The Chemical Synthesis of 2-Acetamido-2-deoxy-4-*O*-(α-L-fucopyranosyl)-3-*O*-(β-D-galactopyranosyl)-D-glucose. The Lewis a Blood-Group Antigenic Determinant[1]

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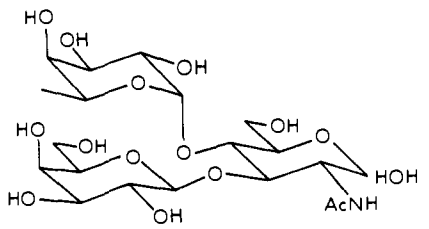
Abstract: Bromide ion catalyzed reaction of tri-*O*-benzyl-L-fucopyranosyl bromide with 2,2,2-trichloroethyl 2-acetamido-6-*O*-acetyl-3-*O*-(tetra-*O*-acetyl-β-D-galactopyranosyl)-2-deoxy-β-D-glucopyranose (**11**) provided the 4-*O*-(tri-*O*-benzyl-α-L-fucopyranosyl) derivative **13a** in 80% yield. Deacetylation, followed by zinc reduction to replace the 2,2,2-trichloroethyl group and then catalytic hydrogenolysis of the benzyl groups, provided the title compound **1.** Preparations of 2-acetamido-2-deoxy-3-*O*-(β-D-galactopyranosyl)-D-glucose (**10**) and 2-acetamido-2-deoxy-6-*O*-(α-L-fucopyranosyl)-3-*O*-(β-D-galactopyranosyl)-D-glucose (**15**) are also reported. ^{13}C NMR spectra are recorded and assigned.

Rege, Painter, Watkins, and Morgan[3] in 1964 presented a proof of structure for the trisaccharide **1** which had earlier been isolated by Dr. J. Thomas (see ref 3) by alkaline degradation of Lewis a (Le^a) substance, and which was serologically active in the Le^a system. The trisaccharide **1** liberated, on acid hydrolysis, the disaccharide 2-acetamido-2-deoxy-3-*O*-(β-D-galactopyranosyl)-D-glucose (**10**) which bears the trivial name lacto-*N*-biose-I,[4] and which was first isolated by degradation of oligosaccharides obtained from human milk[4,5] and later by way of controlled acid hydrolysis of blood group A substance.[6-8] The disaccharide **10** was synthesized by Flowers and Jeanloz.[9]

Methods for the establishment of glycopyranosidic linkages under stereochemical control and applicable to conditions for oligosaccharide synthesis have received extensive investigation in this laboratory.[10-13] This subject has also been pursued in many other laboratories primarily for the provision of oligosaccharide units of interest to antibiotics, antigenic determinants, and enzyme substrates. Our success in recent years in the development of methods for the synthesis of α-linked disaccharide units has made plausible effort directed at the synthesis of oligosaccharides related to the blood-group substances.[14,15] Such efforts are considered of importance for a number of reasons which can be illustrated through consideration of **1.**

The structure of **1** was first postulated[16] on the basis of enzyme specificity requirements. The chemical proof provided by Rege and coworkers[3] was achieved with 10 mg of difficultly available material. This paucity of material for study applies to all oligosaccharide building units of the blood-group substances, and many interesting structures have not yet been obtained from natural sources. Therefore, successful syntheses of such oligosaccharides can be expected to be of importance in better delineating the conformational properties and serological specificities of these antigenic determining structures. An accompanying paper in this issue[17] shows that such structures can be synthesized appropriate for attachment to a high molecular weight matrix and thereby provide antigens for specific antibody production. Thus, the way is now considered clear for detailed investigation of structure–activity relationships through the synthesis of immunogens, and therefore the research presently in progress in this laboratory is primarily concerned with the synthesis of oligosaccharides glycosidically linked to an aglycon which is so functionalized that the structure can be readily attached to polymeric material. However, it was considered important in the first instance to synthesize the reducing oligosaccharide structures for direct comparison with the substance of natural origin.

This communication reports the first chemical syntheses of the trisaccharides **1** and **15.** An accompanying paper in



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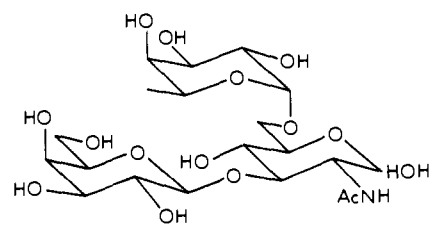

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this issue[18] describes the synthesis of 2-*O*-(α-L-fucopyranosyl)-3-*O*-(α-D-galactopyranosyl)-D-galactose which is considered to be an important component of the blood-group B specific determinant. These accomplishments represent the first reports of syntheses of such complex trisaccharide structures under controlled conditions.

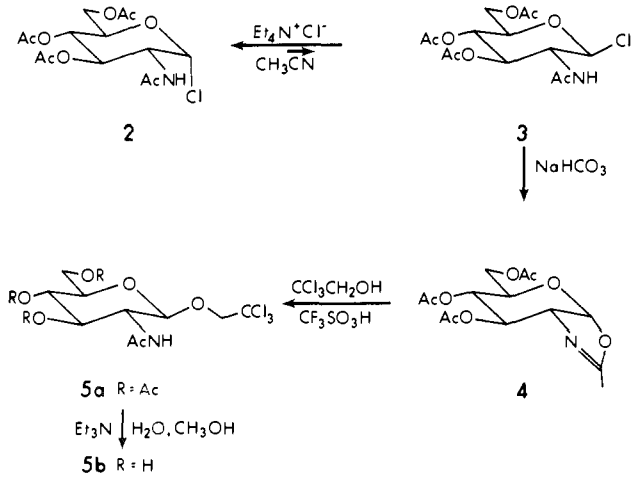
Considering the lability of the α-L-fucopyranosyl group of **1** to acid hydrolysis[19] and the proneness of the β-D-galactopyranosyl group of **1** to elimination in alkaline media[5] (compound **1** is extensively degraded at pH 8.9 at room temperature within 12 hr), special strategies had to be developed for the synthesis of **1** and related structures.

