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Efficient and stereoselective synthesis of methyl 3-*O*-(3,6-anhydro-β-D-galactopyranosyl)-α-D-galactopyranoside and methyl 3,6-anhydro-4-*O*-β-D-galactopyranosyl-α-D-galactopyranoside

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ABSTRACT

Methyl 3-*O*-(3,6-anhydro-β-D-galactopyranosyl)-α-D-galactopyranoside (**3**) and methyl 3,6-anhydro-4-*O*-β-D-galactopyranosyl-α-D-galactopyranoside (**4**) have been synthesised stereoselectively using three coupling procedures. Acceptable yields were achieved using acetylated derivatives as donors and trimethylsilyl triflate as the catalyst. Intramolecular tosylate displacement to form 3,6-anhydro rings proceeded in methanolic sodium methoxide.

INTRODUCTION

Carrageenans are a family of sulphated polysaccharides isolated from red algae[1]. The ability of these polysaccharides to form viscous solutions and hydrated gels has found many applications in the food, cosmetic, and pharmaceutical industries[2]. The primary structure of carrageenans is based on repeating units of (1→3)-linked 3,6-anhydro-α-D-galactopyranosyl-D-galactopyranose (**1**) and (1→4)-linked β-D-galactopyranosyl-3,6-anhydro-D-galactopyranose (**2**). Gelation by carrageenans involves helical structures and aggregates of helices[3,4], and there is strong support for the double helix being the ordered tertiary form in solution at low temperatures[5,6]. The transition from random coil to helix is temperature dependent and correlates with gel formation[7,8]. However, the factors that govern the conformational order–disorder thermal transitions are not well understood.

The results from detailed studies of the polysaccharides are complex[9,10], and the present report is part of a programme directed towards the synthesis of related low-molecular-weight model compounds. The synthesis of various galactopyranoside monosulphates[11] commonly found in carrageenans together with details of the molecular structure of the disaccharide[12] **1** have been reported. We now describe an efficient and stereoselective approach to the syntheses of methyl 3-*O*-(3,6-anhydro-β-D-galactopyra-

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nosyl)-α-D-galactopyranoside (**3**) and methyl 3,6-anhydro-4-*O*-β-D-galactopyranosyl-α-D-galactopyranoside (**4**).

The classical synthesis of 1,2-*trans* glycosidic linkages involves the Koenigs–Knorr reaction[13] (acylated glycosyl halide, hydroxylic compound, insoluble silver catalyst). The use of soluble catalysts such as mercury(II) cyanide, usually in benzene or toluene (Helferich modification[14]), represented a considerable advance and is still used widely. More recent modifications include the use of silver triflate[15] and trimethylsilyl triflate[16] as promoters.

However, no single glycosylation procedure has emerged which can be applied generally since the reaction is markedly dependent on the conditions and the nature of protecting groups on the donor and acceptor molecules[17].

RESULTS AND DISCUSSION

Our strategy was to synthesise β-glycosides by neighbouring-group assistance of a 2-acetate group, using mercuric cyanide, silver triflate, or trimethylsilyl triflate as promoters and a glycosyl bromide or acetylated sugar as the donor. The formation of the 3,6-anhydro ring was to be achieved by a base-catalysed intramolecular displacement of a 6-tosyl group.

Our first approach was to attempt the coupling of methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-galactopyranoside (**6**) and 2,3,4-tri-*O*-acetyl-6-*O*-tosyl-α-D-galactopyranosyl bromide (**13**). Compound **6** was prepared readily by the tin-mediated acetylation of methyl 4,6-*O*-benzylidene-α-D-galactopyranoside[11] (**5**) and **13** was prepared by a modification of a published method[18]. However, attempted coupling of **6** and **13** under various conditions (Table I) failed, presumably due to the low reactivity of HO-3 in **6** because of the presence of the 4,6-*O*-benzylidene group.

