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Grignard additions to 2-uloses: synthesis of stereochemically pure tertiary alcohols

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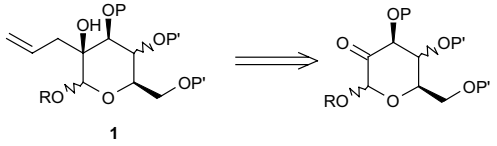
Abstract—The addition of Grignard reagents to a number of 2-uloses has been investigated. Despite initial low diastereoselectivities it was found that tuning the ketone starting materials and studying solvent effects allowed formation of a single alcohol product.

Modified carbohydrate monomers are of both synthetic and pharmaceutical interest. However, the synthesis of chiral tertiary alcohols derived from uloses has received little attention.[1,2] There are only a few examples of Grignard additions to C-2 ketones in the literature[3] and the diastereoselectivities observed vary considerably. This lack of precedent testifies to the difficulty in performing diastereoselective additions of this type to C-2 uloses. During the course of a natural product synthesis we required chiral alcohol **1** and therefore examined its preparation from a carbohydrate source (Scheme 1).

As the C-4 OH was to be removed later in the synthesis, a number of carbohydrate starting materials were considered. The initial starting point was commercially available (+)-(4,6-benzylidene)methyl-α-D-glucopyranoside **2**. Mono-*para*-methoxybenzyl (PMB) protection of **2** is possible using tin acetal chemistry albeit with poor selectivity and only moderate yield however, the two regioisomers are separable by column chromatography.[4] Following literature procedures the desired C-3 OPMB protected alcohol **3** could be generated on a large scale in a 36% yield. Subsequent Swern oxidation of **3** gave the desired C-2 ulose **4** in excellent yield (Scheme 2).[5] Ulose **4** was then treated with allylmagnesium bromide in THF at −78 °C to give a 1:2 mixture of diastereomers **5a** and **5b** in a 78% yield. The diastereoselectivity obtained in this reaction has been previously described by Yoshimura et al.[6] Selective reduction of the benzylidene acetal[7] on treatment with TFA/triethylsilane in CH_2Cl_2 gave a separable mixture of triols **6a** and **6b**. Nuclear Overhauser effect analysis in the ^1H NMR spectra showed the major product to be the undesired C-2 isomer **6a**.



Scheme 1. Retrosynthesis of tertiary alcohol **1**: P and P′ are orthogonal protecting groups.

Although our initial results were therefore disappointing, previous work by Gurjar and Hotha suggested that similar diastereoselective additions were susceptible to solvent effects.[8] Pleasingly, this was found to be case for **4** and by simply changing the solvent from THF to toluene–CH_2Cl_2 (2:1)[9] the reaction proceeded with a 2:1 preference for the desired alcohol **5b**. Varying the solvent further did not lead to any significant enhancement in diastereoselectivity (Table 1).

From the results shown in Table 1 it became apparent that **5b** was formed preferentially in solvents, which are unable to chelate to the Grignard reagent. This suggested that the observed diastereoselectivity may be due to intramolecular chelation of the Grignard reagent. Similar diastereoselective additions on chiral, protected α-hydroxyketones have been achieved by the addition of $MgBr_2 \cdot Et_2O$ prior to organometallic addition.[10] It is thought that a similar chelation mechanism is responsible in this addition and that excess Grignard reagent is,

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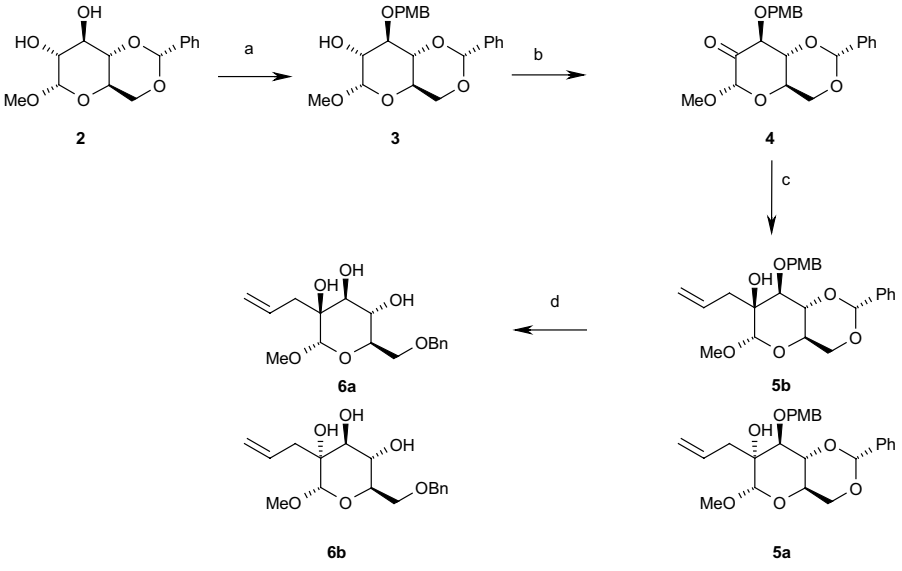
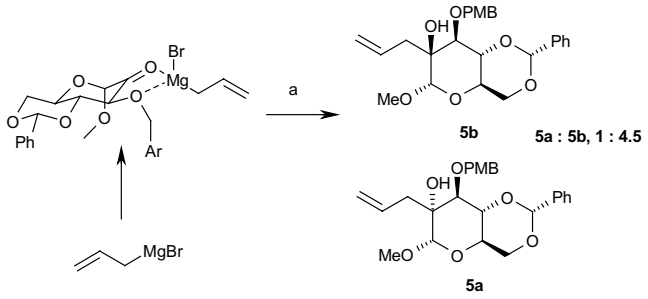


