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SYNTHESIS OF METHYL 2-*O*-β-D-XYLOPYRANOSYL-D-GALACTOPYRANURONATE, A PSEUDOALDOBIOURONIC ESTER

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ABSTRACT

The title compound has been synthesised by a route in which the key step was the condensation of methyl (benzyl 3,4-*O*-isopropylidene-β-D-galactopyranosid)-uronate with 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide, followed by removal of the protecting groups.

INTRODUCTION

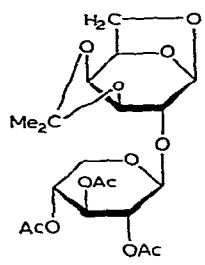
The backbone of pectic substances consists of (1→4)-linked α-D-galactopyranuronic acid residues which may be interspersed with rhamnose residues[1]. In addition, variable amounts of D-galactose, L-arabinose, L-rhamnose and, sometimes, D-xylose are present as side chains, but their sites of attachment are largely unknown. Acidic or enzymic hydrolysis of pectins yields, *inter alia*, pseudoaldobiouronic acids, and in order to facilitate the isolation and identification of such compounds, we have investigated the synthesis of methyl 2-*O*-β-D-xylopyranosyl-D-galactopyranuronate (**12**) and the corresponding α-linked compound.

Besides the synthesis described briefly by Kiss[2], two main routes for the synthesis of pseudoaldobiouronic acids or their derivatives are known, involving (*a*) oxidation of a protected disaccharide with HO-6 unsubstituted[3–5] and (*b*) Koenigs–Knorr condensations[6]. We were unable to prepare the title compound by an adaptation of method (*a*) and hence directed our attention to route (*b*).

RESULTS AND DISCUSSION

The reaction of 1,6-anhydro-3,4-*O*-isopropylidene-β-D-galactopyranose with 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide in the presence of $Hg(CN)_2$ and $HgBr_2$ (Helferich modification of the Koenigs–Knorr reaction) gave a 3:1 mixture of the (1→2)-β- (**1**) and -α-linked (**2**) disaccharide derivatives. Compound **1**, isolated by crystallisation, was de-isopropylidenated to give **3**, which was characterised as the penta-acetate **4**. The $J_{1,2}$ values of 7 Hz for the xylose residues in **1** and **4** indicated H-1 and H-2 to be *trans*.

Attempts to open the 1,6-anhydro ring in **4** by using $TiCl_4$ in an appropriate



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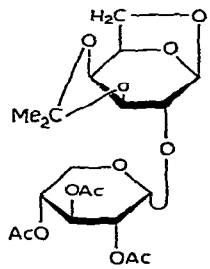

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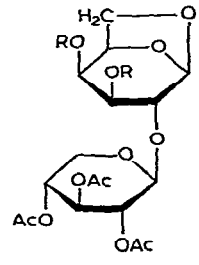
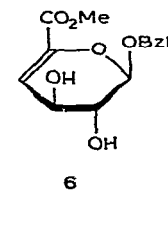


