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STEREOSELECTIVE CHLORINATION OF METHYL β-LACTOSIDE WITH MESYL CHLORIDE IN *N,N*-DIMETHYLFORMAMIDE*†

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ABSTRACT

Treatment of methyl β-lactoside with mesyl chloride in *N,N*-dimethylformamide under a variety of conditions gave complex mixtures of chlorinated products, of which nine were isolated and characterised. Chlorination at a secondary position always occurred with inversion of configuration. When the reaction was conducted at 94° for 9 days, a mixture of the 3,3′,4′,6,6′-pentachloride, the 3,3′,6,6′- and 3,4′,6,6′-tetrachlorides, and the 3,6,6′- and 3′,6,6′-trichlorides was obtained together with the 3′,4′-epoxide of the 6,6′-dichloride, which was an artefact. Under milder conditions, the 6,6′-dichloride was encountered, together with methyl 6-chloro-6-deoxy-β-D-glucopyranoside which had arisen by hydrolysis of the interglycosidic bond. It is particularly noteworthy that displacement occurred at C-3′ of the lactoside, in spite of the *vic*-axial group at C-4′ which should hinder nucleophilic displacement at C-3′. The cause of this anomaly is discussed.

INTRODUCTION

Our studies on the selective replacement of hydroxyl groups by chlorine substitutents in disaccharides with, for example, sulphuryl chloride[1,2] have given useful precursors of amino, deoxy, and other derivatives. Likewise, mesyl chloride in conjunction with *N,N*-dimethylformamide[2,3] reacted with methyl β-maltoside and benzyl β-cellobioside to give products in which reaction had proceeded beyond the stage of chlorination at primary positions[2]. For the maltoside, the first-formed 6,6′-dichloride was transformed into the 3,6,6′-trichloride and subsequently into the 3,4′,6,6′-tetrachloride.

The reaction with the cellobioside was more complex, giving a variety of products in which chlorine atoms were variously introduced at C-6, C-6′, C-3, C-3′, and C-4′. The results suggested that chlorine atoms were introduced only at secondary

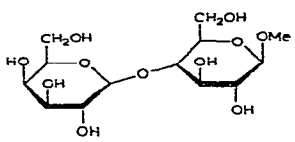
*Dedicated to the memory of Professor Edward J. Bourne.

†The Chemistry of Cellobiose and Lactose: Part IV. For Part III, see R. S. Bhatt, L. Hough, and A. C. Richardson, *Carbohyd. Res.*, 43 (1975) 57–67.

positions which were favourable to S_N2 displacement reactions, according to the rules proposed by Richardson[4]. This principle was supported by the outcome of the reaction of methyl α- and β-D-glucopyranosides and methyl α-D-galactopyranoside with the reagent[2]. In the present study, we have investigated the chlorination of methyl β-lactoside (**1**) with mesyl chloride in *N,N*-dimethylformamide and with sulphuryl chloride.

RESULTS

Treatment of methyl β-lactoside (**1**) with 30 equivalents of mesyl chloride in *N,N*-dimethylformamide at 94° for 9 days gave a mixture of at least ten products (t.l.c.). The mixture was processed as described previously by Edwards *et al.*[2] except that, after concentration of the reaction mixture to dryness, the product was treated



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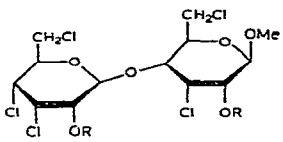

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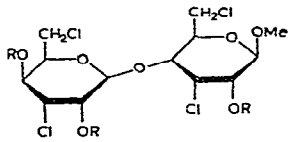

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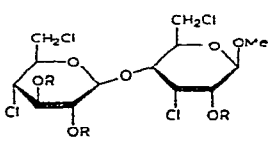

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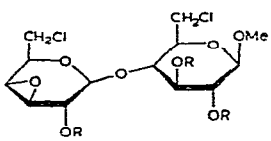

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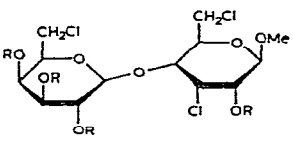

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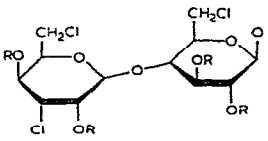

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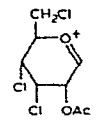
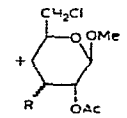


14 *m/e* 259



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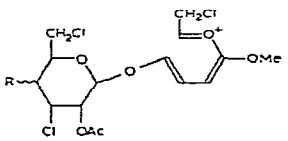
16 R = OAc, *m/e* 279



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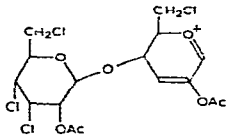
18 R = OAc, *m/e* 459



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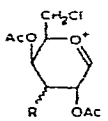

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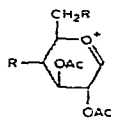
21 R = OAc, *m/e* 307



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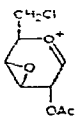
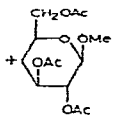
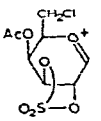
23 R = OAc, *m/e* 331



24 *m/e* 205



25 *m/e* 303



26 *m/e* 285

with sodium methoxide to effect hydrolysis of *O*-formyl groups*. After the methoxide treatment, the product was acetylated and then fractionated on silica gel to give five fractions (*A*–*E*).

Fraction *A* crystallised in 11% overall yield, and elemental analysis indicated that it was a pentachloro derivative of the lactoside. The mass spectrum (Table III) of *A* showed fragments at *m/e* 259 (3 Cl)† and 255 (2 Cl)‡ due to ions **14** and **15**, respectively, which were formed by cleavage of the C-1′–O-4 and C-4–O-4 bonds, respectively. These data clearly indicated that three of the chlorine substituents were attached to the non-reducing ring of the original disaccharide, and two to the reducing ring. The ion at *m/e* 259 readily lost the elements of HCl to give *m/e* 223, followed by the loss of ketene to give *m/e* 181. The loss of the elements of acetic acid from *m/e* 259 was not observed. These observations indicated that a chlorine rather than an acetoxyl group was present at C-3′, and the subsequent loss of ketene was indicative[6] of the presence of a 2′-acetoxyl group. No molecular ion was observed, but fragments of low intensity were noted at *m/e* 435 and 463, corresponding to ions **17** ($M^+ - Cl\bullet - HOAc$) and **19** ($M^+ - OMe\bullet - HCl$). The ion **15** lost either hydrogen chloride [*m/e* 219, (1 Cl)] or acetic acid [*m/e* 195, (2 Cl)]. By analogy with the chlorinations[2] of methyl β-maltoside and of benzyl β-cellobioside, the two positions on the reducing ring that should be susceptible to displacement reactions are C-3 and C-6. Hence, *A* was assigned the structure methyl 2-*O*-acetyl-4-*O*-(2-*O*-acetyl-3,4,6-trichloro-3,4,6-trideoxy-β-D-allopyranosyl)-3,6-dichloro-3,6-dideoxy-β-D-allopyranoside (**3**). The structure **3** was confirmed by the 220-MHz ^{1}H-n.m.r. spectrum (Table I). In particular, the two narrow triplets at τ 5.65 and 4.79, with splittings of ~3 Hz, were particularly characteristic of H-3 of allopyranosyl rings, and the low-field positions of the two signals for H-1,1′ (τ 5.15 and 5.23) indicated that they were deshielded by ~0.5 p.p.m. by the axial substituents at positions 3 and 3′.

