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Regioselective Synthesis of Derivatives of L-Idopyranuronic Acid: A Key Constituent of Glycosaminoglycans

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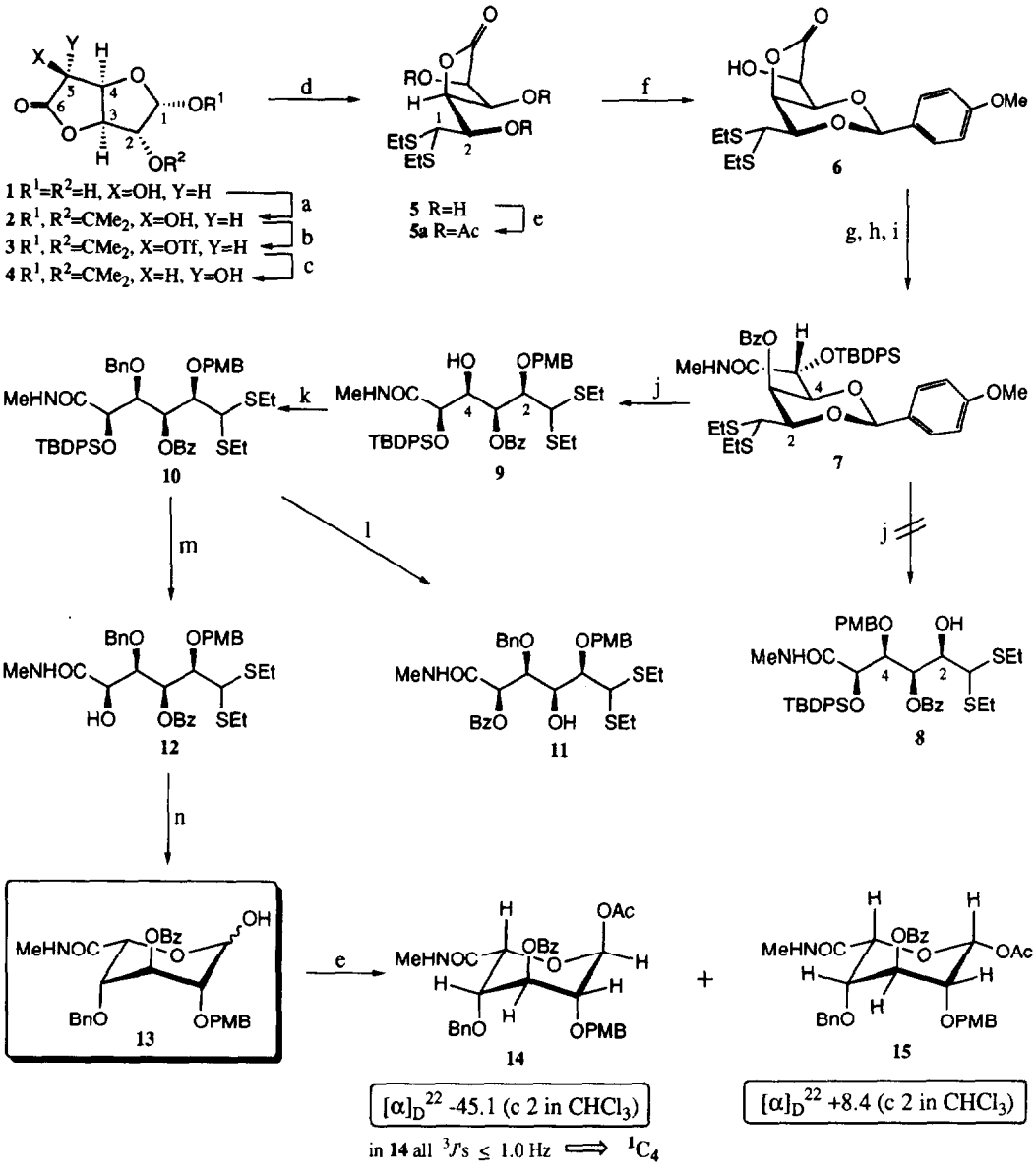
Abstract: Synthesis of new and potentially universal L-idopyranuronic glycosyl-donor and/or -acceptor **13** was performed starting from D-glucofuranurono-6,3-lactone **1**. After simple C-5-epimerization, C-1-thioacetalization and regioselective *p*-methoxybenzylidenation to the hydroxylactone **6**, the lactone ring was opened. The resulting diolamide stereoselectively protected, providing compound **7**. Regioselective reductive cleavage of the 1,3-dioxane ring and subsequent deprotection afforded the target molecule **13**.

