THE SYNTHESIS OF FLUORINATED CARBOHYDRATES

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ABSTRACT

Three types of reaction are of particular value in the synthesis of fluoro sugars, namely, nucleophilic displacements with fluoride salts, epoxide cleavage reactions, and glycal addition reactions. These reactions have been developed to the point where effective syntheses of a wide range of fluoro sugars can be planned on a rational basis.

Nucleophilic displacement usually involves the treatment of sulphonates with fluoride salts. Reagents of the type tetrabutylammonium fluoride -dipolar aprotic solvent are particularly effective for the displacement of secondary sulphonates. An understanding of the steric and polar factors which can adversely influence the displacement of carbohydrate secondary sulphonates and of competing reaction pathways usually allows the evaluation of this route in designing effective syntheses of fluoro sugars. Selection of ring size (furanose, pyranose, septanose derivatives) is an important parameter in synthesis design.

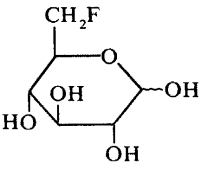
The cleavage of carbohydrate epoxides to give *trans*-fluorohydrins can be effected with reagents such as HF or KHF_2. The reactions usually occur stereospecifically and predictably if the epoxide ring is part of a rigid molecular system such as 1,6-anhydrohexopyranose.

The reagent CF_3OF, which is an effective source of electrophilic fluorine, readily adds to *O*-acetylated glycals to give 2-deoxy-2-fluoro derivatives. 2-Deoxy-2-fluoro-D-glucose can be converted into 3,4,6-tri-*O*-acetyl-2-fluoro-D-glucal and thence by treatment with CF_3OF, into '2,2-difluoro-D-glucose'.

1. INTRODUCTION

Although glycosyl fluoride derivatives (fluoro-alkyl ethers) have long been known[1], it was not until 1941 than an alkyl fluoride type of sugar derivative (namely 6-deoxy-6-fluoro-D-glucose, (I)) was described[2]. Few additional examples were recorded during the next 25 years and in a comprehensive review[3] of halogenated carbohydrates published in 1967, the only crystalline fluorinated derivatives of naturally occurring sugars described in addition to (I) were 3-deoxy-3-fluoro-β-D-arabinose[4] (II), 2-deoxy-2-fluoro-D-ribose[5] (III), 3-deoxy-3-fluoro-α-D-xylose[6] (IV), and 6-deoxy-6-fluoro-α-D-galactose[7] (V).

This situation was not due to lack of interest or endeavour as clearly indicated by the publications of Kent and his coworkers[8], but rather to a lack of general synthetic methods. It is clear from Barnett's review[3] that many of the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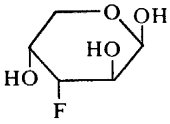
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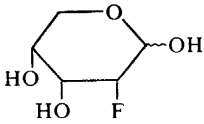
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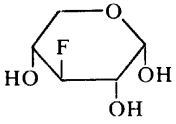
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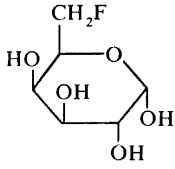
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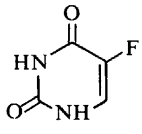
synthetic methods by which chloro, bromo, and iodo derivatives of sugars can be synthesized are not applicable to the fluoro analogues. Moreover, many of the reactions by which fluorinated derivatives have been synthesized in other branches of organic chemistry either fail or take unexpected courses when applied to carbohydrate molecules.

Current interest in fluorinated carbohydrates has undoubtedly been stimulated, at least in part, by observations on other types of fluorinated compounds[9]. A dramatic change in biological activity may result from the introduction of a single fluorine substituent into an organic molecule. Thus, conversion of acetic acid into fluoroacetic acid produces a highly toxic compound. Fluoroacetic acid is converted *in vivo* (lethal synthesis) into fluorocitric acid which inhibits the enzymes succinic dehydrogenase and aconitase thereby blocking the citric acid cycle[10]. 5-Fluorouracil (VI, 5-FU) is transformed *in vivo* in man and animals into 5-fluorodeoxyuridine monophosphate (VII, 5-FUDR), an inhibitor of the enzyme (thymidylate synthetase) responsible for the 5-methylation of deoxyuridine monophosphate. Because certain tumours have enhanced uracil utilization, 5-FUDR can exert a selective cytotoxic effect[11].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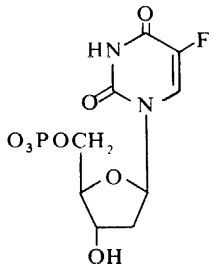
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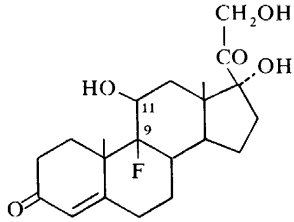
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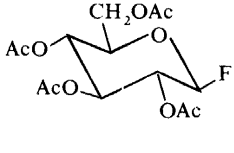
5-FUDR and fluorocitric acid are antimetabolites but the effect of a fluorine substituent may be manifested in other ways. Thus, the glycogenic activity of hydrocortisone is increased more than ten-fold by the introduction of a 9α-fluorine substituent (VIII) possibly because of an electronegativity effect which increases the acidity of the 11β-hydroxyl group[12].

In each of the above examples the fluorine substituent replaces hydrogen whereas for carbohydrates it is a hydroxyl group which is usually replaced. Since a fluorine substituent has a smaller bulk than a hydroxyl group[13] replacement of OH by F in a sugar derivative should not cause marked changes in non-bonded interactions. However, other significant effects might be

expected. For example, whereas a hydroxyl group can act as both hydrogen bond donor and acceptor in interactions with solvent molecules and enzymes, a fluorine substituent at best can function solely as a hydrogen bond acceptor[14]. Thus, the role in the enzyme–substrate complex played by each hydroxyl group in a carbohydrate substrate might be investigated on the basis of the affinity of the corresponding fluoro derivative for the enzyme[15].

As in 9α-fluorohydrocortisone (VIII) a fluorine substituent in a carbohydrate derivative will increase the acidity (and hydrogen bond donating capacity) of any vicinal hydroxyl group. Thus, the competitive inhibition of carbohydrate-utilizing enzymes by at least some of the fluorinated analogues of the substrates is to be expected.

Electronic interactions which involve the large dipole associated with the C–F bond may also be important and they are significant in glycopyranosyl fluorides. The anomeric effect[16], which arises from the interaction of the dipole associated with the C-1–X bond and the resultant dipole associated with the bonds between C-1 and C-5 and the ring oxygen atom in pyranosides, results in axial orientation of the C-1 substituent (X) being preferred. For 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl fluoride (IX) the balance of non-bonded and dipole interactions is such that the principal contributor to the conformational equilibrium is the *C1* chair form with all substituents equatorial[17]. However, the anomeric effect is dominant in 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl fluoride (X ⇌ XI) and the principal contributor to the conformational equilibrium is the *1C* chair form (X) with all substituents axial[18] and not the all equatorial, *C1* form (XI).



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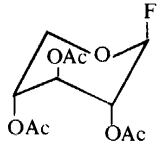

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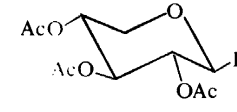

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A more recent interest in fluoro sugars relates to their value in n.m.r. studies. The conformation of many types of sugar derivatives, including fluorinated compounds, can now be determined with reasonable precision on the basis of ^{1}H n.m.r. data[19]. It therefore follows that, for many fluorinated carbohydrates, the steric relationship of the fluorine substituent with most if not all of the protons in the same molecule can also be defined. Thus, fluorinated carbohydrates have considerable value in the determination of the geometrical dependency of the sign and magnitude of vicinal and long-range (^4J and ^5J) F–H couplings[20]. Carbohydrate derivatives containing two fluorine substituents can likewise be used to study F–F couplings[21]. Growing use is also being made of ^{19}F n.m.r. spectroscopy to probe the interaction of enzymes with appropriately fluorinated substrates including carbohydrates[22].

