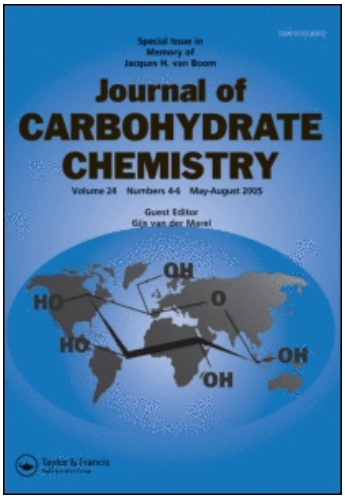

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THE REACTION OF 2,3,4-TRI-*O*-BENZYL-D-GLUCOSE WITH DIETHYLAMINOSULFUR TRIFLUORIDE (DAST)

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ABSTRACT

Treatment of 2,3,4-tri-*O*-benzyl-D-glucose (**1**) with diethylaminosulfur trifluoride (DAST) yielded 3,6-anhydro-2,4-di-*O*-benzyl-β-D-glucopyranosyl fluoride (**11**) as the main product (44%), by way of 3-benzyloxy group participation in the displacement of the intermediate 6-sulfoxo derivative. The desired 6-deoxy-6-fluoro-2,3,4-tri-*O*-benzyl-α- (**2**) and -β-D-glucopyranosyl fluoride (**3**) were formed in a combined yield of <20%. The combined yield of **2** and **3** could be increased three-fold by conducting the reaction in the presence of triethylamine.

INTRODUCTION

This laboratory has used a large number of deoxyfluorosugars as probes in mapping the combining area of (1→6)-β-D-galactan-specific monoclonal immunoglobulins.[1] In connection with a similar study involving antidextran antibodies, a need arose for a series of methyl α-glycosides of isomaltooligosaccharides specifically fluorinated at position 6 of the terminal non-

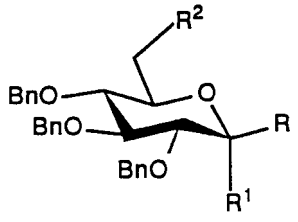
reducing α-D-glucopyranosyl group. To synthesize compounds of the aforementioned class we have decided to explore a strategy in which suitable glycosyl acceptors are coupled with glycosyl donors already fluorinated at the desired position. Herein we describe a method of synthesizing such glycosyl donors **2** and **3**.

RESULTS AND DISCUSSION

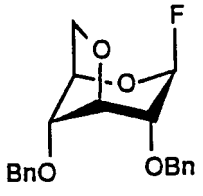
In light of the methods available for the construction of 1,2-*cis*-glycosides, it was desirable to derive the glycosyl donor from 6-deoxy-6-fluoro-D-glucose and to place at *O*-2 of the donor a group which would be readily removable and not capable of anchimeric assistance in the displacement of the leaving group at position 1.

Until recently, glycosyl fluorides were not considered sufficiently reactive to be useful as glycosyl donors in oligosaccharide synthesis. It has been shown,[2] however, that glycosyl fluorides activated with stannous chloride can be useful glycosyl donors in stereocontrolled α-(1,2-*cis*)-glycosylations catalyzed with silver perchlorate. The successful application[3] of this methodology prompted us to design a synthesis of a 2-*O*-benzylated glycosyl fluoride derived from 6-deoxy-6-fluoro-D-glucose which could be used as the glycosyl donor in the synthesis of the target, modified methyl α-glycosides of isomalto-oligosaccharides.

