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Regio and Stereoselective Conversion of Δ^4-Uronic Acids to L-Ido- and D-Glucopyranosiduronic Acids

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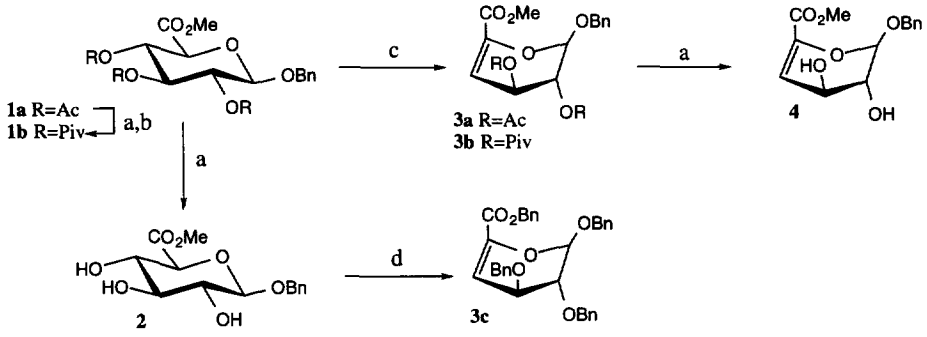
Abstract: Synthesis of L-ido- and D-glucopyranosiduronic acids was performed starting from protected Δ^4-uronic acids **3a-f**. Bromination of the C-4,5 double bond provided the trans-diaxial bromohydrin derivatives **6a-d**, which were converted to the corresponding epoxides **7a-d** in high yields. Direct reduction of these epoxides using borane-tetrahydrofuran complex afforded the D-glucopyranosiduronic acids **9b-d**, while Lewis acid rearrangment through the C-4 keto intermediate **10b-d** afforded the L-idopyranosiduronic acids **11b-d**.

Glycosaminoglycans (GAGs) regulate a number of important biological events through their interaction with diverse proteins.[1] Synthetic oligosaccharide sequences of GAGs, complementary to their protein binding sites, are the targets of our synthetic program. These sequences are ideally suited for gaining insight into the structure-activity-relationship of GAG-protein interactions. GAGs consist of disaccharide repeating units composed of either β-D-glucopyranosiduronic acid (β-D-GlcAp) or α-L-idopyranosiduronic acid (α-L-IdoAp) and hexosamine residues to form linear chains containing *O*-sulfo, *N*-sulfo and *N*-acetyl groups. Polysaccharide lyases break down GAGs into oligosaccharides that contain a non-reducing terminal Δ^4-uronic acid residue.[2] Our laboratory is exploring the use of these oligosaccharides as building blocks for the synthesis of larger GAG oligosaccharides. This approach requires the stereochemically controlled conversion of the non-reducing terminal Δ^4-uronic acid residues to either D-GlcAp or L-IdoAp.

To develop a general strategy for the regio and stereoselective conversion of the Δ^4-uronic acid residues into D-GlcAp or L-IdoAp, the glycal derivatives **3a-f** were chosen as model compounds. These were synthesized from the known methyl (benzyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosid)uronate (**1a**), and **2**, obtained by deacetylation[3] of **1a** (Scheme 1). β-elimination of **1a** and **1b** using 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU)[4] gave the corresponding glycals **3a** and **3b**. The benzyl protected glycal **3c** was obtained in one step by benzylation and β-elimination of **2** using silver oxide (Ag_2O). Deacetylation of **3a** followed by silylation of **4** using 1,3-dichloro-1,1,3,3-tetraisopropyl-1,3-disiloxane ($TIPDSCl_2$) in pyridine or *tert*-butyldimethylsilyl chloride (TBDMSCl) with imidazole afforded the silyl derivatives **3d** (88%) and **3e** (quant.). Isopropylidenation (methoxypropene, *p*-toluenesulfonic acid) of **4** gave the methyl 2,3-di-*O*-isopropylidene β-D-glucopyranuronate **3f** (44%).

Initially, the anti-Markovnikov addition of water to the Δ^4-uronic acids was tested using direct methods based upon those of similar enol-ethers undergoing hydroboration[5] or epoxidation[6]. Hydroboration of **3a** and **3c** using borane-methyl sulfide, borane-tetrahydrofuran complex or 9-borabicyclo[3.3.1]nonane under a variety of conditions failed. An alternative approach relying on direct epoxidation of **3e** and **3f** by using *m*-chloroperbenzoic acid (dichloromethane reflux)[7] or Camps[6] reagent failed. In the latter case a 5-fluoro derivative was isolated after extended reaction times (up to 2 weeks) together with a significant amount of unreacted glycal.



