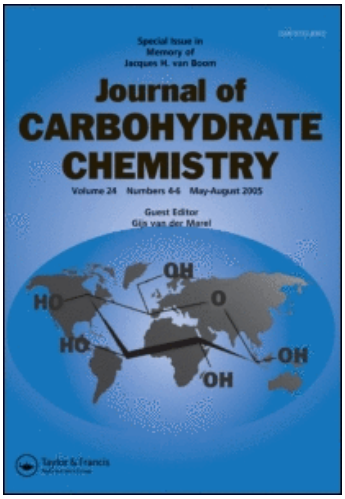

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STUDIES ON THE REACTION OF D-GLUCAL AND ITS DERIVATIVES WITH 1-CHLOROMETHYL-4-FLUORO-1,4-DIAZONIABICYCLO[2.2.2]OCTANE SALTS

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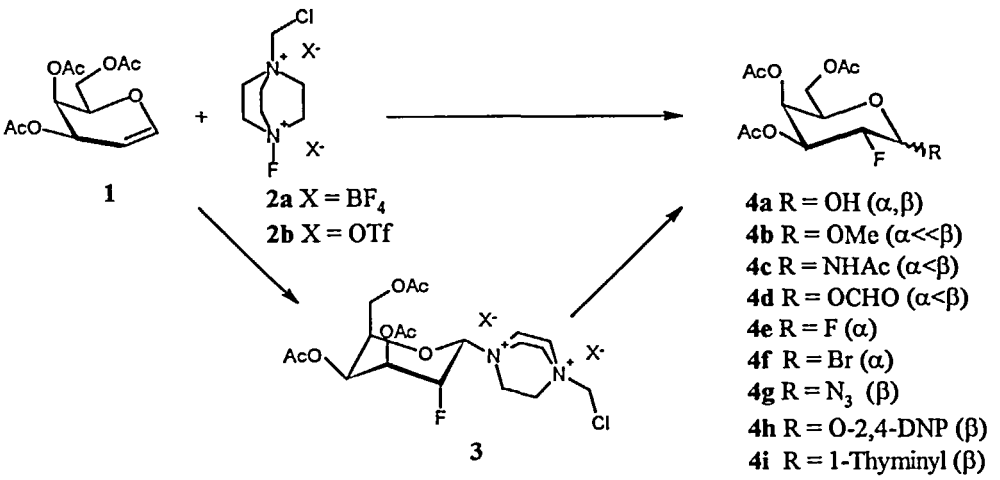
ABSTRACT

The reaction of D-glucal and its derivatives with the electrophilic *N*-F-fluorination reagents F-TEDA tetrafluoroborate and triflate was studied by means of ^{19}F NMR spectroscopy. In all cases mixtures of 2-deoxy-2-fluoro-D-gluco- and -D-mannopyranose derivatives were formed, the ratio of which was dependent on the nature of the *O*-protecting groups. Concerning the products arising from the direct addition of reagents across the double bond, the D-*gluco*-configured compounds (**13-20**) generally showed higher hydrolysis rates than their D-*manno*-counterparts (**21-28**). Product separation was only achieved when single anomers (e.g., 2,4-dinitrophenyl glycosides **29e/37e** and disaccharidic fluorides **35d/43d**) or per-*O*-acetates (e.g. **29f/37f**) were formed.

INTRODUCTION

As we described recently,[1] treatment of 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*lyxo*-hex-1-enitol (tri-*O*-acetyl-D-galactal, **1**) with 1-chloromethyl-4-fluoro-1,4-diazonia-bicyclo[2.2.2]octane bis(tetrafluoroborate)[2] (Selectfluor™, F-TEDA-BF_4, **2a**) exclusively[3] led to derivatives of 2-deoxy-2-fluoro-D-galactopyranose (Scheme 1).



Scheme 1

This reaction was monitored by ^{19}F NMR at room temperature employing a number of solvents. In all cases 1-(3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α-D-galactopyranosyl)-4-chloromethyl-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (**3**) was found to be the predominant product. Simultaneously, products **4a-e**, arising from participation of solvent (water, methanol, acetonitrile or *N,N*-dimethylformamide) and fluoride (originating from counterion tetrafluoroborate[4]) were generated. From compound **3**, useful derivatives of 2-deoxy-2-fluoro-D-galactopyranose, *e.g.*, products **4f-i**, were obtained in good yields by subsequent treatment with the appropriate nucleophiles.

RESULTS AND DISCUSSION

When studying the reaction[3] of 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (tri-*O*-acetyl-D-glucal, **5**) with **2a** under a number of conditions, simultaneous formation of analogous products from the 2-deoxy-2-fluoro-D-*gluco*- (**13/29**) as well as the -D-*manno*-series (**21/37**) was evident from the number of signals and their respective sets of splittings observed in the non-decoupled ^{19}F NMR spectra. The results obtained with 1.2 equivalents of **2a** in systems containing nitromethane[5] or acetone, after 15 h at room temperature, are given in Table 1.

Table 1. ^{19}F NMR Data and Product Ratios [%] from the Reaction[a] of **5** with **2a** in Various Solvents

	$J_{F,H\text{-}1/H\text{-}2/H\text{-}3}$	CH_3NO_2		CH_3NO_2/D_2O (5:1)		Acetone/ D_2O (5:1)	
Product	[Hz]	δ [ppm]	Ratio[%]	δ [ppm]	Ratio[%]	δ [ppm]	Ratio[%]
13	27/47/10	-203.3	32	-199.4	21	-201.3	15
29aα	[b]/49/10			-197.9	7	-199.8	10
29aβ	[b]/50/12			-197.3	11	-199.0	19
29d [c]	[b]/49/10	-205.7	14				
21	20/50/30	-215.1	33	-211.8	26	-213.7	13
37aα	[b]/50/25			-201.6	22	-203.5	40
37aβ	20/50/30			-219.5	9	-221.6	3
37d [c]	[b]/50/25	-208.8	19				
[d]			46:52:2		41:59:0		44:56:0 [e]

a. After 15 h at room temperature.
b. Couplings smaller than 8 *Hz* are usually not resolved in these media.
c. $J_{F\text{-}1,F\text{-}2}$ 20 Hz.
d. Ratio D-*gluco*:D-*manno*:sum of unidentified fluorinated carbohydrates.
e. Fluoroacetone (δ -226.9 ppm, *J* 47 and 47 Hz) was formed additionally.

