Carbohydrate Research, 63 (1978) 51–60

THE SYNTHESIS OF 6-DEOXY-6-FLUORO-α,α-TREHALOSE AND RELATED ANALOGUES*

ANTHONY F. HADFIELD, LESLIE HOUGH, AND ANTHONY C. RICHARDSON
Department of Chemistry, Queen Elizabeth College, London W8 7AH (Great Britain)
(Received July 11th, 1977; accepted for publication July 22nd, 1977)

ABSTRACT

Selective acid-catalysed methanolysis of 2,3,2′,3′-tetra-*O*-benzyl-4,6:4′,6′-di-*O*-benzylidene-α,α-trehalose yielded the monobenzylidene derivative, which was converted into the 4,6-dimesylate. Selective nucleophilic displacement of the primary sulphonyloxy group then gave 2,3-di-*O*-benzyl-6-deoxy-6-fluoro-4-*O*-mesyl-α-D-glucopyranosyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside. Removal of the protecting groups then yielded 6-deoxy-6-fluoro-α,α-trehalose. In addition, 6-deoxy-6-fluoro-4-*O*-mesyl-α,α-trehalose and a derivative of 4-chloro-4,6-dideoxy-6-fluoro-α-D-galactopyranosyl α-D-glucopyranoside were also prepared from the same substrate. Iodide displacement of 2,3-di-*O*-benzyl-4,6-di-*O*-mesyl-α-D-glucopyranosyl 2,3-di-*O*-benzyl-4,6-di-*O*-mesyl-α-D-glucopyranoside afforded the 6-iodide and 6,6′-di-iodide in yields of 31 and 36%, respectively. Similarly, the 6-azide and 6,6′-diazide were isolated in yields of 17 and 21%, respectively.

INTRODUCTION

The symmetry of the trehalose molecule makes the synthesis of symmetrical analogues straightforward, and many such analogues have been prepared. However, the synthesis of non-symmetrical analogues is more difficult and only a few have been described, although they may be of greater biological interest than the symmetrical analogues. For example, 2-amino-2-deoxy-α,α-trehalose[2], 4-amino-4-deoxy-α,α-trehalose[3], and 2-amino-2-deoxy-α-D-glucopyranosyl α-D-mannopyranoside[2] have been isolated from fermentation of some *Streptomyces* species, and show some antibiotic activity. They may function by inhibition of trehalase, which is an important enzyme in the carbohydrate metabolism of some bacteria, most fungi, and other micro-organisms. Insects utilise trehalose as their storage carbohydrate and rely on trehalase for the release of D-glucose. Hence, the development of trehalase inhibitors could have important applications in the insecticide and fungicide fields.

Two approaches are possible to the synthesis of non-symmetrical trehalose derivatives. Firstly, by coupling two monosaccharide units. This approach, which

*Chemical Modification of Trehalose: Part XX. For Part XIX, see Ref. 1.

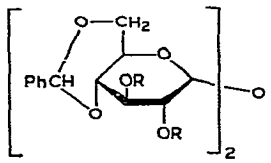
requires the simultaneous formation of two α-linkages has been limited in the pas because most attempts led to mixtures of the α,α-, α,β-, and β,β-trehalose analogues' However, with the recent development of more efficient methods for the synthes of α-D-glucosides, this method is proving more viable, as illustrated, for example, b the synthesis[5] of α-D-glucopyranosyl α-D-xylopyranoside and α-D-glucopyranos α-D-mannopyranoside in good overall yields. Secondly, by utilising trehalose for th synthesis of non-symmetrical derivatives, provided that the two rings can be separatel blocked or modified. Since the reactions of trehalose to give a symmetrical derivativ occur by two consecutive reactions, the second reaction occurs at a lower rate tha the first. If the reaction being performed is first order, then the rates of the tw consecutive reactions will be in the ratio 2:1, hence, theoretically, it should be possibl to isolate the intermediate, non-symmetrical product in 50% yield[6]. For example, th acid-catalysed methanolysis of 4,6:4',6'-di-*O*-benzylidenetrehalose gives[7a] the inte mediate monoacetal, which was isolated in 47% yield. This same monoacetal wa more conveniently prepared, in yields of 35–40%, by treatment of trehalose wit benzaldehyde and zinc chloride[7b]. Selective acylation has been attempted on man occasions, but yields have always left much to be desired. The 70% yield of the 6 methanesulphate reported by Helferich *et al.*[8] could not be reproduced by Birch and by Percheron *et al.*[10]. Selective tosylation of trehalose yields[11] the 6-, 2,6 6,6'-, 2,6,6', and 2,6,2',6'-tosylates, but in rather low yields after chromatography Selective halogenation of trehalose with triphenylphosphine and the appropriate N halosuccinimide yielded[12] 6-bromo- and 6-chloro-6-deoxytrehalose in yields of 37% and 13%, respectively, in addition to the 6,6'-dihalo derivatives. These halo derivative were then used for the preparation of 6-amino-6-deoxy- and 6-deoxy-trehaloses.

