(*R*,*S*)-2,3-EPOXYPROPYL ETHERS AND GLYCOSIDES OF D-GLUCOPYRANOSE

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ABSTRACT

The synthesis of the complete series of (*R*,*S*)-2,3-epoxypropyl ethers and glycosides of D-glucopyranose is described. A standard procedure was employed, which involved treatment of the appropriate, acetylated allyl derivative with *m*-chloroperbenzoic acid in dichloromethane, followed by deacetylation of the product using the Zemplén catalytic method. (*R*,*S*)-2,3-Epoxypropyl α- (**6**) and β-D-glucopyranoside (**7**) and 3-*O*-[(*R*,*S*)-2,3-epoxypropyl]-D-glucose (**24**) were prepared from known allyl derivatives. New syntheses were developed for the 2- (**19**), 4- (**32**), and 6- (**37**) epoxypropyl ethers. 1,6:3,4-Dianhydro-β-D-galactopyranose (**8**), a useful starting material for the synthesis of 2-ethers and 4-substituted derivatives of D-glucose, was used for the preparation of **19** and **32**. Compound **7** is an irreversible inhibitor of yeast hexokinase at a concentration of 50mM.

INTRODUCTION

In designing irreversible inhibitors of enzymes for evaluation as antitumour agents, two approaches may be followed. If the tertiary structure of an enzyme is known and a model can be constructed of the enzyme–substrate complex, the design of inhibitors may be effectively guided. Thus, the type and structure of a substituent and its point of attachment to the substrate can be determined so that, when the modified substrate binds to the enzyme, interactions involving the substituent and particular nucleophilic centres and/or hydrophobic bonding-regions elsewhere in the enzyme molecule will occur. The active site will thereby be blocked and the enzyme inhibited. This approach has been elegantly illustrated with lysozyme[1]. It was predicted that an appropriate alkylating group attached through a β-D-glycosidic linkage to the substrates [β-(1→4)-linked oligomers of 2-acetamido-2-deoxy-D-glucose (chitosaccharides)] would approach closely and thereby react with the carboxylic acid groups in either the amino acid Glu35 or Asp52. Subsequently, it was found that 2,3-epoxypropyl β-glycosides of the above substrates were effective, irreversible inhibitors of lysozyme.

An alternative approach which can be followed in the absence of detailed knowledge of the tertiary structure of enzyme–substrate complexes has been developed

by Baker[2]. Systematic chemical modification of substrates permits exploration for hydrophobic bonding-regions and/or nucleophilic groups of those parts of the enzyme molecule which are peripheral to the active site. In this way, the affinity of modified substrates (inhibitors) for the enzyme can be increased almost a thousandfold[3].

In a programme concerned with the design of selective inhibitors for the hexokinase isozymes[4,5] of hepatomas and other tumours[6], the Baker approach has been used. Definition of the ring size, anomeric configuration, and molecular conformation of the form of D-glucose involved in each isozyme–substrate complex, together with a determination of the role (passive, covalent-bond formation, hydrogen-bond acceptance or donation) of each hydroxyl group, are necessary for the effective design of inhibitors. In addition to model studies using fluorinated derivatives with yeast hexokinase[7], a variety of series of derivatives of D-glucose containing, *inter alia*, substituents sensitive to nucleophilic attack is being synthesised. We now report the synthesis of the complete series of (*R,S*)-2,3-epoxypropyl ethers and glycosides of D-glucopyranose.

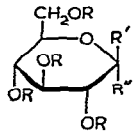
RESULTS AND DISCUSSION

A convenient procedure for the conversion of allylated carbohydrates into the corresponding (*R,S*)-2,3-epoxypropyl derivatives first involves[8] epoxidation of the acetylated allyl derivatives. A boiling solution of *m*-chloroperbenzoic acid in dichloromethane was used to effect this conversion. Subsequent deacetylation of the product, using the Zemplén catalytic procedure, left the epoxide ring intact. This reaction sequence is subsequently referred to as the standard procedure.

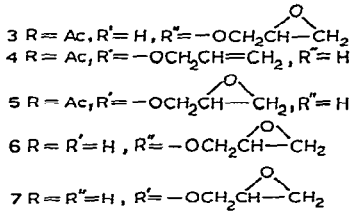
When this synthetic work was initiated, certain, relevant allyl derivatives were known, namely, allyl 2,3,4,6-tetra-*O*-acetyl-α- and β-D-glucopyranoside[9,10] and 3-*O*-allyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose[11]. The last compound was readily convertible, by conventional procedures, into the α- or β-pyranose tetraacetate after removal of the acetal groups by acid hydrolysis. No suitable glucose derivatives with an allyl group at position 2, 4, or 6 were known, and syntheses were therefore developed.

