Tetrahedron Letters,Vol.23,No.29,pp 2927-2930,1982 0040-4039/82/292927-04$03.00/0
Printed in Great Britain

UTILITY OF DAST (DIETHYLAMINOSULFUR TRIFLUORIDE) IN THE CHEMISTRY OF CARBOHYDRATES: SYNTHESIS OF 3,4,6-TRIDEOXY-3,4,6-TRIFLUORO-α-D-GALACTOPYRANOSYL FLUORIDE

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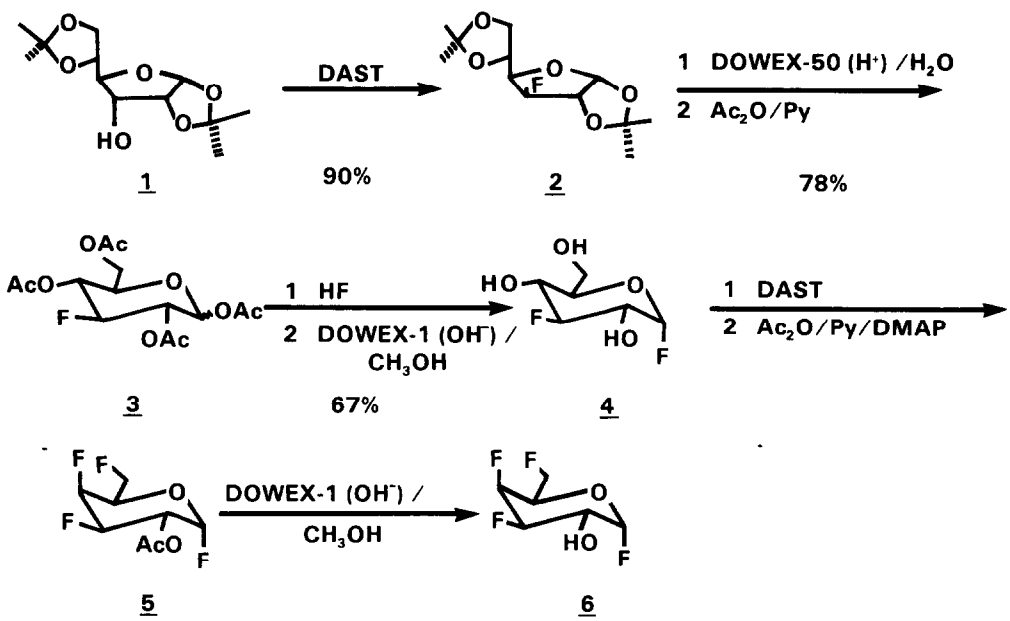
ABSTRACT: The tetrafluorogalactose derivative 6 has been synthesized in five steps starting from a protected allose precursor.

During the past decade, the field of fluorinated carbohydrates has burgeoned into an area of intensive scientific investigation.[1,2] The impetus for this interest has been the known biological activity of these compounds, serving as psuedo-substrates in enzyme inhibition studies. For example, 2-deoxy-2-fluoro hexoses have been shown to inhibit glycoprotein synthesis in uninfected and virus infected yeast cells.[3,4] Another example involves the detrimental effect of 3-deoxy-3-fluoroglucose in the metabolism of Saccharomyces cerevisiae, leading to inhibition of polysaccharide synthesis.[5]

Specifically fluorinated carbohydrates also provide a unique stereochemical framework for investigations of conformation by techniques such as ^{1}H-, ^{13}C-, and ^{19}F-NMR spectroscopy. Although a variety of difluorinated carbohydrates have been investigated in this regard, very few if any, tri- and tetra-fluorinated analogs have similarly been examined: this is primarily due to a lack of efficient synthetic routes into such compounds. This letter details the synthesis of the first tetrafluorinated carbohydrate derivative (6) accompanied with a complete analysis of its ^{13}C-, ^{1}H-, and ^{19}F-NMR spectra.

