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Direct, Mild, and Selective Synthesis of Unprotected Dialdo-Glycosides

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A direct and highly convenient organocatalytic method for the preparation of 1,5-dialdo-pyranosides and 1,4-dialdo-furanosides is presented. The method relies on the chemoselective properties of TEMPO in combination with trichloroisocyanuric acid under very mild, basic conditions. Unprotected glycosides are prepared in a single step in high yields and are efficiently purified with the use of solid-phase imine capture.

Introduction

For many applications in modern synthetic chemistry, the pool of natural compounds is a useful source of building blocks. In particular, the diverse family of carbohydrates provides complex, stereochemically pure structures at moderate cost, and they can serve as reagents and scaffolds in a variety of synthetic protocols.[1–4] Modified carbohydrates are also important components in the development of efficient protein ligands and inhibitors.[5] The selective oxidation of carbohydrate hydroxy groups is in this case a convenient way to introduce new functionalities into the structures and to adjust several of the carbohydrates' fundamental chemical and physical properties. Oxidation of this primary hydroxy group to an aldehyde functionality produces dialdo-glycosides. This is a highly useful route for the preparation of reactive carbohydrate components with intact carbon skeletons. These structures have proved advantageous for a variety of reactions, including reductive amination protocols to produce *N*-linked glycosides and glycoconjugates,[6,7] glycoside oxime formation,[8] olefination reactions[9] and different polymerization protocols.[10,11]

The synthesis of 1,5-dialdo-pyranosides has been addressed over the years, and some enzymatic,[12–14] as well as several synthetic,[12,15] pathways have been reported. The enzymatic procedures use galactose oxidase and are straightforward but are largely limited to galactose derivatives because of the enzymatic specificity for this structure. Purification of the resulting 1,5-dialdo-galactopyranosides has also been reported to be difficult,[12] and crude mixtures are often used in subsequent reactions. Synthetic procedures usually require several steps with sophisticated protecting group strategies, which results in moderate overall yields and considerable amounts of waste products. With the consideration of today's demand from industry and society for more efficient and environmentally adapted processes, the design of simple, safe and effective synthetic routes are becoming more important. Terms such as, toxicity, atom efficiency and waste minimization are now invaluable parts of commercial and research focused synthesis.

In this study, we report a mild, simple and efficient TEMPO-catalyzed oxidation of a range of unprotected methyl glycosides (**1**–**6**) to their corresponding oxo derivatives (**7**–**12**). The transformation is made in one single step and products are isolated in high yield after a simple purification step.

Results and Discussion

TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl) is a very mild oxidation agent that has been previously used in different green and environmentally benign systems.[16–18] Under various conditions, it has been used catalytically and stoichiometrically for the chemoselective oxidation of primary hydroxy groups to aldehydes, carboxylic acids and mixtures thereof.[19–21] The general oxidation mechanism has been the object of several detailed studies, and the currently accepted catalytic cycle in basic media is displayed in Figure 1.[19] However, in order to stop at the aldehyde stage the reaction must generally take place in nonaqueous solvents, most commonly CH_2Cl_2, to avoid overoxidation to the corresponding carboxylic acids.[22–25] These solvents are generally incompatible with polar compounds because of solubility issues, and oxidation is therefore performed with protected structures.

In order to avoid overoxidation and to overcome solubility issues, the use of alternative solvents was addressed in this study. The reaction was found to be best carried out in DMF (Scheme 1), which proved to be an efficient solvent for this transformation as all reactants could be sufficiently

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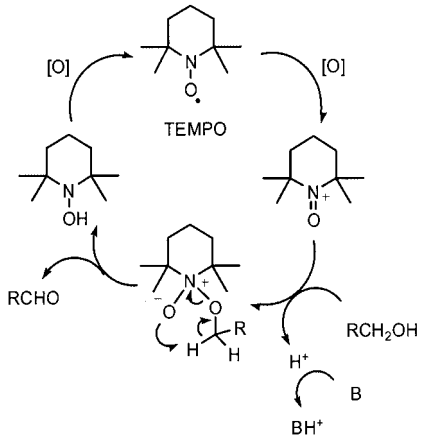
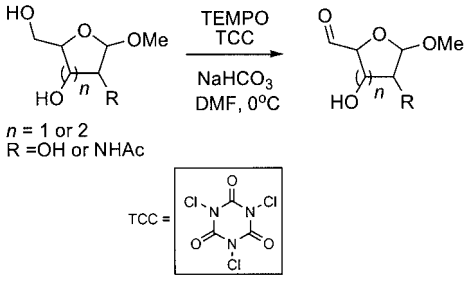


