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Toward the synthesis of fine chemicals from lactose: preparation of D-*xylo* and L-*lyxo*-aldohexos-5-ulose derivatives ☆

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ABSTRACT

The transformation of (5*R*)-2,6-di-*O*-benzyl-5-*C*-methoxy-β-D-galactopyranosyl-(1→4)-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (**8**) into partially protected derivatives of D-*xylo*- and L-*lyxo*-aldohexos-5-ulose has been reported, applying appropriate epimerisation methods to its 3′-*O*- and 4′-*O*-protected alcoholic derivatives.

1. Introduction

Lactose is the most abundant naturally occurring reducing disaccharide, which is obtained from whey as a by-product of the agro-industrial cheese production. Although it has a large worldwide availability, which is estimated at about 500,000 tons/year,[2a] only a low percentage of recovered lactose is utilised mainly in the food, feed and pharmaceutical fields. The chemical valorisation of lactose is achieved through simple transformations into commercially available products such as lactobionic acid,[2] a component of the preservative solution for transplanting organs, lactitol,[2] a suitable component of sugar-free, reduced caloric and low glycemic products and lactulose and galacto-oligosaccharides (GOS),[2] largely used in probiotic therapy.

Since lactose is inexpensive and there is a potential environmental risk connected with the uncontrolled dispersion of whey in freshwater, new synthetic channels need to be investigated in order to synthesise fine chemicals starting from this renewable raw material.

Recently, we planned a synthetic strategy to elaborate the non-reducing unit without modifying the reducing one, as is commonly done. This useful approach takes advantage of the large availability[3] of the two polyacetonides **1** and **2** (Fig. 1), which could be considered as simple β-D-galactopyranosides, due to the complete protection of the D-glucose unit. Aldohexos-5-uloses (**3**) represent an interesting, although yet poorly investigated class of dicarbonyl hexoses,[4] that are useful synthetic intermediates for the preparation of high value-added compounds such as iminosugars[5] and cyclitols, as inositols,[6] or polyhydroxycyclopentanes.[7]

A general approach (Chart 1) to aldohexos-5-uloses (**3**) was developed[8] using the key reaction, the epoxidation–methanolysis of hex-4-enopyranosides of type **5**, which are in turn obtained from 3,4-*O*-isopropylidene-β-D-galactopyranosides (**6**).

In this communication, we present the synthesis of partially protected derivatives of D-*xylo* and L-*lyxo*-aldohexos-5-uloses achieved here from the disaccharide 1′,5′-bis-glycoside **8**, analogous to **4**, which is in turn easily obtained from lactose,[9] following the same general approach outlined in Chart 1. The influence of the

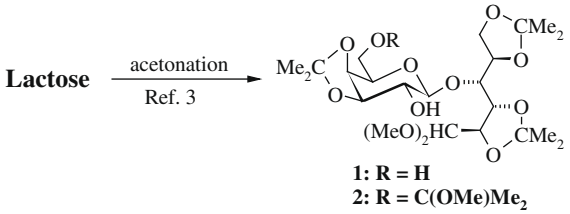

Figure 1. Polyacetonides directly obtained by acetonation of lactose.

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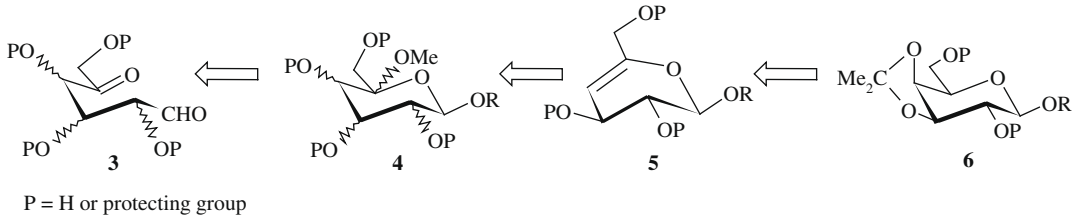


Chart 1. General approach to aldohexos-5-uloses from-D-galactopyranosides.

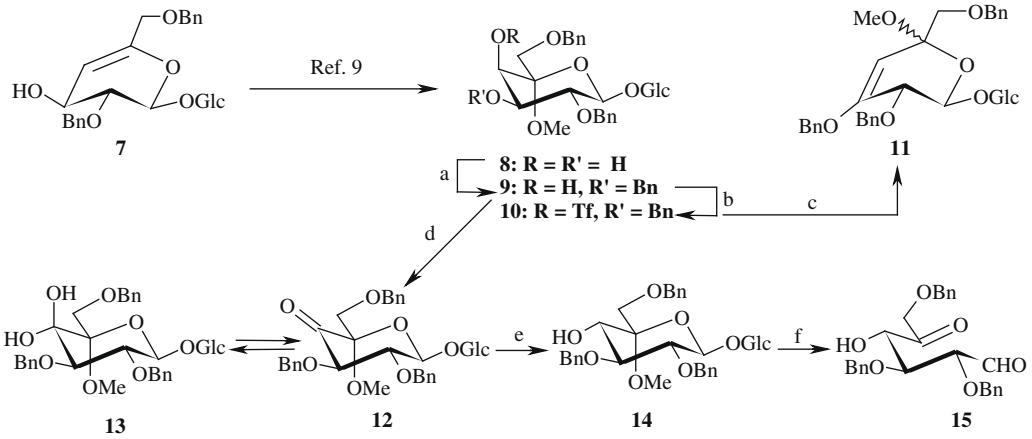
axial C-5′-OMe group on the chemo- and stereoselectivity of some reactions performed on the bis-glycoside unit is also observed and discussed.

