Carbohydrate Research, 40 (1975) 311–321

DEOXYFLUOROKETOHEXOSES*: 4-DEOXY-4-FLUORO-D-SORBOSE AND -TAGATOSE AND 5-DEOXY-5-FLUORO-L-SORBOSE

G. VENKAT RAO**, LAWRENCE QUE, JR.†, LAURANCE D. HALL‡, AND THOMAS P. FONDY††
Department of Biology, Syracuse University, Syracuse, New York 13210 (U. S. A.)
(Received October 25th, 1972; accepted in revised form October 30th, 1974)

ABSTRACT

4-Deoxy-4-fluoro-α-D-sorbose (**6**) was prepared in crystalline form by the action of potassium hydrogen fluoride on 3,4-anhydro-1,2-*O*-isopropylidene-β-D-psicopyranose (**3**) followed by deacetonation. Under identical conditions, 3,4-anhydro-1,2-*O*-isopropylidene-β-D-tagatopyranose (**7**) underwent epoxide migration to give 4,5-anhydro-1,2-*O*-isopropylidene-β-D-fructopyranose (**12**), which after deacetonation yielded 4-deoxy-4-fluoro-D-tagatose (**15**) and 5-deoxy-5-fluoro-α-L-sorbopyranose (**16**), the latter as the crystalline, free sugar. The action of glycol-cleavage reagents on the isopropylidene acetals of the deoxyfluoro sugars was consistent with the assigned structures. The structures were established by ^{13}C n.m.r. studies of the free deoxyfluoro sugars **6** and **16** and of the isopropylidene acetal **13**, and by ^{1}H n.m.r. studies on the acetylated isopropylidene acetals **5** diacetate, **13** diacetate, and **14** diacetate. 5-Deoxy-5-fluoro-L-sorbose (**16**) was biologically active, producing in mice effects characteristic of deoxyfluorotrioses and of fluoroacetate. 4-Deoxy-4-fluoro-D-tagatose (**15**) and 4-deoxy-4-fluoro-D-sorbose (**6**) produced no apparent effects in mice up to a dose of 500 mg/kg. The implications of these findings with respect to transport, phosphorylation, and the action of aldolase on ketohexoses are discussed.

INTRODUCTION

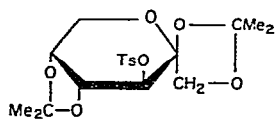
We have proposed[2] that 1-fluoro analogs of 1,3-dihydroxy-2-propanone 3-phosphate and of L-glycerol 3-phosphate (L-1-fluoro-2,3-propanediol 3-phosphate) might be useful in exploiting, for chemotherapy, differences in routes for phosphatidic acid biosynthesis that appear to exist between some types of cancer cells and cor-

*For a preliminary report, see ref. 1.
**Present address: Endo Laboratories, Garden City, New York 11530, U. S. A.
†Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, U. S. A.
‡Department of Chemistry, University of British Columbia, Vancouver 8, Canada.
††Recipient of Research Career Development Award No. 70332 from the National Cancer Institute.

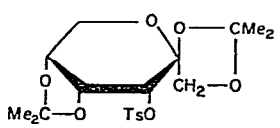
responding normal cells. Although we have undertaken work directly on the phosphorylated deoxyfluorotrioses[3,4], the problem of transport of these possible chemotherapeutic agents into cancer cells is likely to be a serious limitation. We have suggested that certain secondary deoxyfluorohexoses, which might gain access to cancer cells, could generate 1-fluoro-3-hydroxy-2-propanone 3-phosphate intracellularly. One such proposed hexose precursor of deoxyfluorotriose phosphates is 3-deoxy-3-fluoro-D-fructose. This rationale led us to seek methods for the introduction of fluorine into the 3- or 4-position of ketohexoses.

RESULTS AND DISCUSSION

Attempted tosyl-group displacement. — The displacement of secondary sulfonic esters of protected sugar derivatives by treatment with tetrabutylammonium fluoride in acetonitrile, or by alkali metal fluorides in ethylene glycol at elevated temperatures, has been used in the synthesis of secondary deoxyfluoro sugars[5,6]. Such displacement reactions have an advantage over other methods in the ease of predicting the configuration of the subsequently formed sugar, since only one fluorinated product should result. We attempted the displacement of the tosyl group in 1,2:4,5-di-*O*-isopro-



