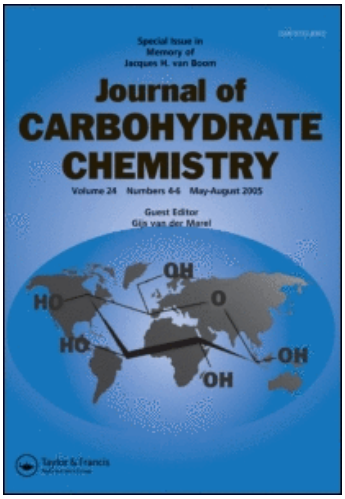

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5-Deoxy-5-fluoro-D-glucofuranose and -L-idofuranose Synthesis and NMR Studies

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ABSTRACT

Starting from 1,2-O-isopropylidene-α-D-gluco- and -ß-L-ido-furanurono-6,3-lactone, 5-deoxy-5-fluoro-α/ß-D-gluco- and -L-ido-furanose, respectively, were prepared by the following sequence of reactions: trifluoromethanesulfonylation, nucleophilic substitution with inversion of configuration, lactone reduction and deprotection. On the basis of *H-H-*, *H-C-*, *H-F-*, and *C-F*-couplings, the stereochemistry of the products is discussed.

When the enzyme modifying properties of various fluorine containing carbohydrates [1] are considered along with the biological significance of D-glucose derivatives modified at the C-5 position,[2] 5-deoxy-5-fluorohexoses emerge as compounds of particular interest. Since there is often difficulty with the regio- and stereoselectivity of reactions introducing fluorine into carbohydrates,[3] 1,2-O-isopropylidene-α-D-glucofuranurono-6,3-lactone (1) was selected as starting material for this study since compound 1 contains a sufficiently rigid structure to avoid some of these synthetic difficulties. Also, since the triflate (2) derived from 1 had been converted in high yield into 1,2-O-isopropylidene-ß-L-idofuranurono-6,3-lac-

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tone (6) by reaction with sodium trifluoroacetate and subsequent deprotection,[4] the possibility for triflate displacement by fluoride ion seemed attractive.

Reaction of 2 with tetra-n-butylammonium fluoride in acetonitrile at room temperature gave, after 24 hours, a 67% yield of 5-deoxy-5-fluoro-1,2-O-isopropylidene-ß-L-idofuranurono-6,3-lactone (3) and 6% of 5-deoxy-5-fluoro-1,2-O-isopropylidene-α-D-glucofuranurono-6,3-lactone (8); in contrast, 1,2-O-isopropylidene-5-O-trifly1-ß-L-idofuranurono-6,3-lactone (7), under the same conditions, gave 54% of 8 and 11% of 3. In each case, a small amount of 6 (from 2) and 1 (from 7) also was isolated due to the water present in the tetra-n-butylammonium fluoride used. TLC monitoring of the mixtures of reactions of 2 and 7 showed that in each case the deoxyfluoro sugar with retained configuration actually resulted from epimerization of the starting material prior to displacement.

Reduction of 3 and 8 with sodium borohydride in methanol led to 5-deoxy-5-fluoro-1,2-O-isopropylidene-ß-L-idofuranose (4, 92%) and 5-deoxy-5-fluoro-1,2-O-isopropylidene-α-D-glucofuranose (9, 89%), respectively. From these two compounds (4 and 9), anomeric mixtures of 5-deoxy-5-fluoro-L-idofuranose (5, 85%) and 5-deoxy-5-fluoro-D-glucofuranose (10, 76%), respectively, were obtained by hydrolysis with aqueous trifluoroacetic acid.

