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The Chemical Synthesis of 2-*O*-(α-L-Fucopyranosyl)-3-*O*-(α-D-galactopyranosyl)-D-galactose. The Terminal Structure of the Blood-Group B Antigenic Determinant[1]

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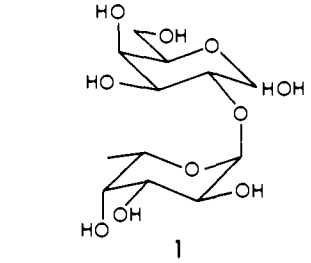
Abstract: Blocking procedures are described, including a 3,4-*O*-(ethyl orthoacetyl) intermediate, to prepare 2,2,2-trichloroethyl 4,6-di-*O*-acetyl-2-*O*-(tri-*O*-benzyl-α-L-fucopyranosyl)-β-D-galactopyranoside which, in turn, was condensed under bromide ion catalyzed conditions using molecular sieve to absorb the liberated hydrogen bromide with tetra-*O*-benzyl-D-galactopyranosyl bromide. Deblocking of the main product provided a trisaccharide which was identical with an authentic sample of the title compound. Procedures arising from model experiments provided new syntheses of 2-*O*-(α-L-fucopyranosyl)-D-galactose and 3-*O*-(α-D-galactopyranosyl)-D-galactose. C^{13} NMR spectra are recorded and assigned.

In view of the promise presented by the halide ion catalyzed approach for the synthesis of α-glycopyranosides,[3-5] the synthesis of 2-*O*-(α-L-fucopyranosyl)-3-*O*-(α-D-galactopyranosyl)-α,β-D-galactose (**3**) appeared an appropriate



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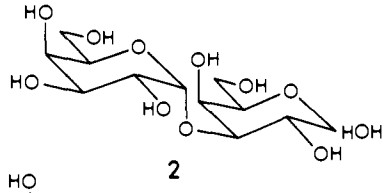

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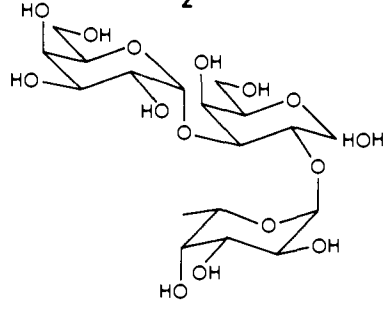


3

synthetic challenge. The successful synthesis of a structure of this complexity with good stereochemical control and yield in the establishment of the two α-glycosidic linkages would provide important insight on the power of modern carbohydrate chemistry in helping to solve through synthesis important problems of enzymology and immunology. Structure **3** represents a portion of the antigenic determinant of the blood-group B substances[6,7] and was isolated as an alkaline degradation product.[6]

The overall strategy used herein for the synthesis of **3** followed closely that described for the synthesis[4] of the main portion of the Lewis a antigenic determinant.[7] The only important departures are (1) a blocking procedure involving the hydrolysis of cyclic orthoacetates to form vicinal axial acetoxy–equatorial hydroxy groupings and (2) the development of conditions for the halide ion catalyzed glycosidation reaction which would minimize if not obviate acetyl group migration. These procedures were established in the first instance by the synthesis of 2-*O*-(α-L-fucopyranosyl)-α,β-D-galactose (**1**) from 1,3,4,6-tetra-*O*-acetyl-α-D-galactopyranose (**5**). Conditions were established that provided substantially pure **1** in better than 80% yield based on compound **5**.

Lemieux and Detert,[8] following the earlier work of Lemieux and Morgan,[9] showed that bromide ion catalyzed reaction of the tetra-*O*-acetyl-α-D-galactopyranosyl bromide with ethanol in the presence of *sym*-collidine provides the orthoester **4** in near quantitative yield and controlled acid hydrolysis of **4** provides **5** in 86% yield. The basis for this procedure was the observation[10] that the hydrolysis of tetra-*O*-acetyl-β-D-glucopyranosyl chloride in the presence of silver acetate provides 1,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose. It was suggested that this course of reaction is most readily understood in terms of a cyclic orthoacid intermediate. King and Albutt[11] extended the observation to a number of cyclohexane-related compounds and found almost exclusive formation of axial ester–equatorial alcohol on hydrolysis of a variety of dioxolenium salts. Recent studies involving the formation of dioxolenium ions by ozonolysis of cyclic acetals[12] have confirmed the intermediacy of the cyclic orthoacid.

King and Albutt[11] proposed a combination of steric and stereoelectronic effects to explain the preferred opening of the orthoacid intermediate to axial ester–equatorial alcohol. Our view is somewhat different. In view of the phenomena referred to as the anomeric and *exo* anomeric effects,[13] the

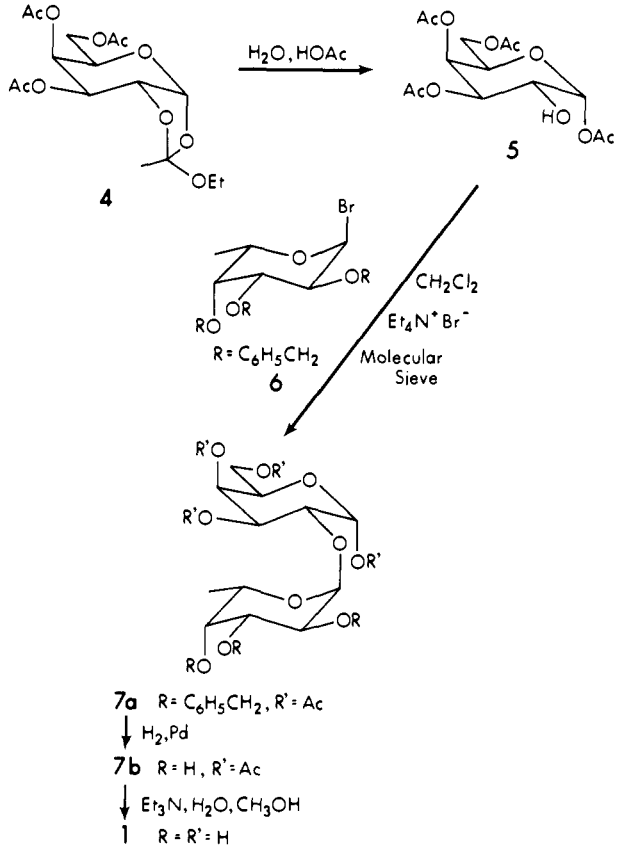
preferred orientation of the hydrogen of the hydroxyl group of the orthoacid intermediate should be synclinal to both oxygens of the dioxolane ring. Considering the near planar conformation of a dioxolane ring and the principles developed by Deslongchamps and coworkers[12,14] for orbital participation, little advantage can be expected for the cleavage of the C-2 to O-1 bond of the dioxolane ring instead of the C-2 to O-3 bond. This situation was considered by King and Albutt.[11] We expect that the main source of the driving force for the formation of the axial ester–equatorial alcohol resides principally in the high energy of the six-membered ring. These rings are strongly distorted toward the half-chair conformation.[9,15] The ring strain cannot be expected to be relieved during cleavage of the quasi-axial oxygen to acyl carbon bond. On the other hand, stretching and eventual cleavage of the quasi-equatorial oxygen to acyl carbon bond is in accord with the six-membered ring relaxing to the energetically favorable chair form as the bond is being broken. It may be noted at this point that somewhat similar results were encountered in our studies on the alcoholysis of tri-*O*-acetyl-1,2-*O*-(alkyl orthoacetyl)-α-D-glucopyranose in the presence of strong proton acids. Details of this investigation were reported in 1963[16] and are contained in a thesis by Morgan.[17] The research was conducted in an effort to establish what then appeared to be a promising method for the synthesis of α-D-glucopyranosides.[18] For example, using methylene chloride as solvent and *p*-toluenesulfonic acid as catalyst, alkyl 3,4,6-tri-*O*-acetyl-α-D-glucopyranosides were formed in yields near 70%. The β anomer was also formed with loss of the 2-acetyl group in yields, normally, of near 20%. The yield of alkyl acetate was near quantitative. It was established in these studies that exchange of the alkoxy group of the orthoester was much faster than glucoside formation. The rapid formation of the cyclic acetoxonium ion which is the intermediate for the exchange supports the above-made contention that the cyclic orthoacid is intermediate in the hydrolysis of these orthoesters. The point here is that, as for the opening of the orthoacid, the opening of the orthoester ring involves preferential cleavage of the quasi-equatorial to acyl carbon bond. Russian workers[19] have reported the alcoholysis of tri-*O*-acetyl-1,2-*O*-(alkyl orthoacetyl)-α-D-glucopyranosides to tetra-*O*-acetyl-β-D-glucopyranosides. This reaction is catalyzed by mercuric bromide. Evidently, under these conditions, reaction of the acetoxonium ion with alcohol with inversion of anomeric center is a more rapid process than is cleavage of the orthoester ring.

