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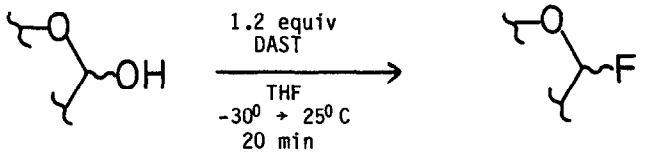
A CONVENIENT, ONE-STEP, HIGH-YIELD REPLACEMENT OF AN ANOMERIC HYDROXYL GROUP BY A FLUORINE ATOM USING DAST. PREPARATION OF GLYCOSYL FLUORIDES.

Gary H. Posner* and Stephen R. Haines*

Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218

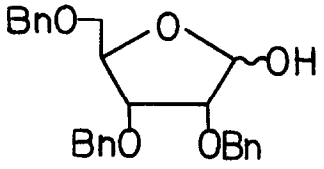
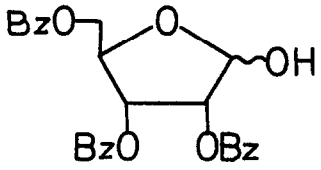
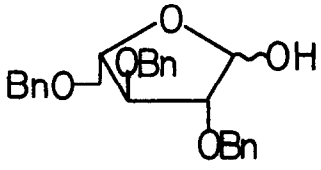
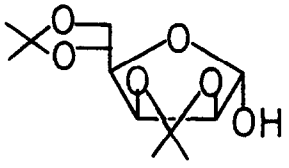
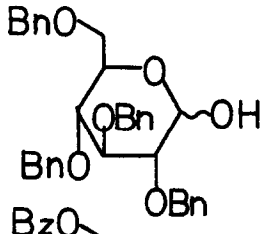
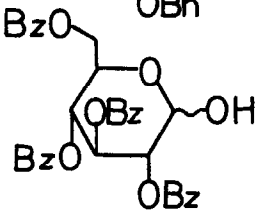
Summary: The anomeric hydroxyl group of various furanose and pyranose hemiacetals can be replaced by a fluorine atom stereoselectively, conveniently, mildly, and on gram-scale using DAST in THF at room temperature.

Glycosyl bromides and chlorides have been used for over eighty years as electrophiles in glycosidic bond-forming reactions.[1] Recently the more stable glycosyl fluorides have been used also for some effective glycosylation reactions.[2-5] Preparation of several glycosyl fluorides directly from the corresponding alcohols has been achieved using 2-fluoropyridinium salts,[3] using hydrogen fluoride-pyridine,[4] and using a hexafluoropropene-amine complex;[6] several indirect preparations of glycosyl fluorides are known[7] including reaction of glycosyl thioethers[5] with diethylaminosulfur trifluoride (DAST) and N-bromosuccinimide. We have found that DAST itself is highly effective for direct, one-step, high-yield, gram-scale conversions of various furanose and pyranose hemiacetals into the corresponding glycosyl fluorides with very good stereochemical selectivity at the anomeric center; commonly used hydroxyl-protecting groups such as benzyl, benzoyl, and acetonide functionalities do not interfere with these rapid (<20 min) fluorinations (eq. 1). Our results are summarized in Table I; anomeric ratios were determined by ^{19}F and ^{1}H NMR, in comparison with literature data, and the melting points of the crystalline glycosyl fluoride products matched those of independently prepared authentic samples.



(1)

Table I.

Hemiacetal	Glycosyl Fluoride % Yield (α:β ratio)	Literature α:β Ratio (ref #)
	90% (1.0:9.9)	1.0:1.4 (3) 1.0:2.9 (6)
	99% (1.0:1.4)	-
	95% (10.5:1.0)	1.1:1.0 (8)
	87% α, 13% β[a] (6.6:1.0)	>10:1 (5)
	99% (1.0:7.7)	1.9:1.0 (8) 1.0:4.0 (8)
	8% α, 84% β[b,c] (1.0:10.5)	-

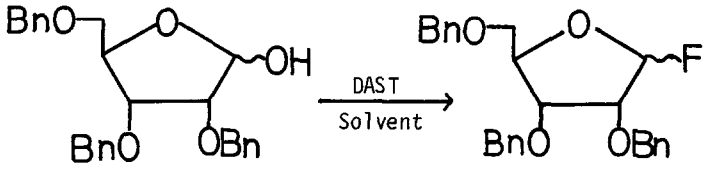
(a) each anomer was isolated by short path column chromatography.
(b) CH_2Cl_2 was used as solvent instead of THF.
(c) each anomer was isolated by preparative tlc.

