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Studies of specifically fluorinated carbohydrates. Part III. A new method for the addition of the elements of "BrF" and of "IF" to unsaturated carbohydrate derivatives

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A smooth addition of the elements of "BrF", to D-glucal triacetate (**1**), occurs when bromine is reacted with **1** in the presence of silver monofluoride and a suitable solvent. This reaction affords a major product 2-bromo-2-deoxy-α-D-mannopyranosyl fluoride triacetate, together with smaller quantities of 2-bromo-2-deoxy-α-D-glucopyranosyl fluoride triacetate and the corresponding β-D-anomer. The structures of these products have been elucidated by fluorine and proton magnetic resonance studies, and confirmed by several independent syntheses. The same three products are obtained when "BrF" is generated *in situ* from *N*-bromosuccinimide and HF; however, under these conditions 2-deoxy-α-D-*arabino*-hexopyranosyl fluoride triacetate is also formed in ca. 7% yield. The Br_2/AgF reagent has also been reacted with several 3,4-dihydro-2*H*-pyran derivatives and with other glycals. In all cases the major product(s) corresponds to the *trans* addition of "BrF". Similar results are obtained for the addition of the elements of "IF" to all of the above derivatives.

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Introduction

In the two previous papers (1) of this series, we described studies of glycopyranosyl fluorides which gave us some insight as to the stereospecific dependencies of the ^{19}F nuclear magnetic resonance (^{19}F n.m.r.) parameters of fluorine attached to the anomeric center of a pyranose sugar. We also indicated the potential which ^{19}F n.m.r. spectroscopy has, as a "stereospecific probe", for studying the conformational symmetries of carbohydrate derivatives. In view of the proven sensitivity of ^{19}F chemical shifts with respect to the environment of a fluorine substituent, it occurred to us that ^{19}F n.m.r. spectroscopy might have a unique potential for studying the course of certain electrophilic addition reactions of unsaturated carbohydrate derivatives. The present study is concerned, in part, with the development of this hypothesis and, in part, with an investigation of the potential of unsaturated carbohydrate derivatives as precursors for specifically fluorinated carbohydrates.[3]

Bowers and co-workers (3) described the *in situ* generation, and addition to alkenes, of the elements of "XF" (where X = Cl, Br, or I) by reaction of the appropriate *N*-haloamide with HF in the presence of the alkene. Pattison and co-workers (4) subsequently applied this procedure to a variety of unsaturated systems and Kent and co-workers (5) also described its application to several glycal derivatives. In spite of the evident success of these studies we felt that the use of anhydrous HF would preclude the general application of the Bowers reagent to unsaturated carbohydrate derivatives and as a result, developed the reaction sequence outlined below. The sequence is basically an extension of the concept developed originally for the addition of "BrOMe" to alkenes (6) and subsequently applied to carbohydrate derivatives by Lemieux and co-workers (7).

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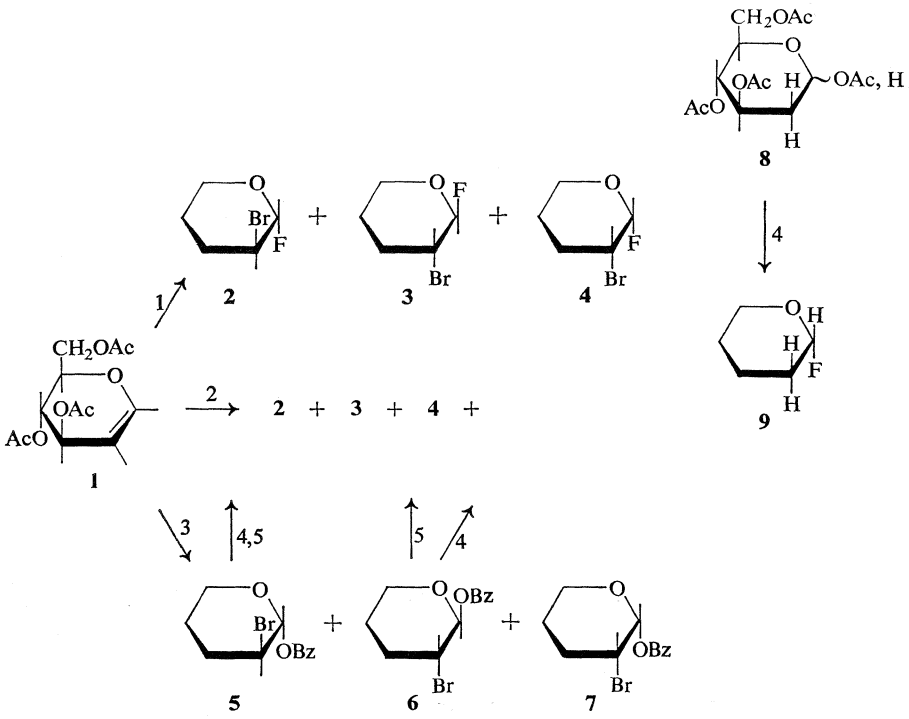
[3]See ref. 2 for a preliminary communication of these studies.



1, Br_2 in C_6H_6, AgF in CH_3CN
2, *N*-bromosuccinimide and anhydrous liquid HF in Et_2O
3, Br_2 in C_6H_6, AgOBz in C_6H_6
4, HF
5, *a*, HBr in HOAc; *b*, AgF in CH_3CN

Flow Sheet 1

Following the usual procedure for electrophilic addition reactions (8) we anticipated reaction of the alkene with bromine to give the appropriate bromonium (or carbonium) ion, plus the bromide anion. Our variant required the immediate removal of this bromide anion, as silver bromide, by reaction with silver monofluoride. Reaction of the concomitantly-formed fluoride anion with the bromonium intermediate, which had been generated in the initial stage of the reaction, should then afford the desired "BrF" adduct. As will be shown below, this hypothetical sequence proved to be successful for "XF" additions (where X = Br, I) to a variety of α,β-unsaturated cyclic ethers.

Subsequent to our studies, a detailed literature search showed that the utilization of the above sequence for effecting the addition of "IF" to cyclohexene had previously been the subject of some controversy. Bergmann and Shahak (9) used an excess of cyclohexene as the reaction solvent and characterized the product as 3-iodocyclohex-1-ene. Schmidt and Meinert (10) used acetonitrile as solvent and reported the isolation of *trans*-2-iodo-cyclohexylfluoride. However, an unsuccessful attempt to repeat this work (11) resulted in the isolation of *N*-acetyl-2-iodo-cyclohexylamine. We have recently shown (12) that when a mixture of acetonitrile and/or benzene is used as solvent, the "IF" adduct of cyclohexene can be obtained in high yield; the reaction follows an exclusively *trans* addition.

Results and Discussion

When an acetonitrile solution of D-glucal triacetate (**1**) was stirred with silver monofluoride, and a solution of bromine (10%, in benzene) was added dropwise, an immediate precipitation occurred. Subsequent work-up of the reaction mixture afforded a syrup, a solution of which showed *three* separate fluorine resonances (Fig. 1) whose shifts were characteristic of pyranosyl

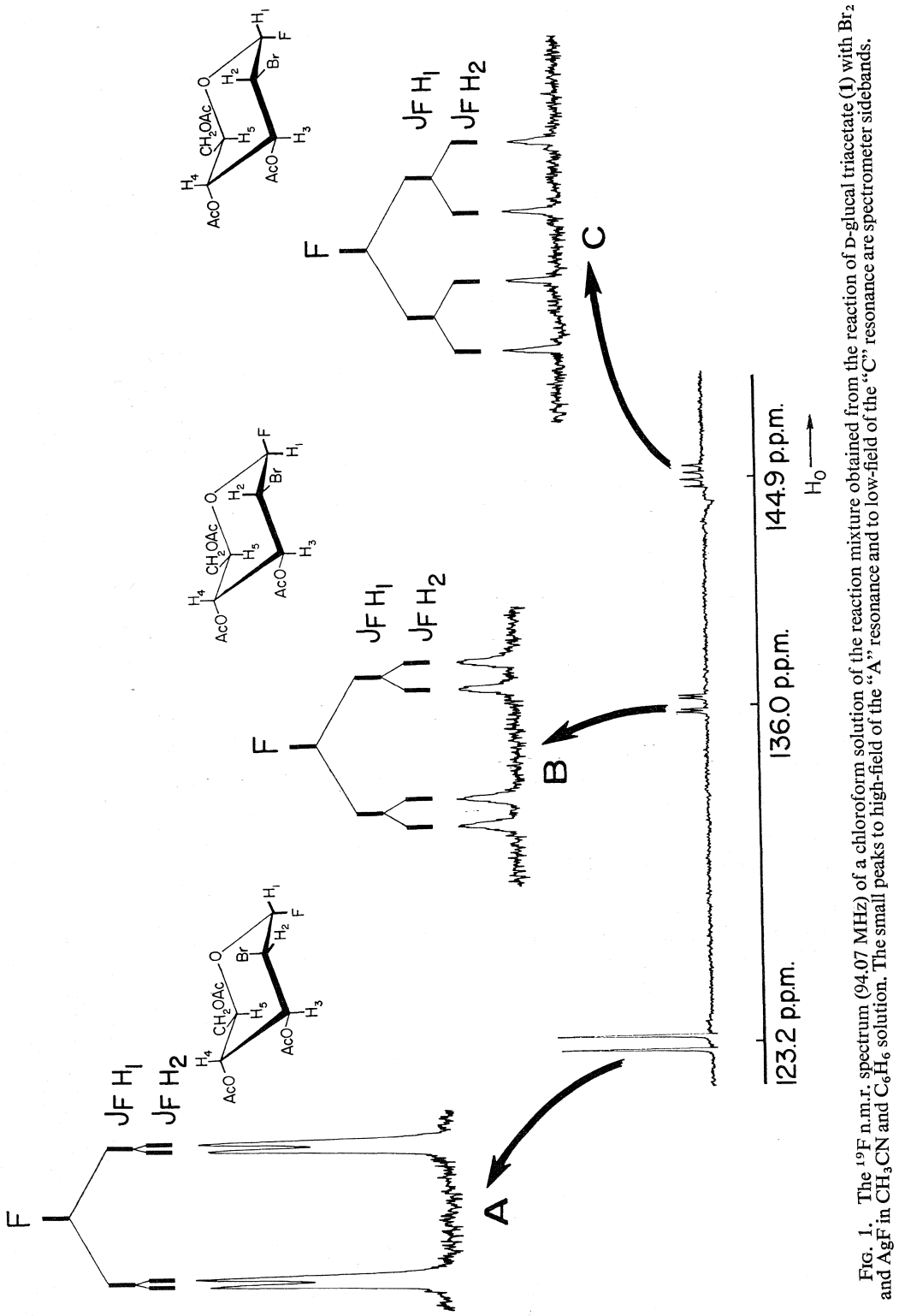


FIG. 1. The ^{19}F n.m.r. spectrum (94.07 MHz) of a chloroform solution of the reaction mixture obtained from the reaction of D-glucal triacetate (**1**) with Br_2 and AgF in CH_3CN and C_6H_6 solution. The small peaks to high-field of the "A" resonance and to low-field of the "C" resonance are spectrometer sidebands.