The hydrolysis of cyclic orthoesters to axial ester–equatorial alcohol promises to be of very considerable advantage in blocking procedures for oligosaccharide synthesis. The procedure was used in this research to establish an alternative route to the disaccharide **2** as a prelude to the synthesis of the trisaccharide **3**, 3-*O*-(α-D-Galactopyranosyl)-α,β-D-galactopyranose (**2**) was previously synthesized from 1,2; 5,6-di-*O*-isopropylidene-α-D-galactofuranose, using both the oximino chloride[20] and the halide ion catalyzed methods for stereochemical control of the glycosidation reaction.[3]

The disaccharide **1** has been isolated as a product of hydrolysis of milk oligosaccharides[21] and blood-group substances.[22] It was first synthesized by Levy, Flowers, and Sharon[23] by way of a Koenigs–Knorr type reaction, using mercuric cyanide as promoter. The yield of α-linked condensation product after extensive chromatographic separation was 41%. The disaccharide **2** is a building unit of the blood-group B antigens and was isolated in 1962 by Painter, Watkins, and Morgan[24a] from this source. Morgan and O'Neill isolated the compound from λ-carrageenan.[24b]

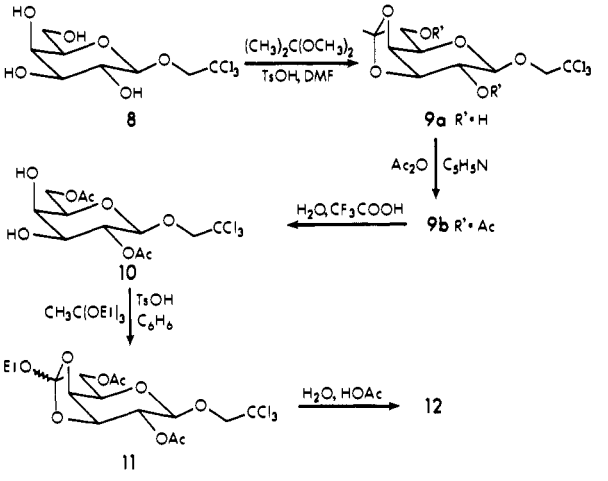
The condensation of **5** with tri-*O*-benzyl-α-D-fucopyranosyl bromide[25] (**6**) under bromide ion catalyzed conditions was first investigated in this laboratory using Hünig's base (diisopropylethylamine) as acid acceptor.[3] The reaction produced a complex reaction mixture, and it became evident that, in the presence of the base, acetyl group migration had occurred from the 1- to the 2-position of **5**. It was demonstrated[3] that the halide ion catalyzed reaction does not require an acid acceptor. Our interest in basic conditions arose as a result of the high sensitivity of many blocking groups to acid. That the overall reaction does not involve a quaternary ammonium glycoside intermediate[26] is evident from the following experiments. Tetra-*O*-benzyl-α-D-glucopyranosyl bromide[27] was reacted for 60 hr at room temperature with an equivalent amount of tetra-*O*-acetyl-6-*O*-trityl-β-D-glucopyranose in methylene chloride which contained equivalent amounts of both hydrogen bromide and tetraethylammonium bromide. Methanol and diisopropylethylamine (2 mol equiv of each) were then added, and the reaction was left for a further 20 hr. The product was deacetylated, and the benzyl groups were removed in the usual manner to provide a water soluble syrup which was applied to a charcoal–Celite chromatography column.[28] The only products isolated were methyl α-D-glucopyranoside, D-glucose, and isomaltose. The yields of the compounds reflected an about 50% completion of the reaction in the initial 60-hr period. The experiment was repeated except that, prior to the addition of the hydrogen bromide in methylene chloride, activated 4 Å molecular sieve was added to the mixture of reactants. Chromatographic examination of the reaction mixture provided no evidence for disappearance of the tetra-*O*-acetyl-6-*O*-trityl-β-D-glucopyranose after 60 hr. The trapping of the hydrogen bromide by the appropriate molecular sieve was therefore highly effective. This application of molecular sieve was first reported by Glaudemans and Fletcher,[29] in the synthesis of a nucleoside and solved the problem of acetyl group migration when utilizing compounds such as **5** in halide ion catalyzed glycosidation reactions. Thus, condensation of **5** with **6** provided chroma-

Scheme I



tographically pure **7a** in 83% yield, Deblocking of **7a** afforded **1** in good yield.