1

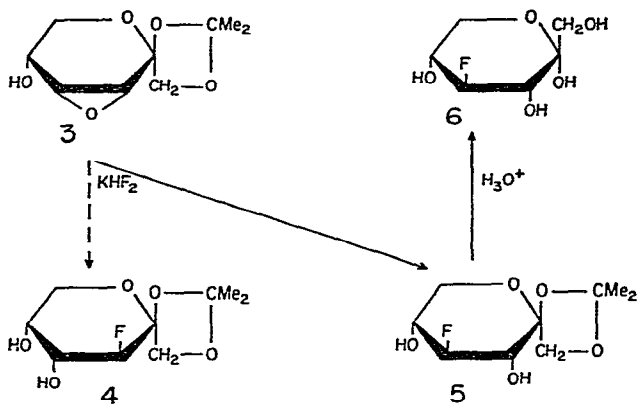


2

pylidene-3-*O*-*p*-tolylsulfonyl-β-D-fructopyranose[7] (**1**), and 1,2:4,5-di-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-β-D-psicopyranose[8,9] (**2**). However, neither of the sulfonic esters underwent displacement, even with such a powerful nucleophilic reagent as sodium azide in refluxing *N*,*N*-dimethylformamide over long periods.

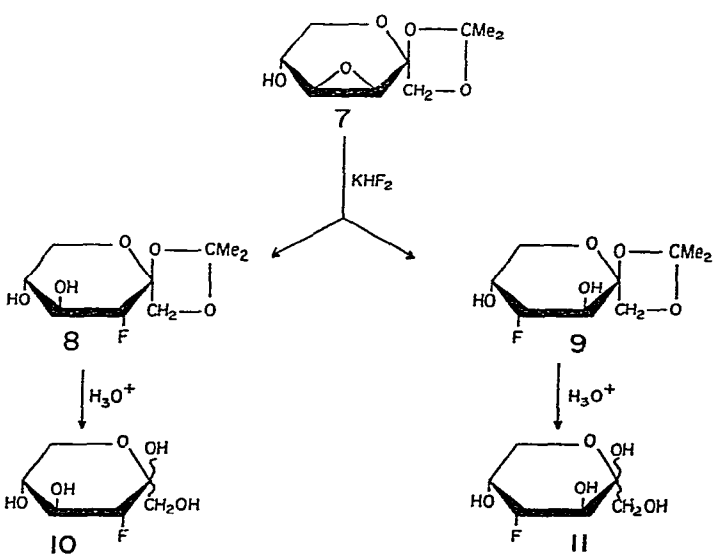
Epoxide cleavage with potassium hydrogen fluoride. — The cleavage of anhydro sugars with hydrogen fluoride at extremely low temperatures, or with potassium hydrogen fluoride in ethylene glycol at elevated temperatures, has been used extensively for the introduction of fluorine into a carbohydrate nucleus[10–12]. The temperature of boiling ethylene glycol has some deleterious effect on the products formed, and limits the use of some protective groups. We have examined the action of potassium hydrogen fluoride on 3,4-anhydro-1,2-*O*-isopropylidene-β-D-psicopyranose[13] (**3**), and 3,4-anhydro-1,2-*O*-isopropylidene-β-D-tagatopyranose[14] (**7**) in refluxing methyl Cellosolve (2-methoxyethanol, b.p. 126°, which is lower than that of ethylene glycol). Scission of the epoxide takes place smoothly, without any charring, and the isopropylidene acetal survives the conditions of the reaction.

Although the synthesis of several deoxyfluorohexoses and pentoses has been reported, it was only recently that a deoxyfluoroketohexose derivative was described[15], and to date none have been prepared as the crystalline, free sugars.



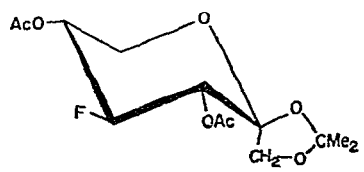
The ring opening of 3,4-anhydro-1,2-*O*-isopropylidene-β-D-psicopyranose (**3**) with potassium hydrogen fluoride in refluxing 2-methoxyethanol should give 3-deoxy-3-fluoro-1,2-*O*-isopropylidene-β-D-fructopyranose (**4**) and 4-deoxy-4-fluoro-1,2-*O*-isopropylidene-β-D-sorbopyranose (**5**). However, only one fluorinated derivative was found; its yield exceeded 80% and no second fluorinated product could be isolated. The crystalline, fluorinated product did not reduce sodium metaperiodate, nor did it react with lead tetraacetate, indicating that it had the sorbose configuration **5**. Deacetonation of compound **5** with aqueous acid gave 4-deoxy-4-fluoro-α-D-sorbopyranose (**6**), which crystallized readily from ethyl acetate–methanol.

