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An Efficient and Highly Stereoselective $\alpha(1\rightarrow4)$ Glycosylation between two D-Galacturonic Acid Ester Derivatives

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Abstract: The highly stereoselective $\alpha(1\rightarrow4)$ coupling between two D-galacturonic acid ester derivatives was accomplished in good yields, for the first time, using a phenylthioglycoside as donor. The method was designed to prepare D-galacturonic acid oligomers with methyl ester groups in definite positions.

Pectin, a constituent of plants cell-walls, consists mainly of partially methyl esterified linear $\alpha(1\rightarrow4)$ linked oligogalacturonic acids and can be degraded by phytopathogenic fungi or bacteria. In view of our continuing interest in pectinases in phytopathogenic *Erwinia chrysanthemi*[1] we recently turned our attention to the design and synthesis of potential inhibitors of these enzymes. To pursue this aim, we needed information about the importance of free acid *versus* methyl ester functions in the substrates for recognition by the enzymes, an issue which has not yet been clarified. Thus oligomers bearing methyl esters in definite positions were required.

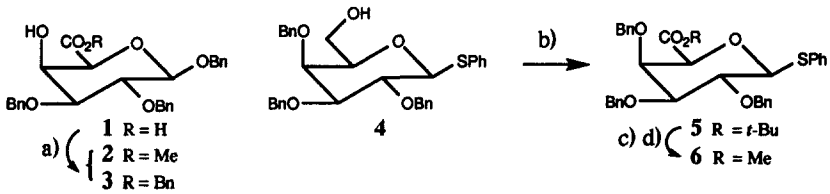
An obvious approach to our target compounds was the $\alpha(1\rightarrow4)$-glycosylation between two suitably protected and differently esterified galacturonic esters. Some years ago, however, Nakahara et al.[2] reported that, using Mukaiyama conditions[3], attempted glycosylation between two methyl esters of D-galacturonic acid gave no yield of expected dimer. This failure was attributed to the low reactivity of both the donor and acceptor due to the electron-withdrawing effect of the carboxylic function. Under the same conditions, the glycosylation between a galactose derivative as donor and a methyl galacturonate as acceptor led to the disaccharide in only 42% yield.[4] These authors then circumvented this problem by performing the glycosylation between two D-galactose units and oxidizing afterwards, in two steps, simultaneously all the primary 6-OH functions into acids. They thus developed an efficient synthesis of D-galacturonic acid oligomers.[5] However this approach was not very convenient for our purpose since it would require extensive protecting group manipulations to differentiate the two 6-OH functions allowing their selective transformations into either carboxylic acid or methyl ester.

More recently, from D-galacturonic derivatives as acceptors and donors, using the trityl-cyanoethylidene condensation method[6], Vogel et al. reported the selective preparation of $\beta(1\rightarrow2)$ and $\beta(1\rightarrow3)$ linked disaccharides in reasonable yields[7] as well as $\beta(1\rightarrow3)$ oligomers of protected methyl D-galacturonate.[8] However, the same conditions applied to the synthesis of $(1\rightarrow4)$ dimers led to a mixture containing a small amount of the α linked

stereoisomer together with anomeric epimers (due to a partial epimerisation of the glycosyl acceptor) of β linked compounds, in 45% overall yield.[7]

Since they are sufficiently stable to withstand protecting group manipulations and can readily be activated, 1-thioglycosides have been known for a long time to be valuable donors in glycosidic bond formation and have recently been exploited in efficient preparations of oligosaccharides.[9] If some examples of glycosylation using thioglycosides of glucuronic acid as donors are known[10], to our knowledge, the same reaction has not yet been reported for their galacturonic analogs. We therefore decided to examine the glycosylation between phenyl-1-thioglycosyl derivatives[11] of D-galacturonic esters as donors and 4-hydroxyl unprotected D-galacturonic esters as acceptors. We report here our preliminary results.[12]

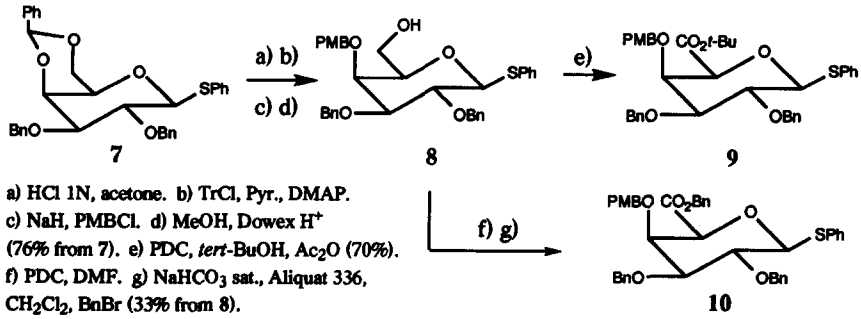
The properly protected glycosyl acceptors **2** and **3**, and donors **5** and **6**, were prepared as depicted in scheme 1. From the sodium salt of the known[13] acid **1** we obtained the corresponding methyl[13] or benzyl esters **2** and **3**. The direct oxidation of the known[14] phenylthioglycoside **4** into *tert*-butyl ester **5** was performed using the modified[10b] Corey and coll. conditions.[15] The corresponding methyl ester **6** was obtained from **5** in two steps.