Lemieux and Vycudilik[20] studied the preparation of 2,2,2-trichloroethyl hexopyranosides by reaction of penta-*O*-acetyl derivatives of hexopyranoses with 2,2,2-trichloroethanol in the presence of Lewis acids in anticipation that the aglycon could be readily removed by zinc reduction following the many applications for this blocking–deblocking technique for carboxyl acids.[21] Indeed, zinc dust reduction in acetic acid of 2,2,2-trichloroethyl glycosides proceeds readily to provide the glycose in excellent yield, and the preparation of **5** was the first stage of this investigation.

The choice of the 2,2,2-trichloroethyl group rather than benzyl, as was used by Flowers and Jeanloz[9] to synthesize the disaccharide **10**, was made as a result of the consideration that the 2,2,2-trichloroethyl group could be removed under conditions which do not affect *O*-benzyl groups as are present, for example, in the intermediate derivative **13c** of **1**. Thus, consideration could be given to the use of **13c** for the building of a higher oligosaccharide.

2,2,2-Trichloroethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside (**5a**) was prepared by reaction of the oxazoline **4** with 2,2,2-trichloroethanol (Scheme I) in

Scheme I

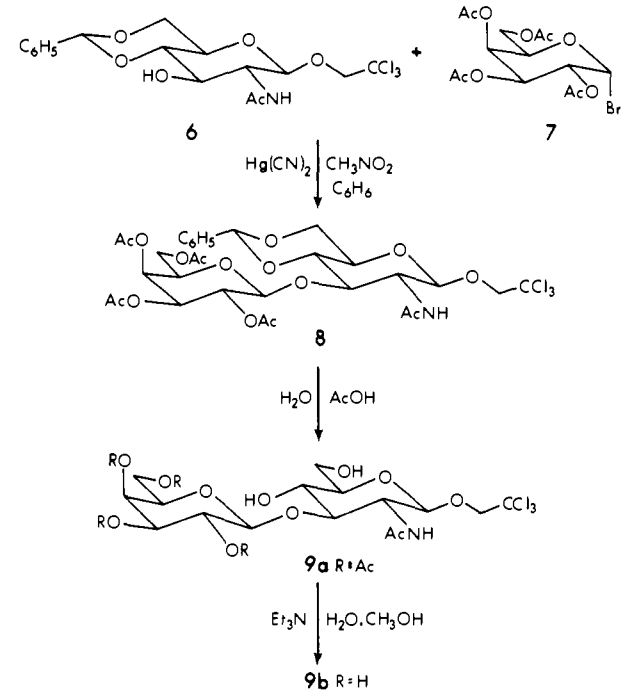


the presence of trifluoromethanesulfonic acid following the general procedure of Zurabyan and coworkers.[22] In our hands, the use of trifluoromethanesulfonic acid gave superior yields (nearly double) to catalysis by *p*-toluenesulfonic acid. The preparation of the oxazoline **4** was also modified. Khorlin and coworkers[23] synthesized **4** from 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride (**2**) by first replacing the chloride by nitrate with inversion of the anomeric center so as to render facile participation of the acetamido group in reaction at the anomeric center using acetone as solvent and *sym*-collidine as base. A 51% yield of **4** was achieved after chromatography. It was apparent, however, that **2** could be converted directly to the oxazoline by employing chloride ion catalysis.[24] Thus, **2** would enter into equilibrium with its β anomer (**3**) and, in the presence of a base, the oxazoline should form. Using tetraethylammonium chloride as catalyst, acetonitrile as solvent, and sodium bicarbonate as base, the reaction provided the oxazoline in near quantitative yield (^{1}H NMR) in a state of high purity through work-up by extraction only. The compound was employed directly in the reaction with 2,2,2-trichloroethanol to form **5a.**

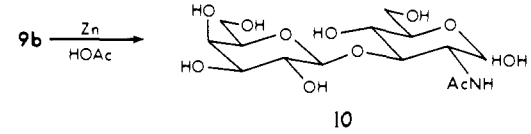
Compound **5a** was deacetylated, and the product (**5b**) was converted to 2,2,2-trichloroethyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranose (**6**) by reaction with benzaldehyde in the presence of zinc chloride[25] but using a modified work-up procedure. Reaction of **6** with 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**7**) following the procedure of Flowers and Jeanloz[9] gave the β-linked product **8** in excellent yield (Scheme II). The compound possessed the expected proton magnetic resonance spectrum and was converted to crystalline trichloroethyl 2-acetamido-2-deoxy-3-*O*-(β-D-galactopyranosyl)-D-glucopyranoside (**9b**) by first acid hydrolysis to remove the benzylidene group to provide **9a,** and then deacetylation using triethylamine in aqueous methanol. Zinc dust reduction of **9b** provided the well-known disaccharide **10** (Scheme III).

The ^{13}C NMR spectra of **9b** and mutarotated **10** are reported in Table I. The signal assignments essentially fol-

Scheme II



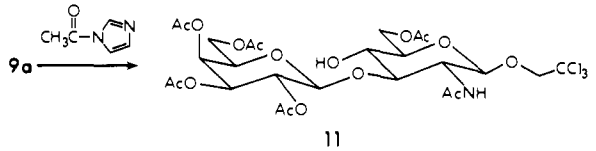
Scheme III



lowed the procedures established by Dorman and Roberts.[26] The first stage of the assignment involved the attribution of signals considered to arise from the β-D-galactopyranosyl group. This was accomplished, as seen in Table I, by comparison with the ^{13}C NMR spectrum for 2,2,2-trichloroethyl β-D-galactopyranoside (**16**). Having made these assignments, the remaining signals were compared with the spectrum for 2,2,2-trichloroethyl 2-acetamido-2-deoxy-β-D-glucopyranoside (**5b**) in the case of compound **9b** and with the spectrum for mutarotated 2-acetamido-2-deoxy-D-glucopyranose (**17**) in the case of the disaccharide **10.** It is readily seen from the content of Table I that good correlation was achieved, and the data serve as further illustration of the value of this relatively new procedure for the confirmation of the structure of an oligosaccharide. The application will be further illustrated by way of the content of Table II, and discussion of the ^{1}H NMR spectra of compounds **9b** and **10** is reserved for consideration along with the ^{1}H NMR spectra of the trisaccharides **1** and **15** (see Table III).