Figure 1. Proposed mechanism for TEMPO-catalyzed alcohol oxidation under basic (B) conditions.[19] [O] indicates secondary oxidant.

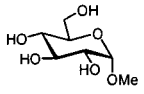
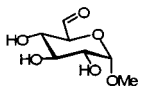
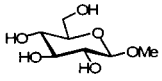
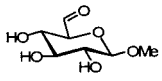
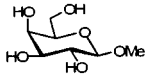
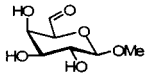
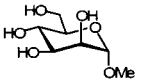
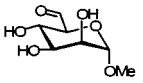
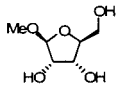
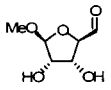
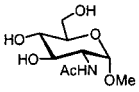
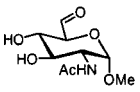
dissolved. DMF is a very polar aprotic solvent that has not previously been used in TEMPO-mediated reactions probably because of its tendency to degrade in oxidative environments. This phenomenon was also observed to a small extent under these mild conditions but was not pronounced enough to prevent oxidation of the starting material. In addition, several alkaline compositions and common secondary oxidants were screened to further optimize the reaction conditions, the majority of which, however, resulted in low conversions or degradation of the final product. In very weakly basic conditions, however, degradation could be completely eliminated.



Scheme 1. TEMPO-catalyzed oxidation of unprotected glycosides.

The most efficient system for the transformation of alcohols into aldehydes was finally identified to be at low temperature with sodium hydrogencarbonate as the base and TCC (trichloroisocyanuric acid) as secondary oxidant. TCC is known to be a very mild and safe oxidant,[26,27] and it has previously been used in TEMPO-based reactions.[27,28] This combination together with TEMPO (2.5 mol-%) in DMF at 0 °C managed to raise the conversion of the reaction up to quantitative yields for the investigated reactant glycosides (Table 1), without any observed decomposition.

Table 1. Synthesis of methyl 1,5-hexodialdo-pyranosides and methyl 1,4-pentodialdo-ribofuranoside.

entry	substrate	product	time (h)	yield (%)
1	 **1**	 **7**	7	79
2	 **2**	 **8**	7	quant.
3	 **3**	 **9**	9	81
4	 **4**	 **10**	7	84
5	 **5**	 **11**	4	65
6	 **6**	 **12**	7	66

The differences in the reaction times of glycosides **1**–**6** should also be noticed. The most likely explanation for these variations can be attributed to steric interference from the neighbouring groups. Thus, riboside **5**, which is the least sterically congested molecule, showed the shortest reaction time. Among the pyranosides, glucosides **1**, **2** and **6** and mannoside **4** all had similar rates, while galactoside **3** clearly stood out as the least reactive structure. This could be due to its axial hydroxy group in the 4-position which lies in close proximity to the reaction centre and could interfere with the reaction.

Purification of unprotected dialdosides has been reported to be difficult,[12] and their sensitive nature considerably limits the options available for purification. In our case, both the separation from DMF and the actual purification were needed in order to isolate our desired compounds. This problem was solved with the use of amino-derivatized solid-phase extraction columns.

The procedure (Figure 2) is based on the reversible reaction between aldehydes and primary amines to form a temporary imine functionality. After filtration, the reaction mixture was passed through the derivatized silica column, which traps the glycosidic aldehyde in the column by its conversion into an imine. The column was then washed

with THF to remove DMF and the impurities from the reaction mixture. Subsequently, a THF/water gradient was applied to hydrolyze the imine bond and to elute the aldehyde in its pure (hydrated) form. Finally, the aldehyde was isolated by freeze-drying the appropriate fractions. Although this purification procedure generally generated pure product, occasional traces (5–10%) of an impurity from the unwanted hydrolysis of the column were observed. This was visualized by TLC analysis as well as by ^{1}H NMR spectroscopy, and was confirmed by passing water through unused columns. This impurity did cause some mixed fractions in the elution process, which limited the yield. This problem could probably be eliminated by small adjustments in the manufacture of the column, which would render the possibility of even higher yields.