Bn = $PhCH_2$
Bz = PhCO

A typical experimental procedure is represented by fluorination of 2,3:5,6-di-O-isopropylidene-α-D-mannofuranose. To this alcohol (1.17 g, 4.52 mmol) in a stirred solution of THF (12 ml) at -30°C under argon gas was added rapidly 0.66 ml (5.4 mmol) of DAST (purchased from Aldrich). The cooling bath was removed immediately. After 20 min at room temperature, tlc indicated complete reaction. The reaction mixture was cooled to -30°C and methanol (0.3 ml) was added. After evaporation of solvent, a normal aqueous work-up in chloroform yielded the crude mixture of fluorides which were separated by short-path chromatography (20 g silica gel, 10:1:1 hexanes:ethyl acetate:1,2-dichloroethane followed by 1:1 hexanes:ethyl acetate). The chromatographically more mobile α-fluoride[5] (1.027 g, 86.7%) was a low melting solid (m.p. <0°C) which had $[\alpha]_D^{25}$-14.2° (c 0.8, $CHCl_3$), ^{1}H-NMR ($CDCl_3$) δ 5.69 (H-1, d, $J_{1,F}$ 59.5 Hz), ^{13}C-NMR ($CDCl_3$) δ 113.7 (C-1, d, $J_{1,F}$ 221.5 Hz), ^{19}F-NMR ($CDCl_3$, C_6F_6) ϕ 130 (dd, $J_{1,F}$ 59.5 Hz, $J_{2,F}$ 6.1 Hz).) The less mobile β-fluoride (0.156 g, 13.2%) crystallised upon removal of the solvent and, after recrystallisation from hexanes, had m.p. 115-116°C, $[\alpha]_D$-7.7° (c 1.1, $CHCl_3$), (Found: C, 55.3; H, 7.3; F, 7.0%. $C_{12}H_{19}FO_5$ requires C, 55.0; H, 7.3; F, 7.2%), ^{1}H-NMR ($CDCl_3$) δ 5.51 (H-1, dd, $J_{1,F}$ 66.5 Hz, $J_{1,2}$ 3.7 Hz), ^{13}C-NMR ($CDCl_3$) δ 107.5 (C-1, d, $J_{1,F}$ 235.6 Hz), ^{19}F-NMR ($CDCl_3$, C_6F_6) ϕ 126 (d of m, $J_{1,F}$ 66.4 Hz, $J_{2,F}$ 15,3 Hz, $J_{3,F}$ 5.4 Hz).

We have found an important effect of solvent on the stereochemical outcome of fluorination of 2,3,5-tri-O-benzyl-D-ribofuranose, as illustrated in Table II. A similar observation was made during fluorination of the α-D-mannofuranose in Table I. Apparently, a polar solvent such as THF is the solvent of choice for these fluorinations; an understanding of the origin of this solvent effect, however, requires further study.

Table II



Solvent	β :α
CH_2Cl_2	2.0
$PhCH_3$	3.7
CCl_4	4.1
Et_2O	4.2
DMTHF (ref. 9)	5.7
THF	9.9

It is clear, therefore, that DAST in THF is a highly effective reagent for mild, direct, convenient, highly stereocontrolled, preparative-scale transformations of glycosyl hemiacetals into glycosyl fluorides.

Acknowledgment

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7. For Reviews on glycosyl fluorides, see
   a. Micheel, F., and Klemer, A., Adv. Carbohydr. Chem., 1961, 16, 85, and
   b. Penglis, A. A. E., Adv. Carbohydr. Chem. Biochem., 1981, 38, 195.

8. Personal communication. We thank Professor T. Mukaiyama and Dr. Y. Hashimoto for kindly supplying us with details of the preparation and physical data of these compounds.

9. 2,5-Dimethyltetrahydrofuran (DMTHF) was purchased from Aldrich; cf. Posner, G. H., and Frye, L. L., Israel J. Chem., 1984, 24, 88.

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