Halide ion catalysis for α-glycopyranoside formation[12] was employed to establish the α-linked L-fucopyranosyl group in the trisaccharides **1** and **15.** To synthesize **1** from **9a,** it was necessary, in the first step, to block the 6-position of the glucosamine residue. Compound **11** was obtained in high yield (Scheme IV) by preferential acetylation using

Scheme IV



N-acetylimidazole.[27] The chromatographically pure product (**11**) was reacted essentially with 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl bromide (**12**) (Scheme V) since the syrupy preparation of **12** consists of over 90% of the α form as indi-

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

Compd[b]	C-1	C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′
5b	103.1	55.9	73.9	70.5	76.6	61.3						
16							104.2	71.3	73.2	69.1	76.0	61.5
9b	102.6	55.0	82.4[a]	69.1	76.1	61.3	103.9	71.3	73.0	69.1	75.8	61.6
17 α	91.2	54.4	71.1	70.5	72.0	61.1						
17 β	95.3	57.1	74.3	70.3	76.3	61.0						
10 α	91.7	53.5	80.9[a]	69.4	71.8	61.0	104.0	71.4	73.2	69.2	75.8	61.3
10 β	95.3	56.3	83.3[a]	69.2	75.8	61.0						

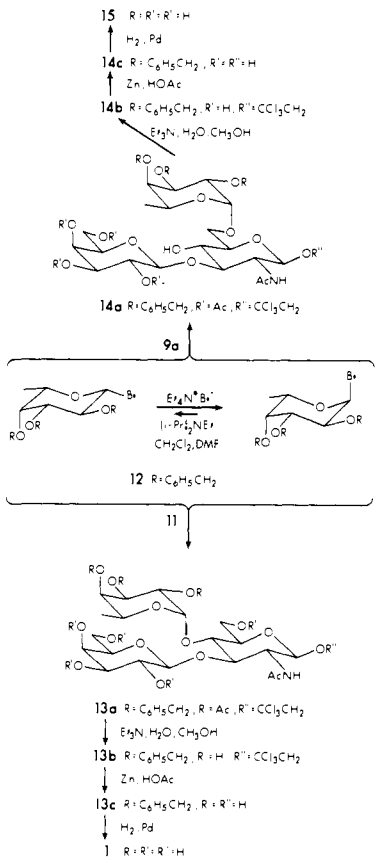
[a] Intersugar aglyconic carbon. [b] 5b: 2,2,2-Trichloroethyl 2-acetamido-2-deoxy-β-D-glucopyranoside, C=O, 175.3; CCl_3, 96.3, CH_2, 81.1; CH_3, 23.0. 9b: 2,2,2-Trichloroethyl 2-acetamido-2-deoxy-3-*O*-(β-D-galactopyranosyl)-β-D-glucopyranoside, C=O, 175.0; CCl_3, 96.6, CH_2, 81.0, CH_3, 23.0. 10: 2-Acetamido-2-deoxy-3-*O*-(β-D-galactopyranosyl)-α,β-glucopyranose; CO, 175.2; CH_3, 22.7, 22.9. 16: 2,2,2-Trichloroethyl β-D-galactopyranoside, CCl_3, 96.4; CH_2, 80.9. 17: 2-Acetamido-2-deoxy-α,β-glucopyranose; CO, 174.9, CH_3, 22.3.

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

Compd[d]	C-1	C-2	C-3	C-4	C-5	C-6	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′	C-1″	C-2″	C-3″	C-4″	C-5″	C-6″
1 α	91.5	54.6	75.3[a,b]	74.8[a,b]	72.1	60.4	103.5	71.2	73.0	68.9	73.0	62.2	98.7	72.6	68.5	69.5	67.4	16.0
1 β	95.4	57.5	76.8[a]	76.1[a]	75.3													
10 α	91.7	53.5	80.9[a]	69.4	71.8	61.0	104.0	71.4	73.2	69.2	75.8	61.3						
10 β	95.3	56.3	83.3[a]	69.2	75.0	61.0												
18													100.0	72.2	68.4	70.1	66.9	15.8
15[c] α	91.9	53.3	80.5[a]	69.0	71.2	69.0[a]	103.9	71.2	73.0	69.1	75.7	61.4	99.9	72.3	68.3	70.0	67.1	15.8
15 β	95.2	56.1	83.0[a]	68.7	75.0	68.7[a]												

[a] Intersugar aglyconic carbons. [b] The assignments for C-3 and C-4 may be reversed. [c] Very weak signals were observed at 100.9, 96.1, 82.6, 61.0, and 55.0 which are not assigned. [d] 1: 2-Acetamido-2-deoxy-4-*O*-(α-L-fucopyranosyl)-3-*O*-(β-D-galactopyranosyl)-α,β-D-glucopyranose, C=O, 174.9; CH_3, 22.8. 10: 2-Acetamido-2-deoxy-3-*O*-(β-D-galactopyranosyl)-α,β-glucopyranose (see Table I). 15: 2-Acetamido-2-deoxy-6-*O*-(α-L-fucopyranosyl)-3-*O*-(β-D-galactopyranosyl)-α,β-D-glucopyranose, C=O, 175.0, 175.2; CH_3, 22.8, 22.5. 18: Methyl α-L-fucopyranoside.

