The Allyl Ether as a Protecting Group in Carbohydrate Chemistry. Part V.† Preparation of Benzyl Ethers of Carbohydrates for Use in Oligosaccharide Synthesis

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The four tri-*O*-benzyl ethers of benzyl α-D-galactopyranoside were prepared from benzyl 6-*O*-allyl-α-D-galactopyranoside. The stability of 4,6-*O*-propylidene derivatives of benzyl-α-D-galactopyranoside in acidic hydroxylic solvents was noted in this work. The condensations of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride with methanol, benzyl 2,3,4-tri-*O*-benzyl-α-D-galactopyranoside, and benzyl 3,4,6-tri-*O*-benzyl-α-D-galactopyranoside in dichloromethane containing triethylamine and tetraethylammonium chloride gave glycosides containing predominantly α-linkages. The ^{13}C n.m.r. spectra of the crystalline α-linked disaccharides, benzyl 6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-galactopyranoside and benzyl 2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-3,4,6-tri-*O*-benzyl-α-D-galactopyranoside were compared with those of the corresponding β-linked isomers. Treatment of 2,3,4,6-tetra-*O*-benzyl-D-glucose dimethyl acetal with an acid catalyst in ether gave predominantly methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside. 3,4,6-Tri-*O*-benzyl-2-dibenzylamino-2-deoxy-D-glucopyranose was prepared from allyl 2-benzamido-2-deoxy-β-D-glucopyranoside, as a potential intermediate for α-glycoside synthesis in the amino-sugar series.

OUR interest in immunochemically important glycolipids has led us to consider the syntheses of oligosaccharides containing both neutral and amino-sugars joined both with α- and with β-linkages. Recent work [1] on oligosaccharide syntheses has shown the value of partially benzylated glycosyl halides for this purpose: our previous publications [2] have shown the value of the allyl ether protecting group in the preparation of partially benzylated carbohydrate derivatives.

We have therefore envisaged a general method of oligosaccharide synthesis using partially benzylated (for 'persistent' blocking [3]) and partially allylated (for 'temporary' blocking [3]) glycosyl halides both for α- and for β-glycoside synthesis. Acyl groups which are conventional protecting groups in glycoside syntheses are sometimes a complicating factor because of reactivity and migration,[4] but are readily removed; allyl groups are readily removed from benzylated carbohydrate derivatives by methods previously described [2a,b] and at the same time are more stable than acyl groups.

For the preparation of α-glycosides using these intermediates we considered initially the method of Ishikawa and Fletcher [5a] in which an α-glycosyl halide (substituted at the 2-position with a non-participating group) is converted in the presence of halide ion into the β-glycosyl halide, which then reacts, at a much greater rate than the α-glycosyl halide, with the aglycone to give predominantly α-glycosides. We have modified this method by incorporating a tertiary base in the reaction mixture as an acid acceptor (*cf.* ref. 5*b*). Recent work on glycoside syntheses using partially benzylated, partially acylated glycosyl halides containing a 2-*O*-benzyl group has indicated [6] that participation by acyl groups on the 4- and 6-positions is important in determining the α-configuration of the glycoside formed, although this is by no means certain since recently Schuerch and his co-workers [4] have shown that other factors such as the relative concentrations of the reacting species are very important in determining the configuration of the glycosidic linkage formed. Our experiments (see later) with fully benzylated glucosyl chloride and low concentrations of aglycones leading to high proportions of α-glycosides appear to confirm the views of Schuerch. However, the mechanism under our reaction conditions may not be simple since we have used triethylamine as a base and this may react with the glucosyl chloride as described previously [1b] to give a further reactive intermediate.

† Part IV, ref. 2*d*.

[1] (*a*) C. Schuerch, *Accounts Chem. Res.*, 1973, 184; (*b*) A. C. West and C. Schuerch, *J. Amer. Chem. Soc.*, 1973, **95**, 1333.

[2] (*a*) J. Gigg and R. Gigg, *J. Chem. Soc.* (*C*), 1966, 82; (*b*) R. Gigg and C. D. Warren, *ibid.*, 1968, 1903; (*c*) P. A. Gent, R. Gigg, and R. Conant, *J.C.S. Perkin I*, 1972, 1535; (*d*) P. A. Gent, R. Gigg, and R. Conant, *ibid.*, 1973, 1858.

[3] P. J. Pfäffli, S. H. Hixon, and L. Anderson, *Carbohydrate Res.*, 1972, **23**, 195.

[4] F. J. Kronzer and C. Schuerch, *Carbohydrate Res.*, 1973, **27**, 379.

[5] (*a*) T. Ishikawa and H. G. Fletcher, *J. Org. Chem.*, 1969, **34**, 563; (*b*) R. U. Lemieux, K. James, and K. B. Hendriks (unpublished) quoted in R. U. Lemieux, K. James, and T. L. Nagabhushan. *Canad. J. Chem.*, 1973, **51**, 42.

[6] (*a*) M. Dejter-Juszynski and H. M. Flowers, *Carbohydrate Res.*, 1973, **28**, 61; (*b*) H. M. Flowers, *ibid.*, 1971, **18**, 211.

It has also been shown [5a,7-9] that methanolysis, in the presence of sodium methoxide, of the fully benzylated α-glycosyl halides gives predominantly the β-methyl glycosides and we reasoned that the reactions of the alkoxides of partially benzylated aglycones with the α-glycosyl halides might lead to a general β-glycoside synthesis from these compounds.

Benzyl ethers of glycosyl halides have been much used recently in the preparation of disaccharides, but *O*-benzyl substituents have been less used for the protection of the aglycone hydroxy-groups, and for a general oligosaccharide synthesis of the type we envisage this would be necessary. Although the use of benzyl ethers avoids some of the problems associated with other groups, *e.g.* migrations and hydrolyses of acyl groups and steric effects due to fused rings in cyclic acetals, it has not been established that the bulky benzyl group is a suitable protecting group for this type of synthesis; also many of the publications dealing with the syntheses of α-linked disaccharides have described work on the 1 ⟶ 6-linked sugars because of the greater reactivity of the primary hydroxy-group. Therefore in order to investigate the application of our proposed synthesis to both primary and secondary hydroxy-groups and to investigate the suitability of the benzyl ether as a 'permanent' blocking group in these syntheses, we have prepared as model aglycones the four tri-*O*-benzyl ethers of benzyl α-D-galactopyranoside. Our initial work on the general oligosaccharide synthesis has involved the formation of disaccharides from 2,3,4,6-tetra-*O*-benzyl-α-D-glucosyl chloride and some of these tri-*O*-benzyl ethers of benzyl α-D-galactopyranoside. Subsequent work will include the use of partially allylated and partially benzylated glucosyl halides, the preparation of which is under investigation.

The alcoholysis of 6-*O*-alkyl-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoses gives [2a,c,10] easily isolable crystalline 6-*O*-alkyl-α-D-galactopyranosides and therefore for the synthesis of the tri-*O*-benzyl ethers of benzyl α-D-galactopyranoside we have used as a starting material benzyl 6-*O*-allyl-α-D-galactopyranoside (2), which was readily prepared from 6-*O*-allyl-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside (1) by the action of acid in benzyl alcohol. Tri-*O*-benzylation of compound (2) followed by isomerisation [2a] of the allyl group in the product (3) gave the prop-1-enyl ether (4), which was hydrolysed by mercury(II) chloride [2b] to give crystalline benzyl 2,3,4-tri-*O*-benzyl-α-D-galactopyranoside (5). This was characterised by methylation and subsequent hydrogenolysis to give 6-*O*-methyl-D-galactose.[11]

Benzyl 6-*O*-allyl-α-D-galactopyranoside (2) was converted into the 3,4-*O*-isopropylidene derivative (6) and the allyl group was then isomerised [2a] to give the prop-1-enyl ether (7). This isomerisation reaction is the first that we have attempted on a pyranose sugar containing an isopropylidene group and it proceeded without complications. On the contrary in the inositol series, the action of potassium t-butoxide in dimethyl sulphoxide on ethers of 1,2-*O*-isopropylidene-*myo*-inositol led [12] to elimination of the isopropylidene group. The prop-1-enyl ether (7) was 2-*O*-allylated and the product (8) was hydrolysed with acid to give the crystalline benzyl 2-*O*-allyl-α-D-galactopyranoside (11). Benzylation of compound (11) and subsequent isomerisation of the allyl group and hydrolysis of the prop-1-enyl ether (13) with mercury(II) chloride gave benzyl 3,4,6-tri-*O*-benzyl-α-D-galactopyranoside (14) as a syrup. For characterisation, this was converted into the known [11b,13] 2-*O*-methyl-D-galactose.

Benzylation of benzyl 6-*O*-allyl-3,4-*O*-isopropylidene-α-D-galactopyranoside (6) and subsequent isomerisation of the allyl group gave benzyl 2-*O*-benzyl-3,4-*O*-isopropylidene-6-*O*-(prop-1-enyl)-α-D-galactopyranoside (10), which was hydrolysed with acid in aqueous methanol to give benzyl 2-*O*-benzyl-α-D-galactopyranoside (15).

