Carbohydrate Research, 167 (1987) 153–173
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

ALTERNATIVE SYNTHESES AND RELATED N.M.R. STUDIES OF PRECURSORS FOR INTERNAL β-D-GALACTOPYRANOSYL RESIDUES IN OLIGOSACCHARIDES, ALLOWING CHAIN EXTENSION AT O-4*

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(Received September 29th, 1986; accepted for publication in revised form, December 15th, 1986)

ABSTRACT

Crystalline 2,3,6-tri-*O*-benzoyl-4-*O*-(bromoacetyl)-α-D-galactopyranosyl chloride (**5**) was prepared from methyl 2,3,6-tri-*O*-benzoyl-4-*O*-(bromoacetyl)-α- or -β-D-galactopyranoside by cleavage with dichloromethyl methyl ether (DCMME) in the presence of zinc chloride. Silver trifluoromethanesulfonate (triflate) condensation of **5** with methyl 2,3,6-tri-*O*-benzoyl-β-D-galactopyranoside gave the corresponding β-linked disaccharide, which was *O*-de(bromoacetyl)ated and the resulting disaccharide nucleophile condensed with **5**. The β-linked trisaccharide obtained was deprotected, to give the methyl β-glycoside of (1→4)-β-linked D-galactotriose. Compound **5** was converted in high yield into the corresponding 1-*O*-β-acetyl derivative, which was *O*-de(bromoacetyl)ated with thiourea to afford crystalline 1-*O*-acetyl-2,3,6-tri-*O*-benzoyl-β-D-galactopyranose (**9**). Condensation of **9** with **5** yielded *O*-[2,3,6-tri-*O*-benzoyl-4-*O*-(bromoacetyl)-β-D-galactopyranosyl]-(1→4)-1-*O*-acetyl-2,3,6-tri-*O*-benzoyl-β-D-galactopyranose (**17**), which was cleaved with DCMME to give the corresponding glycosyl chloride (**20**). The same sequence of reactions involving 1,2,3,6-tetra-*O*-benzoyl-α-D-galactopyranose and 2,3,4,6-tetra-*O*-benzoyl-α-D-galactopyranosyl bromide afforded *O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-benzoyl-α-D-galactopyranosyl chloride, which can be used to construct in an oligosaccharide the terminal, β-linked (1→4)-β-D-galactobiosyl group. Compounds **5**, **17**, and **20**, when used as glycosyl donors, allow further chain extension at O-4 of the (terminal) β-D-galactopyranosyl group. The structures of all mono- and di-saccharide intermediates, including those of orthoesters formed during glycosylations under neutral conditions, were confirmed by combination of homo- and hetero-nuclear-correla-

*Presented at the XIIIth International Carbohydrate Symposium, Ithaca, 10–16 August 1986.
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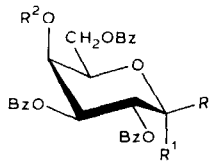
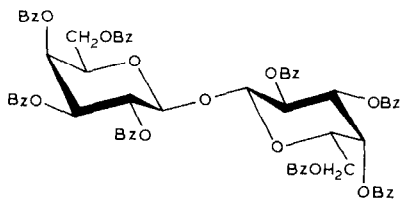


	R	R^1	R^2
1	H	OMe	H
2	H	OMe	$BrCH_2CO$
3	OMe	H	H
4	OMe	H	$BrCH_2CO$
5	H	Cl	$BrCH_2CO$
6	H	Cl	$AcOCH_2CO$
7	OAc	H	$AcOCH_2CO$
8	OAc	H	$BrCH_2CO$
9	OAc	H	H
10	H	OBz	H
11	H	Br	Bz



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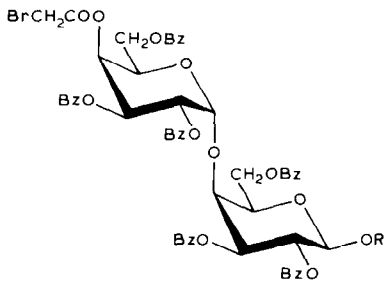
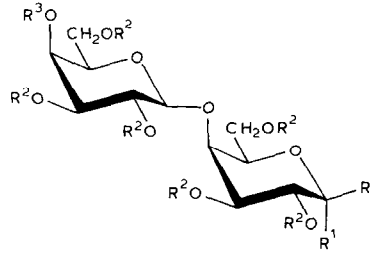


21 R = Me

22 R = Ac



	R	R^1	R^2	R^3
13	OMe	H	Bz	$BrCH_2CO$
14	OMe	H	Bz	H
15	OMe	H	H	H
16	H	OBz	Bz	Bz
17	OAc	H	Bz	$BrCH_2CO$
18	H	OAc	Bz	$BrCH_2CO$
19	H	Cl	Bz	Bz
20	H	Cl	Bz	$BrCH_2CO$

tion n.m.r. experiments. The sites of glycosidic linkages in orthoesters were directly determined by 1 D INAPT n.m.r. experiments. Characteristic features of the ^{1}H- and ^{13}C-n.m.r. spectra of orthoesters which distinguish them from the corresponding oligosaccharides have been summarized.

INTRODUCTION

The *O*-β-D-galactopyranosyl-(1→4)-D-galactopyranosyl or 4-*O*-glycosyl-β-D-galactopyranosyl sequence occurs widely in Nature (for examples, see pertinent citations in refs. 1–6). The (1→4)-α- and -β-linked D-galactobioses and some of their derivatives have been synthesized (*e.g.*, refs. 4–7). When the synthesis requires insertion of a monosaccharide into an interior position of an oligosaccharide, a complex glycosyl donor bearing a selectively removable blocking group must be made available. The strategy for the synthesis of the latter type of compound, allowing further extension of the oligosaccharide chain through O-4 in D-galactose, was discussed in detail by Slife *et al.*[8]. It is clear from that work, as well as from more-recent studies[9,10] in Schuerch's laboratory, that the synthesis of such a glycosyl donor in the D-galactose series is a formidable, multistep procedure. In the present work, we describe an efficient synthesis of crystalline 2,3,6-tri-*O*-benzoyl-4-*O*-(bromoacetyl)-α-D-galactopyranosyl chloride (**5**) and demonstrate its utility in synthesis of the title synthons.

RESULTS AND DISCUSSION

This laboratory recently reported[11–14] syntheses of a large number of D-galacto-oligosaccharides, employing, as glycosyl donors, variously substituted glycosyl chlorides prepared by using dichloromethyl methyl ether (DCMME) as the chlorinating reagent. The methodology of generating glycosyl halides by cleaving acylated glycosides with dihalogenomethyl methyl ethers[15] has been known for a long time. It has been shown that in this way a variety of carbohydrate derivatives, including those bearing acid-labile and alkyl ether[16–18] protecting groups, can be converted into the corresponding glycosyl halides. However, the potential of this methodology for making the glycosyl donors required for syntheses of complex oligosaccharides has not been duly recognized. This may be due, in part, to the commercial unavailability of this class of compound at the time of the development of the methodology. Also, before the introduction of powerful promoters for glycosylation reactions of the triflate and the perchlorate family, glycosyl chlorides had been considered to be more of a chemical curiosity than compounds useful as glycosyl donors in oligosaccharide syntheses.

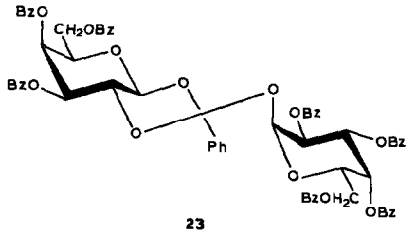
The convenience of using DCMME to generate a complex glycosyl donor from a derivative of a commercially available monosaccharide glycoside is further exemplified here by the preparation of the crystalline halide **5**, which contains a selectively removable, protecting group at O-4. Previous[8,9] attempts at using the

chloroacetyl group to protect this position temporarily were unsuccessful because of incomplete deprotection, or decomposition of the substrate, before the deblocking was complete. We had previously pointed out[19] the advantages of the bromoacetyl[20,21] over the chloroacetyl[22] group as a temporary blocking-group in oligosaccharide syntheses. We also showed[14,23] that use of a benzoyl group as a permanent blocking-group together with a bromoacetyl group as a temporary blocking-group is a very good combination in a compound which is to be used as a glycosyl donor or acceptor in oligosaccharide synthesis. Accordingly, crystalline halide **5** was prepared by cleaving the corresponding methyl α- (**2**) or β-D-glycoside (**4**) with DCMME. To obtain the latter compounds from the corresponding 2,3,6-tri-*O*-benzoyl derivatives[24,25], the standard procedure for (haloacetyl)ation employing pyridine[22] or 2,6-dimethylpyridine[13,21,23] as the catalyst and acid scavenger had to be modified. Due to the low reactivity of OH-4 in **1** and **3**, a large excess (~3 molar equivalents) of the (bromoacetyl)ating reagent had to be used in order to maintain a reasonable reaction-rate. When pyridine, or 2,6-dimethyl- or 2,4,6-trimethyl-pyridine was used[26], extremely dark reaction-mixtures were obtained which were difficult to resolve. The use of triethylamine or diisopropylethylamine strongly promoted benzoyl-group migration[26]. Finally, an excellent yield (~90%) of almost colorless crude products **2** and **4** was obtained by using 1,1,2,2-tetramethylurea as the base.