Scheme V



cated by ^1H NMR spectroscopy. This compound was prepared following the procedure described by Dejter-Juszynski and Flowers.[28] The reaction of **11** with **12** was performed in the presence of tetraethylammonium bromide in sufficient quantity to ensure a very rapid equilibration of **12** with its β anomer since the halide ion catalyzed formation of the α-glycosidic bond is dependent on the more rapid reaction of the β-bromide with the alcohol.[12] Using 2 mol equiv of **12** in the presence of Hünig's base (diisopropylethylamine) to neutralize the liberated hydrogen bromide and with methylene chloride–dimethylformamide (5:1) as solvent, the yield of **13a** appeared near quantitative. The yield of pure crystalline **13a** was 83% based on **11.** No evidence was obtained for β-fucoside formation.

In order to liberate **1** from **13a,** it was necessary first to deacetylate to compound **13b** since normal alkaline conditions used for deacetylation would cause elimination of the β-D-galactopyranosyl group from the reducing product obtained on zinc dust reduction of **13a.** Zinc dust reduction in acetic acid of **13b** then provided 2-acetamido-2-deoxy-3-*O*-(β-D-galactopyranosyl)-4-*O*-(2,3,4-tri-*O*-benzyl-L-fucopyranosyl)-D-glucose (**13c**), and this product was debenzylated to **1** by hydrogenolysis in the presence of palladium on carbon.

Although the disaccharide provided a positive indirect Ehrlich reaction[29] and the trisaccharide **1** did not (as expected because of the substitution at the 4-position of the *N*-acetylglucosamine residue), it seemed desirable to obtain further evidence for the position of the α-L-fucosyl group in **1.** This evidence was obtained by synthesis of the other possible positional isomer of **1,** namely, the trisaccharide **15.**

It could be anticipated that tri-*O*-benzyl-α-L-fucopyranosylation of **9a** would tend to favor the primary 6-position rather than the much more hindered 4-position of the glucosamine residue. Indeed, bromide ion catalyzed fucosylation of **9a** followed by de-O-acetylation of the product gave, as evidenced by thin-layer chromatography, a substance (**14b**) different from that (**13b**) obtained on de-O-acetylation of **13a.** The presence of the glucosamine, galactose, and fucose units in **14b** was evident from the ^1H NMR spectrum. Deblocking of **14b** as described above for **13b** provided the new trisaccharide **15** which, as expected, gave a positive indirect Ehrlich reaction. Therefore, the indication was that the fucosylation of **11** had not been preceded by acetyl group migration from 6- to the 4-position.

The advent of ^{13}C NMR spectroscopy provides ready means to distinguish the structures **1** and **15.** It is well established[30] that the hydroxymethyl-group carbons of hexo-

Table III. Proton Magnetic Resonance Spectra in Deuterium Oxide [Me_4Si–CCl_4 (1:1), ppm, external]

	Chemical shifts, τ (spacing, Hz) Residue						
	Gluco			Galacto	Fuco		
Compd[a]	H-1	H-2[b]	H-C(=O)CH_3	H-1	H-1″	H-5″	H_3-6″
1 α	4.62 (3.0)	5.9	7.69	5.24 (7.0)	4.72 (3.0)	4.97 (6.5)	8.54 (6.5)
1 β	5.26 (7.0)						
15 α	4.52 (3.0)	5.7	7.64	5.22 (7.0)	4.76 (3.0)	>5.5	8.56 (6.5)
15 β	5.26 (7.0)						
10 α	4.58 (3.0)	5.8	>7.73	5.28 (7.0)			
10 β	5.32 (7.0)						

[a] See Table II. [b] From spin decoupling.

pyranoses provide their signal in the region 60 to 63 ppm from Me_4Si (external) with deuterium oxide as solvent, and that this region is generally free of signals from other types of carbons which occur in carbohydrate structures. Thus, it could be anticipated that structure **1** would have signals for two carbons in this region while structure **15** would have only one, the substitution having caused a deshielding of 7–10 ppm.[26] Inspection of Table II shows that this is the case. Furthermore, the ^{13}C NMR spectra, which are reported in Table II and assigned using the procedures described above with reference to Table I, are overall in good accord with the assigned structures. However, certain aspects of these spectra together with the relevant ^1H NMR spectra are worthy of special comment.

As seen in Table I, the introduction of the β-D-galactopyranosyl group at the 3-position of both **5b** and **17** caused a deshielding of the intersugar aglyconic carbon (C-3) by about 9 ppm, and this substitutional effect appears normal for disaccharide structures. A similar deshielding is observed for C-6 of **10** on fucosylation to provide **15** (see Table II). However, inspection of the ^{13}C NMR spectrum for compound **1** required the assignment of signals for the intersugar aglyconic carbons (C-3 and C-4) to substantially (about 5 ppm) lower field than "normal". This effect can plausibly be rationalized as arising from steric crowding of the fucosyl and galactosyl residues at the vicinal 3- and 4-positions of the glucosamine residue and was also observed for the glycoside of this trisaccharide which was used to synthesize a blood-group Le^a specific antigen.[17] The exceptional deshielding of H-5″ of the fucose residue (see Table III) in **1** and not observed for the trisaccharide **15** is discussed in a related paper in connection with the NMR parameters of a β-glycoside of **1**.

The ^1H NMR spectra reported in Table III substantiate the anomeric configurations assigned to these structures and the related precursors. The specific rotation found for **1** was −45.1°, in good agreement with the reported value, −44 ± 3°.[3] Furthermore, **1** possessed the same value for $R_{lactose}$ as was reported by Rege and coworkers[3] for the compound of natural origin. The value of $R_{lactose}$ for compound **15** was 1.00.

