Concerning the Problem of Stereospecific Glycosylation. Synthesis and Methanolysis of some 2-*O*-Benzylated D-Galactopyranosyl and D-Galactofuranosyl Halides[1]

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Received October 7, 1974

JEAN M. J. FRÉCHET and HANS H. BAER. Can. J. Chem. **53**, 670 (1975).

Acetolysis of 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-galactopyranose (**3**) followed by de-*O*-acetylation and *p*-nitrobenzoylation gave 2,3,4-tri-*O*-benzyl-1,6-di-*O*-*p*-nitrobenzoyl-β-D-galactopyranose (**4**) which was converted into 2,3,4-tri-*O*-benzyl-6-*O*-*p*-nitrobenzoyl-α-D-galactopyranosyl bromide (**5**). Benzylation of methyl 4,6-*O*-benzylidene-α-D-galactopyranoside (**6**) gave the 2,3-dibenzyl ether (**7**) which was hydrolyzed to 2,3-di-*O*-benzyl-D-galactose (**8**). *p*-Nitrobenzoylation of **8** furnished 2,3-di-*O*-benzyl-1,5,6-tri-*O*-*p*-nitrobenzoyl-β-D-galactofuranose (**9**) and an isomer, presumably a β-pyranose derivative (**10**). Compound **9** was converted into 2,3-di-*O*-benzyl-5,6-di-*O*-*p*-nitrobenzoyl-β-D-galactofuranosyl bromide (**11**) and chloride (**12**). The new halides **5**, **11**, and **12** as well as known 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl bromide (**1**) and chloride (**2**) were subjected to methanolysis in dichloromethane solution in the presence of methanol alone and in the presence of tetrabutylammonium bromide, mercuric cyanide, and silver tetrafluoroborate, respectively, and the ratios of anomeric glycosides produced were examined by n.m.r. spectroscopy. Factors influencing stereoselectivity in these reactions are discussed. The new methyl α- and β-glycosides derived from **5** (**13** and **14**) and the methyl α-glycoside (**15**) produced from **11** and **12** were isolated, and methyl 2,3,5,6-tetra-*O*-benzyl-α-D-galactofuranoside (**16**) was prepared for the first time.

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Par acétolyse du 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-galactopyranose (**3**) suivie de désacétylation et de *p*-nitrobenzoylation, on a obtenu le 2,3,4-tri-*O*-benzyl-1,6-di-*O*-*p*-nitrobenzoyl-β-D-galactopyranose (**4**) qui est converti en bromure de 2,3,4-tri-*O*-benzyl-6-*O*-*p*-nitrobenzoyl-α-D-galactopyranosyle (**5**). La benzylation du méthyl 4,6-*O*-benzylidène-α-D-galactopyranoside (**6**) a donné l'éther 2,3-dibenzylique (**7**) qui, par hydrolyse, a produit le 2,3-di-*O*-benzyl-D-galactose (**8**). Par *p*-nitrobenzoylation de **8**, on a obtenu le 2,3-di-*O*-benzyl-1,5,6-tri-*O*-*p*-nitrobenzoyl-β-D-galactofuranose (**9**) et un isomère, sans doute le dérivé pyranosique (**10**). Le composé **9** a été transformé en bromure (**11**) et en chlorure (**12**) de 2,3-di-*O*-benzyl-5,6-di-*O*-*p*-nitrobenzoyl-β-D-galactofuranosyle. Ces nouveaux halogénures **5**, **11** et **12**, ainsi que le bromure de 2,3,4,6-tétra-*O*-benzyl-α-D-galactopyranosyle (**1**) et le chlorure correspondant (**2**) qui étaient déja connus, ont été soumis à des réactions de méthanolyse en solution dans le dichlorométhane en présence de méthanol seul, et en présence de bromure d'ammonium tétrabutylé, de cyanure de mercure et de tétrafluoroborate d'argent respectivement. Les quantités de glycosides anomères formées ont été analysées par spectroscopie de r.m.n. Les facteurs qui influencent la stéreosélectivité de ces réactions sont examinés. Les nouveaux méthyl α- et β-glycosides dérivés de **5** (**13** et **14**) et le méthyl α-glycoside (**15**) produit à partir de **11** et **12** ont été isolés; le méthyl 2,3,5,6-tétra-*O*-benzyl-α-D-galactofuranoside (**16**) a été préparé pour la première fois.

Introduction

As groundwork for a long-range project in glycoside and oligosaccharide synthesis we have commenced with the preparation of some new sugar derivatives which, it is hoped, may serve as suitable building stones in syntheses of certain compounds having biological significance, and we have undertaken some studies pertaining to the general problem of stereospecificity in glycoside formation. The present article deals with derivatives of D-galactose. This sugar occurs widely in nature in both α- and β-glycosidic linkage; it is one of the prominent structural units of such important natural products as, for example, gangliosides and other glycolipids, blood group determinants and related glycopeptides, human milk oligosaccharides, immunospecific bacterial polysaccharides, and a great variety of plant hemicelluloses, gums, and mucilages.

The methods most widely used and endowed

[1]Presented in part before the 166th National Meeting of the American Chemical Society, Chicago, Illinois, August, 1973.