Fraction *B* (10%) was a crystalline tetrachloride. The mass spectrum (Table III) contained fragments at *m/e* 283 (2 Cl) and 255 (2 Cl) due to the ions **20** and **15** resulting from the non-reducing and reducing moieties, respectively. The ion *m/e* 283 appeared to lose either HCl (*m/e* 247) or HOAc (*m/e* 223), although the fragment due to the former was the more intense and the related metastable ion was present at *m/e* 215.5 (calc. 215.58); no metastable ion was observed for the loss of acetic acid from *m/e* 283 (calc. 175.72). The ion at *m/e* 247 subsequently lost ketene (*m/e* 205) and then acetic acid (*m/e* 145), for which metastable ions were observed at *m/e* 170 (calc. 170.14) and 102.5 (calc. 102.56). As in the mass spectrum of **3**, the low-intensity ion **18** ($M^+ - Cl\bullet - HOAc$) was noted at *m/e* 459. These observations indicated the presence of a 3′-chlorine, suggesting that *B* was methyl 2-*O*-acetyl-4-*O*-(2,4-di-*O*-acetyl-3,6-dichloro-3,6-dideoxy-β-D-gulopyranosyl)-3,6-dichloro-3,6-dideoxy-β-D-allopyranoside (**5**). The 220-MHz ^{1}H-n.m.r. data (Table I) confirmed the assignment,

*Subsequently it was found that this procedure was unnecessary and could give rise to artefacts.
†Indicates the number of chlorine atoms, as inferred from the isotope peaks.
‡It is probable that the cleavage of the C-4–O-4 bond occurs by an indirect route (see Ref. 5).

TABLE I

^{1}H-N.M.R. PARAMETERS: FIRST-ORDER CHEMICAL SHIFTS (τ) AND COUPLING CONSTANTS (Hz)

Compound	**3**[a]	**5**[a]	**7**[a]	**9**[a]	**11**[b]	**13**[a]	**29**[b]	**30**[a]
Solvent	C_6D_6	C_6D_6	CD_3COCD_3	$CDCl_3$	$CDCl_3$	$CDCl_3$	C_6D_6	CD_3COCD_3
H-1	5.23 (m)	5.21 (d)	4.84 (d)	5.55 (d)	5.19 (d)	5.55 (d)	5.88 (d)	5.13 (d)
H-2	5.25 (m)	~4.82 (m)	5.18 (m)	5.08 (t)	~5.21 (m)	5.06 (dd)		5.18 (dd)
H-3	5.65 (t)	5.45 (t)	4.9 (t)	4.81 (t)	5.02 (t)	4.76 (t)	4.66 (t)	4.95 (t)
H-4	6.37 (dd)	6.29 (dd)	5.72 (dd)	6.11 (t)	6.0 (dd)	6.06 (t)		~5.57 (m)
H-5	6.0 (m)	~5.95 (m)	5.76–6.06		5.83 (m)	6.32 (m)		5.73 (d)
H-6a		6.4 (dd)		6.04–6.39		~6.1–6.6		6.06 (dd)
H-6b		6.48 (dd)	6.12 (dd)					6.15 (dd)
H-1′	5.15 (d)	5.14 (d)	5.18 (m)	5.46 (d)	5.35 (d)	4.96 (d)	5.67 (d)	4.4 (d)
H-2′	4.86 (dd)	4.83 (m)	5.08 (t)	5.31 (d)	4.80 (dd)	5.15 (dd)		5.11 (dd)
H-3′	4.79 (t)	4.72 (t)	4.64 (t)	6.79 (d)	5.0 (dd)	5.41 (t)		4.57 (dd)
H-4′		4.97 (d)	5.75–6.06	6.65 (d)	4.56 (dd)	4.8 (d)	4.45 (d)	4.16 (q)
H-5′	6.28 (m)	~5.95 (m)		5.85 (t)		5.62 (m)		~5.57 (m)
H-6′a		6.78 (dd)	6.16 (dd)	6.04–6.39		~6.1–6.6		6.24 (q)
H-6′b		7.00 (dd)	6.26 (dd)					6.31 (q)
OMe	6.75 (s)	6.74 (s)	6.53 (s)	6.48 (s)	6.48 (s)	6.48 (s)	6.76 (s)	
$J_{1,2}$	8	8	8	8	7.5	8	8	7.8
$J_{2,3}$	3	4	3	9.6	3	9.6	9	3.2
$J_{3,4}$	3	4	3	9.6	3	9.6	9	3.2
$J_{4,5}$	9.6	9.6	9	9.6	9.5	9.6		9
$J_{5,6a}$		2.4						2.5
$J_{5,6b}$		4	2					4.6
$J_{6a,6b}$		12.4	12					12
$J_{1',2'}$	7.8	8	8	8	7.5	8	7.8	8
$J_{2',3'}$	3.6	3	10	0	10	4		11
$J_{3',4'}$	3.6	3	10	3.5	3	4	~3.2	3
$J_{4',5'}$		<1.0		~1	1	<1.0	~1	~1
$J_{5',6'a}$		6	~5.6	6				6
$J_{5',6'b}$		8	~4	7				7.5
$J_{6'a,6'b}$		11	12.4					11.5

[a]220 MHz. [b]100 MHz.

TABLE II

^{1}H-N.M.R. PARAMETERS FOR PRODUCTS OBTAINED BY ACETOLYSIS OF THE PENTA- AND TETRA-CHLORO DERIVATIVES **3** AND **5**, RESPECTIVELY: FIRST-ORDER CHEMICAL SHIFTS (τ) AND COUPLING CONSTANTS (Hz)

