The Allyl Ether as a Protecting Group in Carbohydrate Chemistry. Part IX.† Synthesis of Derivatives of 1,6-Anhydro-β-D-galactopyranose

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1,6-Anhydro-2,3-di-*O*-benzyl-β-D-galactopyranose was prepared by four different methods and isolated and characterised as the crystalline *p*-nitrobenzoate. (*a*) Allylation of 1,6-anhydro-2-*O*-benzyl-β-D-galactopyranose gave a mixture of di- and mono-allyl derivatives. The mono-allyl derivatives were benzylated and the allyl group was removed. (*b*) Phenyl 4-*O*-allyl-2,3-di-*O*-(but-2-enyl)-β-D-galactopyranoside was treated with potassium t-butoxide in dimethyl sulphoxide, which removed the but-2-enyl groups, isomerised the allyl group, and converted the phenyl 4-*O*-(prop-1-enyl)-β-D-galactopyranoside formed into 1,6-anhydro-4-*O*-(prop-1-enyl)-β-D-galactopyranose. Benzyl chloride was then added to the solution to give the 2,3-di-*O*-benzyl derivative and the prop-1-enyl group was subsequently hydrolysed. (*c*) 1,6:2,3-Dianhydro-β-D-talopyranose was converted into the 4-*O*-allyl derivative, which was hydrolysed with base to give 4-*O*-allyl-1,6-anhydro-β-D-galactopyranose. This was benzylated and the allyl group was removed. (*d*) Tritylation of 1,6-anhydro-2-*O*-benzyl-β-D-galactopyranose gave predominantly 1,6-anhydro-2-*O*-benzyl-4-*O*-trityl-β-D-galactopyranose, which was benzylated and the trityl group was removed. The 1,6-anhydro-2,3-di-*O*-benzyl-β-D-galactopyranose was condensed with 2,3,4-tri-*O*-benzyl-6-*O*-(but-2-enyl)-D-galactopyranosyl chloride, under conditions shown previously to give predominantly 1,2-*cis*-glycosidic linkages, to give a disaccharide derivative which was converted into crystalline 1,2,3,6-tetra-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)-α-D-galactopyranose. 1,6-Anhydro-2-*O*-benzyl-4-*O*-trityl-β-D-galactopyranose was converted into crystalline 3-*O*-allyl-1,6-anhydro-2-*O*-benzyl-4-*O*-trityl-β-D-galactopyranose, an intermediate for the synthesis of 1,6-anhydro-2,4-di-*O*-benzyl-β-D-galactopyranose. 1,6:2,3-Dianhydro-4-*O*-benzyl-β-D-talopyranose was converted into 1,6-anhydro-2-azido-4-*O*-benzyl-2-deoxy-β-D-galactopyranose, which was isolated and characterised as the crystalline *p*-nitrobenzoate. Preliminary investigations on the conversion of 1,6-anhydro-2,3-di-*O*-benzyl-4-*O*-*p*-nitrobenzoyl-β-D-galactopyranose into 6-*O*-acetyl-2,3-di-*O*-benzyl-4-*O*-*p*-nitrobenzoyl-D-galactopyranosyl chloride by the action of acetyl chloride in the presence of hydrogen chloride ('chloracetolysis') and on the reaction of *N*-bromosuccinimide with 6-*O*-allyl-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose are also reported.

THE axial 4-hydroxy-group of galactopyranose derivatives in the $^4C_1$ conformation shows low reactivity in glycosidic condensations [1] and this has led to the use of 1,6-anhydro-β-D-galactopyranose derivatives, where the 4-hydroxy-group of the $^1C_4$ conformation is equatorial, for condensations of this type.[2]

4-*O*-(α-D-Galactopyranosyl)-D-galactopyranose residues are components of the oligosaccharide chains of the P^1-antigen,[3] of the glycolipids accumulating in Fabry's disease,[4] and of the Forssman antigen and related glycolipids such as globoside.[5] For the synthesis of this disaccharide component, a suitably protected 1,6-anhydro-β-D-galactopyranose derivative was required for elaboration of the 1,2-*cis*-galactosidic linkage by the methods which we have recently [6] developed.

2,3-Di-*O*-acetyl-1,6-anhydro-β-D-galactopyranose has been prepared [2a,7] but the ease [7] of acetyl migration in this compound, which would probably be enhanced under the basic conditions which are used in our synthetic method,[6] led us to consider the preparation of a more stable intermediate such as 1,6-anhydro-2,3-di-*O*-benzyl-β-D-galactopyranose (10). Three routes for the synthesis of this compound were initially considered and they all involved the use of the allyl ether as a protecting group.

In the first method it was anticipated that treatment of 1,6-anhydro-2-*O*-benzyl-β-D-galactopyranose (4) with allyl bromide and sodium hydroxide under mild conditions would lead to preferential allylation of the equatorial 4-hydroxy-group to give predominantly 4-*O*-allyl-1,6-anhydro-2-*O*-benzyl-β-D-galactopyranose (5), which on subsequent benzylation followed by removal [8] of the allyl group would give the required product (10). This proved to be the case although the 1,6-anhydro-2,3-di-*O*-benzyl-β-D-galactopyranose (10) was not crystalline and had to be separated from 1,6-anhydro-2,4-di-*O*-benzyl-β-D-galactopyranose (11) which was also formed. This was achieved by converting compound (10) into a crystalline *p*-nitrobenzoate (12) which was isolated in 6% overall yield from compound (4). The *p*-nitrobenzoates of compounds (10) and (11) were separated by t.l.c. and the relative proportions of each could therefore be assessed.

The structure of the 1,6-anhydro-2,3-di-*O*-benzyl-β-D-galactopyranose (10) regenerated from the crystalline *p*-nitrobenzoate (12) was confirmed by conversion into the 4-*O*-methyl ether (14), which on hydrogenolysis and subsequent acidic hydrolysis gave 4-*O*-methyl-D-galactose, identical with material prepared previously.[6a]

In the second method the direct conversion of phenyl 4-*O*-allyl-β-D-galactopyranoside (24) into 4-*O*-allyl-1,6-anhydro-β-D-galactopyranose (27) under basic conditions was considered. The mechanism [9] of the formation of

† Part VIII, P. A. Gent and R. Gigg, *Carbohydrate Res.*, in the press.

[1] M. Dejter-Juszynski and H. M. Flowers, *Carbohydrate Res.*, 1975, **41**, 308.

[2] (*a*) D. Shapiro, A. J. Acher, and E. S. Rachaman, *J. Org. Chem.*, 1967, **32**, 3767; (*b*) M. E. Chacon-Fuertes and M. Martin-Lomas, *Carbohydrate Res.*, 1975, **43**, 51.

[3] M. Naiki, J. Fong, R. Leeden, and D. M. Marcus, *Biochemistry*, 1975, **14**, 4831.

[4] Y.-T. Li, S.-C. Li, and G. Dawson, *Biochim. Biophys. Acta*, 1972, **260**, 88; Y.-T. Li and S.-C. Li, *J. Biol. Chem.*, 1971, **246**, 3769.

[5] B. Siddiqui and S.-I. Kakomori, *J. Biol. Chem.*, 1971, **246**, 5766.

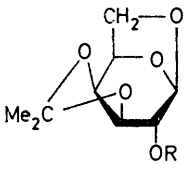
[6] P. A. Gent and R. Gigg, *J.C.S. Perkin I*, (*a*) 1974, 1446; (*b*) 1974, 1835; (*c*) 1975, 361; (*d*) 1975, 1521; (*e*) 1975, 1779.

[7] M. E. Chacon-Fuertes and M. Martin-Lomas, *Carbohydrate Res.*, 1975, **42**, C4.

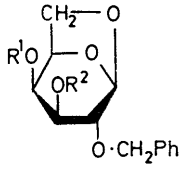
[8] (*a*) J. Gigg and R. Gigg, *J. Chem. Soc.* (*C*), 1966, 82; (*b*) R. Gigg and C. D. Warren, *ibid.*, 1968, 1903.

[9] C. M. McCloskey and G. H. Coleman, *J. Org. Chem.*, 1945, **10**, 184; E. M. Montgomery, N. K. Richtmyer, and C. S. Hudson, *J. Org. Chem.*, 1945, **10**, 194; M. P. Bardolph and G. H. Coleman, *ibid.*, 1950, **15**, 169; A. Dyfverman and B. Lindberg, *Acta Chem. Scand.*, 1950, **4**, 878.