As observed with the D-galactal analogue,[1] this reaction was also subject to the participation of nucleophilic, aprotic solvents. Consequently, acetonitrile caused the appearance of *N*-acetyl glycopyranosylamines (**29b/37b**) and *N,N*-dimethylformamide gave rise to the formation of 1-*O*-formyl glycopyranoses (**29c/37c**). The latter observation is illustrated in Figure 1 showing the spectra obtained from the reaction of tri-*O*-benzyl-D-glucal **6** with **2a** in *N,N*-dimethylformamide/water (5:1).

In these experiments employing **5** or **6**, the ratio of D-*gluco*- to D-*manno*-configured products was dependent on the solvent system used (see Table 1) as well as on the substrate concentration.[6]

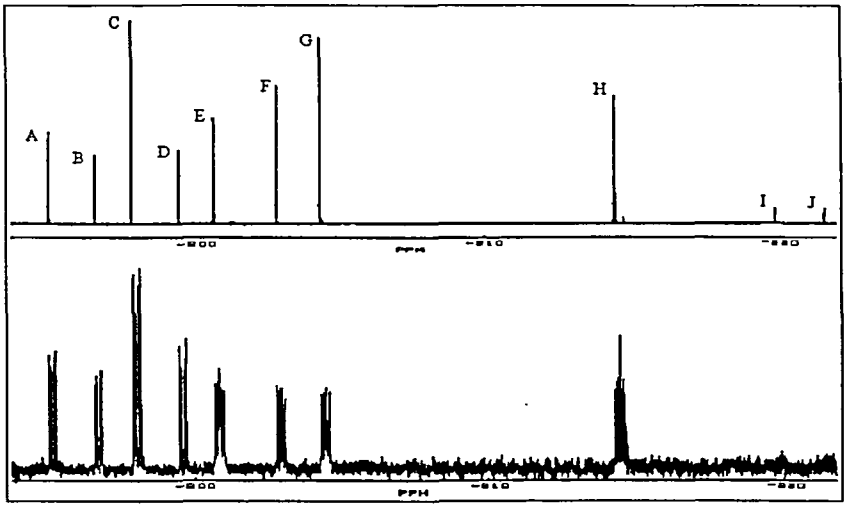
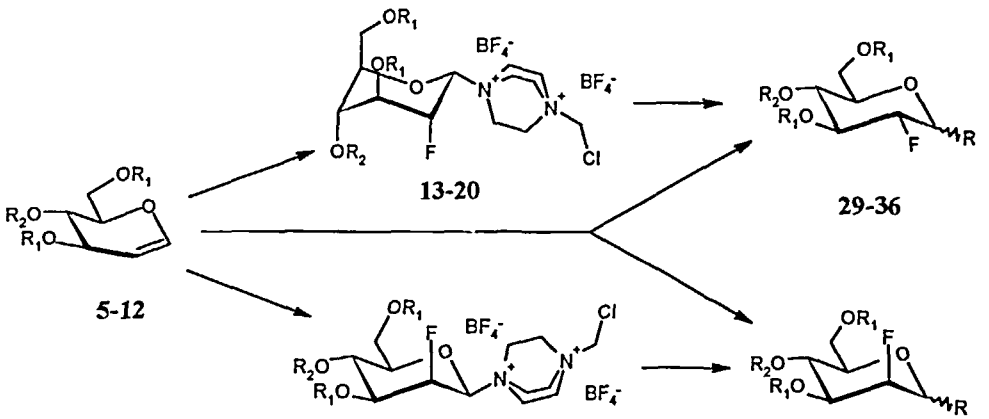


Figure 1. ^{19}F NMR Spectra from the reaction of glucal **6** with **2a** in *N,N*-dimethylformamide/D_2O (3:1) after 15 h at room temperature [proton decoupled mode (above), undecoupled (below)]. Signal-structure correlation: A = **30aβ**, B = **30aα**, C = **30cβ**, D = **30cα**, E = **14**, F = **38aα**, G = **38cα**, H = **22**, I = **38aβ**, J = **38cβ**.

The nature of the *O*-protecting group had a marked effect upon D-*gluco*:D-*manno* ratios. While reactions starting from **5** led to D-*gluco*:D-*manno* ratios ranging from 0.7 to 0.9, **6** afforded products in a ratio of 1.0 to 1.5. The latter finding was supported by the fact that tri-*O*-benzoyl- (**7**) and tri-*O*-pivaloyl-D-glucal (**8**), when analogously treated with **2a** in nitromethane/deuterium oxide (5:1), formed products with D-*gluco*:D-*manno* ratios of 1.7 (from **7**) and 4.2 (from **8**), respectively. The reaction of unprotected D-glucal **9** under the same conditions displayed a D-*gluco*:D-*manno* stereoselection of 0.9. In the absence of water - besides the glycosyl fluorides **33d** and **41d** - 1,6-anhydro-2-deoxy-2-fluoro-β-D-gluco- (**46**) as well as -D-mannopyranose (**47**) were formed[7] in low yields with a D-*gluco*:D-*manno* ratio of 0.3.

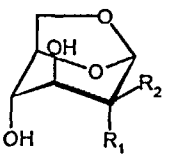
In the D-*galacto*-series,[1] hydrolysis of addition product **3** to the 2-deoxy-2-fluoro sugar **4a** was achieved by heating to reflux for a period of 30 min. To monitor the respective transformation of compounds **13** (into **29a**) and **21** (into **37a**), the reaction mixture of **5** with **2a** in nitromethane/deuterium oxide (5:1) - after quantitative consumption of the starting material at room temperature (Table 1) - was heated to 75 °C.



5 ,13, 21, 29, 37 $R^1 = R^2 = Ac$
6, 14, 22, 30, 38 $R^1 = R^2 = Bn$
7, 15, 23, 31, 39 $R^1 = R^2 = Bz$
8, 16, 24, 32, 40 $R^1 = R^2 = Piv$
9, 17, 25, 33, 41 $R^1 = R^2 = H$
10, 18, 26, 34, 42 $R^1 = Ac$, $R^2 = \alpha$-D-Glc (Ac)
11, 19, 27, 35, 43 $R^1 = Ac$, $R^2 = \beta$-D-Glc (Ac)
12, 20, 28, 36, 44 $R^1 = Ac$, $R^2 = \beta$-D-Gal (Ac)

a R = OH
b R = NHAc
c R = OCHO
d R = F (α)
e R = O-2,4-DNP

Scheme 2



46 $R_1 = F$, $R_2 = H$
47 $R_1 = H$, $R_2 = F$

Samples were taken at 10, 30 and 50 min intervals. After cooling to room temperature and homogenation by addition of *N,N*-dimethylformamide, sample composition was determined by ^{19}F NMR spectroscopy. As can be seen from Figure 2, compound **13** [$_4C^1$-conformation] was rapidly hydrolyzed, whereas **21** [$^4C_1$-conformation] remained almost unaffected. Furthermore, from the time-independent D-*gluco*:D-*manno* ratio, a possible epimerization could be excluded.

