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CHEMICAL MODIFICATION OF TREHALOSE

PART XV[1]. THE SYNTHESIS OF 4,4′-DIDEOXY AND 4,4′,6,6′-TETRADEOXY ANALOGUES

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ABSTRACT

Nucleophilic displacement of 4,4′-di-*O*-mesyl-α,α-trehalose hexabenzoate occurred very readily to give, by a double inversion, the thermodynamically more stable 4,4′-di-iodide in 93% yield with overall retention of configuration. Reductive dehalogenation of the 4,4′-di-iodide with hydrazine hydrate–Raney nickel followed by debenzoylation afforded 4,4′-dideoxytrehalose in high, overall yield. Alternatively, treatment of trehalose with sulphuryl chloride afforded 4,6-dichloro-4,6-dideoxy-α-D-galactopyranosyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside, which underwent selective dehalogenation at the secondary positions on treatment with hydrazine hydrate–Raney nickel. Subsequent nucleophilic displacement of the primary chlorine substituents with sodium acetate in *N*,*N*-dimethylformamide gave, after deacetylation, 4,4′-dideoxy-α,α-trehalose. Repeated treatment of the 4,4′,6,6′-tetrachlorotrehalose derivative with hydrazine hydrate–Raney nickel gave 4,4′,6,6′-tetradeoxy-α,α-trehalose. An alternative route to the tetradeoxy derivative was *via* thiocyanate displacement of the 4,4′,6,6′-tetramethanesulphonate. The tetrathiocyanate, formed in poor yield, was desulphurized with Raney nickel to give the tetradeoxytrehalose. Treatment of 4,6-dichloro-4,6-dideoxy-α-D-galactopyranosyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside with methanolic sodium methoxide yielded, initially, 3,6-anhydro-4-chloro-4-deoxy-α-D-galactopyranosyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside which was transformed into the 3,6:3′,6′-dianhydro derivative. Reductive dechlorination of the dianhydride proceeded smoothly to give the 3,6:3′,6′-dianhydride of 4,4′-dideoxytrehalose.

INTRODUCTION

Our interest in trehalose (**1**, α-D-glucopyranosyl α-D-glucopyranoside) has recently been extended to a study of the chemical basis of sweetness[2–5]. Any research programme based on the relationship between stereochemical structure and organoleptic effect must depend entirely on the correct choice of a model sugar. Evidence

presented by Shallenberger[6] in his AH,B theory of sweetness has been based on tests with reducing sugars which undergo mutarotation in aqueous solutions, giving a mixture of anomers of pyranoses and furanoses. Consequently, it is difficult to relate sweetness with a particular structure. These difficulties may be overcome by the use of α,α-trehalose (**1**), which is an ideal model for such studies since it is sweet, non-reducing, and conformationally stable. As a result of its simple two-fold axis of symmetry about the central glycosidic atom, the pyranose rings are equivalent.

In the previous papers[7–9] in this series, the syntheses of some 2,2′-dideoxy and 3,3′-dideoxy analogues of trehalose were described. We have now extended these studies to the synthesis of some 4,4′-dideoxy analogues, which were required for our organoleptic studies.

RESULTS AND DISCUSSION

Displacement reactions of secondary sulphonyloxy groups of pyranose or furanose derivatives by iodide are fairly rare[10], and the reaction has not been widely utilised in the synthesis of deoxy sugars. However, displacements of secondary sulphonate groups that are vicinal and *trans* to an acetamido function have been employed[11,12], since neighbouring-group participation by the acetamido group facilitated the reaction, which went to completion even in the usually less-effective,

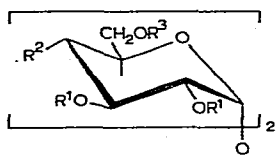
TABLE I

P.M.R. PARAMETERS: FIRST-ORDER CHEMICAL SHIFTS (τ VALUES) AND COUPLING CONSTANTS AT 100 MHz[a]

Compound	**4**[c]	**9**[d]	**10**[c]	**11**[c]	**21**[e]	**26**[d]	**27**[b,f]	**28**[b]
H-1,1′	4.26(d)	4.54(d)	4.73(d)	4.30(d)	4.38(d)	4.74(d)	4.59(d)	4.74(d)
H-2,2′	4.55(dd)	5.71(dd)	4.56(dd)	3.86(m)	4.55(dd)	5.98(dd)	5.66(dd)	4.85(dd)
H-3,3′	3.43(t)	5.51(dd)	4.35(dd)		3.82(t)	5.56(d)	5.49(m)	5.61(dd)
H-4,4′	6.03(t)	5.34(dd)	5.27(dd)	5.40(m)	5.13(t)	5.16(d)	5.39(d)	5.39(d)
H-5,5′	5.39(m)	5.11(td)	5.69(td)	5.71(t)	5.75(m)	5.69(m)	5.49(m)	5.55(m)
H-6a,6a′	5.52(dd)	6·29(d)	6.70(d)	6.93(m)	7.17(d)	5.93(m)	5.70(dd)	5.74(dd)
H-6b,6b′	5.73(dd)						5.79(d)	5.89(d)
$J_{1,2}$	3.6	3.3	3.6		4.0	2.6	2.8	2.7
$J_{2,3}$	10.5	9.5	10.5	~2	9.5	5.1	5.0	5.2
$J_{3,4}$	10.5	3.5	3.4		9.5	~0	0	0
$J_{3,5}$						~1		~0.7
$J_{4,5}$	11.0	1.5	1.6	~1	9.5	1.6	1.5	1.6
$J_{5,6a}$	2.5						2.5	2.5
$J_{5,6b}$	5.5			~7			0	0
$J_{6a,6b}$	−12.0						−10.5	−10.5