1,6-anhydro-derivatives from phenyl β-D-galactopyranosides requires that the 2- and 6-hydroxy-groups should



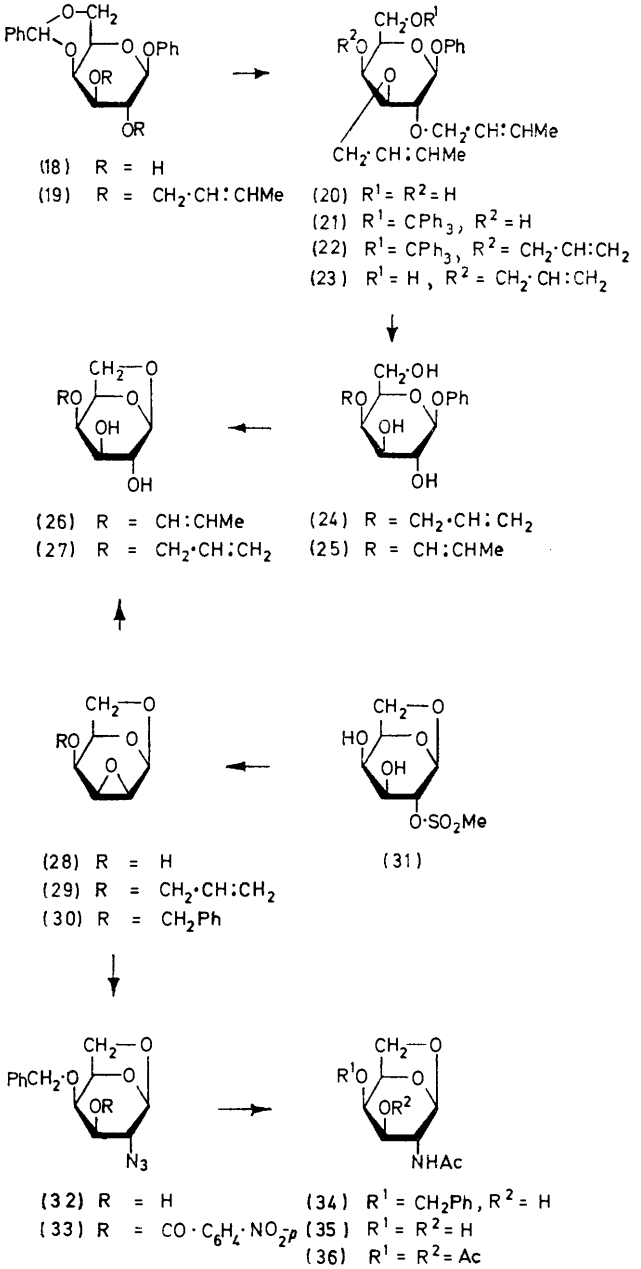
(1) R = H
(2) R = CH_2Ph
(3) R = SO_2Me



(4) $R^1 = R^2 = H$
(5) $R^1 = CH_2{\cdot}CH{:}CH_2$, $R^2 = H$
(6) $R^1 = H$, $R^2 = CH_2{\cdot}CH{:}CH_2$
(7) $R^1 = CH_2{\cdot}CH{:}CH_2$, $R^2 = CH_2Ph$
(8) $R^1 = CH_2Ph$, $R^2 = CH_2{\cdot}CH{:}CH_2$
(9) $R^1 = CH{:}CHMe$, $R^2 = CH_2Ph$
(10) $R^1 = H$, $R^2 = CH_2Ph$
(11) $R^1 = CH_2Ph$, $R^2 = H$
(12) $R^1 = CO{\cdot}C_6H_4{\cdot}NO_2{-}p$, $R^2 = CH_2Ph$
(13) $R^1 = CH_2Ph$, $R^2 = CO{\cdot}C_6H_4{\cdot}NO_2{-}p$
(14) R^1 = Me $R^2 = CH_2Ph$
(15) $R^1 = CPh_3$, $R^2 = H$
(16) $R^1 = CPh_3$, $R^2 = CH_2Ph$
(17) $R^1 = CPh_3$, $R^2 = CH_2{\cdot}CH{:}CH_2$

be unsubstituted, and the normal basic conditions [10] for the reaction involve use of aqueous alkali (*ca.* 1.3N) under reflux for 9 h. We investigated the action of potassium t-butoxide in dimethyl sulphoxide on a model phenyl β-D-galactopyranoside to see if these were suitable basic conditions for the formation of a 1,6-anhydro-ring. Phenyl β-D-galactopyranoside was converted into the 3,4-*O*-isopropylidene derivative. The product, which was contaminated with some 4,6-*O*-isopropylidene derivative (*ca.* 10%; *cf.* ref. 11), was treated with potassium t-butoxide in dimethyl sulphoxide at 50 °C, and t.l.c. showed conversion, during 6 h, into a product running concurrently with authentic 1,6-anhydro-3,4-*O*-isopropylidene-β-D-galactopyranose (1), thus indicating that these basic conditions were satisfactory; the following route to compound (10) was therefore investigated.

Phenyl β-D-galactopyranoside (obtained by deacetylation of phenyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside, prepared by a modification of the method [12] of Helferich and Schmitz-Hillebrecht) was converted into phenyl 4,6-*O*-benzylidene-β-D-galactopyranoside (18),[13] which was treated with 'crotyl bromide' and sodium hydride [14] to give phenyl 4,6-*O*-benzylidene-2,3-di-*O*-(but-2-enyl)-β-D-galactopyranoside (19). Compound (19) was hydrolysed to give crystalline phenyl 2,3-di-*O*-(but-2-enyl)-β-D-galactopyranoside (20), which was converted by way of the trityl ether (21) into the allyl ether (22).



(18) R = H
(19) R = $CH_2{\cdot}CH{:}CHMe$
(20) $R^1 = R^2 = H$
(21) $R^1 = CPh_3$, $R^2 = H$
(22) $R^1 = CPh_3$, $R^2 = CH_2{\cdot}CH{:}CH_2$
(23) $R^1 = H$, $R^2 = CH_2{\cdot}CH{:}CH_2$
(24) R = $CH_2{\cdot}CH{:}CH_2$
(25) R = $CH{:}CHMe$
(26) R = $CH{:}CHMe$
(27) R = $CH_2{\cdot}CH{:}CH_2$
(28) R = H
(29) R = $CH_2{\cdot}CH{:}CH_2$
(30) R = CH_2Ph
(31)
(32) R = H
(33) R = $CO{\cdot}C_6H_4{\cdot}NO_2{-}p$
(34) $R^1 = CH_2Ph$, $R^2 = H$
(35) $R^1 = R^2 = H$
(36) $R^1 = R^2 = Ac$

Acidic hydrolysis of compound (22) gave crystalline phenyl 4-*O*-allyl-2,3-di-*O*-(but-2-enyl)-β-D-galactopyran-

[10] E. M. Montgomery, N. K. Richtmyer, and C. S. Hudson, *J. Amer. Chem. Soc.*, 1943, **65**, 3.
[11] H. M. Flowers, *Carbohydrate Res.*, 1975, **39**, 245.
[12] (*a*) B. Helferich and E. Schmitz-Hillebrecht, *Ber.*, 1933, **66B**, 378; (*b*) C. D. Hurd and W. A. Bonner, *J. Org. Chem.*, 1946, **11**, 50; (*c*) T. Uryu, H. Libert, J. Zachoval, and C. Schuerch, *Macromolecules*, 1970, **3**, 345; (*d*) M. Sözmen, *Comm. Fac. Sci. Univ. Ankara, Ser. B*, 1972, **19**, 99.
[13] R. E. Reeves, *J. Amer. Chem. Soc.*, 1948, **70**, 3963; K. Wallenfels and J. Lehmann, *Annalen*, 1960, **635**, 166; P. Rivaille and L. Szabo, *Bull. Soc. chim. France*, 1963, 716.
[14] P. A. Gent, R. Gigg, and R. Conant, *J.C.S. Perkin I*, 1972, 1535.

oside (23). Compound (23) was treated with potassium t-butoxide in dimethyl sulphoxide, which initially removed [14] the but-2-enyl groups and isomerised [8] the allyl group to give phenyl 4-*O*-(prop-1-enyl)-β-D-galactopyranoside (25), and this was more slowly converted into 1,6-anhydro-4-*O*-(prop-1-enyl)-β-D-galactopyranose (26). Potassium t-butoxide in dimethyl sulphoxide has been shown [15] to be as effective as sodium methylsulphinylmethanide in dimethyl sulphoxide for permethylation reactions, and it was therefore anticipated that it would also be suitable for benzylation reactions. In the reaction mixture containing compound (26) an excess of potassium t-butoxide was present and compound (26) was presumably present as the potassio-derivative. Therefore benzyl chloride was added directly to the reaction mixture and the 1,6-anhydro-2,3-di-*O*-benzyl-4-*O*-(prop-1-enyl)-β-D-galactopyranose (9) was formed (9) directly. The prop-1-enyl group was removed by hydrolysis [8] to give the crude product (10), which was purified by way of the crystalline *p*-nitrobenzoate (12) [isolated in 34% overall yield from compound (23)].

In the third method, 1,6 : 2,3-dianhydro-β-D-talopyranose (28) [16] was converted into the allyl ether (29). It has been shown [17] that alkaline hydrolysis of the 2,3-anhydro-ring in these compounds occurs with almost complete conversion into the *galacto*-derivatives, and compound (29) was hydrolysed in this way to give 4-*O*-allyl-1,6-anhydro-β-D-galactopyranose (27). Benzylation of compound (27) and subsequent removal [8] of the allyl group gave crude 1,6-anhydro-2,3-di-*O*-benzyl-β-D-galactopyranose (10), which was again purified by conversion into the crystalline *p*-nitrobenzoate (12) [isolated in 59% overall yield from compound (28)].

Although the first method is the shortest, the yields are poor owing to the low regioselectivity in the allylation of 1,6-anhydro-2-*O*-benzyl-β-D-galactopyranose (4). This indicated the need for a more bulky alkylating agent, and molecular models showed that compound (4) should be capable of forming a 4-*O*-trityl ether. Trityl ethers have been little used [18] for the protection of secondary hydroxy-groups during preparative work in general carbohydrate chemistry, although there are several examples in steroid [19] and nucleoside [20] chemistry.