We now report on the synthesis of non-symmetrically substituted fluor analogues of trehalose modified at positions 4 and 6, and on their ability to inhib trehalase.

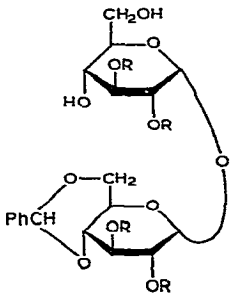
RESULTS AND DISCUSSION

The selective methanolysis of 2,3,2',3'-tetra-*O*-benzoyl-4,6:4',6'-di-*O*-benzyl idene-α,α-trehalose (**1**) can be interrupted[7a] to afford 2,3-di-*O*-benzoyl-4,6-*O* benzylidene-α-D-glucopyranosyl 2,3-di-*O*-benzoyl-α-D-glucopyranoside (**3**) in 47% yield. Since acyl groups are unsuitable blocking-groups when fluoride displacemen reactions of sulphonates are being performed, benzyl groups were used. Thus, th hydrolysis of 2,3,2',3'-tetra-*O*-benzyl-4,6:4',6'-di-*O*-benzylidene-α,α-trehalose[13] (2 was interrupted at the point, as judged by t.l.c., to give the maximum yield of th monoacetal **4**. One component crystallised directly from the product mixture, and wa the 4,6,4',6'-tetraol. The other product was isolated in 22–30% yield by colum chromatography and identified as the desired 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D glucopyranosyl 2,3-di-*O*-benzyl-α-D-glucopyranoside (**5**).

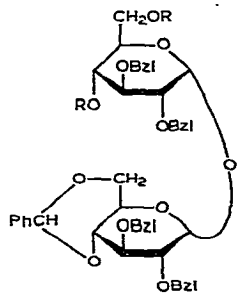
Due to the non-symmetrical nature of the compounds reported herein, first order analysis of their 100-MHz ^{1}H-n.m.r. spectra was difficult, but mass spectrc



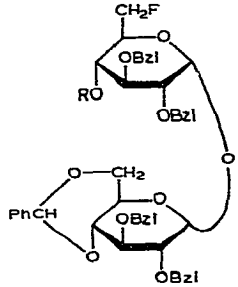
1 R = Bz
2 R = Bzl



3 R = Bz
4 R = Bzl



5 R = H
6 R = Ms



7 R = Ms
8 R = H

TABLE I

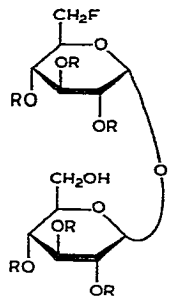
^{19}F-N.M.R. PARAMETERS[a]

Compound	*Solvent*	*F-6*	$J_{F,H-5}$	$J_{F,H-6}$
7	$CDCl_3$	−75.0[b]	24	50
10	$CDCl_3$	−68.6[b]	21	45
11	MeOH	−76.1[b]	27	50
13	$CDCl_3$	−68.4[c]		
15	D_2O	−68.9[b]	~17	~40
14	$CDCl_3$	−68.0[c]		

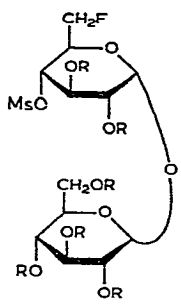
[a]First-order chemical shifts (p.p.m. relative to external hexafluorobenzene) and coupling constants (J, Hz) at 56.45 MHz. [b]Triplet of doublet. [c]Second-order complex multiplet.

metry was useful for structural confirmation of these types of derivatives[13,14]. Major fragmentation takes place by cleavage of the C-1–O-1 bonds (A-series)[15] to give two oxycarbonium ions which differ for non-symmetrically substituted compounds, undergo further stepwise elimination of substituents at C-3 and C-4, and are readily recognised. The mass spectrum of the trimethylsilylated 4,6-diol **4** contained signals at *m/e* 431 and 487 which were assigned to the oxycarbonium ions resulting from the 2,3-di-*O*-benzyl-4,6-*O*-benzylideneglucopyranosyl and 2,3-di-*O*-benzyl-4,6-di-*O*-trimethylsilylglucopyranosyl moieties, respectively. The former ion (*m/e* 431) underwent sequential loss of benzyl alcohol and benzaldehyde, or *vice versa*, giving products having *m/e* 323, 233, and 217. The 4,6-di-*O*-trimethylsilyloxycarbonium ion at *m/e* 487 gave rise to ions at *m/e* 379 and 289 by consecutive loss of benzyl alcohol and trimethylsilanol.

