Halide Ion Catalyzed Glycosidation Reactions. Syntheses of α-Linked Disaccharides[1]

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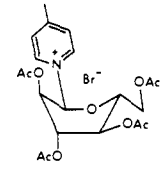
Abstract: Eight α-linked disaccharides were synthesized in good yield and in a highly stereoselective manner by reaction of per-*O*-benzyl-α-glycopyranosyl bromides of the D-gluco, D-galacto, and L-galacto (L-fuco) configurations with suitably protected derivatives of D-glucose and D-galactose in the presence of tetraethylammonium bromide. The main characteristics of the halide ion catalyzed reaction were established by studies of the reactions of tetra-*O*-benzyl-α-D-glucopyranosyl chloride and bromide with simple alcohols. The reaction is considered to proceed by way of the β-glycosyl halide which is brought into rapid equilibrium with the more stable α anomer by way of ion-pair intermediates. The more rapid route provided by the β-glycosyl halide is attributed to the stereoelectronic requirement of an antiparallel orientation of a ring-oxygen lone pair of electrons in both bond breaking and bond making at the anomeric center.

The so-called halide ion catalyzed glycosidation reaction was first announced in 1968.[4] We now report details regarding the characteristics of the reaction and its application to the synthesis of certain α-D-gluco-, α-D-galacto-, and α-L-fucopyranosides. The method complements the so-called oximinochloride method developed in this laboratory.[5,6] This paper and related manuscripts in this issue[7-9] are to demonstrate that the development of these two synthetic methods renders practical for the first time the synthesis of many complex oligosaccharide structures of biological importance.

It is considered of interest to briefly review the observations which led to the establishment in this laboratory of the halide ion catalyzed glycosidation reaction.[4] Experiments were reported[10] shortly thereafter which confirmed the effect of halide ion on the stereochemical course of reaction, and a very recent paper[11] based on these earlier observations has reported syntheses of α-D-glucopyranosides by reaction of tetra-*O*-benzyl-α-D-glucopyranosyl chloride in the presence of tetraethylammonium chloride.

This communication deals only with pyranoid structures and the term glycoside, for example, implies glycopyranoside.

The establishment of the conformational properties of pyranoid structures in solution, especially through the advent of ^{1}H NMR spectroscopy[12] and, as a consequence, the anomeric effect,[13,14] allowed the appreciation[15-18] of the stereochemical aspects of the anomerization phenomenon, a process of basic importance to the understanding of the properties of glycopyranosyl halides. The proneness, in general, of α-haloethers to undergo solvolysis and the implication of the ring-oxygen atom in charge delocalization (oxocarbonium ion formation)[19,20] rendered necessary a reappraisal of neighboring-group participation in reactions at anomeric centers.[21] That is, the basic driving force is ring-oxygen participation, and reactions at the anomeric center of glycopyranosyl halides require, in the first stage as suggested in 1956,[22] the formation of a glycosyloxocarbonium ion–halide ion pair which then may rearrange to a cyclic oxocarbonium ion resulting from neighboring-group participation.[20] Studies of the effect of the electronegativity of the C-2 substituent on ease of solvolysis of glycosyl halides[20,21,23] provided insight on the requirements for glycosyl halide structures to undergo spontaneous solvolysis to intimate ion pairs in weakly polar solvents. A detailed examination of the anomerization of the tetra-*O*-acetyl-D-glucopyranosyl chlorides[21] confirmed the earlier evidence[20,24] for transition states that lead to inversion of the reacting center. More importantly, this study[21] confirmed the conclusion[25] that glycosyl halide anomerization can be made to be a very rapid process so that the thermodynamically less stable form can be made readily available for reaction albeit at necessarily very low concentrations. The early observations[20] that the anomeric 3,4,6-tri-*O*-acetyl-D-glycopyranosyl chlorides tend to undergo acetolysis with inversion of the reacting center, and that the β anomer solvolyzes about 100 times more rapidly were attributed to the conformational properties of separated oxocarbonium ions. However, the remarkable kinetic control of the stereochemical route of the reaction of tetra-*O*-acetyl-α-D-glucopyranosyl bromide with 4-methylpyridine in the presence of bromide ion is indicated by the almost exclusive formation of the high-energy product, *N*-(tetra-*O*-acetyl-α-D-glucopyranosyl)-4-methylpyridinium bromide (**1**). This compound actually exists both in solution and in the crystalline state[26] in the $B_{2,5}$ conformation shown.



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It thus became evident that important stereoelectronic requirements must exist which render more facile the replacement of an equatorial β-halide with inversion of the anomeric center than the replacement with inversion of the axial halide of the α anomer. These inversions have been viewed[23] as arising from shielding by the departing group. Our study[21] of the anomerization of the tetra-*O*-acetyl-D-glucopyranosyl chlorides showed that this process does not readily involve rearrangement of ion pairs but, instead, proceeds readily only in the presence of chloride ion by way of an ion triplet. The corollary to this conclusion is that the intimate ion pairs which precede ion-triplet formation are structurally well defined and different, depending on the anomeric precursor, and become solvated on the opposite side of the anomeric center much more rapidly than the initially formed ions can separate.

The various theoretical interpretations of the anomeric effect[15-18] underline the importance of an antiparallel disposition for effective charge delocalization from an unshared pair of electrons into a geminal polar bond. This stereoelectronic feature which can be thought of as back-

