C-Nucleoside Studies. Part 13.[1] A New Synthesis of 2,3,5-Tri-*O*-benzyl-α(and β)-D-ribofuranosylethyne Involving Benzyloxy Participation, and a Synthesis of α-Showdomycin

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2,3,4,6-Tetra-*O*-benzyl-D-glucitol (5) reacts with toluene-*p*-sulphonyl chloride in pyridine at 60 °C to form mainly the furanoid products 2,3,6-tri-*O*-benzyl-1,4-anhydro-D-glucitol (10) and its 5-toluene-*p*-sulphonate (11) with loss of the 4-*O*-benzyl group. The pyranoid product tetra-*O*-benzyl-1,5-anhydro-D-glucitol preponderates when the intermediate 2,3,4,6-tetra-*O*-benzyl-1-*O*-toluene-*p*-sulphonyl-D-glucitol (6) is converted into its 0–5 oxyanion. Benzyloxy participation has been exploited in a new synthesis of 2,3,5-tri-*O*-benzyl-α (and β)-D-ribofuranosylethyne, (20) and (4), from 2,3,4,5-tetra-*O*-benzyl-*aldehydo*-D-ribose. A synthesis of 2-α-D-ribofuranosylmaleimide, the α-isomer of showdomycin, from (20) is described.

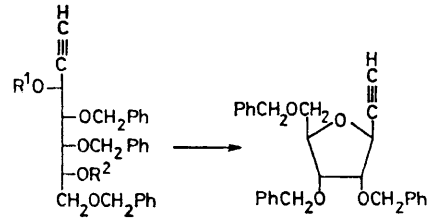
In our studies of *C*-nucleoside synthesis [2] a key reaction has been the cyclisation of acyclic polyol derivatives.[2-7] The β-D-ribofuranosylethyne (4) [2] is derived from the acetylenic D-*altro*-diol (1) by toluene-*p*-sulphonylation in pyridine at 60 °C to give, regioselectively, the 3-sulphonate (2) which undergoes spontaneous ring closure. Exclusive formation of a furanoid ring was ensured by the location of the benzyl groups in (1). We have now carried out some model experiments on the ring closure of 2,3,4,6-tetra-*O*-benzyl-D-glucitol (5) which were designed to give the anhydro-compound (8) containing a pyranoid ring. The results have proved of general interest for the synthesis of both pyranoid and furanoid derivatives.

RESULTS AND DISCUSSION

The diol (5) [8] was prepared from the parent sugar [9] by reduction with sodium borohydride. Treatment with toluene-*p*-sulphonyl chloride (2 mol equiv.) in pyridine [2-4] at 60 °C afforded three products which were isolated by chromatography on silica gel. Tetra-*O*-benzyl-1,5-anhydro-D-glucitol (8), the product of ring-closure through the C-5 hydroxy-group, was isolated in only 12% yield; its structure was proved by hydrogenolysis to give 1,5-anhydro-D-glucitol (9).[10] The major reaction product was 2,3,6-tri-*O*-benzyl-1,4-anhydro-D-glucitol (10) (40%), together with its 5-toluene-*p*-sulphonate (11) (13%). The structure of (10) was shown by hydrogenolysis to 1,4-anhydro-D-glucitol (12),[11] and the structure of (11) by its preparation from (10) by toluene-*p*-sulphonylation. Hydrogenolysis of (11) gave a crystalline 5-toluene-*p*-sulphonate (13).

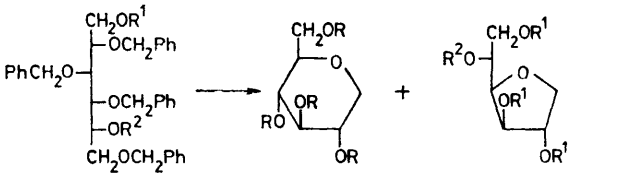
It is clear that in all these reactions the first step involves sulphonylation of the primary hydroxy-group to give the mono-toluene-*p*-sulphonate (6). This is then capable of ring closure by one of two pathways to give a six- or a five-membered ring. The former involves a hydroxy-group and might have been expected to be the preferred pathway, as in (14) ⟶ (15) but ring closure to give the five-membered ring occurs more readily even although it requires loss of a benzyl group, as in the sequence (16) ⟶ (17). The sulphonate (11) may arise by sulphonylation of (10) and/or ring closure of the bis-toluene-*p*-sulphonate (7).

Participation by an ether oxygen atom in the solvolysis of a sulphonate is well known. It is most favourable when the intermediate oxonium ion is part of a five-membered ring (RO-5 participation) and less so when the



(1) $R^1 = R^2 = H$
(2) $R^1 = Ts, R^2 = H$
(3) $R^1 = R^2 = Ts$

(4)