[a]Multiplicity of resonances: d, doublet; dd, double doublet; td, triple doublet; t, triplet; q, quartet; m, multiplet. [b]In deuteriochloroform. [c]In deuteriobenzene. [d]In deuteriopyridine at 100°. [e]At 60 MHz. [f]At 220 MHz.

aprotic solvent butanone. When 4,4′-di-*O*-mesyltrehalose hexabenzoate[13] (3) was treated with sodium iodide in hexamethylphosphoric triamide at 80° for 2–3 days, it was readily transformed into a 4,4′-di-iodo derivative, (93%). However, the p.m.r. spectrum of the product (Table I) was not in accord with the *galacto* configuration of each ring. For example, the H-4,4′ resonance (τ 6.03) was to the high-field side of all other methine and methylene resonances, and was a triplet with a splitting of 11 Hz, which clearly indicated that the iodo groups had been introduced with overall retention of the *gluco* configuration. This can be rationalised by the initial S_N2 displacement of the 4,4′-disulphonate groups by iodide to give the 4,4′-di-iodide with the *galacto* configuration, which then underwent further displacement by iodide, the resulting equilibrium favouring the thermodynamically more-stable, diequatorial form. Obviously, under the conditions employed, an equilibrium situation had been reached favouring the *gluco* configuration to an extent of >93%.



1 $R^1{=}R^3{=}H$, $R^2{=}OH$
2 $R^1{=}Bz$, $R^2{=}OMs$, $R^3{=}Ms$
3 $R^1{=}R^3{=}Bz$, $R^2{=}OMs$
4 $R^1{=}R^3{=}Bz$, $R^2{=}I$
5 $R^1{=}R^3{=}Bz$, $R^2{=}H$
6 $R^1{=}R^2{=}R^3{=}H$
7 $R^1{=}R^3{=}Ac$, $R^2{=}H$

Stevens *et al.*[10] have calculated a standard free-energy difference ($\Delta G^{\ominus}$) of 7.1 kJ.mole^{-1} (1.7 kcal.mole^{-1}) for a related 4-deoxy-4-iodo-glucopyranoside and -galactopyranoside, which favours the glucoside to the extent of ~95% at equilibrium. For the trehalose derivatives, a more-complex equilibrium would be established between the galactosyl galactoside (*A*), the galactosyl glucoside (*B*), and the glucosyl glucoside (*C*). From our results, which show that *C* is favoured to an extent of >93%, it can be estimated that $\Delta G^{\ominus}_{B,C}$ is >7 kJ.mole^{-1} and $\Delta G^{\ominus}_{A,C}$ >14 kJ.mole^{-1}. Hence, at equilibrium, <0.5% of *A* and <4.5% of *B* would be present.

2,3,6-Tri-*O*-benzoyl-4-deoxy-4-iodo-α-D-glucopyranosyl 2,3,6-tri-*O*-benzoyl-4-deoxy-4-iodo-α-D-glucopyranoside (4) was obtained as a colourless, crystalline solid, which slowly turned pink (sometimes yellowish-pink) on standing at room temperature. The colour was discharged on storage *in vacuo* or on heating at 70° for ~1 h, but reappeared on removal from these conditions. No inorganic iodine could be detected (starch–iodide test), and no sign of deterioration was detected during the repeated appearance and discharge of the colour. The reason for this phenomenon remains obscure.

Reductive dehalogenation of the 4,4′-di-iodide 4 with hydrazine hydrate–Raney nickel[7,14] gave the syrupy 4,4′-dideoxy hexabenzoate 5 in 85% yield. Debenzoylation of 5 afforded crystalline 4,4′-dideoxy-α,α-trehalose (6), which was further characterised as its crystalline hexa-acetate 7; the structure of 7 was confirmed by its p.m.r. spectrum (Table II) which was largely first-order. In particular, the methine resonance (H-3,3′) at lowest field appeared as a double triplet (partly overlapping the signals for H-1,1′) at τ 4.60, suggesting the presence of vicinal methylene groups at positions 4

and 4′. The deoxy protons resonated as a broad-limbed 1:3:3:1 quartet at τ 8.77 (H-4*ax*,4′*ax*) and a double double-doublet at τ 7.99 (H-4*eq*, 4′*eq*).

TABLE II

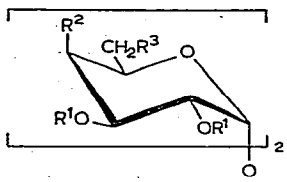
P.M.R. PARAMETERS OF 4,4′-DIDEOXY DERIVATIVES: FIRST-ORDER CHEMICAL SHIFTS (τ VALUES) AND COUPLING CONSTANTS AT 100 MHz IN BENZENE-d_6

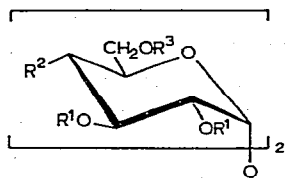
Compound	7	13	30		7	13	30
H-1,1′	4.60(d)	4.71(d)	4.44(d)	$J_{1,2}$	3.5	3.6	3.0
H-2,2′	4.93(dd)	4.94(dd)	4.78(t)	$J_{2,3}$	10.0	10.5	4.6
H-3,3′	4.51(dt)	4.56(dt)	5.80(t)	$J_{2,4eq}$			~1
H-4ax,4′ax	8.77(q)	8.77(q)	7.72(dt)	$J_{3,4eq}$	5.5	5.5	6.0
H-4eq,4′eq	7.99(ddd)	7.90(ddd)	8.93(m)	$J_{3,4ax}$	11.0	10.0	1.0
H-5,5′	5.84(m)	5.87(m)	5.98(m)	$J_{4eq,4ax}$	−12.0	−12.5	−12.4
H-6a,6a′	5.98(dd)	6.87(dd)	6.20(d)	$J_{4eq,5}$	2.4	2.5	2.9
H-6b,6b′	6.17(dd)	7.02(dd)	6.77(dd)	$J_{4ax,5}$	11.0	11.5	1.2
				$J_{5,6a}$	4.4		1.1
				$J_{5,6b}$	6.0	5.7	2.7
				$J_{6a,6b}$	−11.0	−11.5	−9.7