The cleavage of the epoxide **3** resembles its behavior on alkaline scission[13]; treatment of **3** with alcoholic alkali gave extremely small amounts of fructose derivatives, whereas sodium methoxide in alcohol yielded the sorbose derivative in good yield[13].



Treatment of 3,4-anhydro-1,2-*O*-isopropylidene-β-D-tagatopyranose[14] (**7**) with potassium hydrogen fluoride in refluxing 2-methoxyethanol yielded several products, together with 25% of unreacted epoxide. Chromatographic resolution of the products gave 40% of an uncharacterized syrup and 35% of crystalline material. Repeated fractional crystallization of the latter from benzene yielded two monofluorinated products. Of the diols expected (**8** and **9**), only structure **8** should react with glycol-splitting reagents. The product melting at 153–157° did not react with sodium metaperiodate or lead tetraacetate, and therefore it was tentatively assigned the 4-deoxy-4-fluoro-1,2-*O*-isopropylidene-D-fructose structure **9**. The other monofluorinated product melting at 112–114° did consume sodium metaperiodate (very sluggishly, 0.9 mole per mole during 100 h, *trans*-diol), and hence was tentatively assigned the 3-deoxy-3-fluoro-1,2-*O*-isopropylidene-D-sorbose structure **8**. The compound tentatively designated **8**, on mild aqueous acidic treatment, gave a crystalline product tentatively designated 3-deoxy-3-fluoro-D-sorbose (**10**). Similar treatment of the product designated **9** gave a syrup designated as 4-deoxy-4-fluoro-D-fructose (**11**). Both free sugars reduced Benedict's reagent.

^1H and ^{13}C n.m.r. characterization of products. — The ^1H n.m.r. spectra of the di-*O*-acetyl-*O*-isopropylidene derivatives were recorded, and ^{13}C n.m.r. spectra were obtained for the two crystalline, free, fluoro sugars and for the isopropylidene precursor of the fluoro sugar that failed to crystallize. The product from the ring opening of epoxide **3** was conclusively shown to be **5**. Attack of fluoride on **3** could have given **4** and/or **5**. The proton geminal to fluorine can readily be identified by the



5(OAc)

characteristic, large ^{19}F–^1H coupling[16] (~50 Hz), and its multiplicity should provide an unequivocal distinction between **4** and **5**, as well as an approximate conformational assignment. Compound **4** should show the H-3 resonance as a doubletted-doublet whereas **5** should show the H-4 resonance as a doubletted-triplet. The observation, in the ^1H n.m.r. spectrum of the sole fluorinated product from **3**, of a resonance at τ 5.70 showing splittings of ~49, 6, and 7 Hz, readily reduced by ^1H-[^{19}F] decoupling[17], to a triplet having splittings of 6 and 7 Hz, immediately identifies this product as having the D-sorbose configuration **5** with the pyranose ring essentially in the $^5C_2$ conformation.

This assignment is confirmed by the ^{13}C n.m.r. spectrum of the free sugar. Chemical-shift and ^{19}F–^{13}C coupling-constant data for the sugars are presented in Table I. The magnitude of the ^{19}F–^{13}C coupling is dependent upon the distance of the ^{19}F from the ^{13}C in question[18]. A ^{19}F atom bonded directly to ^{13}C gives rise to

a large coupling-constant, in the order of 150–400 Hz. A ^{19}F atom two bonds away from ^{13}C exhibits couplings in the range of 15–40 Hz, whereas those separated by three bonds fall in the range of 0–10 Hz. Four-bond couplings are rarely observed. In addition, three-bond couplings show a Karplus type of dependence on dihedral angle[19,20], the value of the coupling constant being maximal when the dihedral angle is 180° and minimal when the angle is 90°. Thus, an equatorial ^{19}F would give rise to a large, three-bond coupling constant (6–10 Hz), whereas an axial ^{19}F would exhibit a smaller value (0–3 Hz).

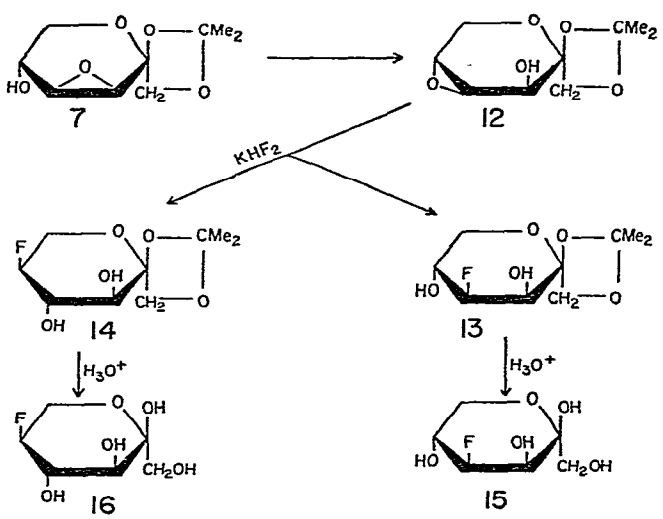
TABLE I

CHEMICAL-SHIFT[a] AND COUPLING-CONSTANT[b] DATA FOR FLUOROKETOHEXOSES[c]