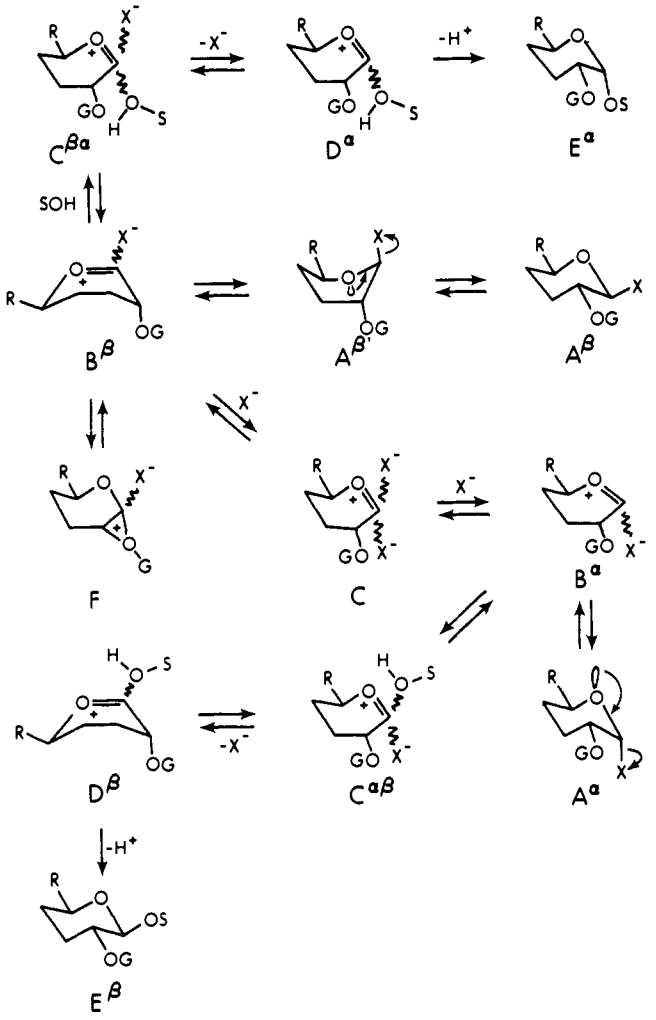


Figure 1. Abbreviated formulas to display intermediates expected to form in the course of the reaction of anomeric glycosyl halides (A^{α} and A^{β}) with an alcohol (SOH) in the presence of halide ion (X^-). The substituent group G infers a weakly (relatively) electronegative group such as benzyl which is not prone to participate in reactions at the anomeric center in such a way as to lead to undesired products. The intermediate ion-alcohol complexes D^{α} and D^{β} once formed may to some extent become solvated to an ion-dialcohol complex (i.e., $C^{\alpha\beta}$ or $C^{\beta\alpha}$ where X^- = SOH). This intermediate, if formed, would not affect the overall stereoselectivity of the reaction since collapse to E^{α} by way of D^{α} is expected to be the energetically more favorable route.

bonding of oxygen to the central carbon of an acetal group appears also to influence the orientation of an aglycon through what has been termed the exo-anomeric effect.[27] Deslongchamps and coworkers[28,29] have recently accumulated convincing evidence for the important role that p orbital to bond orientation plays in heterolytic cleavage of the bond through stabilization of the transition state. For these reasons, it is considered that the explanation of the high reactivity of β-glycopyranosyl halides in comparison with their α anomers in reactions with alcohols must be related to the stereoelectronic requirements for reaction *as well as* to the inherent fact that the β forms are the less thermodynamically stable forms and, therefore, energetically closer to their transition states than are the α anomers. Figure 1 summarizes what is considered to represent the more salient features of the halide ion catalyzed glycosidation process.

The rate-controlling stages for glycoside formation are considered to be the formation of the two molecule-ion pairs D^{α} and D^{β}. A main consideration is solvolysis of the glycosyl halide to the ion pairs B^{α} and B^{β}, involving appropriate orientation of a p orbital on the ring oxygen to provide maximum orbital overlap through antiparallel disposition as the C–X bond is cleaved. Thus, the β-halide must assume a conformation other than the $^4C_1$ conformation of A^{β}. The boat conformation for $A^{\beta'}$ is chosen instead of the previously proposed $^1C_4$ chair form,[20] because the boat conformation was found for *N*-(tetra-*O*-acetyl-α-D-glucopyranosyl)-*p*-methylpyridinium bromide (**1**).[26] The resulting ion pair B^{β} is expected to be of substantially higher energy than that, B^{α}, arising from solvolysis of the α anomer (Figure 2). However, this matter is trivial if the transition states leading to intermediates D^{α} and D^{β} are of higher energy than those leading to either B^{α} or B^{β}. In the case of anomerization, the rates are related to the differences in the free energies of the compounds in the ground state only. Whether or not the solvated ion pairs (i.e., the triplets C, $C^{\alpha\beta}$, $C^{\beta\alpha}$) are energetically less favorable than the precursor ion pairs is not established. These triplets may be of higher energy because of the decrease in the entropy required for their formation. The ion pair B^{β} is written in the conformation that it can be reasonably expected to exist. Conformational change prior to triplet formation is possible but would only represent a further trivial stage. As already mentioned, and crucial to this proposal, is the hypothesis that ion pairs such as B^{α} and B^{β} are not readily interconvertible by simple migration of the halide ion about the edge of the cyclic oxocarbonium ion. This mechanistic proposal follows the principle of microscopic reversibility in that the stereochemical requirements for the removal of a group at an anomeric center are also met in the reverse process. The neutral molecule-oxocarbonium ion complexes D^{α} and D^{β} are expected to be the highest energy intermediates since these lack the strong stabilization of the ionic bonds present in the ion pairs B^{α} and B^{β}, the ion triplet C and the ion pair-molecule triplets $C^{\alpha\beta}$ and $C^{\beta\alpha}$. Equilibration of the ion pair B^{β} with the ion pair F through neighboring-group participation may occur, and indeed evidence for cyclic oxocarbonium ion formation involving the anomeric center appears to exist.[30] The low yield of β-glycoside achieved in itself suggests that reaction by way of F is unimportant. Regardless, since in the first instance ion-pair separation would be required, and the reaction is best performed in solvents of low dielectric constants, the nucleophilic attack by alcohol on F most likely would proceed by way of the ion-molecule pair D^{β}. Thus, the formation of F need not influence the course of the reaction as is indicated by the experimental results. The halide ion catalyzed process can be considered as a special application of the Hammet-Curtin principle[31] in that all conformational changes and the formation of necessary intermediates are rendered trivial in comparison with the accomplish-

