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SYNTHESIS OF GEM-DIFLUOROSACCHARIDES

R.A. Sharma, I. Kavai, Y.L. Fu[+] and M. Bobek*
Department of Experimental Therapeutics, Grace Cancer Drug Center, Roswell Park Memorial Institute, Buffalo, NY 14263.

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The biological properties of fluorinated saccharides and nucleosides have, in recent years, prompted the development of several useful methods for their synthesis[1-3]. In contrast to the considerable interest directed towards the synthesis and chemistry of fluorosugars in which a single fluorine atom becomes attached to carbon, the synthesis of gem-diflurosugars has not been extensively investigated. The first gem-difluorosaccharide, 2-deoxy-2,2-difluoro-D-arabino-hexose[4], has recently been prepared by addition of fluoroxytrifluromethane to 3,4,6-tri-O-acetyl-2-fluoro-D-glucal, followed by hydrolysis. Some gem-difluoromethylene sugar derivatives have been prepared[5,6] by treatment of sugar aldehydes and ketones with (difluoromethylene)triphenylphosphorane.

In connection with our efforts towards the synthesis of potential antitumor nucleosides, it became apparent that a general procedure for the preparation of gem-difluorosaccharides would be of considerable value. We now wish to report such a method based on the fluorination of sugar carbonyl groups. Sugar aldehydes and ketones can readily be prepared by oxidation[7] of the corresponding alcohols.

While aromatic and aliphatic gem-difluorides have been prepared by fluorination of the corresponding carbonyl derivatives, using reagents such as, SF_4[8], SeF_4 · pyridine[9], and dialkylaminosulfur trifluoride[10,11], an earlier attempt to replace the carbonyl oxygen in a sugar derivative, 1,6-anhydro-2,4-dideoxy-2,4-difluoro-β-D-ribo-hexopyranos-3-ulose, by fluorination with $PhSF_3$ failed[12]. We have found that diethylaminosulfur trifluoride[10,11,15] is a useful reagent for the replacement of the carbonyl oxygen in sugars and glycosides protected with the isopropylidene groups. The reaction appears to be general for sugar aldehydes and ketones in the pyranosyl form.

[+] Present address: International Paper Company, Tuxedo Park, N.Y. 10987

The following experimental procedures were found typical for fluorinating sugar aldehydes and ketones.

6-Deoxy-6,6-difluoro-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (4).

Crude 1,2:3,4-di-O-isopropylidene-α-D-galacto-hexodialdo-1,5-pyranose[13] (3, 8.16g, 0.031 mol) was dried by distilling 100 ml of dry toluene from its solution. It was then dissolved in 150 ml of CH_2Cl_2 and 10 ml (0.08 mol) of diethylaminosulfur trifluoride (DEST) was added under N_2 to this solution. The reaction mixture was stirred at room temperature under nitrogen for 16 hrs. It was then washed with $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 and the combined organic solution was dried (Na_2SO_4). The crude product, obtained by evaporating the solvent, was purified on a dry silica gel column using benzene as eluent.

Compound 4 was obtained as an oil (3.78 g, 46% yield) which solidified when kept at room temperature for a few days; m.p. 48-50°.

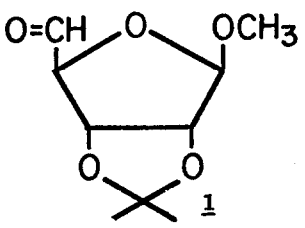
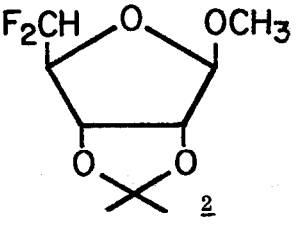
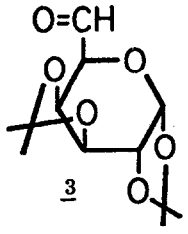
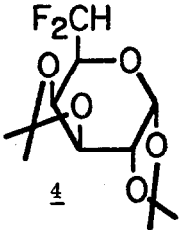
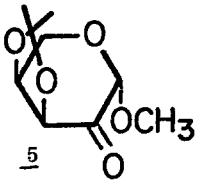
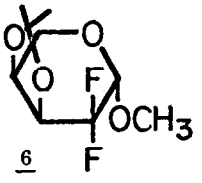
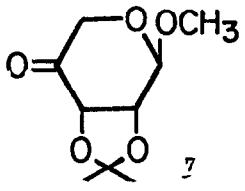
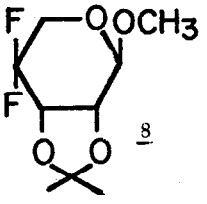
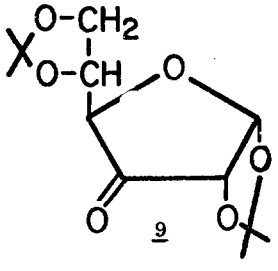
Methyl 2-deoxy-2,2-difluoro-3,4-O-isopropylidene-β-L-erythro-pentopyranoside (6).