Scheme 2. Reagents and conditions: (a) Bu_2SnO, toluene, reflux, 5 h, then PMB-Cl, TBABr, reflux, 24 h, 36%; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, rt, 100%; (c) allylmagnesium bromide (1 M in Et_2O), THF, −78 °C, 1 h, 78% (2:1, **5a**:**5b**); (d) Et_3SiH (5 equiv), TFA (5 equiv), CH_2Cl_2, 0 °C → rt, 93%, (1:2, **6a**:**6b**).

Table 1. Solvent effects on product distribution for the addition of allylmagnesium bromide to ulose **4**

Entry	Conditions	Ratio **5b**:**5a**	Yield (%)
1	Toluene, −78 °C	2:1	76
2	Toluene–CH_2Cl_2 (2:1), −78 °C	2:1	82
3	Toluene–CH_2Cl_2 (3:1), −78 °C	2:1	79
4	Toluene–CH_2Cl_2 (4:1), −78 °C	2:1	80
5	CH_2Cl_2, −78 °C	1.5:1	74
6	DME, −78 °C	1.2:1	68

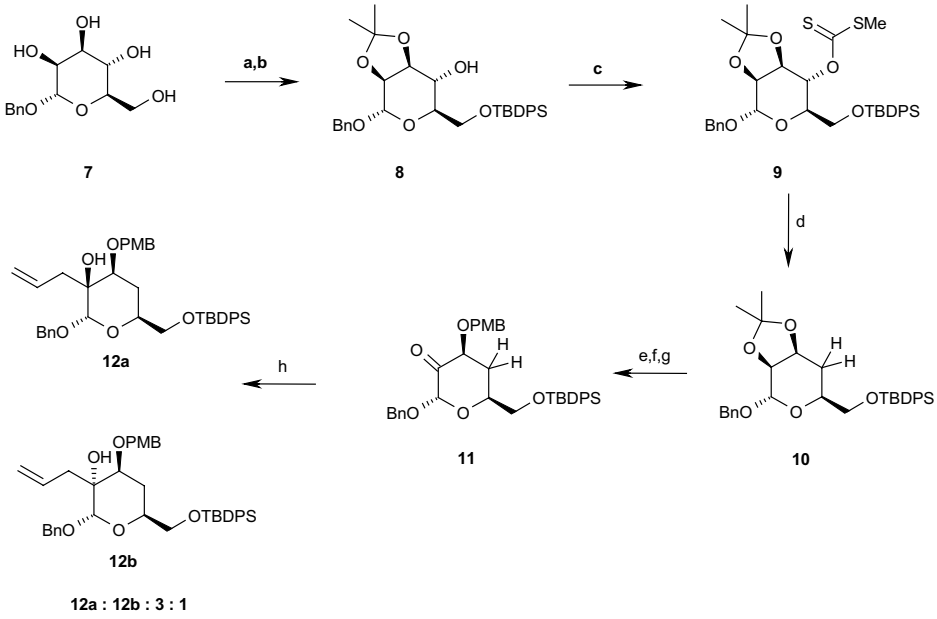
by coordination to the C-3 OH and ketone oxygen, blocking the top face of the ketone in an unreactive conformation. This then allows attack from the lower face by another equivalent of the Grignard reagent leading to the observed diastereoselectivity (Scheme 3). This hypothesis was further supported by the fact that, when we removed the chelating solvent which the Grignard reagent was supplied in (Et_2O) and solubilised the residue with toluene–CH_2Cl_2; the highest levels of diastereoselectivity were observed. Using the conditions described in Scheme 3 led to an optimal 4.5:1 ratio of products in favour of desired alcohol **5b**, which was easily separable from **5a** by chromatography on silica gel.



