A New Synthesis of D-Glycosiduronates from Unprotected D-Uronic Acids

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O-Glycosidation of totally *O*-unprotected D-galacturonic acid **1** in THF provides α-pyranosides **4a** when promoted with $BF_3{\cdot}OEt_2$ whereas β-furanosides **6β** were obtained in the presence of $FeCl_3$; when the same reaction is performed with D-glucuronic acid **2** or 'D-glucurone' **3**, alkyl-D-glucofuranosidurono-6,3-lactones **7** are synthesized in excellent yields and high β-selectivity.

Uronic acid-containing glycoconjugates are involved in transport and detoxification processes[1] and are well known to hold important physiological functions.[2] The synthesis of glycosiduronic acids includes two main approaches.[1a] The first one involves an oxidation of the hydroxymethyl group of a previously synthesized neutral glycoside.[3] Nevertheless, most reagents lack selectivity for the oxidation of the primary alcohol function and suitably protected starting materials are thus required.[4] The second approach is based on methodologies which are essentially similar to those employed for the synthesis of neutral glycosides.[1,5] However, uronic acids are expected to require a higher activation at the anomeric position than their neutral analogues[6] and removal of the protecting groups after conjugation often remains a critical step.[1a]

In this context, direct synthesis of tautomerically and anomerically pure glycosiduronic acids from totally *O*-unprotected uronic acids would be highly desirable. Nevertheless, simplification of the glycosyl donor remains particularly difficult owing to (i) tautomeric equilibria of some sugars in solution;† (ii) *in situ* anomerizations;† and (iii) competitive *O*-glycosydation and esterification processes.[7] Here we report on a new highly steroselective synthesis of either pyranosiduronic acids from D-galacturonic acid **1** or of their furanosiduronic isomers from **1**, D-glucuronic acid **2** or D-glucofuranurono-6,3-lactone ('D-glucurone') **3**.

The coupling of D-galacturonic acid **1** with methanol as an acceptor under homogeneous conditions‡ afforded mixtures of compounds **A** and **C** regardless of the promoter, proving that esterification of the carboxy group of **1** proceeded faster than glycosylation, in accord with previous results.[7] On the other hand, we found a reversal of chemoselectivity towards glycosidation when the reaction was achieved in heterogeneous media at room temperature by using THF as the solvent for the aceptor (0.85 equiv.) and ferric chloride (3 equiv.) as the promoter. Methyl glycosiduronic acids **B** were thus isolated in *ca.* 70% yields.

The next step was to ascertain whether this glycosidation was generally applicable for the stereoselective synthesis of tautomerically pure glycosiduronic acids. Our main results are summarized in Table 1. When D-galacturonic acid **1** was treated at 20 °C with an alcohol (0.85 equiv.) in THF in the presence of a Lewis acid promoter such as $FeCl_3$, $SnCl_4$ or $BF_3{\cdot}OEt_2$ (4

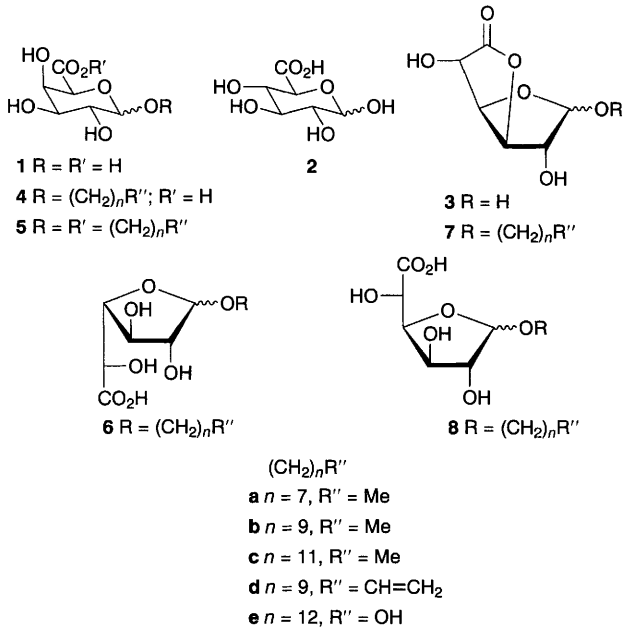

Fig. 1 Donors and products of glycosylation reactions (see Table 1)

