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Synthesis of 2,3-di-*O*-glycosyl derivatives of methyl α- and β-D-glucopyranoside *

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ABSTRACT

The syntheses are described of 2,3-di-*O*-glycosyl derivatives of methyl α- and β-D-glucopyranoside having α-D-manno-, β-D-galacto-, α-L-rhamno-, α-L-fuco-, and β-L-fuco-pyranosyl substituents at O-2 and O-3. The syntheses involved glycosylation of methyl 4,6-*O*-benzylidene-α- (**24**) and -β-D-glucopyranoside (**21**), and substituted derivatives of **21** bearing 2-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-, -(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-, -(2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl)-, and -(2,3,4-tri-*O*-benzoyl-β-L-fucopyranosyl) groups.

INTRODUCTION

As part of the development of a computerised approach to the elucidation of the structure of branched polysaccharides[2], a series of different branched oligosaccharides was required as reference compounds. Previously, series of 2,3-di-*O*-glycosyl derivatives of methyl α-L-rhamnopyranoside and methyl α-D-mannopyranoside have been synthesised[3–6] and studied[6–8] as models with a 2,3-axial–equatorial branch-point. To develop the data base for structures with 2,3-diequatorial branching, the 2,3-di-*O*-glycosyl derivatives of methyl β- (**1–16**) and α-D-glucopyranoside (**17–20**) that had monosaccharide substituents with the α-D, β-D, α-L, and β-L configurations were required. Bis-fucosylated derivatives **15**, **16**, and **20** have been synthesised previously[9]. The syntheses of of other members of this series are now described; the ^1H and ^{13}C NMR spectra of all of these compounds have been published elsewhere[10].

* Synthesis, NMR, and Conformational Studies of Branched Oligosaccharides, Part 11. For Part 10, see ref 1.

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RESULTS AND DISCUSSION

To find the most suitable glycosyl acceptor for the preparation of trisaccharide derivatives with similar monosaccharide substituents at O-2 and O-3, bis-mannosylation of methyl 4,6-*O*-benzylidene- (**21**) and methyl 4,6-*O*-isopropylidene-β-D-glucopyranoside (**22**) with 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl bromide (**25**) under Helferich conditions [acetonitrile–mercuric cyanide (2 equiv)–mercuric bromide (catalytic amount)] was studied. Glycosylation of acetonide **22** was less effective due to partial loss * of the acetal function under the reaction conditions, and gave only a moderate yield of trisaccharide product, separated as the diol **26** (46%) after hydrolysis ** of the mixture. Glycosylation of the benzylidene acetal **21** was successful and gave, after hydrolysis, 84% of trisaccharide **26**. We therefore chose the benzylidene group for the temporary protection of the 4,6-diol function in the glycosyl acceptors.

Glycosylation of **21** with 2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl bromide (**30**) and subsequent hydrolysis afforded trisaccharide **31** in 92% yield. *O*-Debenzoylation of **26** and **31** then gave the respective target trisaccharide methyl glycosides **1** and **11**, the structures of which were established by ^{1}H and ^{13}C NMR data[10]. The Man and Rha units in **1** and **11** were indicated to be α by the characteristic chemical shifts (74.5 and 74.6 ppm for **1**, and 70.1 and 70.3 ppm for **11**) of their C-5 signals in the ^{13}C NMR spectra.

The trisaccharide methyl α-glycosides **17** and **19** were obtained in the same way as their β-methyl analogues. Glycosylation of diol **24** with **25** and **30** and subsequent hydrolysis gave derivatives **27** (84%) and **32** (73%), respectively, which were converted into **17** and **19** by saponification. Their structures were confirmed by ^{13}C NMR data.

For a synthesis of methyl 2,3-di-*O*-β-D-galactopyranosyl-β-D-glucopyranoside (**6**), the glycosylation of diol **21** with 1,2,3,4,6-penta-*O*-acetyl-β-D-galactopyranose (**33**) in the presence of trimethylsilyl triflate[11] was studied first[12]. It was found that, in the presence of 2 equiv of promoter, only monogalactosylated products (~ 20–30%, TLC) were formed. A two-fold increase in the amount of promoter resulted in the formation of trisaccharide **35** and its α-*gluco*-isomer **36** together with a large proportion of decomposition products. The trisaccharides were separated after hydrolysis in the form of diols **37** and **38** in yields of 19 and 13%, respectively. The possible mechanism of the anomerisation during the galactosylation of **21** and of **39** (see below) has been discussed[12]. An effective synthesis of trisaccharide **37** was

* The lability of an isopropylidene group was also noted during mannosylation of methyl 2-*O*-benzoyl-4,6-*O*-isopropylidene-β-D-glucopyranoside (**23**) which, after hydrolysis, gave only 50% of disaccharide **28**.

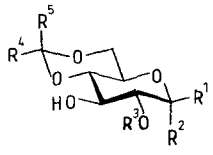
** To simplify the separation of glycosylation products by column chromatography, the mixtures were subjected to acid hydrolysis which removes the benzylidene or isopropylidene groups in almost quantitative yield (see Experimental).

X-(1→2)
Y-(1→3)>β-D-Glc*p*-OMe

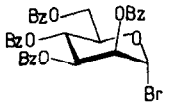
	X	Y
1	α-D-Man*p*	α-D-Man*p*
2	β-D-Gal*p*	α-D-Man*p*
3	α-L-Rha*p*	α-D-Man*p*
4	β-L-Fuc*p*	α-D-Man*p*
5	α-D-Man*p*	β-D-Gal*p*
6	β-D-Gal*p*	β-D-Gal*p*
7	α-L-Rha*p*	β-D-Gal*p*
8	β-L-Fuc*p*	β-D-Gal*p*
9	α-D-Man*p*	α-L-Fuc*p*
10	β-D-Gal*p*	α-L-Fuc*p*
11	α-L-Rha*p*	α-L-Rha*p*
12	β-L-Fuc*p*	α-L-Rha*p*
13	α-D-Man*p*	β-L-Fuc*p*
14	β-D-Gal*p*	β-L-Fuc*p*
15	α-L-Fuc*p*	β-L-Fuc*p*
16	β-L-Fuc*p*	β-L-Fuc*p*

X-(1→2)
Y-(1→3)>α-D-Glc*p*-OMe

	X	Y
17	α-D-Man*p*	α-D-Man*p*
18	β-D-Gal*p*	β-D-Gal*p*
19	α-L-Rha*p*	α-L-Rha*p*
20	β-L-Fuc*p*	β-L-Fuc*p*



21 R^1=OMe, R^2=R^3=R^5=H, R^4=Ph
22 R^1=OMe, R^2=R^3=H, R^4=R^5=Me
23 R^1=OMe, R^2=H, R^3=Bz, R^4=R^5=Me
24 R^1=R^3=R^5=H, R^2=OMe, R^4=Ph



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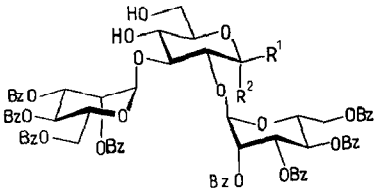
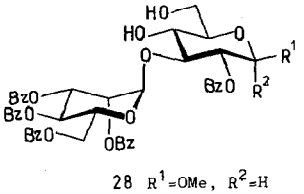
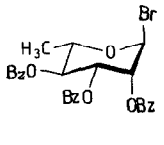


