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SELECTIVE BROMOACETYLATION OF ALKYL HEXOPYRANOSIDES: A FACILE PREPARATION OF INTERMEDIATES FOR THE SYNTHESIS OF (1→6)-LINKED OLIGOSACCHARIDES

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ABSTRACT

Bromoacetylation of methyl β-D-galacto- (**1**), α-D-galacto- (**6**), β-D-gluco- (**18**), α-D-gluco- (**22**), and α-D-manno-pyranoside (**31**), and benzyl β-D-gluco-pyranoside (**27**), gave the corresponding 6-*O*-bromoacetyl derivatives **2, 7, 19, 23, 32,** and **28** in 50–60% yields. Bromoacetylation of methyl 3-*O*-benzyl-β-D-galacto-pyranoside (**11**) afforded methyl 3-*O*-benzyl-6-*O*-bromoacetyl-β-D-galactopyranoside (**12**, 60%) as well as methyl 3-*O*-benzyl-2,6-di-*O*-bromoacetyl-β-D-galacto-pyranoside (**13**, 14%). Compounds **2, 7, 19, 23, 32, 28,** and **12** were benzoylated and the fully protected derivatives obtained were dehaloacetylated with thiourea to afford the methyl 2,3,4-tri-*O*-benzoyl-D-glycopyranosides of β-galactose (**5**), α-galactose (**9**), β-glucose (**21**), α-glucose (**25**), and α-mannose (**34**), as well as benzyl 2,3,4-tri-*O*-benzoyl-β-D-glucopyranoside (**30**) and methyl 3-*O*-benzyl-2,4-di-*O*-benzoyl-β-D-galactopyranoside (**15**). These compounds can be used as nucleophiles for the synthesis of (1→6)-linked oligosaccharides. The conversion **1→5** could be performed without isolation of the intermediates. The treatment of bromoacetyl derivatives with benzoyl chloride in pyridine resulted in the benzoylation of the remaining free hydroxyl groups and the simultaneous substitution of bromine by chlorine, yielding the corresponding mono-*O*-chloroacetyl derivatives. Benzoylations with benzoyl bromide avoided this secondary event. Glycosyl donors differentially substituted to allow further extension of the oligosaccharide chain at position 6 of D-glucose, D-galactose, and D-mannose, and sequentially at positions 6 and 3 in the case of the D-galactosyl donor derived from **15**, were readily obtained by treatment of the appropriate, fully protected methyl glycosides with 1,1-dichloromethyl methyl ether in the presence of a catalytic amount of zinc chloride.

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INTRODUCTION

Chemical synthesis of higher (1→6)-linked oligosaccharides requires the preparation of glycosyl donors allowing extension of the oligosaccharide chain at position 6. We developed a novel strategy for the synthesis of the methyl β-glycosides of (1→6)-β-D-galacto-oligosaccharides, involving the use of haloacetyl groups[1–3] for the temporary protection of the primary position in the intermediates. Specifically, we made 2,3,4-tri-*O*-benzoyl-6-*O*-bromoacetyl-α-D-galactopyranosyl chloride[3] and bromide[4], and demonstrated their usefulness for both stepwise and blockwise synthesis of the desired oligosaccharides, up to and including a hexasaccharide[3,5,6]. The preparation of these glycosyl donors from either D-galactose[4] or methyl β-D-galactopyranoside[3] involved the exchange of a trityl group for a haloacetyl group before the halogenation of the anomeric position could be carried out. A method which, instead of protecting position 6 with a haloacetyl group, takes advantage of the more versatile *tert*-butyldiphenylsilyl group[7], and thus bypasses the tritylation, has also been reported from this laboratory. Since the generally useful properties of haloacetyl groups as temporary blocking groups in oligosaccharide synthesis are well documented[2–6,8–10], facile access to 6-*O*-haloacetylated glycosyl halides would be desirable. We now report on the selective bromoacetylation of the primary hydroxyl group of some alkyl pyranosides of D-galactose, D-glucose, and D-mannose, and the conversion of the formed 6-*O*-bromoacetyl derivatives to the corresponding benzoylated glycosyl chlorides or 6-*O*-deprotected glycopyranosides. The latter two classes of compounds, which in each sugar series can be prepared from one monosaccharide intermediate, are useful glycosyl donors and glycosyl acceptors, respectively, for the synthesis of (1→6)-linked oligosaccharides, as exemplified in the preparation of **36**.

RESULTS AND DISCUSSION

Selective bromoacetylation of hexopyranosides. — The original purpose of this work was to make 2,3,4-tri-*O*-benzoyl-6-*O*-bromoacetyl-α-D-galactopyranosyl chloride more readily available. This compound is extremely useful for the synthesis of higher β-(1→6)-linked D-galacto-oligosaccharides. Previously[3], the preparation of its precursor, methyl 2,3,4-tri-*O*-benzoyl-6-*O*-bromoacetyl-β-D-galactopyranoside (**4**), required sequential tritylation[11], benzoylation, detritylation, and bromoacetylation of **1**, to afford **4** in ~50% overall yield. On attempting direct, selective bromoacetylation we found that treatment of **1** with a slight excess of bromoacetyl bromide under the conditions described in the Experimental afforded mainly methyl 6-*O*-bromoacetyl-β-D-galactopyranoside (**2**), isolated by chromatography in 55% yield. This is in contrast to the results of Hasegawa *et al.*[12], who described the benzoylation of 2-trimethylsilylethyl β-D-galactopyranoside as giving mainly the corresponding 3-derivative.

