# Fluorinated carbohydrates. Part VI.<sup>1</sup> Studies of derivatives of 3-deoxy-3-fluoro-D-galactose<sup>2</sup>

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A synthesis of 3-deoxy-3-fluoro-D-galactose from 1,2:5,6-di-O-isopropylidene- $\alpha$ -D-gulofuranose is described. The <sup>1</sup>H and <sup>19</sup>F n.m.r. spectra of several derivatives of D-galactose and of its 3-deoxy-3-fluoro derivative have been assigned in accord with previously established stereospecific dependencies. Canadian Journal of Chemistry, 48, 3946 (1970)

#### Introduction

Secondary sulfonate groups attached to five and six membered carbocycles can be displaced by fluoride ion using the combination tetra-alkylammonium fluoride-dipolar aprotic solvent (2). In the carbohydrate field, 1,2:5,6-di-O-isopropylidene-3-O-toluene-p-sulfonyl- $\alpha$ -D-allofurannose (5) was converted (3) ( $\sim$  75%) into 3-deoxy-3-fluoro-1,2:5,6-di-O-isopropylidene- $\alpha$ -D-glucofuranose using tetrabutylammonium fluoride in methyl cyanide. We now report a further application of this reagent in the synthesis of 3-deoxy-3-fluoro-D-galactose. Fluorinated hexoses are of interest as potential antitumor agents in connection with the inhibition of glycolysis (4).

#### **Results and Discussion**

1,2:5,6-Di-O-isopropylidene- $\alpha$ -D-gulofuranose is now readily available (5) and the 3-toluene*p*-sulfonate (6) (1) reacted completely during 48 h with tetrabutylammonium fluoride in methyl cyanide at 60° to give a mixture of 3-deoxy-1,2:5,- b-di-O-isopropylidene- $\alpha$ -D-erythro-hex-3-enofuranose (7) (2) and 3-deoxy-3-fluoro-1,2:5,6-di-Oisopropylidene- $\alpha$ -D-galactofuranose (3) in the ratio ca. 1:1.3. The chromatographic properties of compounds 2 and 3 were too similar to permit a convenient large-scale separation but, after platinum-catalyzed hydrogenation of the mixture at room temperature the crystalline fluoro derivative 3 and 3-deoxy-1,2:5,6-di-O-isopropylidene- $\alpha$ -D-xylo-hexofuranose (4) were readily separable by chromatography on Kieselgel.

It is interesting to note the difference in response of tosylates 1 and 5 to tetrabutylammonium fluoride – methyl cyanide. The latter compound reacts much more slowly (3) but apparently gives only fluoride.

Although H-2 is *trans* to the toxyloxy group in compound **5**, presumably elimination does not occur because a bridgehead double bond would result.

Treatment of the fluoro diketal **3** with an aqueous ethanolic suspension of Amberlite IR-120 (H<sup>+</sup>) resin gave crystalline 3-deoxy-3-fluoro-D-galactose (**6**). With acetic anhydride – sodium acetate, the fluoro sugar **6** gave 1,2,4,6-tetra-*O*acetyl-3-deoxy-3-fluoro- $\beta$ -D-galactose (**7**) which could be isomerized (8) with zinc chloride – acetic anhydride into the  $\alpha$ -anomer **8**.

Treatment of 3-deoxy-3-fluoro-D-galactose (6) with boiling 1% methanolic hydrogen chloride for 13 h gave a mixture of products. Chromatog-

<sup>&</sup>lt;sup>1</sup>This paper also constitutes Part IX of a series from University of British Columbia entitled "Studies of specifically fluorinated carbohydrates".

 $<sup>^{2}</sup>$ A preliminary report of some of these results has been published; see ref. 1.