When 1,6-anhydro-2-*O*-benzyl-β-D-galactopyranose (4) was treated with an excess of trityl chloride in pyridine at reflux, conversion into mono- (and a little di-) trityl derivatives was observed. The monotrityl derivatives were separated by chromatography on alumina and benzylated and the trityl groups were subsequently removed by acidic hydrolysis. The di-*O*-benzyl ethers of 1,6-anhydro-β-D-galactopyranose were converted into the *p*-nitrobenzoates and t.l.c. showed that *ca.* 98% of the required isomer (12) was present, indicating the high degree of regioselectivity in the tritylation of compound (4). Crystalline compound (12) was isolated in 12% overall yield from compound (4). The crude 1,6-anhydro-2-*O*-benzyl-4-*O*-trityl-β-D-galactopyranose (15) was also converted into crystalline 3-*O*-allyl-1,6-anhydro-2-*O*-benzyl-4-*O*-trityl-β-D-galactopyranose (17). Removal of the trityl group from compound (17) and subsequent benzylation gave 3-*O*-allyl-1,6-anhydro-2,4-di-*O*-benzyl-β-D-galactopyranose (8), from which the allyl group was removed to give 1,6-anhydro-2,4-di-*O*-benzyl-β-D-galactopyranose (11). Compound (11) was converted into the *p*-nitrobenzoate (13), which was well separated from its isomer (12) on t.l.c.

Of the four methods described above for the preparation of 1,6-anhydro-2,3-di-*O*-benzyl-β-D-galactopyranose (10), the route through the 1,6 : 2,3-dianhydro-β-D-talopyranose (28) is the most convenient, particularly since we have simplified the procedure for the synthesis of compound (28) (see Experimental section). The 2,3-anhydro-ring of compound (28) can also be opened with ammonia [16] and with other alkoxides,[16a] and this compound therefore appeared to be a suitable intermediate for the preparation of other protected derivatives of 1,6-anhydro-β-D-galactopyranose.

Paulsen and Stenzel [21] have shown recently that the 2-azido-group is a suitable non-participating group for the synthesis of α-linked 2-azido-2-deoxy-D-glucose derivatives, which can be converted into α-linked 2-amino-2-deoxy-D-glucose derivatives. α-Linked 2-amino-2-deoxy-D-galactose derivatives occur in glycolipids such as the blood group substances [22] and in the Forssman antigen,[5] and a route to a 2-azido-2-deoxy-D-galactose derivative, suitable for the synthesis of α-linked 2-amino-2-deoxy-D-galactose derivatives, from a derivative of 1,6 : 2,3-dianhydro-β-D-talopyranose (28) was investigated.

Compound (28) was converted into the benzyl ether (30) by the action of benzyl chloride and sodium hydride in dimethylformamide. The benzyl ether (30) was treated with sodium azide and ammonium chloride in dimethyl sulphoxide at 100 °C to give 1,6-anhydro-2-azido-4-*O*-benzyl-2-deoxy-β-D-galactopyranose (32) as the major product (*ca.* 95%) (together with some 1,6-anhydro-3-azido-4-*O*-benzyl-3-deoxy-β-D-idose), and this was purified by conversion into the crystalline *p*-nitrobenzoate (33). For characterisation the azide (32) was reduced to the corresponding amine with lithium aluminium hydride and this was acetylated with acetic anhydride in methanol to give 2-acetamido-1,6-anhydro-4-*O*-benzyl-2-deoxy-β-D-galactopyranose (34). Hydrogenolysis of compound (34) gave the known [16b] 2-acetamido-1,6-anhydro-2-deoxy-β-D-galactopyranose (35), which

[15] J. Eagles, W. M. Laird, R. Self, and R. L. M. Synge, *Biomed. Mass Spectrometry*, 1974, **1**, 43.

[16] (*a*) S. P. James, F. Smith, M. Stacey, and L. F. Wiggin, *J. Chem. Soc.*, 1946, 625; (*b*) R. W. Jeanloz and P. J. Stoffyn, *Methods Carbohydrate Chem.*, 1962, **1**, 221.

[17] R. B. Duff, *J. Chem. Soc.*, 1949, 1597; N. R. Williams, *Adv. Carbohydrate Chem. Biochem.*, 1970, **25**, 109.

[18] J. Staněk, M. Černý, J. Kocourek, and J. Pacák, 'The Monosaccharides,' Academic Press, New York, 1963, p. 319.

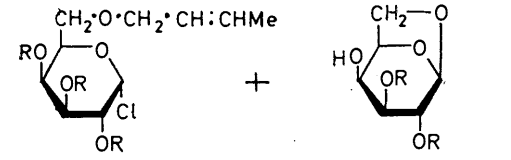
[19] H. J. E. Loewenthal, *Tetrahedron*, 1959, **6**, 269; J. F. W. Keana in 'Steroid Reactions,' ed. C. Djerassi, Holden-Day, San Francisco, 1963, p. 67.

[20] H.-U. Blank and W. Pfleiderer, *Annalen*, 1970, **742**, 1; G. Kowollik, K. Gaertner, and P. Langen, *Tetrahedron Letters*, 1972, 3345.

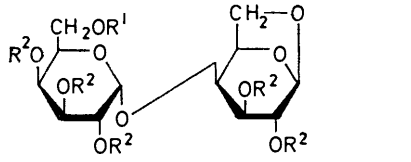
[21] H. Paulsen and W. Stenzel, *Angew. Chem. Internat. Edn.*, 1975, **14**, 558.

[22] W. T. J. Morgan, *Bull. Inst. Pasteur*, 1974, **72**, 131.

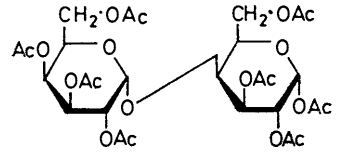
was also converted into the di-*O*-acetate (36), with properties similar to those reported.[16a] The azide (32) should be a suitable intermediate for the preparation of a 2-azido-2-deoxygalactosyl chloride (*cf.* ref. 21 for corresponding work with the *gluco*-derivative), which



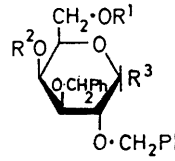
(37) R = CH_2Ph (10) R = CH_2Ph



(38) R^1 = CH_2·CH:CHMe, R^2 = CH_2Ph
(39) R^1 = H, R^2 = CH_2Ph
(40) R^1 = R^2 = H
(41) R^1 = R^2 = Ac



(42)



(43) R^1 = Ac, R^2 = CO·C_6H_4·NO_2-*p*, R^3 = Cl
(44) R^1 = Ac, R^2 = CO·C_6H_4·NO_2-*p*, R^3 = OAc
(45) R^1 = Ac, R^2 = CO·C_6H_4·NO_2-*p*, R^3 = OMe
(46) R^1 = R^2 = H, R^3 = OMe

could be condensed with a molecule of the azide (32) to give an intermediate suitable for the synthesis of the 3-*O*-(2-acetamido-2-deoxy-α-D-galactopyranosyl)-2-acetamido-2-deoxy-D-galactose residue which occurs in the Forssman antigen.[5]

[23] P. A. Gent and R. Gigg, *J.C.S. Perkin I*, 1975, 364.
[24] (*a*) R. D. Guthrie and J. F. McCarthy, *Adv. Carbohydrate Chem.*, 1967, **22**, 11; (*b*) H. Burton and P. F. G. Praill, *J. Chem. Soc.*, 1950, 1203, 2034; 1951, 522; (*c*) L. Zechmeister, *Ber.*, 1923, **56**, 573; A. Jeanes, C. A. Wilham, and G. E. Hilbert, *J. Amer. Chem. Soc.*, 1953, **75**, 3667.

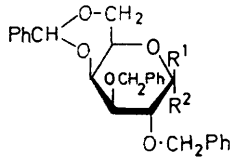
1,6-Anhydro-2,3-di-*O*-benzyl-β-D-galactopyranose (10) was condensed with 2,3,4-tri-*O*-benzyl-6-*O*-(but-2-enyl)-D-galactopyranosyl chloride (37)[23] under conditions which we have shown previously[6] to give predominantly 1,2-*cis*-glycosidic linkages. The crude disaccharide (38) was treated with potassium t-butoxide in dimethyl sulphoxide and the but-2-enyl group was removed[14] to give the crude alcohol (39), as a syrup which also gave a syrupy acetate and *p*-nitrobenzoate. Hydrogenolysis of the crude alcohol (39) gave the crude disaccharide (40), which was acetylated and acetolysed to give the crystalline 1,2,3,6-tetra-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)-α-D-galactopyranose (42), with properties similar to those reported.[2b] Compound (42) was prepared previously[2b] by a Koenigs–Knorr reaction, which gave a mixture of α- and β-linked disaccharides in the ratio 4 : 3.