2,2,2-Trichloroethyl 2,4,6-tri-*O*-acetyl-β-D-galactopyranoside (**12**) was readily prepared in high yield by controlled acid hydrolysis of 3,4-*O*-(ethyl orthoacetyl)-2,6-di-*O*-acetyl-α-D-galactopyranose (**11**). Compound **11** was prepared



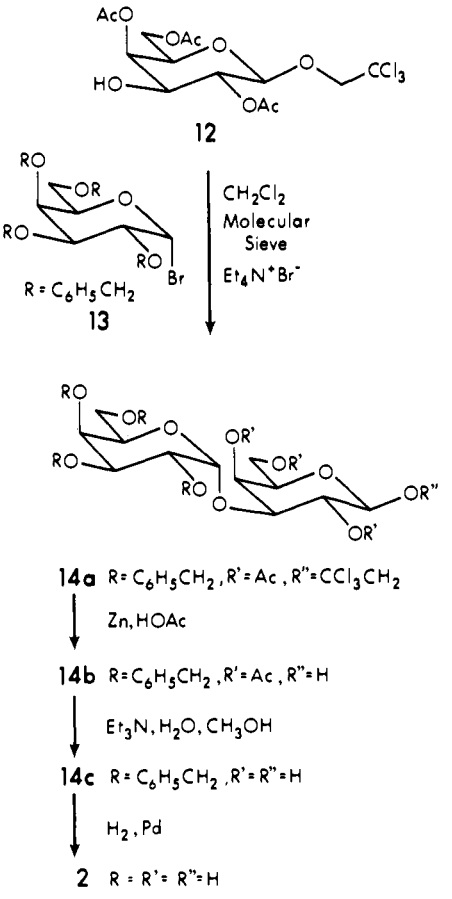
from 2,2,2-trichloroethyl β-D-galactopyranoside (**8**)[30] by way of the intermediates **9a, 9b,** and **10,** following well-known synthetic procedures,[31-33]

Condensation of **12** with tetra-*O*-benzyl-α-D-galactopyranosyl bromide (**13**)[3] in the presence of tetraethylammonium bromide and molecular sieve was examined, The reaction was too slow when pure methylene chloride was used as solvent. However, the use of methylene chloride-*N,N*-dimethylformamide (4;1 v/v) promoted the reaction to completion in 4 days at room temperature. Impure oily **14a** was obtained in 35% yield. Zinc dust reduction of **14a** provided **14b** which was deacetylated to **14c.** Hydrogenolysis of **14c** provided a product characterized as 3-*O*-(α-D-galactopyranosyl)-α,β-galactose (**2**) by direct comparison with an authentic sample (paper chromatography and ^{1}H NMR). A positive test for the 1 → 3 linkage was obtained using the periodate-Schiff test,[34]

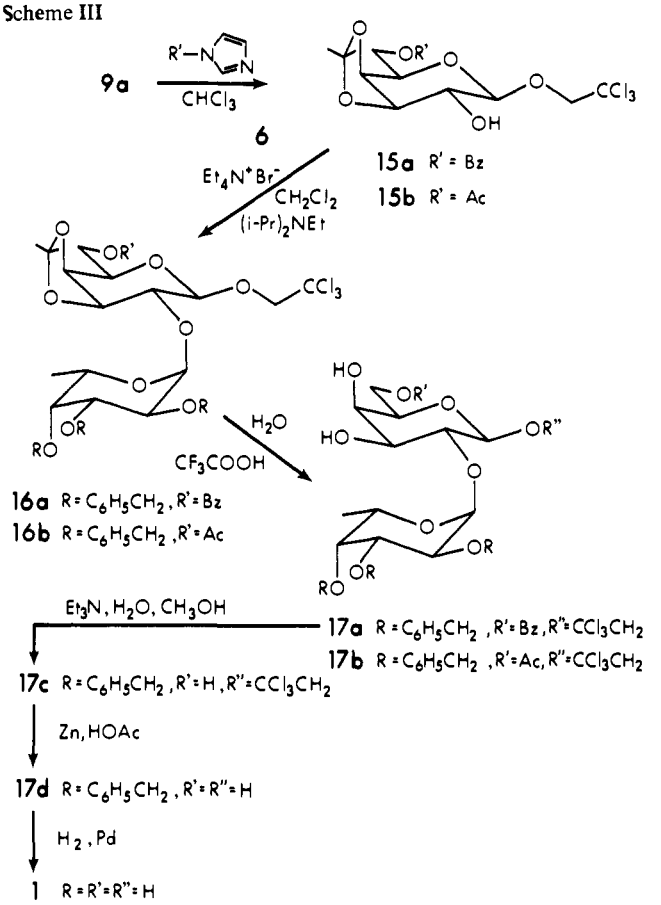
Although the overall yield of **2** from compound **8** was low, the successful preparation of **2** in a readily isolable amount augured well for the successful synthesis of **3** using a similar sequence of reaction, The plan was first to attach the fucosyl residue to form either **16a** or **16b** which could serve as starting materials for the synthesis of **3** following the same procedures as were used to prepare **2** from **9a.**

Compound **9a** was readily 6-O-acylated[35] in excellent yield, using either *N*-benzoylimidazole to form **15a** or *N*-acetylimidazole to form **15b.** α-Fucosylation of both **15a** and **15b** proceeded well, An 82% yield of **16a** was achieved, The lower yield (66%) of **16b** is probably not significant. Standard deblocking procedures applied to **16a** provided 2-*O*-(α-L-fucopyranosyl)-α,β-galactose (**1**), Thus, the utility of **16a** as an intermediate for the synthesis of **3** was established and, by inference, the like utility of **16b.**

Scheme II



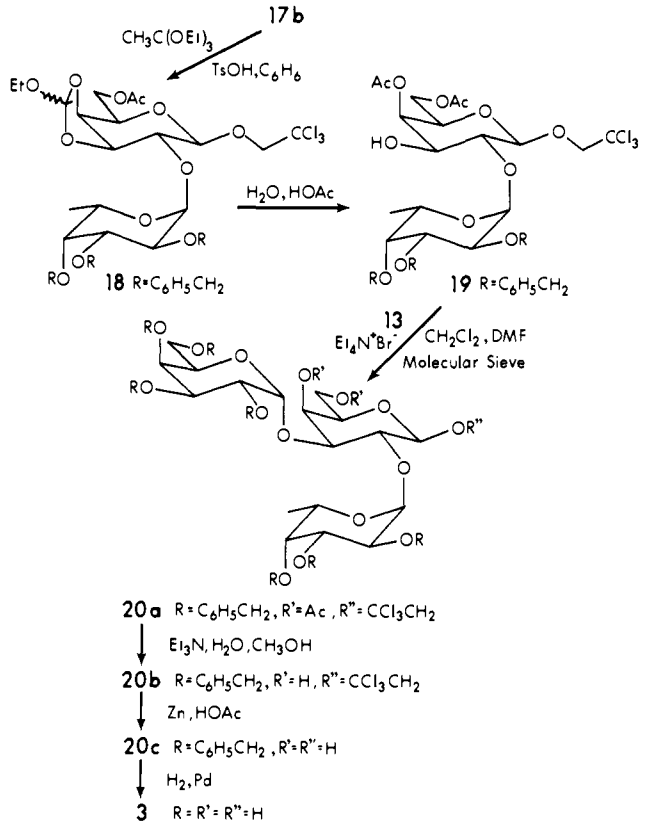
Scheme III



The original plan was to use **16a** for this purpose. Consequently, **16a** was hydrolyzed to remove the isopropylidene group to form **17a,** and this compound was converted to the 3,4-*O*-(ethyl orthoacetyl) derivative, However, attempts to hydrolyze this orthoester showed it to be surprisingly resistant to acceptable reaction conditions, and this synthetic route had to be abandoned. Examination of the analogous compound (**18**) where the 6-substituent is acetyl rather than benzoyl showed (TLC examination) **18** to be readily hydrolyzed to **19** in good yield,