3 R = H
4 R = Ac



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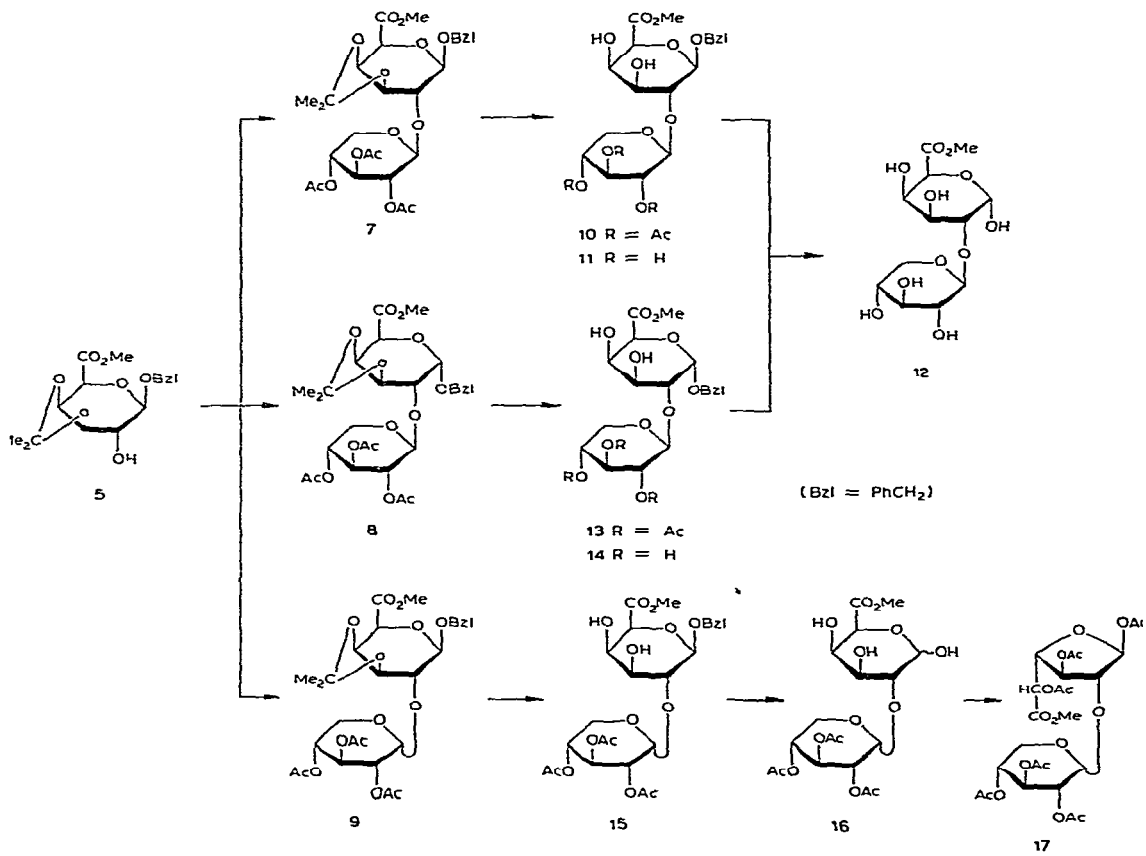
solvent[3,4,7] were unsuccessful; on using boiling chloroform–acetic acid[3] or chloroform–ethanol[4], reaction occurred slowly but no identifiable product could be isolated.

An approach related to that used by Šipoš and Bauer[6] and Hirsch *et al.*[8] was then investigated, utilising methyl (benzyl 3,4-*O*-isopropylidene-β-D-galactopyranosid)uronate (**5**). Compound **5** was prepared from known[9] methyl 1,2,3,4-tetra-*O*-acetyl-α-D-galactopyranuronate by treatment, in sequence, with hydrogen bromide–acetic acid, benzyl alcohol–silver carbonate, methanolic hydrochloric acid[10], and acetone–copper(II) sulphate. Attempted deacetylation in the penultimate stage with



5

7

10 R = Ac
11 R = H

8

13 R = Ac
14 R = H

9

15

16

17

12

(Bzl = $PhCH_2$)

methanolic sodium methoxide gave a product that was assigned the 4-deoxyhex-4-enopyranosiduronate structure **6** on the basis of i.r. and p.m.r. data. However, since the α and β anomer may occur in either the $^2H_1$ or $^1H_2$ conformation and the $J_{2,3}$ coupling constant could not be determined, the configuration at C-1 could not be verified, but is assumed to be α-L because of the route of synthesis and the negative $[\alpha]_D^{20}$ value. The formation of **6** is not unexpected, as uronates having a leaving group at C-4 undergo[11] rapid base-catalysed β-elimination.

Compound **5** was condensed with 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide under Helferich conditions at 50° for 3 h. Chromatography of the reaction mixture gave the (1→2)-β-linked derivative **7** (42% isolated).

