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α-Fucosylation by 2,3,4-tri-O-benzoyl-α-L-fucopyranosyl bromide under Helferich conditions †

Nikolay E. Nifant'ev*, Vera Y. Amochaeva, Alexander S. Shashkov and Nikolay K. Kochetkov

N.D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Moscow (Russian Federation)

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ABSTRACT

Glycosylation of various carbohydrate mono- and di-hydroxy derivatives with 2,3,4-tri-O-benzoyl-α-L-fucopyranosyl bromide under Helferich conditions is stereoselective for acceptors that contain an axial hydroxyl group and/or neighbouring acyloxy, phthalimido, or bulky monosaccharide substituents.

INTRODUCTION

The 2-O-fucosylation[1–3] of methyl α-L-rhamnopyranoside derivatives with 2,3,4-tri-O-benzoyl-α-L-fucopyranosyl bromide (**1**) under Helferich conditions [acetonitrile–mercuric cyanide (2 equiv)–mercuric bromide (catalytic amount)] is stereospecific. Further[4], **1** was used for the stereoselective α-L-fucosylation of the disaccharide acceptor **2**, to yield a substituted derivative of the methyl glycoside of the Le^d (H type 1) blood-group specific trisaccharide.

In order to determine the features of the glycosyl acceptor that favour α-L-fucosylation with **1**, the glycosylation of various carbohydrate mono- and di-hydroxy derivatives has been studied and is now reported as part of a project on the synthesis and NMR and conformational studies of branched oligosaccharides[1–3,5–7].

RESULTS AND DISCUSSION

The following model acceptors were used: diols **3–6** (***a*** series) with β-D-*gluco*, α-D-*gluco*, β-D-*galacto*, and α-D-*manno* configurations, their 2- and 3-benzoates (***b*** and ***c*** series), methyl 4,6-*O*-benzylidene-3-*O*-(4-chlorobenzyl)-β-D-glucopyranoside

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*Corresponding author.

TABLE I
Difucosylation of methyl 4,6-*O*-benzylidene-D-glycopyranosides **3a**, **4a**, **5a**, and **6a**, and of the rhamnoside **7**

	Acceptor	Configuration	Fucosylation products (yield, %)			
			$\beta\beta$ [a]	$\alpha\beta$	$\beta\alpha$	$\alpha\alpha$
1	**3a**	β-D-*gluco*	**3e** (54)	**3i** [b] (20)		**3k** [b] (4)
2	**4a**	α-D-*gluco*	**4f** [c] (61)	**4i** [b] (24)	**4j** [b] (2)	
3	**5a**	β-D-*galacto*	**5e** (45)	**5g** (34)		
4	**6a**	α-D-*manno*	**6f** [c] (44)	**6h** [c] (48)		
5	7	α-L-*manno*	**8** (13)	**9** (64)		

[a] Anomeric configuration of the L-fucopyranosyl residues, respectively, at O-2 and O-3 of the diglycosylated unit. [b] Obtained after acid hydrolysis, then acetylation. [c] Obtained after acid hydrolysis.

(**3d**), methyl 4,6-*O*-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside (**13**), methyl 4-*O*-benzoyl-α-L-rhamnopyranoside (**7**), and its 3-benzoate **10**. These compounds differ in the orientation of the hydroxyl groups to be fucosylated and/or the nature and the orientation of the neighbouring substituents. The results of the mono- and di-fucosylation reactions are summarised in Tables I and II, respectively.

The results reveal selective α-fucosylation of axial hydroxyl groups. Thus, in the mono- and di-fucosylation reactions of mannosides and rhamnosides (HO-2 axial), the efficiency of 2-*O*-α-L-fucosylation is markedly higher than for the glucoside and galactoside acceptors (HO-2 equatorial) (see Table I and entries 1 and 3–6 in Table II).

The presence of a neighboring benzoyl group favours[1–3] α-fucosylation to a higher extent than the presence of a neighbouring benzyl group (entries 1 and 2 in Table II, see also below). A decrease in the reactivity of the acceptor promotes α-fucosylation[1,3], which accords with the results of fucosylation of **3c** and **3d**. Indeed, the total yield of products from **3c** was 24% lower than from **3d**, but the α-stereoselectivity was higher. The difference in reactivities of the acceptors **3c** and **3d** is probably connected with the electron-acceptor or shielding[8] effect of BzO-3 in **3c** (which decreases the nucleophilicity of HO-2), but is not due to possible differences in conformations, because the ^{1}H NMR spectra of **3c** and **3d** (Table III, recorded in CD_3CN since MeCN was the solvent used for glycosylation reactions) indicated similar conformations of **3c** and **3d**.

The presence of a bulky monosaccharide unit near the acceptor hydroxyl group also favours α-fucosylation. Thus, for the 2-*O*-fucosylation of the methyl galactopyranoside derivative **5c** (entry 4 in Table II) and the disaccharide acceptor **2**[4], the α, β-ratios of the fucosylated products were 1 : 1.3 and 9 : 1[4], respectively.

The efficiency of α-L-fucosylation with **1** also depends on the orientation of the substituents around the hydroxyl group to be glycosylated, as illustrated by the results of 3-*O*-fucosylation of the glucoside **4b** and the mannoside **6b** (entries 9 and 11 in Table II) with BzO-2 equatorial and axial, respectively. In contrast, the

stereoselectivities of fucosylation for the pairs **3c** and **4c** or **3b** and **5b** (entries 1, 3, 8, and 10 in Table II) were similar. Thus, the variation of the orientation of neighbouring alkoxy groups does not markedly influence the stereochemistry of fucosylation in contrast to neighbouring benzoate groups[1,3,4].