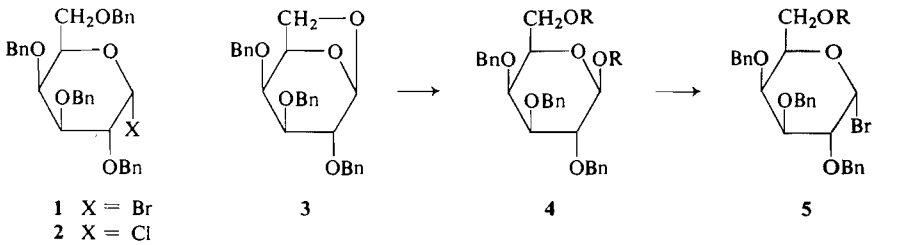
with broad generality for the synthesis of both simple glycosides and more complex oligosaccharides were, at least until recently, the classical Koenigs–Knorr condensation and its newer variants in which a blocked glycosyl halide is condensed with an alcoholic component. However, control of the anomeric configuration in the glycoside thus generated has long been a major problem and is remaining a current concern despite recent progress (1). Whereas the readily available per-*O*-acylated bromides and chlorides of galactose and other sugars having the same C-2 configuration (*e.g.*, glucose and xylose) normally give β-glycosides (1,2-*trans*) with a high degree of stereospecificity, the controlled synthesis of α-glycosides (1,2-*cis*) of these particular sugars is a far more complicated proposition and continues to draw much attention. With the notable exception of the novel, highly promising α-glycoside synthesis of Lemieux and co-workers (2) which in the key step involves addition of alcohol to an intermediate 2-nitrosoglycal, most approaches were aimed at influencing the stereochemical course of nucleophilic substitution at the anomeric center in glycosyl halides. Success in varying measure was achieved over the years by modifying the reaction conditions (such as solvent and choice of acid acceptor) in Koenigs–Knorr type reactions and by employing glycosyl halides that bear a nonparticipating group at C-2, frequently the benzyloxy function (1, 3). Of particular relevancy in this connection was the discovery by Lemieux and co-workers (4), that stable α-glycosyl halides anomerize by halide ion catalysis to give their more highly reactive β-anomers, albeit in low concentration, a phenomenon which can be utilized in α-glycoside synthesis (5–7). It was found, furthermore, that certain specific groups present in positions other than C-2 may influence reaction rates and have a directive effect which can be enlisted for making 1,2-*cis* glycosides (5, 8–14), and such glycosides have also been obtained from reactive glycosyl derivatives possessing an electropositive leaving group (15). Nevertheless, the scope of some of these approaches is still uncertain and a lack of predictability exists. For example, in our syntheses of several stereoisomeric disaccharides by mercuric cyanide-promoted condensation of per-*O*-benzyl-α-D-glucopyranosyl bromide, the type of linkage produced was found to depend strikingly upon the molecular configuration of the alcoholic monosaccharide component, a factor which apparently has received little attention hitherto (16). In extending their work (14, 17) on the stereoselective methanolysis of D-glucopyranosyl sulfonates, Schuerch and co-workers observed unexpected differences when analogous D-galactose derivatives were used (18).

In order to augment special knowledge in glycoside-forming reactions in the D-galactose series, we have now synthesized three new halides in addition to the previously-described 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl bromide (**1**) (16) and the corresponding chloride **2** (19), namely, 2,3,4-tri-*O*-benzyl-6-*O*-*p*-nitrobenzoyl-β-D-galactopyranosyl bromide (**5**), 2,3-di-*O*-benzyl-5,6-di-*O*-*p*-nitrobenzyl-β-D-galactofuranosyl bromide (**11**), and 2,3-di-*O*-benzyl-5,6-di-*O*-*p*-nitrobenzoyl-β-D-galactofuranosyl chloride (**12**). With these five compounds we then made a comparative study of the steric course of glycoside formation with methanol under a variety of conditions.

Synthesis of Glycosyl Halides

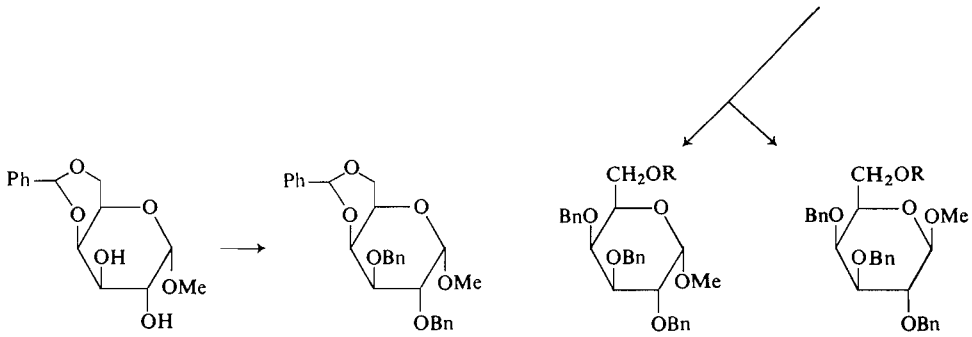
The synthesis of the 6-*p*-nitrobenzoate **5** departed from 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-galactopyranose (**3**) which, by acetolysis and subsequent de-*O*-acetylation and *p*-nitrobenzoylation of the product, was converted into 2,3,4-tri-*O*-benzyl-1,6-di-*O*-*p*-nitrobenzoyl-β-D-galactopyranose (**4**). The bromide **5** was then obtained from **4** by application of the elegant method, first recommended by Fletcher and co-workers (refs. 5 and 20; for further examples see refs. 11–14 and 16) which consists of a facile, quantitative displacement of the C-1 acyloxy function by means of anhydrous hydrogen bromide in dichloromethane solution. Although it seems plausible enough that a β-ester reacts with inversion to yield the stable α-bromide, we shall return to this point for further comment at the end of this section.

