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SYNTHESIS OF DERIVATIVES OF 2-AMINO-2-DEOXY-4-*O*-(α- AND β-D-GALACTOPYRANOSYL)-D-GLUCOSE*

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ABSTRACT

Galactosylation of methyl 6-*O*-acetyl-3-*O*-benzoyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**5**) and its trityl ether **9** with 2,3,4,6-tetra-*O*-benzoyl-α-D-galactopyranosyl bromide (**8**), 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranose (**13**), 3,4,6-tri-*O*-benzoyl-1,2-*O*-(α-*p*-tolythiobenzylidene)-α-D-galactopyranose (**11**), and 3,4,6-tri-*O*-benzoyl-1,2-*O*-(α-cyanobenzylidene)-α-D-galactopyranose (**12**) gave 1,2-*cis*- and 1,2-*trans*-linked disaccharide derivatives in ratios ranging from 3.8:1 to 1:8.5 depending on the conditions of glycosylation. A practical synthesis of the target lactosamine derivative **2** was achieved by the reaction of **5** and **8** in nitromethane in the presence of silver triflate.

INTRODUCTION

The synthesis of a tetrasaccharide 1,2-*O*-(1-cyanoethylidene) derivative **1** tritylated at O-6″, which is a precursor for the preparation of the capsular polysaccharide of *Streptococcus pneumoniae* type 14, required the use of the specifically protected methyl 2-amino-2-deoxylactoside (lactosamine) derivative **2**. Access to **2** could involve either starting from lactosamine or attachment of the benzoylated galactose residue to O-4 of methyl 6-*O*-acetyl-3-*O*-benzoyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**5**). Lactosamine is expensive and its synthesis[1–3] followed by conversion into **2** would require more stages than the second approach which was thus preferred. We now report on the glycosylation of **5** and its trityl ether **9** in connection with the preparation of **2**.

* Dedicated to Professor Hans Paulsen.

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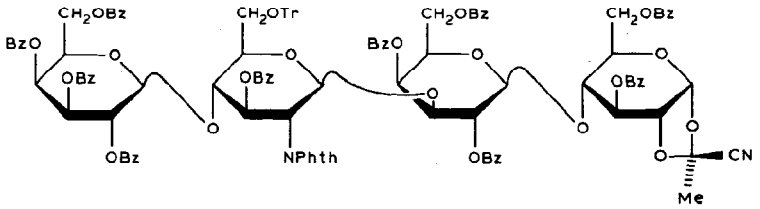

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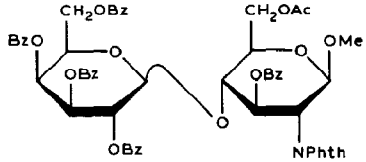

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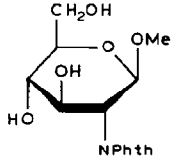

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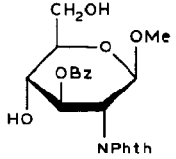

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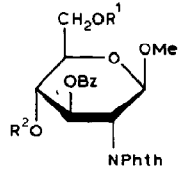
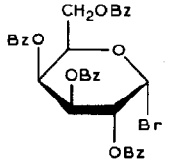


5 R^1 = Ac, R^2 = H

6 R^1 = H, R^2 = Ac

7 R^1 = R^2 = Ac

9 R^1 = Ac, R^2 = Tr



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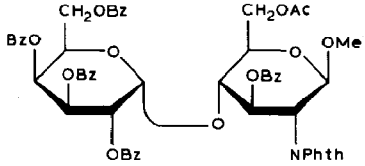

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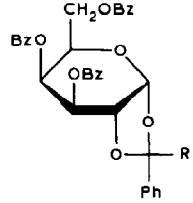


11 R = SC_6H_4Me-*p*

12 R = CN

TABLE I

^{1}H-N.M.R. CHEMICAL SHIFTS (δ, p.p.m.) AND VICINAL PROTON–PROTON COUPLING CONSTANTS (J, Hz) FOR COMPOUNDS **2**, **4–7**, **9**, **10**, **14**, **15**, **17**, AND **18** ($CDCl_3$)