In this hydrolysis reaction an intermediate (observed by t.l.c.) was formed and was stable in the acidic medium but was hydrolysed if the volatile products of hydrolysis (acetone and propionaldehyde) were distilled off [*cf.* the preparation of compound (11)]. The analytical figures for this crystalline intermediate indicated that it was either an isopropylidene or a propylidene derivative of benzyl 2-*O*-benzyl-α-D-galactopyranoside (15), which it gave on further hydrolysis. However, the intermediate was not identical with the 3,4-*O*-isopropylidene derivative prepared from compound (15) and did not react with trityl chloride in pyridine, indicating that it must be the 4,6-*O*-propylidene derivative of compound (15). This was confirmed by the preparation of identical material by the reaction of compound (15) with propionaldehyde, and its structure was confirmed by benzylation and subsequent acidic hydrolysis to give benzyl 2,3-di-*O*-benzyl-α-D-galactopyranoside (19), described later. The accumulation of this derivative in the reaction medium indicates the stability of the 4,6-*O*-propylidene group under these acidic, aqueous conditions and is of interest in connection with the direct conversion of prop-1-enyl ethers into propylidene derivatives by acid catalysts described previously.[2b] In this case it seems that the compound was formed by reaction between propionaldehyde and benzyl 2-*O*-benzyl-α-D-galactopyranoside (15) in the hydrolysis solution and this

[7] A. J. Rhind-Tutt and C. A. Vernon, *J. Chem. Soc.*, 1960, 4637; P. W. Austin, F. E. Hardy, J. G. Buchanan, and J. Baddiley, *ibid.*, 1964, 2128; 1965, 1419.

[8] V. D. Grob, T. G. Squires, and J. R. Vercellotti, *Carbohydrate Res.*, 1969, **10**, 595.

[9] M. N. Preobrazhenskaya and N. N. Suvorov, *Zhur. obshchei. Khim.*, 1965, **35**, 888 [*J. Gen. Chem.* (*U.S.S.R.*), 1965, **35**, 891].

[10] (*a*) C. E. Ballou and H. O. L. Fischer, *J. Amer. Chem. Soc.*, 1954, **76**, 3188; (*b*) R. Gigg and C. D. Warren, *J. Chem. Soc.*, 1965, 2205.

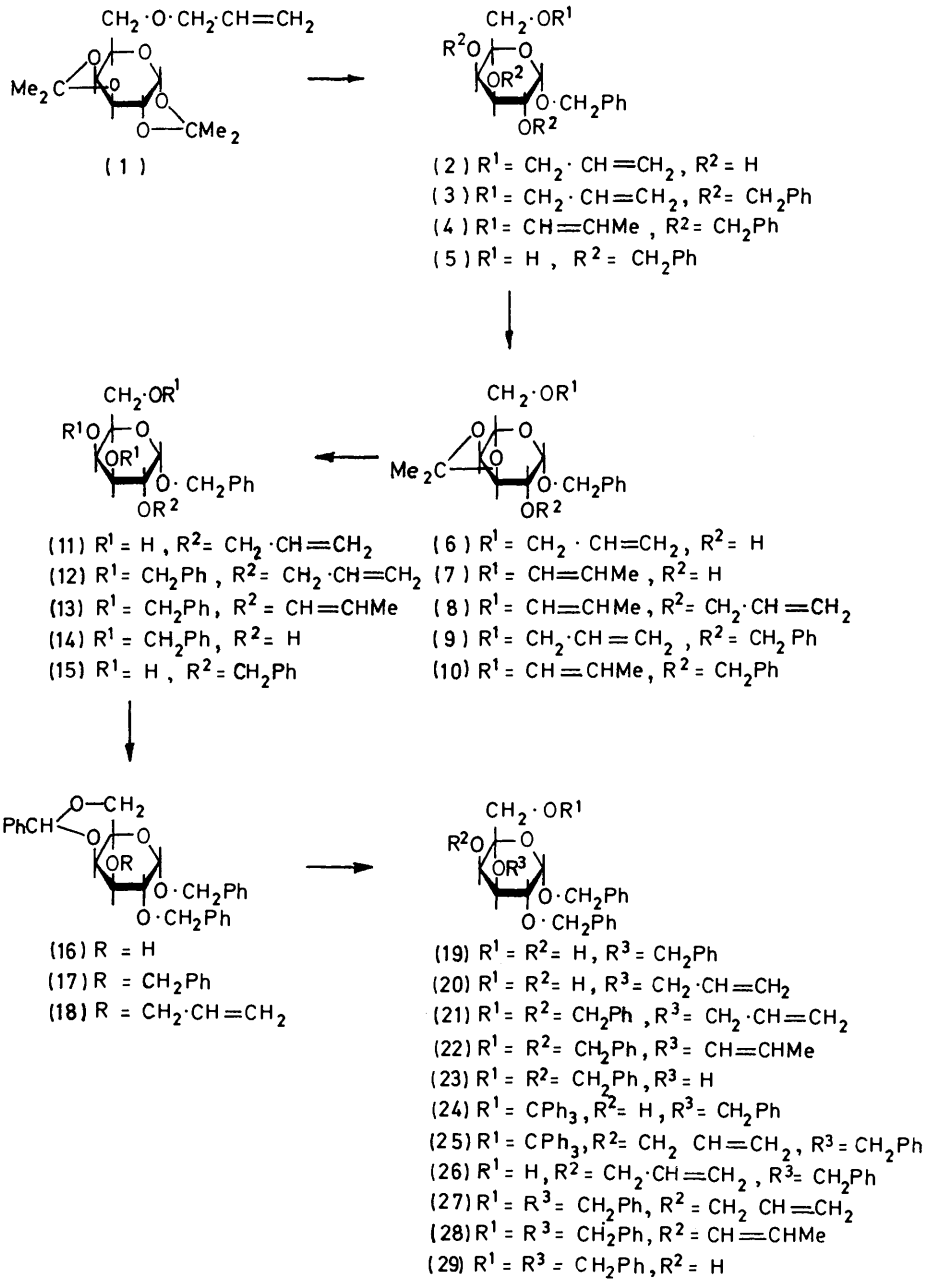
[11] (*a*) E. Pascu and S. M. Trister, *J. Amer. Chem. Soc.*, 1940, **62**, 2301; (*b*) C. G. S. Dutton and Y. Tanaka, *Canad. J. Chem.*, 1962, **40**, 1146.

[12] P. A. Gent and R. Gigg, *J. Chem. Soc.* (*C*), 1970, 2253.

[13] (*a*) D. McCreath and F. Smith, *J. Chem. Soc.*, 1939, 387; (*b*) H. Bouveng and B. Lindberg, *Acta Chem. Scand.*, 1956, **10**, 1283.

was confirmed by the ready formation of the 4,6-*O*-propylidene derivative on heating an acidic aqueous methanolic solution of compound (15) with propionaldehyde. This observation regarding the stability of 4,6-*O*-propylidene derivatives is relevant to the acidic hydrolysis of prop-1-enyl ethers of carbohydrates in general and also suggests a potential use of propylidene derivatives as an alternative to benzylidene derivatives. The formation of this propylidene derivative during the hydrolysis of benzyl 2-*O*-benzyl-3,4-*O*-isopropylidene-6-*O*-(prop-1-enyl)-α-D-galactopyranoside (10) was readily avoided by a prior hydrolysis of the prop-1-enyl ether with mercury(II) chloride.

Benzyl 2-*O*-benzyl-α-D-galactopyranoside (15) was converted into the benzylidene derivative (16) and this was allylated and subsequently hydrolysed with dilute acid to give benzyl 3-*O*-allyl-2-*O*-benzyl-α-D-galactopyranoside (20). Benzylation of compound (20) and subsequent isomerisation of the allyl group gave the prop-1-enyl ether (22), which was hydrolysed with mercury(II) chloride to give the crystalline benzyl 2,4,6-tri-*O*-benzyl-α-D-galactopyranoside (23). This was characterised by conversion into 3-*O*-methyl-D-galactose.[14]



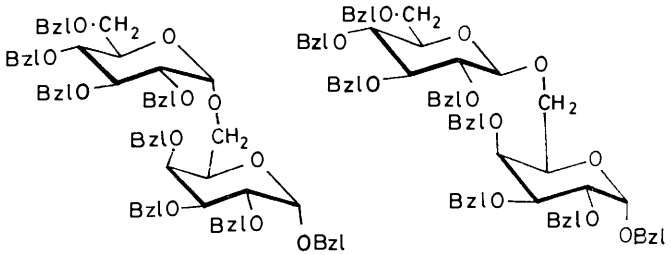
[14] J. S. Brimacombe, A. M. Mofti, and A. K. Al-Radhi, *J. Chem. Soc.* (*C*), 1971, 1363.

Benzylation of benzyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-galactopyranoside (16) followed by acidic hydrolysis gave crystalline benzyl 2,3-di-*O*-benzyl-α-D-galactopyranoside (19), which was tritylated and subsequently allylated to give benzyl 4-*O*-allyl-2,3-di-*O*-benzyl-6-*O*-trityl-α-D-galactopyranoside (25). Acidic hydrolysis of compound (25) followed by benzylation gave benzyl 4-*O*-allyl-2,3,6-tri-*O*-benzyl-α-D-galactopyranoside (27). Compound (27) was converted into the prop-1-enyl ether (28), which was hydrolysed with mercury(II) chloride to give benzyl 2,3,6-tri-*O*-benzyl-α-D-galactopyranoside (29), characterised by conversion into 4-*O*-methyl-D-galactose.[15]

For the investigations of α-glycoside synthesis with these aglycones, 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride was chosen since it is more stable and easier to prepare, without affecting the benzyl groups, than is the corresponding bromide. The chloride was prepared from the corresponding free sugar by the use of thionyl chloride in the presence of zinc chloride.[8] The preferred starting material for the preparation of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose is the mixture of allyl 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosides;[2a] we have found that in the published preparation[16] *via* methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside extensive debenzylation occurs during hydrolysis of the methyl glucoside linkage, resulting in a separation problem and lower yields.

