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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 ¹⁹F 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-Dlyxo-hex-1-enitol (tri-O-acetyl-D-galactal, 1) with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)² (SelectfluorTM, F-TEDA-BF₄, 2a) exclusively³ led to derivatives of 2-deoxy-2-fluoro-D-galactopyranose (Scheme 1).



Scheme 1

This reaction was monitored by ¹⁹F NMR at room temperature employing a number of solvents. In all cases $1-(3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-\alpha-D-galactopyranosyl)-4-chloromethyl-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (3) was found to be the predominant product. Simultaneously, products 4a-e, arising from participation of solvent (water, methanol, acetonitrile or$ *N,N*-dimethylformamide) and fluoride (originating from counterion tetrafluoroborate⁴) 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 reaction³ of 3,4,6-tri-O-acetyl-1,5-anhydro-2-deoxy-D-arabinohex-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 ¹⁹F NMR spectra. The results obtained with 1.2 equivalents of 2a in systems containing nitromethane⁵ or acetone, after 15 h at room temperature, are given in Table 1.

	$J_{\mathrm{F,H-1/H-2/H-3}}$	CH	3NO2	CH ₃ NO ₂ /	D ₂ O (5:1)	Acetone/	D ₂ O (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
29 aα	[b]/49/10			-197.9	7	-199.8	10
29a β	[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
37aa	[b]/50/25			- 201.6	22	-203.5	40
37a β	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]

Table 1.¹⁹F NMR Data and Product Ratios [%] from the Reaction* of 5with 2a in Various Solvents

a. After 15 h at room temperature.

b. Couplings smaller than 8 Hz are usually not resolved in these media.

c. J_{F-1, F-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-mannoconfigured products was dependent on the solvent system used (see Table 1) as well as on the substrate concentration.⁶



Figure 1. ¹⁹F NMR Spectra from the reaction of glucal 6 with 2a in N,N-dimethylformamide/D₂O (3:1) after 15 h at room temperature [proton decoupled mode (above), undecoupled (below)]. Signal-structure correlation: $A = 30a\beta$, $B = 30a\alpha$, $C = 30c\beta$, $D = 30c\alpha$, E = 14, $F = 38a\alpha$, $G = 38c\alpha$, H = 22, $I = 38a\beta$, $J = 38c\beta$.

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-2fluoro- β -D-gluco- (46) as well as -D-mannopyranose (47) were formed⁷ 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.







a R = OH

 $\mathbf{b} \mathbf{R} = \mathbf{NHAc}$

c R = OCHO

e R = 0.2, 4-DNP

 $dR = F(\alpha)$

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)





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 ¹⁹F 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-2fluoro-D-gluco- as well as -D-mannopyranose by means of kinetically controlled hydrolysis



Figure 2. Changes in the product composition, as determined by ¹⁹F NMR spectroscopy, on heating to 75 °C of the reaction mixture obtained from glucal 5 and 2a in nitromethane / D₂O (5:1) after 15 h at room temperature. Structure indication: D-gluco: $\blacktriangle = 13$, $\blacksquare = 29a\alpha$, $\blacklozenge = 29a\beta$; D-manno: $\blacklozenge = 21$, $- = 37a\alpha$, $\ast = 37a\beta$.

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 ¹⁹F 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 attainable⁸. 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 crude⁹ silica gel filtration. From these intermediates, 2-deoxy-2fluoro-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-

	Final [c] and (in par	rentheses) i	nitial [b]	Yield and	percentage	ofisolated	
	percen	tage from re	eaction mor	nitoring	unpolar products			
	D-gluc	o-series	D-mann	10-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	

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

 a. Since the ratios of anomers within the groups 29a-36a and 37a-44a are timedependant, 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 main¹⁰ products were formed, for which - on the basis of their ¹⁹F 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 ⁴C₁-conformation] were deduced. By heating with water to 75 °C for 75 min¹¹, 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).