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raphy on silica gel gave a small amount of material which was not further investigated but was tentatively identified as methyl 3-deoxy-3fluoro- $\beta$ -D-galactofuranoside. The major product was a mixture, viz., methyl 3-deoxy-3-fluoro- $\alpha$ , $\beta$ -D-galactopyranoside, in which the  $\alpha$ -anomer preponderated. Zinc chloride-catalyzed benzylidenation of the mixture, followed by chromatography on silica gel gave methyl 4,6-O-benzylidene-3-deoxy-3-fluoro-α-D-galactopyranoside (9, 56%) and the  $\beta$ -anomer (11, 31%). The anomers 9 and 11 gave crystalline acetates, 10 and 12 respectively.

H<sub>2</sub>C

H<sub>2</sub>Ć

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The proof of the structure of the derivatives in this study rests heavily on their <sup>1</sup>H and <sup>19</sup>F n.m.r. data. Hence particular care was taken to obtain detailed analyses of the spectra of certain key compounds, together with several related model compounds. The n.m.r. data obtained by firstorder analysis of the spectra of derivatives 3, 7, 8 and the model systems 13-16 are given in Tables 1-4; for convenience the pyranose and furanose systems are listed separately.

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To the best of our knowledge no detailed

 $R^{1} = H; R^{2} = OMe; R^{3} = Ac$ 



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# CANADIAN JOURNAL OF CHEMISTRY. VOL. 48, 1970 TABLE 1

	Chemical shifts (t-values, $\phi_c$ -values) of galactopyranose derivatives											
Derivative	H1	H <sub>2</sub>	H <sub>3</sub>	H <sub>4</sub>	H5	H <sub>61</sub>	H <sub>62</sub>	OAc	<sup>19</sup> F			
7*	4.36	4.62	5.30	4.41	← .	5.76–6	.08 →	7.88; 7.94 7.96; 8.00	+200.7			
8*	3.59	4.60	5.14	4.31	←	5.60–6	.05 →	7.89; 7.92 8.00; 8.02	+204.3			
13*	4.25	4.67	4.87	4.56	<del>~</del>	5.68	→ 7	7.84; 7.89 .97 (2); 8.02	—			
14†	3.68	4.80	4.63	5.50	←	5.77–6	$.01 \rightarrow \frac{7}{7}$	.85 (2); 7.97 .99; 8.01				

\*In CDCl<sub>3</sub> solution. †In (CD<sub>3</sub>)<sub>2</sub>CO solution.

	TABLE 2
Coupling constants (H	z) for galactopyranose derivatives

Derivative	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	J₄,5 ∼0.5	$J_{5,6_1} J_{5,6_2} J_{6_16_2}$	$J_{\rm F,2}$	$J_{\rm F,3}$	$J_{\mathrm{F,4}}$	Others	
7*	8.1	9.5	3.8		<i>↓ →</i>	11.5	47.4	5.6		
8*	3.6	10.0	3.6	1.0	, <u></u>	11.4	47.5	~6.4	$J_{\rm F,1} \sim 4.8$	
13*	7.6	10.2	3.3	~0.5	<i>←</i> →	-		_		
14†	3.3	10.0	2.9	1.4	$^{\ddagger} \longrightarrow$		_			

+In (CD<sub>3</sub>)<sub>2</sub>CO solution. ‡Indeterminate.

analysis has previously been given for the ringproton resonances of the pentaacetates of  $\alpha$ - and  $\beta$ -D-galactopyranose.<sup>4</sup> The coupling constants are much as would be anticipated with perhaps, the exception of the rather small value of  $J_{4,5}$ . It seems highly probable that this reflects the configurational dependence of vicinal <sup>1</sup>H-<sup>1</sup>H coupling constants (9-11). Thus, the C<sub>4</sub>—O<sub>4</sub> bond is antiparallel (see A) to the C<sub>5</sub>—H<sub>5</sub> bond as also is the C<sub>5</sub>—O<sub>5</sub> bond with respect to the C<sub>4</sub>—H<sub>4</sub> bond.