(5) $R^1 = R^2 = H$
(6) $R^1 = Ts, R^2 = H$
(7) $R^1 = R^2 = Ts$

(8) $R = CH_2Ph$
(9) $R = H$

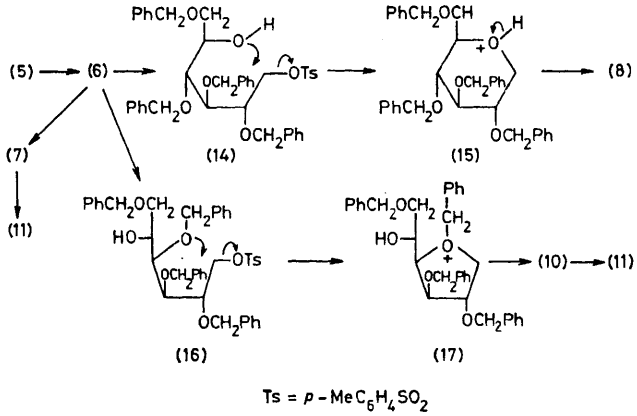
(10) $R^1 = CH_2Ph, R^2 = H$
(11) $R^1 = CH_2Ph, R^2 = Ts$
(12) $R^1 = R^2 = H$
(13) $R^1 = H, R^2 = Ts$

Ts = *p*-$MeC_6H_4SO_2$

ring is six-membered (RO-6 participation).[12,13] There are several known examples of RO-5 participation involving carbohydrate benzyl ethers.[14-17] In most of these the intermediate oxonium ion undergoes benzyl–oxygen cleavage because of the relative stability of the benzyl cation.

It is likely that formation of the anhydride (8) in pyridine solution involves participation by a neutral hydroxy-group, as in the sequence (6) ⟶ (14) ⟶ (15) ⟶ (8). Similar ring closures of polyol sulphonates

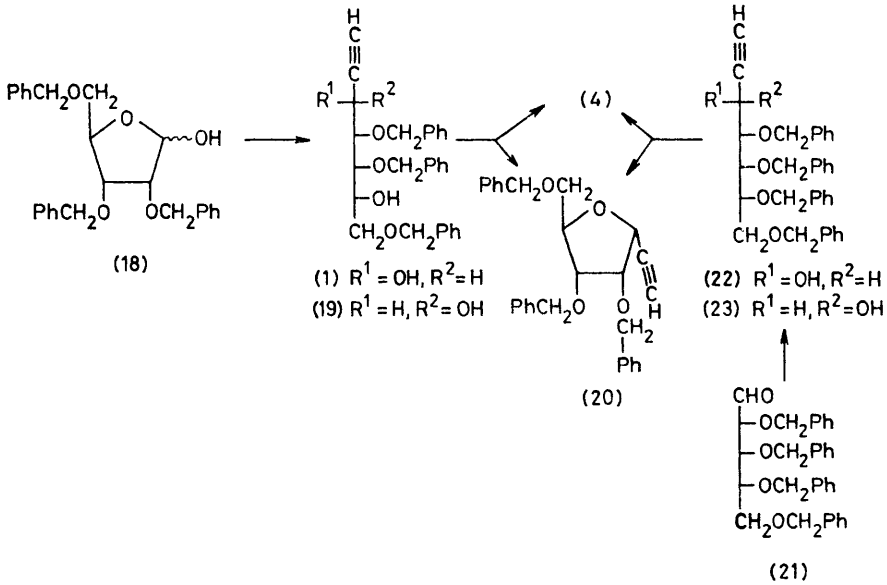
in pyridine to give five-membered rings are well known,[18-22] and a six-membered ring has also been reported.[23] These ring closures must involve participation by a neutral hydroxy-group because the use of more basic conditions, which permits alkoxide formation, gives three-membered rings.[24,25]



It was of interest to examine the effect of generating an alkoxide ion at C-5 in the mono-toluene-*p*-sulphonate (6). An attempt was made to prepare (6) by treatment of the diol (5) with toluene-*p*-sulphonyl chloride in pyridine at 0 °C, but it decomposed on attempted purification. When methanolic sodium methoxide was added to a chloroform solution containing (6) and the mixture was refluxed the major product was the pyranoid anhydride (8) (43%) together with the 1,4-anhydrides (10) (13%) and (11) (20%). In another experiment the diol (5) was treated with the sulphonyl chloride at 0 °C to give the crude mono-toluene-*p*-sulphonate (6), which was heated in chloroform–pyridine to give the 1,4-anhydro-D-glucitols (10) (60%) and (11) (8%) as major products together with the 1,5-anhydride (8) (4%). No attempt was made to optimise these conditions, but it was clear that the presence of a stronger base, sodium methoxide, increased the amount of (8) produced, presumably *via* the oxyanion of (6).

The previous examples of benzyl O-5 participation in carbohydrate chemistry [14-17] have been treated mainly from a mechanistic point of view and have not, to our knowledge, been utilised synthetically. A possible application of benzyloxy participation lay in a new synthesis of the 2,3,5-tri-*O*-benzyl-D-ribofuranosylethynes [(4) and (20)],[2] and their derivatives with substituents on the ethynyl group.[4,7]