The similarity of the results of fucosylation of the 2-*O*-benzoylglucoside **3b** and the 2-deoxy-2-phthalimidoglucoside **13** (entries 8 and 12 in Table II) means that neighbouring phthalimido and benzoyloxy substituents favour α-fucosylation to similar extents.

The above-mentioned results indicate the optimal combination of blocking groups in the acceptor to control the stereochemistry of fucosylation as illustrated with the acceptors **16–19** (**a** series), α-fucosylation of which yields derivatives of the important natural disaccharides, 2-*O*-α-L-fucosyl-D-galactose (H-disaccharide) and 2-acetamido-2-deoxy-3- and -4-*O*-α-L-fucosyl-D-glucose (fragments of blood-group specific substances), and 3-*O*-α-L-fucosyl-D-glucose (fragment of some milk oligosaccharides and bacterial polysaccharides). Glycosylation of **16–19** (**a** series) gives good yields of α-L-fucosylated products (entries 7 and 13–15 in Table II) and confirms that the presence of neighbouring acyl substituents favours α-L-fucosylation.

In order to complete the glycosylation of the acceptors **17a**, **18a**, and **19a**, at least 3 equiv of **1** were necessary, which further reflects the fact that decrease of the reactivity of the acceptor favours α-L-fucosylation.

During glycosylations[9–11] with 2,3,4-tri-*O*-acetyl-α-L-fucopyranosyl bromide (**20**) under Helferich conditions, the marked formation of α-fucosides was also noted, but the yields (> 30%) and α-stereoselectivity were lower than in the reactions with **1**. For example, the reaction of **20** with **16a** (in acetonitrile as in entry 7 in Table II) gave[11] α- and β-fucosylated products in yields of only 28 and 20%, respectively. A change of the solvent to nitromethane–toluene for the reaction of **16a** with **20** improved the ratio of the yields of α- and β-fucosyl derivatives (33 and 7.5%, respectively), but this change did not affect (TLC) glycosylation with **1**.

The glycosylation of **18a** with 2,3,4,6-tetra-*O*-benzoyl-α-D-galactopyranosyl bromide (**21**) under Helferich conditions[12] is also α-stereoselective (α,β-ratio 4:1). Thus, the observed unusual 1,2-*cis*-selectivity in glycosylations with the bromides **1**, **20**, and some other fucose and galactose derivatives (see refs 1, 3, and 9–12) that contain a participating 2-substituent may be a property of glycosyl donors with the *galacto* configuration.

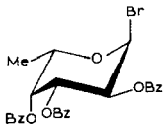
The structures of disaccharide derivatives obtained by glycosylation with **1** were proved by ^{1}H NMR spectroscopy; the anomeric configuration of the fucose residues was indicated by the $J_{1,2}$ values (~ 3.5 Hz for α, and ~ 7.5 Hz for β; Table III).

The structures of the trisaccharide products were established by ^{1}H NMR spectroscopy after removal of protecting groups, as described previously[1–3,6,7]. The ^{1}H NMR data for unsubstituted trisaccharide methyl glycosides **22–32** are given in Table IV. Assignments were accomplished by using a combination of ^{1}H–^{1}H

TABLE II
Fucosylation of the mono-hydroxy acceptors **3b–d, 4b,c, 5b,c, 6b,c, 10, 13, 16a, 17a, 18a,** and **19a**

	Acceptor	Configuration	Neighbouring substituents	Proportion of **1** (equiv)	Separation procedures [a]	α-Fucosylation		β-Fucosylation	
						Product (yield, %)	$[\alpha]_D$ [b] (°)	Product (yield, %)	$[\alpha]_D$ [b] (°)
2-*O*-Fucosylation									
1	**3c**	β-D-*gluco*	MeO-1, BzO-3	2	C	**3n** (39)	−120	**3o** (33)	−26
2	**3d**	β-D-*gluco*	MeO-1, (4-ClBnO)-3	2	A	**3p** (30)	−170	**3q** (66)	−65
3	**4c**	α-D-*gluco*	MeO-1, BzO-3	2	A	**4l** (44)	−132	**4m** (31)	−51
4	**5c**	β-D-*galacto*	MeO-1, BzO-3	2	A	**5l** (42)	−78	**5m** (55)	−25
5	**6c**	α-D-*manno*	MeO-1, BzO-3	3	C	**6n** (73)	−177	**6o** (15)	−204
6	**10**	α-L-*manno*	MeO-1, BzO-3	2	A	**11** (58)	−203	**12** (2)	+15
7	**16a**	α-D-*galacto*	AcO-1,3	2	A	**16b** (51)	−108	**16c** (38)	−65
3-*O*-Fucosylation									
8	**3b**	β-D-*gluco*	BzO-2, PhCHO-4	2	C	**3u** (32)	−114	**3v** (61)	−39
9	**4b**	α-D-*gluco*	BzO-2, PhCHO-4	2	C	**4u** (27)	−76	**4v** (63)	−26
10	**5b**	β-D-*galacto*	BzO-2, PhCHO-4	2	B	**5t** (42)	−101	**5s** (52)	−98
11	**6b**	α-D-*manno*	BzO-2, PhCHO-4	1.5	A	**6r** (14)	−232	**6s** (73)	−126
12	**13**	β-D-*gluco*	NPhth-2, BzO-4	2	A	**14** (36)	−145	**15** (47)	−36
13	**19a**	β-D-*gluco*	BzO-2, BzO-4	3	A	**19b** (74)	−150	**19c** (18)	−66
14	**17a**	β-D-*gluco*	NPhth-2, BzO-4	3.2	A	**17b** (61)	−87	**17c** (~ 20 [c])	
4-*O*-Fucosylation									
15	**18a**	β-D-*gluco*	BzO-3	3.5	A	**18b** (83)	−40	**18c** (10)	−82

[a] See Experimental. [b] Measured for a solution in $CHCl_3$ at 25–30°C ($c \sim 1$). [c] This compound was isolated in admixture with **17b**; the yield was determined on the basis of ^1H NMR data.



