Tetrahedron, 1967, Vol. 23, pp. 1641 to 1646. Pergamon Press Ltd. Printed in Northern Ireland

SELECTIVE ACYLATION OF PYRANOSIDES—II.

BENZOYLATION OF METHYL 6-DEOXY-α-L-GALACTOPYRANOSIDE AND METHYL 6-DEOXY-α-L-MANNOPYRANOSIDE

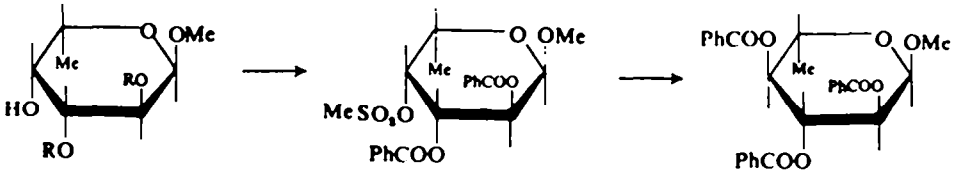
A. C. RICHARDSON
Department of Chemistry, The University, Whiteknights Park, Reading
and
J. M. WILLIAMS*
Department of Chemistry, The University, Bristol

(*Received* 7 *July* 1966; *accepted for publication* 19 *August* 1966)

Abstract—Selective dibenzoylation of methyl 6-deoxy-α-L-galactopyranoside (-α-L-fucopyranoside) and methyl 6-deoxy-α-L-mannopyranoside (-α-L-rhamnopyranoside) gives the amorphous 2,3-dibenzoates in 80% and 50% yields respectively after chromatographic purification. The fucoside dibenzoate may be isolated directly in 85% yield as its crystalline methanesulphonate ester.

SELECTIVE benzoylation of pyranosides has been shown to provide a facile route to to some useful synthetic intermediates.[1] It was shown that the 4-OH group of methyl α-D-glucopyranoside, methyl-α-D-mannopyranoside and methyl-α-D-galactopyranoside was the least reactive towards benzoylation. We have now extended our studies on selective benzoylation to methyl 6-deoxy-α-L-galactopyranoside (α-L-fucopyranoside) and methyl 6-deoxy-α-L-mannopyranoside (α-L-rhamnopyranoside) in order to determine whether the presence of a Me rather than a hydroxy-methyl group at C_5 influences the reactivity of the 4-OH group, and also to widen the range of glycosides with specific protecting benzoate groups.

Reaction of methyl 6-deoxy-α-L-galactopyranoside (I) with 2·1 equivs of benzoyl chloride in pyridine at −40° afforded a chromatographically pure syrupy dibenzoate in 80% yield after column chromatography on silica gel. The dibenzoate gave a crystalline methanesulphonate derivative, which could also be isolated in 85% overall yield directly from methyl fucoside without isolation of the dibenzoate. The



I; R = H

II; R = COPh III IV

methanesulphonate reacted smoothly with sodium benzoate in a mixture of dimethylformamide and dimethylsulphoxide at 130° to give methyl 6-deoxy-α-L-glucopyranoside tri-*O*-benzoate (IV), which was identified by comparison with its enantiomer. Since benzoate replacements of this kind occur with inversion of configuration,[2] the

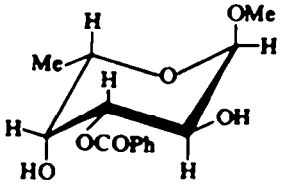
* Present address: Department of Chemistry, University College, Swansea.

[1] J. M. Williams and A. C. Richardson, *Tetrahedron* **23**, 1367 (1967).

[2] E. J. Reist, R. R. Spencer and B. R. Baker, *J. Org. Chem.* **24**, 1618 (1959).

methanesulphonate group must be situated at C_4 as in III and the dibenzoate must therefore be the 2,3-isomer II.

