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Review

Synthesis of deoxyfluoro sugars from carbohydrate precursors☆

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Abstract

Results obtained over the past decade concerning the introduction of the fluorine atom into carbohydrate molecules, either by nucleophilic substitution or electrophilic addition reactions, are summarised. The first section mainly deals with the triflate/fluoride tandem sequence and the DAST-reaction. In the discussion, emphasis is given to the dependency of the reaction course on the stereochemical and protecting group features. Possible reaction pathways are direct substitution (with inversion or retention of configuration), rearrangement (combined with substitution and inversion of configuration at both of the centres involved) and elimination. Based on the assumption of cyclic transition states or transient intermediates (formed through participation of neighbouring groups), far-reaching mechanistic generalisations were made. On this basis, isolated examples from the literature, which are not in accordance with these generalisations, are specifically brought to attention. Results from the recently introduced reaction of safe and easy to handle *N*–F fluorinating agents with glycals are also reported. This approach allows the simple and stereoselective access to a series of 2-deoxy-2-fluoro aldopyranoses, as well as the synthesis of various C-1-substituted derivatives by an easy one-pot reaction. However, the same method applied to furanoid glycals is rather poor with respect to stereoselectivity. Finally, considerations on the importance of fluorine-specific reactions of the S_N-type in related fields of organic synthesis are made.

Keywords: Deoxyfluoro sugars; Fluorination; DAST-reaction; Rearrangements; Electrophilic addition; Glycals; *N*–F reagents

Contents

Abbreviations: AM, alkoxy-migration; RC, ring-contraction; DAST, diethylamino sulfur trifluoride; TASF, tris(dimethylamino)sulfonium difluorotrimethylsilicate; TBAF, tetrabutylammonium fluoride; NFSI, *N*-fluorobenzenesulfonamide; TED, Dabco™, 1,4-diazabicyclo[2.2.2]octane; F–TEDA–BF_4, 1-chloromethyl-4-fluoro-1,4-diazonia-bicyclo[2.2.2]octane bis(tetrafluoroborate); DMF, *N*,*N*-dimethyl formamide; DNP, 2,4-dinitrophenyl; Py, pyridine; n.g., not given.

☆ Deoxyfluoro-sugars are sugar derivatives where an alcoholic moiety has been replaced by fluorine [IUPAC Nomenclature of Carbohydrates, *Carbohydr. Res.*, 297 (1997) 1–97].

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1. Introduction and scope

For the presentation of new developments in the synthesis of fluorine-containing carbohydrates, Tsuchiya's outstanding review from 1990 [1] and that from Card [2] constitute solid points of reference. They described and compared, in a comprehensive way, not only the existing methodologies for the introduction of that 'female' halogen, but also pointed out the many facets of interesting side reactions. In addition, a few other reviews dealing with the synthesis of fluorinated carbohydrates have appeared, but these focussed on special substance classes of compounds, which are out of the scope of this compilation, such as the synthesis of glycosyl fluorides [3] or nucleosides fluorinated in the sugar moiety [4], or were devoted to illustrate the scope and limitations of certain fluorinating agents [5] or discuss general concepts employed for the synthesis of fluorinated organic compounds [6].

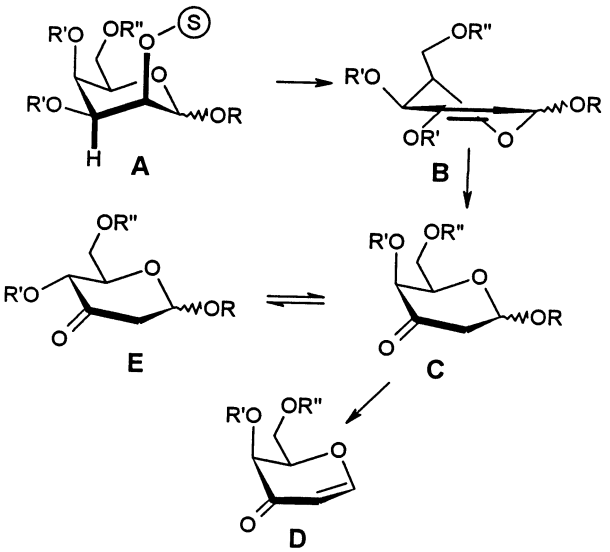
In presenting the results obtained within the last decade, importance will be primarily placed on the fluorination step rather than protecting-group strategies and subsequent chemical modifications of the deoxyfluoro sugar thus formed. Within each section, attention will be drawn to side-reactions observed from selected attempts to introduce fluorine. As far as possible, structural prerequisites as well as mechanistic principles governing these various types of reactions will be discussed[1]. A summary of reported transformations is collected in Tables 1–6 which contain the structures of educts, products, reaction conditions, yields and the respective literature citations. The section dealing with nucleophilic substitution reactions is divided according to the position of fluorine-atom introduction (primary (C-6 or 5), exocyclic secondary (C-5) and endocyclic secondary (C-4, 3 or 2). Reactions with ketoses follow the same classification. No strict separation is made between results obtained with pyranoid and furanoid structures.

[1] References will only be given if facts were not presented in Ref. [1].

2. Introduction of fluorine via nucleophilic substitution reactions in sugar derivatives such as sulfonates, DAST-activated OH-groups, epoxides, epimines and cyclic sulfates

For any nucleophilic substitution reaction, the general poor nucleophilic character of fluoride containing reagents constitutes a constant drawback, despite limited success in 'nucleophilicity/basicity tuning' [6b]. Therefore, substrates containing leaving groups with high nucleofugicity (such as trifluoromethanesulfonates, imidazolesulfonates or DAST-activated species) are commonly preferred and, in many instances, this combination meets the requirements for a preparatively useful transformation.

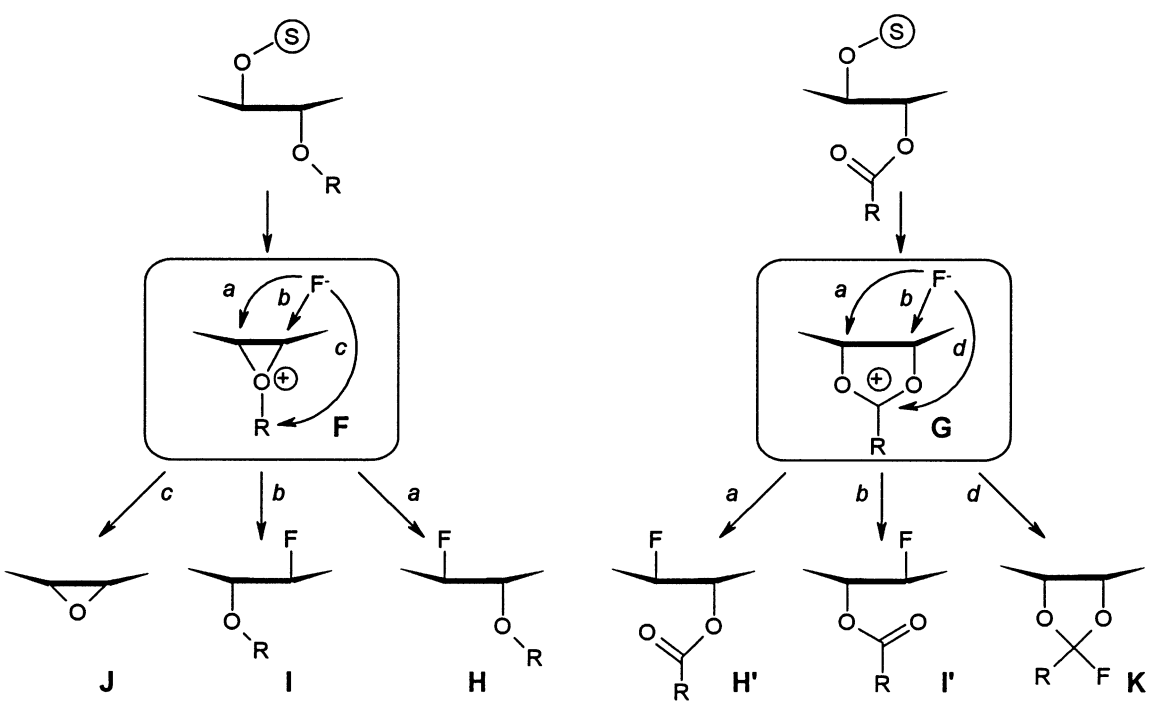
However, it is known that elimination reactions can compete with nucleophilic substitution reactions when the leaving group [OⓈ] is situated in an antiperiplanar orientation to a vicinal hydrogen (as shown in structure **A**, Scheme 1). In addition, this prerequisite for elimination is not necessarily restricted to the conformation preponderating under the reaction conditions. Depending on the nature of the protecting groups, elimination products (**B**) thus formed are enol ethers or esters. These side products may be hydrolysed to give carbonyl compounds of type **C**, which, especially under basic conditions, are also prone to further β-elimination to give **D** or epimerisation at the vicinal chiral centre to form **E**.



Scheme 1.

A comparatively diverse set of alternatives to the direct S_N2 introduction of fluoride arises from the possible 'participation' of either nucleophilic groups located in the neighbourhood of the reaction centre or any nucleophilic solvent. Mechanistically, the principles of carbenium ion chemistry play an important role (Scheme 2). In addition to the direct S_N2 displacement of a leaving group by a solvent molecule, this sensitivity is home for the formation of positively charged cyclic species in transition states or transient intermediates (type **F** or **G**, without restriction of participation to functionalities from vicinal positions). By their opening at the C-atom of the original activation (Path a), substitution by fluoride with retention of configuration under formation of structures **H**/**H**′ occurs. Nucleophilic attack at the other C-atom from the carbohydrate-chain involved in the cyclic structure of the intermediate (Path b) induces a rearrangement such as group migration including ring contraction with inversion of configuration at both positions to give products of type **I**/**I**′. The third route that 'charged intermediate' can follow depends on the nature of the charged atom. The 'oxonium-type' structure **F** also can undergo displacement at the first C-atom of its third substituent (Path c) to form anhydro compound **J** together with, e.g., benzyl fluoride. The 'acyloxonium-type' intermediate **G** can react with a nucleophile (Path d) to give orthoacid derivative **K** [7].

Consequently, the activation for reaction is transferred from the chosen activation site to two further centres, i.e., to the C-atom, where the participating group originally is bound and



Scheme 2.

the first C-atom of the participating group. The working-order within these options (as determined by the differences within the free activation enthalpies) depends on the nucleophilicity of the leaving group and, on the one hand, on the ranking of the individual nucleophilic characters of partners present and, on the other hand, on certain stereochemical prerequisites. Each of these parameters is a function of the reaction conditions and also depends on the nature and position of other, non-participating protecting groups. Therefore, diverging results are often reported from the same type of reaction, especially when one product only is isolated in low to moderate yield.

In principle, the same side-reactions are observed with the reaction of unprotected OH-groups with DAST. Here, in the first, rapid step, an activated species of the structure $-OSF_2NEt_2$ is formed, which, compared with the corresponding sulfonate derivative, tends to react via S_N-displacement rather than eliminate. In addition, formation of anhydro compounds and (during work-up) cyclic sulfites can be observed in cases where an OH-group is close enough to participate.

The nucleophilic ring opening of epoxides, apart from those having a primary carbon atom or a carbon atom which is in α position to a carbonyl group, is generally hampered by the lack of regioselectivity. Furthermore, exceptions to the Fürst–Plattner rule, a rule that predicts the steric relationship of substituents in products obtained by the opening of epoxides of pyranoid sugars to be trans-diaxial, can be observed. This is especially the case when C-2 of aldopyranosides is involved and tetraalkylammonium fluorides are used as the nucleophile source.

In contrast to the situation with non-terminal epoxides, high regioselectivity can be observed with the opening of 2,3-anhydro rings from aldonolactones as well as cyclic sulfates when employing fluoride as the nucleophile.

2.1. Introduction of fluorine at a primary position (Table 1)

Fluorination at C-6 was reported from reaction of DAST with β- and α-D-mannose derivatives **1**, **3**, and **5** [8] (entries 1–3) and β-D-galactopyranosides **7** [9], **9** and **11** [10] (entries 4, 5 and 6). When the 2,4-dimethylbenzoyl group was used for O-protection in the β-lactoside **11** (entry 6) instead of the 2,4,6-trimethylbenzoyl analog in compound **9** (entry 5), acyl migration from O-4′ to O-6′ was observed under standard reaction conditions to give compound **12**. This product then reacted further with DAST, under inversion of configuration, to give 4′-deoxy-4′-fluorocellobioside **13**. Under the same conditions, methyl 4′,6′-*O*-benzylidene-β-lactoside **14** [9] (entry 7) gave the monofluorinated compound **15** in low yield. Partially O-acylated β-lactoside **16** [10] (entry 8) was fluorinated in the same position in good yield, when reacted with DAST in diglyme. Conducting the same reaction in dichloromethane (entry 9) lowered the yield of the desired product **17** because of migration of the anomeric methoxy group to C-6. Consequently, the β-lactosyl fluoride **18** was also isolated. This sort of methoxy-shift from C-1 to C-6 with concomitant fluorination at C-1 had previously been observed [11] when the partially O-benzoylated 'β-D-galactobioside' **19** (entry 10) was subjected to the same reaction conditions. The fact that the β-glycosyl fluoride **20** constituted the major product was accounted for by the participation of the 2-*O*-acyl group, since reaction of the O-benzylated counterpart **21** (entry 11) had led, by participation of O-3, to the 3,6-anhydro compound **22**. With α-D-galactopyranose derivatives, aglycon migration was not observed, but 3,6-anhydro-ring formation as well as elimination and solvent participation were found to occur [12]. In a thorough study [12] towards the synthesis of methyl 6-deoxy-6-fluoro-α-D-galactopyranoside derivative **24**, the triflate/tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) tandem gave the best results (entry 12).

A similar type of anhydro ring formation, as had been found [11] in the reaction of the benzylated D-galactose and D-glucose derivatives with DAST, was also observed in this laboratory[2] with experiments involving 1,2-*O*-isopropylidene-α-D-glucofuranose (**26**) and its derivatives **30**, **32** and **33** (entries 13–16). From the reaction of **26**, in addition to the 6-deoxy-6-fluoro derivative **27** (isolated as the

[2] P. Hadwiger, A.E. Stütz, K. Dax, unpublished results.

Table 1
Results on attempted fluorination at a primary position

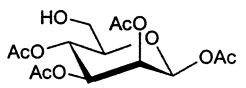
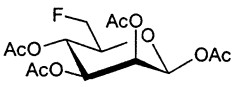
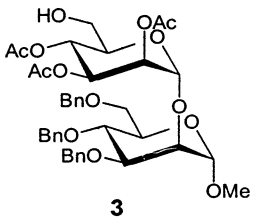
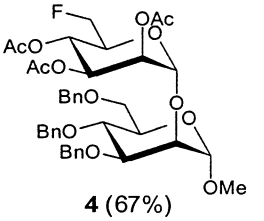
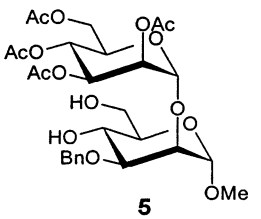
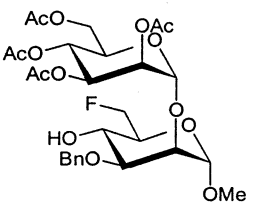
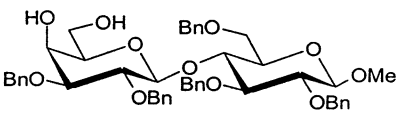
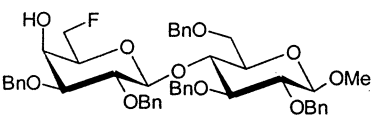
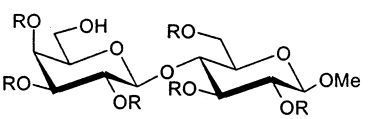
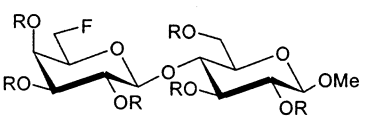
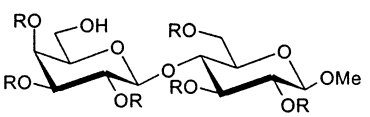
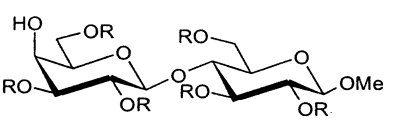
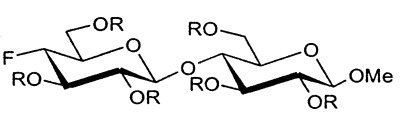
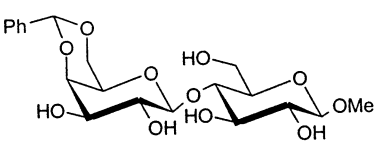
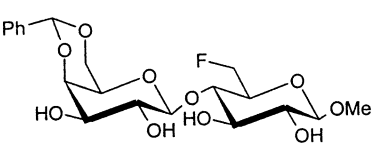
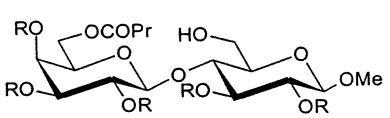
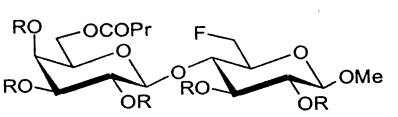
No.	Educt	Reagent	Product(s)	Ref.
1	 **1**	DAST diglyme	 **2** (42%)	[8]
2	 **3**	DAST diglyme	 **4** (67%)	[8]
3	 **5**	DAST diglyme	 **6** (48%)	[8]
4	 **7**	DAST CH_2Cl_2	 **8** (47%)	[9]
5	 **9** R=Me_3Bz	DAST CH_2Cl_2	 **10** (94%)	[10]
6	 **11** R=Me_2Bz	DAST CH_2Cl_2	 **12** (33%)  **13** (24%)	[10]
7	 **14**	DAST CH_2Cl_2	 **15** (31%)	[9]
8	 **16** R=Ac	DAST diglyme	 **17** (68%)	[10]

