FLUORINATION REACTIONS AT C-4 OF METHYL 2-O-BENZYL-3,6-DIDEOXYHEXOPYRANOSIDES WITH DIETHYLAMINOSULFUR TRIFLUORIDE (DAST) AND WITH TRIS(DIMETHYLAMINO)SULFONIUM DIFLUOROTRIMETHYLSILICATE (TASF)

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Fluorination at C-4 of methyl 2-O-benzyl-3,6-dideoxy-α-D-ribo- and α-D-arabino-hexopyranosides(1 and 5) using diethylaminosulfur trifluoride(DAST) proceeded with exclusive retention of configuration. But treating the triflates of 1 and 5 with tris(dimethylamino)sulfonium difluorotrimethylsilicate(TASF) afforded mostly the configurationally inverted fluorides.

KEYWORDS fluorination; 3,6-dideoxyhexopyranose; fluorinated carbohydrate; DAST; TASF; F-H coupling constant; ideal trans-diaxial system

In our studies on the incorporation of monofluorinated 3,6-dideoxyhexopyranose moieties into the artificial antigens structurally related to O-antigens of Salmonella typhi and paratyphi, we have found that the reactions of the equatorial 4-hydroxyl groups of methyl 2-O-benzyl-3,6-dideoxy-α-D-ribo- and α-D-arabino-hexopyranosides(1 and 5) with DAST gave the 4-deoxy-4-fluoro derivatives (2 and 6, respectively) with exclusive retention of configuration.

Although DAST has been widely used to introduce fluorine into carbohydrates,[1-3] the reaction mechanisms are not easily rationalized.[4,5] It was first believed that the direct replacement of the hydroxyl group by a fluorine atom using DAST proceeded via the S_N2 mechanism,[6] but some instances of fluorination with configurational retention have been reported.[4,7-9] We now report another instance in comparison with the fluorination using TASF.[10]

When methyl 2-O-benzyl-3,6-dideoxy-α-D-ribo-hexopyranoside(1) was treated[11] with 3 molar equivalents of DAST in dichloromethane at -13℃ for 2.5 h, methyl 2-O-benzyl-3,4,6-trideoxy-4-fluoro-α-D-ribo-hexopyranoside(2) was obtained in 62% yield but no xylo-isomer 3 was isolated. However, the reaction[12] of the triflate of 1, prepared from 1 by use of trifluoromethanesulfonic anhydride in dichloromethane-pyridine, with 4.5 molar equivalents of TASF in dichloromethane at room temperature for 1.5 h afforded both 2 and 3 in yields of 13 and 54%, respectively (Chart 1).

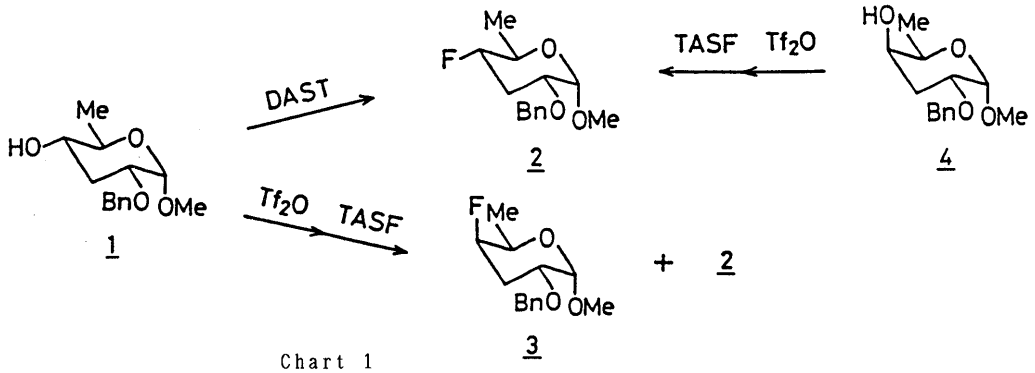

Chart 1

Similarly, 5 was treated with 3 molar equivalents of DAST at -13℃ for 2 h to form methyl 2-O-benzyl-3,4,6-trideoxy-4-fluoro-α-D-arabino-hexopyranoside(6) in 39% yield without isolation of the lyxo-isomer 7. As for the fluorination of the triflate of 5 with TASF in the same manner as that of 1, only the configurationally inverted fluoride 7 was obtained, in 21% yield, accompanied with a 24% yield of the 3,4-unsaturated compound 8 (Chart 2).