Attention was then turned to the acceptor 2,4,6-tri-*O*-benzyl-α-D-galactopyranoside (**9**). The synthesis of **9** involved selective 3-crotylation of methyl α-D-galactopyranoside by tin-mediated reaction with crotyl bromide to give **7**. Benzylation of **7** then gave methyl 2,4,6-tri-*O*-benzyl-3-*O*-crotyl-α-D-galactopyranoside (**8**). The removal of the crotyl group from **8** with potassium *tert*-butoxide gave **9**. Decrotylation of **8** in toluene (80°, 24 h), according to the procedure reported by Anderson *et al.*[19], gave only 20% of **9**. With methyl sulfoxide as solvent (80°, 24 h), the yield was 40%, and with *N,N*-dimethylformamide as the solvent (60°, 2 h) it was 95%.

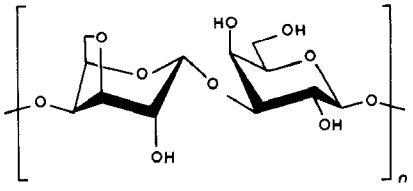
The coupling of **9** with either **13** or 1,2,3,4-tetra-*O*-acetyl-6-*O*-tosyl-α-D-galactopyranose (**12**) under different conditions was investigated (Table I). The optimum conditions involved silver triflate, **13**, and **9** in dichloromethane, which yielded 82% of the β-linked disaccharide derivative **16**. Treatment of **16** with methanolic sodium methoxide removed the *O*-acetyl groups and generated the 3,6-anhydro ring, to yield **17**. Catalytic hydrogenation (10% Pd/C) of **17** then gave 80% of the target disaccharide-glycoside **3**.

The synthesis of **4** involved the acceptor methyl 2,3-di-*O*-acetyl-6-*O*-tosyl-α-D-galactopyranoside (**11**), readily synthesised by tosylation of methyl 2,3-di-*O*-acetyl-α-D-

TABLE I

Glycosidic coupling reactions

Acceptor	*Donor*	*Catalyst*	*Conditons*	*Yield of disaccharide (%)*
6	**13**	AgOTf	CH_2Cl_2, 5°→~20°	0
6	**13**	$Hg(CN)_2$	Benzene, 60°	0
6	**12**	Me_3SiOTf	CH_2Cl_2, 0°→~20°	0
9	**13**	AgOTf	CH_2Cl_2, 5°→~20°	82
9	**13**	$Hg(CN)_2$	Benzene, 60°	40
9	**12**	Me_3SiOTf	CH_2Cl_2, 0°→~20°	45
11	**14**	AgOTf	Toluene, 5°→~20°	76
11	**14**	$Hg(CN)_2$	Benzene, 60°	30
11	**15**	Me_3SiOTf	CH_2Cl_2, 0°→~20°	55



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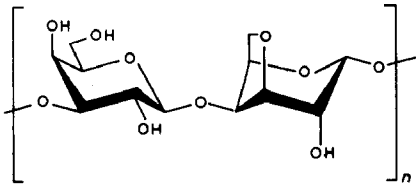

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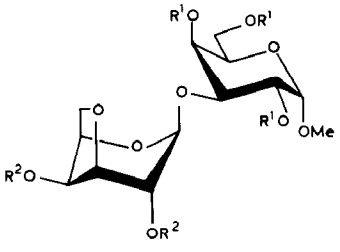
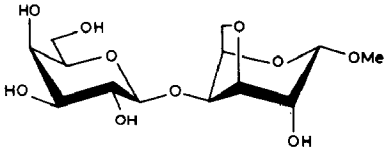


3 $R^1 = R^2 = H$
17 $R^1 = Bn$, $R^2 = H$



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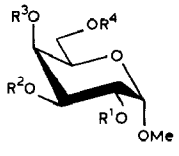
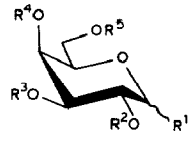
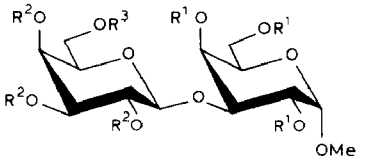