fluorides; there was no evidence for any products having fluorine attached to a secondary carbon (13, 14). The major component (**A**) of this mixture readily crystallized and, as will be shown below, it has the structure 2-bromo-2-deoxy-α-D-mannopyranosyl fluoride triacetate (**2**). A second derivative (**C**), found to be 2-bromo-2-deoxy-α-D-glucopyranosyl fluoride triacetate (**4**), crystallized out more slowly. The third component (**B**) has not to date, been obtained in crystalline form, but it has been shown to be 2-bromo-2-deoxy-β-D-glucopyranosyl fluoride triacetate (**3**). Evidence leading to the structural elucidation of these compounds will now be discussed.

The ^{19}F resonance ($\phi_c = +144.9$) of compound **C**, Fig. 1*c*, showed in addition to the characteristic *geminal* ^{19}F–^{1}H coupling (51.7 Hz) a large (25.1 Hz) *vicinal* ^{19}F–^{1}H coupling, which immediately indicated that this fluorine was *trans-diaxial* with respect to the proton at C-2; therefore, this compound must have the α-D-configuration. Analysis of the proton magnetic resonance (p.m.r.) spectrum, Fig. 2*b*, confirmed that this compound had the D-*gluco* configuration (large *vicinal* couplings of ca. 9 Hz between H-2, H-3; H-3, H-4; and H-4, H-5) and confirmed the α-configuration at C-1 ($J_{1,2} = 2.5$ Hz). On this basis, **C** has the structure 2-bromo-2-deoxy-α-D-glucopyranosyl fluoride triacetate.

The impure sample of derivative **B**, gave a p.m.r. spectrum consistent with the D-*gluco* configuration ($J_{2,3} = 9.0$ Hz) and with the β-configuration at C-1 ($J_{1,2} = 8.0$ Hz). The fact that the ^{19}F chemical shift of this derivative was to low field ($\phi_c = +136.0$) of that of the corresponding α-anomer ($\phi_c = +144.9$) is also consistent (1) with their respective anomeric configurations. The ^{19}F–^{1}H couplings observed in the ^{19}F spectrum (Fig. 1*b*) of this compound are again consistent with the above assignment (*geminal* coupling, 50.3 Hz; *vicinal*, 10.0 Hz). Thus, **B** has the structure, 2-bromo-2-deoxy-β-D-glucopyranosyl fluoride triacetate.

The ^{19}F n.m.r. spectrum of compound **A**, (Fig. 1*a*) exhibited a resonance at ϕ_c +123.1 which had a *vicinal* ^{19}F–^{1}H coupling of 2.9 Hz, which indicated a *gauche* relationship between these substituents. Although the p.m.r. spectrum indicated that this derivative has the D-*manno* configuration ($J_{2,3} = 3.95$ Hz), the *vicinal* H_1–H_2 coupling (1.5 Hz) offered no unequivocal evidence concerning the anomeric configuration. However, the observation that the ^{19}F shift was essentially temperature invariant ($\Delta\phi_c = 0.16$ p.p.m. between $+30°$ and $-80°$), indicated that this derivative has the α-configuration. We had previously observed (1) that the ^{19}F shift of β-D-hexopyranosyl fluorides are temperature dependent whereas those of the α-anomers are essentially invariant. Evidently the replacement of the oxygen substituent at C-2 by a bromine atom does not significantly alter this behavior: thus the ^{19}F shift of **3**, which is assigned the β-D-gluco configuration, changed by 3.2 p.p.m., whilst that of **4**, which is the corresponding α-anomer, changed by only 0.1 p.p.m. over the same temperature range. Thus, a straightforward application of the ^{19}F n.m.r. and p.m.r. methods afforded a facile identification of the three reaction products (**2**, **3**, **4**).

Since this was our first application in the carbohydrate area of this new method of generating "BrF", and also of ^{19}F n.m.r. as a method of structural elucidation in the carbohydrate area, it was felt desirable to confirm the above structural assignments by independent syntheses. The first of these started with the syntheses of 1-*O*-benzoyl-2-bromo-2-deoxy-α-D-mannopyranose triacetate (**5**) and the corresponding β-D-*gluco* isomer **6**. The proof of structure of these two derivatives follows from the known (15) stereochemistry of the Prevost reaction and from consideration of their p.m.r. spectra. These two derivatives were then reacted separately with anhydrous liquid HF, under conditions which are known (16, 17) to afford the most thermodynamically stable glycopyranosyl fluoride, which in the present series is the α-anomer. Reaction of the D-*manno* derivative **5** afforded as the sole product a crystalline material identical in all respects with the derivative previously assigned the α-D-*manno* configuration (**2**). Under identical reaction conditions, the D-*gluco* derivative **6** gave material which was the same in all respects with the compound previously assigned the α-D-*gluco* configuration (**4**). In one such reaction a second, minor component was detected by ^{19}F n.m.r. spectroscopy which gave an identical spectrum with that of the material tentatively assigned the β-D-*gluco* configuration (**3**). Since this derivative isomerized readily to the α-anomer (**4**), this provided further evidence (17) that **3** is the β-D-*gluco* derivative.

Although the above reactions provided reasonable proof for the structures of the two α-anomers, it was desirable to obtain a more satisfactory

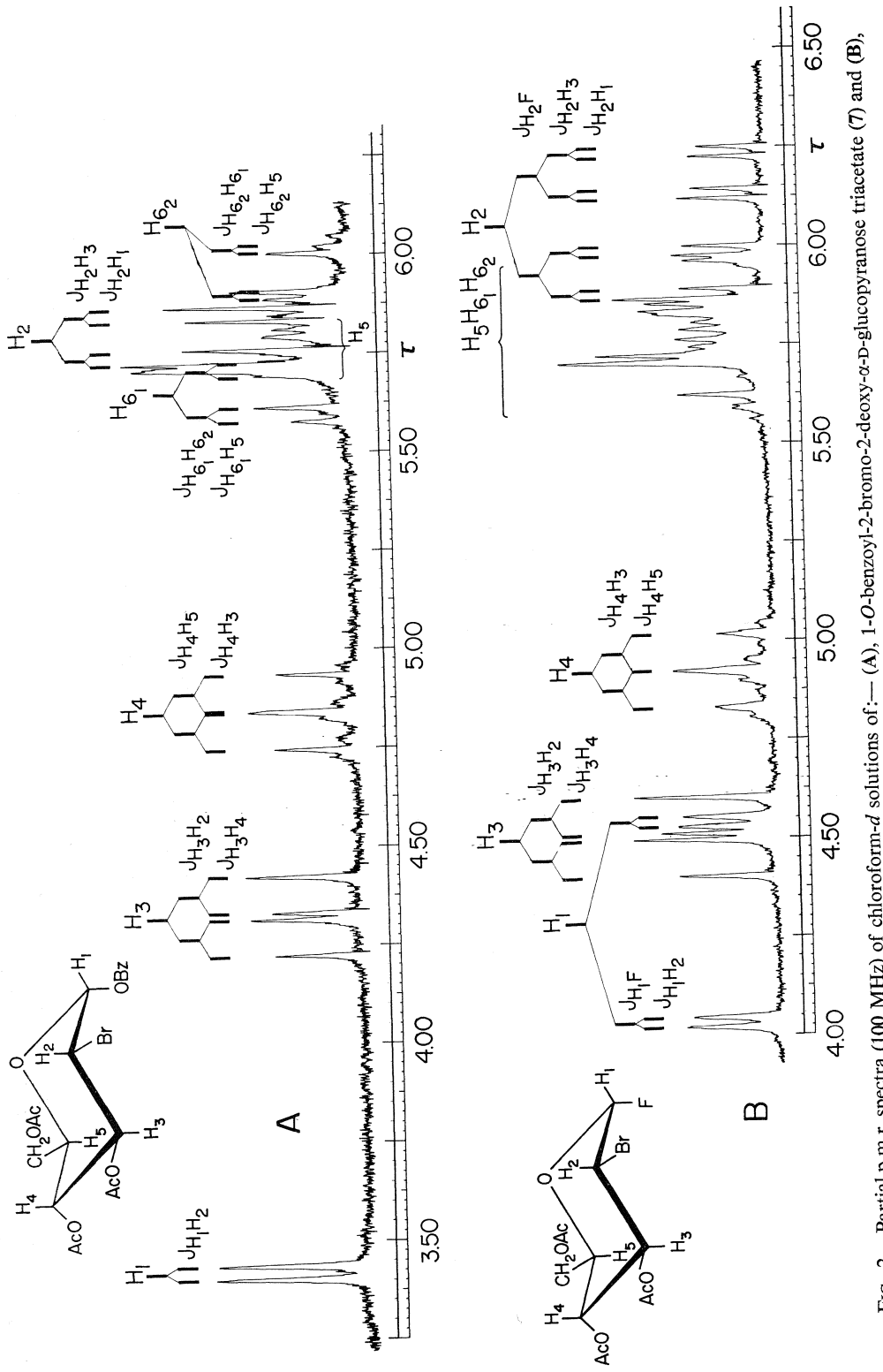
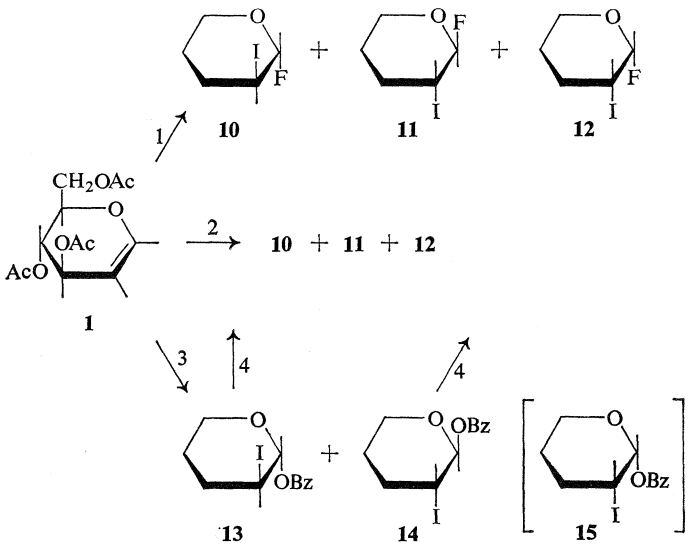