In another condensation at 60° for 65 h, two products resulted, namely, the (1→2)-α-linked compound **9** (major product) and the (1→2)-β-linked benzyl α-glycoside **8**. The $J_{1,2}$ value (3.5 Hz) of the galacturonic acid residue of **8** indicated BzlO-1 to be axial, and the β configuration of the xylose residue was established by the $J_{1,2}$ value of 7.0 Hz, which is similar to that for **7**. Likewise, the corresponding $J_{1,2}$ values (8.0 and 3.8 Hz) for **9** indicate BzlO-1 to be equatorial and the xylose residue to be α-linked. When the condensation of **5** was carried out at room temperature for 18 h, **8** was the only compound which could be isolated subsequently (25% yield). In accordance with Hudson's isorotation rules, the $[\alpha]_D^{20}$ values of **8** and **9** are larger than that for **7**.

Treatment of **7** with aqueous acetic acid removed the isopropylidene group and hydrolysis of the product **10** with aqueous, methanolic hydrochloric acid for 65 h gave mainly methyl (benzyl β-D-galactopyranosid)uronate together with methyl (benzyl 2-*O*-β-D-xylopyranosyl-α-D-galactopyranosid)uronate (**11**, 11%). Catalytic hydrogenolysis of **11** gave methyl 2-*O*-β-D-xylopyranosyl-D-galactopyranuronate (**12**). Application of these reactions to **8** also gave **12** *via* **13** and **14**. The conversion **8**→**14** could also be effected with aqueous, methanolic hydrochloric acid.

In attempting to prepare methyl 2-*O*-α-D-xylopyranosyl-D-galactopyranuronate, **9** was heated with aqueous acetic to remove the 3,4-*O*-isopropylidene group, and the product, presumably **15**, was catalytically debenzylated to give **16**, which could not be isolated pure. Acetylation of the debenzylated material in an acidic medium gave methyl 1,3,5-tri-*O*-acetyl-2-*O*-(2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl)-β-D-galactofuranuronate (**17**), as indicated by the p.m.r. data. Whereas the coupling constants of the xylose residue were consistent with an α-pyranose structure, those for the galacturonic acid residue indicated a furanoid structure. Since only a small amount of **17** was obtained, it was not studied further.

EXPERIMENTAL*

General methods. — Melting points were determined in capillary tubes with short-stem thermometers, and are uncorrected. Optical rotations were measured with

*The i r. and mass spectra of all the compounds described are available on request.

a Perkin–Elmer Model 141 polarimeter. For column chromatography, silica gel 60 (Merck, 35–70 mesh) was used unless otherwise stated. T.l.c. was performed on F-254 silica gel (Merck); the chromatograms were first viewed at 254 nm, and then sprayed with a solution of CrO_3 in conc. sulphuric acid and heated at 125°. P.m.r. spectra at 300 MHz were recorded for solutions in D_2O [internal sodium 2,2,3,3-tetradeuterio-3-(trimethylsilyl)propionate] and $CDCl_3$ and C_5D_5N (internal Me_4Si) with a Varian spectrometer at the Laboratory for Applied Scientific Research (TNO) Delft, The Netherlands. I.r. spectra were recorded with a Perkin–Elmer 225 spectrometer.

Elemental analyses were carried out by the Element Analytical Section of the Institute for Organic Chemistry TNO, Utrecht, The Netherlands, under the supervision of Mr. W. J. Buis.

