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4-DEOXY-4-FLUORO-1,2-*O*-ISOPROPYLIDENE-β-D-*xylo*-HEXULOPYRANOSE

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ABSTRACT

A 5-stage synthesis of the title compound (**11**), the first example of a secondary deoxyfluoroketose, is described*. The synthesis comprised the following reaction sequence: D-fructose→1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose (**4**)→1,2:4,5-di-*O*-isopropylidene-3-*O*-tosyl-β-D-fructopyranose (**3**)→3,4-anhydro-1,2-*O*-isopropylidene-β-D-*ribo*-hexulopyranose (**9**)→4-deoxy-4-fluoro-1,2-*O*-isopropylidene-β-D-*xylo*-hexulopyranose (**11**). Fluoride displacement at C-4 in **9** was effected with tetrabutylammonium fluoride in methyl cyanide. Similar treatment of either **3** or 1,2:4,5-di-*O*-isopropylidene-3-*O*-tosyl-β-D-*ribo*-hexulopyranose (**5**) failed to yield a fluoro derivative. Compound **5** was prepared by the sequence **4**→1,2:4,5-di-*O*-isopropylidene-β-D-*erythro*-hexo-2,3-diulopyranose (**6**)→1,2:4,5-di-*O*-isopropylidene-β-D-*ribo*-hexulopyranose (**7**)→**5**.

INTRODUCTION

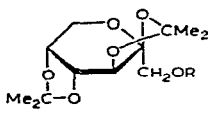
In recent years, numerous deoxyfluorocarbohydrates have been synthesized[1–5], with the ultimate purpose of obtaining biologically active compounds. All the known sugars of this type belong to the aldopentose and aldohexose series. No deoxyfluoroketose has been described hitherto*. We now report the synthesis of 4-deoxy-4-fluoro-1,2-*O*-isopropylidene-D-*xylo*-hexulopyranose, a derivative of the first, secondary deoxyfluoroketohexose.

RESULTS AND DISCUSSION

On the strength of previous experience, and in seeking to prepare fluoro derivatives of ketoses, the method of choice appeared to be the reaction of the sulphonic ester of a fully protected sugar with potassium fluoride. The following starting materials were prepared for this purpose: 2,3:4,5-di-*O*-isopropylidene-1-*O*-tosyl-β-D-fructopyranose (**1**) [obtained from 2,3:4,5-di-*O*-isopropylidene-β-D-fructo-

*Editorial footnote. In press at the time this paper was submitted was a report on the synthesis of 1-deoxy-1-halogeno-D-fructoses: J. E. G. Barnett and G. R. S. Atkins, *Carbohyd. Res.*, 25 (1972) 511.

pyranose[6] (**2**)], 1,2:4,5-di-*O*-isopropylidene-3-*O*-tosyl-β-D-fructopyranose (**3**) [obtained from 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose (**4**)], and 1,2:4,5-di-*O*-isopropylidene-3-*O*-tosyl-β-D-*ribo*-hexulopyranose (**5**). The last compound was prepared by oxidation[7] of **4** with methyl sulphoxide in acetic anhydride, followed by reduction[8] of the resulting ketone **6** with sodium borohydride and tosylation in the usual manner. In the reduction of **6**, no trace of a fructose derivative was detected.



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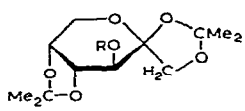
2 R = H



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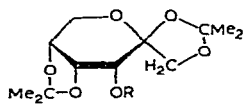

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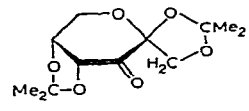

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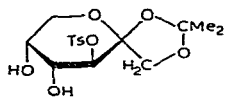

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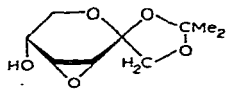

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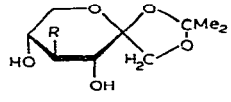
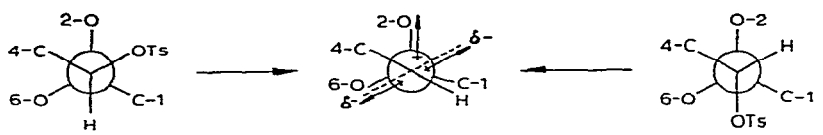