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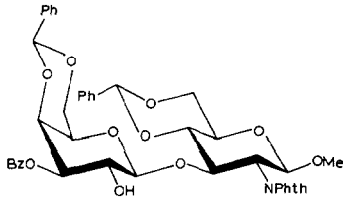

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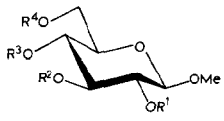
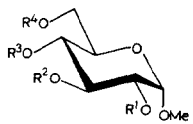
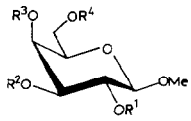


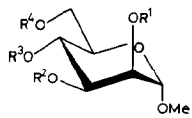
3 a–e, i, k
n–q, u, v



4 a–c, f, i, j,
l, m, u, v



5 a–c, e, g, j,
l, m, s, t



6 a–c, f, h,
n, o, r, s

Substituents in the acceptors

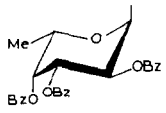
	R^1	R^2	R^3, R^4
a	H	H	PhCH
b	Bz	H	PhCH
c	H	Bz	PhCH
d	H	4-ClBn	PhCH

Substituents in the trisaccharide products

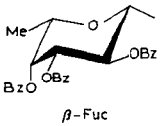
	R^1	R^2	R^3	R^4
e	β-Fuc	β-Fuc	PhCH	
f	β-Fuc	β-Fuc	H	H
g	α-Fuc	β-Fuc	PhCH	
h	α-Fuc	β-Fuc	H	H
i	α-Fuc	β-Fuc	Ac	Ac
j	β-Fuc	α-Fuc	Ac	Ac
k	α-Fuc	α-Fuc	Ac	Ac

Substituents in the disaccharide products

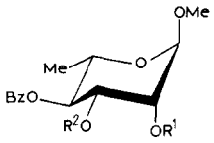
	R^1	R^2	R^3	R^4
l	α-Fuc	Bz	PhCH	
m	β-Fuc	Bz	PhCH	
n	α-Fuc	Bz	Ac	Ac
o	β-Fuc	Bz	Ac	Ac
p	α-Fuc	4-ClBn	PhCH	
q	β-Fuc	4-ClBn	PhCH	
r	Bz	α-Fuc	PhCH	
s	Bz	β-Fuc	PhCH	
t	Bz	α-Fuc	H	H
u	Bz	α-Fuc	Ac	Ac
v	Bz	β-Fuc	Ac	Ac

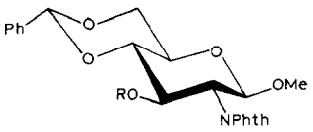


α-Fuc



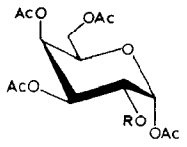
β-Fuc



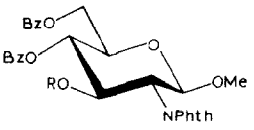


7 $R^1 = R^2 = H$
8 $R^1 = R^2 = \beta$-Fuc
9 $R^1 = \alpha$-Fuc, $R^2 = \beta$-Fuc
10 $R^1 = H$, $R^2 = Bz$
11 $R^1 = \alpha$-Fuc, $R^2 = Bz$
12 $R^1 = \beta$-Fuc, $R^2 = Bz$

13 R = H
14 R = α-Fuc
15 R = β-Fuc

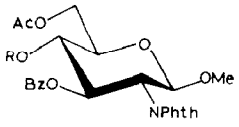


16 a–c

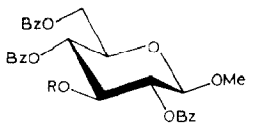


17 a–c

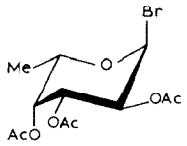
	R
a	H
b	α-Fuc
c	β-Fuc



18 a–c



19 a–c



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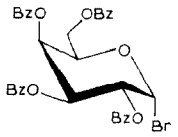


21

COSY and RCT 2D experiments. The anomeric configuration of each L-fucopyranosyl unit was assigned on the basis of the $J_{1,2}$ value. The locations of the α- and β-fucopyranosyl units in **22–32** were determined on the basis of NOE data (Table V) obtained after selective pre-irradiation of H-1 of each fucosyl residue. The minor product **4j** was not *O*-deacylated, and its structure was established on the basis of the ^{1}H NMR data (Table III) and taking into account the structure of its isomer **4i**.

The foregoing data demonstrate further that **1** has potential for the synthesis of oligosaccharides as an alternative to the traditional 2-*O*-benzylated α-L-fucopyranosyl donors, the preparation of which is longer than that of **1**. Moreover, the employment of **1** with suitable acceptors will give derivatives from which benzyl groups can be removed selectively.

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°C. ^{1}H NMR spectra were recorded with a Bruker WM-250 instrument for solutions in $CDCl_3$ (internal Me_4Si) for substituted compounds and in D_2O for the trisaccharide methyl glycosides **22–32**. NOE experiments were performed as described[5].

