$[PPh_4]^+Cl^-$ (300 mg, 0.8 mmol) in water (20 mL) was added to the mother liquor from this crystallization and a white precipitate was formed and collected by filtration, washed with water (2×10 mL), and dried in vacuum at RT to give 277 mg of an anionic mixture. This mixture was separated by multiple preparative TLC on silica gel, using 3% $MeCN/CH_2Cl_2$ as the mobile phase (detection UV 254 nm). The second band, $R_f = 0.5$ was collected and washed out with MeCN. Evaporation of the solvent from combined fractions gave pure $\mathbf{4}^- PPh_4^+$ (174 mg, 6%). White crystals were obtained by diffusion of Et_2O into a concentrated CH_2Cl_2 solution of $\mathbf{4}^- PPh_4^+$. M.p. 350 °C, elemental analysis calcd (%) for $C_{25}H_{27}B_6P$: B 15.33; found B 14.82.

4,5-I_2-$\mathbf{4}^- PPh_4^+$: A solution of $\mathbf{4}^- PPh_4^+$ (35 mg, 0.083 mmol) in CH_2Cl_2 (10 mL) was treated with several portions of solid I_2 (total 44 mg, 0.17 mmol) in the presence of NEt_3 (0.5 mL) under stirring at RT for 0.5 h. The mixture was extracted with 5% aqueous $Na_2S_2O_3$ (20 mL), the CH_2Cl_2 layer collected and filtered through a short column of silica gel. Evaporation of the filtrate gave pure 4,5-I_2-$\mathbf{4}^- PPh_4^+$ (52 mg, 93%). White crystals were obtained by diffusion of Et_2O vapors into a concentrated CH_2Cl_2 solution of 4,5-I_2-$\mathbf{4}^- PPh_4^+$. M.p. 210 °C; elemental analysis calcd (%) for $C_{25}H_{27}B_6PI_2$: B 9.62; found B 9.38.

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[9] a) Crystal structure data for $C_{25}H_{25}B_6I_2P$: $M_r = 675.08$, white crystal, size $0.2 \times 0.18 \times 0.10$ mm^3, triclinic, space group $P\bar{1}$, $a = 7.9841(6)$, $b = 13.2428(9)$, $c = 13.5646(9)$ Å, $\alpha = 96.149(6)$, $\beta = 92.686(5)$, $\gamma = 92.994(6)°$, $V = 1422.02$ Å^3, $T = 293(2)$ K, $Z = 2$, $\rho_{calcd} = 1.577$ Mg m^{-3}, $F(000) = 652$, $\mu(Mo_{K\alpha}) = 2.28$ mm^{-1}, Data collected with a Siemens P4 four-circle diffractometer ($Mo_{K\alpha}$ radiation $\lambda = 71.073$ pm, graphite monochromator); $\theta_{max} = 25°$. A total of 6152 reflections were measured, 4986 unique ($R_{int} = 0.0277$). Absorption correction empirical (by Ψ-scans), min./max. transmission coefficients 0.2453/0.2990, GoF on F^2 was 1.125, $R1$ ($I > 2\rho(I)$) = 0.0358, $wR2 = 0.0924$. Data/restrains/parameters 4956/0/308. Largest difference Fourier peak and hole 1.511 and -1.173 e Å^{-3}. Refinement used SHELXTL V.5.1 (G. M. Sheldrick, SHELXS-97, University of Göttingen, Göttingen (Germany), **1997**). b) CCDC-175525 (4,5-I_2-$\mathbf{4}^- PPh_4^+$). contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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Conformational Locking of the Glycosyl Acceptor for Stereocontrol in the Key Step in the Synthesis of Heparin**

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Glycosaminoglycans (GAGs), including heparin (**A**), are linear oligosaccharides that consist of amino sugars and uronic acids.[1] Many glycosaminoglycans are involved in vital biological functions[2] but still, little is known about the molecular mechanisms responsible for their action. Much progress toward the synthesis of heparin fragments has been reported

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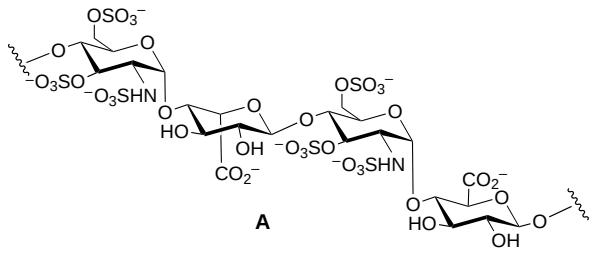