As an alternative and more-direct route to 4,4′-dideoxy and 4,4′,6,6′-tetradeoxy derivatives, the 4,4′,6,6′-tetrachloro derivative described by Helferich[15] seemed to be a plausible starting-material, since reductive dehalogenation before, or after, displacement of the primary chlorine atoms with acetate anion would give the tetradeoxy- and dideoxy-trehaloses, respectively. The 4,4′,6,6′-tetrachloro derivative prepared by Helferich by reaction of trehalose with sulphuryl chloride was isolated as the 2,3:2′,3′-disulphate, from which the sulphate groups were removable by a two-stage hydrolysis. However, Jennings and Jones[16] have found that formation of cyclic sulphate groups in the reaction of carbohydrates with sulphuryl chloride may be avoided by the use of a lower molar ratio of sulphuryl chloride. Using the conditions described by Jennings and Jones, crystalline 4,6-dichloro-4,6-dideoxy-α-D-galactopyranosyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside 2,2′,3,3′-tetrakis(chlorosulphate) (**8**) was obtained in 77% yield. Only a trace of the 2,3:2′,3′-disulphate was observed on t.l.c. The presence of chlorosulphonyloxy groups was shown by the strong i.r. absorption bands at 1430 and 1195 cm^{-1}, in agreement with reported values[16,17]. Dechlorosulphation was easily effected with aqueous, methanolic sodium iodide in the presence of barium carbonate, giving 4,6-dichloro-4,6-dideoxy-α-D-galactopyranosyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside (**9**) in 72% overall yield. The inclusion of barium carbonate was essential, since its absence (*i.e.*, the conditions specified by Jennings and Jones[15]) resulted in the development of acidity, which caused considerable hydrolysis of the glycosidic bond.

The structure of the tetrachloride **9** was confirmed by its p.m.r. spectrum and those of the derived tetra-acetate **10** and tetra-benzoate **11** in benzene-d_6 (Table I). The narrow double-doublet at τ 5.27 (in the spectrum of the tetra-acetate) is a characteristic feature of the H-4 resonance of galactopyranosides[13]. The mass-spectral data

of the tetra-acetate indicated a fragment of *m/e* 283 (containing two chlorine atoms) corresponding to the glycosyloxy carbonium ion arising from the fragmentation of either of the two glycosidic bonds.





8 R^1=SO_2Cl, R^2=R^3=Cl
9 R^1=H, R^2=R^3=Cl
10 R^1=Ac, R^2=R^3=Cl
11 R^1=Bz, R^2=R^3=Cl
12 R^1=R^2=H, R^3=Cl
13 R^1=Ac, R^2=H, R^3=Cl
14 R^1=SO_2Cl, R^2=Cl, R^3=H
15 R^1=SO_2Cl, R^2=H, R^3=Cl
16 R^1=R^3=H, R^2=Cl
17 R^1=R^2=R^3=H
18 R^1=Ac, R^2=R^3=H
19 R^1=Bz, R^2=R^3=SCN
20 R^1=R^3=H, R^2=OH
21 R^1=Bz, R^2=OMs, R^3=SCN
22 R^1=Bz, R^2=OMs, R^3=H

A similar chlorination with sulphuryl chloride was also carried out on 6,6′-dideoxy-α,α-trehalose[18] (**20**) and 4,4′-dideoxy-α,α-trehalose (**6**). In both reactions, crystalline dichlorides were isolated as their 2,2′,3,3′-tetrakis(chlorosulphates) **14** and **15** respectively. Only traces of the corresponding 2,3:2′,3′-disulphates were observed (t.l.c.).

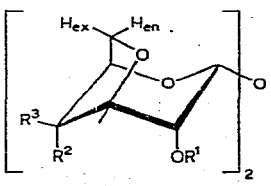
Reductive dechlorination of the chlorodeoxy derivatives **9**, **12**, and **16** was next investigated. Jones and coworkers[19] reported that hydrogenation of methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside over Raney nickel in the presence of potassium hydroxide resulted in complete reductive dechlorination. On the other hand, when the reaction was carried out in the presence of triethylamine, selective dechlorination at the secondary position occurred to give methyl 6-chloro-4,6-dideoxy-α-D-*xylo*-hexopyranoside. In contrast, we found that the reductive dechlorination of the 4,4′,6,6′-tetrachloride **9**, regardless of the choice of acid acceptor (triethylamine, potassium hydroxide, sodium acetate, or barium carbonate) or reducing agent (hydrogen over Raney nickel or hydrazine hydrate–Raney nickel), was always highly selective at C-4,4′, giving 6,6′-dichloro-4,4′,6,6′-tetradeoxy-α,α-trehalose (**12**) in high yield. This product was identical with that prepared by chlorination of 4,4′-dideoxy-α,α-trehalose with sulphuryl chloride. The structure was confirmed by the p.m.r. spectrum (Table II) of the derived tetra-acetate **13** in benzene-d_6. The signals due to the deoxy groups at C-4,4′ were readily recognised as a double double-doublet at τ 7.90 (H-4*eq*,4′*eq*) and a quartet at τ 8.77 (H-4*ax*,4′*ax*). Both the remaining chlorine atoms at C-6 and C-6′ readily underwent displacement when treated with sodium acetate in *N*,*N*-dimethylformamide, giving the 4,4′-dideoxy-trehalose hexa-acetate (**7**) in high yield.

