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SYNTHESIS AND N.M.R. SPECTRA OF METHYL 2-DEOXY-2-FLUORO- AND 3-DEOXY-3-FLUORO-α- AND β-D-GLUCOPYRANOSIDES*

PAVOL KOVÁČ, HERMAN J. C. YEH, AND CORNELIS P. J. GLAUDEMANS
NIDDK, National Institutes of Health, Bethesda, MD 20892 (U.S.A.)

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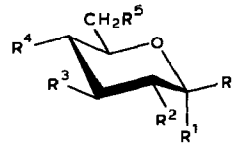
ABSTRACT

Methyl 3-deoxy-3-fluoro-α- and β-D-glucopyranosides and α- and β-D-glucofuranosides were prepared by methanolysis of 3-deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose. Crystalline 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α-D-glucopyranosyl chloride (**2**) and the corresponding glycosyl bromide (**3**) were prepared from 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-β-D-glucopyranose (**1**). Reaction of **2** with methanol under the conditions of both silver triflate- and silver perchlorate-catalyzed glycosylation showed remarkable lack of stereoselectivity for the formation of the corresponding methyl α-glycoside, despite the presence at C-2 of the fluorine functionality presumably not capable of neighboring-group participation. Pure methyl 2-deoxy-2-fluoro-α- and β-D-glucopyranosides were obtained by fractional crystallization from the mixture formed by methanolysis of **1**. The structure of these substances as well as of several other derivatives of 2-deoxy-2-fluoro- and 3-deoxy-3-fluoro-D-glucose were verified by n.m.r. (^{1}H, ^{13}C, and ^{19}F) spectroscopy.

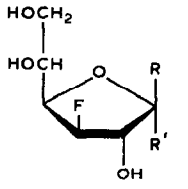
INTRODUCTION

A large number of deoxyfluoro sugars have been used[1–5] in this laboratory as ligands to map subsites in the combining area of monoclonal antibodies that show antigalactan specificity and to study the nature of forces involved in the process of binding of immunoglobulins to their homologous saccharides. A similar study involving dextran-specific monoclonal antibodies required methyl α-D-glycosides of a series of deoxyfluoro-D-glucoses. While the syntheses of methyl 4-deoxy-4-fluoro-α-D-glucopyranoside and methyl 6-deoxy-6-fluoro-α-D-glucopyranoside have been previously reported[6,7], methyl α-glycosides of 2-deoxy-2-fluoro- and 3-deoxy-3-fluoro-D-glucose were hitherto unknown. Here we describe the preparation and characterization of the latter two compounds and report their unambiguously assigned n.m.r.-(^{1}H, ^{13}, and ^{19}F) spectral characteristics.

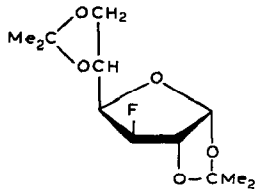
*Dedicated to Dr. R. Stuart Tipson.



	R	R^1	R^2	R^3	R^4	R^5
1	OAc	H	F	OAc	OAc	OAc
2	H	Cl	F	OAc	OAc	OAc
3	H	Br	F	OAc	OAc	OAc
4	OMe	H	F	OAc	OAc	OAc
5	H	OMe	F	OAc	OAc	OAc
6	OMe	H	F	OH	OH	OH
7	H	OMe	F	OH	OH	OH
8	H	OMe	F	OH	O—CHPh—O	
9	OMe	H	F	OH	O—CHPh—O	
10	OMe	H	OH	F	OH	OH
11	H	OMe	OH	F	OH	OH
12	OMe	H	OAc	F	OAc	OAc
13	H	OMe	OAc	F	OAc	OAc
14	H	OMe	OBz	OBz	F	OBz
15	H	OMe	OH	OH	F	OH



	R	R^1
16	OMe	H
17	H	OMe



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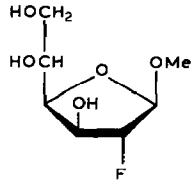

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RESULTS AND DISCUSSION

Synthesis. — Methyl 4-deoxy-4-fluoro-α-D-glucopyranoside (**15**), needed for the binding study, was obtained from the corresponding 2,3,6-tri-*O*-benzoyl derivative[6] (**14**) by debenzoylation (Zemplén). The physical constants observed for **15** compared well with those reported for the compound[7] synthesized independently, and its n.m.r. spectra (Tables I–III) were consistent with the expected structure.