Table 1 (Continued)

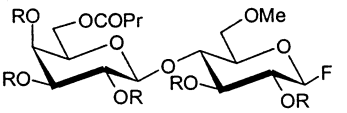
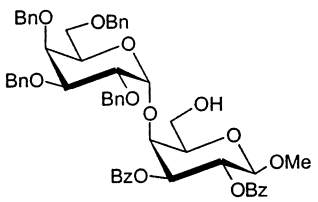
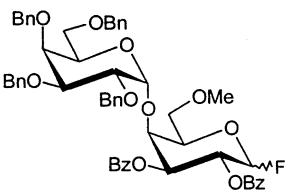
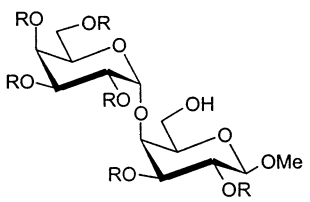
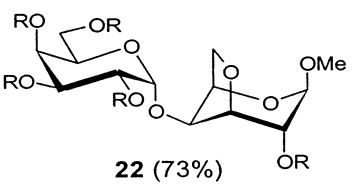
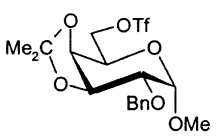
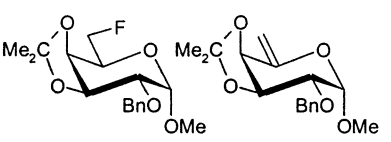
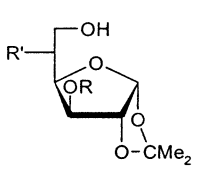
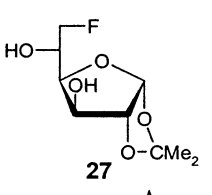
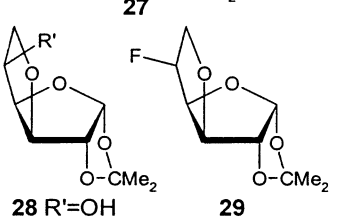
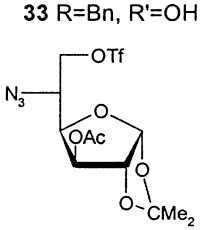
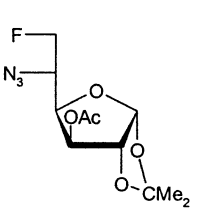
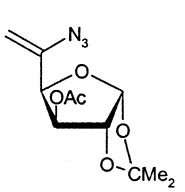
No.	Educt	Reagent	Product(s)	Ref.
9	**16**	DAST CH_2Cl_2	 **17** (32%) **18** (36%)	[10]
10	 **19**	DAST CH_2Cl_2	 **20** (60%); α:β 1:5	[11a]
11	 **21** R=Bn	DAST CH_2Cl_2	 **22** (73%)	[11a]
12	 **23**	TASF CH_2Cl_2	 **24** (83%) **25** (15%)	[12]
13	 **26** R=H, R'=OH	DAST CH_2Cl_2	 **27**  **28** R'=OH **29**	[13], [u.r.]
14	**30** R=R'=H		**31** R'=H	[u.r.]
15	**32** R=Bn, R'=H		**31** R'=H	[u.r.]
16	**33** R=Bn, R'=OH		**29**	[u.r.]
17	 **34**	TBAF MeCN	 **35**  **36** (low yield)	[14]

Table 1 (Continued)

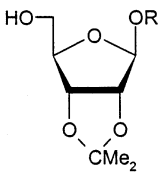
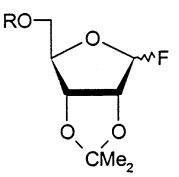
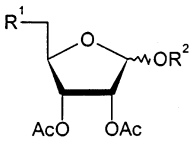
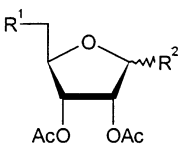
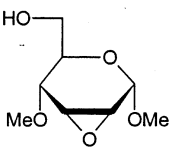
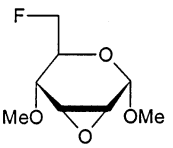
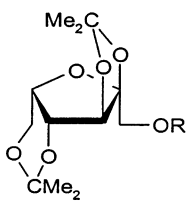
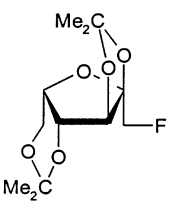
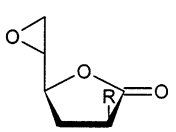
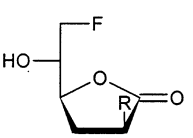
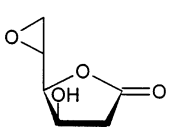
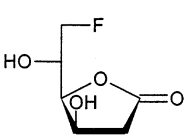
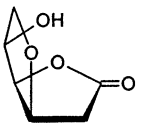
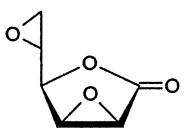
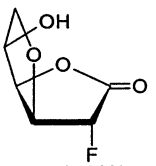
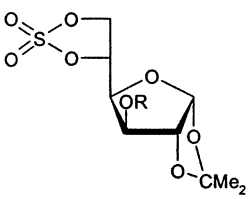
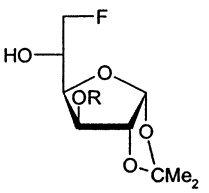
No.	Educt	Reagent	Product(s)	Ref.
18	 **37** R=Me	DAST CH_2Cl_2	 **38** R=Me (55%); β	[15]
19	**39** R=Ac		**40** R=Ac (87%); α β 2:5	[15]
20	 **41** R^1=OH, R^2=Me	DAST CH_2Cl_2	 **42** R^1=OMe, R^2=F (50%); β	[15]
21	**43** R_1=OH, R_2=Ac		**44** R_1=F, R_2=OAc (40%); α:β 1:1.3	[15]
22	 **45**	DAST CH_2Cl_2/Py	 **46** (25%)	[16]
23	 **47** R=H	DAST CH_2Cl_2	 **48** (30%)	[17]
24	**49** R=Tf	TASF THF	**48** (80%)	[17]
25	 **50** R=H	TEA·3 HF	 **51** (55%)	[18a]
26	**50** R=H	TBA·H_2F_3 KHF_2	**51** (70%)	[18b]
27	**52** R=OH	TEA·3 HF	**53** (56%)	[18b]
28	**52** R=OH	TBA·H_2F_3	**53** (65%)	[18b]
29	 **54**	TEA·3 HF	 **55** (65%)	[18a]

Table 1 (Continued)

No.	Educt	Reagent	Product(s)	Ref.
30	**54**	$TBA \cdot H_2F_3$	 **56** (low yield)	[18b]
31	 **57**	cat. $TBA \cdot H_2F_3$ KHF_2	 **58** (10%)	[18b]
32	 **59** R = Ac, Bn or Ms	1) TBAF 2) H_3O^+	 **60** (85-90%)	[19]

sole product in 70% yield in the pioneering work of Card and Reddy [13]), the 3,6-anhydro compound **28** and its fluorinated derivative **29**, showing inverted configuration at C-5, were obtained; the ratio between **28** and **29** depended on the reaction time. The same ring forming reaction was also found to occur with the 5-deoxy derivative **30** and the 3-*O*-benzyl protected derivatives **32** (of **30**) and **33** (of **26**) [for these reactions, generation of benzyl fluoride (δ −206.7 ppm, t, J 48 Hz) was proved by ^{19}F NMR spectroscopy]. To introduce fluorine at C-6 in 3-*O*-acetyl-5-azido-5-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (**34**), to obtain intermediate **35** which could be used for the synthesis of the first fluorinated 1-deoxynojirimycin derivative [14], use was made of the triflate/TBAF-route (entry 17); the substitution was, to a small extent, accompanied by elimination to form **36**.

The substituent shift from C-1 to the primary C-atom, as observed with β-D-hexopyranosides in entries 9 and 10, can also be found in β-D-pentofuranoses, and this observation is not restricted to alkoxy substituents [15]. Methyl β-D-ribofuranosides **37** and **41** (entries 18 and 20) and 1-*O*-acetyl-2,3-*O*-isopropylidene derivative **39** (entry 19), upon treatment with DAST, gave 5-*O*-methyl-β-D- (**38** and **42**) as well as 5-*O*-acetyl-α/β-D-ribofuranosyl fluorides (**40**), respectively. Interestingly, fluorination at C-1, simultaneous to the migration of the substituent from C-1 to C-5, did not proceed with inversion of configuration. This may be due to anomerization under the conditions of the DAST-reaction. Changing the substituent at C-1 from methoxy to acetoxy, as with 1,2,3-tri-*O*-acetyl-D-ribofuranose **43** (entry 21), allowed the synthesis of the expected 5-deoxy-5-fluoro derivative **44** in 40% yield.

Low fluorinated product yields were also obtained from methyl 2,3-anhydro-4-*O*-methyl-α-D-allopyranoside (**45**) [16] (entry 22) as well as 2,3:4,6-di-*O*-isopropylidene-α-L-sorbofuranose (**47**) [17] (entry 23), when DAST was employed as the fluorinating agent. In the latter case, the yield of **48** could be improved to 80% by using the triflate/TASF-route (entry 24).

Opening of 5,6-anhydro compounds **50**, **52**, and **54** (entries 25–30), derived from deoxyhexono-1,4-lactones, was studied by Lundt, Thiem and co-workers. These authors employed complexes of HF with triethylamine, collidine or pyridine [18a] as well as tetrabutyl-

Table 2
Results on attempted fluorination at position 5 in hexofuranoses

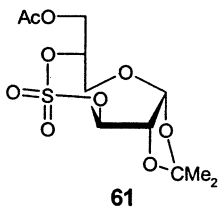
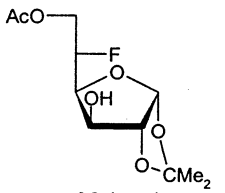
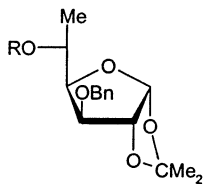
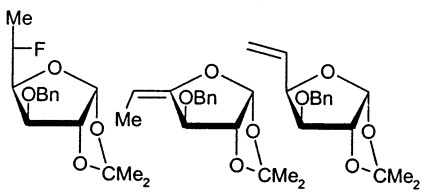
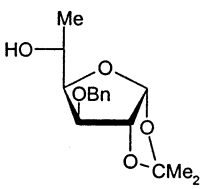
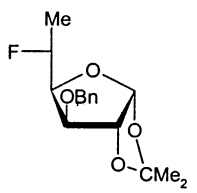
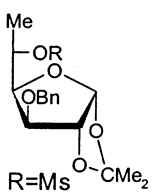
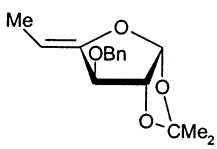
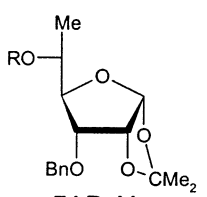
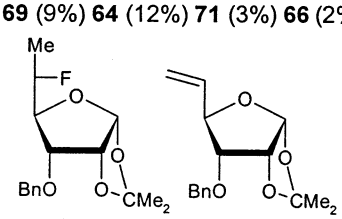
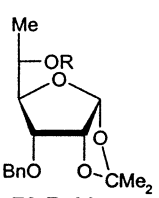
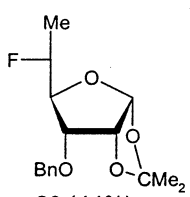
No.	Educt	Reagent	Product(s)	Ref.
1	 **61**	1) TASF/CH_2Cl_2 2) H_3O^+	 **62** (n.g.)	[19]
2	 **63** R=Ms	TBAF/DMF	 **64** (5%) **65** (54%) **66** (37%)	[24]
3	**67** R=Tf	TASF/CH_2Cl_2	**64** (3%) **65** (58%) **66** (35%)	[24]
4	 **68**	DAST/CH_2Cl_2	 **69** (61%) **64** (3%) **65** (5%) **66** (8%)	[24]
5	 **70** R=Ms	TBAF/DMF	 **69** (8%) **71** (43%) **66** (32%)	[24]
6	**72** R=Tf	TASF/CH_2Cl_2	**69** (23%) **71** (25%) **66** (37%)	[24]
7	**73** R=H	DAST/CH_2Cl_2	**69** (9%) **64** (12%) **71** (3%) **66** (2%)	[24]
8	 **74** R=Ms	TBAF/DMF	 **75** (20%) **76** (69%)	[24]
9	**77** R=Tf	TASF/CH_2Cl_2	**75** (23%) **76** (72%)	[24]
10	**78** R=H	DAST/CH_2Cl_2	**75** (39%) **76** (2%)	[24]
11	 **79** R=Ms	TBAF/DMF	 **80** (44%) **76** (45%)	[24]
12	**81** R=Tf	TASF/CH_2Cl_2	**80** (59%) **76** (21%)	[24]
13	**82** R=H	DAST/CH_2Cl_2	**80** (61%) **76** (2%)	[24]

Table 3
Results on attempted fluorination at position 4 in hexopyranoses

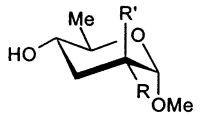
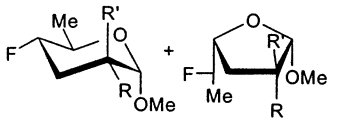
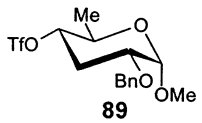
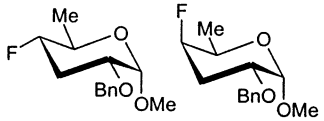
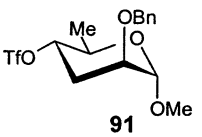
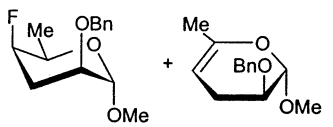
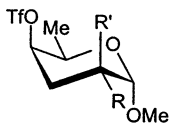
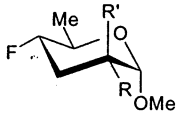
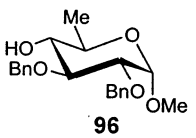
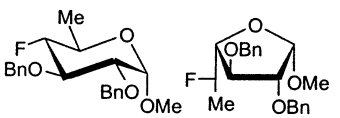
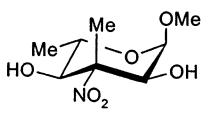
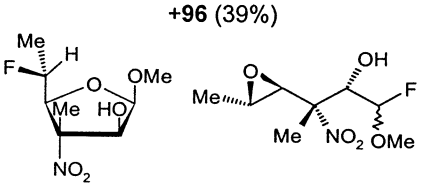
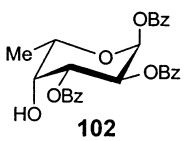
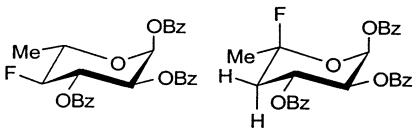
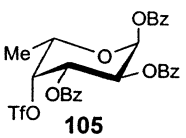
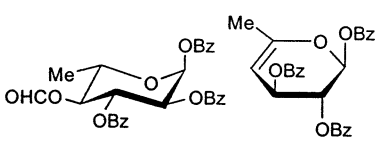
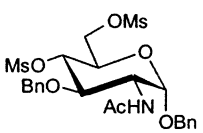
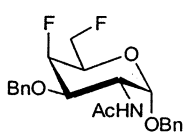
No.	Educt	Reagent	Product(s)	Ref.
1	 **83** R=OBn, R'=H	DAST CH_2Cl_2	 **84** (66%) **85** (17%)	[23]
2	**86** R=H, R'=OBn		**87** (28%) **88** (21%) + 34% **86**	[23] [23]
3	 **89**	TASF CH_2Cl_2	 **84** (13%) **90** (21%)	[23]
4	 **91**	TASF CH_2Cl_2	 **92** (21%) **93** (24%)	[23]
5	 **94** R=OBn, R'=H	TASF CH_2Cl_2	 **84** (66%)	[23]
6	**95** R=H, R'=OBn		**87** (13%) **93** (42%)	[23]
7	 **96**	DAST CH_2Cl_2	 **97** (2%) **98** (38%) +**96** (39%)	[23]
8	 **99**	DAST CH_2Cl_2	 **100** (46%) **101** (40%)	[25]
9	 **102**	DAST CH_2Cl_2	 **103** (60%) **104** (15%)	[26]
10	 **105**	TBAF DMF	 **106** (43%) **107** (4%)	[26]
11	 **108**	TBAF MeCN	 **109** (88%)	[27]