A goat was immunized against authentic Le^a blood group substance.[31] The Le^a specific antibodies thus raised gave, as expected, a strong precipitin reaction[32] with the Le^a glycoprotein. The precipitin reaction was more strongly inhibited by the trisaccharide **1** than by the trisaccharide **15**.[17] Further immunochemical evidence for the structure of **1** was achieved by synthesis of **1** glycosidically linked to the hydroxyl of methyl 9-hydroxynonanoate. This glycoside was then attached, by way of the acyl azide, to the lysine residues of bovine serum albumin to provide an immunogen. The antibodies raised in rabbits and a goat to this antigen effectively precipitated authentic blood-group Le^a substance. This research is the subject of a separate communication in this issue.[17]

Experimental Section

General. The paper chromatograms were descending on Whatman No. 1 paper, using ethyl acetate–pyridine–water (10:4:3 v/v). The paper chromatograms were visualized by the benzidine–trichloroacetic acid reagent.[33] The TLC were developed on a Silica Gel G (E. Merck A. G., Darmstadt) and visualized with 5% sulfuric acid in methanol after heating at 100°. The column chromatograms, unless otherwise stated, were made on silicic acid 100 mesh (Mallinckrodt Chemical Works, St. Louis, Mo.) and prepared using a slurry of the adsorbent in the solvent mixture used to develop the chromatogram.

The ^1H NMR spectra were measured at 100 MHz (Varian HA 100) and the ^{13}C NMR spectra at 22.6 MHz (Bruker HFX-10) and, unless otherwise stated, the solvent was $CDCl_3$.

2-Methyl-4,5-(3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyrano)-Δ^2-oxazoline (4). 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride (**2**)[34] (10.0 g, 22.4 mmol) was dissolved in dry acetonitrile[35] (30 ml) which contained tetraethylammonium chloride (4.00 g, 24 mmol) and anhydrous sodium bicarbonate (4.00 g, 48 mmol). The solution was kept at 55° for 20 min, after which time reaction was complete as indicated by TLC, using diethyl ether–methanol (9.5:0.5) for irrigation. The solvent was removed in vacuo and the residue taken up in methylene chloride (200 ml).

The methylene chloride solution was washed three times with water (100 ml), and each aqueous extract was sequentially extracted (back-extraction) with 200-ml volumes of methylene chloride. The methylene chloride layers were combined and dried over anhydrous sodium sulfate, and the solvent was removed in vacuo to leave a syrup (8.90 g, 99% yield) with $[\alpha]^{27}D$ +16.3° (*c* 1.58, chloroform), and whose NMR spectrum was nearly identical with that of an authentic sample purified by chromatography on Florisil 100–200 mesh (J. T. Baker Chemical Co., Phillipsburg, N.J.), using ethyl acetate–*n*-hexane (8:2) as irrigant [lit.[23] $[\alpha]D$ +10° (*c* 1, chloroform)].

2,2,2-Trichloroethyl 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside (5a). An investigation using *p*-toluenesulfonic acid as catalyst for the alcoholysis of **4** using 2,2,2-trichloroethanol as solvent proved the reaction to be highly selective for the β configuration, but the yields were unacceptably low (near 25%). The use of trifluoromethanesulfonic acid (Diaprep Incorporated, Atlanta, Ga.) provided higher yields of the glycoside (near 50%) but a substantially greater amount of the α anomer, especially at high concentrations of the acid. The following conditions for the preparation **5a** appeared optimum. The courses of the reactions were monitored by TLC, using ethyl acetate as irrigant.

The crude oxazoline (**4**) (8.70 g, 26.5 mol) was dissolved in 100 ml of freshly distilled 2,2,2-trichloroethanol which had been made 0.012 *M* with respect to trifluoromethanesulfonic acid by the addition of 0.1 ml of the acid. The solution was protected from moisture and heated at near 100° for 2 hr, after which time the presence of **4** could no longer be detected. The resulting brown-colored solution was cooled, diluted with methylene chloride (100 ml), and the mixture washed twice with ice-cold saturated sodium bicarbonate solution (100 ml), using methylene chloride to back-extract the aqueous phases. Solvent removal in vacuo left a syrupy product which was applied to a silicic acid column (80 × 3.5 cm), using ethyl acetate–chloroform (1:1) as developing phase. The first fraction to elute from the column, monitored by TLC of 25-ml fractions, was 0.88 g of crystalline α anomer of **5a**, mp 134–137°

(6.1% yield). After two recrystallizations from ether, the melting point was raised to 138–138.5°, $[\alpha]^{25}D$ +98.3° (*c* 1, chloroform).

Anal. Calcd for $C_{16}H_{22}Cl_3NO_9$: C, 40.14; H, 4.63; N, 2.94; Cl, 22.23. Found: C, 39.89; H, 4.71; N, 2.69; Cl, 22.03.

The ^1H NMR spectrum was consistent with that expected for the α anomer of **5a.**

The second and main fraction to elute from the column provided 6.0 g of crystals, mp 185–188° (46% yield). Recrystallization of the product from a preliminary preparation from ethyl acetate raised the melting point to 188–189°, $[\alpha]^{25}D$ −26° (*c* 1, chloroform).

Anal. Calcd for $C_{16}H_{22}Cl_3NO_9$: C, 40.14; H, 4.63; N, 2.94; Cl, 22.23. Found: C, 40.05; H, 4.62; N, 2.64; Cl, 22.27.

The ^1H NMR spectrum was consistent with that expected for the title compound **5a.**

2,2,2-Trichloroethyl 2-Acetamido-2-deoxy-β-D-glucopyranoside (5b). Crude compound **5** (6.0 g), mp 185–188°, was de-*O*-acetylated in 24 ml of a mixture of methanol–water–triethylamine (2:1:1 v/v) at room temperature. After 16 hr, the solvents were removed, and the residue was dissolved in water for treatment with Amberlite IR-120 resin in the acid form to remove residual triethylamine. The resulting aqueous solution was purified by recrystallization from acetone–benzene mixture, mp 170–171°, purified by recrystallization from acetone–benzene mixture, mp 170–171°, $[\alpha]^{25}D$ −33.9° (*c* 1, water). The compound provided a ^1H NMR spectrum in deuterium oxide consistent with that expected for the tile compound **5b,** especially the doublet for the anomeric hydrogen at τ 5.20 with a spacing of 7.8 Hz.

The natural abundance ^{13}C NMR is reported in Table I.

