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TETRAHEDRON

A Novel Direct Route to 2-Deoxy-2-fluoro-aldoses and their Corresponding Derivatives

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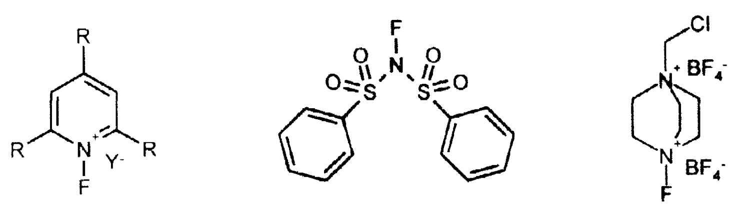
Abstract: A new type of reactive *N*-(2-deoxy-2-fluoro-glycosyl) compound is formed by regioselective *syn*-addition of the electrophilic *N*-F reagent Selectfluor™ to glycals. By subsequent treatment with nucleophiles, 2-deoxy-2-fluoro-aldoses and various C-1-substituted derivatives thereof are easily accessible. Furthermore, the reaction with D-galactal and D-arabinal proceeds stereoselectively, thus allowing the synthesis of 2-deoxy-2-fluoro-D-galactose- and -D-arabinose-derivatives in multi-gram quantities. © 1998 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

Compounds containing 2-deoxy-2-fluoro-aldoses are of increasing importance in biochemical studies[1] as well as medicinal chemistry research.[2] Since their chemical synthesis is hampered by a broad range of restrictions, a vast number of approaches is known.[3] These include strategies like electrophilic addition of *O*-F reagents (*e.g.* acetyl hypofluorite) to glycals.[4] In analogy to this method, a program to investigate the scope and limitations of applying the new class of electrophilic *N*-F fluorinating agents[5] for the transformation of glycals[6] into 2-deoxy-2-fluoro-sugars was undertaken[‡]. From the list of commercially available reagents, 1-fluoropyridinium tetrafluoroborate (**1a**), 1-fluoro-2,4,6-trimethylpyridinium triflate (**1b**), *N*-fluorobenzenesulfonimide (**2**) and 1-chloromethyl-4-fluoro-1,4-diazonia-bicyclo[2.2.2]octane bis(tetrafluoroborate)[7] (Selectfluor™, F-TEDA-BF_4, **3**) were selected (Fig.1).



1a R = H, Y = BF_4
1b R = Me, Y = OTf

2

3

Figure 1. Structures of *N*-F reagents tested

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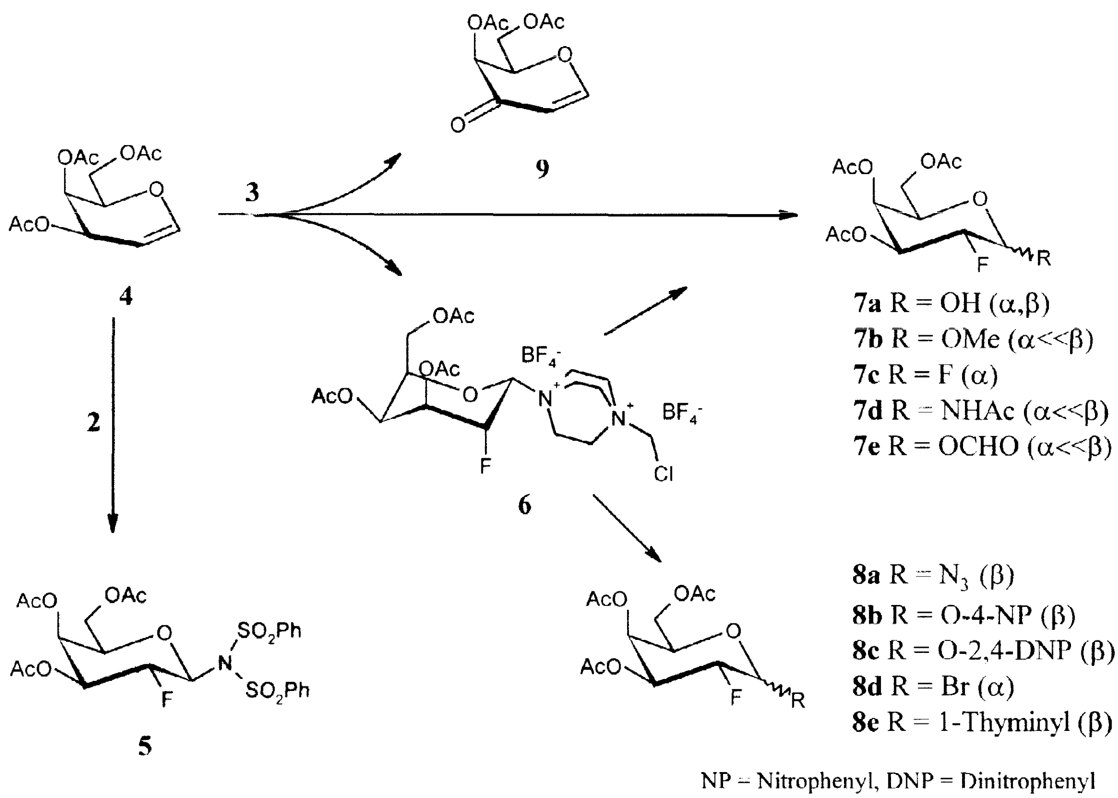
RESULTS AND DISCUSSION