The close similarity between the  ${}^{1}H^{-1}H$  couplings of compounds 13 and 14 and their counterparts in the 3-deoxy-3-fluoro-D-galactose



systems, 7 and 8 respectively, is self evident. Insofar as the coupling constants listed in Table 2 are probably only accurate to  $\pm 0.5$  Hz, most of the pairs of couplings are identical within experimental error. This provides extremely strong evidence for the structures of 7 and 8.

The <sup>19</sup>F–<sup>1</sup>H couplings of compounds 7 and 8 provide further supporting evidence. Thus, we had previously established (12) that in the 3-deoxy-3-fluoro-D-glucose system,  $J_{F,2} \simeq 13$ Hz, which is reasonably close to the values observed for  $J_{F,2}$  in compounds 7 and 8. That  $J_{F,4}$  of compounds 7 and 8 is of smaller magnitude than  $J_{F,4}$  of the D-gluco compounds (~ 13 Hz) was not anticipated; this may be another example

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<sup>&</sup>lt;sup>4</sup>A referee noted that Lemieux and Stevens (21) had previously reported  $J_{1,2}$  8.4 Hz for the  $\beta$ -anomer (13). He also commented that the small size of  $J_{4,5}$  of galactopyranose derivatives had been noted before by Coxon and Fletcher (22) and by Cone and Hough (23). Neither of these papers proffered any rationale for their observation.

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Chemical shifts ( $\tau$ -values;  $\phi_c$ -values) of galacto- and gulo-furanose derivatives

Derivative	H <sub>1</sub>	H <sub>2</sub>	H3	H₄	H5	H <sub>61</sub>	H <sub>62</sub>	Me	<sup>19</sup> F	Others
3*	4.10	5.28	5.18	5.92	5.66	5.94	6.20	8.48; 8.57 8.65; 8.67	+ 187.9	
15*	3.98	5.27	4.83	5.83	5.52	5.86	6.06	8.42; 8.59 8.64; 8.67	_	Ph† 2.0, 2.5
16*	4.13	5.06	4.66	5.83	5.13	5.84	6.36	8.50; 8.58 8.62; 8.70	_	Ph† 2.0, 2.5

\*In CDCl<sub>3</sub> solution. †Complex multiplet.

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TABLE 4
Coupling constants (Hz) for <i>galacto</i> , and <i>gula</i> -furances derivatives

Derivative	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6_1}$	J <sub>5,62</sub>	$J_{6_{1}6_{2}}$	$J_{\rm F,2}$	$J_{\rm F,3}$	$J_{\rm F,4}$
3*	3.9	0.5	3.3	6.9	~6.2	6.4	8.0	15	51.6	23.7
15*	3.9	0.5	2.5	8.1	6.5	6.8	8.5	_	<del></del>	_
16*	4.0	5.6	6.4	9.0	6.5	7.1	8.4	-		_

of the configurational dependence of vicinal  ${}^{19}\text{F}^{-1}\text{H}$  couplings (13, 14).

It is interesting to note that the geminal  $F_3$ — $H_3$  couplings of compounds 7 and 8 are smaller than their counterparts in the D-gluco series (ca. 51 Hz). This relationship is formally analogous to that shown by glycopyranosyl fluorides (13) where compounds in the D-manno series (B) give smaller couplings than do their D-gluco counterparts (C).



The <sup>4</sup>J coupling of ca. 4.8 Hz between the F-3 and H-1 substituents of the  $\alpha$ -tetraacetate **8** is again in accord with the known stereospecificity of such couplings (15).

Analysis of the <sup>1</sup>H n.m.r. spectra of the 3-Obenzoyl-1,2:5,6-di-O-isopropylidene derivatives of D-galactose (15) and D-gulose (16) was straightforward and unambiguous. Comparison of the data obtained for these derivatives, listed in Tables 3 and 4, with that obtained for the 3-fluoro derivative (3) indicates quite unequivocally that the latter has the D-galacto configuration.