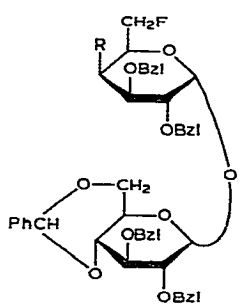
Compound **4** was converted into the 4,6-dimesylate **6** in 84% yield, reaction of which with tetrabutylammonium fluoride[14,16] in boiling acetonitrile for 1 h afforded the crystalline 6-deoxy-6-fluoro-4-mesylate **7** in 79% yield. The ^{19}F-n.m.r. spectrum of **7** (Table I) contained a triplet of doublets, consistent with the presence of fluorine at the primary position. The observed coupling constants ($J_{F,6}$ 52, $J_{F,5}$ 25 Hz) are



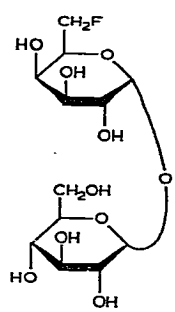
9 R = H
10 R = Ac



11 R = H
12 R = Ac



13 R = OBz
14 R = Cl



15

consistent[17] with the rotamer about the C-5–C-6 bond having fluorine situated anti-periplanar to H-5.

Hydrolysis of the 4-mesyl group of **7** was readily achieved with boiling, methanolic sodium methoxide, to afford the syrupy 4-ol **8**, which was immediately subjected to hydrogenolysis under acid conditions to give 6-deoxy-6-fluoro-α,α-trehalose (**9**) characterised as its crystalline hepta-acetate **10**. The ^{19}F-n.m.r. spectrum of **10** (Table I) was similar to those of **7** and 6,6′-dideoxy-6,6′-difluoro-α,α-trehalose hexa-acetate[13]. Confirmation of the structure of **9** was obtained from the mass spectrum of the hepta-acetate **10**, which showed ions at *m/e* 291 and 331 assigned to the 2,3,4-tri-*O*-acetyl-6-deoxy-6-fluoroglucopyranosyl and 2,3,4,6-tetra-O-acetylglucopyranosyl moieties, respectively. The ion *m/e* 291 underwent successive loss of acetic acid (→*m/e* 231), ketene (→*m/e* 189), and acetic acid (→*m/e* 129), showing that the fluorine substituent was at C-6.

Hydrogenolysis of **7** (palladium-on-charcoal under acidic conditions) afforded 48% of 6-deoxy-6-fluoro-4-*O*-mesyltrehalose (**11**), which was characterised as its hexa-acetate **12**. The ^{19}F-n.m.r. spectrum of **11** (Table I) was consistent with its structure, as were the mass spectra of the per-*O*-trimethylsilyl and hexa-*O*-acetyl derivatives.

Treatment of **7** with sodium benzoate in hexamethylphosphoric triamide at 100° afforded 81% of the crystalline 6-fluoro-4-benzoate **13**, with inversion of configuration. Saponification of **13**, followed by catalytic hydrogenolysis under acidic conditions, gave 6-deoxy-6-fluoro-α-D-galactopyranosyl α-D-glucopyranoside (**15**) which could not be obtained pure. It is of interest that the ^{19}F-n.m.r. spectrum (Table I) of the hexa-acetate of the 6,6′-difluoro-*galacto* isomer of trehalose[14] showed a second-order multiplet at −66.3 p.p.m. relative to hexafluorobenzene in $(CD_3)_2CO$, whereas the crude **15** gave a first-order spectrum containing a triplet of doublets centred at −68.9 p.p.m. with $J_{F,6}$ 40 and $J_{F,5}$ 17 Hz. The magnitude of $J_{F,5}$ is consistent with that (12–18 Hz) for 6-deoxy-6-fluoro-D-galactopyranose derivatives and indicates[16] a gauche configuration between the fluorine and H-5.

