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Glycosylation by sugar 1,2-*O*-(1-cyanobenzylidene) derivatives: influence of glycosyl-donor structure and promoter

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ABSTRACT

3,4,6-Tri-*O*-acetyl-1,2-*O*-(1-cyanobenzylidene)-α-D-galactopyranoses with differently substituted aromatic nuclei have been synthesised and used as glycosyl donors in reactions with the acceptors methyl 2,3,4-tri-*O*-acetyl-6-*O*-trityl-β-D-galactopyranoside (**11**) and methyl 2,4,6-tri-*O*-acetyl-3-*O*-trityl-β-D-galactopyranoside (**12**). The glycosylation of **11** gave only β products. The efficiency and stereoselectivity of the glycosylations of **12** depend on the nature of the substituent in the aromatic ring. The stereoselectivity for the formation of 1,2-*trans*-glycosidic bonds was the highest with the *p*-methoxybenzylidene derivative with triphenylmethylium triflate as the promoter.

INTRODUCTION

Highly effective 1,2-*trans*-glycosylation by sugar 1,2-*O*-(1-cyanobenzylidene) derivatives has been used as a basis for the development of the first general method for the synthesis of regular polysaccharides that contain 1,2-*trans*-glycosidic linkages[1]. A main limitation of this method is the loss of stereoselectivity during the glycosylation of secondary hydroxyl groups of monosaccharide derivatives having the *xylo* and *arabino* configurations[2,3].

Although this defect can be overcome by glycosylation under high pressure[4], a chemical approach with improved stereoselectivity is desirable. The cause of the loss of stereoselectivity remains uncertain, but it may be connected with interference of the concerted mechanism of substitution at the anomeric centre of the donor by nucleophilic attack of the oxygen of the trityl group[1], and hence may depend on the reactivity of both the donor and the acceptor. In this connection, the enhancement of the reactivity of the donor by variation of its structure and modification of the promoter by changing the anion of the triphenylmethylium salt can affect the stereoselectivity.

We now report on the glycosylation of sugar primary and secondary trityl ethers with new 1,2-*O*-(1-cyanobenzylidene) derivatives of D-galactose in which the aromatic nuclei variously contain electron-donating and -withdrawing substituents.

RESULTS AND DISCUSSION

The 1,2-*O*-(1-cyanobenzylidene) derivatives were synthesised as follows. Tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**1**) was transformed into the 1,2-orthoester **2** which was not isolated but converted[5] into the 1,3,4,6-tetra-acetate **3**. Treatment of **3** with an aroyl (benzoyl, *p*-bromobenzoyl, *p*-methoxybenzoyl, 3,4,5-trimethoxybenzoyl, and *p*-cyanobenzoyl) chloride in pyridine–acetonitrile gave the 2-*O*-aroyl derivative **4** (Table I). Compounds **4a–e** were converted into the corresponding α-glycosyl bromides **5a–e**, which were characterised by their $[\alpha]_D$ values (see Experimental and Table II) and, without purification, transformed by the procedure for the synthesis of 1-cyanoalkylidene derivatives[6] (NaCN, Bu_4NBr, and acetonitrile) into the amorphous 3,4,6-tri-*O*-acetyl-1,2-*O*-(1-cyanobenzylidene)-α-D-galactopyranose derivatives **6–10**, isolated in yields of ~ 70% (Table II).

The structures of all of **4–10** were proved by the NMR spectra (Tables III and IV).

Like the 1-cyanoethylidene analogues[6], the cyanobenzylidene derivatives were obtained as mixtures of *exo*- and *endo*-cyano isomers. Since the reactivity of such isomers in glycosylation reactions does not differ substantially (cf. ref 7), the *exo,endo*-mixtures were used in the synthesis of the disaccharide derivatives. The *exo,endo*-CN ratios for **6–10** were determined on the basis of the ^{13}C NMR data.

TABLE I

Synthesis of the 2-aroyl derivatives **4a–e**

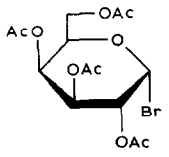
Compound	Yield (%)	$[\alpha]_D$ ($CHCl_3$) (degrees)	Mp (°C from ether–heptane)	Formulae	Calcd	Found
4a	98	+139 (23°C) (*c* 1.7)	94.5–96	$C_{21}H_{24}O_{11}$	C, 55.75; H, 5.31	C, 55.38; H, 5.62
4b	91	+108 (28°C) (*c* 3.2)	144–146	$C_{21}H_{23}BrO_{11}$	C, 47.46; H, 4.33	C, 47.92; H, 4.47
4c	78	+116 (26°C) (*c* 1.4)	89–93	$C_{22}H_{26}O_{12}$	C, 54.77; H, 5.39	C, 54.58; H, 5.55
4d	73	+97 (22°C) (*c* 2.2)				
4e	90	+124 (28°C) (*c* 2.8)	133–134.5	$C_{22}H_{23}NO_{11}$	C, 55.35; H, 4.82	C, 55.17; H, 5.03

TABLE II

Synthesis of the 1-cyanobenzylidene derivatives **6–10** [a]

Compound	Yield (%) [b]	*exo,endo*-CN ratio [c]
6	70	3.2:1
7	66	10.0:1
8	71	5.5:1
9	71	2.9:1
10	7	4.2:1

[a] The $[\alpha]_D^{23-28}$ values ($CHCl_3$) for the precursor α-glycosyl bromides were as follows: **5a** +200° (*c* 1.1); **5b** +166° (*c* 3.5); **5c** +153° (*c* 2.6); **5d** +148° (*c* 2.2); and **5d** +175° (*c* 1.3). [b] After column chromatography on silica gel. [c] Determined from the ratio of integrated intensities of the H-1 signals of the diastereomers (cf. ref 6).



