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A new stereocontrolled access to β-D-mannopyranosides and 2-acetamido-2-deoxy-β-D-mannopyranosides starting from β-D-galactopyranosides†,‡

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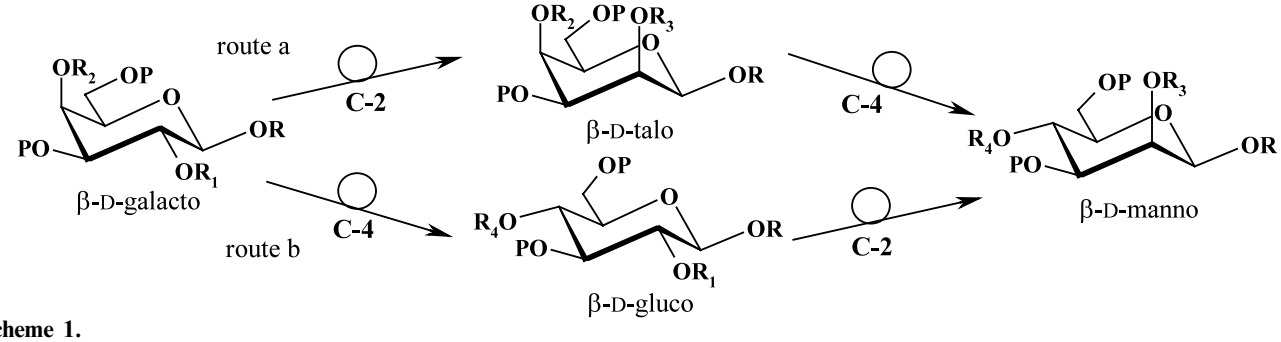
Abstract—A new stereocontrolled synthesis of β-D-mannopyranosides was defined relying on a high yielding sequence based on the following three key steps: (a) a stereospecific inversion at C-2 of β-D-galactopyranosides by an oxidation–reduction procedure; (b) a regiocontrolled formation of 4-deoxy-β-D-*threo*-hex-3-enopyranosides; (c) a regio- and stereocontrolled hydroboration–oxidation of the above enol ethers. The flexibility of this new method was demonstrated by its extension to the synthesis of 2-acetamido-2-deoxy-β-D-mannopyranosides and of an orthogonally protected β-D-mannopyranoside scaffold and, finally, by the transformation of lactose into the two biologically relevant disaccharides with primary structure β-D-Man*p*-(1→4)-D-Glc and β-D-ManNAc*p*-(1→4)-D-Glc.

Several naturally occurring complex oligosaccharide structures contain as relevant component a β-D-Man*p* or a β-D-ManNAc*p* unit. The former type of monosaccharide is a common fragment of the core region of *N*-linked glycoproteins, a class of glycoconjugates having a fundamental role in intercellular signaling,[2] while the second one is largely present in capsular polysaccharides and is involved in the immunological response of either Gram positive or Gram negative bacteria.[3]

The stereocontrolled synthesis of these types of glycosidic linkages remains, however, an important challenge for synthetic chemists, despite the impressive number of efforts in this direction.[4] In the frame of an ongoing project aimed at the chemical valorization of lactose,[1] we have been interested in efficient methods for the transformation of β-D-galactopyranosides into β-D-mannopyranosides analogues, a procedure overall involving the epimerization both at C-2 and C-4.

Although the procedure based on a first epimerization at C-4 followed by a second one at C-2 (Scheme 1, route b) has been reported,[5] we have not found any example of the alternative possibility employing the



Scheme 1.

Keywords: β-D-mannopyranosides; 2-acetamido-2-deoxy-β-D-mannopyranosides; β-D-talopyranosides; epimerization; hydroboration; stereoselectivity.

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inverse epimerization sequence (Scheme 1, route a). We present here a useful way leading to the above result using three consecutive key steps: (a) a stereospecific inversion at C-2 of β-D-galactopyranosides; (b) a regiocontrolled formation of 4-deoxy-β-D-*threo*-hex-3-enopyranosides;[6] (c) a regio- and stereocontrolled hydroboration–oxidation of the above enol ethers (Scheme 2).

