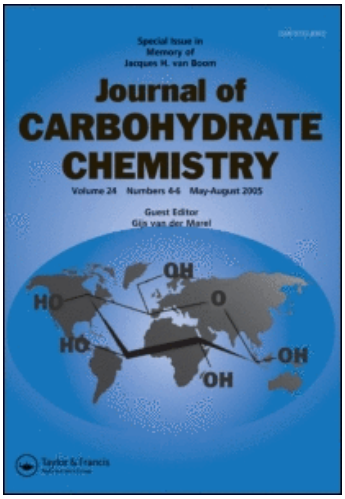

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The Preparation of O-Trifluoromethyl Carbohydrates

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THE PREPARATION OF O-TRIFLUOROMETHYL CARBOHYDRATES

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ABSTRACT

A simple method for the preparation of O-trifluoromethyl carbohydrate derivatives is reported. Carbohydrate derivatives bearing excellent leaving groups can react with tris(dimethylamino)sulfonium trifluoromethoxide ($TAS^+CF_3O^-$) to afford trifluoromethoxy-substituted compounds along with varying amounts of the corresponding deoxyfluoro products. Primary and secondary triflates afford the corresponding trifluoromethyl ethers. Displacement at a secondary center occurs with complete inversion of configuration. Glucosyl bromides react to form mixtures of trifluoromethyl glucosides and glucosyl fluorides.

INTRODUCTION

Fluorinated carbohydrates, particularly deoxyfluoro sugars, have been widely used as biochemical probes.[1-3] The utilization of such derivatives has both stimulated and in turn been enhanced by the development of mild, selective and rapid methods of synthesis.[3,4] One other class of fluorinated carbohydrates that is potentially

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useful in biological applications is the O-perfluoroalkyl carbohydrates. That this class has been virtually unexplored has been due to the lack of a suitably mild method for the introduction of the perfluoroalkoxy substituent. In this paper we wish to report the use of tris(dimethylamino)sulfonium trifluoromethoxide ($TAS^+CF_3O^-$) as a reagent for the introduction of the trifluoromethoxy substituent into carbohydrates. The preparation of trifluoromethyl ethers at both primary and secondary positions as well as trifluoromethyl glycosides is described.

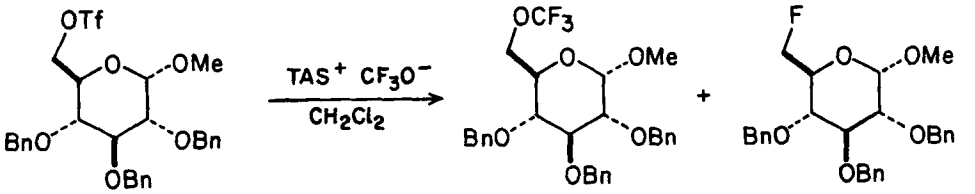
RESULTS AND DISCUSSION

Trifluoromethyl Ethers

The powerful electron-withdrawing character of a fluorine substituent leads one to predict that the trifluoromethoxide anion should be a very poor nucleophile. Studies on the tris(dimethylamino)sulfonium (TAS) salt[5], however, have shown that this species is sufficiently nucleophilic to react with benzyl bromide to form benzyl trifluoromethyl ether.[6] This result suggested that TAS+CF3O- might be reactive toward deoxyhalo sugars allowing one to prepare O-trifluoromethyl derivatives of carbohydrates. Our initial attempts toward this end were unsuccessful. TAS+CF3O- failed to react with either methyl 2,3,4-tri-O-benzyl-6-deoxy-6-iodo-α-D-glucopyranoside or 6-deoxy-6-iodo-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose.

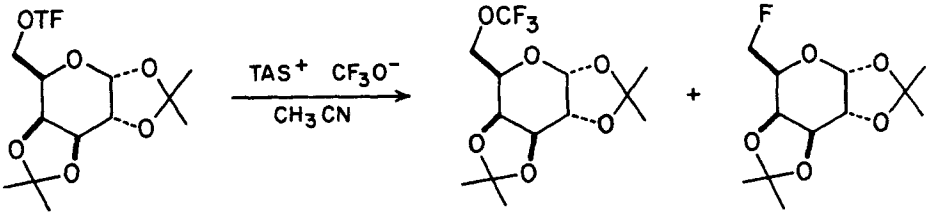
Binkley and co-workers[7,8] have shown that triflate esters of carbohydrates can be useful intermediates in displacement reactions with feeble nucleophiles. We find that with $TAS^+CF_3O^-$ as a nucleophile the desired

displacement on the corresponding primary triflates occurs smoothly. Treatment of triflate 1 with 1.5 equivalents of TAS+CF_3O- in methylene chloride at ambient temperature for 2.5 hours affords the desired 6-O-trifluoromethyl ether 2 (76%) along with the 6-deoxy-6-fluoro compound 3 (18%). The more hindered triflate 4 required more severe conditions. Treatment of 4 with 1.3 equivalents of TAS+CF3O- in refluxing



1 2 (76%) 3 (18%)