A convenient synthesis of a 2-*O*-allyl-D-glucopyranose derivative became possible after the observation that 1,6:3,4-dianhydro-β-D-galactopyranose (**8**) could be easily generated from its readily accessible 2-*O*-tosyl derivative[12], using a photolytic procedure[13]. Allylation of **8**, using silver oxide and allyl bromide in *N,N*-dimethylformamide, gave 2-*O*-allyl-1,6:3,4-dianhydro-β-D-galactopyranose (**9**) in good yield. This method of allylation was preferred because the use of the combination *N,N*-dimethylformamide–sodium hydride–allyl bromide[14] gave approximately equal amounts of **9** and 4-*O*-allyl-1,6:2,3-dianhydro-β-D-gulopyranose (**10**). Presumably, when sodium hydride is added to a solution of **8** in *N,N*-dimethylformamide, an equilibrium is set up between the two ionic species **11** and **12** and subsequent addition of allyl bromide produces the two allyl ethers. The ratio of these allylated products accords well with the ratio of 1,6:3,4-dianhydro-β-D-galactopyranose and

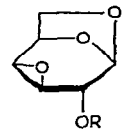
1,6:2,3-dianhydro-β-D-gulopyranose (**13**) formed when these compounds are equilibrated in aqueous sodium hydroxide[15]. Authentic **10** was obtained by treatment of 1,6:2,3-dianhydro-β-D-gulopyranose[15] with *N,N*-dimethylformamide–silver oxide–allyl bromide.



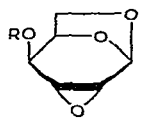
1 R = R′ = H, R″ = $-OCH_2CH=CH_2$
2 R = Ac, R′ = H, R″ = $-OCH_2CH=CH_2$



3 R = Ac, R′ = H, R″ = $-OCH_2CH(O)CH_2$
4 R = Ac, R′ = $-OCH_2CH=CH_2$, R″ = H
5 R = Ac, R′ = $-OCH_2CH(O)CH_2$, R″ = H
6 R = R′ = H, R″ = $-OCH_2CH(O)CH_2$
7 R = R″ = H, R′ = $-OCH_2CH(O)CH_2$

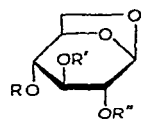


8 R = H
9 R = $-CH_2CH=CH_2$
26 R = Ts

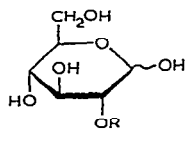


10 R = $-CH_2CH=CH_2$
13 R = H

11 12



14 R = R′ = H, R″ = $-CH_2CH=CH_2$
15 R = R′ = Ac, R″ = $-CH_2CH=CH_2$
25 R = $-CH_2CH=CH_2$, R′ = H, R″ = Ts
27 R = $-CH_2CH=CH_2$, R′ = R″ = H
28 R = $-CH_2CH=CH_2$, R′ = R″ = Ac

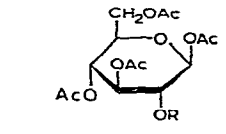


16 R = $-CH_2CH=CH_2$
19 R = $-CH_2CH(O)CH_2$

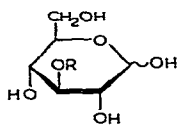
Treatment of the allyl ether **9** with boiling 3M sodium hydroxide gave 2-*O*-allyl-1,6-anhydro-β-D-glucopyranose (**14**) which was characterised as its diacetate **15**. Conventional acetolysis, followed by deacetylation of the product with saturated, methanolic ammonia, gave crystalline 2-*O*-allyl-D-glucose (**16**); the β-tetra-acetate was syrupy. Since this work was completed, an alternative, convenient route to 2-substituted derivatives of D-glucose has been described[16].

The synthetic route to 4-*O*-allyl-D-glucose (**30**) also used 1,6:3,4-dianhydro-2-*O*-tosyl-β-D-galactopyranose (**26**) as starting material. Černý *et al.*[17] showed that the epoxide ring in **26** could be cleaved by treatment with benzyl alcohol and toluene-*p*-sulphonic acid to give 1,6-anhydro-4-*O*-benzyl-2-*O*-tosyl-β-D-glucopyranose. When allyl alcohol was substituted for benzyl alcohol, 4-*O*-allyl-1,6-anhydro-2-*O*-tosyl-β-D-glucopyranose (**25**) was obtained which was detosylated with 3M sodium hydroxide (presumably *via* the intermediate epoxide) to give 4-*O*-allyl-1,6-anhydro-β-D-glucopyranose (**27**). Acetylation of **27** with pyridine–acetic anhydride gave 2,3-di-*O*-acetyl-4-*O*-allyl-1,6-anhydro-β-D-glucopyranose (**28**). Acetolysis of **28** gave crystalline 1,2,3,6-tetra-*O*-acetyl-4-*O*-allyl-β-D-glucopyranose (**29**) which, on deacetylation, yielded crystalline 4-*O*-allyl-D-glucose. The reaction sequence involving acetolysis

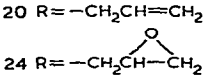
of the 1,6-anhydro ring, followed by deacetylation of the acetylated product, was much preferred to direct, acidic hydrolysis of the anhydro ring because reaction times were shorter and yields higher.