Anal. Calcd for $C_{10}H_{16}Cl_3NO_6 \cdot 0.5H_2O$: C, 33.30; H, 4.74; N, 3.88; Cl, 29.50. Found: C, 33.38; H, 4.66; N, 3.82; Cl, 30.07.

2,2,2-Trichloroethyl 2-Acetamido-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside (6). The above-described crude **5b** (4.42 g) was added to a stirred solution of anhydrous zinc chloride (6.0 g) in freshly distilled benzaldehyde (100 ml) kept in a nitrogen atmosphere. After stirring for 1 hr, *n*-hexane (300 ml) was added. A gummy precipitate formed which was separated by decantation and washed twice with *n*-hexane (300 ml). The viscous residue was triturated with 20 ml of pyridine. After 10 min, 200 ml of methylene chloride was added. The resulting solution was washed with 100 ml of ice-cold saturated aqueous sodium bicarbonate solution. The methylene chloride layer was freed of a precipitate by filtration through Celite and washed twice with cold water while back-extracting the aqueous layers with methylene chloride (300 ml). The combined methylene chloride extracts were dried over anhydrous sodium sulfate and evaporated in vacuo to crystalline residue (4.8 g, 78% yield), mp 218–220°. The melting point was raised to 234° dec by two recrystallizations from methanol–isopropyl alcohol, $[\alpha]^{25}D$ −73.8° (*c* 1, methanol). The ^1H NMR spectrum was consistent with that of the structure assigned to the title compound **6.**

Anal. Calcd for $C_{17}H_{20}Cl_3NO_6$: C, 46.33; H, 4.57; N, 3.17; Cl, 24.13. Found: C, 46.29; H, 4.49; N, 3.08; Cl, 24.40.

2,2,2-Trichloroethyl 2-Acetamido-3-*O*-(tetra-*O*-acetyl-β-D-galactopyranosyl)-4,6-*O*-benzylidene-β-D-glucopyranoside (8). Compound **6** (4.00 g, 9 mmol) was dissolved in 500 ml of a 1:1 mixture of nitromethane and benzene. To ensure dryness, the solution was concentrated by distillation at atmosphere pressure until 100 ml of distillate was collected. Mercuric cyanide (2.00 g) was added and the temperature of the solution adjusted to 60°. While maintaining this temperature and a nitrogen atmosphere, tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**7**) (3.7 g) dissolved in 1:1 nitromethane–benzene (40 ml) was added over a period of 6 hr. After the solution had been stirred at 60° for a further 20 hr, mercuric cyanide (1.00 g) and compound **7** (1.80 g) were added, and the solution was stirred for an additional 40 hr. The reaction mixture was then cooled in ice–water and washed with ice-cold saturated aqueous sodium bicarbonate (100 ml), followed by two washes with ice-cold saturated aqueous sodium chloride (100 ml). After each washing, the aqueous layer was back-extracted with methylene chloride (100 ml). Solvent removal left a syrupy residue which was applied to a silicic acid column (80 × 3.5 cm), and the chromatogram was developed with diethyl ether–benzene (3:1). Material (6.30 g) was obtained, in the 2–3 l. fraction of the effluent, which crystallized on solvent removal, mp 140–145° (91% yield), and which appeared pure by TLC examination. One recrystallization from benzene–*n*-hexane provided pure material, mp 145–146°, $[\alpha]^{25}D$ −11.5° (*c* 1, chloroform).

Anal. Calcd for $C_{31}H_{38}Cl_3NO_{15}$: C, 48.29; H, 4.96; N, 1.81; Cl, 13.79. Found: C, 48.13; H, 5.20; N, 2.21; Cl, 13.49.

The ^1H NMR spectrum showed the following characteristics. The assignments were established by appropriate spin–spin decoupling experiments and comparison with spectrum of compound **6:** τ 2.33–2.76 (m, 5, aromatic), 3.95 (d, 8 Hz, 1, NH), 6.48 (s, 1, benzylidene), 4.60 (d, 8 Hz, 1, H-1), 5.27 (d, 7 Hz, 1, H-1′), 6.89 (q, 8 Hz, 1, H-2), 7.87, (s, 3, *N*-acetyl), 7.97, 8.02 (each s, 6, *O*-acetyl).

2,2,2-Trichloroethyl 2-Acetamido-3-*O*-(tetra-*O*-acetyl-β-D-galactopyranosyl)-2-deoxy-β-D-glucopyranoside (9a). A solution of compound **8** (1.60 g, 2.08 mmol) in 50% aqueous acetic acid (4 ml) was kept at 100° for 30 min. The solvent was removed in vacuo to leave 1.4 g of solid which appeared pure on TLC examination with ethyl acetate as irrigant. Crystallization from ethyl acetate–*n*-hexane gave a product, mp 141–142°, $[\alpha]^{21}D$ +4.5° (*c* 1, chloroform). The ^1H NMR spectrum in CD_3OD was devoid of signal for aromatic protons and was in general accord with that expected for the title compound (**9a**).

Anal. Calcd for $C_{24}H_{34}Cl_3NO_{15}$: C, 42.21; H, 5.02; N, 2.05. Found: C, 42.05; H, 5.13; N, 1.86.

2,2,2-Trichloroethyl 2-Acetamido-2-deoxy-3-*O*-(β-D-galactopyranosyl)-β-D-glucopyranoside (9b). Crude compound **9a** (1.90 g) was de-O-acetylated as described for compound **5a.** The freeze-dried product (1.4 g), mp 183–185°, appeared pure on TLC. Two recrystallizations from ethanol–ethyl acetate raised the melting point to 187–188°, $[\alpha]^{25}D$ −29.3° (*c* 1, water). The partial ^1H NMR spectrum was τ 4.91 (d, 8 Hz, 1, H-1′), 5.34 (d, 7 Hz, 1, H-1, partially superimposed by a doublet of doublets for the CH_2CCl_3 group). The ^{13}C NMR spectrum is reported in Table I and accounted for on the basis of spectra for model compounds.