The blocked β-D-galactofuranosyl halides **11** and **12** were obtained as follows. Methyl 4,6-*O*-benzylidene-α-D-galactopyranoside (**6**) was benzylated to furnish its crystalline 2,3-dibenzyl ether (**7**). Acid hydrolysis of **7** gave 2,3-di-*O*-benzyl-D-galactose (**8**). This free sugar crystallized in a weakly dextrorotatory form ($[\alpha]_D$ +5.3° in chloroform) but the anomeric configuration and the ring structure of the crystalline material were not established, nor was it possible to assess the proportions of tautomeric forms present in solution. However, **8** must to a high degree exist in, or be especially prone to reaction through, a

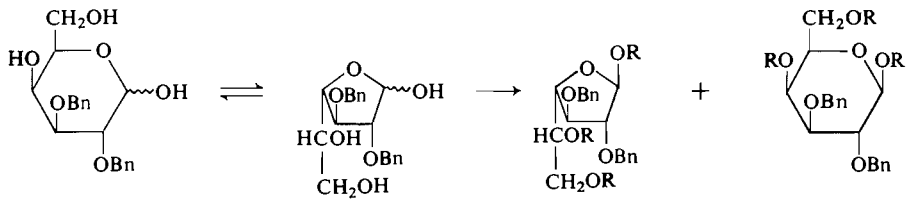


1 X = Br
2 X = Cl

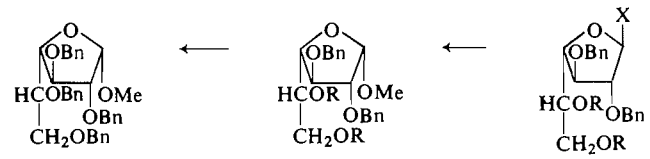
3 **4** **5**



6 **7** **13** **14**



8 **9** **10**



16 **15** **11** X = Br
12 X = Cl

Bn = $PhCH_2^-$; R = p-$NO_2C_6H_4CO^-$

furanose form as *p*-nitrobenzoylation afforded two isomeric triesters, each in 40% yield,[2] of which one showing $[\alpha]_D$ −5.5° was revealed to be 2,3-di-*O*-benzyl-1,5,6-tri-*O*-*p*-nitrobenzoyl-β-D-galactofuranose (**9**) (for proof see later). The other isomer also showed low levorotation ($[\alpha]_D$ −9.1°) and was on this basis tentatively judged to be the corresponding β-pyranose 1,4,6-tri-*p*-nitrobenzoate (**10**). It is known that acylation of galactose tends to give mixtures containing substantial amounts of furanose besides pyranose derivatives (21). Treatment of **9** with anhydrous hydrogen bromide and chloride, respectively, produced the substituted β-D-galactofuranosyl halides **11** and **12** as amorphous solids which exhibited strong levorotation but did not mutarotate. As is also the case with alkyl β-D-galactofuranosides (22), these β-halides are expected to be the thermodynamically more stable anomers because they are free from the unfavorable, 1,2-*cis* substituent interaction which exists in the α-anomers; therefore α-halides, if initially formed from **9**, would be liable to rapid anomerization during the reaction. The triester presumed to have structure **10** gave a dextrorotatory bromo sugar, but further examination of this product was postponed.[3]

We now wish to comment upon the isolation of compound **5**, a stable α-pyranosyl bromide, as the sole reaction product obtained from the β-ester **4**. Neither an n.m.r. spectrum nor the optical rotation, both taken prior to work-up as soon as the precipitation of *p*-nitrobenzoic acid was complete, gave any indication for transitory presence of the (expectedly labile) β-bromide. Similarly, 2,3,4,6-tetra-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-β-D-galactopyranose had given (16) a stable α-bromide exclusively. In the absence of a participating group at C-2, such displacement with simple inversion leading directly to the stable halide would normally be no surprise. However, our findings stand in contrast to results of Ishikawa and Fletcher (5) who obtained crystalline β-bromides from the β-D-*gluco* isomer of **4** and from the corresponding 1,4,6-tri-*p*-nitrobenzoate. These and two other β-bromides (that arose, less surprisingly, from α-esters) all anomerized to their more stable α-anomers but seemed to differ in their tendencies to do so. Thus, the β-D-*gluco* isomer of **5** had a half-life of more than 2 h in dry dichloromethane solution, and stability in the series appeared to increase with the number of *p*-nitrobenzoyl groups present, a phenomenon which the authors (5) ascribed to a long-range effect of that functionality.[4] It might be argued that our β-D-galactopyranose esters may have formed intermediary β-bromides which went undetected owing to very fast anomerization.[5] However, this would still leave open the question by what mechanism labile bromides could arise, with retention of configuration. It has been speculated (5) that probably the steric requirement of the bulky bromide ion in its approach to the glucosyl carbonium ion is involved. An alternative possibility, namely participation by the 2-benzyloxy group, has been regarded both as unlikely (5) and as likely (6). Neither hypothesis readily accounts for the fact that Fréchet and Schuerch (11) obtained only α-bromides when they applied the same method to several 1,6-di-*O*-acyl-2,3,4-tri-*O*-benzyl-β-D-glucopyranosides wherein acyl was benzoyl and *p*-methoxy-, *p*-methyl-, *p*-cyano-, 3,5-dinitro-, and 2,4-dinitrobenzoyl.

Solvolysis of Glycosyl Halides

The halides **1**, **2**, **5**, **11**, and **12** were allowed to react with a 70–90 molar excess of methanol in dichloromethane solution at room temperature unless otherwise stated. The conditions were varied as follows: *A*, without any further addition; *B*, with addition of 4 mol-equiv. of tetrabutylammonium bromide; *C*, with addition of 1 mol-equiv. of mercuric cyanide; *D*, with addition of 1 mol-equiv. of silver tetrafluoroborate at −78°. Reactions according to *A* and *B* were followed polarimetrically and plots of optical rotation *vs.* time yielded first-order rate constants from the expression

[2]In addition, a di-*p*-nitrobenzoate resulting from incomplete acylation was isolated in 10% yield.