TABLE III
^{1}H NMR data (δ in ppm, J in Hz) for the substituted derivatives [a]

Compound	Residue	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
3c [b]		4.47	3.61	5.38	3.81	3.61	3.80	4.33	7.6	9.0	9.0	9.0	10.0	4.7	10.0
3d [b]		4.31	3.38	3.58	3.64	3.43	3.75	4.27	7.6	8.9	8.9	8.9	10.0	4.9	10.0
3n	β-D-Glc	4.59	4.01	5.55	5.16	3.82	4.17	4.33	7.7	9.6	9.6	9.6	2.5	4.7	12.4
	α-L-Fuc	5.46	5.64	5.84	5.75	4.79	1.26		3.4	11.2	3.5	1.2	6.5		
3o	β-D-Glc	4.28	3.85	5.45	5.22	3.69	4.12	4.29	8.0	9.5	9.5	9.5	2.5	5.0	12.4
	β-L-Fuc	4.98	5.57	5.46	5.52	3.85	0.85		7.9	9.7	3.0	<1	6.3		
3p	β-D-Glc	4.55	3.84	3.79	3.74	3.51	3.81	4.43	7.3	8.3	8.3	8.3	10.5	5.0	10.5
	α-L-Fuc	[c]	[c]	5.96	[c]	4.81	1.29				3.4	1.2	6.5		
3q	β-D-Glc	4.19	3.83	3.72	3.64	3.35	3.72	4.30	7.8	7.8	9.3	9.3	10.0	5.0	10.0
	β-L-Fuc	5.21	5.77	5.62	5.73	4.07	1.33		7.9	10.4	3.4	1.0	6.5		
3u	β-D-Glc	4.52	5.30	4.23	5.31	3.76	4.23	4.30	7.5	7.5	8.7	9.2	3.8	4.8	12.5
	α-L-Fuc	5.64	5.58	5.82	5.76	4.47	1.28		3.5	10.6	3.7	1.0	6.6		
3v	β-D-Glc	4.63	5.27	4.27	5.15	3.66	4.10	4.15	8.3	9.2	9.2	9.2	10.0	4.5	10.0
	β-L-Fuc	4.92	5.56	5.45	5.51	3.81	0.90		7.8	10.2	3.3	1.0	6.5		
4l	α-D-Glc	5.02	4.01	5.88	3.69	4.02	3.79	4.35	3.7	9.8	9.8	9.8	10.2	4.6	10.2
	α-L-Fuc	5.52	5.64	5.93	5.83	4.60	1.31		4.0	10.7	3.5	1.2	6.6		
4m	α-D-Glc	4.68	4.08	5.79	3.77	3.93	3.75	4.27	3.7	9.9	9.9	9.9	10.3	4.5	10.3
	β-L-Fuc	4.85	5.66	5.48	5.56	3.83	0.84		8.0	10.5	3.1	1.5	6.4		
4u	α-D-Glc	5.05	5.09	4.54	5.30	3.98	4.15	4.27	3.5	9.3	9.3	10.0	3.0	5.0	12.2
	α-L-Fuc	5.65———			5.75	4.40	1.29					1.3	6.3		
4v	α-D-Glc	5.11	5.16	4.49	5.12	3.89	4.01—4.14		3.7	9.1	9.1	9.1	5.2	3.1	11.8
	β-L-Fuc	4.98	5.58	5.45	5.57	3.79	1.12		7.6	10.3	3.5	1.5	6.0		
4j	α-D-Glc	4.80	4.09	4.27	5.14	3.81	4.05	4.21	3.3	9.4	9.4	10.8	3.0	5.1	12.5
	β-L-Fuc	4.84	5.69	5.54	5.59	3.90	0.99		7.9	10.0	3.3	<1	6.4		
	α-L-Fuc	5.86	5.98	5.72	5.77	4.48	1.27		3.6	10.6	3.2	1.9	6.4		
5l	β-D-Gal	4.61	4.41	5.18	4.49	3.63	4.09	4.39	7.7	10.0	3.0	<1	1.5	1.5	12.6
	α-L-Fuc	5.62	5.75	5.89	5.79	4.87	1.29		3.5	10.6	3.3	<1	6.5		
5m	β-D-Gal	4.22—4.29		5.14	4.58	3.51	4.08	4.34			3.8	<1	1.7	1.3	12.5
	β-L-Fuc	5.12	5.65	5.55	5.64	3.98	1.18		7.5	10.4	3.1	<1	6.4		
5s	β-D-Gal	4.68	5.53	4.20	4.16	3.45	3.90	4.28	8.0	10.0	3.5	<1	2.0	1.7	12.0
	β-L-Fuc	4.94	5.65	5.48	5.58	3.90	0.88		7.7	10.2	3.4	<1	6.3		
5t	β-D-Gal	4.43	5.58	[d]	4.28	3.73	[d]	[d]	7.8	10.0	3.5	<1	5.2		
	α-L-Fuc	5.57	5.60	6.02	5.79	4.75	1.30		3.6	10.4	3.3	1.7	6.5		
5s	β-D-Gal	4.68	5.53	4.20	4.16	3.45	3.90	4.28	8.0	10.0	3.5	<1	2.0	1.7	12.0
	β-L-Fuc	4.94	5.65	5.48	5.58	3.90	0.88		7.7	10.2	3.4	<1	6.3		
6n	α-D-Man	4.63	4.33	5.49	5.66	3.97	4.08—4.21		1.6	3.0	9.8	9.8	3.5	3.5	
	α-L-Fuc	5.36	5.66	5.96	5.65	4.46	0.67		3.6	10.2	3.2	<1	6.4		
6o	α-D-Man	5.03	4.41	5.40—5.52		3.97	4.15	4.27	1.6	2.5		9.2	2.2	4.5	11.8
	β-L-Fuc	4.85	5.76	5.45	5.63	3.89	1.25		7.5	10.1	3.2	<1	6.2		
6r	α-D-Man	4.78	5.39	4.49	4.25	3.90—4.06		4.35	1.6	3.4	10.0	10.0	7.0	3.5	9.6
	α-L-Fuc	5.61	5.56	5.98	5.59	4.71	0.94		3.6	10.2	3.4	<1	6.0		
6s	α-D-Man	4.91	5.51	4.51	3.78	3.90	4.10	4.26	1.6	3.5	9.7	9.7	9.4	4.2	9.4
	β-L-Fuc	5.18	5.67	5.48	5.65	4.04	1.27		7.6	10.2	3.1	<1	6.0		
11	α-L-Rha	4.88	4.39	5.68	5.76	4.11	1.42		2.1	2.9	10.0	9.1	6.2		
	α-L-Fuc	5.33	5.92	5.95	5.86	4.59	1.29		3.5	7.0	3.0	1.0	6.5		
12	α-L-Rha	4.55	4.41	5.47	5.59	3.91	1.16		1.9	3.4	10.2	9.5	6.2		
	β-L-Fuc	4.73	5.77	5.46	5.58	3.82	0.80		8.1	11.0	3.5	1.1	6.5		
14	β-D-Glc	5.00	4.31	4.96	3.85	3.75	3.90	4.45	8.5	10.4	9.0	9.0	10.2	4.6	10.2
	α-L-Fuc	5.16	5.40	5.86	5.49	4.57	0.51		3.6	11.1	3.5	1.5	6.7		