1,6-Anhydro-sugars are relatively resistant to acidic hydrolysis and are usually opened by acetolysis.[24a] Paulsen and Stenzel[21] used this technique with the 1,6-anhydro-2-azido-2-deoxy-D-glucose derivatives and subsequently converted the products by way of the glucosyl bromides into the β-glucosyl chlorides, which were used in the glycosidation reactions. Acetyl chloride has been used for the conversion of acetals into chloro-ethers[25] and for the conversion of sugars into glycosyl chlorides,[24a,26] and we reasoned that the direct conversion of derivatives of 1,6-anhydro-β-D-galactopyranose into the corresponding 6-*O*-acetyl-galactosyl chlorides should be possible by this method. Although the anomeric composition of the chlorides prepared by this method would be uncertain, the methods which we have developed[6] for 1,2-*cis*-glycoside synthesis are satisfactory[6d] with mixtures of α- and β-glycosyl chlorides.

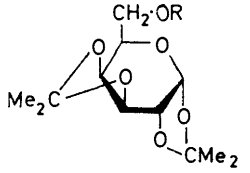
When 1,6-anhydro-2,3-di-*O*-benzyl-4-*O*-*p*-nitrobenzoyl-β-D-galactopyranose (12) was kept with an excess of 'recently distilled' acetyl chloride (*i.e.* distilled *ca.* 7 days before use) at 20 °C for 3 days, complete conversion into a less polar product and a more polar product was observed by t.l.c. When 'freshly distilled' acetyl chloride (*i.e.* distilled directly onto the compound in the receiving flask after rejecting a first fraction from the distillation) was used under the above conditions (or under reflux for 15 h) only a trace of reaction with compound (12) was observed. We rationalised these results as follows: the reaction is equivalent to acetolysis[24a,b] (and could be termed 'chloracetolysis') in that it requires the presence of a proton source to form the acetyl cation[24b] ($MeCO^+$, which is the attacking species) from the acetyl chloride. With 'freshly distilled' acetyl chloride, no hydrogen chloride was present and thus no reaction occurred. With the more aged sample both hydrogen chloride and acetic anhydride were present as contaminants. The presence of the hydrogen chloride allowed the 'chloracetolysis' to proceed, but the presence of the acetic anhydride also allowed a competing acetoly-

[25] J. Gigg and R. Gigg, *J. Chem. Soc.* (*C*), 1968, 16.
[26] L. J. Haynes and F. J. Newth, *Adv. Carbohydrate Chem.*, 1955, **10**, 215.

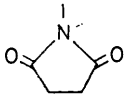
sis to occur. Thus a mixture of the less polar product [6-*O*-acetyl-2,3-di-*O*-benzyl-4-*O*-*p*-nitrobenzoyl-D-galactopyranosyl chloride (43)] from ' chloracetolysis ', and



(47) $R^1 = H$, $R^2 = OMe$
(48) $R^1 = OMe$, $R^2 = H$



(49) $R = CH_2 \cdot CH : CH_2$
(50) $R = CHBr \cdot CH : CH_2$
(51) $R = CH \cdot CH : CH_2$



(52) R = H
(53) $R = O_2S \cdot C_6H_4Me-p$

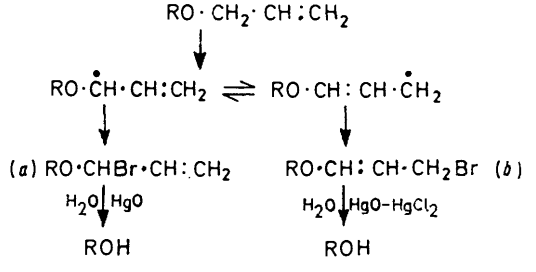
the more polar product [1,6-di-*O*-acetyl-2,3-di-*O*-benzyl-4-*O*-*p*-nitrobenzoyl-D-galactopyranose (44)] from acetolysis were formed in different proportions depending on the acetic anhydride content of the acetyl chloride. The optimum conditions then established for the ' chloracetolysis ' reaction were to use ' freshly distilled ' acetyl chloride with added hydrogen chloride (introduced either by direct addition or by addition of methanol). A room temperature reaction was also preferred since hydrogen chloride could be lost from the reaction mixture under reflux. These explanations support our previous empirical results obtained [25] during the preparation of aliphatic chloro-ethers.

Some related experiments with acetyl bromide (' acetobrominolysis ') [24a] have been reported in the carbohydrate field. The mechanism in some of the reported ' acetobrominolysis ' reactions [24c] must be uncertain since either mixtures of hydrogen bromide in acetic acid and acetyl bromide or mixtures of acetyl bromide and water were used. The ' acetobrominolysis ' reagent in these cases must have contained acetic anhydride (as well as acetyl bromide and hydrogen bromide) and this could lead to an acetolysis reaction with subsequent replacement of the 1-acetoxy-group by hydrogen bromide to give the glycosyl bromides which were observed. Other conditions for the ' chloracetolysis ' reaction, *e.g.* the use of acetylium perchlorate,[24b] are being investigated.

The crude galactosyl chloride (43) obtained by this procedure was treated with dry methanol and silver carbonate to give the methyl glycoside(s) (45) and these were hydrolysed by base to give methyl 2,3-di-*O*-benzyl-D-galactopyranoside(s) (46). Treatment of the diol(s) (46) with benzaldehyde dimethyl acetal gave the benzylidene derivative(s) (47) and (48), both of which have been characterised previously.[27] Trituration of our product with ethanol gave the crystalline methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-galactopyranoside (47), with properties similar to those reported.[27b]

Other methods for the removal of the allyl group have been reported. Kariyone and Yazawa [28] have investigated the oxidative cleavage of allyl ethers with selenium dioxide, and Corey and Suggs [29] have shown that allyl ethers can be isomerised to prop-1-enyl ethers by tristriphenylphosphinerhodium(I) chloride prior to acidic hydrolysis. Ho and Wong [30a] have treated allyl ethers with diethyl azodiformate to give an addition product which is an enol ether and is thus readily hydrolysed by acid or by mercury(II) chloride.[30b] We have considered the reaction of allyl ethers with *N*-bromosuccinimide as a possible alternative method for their cleavage under mild conditions.

Although reviews [31] on the reactions of *N*-bromosuccinimide have not indicated any previous experience with allyl ethers, free-radical bromination might be expected to occur as shown in the Scheme. If the bromo-ether (*a*) were formed it would be expected to be very labile in the presence of weak aqueous base to give the corresponding free alcohol. An alternative free radical bromination could lead to the brominated enol



SCHEME

ether (*b*), which could be hydrolysed with dilute acid [or mercury(II) chloride] to the alcohol. Thus both possible routes could lead to removal of the allyl group.

When 6-*O*-allyl-1,2 : 3,4-di-*O*-isopropylidene-α-D-galactopyranose (49) [32] was treated with *N*-bromosuccinimide in carbon tetrachloride under reflux, t.l.c. indicated conversion predominantly into a less polar product and a more polar product during 1.5 h. T.l.c. also showed

[27] (*a*) J. Schneider, Y.-C. Lee, and H. M. Flowers, *Carbohydrate Res.*, 1974, **36**, 159; (*b*) J. M. J. Fréchet and H. H. Baer, *Canad. J. Chem.*, 1975, **53**, 670.
[28] K. Kariyone and H. Yazawa, *Tetrahedron Letters*, 1970, 2885.
[29] E. J. Corey and J. W. Suggs, *J. Org. Chem.*, 1973, **38**, 3224.
[30] (*a*) T.-L. Ho and C. M. Wong, *Synth. Comm.*, 1974, **4**, 109; (*b*) E. J. Corey and J. W. Suggs, *Tetrahedron Letters*, 1975, 3775.
[31] C. Djerassi, *Chem. Rev.*, 1948, **43**, 271; L. Horner and E. H. Winkelmann, *Angew. Chem.*, 1959, **71**, 349; R. Filler, *Chem. Rev.*, 1963, **63**, 21; W. Foerst, *Newer Methods Prep. Org. Chem.*, 1964, **3**, 151.
[32] R. Gigg and C. D. Warren, *J. Chem. Soc.*, 1965, 2205.

that the polar product was not identical with 1,2 : 3,4-di-*O*-isopropylidene-α-D-galactopyranose (52) (although a small amount of this compound was present) and the potassium permanganate spray reagent indicated that both products were unsaturated. Chromatography of the crude product on alumina gave only a small fraction corresponding to the less polar material and two polar products were eluted from the column in approximately equal proportions (t.l.c.). One of these ran concurrently with compound (52) on t.l.c. and the other was the polar product observed in the reaction mixture before alumina chromatography. The i.r. spectrum of the mixed polar products showed the presence of an imide group.[33a] The reaction of *N*-bromo-imides with enol ethers has been shown [33] to result in the introduction of bromine and an imide group into the molecule, owing to an ionic rather than a radical mechanism.[33] Hydrolysis of the mixed polar fraction with aqueous base gave, as the only isolated product, 1,2 : 3,4-di-*O*-isopropylidene-α-D-galactopyranose (52), characterised as the crystalline toluene-*p*-sulphonate (53).[34]

We postulate that the bromo-derivative (50) is formed initially and that, in part, this alkylates the succinimide present to give the succinimido-derivative (51). On alumina chromatography the remainder of compound (50) is hydrolysed to the alcohol (52) and thus a mixture of compounds (51) and (52) is obtained as the major product. Alkaline hydrolysis of compound (51) would give a labile amino-ether, which would collapse to the alcohol (52), which was thus the only product. This reaction will be studied in more detail to find conditions where the bromo-ether (50) can be hydrolysed, in the reaction medium, directly to the alcohol (52).

