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New accesses to L-iduronyl synthons

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Abstract

$(PhS)_3CLi$ adds with a total L-*ido* selectivity onto 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-dialdose **2**, opening the way to the most efficient preparation of 1,2,4-tri-*O*-acetyl-3-*O*-benzyl-L-iduronyl synthon **8**. Alternatively, in view of combinatorial syntheses, aldehyde **2** allows a good access to vinylic L-*ido* and D-*gluco* synthons which may be converted into uronic acid by a sequence involving a new aldehyde oxidation by *m*-CPBA in aqueous solution.

Keywords: L-idose; L-iduronic acid; glycosaminoglycans; heparin; organometallic; oxidation.

Glycosaminoglycans (GAGs) are linear sulfated polymers of 2-amino sugars and hexuronic acids. They are essential components of connective tissues and are also present at the cell surface, where they bind and regulate the activity of various proteins.[1] The well known heparin, but also heparan sulfate and dermatan sulfate, are GAGs in which the hexuronic moiety is mainly L-iduronic acid. Synthetic oligosaccharide fragments are precious tools to study GAG/protein interactions,[1a–c] but L-idose or L-iduronic are not readily accessible from natural sources. The preparation of L-*ido* synthons is thus a key point in GAG oligosaccharide synthesis and there is a constant need for their efficient preparation.[2] The dialdose **2** has never been considered as a precursor to L-*ido* compounds, since the addition of Grignard reagents onto dialdose derivatives like **2** was reported to exhibit low diastereofacial selectivity.[3,4] We however, undertook a study of the addition of masked carboxylate nucleophiles on **2**, feeling confident that reagents or reaction conditions favouring an L-*ido* selectivity might be found (Scheme 1).

We began our investigations with vinylic organometallic reagents, since an alkenic moiety may be a good precursor to a carboxylic function. As reported, the addition of vinylmagnesium bromide on **2** in Et_2O gave an L-*ido* **3a** to D-*gluco* **4a** ratio of around 60/40,[4] and variations in the reaction temperature or solvent did not result in significant changes in the diastereoselectivity (Table 1). We then turned to other vinylic organometallic reagents but, neither divinylzinc[5] nor vinyllithium[6] led to an increase of the proportions of the D-*gluco* stereomer,[7] while the vinyl cerium reagent[8] led only to degradation of the starting material. Due to the furanose ring conformational flexibility and various chelation

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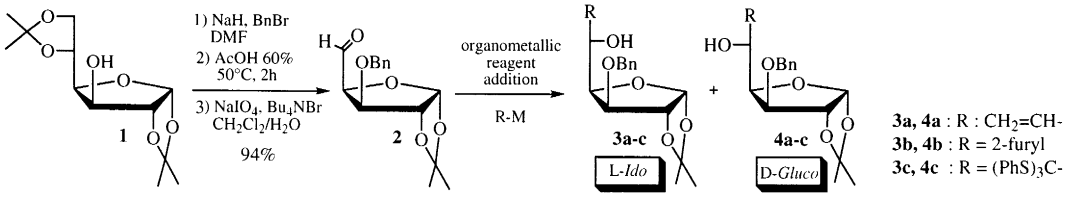


Scheme 1.

possibilities, the stereochemical outcome of organometallic reagent additions on dialdose derivatives like **2** are very difficult to predict, and sterical factors have been shown to be of major importance in the catalyzed addition of allylsilanes.[4] We thus decided to examine the addition of the bulkier carboxylic acid equivalents 2-furyllithium[9] and *tris*-(phenylthio)methyllithium.[10] We found that the L-*ido* diastereomer proportion increased with the steric bulk of the nucleophile (Table 1, entry 7, 9 and 10), and were pleased to find that the reaction was totally stereoselective with $(PhS)_3CLi$,[11] giving compound **3c** as the sole product in 92% yield.[12]