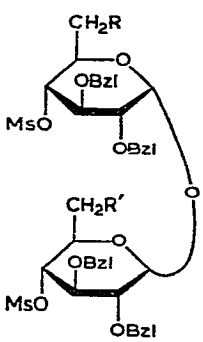
Chloride displacement of the 4-mesyloxy group of **7** was also investigated, as the 4-chloro-6-fluoride **14** should be a useful intermediate for further displacement by

azide and other nucleophilic anions. Treatment of **7** with lithium chloride in hexamethylphosphoric triamide at 80° afforded two products of similar mobility in t.l.c.; from this mixture, the major 4-chloro-6-fluoride **14** was isolated by column chromatography. The ^{19}F-n.m.r. spectrum of the crude reaction mixture contained two resonances, centred near −68 and −76 p.p.m., which reflect the presence of epimeric 4-chlorides having the *galacto* and *gluco* configurations, respectively. The initial nucleophilic displacement would afford a *galacto*-4-chloride which then undergoes further chloride displacement to give the *gluco*-4-chloride. The lack of complete double-inversion, as compared to a similar displacement with iodide anion[18], indicates the better leaving-capacity of the iodo group. The ^{19}F-n.m.r. spectrum (Table I) of **14** showed some second-order character, but basically contained a triplet of doublets centered at −68.0 p.p.m.

Methanolysis of the 4,6:4′,6′-di-*O*-benzylidene acetal **2** gave substantial quantities of the 4,6,4′,6′-tetraol, which was readily converted into the known[13] tetramesylate **16**. The selective displacement of one of the two primary mesyloxy groups in **16** was investigated as a further route to non-symmetrical trehaloses. Treatment of **16** with sodium iodide in acetone afforded two products which were separated by column chromatography. The ^{1}H-n.m.r. spectrum of the major product (~36%) indicated it to be the 6,6′-di-iodide **18**. The same structure was also indicated by the mass spectrum. The minor product (31%) was identified from its mass spectrum as 2,3-di-*O*-benzyl-6-deoxy-6-iodo-4-*O*-mesyl-α-D-glucopyranosyl 2,3-di-*O*-benzyl-4,6-di-*O*-mesyl-α-D-glucopyranoside (**17**).

Treatment of **16** with sodium azide in *N*,*N*-dimethylformamide at 85° for 2 h gave two products which were separated by column chromatography. The ^{1}H-n.m.r. spectrum of the major product (21%) was first-order and indicated it to be the 6,6′-diazide **20**. The non-symmetrical structure of the minor product (17.5%) was indicated to be the 6-azide **19** by the ^{1}H-n.m.r. spectrum, which contained signals for the methyl protons of the 4-, 4′-, and 6′-mesyloxy groups at τ 7.09, 7.17, and 7.18, respectively.

6,6′-Dideoxy-6,6′-difluoro-α,α-trehalose can function as a reversible competitive inhibitor of trehalose[13]. 6-Deoxy-6-fluoro-α-D-glucopyranosyl α-D-glucopyranoside (**9**) is a competitive reversible inhibitor of trehalase isolated from the flight muscle of



16 R = R′ = OMs
17 R = I, R′ = OMs
18 R = R′ = I
19 R = N_3, R′ = OMs
20 R = R′ = N_3

the greenbottle fly (*Lucilia sericata*), and has an affinity some 1.4 times greater than that of the natural substrate. The 6-fluoro-4-mesylate **11** is a weak inhibitor, exhibiting only 20% inhibition at high concentration.

EXPERIMENTAL

General. — Melting points were determined on a Kofler microscope hot-stage apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 141 polarimeter. 100-MHz p.m.r. spectra (internal Me_4Si) were measured by P.C.M.U. (Harwell) on a Varian HA-100 spectrometer. Mass spectra were recorded on an A.E.I. MS-30 spectrometer; trimethylsilyl derivatives were prepared by using "Trisil". Dry-packed column chromatography[13] was performed on Kieselgel 7734 (Merck, 70–230 mesh). *N,N*-Dimethylformamide and hexamethylphosphoric triamide were dried over calcium hydride and distilled under diminished pressure. Anhydrous tetrabutylammonium fluoride was prepared from the clathrate[13,16] $(4Bu_4NF \cdot H_2O)_8$ by drying initially at 55° under reduced pressure and then storing as a 50% solution in anhydrous acetonitrile over a molecular sieve.