To prepare compound **9**, which was to serve as a nucleophile in the synthesis of the disaccharide **17**, conditions had to be found under which an efficient SN2 displacement of the anomeric halogen atom in **5** could be effected. The reaction employing silver acetate[18] did not cause the desired conversion. Under these conditions, the predominant reaction involved halogen displacement in the bromoacetyl group by an acetoxyl group, resulting in the formation of a mixture of the 4-*O*-(acetoxyacetyl) derivatives **6** and **7**. A high yield of **8** from **5** was obtained when the starting glycosyl halide was allowed to react with acetic acid in the presence of silver triflate. Simple *O*-de(bromoacetyl)ation of **8** with thiourea then afforded the desired derivative **9**.

For economic reasons, an excess of the synthetically more valuable halide **5** was not used in the condensation with **3**. The reaction of equimolar amounts of **3** and **5** catalyzed by silver triflate was carried out under base-deficient conditions, essentially as described previously[11]. Although the reaction was highly stereoselective, some α-linked product, namely, **21**, was also formed. The desired disaccharide **13**, obtained in 74% yield, was readily *O*-de(bromoacetyl)ated with thiourea, to give the disaccharide **14** (85%), which was then used as a nucleophile in reactions with **5** and **11** leading to trisaccharides **26** and **27**, respectively.

To obtain glycosyl donors for blockwise extension of oligosaccharides, the disaccharide glycosyl chlorides **19** and **20** were prepared from **16** and **17**, respectively. Compound **17** can itself serve as a glycosyl donor in trimethylsilyl triflate-catalyzed[12,13,27,28] glycosylations. To prepare the disaccharides **16** and **17**, 1,2,3,6-tetra-*O*-benzoyl-α-D-galactopyranose[6] (**10**) and nucleophile **9** were condensed with



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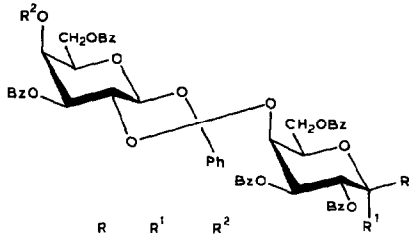
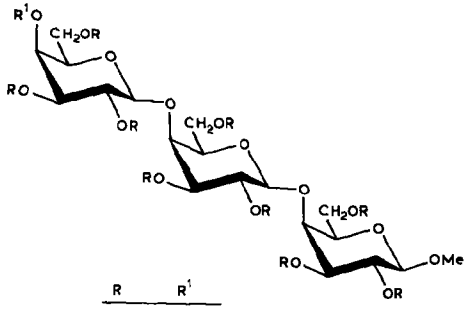
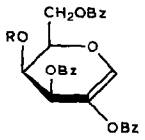


	R	R^1	R^2
24	OAc	H	$BrCH_2CO$
25	OAc	H	Bz



	R	R^1
26	Bz	$BrCH_2CO$
27	Bz	Bz
28	H	H



29 R = $BrCH_2CO$
30 R = Bz

tetra-*O*-benzoyl-α-D-galactopyranosyl bromide (**11**) and the chloride **5**, respectively.

Although these condensations involved the same position (O-4) in D-galactose, the yields of **16** (64%), **17** (44%), **26** (35%), and **27** (41%) were noticeably lower than that of **13** (74%). The difference in yields obtained from the preparations of **13** and **26** in which the same glycosyl donor **5** was employed is particularly interesting, because glycosylation reactions involving other glycosyl chlorides[10,29] and O-4 of D-galactose have typically afforded yields of ~80%. The low yields generally observed in this series may be caused, in part, by the nature of the substituent at O-3, and the markedly lower yield of trisaccharide **26** may be attributable to the bulkiness of the nucleophile used in the synthesis. In cases[10,29] were high yields of glycosylation were recorded for reactions involving the axial 4-hydroxyl group in D-galactose, the vicinal O-3 was protected with a benzyl ether group. The possible effect of neighboring acyl *vs.* alkyl substituents upon the reactivity of hydroxyl groups during glycosylations has been discussed[30]. The aforementioned suggestion regarding the causes of the low yield of **26** is supported by the observation that there was little improvement in the yield of coupling by the use of the more-reactive glycosyl bromide **11**, to give **27** (*c.f.*, the use of **5** in the preparation of **26**).

Whereas side reactions during the condensation of **3** and **5** were negligible (t.l.c.), side reactions observed during the preparation of **16** and **17** were quite prominent. Due to incomplete resolution of the crude products by column

TABLE I

^{1}H-N.M.R. CHEMICAL SHIFTS (δ, P.P.M.)[a,b,c]

Compound	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6a*	*H-6b*	*OMe*	*CH_2Br*	*MeCO*
1	5.219d	5.713dd	5.768dd	4.428bd	4.353bt	4.668dd	4.581dd	3.442s		
2	5.257d	5.627dd	5.928dd	5.820bd	4.56m	4.39m	4.58m	3.465s	3.940d[d] 3.898d[d]	
3	4.683d	5.814dd	5.391dd	4.398bd	4.099bt	4.637dd	4.717dd	3.533s		
4	4.723d	5.741dd	5.539dd	5.778dd	4.286bt	4.671dd	4.417dd	3.565s	3.918s	
5	6.580d	5.798dd	5.986dd	5.884dd	4.877t	4.574dd	4.440dd		3.936d[e] 3.881d[e]	
6[f]	6.578d	5.704dd	6.004dd	5.912bd	4.858t	4.569dd	4.399dd			
7[g]	6.066d	5.806dd	5.631dd	5.852bd	4.406m	4.597dd	4.38m			2.061s
8	6.051d	5.863dd	5.583dd	5.807bd	4.42m	4.600dd	4.42m		3.943s[h] 3.895d[h]	
9[f]	6.01m	5.97m	5.421dd	4.427bt	4.219bt	4.717dd	4.55dd			2.027s
10[f]	6.830d	6.090dd	5.890dd	4.53m	4.49m	4.766dd	4.52m			
13	4.652d (5.028d)	5.592dd (5.801dd)	5.450dd (5.405dd)	4.628bd (5.651bd)	4.137bt (3.969bt)	4.814dd (4.369dd)	4.66m (4.286dd)	3.448s	3.911s	
14	4.63m (4.993d)	5.587dd (5.880dd)	5.435dd (5.237dd)	4.63m (4.27m)	3.739bt (4.117bt)	4.29m (4.861dd)	4.58m (4.58m)	3.401s		
15	4.259d (4.502d)	3.48m (3.49m)	3.65m (3.57m)	4.087bd (3.818dd)	3.64m (3.58m)	3.76m (3.69m)	3.69m (3.66m)	3.478s		
16	6.819d (5.163d)	5.710dd (5.91m)	6.015dd (5.65dd)	4.811dd (5.90m)	4.674bt (4.093t)	4.895dd (4.366dd)	4.597dd (4.266dd)			