There is also a close similarity between the ring-proton couplings of compounds 3 and 15 and

those previously published (16) for 3-O-acetyl-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose  $\{J_{1,2} | 3.6, J_{2,3} < 0.5 \text{ Hz}\}$  and for (12) 3-deoxy-3-fluoro-1,2:5,6-di-O-isopropylidene- $\alpha$ -D-glucofuranose (17)  $\{J_{1,2} \ 3.7, J_{2,3} \ ca. \ 0.8 \ Hz\}$ . On this basis alone it might be concluded that both 3 and 17 favor the same  ${}^{3}T_{2}$  conformation, **D**. However, this is an over-simplified and inaccurate description; the apparent similarity between the values of  $J_{3,4}$  and of  $J_{F,4}$  for 3 and 17 do not allow for the difference of configuration at C-4. The coupling constants for compound 3 appear to be best rationalized on the basis of a preference for a conformation approximating to either the  $V_2$  or  $^{1}V$  conformation (E, F respectively). Either of these conformations would have the merit of positioning the cis oriented  $C_3$ —F and  $C_4$ —H<sub>4</sub> bonds in an eclipsed, or nearly so, orientation. Furthermore, either of these conformations would allow the  $C_2$ — $H_2$  and  $C_3$ — $H_3$  bonds to have the near-90° dihedral separation which is unequivocally dictated by their near-zero coupling constant.

Although it is not possible to distinguish unequivocally between  $\mathbf{E}$  or  $\mathbf{F}$ , it has often been assumed in the past<sup>5</sup> that the ring oxygen of a furanose sugar is one of the "in-plane" atoms:

<sup>5</sup>See refs. 17-19 and references cited therein.

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continuation of that assumption into the present discussion would clearly require the conclusion that 3 favors the V<sub>2</sub> conformation, E. In any event, a chemically significant fact emerges from the inter-comparison between derivatives 3 and 17. Namely, that the inversion of configuration at C-4 causes the furanose ring to change its conformation. Inspection of molecular models indicates that either the V<sub>2</sub> or <sup>1</sup>V conformations would reduce the non-bonded interaction which would otherwise exist if 3 favored the <sup>3</sup>T<sub>2</sub> conformation.

As has been discussed in detail elsewhere (17, 18) it is questionable whether it is realistic to couch any conformational discussion of a furanose system in terms of a single, exclusively populated conformation. The present discussion reinforces a previous suggestion (17, 18) that even *approximate* conformational evaluations of furanose systems can yield *chemically* significant conclusions. In the present situation, it could well be that the derivative has both the <sup>1</sup>V and the  $V_2$  conformers significantly populated, and that the observed coupling constants represent a timeaverage of the couplings of these two forms. There is no way of distinguishing between these two models.

In summary, the n.m.r. parameters of the derivatives discussed above are in close accord with previously established stereospecific dependencies.

# Experimental

Melting points are uncorrected. Thin-layer chromatography was performed using Kieselgel (Merck, 7731) and detection with iodine vapor or concentrated sulfuric acid. Unless otherwise stated, column chromatography was performed on Kieselgel (Merck, 7734). Gas-liquid chromatography was performed on a Pye 104 instrument with flame ionization detection using a column of poly-(ethylene glycol adipate) at  $165^{\circ}$ . Light petroleum refers to the fraction b.p.  $60-80^{\circ}$ .

The n.m.r. spectra were measured with a modified (20) Varian HA-100 spectrometer operating in the "frequency sweep" mode for <sup>1</sup>H resonances and (at 94 MHz) in the "locked, field-sweep" mode for <sup>19</sup>F resonances.