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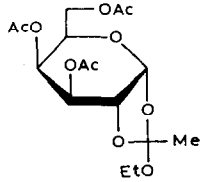

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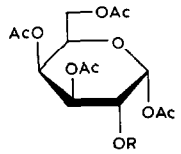
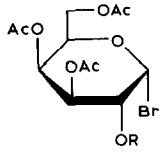
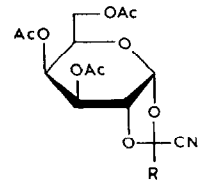




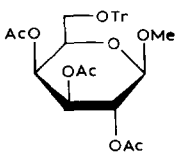


3 R = H
4a,5a R = Bz
4b,5b R = *p*-BrC_6H_4CO
4c,5c R = *p*-$MeOC_6H_4CO$
4d,5d R = 3,4,5-$(MeO)_3$-C_6H_2CO
4e,5e R = *p*-NCC_6H_4CO

6 R = Ph
7 R = *p*-BrC_6H_4
8 R = *p*-$MeOC_6H_4$
9 R = 3,4,5-$(MeO)_3-C_6H_2$
10 R = *p*-NCC_6H_4
17 R = CH_3

For **6**, it was 3.2:1 [cf. 2.8–3.7:1 for the corresponding isomers for 1,2-*O*-(1-cyanoethylidene)-α-D-galactopyranose[8]]. The ratio for the *p*-methoxy derivative **8** was 5.5:1 and 10:1 for the *p*-bromo derivative **7**. The *exo*,*endo*-CN ratio in the 1,2-*O*-(1-cyanoethylidene) series depends on the structure of the parent monosaccharide[6] and probably reflects shielding of the reaction centre of the intermediate dioxalenium cation during attack by the cyanide ion. As can be seen from the above data, the ratio also depends on the nature of the 2′-substituent in the dioxolane ring.

The behaviour of the new glycosyl donors **6–10** in disaccharide synthesis using the acceptors methyl 2,3,4-tri-*O*-acetyl-6-*O*-trityl-β-D-galactopyranoside[9] (**11**) and methyl 2,4,6-tri-*O*-acetyl-3-*O*-trityl-β-D-galactopyranoside (**12**) was explored. The use of **12** was of special interest because glycosylation by the corresponding 1,2-*O*-(1-cyanoethylidene) derivative proceeded with considerable loss of stereoselectivity[2,3].



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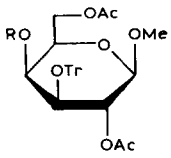

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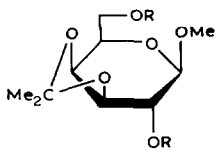
16 R = H



13 R = H
14 R = Ac

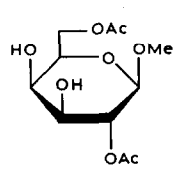


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TABLE III

^{1}H NMR data [a] (δ in ppm, J in Hz) for **4–10**, **12**, **14**, and **16** [b]

Compound	H-1	H-2	H-3	H-4	H-5	H-6A	H-6B	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{6A,5}$	$J_{6B,5}$	$J_{6A,6B}$
4a	6.48		5.5–5.7		4.36	4.12	4.05	3.0				6.8	6.8	11.5
4b	6.52		5.5–5.6		4.39	4.16	4.12	3.0				6.5	6.5	11.5
4c	6.48		5.48–5.53		4.36	4.13	4.07	3.0				7.0	7.0	11.5
4d	6.53	5.48	5.59	5.54	4.38	4.16	4.10	3.8	10.8	3.3	1.5	7.0	7.0	11.5
4e	6.50		5.52–5.56		4.39	4.15	4.09					6.5	7.0	11.0
5a [c]	6.92	5.28	5.57	5.56	4.58	4.18		4.0	11.5	3.5	1.8	6.0	6.0	6.0
5b [c]	6.91	5.31	5.55	5.56	4.58	4.18		4.0	11.5	3.5	2.0	6.0	6.0	6.0
5c [c]	6.92	5.28	5.57	5.56	4.58	4.18		4.0	11.5	3.5	1.7	6.0	6.0	6.0
5d	6.71	5.22	5.57	5.50	4.48	4.16	4.07	4.0	10.0	3.4	1.5	6.0	6.8	11.0
5e	6.79	5.34	5.63	5.58	5.56	4.23	4.15	4.0	10.3	3.5		6.0	6.5	11.5
6 *exo*-CN	6.09	4.52	5.01	5.39	4.31	4.18	4.12	5.0	7.0	3.5	1.8	6.5	6.5	11.5
6 *endo*-CN	5.84	4.52	5.5–5.6		4.5–4.6		4.25	4.2	4.5	7.5		6.8	6.8	12.0
7 *exo*-CN	6.06	4.50	4.95	5.36	4.27	4.17	4.09	5.0	7.0	3.5	2.0	6.8	6.8	11.3
7 *endo*-CN	5.82	4.51	5.53–5.59			4.10–4.23		4.6						
8 *exo*-CN	6.06	4.50	5.02	5.39	4.32	4.18	4.12	5.0	7.0	3.5	2.0	6.8	6.8	11.5
8 *endo*-CN	5.84	4.51	5.5–5.6		4.14	4.24	4.19	4.5	7.5			6.5		11.0
9 *exo*-CN	6.07	4.51	5.07	5.36	4.29	4.18	4.11	5.0	7.0	3.5	1.6	6.5	6.5	11.0
9 *endo*-CN	5.83	4.51	5.56	5.61	4.50	4.24	4.16	4.6				6.5		11.3
10 *exo*-CN	6.10	4.55	4.92	5.36	4.27	4.19	4.11	5.0	7.0	3.5	1.8	6.5	6.5	11.0
10 *endo*-CN	5.83	4.54	5.51–5.60		4.53	4.25	4.15	4.8	6.8			7.0	6.8	11.3
12	4.03	4.43	3.61	4.40	3.26	3.93	3.67	8.3	10.5	3.0	0.8	7.1	6.0	12.0
14	4.26	4.96	4.14–4.21		3.99	4.37		8.0	7.1		2.0	6.0	6.0	6.0
16	4.13	5.41	3.75	2.61	3.26	4.17	4.03	8.0	10.0	3.0	1.0	7.0	6.0	11.5