[3]Preliminary experiments of methanolysis led to mixtures of glycosides which were difficult to analyze and did not promise easy interpretation.

[4]Glaudemans and Fletcher suggested earlier (8) that the strongly electron-withdrawing character of the *p*-nitrobenzoyloxy group renders C-5 electron deficient so that destabilization of an incipient glucosyl carboxonium ion results in strengthening of the C-1—halogen bond. By the same token, β-D-glucopyranosyl halides are stabilized when a strongly electronegative substituent is present at C-2 (3*a*).

[5]In reactions implicating glycosyl carbonium ion intermediates, D-galactopyranose derivatives are generally more reactive than their D-*gluco* isomers. For example, the rates of acid hydrolysis of the pairs of methyl α- and β-pyranosides differ by factors of 5 and 4, respectively (3*b*). Larger factors could possibly apply to halide anomerizations.

TABLE 1. Methanolysis of 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl bromide (**1**) and chloride (**2**)

Halide	Salt added	$t_{1/2}$ (min)	k (ln, s^{-1})	Ratio of methyl glycosides formed (α:β)
1	—	15	7.6×10^{-4}	35:65
1	*n*-Bu_4NBr	3.25	3.8×10^{-3}	75:25
1	$Hg(CN)_2$			2:98
1	$AgBF_4$ (−78°)			3:97
2	—	240	4.8×10^{-5}	37:63
2	$AgBF_4$ (−78°)			5:95

$$k = (1/t) \ln [(\alpha_0 - \alpha_\infty)/(\alpha_t - \alpha_\infty)]$$

Upon completion of the methanolyses, the anomeric composition of the mixture of methyl glycosides formed was determined by measuring the intensity ratio of the methoxyl proton peaks in n.m.r. spectra (11). In those cases where methoxyl peaks were superimposed on a background due to ring protons, adjustment was made by subtraction of the background intensity as obtained from the spectrum of a separate run that was performed with methanol-d_4.

The results obtained with the perbenzylated halides **1** and **2** are shown in Table 1. In line with expectations the bromide **1** was methanolyzed more rapidly than the chloride **2**. The preponderant product formed in both cases in the absence of an additive was the β-glycoside, which is due to direct displacement with inversion in the bulk of reactant. Halide ion liberated during the reaction catalyzes (4) a continuous anomerization of unreacted α-glycosyl halide to its more highly reactive β-anomer which is constantly and rapidly consumed by methanol, also with inversion. This accounts for the considerable proportion of α-glycoside produced. Increasing the halide ion concentration at the outset by addition of tetrabutylammonium bromide promotes anomerization of the glycosyl halide (4), and consequently the α-glycoside becomes the predominant product. The observed enhancement in the rate of methanolysis is consistent with this view. Thus far, the results parallel those obtained (5) with the D-*gluco* isomer of **1** and support the mechanistic picture which has evolved for this type of reaction (4–6, 11, 14, 23). It is important to note, though, that **1** solvolyzed more rapidly than its D-*gluco* isomer; with methanol alone, the rate was twice as large, and addition of bromide ion caused a fivefold increase in **1** and only a twofold increase in the isomer.[5]

The solvolyses performed in the presence of mercuric cyanide or silver tetrafluoroborate almost exclusively gave the β-glycoside. They proceeded extremely fast so that rates could not conveniently be measured. It is reasonable to assume that the rate increase is due to a 'push-pull' mechanism, a concerted process in which the halogen atom is attracted by the metal while the nucleophile attacks C-1 from the back (14, 24). The abstracted halide ion is bound by the metal and therefore unable to cause anomerization in any temporarily surviving glycosyl halide. The minor proportion of α-glycoside that arises nevertheless may perhaps originate from methanol attack on 'free' glycosyl carbonium ion, an event which could occur when from time to time a halide ion is abstracted without the benefit of simultaneous nucleophilic push.

The observations made on the 6-*O*-*p*-nitrobenzoylglycosyl bromide **5** (Table 2) were quite analogous although the ester group present at C-6 evidently caused the methanolyses with and without added tetrabutylammonium bromide to be slower than those of **1**. One experiment was conducted without additive at low temperature (−20°), with the result that the ratio of α-glycoside (**13**) to β-glycoside (**14**) was shifted slightly in favor of the latter, suggesting that temperature dependence of anomerization is somewhat greater than that of solvolysis. The reactions promoted by metal salts again exhibited a high degree of stereoselectivity, giving nearly exclusively the β-glycoside (**14**). Compounds **13** and **14**, which were previously unknown, were isolated in crystalline condition from runs containing tetrabutylammonium bromide and mercuric cyanide, respectively.