Pure methyl 3-deoxy-3-fluoro-α-D-glucopyranoside has not been reported. The compound was obtained[8] in admixture with the β anomer by treatment of

TABLE I

^{1}H- AND ^{19}F-N.M.R. CHEMICAL SHIFTS (P.P.M.) AND ^{1}H–^{1}H COUPLING CONSTANTS (Hz)

Compound	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6a*	*H-6b*	*OCH_3*	*^{19}F*	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
1[a,b]	5.796	4.450	5.389	5.075	3.873	4.100	4.309		−39.172	8.2	9.1	9.5	10.0	2.0	4.3	12.4
2[a,c]	6.241	4.708	5.620	5.097	4.353	4.123	4.328		−31.046	4.4	9.6	9.6	9.7	3.8	4.1	10.4
3[a,d]	6.532	4.544	5.632	5.122	4.302	4.347	4.125		−26.840	4.5	9.2	9.5	10.2	4.6	3.0	10.0
6[e]	4.486	3.934	3.612	3.255	3.320	3.743	3.573	3.410	−38.015	7.8	9.1	8.6	9.8	2.0	5.5	12.3
7[e]	5.009	4.395	3.871	3.416	3.615	3.871	3.710	3.405	−39.198	3.9	9.6	9.1	10.2	2.4	5.3	12.2
8[a,f]	4.926	4.425	4.243	3.467	3.840	4.296	3.722	3.467	−40.543	3.9	9.0	9.3	9.2	4.6	10.3	10.1
9[a,g]	4.503	4.247	4.000	3.528	3.444	4.372	3.769	3.590	−38.594	7.5	8.8	9.2	9.4	4.7	9.8	10.5
10[e]	4.423	3.556	4.432	3.713	3.484	3.933	3.748	3.577	−33.272	8.0	9.0	8.8	10.1	2.2	5.8	12.2
11[e]	4.676	~3.86	4.379	~3.74	~3.67	3.8–3.9		3.426	−36.937	3.8	8.9	8.9	[h]	[h]	[h]	[h]
12[a,i]	4.369	5.118	4.552	5.225	3.618	4.165	4.278	3.509	−34.162	7.9	9.3	9.1	10.1	2.5	4.7	12.3
13[a,j]	~4.98	~4.98	4.814	5.210	3.901	4.125	4.262	3.399	−37.358	[h]	8.2	8.9	10.3	2.3	4.8	12.3
15[e]	4.833	3.612	3.958	4.335	~3.88	3.80–3.86		3.439	−36.363	3.6	9.8	8.8	9.5	[h]	[h]	[h]
16[e]	4.988	4.390	5.115	4.320	3.942	3.733	3.884	3.412	−39.002	<1.0	<1.0	3.8	9.4	5.8	2.5	12.0
17[e]	5.160	4.467	5.138	4.204	3.937	3.680	3.823	3.467	−39.440	<4.5	2.4	4.0	8.2	6.1	2.9	12.1
18[a,k]	5.950	4.700	5.020	4.110	4.290	4.033	4.120		−45.836	3.8	~0	2.2	8.3	4.6	6.0	8.7
19[e]	4.947	4.763	4.310	4.037	3.791	3.686	3.526	3.221	−31.965	~0	~0	4.3	8.7	2.3	6.3	12.3

[a]In $CDCl_3$, referenced to internal Me_4Si for ^{1}H and C_6F_6 for ^{19}F. [b]OAc: 2.181, 2.081, 2.042. [c]OAc: 2.093, 2.088, 2.057. [d]OAc: 2.096, 2.089, 2.074. [e]In D_2O, referenced to internal TSP for ^{1}H and external C_6F_6 for ^{19}F. [f]PhCH: 5.512. [g]PhCH: 5.524. [h]Not determined because of overlapping of signals. [i]OAc: 2.127, 2.106, 2.097. [j]OAc: 2.151, 2.115, 2.107. [k]Me: 1.503, 1.449, 1.368, 1.327.

TABLE II

^{13}C-N.M.R. CHEMICAL SHIFTS (P.P.M.) AND ^{19}F–^{13}C COUPLING CONSTANTS (Hz, IN PARENTHESES)[a]

