Chemical Modification of Trehalose. Part XI.[1] 6,6'-Dideoxy-6,6'-difluoro-αα-trehalose and its *galacto*-Analogue

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2,2',3,3',-Tetra-*O*-benzyl-αα-trehalose (3) was converted into both the 4,4',6,6'-tetramesylate (4) and the 6,6'-ditosylate (5), which underwent displacement of their primary sulphonyloxy-groups by fluoride when treated with tetra-n-butylammonium fluoride in an aprotic dipolar solvent, to give the corresponding 6,6'-difluoro-derivatives. Removal of the protecting groups afforded 6,6'-dideoxy-6,6'-difluoro-αα-trehalose (8).

The 6,6'-difluoro-4,4'-dimesylate (6) derived from the tetramesylate (4) underwent nucleophilic displacement of the 4,4'-disulphonyloxy-groups with benzoate anion to give, after removal of the blocking groups, 6,6'-dideoxy-6,6'-difluoro-αα-*galacto*-trehalose (13).

THE presence of covalently bonded fluorine in biologically important compounds has often been observed to give rise to enhanced or modified biological properties.[2] As a result there has recently been much interest shown in the synthesis of fluorocarbohydrates, in which hydroxy-groups are replaced by fluorine atoms.[3,4] With the exception of the glucopyranosyl fluorides, only one fluoroglucose had been reported prior to 1964, namely 6-deoxy-6-fluoro-D-glucose.[5] However, all the monofluoroglucoses have now been prepared, mainly by Foster and his co-workers,[6] along with many other fluorocarbohydrates. Furthermore, a 4-fluoro-β-D-ribofuranosyl system has been identified in the nucleoside antibiotic nucleodin, but in this case the fluorine atom replaces the 4-proton rather than the hydroxy-group.[7]

The main interest in fluorocarbohydrates stems from the similarity between the hydroxyl-group and the fluorine atom. They are of comparable bulk and capable of acting as hydrogen bond acceptors, although, unlike the hydroxy-group, the fluorine atom is unable to donate a hydrogen bond. As a result, the replacement of a hydroxy-group by a fluorine atom in an enzyme substrate may cause the modified substrate to be strongly bound to the 'active site' of the enzyme without it being metabolised. Consequently fluoro-analogues of carbohydrates are potential competitive enzyme inhibitors.[4] For example, 6-deoxy-6-fluoro-D-glucose is a competitive inhibitor of the utilisation of D-glucose and D-fructose by yeast, functioning as a competitive inhibitor of glucose transport across membranes. Similar results have also been observed in mammalian tissue.[4]

Little is known about the structure, reactivity, and specificity of trehalases, a group of enzymes which are used by organisms for the release of D-glucose from trehalose. This group of enzymes obviously plays an important role in carbohydrate metabolism in species which utilise trehalose as a reserve carbohydrate, for example insects, bacteria, fungi, yeasts, *etc.* Hence a specific inhibitor of the enzyme could function as an insecticide, bacteriocide, or fungicide, *etc.* We have investigated the synthesis of fluoro-derivatives of trehalose, and we describe here some 6,6'-difluoro-analogues.

Initial attempts to introduce the fluoro-group at the 6- and 6'-positions of trehalose were of a speculative nature. Treatment of either 6,6'-ditosyl-αα-trehalose or its hexa-acetate with either potassium fluoride or potassium hydrogen fluoride in ethylene glycol afforded complex mixtures from which no pure products were isolated. This was not surprising since the strongly basic and weakly nucleophilic nature of the fluoride anion means that hydroxy- and acetoxy-groups successfully compete with the fluoride anion for the sulphonyloxy-groups, giving rise to 3,6-anhydro-derivatives [8] and various products of solvolysis. Furthermore, it is generally considered that the only protecting groups compatible with fluoride displacement reactions are those which are non-participating and stable to base, namely acetal and ether groups. Consequently a suitably protected trehalose derivative was prepared, namely 2,2',3,3'-tetra-*O*-benzyl-αα-trehalose (3), by benzylation of the dibenzylidene derivative (1) followed by acid-catalysed ethanolysis. The tetrabenzyl ether (3) was converted, in the usual way, into the 4,4',6,6'-tetra-*O*-mesyl ester (4) and the 6,6'-ditosylate (5) in 89 and 39% yields, respectively.