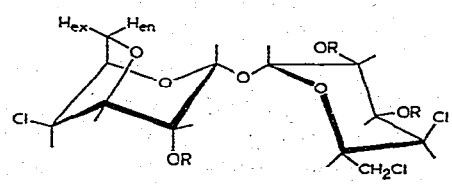
It was surprising to note the resistance of the 6,6′-chloro groups to hydrogenation. Only after repeated treatment (6–10 times) of **9** and **12** with hydrazine hydrate–Raney nickel was 4,4′,6,6′-tetradeoxy-α,α-trehalose (**17**) formed in reasonable yield. We have observed the greater rate of dechlorination at secondary positions by

the hydrazine hydrate–Raney nickel reagent on several occasions[20]. In this respect, the reduction bears a formal analogy to reductions carried out with tributyltin hydride[21], which is known to proceed by way of a radical mechanism, so that abstraction of a secondary chloride is preferred to that at a primary position.

One further method of synthesising the tetradeoxytrehalose was *via* the tetrathiocyanate, analogous to the preparation of 4,6-dideoxy-D-*xylo*-hexose and its 2-amino analogue[22]. The 4,4′,6,6′-tetramethanesulphonate **2** underwent selective replacement at the 6,6′-positions very readily when treated with thiocyanate anion at 80° in *N*,*N*-dimethylformamide. Reductive desulphuration of the resulting dithiocyanate **21** gave 2,3-di-*O*-benzoyl-6-deoxy-4-*O*-mesyl-α-D-glucopyranosyl 2,3-di-*O*-benzoyl-6-deoxy-4-*O*-mesyl-α-D-glucopyranoside (**22**) in 60% yield. When the displacement reaction was prolonged at a higher temperature, extensive decomposition occurred and only a 5% yield of the 4,4′,6,6′-tetrathiocyanato derivative **19** was obtained. By analogy with similar replacement reactions[22], the tetrathiocyanate obtained was assumed to have the *galacto* configuration. Debenzoylation followed by reductive desulphuration gave the tetradeoxy compound in 20% overall yield from **19**.

In view of our past interest[23] in the synthesis and reactions of 3,6:3′,6′-dianhydro-α,α-trehalose (**23**), the conversion of the tetrachloride **9** into a dianhydride derivative by the action of base was investigated. 6-Halo-6-deoxyhexopyranosides are well known to form 3,6-anhydrides on reaction with base[24,25], although Jones and coworkers[26] surprisingly reported that methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside does not react with sodium or potassium hydroxide, even after 6 h at 40°. We found that sodium hydroxide in methanol or ethanol transformed **9** into anhydride products, but only very slowly. However, the use of methanolic sodium methoxide resulted in a greater rate of reaction, and the tetrachloride **9** was rapidly transformed into the 3,6:3′,6′-dianhydride **26**, further characterised as the dibenzoate **27** and diacetate **28**. The p.m.r. spectra (Table I) of the diol **26**, dibenzoate **27**, and diacetate **28** showed that the compounds adopt the expected $^1C_4$ conformation. Long-range, "W" coupling $J_{2,4}$, which was observed[23] in the spectra of the tetra-acetate **25** and tetra-benzoate **24** of 3,6:3′,6′-dianhydro-α,α-trehalose, was absent from the spectrum (Table I) of **26**, indicative of the change in chirality at C-4,4′. The very small values for $J_{3,4}$ (~0) and $J_{4,5}$ (1.6 Hz) suggested dihedral angles near 90°, which was confirmed by molecular models of **26**.





23 R^1=R^3=H, R^2=OH
24 R^1=Bz; R^2=OBz, R^3=H
25 R^1=Ac R^2=OAc, R^3=H
26 R^1=R^2=H, R^3=Cl

27 R^1=Bz, R^2=H, R^3=Cl
28 R^1=Ac, R^2=H, R^3=Cl
29 R^1=R^2=R^3=H
30 R^1=Ac, R^2=R^3=H

31 R=H
32 R=Ac

In the early stages of the reaction, an unknown product was present in comparatively large amounts. This could be isolated by interruption of the reaction followed by chromatography of the mixture, giving the monoanhydride **31** in 40–45% yield. We have noted in an earlier paper[27] that reasonable yields of non-symmetrical products are obtainable if the reaction conditions are carefully controlled. By considering the reaction as two consecutive, first-order reactions, **9**→**31**→ **26**, a simple theoretical treatment[27] of such a system showed that, to a first order of approximation, the amount of the non-symmetrical product should rise in the early stages of the reaction to ~50%. The p.m.r. spectrum of the triacetate **32** of **31** is in accord with the structure (Table III), and the lack of symmetry of the compound was clearly shown by the multiplicity of resonances.

TABLE III

P.M.R. PARAMETERS: FIRST-ORDER CHEMICAL SHIFTS (τ VALUES) AND COUPLING CONSTANTS OF 2,3-DI-*O*-ACETYL-4,6-DICHLORO-4,6-DIDEOXY-α-D-GALACTOPYRANOSYL 2-*O*-ACETYL-3,6-ANHYDRO-4-CHLORO-4-DEOXY-α-D-GALACTOPYRANOSIDE AT 220 MHz IN CHLOROFORM-*d*

Ring	*A*[a]	*B*[b]		*A*[a]	*B*[b]
H-1	4.75(d)	4.59(d)	$J_{1,2}$	3.5	3.5
H-2	4.83(dd)	4.76(m)	$J_{2,3}$	10.5	
H-3	4.73(dd)	5.55(m)	$J_{3,4}$	3.5	0
H-4	5.42(d)	5.33(d)	$J_{4,5}$	1.5	1.5
H-5	5.71(t)	5.73(dd)	$J_{5,6a}$	3.7	2.5
H-6a	6.33(dd)	5.47(dd)	$J_{5,6b}$	3.5	0
H-6b	6.41(dd)	5.84(d)	$J_{6a,6b}$	−11.5	−11.5

[a]2,3-Di-*O*-acetyl-4,6-dichloro-4,6-dideoxy-α-D-galactopyranosyl ring. [b]2-*O*-Acetyl-3,6-anhydro-4-chloro-4-deoxy-α-D-galactopyranosyl ring.