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*
4-Deoxy-4-fluoro-α-D-sorbopyranose (**6**)	64.2	99.1 (10 Hz)	69.8 (17 Hz)	96.8 (178 Hz)	68.8 (17 Hz)	61.8 (10 Hz)
5-Deoxy-5-fluoro-α-L-sorbopyranose (**16**)	64.3	98.4	71.0 (7 Hz)	73.2 (17 Hz)	90.2 (178 Hz)	59.9 (26 Hz)
4-Deoxy-4-fluoro-1,2-*O*-isopropylidene-β-D-tagatopyranose (**13**)[d]	72.3	105.4	67.4 (26 Hz)	90.7 (178 Hz)	64.3 (17 Hz)	61.8

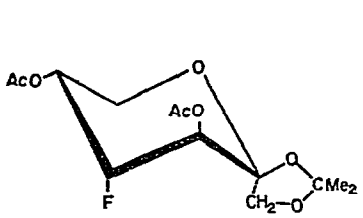
[a]In p.p.m. downfield from external Me_4Si. 1,4-Dioxane as internal standard. δ_{Me_4Si} for 1,4-dioxane, 67.4 p.p.m. [b]In parenthesis under chemical-shift values. [c]Assignments were based on Ref. 21 and ^{19}F–^{13}C coupling constants. [d]δ_{Me_4Si} for isopropylidene methyl carbons, 25.9 and 27.1 p.p.m. δ_{Me_4Si} for isopropylidene quaternary carbon, 113.9 p.p.m.

The ^{13}C n.m.r. spectrum of **5** exhibits six carbon resonances, five of which show ^{19}F–^{13}C coupling. The anomeric-carbon (C-2) resonance is readily identified because of its low field position. It exhibits a coupling constant of 10 Hz, implying an

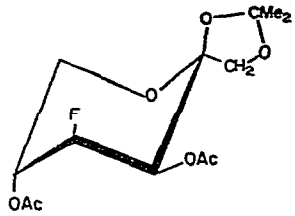


equatorial ^{19}F atom three bonds away. This places the ^{19}F at C-4, in agreement with the ^{1}H n.m.r. assignment. The chemical-shift data and the other coupling constants also support the structure **5**.

One of the products from the cleavage of epoxide **7**, designated as **10**, was not amenable to ^{1}H n.m.r. analysis. The ^{13}C n.m.r. spectrum of the free sugar shows six resonances, only four of which are coupled. The anomeric carbon (C-2) does not exhibit coupling. C-2 in **10** would be expected to show a two-bond coupling of about 20 Hz, but instead, C-6 exhibits this coupling. The product, is thus not the expected compound **10**, but is instead a 5-deoxy-5-fluoroketohexose. Epoxide migration in **7** could occur to form 4,5-anhydro-1,2-*O*-isopropylidene-β-D-fructopyranose **12** (see Acknowledgments). Fluoride attack on epoxide **12** would then produce 4-deoxy-4-fluoro-1,2-*O*-isopropylidene-β-D-tagatopyranose (**13**) and 5-deoxy-5-fluoro-1,2-*O*-isopropylidene-β-L-sorbopyranose (**14**). The rest of the ^{13}C n.m.r. data for the free sugar **16** are consistent with the assigned structure.



$9_{(OAc)}$



$13_{(OAc)}$

The other product from the cleavage of epoxide **7**, originally designated as **9**, showed a proton resonance at τ 5.35 with couplings of ~49, 3, and 3 Hz. The ^{13}C n.m.r. spectrum of the isopropylidene derivative shows an axial ^{19}F at C-4. These observations are consistent with either 4-deoxy-4-fluoro-1,2-*O*-isopropylidene-β-D-fructopyranose (**9**) having the $^{5}C_2$ conformation or 4-deoxy-4-fluoro-1,2-*O*-isopropylidene-β-D-tagatopyranose (**13**) having the $^{2}C_5$ conformation. The latter would be derived from fluoride attack at C-4 on epoxide **12**, the former by attack on C-4 of epoxide **7** prior to epoxide migration. Compound **9** in the $^{5}C_2$ conformation is energetically unfavored, having three bulky groups axially disposed[21]. The favored $^{2}C_5$ conformation of **9**, however, is not consistent with experimental data, and this product is, therefore, assigned as **13**.