Treatment of 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*lyxo*-hex-1-enitol (3,4,6-tri-*O*-acetyl-D-galactal, **4**) with **1a** or **1b**, in acetonitrile and temperatures up to 80 °C, did not lead to a reaction. Employing compound **2**, after 24 hours at 80 °C, a single addition product, *N,N*-di(phenylsulfonyl)-3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-β-D-galactopyranosylamine (**5**), was obtained. Application of **3**, at room temperature, in various solvents and their mixtures with methanol and water, respectively, caused (as evidenced by t.l.c.- and ^{19}F NMR monitoring) rapid and complete consumption of **4** with the simultaneous formation of a range of fluorinated carbohydrates (Scheme 1).



Scheme 1.

Isolation of the products formed using precipitative and chromatographic methods, followed by elucidation of the individual structures by means of NMR spectroscopy[8] and correlation (Table 1) with their respective signals in the ^{19}F NMR spectra[9] allowed the following conclusions.

Introduction of fluorine occurs regio- and stereospecifically with the sole formation of 2-deoxy-2-fluoro-D-galactopyranose derivatives.

Among the products formed, a new *N*-glycosyl compound, 1-(3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α-D-galactopyranosyl)-4-chloromethyl-1,4-diazonia-bicyclo[2.2.2]octane bis(tetrafluoroborate) (**6**), predominates.

Anomeric mixtures of (OH-1-unprotected) 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-D-galactopyranose (**7a**) or the respective methyl glycosides (**7b**) are obtained in the presence of water or methanol.

In the absence of external nucleophiles, participation of fluoride ion (liberated from tetrafluoroborate) and the solvent (acetonitrile or *N,N*-dimethylformamide) gives rise to 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α-D-galactopyranosyl fluoride (**7c**), anomeric mixtures of *N*-acetyl-3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-D-galactopyranosylamine[10] (**7d**) or 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-1-*O*-formyl-D-galactopyranose (**7e**).

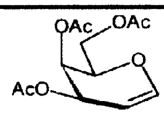
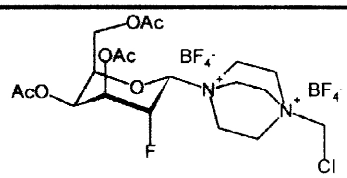
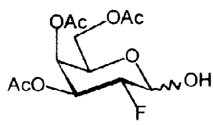
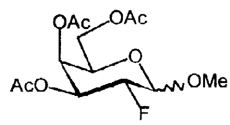
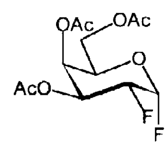
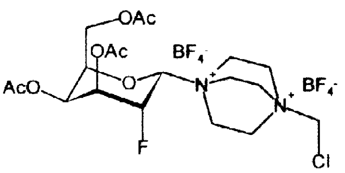
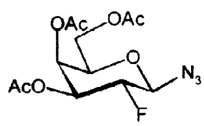
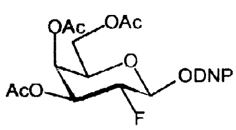
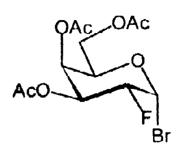
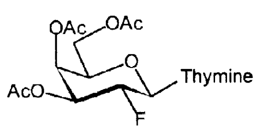
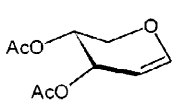
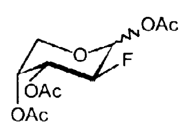
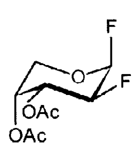
Table 1. Product Ratio [%] as Determined by ^{19}F NMR Spectroscopy[9]

solvent	6	7a	7b	7c	7d	7e	by-products [a]
CH_3NO_2	73			23			4
CH_3NO_2/D_2O (5:1)	58	30					12
CH_3NO_2/CD_3OD (5:1)	49		45	4			2
CH_3CN	54			14	27		5
CH_3CN/D_2O (5:1)	45	23			30		2
Acetone/D_2O (5:1) [b]	49	49					2
DMF/D_2O (5:1)	46	31				22	1