Reductive dechlorination of the anhydro-chloro derivative **26** was again conveniently achieved by using hydrazine hydrate–Raney nickel, yielding the 4,4′-dideoxy dianhydride **29**. The observed coupling constants (Table II) in the p.m.r. spectrum of the 2,2′-diacetate **30** were consistent with a slightly distorted $^1C_4$ conformation, with H-2,2′,3,3′,5,5′ in equatorial positions. As found for 3,6:3′,6′-dianhydrotrehalose[23], a slight deformation of the ring exists, in order to accommodate the anhydro bridge, as suggested by the large values (4.6 and 6.0 Hz, respectively) of $J_{2,3}$ and $J_{3,4eq}$.

EXPERIMENTAL

Evaporations were performed under diminished pressure, and optical rotations were measured at ~20° in a 1-cm cell with a Bendix automatic photoelectric polarimeter, Type 143. Column chromatography was performed on Merck Kieselgel-7734 (70–230 mesh). *N*,*N*-Dimethylformamide and hexamethylphosphoric triamide were dried over calcium hydride and distilled under diminished pressure. Recrystallisations with dichloromethane in conjunction with another solvent were normally

carried out at the b.p. of dichloromethane; the product usually separated out after much of the dichloromethane had boiled off.

2,3,6-Tri-O-benzoyl-4-O-mesyl-α-D-glucopyranosyl 2,3,6-tri-O-benzoyl-4-O-mesyl-α-D-glucopyranoside (**3**). — A mixture of 4,4',6,6'-tetra-*O*-mesyl-α,α-trehalose tetrabenzoate[13] (**2**) (50 g) and sodium benzoate (40 g) was heated in hexamethylphosphoric triamide (150 ml) on a boiling water bath for ~1.5 h; t.l.c. (benzene–ethyl acetate, 6:1) then showed that the reaction was complete. The mixture was stirred with ~50 ml of ethanol and poured into ice–water (1 litre). The precipitate was filtered off, and washed well with water and ethanol to give the crude product (85–95% yield). Three recrystallisations from dichloromethane–ethanol gave **3** (33.8 g, 65%), m.p. 199–201°, $[\alpha]_D$ +186.2° (*c* 0.5, chloroform); lit.[13] m.p. 198–200°, $[\alpha]_D$ +185°.

2,3,6-Tri-O-benzoyl-4-deoxy-4-iodo-α-D-glucopyranosyl 2,3,6-tri-O-benzoyl-4-deoxy-4-iodo-α-D-glucopyranoside (**4**). — A mixture of the 4,4'-disulphonate **3** (25 g) and sodium iodide (25 g) in hexamethylphosphoric triamide (75 ml) was stirred at 80° (bath) for 48–72 h. T.l.c. (benzene–ethyl acetate, 8:1) then showed one major component together with a trace of a slightly slower-moving compound. The viscous mixture was diluted first with ~20 ml of ethanol and then with cold water. The precipitate was filtered off and, without drying, partitioned between dichloromethane and water. The dried ($MgSO_4$) dichloromethane extract was percolated through a short column of silica gel which was then washed with dichloromethane. The eluate was evaporated to a syrup which crystallised from ethanol to give **4** (44.5 g, 93%); after two further recrystallisations, **4** had m.p. 123–124°, $[\alpha]_D$ +155° (*c* 0.6, chloroform) (Found: C, 54.45; H, 3.55; I, 20.95. $C_{54}H_{44}I_2O_{15}$ calc.: C, 54.65; H, 3.71; I, 21.4%).

4-Deoxy-α-D-xylo-hexopyranosyl 4-deoxy-α-D-xylo-hexopyranoside (**6**). — A mixture of the di-iodide **4** (4.7 g), Raney nickel (~7.0 g), barium carbonate (4.7 g), and ethanol (140 ml) was stirred and heated under reflux. Hydrazine hydrate (7.5 ml) was added dropwise during 30 min, and boiling was continued for a further 30 min when t.l.c. (benzene–ethyl acetate, 8:1) showed only one compound. The mixture was filtered through a bed of silica gel, and evaporation gave syrupy **5** (3.2 g, 85%), $[\alpha]_D$ +120.3° (*c* 0.3, chloroform).

A solution of **5** (3.0 g) in dichloromethane (20 ml) and methanol (20 ml) was treated with M sodium methoxide (10 ml) at room temperature for 2 h. The mixture was deionised with Biodeminrolit mixed-bed resin (CO_3^{2-} form) and concentrated to a syrup that crystallised from ethanol to give **6** (0.8 g, 80%), m.p. 185.5–187°, $[\alpha]_D$ +263.3° (*c* 0.4, water) (Found: C, 46.3; H, 7.2. $C_{12}H_{22}O_9$ calc.: C, 46.4; H, 7.15%).

The hexa-acetate **7**, prepared in the usual way (88%), had m.p. 131–132.5° (from ethanol), $[\alpha]_D$ +174.2° (*c* 0.5, chloroform). (Found: C, 50.75; H, 6.2. $C_{24}H_{34}O_{15}$ calc.: 51.25; H, 6.1%).