The tetrasulphonate (4) underwent selective displacement of the primary sulphonyloxy-groups on treatment with tetra-n-butylammonium fluoride in boiling acetonitrile for 1 h to give 2,3-di-*O*-benzyl-6-deoxy-6-fluoro-4-*O*-mesyl-α-D-glucopyranosyl 2,3-di-*O*-benzyl-6-deoxy-6-fluoro-4-*O*-mesyl-α-D-glucopyranoside (6) in 53% yield. The 4- and 4'-sulphonate groups were hydrolysed by sodium methoxide and the syrupy product was immediately hydrogenated with palladium–charcoal under

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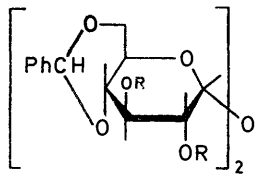
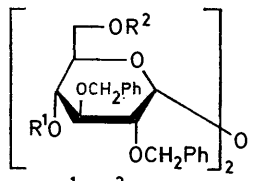
[2] D. H. R. Barton, *Pure Appl. Chem.*, 1970, **21**, 285.
[3] P. W. Kent, *Chem. and Ind.*, 1969, 1128.
[4] J. E. G. Barnett, *Adv. Carbohydrate Chem.*, 1967, **22**, 177.
[5] B. Helferich and A. Gnüchtel, *Ber.*, 1941, **74**, 1035.
[6] A. B. Foster, R. Hems, and J. M. Webber, *Carbohydrate Res.*, 1967, **5**, 292; A. D. Barford, A. B. Foster, J. H. Westwood, and L. D. Hall, *ibid.*, 1969, **11**, 287; A. D. Barford, A. B. Foster, J. H. Westwood, L. D. Hall, and R. N. Johnson, *ibid.*, 1971, **19**, 49; A. B. Foster, R. Hems, and J. H. Westwood, *ibid.*, 1970, **12**, 41; J. Adamson, A. B. Foster, L. D. Hall, R. N. Johnson, and R. H. Hesse, *ibid.*, 1970, **15**, 351.
[7] G. O. Morton, J. E. Lanchaster, G. E. Van Lear, W. Fulmor, and W. E. Meyer, *J. Amer. Chem. Soc.*, 1969, **91**, 1535; I. D. Jenkins, J. P. Verheyden, and J. G. Moffatt, *ibid.*, 1971, **93**, 4323.
[8] M. W. Horner, L. Hough, and A. C. Richardson, *J. Chem. Soc.* (*C*), 1970, 1336; 1971, 99; Y. Ali, L. Hough, and A. C. Richardson, *Carbohydrate Res.*, 1970, **14**, 181.

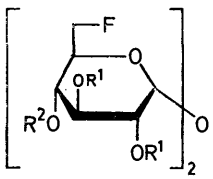
acid conditions to give crystalline 6,6′-dideoxy-6,6′-difluoro-αα-trehalose (8), which was also characterised as its hexa-acetate (9).