The chromatographic fractionation also yielded two other products, namely the hitherto unknown 2,3,4-tribenzoate (11%) and a monobenzoate (6%). The structure of the syrupy monobenzoate was clearly indicated by its PMR spectrum, which showed that one ring proton occurred as a quartet at a lower field (τ 4·79) than all others. Previous work (cf. Ref. 1) has shown that a ring proton attached to the same carbon as a benzoyloxy substituent usually occurs to low field of other ring protons. The spacings of the low-field quartet (10·1 and 3·1 c/s) corresponded to coupling between axial–axial and axial–equatorial protons respectively. The H_1 doublet at



V

τ 5·29 had a spacing of 3·8 c/s, and its asymmetry indicated that it was coupled to a proton to high field. Consequently the low field quartet at τ 4·79 was assigned to H_3, and so the monobenzoate is methyl 3-*O*-benzoyl-6-deoxy-α-L-galactopyranoside (V) for which $J_{1,2} = 3{\cdot}8$, $J_{2,3} = 10{\cdot}1$ and $J_{3,4} = 3{\cdot}1$ c/s. Attempted monobenzoylation of the 6-deoxy galactoside using one molar equiv of benzoyl chloride gave what appeared to be two monobenzoates as major products, of which one appeared to be the 3-benzoate by TLC.

Reaction of methyl 6-deoxy-α-L-mannopyranoside (VI) with 2 molar equivs of benzoyl chloride at room temperature gave an amorphous dibenzoate which was isolated, in 50% yield, as a glass containing small amounts of impurities after column chromatography. The compound was readily characterized as the crystalline monoacetate, which was formed under mild conditions. More vigorous conditions, namely 100° for 21 hr, were required to prepare the toluene-*p*-sulphonate.

It has been demonstrated[3] that migration of acetate ester groups can take place during the sulphonylation of hindered OH groups when forcing conditions are employed. Consequently the sulphonate could not be utilized to provide an unequivocal proof of structure for the dibenzoate.

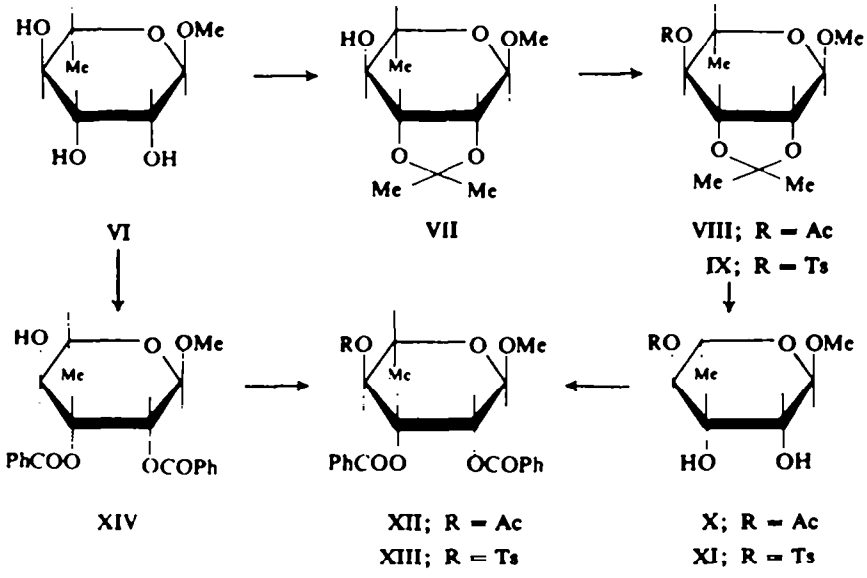
By analogy with the tribenzoylation of methyl α-D-mannopyranoside,[1] it was predicted that the dibenzoate was the 2,3-isomer XIV. Consequently the synthesis of methyl 4-*O*-acetyl-2,3-di-*O*-benzoyl-6-deoxy-α-L-mannopyranoside by a definitive route was undertaken for comparison with the acetate derived from the dibenzoate. Methyl 6-deoxy-α-L-mannopyranoside (VI) was first converted to the 2,3-*O*-isopropylidene derivative[4] which afforded a crystalline acetate (VIII) in 52% yield. Removal of the ketal function by mild acid hydrolysis gave methyl 4-*O*-acetyl-6-deoxy-α-L-mannopyranoside (X) in 76% yield. Previous work[5] has indicated that carboxylic

[3] S. J. Angyal, P. T. Gilham and G. J. H. Melrose, *J. Chem. Soc.*, 5252 (1965).

[4] P. A. Levene and I. E. Muskat, *J. Biol. Chem.* **105**, 431 (1934).