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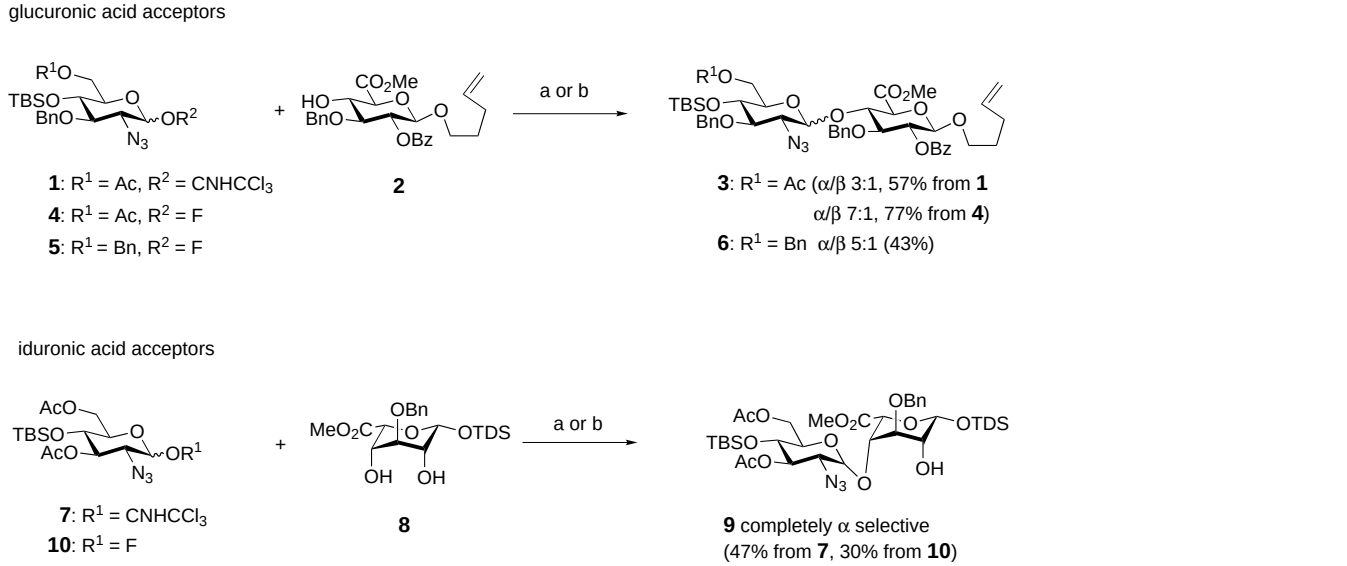
and may provide useful tools for the identification of specific recognition sequences.[3, 4] The most difficult task faced during the assembly of the heparin backbone is the selective installation of the α-glycosidic linkage by coupling glucosamine units and uronic acids. The installation of α-glucosamine linkages, ubiquitous in nature,[5] remains challenging. The C2 amino group of glucosamine is typically masked in the form of a nonparticipating azide[4d, 6] to reduce β-glucoside formation. Anomeric selectivities vary greatly and often require difficult separations. Electronic effects[7] and conformational constraint[8] of the glycosidating agent have been utilized to control the stereochemical outcome of glycosylations. Manipulation of the steric and electronic nature of the glycosyl acceptor to direct glycosylations have received less attention. Two features of the acceptor are known to influence the stereochemical course of the reaction: the intrinsic reactivity of the hydroxy group that functions as nucleophile (axial hydroxy groups are generally less reactive than equatorial hydroxy groups)[9] and steric factors, which result in matched/mismatched pairs of glycosyl donors and acceptors.[10]

Herein we discuss a new method for the stereoselective installation of α-glucosamine linkages by locking the conformation of the monosaccharide acceptor. Several key disaccharide building blocks, previously obtained as anomeric mixtures, were prepared by utilizing this approach.

