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NEW STRATEGY FOR THE SYNTHESIS OF D-GLUCOPYRANOSIDURONIC ACID GLYCOSYL DONORS CONTAINING A LATENT C-4 ACCEPTOR

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Abstract. An effective synthesis of glucuronic acid glycosyl-donor and/or -acceptor was performed starting from D-glucofuranurono-6,3-lactone **1**. After lactonization of benzyl glycoside **3** and regioselective protection of the 4-hydroxyl of **4** with a bulky *tert*-butyldiphenylsilyl group, the lactone was opened with sodium methoxide in methanol followed by benzoylation affording the fully protected methyl ester **9**, in which the C-4 was differentially protected as a latent acceptor. Simple desilylation at C-4 quantitatively gave acceptor **13**, while catalytic hydrogenation, followed by activation of the anomeric center, gave donor **14** and **15**.

Key Words: Glucopyranosiduronic acids, Glycosyl donors

INTRODUCTION

The sulfated glycosaminoglycan (GAG) chains of proteoglycans are essential for many of their biological functions.[1] For example, oligosaccharide domains of heparin,[2] dermatan[3] and heparan sulfate[4] have been reported to specifically interact with antithrombin III, heparin cofactor II, and fibroblast growth factors, respectively.

In conjunction with our studies on the structure-activity relationship of GAG-protein interactions,[5] we are now synthesizing GAG-oligosaccharides. We have

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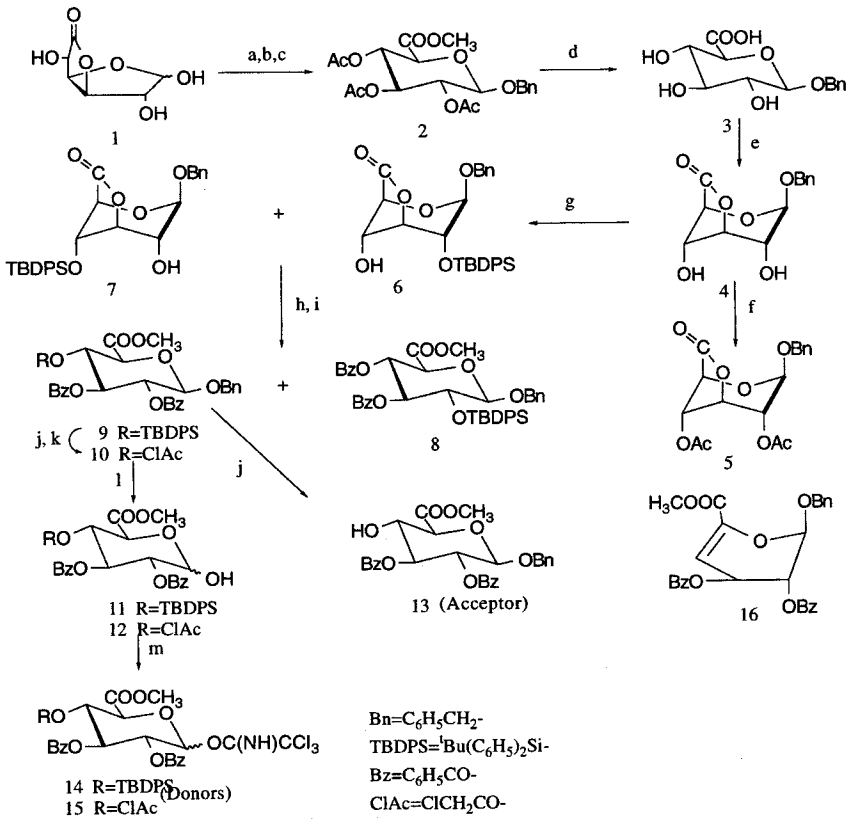
reported[6] the regioselective synthesis of derivatives of L-idopyranosiduronic acid. We report a new strategy for the regioselectively synthesis of D-glucopyranosiduronic acid (GlcA) derivatives suitable as glycosyl donor and/or acceptor.