17	5.970d	5.717dd	5.488dd	4.689bd	4.27m	4.803dd	4.595dd		3.910s	1.971s
	(5.056d)	(5.804dd)	(5.413dd)	(5.640bd)	(3.970bt)	(4.32m)	(4.24m)			
18	6.564d	5.522dd	5.83m	4.674bd	4.52m	4.781bdd	4.53m		3.938s	2.091s
	(5.061d)	(5.81m)	(5.447dd)	(5.648d)	(3.996bt)	(4.343dd)	(4.245dd)			
19	6.578d	5.482dd	5.95m	4.724bd	4.769bt	4.884dd	4.644dd			
	(5.110d)	(5.90m)	(5.583dd)	(5.93m)	(4.136bt)	(4.425dd)	(4.320dd)			
20	6.554d	5.453dd	5.926dd	4.672bd	4.716bt	4.589dd	4.802dd		3.949s	
	(5.050d)	(5.814dd)	(5.489dd)	(5.674)	(4.062bt)	(4.384dd)	(4.297dd)			
21	4.709d	5.855d	5.341dd	4.533bd	4.066bt	4.72m	4.357dd	3.557s	3.892d[k]	
	(5.534d)	(5.744dd)	(6.129dd)	(5.906bd)	(4.949bdd)	(6.137dd)	(3.928dd)		3.771d[k]	
22	6.068d	5.98m	5.392dd	4.615bd	4.231bt	4.691dd	4.341dd		3.774d[d]	2.096s
	(5.563d)	(5.763dd)	(6.172dd)	(5.95m)	(4.976bdd)	(4.141bt)	(3.960dd)		3.832d[d]	
23	5.739d	5.575dd	6.09m	6.07m	4.821bt	4.40m	4.25m			
	(6.310d)	(4.41m)	(5.374dd)	(5.701dd)	(4.40m)	(4.497dd)	(4.28m)			
24	5.981d	5.818dd	5.208dd	4.730bd	4.206bt	4.521dd	4.365dd		3.665d[l]	2.009s
	(5.996d)	(4.453dd)	(4.868dd)	(5.294bdd)	(3.842bt)	(4.158dd)	(4.054dd)		3.601d[l]	
25	5.999d	5.848dd	5.228dd	4.757bd	4.22m	4.512dd	4.375dd			2.011s
	(6.995d)	(4.438dd)	(4.953dd)	(5.547dd)	(3.923bt)	(4.25m)	(4.077dd)			
29	6.890d		6.309dt	5.849dd	4.74m	4.837dd	4.556dd		3.892d[m]	
									3.884d[m]	

[a]Measured at 25° for solutions in $CDCl_3$, except for **15**, which was run in D_2O. [b]Data in parentheses correspond to protons of the nonreducing D-galacto-pyranosyl residue. [c]Peak multiplicities: b, broad; d, doublet; dd, doublet of doublets; m, multiplet; t, triplet. [d]J 11.8 Hz, [e]J 11.7 Hz. [f]$AcOCH_2CO$ resonate at δ 4.804 and 4.699, J 16 Hz; $CH_3CO_2CH_2CO$ resonate at δ 2.122. [g]$AcOCH_2CO$ resonate at δ 4.807 and 4.724, J 16 Hz; $CH_3CO_2CH_2CO$ resonate at δ 2.117. [h]J 11.6 Hz. [i]OH-4, δ 3.178d, $J_{4,OH}$ 4.8 Hz. [j]OH-4, δ 3.120d, $J_{4,OH}$ 4.1 Hz. [k]J 11.0 Hz, [l]J 11.9 Hz. [m]J 12.4 Hz.

TABLE II

^1H–^1H COUPLING CONSTANTS (Hz)[a]

Compound	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
1	3.1	10.7	2.7	<1	5.7	6.9	11.5
2	3.5	10.7	3.3	<1	[b]	[b]	[b]
3	8.0	10.3	3.0	<1	6.6	6.3	11.5
4	7.9	10.4	3.3	<1	6.4	7.5	11.1
5	3.9	10.6	3.2	1.1	6.5	7.0	11.4
6	3.9	10.6	3.2	~1	6.7	6.6	11.4
7	8.3	10.3	3.2	<1	4.8	[b]	9.4
8	8.3	10.3	3.3	~1	9.1	[b]	13.7
9	[b]	9.5	3.1	~1	6.1	6.4	11.5
10	3.7	10.7	2.9	[b]	6.1	[b]	10.6
13	7.7	10.4	2.8	~1	5.5	[b]	11.6
	(7.8)	(10.5)	(3.4)	(~1)	(6.3)	(7.4)	(11.2)
14	7.8	10.4	2.8	<1	[b]	[b]	[b]
	(7.8)	(10.3)	(3.1)	(<1)	(5.4)	([b])	(11.6)
15	7.9	[b]	[b]	~1	[b]	[b]	[b]
	(7.6)	([b])	(3.3)	(0.8)	([b])	([b])	([b])
16	3.6	10.8	2.6	~1	5.3	6.5	11.0
	(7.8)	(10.5)	(3.3)	(~1)	(6.3)	(6.9)	(11.3)
17	8.1	10.3	2.8	~1	5.2	6.7	11.8
	(7.8)	(10.4)	(3.3)	(~1)	([b])	([b])	([b])
18	3.6	10.8	[b]	~1	7.9	[b]	13.6
	(7.9)	(10.6)	((3.4)	(~1)	(6.2)	(7.5)	(11.2)
19	3.8	10.6	[b]	~1	4.8	6.7	11.4
	(7.9)	(10.5)	(3.4)	(~1)	(6.3)	(6.8)	(11.3)
20	3.8	10.8	2.6	~1	6.3	4.9	11.3
	(7.9)	(10.5)	(3.3)	(~1)	(6.3)	(7.3)	(11.2)
21	7.8	10.6	2.6	~1	[b]	7.8	11.0
	(3.5)	(10.9)	(3.2)	(~1)	(8.3)	(5.5)	(10.8)
22	8.1	10.3	2.6	~1	6.2	7.5	11.0
	(3.5)	(11.0)	(3.2)	(~1)	(~8)	(5.4)	(10.9)
23	3.8	9.9	[b]	[b]	[b]	[b]	[b]
	(5.1)	(6.1)	(4.2)	(2.3)	(5.4)	([b])	(8.0)
24	8.0	10.0	3.1	~1	5.8	6.4	11.4
	(5.1)	(6.9)	(3.6)	(1.6)	(6.1)	(7.3)	(11.2)
25	8.2	10.1	3.1	1.0	5.9	6.5	11.5
	(5.1)	(7.1)	(3.5)	(1.4)	(6.0)	(6.8)	(11.3)
29[c]			4.8	2.3	7.6	4.6	11.3

[a]Measured at 25° for solutions in $CDCl_3$, except for **15**, which was run in D_2O; data in parentheses correspond to protons of the nonreducing D-galactopyranosyl residue. [b]Not determined, due to overlapping signals. [c]$J_{1,3}$ 1.2, $J_{3,5}$ 1 Hz.

chromatography, the quantitation of the by-products was not always sought, but some of the by-products formed were isolated, and a brief rationalization of their formation follows. Preparation of **13** involved condensation of a methyl glycoside, a relatively stable nucleophile. This permitted the reaction with the moderately reactive chloride **5** to be conducted under favorable[23,31] base-deficient conditions at

temperatures above 0°. In the preparation of both **16** and **17**, 1-*O*-acyl derivatives were used as nucleophiles. As previously observed[11], these acyl derivatives are less stable than glycosides and may have contributed to lower yields of the desired disaccharides. For example, the partial deblocking of **9**, or of the product **17**, or both, at the anomeric position liberated acetic acid under the conditions of the base-deficient coupling-reaction. The liberated acid reacted in the presence of silver triflate with the glycosyl halide **5** employed to form **8** (see Experimental section). Another side-reaction observed during the condensation of **5** and **9** under acidic conditions was the anomerization of the product **17** to give **18**. Additionally, the formation of a nonreducing (1→1)-linked disaccharide, **12**, from the glycosyl halide employed was observed, as has been previously reported[32,33] for other glycosylations. Although the structure of **18** was readily confirmed by its n.m.r. data (see Tables I and II), a simple, first-order analysis of the ^{1}H-n.m.r. data recorded for **12** did not immediately reveal that the compound was a disaccharide. The 300-MHz, ^{1}H-n.m.r. spectrum of **12** showed seven well resolved sets of signals of equal intensity in the region of ring protons (see Experimental section) and, from the intensity of the signals in the aromatic region, it could be deduced that only 4 benzoyl groups were present. The chemical shift of H-1 (δ 5.2) was too low to be indicative of benzoylation at the anomeric position, and the failure of the compound to react in pyridine with an excess of acetic anhydride implied the absence of a free OH group. Conclusive evidence for the structure was obtained when **12** was *O*-debenzoylated (Zemplén) to give a product that exhibited a peak at *m/z* 360 ($[M + NH_4]^+$) in its ammonia c.i.-mass spectrum. Moreover, the ^{13}C-n.m.r. spectrum of this compound in D_2O contained only 6 signals, and was consistent with the structure of β-D-galactopyranosyl β-D-galactopyranoside. In certain reactions, products of de(hydrohalogen)ation rather than substitution were also formed. These were isolated, and their structures determined by n.m.r. spectroscopy (for isolation of unsaturated products **29** and **30**, see the Experimental section).