[a] summation of unidentified fluorinated carbohydrates [b] additionally, formation of fluoro acetone [δ -226.9 ppm, *J* 47 and 47 Hz] occurred

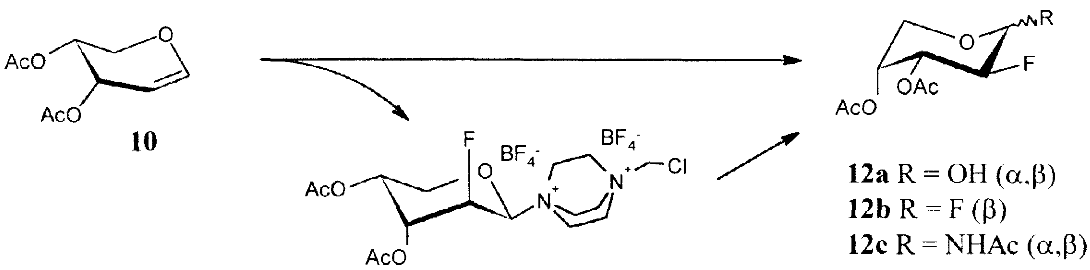
Since reaction monitoring after total consumption of **4** had revealed only slow changes within the proportions of fluorinated products, the mixtures containing water or methanol were heated. Within a few hours, quantitative substitution of the ammonium group at C-1 of compound **6** by the protic co-solvent, to form respectively **7a** and **7b**, occurred. With neat aprotic solvents (besides increased formation of **7c**) no other clean reaction was observed. Intermediate **6** was isolated by precipitation. Subsequent treatment with sodium azide, magnesium bromide, potassium 4-nitrophenolate or 2,4-dinitrophenolate as well as 2,4-bis(trimethylsilyl)thymine, in acetonitrile or nitromethane, gave 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-β-D-galactopyranosyl azide (**8a**), the corresponding α-bromide (**8d**), 4-nitrophenyl (**8b**) or 2,4-dinitrophenyl β-glycoside (**8c**) and 1-(3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-β-D-galactopyranosyl)thymine (**8e**), respectively, in good yields (Table 2). Interestingly, treatment of **4** with **3** in the presence of bromide or phenolate ions did not yield fluorinated carbohydrates. Intermediate **6**, with thiophenolate or xanthate ions, underwent reaction[11] other than nucleophilic substitution at C-1 of the carbohydrate moiety. When performing the reaction of **4** with **3** in boiling acetonitrile, besides **7c**, 4,6-di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*threo*-hex-1-en-3-ulose[12] (**9**) was also isolated from the orange coloured reaction mixture.

Table 2. Selected Transformations

substrate	No	product	No	pro-cedure	yield [%]	$[\alpha]_D$ (*c*, solvent) mp. R_f [a]
	**4**		**6**	A	82 [b]	+10.8° (2.0, MeCN) (foam) 0.0
			**7a**	B1	79	[c] (-) syrup 0.42
			**7b**	B1	76	[c] (-) syrup 0.61
			**7c**	B3	52	+103° (0.9, $CHCl_3$) 58°C 0.55
	**6**		**8a**	C	62	+89.5° (3.0, $CHCl_3$) 84°C 0.63
			**8c**	C	61	-3.6° (1.0, $CHCl_3$) 160°C 0.45
			**8d**	C	66	+162.0° (0.8, $CHCl_3$) syrup 0.63
			**8e**	C	63	+18.6° (0.9, $CHCl_3$) syrup 0.21
	**10**		**12d**	B2	68 [d]	[c] (-) syrup 0.57
			**12b**	B3	45	-187.5° (1.1, $CHCl_3$) 64°C 0.65