Previous work on the synthesis of GlcA-series donor and acceptor focused on the oxidation of the 6-hydroxyl group of glucose derivatives.[7] The recent use of TEMPO[7h] for the selective oxidation of a primary alcohol in the pressence of a secondary one has significantly improved this approach. Here, we wish to report a new method, not requiring oxidation, which was effective for the large scale synthesis of universal glucuronic acid donor and/or acceptor.[8]

RESULTS AND DISCUSSION

The methyl (benzyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosid)uronate **2** was obtained from **1** following the procedure of Tanaka *et al.*[9] Saponification of **2** was accomplished by adding 1N NaOH in aqueous MeOH at 4 °C, then stirred at room temperature for 1-2 h. The solution was neutralized with Amberlite IR-120 (H^+) resin furnishing the glucuronoside **3** as a syrup. After drying under high vacuum for 24 hr, lactonization[10] of **3** was accomplished by heating with acetic anhydride at 80°C for 2 h, at which time TLC showed the reaction complete. The mixture was concentrated under rotary evaporation from toluene and heptane to afford benzyl β-D-glucopyranosidurono-6,3-lactone **4** in good yield. To facilitate structural characterization, **4** was acetylated to give **5** in which $^1C_4$ conformation was confirmed by ^{1}H-NMR data.[11] The low ^3J values ($J_{1,2} < 1$, $J_{2,3}$ 3.6, $J_{3,4}$ 5.1, $J_{4,5}$ 3.8 Hz) indicated all the substituents in **5** to be axial. Selective silylation of the 4-hydroxyl group with *tert*-butyldiphenylsilyl chloride in the presence of imidazole and 4-dimethylaminopyridine generated the mixture containing the 6,3-lactones **6** and **7** in the ratio of 1:8. The lactone ring in the mixture of **6** and **7** (which are difficult to separate at this step) was opened selectively by NaOMe in MeOH (methanolysis) at room temperature. Acylation with benzoyl chloride in the presence of triethylamine (TEA) gave the key intermediate **9** (63% in overall yield from **3**) together with **8** (7.9% in overall yield from **3**) and a third compound of undetermined structure[12] which were separated easily by flush column chromatography. Single frequency ^{1}H NMR decoupling experiments clearly indicated that **9** had a C-4 TBDPS group (δ H-2 = 5.18, H-4 = 4.49 ppm) while **8** had a C-2 TBDPS group (δ H-2 = 3.98, H-4 =



Scheme

(a) MeOH, NaOMe, rt, 3 h; then Py, Ac_2O; (b) HBr, HOAc, rt (5 h), then kept at 4 °C for 24 h; (c) CH_2Cl_2, $PhCH_2OH$ (5 eq.), Ag_2CO_3 (1.5 eq), 4 Å molecular sieves, (59.4% from **1**); (d) 1 N NaOH, MeOH, rt, 1 h; then Amberlite IR-120 (H^+) ion-exchange resin (92%); (e) Ac_2O, 80 °C, 2 h; (f) Py, Ac_2O, rt, 16 h; (g) TBDPSCl, DMAP, Im., DMF, rt, 16 h; (h) NaOMe (catalytic amount), MeOH; rt, 3 h; (i) CH_2Cl_2, BzCl, Et_3N, rt, overnight, (**8**:**9**=1:8, **3** to **9** in 63% overall yield); (j) $3HF{\cdot}Et_3N$, THF, rt, 16 h (92%); (k) $(ClAc)_2O$, CH_2Cl_2, Et_3N, rt, 6 h (89%); (l) H_2, 5% Pd-C, MeOH/EtOAc (1:1), (α predominant), rt (quant.); (m) K_2CO_3, CH_2Cl_2, CCl_3CN, rt, 16 h (89% from **11**, β predominant), (93% from **12**, α predominant)

5.37 ppm). Desilylation of **9** under standard conditions with basic tetrabutylammonium flouoride (TBAF)[13] in THF at 0 °C, caused β-elimination affording α,β-unsaturated derivative **16**, probably the result of the strong basicity of F^-.[14] Further studies showed that desilylation with TBAF-HOAc in THF,[15] gave a mixture of **13** and **16** (the reaction rate and product ratio were strongly affected by the amount of added HOAc). The same reaction in the presence of the nearly neutral $Et_3N{\cdot}3HF$[16] proceeded cleanly, providing only the desired acceptor **13**.

