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Synthesis and antioxidant activity of a novel class of 4,6-O-protected O-glycosides and their utility in disaccharide synthesis

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ABSTRACT

$BF_3{\cdot}Et_2O$-catalysed O-glycosylation of 1,2,3-tri-*O*-acetyl-4,6-*O*-butylidene- and ethylidene-β-D-glucopyranose with different aliphatic and aromatic alcohols proceeds for the most part with complete retention of anomeric configuration. Antioxidant activity of O-glycosides shows significant inhibition (IC_{50} ~77%). 1,3-Dipolar cycloaddition of terminal alkyne derivatives of O-glycosides with glycosyl azide results in disaccharides.

1. Introduction

The ever-increasing importance of the role of carbohydrates in biological processes relating to immunology, virology and a host of life-threatening diseases has created an interest in access to specific sugar-hybrid molecules (Fig. 1).[1] In general, glycosylated products are essential and reliable platforms for the development of many of our existing front-line drugs[2,3] and organic materials.[4,5] Recently, the appreciable understanding of the relationship that exists between the sugars and bioactive entities has shed light on their biological significance.[6,7] In addition, the synthesis of O-glycosides has received considerable attention because of their inhibitory activity, and their role as inducers of glycosidases, as well as their utility as glycosyl donors in the convergent synthesis of oligosaccharides.[8,9] Common natural antioxidants are generally from the family of flavonoids and phenolic acids.[10,11] They serve not only as defensive molecules in prevention of different pathological disorders, but are also used in industry for the prevention of oxidative degradation of polymers and natural pigments.[12]

Despite the development of many elegant strategies to synthesise O-glycosides,[13–17] reactions of per-O-acetylated monosaccharides with aliphatic and aromatic alcohols in the presence of $BF_3{\cdot}Et_2O$, TMSOTf and $AgClO_4$ afford the corresponding O-glycosides in moderate to good yield.[18,19] Mereyala and Gurrala[20] reported the synthesis of allyl and propargyl O-glycosides in the presence of $BF_3{\cdot}Et_2O$, which resulted in high yields with good selectivities. Thus the allyl and propargyl O-glycopyranosides, due to the higher reactivities, are extensively used in the synthesis of oligosaccharides. These groups can be deprotected by various reagents at any length of the growing saccharide chain to obtain the reducing sugar,[21] and further derivatisation with proteins leads to glycoconjugates.[22,23] Furthermore, propargyl O-glycosides[24,25]are of great interest in 'click chemistry' used to provide mimics of various biodynamic carbohydrate structures[26,27] and glycoconjugates.

The recent advance of Cu-catalysed conditions in click chemistry affords superior regioselectivity, high tolerance of other functionalities and quantitative transformation under mild conditions. 1,3-Dipolar cycloaddition reactions have been used in the synthesis of neoglycoconjugates and also in bioconjugation study of glycosides.[28,29] In the search for new methodologies for the synthesis of disaccharides, the use of propynyl O-glycosides can be a versatile and efficient synthon for the construction of disaccharide derivatives. More recently, the alkyne–azide[30] cycloaddition reaction catalysed by Cu(I) has been given more attention for the synthesis of saccharide derivatives.[31,32] This report describes the use of 1-(2-propyn-1-yl) 2,3-di-O-acetyl-4,6-O-protected β-D-glucopyranose for the construction of several disaccharide derivatives by the reaction with sugar azides through triazole ring formation.

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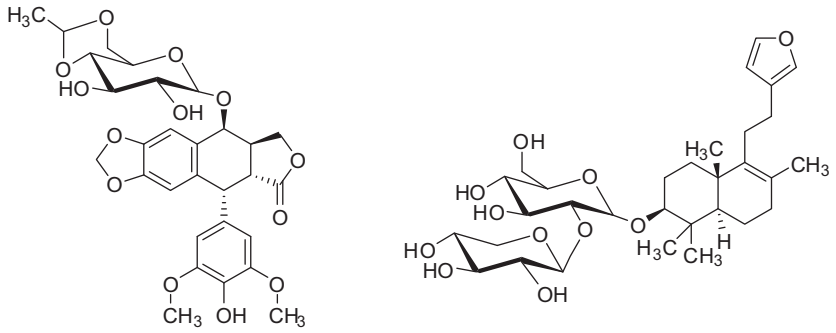


Figure 1. O-Glycosylated sugar hybrid compounds.