Effects of deoxyfluoroketohexoses in mice. — The free fluoro sugars obtained in this work were examined for effects in BDF_1 mice by procedures described recently[4,22]. There were no apparent physiological effects of either 4-deoxy-4-fluoro-D-tagatose (**15**) or of 4-deoxy-4-fluoro-D-sorbose (**6**) at a dose of 500 mg/kg. On the other hand, 5-deoxy-5-fluoro-L-sorbose (**16**) produced striking effects characteristic of deoxyfluorotrioses[4], including extreme lethargy, deep hypothermia, and an approximate LD_{50} of 100 mg/kg (0.6 mmoles/kg). These results are comparable to the observations of O'Brien and Peters[23] on 2-deoxy-2-fluoro-DL-glyceraldehyde, which

exhibited an approximate LD_{50} in mice between 0.2 and 0.5 mmoles/kg. It is apparent that 5-deoxy-5-fluoro-L-sorbose is capable of being transported, and probably undergoes phosphorylation at either C-1 on C-6, or at both, followed by cleavage with aldolase to produce 2-deoxy-2-fluoro-L-glyceraldehyde or its phosphoric ester. The configuration of the vicinal hydroxyl groups at C-3 and C-4 in 5-deoxy-5-fluoro-L-sorbose is identical to the configuration in D-fructose, suggesting that the phosphorylated L-sorbose analog might well be a substrate for aldolase.

EXPERIMENTAL

General methods. — All melting points reported are uncorrected. Optical rotations were determined using a Perkin–Elmer 141 polarimeter. All evaporations were performed under diminished pressure (water aspirator) at 35–40° in a rotary evaporator. T.l.c. was performed on "Chromagram" (Eastman Kodak, Rochester, N.Y.) silica gel or cellulose sheets. Detection was effected by spraying with 4:1 ethanol–sulfuric acid, and heating for 5 min at 105° for the sugar derivatives, and with naphthoresorcinol reagent [0.2% alcoholic naphthoresorcinol (9 vol) and 1 vol 85% phosphoric acid], or Bial's orcinol reagent (2% orcinol in 2M hydrochloric acid) for the free sugars. Paper chromatography was conducted on Whatman No. 1 paper. The adsorbent for column chromatography was silica gel powder (Baker Analyzed Reagent Grade, 3405, 60–200 mesh, J. T. Baker, Co., Phillipsburg, N.J.). Elemental analyses were performed by Galbraith Laboratories Inc., Knoxville, Tenn. 37921.

^{1}H N.m.r. measurements were made with a modified Varian HA-100 spectrometer operating in the frequency-sweep mode. Spectra were recorded in chloroform-*d*, in benzene-d_6, and in acetone-d_6 solutions with tetramethylsilane as the internal reference for the lock system. The parameters were taken from spectra recorded at 250-Hz sweep width, in chloroform-*d* solutions.

^{13}C Fourier-transformed n.m.r. spectra were recorded with a Bruker HFX-90 spectrometer operating at 22.63 MHz and locked on external C_6F_6 with Digilab Models 400-2 pulse generator, 410 C pulse amplifier, and 50–80 proton broad-band decoupler. Spectra were obtained for 4000 transients with a 10-μsec pulse-width and a delay of 0.8 sec.

4-Deoxy-4-fluoro-1,2-O-isopropylidene-β-D-sorbopyranose (5). — To a solution of 3,4-anhydro-1,2-*O*-isopropylidene-β-D-psicopyranose (3, 4 g) {$[\alpha]_D^{24°}$ −50° (*c* 1.12, chloroform), lit.[13] $[\alpha]_D^{20°}$ −47.6°* (*c* 3.2, chloroform); m.p. 91–93°, lit.[13] 92°} in redistilled 2-methoxyethanol (60 ml), anhydrous potassium hydrogen fluoride (10 g) was added, and the mixture was heated for 16 h under reflux. The cooled mixture was poured with gentle stirring into an excess of saturated aqueous sodium hydrogen carbonate to give a solution that was slightly alkaline. After evaporation to dryness, the residue was extracted with three 100-ml portions of methanol, and the combined extract evaporated to dryness. This residue was exhaustively extracted with ether, and the extract evaporated to give a pale-yellow syrup (4.1 g) that readily solidified. T.l.c.

*Sign misprinted in ref. 15.

(7:3 ether–benzene, silica gel) revealed that **3** was absent and one major component was present, together with a very small proportion of slower-migrating component.