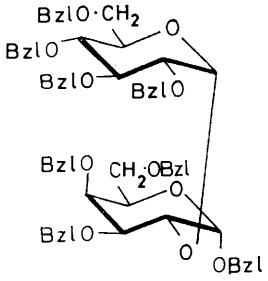
With the assumption that the major factor governing the stereochemistry of the product in the reaction of α-glycosyl halides, containing non-participating groups in the 2-position, in the presence of halide ion is an initial conversion by halide into the corresponding β-glycosyl halide,[5a] we have used tetraethylammonium chloride as a chloride source and triethylamine as an acid acceptor. However, recent work by West and Schuerch[1b] indicates that the β-triethylammonium glycoside might be the reactive species under these conditions. The reactions were carried out in dichloromethane with a two molar proportion of aglycone and a reaction temperature of 80°.

Initial experiments were carried out with methanol as the aglycone; debenzylation of the products and g.l.c. showed the ratio of α- to β-glycosides to be *ca.* 87 : 13. When benzyl 2,3,4-tri-*O*-benzyl-α-D-galactopyranoside (5) was used as the aglycone, with a reaction time of 16·5 h, *ca.* 65% yield of disaccharide was obtained, for which the ratio of α- to β-glycosides was estimated as *ca.* 9 : 1 by ^{13}C n.m.r. spectroscopy. The pure crystalline α-linked disaccharide derivative (30) was obtained by recrystallisation of the product. The pure crystalline β-linked isomer (31) was prepared (for comparative purposes and for quantitative estimation of yields by ^{13}C n.m.r.) by condensation of 2,3,4,6-tetra-*O*-acetylglucosyl bromide with compound (5) under Koenigs–Knorr conditions and subsequent deacetylation and benzylation. The α-glycoside synthesis was also carried out with benzyl 3,4,6-tri-*O*-benzyl-α-D-galactopyranoside (14) as the aglycone and *ca.* 23% yield of disaccharide was obtained. The α-linked disaccharide derivative (32) was obtained in the pure state by recrystallisation. A major by-product in this preparation was the previously described[9] unsaturated sugar (34). The corresponding β-linked disaccharide derivative (33) was also prepared in the crystalline state by carrying out a Koenigs–Knorr reaction between 2,3,4,6-tetra-*O*-acetylglucosyl bromide and compound (14) with subsequent deacetylation and benzylation. The α- and β-linked disaccharides (32) and (33) were resolved in this case by t.l.c. on silica gel. Both ^{13}C and ^{1}H n.m.r. spectra of compounds (32) and (33) were obtained. The glycoside synthesis under these conditions with benzyl 2,3,6-tri-*O*-benzyl-α-D-galactopyranoside (23) as the aglycone gave very low yields of a product which t.l.c. comparison showed could be a disaccharide, but the major product was the unsaturated sugar (34). Much previous work has indicated the lack of reactivity of the 4-position of variously substituted galactopyranosides in glycoside synthesis, and the benzyl ether protecting groups obviously offer no advantage in this respect. The use of benzyl 2,4,6-tri-*O*-benzyl-α-D-galactopyranoside (29) as the aglycone in this glycoside synthesis is under investigation.

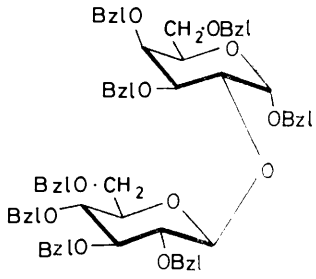


(30)

(31)



(32)



(33)

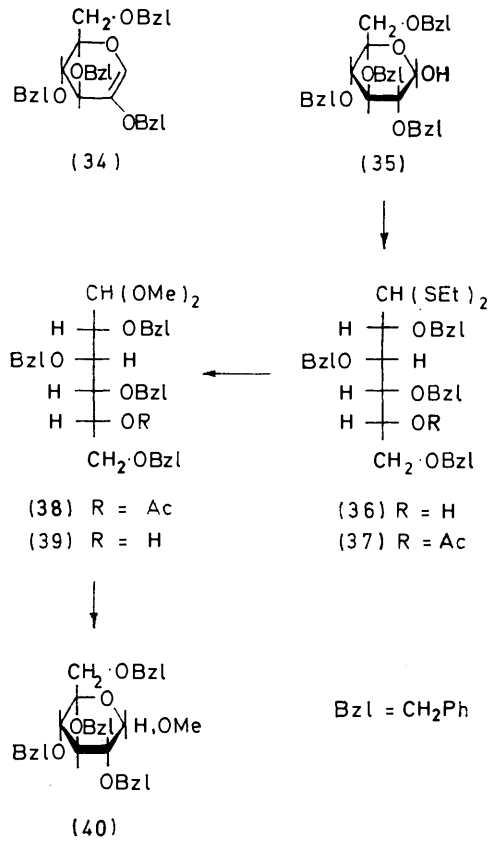
Bzl = CH_2Ph

The protected disaccharides (30)—(33) were converted into the corresponding free disaccharides by hydrogenolysis. Subsequent acidic hydrolysis and chromatography indicated in each case that they contained both glucose and galactose.

[15] (*a*) E. L. Hirst and J. K. N. Jones, *J. Chem. Soc.*, 1946, 506; (*b*) R. W. Jeanloz, *J. Amer. Chem. Soc.*, 1954, **76**, 5684.

[16] C. P. J. Glaudemans and H. G. Fletcher, *Methods Carbohydrate Chem.*, 1972, **6**, 373.

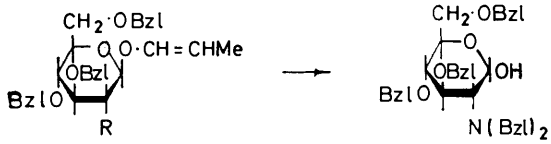
The condensation of the sodium salt of benzyl 2,3,4-tri-*O*-benzyl-α-D-galactopyranoside (5) with 2,3,4,6-tetra-*O*-benzylglucosyl chloride led to extensive formation of



the unsaturated sugar (34) rather than a β-glycoside. However, other methods for the formation of β-glycosides from the fully benzylated glycosyl halides have been described recently [4] and these should be of value for our proposed general oligosaccharide synthesis.

We have also considered a further potential route to α-glycoside synthesis *via* the protected aldose dithioacetals which might be applicable to both neutral and amino-sugars. 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose (35) was converted into the diethyl dithioacetal (36) by the action of ethanethiol in dioxan containing hydrogen chloride. A previous attempt [17] to prepare compound (36) by a similar method had been unsuccessful. The diethyl dithioacetal (36) was converted into the acetate (37) and this was treated in methanol with mercury(II) chloride in the presence of mercury(II) oxide [18] to give 5-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucose dimethyl acetal (38). Basic hydrolysis of compound (38) gave the alcohol (39). Previous work [19] on the treatment of the dimethyl acetals of unprotected D-glucose and D-galactose with acid has shown that methyl α-glycofuranosides are the major products. When the alcohol (39) was treated with acid catalysts in non-hydroxylic solvents the major product was methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (40). The application of this method to the preparation of other glycosides and disaccharides is under investigation. A potentially more versatile route to α-glycosides *via* the β-thioglycosides has been described recently by Ferrier and his co-workers.[20]

For glycoside synthesis in the amino-sugar series we have also considered the use of benzyl ethers as 'permanent' blocking groups on both oxygen and nitrogen atoms. For this purpose the synthesis of 3,4,6-tri-*O*-benzyl-2-dibenzylamino-2-deoxy-D-glucopyranose (45) was investigated. As a starting material we chose the previously prepared [2c] allyl 2-benzamido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranoside, which was converted into the corresponding prop-1-enyl glycoside (41) [2c] by potassium t-butoxide in dimethyl sulphoxide. Compound (41) was benzylated with benzyl chloride and sodium hydride in tetrahydrofuran to give the *N*-benzyl-benzamido-derivative (42). As reported previously,[2d] in contrast to the rapid benzylation of acetamido-groups by this procedure, the benzylation of benzamido-groups is very slow and was only complete after 4 days. A minor by-product of the reaction was shown to be the amide *O*-ether (44). Compound (42) was rapidly reduced by lithium aluminium hydride in ether [21] at room temperature to give prop-1-enyl 3,4,6-tri-*O*-benzyl-2-dibenzylamino-2-deoxy-β-D-glucopyranoside (43). This was rapidly hydrolysed by dilute acid to give 3,4,6-tri-*O*-benzyl-2-dibenzylamino-2-deoxy-D-glucopyranose (45) as a syrup. Both the *O*- and *N*-benzyl protecting groups were readily removed from this compound by hydrogenolysis at atmospheric pressure over palladium–charcoal to give D-glucosamine. The conversion of the