The C-2 epimerization was efficiently achieved applying an oxidation–reduction sequence to the mixed acetals **1** having the sole OH-2 group in the free form.[7] Although the stereoselective C-2 epimerization of β-D-galactopyranosides by oxidation–reduction has been reported,[8] the choice of acetals **1** as selectively protected intermediates represents by far the most efficient entry to β-D-talopyranosides in terms of chemical and stereochemical yields.[9] The transformation of β-D-talopyranoside mixed diacetals analogous of **1** into compounds **2a**–**c**, having the sole OH-4 group free, was achieved with high yield through simple protecting group manipulations.[9]

The enol ethers **3** were successfully obtained through a recently reported method[6] of simultaneous activation–elimination of axial hydroxyl groups with NaH–sulfuryl diimidazole (Im_2SO_2). In the specific case of 4-*O*-deprotected β-D-talopyranosides, this process leads with complete regioselectivity to 4-deoxy-β-D-*threo*-hex-3-enopyranosides (**3a**–**c**)[12] owing to the stereoelectronic assistance offered by the antiperiplanar axial electronegative C-2 substituent to the base-promoted extraction of the axial C-3 hydrogen atom.

The transformation of enol ethers **3** into the targets β-D-mannopyranosides **4** was easily performed by hydroboration–oxidation with borane–dimethyl sulfide complex (BMS). The expected regioselective attack of the boron on the β-enolic carbon of enol ethers[13] has been also reported in the case of glycals[14] and 4-deoxyhex-4-enopyranosides.[15] In these reactions the stereochemical outcome of borane addition is controlled by steric factors directing the boron attack mostly or completely *anti* to the allylic substituent. Hydroboration of **3** gave results in full agreement with the previous picture and a single compound was obtained in high yield[16] having the new 4-OH group in a *trans* orientation with respect to the substituents to the two contiguous carbon atoms.[17]

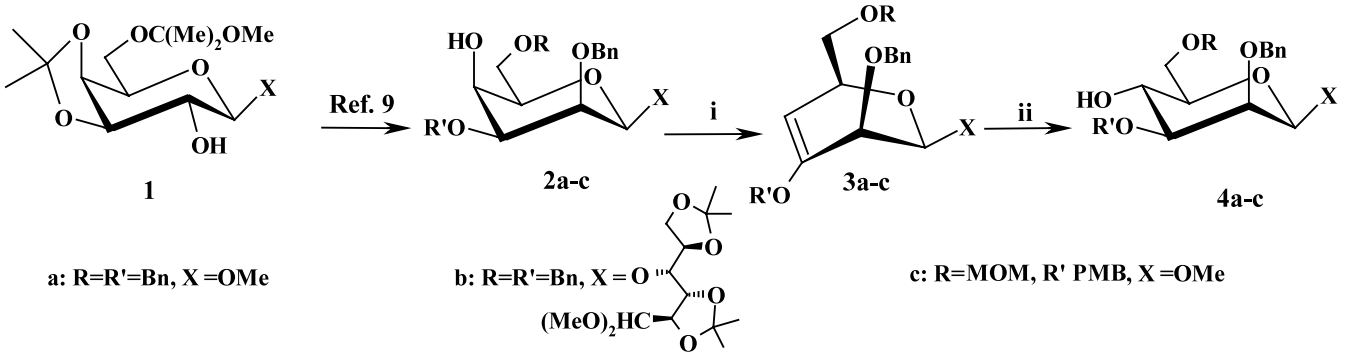
The synthesis of orthogonally protected β-D-mannopyranosides, such as **4c**, is of great interest; this type of compounds, in fact, were reported only recently[18] in the frame of some studies directed to the combinatorial synthesis of bioactive peptidomimetics. The transformation of **1** (X = OMe) into **4c** clearly elucidates the value of the present approach, leading to the target compound with an overall 46% yield in a sequence requiring only two chromatographic purifications.