In the earlier synthesis,[2] reaction of 2,3,5-tri-*O*-benzyl-D-ribofuranose (18) with ethynylmagnesium bromide afforded, in high yield, a mixture (7 : 3) of D-*altro*- and D-*allo*-diols, (1) and (19), which gave the products (4) and (20), respectively, on ring closure. During reaction with toluene-*p*-sulphonyl chloride in pyridine a complication arose because of the C-6 hydroxy-group. Although the β-D-ribofuranosylethyne (4) is the major product (52% from the diol mixture) the bis-toluene-*p*-sulphonate (3) can also be isolated from the reaction. We have now overcome this complication by the use of 2,3,4,5-tetra-*O*-benzyl-*aldehydo*-D-ribose (21) [26] as the substrate for the Grignard reaction. Treatment of (21) with ethynylmagnesium bromide afforded a mixture of D-*altro*- and D-*allo*-alcohols [(22) and (23)] in good yield. When this mixture was treated with toluene-*p*-sulphonyl chloride in pyridine at room temperature the ribofuranosylethynes (4) and (20) were formed in 41 and 42% yield, respectively. Detailed arguments [2,3a] indicate that (4) arose from the D-*altro*-alcohol (22) and (20) from the D-*allo*-alcohol (23). The ring closure is a very clean reaction and, surprisingly, occurs more readily than in the diols (1) and (19), which require heating with the same reagents. The difference is probably due to different rates of toluene-*p*-sulphonylation because in neither



case can a mono-toluene-*p*-sulphonate be detected as an intermediate. There was no evidence for the formation from (22) and (23) of any product containing a pyranoid ring.

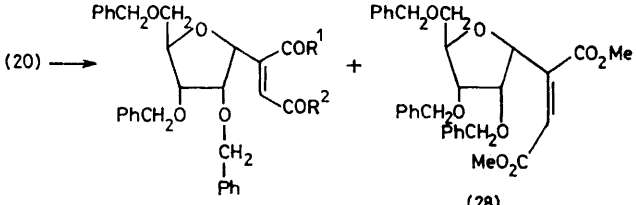
This case of benzyl O-5 participation is one of the most favourable yet reported in the carbohydrate fields. In previous examples [14–17] the toluene-*p*-sulphonates were isolated and subjected to solvolysis. Most of these examples [15–17] have involved formation of a bicyclic system and this may introduce extra conformational energy in the transition state. Although 2,3,4-tri-*O*-benzyl-1,5-di-*O*-toluene-*p*-sulphonylribitol is apparently analogous to the toluene-*p*-sulphonates of (22) and (23), its slow solvolysis in boiling ethanol [14] can be explained by the presence of an electron-withdrawing toluene-*p*-sulphonyloxy-group vicinal to the participating group. There appears to be an analogy between the benzyl O-5 participation in the sulphonates of (22) and (23) and the rapid ring closure (*via* participation of a neutral hydroxy-group) observed in toluene-*p*-sulphonylation of D-ribose di-isobutyl dithioacetal.[20]

The method described has the further advantage that the use of the *aldehydo*-sugar (21), as opposed to the hemiacetal (18), does not require a large excess of Grignard reagent. This may be important if more complex reagents such as 3,3-diethoxypropynylmagnesium bromide [7] are used. A disadvantage from the point of view of synthesising *C*-nucleosides in the naturally-occurring β-series is that reaction of (21) with ethynylmagnesium bromide is not stereoselective, despite the predictions of the Cram cyclic model for steric control.[2] The large number of ether oxygen atoms in an acyclic molecule such as (21) makes predictions very difficult.[27] Finally, it may be noted that there have been two recent examples of ring closure [6,28] to form a furanoid ring accompanied by removal of an acetal protecting group which has fulfilled its purpose.

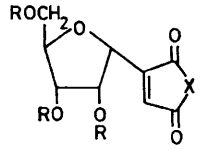
We have recently reported a new synthesis of the *C*-nucleoside antibiotic showdomycin (2-β-D-ribofuranosylmaleimide).[29] It was of interest to prepare the α-isomer (31) from the ethyne (20) since there was some indication that the α-isomer of pyrazofurin shows biological activity,[30] although more recent evidence suggests that this may be due to isomerisation to the active β-isomer.

When the ethyne (20) was treated, in methanol solution, with carbon monoxide (2 atm) in the presence of palladium chloride and mercury(II) chloride [31] it was possible to isolate both the maleate (24) (65%) and fumarate (28) (6%) from the mixture by chromatography. The maleate stereochemistry was initially assigned to the major isomer by analogy with our own [29] and Heck's [31] results, and this was confirmed by detailed examination of the ^{1}H n.m.r. spectrum. The vinylic proton in (24) appeared as a doublet (J 2 Hz) at δ 6.50. Splitting of this signal is due to allylic coupling with the 'anomeric' proton, H-1′. In (28) the signal due to the vinylic proton was a singlet at δ 6.60. The relatively large coupling constant observed in (24) indicated a *cisoid* relationship between the vinylic proton and H-1′, whereas the appearance of the corresponding vinylic proton in (28) as a singlet was consistent with the low coupling constants (0—0.5 Hz) generally associated with protons of this type when in a *transoid* relationship.[32–34]

The chemical shift of H-1′ in the two isomers [δ 4.80 for (24) and δ 5.56 for (28)] calls for comment. Free rotation about the C-1′–C-2 bond enables the maleate (24) to exist in a stable conformation in which both



(24) $R^1 = R^2 = OMe$
(25) $R^1 = R^2 = OH$
(26) $R^1 = NH_2, R^2 = OH$
(27) $R^1 = OH, R^2 = NH_2$



(29) R = CH_2Ph, X = O
(30) R = CH_2Ph, X = NH
(31) R = H, X = NH

ester groups are directed away from H-1′. In the fumarate (28), however, H-1′ is always subject to deshielding by one or other of the ester groups.