In view of its proneness to acetyl group migration and/or deacetylation, no attempt was made to purify **19.** The crude **19** was reacted directly with tetra-*O*-benzyl-α-D-galactopy-

Scheme IV



ranosyl bromide (**13**) under bromide ion catalyzed conditions using molecular sieve as hydrogen bromide acceptor and methylene chloride-*N,N*-dimethylformamide (4:1 v/v) as solvent. Chromatographic separation of the reaction products provided partially deacetylated **20a** in 28% yield. This compound was deacetylated to **20b,** and this product was made pure by chromatography. The yield of **20b** from the blocked disaccharide **19** was 19%. Deblocking of **20b** by way of **20c** to form **3** proceeded in 70% yield. The product obtained from the hydrogenolysis (40 mg) appeared homogeneous on TLC and paper chromatograms and was devoid of signal in the aromatic region. The ^1H NMR spectral parameters are those reported in Table I for compound **3**. In view of the accordance of the ^1H NMR spectrum with expectations for structure **3,** the compound was not further purified.

The ^1H NMR spectra (see Table I) including relative signal intensities were in complete accord with presence of two α-glycosidic linkages, and paper chromatography required high purity. However, the mobility of the compound was substantially less ($R_{lactose}$ = 0.73) than that (1.22) reported for compound **1**,[6] We have no explanation for this discrepancy. In view of the mode of synthesis, there can be no doubt as to the point of attachment of the α-fucosyl group. As expected,[36] limited acid hydrolysis liberated fucose and a compound with the same paper chromatographic mobility as the disaccharide **2**. The possibility did exist, however, that, during the glycosidation of compound **19,** the acetyl group migrated from the 4- to the 3-position and, therefore, the galactosyl group in compound **3** is at the 4- rather than the 3-position. This problem did not appear susceptible to solution by ^{13}C NMR spectroscopy. Nevertheless, the ^{13}C NMR spectrum of **3** was measured but, owing to the limited amount of compound available and complications arising from the existence of a complex tautomeric mixture, the spectrum was not useful.

Evidence for the point of attachment of the galactosyl group in **3** was achieved by way of the periodate-Schiff spray reagent developed by Archibald and Buchanan[34] for the linkage analysis of oligosaccharides. The method depends on determining whether the alkaline degradation of an oligosaccharide yields metasaccharinic acid which is diagnostic for a 1 → 3 linkage or whether the product is isosaccharinic acid which is diagnostic for a 1 → 4 linkage. Not surprisingly, the trisaccharide **3** liberated neither of the saccharinic acids since the route to both the saccharinic acids was blocked by the 2-substituent (the fucosyl group).[37] However, as noted above, limited acid hydrolysis of **3** liberated a disaccharide which gave a strong test for the 1 → 3 linkage, Therefore, the disaccharide was compound **2,** and the trisaccharide must indeed, as expected from the mode of synthesis, have the structure assigned in formula **3**,

Table I, Proton Magnetic Resonance Spectra in Deuterium Oxide [Me_4Si–CCl_4 (1:1), external] at 31°

Compd	Chemical shifts, τ (spacing, Hz)			
	H-1	H-1'	C-6' (C-CH_3)	H-1''
1 α[a]	4.39 (3.6)	4.70 (3.2)	8.55 (6.2)	
1 β	5.11 (7.8)	4.59 (3.2)	8.57 (6.2)	
2 α	4.46 (2.6)	4.60 (3.4)		
2 β	5.11 (6.9)			
3 α[b]	4.54 (3.5)	4.80 (3.0)	8.68 (7.0)	4.70 (3.0)
3 β			8.69 (7.0)	

[a] The α/β ratio was near 3. A low intensity singlet was present in the spectrum at τ 4.45 which may arise from the presence of furanose form. [b] The signal for the β-anomeric proton was not readily detected in a broad band extending from τ 5.0 to 6.3 at 60°. Judging from the relative intensities of two superimposed doublet signals for the CH_3 group, the α/β ratio was about 3. A low intensity singlet was present at τ 4.47, similar to that observed in the spectrum for **1**.

Unequivocal evidence for the successful synthesis of the trisaccharide **3** was achieved by direct comparison with an authentic sample.[38] The compounds showed identical paper chromatographic mobilities, using either pyridine–ethyl acetate–acetic acid–water (5:5:1:3) or 1-butanol–pyridine–water (6:4:3). The colors developed by the aniline oxalate reagent were the same. Furthermore, the synthetic trisaccharide and that of natural origin showed the same, within experimental error, inhibition of the agglutination of human blood-group B erythrocytes by anti-B blood serum using standard test procedures.[39] The minimum amounts per milliliter of the trisaccharide necessary to inhibit the agglutination was about ten times less than the disaccharide **2**. Under the conditions of the test, methyl α-D-galactopyranoside showed no inhibition.[40]

The ^1H NMR spectra for compounds **1, 2,** and **3** are reported in Table I.

Table II presents the natural abundance ^{13}C NMR spectra for the disaccharides **1** and **2** and those for suitable models for the monosaccharide units. The assignments were made in the usual manner[4,41] and took into consideration the relative intensities of the signals.