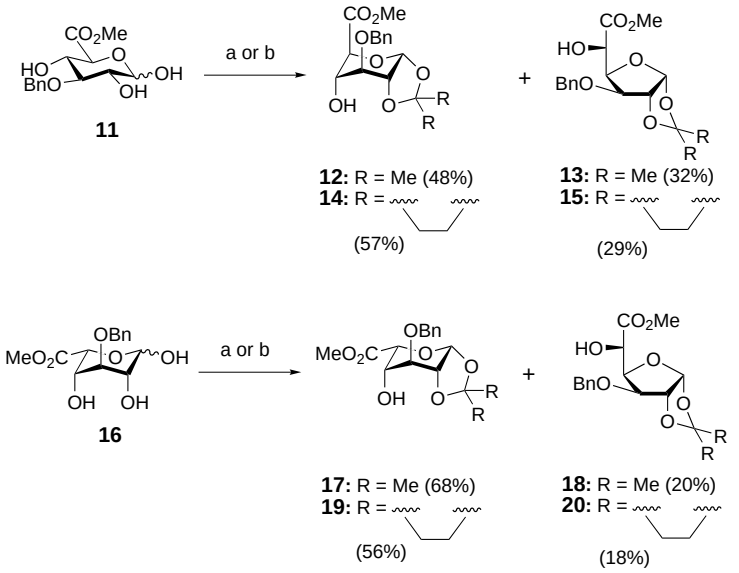
The reaction of C2-azido glucose trichloroacetimidate **1** and fluoride donors **4** and **5**[11] with glucuronic acid acceptor **2**[11] yielded anomeric mixtures of disaccharides **3** and **6** (Scheme 1). Better ratios of α-linked disaccharides were obtained with the slower reacting glycosyl fluorides. Similar results had been reported previously with other glucuronic acid acceptors.[4a,c, 12] Interestingly, glycosylations that involve iduronic acid **8**,[13] resulted exclusively in the formation of α-glucosamine linkages, in accordance with previous reports.[14] To rationalize the markedly different behavior of glucuronic and iduronic acid acceptors, we analyzed the conformational differences of the two monosaccharides. Glucuronic acids preferentially adopt a $^4C_1$ conformation with an equatorial C4 hydroxyl group. Iduronic acid in contrast adopts either a $^1C_4$ conformation with a C4 axial hydroxy group or a skewed-boat $^2S_0$ conformation in oligosaccharide sequences, depending on the substituents on the ring.[15, 16] Apparently, the stereochemical outcome of these glycosylations is related to the conformation of the acceptor.

Based on these observations we intended to use glucuronic acid acceptors in a $^1C_4$ conformation. NMR spectroscopic analysis of glucuronic acids **12** and **14** and iduronic acids **17** and **19**, which carry cyclic isopropylidene protecting groups revealed that these monosaccharides adopt a $^1C_4$ conformation, as judged by the coupling constants ($J_{4,5} \approx 3.5$ Hz ($^4C_1$: $J_{4,5} > 8$ Hz) and $J_{1,2} \approx 2.7$ Hz). Differentially protected uronic acid monomers **12**, **14**, **17**, and **19** were prepared from triols **11** and **16** by formation of isopropylidene[17] or cyclopentylidene[18] acetals upon reaction with 2-methoxypropene or methoxycyclopentene under kinetic control (Scheme 2). In addition to the desired compounds, the corresponding furanosides **13**, **15**, **18**, and **20** were obtained and were resubmitted to 1,2 acetal formation after cleavage of the acetal protective group.

With conformationally constrained glucuronic acid acceptors **12** and **14** in hand, we began to investigate the stereochemical outcome of the coupling reactions (Scheme 3).



Scheme 1. Synthesis of disaccharides by using uronic acid acceptors. a) For **1** and **7**: TBSOTf, CH_2Cl_2, $-20\,^\circ C \rightarrow$RT; b) for **4**, **5**, and **10**: $AgClO_4$, $SnCl_2$,Et_2O, molecular sieves (4 Å), $0\,^\circ C \rightarrow$RT. TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate, Bz = benzoyl, TDS = dimethylthexylsilyl.



Scheme 2. Installation of 1,2-acetal protecting groups as molecular locks of uronic acid monosaccharides. a) 2-Methoxypropene, DMF, CSA; b) methoxycyclopentene, DMF, CSA. DMF = *N*,*N*-dimethylformamide, CSA = camphor sulfonic acid.