When the diester (24) was hydrolysed with aqueous potassium hydroxide in dioxan [29] it afforded the crude diacid (25), which was characterised spectroscopically. Conversion of (25) into the crude anhydride (29) was achieved by means of acetic anhydride. Ammonolysis of (29) to a maleamic acid, presumably a mixture of (26) and (27),[29] was followed by cyclisation using acetyl chloride in dimethylformamide to give the syrupy cyclic imide (30) [43% from the diester (24)] which was fully characterised. Debenzylation of (30) using boron trichloride [29,34] in methylene chloride at −78 °C afforded 2-α-D-ribofuranosylmaleimide (α-showdomycin) (31) as a crystalline hydrate in 57% yield.

α-Showdomycin showed no significant activity when tested against a number of strains of bacteria, fungi, yeasts, certain viruses, and a protozoa. We are indebted to Dr. John G. Moffatt, Syntex Research, Palo Alto, for these results.

EXPERIMENTAL

The general methods used were as stated in Part 2.[3a] Adsorption chromatography was carried out using Kieselgel H Type 60 (Merck); an external pressure was applied to the top of columns. For t.l.c. pre-coated aluminium-backed plates [Kieselgel HF_{254} type 60 (Merck)] were used. Mass spectra were recorded on an AEI MS 30 operating at 70 eV.

2,3,4,6-*Tetra*-O-*benzyl*-D-*glucitol* (5).—To a stirred suspension of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose [9] (24 g) in ethanol (500 ml) and water (30 ml) was added sodium borohydride (17 g). After 12 h at room temperature, 2M acetic acid (1 475 ml) was added, and the solvents removed *in vacuo* to leave a syrup which was partitioned between chloroform and water. The chloroform layer was dried ($MgSO_4$) and evaporated to give the diol (5) as a syrup, $[\alpha]_D$ +18.3° (*c* 0.6 in $CHCl_3$) {lit.,[8] $[\alpha]_D$ +10.3° ($CHCl_3$)}; δ(100 MHz; $CDCl_3$) 3.56—4.20 (10 H, m), 4.50, 4.58, 4.62, 4.70 (each 2 H, s, CH_2Ph), and 7.20—7.44 (20 H, m, Ph); *m/e* 451 (M − CH_2Ph).

Treatment of 2,3,4,6-*Tetra*-O-*benzyl*-D-*glucitol with Toluene*-p-*sulphonyl Chloride*.—The diol (5) (352 mg) and toluene-*p*-sulphonyl chloride (250 mg, 2 mol equiv.) were dissolved in pyridine (4 ml), heated to 60 °C for 5 h, and kept at room temperature overnight. The product was isolated using chloroform to afford a syrup (280 mg) which showed 3 spots on t.l.c. [benzene–ether (3 : 1)]. Chromatography on silica gel (10 g) and elution with benzene gave 2,3,6-*tri*-O-*benzyl*-5-O-*toluene*-p-*sulphonyl*-1,4-*anhydro*-D-*glucitol* (11) as a pure syrup (51 mg, 13%), $[\alpha]_D$ +6° (*c* 0.5 in $CHCl_3$); $\nu_{max.}$ (film) 1 190 and 1 175 cm^{-1} (SO_2Ar); δ(100 MHz; $CDCl_3$) 2.34 (3 H, s, *Me*-C_6H_4), 3.60—4.88 (12 H, m), 5.12—5.32 (1 H, m, H-5), and 7.04—7.82 (19 H, m, Ar); *m/e* 497 (M^+ − CH_2Ph) and 433 (M^+ − $SO_2C_7H_7$) (Found: C, 69.45; H, 6.2. $C_{34}H_{36}O_7S$ requires C, 69.4; H, 6.1%).

Benzene–ether (39 : 1) eluted 2,3,4,6-*tetra*-O-*benzyl*-1,5-*anhydro*-D-*glucitol* (8) as a pure syrup (40 mg, 12%), $[\alpha]_D$ +27.8° (*c* 0.4 in $CHCl_3$); $\nu_{max.}$ (film) showed absence of OH or Ts; δ(100 MHz; $CDCl_3$) 3.04—5.00 (16 H, m) and 7.12—7.48 (20 H, m, Ph); *m/e* 433 (M^+ − CH_2Ph), 342 (M^+ − 2 × CH_2Ph), and 251 (M^+ − 3 × CH_2Ph) (Found: C, 77.3; H, 6.5; $C_{34}H_{36}O_5$ requires C, 77.9; H, 6.9%). Benzene–ether (19 : 1) eluted 2,3,6-*tri*-O-*benzyl*-1,4-*anhydro*-D-*glucitol* (10) as a pure syrup (132 mg, 47%), $[\alpha]_D$ −6° (*c* 1.0 in $CHCl_3$); $\nu_{max.}$ (film) 3 475 cm^{-1} (OH); δ(100 MHz; $CDCl_3$) 2.74 (1 H, d, *J* 6 Hz, 5-OH), 3.50—4.28 (8 H, m), 4.45—4.68 (6 H, m, 3 × CH_2Ph), 7.36 (15 H, s, Ph); *m/e* 434 (M^+) and 343 (M^+ − CH_2Ph) (Found: C, 74.35; H, 7.1; $C_{27}H_{30}O_5$ requires C, 74.65; H, 6.9%).