(41) R = NHBz
(42) R = N(Bzl)Bz
(43) R = N(Bzl)2
(44) R = N=C(OBzl)Ph

(45)

Bzl = CH2Ph

amino-sugar (45) into a suitable derivative for glycoside formation is under investigation. Compound (45) has also been prepared by a different route by Dr. Sinaÿ's group.[22]

EXPERIMENTAL

Solvents were evaporated off under reduced pressure. Optical rotations were measured at 22—24° with a Bendix automatic polarimeter. T.l.c. was carried out on microscope slides coated with silica gel G. The light petroleum

[17] H. G. Fletcher and H. W. Diehl, *Carbohydrate Res.*, **1971**, **17**, 383.
[18] D. Seebach, *Synthesis*, 1969, 17.
[19] B. Capon and D. Thacker, *J. Chem. Soc.* (*B*), **1967**, **1322**.
[20] R. J. Ferrier, R. W. Hay, and N. Vethaviyasar, *Carbohydrate Res.*, 1973, **27**, 55.
[21] V. M. Mićović and M. L. Mihailović, *J. Org. Chem.*, 1953, **18**, 1190.
[22] G. Sall, Thesis, Université de Paris-Sud, Orsay, 1973, p. **43**.

used had b.p. 60—80° unless otherwise stated. In most cases the potassium t-butoxide used was prepared and the isomerisations of allyl groups to prop-1-enyl groups were carried out as described previously.[2a] Recently potassium t-butoxide has become commercially available in the U.K. (from Courtorch Chemicals Ltd., Marsworth, Herts.) and this was used in some cases. This material is more active than the laboratory prepared material and the isomerisations can be carried out rapidly at room temperature.

Benzyl 6-O-*Allyl*-α-D-*galactopyranoside* (2).—A solution of 6-*O*-allyl-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (I) [10b] (27 g) in benzyl alcohol (250 ml) containing hydrogen chloride (7·5 g) was refluxed for 2 h, then neutralised with potassium carbonate, and the inorganic material was filtered off. The benzyl alcohol was evaporated off and the oily residue was dissolved in ether (250 ml). The crystalline product which separated during 15 h was collected and recrystallised from water to give the *benzyl glycoside* (2) (6·3 g), m.p. 130—131·5°, $[\alpha]_D$ +132·3° (*c* 0·8 in MeOH) (Found: C, 62·2; H, 7·1. $C_{16}H_{22}O_6$ requires C, 61·9; H, 7·15%). The ether-soluble material was treated again with hydrogen chloride in benzyl alcohol to give more (2·3 g) of compound (2); total yield 8·6 g (31%).

Benzyl 6-O-*Allyl*-2,3,4-*tri*-O-*benzyl*-α-D-*galactopyranoside* (3).—Sodium hydride (2 g) was added in portions to a stirred solution of compound (2) (5 g) in dry tetrahydrofuran (100 ml) and benzyl chloride (10 ml) and the solution was then heated under reflux for 24 h. T.l.c. (toluene–acetone, 4 : 1) then showed complete conversion of the starting material (R_F 0) into a product (R_F 0·9). The excess of sodium hydride was decomposed by the addition of methanol, water (10 ml) was added, and the solvents were evaporated off. The residue was extracted with chloroform and the solution dried ($MgSO_4$). The crude product was crystallised from methanol to give *compound* (3) (6·2 g), m.p. 78·5—80°, $[\alpha]_D$ +63·4° (*c* 0·8 in $CHCl_3$) (Found: C, 76·5; H, 6·9. $C_{37}H_{40}O_6$ requires C, 76·5; H, 6·9%).

Benzyl 2,3,4-*Tri*-O-*benzyl*-α-D-*galactopyranoside* (5).—The 6-*O*-allyl galactopyranoside (3) (5 g) was isomerised [2a] with potassium t-butoxide in dimethyl sulphoxide and the course of the reaction was followed by t.l.c. (light petroleum–ether, 4 : 1). When the starting material (R_F 0·6) had been entirely converted into the prop-1-enyl ether (4) (R_F 0·8), the product was isolated in the usual way.[2a] The prop-1-enyl compound was hydrolysed with mercury(II) chloride and the product isolated by the general method described previously [2b] and recrystallised from ethyl acetate–light petroleum to give *compound* (5) (3·85 g), m.p. 96—98°, $[\alpha]_D$ +51·1° (*c* 0·8 in $CHCl_3$) (Found: C, 75·2; H, 6·6. $C_{34}H_{36}O_6$ requires C, 75·5; H, 6·7%).

A portion was methylated and subsequently hydrogenated over 10% palladium–charcoal to give 6-*O*-methyl-D-galactose as a syrup, $[\alpha]_D$ +75·5° (final value, *c* 1 in H_2O) {lit.,[11a] $[\alpha]_D$ + 77·0° (final value, *c* 3·1 in H_2O)}, which gave a crystalline phenylhydrazone, m.p. 173—175° (lit.,[11b] 171—173°).

Benzyl 6-O-*Allyl*-3,4-O-*isopropylidene*-α-D-*galactopyranoside* (6).—A solution of benzyl 6-*O*-allyl-α-D-galactopyranoside (2) (17·2 g) in dry acetone (850 ml) containing toluene-*p*-sulphonic acid (0·5 g) was stirred at 20° for 3 h. T.l.c. (toluene–acetone, 1 : 1) then indicated almost complete conversion of the starting material (R_F 0·45) into the product (R_F 0·9). An excess of sodium hydrogen carbonate was added and the acetone was evaporated off. The product was extracted with ethyl acetate and recrystallised from aqueous methanol to give *compound* (6) (15·3 g), m.p. 63—65°, $[\alpha]_D$ +127·8° (*c* 1 in MeOH) (Found: C, 65·3; H, 7·1. $C_{19}H_{26}O_6$ requires C, 65·1; H, 7·5%).

Benzyl 3,4,6-*Tri*-O-*benzyl*-α-D-*galactopyranoside* (14).—Benzyl 6-*O*-allyl-3,4-*O*-isopropylidene-α-D-galactopyranoside (6) (20·9 g) was converted into the prop-1-enyl ether (7) by the action of potassium t-butoxide in dimethyl sulphoxide.[2a] The course of the reaction was followed by periodic isolation of a portion of the product and hydrolysis with a dilute solution of mercury(II) chloride [2b] to decompose the prop-1-enyl ether. T.l.c. (toluene–acetone, 3 : 1) then distinguished between the remaining allyl ether (6) (R_F 0·6), which was not hydrolysed by mercury(II) chloride, and the benzyl 3,4-*O*-isopropylidene-α-D-galactopyranoside (R_F 0·3), obtained by hydrolysis of the prop-1-enyl ether (7). When the reaction was complete, the crude product (7) was isolated, as an oil, in the usual way,[2a] and was treated with allyl bromide and sodium hydride in refluxing benzene to give benzyl 2-*O*-allyl-3,4-*O*-isopropylidene-6-*O*-(prop-1-enyl)-α-D-galactopyranoside (8), as a syrup (22·5 g). Compound (8) was added to a mixture of 0·5N-hydrochloric acid (40 ml) and methanol (120 ml) and the solution was heated in a distillation apparatus; methanol, acetone, and propionaldehyde were distilled off slowly during 30 min, while methanol–water (3 : 1) was added to maintain the volume of solution. T.l.c. (toluene–acetone, 1 : 1) then indicated a major product (R_F 0·4). An excess of sodium hydrogen carbonate was added and the solvents were evaporated off. The residue was extracted with chloroform and the product was chromatographed on alumina. After removal of trace impurities with ether–methanol (9 : 1) the *benzyl* 2-O-*allyl*-α-D-*galactopyranoside* (11) (11·9 g) was eluted with methanol–water (9 : 1) and recrystallised from ether–light petroleum; m.p. 76—78°, $[\alpha]_D$ +178° (*c* 1 in $CHCl_3$) (Found: C, 60·9; H, 7·2. $C_{16}H_{22}O_6$ requires C, 61·9; H, 7·1%). Compound (11) was treated with benzyl chloride and sodium hydride in refluxing tetrahydrofuran until t.l.c. (ether–light petroleum, 1 : 6) showed complete conversion into the product (R_F 0·3), which was isolated in the usual way and isomerised [2a] to the prop-1-enyl ether (13) (R_F 0·4). Compound (13) was hydrolysed with mercury(II) chloride [2b] and the product (14) isolated as a syrup which was chromatographed on alumina. After elution of trace impurities with ether, the *benzyl* 3,4,6-*tri*-O-*benzyl*-α-D-*galactopyranoside* (14) (10·4 g), was eluted with ether–methanol (99 : 1) and obtained as a syrup, $[\alpha]_D$ +80·2° (*c* 1 in $CHCl_3$) (Found: C, 74·9; H, 6·6. $C_{34}H_{36}O_6$ requires C, 75·5; H, 6·7%).

A portion was methylated and subsequently hydrogenated to give 2-*O*-methyl-D-galactose, m.p. 153—157° (lit.,[11b] m.p. 153—156°), $[\alpha]_D$ +60·7 ⟶ +87·1° (*c* 1 in H_2O) {lit.,[13a] $[\alpha]_D^{18}$ +52 ⟶ +94° (*c* 0·5 in H_2O); lit.,[13b] $[\alpha]_D$ +50 ⟶ +84° (*c* 2 in H_2O)}.