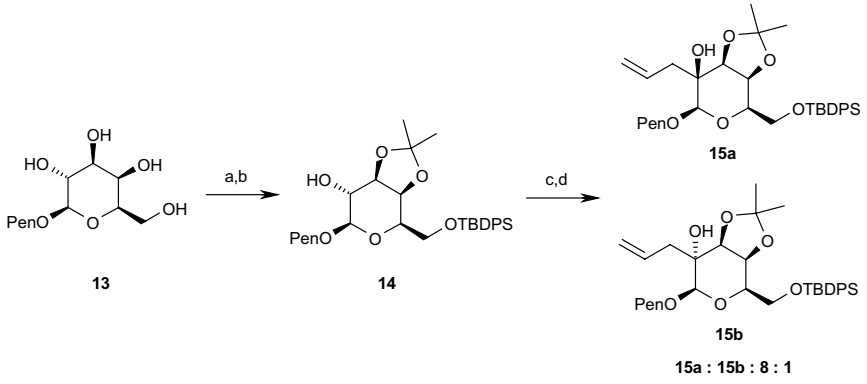
Scheme 3. Reagents and conditions: (a) allylmagnesium bromide, 3:1 toluene–CH_2Cl_2, −78 °C, 84%.

With these initially promising results in hand our attention was then turned to improving the selectivity of the mono-PMB protection. An obvious solution was to switch from glucopyranoside to mannose as the starting carbohydrate. Using standard tin acetal chemistry, PMB protection is possible in excellent yield solely at the C-3 OH.[11] Removal of the C-4 OH prior to the Grignard reaction was also possible. Treatment of commercially available α-benzyl-D-mannose **7** in the presence of imidazole with TBDPSCl in DMF gave the C-6 protected triol. The crude triol was subsequently treated with 2,2-dimethoxypropane in acetone in the presence of a catalytic amount of CSA to give the C-4 alcohol **8** in a 98% yield. Alcohol **8** was then converted into xanthate **9** in quantitative yield upon treatment with NaHMDS in a THF/CS_2 solution at −78 °C followed by addition of iodomethane and warming to room temperature.[12] When subjected to standard Barton McCombie[13] conditions of Bu_3SnH/AIBN in refluxing toluene **9** was smoothly converted into the corresponding 4-deoxymannose derivative **10**. Selective removal of the isopropylidene acetal was accomplished by heating **10** in a 4:1 $AcOH/H_2O$ solution at 80 °C for 2 h. Selective C-3 OH PMB protection followed by Swern oxidation gave the desired 4-deoxyulose **11**. Treatment of ulose **11** with our optimised Grignard conditions gave a 3:1 mixture of alcohols in favour of desired alcohol **12a** (Scheme 4). This marginal lowering of diastereoselectivity is ascribed to the absence of the second ring making **11** more flexible (cf. ulose **4**).

With the second ring required to enhance the diastereoselectivity, a modified approach to alcohol **1** starting from β-D-galactose was devised. It was reasoned that as the C-4 OH is β in galactose a suitable protection strategy might allow better diastereoselectivity. Synthesis of β-*O*-pentenylgalactose **13** from β-D-galactose pentaacetate has been previously reported in the litera-



Scheme 4. Reagents and conditions: (a) TBDPSCl, DMF, imidazole, rt; (b) 2,2-dimethoxypropane, acetone, CSA (cat), 98% over two steps; (c) THF, CS_2 then NaHMDS (1 M in THF), 20 min, −78 °C; then MeI, −78 °C → rt, 100%; (d) Bu_3SnH, AIBN, toluene, 90 °C, 84%; (e) AcOH–H_2O (4:1), 80 °C, 2 h, 78%; (f) Bu_2SnO, MeOH, reflux, 2 h, then DMF, PMB-Cl, CsF, NaI, rt, 24 h, 93%; (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, rt, 100%; (h) allylmagnesium bromide, 3:1 toluene–CH_2Cl_2, −78 °C, 1 h, 78% (3:1, **12a**: **12b**).