Although other pathways could be envisioned, it appeared to us that 2,3,4-tri-*O*-benzyl-D-glucose (**1**) would be a logical starting material for the synthesis of the required glycosyl donor. Since high yielding C-OH → C-F conversions at the anomeric[4-6] and primary position[6,7] using diethylaminosulfur trifluoride (DAST) are well documented (for a recent review, *c.f.* ref.[6]), the problematic nature of the conversion of the readily obtainable[8,9] **1** into 2,3,4-tri-*O*-benzyl-6-deoxy-6-fluoro-α- (**2**) or β-D-glucopyranosyl fluoride (**3**) using DAST was not anticipated. The starting compound **1** was conveniently obtained by deacetylation of the corresponding α- (**9**) or β-di-*O*-acetyl (**10**) derivative,



	R	R^1	R2
1	H,OH		OH
2	H	F	F
3	F	H	F
4	H	OMe	OH
5	H	OMe	F
6	H,OH		OBn
7	H	F	OBn
8	F	H	OBn
9	H	OAc	OAc
10	OAc	H	OAc



11

which were prepared as described by Eby *et al.*[8] The intermediate compounds **9** and **10** were both obtained crystalline and their ^1H and ^{13}C NMR spectra, previously not recorded, were fully consistent with the expected structure.

Introduction of fluorine into carbohydrates using DAST has been done under a variety of conditions.[6] Indeed, some fluorinations have been accomplished at subzero temperatures and without any promotor. In other instances conversions have been

conducted at an elevated temperature and/or in the presence of an organic base. Therefore, to determine the conditions necessary for the difluorination of **1**, model experiments were performed aimed at introducing fluorine solely at either the primary or the anomeric position of D-glucopyranose. Methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**4**) and 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**6**) were used as substrates. We were able to confirm the findings of Posner and Haines[5] that the conversion of **6** mediated by DAST into the corresponding glycosyl fluorides **7** and **8** occurs readily and virtually stoichiometrically, with preferential formation of the β-fluoride **8**. Both compounds **7** and **8** were obtained crystalline, their physical constants agreed closely with those reported and their ^{13}C NMR spectra were consistent with the anticipated structure.

When the glycoside **4** was treated under the conditions which readily effected the conversion **6** → **7** + **8** the corresponding fluoro derivative **5** was formed only in a low yield (TLC), although no starting material remained unchanged (this experiment is not described in the Experimental Section). The reaction had to be conducted at ~70° *and* with an excess of DAST to drive the reaction to completion. The amorphous derivative **5** obtained was identical with the material prepared independently by benzylation of methyl 6-deoxy-6-fluoro-α-D-glucopyranoside and produced NMR spectra consistent with the expected structure.

When **1** was treated with DAST in either tetrahydrofuran, 1,2-dimethoxyethane or diglyme at 60 - 70 °C the starting material rapidly disappeared (TLC) and a stabilization of the product distribution occurred after 20 - 30 min. Three main products were formed, two of which were found by NMR to be the desired glycosyl fluorides **2** and **3** (combined yield ~ 18%, **2**:**3** ~ 1 : 6).* The third