Compound	*Residue*[a]	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6'*	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
2	R	5.34	4.42	6.16	4.13	[b]	4.21	4.46	8.4	11.0	8.6	9.8	4.2	2.0	12.0
	N	4.87	5.71	5.46	5.76	[b]	3.68	[b]	7.8	10.2	3.3	<1	6.7	5.6	10.1
4		5.38	4.42	5.87	[c]	3.73	[c]	[c]	8.1	10.7	8.6		5.0	3.4	12.0
5		5.36	4.43	5.89	3.80 –	3.87	4.47 –	4.57	8.5	10.3	8.6				11.9
6		5.42	4.46	6.10	5.32	3.79	3.70	3.87	8.5	10.6	9.2	9.2	4.0	2.1	12.2
7		5.42	4.47	6.05	5.38	3.98	4.25	4.42	8.1	10.8	9.1	10.0	2.5	4.5	12.1
9		5.42	4.09	6.28	3.68	4.10	3.75	4.41	8.4	10.5	8.4	8.6	6.0	2.4	11.6
10	R	5.43	4.33	6.05	4.36	4.04	4.45	4.77	8.4	10.5	8.5	9.5	4.5	2.5	11.9
	N	5.75	5.67	5.88	6.04	4.75	4.38	4.61	3.7	10.7	3.1	1.4	7.6	5.9	11.1
14	R	5.25	4.35	5.98	5.10	4.01	3.80	4.11	8.0	10.4	8.7	9.4	7.1	1.8	10.3
	N	5.00	5.85	5.65	6.01	4.39	4.46	4.69	7.6	10.1	3.3	<1	6.0	6.3	10.3
15[d]		5.39	4.38	5.95	4.06	3.80	4.27	4.40	8.3	10.5	8.5	9.3	4.0	2.1	11.7
17	R	5.39	4.34	6.09	4.21	3.96	4.37	4.61	8.2	10.5	8.3	9.4	4.7	2.4	11.7
	N	5.38	5.16	5.24	5.44	4.28	4.08	[e]	3.9	10.6	3.0	1.3	3.9		6.4
18	R	5.38	4.38	6.08	4.05	3.91	4.20	4.59	8.3	10.5	8.3	9.9	4.6	2.9	11.5
	N	4.57	5.11	4.88	5.15	[f]	[f]	[f]	7.5	10.4	3.3	<1			

[a]R, "reducing" end; N, "non-reducing" end. [b]3.77–3.94 (m, 3 H, H-5R,5N,6'N). [c]3.90–4.07 (m, 3 H, H-4,6,6'). [d]δ_{SiMe_3} −0.03. [e]$\delta_{H\text{-}6'}$ 4.15, multiplicity not determined. [f]3.35–3.58 (m, 6 H, H-5N, 6R,6'R and OMe). Other signals: aromatic δ 7.04–8.17, OMe 3.40–3.49 (3.07 for **14**), AcO 1.83–2.20.

TABLE II

REACTION CONDITIONS[a] AND YIELDS OF THE DISACCHARIDE DERIVATIVES **2** AND **10**

Run	*Glycosyl donor*	*Glycosyl acceptor*	*Promoter*	*Solvent*	*Temperature (°)*	*Yield (%)*		*Recovery of* **5** *(%)*
						10	**2**	
1	**8**	**5**	$Hg(CN)_2$–$HgBr_2$	MeCN	60–70	42	11	40
2	**8**	**5**	$AgOSO_2CF_3$	Toluene	−25 – −30	67	31	
3	**8**	**5**	$AgOSO_2CF_3$	CH_2Cl_2	−25 – −30	40	42	
4	**8**	**5**	$AgOSO_2CF_3$	$MeNO_2$	−25 – −30	40	53	
5	**8**	**5**	$AgOSO_2CF_3$	MeCN	−25 – −30	42	15	42
6	**8**	**9**	$AgOSO_2CF_3$	CH_2Cl_2	−25 – −30	51	44	
7	**11**	**9**	$TrClO_4$	CH_2Cl_2	20	8	17	69
8	**12**	**9**	$TrClO_4$	CH_2Cl_2	20	19	26	51
9	**12**	**9**	$TrBF_4$	CH_2Cl_2	20	2	17	75
10[b]	**13**	**5**	$Me_3SiOSO_2CF_3$	CH_2Cl_2	20	3	20	31[c]

[a]The ratio of glycosyl donor:glycosyl acceptor:promoter was 2:1:2 for runs 1-6, 1:1:0.1 for runs 7-9, and 1:1:0.8 for run 10. [b]The (1→6)-linked disaccharide derivative **14** was the main product (yield 29%). [c]The yield of the trimethylsilyl ether **15**.