The glycosyl donor containing a latent C-4 glycosyl acceptor, was synthesized by debenzylation of **9** with H_2 and 5% Pd on activated carbon in MeOH/ EtOAc (1:1),[17] quantitatively affording **11**. A mixture of the α,β trichloracetimidates (β predominant) **14** was then easily formed (89% from **11**) by treatment with CCl_3CN in the presence of anhydrous K_2CO_3. Because of concern about the stability of the silyl group in coupling reactions using $BF_3{\cdot}Et_2O$ catalyst,[18] the silyl compound **9** was also converted to chloracetyl compound **10** by desilylation, followed by acylation with chloroacetic anhydride and TEA in anhydrous CH_2Cl_2. Donor **15** (α predominant) was then obtained through debenzylation (H_2, 5% Pd-C) and activation (DBU, CCl_3CN, CH_2Cl_2) of the anomeric center.

It is worth noting that the preparation of 2,3-di-*O*-benzylated derivative is not straightforward by standard benzylation conditions (BnBr and NaH in DMF) using this strategy, as a mixture of the corresponding methyl and benzyl esters are formed.

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11. Selected ^{1}H-NMR data for compounds **3-16** [values of δ_H (500 MHz) were measured for solutions in $CDCl_3$ except **3** which was in D_2O]. For brevity, chemical shifts of aromatic hydrogens have been omitted. **3:** $\delta_H(D_2O)$=3.38 (br t, 1 H, H-2), 3.50 (br t, 1 H, H-3), 3.61 (br t, 1 H, H-4), 3.95 (d, 1 H, $J_{4,5}$=9.7 Hz, H-5), 4.55 (d, 1 H, $J_{1,2}$=8.0 Hz, H-1), 4.70, 4.90 (2 d, 2 H, J =11.7 Hz, PhCH_2); ^{13}C-nmr for **3**: $\delta_C(D_2O)$=74.2, 74.5, 75.7, 77.6, 78.2, 104.2, 131.4, 131.6, 131.7, 139.4, 175.5 ppm. **5**: δ_H=1.98, 2.01 (2 s, 2 x 3 H, 2 CH_3CO), 4.29 (m, 1 H, $J_{3,5}$ < 1, $J_{4,5}$=3.8 Hz, H-5), 4.74, 4.94 (2 d, 2 H, J =12.5 Hz, PhCH_2), 4.92 (br s, 1 H, $J_{1,2}$<1 Hz, H-1), 5.07 (m, 1 H, $J_{3,4}$=5.1, $J_{1,4}$ < 1, $J_{2,4}$=1.2 Hz , H-4), 5.10 (m, 1 H, $J_{2,3}$ =3.6 Hz, H-3), 5.26 (m, 1 H, H-2). **8**: δ_H=0.81 (s, 9 H, (CH_3)$_3$C-), 3.62 (s, 3 H, COOCH_3), 3.98 (dd, 1 H, $J_{1,2}$=7.0 Hz, $J_{2,3}$=9.2 Hz, H-2), 4.20, 4.78 (2 d, 2 H, J =11.0 Hz, PhCH_2), 4.26 (d, 1 H, $J_{4,5}$=9.5 Hz, H-5), 4.74 (d, 1 H, H-1), 5.37 (dd, 1 H, $J_{3,4}$=9.2 Hz, H-4), 5.81 (t, 1 H, H-3). **9**: δ_H=0.82 (s, 9 H, (CH_3)$_3$C-), 3.50 (s, 3 H, COOCH_3),