[5] B. Helferich, H. Bredereck and A. Schneidermuller, *Analyt. Chem.* **458**, 111 (1927); E. J. Reist, R. R. Spencer and B. R. Baker, *J. Org. Chem.* **23**, 1757 (1958); A. C. Richardson, *J. Chem. Soc.* 5364 (1964).

esters do not normally undergo migration under acidic conditions, but in order to check that acetyl migration had not occurred the isopropylidene acetate VIII was reconstituted in 52% yield by reaction of the monoacetate X with acetone in the presence of anhydrous copper sulphate and a trace of sulphuric acid. Furthermore, the monoacetate X consumed 1·04 equivs of sodium metaperiodate. Benzoylation of the 4-*O*-acetate X afforded methyl 4-*O*-acetyl-2,3-di-*O*-benzoyl-6-deoxy-α-L-mannopyranoside (XII) which was identical with the acetate derived by acetylation of the dibenzoate, which must therefore be the 2,3-isomer XIV. The 2,3-dibenzoate-4-toluene-*p*-sulphonate (XIII) was synthesized by an exactly analogous procedure



(VII → IX → XI → XIII) and was identical with that obtained by toluene-*p*-sulphonylation of the dibenzoate at 100°, showing that migration of a benzoyl group had not occurred during the reaction. Similar partial benzoylation studies have been carried out on 6-deoxy-L-mannose (L-rhamnose), and a tribenzoate and a dibenzoate were isolated in fair and poor yields respectively but no structural work was reported.[6]

The above results are analogous to those obtained for methyl α-D-galactopyranoside and methyl α-D-mannopyranoside and consequently the absence of the 6-OH group appears to have little or no effect upon the reactivity of the 4-OH group*. The selective benzoylation of the equatorial OH groups in methyl 6-deoxy-β-D-allopyranoside has recently been reported[7] but neither the homogeneity nor the structure of the dibenzoate was proved.

* It should be noted that in the hexopyranosides the 6-OH group is probably benzoylated first and so the comparison with the 6-deoxy-hexopyranosides actually involves a comparison of the influence of benzoyloxymethyl and Me groups on the 4-OH group.

[6] A. T. Ness, H. B. Fletcher and C. S. Hudson, *J. Amer. Chem. Soc.* 73, 296 (1951).
[7] A. F. Krasso and E. Weiss, *Helv. Chim. Acta* 49, 1113 (1966).

It is noteworthy that the fucoside 2,3-dibenzoate (II) is complimentary to the 3,4-*O*-isopropylidene derivative inasmuch as they provide routes to 4- and 2-substituted derivatives respectively. The derived methanesulphonate (III) undergoes nucleophilic displacement reactions with ease giving 4-substituted derivatives of 6-deoxy-L-glucose. For example preliminary experiments indicate that it reacts smoothly with sodium azide in N,N,-dimethylformamide at 130° to give what is presumably methyl 4-azido-2,3-di-*O*-benzoyl-4-deoxy-α-L-glucopyranoside, thus providing a route to 4-amino-4,6-dideoxy-L-glucose, the enantiomer of which occurs in *Chromobacterium violaceum*[8] and in the antibiotic amicetin as the di-N-methyl derivative[9]. The 4-toluene-*p*-sulphonate (XIII) derived from the rhamnoside appears to be resistant to similar nucleophilic displacement reactions. This resistance has also been observed[1] in methyl 2,3,6-tri-*O*-benzoyl-4-*O*-methanesulphonyl-α-D-mannopyranoside and may be attributed to steric hindrance in the S_N2 transition state caused by the axial 2-benzoyloxy group.

EXPERIMENTAL

For general methods, including selective benzoylation, see Part I.[1]

Dimolar benzoylation of methyl 6-deoxy-α-L-galactopyranoside

Methyl 6-deoxy-α-L-galactopyranoside (0·89 g) in anhyd pyridine (30 ml) was treated with benzoyl chloride (1·2 ml, 2·1 equivs). The crude product could not be crystallized and TLC indicated the presence of one major component together with small amounts of two others. Fractionation of the mixture on a column of silica gel (150 g) using benzene–ether as solvent afforded 3 fractions, the 2,3,4-*tri-O-benzoate* (0·28 g, 11%), large rectangular prisms from ether–light petroleum, m.p. 147–148°, $[\alpha]_D$ −260° (*c* 0·85, chf) (Found: C, 69·0; H, 5·3. $C_{34}H_{28}O_8$ requires: C, 68·6; H, 5·35%); the syrupy 2,3-*dibenzoate* (1·54 g, 80%), $[\alpha]_D$ −187° (*c* 4·03, chf) (Found: C, 64·7; H, 5·7. $C_{31}H_{28}O_7$ requires: C, 65·3; H, 5·7%) and syrupy 3-*O-benzoate* (0·08 g, 6%). The latter in acetone soln showed resonances at τ 4·79 (qu, J's 10·1 and 3·1 c/s), 5·29 (d, J 3·8 c/s), 5·85 (qu, J's 10·1 and 3·8 c/s), 5·9–6·2 (complex m), 6·62 (s, OCH_3), 6·54 and 6·70 (broad s's), 8·78 (d, C—CH_3).