10 R = OH
11 R = F

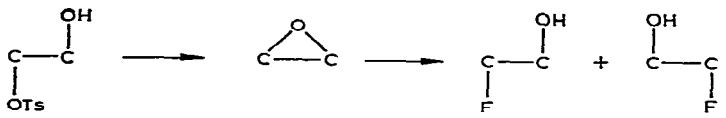
All attempts to replace the tosyl groups in **1**, **3**, and **5** by fluorine substituents failed. The following fluorinating agents were used: potassium fluoride or KHF_2 in acetamide at 190°, in *N*,*N*-dimethylacetamide or in *N*-methylpyrrolidone at their reflux temperatures, or in methyl sulphoxide at 100°, and tetrabutylammonium fluoride in acetonitrile, first at 50° and then at boiling temperature for several days.

It has been shown by p.m.r. studies[8–10] that the di-*O*-isopropylidene derivatives **2**, **4**, and **7** exist in a conformation which reflects a strong anomeric effect[9], and it is reasonable to assume that their toluene-*p*-sulphonates also exist in this conformation. The resistance of the sulphonyloxy group in the ketose derivatives **3** and **5** to fluoride displacement may be explained in terms of the interactions between the permanent dipoles about the anomeric group with those formed during the development of the transition state[12]. The permanent dipoles of the anomeric groups in **3** and **5** are best visualized by Newman projections along the respective C-2–C-3 bonds (**12** and **14**). On going from the ground state to the transition state **13** for each compound, unfavourable dipolar repulsions develop. A similar explanation has been invoked for 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose 1-toluene-*p*-sulphonate which is resistant to nucleophilic attack[13].



12 (*cf.* 3) 13 14 (*cf.* 5)

We therefore employed a different synthetic approach, based on the observation that sugar toluene-*p*-sulphonates containing a vicinal *trans*-hydroxyl group react with fluoride ion *via* an epoxide.



The starting material employed was 1,2-*O*-isopropylidene-3-*O*-tosyl-β-D-fructopyranose (**8**) which was prepared by partial hydrolysis of **3** using 80% acetic acid[6] or 1% sulphuric acid. When **8** was heated with potassium fluoride in *N*,*N*-dimethylacetamide for 90 min, it gave known[6] 3,4-anhydro-1,2-*O*-isopropylidene-D-*ribo*-hexulopyranose (**9**) which proved to be resistant to nucleophilic attack. Treatment of **9** with potassium fluoride in boiling *N*,*N*-dimethylacetamide for a week gave 1,2-*O*-isopropylidene-β-D-*xylo*-hexulopyranose (**10**), probably because of the presence of a small amount of water in the reaction mixture. The use of KHF_2 under similar conditions gave at least eight products (t.l.c.) which were not identified. The reaction **9**→**10** conforms to the Fürst–Plattner rule[14].

When **9** was heated with tetrabutylammonium fluoride in acetonitrile for 3 days, ~50% of the epoxide reacted to give 4-deoxy-4-fluoro-1,2-*O*-isopropylidene-β-D-*xylo*-hexulopyranose (**11**). The ^{19}F n.m.r. spectrum[11] showed two triplets with $J_{F,4}$ 46, $J_{F,3} \approx J_{F,5} \approx 9$ Hz. The peaks were somewhat broad, perhaps indicating long-range coupling. The fluorine substituent in **11** is in an environment similar to that in 2,4-di-*O*-acetyl-3-deoxy-3-fluoro-β-D-xylopyranosyl fluoride, which adopts a *1C* conformation[15]. Thus, it is reasonable to expect a considerable long-range coupling (~2.5 Hz) in **11** between F and H-6*ax*.

EXPERIMENTAL

Thin-layer chromatography (t.l.c.) was performed on microscope slides coated with Kieselgel D-5 (Camag). Optical rotations were measured with a Perkin–Elmer 141 Polarimeter, and n.m.r. spectra with a Varian HA-100D instrument at 100 MHz for ^1H spectra and at 94.1 MHz for ^{19}F spectra. Melting points are uncorrected.