A further extension of the synthetic scheme was devised, taking advantage from the regioselective formation of 2-acetamido-2,4-dideoxy-β-D-*threo*-hex-3-enopyranosides **5a**,**b**.[6]

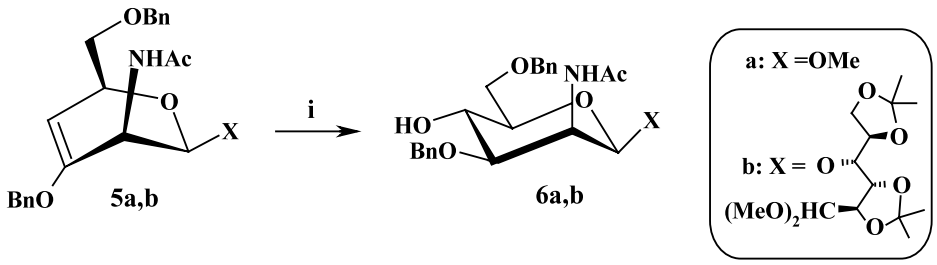
Also in this case, the hydroboration–oxidation of enol ethers **5a**,**b** led with complete chemo-, regio- and stereoselectivity to the β-D-manno configured compounds **6a**,**b** (Scheme 3).[16,17]

All final compounds **4a**–**c** and **6a**,**b** have never been reported but their structure was easily established by NMR analysis, characterized by a set of diagnostic coupling constants [very small $J_{1,2}$ (0–1.6 Hz) and large $J_{3,4}$ and $J_{4,5}$ (9–9.4 Hz)] typical of a mannopyranoside moiety and reported for a lot of analogues.[5b,c,19]

In conclusion, we have presented a new, efficient and flexible method for the regio- and stereocontrolled transformation of β-D-galactopyranosides into β-D-mannopyranosides and 2-acetamido-2-deoxy-β-D-mannopyranosides through the epimerization at C-4 of β-D-talopyranosides never reported in literature. The usefulness of the method has been exemplified by the effective synthesis, starting from lactose, of biologically relevant disaccharide derivatives with primary structure β-D-Man*p*-(1→4)-D-Glc and β-D-ManNAc*p*-(1→4)-D-Glc, and by the synthesis of an orthogonally protected β-D-mannopyranoside scaffold. The use of the above strategy for the preparation of other di- and oligosaccharides containing β-D-mannopyranoside units is



Scheme 2. *Reagents and conditions*: (i) NaH, DMF, 0°C, then Im_2SO_2, −30°C, 3 h, 80–95%; (ii) $BH_3{\cdot}SMe_2$, 2 h, then H_2O_2, NaOH, 2 h, 82–90%.



Scheme 3. *Reagents and conditions*: (i) $BH_3{\cdot}SMe_2$, 2 h, then H_2O_2, NaOH, 2 h, 82–90%.

under investigation in our laboratory and will be presented in due course.

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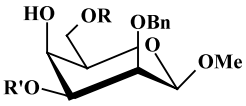
9. The preparation of compounds **2a** and **2b** has been reported in preliminary form.[6] Compound **2c** was prepared through an unreported sequence starting with the oxidation–reduction of **1** (X = OMe), followed by the benzylation of the OH-2 group (BnBr, KOH, 18-crown-6/THF), the hydrolytic removal of the two acetonide function (80% aq. AcOH) to give the triol **7** which was submitted to a stannylidene acetal promoted *p*-methoxybenzylation[10] (Bu_2SnO, toluene, reflux, then PMBCl, Bu_4NI, reflux) to the diol **8**, that was finally regioselectively methoxymethylated at OH-6 (MOMCl, DIPEA/CH_2Cl_2) to give **2c** with an overall yield of 70%.