EXPERIMENTAL

Solvents were evaporated off under reduced pressure. Optical rotations were measured at 22—24 °C with a Bendix automatic polarimeter. T.l.c. was carried out on microscope slides coated with silica gel G unless otherwise stated. The light petroleum used had b.p. 60—80 °C unless otherwise stated. Potassium t-butoxide was obtained from Courtorch Chemicals Ltd., Esgairgynddu, Carmarthenshire.

1,6-*Anhydro*-2-O-*benzyl*-β-D-*galactopyranose* (4).—Penta-*O*-acetyl-β-D-galactopyranose (Koch-Light) (100 g), toluene-*p*-sulphonic acid monohydrate (1.3 g), and phenol (95 g), in a 1 l flask attached to a rotatory evaporator were kept at 95 °C for 1.5 h under vacuum, while the acetic acid distilled off. The flask was cooled and dichloromethane (350 ml) was added, and the solution was washed with 0.5N-sodium hydroxide (1 700 ml) and with water and dried ($MgSO_4$). The solvent was evaporated off and the residue was recrystallised once from ethanol (300 ml) to give phenyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (77 g, 70%), m.p. 123—126°, $[\alpha]_D$ −19.8° (*c* 1 in benzene), $[\alpha]_D$ +9.2° (*c* 2 in $CHCl_3$) {lit.,[12a] m.p. 123—124°, $[\alpha]_D^{17}$ −26.4° (benzene), $[\alpha]_D^{20}$ −0.7° ($CHCl_3$); lit.,[12b] m.p. 124—125°, $[\alpha]_D^{25}$ +2° (*c* 1.75 in $CHCl_3$); lit.,[12c] m.p. 116—119°, $[\alpha]_D^{25}$ +16.2°; lit.,[12d] m.p. 122°, $[\alpha]_D^{20}$ +6.07° ($CHCl_3$)}. The optical rotation of this preparation indicated a small contamination with the α-anomer but it was used without further purification. Phenyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (70 g) and sodium hydroxide (107 g) in water (2 l) were heated under reflux for 11 h. The solution was cooled and 12N-hydrochloric acid (200 ml) was added slowly with stirring; 3N-hydrochloric acid was then added slowly in portions (to pH 3). The solution was evaporated to dryness and the residue was extracted with chloroform–methanol (1 : 1; 2 × 300 ml). The extract was filtered and evaporated and the residue (22 g) was treated with acetone (2 l) containing toluene-*p*-sulphonic acid (25 g). The mixture was stirred at 20 °C until t.l.c. (toluene–acetone, 1 : 1) showed complete conversion of the 1,6-anhydro-β-D-galactopyranose (R_F 0.1) into the isopropylidene derivative (1) (R_F 0.8) (*ca.* 4 h). An excess of sodium hydrogen carbonate was added and the solvent was evaporated off. The crude product (25 g) was extracted with chloroform and was treated with an excess of benzyl chloride and sodium hydride in dimethylformamide at 20 °C. T.l.c. (toluene–acetone, 3 : 1) showed complete conversion of the starting material (1) (R_F 0.6) into the benzyl ether (2) (R_F 0.9) after 2 h. Methanol was added to destroy the excess of sodium hydride, the solution was diluted with water, and the product (35 g) was extracted with ether. A portion was recrystallised from light petroleum to give 1,6-*anhydro*-2-O-*benzyl*-3,4-O-*isopropylidene*-β-D-*galactopyranose* (2), m.p. 83—85°, $[\alpha]_D$ −78.2° (*c* 1 in $CHCl_3$) (Found: C, 65.8; H, 6.9. $C_{16}H_{20}O_5$ requires C, 65.7; H, 6.9%). The crude product (30 g) was taken up in N-hydrochloric acid–methanol (1 : 9, 500 ml) and the solution was heated under reflux for 45 min; t.l.c. (as above) then showed complete conversion of the isopropylidene derivative (2) into the product (4) (R_F 0.4). An excess of sodium hydrogen carbonate was added and the solvents were evaporated off. The product (23 g) was extracted from the residue with chloroform and recrystallised from ethyl acetate–light petroleum to give 1,6-*anhydro*-2-O-*benzyl*-β-D-*galactopyranose* (4), m.p. 105—107°, $[\alpha]_D$ −37° (*c* 1 in $CHCl_3$) (Found: C, 62.2; H, 6.2. $C_{13}H_{16}O_5$ requires C, 61.9; H, 6.4%).

Phenyl 4,6-O-*Benzylidene*-2,3-*di*-O-(*but*-2-*enyl*)-β-D-*galactopyranoside* (10).—Phenyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (55 g) in dry methanol (450 ml) containing sodium methoxide (500 mg) was kept at 20 °C until t.l.c. (toluene–acetone, 1 : 2) showed complete conversion of the starting material (R_F 1) into phenyl β-D-galactopyranoside [R_F 0.25—by comparison with authentic material (Koch-Light)]. Water (1 ml) and solid carbon dioxide were added to the solution and the solvents were evaporated off. The last traces of water were removed by distillation of toluene and ethanol from the residue and the crude product was then converted into the benzylidene derivative (18) as described previously.[13] Sodium hydride (10 g) was added in portions to a solution of phenyl 4,6-*O*-benzylidene-β-D-galactopyranoside (18) (45 g) in dry dimethylformamide (200 ml) containing 'crotyl bromide' (40 ml) and the mixture was stirred at 20 °C until t.l.c. (toluene–acetone, 4 : 1) showed complete conversion of the starting material (R_F 0) into the product (R_F 0.8). Methanol was added to destroy the excess of sodium hydride, the solution was diluted with water, and the product (55 g) was extracted with ether. For analysis a portion of the crude product was recrystallised from methanol and from ethyl acetate–light petroleum to give *phenyl* 4,6-O-*benzylidene*-2,3-*di*-O-

[33] (*a*) K. Schank and W. Pack, *Chem. Ber.*, 1969, **102**, 1892; *b*) E. M. Gaydou, *Tetrahedron Letters*, 1972, 4055.

[34] A. B. Foster, W. G. Overend, M. Stacey, and L. F. Wiggins, *J. Chem. Soc.*, 1949, 2542.

(*but-2-enyl*)-β-D-*galactopyranoside* (19), m.p. 153—155°, $[\alpha]_D$ −3.0° (*c* 1 in $CHCl_3$) (Found: C, 71.7; H, 7.1. $C_{27}H_{32}O_6$ requires C, 71.7; H, 7.1%).

Phenyl 2,3-*di*-O-(*but-2-enyl*)-β-D-*galactopyranoside* (20).—Phenyl 4,6-*O*-benzylidene-2,3-di-*O*-(but-2-enyl)-β-D-galactopyranoside (19) (20 g) in N-hydrochloric acid–methanol (1 : 9, 500 ml) was heated under reflux for 20 min; t.l.c. (toluene–acetone, 4 : 1) then showed complete conversion of the starting material (R_F 0.8) into the product (R_F 0.3). The solution was cooled, an excess of sodium hydrogen carbonate was added, and the solvents were evaporated off. The product (16 g) was extracted from the residue with chloroform and the solution was dried (K_2CO_3) and evaporated. For analysis a portion was recrystallised from ether–light petroleum (b.p. 40—60°) to give *phenyl* 2,3-*di*-O-(*but-2-enyl*)-β-D-*galactopyranoside* (20), m.p. 85—87°, $[\alpha]_D$ −16.9° (*c* 1 in $CHCl_3$) (Found: C, 66.5; H, 8.0. $C_{20}H_{28}O_6$ requires C, 65.9; H, 7.7%).

Phenyl 4-O-*Allyl*-2,3-*di*-O-(*but-2-enyl*)-β-D-*galactopyranoside* (23).—Phenyl 2,3-di-*O*-(but-2-enyl)-β-D-galactopyranoside (20) (15 g) and triphenylmethyl chloride (15 g) in dry pyridine (100 ml) were kept at 50 °C for 3 h when t.l.c. (toluene–acetone, 4 : 1) showed complete conversion of compound (20) (R_F 0.3) into the trityl derivative (21) (R_F 0.85). Dry methanol was added to react with the excess of triphenylmethyl chloride and the product (and methyl triphenylmethyl ether) were isolated in the usual way and dissolved in dry dimethylformamide (100 ml) containing allyl bromide (5 ml). Sodium hydride (2 g) was added in portions at 20 °C, and after 1 h at 20 °C t.l.c. (toluene–acetone, 10 : 1) showed complete conversion of compound (21) (R_F 0.1) into the allyl ether (22) (R_F 0.85). The product was isolated in the usual way and treated with 0.1N-hydrogen chloride in methanol at reflux for 15 min; t.l.c. (as above) then showed complete conversion of compound (22) into the product (23) (R_F 0.3) and methyl triphenylmethyl ether. An excess of sodium hydrogen carbonate was added and the solvent was evaporated off. The products were extracted with ether and chromatographed on alumina. Elution with ether removed the methyl triphenylmethyl ether and elution with ether–methanol (49 : 1) gave *phenyl* 4-O-*allyl*-2,3-*di*-O-(*but-2-enyl*)-β-D-*galactopyranoside* (23), (14 g), m.p. 87—88° (from light petroleum), $[\alpha]_D$ −23.0° (*c* 1 in $CHCl_3$) (Found: C, 68.6; H, 8.0. $C_{23}H_{32}O_6$ requires C, 68.3; H, 8.0%)