[a] ethyl acetate/cyclohexane (1:1) [b] crude yield [c] mixture of anomers [d] additionally 7% of the corresponding D-*ribo*-configurated isomers were obtained (α/β 1:2)

Similar results to those found with D-galactal **4** were obtained from the reaction of 3,4-di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*erythro*-pent-1-enitol (di-*O*-acetyl-D-arabinal, **10**) with **3** (Scheme 2). When carried out in acetone/water, exclusive formation of products with D-*arabino*-configuration, namely 1-(3,4-di-*O*-acetyl-2-deoxy-2-fluoro-β-D-arabinopyranosyl)-4-chloromethyl-1,4-diazonia-bicyclo[2.2.2]octane bis(tetrafluoroborate) (**11**[13]) and the anomers of 3,4-di-*O*-acetyl-2-deoxy-2-fluoro-D-arabinopyranose[14] (**12a**), was observed. The same experiment performed in nitromethane/water produced a minor proportion of the D-*ribo*-isomer.[15] Reaction in acetonitrile led to β-configurated difluoride **12b** as well as, through participation of the solvent, *N*-acetyl-3,4-di-*O*-acetyl-2-deoxy-2-fluoro-D-arabinopyranosylamine[16] (**12c**).



10

11

12a R = OH (α,β)
12b R = F (β)
12c R = NHAc (α,β)

Scheme 2

In contrast to the results obtained with D-galactal **4**, pronounced stereoselectivity was not observed in the reaction of derivatives of 1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (D-glucal) including disaccharidic analogues derived from maltose, cellobiose and lactose, respectively. Here, without exception, mixtures of the corresponding derivatives of 2-deoxy-2-fluoro-D-glucopyranose and -D-mannopyranose [including (2-deoxy-2-fluoro-glycosyl) ammonium intermediates[17] of type **6** (*gluco*) and **11** (*manno*)] were formed. The composition of these mixtures also varied depending on the nature of the protecting group.[18] When starting from *O*-unprotected D-glucal, an inseparable mixture of 1,6-anhydro-2-deoxy-2-fluoro-β-D-gluco- and -manno pyranose[19] was obtained in moderate yield.

Concerning the mechanism of this „glycal-Selectfluor™ reaction“, conclusions can be drawn from the unique stereochemistry of the direct addition products (**6** or **11**). In each case, even under inversion of otherwise preponderating chair conformations, they possess axially oriented fluorine and equatorially arranged ammonium substituents. For their formation, a concerted *syn*-addition, not yet observed with *N*-halogeno compounds[20] including *N*-F reagents, may be anticipated. In addition, depending on the reaction temperature, at least two other competing pathways[21] appear to exist. Possibly, formation of a 2-deoxy-2-fluoro-glycosyl species (*e.g.* glycosylium ion) occurs, which spontaneously reacts with nucleophiles to give compounds of the type **7a-e** (thus diminishing the attainable yield of the products **8a-e**). Additionally, at higher temperatures an obviously radical initiated oxidation process with formation of compounds like 4,6-di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*threo*-hex-1-en-3-ulose (**9**) takes place. Whereas for the reaction of intermediate **6**, with nucleophiles, to yield 1,2-*trans*-configurated products **8a, b, c** and **e**, a S_N2-mechanism is obvious, compounds such as **7c** and **8d** must be formed through a subsequent anomerization to the thermodynamically more stable anomer.

From these findings, short and simple procedures for the preparation of derivatives of 2-deoxy-2-fluoro-D-galacto- and -D-arabinopyranose, valuable in biochemical studies as well as chemical synthesis, were established; their NMR data are collected in Tab. 3 (^{13}C), Tab. 4 (^{1}H) and Tab. 5 (^{19}F), respectively.

Table 3. ^{13}C NMR Data ($CDCl_3$), δ [ppm] (J [Hz])