TABLE III

^{13}C-N.M.R. DATA FOR COMPOUNDS **2**, **10**, **14**, **17**, AND **18** ($CDCl_3$; δ, p.p.m.; *J*, Hz)

Compound	*Residue*[a]	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*OCH₃*	$J_{C-1,H-1}$
2	R	99.2	54.9	71.4	76.9	72.9	62.0	57.0	158.7
	N	101.2	70.2	71.9	67.6	71.4	60.9		158.7
10	R	98.7	55.1	73.6	74.7	72.7	63.1[b]	57.0	162.8
	N	97.2	68.3	67.9	68.8	67.9	61.9[b]		172.0
14	R	98.9	54.9	71.6	70.3	73.7	68.8	56.6	161.1
	N	101.8	70.0	71.8	68.4	71.8	62.2		161.1
17	R	98.9	55.2	74.8	74.1	72.8	61.5	56.9	
	N	96.8	66.8	67.6	68.0	67.4	63.3		
18	R	99.2	55.0	71.7	77.3	72.9	60.1	57.0	
	N	100.9	69.5	71.1	66.5	70.7	62.4		

[a]R, "reducing" end; N, "non-reducing" end. [b]Assignments may be interchanged. Other signals: C=O, 164.9–170.7; aromatic, 123.0–134.2; CH_3CO, 20.4–20.9 p.p.m.

RESULTS AND DISCUSSION

Benzylidenation of the known[4,5] methyl 2-deoxy-2-phthalimido-β-D-glucopyranoside (**3**) followed by benzoylation and deacetalation afforded the diol **4** in 76% overall yield. The selective acetylation of **4** gave mainly the 6-acetate **5** (86%), which could easily be separated from the 4-acetate **6** (3%) and 4,6-diacetate **7** (10%) by crystallisation and column chromatography. The ^{1}H-n.m.r. data for **4**–**7** were in accord with their structures (see Table I).

Treatment of **5** at 60–70° with 2 mol of 2,3,4,6-tetra-*O*-benzoyl-α-D-galactopyranosyl bromide (benzobromogalactose, **8**) under Helferich conditions [acetonitrile–mercuric cyanide (2 mol)–mercuric bromide (catalytic amount)] gave a mixture of the anomeric disaccharide derivatives **2** and **10** in which the latter (1,2-*cis*-linked) markedly preponderated (Table II, run 1). No disaccharide derivatives were formed on attempted reaction at room temperature.

The structures of **2** and **10** were established on the basis of ^{1}H- and ^{13}C-n.m.r. data (Tables I and III). Thus, in particular, the low-field shift of the signal for C-4 in the spectra of **2** (δ 76.9) and **10** (δ 74.7) shows the galactosylation site to be O-4. The $J_{H-1',H-2'}$ and $J_{C-1',H-1'}$ values for **2** (7.8 and 158.7 Hz) and **10** (3.7 and 172.0 Hz) establish the β and α configurations, respectively.

The reactions of **5** and **8** in the presence of silver triflate and in various solvents (Table II, runs 2–5) showed that increase in the polarity of the solvent (toluene → dichloromethane → nitromethane, runs 2–4) favoured the formation of the 1,2-*trans*-linked derivative **2**, whereas the result with acetonitrile (run 5) shows this dependence to be complex and ambiguous.

The reaction of 2-amino-2-deoxy-D-glucose derivatives with 2-*O*-acylgalactosyl halides to give a (1→4) linkage has a low efficiency when O-6 and especially O-3 in the acceptor bear acyl substituents[6], whereas, with alkyl substituents (*e.g.* allyl, benzyl, or methyl), the efficiency and stereoselectivity are high[7–14]. The lack of stereoselectivity of glycosylation in combination with high total yield of disaccha-

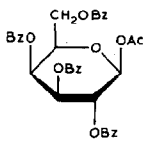
ride derivatives has been observed with 3,4,6-tri-*O*-benzyl-2-*O*-*p*-nitrobenzoyl-α-D-galactopyranosyl bromide as the donor[14]. Replacement of the alcohol **5** by its trityl ether **9** did not solve this problem since, although the reaction of **9** with **8** increased the total yield of **2** and **10**, the stereoselectivity was not improved (Table II, run 6). The trityl ether **9** was prepared by treatment of **5** with triphenylmethylium perchlorate in the presence of 2,4,6-trimethylpyridine[15]. That the trityl group was located at O-4 was proved by regeneration of **5** upon treatment of **9** with aqueous trifluoroacetic acid; the ^{1}H-n.m.r. spectrum of **9** was not informative.