a) $NaHCO_3$ sat., Aliquat 336, CH_2Cl_2, MeI (60%) or BrBn (65%). b) PDC, *tert*-BuOH, Ac_2O (70%).
c) CF_3CO_2H, CH_2Cl_2. d) CH_2N_2 (68% from **5**).

Scheme 1

Having prepared the designed glycosyl donors and acceptors we then turned to the pivotal glycosidation step. Results are summarized in Table (entries 1 and 2). Using *N*-iodosuccinimide-trifluoromethanesulfonic acid as promoter[16], the thioglysoside donor **6** reacted smoothly, at low temperature, with the glycosyl acceptor **3** to give very stereoselectively the $\alpha(1\rightarrow4)$ linked product **11α** (scheme 3) in very good yield.[17,18] The coupling between donor **5** and acceptor **2** was achieved under the same conditions, however somewhat less efficiently, and furnished exclusively the dimer **12α**. We thus obtained the precursors of the two mono-methylated D-galacturonic acid dimers and, in view of these encouraging results, we next envisaged the preparation of a trimer. For that purpose the 4'-*O*-*p*-methoxybenzyl (PMB) protected dimer **13α** was prepared (table, entry 3) from the corresponding glycosyl donor **9**, obtained in five steps from **7** (scheme 2), and acceptor **3**.



a) HCl 1N, acetone. b) TrCl, Pyr., DMAP.
c) NaH, PMBCl. d) MeOH, Dowex H^+
(76% from **7**). e) PDC, *tert*-BuOH, Ac_2O (70%).
f) PDC, DMF. g) $NaHCO_3$ sat., Aliquat 336,
CH_2Cl_2, BnBr (33% from **8**).

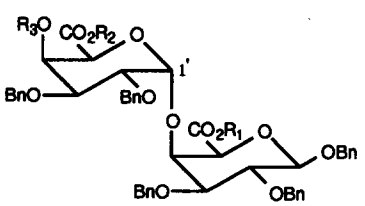
Scheme 2

The selective deprotection of the 4'-OH (Dichlorodicyanoquinone/CH_2Cl_2/H_2O; 75%) in 13α led to the dimeric glycosyl acceptor 14α. Unfortunately, under the coupling conditions used above, even when the reaction temperature was raised up to 20°C, the glycosylation did not take place. We hypothesized that the lower reactivity of the 4'-hydroxyl group in 14α was due to the bulkiness of the *tert*-butyl group. Therefore, from donor **10** and acceptor **3**, we then prepared the dimer 15α (table, entry 4) bearing now a sterically less hindering benzyl ester. After selective release of the PMB protecting group (86%) the dimeric acceptor 16α thus obtained was exposed to the glycosyl donor **2**. T.l.c. examination of the reaction mixture showed that the glycosylation proceeded very slowly at -60°C. Therefore the temperature was raised to -10°C. Using a twofold excess of donor we finally obtained the expected trimer **17** (table, entry 5) in 45 % yield along with recovered acceptor (50%).

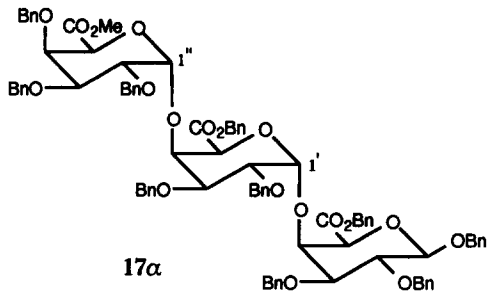
Table: Results of Glycosylation Reactions

entry	donor	acceptor	temp (°C)	time (h)	product	yield (%)	α/β ratio
1	**6**	**3**	-60	2.5	**11**	91	95/5
2	**5**	**2**	-60	2	**12**	70	>95/5[a]
3	**9**	**3**	-60	1	**13**	70	>95/5[a]
4	**10**	**3**	-60	1.4	**15**	78	>95/5[a]
5	**2**	**16α**	-10	4	**17**	45 (90)[b]	95/5[c]

a) β anomer not detectable in the ^{1}H-NMR spectrum of the crude product. b) based on recovered acceptor. c) determined on the ^{1}H-NMR spectrum of the crude product.