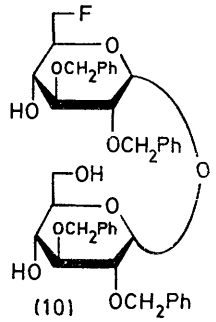
(1) R = H
(2) R = CH_2Ph



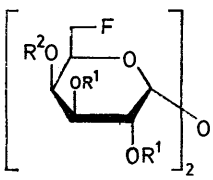
(3) $R^1 = R^2 = H$
(4) $R^1 = R^2 = MeSO_2$
(5) $R^1 = H, R^2 = p\text{-}MeC_6H_4\cdot SO_2$



(6) $R^1 = PhCH_2, R^2 = MeSO_2$
(7) $R^1 = PhCH_2, R^2 = H$
(8) $R^1 = R^2 = H$
(9) $R^1 = R^2 = Ac$



(10)

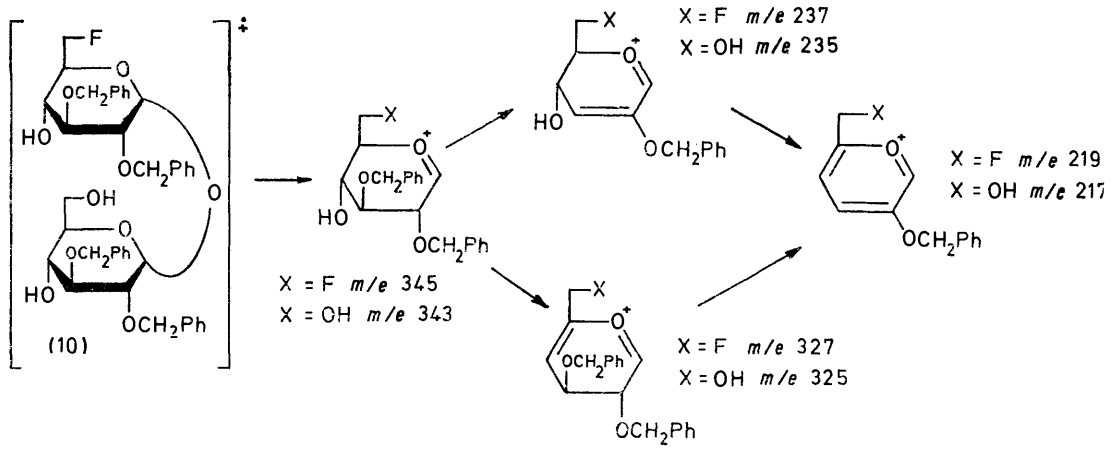


(11) $R^1 = PhCH_2, R^2 = PhCO$
(12) $R^1 = PhCH_2, R^2 = H$
(13) $R^1 = R^2 = H$
(14) $R^1 = R^2 = Ac$

The 6,6′-ditosylate (5) was also subjected to fluoride displacement under similar conditions except that *NN*-dimethylformamide was used as solvent. This resulted in a mixture of two products which were fractionated chromatographically to give the 6,6′-difluoride (7) (54%) as well as the minor product (11%). The mass spectrum of the unknown side-product contained an ion at *m/e* 613·2436 corresponding to $C_{33}H_{38}FO_{10}$, which must have been formed from the molecular ion by loss of a benzyl radical. This suggested that the unknown ($C_{40}H_{45}FO_{10}$) was 2,3-di-*O*-benzyl-6-deoxy-6-fluoro-α-D-glucopyranosyl 2,3-di-*O*-benzyl-α-D-glucopyranoside (10). This structure was further substantiated by the presence of ions at *m/e* 345 and 343 corresponding to the two oxycarbonium ions formed by cleavage of one or the other of the two glycosidic bonds. Further pairs of ions at *m/e* 327, 325 and 237, 235 corresponded to the loss of the elements of water and benzyl alcohol respectively from the two oxycarbonium ion fragments. The series of doublets was completed by the appearance of ions at *m/e* 219, 217 due to the loss of both water and benzyl alcohol (Scheme). The origin of this non-symmetrical product in the reaction mixture is obscure, but it may result either from attack of fluoride at sulphur or from the presence of traces of water, although reactions were always performed, as far as was possible, under anhydrous conditions.