# 3-Deoxy-3-fluoro-1,2:5,6-di-O-isopropylidene-α-Dgalactofuranose

A mixture of 1,2:5,6-di-O-isopropylidene-3-O-toluenep-sulfonyl- $\alpha$ -D-gulofuranose (6) (2.5 g), tetrabutylammonium fluoride (8.8 g, 5.5 mole), and acetonitrile (25 ml, distilled from phosphorus pentaoxide) was stirred at 60-65° and monitored by t.l.c. (benzene-ether, 9:1). After 48 h, no starting material ( $R_F \sim 0.2$ ) survived and the product had  $R_F \sim 0.5$ . The reaction mixture was concentrated under diminished pressure and the syrupy residue was eluted from silica gel (Hopkin & Williams) with ether – light petroleum (1:1) to yield a syrupy major product (1.3 g), b.p. 90–100° (bath)/0.1 mm, which was homogeneous in t.l.c., but which, on examination by g.l.c.,  $v_{max}$ (liquid) 1660 cm<sup>-1</sup> (C=C) showed two components in approximately equal proportions, with retention times of *ca*. 20 (identical with that of 1,2:5,6di-O-isopropylidene-D-*erythro*-hex-3-enofuranose(7)) and 28 min.

A solution of the product mixture in ethanol (80 ml) was hydrogenated at atmospheric pressure over 5% palladized charcoal (600 mg). After 4 h, uptake of hydrogen was complete and the product showed two components in g.l.c. (retention times 28 and 41 min) and t.l.c. (benzene-ether, 9:1;  $R_F \sim 0.5$  and  $\sim 0.2$ ). Filtration of the mixture and concentration under diminished pressure yielded a syrup which showed no i.r. absorption at *ca.* 1660 cm<sup>-1</sup>.

Column chromatography (benzene-ether, 9:1) of the mixture yielded, as the faster moving component, 3-deoxy-3-fluoro-1,2:5,6-di-O-isopropylidene- $\alpha$ -D-galactofuranose (0.65 g, 41%), m.p. 48–49° [from ether – light petroleum (b.p. 80–100°)],  $[\alpha]_D^{25} - 30^\circ$  (c 1, chloroform). Anal. Calcd. for C<sub>12</sub>H<sub>19</sub>FO<sub>5</sub>: C, 55.0; H, 7.3; F, 7.3. Found: C, 55.4; H, 7.35; F, 7.3.

Further elution with benzene-ether (6:1) gave a product (0.58 g, 34%), m.p. 78.5–80° (from light petroleum),  $[\alpha]_{D}^{25} - 32°$  (c 4.0, ethanol) which was identical with 3-deoxy-1,2:5,6-di-O-isopropylidene- $\alpha$ -D-xylo-hexose (m.p. 81°,  $[\alpha]_{D}^{20} - 31.8°$  (ethanol)).

### 3-Deoxy-3-fluoro-D-galactose

A solution of 3-deoxy-3-fluoro-1,2:5,6-di-O-isopropylidene- $\alpha$ -D-galactofuranose (0.23 g) in ethanol (10 ml) and water (20 ml) was stirred at 60–65° with Amberlite IR-120 (H<sup>+</sup>) resin (ca. 2 ml). The hydrolysis was monitored by t.l.c. (ethyl acetate) and was shown to be complete in 6 h. Concentration of the filtered solution gave a chromatographically homogeneous crystalline product which, on recrystallization from ethyl acetate – ethanol, yielded 3-deoxy-3-fluoro-D-galactose (0.147 g, 91%), m.p. 114-116°, [ $\alpha$ ]<sub>D</sub><sup>25</sup> +87°  $\rightarrow$  +76° (24 h, equil., c 0.5, water),  $R_{\rm F} \sim 0.3$  (t.l.c., ethyl acetate – ethanol, 9:1), and  $R_{\rm G}$  2.04 (chromatography on Whatman No. 1 paper, butanol – acetic acid – water, 5:2:3, brown spot with aniline hydrogen phthalate).

Anal. Calcd. for  $C_6H_{11}FO_5$ : C, 39.6; H, 6.05; F, 10.5. Found: C, 39.5; H, 5.9; F, 10.9.