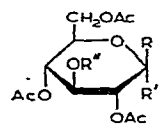
17 R = $-CH_2CH-CH_2$ (O)
18 R = $-CH_2CH=CH_2$



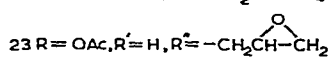
20 R = $-CH_2CH=CH_2$



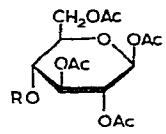
24 R = $-CH_2CH-CH_2$ (O)



21 R = H, R' = OAc, R'' = $-CH_2CH=CH_2$
22 R = OAc, R' = H, R'' = $-CH_2CH=CH_2$

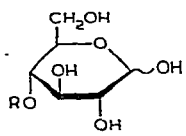


23 R = OAc, R' = H, R'' = $-CH_2CH-CH_2$ (O)

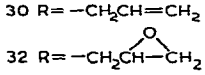


29 R = $-CH_2CH=CH_2$

31 R = $-CH_2CH-CH_2$ (O)



30 R = $-CH_2CH=CH_2$



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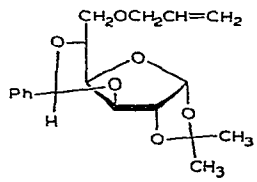

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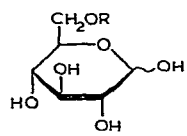
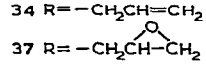
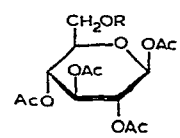


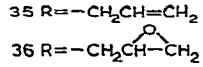
34 R = $-CH_2CH=CH_2$



37 R = $-CH_2CH-CH_2$ (O)



35 R = $-CH_2CH=CH_2$



36 R = $-CH_2CH-CH_2$ (O)

The route chosen for the synthesis of 6-*O*-allyl-D-glucose (**34**) was based on Bell's preparation[18] of 6-*O*-methyl-D-glucose. Allylation of 3,5-*O*-benzylidene-1,2-*O*-isopropylidene-α-D-glucofuranose[19], followed by hydrolysis of the product using Amberlite IR-120(H^+) resin, gave crystalline 6-*O*-allyl-D-glucose; the β-tetraacetate (**35**) was also crystalline.

Treatment of each of the tetra-acetates, **2**, **4**, **18**, **22**, **29**, and **35** with *m*-chloroperbenzoic, followed by Zemplén deacetylation of the products, gave the corresponding epoxypropyl derivatives, **6**, **7**, **19**, **24**, **32**, and **37**. In contrast to the six allyl derivatives of D-glucopyranose, which are crystalline, all six epoxypropyl derivatives failed to crystallise. Presumably this is because the conversion of an allyl group into an epoxypropyl group creates a new asymmetric centre and a mixture of diastereoisomers is formed. No separation of the diastereoisomers was observed during thin-layer chromatography, and therefore no attempts were made to fractionate the (*R*,*S*)-mixtures. Attempts to re-acetylate the sugars were unsuccessful, except in the case of the 4-substituted sugar where a poor yield of the tetra-acetate was obtained. The n.m.r. spectra of the products from the attempted reacetylations contained peaks at τ 8.0 corresponding to more than 4 acetate groups, which could be explained by acetolysis of the epoxide ring.

However, the n.m.r. spectrum (D_2O, internal MeCN) of each of the epoxypropyl sugars contained the characteristic multiplet [the chemical shift (δ) of which was between 0.5 and 1.0 p.p.m. downfield of the MeCN signal] shown by the methylene protons of the epoxide group in 1-chloro-2,3-epoxypropane. When each of the

compounds **6**, **7**, **19**, **24**, **32**, and **37** was incubated at a concentration of 50mM with yeast hexokinase, **7** was found to be an irreversible inhibitor of the enzyme, whereas the other compounds were inactive. The inactivation progressed with time and was essentially complete after 24 h. Details of this work will be reported elsewhere[20]. Compound **7** has been shown[21] to be actively accumulated by hamster intestinal slices, but no evidence for the formation of covalent bonds by reaction between **7** and the carrier was found.

EXPERIMENTAL

Melting points are corrected. Optical rotations were determined for 1–2% solutions (path length 10 cm) in chloroform (unless stated otherwise) using a Perkin–Elmer 141 polarimeter. N.m.r. spectra were determined at 60 MHz on solutions in $CDCl_3$ with internal Me_4Si, or in D_2O with internal MeCN (chemical shifts, δ, are in p.p.m. downfield of the signal for MeCN), using a Perkin–Elmer R-10 spectrometer. The following abbreviations are used, *s* singlet, *d* doublet, *t* triplet, *m* multiplet. Thin-layer chromatography (t.l.c.) was performed on Kieselgel 7731 (Merck) with detection by conc. sulphuric acid at 120°. Kieselgel 7734 was used for column chromatography. Paper ionophoresis was performed with a Shandon Universal electrophoresis unit, using Whatman No. 4 or No. 1 paper, a borate buffer[22] (pH 10), and detection with alkaline silver nitrate[23]; mobilities (M_G) are expressed relative to that (1.00) of D-glucose. Paper chromatography was performed on Whatman No. 1 paper, using 1-butanol–ethanol– water (4:1:1) and detection as for t.l.c.; mobilities (R_G) are expressed relative to that (1.00) of D-glucose.