A side reaction observed during the glycosylations conducted under non-acidic conditions was the formation of orthoesters. Compounds **23** and **24** were isolated as by-products from the preparation of **16** and **17**, whereas orthoester **25** was the major product of the condensation of halide **11** with **9**. The formation under non-acidic conditions, and eventual conversion of the orthoester **24** into the disaccharide **17**, could be monitored by t.l.c. The reaction of the chloride **5** with the nucleophile **9** is a relatively slow process. Thus, the early stages of the reaction took place under basic conditions, although the amount of base added at the outset of the reaction was insufficient to neutralize *all* of the triflic acid to be formed. These conditions are favorable to survival of an orthoester. Indeed, when the course of the reaction was checked by t.l.c. before all of the **5** had reacted (see Experimental section, preparation of **17**, procedure b), there was present a component that co-chromatographed with **24**. When all of the **5** had been consumed, and the reaction mixture had become acidic, the compound that had co-chromatographed with **24**

TABLE III

^{13}C-N.M.R. CHEMICAL SHIFTS (δ)[a]

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C-1'*	*C-2'*	*C-3'*	*C-4'*	*C-5'*	*C-6'*	*OMe*	*CH_2Br*	*OAc*
1	97.42	68.89	70.81	68.11	67.73	63.54							55.36		
2	97.49	68.79	68.05	70.32	66.27	61.84							55.68	24.79	
3	102.08	69.48	74.14	67.20	72.32	62.92							56.72		
4	102.22	69.27	71.46	69.16	70.67	61.28							57.14	24.71	
5	91.35	68.25	67.76	69.33	69.48	61.05								24.57	
6[b]	91.28	68.43	67.42	68.75	69.58	61.15									20.19
7[c]	92.06	68.28	71.10	68.33	71.75	61.20								24.61	20.63
8	92.15	68.28	71.47	68.91	71.78	61.10									20.74
9	92.30	68.48	74.02	66.97	73.38	62.71									20.75
10	90.85	67.23	70.89	67.50	70.57	62.65									
13	101.70	68.99	73.87	72.50	72.05	63.51	100.76	69.66	71.27	68.94	70.72	60.88	55.82	24.75	
14	101.64	68.97	74.02	71.80	72.19	63.46	100.67	69.93	73.89	67.21	72.56	62.44	55.61		
15	103.86	71.56	73.39	77.30	74.39	60.66	104.40	71.41	72.91	68.77	75.25	61.16	57.31		
16	90.69	67.70	70.61	73.19	70.67	63.27	101.07	70.17	71.41	67.81	71.30	61.42			
17	92.15	68.49	73.78	72.28	73.18	63.41	100.66	69.69	71.30	68.91	70.80	60.91		24.74	20.72
18	89.89	67.53	70.35[d]	73.41	70.42[d]	63.35	101.02	69.68	71.12	68.92	70.79	60.79		24.84	20.84
19	91.82	68.91	69.92	73.35	71.21	63.22	101.21	70.14	71.26	67.83	71.33	61.44			
20	91.80	68.85	69.96	73.54	71.17	63.25	101.17	69.71	71.02	68.95	70.88	60.86		24.79	
21	101.95	69.28	73.62	75.41	71.85	61.14	98.55	68.96	67.76	69.86	67.10	60.60	56.57	24.76	
22	91.99	68.32	73.57	75.36	72.80	60.90	98.72	68.86	67.67	69.78	67.12	60.56		24.70	20.73
23[e]	90.92	68.93	67.96	68.83	67.47	61.96	98.64	73.03	69.65	65.96	68.70	62.12			
24[f]	92.04	68.32	73.48	67.96	73.13	63.12	98.26	73.68	69.54	67.43	68.02	60.98		24.54	20.74
25[g]	92.03	68.32	73.50	67.91	73.12	63.08	98.45	73.88	69.90	66.24	68.48	61.56			20.73
29	139.23	127.14	64.36	65.99	73.07	61.53								24.91	

[a]All spectra measured in $CDCl_3$ at 25°, except for **15**, which was run in D_2O. [b]$AcOCH_2CO$, δ 60.22; $AcOCH_2CO$, δ 20.19. [c]$AcOCH_2$, δ 60.19, $AcOCH_2CO$, δ 20.14. [d]Assigned by comparison with the spectra of **13, 19,** and **20**. [e]The quaternary orthoester carbon atom resonates at δ 120.09. [f]The quaternary orthoester carbon atom resonates at δ 120.85. [g]The quaternary orthoester carbon atom resonates at δ 120.76.

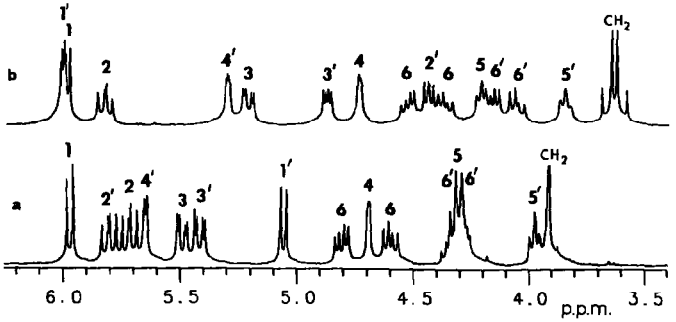


Fig. 1. Expanded 300-MHz, ^{1}H-n.m.r. spectra showing the saccharide-ring proton signals of (a) the disaccharide **17** and (b) the corresponding orthoester **24**.

was no longer present; it presumably rearranged[31,34,35] under acidic conditions to the desired disaccharide **17**.

Unambiguous ^{1}H- and ^{13}C-n.m.r. assignments for both the oligosaccharides and orthoesters (see Table I–III) were determined from homonuclear COSY and heteronuclear CSCM *J* correlation experiments as previously described[11,35]. A brief description of the characteristic features of the n.m.r. spectra of the orthoesters which allow them to be readily distinguished from the corresponding disaccharides follows. Fig. 1 compares the ^{1}H-n.m.r. spectrum of the orthoester **24** with that of the corresponding disaccharide **17**. The chemical shifts for H-2′, H-3′, and H-4′ of the orthoester appear upfield by 1.4, 0.5, and 0.4 p.p.m. relative to H-2′, H-3′, and

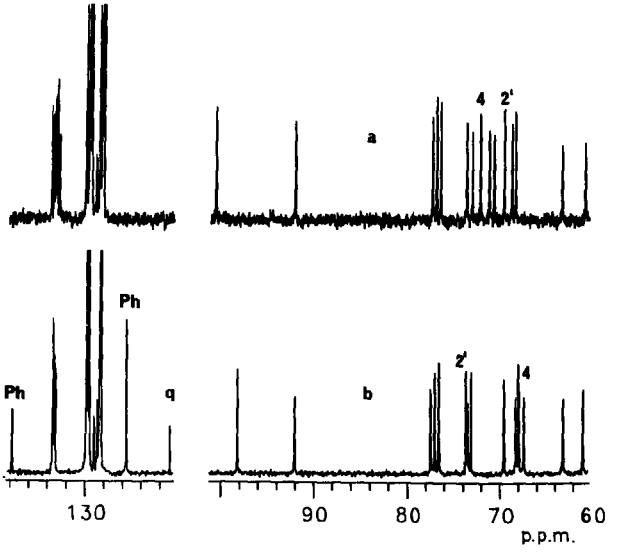


Fig. 2. Expanded 75-MHz, ^{13}C-n.m.r. spectra of (a) the disaccharide **17** and (b) the corresponding orthoester **24**. [*q* denotes orthoester carbon; *Ph* denotes resonances due to carbon atoms of the phenyl ring attached to the orthoester carbon atom; For detailed, carbon-signal assignments see Table III.]