3-Deoxy-3-fluoro-α-D-glucopyranosyl fluoride 4, the key prefluorinated precursor needed for the synthesis of 6, was obtained in 47% overall yield from commercially available 1,2:5,6-Di-O-isopropylidene-α-D-allose[6] via modified literature methods (scheme).[7] Compound 4 (4 g) was purified by crystallization from acetonitrile (10 mL); mp 232°C (dec); $[\alpha]_D^{22}$ +99.8° (c 2, MeOH); ^{1}H NMR (CD_3OD) δ 5.75 (ddd, 1H, J = 3.1, 4.1 and 53.3 Hz), 4.65 (dt, 1H, J = 53.3 and 53.7 Hz), 4.01 - 3.77 (m,5H).[8] This compound was then converted to 6 in the following manner. Powdered 4 (2 g, 10.9 mmol) was added to neat DAST[9] (10.1 g, 62.7 mmol) at room temperature, under nitrogen. The resulting heterogeneous reaction mixture was mechanically stirred for 5 d and then quenched, at 0°C, by the addition of a pyridine-acetic anhydride solution (100 mL, 2:1 v/v) containing 4-dimethylaminopyridine (0.1 g). After 1 d at room temperature, this solution was poured into ice water and processed by extraction with chloroform (4 x 100 mL). Standard work-up followed



1 2 3 4 5 6

SCHEME

by chromatography on silica gel;[10] using 5% ethyl acetate-hexane as eluant, gave 5 (R_f 0.13); yield 1.21 g (48%); mp 59-60°C; $[\alpha]_D^{22}$ + 124.2° (c 2, $CHCL_3$).[11] Deacetylation of this material, using Dowex-1 (OH^-, 1 g) in methanol (100 mL), gave 6 as flaky white crystals: yield 0.8 g (96%); mp 120.5-122°C; $[\alpha]_D^{22}$ + 96.05° (c 2, MeOH).[12]

The regiochemistry and stereochemistry of the final product was established by detailed multinuclear NMR experiments; tables 1 and 2 summarize the chemical shifts and coupling constants, respectively. A perusal of this data provides good evidence for the introduction of fluorine at positions 4 and 6. Thus, the proton decoupled ^{19}F-NMR spectrum produces a doublet for F-1, with J = 3.7 Hz, indicating long range coupling to F-3 and confirming the absence of fluorine at C-2. The stereochemistry at C-4 is clearly evident from the large trans diaxial vicinal couplings obtained for F-4 ($^3J_{H_3F_4}$ = 26.8 Hz; $^3J_{H_5F_4}$ = 28.7 Hz) which contrasts with the smaller coupling constants expected for a H_aF_e vicinal arrangement ($^3J_{F_3H_2}$ = 11 Hz). The recent reported conversion of methyl-α-D-glucopyranoside to methyl

TABLE 1. CHEMICAL SHIFTS (PPM) AND MULTIPLICITIES IN THE NMR SPECTRA OF 6.[a]

RING POSITION / NUCLEUS	1.	2.	3.	4.	5.	6.	6'.
H-1[b]	5.84,ddd	4.21,m (dt)	4.94,m (dddd)	5.27,ddd	4.57,m	4.80,m	4.73,m
C-13[c]	108.95,dd	67.95,td	89.41,dd	88.09,ddd	71.20,td	81.78,dd	
F-19[d]	-154.3,d		-221.28,dd	-207.11,d		-232.5,s	
F-19[e]	-154.3,ddd		-221.28,m	-207.11,bd(overlapping dd)		-232.5,td	

[a]Multiplicities reported in brackets must be considered tentative first order assignments

[b]Fully coupled spectrum recorded at 350 MHz using CD_3OD as solvent and TMS as an internal reference[15]

[c]Proton decoupled spectrum recorded at 25 MHz using CD_3OD as solvent and TMS as an internal reference

[d]Proton decoupled spectrum recorded at 93.63 MHz using CD_3OD as solvent and $CFCl_3$ as an internal reference