Crystallization of the crude product from benzene or light petroleum ether (b.p. 30–60°) yielded 3.1 g of compound **5**, m.p. 105–107°. The crude product (4.1 g) was also be purified by column chromatography; it was placed on a column of silica gel (2.5 × 45 cm, 80 g) that was eluted with 7:3 ether–benzene. The pure product (3.2 g) was obtained from the first three 100-ml fractions. Recrystallization from ether–light petroleum yielded **5** having m.p. 105–107°, $[\alpha]_D^{24°}$ −73.6°* (*c* 2.2, chloroform) (Found: C, 48.77; H, 6.78; F, 8.75. $C_9H_{15}FO_5$ calc.: C, 48.66; H, 6.80; F, 8.55).

The later fractions obtained from the column with increased concentrations of ether in the eluant yielded a small amount of syrup that crystallized after several weeks; m.p. 54–56°. Elemental analyses indicated that the product contained no fluorine.

Conventional acetylation of the crystalline product **5** with acetic anhydride–pyridine at room temperature gave 3,5-di-*O*-acetyl-4-deoxy-4-fluoro-1,2-*O*-isopropylidene-β-D-sorbopyranose which, on recrystallization from ligroin had m.p. 91°, $[\alpha]_D^{24°}$ −38° (*c* 0.8, ethanol). (Found: C, 51.10; H, 6.10; F, 6.07. $C_{13}H_{19}FO_7$ calc.: C, 50.98; H, 6.25; F, 6.20%).

*4-Deoxy-4-fluoro-*D*-sorbose* (**6**). — Compound **5** (2 g) in sulfuric acid (75 ml 25mM) was heated for 3 h in a boiling-water bath. After cooling and neutralization with solid barium carbonate, the suspension was filtered and the filtrate clarified by treatment with Celite (Johns–Manville) filter-aid. The clear filtrate was then evaporated to dryness to yield a pale syrup. Repeated evaporation of ethanol from this syrup afforded a brittle solid. Recrystallization from 9:1 ethyl acetate–methanol yielded crystalline **6**; m.p. 129–131°, $[\alpha]_D^{24°}$ +49° (*c* 2, water, unchanged during 48 h). (Found: C, 39.05; H, 6.11; F, 10.16. $C_6H_{11}FO_5$ calc.: C, 39.57; H, 6.08; F, 10.43%).

*3,4-Anhydro-1,2-*O*-isopropylidene-β-*D*-tagatopyranose* (**7**). — The procedure for the preparation of this epoxide was essentially the same as reported[14], except for the last step and the method of isolation.

To a solution of 3,5-di-*O*-acetyl-1,2-*O*-isopropylidene-4-*O*-(β-naphthalenesulfonyl)-D-fructose (60.1 g) in boiling, abs. methanol (500 ml) (under reflux and with stirring) was added a solution of sodium methoxide (2.8 g of sodium in 50 ml of abs. methanol) during 45 min. Heating was continued for an additional 2.5 h, during which time sodium β-naphthalenesulfonate separated out. The inorganic salt was filtered off and the filtrate concentrated to low volume. Additional precipitate was removed and the filtrate was evaporated to dryness. The residue was extracted twice with 250-ml portions of benzene, the combined extract was filtered, and the solvent evaporated off to yield a brown syrup. The syrup was redissolved in 25 ml of methanol, and the solution was poured into 500 ml of ice-cold water in a thin stream with vigorous stirring. After completion of the addition, stirring was continued for 10 min

*The levorotation has been confirmed by Richard Pero in our laboratory on the same preparation of **5**, and is at variance with a dextrorotation previously reported[15].

and the cloudy mixture was kept overnight. The solid that separated out was filtered off and the clear filtrate evaporated to dryness to yield a pale-yellow syrup (24 g). The last traces of water were removed by repeated evaporation of toluene from the residue. T.l.c. (7:3 ether–benzene, silica gel) indicated the presence of two components that migrated close to each other.

The crude product (4 g) was placed in a column of silica gel (2.5 × 45 cm, 80 g) and eluted with 7:3 ether–benzene. The material that emerged in the first two 50-ml fractions, on evaporation yielded a crystalline mass (1.85 g), m.p. 81–82° (lit.[14] m.p. 79–81°). Further elution with increased concentrations of ether yielded 2 g of a syrup that did not solidify on long standing.

The simple chromatographic procedure for isolation of the pure epoxide dispenses with the elaborate method described in the literature, which calls for an additional step, acetylation of the crude syrup, followed by purification of the 5-acetate, and finally deacetylation of the purified acetate and high-vacuum distillation of the epoxide. By this slightly modified procedure, approximately 12 g of the epoxide was obtained for the entire preparation as described.