Since 1967, new, general methods for the synthesis of fluoro sugars have emerged and, as a consequence many fluoro sugars are now accessible in quantities adequate to permit a thorough evaluation of chemical properties and biological activity. These developments, coupled with the growing

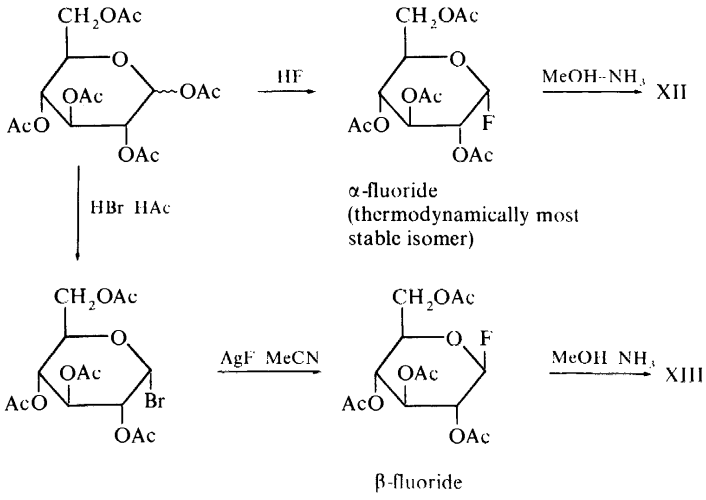
interest in fluorinated carbohydrates, make it appropriate to review the methods available for their synthesis†.

Most of the recent effort in the fluoro sugar field has been associated with the synthesis of modified nucleosides[23] and fluorinated hexoses. The usual objective of fluoro sugar synthesis is the evaluation of biological activity and if this aim is to be fully achieved then the derivatives must be readily available at least on a decagram scale. Therefore there is a need for short, high-yielding syntheses of fluoro sugars. This criterion, which applies to all types of potentially biologically active molecules, is often overlooked in synthetic work.

It is convenient to consider the synthesis of fluoro sugars from the standpoint of general reactions rather than a particular type of derivative. An appreciation of the scope and limitations of these general reactions will more readily allow the selection of a synthetic route for a particular fluoro sugar.

2. GLYCOSYL FLUORIDES (FLUORO-ALKYL ETHERS)

Since the synthetic routes for glycosyl fluorides are well established and exemplified[1] they need not be considered in this review other than to note the general routes of synthesis of the α- and β-fluorides as exemplified by the D-glucopyranose series. Because of the anomeric effect the α-anomer is,



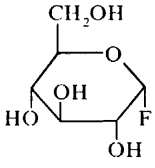
Scheme 1. Synthesis of α- and β-D-glucopyranosyl fluoride[1].

thermodynamically, the more stable form. Of the glycosyl halides, only the fluorides are stable in the unprotected form. Thus, α-(XII) and β-D-glucopyranosyl fluoride (XIII) are crystalline solids[1] of moderate stability and they have been used in enzyme inhibition studies[15, 24].

The procedures in *Scheme 1* have been used to synthesize the α- and

† A general review of fluoro sugars has been made by P. W. Kent in *Carbon-Fluorine Compounds*, p. 169. CIBA Foundation Symposium, Elsevier, Amsterdam (1972).

β-glycopyranosyl fluorides of various 3- and 4-fluoro sugars[21b,c] and of 6-deoxy-6-fluoro-D-glucose[25].



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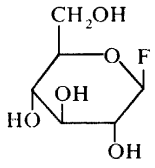

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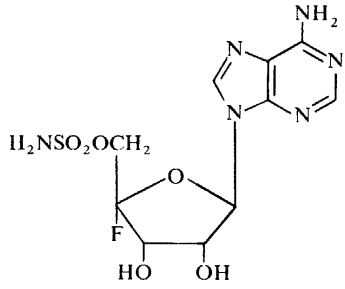


(XIV)

The discovery[26] that the antibiotic nucleocidin (XIV) is a glycosyl fluoride will undoubtedly stimulate new work on this class of compound and on the biological mobilization of fluorine. Nucleocidin is an atypical fluorinated carbohydrate in that F replaces H; its synthesis is described in Section 6.

3. SYNTHESIS OF FLUORO SUGARS OF THE ALKYL FLUORIDE TYPE

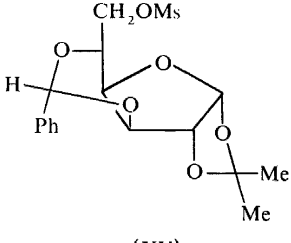
Three general routes now available for the synthesis of fluoro sugars involve nucleophilic displacements (usually of sulphonates) with fluoride salts, epoxide cleavage reactions, and glycal addition reactions. Our specific interest in developing these routes was the synthesis of fluoro derivatives of D-glucopyranose and certain related compounds which were required in an investigation[15] of the substrate specificities of the hexokinase isoenzymes of normal and cancer tissue.

Alternative syntheses are now available for many fluoro sugars but the route of choice will usually be governed by the accessibility of the relevant intermediates (and their cost) and not necessarily by the location of the fluorine substituent.

4. NUCLEOPHILIC DISPLACEMENTS WITH FLUORIDE SALTS

4.1 Primary sulphonates

Fluoride displacement reactions are usually effected on sugar sulphonates



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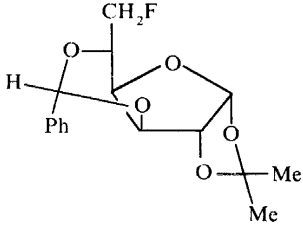

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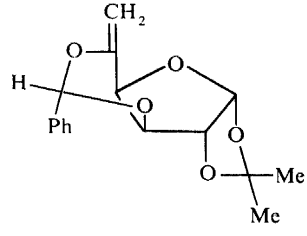
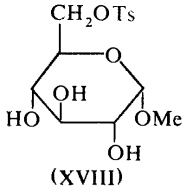


(XVII)

and although the kinetics have not been investigated these reactions presumably are S_N2 in type. Potassium fluoride is the salt frequently employed for the displacement of primary sulphonates. In the original synthesis[2] of 6-deoxy-6-fluoro-D-glucose(I),3,5-*O*-benzylidene-1,2-*O*-isopropylidene-6-*O*-mesyl-α-D-glucofuranose (XV) was treated with potassium fluoride dihydrate in methanol. In addition to the fluoride (XVI), the unsaturated compound (XVII) is formed.

When the potassium fluoride–methanol reagent was applied[7] to 1,2:3,4-di-*O*-isopropylidene-6-*O*-mesyl-α-D-galactopyranose under vigorous conditions, since nucleophilic displacements of the sulphonate group in this compound are sterically hindered[27], the 6-*O*-methyl ether was formed in addition to the 6-fluoride. The formation of 6-*O*-alkyl derivatives was greatly reduced when ethane-1,2-diol was the reaction solvent with either anhydrous potassium fluoride or its dihydrate. This modified reagent was used in syntheses of 6-deoxy-6-fluoro-D-galactose[7] and 5-deoxy-5-fluoro-D-ribose[7], and in an improved synthesis[25] of 6-deoxy-6-fluoro-D-glucose. *N*,*N*-Dimethylformamide has also been used as a reaction solvent for fluoride displacement reactions[28].