[a] Other signals: aromatic 7.2–7.5 (for **12**) and 7.2–7.6 (for **16**), OH 2.31 (for **16**), OMe 3.43 (for **12**), 3.47 (for **14**), and 3.43 (for **16**). Signals of the aromatic protons are omitted. [b] For solutions in $CDCl_3$, unless stated otherwise. [c] For solutions in CD_3CN.

TABLE IV

^{13}C NMR data [a] (δ in ppm) for **4–10**, **12**, **14**, and **16** [b]

Compound	C-1	C-2	C-3	C-4	C-5	C-6	OMe	CN
12	102.6	70.5	72.8	69.8	71.5	62.4	56.7	
14	101.3	72.7	77.0	73.6	70.9	63.5	56.5	
16	101.9	70.2	74.3	67.3	71.6	62.8	56.2	
4a	89.7	67.5	67.6	67.2	68.8	61.3		
4b	87.9	67.4 [c]	67.5 [c]	67.6 [c]	68.9	61.3		
4c	89.8	67.5	67.6	66.9	68.8	61.2	55.4	
4d	89.8	67.6	67.6	67.3	68.9	61.2	56.2	
4e	89.6	67.6	68.2	67.3	68.9	61.2		117.2
5a [d]	89.4	68.1	67.8	67.2	71.7	61.0		
5b [d]	89.3	68.3	67.8	67.2	71.8	61.1		
5c [d]	89.8	67.9	67.9	67.3	71.8	61.1	55.4	
5e	87.7	68.8	67.9	67.0	71.3	60.8		117.3
6 *exo*-CN	99.4	73.2	70.9	65.4	69.9	61.3		116.6
6 *endo*-CN	99.1	75.7	70.2	65.9	69.5	61.3		[e]
7 *exo*-CN	99.3	73.5	70.7	65.3	70.0	61.1		116.1
7 *endo*-CN	99.2	75.8	69.4	65.9	70.2	61.1		[e]
8 *exo*-CN	99.2	63.3	70.9	65.5	70.0	61.3	55.5	116.7
8 *endo*-CN	99.0	75.8	69.6	66.1	70.2	61.2		117.2
9 *exo*-CN	99.4	73.0	70.6	65.3	69.9	61.2		116.5
9 *endo*-CN	99.1	75.4	69.4	65.9	70.1	60.8		117.0
10 *exo*-CN	99.6	73.8	70.6	65.3	70.3	61.1		117.7
10 *endo*-CN	99.4	76.1	69.3	65.9	70.4	61.1		[e]

[a] Other signals: for **12**, 127.5, 127.8, 129.2, and 144.3 (Ph); for **16**, 127.5, 127.9, 128.9, and 144.3 (Ph). [b] For solutions in $CDCl_3$, unless stated otherwise. [c] Assignment for the signals may be interchanged. [d] For solutions in CD_3CN. [e] Low intensity of the signal.

The trityl ether **12** was obtained as follows. Acetylation of methyl 3,4-*O*-isopropylidene-β-D-galactopyranoside[9] (**13**) afforded **14**, which was deisopropylidenated using trifluoroacetic acid[10] to give the crystalline diol **15**. Treatment of **15** with triphenylmethylium perchlorate in the presence of 2,4,6-collidine[7] gave 84% of the 3-trityl ether **16**, which could be obtained (86%) from **14** without the isolation of **15**. Reaction of **16** with acetic anhydride–pyridine in the presence of a catalytic amount of 4-dimethylaminopyridine[11] gave the desired acceptor **12**.