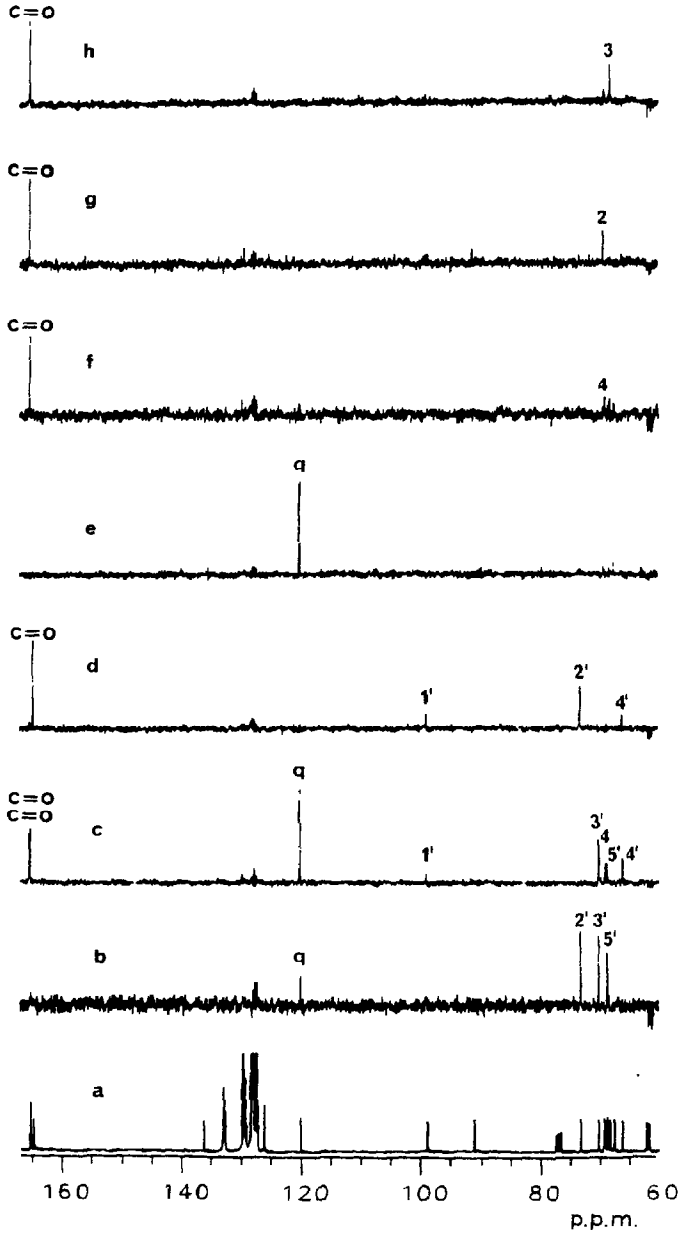


Fig. 3. INAPT spectra of the orthoester **23** in C_6D_6. (a) Regular, proton-decoupled ^{13}C-n.m.r. spectrum, (b) INAPT spectra obtained by transfer from H-1′, (c) H-2′, H-6, H-6′, (d) H-3′, (e) H-1, (f) H-2, (g) H-3, and (h) H-4. [The quaternary, orthoester carbon atom is denoted q. Negative resonances at ~62 p.p.m. are residual quadrature images of the strong solvent peak.]

H-4′ of the disaccharide. The H-1′ signal of **24** is shifted ~1 p.p.m. downfield, relative to that of H-1′ of **17**. The coupling constant between H-1′ and H-2′ of the orthoester is diminished to 5.1 (from 7.8 Hz) in the spectrum of the disaccharide indicating that H-1′ is still axial but that the primed ring is flattened somewhat. The ^{13}C-n.m.r. spectra of the orthoesters are particularly characteristic, as shown in Fig. 2. The chemical shift of the signal of the quaternary orthoester carbon atom, at δ ~120, is unique, and diagnostic of an orthoester. The two new signals, at δ ~126 and ~136, corresponding to carbon atoms of the phenyl ring attached to the orthoester carbon atom, are diagnostic of an orthobenzoate. Also important are the chemical shifts of C-2′ and C-4, the signals of which are shifted by −4 and +4 p.p.m., respectively, for the orthoester relative to the disaccharide. Particularly striking here is the chemical shift of the signal of C-4. This carbon atom does not experience the usual, strong deshielding substitution-effect of carbon atoms involved in the C–O–C linkage. The same holds for C-1 of **23**.

Determination of the linkage in an orthoester is complicated by the oxygen bridges, which disrupt the connectivity map produced by the correlation experiments. This gap in n.m.r. connectivity information was bridged with long-range ^{1}H–^{13}C *J* correlation 1-D INAPT experiments[36,37], which transfer polarization from a selected proton only to carbon atoms that have a significant scalar interaction with that proton, *i.e.*, carbon atoms that are two or three bonds removed from that proton. An example of this technique is given in Fig. 3. Fig. 3a shows the regular ^{1}H-decoupled ^{13}C n.m.r. spectrum of **23**. Figs. 3b–h show the spectra obtained with the INAPT experiment by transfer from selected protons. It is clear from Figs. 3b and 3e that the orthoester carbon atom is attached at H-1′ and H-1, as the signal of the orthoester carbon atom is observed due to three-bond polarization transfer from H-1′ and H-1 across the bridging oxygen atoms. This 1↔1 linkage was unexpected, because compound **23** was isolated from the reaction of the glycosyl halide **11** with compound **10** having a free hydroxyl group at C-4. Compound **23** resulted, in fact, from the reaction of halide **11** with the inadvertently formed product of its hydrolysis. The third linkage through oxygen is securely assigned to H-2′ by comparison to the spectrum of **25**, even though H-2′, H-6, and H-6′ signals all overlap in the proton spectrum, resulting in polarization transfer to two carbonyl groups *and* the orthoester carbon atom (see Fig. 3c). The power and general applicability of the INAPT experiment for the assignment of oxygen linkages is demonstrated in Fig. 3, in that polarization transfer to a carbonyl or orthoester carbon atom is observed from each proton selected. In addition, polarization transfer *via* two- and three-bond coupling to many of the ring-carbon atoms is observed as well.

EXPERIMENTAL

General methods. — Melting points were determined with a Büchi melting-point apparatus. Optical rotations for solutions in chloroform (except for com-

pounds **15** and **28**, which were measured in water) were measured at 25° with a Perkin–Elmer automatic polarimeter, Model 241 MC. Thin-layer chromatography (t.l.c.) on precoated slides of Silica Gel 60 F_{254} (Analtech) was performed with solvents of appropriately adjusted polarity, consisting of *A*, toluene–ethyl acetate; *B*, toluene–acetone; *C*, carbon tetrachloride–acetone; *D*, carbon tetrachloride–ethyl acetate; and *E*, chloroform–methanol. Detection was effected by (*a*) charring with 5% (v/v) sulfuric acid in ethanol; (*b*) spraying with 1% potassium permanganate in acetone, which immediately revealed alkenic components as yellow spots on a violet background; and (*c*) u.v. light. Preparative chromatography was performed by gradient elution from columns of Silica gel 60 (Merck, No. 9385, 0.04–0.063 mm, or No. 15111, 0.015–0.04 mm). For purification of **14**, the silica gel was deactivated with 5% of water.

The instruments and techniques used for n.m.r. spectroscopy and ammonia c.i. mass spectrometry, as well as other general methodologies, were those previously described[11,13,38]. The n.m.r. data listed in Tables I–III were obtained in an unequivocal manner by 1 D or 2 D homo- and hetero-nuclear correlation experiments. These were performed at 25° for solutions in $CDCl_3$, using a Nicolet NT-300 WB spectrometer. The chemical shifts are reported relative to the solvent peak ($CDCl_3$, δ 77.0, ^{13}C) or Me_4Si (^1H), except for compound **15**, which was examined in D_2O and its chemical shifts referenced to internal MeOH (δ 49.0, ^{13}C) and DOH (δ 4.7, ^1H). INAPT spectra[36,37] of the orthoesters were recorded with the delays $\Delta_2/2$ and $\Delta_1/2$ set to 45.5 and 40.5 ms, respectively, and the soft 90° pulse was set to 10 ms. INAPT spectra of **23** were recorded in C_6D_6, the use of which was necessary in order separate overlapping resonances in the ^1H-n.m.r. spectrum. A COSY experiment was also performed on this sample in C_6D_6, to ensure proper ^1H-n.m.r. assignments for the INAPT experiments.

*1,2,3,6-Tetra-*O*-benzoyl-α-*D*-galactopyranose* (**10**). — This compound (previously not fully characterized) was prepared essentially as described by Garegg and Hultberg[6], and obtained as a pure (t.l.c., ^1H- and ^{13}C-n.m.r.) amorphous solid when the final purification of the product was achieved by chromatography employing solvent *D*, $[\alpha]_D$ +179.4° (*c* 0.5).

Anal. Calc. for $C_{34}H_{28}O_{10}$: C, 68.44; H, 4.73. Found: C, 68.35; H, 4.78.

*Methyl 2,3,6-tri-*O*-benzoyl-4-*O*-(bromoacetyl)-α-*D*-galactopyranoside* (**2**). — Tetramethylurea (0.36 mL, 3 mmol) followed by solid **1** (ref. 24) (0.5 g, 1 mmol) was added at 0° to a solution of bromoacetyl bromide (0.263 mL, 2.9 mmol) in dry 1,2-dimethoxyethane (3 mL). Cooling was discontinued, and the mixture was stirred at room temperature until t.l.c. (solvent *A*) showed that the reaction was complete (18–24 h). After evaporation, the residue was partitioned between water and dichloromethane and, after drying, the organic phase was evaporated to dryness (70°/133 Pa). Crystallization of the residue from methanol containing a few drops of dichloromethane gave pure **2** (0.58 g, 94%); m.p. 100–101°, $[\alpha]_D$ +104.3° (*c* 1.5).