1,6-Anhydro-3,4-O-isopropylidene-2-O-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl)-β-D-galactopyranose (**1**). — A mixture of 1,6-anhydro-3,4-*O*-isopropylidene-β-D-galactopyranose[12] (4.04 g, 20 mmol), $Hg(CN)_2$ (2.53 g, 10 mmol), $HgBr_2$ (3.60 g, 10 mmol), and freshly prepared 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide[13] (6.78 g, 20 mmol) in acetonitrile (50 ml) was stirred at 50° in the dark. After 1 h, more glycosyl bromide (1 g) dissolved in acetonitrile (10 ml) was added. Stirring was continued for 1 h at 50° and for 68 h at room temperature. The mixture was then poured into water–chloroform. The aqueous layer was extracted with chloroform, and the extract was washed with water, dried (Na_2SO_4), and concentrated. T.l.c. (ether, saturated with water) showed two main and several minor spots. Elution from silica gel with chloroform gave a mixture of the two main components, crystallisation of which from ether gave **1** (2.45 g, 27%), m.p. 170–171°, $[\alpha]_D^{20}$ −59° (*c* 0.52, methanol). P.m.r. data ($CDCl_3$): 1,6-anhydro-D-galactose residue, δ 5.5 ($J_{1,2}$ 1.5 Hz, H-1), 3.7 ($J_{2,3}$ 1.5 Hz, H-2), 4.08 ($J_{3,4}$ 6.5 Hz, H-3), 4.42 ($J_{4,5}$ 6 Hz, H-4), 4.52 ($J_{5,6exo}$ 5.0 Hz, H-5), 4.08 ($J_{6endo,6exo}$ 7.5 Hz, H-6*endo*), 3.49 (H-6*exo*), 1.35 and 1.53 (isopropylidene); β-D-xylose residue, δ 4.67 ($J_{1,2}$ 7 Hz, H-1), 4.94 ($J_{2,3}$ 8.5 Hz, H-2), 5.17 ($J_{3,4}$ 8.5 Hz. H-3), 4.97 ($J_{4,5}$ 5, $J_{4,5'}$ 9 Hz, H-4), 4.16 ($J_{5,5'}$ 12 Hz, H-5), 3.30 (H-5'), 2.05, 2.06, and 2.07 (acetyl groups).

Anal. Calc. for $C_{20}H_{28}O_{12}$: C, 52.17; H, 6.13. Found: C, 52.16; H, 6.14.

3,4-Di-O-acetyl-1,6-anhydro-2-O-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl)-β-D-galactopyranose (**4**). — A mixture of **1** (2 g) and aqueous 20% acetic acid (100 ml) was boiled under reflux for 2 h. T.l.c. then indicated the reaction to be complete. Solvents were evaporated *in vacuo* and residual traces were removed by distillation *in vacuo* of toluene from the oily residue (presumably **3**), which was then acetylated conventionally with acetic anhydride–pyridine at 0° to give **4**, m.p. 73–74° (from methanol), $[\alpha]_D^{20}$ −53° (*c* 0.2, methanol).

Anal. Calc. for $C_{21}H_{28}O_{14}$: C, 50.00, H, 5.60. Found: C, 49.78; H, 5.58.

Methyl (benzyl 3,4-O-isopropylidene-β-D-galactopyranosid)uronate (**5**). — A stirred solution of methyl 1,2,3,4-tetra-*O*-acetyl-α-D-galactopyranuronate[9] (18.2 g, 48.4 mmol) in acetic acid (180 ml) was saturated during 10 min with hydrogen bromide. After 30 min, the excess of HBr and acetic acid were evaporated *in vacuo* at ~30°. Final traces of acetic acid were removed by distillation of toluene (3 × 100 ml)

from the residue. The oily α-glycosyl bromide[14] was not purified, but stirred with benzyl alcohol (36 ml) and silver carbonate (15 g) for 20 h at room temperature in the dark. Ether was added, silver salts were removed, the filtrate was concentrated, and the residue was eluted from a column (25 × 4 cm) of silica gel by using pentane–ether mixtures. The fractionation was monitored by t.l.c. (ether saturated with water). The appropriate fractions were combined and concentrated, and the residue was recrystallised from ether–pentane to give methyl (benzyl 2,3,4-tri-*O*-acetyl-β-D-galactopyranosid)uronate (13.65 g, 67%), m.p. 108.5–109.5°, $[\alpha]_D^{20}$ −12° (*c* 0.5, methanol).

To a solution of the foregoing compound (20 g) in methanol (360 ml) was added 37% hydrochloric acid (40 ml). After 72 h at room temperature, lead carbonate (96 g) was added, the mixture was stirred for 1 h, filtered through Hyflo Supercel, and concentrated, and the residue was crystallised from ethanol (150 ml) to give methyl (benzyl β-D-galactopyranosid)uronate (11 g, 78%), m.p. 165–166°, $[\alpha]_D^{20}$ −56.5° (*c* 0.43, methanol), which was sufficiently pure for the next reaction. Recrystallisation from ethyl acetate gave material having m.p. 167–168°, $[\alpha]_D^{20}$ −71° (*c* 0.5, methanol).