(R,S)-*2,3-Epoxypropyl 2,3,4,6-tetra*-O-*acetyl-α* (**3**) *and -β-*D-*glucopyranoside* (**5**). — The mixture of glycosides obtained[9] by treating D-glucose with boiling allyl alcoholic hydrogen chloride was chromatographed[24] on BioRad AG1 x4 (HO^-) resin (200–400 mesh) to give allyl α-D-glucopyranoside (**1**), m.p. 100–101°, $[\alpha]_D^{30}$ +155° (*c* 1.5, water); lit.[9] m.p. 100.5–101.5°, $[\alpha]_D^{25}$ +151.5° (*c* 5, water). Treatment of **1** with pyridine–acetic anhydride gave the tetra-acetate[10] **2**, m.p. 55–56°, $[\alpha]_D^{30}$ +141°.

A solution of **2** (4 g, 11.3 mmoles) and *m*-chloroperbenzoic acid (8 g, 43.3 mmoles) in dichloromethane (100 ml) was boiled for 3 h, after which time no starting material remained (t.l.c., ether). The solution was kept overnight at 2° and then filtered and concentrated. Elution of the residue from Kieselgel, followed by combination and concentration of the appropriate fractions, gave **3** (3.68 g, 89%), b.p. 210° (bath)/0.1 mmHg, $[\alpha]_D^{30}$ +114° (Found: C, 50.5; H, 5.7. $C_{17}H_{24}O_{11}$ calc.: C, 50.5; H, 6.0%). N.m.r. data ($CDCl_3$): τ 7.90 (*s*, 6 protons, OAc), 7.95 (*s*, 6 protons, OAc).

Likewise, allyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside[10] (**4**) (m.p. 82–84°, $[\alpha]_D^{30}$ −20°) was converted into **5** (58%), m.p. 105–106°, $[\alpha]_D^{30}$ −19°; lit.[21] m.p. 115–117°, $[\alpha]_D^{30}$ −18.9° (Found: C, 50.4; H, 5.7%).

(R,S)-*2,3-Epoxypropyl* α-(**6**) *and* β-D-*glucopyranoside* (**7**). — The tetra-acetate **3** (1.4 g) was de-acetylated (Zemplén) by dissolution in dry methanol (50 ml) containing

a small amount of sodium methoxide, followed by storage at 2° overnight. The solution was neutralised with gaseous carbon dioxide and concentrated, and the residue was eluted with ether–methanol (4:1) from Kieselgel to give **6** (0.6 g, 73%) as a syrup, $[\alpha]_D^{30}$ +104° (*c* 1, water), R_G 1.7, M_G 0.10.

Zemplén deacetylation of **5** gave **7** (78%) as a syrup, $[\alpha]_D^{30}$ −21° (*c* 1, water), R_G 1.8, M_G 0.15; lit.[21] $[\alpha]_D$ −35.8° (*c* 0.18, methanol). The n.m.r. spectra (D_2O) of **6** and **7** each contained a multiplet at δ 0.5–1.0 ().

2-O-Allyl-1,6:3,4-dianhydro-β-D-galactopyranose (**9**). — (*a*) A solution of 1,6:3,4-dianhydro-β-D-galactopyranose[13] (**8**, 0.5 g) in *N*,*N*-dimethylformamide (10 ml) and allyl bromide (5 ml) was stirred with silver oxide[25] (1 g) for 4 days at room temperature in the dark. The filtered mixture was diluted with water (50 ml) and extracted with chloroform in the usual manner. The extract was dried ($MgSO_4$) and concentrated, and the residue was distilled to give **9** (0.4 g, 65%), b.p. 120–130° (bath)/0.1 mmHg, $[\alpha]_D^{30}$ −51° (Found: C, 58.2; H, 6.5. $C_9H_{12}O_4$ calc.: C, 58.7; H, 6.6%). N.m.r. data ($CDCl_3$): τ 4.0 (*m*, –CH=), 4.75 (*s*, H-1), 5.2 (*t*, $J_{4,5} = J_{5,6ex} = 5$ Hz, H-5), 5.85 (*d*, $J_{1',2'}$ 6 Hz, =CH–CH_2–O methylene), 6.1 (*d*, *J* 7 Hz, H-6 *endo*)[26].