FIG. 2. Partial p.m.r. spectra (100 MHz) of chloroform-*d* solutions of:— (**A**), 1-*O*-benzoyl-2-bromo-2-deoxy-α-D-glucopyranose triacetate (**7**) and (**B**), 2-bromo-2-deoxy-α-D-glucopyranosyl fluoride triacetate (**4**).



1, I_2 in C_6H_6, AgF in CH_3CN
2, *N*-iodosuccinimide and anhydrous liquid HF in Et_2O
3, I_2 in C_6H_6, AgOBz in C_6H_6
4, HF

Flow Sheet 2

synthesis for the β-D-*gluco* derivative (**3**). Partial success of this objective was attained as follows. Reaction of the β-D-*gluco*-bromo-benzoate (**6**) with HBr in glacial acetic acid afforded the corresponding glucopyranosyl bromide (18). The p.m.r. spectrum of this crude product showed that no starting material remained and that the bromide had the α-D-*gluco* configuration. This bromide was then reacted, without purification, with silver monofluoride in acetonitrile solution. This reaction afforded in high yield, as the sole glycosyl fluoride {^{19}F n.m.r. showed that none of the *cis* product (α-anomer) was formed}, material having spectral properties identical with those of the β-D-glucosyl fluoride (**3**). Initially, this syrupy material was contaminated with some of the bromo-benzoate (**6**) which was partially removed by crystallization. However, all attempts to crystallize **3** have failed, even though it contains less than 5% of impurities (p.m.r.); thin-layer chromatography (t.l.c.) shows only one spot. A similar reaction sequence, starting with the D-*manno* bromo-benzoate (**5**) gave as the sole glycosyl fluoride (^{19}F n.m.r.) the α-D-mannosyl fluoride (**2**). This reaction demonstrates that the bromine at C-2 participates during these exchange reactions. Again the fluoride was contaminated with its bromo-benzoate precursor; however, since the crude bromide did not contain any starting material (p.m.r.), the bromo-benzoate (**5**) must have been formed during the exchange reaction itself (see later). The mannosyl fluoride (**2**) was obtained pure after fractional crystallization.

To characterize further the α-D-*manno* derivative (**2**) attempts were made to remove the bromine substituent from C-2 by hydrogenolysis, which should afford the known (19) 2-deoxy-α-D-*arabino*-hexopyranosyl fluoride triacetate (**9**). Although a pure specimen could not be isolated from an atmospheric hydrogenolysis (palladium catalyst), it was present in the reaction product to the extent of ca. 40% as evidenced by both ^{19}F n.m.r. and p.m.r. spectroscopy. The ^{19}F n.m.r. spectrum showed, apart from a small amount of the starting material remaining, and the desired product **9**, *no other glycosyl fluoride resonances*. Interestingly the p.m.r. spectrum showed that the major by-product of the hydrogenolysis was D-glucal triacetate (**1**). Since the bromo-fluoro derivative (**2**) could be recovered in high yield after stirring with diethylamine and palladium–charcoal at 100° for 2 h, this by-product could not have come directly from **2**.

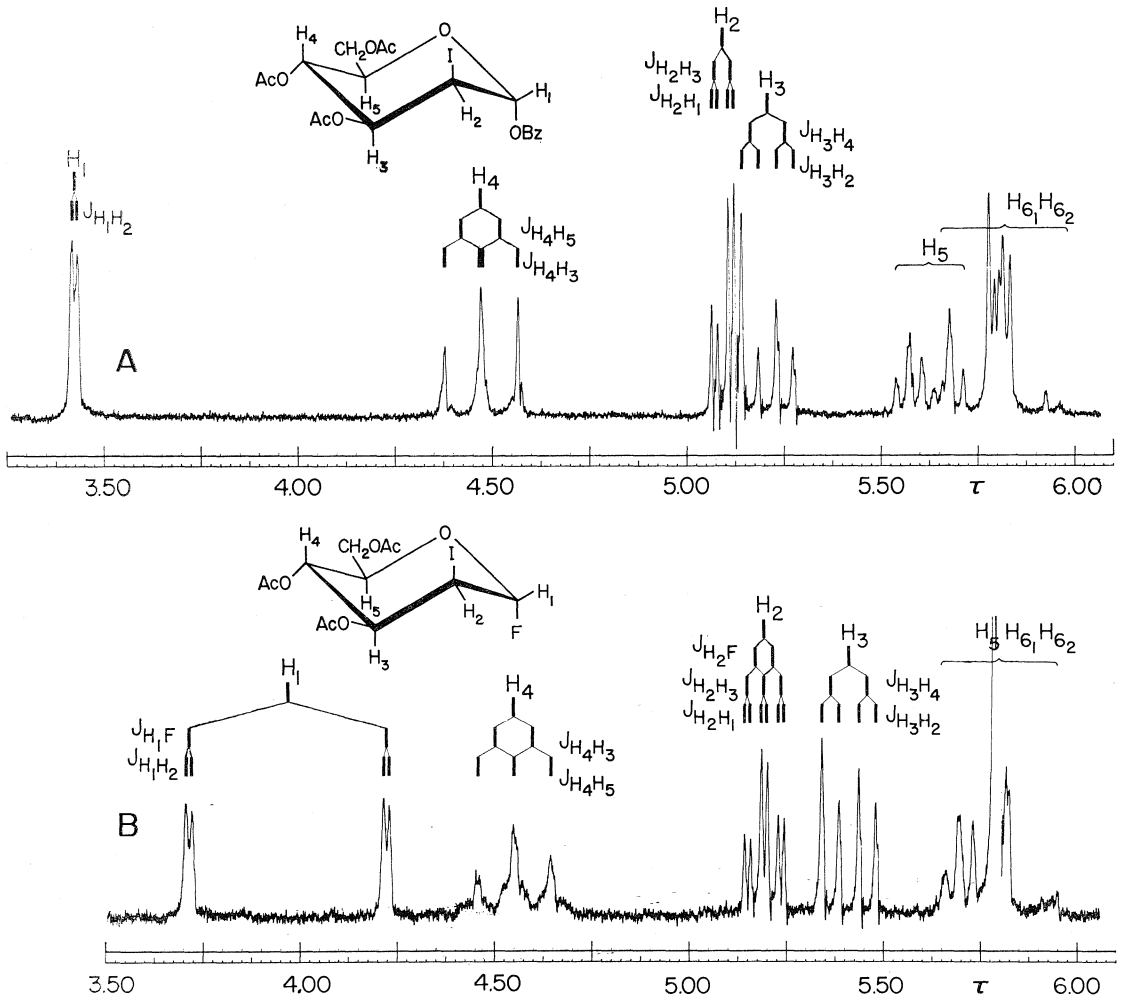


FIG. 3. Partial p.m.r. spectra (100 MHz) of acetone-d_6 solutions of:— (**A**), 1-*O*-benzoyl-2-deoxy-2-iodo-α-D-mannopyranose triacetate (**13**) and (**B**), 2-deoxy-2-iodo-α-D-mannopyranosyl fluoride triacetate (**10**).

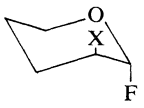
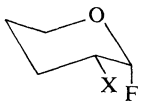
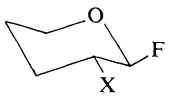
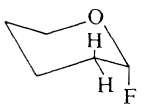
The demonstrated success of the Br_2/AgF reagent for effecting the addition of "BrF" to D-glucal triacetate (**1**), prompted us to extend this approach to the addition of "IF" to **1**. Flow Sheet 2 outlines the reactions which were studied and the products which were isolated. Since the basic format of this part of the work parallels that described above for the addition of "BrF", a detailed discussion will not be given. The details are outlined in the Experimental section and the product ratios are given in Table I. It is sufficient to state here that the products isolated in crystalline form were shown to be 2-deoxy-2-iodo-α-D-mannopyranosyl fluoride triacetate (**10**), 2-deoxy-2-iodo-α-D-glucopyranosyl fluoride triacetate (**12**); an impure sample of syrupy 2-deoxy-2-iodo-β-D-glucopyranosyl fluoride triacetate (**11**) was also isolated. The ^1H spectrum of the α-D-*manno* derivative (**10**) is shown in Fig. 3*b*, together with that of the corresponding 1-*O*-benzoate (**13**) (Fig. 3*a*) for comparison.

At this point, a comparison will be made of the procedure for adding the elements of "XF" outlined above and the Bowers method (3) together with a discussion of points of mechanistic interest.