Glycosaminoglycans regulate a number of important biological events by interacting with a diverse group of proteins[1]. For example, heparin, heparan sulfate and dermatan sulfate inhibit the serine protease thrombin by binding to antithrombin III and heparin cofactor II, causing an inhibition of blood coagulation[2]. Synthetic oligosaccharide sequences of these polydisperse glycosaminoglycans, corresponding to protein binding sites, are the targets of our synthetic program. These sequences are ideally suited for gaining insight into the structure - activity relationship of glycosaminoglycan - protein interactions. The α-L-idopyranuronic acid (α-L-IdoAp) is a key constituent of glycosaminoglycuronans and their synthetic oligosaccharide analogues and mimetics. α-L-IdoAp alternates with hexosamine residues to form linear chains that can be *N*-sulfated, *O*-sulfated and *N*-acetylated. Since α-L-IdoAp and its derivatives are not commercially available, we devised an approach for the synthesis of potentially universal L-IdoAp-glycosyl-donor and/or -acceptor. Our strategy is based on the orthogonal stability of the selected protecting groups.

The multistep procedures in previous reports[3] provide low yields and/or poor stereocontrol and require multiple chromatographic purifications. Therefore, a strategy was developed to prepare an L-IdoAp-synthon in high overall yield, using a minimum number of chromatographic steps and in a fully regio- and stereo-controlled manner.

The efficiency of this approach is demonstrated by the optimal selection and order of introduction and removal of protective groups, as well as by the convenient C-5-epimerization to afford the desired target molecule. Thus, the 1,2-*O*-isopropylidene-β-L-idofuranurono-6,3-lactone **4** (Scheme) was obtained in high yield from D-glucofuranurono-6,3-lactone **1** through a slight modification of the procedure of Csuk *et al.*[4] After the inversion of configuration at C-5, the resulting trifluoroacetate was readily hydrolyzed to **4** by simply adding water to the reaction mixture. Treatment of **4** with a 3 / 1 - ratio of ethanethiol and concentrated hydrochloric acid resulted in 1,2-de-isopropylidenation with simultaneous C-1-thioacetalization providing compound **5** in quantitative yield.



Scheme

(a) acetone, cat. H_2SO_4, rt, 4 h; (b) Tf_2O, Py, CH_2Cl_2, -20°C, 1 h; (c) F_3CCO_2Na, DMF, rt, 30 min; H_2O (92% from **1**); (d) EtSH, conc. HCl, 4°C, 1 h (quant.); (e) Ac_2O, Py (quant.); (f) anisaldehyde, cat. $TsOH.H_2O$, drierite, 3 h (86%); (g) 2M H_2NMe in THF, 4°C, 15 min (quant.); (h) TBDPSCl, Im., DMF, rt, 8 h (92%); (i) BzCl, Et_3N, DMAP, CH_2Cl_2, rt, 7 d (90%); (j) $NaB(CN)H_3$, TMSCl, MeCN, MS 4A, 0°C, 2 h (quant.); (k) BnBr, Ag_2O, MS 4A, CH_2Cl_2, rt, 12 h (86%); (l) TBAF, THF, 12 h (76%); (m) 3HF.NEt_3 THF, rt, 48 h (91%); (n) $HgCl_2$, HgO, acetone, H_2O, rt, 3.5 h (89% from **10**)

To facilitate structural characterization, **5** was acetylated to give **5a**. Treatment of the thioacetallactone **5** with excess *p*-anisaldehyde in the presence of drierite and a catalytic amount of *p*-toluenesulfonic acid ($TsOH.H_2O$) resulted in the regioselective formation of the 2,4-*O*-*p*-methoxybenzylidene derivative **6**. An attempt to open the lactone ring in **6** by methanolysis clearly demonstrated the expected sensitivity of the corresponding methyl ester and its easy reversion to the starting lactone. To overcome this problem, the ring was opened to L-iduronamide by a reaction with methyl amine in tetrahydrofuran. The fully protected amide **7** was obtained in excellent yield after regioselective 5-*O*-silylation with the bulky *tert*-butyldiphenylsilyl chloride (TBDPSCl)[5] and subsequent 3-*O*-benzoylation.