In summary, the original conclusions drawn¹ 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 ${}_{4}C^{1}$ - vs. ${}^{4}C_{1}$ -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, ¹⁹F, ¹³C 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 reported¹² (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

Product	δ _{F2}	$J_{\rm F2-H1}$	$J_{ m F2-H2}$	J _{F2-H3}	Product	δ _{F2}	$J_{ m F2-H1}$	$J_{ m F2-H2}$	J _{F2-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
29a β	-199.7	2.6	50.9	14.3	37aβ	-223.1	(19)	(52)	(27)
30aa	-197.8		49.5	12.5	38aa	-204.7	7.0	49.8	29.5
30a β	-195.7		51.1	14.6	38a β	-222.9	18.2	50.9	29.4
31aa	-200.0		49.8	11.3	39aa	-204.9	6.4	50.0	28.3
31a β	-199.3		51.9	13.3	39a β				
32aα	-201.2		49.6	11.5	40aa	-205.8	7	50	28
32 aβ	-200.7		51.0	13.6	40a β				
33aα	-199.6		48.6	13.1	41aα	-204.9	7	49.3	31.1
33aβ	-199.5		51.5	13.6	41aß				
34aα	-200.3	0	49.6	10.9	42aα	-205.3	6.8	50.0	28.3
34 aβ	-201.1	0	50.6	13.1	42a β	-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	43a β				
36aα	-199.6	0	49.8	11.9	44aa	-204.3	6.6	49.9	29.0
36aβ	-199.0	0	51.8	14.0	44aβ				
29e β	-199.0	3.7	49.9	14.8	37ea	-205.7	5.8	48.5	29.0
35eβ	-197.5	3.4	49.3	15.7	43ea				
29fa	-202.6	0	48.6	12.2	37fa	-204.2	8.5	49.7	27.6
29f β	-201-2	3.1	50.8	14.4	37f β	-220.0	19.0	51.1	27.0
46	-188,1	0	45	18	47	-207.8	0	45	0

Table 3.¹⁹F NMR Data of Isolated Products^a

a. 1,2-Difluorides are not included.

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

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

Table 5.

¹³C NMR Data of O-1 Unprotected Products

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

30	94.6	94.4	83.3	n.r.	n.r.	69.9	
aβ	(23)	(185)	(17)				
31	90.5	88.3	70.8	69.0	67.7	62.8	
aα	(21.4)	(194.3)	(19.2)	(7.3)			
31	95.0	91.0	73.0	69.2	72.3	63.1	
aβ	(22.5	(190.5)	(19.8)	(8)			
32	90.2	88.3	70.1	67.1	67.7	61.7	
aα	(21.1)	(193.2)	(19.1)	(7.2)			
32	94.7	91.0	72.4	67.3	72.5	61.7	
aβ	(22.9)	(190.3)	(19.6)	(n.r.)			
33	90.7	91.3	72.1	70.2	72.2	61.4	
aα	(21.3)	(185.4)	(17)	(8.6)			
33	94.7	94.0	75.0	70.3	77.0	61.6	
aβ	(22.5)	(183.0)	(17.1)	(8.7)			
34	89.8	88.5			n.r.		
aα	(21.2)	(193.9)					
34	94.2	91.1			n.r.		
aβ	(23.1)	(190)					
36	89.9	88.2			n.r.		
aα	(21.5)	(192.5)					
36	94.3	90.8			n.r.		
aβ	(22.8)	(190.0)					
21	92.7	86.0	70.8	65.4	76.7	62.2	TEDA 50.9,
	(15.2)	(189.2)	(17.1)				51.3 CH ₂ Cl 70 2
37	91.7	87.5	69.7	66.0	68.3	62.4	
aa.	(29.2)	(179.0)	(16.6)				
38	92.0	87.1	78.2	n.r.	72.2	69.3	
aα	(29.6)	(175.8)	(17.2)				
39	92.1	87.6	70.5	66.8	68.8	63.2	
aα	(29.3)	(179.5)	(16.7)				
41	92.9	91.4	69.7	67.2	71.9	60.8	
aα	(28.6)	(173.4)	(17.5)				
41	93.4	911.9	72.1	66.9	76.0	60.9	
aβ	(15.8)	(179.9)	(17)	(2)			
42	91.4	87.1			n.r.		
aα	(28.9)	(177.1)					
43	91.7	88.0	69.4	74.0	69.3	62.1	100.9, 71.7,
aα	(29.6)	(177.2)	(16.5)				73.0, 68.0, 71.8, 61.8
44	91.5	87.9			n.r.		,
aα	(28.8)	(177.4)					
	· · · · ·						

Table 5. Continued

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Table 6.

