# The Allyl Ether as a Protecting Group in Carbohydrate Chemistry. Part VII.[1] The 2-*O*-Allyl Group as a Non-participant in 1,2-*cis*-Glycoside Synthesis

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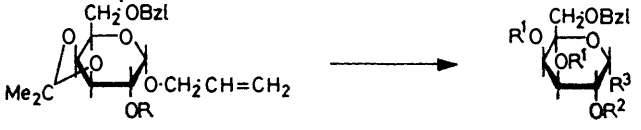
2-*O*-Allyl-3,4,6-tri-*O*-benzyl-D-galactopyranose was prepared and converted into the corresponding galactosyl chloride. The chloride was condensed with benzyl 2,3,4-tri-*O*-benzyl-α-D-galactopyranoside to give crystalline benzyl 6-*O*-(2-*O*-allyl-3,4,6-tri-*O*-benzyl-α-D-galactopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-galactopyranoside. The allyl group was removed from this fully protected disaccharide to give a disaccharide derivative suitable for conversion into a trisaccharide or for oxidation to a ketone and subsequent conversion into a disaccharide containing an α-linked 2-amino-2-deoxy-sugar.

We have previously [2] outlined a general oligosaccharide synthesis in which *O*-benzyl groups are used for 'persistent' blocking and *O*-allyl groups for 'temporary' blocking during the elongation of the oligosaccharide chain, and have also developed [2] a practical, stereoselective 1,2-*cis*-glycoside synthesis in which benzylated intermediates are used. Subsequently we synthesised [1] benzyl 6-*O*-[2,3,4-tri-*O*-benzyl-6-*O*-(but-2-enyl)-α-D-galactopyranosyl]-2,3,4-tri-*O*-benzyl-α-D-galactopyranoside, thus showing that it was possible to prepare a partially allylated and partially benzylated glycosyl halide and to use it in 1,2-*cis*-glycoside synthesis.

In the preparation of 1,2-*cis*-glycosides it is necessary to use a non-participating group on the 2-position of the glycosyl halide. This is usually a benzyl group, although others have been used.[3] For our general synthesis it was necessary to show that we could prepare a glycosyl halide with a 2-*O*-allyl group and that the latter would act as a suitable non-participating group.

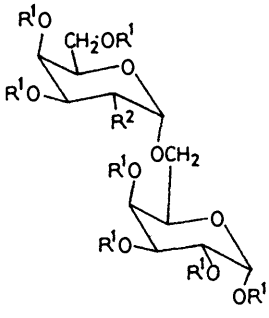
For this purpose, allyl 6-*O*-benzyl-3,4-*O*-isopropylidene-α-D-galactopyranoside [4] (1) was converted into the but-2-enyl ether (2) and the isopropylidene group was subsequently removed to give allyl 6-*O*-benzyl-2-*O*-(but-2-enyl)-α-D-galactopyranoside (3). The diol (3) was converted into the benzyl ether (4) and this was treated with potassium t-butoxide in dimethyl sulphoxide, which removed [5] the but-2-enyl group and isomerised [4] the allyl group to give prop-1-enyl-3,4,6-tri-*O*-benzyl-α-D-galactopyranoside (6). Compound (6) was converted into the allyl ether (7) and the prop-1-enyl group was removed with dilute acid to give crystalline 2-*O*-allyl-3,4,6-tri-*O*-benzyl-D-galactopyranose (8). For characterisation, compound (8) was reduced with sodium borohydride and the allyl group was subsequently removed [4] from the 2-*O*-allyl-3,4,6-tri-*O*-benzyl-D-galactitol obtained to give the known [4] 3,4,6-tri-*O*-benzyl-D-galactitol.