Proof of the structures of these compounds 3-5 and 8-10 arises from their analytical data, their ^{1}H, ^{13}C, and ^{19}F NMR spectra (Tables 1 and 2 and the Experimental section), and spectral comparisons with their unfluorinated counterparts.[5] Since the isopropylidene ring fixes the conformation of the tetrahydrofuran ring ($^{3}T_{2}$, ref. 7), the value of the $J_{H-4,H-5}$ coupling constant (Table 3) serves to confirm the configurational assignment[10] at C-5 in lactones 3 and 8 and to shed light on the conformation of the side chain in the furanoses 4 and 9.[14]

Additional stereochemical information can be obtained from the *F-H* and *F-C* coupling constants (Tables 1 and 2). The most striking of the coupling constants is the five bond *H-F* coupling

TABLE 1: CARBON-13 CHEMICAL SHIFT [δ, ppm] AND FLUORINE - CARBON COUPLINGS [*J*, *Hz*][a]

	3[b]	8[b]	4[c]	9[c]	5α[d]	5ß[d]	10α[d]	10ß[d]
1	106.5	107.6	105.7	106.1	102.6	96.7	97.5	103.1
2	82.2	82.7	86.4	86.3	81.1	76.5	76.4	81.0
3	85.1	81.7 *5.9*	75.2 *8.8*	74.7	75.2 *5.8*	75.2 *5.8*	75.7	75.3
4	80.0 *28.0*	76.6 *14.7*	80.7 *19.1*	78.8 *30.9*	80.2 *17.7*	77.3 *17.7*	76.4 *28.4*	79.2 *28.4*
5	87.3 *185.3*	86.2 *206.9*	94.6 *170.6*	91.5 *167.6*	93.6 *172.9*	94.5 *170.6*	92.0 *167.7*	92.0 *167.7*
6	169.1 *20.6*	168.0 *23.8*	62.0 *22.0*	62.9 *19.1*	61.8 *20*	61.8 *20*	62.0 *19.1*	62.3 *20.5*
CMe_2	113.7 27.1 26.6	114.0 27.1 26.7	111.1 27.0 26.4	112.2 27.1 26.5				

a) 22.62 MHz; resolution: 1.45 *Hz* per datapoint; b) $CDCl_3$;
c) acetone-d_6; d) D_2O

TABLE 2: PROTON CHEMICAL SHIFT [δ, ppm] AND PROTON - FLUORINE COUPLINGS [*J*, *Hz*][a]

	3[b]	8[b]	4[c]	9[c]
1	5.95 *1.2*	6.08	5.92	5.84 *1.6*
2	4.87	4.87 *3.5*	4.48 *3.5*	4.47
3	5.10	4.90 *1.3*	4.2	4.17 d)
4	4.96 *8.7*	5.08 *1.0*	4.27 *14.0*	4.17 d)
5	4.93 *48.3*	5.33 *48.0*	4.70 *50.0*	4.74 *47.0*
6a			3.82 *23.2*	3.86 *30.0*
6b			3.77 *19.0*	3.65 *30.0*
CMe_2	1.58 1.40	1.55 1.38	1.47 1.33	1.47 1.29

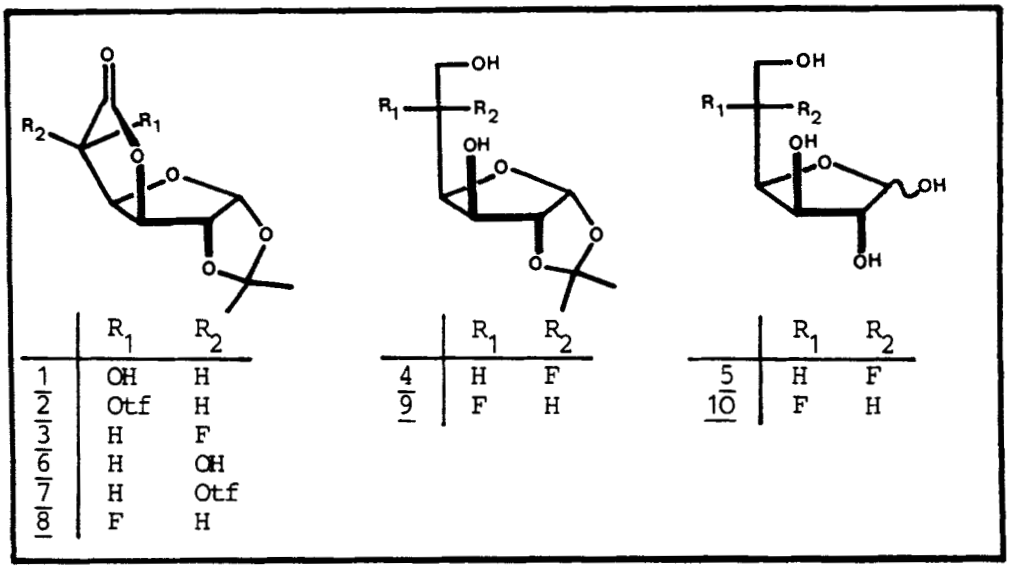
a) 200 MHz; b) $CDCl_3$; c) $CDCl_3/D_2O$; d) not detected