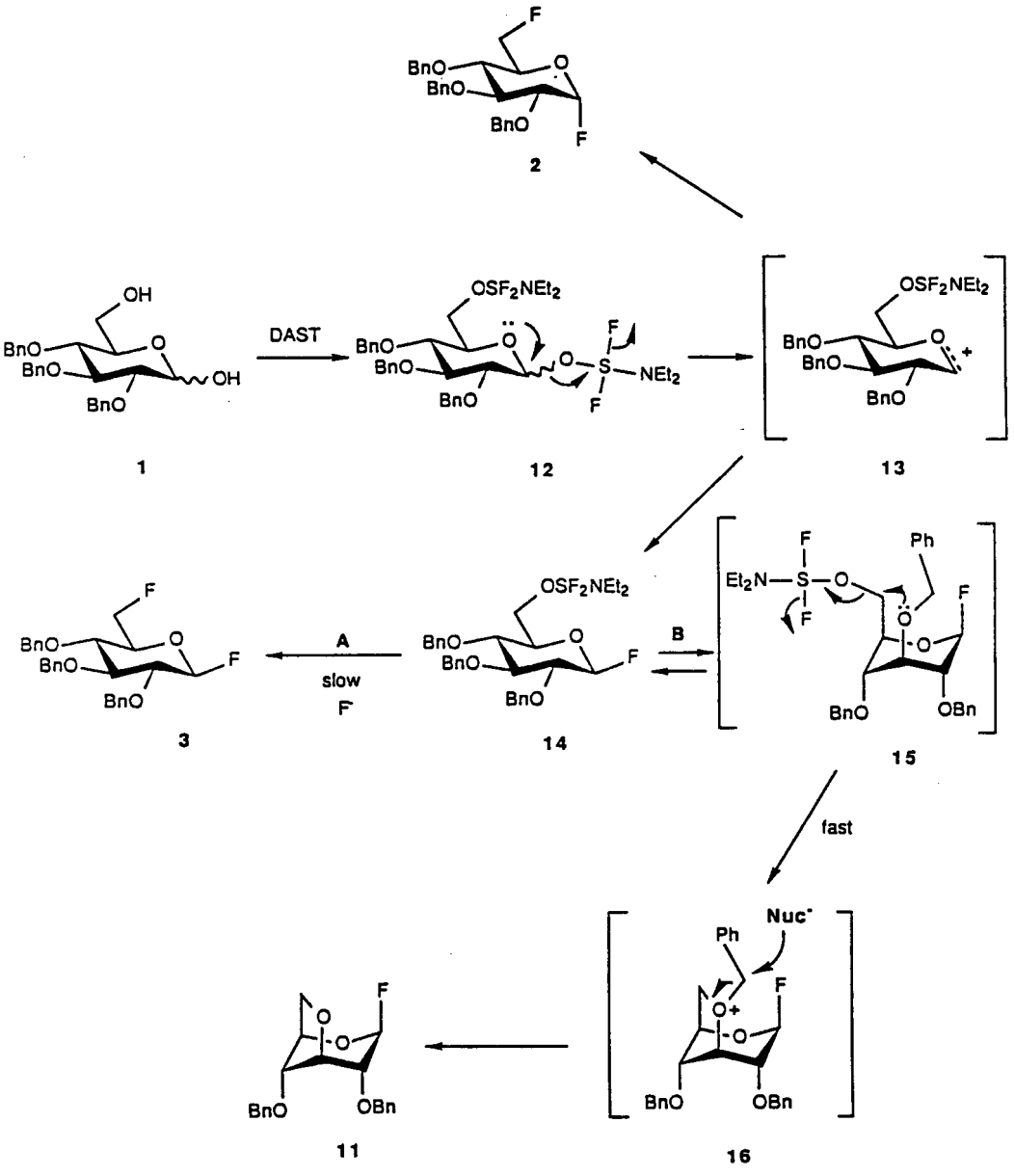
*It is noteworthy that the β-fluoro (as determined by NMR spectroscopy) derivative **3**, similar to the case of **8**, showed a more positive specific optical rotation than the corresponding α-glycosyl fluoride (*c.f.* data in the Experimental)

component, which according to TLC appeared to be the main reaction product, was crystalline but decomposed on contact with air. The substance showed noticeable sensitivity towards traces of acid, such as in common chloroform, and decomposed within a few hours when its solution in $CDCl_3$ was kept at room temperature. Due to its instability, the yield reported in the Experimental does not necessarily reflect the actual amount of the substance formed in the described reaction. The material was found to be more stable in the presence of an organic base. When isolated using an elution solvent containing 0.1% of pyridine the material could be recrystallized. This material gave correct analytical and MS data for a deoxyfluoro anhydro-di-*O*-benzyl-hexose, and is formulated as 3,6-anhydro-2,4-di-*O*-benzyl-β-D-glucopyranosyl fluoride (11). When the reaction of **1** with DAST was conducted in the presence of an organic base the formation of the desired glycosyl fluorides **2** and **3** was enhanced, with the concomitant suppression of the formation of **11**. Of the bases employed (experiments involving 4-dimethylaminopyridine, pyridine, 2,4,6-trimethylaminopyridine, tetramethylurea or diisopropylethylamine are not described in the Experimental) triethylamine gave the best results. Although formation of several minor by-products (same as and different from those formed in the absence of a base) was observed, compounds **2** and **3** were isolated in a combined yield of ~60%.