The mesylate (XV) is obtained by a 4-stage synthesis from D-glucose and in seeking a shorter synthesis, the reaction of methyl 6-*O*-tosyl-α-D-glucopyranoside ((XVIII), obtainable from D-glucose in 2 stages) with potassium fluoride in ethane-1,2-diol was investigated[25]. The fluoride (XIX) was



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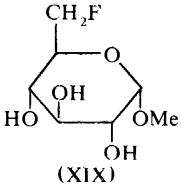

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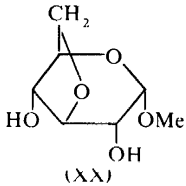

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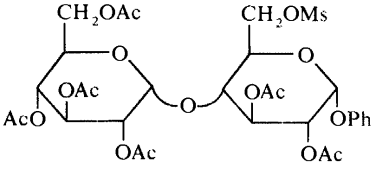

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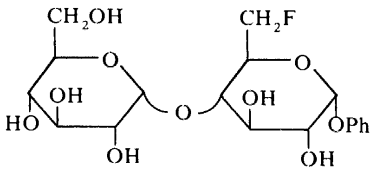

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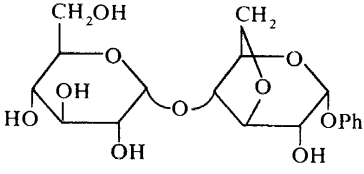


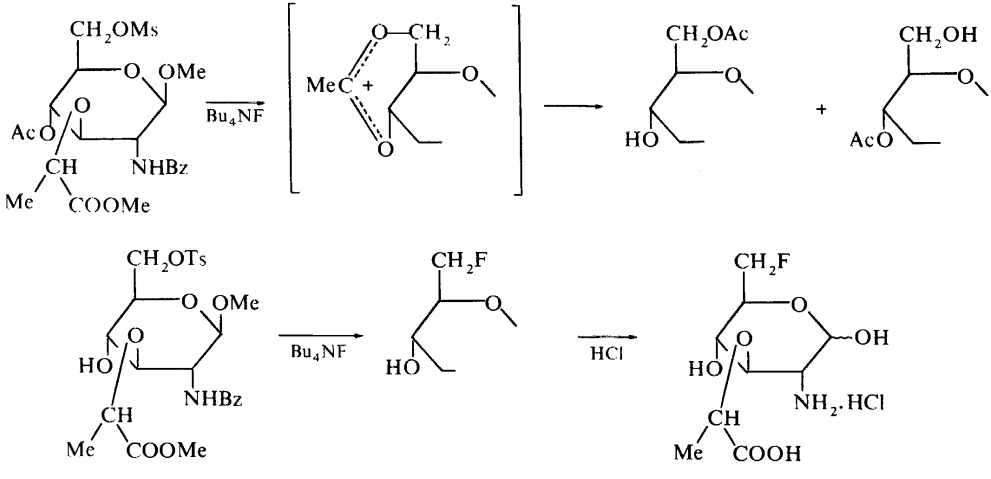
(XXIII)

accompanied by the 3,6-anhydride (XX), but the difficulty in separating compounds (XIX) and (XX) largely deprived the shortened synthesis of

convenience. Similar results were obtained on treatment[29] of phenyl 2,2′,3,3′,4′,6′-hexa-*O*-acetyl-6-*O*-mesyl-α-D-maltoside (XXI) with anhydrous potassium fluoride in 2-methoxyethanol (methyl cellosolve) which gave a mixture of the fluoride (XXII) and the 3,6-anhydride (XXIII).

Several sugar derivatives containing a primary fluorine substituent have been obtained by reaction of the appropriate sulphonates with tetrabutylammonium fluoride (with a variety of solvents, both protic and aprotic), e.g. 6-deoxy-6-fluoromuramic acid[30], 5-deoxy-5-fluoro-D-xylose[31], 2′,5′-dideoxy-5′-fluororibonucleosides[32], 6,6′-dideoxy-6,6′-difluoro-αα-trehalose and its *galacto* analogue[33a], and 1-deoxy-1-fluoro-D-fructose[33b].

The synthesis of 6-deoxy-6-fluoromuramic acid (*Scheme 2*) illustrates a further point which must be borne in mind when designing syntheses of fluoro sugars. When the muramic acid derivative, methyl 4-*O*-acetyl-2-benzamido-2-deoxy-6-*O*-mesyl-3-*O*-[D-1-(methoxycarbonyl)ethyl]-β-D-glucopyranoside, was treated with tetrabutylammonium fluoride in butan-2-one, a mixture of 4,6-diol monoacetates was obtained, presumably because AcO-4 participated in the solvolysis of MsO-6. However, the corresponding 6-tosylate with HO-4 unblocked underwent smooth fluoride displacement and hydrolysis of the product gave 6-deoxy-6-fluoromuramic acid.



Scheme 2. Synthesis of 6-deoxy-6-fluoromuramic acid[30].

Although fluoride displacement of primary sulphonates can usually be effected without difficulty, relatively vigorous reaction conditions are necessary with certain compounds, e.g. 1,2:3,4-di-*O*-isopropylidene-6-*O*-mesyl-α-D-galactopyranose[7] and 3-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-tosyl-α-D-xylofuranose[31]. An explanation for these observations has been advanced[34] in terms of steric and polar interactions in the transition state.

4.2 Secondary sulphonates

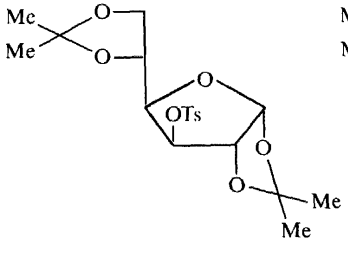
Walden inversion accompanies fluoride displacement reactions of second-

arysulphonates as would be expected for S_N2 reactions. Considerable success in fluoride displacements of carbohydrate secondary sulphonates has followed the introduction of the reagent tetrabutylammonium fluoride–dipolar aprotic solvent[35]. Because of solvation, fluoride ion in a protic solvent is a relatively poor nucleophile, but, in dipolar aprotic solvents, only cations are strongly solvated and the nucleophilicity of fluoride ion is significantly enhanced. More effective solvation in the transition state may also contribute[34] to the efficiency of this type of reagent which was first used in the steroid field[36]. Detailed descriptions of the preparation of tetrabutylammonium fluoride have been recorded[31,37] but the most convenient procedure involves[33] dehydration of the clathrate $(4Bu_4NF, H_2O)_8$.

4.3 Furanose derivatives

Fluoride displacement reactions of secondary sulphonates attached to furanoid rings have not been systematically investigated so that the importance of steric factors and alternative reaction pathways (e.g. elimination) has not been fully defined. One class of furanoid derivative that has been extensively studied includes 1,2-*O*-isopropylidenehexofuranoses. These compounds contain a *cis*-fused trioxabicyclo[3,3,0]octane system and substituents attached to an *exo* position (e.g. the sulphonate group in 1,2:5,6-di-*O*-isopropylidene-3-*O*-tosyl-α-D-glucofuranose (XXIV)) are remarkably resistant to displacement by charged nucleophiles[38] presumably because nucleophiles approaching from the *endo* direction are sterically hindered. On the other hand, *endo* sulphonates are readily displaced; thus the conversion of 1,2:5,6-di-*O*-isopropylidene-3-*O*-tosyl-α-D-allofuranose (XXV) into the 3-fluoro-D-*gluco* compound (XXVI) is readily effected[35,39] with tetrabutylammonium fluoride in acetonitrile. This was the first application of the reagent in the carbohydrate field. Although H-2 and TsO-3 are *trans* in compound (XXV), elimination does not occur since a bridgehead double bond would result. However, in the corresponding *gulo* compound (XXVIII), H-4 and TsO-3 are *trans* and elimination (to give (XXX)) occurs[40] to approximately the same extent as fluoride displacement to yield the 3-fluoro-D-*galacto* derivative (XXIX). Acid hydrolysis of compounds (XXVI) and (XXIX) yields 3-deoxy-3-fluoro-D-glucose[39] (XXVII) and 3-deoxy-3-fluoro-D-galactose[40] (XXXI), respectively.

A third example in this category involves the treatment of 1,2:5,6-di-*O*-isopropylidene-3-*O*-tosyl-β-L-talofuranose with tetrabutylammonium fluor-



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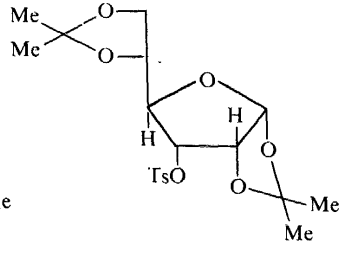

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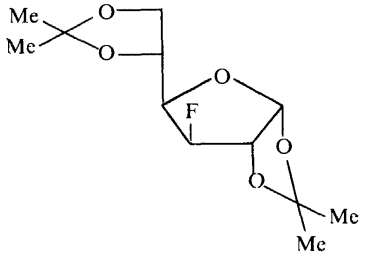

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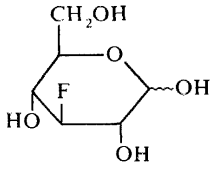
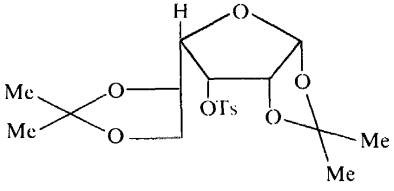
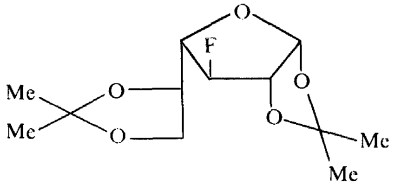