1,2-Thio-orthoesters and 1,2-*O*-cyanoalkylidene derivatives have been used for stereospecific 1,2-*trans*-glycosylation[16–18], although loss of stereospecificity with these reagents is also documented[17,19,20]. When **9** reacted with the 1,2-thio-orthoester **11** and the 1,2-*O*-(α-cyanobenzylidene) derivative **12** (Table II, runs 7–9), the stereoselectivity of glycosylation was higher than with **8** but the yields of **2** and **10** were unsatisfactory. This result is in accord with the low efficiency of glycosylation of a 4-*O*-tritylated 2-acetamido-2-deoxy-D-glucose derivative with galactose 1,2-thio-orthoester[18]. The 4-*O*-glycosylation of 2-amino-2-deoxy-D-glucose derivatives with galactose 1,2-orthoesters[21,22] is non-stereospecific. The use of triphenylmethylium tetrafluoroborate as a catalyst (run 9) instead of perchlorate (run 8) favours 1,2-*trans*-stereoselectivity of glycosylation which is consistent with earlier observations[23].

Galactosylation of the alcohol **5** with 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranose (**13**) in the presence of trimethylsilyl triflate (run 10) was also studied in view of a synthesis of a lactosamine derivative using β-D-galactopyranose penta-acetate[24]. Interaction of **5** with **13** afforded, in addition to the (1→4)-linked disaccharide derivatives **2** and **10**, the (1→6)-linked allo-lactosamine derivative **14**, the yield of which exceeded those of **2** and **10** combined. The formation of **14** is probably due to 6→4 acetyl migration. The *O*-trimethylsilyl derivative **15** was also isolated, and its structure determined from the ^{1}H-n.m.r. data (Table I) and the regeneration of **5** on acid hydrolysis. The structure of **14** was indicated by the ^{1}H- and ^{13}C-n.m.r. data (Tables I and III). In particular, the low-field position of the signal of C-6 (δ 68.8) shows that galactosylation had occurred at O-6 and the $J_{H\text{-}1',H\text{-}2'}$ and $J_{C\text{-}1',H\text{-}1'}$ values (8.0 and 161.1 Hz, respectively) indicated the bond to be β.

Thus, the galactosylation of the alcohol **5** and its trityl ether **9** with mono- and bi-cyclic glycosylating agents lacks stereospecificity and, in some reactions, the 1,2-*cis*-linked disaccharide **10** was the preponderant product. Relatively high 1,2-*trans*-selectivity was observed with the glycosyl donors **13** and **12** (in the presence of triphenylmethylium tetrafluoroborate), but the yields of the target disaccharide derivative **2** were low. Under the conditions of run 4 (Table II), **2** was formed with highest efficiency and they were chosen for its preparation. The 5-mmolar-scale galactosylation of **5** gave **2** and **10** in yields of 44 and 40%, respectively.

Although runs 1, 2, and 5 (Table II) were unsatisfactory for the synthesis of **2**, the conditions employed (especially those of run 2) may be suitable for the prepara-



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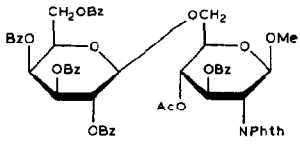

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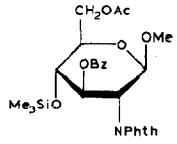

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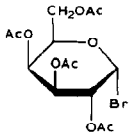

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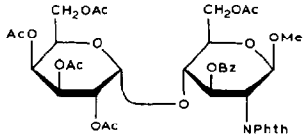

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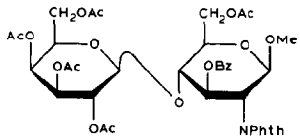

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tion of 4-*O*-(α-D-galactopyranosyl) derivatives of 2-amino-2-deoxy-D-glucose.