This finding initiated experiments to synthesize pure derivatives of 2-deoxy-2-fluoro-D-gluco- as well as -D-mannopyranose by means of kinetically controlled hydrolysis

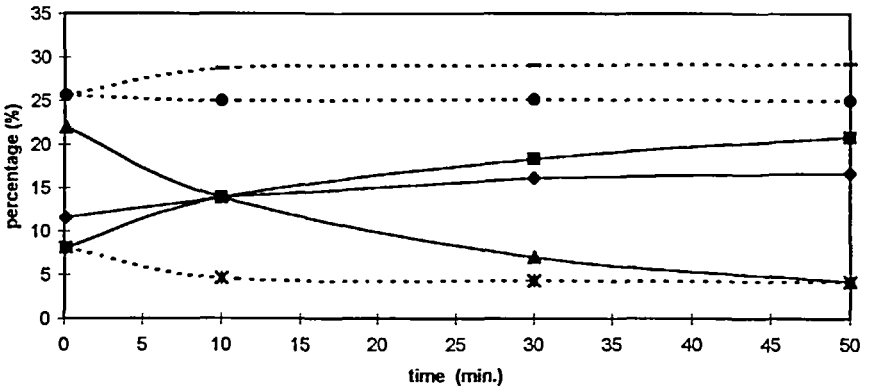


Figure 2. Changes in the product composition, as determined by ^{19}F NMR spectroscopy, on heating to 75 °C of the reaction mixture obtained from glucal **5** and **2a** in nitromethane / D_2O (5:1) after 15 h at room temperature. Structure indication: D-*gluco*: ▲ = **13**, ■ = **29a**α, ◆ = **29a**β; D-*manno*: ● = **21**, – = **37a**α, ∗ = **37a**β.

of the direct addition products (type **13** and **21**). Consequently, the D-glucal derivatives **5-12**, including those derived from disaccharides maltose, cellobiose and lactose, were treated with 1.2 equivalents of **2a** in nitromethane/deuterium oxide (5:1) at room temperature with vigorous stirring. After 15 h, the respective (*initial*) ratios of products formed were determined by ^{19}F NMR spectroscopy; then the reaction mixtures were heated to 85-90 °C for 30 min and their (*final*) product ratios recorded. As evident from Table 2, especially when comparing the data listed in column 2 with those in column 4, pure D-*manno*-derivatives seemed to be attainable[8]. An exception to this is the *O*-benzyl protected representative **6**, where addition products **14** and **22** were obviously hydrolysed much faster. Finally, the mixtures of the respective 2-deoxy-2-fluoro-sugars **29a-44a** were separated (Table 2, columns 6-8) from unhydrolyzed polar products **21** and **23-28** by removal of solvent and crude[9] silica gel filtration. From these intermediates, 2-deoxy-2-fluoro-D-mannopyranose derivatives were only formed very slowly by boiling in the presence of water.

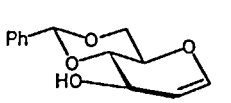
These results differed considerably from the clear-cut stereoselectivity observed in the analogous reaction starting from derivatives of D-galactal and D-arabinal.[1] To take advantage of the energetic discrimination between the transition states leading to D-*gluco*-

Table 2. Ratios [%] of Products[a] from the Reaction of Glycals **5-12** with **2a** in Nitromethane/Water (5:1) as Determined by ^{19}F NMR Spectroscopy

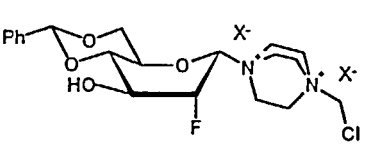
	Final [c] and (in parentheses) *initial* [b] percentage from reaction monitoring				Yield and percentage of isolated unpolar products		
	D-*gluco*-series		D-*manno*-series		yield	D-*gluco*	D-*manno*
	13-20	**29a-36a**	**21-28**	**37a-44a**	[%]	**29a-36a**	**37a-44a**
5	0 (21)	41 (20)	26 (26)	33 (33)	61	56	44
6	0 (28)	50 (22)	0 (31)	50 (19)	93	51	49
7	0 (35)	63 (28)	17 (18)	20 (19)	74	80	20
8	0 (45)	81 (36)	8 (8)	11 (11)	85	90	10
9	2 (8)	41 (36)	15 (15)	39 (39)	43[d]	67[d]	33[d]
10	0 (29)	55 (26)	20 (22)	25 (23)	66	62	38
11	0 (32)	65 (33)	17 (17)	18 (18)	75	80	20
12	0 (31)	64 (33)	16 (18)	20 (18)	65	78	22

a. Since the ratios of anomers within the groups **29a-36a** and **37a-44a** are time-dependant, sums are given only. Occasionally and in small proportions, fluorides **29d-44d** as well as other, yet unidentified structures, were formed and are omitted here.
b. *Initial*: after 15 h at room temperature.
c. *Final*: conditions as in [b] plus 30 min at 85-90 °C.
d. Isolated as per-*O*-acetates **29f/37f**.

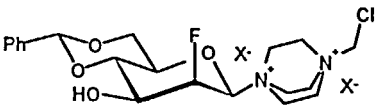
(type **13**) vs. D-*manno*-configured structures (type **21**), we studied the same reaction starting from conformationally more rigid 4,6-*O*-benzylidene-D-glucal (**48**) with **2a** as well as **2b**. After 15 h at room temperature, two main[10] products were formed, for which - on the basis of their ^{19}F NMR data - structures **49** [δ -187.5 ppm; *J* 49, 26 and 22 *Hz;* unusual boat conformation] and **50** [δ -216 ppm; *J* 51, 27 and 24 *Hz*, normal $^4C_1$-conformation] were deduced. By heating with water to 75 °C for 75 min[11], compound **49** was quantitatively transformed into **33a** (α:β 2:3), whereas **50** gave a 3:2 mixture of **41a** (α:β 5:2) and **17** (by simple de-*O*-benzylidenation).