Experimental Section

General, The techniques and materials used in this investigation have been described in a related publication in this issue.[4] Unless otherwise indicated, all paper chromatograms were made using Whatman No. 1 paper, developed with ethyl acetate–pyridine–water (10:4:3) and sprayed with benzidine–trichloroacetic acid mixture.[42] The column chromatograms using silicic acid were prepared from 100-mesh material supplied by Mallinckrodt Chemical Works, St. Louis, Mo. The molecular sieve was activated by heating at 150° for 12 hr just prior to use. All solvent extracts were dried over anhydrous sodium sulfate. All catalytic hydrogenations were performed at 50 psig of hydrogen for 24 hr, using a 1% solu-

Table II. ^{13}C Nuclear Magnetic Resonance Chemical Shifts in Deuterium Oxide Relative to $Me_4Si-CCl_4$ (1:1) (ppm, external)

Compd		C-1	C-2	C-3	C-4	C-5	C-6	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'
21	α	92.7	69.7	68.8	69.7	70.9	61.7						
21	β	96.9	72.3	73.3	69.2	75.6	61.7						
22								100.0	72.2	68.4	70.1	66.9	15.8
1	α	92.3	78.1[a]	68.8	69.8	70.5	61.5	101.6	72.2	68.8	69.8	67.6	15.6
1	β	96.1	79.7[a]	72.2	68.8	75.3	61.5	100.2	72.2	68.8	69.8	67.3	15.6
23[b]								99.6	69.8	69.8	68.9	72.3	61.7
2	α	92.7	67.2	74.5[a]	66.0	70.8	61.3	95.5	71.4	69.6	68.8	74.4	61.3
2	β	95.7	71.3	77.8[a]	65.3	75.3	61.2	96.7	69.6	69.6	68.6	71.3	61.3

[a] Intersugar aglyconic carbon. [b] For methyl α-D-galactopyranoside, the assignments were C-1, 100.7; C-2, 70.8; C-3, 71.1; C-4, 69.8; C-5, 72.1; C-6, 62.7 [A. S. Perlin, B. Casu, and H. J. Koch, *Can. J. Chem.*, **48**, 2596 (1970)]. [c] **1**α: 2-*O*-(α-L-Fucopyranosyl)-α-D-galactopyranose. **1**β: 2-*O*-(α-L-Fucopyranosyl)-β-D-galactopyranose. **2**α: 3-*O*-(α-D-Galactopyranosyl)-α-D-galactopyranose. **2**β: 3-*O*-(α-D-Galactopyranosyl)-β-D-galactopyranose. **21**α: α-D-Galactopyranose. **21**β: β-D-Galactopyranose. **22**: Methyl α-L-fucopyranoside; OCH_3, 55.6. **23**: 2,2,2-Trichloroethyl α-D-galactopyranoside, CCl_3, 96.5; CH_2, 79.6.

tion of the compound in 95% ethanol and a weight of the 5% palladium on powdered charcoal catalyst (Matheson Coleman and Bell, East Rutherford, N.J.) equal to the weight of the compound. All de-O-acetylations employed triethylamine in aqueous methanol. After solvent removal, the residue was dissolved in either water or methanol for deionization and the resulting solution either freeze-dried or evaporated to dryness in vacuo. Unless otherwise stated, the ^1H NMR spectra were measured in $CDCl_3$.

1,2-*O*-(Ethyl orthoacetyl)-3,4,6-tri-*O*-acetyl-α-D-galactopyranose (4). This compound was prepared[8] in near quantitative yield as a yellowish oil from tetra-*O*-acetyl-α-D-galactopyranosyl bromide[43] following the directions reported by Lemieux and Morgan[9] for the preparation of the gluco isomer. The ^1H NMR spectrum required the assigned structure with an about 7:3 ratio for the exo and endo isomers.[8] Exo isomer: τ 4.20 (d, 5 Hz, 1, H-1), 4.58 (q, 2.5 and 3.5 Hz, 1, H-4), 4.94 (q, 3.5 and 6.5 Hz, 1, H-3), 7.88 (s, 3, 1 acetyl), 7.95 (s, 6, 2 acetyl), 8.32 (s, 3, orthoacetyl methyl).

1,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranose (5). The crude orthoester (**4**) (4.5 g) was dissolved in 95% aqueous acetic acid (15 ml). The optical rotation of the solution was constant after 15 min at room temperature, and the solvent was removed at room temperature, using a high vacuum pump and rotary evaporator. The resulting colorless syrup was dissolved in ether. Addition of *n*-hexane caused crystallization to provide 3.6 g (86% yield) of white crystalline product, mp 145–149°. Recrystallization from the same solvent raised the melting point to 148–150°, $[\alpha]^{25}D$ +142° (*c* 1, chloroform); lit.[44] mp 151°, $[\alpha]^{18}D$ + 142.7° (*c* 2.5, chloroform).

The ^1H NMR spectrum: τ 3.67 (d, 4.0 Hz, 1, H-1), 4.50 (q, 1.5 and 3.5 Hz, 1, H-4), 4.80 (q, 3.5 and 10.5 Hz, 1, H-3), 5.95 (q, 4.0 and 10.5 Hz, 1, overlapped signal, H-2), 7.82, 7.85, 7.94, and 7.96 (each s, 3, acetyl).

1,3,4,6-Tetra-*O*-acetyl-2-*O*-(tri-*O*-benzyl-α-L-fucopyranosyl)-α-D-galactopyranose (7a). The tetraacetate **5** (1.045 g, 3 mmol) was dissolved in purified[45] methylene chloride (20 ml) which contained tetraethylammonium bromide (1.26 g, 6 mmol) and molecular sieve (3.5 g). Tri-*O*-benzyl-α-L-fucopyranosyl bromide (**6**) (about 6 mmol[25] freshly prepared from 3.5 g of tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-α,β-L-fucopyranose) was added, and the mixture was stirred at room temperature for 4 days. The solids were removed by filtration through a bed of Celite, and the filtrate was washed twice with water (50 ml) while back-extracting each aqueous wash with methylene chloride using three separatory funnels. The combined methylene chloride extracts were dried and evaporated to dryness. The residue was chromatographed on silicic acid column (60 × 2.3 cm), using diethyl ether–*n*-hexane (3:1). Solvent removal from the main band (homogeneous on TLC) provided 1.91 g (83%) of material which was crystallized from ether to yield 1.26 g of crystalline material, mp 55–58°, $[\alpha]^{20}D$ +10.1° (*c* 1, chloroform). The ^1H NMR spectrum was in agreement with that expected for **7a**, in particular, τ 3.78 (d, 3.5 Hz, 1, H-1'), and 8.94 (d, 6 Hz, 3, CCH_3). One of the four acetyl group signals was shifted to τ 8.34 with the other three at τ 7.94, 7.98, and 8.06.

Anal. Calcd for $C_{41}H_{48}O_{14}$: C, 64.38; H, 6.32. Found: C, 64.61; H, 6.49.

1,3,4,6-Tetra-*O*-acetyl-2-*O*-(α-L-fucopyranosyl)-α-D-galactose (7b). Compound **7a** (1.50 g) was hydrogenolyzed. Catalyst and solvent removal provided a quantitative yield (900 mg) of chromatographically homogeneous material which crystallized from absolute ethanol (440 mg, 45% yield), mp 100–101°, $[\alpha]D$ +11.8° (*c* 1, water). The ^1H NMR spectrum was devoid of signal for aromatic protons and in accord with that expected for **7b**.