A mixture of the foregoing compound (11 g), anhydrous cupric sulphate (110 g), and acetone (1.25 litres) was stirred at room temperature for 72 h, filtered through Hyflo Supercel, and concentrated *in vacuo*. T.l.c. (ethyl acetate saturated with water) then showed that a small amount of starting material was still present. Elution of the material from a column (20 × 3 cm) of silica gel with ether, followed by recrystallisation of the product from ether, gave the title compound (9.92 g, 80%), m.p. 116.5–117.5°, $[\alpha]_D^{20}$ −36° (*c* 0.56, methanol).

Anal. Calc. for $C_{17}H_{22}O_7$: C, 60.35; H, 6.55. Found: C, 60.46; H, 6.57.

*Methyl (benzyl 4-deoxy-α-*L*-threo-hex-4-enopyranosid)uronate* (**6**). — To a suspension of methyl (benzyl 2,3,4-tri-*O*-acetyl-β-D-galactopyranosid)uronate (2 g) in methanol (50 ml) was added sodium methoxide (1.10 g). The mixture was kept at room temperature for 1 h and then neutralised with acetic acid, and the solvent was evaporated *in vacuo*. A solution of the syrupy residue in ethanol was filtered, and concentrated *in vacuo*, and the residue was eluted from silica gel with chloroform–methanol (9:1) to give **6** (820 mg). Recrystallisation from ethanol gave material having m.p. 139–140°, $[\alpha]_D^{20}$ −94.5° (*c* 0.5, methanol). P.m.r. data ($CDCl_3$): δ 5.24 (dd, $J_{1,2}$ 3.0, $J_{1,4}$ 1.0 Hz, H-1), 3.88–4.08 (H-2,3), 6.24 (dd, $J_{3,4}$ 4.0 Hz, H-4), 3.83 (s, CO_2Me), 4.67 and 4.86 (2 d, $J_{A,B}$ 12 Hz, benzylic protons), 7.3–7.4 (m, Ph), 2.91 (d, *J* 5 Hz, OH), and 2.98 (d, *J* 10 Hz, OH).

Anal. Calc. for $C_{14}H_{16}O_6$: C, 60.00; H, 5.75. Found: C, 60.21; H, 5.95.

Condensations of **5** *with 2,3,4-tri-*O*-acetyl-α-*D*-xylopyranosyl bromide.* — (*a*) To a mixture of **5** (1.9 g, 5.6 mmol), $Hg(CN)_2$ (1.25 g, 4.9 mmol), and $HgBr_2$ (1.8 g, 5 mmol) in dry acetonitrile (25 ml) was added the title bromide (6 g, 17.7 mmol). The mixture was stirred in the dark at 50° for 3 h, and concentrated *in vacuo*, and the residue was eluted from a column (30 × 2.2 cm) of silica gel with light petroleum–ether mixtures. The appropriate fractions were combined and concentrated, and the

TABLE I

P.M R. DATA (300 MHz) FOR **7–9**, **11**, AND **12** (CHEMICAL SHIFTS ON δ SCALE, J IN Hz)