4,6-Dichloro-4,6-dideoxy-α-D-galactopyranosyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside (**9**). — Anhydrous α,α-trehalose (50 g, prepared from the commercially available dihydrate by drying at 70° *in vacuo* for several hours) was partially

dissolved in dry pyridine (200 ml), and chloroform (500 ml, dried over Na_2SO_4) was added; precipitation of some of the trehalose occurred. The mixture was vigorously stirred and cooled in acetone–solid carbon dioxide (~ −70°). Redistilled sulphuryl chloride (130 ml) was then added drop-wise during 45 min. The heterogeneous mixture was vigorously stirred in the freezing mixture for a further 2–3 h and then allowed to attain room temperature. A white, insoluble material was filtered off and thoroughly washed with chloroform. The combined filtrate and washings were then washed successively with 10% sulphuric acid, saturated, aqueous sodium hydrogen carbonate, and distilled water, and dried (Na_2SO_4). Evaporation afforded a crystalline solid (77%), m.p. 197–199° (softening from 170°). Further recrystallisations from ethanol did not improve the melting point. T.l.c. showed one major component and a trace of a slightly slower-moving compound. This is probably a mixture of the 2,2′,3,3′-tetrakis(chlorosulphate) **8** and 2,3:2′,3′-disulphate.

Without further purification, the product (25 g) was dissolved in hot methanol (375 ml), and the solution was cooled to room temperature. Barium carbonate (20 g) was added followed, slowly, by a solution of sodium iodide (12.5 g) in aqueous methanol (1:1, 75 ml). When effervescence ceased (~30 min), the mixture was treated with a few drops of 10% aqueous sodium thiocyanate to remove any remaining iodine, and then deionised with Biodeminrolit mixed-bed resin (CO_3^{2-} form). The solution was filtered and concentrated to dryness, and the residue was recrystallised from acetone–water to give **9** (10.3 g, 94%), m.p. 229–230°, $[\alpha]_D$ +325° (*c* 0.4, pyridine) (Found: C, 34.3; H, 4.5; Cl, 34.0. $C_{12}H_{18}Cl_4O_7$ calc.: C, 34.6; H, 4.35; Cl, 34.15%).

The tetra-acetate **10**, prepared in the usual way (90%), had m.p. 226–228° (from ethanol), $[\alpha]_D$ +213.4° (*c* 0.4, chloroform) (Found: C, 40.45; H, 4.6; Cl, 23.3. $C_{20}H_{26}Cl_4O_{11}$ calc.: C, 41.1; H, 4.5; Cl, 24.3%).

The tetrabenzoate **11**, prepared in the usual way (93%), had m.p. 174–176° (from ethanol), $[\alpha]_D$ +280.7° (*c* 0.6, chloroform) (Found: C, 58.0; H, 4.0; Cl, 17.1. $C_{40}H_{34}Cl_4O_{11}$ calc.: C, 57.7; H, 4.1; Cl, 17.1%).

*6-Chloro-4,6-dideoxy-α-*D-xylo-*hexopyranosyl 6-chloro-4,6-dideoxy-α-*D-xylo-*hexopyranoside* (**12**). — (*a*) To a solution of tetrachloride **9** (5 g) in ethanol (150 ml) was added Raney nickel (~7.5 g) and barium carbonate (5 g). The mixture was stirred and boiled under reflux, and hydrazine hydrate (10 ml) was added drop-wise during 30 min. The mixture was stirred under reflux for a further 30 min, after which the solution was filtered through Kieselguhr and evaporated to a syrup. The 6,6′-dichloride **12** crystallised from ethanol as fine needles (3 g, 90%), m.p. 97–100° (loss of solvent of crystallisation) and 105–107°, $[\alpha]_D$ +170.2° (*c* 0.4, ethanol) (Found: C, 42.5; H, 6.45; Cl, 17.9. $C_{12}H_{20}Cl_2O_7 \cdot C_2H_6O$ calc.: C, 42.75; H, 6.6; Cl, 18.1%).

(*b*) 4,4′-Dideoxy-α,α-trehalose (**6**, 1 g) was treated with sulphuryl chloride (2.6 ml), as described for **1**. Crystallisation of the product from ethanol yielded the 2,2′,3,3′-tetrakis(chlorosulphate) **15** (13 g, 65%), m.p. 180.5–182°, $[\alpha]_D$ +80.7° (*c* 0.3, methanol) (Found: C, 20.05; H, 2.25; Cl, 29.1; S, 17.7. $C_{12}H_{16}Cl_6O_{15}S_4$ calc.: C, 19.45; H, 2.15; Cl, 28.75; S, 17.25%).

Dechlorosulphation was carried out as described above, using sodium iodide in aqueous methanol (1:1) in the presence of barium carbonate, giving a sample identical with that obtained in (*a*).

The tetraacetate **13**, prepared in the usual way (85%), had m.p. 173–175° (from ethanol), $[\alpha]_D$ +187° (*c* 0.5, chloroform) (Found: C, 46.9; H, 5.5; Cl, 13.5. $C_{20}H_{28}Cl_2O_{11}$ calc.: H, 46.6; H, 5.5; Cl, 13.8%).

4,4'-Dideoxy-α,α-trehalose (**6**). — The 6,6'-dichloro-tetra-acetate **13** (2.5 g) was stirred with sodium acetate (2.5 g) in hexamethylphosphoric triamide (25 ml) at 80° for 5 h. Treatment of the mixture with water gave a white precipitate which was filtered off, washed well with water, dried, and recrystallised from ethanol to give the hexa-acetate **7** (1.5 g, 70%), m.p. 130–132°, $[\alpha]_D$ +174° (*c* 0.3, chloroform), identical with that obtained previously.

