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Note

Synthesis of methyl *O*-α-L-fucopyranosyl-(1→2)-*O*-β-D-galactopyranosyl-(1→3)-2-acetamido-2-deoxy-β-D-glucopyranoside, using 2,3,4-tri-*O*-benzoyl-α-L-fucopyranosyl bromide as the α-L-fucosylating agent

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In studies[1,2] of the glycosylation of methyl α-L-rhamnopyranoside derivatives (HO-2 unsubstituted) with 2,3,4-tri-*O*-benzoyl-α-L-fucopyranosyl bromide (**11**) under Helferich conditions [acetonitrile–mercuric cyanide (2 equiv.)–mercuric bromide (catalytic amount)], α-linked products were formed if there was a benzoyl group or a monosaccharide residue at position 3. Glycosylations[3–5] with acetobromofucose under Helferich conditions also gave α-fucosides, but the yield (>30%) and stereoselectivity were lower than in the reactions with **11**.

We now describe α-L-fucosylation with **11** in the synthesis of the trisaccharide methyl glycoside **13** which contains the 2-*O*-α-L-fucopyranosyl-β-D-galactopyranose moiety and is a model for a ^{13}C-n.m.r. study of the *Salmonella arizonae* O45 polysaccharide[6]. Compound **13** is the methyl glycoside of the Le^d (H type 1) blood-group-specific trisaccharide, which has been synthesised[7] together with the 8-methoxycarbonyloctyl[8] and 4-nitrophenyl[9] glycoside.

Glycosylation of methyl 4,6-*O*-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside (**2**) with ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (**3**) in the presence of nitrosyl tetrafluoroborate[10] afforded 76% of the β-linked disaccharide derivative **5**. Glycosylation of **2** with 1,2,3,4,6-penta-*O*-acetyl-β-D-galactopyranose (**4**, 2 equiv.) in the presence of trimethylsilyl triflate (0.5–2 equiv.) was less effective and gave only 20–30% of **5**. That the galactosyl unit in **5** was β followed from ^{1}H-n.m.r. data in Table I ($J_{1,2}$ 7.9 Hz).

O-Deacetylation of **5** gave tetraol **6** which, on treatment with benzaldehyde dimethyl acetal, gave the 4,6:4′,6′-di-*O*-benzylidene derivative **7** (82% from **5**). Treatment of **7** with benzoyl cyanide in the presence of a catalytic amount of triethylamine[11] gave 91% of the 3′-benzoate **8**. The location of the benzoyl group in **8** was indicated by the low-field chemical shift of the resonance for H-3′ (δ 4.77) and confirmed by deuterium exchange which simplified the signal of H-2′ (δ 4.03).

Glycosylation of **8** with **11** under Helferich conditions, followed by removal of the

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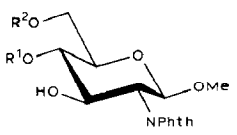
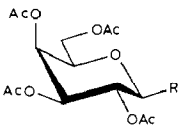
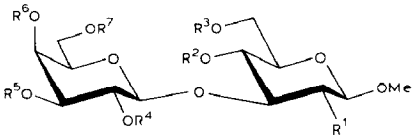


1 $R^1 = R^2 = H$
2 $R^1, R^2 = PhCH$



3 R = SEt
4 R = OAc



5 R^1 = NPhth, R^2, R^3 = PhCH, $R^4 = R^5 = R^6 = R^7$ = Ac
6 R^1 = NPhth, R^2, R^3 = PhCH, $R^4 = R^5 = R^6 = R^7$ = H
7 R^1 = NPhth, $R^2, R^3 = R^6, R^7$ = PhCH, $R^4 = R^5$ = H
8 R^1 = NPhth, $R^2, R^3 = R^6, R^7$ = PhCH, R^4 = H, R^5 = Bz
9 R^1 = NPhth, $R^2 = R^3$ = H, $R^4 = R^5 = R^6 = R^7$ = Ac
10 R^1 = NHAc, $R^2 = R^3 = R^4 = R^5 = R^6 = R^7$ = H

TABLE I

^{1}H-N.m.r. data[a] ($CDCl_3$) (δ in p.p.m., J in Hz) for **2**, **5**, **7**, **8**, **12**, and **14**