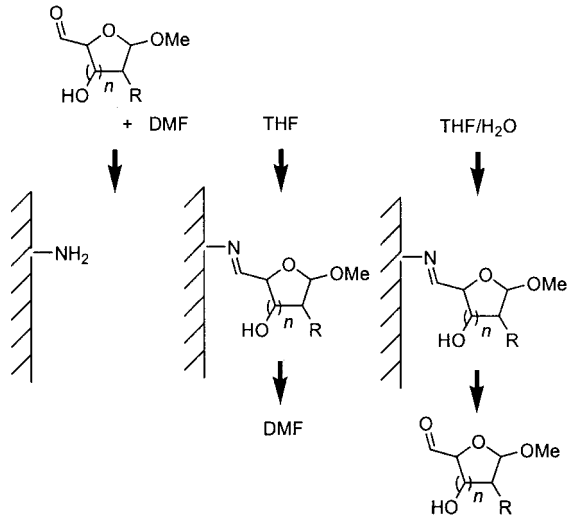


Figure 2. Efficient solid-phase capture/release of dialdo-glycosides.

The reaction was generally optimized for laboratory-scale transformations at milligram glycoside amounts. However, the reaction was also performed in gram-scale quantities for some of the substrates, which resulted in similar conversions and reaction rates. This demonstrates that the procedure is a possible candidate for large-scale or industrial applications. The solid-phase columns are also very adaptable to large-scale syntheses, with the possibility of multiple reuses and recycling of the solvent.

Conclusions

In conclusion, a safe and efficient organocatalytic route for the preparation of unprotected dialdo-glycosides in high yields has been developed. The procedure is very mild, and all reagents are cheap and readily available. Procedures that involve cumbersome protecting group strategies are completely eliminated. By taking advantage of the chemoselectivity and oxidation efficiency of TEMPO, polar aldehyde compounds could be prepared and easily purified in a single step.

Experimental Section

General Methods: All commercially available starting materials and solvents were of reagent grade and dried prior to use. Chemical reactions were monitored by thin-layer chromatography with precoated silica gel 60 (0.25 mm thickness) plates (Macherey–Nagel). Solid-phase extraction was performed with Sep-Pak® NH_2 cartridges (6 CC, 1 g) (Waters Corporation). ^{1}H- and ^{13}C NMR spectra were recorded with a Bruker Avance 400 instrument or a Bruker DMX 500 instrument at 298 K in D_2O, with the residual signals from H_2O (^{1}H NMR: δ = 4.70 ppm) as an internal standard. ^{1}H NMR peak assignments were made by first order analysis of the spectra, supported by standard ^{1}H-^{1}H correlation spectroscopy (COSY). High resolution mass spectra (HRMS) were performed by the Chemical Center, Lund Institute of Technology, Lund, Sweden. All compounds were analyzed in their hydrate form.

Representative Oxidation: Sodium hydrogencarbonate (650 mg, 7.74 mmol) and TEMPO (1 mg, 6.40 μmol) were added to a stirred solution of methyl α-D-mannopyranoside (**4**, 50 mg, 0.257 mmol) in DMF (50 mL). The reaction was cooled to 0 °C and TCC (45 mg, 0.196 mmol) was added. After 7 h of continuous stirring at 0 °C, the reaction mixture was filtered and passed through a Sep-Pak® amino-derivatized solid-phase extraction column (1 g, 6 mL). The column was washed with THF (40 mL), and the product was eluted with a THF/H_2O gradient (1→30% H_2O). Fractions that contained the product (TLC analysis) were freeze-dried to yield the desired aldehyde (42 mg, 85%).

Supporting Information (see footnote on the first page of this article): Spectroscopic data of compounds **7** to **12**.

Acknowledgments

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