Compound	**31**[a]	**32**[a]	**37**[b]	**38**[b]	**34**[a]	**35**[a]
Solvent	C_6D_6	CD_3COCD_3	C_6D_6	C_6D_6	C_6D_6	CD_3COCD_3
H-1(α)		3.76(d)		3.55(d)		3.76(d)
H-1(β)	3.48(d)		3.65(d)		3.51(d)	
H-2	5.33(dd)	4.94(t)	4.7(dd)	4.72(t)	4.77(dd)	4.92(t)
H-3	5.7(t)[c]	5.6(t)	5.43(t)	5.63(t)	5.49(t)	5.3(t)
H-4	6.14(dd)		4.85(dd)	4.68(d)	6.09(dd)	5.48–5.65
H-5			5.77(dt)	5.45(m)	~5.96(m)	
H-6a	6.58(m)		6.78(dd)	6.78	6.58(m)	6.11(m)
H-6b			6.92(dd)	6.86		
H-1′	5.21(d)	4.62(d)			5.18(d)	4.68(d)
H-2′	4.77(dd)				4.86(dd)	4.98(dd)
H-3′	4.7(t)	4.76(t)			4.66(t)	4.74(t)
H-4′	6.58(m)				5.03(d)	4.84(dd)
H-5′					~5.96(m)	5.48–5.65
H-6′a	6.85				6.82(dd)	6.28(dd)
H-6′b					7.05(dd)	6.36(dd)
$J_{1,2}$(α)		4		4		4
$J_{1,2}$(β)	8.4		8		8	
$J_{2,3}$	3.6	3.6	4	4	3.6	3.6
$J_{3,4}$	3.6	3.6	4	4	3.6	3.6
$J_{4,5}$	10		1.5	~1	9	
$J_{5,6a}$			6.5	~6		
$J_{5,6b}$			7.5	~7		
$J_{6a,6b}$			11	($J_{1,3}$ ~ 1)		
$J_{1',2'}$	8	7.8			8	8
$J_{2',3'}$	3.6	4			4	4
$J_{3',4'}$	3.6	4			4	4
$J_{4',5'}$					<1.0	~1.5
$J_{5',6'a}$					8	6
$J_{5',6'b}$					5	4
$J_{6'a,6'b}$					11.6	12

[a]At 220 MHz. [b]At 100 MHz. [c]Confirmed by spin-decoupling.

particularly the two narrow triplets for H-3,3′ at τ 5.45 and 4.72 with splittings of 3–4 Hz, and the narrow doublet for H-4′ at τ 4.97 with splittings of ~3 and 0.5 Hz, which is characteristic of an axial substituent at C-4 of a hexopyranose ring. The low-field positions of the two anomeric protons (τ 5.14 and 5.21) were also indicative of axial chlorine substituents at C-3 and C-3′.

Fraction *C* was crystalline and isomeric with *B*. As with *B*, the mass spectrum (Table III) contained fragments at *m/e* 283 (2 Cl) and 255 (2 Cl) due to ions **22** and **15**, indicating that each of the two pyranosyl rings contained two chlorine substituents. However, in this case, the ion *m/e* 283 lost acetic acid to give a more-intense fragment at *m/e* 223, for which a metastable ion was observed at *m/e* 175.7 (calc. 175.72). These

TABLE III

MASS-SPECTRAL DATA BASED ON ^{35}Cl (ISOTOPE FRAGMENTS OMITTED)

m/e	3	5	7	9	11	13	29	30
571							0.2	
547					0.4			
519		0.2						
507							2.7	
499	0.2							
483					3.0	9.1	1.1	
463	0.12							
461								8.3
459		0.5	0.5					
451				0.06				
435	1.20							
405				4.2				
381				2.2				
367				0.1		3.8	0.8	
343	0.50	0.3	0.1		0.4			
307					59.0		84.1	
285								100
283	0.30	7.1	5.0			36.4		
281								
279				2.1		63.6	56.2	
259	42.2							
255	2.40	2.0	0.8		7.5			13.8
247		1.6			8.4	16.6	4.2	
243				0.9		1.5	7.5	
225								13.8
223	35.5	0.8	17.8					
219	1.1	1.7	0.7	1.7	3.8	65.1	23.7	29.2
205		11.2		56.3	47.3	51.5	26.6	
195	4.2	1.5	0.6	15.8	3.4		47.3	13.8
187		5.34			21.1	50.0	11.6	
183				0.5				
181	13.3		5.6					
163		1.3						
145	6.0	26.7	2.0		100	81.8		
117	12.6	16.8	2.8		13.3	80.3	47.3	
43	100	100	100	100	10.6	100	100	43.1

data strongly indicate a 3′-acetoxyl group, particularly since the loss of HCl from *m/e* 283 was not observed. The subsequent loss of ketene from *m/e* 223 to give an intense ion at *m/e* 181 further indicated the presence of a 2′-acetoxyl group. These observations are in accord with the positioning of the chlorine atoms in the non-reducing ring at C-4′ and C-6′. By analogy with the previous fractions, the two chlorine atoms on the non-reducing ring must be located at C-3 and C-6; hence, *C* is methyl 2-*O*-acetyl-4-*O*-(2,3-di-*O*-acetyl-4,6-dichloro-4,6-dideoxy-β-D-glucopyranosyl)-3,6-dichloro-3,6-dideoxy-β-D-allopyranoside (7). The structure of *C* was confirmed by its 220-MHz ^{1}H-n.m.r. spectrum, in which the resonances due to H-2′ and H-3′ appeared as a pair of wide triplets (splittings 8–10 Hz), which could only arise from a

glucopyranosyl ring. Furthermore, the H-3 resonance (as in *A* and *B*) was a typical narrow triplet that indicated chlorination at C-3.

Fraction *D* was obtained crystalline in 7% yield. The mass spectrum showed a prominent fragment at *m/e* 205 (1 Cl) and a fragment of lesser intensity at *m/e* 279 (1 Cl) due to the ions **24** and **16**, respectively. Assuming that these ions were those formed by cleavage of the bonds about the interglycosidic oxygen atom, the molecular weight of *D* would be 500 (*i.e.*, 205+279+16) based on ^{35}Cl. However, as is common in this type of compound, there was no molecular ion at *m/e* 500, but the ions at *m/e* 451 ($M-CH_2Cl$), 405 ($M-Cl\bullet-HOAc$), and 381 ($M-OAc\bullet-HOAc$) were indicative of a molecular weight of 500. Hence, the ion at *m/e* 205 was due to the oxycarbonium ion resulting from the non-reducing ring, and its molecular weight indicated that it arose from a monoacetyl-monoanhydro-monochloro-monodeoxy-hexopyranosyl ring. On the basis of the ion at *m/e* 279, the reducing ring was obviously monochlorinated, probably at C-6, with the other two hydroxyl groups acetylated.