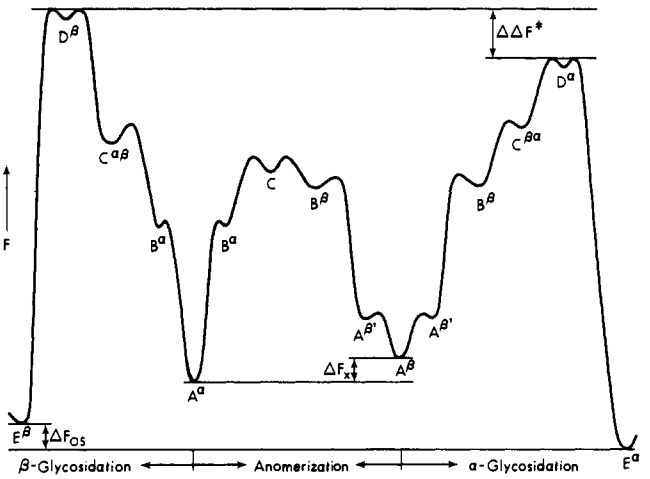


Figure 2.

ment of the least stable intermediates D^{α} and D^{β}. When D^{α} is more stable than D^{β}, α-glycoside (E^{α}) formation will be promoted as was found in the reactions studied to date. The relative stabilities of the intermediates D^{α} and D^{β} will of course vary with variations in the glycosyl group as well as the alcohol (SOH) and, in certain instances, the desired reaction may not be achieved.

It may be noted that the conclusions reached with reference to the conformational requirements for the halide ion catalyzed process depicted in Figure 1 are likely followed closely in enzyme catalyzed processes for substitution at the anomeric center of glycopyranosides. Indeed, the half-chair conformations of $C^{\beta\alpha}$ and $C^{\alpha\beta}$ have already been implicated.[32]

In view of the above theoretical considerations, it was possible to envisage the following criteria for successful halide ion catalyzed glycosidation.

(a) The glycosidation reaction must be carried out under conditions wherein the halide ion concentration is maintained at a level adequate to cause anomerization of the glycosyl halides at a rate substantially greater than the glycosidation by way of the α-halide to form the β-glycoside.

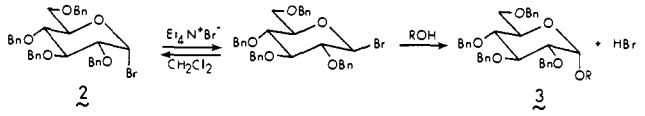
(b) A glycosyl halide must be used that is sufficiently prone to solvolysis that its reaction with an alcohol does not require assistance by some special agent such as silver or mercuric ions or strongly polar solvents.

(c) The reaction conditions should minimize side reactions involving loss of protecting groups which are either base or acid labile, dehydrohalogenation, and/or the formation of stable glycosidic products other than the desired α-glycoside.

In order to circumvent orthoester formation, Baddiley and coworkers[33] introduced the use of *O*-benzylated glycopyranosyl halides for the preparation of glycosides. Using tetra-*O*-benzyl-α-D-glucopyranosyl chloride,[33] silver ion assisted reactions provided useful syntheses of a number of interesting α-D-glycosides, but these were formed along with substantial amounts of the β anomers.

Accordingly, the compound was thought to be a suitable candidate for halide ion catalyzed glycosidation. The compound was engaged in a reaction with 2 mol/equiv of methanol in acetonitrile containing 1 mol equiv each of tetraethylammonium chloride and diisopropylethylamine (Hünig's base).[34] No reaction was evident within several hours at room temperature, although anomerization of the chlorides was expected to occur under these conditions. However, when the reaction temperature was raised to 100°, an 80% yield of methyl tetra-*O*-benzyl-α-D-glycopyranoside was achieved in 2.5 hr as assessed by NMR.[4] The amine was added to ensure that, if formed, the β-glucoside would not anomerize because of the medium having become strongly acidic. When the same reaction was conducted using silver perchlorate instead of the tetraethylammonium chloride, reaction was rapid at room temperature, and the product provided a near quantitative yield of a 11:2 mixture of the β- and α-glucosides, respectively.[4] In view of the low reactivity displayed by the glycosyl chloride, attention was turned to the corresponding bromide **2**. Several laboratories[10,35,36] have reported the preparation of tetra-*O*-benzyl-α-D-glucopyranosyl bromide (**2**) as an unstable syrupy product which could not be well characterized. That the compound exists largely in the α form was evident from its NMR spectrum. The material used in this research was a colorless product which contained at least 95% of the expected bromine and when reacted with silver acetate in acetic acid–acetic anhydride gave at least a 90% yield of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-β-D-glucose. The compound decomposed extensively within 1 day when stored at room temperature as a syrup. However, the compound appeared fully stable over a 2-day period at room temperature when dissolved in methylene chloride with or without the presence of equimolar amounts of Hünig's base and/or tetraethylammonium bromide. The compound could be stored indefinitely at or near −80°.

The reaction of **2** with alcohols in methylene chloride and in the presence of tetraethylammonium bromide was found to proceed readily at room temperature to provide high yields of alkyl tetra-*O*-benzyl-α-D-glucopyranosides (**3**).



2 **3**

The reaction was effectively quenched when tetraethylammonium chloride was used instead of the bromide as was expected in view of the above-mentioned lower reactivity of tetra-*O*-benzyl-α-D-glucopyranosyl chloride. Typical yields and stereochemical routes of reaction using the methyl, isopropyl, and *tert*-butyl alcohols and equimolar amounts of **2** and tetraethylammonium bromide are given in Table I. It should be emphasized at this point that the yields reported in Table I and those of the disaccharides to be reported later on are not to be interpreted as the maximum yields achievable by this synthetic method. There can be no doubt that a careful study of all the reaction parameters would lead to improved reaction conditions in most cases. Such studies were beyond the scope of this research program.

It is seen from Table I that the lower temperature improved the yield and favored the formation of the α-glycoside. With the more hindered isopropyl and *tert*-butyl alcohols, dehydrobromination of **2** to 1,5-anhydrotetra-*O*-benzyl-D-*arabino*-hex-1-enitol was readily apparent from the NMR of the products formed at 60° but not for the reactions at 25°.