[e]Coupled spectrum recorded at 93.63 MHz using CD_3OD as solvent and $CFCl_3$ as an internal reference

TABLE 2. HOMONUCLEAR AND HETERONUCLEAR COUPLING CONSTANTS OF 6. (Hz)

RING POSITION X-Y / COUPLING NUCLEI	1-1	1-3	2-1	2-3	2-4	3-3	3-4	4-3	4-4	4-6	5-3	5-4	5-6	5-6'	5-F_6	6-4	6-6'	6-F_6
^1H_x - ^1H_y			5.4	10.1			2.7						5.2	6.5			9.5	
^1H_x - $^{19}F_y$	53.0	2.9	25.0	11.0		47.2	26.8		51.4			28.7			14.20			47.0
$^{13}C_x$ - $^{19}F_y$	226.8	11.0	22.7	22.7	∿2.0	188.7	18.4		181.7	6.6	3.7	21.0			21.0			169.3
$^{19}F_x$ - $^{19}F_y$		3.7					13.7	13.7										

4,6-dideoxy-4,6-difluoro-α-D-galactopyranoside employing DAST, lends further credence to these conclusions.[13,14] A full report on further applications of this methodology to the field of carbohydrates will be reported in the near future.

REFERENCES

1. A comprehensive review on the chemistry and biochemistry of fluorinated carbohydrates can be found in ref. 2.
2. A. A. Penglis, Adv. Carb. Chem. Biochem., 38, p. 195-285, R. S. Tipson and D. Horton, Eds., Academic Press, N.Y., 1981.
3. M. F. G. Schmidt, R. T. Schwarz and H. Ludwig, J. Virol., 18, 819, (1976).
4. P. Biely, J. Kovarik and S. Bauer, J. Bacteriol, 115, 1108 (1973).
5. N. F. Taylor, Ciba Found. Symp., 215-238 (1972).
6. Pfanstiehl Labs, Inc., Waukegan, IL 60085.
7. T. J. Tewson and M. J. Welch, J. Org. Chem., 43 (6), 1090 (1978); A. B. Foster, R. Hems and J. M. Webber, Carb. Res., 5, 292 (1967); L. D. Hall, R. N. Johnson, A. B. Foster and J. H. Westwood, Can. J. Chem., 41, 236 (1971)
8. Anal. Calcd. for $C_6H_{10}O_4F_2$: C,39.14; H,5.47; F,20.64
   Found: C,38.96; H,5.58; F,20.45.
9. DAST was prepared by the method of W. J. Middleton, J. Org. Chem., 40 (5), 574 (1974); this material is also available from Aldrich Chem. Co., Milwaukee, Wis 53233.
10. Chromatography was performed on a Waters Prep 500A HPLC system employing PREP-PAK cartridges (375 g silica gel).
11. Anal. Calcd. for $C_8H_{10}O_3F_4$: C,41.75; H,4.41; F,33.02
    Found: C,41.85; H,4.38; F,32.89.
12. Anal. Calcd. for $C_6H_8O_2F_4$: C,38.31; H,4.29; F,40.40
    Found: C,38.32; H,4.40; F,40.25.
13. C. W. Somawardhana and E. G. Brunngraber, Carb. Res., 94, (1981), C14-C15.
14. R. J. Kaufman, G. H. Klemm and R. S. Sidhu unpublished results. We have confirmed this observation independently by obtaining a single crystal X-ray analysis of the final product. The space group of this molecule was determined to be $P2_1$ with a = 7.564 (4)Å, b = 4.964(3)Å, c = 11.944(8) Å, β = 102.69(5)°. The structure was solved by direct phasing methods and refined to a discrepancy factor (r) of 0.0781 based on 704 observed reflections.

15. We thank Prof. W. H. Urry, Dept. of Chemistry, University of Chicago, Illinois, for his help in obtaining these spectra.

(Received in USA 4 February 1982)