1,6 : 2,3-*Dianhydro*-β-D-*talopyranose* (28).[16]—1,6-Anhydro-3,4-*O*-isopropylidene-β-D-galactopyranose (1) was converted into the methanesulphonate (3) as described previously.[16] A solution of the methanesulphonate (3) (19.7 g) in methanol (250 ml) and N-sulphuric acid (28 ml) was heated under reflux for 5 h; t.l.c. (toluene–acetone, 2 : 1) then showed almost complete conversion of compound (3) (R_F 0.7) into 1,6-anhydro-2-*O*-methylsulphonyl-β-D-galactopyranose (31) (R_F 0.25). Barium hydroxide (26 g) and methanol (100 ml) were added and the mixture was stirred at 20 °C for 1.5 h; t.l.c. (ether) then showed complete conversion of compound (31) (R_F 0.1) into the epoxide (28) (R_F 0.2). Solid carbon dioxide was added and the solvents were evaporated off. The product was extracted from the residue with acetone; evaporation of the extract gave 1,6 : 2,3-dianhydro-β-D-talopyranose (28) (8.5 g, 72%), m.p. 134—135° (from ether–acetone), $[\alpha]_D$ −85.3° (*c* 0.7 in H_2O) {lit.,[16b] m.p. 133—134°, $[\alpha]_D^{22}$ −88° (*c* 0.7 in H_2O)}.

1,6-*Anhydro*-2,3-*di*-O-*benzyl*-4-O-p-*nitrobenzoyl*-β-D-*galactopyranose* (12).—(*a*) 1,6-Anhydro-2-*O*-benzyl-β-D-galactopyranose (4) (2.5 g, 10 mmol), benzene (150 ml), allyl bromide (1.3 g, 11 mmol), and powdered sodium hydroxide (1 g) were stirred vigorously at 50 °C and the reaction was followered by t.l.c. (toluene–acetone, 3 : 1), which showed conversion of compound (4) (R_F 0.4) into the monoallyl ethers [(5) and (6)] (R_F 0.6) and the diallyl ether (R_F 0.8). After 30 h, water was added and the benzene layer was separated, dried (K_2CO_3), and evaporated. The crude product was chromatographed on alumina; elution with ether–methanol (199 : 1) gave the diallyl ether, and elution with ether–methanol (49 : 1) gave the monoallyl ethers [(5) and (6)] (700 mg, 24%). The monoallyl ethers were treated with an excess of sodium hydride and benzyl chloride in dimethylformamide at 20 °C until t.l.c. (as above) showed complete conversion of the starting materials (R_F 0.6) into the products [(7) and (8)] (R_F 0.9). The products were isolated in the usual way and treated with potassium t-butoxide in dimethyl sulphoxide at 50 °C until t.l.c. (toluene–acetone, 4 : 1) showed complete conversion of the allyl ethers [(7) and (8)] (R_F 0.75) into the prop-1-enyl ethers (R_F 0.8) (*ca.* 15 min). The prop-1-enyl ethers were isolated in the usual way and treated with N-hydrochloric acid–acetone (1 : 9; 50 ml) at reflux for 15 min; t.l.c. (as above) then showed complete conversion of the prop-1-enyl ethers into the alcohols (10) and (11) (R_F 0.45). An excess of sodium hydrogen carbonate was added and the solvents were evaporated off. The products were extracted from the residue with ether, the solution was dried (K_2CO_3) and evaporated, and the residue was treated with an excess of *p*-nitrobenzoyl chloride in dry pyridine at 20 °C for 4 h. An equal volume of dichloromethane was added, followed by water, and the mixture was stirred at 20 °C for 30 min to decompose the anhydride of *p*-nitrobenzoic acid. The *p*-nitrobenzoates were isolated in the usual way and t.l.c. [ether–light petroleum (b.p. 40—60°) (1 : 1) on precoated silica gel plates (Merck No. 5737)] showed the presence of the isomeric *p*-nitrobenzoates (12) (R_F 0.5) and (13) (R_F 0.6), with compound (12) predominant. Crystallisation of the mixed isomers from methanol gave the p-*nitrobenzoate* (12) [0.3 g, 6% from compound (4)], m.p. 111—113°, $[\alpha]_D$ −19.3° (*c* 1 in $CHCl_3$) (Found: C, 65.9; H, 5.4; N, 2.8; $C_{27}H_{25}NO_8$ requires C, 66.0; H, 5.1; N, 2.85%).

(*b*) Phenyl 4-*O*-allyl-2,3-di-*O*-(but-2-enyl)-β-D-galactopyranoside (23) (1 g) and potassium t-butoxide (2 g) in dry dimethyl sulphoxide (20 ml) were kept at 50 °C for 6 h. T.l.c. (toluene–acetone, 1 : 1) (which was carried out by treating a portion of the reaction mixture with water and solid carbon dioxide and then evaporating to dryness and extracting the products with chloroform) showed a rapid conversion of compound (23) (R_F 1) into phenyl 4-*O*-(prop-1-enyl)-β-D-galactopyranoside (25) (R_F 0.5), which was then slowly converted into the 1,6-anhydro-derivative (26) (R_F 0.6) together with by-products (R_F 0.75 and 0.8) and other trace products. The solution was cooled to 20 °C, benzyl chloride (2 ml) was added, and the mixture was kept at 50 °C for 2 h. Water was added and the products were extracted with ether. T.l.c. (toluene–acetone, 10 : 1) then showed a major product (9) (R_F 0.7) and by-products (R_F 0.85). The crude product was treated with mercury(II) oxide (500 mg) and mercury(II) chloride (500 mg)[8b] in acetone–water (9 : 1, 25 ml) at 20 °C for 15 min; t.l.c. (as above) then showed conversion of the major product into the alcohol (10) (R_F 0.3), which was isolated in the usual way[8b] and chromatographed on alumina. Elution with ether removed impurities; elution with ether–methanol (49 : 1) gave the crude product (10) as a syrup (800 mg),

which was converted into the *p*-nitrobenzoate (12) as in (*a*). Recrystallisation from methanol (20 ml) gave compound (12) (420 mg, 34%), identical with the material described in (*a*).

(*c*) 1,6 : 2,3-Dianhydro-β-D-talopyranose (28) (8.8 g) was treated with an excess of sodium hydride and allyl bromide in dimethylformamide at 20 °C. T.l.c. (ether–ethyl acetate, 19 : 1) showed complete conversion of compound (28) (R_F 0.25) into the allyl ether (29) (R_F 0.85) after 1 h. The product was isolated in the usual way and treated with dioxan (100 ml) and 3N-sodium hydroxide (200 ml) at reflux for 18 h; t.l.c. (as above) then showed complete conversion of compound (29) into 4-*O*-allyl-1,6-anhydro-β-D-galactopyranose (27) (R_F 0.2). Solid carbon dioxide was added and the solvents were evaporated off. The residue was extracted with chloroform–methanol (1 : 1), the solvents were evaporated off, and the crude product was treated with an excess of sodium hydride and benzyl chloride in dimethylformamide at 20 °C for 3 h; t.l.c. (as above) then showed complete conversion of the diol (27) into the benzyl ether (7) (R_F 0.9). The product (15.7 g, 80%) was isolated in the usual way and treated with potassium t-butoxide in dry dimethyl sulphoxide [8] at 50 °C until t.l.c. [ether–light petroleum (b.p. 40—60°), 1 : 1] showed complete conversion of the allyl ether (7) (R_F 0.6) into the prop-1-enyl ether (9) (R_F 0.75). The product was isolated and hydrolysed with acid in the usual way [8a] to give the crude alcohol (10) (14 g) (R_F 0.2, as above), which was chromatographed on alumina. Elution with ether removed contaminants and elution with ether–methanol (19 : 1) gave the alcohol (10) (10.3 g, 73%) which was converted into the *p*-nitrobenzoate. Recrystallisation from methanol gave compound (12) (12 g), identical with the material described above.