Repetition of the experiments described in Table I but without the presence of the base provided products that were indistinguishable from those obtained using the base. Thus, it was apparent that the base offers no important catalytic effect and is not involved in the formation of a reactive intermediate. West and Schuerch[37] have recently reported the development of *N*-(tetra-*O*-benzyl-β-D-glucopyranosyl) salts of tertiary amines as reagents for α-glucoside synthesis. As was indicated in our report of the discovery of such labile compounds,[38] this approach was investigated. However, it was found unpromising in our hands and was abandoned. The use of triethylamine instead of Hünig's base had no appreciable effect on the rate or route of reaction, however, the extent of dehydrobromination was greater. Further research involving the use of bases to buffer the halide ion catalyzed glycosidation reactions is reported in a related paper in this issue[8] where the use of molecular sieves is introduced. This modification eliminated the acetyl group migration which occurred in the presence of Hünig's base when an attempt was made to prepare the disaccharide **9** from 1,3,4,6-tetra-*O*-acetyl-α-D-galactopyranose. The α-L-fucosides **11** and, likely, **10** were formed as will be discussed below.

The effect of solvent on yield and stereoselectivity in the reaction of **2** with ethanol was investigated. The yields were highest (over 90%) using benzene and methylene chloride, somewhat lower (about 80%) with acetonitrile, only 60–70% using dioxane or nitromethane, and very low (<20%) using *N*,*N*-dimethylformamide or dimethyl sulfoxide. The reason for these results was not investigated but is probably related to decomposition of **2**. The solvent also affected the stereochemical route of reaction. The α:β ratio of the glycosides was over 8 for the weakly basic solvents benzene, methylene chloride, and nitromethane and fell to below 6.6

Table I. Bromide Ion Catalyzed Preparation of Alkyl Tetra-*O*-benzyl-α-D-glucopyranosides[a]

Alcohol	Reaction Temp, °C	Reaction Time, hr	Yield of glycoside α form[b]	Yield of glycoside β form[c]
CH_3OH	25	40	95	Trace
	60	6	87	10
$(CH_3)_2CHOH$	25	40	81	5
	60	6	65[d]	10
$(CH_3)_3COH$	25	40	70	5
	60	6	65[d]	10

[a] Using a 0.1 *M* solution of syrupy tetra-*O*-benzyl-α-D-glucopyranosyl bromide in methylene chloride, molar equivalents of tetraethylammonium bromide and diisopropylethylamine, and 1.1 molar equivalent of the alcohol. [b] Estimated by integration of the NMR spectra of the isolated products. [c] Estimated by TLC examination. [d] The presence of 1,5-anhydrotetra-*O*-benzyl-D-*arabino*-hex-1-enitol in the crude product was detected by NMR.

for dioxane and acetonitrile. Because of the relative ease of purification, high stability, insolubility in water, but otherwise good solvent properties, methylene chloride seemed the solvent of choice, and the investigations to date have been largely restricted to this solvent.

The effect of bromide ion concentration on rate and route of reaction was not investigated in detail but Table II reports the results obtained in one series of experiments. It is seen that, in the presence of an equivalent amount of tetraethylammonium bromide, there was formed a near 7% yield of methyl β-glycoside within 5 min, but this yield increased to 20% in the absence of bromide ion at the start of the reaction. The reason for the rapid initial formation of β-glycoside in the presence of the added bromide ion remains obscure. It may be related in part to the rate of the dissolution of the tetraethylammonium bromide, but the possibility also exists that there is present in the syrupy **2** (about 95% pure) a highly reactive impurity which forms the β-glycoside or what appears to be β-glycoside. In any event, the results shown in Table II require the latter stages of the reaction to be highly selective for the formation of α-glycoside. As seen in Table II, in the absence of added halide ion, β-glycoside was initially the main product of the reaction. However, after about 25% reaction, α-glycoside was formed preferentially. The overall rate of reaction was only slightly less. These results are similar to the reaction of tetra-*O*-acetyl-α-D-glucopyranosyl bromide with pyridine in that the liberation of bromide caused an increase in rate of reaction with the route changing from formation mainly of β-pyridinium glycoside to almost exclusive formation of the α anomer.[25] Results such as those reported in Table II suggest that as low as a 0.25 mol equiv of bromide ion would provide fully effective catalysis. However, this matter has not been investigated. In all the syntheses of oligosaccharides to date, 1 mol equiv of bromide ion was used.

Steric hindrance of the hydroxyl of the reacting alcohol was found, as expected, to decrease the rate of reaction. The reaction with methanol was about two times faster than that with isopropyl alcohol and about 10 times faster than that with *tert*-butyl alcohol (this latter rate may be in substantial error, having been estimated from somewhat inadequate NMR data). Using isopropyl alcohol as reactant and the conditions otherwise as reported in Table II, the reaction was near 50% completed in 10 min at 80°, 40 min at 60°, and 6 hr at 40°. Assuming that *tert*-butyl alcohol represents a reactivity near that of a secondary hydroxyl group in a disaccharide synthesis, a reaction time of near 2 days at room temperature would be required. Indeed, the examination of the course of such reactions indicated that reaction time of 2 to 4 days may be needed. Higher yields could be effected by using an excess of the glycosyl bromide.[7]

Table II. Effect of Bromide Ion on Rate and Stereochemical Route of Reaction[a]

Reaction time, min	Composition of the product, (%)[b] α-Glycoside	β-Glycoside	Residual 2
5	13 (3)	7 (20)	80 (77)
15	45 (7)	8 (21)	47 (72)
30	66 (14)	8 (24)	26 (62)
60	78 (31)	9 (26)	13 (43)
120	81 (59)	9	10 (21)

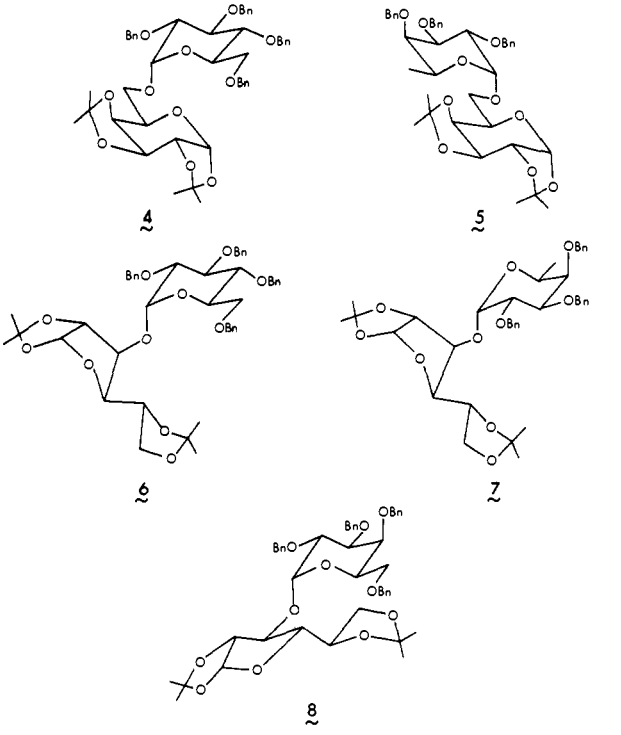
[a] Reaction of syrupy tetra-*O*-benzyl-α-D-glucopyranosyl bromide (0.1 *M* in methylene chloride) with 2 molar equiv of methanol in the presence of a molar equivalent of diisopropylethylamine. [b] In the presence of a molar equivalent of tetraethylammonium bromide and, in brackets, in the absence of added bromide salt.