No	δ C-1 (J_{C1-F2})	δ C-2 (J_{C2-F2})	δ C-3 (J_{C3-F2})	δ C-4 (J_{C4-F2})	δ C-5	δ C-6	substituents [a]
5	86.6 (26.1)	86.0 (186.1)	72.2 (18.6)	67.5 (8.2)	73.7	60.7	$PhSO_2$ 141.0/ 139.7/ 134.2/ 134.0/ 129.0/ 128.8/ 128.6
6	88.7 (15.0)	84.8 (188.1)	66.8 (28.8)	63.9 (-)	75.9	59.4	TEDA 50.8/ 50.2 CH_2Cl 69.6
7aα	90.7 (21.4)	85.8 (189.1)	68.0 (18.8)	68.8 (7.8)	66.3	61.7	
7aβ	94.9 (23.1)	89.1 (186.3)	71.1 (19.0)	67.9 (9)	70.8	61.5	
7bα	97.5 (20)	85.5 (185)	n.r.	68.7 (7.5)	66.4	61.6	OMe 55.7
7bβ	101.7 (22.8)	88.0 (186.9)	71.1 (18.9)	67.7 (8.4)	70.7	61.1	OMe 57.4
7c	104.1 (23.5/ J_{C1-F1} 230.5)	84.4 (191.2/ J_{C2-F1} 25.3)	67.7 (25.1)	67.8 (1.6)	69.0 (J_{C5-F1} 3.2)	61.1	
7dβ	77.7 (23.3)	86.9 (188.2)	71.6 (18.7)	68.0 (8.1)	72.5	61.1	NHAc 169.9/ 23.4
7eα	88.8 (24)	84.1 (191.7)	67.6 (16)	68.1 (9.5)	69.1	61.1	OCHO 158.5
7eβ	91.1 (24.9)	86.6 (188.7)	70.8 (18.7)	67.4 (8.2)	72.0	60.9	OCHO 158.5
8a	88.0 (23.1)	87.4 (188.7)	70.9 (18.8)	67.5 (8.2)	72.8	61.1	
8b	98.2 (23.8)	87.3 (189.2)	70.8 (19.1)	67.4 (8.2)	71.5	61.3	*p*-NP 116.8 125.8 143.4 161.1
8c	98.9 (24.7)	87.0 (190.0)	70.4 (19.2)	67.0 (8.2)	72.0	61.2	DNP 117.7/ 121.8/ 128.7/ 140.0/ 142.2/ 153.6
8d	86.9 (25.6)	84.2 (195.0)	68.9 (18.0)	67.5 (7.6)	71.3	60.7	
8e	80.2 (24.6)	85.8 (190.1)	71.2 (18.3)	67.9 (8.0)	73.9	61.2	Thymine 112.7/ 133.9/ 150.6/ 163.37/ 12.7
12b	104.7 (23.3/ J_{C1-F1} 229.5)	85.0 (190.8/ J_{C2-F1} 25.6)	67.3 (18.9)	68.8 (7.7)	62.6 (J_{C5-F1} 3.3)	-	

[a] data for *O*-acetyl groups are omitted

Table 4. ^{1}H NMR Data ($CDCl_3$), δ [ppm] (J [Hz])