1 ← **26** R^1=OMe, R^2=H
17 ← **27** R^1=H, R^2=OMe



28 R^1=OMe, R^2=H
29 R^1=H, R^2=OMe



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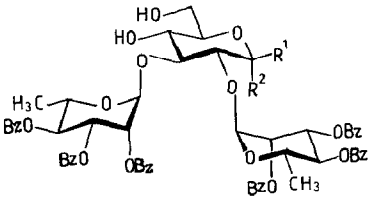
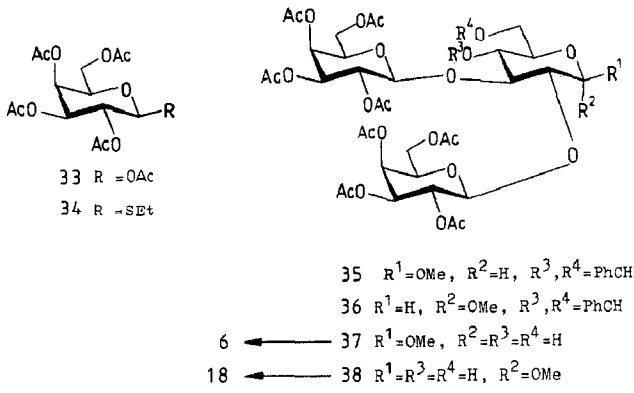


11 ← **31** R^1=OMe, R^2=H
19 ← **32** R^1=H, R^2=OMe



achieved by the glycosylation of diol **21** with ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (**34**) in the presence of nitrosyl tetrafluoroborate[13] and subsequent hydrolysis, which gave the diol **37** in 79% yield. *O*-Deacetylation of **37** and **38** then afforded the target trisaccharides **6** and **18**. The β configuration of the Glc unit in **6** and the Gal units in **6** and **18** was indicated by the ^{1}H NMR spectra ($J_{1,2}$ 7.5–7.8 Hz) and the α-D-*gluco* configuration in **18** by $J_{1,2}$ 3.6 Hz.

Since **2–5**, **7–10**, and **12–14** contain different substituents at O-2 and O-3, their syntheses were begun by the preparation of the (1 → 2)-linked precursors **43**, **47**, **52**, and **60**. The alternative (1 → 3)-linked disaccharides were not used as possible intermediates, because it was assumed that the subsequent glycosylation of O-3 would be more easy than that of O-2, the nucleophilicity of which is reduced by the electron-withdrawing effect of the neighbouring acetal fragment of the anomeric centre.

For the syntheses of **43**, **47**, **52**, and **60**, methyl 4,6-*O*-benzylidene-3-*O*-(4-chlorobenzyl)-β-D-glucopyranoside (**39**) was used as glycosyl acceptor. The 4-chlorobenzyl protecting group was chosen because of its good crystallization properties[14,15]. Compound **39** was prepared from the diol **21** by regioselective alkylation via the 2,3-dibutylstannylidene intermediate. This reaction gave **39** and its 2-*O*-(4-chlorobenzyl) isomer **40** in yields of 72 and 22%. The location of the free OH group in **39** and **40** was proved by the fact that the signal of H-3 in the ^{1}H NMR spectrum of **40** was simplified by deuterium exchange upon addition of CD_3OD. Such analysis was not possible for **39** because of overlap of signals (Table I).

For the synthesis of precursors **43**, **47**, and **52**, the glucoside **39** was subjected to glycosylation with **25**, **30**, and 2,3,4-tri-*O*-benzoyl-α-L-fucopyranosyl bromide (**49**) under Helferich conditions. Mannosylation and rhamnosylation were effective and stereospecific, and hydrolysis gave the respective disaccharide diols **41** and **45** in yields of 84 and 90%. The reaction of **39** with **49** gave the desired 1,2-trans-linked disaccharide **50** (66%) together with the 1,2-cis-linked isomer **54** (30%). That the Fuc unit in **50** was β followed from the ^{1}H NMR data in Table I ($J_{1',2'}$ 8.0 Hz).

The $J_{1',2'}$ value for **54** was not determined due to overlap of signals (see Table I), but the location of the resonance of H-5′ (δ 4.81 ppm) unambiguously confirms the α-Fuc configuration in **54**. Catalytic hydrogenolysis of compounds **41**, **45**, and **50** gave the corresponding triols **42**, **46**, and **51**, benzylidenation of which afforded the required monohydroxy derivatives **43**, **47**, and **52** in overall yields of 91, 86, and 81%.

The synthesis of the fourth disaccharide precursor, compound **60**, was achieved by the glycosylation of **39** with pentaacetate **33** (2 equiv) in the presence of trimethylsilyl triflate and subsequent acid hydrolysis, hydrogenolysis, and benzylidenation. The efficiency of the glycosylation step, as in the reaction of **33** with diol **21** (see above), depended on the amount and on the manner of addition of promoter[12]. Thus, in the presence of 1 equiv of trimethylsilyl triflate and even with continuous stirring, only 30–40% of **39** was galactosylated. Glycosylation in the presence of 2 equiv of trimethylsilyl triflate added in two portions with an interval of 16 h gave, after hydrolysis, disaccharide **56** in 67% yield. However, the use of 2 equiv of trimethylsilyl triflate added in one portion gave, after hydrolysis, a mixture of the diols **56** and **57** differing in the configuration of the anomeric centre of the Glc residues. Compounds **56** and **57** were separated in the form of triols **58** and **59** obtained after catalytic hydrogenolysis. The β configurations of the Glc unit in **58** and the Gal units in **58** and **59** followed from the ^{1}H NMR data in Table I ($J_{1,2}$ 7.7–7.9 Hz). Likewise, the $J_{1,2}$ value (3.3 Hz) showed the α configuration of the Glc unit in **59**.

The syntheses of **2–4**, which contained a 3-*O*-α-D-mannopyranosyl residue, were achieved by glycosylation of **60**, **47**, and **52** with the glycosyl bromide **25** (2 equiv) under Helferich conditions and subsequent hydrolysis, which afforded **61–63** in yields of 94, 91, and 62%. *O*-Debenzoylation of **61–63** then gave the respective target trisaccharide methyl glycosides **2–4**.

Before beginning the synthesis of **5**, **7**, and **8**, which contain a 3-*O*-β-D-galactopyranosyl residue, the model glycosylations of methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-β-D-glucopyranoside[16] (**64**) with thiogalactoside **34** and 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl trichloroacetimidate[16] (**67**) were studied in order to determine the better 3-*O*-β-D-galactosylating agent. Glycosylation of **64** with **34** in the presence of nitrosyl tetrafluoroborate and subsequent hydrolysis gave disaccharide **69** in 57% yield. The yield in this reaction was lower than in other glycosylation reactions with **34** (see above and refs 5 and 17) and was connected with the loss of the benzylidene group under the reaction conditions. This undesirable process depends on the reaction time and progressed after stirring of the mixture for more than 40 min. Thus, the use of **34** (in the presence of nitrosyl tetrafluoroborate) cannot be recommended for the glycosylation of acceptors with low reactivity.

Glycosylation of **64** with **67** in the presence of a catalytic amount of trimethylsilyl triflate[16,18–20] gave, after hydrolysis, disaccharide **69** in 94% yield, encouraging us to use **67** for the syntheses of **5**, **7**, and **8**. These reactions of disaccharide

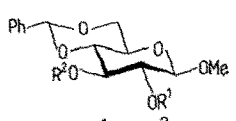
TABLE I

^{1}H NMR data (δ in ppm, J in Hz) for compounds **28**, **29**, **39**–**41**, **43**–**45**, **47**, **48**, **50**, **52**, **54**, **56**, **58**–**60**, **68**–**70**, **79**, **81**, and **89** [a]