The successful preferential 6-*O*-bromoacetylation of **1** prompted us to extend

the technique to a variety of other alkyl hexopyranosides. Upon treatment of the methyl D-glycopyranosides of α-galactose (**6**), β-glucose (**18**), α-glucose (**22**), and α-mannose (**31**), as well as benzyl β-D-glucopyranoside (**27**), with bromoacetyl bromide, the corresponding methyl and benzyl 6-*O*-bromoacetyl derivatives **7, 19, 23, 32,** and **28** were formed as major products in isolated yields of 48%, 56%, 61%, 51%, and 53%, respectively. The partially protected glycoside, methyl 3-*O*-benzyl-β-D-galactopyranoside (**11**), readily available[13] from **1**, was preferentially bromoacetylated at *O*-6 also, affording methyl 3-*O*-benzyl-6-*O*-bromoacetyl-β-D-galactopyranoside (**12**) in 60% yield. In that case, the 2,6-di-*O*-bromoacetyl derivative **13** was also isolated, in 14% yield.

Benzoylation. — Due to the known, undesirable side reactions of haloacetyl groups with pyridine[1,14], the benzoylation of **2** was first attempted with benzoyl chloride, and 2,4,6-trimethylpyridine as a non-nucleophilic base, but this mixture showed itself to be too weak an acylating reagent. Various solvents were tried, but all attempts to obtain an acceptable yield of the fully protected substance were unsuccessful (t.l.c.). Only a small amount of material showing the same chromatographic mobility as authentic[3] **4** was formed, the main constituents of the reaction mixture being products of the partial benzoylation of **2**. The use of benzoyl cyanide or benzoic anhydride as the benzoylating agent did not change the situation appreciably. A faster rate of benzoylation was expected with pyridine as the base, since from the hydrolysis of acyl chlorides it is known[15] that nucleophilic catalysis with pyridine is 10^5 times faster than with 2,4,6-trimethylpyridine. Indeed, the smooth benzoylation of **2** was eventually achieved by treatment with an excess of the freshly prepared adduct of pyridine and benzoyl chloride in acetonitrile at 45–50°, while any excess of pyridine over benzoyl chloride was avoided. However, the single product formed (indistinguishable by t.l.c. from an authentic sample of **4**) showed in its ammonia c.i.m.s. peaks indicating that halogen exchange had occurred in the bromoacetyl group. This was confirmed by n.m.r. spectroscopy (Tables I and III) as well as elemental analysis, and thus the product was assigned structure **3**. The ease with which nucleophilic substitutions of halogens in haloacetates take place is well documented[14]. The problem was avoided by the use of benzoyl bromide, instead of benzoyl chloride, for the acylation of **2**, which readily gave **4**. Similarly, treatment of **7, 19,** and **23** with benzoyl chloride gave **8, 20,** and **24**, respectively, while treatment of **12, 28,** and **32** with benzoyl bromide gave the corresponding **14, 29,** and **33**.

Dehaloacetylation. — We previously observed extensive acyl-group migration during the dechloroacetylation of 1,2,3,4-tetra-*O*-acetyl-6-*O*-chloroacetyl-β-D-galactopyranose[16]. Therefore, we subsequently turned to the more readily removable bromoacetyl group[17]. In the present work, however, no observable acyl-group migration occurred in the de*chloroacetylation* of the *benzoylated* compounds **3, 8, 20,** and **24** with thiourea, which afforded glycosides **5, 9, 21,** and **25** as sole products in 92–100% yields. Similarly satisfactory dechloroacetylation with hydrazine dithiocarbonate has been described[10]. Moreover, the conversion **1**→**5** (35% over 3

TABLE I

^{1}H-N.M.R. CHEMICAL SHIFTS IN $CDCl_3$

Compound	*Chemical shifts (δ, p.p.m.) and multiplicities*									
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6a*	*H-6b*	CH_2X[a]	OCH_3	CH_2Ph
2[b]	4.14m	3.48m	3.31dt	3.81dd	3.76ddd	4.41dd	4.30dd	3.99s	3.51s	
3	4.73d	5.78dd	5.58dd	5.90bd	4.25bt	4.44dd	4.37dd	4.06s	3.59s	
4	4.75d	5.78dd	5.59dd	5.90bd	4.26bt	4.46dd	4.36dd	3.83s	3.60s	
7[b]	4.70d	3.77dd	3.71dd	3.87bd	3.31bt	4.36dd	4.30dd	3.98s	3.40s	
8	5.30d	5.66dd	5.95dd	5.93bs	4.51bt	4.38dd	4.33dd	4.06s	3.49s	
9	5.28d	5.72dd	5.99dd	5.86d	4.33t	3.79ddd	3.64ddd		3.48s	
10	6.63d	3.84m	5.83dd	5.84m	4.84bt	4.40d[c]		4.06s		
12[b]	4.51d	3.66dd	3.38dd	4.01bd	3.70m	4.41dd	4.30dd	3.97s	3.51s	4.75d, 4.65d
13[b,d]	4.37d	5.14dd	3.63dd	4.11d	3.80m	4.43dd	4.34dd	3.98s	3.45s	4.73d, 4.52d
14	4.52d	5.52dd	3.79dd	5.82bd	4.00bt	4.38dd	4.34dd	3.84s	3.52s	4.69d, 4.59d
15	4.52d	5.60dd	3.83dd	5.74bd	3.79m[c]		3.64m		3.50s	4.66d, 4.49d
16	6.56d	5.59dd	4.27dd	5.95dd	4.62m	4.35m[c]		3.82s		4.77d, 4.59d
17[e]	4.67d	5.64dd	5.49ddd	5.79dd	4.16dt	4.41dd	4.31dd	3.83s	3.57s	
19[b]	4.18m	3.30m	3.36bt	3.16bt	3.30m	4.49dd	4.30dd	4.00s	3.50s	
20	4.75d	5.50dd	5.89t	5.58t	4.05ddd	4.46dd	4.41dd	4.11s	3.56s	
21[f]	4.76d	5.51dd	5.95t	5.50t	3.92		3.74m[c]		3.57s	
23	4.65d	3.31m	3.61t	3.31m	3.73ddd	4.47dd	4.28dd	3.99s	3.41s	
24	5.24d	5.27dd	6.16t	5.58t	4.31ddd	4.44dd	4.36dd	4.13s	3.49s	
26	6.54d	5.46dd	6.24t	5.68t	4.63m	4.48dd	4.39dd	4.17d 4.13d		
28[b]	4.35d	3.36		3.24m[c]	3.47dt	4.52dd	4.32dd	4.01s		4.86d, 4.64d
29	4.83d	5.59dd	5.83t	5.58t	4.00m	4.43m[c]		3.88s		4.94d, 4.72d
30	4.85d	5.59dd	5.88t	5.50bt	3.86m	3.75m[c]				4.92d, 4.74d
32[b]	4.62bs	3.80dd	3.68		3.61m[c]	4.50dd	4.30dd	4.01s	3.37s	
33	5.00d	5.68t	5.89dd	5.95t	4.34m	4.44dd	4.40dd	3.88s	3.54s	
34	5.00d	5.70dd	5.99dd	5.87t	4.08bdt	3.82m[c]			3.49s	
35	6.27d	5.38dd	6.15dd	6.04t	4.61dt	4.50dd	4.42dd	3.89s		