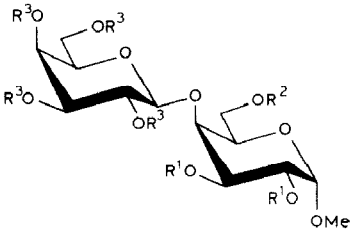
5 $R^1 = R^2 = H$, R^3, $R^4 = PhCH$
6 $R^1 = Ac$, $R^2 = H$, R^3, $R^4 = PhCH$
7 $R^1 = R^3 = R^4 = H$, $R^2 = crotyl$
8 $R^1 = R^3 = R^4 = Bn$, $R^2 = crotyl$
9 $R^1 = R^3 = R^4 = Bn$, $R^2 = H$
10 $R^1 = R^2 = Ac$, $R^3 = R^4 = H$
11 $R^1 = R^2 = Ac$, $R^3 = H$, $R^4 = Ts$



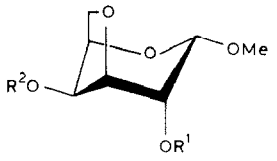
12 $R^1 = OAc$, $R^2 = R^3 = R^4 = Ac$, $R^5 = Ts$
13 $R^1 = Br$, $R^2 = R^3 = R^4 = Ac$, $R^5 = Ts$
14 $R^1 = Br$, $R^2 = R^3 = R^4 = R^5 = Ac$
15 $R^1 = OAc$, $R^2 = R^3 = R^4 = R^5 = Ac$



16 R^1 = Bn, R^2 = Ac, R^3 = Ts



18 R^1 = Ac, R^2 = Ts, R^3 = Ac



19 R^1 = Bn, R^2 = H
20 R^1 = H, R^2 = Bn

galactopyranoside[20], and the donors 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide[21] (**14**) and 1,2,3,4,6-penta-*O*-acetyl-D-galactose[22] (**15**). The coupling of **11** and **14** was performed with either silver triflate or mercuric cyanide as the catalysts, and that of **11** and **15** with trimethylsilyl triflate as the catalyst (Table I). Silver triflate again produced the best results and yielded 76% of the disaccharide derivative **18**. Treatment of **18** with methanolic sodium methoxide effected *O*-deacetylation and formation of the 3,6-anhydro ring, to yield the target disaccharide-glycoside **4**.

The ^{1}H-n.m.r. data for **3** and **4** are given in Table II. The β linkages in the disaccharide derivatives **16** and **18** were confirmed by the $J_{1',2'}$ values (7.9 Hz for each compound).

After the completion of our work, Bernabé *et al.*[23] reported a synthesis of **4** using a mercuric cyanide-assisted coupling of methyl 3,6-anhydro-2-*O*-benzyl-α-D-galactopyranoside (**19**) with a galactosyl bromide. However, the preparation of **19** by monobenzylation of methyl 3,6-anhydro-α-D-galactopyranoside gave a mixture of the 2-*O*- (**19**) and 4-*O*-benzyl (**20**) derivatives which required a difficult chromatographic separation. The synthesis of **4** described above is straightforward and high-yielding.

The yields in the coupling reactions depend on the catalyst and the protecting groups in the acceptor. Silver triflate proved to be superior to mercuric cyanide and trimethylsilyl triflate. However, the trimethylsilyl triflate reaction has the advantage of a simpler work-up procedure, and, since AcO-1 is the leaving group, the need to make glycosyl halides is avoided.

EXPERIMENTAL

General methods. — Melting points were determined in capillary tubes with a

TABLE II

^{1}H-N.m.r. data for **3** and **4**

Chemical shifts (δ, p.p.m.)								
3	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	OMe
	4.510	3.725	4.260	3.730	3.905	3.610	3.582	3.538
	H-1′	H-2′	H-3′	H-4′	H-5′	H-6′a	H-6′b	
	4.724	3.70	3.952	4.164	4.023	3.880	3.745	
4	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	OMe
	4.846	4.042	4.525	4.550	4.660	4.20	3.975	3.525
	H-1′	H-2′	H-3′	H-4′	H-5′	H-6′a, H-6′b		
	4.552	3.520	3.652	3.924	3.716	3.750		
Coupling constants (J, *Hz*)								
3	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$	
	3.5	9.3	<0.5	<0.5	8.0	5.0	−9.6	
	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'}$	$J_{5',6'a}$	$J_{5',6'b}$	$J_{6'a,6'b}$	
	<0.5	5.0	<0.5	1.8	2.9	<0.5	−9.8	
4	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$	
	2.5	5.4	<0.5	1.9	<0.5	3.0	−10.9	
	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'}$	$J_{5',6'a}$	$J_{5',6'b}$	$J_{6'a,6'b}$	
	7.6	10.0	3.5	<0.5	–	–	–	