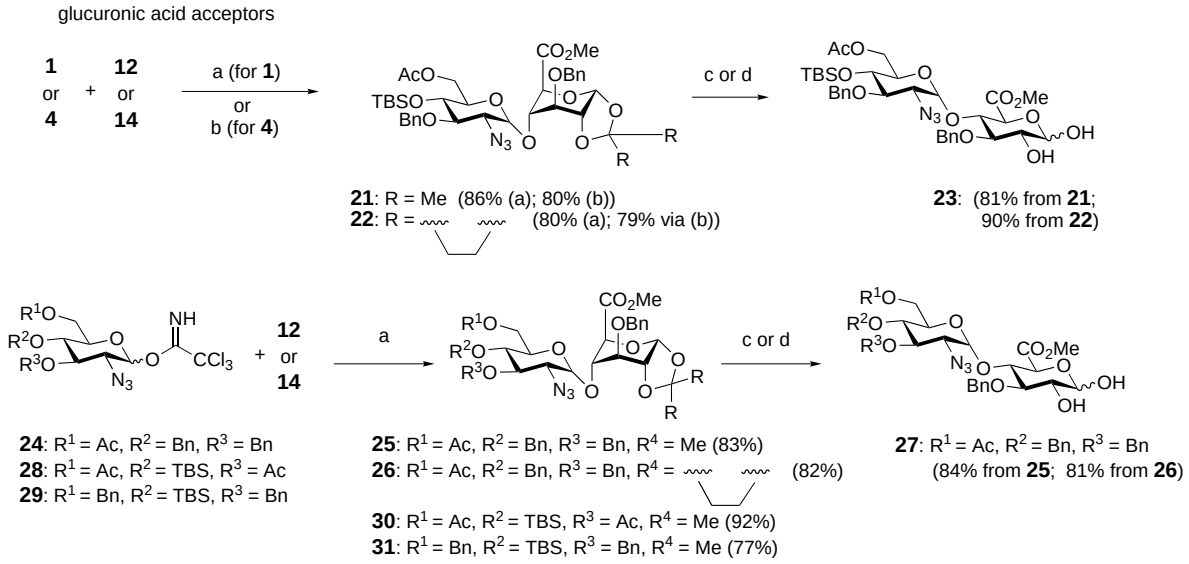
Coupling of glycosyl trichloroacetimidate **1** or glycosyl fluoride **4** with acceptors **12** and **14** resulted exclusively in the formation of α-linked disaccharides **21** (from **12**) and **22** (from **14**) in very good yields (Scheme 3). The exact nature of the cyclic protecting group (isopropylidene or cyclopentylidene) and the anomeric leaving group did not influence the selectivity of the coupling reaction. Since glycosyl trichloroacetimidates performed slightly better than glycosyl fluorides, further coupling reactions were performed with these donors. The coupling reactions of donor **24** with acceptors **12** and **14** and the coupling reactions of donors **28** and **29** with acceptor **12** were completely α-selective, as expected, and produced **25** (**24**+**12**), **26** (**24**+**14**), **30** (**28**+**12**), and **31** (**29**+**12**) as the only products (Scheme 3). Complete α-selectivity of the coupling reactions greatly simplifies access to disaccharide modules for heparin assembly and purification of the reaction products.

In addition to their use as molecular locks, 1,2-acetals are convenient for the differential protection of monosaccharides and were applied to iduronic acid acceptors. Coupling of glycosyl donors **1** and **28** with iduronic acid acceptors **17** and **19** furnished disaccharides **32** (**1**+**17**), **33** (**28**+**17**), and **34** (**28**+**19**). After the cyclic acetal protecting groups served their purpose they were readily removed to yield disaccharide diols **23** (from **21** and **22**), **27** (from **25** and **26**), **35** (from **32**), and **36** (from **33** and **34**), ready for further functionalization and incorporation as key building blocks into the modular assembly of heparin oligosaccharides (Scheme 4).

In summary, we have demonstrated a new concept for stereochemical control in the key step in the synthesis of heparin. Locking the conformation of the glucuronic acid acceptor allowed the completely selective preparation of the desired *cis* glycosides. This approach greatly simplified the preparation of disaccharide modules for the stereoselective assembly of heparin oligosaccharides. Work in this area is underway and will be reported in due course.