Benzyl 2-O-*Benzyl*-α-D-*galactopyranoside* (15).—Sodium hydride (5 g) was added slowly to a solution of benzyl 6-*O*-allyl-3,4-*O*-isopropylidene-α-D-galactopyranoside (6) (25 g) in dry benzene (500 ml) and benzyl chloride (25 ml) and the solution was heated under reflux for 4 h. T.l.c. (toluene–acetone, 5 : 1) then showed complete conversion of the starting material (R_F 0·5) into a product (R_F 0·65). The product (9) was isolated in the usual way and isomerised [2a] to give benzyl 2-*O*-benzyl-3,4-*O*-isopropylidene-6-*O*-(prop-1-enyl)-α-D-galactopyranoside (10) (R_F 0·75) as a syrup. The prop-1-enyl group was removed with mercury(II) chloride [2b] and the product was heated under reflux with

methanol (90 ml) and 0·5N-hydrochloric acid (30 ml) for 1 h. T.l.c. (toluene–acetone, 5 : 1) then showed a major product (R_F 0·1). An excess of sodium hydrogen carbonate was added and the solvents were evaporated off. The residue was extracted with chloroform and the product was recrystallised from ethyl acetate–light petroleum to give *benzyl* 2-O-*benzyl*-α-D-*galactopyranoside* (15) (14·9 g), m.p. 122—123°, $[\alpha]_D$ +147·2° (*c* 1 in MeOH) (Found: C, 66·65; H, 6·65. $C_{20}H_{24}O_6$ requires C, 66·65; H, 6·7%).

Benzyl 2-O-*Benzyl*-4,6-O-*propylidene*-α-D-*galactopyranoside*.—(*a*) Benzyl 2-*O*-benzyl-3,4-*O*-isopropylidene-6-*O*-(prop-1-enyl)-α-D-galactopyranoside (10) (14·9 g) was heated under reflux in methanol (90 ml) and 0·5N-hydrochloric acid (30 ml) for 1 h. T.l.c. (toluene–acetone, 5 : 1) then showed the absence of starting material (R_F 0·75) and the presence of two products (R_F 0·5 and 0·1). An excess of sodium hydrogen carbonate was added and the solvents were evaporated off. The product was chromatographed on alumina; elution with ether–methanol (19 : 1) gave the product of R_F 0·5 (2·4 g) and elution with methanol–water (1 : 1) gave benzyl 2-*O*-benzyl-α-D-galactopyranoside (15) (7 g; R_F 0·1). The product of R_F 0·5 was recrystallised from ethyl acetate–light petroleum to give *benzyl* 2-O-*benzyl*-4,6-O-*propylidene*-α-D-*galactopyranoside*, m.p. 119—121°, $[\alpha]_D$ +125° (*c* 1 in $CHCl_3$) (Found: C, 69·5; H, 7·0. $C_{23}H_{28}O_6$ requires C, 69·0; H, 7·05%).

(*b*) A solution of benzyl 2-*O*-benzyl-α-D-galactopyranoside (15) (50 mg) in propionaldehyde (0·7 ml) containing toluene-*p*-sulphonic acid (10 mg) was stirred at 20° for 30 min. T.l.c. (toluene–acetone 3 : 1) then showed complete conversion of the starting material (R_F 0·1) into a product (R_F 0·6). An excess of sodium hydrogen carbonate was added and the propionaldehyde was evaporated off. The product was extracted with chloroform and recrystallised from ethyl acetate–light petroleum; m.p. and mixed m.p. 116—118°, $[\alpha]_D$ +125·4° (*c* 0·6 in $CHCl_3$). The i.r. spectra of the compounds prepared by the two methods were identical.

For characterisation, the benzyl 2-*O*-benzyl-4,6-*O*-propylidene-α-D-galactopyranoside was benzylated in the usual manner and the product was hydrolysed with methanol–2N-hydrochloric acid (3 : 1) for 1·5 h with the methanol being allowed to distill off and the volume being maintained by the addition of methanol–water (3 : 1). T.l.c. (toluene–acetone, 3 : 1) then showed conversion of the starting material (R_F 0·75) into a product (R_F 0·25), which was isolated in the usual way and chromatographed on alumina with ethyl acetate–methanol (9 : 1) as eluant. Recrystallisation from ethyl acetate–light petroleum gave benzyl 2,3-di-*O*-benzyl-α-D-galactopyranoside, m.p. 121·5—122·5°, mixed m.p. 118—120°, $[\alpha]_D$ +88·2° (*c* 1 in $CHCl_3$), identical (i.r. spectrum) with the material prepared as described later.

Benzyl 2-O-*Benzyl*-4,6-O-*benzylidene*-α-D-*galactopyranoside* (16).—Benzyl 2-*O*-benzyl-α-D-galactopyranoside (15) (5·4 g), benzaldehyde (100 ml), and zinc chloride (5 g) were stirred vigorously for 0·5 h. T.l.c. (acetone–toluene, 1 : 1) then showed complete conversion of the starting material (R_F 0·4) into a product (R_F 0·7). (For t.l.c. a portion of the mixture was removed, sodium carbonate was added, and the benzaldehyde was evaporated onto a cold finger.) The reaction mixture was poured with stirring into ice–water (200 ml) and light petroleum (200 ml) and the crystalline product (5·1 g) which separated was filtered off and washed with water and light petroleum. For analysis a portion was recrystallised from ethyl acetate–light petroleum to give the *benzylidene derivative* (16) containing ethyl acetate of crystallisation; m.p. 131·5—133°, $[\alpha]_D$ +103° (*c* 1 in $CHCl_3$) [Found: C, 71·5; H, 6·2. $(C_{27}H_{28}O_6)_4MeCO_2Et$ requires C, 71·5; H, 6·4%]. The *acetate* of compound (16) had m.p. 99—100° (from ethyl acetate–light petroleum), $[\alpha]_D$ +145·9° (*c* 0·5 in $CHCl_3$) (Found: C, 71·2; H, 6·4. $C_{29}H_{30}O_7$ requires C, 71·0; H, 6·2%).

Benzyl 2,3-*Di*-O-*benzyl*-4,6-O-*benzylidene*-α-D-*galactopyranoside* (17).—Compound (16) was benzylated in the usual manner to give *compound* (17), m.p. 138·5—140° (from ethyl acetate–light petroleum), $[\alpha]_D$ +96·7° (*c* 1 in $CHCl_3$) (Found: C, 75·4; H, 6·2. $C_{34}H_{34}O_6$ requires C, 75·8; H, 6·4%).

Benzyl 2,3-*Di*-O-*benzyl*-α-D-*galactopyranoside* (19).—A suspension of compound (17) (3·6 g) in 0·5N-hydrochloric acid (18 ml) and methanol (54 ml) was heated under reflux for 20 min. The starting material had then dissolved and t.l.c. (toluene–acetone, 5 : 1) showed complete conversion of the starting material (R_F 0·8) into a single product (R_F 0·3). An excess of sodium hydrogen carbonate was added and the solvents were evaporated off. The product was extracted with chloroform and recrystallised from ethyl acetate–light petroleum to give *compound* (19) (3 g), m.p. 116—118°, $[\alpha]_D$ +87·3° (*c* 1 in $CHCl_3$) (Found: C, 71·6; H, 6·6. $C_{27}H_{30}O_6$ requires C, 72·0; H, 6·7%).

Benzyl 2,3,6-*Tri*-O-*benzyl*-α-D-*galactopyranoside* (29).—Benzyl 2,3-di-*O*-benzyl-α-D-galactopyranoside (19) (3 g) was treated with trityl chloride in pyridine to give the 6-*O*-trityl derivative (24) and the crude product was converted into the allyl ether (25) in the usual way. A solution of the crude product (25) in methanolic 0·1N-hydrogen chloride was heated under reflux for 10 min. T.l.c. (light petroleum–ether, 2 : 1) then showed complete conversion of compound (25) (R_F 0·8) into a single product (R_F 0·2). An excess of sodium hydrogen carbonate was added, the methanol was evaporated off, and the crude product was chromatographed on alumina. After elution of by-products with ether–light petroleum (1 : 1), benzyl 4-*O*-allyl-2,3-di-*O*-benzyl-α-D-galactopyranoside (26) (2·6 g; containing some triphenylmethanol) was eluted with ether–methanol (99 : 1). Compound (26) was benzylated in the usual manner and the product (27) was treated with potassium t-butoxide in dimethyl sulphoxide.[2a] When t.l.c. indicated complete conversion of the starting material (R_F 0·8) into the prop-1-enyl ether (28) (R_F 0·9) the product was isolated and hydrolysed with mercury(II) chloride [2b] to give a product (R_F 0·4) which was isolated in the usual way [2b] and chromatographed on silica gel (Mallinckrodt Silicar CC4 Special). After removal of by-products with toluene–acetone (99 : 1), the *benzyl* 2,3,6-*tri*-O-*benzyl*-α-D-*galactopyranoside* (29) (3 g) was eluted with toluene–acetone (39 : 1) as a syrup, $[\alpha]_D$ +69·0° (*c* 0·6 in $CHCl_3$) (Found: C, 75·2; H, 7·2. $C_{34}H_{36}O_6$ requires C, 75·5; H, 6·7%).