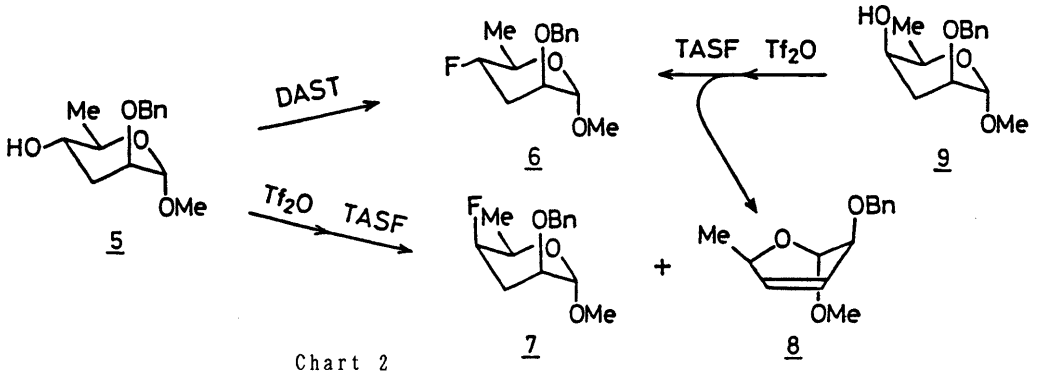

Chart 2

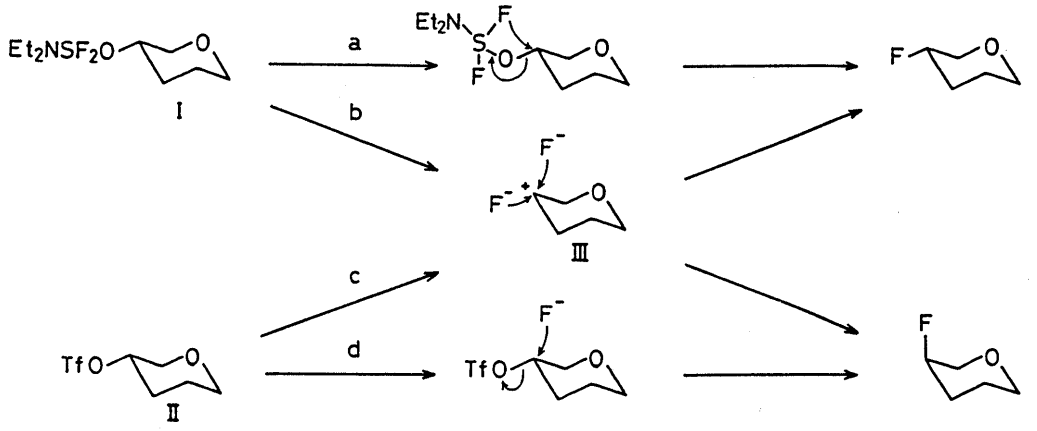

Chart 3

In the fluorination with DAST, the SN2 reaction of the intermediate I in Chart 3 is negligible because no configurationally inverted fluoride was produced. The fact that even the reaction of 1 with 1.2 equivalents of DAST at -13℃ for 0.5 h with post-stirring at room temperature for 1.5 h gave only 2 in 66% yield implies the higher plausibility of the SNi mechanism (pathway a). However, pathway b via carbocation III cannot be neglected, as the attack of fluoride anion against C-4 from the β-side of the pyranose ring must be interfered with the repulsive effect of ring oxygen.

In contrast, the fact that inversion of configuration at C-4 predominantly occurred in the fluorination with TASF suggests that the reaction of triflate II is likely to proceed through pathway d (Chart 3). Minor production of the configurationally retained fluoride 2 from the triflate of 1 indicates that pathway c via III also contributed to the reaction, but only in part, because, if it were the main course, repulsion between fluoride anion and ring oxygen would have allowed the dominant attack on III from the α-side of the pyranose ring to give 2 as the major product.

The lower yields of fluorides for the reactions of 5 in both methods than those of 1 are considered to be due to the steric and electric hindrance by the axial benzyloxyl group at C-2.

The fluorides, 2 and 6, were also prepared from methyl 2-O-benzyl-3,6-dideoxy-α-D-xylo-[13] and lyxo-hexopyranosides(4 and 9) by the reactions of their triflates with TASF in yields of 19 and 13%, respectively. In the reaction of 9, compound 8 was isolated in 42% yield as the major product. The treatment of 4 and 9 with DAST gave some unidentified products, but no fluorides were included therein. The synthesis of 1, 4, 5, and 9 are to be published elesewhere.