The free sugar (8) was converted into the anomeric mixture of *p*-nitrobenzoates, and this was treated with hydrogen chloride in ether–dichloromethane to give 2-*O*-allyl-3,4,6-tri-*O*-benzyl-D-galactopyranosyl chloride (9). This method usually gives the α-halide but we did not further investigate the anomeric configuration of compound (9). We have shown in our previous work [1,2] that benzylated glycosyl chlorides are very suitable for 1,2-*cis*-glycoside synthesis. Their stability is high



(1) R = H
(2) R = $CH_2CH{:}CHMe$

(3) $R^1$=H, $R^2$=$CH_2{\cdot}CH{:}CHMe$, $R^3$=$O{\cdot}CH_2{\cdot}CH{:}CH_2$
(4) $R^1$=Bzl, $R^2$=$CH_2CH{:}CHMe$, $R^3$=$O{\cdot}CH_2CH{:}CH_2$
(5) $R^1$=Bzl, $R^2$=H, $R^3$=$O{\cdot}CH_2{\cdot}CH{:}CH_2$
(6) $R^1$=Bzl, $R^2$=H, $R^3$=$O{\cdot}CH{:}CHMe$
(7) $R^1$=Bzl, $R^2$=$CH_2CH{:}CH_2$, $R^3$=$O{\cdot}CH{:}CHMe$
(8) $R^1$=Bzl, $R^2$=$CH_2CH{:}CH_2$, $R^3$=OH
(9) $R^1$=Bzl, $R^2$=$CH_2{\cdot}CH{:}CH_2$, $R^3$=Cl



Bzl = $CH_2Ph$

(10) $R^1$=Bzl, $R^2$=$O{\cdot}CH_2CH{:}CH_2$
(11) $R^1$=Bzl, $R^2$=$O{\cdot}CH{:}CHMe$
(12) $R^1$=Bzl, $R^2$=OH
(13) $R^1$=Bzl, $R^2$=OBzl

enough to allow solutions in organic solvents to be washed with (or to be kept for several days in contact with) aqueous sodium hydrogen carbonate without hydrolysis, although they are hydrolysed quite rapidly after being applied to silica gel t.l.c. plates. The pure chlorides are also stable for long periods. The benzylated glycosyl bromides are less stable and debenzylation is sometimes observed in their preparation.[6]

[1] Part VI, P. A. Gent and R. Gigg, *J.C.S. Perkin I*, 1974, 1835.
[2] P. A. Gent and R. Gigg, *J.C.S. Perkin I*, 1974, 1446.
[3] N. K. Kochetkov, O. S. Chizhov, and A. F. Bochkov in M.T.P. Internat. Rev. Sci., Org. Chem., Series I, vol. 7, Carbohydrates, ed. G. O. Aspinall, 1972, p. 147; G. Wulff and G. Röhle, *Angew. Chem. Internat. Edn.*, 1974, **13**, 157; C. Schuerch, *Accounts Chem. Res.*, 1973, 184.
[4] J. Gigg and R. Gigg, *J. Chem. Soc.* (*C*), 1966, 82.
[5] P. A. Gent, R. Gigg, and R. Conant, *J.C.S. Perkin I*, 1972, 1535.
[6] R. U. Lemieux and T. Kondo, *Carbohydrate Res.*, 1974, **35**, C4.

The galactosyl chloride (9) was condensed with benzyl 2,3,4-tri-*O*-benzyl-α-D-galactopyranoside [2] under the conditions described previously [2] for 1,2-*cis*-glycoside synthesis to give a fully protected disaccharide fraction. One of the advantages of preparing these disaccharides which are fully protected with non-polar groupings (allyl and benzyl ethers) is that the disaccharide fraction is readily separated from any excess of aglycone or free sugar (derived from excess of glycosyl chloride) by a single passage through alumina. The disaccharide fraction was recrystallised to give benzyl 6-*O*-(2-*O*-allyl-3,4,6-tri-*O*-benzyl-α-D-galactopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-galactopyranoside (10). The structure of compound (10) was confirmed by removal [4] of the allyl group to give the crystalline alcohol (12), which was benzylated to give benzyl 6-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-galactopyranoside (13) identical with the material described previously.[1]

The ease of crystallisation of all the per-*O*-benzylated disaccharide derivatives which we have prepared in this and previous [1,2] work facilitates the removal of the 1,2-*trans*-glycosides which are also formed in *ca.* 10% yield [2] in these syntheses, and augurs well for future oligosaccharide syntheses along these lines.