*1,2:4,5-Di-*O*-isopropylidene-β-*D-erythro-*hexo-2,3-diulopyranose* (**6**). — 1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranose (**4**, 10 g) was dissolved in methyl sulphoxide (200 ml, distilled from calcium hydride), acetic anhydride (100 ml) was added, and the mixture was kept at room temperature and monitored by t.l.c. (25% acetone in toluene). After 20 h, the solvents were removed *in vacuo*, and finally at ≯65°/0.5 mmHg, and the syrupy residue was freed from traces of methyl sulphoxide by elution from Kieselgel 7734 with 25% acetone in toluene. The product was recrystallised from light petroleum (b.p. 60–80°) to give **6** (6 g, 60%) as colourless needles, m.p. 106°, $[\alpha]_D^{22}$ −122.6° (*c* 0.92, chloroform).

Anal. Calc. for $C_{12}H_{18}O_6$: C, 55.81; H, 6.99; Mol. wt., 258. Found: C, 56.04;

H, 7.19; Mol. wt. (mass spectrum), 258. The mass spectrum also shows additional peaks at *m/e* 243 ($M-CH_3$), 200 ($M-C_3H_6O$), 143, and 114.

1,2:4,5-Di-O-isopropylidene-3-O-tosyl-β-D-ribo-hexulopyranose (**5**). — To a solution of **6** (6 g) in 70% aqueous ethanol (300 ml), sodium borohydride (6 g) was added slowly. Reduction was complete within 30 min (t.l.c., 2% methanol in chloroform). After 2 h, the mixture was extracted with chloroform and the extract dried (Na_2SO_4) and concentrated. The residual syrup solidified slowly. Hydrolysis of a sample with boiling 5% sulphuric acid, followed by paper chromatography on Whatman No. 1 paper, showed the product to be *ribo*-hexulose.

A solution of the crude reduction product in pyridine (100 ml) was treated slowly with an excess of toluene-*p*-sulphonyl chloride, and the solution was kept at 0° for 24 h and then poured onto ice. The product was recrystallized from light petroleum (b.p. 60–80°) and then methanol to give **5**, m.p. 114°, $[\alpha]_D^{22}$ −159° (*c* 0.82, chloroform).

Anal. Calc. for $C_{19}H_{26}O_8S$: C, 55.07; H, 6.28; S, 7.73. Found: C, 54.94; H, 6.25; S, 7.57.

The mass spectrum contained the following peaks: *m/e* 399 ($M-CH_3$), 341 ($M-CH_3-C_3H_6O$), 259 ($M-C_7H_4OS$), 215, 192, 185.

3,4-Anhydro-1,2-O-isopropylidene-D-ribo-hexulopyranose[6] (**9**). — A solution of **3** (3 g) in methanol (60 ml) and 10% sulphuric acid (6.6 ml) was kept overnight at room temperature, then neutralized with potassium carbonate, and evaporated. The resulting white solid, which still contained inorganic salts, was recrystallised from a large amount of water to give 1,2-*O*-isopropylidene-3-*O*-tosyl-β-D-fructopyranose[6] (**8**, 1.2 g), m.p. 124°. Alternatively, the hydrolysis was carried out with 80% acetic acid.

A solution of **8** (7 g) in *N,N*-dimethylacetamide (50 ml) was heated under reflux with freshly dried potassium fluoride (20 g), with vigorous stirring. After 2.5 h, only traces of **8** remained (t.l.c., ethyl acetate–cyclohexane, 1:1). The cooled mixture was filtered and evaporated at 0.5 mmHg. Chloroform was then added, causing the precipitation of potassium toluene-*p*-sulphonate. The mobile syrup, which remained after evaporation of the filtered solution, was freed from contaminating *N,N*-dimethylacetamide by elution from Kieselgel 7733 (prewetted with cyclohexane) with cyclohexane–ethyl acetate (1:1). Recrystallisation of the product from light petroleum (b.p. 60–80°) gave **9** (50%) as white needles, m.p. 91°, $[\alpha]_D^{22}$ −47° (*c* 0.1, chloroform); lit.[6] m.p. 92°, $[\alpha]_D^{30}$ +47.6°.