[a]Methylene protons of the haloacetyl groups. [b]In D_3COD. [c]No assignment due to overlapping. [d]3.90d, 3.83d, 2-OCCH_2Br. [e]7.90s, CHO. [f]Consistent with that reported in ref. 21.

TABLE II

^{1}H-N.M.R. COUPLING CONSTANTS

Compound	*Coupling constants (Hz)*							
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$	J_{CH_2Ph}
2[a]	7.6	[b]	2.7	1.3	7.4	4.9	11.3	
3	7.8	10.3	3.4	<1.0	5.2	4.6	11.3	
4	7.9	10.2	2.8	<1.0	6.6	5.6	11.2	
7[a]	3.4	10.0	3.1	<1.0	7.7	4.6	11.3	
8	3.5	9.8	3.4	<1.0	6.2	6.2	11.3	
9	3.6	10.7	3.4	<1.0	6.7	6.7	12.6	
10	3.9	11.5	4.0	<1.0	6.3	[b]	[b]	
12[a]	7.8	9.6	3.2	1.0	7.4	4.9	11.2	11.9
13[a,c]	7.7	9.9	3.2	<1.0	7.5	4.5	11.4	12.0
14	8.0	10.0	3.3	<1.0	6.7	6.1	11.2	12.8
15	8.3	10.0	3.3	<1.0	[b]	[b]	[b]	12.7
16	3.9	10.1	3.9	<1.0	6.2	4.6	[b]	12.2
17	7.8	10.5	2.7	<1.0	6.8	6.0	11.4	
19[a]	9.7	~9.0	9.0	8.0	[b]	5.9	11.8	
20	7.8	9.7	9.7	9.7	4.7	3.2	11.7	
21	7.9	9.7	9.7	9.7	[b]	[b]	[b]	
23[a]	3.7	9.2	9.2	10.0	1.7	6.1	11.8	
24	3.6	9.7	9.7	9.7	5.0	2.7	12.2	
26[d]	4.0	10.0	10.0	10.0	4.2	2.5	12.6	
28	7.7	[b]	[b]	5.8	6.0	2.0	11.8	11.8
29	7.9	9.6	9.6	9.6	5.0	[b]	[b]	12.5
30	8.0	9.8	9.7	9.5	[b]	[b]	[b]	12.7
32[a]	1.6	2.8	[b]	[b]	1.7	5.8	11.8	
33	2.3	2.3	10.0	9.1	4.9	2.5	12.0	
34	1.6	3.3	10.0	10.0	4.0	2.5	[b]	
35	1.7	3.1	10.2	10.0	4.2	2.2	12.4	

[a]In D_3COD. [b]No assignment due to overlapping. [c]J_{CH_2Br} 12.4 Hz. [d]J_{CH_2Cl} 15 Hz.

steps) could be carried out without isolation of intermediates. Debromoacetylation of **14, 29,** and **33** gave the corresponding 6-*O*-unprotected glycosides **15, 30,** and **34** in 93–100% yields.

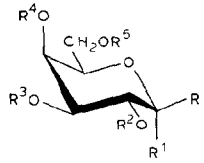
Preparation of glycosyl chlorides. — Methyl glycosides are easily converted into the corresponding glycosyl chlorides by treatment with dichloromethyl methyl ether (DCMME) in the presence of a catalytic amount of zinc chloride[18]. In this way, glycosyl chlorides **10** and **26** were obtained from **3** and **20** in 82 and 87% yield, respectively. As suggested previously[3,19], the cleavage of the starting methyl β-glycosides was accompanied by anomerization, affording the corresponding methyl α-D-glycosides **8** and **24**, which were isolated in 12 and 11% yield, respectively. To convert α-glycopyranosides, *e.g.* **8** or **33**, into the corresponding glycosyl chlorides required longer reaction times (~24 h) than for their β-counterparts (~4 h for **3** and **20**). Methyl 3-*O*-benzyl-2,4-di-*O*-benzoyl-6-*O*-bromoacetyl-β-D-galactopyranoside (**14**) was considerably less reactive in its conversion to **16** than was

TABLE III

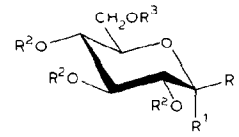
^{13}C-N.M.R. CHEMICAL SHIFTS IN $CDCl_3$