Table III. Bromide Ion Catalyzed Glycosidations[a]

Product	Yield, %[b]	Disaccharide obtained on deblocking
4	65	6-*O*-(α-D-Glucopyranosyl)-D-galactose
5	63	6-*O*-(α-L-Fucopyranosyl)-D-galactose
6	42	3-*O*-(α-D-Glucopyranosyl)-D-glucose
7	47	3-*O*-(α-L-Fucopyranosyl)-D-glucose
8	62	3-*O*-(α-D-Galactopyranosyl)-D-galactose

[a] All reactions were in methylene chloride (30 ml) at room temperature using 10 mmol of glycosyl bromide and near equivalent amount of di-*O*-isopropylidene sugar, diisopropylethylamine, and tetraethylammonium bromide. [b] No evidence for the formation of β anomer was obtained in any of the experiments.

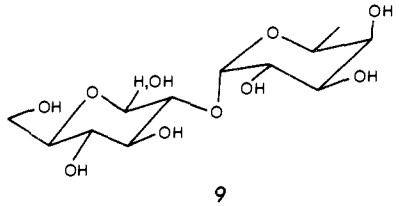
Having established the general conditions required for successful halide ion catalyzed reactions, a number of syntheses of disaccharide structures were attempted using tri-*O*-benzyl-α-L-fucopyranosyl bromide and tetra-*O*-benzyl-α-D-galactopyranosyl bromide as well as compound **2**. In every case, the conditions involved the use of methylene chloride as solvent. In other syntheses,[7,8] the addition of a small amount of *N,N*-dimethylformamide seemed more effective. Near molar equivalents of the per-*O*-benzyl-α-hexopyranosyl bromide, the appropriately blocked monosaccharide, tetraethylammonium bromide, and Hünig's base were used. The yields of the isolated α-linked blocked disaccharide products (compounds **4** to **8**) are reported in Table III. It is seen that the reaction proved as successful in form-



ing 6-deoxy-α-L- and α-D-galactosyl derivatives as in forming α-D-glucosyl compounds.

The disaccharides obtained on removal of the blocking groups are listed in Table III. The literature related to 6-*O*-(α-D-glucopyranosyl)-D-galactose and 3-*O*-(α-D-glucopyranosyl)-D-glucose has recently been reviewed in connection with their syntheses by the oximinochloride method.[5] 6-*O*-(α-L-Fucopyranosyl)-D-galactose and 3-*O*-(α-L-fucopyranosyl)-D-glucose appear to be new disaccharides. 3-*O*-(α-D-Galactopyranosyl)-D-galactose is a building unit of the antigenic determinant for the B human blood group. An alternate synthesis is reported in an accompanying paper in this issue,[8] where the related literature is reviewed. Recently, Kronzer and Schuerch[39] reported failure in an attempt to synthesize this disaccharide using quaternary ammonium salts derived from 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl bromide.

An effort to synthesize 2-*O*-(α-L-fucopyranosyl)-D-galactose (**9**) by reaction of tri-*O*-benzyl-α-L-fucopyranosyl bromide with 1,3,4,6-tetra-*O*-acetyl-α-D-galactopyranose provided α-fucosides in 63% yield, but the main product of the reaction (33% yield) appeared to be α-L-fucopyranosyl α-D-galactopyranoside (**10**). Both compound **9** and α-L-fucopyranosyl β-D-galactopyranoside (**12**) were obtained in 15% yield. This result is accounted for by rearrangement under the influence of Hünig's base of the 1,3,4,6-tetraacetate to 2,3,4,6-tetra-*O*-acetyl-α-D-galactose which mutarotated to its β anomer. The acetyl group migration did not occur when molecular sieve was used to absorb the hydrogen bromide.[7]



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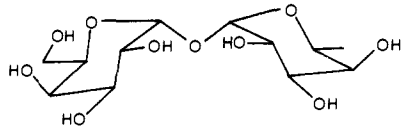

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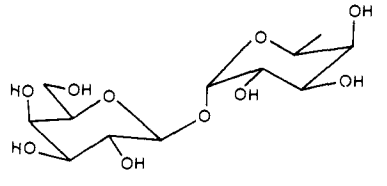

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Experimental Section

General. The thin-layer chromatograms utilized Silica Gel G (E. Merck A.G.). The column chromatograms were prepared from 100 mesh silicic acid (Mallinckrodt Chemical Works). All solvent removal was with a rotary evaporator using the vacuum from a water aspirator. The ^{1}H NMR spectra were measured with either Varian A-60 or HA-100 spectrometers. Anhydrous solvents were prepared following standard procedures.[40] Skellysolve B refers to hexane supplied by Minnesota Solvents and Chemical Corp. All smaller scale manipulations of liquids were made with syringes, and the dried flasks and solvent storage bottles were protected from the atmosphere with serum caps. The melting points are uncorrected.

Tetra-*O*-benzyl-D-glucopyranosyl Chloride and Bromide (2). Initially, methyl tetra-*O*-benzyl-α-D-glucopyranoside was prepared, following the procedure of Tate and Bishop.[41] However, the procedure of Brown and coworkers[42] proved generally more satisfactory. This compound and other benzyl ethers prepared in this research proved susceptible to autooxidation and should be stored in stoppered flasks preferably in the dark. More recently, the general method for benzylation using benzyl bromide and *N,N*-dimethylformamide (DMF) as solvent and quenching of the reaction with methanol[43] has proved most effective.