48



49



50

In summary, the original conclusions drawn[1] from the reaction of D-galactal derivatives with F-TEDA salts concerning the mechanism has now been extended to include the influence of solvent and protecting group on stereoselectivity and hydrolysis rates of $_4C^1$- vs. $^4C_1$-conformed addition products. Furthermore, from reactions starting with unprotected D-glucal or rigid derivatives thereof, intramolecular participation of OH-6 and formation of boat conformed addition products, respectively, have also been found.

In the case of reaction products **29a-44a**, chromatographic separation of the respective D-*gluco*- from the D-*manno*-configured counterpart (each being present as anomeric mixture) failed. Therefore we looked for chromatographically separable derivatives, especially those in demand for studies of enzymatic glycosylation reactions. Initially, products formed as single anomers, such as the α-configured disaccharidic glycosyl fluorides **35d/43d** or the 1,2-*trans*-configured 2,4-dinitrophenyl glycosides **29e/37e**, were found to be separable by chromatography and fractional crystallization, respectively. Furthermore, pure 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-D-gluco- **(29f)** and -D-mannopyranose **(37f)** were chromatographically isolated from the mixture obtained by acetylation of **29a/37a** or **33a/40a**.

From all products isolated, ^{19}F, ^{13}C and ^1H NMR spectra were recorded. However, due to signal crowding, complete interpretation was not possible in those cases where inseparable mixtures of epimers and/or anomers (as well as disaccharidic structures) had been obtained. This was also found to be the case with most of the β-D-*manno* configured products, which were formed in minor proportions only. The data obtained which are not yet reported[12] (or not in agreement with those previously published) are collected in Tables 3-8.

EXPERIMENTAL

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

Table 3. ^{19}F NMR Data of Isolated Products[a]

Product	δ_{F2}	$J_{F2\text{-}H1}$	$J_{F2\text{-}H2}$	$J_{F2\text{-}H3}$	Product	δ_{F2}	$J_{F2\text{-}H1}$	$J_{F2\text{-}H2}$	$J_{F2\text{-}H3}$
13	-202.0	28.1	45.8	10.3	**21**	-214.5	21.2	51.6	30.1
29aα	-200.3		49.7	12.0	**37aα**	-204.6	6.8	50.0	29.6
29aβ	-199.7	2.6	50.9	14.3	**37aβ**	-223.1	(19)	(52)	(27)
30aα	-197.8		49.5	12.5	**38aα**	-204.7	7.0	49.8	29.5
30aβ	-195.7		51.1	14.6	**38aβ**	-222.9	18.2	50.9	29.4
31aα	-200.0		49.8	11.3	**39aα**	-204.9	6.4	50.0	28.3
31aβ	-199.3		51.9	13.3	**39aβ**				
32aα	-201.2		49.6	11.5	**40aα**	-205.8	7	50	28
32aβ	-200.7		51.0	13.6	**40aβ**				
33aα	-199.6		48.6	13.1	**41aα**	-204.9	7	49.3	31.1
33aβ	-199.5		51.5	13.6	**41aβ**				
34aα	-200.3	0	49.6	10.9	**42aα**	-205.3	6.8	50.0	28.3
34aβ	-201.1	0	50.6	13.1	**42aβ**	-223.6	(20)	(50)	(30)
35aα	-199.7	0	49.6	12.0	**43aα**	-204.3	6.8	49.8	29.2
35aβ	-199.1	2.0	51.0	14.0	**43aβ**				
36aα	-199.6	0	49.8	11.9	**44aα**	-204.3	6.6	49.9	29.0
36aβ	-199.0	0	51.8	14.0	**44aβ**				
29eβ	-199.0	3.7	49.9	14.8	**37eα**	-205.7	5.8	48.5	29.0
35eβ	-197.5	3.4	49.3	15.7	**43eα**				
29fα	-202.6	0	48.6	12.2	**37fα**	-204.2	8.5	49.7	27.6
29fβ	-201-2	3.1	50.8	14.4	**37fβ**	-220.0	19.0	51.1	27.0
46	-188.1	0	45	18	**47**	-207.8	0	45	0

a. 1,2-Difluorides are not included.

Table 4. ^{19}F NMR Data of 2-Deoxy-2-fluoro-D-glycosyl Fluorides

	δ_{F1}	$J_{F1\text{-}H1}$	$J_{F1\text{-}H2}$	$J_{F1\text{-}H5}$	δ_{F2}	$J_{F2\text{-}H1}$	$J_{F2\text{-}H2}$	$J_{F2\text{-}H3}$	$J_{F1\text{-}F2}$
29dα	-151.5	52	23		-204.5		47	13	20
30dα	-150.6	54	24		-201.7		48	13	20
31dα	-150.6	53	24		-203.9		48	12	19
32dα	-151.0	53	24		-205.2		48	11	19
33dα	-149.9	54	24		-204.1		48	13	20
34dα	-151.0	53	24		-205.3		48	11	19
35dα	-151.1	54	25		-203.9		47	11	18
36dα	-151.1	52	24		-203.9		48	12	19
37dα	-144.1	49			-207.7		48	27	20
38dα	-143.1	49		2	-207.4	3	48	28	20
39dα	-143.3	49			-207.8	3	48	28	20
40dα	-144.1	49			-208.3	3	49	26	20
42dα	-144.1	49			-208.2	2	49	26	20
44dα	-143.3	49			-207.2		47	27	20

Table 5. ^{13}C NMR Data of *O*-1 Unprotected Products

	C-1 $J_{C1\text{-}F2}$	**C-2** $J_{C2\text{-}F2}$	**C-3** $J_{C3\text{-}F2}$	**C-4** $J_{C4\text{-}F2}$	**C-5**	**C-6**	**others**
13	91.0 (14.4)		69.0 (29.5)	67.3	78.6	61.7	TEDA 49.8, 50.3 CH_2Cl 69.9
29 aα	90.1 (21.3)	87.8 (193.1)	70.6 (19.4)	68.1 (7.0)	67.1	62.0	
29 aβ	94.6 (22.9)	90.5 (190.2)	72.8 (19.6)	68.2 (7.8)	71.9	62.0	
30 aα	90.6 (21.3)	91.7 (190.3)	80.3 (16.3)	n.r.	71.1	68.7	