The position of the anhydro ring was indicated by the 220-MHz ^1H-n.m.r. spectrum of *D*, which was largely first-order in character. Particularly informative was a high-field AB quartet centered at $\tau \sim 6.73$, which was suggestive of an epoxide ring. Neither of these AB protons was coupled substantially to any other protons, which suggested that neighbouring hydrogen atoms were *trans*[7] to those at the epoxide bridgehead. The two anomeric hydrogens gave signals at τ 5.46 and 5.55 with couplings of ~8 Hz, which indicated that the epoxide ring was not at C-2′,3′ but must be at C-3′,4′. This location was suggested by the appearance of the H-2′ resonance at τ 5.31 as a doublet with a splitting of ~8 Hz. The lack of coupling between H-2′ and H-3′ indicated that they were *trans*, which placed the epoxide ring at C-3′,4′ *cis* to H-5′. At first sight, the lack of substantial coupling between H-4′ and H-5′, which would be *cis* and therefore expected to display a coupling of ~2–3 Hz, did not agree with this assignment. However, the greater broadening of the H-4′ resonance lines indicated that $J_{2',3'} < J_{4',5'} \approx 0.5$–1 Hz. The small $J_{4',5'}$ coupling might be due to an electronegativity effect which is known to decrease the value of this coupling constant in galactosides, gulosides, *etc.* The resonances due to H-2, H-3, and H-4, which all appeared as wide triplets, indicated that there had been no substitution at secondary positions in the reducing ring, and hence that the chlorine atom on this ring was located at the primary position. Hence, *D* was identified as methyl 2,3-di-*O*-acetyl-4-*O*-(2-*O*-acetyl-3,4-anhydro-6-chloro-6-deoxy-β-D-galactopyranosyl)-6-chloro 6-deoxy-β-D-glucopyranoside (**9**).

Fraction *E* (14%) was an amorphous solid which was shown by n.m.r. spectroscopy to be a mixture of two trichloro-tetra-acetates. Fractional crystallisation of the mixture afforded one of the components (*E1*) pure in ~2.5% overall yield. The other component (*E2*) was obtained only with difficulty (0.8% overall yield) by chromatographic refractionation of the mother liquor. The mass spectrum of *E1* showed an intense ion at *m/e* 307 (1 Cl) and a less-intense ion at *m/e* 255 (2 Cl) due to ions **21** and **15**, respectively. These ions indicated that only one chlorine substituent was present on the non-reducing ring, presumably at C-6′, and two were present on

the reducing ring which, by analogy with the previous products, were most probably at C-3 and C-6. This indicated that *E1* was the 3,6,6′-trichloride **11**. By contrast, the mass spectrum of *E2* contained ions at *m/e* 283 (2 Cl) and 279 (1 Cl) due to **20** and **16**, respectively, showing that two chlorine substituents were present on the non-reducing ring and the other on the reducing moiety. The loss of HCl from *m/e* 283 to give a relatively intense ion at *m/e* 247 indicated that one of the two chlorine substituents on the non-reducing ring was situated at C-3′, which was further substantiated by the fact that loss of HOAc from *m/e* 283 was not observed. The subsequent loss of ketene (*m/e* 215) from *m/e* 247 indicated the presence of the 2′-acetoxyl group. Hence *E2* must be the 3′,6,6′-trichloride **13**. The ^{1}H-n.m.r. spectra of the two trichlorides **11** and **13** were in complete accord with the assigned structures (Table I).

When the chlorination of **1** was performed with a lower proportion of mesyl chloride (10 equiv.) and at a lower temperature (60°), a less-complex mixture was obtained, which contained two major and several minor components. The mixture was partially fractionated by column chromatography and the two major components were obtained pure.

The first-eluted component (15%) was crystalline, and its mass spectrum indicated that it was not a disaccharide; comparison with the authentic specimen[8] proved that it was methyl 2,3,4-tri-*O*-acetyl-6-chloro-6-deoxy-β-D-glucopyranoside (**27**).

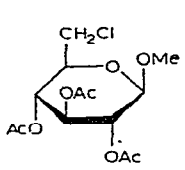
The second major component (25%) was crystalline and its mass spectrum had ionic fragments at *m/e* 307 (1 Cl) and 279 (1 Cl) attributed to ions **21** and **16**, respectively, indicating that each of the pyranosyl rings was monochlorinated. The successive loss of acetic acid, ketene, and then acetic acid from **21** suggested the presence of a chlorine atom at C-6′. The ^{1}H-n.m.r. spectrum was largely second-order due to overlapping resonances, but the two anomeric hydrogen resonances were observable at τ 5.67 and 5.88, which are normal for H-1 of β-glucopyranosides, thus indicating that equatorial 3- and 3′-acetoxyl groups were present. Furthermore, the characteristic narrow doublet for H-4′ was observed at τ 4.45, indicating that chlorination had not taken place at C-4′. Together with the known selectivity of the reagent for primary hydroxyl groups, these data identify this component as the 6,6′-dichloride **29**.

When the chlorination of **1** was repeated at room temperature, an apparently homogeneous component was isolated (36% yield). However, its mass spectrum displayed prominent ions at *m/e* 331, 307 (1 Cl), 303, and 279 (1 Cl) due to ions **23**, **21**, **25**, and **16**, respectively. These data suggested that the fraction was a mixture of the 6- and 6′-chlorides, and this was confirmed by the n.m.r. spectrum. The components could not be separated either by fractional crystallisation or by chromatography and therefore were not further investigated.

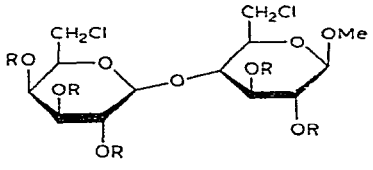
For comparative purposes, the chlorination of methyl β-lactoside (**1**) with sulphuryl chloride was investigated. When 10 molar equivalents of the reagent were used, a mixture was obtained containing (t.l.c.) a fast-moving, major component and several minor components. *O*-Dechlorosulphation of the chloroform-soluble products

with sodium iodide in methanol, followed by acetylation and chromatography, afforded a 16% yield of the 3,3′,4′,6,6′-pentachloride **3**, identical with that obtained previously.

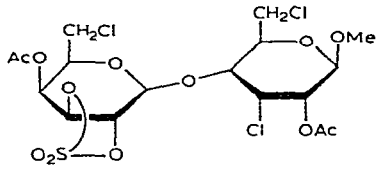
Repetition of the reaction with 5 mol. of sulphuryl chloride gave a less-complex mixture which, on chromatography, yielded two pure components. The first component, obtained crystalline in 6% yield, gave a mass spectrum (Table III) which contained a prominent peak at *m/e* 285 (1 Cl) and a less-intense peak at *m/e* 255 (2 Cl) due to ions **26** and **15**, respectively. Assuming that these ions were formed by cleavage about the interglycosidic oxygen, the molecular weight of the unknown component would be 556 (*i.e.*, 285+255+16) based on ^{35}Cl. Although no molecular ion was observed at 556, the ion at *m/e* 461 (M−Cl•−HOAc) supported this contention. Accurate mass measurements of the ion at *m/e* 285 indicated the formula $C_8H_{10}ClO_7S$, which correspondended to ion **26** derived from a 4-*O*-acetyl-6-chloro-6-deoxy-β-D-galactopyranoside 2,3-sulphate. The ion at *m/e* 255 (2 Cl) must be **15** for reasons outlined previously, indicating that the product was the 3,6,6′-trichloro-2′,3′-sulphate **30**.