Comparison of Tables 1 and 2 shows that replacement of the 6-*O*-benzyl group by the *p*-nitrobenzoate function had a negligible influence upon the steric outcome of all the reactions here inves-

TABLE 2. Methanolysis of 2,3,4-tri-*O*-benzyl-6-*O*-*p*-nitrobenzoyl-α-D-galactopyranosyl bromide (**5**)

Salt added	$t_{1/2}$ (min)	k (ln, s^{-1})	Ratio of methyl glycosides formed (α:β)
—	42.5	2.4×10^{-4}	31:69
— (−20°)			24:76
n-Bu_4NBr	14	8.2×10^{-4}	70:30
$Hg(CN)_2$			3:97
$AgBF_4$			5:95

tigated. As far as the methanolyses with and without added bromide ion are concerned, this contrasts sharply with the behavior of the corresponding D-*gluco* derivatives where remarkable shifts in the anomeric product ratio were observed as the nature of the C-6 substituent was varied. Thus, the D-*gluco* isomer of **5** gave 90–96% α-glucoside (5, 11) whereas the corresponding 6-*p*-methoxybenzoate gave 93% β-glucoside (11); other C-6 substituents led to intermediate α/β ratios (11). In related studies, Schuerch and coworkers noted similar, wide ranges of stereoselectivity in diversely 6-substituted D-glucopyranosyl derivatives but at the same time, they observed directive effects of solvent (14, 17). In the D-*galacto* series, on the other hand, selectivity was greatly reduced and certain solvent effects were opposite (18). The results obtained in the D-*gluco* series have been rationalized in terms of a sensitive balance between two competing, key reactions whose rates are of similar order of magnitude but variable depending on the medium and the structure of the substrate; namely, the methanolysis of α-halide to give β-glycoside, and the anomerization of α-halide to form β-halide which subsequently reacts very rapidly to yield α-glycoside (14, 17).[6] Elaborating on this concept (4–6) with regard to the *galacto* series we suggest that both processes are affected, but not necessarily in equal manner, by inductive variation in the electron density at C-5, which should influence the stability and character of intermediary C-1 carbonium ion or ion-pair (*cf.* footnote 4), and also by the dipolar effect of axial O-4. The latter, probably, supplements the anomeric effect in opposing equatorial placement of electronegative groups at C-1, with halogen atoms being opposed more strongly than the methoxyl group. Thus α → β halide anomerization may be retarded and consequently, high proportions of α-pyranosides are less readily obtained in the *galacto* series than in the *gluco* series.

The results of methanolyses of the β-furanosyl halides **11** and **12** are given in Table 3. It is seen that the reactions both with methanol alone and with added tetrabutylammonium bromide were completely stereospecific as far as could be judged from n.m.r. spectra, the product being the methyl α-furanoside **15**. Evidently the methanolysis proceeds with inversion as in the preceding cases, but there is no prior anomerization in part of the glycosyl halide, not even in the presence of excess bromide ion which has no influence on the product composition and merely causes a slight increase in the reaction rate (probably a kinetic salt effect). Compared with its pyranoid counterparts **1** and **4**, the furanoid bromide **11** was considerably more reactive. The pair of chlorides **2** and **12** exhibited the same trend but their rate difference was relatively small. Two opposing factors appear to operate, namely, the generally recognized greater reactivity of furanosyl halides originating from conformational features, and inductive stabilization by the *p*-nitrobenzoyl groups (8). The first factor seems more important in the bromides, and the second factor, in the chlorides. Absence of halide anomerization in both **11** and **12** can be explained by assuming that, in generating the sterically unfavorable furanoid 1,2-*cis* arrangement, halide ions are at a serious disadvantage in competition with methanol molecules. An additional factor could possibly arise from hydrogen bonding of the ether oxygen atom at C-2 with the incoming methanol, assisting in its approach from the α-side of the ring, whereas a halogen ion on the same path would find no such assistance.

Also characterized by complete stereospecificity were the metal salt-assisted reactions of **12**, whereas selectivity was slightly lower in those of **11** (Table 3).

[6]Nonbonded interaction between the C-6 acyl carbonyl group and the anomeric center, as proposed earlier (11), does not satisfactorily explain the more recent findings.

TABLE 3. Methanolysis of 2,3-di-*O*-benzyl-5,6-di-*O*-*p*-nitrobenzoyl-β-D-galactofuranosyl bromide (**11**) and chloride (**12**)

Halide	Salt added	$t_{1/2}$ (min)	k (ln, s^{-1})	Ratio of methyl glycosides formed (α:β)
11	—	2.8	4.2×10^{-3}	100:0
11	n-Bu_4NBr	1.8	6.3×10^{-3}	100:0
11	$Hg(CN)_2$			96:4
11	$AgBF_4$ (−78°)			95:5
12	—	145	6.2×10^{-5}	100:0
12	n-Bu_4NBr			100:0
12	$Hg(CN)_2$			100:0
12	$AgBF_4$ (−78°)			100:0

The methyl α-furanoside **15** was isolated in crystalline condition. Proof of structure was provided by its treatment with benzyl chloride and potassium hydroxide which replaced the *p*-nitrobenzoyl groups by benzyl groups to give methyl 2,3,5,6-tetra-*O*-benzyl-α-D-galactofuranoside (**16**). The n.m.r. spectrum of this new compound was superimposable on that of an identical product obtained by benzylation of authentic methyl α-D-galactofuranoside but differed clearly from the spectra of perbenzylated methyl β-D-galactofuranoside and methyl α- and β-D-galactopyranosides.

Experimental

Optical rotations were measured at approximately 25° in a Perkin-Elmer 141 automatic polarimeter. The n.m.r. data were obtained with a Varian HA 100 instrument using tetramethylsilane as internal standard.

Preparation of Fully Benzylated Methyl D-*Galactosides*

Samples of the fully benzylated methyl α- and -β-D-galactopyranosides and -furanosides were required as standards for identification of methanolysis products. They were prepared as follows.