2,3-Di-*O*-benzyl-6-deoxy-6-fluoro-4-*O*-mesyl-α-D-glucopyranosyl 2,3-di-*O*-benzyl-6-deoxy-6-fluoro-4-*O*-mesyl-α-D-glucopyranoside (6) was a suitable precursor for the synthesis of the 6,6′-difluoro-*galacto*-isomer (13). On treatment with sodium benzoate in hexamethylphosphoric triamide the two sulphonyloxy-groups of (6) underwent displacement by benzoate with inversion of configuration. The resulting syrupy 4,4′-dibenzoate (11) was de-*O*-benzoylated to the crystalline diol (12), which was obtained in 30% overall yield from (6). Subsequent catalytic hydrogenolysis under acidic conditions afforded crystalline 6,6′-dideoxy-6,6′-difluoro-*galacto*-trehalose (13) in 43% yield, which was also characterised as the hexa-acetate (14).

The structures of the foregoing compounds were supported by their ^1H n.m.r. spectra (Table 1). In particular the *galacto*-configuration of the hexa-acetate (14) was supported by the appearance of a narrow quartet



SCHEME

at τ 4·45 (splittings of 2·5 and 1·0 Hz) which is a characteristic feature of hexopyranosides bearing an equatorial hydrogen atom at C-4 in the C_1^4 conformation.[9] The ^{19}F

[9] E. M. Bessell, A. B. Foster, J. H. Westwood, L. D. Hall, and R. N. Johnson, *Carbohydrate Res.*, 1971, **19**, 39.

n.m.r. spectra of the 6,6′-difluoro-derivatives (6), (9), and (14) were in accord with the presence of a CH_2F grouping.[10] In the case of the glucopyranosides (6) and (9) the resonance was first-order and appeared as a triplet of doublets showing a coupling of about 47 Hz to the 6-protons and a coupling of about 23 Hz to the 5-protons. The relatively large value for $J_{F,5}$ suggested that the most favoured rotamer about each C(5)–C(6) bond was that in which the fluorine was *anti* to H-5 (*cf.* Phillips and Wray [11]). These values also agreed with those obtained from the ^1H n.m.r. spectra (Table 1). In contrast, the ^{19}F n.m.r. spectrum of the *galacto*-isomer (14) was largely second-order so that the coupling constants could not be measured with any confidence.

This work constitutes the first synthesis of fluorine-containing disaccharides, although while this work was in progress the synthesis of phenyl 6-deoxy-6-fluoro-α-maltoside was described.[12] Preliminary studies with several trehalases have revealed that 6,6′-dideoxy-6,6′-difluoro-trehalose functions as an inhibitor.[13]

TABLE 1

^1H N.m.r. parameters: first-order chemical shifts (τ values) and coupling constants (Hz) at 100 MHz

Compound	(4) [a]	(5) [d]	(6) [b]	(7) [d]	(9) [c]	(12) [d]	(14) [c]
H-1, H-1′	4·80(d)	4·98(d)	4·62(d)	4·81(d)	4·64(d)	4·47(d)	
H-2, H-2′	6·34(q)		6·28(q)	6·48(q)	4·95(q)	5·90(q)	4·65(cm)
H-3, H-3′	5·96(t)		5·72(t)	6·15(t)	4·46(t)	5·72(q)	
H-4, H-4′	5·47(t)		5·22(t)	6·48(q)	4·92(t)		4·45(q)
H-5, H-5′	5·76(sx)			5·91(cm)	5·87(cm)		5·2—5·8
H-6a, H-6′a				5·68(m)	5·46(q)		(cm)
H-6b, H-6′b							
O_2SMe	7·08	(OTs)					
	7·15	7·80					
CH_2Ph	4·90(d)	5·04(d)	5·01(d)	4·98(d)			
	5·23(d)	5·28(d)	5·24(d)	5·28(d)			
OAc					7·96		7·89
					7·98		7·93
					8·02		8·07
$J_{1,2}$	3·5	3·5	3·5	3·3	3·5	*ca.* 3	
$J_{2,3}$	*ca.* 1·1		9·5	9·4	10·0	*ca.* 10	
$J_{3,4}$	*ca.* 10		*ca.* 10	*ca.* 9	9·2	*ca.* 3	2·5
$J_{4,5}$	*ca.* 10		*ca.* 10	10·0	10·5		1·0
$J_{5,6a}$	*ca.* 3						
$J_{5,6b}$	*ca.* 3						
$J_{6F,6H}$			47	47	47		
$J_{6F,5H}$				25—27	23—25		

