Chemical Modification of Trehalose. Part XIII.[1] Synthesis of Some 4,4'-Difluoro- and 4,4',6,6'-Tetrafluoro-analogues

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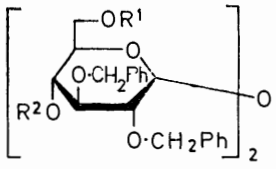
Suitably protected 4,4'-disulphonates and 4,4',6,6'-tetrasulphonates of trehalose and *galacto*-trehalose have been subjected to fluoride displacement reactions with tetra-n-butylammonium fluoride in acetonitrile. In the cases of the trehalose sulphonates the reactions proceeded with configurational inversion at C-4 to give the appropriate di- and tetra-fluoro-*galacto*-trehalose derivatives in moderate yields from which the protecting groups were subsequently removed. On the other hand, the *galacto*-trehalose sulphonates underwent extensive elimination and in consequence the required di- and tetra-fluorotrehaloses were only obtained in poor yields.

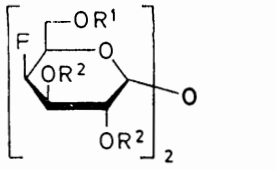
THE interest in fluoro-derivatives of trehalose as potential enzyme inhibitors *etc.* has been outlined previously in our paper on 6,6'-dideoxy-6,6'-difluorotrehalose and its *galacto*-analogue.[2] These studies have now been extended to the synthesis of 4,4'-difluoro- and 4,4',6,6'-tetrafluoro-derivatives of trehalose and its *galacto*-analogue, from the same starting material, namely 2,2',3,3'-tetra-*O*-benzyltrehalose (1).[2] The 6- and 6'-positions of (1) were protected by tritylation and, without isolation, the ditritylate was mesylated to give the 4,4'-dimesyl-6,6'-ditritylate (2) in 25% overall yield. Reaction of the latter (2) with tetra-n-butylammonium fluoride in acetonitrile [3] afforded a mixture of products, presumably because of competing elimination reactions. Nevertheless the required 4,4'-difluoro-derivative (4) was isolated by chromatography on silica gel in 21% yield. Detritylation with methanolic hydrogen chloride gave a syrupy diol, which was then debenzylated by catalytic hydrogenolysis under acid conditions. The resulting disaccharide (5) was obtained crystalline in 71% yield from (4) and further characterised as its hexa-*O*-acetate (6). An analogous synthesis of 4-deoxy-4-fluoro-D-galactose has been reported.[4]

The structures of the products (4) and (6) were confirmed by their ^1H and ^{19}F n.m.r. spectra (Tables 1 and 2). In each case the H-4,H-4' resonance was observed as a wide doublet of doublets in which $J_{4\text{-F},4\text{-H}}$ was about 50 Hz and $J_{3\text{-H},4\text{-H}}$ about 3 Hz. The coupling between H-4 and H-5, always small in galactosides (1—2 Hz),[5] was not clearly resolved but was estimated to be about 1 Hz. The ^{19}F n.m.r. spectrum was observed as a doublet of triplets in which the values of $J_{4\text{-F},3\text{-H}}$ and $J_{4\text{-F},5\text{-H}}$ (29 Hz) were consistent with an antiperiplanar relationship between the fluorine and the two vicinal hydrogen atoms.[4]

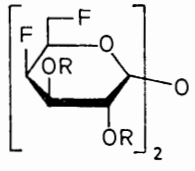
Past experience with the mass spectrometry of trehalose derivatives [2,6] has shown that the major fragmentation pathway involves the cleavage of the C(1)—O(1) bonds (A-series) [7] to give the two oxycarbonium ions (identical in symmetrical derivatives) which then undergo stepwise elimination of substituents at C-3 and C-4. The mass spectrum of compound (6) showed an intense peak at *m/e* 291 which underwent



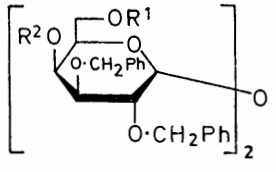
(1) $R^1 = R^2 = H$
(2) $R^1 = CPh_3, R^2 = MeSO_2$
(3) $R^1 = R^2 = MeSO_2$



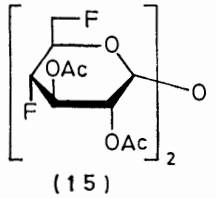
(4) $R^1 = CPh_3, R^2 = CH_2Ph$
(5) $R^1 = R^2 = H$
(6) $R^1 = R^2 = Ac$



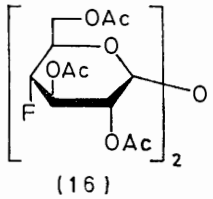
(7) R = CH_2Ph
(8) R = $CH_2 \cdot C_6H_{11}$
(9) R = H
(10) R = Ac