Kent and co-workers (5) have studied the Bowers addition of "BrF" and "IF" to D-glucal

TABLE I

Product ratios for the addition of the elements of "XF" and of "XOBz" to D-glucal triacetate (**1**)

		Products*			
					
$AgF+X_2$	X=Br	70%	9%	21%	—
	X=I	60%	6%	34%	—
HF+NXS†	X=Br	55%	9%	30%	7%
	X=I	71%	23%	3%	0%
$AgOBz+X_2$	X=Br	31%	26%	42%	—
	X=I	64%	8%	28%	—

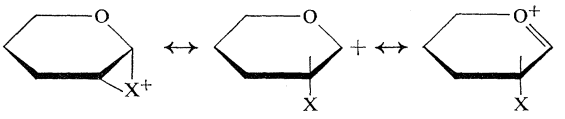
*Ratios determined by integration of the ^{19}F n.m.r. and/or p.m.r. spectra.
†NXS = *N*-halosuccinimide.

triacetate. This reaction has been repeated during the present study and with the aid of ^{19}F n.m.r. spectroscopy, the products (shown in Table I), together with their ratios, have been found. The major components, which Kent reported as the β-D-*manno* derivatives were found to be identical with the α-D-mannopyranosyl fluorides (**2** and **10**) described in this paper. It is evident that the published (5) description of these derivatives as possessing the β-D-manno configuration, will have to be corrected; as a direct result it is necessary for Kent's proof of a "*cis*" mechanism to withstand closer examination. It is noteworthy that in the Bowers addition of "BrF" to D-glucal triacetate (**1**) a product arising from the addition of HF across the double bond is formed, namely, 2-deoxy-α-D-*arabino*-hexopyranosyl fluoride triacetate (**9**). The formation of this product was not anticipated since Pedersen (20) had shown that treatment of **1** with anhydrous HF affords 4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hexosyl fluoride. However, neglecting the above "by-product", the product ratios, resulting from these two different methods for generating "XF", are extremely close; thus for **1**, the two methods may follow a similar mechanism.

Before discussing any details of this mechanism it is necessary to consider the stereospecificity of some of the reactions encountered during the proof of structure of the "BrF" adducts. The most important of these concerns the fluorine exchange reactions of the glycosyl bromides involved in the conversion of **5** to **2** and of **6** to **3**. In both instances this reaction proceeds to give exclusively that glycosyl fluoride having the fluorine *trans* to the C_2-halogen substituent. It is particularly significant that the conversion of **6** to **3** *does not* lead to the formation of any of the α-anomer, which is formed, in ca. 9% yield, during the "XF" addition reaction itself. This finding immediately excludes the possibility, which we have thus far ignored, that the "XF" addition itself merely involves the formation of the 1,2-dibromide(s) (18) which subsequently react(s) with the silver fluoride to give the glycosyl fluoride(s).

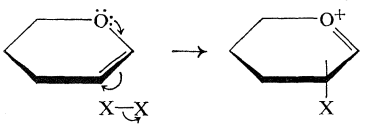
The conversion of **5** exclusively to **2** demonstrates conclusively that a halogen atom (bromine) at C-2 of a pyranose carbohydrate controls the course of the exchange reaction at C-1, when silver fluoride is used to effect this exchange. This exchange proceeds with 100% retention of configuration at C-1, possibly via an S_Ni mechanism, in which the bromine at C-2 participates in the ejection of the halide from C-1, forming a halonium type intermediate, which subsequently reacts with the incoming nucleophile, F^-.

This observed participation of halogen (bromine) at C-2 in exchange reactions at C-1 has an important significance as to the proposed mechanism (5, 21) for electrophilic addition reactions of glycals. Lemieux and Fraser-Reid (7) proposed for such reactions that the initiating step is the formation of a cyclic halonium ion and that the actual transition state ". . . . can be expected to be a resonance hybrid of the following canonical structures" (for example)



A B C

This statement is acceptable insofar that **A** could clearly afford a *trans* product, whilst both **B** and **C** could lead to either *trans* or (more importantly) *cis* products. However, it is difficult to see why a cyclic halonium ion (**A**) formed during a direct "XF" addition should be in resonance with **B** and **C**, whereas the cyclic halonium ion postulated for the halogen exchange reaction is apparently (by lack of formation of *cis* products) not in resonance with either **B** or **C**. Several possible rationales can be offered for this apparent dilemma, although it must be emphasized that no definitive experimental evidence is presently available. One is that it is totally inappropriate to compare the "XF" addition reaction with the exchange reaction. However, since particular attempts were made during this work to keep the reaction conditions of these two sequences as near identical as possible, this seems to beg the issue. A second rationale is that in the case of electrophilic additions, the initially formed ion has the form (**C**); its formation could result from anchimeric assistance from the ring oxygen as indicated below. This ion could then react directly with F^- to give either *cis* or *trans*



C

products. Alternatively, it could change to, or be in resonance with, the carbonium ion (**B**) which would also lead to *cis* or *trans* products; or it could change to **A** which, by analogy with the AgF exchange reactions, would necessarily lead exclusively to the *trans* product. To account for the exclusive formation of *trans* products during AgF exchange reactions, it would be necessary to postulate that reaction of a halonium ion such as **A** with F^- be very fast compared with the possible equilibrium between **A** and **B** or **C**.

In view of the paucity of really definite data it is not worthwhile pursuing this discussion further at this time. It is, however, interesting to note the similarity between the product ratios for the "XF" additions described in this study and those previously reported by Lemieux and Fraser-Reid (7) for "XOR" additions; in many instances the basic characteristics of the "XF" and "XOR" reactions would appear to be similar. If this is generally the case, it seems reasonable to suggest that studies of "XF" addition reactions may serve as convenient models for gaining insight as to the nature of the more general "XOR" additions. Thus, advantage can be taken of the wide dispersion of ^{19}F chemical shifts to monitor the product ratios and to determine in a facile and unequivocal fashion the configurations of the products arising from these reactions.

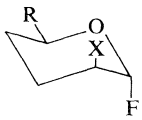
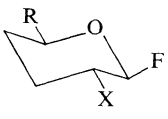
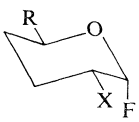
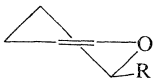
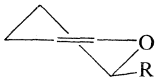
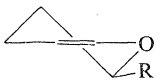
Already one situation has been encountered where such a "model" study proved to be useful. During the course of reactions leading to the stereoselective syntheses of the "XF" adducts, it was necessary to effect the addition of "XOBz" to D-glucal triacetate (**1**). Following closely the method of Lemieux and Levine (15) the two products arising from *trans* addition of "IOBz" were isolated. However, the observation, by ^{19}F n.m.r. spectroscopy, of ca. 9% of the α-D-*gluco* adduct from an "IF" addition to **1**, prompted the reinvestigation of the original "IOBz" addition. Inspection of the crude reaction mixture by p.m.r. spectroscopy revealed the presence (ca. 8%) of an anomeric resonance corresponding to the α-D-*gluco* derivative. Following a similar reaction sequence, "BrOBz" addition to **1** resulted in significant amounts (ca. 26%) of the *cis*, or α-D-*gluco*, adduct (**7**).

It is, therefore, clearly established that electrophilic addition reactions can result in *cis* addition to the double bond of acetylated glycals, although the *cis* product is usually a minor component. This result should be compared with those found for electrophilic addition reactions to cycloalkenes, in which *trans* additions are generally (though not exclusively) observed (8, 12) for those reactions proceeding via an ionic mechanism. It follows that the ring oxygen of the glycals must significantly alter the nature of the reaction, thus allowing the formation of *cis* products.

It is convenient at this time to discuss the use of ^{19}F n.m.r. for determining the nature and ratio of the products arising from "XF" addition reactions to other α,β-unsaturated cyclic ethers. Since most of these products were not in an analytically pure state and were identified mainly

TABLE II

Product ratios for the addition of the elements of "XF" to some 3,4-dihydro-2*H*-pyrans

Reactant	Reaction	% yield and configuration of products		
				
 **(16)** R = H	BrF* BrF† IF*	84 (**19**) 55–60 (**19**) 95 (**21**)	— — —	16 (**20**) 40–45 (**20**) ca. 5 (**22**)
 **(17)** R = CH_2OAc	BrF* IF*	57 (**23**) 78 (**26**)	20 (**24**) 17 (**27**)	18 (**25**) ca. 5 (**28**)
 **(18)** R = CH_2OTs	BrF* BrF† IF*	66 (**29**) 55 (**29**) 76 (**32**)	25 (**30**) — (**30**) 18 (**33**)	6 (**31**) 45 (**31**) 5 (**34**)

*"XF" generated from AgF and X_2.
†"BrF" generated from anhydrous liquid HF and *N*-bromosuccinimide.

on the basis of their ^{19}F n.m.r. parameters, these results have not been used during the discussion of possible mechanisms for the "XF" addition reaction. The results arising from these reactions are summarized in Table II. The ^{19}F n.m.r. parameters for these reaction products will be found in the Experimental section.

The "XF" addition reactions of dihydropyran (**16**) resulted in the formation of *two* products; these are the trans-diaxial (α-*manno*)[4] and *cis* (α-*gluco*)[4] isomers. Their identification is straightforward since the *cis* isomers (**20, 22**) displayed large (ca. 25 Hz) *vicinal* ^{19}F–^{1}H couplings, indicative of a *trans-diaxial* arrangement, whereas, the *trans* isomers (**19, 21**) showed small (ca. 1.5 Hz) couplings. The product ratios found for the "XF" reactions (AgF + X_2) are as expected, 80% *trans*. The unusually large percentage of *cis* (**20**) formation found for the Bowers reaction may reflect the fact that there is now equilibrium control over the product ratio.