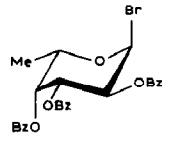
Compound	*Residue*	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6a*	*H-6b*
2		5.14	4.14	4.51	3.53——3.67		3.80	4.36
5	Glc	5.08	4.30	4.75	3.82	3.64	3.88	4.40
	Gal	4.56	5.00	4.75	5.20	3.50	3.83	4.04
8	Glc	5.42	4.35	4.88	3.87	3.80	3.89	4.47
	Gal	4.43	4.03	4.77	4.30	3.18	2.63	3.50
12	Fuc	5.47	5.59	5.77	5.93	4.81	1.34	
14	Fuc	4.70	5.35	4.63	5.37	3.28	1.08	
		$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
2		8.5	10.5	10.1	4.1	10.0		
5	Glc	8.4	10.2	8.5	8.5	10.0	4.6	10.0
	Gal	7.9	10.5	3.5	1.0	5.0	8.1	11.0
8	Glc	8.5	10.0	8.7	8.7	10.0	4.6	10.0
	Gal	8.5	10.0	3.8	<1	1.3	1.6	12.5
12	Fuc	3.7	10.6	3.5	<1	6.7		
14	Fuc	7.8	10.5	3.5	<1	6.5		

[a]Other signals: aromatic, δ 7.20–8.20; OMe, 3.40–3.48; AcO, 1.55–2.10 (for **5**); PhCH, 5.54 (for **2**), 5.59 (for **5**), 5.28 and 5.64 (for **8**).

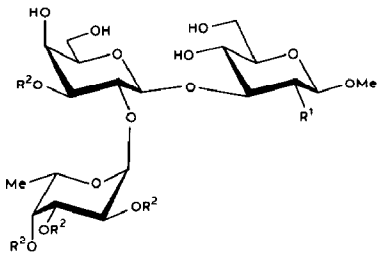
benzylidene groups by acid hydrolysis, and column chromatography gave 71% of the α-fucosylated product **12** and 13% of a 1:1.5 mixture of **12** and the β isomer **14**. Thus, the glycosylation of **8** with **11** involved high α-stereoselectivity (α,β-ratio ~ 9:1). That the fucosyl unit was α in **12** and β in **14** followed from the respective $J_{1,2}$ values (3.7 and 7.8 Hz).

Hydrazinolysis of **12** and *N*-acetylation then gave the target trisaccharide methyl glycoside **13**.

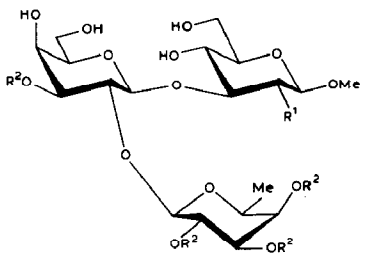
In addition to **13**, methyl 2-acetamido-2-deoxy-3-*O*-β-D-galactopyranosyl-β-D-glucopyranoside (**10**) was obtained in three steps (acid hydrolysis–hydrazinolysis–*N*-acetylation). Compound **10** was also required for the study of the *Salmonella arizonae*



11



12 R^1 = NPhth, R^2 = Bz
13 R^1 = NHAc, R^2 = H



14 R^1 = NPhth, R^2 = Bz

O45 polysaccharide[6]. The ^{1}H- and ^{13}C-n.m.r. data for **10** and **13** are given in Tables II and III. Assignments of ^{1}H-n.m.r. spectra were accomplished using a combination of ^{1}H–^{1}H COSY and RCT 2D experiments, and those of ^{13}C-n.m.r. spectra using 2D ^{1}H–^{13}C correlated spectroscopy.

The above results demonstrate further that α-L-fucosylation with the donor **11** is an alternative to the traditional 2-*O*-benzylated α-L-fucosyl donors. The factors that determine the effectivenes of **11** for α-fucosylation are under investigation.

TABLE II

^{1}H-N.m.r. data[a] (D_2O) (δ in p.p.m., J in Hz) for **10** and **13**

Compound	*Residue*	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6a*	*H-6b*
10	Glc	4.50	3.94	3.79	3.55	3.49	3.80	3.95
	Gal	4.43	3.52	3.65	3.92	3.68		3.81
13	Glc	4.38	3.81	4.02	3.47	3.57	3.80	3.98
	Gal	4.66	3.61	3.86	3.92	3.70		
	Fuc	5.22	3.80	3.71	3.80	4.33	1.25	
		$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
10	Glc	8.1	10.0	9.6	9.6	5.4	2.0	12.4
	Gal	7.5	9.6	3.2	<1			
13	Glc	8.2	10.3	9.0		5.4	1.6	12.4
	Gal	7.6	9.5	3.3	<1	4.0	7.8	
	Fuc	3.9	10.0	3.1	<1	6.8		

[a]Other signals, respectively, for **10** and **13**: NAc at 2.03 and 2.08 p.p.m.; OMe at 3.53 and 3.52 p.p.m.