. ¹³C NMR Data of Products Substituted at C-1 Other than OH

	C-1	C-2	C-3	C-4	C-5	C-6	others
	J_{C1-F1}, J_{C1-}	J_{C2-F1}, J_{C2-F2}	J_{C3-F2}	J_{C4-F2}	J_{C5-F1}	-	
	F2						
29	103.7	87.0	70.0	66.9	70.0	61.3	
dα	(231.4,	(26.0,	(19.6)	(7.8)	(4)		
	23.2)	195.2)	. ,		~ /		
30	104.5	90.9		n.r.			
dα	(228.0,	(26.3,					
	23.9)	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,	(26.0,	(19.4)	(7.7)	(4.1)		
	23.2)	195.3)					
33	106.0	91.3	72.7	70.1	76.2	61.8	
dα	(226.0,	(26.0,	(17.3)	(8.2)	(3.1)		
	23.8)	188.7)					
35	103.4	87.2	69.2	74.9	70.7	61.1	100.4, 71.6,
dα	(231.1,	(26.0, 195.)	(19.2)	(7.3)	(4.1)		72.0, 67.8,
	23.1)						72.9, 61.6
36	103.4	87.3	69.4	74.6	70.7	61.3	100.7, 69.1,
dα	(230.8,	(25.8,	(19.2)	(7.7)	(2.8)		70.8, 66.7,
	22.4)	195.1)					71.0, 60.9
37	104.4	85.2	69.2	64.9	71.2	61.7	
dα	(222.3,	(42.3,	(16.5)				
	30.6)	180.8)					
38	105.0	85.1		n. r.			
dα	(219.3,	(42.1,					
	31.4)	177.8)					
44	104.4	85.4	69.0	72.7	71.5	61.5	101.1, 69.1,
dα	(222.0,	(41.7,	(15)		(2.4)		70.7, 66.7,
	31.5)	179.1)		·- ·			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,
			<i>(</i>) 1	64.0	5 0 0	<i></i>	72.2, 61.4
37	96.4	85.8	69.1	64.8	70.9	61.5	
ecc	(-, 31.8)	(-, 181.5)	(10.7)	(n)	<i></i>	<i>~</i> • • •	
29	88.4	86.2	70.6	67.4	69.6	61.4	
fα	(-, 20.2)	(-, 193.8)	(19.8)	(8)		<i></i>	
29	91,3	88.2	72.7	67.6	72.8	61.4	
fß	(-, 24.2)	(-, 192.3)	(22.6)	(7.4)			

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		п.г.			
fα	(-, 22.2)	(-, 181.5)					
35	91.2	88.4		п.г.			
fβ	(-, 24.3)	(-, 191.9)					
43	90.0	86.2		n. r .			
fα	(-, 31.7)	(-, 178.5)					

Table 6. Continued

Table 7.

¹H NMR Data of O-1 Unprotected Products

	δ H-1	δ Η-2	δ Η-3	δ Η-4	δ Η-5	δ H-6 a	δ H-6b	others
	$(J_{\rm H1-F},$	$(J_{\rm H2-F,})$	$(J_{\mathrm{H3-F}},$	$(J_{\rm H4-F},$	$(J_{ ext{H5-H6a}},$	$(J_{ m H6a-H6b})$		
	$J_{ m H1-H2}$)	$J_{\rm H2-H3}$,)	J _{H3-H4})	$J_{ m H4-H5}$)	$J_{ m H5-H6b})$			
29	5.43	4.47	5.55	4.99		4.0-4.3		
aα	(0, 3.7)	(49.4,	(11.9,	(-, 9.9)		n.r.		
		9.5)	9.5)					
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,	(11.4,	(0, 9.7)		n.r.		
		9.5)	9.7)					
32	5.44	4.46	5.61	5.08		4.0-4.4		
aα	(0, 3.6)	(49.7,	(11.7,	(0, 9.9)		n.r.		
		9.6)	9.6)					
32	4.89	n. r .	5,34	5.08	3.76	4.0-4	.4	
aβ	(2.8, 7.9)		(13.7,	(0, 9.9)	(4.3, 1.8)	n.r.		
			9.5)					
33	5.38	4.35			3.35-3.85			
aα	(0, 3.9)	(49.4,			n.r.			
		9.4)						
33	4.84	4.03			3.35-3.85			
aβ	(2.3, 7.8)	(51.1,			n.r.			
• •		· 9.0)						
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)					

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

Table 7. Continued

Table 8.