Stuart melting-point apparatus and are uncorrected. T.l.c. was performed on Silica Gel 60 (Merck) with detection by charring with sulphuric acid. Column chromatography was performed on silica gel (Merck 70–230) and flash chromatography on silica gel (40–70 μm, MN). ^{1}H-N.m.r. spectra were recorded with a Varian XL-300 or Jeol GX-400 spectrometer on solutions in $CDCl_3$ (internal Me_4Si) or D_2O and CD_3OD [internal sodium 3-(trimethylsilyl)-1-propanesulphonate (δ 0) or acetone (δ 2.225)]. Optical rotations were determined with a Thorn Type 243 automatic polarimeter at 24°, using a 1-cm cell. Elemental analyses were performed by the analytical service of the Department of Chemistry, University of Leeds.

Benzene and toluene were distilled and dried over sodium wire. Dry alcohol-free dichloromethane was obtained by washing with water, drying over calcium chloride, distillation from phosphorus pentaoxide, and storage over 4Å molecular sieves. All coupling reactions were carried out under argon.

*2,3,4-Tri-*O*-acetyl-6-*O*-tosyl-α-*D*-galactopyranosyl bromide*[18] (**13**). — A mixture of 1,2,3,4-tetra-*O*-acetyl-6-*O*-tosyl-D-galactopyranose[18] (**12**, 1 g) and 30% hydrogen bromide–acetic acid (2 mL) was stirred at room temperature for 1 h, then poured onto ice (50 g). Ethyl acetate (100 mL) was added, and the organic layer was separated washed with saturated aqueous sodium hydrogen carbonate (50 mL) and water (50 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was crystallised from ether to yield **13** (0.8 g, 80%), m.p. 143–145° (dec.), $[\alpha]_D$ +97° (*c* 1, chloroform); lit.[18] m.p.

149°, $[\alpha]_D$ +165° (*c* 0.9, chloroform). ^{1}H-n.m.r. data ($CDCl_3$): δ 7.78 and 7.48 (ABd, 4 H, aromatic H), 6.60 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1). 5.470 (dd, 1 H, $J_{3,4}$ 3.2, $J_{4,5}$ 3.8 Hz, H-4), 4.971 (dd, 1 H, $J_{2,3}$ 10.6 Hz, H-2), 5.356 (dd, 1 H, $J_{2,3}$ 10.6, $J_{3,4}$ 3.2 Hz, H-3), 4.432 (t, 1 H, H-5), 4.121 (dd, 1 H, $J_{5,6a}$ 3.8, $J_{6a,6b}$ 10.9 Hz, H-6a), 4.065 (dd, 1 H, $J_{5,6b}$ 3.8 Hz, H-6b), 2.45 (s, 3 H, Ts*Me*), 2.250 (s, 3 H, OAc), 2.20 (s, 3 H, OAc), 2.0 (s, 3 H, OAc).

*Methyl 3-*O*-crotyl-*α*-*D*-galactopyranoside* (**7**). — A stirred mixture of methyl α-D-galactopyranoside (3.8 g, 20 mmol) and dibutyltin oxide (4.8 g, 20 mmol) in dry toluene (100 mL) was heated under reflux until the solution went clear (~ 10 h), then cooled to 60°. Crotyl bromide (4.2 g, 30 mmol) was added and the mixture was maintained at 60° until the reaction was complete (12 h). The solvent was evaporated *in vacuo* and column chromatography (4:1 EtOAc–MeOH) of the residue gave **7** (4 g, 83%), isolated as a syrup, $[\alpha]_D$ +30° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 5.685 (m, 2 H, CH = CH), 4.868 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 4.125 (m, 2 H, = CHCH_2), 4.10 (bt, 1 H, H-5), 3.880 (dd, 1 H, $J_{2,3}$ 9.8 Hz, H-2), 3.842 (m, 2 H, H-4,6a), 3.695 (m, 1 H, H-6b), 3.482 (dd, 1 H, $J_{3,4}$ 3.2 Hz, H-3), 3.403 (s, 3 H, OMe), 1.70 (m, 3 H, *Me*CH =).