Monomolar benzoylation of the glycoside showed low selectivity. TLC indicated that a small amount of the dibenzoate was formed together with two monobenzoates formed in approximately equal amounts, of which one co-chromatographed with the 3-*O*-benzoate, and some unchanged starting material remained. The mixture was not separated.

Methyl 2,3-di-O-benzoyl-6-deoxy-4-O-methanesulphonyl-α-L-galactopyranoside

(a) The syrupy dibenzoate (175 mg) in dry pyridine (5 ml) was treated with methanesulphonyl chloride (0·04 ml, 1·2 equivs) and kept at room temp for 24 hr. The reaction mixture was treated with one drop of water and then poured into cold water. After standing overnight at +5°, the solid was filtered off and washed well with water; yield 186 mg (90%), m.p. 162–164°, [α] −159° *c* 1·03, chf). (Found: C, 56·8; H, 5·25; S, 6·9. $C_{28}H_{28}O_9S$ requires: C, 56·85; H, 5·2; S, 6·9%.)

(b) Methyl 6-deoxy-α-L-galactoside (0·89 g) in dry pyridine (30 ml) was benzoylated with benzoyl chloride (1·21 ml) as described previously, but after 26 hr methanesulphonyl chloride (0·46 ml, 1·2 equiv) was added. After standing ambient overnight the reaction mixture was poured into iced-water (150 ml) whereupon the crude product separated (2·32 g, m.p. 145–160°). Recrystallization from chf–light petroleum (b.p. 80–100°) gave the *methanesulphonate* (1·96 g, 85%), m.p. 163–163·5°.

Nucleophilic replacement reactions of methyl 2,3,-di-O-benzoyl-6-deoxy-4-O-methane-sulphonyl-α-L-galactopyranoside

(a) *With benzoate.* A soln of the 4-sulphonate (107 mg) in a mixture of N,N-dimethylformamide (2 ml) and DMSO (1 ml) was heated at 130° for 25 hr with sodium benzoate (70 mg). TLC indicated

[8] C. L. Stevens, P. Blumbergs, F. A. Daniher, R. W. Wheat, A. Kujomoto and E. L. Rollins, *J. Amer. Chem. Soc.* **85**, 3061 (1963).

[9] C. L. Stevens, P. Blumbergs and F. Daniher, *J. Amer. Chem. Soc.* **85**, 1552, (1963).

that one product was formed. The cooled reaction mixture was then partitioned between chf (2 × 10 ml) and water (5 ml). The combined chf layers were washed with water (2 × 10 ml) and then dried ($MgSO_4$). Concentration of the organic layer gave a crystalline residue (105 mg, m.p. 130–146°), recrystallization of which from EtOH and then from MeOH gave methyl 6-deoxy-α-L-glucopyranoside tri-*O*-benzoate (57 mg, 50%), m.p. 147–148°, $[\alpha]_D$ −57° (*c* 0·42, chf, the IR spectrum of which was identical with an authentic specimen of the D-enantiomorph [m.p. 148–148·5, $[\alpha]_D$ +53° (*c* 0·62, chf)], prepared from methyl 6-deoxy-α-D-glucopyranoside.[10] The m.p. of the glucoside was very sensitive to small amounts of impurities, starting material in this case as indicated by TLC, hence the low yield of pure product.

(b) *With azide.* The methanesulphonate (193 mg) in N,N-dimethylformamide (3 ml) was heated with sodium azide (81 mg) at 130° for 19 hr. TLC (benzene–ether, 5:1) showed that the displacement proceeded smoothly to give the azide and a trace of a less mobile compound. The reaction mixture was poured into water (20 ml), and chf extraction afforded a syrupy product which did not crystallize even after purification by preparative TLC. The IR spectrum indicated the presence of an azide group (ν_{max} 2100 cm^{-1}) and the absence of sulphonate groups. The product was not further characterized.