The ability to produce α-linked disaccharides with a free 2-hydroxy-group but otherwise fully protected with benzyl groups should allow the preparation of trisaccharides from these compounds and should also allow the preparation of 2-oxo-derivatives which can subsequently be reduced (*cf.* ref. 7 for similar work with 1,2-*trans*-glycosides) or converted into amines to give oligosaccharides containing α-linked 2-amino-2-deoxy-sugars. These reactions are being investigated with the disaccharide (12) from which an α-linked galactosamine derivative should be available (*cf.* ref. 8). α-Linked galactosamine containing oligosaccharides occur in glycolipids such as the blood group substances [9] and the Forssman hapten.[10]

A condensation of the galactosyl chloride (9) with benzyl 2,4,6-tri-*O*-benzyl-α-D-galactopyranoside [2] has also been achieved in lower yield and this reaction is being investigated in more detail since benzyl 3-*O*-(2-*O*-allyl-3,4,6-tri-*O*-benzyl-α-D-galactopyranosyl)-2,4,6-tri-*O*-benzyl-α-D-galactopyranoside should be a suitable intermediate for the preparation of the blood group A and B active disaccharides.[9]

## EXPERIMENTAL

General experimental details are as described previously.[1]

2-O-*Allyl*-3,4,6-*tri*-O-*benzyl*-D-*galactopyranose* (8).—Allyl 6-*O*-benzyl-3,4-*O*-isopropylidene-α-D-galactopyranoside (1) [4] (17 g) was treated with an excess of sodium hydride and 'crotyl bromide' in benzene at reflux for 1 h; t.l.c. (toluene–acetone, 3 : 1) then showed complete conversion of the starting material ($R_F$ 0·1) into the but-2-enyl ether (2) ($R_F$ 0·6). The product was isolated in the usual way [5] and added to 0·5N-hydrochloric acid (40 ml) and methanol (120 ml), and the mixture was heated under reflux for 30 min; t.l.c. (ether–light petroleum, 1 : 1) then showed complete conversion of the isopropylidene derivative (2) ($R_F$ 0·9) into the diol (3) ($R_F$ 0·1). An excess of sodium carbonate was added, the solvents were evaporated off, and the product was extracted with ether. The crude product (3) (18 g) was treated with an excess of sodium hydride and benzyl chloride in dimethylformamide at 40° during 2 h; t.l.c. (ether–light petroleum, 1 : 1) then showed complete conversion of the diol (3) ($R_F$ 0·1) into the tri-*O*-benzyl derivative (4) ($R_F$ 0·95). The crude product (4) was isolated in the usual way and the excess of benzyl chloride was removed at 95° and 2 mmHg. The product (25 g; syrup) was then treated with potassium t-butoxide (10 g) in dimethyl sulphoxide (200 ml) at 50° and the reaction was followed by t.l.c. (ether–light petroleum, 1 : 1). The starting material ($R_F$ 0·95) was rapidly converted into allyl 3,4,6-tri-*O*-benzyl-α-D-galactopyranoside (5) ($R_F$ 0·5), and this was then converted into the corresponding prop-1-enyl glycoside (6) ($R_F$ 0·6) during 1 h. The product (6) was isolated in the usual way [4] and treated with an excess of sodium hydride and allyl bromide in refluxing benzene for 1 h; t.l.c. (ether–light petroleum, 1 : 1) then showed complete conversion of the alcohol (6) into prop-1-enyl 2-*O*-allyl-3,4,6-tri-*O*-benzyl-α-D-galactopyranoside (7) ($R_F$ 0·95). Compound (7) was isolated in the usual way [4] and added to a mixture of acetone (400 ml) and N-hydrochloric acid (40 ml) and the solution was heated under reflux for 30 min; t.l.c. (ether–light petroleum, 1 : 2) then showed complete conversion of compound (7) ($R_F$ 0·8) into 2-*O*-allyl-3,4,6-tri-*O*-benzyl-D-galactopyranose (8) ($R_F$ 0·5). The product was isolated in the usual way and chromatographed on neutral alumina. Elution with ether–light petroleum (1 : 1) removed non-polar contaminants and elution with ether gave the pure 2-O-*allyl*-3,4,6-*tri*-O-*benzyl*-D-*galactopyranose* (8) (16 g), m.p. 90—92° (from ether–light petroleum, 1 : 3), $[\alpha]_D$ +24·9 ⟶ +19·4° (24 h; *c* 1 in $CHCl_3$) (Found: C, 73·8; H, 6·9. $C_{30}H_{34}O_6$ requires C, 73·4; H, 7·0%).