Anal. Calc. for $C_{11}H_{20}O_6$: C, 53.23; H, 8.06. Found: C, 52.92; H, 7.88.

*Methyl 2,4,6-tri-*O*-benzyl-3-*O*-crotyl-*α*-*D*-galactopyranoside* (**8**). — To a suspension of sodium hydride (1.5 g, 60 mmol) in dry *N,N*-dimethylformamide (50 mL) was added a solution of **7** (2.4 g, 10 mmol) in *N,N*-dimethylformamide (10 mL) dropwise at 5°. The mixture was stirred at 5° for 1 h, a solution of benzyl bromide (7.1 mL, 60 mmol) in *N,N*-dimethylformamide (10 mL) was then added dropwise, and the mixture was allowed to warm to room temperature and then stirred overnight. Excess of sodium hydride was destroyed with methanol (10 mL), the mixture was diluted with dichloromethane (200 mL) and water (100 mL), and the organic layer was separated, washed with water (100 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography (1:4 EtOAc–hexane) of the residue gave **8**, isolated as a syrup (3.8 g, 76%), $[\alpha]_D$ +28° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.74–7.20 (m, 15 H, 3 Ph), 5.686 (m, 2 H, CH = CH), 4.952 and 4.825 (ABq, 2 H, PhCH_2), 4.665 and 4.545 (ABq, 2 H, PhCH_2), 4.486 and 4.40 (ABq, 2 H, PhCH_2), 4.645 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 4.155 (m, 2 H, = CHCH_2), 3.945 (dd, 1 H, $J_{1,2}$ 3.8 $J_{2,3}$ 10.0 Hz, H-2), 3.880 (m, 2 H, H-4,5), 3.792 (dd, 1 H, $J_{3,4}$ 3.2 Hz, H-3), 3.525 (dd, 2 H, $J_{5,6a}$ 6.3, $J_{6a,6b}$ 10.6 Hz, H-6a,6b), 3.406 (s, 3 H, OMe), 1.695 (m, 3 H, *Me*CH =).

Anal. Calc. for $C_{32}H_{38}O_6$: C, 74.13; H, 7.34. Found: C, 73.98; H, 7.0.

*Methyl 2,4,6-tri-*O*-benzyl-*α*-*D*-galactopyranoside* (**9**). — To a solution of **8** in *N,N*-dimethylformamide (20 mL) was added potassium *tert*-butoxide (3.3 g, 30 mmol) and the mixture was heated at 60° for 2 h. The reaction was cooled, water (50 mL) was added, the mixture was extracted with ether (3 × 50 mL), and the combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Column chromatography (1:4 EtOAc–hexane) of the residue gave **9**, isolated as a syrup (2.3 g, 86%), $[\alpha]_D$ +43° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.23–7.70 (m, 15 H, 3 Ph), 4.818 and 4.685 (ABq, 2 H, PhCH_2), 4.682 and 4.60 (ABq, 2 H, PhCH_2), 4.520 and 4.431 (ABq, 2 H, PhCH_2), 4.690 (d, 1 H, $J_{1,2}$ 3.1 Hz, H-1), 4.045 (dd, 1 H, $J_{3,4}$ 2.7, $J_{2,3}$ 10.0 Hz, H-3), 3.943 (bt, 1 H, H-5), 3.913 (bd, 1 H, H-4), 3.783 (dd, 1 H, H-2), 3.566 (d, 2 H, $J_{5,6a}$ 6.5, $J_{6a,6b}$ 10.6 Hz, H-6a,6b), 3.340 (s, 3 H, OMe).

Anal. Calc. for $C_{28}H_{32}O_6$: C, 72.41; H, 6.90. Found: C, 72.15; H, 6.75.