Compound	C-1	C-2	C-3	C-4	C-5	C-6	OMe
1	91.31	88.27	72.78	67.74	72.82	61.41	
	(24.2)	(192.6)	(19.7)	(6.9)			
2	89.61	86.71	70.29	67.06	70.55	61.13	
	(24.2)	(198.6)	(19.1)	(6.6)			
3	85.27	86.31	71.09	66.70	72.17	60.88	
	(24.9)	(198.6)	(19.1)	(7.3)			
6	100.75	92.00	74.18	69.42	76.09	60.63	57.08
	(23.4)	(182.6)	(16.8)	7.3			
7	96.68	90.07	71.49	69.25	71.58	60.43	54.90
	(20.5)	(186.1)	(17.6)	(8.1)			
8[b]	97.87	90.29	69.33	80.63	61.99	68.82	55.57
	(21.0)	(191.6)	(17.4)	(9.0)			
9[c]	101.91	92.57	72.35	79.95	66.05	68.52	57.44
	(22.9)	(186.9)	(19.5)	(8.4)			
10	102.53	71.75	96.56	68.01	74.68	60.48	57.42
	(11.7)	(17.6)	(181.7)	(17.6)	(8.8)		
11	99.34	69.80	95.12	67.92	71.01	60.24	55.20
	(10.7)	(17.5)	(179.1)	(17.9)	(7.1)		
12	101.17	71.29	91.79	68.45	71.02	61.82	57.00
	(11.1)	(17.9)	(190.1)	(18.0)	(8.7)		
13	97.08	71.23	89.42	68.49	66.97	61.84	55.58
	(8.8)	(17.1)	(188.3)	(19.6)	(7.2)		
15	99.22	70.88	71.48	89.17	69.16	60.01	55.23
		(8.5)	(17.7)	(180.1)	(23.8)		
16	109.88	77.169	94.86	80.94	69.12	63.50	55.37
		(27.8)	(184.6)	(20.5)	(8.8)		
17	102.79	75.53	97.12	77.14	68.89	63.10	55.78
	(4.4)	(27.8)	(183.2)	(20.5)	(8.8)		
18[d]	105.14	82.54	93.78	80.66	71.88	67.16	
		(35.1)	(183.5)	(19.4)	(7.1)		
19	107.49	100.44	74.86	82.37	71.64	64.59	55.37
	(34.4)	(178.0)	(26.4)				

[a]For solvents of measurements refer to Table I; measurement in $CDCl_3$, reference to Me_4Si. measurements in D_2O referenced to CH_3OH (δ 49.0). [b]PhCH: 102.07. [c]PhCH: 101.97. [d]Me_2C: 109.43, 112.8.

3-deoxy-3-fluoro-D-glucose with methanolic HCl. Experimental details were not given[8], nor was the mixture resolved. When we treated 3-deoxy-3-fluoro-D-glucose with methanol containing 2.5% HCl for 24 h at room temperature, three methyl glycosides were formed, as indicated by t.l.c. The crude product was resolved by column chromatography but none of the three pure methyl glycoside obtained in this way (**10, 16**, and **17**) was the desired α anomer **11**, as shown by n.m.r. spectroscopy (Tables I–III). When treated with boiling methanol and benzene containing 5% of HCl, 3-deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**18**), the synthetic precursor of 3-deoxy-3-fluoro-D-glucose, was converted into two methyl pyranosides, **10** and **11**, which were resolved by column chromatography as

TABLE III

^{19}F–^{1}H COUPLING CONSTANTS (Hz)[a,b]

Compound	*Coupling constants*					
1	$J_{F-2,H-1}$	3.0 (3.1) ; $J_{F-2,H-2}$	50.7 (50.8) ; $J_{F-2,H-3}$	14.1 (14.3)		
2	$J_{F-2,H-1}$	~0 ; $J_{F-2,H-2}$	49.2 (49.2) ; $J_{F-2,H-3}$	11.5 (11.5)		
3	$J_{F-2,H-1}$	1.2 (1.4) ; $J_{F-2,H-2}$	49.5 (49.3) ; $J_{F-2,H-3}$	11.3 (11.3)		
6	$J_{F-2,H-1}$	2.2 ; $J_{F-2,H-2}$	51.3 (51.6) ; $J_{F-2,H-3}$	15.3 (15.6)		
7	$J_{F-2,H-1}$	~0 ; $J_{F-2,H-2}$	48.8 (49.0) ; $J_{F-2,H-3}$	13.6 (13.3)		
8	$J_{F-2,H-1}$	~0 ; $J_{F-2,H-2}$	48.6 (48.7) ; $J_{F-2,H-3}$	12.7 (12.7)		
9	$J_{F-2,H-1}$	3.6 (3.5) ; $J_{F-2,H-2}$	49.9 (50.0) ; $J_{F-2,H-2}$	15.3 (15.3)		
10	$J_{F-3,H-2}$	13.6 (13.5) ; $J_{F-3,H-3}$	52.9 (52.9) ; $J_{F-3,H-4}$	13.8 (13.5) ; $J_{F-3,H-5}$	1.2	
11	$J_{F-3,H-2}$	(13.2) ; $J_{F-3,H-3}$	54.0 (54.8) ; $J_{F-3,H-4}$	(13.2) ; $J_{F-3,H-1}$	3.5 (3.3)	
				$J_{F-3,H-5}$	(1.5)	
12	$J_{F-3,H-2}$	13.3 (13.1) ; $J_{F-3,H-3}$	51.9 (51.7) ; $J_{F-3,H-4}$	12.6 (12.4) ; $J_{F-3,H-5}$	1.2	
				$J_{F-3,H-6a}$	1.4	
13	$J_{F-3,H-2}$	~(12.7) $J_{F-3,H-3}$	~(53.0) ; $J_{F-3,H-4}$	13.6 (12.7)		
15	$J_{F-4,H-3}$	15.8 (15.9) ; $J_{F-4,H-4}$	50.9 (51.3) ; $J_{F-4,H-4}$	(2.4) ; $J_{F-4,H-2}$	0.7	
16	$J_{F-3,H-2}$	11.4 (11.6) ; $J_{F-3,H-3}$	50.8 (50.8) ; $J_{F-3,H-4}$	28.1 (28.1)		
17	$J_{F-3,H-2}$	21.9 (21.8) ; $J_{F-3,H-3}$	52.8 (52.8) ; $J_{F-3,H-4}$	25.9 (25.7)		
18	$J_{F-3,H-2}$	10.7 (10.8) ; $J_{F-3,H-3}$	49.8 (49.8) ; $J_{F-3,H-4}$	29.0 (29.0)		
19	$J_{F-2,H-1}$	13.6 (13.4) ; $J_{F-2,H-2}$	48.5 (48.1) ; $J_{F-2,H-3}$	(13.0)		