Glycosylation of **11** and **12** severally by the 1,2-*O*-(1-cyanobenzylidene) derivatives **6–10** was carried out in dichloromethane with a 10% excess of the donor in the presence of 10 mol% of triphenylmethylium perchlorate as promoter and by the high-vacuum technique[12]. After 17 h at 20°C, each reaction was quenched with pyridine–water[13], and the amorphous disaccharide derivatives **18** and **19** were isolated by column chromatography (Table V) and characterised by their $[\alpha]_D$ values and ^1H and ^{13}C NMR spectra (Tables V–VII).

Glycosylations of the acceptor **11** with the primary trityloxy group were stereospecific and only the β products **18** were obtained regardless of the substituent in the aromatic nuclei of the donor. These results are similar to those obtained with the corresponding 1-cyanoethylidene derivative **17**, but the yields were higher (90–98%).

TABLE V

Glycosylation of the trityl ethers **11** and **12** by the 1-cyanoalkylidene derivatives **6–10** and **17** in the presence of triphenylmethylium perchlorate

Donor	Trityl ether	Disaccharide derivatives			
		Product(s)	Yield(%) [a]	$[\alpha]_D^{23-26}$ ($CHCl_3$) (degrees)	α,β-ratio
6	**11**	**18a**	87	+2 (*c* 2.3)	[b]
7	**11**	**18b**	98	+2 (*c* 2.0)	[b]
8	**11**	**18c**	97	+5 (*c* 2.6)	[b]
9	**11**	**18d**	98	+4 (*c* 1.7)	[b]
10	**11**	**18e**	57	+1 (*c* 2.3)	[b]
17	**11**	**18f**	73	−7 (*c* 1.6)	[b]
6	**12**	**19a-β**	79	+23 (*c* 1.5)	1:3.9
		19a-α		+87 (*c* 2.0)	
7	**12**	**19b-β**	71	+30 (*c* 2.2)	1:2.5
		19b-α		+101 (*c* 1.2)	
8	**12**	**19c-β**	95	+34 (*c* 2.2)	1:8.2
		19c-α		+58 (*c* 1.4)	
9	**12**	**19d-β**	90	+27 (*c* 1.9)	1:8.3
		19d-α		+95 (*c* 1.9)	
10	**12**	**19e-β**	53	+23 (*c* 2.2)	1:3.5
		19e-α		+95 (*c* 2.0)	
17	**12**	**19f-β**	72	−6 (*c* 2.0)	1:2.2
		19f-α		+66 (*c* 1.8)	
17c	**12**	**19f-β**	55		1:8.3
		19f-α			
8c	**12**	**19c-β**	85		1:26
		19c-α			

[a] After column chromatography. [b] β Isomer only. [c] Triphenylium triflate was the promoter.

For the glycosylations of the acceptor **12** bearing a secondary trityloxy group, the α,β-ratio of the whole disaccharide fraction was determined by ^1H NMR spectroscopy before the α and β isomers were isolated. The results (Table V) show that the stereochemical outcome of glycosylations depended on the nature of the substituent in the aromatic moiety of the donor. Thus, the unsubstituted 1,2-*O*-(1-cyanobenzylidene) derivative **6** and the *p*-bromo (**7**) and *p*-cyano (**10**) derivatives have no substantial influence on the stereoselectivity of glycosylations when compared with glycosylation by the corresponding 1,2-*O*-(1-cyanoethylidene) derivatives **17**; the α,β-ratio for the galactosyl-(1 → 3)-galactopyranose derivatives **19** was 1:2.5–4.0 (cf. 1:2.2 for **17**) and the yields were similar.

In contrast, the donors **8** (*p*-methoxy) and **9** (3,4,5-trimethoxy) showed considerably increased stereoselectivity. The α,β-ratio (**19-α**/**19-β**) became 1:8.2–8.3 and the yields were much higher (90–95%).

The above results indicate the usefulness of these new glycosyl donors for the stereospecific synthesis of 1,2-*trans*-glycosides. As mentioned above, the loss of stereoselectivity could be due to interference with the synchronous character of the

substitution at the anomeric centre. This effect can occur when the acceptor sterically hinders the attack of its trityl oxygen in the bicyclic dioxalenium intermediate (cf. ref 3) and/or the reactivity of this intermediate is too low (cf., for example, ref 1) so that it isomerises into a monocyclic non-stereospecifically reacting glycosyl cation. With the sterically unhindered 6-trityloxy group of the acceptor **11**, the glycosylations are stereospecific because nucleophilic attack of the intermediate proceeds more rapidly than its isomerisation into a glycosyl cation. In contrast, for the sterically more-hindered oxygen atom of the 3-trityloxy group in **12** (cf. ref 14), the reactivity of the donor becomes important. Probably the donors **8** and **9** with electron-donating substituents produce a more stable dioxalenium cation than do donors **6** and **7** and, at the same time, the stability of monocyclic glycosyl cation does not depend substantially on the nature of substituents in the 2-*O*-benzoyl group. Consequently, isomerisation of the dioxalenium cation into a glycosyl cation is inhibited more seriously and the stereoselectivity of the glycosylation is enhanced in comparison with glycosylation by 1-cyanoethylidene compounds.