The described conversion **1** → **2** + **3** + **11** may be rationalized as shown in Scheme **1**. According to the proposed mechanism both hydroxyl groups in **1** could react quickly with DAST to give the disulfoxo intermediate **12**. Based on the above observation that anomeric hydroxyl groups react more readily than primary hydroxyl groups to give the corresponding fluorides, it is likely that the fluoride displacement at C-1 occurs first giving rise to **2** and **14** *via* the glucosyloxonium species **13**. The intermediate **14** can then react by one of two competitive pathways: **A** to give **3** or **B** to give **11**. In the absence of base, the benzyloxy group in the $^1C_4$ (D) conformation (**15**) participates to displace the 6-sulfoxy moiety at C-6 (pathway **B**) at a competitive

rate to that of pathway **A** thereby affording **11** eventually as the major product. The relatively poor reactivity of fluoride ion under these conditions is not surprising since the already low nucleophilic character of fluoride ion[10] would be lessened further by the preponderance of fluoride in the form of hydrogen fluoride.[11] In the presence of base, the reaction apparently proceeds largely *via* pathway **A** rather than **B**. Under these conditions, the increased yield of **2** and **3** (pathway **A**) may be attributed to the enhancement of the nucleophilicity of fluoride by liberation of fluoride ion from hydrogen fluoride. Thus, the presence of a base makes the attack at the 6-sulfoxylated carbon by the fluoride ion (pathway **A**) faster than that by the benzyloxy group (pathway **B**). Hence more **2** (and **3**) and less **11** is formed.

The proposed structure **11** containing a 3,6-anhydro ring and a pyranose ring in a $^{1}C_{4}$ (D) conformation is supported by analysis of its ^{1}H, ^{13}C, and ^{19}F NMR spectral data. Fluorination at C-1 is evident from the large $J_{F,C-1}$ (219.5 Hz) and large $J_{F,H-1}$ (56 Hz), as well as the large downfield shifts exhibited by the anomeric proton (δ 5.84) and carbon (δ 108.51). The presence of a 3,6-anhydro ring was deduced from the results of a XCORFE 2 D experiment[12] which establishes long-range carbon-proton connectivities. The experiment showed ^{13}C-^{1}H correlations between C-3 and H-6a and H-6b as well as between C-6 and H-3 through 3-bond long-range C-H couplings. Moreover, the spin-spin coupling constants involving protons H-4,5,6a, and H-6b (see Experimental Section) are in agreement with the values reported[13,14] for a number of 3,6-anhydrohexopyranosides. The results of the XCORFE 2-D experiment also established the location of the two benzyl groups present in the molecule. The conformational change requisite for the 3,6-anhydro ring closure is evidenced by vicinal coupling constants indicative of the equatorial orientation of H-2 to H-5. That is, in the $^{1}C_{4}$ (D) conformation of **11** H-2 to H-5 exhibit small vicinal coupling constants (2.9 - 5.1 Hz), which are contrasted to the large vicinal *trans*-diaxial coupling constants observed for the same protons in the $^{4}C_{1}$ conformation of D-glucose



Scheme 1

(J ~7-10 Hz). Consistent with the $^1C_4$ (D) conformation, and as anticipated for protons of equatorial rather than axial orientation (*c.f.* **10**) H-3, H-4 and H-5 in **11** resonate at lower[15] field. The values observed for $^3J_{F,H-2}$ (14.7 Hz) and $^3J_{H-1,H-2}$ (~0.8) suggest a *gauche* relationship between H-2 and each of F-1 and H-1, which is consistent with the $^1C_4$ (D) conformation wherein H-2 is equatorial.