[a]For solvents of measurement refer to Table I; measurements in $CDCl_3$ referenced to internal C_6F_6; measurements in D_2O referenced to external C_6F_6. [b]Numbers in parentheses extracted from ^{19}F-n.m.r. spectra.

their acetyl derivatives **12** and **13**. The isolated methyl α-glycoside **13** was deacetylated to give the desired compound **11** in crystalline form.

To prepare methyl 2-deoxy-2-fluoro-α-D-glucopyranoside (**7**) several approaches were investigated. An attempt to introduce fluorine into position 2 of methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside using diethylaminosulfur trifluoride (DAST) as a fluoride-ion source, expected to give the corresponding D-*gluco* derivative, was unsuccessful[9], apparently because of the participation of the axial methoxyl group at C-1. Therefore, the hitherto unknown 2-deoxy-2-fluoro-3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl chloride (**2**) and the corresponding bromide (**3**) were prepared and treated with methanol under various conditions. The formation of an α-(*cis*) product in high yield from the silver triflate-catalyzed glycosylations, involving α-glycosyl chlorides bearig a nonparticipating group at C-2, has been reported[10,11]. However, the reaction of **2** with methanol produced a mixture of glycosides **4** and **5** in which the β-glycoside **4** preponderated, as shown by ^{1}H-n.m.r. spectroscopy. Igarashi *et al.*[12] converted 3,4,6-tri-*O*-acetyl-2-deoxy-2-chloro-α-D-glucopyranosyl chloride into the corresponding methyl α-glycoside with high stereoselectivity using silver perchlorate-catalyzed glycosylations. As shown by n.m.r. spectrscopy of the formed glycosides, the reaction of **2** with methanol under those conditions was *not* highly stereoselective: the formation of the α-glycoside was only slightly favored over that of its β counterpart. It has

been pointed out[13] that, with a very reactive nucleophile, it is difficult to achieve high α-(*cis*) stereoselectivity in a glycosylation reaction involving an α-glycosyl halide bearing a non-participating group at C-2 and a very powerful promotor. A comparison of our results with those obtained by Igarashi *et al.*[12] indicate that under the foregoing conditions involving a powerful promotor, silver perchlorate or silver triflate, the (strongly electronegative) fluorine atom present at C-2 may have had a further adverse effect upon the α-stereoselectivity, as evidenced by the observed high relative yield of the methyl β-(*trans*)-glycoside in the cases described here. We did observe formation of the α-glycoside **5** with high stereoselectivity from the chloride **2** under the conditions of halide-ion catalyzed glycosylation[14], but the reaction was impracticably slow, and the desired product was formed in only moderate yield (40–50%). The use of bromide **3** as a starting material in this reaction did not change the situation favorably.

As it was found that there was no advantage to using glycosyl halides **2** and **3** as synthetic precursors for **7**, the latter compound was eventually prepared from the acetate **1** by simple methanolysis, followed by fractional crystallization of the methyl α- and β-glycosides (**7** and **6**) formed. In anticipation of improving the yield of pure α and β anomers **7** and **6**, an attempt was made to resolve the two glycosides in the form of the corresponding 4,6-*O*-benzylidene derivatives. Both anomers **8** and **9** were eventually obtained pure and crystalline by a combination of chromatography and fractional crystallization, but the procedure was not suitable for a large-scale preparation.

N.m.r. spectroscopy. — The anomeric configuration of the glycosides prepared was tentatively deduced from the optical-rotation data. Conclusive assignment of overall structures of the derivatives described here was based on ^{1}H-, ^{13}C-, and ^{19}F-n.m.r. spectral data (Tables I–III). Verification of the position of fluorination in a carbohydrate may be based on its ^{13}C-n.m.r. spectrum where the carbon atom attached to fluorine is expected to exhibit a large one-bond coupling-constant $^{1}J_{FC}$ ~180–200 Hz (ref. 19). Alternatively, diagnostic of the site of fluorination is the large geminal coupling-constant, $^{2}J_{FH}$ ~48–54 Hz, exhibited in the ^{1}H-n.m.r. spectrum by the proton bonded to the fluorinated carbon atom. Thus, compounds **1–9** and **19** clearly show fluorination at C-2, whereas compounds **10–13** and **16–18** are 3-deoxy-3-fluoro derivatives, and compounds **14** and **15** are 4-deoxy-4-fluoro derivatives.