[a] In [^2H]chloroform at ambient probe temperature. [b] In [$^2H_5$]pyridine at 110°. [c] In [$^2H_6$]acetone at ambient probe temperature. [d] In [$^2H_5$]pyridine at 100°.

sx = Sextet; cm = complex multiplet.

TABLE 2

^{19}F n.m.r. parameters

Compd.	Solvent	Chemical shift (p.p.m.) upfield from C_6F_6	Chemical shift (p.p.m.) upfield from $F_3C{\cdot}CO_2H$	J/Hz 6F,6H	J/Hz 6F,5H
(6)	[$^2H_5$]Pyridine	68·5 [a]	153 [a]	47	22·5
(9)	[$^2H_6$]Acetone	63·0 [a]		47	23
(14)	[$^2H_6$]Acetone	66·3 [b]	126 [b]		

[a] Triplet of doublets. [b] Second-order complex multiplet.

EXPERIMENTAL

For general notes see ref. 14. Anhydrous acetonitrile was prepared by distillation from phosphorus pentoxide. Anhydrous tetra-n-butylammonium fluoride was prepared from the clathrate $(4Bu_4NF,H_2O)_8$ by drying initially at 55° *in vacuo* and then at room temperature *in vacuo* over phosphorus pentoxide until no further absorption of water by the desiccant was observed (usually 4—7 days). The reagent was then powdered and stored *in vacuo* over phosphorus pentoxide.[15] Dry column chromatography was performed on Kieselgel Merck 7734 (70—235 mesh). The silica gel was packed dry into a glass column and a concentrated solution of the mixture applied to the top of the column and allowed to percolate through the silica. The top of the column was then covered with a little fresh silica gel and elution was performed in the usual way, with fractions being collected and analysed by t.l.c. This method has the advantage that components moved through the column as narrow bands with the minimum of diffusion. Furthermore, elution from the column was much more rapid and separations were improved.

2,3-*Di*-O-*benzyl*-α-D-*glucopyranosyl* 2,3-*Di*-O-*benzyl*-α-D-*glucopyranoside* (3).—To a solution of di-*O*-benzylidene-αα-trehalose (1) [16] (25 g) in dioxan (300 ml) were added benzyl chloride (190 ml) and powdered potassium hydroxide (*ca.* 85 g). The mixture was heated at 100° with stirring and protection from moisture, and after 1 h a further charge of benzyl chloride (190 ml) and potassium hydroxide (85 g) was added. The reaction was continued overnight, after which t.l.c. (ether–light petroleum, 1 : 1) indicated completion. The mixture was then cooled and filtered through a pad of Hyflo supercel, which was washed well with dioxan. The combined filtrate and washings were evaporated (65—

[10] L. Evelyn and L. D. Hall, *Chem. and Ind.*, 1968, 1183.
[11] L. Phillips and V. Wray, *J. Chem. Soc.* (*B*), 1971, 1618.
[12] H. Arita and Y. Matsushima, *J. Biochem.*, 1971, **69**, 409.
[13] E. Bar-Guilloux, personal communication.
[14] L. Hough, A. C. Richardson, and E. Tarelli, *J. Chem. Soc.* (*C*), 1971, 1732.
[15] R. C. Young, Ph.D. Thesis, Oxford University, 1968.
[16] L. Hough, P. A. Munroe, and A. C. Richardson, *J. Chem. Soc.* (*C*), 1971, 1090.