(11) $R^1 = R^2 = Bz$
(12) $R^1 = R^2 = H$
(13) $R^1 = R^2 = MeSO_2$
(14) $R^1 = CPh_3, R^2 = MeSO_2$



(15)



(16)

successive loss of acetic acid (*m/e* 231), keten (*m/e* 189), and hydrogen fluoride (*m/e* 169) as outlined in the Scheme. This fragmentation pattern was also observed in the mass spectrum of methyl 4-deoxy-4-fluoro-α-D-galactopyranoside triacetate [4] and the corresponding glucopyranoside.[8,9]

[1] Part XII, L. Hough, P. A. Munroe, A. C. Richardson, Y. Ali, and S. T. K. Bukhari, *J.C.S. Perkin I*, 1973, 287.
[2] L. Hough, A. K. Palmer, and A. C. Richardson, *J.C.S. Perkin I*, 1972, 2513.
[3] H. B. Henbest and W. R. Jackson, *J. Chem. Soc.*, 1962, 954.
[4] D. M. Marcus and J. H. Westwood, *Carbohydrate Res.*, 1971, **17**, 269.
[5] M. W. Horner, L. Hough, and A. C. Richardson, *J. Chem. Soc.* (*C*), 1970, 1336; G. Birch and A. C. Richardson, *ibid.*, p. 749; Y. Ali, L. Hough, and A. C. Richardson, *Carbohydrate Res.*, 1970, **14**, 181.
[6] A. C. Richardson, unpublished results.
[7] N. K. Kochetkov and O. S. Chizhov, *Adv. Carbohydrate Chem.*, 1966, **21**, 39.
[8] O. S. Chizhov, V. I. Kadentsev, B. M. Zolotarev, A. B. Foster, M. Jarman, and J. H. Westwood, *Org. Mass. Spectrometry*, 1971, **5**, 437.
[9] A. B. Foster, R. Hems, and J. H. Westwood, *Carbohydrate Res.*, 1970, **15**, 41.

TABLE 1

^{1}H N.m.r. parameters: first-order chemical shifts (τ values) and proton–proton coupling constants at 100 MHz; for proton–fluorine coupling constants see Table 2

Compd.	(2) [a,b]	(4) [a,b]	(4) [b,c]	(6) [d]	(8) [a]	(8) [e]	(9) [a]	(11) [b,e]	(13) [b,c]	(14) [b,e]	(15) [d]	(16) [e]
H-1	4·52(d)	4·67(d)	4·25(d)	4·75(d)	4·80(d)	4·24(d)	4·52(d)	4·33(d)	4·56(d)	4·00(d)	4·72(t)	4·62(t)
H-2	6·26(dd)	*ca.* 6·1	6·5—	4·3—				5·72(dd)	6·03(dd)	5·75(d)	5·06(dd)	4·91(dd)
H-3	5·96(t)	(cm) *	6·8 (cm) *	4·8 (cm) *				5·54(dd)	5·79(dd)	5·48(dd)	4·42(dt)	4·19(dt)
H-4		5·25(dd)	4·75(dd)	4·95(dd)	5·10(dd)	4·77(dd)	5·05(dd)	3·85(dd)	4·64(d)	4·33(d)	5·39(dt)	5·43(dt)
H-5	5·76(cm)*	5·66(dt)	5·30(dt)	5·60(dt)								
H-6a	6·90(dd)	6·74 (cm)*	6·46(dd)					5·3—5·5 (cm)*	5·65(dd)	6·12(dd)	5·4(dd)	5·6—5·8 (cm) *
H-6b	6·67(d)		6·31 (cm) *	5·75 (cm)*					5·48(dd)	6·43(dd)		
$J_{1,2}$	3·5	*ca.* 3	*ca.* 3	*ca.* 3	*ca.* 3	3	3	3·0	3·5	3·0	3·7	3·5
$J_{2,3}$	9·7							10·0	10·0	*ca.* 10	10·2	10·0
$J_{3,4}$	9·5	*ca.* 3	*ca.* 2·5	*ca.* 2	*ca.* 2	*ca.* 2	*ca.* 2	2·8	3·0	*ca.* 2	10·0	8·7
$J_{4,5}$	9·0	*ca.* 1	*ca.* 1	*ca.* 1	*ca.* 1	*ca.* 1	*ca.* 1	1·5	*ca.* 1	*ca.* 1	or 8·5	*ca.* 9
$J_{5,6a}$	4·5		6·5	*ca.* 7·5			5·7		5·5	5·5	3·0	
$J_{5,6b}$	*ca.* 2			*ca.* 7·5			5·7		6·2	6·7		
$J_{6a,6b}$	10·0		10·5						9·7	9·5		

[a] [^{2}H]Chloroform. [b] Benzylic protons in the region τ 5·1—5·3. [c] [$^2H_5$]Pyridine at *ca.* 100°. [d] [$^2H_6$]Acetone. [e] [$^2H_5$]Pyridine at ambient temperature.