Compound	Residue	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
28	Glc	4.60	5.38	4.15	4.06	3.48	4.10	4.06	8.0	9.1	9.1	9.1			
	Man	5.60	5.87	5.76	6.10	4.23	3.80	4.09	2.2	3.2	10.3	10.3	2.6		
29	Glc	4.90	5.11	4.29		3.59			3.6	10.0	10.0				
	Man	5.58	5.69	5.56	5.43	4.26			2.0	3.2	10.2	10.2			
39		4.33	[b]	[b]	3.81	[b]	[b]	4.37	7.3		10.1	10.1		4.3	10.1
40 [c]		4.42	3.34	3.85	3.79	3.43	3.54	4.36	7.8	9.0	9.4	9.4	9.9	4.8	9.9
41	Glc	4.46	3.76	3.64	3.70	3.40	3.82	3.88	7.6	9.3	9.3	9.3	7.7	3.5	7.7
	Man	5.66	5.77	5.88	6.09	4.62	4.20	4.58	2.0	3.2	10.1	10.1	12.2	2.2	12.2
43	Glc	4.53	3.74	3.97	3.40—3.54		3.80	4.41	7.5	8.8	8.8			4.2	10.1
	Man	5.55	5.81	5.97	6.18	5.03	4.46	4.78	2.0	3.4	10.0	10.0	4.3	2.5	12.0
44	Glc	4.91	4.99	[d]					3.3	9.6					
	Man	5.10	[d]	[d]	5.86	4.14	3.92	4.33	1.5		9.7	9.7	4.0	2.5	12.1
45	Glc	4.41	3.55————		3.66	3.34	3.76——	3.92	7.6						
	Rha	5.34	5.71	5.78	5.62	4.47	1.30		2.1	3.6	10.1	10.0	6.5		
47	Glc	4.48	3.68	3.95	3.52	3.45	3.79	4.37	7.3	7.8	7.8	9.2	9.7	4.5	9.7
	Rha	5.52	5.78	5.82	5.66	4.48	1.36		1.9		9.9	9.9	3.9		
48	Glc	4.87	3.78	4.47	3.62—3.70		3.76		3.9	9.8	9.8				
	Rha	5.05	5.24	5.66	4.47	4.21	1.20		2.0	3.5	9.8	9.8	6.3		
50	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
	Fuc	5.21	5.77	5.62	5.73	4.07	1.33		8.0	10.4	3.4	1.0	6.5		
52	Glc	4.21	3.39	3.88	3.55	3.37	3.72	4.27	7.9	8.7	8.7	9.6	10.3	4.7	10.3
	Fuc	4.90	5.72	5.57	5.69	4.17	1.32		7.9	10.8	3.0	0.5	6.5		

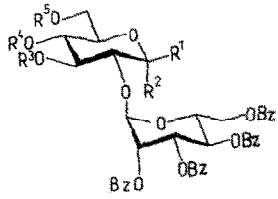
54	Glc	4.55	3.84	3.79	3.74	3.51	3.81	4.25	7.3	8.3	8.3	8.3	10.5	5.0	10.5	
	Fuc	[e]	[e]	5.96	[e]	4.81	1.29				3.4	1.2	6.5			
56	Glc	4.32	3.39	——	3.50	3.21	3.68	—3.83	7.6							
	Gal	4.87	5.19	4.93	5.33	3.88	4.05	—4.19	7.6	10.3	3.4	1.1				
58	Glc	4.27	3.24	3.35	—3.46	3.22	3.67	—3.84	7.8	8.7				11.5	4.5	11.5
	Gal	4.74	5.13	4.97	5.33	3.90	4.08	—4.12	7.9	10.3	3.5	1.2	6.2	6.2	0	
59	Glc	4.77	3.41	3.77	3.41	3.52	3.73	—3.81	3.3	9.3	9.3	8.7	8.8	3.4	8.8	
	Gal	4.64	5.21	4.98	5.33	3.90	4.02	—4.15	7.7	10.0	3.3	1.2	6.3	6.3	11.4	
60	Glc	4.41	3.41	3.79	3.49	3.37	3.74	4.32	7.6	9.1	9.1	9.1	10.1	4.5	10.1	
	Gal	4.77	5.19	5.01	5.38	3.93	4.13	—4.17	8.1	9.9	3.4	1.3	6.7	6.7	0	
68 [f]		5.60	5.18	5.36	5.53	4.41	4.11	4.17	2.6	10.5	3.3	1.6	6.8	6.0	11.5	
69	Glc	4.46	5.19	3.80	3.68	3.35	—3.50	[g]	7.5	8.8	8.8	8.8				
	Gal	4.55	5.18	4.83	5.32	[g]	4.08	—4.20	7.9	10.4	3.1	1.0				
70	Glc	4.92	—4.99	4.12												
	Gal	4.64	5.10	4.84	5.31	4.02			7.6	10.2	3.3	1.0				
79 [h]	Glc	4.23	5.62	3.85	5.19	3.31	4.16	4.25	8.0	9.1	9.1	9.6	3.6	5.0	12.4	
	Fuc	5.41	5.38	5.43	5.43	3.98	1.00		3.6	9.5	3.6	1.6	6.5			
81	Glc	4.40	5.06	3.82	3.64	3.31	3.74	3.85	8.3	9.5	9.5	9.5	4.5	3.3	12.5	
	Fuc	4.65	5.01	4.84	4.93	3.26	0.59		7.9	10.4	3.5	0.5	7.0			
89	Glc	5.02	4.98	4.22	3.74	3.66	3.82	—3.85	3.6	9.2	9.2	8.6				
	Rha	5.26	5.39	5.70	5.53	4.50	1.35		2.0	3.4	10.1	10.0	5.8			

[a] For solutions in $CDCl_3$, unless stated otherwise. [b] 3.40–3.74 [m, 7 H, H-2, 3, 5, 6a, OMe(3.58)]. [c] 2.52 (d, 1 H, OH, J 2.4 Hz). [d] 5.49–5.67 (m, 3 H, H-3Glc, H-2,3Man). [e] 5.80–5.88 (m, 3 H, H-1, 2, 4). [f] $J_{H\text{-}1,F}$ 52.0 Hz, $J_{H\text{-}2,F}$ 23.0 Hz. [g] 3.98–4.04 (m, 2 H, H6b-Glc, H5-Gal). [h] For solution in C_6D_6. Other signals: aromatic, δ 6.90–8.20; OMe, 3.29–3.64, 2.90 (for **52**); AcO, 1.50–2.30; PhC*H*, 5.51–5.62; 4-ClPhCH_2, 4.50–5.12.



39 R^1=H, R^2= 4-ClBn

40 R^1= 4-ClBn, R^2=H

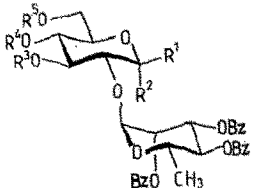


41 R^1=OMe, R^2=R^4=R^5=H, R^3= 4-ClBn

42 R^1=OMe, R^2=R^3=R^4=R^5=H

43 R^1=OMe, R^2=R^3=H, R^4,R^5=PhCH

44 R^1=R^4=R^5=H, R^2=OMe, R^3=Bz

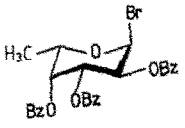


45 R^1=OMe, R^2=R^4=R^5=H, R^3= 4-ClBn

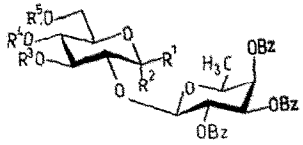
46 R^1=OMe, R^2=R^3=R^4=R^5=H

47 R^1=OMe, R^2=R^3=H, R^4,R^5=PhCH

48 R^1=R^4=R^5=H, R^2=OMe, R^3=Bz



49

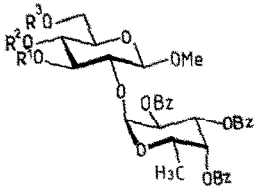


50 R^1=OMe, R^2=R^4=R^5=H, R^3= 4-ClBn

51 R^1=OMe, R^2=R^3=R^4=R^5=H

52 R^1=OMe, R^2=R^3=H, R^4,R^5=PhCH

53 R^1=R^4=R^5=H, R^2=OMe, R^3=Bz

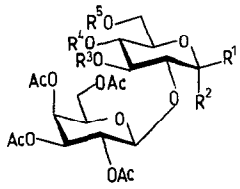


54 R^1= 4ClBn, R^2,R^3=PhCH

55 R^1=Bz, R^2=R^3=Ac

precursors with **67** gave the trisaccharide derivatives **71**, **73**, and **75** in 58, ~50, and 75% yields. Acid hydrolysis of **71**, **73**, and **75** and subsequent *O*-deacylation gave, first, **72**, **74**, and **76**, and then the target trisaccharides **5**, **7**, and **8**. The β configuration of the Gal units in **5**, **7**, and **8** as well as in disaccharide **69** (Table I) was indicated by the ^{1}H NMR data ($J_{1,2}$ 7.5–7.9 Hz).