Glycosidation of D-*Galactose*

D-Galactose was converted into a mixture of methyl glycosides and the (known) products were separated chromatographically by use of the procedure of Baddiley and co-workers (25), with minor modifications. A suspension of the sugar (5 g) in absolute methanol (40 ml) containing 0.4 ml sulfuric acid was refluxed for 2 h. The cooled solution was neutralized with calcium carbonate, filtered, and evaporated to give a syrup which, with a small amount of added water, was placed on a column containing approximately 200 g of anion exchange resin AG1-X2 (OH^-) of Bio-Rad Laboratories, Richmond, Calif. Elution was performed with carbon dioxide-free, distilled water and monitored by polarimetry of all fractions (8 ml). It yielded methyl α-D-galactopyranoside (fractions 16–20, 1.2 g), methyl β-D-galactopyranoside (fractions 24–32, ~0.1 g), methyl α-D-galactofuranoside (fractions 36–53, 0.66 g), and methyl β-D-galactofuranoside (fractions 85–180, 2.17 g). Intermediate, mixed fractions were discarded.

*Methyl 2,3,4,6-Tetra-O-benzyl-α- and -β-*D-*galactopyranosides*

Methyl α- and β-D-galactopyranoside, respectively, were benzylated with benzyl chloride and potassium hydroxide as described (19), or by use of the method (26) detailed in the next paragraph. The OCH_3 signal of the benzylated α-pyranoside was at δ 3.35, and that of the β-pyranoside at δ 3.51 (in $CDCl_3$).

*Methyl 2,3,5,6-Tetra-O-benzyl-α-*D-*galactofuranoside (16) and its β-Anomer*

To a solution of sodium hydride (0.55 g; oil dispersion, 55% pure) in dimethyl sulfoxide (3 ml) was added dropwise a solution of methyl α-D-galactofuranoside (0.45 g) in dimethyl sulfoxide (3 ml). The mixture was stirred for 30 min, after which benzyl chloride (3 ml) was added dropwise and stirring was continued for another 2.5 h. The reaction mixture was then poured into ice water (50 ml) which was extracted three times with chloroform. The dried ($MgSO_4$) extract was evaporated at 2 mm Hg, leaving an oil which was passed through a small column of silica gel (20 g) by means of benzene–ether (99:1). Compound **16** was obtained as a colorless oil (965 mg, 75%) showing $[\alpha]_D$ +20° (*c* 2, $CHCl_3$). The OCH_3 signal occurred at δ 3.29 (in $CDCl_3$).

Anal. Calcd. for $C_{35}H_{38}O_6$ (554.7): C, 75.79; H, 6.91. Found: C, 75.54; H, 7.01.

The same procedure applied to methyl β-D-galactofuranoside furnished the β-anomer of **16**, $[\alpha]_D$ −49° (*c* 2, $CHCl_3$), as reported (26). Its OCH_3 signal occurred at δ 3.33, and its pattern of ring proton signals was distinctively different from that of **16**.

*2,3,4,6-Tetra-O-benzyl-α-*D-*galactopyranosyl Bromide (1) and Chloride (2)*

Preparation of the bromide **1** via the corresponding 1-*p*-nitrobenzoate has been described (16). The chloride **2** was obtained in analogous fashion (11, 14, 20). Dry hydrogen chloride gas was passed through a solution of the 1-*p*-nitrobenzoate (1 g of crystalline β-anomer) in dry dichloromethane (50 ml), with exclusion of moisture and at room temperature. After 20 min, *p*-nitrobenzoic acid began to precipitate, the gas stream was stopped, and the tightly stoppered vessel was placed in a refrigerator for 3 days. The mixture was then filtered to remove *p*-nitrobenzoic acid (239 mg, 97%) and the filtrate was evaporated *in vacuo* at room temperature. Several portions of added dichloromethane were evaporated from the remaining, faintly yellow syrup of **2** which showed $[\alpha]_D$ +146.5°

(*c* 1.6, benzene). Reported (19) for **2** obtained from 2,3,4,6-tetra-*O*-benzyl-D-galactose and thionyl chloride, $[\alpha]_D$ +147° (*c* 2, benzene). The n.m.r. spectrum of **2** showed a doublet for H-1 at δ 6.14 ($J_{1,2}$ = 3.5 Hz).

2,3,4-Tri-O-benzyl-1,6-di-O-p-nitrobenzoyl-β-D-galactopyranose (4)

A solution of 10.3 g of 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-galactopyranose (**3**) (27) in warm acetic anhydride (100 ml) was cooled in an ice water bath and mixed with a chilled solution of concentrated sulfuric acid (0.1 ml) in acetic anhydride (5 ml). After 3 min the mixture was poured into, and stirred with, ice water (600 ml) whereby the product of acetolysis separated as an oil. After 45 min the aqueous phase was decanted and replaced by fresh water (600 ml) which was removed after 24 h. The oily product was then dissolved in chloroform and washed with 5% sodium bicarbonate solution and water. After drying, the solvent was evaporated and the nearly colorless product (12 g) was deacetylated overnight, at room temperature, in methanol containing a small amount of sodium methoxide. The methanol was evaporated after neutralization with acetic acid and the product was dissolved in pyridine (100 ml) and allowed to react overnight at 25° with *p*-nitrobenzoyl chloride (15 g). The reaction mixture was treated with ice water and the precipitated product was taken up in chloroform. The solution was washed successively with water, sodium bicarbonate solution and water, then dried and evaporated to give a residue which was crystallized from ethyl acetate – petroleum ether (b.p. 30–60°). The yield was 8.2 g (49%) of **4**, m.p. 152–153°, $[\alpha]_D$ −6.6° (*c* 2, $CHCl_3$). The n.m.r. spectrum showed a doublet at δ 5.94 (H-1, $J_{1,2}$ = 7.5 Hz) indicative of the β-anomeric configuration.

Anal. Calcd. for $C_{41}H_{36}N_2O_{12}$ (748.9): C, 65.77; H, 4.85; N, 3.74. Found: C, 65.62; H, 4.85; N, 3.78.