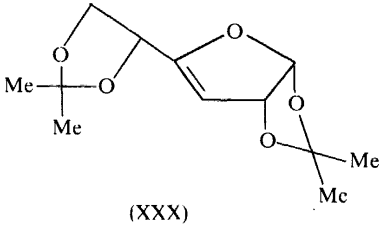
(XXVII)



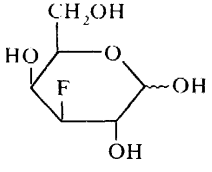
(XXVIII)



(XXIX)

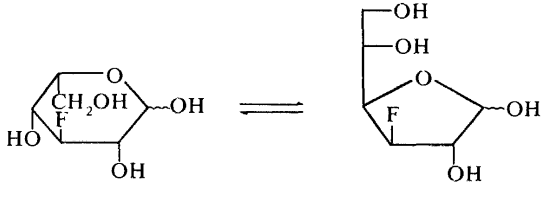


(XXX)

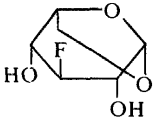


(XXXI)

ide acetonitrile to yield 3-deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-β-L-idofuranose[41]. However, a more convenient entry[42] into the 3-fluoro-L-*ido* series is afforded by the ready availability of the 3-fluoro-D-glucose derivative

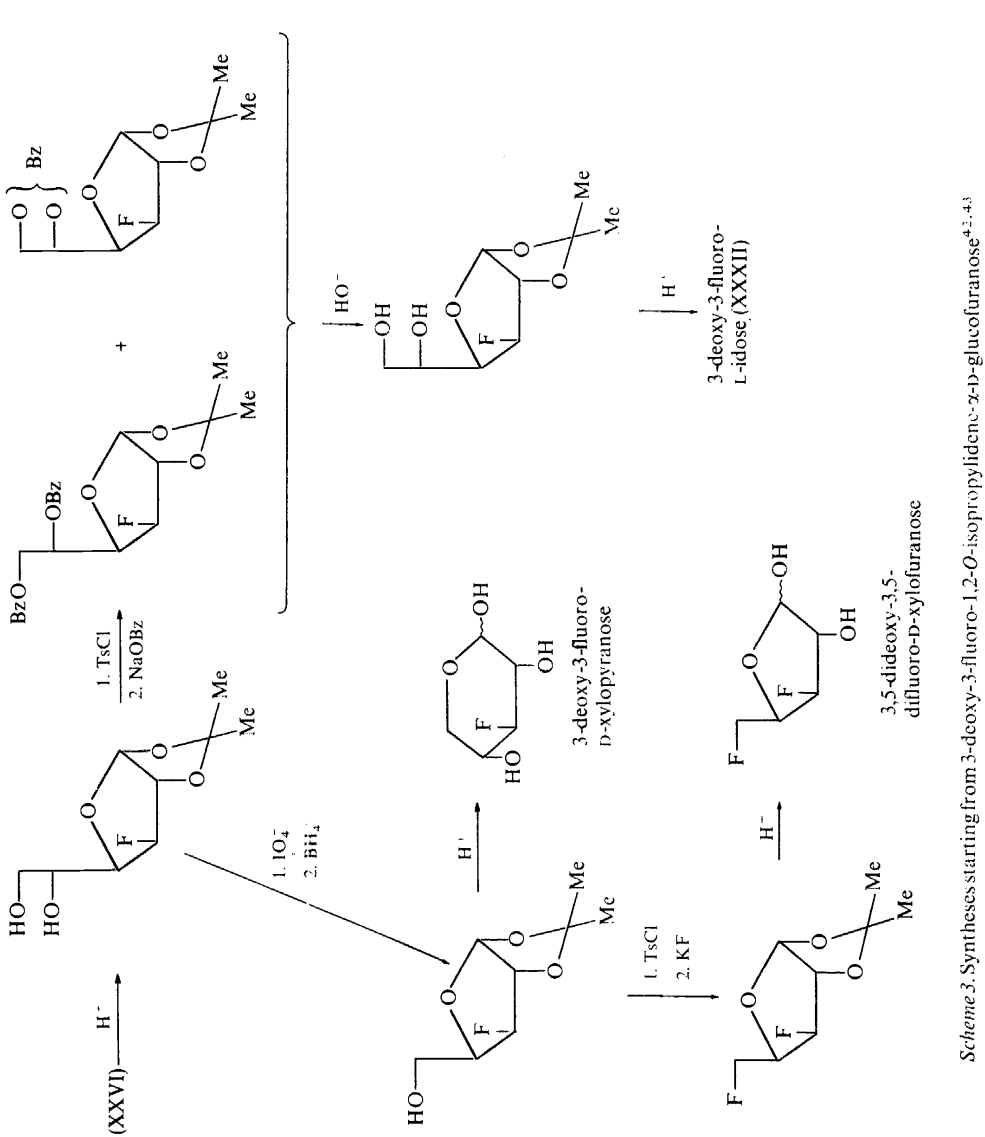


(XXXII)



(XXXIII)

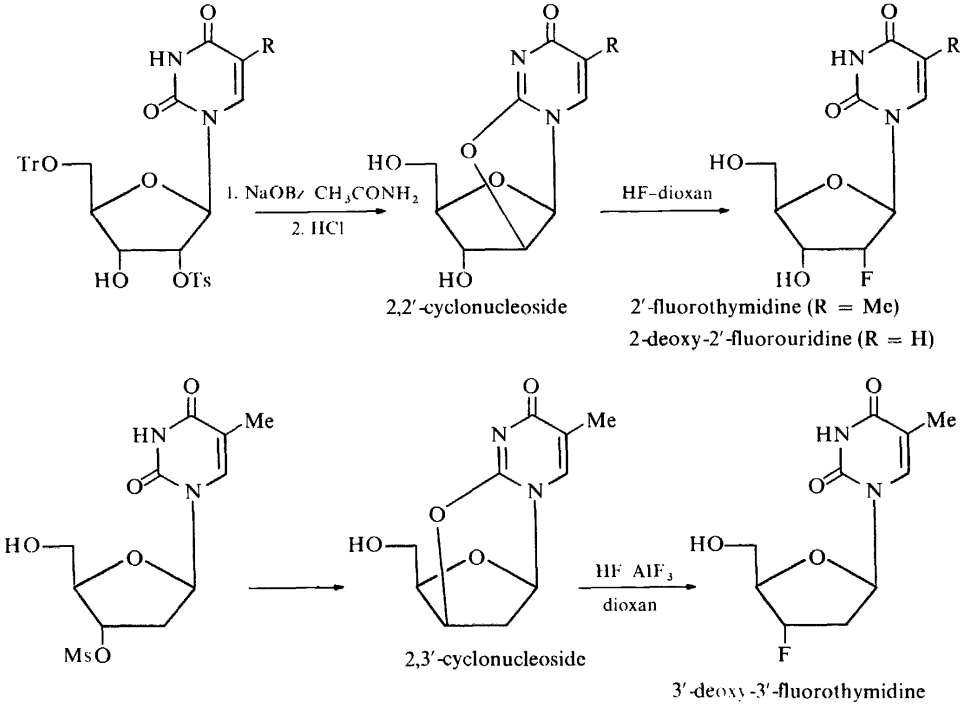
(XXVI). The relevant reaction sequence, which is shown in *Scheme 3* together with that for 3,5-dideoxy-3,5-difluoro-D-xylofuranose[43], illustrates how a readily available fluoro sugar derivative can serve as a starting point for new



Scheme 3. Syntheses starting from 3-deoxy-3-fluoro-1,2-*O*-isopropylidene-α-D-glucofuranose[42,43]

syntheses. Acid hydrolysis of 3-deoxy-3-fluoro-1,2-*O*-isopropylidene-β-L-idofuranose (*Scheme 3*) affords 3-deoxy-3-fluoro-L-idose (XXXII) which exists in aqueous solution as a four-component mixture of furanose and pyranose forms and which is further and extensively converted by acid into the 1,6-anhydride[44] (XXXIII) as is the parent sugar under similar conditions[45].