Before the synthesis of **13** and **14**, which contained a 3-*O*-β-L-fucopyranosyl residue, the model glycosylation of **64** with ethyl 2,3,4-tri-*O*-acetyl-1-thio-β-L-fucopyranoside[15] (**77**) and the fucosyl bromide **49** were studied in order to determine the better 3-*O*-β-L-fucosylating agent. Glycosylation of **64** with **49** gave[9] a mixture of α and β disaccharides, which were separated in the form of the 4,6-diacetates **78** (32%) and **80** (61%). The reaction of **64** with **77** in the presence of nitrosyl tetrafluoroborate was more stereoselective and gave after hydrolysis a



56 R^1=OMe, R^2=R^4=R^5=H, R^3= 4-ClBn

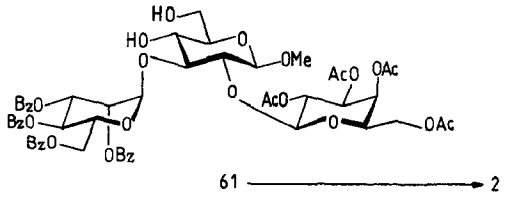
57 R^1=R^4=R^5=H, R^2=OMe, R^3= 4-ClBn

58 R^1=OMe, R^2=R^3=R^4=R^5=H

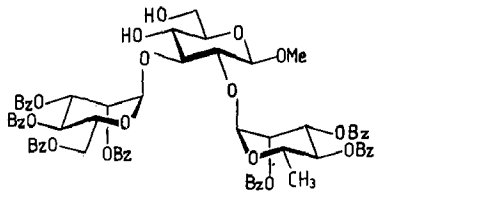
59 R^1=R^3=R^4=R^5=H, R^2=OMe

60 R^1=OMe, R^2=R^3=H, R^4,R^5=PhCH

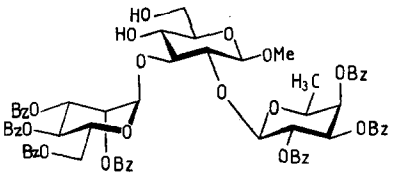
1:8 mixture (82%) of the α- and β-fucosylglucosides **79** and **81**. Glycosylation of **64** with **77** proceeds more rapidly than with the D-*galacto* analogue **34**, and therefore was not accompanied by side reactions. The 1,2-trans-linked disaccharide **81** was separated by column chromatography, and the 1,2-cis-linked product **79** was



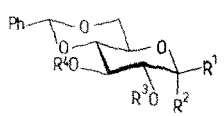
61 ⟶ 2



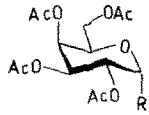
62 ⟶ 3



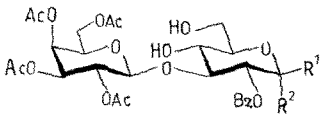
63 ⟶ 4



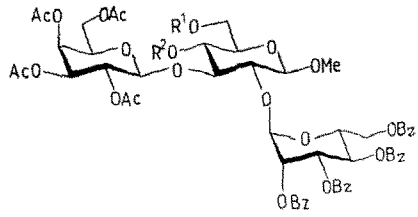
64 R^1=OMe, R^2=R^4=H, R^3=Bz
65 R^1=R^4=H, R^2=OMe, R^3=Bz
66 R^1=R^3=H, R^2=OMe, R^4=Bz



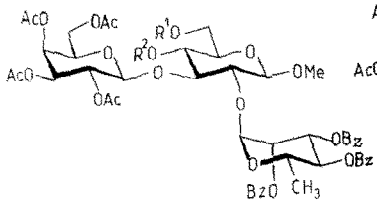
67 R= $CCl_3C(=NH)O$
68 R=F



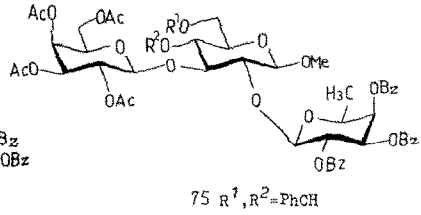
69 R^1=OMe, R^2=H
70 R^1=H, R^2=OMe



71 R^1,R^2=PhCH
5 ← 72 R^1=R^2=H



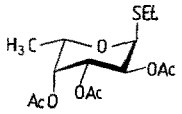
73 R^1,R^2=PhCH
7 ← 74 R^1=R^2=H



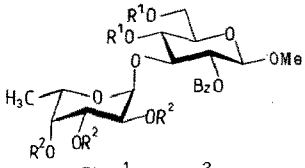
75 R^1,R^2=PhCH
8 ← 76 R =R =Ac

identified in the mixture by ^{1}H NMR spectroscopy. In $CDCl_3$, the signals of **79** overlapped those of **81**, but in C_6D_6 all signals of **79** were identified and showed the α configuration of the Fuc unit ($J_{1,2}$ 3.6 Hz).

Taking advantage of the finding that the glycosylation of **64** by **49** was effective (total yield of products > 93%) and not stereoselective, we used **49** for the fucosylation of disaccharides **43** and **60**, aiming to synthesise in each of these reactions the pairs of isomeric trisaccharides with the necessary combinations of anomeric configurations of the substituents at O-2 and O-3. As was expected, the fucosylation of **43** and **60** with **49** gave the pairs of isomeric trisaccharide products, separated as the diols **83** and **84** (yields 22 and 28%) in the former case, and as the 4,6-diacetates **85** and **86** (yields 38 and 32%) in the latter. *O*-Deacylation of **83–86** then gave the respective target trisaccharides **9**, **13**, **10**, and **14**. The α configuration of the Fuc units in **9** and **10** was indicated by ^{1}H NMR data ($J_{1,2}$ 3.6 and 3.5

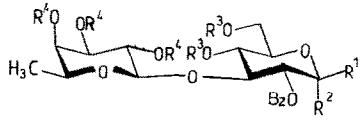


77



78 R^1=Ac , R^2=Bz

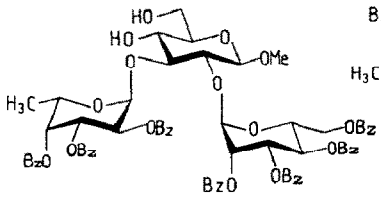
79 R =R =Ac



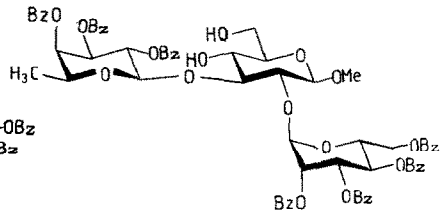
80 R^1=OMe, R^2=H, R^3=Ac, R^4=Bz

81 R^1=OMe, R^2=R^3=H, R^4=Ac

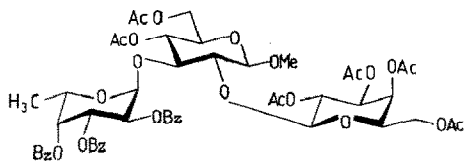
82 R^1=H, R^2=OMe, R^3=Ac, R^4=Bz



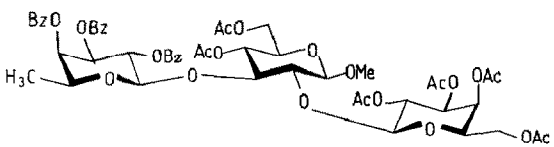
83 ⟶ 9



13 ⟵ 84



85 ⟶ 10



86 ⟶ 14

R-(1 → 2)-β-D-Glc*p*-OMe		R-(1 → 3)-β-D-Glc*p*-OMe
90	R = α-D-Man*p*	**95**
91	R = β-D-Gal*p*	**96**
92	R = α-L-Fuc*p*	**97**
93	R = α-L-Rha*p*	**98**
94	R = β-L-Fuc*p*	**99**

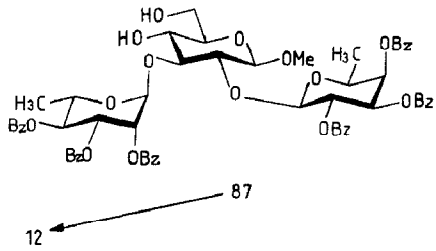
R-(1 → 2)-α-D-Glc*p*-OMe		R-(1 → 3)-α-D-Glc*p*-OMe
100	R = α-D-Man*p*	**104**
101	R = β-D-Gal*p*	**105**
102	R = α-L-Rha*p*	**106**
103	R = β-L-Fuc*p*	**107**

Hz). Likewise, the $J_{1,2}$ values for the Fuc residues in **13** and **14** (7.5 and 7.6 Hz) confirmed their β configuration.