(*b*) A solution of **8** (0.5 g, 3.5 mmoles) in *N*,*N*-dimethylformamide (100 ml) was stirred with sodium hydride (0.2 g, 8 mmoles) for 1 h at room temperature[14]. Allyl bromide (3.2 g, 24.4 mmoles) was then added to the cooled (~0°) solution. After 20 h, methanol (10 ml) was added to destroy the excess of sodium hydride, and the mixture was concentrated. The residue was dissolved in water (100 ml) and extracted with chloroform (2 × 100 ml). Examination of the combined and dried ($MgSO_4$) extracts by t.l.c. (ether–light petroleum, 2:3) revealed two products. Elution of the mixture from Kieselgel with the same solvent mixture gave first 4-*O*-allyl-1,6:2,3-dianhydro-β-D-gulopyranose (**10**, 0.15 g), b.p. 100° (bath)/0.5 mmHg, $[\alpha]_D^{30}$ 0 ±5° (Hilger, Mark III polarimeter) (Found: C, 59.2; H, 6.5. $C_9H_{12}O_4$ calc.: C, 58.7; H, 6.6%). N.m.r. data ($CDCl_3$): τ 4.1 (*m*, –CH=), 4.5 (*s*, H-1), 4.7 (*m*, CH_2=), 5.6 (*t*, H-5), 5.9 (*d*, $J_{1',2'}$ 5 Hz, =CH–CH_2–O methylene), 6.2 (*d*, $J_{6en,6ex}$ 5 Hz, H-6 *endo*).

Allylation of 1,6:2,3-dianhydro-β-D-gulopyranose[15] (**13**, 0.58 g) with *N*,*N*-dimethylformamide–silver oxide–allyl bromide[25], as described in (*a*), gave a product (0.38 g, 50%), b.p. 100–120° (bath)/0.1 mmHg, $[\alpha]_D^{30}$ +3°, which was identical (n.m.r. data) with the product **10** described above.

Eluted second was **9** (0.13 g), the n.m.r. spectrum of which was identical to that of the product described in (*a*).

2-O-Allyl-1,6-anhydro-β-D-glucopyranose (**14**). — Compound **9** (2.4 g) was treated with boiling 3M sodium hydroxide (10 ml) for 2 h. The cooled solution was neutralized with M hydrochloric acid and concentrated, and the residue was eluted with ether from Kieselgel to give **14** (1.03 g, 40%) as a homogeneous syrup (t.l.c.), $[\alpha]_D^{30}$ −51°. N.m.r. data: τ 4.1 (*m*, –CH=), 4.5 (*s*, H-1), 4.6 (*m*, CH_2=), 5.9 (*d*, $J_{1',2'}$ 6 Hz, =CH–CH_2O methylene).

3,4-Di-*O*-acetyl-2-*O*-allyl-1,6-anhydro-β-D-glucopyranose (**15**), obtained by

conventional treatment of **14** with pyridine–acetic anhydride and purified by elution from Kieselgel with ether–light petroleum (3:1), had b.p. 150° (bath)/0.15 mmHg, $[\alpha]_D^{30}$ −93.5° (Found: C, 54.1; H, 6.1. $C_{13}H_{18}O_7$ calc.: C, 54.5, H, 6.3%). N.m.r. data: τ 4.1 (*m*, –CH=), 4.5 (*s*, H-1), 4.6 (*m*, CH_2=), 5.0–7.0 (complex, second order), 7.85, 7.90 (*s*, AcO).

2-O-Allyl-D-glucose (**16**). — A solution of 2-*O*-allyl-1,6-anhydro-β-D-glucopyranose (**14**, 1 g) in acetic anhydride (5 ml) was treated[27] with conc. sulphuric acid (0.1 ml). After storage for 20 min at room temperature, the mixture was neutralised (aqueous $NaHCO_3$) and extracted with chloroform in the usual manner to give the syrupy αβ-tetra-acetate of **16** (1.6 g, 85%). N.m.r. data ($CDCl_3$): τ 3.7 (*d*, $J_{1,2}$ 4 Hz, H-1, α-pyranose), 4.1 (*m*, –CH=), 4.4 (*d*, $J_{1,2}$ 8 Hz, H-1, β-pyranose), 7.80 (*s*, 3 protons, OAc), 7.90 (*s* 9 protons, OAc).

The tetra-acetate (1.6 g) was treated at room temperature with an excess of saturated, methanolic ammonia. After 16 h, starting material could not be detected by t.l.c. (ethyl acetate–ethanol, 6:1). Concentration of the mixture and elution of the residue from Kieselgel with ethyl acetate gave, on combination and concentration of the appropriate fractions, 2-*O*-allyl-D-glucose (0.55 g, 65%), m.p. 146–147° (from ethyl acetate), $[\alpha]_D^{30}$ +82° (5 min)→+65° (equil., water), M_G 0.36 (Found: C, 48.8; H, 7.0. $C_9H_{16}O_6$ calc.: C, 49.1; H, 7.3%).