For characterisation, a portion of compound (29) was methylated and subsequently hydrogenated to give 4-*O*-methyl-D-galactose, m.p. 205—210° (from methanol), $[\alpha]_D$ +53·7 ⟶ +80·6° (24 h) (*c* 1 in H_2O) {lit.,[15a] m.p. 207°, $[\alpha]_D$ +62 ⟶ +92° (9 h; *c* 1·5 in H_2O); lit.,[15b] m.p. 218—221°, $[\alpha]_D$ +61 ⟶ +83° (17 h; *c* 2·17 in H_2O)}.

Benzyl 3-O-*Allyl*-2-O-*benzyl*-4,6-O-*benzylidene*-α-D-*galactopyranoside* (18).—Benzyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-galactopyranoside (16) was treated with allyl bromide and sodium hydride in refluxing benzene and the product isolated in the usual way to give *compound* (18), m.p. 134·5—135·5° (from ethyl acetate–light petroleum), $[\alpha]_D$

+110·8° (*c* 0·9 in $CHCl_3$) (Found: C, 73·6; H, 6·5. $C_{30}H_{32}O_6$ requires C, 73·75; H, 6·6%).

Benzyl 3-O-*Allyl*-2-O-*benzyl*-α-D-*galactopyranoside* (20).—Compound (18) (1·4 g) was treated with 0·5N-hydrochloric acid (12 ml) and methanol (36 ml) under reflux for 25 min; t.l.c. (toluene–acetone, 4 : 1) then showed conversion of the starting material (R_F 0·8) into a product (R_F 0·4). The product (1·3 g) was isolated in the usual way and recrystallised from ethyl acetate–light petroleum to give *compound* (20), m.p. 75—76°, $[\alpha]_D$ +105·9° (*c* 0·6 in $CHCl_3$) (Found: C, 69·45; H, 7·2. $C_{23}H_{28}O_6$ requires C, 69·0; H, 7·0%).

Benzyl 2,4,6-*Tri*-O-*benzyl*-α-D-*galactopyranoside* (23).—Compound (20) was benzylated in the usual manner to give benzyl 3-*O*-allyl-2,4,6-tri-*O*-benzyl-α-D-galactopyranoside (21) (R_F 0·5 in light petroleum–ether, 3 : 1). The allyl group of compound (21) was isomerised [24a] in the usual way to give the prop-1-enyl ether (22) (R_F 0·6), which was treated with mercury(II) chloride [24b] to give *benzyl* 2,4,6-*tri*-O-*benzyl*-α-D-*galactopyranoside* (23), m.p. 79—82° (from ethyl acetate–light petroleum), $[\alpha]_D$ +84·7° (*c* 0·55 in $CHCl_3$) (Found: C, 75·6; H, 6·7. $C_{34}H_{36}O_6$ requires C, 75·5; H, 6·7%).

For characterisation, a portion was methylated and subsequently hydrogenated to give 3-*O*-methyl-D-galactose as a syrup, which was difficult to crystallise. After several weeks in a small quantity of ethanol at 4°, crystals separated. After filtration and washing with ether the product had m.p. 137—141°, $[\alpha]_D$ +95° (final, *c* 0·5 in H_2O), and was identical (i.r. spectrum and t.l.c.) with an authentic sample [2c] {lit.,[14] m.p. 143—145°, $[\alpha]_D$ +106·5° (*c* 1·6 in H_2O)}.

Methyl 2,3,4,6-*Tetra*-O-*acetyl*-α- *and* -β-D-*glucopyranosides*.—2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl chloride [8] (0·45 g, 0·8 mmol), dry dichloromethane (2 ml), dry methanol (0·07 ml, 1·7 mmol), dry triethylamine (0·23 ml, 1·6 mmol), and dry tetraethylammonium chloride (0·14 g, 0·8 mmol) were sealed in an ampoule under vacuum and kept at 80° for 18 h. T.l.c. (ether–light petroleum, 2 : 3) then showed the absence of starting material (R_F 0·75) and the presence of a major product (R_F 0·5). The mixture was diluted with chloroform and the solution was washed with water and dried (Na_2SO_4). A portion (0·18 g) of the syrupy product (0·27 g) was hydrogenated over 10% palladium–charcoal and the product was acetylated with acetic anhydride in pyridine to give a mixture of anomers of methyl 2,3,4,6-tetra-*O*-acetyl-D-glucopyranoside (0·12 g). G.l.c. on 3% ECNSS-M on GasChrom Q at 182° showed the ratio of α- to β-anomers to be 87 : 13. Authentic samples of the anomers were prepared by acetylation of the anomers of methyl-D-glucopyranoside.

Benzyl 2,3,4-*Tri*-O-*benzyl*-6-O-(2,3,4,6-*tetra*-O-*benzyl*-α-D-*glucopyranosyl*)-α-D-*galactopyranoside* (30).—2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl chloride [8] (1·6 g, 2·9 mmol), benzyl 2,3,4-tri-*O*-benzyl-α-D-galactopyranoside (5) (3 g, 5·5 mmol), dry triethylamine (0·8 ml, 5·8 mmol), dry tetraethylammonium chloride (0·5 g, 3 mmol), and dry dichloromethane (3 ml) were sealed in an ampoule under vacuum and kept at 80° for 16·5 h. T.l.c. (ether–light petroleum, 1 : 1) then showed the presence of a trace of the chloride (R_F 0·8), a major product (R_F 0·7), and the excess of compound (5) (R_F 0·2). The mixture was diluted with dichloromethane, washed with water, and dried ($MgSO_4$). The product was chromatographed on alumina; elution with ether–light petroleum (2 : 1) gave the 'mixed disaccharide fraction' (2 g). The ^{13}C n.m.r. spectrum of this material (see later) indicated the presence of 91 ± 5% of the α-linked disaccharide. A portion was recrystallised from ethyl acetate–light petroleum to give *compound* (30), m.p. 112—113·5°, $[\alpha]_D$ +62·3° (*c* 0·8 in $CHCl_3$) (Found: C, 76·5; H, 6·8. $C_{68}H_{70}O_{11}$ requires C, 76·8; H, 6·6%); for ^{13}C n.m.r. data see later.

A portion of the 'mixed disaccharide fraction' (1·1 g) was hydrogenated over 10% palladium–charcoal to give the free disaccharide fraction (0·36 g), $[\alpha]_D$ +110° (*c* 1·3 in H_2O) {lit.,[6b] $[\alpha]_D^{25}$ +123° (*c* 1 in H_2O); lit.,[23] $[\alpha]_D$ +125° (*c* 1 in H_2O); lit.,[24a] $[\alpha]_D^{20}$ +123·1° (*c* 1·5 in H_2O); lit.,[24b] $[\alpha]_D$ +126° (H_2O) for 6-*O*-(α-D-glucopyranosyl)-D-galactose}, this rotation indicating again the high content of α-linked disaccharide. A portion of this product was hydrolysed in N-hydrochloric acid at 100° for 1 h. Descending paper chromatography in n-butanol–pyridine–water–acetic acid (6 : 4 : 3 : 1) showed the presence of glucose and galactose (by comparison with authentic standards) in the hydrolysate. A portion of the free disaccharide fraction (200 mg) was reduced with sodium borohydride in the usual manner to give a mixture of alditols (180 mg). A portion of the alditol fraction (12 mg) was taken up in dry pyridine (1 ml), hexamethyldisilazane (0·4 ml) and trimethylchlorosilane (0·25 ml) were added, and the solution was kept at 20° for 2·5 h. Hexane (3 ml) and water (3 ml) were added and the hexane layer was separated, washed with water, dried ($MgSO_4$), and evaporated to give the per-*O*-trimethylsilyl-alditols (32 mg). The 100 MHz ^1H n.m.r. spectrum of the product showed a well resolved doublet (τ 5·3) with a coupling constant (3·1 Hz) indicative of an α-linkage.[25] The product could not be separated by g.l.c. analysis from the corresponding β-linked trimethylsilyl disaccharide (see later) under the conditions reported previously [6b] for the separation of these compounds.

