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$PhBCl_2$ promoted reductive opening of 2′,4′-*O*-*p*-methoxybenzylidene: new regioselective differentiation of position 2′ and 4′ of α-L-iduronyl moieties in disaccharide building blocks ☆

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Abstract—We describe a new protocol for the challenging differentiation of the position 2′ and 4′ of L-iduronyl moieties located at the nonreducing end of various disaccharide building blocks. This methodology is based on the introduction of a 2′,4′-*O*-*p*-methoxybenzylidene group, followed by a totally regioselective reductive opening of this acetal by the $PhBCl_2/Et_3SiH$ reagent system. L-Iduronyl moieties protected by a 4′-*O*-*p*-methoxybenzyl group were thus obtained regioselectively and efficiently.

Heparan sulfate (HS) is a linear sulfated polysaccharide in which a basic disaccharide, composed of an uronic acid (1→4)-linked to a 2-deoxy-2-aminoglucose, is repeated throughout the sequence. HS chains, either at the cell surface or in the extracellular matrix, interact and regulate the activity of numerous proteins such as growth factors, cytokines, chemokines, viral proteins and coagulation factors.[1,2] HS is one of the most heterogeneous biopolymers since various epimerisation and sulfation patterns (sulfoforms) may occur along the chain.[3–5] We have recently published efficient routes to one D-glucuronyl and the two L-iduronyl-containing building blocks **1** and **2** (Scheme 2) that we are currently using for the combinatorial synthesis of HS fragments.[6] One key step in the preparation of **1** and **2** is the differentiation of the positions 2′ and 4′ in the α-L-iduronyl moiety, which is always considered as an important challenge.[7–14] Our first strategy relied on stannylene-mediated regioselective acetylation of position 2′.[6] We describe here that the differentiation of the positions 2′ and 4′ may also be efficiently performed using $PhBCl_2/Et_3SiH$[15,6]-mediated reductive opening of a 2′,4′-*O*-*p*-methoxybenzylidene moiety in Et_2O as solvent.[6] Indeed, in such conditions, the 4′-*O*-*p*-methoxybenzyl product is obtained with total regioselectivity. This $PhBCl_2/Et_3SiH$ based procedure complements nicely the use of $NaBH_3CN/Me_3SiCl$, which was recently described by Martin–Lomas and his co-workers to give the regioisomeric 2-*O*-*p*-methoxybenzyl product with β-L-iduronyl monosaccharide building blocks.[14] To our knowledge, this is the first time that the $PhBCl_2/Et_3SiH$ system has been used to perform regioselective reductive opening of acetals in systems less classical than 4,6-protected hexose-derivatives.[6,15,16]

In the course of this study, we first reinvestigated the preparation of disaccharides **7** and **8** (Scheme 1). Our previous approach[6] was based on the condensation of the easily available L-iduronyl bromide **3**[17–19] with acceptors **5** or **6**.[6] Since L-iduronyl trichloroacetimidates have been reported to be superior donors to fluoro- or thio-derivatives in glycosylation reactions,[8] we decided to study the glycosylating properties of trichloroacetimidate **4** onto acceptors **5** and **6**. Trichloroacetimidate **4** was prepared in two high yielding steps from bromide **3** (Scheme 1), and the glycosylation conditions were optimised with acceptor **5**. We found that the reaction was more efficient when performed with two successive additions of promotor. First 0.02 equiv of TMSOTf was added to a solution of donor **4** (1.3 equiv) and acceptor **5** in dichloromethane, resulting in the rapid formation (20 min) of an *ortho*-ester intermediate, which rearranged smoothly into disaccharide **7** upon further addition of 0.05 equiv of TMSOTf, giving disaccharide **7**

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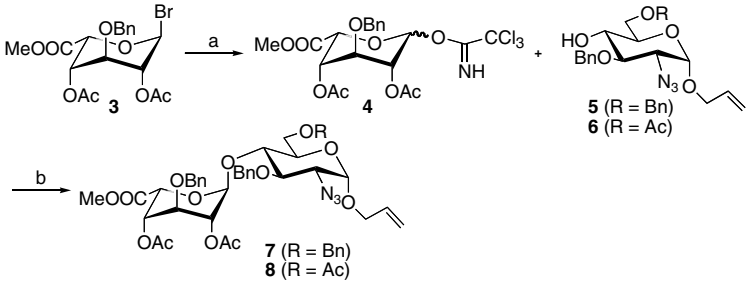
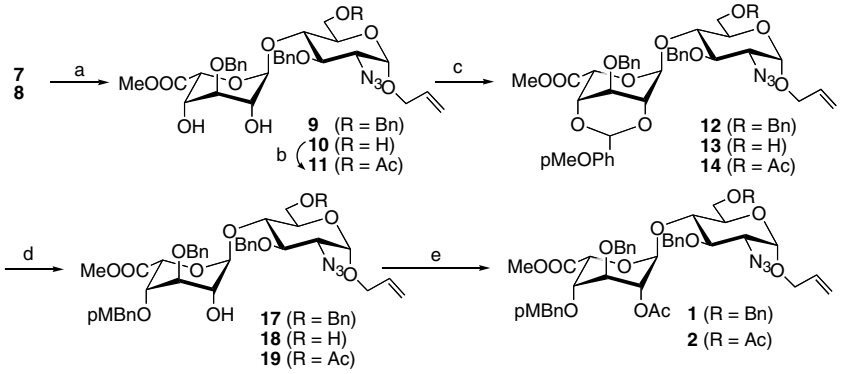


Scheme 1. Reagents and conditions: (a) (i) HgO, $HgCl_2$, acetone/H_2O, 88%. (ii) CCl_3CN, K_2CO_3, CH_2Cl_2, 86%. (b) TMSOTf, CH_2Cl_2, 0 °C, 91% (**7**) and 92% (**8**), see supplementary material for details.