2-*O*-(α-L-Fucopyranosyl)-α,β-galactose (1). Compound **7b** (380 mg) was dissolved in a triethylamine–water–methanol (1:4:11) mixture (32 ml) and the solution left at room temperature for 16 hr. The syrupy product, $[\alpha]^{20}D$ −53.1° (*c* 1,2, water) (lit.[23] −57°), possessed ^1H NMR and ^{13}C NMR spectra in accordance with structure **1** (see Table I). Paper chromatography using ethyl acetate–pyridine–water (10:4:3) showed $R_{lactose}$ = 1.56, in good agreement with the reported value[15] 1.58. ^1H NMR parameters are reported in Table I and the natural abundance ^{13}C NMR in Table II.

2,2,2-Trichloroethyl 3,4-*O*-Isopropylidene-β-D-galactopyranoside (9a). 2,2,2-Trichloroethyl β-D-galactopyranoside,[22] mp 151–152°, $[\alpha]D$ −17.0° (*c* 1, water) (13.5 g, 43.5 mmol), 2,2-dimethoxypropane (10.8 g, 102 mmol) and *p*-toluenesulfonic acid monohydrate (120 mg) were dissolved in dry *N,N*-dimethylformamide (120 ml), and the solution was heated at 80° for 30 min. The solution was cooled, and triethylamine (3 ml) was added. The solution was evaporated in vacuo, and residual syrup was taken up in methylene chloride. After washing with aqueous sodium bicarbonate followed by water, the methylene chloride solution was dried. Evaporation left a crystalline solid which was recrystallized from acetone, mp 150°, $[\alpha]^{25}D$ +2.9° (*c* 1, water). Chromatographic purification of the material present in the mother liquor, using ethyl acetate–*n*-pentane (2:1) and a silicic acid column (80 × 3.5 cm) provided an additional 4.6 g of product, mp 147–150° (79% total yield).

Anal. Calcd for $C_{11}H_{17}Cl_3O_6$: C, 37.57; H, 4.87; Cl, 30.24. Found: C, 37.79; H, 5.06; Cl, 30.29.

The ^1H NMR spectrum was in accord with that expected for **9a**.

2,2,2-Trichloroethyl 2,6-Di-*O*-acetyl-3,4-*O*-isopropylidene-β-D-galactopyranoside (9b). Compound **9a** (6.00 g) was dissolved in acetic anhydride (10 ml) and pyridine (20 ml), and the solution was left for 16 hr at room temperature. Standard δ work-up provided a quantitative yield of essentially pure **9b** (TLC). Recrystallization from diethyl ether–*n*-hexane gave product, mp 97–98°, $[\alpha]^{25}D$ +9.3° (*c* 1, chloroform).

Anal. Calcd for $C_{15}H_{21}O_8Cl_3$: C, 41.34; H, 4.85; Cl, 24.41. Found: C, 41.11; H, 5.04; Cl, 24.15.

The ^1H NMR spectrum agreed with the structural assignment.

2,2,2-Trichloroethyl 2,4,6-Tri-*O*-acetyl-β-D-galactopyranoside (12). Compound **9b** (6.00 g) was dissolved in 90% trifluoroacetic acid[32] (30 ml) and the solution kept at room temperature for 10 min. The solution was efficiently taken to dryness in vacuo and the residue dried overnight in vacuo. The ^1H NMR spectrum agreed with structure **10** for this product which was not further characterized.

The product **10** was added to a mixture of dry benzene (40 ml), triethyl orthoacetate (35 ml), and *p*-tolunesulfonic acid monohydrate (10 mg). Reaction was complete (TLC) after stirring for 1 hr at room temperature. Triethylamine (2 ml) was added, and the solution was poured into ice–water. Extraction with diethyl ether in the usual manner provided a syrupy product (**11**) which contained triethyl orthoacetate (^1H NMR), and which was not further characterized.

The crude **11** was dissolved in 80% aqueous acetic acid (100 ml), and the solution was kept at room temperature for 10 min. The solution was then taken to dryness in vacuo. A crystalline product

was obtained in quantitative yield (6.12 g) which appeared about 90% pure on tlc examination, using ethyl acetate–*n*-pentane (2:1). Purification by recrystallization first from isopropyl alcohol–water and then ethyl acetate–*n*-hexane provided pure **12**, mp 137–138°, $[\alpha]^{25}D$ −19.2° (*c* 1, chloroform).

Anal. Calcd for $C_{14}H_{19}O_9Cl_3$: C, 38.42; H, 4.37; Cl, 24.32. Found: C, 38.54; H, 4.26; Cl, 24.26.

The ^1H NMR spectrum: τ 4.63 (q, 1.2 and 3.5 Hz, 1, H-4), 4.89 (q, 8.0 and 10.0 Hz, 1, H-2), 5.24 (d, 8.0 Hz, 1, H-1), 5.87 (t, 5.5 Hz, 2, H-6 and H-6′), 6.12 (q, either 1.2 or 3.5 and 10 Hz, 1, H-3 superimposed on H-5), 6.12 (m, 1, H-5), 7.81, 7.87, 7.92 (each s, 3, acetyl), doublet of doublets, 12 Hz, centered at τ 5.59 and 5.86, CCl_3CH_2.

2,2,2-Trichloroethyl 2,4,6-Tri-*O*-acetyl-3-*O*-(tetra-*O*-benzyl-α-D-galactopyranosyl)-β-D-galactopyranoside (14a). Compound **12** (1.06 g, 2.42 mmol) was dissolved in methylene chloride (16 ml) and *N,N*-dimethylformamide (4 ml), containing tetraethylammonium bromide (1.1 g, 5 mmol) and molecular sieve (2.5 g). Tetra-*O*-benzyl-α-D-galactopyranosyl bromide (**13**),[3] freshly prepared from 5 mmol of tetra-*O*-benzyl-1-*p*-nitrobenzoyl-β-D-galactopyranose (3.44 g), was then added, and the solution was stirred for 4 days at room temperature. Work-up described for **7a** gave an oily product which was applied to a silicic acid column (60 × 2.3 cm) for chromatography, using diethyl ether–*n*-hexane. The main fraction (established by TLC) on evaporation gave 800 mg (35% yield) of an oil, $[\alpha]^{20}D$ +42.8° (*c* 1.1, chloroform). The ^1H NMR indicated the compound to be substantially impure. The assigned structure (**14a**) is based on the characterization of the derivative **2**.