TABLE III (continued)
^{1}H NMR data (δ in ppm, J in Hz) for the substituted derivatives [a]

Compound	Residue	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
15	β-D-Glc	5.33	4.31	4.73	3.60–3.70		3.74	4.36	8.6	10.4	8.9			8.5	
	β-L-Fuc	4.92	5.51	5.53	5.43	3.84	0.55		8.0	10.2	3.1	< 1	6.2		
16b	α-D-Gal	6.42	4.26	5.20	5.41	4.30			4.0	10.5	3.3	1.5			
	α-L-Fuc	5.61	5.54	5.85	5.73	4.43	1.30		4.0	10.5	3.3	1.5	6.4		
16c	α-D-Gal	6.33	4.39	5.32	5.48	4.24			4.0	10.3	3.5	1.5			
	β-L-Fuc	4.91	5.73	5.51	5.71	4.09	1.35		8.2	10.5	3.6	< 1			
17b	β-D-Glc	5.12	4.47	5.04	5.62	4.10	4.47	4.63	8.5	10.5	8.7	9.9	4.9	3.7	12.0
	α-L-Fuc	5.48	5.22	5.77	5.45	4.31	0.83		3.7	10.9	3.6	1.5	6.2		
18b	β-D-Glc	5.39	4.32	6.09	4.08	3.94	4.16	4.76	8.7	11.0	8.7	10.0	4.1	2.3	12.2
	α-L-Fuc	5.46	5.54	5.93	5.62	4.37	0.86		3.5	11.0	3.6	1.7	6.5		
18c	β-D-Glc	5.30	4.24	5.86	4.16	3.86	4.37	4.62	8.6	10.9	9.2	9.2	5.9	2.6	12.5
	β-L-Fuc	4.80	5.51	5.14	5.52	3.90	1.24		8.0	10.5	3.5	1.1	6.5		
19b	β-D-Glc	4.60	5.36	4.49	5.71	4.15	4.48	4.70	7.5	8.4	8.7	8.7	5.3	3.6	12.0
	α-L-Fuc	5.64	5.57	5.75	5.43	4.17	0.72		3.6	10.8	3.5	1.7	6.2		
19c	β-D-Glc	4.77	5.31	4.54	5.49	3.98	4.37	4.50	7.8	9.3	9.3	9.3	5.8	3.9	12.1
	β-L-Fuc	4.92	5.56	5.18	5.48	3.85	0.92		7.7	10.5	3.5	< 1	6.2		

[a] For solutions in $CDCl_3$, unless stated otherwise. [b] For a solution in CD_3CN. [c] 5.80–5.88 (m, 3 H, Fuc H-1,2,4). [d] 3.98–4.10 (m, 3 H, Gal H-3,6a,6b). Other signals: aromatic δ 6.90–8.20; OMe 3.29–3.68 (2.84 for **4j**); AcO 1.70–2.20; PhC*H* 5.45–5.77; 4-ClPhCH_2 4.20–4.90.

Dichloromethane was washed with concd H_2SO_4 and water, dried ($CaCl_2$), 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.

TLC was performed on Kieselgel-60 (Merck) with EtOAc–toluene (*A*, 1:2; *B*, 1:1; *C*, 1:7), $CHCl_3$–EtOH (*D*, 9:1), and EtOAc–heptane (*E*, 2:3; *F*, 1:1), and 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.

Glycosyl acceptors.—The syntheses of the glycosyl acceptors **3a**[13], **3b**[14], **3c**[14], **3d**[6], **4a**[13], **4b**[15], **4c**[15], **5a**[13], **5b**[16], **5c**[17], **6a**[18], **6b**[17], **6c**[17], **7**[19], **10**[19], **13**[4], **16a**[20], **17a**[21], **18a**[12], and **19**[22] have been reported.

Trisaccharide syntheses (Table I).—*(a) Fucosylation of 7.* A solution of **7** (113 mg, 0.4 mmol), $Hg(CN)_2$ (607 mg, 2.4 mmol), $HgBr_2$ (50 mg), and 4A molecular sieves in MeCN (6 mL) was stirred for 45 min at 20°C under Ar. Using a syringe, a solution of **1** [prepared[2] from tetra-*O*-benzoyl-L-fucopyranose (1.39 g, 2.4 mmol)] was introduced portionwise during 1 h. The mixture was stirred for 1 h, $CHCl_3$ (10 mL) and satd aq KBr (10 mL) were added, and the mixture was stirred for 10 min and filtered through Celite. The organic layer was washed with aq KBr and water, filtered through cotton, and concentrated. Column chromatography of the residue gave methyl 4-*O*-benzoyl-2,3-di-*O*-(2,3,4-tri-*O*-benzoyl-β-L-fucopyranosyl)-α-L-rhamnopyranoside (**8**; 62 mg, 13%) and methyl 4-*O*-benzoyl-2-*O*-(2,3,4-tri-*O*-benzoyl-α-L-fucopyranosyl)-3-*O*-(2,3,4-tri-*O*-benzoyl-β-L-fucopyranosyl)-α-L-rhamnopyranoside (**9**; 307 mg, 64%).