Experimental Section

21: Glucosamine **1** (1.87 g, 3.14 mmol) and glucuronic acid **12** (850 mg, 2.51 mmol) were coevaporated with toluene and then dissolved in anhydrous CH_2Cl_2 (31 mL) before freshly activated powdered molecular sieves (4-Å, 700 mg) were added. TBSOTf (72 μL, 0.314 mmol) was added dropwise at −78 °C, and the mixture was then warmed to room temperature over 2.5 h. Triethylamine (0.5 mL) was added, the mixture was filtered through a pad of celite, and the solvent was removed under reduced pressure. Flash chromatography on silica gel (hexanes/EtOAc 85:15) afforded **21** (1.68 g, 86 %) as a colorless foam. $[\alpha]_D^{24} = +97.2$ ($c = 2.55$, CH_2Cl_2); IR (thin film on NaCl): $\tilde{\nu} = 3032$, 2953, 2930, 2858, 2106, 1746, 1455, 1250 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.40-7.27$ (m, 10H; H_{ar}),



Scheme 3. Synthesis of disaccharides by using "locked" glucuronic acid acceptors. a) TBSOTf, molecular sieves (4 Å), CH_2Cl_2, −78 °C→RT; b) $AgClO_4$, $SnCl_2$, Et_2O, molecular sieves (4 Å), 0 °C→RT; c) for **21** and **25**: dichloroacetic acid (aqueous, 75 %); d) for **22** and **26**: dichloroacetic acid (aqueous, 50 %).

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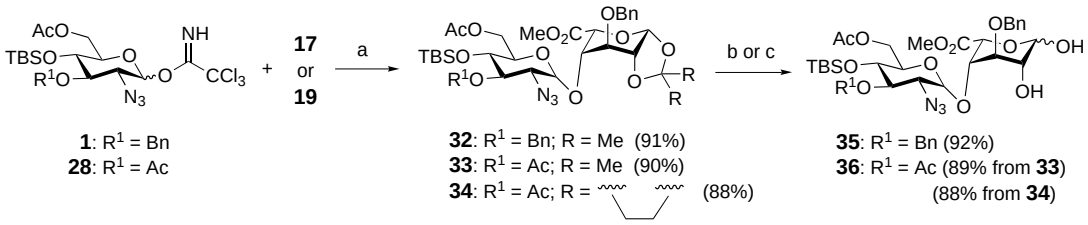
iduronic acid acceptors



1: R^1 = Bn
28: R^1 = Ac

32: R^1 = Bn; R = Me (91%)
33: R^1 = Ac; R = Me (90%)
34: R^1 = Ac; R = (88%)

35: R^1 = Bn (92%)
36: R^1 = Ac (89% from **33**)
(88% from **34**)

Scheme 4. Synthesis of disaccharides by using iduronic acid acceptors. a) TBSOTf, molecular sieves (4 Å), CH_2Cl_2, $-78\,^\circ C \rightarrow RT$; b) for **32** and **33**: dichloroacetic acid (aqueous, 75 %); c) for **34**: dichloroacetic acid (aqueous, 50 %).

5.78 (d, $J = 3.7$ Hz, 1H; H1B), 5.17 (d, $J = 3.7$ Hz, 1H; H1A), 4.88 (d, $J = 11.0$ Hz, 1H; $ArCH_2$), 4.78 (d, $J = 11.0$ Hz, 1H; $ArCH_2$), 4.68 (s, 2H; $ArCH_2$), 4.59 (d, $J = 6.1$ Hz, 1H; H5B), 4.38 (dd, $J = 2.1$, 11.9 Hz, 1H; H6Aa), 4.25 – 4.21 (m, 2H; H-2B, H4B), 4.09 – 4.05 (m, 2H; H6Ab, H3B), 3.89 – 3.85 (m, 1H; H5A), 3.74 (dd, $J = 8.5$, 10.4 Hz, 1H; H3A), 3.71 (s, 3H; OCH_3), 3.63 (dd, $J = 8.5$, 9.8 Hz, 1H; H4A), 3.25 (dd, $J = 3.7$, 10.4 Hz, 1H; H2A), 2.08 (s, 3H; $COCH_3$), 1.63 (s, 3H; isopropylidene CH_3), 1.39 (s, 3H; isopropylidene CH_3), 0.89 (s, 9H; *t*Bu), 0.02 (s, 3H; CH_3), 0.00 ppm (s, 3H; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 170.9$, 170.1, 138.1, 137.3, 128.6, 128.4, 128.2, 128.0, 127.7, 127.5, 111.0, 98.2, 95.7, 80.0, 76.0, 75.6, 75.1, 73.9, 72.3, 71.9, 71.3, 71.2, 63.6, 62.9, 52.5, 27.6, 26.0, 25.9, 21.0, 18.1, −3.6, −4.8 ppm; MS (FAB): calcd for $C_{38}H_{53}N_3O_{12}Si$: 771.3399; found: 771.3386 $[M]^+$.

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