Compound		*Galacturonic acid residue*					*Xylose residue*						*Other signals*				
		H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-5'*	*Ph*	*PhCH₂*	*CO₂Me*	*Ac*	*CMe₂*
7	($CDCl_3$)	4.42	3.82	4.17	4.43	4.32	4.86	4.92	5.11	4.89	4.08	3.21	7.3–7.4	4.64, 5.02	3.84	2.00, 2.04, 2.06	1.33, 1.50
	(C_5D_5N)	4.86	4.24	4.57	4.80	4.87	5 39	5.46	5.66	5.27	3.58	4.35	7.29, 7.38, 7.57		3.75	1.98, 2.04, 2.07	1.36, 1.51
8	($CDCl_3$)	5.11	3 87	4.34	4.46	4.65	4.79	4.96	5.18	4.91	4.01	3.23	7.2–7.3	4.72, 4.59	3 83	2.02, 2.03, 2.04	1.32, 1 48
	(C_5D_5N)	5.40	4.23	4.63	4.76	5 03	5.23	5.43	5.68	5.26	4.21	3.57	7.30, 7.38, 7.39	4.66, 4.85	3.76	1.98, 2.02, 2.07	1.37, 1.50
9	($CDCl_3$)	4.44	3.80	4.25	4.48	4.37	5.39	4.91	5.46	4.96	4.02	3.72	7.2–7.4	4.37, 4.98	3.86	1.83, 2.01, 2.03	1.37, 1.51
	(C_5D_5N)	4.94	4.11	4.41	4.79	4.93	5.90	5.39	6.09	5.43	4.46	4.05	7.27, 7.36, 7.48	4.81, 5.14	3.76	1.90, 1.99, 2.08	1.35, 1.48
11	(D_2O)	4.59[a]	3.75	3.90	4.29	4.45	4.62[a]	3.29	3.42	3.59	3.85	3.13	7.4–7.5	4.72, 4.79	3.83		
12	(D_2O)	5.50	3.89	4.14	4.38	4.82	4.57	3.36	3.46	3.63	3 96	3.34			3.82		

[a]Assignment may be reversed.

		Galacturonic acid residue				*Xylose residue*					
		$J_{1,2}$	$J_{2,3}$	$J_{2,4}$	$J_{4,5}$	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,5'}$
7	($CDCl_3$)	7.5	6.0	6.0	2.5	6.5	8.0	8.0	5.0	8.0	12.0
8	($CDCl_3$)	3.5	8.0	5.5	3.0	7.0	9.0	9.0	5.0	9.0	12.0
9	($CDCl_3$)	8 0	8.0	8.0	2.5	3.8	10 0	10.0	6.0	11.0	11.0
11	(D_2O)	8.0	10.0	3.5	1.5	8.0	9.5	9.5	5.0	11.5	12.0
12	(D_2O)	3.5	10.5	3.0	1.0	7 5	9 5	9.0	5.5	10.5	11.5

residue was crystallised from ether and recrystallised from methanol to give **7** (1.42 g, 42%), m.p. 180–182°, $[\alpha]_D^{20}$ −58° (*c* 0.43, methanol–chloroform, 1:1). See Table I for n.m.r. data.

Anal. Calc. for $C_{28}H_{36}O_{14}$: C, 56.37; H, 6.08. Found: C, 56.30; H, 6.10.

(*b*) A mixture of reactants, as in (*a*), was stirred at 60° for 65 h and then worked-up in a similar manner to give **8** (150 mg), m.p. 163.5–165°, $[\alpha]_D^{20}$ +38° (*c* 0.5, methanol), and **9** (290 mg), m.p. 173–173.5°, $[\alpha]_D^{20}$ +61° (*c* 0.94, methanol). See Table I for n.m.r. data.

Anal. Calc. for $C_{28}H_{36}O_{14}$ (**9**): C, 56.37; H, 6.08. Found: C, 56.57; H, 6.13.

(*c*) When the condensation of reactants, as in (*a*), was conducted at room temperature for 18 h, **8** was obtained (25%).

*Methyl 2-*O*-β-*D*-xylopyranosyl-*D*-galactopyranuronate* (**12**). — A suspension of **7** (0.7 g) in 20% aqueous acetic acid (50 ml) was heated at ~100° for 2 h. The solution was then extracted with dichloromethane (4 × 20 ml), and the combined extracts were dried (Na_2SO_4) and concentrated. The residue was eluted from a column (10 × 1.5 cm) of silica gel (Mallinckrodt, 100 mesh) with dichloromethane–ethyl acetate mixtures to give a product (350 mg) which contained only minor impurities (t.l.c., ethyl acetate saturated with water). A solution of this material in 4:1 methanol–conc. hydrochloric acid (25 ml) was kept at room temperature for 65 h, and then neutralised with lead carbonate, filtered through Hyflo-Supercel, and concentrated *in vacuo*. The residue was eluted from a column (15 × 1.5 cm) of silica gel with dichloromethane–ethyl acetate (1:1) to give two products which were re-crystallised from ethyl acetate. Methyl (benzyl 2-*O*-β-D-xylopyranosyl-β-D-galacto-pyranosid)uronate (**11**; 30 mg, 11%) had m.p. 187–189°. The product (145 mg) with higher R_F value (t.l.c.; ethyl acetate–acetic acid–water–formic acid, 18:4:3:1) was methyl (benzyl β-D-galactopyranosid)uronate, m.p. 167.5–168.5°.