TABLE III

^{13}C-N.m.r. data[a] (D_2O) (δ in p.p.m.) for **10** and **13**

Compound	*Residue*	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*
10	Glc	102.9	55.7	84.1	70.2	76.8	62.2
	Gal	104.7	72.1	73.9	69.9	76.6	62.2
13	Glc	103.9	56.0	79.0	70.1	76.9	62.2
	Gal	101.5	78.0	74.9	70.5	76.5	62.4
	Fuc	100.8	69.5	70.1	73.1	67.8	16.4

[a]Other signals, respectively, for **10** and **13**: NAc at 23.6 and 23.5 (Me) and 175.9 and 175.0 (CO) p.p.m.; OMe at 58.3 and 58.4 p.p.m.

EXPERIMENTAL

General. — Melting points were determined with a Kofler apparatus and are uncorrected. Optical rotations were determined with a JASCO DIP-360 digital polarimeter at 26–30°. ^{1}H-N.m.r. spectra for substituted compounds were recorded with a Bruker WM-250 instrument for solutions in $CDCl_3$ (internal Me_4Si). The 1D- and 2D-n.m.r. spectra of **10** and **13** were recorded in D_2O at 30°, using Bruker WM-250 (for ^{1}H) and AM-300 (for ^{13}C) spectrometers with acetone as the reference (^{1}H, 2.225 p.p.m.; ^{13}C, 31.45 p.p.m.). 1D and 2D experiments with **10** and **13** were performed as described in ref. 12. The n.m.r. data are recorded in Tables I–III.

Dichloromethane was washed with conc. H_2SO_4 and water, dried with $CaCl_2$, and distilled from CaH_2. Acetonitrile was distilled from P_2O_5 and then from CaH_2. Freshly distilled solvents were used in all experiments.

T.l.c. was performed on Kieselgel-60 (Merck) with EtOAc–toluene (*A* 1:2, *B* 1:1) and $CHCl_3$–EtOH (*C* 9:1), with detection by charring with H_2SO_4. Column chromatography was performed on Silica Gel L 40/100 μm (C.S.F.R.) by gradient elution with benzene–EtOAc.

*Methyl 4,6-O-benzylidene-2-deoxy-2-phthalimido-β-*D*-glucopyranoside* (**2**). — To a solution of methyl 2-deoxy-2-phthalimido-β-D-glucopyranoside[13,14] (**1**; 3.3 g, 10.2 mmol) in acetonitrile (15 mL) were added benzaldehyde dimethyl acetal (4.1 mL, 27 mmol) and $TsOH \cdot H_2O$ (~ 20 mg). The mixture was kept for 16 h at 20°, pyridine (0.1 mL) was added, and the mixture was concentrated *in vacuo*. Column chromatography of the residue gave amorphous **2** (3.6 g, 86%), $[\alpha]_D$ −32° (*c* 1, $CHCl_3$), R_F 0.61 (solvent *A*); lit.[15] $[\alpha]_D$ −33° ($CHCl_3$).

The ^{1}H-n.m.r. data are listed in Table I; the attribution of the signals for H-3 and H-4 is the reverse of that reported[15].

*Methyl 4,6-O-benzylidene-2-deoxy-2-phthalimido-3-O-(2,3,4,6-tetra-O-acetyl-β-*D*-galactopyranosyl)-β-*D*-glucopyranoside* (**5**). — A mixture of **2** (206 mg, 0.5 mmol), **3** (293 mg, 0.75 mmol), molecular sieves 4 Å, and CH_2Cl_2 (6 mL) was stirred for 45 min at 20° under Ar. $NOBF_4$ (88 mg, 0.75 mmol) was added, the mixture was stirred for 1 h at 20°, then diluted with $CHCl_3$ (10 mL), filtered through Celite, and washed with aq. $NaHCO_3$ and water, and the solvent was evaporated. Column chromatography of the residue gave **5** (283 mg, 76%), $[\alpha]_D$ −9° (*c* 2, $CHCl_3$), R_F 0.35 (solvent *A*).

The ^{1}H-n.m.r. data are listed in Table I.

*Methyl 4,6-O-benzylidene-3-O-(4,6-O-benzylidene-β-*D*-galactopyranosyl)-2-deoxy-2-phthalimido-β-*D*-glucopyranoside* (**7**). — A solution of **5** (371 mg, 0.5 mmol) in methanolic 0.1M MeONa (10 mL) was kept for 40 min at 20° until the conversion into **6** [R_F 0.16 (solvent *C*)] was complete. The solution was neutralised with KU-2 (H^+) resin, filtered, and concentrated to dryness. The residue (**6**) was then benzylidenated as described for the preparation of **2**. Column chromatography of the product gave amorphous **7** (272 mg, 82%), $[\alpha]_D$ −5° (*c* 2, $CHCl_3$), R_F 0.15 (solvent *B*).