$TAS^+ \equiv (Me_2N)_3S^+$



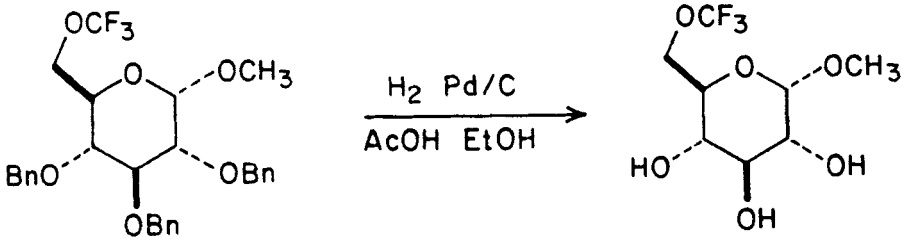
4 5 (52%) 6 (36%)

acetonitrile for 45 minutes afforded the 6-O-trifluoromethyl ether 5 (52%) and 6-deoxy-6-fluoro compound 6 (36%).

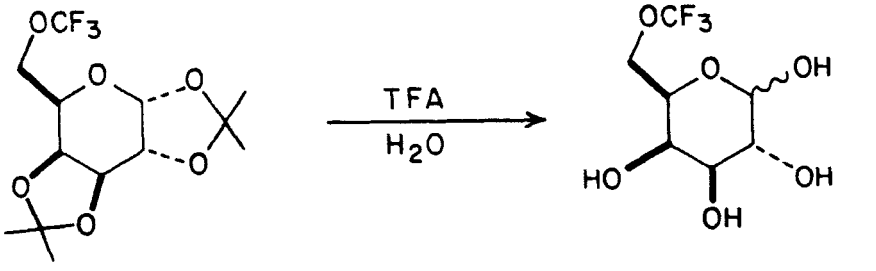
The appearance of the deoxyfluoro products was unexpected in that this type of product was not seen in the reaction of TAS+CF3O- with benzyl bromide.[6] Since trifluoromethyl ethers such as 2 and 5 are found to be

quite stable[9], it appears that the deoxyfluoro products are primary products. Such products could result from (a) delivery of fluoride to the electrophilic center by CF_3O^- (ambident reactivity) or (b) decomposition of the reagent releasing fluoride which subsequently reacts with triflate. The observation that the less reactive triflate requiring more severe conditions gives more deoxyfluoro product is more consistent with the latter possibility.[10]

Deprotection of 2 via catalytic hydrogenolysis proceeded uneventfully to afford methyl 6-O-trifluoromethyl-α-D-glucopyranoside (7) in 71% yield. Glucoside 7 is unusual in that it is sufficiently volatile to be easily sublimed at 100°C/0.2 torr. Deprotection of 5 in aqueous trifluoroacetic acid gave 6-O-trifluoromethyl-D-galactose (8) in 95% yield.

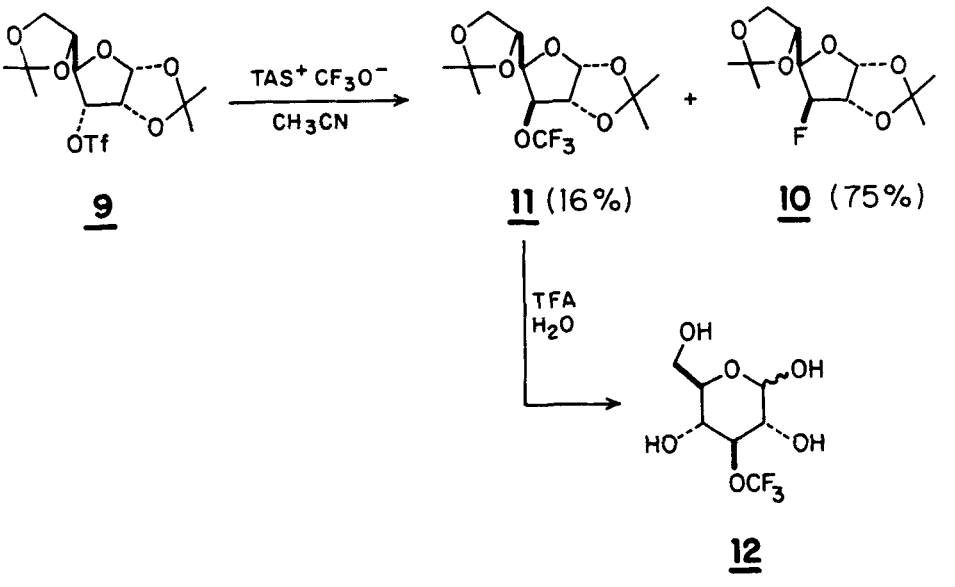


2 7



5 8

The successful reaction of TAS+CF3O- with primary triflates prompted us to attempt a displacement on a secondary triflate. The substrate chosen was the triflate ester of 1,2:5,6-di-O-isopropylidene-α-D-allofuranose (9). This material was considerably less reactive requiring treatment with 1.2 equivalents of $TAS^+CF_3O^-$ in refluxing acetonitrile for 5 hours to



9 11 (16%) 10 (75%)