1,3,4,6-Tetra-O-acetyl-2-O-[(R,S)-2,3-epoxypropyl]-β-D-glucopyranose (**17**). — Acetylation of **16** (0.35 g) using sodium acetate–acetic anhydride in the normal way[28] gave, after elution of the product from Kieselgel with ether–light petroleum (1:1), 1,3,4,6-tetra-*O*-acetyl-2-*O*-allyl-β-D-glucopyranose (**18**, 0.58 g, 95%), b.p. 210° (bath)/0.1 mmHg), $[\alpha]_D$ +6° (Found: C, 52.6; H, 6.3. $C_{17}H_{24}O_{10}$ calc.: C, 52.6; H, 6.2%). N.m.r. data ($CDCl_3$): τ 4.1 (*m*, –CH=), 4.35 (*d*, $J_{1,2}$ 8 Hz, H-1), 4.6–7.0 2nd order), 7.90 (*s*, 9 protons, OAc), 7.95 (*s*, 3 protons, OAc).

Treatment of **18** with *m*-chloroperbenzoic acid–dichloromethane (see preparation of **3**) gave **17** (80%), b.p. 220° (bath)/0.1 mmHg, $[\alpha]_D^{30}$ +39° (Found: C, 50.9; H, 5.9. $C_{17}H_{24}O_{11}$ calc.: C, 50.5; H, 6.0%). N.m.r. data ($CDCl_3$): τ 4.35 (*d*, $J_{1,2}$ 8 Hz, H-1), 6.8–7.1 (*m*, –C*H*–CH_2), 7.1–7.6 (*m*, –CH–C*H*$_2$), 7.85 (*s*, 3 protons, OAc), 7.90 (*s*, 6 protons, OAc), 7.95 (*s*, 3 protons, OAc).

2-O-[(R,S)-2,3-epoxypropyl]-D-glucose (**19**). — Zemplén deacetylation of **17** gave **19** (54%) as a syrup, $[\alpha]_D^{30}$ +37° (equil., water), R_G 1.8, M_G 0.30. N.m.r. data (D_2O): δ 0.5–1.0 (*m*, –CH–C*H*$_2$).

An attempt to re-acetylate **19**, using pyridine–acetic anhydride at 2°, was unsuccessful, giving an uncharacterised product with an R_F value (t.l.c., ether) higher than that of **17**.

Tetra-acetates of 3-O-allyl-D-glucose. — Conventional reaction of 3-*O*-allyl-D-glucose[29] (**20**) [m.p. 129–130°, $[\alpha]_D$ +57° (equil., water), M_G 0.78] with acetic anhydride–pyridine, followed by treatment of the product with zinc chloride–acetic

anhydride[30], gave the crude α-tetra-acetate (60%), b.p. 175° (bath)/0.5 mmHg. Crystallisation from ether–light petroleum and recrystallisation from ether gave 1,2,4,6-tetra-*O*-acetyl-3-*O*-allyl-α-D-glucopyranose (**21**), m.p. 103–105°, $[\alpha]_D^{30}$ +110° (Found: C, 51.7; H, 6.0. $C_{17}H_{24}O_{10}$ calc.: C, 52.6; H, 6.2%). N.m.r. data ($CDCl_3$): τ 3.7 (*d* $J_{1,2}$ 4 Hz, H-1).

3-*O*-Allyl-D-glucose (9.5 g) was treated with a boiling solution of sodium acetate in acetic anhydride in the usual manner[28]. Two recrystallisations of the crude product from ethanol gave 1,2,4,6-tetra-*O*-acetyl-3-*O*-allyl-β-D-glucopyranose (**22**, 5.5 g, 35%), m.p. 116–117°, $[\alpha]_D^{30}$ +8° (Found: C, 52.8; H, 6.3%). N.m.r. data ($CDCl_3$): τ 4.35 (*d*, $J_{1,2}$ 8 Hz, H-1).

*1,2,4,6-Tetra-*O*-acetyl-3-*O*-[(R,S)-2,3-epoxypropyl]-β-D-glucopyranose* (**23**). — Treatment of the tetra-acetate **22** with *m*-chloroperbenzoic acid–dichloromethane (see preparation of **3**) gave **23** (75%), m.p. 121–122°, $[\alpha]_D^{30}$ −3° (Found: C, 50.5; H, 5.8. $C_{17}H_{24}O_{11}$ calc.: C, 50.5; H, 6.0%). N.m.r. data ($CDCl_3$): τ 4.35 (*d*, $J_{1,2}$ 8 Hz, H-1), 6.9–7.1 (*m*, $-CH(O)-CH_2$), 7.2–7.6 (*m*, $-CH(O)-CH_2$), 7.90 (*s*, 9 protons, OAc), 7.92 (*s*, 3 protons, OAc).

*3-*O*-[(R,S)-2,3-epoxypropyl]-D-glucose* (**24**). — Zemplén deacetylation of **23** gave **24** (73%) as a syrup, $[\alpha]_D^{30}$ +45° (equil., water], R_G 2.0, M_G 0.70. N.m.r. data (D_2O): δ 0.5–1.0 (*m*, $-CH(O)-CH_2$).

An attempt to re-acetylate **24**, using pyridine–acetic anhydride at 2°, was unsuccessful.