Scheme 2. Reagents and conditions: (a) K_2CO_3, MeOH, quant. (b) PPh_3, DIAD, AcOH, THF, 85%. (c) *p*-MeOPh$(OMe)_2$, camphorsulfonic acid, CH_2Cl_2, 90% (**12**), 62% (**13**, after methanolysis of **15** and **16**), 83% (**14**), see supplementary material for details. (d) $PhBCl_2$, Et_3SiH, 4 Å, Et_2O, −78 to −40 °C, 90% (**17**), 71% (**18**), 84% (**19**). (e) Ac_2O, pyridine, quant.

in 91% isolated yield. Under the same conditions, the condensation with acceptor **6** gave disaccharide **8** in 92% yield. Using this procedure, we were able to prepare up to 9 g of disaccharide in a single batch without affecting the isolated yields.

Disaccharides **7** and **8** were then deacetylated, using standard conditions, giving disaccharides **9** and **10** in quantitative yields (Scheme 2). The introduction of the 2′,4′-*O*-*p*-methoxybenzylidene moiety on **9**, using *p*-anisaldehyde dimethyl acetal and acid catalysis (Scheme 2), proved to be more difficult than anticipated. We found that prolonged heating at high temperature should be avoided in order to preclude the formation of side products, arising probably from a cycloaddition between the azide and allyl moieties.[20] We thus performed the reaction in methylene chloride, which allowed the removal of the methanol formed, and afforded disaccharide **12** in 90% yield. We then used these optimised conditions with triol **10**, but along with the expected disaccharide **13** we obtained the mixed acetals **15** and **16** (Fig. 1). Unfortunately selective methanolysis of the unwanted acetals lead also to partial cleavage of the 2′,4′-*O*-*p*-methoxybenzylidene moiety and thus disaccharide **13** was only isolated in 62% after the two steps. In order to avoid the formation of the side products **15** and **16** and to prepare a precursor of disaccharide **2**, we treated disaccharide **10** with acetyl chloride in pyridine at 0 °C, but the regioselectivity was low and we obtained a mixture of products. We thus turned to a Mitsunobu reaction (Scheme 2), which gave regioselectively the mono-acetylated compound **11** in 85% yield. As expected, this 6-OH protected derivative **11** was more efficiently converted (84%) than **10** to its 2′,4′-*O*-*p*-methoxybenzylidene protected derivative.

The three disaccharides **12**–**14** were then subjected to $PhBCl_2/Et_3SiH$ in Et_2O as described (Scheme 2).[6] In all cases we obtained a single regioisomer in good to excellent yields: **17** (90%), **18** (71%) or **19** (84%). The

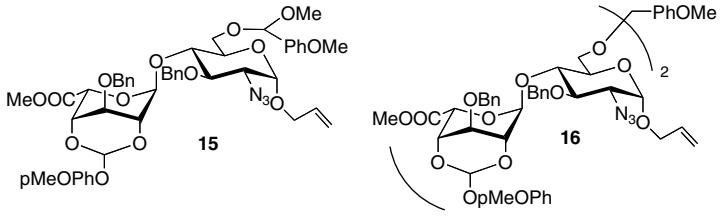


Figure 1. Side products formed in the preparation of disaccharide **13**.

Figure 2. Model for the regioselective complexation of $PhBCl_2$.

regioselectivity of the reaction, that is, the liberation of position 2′, was ascertained by performing an acetylation of these three compounds. Compound **17** lead to the known disaccharide **1**,[6] while disaccharides **18** and **19** gave **2**, whose structure has already been established unambiguously.[6] Moreover, respective 1.21 and 1.34 ppm downfield shifts of the H-2′ chemical shifts of **17** and **19** were observed upon acetylation, confirming the regioselectivity. $PhBCl_2$ has been reported to act as a bulky Lewis acid, which allows regioselective complexation of the less hindered oxygen in cyclic 4,6-acetals.[6,15] This trend is confirmed in this work where, in all the substrates, the 2-azidoglucose moiety is in an axial position, since the α-L-iduronic acid is locked in the $^1C_4$ conformation by the *p*-methoxybenzylidene ring (Fig. 2). Thus, complexation of O-4′ is disfavoured by a gauche interaction with the C-5′ carboxymethyl group, while this interaction is relieved when complexation occurs with O-2′.

We have thus shown that a 2′,4′-*O*-*p*-methoxybenzylidene group may be efficiently introduced in various disaccharides containing an L-iduronyl moiety at the nonreducing end. These acetals were reductively opened, using the $PhBCl_2/Et_3SiH$ system, with total regioselectivity to give the 4′-*O*-*p*-methoxybenzylidene-protected derivatives. In addition to carbohydrate chemistry, such findings should be useful in the area of poly-hydroxylated compounds.

Supplementary material to be published alongside the article

- ^1H and ^{13}C data for both anomers of imidate **4**.
- Glycosylation procedure for the preparation of **7** and **8**.
- Procedure for the preparation of 2′,4′-*O*-*p*-methoxybenzylidene derivatives **12**, **13** and **14** and their ^1H, ^{13}C and elemental analysis data.
- Procedure for the regioselective reductive opening of 2′,4′-*O*-*p*-methoxybenzylidene moieties in **12**, **13** and **14**.
- ^1H and ^{13}C data for **17** and **19**.

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