Anal. Calc. for $C_{30}H_{27}BrO_{10}$: C, 57.42; H, 4.33; Br, 12.73. Found: C, 57.43; H, 4.35; Br, 12.78.

Methyl 2,3,6-tri-O-benzoyl-4-O-(bromoacetyl)-β-D-galactopyranoside (**4**). — Compound **3** (ref. 25) (0.5 g, 1 mmol) was treated as just described for the preparation of **2**. The crude product **4** (0.65 g, ~100%) was sufficiently pure for use in the next step. For combustion analysis, a portion was chromatographed to give pure **4** as a glassy solid, $[\alpha]_D$ +36° (*c* 1.2).

Anal. Calc. for $C_{30}H_{27}BrO_{10}$: C, 57.42; H, 4.33; Br, 12.73. Found: C, 57.33; H, 4.33; Br, 12.78.

2,3,6-Tri-O-benzoyl-4-O-(bromoacetyl)-α-D-galactopyranosyl chloride (**5**). — (*a*) Finely powdered, freshly fused zinc chloride (20 mg) was added to a solution of the α-glycoside **2** (1.25 g, 2 mmol) in DCMME (2 mL), and the mixture was stirred, with the exclusion of moisture, at 80° (bath) in a round-bottomed flask equipped with a small Dry Ice condenser. When t.l.c. (solvent *A*) showed that only traces of the starting material remained, (~6 h)* the dark solution was diluted with toluene, and evaporated, and the residue was chromatographed, to give pure **5** (1 g, 80%); m.p. 105–107° (sint. ~100°; from ether–isopropyl alcohol, twice), $[\alpha]_D$ +134° (*c* 1.2).

Anal. Calc. for $C_{29}H_{24}BrClO_9$: C, 55.12; H, 3.82; Br, 12.65; Cl, 5.61. Found: C, 55.20; H, 3.84; Br, 12.60; Cl, 5.59.

(*b*) When treated as described for **2**, pure compound **4** gave chloride **5** in essentially the same yield. During the reaction, partial anomerization of **4** to give **2** occurred. Both glycosides were eventually converted into **5**, by reactions conveniently monitored by t.l.c. in 20:1 toluene–acetone: R_F: **4**, 0.4; **2**, 0.45; and **5**, 0.55.

Conversion of crude **4** into **5** required use of larger relative amounts of the reagents.

Methyl O-[*2,3,6-tri-O-benzoyl-4-O-(bromoacetyl)-α-* (**21**) *and -β-D-galactopyranosyl)]-(1→4)-2,3,6-tri-O-benzoyl-α-D-galactopyranoside* (**13**). — A solution of **3** (2.24 g, 4.4 mmol), **5** (2.8 g, 4.4 mmol), and 2,4,6-trimethylpyridine (0.55 mL, 4.2 mmol) in 1:1 nitromethane–toluene (10 mL) was added at 0° to a solution of silver triflate (1.15 g, 4.5 mmol) in the same solvent (10 mL). Cooling was terminated, and the mixture became acidic to litmus after 45 min. After 2 h, when t.l.c. (solvent *B*) showed that all of the **5** had reacted and that only traces of **3** remained, the mixture was made neutral with 2,4,6-trimethylpyridine, filtered, the filtrate evaporated, and a solution of the residue in dichloromethane washed with aqueous sodium thiosulfate solution, dried, and evaporated, and the crude product chromatographed to give first the α-linked disaccharide **21** (350 mg, 6.5%), m.p. 199–200° (from dichloromethane–methanol), $[\alpha]_D$ +98° (*c* 0.9).

Anal. Calc. for $C_{57}H_{49}BrO_{18}$: C, 62.12; H, 4.48; Br, 7.25. Found: C, 62.25; H, 4.50; Br, 7.30.

*If the zinc chloride changes from a powder to a sticky mass, indicative of the action of moisture, more zinc chloride is added; if a Dry Ice condenser is not used, more DCMME may have to be added, to replace that lost, due to its volatility, during the reaction.

Eluted next was the desired disaccharide **13** (3.59 g, 74%), $[\alpha]_D$ +74.5° (*c* 0.9).

Anal. Calc. for $C_{57}H_{49}BrO_{18}$: C, 62.12; H, 4.48; Br, 7.25. Found: C, 62.12; H, 4.49; Br, 7.24.

Methyl O-(2,3,6-tri-O-benzoyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-O-benzoyl-β-D-galactopyranoside (**14**). — A solution of thiourea (830 mg, 10.8 mmol) in methanol (15 mL) was added to a solution of **13** (4 g, 3.6 mmol) in dichloromethane (35 mL). The solution was kept at room temperature until t.l.c. showed that the reaction was complete (15–30 min), worked up as described for the preparation of **9**, and the crude product chromatographed, to give pure **14** (2.9 g, 85.7%); $[\alpha]_D$ +94° (*c* 0.7).

Anal. Calc. for $C_{55}H_{48}O_{17}$: C, 67.33; H, 4.93. Found: C, 67.23; H, 4.97.

Methyl O-β-D-galactopyranosyl-(1→4)-β-D-galactopyranoside (**15**). — Compound **14** (400 mg) was dissolved in methanol (50 mL), and M sodium methoxide in methanol was added until the solution was strongly alkaline. The solution was kept overnight at 40–50°, cooled to room temperature, made neutral with Dowex 50 W (H^+) resin, and evaporated. Crystallization from methanol gave pure **15** (110 mg, 76%); m.p. 217–218°; lit.[7] m.p. 218–220°.

Methyl O-[2,3,6-tri-O-benzoyl-4-O-(bromoacetyl)-β-D-galactopyranosyl]-(1→4)-O-(2,3,6-tri-O-benzoyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-O-benzoyl-β-D-galactopyranoside (**26**). — A solution of **14** (0.49 g, 0.5 mmol), **5** (0.345 g, 0.55 mmol) and 2,4,6-trimethylpyridine (66 μL, 0.5 mmol) in CH_2Cl_2 (10 mL) was added at room temperature to a suspension of silver triflate (167 mg, 0.65 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 30 min, when t.l.c. (solvent *A*) showed that all of the **5** had been consumed and that a large proportion of unchanged **14** was still present. Equimolar amounts of **5**, silver triflate, and 2,4,6-trimethylpyridine (0.5 mmol) were added and, after 30 min, the mixture was processed and the crude product chromatographed. The major product was amorphous **26** (0.28 g, 35%; or 81% based on the amount of reacted **14** of which 0.275 g was recovered by continuous elution), $[\alpha]_D$ +80° (*c* 1.3); ^{13}C-n.m.r. (75 MHz, $CDCl_3$): δ 101.67 (C-1), 100.50, 100.33 (C-1',1''), 74.14, 74.10 (C-3,3'), 72.32 (2 C, C-4,4'), 71.87 (C-5), 71.36, 71.30 (C-5',3''), 72.05 (C-5''), 70.09, 69.81 (C-2,2'), 69.22, 69.12 (C-2,4''), 63.66 (C-6), 63.02 (C-6'), 60.98 (C-6''), 55.60 (Me), and 24.84 (CH_2Br).

Anal. Calc. for $C_{84}H_{71}BrO_{26}$: C, 64.00; H, 4.54; Br, 5.06. Found: C, 64.52; H, 4.55; Br, 5.14.

Methyl O-(2,3,4,6-tetra-O-benzoyl-β-D-galactopyranosyl)-(1→4)-(2,3,4-tri-O-benzoyl-β-D-galactopyranosyl)-2,3,4-tri-O-benzoyl-β-D-galactopyranoside (**27**). — A solution of silver triflate (167 mg, 0.65 mmol) in 1:1 nitromethane–toluene (5 mL) was added dropwise at 0° to a solution of **14** (0.49 g, 0.5 mmol), **11** (0.363 g, 0.55 mmol), and 2,4,6-trimethylpyridine (66 μL, 0.5 mmol) in the same solvent (5 mL). After 20 min, when t.l.c. showed that a large amount of unchanged **14** was still present but that all of the **11** had been consumed, the acid was neutralized with 2,4,6-trimethylpyridine and, after conventional processing, chromatography

yielded the major, amorphous product **27** (0.32 g, 41%); $[\alpha]_D$ +101° (*c* 1.3); ^{13}C-n.m.r. (75 MHz, $CDCl_3$): δ 101.62 (C-1), 100.48, 100.26 (C-1,1′), 74.16, 74.07 (C-3,3′), 72.26 (2 C, C-4,4′), 71.77 (C-5), 71.54 (2 C, C-5′,3″), 70.85 (C-5″), 70.27, 72.09 (C-2,2′), 69.15 (C-2), 67.95 (C-4″), 63.60 (C-6), 62.76 (C-6′), 61.54 (C-6″), and 55.51 (Me).