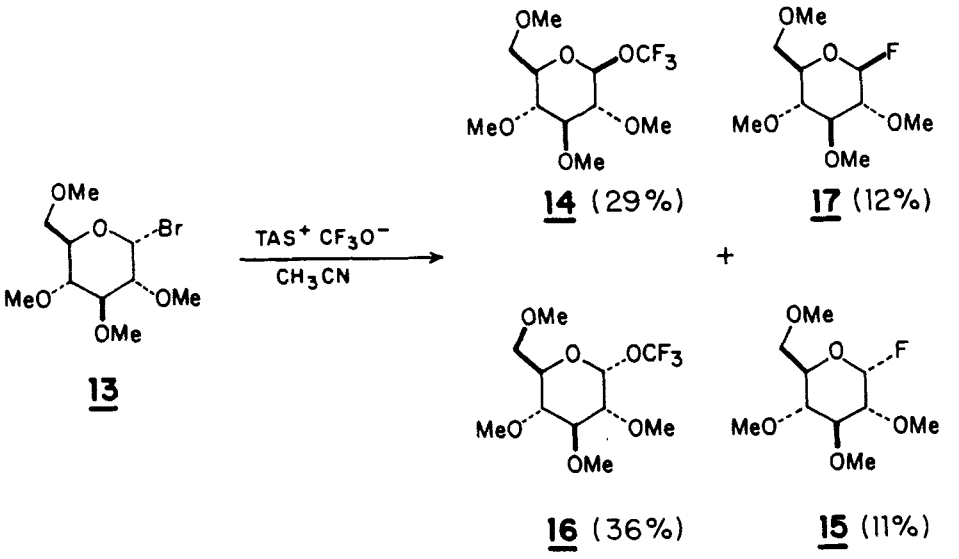
12

effect complete consumption. In this case the deoxyfluoro compound 10 was isolated as the major product in 75% yield but the desired 3-O-trifluoromethyl ether 11 could still be obtained albeit in only 16% yield. The displacement occurs with complete inversion of configuration at the reactive center (C-3) for both products. The gluco configuration is assigned on the basis of a lack of coupling between H-2 and H-3 ($J_{2,3} = 0$) in the ^1H NMR spectrum of both 10 and 11.

Deprotection of 11 under acidic conditions afforded 3-O-trifluoromethyl-D-glucose (12) in 79% yield. The ^1H NMR spectrum of both anomers of 12 showed an apparent triplet (J = 9 Hz) for H-3 firmly establishing the gluco configuration.

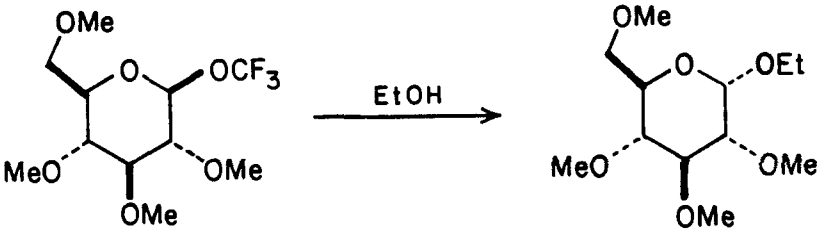
Trifluoromethyl Glucosides

Another category of electrophilic carbohydrate derivatives capable, in principle, of reacting with TAS+CF3O- is the glycosyl halides. Such a reaction would lead to trifluoromethyl glycosides. Several



trifluoromethyl glycosides have been reported but these were all 2-deoxy-2-fluoro systems resulting from the addition of trifluoromethyl hypofluorite to glycal derivatives.[11] Simple trifluoromethyl glycosides have not been reported.

To facilitate isolation and spectroscopic analysis, we decided to work with the 2,3,4,6-tetra-O-methyl-D-glucose system. Reaction of 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl bromide (13) with 1.1 equivalents of $TAS^+CF_3O^-$ in acetonitrile at ambient temperature for 2 hours afforded a mixture which was partially resolved by flash chromatography. The β-trifluoromethyl glucoside 14 (29%) and the α-glucosyl fluoride 15 (11%) were isolated and characterized in pure form. The α-trifluoromethyl glucoside 16 (36%) and the β-glucosyl fluoride 17 (12%) co-eluted and were



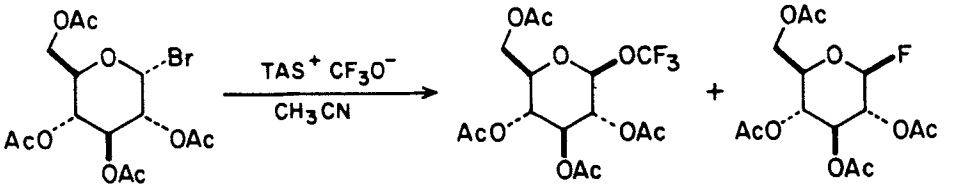
14 **18**

found to be inseparable by chromatography or distillation; however, their structures could be assigned tentatively using ^1H and ^{19}F NMR spectroscopy.

β-Trifluoromethyl glucoside 14 was found to be exceptionally volatile subliming rapidly at 25°C/0.1 torr. The compound is stable on silica gel but in ethanol solution it undergoes a slow, uncatalyzed

solvolysis with a half-life of roughly 17 hours. This solvolysis occurs with virtually complete selectivity (>50:1) for the net inversion product 18.