3-*O*-(α-D-Galactopyranosyl)-D-galactose (2). The above-described crude **14a** (530 mg, 0.55 mmol) was reduced with zinc dust (530 mg) in glacial acetic acid (2 ml) within 3 hr (TLC, using diethyl ether–hexane 2:1). The solution was filtered, and the filtrate was poured into ice-cold saturated aqueous sodium bicarbonate solution (20 ml). The resulting mixture was extracted thoroughly with methylene chloride (40 ml). Solvent removal in vacuo and purification by thick (0.7 mm) layer chromatography on silica gel PF 254[46] plates (20 × 20 cm) using diethyl ether–hexane 2:1 provided 210 mg (45% yield) of product homogeneous by TLC. This compound, expected to be **14b**, was not characterized. De-O-acetylation gave compound **14c** which was subjected to hydrogenolysis of the benzyl groups. A compound (70 mg, 52% yield from **14a**) was obtained which was identical (^1H NMR, see Table I) and paper chromatography led to an authentic sample[4] of **2**. A further proof of structure was achieved by the use of the procedure for linkage analysis reported by Archibald and Buchanan.[34] Following their directions, compound **2** (1.0 mg) was dissolved in 1 *N* sodium hydroxide (0.1 ml) and heated for 3 hr at 100°. After being cooled, the solution was passed through a column containing Dowex-50 (NH_4^+) resin (1 ml) which was then washed with water (5 ml). The eluate was evaporated to dryness in vacuo, dissolved in water, and applied to paper for chromatography, using *n*-propyl alcohol–water–concentrated ammonia (7:2:1) as solvent. On spraying the chromatogram with the periodate and Schiff reagents,[47] a purple-blue spot diagnostic for metasaccharinic acid appeared within 5 min.

2,2,2-Trichloroethyl 6-*O*-Benzyl-3,4-*O*-isopropylidene-β-D-galactopyranoside (15a). Imidazole (1.55 g, 22 mmol) was dissolved in purified chloroform (20 ml), the solution was cooled in ice–water, and benzoyl chloride (1.6 g, 11 mmol) was added slowly with stirring. The precipitated imidazole hydrochloride was removed by filtration and 2,2,2-trichloroethyl 3,4-*O*-isopropylidene-β-D-galactopyranoside (**9a**) (4 g, 11 mmol), dissolved in chloroform (40 ml), was added to the filtrate. The solution was heated under reflux for 2 days. The cooled solution was poured into ice-cold saturated aqueous sodium bicarbonate solution (50 ml) and the chloroform layer washed with saturated aqueous sodium chloride solution. The two aqueous solutions were successively extracted with methylene chloride. The combined organic phases were dried and evaporated to dryness. The syrupy product, 5.2 g, was applied to a silicic acid column (60 × 2.3 cm) for chromatography using ethyl acetate–*n*-hexane (1:2) as developing phase.

The first fraction (160 mg, 2.5% yield), after recrystallization from ether, mp 127°, $[\alpha]^{25}D$ +10.5° (*c* 1, chloroform), was characterized by ^1H NMR and analysis as 2,2,2-trichloroethyl 2,6-di-*O*-benzoyl-3,4-*O*-isopropylidene-β-D-galactopyranoside.

The second and main fraction to elute from the column was virtually pure ^1H NMR syrupy **15a** (4.2 g, 81% yield), $[\alpha]^{25}D$ +11.5° (*c* 1, chloroform) which resisted crystallization.

Anal. Calcd for $C_{18}H_{21}O_7Cl_3$: C, 47.44; H, 4.64; Cl, 23.33. Found: C, 47.39; H, 4.56; Cl, 23.39.

The ^1H NMR spectrum: τ 1.84–2.00 (m, 2, aromatic), 2.30–2.80 (m, 3, aromatic), 5.36 (d, 6.0 Hz, 1, H-1), 5.40–6.40 (m, 8), 7.34 (m, 1, hydroxyl), 8.40 (s, 3, isopropyl), 8.60 (s, 3, isopropyl).

2,2,2-Trichloroethyl 6-*O*-Acetyl-3,4-*O*-isopropylidene-β-D-galactopyranoside (15b). Starting with compound **9a** (1.36 g, 3.88 mmol) and using the same procedure as described above for the preparation of **15a** except that acetyl chloride (310 mg, 4 mmol) was used instead of benzoyl chloride, syrupy product (1.6 g) was obtained which was applied to a silicic acid column (60 × 2.3 cm) for chromatography using diethyl ether–benzene (2:1) as developing phase. The first fraction gave 240 mg (7% yield) of the 2,6-di-*O*-acetyl derivative of **9a** as was evident from the ^1H NMR.

The second and main fraction provided 2.20 g (73% yield) of a syrupy substance, $[\alpha]^{25}D$ +12.7° (*c* 1.02, chloroform) which resisted crystallization.

Anal. Calcd for $C_{13}H_{19}O_7Cl_3$: C, 39.66; H, 4.86; Cl, 27.02. Found: C, 39.56; H, 4.89; Cl, 26.76.

The ^1H NMR spectrum was in accord with the structure assigned to **15b**; τ 5.40–6.50 (m, 9), 6.90 (m, 1, hydroxyl), 7.88 (s, 3, acetyl), 8.46 (s, 3, isopropyl), 8.62 (s, 3, isopropyl).

2,2,2-Trichloroethyl 6-*O*-Benzoyl-2-*O*-(tri-*O*-benzyl-α-fucopyranosyl)-3,4-*O*-isopropylidene-β-D-galactopyranoside (16a). Bromide ion catalyzed condensation of **15a** (650 mg, 1.4 mmol) with the fucosyl bromide **6** (about 2 mmol) under the same conditions as described above for the preparation of **7a** provided an oily product (1.5 g) which was applied to a silicic acid column (54 × 2 cm) using ethyl acetate–hexane (1:2) as developing phase. The major band found in the effluent contained 1.00 g of the expected compound **16a** (82% yield), $[\alpha]^{25}D$ −38.0° (*c* 1, chloroform). The ^1H NMR spectrum: τ 1.76–2.10 (m, 2, aromatic), 2.3–3.0 (m, 18, aromatic) 4.46 (d, 3 Hz, 1, H-1′), 4.80–6.60 (m, 19), 8.47 (s, 3, isopropyl), 8.63 (s, 3, isopropyl), 8.89 (d, 6 Hz, 3, methyl).

Anal. Calcd for $C_{45}H_{49}O_{11}Cl_3$: C, 61.96; H, 5.66, Cl, 12.18. Found; C, 62.16; H, 5.88; Cl, 12.17.

2,2,2-Trichloroethyl 6-*O*-Acetyl-2-*O*-(tri-*O*-benzyl-α-L-fucopyranosyl)-3,4-*O*-isopropylidene-β-D-galactopyranoside (16b). Bromide ion catalyzed condensation of **15b** (2.18 g, 5.56 mmol) with fucosyl bromide **6** (about 11 mmol). Chromatography as described above for the purification of **16a** provided 3.0 g (66% yield) of oily compound **16b**, $[\alpha]^{25}D$ −47.3° (*c* 1, chloroform). The ^1H NMR spectrum was consistent with the proposed structure: τ 2.40–3.10 (m, 15, aromatic), 4.53 (d, 3 Hz, 1, H-1′), 4.90–6.60 (m, 19), 8.03 (s, 3, acetyl), 8.59 (s, 3, isopropyl), 8.75 (s, 3, isopropyl), 8.99 (d, 6 Hz, 3, methyl).