No	δ H-1 (J_{H1-F}, J_{H1-H2})	δ H-2 (J_{H2-F}, J_{H2-H3})	δ H-3 (J_{H3-F}, J_{H3-H4})	δ H-4 (J_{H4-F}, J_{H4-H5})	δ H-5 (J_{H5-H6a}, J_{H5-H6b})	δ H-6a ($J_{H6a-H6b}$)	δ H-6b	substituents [a]
5	5.62 (2.8/ 9.0)	5.66 (53.1/9.2)	5.16 (13.7/ 3.3)	5.43 (-,2.6)		3.88-4.06 n.r. [b]		$PhSO_2$ 7.5-7.7, 8.0-8.2, (m)
6		5.2-5.6 n.r.			4.6-4.8 n.r.		4.0-4.3 n.r.	TEDA 4.0-4.3, (m) CH_2Cl 5.27 (s)
7aα	5.38-5.54, n.r. (-,3.7)	4.75 (50.2/ 9.7)	5.38-5.54 n.r.		4.48 (6.6/ 6.6)	3.95-4.15 n.r.		
7aβ	5.38-5.54, n.r. (n.r./ 7.5)	4.47 (51.3/ 9.8)	5.11 (12.9/ 3.5)		3.95-4.15 n.r.			
7bα	5.0 (-/ 3.5)	4.75 (50/10)			n.r.			OCH_3 3.46 (s)
7bβ	4.49 (2.2/ 7.7)	4.48 (52.7/ 9.6)	5.10 (13.4/ 3.5)	5.41 (n.r.)	3.92 (6.6/ 6.6)	4.05-4.25 n.r.		OCH_3 3.59 (s)
7c	5.84 (-/ 2.9/ J_{H1-F1} 53.1)	4.77 (48.8/ 10.1 J_{H2-F1} 23.3)	5.40 (11.1/ 3.3)	5.53 (3.3/ 1.1)	4.40 (6.2/ 6.2)	4.0-4.2 n.r.		
7dβ	5.35 (3.0/ 9.0)	4.48 (51.4/ 9.5)	5.17 (12.4/ 3.5)	5.44 (3.0/ n.r.)		4.0-4.2 n.r.		NH 6.48 (J_{NH-H1} 9.4)
7eα	6.56 (-/ 3.8)	4.92 (50/10)	5.3-5.55 n.r.			4.0-4.4 n.r.		OCHO 8.16 (s)
7eβ	5.88 (4.1/ 8.0)	4.66 (51.3/ 9.8)	5.19 (13.1/ 3.5)	5.52 (3.5/ 1.8)		4.0-4.4 n.r.		OCHO 8.12 (s)
8a	4.81 (4.0/ 8.5)	4.42 (50.8/ 9.7)	5.12 (13.0/ 3.5)	5.42 (2.6/ 1)		3.88-4.18 n.r.		
8b	5.29 (4.0/ 7.5)	4.81 (51.1/ 9.8)	5.25 (13.3/ 3.5)	5.50 (3/ -)		4.05-4.30 n.r.		*p*-NP 7.13 /8.20 (d each)
8c	5.41 (4.6/ 7.3)	4.89 (50.7/ 9.7)	5.25 (13.4/ 3.5)	5.41 (2.5/ -)		4.05-4.25 n.r.		DNP 7.44 (d) 8.42 (dd) 8.76 (d)
8d	6.60 (-/ 4.2)	4.74 (50.0/ 9.6)	5.45 (13.4/ 3.3)	5.50 (3.5/ 1.2)	4.49 (6.2/ 6.8)	4.15 (11.4)	4.09	
8e	5.94 (3.7/ 9.2)	4.68 (51.3/ 9.6)	5.29 (12.3/ 3.5)	5.48 (3.0/ -)		4.0-4.2 n.r.		Thymine 7.05/ 1.93 (s each)
12b	5.82 (-/ 2.7/ J_{H1-F1} 53.1)	4.79 (48.5/ 10/ J_{H2-F1} 23.3)	5.3-5.45 n.r.		5a: 4.11 (-/-/ $J_{H5a-H5b}$ 13.2)	5b: 3.77 (J_{H5b-H4} 1.6/ J_{H5b-F1} 1.6)		

[a] data for acetyl groups are omitted [b] not resolved

Table 5. ^{19}F NMR Data ($CDCl_3$), δ [ppm], *J* [Hz]

No	δ F-1	δ F-2	$J_{F2\text{-}H1}$	$J_{F2\text{-}H2}$	$J_{F2\text{-}H3}$	$J_{F2\text{-}H4}$	$J_{F1\text{-}H1}$	$J_{F1\text{-}H2}$	$J_{F1\text{-}F2}$
5		-203.8		53.3	13.5				
6 [a]		-204.2	25.5	46.0	10.5				
7aα		-207.0		50.1	10.9	3.6			
7aβ		-207.5	3.3	51.5	13.0				
7bα		-209.2		49.8	10.9	3.4			
7bβ		-207.3	2.4	52.7	13.3	2.4			
7c	-152.6	-211.3		49	14		51.1	24.1	18
7dβ		-204.9		51.1	13.4				
7eα		-209.5		49.0	11.1	3.5			
7eβ		-208.6	3.5	52.9	13.0	3.0			
8a		-205.5	3.3	51.0	12.9	3.3			
8b		-207.1	3.5	51.3	13.3	3.2			
8c		-206.7	3	50	15	3			
8d		-195.3		50.9	10.4	3.3			
8e		-207.3		51.2	12.3				
12b	-155.2	-209.3		50	14		52	22	18

[a] BF_4^- δ -150.2 ppm

EXPERIMENTAL SECTION

General Methods. Melting points were determined with a Tottoli apparatus (Büchi 300) and are uncorrected. Optical rotations were measured with a Jasco DIP-360 digital polarimeter at 589 nm at ambient temperature. NMR spectra were recorded at 300.13 or 200 MHz (^1H), 75.47 or 50.29 MHz (^{13}C) and 282.4 MHz (^{19}F) - using a Bruker MSL 300 and a Varian Gemini 200 apparatus, respectively; as reference standards tetramethylsilane (^1H and ^{13}C NMR) and trichlorofluoromethane (^{19}F NMR) were used. TLC was performed on silica-gel 60 F_{254} precoated aluminum plates (Merck 5554) with detection by charring after spraying with vanillin/sulfuric acid (1%). The R_f values given were determined using ethyl acetate/cyclohexane 1:1 (v:v). For column chromatography, silica gel 60, 230-400 mesh (Merck 9385), was used. „Normal work-up" means: filtration (where heterogenous), evaporation of the solvent *in vacuo*, dissolution of the residue in dichloromethane followed by extraction with water (or 5% sodium hydrogen carbonate and water), drying of the organic phase with sodium sulphate and removal of dichloromethane by distillation.