Table 5. Continued

30 aβ	94.6 (23)	94.4 (185)	83.3 (17)	n.r.	n.r.	69.9	
31 aα	90.5 (21.4)	88.3 (194.3)	70.8 (19.2)	69.0 (7.3)	67.7	62.8	
31 aβ	95.0 (22.5	91.0 (190.5)	73.0 (19.8)	69.2 (8)	72.3	63.1	
32 aα	90.2 (21.1)	88.3 (193.2)	70.1 (19.1)	67.1 (7.2)	67.7	61.7	
32 aβ	94.7 (22.9)	91.0 (190.3)	72.4 (19.6)	67.3 (n.r.)	72.5	61.7	
33 aα	90.7 (21.3)	91.3 (185.4)	72.1 (17)	70.2 (8.6)	72.2	61.4	
33 aβ	94.7 (22.5)	94.0 (183.0)	75.0 (17.1)	70.3 (8.7)	77.0	61.6	
34 aα	89.8 (21.2)	88.5 (193.9)			n.r.		
34 aβ	94.2 (23.1)	91.1 (190)			n.r.		
36 aα	89.9 (21.5)	88.2 (192.5)			n.r.		
36 aβ	94.3 (22.8)	90.8 (190.0)			n.r.		
21	92.7 (15.2)	86.0 (189.2)	70.8 (17.1)	65.4	76.7	62.2	TEDA 50.9, 51.3 CH_2Cl 70.2
37 aα	91.7 (29.2)	87.5 (179.0)	69.7 (16.6)	66.0	68.3	62.4	
38 aα	92.0 (29.6)	87.1 (175.8)	78.2 (17.2)	n.r.	72.2	69.3	
39 aα	92.1 (29.3)	87.6 (179.5)	70.5 (16.7)	66.8	68.8	63.2	
41 aα	92.9 (28.6)	91.4 (173.4)	69.7 (17.5)	67.2	71.9	60.8	
41 aβ	93.4 (15.8)	911.9 (179.9)	72.1 (17)	66.9 (2)	76.0	60.9	
42 aα	91.4 (28.9)	87.1 (177.1)			n.r.		
43 aα	91.7 (29.6)	88.0 (177.2)	69.4 (16.5)	74.0	69.3	62.1	100.9, 71.7, 73.0, 68.0, 71.8, 61.8
44 aα	91.5 (28.8)	87.9 (177.4)			n.r.		

Table 6. ^{13}C NMR Data of Products Substituted at C-1 Other than OH

	C-1 J_{C1-F1},J_{C1-F2}	C-2 J_{C2-F1},J_{C2-F2}	C-3 J_{C3-F2}	C-4 J_{C4-F2}	C-5 J_{C5-F1}	C-6	others
29	103.7	87.0	70.0	66.9	70.0	61.3	
dα	(231.4, 23.2)	(26.0, 195.2)	(19.6)	(7.8)	(4)		
30	104.5	90.9		n.r.			
dα	(228.0, 23.9)	(26.3, 192.0)					
31	103.7	87.4	70.0	67.8	70.3	62.1	
dα	(230, 24)	(26, 196)	(20)	(8)			
32	103.6	87.5	69.5	66.1	70.4	61.0	
dα	(231.3, 23.2)	(26.0, 195.3)	(19.4)	(7.7)	(4.1)		
33	106.0	91.3	72.7	70.1	76.2	61.8	
dα	(226.0, 23.8)	(26.0, 188.7)	(17.3)	(8.2)	(3.1)		
35	103.4	87.2	69.2	74.9	70.7	61.1	100.4, 71.6,
dα	(231.1, 23.1)	(26.0, 195.)	(19.2)	(7.3)	(4.1)		72.0, 67.8, 72.9, 61.6
36	103.4	87.3	69.4	74.6	70.7	61.3	100.7, 69.1,
dα	(230.8, 22.4)	(25.8, 195.1)	(19.2)	(7.7)	(2.8)		70.8, 66.7, 71.0, 60.9
37	104.4	85.2	69.2	64.9	71.2	61.7	
dα	(222.3, 30.6)	(42.3, 180.8)	(16.5)				
38	105.0	85.1		n.r.			
dα	(219.3, 31.4)	(42.1, 177.8)					
44	104.4	85.4	69.0	72.7	71.5	61.5	101.1, 69.1,
dα	(222.0, 31.5)	(41.7, 179.1)	(15)		(2.4)		70.7, 66.7, 71.0, 61.0
29	98.4	88.5	71.8	67.4	72.8	61.6	
eβ	(-, 25.2)	(-, 193.0)	(20.7)	(7.1)			
35	97.9	88.7	71.7	75.3	72.8	61.6	100.8, 71.6,
eβ	(-, 26.1)	(-, 191.7)	(21.1)	(6.4)			73.3, 67.8, 72.2, 61.4
37	96.4	85.8	69.1	64.8	70.9	61.5	
eα	(-, 31.8)	(-, 181.5)	(16.7)				
29	88.4	86.2	70.6	67.4	69.6	61.4	
fα	(-, 20.2)	(-, 193.8)	(19.8)	(8)			
29	91.3	88.2	72.7	67.6	72.8	61.4	
fβ	(-, 24.2)	(-, 192.3)	(22.6)	(7.4)			

Table 6. Continued

46	98.5	87.7	70.1	69.8	76.2	65.0
	(-, 29.1)	(-, 177.8)	(18.4)	(5.9)		
47	98.7	85.8	69.1	72.3	76.1	65.0
	(-, 27.3)	(-, 185.8)	(15.1)	(3.6)		
35	88.4	86.5		n.r.		
fα	(-, 22.2)	(-, 181.5)				
35	91.2	88.4		n.r.		
fβ	(-, 24.3)	(-, 191.9)				
43	90.0	86.2		n.r.		
fα	(-, 31.7)	(-, 178.5)				