(*d*) 1,6-Anhydro-2-*O*-benzyl-β-D-galactopyranose (4) (1.05 g, 4 mmol) and triphenylmethyl chloride (2 g, 7.2 mmol) in dry pyridine (25 ml) were heated under reflux for 10 h. T.l.c. (toluene–acetone, 2 : 1) then showed the presence of a trace of compound (4) (R_F 0.25), a major tritylated product (R_F 0.8), and a trace of another tritylated product (R_F 0.95). Methanol was added to react with the excess of triphenylmethyl chloride and the products were isolated in the usual way and chromatographed on alumina. Elution with ether removed by-products; elution with ether–methanol (19 : 1) gave the crude 1,6-anhydro-2-*O*-benzyl-4-*O*-trityl-β-D-galactopyranose (15) (1 g, 50%). The crude product was treated with an excess of sodium hydride and benzyl chloride in dimethylformamide at 50 °C for 18 h when t.l.c. [ether–light petroleum (b.p. 40—60°) (1 : 2) on precoated silica gel plates (Merck No. 5737)] showed complete conversion of the crude alcohol (15) (R_F 0.25) into the crude dibenzyl ether (16) (R_F 0.6). The product was isolated in the usual way and treated with N-hydrochloric acid–acetone (1 : 9; 50 ml) at reflux for 6 h; t.l.c. (as above) then showed complete conversion of the trityl derivative (16) into the crude alcohol (10) (R_F 0.2). An excess of sodium hydrogen carbonate was added, the solvents were evaporated off, and the product was extracted with ether and chromatographed on alumina. Elution with ether removed triphenylmethanol; elution with ether–methanol (49 : 1) then gave the crude alcohol (10) (320 mg, 52%), which was converted into the *p*-nitrobenzoate as described above. T.l.c. [ether–light petroleum (b.p. 40—60°) (1 : 1) on precoated silica gel plates (Merck No. 5737)] showed the presence of the *p*-nitrobenzo (12) (R_F 0.5) (*ca.* 98%) and the isomeric *p*-nitrobenzoate (13) (R_F 0.6) (*ca.* 2%), indicating the high regioselectivity in the tritylation. The crude *p*-nitrobenzoate was recrystallised from methanol to give compound (12) (210 mg), identical with the material described above.

4-O-*Methyl*-D-*galactose*.—The *p*-nitrobenzoate (12) (270 mg) and sodium hydroxide (1 g) were stirred in methanol (25 ml) at 20 °C for 3 h; t.l.c. (toluene–acetone, 4 : 1) then showed complete conversion of compound (12) (R_F 0.8) into the alcohol (10) (R_F 0.5). Solid carbon dioxide was added, the solution was evaporated to dryness, and the product was extracted with ether and treated with an excess of methyl iodide and sodium hydride in benzene at reflux for 2 h. T.l.c. (as above) then showed complete conversion of compound (10) into the methyl ether (14) (R_F 0.6). The product (195 mg) was isolated in the usual way and treated with hydrogen over palladium–charcoal in glacial acetic acid at atmospheric pressure for 15 h. T.l.c. (toluene–acetone, 1 : 1) then showed a major product (R_F 0.3). The product (95 mg) was isolated in the usual way and treated with 2N-sulphuric acid at reflux for 5 h; t.l.c. (as above) then showed complete conversion of the starting meterial (R_F 0.3) into a product (R_F 0). An excess of barium carbonate was added and the solution was stirred until neutral, filtered, and evaporated to dryness. The product (100 mg) was crystallised from methanol (5 ml) to give 4-*O*-methyl-D-galactose (40 mg), m.p. and mixed m.p. (with material prepared previously [6a]) 210—215° (decomp.).

3-O-*Allyl*-1,6-*anhydro*-2-O-*benzyl*-4-O-*trityl*-β-D-*galactopyranose* (17).—Crude 1,6-anhydro-2-*O*-benzyl-4-*O*-trityl-β-D-galactopyranose (15) (900 mg) was treated with an excess of allyl bromide and sodium hydride in benzene at reflux for 8 h; t.l.c. (toluene–acetone, 10 : 1) then showed complete conversion of the alcohol (15) (R_F 0.65) into the allyl ether (17) (R_F 0.8), which was isolated in the usual way and recrystallised from ether–light petroleum (b.p. 40—60°) and from methanol to give the *allyl ether* (17) (540 mg, 55%), m.p. 178—180°, $[\alpha]_D$ −60.1° (*c* 1 in $CHCl_3$) (Found: C, 78.1; H, 6.5. $C_{35}H_{34}O_5$ requires C, 78.6; H, 6.4%). Compound (17) (460 mg) in N-hydrochloric acid–acetone (1 : 9; 50 ml) was heated under reflux for 6 h; t.l.c. (as above) then showed complete conversion of compound (17) (R_F 0.8) into the alcohol (6) (R_F 0.4). An excess of sodium hydrogen carbonate was added, the solvents were evaporated off, and the products were extracted with ether and chromatographed on alumina. Elution with ether removed triphenylmethanol; elution with ether–methanol (49 : 1) gave 3-*O*-allyl-1,6-anhydro-2-*O*-benzyl-β-D-galactopyranose (6) as a syrup. This was benzylated and the allyl group was removed as described above for compound (5) to give 1,6-anhydro-2,4-di-*O*-benzyl-β-D-galactopyranose (11) as a syrup. This was converted into the *p*-nitrobenzoate (13), also obtained as a syrup. T.l.c. [ether–light petroleum (b.p. 40—60°) (1 : 1) on precoated silica gel plates (Merck No. 5737)] against standards of the mixed *p*-nitrobenzoates (12) and (13), prepared by method (*a*) above, showed the presence of the isomer (13) (R_F 0.6) only.

1,6-*Anhydro*-2-*azido*-4-O-*benzyl*-2-*deoxy*-3-O-p-*nitrobenzoyl*-β-D-*galactopyranose* (33).—1,6 : 2,3-Dianhydro-β-D-talopyranose (28) (10 g) and benzyl chloride (20 g) in dimethylformamide (200 ml) were kept at 20 °C, sodium hydride (4 g) was added in portions, and the solution was stirred at 20 °C for 2 h. T.l.c. (toluene–acetone, 2 : 1) then showed complete conversion of compound (28) (R_F 0.25) into the benzyl ether (30) (R_F 0.75). The solution was diluted with ether (200 ml) and methanol was added slowly to decompose the excess of sodium hydride. Water (500 ml) was added and the ether layer was separated, washed with saturated

potassium chloride solution, dried (K_2CO_3), and evaporated. The excess of benzyl chloride was removed at 90 °C and 5 mmHg on the rotatory evaporator to give the crude 1,6 : 2,3-dianhydro-4-*O*-benzyl-β-D-talopyranose (30) (18 g) as a syrup. This was taken up in dimethyl sulphoxide (500 ml), sodium azide (52 g) and ammonium chloride (32 g) were added, and the mixture was kept at 100 °C for 70 h. T.l.c. (toluene–acetone, 10 : 1) then showed almost complete conversion of compound (30) (R_F 0.5) into a major product (*ca.* 95%) (R_F 0.4) and a minor product (R_F 0.3). Water (1 l) was added and the products were extracted with ether. The solution was dried (K_2CO_3) and evaporated to give a syrup (19.5 g), which was converted into *p*-nitrobenzoates in the usual way. The product was recrystallised from methanol (500 ml) to give the *azide* (33) (19.5 g, 65%), m.p. 115—117°, $[\alpha]_D$ +4.2° (*c* 1 in $CHCl_3$) (Found: C, 56.6; H, 4.5; N, 13.0. $C_{20}H_{18}N_4O_7$ requires C, 56.3; H, 4.3; N, 13.1%).

2-*Acetamido*-3,4-*di*-O-*acetyl*-1,6-*anhydro*-2-*deoxy*-β-D-*galactopyranose* (36).[16a]—The *p*-nitrobenzoate (33) (1 g) and sodium hydroxide (500 mg) in methanol (25 ml) were stirred at 20 °C for 10 h. Solid carbon dioxide was added and the solution was evaporated to dryness. Water was added and the azide (32) (650 mg) was extracted with ether. The solution was dried (K_2CO_3) and evaporated and the product was treated with an excess of lithium aluminium hydride in tetrahydrofuran at reflux during 5 h. T.l.c. (toluene–acetone, 10 : 1) then showed complete conversion of the azide (32) (R_F 0.4) into the corresponding amine (R_F 0). Ethyl acetate was added slowly to the cooled solution to decompose the excess of hydride, then water was added slowly, the solvent was evaporated off, and the product was extracted with chloroform. The solution was dried (K_2CO_3) and evaporated and the crude product was taken up in methanol (50 ml). Acetic anhydride (3 ml) was added with stirring, and after 1 h t.l.c. (ethyl acetate) showed complete conversion of the amine (R_F 0.05) into the acetamido-derivative (34) (R_F 0.4). The solvent was evaporated off and the crude acetamido-derivative (34) was obtained as a syrup, which was treated with hydrogen over palladium–charcoal in methanol at atmospheric pressure until no more hydrogen was absorbed. Filtration and evaporation left crude 2-acetamido-1,6-anhydro-2-deoxy-β-D-galactopyranose (35), a portion of which was recrystallised from ether–methanol to give the pure acetamido-derivative (35), m.p. 205°, $[\alpha]_D$ −5.8° (*c* 1 in MeOH) {lit.,[16b] m.p. 209—210°, $[\alpha]_D^{25}$ −5° (*c* 1 in MeOH)}. The remainder of compound (35) was treated with acetic anhydride in pyridine to give the acetate (36), m.p. 213–215° (from ethanol), $[\alpha]_D$ −76.5° (*c* 0.5 in H_2O); $[\alpha]_D$ −41.1° (*c* 0.5 in $CHCl_3$) {lit.,[16a] m.p. 207°, $[\alpha]_D$ −73.5° (*c* 0.74 in H_2O), $[\alpha]_D^{22}$ −36° (*c* 0.55 in $CHCl_3$)}.