The stereochemical assignment for fluorine (and proton) at C-1 in **11** could not be unequivocally made based solely on the ^3J coupling constants since both fluorine and proton at C-1 would be *gauche* to an equatorially oriented H-2 and, therefore, similar values would be expected for both α- and β-anomers. The assignment of the β-configuration in **11** is based on the observed long range coupling constants (determined from the HOM2DJ experiment) $^4J_{1,3}$ (1.1 Hz) and $^4J_{2,4}$ (0.7 Hz) attributed to the "W" arrangement of the coupled equatorial protons. The unusually large downfield ^{19}F chemical shift found in the spectrum of **11** (δ 57.8 *v.s.* δ ~14.0-27.0 ppm commonly found[16-19] in the spectra of glycosyl fluorides) could be attributed to the deshielding of the fluorine atom by the oxygen in the axially oriented 3,6-anhydro bridge.

EXPERIMENTAL

General methods.— Melting points were determined on a Kofler hot-stage. Unless otherwise stated, optical rotations were measured at 22° (c ~1), using a Perkin-Elmer automatic polarimeter, Model 241 MC. Thin-layer chromatography (TLC) on glass slides precoated with silica gel (Analtech or Whatmann) and preparative chromatography on columns of silica gel (Merck, cat. No. 9385) was performed with solvent mixtures of appropriately adjusted polarity consisting of *A.* carbon tetrachloride-acetone, *B.* toluene-ethyl acetate, and *C.* toluene-acetone. Detection was effected by charring with 5% (v/v) sulfuric acid in ethanol. Desorptive CI mass spectra were recorded using ammonia as the reagent gas and a Finnigan 4500 spectroameter. ^1H and ^{13}C NMR

spectra were measured at ambient temperature on a Varian XL 300 spectrometer using tetramethylsilane (hexafluorobenzene for ^{19}F) as the internal standard. Where required, proton-signal assignments were supported by homonuclear selective decoupling experiments. Unless otherwise stated, carbon-signal assignments were made by mutual comparison of the spectra using as aids the assigned[20] spectra of methyl 2,3,4,6-tetra-*O*-methyl-α- and β-D-glucopyranosides. Signals of secondary carbons were identified by DEPT experiments. Spectral assignments for **11** (for proton-signal assignments for **11** see **Fig.** 1) were verified by homonuclear decoupling, heteronuclear shift correlation 2D experiments (HETCOR), and heteronuclear shift correlation with fixed evolution time (XCORFE) 2D experiments. DAST was purchased from Aldrich Chemical Company, and distilled prior to use. 2,3,4,6-Tetra-*O*-benzyl-D-glucose (**6**) was purchased from Pfanstiehl Chemical Company, and used as supplied. Solutions in organic solvents were dried with anhydrous sodium sulfate and concentrated at 40°/15 mmHg.

2,3,4-Tri-*O*-benzyl-D-glucose (**1**).— This compound was obtained by slight modification of the procedure described by Eby *et al.*[8] Thus, a solution of concentrated sulfuric acid (1.5 mL) in a mixture of acetic anhydride (300 mL) and acetic acid (100 mL) was quickly added to **6** (50 g) contained in a 2 l round bottomed flask. The mixture was hand-stirred until all starting material dissolved (~1 min) and left at room temperature for 20 min. After addition of sodium acetate trihydrate (20 g), the mixture was concentrated to dryness by azeotropic distillation with toluene. The residue was triturated with dichloromethane, dried with anhydrous sodium sulfate, filtered, and the filtrate was concentrated. The crude product was chromatographed (900 g of silica gel, solvent A) to give first a fraction (29 g) largely enriched in the faster moving 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranose (**9**). The syrupy material partially crystallized on standing for ~1 week, and crystallization from methanol (twice) gave **9**: (18 g), mp 68-69 °C, $[\alpha]_D$ +69° (*c* 1, chloroform), lit.[9] mp