Table 7. ^{1}H NMR Data of *O*-1 Unprotected Products

	δ H-1 ($J_{H1\text{-}F}$, $J_{H1\text{-}H2}$)	δ H-2 ($J_{H2\text{-}F}$, $J_{H2\text{-}H3}$,)	δ H-3 ($J_{H3\text{-}F}$, $J_{H3\text{-}H4}$)	δ H-4 ($J_{H4\text{-}F}$, $J_{H4\text{-}H5}$)	δ H-5 ($J_{H5\text{-}H6a}$, $J_{H5\text{-}H6b}$)	δ H-6a ($J_{H6a\text{-}H6b}$)	δ H-6b	others
29	5.43	4.47	5.55	4.99		4.0-4.3		
aα	(0, 3.7)	(49.4, 9.5)	(11.9, 9.5)	(-, 9.9)		n.r.		
29	4.88	n.r.	n.r.	4.99	3.74		4.0-4.3	
aβ	n.r.			(0, 10.0)	(4.5, 2.5)		n.r.	
31	5.60	4.73	6.14	5.67		4.35-4.7		
aα	(0, 3.6)	(51.9, 9.5)	(11.4, 9.7)	(0, 9.7)		n.r.		
32	5.44	4.46	5.61	5.08		4.0-4.4		
aα	(0, 3.6)	(49.7, 9.6)	(11.7, 9.6)	(0, 9.9)		n.r.		
32	4.89	n.r.	5.34	5.08	3.76		4.0-4.4	
aβ	(2.8, 7.9)		(13.7, 9.5)	(0, 9.9)	(4.3, 1.8)		n.r.	
33	5.38	4.35			3.35-3.85			
aα	(0, 3.9)	(49.4, 9.4)			n.r.			
33	4.84	4.03			3.35-3.85			
aβ	(2.3, 7.8)	(51.1, 9.0)			n.r.			
34	5.53	n.r.	5.63			n.r.		
aα	(0, 3.9)		(11, 10)					
35	5.39	n.r.	5.54			n.r.		
aα	(0, 3.7)		(11.9, 9.4)					

(continued)

Table 7. Continued

36 aα	5.33 (0, 3.4)	n.r.	5.50 (11.5, 10)			n.r.	
37 aα	n.r.	4.75 (49.9, 2.0)			n.r.		
38 aα	5.33 (7.0, 1.7)			n.r.			
39 aα	n.r.	5.03 (51.8,. 2.2)			n.r.		
41 aα	5.33 (7.3, 1.7)	4.67 (49.8, 1.7)			3.4-4.0 n.r.		
41 aβ	4.97 (20.5, 0)	4.73 (51.3, 2.3)			3.4-4.0 n.r.		
43 aα	5.31 (7.1, 2.2)	4.74 (50.0, 2.4)	5.32 (29.3, 9.2)	n.r.		4.0-4.2 n.r.	

Table 8. ^{1}H NMR Data of Products Substituted at C-1 Other than OH

	δ H-1 (J_{H1-F1}, J_{H1-F2}, J_{H1-H2})	δ H-2 (J_{H2-F1} J_{H2-F2} J_{H2-H3},)	δ H-3 (J_{H3-F2}, J_{H3-H4})	δ H-4 (J_{H4-F2} J_{H4-H5})	δ H-5 (J_{H5-F1} J_{H5-H6a}, J_{H5-H6b})	δ H-6a ($J_{H6a-H6b}$)	δ H-6b	others
29 dα	5.79 (52.7 0 2.8)	4.53 (23.7 48.0 9.5)	5.54 (12.3 9.7)	5.08 (0 9.7)		4.05-4.33 n.r.		
32 dα	5.80 (51.8 0 2.9)	4.53 (23.8 48.3 9.6)	5.60 (12.0 9.8)	5.14 (0 9.8)		4.05-4.25 n.r.		
33 dα	5.75 (54.2 0 2.9)	4.29 (24.3 48.3 9.4)	3.86 (13.6 9.2)	3.45 (0 9.2)		3.65-3.90 n.r.		
34 dα	5.74 (53.2, 0, 2.7)	4.36 (24, 48, 10)	5.63 (11.2, 9.5)		3.85-4.6 n.r.			

Table 8. Continued

35 dα	5.72 (53.1, 0, 2.7)	4.43 (23.6, 48.6, 9.8)	5.51 (12.1, 9.6)	3.76 (9.8)		4.45-4.6 n.r.	
36 dα	5.75 (52.9, 0, 2.6)	4.44 (24, 48, 10)	5.56 (12.0, 9.6)	3.81 (0, 9.6)		4.0-4.2 n.r.	
37 dα	5.76 (48.4 2 2)	4.89 (2 48.8 2)	5.25 (27.7 2.3)	5.40 (0 10.1)		4.05-4.35 n.r.	
42 dα	5.67 (48, 4, 2)	4.82 (0, 48.8, 2.2)			n.r.		
43 dα	5.62 (48.7, 3.9, 2.0)	4.84 (0, 49.1, 2.2)			n.r.		
44 dα	5.66 (48.7, 3.9,2.1)	4.85 (0,49.0, 2.4)	5.05-5.25 n.r.			n.r.	
29 eβ	5.44 (0, 3,4, 7.1)	4.69 (0, 49.8, 8.6)	5.43 (15.2, 9.4)	5.12 (0, 9.5)	4.00 (4.9, 2.8)	4.25 (12.5)	4.20
35 eβ	5.44 (0, 3.5, 7)	4.62 (0, 48.2, 7.5)	5.1-5.5 (n.r.)	3.85-3.95 (n.r.)		4.59 (12, n.r)	4.07 (n.r.)
37 eα	5.95 (0, 6.2, 1.9)	5.10 (0, 48.7, 2.5)	5.43 (29.1, 11.9, 9.4)	5.48 (n.r.)	4.05-4.15 (n.r.)	4.25 (12.8, 5.1)	4.05-4.15 (n.r.)
29 fα	6.41 (0, 0, 4.1)	4.65 (0, 48.5, 9.5)	5.55 (12.0, 9.7)	5.08 (0, 10.2)		4.0-4.3 n.r.	
29 fβ	5.78 (0, 3.1, 8.2)	4.44 (0, 50.8, 9.1)	5.37 (14.2, 9.3)	5.06 (10.1)	3.85 (4.6, 2.2)	4.29 (12.6)	4.10
37 fα	6.27 (0, 6.5, 2.1)	4.74 (0, 48.7, 2.4))	5.25 (27.3, 10.1	5.41 (1.1, 10.1)	4.05 (4.7, 2.4)	4.28 (12.7)	4.11
37 fβ	5.79 (0, 18.9)	4.86 (0, 51.1, 2.4)	5.05 (27.0, 9.9)	5.36 (1.0, 9.9)	3.80 (4.7, 2.4)	4.29 (12.5)	4.14

polarimeter at 589 nm at ambient temperature. NMR spectra were recorded at 300.13 or 200 MHz (^{1}H), 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 (^{1}H 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%). For column chromatography, silica gel 60, 230-400 mesh (Merck 9385) was used; eluent A: ethyl acetate/cyclohexane 1:3; B: ethyl acetate/cyclohexane 1:5; C: ethyl acetate/cyclohexane 1:1; D: chloroform/methanol 30:1. Microanalyses were carried out by the Institute of Physical Chemistry, University of Vienna.