Scheme 1

(a) NaOMe, MeOH, rt; (b) Piv-Cl, Pyridine, rt, 12h (65-70% from **1**); (c)DBU, CH_2Cl_2, rt, 7-30h (90%); (d)Ag_2O, BnBr, DMF, rt, 48h (40%)

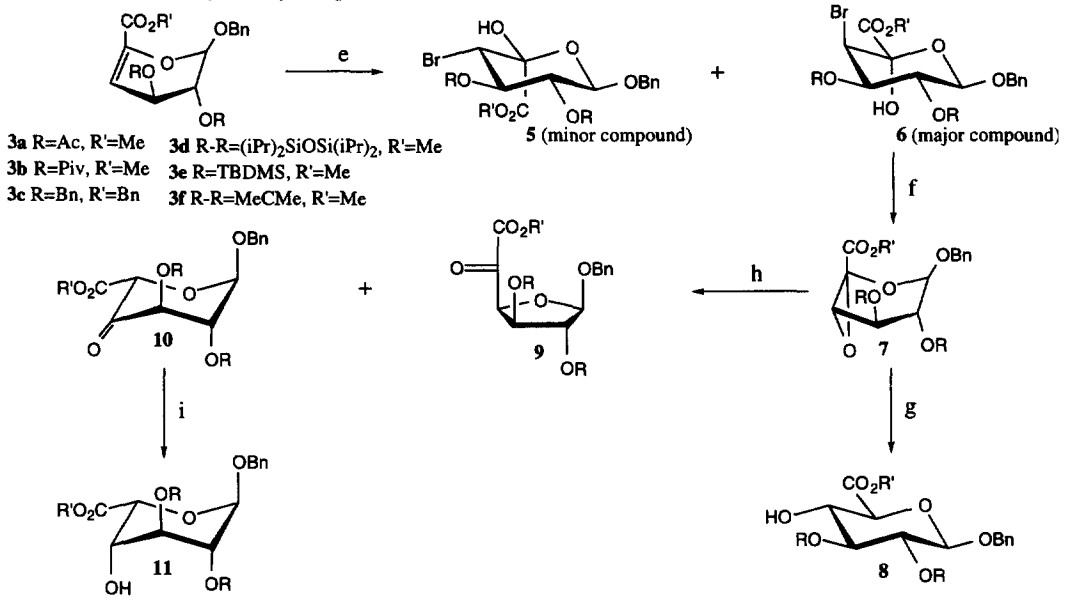
Indirect epoxidation through the intermediate trans-diaxal bromohydrin was performed next (Scheme 2). Reaction of the Δ^4-uronates **3a-d** with N-bromosuccinimide (NBS) in aqueous tetrahydrofuran (THF) afforded a mixture of trans-diequatorial and trans-diaxial bromohydrins **5a-d** and **6a-d** with good (**5a**:**6a**=1.0:3.5, 57%; **5c**:**6c**=2.3:7.2, 95%) to excellent selectivity and yields (**5b**:**6b**=1.0:4.0, 99% **5d**:**6d**=1.0:9.8, 96%). The structure and absolute configurations were confirmed by fast atom bombardment-mass spectroscopy (FAB-MS) and by the vicinal coupling constants obtained by ^{1}H NMR.[8] Unexpectedely, reaction of **3e** and **3f** with NBS failed. The steric hindrance generated by the presence of the two bulky TBDMS groups in **3e** might offer a partial explanation for this observation.

Treatment of the trans-diaxial bromohydrins **6a-d** with DBU in acetonitrile or Ag_2O in DMF:THF afforded the corresponding epoxide products in good to excellent yields. However, the epoxides obtained with DBU display instability during work-up and purification, affording lower yields (**7a**, DBU-CH_3CN, 15%; **7b**, DBU-CH_3CN, 20%; Ag_2O, DMF:THF, 67%; **7c**, DBU-CH_3CN, 67%; Ag_2O, DMF:THF, 60%). In the case of the silyl acetal compound **3d**, the corresponding epoxide was obtained without further purification in excellent yield (Ag_2O, DMF:THF, 92%). The advantage of using Ag_2O is the ready removal of the insoluble silver salts by filtration which did not result in the product decomposition observed on the work-up of DBU generated epoxides. The C5 configurations for compounds having a quaternary C5 position (**5**, **6** and **7**) could not be assigned by ^{1}H NMR, but can be presumed on the basis of the chemistry used for their preparation and subsequent reactions.