The alcohol **5** was reacted with 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (acetobromogalactose, **16**) in order to compare the reactivities of **8** and **16**, the former being reported[25] to be the more efficient galactosylating agent. Condensation of **16** with **5** under the conditions of run 4 (Table II) gave, after acetylation, the disaccharide derivatives **17** and **18** in yields of 20 and 32.5%, respectively, and the diacetate **7** (39%) was also isolated. The ^{1}H- and ^{13}C-n.m.r. data of **17** and **18** accord with the structures assigned. Thus, benzobromogalactose is a more effective galactosylating agent than acetobromogalactose, but the 1,2-*trans*-selectivity of the latter in the reaction with alcohol **5** was higher.

EXPERIMENTAL

Melting points were determined with a Kofler apparatus and optical rotations, for solutions in chloroform, with a A1-EPN (U.S.S.R.) automatic polarimeter at 20 ±2°. N.m.r. spectra were recorded with a Bruker WM-250 instrument for solutions in $CDCl_3$ (internal Me_4Si). Nitromethane was distilled from urea at 100 mmHg, then from P_2O_5 (twice), and finally from CaH_2. Dichloromethane was washed with conc. H_2SO_4 and water, dried with $CaCl_2$, and distilled from CaH_2. Toluene was dried with $CaCl_2$ and distilled from Na. Acetonitrile was distilled from P_2O_5 and then from CaH_2. Freshly distilled solvents were used in all experiments. 2,4,6-Trimethylpyridine was distilled from KOH and then from CaH_2. Tetramethylurea was distilled and stored over molecular sieves 3Å. Triphenylmethylium perchlorate and tetrafluoroborate were synthesised as described[26] and futher purified[27] when used as catalysts for glycosylation. Silver triflate was prepared as described[28]. Column chromatography was performed on Silica Gel L 40/100 μm (C.S.S.R.), using a benzene–ethyl acetate gradient. Kieselgel 60 (Merck) was used for t.l.c. with ethyl acetate–toluene mixtures (*A*, 1:10; *B*, 1:4; *C*, 1:2; *D*, 1:1) and *E*, 1:4 acetone–benzene, and with detection by charring with sulphuric acid.

Methyl 3-O-benzoyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**4**). — To a solution of methyl 2-deoxy-2-phthalimido-β-D-glucopyranoside[4-5] (**3**; 4.5 g, 13.9 mmol) in acetonitrile (20 mL) were added benzaldehyde dimethyl acetal (13 mL, ~70 mmol) and $TsOH \cdot H_2O$ (~20 mg). The mixture was kept for 17 h at 20°, and then pyridine (6 mL) was added followed by benzoyl chloride (5.8 mL), dropwise with cooling. The mixture was stored for ~3 h at 20°, MeOH (5 mL) was then added, the mixture was concentrated to dryness, and toluene was distilled repeatedly from the residue *in vacuo*. A solution of the residue in aqueous 90% trifluoroacetic acid (20 mL) was kept for ~1 h at room temperature, then poured into ice-water (200 mL), and extracted with $CHCl_3$ (150 mL plus 2 × 50 mL). The combined extracts were washed with aqueous $NaHCO_3$ and water, filtered, and concentrated. The residue was crystallised from chloroform–hexane and purified by column chromatography ($CHCl_3$–MeOH, 93:7) to give **4** (4.5 g, 76%), m.p. 168–169° (from chloroform–hexane), $[\alpha]_D$ +112° (*c* 0.9), R_F 0.15 (solvent *D*).

Anal. Calc. for $C_{22}H_{21}NO_8$: C, 61.82; H, 4.95; N, 3.28. Found: C, 62.03; H, 5.24; N, 3.34.

Methyl 6-O-acetyl-3-O-benzoyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**5**). — To a stirred solution of **4** (1.4 g, 3.3 mmol) and pyridine (0.8 mL) in dry chloroform (10 mL) was added a solution of acetyl chloride (0.225 mL, 3.6 mmol) in dry chloroform (5 mL) dropwise during 1 h at 20°. Stirring was continued for 20 min, the solution was concentrated, and toluene was evaporated from the residue, which was then crystallised from chloroform–hexane to give **5**. Column chromatography of the mother liquor (benzene–acetone) gave the diacetate **7**, more **5**, and the 4-acetate **6**.

Compound **5** (1.33 g, 86%) had m.p. 181–184° (from chloroform–hexane), $[\alpha]_D$ +99° (*c* 0.7), R_F 0.42 (solvent *C*) and 0.47 (solvent *E*).