* Complex multiplet.

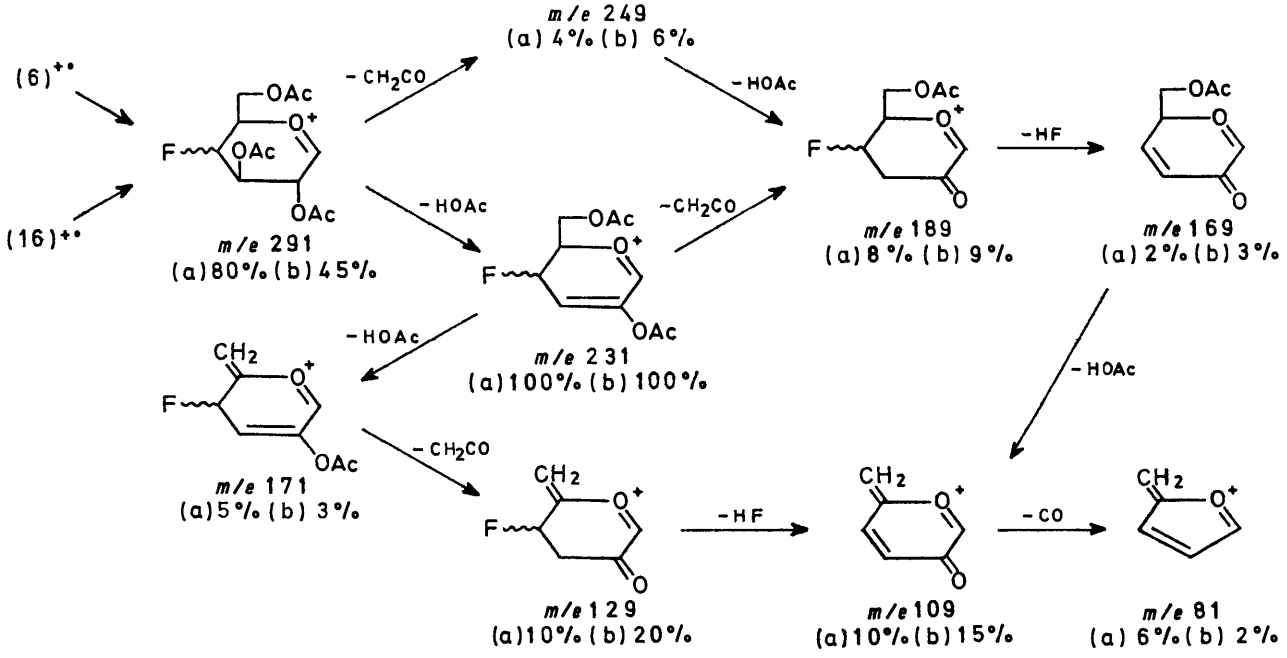
TABLE 2

^{19}F N.m.r. parameters: coupling constants (Hz) and chemical shifts (p.p.m. upfield from hexafluorobenzene unless otherwise stated); coupling constants in parentheses are values derived from the ^{1}H n.m.r. spectrum

Compound	(4) [a,b]	(6) [c,d]	(8) [a,b]	(8) [c,d]	(9) [a,d]	(10) [c,d]	(15) [c,d]	(16) [a,e]
F-4,F-4′	54·0(dt)	53·1(dt)	53·7(dt)	55·8(dt)	139·9 *	54·8	34·3(dd)	
$J_{F\text{-}4,H\text{-}4}$	49 (*ca.* 50)	51 (*ca.* 50)	50 (*ca.* 50)	48 (*ca.* 50)	50 (*ca.* 51)	51	52 (*ca.* 50)	(*ca.* 50)
$J_{F\text{-}4,H\text{-}3}$	30 (*ca.* 30)	29	28	28	32	30	15 (15)	(*ca.* 14)
$J_{F\text{-}4,H\text{-}5}$	30 (*ca.* 30)	29 (*ca.* 26)	28	28	32	30	<5	
$J_{F\text{-}4,H\text{-}1}$	(0)	(0)					(3·8)	(4·0)
F-6,F-6′			67·5(td)	+67·8 (cm) †	151(td) *	66·6	70·6(td)	
$J_{F\text{-}6,H\text{-}6}$			48		47 (46·5)	48	47·5 (*ca.* 45)	
$J_{F\text{-}6,H\text{-}5}$			13		15	14	25	

* Upfield from external trifluoroacetic acid. † Complex multiplet.