Methyl 2,4,6-tri-O-benzyl-3-O-(2,3,4-tri-O-acetyl-6-O-tosyl-α-D-galactopyranosyl)-α-D-galactopyranoside (**16**). — (*a*) To a mixture of **9** (0.23 g, 0.5 mmol), **13** (0.39 g, 0.75 mmol), and powdered 4Å molecular sieves (1 g) in dichloromethane (25 ml) was added silver triflate (0.2 g, 0.75 mmol) at 5°. The mixture was stirred at 5° for 30 min, then at room temperature for 1 h, filtered through Celite, and concentrated *in vacuo*. Column chromatography (1:3 EtOAc–hexane) of the residue yielded **16** (0.35 g, 82%), isolated as a syrup, $[\alpha]_D$ +50° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.760 (d, 2 H, aromatic H), 7.345–7.250 (m, 17 H, 3 Ph and aromatic H), 5.360 (dd, 1 H, $J_{3',4'}$ 3.4, $J_{4',5'}$ 1.0 Hz, H-4'), 5.265 (dd, 1 H, $J_{1',2'}$ 7.9, $J_{2',3'}$ 10.4 Hz, H-2'), 4.965 (dd, 1 H, H-3'), 4.980 (d, 1 H, H-1'), 4.940 (bt, 1 H, H-5'), 4.720 and 4.545 (ABq, 2 H, PhCH_2), 4.520 and 4.480 (ABq, 2 H, PhCH_2), 4.460 and 4.421 (ABq, 2 H, PhCH_2), 4.585 (s, 1 H, H-1), 4.182 (dd, 1 H, $J_{2,3}$ 7.8, $J_{3,4}$ 3.2 Hz, H-3), 4.121 (dd, 1 H, $J_{5',6'a}$ 7.1, $J_{6'a,6'b}$ 10.6 Hz, H-6'a), 4.025 (dd, 1 H, $J_{5',6'b}$ 6.7 Hz, H-6'b), 3.955 (d, 1 H, H-2), 3.90 (m, 1 H, H-5), 3.862 (dd, 1 H, $J_{4,5}$ 0.9 Hz, H-4), 3.562 (dd, 1 H, $J_{5,6a}$ 6.0, $J_{6a,6b}$ 11.0 Hz, H-6a), 3.498 (dd, 1 H, $J_{5,6b}$ 4.5 Hz, H-6b), 3.625 (s, 3 H, OMe), 2.850 (s, 3 H, Ts*Me*), 2.081, 2.055, and 1.998 (3 s, each 3 H, 3 OAc).

Anal. Calc. for $C_{47}H_{54}O_{16}S$: C, 62.25; H, 5.96; S, 3.53. Found C, 62.10; H, 5.72; S, 3.64.

(*b*) A stirred mixture of **9** (0.46 g, 1 mmol), **13** (0.78 g, 1.5 mmol), mercuric cyanide (0.71 g, 3 mmol), and powdered 4Å molecular sieves (1 g) in benzene (25 mL) was heated at 60° for 12 h, then cooled, washed with saturated aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography of the residue as in (*a*) yielded **16** (0.33 g, 40%).

(*c*) To a stirred mixture of **9** (0.46 g, 1 mmol), 1,2,3,4-tetra-*O*-acetyl-6-*O*-tosyl-D-galactopyranose[18] (**12**; 0.5 g, 1 mmol), powdered 4Å molecular sieves (1 g), and tetramethylurea (0.2 g, 2 mmol) in dichloromethane (20 mL) was added trimethylsilyl triflate (0.4 g, 2 mmol) at 0°. The mixture was allowed to warm to room temperature and stirred for 12 h. Standard workup yielded **16** (0.37 g, 45%).