*Methyl 3-O-(3-O-benzoyl-4,6-O-benzylidene-β-*D*-galactopyranosyl)-4,6-O-benzylidene-2-deoxy-2-phthalimido-β-*D*-glucopyranoside* (**8**). — To a stirred solution of **7**

(220 mg, 0.33 mmol) in acetonitrile (5 mL) were added benzoyl cyanide (45 mg, 0.34 mmol) and one drop of triethylamine. The mixture was stirred for 10 min, MeOH (2 mL) was added, the mixture was stirred for 5 min, the solvent was evaporated, and MeOH (5 mL) was evaporated from the residue. Column chromatography of the residue gave **8** (230 mg, 91%), m.p. 188–190° (from benzene–heptane), $[\alpha]_D$ +67° (*c* 0.8, $CHCl_3$), R_F 0.70 (solvent *B*).

Anal. Calc. for $C_{42}H_{39}NO_{13}$: C, 65.88; H, 5.13; N, 1.83. Found: C, 65.88; H, 5.20; N, 2.08.

The ^{1}H-n.m.r. data are listed in Table I.

Methyl 2-acetamido-2-deoxy-3-O-(β-D-galactopyranosyl)-β-D-glucopyranoside (**10**). — To a solution of **5** (148 mg, 0.2 mmol) in $CHCl_3$ (2 mL) was added aqueous 90% trifluoroacetic acid (1 mL). The mixture was stirred for 40 min, then diluted with $CHCl_3$ (20 mL), washed with water, aq. $NaHCO_3$, and water, filtered through cotton, and concentrated. Column chromatography of the residue gave the diol **9** (106 mg, 81%), a solution of which in aq. 96% EtOH (10 mL) and 99% hydrazine hydrate (2 mL) was boiled under reflux for 10 h. The mixture was concentrated and water (3 × 3 mL) was distilled from the residue, a solution of which in MeOH (10 mL) and water (2 mL) was treated with Ac_2O (4 mL) for 17 h at 20°, then concentrated. A solution of the residue in water (10 mL) was washed with 1-butanol (3 × 5 mL), then concentrated, and the residue was subjected to gel filtration on fracto-gel TSK HW-40(S) (25–40 μm, V_0 50 mL), in 0.01M acetic acid, to give amorphous **10** (53 mg, 83%), $[\alpha]_D$ −30° (*c* 1, H_2O).

The ^{1}H- and ^{13}C-n.m.r. data are listed in Tables II and III.

Glycosylation of **8** *with* **11**. — A solution of **8** (153 mg, 0.2 mmol), $Hg(CN)_2$ (127 mg, 0.5 mmol), $HgBr_2$ (70 mg), and molecular sieves 4 Å in acetonitrile (2 mL) and CH_2Cl_2 (1 mL) was stirred for 45 min at 20° under Ar. Using a syringe, a solution of **11** [prepared[2] from tetra-*O*-benzoyl-L-fucopyranose (290 mg, 0.5 mmol)] was introduced portionwise during 1 h. The mixture was stirred for 1 h, and $CHCl_3$ (10 mL) and sat. aq. KBr (10 mL) were added. The mixture was stirred for 10 min, then filtered through Celite, and the organic layer was washed with aq. KBr and water, filtered through cotton, and concentrated. A solution of the residue in $CHCl_3$ (2 mL) was treated with aq. 90% trifluoroacetic acid as described for the preparation of **9** from **5**. Column chromatography of the product gave methyl *O*-(2,3,4-tri-*O*-benzoyl-α-L-fucopyranosyl)-(1→2)-*O*-(3-*O*-benzoyl-β-D-galactopyranosyl-(1→3)-2-deoxy-2-phthalimido-β-D-glucopyranoside (**10**; 149 mg, 71%) and a mixture (28 mg, 13%) of **12** and its β isomer **14**.

Compound **12** was amorphous and had $[\alpha]_D$ +9° (*c* 2, $CHCl_3$), R_F 0.33 (solvent *C*).

The ^{1}H-n.m.r. data for **12** and **14** are listed in Table I.

Methyl O-α-L-*fucopyranosyl-(1→2)*-O-β-D-*galactopyranosyl-(1→3)-2-acetamido-2-deoxy-β-D-glucopyranoside* (**13**). — Compound **12** (149 mg, 0.14 mmol) was subjected to hydrazinolysis and subsequent *N*-acetylation, as described above for the preparation of **10** from **9**, to give amorphous **13** (61 mg, 80%), $[\alpha]_D$ −66.5° (*c* 0.4, H_2O).

The ^{1}H- and ^{13}C-n.m.r. data are listed in Tables II and III.

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