Methyl 3,4-O-isopropylidene-β-L-erythro-pentuloso-pyranoside (5, 1.95 g, 0.0097 mol), which was prepared by the oxidation of methyl 3,4-O-isopropylidene-β-L-arabino-pyranoside by DMSO-Ac_2O, was dried by distilling approximately 100 ml of dry toluene from its solution. It was then dissolved in 100 ml of benzene and to this solution was added under N_2 3 ml (0.024 mol) of DEST. The reaction mixture was refluxed for 16 hrs under N_2, cooled, and then washed with $NaHCO_3$ solution. The aqueous layer was washed with $CH Cl_3$ (50 ml) and the combined organic solution was dried (Na_2SO_4). Evaporation of this solution and purification of the residue on a dry silica gel column, using benzene as the eluent, gave 0.54 g (25% yield) of syrupy 6.

Satisfactory analytical data (C, H, F) were obtained for compounds 2, 4, 6 and 8. These compounds were further characterized by mass and ^{19}F magnetic resonance spectroscopy. In the mass spectra of these derivatives, M^+-15 peaks were obtained, resulting from the loss of one CH_3 group, which is a characteristic feature for sugar derivatives containing an isopropylidene group[14].

The application of this method to the synthesis of other gem-difluorosaccharides and to gem-difluoronucleosides is underway in our laboratory.

Table 1 - Some Physical and Chemical Characteristics of Newly Prepared gem-Difluorosugar Derivatives

Carbonyl Compound	Product	Yield[a]	Mass Spectrum (m/e)	^{19}F NMR Chemic: Shift[b] (ppm)
 1	 2	45%	209(M^+ - 15)	129.0[c]
 3	 4	46%	265(M^+ - 15)	131.6(Fa)[d] 133.6(Fb)
 5	 6	25%	209(M^+ - 15)	126.2(Fa)[e] 146.1(Fb)
 7	 8	36%	224(M^+) 209(M^+ - 15)	113.1(Fa)[f] 115.9(Fb)
 9	Decomposition			

a) Yields were not optimized, b) measured in $CDCl_3$ - $CFCl_3$(ϕ_c value), c) q, J_{FH} 10 Hz, $J_{FH(4)}$ 56 Hz

d) m, J_{FaFb} 298.2 Hz, J_{FaH} 10 Hz, $J_{FaH(5)}$ 57.3 Hz, J_{FbH} 5.5 Hz, $J_{FbH(5)}$ 54.7 Hz, e) complex multi

f) complex multiplets J_{FaFb} 256.5 Hz

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References

1. A.B. Foster and J.H. Westwood, Rev. Pure Appl. Chem., 35, 147 (1968).

2. J. Podešva and J. Pacák, Chem. Listy, 67, 785 (1973).

3. M.J. Robins, M. MacCoss, S.R. Naik, and G. Ramani, J. Amer. Chem. Soc. 98, 7381 (1976).

4. J. Adamson, A.B. Foster, and J.H. Westwood, Carbohyd. Res., 18, 345 (1971).

5. J.M.J. Tronchet, B. Baehler, and A. Bonenfant, Helv. Chim. Acta, 59, 941 (1976).

6. J.M.J. Tronchet, D. Schwarzenbach, and F. Barbalat-Rey, Carbohyd. Res., 46, 9 (1976).

7. J.G. Moffatt, in "Techniques and Applications in Organic Synthesis, Vol. II, 1, (Ed. R.L. Augustine and D.J. Tucker), Marcel Dekker, New York, New York, 1971.

8. W.A. Sheppard and C.M. Sharts, "Organic Fluorine Chemistry, " W.A. Benjamin, New York, NY 1969.

9. G.A. Olah, M. Nojima, and I. Kerekes, J. Amer. Chem. Soc., 96, 925 (1974).

10. L.N. Markovskij, V.E. Pashinnik, and A.V. Kirsanov, Synthesis, 787 (1973).

11. W.J. Middleton, J. Org. Chem., 40, 574 (1975).

12. D. Stropová, Thesis, Charles University, Prague, Czechoslovakia, 1971, J. Podešva and J. Pacák, Chem. Listy, 67, 785 (1973).

13. D. Horton, M. Nakadate, and J.M.J. Tronchet, Carbohyd. Res., 7, 56 (1968).

14. D.C. DeJongh and K. Biemann, J. Amer. Chem. Soc., 86, 67 (1964).

15. M. Sharma and W. Korytnyk, Tetrahedron Lett., 573 (1977).