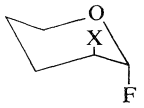
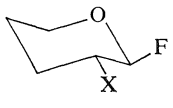
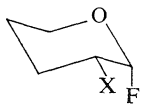
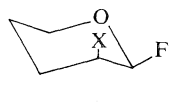
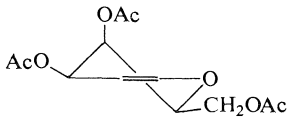
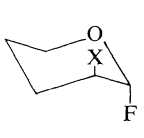
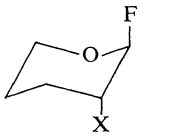
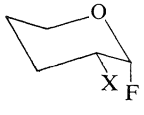
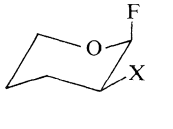
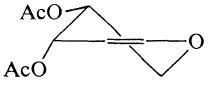
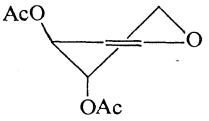
The "XF" additions (X_2 + AgF) to the "C-5" substituted dihydropyrans[4] **17** and **18** resulted in formation of *two trans* isomers and a smaller percentage of the *cis* isomer (α-*gluco*). These results are qualitatively the same as those found previously for D-glucal triacetate (**1**). The high percentage of *cis* product (**31**) arising from the "BrF" (Bowers) reaction to **18** could be a result of isomerization of the *trans-diequatorial* isomer (β-*gluco*) to the more stable *cis* isomer (α-*gluco*) as the former could not be detected.

Results of "XF" (X_2 + AgF) addition to three other glycals are summarized in Table III. Tentative identification of these reaction products followed from comparison with the results found for D-glucal triacetate **1** and their ^{19}F n.m.r. parameters which can be found in the Experimental section. The product ratios arising from "XF" addition to D-galactal triacetate (**35**) appear to reflect the fact that there is now an axially oriented acetoxy substituent at C-4 {low percentage of the α-D-*talo* isomers **38** and **41**} and

[4]We have used the expressions "α-*gluco*" and "α-*manno*" in order to facilitate comparison of these results with those described earlier. Strictly, this nomenclature is incorrect, as also is the reference to "C-5 substituted dihydropyrans".

TABLE III

Product ratios for the addition of the elements of "XF" to glycals*

Reactant	Reaction	% yield and configuration of products			
					
 (35)	BrF IF	34 (**38**) 25 (**41**)	43 (**39**) 41 (**42**)	24 (**40**) 34 (**43**)	— —
					
 (36)	BrF IF	62 (**44**) 49 (**47**)	20 (**45**) 38 (**48**)	18 (**46**) 13 (**49**)	— —
 (37)	BrF IF	55 (**51**) 46 (**55**)	32 (**52**) 43 (**56**)	5 (**53**)† 8 (**57**)†	8 (**54**)† 3 (**58**)†

*"XF" addition reactions using X_2 and AgF.
†Identification *tentative*, see Experimental.

these results are in agreement with those reported by Lemieux and Fraser-Reid (7) for "XOR" addition reactions.

Identification of the reaction products arising from "XF" addition to the pentals (**36**) and (**37**) are tentative. They were identified on the basis of their *vicinal* ^{19}F–^{1}H couplings and the fact that the *trans-diaxial* isomers are expected to be the preferred ones. Nevertheless, there is one very interesting result that does not depend on the precise identification of the individual products. It was noted that "XF" (X = Br,I) additions to D-xylal diacetate **37** results in the formation of all *four* diastereoisomers, whereas, only three are formed in the case of D-arabinal diacetate **36**. This result may reflect the difference in the ground state conformations of these two molecules, which are shown in Table III, (these conformations were deduced from detailed analysis of their p.m.r. spectra). The conformation of D-arabinal diacetate is such that both acetate substituents are in stereo-electronically favorable orientations; the one at C-3 is *pseudo-axial* {allylic effect (22)} and the acetate at C-4 is *equatorial*. In contrast, D-xylal diacetate has the acetate at C-4, *axially* oriented, in the ground state conformation. As soon as either of these glycals react with halogen, the allylic effect of the double bond will be removed: for D-arabinal diacetate the resulting (carbonium?) ion will be in an energetically stable ground state; however, for D-xylal diacetate, the ion will have at least two substituents axially oriented and will therefore be energetically metastable with respect to the inverted ($^{4}C_{1}$-D) conformer. In the event that the rate of conformational inversion exceeds the rate of attack by F^{-}, it is clearly possible for the intermediate ion to form products from either of its

two possible conformers and hence to form four, rather than three, adducts.

The addition of "IOBz" to D-arabinal diacetate and to D-xylal diacetate resulted in syrupy mixtures of three and four products, respectively. Only one component, from the D-arabinal addition reaction was obtained crystalline. It proved to be 1-*O*-benzoyl-2-deoxy-2-iodo-β-D-ribopyranose diacetate (**50**) (p.m.r. evidence; see Experimental section). Since further attempts to obtain these materials in crystalline form are to be made, we shall not discuss them further at this time. It is unfortunate that the isomeric sets of derivatives have similar mobilities on t.l.c. plates.

In conclusion, we have shown that ^{19}F n.m.r. spectroscopy provides a facile method for identifying the products arising from the addition of the elements of "XF" to unsaturated carbohydrate systems. We further suggest that advantage can be taken of the considerable steric sensitivity of ^{19}F chemical shifts to use "IF" additions as models for other "IOR" addition reactions; we are continuing to develop this approach and to study the effect of solvent changes on the product ratios. It is regrettable that the concept of *cis* addition of the elements of "XF" to glycals should have as its foundation the incorrect assignment of a structure (the α-D-*manno* derivatives (**2**) and (**10**)), since the result is evidently quite general and of some importance as far as electrophilic addition reactions to α,β-unsaturated cyclic ethers are concerned. Since the acceptance of a preliminary communication of these results (2), Dr. Kent has informed us[5] that he has independently revised the structure for "BrF" adduct (**2**) derived from D-glucal triacetate (**1**), and now concurs with the α-D-*manno* configuration.

A detailed discussion of the n.m.r. parameters of the derivatives whose syntheses have been described in this paper will be given later in this series.

Experimental

The general methods and nuclear magnetic resonance (n.m.r.) measurements followed the format outlined previously (1).

Electrophilic Addition Reactions of D-*Glucal Triacetate (**1**) Addition of the Elements of "BrF"*

(a) Generated from Br_2 and AgF—D-Glucal triacetate (**1**)[6] (1.36 g) in dry acetonitrile (ca. 25 ml) was stirred vigorously with powdered silver monofluoride[7] (4 g). A solution of bromine (0.85 g, 10% w/v in benzene) was then added dropwise. After completion of the bromine addition (ca. 10 min), the solution was stirred for a further 20 min and then filtered from the copious precipitate of silver halide. To this solution were added 5 ml of saturated aqueous sodium chloride, the precipitated silver chloride was removed, the filtrate was concentrated to ca. 10 ml and chloroform (30 ml) was added. The chloroform solution was extracted successively with aqueous sodium thiosulfate, aqueous sodium bicarbonate and water. After drying (Na_2SO_4), evaporation produced a clear syrup (1.8 g, 97%). Inspection (by proton magnetic resonance (p.m.r.)) of the crude reaction product showed that no starting material remained and ^{19}F n.m.r. showed the presence of *three* glycopyranosyl fluorides which were subsequently identified as:—2-bromo-2-deoxy-α-D-mannopyranosyl fluoride triacetate (**2**) 70%, ϕ_c +123.2, $J_{1,F}$ 50.2 Hz; $J_{2,F}$ 2.85 Hz; 2-bromo-2-deoxy-β-D-glucopyranosyl fluoride triacetate (**3**) 21%, ϕ_c +136.0, $J_{1,F}$ 50.3 Hz; $J_{2,F}$ 10.0 Hz and 2-bromo-2-deoxy-α-D-glucopyranosyl fluoride triacetate (**4**) 9%, ϕ_c +144.9, $J_{1,F}$ 51.5 Hz; $J_{2,F}$ 25.2 Hz.

After work-up, the reaction mixture was dissolved in boiling diethyl ether and on cooling the solution deposited crystals (0.98 g), m.p. 137–142°; addition of light petroleum afforded a second crop of the same material (0.13 g), total yield 1.11 g; 56%. Recrystallization from ethanol afforded pure **2** as prismatic crystals m.p. 138–140°, $[\alpha]_D^{22}$ −32.0° (*c*, 2.06).

Anal. Calcd. for $C_{12}H_{16}O_7BrF$: C, 38.8; H, 4.3; F, 5.1. Found: C, 39.0; H, 4.5; F, 5.0.

The mother liquors remaining after isolation of **2** were evaporated and the resulting syrup dissolved in ethanol and cooled to −5°; after several weeks an impure sample of **4** was obtained (0.12 g, 6%). Recrystallization, twice from aqueous ethanol afforded pure **4** as fine needles; m.p. 120–121°, $[\alpha]_D^{22}$ +134.5° (*c*, 1.80).

Anal. Calcd. for $C_{12}H_{16}O_7BrF$: C, 38.8; H, 4.3; F, 5.1. Found: C, 39.0; H, 4.45; F, 4.95.

The residual syrup from above was shown (by n.m.r.) to contain mainly the β-D-*gluco* isomer (**3**) together with smaller quantities of the other isomers (**2**) and (**4**). Fortunately this syrup was sufficiently pure for detailed n.m.r. analysis; it has so far failed to crystallize.

Reinvestigation of the above reaction, using only benzene as solvent, yielded the same three isomers, but in quite different ratios and the overall yield of adducts was only 83%; the α-D-*manno* isomer (**2**), 42%, the β-D-*gluco* isomer (**3**), 42% and the α-D-*gluco* isomer (**4**) 16%.

(b) Generated from N-bromosuccinimide and anhydrous liquid HF—Following the procedure outlined by Kent *et al.* (5*a*), this reaction was repeated several times, using slightly different reaction times. The yields reported are

[5]P. W. Kent. Private communication, December 27, 1967.

[6]**1** was a commercial sample from the Aldrich Chemical Co., Milwaukee, Wisconsin, which was purified by recrystallization from aqueous ethanol.