Benzyl 2,3,4-*Tri*-O-*benzyl*-6-O-(2,3,4,6-*tetra*-O-*benzyl*-β-D-*glucopyranosyl*)-α-D-*galactopyranoside* (31).—A mixture of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (0·45 g), benzyl 2,3,4-tri-*O*-benzyl-α-D-galactopyranoside (5) (0·6 g), mercury(II) cyanide (0·28 g), dry benzene (20 ml), and dry nitromethane (20 ml) was stirred at 40° for 24 h. T.l.c. (ether–light petroleum, 3 : 1) showed the presence of some unchanged compound (5) (R_F 0·7) and therefore more acetobromoglucose (0·22 g) and mercury(II) cyanide (0·14 g) were added and the mixture was stirred at 40° for 24 h. T.l.c. then indicated the absence of compound (5). The mixture was diluted with benzene and the solution was washed with saturated sodium hydrogen carbonate solution and water and dried (Na_2SO_4). The product (1·4 g) was chromatographed on neutral alumina. Elution with ether gave benzyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-galactopyranoside (0·9 g) as a syrup, and this was hydrolysed with N-sodium hydroxide in methanol to give benzyl 2,3,4-tri-*O*-benzyl-6-*O*-(β-D-glucopyranosyl)-α-D-galactopyranoside as a syrup (0·64 g). A solution of the latter (0·36 g) in *NN*-dimethylformamide (10 ml) and benzyl chloride (1 ml) containing sodium hydride (200 mg) was stirred at 20° for 3 days. T.l.c. (ether–light petroleum, 2 : 1) then showed complete

[23] I. J. Goldstein and W. J. Whelan, *J. Chem. Soc.*, 1963, 4264.
[24] (*a*) B. Helferich and W. M. Muller, *Chem. Ber.*, 1973, **106**. 941; (*b*) H. B. Boren, G. Ekborg, K. Eklind, P. J. Garegg, A. Pilotti, and C. G. Swahn, *Acta Chem. Scand.*, 1973, **27**, 2639.
[25] C. G. Hellerqvist, O. Larm, and B. Lindberg, *Acta Chem. Scand.*, 1971, **25**, 743; J. P. Kamerling, M. J. A. deBie, and J. F. G. Vliegenthart, *Tetrahedron*, 1972, **28**, 3037.

conversion of the starting material into a single product (R_F 0·9). Methanol was added to decompose the excess of sodium hydride and then water (50 ml) and chloroform (50 ml) were added. The chloroform layer was separated and dried ($MgSO_4$) and the product was chromatographed on alumina. Elution with ether–light petroleum (2 : 1) gave the product (0·25 g), which was recrystallised from ethyl acetate–light petroleum to give *compound* (31), m.p. 115·5—117·5, $[\alpha]_D$ +33·5° (*c* 0·8 in $CHCl_3$) (Found: C, 76·9; H, 6·8. $C_{68}H_{70}O_{11}$ requires C, 76·8; H, 6·6%).

A portion of the intermediate benzyl 2,3,4-tri-*O*-benzyl-6-*O*-(β-D-glucopyranosyl)-α-D-galactopyranoside (0·28 g) was hydrogenated over 10% palladium–charcoal to give 6-*O*-(β-D-glucopyranosyl)-D-galactose (0·12 g), $[\alpha]_D$ +14·3° (*c* 0·9 in H_2O) {lit.,[6b] $[\alpha]_D^{25}$ +19° (*c* 1 in H_2O); lit.,[23] $[\alpha]_D$ +10° (*c* 1 in H_2O); lit.,[26] $[\alpha]_D$ +13·9°}. This material was reduced with sodium borohydride and converted into the per-*O*-trimethylsilyl derivative as already described. The 100 MHz ^1H n.m.r. spectrum of the product was easily distinguished from that of the corresponding α-linked alditol disaccharide since the anomeric proton signal was further upfield [25] and was not readily distinguished, by first-order analysis, from the other proton signals.

Benzyl 3,4,6-*Tri*-O-*benzyl*-2-O-(2,3,4,6-*tetra*-O-*benzyl*-α-D-*glucopyranosyl*)-α-D-*galactopyranoside* (32).—A mixture of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride (2·8 g, 5 mmol), benzyl 3,4,6-tri-*O*-benzyl-α-D-galactopyranoside (14) (1·35 g, 2·5 mmol), dry triethylamine (1·4 ml, 10 mmol), dry tetraethylammonium chloride (0·8 g, 5 mmol), and dry dichloromethane (4 ml) was sealed in an ampoule under vacuum and kept at 80° for 66 h. T.l.c. (ether–light petroleum, 1 : 1) then indicated the presence of two major products (R_F 0·75 and 0·9) together with unchanged alcohol (14) (R_F 0·6). The mixture was diluted with dichloromethane and the solution was washed with water and dried ($MgSO_4$). The crude product (3·9 g) was chromatographed on alumina. Elution with ether gave a mixture of the two major products (1·3 g) and then the product of R_F 0·75 alone (0·5 g). The mixed products were chromatographed on silica gel (Mallinckrodt CC4 Special); elution with toluene gave the product of R_F 0·9 (0·7 g) and toluene–acetone (49 : 1) gave the product of R_F 0·75 (0·1 g). A portion of the product of R_F 0·9 was recrystallised from ethyl acetate–light petroleum to give 2,3,4,6-tetra-*O*-benzyl-1-deoxy-D-*arabino*-hex-1-enopyranose (34), m.p. 68·5—69°, $[\alpha]_D$ −6·2° (*c* 0·9 in $CHCl_3$) {lit.,[9] m.p. 66—66·5°, $[\alpha]_D^{20}$ −5·1° (*c* 1·6 in $CHCl_3$)} (Found: C, 78·3; H, 6·7. Calc. for $C_{34}H_{34}O_5$: C, 78·1; H, 6·6%).

A portion of the product of R_F 0·75 was recrystallised from ethyl acetate–light petroleum to give *compound* (32), m.p. 98·5—99°, $[\alpha]_D$ +75·2° (*c* 1 in $CHCl_3$) (Found: C, 57·2; H, 6·4. $C_{68}H_{70}O_{11}$ requires C, 76·8; H, 6·6%); yield 0·6 g [23% based on starting alcohol (14)].

Compound (32) was hydrogenated over 10% palladium–charcoal to give 2-*O*-(α-D-glucopyranosyl)-D-galactose, which was recrystallised from methanol–ethyl acetate. On heating, the product foamed at 107° and formed a meniscus with decomposition at 205°; $[\alpha]_D$ +130° ⟶ +142° (65 h; *c* 0·6 in H_2O). A portion of this disaccharide was hydrolysed with N-hydrochloric acid at 100° for 1 h. T.l.c. (propan-1-ol–ethyl acetate–water, 5 : 1 : 1) of the hydrolysate on a precoated Eastman Chromagram (K541V, Polyamide) impregnated with 0·2M-phosphate buffer (pH 6·8) [27] enabled identification of galactose (R_F 0·41) and glucose (R_F 0·54) by comparison with standard samples.

Benzyl 3,4,6-*Tri*-O-*benzyl*-2-O-(2,3,4,6-*tetra*-O-*acetyl*-β-D-*glucopyranosyl*)-α-D-*galactopyranoside*.—Compound (14) (0·75 g) was dissolved in dry benzene (30 ml) and dry nitromethane (30 ml), and *ca.* 20 ml of the solvent was distilled off. 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (0·75 g) and mercury(II) cyanide (0·5 g) were then added and the mixture was stirred at 40° for 24 h. T.l.c. (ether–light petroleum, 1 : 1) showed a product (R_F 0·2) together with unchanged compound (14) (R_F 0·4). More bromo-sugar (0·64 g) was added and after 22 h the starting material had been converted completely into the product (R_F 0·2). The crude *product* (2·1 g) was isolated in the usual way and crystallised from methanol; yield 0·9 g, m.p. 114—115·5°, $[\alpha]_D$ +31·6° (*c* 0·5 in $CHCl_3$) (Found: C, 66·1; H, 6·4. $C_{48}H_{54}O_{15}$ requires C, 66·2; H, 6·25%).

Benzyl 3,4,6-*Tri*-O-*benzyl*-2-O-(2,3,4,6-*tetra*-O-*benzyl*-β-D-*glucopyranosyl*)-α-D-*galactopyranoside* (33).—The foregoing disaccharide derivative was deacetylated and benzylated as for the preparation of compound (31) to give *compound* (33), m.p. 87—88° (from ethyl acetate–light petroleum), $[\alpha]_D$ +43·9° (*c* 0·9 in $CHCl_3$) (Found: C, 77·35; H, 6·8. $C_{68}H_{70}O_{11}$ requires C, 76·8; H, 6·6%).

Compound (32) (R_F 0·5) and compound (33) (R_F 0·63) were readily resolved by t.l.c. (ether–light petroleum, 1 : 1) on a Merck Kieselgel F_{254} plate. Compound (33) was hydrogenated over 10% palladium–charcoal to give 2-*O*-(β-D-glucopyranosyl)-D-galactose, which was recrystallised from glacial acetic acid. On heating, this compound changed its crystalline structure at 130° and formed a meniscus (with decomposition) at 190—192°; $[\alpha]_D$ +33·6 ⟶ +34·8° (24 h; *c* 0·5 in H_2O) {lit.,[28] m.p. 164—170° (from methanol, ' immediately after recrystallisation '), m.p. 170—190° (' after standing for a few days in the atmosphere '); $[\alpha]_D^{17}$ +42° ⟶ +40·6° (*c* 0·72 in H_2O); lit.,[29] m.p. 171—172° (from aqueous acetic acid), $[\alpha]_D$ +42·6° (H_2O); lit.,[30] m.p. 171—172°, $[\alpha]_D$ +32° (*c* 1·7 in H_2O)}.

A portion of the disaccharide was hydrolysed in N-hydrochloric acid at 100° for 1 h and the products were chromatographed as described for the corresponding α-isomer to show the presence of both glucose and galactose.

The ^1H n.m.r. spectra of compounds (32) and (33) were obtained with a Varian HR-220 spectrometer (Harwell) for solutions in deuteriochloroform with tetramethylsilane as an internal reference. Compound (32) showed τ 4·8 (1H, d, $J_{1,2}$ 3·5 Hz, H-1) and 5·0 (1H, d, $J_{1',2'}$ 3·5 Hz, H-1'); compound (33) showed τ 4·7 (1H, d, $J_{1,2}$ 3·5 Hz, H-1) and 5·0 (1H, d, $J_{1',2'}$ 11 Hz, H-1').