[a] In pyridine. [b] At 56 MHz. [c] In acetone. [d] At 94 MHz. [e] ^{19}F N.m.r. spectrum not determined.



SCHEME Major fragmentation pathways of (6) and (16) giving the relative percentage abundances [(a) refers to that from the *galacto*-isomer (6) and (b) to that from the *gluco*-isomer (16) relative to *m/e* 231] *

* The base peak for each spectrum was *m/e* 43 (CH_3CO^+) (*ca.* 140% relative to *m/e* 231).

When 2,2',3,3'-tetra-*O*-benzyl-αα-trehalose tetramesylate [2] (3) was heated with tetrabutylammonium fluoride in acetonitrile for 5 days it was converted into the syrupy tetrafluoro-derivative (7), which was isolated in 62% yield. Hydrogenolysis over palladium–charcoal under acidic conditions then gave the tetrafluoro-disaccharide (9) as a crystalline propan-2-ol solvate. It was also converted into a crystalline tetra-acetate (10). The presence of acid seemed to be essential for hydrogenolysis, since under neutral conditions the reaction was sluggish and incomplete. Early difficulties with this deblocking procedure prompted us to try hydrogenolysis over Adams catalyst. A highly crystalline product was obtained in 64% yield which was shown to be the tetra-*O*-cyclohexylmethyl ether (8) which resulted from the reduction of the aromatic rings of the benzyl groups. Predictably, the presence of so many fluorine atoms in the same molecule resulted in very complex ^{1}H n.m.r. spectra for compounds (8)—(10) such that in the case of the tetra-acetate (10) no certain assignments could be made. However the H-4,H-4' resonance could be discerned in the spectra of (8) and (9) as a wide doublet of doublets similar to that described for the 4,4'-difluoro-derivatives (4) and (6). Furthermore, the spectrum of the parent tetrafluoro-disaccharide (9) revealed the H-6,H-6' resonance as a double doublet (J 47 and 5·7 Hz) indicative of fluorine at the 6- and 6'-positions. The ^{19}F n.m.r. spectra of compounds (8)—(10) all showed two resonances separated by about 11—14 p.p.m. (Table 2). The F-6,F-6' resonance appeared as a triplet of doublets with J values (*ca.* 48 and 14 Hz) similar to those reported for 6-deoxy-6-fluoro-D-galactose derivatives.[2,10,11] The resonance due to F-4,F-4' appeared to lower field as two overlapping triplets. The couplings between the 4-fluorine atom and the 3- and 5-protons were similar (*ca.* 30 Hz), indicative of antiperiplanar relationships between the fluorine atom and the vicinal protons. In the ^{19}F n.m.r. spectrum of (10), broad-band decoupling of the protons caused the two resonances to collapse into singlets, indicating the absence of significant ^{19}F–^{19}F coupling.

Synthesis of 4,4'-difluoro- and 4,4',6,6'-tetrafluoro-trehalose necessitated starting from the appropriate sulphonate esters of *galacto*-trehalose derivatives. The required derivatives were prepared from the 4,4',6,6'-tetramesylate (3), which underwent S_N2 displacement of all four sulphonate groups on treatment with sodium benzoate in hexamethylphosphoric triamide to give the tetrabenzoate (11). De-*O*-benzoylation with sodium methoxide afforded syrupy 2,2',3,3'-tetra-*O*-benzyl-*galacto*-αα-trehalose (12), which was converted into the tetramesylate (13) in 47% overall yield from (3) and, by sequential tritylation and mesylation, into the 4,4'-dimesyl-6,6'-ditritylate (14) obtained in 29% overall yield from (3). The ^{1}H n.m.r. spectra of (11), (13), and (14) were all in accord with the assigned structures (Table 1); in particular the low-field narrow double doublets, a characteristic feature of H-4 of galactopyranosides,[2,5] were clearly visible.

Treatment of each of the two sulphonate esters, (13) and (14), with tetrabutylammonium fluoride in boiling acetonitrile resulted in both cases in a mixture of compounds which defied purification by column chromatography. However reductive hydrogenolysis under acidic conditions followed by acetylation and chromatographic fractionation afforded very low yields of 4,4',6,6'-tetradeoxy-4,4',6,6'-tetrafluoro-αα-trehalose tetra-acetate (15) and 4,4'-dideoxy-4,4'-difluoro-αα-trehalose hexa-acetate (16), respectively. The low yields were undoubtedly due to extensive elimination occurring during the fluoride displacement reaction, which would be expected to be more competitive in the *galacto*-series because of the antiperiplanar relationship between the 4-sulphonyloxy-groups and the two vicinal protons at the 3- and 5-positions. Indeed the i.r. spectrum of each reaction product prior to reduction showed a band at 1670 cm^{-1} indicative of unsaturation. Assuming that elimination was the only competing reaction and that the 4-sulphonate could give rise to both the 3- and 4-enes and the 6-sulphonate group to the 5-ene, then the total number of possible products which can arise from the tetrasulphonate (13) is *nineteen* and the total that can arise from the 4,4'-disulphonate (14) is *six*. As a result of these considerations it is hardly surprising that only low yields of the required fluoro-disaccharides could be isolated from these reactions. In the case of the 4,4'-disulphonate (14) a side product was isolated in poor yield which could not be identified. The mass spectrum of the side product contained fragments of *m/e* 291, 231, 189, 171, 169, 129, and 109 indicative of one of the hexose units being 4-deoxy-4-fluoro-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl (see Scheme).