Glycosylation of disaccharide **52** by **30** under Helferich conditions and subsequent hydrolysis gave compound **87** (81%), which was then *O*-debenzoylated to give the target trisaccharide **12**. Its structure was confirmed by ^{13}C NMR data[10].

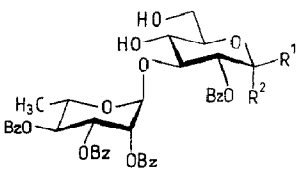
In addition to the trisaccharide methyl glycosides, the disaccharide methyl glycosides **90–107** were also synthesised since their ^{13}C NMR data[10] were necessary for the calculation of the deviation from additivity values in the spectra of **1–20**.

Compounds **90–107** were obtained after deprotection of the respective substituted precursors **42**, **58**, **55**, **46**, **51**, **28**, **69**, **78**[9], **88**, **80**[9], **44**, **59**, **48**, **53**[9], **29**, **70**, **89**, and **82**[9] under the usual conditions. Rhamnosyl-glucosides **88**, **48**, and **89** and mannosyl-glucosides **44** and **29** were prepared in 81–96% yields by glycosylation of **64** and methyl 2-*O*- (**65**) and 3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside[16] (**66**) with bromides **30** and **25** under Helferich conditions and subsequent hydrolysis.



87

12



88 R^1 = OMe, R^2 = H
89 R^1 = H, R^2 = OMe

Glycosylation of **65** with imidate **67** promoted by trimethylsilyl triflate, with subsequent hydrolysis, gave disaccharide **70** in rather moderate yield (43%). This differed markedly from the result of glycosylation of the β-glucoside **64** with **67** which afforded the disaccharide **69** in a yield of 94% (see above). The difference in yields of disaccharides **69** and **70** is due to the lower reactivity of the α-glucoside **65** whose glycosylation attained only ~ 50% (TLC). A more effective synthesis of **70** was performed by glycosylation of **65** with **67** in the presence of the milder promoter, boron trifluoride etherate. In this case, the yield of **70** was 87%. Glycosylation in the presence of boron trifluoride etherate was accompanied by the formation of 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl fluoride (**68**), which was separated from the mixture in a yield of 21% based on **67**. Its structure was confirmed by the ^{1}H NMR spectrum which coincided with that of the previously synthesised compound[21]. Apparently, the formation of glycosyl fluorides has not previously been observed in glycosylations with glycosyl trichloroacetimidates in the presence of boron trifluoride etherate.

The details of the NMR study of the trisaccharide methyl glycosides **1**–**20** have been considered in a separate paper[10].

EXPERIMENTAL

General.—The reagents and solvents as well as the NMR instruments used in this work have been described[5,7,8]. Optical rotations for substituted compounds were determined on solutions in $CHCl_3$ and for oligosaccharides **1**–**20** and **91**–**107** in water with a Jasco DIP-360 digital polarimeter at 26–30°C.

TLC was performed on Kieselgel-60 (Merck) with EtOAc–toluene (*A*, 1:1; *B*, 1:2; *C*, 1:6), EtOAc (*D*), chloroform–EtOH (*E*, 19:1), and EtOAc–heptane (*F*, 1:1; 3 elutions), 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.

*Methyl 2,3-di-*O*-(2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl)-β-D-glucopyranoside* (**26**).—(*a*) A mixture of **22**[22] (120 mg, 0.5 mmol), $Hg(CN)_2$ (504 mg, 2.0 mmol), $HgBr_2$ (100 mg), and 4A molecular sieves in MeCN (10 mL) was stirred for 45 min under Ar at 20°C. Using a syringe, a solution of mannosyl bromide **25** [prepared[3] from penta-*O*-benzoyl-D-mannopyranose (1.4 g, 2 mmol)] in MeCN (10 mL) was added portionwise during 1 h. The mixture was stirred for 16 h, then concentrated, diluted with $CHCl_3$ (50 mL) and satd aq KBr (50 mL), and filtered through Celite. The organic layer was separated, washed with satd aq KBr and water, then filtered through cotton, and concentrated. To a solution of the residue in $CHCl_3$ (15 mL) was added aq 90% CF_3CO_2H (3 mL). The mixture was stirred for 40 min and co-evaporated with toluene (3 × 5 mL). Column chromatography of the residue gave amorphous **26** (310 mg, 46%); $[\alpha]_D$ −35° (*c* 1); R_F 0.47 (solvent *A*).

(*b*) Glycosylation of **21**[23] (85 mg, 0.3 mmol) with **25** [prepared[3] from penta-*O*-benzoyl-D-mannopyranose (840 mg, 1.2 mmol)] was processed as described above.

The resulting mixture of products was diluted with $CHCl_3$ (10 mL), and aq 90% CF_3CO_2H (3 mL) was added. The mixture was stirred for 40 min, diluted with $CHCl_3$ (20 mL), washed with water, aq $NaHCO_3$, and water, then filtered through cotton, and concentrated. Column chromatography of the residue gave 360 mg (84%) of **26**.

Methyl 2,3-di-O-(2,3,4,6-tetra-O-benzoyl-α-D-mannopyranosyl)-α-D-glucopyranoside (**27**).—Glycosylation of **24**[22] (56 mg, 0.2 mmol) with **25** [prepared[3] from penta-*O*-benzoyl-D-mannopyranose (560 mg, 0.8 mmol)] and subsequent hydrolysis, as for the synthesis of **26**, gave amorphous **27** (197 mg, 73%); $[\alpha]_D$ +3° (*c* 1); R_f 0.47 (solvent *A*).

Methyl 2-O-benzoyl-3-O-(2,3,4,6-tetra-O-benzoyl-α-D-mannopyranosyl)-β-D-glucopyranoside (**28**).—Glycosylation of **23**[24] (170 mg, 0.5 mmol) with **25** [prepared[3] from penta-*O*-benzoyl-D-mannopyranose (700 mg, 1 mmol)] and subsequent hydrolysis, as for the synthesis of **26**, gave amorphous **28** (230 mg, 50%); $[\alpha]_D$ +25° (*c* 1.2); R_f 0.31 (solvent *A*). The ^1H NMR data are listed in Table I.

Methyl 2-O-benzoyl-3-O-(2,3,4,6-tetra-O-benzoyl-α-D-mannopyranosyl)-α-D-glucopyranoside (**29**).—Glycosylation of **65**[25] (69 mg, 0.18 mmol) with **25** [prepared[3] from penta-*O*-benzoyl-D-mannopyranose (252 mg, 0.36 mmol)] and subsequent hydrolysis, as for the synthesis of **26**, gave amorphous **29** (136 mg, 86%); $[\alpha]_D$ +67° (*c* 1); R_f 0.44 (solvent *A*). The ^1H NMR data are listed in Table I.

Methyl 2,3-di-O-(2,3,4-tri-O-benzoyl-α-L-rhamnopyranosyl)-β-D-glucopyranoside (**31**).—Glycosylation of **21**[23] (56 mg, 0.2 mmol) with **30** [prepared[3] from tetra-*O*-benzoyl-L-rhamnopyranose (1.16 g, 2.0 mmol)] and subsequent hydrolysis, as for the synthesis of **26**, gave amorphous **31** (512 mg, 92%); $[\alpha]_D$ +161° (*c* 1.4); R_f 0.48 (solvent *A*).