Table 3 (Continued)

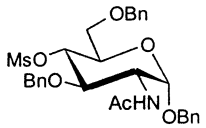
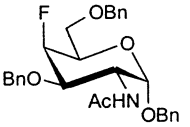
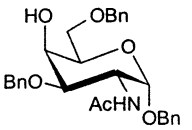
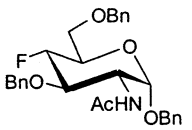
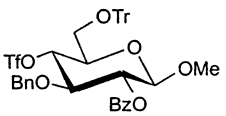
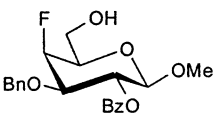
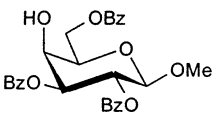
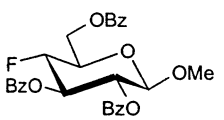
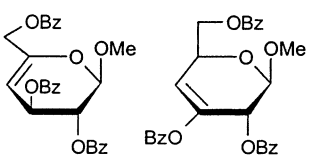
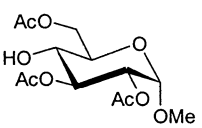
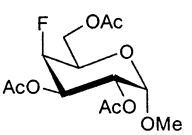
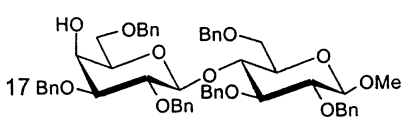
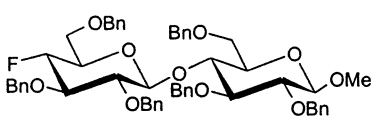
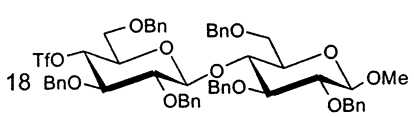
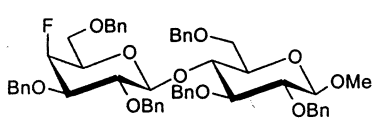
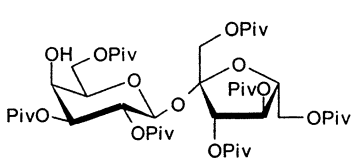
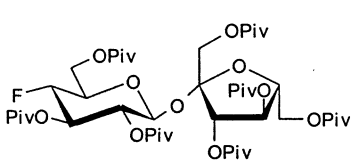
No.	Educt	Reagent	Product(s)	Ref.
12	 **110**	TBAF MeCN	 **111** (90%)	[27]
13	 **112**	DAST CH_2Cl_2	 **113** (85%)	[27]
14	 **114**	1) A-26 [F⁻] benzene 2) H_3O^+	 **115** (38%)	[28]
15	 **116**	DAST dimethoxy ethane/Py	 **117** (48%)  **118** (23%) **119** (13%)	[29]
16	 **120**	DAST CH_2Cl_2 DMAP	 **121** (39%)	[30]
17	 **122**	DAST CH_2Cl_2	 **123** (60%)	[9]
18	 **124**	TBAF benzene	 **125** (66%)	[9]
19	 **126**	DAST diglyme	 **127** (68%)	[31]

Table 3 (Continued)

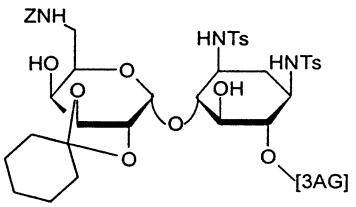
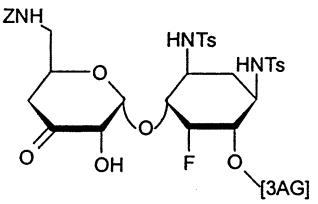
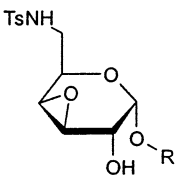
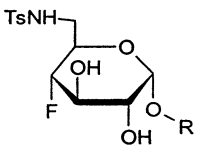
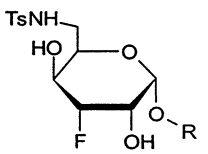
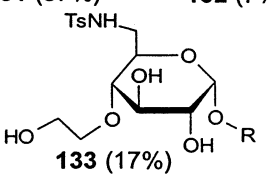
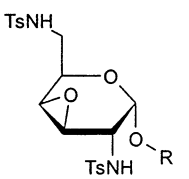
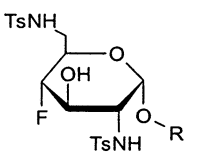
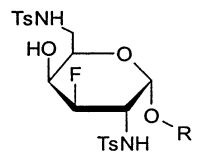
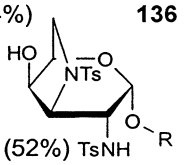
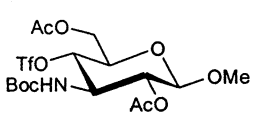
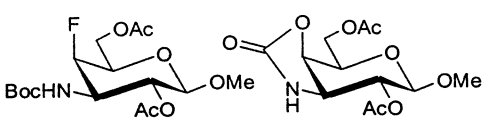
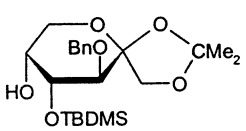
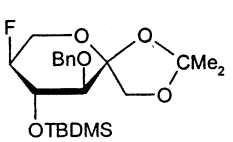
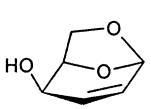
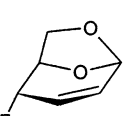
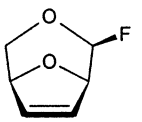
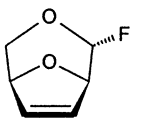
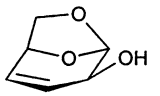
No.	Educt	Reagent	Product(s)	Ref.
20	 **128** (3AG=protected 3-aminodeoxy-α-D-glucose)	1) DAST CH_2Cl_2 2) H_2O	 **129** (50%)	[32]
21	 **130** R=[DOS-O-3AG] DOS=protected 2-deoxystreptamine	KHF_2 glycol	 **131** (37%)  **132** (7%)  **133** (17%)	[32]
22	 **134** R=[DOS-O-3AG]	KHF_2 glycol	 **135** (24%)  **136** (2%)  **137** (52%)	[32]
23	 **138**	TBAF/MeCN	 **139** (70%) **140** (20%)	[33]
24	**138**	TBAF/benzene	**139** (14%) **140** (69%)	[33]
25	 **141**	DAST/Py benzene	 **142** (62%)	[34]
26	 **143**	DAST/CH_2Cl_2 (20 °C/5 h)	 **144** (50%)	[35]

Table 3 (Continued)

No.	Educt	Reagent	Product(s)	Ref.
27	**143**	$DAST/CH_2Cl_2$ (-80 °C/10′)	 **145** (32%)  **146** (16%)	[35]
28	**143**	DAST/DMF (-50 °C/20′)	 **147** (50%)	[35]

ammonium dihydrogentrifluoride (TBA·H_2F_3) and a combination of the latter reagent with KHF_2 [18b]. In general, regioselective attack of fluoride at C-6 occurred with moderate to good yields. An exception to this was the reaction of TBA·H_2F_3 (entry 30) with educt **54** (this compound has a free hydroxyl group at C-3 and the side-chain on the same face of the lactone ring) to give the 3,6-anhydro derivative **56** as the sole product in low isolated yield. The same finding was made with the diepoxide **57** (entry 31), where the 2,3-anhydro ring was preferentially opened.

Confirmation of the superiority of cyclic sulfates to epoxides as educts in nucleophilic substitution reactions can be gained from the excellent results reported [19] with the 5,6-*O*-sulfonyl derivatives **59** of 3-*O*-protected 1,2-*O*-isopropylidene-α-D-glucofuranoses (entry 32).

2.2. Introduction of fluorine at C-5 of hexofuranosides (Table 2)

As a general drawback, nucleophilic substitution at C-5 of D-glucofuranose derivatives is prone to S_Ni-reactions, either by a 3-OH moiety giving 3,5-anhydro derivatives [20] or a 6-*O*-acyl group leading to acyl migration with inversion of configuration at C-5 and entry of the nucleophile at C-6 [21]. Therefore, compounds of type **62** had previously been prepared from 1,2-*O*-isopropylidene-α-D-glucofuranurono-6,3-lactone [22], using the triflate/TBAF-route or DAST, followed by reduction of the lactone functionality. Recently, these difficulties have been overcome [19] by the regioselective opening of the 3,5-*O*-sulfonyl derivative **61** with TASF in dichloromethane (entry 1). After hydrolysis of the hemisulfate formed, 5-deoxy-5-fluoro-β-L-idofuranose **62** was isolated and products arising from elimination were found in minor proportion (1%) only (see next paragraph).

Initiated by an observed ring-contraction reaction [23] found upon the attempted introduction of fluorine at C-4 (see Section 2.3) of methyl 3,6-dideoxyhexopyranosides, Morishima and co-workers [24] started a whole series of experiments to elucidate the parameters governing the outcome of fluorination reactions at C-5 of 6-deoxy-1,2-*O*-isopropylidene hexofuranoses. It was found that transformations starting from sulfonates (entries 2, 3, 5, 6, 8, 9, 11, and 12) were generally dominated by elimination, whereas in DAST-reactions (entries 4, 7, 10, and 13) substitution by fluoride preponderated. Employing DAST, striking discrepancies in the stereochemical course of the substitution reaction were observed. Retention of configuration prevailed with D-glucose and L-idose derivatives (**68** and **73**), respectively, whereas their D-allo- and L-talo counterparts (**78** and **82**) only gave inversion. The authors explained these diverging results on the basis of steric hindrance by the 3-benzyloxy group (in the D-gluco/L-ido-case located on the same side of the THF-ring as the reaction centre) and a S_Ni-mechanism operating 'via an ion-pair intermediate in the solvent cage' [24b]. A possible 'anchimeric assistance' by the oxygen atom of the benzyloxy group was not taken into consideration.

Table 4
Results on attempted fluorination at position 3

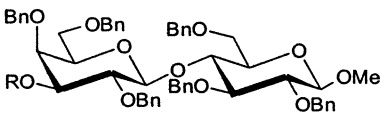
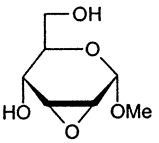
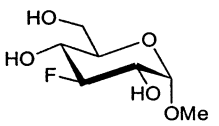
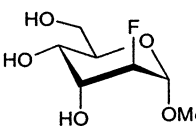
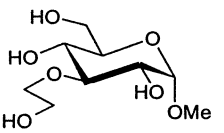
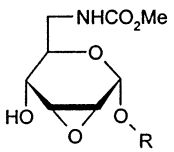
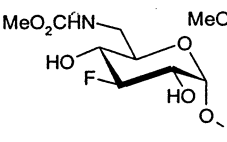
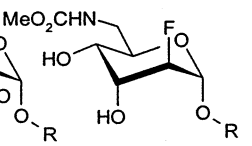
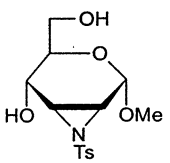
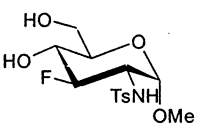
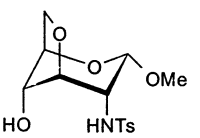
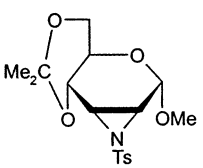
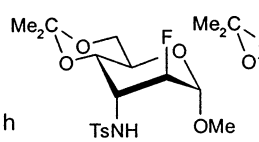
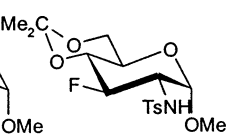
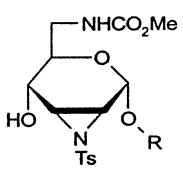
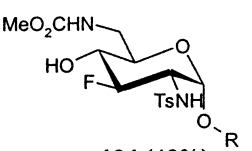
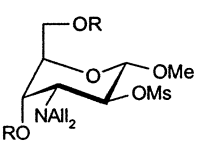
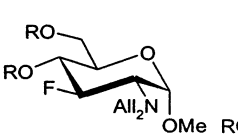
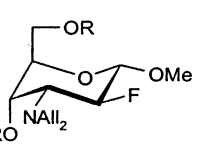
No.	Educt	Reagent	Product(s)	Ref.
1	 **148** R=H	DAST CH_2Cl_2	Complex mixture of fluorinated products	[9]
2	**149** R=Tf	TBAF CH_2Cl_2	Elimination products only	[9]
3	 **150**	KHF_2 diethylene glycol	 **151** (48%)  **152** (trace)  **153** (trace)	[16]
4	 **154** R=[DOS-O-3AG]	KHF_2 diethylene glycol	 **155** (31%)  **156** (16%)	[16]
5	 **157**	KHF_2 DMF	 **158** (39%)  **159** (40%)	[36]
6	 **160**	KHF_2 DMF 150 °C/5 h	 **161** (35%)  **162** (10%)	[36]
7	**160**	150 °C/168 h	**162** (33%)	[36]
8	 **163** R=[DOS-O-3AG]	KHF_2 DMF 150°C/2 h	 **164** (49%)	[36]
9	 **165** R=Ac	$Et_3N \cdot 3\,HF$ Et_3N/MeCN	 **166** (87%)  **167** (12%)	[37]

Table 4 (Continued)

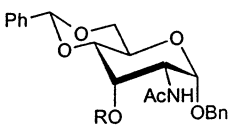
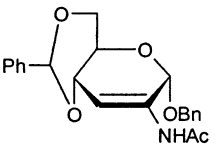
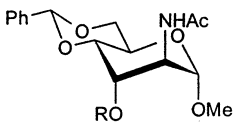
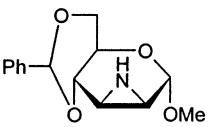
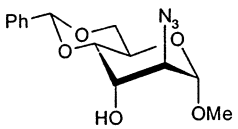
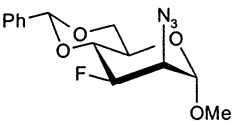
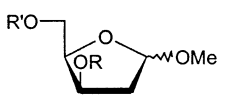
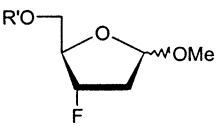
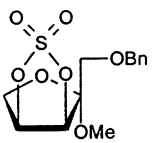
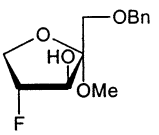
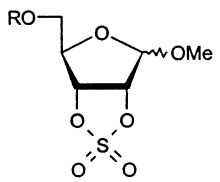
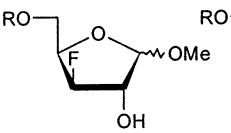
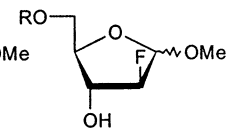
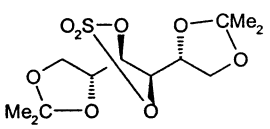
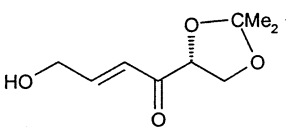
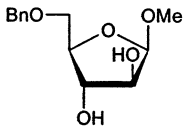
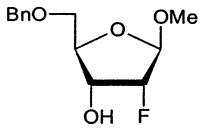
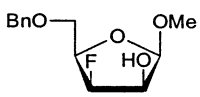
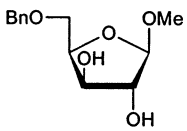
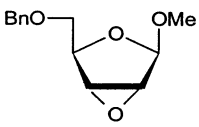
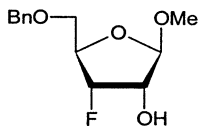
No.	Educt	Reagent	Product(s)	Ref.
10	**168** R=Ms	$Et_3N \cdot 3\,HF$ MeCN	**169** (40%) **170** (16%)	[37]
11	 **171** R=H	DAST benzene	 **172** (n.g.)	[38]
12	**173** R=Ms	TBAF MeCN	**172** (75%)	[38]
13	 **174** R=H	DAST benzene	 **175** (n.g.)	[38]
14	**176** R=Ms	TBAF MeCN	**175** (n.g.)	[38]
15	 **177**	DAST benzene	 **178** (85%)	[38]
16	 **179** R=H, R'=4-PhBz, β	DAST CH_2Cl_2	 **180** (43%); β	[39a]
17	**181** R=Tf R'=Piv, Tr, Bz etc.	TBAF MeCN	**180** (72-87%); α+β	[40]
18	 **182**	1) TBAF DMF 2) H_3O^+	 **183** (75%)	[41]
19	 **184** R=Piv, Bz, Tr, etc.	1) TBAF MeCN 2) H_3O^+	 **185** (62%)  **186** (trace)	[42]
20	 **187**	TBAF MeCN	 **188**	[u.r.]