A type of fluoride displacement unique to the nucleoside field involves the cleavage of cyclonucleosides with hydrogen fluoride. Two examples have been reported involving O^2,2′-cyclo-1-(β-D-arabinofuranosyl)thymine and uracil[46] and O^2,3′-cyclo-1-(2′-deoxy-β-D-*threo*-pentofuranosyl)thymine[47] and the



Scheme 4. Fluoride displacement reactions of cyclonucleosides[46,47].

reactions are shown in *Scheme 4*. These reactions, which apparently are acid catalyzed are formally analogous to those involving epoxide cleavage described in Section 5.

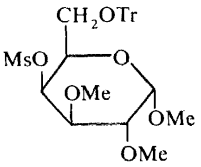
4.4 Pyranose derivatives

The steric and polar factors which influence nucleophilic displacement reactions, *inter alia*, of pyranose secondary sulphonates have been summarized by Richardson[34] and they must be taken into account in designing syntheses of fluoro sugars. Pyranoside 2-sulphonates are usually resistant to displacement reactions with charged nucleophiles but pyranoside 3- and 4-sulphonates should be reactive in the absence of substituents which are β-*trans*-axial or vicinal-*cis*-axial with respect to the sulphonate group.

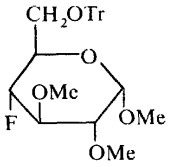
Pyranose 4-sulphonates with the *galacto* and *gluco* configurations satisfy these requirements and undergo fluoride displacement reactions with tetrabutylammonium fluoride–acetonitrile.

The value of these synthetic routes to 4-fluoro derivatives of D-glucose and D-galactose is limited by their multistage nature. Thus, treatment[48] of methyl 4-*O*-mesyl-2,3-di-*O*-methyl-6-*O*-trityl-α-D-galactopyranoside ((XXXIV), obtainable in six stages starting with D-galactose) with tetrabutylammonium fluoride–acetonitrile gave the 4-fluoro-D-glucose derivative (XXXV) together with an unidentified unsaturated product. This reaction constituted the first example of the direct fluoride displacement of a pyranoid secondary sulphonate. Sequential removal of the trityl group from compound (XXXV) with acid and the methyl ether groups with boron trichloride gave 4-deoxy-4-fluoro-D-glucose (XXXVI).

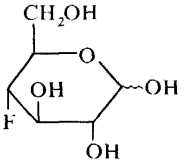
The displacement of pyranoid secondary sulphonates by charged nucleophiles usually requires a dipolar aprotic solvent[34]. It is therefore interesting to note that following detritylation of compound (XXXV), treatment of the product (XXXVII) with caesium fluoride in boiling ethane-1,2-diol gave the corresponding 4-fluoro-D-glucose derivative in moderate yield.



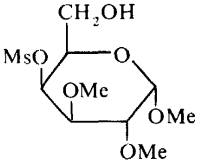
(XXXIV)



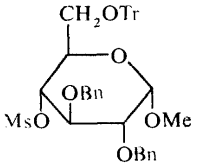
(XXXV)



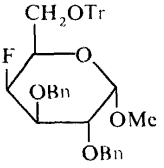
(XXXVI)



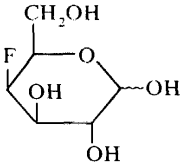
(XXXVII)



(XXXVIII)



(XXXIX)



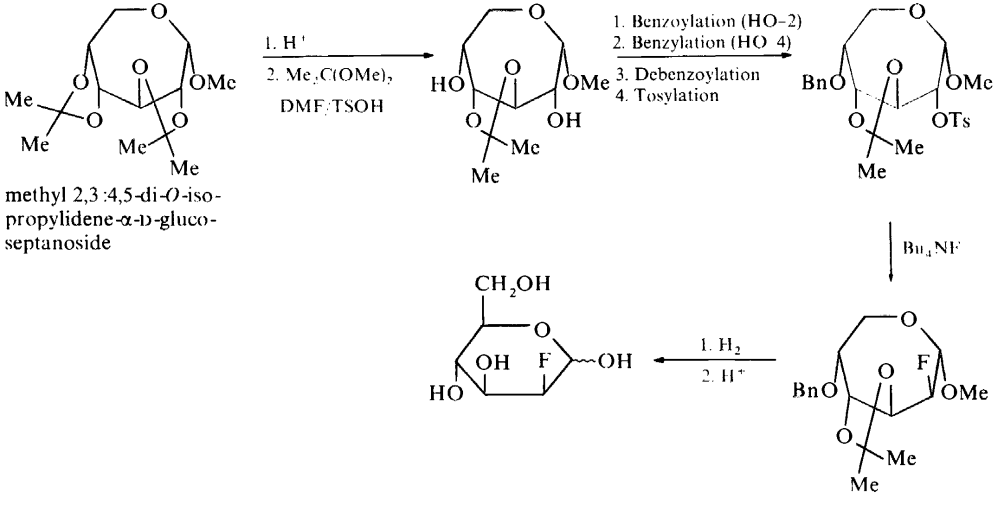
(XL)

In a parallel synthesis of 4-deoxy-4-fluoro-D-galactose[49], benzyl ether groups were used in preference to methyl ether groups for blocking positions 2 and 3. Thus, methyl 2,3-di-*O*-benzyl-4-*O*-mesyl-6-*O*-trityl-α-D-glucopyranoside ((XXXVIII), obtainable in six stages from D-glucose) reacted with tetrabutylammonium fluoride–acetonitrile less readily than the *galacto* analogue (XXXIV) but gave the 4-fluoro-D-galactose derivative (XXXIX) together with small amounts of unsaturated products. Removal of the blocking groups from compound (XXXIX) gave 4-deoxy-4-fluoro-D-galactose (XL).

4.5 Septanose derivatives

Treatment[50] of D-glucose with acetone–methanol–hydrogen chloride

gives mainly methyl 2,3:4,5-di-*O*-isopropylidene-αβ-D-glucoseptanoside[51] and makes these hitherto inaccessible compounds readily available. The α-anomer can be readily converted[50] as shown in *Scheme* 5 into methyl 5-*O*-benzyl-3,4-*O*-isopropylidene-2-*O*-tosyl-α-D-glucoseptanoside which is



methyl 2,3:4,5-di-*O*-isopropylidene-α-D-glucoseptanoside

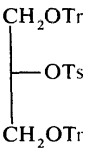
Scheme 5. Utilization of a glucoseptanose 2-sulphonate derivative in a synthesis of 2-deoxy-2-fluoro-D-mannose[50].

converted by tetrabutylammonium fluoride–acetonitrile into the corresponding 2-fluoro-D-mannoseptanose derivative. Although the fluoride displacement proceeds relatively slowly, an acceptable yield of product is ultimately formed. The susceptibility of the D-glucoseptanose 2-sulphonate derivative in *Scheme* 5 to nucleophilic displacement is in marked contrast to the resistance of pyranoid 2-sulphonates to displacement with charged nucleophiles. The availability of septanose derivatives adds a new parameter in carbohydrate synthesis.

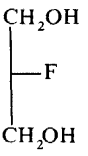
4.6 Acyclic derivatives

Only one fluoride displacement of an acyclic carbohydrate secondary sulphonate has been reported. Treatment[52] of 2-*O*-tosyl-1,3-di-*O*-tritylglycerol (XLI) with tetrabutylammonium fluoride–acetonitrile gave a high yield of the 2-fluoro derivative. Detritylation then gave 2-deoxy-2-fluoroglycerol (XLII).

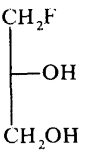
1-Deoxy-1-fluoro-D-glycerol (XLIII) was obtained[52] *via* a fluoride displacement reaction on 2,3-*O*-isopropylidene-1-*O*-tosyl-D-glycerol (derived from 1,2:5,6-di-*O*-isopropylidene-D-mannitol). When the 2,3-ditosylate of the D-isomer (XLIII) was subjected to a benzoate displacement reaction (NaOBz–DMF) and the product debenzoylated with acid, 1-deoxy-1-fluoro-L-glycerol was produced.