1,2-O-Isopropylidene-β-D-xylo-hexulopyranose (**10**). — When the treatment of **8** with potassium fluoride in *N,N*-dimethylacetamide was continued for 3 days, **9**, formed first, was slowly converted (to the extent of 50%) into a product of lower R_F value. The crude product mixture was eluted from Kieselgel 7734 with cyclohexane–ethyl acetate (1:4). Combination and concentration of the appropriate fractions gave **10**, m.p. 148° (from ethanol), $[\alpha]_D^{21}$ −16.2° (*c* 1.4, water).

Anal. Calc. for $C_9H_{16}O_6$: C, 49.09; H, 7.27. Found: C, 49.35; H, 7.28.

Hydrolysis of a sample of **10** with boiling 10% sulphuric acid, followed by neutralisation with aqueous barium hydroxide and evaporation under reduced

pressure, gave a product with $[\alpha]_D$ +36° and the same R_F value as D-*xylo*-hexulose (paper chromatography, 1-butanol–acetic acid–water, 4:1:5).

*4-Deoxy-4-fluoro-1,2-*O*-isopropylidene-β-*D-xylo-*hexulopyranose* (**11**). — A solution of **9** (3 g) and tetrabutylammonium fluoride (30 g) in freshly distilled acetonitrile (60 ml) was heated for 8 days. The reaction was followed by t.l.c. At the end of this period, 50% of **9** had been converted into a product having an R_F value intermediate between those of **9** and **10**. The solvent was removed at 0.5 mmHg, and the residue was eluted from Kieselgel 7733 with ethyl acetate–cyclohexane (1:4) to give a mixture of **9** and **11**. Further chromatography on Kieselgel 7734, by elution with an ethyl acetate–cyclohexane gradient (5→20% of ethyl acetate), gave homogeneous **11** which was precipitated from ether by light petroleum and finally recrystallized from a large amount of light petroleum (b.p. 60–80°). The product, obtained as colourless needles, had m.p. 108°, $[\alpha]_D^{22}$ +77° (*c* 0.1, chloroform).

Anal. Calc. for $C_9H_{15}FO_5$: C, 48.64; H, 6.75; F, 8.55. Found: C, 48.46; H, 6.69; F, 8.73.

The mass spectrum showed peaks at *m/e* 207, 189, 187, 149, and 147, and the ^{19}F n.m.r. spectrum ($CDCl_3$) exhibited two triplets centered at 195.6 p.p.m. (CF_3Cl) with $J_{F,4}$ 46, $J_{F,3} \approx J_{F,5} \approx 9$ Hz. The ^1H spectrum showed, *inter alia*, two triplets with $J_{4,F}$ 47, $J_{3,4}$ 5, and $J_{4,5}$ 3 Hz.

REFERENCES

1 P. W. Kent, *Chem. Ind. (London)*, (1969) 1128.
2 D. M. Marcus and J. H. Westwood, *Carbohyd. Res.*, 17 (1971) 269.
3 J. Adamson and D. H. Marcus, *Carbohyd. Res.*, 13 (1970) 314.
4 A. D. Barford, A. B. Foster, J. H. Westwood, L. D. Hall, and R. N. Johnson, *Carbohyd. Res.*, 19 (1971) 49.
5 E. M. Bessell, A. B. Foster, J. H. Westwood, L. D. Hall, and R. N. Johnson, *Carbohyd. Res.*, 19 (1971) 39.
6 H. Ohle and F. Just, *Ber.*, 68 (1935) 601.
7 W. Sowa and G. H. S. Thomas, *Can. J. Chem.*, 44 (1966) 836.
8 G. M. Cree and H. S. Perlin, *Can. J. Biochem.*, 46 (1968) 765.
9 E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, *Conformational Analysis*, Interscience, New York, 1965, p. 408.
10 R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Amer. Chem. Soc.*, 80 (1958) 6098.
11 R. A. Dwek, P. W. Kent, P. T. Kirby, and A. S. Harrison, *Tetrahedron Lett.*, (1970) 2987.
12 A. C. Richardson, *Carbohyd. Res.*, 10 (1969) 395.
13 L. Hough and A. C. Richardson, in F. S. Coffey (Ed.), *Rodd's Chemistry of Carbon Compounds*, Vol. 1F, Elsevier, Amsterdam, 1967, p. 403.
14 Ref. 9, p. 102.
15 L. D. Hall, R. N. Johnson, A. B. Foster, and J. H. Westwood, *Can. J. Chem.*, 49 (1971) 236.