The hydrolysis of the methyl tetra-*O*-benzyl-α-D-glucopyranoside to crystallize 2,3,4,6-tetra-*O*-benzyl-α-D-glucose followed the procedure of Tate and Bishop.[41]

The 2,3,4,6-tetra-*O*-benzyl-α-D-glucose was converted to pure crystalline tetra-*O*-benzyl-1-*O*-(*p*-nitrobenzoyl)-α-D-glucopyranose in 80% yield, following the procedure recommended by Glaudemans and Fletcher.[44]

The tetra-*O*-benzyl-1-*O*-(*p*-nitrobenzoyl)-α-D-glucopyranose was converted to compound **2**, following the procedure described by Ishikawa and Fletcher.[10] As expected for reasons of the anomeric effect, the syrupy product exists largely (over 90% NMR) in the α form. The compound is highly unstable and could only be successfully stored at near −80°. Prior to each use, the purity was checked by examination of the NMR spectrum and optical rotation, $[\alpha]^{24}$D 105° (*c* 2.7, chloroform).

Syrupy tetra-*O*-benzyl-α-D-glucopyranosyl chloride, $[\alpha]^{24}$D +93° (*c* 3.2, benzene) was prepared, following the procedure of Baddiley *et al.*[33]

Standards for the Kinetic Investigations. Benzylation of methyl β-D-glucopyranoside provided methyl tetra-*O*-benzyl-β-D-glucopyranoside which was recrystallized from ethanol, mp 68–69°, $[\alpha]^{23}$D +11° (*c* 5, dioxane). NMR and elementary analyses were in accord with the assigned structure.

1,5-Anhydro-tetra-*O*-benzyl-D-*arabino*-hex-1-enitol was prepared according to the procedure presented by Preobrazhenskaya and Suvorov.[36]

Reaction of the bromide **2** with silver acetate in anhydrous acetic acid containing about 10% acetic anhydride provided a quantitative yield of what appeared to be (NMR) 95% pure tetra-*O*-benzyl-β-D-glycopyranosyl acetate. The acetyl signal was at τ 8.01.

Acetylation of 2,3,4,6-tetra-*O*-benzyl-α-D-glucose at 0° in 2:1 pyridine–acetic anhydride gave a 95% yield of syrupy product, $[\alpha]^{24}$D +50° (*c* 2, benzene). The signal for acetyl group at τ 7.92 was ten times more intense than the signal at τ 8.01, indicating an α to β ratio of 10:1.

Kinetic Investigations. All reactions were carried out in sealed glass tubes. The reactions were quenched by rapid cooling in a Dry Ice–acetone bath. Excess tetra-*O*-benzyl-D-glucopyranosyl bromide (**2**) was estimated by conversion to tetra-*O*-benzyl-β-D-glucopyranosyl acetate. When methanol was used as reactant, the relative intensities of signals for methoxy group and acetoxy group were determined at 100 MHz to estimate the extent of reaction. The relative intensities of the signals for the methyl α- and β-glycosides were used to estimate the anomeric composition of the product. Synthetic mixtures were used for calibration purposes. When alcohols other than methanol were used as reactants, pure methyl tetra-*O*-benzyl-α-D-glucopyranoside was used in the reaction mixture to serve as an internal standard. The relative intensity of the signal for the methoxy group and a signal characteristic of newly formed glycoside was used as a measure of the extent of glycosidation. Control on the survival of tetra-*O*-benzyl-D-glucopyranosyl bromide was established by treatment of the crude product with silver acetate as described above.

The conclusions reached by NMR analysis as to product composition were checked in several instances by de-O-benzylation using standard palladium on charcoal hydrogenolysis of the product followed by analysis of the alkyl glucopyranoside content using gas chromatography. The compounds were converted to their poly-*O*-trimethylsilyl derivatives prior to chromatography according to the procedure of Sweeley and coworkers.[45]

The rates of reaction were estimated using the following procedure. However, in certain cases, a rough measure of the rate of reaction was estimated from the rate of decay of the signal for the anomeric hydrogen of the glycosyl bromide.

Tetra-*O*-benzyl-α-D-glucopyranosyl bromide (**2**) (0.5 mmol) (calculated using the estimated purity) was dissolved in 5 ml of the

pure solvent. If tetraalkylammonium halide, amine, or alcohol were to be present in the reaction mixture, the selected amounts of those materials were rapidly added, and the solution was near quantitatively transferred to a glass tube possessing a constriction to facilitate sealing. The sealed tube was placed in a thermostated bath within 5 min of the beginning of the preparation. After a given interval time, the tube was placed in a Dry Ice–acetone mixture. The content of the opened tube was then poured into a flask containing silver acetate (4 mmol), acetic acid (2 mmol), and acetic anhydride (1 mmol). After shaking in the dark for 1 hr, the silver salts were removed and thoroughly washed with methylene chloride. The combined filtrates were then twice washed with water with the water layer each time being back-extracted twice with methylene chloride. The combined methylene chloride extracts were dried over potassium carbonate, and the solvent was removed. Benzene (20 ml) was added to the residue, and this solvent was removed in vacuo. This procedure was repeated twice to ensure removal of all traces of acetic acid. The syrupy, normally colorless product was kept overnight in a high vacuum prior to NMR examination in $CDCl_3$ at 100 MHz. The results of a typical reaction are presented in Table II.

Tri-*O*-benzyl-α-L-fucopyranosyl Bromide. This compound was prepared following a modified version of the procedure of Dejter-Juszynski and Flowers.[46]

Tetra-*O*-benzyl-α-D-galactopyranosyl Bromide. As recently reported by Kronzer and Schuerch,[39] tetra-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-D-galactopyranose does not readily provide a crystalline anomer. Initially the α–β mixture was used to prepare high quality tetra-*O*-benzyl-α-D-galactopyranosyl bromide, using the same conditions as described above for the preparation of **2.** The compound was highly prone to decomposition when isolated as an oil and was prepared immediately prior to use.

Subsequently, the tetra-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-β-D-galactopyranose crystallized, [mp 105.5–106°; $[\alpha]_D$ −43° (*c* 1, in chloroform); 40% yield], and this compound was used for the preparation of the glycosyl bromide.