To a solution of **7** (1 g) in methanol (20 ml) was added methanolic sodium methoxide (0.1M, 5 ml). After 2 h at room temperature, the solution was deionised with Biodeminrolit mixed-bed resin (CO_3^{2-} form) and concentrated, and the resulting syrup was partitioned between water and light petroleum. The aqueous layer was concentrated to a syrup which crystallised from ethanol to give **6** (0.4 g, 74%), m.p. 186–188°, $[\alpha]_D$ +262° (*c* 0.3, water), identical with that obtained previously.

4-Chloro-4,6-dideoxy-α-D-galactopyranosyl 4-chloro-4,6-dideoxy-α-D-galactopyranoside (**16**). — 6,6'-Dideoxy-α,α-trehalose (1 g) was treated with sulphuryl chloride (2.6 ml) as described for **1**. Crystallisation of the product from ethanol gave the 2,2',3,3'-tetrakis(chlorosulphate) **14** (1.4 g, 72%), m.p. 193–195°, $[\alpha]_D$ +165° (*c* 0.4, methanol) (Found: C, 19.3; H, 2.05; Cl, 28.8; S, 17.15. $C_{12}H_{16}Cl_6O_{15}S_4$ calc.: C, 19.45; H, 2.15; Cl, 28.75; S, 17.25%).

Dechlorosulphation in the usual way, using sodium iodide in aqueous methanol (1:1), gave **16** (82%), m.p. 113–115° (from ethanol), $[\alpha]_D$ +228° (*c* 0.9, water) (Found: C, 41.15; H, 6.05; Cl, 20.8. $C_{12}H_{20}Cl_2O_7$ calc.: C, 41.5; H, 5.75; Cl, 20.5%).

2,3-Di-O-benzoyl-6-deoxy-4-O-mesyl-6-thiocyanato-α-D-glucopyranosyl 2,3-di-O-benzoyl-6-deoxy-4-O-mesyl-6-thiocyanato-α-D-glucopyranoside (**21**). — The 4,4',6,6'-tetramethanesulphonate **2** (1.1 g) was heated with potassium thiocyanate (4.2 g) in *N,N*-dimethylformamide (15 ml) for 4–6 h. T.l.c. (benzene–ethyl acetate, 15:1) showed that only one product (faster than the starting material) was formed. The precipitated potassium methanesulphonate was filtered off and washed with acetone. The combined filtrate and washings were treated with water, and the precipitated product was filtered off and recrystallised thrice from methanol to give **21** (0.64 g, 63%), m.p. 188–189°, $[\alpha]_D$ +203° (*c* 0.4, chloroform) (Found: C, 53.15; H, 3.9; N, 2.45; S, 12.95. $C_{44}H_{40}N_2O_{17}S_4$ calc.: C, 53.0; H, 4.0; N, 2.85; S, 12.85%).

2,3-Di-O-benzoyl-4,6-dideoxy-4,6-dithiocyanato-α-D-galactopyranosyl 2,3-di-O-benzoyl-4,6-dideoxy-4,6-dithiocyanato-α-D-galactopyranoside (**19**). — The 4,4',6,6'-tetramethanesulphonate **2** (3 g) was heated with potassium thiocyanate (10 g) in hexamethylphosphoric triamide (20 ml) for 48 h at 80°. The thick syrup was cooled to room temperature and then diluted with chloroform (30 ml), and the inorganic material was removed by filtration and washed with chloroform and ethanol. The

filtrate and washings were combined and concentrated to give a black paste which was partitioned between water (50 ml) and chloroform (50 ml), and the organic layer was washed with water (2 × 50 ml), dried (Na_2SO_4), decolourised (charcoal), and concentrated to a syrup. Crystallisation from ethanol gave the dithiocyanate **21** (0.99 g, 36%).

The mother liquor was concentrated, and the syrupy residue was eluted from a column of silica gel with benzene–ethyl acetate (8:1); 10-ml fractions were collected. Fractions 5–9 contained a mixture of two compounds (70 mg), and syrupy 4,4',6,6'-tetrathiocyanate **19** (140 mg, 5%) was eluted in fractions 11–15 (Found: C, 57.1; H, 3.5; N, 6.1; S, 13.55. $C_{44}H_{34}N_4O_{11}S_4$ calc.: C, 57.25; H, 3.7; N, 6.05; S, 13.9%).

A further 110 mg (9%) of compound **21** was present in fractions 17–22.

2,3-Di-O-benzoyl-6-deoxy-4-O-mesyl-α-D-glucopyranosyl 2,3-di-O-benzoyl-6-deoxy-4-O-mesyl-α-D-glucopyranoside (**22**). — A solution of the 6,6'-dithiocyanate **21** (0.7 g) in ethanol (150 ml) was boiled under reflux with Raney nickel (~7 g) for 2 h; t.l.c. (benzene–ethyl acetate, 15:1) then showed that the reaction was complete. Removal of the catalyst (by filtration through Kieselguhr) and solvent gave a syrup which crystallised in the presence of ethanol. Three recrystallisations gave **22** (0.15 g, 25%), m.p. 228–231°, $[\alpha]_D$ +237° (*c* 0.8, chloroform) (Found: C, 57.55; H, 4.75; S, 7.1. $C_{42}H_{42}O_{17}S_2$ calc.: C, 57.1; H, 4.8; S, 7.25%).

4,6-Dideoxy-α-D-xylo-hexopyranosyl 4,6-dideoxy-α-D-xylo-hexopyranoside (**17**). — (*a*) Six to ten successive reductions (using hydrazine hydrate–Raney nickel), as described above, of the 6,6'-dichloride **12** or the 4,4',6,6'-tetrachloride **9** gave **17** (60–70% yield), m.p. 179–182° (from ethanol), $[\alpha]_D$ +200.5° (*c* 0.5, ethanol) (Found: C, 51.85; H, 8.1. $C_{12}H_{22}O_7$ calc.: C, 51.8; H, 7.95%).