Action of potassium hydrogen fluoride on 3,4-anhydro-1,2-O-isopropylidene-β-D-tagatopyranose (**7**). — To a solution of **7** (4 g) in redistilled 2-methoxyethanol (40 ml) was added anhydrous potassium hydrogen fluoride (10 g), and the mixture was boiled for 16 h under reflux. The mixture was processed as already described, to yield a pale-yellow syrup.

Examination of the syrup by t.l.c. (7:3 ether–benzene, silica gel) revealed the presence of unreacted epoxide, and several slower-moving components. The syrup was placed on a column of silica gel (2.5 × 45 cm) and eluted with 7:3 ether–benzene. The first and second 50-ml fractions were combined and on evaporation yielded 1 g of the starting epoxide. The next three fractions yielded 1.5 g of a crystalline material that melted at 102–106°. Further elution with increased amounts of ether yielded a syrup that became semi-solid on standing*.

4-Deoxy-4-fluoro-1,2-O-isopropylidene-β-D-tagatopyranose (**13**). — The foregoing crystalline material migrated slower than the starting epoxide on t.l.c. and had the same mobility as compound **5**. Two further recrystallizations from benzene raised the m.p. to 153–157° (0.75 g), $[\alpha]_D^{24°}$ −83° (*c* 2, chloroform). (Found: C, 48.46; H, 6.93; F, 8.92. $C_9H_{15}FO_5$ calc.: C, 48.46; H, 6.80; F, 8.55%).

Acetylation produced 3,5-di-*O*-acetyl-4-deoxy-1,2-*O*-isopropylidene-β-D-tagatopyranose (**13** diacetate) which, on recrystallization from ligroin, had m.p. 64–66°, $[\alpha]_D^{24°}$ −97° (*c* 0.8, ethanol). (Found: C, 51.35; H, 6.43; F, 6.22. $C_{13}H_{19}FO_7$ calc.: C, 50.98; H, 6.25; F, 6.20%).

5-Deoxy-5-fluoro-1,2-O-isopropylidene-α-L-sorbopyranose (**14**). — The mother liquors from all recrystallizations of **13** were pooled and evaporated to yield a crystalline residue. This was dissolved in the minimal volume of ether and kept for several days at 0°. Rectangular tablets (0.5 g), m.p. 112–114°, were obtained, $[\alpha]_D^{24}$ −76°

*Upon extended standing this material also crystallized, but further work-up yielded only **13** and **14**.

(*c* 2, chloroform) (Found: C, 49.22; H, 6.64; F, 8.27. $C_9H_{15}FO_5$ calc.: C, 48.66; H, 6.80; F, 8.55%).

After acetylation of **14**, the resultant 3,4-di-*O*-acetyl-5-deoxy-5-fluoro-1,2-*O*-isopropylidene-α-L-sorbopyranose on recrystallization from ligroin had m.p. 68–69°, $[\alpha]_D^{24}$ −37° (*c* 0.8, ethanol). (Found: C, 51.50; H, 6.28; F, 6.6. $C_{13}H_{19}FO_7$ calc.: C, 50.98; H, 6.25; F, 6.20%).

*4-Deoxy-4-fluoro-*D*-tagatose* (**15**). — Compound **13** was deacetonated as described for compound **5**. The free sugar was obtained only as a syrup (0.65 g), even after column-chromatographic purification, $[\alpha]_D^{24}$ −1.7° (*c* 0.77, water).

*5-Deoxy-5-fluoro-α-*L*-sorbopyranose* (**16**). — Deacetonation of **15** yielded a solid that crystallized from 9:1 ethyl acetate–methanol to give 0.65 g, of **16**, m.p. 122–124°, $[\alpha]_D^{24}$ −36° (*c* 0.9, water, the rotation was unchanged during 49 h). (Found: C, 39.58; H, 5.95; F, 10.11. $C_6H_{11}FO_5$ calc.: C, 39.57; H, 6.08; F, 10.43%).

Action of glycol-splitting reagents on compounds **5**, **13**, *and* **14**. — The action of sodium metaperiodate in acetate buffer (pH 5.5) and lead tetraacetate in acetic acid was examined on the three fluorohydrins, together with the known 3-*O*-acetyl-1,2-*O*-isopropylidene-D-fructose[24] as reference standard. The diols (**5** and **13**) consumed no metaperiodate or lead tetraacetate even after several days, whereas the diol **14** consumed 0.9 mole of periodate per mole of compound during 4 days. The reference compound reduced one mole of the cleaving reagent per mole of the hexose within 24 h.