Direct reduction of epoxides **7b-d** with boran-tetrahydrofuran complex (BH_3.THF) afforded the D-GlcAp derivatives in low (**8b**, 18%; **8d**, 31%) to good yields (**8c**, 84%). During this reaction, a more polar product was formed. Although it was not isolated, it probably resulted from ester reduction or borate complexation to the newly formed hydroxyl group. The stereochemical outcome of this reaction suggests an initial complexation between the epoxide oxygen and the borane. ^{1}H NMR spectroscopy[8] and physical data for **8c** were in agreement with those previously reported.[9]

The reaction of epoxide **7c** with boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) led in nearly quantitative yield to the C-4 keto product **10c**. Structural identification of **10c** was not possible from initial ^{1}H NMR.[8] However, two of the remaining four ring protons were singlets, indicating either very small vicinal coupling or no adjacent protons. The presence of the ketone functionality was observed by ^{13}C NMR showing a signal at 188 ppm, and IR showing two carbonyl stretches, one at 1762cm^{-1}, and one at 1758cm^{-1}, indicated a second carbonyl in addition to that of the ester. Mass spectroscopy showed equivalent molecular-ions for **7c** and **10c**. However, treatment of the epoxide **7b** with $BF_3{\cdot}OEt_2$ afforded a complex mixture of products, probably due to a fluorine addition to the epoxide.[10] Investigation of a number of other Lewis acid catalysts for the rearrangment of **7b** to **10b** revealed that an apparent furanoside product **9b** was formed by ring contraction competing with hydrogen migration. Furanoside **9b** showed a carbonyl signal in ^{13}C NMR, and has the same molecular-ion as the pyranoside product **10b**.[11] The reason of the presence of a furanoside product in Lewis acid-promoted

rearrangment of **7b**, which had not been previously detected for the fully benzyl protected epoxide **7c**, is not well understood. It is possible that either steric or electronic effects, due to the difference in ether *vs.* ester protecting groups, are responsible. Scandium (III) triflate ($Sc(OTf)_3$) provided the best yield and selectivity for the rearrangment of **7b** (**9b**:**10b**=2.3:6.9, 93%). Subsequent hydride reductions of **10b** and **10c** using sodium borohydride in ethanol afforded the α-L-iduronic acid derivatives **11b-c** in excellent yields (90%). However, $Sc(OTf)_3$ promoted rearrangment of the epoxide **7d** leading to the furanoside derivative as the major product (**furanoside**:**pyranoside 11d**=3.8:1.0, 40%). Evidence of the formation of the desired α-L-IdoAp **11b-d** was obtained by proton NMR.[7] A typical vicinal coupling for the $^1C_4$ chair conformation of IdoAp of $J_{1,2} = J_{4,5} < 1$Hz was observed. Additionally, long range coupling between the 2,4 and 1,3 protons displays the equatorial orientation of all four protons. Moreover, in **11b**, a nuclear Overhauser effect (NOE) was observed between H-5 and an anomeric benzyl methylene proton.



Scheme 2

(e) NBS, THF:H_2O (2:1), rt, 12h (57-96%); (f) Ag_2O, DMF:THF (2:1), rt, 7h (60-92%); (g) BH_3.THF, THF, rt, 8h (18-84%); (h)$Sc(OTf)_3$, $CDCl_3$, rt, 30min (63-93%); (i) $NaBH_4$, EtOH, 30min, rt (90-95%).

Conversion of Δ^4-uronic monosaccharides has been achieved through stereoselective epoxide opening using appropriate reagents to give either α-L-IdoAp or β-D-GlcAp. We will use this strategy for the conversion of the terminal Δ^4-uronic residue of oligosaccharides obtained by lyase treatment of GAGs. These C-4 IdoAp or GlcAp acceptors should be incorporated in GAG oligosaccharides after introduction of a neighboring participating group at the reducing end, activation to a glycosyl donor and selective *O*-deprotection and subsequent sulfation.