(XLI)



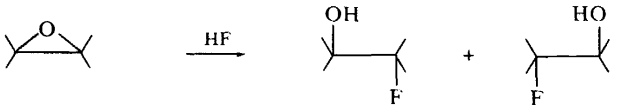
(XLII)



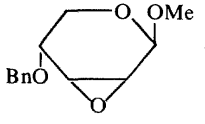
(XLIII)

5. EPOXIDE CLEAVAGE REACTIONS

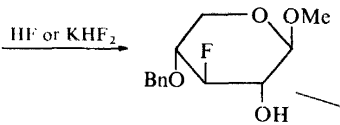
The reaction of epoxides with hydrogen fluoride or its equivalent (KHF_2, BF_3–HF) yields *trans*-fluorohydrins. Theoretically, two fluorohydrins

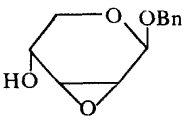


can be formed which will be positional isomers if the precursor epoxide is not symmetrical. For epoxides of conformationally flexible carbohydrates, one fluorohydrin often preponderates greatly but one product is usually formed exclusively when the epoxide ring is attached to a rigid molecule. The first

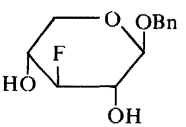


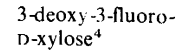
methyl 2,3-anhydro-4-*O*-benzyl-β-D-ribopyranoside[4]



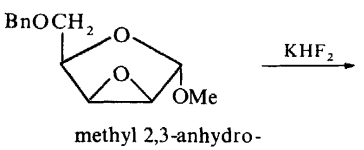


benzyl 2,3-anhydro-β-D-ribopyranoside[6]

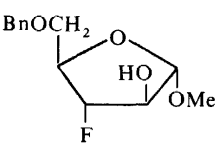


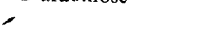


3-deoxy-3-fluoro-D-xylose[4]

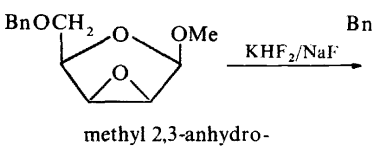


methyl 2,3-anhydro-5-*O*-benzyl-α-D-lyxofuranoside[4]

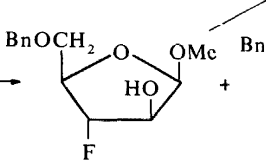


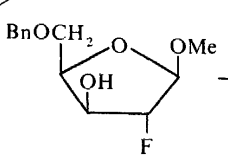


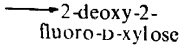
3-deoxy-3-fluoro-D-arabinose



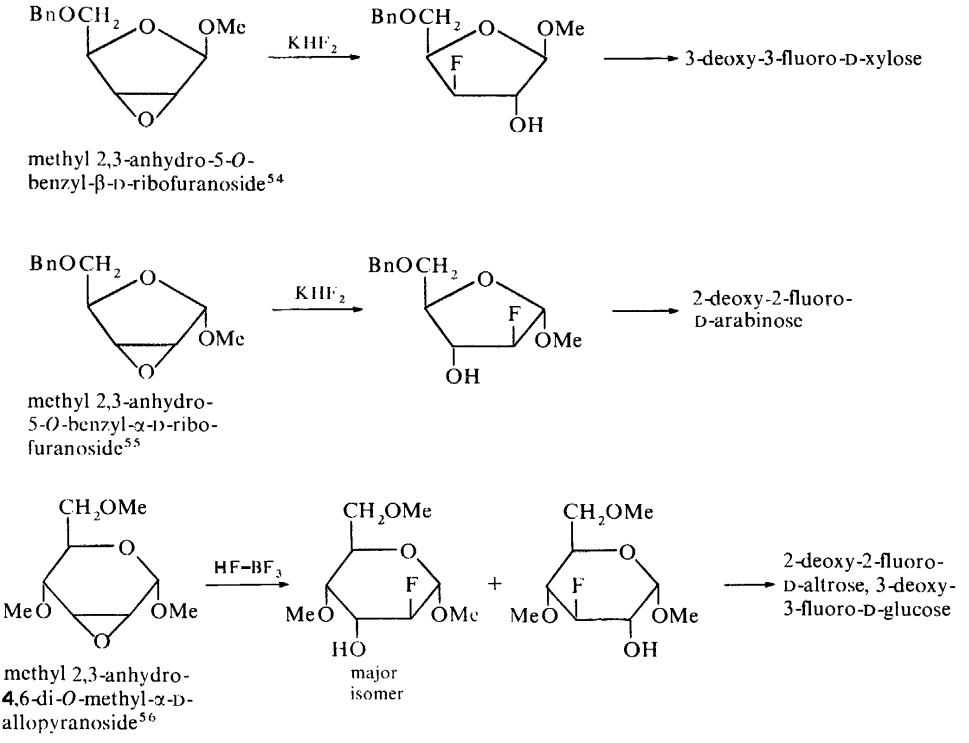
methyl 2,3-anhydro-5-*O*-benzyl-β-D-lyxofuranoside[53]







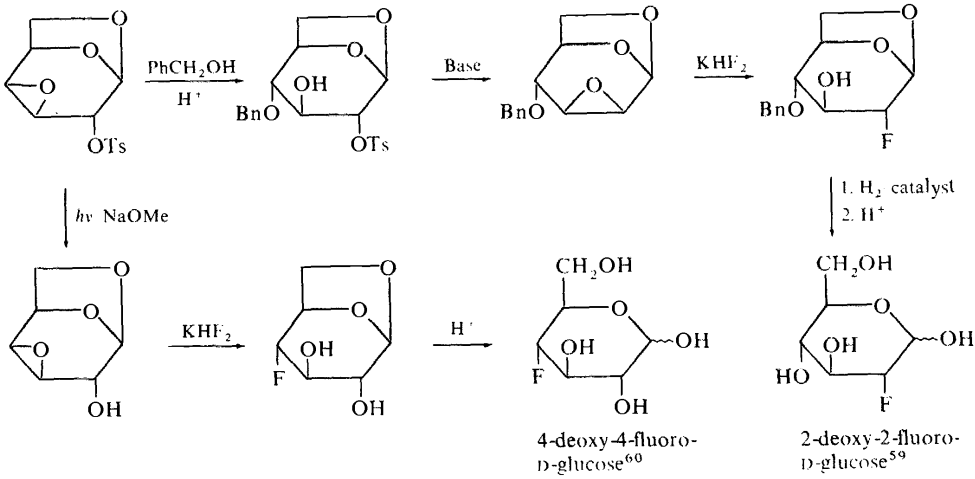
2-deoxy-2-fluoro-D-xylose



Scheme 6. Fluoro sugar syntheses from epoxides of monocyclic carbohydrates.

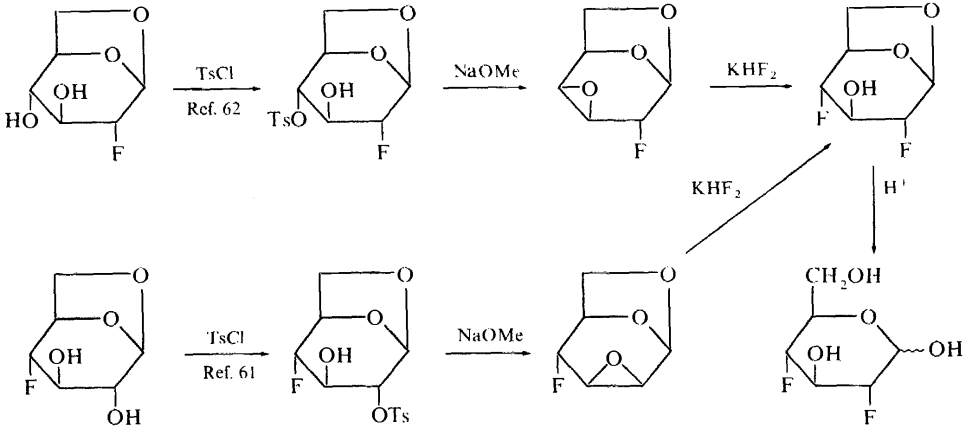
secondary fluoro sugars in both the pentose and the hexose series were obtained by the epoxide route as shown in *Scheme 6*. In each of these syntheses, epoxide derivatives of monocyclic carbohydrates were used. Of particular interest are the anomeric methyl 2,3-anhydro-5-*O*-benzyl-D-ribofuranosides. Whereas epoxide cleavage with KHF_2 of the α-anomer yields[55] mainly a 2-fluoro-D-arabinose product, the β-anomer under similar conditions gives[54] preponderantly the 3-fluoro-D-xylose derivative. An understanding of the factors which influence epoxide cleavage in these compounds would be valuable in the context of planning syntheses based on the epoxide route.