Samples for ^{19}F NMR reaction monitoring were taken from solutions (2 ml) of **4** or **10** (40 mg) and **3** (60 mg, 1.2 equivalents) in the mixture of the respective solvent with D_2O or CD_3OD; when neat nitromethane or acetonitrile was used, $CDCl_3$ was added prior to measurement.

Procedure A: To a solution of **4** (2.00 g, 7.35 mmol) in nitromethane abs. (30 ml) is added **3** (2.60 g, 7.35 mmol) and stirred vigorously at room temperature overnight. After addition of ethyl acetate (40 ml) a precipitate forms (reagent after fluorine delivery), which is removed by filtration and washed with nitromethane (10 ml). Filtrate and washings are concentrated *in vacuo* and the residue is dissolved in acetonitrile (5 ml). Slow addition of ethyl acetate/cyclohexane [100 ml, 1:1 (v:v)] causes deposition of product **6** as an oil, which is separated by centrifugation. After decanting and evaporation of the remaining solvent, crude **6** (3.76 g, 82%) is obtained as a white foam. R_f (**4**) 0.53; R_f (**6**) 0.0.

Procedure B1: To a 10% solution of glycal **4** or **10** in nitromethane/water or nitromethane/methanol (5:1, v/v) are added 1.2 equivalents of reagent **3** under vigorous stirring at room temperature. After quantitative consumption of the starting material (a few hours) the mixture is heated to reflux for a period of half an hour.

After evaporation of the solvent, products are isolated by chromatography (ethyl acetate/cyclohexane 1:3). R_f (**7a**) 0.42; R_f (**7b**) 0.61; R_f (**10**) 0.75; R_f (**12a**) 0.45.

Procedure B2: The residue obtained by procedure B1 is acetylated according to a standard protocol and the peracetates isolated by chromatography (ethyl acetate/cyclohexane 1:4).

Procedure B3: This procedure is identical to B1, except that nitromethane abs. is used as sole solvent. R_f (**7c**) 0.55; R_f (**12b**) 0.65.

Procedure C: To a 5% solution of crude **6** in acetonitrile abs. or nitromethane abs. 2 equivalents of the appropriate nucleophile [sodium azide, potassium 4-nitrophenolate, sodium 2,4-dinitrophenolate, magnesium bromide or 2,4-bis(trimethylsilyl)thymine] are added. This mixture is allowed to react, at reflux temperature, until total consumption of **6** (10-30 min). After normal work-up, the products are isolated by chromatography [ethyl acetate/cyclohexane 1:4 (v:v)]; **8c** crystallizes from ethanol. R_f (**8a**) 0.63; R_f (**8b**)[22] 0.59; R_f (**8c**) 0.45; R_f (**8d**) 0.63; R_f (**8e**) 0.21.

***N*-Acetyl-3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-D-galactopyranosylamine** (**7d**) is obtained from a reaction of **4** (1.00 g, 3.67 mmol) and **3** (1.55 g, 4.38 mmol) in acetonitrile abs. (12 ml). After 15 h at room temperature, **7d**[10] (α/β 1:11; 0.15 g, 12%) and **7c** (0.40 g, 35%), are isolated by chromatography. R_f (**7d**) 0.22.

3,4,6-Tri-*O*-acetyl-2-deoxy-2-fluoro-1-*O*-formyl-D-galactopyranose (**7e**, α/β 4:13; 0.18 g, 14%) is isolated from an analogous protocol as described for **7d,** but using *N,N*-dimethylformamide/water (5:1) as solvent. R_f (**7e**) 0.53.

4,6-Di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*threo*-hex-1-en-3-ulose (9): To a boiling solution of **4** (1.00 g, 3.67 mmol) in acetonitrile abs. is added **3** (1.55 g, 4.38 mmol). After quantitative consumption of **4** (ca. 30 min.), the orange coloured reaction mixture is evaporated. From the residue, UV-active product **9**[12] (0.11 g, 14%) as well as **7a**, **7c** and **7d** are isolated by chromatography [ethyl acetate/cyclohexane 1:3 (v:v)]. R_f (**9**) 0.41.