### 1,2,4,6-Tetra-O-acetyl-3-deoxy-3-fluoro-α- and -β-D-galactopyranose

When 3-deoxy-3-fluoro-D-galactose (180 mg) was treated with a boiling solution of sodium acetate (100 mg) in acetic anhydride (5 ml) for 10 min and the  $\beta$ -tetraacetate was isolated in the usual manner, the title compound (120 mg, 35%) was obtained m.p. 126–127° (from ethanol – light petroleum),  $[\alpha]_{D}^{25} + 35^{\circ}$  (c 0.8, chloroform).

Anal. Calcd. for  $C_{14}H_{19}FO_9$ : C, 48.0; H. 5.4. Found: C, 48.15; H, 5.25.

A solution of the foregoing  $\beta$ -anomer (130 mg) and zinc chloride (100 mg) in acetic anhydride (4 ml) was heated at *ca.* 100° for 10 min (8), then poured into icewater (40 ml) and extracted with chloroform (4 × 25 ml) in the usual way. Column chromatography (light petroleum – ether, 1:2) then yielded a homogeneous fraction (110 mg) which, after two recrystallizations from ethanol – light petroleum, afforded the α-tetraacetate (40 mg, 32%), m.p. 97–99°,  $[\alpha]_{\rm D}^{2.5} + 126°$  (*c* 1.1, chloroform). (Found: C, 48.3; H, 5.3.)

### Methyl Glycosidation of 3-Deoxy-3-fluoro-D-galactose

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A solution of 3-deoxy-3-fluoro-D-galactose (200 mg) in 1% methanolic hydrogen chloride (2 ml) was heated under reflux, and the reaction was followed by t.l.c. (ethyl acetate – ethanol, 95:5). After 13 h, only traces of starting material ( $R_F \sim 0.2$ ) remained and there were two major products ( $R_F \sim 0.4$ ,  $\sim 0.6$ ). The cooled reaction mixture was neutralized (PbCO<sub>3</sub>), filtered, and concentrated under diminished pressure. Column chromatography (ethyl acetate – ethanol, 95:5) of the residue gave first a product (46 mg,  $R_F \sim 0.6$ ) which was apparently homogeneous since the n.m.r. spectrum, (D<sub>2</sub>O, Perkin–Elmer R-10) showed, *inter alia*, singlets at  $\tau$  6.62 and 5.02 attributable, respectively, to OMe and H-1. After recrystallization from ethyl acetate, the compound had m.p.  $101-102^\circ$ ,  $[\alpha]_D^{25} - 13^\circ$  (c 0.6, ethanol).

Anal. Calcd. for  $C_7H_{13}FO_5$ : C, 42.9; H, 6.6. Found: C, 43.1; H, 6.5.

This minor product, which was not further investigated, is possibly methyl 3-deoxy-3-fluoro- $\beta$ -D-galactofuranoside.

The n.m.r. spectrum (pyridine, Perkin–Elmer R-10) of the second product (152 mg,  $R_{\rm F} \sim 0.4$ ) eluted from the column contained two signals (ratio *ca.* 3:2) attributable to OMe groups. Crystallization of the mixture from ethyl acetate gave methyl 3-deoxy-3-fluoro- $\alpha$ D-galactopyranoside, m.p. 160–170°,  $[\alpha]_{\rm D}^{2.5} + 150°$  (*c* 1, methanol) containing (n.m.r.) a small amount of the  $\beta$ -anomer.

Anal. Calcd. for C<sub>7</sub>H<sub>13</sub>FO<sub>5</sub>: C, 42.9; H, 6.6; F, 9.7. Found: C, 42.9; H, 6.6; F, 9.9.

After treatment of the pyranoside mixture (200 mg) with zinc chloride (200 mg) and benzaldehyde (3 ml) at room temperature in the usual manner for 16 h, only traces of starting material survived (t.1.c., chloroform) and two major products at ( $R_F \sim 0.2$ ,  $\sim 0.3$ ) were present. Column chromatography (chloroform) of the mixture

afforded, first, a product (162 mg, 56%) which was recrystallized from ethanol – light petroleum to give methyl 4,6-*O*-benzylidene-3-deoxy-3-fluoro- $\alpha$ -D-galacto-pyranoside, m.p. 160–161°,  $[\alpha]_{D}^{25}$  + 144° (c 0.5 chloroform).