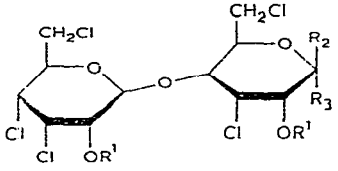
27



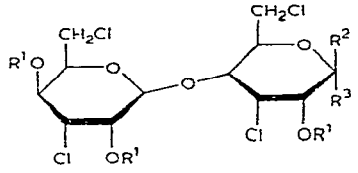
28 R = H
29 R = Ac



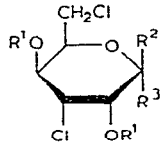
30



31 R^1 = Ac, R^2 = OAc, R^3 = H
32 R^1 = Ac, R^2 = H, R^3 = OAc
33 R^1 = H, R^2, R^3 = H, OH



34 R^1 = Ac, R^2 = OAc, R^3 = H
35 R^1 = Ac, R^2 = H, R^3 = OAc
36 R^1 = H, R^2, R^3 = H, OH



37 R^1 = Ac, R^2 = OAc, R^3 = H
38 R^1 = Ac, R^2 = H, R^3 = OAc

The 220-MHz ^1H-n.m.r. spectrum of **30** was largely first-order and confirmed the structural assignment. The relatively high-field position of H-6,6′ (Table I) indicated that these protons were adjacent to the less-deshielding chlorine atoms at C-6 and C-6′. The narrow triplet for H-3 at τ 4.95 with splittings of ~3 Hz was diagnostic of the *allo* configuration of the reducing ring, and the double-doublets for H-3′ and H-4′ at τ 4.57 and 4.16, respectively, and the associated coupling constants ($J_{2',3'}$ 11, $J_{3',4'}$ 3, and $J_{4',5'}$ 1.2 Hz) established the *galacto* configuration of the non-reducing ring. Furthermore, the low-field position of the signal for H-4′

indicated the presence of an acetoxyl group. These data confirm the structure of the trichloride as methyl 2-*O*-acetyl-4-*O*-(4-*O*-acetyl-6-chloro-6-deoxy-β-D-galacto-pyranosyl 2,3-sulphate)-3,6-dichloro-3,6-dideoxy-β-D-allopyranoside (**30**).

The other component, obtained in only 2% yield, was the 6,6′-dichloride **29**, identical with that obtained previously.

The fair yields of the 3,3′,4′,6,6′-pentachloride **3** and 3,3′,6,6′-tetrachloride **5** obtained from the reaction of **1** with mesyl chloride-*N*,*N*-dimethylformamide prompted us to completely deprotect these chloro derivatives by sequential acetolysis and de-esterification.

Acetolysis of the 3,3′,4′,6,6′-pentachloride **3**, using 1.5% sulphuric acid in acetic anhydride, gave a mixture containing two major components which were isolated (40 and 6%) by column chromatography. The 220-MHz ^{1}H-n.m.r. spectra of these components (Table II) indicated that they were the β and α anomers of the anticipated 1-acetate **31** and **32**, respectively. Low-temperature de-esterification of the β anomer **31** with methanolic sodium methoxide afforded 3,6-dichloro-3,6-dideoxy-4-*O*-(3,4,6-trichloro-3,4,6-trideoxy-β-D-allopyranosyl)-D-allopyranose (**33**) in 60% yield.

Acetolysis of the 3,3′,6,6′-tetrachloride **5** with 1.5% sulphuric acid in acetic anhydride resulted in a mixture of four products, all of which were isolated by column chromatography. The fastest-moving component (4%) was crystalline, but its ^{1}H-n.m.r. spectrum clearly indicated that it was not a disaccharide derivative. The spectrum (Table II) displayed three sharp singlets around τ 8.5 indicative of a tri-acetate. A low-field, wide doublet at τ 3.65 ($J_{1,2}$ 8 Hz) was assigned to H-1, indicating the β anomer of the 1-acetate. The narrow triplet at τ 5.43 with splittings of 4 Hz was indicative of an axial 3-chloro substituent. A double doublet at τ 4.85 (splittings 4.0 and 1.5 Hz) was suggestive of an equatorial H-4. These facts, coupled with the presence of a 4-axial substituent and the analytical data, indicated that the component was 1,2,4-tri-*O*-acetyl-3,6-dichloro-3,6-dideoxy-β-D-gulopyranose (**37**).

The component next eluted from the column (1.5%) was isomeric with **37**, and its n.m.r. data (Table II) showed to it be the α anomer **38**.

The component (35%) eluted third was crystalline, and the 220-MHz ^{1}H-n.m.r. spectrum (Table II) showed it to the required β anomer of the 1-*O*-acetyl-3,3′,6,6′-tetrachloride **34**.

The component (5%) of lowest mobility was shown by the ^{1}H-n.m.r. data (Table II) to be the α anomer **35** of the preceding 1-acetate **34**.

De-esterification of **34** with cold, methanolic sodium methoxide afforded 3,6-dichloro-3,6-dideoxy-4-*O*-(3,6-dichloro-3,6-dideoxy-β-D-gulopyranosyl)-D-allose (**36**) in 65% yield.

DISCUSSION

Previous studies of the selectivity of the reaction of carbohydrates with mesyl chloride–*N*,*N*-dimethylformamide have shown that where chlorination occurs at

secondary positions of a pyranoid ring, it does so only at positions where steric and polar factors are favourable for the formation of the S_N2 transition state[4], in spite of the fact that earlier work[3] has suggested that the "nucleophilic displacement stage" may not be the rate-limiting step. If this is so, and the formation of the formiminium ester ($R–O–CH=\overset{+}{N}Me_2\ Cl^-$) is slow and rate-limiting, then the chloride-displacement step could be considered as product-determining.

Thus, chlorination of methyl β-lactoside (**1**) would be expected to occur at C-3, C-4′, C-6, C-6′, and C-3′ if preceded by displacement at C-4′, which would convert the impeding 4′-axial group into an equatorial substituent. It was therefore surprising to find substantial proportions of the 3,3′,6,6′-tetrachloride **4** and the 3′,6,6′-trichloride **12** in the reaction mixture. These observations raised the question of whether these 3′-substituted products arose by direct substitution, or were formed from the 3′,4′-epoxide **8**, which was also present in substantial proportion in the reaction mixture. Before this point could be resolved, it was necessary to establish whether the epoxide **8** was a reaction product or whether it was an artefact formed during the processing of the reaction mixture, which involved treatment with sodium methoxide in order to hydrolyse formic esters.

When the reaction was conducted at 94°, but the treatment with base was omitted, the epoxide **8** (which had a mobility similar to that of the two trichlorides **11** and **13**) was not detected in the reaction mixture by the spray reagent described by Buchanan[9], whereas the product mixture obtained *via* the base treatment reacted strongly with this reagent. Thus, the epoxide **8** was an artefact formed during the treatment with sodium methoxide.