***N,N*-Di(phenylsulphonyl)-3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-β-D-galactopyranosylamine (5).** A solution of **4** (1.00 g, 3.67 mmol) and *N*-fluorobenzenesulfonimide (**2**, 1.39 g, 4.41 mmol) in acetonitrile abs. (15 ml) is heated to 80°C for 24 h. After normal work-up, compound **5** (0.65 g, 30%) is isolated by chromatography [ethyl acetate/cyclohexane 1:3 (v:v)] and recrystallized from ethanol. R_f (**5**) 0.51; mp. 189 °C; $[\alpha]_D^{20}$ +23.9° (c 1.1, $CHCl_3$).

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9. Due to solvent dependance of the chemical shift, representative values for F-2 signals are given:
a) $MeCN/D_2O$: **6** (-203.2 ppm); **7a** (-205.7 and 205.9 ppm); **7d** (-204.8 and-205.0 ppm);
b) $MeNO_2/CD_3OD$: **6** (-203.1 ppm); **7b** (-206.3 and -207.9 ppm);
c) $MeNO_2$: **6** (-205.1 ppm); **7c** (-212.2 ppm);
d) DMF/ D_2O: **6** (-204.3 ppm); **7a** (-205.6 and 205.9 ppm); **7e** (-208.1 and -208.8 ppm).
Characteristic sets of coupling-constants are: *46/25/10 Hz* (**6**); *50/10/3 Hz* (α-anomer of **7a, b, d** and **e**); *52/13/4 Hz* (β–anomer of **7a, b, d** and **e**) and *50/20/12 Hz* (**7c**); $J < 8$ Hz in most cases not resolved.
10. The structure of the β-anomer was verified by independent synthesis starting from **8a** by means of reduction followed by *N*-acetylation.
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13. ^{19}F NMR data: δ -206.6 ppm (*J 47* and *25 Hz*) -150.2 ppm (BF_4^-); $^4C_1$-conformer.
14. ^{19}F NMR data: δ -204.6 ppm (*J 49* and *8 Hz*); δ -204.1 ppm (*J 51* and *12 Hz*); both anomers in „normal“ $_4C^1$-conformation. *O*-Acetylation gave 1,3,4-tri-*O*-acetyl-2-deoxy-2-fluoro-D-arabinopyranose (**12d**); for data see: M. Bols, I. Lundt, *Acta Chem. Scand.* **1990**, *44*, 252-256.
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16. ^{19}F NMR data: δ –202.4 ppm (*J 50* and *13 Hz*).
17. ^{19}F NMR data and relative proportions (%) for products formed from the reaction of tri-*O*-acetyl-D-glucal in Me_2CO/D_2O:
δ –199.0 ppm (*J 50* and *13 Hz*) and -199.8 ppm (*J 49* and *11 Hz*); 2-F-Glc-OH, 29.3%.
δ -203.5 ppm (*J 50* and *30 Hz*) and -221.6 ppm (*J 50, 30* and *20 Hz*); 2-F-Man-OH; 42.7%.
δ -201.3 ppm (*J 48, 24* and *10 Hz*); $_4C^1$-conformer of the (2-F-Glc)-intermediate; 14.9%.
δ -213.7 ppm (*J 50, 30* and *20 Hz*); $^4C_1$-conformer of the (2-F-Man)-intermediate; 13.2%.
18. These results will be published elsewhere.
19. ^{19}F NMR data: δ -188.1 ppm (*J 45* and *18 Hz*) and -207.8 ppm (*J 45 Hz*); rel. intensities 1:3.
20. a) *N*-Iodo- and *N*-bromopyridinium compounds add to glycals under formation of products with 1,2-*trans*-diaxial arranged substituents (Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2205-2213); see also „halogenoglycosyloxylation“ (*e.g.* Thiem, J.; Klaffke, W. *J. Org. Chem.* **1988**, *54*, 2006-2009) and „halogenosulphamidation/sulphamidoglycosyloxylation“ (Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 5811-5819); b) for the reaction with *N*-fluoropyridinium compounds see ref. 6; c) product **5** from these experiments shows 1,2-*trans*-diequatorial grouping.
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22. Syrupy **8b**, containing minor impurities, was obtained in 51% yield.