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Stereoselective synthesis of β-D-GlcNAc-(1 → 4)-D-Glc disaccharide starting from lactose ☆

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ABSTRACT

The stereoselective preparation of the β-D-GlcNAc-(1 → 4)-D-Glc disaccharide starting from known 4-*O*-[6-*O*-(1-methoxy-1-methylethyl)-3,4-*O*-isopropylidene-β-D-talopyranosyl]-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (**2**), in turn easily obtained from lactose, is reported. Key steps of this new procedure, that avoids the glycosylation reaction, are (a) a first epimerization at C-4′ through an unusual procedure involving a completely stereospecific hydroboration–oxidation of the enol ether group of the hex-4-enopyranoside **4**, obtained from **3** by base promoted acetone elimination, (b) an amination with inversion by S_N2 reaction on an imidazylate intermediate, and, finally, (c) N-acetylation followed by complete deprotection.

1. Introduction

N-Acetylhexosamines are an important class of monosaccharides found in many types of natural bioactive compounds.[1] They are present in different types of glycoconjugates (glycolipids, lipopolysaccharides, and proteins),[2] glycosaminoglycans (heparin, dermatan, chondroitin, and hyaluronic acid),[3] blood group determinants,[4] and in the antigenic determinant of various pathogens.[5] Owing to the difficulties in the stereoselective chemical formation of 1,2-*cis*-hexosaminyl bonds (β-D-manno and β-D-talo series),[6] we have directed our attention to an approach involving regio- and stereoselective manipulations of β-D-galactopyranosides.[7] Lactose is a cheap and naturally abundant disaccharide which can be transformed into a number of useful analogues such as β-D-ManNAc-(1 → 4)-D-Glc, and β-D-TalNAc-(1 → 4)-D-Glc.[7a] Recently, the synthesis of β-D-GalNAc-(1 → 4)-D-Glc disaccharide from lactose has also been performed.[8] The preparation of a further hexosaminyl analogue of the series, that contains the β-D-GlcNAc unit, is reported here, starting from an intermediate obtained in our previous work.[7,8] This approach avoids the glycosylation step, while previous syntheses of the β-D-GalNAc-(1 → 4)-D-Glc disaccharide all involved the coupling of a suitably protected glucosamine donor with a glucopyranoside acceptor selectively deprotected on OH-4.[9b–d] Interestingly, some derivatives of this disaccharide have been considered recently for their aphicidal activity.[9a]

The synthesis of the target disaccharide started from the mixed tetra-acetonide β-D-talopyranosyl disaccharide **2**, easily obtained in high yield by C-2′ epimerization of corresponding lactose derivative **1** (Fig. 1).[10]

The planned approach utilizes two stereocontrolled procedures: epimerization of C-4′ and amination with inversion of configuration at C-2′, as outlined in Chart 1.

2. Results and discussion

The first transformation involves as key step the regio- and stereoselective hydroboration–oxidation of the intermediate vinyl ether **4** (Scheme 1). Compound **2** was transformed into the completely protected derivative **3** by Williamson *p*-methoxybenzylation of 2′-OH followed by selective and mild acidic hydrolysis (5% aq HCl) of the 6′-*O*-methoxyisopropyl acetal and finally 6′-O-benzylation. Compound **3** was obtained in good overall yield (83%) with only one purification step.

The acetone elimination reaction was carried out according to the conditions previously optimised for the *talo* series.[11] Treatment of compound **3** with *t*-BuOK in THF at reflux gave the corresponding vinyl ether in high yield which was directly subjected to a standard benzylation reaction to afford **4** in 77% yield over two steps. The elimination reaction required milder conditions with respect to those used for 3,4-*O*-isopropylidene-D-galactopyranoside analogues.[12] The enhanced reactivity of the *talo* series is probably related to the unfavourable *syn* interaction between the axial

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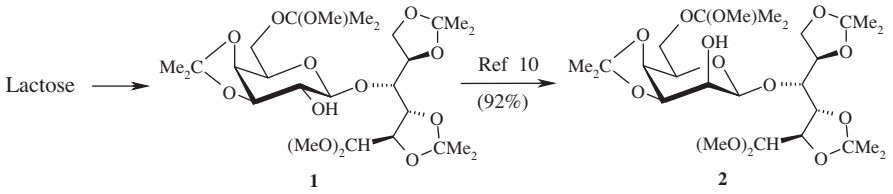


Figure 1. Transformation of lactose into talopyranosyl derivative **2**.

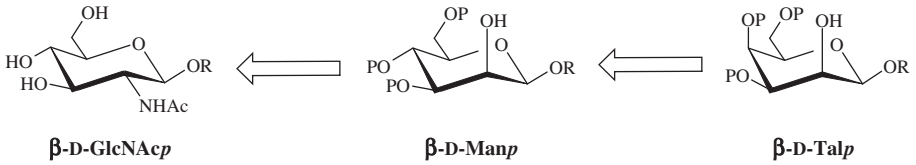


Chart 1. Retrosynthetic approach to a β-D-*N*-acetylglucosamine glycosyl unit starting from a β-D-talopyranoside.