11α $R_1 = R_3 = Bn$ $R_2 = Me$
12α $R_1 = Me$ $R_2 = tert\text{-}Bu$ $R_3 = Bn$
13α $R_1 = Bn$ $R_2 = tert\text{-}Bu$ $R_3 = PMB$
14α $R_1 = Bn$ $R_2 = tert\text{-}Bu$ $R_3 = H$
15α $R_1 = R_2 = Bn$ $R_3 = PMB$
16α $R_1 = R_2 = Bn$ $R_3 = H$



17α

Scheme 3

In conclusion we describe here, for the first time, to our knowledge, the stereoselective α(1→4) glycosylation between two D-galacturonic acid ester derivatives giving rise to disaccharides in good yields. This approach was designed as a means for obtaining either free acid or methyl ester groups in definite position in the deprotected final compounds. The method seems to be suitable for the further preparation of D-galacturonic acid oligomers methyl esterified in definite positions, since we were able to obtain, though in modest yield, a trimer. A more detailed investigation of the importance of the nature of both the thioglycoside and of the activating agents[9] on the yield and selectivity of glycosylation is under investigation.

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11. Though phenyl thioglycosides are known to be less reactive than their alkyl counterparts (see ref 9d) they are more readily prepared and give about the same α-stereoselectivity (see : Sun, L.; Li, P.; Zhao, K. *Tetrahedron Lett.* **1994**, *35*, 7147-7150).
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17. The spectral and analytical data for new compounds are in full agreement with the proposed structures. In particular, the evidence for the α-configuration was clear from the small coupling constant between anomeric H-1' (dimers **11**α, **12**α, **13**α and **15**α) or H-1' and H-1" (trimer **17**α) and vicinal protons in the ^{1}H-NMR spectra. The observed deshielding effect (about 0.8 ppm, compared to H-1) for H-1' and H-1" is also in good agreement with an equatorial orientation for these protons. Selected NMR data (^{1}H 300 MHz; ^{13}C 75 MHz, $CDCl_3$): **11**α, 5.25 (d, 1H, $J_{1',2'}$ = 3 Hz, H-1'), 4.43 (d, 1H, $J_{1,2}$ = 7.6 Hz, H-1), 102.5 (C-1), 99.6 (C-1'); **12**α, 5.19 (d, 1H, $J_{1',2'}$ = 2.5 Hz, H-1'), 4.42 (d, 1H, $J_{1,2}$ = 7.7 Hz, H-1), 102.5 (C-1), 99.3 (C-1'); **13**α, 5.21 (d, 1H, $J_{1',2'}$ = 2.8 Hz, H-1'), 4.40 (d, 1H, $J_{1,2}$ = 7.7 Hz, H-1), 102.7 (C-1), 99.7 (C-1'); **15**α, 5.25 (d, 1H, $J_{1',2'}$ = 3 Hz, H-1'), 4.40 (d, 1H, $J_{1,2}$ = 7.6 Hz, H-1), 102.7 (C-1), 99.9 (C-1'); **17**α : 5.32 (d, 1H, $J_{1',2'}$ = 2.9 Hz, H-1'), 5.13 (d, 1H, $J_{1",2"}$ = 3.3 Hz, H-1"), 4.42 (d, 1H, $J_{1,2}$ = 7.6 Hz), 102.7 (C-1), 99.9, 99.3 (C-1', C-1").
18. All yields are for purified compounds. General procedure for glycosylation: to a solution of dried (P_2O_5, 0.1 Torr, 24h) donor (1.2 mmol) and acceptor (1.0 mmol) in 6 ml of CH_2Cl_2 distilled from P_2O_5, was first added 0.285 g (1.3 mmol) of freshly crystallized (dioxane-CCl_4) and dried (P_2O_5) *N*-iodosuccinimide, followed by 1.3 g of dried (0.1 Torr, 300°C 1h) 4Å molecular sieves and finally 12.5 ml of Et_2O distilled from Na/benzophenone. The magnetically stirred suspension was cooled to -60°C under dry nitrogen and 0.315 ml (0.1 mmol) of a solution of 0.03 ml of trifluoromethanesulfonic acid in CH_2Cl_2 (1ml) was added (syringe). When the donor had disappeared (t.l.c.; pentane/diethylether, 1/2, v/v) the reaction mixture was poured into saturated aq. $NaHCO_3$ solution (20ml). A small amount of $Na_2S_2O_5$ was added until decoloration. After extraction with Et_2O (3x50ml), the organic layers were collected and dried ($MgSO_4$). The solvent was evaporated *in vacuo* and the crude product purified by chromatography on silicagel (eluents: **11**α,**12**α, pentane/diethylether, 1/1; **13**α,**14**α, pentane/ethyl acetate, 3/1; **15**α, pentane/dichloromethane/diethylether, 6/4/0.5; **16**α, pentane/diethylether, 3/1; **17**α, dichloromethane/diethylether, 40/1).

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