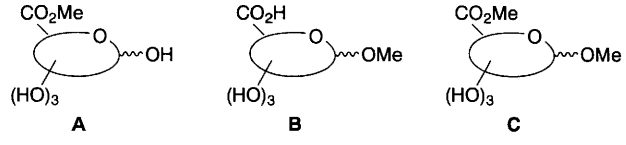

Table 1 *O*-Glycosidations of sugars **1–3**

Entry	Donor[a]	Acceptor (molar equiv.)	Promoter (molar equiv.)	Additive (molar equiv.)	Reaction time/h[b]	Compound (yield %)	α:β ratio[d]
1	**1**	*n*-octanol (0.85)	$BF_3{\cdot}OEt_2$ (4)	—	25	**4a** (65)	24:1
2	**1**	*n*-decanol (0.85)	$BF_3{\cdot}OEt_2$ (4)	—	26	**4b** (61)	19:1
3	**1**	*n*-dodecanol (0.85)	$BF_3{\cdot}OEt_2$ (4)	—	30	**4c** (62)	13:1
4	**1**	*n*-octanol (2)	$FeCl_3$ (3)	$CaCl_2$ (2)	48	**5a** (67)	1:9
5	**1**	*n*-dodecanol (2)	$FeCl_3$ (3)	$CaCl_2$ (4)	72	**6c** (45)	1:8
6	**1**	*n*-decanol (2)	$FeCl_3$ (3)	$CaCl_2$ (2)	48	**6b** (78)	1:9
7	**1**	undecen-1-ol (1.8)	$FeCl_3$ (3)	$CaCl_2$ (2)	72	**6d** (67)	1:9
8	**1**	dodecane-1,12-diol (2)	$FeCl_3$ (3)	$CaCl_2$ (2)	72	**6e** (56)	1:9
9	**2**	*n*-dodecanol (2)	$BF_3{\cdot}OEt_2$ (2)	—	1[c]	**7c** (93)	1:11
10	**2**	dodecane-1,12-diol (2)	$BF_3{\cdot}OEt_2$ (2)	—	2[c]	**7e** (56)	1:10
11	**3**	*n*-octanol (2)	$BF_3{\cdot}OEt_2$ (2)	—	48	**7a** (93)	1:7
12	**3**	*n*-dodecanol (2)	$BF_3{\cdot}OEt_2$ (2)	—	1[c]	**7c** (95)	1:11

[a] See Fig. 1 for structures of donors and products. [b] Reactions were carried out under a nitrogen atmosphere at room temp. unless otherwise stated by using 20 mmol of the donor and 17–40 mmol of the acceptor in 40 ml of anhydrous THF. [c] The mixtures were stirred at 66 °C for 1–2 h under a nitrogen atmosphere. [d] The ratio was determined by 400 MHz ^1H NMR.

equiv.), mixtures of the four expected glycosides were obtained with, however, a marked preference for the α-pyranosidic and β-furanosidic compounds, **4α** and **6β**, respectively. Fortunately, in the case of the BF_3·OEt_2-promoted reactions, the proportion of α-pyranosides **4α** could be noticeably increased by subsequent ring expansion and anomerization through concentration of the reaction mixture at 30 °C for 1 h.§ D-Galactopyranosiduronic acids **4** were thus obtained in 60–65% yields and with high stereocontrol (see Table 1, entries 1–3). Compounds **4**¶ were isolated without any chromatography by crystallization from ethyl acetate and their structural assignments[8] were based on NMR data.

To further demonstrate the utility of our methodology, we next explored the Lewis acid-promoted glycosidation of D-galacturonic acid in the presence of alkaline earth cations. Sugar acids are expected to have a much stronger complexing ability than neutral carbohydrates since calcium complexes of polysaccharides containing uronic units are probably implicated, *inter alia*, in calcium storage[9] and calcium dependent cell–cell adhesion.[10] We therefore assumed that the course of the glycosidation of D-galacturonic acid may be affected by calcium ions.[11] Indeed, when the reaction of **1** with various acceptors was performed in THF in the presence of $FeCl_3$ (3 equiv.) and $CaCl_2$ (2 equiv.), D-galactofuranosiduronic acids **6** were obtained with good yields and high β-selectivity (entries 4, 6–8 in Table 1). It was also found that increasing the amount of calcium chloride slowed down both the reaction rate (entry **5** in Table 1) and the anomerization of the α-furanoside **6cα**, formed at the beginning of the reaction, to the β-anomer **6cβ**. Pure materials **6β** were isolated after work-up by simple crystallization from diethyl ether–light petroleum. The application of the present heterogeneous methodology to dodecane-1,12-diol was noteworthy since the monoglycosylated derivative **6e** was exclusively obtained. The furanoside form and the β-configuration of compounds **6a–e**¶ were ascertained by NMR spectroscopy and by comparison with previously published data based on methyl(methyl-D-galactosiduronates).[8]