It is known[19] that the range of ^{19}F-n.m.r. chemical shifts is at least one order of magnitude greater than the range of the corresponding ^{1}H-n.m.r. chemical shifts, and ^{19}F-n.m.r. chemical shifts have been used as a tool in the assignment of the site of fluorination in carbohydrates. However, the position of fluorine in the derivatives studied could not be unambiguously determined solely on the basis of the observed ^{19}F-n.m.r. chemical shifts (Table III). This should not be surprising, as the ^{19}F-n.m.r. chemical shift is also known to be rather sensitive to the orientation of the fluorine atom with respect to the sugar ring, as well as to the configuration and the nature of substituents at both adjacent and remote positions in the molecule.

The stereochemistry at C-1 and the overall conformation of pyranosides may be deduced from the values of the vicinal coupling-constants, which generally depend upon the orientation of the coupled nuclei. It has been established that vicinal *trans*-antiperiplanar and gauche-oriented *cis*-protons show coupling constants of 7.5–10.0 and 2.5–4.5 Hz, respectively. The small coupling-constants $^3J_{1,2}$ (3.6–4.5 Hz) observed for compounds **2, 3, 7, 8, 11**, and **15** are consistent with a *cis*-gauche arrangement of H-1*e* and H-2*a*, confirming that these compounds are α anomers. The β stereochemistry of compounds **1, 6, 9, 10**, and *12* similarly follows from the relatively large coupling-constants $^3J_{1,2}$ (7.5–8.2 Hz) observed. Also, the large vicinal coupling-constants $^3J_{2,3}$ (8.2–9.8 Hz), $^3J_{3,4}$ (8.6–9.6 Hz) and $^3J_{4,5}$ (9.2–10.3 Hz) observed in the studied D-glucopyranosides shows that the $^4C_1$(D) conformation of these molecules remains unaffected by the fluorination, the protons at C-2 through C-5 being all in axial disposition. This fact justifies in an important way the use of fluoro analogs in studies involving binding of antibodies to carbohydrates. The furanose structures of **16–19** follow[20] clearly from both their ^{1}H- and ^{13}C-n.m.r. spectral data (Table I and II). Although the anomeric hydrogen of the α anomer in the furanoside **17** resonates at a lower field than that of its β counterpart **16**, the difference in their chemical shift is much smaller than that found in the series of pyranosides studied herein. The very small coupling-constant ($^3J_{1,2}$ <1 Hz) observed for **16** and **19** is consistent with a β anomer, where the dihedral angle between the two coupled protons is close to 90°.

The stereochemistry at C-1 in an anomeric pair may also be deduced from the ^{1}H-n.m.r. chemical shift observed for anomeric protons, as an equatorial hydrogen (as in the α-D- form) is known to resonate at a lower field (by 0.2–0.5 p.p.m.) than that an axial one (as in the β form). Thus, data observed for compounds **7, 8, 11**, and **13** are consistent with their α configuration, whereas those observed for **6, 9, 10**, and **12** establish the β configuration of these compounds. The same conclusion may be drawn independently from the ^{13}C-n.m.r. chemical shifts (Table I) observed for anomeric carbon atoms of these compounds.

Having determined the structure of the individual derivatives by ^{1}H- and ^{13}C-n.m.r. spectroscopy, the effect of the stereochemistry at C-1 upon the ^{19}F chemical shift in 2-deoxy-2-fluoro- and 3-deoxy-3-fluoro-D-glucopyranosides could be determined. Analysis of the data in Table III shows that the ^{19}F in the β forms of the 2-fluoro derivatives resonates at a lower field (by 1.2–1.9 p.p.m.) than that in its α counterparts. In the spectra of 3-deoxy-3-fluoro-β-D-glucose derivatives, the signal of ^{19}F is shifted downfield by 3.2–3.7 p.p.m. as compared to that in the spectra of the α compounds.