As a possible route to the free trifluoromethyl-β-D-glucopyranoside, acetobromoglucose (19) was examined as a substrate. Treatment of 19 with 1.1 equivalents



19 20 (14%) 21 (37%)

of TAS+CF_3O^- in acetonitrile at ambient temperature for 45 hours afforded a complex mixture still containing unreacted 19. Flash chromatography did allow the isolation of the desired β-trifluoromethyl glucoside 20 (14%) along with the β-glucosyl fluoride 21 (37%). All attempts however to deacetylate 20 without concomitant loss of the trifluoromethoxy group were unsuccessful.

SUMMARY AND CONCLUSIONS

The preparation of O-trifluoromethyl sugar derivatives through the reaction of TAS+CF_3O^- with electrophilic carbohydrate species is both straightforward and general. The ready availability of triflate esters of carbohydrates and glycosyl halides suggests that this methodology should be quite versatile and applicable to complex systems.

The trifluoromethoxy group is more electron-withdrawing yet more lipophilic than the methoxy group.

As such, this should be a useful substituent for studying carbohydrate interactions. The physical, chemical, and biological properties of O-trifluoromethyl carbohydrates will be the subject of a future study.

EXPERIMENTAL

Materials and Methods. Proton NMR spectra were measured at 360 MHz on a Nicolet 360-WB spectrometer. Carbon-13 NMR spectra were measured at 75.71 MHz with broadband proton decoupling on a Nicolet NT-300 spectrometer. Fluorine-19 NMR spectra were measured at either 94.6 MHz on a Varian XL-100 spectrometer or 188 MHz on a Nicolet NT-200 spectrometer. ^{19}F NMR chemical are referenced to internal chlorotrifluoromethane (F-11). The mass spectra were obtained on a VG-70-70 high resolution mass spectrometer. Combustion analyses were performed by Micro-Analysis, Inc. (Wilmington, DE). Optical rotations were measured on a Perkin-Elmer 241MC instrument. Melting points are uncorrected.

Flash chromatography was performed on silica gel (EM Reagents, Silica 60, 230-400 mesh). Methylene chloride was distilled from phosphorus pentoxide. Acetonitrile and pyridine were distilled from calcium hydride. All other materials were standard reagent grade and were used as received.

Crystalline tris(dimethylamino)sulfonium trifluoromethoxide (TAS+ CF_3O^-) was prepared as described by Farnham et al.[5] and stored in a tightly sealed bottle in a dessicator.

General Method for the Reaction of Tris(dimethylamino)sulfonium Trifluoromethoxide (TAS+CF_3O^-) with Carbohydrate Derivatives. TAS+CF_3O^- is a very

hydroscopic, crystalline solid which must be handled under an inert atmosphere. In a typical experiment, an excess of TAS+CF3O- was loaded into a septum-capped Schlenk flask in a glove-bag filled with argon. Dry solvent was added via syringe. A solution of the carbohydrate derivative in the same dry solvent was added to the TAS+CF3O- solution by cannulation and the reaction allowed to proceed under a slight pressure of argon. Subsequent steps (work-up, chromatography, etc.) were carried out in air and required no special precautions.

Preparation of Methyl 2,3,4-Tri-O-benzyl-6-O-trifluoromethanesulfonyl-α-D-glucopyranoside (1).[12] The procedure of Binkley et al.[7] was employed. A solution of methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside[13] (4.98 g, 10.7 mmol) in methylene chloride (100 mL) containing pyridine (2.0 mL, 25 mmol) was cooled to 0°C and trifluoromethanesulfonic anhydride (2.0 mL, 12 mmol) was added. After stirring at 0°C for 30 min, the reaction mixture was washed with water (200 mL), then 5% aqueous HCl (200 mL), and dried over Na_2SO_4. Filtration through a short column of silica gel (Baker 40-140 M, 4 x 4.5 cm) followed by evaporation afforded 1 (5.58 g, 87%) as a pale orange syrup which crystallized slowly on standing: $[\alpha]_D^{25}$ +40.7° (c = 1.0, $CHCl_3$); H^1 NMR ($CDCl_3$): δ 3.37 (s, OCH3), 3.42 (dd, H-4, $J_{3,4}$ = 9 Hz, $J_{4,5}$ = 10 Hz), 3.53 (dd, H-2, $J_{2,3}$ = 9.5 Hz, $J_{1,2}$ = 3.5 Hz), 3.86 (ddd, H-5, $J_{5,6A}$ = 5 Hz, $J_{5,6B}$ = 2 Hz), 4.01 (t, H-3), 4.45 (dd, H-6A, $J_{6A,6B}$ = 10.5 Hz), 4.54 (dd, H-6B), 4.60 (d, H-1), 5.05-4.55 (d's, 6H), 7.4-7.2 (m, 15H). Anal. Calcd for $C_{29}H_{31}O_8F_3S$: C 58.38, H 5.24. Found: C 58.15, H 5.27.