One further possibility remained. The epoxide might be formed during the reaction of **1** with mesyl chloride–*N*,*N*-dimethylformamide but react so rapidly that it would not be detectable. Indeed, we were able to show by t.l.c. that, under the conditions of the chlorination, the epoxide was rapidly converted into the 3′,6,6′-trichloride **12**. If the 3′-chlorine in **4** and **12** was introduced by way of the epoxide, then it should be possible to observe the conversion of a 3,4′,6,6′-tetrachloride **6** into the isomeric 3,3′,6,6′-tetrachloride **4** *via* the 3′,4′-epoxide.

However, when the 3,4′,6,6′-tetrachloride **7** was *O*-deacetylated and the resulting triol treated with mesyl chloride in *N*,*N*-dimethylformamide, t.l.c. showed that it was converted solely into the 3,3′,4′,6,6′-pentachloride **2**, and that at no stage could the isomeric 3,3′,6,6′-tetrachloride **4** be detected. These results established beyond doubt that the 3′-chloro group was not introduced *via* the epoxide and must have arisen by direct displacement at C-3′.

Bearing in mind that the chloride-displacement step is not rate-limiting, it is perhaps not surprising to find anomalies in the site of substitution. Indeed, the formation of the formiminium ester ($RO–CH=\overset{+}{N}Me_2\ Cl^-$) might bear a formal analogy with acylation with acid chlorides. A recent study of the selective benzoylation of methyl β-lactoside revealed that HO-3′ is abnormally reactive and is benzoylated more readily than the primary hydroxyl group at C-6; hence an abnormally high

concentration of the 3'-*O*-formyliminium ion might give rise to the apparently anomalous substitution noted above.

EXPERIMENTAL

Reaction of methyl β-lactoside (**1**) *with the mesyl chloride*–N,N-*dimethylformamide reagent.* — (*a*) A stirred solution of **1** (4 g) in anhydrous *N*,*N*-dimethylformamide (52 ml) was cooled in an ice-bath, and mesyl chloride (26 ml, 30 mol.) was slowly added. When the addition was complete, the mixture was stirred at 94° for 9 days; t.l.c. (dichloromethane–methanol, 15:1) then showed several products. The reaction mixture was diluted with 1-propanol, kept at 94° for 2 h, then cooled, and stirred at room temperature overnight; this process destroyed the excess of mesyl chloride. The mixture was then concentrated to dryness, a solution of the resulting semi-solid mass in methanol was cooled in an ice-bath, and freshly prepared, methanolic sodium methoxide was carefully added to pH 9. The mixture was stirred at room temperature for 3 h, the filtered solution was evaporated to dryness, a solution of the resulting brown solid in anhydrous pyridine (50 ml) was cooled in an ice-bath, and acetic anhydride (20 ml) was slowly added. The mixture was stirred at room temperature for 20 h; t.l.c. (chloroform–ethyl acetate, 30:1) then showed ten components. The acetylation mixture was poured into ice–water, and the resulting brown solid was filtered off and dried. A preliminary purification was conducted by allowing a solution in chloroform–ethyl acetate (1:1) to percolate through a column containing a 1:1 (v/v) mixture of silica gel and charcoal. The eluate was concentrated, and fractionated on silica gel by dry-packed column chromatography[12], using dichloromethane–ethyl acetate (40:1).

Fraction *1*, on crystallisation from chloroform–light petroleum, gave methyl 2-*O*-acetyl-4-*O*-(2-*O*-acetyl-3,4,6-trichloro-3,4,6-trideoxy-β-D-allopyranosyl)-3,6-dichloro-3,6-dideoxy-β-D-allopyranoside (**3**; 0.63 g, 11%), m.p. 206–208°, $[\alpha]_D$ −69° (*c* 1, chloroform) (Found: C, 38.5; H, 4.45; Cl, 33.2. $C_{17}H_{23}Cl_5O_8$ calc: C, 38.3; H, 4.3; Cl, 33.3%).

Fraction *2*, on crystallisation from chloroform–light petroleum, yielded 0.62 g (10%) of methyl 2-*O*-acetyl-4-*O*-(2,4-di-*O*-acetyl-3,6-dichloro-3,6-dideoxy-β-D-gulopyranosyl)-3,6-dichloro-3,6-dideoxy-β-D-allopyranoside (**5**), m.p. 147–148.5°, $[\alpha]_D$ −51° (*c* 1, chloroform) (Found: C, 41.3; H, 4.75; Cl, 25.8. $C_{19}H_{26}Cl_4O_{10}$ calc.: C, 41.0; H, 4.65; Cl, 25.55%).

Fraction *3* was crystallised from chloroform–light petroleum to give methyl 2-*O*-acetyl-4-*O*-(2,3-di-*O*-acetyl-4,6-dichloro-4,6-dideoxy-β-D-glucopyranosyl)-3,6-dichloro-3,6-dideoxy-β-D-allopyranoside (**7**; 1.1 g, 18%), m.p. 134–135.5°, $[\alpha]_D$ −72° (*c* 1, chloroform) (Found: C, 40.85; H, 4.7; Cl, 25.36. $C_{19}H_{26}Cl_4O_{10}$ calc.: C, 41.0; H, 4.65; Cl, 25.55%). Compound **7** (0.1 g) was carefully *O*-deacetylated with 0.1M methanolic sodium methoxide (pH 7.5–8) at −15 to −20°. After the usual work-up, a solution of the resulting residue (0.05 g, 62%) in anhydrous *N*,*N*-dimethylformamide (0.06 ml) was cooled in an ice-bath and treated with mesyl chloride

(0.03 ml, 30 mol.). The reaction mixture was then kept at 94° for 10 h and monitored by t.l.c. (dichloromethane–methanol, 15:1), using the diol **2*** and triol **4*** as standards. T.l.c. indicated that the tetrachloro derivative **6** reacted to give a product that moved identically with the 3,3′,4′,6,6′-pentachloride **2**; at no stage in the course of the reaction was the isomeric 3,3′,6,6′-tetrachloride **4** detected.

Fraction *4* crystallised from chloroform–light petroleum to give methyl 2,3-di-*O*-acetyl-4-*O*-(2-*O*-acetyl-3,4-anhydro-6-chloro-6-deoxy-β-D-galactopyranosyl)-6-chloro-6-deoxy-β-D-glucopyranoside (**9**; 0.39 g, 7%), m.p. 179–181.5°, $[\alpha]_D$ −57° (*c* 1, chloroform) (Found: C, 45.6; H, 5.45; Cl, 13.95. $C_{19}H_{26}Cl_2O_{11}$ calc.: C, 45.5; H, 5.2; Cl, 14.15%).

Fraction *5* was an amorphous powder (0.9 g, 14%) that was homogeneous by t.l.c. in many systems. However, the 60-MHz ^{1}H-n.m.r. spectrum showed it to be a mixture of two tetra-acetates in the ratio 1:1, which were separated as follows.