Anal. Calcd for $C_{16}H_{26}Cl_3NO_{11}$: C, 37.33; H, 5.09; N, 2.72. Found: C, 37.44; H, 5.21; N, 3.19.

2-Acetamido-2-deoxy-3-*O*-(β-D-galactopyranosyl)-α,β-D-glucopyranose (10). Compound **9b** (300 mg) was stirred at room temperature with glacial acetic acid (3 ml) and zinc dust (300 mg) for 48 hr. The solution was filtered free of solid and treated with hydrogen sulfide. The precipitated zinc sulfide was removed by filtration and the filtrate freeze-dried. The resulting solid on examination on paper chromatography, using *n*-butyl alcohol–ethanol–water (10:1:2), showed the product to be pure and to possess $R_{glucose}$ = 0.50 in close agreement with that reported, $R_{glucose}$ = 0.49, by Flowers and Jeanloz,[9] using these same conditions. Using ethyl acetate–pyridine–water (10:4:3), $R_{lactose}$ = 1.89. The material was taken up in water and applied to a column of acid-washed Darco G60–Celite 545 (3 × 1 cm)[36] and eluted with water (50 ml). Freeze-drying provided a colorless solid which was crystallized from methanol. After two recrystallizations, mp 197°, $[\alpha]^{25}D$ +22° → +7° (after 24 hr) (*c* 1.0, water) [lit.[9] mp 193–194°, $[\alpha]^{23}D$ +32° → +14.5° (*c* 1.58, water)]. The ^{13}C NMR is reported and rationalized in Table I. The assignments for the ^1H NMR spectrum in D_2O could be made using appropriate spin–spin decoupling experiments and are reported in Table III.

The indirect Ehrlich test as described by Aminoff, Morgan, and Watkins[29] was positive, indicating that position 4 was free.

2,2,2-Trichloroethyl 2-Acetamido-6-*O*-acetyl-3-*O*-(tetra-*O*-acetyl-β-D-glucopyranosyl)-2-deoxy-β-D-glucopyranoside (11). Imidazole (272 mg, 4.1 mmol) was dissolved in purified chloroform (5 ml), and acetyl chloride (157 mg, 2.0 mmol) was added slowly with cooling.[27] The precipitated imidazole hydrochloride was removed by filtration, and compound **9a** (1.60 g, 2.08 mmol) was added to the filtrate. The solution was kept at 80° for 6 days. The solution was washed with water, dried over anhydrous sodium sulfate, and evaporated in vacuo to a clear syrup which was chromatographed on a silicic acid column (60 × 2.3 cm) using ethyl acetate as developing phase. The main fraction eluted appeared pure on TLC and crystallized readily. The yield was 985 mg (76%), mp 121–122°, $[\alpha]^{27}D$ +0.3° (*c* 1, chloroform).

Anal. Calcd for $C_{26}H_{36}Cl_3NO_{16}$: C, 43.08; H, 5.00; N, 1.93; Cl, 14.67. Found: C, 42.87; H, 5.07; N, 2.24; Cl, 14.92.

The ^1H NMR spectrum clearly supported that one *O*-acetyl group had been inserted into **9a:** τ 3.58 (d, 7 Hz, 1, NH), 4.60 (d, ~7 Hz, 1, H-1), 4.75 (s, 1, OH), 6.72 (q, 7 Hz, 1, H-2, spin decoupling), 7.84 (s, 3, *N*-acetyl), 7.91, 8.02 (each s, 6, *O*-acetyl), 7.95 (s, 3, *O*-acetyl) are the signals which could be assigned.

2,2,2-Trichloroethyl 2-Acetamido-6-*O*-acetyl-3-*O*-(β-D-tetra-*O*-acetyl-β-D-galactopyranosyl)-4-*O*-(tri-*O*-benzyl-β-L-fucopyranosyl)-2-deoxy-β-D-glucopyranoside (13a). Compound **11** (1.45 g, 2 mmol) was dissolved in a mixture of methylene chloride (15 ml) and *N,N*-dimethylformamide (3 ml) which contained tetraethylammonium bromide (430 mg, 2.0 mmol) and diisopropylethylamine (0.36 ml, 2.1 mmol), tri-*O*-benzyl-α-L-fucopyranosyl bromide (about 4 mmol), freshly prepared from 4 mmol of 1-*O*-*p*-nitrobenzoyl-2,3,4-tri-*O*-benzyl-β-L-fucopyranose,[28] was added and the solution kept at room temperature for 4 days. The solution was washed twice with water (50 ml) while back-extracting with methylene chloride. Solvent removal left a brown-colored syrup which was applied to a silicic acid column (60 × 2.3 cm) for chromatography using ethyl acetate–*n*-hexane (2:1) as the developing phase. The major band found in the effluent contained 2.10 g of substance which crystallized. Recrystallization from methylene chloride–diethyl ether gave 1.89 g (83% yield), mp 194–195°, $[\alpha]^{27}D$ −55.8° (*c* 1, chloroform). The ^1H NMR spectrum required high purity: τ 2.52–2.90 (m, 15, aromatic), 3.81 (d, 8 Hz, 1, NH), 4.60–6.40 (m, 27), 7.83 (s, 6, *N*-acetyl and *O*-acetyl), 8.01, 8.23 (each s, 3, *O*-acetyl), 8.05 (s, 6, *O*-acetyl), 8.79 (d, 6 Hz, 3, fucose methyl group).

Anal. Calcd for $C_{53}H_{64}Cl_3NO_{20}$: C, 55.76; H, 5.65. Found: C, 55.55; H, 5.68.

The mother liquors from the recrystallization were concentrated to a crystalline solid, the ^1H NMR spectrum of which was nearly identical with that described above, $[\alpha]^{27}D$ −64.3° (*c* 1, chloroform).