Table 4 (Continued)

No.	Educt	Reagent	Product(s)	Ref.
21	 **189**	DAST CH_2Cl_2/Py	 **190** (41%)  **191** (21%)	[43]
22	 **192**	DAST CH_2Cl_2/Py	 **193** (36%)  **194** (33%)	[43]

2.3. Introduction of fluorine at C-4 of pyranosides (Table 3)

As cited above, the work of Morishima's group on the synthesis of 5-deoxy-5-fluorohexofuranoses was initiated by the findings they had made in experiments carried out to introduce fluorine at C-4 of 2-O-protected 3,6-dideoxy hexopyranosides [23]. These results (entries 1–6) are quite illustrative for the ambiguities connected with fluorination reactions. Triflates, during their treatment with TASF (entries 3–6), tended to substitution with inversion rather than retention of configuration and, as far as antiperiplanar orientation to a vicinal hydrogen was given, or reachable under reaction conditions, elimination. Concerning the use of DAST, in all cases educts containing a 4-OH group in the equatorial orientation (those with axial 4-OH groups gave mixtures of products that did not contain fluorine) underwent fluorination at C-4 with retention of configuration or ring-contraction and concomitant introduction of fluorine at C-5 with inversion of configuration. The latter outcome, also observed in part with the 6-deoxy-D-glucopyranoside derivative **96** (entry 7), was explained on the basis of a nucleophilic attack of the antiperiplanar oriented ring-oxygen to form some kind of 'alkyloxiranium ion', which could be opened, by fluoride, at C-4 or C-5.

The reaction of DAST with methyl 3,6-dideoxy-3-*C*-methyl-3-nitro-α-L-glucopyranoside [25] (**99**, entry 8) gave 5-deoxy-5-fluoro hexofuranoside (**100**, 46%) by the same type of THP-ring contraction. In addition, 4,5-anhydro compound **101** (40%), with inverted configuration at C-4 and the structure of an otherwise 'open-chain glycosyl fluoride', was afforded. In this case, opening of the alkyloxiranium ion, formed by the attack of the ring oxygen at C-4, had taken place (with inversion of configuration) at C-5 and C-1, respectively.

Another type of interesting side-reaction, found upon attempted fluorination with DAST, was observed with 1,2,3-tri-*O*-benzoyl-6-deoxy-α-L-galactopyranose (**102**, entry 9) by Lindhorst and Thiem [26]. These authors described isolation of 4-deoxy-5-fluoro compound **104** (15%) in addition to the expected 4-deoxy-4-fluoro-α-L-glucose derivative **103** (60%). The mechanism, assumed to involve elimination followed by fluoride addition at C-5 and protonation, might also be explained by a hydride-shift (out of the antiperiplanar orientation of the leaving group at C-4 and hydrogen at C-5); reaction of the 'glycal type' **107** with fluoride should give rise to a (acid-catalysed) Ferrier-rearrangement. From the treatment of the corresponding triflate **105** (entry 10) with TBAF in DMF, a fluorine-containing sugar was not obtained. Instead the 4-formate **106**, formed by reaction with DMF under inversion of configuration, and the labile product of elimination **107** was isolated.

Concerning educts which were 'not deoxygenated' in the neighbourhood of the reaction centre (C-3 and/or C-6) [9,27–32], possible side-reactions in attempted fluorinations are limited to eliminations only, as can be judged

Table 5
Results on attempted fluorination at position 2

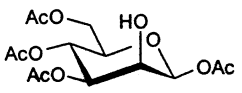
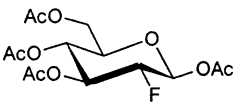
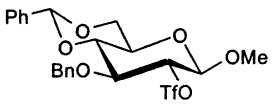
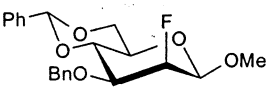
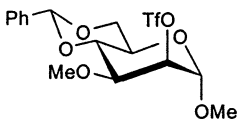
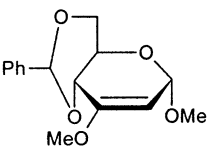
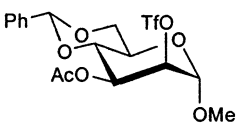
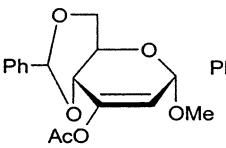
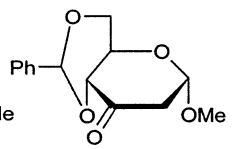
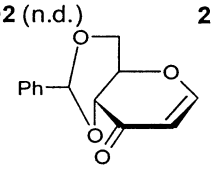
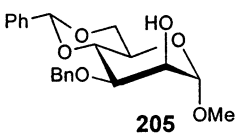
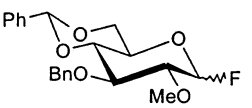
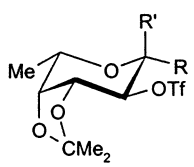
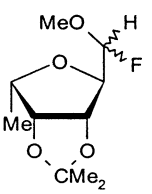
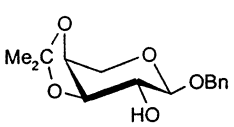
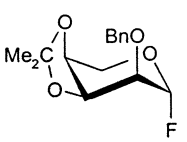
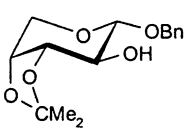
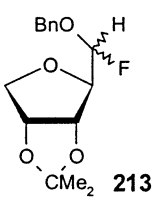
No.	Educt	Reagent	Product(s)	Ref.
1	 **195**	DAST diglyme	 **196** (77%)	[44]
2	 **197**	TBAF/MeCN	 **198** (77%)	[45]
3	 **199**	TBAF/MeCN	 **200** (82%)	[46]
4	 **201**	TBAF MeCN	 **202** (n.d.)  **203** (18%)  **204** (13%)	[46]
5	 **205**	DAST diglyme	 **206** (76%); α:β 4:15	[49]
6	 **207** R=H, R'=OMe	$Et_3N \cdot 3HF$ Et_3N/MeCN	 **208** (55%); (1R):(1S)=1:3	[50]
7	**209** R=OMe, R'=H		**208** [55%; (1R)]; (1S) traces only	[50]
8	 **210**	DAST CH_2Cl_2	 **211** (66%)	[51]
9	 **212**	DAST CH_2Cl_2	 **213** (60%)	[u.r.]

Table 5 (Continued)

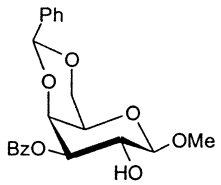
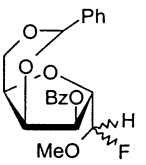
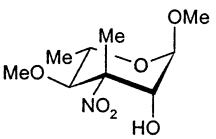
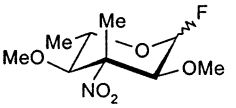
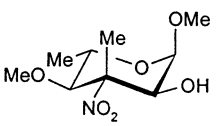
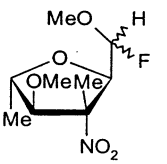
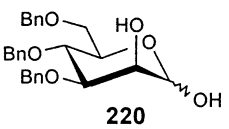
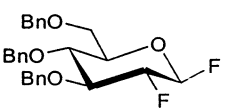
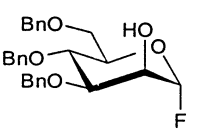
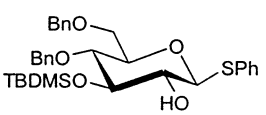
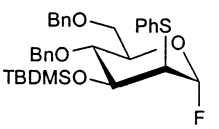
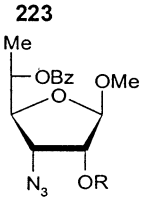
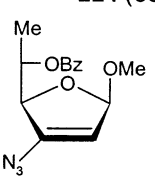
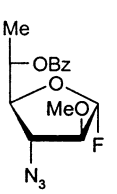
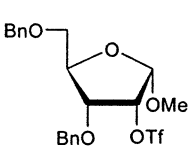
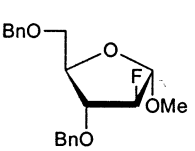
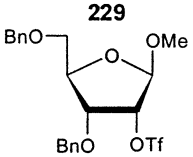
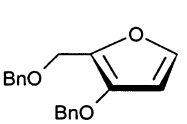
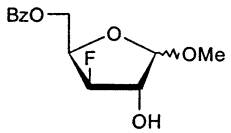
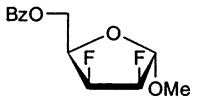
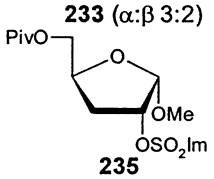
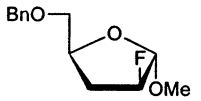
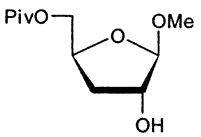
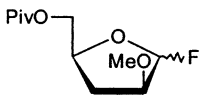
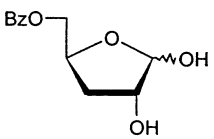
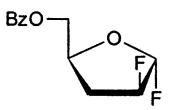
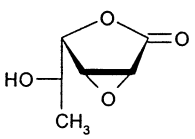
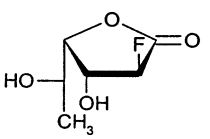
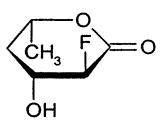
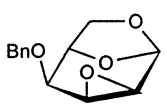
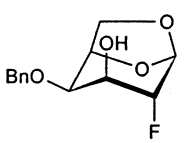
No.	Educt	Reagent	Product(s)	Ref.
10	 **214**	DAST CH_2Cl_2	 **215** (n.g.)	[u.r.]
11	 **216**	DAST CH_2Cl_2	 **217** (58%); α:β 1:1,3	[25]
12	 **218**	DAST CH_2Cl_2	 **219** (70%); (1R):(1S)=1:3	[25]
13	 **220**	DAST CH_2Cl_2	 **221** (36%)  **222** (18%); α only	[53]
14	 **223**	DAST CH_2Cl_2	 **224** (88%)	[51]
15	 **225** (R=Tf)	TBAF THF	 **226** (51%)	[55]
16	**227** (R=H)	DAST/toluene	 **228** (50%)	[55]
17	 **229**	TBAF/THF	 **230** (62%)	[56]
18	 **231**	TBAF/THF	 **232** (76%)	[56]

Table 5 (Continued)

No.	Educt	Reagent	Product(s)	Ref.
19	 **233** (α:β 3:2)	DAST CH_2Cl_2/Py	 **234** (45%); α only	[57]
20	 **235**	TBAF diisopropyl ether	 **236** (66%)	[42]
21	 **237**	DAST MeCN	 **238** (46%)	[u.r.]
22	 **239**	DAST/CH_2Cl_2	 **240** (50%)	[58]
23	 **241**	$Et_3N \cdot 3$ HF	 **242** (43%)  **243** (43%)	[59]
24	 **244**	KHF_2 glycol	 **245** (20%)	[35]

from the isolated products. The results depicted in entries 11–20 may be generalized[3] as follows:

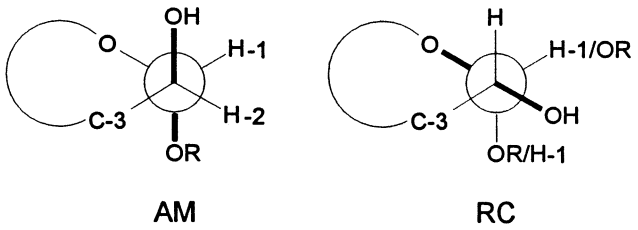
1. An equatorial 4-OH may be substituted by fluorine with inversion of configuration by the sulfonate/fluoride route as well as by DAST-reaction. However, both methods are sensitive to steric interference of the protecting group at C-6 [27];
2. An axial 4-OH is best substituted by fluorine with inversion of configuration by treatment with DAST. The corresponding sulfonates tend to give elimination exclusively. As can be seen from the reaction of the D-galactose derivative **116** with DAST (entry 15), elimination may occur on either side of the alcohol moiety [29].

Two exceptions to these generalisations were found:

A single case of retention of configuration has been reported, i.e., the reaction of a disaccharide with DAST [9], which contained an unprotected equatorial 4-OH group in its β-D-glucopyranosyl moiety. However, with a (similarily protected) α-D-glucosaminide [27], fluorination with inversion of configuration has been observed, albeit in low yield.

Reacting DAST with the 4′-*epi*-kanamycin A derivative **128** (entry 20) afforded, as the

[3] In those cases where disaccharides are involved, the NMR data given do not prove unambiguously (or are not fully consistent with) the structural assignments.



Scheme 3.

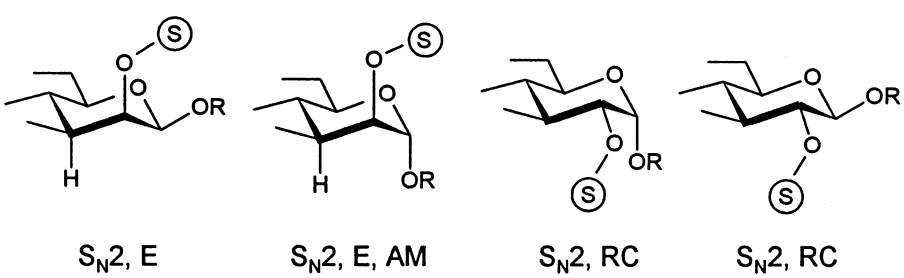
sole product, 4′-deoxy-3′-ulose **129** [32]. The reaction was proposed to have been initiated by a hydride shift from C-3′ to C-4′ together with fluorination, involving inversion of configuration, at C-5 of the deoxystreptamine moiety.

The introduction of fluorine equatorially at C-4′ of kanamycin A and B has been reported by the Tsuchiya–Umezawa group, although in low yield. For this purpose, the epoxide route was chosen and KHF_2 together with ethanediol (150 °C) employed [32]. Contrary to the prediction of the Fürst–Plattner rule, it was found that a diequatorial opening predominated over the diaxial option (possible reasons for this were discussed in detail). Consequently, from the reaction of the kanamycin A derivative **130** (showing a D-galacto configuration in the former 6-amino-6-deoxy-D-glucose (X′-) part, entry 21) they isolated products **131** (diequatorial, D-gluco, 37%) and **132** (diaxial, D-gulo, 7%). In addition, the 4′-*O*-(2-hydroxyethyl) derivative **133** arising from the participation of the solvent and also a minor fraction resulting from loss of the whole X′-part were formed. Reaction of the corresponding kanamycin B derivative **134** (entry 22), under the same conditions, gave the expected 4′-deoxy-4′-fluoro compound **135** with D-gluco configuration in 24% yield only. Interestingly, through the participation of the tosylamino group at C-2′, a 2′,3′-*N*-tosylepimino intermediate was formed. Its opening led to the generation of 3′-deoxy-3′-fluoro **136** and 3′-deoxy-3′,6′-*N*-tosylimino **137** derivatives, both with retained (doubly inverted) configuration at C-3′. Concerning the participation of protected NH_2-groups in substitution reactions, it should be noted that an (equatorial) carbamate group can attack, via the carbonyl moiety, an adjacent (also equatorial) sulfonate and may induce an S_Ni-reaction. This results in the loss of the alkoxy group and formation of a cyclic carbamate with inversion of configuration at the reaction centre (entry 23) [33]. Furthermore, the extent of product formation was found to depend dramatically on the nature of the solvent employed (entry 24).

Smooth introduction of fluorine with inversion of configuration at C-5[4] of the β-D-fructopyranose derivative **141** (entry 25) was achieved by the reaction of this compound with DAST in benzene–pyridine [34].

Strikingly different structures were reported [35] to be afforded from the reaction of DAST with 1,6-anhydro-2,3-dideoxy-β-D-*threo*-hex-2-enopyranose (**143**) by merely changing the temperature or solvent. Whereas treatment of **143** with DAST in dichloromethane at room temperature (entry 26) led to the formation of the respective fluoride with inversion of configuration (**144**), cooling this system to −80 °C (entry 27) resulted in ring-contraction (by attack of the THP-oxygen at C-2) with a concurrent allylic rearrangement and introduction of fluoride at C-1 to give 2,5-anhydro-3,4-dideoxy-β-D-*erythro*-hex-3-enoseptanosyl fluorides **145** (36%) and **146** (16%). When **143** was treated with DAST in DMF at −50 °C (entry 28), another type of rearrangement took place to yield (after hydrolysis of the formate) 1,6-anhydro-3,4-dideoxy-β-D-*erythro*-

[4] Comparable to C-4 in aldopyranoses.



Scheme 4.