Anal. Calcd. for  $C_{14}H_{17}FO_5$ : C, 59.2; H, 6.0. Found: C, 58.8; H, 5.9.

The acetate had m.p. 158–159°,  $[\alpha]_D^{25} + 152^\circ$  (c 0.5, chloroform).

Anal. Calcd. for  $C_{16}H_{19}FO_6$ : C, 58.9; H, 5.8. Found: C, 58.45; H, 5.6.

Eluted second was material (90 mg, 31%) which, on recrystallization from ethanol – light petroleum, gave methyl 4,6-*O*-benzylidene-3-deoxy-3-fluoro- $\beta$ -D-galactopyranoside, m.p. 197–199° ( $\alpha$ ]<sub>D</sub><sup>25</sup> – 36° (*c* 0.55, chloroform). (Found: C, 59.3; H, 5.7). The acetate had m.p. 168–169°, [ $\alpha$ ]<sub>D</sub><sup>25</sup> + 8° (*c* 0.5, chloroform). (Found: C, 59.35; H, 6.0).

## 3-O-Benzoyl-1,2:5,6-di-O-isopropylidene-α-D-gulo-

furanose

Treatment of 1,2:5,6-di-O-isopropylidene- $\alpha$ -D-gulofuranose (5) (1 g) with dry pyridine (20 ml) and benzoyl chloride (1.66 g) in the usual way gave the title benzoate (1.1 g), m.p. 153.5–154.5°,  $[\alpha]_D^{25} + 55^\circ$  (c 0.5, chloroform).

Anal. Calcd. for  $C_{19}H_{24}O_7$ : C, 62.6; H, 6.6. Found: C, 62.9; H, 6.9.

# Spectral Assignments

The overall assignments of the  ${}^{1}$ H n.m.r. spectra of derivatives 3, 7, 8, 13, 14, 15, and 16 were generally straightforward, with the sole exception of the C-5, -6 proton resonances of the pyranose derivatives 7, 8, 13, 14. These resonances were so closely coupled that an analysis was not accessible without recourse to computer techniques; it was not deemed worth-while to attempt this. Fortunately the other ring-proton resonances were sufficiently chemically shifted to enable a first order analysis to be applied.

The spectrum of the  $\alpha$ -tetraacetate (8), which is typical of those obtained from the pyranose derivatives, is shown in Fig. 1. The anomeric proton at low field showed as a triplet in this instance because of approximately equal couplings with both H-2 and F-3. The  $\beta$ -anomer 7 showed no such coupling with F-3. Clearly resolved in Fig. 1 is the rather small coupling between H-4 and -5. It is interesting to note the increased intensity build up in the H-3 quartet at  $\tau$  4.7 of the transitions associated with  $J_{2,3}$ ; the intensity slant of the corresponding  $J_{2,3}$ transitions is less marked. This reflects the difference in second order perturbations of the two halves of the H-3 resonance, the higher-field being the more weakly coupled to H-2.



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FIG. 2. Partial 100 MHz p.m.r. spectrum of 3-deoxy-3-fluoro-1,2:5,6-di-O-isopropylidene-α-D-galactofuranose (3) in CDCl<sub>3</sub> solution. The first-order assignments are as indicated.

The <sup>1</sup>H n.m.r. spectrum of 3-deoxy-3-fluoro-1,2:5,6-di-O-isopropylidene-α-D-galactofuranose (3), shown in Fig. 2, is a nice illustration as to the complexity of a spectrum which can be assigned intuitively, without recourse to either decoupling or computer facilities. Straightforward matching of the spectral splittings suffices to identify all of the transitions. It is important to note that several of the resonances, particularly those of H-2 and -3, evidence a number of long-range couplings which are not detailed in this paper; they will be discussed in another context elsewhere.

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