2-Acetamido-2-deoxy-4-*O*-(α-L-fucopyranosyl)-3-*O*-(β-D-galactopyranosyl)-α,β-D-glucopyranose (1). Crude **13a** (2.00 g, 1.8 mmol) was dissolved in 55 ml of a methanol–water–triethylamine (6:2:3) mixture and the solution left for 16 hr at room temperature. Evaporation and treatment of a methanolic solution of the residue with Amberlite 120 H^+ resin as described for the preparation of **5a** provided a triethylamine-free solution which was taken to dryness in vacuo to provide crude **13b** (1.60 g, 98% yield). The ^1H NMR spectrum showed the compound to be completely de-O-acetylated.

Crude compound **13b** (760 mg) was reduced with zinc in acetic acid as described for the preparation of **10**. However, after the reduction (2 hr), the solution was poured into ice-cold saturated aqueous sodium bicarbonate solution, and the resulting mixture was extracted thoroughly with ethyl acetate. Solvent removal in vacuo left 540 mg (83% yield) of product which appeared pure on TLC examination, using ethyl acetate–dioxane–water (2:2:1 upper phase).

The above-described crude **13c** (540 mg) was dissolved in 95% ethanol (60 ml), 540 mg of 5% palladium on powdered charcoal catalyst was added (Matheson Coleman and Bell, East Rutherford, N.J.) and the mixture shaken in a hydrogen atmosphere (50 psig) at room temperature for 24 hr. The catalyst was removed by filtration and washed with 95% ethanol, and the combined filtrates were evaporated to dryness. The crude product (340 mg) was taken up in a little water for application to a charcoal–Celite column (3 × 1 cm), as described for the purification of **10**. This treatment removed all traces of weak signals for aromatic protons present in the ^1H NMR spectrum of the crude product. Examination of this product (246 mg, 69% yield from **13c**, 56% from **13a**) by paper chromatography indicated high purity (one spot) with $R_{lactose}$ = 0.68, the value reported for the title compound **1** by Rege and coworkers.[3] Furthermore, the specific rotations were very similar, $[\alpha]^{25}D$ −45.1° (*c* 1, water) [lit.[3] $[\alpha]^{22}D$ −44 ± 3° (*c* 0.3, water)]. The indirect Ehrlich color reaction was negative.[29]

The ^{13}C NMR and ^1H NMR spectra are reported in Table II and III, respectively.

2-Acetamido-2-deoxy-6-*O*-(α-L-fucopyranosyl)-3-*O*-(β-D-galactopyranosyl)-α,β-D-glucopyranose (15). The diol **9a** (420 mg, 0.61 mmol) was reacted with tri-*O*-benzyl-L-fucopyranosyl bromide under the same conditions as described for the preparation of **13a** from 11. The chromatographic separation of the products of reaction provided a crystalline product (**14a**) (300 mg, 45% yield) which was recrystallized from ethyl acetate, mp 144–145°, $[\alpha]^{25}D$ −26.5° (*c* 1, chloroform).

Anal. Calcd for $C_{51}H_{62}Cl_3NO_{19}$: C, 55.71; H, 5.68; N, 1.27; Cl, 9.67. Found: C, 55.70; H, 5.67; N, 1.26; Cl, 9.72.

The diol **9a** was recovered in 45% yield.

The ^1H NMR spectrum (**14a**): τ 2.50–2.95 (m, 15, aromatic), 4.08 (d, 7 Hz, 1 NH), 4.58–7.00 (m, 28), 7.90 (s, 3, *N*-acetyl), 7.95, 7.99 (each s, 3, *O*-acetyl), 8.06 (s, 6, *O*-acetyl), 8.90 (d, 6 Hz, 3, fucose methyl group).

De-O-acetylation of **14a** (250 mg, 0.22 mmol) under the conditions used for the de-O-acetylation of **13a** to **13b** gave a product (**14b**) which moved slower on TLC, using ethyl acetate–dioxane 1:1, than did **13b** (R_{13b}/R_{14b} = 1.96. The compound was obtained in 90% yield.

The ^1H NMR spectrum was consistent with that expected for **14b** but was different from the spectrum of **13b.** Zinc dust reduction of **14b** (170 mg, 0.18 mmol) under the conditions used for the conversion of **13b** to **13c** provided crude **14c** (135 mg, 95% yield) which was subjected to hydrogenolysis of the benzyl groups as described for the conversion of **13** to **1**. The crude product was passed through a column of charcoal–Celite as described for the preparation of **1** to yield a white amorphous powder, $[\alpha]^{27}D$ −43.0° (*c* 1, water), $R_{lactose}$ = 1.00. The ^{13}C NMR spectrum of this product is reported in Table II where it is seen that the chemical shifts are in accord with structure assigned to compound **15.** The ^1H NMR spectrum in deuterium oxide is reported in Table III. The indirect Ehrlich color reaction[29] was positive.

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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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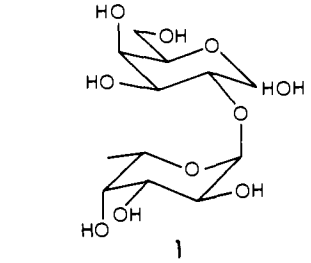
Abstract: Blocking procedures are described, including a 3,4-*O*-(ethyl orthoacetyl) intermediate, to prepare 2,2,2-trichloroethyl 4,6-di-*O*-acetyl-2-*O*-(tri-*O*-benzyl-α-L-fucopyranosyl)-β-D-galactopyranoside which, in turn, was condensed under bromide ion catalyzed conditions using molecular sieve 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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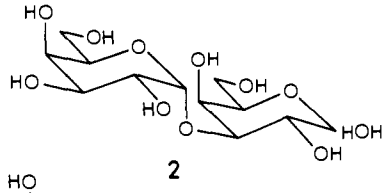

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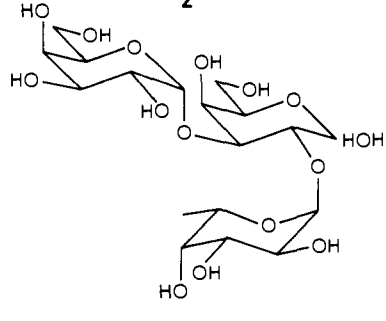

3

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