(*b*) Hydrogenation of 4,4'-dichloro-4,4',6,6'-tetradeoxytrehalose (**16**) (as described above) proceeded with greater ease, giving **17** (67% yield) identical with that obtained in (*a*).

(*c*) To a solution of the 4,4',6,6'-tetrathiocyanate **19** (0.5 g) in ethanol (25 ml) was added 0.1M methanolic methoxide (5 ml). After 3 h at room temperature, the solution was passed through a short column of silica gel (20 g), which was then washed with dichloromethane–methanol (2:1). The eluate was concentrated to dryness and the thin, oily liquid was washed several times with light petroleum. A solution of the resulting syrup in ethanol (20 ml) was boiled under reflux with a suspension of Raney nickel (~5 g) for 3 h. Removal of the catalyst, concentration of the solution, and recrystallisation of the product gave **17** (30 mg, 20%) identical with that obtained above.

The tetra-acetate **18**, prepared in the usual way (87%), had m.p. 165–167° (from ethanol), $[\alpha]_D$ +185.4° (*c* 0.5, chloroform) (Found: C, 53.35; H, 6.5. $C_{20}H_{30}O_{11}$ calc.: C, 53.8; H, 6.7%).

3,6-Anhydro-4-chloro-4-deoxy-α-D-galactopyranosyl 3,6-anhydro-4-chloro-4-deoxy-α-D-galactopyranoside (**26**). — To a solution of **9** (5 g) in methanol (75 ml) was added methanolic M sodium methoxide (15 ml). The solution was heated under reflux for 2 h; t.l.c. then showed that all the starting material had been consumed and two

faster-moving compounds (in nearly equal proportions) were formed. The reaction mixture was heated for a further 2 h, cooled, and neutralised with Biodeminrolit mixed-bed resin (CO_3^{2-} form). The product crystallised out on filtering the solution, and two recrystallisations gave **26** (2.7 g, 65%), m.p. 220–222° (dec.), $[\alpha]_D$ +30.8° (*c* 0.2, ethanol) (Found: C, 42.2; H, 4.85; Cl, 20.55. $C_{12}H_{16}Cl_2O_7$ calc.: C, 42.0; H, 4.65; Cl, 20.7%).

The compound turned black after storage for 3–4 weeks at room temperature. Dissolution of this solid in ethanol left a black sediment. T.l.c. showed only the presence of the dianhydride in solution. Colourless crystals of the dianhydride **26** were obtained on recrystallisation.

The diacetate **28**, prepared in the usual way (95%), had m.p. 234–236° (dec.) (from ethanol), $[\alpha]_D$ +97.5° (*c* 0.4, chloroform) (Found: C, 45.6; H, 5.25; Cl, 16.55. $C_{16}H_{20}Cl_2O_9$ calc.: C, 45.0; H, 4.7; Cl, 16.6%).

The dibenzoate **27**, prepared in the usual way (benzoyl chloride–pyridine) (82%), had m.p. 238–239° (from ethanol), $[\alpha]_D$ −18.5° (*c* 0.4, chloroform) (Found: C, 56.9; H, 4.5; Cl, 13.15. $C_{26}H_{24}Cl_2O_9$ calc.: C, 56.6; H, 4.35; Cl, 12.9%).

*3,6-Anhydro-4-chloro-4-deoxy-α-*D*-galactopyranosyl 4,6-dichloro-4,6-dideoxy-α-*D*-galactopyranoside* (**31**). — To a solution of **9** (2.5 g) in methanol (35 ml) was added methanolic M sodium methoxide (7.5 ml). The solution was heated under reflux for 2 h, deionised with Biodeminrolit mixed-bed resin (CO_3^{2-} form), and concentrated to dryness. The resulting, crystalline residue was washed several times with ethanol and recrystallised from ethanol to give the dianhydride **26** (0.88 g, 40%) identical with that obtained above. The filtrate and washings were combined and concentrated to a syrup that was chromatographed on a charcoal–Celite (1:1) column (2.5 × 45 cm). Elution with 75% aqueous ethanol gave **31** as a white solid (0.98 g, 43%), m.p. 102–105°, $[\alpha]_D$ +133° (*c* 0.2, ethanol) (Found: C, 38.05; H, 4.75; Cl, 28.05. $C_{12}H_{17}Cl_3O_7$ calc.: C, 37.95; H, 4.5; Cl, 28.05%).

The triacetate **32**, prepared in the usual way (85%), had m.p. 170–172° (from ethanol), $[\alpha]_D$ +195° (*c* 0.37, chloroform) (Found: C, 43.3; H, 4.5; Cl, 21.2. $C_{18}H_{23}Cl_3O_{10}$ calc.: C, 42.75; H, 4.55; Cl, 21.1%).

*3,6-Anhydro-4-deoxy-α-*D*-xylo-hexopyranosyl 3,6-anhydro-4-deoxy-α-*D*-xylo-hexopyranoside* (**29**). — Six successive hydrogenations of the dichloro-dianhydride **26** (2 g), using hydrazine hydrate–Raney nickel as described above, followed by crystallisation of the product from acetone, gave **29** (1.1 g, 69%), m.p. 189–195° (dec.), $[\alpha]_D$ +154° (*c* 0.26, ethanol); the m.p. was not improved by further recrystallisations from ethanol (Found: C, 52.9; H, 6.6. $C_{12}H_{18}O_7$ calc.: C, 52.55; H, 6.55%).

The diacetate **30**, prepared in the usual way (87%), had m.p. 190–192° (from ethanol), $[\alpha]_D$ +98.5° (*c* 0.3, chloroform) (Found: C, 53.4; H, 6.3. $C_{16}H_{22}O_9$ calc.: C, 53.65; H, 6.15%).

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