2,3-Di-O-benzyl-4,6-O-benzylidene-α-D-glucopyranosyl 2,3-di-O-benzyl-α-D-glucopyranoside (**4**). — To a solution of di-*O*-benzylidene-α,α-trehalose[19] (**2**, 30 g) in 1,4-dioxane (350 ml) were added benzyl chloride (240 ml) and sodium hydroxide (100 g). The mixture was stirred vigorously and boiled under reflux for 7 h; t.l.c. (ethyl acetate–light petroleum, 1:2) then indicated that the reaction was virtually complete. The cooled mixture was filtered through a pad of Hyflo Supercel, which was washed well with 1,4-dioxane. The combined filtrate and washings were concentrated *in vacuo* to a viscous liquid, to a solution of which in dichloromethane (100 ml) and methanol (100 ml) at 0° was cautiously added acetyl chloride (4 ml). The mixture was kept at room temperature, monitored by t.l.c. (ethyl acetate–light petroleum, 1:2) until ~75% of the starting material had reacted, made neutral ($PbCO_3$), and concentrated to dryness. Treatment of the syrupy residue with carbon tetrachloride gave 2,3,2′,3′-tetra-*O*-benzyltrehalose (12 g, 29.5%). The remaining solution was concentrated to small bulk, and applied to a dry-packed column of silica gel[13]. Initial elution with light petroleum–ethyl acetate (2:1) removed unreacted **2**, and ethyl acetate–light petroleum (2:1) then afforded **4** (10 g, 22%), m.p. 54–56° (from ethanol–light petroleum), $[\alpha]_D$ +82° (*c* 1, chloroform) (Found: C, 71.4; H, 6.5. $C_{47}H_{50}O_{11}$ calc.: C, 71.4, H. 6.35%). Mass spectrum (of the 4,6-di-*O*-trimethylsilyl derivative): *m/e* 487 (0.8%), 447 (2.8), 431 (6.3), 397 (3.6), 341 (2.8), 339 (4.4), 325 (2.8), 339 (4.4), 325 (2.9), 233 (7.1), 217 (5.0), and 181 (100, PhC^+HCH_2Ph).

2,3-Di-O-benzyl-4,6-di-O-mesyl-α-D-glucopyranosyl 2,3-di-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside (**6**). — Mesyl chloride (0.5 g) was added to a cold solution (< 0°) of **4** (1 g) in anhydrous pyridine. The solution was allowed to attain room temperature and was stored for 1 h; t.l.c. (light petroleum–ethyl acetate, 1:1) then indicated one product. The mixture was diluted with chloroform (5 ml) and

washed with cold, dilute hydrochloric acid. The dried ($MgSO_4$) chloroform solution was concentrated to a syrup, which was crystallised from ethanol–light petroleum to give **6** (1.0 g, 84%), m.p. 152–154°, $[\alpha]_D$ +96° (*c* 1, chloroform) (Found: C, 61.8; H, 5.8. $C_{49}H_{54}O_{15}S_2$ calc.: C, 62.15; H, 5.7%). Mass spectrum: *m/e* 515 (1.3%), 499 (0.1), 447 (1.0), 431 (2.0), 407 (1.0), 391 (1.0), 341 (1.6), 339 (1.8), 311 (0.5), 295 (1.3), 233 (7.1), 217 (5.0), and 181 (100, PhC^+HCH_2Ph).

2,3-Di-O-benzyl-6-deoxy-6-fluoro-4-O-mesyl-α-D-glucopyranosyl 2,3-di-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside (**7**). — A solution of **6** (10 g) in 50% tetrabutylammonium fluoride in acetonitrile (30 ml) was boiled under reflux for 1 h. The product was eluted from a dry-packed column of silica gel with light petroleum–ethyl acetate (3:1), affording **7** (7.3 g, 79%), m.p. 163.5–165° (from light petroleum–ethanol), $[\alpha]_D$ +36.5° (*c* 1, chloroform) (Found: C, 66.0; H, 6.0. $C_{48}H_{51}FO_{12}S$ calc.: C, 66.2; H, 5.8%).

6-Deoxy-6-fluoro-α-D-glucopyranosyl α-D-glucopyranoside (**9**). — A solution of **7** (4 g) in methanolic 3M sodium methoxide (50 ml) was boiled under reflux for 16 h, and t.l.c. (light petroleum–ethyl acetate, 3:1) then indicated reaction to be complete. The cooled solution was percolated through a dry-packed column of silica gel (50 g), which was then eluted with ethyl acetate. Concentration of the total eluate afforded a syrupy product, which was immediately dissolved in 1% ethanolic hydrogen chloride (150 ml) and hydrogenated over palladium-on-charcoal at 50 p.s.i. for 24 h. T.l.c. (methanol–ethyl acetate, 1:1) then indicated one major product. The mixture was neutralised ($PbCO_3$) and concentrated, and the syrupy product was eluted from a column of silica gel with ethyl acetate–methanol (2:1), affording **9** (0.6 g, 36%) as an amorphous solid, $[\alpha]_D$ +174° (*c*, 1 methanol), which was chromatographically homogeneous but failed to give a satisfactory analysis. Mass spectrum (of the hepta-*O*-trimethylsilyl derivative): *m/e* 451 (0.1%), 381 (1.4), 361 (10), 291 (14.1), 204 (8.9), and 73 (100, Me_3Si^+).