Methyl 2,3-di-O-(2,3,4-tri-O-benzoyl-α-L-rhamnopyranosyl)-α-D-glucopyranoside (**32**).—Glycosylation of **24**[22] (85 mg, 0.3 mmol) with **30** [prepared[3] from tetra-*O*-benzoyl-L-rhamnopyranose (696 mg, 1.2 mmol)] and subsequent hydrolysis, as for the synthesis of **26**, gave amorphous **32** (281 mg, 84%); $[\alpha]_D$ +177.5° (*c* 1); R_f 0.42 (solvent *A*).

Glycosylation of **21** *with* **33**.—A mixture of **21**[23] (282 mg, 1 mmol), **33** (1.56 g, 4 mmol), and 4A molecular sieves in CH_2Cl_2 (10 mL) was stirred for 45 min at 20°C under Ar, and trimethylsilyl triflate (0.8 mL, 4 mmol) was added. The mixture was stirred for 40 h at 20°C, then diluted with $CHCl_3$ (30 mL), filtered through Celite, washed with water, aq $NaHCO_3$, and water, and concentrated. The residue was hydrolysed as for the synthesis of **26**. Column chromatography then gave **37** (160 mg, 19%) and its α-methyl isomer **38** (110 mg, 13%).

Compound **37** was amorphous and had $[\alpha]_D$ −5° (*c* 1); R_f 0.42 (solvent *D*).

Compound **38** was amorphous and had $[\alpha]_D$ +14° (*c* 1); R_f 0.53 (solvent *D*).

Glycosylation of **21** *with* **34**.—A mixture of **21**[23] (85 mg, 0.3 mmol), **34**[16] (470 mg, 1.2 mmol), and 4A molecular sieves in CH_2Cl_2 (5 mL) was stirred for 45 min at 20°C under Ar, and $NOBF_4$ (143 mg, 1.2 mmol) was added. The mixture was stirred for 30 min at 20°C, then satd aq $NaHCO_3$ (10 mL) and $CHCl_3$ (30 mL) were

added. The mixture was filtered through Celite, washed with aq $NaHCO_3$ and water, and concentrated. The residue was hydrolysed as for the synthesis of **26**. Column chromatography then gave **37** (202 mg, 79%).

Methyl 4,6-O-benzylidene-2-O-(4-chlorobenzyl)- (**40**) *and-3-O-(4-chlorobenzyl)-β-D-glucopyranoside* (**39**).—A mixture of **21**[23] (3.1 g, 11 mmol) and Bu_2SnO (3.0 g, 12 mmol) in benzene (190 mL) was boiled under reflux for 2 h with azeotropic removal of water. The temperature was reduced to 40–50°C, and Bu_4NBr (3.9 g, 12.1 mmol) and 4-chlorobenzyl bromide (5.7 g, 27.5 mmol) were added. The mixture was boiled for 20 h, and the solvent was evaporated and co-evaporated with water (2 × 5 mL). A solution of the residue in $CHCl_3$ (100 mL) was washed with water (5 × 70 mL), filtered through cotton, and concentrated. Crystallisation of the residue from EtOAc–hexane and subsequent column chromatography gave **40** (980 mg, 22%) and **39** (3.22 g, 72%).

Compound **39** had mp 192–193°C (from EtOAc–hexane); $[\alpha]_D$ −47° (*c* 1.9); R_f 0.45 (solvent *B*).

Compound **40** had mp 167–168°C (from EtOAc–hexane); $[\alpha]_D$ −27° (*c* 0.8); R_f 0.64 (solvent *B*).

Anal. Calcd for $C_{21}H_{23}O_6Cl$: C, 61.99; H, 5.70; Cl, 8.71. Found for **39**: C, 62.83; H, 5.77; Cl, 8.83; for **40**: C, 62.05; H, 6.07; Cl, 8.80.

The ^1H NMR data for **39** and **40** are listed in Table I.

Methyl 3-O-(4-chlorobenzyl)-2-O-(2,3,4,6-tetra-O-benzoyl-α-D-mannopyranosyl)-β-D-glucopyranoside (**41**).—Glycosylation of **39** (1.0 g, 2.46 mmol) with **25** [prepared[3] from penta-*O*-benzoyl-D-mannopyranose (4.2 g, 6.0 mmol)] and subsequent hydrolysis, as for the synthesis of **26**, gave amorphous **41** (1.86 g, 84%); $[\alpha]_D$ −14° (*c* 0.8); R_f 0.34 (solvent *A*). The ^1H NMR data are listed in Table I.

Methyl 4,6-O-benzylidene-2-O-(2,3,4,6-tetra-O-benzoyl-α-D-mannopyranosyl)-β-D-glucopyranoside (**43**).—A solution of **41** (1.86 g, 2.1 mmol) in EtOH (30 mL) was shaken with 10% Pd–C at 41°C under H_2 (1 atm) for 20 h, then filtered, and the solvent was evaporated in vacuo. Column chromatography of the residue gave amorphous triol **42** (1.55 g 97%); R_F 0.48 (solvent *D*). A solution of **42** (1.1 g, 1.4 mmol), benzaldehyde dimethyl acetal (0.63 mL, 4.2 mmol), and $TsOH \cdot H_2O$ (10 mg) in MeCN (10 mL) was kept for 30 min at 20°C, then diluted with $CHCl_3$ (70 mL), washed with aq $NaHCO_3$ and water, filtered through cotton, and concentrated. Column chromatography of the residue gave amorphous **43** (1.14 g, 94%); $[\alpha]_D$ −55° (*c* 1); R_f 0.38 (solvent *C*). The ^1H NMR data are listed in Table I.

Methyl 3-O-(4-chlorobenzyl)-2-O-(2,3,4-tri-O-benzoyl-α-L-rhamnopyranosyl)-β-D-glucopyranoside (**45**).—Glycosylation of **39** (1.0 g, 2.46 mmol) with **30** [prepared[3] from tetra-*O*-benzoyl-L-rhamnopyranose (2.9 g, 5.0 mmol)] and subsequent hydrolysis, as for the synthesis of **26**, gave amorphous **45** (1.72 g, 90%); $[\alpha]_D$ +105° (*c* 1.7); R_f 0.23 (solvent *A*). The ^1H NMR data are listed in Table I.

Methyl 4,6-O-benzylidene-2-O-(2,3,4-tri-O-benzoyl-α-L-rhamnopyranosyl)-β-D-glucopyranoside (**47**).—Catalytic hydrogenolysis of **45** (1.6 g, 2.1 mmol), as for the synthesis of **42**, gave amorphous **46** (1.42 g, 93%); R_f 0.48 (solvent *D*). Compound

46 (1.1 g, 1.7 mmol) was then benzylidenated as for the preparation of **43**, to give **47** (1.15 g, 92%); $[\alpha]_D$ +62.5° (*c* 1); R_f 0.40 (solvent *C*). The ^{1}H NMR data are listed in Table I.

Methyl 4,6-O-benzylidene-3-O-(4-chlorobenzyl)-2-O-(2,3,4-tri-O-benzoyl-α- (**54**) *and -β-L-fucopyranosyl)-β-D-glucopyranoside* (**50**).—Glycosylation of **39** (179 mg, 0.44 mmol) with **49** [prepared[3] from tetra-*O*-benzoyl-L-fucopyranose (580 mg, 1 mmol)], as for the synthesis of **26** (without hydrolysis step), gave **50** (250 mg, 66%) and **54** (115 mg, 30%).

Compound **50** had mp 189–190°C (from EtOAc–hexane); $[\alpha]_D$ −65° (*c* 1); R_f 0.42 (solvent *C*).

Anal. Calc. for $C_{48}H_{45}O_{13}Cl$: C, 66.63; H, 5.24; Cl, 4.10. Found: C, 66.95; H, 5.47; Cl, 3.64.

