Tetrahedron Letters No. 6, pp 573 - 576, 1977. Pergamon Press. Printed in Great Britain.

A GENERAL AND CONVENIENT METHOD FOR SYNTHESIS OF 6-FLUORO-6-DEOXYHEXOSES

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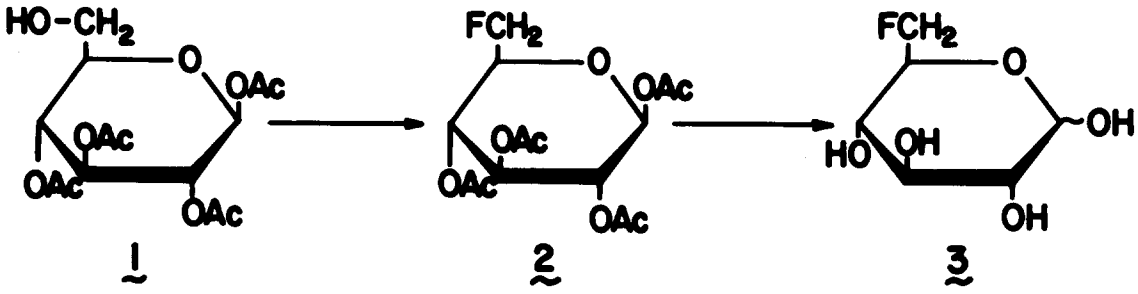
(Received in USA 28 December 1976; received in UK for publication 12 January 1977)

There have been considerable interest in the chemistry and biological activity of the fluorinated carbohydrates. Replacement of the OH group with F introduces relatively small changes in the polarity and Van der Waals radii of the fluorinated carbohydrate analogues.[1,2] Such analogues have been utilized for studies of the active sites of enzymes and of membrane transport systems[2]; of chemotherapeutic interest is the observation that 6-fluoro-6-deoxy-D-glucopyranose (3) was active against solid tumors.[3] At present, the synthesis of 6-fluoro-6-deoxypyranoses is fraught with difficulties, as the fluorinating agents require vigorous reaction conditions and appropriate blocking groups that can withstand those conditions, such as acetal and benzyl groups. Even then, serious side reactions are often encountered.[1]

We have found that the recently introduced fluorinating agent diethylaminosulfur trifluoride[4] is mild enough that O-acetyl groups are adequate for protection. This finding is illustrated by the following synthesis of 6-fluoro-6-deoxy-D-glucopyranose (3) from the readily available 1,2,3,4-tetra-O-acetyl-β-D-glucopyranose (1):



1 2 3

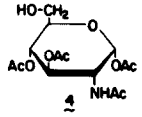
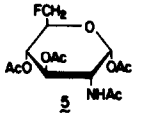
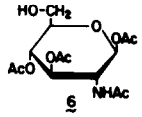
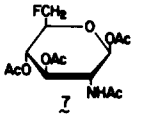
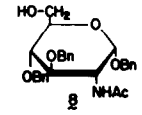
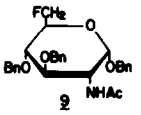
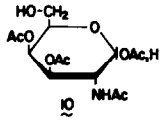
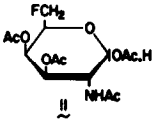
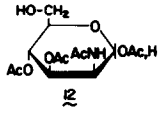
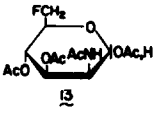
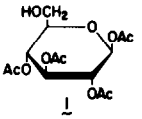
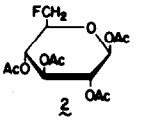
A solution of 1 (350 mg, 1.01 mmol) in diglyme (3 ml, dry) was added to a cooled (-10°) and stirred solution of diethylaminosulfur trifluoride (0.5 ml, 4.0 mmol) in diglyme (3 ml). The temperature was slowly raised to 60° and maintained there for 3 hr. The reaction mixture was poured into ice, and the precipitated product was recrystallized from ethanol-ether; m.p. 125-126° (lit.[6] m.p. 125-126°); yield 300 mg (85%). The acetyl derivative has been deacetylated[7] (2:1:1 MeOH-H_2O-Et_3N) to 3.