EXPERIMENTAL

General methods. — Melting points were measured with a Büchi melting-point apparatus. Optical rotations for solutions in $CHCl_3$ (compounds **2, 3, 8**, and **9**) or water were measured at 25° with a Perkin–Elmer automatic polarimeter,

Model 241 MC. T.l.c. on precoated slides of Silica Gel G (Analtech) was performed with solvents of appropriately adjusted polarity, consisting of *A*, petroleum ether–Et_2O; *B*, CH_2Cl_2–MeOH; *C*, CCl_4–Me_2CO; *D*, PhMe–EtOAc; and *E*, PhMe–Me_2CO. Detection was effected by charring with 5% (v/v) sulfuric acid in ethanol and, where applicable, with u.v. light. Preparative chromatography was performed by gradient elution from columns of Silica Gel 60 (Merck, Prod. No. 9385 or 1511). DAST was purchased from Aldrich Chemical Company and distilled under diminished pressure. The solution of hydrogen bromide in acetic acid (33%) was purchased from Fluka Chemical Company. Solutions of HCl in methanol were freshly prepared by addition of a calculated amount of acetyl chloride to anhydrous methanol. The ^1H-, ^{13}C-, and ^{19}F-n.m.r. spectra were routinely taken at 23° with Varian XL 300, Jeol FX 100, and Varian HR 220 spectrometers. The conditions of measurements are given in Tables I–III or here as required.

*Methyl 4-deoxy-4-fluoro-α-*D*-glucopyranoside* (**15**). — Methanolic NaOMe (M, 5 mL) was added to a warm solution of **14** (prepared as described[6], 1 g), in MeOH (50 mL), and the mixture was kept overnight at room temperature. After neutralization with Dowex 50 W (H^+) resin, the solution was concentrated and crystallization from Me_2CO–EtOAc gave pure **15** (0.3 g, 77%), m.p. 126–127°, $[\alpha]_D$ +138° (*c* 1.8); lit.[7] m.p. 129–130°, $[\alpha]_D$ +131°.

*3-Deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-α-*D*-glucofuranose* (**18**). — The experimental details of the following high-yielding procedure for the preparation of **18** were kindly provided[15] by one of the authors of the original Preliminary Communication[16]. Thus, a solution of DAST (0.7 mL, 5.7 mmol) in dry C_5H_5N (1.7 mL) was added at 0° to a solution of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose[17] (1 g, 3.8 mmol). Cooling was removed and the mixture was heated for 1 h at 70° (bath). While almost no product could be detected by t.l.c. (solvent *A*) before the mixture was heated, the reaction was complete at this point, and one faster-migrating product was formed. The mixture was cooled (0°), MeOH (1 mL) was added, and the crude product was partitioned between CH_2Cl_2 and $NaHCO_3$. The organic phase was concentrated, and the residue was eluted from a short column of silica gel to give pure (t.l.c., n.m.r.) **18** (0.88 g, 87%) as a colorless oil. A yield of ~64% has been previously reported[21,22] for this conversion.

Methyl 3-deoxy-3-fluoro-α- (**17**) *and -β-*D*-glucofuranoside* (**16**), *and methyl 3-deoxy-3-fluoro-β-*D*-glucopyranoside* (**10**). — A solution of 3-deoxy-3-fluoro-D-glucose [prepared[18] from **18** (1.2 g)] in MeOH containing 2.5% HCl (40 mL) was kept for 24 h at room temperature. T.l.c. (solvent *B*) showed that only traces of the starting material remained, and that three products were formed of which the slowest migrating preponderated. After neutralization with Amberlite IR-45 (CO_3^{2-}) resin and concentration, chromatography gave first the α-furanoside **17** (60 mg), m.p. 77–78°, $[\alpha]_D$ +106° (*c* 1).

Anal. Calc. for $C_7H_{13}FO_5$: C, 42.86; H, 6.68; F, 9.68. Found: C, 42.76; H, 6.72; F, 9.50.

Eluted next was the amorphous β-furanoside **16** (230 mg), $[\alpha]_D$ −86° (*c* 1).

Anal. Calc. for $C_7H_{13}FO_5$: C, 42.86; H, 6.68; f, 9.68. Found: C, 42.93; H, 6.85; F, 9.88.

Eluted last was the β-pyranoside **10** (270 mg), m.p. 129.5–130°, $[\alpha]_D$ −33.5° (*c* 1.2).

Anal. Calc. for $C_7H_{13}FO_5$: C, 42.86; H, 6.68; F, 9.68. Found: C, 42.76; H, 6.35; F, 9.54.

Intermediate, mixed fractions were also obtained.

*Methyl 3-deoxy-3-fluoro-α-*D*-glucopyranoside* (**11**). — Acetyl chloride (8 mL), followed by the di-*O*-isopropylidene derivative **18** (1.3 g), was added with stirring at 0° to a mixture of MeOH (50 mL) and C_6H_6 (20 mL). The solution was heated for 24 h under reflux with the exclusion of atmospheric moisture. Two products were formed, as shown by t.l.c. (solvent *B*). The faster-migrating component (trace amount) was indistinguishable from **17**, and the major, slower migrating product co-chromatographed with **10**. The mixture was processed as already described for the preparation of **10, 16**, and **17** and chromatographed, to remove the minor component. The major product, which consisted of a mixture of **10** and **11** (~1:2.5, n.m.r.) migrated in several solvents as a single spot. It was acetylated with Ac_2O–C_5H_5N and the two products formed were readily separated by column chromatography (solvent *C*). The faster-migrating product was (n.m.r.) methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α-D-glucopyranoside (**13**) and the slower-migrating one was the β anomer **12**, both obtained as amorphous solids.

