduction was attempted.[24] Birch reduction provided the thermodynamically more stable equatorial amine, and successive acylation produced peracetyl 3-amino glucose **14** in 63% yield (Scheme 5a). This substitution pattern, known as kanosamine, is found in aminoglycoside antibiotics.[25] The Birch reduction of **13** is complementary to the hydrogenation of **13** with Adams' catalyst, which resulted in the axial amine.[7]

Scheme 5. Synthesis of Kanosamine and Cyanohydrin Formation



Next, on the basis of the reasoning that small nucleophiles and reagents add to the bottom face, the gluco-configured derivative of **9** was prepared from **1** with the small nucleophile sodium cyanide.[26] A diastereomeric mixture (1:3.7 allo/gluco) in a total yield of 74%, with *gluco*-cyanohydrin **15** being the major product, was obtained (Scheme 5b). The diastereoisomers could be separated, and a pure fraction of **15** was hydrogenated, yielding the aminomethyl-branched glucoside **16**.

An alternative strategy had to be embraced to prepare the gluco-configured derivatives of methyl-branched **3** and epoxide **7**. The ketone was converted into a methylidene group, and the alkene was subsequently functionalized. This sequence has been utilized for the epoxidation of protected 3-methylidene glucosides from the top face (i.e., the same face selectivity as nucleophilic addition to the ketone).[27] Applying this reaction sequence to unprotected ketone **1** required a method to introduce the methylidene. The Wittig and Peterson olefination of keto-saccharide **1** did not work well, which is attributed to the high basicity of the reagents (Table S4).[28] An effective methylenation of **1** was achieved with the Nysted reagent ($Zn(CH_2ZnBr)_2{\cdot}THF$).[29] 4 equiv of the reagent was required, but after careful purification in which zinc salts were removed by precipitation, **17** was obtained in 55% yield (Scheme 6a).

The epoxidation of **17** with *m*-CPBA surprisingly resulted in a diastereomeric mixture (1:1 allo/gluco), presumably induced by the neighboring hydroxy groups. Hence dimethyldioxirane (DMDO) was used.[30] This solely produced the desired gluco-configured epoxide **18** in quantitative yield (Scheme 6b). An attempt to convert **18** into methyl-branched glucoside **19** by the hydrogenolysis of **18** was unsuccessful. Therefore, **19** was prepared from **17** via an oxymercuration–demercuration

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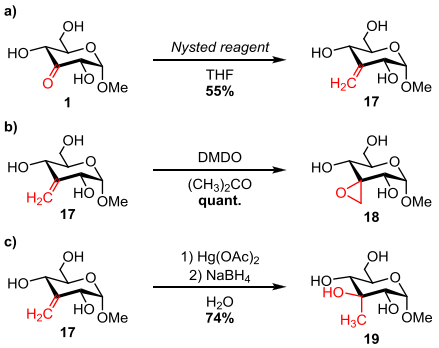
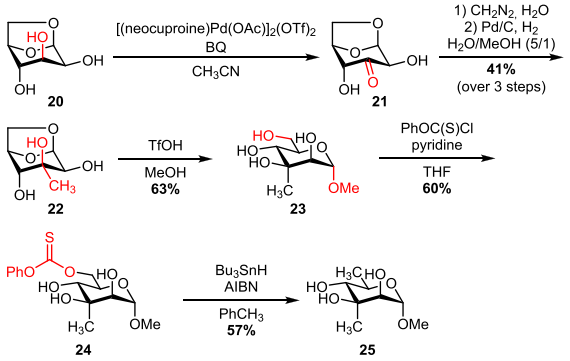
Scheme 6. Methylenation and Further Modifications



reaction (Scheme 6c).[31] With this method, the hydroxy group was introduced from the least sterically hindered face of the methylene moiety, resulting in diastereomerically pure **19**.

Finally, because the stereochemistry of the studied reactions is substrate-controlled, a (forced) ring-flip of the substrate necessarily leads to addition from the opposite face. This tactic was illustrated in a synthesis of methyl α-D-evalose (**25**), a rare branched sugar (Scheme 7). Evalose, or 6-deoxy-3-*C*-methyl

Scheme 7. Synthesis of Methyl α-D-Evalose



mannose, is a constituent of the orthosomycin antibiotics and of bacterial lipopolysaccharides.[32−35] The synthesis started from the commercially available 1,6-anhydro-β-D-mannopyranoside (**20**), locked in the $^1C_4$ conformation, which was regioselectively oxidized in the first step to keto-saccharide **21**.[5] Crude **21** was subjected to epoxide formation with diazomethane followed by hydrogenolysis. Methyl-branched mannoside **22** was isolated in a yield of 41% over three steps. After the acid methanolysis of **22**, the C6 in **23** had to be deoxygenated. The conversion of the hydroxy group into a good leaving group, suitable for subsequent reduction, invariably led to intramolecular ring formation with the C3−OH.[35] Therefore, radical deoxygenation via a Barton−McCombie reaction was selected. The C6−OH was converted into its thionocarbonate with *O*-phenyl chlorothionoformate. The removal of the thionocarbonate moiety required optimization but finally resulted in **25** in a yield of 57%. Overall, methyl α-D-evalose (**25**) was prepared in six steps, the shortest route to date.

In conclusion, protecting groups are obsolete not only in the regioselective oxidation of glucose, as previously shown, but also in a variety of stereoselective modifications of the resulting carbonyl function. The protecting-group-free modification of methyl 3-keto glucose **1** allows the stereoselective preparation of rare sugars and the installation of new handles and reactive groups. The stereoselectivity is substrate-controlled, and the allose- and glucose-configured products could be synthesized in a complementary fashion. The reactions with carbon nucleophiles predominantly resulted in allo-configured products, whereas sodium cyanide gave the opposite gluco-stereoisomer. Other gluco-configured products were prepared by the further functionalization of the 3-methylene derivative of **1** and the selective reduction of the 3-imino derivative to kanosamine. The transformations herein can potentially be applied to other keto-saccharides as well. By merging the preparation of keto-saccharides and the modifications herein, the straightforward preparation of chemical biology probes and new building blocks is permitted. This has been demonstrated by the labeling of maltose-binding protein with modified maltoheptaose.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01986.

Detailed experimental procedures, biological experiments, X-ray structures of compounds **1** and **7**, and copies of NMR spectra and HRMS (PDF)

Accession Codes

CCDC 1995084 and 1995088 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(28) Besides Wittig and Peterson olefination, the Petasis and Kauffmann olefinations of **1** also did not work well. The Petasis reaction led to the addition of cyclopentadiene to the carbonyl group, leading to **28**. See the Supporting Information, Table S4.
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