Three slow crystallisations of the product from chloroform–light petroleum gave methyl 2-*O*-acetyl-4-*O*-(2,3,4-tri-*O*-acetyl-6-chloro-6-deoxy-β-D-galactopyranosyl)-3,6-dichloro-3,6-dideoxy-β-D-allopyranoside (**11**) (0.16 g, 2.5%), m.p. 167.5–168°, $[\alpha]_D$ −22° (*c* 0.8, chloroform) (Found: C, 43.7; H, 5.15. $C_{21}H_{29}Cl_3O_{12}$ calc.: C, 43.5; H, 5.0%).

The mother liquors from the recrystallisations were carefully refractionated on silica gel–charcoal, using chloroform–ethyl acetate (4:1). This gave 0.05 g (0.8%) of methyl 2,3-di-*O*-acetyl-4-*O*-(2,4-di-*O*-acetyl-3,6-dichloro-3,6-dideoxy-β-D-gulopyranosyl)-6-chloro-6-deoxy-β-D-glucopyranoside (**13**), m.p. 83–85°, $[\alpha]_D$ −40° (*c* 0.87, chloroform) (Found: C, 43.3; H, 5.2. $C_{21}H_{29}Cl_3O_{12}$ calc.: C, 43.5; H, 5.0%).

(*b*) Methyl β-lactoside (**1**) was treated with 30 equivalents of the reagent as in (*a*), but during work-up the treatment with base was omitted. T.l.c. (chloroform–ethyl acetate, 30:1) showed a very similar mixture. The product mixtures from (*a*) and (*b*) were subjected to comparative t.l.c. on a single plate that was then sprayed with a 5% solution of sodium iodide in butan-1-ol containing a little Methyl Red, and heated at 140° for 4–5 min[9]. The mixture from (*a*) gave a yellow spot (coincident with the 3′,4′-epoxide **9**) on a red background, whereas the product from (*b*) did not give any response.

(*c*) A stirred solution of **1** (2 g) in anhydrous *N*,*N*-dimethylformamide (9 ml) was cooled in an ice-bath, and mesyl chloride (4.3 ml, 10 mol.) was slowly added. The mixture was kept at 60° for 6 days and then processed as in (*a*) to give an acetylated product that contained (t.l.c.) two major products and several minor components. The mixture was fractionated on a dry-packed column[12] of silica gel with dichloromethane–ethyl acetate (20:1).

The first-eluted fraction gave a crystalline residue which was recrystallised from chloroform–light petroleum to give methyl 2,3,4-tri-*O*-acetyl-6-chloro-6-deoxy-β-D-glucopyranoside (**27**, 15%), m.p. and mixture m.p. 140–141°; lit.[8] m.p. 141°.

*The diol **2** and triol **4** were prepared from the parent penta- and tetra-chloro derivatives **3** and **5** by careful treatment with methanolic sodium methoxide at between −15 and −20°.

The second fraction was crystalline, and recrystallisation from chloroform–light petroleum gave methyl 2,3-di-*O*-acetyl-4-*O*-(2,3,4-tri-*O*-acetyl-6-chloro-6-deoxy-β-D-galactopyranosyl)-6-chloro-6-deoxy-β-D-glucopyranoside (**29**; 0.85 g, 25%), m.p. 95–98°; $[\alpha]_D$ −22° (*c* 1, chloroform) (Found: C, 46.05; H, 5.6; Cl, 11.5. $C_{23}H_{32}Cl_2O_{14}$ calc.: C, 45.75; H, 5.3; Cl, 11.75%).

(*d*) A stirred solution of **1** (2 g) in anhydrous *N*,*N*-dimethylformamide (9 ml) was cooled in an ice-bath, and mesyl chloride (4.3 ml, 10 mol.) was slowly added. The mixture was then stirred at room temperature for 6 days and processed as in (*a*) to give an acetylated mixture from which the major component was isolated by chromatographic fractionation in 36% yield. The ^{1}H-n.m.r. spectrum and mass spectrum showed it to be a mixture of the 6- and 6′-monochloro derivatives.

Reaction of methyl β-lactoside (**1**) *with sulphuryl chloride.* — (*a*) A stirred solution of **1** (2 g) in chloroform (20 ml) and anhydrous pyridine (15 ml) was cooled to −78°, and slowly treated with sulphuryl chloride (4.6 ml, 10 mol.). The reaction mixture was then allowed to warm-up to between −40 and −50°, stirred for 3 h, allowed to attain room temperature, and stirred for 15–20 h. T.l.c. (chloroform–methanol, 6:1) then showed a mixture of several products. The mixture was poured into vigorously stirred, ice-cold 10% sulphuric acid (100 ml). The sticky, white precipitate* was filtered off, washed well with chloroform, and not further investigated. The filtrate was extracted with chloroform, and the extract washed successively with saturated, aqueous sodium hydrogen carbonate and water, dried ($MgSO_4$), and concentrated. A solution of the resulting residue in methanol (20 ml) was treated with aqueous, methanolic sodium iodide (1:1:1, v/v/w), when evolution of iodine and sulphur dioxide took place. The mixture was stirred at room temperature for 10–15 min, neutralized with barium carbonate, filtered through Hyflo-Supercel, and concentrated to dryness. A solution of the residue in water (5 ml) containing a few crystals of sodium thiosulphate was then repeatedly extracted with chloroform, and the extract dried ($MgSO_4$) and concentrated. The resulting residue was acetylated with pyridine (8 ml) and acetic anhydride (5 ml). After the usual work-up, the resulting mixture was fractionated on a dry-packed column[12] of silica gel, using ethyl acetate–light petroleum (1:6). The fractions containing the major component were concentrated and the residue was crystallised from chloroform–light petroleum to give the 3,3′,4′,6,6′-pentachloride **3** (0.48 g, 16%), m.p. 206–208°, identical (i.r. and mixture m.p.) with the product obtained from the mesyl chloride–*N*,*N*-dimethylformamide reaction.

(*b*) A solution of **1** (2 g) in chloroform (20 ml) and pyridine (15 ml) was cooled to −78° and sulphuryl chloride (2.5 ml, 5.1 mol.) added dropwise. The stirred reaction mixture was then kept at between −40 and −50° for 3 h, and at room temperature for a further 3 h. The mixture was then processed as in (*a*) to give an acetylated product that was fractionated on a dry-packed column of silica gel, using dichloromethane–ethyl acetate (25:1).

*A white precipitate insoluble in chloroform and other organic solvents was also observed[11] during work-up in reactions of sucrose with sulphuryl chloride.

The first-eluted fraction, when recrystallised from chloroform–light petroleum, gave methyl 2-*O*-acetyl-4-*O*-(4-*O*-acetyl-6-chloro-6-deoxy-β-D-galactopyranosyl 2,3-sulphate)-3,6-dichloro-3,6-dideoxy-β-D-allopyranoside (**30**; 0.17 g, 6%), m.p. 161° (dec.), $[\alpha]_D$ −38° (*c* 1, chloroform) (Found: C, 36.4; H, 3.95; Cl, 19.0. $C_{17}H_{23}Cl_3O_{12}S$ calc.: C, 36.6; H, 4.1; Cl, 19.1%).