Anal. Calc. for $C_{24}H_{23}NO_9$: C, 61.40; H, 4.94; N, 2.98. Found: C, 61.31; H, 4.57; N, 3.11.

Methyl 4-*O*-acetyl-3-*O*-benzoyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**6**; 50 mg, 3%) was amorphous and had $[\alpha]_D$ +122° (*c* 0.55), R_F 0.24 (solvent *E*).

Anal. Found: C, 61.44; H, 5.10; N, 2.80.

Methyl 4,6-di-*O*-acetyl-3-*O*-benzoyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**7**; 0.17 g, 10%) was amorphous and had $[\alpha]_D$ +105° (*c* 1.05), R_F 0.64 (solvent *E*).

Anal. Calc. for $C_{26}H_{25}NO_{10}$: C, 61.06; H, 4.93; N, 2.74. Found: C, 61.20; H, 5.02; N, 2.96.

The ^{1}H-n.m.r. data for **5**–**7** are listed in Table I.

Methyl 6-O-acetyl-3-O-benzoyl-2-deoxy-4-O-trityl-2-phthalimido-β-D-glucopyranoside (**9**). — To a stirred solution of **5** (0.94 g, 2 mmol) and 2,4,6-trimethylpyridine (0.58 mL, 4 mmol) in dry dichloromethane (20 mL) was added triphenylmethylium perchlorate (0.82 g, 2.4 mmol) portionwise during 1 h. The solution was stirred for 17 h, treated with 3:1 pyridine–methanol (1 mL), diluted with chloroform

(70 mL), washed with water (3 × 30 mL), and concentrated. Column chromatography of the residue gave **9** (1.40 g, 99%; 81% after crystallisation from ether–hexane), m.p. 195–196.5°, $[\alpha]_D$ +223° (*c* 1.8), R_F 0.46 (solvent *B*).

Anal. Calc. for $C_{43}H_{37}NO_9$: C, 72.56; H, 5.24; N, 1.97. Found: C, 72.64; H, 5.43; N, 1.91.

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

3,4,6-Tri-O-*benzoyl-1,2*-O-*(α*-p-*tolylthiobenzylidene)*-α-D-*galactopyranose* (**11**). — Following the general procedure for the preparation of sugar 1,2-thioorthoesters[29], a solution of benzobromogalactose **8** (3.30 g, 5.0 mmol) in nitromethane (5 mL) was heated with *p*-toluenethiol (0.59 g, 4.8 mmol) and 2,4,6-trimethylpyridine (1.2 mL, 7.5 mmol) for 30 min at 60–70°. Conventional work-up then gave amorphous **11** (2.32 g, 69%), $[\alpha]_D$ +54° (*c* 1.15), R_F 0.79 (ether–benzene, 1:13).

Anal. Calc. for $C_{41}H_{34}O_9S$: C, 70.07; H, 4.88; S, 4.56. Found: C, 69.61; H, 4.98; S, 4.55.

3,4,6-Tri-O-*benzoyl-1,2*-O-*(α-cyanobenzylidene)*-α-D-*galactopyranose* (**12**). — Using the conditions for the preparation of sugar 1,2-*O*-cyanoalkylidene derivatives[30], a solution of **8** (3.30 g, 5.0 mmol) in acetonitrile (10 mL) was stirred with tetrabutylammonium bromide (0.75 g, 2.5 mmol) for 0.5 h at room temperature. Finely ground, dry sodium cyanide (1.23 g, 25 mmol) was then added and stirring was continued for 17 h. Conventional work-up gave amorphous **12** (0.90 g, 30%), $[\alpha]_D$ +87° (*c* 0.7), R_F 0.50 (ethyl acetate–heptane, 1:2) and 0.63 (ethyl acetate–benzene, 1:8).

Anal. Calc. for $C_{35}H_{27}NO_9$: C, 69.42; H, 4.49; N, 2.31. Found: C, 69.44; H, 4.51; N, 2.38.