Compound	*Chemical shifts (δ, p.p.m.)*									
	C-1	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	CH_2X[a]	OCH_3	*CO*	CH_2Ph
2[b]	105.78	72.28	73.69	70.20	74.66	66.21	26.45	57.34	169.06	
3	102.41	69.59	71.68	68.00	71.04	63.31	40.54	57.22		
4[c]	102.30	69.50	71.60	68.00	71.00	63.40	25.20	57.30		
7[b]	101.55	69.54	70.94	70.09	71.24	66.65	26.38	55.79	168.96	
8	97.68	69.11[d]	69.21[d]	68.26	66.55	63.82	40.53	55.82		
9	97.62	69.20[d]	70.12[d]	69.61[d]	68.45	60.90		55.72		
10	91.41	67.85	68.65	68.13	69.77	62.93	40.45			
12[b]	105.76	71.65	82.10	67.11	73.59	66.09	26.36	57.22	168.80	72.69
12[e]	103.80	69.74	79.95	65.31	72.24	65.05	26.13	47.33	169.66	71.44
13[b]	103.10	73.83[d]	79.98	66.98	73.66[d]	65.96	26.50	57.06	168.80	72.37
							26.37		168.00	
14	102.33	71.04[f]	76.09	66.54	71.04[f]	63.93	25.29	56.90		71.04[f]
15	102.46	71.33	76.37	67.18	73.92	60.68		56.92		70.91
16	91.99	69.99[d]	72.45	67.15	70.08[d]	63.51	25.18			71.74
17[g]	102.34	69.33	71.01	67.73	70.36	63.30	25.13	57.18		
19[b]	105.33	75.12[d]	77.83	71.50	74.92[d]	66.13	26.43	57.29	168.94	
20	102.11	69.33[d]	71.99	72.75	71.72[d]	63.95	40.67	57.20		
21	102.14	71.86	72.86	69.63	74.71	61.39		57.17		
23[b]	101.31	73.46	75.04	71.78[d]	70.98[d]	66.34	26.42	55.72	168.97	
24	97.15	71.93	70.22	69.19	67.41	63.99	40.67	55.78		
26	90.35	71.58	70.65	69.63	67.94	63.06	40.64			
28[b]	103.28	75.21[d]	77.92	71.63[d]	75.05[d]	66.23	26.51		168.98	71.91
29	99.28	71.05[d]	72.77	69.45	72.02[d]	64.14	25.48			70.61
30	99.63	71.84	72.84	69.64	74.70	61.43				70.89
32[b]	102.75	71.85	71.85	68.54	72.50	66.59	26.56	55.35	169.05	
33	98.72	70.39	69.82	66.94	68.48	64.39	25.33	55.66		
34	98.75	70.92	70.57	67.29	69.74	61.42		55.44		
35	88.79	72.37	71.21	65.96	68.60	63.36	25.22			

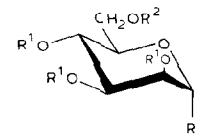
[a]Carbon of the haloacetyl group. [b]In D_3COD. [c]Taken from ref. 3. [d]Uncertain assignment. [e]In D_2O. [f]One peak. [g]159.70, *C*HO.



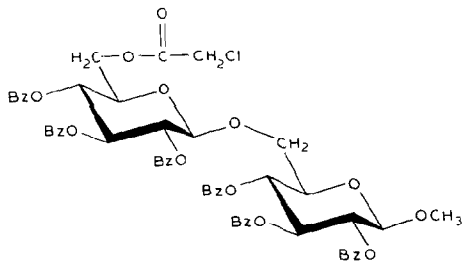
	R	R^1	R^2	R^3	R^4	R^5
1	OMe	H	H	H	H	H
2	OMe	H	H	H	H	$BrCH_2CO$
3	OMe	H	Bz	Bz	Bz	$ClCH_2CO$
4	OMe	H	Bz	Bz	Bz	$BrCH_2CO$
5	OMe	H	Bz	Bz	Bz	H
6	H	OMe	H	H	H	H
7	H	OMe	H	H	H	$BrCH_2CO$
8	H	OMe	Bz	Bz	Bz	$ClCH_2CO$
9	H	OMe	Bz	Bz	Bz	H
10	H	Cl	Bz	Bz	Bz	$ClCH_2CO$
11	OMe	H	H	Bn	H	H
12	OMe	H	H	Bn	H	$BrCH_2CO$
13	OMe	H	$BrCH_2CO$	Bn	H	$BrCH_2CO$
14	OMe	H	Bz	Bn	Bz	$BrCH_2CO$
15	OMe	H	Bz	Bn	Bz	H
16	H	Cl	Bz	Bn	Bz	$BrCH_2CO$
17	OMe	H	Bz	CHO	Bz	$BrCH_2CO$



	R	R^1	R^2	R^3
18	OMe	H	H	H
19	OMe	H	H	$BrCH_2CO$
20	OMe	H	Bz	$ClCH_2CO$
21	OMe	H	Bz	H
22	H	OMe	H	H
23	H	OMe	H	$BrCH_2CO$
24	H	OMe	Bz	$ClCH_2CO$
25	H	OMe	Bz	H
26	H	Cl	Bz	$ClCH_2CO$
27	OBn	H	H	H
28	OBn	H	H	$BrCH_2CO$
29	OBn	H	Bz	$BrCH_2CO$
30	OBn	H	Bz	H



	R	R^1	R^2
31	OMe	H	H
32	OMe	H	$BrCH_2CO$
33	OMe	Bz	$BrCH_2CO$
34	OMe	Bz	H
35	Cl	Bz	$BrCH_2CO$



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methyl 2,4,6-tri-*O*-benzoyl-3-*O*-benzyl-β-D-galactopyranoside in a similar reaction[19]. Apparently, a 6-*O*-haloacetyl group decreases reactivity at the anomeric center. The reaction of **14** was accompanied by successive debenzylation and (dichloromethyl)ation at *O*-3, and further conversion[19] of the dichloromethyl group, to give **17** as a minor by-product. Crystalline galactosyl chloride **16** is a versatile glycosyl donor, containing *two* selectively removable blocking groups. It allows for sequential extension of the oligosaccharide chain at positions 3 and 6 of a terminal D-galactose unit in any desired order, and is therefore useful for the

preparation of branched-chain oligosaccharides related for example to some blood-group determinants[20].