A solution of **11** (30 mg) in methanol (5 ml) was hydrogenated over 100 mg of 10% palladium-on-charcoal at 250 kPa for 6 h, filtered through Hyflo-Supercel, and concentrated to give **12** (23 mg), which was homogeneous in t.l.c. (ethyl acetate–acetic acid–formic acid–water, 9.4:1:3). The p.m.r. data are given in Table I.

A mixture of **8** (340 mg), methanol (20 ml), and conc. hydrochloric acid (2 ml) was stirred at room temperature for 18 h, neutralised with lead carbonate, filtered through Hyflo-Supercel, and concentrated *in vacuo*. The oily residue crystallised from ethanol, to give **14** (140 mg, yield 57%), m.p. 178–179°, $[\alpha]_D^{20}$ +72° (*c* 0.5, methanol).

*Methyl 1,3,5-tri-*O*-acetyl-2-*O*-(2,3,4-tri-*O*-acetyl-α-*D*-xylopyranosyl)-β-*D*-galac-tofuranuronate* (**17**). — A mixture of **9** (0.2 g) and 20% aqueous acetic acid (50 ml) was boiled under reflux for 2 h, and then extracted with dichloromethane (4 × 10 ml). The combined extracts were concentrated and the oily residue was eluted from silica gel with ether to give oily **15**, a solution of which in methanol (50 ml) was hydro-genated over 100 mg of 10% palladium-on-charcoal at 300 kPa. The mixture was filtered through Hyflo-Supercel and concentrated to give an oily residue (**16**) which was homogeneous in t.l.c. (ethyl acetate saturated with water). To a mixture of

acetic anhydride (10 ml) and 4 drops of 60% perchloric acid at 0° was added a solution of **16** in ethyl acetate (10 ml) and acetic acid (2 ml). The solution was kept at room temperature for 3 h. After the addition of ice (20 g), the mixture was stirred for 1 h, diluted with water, and extracted with dichloromethane (4 × 15 ml). The combined extracts were dried (Na_2SO_4) and concentrated. T.l.c. (ether saturated with water) of the residue showed three spots. The mixture was eluted from silica gel with pentane–ether mixtures to give **17** (33 mg) as a chromatographically homogeneous solid (t.l.c., ether saturated with water), $[\alpha]_D^{20}$ +60° (*c* 1.66, methanol). P.m.r. data ($CDCl_3$): galacturonic acid residue, δ 6.06 ($J_{1,2}$ 1.0 Hz, H-1), 4.26 ($J_{2,3}$ 1.5, $J_{2,4}$ 5.0 Hz, H-2), 5.15 (H-3), 4.67 ($J_{4,5}$ 3.0 Hz, H-4), 5.40 (H-5), 3.80 (s, CO_2Me); α-D-xylose residue, δ 5.30 ($J_{1,2}$ 4.0 Hz, H-1), 4.79 ($J_{2,3}$ 10.5 Hz, H-2), 5.44 ($J_{3,4}$ 10.5 Hz, H-3), 4.97 ($J_{4,5}$ 6.0, $J_{4,5'}$ 10.5 Hz, H-4), 3.82 ($J_{5,5'}$ 11 Hz, H-5), 3.72 (H-5'); 2.03, 2.04, 2.08, 2.09, 2.12, and 2.28 (acetyl groups).

The two other components, which had lower R_F values, were not isolated pure.

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