¹H 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 _{115-F1} J _{115-H6a} , J _{H5-H6b})	δ H-6a (J _{H6a-H6b})	δ H-6 b	others
20	5 70	1 57	5 5 1	5 00		1 05 1 33		
29	5.19	4.55	5.54	5.08		4.03-4.33		
dα	(52.7	(23.7	(12.3	(0		n.r.		
	0	48.0	9.7)	9.7)				
	2.8)	9.5)						
32	5.80	4.53	5.60	5.14		4.05-4.25		
dα	(51.8	(23.8	(12.0	(0		n. r.		
	0	48.3	9.8)	9.8)				
	2.9) .	9.6)		,				
33	5.75	4.29	3.86	3.45		3.65-3.90		
dα	(54.2	(24.3	(13.6	(0		n.r.		
	0	48.3	9.2)	9.2)				
	2.9)	9.4)						
34	5.74	4.36	5.63		3.85	-4.6		
dα	(53.2, 0,	(24, 48,	(11.2,		n .:	r.		
	2.7)	10)	9.5)					

35 5.72 4.43 5.51 3.76 4.45-4.6 dα (53.1, (23.6, (12.1, (9.8) n.r.)) 0, 48.6, 9.6) 0.7.7 9.8) 36 5.75 4.44 5.56 3.81 4.0-4.2 dα (52.9, (24, (12.0, (0, 9.6) n.r.)) 0, 48, 9.6) 0.7.7 2.6) 10) 37 5.76 4.89 5.25 5.40 4.05-4.35 dα (48.4 (2 (27.7) 0 n.r. 2 48.8 2.3) 10.1 10.1 2) 2) 42 5.67 4.82 n.r. da (48.4, 2) (0, 48.8, 2.0) 10.1 2) 2) 2) 2) 43 5.62 4.84 n.r. dα (48.7, (0, 49.0, n.r.) n.r. 3.9, 49.1, 2.0 2.2) 44 5.66 4.85 5.05-5.25 n.r. dα (48.7, (0, 49.9, n.r.) 1.7 1.7 1.7 1.7 1.7 29 5.44 4.69 5.15 3.85-3.95 4.59 4.07 eβ (0, 3.4, (0, 49.
dα (53.1, (23.6, (12.1, (9.8)) n.r. 0, 48.6, 9.6) 2.7) 9.8) 36 5.75 4.44 5.56 3.81 4.0-4.2 dα (52.9, (24, (12.0, (0, 9.6)) n.r. 0, 48, 9.6) 2.6) 10) 37 5.76 4.89 5.25 5.40 4.05-4.35 dα (48.4 (2 (27.7) (0 n.r. 2 48.8 2.3) 10.1) 10.1 10.1 2) 2) 2) 2) 2 10.1 10.1 42 5.67 4.82 n.r. 10.1 10.1 10.1 20) 2.2) 2 10.1 10.1 10.1 10.1 10.1 43 5.62 4.84 n.r. 10.1 10.1 10.1 10.1 20) 2.2) 44 5.66 4.85 5.05-5.25 n.r. 10.1 33 5.44 4.69 5.43 5.12 4.00 4.25 4.20 6 (0,3.4, (0,49.8, (15.2, (0,9.5) (4.9,2.8) (12.5)) 11.1 </th
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2.6) 10) 37 5.76 4.89 5.25 5.40 4.05-4.35 d α (48.4 (2 (27.7 (0 n.r. 2 48.8 2.3) 10.1) 2) 2) 42 5.67 4.82 n.r. d α (48,4,2) (0,48.8, 2.2) 43 5.62 4.84 n.r. d α (48.7, (0, 3.9, 49.1, 2.0) 2.2) 44 5.66 4.85 5.05-5.25 n.r. d α (48.7, (0,49.0, n.r. 3.9,2.1) 2.4) 29 5.44 4.69 5.43 5.12 4.00 4.25 4.20 e β (0,3.4, (0,49.8, (15.2, (0,9.5) (4.9,2.8) (12.5) 7.1) 8.6) 9.4) 35 5.44 4.62 5.1-5.5 3.85-3.95 4.59 4.07 e β (0,3.5, (0,48.2, (n.r.) (n.r.) (12, n.r) (n.r.) 7) 7.5) 37 5.95 5.10 5.43 5.48 4.05- 4.25 4.05- e α (0,6.2, (0,48.7, (29.1, (n.r.) 4.15 (12.8, 4.15 1.9) 2.5) 11.9, (n.r.) 5.1) (n.r.) 29 6.41 4.65 5.55 5.08 4.0-4.3 f α (0,0, (0,48.5, (12.0, (0,10.2) n.r. 4.1) 9.5) 9.7) 29 5.78 4.44 5.37 5.06 3.85 4.29 4.10 f β (0,3.1, (0,50.8, (14.2, (10.1)) (4.6,2.2) (12.6) 8.2) 9.1) 9.3) 37 6.27 4.74 5.25 5.41 4.05 4.28 4.11 f α (0,6.5, (0,48.7, (27.3, (1.1, (4.7,2.4) (12.7)
37 5.76 4.89 5.25 5.40 4.05-4.35 dα (48.4 (2 (27.7 (0 n.r. 2 48.8 2.3) 10.1) 2) 2) n.r. dα (48.4, 2) (0, 48.8, 2.2) 43 5.62 4.84 n.r. dα (48.7, (0, 2.2) 44 5.66 4.85 5.05-5.25 n.r. dα (48.7, (0, 49.0, n.r. 3.9,2.1) 2.4) 29 5.44 4.69 5.43 5.12 4.00 4.25 4.20 eβ (0, 3, 4, (0, 49.8, (15.2, (0, 9.5) (4.9, 2.8) (12.5) 35 5.44 4.62 5.1-5.5 3.85-3.95 4.59 4.07 eβ (0, 3.5, (0, 48.2, (n.r.) (n.r.) (n.r.) (n.r.) (12.8, 4.15 1.9) 2.5) 11.9, (n.r.) 4.15 (12.8, 4.15 1.9) 2.5) 11.9, (n.r.) 4.15 (12.8, 4.15 1.9)
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eβ(0, 3,4, 7.1)(0, 49.8, 8.6)(15.2, 9.4)(0, 9.5)(4.9, 2.8) (4.9, 2.8)(12.5)355.444.625.1-5.5 $3.85-3.95$ 4.59 4.07 eβ(0, 3.5, 7.5)(0, 48.2, 7.5)(n.r.)(n.r.)(12, n.r)(n.r.)7)7.5)7.5)7.57.57.5)7.5)375.955.105.435.48 $4.05 4.25$ $4.05-$ eα(0, 6.2, (0, 48.7, 1.9)(29.1, 2.5)(n.r.) 4.15 (12.8, (12.8, (1.1, (1.7,)) 4.15 1.9)2.5)11.9, 9.4)(n.r.) 5.1) (n.r.)(n.r.)296.414.655.555.08 $4.0-4.3$ fα(0, 0, (0, 48.5, 4.12, (12.0, (0, 10.2))n.r. 4.10 fβ(0, 3.1, (0, 50.8, 8.2)9.7)9.3) 37 6.27 4.74 5.25 5.41 4.05 4.28 4.11 fα(0, 6.5, (0, 48.7, (0, 48.7, (27.3, (1.1, (1.1, (4.7, 2.4))(12.7) 4.11
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Table 8. Continued