Being interested in 6-fluoro-6-deoxy analogues of 2-amino-2-deoxy sugars as potential cell-surface modifiers and inhibitors,[8] we prepared the starting materials for these analogues by tritylation, acetylation, and detritylation (Table 1, first column). The starting materials were subjected to the fluorination reaction, as outlined in Table 1. The yields were satisfactory in most cases, and the products were crystalline, except for 11 and 13, which were mixtures of a α- and β-anomers, as were starting materials 11 and 12, respectively. Fluorination of the benzylated D-glucosamine analogue 8 (Bn = benzyl) was also included, to indicate tha applicability of the method in the presence of other blocking groups. To establish the specificity of the reaction, benzyl-2-acetamido-2-deoxy-α-D-glucopyranoside was treated with the fluorinating agent, and the 6-fluoro-6-deoxy derivative was obtained, as shown by the ^{19}F NMR spectrum of the product, indicating that the reaction is specific for the primary hydroxyl group.

The 6-fluoro-6-deoxy carbohydrates prepared gave the correct chemical analyses and were characterized by ^1H and ^{19}F NMR spectra. The latter gave a sextet for all of the carbohydrate analogues that were examined, because of geminal and vicinal couplings of ^{19}F protons.[9] The α and β anomers 5 and 7, respecitively, are characterized by slightly different chemical shifts and vicinal coupling constants. The geminal coupling constants, however, remained essentially the same throughout the series. A considerably smaller vicinal $^{19}F^1H$ coupling constant for the 6-fluorodeoxygalactose

derivative 11 is due to destabilization of the predominantly anti C_5H-C_6F rotamer (prevalent in gluco and manno derivatives) in the galactopyranoses, probably because of the axial acetoxy function at C-4, as has been pointed out by Hall.[9]

Table 1- Reaction Conditions for the Preparation, Yields and ^{19}F NMR Spectra of 6-Fluoro-6-Deoxyhexoses.

Starting Material	Product	Reaction Conditions[a]	Yield[b]	Chemical Shift[c] (ppm)	^{19}F NMR Geminal ^{19}F-^1H coupling (Hz)	Vicinal ^{19}F-^1H coupling (Hz)
 4	 5	At 0° for 1hr, then at 40° for 1hr.	80%	233.1	46.9	23.0
 6	 7	At -10° for 10-15min, then at 25° for 2hrs.	85.2%	232.5	48.2	21.8
 8	 9	In CH_2Cl_2 at 0° for 1hr, then at 25° for 1hr.	92%	233.7	47.5	22.5
 10	 11	At 0° for 10-15min, then at 25° for 1.5hrs.	68%	230.8[d]	47.5[d]	18.5[d]
 12	 13	At -10° for 10-15min, then at 25° for 1.5hrs.	70%	234.0[e] 233.3[e]	49.5[e] 47.5[e]	26.0[e] 23.5[e]
 1	 2	At -10° for 10-15min, then at 60° for 3hrs.[f]	85%	233.5	48.2	22.0

(a) Reaction carried out in diglyme unless otherwise stated, (b) By isolation
(c) In $CDCl_3$ $CFCl_3$ (ϕ_c value); (d) Spectrum of the predominant anomer
(e) Anomer not assigned; (f) See text for details

Acknowledgments

This study was supported in part by research grants (CA-08793 and CA-16065) from the National Institutes of Health. We are indebted to Dr. William Middleton for advice. We also thank Ms. Onda Dodson Simmons for determining the NMR spectra.

References

1. P.W. Kent, in "Ciba Foundation Symposium on Carbon-Fluorine Compounds," Elsevier, Associated Publishers, New York, 1972, p. 169.

2. J.E.G. Barnett, idem, p. 95.

3. E.M. Bessel, V.D. Courtenay, A.B. Foster, M. Jones, and J.H. Westwood, Europ. J. Cancer 9, 463 (1973).

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

5. (a) Organic Syntheses, E.C. Horning, ed., Collective Volume 3, John Wiley & Sons, New York 1955, p. 432.

(b) B. Helferich and W. Klein, Ann. 450, 219 (1926).

6. B. Helferich and A. Gnuchtel, Chem. Ber. 74, 1035 (1941).

7. R.U. Lemieux and H. Driguez, J. Am. Chem. Soc. 97, 4063 (1975).

8. M. Sharma, R. Bernacki and W. Korytnyk, Fed. Proc. 34, 574 (1975).

9. L. Evelyn and L.D. Hall, Carbohydrate Res. 47, 285 (1976).