Conventional treatment of **9** with acetic anhydride–pyridine gave the hepta-acetate **10** (41%), m.p. 109–110°, $[\alpha]_D$ +171° (*c* 0.5, chloroform) (Found: C, 49.3; H, 5.5. $C_{26}H_{35}FO_{17}$ calc.: C, 48.9; H, 5.5%); lit.[20] m.p. 82–83°, $[\alpha]_D$ + 170°. Mass spectrum: *m/e* (2.2%), 291 (3.5), 271 (0.3), 231 (1.8), 229 (0.5), 211 (0.3), 189 (8.7), 171 (4.0), 169 (12.1), 129 (12.6), and 43 (100, Ac^+).

6-Deoxy-6-fluoro-4-O-mesyl-α-D-glucopyranosyl α-D-glucopyranoside (**11**). — To a solution of **8** (1.5 g) in ethanol (100 ml) and ether (50 ml) was added conc. hydrochloric acid (2 ml). The solution was hydrogenated over palladium-on-charcoal at 55 p.s.i.; t.l.c. (methanol–ethyl acetate, 1:4) indicated that one major product had been formed. The neutralised ($PbCO_3$) solution was concentrated, together with silica gel, to give a mobile white powder, which was applied to a dry-packed column of silica gel and eluted with methanol–ethyl acetate (1:4) to afford **11** (0.35 g, 48%) as an amorphous powder, $[\alpha]_D$ +173° (*c* 1, methanol) (Found: C, 36.8; H, 5.6. $C_{13}H_{23}FO_{12}S$ calc.: C, 36.95; H, 5.45%). Mass spectrum (of the hexa-*O*-trimethylsilyl derivative): *m/e* 451 (0.2%), 387 (0.6), 361 (17.8), 331 (4.5), 297 (3.1), 291 (10.0), 271 (2.5), 217 (17.8), 204 (14.1), 201 (1.1), and 73 (100, Me_3Si^+).

Conventional treatment of **11** with acetic anhydride–pyridine gave the hexa-acetate **12** (84%), m.p. 82–85°, $[\alpha]_D$ +143° (*c* 1, chloroform) (Found: C, 44.5; H, 5.4. $C_{25}H_{35}FO_{18}S$ calc.: C, 44.5; H, 5.2%).

4-O-Benzoyl-2,3-di-O-benzyl-6-deoxy-6-fluoro-α-D-galactopyranosyl 2,3-di-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside (**13**). — A mixture of **7** (4.4 g), hexamethylphosphoric triamide (30 ml), and sodium benzoate (2 g) was maintained at 100° for 16 h, and t.l.c. (light petroleum–ethyl acetate, 3:1) then indicated one major product. The solution was diluted with ethyl acetate and extracted with water (3 × 50 ml). The combined aqueous layers were then extracted with ethyl acetate (2 × 25 ml). The combined organic solutions were concentrated after drying ($MgSO_4$). Elution of the residue from a dry-packed column of silica gel with ethyl acetate–light petroleum (1:3) afforded **13** (3.7 g, 81.5%), m.p. 52–54°, $[\alpha]_D$ +138° (*c* 1, chloroform) (Found: C, 72.5; H, 6.2. $C_{54}H_{53}FO_{11}$ calc.: C, 72.3, H, 5.9%). Mass spectrum: *m/e* 465 (0.9%), 449 (7.8), 447 (1.0), 431 (1.6), 359 (2.5), 357 (0.8), 343 (0.6), 341 (1.6), 339 (1.3), 325 (0.4), 323 (0.6), 251 (3.6), 235 (2.5), 233 (1.6), 217 (0.6), and 181 (100, PhC^+HCH_2Ph).

2,3-Di-O-benzyl-4-chloro-4,6-dideoxy-6-fluoro-α-D-galactopyranosyl 2,3-di-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside (**14**). — A mixture of **7** (3 g), hexamethylphosphoric triamide (10 ml), and lithium chloride (3 g) was heated to 80° for 24 h; t.l.c. (light petroleum–ethyl acetate, 3:1) then indicated two products of similar mobility, the most mobile being the major. The mixture was processed as described for **13**, and the resulting syrupy product was eluted from a dry-packed column of silica gel with ethyl acetate–light petroleum (1:8) to give, first, **14** (2 g, 71.5%), m.p. 121–123° (from methanol), $[\alpha]_D$ +116° (*c* 0.6, chloroform) (Found: C, 69.3; H, 5.9. $C_{47}H_{48}ClFO_9$ calc.: C, 69.6; H, 5.9%). Mass spectrum: *m/e* 447 (4.0%), 431 (6.3), 381 (1.1), 365 (0.3), 341 (4.5), 339 (2.5), 325 (1.0), 323 (1.0), 273 (1.8), 257 (0.6), 233 (6.3), 217 (3.5), and 181 (100, PhC^+HCH_2Ph). Subsequent fractions contained mixtures of the two components.