Anal. Calc. for $C_{89}H_{74}O_{26}$: C, 68.54; H, 4.78. Found: C, 68.58; H, 4.80.

When two equivalents of **11** were used in this reaction, the nucleophile **14** reacted almost completely. However, purification of the product **27** was more difficult due to the presence of a larger amount of by-products formed from the excess of the glycosyl halide used. It required multiple chromatography, and was accompanied by losses due to manipulation.

Methyl O-*β*-D-*galactopyranosyl-(1→4)-β*-D-*galactopyranosyl-(1→4)-β*-D-*galactopyranoside* (**28**). — Hot methanol (10 mL) was added to a warm (~50°) solution of **26** (80 mg) in toluene (3 mL), followed by M methanolic sodium methoxide until the solution was strongly alkaline; it was then heated for 6 h at 50–60°, cooled to room temperature, made neutral with Dowex 50 W (H^+) resin, and evaporated. Some colored material was removed by elution of the crude product from a column of silica gel with solvent *E*, and lyophilization gave pure **28** (22 mg, 82%) as a hygroscopic solid; $[\alpha]_D$ +20° (*c* 1); ^{13}C-n.m.r. (75 MHz, D_2O, interpretation of the data based on comparison with the spectrum of **15**, also taking into account the ^{13}C-n.m.r. chemical shifts observed[38,39] for the carbon atoms in the terminal β-D-galactopyranosyl group in methyl 3-*O*- and 6-*O*-β-D-galactopyranosyl-β-D-galactopyranoside): δ 104.51, 104.48 (C-1,1′), 103.84 (C-1), 77.88 (C-4′), 77.31 (C-4), 75.28 (C-5″), 74.55, 74.44 (C-5,5′), 73.41 (2 C, C-3,3′), 72.92 (C-3″), 72.00, 71.52, 71.41 (C-2,2′,2″), 68.75 (C-4), 61.11 (C-6″), 60.78, 60.64 (C-6,6′), and 57.26 (Me).

*4-*O*-(Acetoxyacetyl)-2,3,6-tri-*O*-benzoyl-α*-D-*galactopyranosyl chloride* (**6**) *and 4-*O*-(acetoxyacetyl)-1-*O*-acetyl-2,3,6-tri-*O*-benzoyl-β*-D-*galactopyranose* (**7**). — A mixture of **5** (1.1 g, 1.74 mmol), Drierite (1 g), and silver acetate (0.29 g, 1.74 mmol) in acetonitrile (5 mL) was stirred in the dark for 72 h at room temperature. T.l.c. (solvent *B*) then showed that ~50% of the starting material was still present, and that two slower-moving products, one greatly preponderating, had been formed. A fresh portion of silver acetate (0.3 g) was added, and the mixture was stirred for 2 more days. After filtration, and evaporation of the filtrate, the residue, which still contained a small amount of unchanged **5**, was chromatographed to give, first, pure **6** (0.7 g, 65%); $[\alpha]_D$ +127° (*c* 0.4).

Anal. Calc. for $C_{31}H_{27}ClO_{11}$: C, 60.93; H, 4.45; Cl, 5.80. Found: C, 60.80; H, 4.48; Cl, 5.73.

Continued elution gave **7** (0.17 g, 15%); $[\alpha]_D$ +49.5° (*c* 2.2).

Anal. Calc. for $C_{33}H_{30}O_{13}$: C, 62.45; H, 4.76. Found: C, 62.43; H, 4.79.

*1-*O*-Acetyl-2,3,6-tri-*O*-benzoyl-4-*O*-(bromoacetyl)-β*-D-*galactopyranose* (**8**). — Silver triflate (5.36 g, 20.86 mmol) was added to a solution of **5** (11 g, 17.4 mmol) and 2,4,6-trimethylpyridine (2.6 mL, 19.67 mmol) in acetic acid (44 mL). The mixture was stirred at room temperature, with the exclusion of moisture, until t.l.c. (solvent *A*) showed that the reaction was complete (1–2 h). After addition of

toluene (50 mL), the mixture was filtered, the filtrate evaporated to dryness, and a solution of the residue in dichloromethane was washed successively with an aqueous solution of sodium thiosulfate and water, dried, and evaporated. Crystallization from isopropyl alcohol gave **8** (10.43 g, 91%), which was sufficiently pure for the next step. Recrystallization of a portion from the same solvent gave pure **8**; m.p. 151–152°, $[\alpha]_D$ +64° (*c* 0.9).

Anal. Calc. for $C_{31}H_{27}BrO_{11}$: C, 56.80; H, 4.15; Br, 12.19. Found: C, 56.89; H, 4.21; Br, 12.28.

1-O-Acetyl-2,3,6-tri-O-benzoyl-β-D-galactopyranose (**9**). — A solution of thiourea (2.61 g, 34.33 mmol) in methanol (35 mL) was added with stirring to a solution of **8** (7.5 g, 11.44 mmol) in dichloromethane (20 mL). A precipitate was formed, but this shortly dissolved, and, after 1 h t.l.c. (solvent *A*) showed that only traces of **8** remained. The mixture was evaporated, and a solution of the residue in dichloromethane was successively washed with a mixture of saturated solutions of sodium hydrogencarbonate and sodium chloride, and then water, dried, and evaporated, and crystallization from toluene–isopropyl ether gave **9** (5.05 g, 83%); m.p. 151–152° (after recrystallization from the same solvent), $[\alpha]_D$ +78.3° (*c* 0.65).

Anal. Calc. for $C_{29}H_{26}O_{10}$: C, 65.16; H, 4.90. Found: C, 65.28; H, 4.96.

O-(2,3,4,6-Tetra-O-benzoyl-β-D-galactopyranosyl)-(1→4)-1,2,3,6-tetra-O-benzoyl-α-D-galactopyranose (**16**). — (*a*) A solution of 2,3,4,6-tetra-*O*-benzoyl-α-D-galactopyranosyl bromide[23] (1.3 g, 2 mmol), 1,2,3,6-tetra-*O*-benzoyl-α-D-galactopyranose[6] (0.59 g, 1 mmol), and 2,4,6-trimethylpyridine (0.265 mL, 2 mmol) in dichloromethane (10 mL) was added dropwise at −25° to a suspension of silver triflate (0.54 g, 2.1 mmol) in dichloromethane (5 mL). The mixture was stirred for 1 h at −20°, worked up as described for the preparation of **13**, and the crude product chromatographed. The first compound collected was one of the minor by-products (R_F 0.8; *c.f.*, 0.5 for **16**; solvent *B*, immediate detection with reagent *b*), shown by n.m.r. spectroscopy to be the alkene **30**; ^{1}H-n.m.r. (220 MHz, $CDCl_3$): δ 6.94 (d, 1 H, $J_{1,3}$ 1 Hz, H-1), 6.39 (dd, 1 H, $J_{3,4}$ 5 Hz, H-3), 6.04 (dd, 1 H, $J_{4,5}$ 2 Hz, H-4), 4.95–4.77 (m, 2 H, H-5,6a), and 4.60 (dd, 1 H, $J_{5,6b}$ 3.5, $J_{6a,6b}$ 10.5 Hz, H-6b).

Later eluted was a compound identified by n.m.r. spectroscopy as the ortho-ester **23**.

Continued elution gave unidentified by-products and then the major component of the reaction mixture, namely, **16** (0.47 g, 40%); m.p. 200–200.5° (from ethyl acetate–methanol), $[\alpha]_D$ +146° (*c* 0.7).

Anal. Calc. for $C_{68}H_{54}O_{19}$: C, 69.49; H, 4.63. Found: C, 69.57; H, 4.65.

Eluted last was the nonreducing disaccharide 2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl 2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranoside (**12**); m.p. 128–130° (from CH_2Cl_2–ether), $[\alpha]_D$ +67.5° (*c* 0.66); ^{1}H-n.m.r. (300 MHz, $CDCl_3$): δ 5.96 (bd, 2 H, $J_{4,5}$ <1 Hz, H-4,4'), 5.75 (dd, 2 H, $J_{2,3}$ 10 Hz, H-2,2'), 5.56 (dd, 2 H, $J_{3,4}$ 3.2 Hz, H-3,3'), 5.24 (d, 2 H, $J_{1,2}$ 8 Hz, H-1,1'), 4.47 (dd, 2 H, $J_{6a,6b}$ 10 Hz, H-6a,6'a), 4.28 (bt, 2 H, $J_{5,6a} = J_{5,6b}$ = 6 Hz, H-5,5'), 4.19 (dd, 2 H, H-6b,6'b); ^{13}C-n.m.r. (75 MHz, $CDCl_3$, interpretation based on the ^{13}C-n.m.r. chemical shifts

observed[39] for the carbon atoms in the β-D-galactopyranosyl group in methyl *O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-(1→6)-2,3,4-tri-*O*-benzoyl-β-D-galactopyranoside: δ 99.23 (C-1,1'), 71.88, 71.70 (C-3,3',5,5), 69.58 (C-2,2'), 67.86 (C-4,4'), and 61.87 (C-6,6').