Suprisingly, the reductive cleavage of the 2,4-*O*-(*p*-methyoxybenzylidene) acetal with sodium cyanoborohydride - trimethylsilyl chloride[6] gave the 2-*O*-(*p*-methoxybenzyl)-derivative **9** with complete regioselectivity and in nearly quantitative yield. According to Johansson and Samuelsson[6] regioselection should have resulted in **8** due to a) the steric bulk exerted by the TBDPS-group on *O*-5 affording kinetic control of the reaction and b) the 'steric-approach control'[7] of the trimethylsilyl electrophile. The opposite regioselectivity, affording **9**, was also observed when using other Lewis acids ($SnCl_4$ or $BF_3.OEt_2$) as electrophiles. Presumably the reason for this 'opposite' regioselection can be explained by the specific surrounding of the both acetal *O*-atoms in **7**: the C-4-oxygen has both a β carbonyl and a β oxygen withdrawing electron density, thus it does not have sufficient basicity to form the intermediate *p*-methoxybenzilium ion. The C-2-oxygen has two β sulfur atoms and should have no trouble donating a lone electron pair to stabilize the oxonium ion. The structure of **9** was unequivocally established by the strong NOE observed between the protons at C-2 and at the thioacetal portions.

After *O*-4-benzylation[8], desilylation under standard conditions, with basic tetrabutylammonium fluoride, caused an *O*-3 → *O*-5-migration of the benzoyl group affording compound **11**. The same reaction in the presence of the nearly neutral $Et_3N.3HF$[9] proceeded cleanly providing the desired alcohol **12**. Deprotection of the thioacetal group, exploiting the high thermodynamic affinity of Hg(II)-salts for sulfur, and subsequent spontaneous pyranose ring closure led to the target molecule **13**. Acetylation of **13** gave the corresponding α- and β-acetyl derivatives in a 6 / 1 - ratio. All compounds were characterized by their ^{1}H-NMR[10] and other physical data. Remarkably, only five chromatographic purification steps were applied throughout the whole reaction sequence (for compounds **4**, **6**, **7**, **10** and **13**).

The L-IdoAp-synthon **13** should be easily incorporated in glycosaminoglycan fragments after: 1) selective *O*-2-deprotection and introduction of a neighboring participating group; 2) *O* -1-activation to a glycosyl donor; 3) selective *O*-4-deprotection to a glycosyl acceptor; 4) selective *O*-2-deprotection and subsequent sulfation. Commonly used uronic esters glycosyl donors are often very unreactive due to the negative influence of the carboxylic group on the stabilization of the intermediate oxocarbenium cation. We propose to decrease this unfavorable interaction by performing the glycosidation with uronamide donors. Chemoselective deamination of the uronamide moiety to a carboxylic acid or ester *via* the *N*-methyl-*N*-nitrosoamide[11] will be subsequently performed.