TABLE IV

^{1}H NMR data[a] (δ in ppm, J in Hz) for trisaccharide methyl glycosides **22–32**

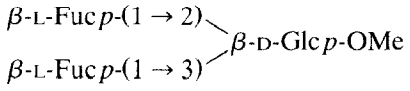
Compound	Residue	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
22	β-D-Glc-OMe	4.54	3.63	4.01	3.59	3.45	3.72	3.91	7.8	9.2	9.2	9.2	5.2	2.4	12.2
	β-L-Fuc-(1 → 2)	4.72	3.51	3.65	3.73	3.76	1.26		7.8	9.9	3.5	< 1	6.6		
	β-L-Fuc-(1 → 3)	4.77	3.59	3.65	3.73	3.82	1.27		7.5	10.0	3.5	< 1	6.6		
23	β-D-Glc-OMe	4.48	3.38	3.94	3.64	3.45	3.72	3.91	7.9	8.8	9.0	10.0	5.9	2.1	12.2
	α-L-Fuc-(1 → 2)	5.11	3.72	3.83	3.79	4.21	1.21		4.0	10.0	3.3	< 1	6.6		
	β-L-Fuc-(1 → 3)	4.78	3.52	3.65	3.74	3.78	1.28		7.9	9.9	3.6	< 1	6.5		
24	β-D-Glc-OMe	4.48	[b]	3.75	[b]	[b]	3.73	3.93	8.0	8.0	8.0		5.1	2.0	12.2
	α-L-Fuc-(1 → 2)	5.30	3.79	3.86	3.81	4.36	1.17		3.5	10.2	2.8	< 1	6.5		
	α-L-Fuc-(1 → 3)	5.37	3.79	——	3.87	4.23	1.19		4.0			< 1	6.6		
25	α-D-Glc-OMe	4.93	3.94	4.01	3.63	——	3.68	3.74	3.87	3.2	9.6	7.8			1.6	12.5
	β-L-Fuc-(1 → 2)	4.51	3.56	——	3.66	3.74	3.78	1.26		7.6			< 1	6.5		
	β-L-Fuc-(1 → 3)	4.72	3.57	3.66	3.74	3.80	1.26		7.6	10.0	3.0	< 1	6.5		
26	α-D-Glc-OMe	4.97	3.62	3.95	3.64	——	3.72		3.7	10.0					
	α-L-Fuc-(1 → 2)	5.04	3.68	3.87	3.87	4.13	1.26 [c]		4.3	10.0	3.2	< 1	6.6		
	β-L-Fuc-(1 → 3)	4.62	3.54	3.67	3.75	3.80	1.32 [c]		8.0	10.2	3.5	1.5	6.6		
27	β-D-Gal-OMe	4.52	3.84	4.09	4.14	3.68			8.0	9.8	3.4	< 1			
	β-L-Fuc-(1 → 2)	4.58	3.62	——	3.71	3.76	3.78	1.28	7.8		3.0	< 1	7.4		
	β-L-Fuc-(1 → 3)	4.73	3.52	3.67	3.76	3.77	1.28		7.6	10.2	3.5	< 1	7.4		
28	β-D-Gal-OMe	4.41	3.58	4.01	4.11	3.62	3.52	——	3.90	7.6	9.8	3.1	< 1		
	α-L-Fuc-(1 → 2)	5.08	3.70	3.62	3.80	3.70	1.18		3.6	10.0	3.2	< 1	6.5		
	β-L-Fuc-(1 → 3)	4.46	3.51	3.63	3.77	3.72	1.24		7.5	10.0	3.3	1.5	6.3		
29	α-D-Man-OMe	4.90	4.31	3.95	3.90	3.67	3.79	3.89	1.7	3.5	9.6	9.6	5.5	2.5	12.0
	β-L-Fuc-(1 → 2)	4.73	3.49	3.66	3.73	3.76	1.26		7.8	10.0	3.4	1.1	5.0		
	β-L-Fuc-(1 → 3)	4.54	3.52	3.65	3.72	3.78	1.24		7.6	9.9	3.5	1.1	4.9		
30	α-D-Man-OMe	4.85	4.08	4.00	3.97	3.65	3.78	——	3.91	1.6	2.9	9.4	9.4		
	α-L-Fuc-(1 → 2)	4.97	3.76	3.95	3.85	4.45	1.23		3.8	10.0	3.0	< 1	5.0		
	β-L-Fuc-(1 → 3)	4.63	3.53	3.65	3.74	3.76	1.26		7.5	9.9	2.7	< 1	5.1		
31	α-L-Rha-OMe	4.85	4.23	3.92	3.55	3.71	1.32		1.8	3.6	9.7	9.7	6.2		
	β-L-Fuc-(1 → 2)	4.45	3.51	3.62	3.74	3.76	1.26		7.9	9.8	3.4	1.0	6.6		
	β-L-Fuc-(1 → 3)	4.50	3.54	3.65	3.73	3.78	1.25		7.9	9.8	3.4	1.0	6.4		
32	α-L-Rha-OMe	4.84	4.07	4.01	3.65	3.73	1.34		1.8	3.2	9.5	9.5	5.8		
	α-L-Fuc-(1 → 2)	5.13	3.76	3.91	3.82	4.13	1.21		3.8	10.6	3.4	< 1	6.8		
	β-L-Fuc-(1 → 3)	4.47	3.53	3.67	3.76	3.79	1.26		7.8	10.8	3.3	< 1	6.5		

[a] Signals of OMe at δ 3.40–3.57. [b] 3.43–3.55 (m, 3 H, Glc H-2,4,5). [c] Assignments may be interchanged.