1,2,3,6-*Tetra*-O-*acetyl*-4-O-(2,3,4,6-*tetra*-O-*acetyl*-α-D-*galactopyranosyl*)-α-D-*galactopyranose* (42).[2b]—A mixture of 2,3,4-tri-*O*-benzyl-6-*O*-(but-2-enyl)-D-galactopyranosyl chloride (37)[23] (2.7 g, 5.2 mmol), 1,6-anhydro-2,3-di-*O*-benzyl-β-D-galactopyranose (10) (1 g, 2.9 mmol), dry tetraethylammonium chloride (0.86 g, 5.2 mmol), triethylamine (0.75 ml, 5.4 mmol), and dry dichloroethane (15 ml) was heated under reflux for 19 h. T.l.c. [ether–light petroleum (b.p. 40—60°), 1 : 2] then showed two major products (R_F 0.3 and 0.65), some alcohol (10) (R_F 0.15) and chloride (37) (R_F 0.8), and trace products (R_F 0.35 and 0.6). The product R_F 0.65 ran concurrently with 2,3,4-tri-*O*-benzyl-6-*O*-(but-2-enyl)-1-deoxy-D-*lyxo*-hex-1-enopyranose,[6e] and the product of R_F 0.3 was presumed to be the crude disaccharide (38). Water (0.5 ml) was added and the solution was heated under reflux for 1 h. Chloroform (20 ml) was added, the solution was washed with water and dried (K_2CO_3), and the product (3.8 g) was chromatographed on alumina. Elution with ether–light petroleum (b.p. 40—60°) (2 : 1) gave first a mixture of the two major products (R_F 0.3 and 0.65) (1.7 g) and then the crude disaccharide (38) (R_F 0.3) (0.6 g). The mixed products were chromatographed on silica gel; elution with toluene–ether (24 : 1) gave a mixed fraction (0.5 g) and the crude disaccharide (38) (R_F 0.3) (1 g). The crude disaccharide (38) (1 g) was treated with an excess of potassium t-butoxide in dimethyl sulphoxide [14] at 20 °C for 3 h; t.l.c. [ether–light petroleum (b.p. 40—60°), (2 : 1)] then showed complete conversion of the starting material (R_F 0.7) into the crude alcohol (39) (R_F 0.4). The product (900 mg) was isolated in the usual way and obtained as a syrup. A solution of the crude alcohol (39) (340 mg) in glacial acetic acid (10 ml) was treated with hydrogen over 10% palladium–charcoal at 20 °C for 19 h. The solution was filtered through Celite and evaporated to give the crude disaccharide (40) (190 mg), which was treated with acetic anhydride in pyridine to give the crude acetate (41) (263 mg) as a syrup. T.l.c. (ethyl acetate–benzene, 5 : 3) [2b] showed a major product (R_F 0.8) together with trace products (R_F 0.7 and 0.85). A mixture of acetic anhydride (7 ml), acetic acid (3 ml), and concentrated sulphuric acid (0.2 ml) was cooled to 0 °C and added to the acetate (41), and the solution was kept at 20 °C for 20 min. It was then poured into a solution of sodium hydrogen carbonate (1.25 g) in water (100 ml) at 0 °C, and the mixture was stirred for 20 min and extracted with chloroform (3 × 50 ml). The extract was washed with saturated potassium chloride solution, dried ($MgSO_4$), and evaporated. Toluene was evaporated from the residue to remove acetic acid, and the crude acetate (42) (324 mg) was obtained as a syrup which on t.l.c. (ether–benzene, 3 : 1) [2b] showed a major product (R_F 0.45) with trace products (R_F 0.4, 0.6, 0.65, and 0.75). The α- and β-linked disaccharides are separated in this solvent system [2b] and the presence of a single major product indicated a high degree of stereoselectivity in the glycosidation reaction. The product was dissolved in ethanol (10 ml) and the acetate (42) (150 mg) crystallised; m.p. 155—157°, $[\alpha]_D$ +133° (*c* 1 in $CHCl_3$) {lit.,[2b] m.p. 153—154°, $[\alpha]_D$ +138° (*c* 2 in $CHCl_3$)}.

Action of Acetyl Chloride and Hydrogen Chloride on 1,6-*Anhydro*-2,3-*di*-O-*benzyl*-4-O-p-*nitrobenzoyl*-β-D-*galactopyranose* (12).—After rejection of a first fraction from a distillation of acetyl chloride, a receiving flask containing compound (12) (1 g) was attached to the distillation apparatus and acetyl chloride (*ca.* 25 ml) was collected on the compound. A jet of hydrogen chloride from a cylinder was directed into the flask for 1 s, and the flask was then stoppered and kept at 20 °C. T.l.c. [ether–light petroleum (b.p. 40—60°) (1 : 1) on precoated silica gel plates (Merck No. 5737)] after 24 h showed the presence of compound (12) (R_F 0.6) and the chloride (43) (R_F 0.7) (*ca.* 1 : 1) together with a small amount of the presumed acetate (44) (R_F 0.5), and a trace of the free sugar (R_F 0.2) resulting from the hydrolysis of the chloride (43) on the plate.[6c] After 70 h at 20 °C, t.l.c. showed complete conversion of compound (12) into the chloride (43) (*ca.* 90%) and the acetate (44) and traces of other products. Dry benzene (25 ml) was added, the solvents were evaporated off, and a further quantity of dry benzene (25 ml) was added and evaporated off. Dry methanol (25 ml) and silver carbonate (10 g) were added to the residue and the mixture

was stirred at 20 °C for 3 h. T.l.c. (as above) then showed complete conversion of the chloride (43) into the methyl glycoside(s) (45) (R_F 0.5). The silver salts were filtered off and sodium hydroxide (4 g) was added to the solution, which was then heated under reflux for 30 min; t.l.c. [toluene–acetone, 2 : 1 on precoated silica gel plates (Merck No. 5737)] showed complete conversion of the esters (45) into the diol(s) (46) (R_F 0.5). Water (20 ml) was added, the methanol was evaporated off, and the product was extracted from the aqueous layer with ether. The solution was dried (K_2CO_3) and evaporated and benzene was evaporated from the residue (720 mg). The residue was dissolved in benzaldehyde dimethyl acetal (10 ml), toluene-*p*-sulphonic acid (5 mg) was added, and the solution was kept at 20 °C for 2 h. T.l.c. [ether–light petroleum (b.p. 40—60°) (2 : 1) on precoated silica gel plates (Merck No. 5737)] showed complete conversion of the diol(s) (46) into the benzylidene derivative(s) (47) and (48) (R_F 0.6 and 0.65). An excess of saturated sodium hydrogen carbonate solution was added and the solvents were evaporated off. The product was extracted with chloroform and crystallised from ethanol to give methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-galactopyranoside (47) (250 mg), m.p. 173—175°, $[\alpha]_D$ +73.4° (*c* 2 in $CHCl_3$) (R_F 0.65) {lit.,[27b] m.p. 176—177°, $[\alpha]_D$ +77° (*c* 2.4 in $CHCl_3$)}.

Action of N-*Bromosuccinimide on* 6-O-*Allyl*-1,2 : 3,4-*di*-O-*isopropylidene*-α-D-*galactopyranose* (49).—A mixture of 6-*O*-allyl-1,2 : 3,4-di-*O*-isopropylidene-α-D-galactopyranose (49) (2 g, 6.7 mmol) and *N*-bromosuccinimide (2 g, 11.2 mmol) in carbon tetrachloride (40 ml) was heated under reflux and the reaction was followed by t.l.c. [ether–light petroleum (b.p. 40—60°), 1 : 1], which showed conversion of compound (49) (R_F 0.8) into two major products (R_F 0.1 and 0.9, both of which gave an immediate positive reaction with the potassium permanganate spray reagent) with a trace of a product (R_F 0.25) which ran concurrently with 1,2 : 3,4-di-*O*-isopropylidene-α-D-galactopyranose (52). After 1.5 h, only a trace of compound (49) remained and the solution was cooled and saturated sodium hydrogen carbonate solution (10 ml) was added. Chloroform (50 ml) was added and the organic layer was separated, dried (K_2CO_3), and evaporated to give the crude product (3.4 g) which was chromatographed on basic alumina. Elution with ether gave non-polar products (R_F 0.8 and 0.9) (450 mg), and elution with ether–methanol (49 : 1) gave the polar products (R_F 0.1 and 0.25; 1.6 g; *ca.* 1 : 1). The i.r. spectrum of the polar products showed absorptions at 1 715 and 1 780 cm^{-1} characteristic of an imide group.[33a] The mixture of polar products (420 mg) in ethanol–water (1 : 1, 25 ml) containing sodium hydroxide (2 g) was heated under reflux for 5.5 h. Solid carbon dioxide was added, the solution was evaporated to dryness, and the residue was extracted with chloroform. The product (340 mg; R_F 0.25, as above) was treated with toluene-*p*-sulphonyl chloride (1 g) in dry pyridine (20 ml) at 20 °C for 5 h; the solution was then diluted with water and the crystalline 1,2 : 3,4-di-*O*-isopropylidene-6-*O*-tosyl-α-D-galactopyranose (53) (380 mg) was filtered off; m.p. 92—93°, $[\alpha]_D$ −63.1° (*c* 1 in $CHCl_3$) {lit.,[34] m.p. 89—91°, $[\alpha]_D$ −63.4° ($CHCl_3$)}.

We thank Mr. R. Conant for technical assistance.

[5/2459 *Received*, 17*th December*, 1975]