These results present evidence that calcium complexes in the presence of $FeCl_3$ in THF involve galacturonic acid **1** and its glycosides in the furanosidic rather than the pyranosidic form. From this study we propose that complexing of calcium ions with HO-2, HO-5 and the carboxy group may explain both the absence of any esterification even in the presence of two molar equivalents of the acceptor, and the exclusive formation of the kinetically favoured furanosidic products (Scheme 1). The anomerization of the α-furanosides to the more stable β-anomers may thus occur through two pathways involving either endocyclic [path (*a*)] or exocyclic [path (*b*)] bond cleavage. We assume that path (*a*) should prevail and our assumption was further supported by a separate experiment where an anomeric mixture of α,β-furanosides **6c** was anomerized in THF to yield the β-anomer in the presence of $FeCl_3$ and $CaCl_2$ without any release of alcohol or ring expansion. To our knowledge, it is the first time that D-galactosiduronic acids have been obtained from the *O*-unprotected glycosyl donor. The undeniable advantage of our methodology lies with the possibility of obtaining either the α-pyranoid or the β-furanoid forms.

From these favourable results, we finally attempted our glycosidation methodology in the D-glucuronic series. Chittenden and coworkers reported recently a new synthesis of alkyl-D-glucofuranosidurono-6,3-lactones but yields remained in the range 20–30%.[12] Treatment of D-glucuronic acid **2** or (better) 'D-glucurone' **3** with an alcohol (2 equiv.) and BF_3·OEt_2 (2 equiv.) in refluxing THF (Table 1, entries 9–12) provided crystalline furanoside lactones **7** in good to excellent yields and high stereoselectivity (β: α = 10 : 1). Lactones **7α** and **7β** were easily purified by silica gel column chromatography (eluent, diethyl ether and then diethyl ether : methanol, 9 : 1) and compounds **7β** could then be saponified in high yields (2.5 mol dm^{-3} NaOH in water : acetone; 15 min at room temp.) into crystalline β-D-glucofuranosidic acids **8**.

The results reported here are of much interest as this is one of the very few examples where *O*-glycosiduronic acids have been synthesized without protecting groups. These new compounds should find wide applications as new surfactants[13] and liquid crystals.[14] Further research on the utility of this novel route for the synthesis of neutral alkylglycosides[15] and disaccharides is in progress.

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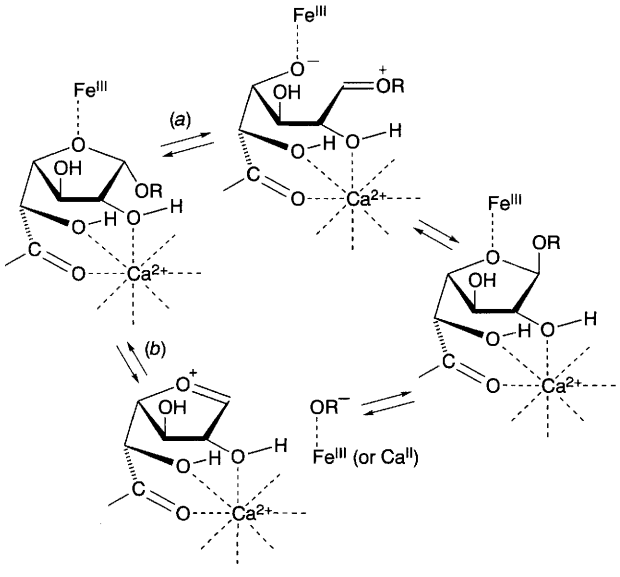

Scheme 1

Footnotes

† The behaviour of uronic acids **1** and **2** in $(CD_3)_2SO$ was investigated by ^1H NMR (300 MHz). Tautomeric and anomeric compositions were determined at 20 °C (*a*) 10 min and (*b*) 24 h after dissolution. The anomeric H-1 protons of furanoid (f) and pyranoid (p) forms gave distinct signals in the low field region δ 4.2–5.0.

Saccharide		Tautomers and/or anomers (%) α-p	β-p	α-f	β-f
1	(*a*)	90	3	1	6
	(*b*)	20	20	15	45
2	(*a*)	30	70	—	—
	(*b*)	50	50	—	—

‡ **1** (10 mmol) was dissolved in anhydrous methanol (20 ml). The promoter (BF_3·OEt_2 or $FeCl_3$, 30–40 mmol) was then added at room temp. The mixture was then stirred for 12 h at the same temp. or for 1 h in refluxing methanol. Mixtures of compounds **A** and **C** were purified by silica gel column chromatography (eluent, CH_2Cl_2 : MeOH 9 : 1).

§ Concentration of the reaction mixture involved partial esterification of compounds **4** to yield 10–15% of **5**. Saponification of the mixtures (2.5 mol dm^{-3} NaOH inwater : acetone; 15 min at room temp.) after work-up yielded the expected compounds **4**.

¶ Elemental analyses and spectrometric data were in agreement with the structures assigned.

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