Dimolar benzoylation of methyl 6-deoxy-α-L-mannopyranoside

Methyl 6-deoxy-α-L-mannopyranoside (7·7 g) was dissolved in dry pyridine (50 ml) and benzoyl chloride (10 ml; 2 moles) was then added in about 4 portions with simultaneous cooling of the reaction mixture under running tap water. After the addition was complete the reaction mixture was kept for 1 hr at room temp and then poured into a large excess of water. The mixture was then extracted with ether (100 ml) and the ethereal layer washed with dil HClaq (4 × 50 ml) and dil NaOHaq (50 ml) followed by water. After drying ($MgSO_4$) the ethereal layer was concentrated to a glass (14 g; 84% based on the dibenzoate). Examination of the product by TLC using ether–light petroleum (2:1 v/v) indicated the presence of 4 components. The faster material co-chromatographed with methyl α-L-rhamnoside tri-*O*-benzoate and was present in small amounts only. Two components moved with medium mobility and of these the slower was present in small amounts only whereas the other was the major product of the reaction mixture. A much slower moving component was present in trace amounts only.

Distillation of the product at 205–215°/0·4 min did not remove the impurities. Partial separation of the components was achieved on a column of silica gel using ether–light petroleum (2:1 v/v) as eluent. The major component, *methyl 6-deoxy* α-L-*mannopyranoside* 2,3-*di*-O-*benzoate* (8·3 g; 50%) was obtained contaminated with a small amount of the component having a similar mobility on TLC. The NMR spectrum showed two peaks due to OMe, at τ's 6·61 and 6·58 in a ratio 7:1 indicating that the major product was present to the extent of 88%. The glass had $[\alpha]_D$ +76° (*c* 3·4, chf). (Found: C, 65·5; H, 5·7; $C_{21}H_{22}O_7$ requires: C, 65·3; H, 5·7%.)

Acetylation of crude dibenzoate

The glass (1·2 g) was dissolved in pyridine (5 ml) and the soln treated with Ac_2O (5 ml). TLC indicated that the reaction was rapid and complete within ca. 15 min. After ca. 1 hr the reaction mixture was poured into water and the product isolated by ether extraction. The syrup so obtained crystallised and recrystallized from EtOH afforded a *monoacetyl dibenzoate* (0·67 g, 50%), m.p. 40–60°, $[\alpha]_D$ +111° (*c* 2, chf). (Found: C, 64·2; H, 5·7. $C_{23}H_{24}O_7$ requires: C, 64·35; H, 5·6%.) Repeated recrystallization from EtOH did not alter the wide range of the m.p.

Toluene-p-sulphonylation of the crude dibenzoate

The dibenzoate (2·4 g) was dissolved in pyridine (25 ml) and toluene-*p*-sulphonyl chloride (6 g) added. TLC indicated that the reaction was extremely slow at room temp so the mixture was heated on a water bath for 21 hr, when chromatography indicated that reaction was complete. The reaction mixture was then poured into water and the precipitated gum isolated by extraction with ether. The resulting syrup crystallized and was recrystallized from EtOH to give the *toluene-p-sulphonate*, m.p. 103–106°, $[\alpha]_D$ +163° (*c* 1·5, chf) (1·66 g; 51%). A further recrystallization from EtOH gave the analytical sample, m.p. 107–109°. (Found: C, 62·0; H, 5·45. $C_{28}H_{28}O_9S$ requires C, 62·2; H, 5·2%.)

[10] J. S. Brimacombe, M. C. Cook and L. C. N. Tucker, *J. Chem. Soc.* 2292 (1965).

Methyl 4-O-acetyl-6-deoxy-2,3-O-isopropylidene-α-L-mannopyranoside

Methyl 6-deoxy-2,3-*O*-isopropylidene-α-L-mannopyranoside[8] (4·6 g) was dissolved in pyridine (20 ml) and treated with Ac_2O (20 ml). TLC indicated that the reaction was complete after ca. 10 min. After 30 min at room temp the reaction mixture was poured into water and the precipitated gum was isolated by extraction with ether as before. The resulting product crystallized and recrystallization from aqueous MeOH gave the 4-*O-acetate* (2·9 g; 52%), m.p. 61–63°, $[\alpha]_D$ −14·5° (*c* 2·8, chf). (Found; C, 55·6; H, 7·45. $C_{15}H_{26}O_8$ requires: C, 55·4; H, 7·7%.)