2,3-Di-O-benzyl-6-deoxy-6-iodo-4-O-mesyl-α-D-glucopyranosyl 2,3-di-O-benzyl-6-deoxy-6-iodo-4-O-mesyl-α-D-glucopyranoside (**18**) *and 2,3-di-O-benzyl-6-deoxy-6-iodo-4-O-mesyl-α-D-glucopyranosyl 2,3-di-O-benzyl-4,6-di-O-mesyl-α-D-glucopyranoside* (**17**). — A solution of the 4,6,4′,6′-tetramesylate[14] **16** (10 g) and sodium iodide (5 g) in acetone (100 ml) was boiled under reflux for 40 h; t.l.c. (light petroleum–ethyl acetate, 2:1) then indicated two major products. Silica gel (~10 g) was added, the solvent was evaporated, and the resulting dry powder was applied to a dry-packed column of silica gel. Elution with light petroleum–ethyl acetate (1:3) afforded **18** (3.8 g, 36%), m.p. 159–160° (from light petroleum–ethanol), $[\alpha]_D$ +105.5° (*c* 1, chloroform) (Found: C, 46.8; H, 4.55. $C_{42}H_{48}I_2O_{13}S_2$ calc.: C, 46.75; H, 4.5%). Mass spectrum: *m/e* 547 (8.7%), 531 (0.6), 451 (0.2), 439 (3.5), 435 (0.4), 423 (0.9), 343 (0.6), 327 (1.0), and 181 (100, PhC^+HCH_2Ph). N.m.r. data ($CDCl_3$): τ 4.54 (d, 2 H, $J_{1,2}$ 3 Hz, H-1,1′), 5.66 (t, 2 H, $J_{4,5}$ 9 Hz, H-4,4′), 5.91 (t, 2 H, $J_{3,4}$ 9 Hz, H-3,3′), 6.02 (td, 2 H, $J_{5,6a}$ 8 Hz, $J_{5,6b}$ ~2 Hz, H-5,5′), 6.30 (dd, $J_{2,3}$ 9.5 Hz, H-2,2′), 6.59 (dd, 2 H, $J_{6a,6b}$ 11 Hz, H-6a,6′a), 6.90 (dd, 2 H, H-6b,6′b), and 7.19 (6 H, 2 Ms).

Further elution with light petroleum–ethyl acetate (1:2) afforded **17** (3.2 g, 31%), m.p. 58–60° (from light petroleum–ethanol), $[\alpha]_D$ +108° (*c* 1, chloroform) (Found: C, 49.5; H, 5.0. $C_{43}H_{51}IO_{16}S_3$ calc.: C, 49.3; H, 4.9%). Mass spectrum: *m/e* 547 (4.4%), 531 (1.0), 515 (1.7), 499 (0.1), 451 (1.1), 439 (2.8), 435 (1.0), 423 (1.1), 407 (2.2), 391 (1.7), 343 (1.5), 327 (2.8), 311 (1.4), 295 (2.2), and 181 (100, PhC^+HCH_2Ph).

*6-Azido-2,3-di-*O*-benzyl-6-deoxy-4-*O*-mesyl-α-*D*-glucopyranosyl 6-azido-2,3-di-*O*-benzyl-6-deoxy-4-*O*-mesyl-α-*D*-glucopyranoside* (**20**) *and 6-azido-2,3-di-*O*-benzyl-6-deoxy-4-*O*-mesyl-α-*D*-glucopyranosyl 2,3-di-*O*-benzyl-4,6-di-*O*-mesyl-α-*D*-glucopyranoside* (**19**). — A mixture of **16** (10 g), sodium azide (2 g), and *N,N*-dimethylformamide (30 ml) was heated at 85° for 2 h and at 75° for a further 16 h; t.l.c. (light petroleum–ethyl acetate, 2:1) then revealed two products of approximately equal abundance. The mixture was poured into water, and the white precipitate was collected, washed with light petroleum, and eluted from a dry-packed column of silica gel with light petroleum–ethyl acetate (3:1) to give **20** (1.9 g, 21%), m.p. 117–118° (from light petroleum–ethanol), $[\alpha]_D$ +119° (*c* 1, chloroform) (Found: C, 55.4; H, 5.0; S, 7.35. $C_{42}H_{48}N_6O_{13}S_2$ calc.: C, 55.5; H, 5.3; S, 7.05%). N.m.r. data ($CDCl_3$) τ 4.75 (d, 2H, $J_{1,2}$ 3 Hz, H-1,1′), 5.53 (t, 2 H, $J_{4,5}$ 10 Hz, H-4,4′), 5.80 (dd, 2 H, $J_{5,6}$ 4 Hz, H-5,5′), 5.96 (t, 2 H, $J_{3,4}$ 9 Hz, H-3,3′), 6.34 (dd, 2 H, $J_{2,3}$ 9.0 Hz, H-2,2′), 6.70 (d, 4 H, H-6,6′), and 7.18 (s, 6 H, 2 Ms).