2,3,4-Tri-O-benzyl-6-O-p-nitrobenzoyl-α-D-galactopyranosyl Bromide (5)

Compound **4** (1 g) was dissolved in dry dichloromethane (25 ml) saturated with hydrogen bromide gas, at room temperature. After 2 min, *p*-nitrobenzoic acid started to precipitate, and after 10 min it was collected by filtration (214 mg, 96%). The filtrate was evaporated to yield a nearly colorless heavy oil from which several portions of added dichloromethane were evaporated *in vacuo*. The product could not be crystallized. It had $[\alpha]_D$ +100° (*c* 2.6, CH_2Cl_2), and its n.m.r. spectrum showed a doublet at δ 6.53 (H-1, $J_{1,2}$ = 1.4 Hz).

Methyl 2,3-Di-O-benzyl-4,6-O-benzylidene-α-D-galactopyranoside (7)

A mixture of 11 g of methyl 4,6-*O*-benzylidene-α-D-galactopyranoside (**6**) (28), powdered potassium hydroxide (20 g), and benzyl chloride (120 ml) was stirred at 105° for 6 h. After cooling, the mixture was shaken with water (150 ml) and chloroform (150 ml). The organic phase was separated, washed with water, and dried over magnesium sulfate. Chloroform was evaporated and remnant benzyl chloride was removed partially by evaporation at 2 mm Hg and finally by steam distillation. The product **7** was then crystallized from ethanol as white plates, m.p. 174–175°, in a yield of 13.8 g (76%). Recrystallization from petroleum ether gave long needles; m.p. 176–177°, $[\alpha]_D$ +77° (*c* 2.4, $CHCl_3$).

Anal. Calcd. for $C_{28}H_{30}O_6$ (462.6): C, 72.71; H, 6.54. Found: C, 72.81; H, 6.63.

2,3-Di-O-benzyl-D-galactose (8)

A solution of 7 (12.5 g) in dioxane (300 ml) and 2 *N* sulfuric acid (90 ml) was refluxed for 3 days. The cooled solution was neutralized with barium carbonate, filtered, and evaporated to give a syrup which was extracted with petroleum ether for removal of benzaldehyde. The remaining material was chromatographed in a column of silica gel (250 g). Elution with benzene–ether (97:3) produced, first, several fractions containing incompletely hydrolyzed material (3.6 g), then a noncrystallizable oil (0.4 g) having $[\alpha]_D$ +43°, and finally, compound **8** (4.1 g, 42%) which crystallized from ether and showed m.p. 74–76°, $[\alpha]_D$ +5.3° (*c* 2, $CHCl_3$).

Anal. Calcd. for $C_{20}H_{24}O_6$ (360.4): C, 66.65; H, 6.71. Found: C, 66.50; H, 6.68.

2,3-Di-O-benzyl-1,5,6-tri-O-p-nitrobenzoyl-β-D-galactofuranose (9) and Isomer (10)

To compound **8** (3.95 g) in dry pyridine (40 ml) was added *p*-nitrobenzoyl chloride (8 g) at 0°. The reaction mixture was then stirred overnight at ambient temperature and processed with ice water (600 ml) in the usual manner. The solid product was washed thoroughly with water and then briefly with ice cold, 0.6 *N* hydrochloric acid. It was dissolved in dichloromethane, the solution was washed repeatedly with sodium bicarbonate solution and then with water, and after drying ($MgSO_4$) the solvent was removed again. The residue upon drying in high vacuum weighed 8.69 g, and t.l.c. revealed that it contained three products besides a small amount of *p*-nitrobenzoic acid. The crude material was passed through a column of silica gel (270 g) by means of benzene–ether (98:2). The fastest-moving component (**9**) was obtained as an amorphous powder (3.5 g, 40%) exhibiting $[\alpha]_D$ −5.5° (*c* 2, $CHCl_3$). It could not be crystallized but was homogeneous in t.l.c. (benzene–ether 7:1).

Anal. Calcd. for $C_{41}H_{33}N_3O_{15}$ (807.7): C, 60.97; H, 4.12; N, 5.20. Found: C, 61.02; H, 4.20 N, 5.19.

The second compound eluted from the column was also an amorphous, chromatographically homogeneous powder (3.5 g, 40%). It showed $[\alpha]_D$ −9.1° (*c* 2.5, $CHCl_3$) and was tentatively assumed to be 2,3-di-*O*-benzyl-1,4,6-tri-*O*-*p*-nitrobenzoyl-β-D-galactopyranose (**10**).

Anal. Calcd. for $C_{41}H_{33}N_3O_{15}$ (807.7): C, 60.97; H, 4.12; N, 5.20. Found: C, 60.80; H, 4.21; N, 5.27.

Finally, after a mixed fraction which was discarded, the most slowly moving component was eluted (952 mg); $[\alpha]_D$ −2° (*c* 1.5, $CHCl_3$). According to n.m.r. and i.r. spectra it contained a hydroxyl group and only two *p*-nitrobenzoyl groups.

2,3-Di-O-benzyl-5,6-di-O-p-nitrobenzoyl-β-D-galactofuranosyl Bromide (11)

Compound **9** (680 mg) was treated with anhydrous hydrogen bromide in dichloromethane as described above for the preparation of **5**. The *p*-nitrobenzoic acid collected weighed 133 mg (95%). The bromide **11** was obtained as a slightly colored, amorphous solid, $[\alpha]_D$ −59.4° (*c* 1.2, CH_2Cl_2).