The effect of changing the anion of the triphenylmethylium salt promoter on the stereochemical course of glycosylation was also investigated. The use of triphenylmethylium triflate led to considerably improved stereoselectivity. Thus, glycosylation of **12** by the 1,2-*O*-(1-cyanoethylidene) derivative **17** gave products with an α,β-ratio of 1 : 8.3 (cf. 1 : 2.2 for triphenylmethylium perchlorate, although the yield was slightly lower). Moreover, glycosylation of **12** with the *p*-methoxybenzylidene derivative **8** in the presence of triphenylmethylium triflate gave products (85%) with an α,β-ratio of 1 : 26. Hence, the use of **8** as the donor with triphenylmethylium triflate as the promoter makes the glycosylation effective and highly stereoselective.

The higher stereoselectivity obtained when triphenylmethylium perchlorate was replaced by the triflate could reflect the lower nucleophilicity of the latter ion in comparison with perchlorate[15,16], which should diminish the competitive reaction of the anion with dioxalenium cation to give a 1,2-*cis*-glycosidic linkage through a double-inversion process at the anomeric centre of the donor (cf. ref 17).

The new modification of the trityl–cyanoethylidene glycosylation reaction reported above avoids one of the most serious limitations of the reaction and considerably widens the scope of the method.

EXPERIMENTAL

General methods.—Optical rotations were determined with a Jasco DIP-360 polarimeter. Melting points were obtained with a Kofler block and are uncorrected. NMR spectra (internal Me_4Si) were recorded with a Bruker WM-250 spectrometer (250 MHz for ^1H and 62.89 MHz for ^{13}C). The ^1H signals were assigned by using selective homonuclear resonance and ^{13}C signals by using selective heteronuclear resonance.

TABLE VI

^{1}H NMR data [a] ($CDCl_3$, δ in ppm, J in Hz) for the disaccharide derivatives **18a–f** and **19a–f**

Residue		H-1	H-2	H-3	H-4	H-5	H-6A	H-6B	OMe	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6A}$	$J_{5,6B}$	$J_{6A,6B}$
18a	β-D-Gal*p*-OMe	4.18	5.05	4.88	5.28	3.77	3.83	3.64	3.12	8.25	10.5	3.5		3.8	7.5	10.3
	β-D-Gal*p*	4.65	5.40	5.16	5.39	3.95	4.10–4.17			7.5	11.0			6.2	6.2	
18b	β-D-Gal*p*-OMe	4.21	5.08	4.90	5.29	3.78	3.84	3.65	3.18	8.0	10.5	4.0		3.75	6.75	10.5
	β-D-Gal*p*	4.64	5.40	4.16	5.40	3.95	4.18	4.12		8.25	11.0	3.75		6.75	6.76	11.0
18c	β-D-Gal*p*-OMe	4.19	5.06	4.89	5.28	3.78	3.83	3.65	3.17	8.25	10.5	4.0		6.0	7.0	10.5
	β-D-Gal*p*	4.64	5.39	5.15	5.39	3.94	4.08–4.18		3.81	7.5	10.5	3.75				
18d	β-D-Gal*p*-OMe	4.21	5.08	4.90	5.31	3.79	3.86	3.65	3.2	8.0	10.5	3.5	1.0	3.5	6.75	9.75
	β-D-Gal*p*	4.65	5.38	5.22	5.40	3.95	4.18	4.12	3.86 (3 OMe)	8.0	10.5	3.4	1.2	7.0	6.5	11.45
18e	β-D-Gal*p*-OMe	4.23	5.09	4.91	5.30	3.78	3.85	3.67	3.22	8.0	10.5	3.5		4.5	6.5	9.5
	β-D-Gal*p*	4.65	5.41	5.19	5.42	3.97	4.19	4.13		8.0	10.5	3.5	1.0	6.75	6.5	11.5
18f	β-D-Gal*p*-OMe	4.32	5.10	4.92	5.29	3.80–3.85	3.77	3.67	3.44	7.5	11.0	3.4		5.0	6.9	11.0
	β-D-Gal*p*	4.48	5.09	4.91	5.29	3.85	4.10	4.04		8.25	11.0	3.4	1.25	7.0	7.0	11.75
19a-β	β-D-Gal*p*-OMe	4.19	5.06	3.79	5.41	3.72–3.85	3.91–4.23		3.36	8.0	10.0	3.5				11.7
	β-D-Gal*p*	4.70	5.35	5.13	5.34–5.37		3.91–4.23			8.0	11.0	3.5				
19a-α	β-D-Gal*p*-OMe	4.32	5.24	3.91	5.36	3.79	4.14	4.03	3.51	8.0	10.75	3.5	1.25	6.5	7.0	11.5
	α-D-Gal*p*	5.44	5.44–5.49	5.31–5.39	5.53	4.34	4.25	4.09		3.35		3.2	1.5	6.9	6.0	11.25
19b-β	β-D-Gal*p*-OMe	4.22	5.08	3.82	5.42	3.78	4.20	4.14	3.40	8.25	10.75	3.25		6.0	7.0	12.0
	β-D-Gal*p*	4.70	5.34	5.15	5.38	3.93	4.14	4.04		8.25	11.25	4.0		7.0	7.75	12.0