[7]The silver monofluoride was a commercial sample from Harshaw Chemical Co. Cleveland, Ohio, and was ground to a fine powder before use.

average results. Anhydrous hydrogen fluoride (10 g) was added to anhydrous diethyl ether (18 g) in a polythene bottle cooled to ca. −78° (solid-CO_2/acetone). *N*-Bromosuccinimide (4.0 g) and D-glucal triacetate (**1**) (5.0 g) were added, portionwise, to the stirred solution, over the course of ca. 10 min. After 0.5–2 h at −78°, the temperature was raised to 0° for a further 0.5–2 h. After dilution with anhydrous diethyl ether, the solution was decomposed by pouring directly into an ice-cold, saturated aqueous solution of sodium bicarbonate. The ethereal layer was subsequently extracted with water, dried (Na_2SO_4), and evaporated. Investigation (p.m.r.) of the crude reaction product showed that no starting material remained and ^{19}F n.m.r. showed the presence of *four* glycopyranosyl fluorides which were identified on the basis of their ^{19}F chemical shifts and ^{19}F–^1H coupling constants, as the α-D-*manno* isomer (**2**) ca. 55%, the β-D-*gluco* isomer (**3**) ca. 30% and the α-D-*gluco* isomer (**4**) ca. 9%; the fourth resonance has been identified (19) as 2-deoxy-α-D-*arabino*-hexopyranosyl fluoride triacetate (**9**) ca. 8%, ϕ_c +131.1, $J_{1,F}$ 51.2 Hz; $J_{2e,F}$ 5.0 Hz; $J_{2a,F}$ 38.0 Hz.

The syrupy mixture was dissolved in diethyl ether and on cooling, the solution deposited **2** (1.85 g, 32%). Recrystallization from 1:5 v/v chloroform – light petroleum afforded pure **2** m.p. and mixture m.p. 139–140°, with the compound obtained above. The remaining compounds from this reaction were not isolated as they had been previously characterized in this study.

The α-D-*manno* isomer **2** was heated under reflux for 24 h in acetonitrile containing a molar excess of silver monofluoride and was recovered unchanged. It was also unaffected when resubjected to treatment with *N*-bromosuccinimide and anhydrous HF as described above.

Partial hydrogenolysis of **2**, at atmospheric pressure (10% palladium–charcoal catalyst, diethylamine as acid acceptor) in methanol solution gave (n.m.r. evidence) the 2-deoxy fluoride (**9**) together with unreacted starting material (**2**) and D-glucal triacetate (**1**). The α-D-*manno* derivative (**2**) was unaltered when heated under reflux in methanol solution containing diethylamine and palladium–charcoal catalyst.

Addition of the Elements of "IF"

(a) Generated from I_2 and AgF—Following the same procedure (as described above for the generation of "BrF" from Br_2 and AgF), D-glucal triacetate (**1**) (1.36 g) was reacted with I_2 (1.25 g) and AgF (2 g) to form a clear syrup in 98% yield. This syrup contained (^{19}F n.m.r.) *three* glycopyranosyl fluorides: 2-deoxy-2-iodo-α-D-mannopyranosyl fluoride triacetate (**10**) 60%, ϕ_c + 116.9, $J_{1,F}$ 51.7 Hz; $J_{2,F}$ 3.9 Hz; 2-deoxy-2-iodo-β-D-glucopyranosyl fluoride triacetate (**11**) 34%, ϕ_c +132.3, $J_{1,F}$ 49.9 Hz; $J_{2,F}$ 9.3 Hz and 2-deoxy-2-iodo-α-D-glucopyranosyl fluoride triacetate (**12**) 6%, ϕ_c + 139.8, $J_{1,F}$ 50.5 Hz; $J_{2,F}$ 27.8 Hz.

The α-D-*manno* isomer (**10**) was obtained crystalline from an ether solution of the reaction mixture and was crystallized from ethanol to give pure **10** as prismatic crystals (yield 1.0 g, 47%); m.p. 155–156°, $[\alpha]_D^{22}$ −46.1° (*c*, 2.54).

Anal. Calcd. for $C_{12}H_{16}O_7FI$: C, 34.45; H, 3.85; F, 4.55. Found: C, 34.7; H, 4.0; F, 4.65.

The mother liquors remaining from crystallization of **10** were concentrated to a syrup which was dissolved in ethanol. The α-D-*gluco* isomer (**13**) was obtained from this solution after several weeks of standing at 0°. Recrystallization from aqueous ethanol afforded fine needles (yield 0.10 g, 4.8%); m.p. 143–144°, $[\alpha]_D^{22}$ +180.5° (*c*, 2.72).

Anal. Calcd. for $C_{12}H_{16}O_7FI$: C, 34.45; H, 3.85; F, 4.55. Found: C, 34.6; H, 4.0; F, 4.65.

The mother liquors were found (n.m.r.) to contain mainly the β-D-*gluco* isomer (**11**). Column chromatography (silica gel, 1% MeOH in CH_2Cl_2 as eluant) yielded a clear syrup which was sufficiently pure for detailed n.m.r. analysis. To date, this compound has not been obtained crystalline.

Upon reinvestigation of this reaction, using only benzene for solvent, the same three isomers were obtained (yield 79%) in the following ratio: the α-D-*manno* isomer (**10**) 33%, the β-D-*gluco* isomer (**11**) 45%, and the α-D-*gluco* isomer (**12**) 22%.

(b) Generated from N-iodosuccinimide and anhydrous liquid HF—Following the procedure of Wood *et al.* (5*b*), a partially crystalline mass was obtained which contained (^{19}F n.m.r.) the same *three* glycopyranosyl fluorides in the following ratios: the α-D-*manno* isomer (**10**) 71%, the β-D-*gluco* isomer (**11**) 3%, and the α-*gluco* isomer (**12**) 23% together with a small (3%) unidentifiable resonance at ϕ_c +125.3. None of the deoxy isomer (**9**) could be detected.

Addition of the Elements of "BrOBz"

D-Glucal triacetate (**1**) (1.36 g) was dissolved in benzene (25 ml) to which was added silver benzoate[8] (2.5 g); 8.5 ml of a bromine solution (10% w/v in benzene) were added dropwise to the stirred suspension. After a further 20 min, the suspension was filtered and the filtrate was then extracted successively with aqueous sodium bicarbonate and water. The benzene solution was dried (Na_2SO_4) and evaporated to a clear syrup (2.23 g).

Inspection (by p.m.r.) of this crude reaction product indicated four anomeric resonances, which were attributed to the four isomeric "BrOBz" adducts. They were formed in the following yields: the α-D-*manno* isomer (**5**) 31%, τ H_1 = 3.44, $J_{1,2}$ 1.8 Hz; α-D-*gluco* isomer (**7**) 26%, τ H_1 = 3.43, $J_{1,2}$ 3.5 Hz; β-D-*gluco* isomer (**6**) 42%, τ H_1 = 3.94, $J_{1,2}$ 9.1 Hz; and β-D-*manno* isomer 2%, τ H_1 = 3.56, $J_{1,2}$ 3.5 Hz.

This crude reaction product was dissolved in a minimum of boiling ethanol and left at room temperature overnight, during which time crystals (1.61 g, 68%) were deposited. These were shown (by p.m.r.) to be an almost equal mixture of the two *trans* isomers (**5**) and (**6**).

The mother liquors were cooled to ca. 0° and after several weeks fine needle shaped crystals were deposited (0.55 g, 23%); recrystallization from aqueous ethanol afforded pure 1-*O*-benzoyl-2-bromo-2-deoxy-α-D-glucopyranose triacetate (**7**) m.p. 112–113°, $[\alpha]_D^{25}$ +213° (*c*, 0.89).

Anal. Calcd. for $C_{19}H_{21}O_9Br$: C, 48.2; H, 4.45; Br, 17.0. Found: C, 48.0; H, 4.5; Br, 17.0.

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[8]Silver benzoate was formed by reacting equimolar aqueous solutions of silver nitrate and sodium benzoate; the crude precipitate was washed with copious amounts of water, filtered (suction), and dried at 120° for 8 h.

The mixture of **5** and **6** was separated in the manner of Lemieux and Levine (15) and was each recrystallized from aqueous ethanol. 1-*O*-Benzoyl-2-bromo-2-deoxy-α-D-mannopyranose triacetate (**5**) had m.p. 168–169°, $[\alpha]_D^{28}$ +62.3° (*c*, 1.54).

Anal. Calcd. for $C_{19}H_{21}O_9Br$: C, 48.2; H, 4.45; Br, 17.0. Found: C, 48.0; H, 4.5; Br, 17.1.

1-*O*-Benzoyl-2-bromo-2-deoxy-β-D-glucopyranose triacetate (**6**) had m.p. 161–162°, $[\alpha]_D^{28}$ +15.3° (*c*, 0.72).

Anal. Calcd. for $C_{19}H_{21}O_9Br$: C, 48.2; H, 4.45; Br, 17.0. Found: C, 48.05; H, 4.6; Br, 17.1.

When the above reaction was repeated using acetonitrile to dissolve the D-glucal triacetate (**1**), the same four products were observed (by n.m.r.) in the following ratios; the α-D-*manno* isomer (**5**) 20%, the β-D-*gluco* isomer (**6**) 35%, the α-D-*gluco* isomer (**7**) 40% and the β-D-*manno* isomer 6%.

Addition of the Elements of "IOBz"

The two isomeric *trans* 1-*O*-benzoyl-2-deoxy-2-iodo-D-pyranose triacetates, **13** and **14**, were obtained by a variant of the method described by Lemieux and Levine (15). 1.36 g of **1** in benzene solution, was used and the iodine (1.35 g) was dissolved in benzene (10% w/v) and added dropwise to the stirred solution.

Investigation (by n.m.r.) of the crude reaction product showed the presence of a third product, not reported by Lemieux and Levine. It was assigned to 1-*O*-benzoyl-2-deoxy-2-iodo-α-D-glucopyranose triacetate (**15**) (τ H-1 = 3.42; $J_{1,2}$ 3.0 Hz). The product ratios as determined by p.m.r. were:— α-D-*manno* isomer (**13**) 46%, the α-D-*gluco* isomer (**15**) 8%, and the β-D-*gluco* isomer (**14**) 46%.