Further elution gave **19** (1.65 g, 17%), m.p. 165–167° (from light petroleum–ethanol), $[\alpha]_D$ +122.5° (*c* 1, chloroform) (Found: C, 53.6; H, 5.2; N, 4.6; S, 10.3. $C_{43}H_{51}N_3O_{16}S_3$ calc.: C, 53.7; H, 5.3; N, 4.4; S, 10.0%).

ACKNOWLEDGMENTS

The authors thank the Physico-Chemical Measurements Unit at Harwell for the ^{1}H-n.m.r. spectra, Queen Elizabeth College for the award (to A.F.H.) of a demonstratorship (1971–1974), the Wellcome Foundation (Cooper Technical Bureau) for trehalase studies, and Professor J. Defaye (C.N.R.S. Grenoble) for his co-operation in the exchange of results.

REFERENCES

1 C. K. Lee and M. G. Lindley *Carbohydr. Res.*, 63 (1978) 277–282.
2 F. Arcamone and F. Bizioli, *Gazz. Chim. Ital.*, 87 (1957) 896–902; S. Umezawa, K. Tatsuta and R. Muto, *J. Antibiot., Ser. A*, 20 (1967) 388–389; M. Uratomoto, N. Otaka, and Y. Yonehara, *ibid.*, (1967) 236–237.
3 H. Naganawa, N. Usui, T. Takita, M. Hamada, K. Maeda, and H. Umezawa, *J. Antibiot., Ser. A*, 27 (1974) 145–146.
4 A. Klemer and R. Kutz, *Tetrahedron Lett.*, (1969) 1693; A. Klemer, E. Buhe, R. Kutz, S. Chahin, and L. Kleefeldt, *Justus Liebigs Ann. Chem.*, 739 (1970) 185–193.
5 E. Bar-Guilloux, J. Defaye, H. Driguez, and D. Robic, *Carbohydr. Res.*, 45 (1975) 217–236.
6 S. Glasstone, *Textbook of Physical Chemistry*, MacMillan, London, 2nd edition, 1956, p. 1075.
7 (a) A. C. Richardson and E. Tarelli, *J. Chem. Soc.*, C, (1971) 3733–3735; (b) C. K. Lee, *Carbohydr. Res.*, 50 (1976) 152–157.

8 B. HELFERICH AND G. VON STRYK, *Ber.*, 14 (1941) 1794–1798.
9 G. BIRCH, *J. Chem. Soc.*, (1965) 3489–3490.
10 E. R. GUILLOUX, F. PERCHERON, AND J. DEFAYE, *Carbohydr. Res.*, 10 (1969) 267–278.
11 R. TOUBIANA, M. J. TOUBIANA, B. C. DAS, AND A. C. RICHARDSON, *Biochimie*, 55 (1973) 569–573.
12 S.-HANESSIAN AND P. LAVALLÉE, *Carbohydr. Res.*, 28 (1973) 303–311.
13 L. HOUGH, A. K. PALMER, AND A. C. RICHARDSON, *J. Chem. Soc. Perkin Trans. 1*, (1972) 2513–2517.
14 L. HOUGH, A. K. PALMER, AND A. C. RICHARDSON, *J. Chem. Soc. Perkin Trans. 1*, (1973) 784–788.
15 N. K. KOCHETKOV AND O. S. CHIZHOV, *Adv. Carbohydr. Chem.*, 21 (1966) 39–93.
16 R. C. YOUNG, Ph.D. Thesis, Oxford University, 1968.
17 L. PHILIPS AND V. WRAY, *J. Chem. Soc., C*, (1971) 1618–1624.
18 G. G. BIRCH, C. K. LEE, AND A. C. RICHARDSON, *Carbohydr. Res.*, 36 (1974) 97–109.
19 G. G. BIRCH AND A. C. RICHARDSON, *J. Chem. Soc., C*, (1970) 749–752.
20 J. DEFAYE, H. DRIGUEZ, B. HENRISSAT, J. GELAS, AND E. BAR-GUILLOUX, *Carbohydr. Res.*, 63 (1978) 41–49.