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10. Selected ^{1}H-NMR data for compounds **4**-**15** [values of σ_H (500 MHz) were measured for solutions in $CDCl_3$]: **4** σ_H = 3.32 (d, 1 H, $J_{5,OH}$ = 3.6 Hz, OH), 4.33 (d, 1 H, $J_{4,5}$ = 0.0 Hz, H-5), 4.79 (d, 1 H, $J_{3,4}$ = 3.1 Hz, H-4), 3.32 (d, 1 H, $J_{5,OH}$ = 3.6 Hz, OH), 5.06 (d, 1 H, H-3), 5.93 (d, 1 H, H-1). **5a** σ_H = 3.82 (d, 1 H, $J_{1,2}$ = 4.0 Hz, H-1), 5.09 (dd, 1 H, $J_{2,3}$ = 7.5 Hz, $J_{3,4}$ = 3.3 Hz, H-3), 5.59 (dd, 1 H, H-2), 5.71 (d, 1 H, $J_{4,5}$ = 5.1 Hz, H-5), 5.78 (dd, 1 H, H-4). **6** σ_H = 3.23 (br s, 1 H, OH), 4.00 (d, 1 H, $J_{2,3}$ = 0.0 Hz, $J_{1,2}$ = 10.3 Hz, H-2), 4.20 (d, 1 H, H-1), 4.31 (br d, 1 H, $J_{4,5}$ = 2.1 Hz, H-5), 4.54 (d, 1 H, $J_{3,4}$ = 0.0 Hz, H-4), 5.11 (s, 1 H, H-3). **7** σ_H = 2.52 (d, 3 H, $J_{HC,HN}$ = 5.5 Hz, H_3CNH), 3.92 (d, 1 H, $J_{2,3}$ = 0.0 Hz, $J_{1,2}$ = 6.9 Hz, H-2), 3.94 (d, 1 H, H-1), 4.02 (d, 1 H, $J_{4,5}$ = 8.2 Hz, H-5), 4.32 (d, 1 H, $J_{3,4}$ = 0.0 Hz, H-4), 5.43 (s, 1 H, H-3), 6.21 (br d, 1 H, *H*-N). **9** σ_H = 1.92 (d, 3 H, $J_{HC,HN}$ = 4.9 Hz, H_3CNH), 3.94 (d, 1 H, $J_{1,2}$ = 2.9 Hz, H-1), 3.98 (dd, 1 H, $J_{3,4}$ = 0.0 Hz, $J_{4,5}$ = 7.3 Hz, $J_{4,HO}$ = 9.9 Hz, H-4), 4.22 (dd, 1 H, $J_{2,3}$ = 8.4 Hz, H-2), 4.38 (d, 1 H, H-5), 5.16 (d, 1 H, *H*-O), 6.09 (d, 1 H, H-3), 6.38 (br d, 1 H, *H*-N). **10** σ_H = 2.01 (d, 3 H, $J_{HC,HN}$ = 4.9 Hz, H_3CNH), 3.84 (d, 1 H, $J_{1,2}$ = 3.6 Hz, H-1), 3.96 (dd, 1 H, $J_{2,3}$ = 7.9 Hz, H-2), 4.18 (dd, 1 H, $J_{3,4}$ = 1.9 Hz, $J_{4,5}$ = 6.1 Hz, H-4), 4.43 (d, 1 H, H-5), 6.01 (dd, 1 H, H-3), 6.50 (br d, 1 H, *H*-N). **12** σ_H = 2.12 (d, 3 H, $J_{HC,HN}$ = 4.9 Hz, H_3CNH), 3.94 (d, 1 H, $J_{1,2}$ = 2.9 Hz, H-1), 3.99 (dd, 1 H, $J_{2,3}$ = 7.1 Hz, H-2), 4.25 (dd, 1 H, $J_{3,4}$ = 2.2 Hz, $J_{4,5}$ = 4.9 Hz, H-4), 4.31 (ddd, 1 H, $J_{5,HO}$ = 7.9 Hz, H-5), 5.90 (dd, 1 H, H-3), 6.21 (br d, 1 H, *H*-N). **14** σ_H = 2.80 (d, 3 H, $J_{HC,HN}$ = 5.4 Hz, H_3CNH), 3.64 (br s, 1 H, H-2), 4.86 (br s, 1 H, H-5), 5.21 (br s, 1 H, H-3), 5.59 (br s, 1 H, H-3), 6.21 (br s, 1 H, H-1), 6.61 (br d, 1 H, *H*-N), all ^3J's in the pyranose portion of the molecule were smaller than 1.0 Hz demonstrating its $^1C_4$ conformation. **15** σ_H = 2.81 (d, 3 H, $J_{HC,HN}$ =5.3 Hz, H_3CNH), 3.67 (ddd, 1 H, $J_{1,2}$ = 1.7 Hz, $J_{2,3}$ = 2.7 Hz, $^4J_{2,4}$ = 0.9 Hz, H-2), 4.69 (d, 1 H, $J_{4,5}$ = 1.7 Hz, H-5), 5.30 (ddd, $J_{3,4}$ = 2.7 Hz, H-4), 5.63 (dd, 1 H, H-3), 5.87 (d, 1 H, H-1).
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