Hydrogenolysis of 2,3,4,6-*Tetra*-O-*benzyl*-1,5-*anhydro*-D-*glucitol* (8).—The tetrabenzyl ether (8) (2.5 g) in ethanol (50 ml) was hydrogenated at atmospheric pressure over a 5% Pd–charcoal catalyst for 29 h. After filtration through Celite the solution was concentrated to give a crystalline residue which was recrystallised from methanol–benzene to give 1,5-anhydro-D-glucitol (536 mg, 69%), m.p. 143—144 °C, $[\alpha]_D$ +45° (*c* 1.0 in H_2O), identified by comparison with an authentic sample (mixed m.p., i.r. spectrum, paper chromatography) supplied by Dr. E. Zissis {lit.,[10] m.p. 142—143 °C, $[\alpha]_D$ +42.3° (H_2O)}.

Hydrogenation of 2,3,6-*Tri*-O-*benzyl*-1,4-*anhydro*-D-*glucitol* (10).—The tribenzyl ether (2.4 g) in ethanol (50 ml) was hydrogenated as for (8) above. The crystalline residue was recrystallised from isopropyl alcohol to give 1,4-anhydro-D-glucitol (12) (613 mg, 68%), m.p. 115—116 °C, $[\alpha]_D$ −18° (*c* 1.0 in H_2O), identified by comparison with an authentic sample (mixed m.p., i.r. spectrum, paper chromatography) supplied by Dr. E. Zissis {lit.,[11] m.p. 115—116 °C, $[\alpha]_D$ −21.0° (H_2O)}.

2,3,6-*Tri*-O-*benzyl*-5-O-*toluene*-p-*sulphonyl*-1,4-*anhydro*-D-*glucitol* (11) *from Tri*-O-*benzyl*-1,4-*anhydro*-D-*glucitol* (10).—The tribenzyl ether (10) (150 mg) and toluene-*p*-sulphonyl chloride (131 mg, 2 mol equiv.) were dissolved in pyridine and the solution kept at 60 °C for 2 days. The product was isolated by means of chloroform and the resulting syrup purified by chromatography on silica. The pure syrup was indistinguishable (t.l.c., i.r., ^1H n.m.r.) from the sulphonate (11) described above.

5-O-*Toluene*-p-*sulphonyl*-1,4-*anhydro*-D-*glucitol* (12).—The sulphonate (11) (1.4 g) in ethanol was hydrogenated in the presence of 5% Pd–charcoal (750 mg) for 17 h. After removal of the catalyst by filtration the solution was evaporated to give a crystalline residue. Recrystallisation from ethanol–benzene gave the 5-*toluene*-p-*sulphonate* (12) (65 mg, 86%), m.p. 107—108 °C, $[\alpha]_D$ −21° (*c* 1.0 in H_2O); $\nu_{max.}$ KBr 1 190 and 1 175 cm^{-1} (SO_2Ar); δ[100 MHz; $(CD_3)_2SO$] 2.44 (3 H, s, *Me*-C_6H_4), 3.00—5.00 (11 H, m), and 7.40, 7.48, 7.84, 7.92 (4 H, AB q, C_6H_4); *m/e* 146 (M − TsOH) (Found: C, 49.3; H, 5.9. $C_{13}H_{18}O_7S$ requires C, 49.05; H, 5.7%).

Reaction of 2,3,4,6-*Tetra*-O-*benzyl*-1-O-*tolylsulphonyl*-D-*glucitol* (6).—(a) *With sodium methoxide*. The diol (5) (6.450 g) and toluene-*p*-sulphonyl chloride (4.522 g, 2 *mol* equiv.) were dissolved in pyridine (60 ml) at 0 °C and kept at 0 °C for 3 days. The product was carefully isolated using chloroform (*ca.* 100 ml) and added to methanol (7 ml) containing sodium methoxide [from Na (250 mg)]. The mixture was refluxed for 3 h. Isolation of the product using chloroform, followed by chromatography on silica as described before, gave the sulphonate (11) (1.402 g, 20%), the 1,5-anhydride (8) (2.643 g, 43%), and the 1,4-anhydride (10) (691 mg, 13%).

(b) *With pyridine*. The diol (5) (6.00 g) and toluene-*p*-sulphonyl chloride (4.30 g, 2 mol equiv.) were kept together in pyridine at 0 °C for 5 h. The product was carefully isolated using chloroform (*ca.* 50 ml); pyridine (60 ml) was added to the mixture which was refluxed for 2 h. Chromatography using silica gel afforded the sulphonate (11) (506 mg, 8%), the 1,5-anhydride (8) (222 mg, 4%), the 1,4-anhydride (10) (2.754 g, 60%), and unchanged diol (5) (300 mg, 5%).

2,3,5-*Tri*-O-*benzyl*-β (*and* α)-D-*ribofuranosylethyne* [(4) *and* (20)].—Ethylmagnesium bromide [prepared from magnesium (3.45 g) in dry tetrahydrofuran (THF) (100 ml) and ethyl bromide (15.45 g) in dry THF (120 ml)], was added dropwise to dry THF saturated with acetylene, with acetylene bubbling into the solution. The flow of acetylene was continued for a further hour after the addition of ethylmagnesium bromide was complete.