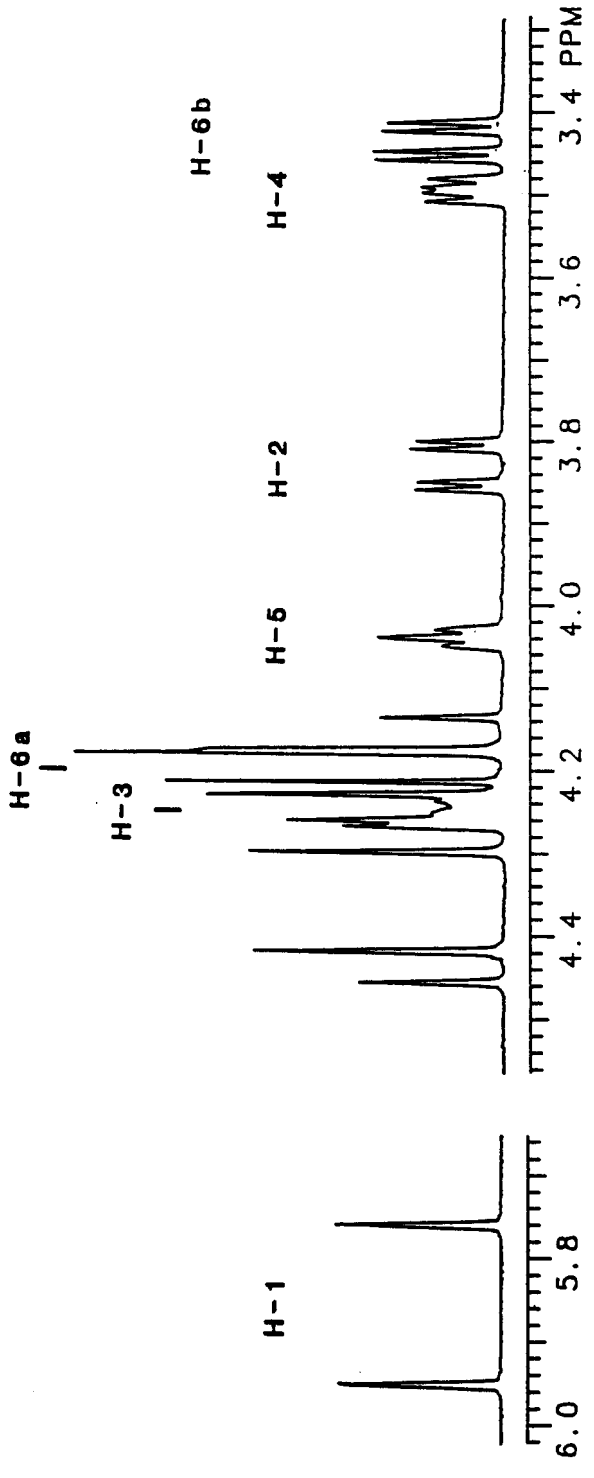


FIG. 1. Partial ^{1}H NMR spectrum of 11.

66 °C, $[\alpha]_D$ +62.5°, lit.[21] mp 64-65.5 °C, $[\alpha]_D$ +68°. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.20 (m, 15 H, aromatic protons), 6.32 (d, 1 H, $J_{1,2}$ 3.7 Hz, H-1), 5.01-4.55 (6 x d, 6 H, J~ 11 Hz, benzylic protons), 4.29 (dd, 1 H, $J_{5,6a}$ 4 Hz, $J_{6a,6b}$ 12.2 Hz, H-6a), 4.23 (dd, 1 H, H-6b), 4.00 (t, 1 H, $J_{3,4}$ 9.5 Hz, H-3), 3.93 (dt, $J_{5,6}$ 2.7 Hz, H-5), 3.67 (dd, 1 H, $J_{2,3}$ 9.3 Hz, H-2), 3.56 (dd, 1 H, $J_{3,4}$ 9.3 Hz, $J_{4,5}$ 10.2 Hz, H-4), 2.01, 2.13 (2 x s, 2 x 3H, 3 x OAc). ^{13}C NMR (75 MHz, $CDCl_3$): δ 89.67 (C-1), 81.66 (C-3), 78.91 (C-2), 76.61 (C-4), 75.74, 75.27, 73.21 (3 x 1 C, 3 x CH_2-benzylic), 71.11 (C-5), 62.69 (C-6).