Methyl 3-O-(3,6-anhydro-β-D-galactopyranosyl)-2,4,6-tri-O-benzyl-α-D-galactopyranoside (**17**). — A solution of **16** (0.1 g) in dry methanol (10 mL) was treated with methanolic M sodium methoxide solution (1 mL) at room temperature overnight, then neutralised with IRC-120 (H^+) resin, filtered, and concentrated *in vacuo*. Column chromatography (2:1 EtOAc–hexane) of the residue gave **17** (0.6 g, 82%), isolated as a syrup, $[\alpha]_D$ +55° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.40–7.262 (m, 15 H, 3 Ph), 4.980 and 4.642 (ABq, 2 H, PhCH_2), 4.588 and 4.546 (ABq, 2 H, PhCH_2), 4.520 and 4.422 (ABq, 2 H, PhCH_2), 4.892 (s, 1 H, H-1'), 4.790 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), 4.350 (d, 1 H, $J_{4',5'}$ 1.7 Hz, H-4'), 4.305 (d, 1 H, $J_{2',3'}$ 9.4 Hz, H-3'), 4.237 (bt, 1 H, H-5'), 4.156 (dd, 1 H, $J_{5',6'a}$ 2.9, $J_{6'a,6'b}$ 9.8 Hz, H-6'a), 4.10 (dd, 1 H, $J_{2,3}$ 10.2, $J_{3,4}$ 2.7 Hz, H-3), 4.045 (d, 1 H, H-2'), 4.062 (dd, 1 H, H-2), 3.962 (d, 1 H, H-6'b), 3.940 (m, 2 H, H-4,5), 3.582 (t, 1 H, H-6a), 3.545 (dd, 1 H, $J_{6a,6b}$ 8.9, $J_{5,6b}$ 5.1 Hz, H-6b), 3.395 (s, 3 H, OMe).

Anal. Calc. for $C_{34}H_{40}O_{10}$: C, 67.10; H, 6.58. Found: C, 67.30; H, 6.35.

Methyl 3-O-(3,6-anhydro-β-D-galactopyranosyl)-α-D-galactopyranoside (**3**). — A solution of **17** (0.06 g, 0.1 mmol) in methanol (5 mL) was treated with Pd/C (10%, 0.01

g), and the mixture was stirred under hydrogen overnight, then filtered through Celite, and concentrated *in vacuo*. Column chromatography (2:1 EtOAc–MeOH) of the residue yielded **3** (0.3 g, 91%), m.p. 202–204° (from MeOH–EtOAc), $[\alpha]_D$ +60° (*c* 1, methanol). For the ^{1}H-n.m.r. data, see Table II.

Anal. Calc. for $C_{13}H_{22}O_{10}$: C, 46.15; H, 6.51. Found: C, 45.95; H, 6.68.

*Methyl 2,3-di-*O*-acetyl-6-O-tosyl-*α*-*D*-galactopyranoside* (**11**). — To a solution of methyl 2,3-di-*O*-acetyl-α-D-galactopyranoside[20] (**10**; 3.6 g, 13 mmol) in dry pyridine (25 mL) was added *p*-toluenesulphonyl chloride (2.85 g, 15 mmol) at 5°. The mixture was allowed to warm to room temperature and stirred for 24 h. Most of the pyridine was evaporated *in vacuo*, the residue was washed several times with cold water, then dissolved in ethanol (50 mL), and the solution was concentrated. Column chromatography (EtOAc) of the residue yielded **11** (4.8 g, 87%), isolated as a syrup, $[\alpha]_D$ +130° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.80 and 7.35 (AB doublets, 4 H, aromatic H), 5.241 (dd, 1 H, $J_{3,4}$ 2.9, $J_{2,3}$ 10.6 Hz, H-3), 5.172 (dd, 1 H, $J_{1,2}$ 3.3 Hz, H-2), 4.90 (d, 1 H, H-1), 4.243 (dd, 1 H, $J_{5,6a}$ 5.0, $J_{6a,6b}$ 10.4 Hz, H-6a), 4.175 (dd, 1 H, $J_{5,6b}$ 6.6 Hz, H-6b), 4.123 (m, 1 H, H-4), 4.056 (bt, 1 H, H-5), 3.35 (s, 3 H, OMe), 2.42 (s, 3 H, Ts*Me*), 2.08 (s, 3 H, OAc), 2.04 (s, 3 H, OAc).

Anal. Calc. for $C_{18}H_{24}O_{10}S$: C, 50.00; H, 5.55; S, 7.40. Found: C, 50.26; H, 5.65; S, 7.20.