For characterisation, compound (8) (1 g) was reduced with sodium borohydride in ethanol; t.l.c. (ether–light petroleum, 2 : 1) showed conversion of compound (8) ($R_F$ 0·95) into 2-*O*-allyl-3,4,6-tri-*O*-benzyl-D-galactitol ($R_F$ 0·6). The product was isolated and treated with an excess of potassium t-butoxide in dimethyl sulphoxide to convert [4] the allyl ether into the prop-1-enyl ether ($R_F$ 0·7). The 2-*O*-(prop-1-enyl)-3,4,6-tri-*O*-benzyl-D-galactitol was isolated in the usual way [4] and treated with N-hydrochloric acid (2·5 ml) and methanol (25 ml) at reflux in a distillation flask, and the solvents (and released propionaldehyde) were distilled off slowly during 30 min while the volume of the mixture was maintained constant by adding methanol–water (10 : 1). Water (50 ml) was added to the flask and the methanol was distilled off. The precipitated product (730 mg) was filtered off, dried, and recrystallised from benzene–cyclohexane to give 3,4,6-tri-*O*-benzyl-D-galactitol, m.p. 99—101°, mixed m.p. (with material prepared previously [4]) 99—101°.

2-O-*Allyl*-3,4,6-*tri*-O-*benzyl*-D-*galactopyranosyl Chloride* (9).—2-*O*-Allyl-3,4,6-tri-*O*-benzyl-D-galactopyranose (8) (4 g)

[7] H. B. Boren, G. Ekborg, K. Eklind, P. J. Garegg, A. Pilotti, and C.-G. Swahn, *Acta Chem. Scand.*, 1973, **27**, 2639.
[8] R. U. Lemieux, K. James, T. L. Nagabhushan, and Y. Ito, *Canad. J. Chem.*, 1973, **51**, 33; R. U. Lemieux, K. James, and T. L. Nagabhushan, *ibid.*, p. 48.
[9] W. T. J. Morgan, *Bull. Institut Pasteur*, 1974, **72**, 131.
[10] B. Siddiqui and S. Hakamori, *J. Biol. Chem.*, 1971, **246**, 5766.

was dissolved in dry pyridine (20 ml) containing *p*-nitrobenzoyl chloride (2 g) and the solution was kept at 20° for 4 h; t.l.c. (ether–light petroleum, 1 : 4) then showed complete conversion of the free sugar (8) ($R_F$ 0) into the anomeric *p*-nitrobenzoates ($R_F$ 0·3). The product (5·5 g) was isolated in the usual way and dissolved in dry ether (25 ml) and dry dichloromethane (25 ml), and dry hydrogen was then passed through the solution for 1 h; t.l.c. (as above) then showed complete conversion into the chloride (9) ($R_F$ 0·8). The mixture was kept at 20° for 3 h and the solvents were evaporated off. The residue was dissolved in chloroform and the solution was washed with saturated sodium hydrogen carbonate solution and water, dried ($MgSO_4$), and evaporated to give the chloride (9) (3·4 g) as a syrup.