This reaction was repeated, using an acetonitrile solution of D-glucal triacetate (**1**). The same products were observed in the following ratios: the α-D-*manno* isomer (**13**), 64%; the β-D-*gluco* isomer, (**14**) 28%; and the α-D-*gluco* isomer (**15**) 8%.

The α-D-*gluco* isomer (**15**) was not isolated from the mother liquors. The α-D-*manno* isomer (**13**) had m.p. 160–161°, lit. (15) m.p. 159.5–160°, $[\alpha]_D$ +45.3° and the β-D-*gluco* isomer (**14**) had m.p. 150–151°, lit. (15) m.p. 150–151.5°, $[\alpha]_D$ +2.2°.

Stereoselective Syntheses of Products Formed during the Addition Reactions of D-*Glucal Triacetate*

2-Bromo-2-deoxy-α-D-mannopyranosyl fluoride triacetate (2)—1-*O*-Benzoyl-2-bromo-2-deoxy-α-D-mannopyranose triacetate (**5**) (0.25 g) was converted to the 2-bromo-2-deoxy-α-D-mannopyranosyl bromide triacetate (18) which was immediately dissolved in acetonitrile (20 ml) containing silver monofluoride (1 g). The solution was then shaken for ca. 20 min (no more precipitate was formed after ca. 15 min). Work-up, following the procedure described previously (1) for halogen exchange reactions, produced a clear syrup which contained (^{19}F n.m.r.) only *one* fluoride (**2**); however, p.m.r. showed the presence of ca. 20% of the starting material (**5**).

This syrup was dissolved in ethanol and the benzoate (**5**) was precipitated (0.050 g, m.p. 171–174°) leaving a colorless solution which contained mainly the desired fluoride. This solution was evaporated, dissolved in 3 ml of chloroform, petroleum ether (20 ml) was added and the solution cooled to ca. 5°. Crystals of **2** m.p. 137–142° were deposited which were recrystallized from aqueous ethanol (0.102 g, 51%) m.p. 138–140°.

The fluoride (**2**) was also prepared, as described (1) for the formation of α-D-glucopyranosyl fluoride tetraacetate, from the benzoate (**5**) (0.05 g) by action of anhydrous liquid HF. The desired compound (**2**) was obtained in 63% yield; m.p. and mixture m.p. with samples obtained previously, 139–140°.

This compound was identical in every respect with the product obtained in the bromofluorination reactions described above.

2-Bromo-2-deoxy-β-D-glucopyranosyl fluoride triacetate (3)—1-*O*-Benzoyl-2-bromo-2-deoxy-β-D-glucopyranose triacetate (**6**) (0.25 g) was converted as described above to the 2-bromo-2-deoxy-α-D-glucopyranosyl bromide triacetate, which was immediately dissolved in acetonitrile (20 ml) containing silver monofluoride (1 g). Starting material (0.053 g, 21%) was isolated from this reaction leaving the desired fluoride (**3**) (0.095 g, 62%). This product, however, has not been obtained either pure or crystalline. ^{19}F n.m.r. showed only the desired fluoride, none of the corresponding *cis* isomer (**4**) could be detected

2-Bromo-2-deoxy-α-D-glucopyranosyl fluoride triacetate (4)—1-*O*-Benzoyl-2-bromo-2-deoxy-β-D-glucopyranose triacetate (**6**) (0.25 g) was converted, in the manner described (1) for the formation of α-D-glucopyranosyl fluoride tetraacetate, with anhydrous hydrogen fluoride, into the desired fluoride (**4**) (0.11 g, 58%) with m.p. and mixture m.p. with sample obtained previously, 120–121°.

2-Deoxy-2-iodo-α-D-mannopyranosyl fluoride triacetate (10)—1-*O*-Benzoyl-2-deoxy-2-iodo-α-D-mannopyranose triacetate (**13**) (0.25 g) was reacted in the usual manner with anhydrous hydrogen fluoride to give the desired fluoride (**10**), (0.10 g, 50%) with m.p. and mixture m.p. with a sample previously obtained, 153–155°.

2-Deoxy-2-iodo-α-D-glucopyranosyl fluoride triacetate (12)—1-*O*-Benzoyl-2-deoxy-2-iodo-β-D-glucopyranose triacetate (**14**) (0.25 g) was subjected, in the usual manner, to react with hydrogen fluoride. The desired fluoride (**12**) was formed in a yield of 60%; m.p. and mixture m.p. with a sample obtained previously, 142–144°.

The above halogenofluorinations (bromine and iodine) were also performed on the following model compounds; vinyl acetate, 3,4-dihydro-2*H*-pyran (**16**), the acetate of 3,4-dihydro-2*H*-pyran-2-methanol (**17**), and the *p*-toluenesulfonate of 3,4-dihydro-2*H*-pyran-2-methanol (**18**). In each case, the product had halogen at C-2 and fluorine at C-1[9]: with the exception of those from the tosylate (**18**), the products were unstable liquids or oils which could not be isolated in a pure state. However, it was possible to determine their product ratios by ^{19}F n.m.r.

Reactions of Vinyl Acetate[10]

(a) Bromofluorination, "BrF" generated from Br_2 and AgF—This bromofluorination afforded only *one* fluorine

[9]These reaction products are given trivial names. It is felt that these trivial names adequately describe the reaction products and facilitate greatly the comparison between these reaction products and those described previously for the D-glucal triacetate adducts. See also footnote[4] given in the discussion.

[10]Vinyl acetate was a commercial sample from the Aldrich Chemical Co., Inc., Milwaukee, Wisconsin.

containing product; ϕ_c +121.9, (doubletted triplet) J_{gem} ca. 50 Hz, J_{vic} ca. 15 Hz. Solely on the basis of the ^{19}F n.m.r. data, it was concluded that the product had the structure $CH_2BrCHFOAc$.

*Reactions of 3,4-Dihydro-2H-Pyran (**16**)*[11]

(a) Bromofluorination, "BrF" generated from Br_2 and AgF—This bromofluorination of **16** afforded *two* fluorine containing products: the *trans* isomer (**19**) 84%, ϕ_c +122.8, $J_{1,F}$ 51.3 Hz, $J_{2,F}$ 4.6 Hz and the *cis* isomer (**20**) 16%, ϕ_c +149.4, $J_{1,F}$ 52.2 Hz, $J_{2,F}$ 26.3 Hz.

(b) Bromofluorination, "BrF" generated from N-bromosuccinimide and anhydrous liquid HF—Following the general procedure as outlined for the reaction of D-glucal triacetate (**16**) afforded a yellow syrup which contained (^{19}F n.m.r.) the same *two* fluorine resonances: these were assigned to the *trans* isomer (**19**) 55–60% and *cis* isomer (**20**) 40–45%.

(c) Iodofluorination, "IF" generated from I_2 and AgF—The iodofluorination of **16** also yielded *two* compounds; the *trans* isomer (**21**) ca. 95%, ϕ_c +117.5, $J_{1,F}$ 51.3 Hz, $J_{2,F}$ 5.2 Hz and the *cis* isomer ca. 5%, ϕ_c +143.5, $J_{1,F}$ 51.1 Hz, $J_{2,F}$ 27.2 Hz.

(d) Iodofluorination, "IF" generated from N-iodosuccinimide and anhydrous liquid HF—When this iodofluorination reaction was attempted, a black tar was obtained, which did not contain any fluorine organic products.

*Reactions of the Acetate of 3,4-Dihydro-2H-Pyran-2-Methanol (**17**)*[12]

(a) Bromofluorination, "BrF" generated from Br_2 and AgF—The bromofluorination of the acetate (**17**), b.p. 104–106°, 15 mm led to the formation of the *trans-diaxial* (α-*manno*) isomer (**23**) 57%, ϕ_c +119.7, $J_{1,F}$ 51.1 Hz, $J_{2,F}$ 4.0 Hz; the *trans-diequatorial* (β-*gluco*) isomer (**24**) 20%, ϕ_c +126.9, $J_{1,F}$ ca. 52 Hz and the *cis* (α-*gluco*) isomer (**25**) 18%, ϕ_c +147.1, $J_{1,F}$ 51.6 Hz, $J_{2,F}$ 26.0 Hz. (A minor unidentified resonance at ϕ_c +121.9 was also detected.)

(b) Iodofluorination, "IF" generated from I_2 and AgF—The iodofluorination of **27** resulted in the formation of the *trans-diaxial* (α-*manno*) isomer (**26**) 78%, ϕ_c +114.5, $J_{1,F}$ 51.4 Hz, $J_{2,F}$ 5.0 Hz; the *trans-diequatorial* (β-*gluco*) isomer (**27**) 17%, ϕ_c +122.3 $J_{1,F}$ ca. 50 Hz and the *cis* (α-*gluco*) isomer (**28**) ca. 5%, ϕ_c ca. +141. (This resonance was too weak for an accurate determination of ϕ_c or of the coupling constants.) No other ^{19}F resonances were discernible.

*Reactions of the p-Toluenesulfonate of 3,4-Dihydro-2H-Pyran-2-Methanol (**18**)*

(a) Bromofluorination, "BrF" generated from Br_2 and AgF—The bromofluorination of **18**, (m.p. 46.5–47.5°) afforded the *trans-diaxial* (α-*manno*) isomer (**29**) 66%, ϕ_c +120.1, $J_{1,F}$ 50.5 Hz, $J_{2,F}$ 3.7 Hz; the *trans-diequatorial* (β-*gluco*) isomer (**30**) 25%, ϕ_c +125.8 $J_{1,F}$ ca. 51 Hz and the *cis* (α-*gluco*) isomer (**31**) 6%, ϕ_c +147.5, $J_{1,F}$ 52.0 Hz, $J_{2,F}$ 26.0 Hz, together with two other very minor, unidentified resonances.

(b) Bromofluorination, "BrF" generated from N-bromosuccinimide and anhydrous liquid HF—The bromofluorination of **18** (5 g) afforded a crystalline mass (1.4 g, 20%): m.p. 106–110°. ^{19}F n.m.r. showed this reaction product to consist of almost equal portions of the *trans-diaxial* (α-*manno*) isomer (**29**) ca. 55%, and the *cis* (α-*gluco*) isomer (**31**) ca. 45%. Successive recrystallizations (7 times) failed to separate these two isomers; m.p. 121–122.5°.