Preparation of Methyl 2,3,4-tri-O-benzyl-6-O-trifluoromethyl-α-D-glucopyranoside (2). Triflate 1 (4.26 g, 7.14 mmol) and TAS+CF3O- (2.61 g, 10.7 mmol) were stirred in methylene chloride (70 mL) at ambient temperature for 2.5 hours. (See General Procedure.) The reaction mixture was stripped down and the residue subjected to repeated flash chromatography (4 x 60 cm column) in 1:6 ethyl acetate/hexane to afford the the trifluoromethyl ether 2 (2.90 g, 76%) and methyl 2,3,4-tri-O-benzyl-6-deoxy-6-fluoro-α-D-glucopyranoside (3; 0.61 g, 18%).

The trifluoromethyl ether 2 was recrystallized from hexane to afford white flakes: mp 64-65°C; $[\alpha]_D^{25}$ +17.6° (c = 0.99, $CHCl_3$); ^{19}F NMR ($CDCl_3$): δ -61.5 (s); ^1H NMR ($CDCl_3$): δ 3.37 (s, OMe), 3.50 (dd, H-4, $J_{3,4}$ = 8.7 Hz, $J_{4,5}$ = 9.5 Hz), 3.54 (dd, H-2, $J_{1,2}$ = 3.4 Hz, $J_{2,3}$ = 9.6 Hz), 3.81 (td, H-5, $J_{5,6A}$ = $J_{5,6B}$ = 3.0 Hz), 4.01 (t, H-3), 4.08 (m, H-6A,6B), 4.60 (d, H-1), 4.45 -

The deoxyfluoro compound 3 was characterized spectroscopically as a colorless syrup: $[\alpha]_D^{25}$ + 13.8° (c = 0.99, $CHCl_3$); ^{19}F NMR ($CDCl_3$): δ -234.5 (td, $J_{6A,F}$ = $J_{6B,F}$ = 47.5 Hz, $J_{5,F}$ = 28.5 Hz). ^1H NMR ($CDCl_3$): δ 3.37 (s, OMe), 3.55 (m, H-2,4), 3.73 (br dd, H-5, $J_{5,F}$ = 28.5 Hz, $J_{4,5}$ = 10.0 Hz), 4.01 (t, H-3, $J_{3,4}$ = 9.3 Hz), 4.65 - 4.40 (m, H-1,6A,6B), 5.0 - 4.65 (d's, 6H), 7.4 - 7.25 (m, 15H).

Preparation of Methyl 6-O-Trifluoromethyl-α-D-glucopyranoside (7). Tribenzyl ether 2 (1.62 g, 3.01 mmol) was dissolved in 5:1 ethanol/acetic acid (72 mL), 10% palladium on carbon (0.3 g) was added and the mixture was shaken under 30 psig hydrogen. Additional catalyst (0.3 g) was added after 2 hours. After 6 hours the catalyst was removed by filtration, the

filtrate evaporated and the residue subjected to flash chromatography (2 x 20 cm column) in ethyl acetate. Sublimation (100°C/0.2 torr) afforded pure 7 (0.56 g; 71%) as a colorless solid: mp 116-117.5°C; $[\alpha]_D^{25}$ = 116.2° (c = 1.0, H_2O); ^{19}F NMR (CD_3COCD_3): δ -60.4 (s); ^1H NMR δ(CD_3COCD_3 + trace D_2O): 3.35 (dd, H-4, $J_{3,4}$ = 8.9 Hz, $J_{4,5}$ = 10.1 Hz), 3.39 (s, OMe), 3.46 (dd, H-2, $J_{1,2}$ = 3.7 Hz, $J_{2,3}$ = 9.7 Hz), 3.70 (t, H-3), 3.79 (ddd, H-5, $J_{5,6A}$ = 6.1 Hz, $J_{5,6B}$ = 2.0 Hz), 4.21 (dd, H-6A, $J_{6A,6B}$ = 10.6 Hz), 4.34 (dd, H-6B), 4.72 (d, H-1); Anal. Calcd for $C_8H_{13}F_3O_6$: C 36.65, H 5.00, Found: C 36.36, H 4.86.

Preparation of 1,2:3,4-Di-O-isopropylidene-6-O-trifluoromethyl-α-D-galactopyranose (5). Triflate 4[7] (7.85 g, 20.0 mmol) and TAS+CF3O- (5.98 g, 24.3 mmol) were refluxed in 120 mL of acetonitrile for 45 minutes. (See General Procedure.) Evaporation followed by repeated flash chromatography (6.5 x 27 cm column) in 1:6 ether/cyclopentane afforded the trifluoromethyl ether 5 as a colorless crystalline solid (3.41 gm, 52%) and 6-deoxy-6-fluoro-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (6) as a colorless syrup (1.87 g, 36%).