*Methyl 2,3-di-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-α-6-O-tosyl-D-galactopyranoside* (**18**). — (*a*) To a stirred mixture of **11** (1.7 g, 4 mmol), 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide[21] (**14**; 2.4 g, 6 mmol), and powdered 4Å molecular sieves (2 g) in dry toluene (25 mL) were added 2,4,6-trimethylpyridine (1.2 mL, 8 mmol) and silver triflate (2 g, 8 mmol) at 5°. The mixture was allowed to warm to room temperature, stirred for 2 h, filtered through Celite, and concentrated *in vacuo*. Column chromatography (1:1 EtOAc–hexane) of the residue yielded **18** (2.2 g, 76%), isolated as an amorphous solid $[\alpha]_D$ +63° (*c* 1, chloroform). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.80 and 7.552 (ABq, 4 H, aromatic H), 5.650 (dd, 1 H, $J_{2',3'}$ 10.6, $J_{3',4'}$ 3.5 Hz, H-3'), 5.440 (dd, 1 H, $J_{4',5'}$ 1.0 Hz, H-4'), 5.340 (d, 1 H, $J_{1',2'}$ 7.9 Hz, H-1'), 5.241 (dd, 1 H, $J_{2,3}$ 10.6, $J_{3,4}$ 2.9 Hz, H-3), 5.172 (dd, 1 H, $J_{1,2}$ 3.2 Hz, H-2), 5.08 (dd, 1 H, H-2'), 4.922 (d, 1 H, H-1), 4.31–4.23 (m, 5 H, H-4,5,6a,6b,5'), 4.122 (ABdd, 1 H, $J_{6'a,6'b}$ 11.4, $J_{5',6'a}$ 5.6 Hz, H-6'a), 4.04 (ABdd, 1 H, $J_{5',6'b}$ 7.2 Hz, H-6'b), 3.412 (s, 3 H, OMe), 2.422 (s, 3 H, Ts*Me*), 2.14, 2.11, 2.08, 2.06, 2.04, and 1.99 (6 s, each 3 H, 6 OAc).

Anal. Calc. for $C_{32}H_{42}O_{19}S$: C, 50.39; H, 5.51; S, 4.20. Found: C, 50.16; H, 5.75; S, 4.48.

(*b*) A stirred mixture of **11** (0.43 g, 1 mmol), 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**14**; 0.6 g, 1.5 mmol), mercuric cyanide (0.71 g, 3 mmol), and powdered 4Å molecular sieves (1 g) in benzene (25 mL) was heated at 60° for 12 h. Standard workup yielded **18** (0.23 g, 30%).

(*c*) To a mixture of **11** (0.43 g, 1 mmol), 1,2,3,4,6-penta-*O*-acetyl-D-galactopyranose[22] (**15**; 0.39 g, 1 mmol), tetramethylurea (0.2 g, 2 mmol), and powdered 4Å molecular sieves (1 g) in dichloromethane (20 mL) was added trimethylsilyl triflate (0.5 g, 2.5 mmol) at 5°, and the mixture was stirred at room temperature for 12 h. Standard workup yielded **18** (0.42 g, 55%).

Methyl 3,6-anhydro-4-O-α-D-galactopyranosyl-β-D-galactopyranoside (**4**). — A solution of **18** (0.8 g, 2.36 mmol) in dry methanol (10 mL) was treated with methanolic M sodium methoxide (2 mL) at room temperature. After 12 h, the solution was neutralised with IRC-120 (H^+) resin, filtered, and concentrated. Column chromatography (3:1 EtOAc–MeOH) of the residue yielded **4** (0.3 g, 86%), m.p. 205° (dec.) (from 2-propanol–water), $[\alpha]_D$ +52° (*c* 1, methanol); lit.[23] m.p. 207°, $[\alpha]_D$ +42° (*c* 1, methanol). For the ^{1}H-n.m.r. data, see Table II.

Anal. Calc. for $C_{13}H_{22}O_{10}$: C, 46.15; H, 6.51. Found: C, 45.95; H, 6.65.

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