More recent work has utilized epoxides derived from 1,6-anhydro-β-D-glucopyranose. The bridged bicyclic system in these compounds greatly reduces the flexibility of the pyranose ring so that epoxide cleavage is usually stereospecific and predictable giving *trans*-diaxial products in accord with the Fürst–Plattner rule. Sulphonylation of 1,6-anhydro-β-D-glucopyranose yields[57] the 2,4-ditosylate because HO-3 is sterically hindered. The ditosylate is converted by base[58] into 1,6:3,4-dianhydro-2-*O*-tosyl-β-D-galactopyranose and the reaction sequences shown in *Scheme 7* have been used to convert this dianhydride into 2-deoxy-2-fluoro-D-glucose[59] and 4-deoxy-4-fluoro-D-glucose[60,61]. The latter synthesis is a more efficient route to 4-deoxy-4-



Scheme 7. Fluoro sugar syntheses from 1,6:3,4-dianhydro-2-*O*-tosyl-β-D-galactopyranose[59, 60].

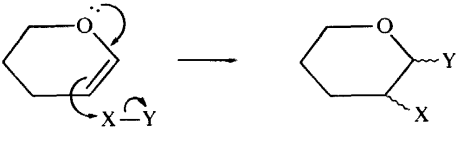
fluoro-D-glucose than the alternatives[48]. Intermediates in the syntheses in *Scheme* 7, namely, 1,6-anhydro-2-deoxy-2-fluoro-β-D-glucopyranose[59] and the 4-fluoro analogue[61] have been used in syntheses of 2,4-dideoxy-2,4-difluoro-D-glucose[61, 62] as shown in *Scheme* 8.



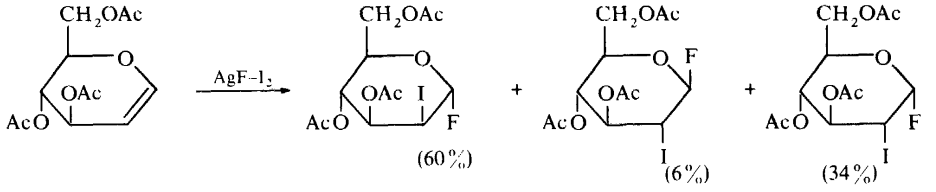
Scheme 8. Syntheses of 2,4-dideoxy-2,4-difluoro-D-glucose[61, 62].

6. GLYCAL ADDITION REACTIONS

Glycals (enol ethers) constitute a widely-exemplified class of carbohydrate derivative which are of particular value for the synthesis of 2-substituted derivatives. In ionic, 1,2-addition reactions it is usually C-2 of a glycal which behaves as a nucleophilic centre so that reaction proceeds along the pathway

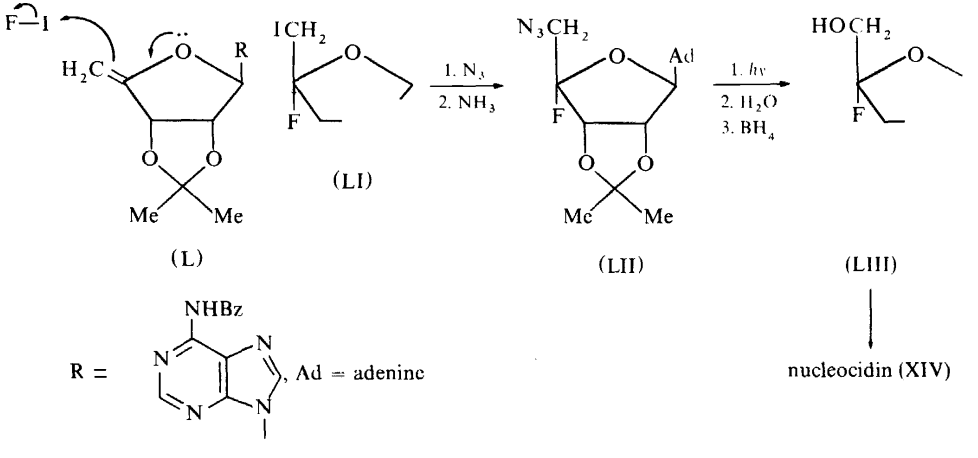


(XLIV) (XLV)



(XLVI) (XLVII) (XLVIII) (IL)

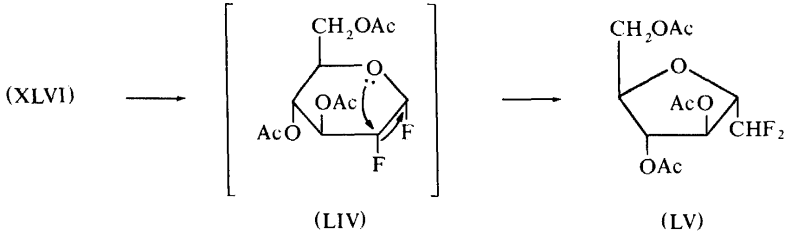
(XLIV) → (XLV). Thus, the mixed halogen F–I (generated from silver fluoride and iodine), which can be regarded as a source of electrophilic iodine, adds preponderantly *trans* to 3,4,6-tri-*O*-acetyl-D-glucal (XLVI) to give[63] the α-D-*manno* (XLVII), β-D-*gluco*-(XLVIII), and α-D-*gluco*-(IL) 2-deoxy-2-iodoglycosyl fluorides. This reaction pathway has been elegantly utilized[25] in the synthesis of the antibiotic nucleocidin (XIV) which contains both an *N*-glycoside and a glycosyl fluoride grouping. Treatment of the exo-methylene nucleoside (L) (derived from adenosine) with iodine-silver fluoride



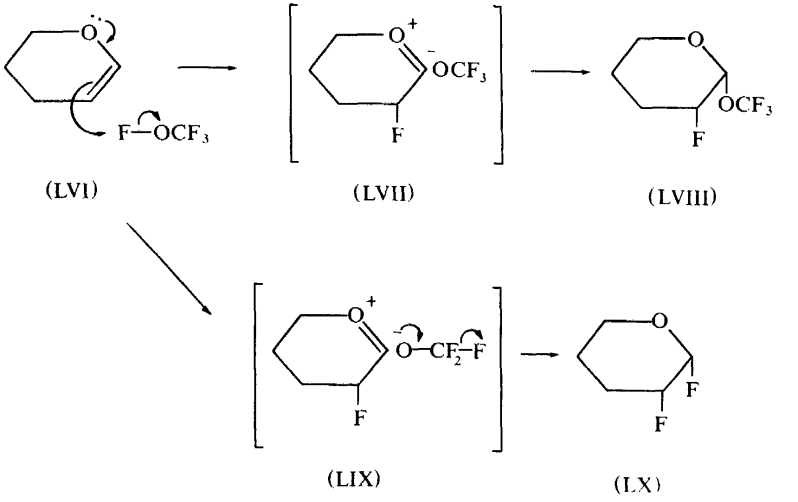
gave a mixture of the epimeric 5′-deoxy-4′-fluoro-5′-iodonucleosides; the ratio of β-D-*ribo* and α-L-*lyxo* isomers was markedly solvent dependent. The β-D-*ribo* isomer (LI) was separated, treated with lithium azide and the product saponified to give the 5′-azide (LII) which was converted by standard reactions into the 5′-hydroxy compound (LIII). Treatment of the 5′-*O*-tributyltin derivative of (LIII) with sulphamoyl chloride followed by hydrolysis with aqueous trifluoracetic acid gave nucleocidin (XIV).