TABLE 3: PROTON - PROTON COUPLINGS [Hz] a)

	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{3,5}$	$J_{2,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
3	3.7		3.3	0.4	0.3	0.4			
8	3.6	0.6	2.8		0.5	4.0			
4	3.8		3.5			7.9	3.6	4.6	12.6
9	3.5		2.8			7.9	2.4	5.6	13.1

a) 200 MHz

in compounds 3 and 9 and the similar *H-F* five bond coupling in 4 and 8. These couplings indicate an almost identical stereochemical arrangement of the fluorine atoms within



	R_1	R_2
1	OH	H
2	Otf	H
3	H	F
6	H	OH
7	H	Otf
8	F	H

	R_1	R_2
4	H	F
9	F	H

	R_1	R_2
5	H	F
10	F	H

the two pairs of compounds (3 and 9 plus 4 and 8). These five bond couplings also constitute support for the suggestion[17] that "a *trans*-coplanar relationship to the bond that is the midpoint of the coupling pathway"[18] is a prerequisite for this coupling to be operative.

Interestingly, the observed $^{5}J_{H-5,H-2}$ coupling, reported [12] for various derivatives of L-idofuranurono-6,3-lactone, could not be found in 3. Further confirmation of the spatial arrangement of groups in these molecules comes from ^{3}J coupling constants (i.e., $J_{F,H-4}$ and $J_{F,C-3}$) which are known to exhibit a Karplus like relationship. The anomeric ratios in 5 and 10, as determined by ^{1}H NMR, [20] are both about 1:1.

EXPERIMENTAL

General Methods. Melting points were determined with a Tottoli apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. TLC was performed on silica gel 60 F_{254} precoated plates (Merck 5554) using toluene - ethyl acetate (2:1, *A*), ethyl acetate (*B*), and ethyl acetate - methanol (9:1,*C*), respectively. Column chromatography [21] on silica gel 60, using 230-400 mesh (Merck 9385), was conducted by eluting with toluene - ethyl acetate (10:1). NMR Spectra were recorded with a Bruker WH-90-DS and a Varian XL-200 NMR spectrometer. MS Data were obtained with a Finnigan MAT-212 instrument (chemical ionization using isobutane). Tetra-n-butylammonium fluoride trihydrate (Fluka 86872) was dried at 80 °C and 10 Pa for 3 days prior to use.

5-Deoxy-5-fluoro-1,2-O-isopropylidene-ß-L-idofuranurono-6,3-lactone (3). To a solution of 1 [22] (2.16 g, 10 mmol) in dichloromethane - pyridine [19:1 (v/v), 50 mL] trifluoromethanesulfonic anhydride (3.26 g, 1.9 mL, 11.5 mmol) was added at 4 °C. When TLC (*A*) showed quantitative formation of triflate 2 [R_f 0.73, R_f(1) 0.30; 15 min] the reddish solution was diluted with dichloromethane (50 mL) and washed successively with 1M hydrochloric acid, saturated aqueous sodium hydrogen carbonate and water (50 mL each). After drying over sodium sulfate and filtration, the solvent was evaporated at <30 °C and the residue, [23] dissolved in acetonitrile (25 mL), treated with tetra-n-butylammonium fluoride (1.7 g, 6.5 mmol) at room temperature. After quantitative reaction (18 h) the solvent