Sublimation (25°C/0.04 torr) afforded an analytical sample of 5: mp 53.5-55.5°C; $[\alpha]_D^{25}$ -46.8° (c = 1.01, $CHCl_3$); ^{19}F NMR ($CDCl_3$): δ -61.1 (s); H-1 NMR ($CDCl_3$): δ 1.34 (s,6H), 1.45 (s,3H), 1.54 (s,3H), 4.04 (m, H-5), 4.08 (dd, H-6A, $J_{5,6A}$ = 6.6 Hz, $J_{6A,6B}$ = 9.9 Hz), 4.14 (dd, H-6B, $J_{5,6B}$ 5.4 Hz), 4.25 (dd, H-4, $J_{3,4}$ = 7.9 Hz, $J_{4,5}$ = 1.8 Hz), 4.34 (dd, H-2, $J_{1,2}$ = 5.0 Hz, $J_{2,3}$ = 2.5 Hz), 4.64 (dd, H-3), 5.54 (d, H-1). Anal. Calcd for $C_{13}H_{19}F_3O_6$: C 47.56, H 5.83, Found: C 47.60, H 5.77.

The known deoxyfluoro compound 6 was identified spectroscopically: $[\alpha]_D^{25}$ -47.1° (c = 1.01, $CHCl_3$);

(Lit.[14] -48.3°, $CHCl_3$); ^{19}F NMR ($CDCl_3$): δ -229.5 (td, $J_{F,6A} = J_{F,6B}$ = 45 Hz, $J_{F,5}$ = 13 Hz); ^1H NMR ($CDCl_3$): δ 1.34 (s, 6H), 1.45 (s, 3H), 1.55 (s, 3H), 4.08 (m, H-5), 4.27 (dd, H-4, $J_{3,4}$ = 7.9 Hz, $J_{4,5}$ = 2.0 Hz), 4.35 (dd, H-2, $J_{1,2}$ = 5.0 Hz, $J_{2,3}$ = 2.5 Hz), 4.54 (ddd, H-6A, $J_{5,6A}$ = 6.9 Hz, $J_{6A,6B}$ = 9.5 Hz), 4.58 (ddd, H-6B, $J_{5,6B}$ = 5.2 Hz), 4.63 (dd, H-3), 5.55 (d, H-1).

Preparation of 6-O-Trifluoromethyl-D-galactose (8). The diacetonide 5 (1.64 g; 5.00 mmol) was stirred at ambient temperature in a mixture of water (5 mL) and trifluoroacetic acid (20 mL) for 2 hours. Evaporation followed by flash chromatography (2 x 44 cm column) in 30:1 ethyl acetate/ethanol gave 8 (1.18 g, 95%) as a colorless amorphous solid: mp 62-67°C; $[\alpha]_D^{25}$ + 51.0 --> +47.8° (c = 1.0, H_2O); Anal. Calcd for $C_7H_{11}F_3O_6$: C 33.88, H 4.47, Found C 33.80, H 4.61. The NMR spectra of 8 in acetone-d_6 containing a trace of D_2O showed the α-pyranose, β-pyranose, α-furanose and β-furanose forms in roughly a 4:4:1:1 ratio[18]: ^{19}F NMR: -60.17 and -60.14 (s's, α-p and β-p), δ-60.01 and -59.99 (s's, α-f and β-f); ^1H NMR: 3.5 - 4.3 (m, 6H), 4.50 (d, β-p H-1, $J_{1,2}$ = 7.4 Hz), 5.18 (d, β-f H-1, $J_{1,2}$ = 1.0 Hz), 5.19 (d, β-p H-1, $J_{1,2}$ = 3.7 Hz), 5.22 (d, α-f H-1, $J_{1,2}$ = 4.3 Hz); ^{13}C NMR: δ 68-85 (many peaks), 93.8 (α-p C-1), 97.3 (α-f C-1), 98.4 (β-p C-1), 104.1 (β-f C-1), 122.7 (q, CF_3O-, $J_{C,F}$ = 252 Hz).

Preparation of 1,2:5,6-Di-O-isopropylidene-3-O-Trifluoromethyl-α-D-glucofuranose (11). Triflate 9[7] (19.3 g, 49.2 mmol) and TAS+CF3O- (14.8 g, 59.4 mmol) were refluxed in acetonitrile (150 mL) for 5

hours. (See General Procedure.) Evaporation and repeated flash chromatography resolved the reaction mixture into the trifluoromethyl ether 11 and 3-deoxy-3-fluoro-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose 10.

Kugelrohr distillation (68-73°C/0.1 torr) afforded pure 11 (2.60 g, 16%) as a colorless syrup: $[\alpha]_D^{25}$ -28.3° (c = 1.1, $CHCl_3$); ^{19}F NMR ($CDCl_3$): δ -59.3 (s); ^1H NMR ($CDCl_3$): δ 1.33 (s, 3H), 1.34 (s, 3H), 1.43 (s, 3H), 1.51 (s, 3H), 4.00 (dd, H-6A, $J_{5,6A}$ = 5.1 Hz, $J_{6A,6B}$ = 8.7 Hz), 4.10 (dd, H-6B, $J_{5,6B}$ = 6.0 Hz), 4.17 (dd, H-4, $J_{3,4}$ = 2.7 Hz, $J_{4,5}$ = 7.9 Hz), 4.26 (m, H-5), 4.68 (d, H-3), 4.70 (d, H-2, $J_{1,2}$ = 3.6 Hz), 5.93 (d, H-1); Anal. Calcd for $C_{13}H_{19}F_3O_6$: C 47.56, H 5.83, Found C 47.93, H 5.85.