A solution of 2,3,4,5-tetra-*O*-benzyl-*aldehydo*-D-ribose (21) [26] (3.0 g) in dry THF (75 ml) was added dropwise to the Grignard solution, a steady stream of acetylene being passed through the mixture during the addition and for a further 2 h. The reaction mixture was concentrated *in vacuo*, diluted with ether (150 ml), and the solution washed with aqueous ammonium chloride (10% w/v, 3 × 200 ml) and water (3 × 200 ml). The ether solution was dried (Na_2SO_4), filtered through charcoal/Celite, and evaporated to give a thin syrup (3.1 g, 98%) consisting of the D-*altro*- and D-*allo*-acetylenic alcohols (1) and (19); $\nu_{max.}$ (film) 3 440 (OH), 3 290 (≡CH) and 2 090w cm^{-1} (C≡C); δ(100 MHz; $CDCl_3$) 2.43 (1 H, d, HC≡C), 3.44—4.84 (15 H, m), and 7.24 (20 H, s, 4 × Ph). The mixture of (1) and (19) (1.0 g) and toluene-*p*-sulphonyl chloride (800 mg, 2.25 mol equiv.) were dissolved in pyridine and kept at room temperature overnight. T.l.c. [toluene–ethyl acetate (10 : 1)] showed the formation of two products of slightly greater polarity (R_F 0.61 and 0.49) than the starting materials.

The products were isolated using chloroform and chromatographed on silica gel. Light petroleum–ether (17 : 3) eluted 2,3,5-tri-*O*-benzyl-β-D-ribofuranosylethyne (4), crystallised from ethanol (330 mg, 41%), m.p. 64—65 °C, $[\alpha]_D$ +8.8° (*c* 0.61 in $CHCl_3$), indistinguishable (t.l.c. mixed m.p., i.r. and ^1H n.m.r. spectra) from an authentic sample [2] {lit.,[2] $[\alpha]_D$ +9.7° ($CHCl_3$)}.

Further elution with light petroleum–ether (4 : 1) gave 2,3,5-tri-*O*-benzyl-α-D-ribofuranosylethyne (20), crystallised from ethanol–water (3 : 1) (335 mg, 42%), m.p. 52—53 °C, $[\alpha]_D$ +77° (*c* 1.0 in $CHCl_3$), indistinguishable (t.l.c., m.p., i.r. and ^1H n.m.r. spectra) from an authentic sample [2] {lit.,[2] $[\alpha]_D$ +79.7° ($CHCl_3$)}.

*Dimethyl 2-(2,3,5-Tri-*O*-benzyl-α-D-ribofuranosyl)-maleate* (24) *and -fumarate* (28).—A solution of the ethyne (20) (301 mg) in dry methanol (30 ml) was stirred in a Schlenk tube for 21 h at room temperature with palladium chloride (131 mg, 1.05 mol equiv.) and mercury(II) chloride (200 mg, 1.05 mol equiv.) in the presence of carbon monoxide (2 atm). Solids were removed by filtration, and the filtrate concentrated to a syrup which was chromatographed on silica gel (8 g). Elution with light petroleum–ether [(5 : 1) then (9 : 2)] gave *dimethyl* 2-(2,3,5-*tri*-O-*benzyl*-α-D-*ribofuranosyl*)*fumarate* (28) as a pure syrup (24 mg, 6%), $[\alpha]_D$ −52.3° (*c* 0.86 in $CHCl_3$); $\nu_{max.}$ (film) 1 727 cm^{-1} (C=O); δ(100 MHz, $CDCl_3$) 3.58 and 3.85 (each 3 H, s, OMe), 3.40—4.68 (11 H, m), 5.56 (1 H, d, $J_{1',2'}$ 4 Hz, H-1'), 6.60 (1 H, s, H-3), and 6.96—7.36 (15 H, m, Ph); *m/e* 546 (w, M^+), 531 (w, M^+ − Me), 515 (m, M^+ − OMe), 469 (m) (M^+ − Ph), 455 (s) (M^+ − CH_2Ph) (Found: C, 69.9; H, 6.2. $C_{32}H_{34}O_8$ requires C, 70.3; H, 6.2%).

Elution with light petroleum–ether [(4 : 1) then (7 : 2)] gave *dimethyl* 2-(2,3,5-*tri*-O-*benzyl*-α-D-*ribofuranosyl*)*maleate* (24) (251 mg, 65%), $[\alpha]_D$ +39.8° (*c* 1.68 in $CHCl_3$); $\nu_{max.}$ (film) 1 727 cm^{-1} (C=O); δ(100 MHz, $CDCl_3$) 3.66 and 3.72 (each 3 H, s, OMe), 3.40—4.64 (11 H, m), 4.80 (1 H, dd, $J_{1',2'}$ 4, $J_{1',3}$ 2 Hz, H-1'), 6.50 (1 H, d, $J_{3,1'}$ 2 Hz, H-3), and 7.26 (15 H, s, Ph); *m/e* 546 (w, M^+), 515 (m, M^+ − OMe), 487 (m, M^+ − CO_2Me), 469 (w), M^+ − Ph, 455 (s) (M^+ − CH_2Ph) (Found: C, 70.3; H, 6.3%).