The two fluorinated trehaloses (15) and (16) were characterised beyond doubt by their n.m.r. spectra. The ^{1}H n.m.r. spectrum of the 4,4'-difluoro-derivative (16) showed the H-1,H-1' resonance as a triplet at τ 4·62 due to coupling not only to the H-2's but also to the F-4's (*ca.* 3—4 Hz). Such a $^5J_{F,H}$ coupling is a characteristic feature of 4-deoxy-4-fluoro-α-D-glucopyranoses [9] and demonstrates the structure of our product unequivocally. In addition the H-2,H-2' resonance appeared as a double doublet at τ 4·91 with a further small coupling (*ca.* 1 Hz), presumably to the F-4's, of value similar to those observed in the 4-deoxy-4-fluoro-α-D-glucopyranose series.[9] The H-3,H-3' resonance was observed at τ 4·19 as a double triplet; the largest splitting (15 Hz) being the $^3J_{4\text{-}F,3\text{-}H}$ coupling, which suggested a synclinal relationship between F-4 and H-3. The ^{1}H n.m.r. spectrum of the 4,4',6,6'-tetrafluoro-derivative (15) was similar and was considerably simplified by decoupling of F-4,F-4' which collapsed the H-1,H-1' triplet into a doublet and simplified the H-3,H-3' multiplet into a triplet (see Table 1). The ^{19}F n.m.r. spectrum of (15) consisted of two resonances; a high-field triplet of doublets consistent with

[10] L. Evelyn and L. D. Hall, *Chem. and Ind.*, 1968, 1183.
[11] L. Phillips and V. Wray, *J. Chem. Soc.* (*B*), 1971, 1618.

F-6,F-6′ and a lower field doublet of doublets which was consistent with F-4,F-4′. The small value for the coupling $^3J_{4\text{-}F,5\text{-}H}$ which was too small to be resolved in the ^{19}F n.m.r. spectrum was consistent with an equatorial/axial orientation for F-4 and H-5. Broad-band decoupling of the protons caused the two ^{19}F resonances to collapse to two singlets, showing, as in the case of the *galacto*-analogue, the absence of significant interfluorine coupling.

The mass spectrum of (16) was similar to that of the *galacto*-analogue (6) inasmuch as the major fragmentation observed was as outlined in the Scheme.

EXPERIMENTAL

For general methods see ref. 2. Optical rotations were performed in chloroform unless otherwise stated.

2,3-*Di*-O-*benzyl*-4-O-*mesyl*-6-O-*trityl*-α-D-*glucopyranosyl* 2,3-*Di*-O-*benzyl*-4-O-*mesyl*-6-O-*trityl*-α-D-*glucopyranoside* (2).—2,2′,3,3′-Tetra-*O*-benzyl-αα-trehalose [2] (1) (10 g) was dissolved in pyridine (100 ml), chloro(triphenyl)methane (13·5 g) was added, and the mixture was heated at 70—75° for *ca.* 10 h. T.l.c. (benzene–methanol, 9 : 1) then indicated that the reaction was complete. The mixture was cooled, treated with methanesulphonyl chloride (30 ml), stored overnight at 0—5°, and then poured, with stirring, into ice–water. The precipitate was filtered off, washed well with water, and then dissolved in methylene chloride; the solution was dried ($MgSO_4$), decolourised with charcoal, and evaporated to dryness. The residue was co-distilled with toluene several times in an effort to free it from residual pyridine. Finally, recrystallisation from propan-2-ol afforded the 6,6′-*dityrityl*-4,4′-*dimesylate* (8·6 g, 45%), m.p. 109—112°, $[\alpha]_D$ +86° (*c* 1) (Found: C, 71·55; H, 6·2; S, 4·7. $C_{80}H_{78}O_{15}S_2$ requires C, 71·55; H, 5·8; S, 4·75%).