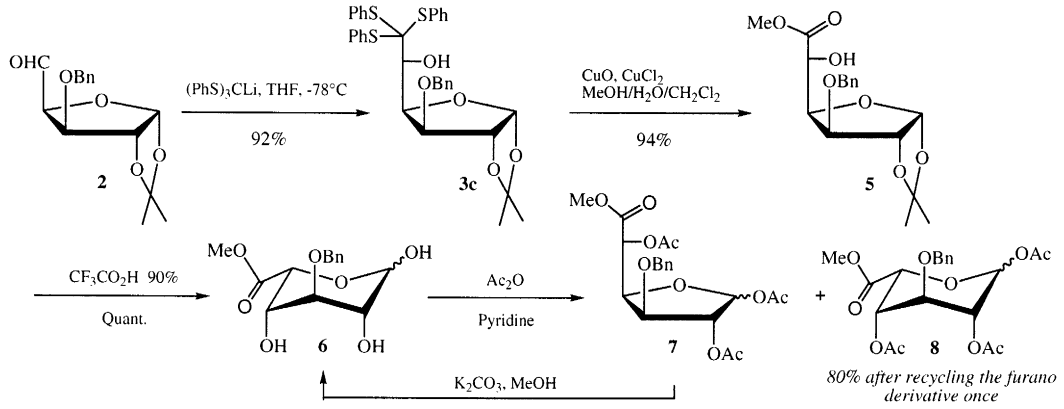
Table 1

Entry	Organometallic reagent	Solvent	Temperature	L-*ido*/D-*gluco* ratio[a]	Isolated yield[b]
1	CH_2=CHMgBr	Et_2O	-40°C	56/44	78%
2	CH_2=CHMgBr	Et_2O	20°C	59/41	93%
3	CH_2=CHMgBr	Toluene	20°C	64/36	85%
4	CH_2=CHMgCl	Toluene	20°C	**50/50**	90%
5	$(CH_2=CH)_2Zn$	Et_2O	0°C	42/58	n.d.
6	CH_2=$CHCeCl_2$	Et_2O	-78°C	-	degradation
7	CH_2=CHLi	Et_2O	0°C	26/74	42%
8	CH_2=CHLi	Et_2O + TMEDA	0°C	37/63	59%
9	2-furyllithium	THF	0°C	60/40	82%
10	$(PhS)_3CLi$	THF	-78°C	**100/0**	92%

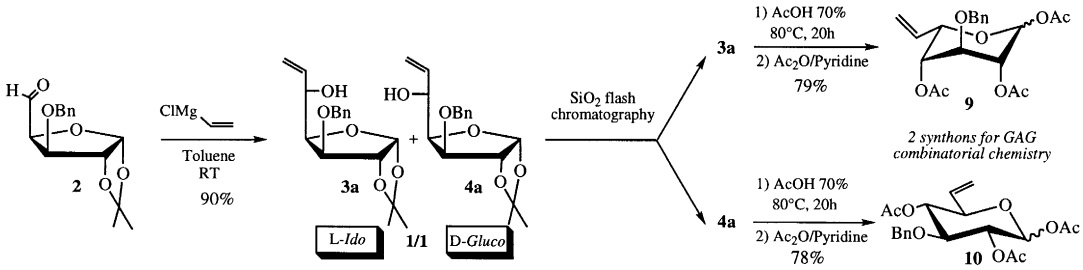
a)Determined in the ^{13}C NMR spectra of the crude reaction mixture.[13] b) After separation of both diastereomers by flash chromatography.

The totally stereoselective addition of $(PhS)_3CLi$ is a key step in the short preparation of synthon **8** (Scheme 2). Orthothioesters were previously converted to the corresponding methyl esters using mercuric salts as catalysts[14] but we found that the much less toxic copper salts mixture $CuCl_2/CuO$[15] allows the same transformation in even better yields. Methyl ester **5** was thus prepared in 94% from **3c**,[16] instead of 85% with mercuric salts. The furano derivative **5** was then converted into its acetylated pyrano counterpart **8**, a useful synthon in which position 3 is already differentiated.[1a,2a] The overall yield of this new preparation is 65% from commercial diacetone glucose **1**, whereas previously reported yields are in the range of 25 to 30%,[1a,2a,f] making our strategy the most attractive access to the useful L-iduronyl synthon **8**.

We have recently prepared a combinatorial library of GAGs sulfo-forms in which the hexuronic acid was restricted to D-glucuronic acid.[17] In order to obtain libraries encompassing the whole of GAGs molecular diversity we also needed to introduce L-iduronic acid in the oligosaccharidic framework. We thus decided to take advantage of the possibility to prepare **3a** and **4a** in an equimolar ratio (Table 1, entry 4) to synthesize L-*ido* and D-*gluco* synthons having the same protecting group pattern and thus suitable for GAGs combinatorial syntheses. Compounds **3a** and **4a** were easily separated by flash chromatography and further converted to their acetylated pyrano counterparts **9** and **10** (Scheme 3).

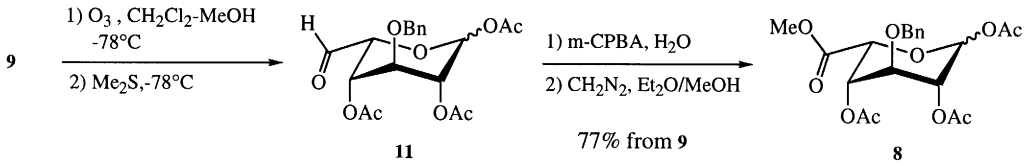


Scheme 2.



Scheme 3.

Compounds **9** and **10** are new L-iduronyl and D-glucuronyl synthons, in which a double bond is used as a carboxylic acid precursor, and preliminary works have shown that they may be transformed into efficient glycosyl donors. Their alkenic moiety may be easily converted into a carboxymethyl function using a three-step protocol involving a new aldehyde oxidation by *m*-CPBA in aqueous solution[18] (Scheme 4). Aldehyde **11**, generated by ozonolysis of **9** followed by reductive workup, was thus oxidized into a free carboxylic acid which was further esterified into compound **8** in 77% overall yield. This 'double bond' approach is thus an attractive alternative, in GAGs syntheses, to the use of uronic acids which are always prone to β-elimination or epimerisation in basic conditions.