Table 6
Results on electrophilic addition to glycals

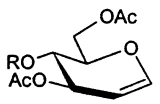
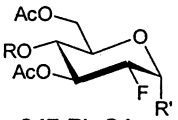
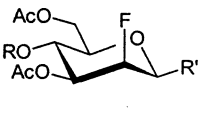
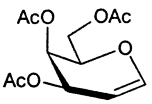
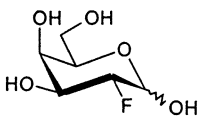
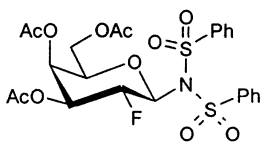
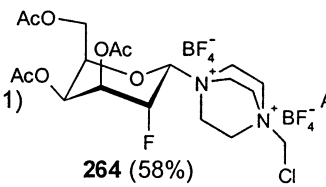
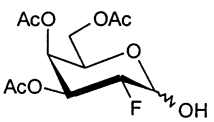
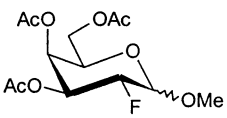
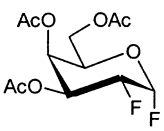
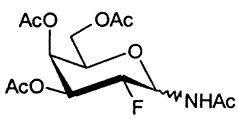
No.	Educt	Conditions	Product(s)	Ref.
1	 **246** R=α-D-Glc(Ac)	$AcOF/CFCl_3$ 0 °C	 **247** R'=OAc  **248** R'=OAc **247**:**248** = 2:1, yield n.g.	[60]
2	**246**	$AcOF/CFCl_3$ -78 °C	**247**:**248** = 6:1, yield n.g.	[60]
3	**246**	$F_2/CFCl_3$	**249** R'=F (20%) **250** R'=F **249**:**250** = 1.3:1	[60]
4	**251** R= β-D-Glc(Ac)	AcOF $CFCl_3$/MeCN (10:1)	**252** R'=OAc (19%) **253** R'=OAc **252**:**253** = 1.5:1	[60]
5	**251**	1) **261** $MeNO_2/H_2O$ (5:1) RT/12 h 2) 100 °C/0.5 h	**254** R'=OH (60%) **255** R'=OH (15%)	[65b]
6	 **256**	1) $XeF_2/CFCl_3$ 2) H_3O^+	 **257** (63%)	[61a]
7	**256**	**260**/MeCN 80 °C/24 h	 **263** (30%)	[65a]
8	**256**	**261** $MeNO_2/H_2O$ (5:1) RT/12 h	 **264** (58%)  **265** (30%)	[65a]
9	**256**	**261** $MeNO_2$/MeOH (5:1) RT/12 h	 **264** (49%) **266** (45%);α<<β  **267** (4%)	[65a]
10	**256**	**261**/$MeNO_2$ RT/12 h	**264** (73%) **267** (23%)	[65a]
11	**256**	**261**/MeCN RT/12 h	 **264** (54%) **267** (14%) **268** (27%);α<<β	[65a]

Table 6 (Continued)

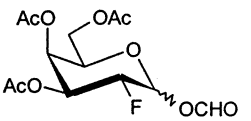
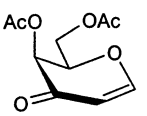
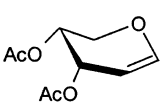
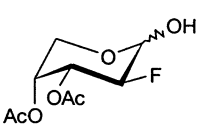
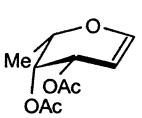
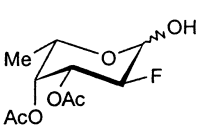
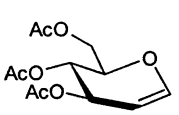
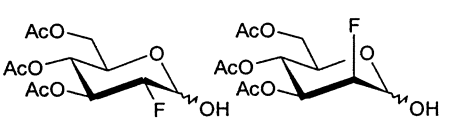
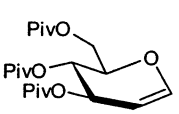
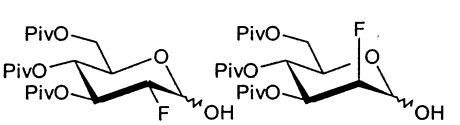
No.	Educt	Conditions	Product(s)	Ref.
12	**256**	**261** MeCN/H_2O (5:1) RT/12 h	**264** (45%) **265** (23%) **268** (30%)	[65a]
13	**256**	**261** acetone/H_2O (5:1) RT/12 h	**264** (49%) **265** (49%)	[65a]
14	**256**	**261** DMF/H_2O (5:1) RT/12 h	 **264** (46%) **265** (31%) **269** (22%);α<<β	[65a]
15	**256**	**261** $MeNO_2$/H_2O (5:1) 1) RT/12 h 2) 100°C/0.5 h	**265** (79%)	[65a]
16	**256**	**261** $MeNO_2$/MeOH (5:1) 1) RT/12 h 2) 80 °C/0.5 h	**266** (76%)	[65a]
17	**256**	**261** $MeNO_2$ 1) RT/12 h 2) 100 °C/0.5 h	**267** (52%)	[65a]
18	**256**	**261**/MeCN reflux	 **275** (14%) **267** and **268** in lower yield	[65a]
19	 **276**	**261** acetone/H_2O (5:1) 1) RT/12 h 2) 70 °C/0.5 h	 **277** (isolated as peracetates, 68%)	[65a]
20	 **278**	**261** $MeNO_2$/H_2O (5:1) 1) RT/12 h 2) 100 °C/0.5 h	 **279** (87%)	[65c]
21	 **280**	**261** $MeNO_2$/H_2O (5:1) 1) RT/12 h 2) 100 °C/0.5 h	 **281** **282** **281**:**282** = 1.3:1 (61%)	[65b]
22	 **283**	**261** $MeNO_2$/H_2O (5:1) 1) RT/12 h 2) 100 °C/0.5 h	 **284** **285** **284**:**285** = 9:1 (85%)	[65b]

Table 6 (Continued)

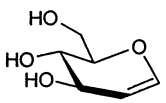
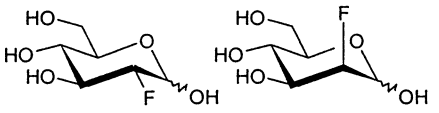
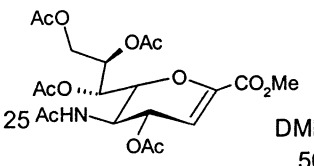
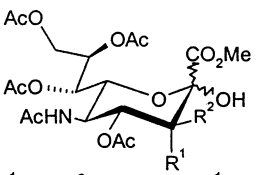
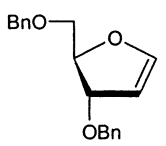
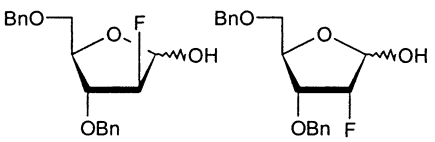
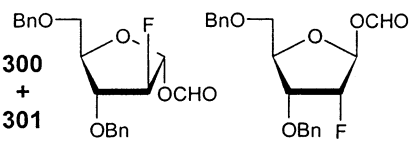
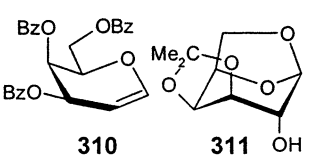
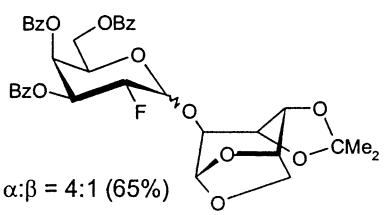
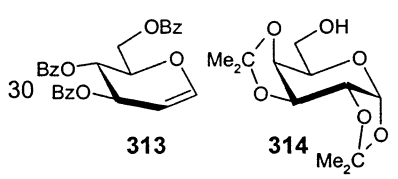
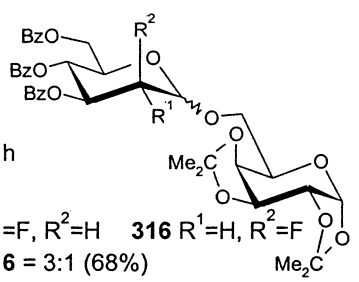
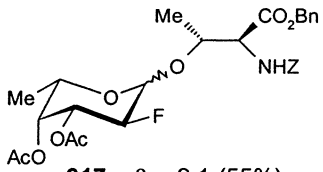
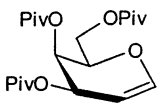
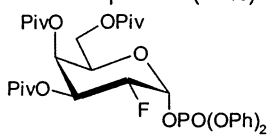
No.	Educt	Conditions	Product(s)	Ref.
23	 **288**	**261** H_2O RT/1 h	 **289** **290** **289**:**290** = 1:2 (85%) (isolated as peracetates)	[64a]
24	**288**	**261** $MeNO_2/H_2O$ (5:1) 1) RT/15 h 2) 85-90 °C/0.5 h	**289**:**290** = 2:1 (43%) (isolated as peracetates)	[65b]
25	 **296**	**261** DMF/H_2O (3:1) 50 °C/12 h	 **297** R^1=F, R^2=H **298** R^1=H, R^2=F **297**:**298** = 3:1 (80%)	[64a]
26	 **299**	**261** DMF/H_2O RT/12 h	 **300** **301** **300**:**301** = 22:3 (73%)	[64a]
27	**299**	**261** DMF/H_2O RT/12 h	 **302** **303** **300**α:**301**β:**302**:**303** = 9:3:2:2 (50%)	[u.r.]
28	**299**	**261** acetone/H_2O (3:1) 1) RT/1.5 h 2) 40 °C/0.5 h	**300**:**301** = 2:1 (37%)	[u.r.]
29	 **310** **311**	**262** $MeNO_2$ 1) RT/6 h 2) **311**, 100 °C/1 h	 **312** α:β = 4:1 (65%)	[64b]
30	 **313** **314**	**262** $MeNO_2$ 1) RT/6 h 2) **314**, 100 °C/1 h	 **315** R^1=F, R^2=H **316** R^1=H, R^2=F **315**:**316** = 3:1 (68%)	[64b]

Table 6 (Continued)

No.	Educt	Conditions	Product(s)	Ref.
31	**278**	**262** $MeNO_2$ 1) RT/6 h 2) threonine, 100°C/1 h	 **317** α:β = 2:1 (55%)	[64b]
32	 **318**	**262** $MeNO_2$ 1) RT/6 h 2) diphenyl phosphate 100 °C/1 h	 **319** α:β = 7:3 (70%)	[64b]

hex-3-enopyranose (**147**). The mechanism involved was found [35] to be a hetero-Cope rearrangement involving the (isolable) 4-formate that was formed from the reaction of **143** and DAST-activated DMF.

2.4. Introduction of fluorine at C-3 (Table 4)

With the exception of D-glucosamine derivatives, preparation of pyranose derivatives unprotected at O-3 is laborious. Consequently, new contributions to this topic are rare and the results — as exemplified by those reported [9] from reactions with derivatives of methyl β-lactosides **148** and **149** (entries 1 and 2) — are rather discouraging. However, transformations carried out with the D-glucosamine series shed much light on the special types of neighbouring-group participation possible and this compensates for other deficiencies.

In their systematic efforts to develop kanamycin antibiotics effective against resistant bacteria, Tsuchiya's team [16,36] also prepared the corresponding 3′-deoxy-3′-fluoro derivatives of kanamycin A and B. Initially, they thoroughly studied [16] the regioselectivity of the ring opening reaction of differently protected derivatives of methyl 2,3-anhydro-α-D-allopyranoside with KHF_2 in various solvents and carried out theoretical studies on the influence of the protecting groups. As was found with 3,4-anhydro compounds (Section 1.3), products, including those from participation of the solvent ethanediol, resulting from diequatorial opening, predominated. A typical example of this observation is demonstrated by the reaction of the 4,6-O-unprotected derivative **150** (entry 3). The corresponding reaction with kanamycin A derivative **154** (entry 4) led to the desired 3′-deoxy-3′-fluoro compound **155** (31%) and the corresponding 2′-deoxy-2′-fluoro product with the D-altro configuration **156** (16%). For the synthesis of 3′-deoxy-3′-fluoro kanamaycin B, the strategy had to be changed as a 2,3-*N*-tosylepimino compound was required as the precursor [36]. Experiments with a 4,6-O-unprotected monosaccharide model **157** (entry 5) indicated that not only fluorination occurred at C-3 (to give **158**), but also 6-OH attacked intramolecularily to form the 3,6-anhydro derivative **159**. With the 4,6-*O*-isopropylidene protected derivative **160** (entries 6 and 7) an interesting time-dependency of the ratio of products with diaxial to those with diequatorial orientation of substituents at C-2 and C-3, respectively, was observed. The kinetically favoured, D-altro product **161** was converted into the thermodynamically more stable D-gluco isomer **162**, evidently via structure **160**. Finally, reaction of **163** (entry 8) gave the desired 3′-deoxy-3′-fluoro kanamycin B derivative **164** as the sole product (49%).

The synthesis of 2-amino-2,3-dideoxy-3-fluoro-D-glucose was also the subject of a study by Picq's group [37], although these workers started from derivatives of methyl 3-deoxy-3-diallylamino-2-*O*-methylsulfonyl-α-D-altropyranosides **165** and **168** [37a] (entries 9 and 10). Upon treatment with complexes of Et_3N with HF, the intermediate *N*,*N*-diallylaziridinium ion with a D-allo configuration was formed, which was opened preferentially

by fluoride at C-3 to give **166** and **169**, respectively. Consequently, this caused migration of the amino substituent and inversion of configuration at both centres. Subsequently, the 4,6-di-*O*-mesyl derivative **169** was treated with tetraethylammonium hydrogendifluoride ($Et_4N{\cdot}HF_2$) and fluorinated further at C-6 to give a 3,6-dideoxy-3,6-difluoro-D-glucosaminide. This product was also directly available from **168** employing $Et_3N{\cdot}3$ HF in MeCN–Et_3N [37b]. [Addendum in proof: obviously in accordance with previous findings [37c], the ^1H NMR data ($CDCl_3$) given for **165** and 2,6-dideoxy-3-diallylamino-2,6-difluoro-4-*O*-methylsulfonyl-α-D-altropyranoside show $J_{1,2}$ of 4.6 and 3.5 Hz together with $J_{4,5}$ of 1.5 and 4 Hz, respectively. Tsuchiya and co-workers [36] reported *J* values of 2 and 8.5 Hz, respectively, for methyl 4,6-di-*O*-acetyl-2,3-dideoxy-2-fluoro-3-tosylamino-α-D-altro-pyranoside (pyridine-d_5)].

Additional valuable information about the side reactions taking place when attempting to fluorinate in the neighbourhood of a protected NH_2 functional group was disclosed by Korytnyk's group [38]. Reactions of the 4,6-*O*-benzylidene protected D-allosamine **171** or its corresponding 3-*O*-mesyl derivative **173** (entries 11 and 12) with DAST and TBAF in acetonitrile only led to the elimination product **172**. However, the 4,6-di-*O*-benzyl protected analogue of **173** gave, with inversion of configuration, the 3-deoxy-3-fluoro sugar, albeit in low yield. Unsatisfactory results were also obtained with the D-altrosaminides **174** and **176** (entries 13 and 14). In these cases, the epimino compound **175**, with D-manno configuration, was the sole product formed. When the NH_2 functional group was protected with a phthaloyl moiety, **175** was isolated in 84% yield by the mesylate/TBAF route. The desired 2-acetamido-2,3-dideoxy-3-fluoro-D-mannose was reported to have been obtained[5] by the reaction of DAST with 2-azido-2-deoxy-D-altropyranoside **177** (entry 15) followed by reduction of the azido moiety in **178** and N-acetylation.

Derivatives of 2,3-dideoxy-3-fluoro-D-*erythro*-pentofuranose, e.g., **180**, are of special interest in nucleoside chemistry. For their synthesis, two strategies, both setting out from 2-deoxy-D-*erythro*-pentose-(2-deoxy-D-ribose), have been elaborated. They make use of the principle of double-inversion; in the first step either by oxidation–reduction [39a] or S_N2-reaction [40]. In the case of the α anomer, the approach cited first did not lead to inversion of configuration[6] as apparent from comparison of published NMR data for educts [39b] and products [39a]. Introduction of fluorine into the β anomer of **179** [39a] (entry 16) was achieved with DAST, while anomeric mixtures as well as pure α anomers of **181** [40] (entry 17) were fluorinated by the sulfonate/fluoride-route. In the latter case, minor proportions of unsaturated products were also isolated from the reaction mixture.

Another fascinating facet of cyclic sulfate chemistry in the carbohydrate field has been disclosed within the past years and relates to the regio- and stereoselective introduction of fluorine (and any other nucleophile) at C-3 of furanoid rings. Opening under inversion of configuration at C-4[7] of compound **182**, the 3,4-cyclic sulfate of methyl β-L-ribuloside [41] (entry 18), is easily explained by taking into account steric requirements. However, the clear-cut C-3-regioselectivity observed in the reaction of 2,3-cyclic sulfates (**184**) of alkyl D-ribofuranosides [42] (entry 19) was surprising. The same selectivity was observed with cyclic sulfates of all hexo- and pentofuranosides having the 2,3-cis configuration[8].

An unexpected 'refusal' of fluorination was observed in our laboratory (unpublished results) when the cyclic sulfate **187** of 1,2:5,6-di-*O*-isopropylidene-D-mannitol was treated with TBAF in MeCN (entry 20) to give the 4,5-unsaturated 3-ulose **188** as the sole product.

Mikhailopulo and Sivets [43] explored the reaction of DAST with methyl β-D-arabino-**189** as well as β-D-xylofuranoside **192**, protected at O-5 only (entries 21 and 22).

[5] The NMR data given do not provide conclusive evidence for the assigned structure.

[6] Alkyl 2-deoxy-α-D-*threo*-pentofuranosides characteristically show [40], for H-1, a triplet with 4.3 Hz and, for C-4, a shift-value of 79–80 ppm, whereas D-*erythro* isomers exhibit, for H-1, a doublet with 4.3 Hz and, for C-4, a δ value of 84–85 ppm.