Chromatographic examination of the deoxyfluoroketohexoses. — The three deoxyfluoroketohexoses (**6**, **15**, and **16**) were examined by t.l.c. on cellulose sheets with 3:2:6:24 butanol–pyridine–acetic acid–water together with D-fructose and L-sorbose as reference ketohexoses, and naphtholresorcinol for detection. The deoxyfluoroketohexoses migrated faster than the reference ketohexoses. The color of the spot for the 5-deoxy-5-fluoro-L-sorbose **16** was blue-green, whereas the others were generally purple.

Descending paper chromatography of the three deoxyfluoroketohexoses was performed on Whatman No. 1 paper with two different solvent systems, with Bial's orcinol reagent and naphthoresorcinol for detection. A solvent system of 5:1:4 butanol–acetic acid–water gave an R_F value for the deoxyfluoroketohexoses of 0.34 and for the reference ketoses 0.18. With the solvent system used for cellulose t.l.c., the deoxyfluoroketohexoses on paper chromatography had an R_F value of 0.61, whereas the reference ketoses had an R_F of 0.43. The same color differentiation already noted was observed.

ACKNOWLEDGMENTS

We are grateful to a referee who, in the course of reviewing this work for publication, suggested that epoxide migration of **7** to **12** was equally consistent with the data to that point. Subsequent ^{13}C n.m.r. spectral analysis undertaken in collaboration with L.Q., Jr., proved the suggestion to be correct.

Richard Pero carried out the synthesis of non-fluorinated model compounds for use in confirming the ^{13}C n.m.r. assignments.

This work was supported by Grant CA-10250 from the National Cancer Institute.

REFERENCES

1 G. V. Rao and T. P. Fondy, *Abstr. Papers Amer. Chem. Soc. Meeting*, 164 (1972) carb 21.
2 T. P. Fondy, G. S. Ghangas, and M. J. Reza, *Biochemistry*, 9 (1970) 3272.
3 G. S. Ghangas and T. P. Fondy, *Biochemistry*, 10 (1971) 3204.
4 T. P. Fondy, R. W. Pero, K. L. Karker, G. S. Ghangas, and F. H. Batzold, *J. Med. Chem.*, 17 (1974) 697.
5 A. B. Foster, R. Hems, and J. M. Webber, *Carbohyd. Res.*, 5 (1967) 292.
6 A. B. Foster, R. Hems, and J. H. Westwood, *Carbohyd. Res.*, 15 (1970) 41.
7 T. N. Montgomery, *J. Amer. Chem. Soc.*, 56 (1934) 419.
8 K. James, A. R. Tatchell, and P. K. Ray, *J. Chem. Soc.*, (C), (1967) 2684.
9 R. S. Tipson, R. F. Brady, Jr., and B. F. West, *Carbohyd. Res.*, 16 (1971) 383.
10 J. F. Codington, I. L. Doerr, and J. J. Fox, *J. Org. Chem.*, 29 (1964) 558.
11 I. Johansson and B. Lindberg, *Carbohyd. Res.*, 1 (1966) 467.
12 J. A. Wright and N. F. Taylor, *Carbohyd. Res.*, 3 (1967) 333.
13 H. Ohle and F. Just, *Ber.*, 68 (1935) 601.
14 H. Ohle and C. A. Schultz, *Ber.*, 71 (1938) 2302.
15 M. Sarel-Imber and E. D. Bergmann, *Carbohyd. Res.*, 27 (1973) 73.
16 L. D. Hall, J. F. Manville, and N. S. Bhacca, *Can. J. Chem.*, 47 (1969) 1.
17 R. Burton and L. D. Hall, *Can. J. Chem.*, 48 (1970) 59.
18 J. B. Stothers, *Carbon-13 NMR Spectroscopy*, Academic Press, New York, 1972, p. 362.
19 D. D. Giannini, P. A. Kollman, N. S. Bhacca, and M. E. Wolff, *J. Amer. Chem. Soc.*, 96 (1974) 5462.
20 M. Karplus, *J. Chem. Phys.*, 30 (1958) 11.
21 L. Que, Jr., and G. R. Gray, *Biochemistry*, 13 (1974) 146.
22 T. P. Fondy, K. L. Karker, C. Calcagnino, and C. A. Emlich, *Cancer Chemother. Rpts.*, 58 (1974) 317.
23 R. D. O'Brien and R. A. Peters, *Biochem. Pharmacol.*, 1 (1958) 3.
24 P. A. J. Gorin, L. Hough, and J. K. N. Jones, *J. Chem. Soc.*, (1955) 2699.