TABLE V
The characteristic NOE values (%) observed after pre-irradiation of H-1 of each terminal fucose residue in the trisaccharide methyl glycosides **23, 26, 28, 30,** and **32**

Compound	Observed NOE [a]							
	Pre-irradiation of H-1′		Pre-irradiation of H-1″					
	H-2	H-2′	H-2	H-3	H-4	H-2″	H-3″	H-5″
23	14.1	12.8		9.0		2.8	6.0	8.4
26	13.1	12.4		12.3		3.1	7.3	10.0
28	15.8	12.5		11.4	8.7		10.1	12.6
30	8.4	13.2		9.0		5.1	6.3	9.7
32	11.4	12.4	3.9	6.7			5.5	7.4

[a] H-1′ and H-1″ refer to the (1 → 2)- and (1 → 3)-linked residues, respectively.



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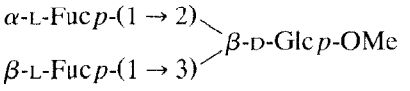

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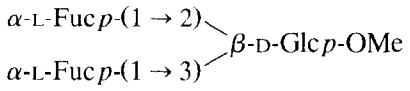

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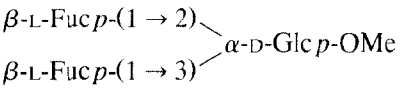

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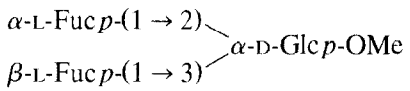

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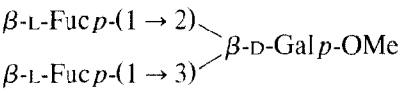

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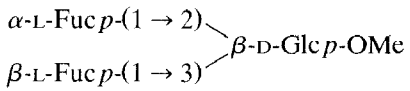

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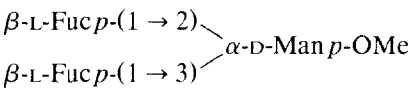

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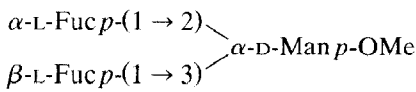

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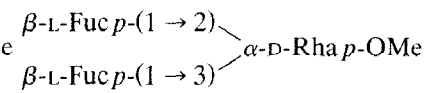

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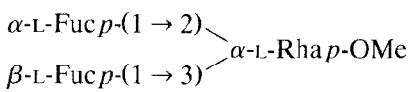

32

Compound **8** was amorphous and had $[\alpha]_D$ −137° (*c* 1, $CHCl_3$), R_f 0.48 (solvent *F*, 3 elutions).

Compound **9** had mp 164–167°C (from EtOAc–hexane), $[\alpha]_D$ −202° (*c* 0.7, $CHCl_3$), and R_f 0.46 (solvent *F*, 3 elutions). *Anal.* Calcd for $C_{68}H_{62}O_{20}$: C, 68.11; H, 5.21. Found: C, 68.34; H, 4.87.

(*b*) *Fucosylation of* ***6a***. Glycosylation of **6a** (212 mg, 0.75 mmol) with **1** [prepared[2] from tetra-*O*-benzoyl-L-fucopyranose (1.74 g, 3 mmol)] was performed, and the mixture was processed, as in (*a*). A solution of products in $CHCl_3$ (2 mL) was stirred with aq 90% trifluoroacetic acid for 40 min, diluted with $CHCl_3$ (40 mL), washed with water, aq $NaHCO_3$, and water, filtered through cotton, and concentrated. Column chromatography of the residue gave methyl 2,3-di-*O*-(2,3,4-tri-*O*-benzoyl-β-L-fucopyranosyl)-α-D-mannopyranoside (**6f**; 291 mg, 44%) and methyl 2-*O*-(2,3,4-tri-*O*-benzoyl-α-L-fucopyranosyl)-3-*O*-(2,3,4-tri-*O*-benzoyl-β-L-fucopyranosyl)-α-D-mannopyranoside (**6h**; 313 mg, 48%).

Compound **6f** was amorphous and had $[\alpha]_D$ −185° (*c* 2, $CHCl_3$), R_f 0.21 (solvent *B*).

Compound **6h** was amorphous and had $[\alpha]_D$ −153° (*c* 2, $CHCl_3$), R_f 0.25 (solvent *B*).

(*c*) *Fucosylation of* ***3a***. Glycosylation of **3a** (212 mg, 0.75 mmol) with **1** [prepared[2] from tetra-*O*-benzoyl-L-fucopyranose (1.74 g, 3 mmol)] was performed as in (*a*). Column chromatography of the products gave methyl 4,6-*O*-benzylidene-2,3-di-*O*-(2,3,4-tri-*O*-benzoyl-β-L-fucopyranosyl)-β-D-glucopyranoside [**3e**; 486 mg, 54%, $[\alpha]_D$ −170° (*c* 1, $CHCl_3$), R_f 0.48 (solvent *C*)] and a mixture [220 mg, 24%, R_f 0.58 (solvent *C*)] of other glycosylation products. Acid hydrolysis of the mixture as for the preparation of **6f** and **6h**, subsequent acetylation (Ac_2O–pyr), and column chromatography gave methyl 4,6-di-*O*-acetyl-2-*O*-(2,3,4-tri-*O*-benzoyl-α-L-fucopyranosyl)-3-*O*-(2,3,4-tri-*O*-benzoyl-β-L-fucopyranosyl)-β-D-glucopyranoside (**3i**; 176 mg, 20%) and methyl 4,6-di-*O*-acetyl-2,3-di-*O*-(2,3,4-tri-*O*-benzoyl-α-L-fucopyranosyl)-β-D-glucopyranoside (**3k**; 34 mg, 4%).