Anal. Calcd. for $C_{34}H_{29}BrN_2O_{11}$ (721.5): C, 56.60; H, 4.05; Br, 11.08; N, 3.88. Found: C, 56.42; H, 4.17; Br, 10.87; N, 4.12.

2,3-Di-O-benzyl-5,6-di-O-p-nitrobenzoyl-β-D-galactofuranosyl Chloride (12)

Compound **9** (1.364 g) dissolved in a minimum amount of dichloromethane was added at room temperature to a saturated solution of anhydrous hydrogen chloride in dichloromethane (50 ml). Hydrogen chloride was passed through the solution continuously for 3 h and the closed vessel was then left standing for 36 h, after which t.l.c. indicated the reaction to be complete. By partial evaporation, the major part of *p*-nitrobenzoic acid precipitated (226 mg, 80%). The filtrate therefrom was rapidly washed with an ice cold sodium bicarbonate solution and with water. The dried ($MgSO_4$) solution was then treated with activated charcoal, filtered through Celite, and evaporated to furnish **12** (1.036 g, 90.6%) as an almost colorless solid; $[\alpha]_D$ −31.4° (*c* 2.3, CH_2Cl_2).

Methyl 2,3,4-Tri-O-benzyl-6-O-p-nitrobenzoyl-α-D-galactopyranoside (13)

The product obtained upon work-up of a methanolysis of **5** in the presence of tetrabutylammonium bromide (see a subsequent section) was crystallized from ethyl acetate – petroleum ether and recrystallized from anhydrous ether. It had m.p. 115–117° and $[\alpha]_D$ −3.5° (*c* 2, $CHCl_3$). The OCH_3 signal was at δ 3.34.

Anal. Calcd. for $C_{35}H_{35}NO_9$ (613.6): C, 68.50; H, 5.75; N, 2.28. Found: C, 68.62; H, 5.94; N, 2.36.

Methyl 2,3,4-Tri-O-benzyl-6-O-p-nitrobenzoyl-β-D-galactopyranoside (14)

The product obtained upon work-up of a methanolysis of **5** in the presence of mercuric cyanide was crystallized from ether and recrystallized from ethyl acetate – petroleum ether. It had m.p. 135–137° and $[\alpha]_D$ −33.5° (*c* 2.5, $CHCl_3$). The OCH_3 signal was at δ 3.53.

Anal. Calcd. for $C_{35}H_{35}NO_9$ (613.6): C, 68.50; H, 5.75; N, 2.28. Found: C, 68.61; H, 5.78; N, 2.47.

Methyl 2,3-Di-O-benzyl-5,6-di-O-p-nitrobenzoyl-α-D-galactofuranoside (15)

The product obtained by methanolysis of **11** in the presence of tetrabutylammonium bromide (see a subsequent section) was **15**. Recrystallized from ethyl acetate – petroleum ether it showed m.p. 116–118°, $[\alpha]_D$ +55.7° (*c* 2, $CHCl_3$).

Anal. Calcd. for $C_{35}H_{32}N_2O_{12}$ (672.6): C, 62.50; H, 4.80; N, 4.16. Found: C, 62.43; H, 4.72; N, 4.34.

A sample of **15** (350 mg) was treated with benzyl chloride (12 ml) and powdered potassium hydroxide (1 g) at 105° for 5 h. The reaction mixture was partitioned between chloroform and water. The dried chloroform phase was evaporated, eventually at 2 mm Hg to remove excess benzyl chloride. The oily residue was purified by passage through a silica gel column (30 g) with benzene containing 0.5% ether. There was obtained 167 mg (58%) of **16** whose n.m.r. spectrum was identical in every detail with that of **16** obtained from methyl α-D-galactofuranoside.

Methanolyses

(A) With Methanol Alone

A sample of glycosyl halide (approximately 100 mg, 0.14–0.18 mmol) was accurately weighed in a 5-ml volumetric flask and dissolved in dry dichloromethane (4.4 ml). Methanol (0.50 ml, 12.7 mmol) was added, and the volume was made up to 5 ml with dichloromethane. The change in optical rotation with time was recorded, a 1-dm tube being used. The first recording was usually made after 1 min. When the rotation had become constant, the solution was diluted with dichloromethane, washed once with aqueous sodium bicarbonate and once with water, dried over magnesium sulfate, and evaporated with eventual addition of several portions of carbon tetrachloride. The ratio of anomeric glycosides in the residue was then determined by integration of the OCH_3 signals of the n.m.r. spectrum in $CDCl_3$, at 250 Hz sweep width.

(B) In the Presence of Tetrabutylammonium Bromide

The procedure was the same as in *A* except that 200 mg of $(n\text{-}C_4H_9)_4NBr$ was added immediately prior to the addition of methanol and that, in work-up, two sodium bicarbonate and three water washings were included.

(C) In the Presence of Mercuric Cyanide

The procedure was the same as in *A* exeept that 40 mg (0.16 mmol) of $Hg(CN)_2$ was added prior to the addition of methanol. The reactions were too fast for polarimetric rate determination, and the runs were processed after one to several hours as convenient.

(D) In the Presence of Silver Tetrafluoroborate

In a typical experiment, a solution of glycosyl halide (160 mg) in dichloromethane (10 ml) was cooled to −78°, and approximately 95 mg of $AgBF_4$ was quickly introduced. (The reagent is very hygroscopic; rapid handling is more important than accurate weighing.) The mixture was first stirred in the dark for 10 min, methanol (0.5 ml) was then added, and stirring was continued for 1 h. The reaction mixture was filtered through Celite and then processed as in *A*.

Financial support of this work by the National Research Council of Canada is gratefully acknowledged. Miss Geneviève Pellé is thanked for technical assistance.

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