Scheme 5. Reagents and conditions: (a) TBDPSCl, DMF, imidazole, rt; (b) 2,2-dimethoxypropane, acetone, CSA (cat), 85% over two steps; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C → rt; (d) allylmagnesium bromide, THF, −78 °C, 1 h, 76% over two steps (8:1, **15a**:**15b**).

ture.[14] The *O*-pentenyl group was chosen for its ease of removal at a latter stage in the synthesis. Although it is worth noting that switching from the α-sugar to the β-sugar (cf. **4** or **11** vs **13**) may also have a consequence on the facial selectivity of this addition. In **13** the *cis* C-1 and C-3 substituents occupy equatorial positions, this may lead to the major nucleophilic approach from the opposite lower face. Conversely in **4** and **11** C-1 and C-3 have a *trans* relationship with the C-1 group occupying an axial position and hence, as is observed, directing the nucleophilic attack preferentially from the top face.[15] When **13** was treated with TBDPSCl followed by 2,2-dimethoxypropane as described for the mannose derivative, the C-2 OH alcohol **14** was formed in 85% yield. Swern oxidation of **14** gave the corresponding ulose, which was directly treated at −78 °C with allylmagnesium bromide giving rise to an improved 8:1 mixture of alcohols **15a** and **16b** in favour of the desired alcohol **15a** (Scheme 5).

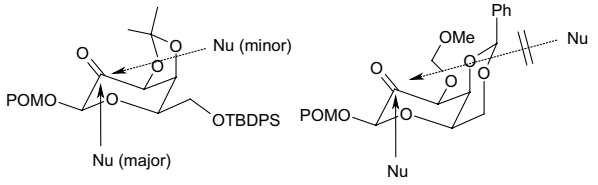
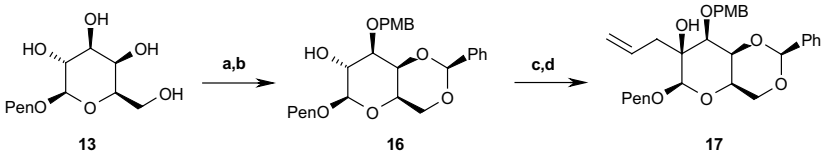


Figure 1. Proposed inhibition of nucleophile approach from the upper face.

This increased diastereoselectivity was thought to be primarily due to the isopropylidene acetal blocking the upper face of **14**. Although the presence of the β-substituents at C-1 and C-3 may also influence this enhanced selectivity (as previously discussed). Therefore, we reasoned that if the protecting group ring was formed between the C-4 and C-6 OH groups the reaction of the nucleophile from the top face might be inhibited altogether (Fig. 1).



Scheme 6. Reagents and conditions: (a) benzaldehyde dimethylacetal, MeCN, CSA (cat), reflux, 1 h, 88%; (b) Bu_2SnO, toluene, reflux, 2 h, then PMB-Cl, TBAI, reflux, 24 h, 79%; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, $-78\,^{\circ}C \rightarrow$ rt; (d) allylmagnesium bromide, THF, $-78\,^{\circ}C$, 1 h, 76% over two steps.

Table 2. Addition of Grignard reagents to ulose **16**

Entry	Conditions	Yield (%)
1	MeMgBr (3 equiv), THF, $-78\,^{\circ}C$	88
2	EtMgBr (3 equiv), THF, $-78\,^{\circ}C$	70
3	PhMgBr (3 equiv), THF, $-78\,^{\circ}C$	67

Accordingly, derivative **13** was treated with benzaldehyde dimethyl acetal in MeCN at reflux in the presence of a catalytic amount of CSA to give the 4,6-benzylidene acetal. Mono-PMB protection of 4,6-benzylidene acetal, using tin chemistry, was much more selective than with pyranoside **2** and galactose **13** and occurred in quantitative yield with a 4:1 ratio in favour of the desired C-3 PMB protected alcohol **16**.[16] Swern oxidation of **16** gave the unstable ulose, which was directly treated with allylmagnesium bromide in THF at $-78\,^{\circ}C$. Analysis of the crude reaction mixture showed that alcohol **17** had been formed as a single diastereomer, and could be isolated after chromatography in 76% yield for the two steps. The assigned structure was confirmed by X-ray diffraction analysis of a single crystal of **17** (Scheme 6).

To test the generality of the Grignard addition, three common Grignard reagents were added to the ketone derived from substrate **16** after Swern oxidation. All products were generated as single diastereomers and in good yields (Table 2). It is worth noting that as the size of Grignard reagent increases the yield of product drops. The decrease in yield, albeit small, may be due to the slower reactivity of bulky Grignards as compared to the very reactive allyl Grignard reagent.

In summary, we have shown that 2-uloses derived from a number of modified carbohydrates undergo stereoselective reactions with allylmagnesium bromide. By appropriate choice of carbohydrate starting material and a suitable protection strategy enantiopure C-2 tertiary alcohols can be prepared in excellent yields from a variety of Grignard reagents.

Acknowledgements

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