Later fractions contained the 6,6'-dichloride **29** (2%), m.p. 95–98° (from chloroform–light petroleum), identical (i.r. and mixture m.p.) with the product obtained from the mesyl chloride–*N*,*N*-dimethylformamide reaction.

Acetolysis of the 3,3'4',6,6'-pentachloride **3**. — A solution of the pentachloride **3** (0.5 g) in acetic anhydride (1 ml) was cooled in an ice bath, and cold, 1.5% sulphuric acid in acetic anhydride (3 ml) was slowly added. When the addition was complete, the mixture was stirred at room temperature for 20 h; t.l.c. (dichloromethane–ethyl acetate, 60:1) then indicated two major and two minor components. The mixture was poured into ice–water and extracted with chloroform, and the extract was washed successively with saturated, aqueous sodium hydrogen carbonate and water, dried ($MgSO_4$), and concentrated to a residue which was fractionated on a dry column of silica gel with dichloromethane–ethyl acetate (100:1).

The fractions containing the first major component were evaporated to a crystalline mass which was recrystallised from chloroform–light petroleum to give 1,2-di-*O*-acetyl-4-*O*-(2-*O*-acetyl-3,4,6-trichloro-3,4,6-trideoxy-β-D-allopyranosyl)-3,6-dichloro-3,6-dideoxy-β-D-allopyranose (**31**; 0.2 g, 40%), m.p. 188–189.5°, $[\alpha]_D$ −55° (*c* 1, chloroform) (Found: C, 38.4; H, 3.9; Cl, 31.45. $C_{18}H_{23}Cl_5O_9$ calc.: C, 38.55; H, 4.1; Cl, 31.65%).

The second fraction was crystallised from chloroform–light petroleum to give 1,2-di-*O*-acetyl-4-*O*-(2-*O*-acetyl-3,4,6-trichloro-3,4,6-trideoxy-β-D-allopyranosyl)-3,6-dichloro-3,6-dideoxy-α-D-allopyranose (**32**; 0.03 g, 6%), m.p. 234–235°, $[\alpha]_D$ +6° (*c* 0.4, chloroform) (Found: C, 38.5; H, 4.0; Cl, 31.5. $C_{18}H_{23}Cl_5O_9$ calc.: C, 38.55; H, 4.1; Cl, 31.65%).

3,6-Dichloro-3,6-dideoxy-4-O-(3,4,6-trichloro-3,4,6-trideoxy-β-D-allopyranosyl)-D-allopyranose (**33**). — A solution of the triacetate **31** (0.2 g) in methanol (5 ml) was cooled to about −20°, and treated carefully with 1–2 drops of freshly prepared 0.4M methanolic sodium methoxide (pH 7.5–8). The mixture was stored in the freezer at −20° for 4 days, and t.l.c. (dichloromethane–methanol, 15:1) then showed one major component. After neutralization with Amberlite IR-120(H^+) resin, the mixture was evaporated at room temperature and the residue was fractionated on silica gel with dichloromethane–methanol (25:1) to give **33** (0.09 g, 60%), m.p. 155–159°, $[\alpha]_D$ +28.5 (3 min) → +29° (30 min, constant value) (*c* 0.7, water) (Found: C, 33.9; H, 3.95; Cl, 40.65. $C_{12}H_{17}Cl_5O_6$ calc.: C, 33.15; H, 3.9; Cl, 40.85%).

Acetolysis of the 3,3',6,6'-tetrachloride **5**. — Compound **5** (0.5 g) was acetolysed as described above, using 1.5% sulphuric acid in acetic anhydride. After the usual work-up, the product was fractionated by dry-column chromatography[12] on silica gel, using dichloromethane–ethyl acetate (120:1).

The first fraction was recrystallised from chloroform–light petroleum to give

1,2,4-tri-*O*-acetyl-3,6-dichloro-3,6-dideoxy-β-D-gulopyranose (**37**; 17 mg, 4%), m.p. 145–146°, $[\alpha]_D$ −45° (*c* 0.4, chloroform) (Found: C, 41.8; H, 4.6. $C_{12}H_{16}Cl_2O_7$ calc.: C, 42.0; H, 4.65%).

The second fraction was recrystallised from dichloromethane–light petroleum to give 1,2,4-tri-*O*-acetyl-3,6-dichloro-3,6-dideoxy-α-D-gulopyranose (**38**; 7 mg, 1.5%), m.p. 104–105°, $[\alpha]_D$ +21° (*c* 1.1, chloroform) (Found: C, 41.9; H, 4.6. $C_{12}H_{16}Cl_2O_7$ calc.: C, 42.0; H, 4.65%).

The third fraction, which contained the major component, was recrystallised from chloroform–light petroleum to give 1,2-di-*O*-acetyl-4-*O*-(2,4-di-*O*-acetyl-3,6-dichloro-3,6-dideoxy-β-D-gulopyranosyl)-3,6-dichloro-3,6-dideoxy-β-D-allopyranose (**34**; 0.17 g, 35%), m.p. 176–179°, $[\alpha]_D$ −31° (*c* 0.2, chloroform) (Found: C, 41.0; H, 4.3; Cl, 24.1. $C_{20}H_{26}Cl_4O_{11}$ calc.: C, 41.1; H, 4.45; Cl, 24.3%).

The fourth fraction was crystallised from chloroform–light petroleum to give 1,2-di-*O*-acetyl-4-*O*-(2,4-di-*O*-acetyl-3,6-dichloro-3,6-dideoxy-β-D-gulopyranosyl)-3,6-dichloro-3,6-dideoxy-α-D-allopyranose (**35**; 25 mg, 5%), m.p. 218–219°, $[\alpha]_D$ +22.5° (*c* 1 chloroform) (Found: C, 40.9; H, 4.4. $C_{20}H_{26}Cl_4O_{11}$ calc.: C, 41.1; H, 4.45%).

*3,6-Dichloro-3,6-dideoxy-4-*O*-(3,6-dichloro-3,6-dideoxy-β-D-gulopyranosyl)-D-allopyranose* (**36**). — A solution of the β-tetraacetate **34** (0.65 g) in methanol (5 ml) was cooled to between −15 and −20°, and carefully treated with 1–2 drops of freshly prepared 0.4M methanolic sodium methoxide. The mixture was kept in the freezer at −20° for 4 days and then processed in the usual way. The product crystallised from methanol–chloroform to give **36** as a white powder (0.227 g, 65%), m.p. 140–144° (dec.), $[\alpha]_D$ +19 → +21° (60 h) (*c* 0.5, water) (Found: C, 34.6; H, 4.3; Cl, 34.0 $C_{12}H_{18}Cl_4O_7$ calc.: C, 34.6; H, 4.3; Cl, 34.15%).

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