2-(2,3,5-*Tri*-O-*benzyl*-α-D-*ribofuranosyl*)*maleimide* (30).—To a solution of the dimethyl ester (24) (750 mg) in 1,4-dioxan (35 ml) was added solid potassium hydroxide (307 mg, 4 mol equiv.) and water (7 ml). The mixture was stirred for 1.5 h, solid potassium hydroxide (307 mg) added, and stirring continued for 22.5 h. After acidification (2M hydrochloric acid, 15 ml), the product was extracted with chloroform (2 × 40 ml). Evaporation of the solvent and drying of the residue by co-evaporation with benzene afforded the crude diacid (25) (714 mg, 100%); $\nu_{max.}$ (film) 1 715 cm^{-1} (C=O); δ(100 MHz; $CDCl_3$) 3.84—4.96 (12 H, m), 6.80 (1 H, s, H-3), 7.26 (15 H, m, Ar), and 9.96 (2 H, br s, exchangeable with D_2O, OH); *m/e* 500 (M^+ − H_2O), 456 (M^+ − H_2O − CO_2), and 409 (M^+ − H_2O − CH_2Ph).

The crude dicarboxylic acid (25) (1.35 g) was dissolved in acetic anhydride (10 ml) and kept at room temperature for 20 h. Evaporation of solvents *in vacuo* followed by co-evaporation with fresh acetic anhydride afforded the crude anhydride (29) (1.31 g) as a syrup which did not crystallise. Treatment of the syrup, dissolved in ether (100 ml), with a stream of dry ammonia for 10 min at 0 °C afforded, on evaporation, the crude maleamic acid(s) (26) and/or (27) as a residue (1.35 g) which was immediately treated with acetyl chloride (6.2 ml, 30 mol equiv.) in dimethylformamide (20 ml) at room temperature for 20 h. Water (60 ml) was added and the solution extracted with chloroform (2 × 50 ml). The chloroform extract was evaporated and co-evaporated with xylene. Chromatography on silica gel with light petroleum–ether [(9 : 1) gradually changing to (3 : 1)] afforded the imide (30), the major product, as a pure syrup [561 mg, 43% from (24)], $[\alpha]_D$ +34.7° (*c* 0.23 in $CHCl_3$); $\nu_{max.}$ (film) 3 265 (NH) and 1 784, 1 724 cm^{-1} (C=O); δ(100 MHz; $CDCl_3$) 3.54 (1 H, dd, $J_{5'a,5'b}$ 11, $J_{5'a,4'}$ 3 Hz, H-5'a), 3.74 (1 H, dd, $J_{5'b,5'a}$ 11, $J_{5'b,4'}$ 3 Hz, H-5'b), 4.02—4.76 (9 H, m), 4.94 (1 H, dd, $J_{1',2'}$ 2, $J_{1',3'}$ 2 Hz), 6.58 (1 H, dd, $J_{3,1'}$ 2, $J_{3,NH.}$ 2 Hz, H-3), 7.27 (15 H, m, Ar), and 7.72 (1 H, br s, exchangeable with D_2O, NH); *m/e* 499 (M^+) and 408 (M^+ − CH_2Ph) (Found: C, 72.1; H, 6.1; N, 3.0. $C_{30}H_{29}NO_6$ requires 72.1; H, 5.8; N, 2.8%).

2-α-D-*Ribofuranosylmaleimide* (31).—A solution of boron trichloride (16 g) in methylene chloride (50 ml) was cooled to −78 °C in an acetone–solid CO_2 bath. To this solution was slowly added the tribenzyl ether (30) (740 mg) in methylene chloride. The reaction was stirred at −78 °C for 5 h, the cooling bath was removed, and methanol–methylene chloride (1 : 1, v/v) (100 ml) was added dropwise. After removal of solvents *in vacuo* the residue was treated with methanol followed by evaporation (4 × 80 ml). The residue was dissolved in methanol and silica (*ca.* 5 g added). After evaporation the silica was made into a slurry with light petroleum and added to a column already prepared in that solvent. Elution with light petroleum–ethyl acetate [(6 : 1) ⟶ (1 : 1)] removed impurities while ethyl acetate–acetone [(99 : 1) ⟶ (24 : 1)] eluted the ribosylmaleimide (31) which crystallised from acetone–ether as a hydrate (210 mg, 57%), m.p. 139—140 °C, $[\alpha]_D$ −77.0° (*c* 0.74 in H_2O); $\nu_{max.}$ (KBr) 3 570, 3 430, 3 350 (OH, NH), and 1 780 and 1 690 cm^{-1} (C=O); δ(100 MHz, CD_3CO_2D–D_2O) 3.6—4.6 (5 H, m), 5.04 (1 H, dd, $J_{1',2'}$ 6, $J_{1',3}$ 2.5 Hz, H-1'), and 6.68 (1 H, d, $J_{3,1'}$ 2.5 Hz, H-3); *m/e* 211 (M^+ − H_2O), 140 (M^+ − $C_3H_5O_3$), and 126 (maleimide +30) (Found: C, 43.8; H, 5.3; N, 5.6. $C_9H_{11}NO_6 \cdot H_2O$ requires C, 43.7; H, 5.3; N, 5.7%).