The known deoxyfluoro compound 10 was Kugelrohr distilled (85-90°C/0.1 torr, (Lit.[15] 66-70°C/0.03 torr)) and identified spectroscopically: $[\alpha]_D^{25}$ -20.0° (c = 1.23, $CHCl_3$); (Lit.[15] -22 (c = 1, $CHCl_3$)); ^{19}F NMR ($CDCl_3$): δ -205.9 (ddd, $J_{2,F}$ = 11 Hz, $J_{3,F}$ = 47 Hz, $J_{4,F}$ = 28 Hz); ^1H NMR($CDCl_3$): δ 1.33 (s, 3H), 1.37 (s, 3H), 1.45 (s, 3H), 1.50 (s, 3H), 4.03 (dd, H-6A, $J_{5,6A}$ = 4.8 Hz, $J_{6A,6B}$ = 8.8 Hz), 4.11 (ddd, H-4, $J_{3,4}$ = 2.2 Hz, $J_{4,5}$ = 8.3 Hz), 4.12 (dd, H-6B, $J_{5,6B}$ = 6.1 Hz), 4.29 (m, H-5), 4.70 (dd, H-2, $J_{1,2}$ = 3.7 Hz), 5.01 (dd, H-3), 5.95 (d, H-1).

Preparation of 3-O-Trifluoromethyl-D-glucose (12). Diacetonide 11 (1.97 g, 6.00 mmol) was stirred in a mixture of water (6 mL) and trifluoroacetic acid (24 mL) at ambient temperature for 2 hours. Evaporation followed by flash chromatography (4 x 30 cm column) in 15:1 ethyl acetate/ethanol afforded 12 (1.07 g, 72%) as a colorless amorphous solid: mp 157.5-166.5°C;

$[\alpha]_D^{25}$ +60.3° --> +53.5° (c = 0.76, H_2O); Anal. Calcd for $C_7H_{11}F_3O_6$: C 33.88, H 4.47, Found C 33.72, H 4.60. The NMR spectra showed a mixture of pyranose anomers with the α anomer predominating: ^{19}F NMR(acetone-d_6): (α/β 2:1) δ -55.02 (s, α-anomer), -54.93 (s,β-anomer); ^1H NMR(acetone-d_6 + trace D_2O): (α/β 2:1) δ 3.3 - 3.9 (m, 5H), 4.12 (t, β H-3, $J_{2,3} = J_{3,4}$ = 9.1 Hz), 4.34 (t,α H-3, $J_{2,3} = J_{3,4}$ = 9.3 Hz), 4.60 (d, β H-1, $J_{1,2}$ = 7.8 Hz), 5.19 (d, α H-1, $J_{1,2}$ = 3.6 Hz); ^{13}C NMR (D_2O): (α/β c. 1:1)[18] δ 60.2, 60.4, 67.2, 67.3, 69.4, 70.9, 72.0, 75.1, 81.2, 83.1, 91.9 (α C-1), 95.2 (β C-1), 121.2 (q, CF_3O-, $J_{F,C}$ = 254 Hz), 121.3 (q, CF_3O-, $J_{F,C}$ = 255 Hz).

Reaction of TAS+CF_3O- with 2,3,4,6-Tetra-O-methyl--α-D-glucopyranosyl bromide (13). Bromide 13[16] (7.29 g, 24.4 mmol) and TAS+CF3O- (6.74 g, 27.0 mmol) were stirred at ambient temperature in acetonitrile (150 mL) for 2 hours. (See General Procedure.) Evaporation followed by repeated flash chromatography (4 x 60 cm column) in 1:3 ethyl acetate/hexane afforded trifluoromethyl 2,3,4,6-tetra-O-methyl-β-D-glucopyranoside (14, 2.14 gm, 29%), 2,3,4,6-tetra-O-methyl-α-D-glucopyranosyl fluoride (15, 0.63 g, 11%) and an inseparable mixture (3.34 g) of trifluoromethyl 2,3,4,6-tetra-O-methyl-α-D-glucopyranoside (16, 36%) and 2,3,4,6-tetra-O-methyl-β-D-glucopyranosyl fluoride (17, 12%).

The β-trifluoromethyl glucoside 14 was sublimed twice (25°C/0.1 torr) to afford clusters of colorless needles: mp 39.5-41.5°C; $[\alpha]_D^{25}$ +3.1° (c = 2.0, $CHCl_3$); MS (HR-EI): Calcd. for $C_{11}H_{19}F_3O_6$: 304.1133, Found 304.1130; ^{19}F NMR($CDCl_3$): -59.21 (s); ^1H NMR ($CDCl_3$): 3.11 (t, 1H, J = 8.1 Hz), 3.18 (t, 1H, J =

8.6 Hz), 3.25 (t, 1H, J = 9.0 Hz), 3.33 (ddd, H-5, $J_{4,5}$ = 7.6 Hz, $J_{5,6A}$ = 3.8 Hz, $J_{5,6B}$ = 2.1 Hz), 3.41 (s, OMe), 3.54 (s, OMe), 3.57 (s, OMe), 3.57 (dd, H-6A, $J_{6A,6B}$ = 10.9 Hz), 3.63 (s, OMe), 3.64 (dd, H-6B), 4.85 (d, H-1, $J_{1,2}$ = 7.6 Hz); Anal. Calcd for $C_{11}H_{19}F_3O_6$: C 43.42, H 6.29, Found 43.70, H 6.23.