4,6-*Di*-O-*benzoyl*-2,3-*di*-O-*benzyl*-α-D-*galactopyranosyl* 4,6-*Di*-O-*benzoyl*-2,3-*di*-O-*benzyl*-α-D-*galactopyranoside* (11).—2,2′,3,3′-Tetra-*O*-benzyl-αα-trehalose tetramesylate [2] (3) (25 g) was dissolved in redistilled hexamethylphosphoric triamide (125 ml) and sodium benzoate (30 g) was added. The mixture was maintained at 100° for 48 h, then poured into water. The precipitate was filtered off, washed well with water, and dried. This product was difficult to crystallise but was suitable for the next stage without further purification. A sample crystallised from ethanol as an *alcoholate*, m.p. 94—96°, $[\alpha]_D$ +91·5° (*c* 1) (Found: C, 71·7; H, 5·9. $C_{68}H_{62}O_{15},C_2H_6O$ requires C, 72·1; H, 5·9%).

2,3-*Di*-O-*benzyl*-4-O-*mesyl*-6-O-*trityl*-α-D-*galactopyranosyl* 2,3-*Di*-O-*benzyl*-4-O-*mesyl*-6-O-*trityl*-α-D-*galactopyranoside* (14).—The crude tetrabenzoate (11) [from 25 g of (3)] was dissolved in a mixture of 0·05N-sodium methoxide (100 ml) and methylene chloride (100 ml) and kept at room temperature until t.l.c. (chloroform–methanol, 9 : 1) indicated that de-*O*-benzoylation was complete. In order to remove inorganic material the mixture was then passed through a column of silica gel (150 g) and eluted with methylene chloride–methanol (3 : 1). The eluate was evaporated to give the syrupy tetraol (12), which did not crystallise. The syrup was dissolved in pyridine and the solution evaporated to dryness in order to remove the last traces of water; [12] the residue was then dissolved in dry pyridine (80 ml) and chloro(triphenyl)methane (15 g) was added. The mixture was heated at 70° overnight and then, after cooling to 5°, treated with methanesulphonyl chloride (20 ml) and stored at room temperature for 18 h. Decomposition with water produced a gum which was extracted with methylene chloride in the usual way; the product was freed from residual triphenylmethanol by dry column chromatography on silica gel [light petroleum–ethyl acetate (10 : 1)]. The *dityrityl dimesylate* (9·3 g, 29%), crystallised from methylene chloride–ethanol, had m.p. 121—123°, $[\alpha]_D$ +66·5° (*c* 1) (Found: C, 70·9; H, 5·9. $C_{80}H_{78}O_{15}S_2$ requires C, 71·5; H, 5·8%).

2,3-*Di*-O-*benzyl*-4,6-*di*-O-*mesyl*-α-D-*galactopyranosyl* 2,3-*Di*-O-*benzyl*-4,6-*di*-O-*mesyl*-α-D-*galactopyranoside* (13).—The syrupy tetrabenzyl-*galacto*-trehalose (12) [from 20 g of (3)] [2] was dissolved in dry pyridine (100 ml), cooled to 0°, and treated with methanesulphonyl chloride (12 ml). The reaction was complete after 12 h (t.l.c. in benzene–ether, 2 : 1). The mixture was decomposed with ice–water and the precipitate filtered off. Recrystallisation from methylene chloride–cthanol gave the tetramesylate as a *monohydrate* (9·45 g, 47%), m.p. 167—169°, $[\alpha]_D$ +109° (*c* 1) (Found: C, 51·0; H, 5·5; S, 12·45. $C_{44}H_{54}O_{19}S_4,H_2O$ requires C, 51·15; H, 5·45; S, 12·4%), $\nu_{max.}$ 3500 and 1650 cm^{-1} (H_2O); the n.m.r. spectrum ([$^2H_5$]pyridine) also showed water absorption.

2,3-*Di*-O-*benzyl*-4-*deoxy*-4-*fluoro*-6-O-*trityl*-α-D-*galacto-pyranosyl* 2,3-*Di*-O-*benzyl*-4-*deoxy*-4-*fluoro*-6-O-*trityl*-α-D-*galactopyranoside* (4).—The 4,4′-dimesylate (2) (15·3 g) was thoroughly dried and added to a solution of anhydrous tetrabutylammonium fluoride [2] (70 g) in anhydrous acetonitrile (75 ml). The mixture was heated under reflux with constant stirring and protection from atmospheric moisture. The reaction was monitored by t.l.c. (light petroleum–diethyl ether, 4 : 6) and was judged to be complete after 6 days, when it contained several components. Silica gel was then added and the slurry was evaporated to a dry solid, which was then placed on a column of dry silica gel (600 g) and eluted with light petroleum–diethyl ether (8 : 1). The fastest-moving component, which crystallised in the tubes of the fraction collector, was the 4,4′-*difluoro-derivative* (2·83 g, 21%), m.p. 166—169° (from methylene chloride–light petroleum), $[\alpha]_D$ +57° (*c* 1) (Found: C, 78·6; H, 5·90; F, 3·1. $C_{74}H_{36}F_2O_9$ requires C, 78·6; H, 6·0; F, 3·2%).