[7] Corresponds to C-3 in aldofuranoses.

[8] S. Schuppler, *Thesis for Diploma*, Technical University Graz (1994).

Whereas the arabino compound **189** gave rise to two fluorinated products with inversion of configuration at C-2 (to form **190**) or C-3 (to give **191**), the xylo counterpart **192** resulted in the 2,3-anhydro compound **193** and the 'fluorohydrine' **194** where fluorination, with inversion of configuration, had taken place at C-3. The latter results were thought to imply that DAST-activation of the hydroxyl group at C-3 was dominant and the observed products were being formed from either attack at O-2 (leading to **193**) or the external fluoride (giving rise to **194**).

2.5. Introduction of fluorine at C-2 (Table 5)

With regard to nucleophilic displacement reactions at C-2 of furanoid and pyranoid derivatives of aldoses and aldosides, recent results in this field with respect to reaction pathways are seldom. However, the knowledge accumulated to date concerning product as well as side-product formation allow a more general discussion[9] of the types of reactions observed including stereochemical prerequisites and consequences. A generalisation concerning their complex interdependencies, governed by the educt configuration, nature of translocated protecting groups, mode of activation, source of nucleophilic fluoride, pH value, solvent, temperature and so on, is not the topic of this article. Furthermore, possible participation of neighbouring-groups at C-3, outlined in Scheme 2, has also been omitted here, as it is treated in detail in Ref. [1].

1. Straightforward S_N2-displacement by fluoride employing DAST or the triflate/fluoride route is possible with all configurations[10]. This situation is exemplified by the efficient synthesis of 2-deoxy-2-fluoro-D-glucose derivative **196** from 1,3,4,6-tetra-*O*-acetyl-β-D-mannopyranose [44] (**195** entry 1) as well as the successful transformation of methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-triflyl-β-D-glucopyranoside (**197**) into the corresponding 2-deoxy-2-fluoro-β-D-mannoside **198** (entry 2) [45]. In the case of furanoses, this reaction is largely restricted to 1,2-cis configured educts.
2. Elimination (E) arises from an antiperiplanar orientation of a leaving group at C-2 and hydrogen at C-3 and is especially favoured in the sulfonate/fluoride route. For example, triflates **199** and **201** [46] (entry 3 and 4) are transformed into enol derivatives **200** and **202**, respectively. Products such as enol acetate **202** (entry 4) may be cleaved, by removal of the acyl group under the reaction conditions, to give 2-deoxy-3-uloses of type **203** (the latter was isolated only in the case of treatment of **201** with CsF instead of TBAF), which again are prone to further elimination. To date, compounds such as the 1,2-unsaturated 3-ulose **204** have been isolated[11] [46–48].
3. The third reaction pathway is induced by the intramolecular attack of one of the two O-atoms directly bound to the anomeric centre (aglycon or ring-oxygen). This leads to an alkyloxiranium ion, which is immediately opened, by fluoride, at C-1 under migration of its 'attacking' substituent to C-2 and inversion of configuration at both centres involved. Depending on the nature of the participating substituent, either a product of aglycon migration (AM) or ring-contraction (RC) arises. Illustrative examples for both types of reactions in the pyranose series can be found in reports from Kovác and co-workers [49] (entry 5) and Baer and co-workers [50] (entries 6 and 7). As can be seen from a comparison of the steric relationship of the groups directly involved in the reaction, in educt structure **205** on the one hand and **207** or **209** on the other, an antiperiplanar orientation of the leaving group at C-2 and the respective migrating group at C-1 is a com-

[9] In many cases of failed fluorination reactions at C-2 of pyranosides, the role of structure, configuration, as well as kinetic parameters has been subject to discussion. To illustrate the set of possible reactions and to identify discriminative parameters, an arbitrary selection has been made from the large number of examples known until 1990. These are depicted in Table 5.

[10] For a general discussion of steric and electrostatic interactions in direct displacement reactions, at C-2 of pyranosides, see: [Miljkovic and co-workers, *J. Org. Chem.*, 39 (1974) 3223–3226].

[11] Products formed by elimination of hydrogen at C-4 and ring oxygen at C-5 liberate the aldehyde functionality at C-1, thus giving cause to decomposition (compare sum of yields of isolated products in, e.g., entry 4).

mon feature (as illustrated by Newman projections in Scheme 3). Consequently, the structural prerequisite for the 1,2-alkoxy shift seems to be a diaxial orientation of the aglycon and the OH-group as given in **205**. The reaction is best performed by treatment with DAST (entry 5), since the corresponding triflates are rather prone to elimination (entries 3 and 4). For the ring-contracting mode, as in **207** and **209**, only an equatorial orientation of the triflate group (or OH-group to be activated by DAST), but no specific anomeric configuration, appears to be essential[12].

From these options [S_N2, E, AM, and RC], distinct combinations of these possible reaction pathways for any aldopyranoside containing an equatorially oriented substituent at C-3 are deduced, with the uncertainties of the conformational situation under the reaction conditions and summarised in Scheme 4 (see also footnote 12).

When proving the validity of these postulations with published results, two contradictory examples could be found in the literature involving alkoxy group migrations [51]. Namely, the reaction of DAST with benzyl 3,4-*O*-isopropylidene-α-L-arabinopyranoside (**210**, entry 8) and a disaccharidic β-D-galactopyranoside derivative. Both educts, in their preponderating conformation, possess an equatorial OH-group, and should therefore be prone to ring-contraction (RC) and not to an 1,2-alkoxy shift (AM). As NMR data for the products were not published, we chose to prove this aglycon migration experimentally. From the reaction of α-D-arabinopyranoside **212** (the enantiomer of **210**, entry 9) with 3 equivalents of DAST in dichloromethane at room temperature, we isolated the ring-contracted product **213** in 60% yield by chromatography. ^{19}F NMR spectra, taken from the crude reaction mixture, did not show additional signals[13] corresponding to ribopyranosyl fluorides or 2-deoxy-2-fluoro-riboside which would have been formed by AM-reaction and S_N2-displacement, respectively. Consequently, we were not able to reproduce (or even to obtain analytical evidence for) the formation of published structure **211**.

With this result in hand, and reconsidering the collection of structures having been under study so far, our attention was called to the possible role of acetal protecting groups. This kind of protection, as present in 3,4-*O*-isopropylidene or 4,6-*O*-benzylidene educts shown in Table 5, is obviously not a prerequisite for any specific type of reaction being discussed here, since comparable results have been obtained with mono- as well as bicyclic educts [50,51]. However, from reactions carried out to date with 3,4-*O*-isopropylidene protected educts of arabino or galacto configurations, ring contractions were only reported ([50], our own results in entry 9), whereas no such reaction could be found with 4,6-*O*-benzylidene protected hexopyranosides (see also footnote 12). Since all of the latter educts were exclusively of the *trans*-decalin type (corresponding to an erythro configuration at C-4 and 5, as in glucose), we carried out the DAST-reaction with a single representative of the *cis*-decalin type, namely methyl 3-*O*-benzoyl-4,6-*O*-benzylidene-β-D-galactopyranoside (**214**, entry 10). Exclusive formation of ring contracted products **215** supported the principle that 4,6-*O*-benzylidene hexopyranosides of the *trans*-decalin type containing an equatorial OH-group at C-2, obviously for reasons of ring-strain, are not subject to ring-contraction reactions (but may give slow aglycon migration instead[12]).

Nevertheless, a thorough comparison of individual reaction patterns cannot be made, because most of the related transformations described in the literature were obtained under differing conditions and the yield of the respective main product is only reported. To illustrate this point, reference is made to the contribution of Szarek and co-workers [52] who, by treatment of a series of 2-triflates with TASF instead of TBAF, widened the scope and limitations of the S_N2-reaction pathway.

A single, but very interesting study on the fluorination of hexopyranosides at position 2

[12] A special exception to these generalisations was very recently found in the reaction of methyl 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside with DAST in which no ring-contraction, but (slow) aglycon migration was observed (unpublished results).

[13] Representative ^{19}F NMR data are, for products of RC-reactions, δ 134–143 ppm ($J_{F,H-1}$ 63–68 Hz), for those from AM-reactions, 135–150 ppm ($J_{F,H-1}$ 48–54 Hz) and, for products of direct S_N2-reaction, 190–220 ppm ($J_{F,H-1}$ 47–54 Hz).

(and 4) was published recently [25]. It not only introduces a new type of rearrangement with respect to attempted fluorination at C-4 (4,5-anhydro ring formation, see entry 8 in Table 3), but also perfectly fits into the generalizations made above concerning possible side-reactions. The results obtained with the epimeric pair of 2-O-unprotected 3,6-dideoxy-3-*C*-methyl-3-nitro-4-*O*-methyl-L-hexopyranosides **216** and **218**, clearly manifest the structural diacritics inducing 1,2-alkoxy migration (entry 11) and ring-contraction (entry 12), respectively. The group of ring-contraction reactions of the mode described in this section can also be accompanied by a simultaneous allylic rearrangement as is the case in the reaction of 1,6-anhydro-2,3-dideoxy-β-D-*threo*-hex-2-enopyranose (**143**) with DAST at low temperature [35] (entry 27 in Table 3).

The nature of the C-1 substituent is also an important parameter in these reactions and restricts the given generalisations, which are exclusively deduced from results with alkyl pyranosides. Whereas glycopyranosyl fluorides do not show any tendency to undergo either AM- or RC-reactions (for example, as evident from the isolation of α-D-mannopyranosyl fluoride **222** [53], entry 13), 2-O-unprotected thioglycosides **223** (as shown in entry 14) and azides are prone to 1,2-migration [51] without any specific steric requirements. This result should be compared with that obtained from thioglycosides in iodonium ion catalyzed glycosylation reactions [54].

In the furanoid series, introduction of fluorine at C-2 is also hampered by side-reactions. Hasegawa and co-workers [55] in their studies with methyl 3-azido-5-*O*-benzoyl-3,6-dideoxy-α-L-talofuranosides **225** and **227**, possessing 1,2-trans orientation, observed elimination (entry 15) when taking the triflate/fluoride route and, for the first time, 1,2-alkoxy-shift when using the DAST-reaction. The dependence of the reaction outcome on the anomeric configuration with methyl 3,5-di-*O*-benzyl-2-*O*-triflyl-D-ribofuranosides **229** and **231** had been observed previously by Fox and co-workers [56]. The α anomer **229** (entry 17), containing a 1,2-cis relation, was subject to S_N2-reaction, whereas the β anomer **231** gave (double) elimination to form the furan derivative **232** (entry 18). The same selectivity was also observed [57] with methyl 5-*O*-benzoyl-3-deoxy-3-fluoro-D-xylofuranosides **233** (entry 19) and methyl 3-deoxy-2-*O*-imidazolylsulfonyl-α-D-*erythro*-pentofuranoside [42] (**235**, entry 20). The O-2 unprotected β anomer[14] **237** (entry 21), upon treatment with DAST, gave mainly products arising from 1,2-alkoxy migration. Reacting an anomeric mixture of 1,2-O-unprotected counterpart **239** with DAST furnished 2,3-dideoxy-2-fluoro-α-D-*threo*-pentofuranosyl fluoride (**240**) in 50% yield [58]. Exactly the same result, fluorination at C-2 taking place out from a 1,2-cis orientation (within the rapidly formed glycosyl fluorides) only, was described earlier [53] with the 1,2-O-unprotected D-mannopyranose derivative **220** (entry 13). Investigations conducted by Mikhailopulo and Sivets [43] on the DAST-reaction with 2,3-O-unprotected D-arabino- and D-xylofuranosides (**189** and **192**) were presented in the preceding section (Table 4, entries 21 and 22). Ring-contraction with furanosides has not yet been observed.

Whereas introduction of fluorine at position 2 of aldoses is hampered by an even broader range of restrictions than observed for other positions, a relatively easy access to 2-deoxy-2-fluoro aldonolactones was described by Lundt and co-workers [18,59]. These authors introduced 2,3-epoxylactones as valuable educts for regio- and stereoselective fluorination at C-2. From their studies with various epoxides as well as fluorinating agents, the reaction of 2,3-anhydro-6-deoxy-L-mannono-1,4-lactone (**241**) with $Et_3N{\cdot}3$ HF produced a mixture of 2-deoxy-2-fluoro-L-gulono-1,4- and -1,5-lactones (**242** and **243**) as given in the Table (entry 23). To obtain the corresponding fluorinated aldose, reduction (e.g., by using diisoamylborane) has to be carried out (yield approximately 65%). Another example of regioselective (but low yielding) epoxide opening, at C-2, by fluoride was found [35] with 1,6:2,3-dianhydro-β-D-talopyranose **244** (entry 24).

[14] Easy access to 3-deoxy-D-*erythro*-pentofuranosides was allowed by reacting 2,3-cyclic sulfates of alkyl D-ribofuranosides of type **184** with sodium borohydride [(Table 4, entry 19) [42] and footnote 8].

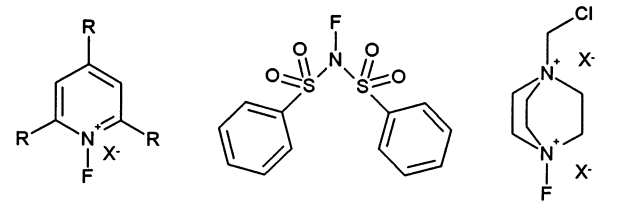
3. Introduction of fluorine via electrophilic addition reactions to glycals using fluorine, xenon difluoride or electrophilic *O*–F- and *N*–F-reagents (Table 6)

For the synthesis of 2-deoxy-2-fluoro aldoses, addition reactions of electrophilic fluorination reagents to the double-bond of glycals constitute a valuable synthetic alternative to the S_N-strategy [1,5e,f]. However, the addition step is generally hampered by the uncertainties of stereo- (but not regio-) selectivity and problems with safety are also encountered with the handling of poisonous gases such as fluorine or acetyl hypofluorite.

In the last few years, acetyl hypofluorite as well as fluorine have been applied [60] to acetylated glycals derived from cellobiose, maltose and maltotriose. Stereoselectivity was found to be worse than that reported from monosaccharidic glucal derivatives. Accordingly, in all examples, mixtures (from 1:1 to 2:1) of 2-deoxy-2-fluoro derivatives with the α-D-gluco- and β-D-manno configuration, as generated by regiospecific syn-addition to the double-bond at 0 °C, were formed. An interesting increase of selectivity (from 2:1 to 6:1) was observed upon cooling the reaction of maltal **246** with acetyl hypofluorite from 0 to − 78 °C (entries 1 and 2). Further transformations of **246** and cellobial **251** are shown in entries 3 and 4.

Xenon difluoride, solid and easy to handle, was used in the synthesis of 2-deoxy-2-fluoro-D-galactose [61a] (**257**, entry 6). An addition reaction, in the absence of an acidic catalyst, to tri-*O*-acetyl-D-galactal **256** showed stereospecifity in agreement with results obtained from other electrophilic agents. A trace amount of 2-deoxy-D-*lyxo*-hexopyranose, being formed through hydration of the double-bond under the reaction conditions, was also isolated.

In 1990, Umemoto and co-workers [62] studied the reactions of enol alkyl ethers (including dihydropyran and -furan) with *N*-fluoro-pyridinium salts of type **258** and obtained a mixture of cis and trans configurated addition products having regioselectively bound fluorine to C-2 and the pyridinio-moiety of the reagent to C-1.



258 R=H, X=BF_4
259 R=Me, X=OTf

260

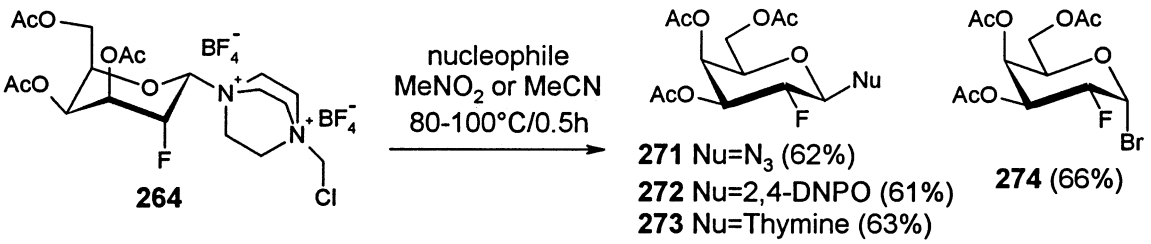
261 X=BF_4
262 X=OTf

The performance of new electrophilic fluorinating agents of the *N*–F-class [63], showing high power in the fluorination of aromatics, carbanions and olefins, just to mention a few, indicated that these compounds could also be of use as glycal fluorinating agents. In 1997, reaction of commercially available compounds **258**–**261** with a number of different glycals was examined [64a,65a]. Treating the D-galactal derivative **256** with *N*-fluoro-pyridinium salts **258** and **259** did not give a significant reaction, whereas *N*-fluorobenzenesulfonimide **260** (entry 7) led to the formation of the 2-deoxy-2-fluoro-β-D-galactopyranosylamine derivative **263** in low yield [65a]. Interestingly, 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate) [66] (F–TEDA–BF_4, Selectfluor™, **261**) rapidly reacted with glycals at room temperature to produce 2-deoxy-2-fluoro-sugar derivatives. However, comparison of the reports from Wong's group [64a], with those from our laboratory [65a], reveal some discrepancies, especially results concerning the nature of the substituent at C-1 in products formed under comparable conditions[15]. Due to the fact that a considerable number of experiments described in [64a] could not be reproduced in our hands, this section will concentrate on our own findings.