Deacetylation (Zemplén) of **13** gave **11**, m.p. 114–115°, $[\alpha]_D$ +161° (*c* 1).

Anal. Calc. for $C_7H_{13}FO_5$: C, 42.86; H, 6.68; F, 9.68. Found: C, 42.57; H, 6.54; F, 9.69.

*3,4,6-Tri-*O*-acetyl-2-deoxy-2-fluoro-α-*D*-glucopyranosyl chloride* (**2**). — To a solution of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-fluoro-β-D-glucopyranose[23] (**1**) (0.7 g) in dichloromethyl methyl ether (0.6 mL) was added freshly fused $ZnCl_2$ (~10 mg), and the mixture was heated for 30 min with the exclusion of moisture at 70° (bath). T.l.c. (solvent *D*) showed that all starting material was consumed and that a single, faster-migrating product was formed. The mixture was diluted with PhMe and concentrated. This operation was repeated, and a solution of the residue in CH_2Cl_2 was washed with ice–water, dried and evaporated to give a solid residue (0.65 g, ~100%). Crystallization from anhydrous EtOH gave pure **2**, m.p. 105.5–106°, $[\alpha]_D$ +196°, (*c* 1).

Anal. Calc. for $C_{12}H_{16}ClFO_7$: C, 44.12; H, 4.94; Cl, 10.85; F, 5.82. Found: C, 44.30; H, 4.83; Cl, 10.71; F, 5.78.

*3,4,6-Tri-*O*-acetyl-2-deoxy-2-fluoro-α-*D*-glucopyranosyl bromide* (**3**). — To a solution of **1** (1 g) in CH_2Cl_2 (5 mL) was added a solution of HBr in HOAc (10 mL) and the solution was kept for 1.5 h at room temperature. T.l.c. (solvent *E*) then showed that the reaction was complete and that one, faster-moving product was formed. After concentration, with several additions of PhMe to remove AcOH, the residue was dissolved in anhydrous Et_2O and pure **3** crystallized (0.93 g, 88%) on addition of petroleum ether, m.p. 86–87°, $[\alpha]_D$ +319° (*c* 1.5).

Anal. Calc. for $C_{12}H_{16}BrFO_7$: C, 38.83; H, 4.34; Br, 21.52; F, 5.11. Found: C, 39.11; H, 4.49; Br, 21.76; F, 4.91.

Methyl 3,4,6-tri-O-acetyl-2-deoxy-2-fluoro-α,β-D-glucopyranoside (**5** and **4**, respectively). — (*a*) A solution of the chloride **2** (33 mg, 0.1 mmol), 2,4,6-trimethylpyridine (0.014 mL, ~0.1 mmol) and MeOH (0.005 mL, 0.125 mmol) in CH_2Cl_2 (1 mL) was added dropwise at −30° to a suspension of silver triflate (31 mg, 0.12 mmol) in CH_2Cl_2 (1 mL). No AgCl precipitated during 15 min. The temperature was raised to −10° and the suspension was stirred for 6 h at this temperature. T.l.c. (solvent *E*) showed that the reaction was complete and, after conventional processing, the crude product was eluted from a small column of silica gel to give the major product which was eluted as a single zone. The ^{1}H-n.m.r. spectrum (220 MHz, $CDCl_3$) showed, *inter alia,* singlets at δ 3.47 and 3.58 for the 1-OMe groups, reflecting the presence of the title compouns in an approximate ratio of **5**:**4** = 2:3; ^{13}C-n.m.r. (25 MHz, $CDCl_3$): δ 101.4 (d, J_{FC} 22 Hz, C-1β), 97.0 (d, J_{FC} 21.8 Hz, C-1α), 89.4 (d, J_{FC} 190.2 Hz, C-2β), 87.4 (d, J_{FC} 194 Hz, C-2α), 72.8 (d, J_{FC} 20.3 Hz, C-3β), 71.8 (C-5α,β), 70.7 (d, J_{FC} 20.7 Hz, C-3α), 68.3, 68.1 (2 d, J_{FC} 5.2 and 5 Hz, C-4α,β), 61.8 (C-6α,β), 57.3 (Meβ), and 55.7 (Meα).

(*b*) A solution of the chloride **2** (33 mg, 0.1 mmol), MeOH (0.01 mL, 0.25 mmol) and 2,4,6-trimethylpyridine (0.014 mL, ~0.1 mmol) in Et_2O (3 mL) was added at −20° to a solution of $AgClO_4$ (25 mg, 0.12 mmol) in ether (2 mL). Cooling was discontinued and the mixture was stirred overnight. After conventional processing, examination of the major product by n.m.r. spectroscopy (compare earlier) showed that in the mixture of the title glycosides formed the α anomer **5** only slightly predominated over **4**.