Glycosidations of Di-*O*-isopropylidenehexoses. The per-*O*-benzylhexopyranosyl bromide (10 mmol) was dissolved in 30 ml of methylene chloride and, to this solution, there were added tetraethylammonium bromide (2.1 g, 10 mmol), diisopropylethylamine (1.7 ml, 10 mmol), and the di-*O*-isopropylidenehexose (2.9 g, 11 mmol). The mixture was stirred until homogeneous and was kept for 2 days at room temperature. The solution was then diluted with methylene chloride (50 ml) and washed sequentially with water, dilute hydrochloric acid and water. After drying over sodium sulfate, the solution was taken to dryness. The resulting oil was applied to 4 × 65 cm chromatographic column prepared from silicic acid using diethyl ether:Skellysolve B (1:3) as developing phase. In each case, the first major band to be eluted was the desired product.

Deblocking Procedures. (a) Hydrogenolysis. The chromatographically purified product of the glycosidation reaction was dissolved in 95% ethanol (250 ml), 5% palladium on carbon (5 g) was added, and the mixture was agitated at room temperature in a hydrogen atmosphere at 60 psi for 2 days. The catalyst was removed by filtration, and the mother liquor was concentrated to a syrup which was dissolved in water for application to a 2.2 × 75 cm column of Dowex 1-X8, 200–400 mesh resin on the OH^- form. Elution with water provided the chromatographically purified di-*O*-isopropylidene α-linked disaccharide.

(b) Hydrolysis of the Isopropylidene Groups. A 10% solution of the di-*O*-isopropylidene disaccharide in 90% aqueous trifluoroacetic acid[47] was prepared and kept at room temperature for 15 min. The solution was then rapidly concentrated in vacuo to an oil which turned into an amorphous powder on trituration with ether. This product was dissolved in water for application to a CGC 241 ion exchange resin in the potassium form (200–400 mesh, supplied in the sodium form by J. T. Baker Chemical Co., Phillipsburg, N.J.). Elution with water provided the chromatographically pure disaccharide.

6-*O*-(α-D-Glucopyranosyl)-D-galactose. The reaction of tetra-*O*-benzyl-α-D-glucopyranosyl bromide (**2**) with 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose gave a 65% yield of colorless syrup, $[\alpha]^{24}_D$ +10.1° (*c* 2, chloroform). The ^1H NMR spectrum was in accord with expectation for structure 4, and the relative intensities of the signals were in keeping with a high degree of purity.

Anal. Calcd for $C_{46}H_{54}O_{11}$: C, 70.57; H, 6.95. Found: C, 69.47; H, 6.90.

The hydrogenolysis provided the previously described 6-*O*-(α-D-glucopyranosyl)-1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose which was hydrolyzed to the title compound. The overall yield was 75%. The product was identical in all respects with that previously described.[5]

6-*O*-(α-L-Fucopyranosyl)-D-galactose. The reaction of tri-*O*-benzyl-α-L-fucopyranosyl bromide, $[\alpha]^{24}_D$ −216° (*c* 1.5, chloroform), with 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose gave a 62.5% yield of crystalline product (**5**), mp 116–117°, $[\alpha]^{27}_D$ −117° (*c* 2, dichloromethane), after recrystallization from Skellysolve B. The ^1H NMR spectrum was in agreement with the assigned structure.

Anal. Calcd for $C_{39}H_{48}O_{10}$: C, 69.21; H, 7.15. Found: C, 68.98; H, 6.99.

The hydrogenolysis provided an 82% yield of syrup, $[\alpha]^{23}_D$ −128° (*c* 1.6, water), whose ^1H NMR spectrum was in complete accord with that expected for 6-*O*-(α-L-fucopyranosyl)-1,2;3,4-di-*O*-isopropylidene-α-*D*-galactopyranose.

Anal. Calcd for $C_{18}H_{30}O_{10}$: C, 53.21; H, 7.39. Found: C, 53.48; H, 7.48.

The hydrolysis of the isopropylidene groups proceeded in 75% yield to provide an amorphous powder, $[\alpha]^{26}_D$ −67° (*c* 0.65, water). The ^1H NMR spectrum in D_2O showed doublet signals for the anomeric hydrogen of the galactose residue at τ 5.15 (spacing 7.5 Hz, β form) and 4.47 (spacing 2.5 Hz, α form). The doublet signal for the anomeric hydrogen of the fucosyl residue was at τ 4.81 (spacing 3.0 Hz), and that for the methyl group at τ 8.52 (spacing 6.5 Hz).

3-*O*-(α-D-Glucopyranosyl)-D-glucose. The reaction of tetra-*O*-benzyl-α-D-glucopyranosyl bromide (**2**) with 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose provided a 42% yield of crystalline material, mp 90–91°, $[\alpha]^{22}_D$ +46° (*c* 2.9, chloroform). The ^1H NMR spectrum was in accord with that expected for structure **6.**

Anal. Calcd for $C_{46}H_{54}O_{11}$: C, 70.57; H, 6.95. Found: C, 70.53; H, 6.85.

The hydrogenolysis provided the previously described 3-*O*-(α-D-glucopyranosyl)-1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose[5] which was hydrolyzed to the title compound. The overall yield was 65% of an amorphous product identical in all respects with that previously described.[5]

3-*O*-(α-L-Fucopyranosyl)-D-glucose. The reaction of tri-*O*-benzyl-α-L-fucopyranosyl bromide with 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose provided an oily product, $[\alpha]^{27}_D$ −97° (*c* 2, chloroform), whose ^1H NMR spectrum was in all respects in excellent agreement for structure **7.**

Anal. Calcd for $C_{39}H_{48}O_{10}$: C, 69.21; H, 7.15. Found: C, 69.17; H, 7.22.

The hydrogenolysis proceeded in 72% yield to provide a crystalline product, mp 92–94°, $[\alpha]^{23}_D$ −122.5° (*c* 1.4, water). The ^1H NMR spectrum was in complete accord with that expected for 3-*O*-(α-L-fucopyranosyl)-1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose.

Anal. Calcd for $C_{18}H_{30}O_{10}$: C, 53.21; H, 7.39. Found: C, 53.15; H, 7.63.