Reaction of **261** with 3,4,6-tri-*O*-acetyl-D-galactal (**256**) led to products with the D-galacto configuration exclusively[16]. The major product was found to be the *N*-(2-deoxy-2-fluoro-α-D-galactopyranosyl)ammonium com-

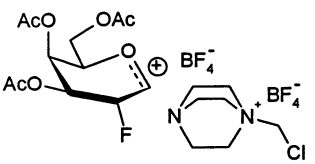
[15] In Wong's paper [64a], the formation of (polar and stable) products from the direct addition of the reagent to the double bond of pyranoid glycals, as well as the role played by nucleophilic solvents such as DMF or acetonitrile, even in the presence of water, was not described.

[16] A report claiming the formation of a 25% talo-compound proportion [64a] in DMF–water was later recalled without giving details [64b].



Scheme 5.

pound **264**, which was obviously formed from the syn-addition of the reagent across the double bond of the glycal. Depending on the solvent system used, **264** was accompanied by a number of 2-deoxy-2-fluoro-D-galactopyranose derivatives, namely **265**–**269**[17], which only differ in the substituent at C-1 (entries 8–14; the percentage given was determined from the crude reaction mixture by ^{19}F NMR; the balance to 100 represents the sum of unidentified fluorinated products). Their common origin was thought [65a] to arise from the participation of any other nucleophilic species in the reaction mixture, such as solvents (water, methanol, acetonitrile, or DMF) or fluoride ion stemming from tetrafluoroborate[18] or even acetyl groups as could be seen from the product distribution[17]. Except D-galactosyl fluoride **267** (α anomer only) and the 1-O-unprotected derivative **265** (α/β), anomeric pairs were detected with the β anomer clearly dominating. Monitoring of the ratios of fluorine-containing products during the reaction by ^{19}F NMR disclosed that, at room temperature, fluoro sugars **265**–**269** and the product of syn-addition (**264**) were obviously generated in parallel reactions and that, under these conditions, **264** is not a precursor for structures **265**–**269**. Consequently, the possible reaction mechanism for the initial stage of the reaction might consist of the formation of the highly reactive '2-fluoro oxocarbenium ion' **270**, which immediately reacts with either the tertiary amine moiety of the reagent to give the syn-addition product **264** or any other nucleophile available to give structures **265**–**269**. The existence of this highly reactive, unselective species of type **270** is further supported by the product distributions shown in entries 8–14. This observation by no means relates to the nucleophilicities of the partners available.



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However, after total consumption of the starting material, reaction mixtures which contained water or methanol were heated to reflux. This led to formation of compounds **265** or **266** from addition product **264** by substitution of the ammonio group at C-1 (entries 15 and 16; compare entries 8 and 9, respectively). As expected, when mixtures containing water and acetonitrile or DMF (i.e., entries 12 and 14) were heated, in accordance to the nucleophilic power of partners present, displacement of the ammonio substituent in **264** with water only was observed. With neat aprotic solvents, besides the increased formation of α-D-galactosyl fluoride **267**, a clean reaction was not observed (entry 17). The main product **264**, after isolation from the reaction mixture by precipitation and subsequent treatment with various nucleophiles at elevated temperatures (Scheme 5), was found to be a valuable precursor for the interesting structures **271**–**274**[19], in isolated yields ranging from 60 to 65%.

[17] ^{19}F NMR monitoring of the reaction had disclosed [65a], that, in addition to compounds **264**–**269**, further fluorinated by-products were formed in low yields. From these, we recently identified the anomeric pair of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-D-galactopyranose (for NMR data see: R. Csuk, B. Glänzer, Adv. Carbohydr. Chem. Biochem., 46 (1988) 73–177).

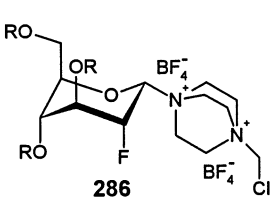
[18] This was proved by the use of the corresponding triflate salt (**262**) [66] with a D-glucal derivative [65b].

[19] Together with β anomers **271**–**273**, small proportions of the corresponding α anomers were also formed.

[20] Reaction in $MeNO_2$–water also led to a small (7%) proportion of the D-ribo counterparts [65a].

Interestingly, when **256** was reacted with **261** in refluxing acetonitrile, formation of 1,2-unsaturated 3-ulose **275**, in addition to otherwise known fluorinated products (entry 18), was observed.

Results from the reaction of **261** with other glycals in the presence of water are presented in entries 19–28. A stereoselective fluorination reaction also occurred with D-arabinal **276** in acetone–water[20] [65a] (entry 19) and L-fucal **278** in nitromethane–water [65c] (entry 20) giving 2-deoxy-2-fluoro-D-arabinose **277** and -L-fucose derivatives **279**, respectively. The stereoselectivity of the reaction with D-glucal derivatives was found [65b] to be strongly dependent on the protecting groups used. This point is evident from a comparison of the results found with *O*-acetyl and *O*-pivaloyl protected D-glucals **280** and **283** in nitromethane–water (entries 21 and 22) as well as those obtained from the reaction of cellobial **251** (entry 5). Interestingly, the D-gluco products arising from the direct addition of reagent **261** to the double bond of differently protected derivatives of D-glucal (as **286**, showing $^{1}C_{4}$-conformation) were rapidly hydrolysed at 75 °C. Their $^{4}C_{1}$-conformed counterparts with D-manno configuration **287**, under the same conditions, remained almost unaffected (except when R = benzyl). From these results, it became evident [65b] that the isolated yield of unpolar products with D-manno configuration is reduced by the percentage of unhydrolysed **287**. In addition, the D-gluco:D-manno ratio observed for **281**/**282** and **284**/**285**, respectively, does not reflect the true degree of stereoselectivity initially produced. Hence, kinetically controlled substitution, by a nucleophile, of the ammonio group at C-1 in product **286** allowed separation of 2-deoxy-2-fluoro sugars with gluco and manno configuration out of the mixture **286**/**287** [65c].



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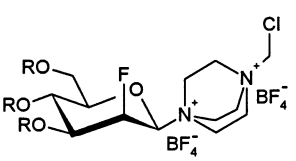
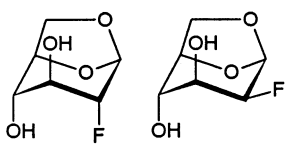


287

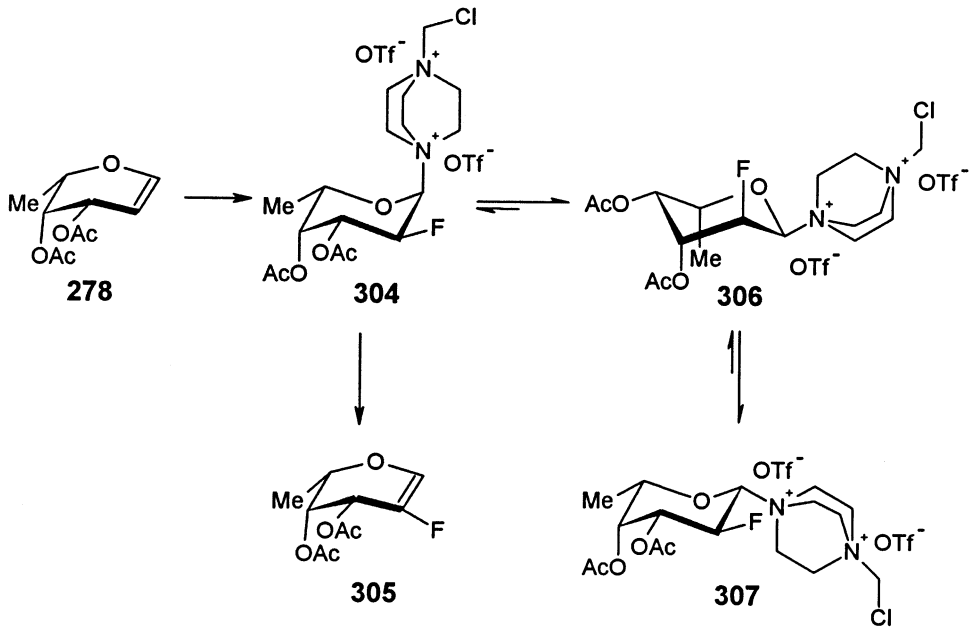
This observation could explain the strongly diverging product stereoselectivities and yields (in both cases products were isolated as per-acetates) reported for the reaction of unprotected D-glucal **288** with tetrafluoroborate **261** in water (entry 23, 1 h at room temperature followed by evaporation to dryness) [64a] or nitromethane–water (entry 24, 15 h at room temperature followed by 30 min at 85–90 °C) [65b]. The same reaction carried out in pure acetonitrile at room temperature for 12 h brought to light a new type of participation from the initial phase of the reaction, namely intramolecular attack of the oxygen atom at C-6, because 1,6-anhydro-2-deoxy-2-fluoro-β-D-gluco- (**291**) and -β-D-mannopyranose (**292**) were isolated as by-products [65b].



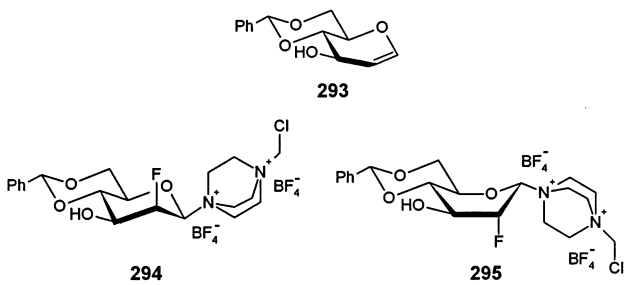
291 **292**

Additional proof for the existence of the highly reactive '2-fluoro oxocarbenium ion' **270** was found in experiments which were originally undertaken to raise the stereoselectivity of the D-glucal/F–TEDA reaction. Employing the conformationally more rigid 4,6-*O*-benzylidene-D-glucal **293** and **261** in nitromethane, besides the expected (chair form) addition product with the D-manno configuration (**294**), the (boat form) D-gluco-analogue **295** was also produced in almost an equal amount. Once more, this finding indicates that 'steric approach control' determines the stereoselectivity of this reaction. As soon as the syn-addition product is formed, the ammonio substituent at C-1 (taking the equatorial position) dictates the conformation. As expected (boat) **295** showed a higher reactivity [65b] with respect to the hydrolysis[21] of the C–N bond than (chair) **294**.

[21] Concomitantly, the benzylidene acetal was cleaved in both cases.



Scheme 6.



The respective reaction of sialic acid derived glycal **296** in DMF–water for 12 h at 50 °C (entry 25) is reported [64a] to have given, in 80% yield, 3-deoxy-3-fluoro-derivatives **297** and **298** in a ratio of 3:1.

Wong and co-workers [64a] described that reaction of highly reactive, benzyl protected furanoid glycal **299** with **261** (DMF–water at room temperature for 12 h) afforded a 22:3 mixture of 2-deoxy-2-fluoro-D-arabino- (**300**) and -D-ribofuranose derivatives (**301**) in 73% yield (entry 26). However, in our laboratory[22], under the same conditions (i.e., room temperature only), a mixture of **300** and **301** together with their corresponding 1-*O*-formyl derivatives **302** and **303** was obtained in 50% yield[23]. The product ratio for **300**:**301**:**302**:**303** was approximately 9:3:2:2 and, interestingly, all products showed exclusively the 1,2-trans configuration (entry 27). When carrying out the same reaction in acetone–water, an inseparable mixture containing both anomers of products **300** and **301** was isolated by chromatography in moderate yield (entry 28). To date, even in the absence of nucleophiles capable of attack[24], a product of direct addition of reagent **261** or **262** to the double-bond of glycal **299** could not be identified among products detected by ^{19}F NMR spectroscopy.

Very recently Wong and co-workers [64b] published results about mechanistic studies on this glycal/Selectfluor reaction and extended their original work [64a] on the direct, one-step synthesis of alkyl glycosides (including disaccharides) of 2-deoxy-2-fluoro hexopyranoses to biochemically interesting derivatives such as cardiac and anthracycline glycosides, glycosyl phosphates and phosphonates. Due to the amount of material published, only a few selected examples can be discussed here.

The mechanistic studies were also carried out, in part, with NMR spectroscopy. Here the reactions of differently protected deriva-

[22] B.J. Paul, M. Albert, J. Ortner, K. Dax, unpublished results.

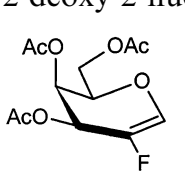
[23] Educt **299**, as seen with the whole class of furanoid glycals, is prone to allylic rearrangement and the product thus formed does not react with **261** or **262**.

[24] In dry nitromethane, the reaction mixture containing **299** and triflate **262** turned a deep blue.

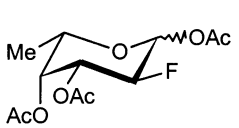
[25] Couplings up to 10 Hz are usually not detected in spectra taken from crude reaction mixtures.

tives of D-galactal, L-fucal as well as D-glucal with the tetrafluoroborate **261** and triflate **262**, respectively, were investigated. The latter was generally found to produce higher yields of products than **261**. Of special interest are the results obtained from monitoring the reaction of L-fucal **278** with triflate **262** in nitromethane at room temperature by ^{1}H and ^{19}F NMR spectroscopy. In contrast to their own reports from the reaction of **278** with **261** in DMF–water [64a], here the formation of polar addition product **306** with inverted chair conformation (analogous to the generation of **264** in the reaction of D-galactal **256** with **261** shown in entry 8 [65a]) was observed. A by-product appearing in the initial stages of the reaction which remained unchanged with respect to concentration throughout the course of the reaction, even after quantitative consumption of the starting material, was reported (without giving further details) to have the structure of 2-deoxy-2-fluoro-L-fucal **305** [64b]. Its formation was thought to be caused by elimination. From the steric prerequisite for such a reaction, antiperiplanar orientation of the ammonio substituent at C-1 and hydrogen at C-2, Wong and co-workers postulated (syn-addition) product **304** (in the normal chair conformation) to be the very first structure generated in this reaction sequence (Scheme 6).

With certainty, the NMR data for this by-product, as taken from the illustration given [64b] (^{19}F NMR (CD_3NO_2): δ-207–208 ppm, dd, J 50–55 and 10–15 Hz), are not adequate to support the postulated structure **305**, since the corresponding 2-deoxy-2-fluoro-D-galactal derivative **308** shows, in $CDCl_3$, δ −168.7 ppm with J 5 and 4 Hz[25] [60]. From the similarity of the ^{19}F NMR data with those obtained from 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-D-galactopyranose[17] ($CDCl_3$; β anomer: δ −208.4 ppm, J 52, 13, 4 and 3 Hz; α anomer: δ −209.4 ppm, J 49, 11 and 3 Hz), we suggest that the by-product is 1,3,4-tri-*O*-acetyl-2-deoxy-2-fluoro-L-fucopyranose **309**.



308



309

In following the reaction of **278** with **262** at room temperature, Wong and co-workers [64b], after quantitative consumption of the starting material (3 h), observed by NMR spectroscopy slow anomerisation[26] of product **306** having α-configuration into the thermodynamically more stable β anomer **307** (Scheme 6). The conversion of **306** to **307** reached[27] 95% after 72 h. Addition of water, at room temperature, to the 1-day-old mixture of **306** and **307** and stirring for another 24 h afforded **279** quantitatively from 'inverted' chair conformer **306**. The more stable β anomer **307** (in the 'normal' chair conformation) had to be heated to 75 °C for 1 h to yield the same result.

Surprisingly, the interpretations given by Wong and co-workers [64b] concerning the experiments where **306** or **307** were used as starting materials did not consider the ability of these compounds to equilibrate under the reaction conditions applied. In addition, the strikingly different reaction rates of nucleophiles with compounds **306** and **307**, combined with the lack of evidence for 100% conversion before work-up, suggests to us that the α/β-ratios determined for isolated products (in moderate to good yields) do not constitute a solid base for mechanistic discussions.

Although the authors had accepted, for this 'glycal/Selectfluor/nucleophile' reaction, a mechanism of a two stage nature (explicitly syn-addition followed by S_N-reaction) they designated it, without giving any explanation or reason, as an 'electrophilic fluorination–nucleophilic addition' reaction [64b].

Results which were described for a series of reactions employing **278** together with **261** or **262** and benzyl alcohol (as nucleophile) are not conclusive especially upon consideration

[26] The same reaction had been observed with the *syn*-addition product of D-gluco configuration (**286**), but only the polar nature (and not the entire structure) of the product had been recognized [Ref. 65b, footnote 6].

[27] The tendency to anomerise, obviously depends on the structure, since in own experiments, the triflate analogue of (D-galacto configurated) **264** was found to anomerise, within 40 h at room temperature, to an extent of 7% only.

of the conflicting explanations presented in this context[28].