1-O-*Acetyl-2,3,4,6-tetra*-O-*benzoyl-β*-D-*galactopyranose* (**13**). — Following the procedure for the preparation of glycosyl acetates[31,32], a solution of **8** (0.66 g, 1.0 mmol) in glacial acetic acid (10 mL) was stirred with mercuric acetate (0.64 g, 2.0 mmol) until dissolution was complete and then left overnight at 20°. The solution was diluted with chloroform (50 mL), washed with saturated aqueous potassium bromide (2 × 30 mL) and water, filtered, and concentrated, and the residue was dried *in vacuo* to give amorphous **13** (0.62 g, 97%), $[\alpha]_D$ +133° (*c* 0.55), R_F 0.54 (solvent *A*). ^{1}H-n.m.r. data: δ 8.15–7.20 (m, 20 H, 4 Ph), 6.11 (d, 1 H, $J_{1,2}$ 8.2 Hz, H-1), 6.05 (dd, 1 H, $J_{3,4}$ 3.4, $J_{4,5}$ 0.8 Hz, H-4), 5.93 (dd, 1 H, $J_{2,3}$ 10.3 Hz, H-2), 5.68 (dd, 1 H, H-3), 4.65 (dd, 1 H, $J_{5,6}$ 5.2, $J_{6,6'}$ 9.9 Hz, H-6), 4.48 (ddd, 1 H, $J_{5,6'}$ 6.0 Hz, H-5), 4.43 (dd, 1 H, H-6'), 2.11 (s, 3 H, AcO).

Anal. Calc. for $C_{36}H_{30}O_{11}$: C, 67.71; H, 4.74. Found: C, 67.36; H, 4.85.

Synthesis of methyl 6-O-*acetyl-3*-O-*benzoyl-2-deoxy-2-phthalimido-4*-O-*(2,3,4,6-tetra*-O-*benzoyl*-α- (**2**) *and -β*-D-*galactopyranosyl)*-β-D-*glucopyranoside* (**10**). — The results are summarised in Table II. Column chromatography was used to isolate the products, which were identified by ^{1}H-n.m.r. spectroscopy.

(*a*) *Run 1.* To a solution of **5** (0.25 g, 0.53 mmol), mercuric cyanide (0.25 g, 1.0 mmol), and mercuric bromide (30 mg) in dry acetonitrile (4 mL) was added a

solution of **8** (0.66 g, 1.0 mmol) in dry acetonitrile (10 mL). The mixture was heated for 5 h at 60–70°, left overnight at 20°, then diluted with chloroform (70 mL), and worked-up as described above for the preparation of **13**, to give **10** (230 mg, 42%), **2** (60 mg, 11%), and **5** (100 mg, 40%).

Compound **2** was amorphous and had $[\alpha]_D$ +70° (*c* 0.5), R_F 0.40 (solvent *B*).

Anal. Calc. for $C_{58}H_{49}NO_{18}$: C, 66.47; H, 4.77; N, 1.34. Found: C, 66.14; H, 4.77; N, 1.30.

Compound **10** was amorphous and had $[\alpha]_D$ +121° (*c* 0.4), R_F 0.48 (solvent *B*).

Anal. Found: C, 66.81; H, 4.55; N, 1.53.

The n.m.r. data for **2** and **10** are listed in Tables I and III.

(*b*) *Runs 2–5.* A solution of **5** (235 mg, 0.5 mmol), silver triflate (257 mg, 1.0 mmol), and tetramethylurea (90 μL, ~1 mmol) in the solvent specified (10 mL in run 2 and 5 mL in the others) was stirred, with protection from light, at −25 to −30° and a solution of **8** (660 mg, 1.0 mmol) in the appropriate solvent (5 mL) was added dropwise during 1 h. Stirring was continued for 1 h at this temperature and then for 1–2 h at 20°. The mixture was diluted with chloroform (80 mL), filtered, washed with aqueous 5% sodium thiosulphate (2 × 50 mL) and water (2 × 50 mL), and then concentrated, and the residue was chromatographed.

Galactosylation of **5** (5.0 mmol) under the conditions of the run 4 gave 44% of **2** and 40% of **10**.

(*c*) *Run 6.* The glycosylation of **9** (355 mg, 0.5 mmol) was performed as described above but with the omission of the tetramethylurea.