19b-α β-D-Gal*p*-OMe	4.30	5.22	3.89	5.29–5.37	3.78	4.14	4.02	3.50	8.0	10.5	3.2	1.0	7.0	7.0	11.0
α-D-Gal*p*	5.38–5.46		5.33	5.50	4.27–4.34	4.23	4.07		3.2		3.2	1.25	6.5	6.8	11.0
19c-β β-D-Gal*p*-OMe	4.23	5.10	3.82	5.44	3.79	4.14–4.21	3.94	3.40	7.3	10.5	3.9		5.5		
β-D-Gal*p*	6.71	5.36	5.15	5.38	3.97–4.14			3.85	8.5	10.5	3.8	1.0			
19c-α β-D-Gal*p*-OMe	4.30	5.22	3.89	5.35	3.78	4.12	4.01	3.50	7.8	10.5	3.5		7.5	7.5	11.9
β-D-Gal*p*	5.44	5.40	5.31	5.50	4.31	4.22	4.06	3.84	3.5	11.0	3.2	1.0	6.8	6.0	11.0
19d-β β-D-Gal*p*-OMe	4.23	5.10	3.82	5.43	3.78	4.18	4.02	3.41	8.0	10.0	3.8		5.5	7.2	11.9
β-D-Gal*p*	4.71	5.34	5.20	5.37	3.93	4.19	4.09	3.89 (3 OMe)	7.5	11.0	3.5	1.0	6.5	7.0	11.2
19d-α β-D-Gal*p*-OMe	4.31	5.23	3.90	5.36	3.78	4.14	4.02	3.50	8.0	10.5	3.4		6.8	7.0	11.0
α-D-Gal*p*	5.44–5.47	5.34–5.38		5.5	4.29	4.23	4.0	3.90–3.92 (3 OMe)					7.0	6.0	10.5
19e-β β-D-Gal*p*-OMe	4.21	5.04	3.83	5.41	3.79	4.16	4.04	3.39	8.0	10.0	3.5	1.0	6.0	7.0	11.8
β-D-Gal*p*	4.69	5.33	5.16	5.38	3.93	4.21	4.10		8.0	10.5	3.5	1.0	6.5	7.0	11.2
19e-α β-D-Gal*p*-OMe	4.31	5.21	3.91	5.51	3.79	4.15	4.02	3.49	8.0	10.5	3.0	1.0	6.9	7.0	11.2
α-D-Gal*p*	5.29–5.38		5.41–5.47		4.33	4.23	4.07						6.5	6.0	11.0
19f-β β-D-Gal*p*-OMe	4.23	5.10	3.78	5.31	3.80	4.09	4.01	3.41	8.0	10.0	3.6		5.4	6.8	11.3
β-D-Gal*p*	4.50	5.00	4.85	5.27	3.80	4.09	3.01		7.8	10.5	3.5		5.4	6.8	11.3
19f-α β-D-Gal*p*-OMe	4.30	5.2	3.87	5.34	3.81	4.17	4.10	3.49	8.4	10.5	3.0		7.0	7.0	11.8
α-D-Gal*p*	5.23	5.25	5.10	5.43	4.25	4.16	4.01		3.5	10.0	3.5	1.4	7.0	6.2	11.0

[a] Chemical shift data for the aromatic protons are omitted.

TABLE VII

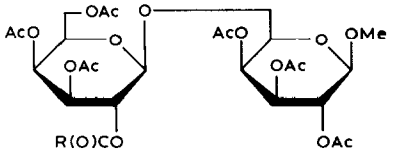
^{13}C NMR data [a] ($CDCl_3$, δ in ppm) for the disaccharide derivatives **18a–f** and **19a–f**

	C-1 / C-1′	C-2 / C-2′	C-3 / C-3′	C-4 / C-4′	C-5 / C-5′	C-6 / C-6′	OCH_3
18a	101.7	68.8	70.8 [b]	67.8	72.5 [b]	67.6	56.5
	101.1	69.2	70.7 [b]	66.9	70.7 [b]	61.1	
18b	101.6	68.7	70.7	67.7	72.3	67.4	56.3
	100.8	69.5	70.5	66.9	70.7	61.0	
18c	101.8	68.9	70.9 [b]	67.9	72.6	67.8	56.5
	101.3	68.9	70.8 [b]	67.1	70.8 [b]	61.2	55.4
18d	101.8	68.9	70.9 [b]	67.8	72.5	67.7	56.6
	101.2	69.5	70.5	67.1	70.9 [b]	61.2	56.2 (3 OCH_3)
18e	101.9	68.8	70.9 [b]	67.8	72.5	67.7	56.6
	100.7	70.2	70.6	67.1	70.9 [b]	61.2	
18f	101.9	68.5	70.9 [b]	67.5	72.1	66.9	56.8
	101.0	68.7	70.6 [b]	66.7	70.7 [b]	61.1	
19a-β	101.8	70.1	77.5	69.4	71.4 [b]	62.5	56.5
	101.3	68.7	70.9	66.9	70.7 [b]	60.9	
19a-α	102.4	69.8	73.2	65.1	71.1	61.7	56.6
	93.4	67.7 [b]	67.2	68.2	67.5 [b]	61.7	
19b-β	101.8	70.3	77.1	68.8	71.4	62.4	56.6
	101.1	69.8	70.6	66.9	70.9	60.9	
19b-α	102.3	69.8	73.4	65.2	71.1	61.6	56.6
	93.6	68.1	67.3	68.1	67.4	61.6	
19c-β	101.8	70.1	77.5	68.7	71.4	62.5	56.5
	101.4	69.1	70.8	66.9	70.9	61.0	55.5
19c-α	102.9	69.8	73.4	65.1	71.1	61.7	56.7
	93.8	67.5	67.2	68.2	67.5	61.7	55.6
19d-β	101.8	70.2	77.5	68.7	71.3	62.4	56.5
	101.3	69.9	70.4	66.9	70.9	60.9	56.3 (3 OCH_3)
19d-α	102.2	69.6	73.3	64.9	70.8	61.5	56.9
	93.4	67.2	67.2	67.9	67.0	61.5	56.4 (3 OCH_3)
19e-β	101.7	70.5	76.5	68.8	71.2	62.3	56.6
	100.9	70.3	70.3	66.8	70.9	60.9	
19e-α	102.3	69.5	72.9	65.0	70.6	61.5	56.8
	92.9	67.2	67.2	67.9	67.1	61.5	
19f-β	101.7	70.7	75.8	68.9	71.3 [b]	62.1	56.8
	101.0	68.6	70.7	66.7	70.7 [b]	60.9	
19f-α	102.3	69.4	72.8	65.0	70.8	61.5	56.9
	93.3	67.3 [b]	66.5	67.8 [b]	66.8 [b]	61.5	