EXPERIMENTAL

General methods. — Optical rotations were measured at 25° with a Perkin–Elmer automatic polarimeter, Model 241 MC. Thin-layer chromatography on pre-coated slides of Silica Gel G F254 (Analtech) was performed with solvent mixtures of appropriately adjusted polarity consisting of *A*, dichloromethane–methanol; *B*, carbon tetrachloride–acetone; *C*, toluene–ethyl acetate. Detection was effected by charring with 5% sulfuric acid in ethanol and, when applicable, with u.v. light. Preparative chromatography was performed by gradient elution from columns of Silica Gel 60 (Merck, particle size 0.015–0.040 mm, or Fluka, particle size 0.04–0.063 mm). To chromatograph glycosyl chlorides, the silica gel was dried for 24 h at 150°. N.m.r. data were extracted from spectra measured at 25° with a Varian XL 300 spectrometer, and are presented in Tables I–III. Proton-signal assignments were made by first-order analysis of the spectra, and were supported by homonuclear decoupling experiments. Of the two magnetically non-equivalent geminal protons attached to C-6, the one resonating at a lower field is denoted H-6a and the one resonating at a higher field is denoted H-6b. Carbon-signal assignments were made by mutual comparison of series of spectra, and by comparison with spectra of related substances. Ammonia c.i. mass spectra were recorded with a Finnigan 10151D spectrometer. Desorptive c.i. mass spectra were recorded with an Extrel ELQ-400 mass spectrometer equipped with a Vacuumetrics d.c.i. probe. Reactions requiring anhydrous conditions were performed under N_2 in common laboratory glassware. Unless stated otherwise, solutions in organic solvents were dried with anhydrous sodium sulfate, and concentrated at 2 kPa and 40°.

Methyl 6-O-bromoacetyl-β-D-galactopyranoside (**2**). — To a solution of **1** (5.83 g, 30.0 mmol) and 2,4,6-trimethylpyridine (4.85 g, 40.0 mmol) in *N,N*-dimethylformamide (DMF) (150 mL) was added dropwise with stirring at −50° a solution of bromoacetyl bromide (7.87 g, 39.0 mmol) in toluene (10 mL). Stirring was continued for 0.5 h at −50°, the mixture was allowed to warm to room temperature, toluene (150 mL) was added, the solids were filtered off, and the filtrate was concentrated. The residue was triturated with acetone (50 mL), the mixture was filtered, and the filtrate concentrated. The residue was chromatographed on a column of silica gel (solvent *A*, 10:1), to yield **2** (5.20 g, 55%), m.p. 144° (from ethanol), $[\alpha]_D$ −7.7° (*c* 1.1, methanol).

Anal. Calc. for $C_9H_{15}BrO_7$: C, 34.30; H, 4.80; Br, 25.36. Found: C, 34.38; H, 4.81; Br, 25.28.

The following compounds were made by the procedure just described.

Methyl 6-O-bromoacetyl-α-D-galactopyranoside (**7**). — From **6** (5.83 g, 30.0 mmol), to give 4.57 g (48%), m.p. 159° (from ethanol), $[\alpha]_D$ +110.0° (*c* 1.4, methanol).

Anal. Calc. for $C_9H_{15}BrO_7$: C, 34.30; H, 4.80; Br, 25.36. Found: C, 34.39; H, 4.82; Br, 25.43.

Methyl 6-O-bromoacetyl-β-D-glucopyranoside (**19**). — From **18** (5.83 g, 30.0 mmol), to give 5.28 g (56%), m.p. 143° (from ethanol), $[\alpha]_D$ −18.7° (*c* 1.1, methanol).

Anal. Calc. for $C_9H_{15}BrO_7$: C, 34.30; H, 4.80; Br, 25.36. Found: C, 34.39; H, 4.83; Br, 25.48.

Methyl 6-O-bromoacetyl-α-D-glucopyranoside (**23**). — From **22** (5.83 g, 30.0 mmol), to give 5.80 g (61%), as a white foam, $[\alpha]_D$ +101.5° (*c* 1.4, methanol).

Anal. Calc. for $C_9H_{15}BrO_7$: C, 34.30; H, 4.80; Br, 25.36. Found: C, 34.40; H, 4.84; Br, 25.28.

Methyl 6-O-bromoacetyl-α-D-mannopyranoside (**32**). — From **31** (5.83 g, 30.0 mmol), to give 4.87 g (51%), as a colorless oil, $[\alpha]_D$ +58.7° (*c* 1.2, methanol).

Anal. Calc. for $C_9H_{15}BrO_7$: C, 34.30; H, 4.80; Br, 25.36. Found: C, 34.27; H, 4.82; Br, 25.45.

Methyl 3-O-benzyl-6-O-bromoacetyl-β-D-galactopyranoside (**12**). — To a solution of **11** (ref. 13) (2.55 g, 9.0 mmol) and 2,4,6-trimethylpyridine (1.62 g, 13.3 mmol) in tetrahydrofuran (THF) (100 mL) was added at −50° a solution of bromoacetyl bromide (2.62 g, 13.0 mmol) in THF (10 mL). After being stirred at −50° for 0.5 h, the mixture was brought to room temperature, filtered, and concentrated. The residue was chromatographed on a column of silica gel (solvent *A*, 25:1), yielding first **13** (0.65 g, 14%), m.p. 119° (from 1:1 ethyl acetate:hexane), $[\alpha]_D$ +16.9° (*c* 0.5, methanol).

Anal. Calc. for $C_{18}H_{22}Br_2O_8$: C, 41.09; H, 4.21; Br, 30.37. Found: C, 41.18; H, 4.24; Br, 30.32.

Eluted next was **12** (2.18 g, 60%), m.p. 113° (from 1:1 ethyl acetate–hexane), $[\alpha]_D$ +13.9° (*c* 0.5, methanol).

Anal. Calc. for $C_{16}H_{21}BrO_7$: C, 47.42; H, 5.22; Br, 19.72. Found: C, 47.50; H, 5.23; Br, 19.64.

Benzyl 6-O-bromoacetyl-β-D-glucopyranoside (**28**). — The compound was prepared by the procedure just described, from **27** (2.30 g, 8.5 mmol), 2,4,6-trimethylpyridine (1.45 g, 12.0 mmol) in THF (100 mL), and bromoacetyl bromide (2.24 g, 11.1 mmol) in THF (10 mL). The yield was 1.78 g (53%), m.p. 154–155° (from ethanol), $[\alpha]_D$ −38.1° (*c* 1.1, methanol).