4-*Deoxy*-4-*fluoro*-α-D-*galactopyranosyl* 4-*Deoxy*-4-*fluoro*-α-D-*galactopyranoside* (5).—The tetrabenzyl ether (4) (1·25 g), dissolved in a mixture of 1% ethanolic hydrogen chloride (50 ml) and chloroform (50 ml), was kept at room temperature for about 1 h; then, after neutralisation ($PbCO_3$), the solution was evaporated to a syrup. The syrup was freed from triphenylmethanol by dry column chromatography on silica gel [light petroleum–diethyl ether (4 : 1)].* The syrupy diol obtained was dissolved in ethanolic 1% hydrogen chloride (150 ml) and hydrogenated over palladium–charcoal at 40 lb in^{-2}. Evaporation, after removal of the catalyst, afforded the 4,4′-*difluoride* (from ethanol) (0·26 g, 71%), m.p. 125—128°, $[\alpha]_D$ +188° (*c* 0·5 in H_2O) (Found: C, 39·45; H, 6·1. $C_{12}H_{20}F_2O_8,H_2O$ requires C, 39·6; H, 6·05%), $\nu_{max.}$ 1620 cm^{-1} (H_2O).

The *hexa-acetate*, prepared (78%) with acetic anhydride–pyridine, had m.p. 139—141°, $[\alpha]_D$ +166° (*c* 1) (Found: C, 48·3; H, 5·8. $C_{24}H_{32}F_2O_{15}$ requires C, 48·15; H, 5·35%).

* It was preferable to remove the triphenylmethanol at this stage since the subsequent hydrogenation converted it into triphenylmethane which proved difficult to remove.

[12] G. Birch, *J. Chem. Soc.*, 1965, 3489.

4,6-Dideoxy-4,6-difluoro-α-D-galactopyranosyl 4,6-Dideoxy-4,6-difluoro-α-D-galactopyranoside (9).—The tetrabenzyl tetramesylate (3) (5 g) was thoroughly dried and added to anhydrous tetrabutylammonium fluoride (23·5 g) in dry acetonitrile (25 ml). The mixture was heated gently under reflux for 5 days, after which no further reaction was apparent (t.l.c. in benzene–ether, 20 : 1). The mixture was then partly concentrated, silica gel was added, and concentration was continued until a dry solid was obtained. This was placed on a column of dry silica gel (600 g) and eluted with benzene–ether (20 : 1). The first eluted component (2·15 g, 62%) was the tetrafluoro-derivative (7), but this did not crystallise and was carried through to the next stage without further characterisation.

A sample of the product (2 g) was hydrogenated over palladium–charcoal at 60 lb in^{-2} and under acidic conditions (HCl). The reaction appeared to be rather sluggish (t.l.c.) and consequently the catalyst was replaced by a fresh batch after 18 h. When the reaction was complete filtration and evaporation gave a foamy syrup. The product was crystallised with some difficulty and was obtained as an *alcoholate* (0·32 g, 21%), m.p. 94—96° (from propan-2-ol), $[\alpha]_D$ +187° (*c* 1 in H_2O) (Found: C, 44·0; H, 6·75; F, 18·55. $C_{12}H_{18}F_4O_7,C_3H_8O$ requires C, 43·9; H, 6·35; F, 18·55%), τ 8·92 (6H, d) and 6·00 (1H, septet) (Pr^iOH).

The *tetra-acetate*, prepared (94%) in the usual way, had m.p. 159—162° (from ethanol), $[\alpha]_D$ +200° (*c* 1) (Found: C, 46·5; H, 5·2. $C_{20}H_{26}F_4O_{11}$ requires C, 46·35; H, 5·0%).

2,3-Di-O-cyclohexylmethyl-4,6-dideoxy-4,6-difluoro-α-D-galactopyranosyl 2,3-Di-O-cyclohexylmethyl-4,6-dideoxy-4,6-difluoro-α-D-galactopyranoside (8).—The syrupy tetrabenzyltetrafluoro-disaccharide (7) (1 g) was dissolved in ethanol (100 ml) and hydrogenated at 60 lb in^{-2} over Adams catalyst for about 20 h. The reaction was incomplete (t.l.c. in ether–light petroleum, 1 : 4) so fresh catalyst (3 × 50 mg) was added at intervals while the hydrogenation was continued during 3 days. Filtration and concentration afforded a highly crystalline product. Recrystallisation from ethanol gave the *tetracyclohexylmethyl ether* (0·66 g, 64%), m.p. 144—146°, $[\alpha]_D$ +128° (*c* 1) (Found: C, 65·75; H, 8·9; F, 11·25. $C_{40}H_{66}F_4O_7$ requires C, 65·5; H, 9·0; F, 10·35%), τ 8·2 and 8·9 (44H, broad peaks, cyclohexyl protons) and 6·45 and 6·63 (ABq) (8H, $O{\cdot}CH_2$).