Compound **3i** was amorphous and had $[\alpha]_D$ −171° (*c* 1, $CHCl_3$), R_f 0.31 (solvent *E*).

Compound **3k** was amorphous and had $[\alpha]_D$ −190° (*c* 1, $CHCl_3$), R_f 0.39 (solvent *E*).

(d) *Fucosylation of* ***4a***. Glycosylation of **4a** (212 mg, 0.75 mmol) with **1** [prepared[2] from tetra-*O*-benzoyl-L-fucopyranose (1.74 g, 3 mmol)] was performed as in (*b*). Column chromatography of the hydrolysed products gave methyl 2,3-di-*O*-(2,3,4-tri-*O*-benzoyl-β-L-fucopyranosyl)-α-D-glucopyranoside [**4f**; 508 mg, 61%, $[\alpha]_D$ −138° (*c* 1, $CHCl_3$), R_f 0.3 (solvent *B*)] and a mixture [220 mg, 26%, R_f 0.45–0.5 (solvent *B*)] of other glycosylation products. Acetylation (Ac_2O–pyr) of the mixture and subsequent column chromatography gave methyl 4,6-di-*O*-acetyl-2-*O*-(2,3,4-tri-*O*-benzoyl-α-L-fucopyranosyl)-3-*O*-(2,3,4-tri-*O*-benzoyl-β-L-fucopyranosyl)-β-D-glucopyranoside (**4i**; 208 mg, 23%) and methyl 4,6-di-*O*-acetyl-3-*O*-(2,3,4-tri-*O*-benzoyl-α-L-fucopyranosyl)-2-*O*-(2,3,4-tri-*O*-benzoyl-β-L-fucopyranosyl)-β-D-glucopyranoside (**4j**; 19 mg, 2%).

TABLE VI
Preparation of unsubstituted trisaccharide methyl glycosides **22–32**

Compound	Precursor (mg, deprotection method [a])	Yield, mg (%)	$[\alpha]_D$(°) (*c*, H_2O)
22	**3e** (196, B)	74 (93)	−17 (1.5)
23	**3i** (136, A)	49 (89)	−73 (1)
24	**3k** (30, A)	11 (87)	−127 (0.5)
25	**4f** (458, A)	167 (83)	+48 (1)
26	**4i** (76, A)	28 (88)	+8 (1)
27	**5e** (87, B)	29 (81)	+12 (1)
28	**5g** (91, B)	26 (75)	−62 (1)
29	**6f** (313, A)	116 (84)	+12 (2)
30	**6h** (240, A)	87 (83)	−47 (2)
31	**8** (250, A)	75 (78)	−1 (2)
32	**9** (250, A)	90 (92)	−40 (1)

[a] See Experimental.

Compound **4i** was amorphous and had $[\alpha]_D$ −127° (*c* 1, $CHCl_3$), R_f 0.31 (solvent *F*).

Compound **4j** was amorphous and had $[\alpha]_D$ −137° (*c* 1, $CHCl_3$), R_f 0.24 (solvent *F*).

(*e*) *Fucosylation of* ***5a***. Glycosylation of **5a** (212 mg, 0.75 mmol) with **1** [prepared[2] from tetra-*O*-benzoyl-L-fucopyranose (1.74 g, 3 mmol)] was performed as in (*c*). Column chromatography of the products gave methyl 4,6-*O*-benzylidene-2,3-di-*O*-(2,3,4-tri-*O*-benzoyl-β-L-fucopyranosyl)-β-D-glucopyranoside [**5e**; 404 mg, 45%, $[\alpha]_D$ −166° (*c* 1, $CHCl_3$), R_f 0.16 (solvent *C*)] and a mixture [340 mg, R_f 0.2 (solvent *C*)] of **5g** and an impurity. Acid hydrolysis of the mixture, subsequent acetylation (Ac_2O–pyr), and column chromatography of the products gave methyl 4,6-di-*O*-acetyl-2-*O*-(2,3,4-tri-*O*-benzoyl-α-L-fucopyranosyl)-3-*O*-(2,3,4-tri-*O*-benzoyl-β-L-fucopyranosyl)-β-D-galactopyranoside (**5i**; 283 mg, 34%) as an amorphous powder, $[\alpha]_D$ −144° (*c* 1, $CHCl_3$), R_f 0.25 (solvent *A*).

Preparation of the trisaccharide methyl glycosides **22–32** *(Table VI).*—(*a*) *Procedure A.* The acylated precursor (100–300 mg) was treated with 0.1 M MeONa in MeOH (10 mL) for 16–20 h at 20°C. The solution was neutralised with KU-2 (H^+) resin, filtered, and concentrated. The residue was partitioned between water (10 mL) and $CHCl_3$ (10 mL); the aqueous layer was washed with $CHCl_3$ (4 × 10 mL), then concentrated. GPC of the residue on fracto-gel TSK HW-40(S) (25–40 μm, V_0 50 mL) by elution with deionised water gave the product as an amorphous powder.

(*b*) *Procedure B.* The benzylidenated compound was hydrolysed with acid as for the preparation of **6f** and **6h**, and then treated with MeONa and purified as in Procedure A.

The ^1H NMR data for **22–33** are listed in Tables IV and V.

Disaccharide syntheses (Table II).—(*a*) *Procedure A.* The reaction was performed as described for the difucosylation of **7**.

(*b*) *Procedure B.* The reaction was performed and continued (including acid hydrolysis) as described for the difucosylation of **6a**.

(*c*) *Procedure C.* The reaction was performed as described for the difucosylation of **7**; the products were hydrolysed with acid, acetylated (Ac_2O–pyr), and then fractionated by column chromatography.

The ^1H NMR data of the products are listed in Table III.

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