Compound **54** was amorphous and had $[\alpha]_D$ −170° (*c* 1); R_f 0.54 (solvent *C*). The ^{1}H NMR data for **50** and **54** are listed in Table I.

Methyl 4,6-O-benzylidene-2-O-(2,3,4-tri-O-benzoyl-β-L-fucopyranosyl)-β-D-glucopyranoside (**52**).—Catalytic hydrogenolysis and subsequent benzylidenation of **50** (1.32 g, 1.52 mmol), as for the syntheses of **42** and **43**, gave, first, **51** and then amorphous **52** (851 mg, 81%); $[\alpha]_D$ −109° (*c* 1); R_f 0.20 (solvent *C*). The ^{1}H NMR data are listed in Table I.

Glycosylation of **39** *with* **33**.—(*a*) A mixture of **39** (406 mg, 1 mmol), **33** (780 mg, 2 mmol), and 4A molecular sieves in CH_2Cl_2 (10 mL) was stirred for 45 min at 20°C under Ar, and trimethylsilyl triflate (190 μL, 1 mmol) was added. The mixture was stirred for 16 h at 20°C and more trimethylsilyl triflate (190 μL, 1 mmol) was added. After stirring for 5 h, the mixture was processed and hydrolysed as for the glycosylation of **21** with **33**, to give amorphous **56** (432 mg, 67%); $[\alpha]_D$ −52° (*c* 1); R_f 0.58 (solvent *D*).

(*b*).—A mixture of **39** (1 g, 2.46 mmol), **33** (1.92 g, 4.92 mmol), and 4A molecular sieves in CH_2Cl_2 (10 mL) was stirred for 45 min at 20°C under Ar, and trimethylsilyl triflate (1 mL, ~5 mmol) was added. The mixture was stirred for 20 h at 20°C and processed and hydrolysed as described above to give a mixture (1.13 g, 71%) of **56** and **57**. Catalytic hydrogenolysis of this mixture, as for the synthesis of **42**, and subsequent column chromatography gave **58** (358 mg, 28%), **59** (60 mg, 5%), and 440 mg (34%) of a 4:1 (^{1}H NMR) mixture of **58** and **59**.

Compound **58** was amorphous and had $[\alpha]_D$ −2° (*c* 0.8); R_f 0.40 (solvent *E*).

Compound **59** was amorphous and had $[\alpha]_D$ +57° (*c* 1.3); R_f 0.38 (solvent *E*).

The ^{1}H NMR data for **56**, **58**, and **59** are listed in Table I.

Methyl 4,6-O-benzylidene-2-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-β-D-glucopyranoside (**60**).—Catalytic hydrogenolysis and subsequent benzylidenation of **56** (486 mg, 0.75 mmol), as for the syntheses of **42** and **43**, gave amorphous **60** (293 mg, 74%); $[\alpha]_D$ −27° (*c* 1); R_f 0.52 (solvent *A*). The ^{1}H NMR data are listed in Table I.

Methyl 2-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-3-O-(2,3,4,6-tetra-O-benzoyl-α-D-mannopyranosyl)-β-D-glucopyranoside (**61**).—Glycosylation of **60** (184

mg, 0.3 mmol) with **25** [prepared[3] from penta-*O*-benzoyl-D-mannopyranose (560 mg, 0.8 mmol)] and subsequent hydrolysis, as for the synthesis of **26**, gave amorphous **61** (204 mg, 62%); $[\alpha]_D$ −24° (*c* 1); R_f 0.60 (solvent *D*).

Methyl 3-O-(2,3,4,6-tetra-O-benzoyl-α-D-mannopyranosyl)-2-O-(2,3,4-tri-O-benzoyl-α-L-rhamnopyranosyl)-β-D-glucopyranoside (**62**).—Glycosylation of **47** (222 mg, 0.3 mmol) with **25** [prepared[3] from penta-*O*-benzoyl-D-mannopyranose (420 mg, 0.6 mmol)] and subsequent hydrolysis, as for the synthesis of **26**, gave amorphous **62** (347 mg, 94%); $[\alpha]_D$ +27° (*c* 1); R_f 0.18 (solvent *B*).

Methyl 3-O-(2,3,4,6-tetra-O-benzoyl-α-D-mannopyranosyl)-2-O-(2,3,4-tri-O-benzoyl-β-L-fucopyranosyl)-β-D-glucopyranoside (**63**).—Glycosylation of **52** (222 mg, 0.3 mmol) with **25** [prepared[3] from penta-*O*-benzoyl-D-mannopyranose (280 mg, 0.4 mmol)] and subsequent hydrolysis, as for the synthesis of **26**, gave amorphous **63** (334 mg, 91%); $[\alpha]_D$ −29° (*c* 1.4); R_f 0.28 (solvent *A*).

Methyl 2-O-benzoyl-3-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-β-D-glucopyranoside (**69**).—(*a*) Glycosylation of **64**[16] (193 mg, 0.5 mmol) with **34**[16] (294 mg, 0.75 mmol) and subsequent hydrolysis, as for the synthesis of **37**, gave amorphous **69** (180 mg, 57%); $[\alpha]_D$ −4° (*c* 1); R_f 0.48 (solvent *D*).

(*b*). A mixture of **64**[16] (96.5 mg, 0.25 mmol), **67**[16] (148 mg, 0.3 mmol), and 4A molecular sieves in CH_2Cl_2 (2 mL) was stirred for 30 min at 20°C under Ar, and trimethylsilyl triflate (19 μL, 0.1 mmol) was added. The mixture was stirred for 30 min, then processed and hydrolysed as in (*a*) to give **69** (148 mg, 94%). The ^1H NMR data are listed in Table I.

Methyl 2-O-benzoyl-3-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-α-D-glucopyranoside (**70**).—(*a*) Glycosylation of **65**[25] (96.5 mg, 0.25 mmol) with **67**[16] (148 mg, 0.3 mmol) in the presence of trimethylsilyl triflate (19 μL, 0.1 mmol) and subsequent hydrolysis, as for the synthesis of **69** (run *b*), gave amorphous **70** (81 mg, 43%); $[\alpha]_D$ +66° (*c* 1); R_f 0.53 (solvent *D*).

(*b*) A mixture of **65**[25] (96.5 mg, 0.25 mmol), **67**[16] (148 mg, 0.3 mmol), and 4A molecular sieves in CH_2Cl_2 (2 mL) was stirred for 30 min at 20°C under Ar, and a 0.1 M solution (2 mL) of boron trifluoride etherate in CH_2Cl_2 was added at −25 to −30°C. The mixture was stirred for 30 min at −25 to −30°C, then processed and hydrolysed as in (*a*) to give **70** (136 mg, 87%) and 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl fluoride (**68**; 29 mg, 21%); R_f 0.53 (solvent *D*).

The ^1H NMR data for **68** and **70** are listed in Table I.

Methyl 3-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-2-O-(2,3,4,6-tetra-O-benzoyl-α-D-mannopyranosyl)-β-D-glucopyranoside (**72**).—Glycosylation of **43** (215 mg, 0.25 mmol) with **67**[16] (148 mg, 0.5 mmol), as for the reaction of **64** with **67** but without the hydrolysis step, gave amorphous **71** (171 mg, 58%); R_F 0.55 (solvent *A*), and the recovery of **43** (58 mg, 27%). Compound **71** was hydrolysed as for the preparation of **26** to give amorphous **72** (143 mg, 91%); $[\alpha]_D$ −26° (*c* 1); R_f 0.48 (solvent *D*).

Methyl 3-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-2-O-(2,3,4-tri-O-benzoyl-α-L-rhamnopyranosyl)-β-D-glucopyranoside (**74**).—Glycosylation of **47** (148 mg,

0.2 mmol) with **67**[16] (197 mg, 0.4 mmol), as for the synthesis of **69** (including the hydrolysis step), gave amorphous **74** (90 mg, 46%); $[\alpha]_D$ +60° (*c* 1); R_f 0.55 (solvent *D*); and **46** (58 mg, 45%) formed as the result of hydrolysis of unreacted **47**.