Methyl 4-O-acetyl-6-deoxy-α-L-mannopyranoside

The 4-*O*-acetyl-2,3-ketal (1·27 g) was dissolved in MeOH (8 ml) containing 2% HCl, and the reaction followed chromatographically (ether-light petroleum 2:1 v/v). The reaction was complete within ½ hr. After 50 min the reaction mixture was neutralized with an excess solid $NaHCO_3$, diluted with ether, and after a further ½ hr the mixture was filtered and concentrated. The resulting syrup was dissolved in warm ether and the cloudy soln filtered. Addition of light-petroleum gave *fine needles* (0·82 g; 76%), m.p. 112–116° with premelting from 106°, $[\alpha]_D$ −55° (*c* 1·8, H_2O). (Found: C, 49·05; H, 7·4. $C_9H_{16}O_6$ requires: C, 49·0; H, 7·3%.) The product reduced 1·04 moles of periodate during the course of 16 hr.

The above acetate (124 mg) in acetone (10 ml) was treated with $CuSO_4H_2O$ (*ca.* 1 g) and 1 drop of H_2SO_4. The mixture was shaken overnight, and then neutralized by the addition of a few drops of conc NH_4OH. Filtration followed by concentration gave a crystalline residue, recrystallization of which from aqueous MeOH yielded methyl 4-*O*-acetyl-6-deoxy-2,3-*O*-isopropylidene-α-L-mannopyranoside (98 mg; 52%), m.p. 61–63°, identified by its IR spectrum.

Methyl 4-O-acetyl-2,3-di-O-benzoyl 6-deoxy-α-L-mannopyranoside

The above 4-*O*-acetate (0·6 g) in pyridine (6 ml) was treated with benzoyl chloride (1 ml) and the mixture kept at room temp for 2 hr. The reaction mixture was then poured into water and the product isolated by ether extraction. The resulting colourless syrup was crystallized from EtOH to give the *dibenzoate*, (0·77 g; 66%) m.p. 40–60°. The IR spectrum was identical with the acetate prepared by acetylation of the rhamnoside dibenzoate.

Methyl 2,3-di-O-benzoyl-6-deoxy-4-O-toluene-p-sulphonyl-α-L-mannopyranoside

Methyl-6-deoxy-2,3-*O*-isopropylidene-α-L-mannopyranoside (9·3 g) was dissolved in dry pyridine (25 ml) and toluene-*p*-sulphonyl chloride (18 g) added. The reaction was slow but was conveniently followed by TLC (ether–light petroleum, 2:1 v/v). The reaction was complete after 48 hr and the mixture was treated with water. Chf extraction yielded the sulphonate as a syrup (14 g; 90%), $[\alpha]_D$ +19° (*c* 2, chf) which did not crystallize. Levene and Muskat[9] record m.p. 58°, $[\alpha]_D$ +14° (MeOH) for this compound.

A portion (1·53 g) of the above product was dissolved in MeOH (10 ml) and then treated with MeOH (20 ml) containing *ca.* 2% HCl. After 45 min optical rotation had attained a constant value of −0·200° from an initial extrapolated value of +0·120° (0·1 dm tube). At this stage the acid was neutralized by addition of an excess of solid $NaHCO_3$, and the supernatant soln decanted from the solid material. Concentration afforded a syrup contaminated with a little inorganic material, which was removed by fractionation between chf and water, followed by concentration of the dried organic layer to a colourless syrup (*ca.* 1·2 g) which did not crystallize.

The product was then benzoylated in pyridine (10 ml) with benzoyl chloride (3 ml). Chromatography showed that the reaction was rapid and after 2 hr the reaction was worked through in the usual manner. The resulting product crystallized with ease from EtOH to give the sulphonate (1·17 g; 52% overall), m.p. 108–109°. The IR spectrum of the product was identical with that of the toluene-*p*-sulphonate derived from the rhamnoside dibenzoate.

Acknowledgements—We thank Dr. L. Hough for his advice and encouragement, and we are indebted to Dr. C. Cone and Dr. J. S. Brimacombe for generous gifts of methyl α-L-fucopyranoside and methyl 6-deoxy-α-D-glucopyranoside respectively.