*4-*O*-Allyl-1,6-anhydro-2-*O*-tosyl-β-D-glucopyranose* (**25**). — A solution of 1,6:3,4-dianhydro-2-*O*-tosyl-β-D-galactopyranose[12] (**26**, 20 g), allyl alcohol (30 ml), and toluene-*p*-sulphonic acid (2 g) in benzene (200 ml) was boiled under reflux[17]. After 11 h, no starting material remained (t.l.c., chloroform). The solution was concentrated and the residue was eluted from Kieselgel with chloroform. Combination and concentration of the appropriate fractions gave the crude product (20.5 g, 85%) which was recrystallized from ether–light petroleum to give **25**, m.p. 90–91°, $[\alpha]_D^{30}$ −33° (Found: C, 53.5; H, 5.4; S, 9.3. $C_{16}H_{20}O_7S$ calc.: C, 53.9; H, 5.7; S, 9.0%).

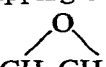
*2,3-Di-*O*-acetyl-4-*O*-allyl-1,6-anhydro-β-D-glucopyranose* (**28**). — A suspension of the foregoing compound **25** (20.5 g, 58 mmoles) in 3M sodium hydroxide (150 ml, 0.57 mole) was boiled under reflux for 2 h. The solution was neutralized to pH 7 (pH meter) with M hydrochloric acid, concentrated, and extracted with boiling ethyl acetate. Insoluble material was collected from the cooled mixture and extracted with boiling ethyl acetate. Concentration of the combined extracts gave 4-*O*-allyl-1,6-anhydro-β-D-glucopyranose (**27**) as a syrup (10.7 g, 90%).

Conventional treatment of **27** with pyridine–acetic anhydride gave **28** (90%), b.p. 150°/0.1 mmHg, $[\alpha]_D^{30}$ −29° (Found: C, 54.5; H, 6.3. $C_{13}H_{18}O_7$ calc.: C, 54.5; H, 6.3%). N.m.r. data ($CDCl_3$): τ 4.1 (*m*, –CH=), 4.6 (*d*, $J_{1,2}$ 1 Hz, H-1), 4.2 (*m*, CH_2=), 7.90 (*s*, 6 protons, OAc).

1,2,3,6-Tetra-O-acetyl-4-O-allyl-β-D-glucopyranose (**29**). — The di-acetate **28** (10 g) was acetolysed essentially as described above (see preparation of **16**). The crude product (10.3 g, 76%) was crystallised from ethanol–light petroleum to give **29**, m.p. 104–105°, $[\alpha]_D^{30}$ −2° (Found: C, 52.6; H, 6.3. $C_{17}H_{24}O_{10}$ calc.: C, 52.6; H, 6.2%).

N.m.r. data ($CDCl_3$): τ 4.3 (*d*, $J_{1,2}$ 8 Hz, H-1), 5.95 (*d*, $J_{1',2'}$ 5 Hz, $=CH-CH_2-O$ methylene), 7.90 (*s*, 6 protons, OAc), 7.92, (*s* 3 protons, OAc), 7.98 (*s*, 3 protons, OAc).

4-O-Allyl-D-glucose (**30**). — Saponification of **29** with methanolic ammonia gave 4-*O*-allyl-D-glucose, m.p. 107–109° (from ethyl acetate), $[\alpha]_D^{30}$ +97° (3 min)→ +76° (equil., water), M_G 0.30 (Found: C, 49.0; H, 7.2. $C_9H_{16}O_6$ calc.: C, 49.1; H, 7.3%).

1,2,3,6-Tetra-O-acetyl-4-O-[(R,S)-2,3-epoxypropyl-β-D-glucopyranose (**31**). — Treatment of **29** with *m*-chloroperbenzoic acid–dichloromethane (see preparation of **3**) gave **31** (90%), m.p. 118–120° (from ethanol), $[\alpha]_D^{30}$ −9° (Found: C, 50.3; H, 5.7. $C_{17}H_{24}O_{11}$ calc.: C, 50.5; H, 6.05%). N.m.r. data ($CDCl_3$): τ 4.25 (*d*, $J_{1,2}$ 7 Hz, H-1), 4.7 and 5.0 (overlapping triplets, H-2 and H-3), 5.5–6.6 (complex 2nd order), 6.7–7.6 (three multiplets, ).

4-O-[(R,S)-2,3-epoxypropyl]-D-glucose (**32**). — Zemplén deacetylation of **31** gave **32** as a homogeneous syrup (55%), $[\alpha]_D^{30}$ +57° (equil., water), R_G 1.8, M_G 0.20. N.m.r. data (D_2O): δ 0.5–1.0 (*m*, ).