2. Results and discussion

Preliminary attempts to obtain 1,5-bis-glycopyranosides of the D-*xylo* series through epoxidation–methanolysis of a 3′-*O*-protected derivative of the known disaccharide hex-4′-enopyranoside **7**,[9] following the method which was previously used in monosaccharide series,[8b] were abandoned due to the difficulties encountered in the separation of the complex crude diastereoisomeric mixture. An alternative way based on the regioselective protection of 3′-OH of the known diol **8**,[9] followed by stereoselective epimerisation at C-4′ (Scheme 1), was then considered. The first step was easily achieved through a stannylidene acetal-mediated alkylation. The method, which has largely been used to differentiate 1,2-*cis*-diols of a sugar,[10] has never been reported until now, on a 1,5-bis-glycopyranoside. As in the case of β-D-galactopyranosides,[10] the alkylation took place with complete regioselectivity on the 3′-OH group, leading in almost quantitative yield to the alcohol **9**.

The first C-4′ epimerisation strategy was attempted via an S_N2 displacement on the triflate **10**, which was obtained from **9** in high isolated yield (88%) by treatment with Tf_2O in pyridine. Surprisingly, the treatment of **10** with Bu_4NNO_2 in toluene led to the formation of enol ether **11**, isolated in 70% yield, instead of the desired inverted bis-glycoside **14**. This result is quite unexpected in light of the high yields reported for nucleophilic substitutions of structurally related 4-*O*-triflates of galactopyranosides[11] and is evidently due to some interference between the axial 5′-OMe group and the nucleophile approaching the vicinal reacting centre. The complementary strategy based on an oxidation–reduction sequence of **9** was thus explored. Also in the oxidation of **9**, the presence of the axial C-5′ methoxyl group sensibly influenced the reaction. Swern oxidation attempts failed completely, while treatment with PCC showed a low conversion even after long reaction times. Better results were obtained with the TPAP–NMO system, employing, however, an unexpectedly high catalyst molar ratio (40%) with respect to that usually needed (5%).[12] NMR analysis of the crude oxidation product showed a mixture of the 4′-ulosyl derivative **12** (C-4′ ^{13}C chemical shift: 198.3 ppm) and of its hydrate **13** (C-4′ ^{13}C chemical shift: 97.1 ppm). In the crude oxidation mixture, compounds **12** and **13**, which were isolated in about 89% yield, were present in about 4:1 ratio, as determined on the basis of the relative intensity of the ^{13}C 5′-OMe signals. Chromatographic purification led again to a mixture of **12** and **13** in the same 4:1 ratio, but with substantial loss of product, lowering the yield to a modest 56%. The reduction of the crude oxidation mixture with $NaBH_4$ in MeOH led to **14** and **9** in 64% and 20% isolated yields, respectively, indirectly confirming the structures of **12** and **13** and the extensive loss of the uloside during the chromatography on silica gel. In the case of the hydride reduction, the presence of the axial 5′-OMe group was beneficial for the stereoselectivity, determining the prevalence, although not complete, of attack on the β-face. This result is at variance with respect to the hydride reduction of analogous 4-keto-D-*arabino*-hexopyranosides, mainly leading to D-galactopyranosides.[13] Finally, the target 2,6-di-*O*-benzyl-D-*xylo*-aldohexos-5-ulose (**15**) was obtained from **14** (72% yield) by acid hydrolysis with CF_3COOH in CH_3CN–water (50 °C, 12 h) and by separation from D-glucose by extraction with EtOAc. As previously reported,[8b] **15** was present in CD_3CN as a 55:45 α,β-1,4-furanose mixture, as confirmed by NMR analysis.

The preparation of L-*lyxo* derivatives was based on the same approach used in the monosaccharide series,[8c] providing an oxidation–reduction sequence of a 3-OH free 1,5-bis-methyl L-*arabino*-hexopyranoside, obtained through the completely regioselective



Scheme 1. Stereoselective synthesis of 2,3,6-tri-*O*-benzyl-D-*xylo*-hexos-5-ulose. Reagents and conditions: (a) Bu_2SnO, $C_6H_5CH_3$, reflux, 12 h, then BnBr, Bu_4NBr, reflux, 1.5 h (94%); (b) Tf_2O, 1:1 CH_2Cl_2-Py, rt, 6 h (88%); (c) Bu_4NNO_2, $C_6H_5CH_3$, reflux, 8 h (70%); (d) TPAP, NMO, CH_2Cl_2, 4 Å, rt, 4 h; (e) $NaBH_4$, MeOH, rt, 1.5 h, (64% from **9**); (f) 90% aq CF_3COOH, 4:1 CH_3CN-H_2O, 50 °C, 12 h (72%).