Methyl 3-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-2-O-(2,3,4-tri-O-benzoyl-β-L-fucopyranosyl)-β-D-glucopyranoside (**76**).—Glycosylation of **52** (148 mg, 0.2 mmol) with **67**[16] (197 mg, 0.4 mmol), as for the reaction of **64** with **67** (without the hydrolysis step), gave amorphous **75** (160 mg, 75%), which was hydrolysed as for the preparation of **26**, to give amorphous **76** (135 mg, 91%); $[\alpha]_D$ −79° (*c* 1); R_f 0.50 (solvent *D*).

Glycosylation of **64** *with ethyl 2,3,4-tri-O-acetyl-1-thio-β-L-fucopyranoside* (**77**).—Glycosylation of **64** (193 mg, 0.5 mmol) with **77**[16], as for the reaction of **64** with **34** (including the hydrolysis step), gave methyl 2-*O*-benzoyl-3-*O*-(2,3,4-tri-*O*-acetyl)-β-L-fucopyranosyl)-β-D-glucopyranoside (**81**; 181 mg, 63.5%) and a 1 : 1 (^{1}H NMR) mixture of **81** and its α-fucosyl isomer **79** (52 mg, 18%). Compound **81** was amorphous and had $[\alpha]_D$ −8° (*c* 1); R_f 0.60 (solvent *D*).

The ^{1}H NMR data for **79** and **81** are listed in Table I.

Methyl 2-O-(2,3,4,6-tetra-O-benzoyl-α-D-mannopyranosyl)-3-O-(2,3,4-tri-O-benzoyl-α- and -β-L-fucopyranosyl)-β-D-glucopyranoside (**83** and **84**).—Glycosylation of **43** (258 mg, 0.3 mmol) with **49** [prepared[3] from tetra-*O*-benzoyl-L-fucopyranose (435 mg, 0.75 mmol)] and subsequent hydrolysis, as for the synthesis of **26**, gave **83** (82 mg, 22%) and **84** (103 mg, 28%).

Compound **83** was amorphous and had $[\alpha]_D$ −114° (*c* 1); R_f 0.38 (solvent *A*).

Compound **84** was amorphous and had $[\alpha]_D$ −45° (*c* 1); R_f 0.20 (solvent *A*).

Methyl 4,6-di-O-acetyl-3-O-(2,3,4-tri-O-benzoyl-α- and -β-L-fucopyranosyl)-2-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-β-D-glucopyranoside (**85** *and* **86**). Glycosylation of **60** (245 mg, 0.4 mmol) with **49** [prepared[3] from tetra-*O*-benzoyl-L-fucopyranose (580 mg, 1 mmol)] and hydrolysis as for the synthesis of **26**, with subsequent acetylation (Ac_2O, Py, 20°C), gave **85** (163 mg, 38%) and **86** (137 mg, 32%).

Compound **85** was amorphous and had $[\alpha]_D$ −129° (*c* 1); R_f 0.53 (solvent *A*).

Compound **86** was amorphous and had $[\alpha]_D$ −76° (*c* 1); R_f 0.42 (solvent *A*).

Methyl 2-O-(2,3,4-tri-O-benzoyl-β-L-fucopyranosyl)-3-O-(2,3,4-tri-O-benzoyl-α-L-rhamnopyranosyl)-β-D-glucopyranoside (**87**).—Glycosylation of **52** (148 mg, 0.2 mmol) with **30** [prepared[3] from tetra-*O*-benzoyl-L-rhamnopyranose (230 mg, 0.4 mmol)] and subsequent hydrolysis, as for the synthesis of **26**, gave amorphous **87** (180 mg, 81%); $[\alpha]_D$ +43° (*c* 1); R_f 0.38 (solvent *A*).

Methyl 2-O-benzoyl-3-O-(2,3,4-tri-O-benzoyl-α-L-rhamnopyranosyl)-β-D-glucopyranoside (**88**).—Glycosylation of **64**[16] (116 mg, 0.3 mmol) with **30** [prepared[3] from tetra-*O*-benzoyl-L-rhamnopyranose (350 mg, 0.6 mmol)] and subsequent hydrolysis, as for the synthesis of **26**, gave amorphous **88** (200 mg, 88%); $[\alpha]_D$ +150° (*c* 1.4); R_f 0.30 (solvent *A*). The ^{1}H NMR data are listed in Table I.

Methyl 2-O-benzoyl-3-O-(2,3,4-tri-O-benzoyl-α-L-rhamnopyranosyl)-α-D-gluco-

pyranoside (**89**).—Glycosylation of **65**[25] (77 mg, 0.2 mmol) with **30** [prepared[3] from tetra-*O*-benzoyl-L-rhamnopyranose (232 mg, 0.4 mmol)] and subsequent hydrolysis, as for the synthesis of **26**, gave amorphous **89** (148.5 mg, 96%); $[\alpha]_D$ +178° (*c* 1); R_F 0.36 (solvent *A*). The ^{1}H NMR data are listed in Table I.

Preparation of trisaccharide methyl glycosides **1–20**, *and disaccharide methyl glycosides* **90–107** (Table II).—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

TABLE II

Preparation of unsubstituted trisaccharide methyl glycosides **1–14** and **17–19** and disaccharide methyl glycosides **90–107** [a]

Compound	Protected precursor (mg)	Yield mg (%)	$[\alpha]_D$ (deg) (*c*, H_2O)
1	**26** (306)	106 (90)	+51 (2.1)
2	**61** (190)	72 (82)	+25 (1.5)
3	**62** (347)	134 (95)	−6 (1.7)
4	**63** (280)	91 (80)	+26 (1.5)
5	**72** (120)	54 (95)	+22 (1)
6	**37** (173)	80 (77)	−2 (1.6)
7	**74** (83)	38 (89)	−37 (1)
8	**76** (123)	61 (93)	−15 (1)
9	**83** (81)	29 (88)	−45 (0.6)
10	**85** (142)	63 (97)	−82 (0.9)
11	**31** (203)	95 (94)	−75 (1.9)
12	**87** (180)	71 (91)	−55 (1)
13	**84** (99)	36 (89)	+17 (0.7)
14	**86** (130)	52 (86)	−12 (0.8)
17	**27** (187)	63 (88)	+128 (1.3)
18	**38** (79)	39 (84)	+50 (0.8)
19	**32** (79)	87 (81)	−4 (1.7)
90	**42** (199)	77 (84)	+35 (1.5)
91	**58** (199)	134 (97)	−2 (2.2)
92	**55** (156)	57 (90)	−128 (0.9) [b]
93	**46** (188)	90 (92)	−54 (1.8)
94	**51** (180)	77 (89)	−13 (1.5)
95	**28** (185)	47 (63)	+48 (1)
96	**69** (160)	74 (82)	−6 (1.5)
97	**78** (104)	39 (93)	−127 (1)
98	**88** (173)	69 (97)	−62 (1.4) [c]
99	**80** (198)	76 (94)	−13 (0.7)
100	**44** (147)	51 (93)	+129 (1)
101	**59** (38)	21 (80)	+70 (1)
102	**48** (128)	50 (87)	+43 (1)
103	**53** (103)	39 (85)	+91 (1.1)
104	**29** (120)	41 (85)	+150 (0.8)
105	**70** (163)	56 (69)	+98 (1.1)
106	**89** (135)	58 (95)	+37 (1.1) [d]
107	**82** (157)	57 (89)	+100 (1)

[a] See Experimental. [b] $[\alpha]_D$ −99° (*c* 1, H_2O)[26]. [c] $[\alpha]_D$ −61° (*c* 1, H_2O)[27]. [d] $[\alpha]_D$ +38° (*c* 1, H_2O)[28].

partitioned between water (10 mL) and $CHCl_3$ (10 mL). The aqueous layer was washed with $CHCl_3$ (4×10 mL), the concentrated, and the residue subjected to gel filtration on Fracto-gel TSK HW-40 (S) (25–40 μm, V_o 50 mL) in deionized water to give the product as an amorphous powder.

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