*Benzyl* 6-O-(2-O-*Allyl*-3,4,6-*tri*-O-*benzyl*-α-D-*galactopyranosyl*)-2,3,4-*tri*-O-*benzyl*-α-D-*galactopyranoside* (10).—A mixture of the chloride (9) (3·4 g, 6·7 mmol), benzyl 2,3,4-tri-*O*-benzyl-α-D-galactopyranoside [2] (6·9 g, 12·8 mmol), dry triethylamine (2 ml, 14·3 mmol), dry tetraethylammonium chloride (1·05 g, 6·5 mmol), and dry dichloromethane (6 ml) was sealed in an ampoule under vacuum and kept at 80° for 7 h; t.l.c. (ether–light petroleum, 1 : 1) showed the presence of a major product ($R_F$ 0·7) and a minor product ($R_F$ 0·6) together with the excess of aglycone ($R_F$ 0·4) and the free sugar (8) [$R_F$ 0·4; produced by hydrolysis of the chloride (9) and detected by its rapid reaction with potassium permanganate]. The mixture was diluted with dichloromethane and the solution was washed with water and dried ($MgSO_4$). The crude product (10·3 g) was chromatographed on alumina. Elution with ether gave the disaccharide fraction (3 g, 44% based on chloride), which was recrystallised from ethyl acetate–light petroleum (b.p. 60—80°) to give the *protected disaccharide* (10) (2·3 g), m.p. 104—107°, $[\alpha]_D$ +66·3° (*c* 1 in $CHCl_3$) (Found: C, 75·3; H, 6·9. $C_{64}H_{68}O_{11}$ requires C, 75·9; H, 6·8%).

*Benzyl* 2,3,4-*Tri*-O-*benzyl*-6-O-(3,4,6-*tri*-O-*benzyl*-α-D-*galactopyranosyl*)-α-D-*galactopyranoside* (12).—A solution of the allylated disaccharide (10) (2·1 g) in dry dimethyl sulphoxide (25 ml) containing potassium t-butoxide (1 g) was kept at 45° for 1 h; t.l.c. (ether–light petroleum, 1 : 1) then showed complete conversion of the allyl ether (10) ($R_F$ 0·6) into the prop-1-enyl ether (11) ($R_F$ 0·7). The product was isolated in the usual way [4] and dissolved in acetone (36 ml) and water (4 ml). Mercury(II) oxide (0·7 g) and mercury(II) chloride (0·7 g) were added and the mixture was stirred at 20° for 10 min; t.l.c. (as above) then showed complete conversion of the prop-1-enyl ether ($R_F$ 0·7) into a single product ($R_F$ 0·2), which was isolated in the usual way [11] to give *compound* (12) as the monohydrate (1·3 g), m.p. 107—108·5° (from aqueous acetone), $[\alpha]_D$ +77·2° (*c* 1 in $CHCl_3$) (Found: C, 73·7; H, 6·5. $C_{61}H_{64}O_{11},H_2O$ requires C, 73·9; H, 6·7%).

*Benzyl* 2,3,4-*Tri*-O-*benzyl*-6-O-(2,3,4,6-*tetra*-O-*benzyl*-α-D-*galactopyranosyl*)-α-D-*galactopyranoside* (13).—Compound (12) (70 mg) was treated with an excess of sodium hydride and benzyl chloride in dimethylformamide at 40° during 2 h; t.l.c. (ether–light petroleum, 1 : 1) then showed complete conversion of the alcohol (12) ($R_F$ 0·2) into the benzyl derivative (13) ($R_F$ 0·7). The product was isolated in the usual way and chromatographed on alumina. Elution with ether–light petroleum (1 : 4) removed the non-polar contaminants and elution with ether–light petroleum (1 : 1) gave the product (13) (30 mg), m.p. 111—112·5° (from methanol), mixed m.p. 110—112°, $[\alpha]_D$ +62·1° (*c* 1 in $CHCl_3$) {lit.,[1] m.p. 112—114°, $[\alpha]_D$ +61° (*c* 1 in $CHCl_3$)}.

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[11] R. Gigg and C. D. Warren, *J. Chem. Soc.* (*C*), 1968, 1903.