(*c*) Chloride **2** (33 mg, 0.1 mmol) was added to a stirred mixture of MeOH (0.01 mL, 0.25 mmol), 3Å molecular sieve (150 mg), Et_4NBr (21 mg, 0.1 mmol) and 2,4,6-trimethylpyridine (0.01 mL) in C_6H_6 (1 mL), and the mixture was stirred in a closed vessel for 2 days at 50°. No reaction occurred, as shown by t.l.c. Methanol (0.01 mL) and *N,N*-dimethylformamide (5 drops) were added, followed by Et_4NBr (20 mg) and C_6H_5 (1 mL), and stirring was continued for a total of 14 days while the reaction was occasionally monitored by t.l.c. The mixture of the title glycosides was the major component of the mixture, which also contained the product of hydrolysis of **2** (~30%), unchanged **2** (~10%) and minor by-products. After conventional processing, the n.m.r. spectrum of the major product, isolated in ~50% yield, showed that in the formed mixture of the glycosides **4** and **5** the α anomer **5** largely predominated.

When glycosyl bromide **3** was used as the starting material in the same experiment, a larger amount of byproducts was formed, at the expense of **4** and **5**.

Methyl 2-deoxy-2-fluoro-α- (**7**) *and β-D-glucopyranoside* (**6**). — (*a*) Acetyl chloride (22 mL) was added under anhydrous conditions to a solution of **1** (3.7 g) in a mixture of MeOH (150 mL) and C_6H_6 (50 mL), and the mixture was heated for 24 h under reflux. After conventional processing, the crude product was chromatographed (solvent *B*). Eluted first was a small amount of material shown

by n.m.r. spectroscopy to be the β-furanoside **19**. The zone containing the major product was collected in two portions. The title glycoside **6** was obtained by fractional crystallization from the front fractions of the zone, and the α-glycoside **7** was obtained in the same way from the last fractions of the main zone:

Compound **6** had m.p. 150–151° (after several recrystallization from Me_2CO–EtOAc), $[\alpha]_D$ −26.5° (*c* 0.5).

Anal. Calc. for $C_7H_{13}FO_5$: C, 42.85; H, 6.67; F, 9.68. Found: C, 2.93; H, 6.81; F, 9.41.

Compound **7** had m.p. 141.5–142° (after several recrystallizations from 2-propanol), $[\alpha]_D$ +153° (*c* 0.8).

Anal. Calc. for $C_7H_{13}FO_5$: C, 42.85; H, 6.67; F, 9.68. Found: C, 42.87; H, 6.79; F, 9.43.

The combined mother liquors, containing a mixture of **6** and **7**, were processed as described in the preparation of **8** and **9**.

(*b*) Conventional cleavage of the benzylidene group from **8** and **9** by catalytic hydrogenolysis over Pd–C gave, respectively, products indistinguishable from **7** and **6** already described.

(*c*) A solution of the chloride **2** (20 mg) in methanolic NaOMe (M, 1 mL) was kept for 40 h at room temperature. The solution was neutralized with Dowex 50 W (H^+) resin and concentrated. Examination of the crude product by n.m.r. spectroscopy showed that a mixture of the title glycosides was formed, where the β anomer **7** largely predominated.

Methyl 4,6-O-benzylidene-2-deoxy-2-fluoro-α- (**8**) *and -β-*D*-glucopyranoside* (**9**). — The combined mother liquor from crystallization of **6** and **7** (1.3 g) was dissolved in *N,N*-dimethylformamide (5 mL) and anhydrous *p*-toluenesulfonic acid (5 mg) followed by benzaldehyde dimethyl acetal (5 mL) were added. The mixture was stirred at 65–70° (bath) in a round-bottom flask that was attached through a condenser to a water aspirator. After 2 h, t.l.c. (solvent *C*) showed that the reaction was complete and that essentially two, very poorly separated, products were formed. Solid $NaHCO_3$ was added, the mixture was stirred for 0.5 h, and, after concentration, the residue was partitioned between CH_2Cl_2 and water. The organic phase was dried, concentrated, and the crude product was chromatographed. Compound **9**, m.p. 188–188.5° (from 2-propanol, twice), $[\alpha]_D$ −57.4° (*c* 0.7), was obtained from the first fractions of the major zone enriched in this component.

Anal. Calc. for $C_{14}H_{17}FO_5$: C, 59.14; H, 6.03; F, 6.68. Found: C, 58.90; H, 6.08; F, 6.67.

Compound **8**, m.p. 160–161° (from ethanol, twice), $[\alpha]_D$ +108.2° (*c* 0.8), was obtained from the last fractions of the same zone, enriched in this component.

Anal. Calc. for $C_{14}H_{17}FO_5$: C, 59.14; H, 6.03; F, 6.68. Found: C, 59.15; H, 6.09; F, 6.85.

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