The compound remained unchanged when its solution in pyridine was treated overnight with an excess of acetic anhydride. A small portion was debenzoylated (Zemplén) to give β-D-galactopyranosyl β-D-galactopyranoside; ammonia c.i.m.s.: *m/z* 360 ([M + 18]$^+$); ^{13}C-n.m.r. (75 MHz, $CDCl_3$, interpretation based on the ^{13}C-n.m.r. chemical shifts found[39] for carbon atoms in the β-D-galactopyranosyl group in methyl 6-*O*-β-D-galactopyranosyl-β-D-galactopyranoside): δ 99.97 (C-1,1'), 75.53 (C-5,5'), 72.87 (C-3,3'), 70.59 (C-2,2'), 68.77 (C-4,4'), and 61.21 (C-6,6').

(*b*) A solution of silver triflate (0.563 g, 2.2 mmol) and 2,4,6-trimethylpyridine (0.132 mL, 1 mmol) in 1:1 toluene–nitromethane (10 mL) was added dropwise during 10 min at −15° to a solution of nucleophile **10** (0.59 g, 1 mmol) and glycosyl bromide **11** (1.32 g, 2 mmol) in dichloromethane, followed by slow (10 min) addition of 2,4,6-trimethylpyridine (0.132 mL, 1 mmol) in dichloromethane (10 mL)*. The mixture was stirred for 1 h, while it was allowed to attain room temperature. After processing as already described, the major product was isolated by chromatography, to give **16** (0.75 g, 64%).

O-[2,3,6-Tri-O-benzoyl-4-O-(bromoacetyl)-α- (**22**) *and -β-D-galactopyranosyl]-(1→4)-1-O-acetyl-2,3,6-tri-O-benzoyl-β-D-galactopyranose* (**17**). — (*a*) A solution of **9** (0.534 g, 1 mmol), **5** (0.95 g, 1.5 mmol), and 2,4,6-trimethylpyridine (0.205 mL, 1.55 mmol) in dichloromethane (10 mL) was added at room temperature to a suspension of silver triflate (0.437 g, 1.7 mmol) in dichloromethane (5 mL), and the mixture was stirred for 2 h*. After processing as already described, the mixture was chromatographed (solvent *C*) to give, first, minor by-products moving in t.l.c. only slightly faster than the major product **17**: these were (*1*) the α-linked disaccharide, (40 mg, 3.5%); m.p. 203–204° (from acetone–methanol), $[\alpha]_D$ +111.3° (*c* 0.4).

Anal. Calc. for $C_{58}H_{49}BrO_{19}$: C, 61.65; H, 4.37; Br, 7.07. Found: C, 61.57; H, 4.39; Br, 7.15.

And (*2*) the orthoester **24** (108 mg, 9.5%); $[\alpha]_D$ +66° (*c* 0.8).

Anal. Calc. for $C_{58}H_{49}BrO_{19}$: C, 61.65; H, 4.37; Br, 7.07. Found: C, 61.78; H, 4.39; Br, 7.14.

Further elution gave **17** (0.62 g, 55%); m.p. 148–150° (sint. 143°; from ether containing a few drops of dichloromethane, twice), $[\alpha]_D$ +82° (*c* 1.03).

Anal. Calc. for $C_{58}H_{49}BrO_{19}$: C, 61.65; H, 4.37; Br, 7.07. Found: C, 61.85; H, 4.42; Br, 7.14.

(*b*) A solution of **9** (0.534 g, 1 mmol), **5** (0.95 g, 1.5 mmol), and 2,4,6-tri-

*If the mixture becomes acidic to litmus within 10 min after addition of all of the reagents, a few more drops of collidine are added. Keeping the acidic mixture at room temperature for a longer period of time results in noticeable decomposition, and drastically lowers the yield of the desired product.

methylpyridine (0.185 mL, 1.4 mmol) in dichloromethane (8 mL) was added at room temperature to a stirred suspension of silver triflate (0.334 g, 1.3 mmol) in dichloromethane (5 mL). The mixture became slightly acidic after 45 min and was rendered neutral after 1 h by addition of 2,4,6-trimethylpyridine. After processing as already described, the crude product was chromatographed. First eluted was an amorphous compound shown by n.m.r. spectroscopy to be the alkene **29**, $[\alpha]_D$ −20.5° (*c* 1.7).

Anal. Calc. for $C_{29}H_{24}BrO_9$: C, 58.39; H, 4.56; Br, 13.39. Found: C, 58.65; H, 3.97; Br, 13.69.

The compound eluted next had m.p. 151–151.5° (from ether–isopropyl ether), and it was shown by m.p. and by n.m.r. spectroscopy to be the acetate **8**.

Continued elution afforded the α-linked product **22** (15 mg, 1.3%), followed by the desired product **17** (0.497 g, 44%), and the α-acetate **18**, m.p. 195–196° (from dichloromethane–ethanol), $[\alpha]_D$ +88° (*c* 0.4).

Anal. Calc. for $C_{58}H_{49}BrO_{19}$: C, 61.65; H, 4.37; Br, 7.07. Found: C, 61.75; H, 4.41; Br, 7.12.

The orthoester **24** initially formed (t.l.c.) was not present at the final stages of the reaction, and some decomposition/deblocking was evident from the presence in the reaction mixture (t.l.c.) of components more polar than the starting nucleophile **9**.

2,3,4,6-Tetra-O-benzoyl-α-D-galactopyranose-1,2-(1-O-acetyl-2,3,6-tri-O-benzoyl-β-D-galactopyranosyl) orthobenzoate (**25**). — A solution of **9** (0.53 g, 1 mmol), **11** (0.79 g, 1.2 mmol), and 2,4,6-trimethylpyridine (0.16 mL, 1.21 mmol) in dichloromethane (10 mL) was added at +20° to a suspension of silver triflate (0.335 g, 1.3 mmol) in dichloromethane (5 mL). The mixture was stirred while it was allowed to reach room temperature, and then until t.l.c. (solvent *C*) showed that all of the **11** had reacted (15–20 min). After processing as already described, chromatography gave pure **25** (700 mg, 63%); $[\alpha]_D$ +81° (*c* 0.9).

Anal. Calc. for $C_{63}H_{72}O_{19}$: C, 67.99; H, 4.70. Found: C, 68.06; H, 4.73.

O-(2,3,4,6-Tetra-O-benzoyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-O-benzoyl-α-D-galactopyranosyl chloride (**19**). — DCMME (3.8 mL) and then freshly fused $ZnCl_2$ (15 mg) were added to a solution of **16** (1.9 g) in chloroform (7.6 mL), and the mixture was stirred for 3 h at 60–65°. T.l.c. (solvent *B*) then showed that only traces of the starting material remained and that a single, faster-migrating product had been formed. After processing as described for the preparation of **5**, chromatography yielded pure, amorphous **19** (1.7 g, 91.5%); $[\alpha]_D$ +133° (*c* 0.6).

Anal. Calc. for $C_{61}H_{49}ClO_{17}$: C, 67.24; H, 4.53; Cl, 3.25. Found: C, 67.14; H, 4.56; Cl, 3.25.

O-[2,3,6-Tri-O-benzoyl-4-O-(bromoacetyl)-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-O-benzoyl-α-D-galactopyranosyl chloride (**20**). — The 1-*O*-acetyl derivative **18** (200 mg) in chloroform (0.5 mL) was treated with DCMME (0.5 mL) and a catalytic amount of $ZnCl_2$ for 30 min at 45°. T.l.c. (solvent *B*) then showed that the reaction was complete, and that one faster-migrating product had been formed.

After processing as described for the preparation of **5**, chromatography gave pure **20** (180 mg, 90%); $[\alpha]_D$ +100° (*c* 1).

Anal. Calc. for $C_{56}H_{46}BrClO_{17}$: C, 60.79; H, 4.19; Br, 7.22; Cl, 3.20. Found: C, 60.93; H, 4.20; Br, 7.20; Cl, 3.07.

ACKNOWLEDGMENT

The purchase of the NT-300 spectrometer used in this work was made possible, in part, by Grant PCM-8115599 to the University of Missouri from the National Science Foundation.

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