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REFERENCES

[1] Part 12, J. G. Buchanan, S. J. Moorhouse, and R. H. Wightman, preceding paper.
[2] Part 1, J. G. Buchanan, A. R. Edgar, and M. J. Power, *J. Chem. Soc., Perkin Trans. 1*, 1974, 1943.
[3] J. G. Buchanan, A. D. Dunn, and A. R. Edgar, *J. Chem. Soc., Perkin Trans. 1*, (*a*) 1975, 1191; (*b*) 1976, 68.
[4] J. G. Buchanan, A. D. Dunn, A. R. Edgar, R. J. Hutchison, M. J. Power, and G. C. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1786.
[5] J. G. Buchanan, M. E. Chacón-Fuertes, and R. H. Wightman, *J. Chem. Soc., Perkin Trans. 1*, 1979, 244.
[6] J. G. Buchanan, M. E. Chacón-Fuertes, A. Stobie, and R. H. Wightman, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2561.
[7] J. G. Buchanan, A. R. Edgar, R. J. Hutchison, A. Stobie, and R. H. Wightman, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2567.
[8] Y. Rabinsohn and H. G. Fletcher, jun., *J. Org. Chem.*, 1967, **32**, 3452.
[9] C. P. J. Glaudemans and H. G. Fletcher, jun., in 'Methods in Carbohydrate Chemistry,' ed. R. L. Whistler and J. N. BeMiller, Academic Press, New York and London, 1972, vol. 6, p. 373.
[10] H. G. Fletcher, jun., *J. Am. Chem. Soc.*, 1947, **69**, 706.

[11] S. Soltzberg, R. M. Goepp, jun., and W. Freudenberg, *J. Am. Chem. Soc.*, 1946, **68**, 919.
[12] S. Winstein, E. Allred, R. Heck, and R. Glick, *Tetrahedron*, 1958, **3**, 1; E. L. Allred and S. Winstein, *J. Am. Chem. Soc.*, 1967, **89**, 3991, 3998, 4008, 4012.
[13] B. Capon, *Q. Rev.* (*London*), 1964, **18**, 45; B. Capon and S. P. McManus, 'Neighbouring Group Participation,' vol. 1, Plenum, New York, 1976.
[14] G. R. Gray, F. C. Hartman, and R. Barker, *J. Am. Chem. Soc.*, 1965, **30**, 2020.
[15] J. S. Brimacombe and O. A. Ching, (*a*) *J. Chem. Soc. C*, 1968, 1642; (*b*) *Carbohydr. Res.*, 1968, **8**, 82; (*c*) *ibid.*, 1969, **9**, 287.
[16] J. S. Brimacombe, *Fortschr. Chem. Forsch.*, 1970, **14**, 367.
[17] J. P. H. Verheyden, A. C. Richardson, R. S. Bhatt, B. D. Grant, W. L. Fitch, and J. G. Moffatt, *Pure Appl. Chem.*, 1978, **50**, 1363.
[18] H. Ohle and E. Dickhauser, *Ber.*, 1925, **58**, 2593.
[19] H. Zinner, H. Brandhoff, H. Schmandke, H. Kristen, and R. Haun, *Chem. Ber.*, 1959, **92**, 3151.
[20] J. Defaye and D. Horton, *Carbohydr. Res.*, 1970, **14**, 128; J. Defaye, *Advan. Carbohydr. Chem. Biochem.*, 1970, **25**, 181.
[21] J. M. Cox and L. N. Owen, *J. Chem. Soc. C*, 1967, 1121.
[22] M. Mort, B. E. Stacey, and B. Tierney, *Carbohydr. Res.*, 1975, **43**, 183.
[23] B. Matsuhiro and A. B. Zanlungo, *Carbohydr. Res.*, 1978, **63**, 297.
[24] M. Jarman and W. C. J. Ross, *Carbohydr. Res.*, 1969, **9**, 139.
[25] R. S. Tipson and A. Cohen, *Carbohydr. Res.*, 1968, **7**, 232; D. R. Hicks and B. Fraser-Reid, *Can. J. Chem.*, 1974, **52**, 3367.
[26] P. J. Garegg, B. Lindberg, K. Nilsson, and C.-G. Swahn, *Acta. Chem. Scand.*, 1973, **27**, 1595.
[27] W. C. Still and J. A. Schneider, *Tetrahedron Lett.*, 1980, 1035.
[28] D. B. Collum, J. H. McDonald, III, and W. C. Still, *J. Am. Chem. Soc.*, 1980, **102**, 2120.
[29] J. G. Buchanan, A. R. Edgar, M. J. Power, and C. T. Shanks, *J. Chem. Soc., Perkin Trans. 1*, 1979, 225.
[30] G. E. Gutowski, M. O. Chaney, N. D. Jones, R. L. Hamill, F. A. Davis, and R. D. Miller, *Biochem. Biophys. Res. Commun.*, 1973, **51**, 312.
[31] R. F. Heck, *J. Am. Chem. Soc.*, 1972, **94**, 2712.
[32] J. W. Emsley, J. Feeney, and L. H. Sutcliffe, 'High Resolution Nuclear Magnetic Resonance Spectroscopy,' vol. 2, Pergamon Press, Oxford, 1966, pp. 726—741.
[33] P. Singh, *J. Org. Chem.*, 1972, **37**, 836.
[34] G. Trummlitz and J. G. Moffatt, *J. Org. Chem.*, 1973, **38**, 1841.