Samples for ^{19}F NMR reaction monitoring were taken from the mixture of the respective glycal (0.15 mmol) and 1.2 equivalents **2a** (42 mg) or **2b** (56 mg) in the respective solvent system (2 mL). Prior to measurement, samples from reactions in neat CH_3NO_2 were mixed with $CDCl_3$ (as reference standard, 20 vol%) and those from CH_3NO_2 /D_2O were homogenated by the addition of DMF (20 vol%).

Glycals **5**, **10**, **11** and **12** were prepared from the corresponding per-*O*-acetylated glycopyranosyl bromides[13] by reduction with zinc dust and *N*-methylimidazole in refluxing ethyl acetate.[14] De-*O*-acetylation of **5** led to unprotected glucal **9**, from which educts **6**, **7** and **8** were obtained by *O*-protection. 4,6-*O*-Benzylidene-D-glucal **45** was donated by Chemprosa (Lannach, Austria). Fluorinating agent **2a** was bought from Aldrich; triflate salt **2b** from Manchester Organics (Manchester, GB).

Pairs of 3,4,6-*O*-Protected 2-Deoxy-2-fluoro-D-gluco- and -D-mannopyranoses 29a[15]/37a, 30a/38a, 31a/39a, 32a/40a, 34a/42a, 35a[16]/43a or 36a/44a: To a 10% solution of glucal **5**, **6**, **7**, **8**, **10**, **11** or **12** in nitromethane/water (5:1), **2a** (1.2 equivalents) was added with vigorous stirring at room temperature. After quantitative consumption of the starting material (generally overnight) the mixture was heated to reflux for 1 h. Subsequently, the solvent was removed under reduced pressure and the residue dissolved in dichloromethane. This was extracted with aqueous sodium hydrogen carbonate (5%). From the syrup obtained after concentration of the dried (Na_2SO_4) organic phase, the mixture of the respective *O*-1 unprotected 2-deoxy-2-fluoro-D-gluco- and -D-mannopyranose derivatives was isolated by chromatography using eluent A for products

from **5**, **7** and **8**; B for products from **6**; C for products from **10** and **12** or D for products from **11**. Yields and D-*gluco*:D-*manno* ratios are given in Table 2, columns 6-8.
R_f-Value (eluent C) for **29a/37a**: 0.32; for **30a/38a**: 0.61; for **31a/39a**: 0.55; for **32a/40a**: 0.68; for **34a/42a**, **35a/43a** and **36a/44a**: 0.15.

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-fluoro-D-gluco-[17] (29f) and -D-mannopyranose[17] (37f) were formed by acetylation of the crude reaction mixture **29a/37a** or **33a[17]/41a[17]** (obtained from **5** or **9** as described above) and were separated by chromatography using eluent A. Compound **29f** (α:β 2:1): 34 or 19%, R_f 0.55 (C); **37f** (α:β 2:3): 27 or 17%, R_f 0.50 (C).

1,6-Anhydro-2-deoxy-2-fluoro-β-D-gluco- (46) and -β-D-mannopyranose (47) were obtained from the reaction of **9** (197 mg, 1.37 mmol) with **2a** (620 mg, 1.76 mmol) in acetonitrile (8 mL) at room temperature overnight. From the residue obtained after concentration *in vacuo*, a 1:3-mixture (60 mg, 27 %) of **46** and **47** was separated by chromatography using dichloromethane/methanol (20:1) as eluent. R_f 0.30 (chloroform/methanol 9:1).

Pairs of 3,4,6-*O*-Protected 2-Deoxy-2-fluoro-α-D-gluco- and -α-D-mannopyranosyl Fluorides 29d[18]/37d[18], 30d/38d, 31d/39d and 32d/40d: Glucal **5**, **6**, **7** or **8** was treated as described above with **2a**, but using absolute nitromethane as the sole solvent. After quantitative consumption of the starting material, the mixture was heated to 50 °C for 1 h. Further work-up and chromatographic isolation was identical to that given above. The yield of the respective product mixture ranged between 25 and 45% with approximate D-*gluco*:D-*manno* ratios of 1:1 (**29d/37d**), 2:3 (**30d/38d**), 4:1 (**31d/39d**) and 10:1 (**32d/40d**). R_f value (C) for **29d/37d**: 0.60; for **30d/38d**: 0.75; for **31d/39d**: 0.66; for **32d/40d**: 0.77.

Within the corresponding pairs of disaccharidic 1,2-difluorides **34d/42d**, **35d/43d** and **36d/44d**, obtained from glycals **10**, **11** and **12**, respectively, differences in R_f-values (0.25 vs. 0.35, eluent C) made possible, at least in part, chromatographic separation. Thus **3,6-di-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-2-deoxy-2-fluoro-α-D-gluco-[15] (34d**, 11%, oil) and **-α-D-mannopyranosyl fluoride (42d**, 19%, oil), **3,6-di-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-2-deoxy-2-fluoro-α-D-gluco-[16] (35d**, 10%, white crystals) and **-α-D-mannopyranosyl fluoride (43d**, 16%, oil) as

well as **3,6-di-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-2-deoxy-2-fluoro-α-D-gluco- (36d**, 8%, oil) and **-α-D-mannopyranosyl fluoride (44d**, 13%, oil) were separated by chromatography (eluent C for products from **10** and **12**, eluent D for those from **11**).

35d: mp 183 °C, $[\alpha]_D^{20}$ +52.9 (*c* 1.05, chloroform).

Anal. Calcd for $C_{24}H_{32}F_2O_{15}$ (598.51): C, 48.16; H, 5.39; F, 6.35. Found: C, 48.38; H, 5.58; F, 6.16.

1-(3,4,6-Tri-*O*-acetyl-2-deoxy-2-fluoro-α-D-glucopyranosyl)- (13) and 1-(2,3,6-Tri-*O*-acetyl-2-deoxy-2-fluoro-β-D-mannopyranosyl)-4-chloromethyl-1,4-diazoniabicyclo[2.2.2]octane Bis(tetrafluoroborate) (21) were obtained, as a crude mixture, from the reaction of **5** with **2a** by following the protocol[1] for the isolation of the α-D-*galacto*-isomer. After separation of the reagent having delivered fluorine (by addition of ethyl acetate followed by filtration), evaporation of the solvent and dissolving of the residue in acetonitrile, the mixture of **13** and **21** was precipitated by the addition of ethyl acetate/cyclohexane and separated by centrifugation in 54 % yield.