(*d*) *Run 7.* Using the conditions of glycosylation with sugar 1,2-thio-orthoesters[18], to a stirred solution of **9** (355 mg, 0.5 mmol) and triphenylmethylium perchlorate (17 mg, 0.05 mmol) in dry dichloromethane (5 mL) was added dropwise a solution of **11** (351 mg, 0.5 mmol) in dichloromethane at such a rate as to retain the yellow colour of the mixture. The mixture was stirred for 20 min and then treated with aqueous 90% trifluoroacetic acid (3 mL) for 15–20 min. The solution was poured into water (200 mL) and extracted with chloroform (3 × 30 mL), the combined extracts were washed with water (200 mL), saturated aqueous sodium hydrogencarbonate (50 mL), and water, and concentrated, and the residue was chromatographed.

(*e*) *Runs 8 and 9.* Glycosylation of **9** (284 mg, 0.4 mmol) with **12** (242 mg, 0.4 mmol) was performed in dichloromethane (2 mL) for 17 h at room temperature in the presence of triphenylmethylium perchlorate (14 mg, 0.04 mmol; run 8) or tetrafluoroborate (12 mg, 0.04 mmol; run 9), using the vacuum technique[17]. The catalyst was destroyed by addition of 3:1 methanol–pyridine (0.2 mL). No **12** or **9** was then detected in the reaction mixtures. The products **2**, **10**, and **5** were isolated by column chromatography.

(*f*) *Run 10.* A mixture of **5** (120 mg, 0.25 mmol), **13** (160 mg, 0.25 mmol), and molecular sieves 4Å in dry dichloromethane (5 mL) was stirred under argon at 20°, trimethylsilyl triflate (20 μL, ~0.1 mmol) was added with a syringe, and stirring was

continued overnight. T.l.c. then revealed 5–10% of products. More (20 μL) promoter was added and the mixture was stirred for 40 h. The reaction mixture then contained (t.l.c.) **2**, **5**, **10**, **14**, and **15**. Addition of triethylamine (0.2 mL) converted **5** into **15**. The mixture was diluted with chloroform (50 mL), filtered, washed with water, and concentrated. Column chromatography then gave **2**, **10**, methyl 6-*O*-acetyl-3-*O*-benzoyl-2-deoxy-2-phthalimido-4-*O*-trimethylsilyl-β-D-glucopyranoside [**15**; 42 mg, 31%; R_F 0.55 (solvent *B*) and 0.31 (solvent *A*)], and methyl 4-*O*-acetyl-3-*O*-benzoyl-2-deoxy-2-phthalimido-6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-β-D-glucopyranoside (**14**; 76 mg, 29%), foam, $[\alpha]_D$ +106° (*c* 2.5), R_F 0.55 (solvent *B*) and 0.29 (solvent *A*).

Anal. Calc. for $C_{58}H_{49}NO_{18}$: C, 66.47; H, 4.71; N, 1.34. Found: C, 65.96; H, 5.17; N, 1.30.

Compound **15** was treated with aqueous 90% trifluoroacetic acid (2 mL) for 20 min (the reaction was monitored by t.l.c.), and the solution was diluted with chloroform (30 mL), washed with water (2 × 30 mL), and concentrated to give **5** (~25 mg).

Methyl 6-O-acetyl-3-O-benzoyl-2-deoxy-2-phthalimido-4-O-(2,3,4,6-tetra-O-acetyl-α- (**17**) *and -β-D-galactopyranosyl)-β-D-glucopyranoside* (**18**). — Glycosylation of **5** (235 mg, 0.5 mmol) with acetobromogalactose **16** (420 mg, 1.0 mmol) was carried out under the conditions of run 4. In order to facilitate chromatographic separation, the worked-up reaction mixture was treated with acetic anhydride (2 mL) in pyridine (2 mL) for 17 h at 20°. Methanol (2 mL) was added and, after 15 min, the mixture was concentrated. Toluene (3 × 5 mL) was then evaporated from the residue which was chromatographed to give **7** (80 mg, 39%), **17** (80 mg, 20%), and **18** (130 mg, 32.5%).

Compound **17** was amorphous and had $[\alpha]_D$ +218° (*c* 0.1), R_F 0.5 (solvent *D*).

Anal. Calc. for $C_{38}H_{41}NO_{18}$: C, 57.07; H, 5.17; N, 1.75. Found: C, 57.18; H, 5.25; N, 1.84.

Compound **18** had m.p. 236–237° (from chloroform–hexane), $[\alpha]_D$ +61.8° (*c* 0.45), R_F 0.40 (solvent *D*).

Anal. Found: C, 56.94; H, 5.40; N, 1.75.

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