2-*O*-(α-L-Fucopyranosyl)-α,β-galactopyranose (1). A solution of either compound **16a** (195 mg, 0.22 mmol) or compound **16b** (405 mg, 0.5 mmol) in 80% aqueous trifluoroacetic acid (5 or 10 ml) was kept at room temperature for 30 min. The solvent was removed in vacuo to leave a product which was applied to a silicic acid column (54 × 2 cm) using diethyl ether–hexane (4:1) as developing phase. Compounds **17a** and **17b** were obtained in 65 and 66% yield, respectively. The ^1H NMR spectra were devoid of signal for isopropylidene protons. De-O-benzoylation of **17a** using a catalytic amount of sodium methoxide in methanol and de-O-acetylation of **17b** using triethylamine in aqueous methanol provided the same product (TLC and ^1H NMR), namely, **17c** in 90 and 92% yields, respectively, with $[\alpha]^{25}D$ −67.6° (*c* 0.83, chloroform) for the product derived from **17b**. The ^1H NMR spectrum was in general accord with that expected for the compound **17c**.

Compound **17c** (200 mg, 0.27 mmol) was stirred at room temperature with glacial acetic acid (2 ml), zinc dust (200 mg), and sodium acetate (200 mg) for 3 hr, at which time the reaction appeared complete (TLC using ethyl acetate). The solution was filtered free of solid, and the filtrate was poured into ice-cold saturated aqueous sodium bicarbonate solution. The resulting mixture was extracted thoroughly with ethyl acetate. Solvent removal in vacuo left 150 mg (92% yield) of product **17d** which appeared pure on TLC examination (ethyl acetate) and was used without further characterization.

Hydrogenolysis of the crude **17d** under standard method gave 80 mg (almost quantitative yield) of compound which was identical (^1H NMR and paper chromatography) with **1** prepared from **7a**.

2,2,2-Trichloroethyl 4,6-Di-*O*-acetyl-2-*O*-(tri-*O*-benzyl-α-L-fucopyranosyl)-β-D-galactopyranoside (19), Compound **17b** (920 mg, 1.2 mmol) was added to a stirred solution of triethyl orthoacetate (4 ml) and *p*-toluenesulfonic acid (1 mg) in benzene (16 ml). After stirring for 2 hr at room temperature, reaction appeared complete as evidenced by TLC using diethyl ether–hexane (4:1). Triethylamine (0.4 ml) was added. The resulting solution was washed with 100 ml of water while back-extracting the aqueous layer with methylene chloride (200 ml). The organic phases were combined and evaporated in vacuo to a foamy residue (**18**) which was treated with 80% aqueous acidic acid (40 ml) for 1 hr at room temperature, after which time the TLC using diethyl ether–hexane (4:1) showed no evidence for **18**. The solution was evaporated in vacuo, methylene chloride (200 ml) was added, and the resulting solution was washed with ice–water (80 ml) while back-extracting with methylene chloride (200 ml). Evaporation left an oily compound (**19**) (960 mg), quantitative yield, which appeared pure on TLC. The ^{1}H NMR spectrum was consistent with that expected for the title compound **19**, especially two singlets at τ 7.92 and 7.98 for the two acetyl groups.

2,2,2-Trichloroethyl 2-*O*-(Tri-*O*-benzyl-α-L-fucopyranosyl)-3-*O*-(tetra-*O*-benzyl-α-D-galactopyranosyl)-β-D-galactopyranoside (20b), The above crude product **19** (640 mg, 0.8 mmol) was dissolved in a mixture of methylene chloride (10 ml) and *N,N*-dimethylformamide (2.5 ml) which contained tetraethylammonium bromide (430 mg, 2.0 ml) and molecular sieve (2.00 g). Tetra-*O*-benzyl-α-D-galactopyranosyl bromide (about 4 mmol) (freshly prepared from 4 mmol of 1-*O*-*p*-nitrobenzoyl-2,3,4,6-tetra-*O*-benzyl-α,β-D-galactopyranose) was added, and the solution was kept at room temperature for 4 days. The solution was freed of a precipitate by filtration through Celite and washed twice with cold water (25 ml) while back-extracting the aqueous layers with methylene chloride (50 ml). The combined methylene chloride extracts were evaporated in vacuo. The syrupy residue was applied to a silicic acid column (80 × 3.5 cm), and the chromatogram was developed with diethyl ether–hexane (1:3). A compound (300 mg, 28% yield) which eluted from the column had a ^{1}H NMR spectrum consistent with that expected for **20a** except that the intensities for the two singlet signals due to acetyl protons were not equal.

De-O-acetylation of the above crude compound followed by purification on silicic acid column (54 × 2 cm) using diethyl ether–hexane (4:1) gave an analytically pure compound **20b** (150 mg, 19% yield from **19**, $[\alpha]^{25}$D −14.0° (*c* 0.25, chloroform). The ^{1}H NMR spectrum was consistent with the assigned structure.

Anal. Calcd for $C_{69}H_{75}O_{15}Cl_3$: C, 66.26; H, 6.04; Cl, 8.50. Found: C, 65.98, H, 6.20; Cl, 8.63.

2-*O*-(α-L-Fucopyranosyl)-3-*O*-(α-D-galactopyranosyl)-α,β-D-galactose (3), Zinc dust reduction of **20b** (140 mg, 0.11 mmol) under the conditions used for the conversion of **14a** to **14b** provided a compound which was purified by thick (0.7 mm) layer chromatography as described for **14b** using ethyl acetate–benzene (2:1) as eluent. The product (90 mg, 70% yield) expected to be **20c** was not characterized except by hydrogenolysis to **3**, Using 30 mg for the hydrogenolysis, 14 mg of compound **3** was obtained. Paper chromatography ($R_{lactose}$ = 0.73) and ^{1}H NMR (see Table I) indicated a high state of purity and the material, $[\alpha]^{24}$D +35.2° (*c* 1.1, water), was not further purified.

Acid hydrolysis of **3** (1 mg) under the conditions prescribed by Kabat, Baer, Bezer, and Knaub[36] liberated fucose and a compound with the same chromatographic mobility as compound **2**,

The solution from the acid hydrolysis was passed through a column of Amberlite IRA resin (2 ml) (Mallinkrodt) in the carbonate form. The resin was washed with water (5 ml), and the combined neutral eluate was evaporated in vacuo to dryness. The residue was submitted to the alkaline degradation-periodate-Schiff linkage test.[34] A control experiment using compound **2** was performed. Both preparations provided the expected purple-blue spot within 5 min and possessed the same R_f value.

Under the conditions of the linkage test, galactose gives a positive test for metasaccharinic acid, but the weak coloration developed very slowly (about 15 min). Fucose provides a positive test, but the R_f value of the product from the alkaline degradation is greater than that of metasaccharinic acid, and the spot develops much more slowly (about 30 min).

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