70°) to a viscous liquid, which was co-distilled several times with cyclohexane. An equal volume of 2% hydrogen chloride in ethanol was then added to the liquid, and the mixture was heated gently under reflux. The reaction was monitored by t.l.c. (chloroform–methanol, 9 : 1) and when complete was neutralised with an excess of lead carbonate. The mixture was then filtered, and evaporated to an oil which crystallised upon addition of light petroleum to give the *tetrabenzyl disaccharide* (22·7 g, 66%), m.p. 186—188°, $[\alpha]_D$ +120° (*c* 1) (Found: C, 68·05; H, 6·6. $C_{40}H_{46}O_{11}$ requires C, 68·3; H, 6·55%).

2,3-*Di*-O-*benzyl*-4,6-*di*-O-*methylsulphonyl*-α-D-*glucopyranosyl* 2,3-*Di*-O-*benzyl*-4,6-*di*-O-*methylsulphonyl*-α-D-*glucopyranoside* (4).—A solution of the tetrabenzyltrehalose (3) (10 g) in pyridine (50 ml) was cooled in ice–water, and methanesulphonyl chloride (12 ml) was added. The mixture was stored overnight at 0—5°, and then poured slowly into stirred ice–water. The off-white precipitate was filtered off, washed well with water, and the final traces of pyridine were removed by azeotropic distillation with toluene. Trituration with light petroleum gave a solid which crystallised from methylene chloride–ethanol to give the *tetramethanesulphonate* (12·85 g, 89%), m.p. 175—178°, $[\alpha]_D$ +112° (*c* 1) (Found: C, 51·8; H, 5·35; S, 12·85. $C_{44}H_{54}O_{19}S_4$ requires C, 52·1; H, 5·35; S, 12·65%).

2,3-*Di*-O-*benzyl*-6-O-p-*tolylsulphonyl*-α-D-*glucopyranosyl* 2,3-*Di*-O-*benzyl*-6-O-p-*tolylsulphonyl*-α-D-*glucopyranoside* (5).—Toluene-*p*-sulphonyl chloride (6 g) was added to a cold solution (−10°) of 2,2′,3,3′-tetrabenzyltrehalose (3) (5 g) in anhydrous pyridine (50 ml). The mixture was stirred and kept at −10° for 17 h, after which reaction was complete as indicated by t.l.c. (benzene–ether, 8 : 1). The mixture was poured into ice–water, and the resulting syrup was extracted with methylene dichloride and processed in the usual way. The 6,6′-*bistoluene*-p-*sulphonate* (2·65 g, 39%) had m.p. 141—143° (from isopropyl alcohol–light petroleum), $[\alpha]_D$ +81° (*c* 1) (Found: C, 64·2; H, 5·7. $C_{54}H_{58}O_{15}S_2$ requires C, 64·2; H, 5·75%).

2,3-*Di*-O-*benzyl*-6-*deoxy*-6-*fluoro*-4-O-*methylsulphonyl*-α-D-*glucopyranosyl* 2,3-*Di*-O-*benzyl*-6-*deoxy*-6-*fluoro*-4-O-*methylsulphonyl*-α-D-*glucopyranoside* (6).—Anhydrous tetra-n-butylammonium fluoride (63 g) was dissolved in anhydrous acetonitrile (180 ml) and the thoroughly dried tetramethanesulphonate (4) (30 g) was quickly added. Throughout these manipulations care was taken to protect the mixture from atmospheric moisture. The mixture was then heated under reflux for 65 min; t.l.c. (benzene–ether, 8 : 1) then indicated that reaction was complete and that only one major component had been formed. The mixture was cooled and fractionated between ether and water. The aqueous layer was washed well with ether (3 × 200 ml) and the combined ethereal extracts were dried ($MgSO_4$) and evaporated to a syrup, which was purified by column chromatography on silica gel (300 g), with ethyl acetate–light petroleum (40 : 60) as eluant. The eluate was evaporated to a syrup, which was dissolved in ethyl acetate and treated twice with decolourising charcoal. Crystallisation from ethyl acetate–light petroleum gave the 6,6′-*difluoride* (13·5 g, 53%), m.p. 139·5—141·5°, $[\alpha]_D$ +124° (*c* 1) (Found: C, 58·75; H, 5·65; F, 4·65; S, 7·3. $C_{42}H_{48}F_2O_{13}S_2$ requires C, 58·45; H, 5·55; F, 4·4; S, 7·4%).