7: R=R'=H
8: R=H, R'=PMB

10. The regioselective opening at C-3 of the 3,4-*O*-stannylidene acetals of the β-D-talo derivatives is identical to that of their β-D-galactopyranoside analogs,[11] pointing to a similar conformational situation.
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12. Compounds **3a** and **3b** were previously reported.[6] Compound **3c** was prepared with the same procedure[6] from **2c**. Selected NMR (^1H, 200 MHz ^{13}C, 50 MHz, $CDCl_3$) data of **3c**: δ_H 3.60 (dd, 1H, $J_{5,6a}=5.5$ Hz, $J_{6a,6b}=10.1$ Hz, H-6a), 3.74 (dd, 1H, $J_{5,6b}=6.1$ Hz, H-6b), 4.51 (d, 1H, $J_{1,2}=2.1$ Hz, H-1), 4.90 (d, 1H, $J_{4,5}=1.8$ Hz, H-4), δ_C 98.2 (C-4), 101.5 (C-1), 152.3 (C-3).
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16. Compound **4a**: 90% yield, white foam, mp 95–100°C, $[\alpha]_D$ −97 (*c* 1.0, $CHCl_3$); **4b**: 82% yield, syrup, $[\alpha]_D$ −61 (*c* 0.9, $CHCl_3$); **4c**: 66% yield from **2c**, white solid, mp 86–88°C (EtOAc–hexane), $[\alpha]_D$ −101 (*c* 0.9, $CHCl_3$); **6a**: 75% yield, white needles, mp 99–100°C (EtOAc–hexane), $[\alpha]_D$ −42 (*c* 0.9, $CHCl_3$); **6b**: 80% yield, white solid, mp 185–190°C (dec.) (EtOAc–hexane), $[\alpha]_D$ −50 (*c* 1.5, $CHCl_3$).
17. Selected NMR data (^1H, 200 MHz ^{13}C, 50 MHz). Compound **4a**: δ_H ($CDCl_3$) 3.30 (dd, 1H, $J_{2,3}=2.9$ Hz, H-3), 3.95 (t, 1H, $J_{3,4}=J_{4,5}=9.4$ Hz, H-4), 4.32 (s, 1H, H-1), δ_C ($CDCl_3$) 68.1 (C-4), 102.7 (C-1); **4b**: δ_H ($CDCl_3$) 3.25 (dd, 1H, $J_{2,3}=3.0$ Hz, H-3′), 4.00 (t, 1H, $J_{3',4'}=J_{4',5'}=9.4$ Hz, H-4′), 4.76 (s, 1H, H-1′), δ_C ($CDCl_3$) 68.3 (C-4′), 102.3 (C-1′); **4c**: δ_H ($CDCl_3$) 3.26 (dd, 1H, $J_{2,3}=2.9$ Hz, H-3), 3.91 (t, 1H, $J_{3,4}=J_{4,5}=9.4$ Hz, H-4), 4.34 (s, 1H, H-1), δ_C ($CDCl_3$) 67.1 (C-4), 102.6 (C-1); **6a** characterized by its 4-*O*-acetate: δ_H (C_6D_6) 3.44 (dd, 1H, $J_{2,3}=4.3$ Hz, H-3), 3.98 (d, 1H, $J_{1,2}=1.6$ Hz, H-1), 5.00 (ddd, 1H, $J_{2,NH}=9.3$

Hz, H-2), 5.47 (t, 1H, $J_{3,4}=J_{4,5}=9.0$ Hz, H-4), δ_C (C_6D_6) 49.0 (C-2), 68.5 (C-4), 100.9 (C-1); **6b**: δ_H (C_6D_6) 3.38 (dd, 1H, $J_{2',3'}=4.0$ Hz, H-3′), 3.88 (t, 1H, $J_{3',4'}=J_{4',5'}=9.4$ Hz, H-4′), 4.96 (d, 1 H, $J_{1',2'}=$ 1.0 Hz, H-1′), 5.18 (ddd, 1H, $J_{2',NH}=9.8$ Hz, H-2′), δ_C (C_6D_6) 49.3 (C-2′), 67.0 (C-4′), 100.7 (C-1′).

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