Scheme 4.

The 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-dialdose **2** is thus a versatile precursor of useful L-*ido* and D-*gluco* synthons for GAGs fragments synthesis. Our new stereoselective access to the L-iduronyl synthon **8** is a keystone in the synthesis of heparin type C_2-symmetric neoconjugates,[19] while the alkenic uronyl synthons **9** and **10** are currently used for the preparation of combinatorial libraries of L-iduronyl and D-glucuronyl containing GAGs.

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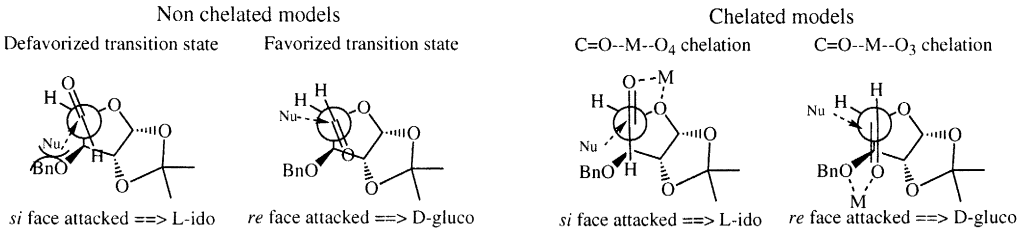

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11. In addition to steric effects, the exceptional diastereoselectivity observed in the addition of $(PhS)_3CLi$ may also take its source in the presence of the sulfur atoms which may promote the formation of a complex between the two reactants.
12. A solution of *tris*-(phenylthio)methane (2.635 g, 7.74 mmol, 1.2 equiv.) in 10 mL dry THF was cooled to −78°C and *n*-butyllithium (5 mL of 1.4 M solution in hexane, 7.09 mmol, 1.1 equiv.) was added. The mixture was kept under stirring at −78°C for 1 h 30 min and then a solution of 1.8 g aldehyde **2** (6.45 mmol) in 10 mL dry THF was added dropwise. After 1 h at −78°C and warming to room temperature, the reaction was quenched with 50 mL aqueous saturated NH_4Cl solution. The aqueous phase was extracted with Et_2O (3×50 mL), the combined organic phases were washed with brine (50 mL), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel flash chromatography, eluting first the excess *tris*-(phenylthio)methane with AcOEt/petroleum ether 10/90 and then **3c** with AcOEt/ CH_2Cl_2 20/80, giving 3.7 g (5.93 mmol, 92%) which may be recrystallized from AcOEt/ petroleum ether 20/80 : mp 110°C. ^{1}H NMR (250 MHz, $CDCl_3$, ref. TMS) δ 7.730–7.650 (m, 6H, Ph), 7.380–7.190 (m, 12H, Ph), 7.110–7.030 (m, 2H, Ph), 6.004 (d, 1H, J=3.5 Hz, H_1), 4.805 (dd, 1H, J=3.5, 2.5 Hz, H_4), 4.525 (d, 1H, J=3.5, H_2), 4.492 (d, 1H, J=12.0 Hz, CH_2Ph), 4.220 (dd, 1H, J=7.0, 2.5 Hz, H_5), 4.215 (d, 1H, J=12.0 Hz, CH_2Ph), 3.604 (d, 1H, J=3.5 Hz, H_3), 3.280 (d, 1H, J=6.5 Hz, OH), 1.496 and 1.323 (2s, 6H, CMe_2). ^{13}C NMR (62.9 MHz) δ: 136.9–136.5, 131.3, 129.1–127.6 (arom.), 112.1 (CMe_2), 104.1 (C_1), 83.0/81.8 (C_4/C_5), 79.9 (C(SPh)$_3$), 77.7 (C_2), 72.8 (C_3), 27.1/26.5 (CMe_2). Anal. calcd for $C_{34}H_{34}O_5S_3$: C, 65.99; H, 5.54; O, 12.93; S, 15.54. Found: C, 65.71; H, 5.56; O, 13.23; S, 15.32. $[\alpha]_D^{32}$=13 ($CHCl_3$, 1.1). IR (KBr) : 3525 cm^{-1} (ν_{OH}); 3047 cm^{-1} ($\nu_{CH\ arom}$).
13. For the vinyl derivatives **3a** and **4a** the diastereomeric ratio was determined using peaks at δ 116.86/115.75 (=CH_2; L-*ido*/D-*gluco*); 111.69/111.48 (CMe_2 L-*ido*/D-*gluco*); 104.93/104.80 (C_1; D-*gluco*/L-*ido*). For the 2-furyl derivatives **3b** and **4b**, signals at δ 107.49/107.31 and 66.07/65.64 were used, the stereochemistry of the major product being ascertained after ozonolysis (Schmidt, G.; Fukuyama, T.; Akaska, K.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 259–261) and methylation with diazomethane which gave compound **5**. For the *tris*-phenylthio product **4c**, only one stereomer was detected by ^{1}H and ^{13}C NMR.

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