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8. Selected ^{1}H-NMR data for compounds **6-12** [values of δ_H (500 MHz) were measured for solutions in $CDCl_3$ containing tetramethylsilane internal standard]: **6b** δ_H = 4.17 (s, 1 H, OH), 4.57 (br s, 1H, H-2), 4.64 (d, 1H, H-4, overlapping with CH_2Ph), 5.17 (d, 1H, $J_{1,2}$ = 8.1 Hz, H-1), 5.32 (dd, 1 H, $J_{2,3}$ = 10 Hz, $J_{3,4}$ = 3.9 Hz, H-3). **7b** δ_H = 3.60 (m, 1 H, $J_{3,4}$ < 1 Hz, H-4), 4.84 (ddd, 1 H, $J_{1,2}$ 9.4 Hz, H-2), 4.98 (dd, 1 H, H-1), 5.19 (m, 1H, H-3). **8b** δ_H = 3.92 (d, 1 H, $J_{4,5}$ = 9.7 Hz, H-5). 3.98 (m, 1 H, H-4), 4.61 (d, 1 H, $J_{1,2}$ = 7.9 Hz, H-1), 5.03-5.13 (m, 2 H, H-2,3). **10b** δ_H = 5.01 (s, 1 H,H-5), 5.18 (s, 1 H, H-1), 5.61-5.68 (m, 2H, H-2,3). **11b** δ_H = 4.43 (dd, 1 H, $J_{3,4}$= 8.1 Hz, H-4), 4.56 (dd, 1 H, $J_{2,3}$ = 5.5 Hz, H-3), 5.05 (m, 1 H, H-5), 5.07 (m, 1 H, H-1), 5.37 (dd, 1 H, $J_{1,2}$ = 1.2 Hz, H-2). **6c** δ_H = 3.56 (dd, 1 H, $J_{1,2}$ = 8.0 Hz, $J_{2,3}$ = 8.9 Hz, H-2), 3.95 (dd, 1 H, $J_{3,4}$ = 11 Hz, H-3), 3.33 (d, 1 H, H-4), 4.58 (d, 1 H, OH), 5.15 (d, 1 H, H-1). **7c** δ_H = 3.54 (dd, 1 H, $J_{1,2}$ = $J_{2,3}$ = 5.5 Hz, H-2), 3.64 (s, 1 H, H-4), 3.94 (d, 1 H, H-3), 4.90 (d, 1 H, H-1). **8c** δ_H = 2.73 (d, 1 H, $J_{4,OH}$ = 2.3 Hz, OH), 3.48-3.55 (m, 2 H, H-2,3), 3.85 (d, 1 H, $J_{4,5}$ = 9.8 Hz, H-5), 3.90 (m, 1 H,H-4), 4.55 (d, 1 H, $J_{1,2}$ = 7.3 Hz, H-1). **10c** δ_H = 3.99 (s, 1H, H-5), 4.60 (d, 1H, $J_{2,3}$ = 6.9 Hz, H-2), 5.26 (s, 1H, H-1), 5.66 (d, 1H, H-3). **11c** δ_H = 3.57 (d, 1 H, $J_{4,OH}$= 7.5 Hz, OH), 4.13 (dd, 1 H, $J_{1,2}$ = 2.5 Hz, $J_{1,3}$ < 1 Hz, H-1), 4.18 (dd, 1 H, $J_{2,3}$ = 6.0 Hz, H-2), 4.59 (m, 1 H, H-4), 4.75 (dd, 1 H, $J_{3,4}$ = 5.0 Hz, H-3), 5.12 (m, 1 H, H-5). **6d** δ_H = 4.03 (t, 1 H, $J_{1,2}$ = $J_{2,3}$ = 7.5 Hz, H-2), 4.20 (dd, 1 H, $J_{3,4}$ = 3.7 Hz, H-3), 4.38 (d, 1 H, H-4), 4.94 (d, 1 H, H-1). **7d** δ_H = 3.51 (s, 1 H, H-4), 3.67 (t, 1 H, $J_{1,2}$ = $J_{2,3}$ = 7.6 Hz, H-2), 4.12 (d, 1 H, H-3), 4.77 (d, 1 H, H-1). **8d** δ_H = 2.67 (d, 1 H, $J_{4,OH}$ = 2.1 Hz, OH), 3.64-3.66 (m, 2 H, H-2,5), 3.79 (m, 1 H, H-4), 3.85 (t, 1 H, $J_{2,3}$ = 9.8 Hz, H-3), 4.33 (d, 1 H, $J_{1,2}$ = 7.4 Hz, H-1). **Acetylated 11d** ($^1C_4$) δ_H = 4.52 (d, 1 H, $J_{4,5}$= 1.7 Hz, H-5), 4.53 (m, 1 H, H-2), 4.93 (m, 1 H, H-3), 4.98 (d, 1 H, $J_{1,2}$ = 3.7 Hz, H-1), 5.66 (d, 1 H, H-4).
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11. In the case of **10b**, the C5 configuration was confirmed by the subsequent ^{1}H-NMR analysis of **11b**. The C4 configuration in the furanoside **9b** was assigned on the basis of the ^{1}H coupling constants. H-1, H-2 and H-3 have a trans configuration and the following J values : $J_{1,2}$ = 4.6 Hz and $J_{2,3}$ = 4.0 Hz. The higher value of $J_{3,4}$= 6.5 Hz indicates a cis relationship between H-3 and H-4.

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