2,3-*Di*-O-*benzyl*-6-*deoxy*-6-*fluoro*-α-D-*glucopyranosyl* 2,3-*Di*-O-*benzyl*-6-*deoxy*-6-*fluoro*-α-D-*glucopyranoside* (7).—The 6,6′-bistoluene-*p*-sulphonate (5) (1 g) was added to a solution of tetra-n-butylammonium fluoride (3 g, 11 mol. equiv.) in anhydrous *NN*-dimethylformamide (7 ml). The stirred solution was heated at 80° until no further reaction occurred (4·5 h) as indicated by t.l.c., and then poured into water, extracted with ether, and worked up in the usual way. The syrupy mixture obtained was fractionated by dry column chromatography with ethyl acetate–light petroleum (1 : 2) as eluant. The fastest moving component was the 6,6′-*difluoride* (0·4 g, 54%), m.p. 117—120° (from isopropyl alcohol–light petroleum), $[\alpha]_D$ +125° (*c* 1) (Found: C, 68·0; H, 6·5. $C_{40}H_{44}F_2O_9$ requires C, 68·0; H, 6·25%).

A minor slower-moving component was subsequently eluted and was recrystallised from ethanol–light petroleum (80 mg, 11%) to give 2,3-*di*-O-*benzyl*-6-*deoxy*-6-*fluoro*-α-D-*glucopyranosyl* 2,3-*di*-O-*benzyl*-α-D-*glucopyranoside*, m.p. 144—146°, $[\alpha]_D$ +127° (*c* 0·5) (Found: C, 68·2; H, 6·35. $C_{40}H_{45}FO_{10}$ requires C, 68·2; H, 6·4%), τ ($CDCl_3$) 2·70 (20H, m, aromatic), 4·80 (2H, pair of overlapped doublets separated by *ca.* 1 Hz, $J_{1,2} \simeq J_{1'2'} = 3{\cdot}5$ Hz), 5·10 (8H, two slightly separated AB quartets, benzylic protons), 5·30—6·50 (12H; 2-,2-′,3-,3′-,4-,4′-,5-,5′-, 6- and 6′-protons, overlapped multiplets), and 7·88br (3H, s, 3 × OH).

6-*Deoxy*-6-*fluoro*-α-D-*glucopyranosyl* 6-*Deoxy*-6-*fluoro*-α-D-*glucopyranoside* (8).—The 6,6′-difluoro-4,4′-dimethanesulphonate (6) (1 g) was heated under reflux with freshly prepared 3N-sodium methoxide (15 ml) for *ca.* 5 h or until t.l.c. indicated completion. The mixture was then passed down a column of silica gel and eluted with methylene dichloride–methanol (3 : 1) to give a clear syrup shown to be homogeneous on t.l.c. The i.r. spectrum of compound (7) indicated C–F (990—1160) and OH (3400 cm^{-1}) absorptions, but no sulphonate bands. This product was subsequently obtained crystalline *via* the 6,6′-bistoluene-*p*-sulphonate (5) (see before).