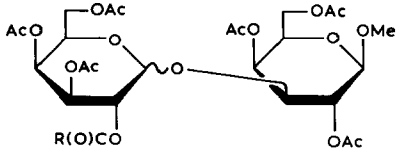
[a] Chemical shift data for the aromatic carbons are omitted. [b] Assignments of the signals for the compound may by interchanged.

Column chromatography was performed on Silica Gel L (100–160 μm, Chemapol) with gradient elution. TLC was performed on Kieselgel 60 (Merck), using 19:1 $CHCl_3$–MeOH (*A*), benzene–EtOAc, 3:1 (*B*) and 17:3 (*C*), with detection by charring with H_2SO_4.

Acetonitrile was dried over $CaCl_2$ and then distilled successively from $CaCl_2$, P_2O_5, and CaH_2. Ether, pyridine, and 2,4,6-collidine were each dried over KOH and distilled from KOH and then from CaH_2. NaCN was ground and dried over



18a R = Ph
18b R = *p*-BrC_6H_4
18c R = *p*-$MeOC_6H_4$
18d R = 3,4,5-$(MeO)_3$-C_6H_2
18e R = *p*-NCC_6H_4
18f R = Me



19a R = Ph
19b R = *p*-BrC_6H_4
19c R = *p*-$MeOC_6H_4$
19d R = 3,4,5-$(MeO)_3$-C_6H_2
19e R = *p*-NCC_6H_4
19f R = Me

P_2O_5 for 10 h at 100°C. Tetrabutylammonium bromide was purified by reprecipitation from EtOAc and dried over P_2O_5 at 20°C. Triphenylmethylium perchlorate was prepared as described[18] and recrystallised from nitromethane–ether. Triphenylmethylium triflate was prepared from triphenylmethylium chloride and silver triflate in nitromethane.

*1,3,4,6-Tetra-*O*-acetyl-2-*O*-aroyl-α-*D*-galactopyranoses* (**4**).—To a solution of the tetra-acetate **3**[19] (10 mmol) in acetonitrile (2 mL) and pyridine (2 mL) was added, with stirring at room temperature, the appropriate aroyl chloride (11.5 mmol) or its solution in acetonitrile (1.5 mL). When the reaction was complete (TLC), MeOH (60 μL) was added, and, after 30 min, the mixture was diluted with 1:2 $CHCl_3$–hexane (90 mL), washed with water, M H_2SO_4, satd aq $NaHCO_3$, and water, filtered, dried, and concentrated. The residue was crystallised from ether (25 mL) and heptane (40 mL). The results are given in Table I.

*3,4,6-Tri-*O*-acetyl-2-*O*-aroyl-*D*-galactopyranosyl bromides* (**5**).—To a solution of **4** (0.1 mol) in $CHCl_3$ (50 mL) were added Ac_2O (6 mL), AcBr (0.3 mol), and AcOH (16 mL). Then, to the stirred mixture was added a solution of H_2O (0.3 mol) in AcOH (17 mL) with external cooling to maintain the temperature at 20°C. After 2 h, the mixture was poured into ice–water and extracted with 1:2 $CHCl_3$–hexane. The upper layer was washed successively with chilled water, satd aq $NaHCO_3$, and water, dried, and concentrated to give **5** as an oil, in nearly quantitative yield (see Table II), which was used without purification for the next stage.

*3,4,6-Tri-*O*-acetyl-1,2-*O*-(1-cyanoarylidene)-α-*D*-galactopyranoses* (**6–10**).—To a solution of **5** (5 mmol) in acetonitrile (15 mL) were added tetrabutylammonium bromide (2.1 mmol) and NaCN (25 mmol). The mixture was stirred for 12 h at 20°C when a test[6] indicated the absence of **5**. The mixture was diluted with 1:2 $CHCl_3$–hexane (200 mL), washed with water (2 × 50 mL), aq 5% $KHSO_4$ (2 × 50 mL), satd aq $NaHCO_3$ (50 mL), and water (4 × 50 mL), dried, and concentrated. Column chromatography (benzene–EtOAc, 1:2) of the residue gave amorphous **6–10**, each as a mixture of *endo*- and *exo*-CN-isomers. The yields and the ratios of the isomers, determined by ^1H NMR spectroscopy, are given in Table II.