Much work has been done [64b] towards the one-pot synthesis of glycosyl derivatives, which contain a 2-deoxy-2-fluoro sugar moiety (glycosides, disaccharides, glycosyl phosphates and phosphonates), most of which are of biochemical interest. The reactions with D-galactal and L-fucal showed strict stereoselectivity in the addition step, whereas that of D-glucal gave mixtures of D-gluco- and D-manno products. As illustrated in entries 29–32, in most cases, anomeric mixtures of final products[29] were formed. In our hands, employing tetrafluoroborate **261** together with various glycals for the direct synthesis of disaccharides as well as glycosylamino acids, both containing a 2-deoxy-2-fluoro-glycosyl moiety, only discouraging results were obtained. In the latter case we chose [65c] a route via the corresponding glycosyl trichloroacetimidate.

Although the scope and limitations of electrophilic addition reactions using these (cheap, safe and easy to handle) *N*–F-reagents are still under investigation and the mechanism of this reaction is not fully elucidated, this method opens easy access to a series of 2-deoxy-2-fluoro aldopyranoses in a stereoselective manner. As shown in Table 6, an additionally attractive feature of this method consists in the direct approach to various C-1-substituted derivatives thereof.

4. Selected transformations of fluorinated carbohydrates

In the general approaches described above, introduction of a fluorine atom was attempted with highly functionalised starting materials which already contained the constitutional and stereochemical features of the target molecule. In an extension to this, certain deoxyfluoro sugars have been synthesised by transformations setting out from more easily available fluorinated relatives. Methods recently used were, for example, the inversion of configuration in the neighbourhood of the fluorinated position (by oxidation/reduction) or epimerization at the fluorinated position in the ulose state followed by reduction [67], chain-elongation [68] as well as epimerization [69]. However these methods lack stereoselectivity.

Synthesis of geminal difluorides has recently been reviewed by Tozzer and Herpin [6f]. Although a number of successful transformations of carbohydrate derived carbonyl compounds into gem-difluorides is known [17,27,35,70] employing DAST, these reactions are also prone to alkoxy group migrations as well as ring-contraction reactions (see Section 4).

Divergent regioselectivity was observed when 2-acetoxy- and 2-acetamido-D-glucal, respectively, were treated with acetyl hypofluorite [60]. Whereas the enolester gave a 1,2-di-*O*-acetyl-2-fluoro compound, the enamine derivative led to a 2-*O*-acetyl-2-acetamido glycosyl fluoride. In both cases, the stereochemical course paralleled the one known from the reaction with D-glucal.

Introduction of fluorine at position 5 of α- as well as β-D-glucopyranosyl fluoride was achieved by radical bromination followed by a halogen-interchange reaction under retention of configuration [71].

5. Wider scope of fluorination reactions discussed (Table 7)

With respect to general preparative methods employed in organic chemistry, it is not surprising that the initially unexpected side reactions of nucleophilic substitutions, such as ring-contraction and participation of benzyloxy groups, were found to be fruitful methods for preparative purposes in addition to fluorination.

Ring-contraction, with inversion of configuration at C-2, as observed with 2-triflates of

[28] As an example, it is stated that for the reaction in acetonitrile (in contrast to the situation with nitromethane) a base or proton sponge is necessary to deprotonate the nucleophile and that using a stoichiometric quantity (instead of an excess) of the nucleophile markedly improves the yields. The results reported are: (i) reaction, in acetonitrile without a proton sponge, of **278** with **261** and excess benzyl alcohol at room temperature gives 71% of benzyl β-glycoside, (ii) reacting syn-addition product **306** in nitromethane with 3 equivalents of benzyl alcohol at room temperature, leads to 2.4% (α:β 1:1) of glycosides and (iii) heating this latter reaction mixture to 90 °C yields 26% (α:β 1:5) of anomers.

[29] The NMR data for 2-deoxy-2-fluoro-D-galactopyranosides **312** are given under the heading 'α-gluco' and 'α-manno' glycoside.

Table 7
Miscellaneous results with relation to reactions shown in Tables 1–5

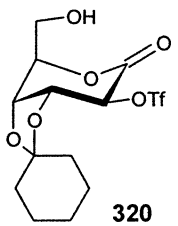
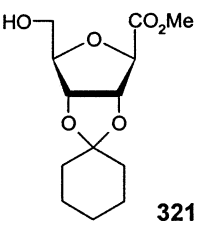
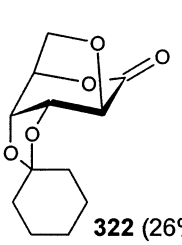
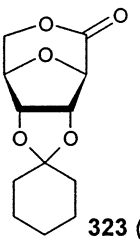
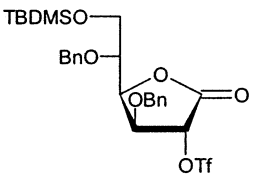
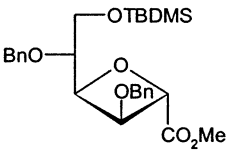
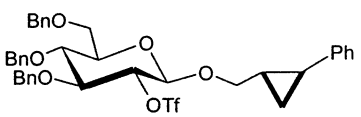
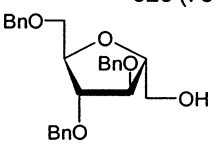
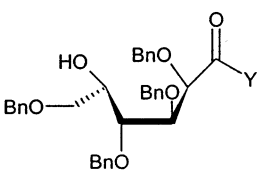
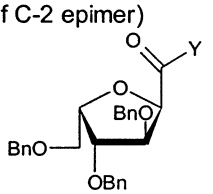
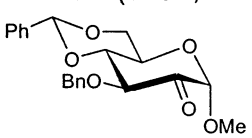
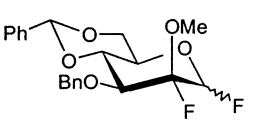
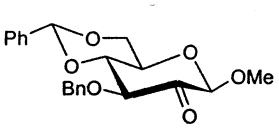
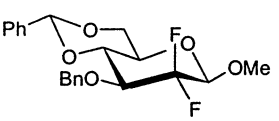
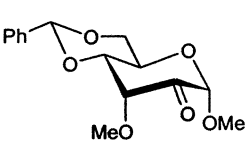
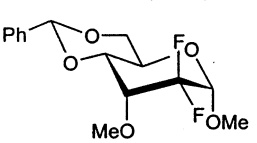
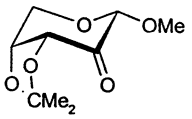
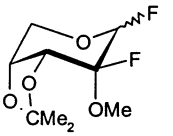
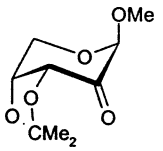
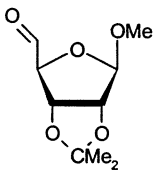
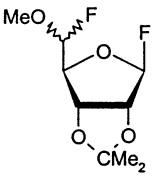
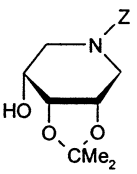
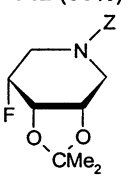
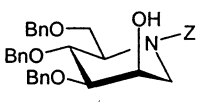
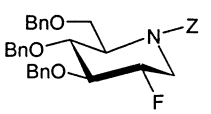
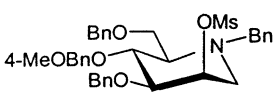
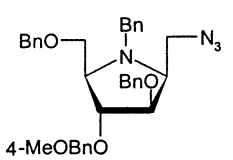
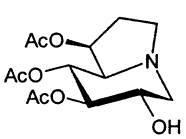
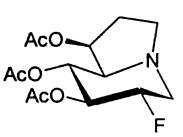
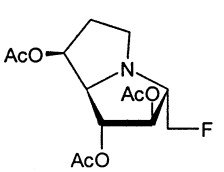
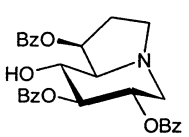
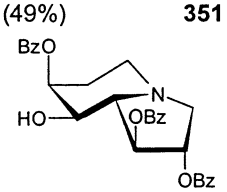
No.	Educt	Reagent	Product(s)	Ref.
1	 **320**	K_2CO_3 MeOH	 **321** (94%)	[73]
2	**320**	NaOAc DMF	 **322** (26%)  **323** (46%)	[73]
3	 **324**	K_2CO_3 MeOH	 **325** (75%)	[73]
4	 **326**	1) Py/H_2O DMF 2) $NaBH_4$	  **327** (79%, plus traces of C-2 epimer) **328** (90%)	[75]
5	 **329** (Y=OR, NHR)	DAST CH_2Cl_2	 **330**	[76]
6	 **331**	DAST benzene (reflux)	 **332** (43%); α>>β	[77a]
7	 **333**	DAST CH_2Cl_2	 **334** (80%)	[77a]
8	 **335**	DAST CH_2Cl_2	 **336** (39%)	[77a]

Table 7 (Continued)

No.	Educt	Reagent	Product(s)	Ref.
9	 **337**	DAST benzene	 **338** α<β	[77a]
10	 **339**	DAST CH_2Cl_2	**338** (72%); α>β	[77a]
11	 **341**	DAST CH_2Cl_2	 **342** (56%)	[15]
12	 **343**	DAST CH_2Cl_2	 **344** (66%)	[17]
13	 **345**	DAST CH_2Cl_2/Py	 **346** (53%)	[78]
14	 **347**	LiN_3 DMF	 **348** (72%)	[79]
15	 **349**	DAST CH_2Cl_2	 **350** (49%)  **351** (19%)	[80a]
16	 **352**	DAST CH_2Cl_2	 **353** (52%)	[80b]

aldopyranosides upon attempted nucleophilic substitution (Section 2.5 and, in a similar manner, observed by Fleet and co-workers [72] using nucleophiles other than fluoride), were also found to be operative [73] with 2-triflates of aldonolactones. Accordingly, D-altrono-1,5-lactone derivative **320**, when treated with potassium carbonate in methanol (entry 1) — under inversion of configuration at C-2-led to methyl 2,5-anhydro-D-allonate **321**. However, reacting the same starting material (**320**) with sodium acetate in DMF (entry 2) simultaneously gave 2,6-anhydro-D-altrono-1,5-lactone **322** (with retention of configuration at C-2) and the (ring-contracted) 2,5-anhydro-D-allono-1,6-lactone **323** (with inversion of configuration at C-2). The mechanistic explanation given for the formation of these products includes, for the reaction given in entry 1, lactone ring opening by methoxide followed by an anhydro ring closure. For reactions shown in entry 2, two mechanistic pathways are envisaged, namely, on the one hand, base catalyzed epimerization at C-2 of triflate **320** before ring-closure to give **322** and, on the other, lactone opening by O-6 followed by nucleophilic substitution at C-2 (by the former lactone oxygen) to give **323**, respectively. In view of the mechanistic principles discussed with aldopyranosides, assumption of an 'oxiranium ion-type' intermediate (comprising of C-1, C-2 and lactone oxygen), which is opened by O-6, either at C-2 (to give **322**) or at C-1 (to yield **323**), would be a pathway which more easily explains product formation.

Ring-contraction, observed with the 2-triflate **324** of D-glucono-1,4-lactone, to form methyl 2,4-anhydro-D-mannonate **325** (entry 3) is of special interest, since this type of oxetane formation has not yet been found with aldofuranosides.

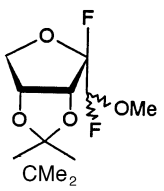
Ring-contraction of alkyl 3,4,6-tri-*O*-benzyl-2-*O*-triflyl-β-D-glucopyranosides, by treatment with pyridine–water in DMF, was reported recently by Spilling and co-workers [74]. This method was also used [75] in the synthesis of the chiral cyclopropane derivative **328** (entry 4). Asymmetric cyclopropanation of 3-phenylallyl 3,4,6-tri-*O*-benzyl-β-D-glucopyranoside, in which the sugar moiety operates as a chiral auxiliary, followed by triflation afforded the 2-triflate **326**. Cleavage of **326** by a (base induced) ring-contraction reaction followed by borohydride reduction of the 2,5-anhydro-D-mannose furnished both 2,5-anhydro-D-mannitol **327** and the aglycone **328**.

Benzyloxy group participation observed during attempted fluorinations using DAST with concomitant anhydro ring formation under inversion of configuration at the activated site was elaborated upon by Lellouche and co-workers [76] to give a powerful method for the synthesis of 2,5-anhydro-aldonic acid (and other sugar) derivatives. This is exemplified by the reaction of the 5-OH unprotected D-gluconic acid derivative **329** with DAST to yield, with inversion of configuration at C-5, the 2,5-anhydro-L-idonic acid derivative **330** (entry 5).

The validity of the generalisations made in this article concerning substrates where the oxygen has been replaced with nitrogen in the tetrahydropyran (or tetrahydrofuran) ring and the DAST reaction with a carbonyl moiety has also to be considered. As will be seen, comparison of results reported from DAST reactions of 2-OH unprotected glycosides with those of the corresponding 2-uloses, obviously raises further questions. However, observations made with 1-deoxy-piperidinoses such as 1-deoxy-nojirimycin confirm assumptions made on the stereochemical prerequisites for the formation of cyclic intermediates and their importance in product development.

Diverging results were reported [77] for the reaction of alkyl aldopyranosid-2-uloses such as **331**, **333**, **335**, **337** and **339** (entries 6–10) with DAST. Whereas (intended) geminal difluorination occurred in the case of **333** and **335** only, 1,2-alkoxy-migration was reported to have taken place in the cases of **331**, **337**, and **339** (for **337**, gem-difluorination had been reported previously [77b]). From the outcome of attempted fluorinations of C-2 of aldopyranosides, we had drawn the conclusion (Section 2.5) that 1,2-alkoxy-shifts do not occur in structures provided with *cis*-3,4-*O*-alkylidene protection (as seen with **337** and **339**) and that, in this case, ring-contraction is favoured. To prove the structural assignment of 1,2-difluoride **338**, we simply compared the geminal couplings observed between fluorine and hydrogen at C-1 ($J_{F\text{-}1,H\text{-}1}$) in **338** and **332**. (According to another generalisation made about

RC- and AM-reactions, namely, that a 4,6-*O*-benzylidene protected hexopyranoside of the *trans*-decalin type as **331** cannot be subject to ring-contraction, 1,2-difluoride **332** should have a pyranoid structure.) From the values for $J_{F\text{-}1,H\text{-}1}$ published, 50.5 (**332**) and 64.6 Hz (**338**) [77a], it can be deduced[13] that compound **338** could be a ring-contracted product[30], possibly of the constitution depicted in formula **340**.



340

Another interesting example of alkoxy group migration was observed upon attempted gem-difluorination [15] of aldehyde **341** with DAST (entry 11). The same reaction pathway was also found in the reaction of alcohol **37** with the same fluorinating reagent (Table 1, entry 18).

Replacing oxygen with nitrogen in the sugar ring (as for example in piperidinoses such as nojirimycin) and the role thereof has not yet been examined. However, DAST reactions as well as sulfonate displacements with a few 1-deoxy derivatives have already been carried out. Results include fluorination with retention (entry 12 [17] and 15) as well as inversion of configuration (entry 13) and ring-contraction (entries 14 and 15). 3,4,6-Tri-*O*-benzyl-*N*-benzyloxycarbonyl-1-deoxy-mannojirimycin [78] (**345**, entry 13), only in the presence of pyridine, gave a clean S_N2-reaction, otherwise substitution with inversion as well as retention was observed. Treatment (entry 14) of **347**, the 2-mesylate of a differently protected derivative of the same parent 1-deoxy-mannojirimycin, with azide, gave rise to the formation of ring-contracted product **348** with the D-gluco configuration [79]. The only possible explanation was attack of the ring-nitrogen at C-2 when an equatorial orientation of the leaving group (by conformational inversion of the ring-system) occurred. Of special interest are the exhaustive studies [80] concerning the reactions of DAST with 6- and 8-OH-unprotected castanospermine derivatives **349** (entry 15) and **352** (entry 16), respectively. In the first case, via an aziridinium ion, fluorination with retention of configuration (to give castanospermine derivative **350**) together with ring-contraction and fluorination at the neighbouring position within the aziridine ring (both with inversion, to produce australine derivative **351**) was observed [80a]. Formation of **353** from **352** — by a piperidine–pyrrolidine ring-contraction, without substitution by fluorine (but participation of the neighbouring benzoyloxy group), under inversion of configuration at both centres — also involved an intermediate aziridinium ion [80b].

6. Concluding remarks

Finally it should be added that many of the strikingly divergent results observed with these fluorination reactions and described here, may be seen in relation to the reported yields. Isolation of a single product out of a multi-product reaction mixture does not imply total exclusion of any other reaction path. Another cause for the 'inhomogenity' of reported results arises from the poor documentation and/or assignment of spectral data. This may in part also be caused by editorial issues concerning the presentation of these data in an 'unintelligible raw' after the description of the experiment instead of in a table (where deviations as well as simple typing errors are easily seen).

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[30] Reconsideration of the structural assignment is already in progress by the original authors. The mechanism of this 2-ulose/DAST reaction leading to these configurations, at C-2, as given for products such as **338** formed from alkoxy-migration as well as the role of the axial 3-methoxy group in **335** will be examined further.

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