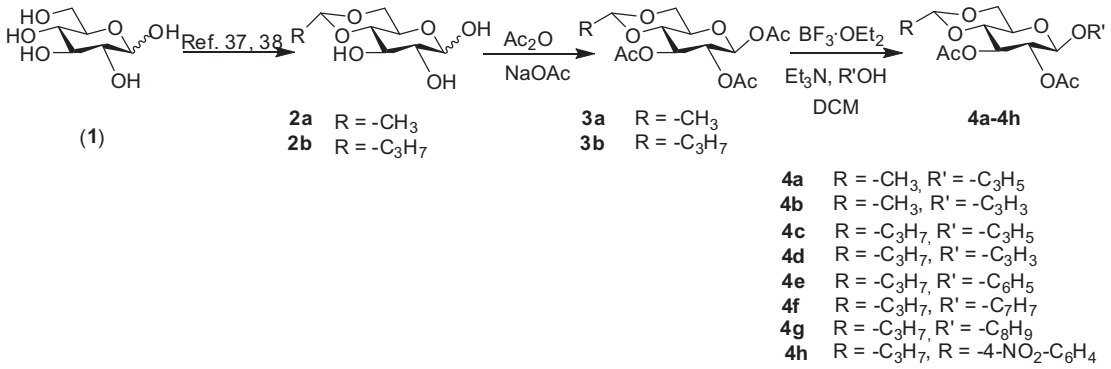
Phenols, in their capacity as hydrogen donors, react with lipid radicals[33] to form phenoxy radicals and are effective chain-breaking antioxidants. However, phenol is inactive as an antioxidant, but an alkyl substituent at either *ortho* or *para* position increases the electron density on the hydroxyl group and thus increases its activity towards the generation of lipid radicals.[34] Thus it has been proposed that these two potentially useful properties could be combined in a properly functionalised phenol that might act as an efficient drug.[35] In addition to our ongoing research[36] in the area of sugar chemistry, here we report the influence of the sugar skeleton and aglycon motifs on antioxidant properties using the 1,1-diphenyl-2-picrylhydrazide (DPPH) radical-scavenging activity assay.

2. Results and discussion

2.1. Synthesis of 4,6-O-protected O-glycosides (4a–h)

4,6-*O*-Ethylidene-D-glucopyranose (**2a**) and 4,6-*O*-butylidene-D-glucopyranose (**2b**) were synthesised from D-glucose (**1**) by adopting the literature procedures.[37,38] These compounds were also characterised using different spectral techniques. Acetylation of the acetals **2a** and **2b** was (Scheme 1) carried out using acetic anhydride and sodium acetate and resulted in the formation of the corresponding β-acetylated products **3a** and **3b**. The strategy followed in the synthesis of the O-glycosides basically relied on the difference in the hard and soft basicities of the anomeric and aglycon alcohol moieties. In general a hard Lewis acid like $BF_3{\cdot}Et_2O$ catalyses the loss of the acetate group from the anomeric carbon without affecting the other functionalities. Thus, O-glycosylation of compounds **3a** and **3b** with aliphatic alcohols (allyl alcohol and propargyl alcohol) and aromatic alcohols (phenol, *p*-methylphenol, *p*-ethylphenol and *p*-nitrophenol) resulted in the formation of the corresponding expected O-glycosides (**4a**–**h**) (Table 1) in 40–72% yield. Use of 2.5 equiv of $BF_3{\cdot}Et_2O$, 1.0 equiv of protected sugar and 1.5 equiv of alcohol resulted in higher selectivity (95%). Thus the high β-selectivity in O-glycosylation reactions under acidic conditions is attributed to the neighbouring group effect (C-2 substituent) via the formation of an oxazolinium ion that results in the preferential formation of the 1,2-*trans*-glycosylated product. Evidence for the mechanistic hypothesis is obtained from the single-crystal XRD analysis of the product, which is derived from the stabilisation of the oxazolinium intermediate. The aliphatic allyl and propargyl alcohols react with **3a** and **3b** to give the β product only. The multiplet at δ ~5.0–6.0 in the ^{1}H NMR spectrum and the peaks at δ ~72.0 and ~56.0 in the ^{13}C NMR spectrum confirm the formation of O-allyl glycosides **4a** and **4c**. Moreover the structure of **4a** is confirmed through a single-crystal XRD analysis. The characteristic triplet at δ ~2.39 (J 2.4 Hz) for the terminal alkyne group in ^{1}H NMR spectrum and peaks at δ ~56.1 and 66.4 in the ^{13}C NMR spectrum confirm the formation of **4b** and **4d**. The reactivities of aromatic alcohols depend on the substitution on the aromatic ring, and it is observed that the presence of electron-releasing groups increase the rate of the reaction. The anomeric proton appears as a doublet at δ 5.13 (d, J 7.5 Hz), 5.07 (d, J 7.5 Hz), 5.08 (d, J 7.2 Hz) and 5.28 (broad peak) with a coupling constant of J ~7.5 Hz, which confirms the β anomeric form in compounds **4e**–**h**.

The α:β ratio has been calculated from the reaction mixture by using ^{1}H NMR spectroscopy. However, after purification by column chromatography, the product obtained was found to be only the β



Scheme 1. Synthesis of O-glycosyl derivatives (**4a**–**h**).