The F-H coupling constants observed in ^{1}H-NMR spectra of methyl 2-O-benzyl-3,4,6-trideoxy-4-fluoro-α-D-ribo-, arabino-, xylo-, and lyxo-hexopyranosides(2, 3, 6, and 7) are depicted in Fig. 1. The diaxial $^3J_{F,H-3}$ of 44.8 Hz and 43.7 Hz observed for 3 and 7, respectively, are very close to the unperturbed value of 43.5 Hz for diaxial $^3J_{F,H}$.[14] This indicates that the axial H on deoxygenated carbon(C-3) and the axial F on C-4 in vicinal disposition of methyl 3,6-dideoxy-α-D-hexopyranoside are in ideal trans-diaxial relationship.[15]

The ^{13}C-NMR data shown in Table I are satisfactory for the structures of the fluorides 2, 3, 6, and 7.

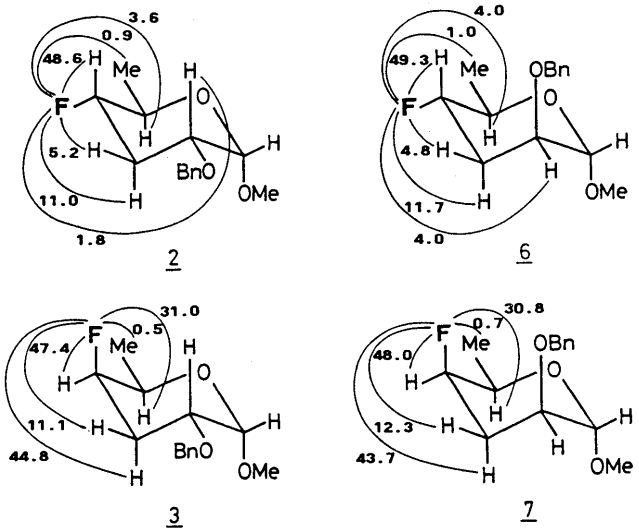

Fig. 1. F-H Coupling Constants for 2, 3, 6, and 7 (in Hz, Measured at 300 MHz in $CDCl_3$)

Table I. ^{13}C-NMR Data for 2, 3, 6, and 7 (Measured at 75.4 MHz in $CDCl_3$)

Compound	δ (ppm) ($J_{C,F}$ (Hz))					
	C-1	C-2	C-3	C-4	C-5	C-6
2	96.9	73.5	30.9	90.3	65.8	17.1
		(11.1)	(19.2)	(180.2)	(24.5)	
3	97.8	70.4	29.9	90.2	64.7	15.7
			(21.0)	(177.5)	(19.5)	(6.5)
6	98.0	75.4	30.2	89.4	66.8	17.4
		(11.9)	(19.2)	(174.6)	(24.5)	
7	99.3	70.3	27.8	87.1	64.8	16.1
			(20.1)	(181.6)	(19.9)	(7.2)

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REFERENCES AND NOTES

1) T. Tsuchiya, Yuki Gosei Kagaku Kyokai Shi, 42, 544 (1984).
2) P. J. Card, J. Carbohydr. Chem., 4, 451 (1985).
3) N. F. Taylor(ed.), "Fluorinated Carbohydrates; Chemical and Biochemical Aspects," ACS Symp. Ser. 374, American Chemical Society, Washington, D. C., 1988.
4) T. Torii, T. Tsuchiya, and S. Umezawa, Carbohydr. Res., 116, 289 (1983).
5) J. D. Moyer, O. Reizes, N. Malinowski, C. Jiang, and D. C. Baker, Chapter 4 of Ref. 3.
6) T. J. Tewson and M. J. Welch, J. Org. Chem., 43, 1090 (1978).
7) S. Castillon, A. Dessinges, R. Faghih, G. Lukacs, A. Olesker, and T. T. Thang, J. Org. Chem., 50, 4913 (1985).
8) S. S. Yang, T. R. Beattie, and T. Y. Shen, Synth. Commun., 16, 131 (1986).
9) C. Jiang, J. D. Moyer, and D. C. Baker, J. Carbohydr. Chem., 6, 319 (1987).
10) B. Doboszewski, G. W. Hay, and W. A. Szarek, Can. J. Chem., 65, 412 (1987).
11) The procedure using DAST is that slightly modified from P. J. Card and G. S. Reddy, J. Org. Chem., 48, 4734 (1983).
12) The procedure using TASF is according to that described in Ref. 10.
13) C. L. Stevens, K. W. Schultz, D. J. Smith, and P. M. Pillai, J. Org. Chem., 40, 3704 (1975).
14) The observed value for cyclohexyl fluoride in R. J. Abraham and L. Cavalli, Mol. Phys., 9, 67 (1965).
15) L. Phillips and V. Wray, J. Chem. Soc., B, 1971, 1618.

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