A solution of **32** (0.13 g) in a mixture of pyridine (3 ml) and acetic anhydride (2 ml) was stored overnight at 2°. After several concentrations with toluene, the residue was eluted with ether from Kieselgel to give, as one fraction, syrupy material (0.12 g) which deposited crystals (0.02 g) from ethanol; m.p. 126–128° alone and 127–128° in admixture with authentic **31**, $[\alpha]_D^{30}$ −7°. N.m.r. data ($CDCl_3$) for syrupy material: τ 3.7 (*d*, $J_{1,2}$ 4 Hz, H-1, α-pyranose), 4.25 (*d*, $J_{1,2}$ 8 Hz, H-1, β-pyranose), 6.7–7.6 (three multiplets, ); αβ ratio 1:1.

6-O-Allyl-3,5-O-benzylidene-1,2-O-isopropylidene-α-D-glucofuranose (**33**). — Sodium hydride (6.2 g) was added to a solution of 3,5-*O*-benzylidene-1,2-*O*-isopropylidene-α-D-glucofuranose[19] (20 g) in *N,N*-dimethylformamide (200 ml). After 30 min, allyl bromide (61 g) was added to the cooled (~0°) mixture. The reaction was monitored by t.l.c. (ether–light petroleum, 1:1) and found to be complete after 3 days. The mixture was then concentrated and poured into water. The product (18.5 g, 82%) was collected, dried, and recrystallised from ethanol to give **33**, m.p. 71–72°, $[\alpha]_D^{30}$ +2° (Found: C, 65.3; H, 6.9. $C_{19}H_{24}O_6$ calc.: C, 65.6; H, 6.9%). N.m.r. data ($CDCl_3$): τ 2.4–2.8 (*m*, Ph), 4.0 (*d*, H-1), 4.05 (*s* Ph–C*H*), 3.8–4.5 (*m*, C*H*=CH_2), 8.5 and 8.7 (*s*, CH_3). Mass-spectral data (AEI MS-12, direct insertion, 70 eV, ion-source temperature 100°): *m/e* 348 (M^+, 80%), 333 ($M-CH_3$, 10%), 307 ($M-CH_2=CH-CH_2$, 4%), 277 ($M-CH_2OCH_2CH=CH_2$, 28%).

6-O-Allyl-D-glucose (**34**). — A solution of **33** (15 g) in ethanol (200 ml) and water (700 ml) was stirred with Amberlite IR-120(H^+) resin (150 ml) for 4 h at 70°, and then filtered and concentrated. Recrystallization of the residue from ethyl acetate–ethanol (10 ml, 4:1) gave **34** (3.4 g, 36%), m.p. 128–129°, $[\alpha]_D^{30}$ +75° (5 min) → +48° (equil., water), M_G 0.65 (Found: C, 49.2; H, 7.2. $C_9H_{16}O_6$ calc.: C, 49.1; H, 7.3%).

1,2,3,4-Tetra-O-acetyl-6-O-[(R,S)-2,3-epoxypropyl]-β-D-glucopyranose (**36**). — The foregoing ether, **34** (3.4 g), was treated with acetic anhydride–sodium acetate to yield a product (5.36 g) which, on recrystallization from ethanol, gave 1,2,3,4-tetra-*O*-acetyl-6-*O*-allyl-β-D-glucopyranose (**35**, 3.3 g, 55%), m.p. 66–67°, $[\alpha]_D^{30}$ +27° (Found: C, 52.85; H, 6.4. $C_{17}H_{24}O_{10}$ calc.: C, 52.6; H, 6.2%). N.m.r. data ($CDCl_3$): τ 4.0 (*m*, –CH=), 4.3 (*d*, $J_{1,2}$ 7 Hz, H-1), 4.5–5.2 (complex 2nd order), 6.0 (*d*, *J* 5 Hz, =CH–CH_2–O), 6.1–6.6 (complex 2nd order), 7.90 (*s*, 3 protons, OAc), 8.00 (*s*, 9 protons, OAc).

Treatment of **35** with *m*-chloroperbenzoic acid–dichloromethane (see preparation of **3**) gave **36** (80%), b.p. 230° (bath)/0.1 mmHg, $[\alpha]_D$ +37° (Found: C, 50.1, H, 5.7. $C_{17}H_{24}O_{11}$ calc.: C, 50.5; H, 6.0%). N.m.r. data ($CDCl_3$): τ 4.25 (*d* $J_{1,2}$ 8 Hz, H-1), 6.8–7.0 (*m*, –C*H*(O)–CH_2), 7.1–7.5 (*m*, –C*H*(O)–CH_2), 7.95 (*s*, 3 protons, OAc), 7.97, (*s*, 6 protons, OAc), 7.98 (*s*, 3 protons, OAc).

6-O-[(R,S)-2,3-epoxypropyl]-D-glucose (**37**). — Zemplén deacetylation of the acetate **36** gave syrupy **37** (70%), $[\alpha]_D$ +56° (equil., water), R_G 1.7, M_G 0.60. N.m.r. data (D_2O): δ 0.5–1.0 (*m*, –C*H*(O)–CH_2).

An attempt to re-acetylate **37**, using acetic anhydride–pyridine at 2°, was unsuccessful.

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