polarimeter at 589 nm at ambient temperature. NMR spectra were recorded at 300.13 or 200 MHz (¹H), 75.47 or 50.29 MHz (¹³C) and 282.4 MHz (¹⁹F) - using a BRUKER MSL 300 and a VARIAN Gemini 200 apparatus, respectively. As reference standards tetramethylsilane (¹H and ¹³C NMR) and trichlorofluoromethane (¹⁹F 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 ¹⁹F 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 CH₃NO₂ were mixed with CDCl₃ (as reference standard, 20 vol%) and those from CH₃NO₂ /D₂O were homogenated by the addition of DMF (20 vol%).

Glycals 5, 10, 11 and 12 were prepared from the corresponding per-O-acetylated glycopyranosyl bromides¹³ 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 (Na₂SO₄) 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-mannopyranose¹⁷ (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 29d¹⁸/37d¹⁸, 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_r-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-2fluoro- 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 C₂₄H₃₂F₂O₁₅ (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 protocol¹ for the isolation of the α -D-galactoisomer. 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 (Na₂SO₄). 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 C₁₈H₁₉FN₂O₁₂ (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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- 4. This was proven by the reaction of 1 with the corresponding triflate salt 2b (1chloromethyl-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 ¹⁹F 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 Dmanno-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.
- Therefore, total yields (column 6) and the respective percentage of D-gluco- and Dmanno-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.
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