Anal. Calc. for $C_{15}H_{19}BrO_7$: C, 46.05; H, 4.90; Br, 20.43. Found: C, 46.14; H, 4.95; Br, 20.35.

Methyl 2,3,4-tri-O-benzoyl-6-O-chloroacetyl-β-D-galactopyranoside (**3**). — A freshly prepared solution of pyridine (1.978 g, 25.0 mmol) and benzoyl chloride (3.795 g, 27.0 mmol) in acetonitrile (10 mL) was quickly added to a suspension of **2** (1.575 g, 5.0 mmol) in acetonitrile (10 mL), whereupon **2** dissolved. After 1 h at 45–50° t.l.c. (solvent *B*, 5:1) showed that the reaction was complete. After cooling to room temperature and dilution with a small amount of water, the mixture was partitioned between water and ethyl acetate. The combined organic layers were

washed successively with dilute HCl and sodium hydrogencarbonate solution, dried, and concentrated. The residue was chromatographed on a column of silica gel (solvent *B*, 10:1), yielding **3** (2.43 g, 83%), white foam, $[\alpha]_D$ +145.7° (*c* 1.3, chloroform); c.i.m.s.: *m/z* 551 and 553 (~7:3) $(MH - MeOH)^+$.

Anal. Calc. for $C_{30}H_{27}ClO_{10}$: C, 61.81; H, 4.67; Cl, 6.08. Found: C, 61.80; H, 4.71; Cl, 6.00.

The following compounds were made by the procedure just described:

Methyl 2,3,4-tri-O-benzoyl-6-O-chloroacetyl-α-D-galactopyranoside (**8**). — From **7** (1.58 g, 5.0 mmol), to give 2.68 g (92%), white foam, $[\alpha]_D$ +189.7° (*c* 1.0, chloroform); c.i.m.s.: *m/z* 551 and 553 (~7:3) $(MH - MeOH)^+$.

Anal. Calc. for $C_{30}H_{27}ClO_{10}$: C, 61.81; H, 4.67; Cl, 6.08. Found: C, 62.01; H, 4.76; Cl, 5.96.

Methyl 2,3,4-tri-O-benzoyl-6-O-chloroacetyl-β-D-glucopyranoside (**20**). — From **19** (1.58 g, 5.0 mmol), to give 2.90 g (99.5%), white foam, $[\alpha]_D$ −5.0° (*c* 0.5, chloroform); c.i.m.s.: *m/z* 551 and 553 (~7:3) $(MH - MeOH)^+$.

Anal. Calc. for $C_{30}H_{27}ClO_{10}$: C, 61.81; H, 4.67; Cl, 6.08. Found: C, 62.04; H, 4.76; Cl, 6.06.

Methyl 2,3,4-tri-O-benzoyl-6-O-chloroacetyl-α-D-glucopyranoside (**24**). — From **23** (1.58 g, 5.0 mmol), to give 2.64 g (90%), white foam, $[\alpha]_D$ +51.2° (*c* 0.4, chloroform); c.i.m.s.: *m/z* 551 and 553 (~7:3) $(MH - MeOH)^+$.

Anal. Calc. for $C_{30}H_{27}ClO_{10}$: C, 61.81; H, 4.67; Cl, 6.08. Found: C, 61.86; H, 4.67; Cl, 6.18.

Methyl 2,3,4-tri-O-benzoyl-6-O-bromoacetyl-β-D-galactopyranoside (**4**). — From **2** (1.58 g, 5.0 mmol) suspended in acetonitrile (10 mL), and a freshly prepared solution of pyridine (2.37 g, 30.0 mmol) and benzoyl bromide (5.92 g, 32.0 mmol) in acetonitrile (10 mL), to give after 1 h at room temperature 2.38 g (76%), white foam, $[\alpha]_D$ +152° (*c* 1.0, chloroform), lit.[3] $[\alpha]_D$ +159° (*c* 1.2, chloroform).

Benzyl 2,3,4-tri-O-benzoyl-6-O-bromoacetyl-β-D-glucopyranoside (**29**). — From **28** (1.17 g, 3.0 mmol) dissolved in acetonitrile (6 mL), pyridine (1.42 g, 18.0 mmol) and benzoyl bromide (3.55 g, 19.2 mmol) in acetonitrile (6 mL), to give after 1 h at room temperature 1.95 g (92%), white foam, $[\alpha]_D$ −22.6° (*c* 1.1, chloroform).

Anal. Calc. for $C_{36}H_{31}BrO_{10}$: C, 61.46; H, 4.44; Br, 11.36. Found: C, 61.75; H, 4.46; Br, 11.14.

Methyl 2,3,4-tri-O-benzoyl-6-O-bromoacetyl-α-D-mannopyranoside (**33**). — From **32** (1.58 g, 5.0 mmol), to give after 1 h at room temperature 2.64 g (84%), white foam, $[\alpha]_D$ −111.7° (*c* 1.3, chloroform); c.i.m.s.: *m/z* 595 and 597 (~1:1) $(MH - MeOH)^+$.

Anal. Calc. for $C_{30}H_{27}BrO_{10}$: C, 57.43; H, 4.34; Br, 12.74. Found: C, 57.45; H, 4.36; Br, 12.83.

Methyl 2,4-di-O-benzoyl-3-O-benzyl-6-O-bromoacetyl-β-D-galactopyranoside (**14**). — From **12** (405 mg, 1.0 mmol) in acetonitrile (2 mL), pyridine (316 mg, 4.0 mmol) and benzoyl bromide (833 mg, 4.5 mmol) in acetonitrile (2 mL), to give

after 1 h at room temperature 530 mg (87%), white foam, $[\alpha]_D$ +104.8° (*c* 1.1, chloroform).

Anal. Calc. for $C_{30}H_{29}BrO_9$: C, 58.74; H, 4.77; Br 13.03. Found: C, 58.85; H, 4.79; Br, 12.95.