The hydrolysis of the isopropylidene groups proceeded in 80% yield to afford a white amorphous powder, $[\alpha]^{26}_D$ −86° (*c* 1, in water). The ^1H NMR spectrum in D_2O showed the doublet signal for anomeric hydrogen of the β-glucose residue at τ 5.08 (spacing 8.0 Hz). The signal for the anomeric hydrogen of the α-glucose residue was superimposed on the signal for the anomeric hydrogen of the α-fucosyl residue. These signals occurred as an ill-defined quartet centered at τ 4.50. The spacings (~3 Hz) observed were in general accord with the assigned configurations. The signal for the methyl group was at τ 9.55 (spacing 6.5 Hz).

3-*O*-(α-D-Galactopyranosyl)-D-galactose. The reaction of tetra-*O*-benzyl-α-D-galactopyranosyl bromide with 1,2;5,6-di-*O*-isopropylidene-α-D-galactofuranose[48] gave a 62% yield of crystalline 3-*O*-(tetra-*O*-benzyl-α-D-galactopyranosyl)-1,2;5,6-di-*O*-isopropylidene-α-D-galactofuranose (**8**). The examination of the crude product provided no information for the formation of the β anomer of **8.** The crystalline material was obtained after chromatography and recrystallization from diethyl ether–hexane, mp 120–120.5°, $[\alpha]^{25}_D$ +36.8° (*c* 0.8, chloroform). The ^1H NMR spectrum was in accord with the assigned structure.

Anal. Calcd for $C_{46}H_{54}O_{11}$: C, 70.56; H, 6.95. Found: C, 70.76; H, 7.02.

Hydrogenolysis gave a syrupy, chromatographically pure compound, $[\alpha]^{25}D$ +87.5° (*c* 1.4, water), which possessed an ^1H NMR spectrum compatible with that to be expected for 3-*O*-(α-D-galactopyranosyl)-1,2;5,6-di-*O*-isopropylidene-α-D-galactofuranose and identical with this product obtained by way of the oximinochloride method.[49]

Anal. Calcd for $C_{18}H_{30}O_{11}$: C, 51.18; H, 7.16. Found: C, 49.76; H, 7.32.

Hydrolysis of the above compound gave 3-*O*-(α-D-galactopyranosyl)-D-galactose as an amorphous white powder in 70% yield. The product appeared pure on paper chromatograms, and the equilibrium specific rotation, +184° (*c* 1.25, water), was substantially higher than that (+155°) reported in the literature.[50]

Anal. Calcd for $C_{12}H_{22}O_{11}$: C, 42.10; H, 6.48. Found: C, 41.84; H, 6.41.

As expected, the ^1H NMR spectrum in D_2O displayed a broad band for 12 hydrogens in the region τ 5.44–6.13, a doublet signal for one hydrogen at τ 4.57 (spacing, 3.0 Hz), and doublet signals at τ 4.43 (spacing, 2.0 Hz) and 5.08 (spacing 7.0 Hz) with total intensity for one hydrogen.

Other α-L-Fucopyranosyl Derivatives of Galactose. The reaction of tri-*O*-benzyl-α-L-fucopyranosyl bromide with 1,3,4,6-tetra-*O*-acetyl-α-D-galactopyranose[7] gave an oil which on TLC showed the presence of three components which could be considered derivatives of disaccharides. Column chromatography using a 1:1 mixture of diethyl ether and Skellysolve B provided three fractions with signals for phenyl, acetyl, and fucose *C*-methyl groups in the ^1H NMR spectra that had intensities in the ratios 3:4:1, respectively. The yields of these fractions in order of elution were 33, 15, and 15%, and the specific rotations in chloroform were +21.3, +5.6, and −39.2°, respectively.

The first fraction was subjected to hydrogenolysis, and the crystalline product was recrystallized from ethyl alcohol, mp 134–135°, $[\alpha]^{23}D$ +26.7° (*c* 0.5, water). The ^1H NMR spectrum was complex, and signals other than those for four acetyl groups and one fucose *C*-methyl group could not be readily assigned. The compound is provisionally assigned the structure α-L-fucopyranosyl 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranoside.

Anal. Calcd for $C_{20}H_{30}O_{14}$: C, 48.59; H, 6.12. Found: C, 48.50; H, 6.24.

Deacetylation of the above material, under standard conditions using triethylamine in 50% aqueous methanol, gave a crystalline product, mp 231–233°, $[\alpha]^{23}D$ +2.9° (*c* 1, water). The chemical and ^1H NMR spectral data for this compound were inadequate for proper characterization. Therefore, the assignment of the structure, α-L-fucopyranosyl α-D-galactopyranoside (**10**) is strictly provisional.

Debenzylation of the second fraction also produced a crystalline product, mp 192–193°, $[\alpha]^{23}D$ +16.5° (*c* 1, water), after recrystallization from ethyl acetate–Skellysolve B. The ^1H NMR spectrum was in good accord for 1,3,4,6-tetra-*O*-acetyl-2-*O*-(α-L-fucopyranosyl)-α-D-galactopyranose. Deacetylation afforded a product which was identical (^1H NMR, paper chromatography) with 2-*O*-(α-L-fucopyranosyl)-D-galactose (**9**).[7]

The third fraction, on debenzylation, gave a crystalline product which was recrystallized from ethanol, mp 103–104°, $[\alpha]^{23}D$ −95° (*c* 1, water).

The ^1H NMR spectrum was too complex for detailed interpretation but showed the presence of four acetyl groups and the fucose *C*-methyl group. The structure α-L-fucopyranosyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside is assigned on the basis of the mode of synthesis and the structure of the product obtained on de-O-acetylation. Deacetylation gave a product, $[\alpha]^{24}D$ −125° (*c* 0.9, water), which resisted crystallization. Doublets for the anomeric hydrogens of the fucosyl and galactosyl residues were present at τ 4.51 (spacing, 3.5 Hz) and 5.25 (spacing, 8.0 Hz), respectively. The spectrum showed no evidence of mutarotation. The remainder of the spectrum possessed signals with total intensity corresponding to ten hydrogens plus the fucose *C*-methyl group doublet at τ 8.69 (spacing 6.5 Hz). Therefore, the structure α-L-fucopyranosyl β-D-galactopyranoside (**11**) is assigned to this compound.

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References and Notes

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