was evaporated and the mixture separated by column chromatography. The first compound eluted was 3 [1.45 g, 67%, R_f (*A*) 0.77], followed by 8 (0.13 g, 6%, R_f 0.57) and finally 6 (0.17 g, 8%, R_f 0.45). Compound 3 had the following properties: mp 98.5-99 °C, $[\alpha]_D^{20}$ +88.5° (c 1, acetone); ^{19}F NMR ($CDCl_3$) δ -199.7 (rel. to $CFCl_3$); MS *m/z* 219 (MH^+).

Anal. Calcd for $C_9H_{11}FO_5$ (218.2): C, 49.54; H, 5.08. Found: C, 49.24; H, 4.62.

5-Deoxy-5-fluoro-1,2-O-isopropylidene-ß-L-idofuranose (4). To a solution of 3 (1.0 g, 4.6 mmol) in methanol (20 mL) sodium borohydride (0.24 g, 5 mmol) was added with stirring at room temperature. After quantitative reaction [R_f (*B*) 0.57, 3 h] ethyl acetate (5 mL) was added, the solution filtered, and the solvent evaporated. Boric acid was removed as its methyl ester (formed on addition of methanol) by destillation. From the residue, 4 crystalized. The yield was 0.94 g (92%), mp 104-106 °C, $[\alpha]_D^{20}$ -21.5° (c 1, acetone).

Anal. Calcd for $C_9H_{15}FO_5$ (222.2): C, 48.64; H, 6.80. Found: C, 48.73; H, 6.85.

5-Deoxy-5-fluoro-α/ß-L-idofuranose (5). A solution of 4 (0.80 g, 3.6 mmol) in trifluoroacetic acid - water [1:1 (v/v), 16 mL] was stirred at 40 °C for 24 h. After evaporation of the solvent, the residue was dissolved in water (20 mL) and neutralized by treatment with strongly basic anion exchange resin (Merck 4767). After filtration and evaporation, 5 resulted as colourless syrup (0.56 g, 85%); R_f (*C*) 0.27; ^{1}H NMR (D_2O) *H*-1 δ 5.46 (ß-L, 53%), 5.24 (α-L, 47%).

5-Deoxy-5-fluoro-1,2-O-isopropylidene-α-D-glucofuranurono-6,3-lactone (8). Starting from 6 [4] and applying exactly the same procedure as given for the synthesis of 3, compounds 3 (11%), 8 (54%) and 1 (10%) were obtained. The intermediate triflate 7 [23] showed R_f (*A*) 0.57. Compound 8 had the following properties: mp

96-98 °C, $[\alpha]_D^{20}$ +69.6° (c 1, acetone); ^{19}F NMR ($CDCl_3$) δ -216.3 (rel. to $CFCl_3$); MS *m/z* 219 (MH^+).

Anal. Calcd for $C_9H_{11}FO_5$ (218.2): C, 49.54; H, 5.08. Found: C, 49.12; H, 4.63.

5-Deoxy-5-fluoro-1,2-O-isopropylidene-α-D-glucofuranose (9). Compound 9 was formed in 89% yield from the reduction of 8 (carried out as given for the L-*ido*-isomer 4); mp 108-110 °C, $[\alpha]_D^{20}$ -6.5° (c 1, acetone), R_f (*B*) 0.66.

Anal. Calcd for $C_9H_{15}FO_5$ (222.2): C, 48.64; H, 6.80. Found: C, 48.84; H, 6.74.

5-Deoxy-5-fluoro-α/ß-D-glucofuranose (10) was obtained from 9 by treatment with aqueous trifluoroacetic acid in 76% yield as a colourless syrup; R_f (*C*) 0.32; ^1H NMR (D_2O) *H*-1 δ 5.44 (α-D, 45%), 5.26 (ß-D, 55%).

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