4.21 (d, 1 H, $J_{4,5}$=8.8 Hz, H-5), 4.49 (t, 1 H, $J_{3,4}$=8.8 Hz, H-4), 4.60, 4.84 (2 d, 2 H, J =12.5 Hz, PhCH_2), 4.82 (d, 1 H, $J_{1,2}$=8.1 Hz, H-1), 5.18 (dd, 1 H, $J_{2,3}$=8.4 Hz, H-2), 5.57 (dd, 1 H, H-3). **10**: δ_H =3.80 (s, 3 H, COOCH_3), 3.94 (2d, 2 H, ClCH_2CO), 4.24 (d, 1 H, $J_{4,5}$=9.9 Hz, H-5), 4.68, 4.95 (2 d, 2 H, J =12.5 Hz, PhCH_2), 4.80 (d, 1 H, $J_{1,2}$=7.3 Hz, H-1), 5.53 (dd, 1 H, $J_{2,3}$=9.2 Hz, H-2), 5.56 (dd, 1 H, $J_{3,4}$=9.5 Hz, H-4), 5.67 (dd, 1 H, H-3). **11:** (α anomer) δ_H =0.82 (s, 9 H, (CH_3)$_3$C-), 3.50 (s, 3 H, COOCH_3), 4.44 (t, 1 H, $J_{3,4}$=$J_{4,5}$ =9.0 Hz, H-4), 4.75 (d, 1 H, H-5), 4.93 (dd, 1 H, $J_{1,2}$=3.5 Hz, $J_{2,3}$=9.6 Hz, H-2), 5.61 (d, 1 H, H-1), 6.01 (dd, 1 H, H-3). **13**: δ_H = 3.30 (d, 1 H, $J_{4,HO}$=3.3 Hz, OH), 3.89 (s, 3 H, COOCH_3), 4.15 (d, 1 H,$J_{4,5}$ =9.8 Hz, H-5), 4.22 (ddd, 1 H, $J_{3,4}$=9.2 Hz, H-4), 4.69, 4.93 (2 d, 2 H, J =12.4 Hz, PhCH_2), 4.76 (d, 1 H, $J_{1,2}$=7.7 Hz, H-1), 5.46 (dd, 1 H, $J_{2,3}$=9.5 Hz, H-2), 5.52 (dd, 1 H, H-3. **14:** (α anomer) δ_H = 0.85 (s, 9 H, (CH_3)$_3$C-), 3.65 (s, 3 H, COOCH_3), 4.27 (d, 1 H, $J_{4,5}$=8.0 Hz, H-5), 4.49 (dd, 1 H, $J_{3,4}$=7.6 Hz, H-4), 4.51, 4.94 (2 d, 2 H, J =11.6 Hz, PhCH_2), 5.18 (dd, 1 H, $J_{2,3}$=8.0 Hz, H-2), 5.57 (dd, 1 H, H-3), 6.11 (d, 1 H, $J_{1,2}$=3.1 Hz, H-1). 8.70 (br s, 1 H, NH). **15**: δ_H =3.78 (s, 3 H, COOCH_3), 3.96 (2d, 2 H, ClCH_2CO), 4.63 (d, 1 H, $J_{4,5}$=9.9 Hz, H-5), 5.53 (dd, 1 H, $J_{1,2}$=3.7 Hz, $J_{2,3}$=9.9 Hz, H-2), 5.59 (t, 1 H, $J_{3,4}$=9.9 Hz, H-4), 6.11 (t, 1 H, H-3), 6.85 (d, 1 H, H-1), 8.70 (s, 1 H, NH). **16**: δ_H =3.83 (s, 3 H, COOCH_3), 4.72, 4.98 (2 d, 2 H, J =11.7 Hz, PhCH_2), 5.55 (br s, 1 H, H-2), 5.57 (br s, 1 H, H-1), 5.59 (br d, $J_{3,4}$=4.8 Hz, H-3), 6.43 (d, 1 H, H-4).

12. Basic properties of this unknown compound: m.p. 122-124 °C (uncorrected); FABMS m/z 413 $(M+H)^+$; ^{1}H NMR δ_H($CDCl_3$)=1.65 (s, 3 H), 4.43 (d, 1 H, J =3.0 Hz), 4.54, 4.88 (2 d, 2 H, J=11.7 Hz, PhCH_2), 4.99 (br s, 1 H), 5.16 (br s, 1 H), 5.22 (br s, 2 H), 7.30-8.15 (m, 10 H).
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17. Surprisingly, hydrogenation of **9** in 90% EtOH, EtOAc or MeOH did not work well, while a mixture of EtOAc and MeOH (1:1) gave an excellent yields; Hydrogenation of **8**, gave good yields in either 90% EtOH, EtOAc or MeOH.
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