*Methyl 2,3,4-tri-*O*-benzoyl-β-*D*-galactopyranoside* (**5**). — *a. From* **1** *without isolation of intermediates.* Compound **1** (1.94 g, 10.0 mmol) and 2,4,6-trimethylpyridine (1.62 g, 13.3 mmol) in DMF (50 mL) were treated with a solution of bromoacetyl bromide (2.62 g, 13.0 mmol) in toluene (10 mL) as described for the preparation of **2**. Crude **2** was dissolved in acetonitrile (10 mL) and benzoylated with benzoyl chloride (7.73 g, 55.0 mmol) and pyridine (3.95 g, 50.0 mmol) in acetonitrile (10 mL), as described for the preparation of **3**. Crude **3** was dissolved in methanol (10 mL), and after the addition of thiourea (3.80 g, 50.0 mmol) in methanol (30 mL) the solution was heated to 50°. T.l.c. (solvent *B*, 5:1) showed complete conversion of **3** to **5** after 3 h. The solution was cooled to room temperature, and partitioned between water and ethyl acetate. The combined organic layers were successively washed with dilute HCl and sodium hydrogencarbonate solution, dried, and concentrated. The residue was chromatographed on a column of silica gel (solvent *B*, 5:1) yielding **5** (1.77 g, 35%), m.p. 90–91° (from 1:1 diethyl ether–hexane). The substance is dimorphous; on further heating, the melt crystallized slowly at 130°, and showed m.p. 157° (lit.[6] m.p. 157–158°).

b. From purified **3**. Compound **3** (314 mg, 0.54 mmol) and thiourea (152 mg, 2.0 mmol) in methanol (10 mL), treated as just described for the conversion **3**→**5**, gave 273 mg (100%) of **5**, m.p. 90–91°.

The following compounds were made by the same procedure.

*Methyl 2,3,4-tri-*O*-benzoyl-α-*D*-galactopyranoside* (**9**). — From **8** (292 mg, 0.5 mmol) and thiourea (152 mg, 2.0 mmol) in methanol (10 mL), to give 234 mg (92%), white foam, $[\alpha]_D$ +248.4° (*c* 1.2, chloroform).

Anal. Calc. for $C_{28}H_{26}O_9$: C, 66.40; H, 5.17. Found: C, 66.67; H, 5.28.

*Methyl 2,3,4-tri-*O*-benzoyl-β-*D*-glucopyranoside* (**21**). — From **20** (292 mg, 0.5 mmol) and thiourea (152 mg, 2.0 mmol) in methanol (10 mL), to give 253 mg (100%), white foam, $[\alpha]_D$ −6.6° (*c* 1.1, chloroform).

Anal. Calc. for $C_{28}H_{26}O_9$: C, 66.40; H, 5.17. Found: C, 66.17; H, 5.23.

*Methyl 2,3,4-tri-*O*-benzoyl-α-*D*-glucopyranoside* (**25**). — From **24** (314 mg, 0.54 mmol) and thiourea (152 mg, 2.0 mmol) in methanol (10 mL), to give 258 mg (94%), m.p. 149° (from 1:1 benzene–hexane) lit.[22] m.p. 148–149°.

*Methyl 2,4-di-*O*-benzoyl-3-*O*-benzyl-β-*D*-galactopyranoside* (**15**). — A solution of **14** (307 mg, 0.5 mmol) and thiourea (152 mg, 2.0 mmol) in methanol (10 mL) was stirred at room temperature. T.l.c. (solvent *B*, 5:1) showed complete conversion after 0.5 h. After processing as described for the preparation of **5** (method *b*), compound **15** (228 mg, 93%) was obtained as a white foam, $[\alpha]_D$ +147° (*c* 1.4, chloroform).

Anal. Calc. for $C_{28}H_{28}O_8$: C, 68.28; H, 5.73. Found: C, 68.19; H, 5.75.

The following compounds were made by the procedure used for **15**.

Benzyl 2,3,4-tri-O-benzoyl-β-D-glucopyranoside (**30**). — From **29** (352 mg, 0.5 mmol) and thiourea (152 mg, 2.0 mmol) in methanol (10 mL), to give after 2 h at room temperature 291 mg (100%), white foam, $[\alpha]_D$ −23.1° (*c* 1.1, chloroform), lit.[10] $[\alpha]_D$ −21° (*c* 1.9, chloroform).

Methyl 2,3,4-tri-O-benzoyl-α-D-mannopyranoside (**34**). — From **33** (324 mg, 0.5 mmol) and thiourea (152 mg, 2.0 mmol) in methanol (10 mL), to give 250 mg (99%), m.p. (from 1:1 benzene–hexane) 152°, $[\alpha]_D$ −154° (*c* 1.1, chloroform), lit.[23] m.p. 143–145°, $[\alpha]_D$ −160°.

2,3,4-Tri-O-benzoyl-6-O-chloroacetyl-α-D-galactopyranosyl chloride (**10**). — *a*. To a solution of **3** (9.91 g, 17.0 mmol) in DCMME (22.5 mL) was added freshly fused $ZnCl_2$ (125 mg), and the mixture was heated at 80° with exclusion of moisture. T.l.c. (solvent *B*, 5:1) showed the formation of two faster moving products. After 4 h, when all starting material disappeared, the brown mixture was concentrated by co-evaporation with toluene, and the residue was chromatographed on a column of silica gel (solvent *B*, 25:1), yielding first **10** (8.19 g, 82%), foam, $[\alpha]_D$ +244.1° (*c* 1.3, chloroform).

Anal. Calc. for $C_{29}H_{24}Cl_2O_9$: C, 59.30; H, 4.12; Cl, 12.07. Found: C, 59.27; H, 4.17; Cl, 12.14.

Eluted next was amorphous **8** (1.20 g, 12%).

b. Product **8** (2.20 g, 3.8 mmol) in DCMME (5 mL), chloroform (5 mL), and $ZnCl_2$ (~70 mg), was treated as just described. After 24 h, the brown solution still contained a large amount of unchanged **8**. Chromatography yielded first **10** (0.93 g, 40%), then unchanged **8** (1.33 g, 60%).