Anal. Calcd. for $C_{13}H_{16}O_4BrFS$: C, 42.5; H, 4.35; F, 5.2. Found: C, 42.4; H, 4.4; F, 5.25.

(c) Iodofluorination, "IF" generated from I_2 and AgF—The iodofluorination of **18** afforded three products. They were identified (by ^{19}F n.m.r.) as the *trans-diaxial* (α-*manno*) isomer (**32**) 76%, ϕ_c +114.8, $J_{1,F}$ 51.5 Hz, $J_{2,F}$ 5.1 Hz; the *trans-diequatorial* (β-*gluco*) isomer (**33**) 18%, ϕ_c +121.0, $J_{1,F}$ ca. 50 Hz and the *cis* (α-*gluco*) isomer (**34**) 5%, ϕ_c ca. +141.

*Reactions of D-Galactal Triacetate (**35**)*

(a) Bromofluorination, "BrF" generated from Br_2 and AgF—In the manner described for "BrF" addition to **1**, D-galactal triacetate[13] (**35**) (1.36 g) was reacted in acetonitrile solution with bromine and silver monofluoride. A 98% yield of a light amber syrup was obtained, which so far has failed to crystallize; ^{19}F n.m.r. showed that *three* glycopyranosyl fluorides were formed. Their structures were tentatively assigned, on the basis of their ϕ_c values and first order ^{19}F–^{1}H coupling constants, and by analogy with the products obtained from D-glucal triacetate as: 2-bromo-2-deoxy-α-D-talopyranosyl fluoride triacetate (**38**) 34%, ϕ_c +121.4, $J_{1,F}$ 49.8 Hz, $J_{2,F}$ 4.6 Hz, 2-bromo-2-deoxy-β-D-galactopyranosyl fluoride triacetate (**39**) 43%, ϕ_c +135.6, $J_{1,F}$ 49.7 Hz, $J_{2,F}$ 10.0 Hz and 2-bromo-2-deoxy-α-D-galactopyranosyl fluoride triacetate (**40**), 24%, ϕ_c +145.0, $J_{1,F}$ 50.5 Hz, $J_{2,F}$ 25.1 Hz. {Compare with those results reported by Kent *et al.* (21*b*).}

(b) Iodofluorination, "IF" generated from I_2 and AgF—A 96% yield of a clear syrup was obtained, which has failed to crystallize. Again ^{19}F n.m.r. showed that *three* glycopyranosyl fluorides had been formed. Tentatively, these have the structures 2-deoxy-2-iodo-α-D-talopyranosyl fluoride triacetate (**41**), 25%, ϕ_c +114.6, $J_{1,F}$ 50.5 Hz, $J_{2,F}$ 6.3 Hz; 2-deoxy-2-iodo-β-D-galactopyranosyl fluoride triacetate (**42**) 41%, ϕ_c +130.8, $J_{1,F}$ 49.8 Hz, $J_{2,F}$ 10.2 Hz and 2-deoxy-2-iodo-α-D-galactopyranosyl fluoride triacetate (**43**) 34%, ϕ_c +139.4, $J_{1,F}$ 50.0 Hz, $J_{2,F}$ 27.6 Hz.

*Reactions of D-Arabinal Diacetate (**36**)*[14]

(a) Bromofluorination, "BrF" generated from Br_2 and AgF—Following the established procedure a syrup was obtained from **36** (1.0 g) in 93% yield, which has not crystallized. ^{19}F n.m.r. showed only *three* anomeric fluorine resonances. They were tentatively assigned as: 2-bromo-2-deoxy-α-D-arabinopyranosyl fluoride diacetate (**44**) 62%, ϕ_c +126.4, $J_{1,F}$ 50.5 Hz, $J_{2,F}$ 3.5 Hz; 2-bromo-2-deoxy-β-D-ribopyranosyl fluoride diacetate

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[11]3,4-Dihydro-2*H*-pyran, was a commercial sample from Eastman Organic Chemicals, Rochester, New York.

[12]3,4-Dihydro-2*H*-pyran-2-methanol was a gift from Shell Chemical Co., New York.

[13]D-Galactal triacetate (**35**), was a commercial sample from Koch Light Laboratories Ltd., England and was used as received.

[14]D-Arabinal diacetate (**36**), was prepared by Miss Zinat Mia, according to the procedure of Humoller (23); had b.p. (1 mm) 90°; lit. (23) b.p. 0.3 mm) 79°; $[\alpha]_D$ +266°.

(**45**), 20%, ϕ_c +127.9, $J_{1,F}$ 50.4 Hz, $J_{2,F}$ 3.4 Hz and 2-bromo-2-deoxy-α-D-ribopyranosyl fluoride diacetate (**46**), 18%, ϕ_c +147.6, $J_{1,F}$ 51.3 Hz, $J_{2,F}$ 25.1 Hz. {Compare with the results of Kent *et al.* (21*a*).}

(b) Iodofluorination, "IF" generated from I_2 and AgF—An 82% yield of a clear syrup was obtained from **36** (1.0 g) which so far has failed to crystallize. ^{19}F n.m.r. showed only three anomeric resonances. These resonances were tentatively assigned as: 2-deoxy-2-iodo-α-D-arabino-pyranosyl fluoride diacetate (**47**) 49%, ϕ_c +121.6, $J_{1,F}$ ca. 50 Hz, $J_{2,F}$ ca. 5 Hz; 2-deoxy-2-iodo-β-D-ribopyranosyl fluoride diacetate (**48**) 38%, ϕ_c +123.9, $J_{1,F}$ 51.0 Hz, $J_{2,F}$ 6.5 Hz and 2-deoxy-2-iodo-α-D-ribopyranosyl fluoride diacetate (**49**) 13%, ϕ_c +141.9 $J_{1,F}$ 50.7 Hz, $J_{2,F}$ 27.6 Hz.

(c) Iodobenzoylation—Following the same procedure as described for D-glucal triacetate (**1**), Miss Zinat Mia effected the addition "IOBz" to **36** in benzene solution and obtained a semi-crystalline syrup which was found (by p.m.r.) to contain three anomeric resonances.

One isomer was obtained crystalline, from an ethanol solution and was recrystallized twice from aqueous ethanol to afford hard needles of 1-*O*-benzoyl-2-deoxy-2-iodo-β-D-ribopyranose diacetate (**50**), m.p. 129–130° $[\alpha]_D^{27}$ −26.5° (*c*, 1.46).

Anal. Calcd. for $C_{16}H_{17}O_7I$: C, 42.85; H, 3.8; I, 28.3. Found: C, 42.6; H, 3.9; I, 28.1.

This component (**50**) accounted for 45% of the reaction product.

Reactions of D-*Xylal Diacetate (**37**)*[15]

(a) Bromofluorination, "BrF" generated from Br_2 and AgF—Following the established procedure a clear syrup was obtained from **37** in 91% yield which has to date failed to crystallize. ^{19}F n.m.r. showed that all *four* isomeric "BrF" adducts were formed. They are (the structures are tentative):— 2-bromo-2-deoxy-α-D-lyxo-pyranosyl fluoride diacetate (**51**) 55%, ϕ_c +126.7, $J_{1,F}$ 50.1 Hz, $J_{2,F}$ 3.5 Hz; 2-bromo-2-deoxy-β-D-xylopyranosyl fluoride diacetate (**52**) 32%, ϕ_c +128.0, $J_{1,F}$ 51.0 Hz, $J_{2,F}$ 9.0 Hz; the β-D-*lyxo* or the α-D-*xylo* isomer (**53**) 5%, ϕ_c +144.1, $J_{1,F}$ 50.8 Hz, $J_{2,F}$ 26.8 Hz and the α-D-*xylo* or the β-D-*lyxo* isomer (**54**) 8%, ϕ_c +146.5, $J_{1,F}$ 50.3 Hz, $J_{2,F}$ 25.1 Hz.

(b) Iodofluorination, "IF" generated from I_2 and AgF—Following the established procedure a colorless syrup was obtained, which has failed to crystallize. ^{19}F n.m.r. again showed that all *four* isomeric "IF" adducts were formed.

The resonances were tentatively assigned as: 2-deoxy-2-iodo-α-D-lyxopyranosyl fluoride diacetate (**55**) 46%, ϕ_c +120.4, $J_{1,F}$ 50.0 Hz, $J_{2,F}$ 3.5 Hz; 2-deoxy-2-iodo-β-D-xylopyranosyl fluoride diacetate (**56**) 43%, ϕ_c +122.5, $J_{1,F}$ 51.1 Hz, $J_{2,F}$ 9.2 Hz; the α-D-*xylo* or β-D-*lyxo* isomer (**57**) 8%, ϕ_c +138.0, $J_{1,F}$ 50.8 Hz, $J_{2,F}$ 29 Hz and the β-D-*lyxo* or α-D-*xylo* isomer (**58**) 3%, ϕ_c +141.1, $J_{1,F}$ 50.8 Hz, $J_{2,F}$ 29 Hz.

(c) Iodobenzoylation—When "IOBz" was reacted with **37** (1.0 g) in the manner described above for the reaction with D-glucal triacetate in acetonitrile solution, a light-yellow syrup was obtained (2.1 g, 94%). It was not possible to obtain any crystalline products from this reaction and although p.m.r. showed the presence of four anomeric resonances, they could not be assigned.

[15]D-Xylal diacetate (**37**), was prepared, with the assistance of Mrs. Liane Evelyn following the procedure of Weygand (24); had m.p. 37–39°, lit. m.p. 40°, $[\alpha]_D$ −314.7°.

Note added in proof: Since the preparation of this manuscript Campbell *et al.* (25) have reported an X-ray study of the major product from their addition of "BrF" to D-glucal triacetate. On this basis they have revised their original assignment of the β-D-*manno* configuration to the, correct, α-D-*manno* configuration. Their structure of the corresponding "IF" adduct must be similarly corrected.

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