The conversion of glycals into 2-deoxy-2-fluoro sugars requires the

addition of molecular fluorine or of a reagent which generates electrophilic fluorine. The direct addition of molecular fluorine to glycals has not been reported although adequate control of the reagent is now possible[64]. Treatment[65] of 3,4,6-tri-*O*-acetyl-D-glucal (XLVI) with lead tetra-acetate-hydrogen fluoride, a reagent which converts steroid olefins into *cis* difluorides[66], yields 3,4,6-tri-*O*-acetyl-2,5-anhydro-1-deoxy-1,1-difluoro-D-mannitol (LV). The reaction was postulated to involve formation and rearrangement of the 1,2-difluoride (LIV). However, the *cis*-difluorides (LXII) (=LIV) and (LXIV), described below, did not rearrange when treated with lead tetra-acetate-hydrogen fluoride[67].

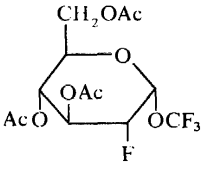


A group of reagents, the fluoroxyperfluoro-alkanes ($C_nF_{2n-1}OF$), which, in effect, generate electrophilic fluorine in addition reactions to appropriately activated olefins has been introduced by Barton *et al.*[68] The most frequently used member of the series, fluoroxytrifluoromethane (CF_3OF) adds to activated olefins by two mechanisms[69]. For example, addition of CF_3OF to a glycal



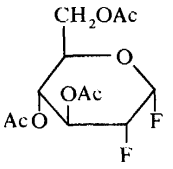
(LVI) yields the ion-pair (LVII) which can collapse to give the trifluoromethyl glycoside (LVIII). Depending on the stability of the oxonium ion component of the ion-pair is the extent of the second reaction pathway which involves loss of COF_2 from the counter-ion CF_3O^- (LIX) with subsequent collapse to give the difluoride (LX). The addition products (LVIII) and (LX)

are exclusively *cis*. Thus, treatment[67,70] of 3,4,6-tri-*O*-acetyl-D-glucal (XLVI) with CF_3OF in $CFCl_3$ at $-70°C$ gave the 2-deoxy-2-fluoro derivatives (LXI)–(LXIV). The α-D-glucopyranose derivatives (LXI) and (LXII) pre-



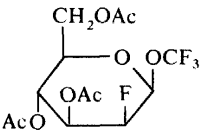
(26%)

(LXI)



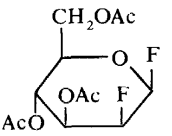
(34%)

(LXII)



(~5.5%)

(LXIII)

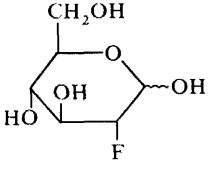


(~7.5%)

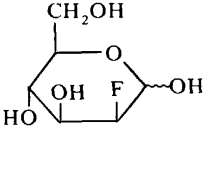
(LXIV)

ponderated as would be expected by analogy with the addition of, for example, chlorine[71] and nitrosyl chloride[72] to 3,4,6-tri-*O*-acetyl-D-glucal; the course of the latter reactions has been rationalized in stereo-electronic terms[72].

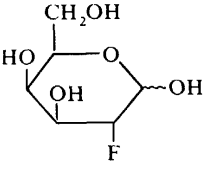
Acidic hydrolysis[67] of the trifluoromethyl glucoside (LXI) or the glucosyl fluoride (LXII) gave 2-deoxy-2-fluoro-D-glucose (LXV). This route of



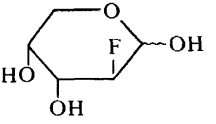
(LXV)



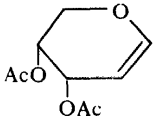
(LXVI)



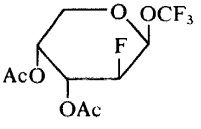
(LXVII)



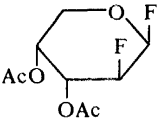
(LXVIII)



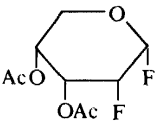
(LXIX)



(LXX)



(LXXI)



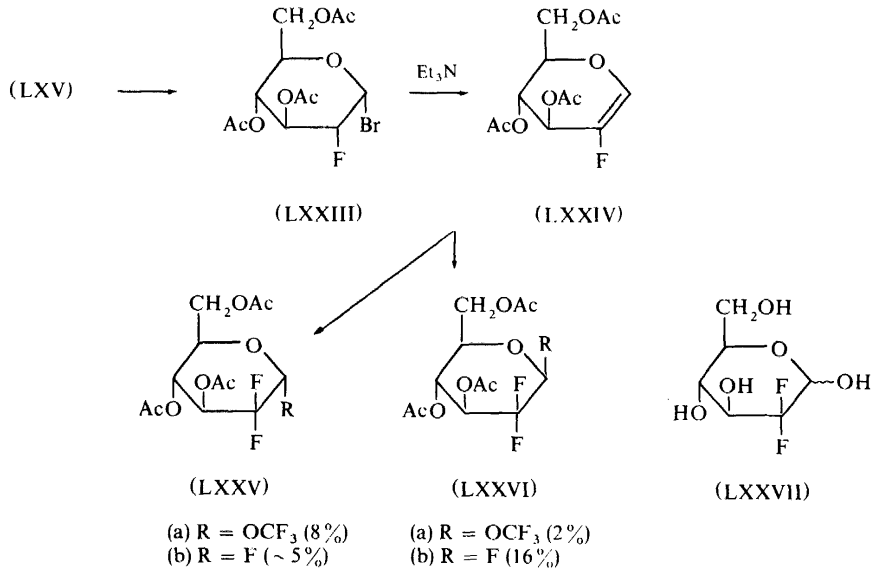
(LXXII)

synthesis of 2-deoxy-2-fluoro-D-glucose involves four stages starting from D-glucose and is more convenient than an earlier seven-stage synthesis starting from 1,6-anhydro-D-glucopyranose[59] (*Scheme* 7). 2-Deoxy-2-fluoro-D-mannose (LXVI) was obtained[67] by acid hydrolysis of the trifluoromethyl mannoside (LXIII) and the mannosyl fluoride (LXIV).

The CF_3OF reaction has been applied to other glycals. Thus, 2-deoxy-2-fluoro-D-galactose (LXVII) has been synthesised[73] from 3,4,6-tri-*O*-acetyl-D-galactal. Only traces (~5 per cent) of the *talo* compounds were formed in this reaction. In the pentose series, the addition of CF_3OF to 3,4-di-*O*-acetyl-D-arabinal (LXIX) was first described by Dwek *et al.*[74] but in a more thorough study Robins and co-workers[75] showed that the main products were the 2-deoxy-2-fluoro-β-D-*arabino* compounds (LXX) and (LXXI)

each of which could be hydrolyzed with acid to give 2-deoxy-2-fluoro-D-arabinose (LXVIII). Only traces (~2 per cent) of one D-*ribo* compound, namely, the 2-deoxy-2-fluoro-α-D-ribosyl fluoride (LXXII), were isolated. Although hydrolysis of compound (LXXII) with acid gave 2-deoxy-2-fluoro-D-ribose this synthesis route was not as convenient as that involving the 2,2′-cyclonucleoside (*Scheme 4*) as an intermediate[5].

2-Deoxy-2-fluoro-D-glucose was readily converted by conventional methods into the acetobromo derivative (LXXIII). Elimination of the elements of hydrogen bromide from compound (LXXIII) was effected with triethylamine to give the 2-fluoroglycal (LXXIV) with which CF_3OF readily



reacted[76] yielding the expected four products (LXXVa, b) and (LXXVIa, b). Acid hydrolysis, for example, of the trifluoromethyl α-glycoside (LXXVa) gave 2-deoxy-2,2-difluoro-D-*arabino*-hexose ((LXXVII). '2,2-difluoro-glucose').

A detailed review of the biological activity of fluorinated carbohydrates will be presented elsewhere[77] but it might be noted here that 2,2-difluoro-glucose (LXXVII) is a better substrate for yeast hexokinase than is D-glucose and it is a strong inhibitor of D-glucose phosphorylation. This suggests that in D-glucose either HO-1 or HO-3 or both act as hydrogen bond donors in the enzyme–substrate complex. Because of the high electronegativity of the CF_2 group the acidity of HO-1 and HO-3 in compound (LXXVII) will be enhanced (*cf.* 9α-fluoro-hydrocortisone (VIII)) and this will promote formation of the enzyme–substrate complex.

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