The following compounds were made by the procedure just described (*a*).

2,3,4-Tri-O-benzoyl-6-O-chloroacetyl-α-D-glucopyranosyl chloride (**26**). — From **20** (1.17 g, 2.0 mmol) and $ZnCl_2$ (~25 mg) in DCMME (2.5 mL), to give 1.02 g (87%), foam, $[\alpha]_D$ +60.1° (*c* 1.2, chloroform).

Anal. Calc. for $C_{29}H_{24}Cl_2O_9$: C, 59.3; H, 4.12; Cl, 12.07. Found: C, 59.20; H, 4.13; Cl, 12.13.

Eluted next was **24** (0.13 g, 11%), isolated as a white foam.

2,3,4-Tri-O-benzoyl-6-O-bromoacetyl-α-D-mannopyranosyl chloride (**35**). — From **33** (628 mg, 1.0 mmol) and $ZnCl_2$ (~20 mg) in DCMME (2 mL), to give after 24 h 535 mg (85%), foam, $[\alpha]_D$ −73.8° (*c* 1.2, chloroform).

Anal. Calc. for $C_{29}H_{24}BrClO_9$: C, 55.13; H, 3.83; Br, 12.65; Cl, 5.61. Found: C, 54.90; H, 3.86; Br, 12.74; Cl, 5.65.

2,4-Di-O-benzoyl-3-O-benzyl-6-O-bromoacetyl-α-D-galactopyranosyl chloride (**16**) *and methyl 2,4-di-O-benzoyl-3-O-formyl-6-O-bromoacetyl-β-D-galactopyranoside* (**17**). — A solution of **14** (480 mg, 0.78 mmol) and $ZnCl_2$ (~5 mg) in DCMME (1 mL) and chloroform (5 mL) was heated at 60° under nitrogen. After 6 h, t.l.c. (solvent *B*, 5:1) indicated nearly complete conversion of **14** into two faster moving and two slower moving products. The mixture was processed as described for the preparation of **10**, and elution from a column of silica gel (solvent *B*, 25:1) yielded first **16** (282 mg, 59%), m.p. (from 1:2 benzene–hexane) 117°, $[\alpha]_D$ +196.4° (*c* 1.0, chloroform).

Anal. Calc. for $C_{29}H_{26}BrClO_8$: C, 56.37; H, 4.24; Br, 12.93; Cl, 5.74. Found: C, 56.43; H, 4.25; Br, 12.89; Cl, 5.72.

Eluted next was **16** (56 mg) contaminated with an unidentified minor by-product.

Further elution gave **17** (21 mg, 5%), white foam, $[\alpha]_D$ +74.5° (*c* 1.1, chloroform), c.i.m.s.: *m/z* 568, 570 (~1:1) $(MH + NH_3)^+$, 519, and 521 (~1:1) $(MH - MeOH)^+$.

Methyl O-(2,3,4-tri-O-benzoyl-6-O-chloroacetyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-O-benzoyl-β-D-glucopyranoside (**36**). — A solution of **21** (659 mg, 1.30 mmol), **26** (826 mg, 1.41 mmol), and 2,4,6-trimethylpyridine (164 mg, 1.35 mmol) in dichloromethane (10 mL) was added under argon at room temperature to a stirred suspension of silver trifluoromethanesulfonate (437 mg, 1.70 mmol) in dichloromethane (10 mL). After 15 min, when t.l.c. (solvent *C*, 10:1) showed complete conversion of the starting material, the reaction mixture was neutralized with 2,4,6-trimethylpyridine, filtered, and partitioned between dichloromethane and sodium thiosulfate solution, and the organic phase was dried. The solid residue left after evaporation of the solvent was recrystallized from dichloromethane–ethanol, to give 884 mg of **36**. The material in the mother liquor was chromatographed (solvent *B*, 10:1) to give 136 mg. Total yield 1.02 g (74%), m.p. 215–216°, $[\alpha]_D$ −16° (*c* 1.1, chloroform); ^{1}H-n.m.r. (in $CDCl_3$): δ 5.87 (t, 1 H, $J_{2,3} = J_{3,4}$ 9.7 Hz, H-3), 5.82 (t, 1 H, $J_{2',3'} = J_{3',4'}$ 9.6 Hz, H-3'), 5.52 (t, 1 H, $J_{4,5}$ 9.7 Hz, H-4), 5.50 (dd, 1 H, $J_{1',2'}$ 7.9 Hz, H-2'), 5.37 (dd, 1 H, $J_{1,2}$ 7.9 Hz, H-2), 5.32 (t, 1 H, $J_{4',5'}$ 9.5 Hz, H-4'), 4.95 (d, 1 H, H-1'), 4.53 (d, 1 H, H-1), 4.38 (dd, 1 H, $J_{5',6'a}$ 5.9 Hz, H-6'a), 4.31 (dd, 1 H, $J_{5',6'b}$ 2.6 Hz, $J_{6'a,6'b}$ 11 Hz, H-6'b), 4.09–3.96 (m, 3 H, H-5,5',6a), 4.02 (s, 3 H, OCH_3), 3.83 (dd, 1 H, $J_{5,6b}$ 7.9 Hz, $J_{6a,6b}$ 11.1 Hz, H-6b), 3.17 (s, 2 H, CH_2Cl); ^{13}C-n.m.r. (in $CDCl_3$): δ 101.76 (C-1), 101.37 (C-1'), 73.90 (C-2'), 72.88, 72.68 (C-3,3'), 72.05, 71.84, 71.74 (C-2,5,5'), 69.98 (C-4), 69.22 (C-4'), 68.82 (C-6), 63.87 (C-6'), 56.76 (OCH_3), 40.59 (CH_2Cl).

Anal. Calc. for $C_{57}H_{49}ClO_{18}$: C, 64.74; H, 4.67; Cl, 3.35. Found: C, 64.83; H, 4.71; Cl, 3.45.

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