The syrup was dissolved in ethanol (100 ml) containing 1% hydrogen chloride and the mixture was hydrogenated over palladium–charcoal at 55 lb in^{-2} for 24 h. The catalyst was then filtered off and the solution neutralised ($PbCO_3$) and evaporated. The resulting syrup was dissolved in ethanol, decolourised with charcoal, and evaporated to a crystalline solid (0·25 g, 63%). Recrystallisation from ethanol gave 6,6′-*dideoxy*-6,6′-*difluorotrehalose*, m.p. 239—245°, $[\alpha]_D$ +161° (*c* 1 in H_2O) (Found: C, 41·35; H, 6·0; F, 11·0. $C_{12}H_{20}F_2O_9$ requires C, 41·60; H, 5·80; F, 11·0%).

The *hexa-acetate* (9) (88%) had m.p. 205—209° (from ethanol), $[\alpha]_D$ +175·5° (*c* 1) (Found: C, 48·3; H, 5·3; F, 6·45. $C_{24}H_{32}F_2O_{15}$ requires C, 48·15; H, 5·35; F, 6·35%).

2,3-*Di*-O-*benzyl*-6-*deoxy*-6-*fluoro*-α-D-*galactopyranosyl* 2,3-*Di*-O-*benzyl*-6-*deoxy*-6-*fluoro*-α-D-*galactopyranoside* (12).—The 4,4′-dimethanesulphonate (6) (8 g) was dissolved in hexamethylphosphoric triamide (40 ml), sodium benzoate (5 g) was added, and the mixture was heated at 100° for 47 h. The mixture was then cooled and poured into ice–water, and the white precipitate filtered off and washed well with water. The air-dried solid was purified by chromatography on silica gel (200 g) with ethyl acetate as eluant to give the dibenzoate (11) as a chromatographically homogeneous syrup. A solution of the syrup in methylene dichloride (50 ml) and 0·5N-sodium methoxide (50 ml) was set aside at room temperature overnight, and then neutralised by passage through a silica gel column (200 g), with methylene dichloride–methanol (3 : 1) as eluant. Evaporation of the eluate gave a syrup, which was dissolved in chloroform, washed with sodium hydrogen carbonate solution, and dried ($MgSO_4$). Evaporation afforded a

solid, crystallisation of which from methylene dichloride–ethanol afforded the 6,6′-*difluoro*-4,4′-*diol* (2 g, 30%), m.p. 152—155°, $[\alpha]_D$ +150° (*c* 1) (Found: C, 68·0; H, 6·25. $C_{40}H_{44}F_2O_9$ requires C, 68·1; H, 6·2%).

6-*Deoxy*-6-*fluoro*-α-D-*galactopyranosyl* 6-*Deoxy*-6-*fluoro*-α-D-*galactopyranoside* (13).—The tetrabenzyl ether (12) (1 g) was dissolved in ethanol (200 ml) containing 1% hydrogen chloride and hydrogenated over palladium–charcoal at 55 lb in for 24 h. Removal of the catalyst, neutralisation, and then decolourisation with charcoal were carried out as before. Evaporation to dryness gave a white solid, crystallisation of which from ethanol gave 6,6′-*dideoxy*-6,6′-*difluoro*-galacto-*trehalose* (0·21 g, 43%), m.p. 235—244°, $[\alpha]_D$ +246° (*c* 1 in H_2O) (Found: C, 41·1; H, 5·85; F, 11·0. $C_{12}H_{20}F_2O_9$ requires C, 41·6; H, 5·8; F, 11·0%).

The *hexa-acetate* (14) (60%) had m.p. 172—175°, $[\alpha]_D$ +179° (*c* 1) (Found: C, 48·3; H, 5·45. $C_{24}H_{32}F_2O_{15}$ requires C, 48·2; H, 5·35%).

We thank the Wellcome Trust for a studentship (for A. K. P.) and the Physico-Chemical Measurements Unit, Harwell, for all the ^1H n.m.r. spectra and some ^{19}F n.m.r. spectra. We are indebted to Dr. L. Phillips (Imperial College) for the determination of several ^{19}F n.m.r. spectra.

[2/1080 *Received*, 12*th May*, 1972]