2,4-Dinitrophenyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-fluoro-α-D-gluco-[15] (29e) and -α-D-mannopyranoside (37e). To the crude mixture of **13** and **21**, obtained by the procedure given above from the reaction of **5** (3.00 g, 11.0 mmol) and **2a** (4.20 g, 11.9 mmol) in absolute nitromethane (45 mL), nitromethane (50 mL) and potassium 2,4-dinitrophenolate (2.80 g, 12.6 mmol) were added. This mixture was heated to reflux for 1 h, then filtered and concentrated to dryness. A solution of the residue (dichloromethane, 80 mL) was extracted three times with aqueous sodium hydrogen carbonate solution (5%, 20 mL each) and dried (Na_2SO_4). From a hot solution of the residue in absolute ethanol crystals formed, which - after two further crystallizations from ethanol - consisted of pure **29e**: 0.99 g (19%), mp 147 °C, $[\alpha]_D^{20}$ +4.6 (*c* 0.94, chloroform), R_f 0.42 (C). From the original mother liquor, pure **37e** was obtained by further crystallizations: 0.88 g (17%), m.p. 217 °C, $[\alpha]_D^{20}$ +167 (*c* 0.97, chloroform), R_f 0.56 (C).

Anal. Calcd for $C_{18}H_{19}FN_2O_{12}$ (474.35): C, 45.58; H, 4.04; F, 4.01. Found for **29e**: C, 45.74; H, 4.11; F, 4.11. Found for **37e**: C, 45.83; H, 4.03; F, 3.95.

Reaction of 1,5-Anhydro-4,6-*O*-benzylidene-2-deoxy-D-*arabino*-hex-1-enitol (48) with 2a: A solution of **48** (150 mg, 0.64 mmol) and **2a** (250 mg, 0.71 mmol) in

absolute nitromethane (2.0 mL) was stirred overnight at room temperature. Water (0.2 mL) was then added and the mixture heated to 75 °C for 3 h. After evaporation of the solvents, the residue was acetylated according to a standard protocol. From the product mixture, **29f** (63 mg, 28%) and **37f** (57 mg, 25%) were isolated by chromatography using eluent A.

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REFERENCES AND NOTES

1. M. Albert, K. Dax and J. Ortner, *Tetrahedron*, **54**, 4839 (1998).
2. R. E. Banks, M. K. Besheesh, S. N. Mohialdin-Khaffaf and I. Sharif, *J. Chem. Soc., Perkin Trans. 1*, 2069 (1996).
3. Compare: M. D. Burkart, Z. Zhang, S.-C. Hung and C.-H. Wong, *J. Am. Chem. Soc.*, **119**, 11743 (1997).
4. This was proven by the reaction of **1** with the corresponding triflate salt **2b** (1-chloromethyl-4-fluoro-1,4-diazonia-bicyclo[2.2.2]octane ditriflate [ref. 2]) in nitromethane, where no D-galactopyranosyl fluoride **4e** was formed.
5. The system nitromethane/water is heterogeneous; during the reaction, vigorous stirring was maintained and, to effect homogenation, *N,N*-dimethylformamide was added before ^{19}F NMR measurements.
6. Only when conducting experiments with **5** and **2a** or **2b** in concentrations of approximately 10 % or more in pure acetonitrile or nitromethane, did an additional signal at δ -201.7 ppm with a relative intensity of 12 % appear. The non-decoupled mode disclosed - unprecedented in these studies - a broad doublet [*J* 44 *Hz*]. When applying the product isolation protocol (precipitation and chromatography) previously described [ref. 1], the new product was found - together with **13** and **21** - in the polar fraction.
7. Both products arose in the initial phase of the reaction and were not formed out of the respective addition products **17** and **25**.

8. The number given in column 4, Table 2, represents the maximum yield on pure D-*manno*-configured products obtained by this procedure. The 81:11-selectivity found with the nonpolar products from the reaction of the *O*-pivaloyl protected glucal **8** is of interest for the production of pure 2-deoxy-2-fluoro-D-glucose.
9. Therefore, total yields (column 6) and the respective percentage of D-*gluco*- and D-*manno*-configured products in the isolated mixtures (column 7 and 8) are given without any comment.
10. Depending on the reagent used, the reaction mixtures contained proportions of 4,6-*O*-benzylidene-2-deoxy-2-fluoro-α-D-gluco- [δ 205.5 ppm, *J* 48, 17, 17 Hz] and -α-D-mannopyranosyl fluoride [δ 209.5 ppm, *J* 47, 25, 20 Hz] and/or their analogues with an OH-group at C-1. In the course of the following hydrolysis reaction [ref. 11] they were transformed into the unprotected glycosyl fluorides **33d** and **41d** or - as **49** and **50** - into **33a** and **41a**.
11. These conditions have been found in previous experiments with methyl 4,6-*O*-benzylidene-α-D-glucopyranoside and **2a** or **2b** to quantitatively cleave the acetal group.
12. For a collection of relevant data see: R. Csuk and B. Glänzer, *Adv. Carbohydr. Chem. Biochem.*, **46**, 73 (1988) and references cited therein.
13. R. U. Lemieux, *Meth. Carbohydr. Chem.*, **2**, 221 (1963).
14. J. Broddefalk, U. Nilsson and J. Kihlberg, *J. Carbohydr. Chem.*, **13**, 129 (1994).
15. S. G. Withers, I. P. Street, P. Bird and D. H. Dolphin, *J. Am. Chem. Soc.*, **109**, 7530 (1987); L. A. Berven, D. Dolphin and S. G. Withers, *Can. J. Chem.*, **68**, 1859 (1990).
16. J. D. McCarter, M. J. Adam, C. Braun, M. Namchuk, D. Tull and S. G. Withers, *Carbohydr. Res.*, **249**, 77 (1993).
17. J. Adamson, A. B. Foster, L. D. Hall, R. N. Johnson and R. H. Hesse, *Carbohydr. Res.*, **15**, 351 (1970).
18. L. D. Hall, R. N. Johnson, J. Adamson and A. B. Foster, *Can. J. Chem.*, **49**, 118 (1971).