Methyl 2,6-di-O-acetyl-3,4-O-isopropylidene-β-D-galactopyranoside (**14**).—A solution of **13**[9] (5.1 g, 21.7 mmol) in pyridine (25 mL) was treated with Ac_2O (21 mL, 217 mmol) at room temperature overnight. The mixture was cooled to 10°C, MeOH (2 mL) was added, and, after 30 min, the mixture was poured into ice–water (400 mL) and extracted with $CHCl_3$ (200 mL). The extract was washed with water (3 × 150 mL), aq 5% $KHSO_4$ (2 × 100 mL), and water (3 × 150 mL), dried, and concentrated to give **14** (6.36 g, 95%); R_f 0.57 (solvent *A*); mp 92–93°C (from ether–pentane); $[\alpha]_D^{23}$ +24° (*c* 2.3, $CHCl_3$). Anal. Calcd for $C_{14}H_{22}O_8$: C, 52.83; H, 6.92. Found: C, 52.41; H, 6.97.

Methyl 2,6-di-O-acetyl-3-O-trityl-β-D-galactopyranoside (**16**).—To a solution of **14** (3.49 g, 11 mmol) in $CHCl_3$ (20 mL) and MeOH (7 mL) was added aq 90% trifluoroacetic acid (20 mL) at room temperature. After 5 min, the mixture was concentrated with toluene (2 × 40 mL), then with EtOH–heptane–toluene (1:1:5, 40 mL), and dried in vacuo over P_2O_5 to give **15** (3 g). To a solution of **15** in CH_2Cl_2 (50 mL) were added 2,4,6-collidine (1.72 mL, 12.7 mmol) and triphenylmethylium perchlorate (4.14 g, 11.9 mmol). After 40 min, the solution was treated with MeOH–pyridine (1:3, 0.75 mL), diluted with $CHCl_3$ (90 mL), washed with water (4 × 100 mL), dried, and concentrated The residue was crystallised from ether (40 mL) to afford **16** (4.91 g, 86%); R_f 0.5 (solvent *A*); mp 160–161°C (from ether); $[\alpha]_D^{23}$ +5° (*c* 2.0, $CHCl_3$). Anal. Calcd for $C_{30}H_{32}O_8$: C, 69.23; H, 6.15. Found: C, 68.93; H, 6.11.

Methyl 2,4,6-tri-O-acetyl-3-O-trityl-β-D-galactopyranoside (**12**).—To a solution of **16** (5.6 g, 11 mmol) in pyridine (10 mL) were added Ac_2O (5 mL, 53 mmol) and 4-dimethylaminopyridine (131 mg, 1.1 mmol). After 2 h, the mixture was cooled to 10°C, then diluted with MeOH, and, after 30 min, 1:2 $CHCl_3$–hexane (300 mL) was added. The mixture was washed with water, aq 5% $KHSO_4$, water, satd aq $NaHCO_3$, and water, dried, and concentrated. Column chromatography (benzene → benzene–EtOAc, 5:1) afforded **12** (5.8 g, 96%); R_f 0.56 (solvent *B*) and 0.33 (solvent *C*); $[\alpha]_D^{25}$ +35° (*c* 1.6, $CHCl_3$).

Recrystallisation from ether gave **12** with mp 125–127°C, $[\alpha]_D^{28}$ +36° (*c* 2.4, $CHCl_3$). Anal. Calcd for $C_{32}H_{34}O_9$: C, 68.33; H, 6.05. Found: C, 69.15; H, 6.34.

Glycosylation reactions.—Each reaction was carried out in an inverted Y-shaped tube[12], the top of which was connected to a vacuum system (10^{-3} mmHg). In one limb of the tube was placed a solution of the trityl ether (**11** or **12**, 0.9 mmol) and 1-cyanobenzylidene derivative (**6–10**, 0.8 mmol) in nitromethane (2 mL), and in the other limb, a solution of triphenylmethylium perchlorate or triphenylmethylium triflate (0.08 mmol) in nitromethane (0.2 mL). The solutions were freeze-dried at 10^{-3} mmHg, benzene (~ 1.0 mL, twice distilled from CaH_2 at 10^{-3} mmHg) was distilled into the first limb, and, after complete dissolution of the reagents, lyophilisation was repeated followed by drying of the residues for 2 h at 50°C. Dichloromethane (2.0 mL, twice distilled from CaH_2 at 10^{-3} mmHg) was distilled into the tube and the solutions in the two limbs were mixed. The resulting clear-yellow solution was left at 20°C for 17 h in the dark, the reaction was

quenched with aq 2% pyridine (0.05 mL), and the solution was diluted with $CHCl_3$ (50 mL), washed with water (2 × 30 mL), dried, and concentrated. After column chromatography of the residue (gradient benzene–EtOAc, 0–70%), the fractions containing the disaccharide derivative were combined, then concentrated in vacuo, and the residue was subjected to NMR analysis in order to determine the α,β-ratio (integrated intensities of the H-1′ resonances).

Column chromatography (benzene–EtOAc, 3:2) then gave the individual, amorphous, isomeric disaccharide derivatives. The $[\alpha]_D$ values are given in Table V, and the ^1H and ^{13}C NMR spectra in Tables VI and VII.

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