2,3,6-Tri-O-acetyl-4-deoxy-4-fluoro-α-D-glucopyranosyl 2,3,6-Tri-O-acetyl-4-deoxy-4-fluoro-α-D-glucopyranoside (16).—The *galacto*-4,4′-dimesylate (14) was dried thoroughly and added to a solution of tetrabutylammonium fluoride (46 g) in anhydrous acetonitrile (50 ml). The mixture was heated under reflux; it had turned black within 30 min and after 18 h all the starting material had disappeared (t.l.c. in ethyl acetate–light petroleum, 1 : 2). The mixture was then poured into water and the precipitate was filtered off. The product appeared to be a mixture of several components of similar mobility on t.l.c. in several solvent systems and attempts at a separation failed to give any pure component. The i.r. spectrum indicated unsaturation (1670 cm^{-1}). The mixture was then hydrogenated in ethanolic (1%) hydrogen chloride over palladium–charcoal at 50 lb in^{-2}. After removal of the catalyst and evaporation the residue was taken up in a little water and a little residual triphenylmethane was filtered off. The aqueous solution was then concentrated to dryness and the residual syrup was dissolved in pyridine (20 ml) and treated with acetic anhydride (7 ml). Next day the mixture was evaporated to dryness and co-distilled several times with toluene to remove the last traces of pyridine. Finally, silica gel was added to the toluene solution and the slurry was dried on a rotary evaporator. The solid was then applied to a dry column of silica gel (40 g) and eluted with ethyl acetate–light petroleum (1 : 2). The first eluted component (8 mg) was crystalline [m.p. 108—113° (from ethanol)] (Found: C, 47·7; H, 5·65%) but was not characterised owing to lack of material; τ (by spectral accumulation) 3·95 (d, *J* 7·5 Hz), 4·21 (t, *J* 9 Hz), 5·03 (t, *J* 9 Hz), 4·56 (t, *J* 8·5 Hz), 4·69 (t, *J* 7·5 Hz), and 5·4—6·0 (complex m). The large splitting in the (presumably) anomeric proton doublet resonance tended to suggest that this was not αα-linked disaccharide.

The second component (29 mg) was the required *4,4′-difluoro-derivative*, m.p. 95—97° (from ethanol–light petroleum), $[\alpha]_D$ +104° (*c* 0·25) (Found: C, 47·9; H, 5·3. $C_{24}H_{32}F_2O_{15}$ requires C, 48·15; H, 5·35%). No further pure fractions were obtained from the column.

2,3-Di-O-acetyl-4,6-dideoxy-4,6-difluoro-α-D-glucopyranosyl 2,3-Di-O-acetyl-4,6-dideoxy-4,6-difluoro-α-D-glucopyranoside (15).—The *galacto*-tetramesylate (13) (5·2 g) was dried thoroughly and added to a solution of anhydrous tetrabutylammonium fluoride (26 g) in anhydrous acetonitrile (25 ml). The mixture was heated under reflux for 96 h, then poured into water, and the product was isolated by extraction with chloroform (6 × 50 ml). T.l.c. (benzene–ether, 20 : 1) indicated that the product was a mixture of several components. A partial fractionation was achieved by chromatography on silica gel (100 g): a mixture of several fast-moving components was isolated, all with similar R_F values, $\nu_{max.}$ 1670 cm^{-1} (unsaturation). This mixture was hydrogenated over palladium–charcoal as previously described and the product was acetylated (acetic anhydride–pyridine). The last traces of pyridine were removed from the product by several co-distillations with toluene and the final toluene solution was then treated with a little silica gel. The mixture was evaporated to a dry solid in a rotary evaporator; the solid was then applied to a column of dry silica gel (40 g) and eluted with ether–light petroleum (1 : 1). Only the fastest moving component was isolated pure (16 mg); this was the *tetrafluoro-disaccharide*, m.p. 159—168° (some presoftening) (from ethanol), $[\alpha]_D$ +101° (*c* 0·12) (Found: C, 46·8; H, 5·3. $C_{20}H_{26}F_4O_{11}$ requires C, 46·4; H, 5·0%).

A second fraction was a mixture of several components of similar chromatographic mobility, which crystallised from ethanol (170 mg) and could not be further fractionated; $\nu_{max.}$ 1075 (C–F) and 1720 cm^{-1} (OAc).

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