The α-glucosyl fluoride 15 was identified spectroscopically: ^{19}F NMR ($CDCl_3$): δ -149.89 (dd, $J_{F,H-1}$ = 53.5 Hz, $J_{F,H-2}$ = 25 Hz); ^1H NMR ($CDCl_3$) δ3.20 (ddd, H-2, $J_{1,2}$ = 2.7 Hz, $J_{2,3}$ = 9.6 Hz), 3.28 (t, H-4, $J_{3,4}$ = $J_{4,5}$ = 10.2 Hz), 3.41 (s, OMe), 3.54 (s, OMe), 3.55 (s, OMe), 3.55 (obscured, H-3), 3.60 (m, H-6A, 6B), 3.64 (s, OMe), 3.78 (dt, H-5, $J_{5,6A}$ = $K_{5,6B}$ = 2.7 Hz), 5.67 (dd, H-1).

The mixture of α-trifluoromethyl glucoside 16 and β-glucosyl fluoride 17 was tentatively characterized spectroscopically. Glucoside 16 exhibited: ^{19}F NMR ($CDCl_3$): -58.68 (s); ^1H NMR ($CDCl_3$): δ 3.27 (dd, H-2, $J_{1,2}$ = 3.5 Hz, $J_{2,3}$ = 9.7 Hz), 3.3 - 3.65 (m, 4H), 3.41 (s, OMe), 3.51 (s, OMe), 3.55 (s, OMe), 3.64 (s, OMe), 3.76 (dt, H-5, $J_{4,5}$ = 10.1 Hz, $J_{5,6A}$ = $J_{5,6B}$ = 2.5 Hz), 5.64 (d, H-1). β-Glucosyl fluoride 17 was tentatively identified by key spectroscopic features: ^{19}F NMR ($CDCl_3$): δ -138.68 (brd, $J_{F,H-1}$ = 53 Hz); ^1H NMR ($CDCl_3$): 5.11 (dd, H-1, $J_{1,2}$ = 6.5 Hz).

Reaction of 2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl bromide (19) with TAS+CF_3O-. The bromide 19 (1.27 g, 3.09 mmol) and TAS+CF_3O- (0.84 g, 3.37 mmol) were stirred in acetonitrile (20 mL) at ambient temperature for 45 hours. (See General Procedure.) TLC (Silica gel, 1:1 ethyl acetate/hexane) showed a complex mixture still containing some unreacted 19. Evaporation followed by flash chromatography (2 x 54 cm column) in 2:3 ethyl acetate/ benzene allowed the

isolation of two relatively pure major components: trifluoromethyl 2,3,4,6-tetra-O-acetyl-β-D-glucopyranoside (20, 0.23 g, 14%) and 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl fluoride (21, 0.41 g, 37%).

The β-trifluoromethyl glucoside 20 was rechromatographed and recrystallized from ether/hexane to afford long, colorless needles: mp 128.5-129.5°C; $[\alpha]_D^{25}$ -1.1° (c = 0.93, $CHCl_3$); ^{19}F NMR ($CDCl_3$): -59.74 (s); ^1H NMR ($CDCl_3$): 2.02 (s, OAc), 2.04 (s, OAc), 2.07 (s, OAc), 2.10 (s, OAc), 3.83 (ddd, H-5, $J_{4,5}$ = 9.9 Hz, $J_{5,6A}$ = 2.3 Hz, $J_{5,6B}$ = 4.8 Hz), 4.15 (dd, H-6A, $J_{6A,6B}$ = 12.5 Hz), 4.31 (dd, H-6B), 5.05 - 5.3 (m, 4H); Anal. Calcd for $C_{15}H_{19}F_3O_{10}$: C 43.28, H 4.60, Found C 43.05, H 4.69. (Assignment of anomeric stereochemistry for this compound is made indirectly. The resonances for H-1 and H-2 are obscured, precluding a direct measurement of $J_{1,2}$. The chemical shift of H-1 (ca. 5.2) is more consistent with the β-stereochemistry. This contention is supported by the detection of a trace product in the chromatographic eluent whose spectroscopic features are consistent with the corresponding α-trifluoromethyl glucoside: ^{19}F NMR ($CDCl_3$): δ -59.30 (s); ^1H NMR ($CDCl_3$): 5.97 (d, $J_{1,2}$ = 3.7 Hz).

The known β-fluoride 21[17] was identified by comparison of key spectroscopic features with the literature values: ^{19}F NMR ($CDCl_3$): δ -137.86 (dd, $J_{F,H-1}$ = 51.5 Hz, $J_{F,H-2}$ = 10.5 Hz); ^1H NMR $CDCl_3$): 5.36 (dd, H-1, $J_{1,2}$ = 6.0 Hz).

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