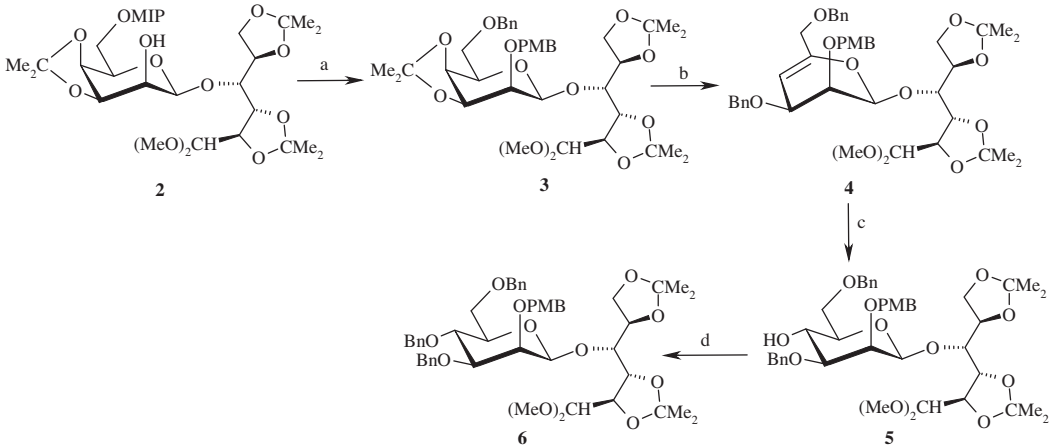
2-OR group and the 3,4-*O*-isopropylidene ring. The high strain release is presumably the reason for the observed complete regioselective elimination of acetone. It is also interesting to pinpoint that starting from the *talo* series, the regioselective preparation of hexenopyranosides can now be achieved by two complementary routes. We recently reported the high yielding NaH/Im_2SO_2 mediated preparation of 4-deoxy-D-*threo*-hex-3-enopyranosides,[10,13] while here an approach to the 4-deoxy-D-*erythro*-hex-4-enopyranoside is described.

The C-4′ epimerization was accomplished with the hydroboration–oxidation reaction ((a) BH_3SMe_2 in THF; (b) H_2O_2/NaOH/H_2O; 80% yield). The subsequent benzylation reaction of **5** afforded **6** in 93% yield and the coupling constant pattern confirmed the *manno* configuration ($J_{3',4'}$ 9.4 Hz, $J_{4',5'}$ 9.6 Hz). The regioselectivity of the hydroboration step is not surprising in light of the polarity of the vinyl ether double bond. The complete stereoselectivity obtained is attributed to the orientation of the substituents, and in particular the axial 2′-OR group, which all shield the *beta* face from the borane coordination.

The orthogonal *p*-methoxybenzyl group was removed using DDQ in a mixture of CH_2Cl_2–H_2O (76% yield) and the leaving group was then introduced by treating **7** with imidazyl sulfate (Im_2SO_2) and NaH in DMF at −30 °C (Scheme 2). The corresponding imidazylate **8**, isolated pure by flash chromatography in 83% yield, was then subjected to a S_N2 displacement with NaN_3 in DMF at 100 °C, and afforded the azido derivative **9** in 92% yield ($J_{1',2'}$ 7.8 Hz, $J_{2',3'}$ 9.1 Hz). This result confirms the usefulness of the imidazylate leaving group in comparison with other aryl and alkyl sulfonates[14] for performing efficient substitution in position 2 of a pyranoside. The first step of the deprotection strategy consisted of a hydrogenolysis (H_2, Pd/C) in the presence of Ac_2O. These conditions allowed for benzyl group removal, reduction of the azido function, and direct N-acetylation.

The target compound **11** was finally obtained by complete deprotection of **10** via acidic hydrolysis of all acetals using 80% aq AcOH at 80 °C: this exposes the C-1 aldehyde group and thus a concomitant six-membered ring closure occurs. The structure of **11** as well as its anomeric composition (α/β ratio about 2:3) was established on the basis of its NMR spectra. The ^{13}C NMR signals (see Table 1) were assigned by comparison with those of α-, β-cellobiose[15] and with those of methyl 2-acetamido-2-deoxy-β-D-glucopyranoside.[16]

In conclusion, we reported an easy access to the β-D-GlcNAc-(1 → 4)-D-Glc disaccharide starting from lactose. This approach is based on high yielding and stereoselective manipulations of the natural disaccharide skeleton and avoids the time consuming classical preparation of protected monosaccharide donor and acceptor. In addition, it bypasses the difficulties previously encountered in



Scheme 1. Stereoselective synthesis of 4'-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-*p*-methoxybenzyl-β-D-mannopyranosyl)-2,3:5,6-di-*O*-isopropylidene*aldehydo*-D-glucose dimethyl acetal (**6**). Reagents and conditions: (a) (1) PMBCl, NaH, DMF, room temp, 2 h; (2) CH_2Cl_2 and 5% aq HCl; (3) BnBr, NaH, DMF, room temp, 12 h, (83%); (b) (1) *t*-BuOK, THF, reflux, 20 min; (2) BnBr, NaH, DMF, room temp, 12 h (77%); (c) BH_3 Me_2S (5 M, Et_2O), THF, room temp, 5 h, then H_2O, 10% NaOH, 35% aq H_2O_2, room temp, 2 h (80%); (d) BnBr, NaH, DMF, room temp, 12 h (93%).