Carbon-13 *N.m.r. Spectra of Compounds* (30)—(33).—^{13}C N.m.r. spectra (25·2 MHz) were obtained with a Varian XL-100 spectrometer operating in the Fourier transform mode with complete proton decoupling. Deuteriochloroform was used as solvent and the acquisition time was 0·8 s, with a pulse width of 100 μs and a sweep width of 5 kHz. The chemical shifts [31] of the anomeric carbon atoms were

[26] K. Freudenberg, A. Wolf, E. Knopf, and S. A. Zaheer, *Ber.*, 1928, **61**, 1743.
[27] E. Moczar, M. Moczar, G. Schillinger, and L. Robert, *J. Chromatog.*, 1967, **31**, 561.
[28] T. Kawasaki and T. Yamuchi, *Chem. and Pharm. Bull.* (*Japan*), 1963, **11**, 1221.
[29] A. M. Gakhokidze and N. D. Kutidze, *Zhur. obshchei Khim.*, 1952, **22**, 139 [*J. Gen. Chem.* (*U.S.S.R.*), 1952, **22**, 167].
[30] P. Kooiman, *Carbohydrate Res.*, 1968, **7**, 200.
[31] H. J. Jennings and I. C. P. Smith, *J. Amer. Chem. Soc.*, 1973, **95**, 606; T. Usui, N. Yamaoka, K. Matsuda, K. Tuzimura, H. Sugiyama, and S. Seto, *J.C.S. Perkin I*, 1973, 2425.

measured in p.p.m., downfield positive, from internal tetramethylsilane.

(*a*) Pure benzyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-α-D-galactopyranoside (30), 20,000 transients: α-galactose 95·3; α-glucose 97·0.

(*b*) Pure benzyl 2,3,4-tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-α-D-galactopyranoside (31), 8511 transients: α-galactose 95·8; β-glucose 103·5.

(*c*) Crude product from preparation of compound (30), 63,143 transients: α-galactose 95·5; α-glucose 97·2. From an expanded part of the spectrum (3000—2700 Hz) the peak areas corresponding to the α-glucose and β-glucose anomeric carbon atoms showed that 91 (±5)% of the α-linked disaccharide was present.

(*d*) Pure benzyl 3,4,6-tri-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-α-D-galactopyranoside (32), 64,833 transients; α-galactose 94·4; α-glucose 95·5.

(*e*) Pure benzyl 3,4,6-tri-*O*-benzyl-2-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-α-D-galactopyranoside (33), 50,000 transients: α-galactose 99·2; β-glucose 104·0.

2,3,4,6-*Tetra*-O-*benzyl*-D-*glucose Diethyl Dithioacetal* (36).—A solution of 2,3,4,6-tetra-*O*-benzyl-D-glucose (35) (10 g) in dry dioxan (100 ml) and ethanethiol (50 ml) containing hydrogen chloride (1 g) was kept at room temperature and the course of the reaction was followed by t.l.c. (toluene–acetone, 9 : 1). After 24 h the starting material (R_F 0·5) had been converted into the two major products (R_F 0·75 and 0·85). An excess of sodium hydrogen carbonate was added and the solvents were evaporated off. The residue was extracted with ether and the solution was dried ($MgSO_4$) and passed through alumina. Continued elution with ether removed the product of R_F 0·85 (presumably the ethyl thioglycosides) (6 g) and elution with ether–methanol (30 : 1) gave the *diethyl dithioacetal* (36) (R_F 0·75; 6·7 g, 56%) as a syrup, $[\alpha]_D$ +19·5° (*c* 2·3 in $CHCl_3$) (Found: C, 70·0; H, 7·3; S, 9·6. $C_{38}H_{46}O_5S_2$ requires C, 70·6; H, 7·2; S, 9·9%).

Compound (36) was acetylated with acetic anhydride in pyridine to give 5-O-*acetyl*-2,3,4,6-*tetra*-O-*benzyl*-D-*glucose diethyl dithioacetal* (37) as a syrup, $[\alpha]_D$ +17·5° (*c* 2·45 in $CHCl_3$) (Found: C, 69·5; H, 7·2; S, 9·35. $C_{40}H_{48}O_6S_2$ requires C, 69·7; H, 7·0; S, 9·3%).

2,3,4,6-*Tetra*-O-*benzyl*-D-*glucose Dimethyl Acetal* (39).—Compound (37) (2 g), mercury(II) chloride (2 g), and mercury(II) oxide (2 g) were stirred at 20° in dry methanol (200 ml) for 4 h. T.l.c. (toluene–acetone, 25 : 1) then showed complete conversion of compound (37) (R_F 0·7) into a product (R_F 0·4). The mixture was filtered through Celite and the methanol evaporated off. The residue was taken into ether and the solution was washed with saturated potassium iodide solution (to remove mercury salts), dried ($MgSO_4$), and evaporated to give 5-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucose dimethyl acetal (38) (1·38 g) as a syrup. Compound (38) was treated with an excess of sodium hydroxide in methanol to give 2,3,4,6-*tetra*-O-*benzyl*-D-*glucose dimethyl acetal* (39) as a syrup, $[\alpha]_D$ +14·3° (*c* 3·3 in $CHCl_3$) (Found: C, 73·55; H, 7·4. $C_{36}H_{42}O_7$ requires C, 73·7; H, 7·2%).

Action of Acid Catalysts on Compound (39).—A solution of 2,3,4,6-tetra-*O*-benzyl-D-glucose dimethyl acetal (39) (100 mg) and toluene-*p*-sulphonic acid (1 mg) in dry ether (10 ml) was kept at room temperature and the course of the reaction was followed by t.l.c. (toluene–acetone, 25 : 1). After 40 h, *ca.* 30% of the starting material (R_F 0·3) had been converted into two products (R_F 0·5 and 0·55) in the ratio *ca.* 4 : 1. Under the same conditions, standard samples of methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside and its β-anomer prepared by the benzylation of the corresponding methyl D-glucopyranosides (Koch–Light Labs. Ltd.) had R_F 0·5 and 0·55, respectively. The reaction mixture was heated under reflux for 1·5 h, after which the starting material had been converted completely into the methyl glucosides (in the same ratio as before) together with a small amount of material which had the same R_F value as 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose.

In benzene solution, at room temperature, in the presence of toluene-*p*-sulphonic acid, compound (39) was converted into a mixture of the methyl α- and β-glycosides in the ratio *ca.* 5 : 4.

3,4,6-*Tri*-O-*benzyl*-2-*dibenzylamino*-2-*deoxy*-D-*glucopyranose* (45).—A solution of prop-1-enyl 2-benzamido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranoside (41) [2c] (2·1 g) in dry tetrahydrofuran (50 ml) and benzyl chloride (4 ml) containing sodium hydride (0·5 g) was heated under reflux for 4 days. T.l.c. (carbon tetrachloride–acetone, 15 : 1) then indicated complete conversion of the starting material (R_F 0·2) into a major product (R_F 0·4) and a minor product (R_F 0·6). The major product was isolated in the usual way to give crude compound (42) (2·8 g) as a syrup. A solution of compound (42) in ether was added to an excess of lithium aluminium hydride in ether and the solution was heated under reflux for 15 min. Ethyl acetate was added slowly to decompose the excess of hydride and water was then added dropwise with stirring until the inorganic material was in the form of a fine white powder, which was filtered off. Evaporation gave prop-1-enyl 3,4,6-tri-*O*-benzyl-2-dibenzylamino-2-deoxy-β-D-glucopyranoside (43) as a syrup (2·8 g). A solution of compound (43) in acetone-N-hydrochloric acid (9 : 1; 50 ml) was extracted under reflux for 1 h, then diluted with water and extracted with ethyl acetate. The extract was washed with saturated potassium chloride solution and dried ($MgSO_4$). T.l.c. (as before) showed a major product (R_F 0·3) with trace impurities and the product was chromatographed on silica gel (Mallinckrodt Silicar CC-4). After elution of trace impurities with carbon tetrachloride, elution with carbon tetrachloride–acetone (20 : 1) gave *compound* (45) (2·2 g) as a syrup, $[\alpha]_D$ −32·7 ⟶ −37·7° (21 h; *c* 0·8 in $CHCl_3$) (Found: C, 77·55; H, 6·8; N, 2·1. $C_{41}H_{43}NO_5$ requires C, 78·2; H, 6·9; N, 2·2%).

Compound (45) (320 mg) was hydrogenated in glacial acetic acid over 10% palladium–charcoal for 3 days at 20° to give a product (112 mg) which had R_F values identical with those of an authentic sample of D-glucosamine hydrochloride when chromatographed on Whatman No. 3 paper (benzene–butanol–pyridine–water, 1 : 5 : 2 : 3) and on Eastman Chromagram K541V polyamide sheet impregnated with 0·2M-phosphate buffer (pH 6·8) [27] (ethanol–0·880 ammonia–water, 85 : 0·5 : 14·5) (detected with 2,3,5-triphenyltetrazolium hydroxide).

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