Continued elution gave an intermediate, mixed fraction the last portions of which contained material largely enriched in the slower moving β-isomer **10**. Concentration of its solution in hexane gave a solid residue (1.19 g). Recrystallization from ethanol gave material melting at 70-71 °C, $[\alpha]_D$ +22° (*c* 1, chloroform), lit.[9] mp 63-63.5 °C, $[\alpha]_D$ +17.4°. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 - 7.57 (m, 15 H, aromatic protons), 5.57 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 4.90-4.51 (m, 6 H, benzylic protons), 4.24 (dd, 1 H, $J_{6a,6b}$ 11.9 Hz, H-6a), 4.18 (dd, 1 H, H-6b), 3.70 (t, 1 H, $J_{3,4}$ 8.4 Hz, H-3), 3.60 (ddd, 1 H, $J_{5,6a}$ 2.4 Hz, $J_{5,6b}$ 3.9 Hz, H-5), 3.52 (dd, 1 H, $J_{2,3}$ 9.4 Hz, H-2), 3.51 (dd, 1 H, $J_{4,5}$ 9.7 Hz, H-4), 2.00, 1.97 (2 x s, 2 x OAc). ^{13}C NMR (75 MHz, $CDCl_3$): δ 93.88 (C-1), 84.80 (C-3), 81.09 (C-2), 77.02 (C-4), 75.78, 75.06 (1C, 2C, 3 x CH_2-benzylic), 73.79 (C-5), 62.75 (C-6).

Compounds **9** and **10** were obtained in a combined yield of 85%. Deacetylation of either **9** or **10** gave **1** in a virtually quantitative yield. The compound was crystallized from isopropyl ether, yielding several crops, the melting points of which varied depending on the anomeric composition. An anomerically pure sample was not obtained, even the sample showing an mp higher than that reported (mp 98-100 °C, lit.[8,9] mp 90-91 °C) was a mixture of α- and β-forms, as shown by ^{13}C NMR (75 MHz, $CDCl_3$): δ 97.33 (C-1β), 91.09 (C-1α), 84.49 (C-3β), 83.22 (C-2β), 81.58 (C-3α), 80.04 (C-2α), 77,63 (C-4α,β), 75.41 (C-5β), 75.68, 75.02, 74.78 (CH_2-benzylic, β), 75.68, 75.02, 73.23 (CH_2-benzylic, α), 71.02 (C-5α), 61.95 (C-6α), 61.85 (C-6β).

2,3,4,6-Tetra-*O*-benzyl-α-D- (7) and -β-D-glucopyranosyl fluoride (8).— To a cold (-30 °C) solution of **6** (5.4 g, 10 mmol) in tetrahydrofuran (50 mL) was added DAST (1.5 mL, 12 mmol). The mixture was allowed to warm to room temperature and after 30 min TLC (solvent *B*) showed that the reaction was complete. Two much faster moving, poorly separared products were formed, of which the faster moving largely predominated. After cooling to -20°, methanol was added, and the mixture was concentrated. The residue was partitioned between dichloromethane and a 1:1 mixture of aqueous, saturated solutions of sodium chloride and sodium hydrogen carbonate. The organic phase was dried, concentrated and the residue was chromatographed (solvent *B* containing 0.1% of pyridine) to give initially **8** (4.9 g). Crystallization from isopropyl ether (twice) gave pure **8**: mp 48-48.5 °C, $[\alpha]_D$ +38° (*c* 0.8, chloroform), lit.[2] mp 42-44 °C, $[\alpha]_D$ +31°. ^{13}C NMR (75 MHz, $CDCl_3$): δ 109.84 ($J_{F,C}$ 215.8 Hz, C-1), 83.44 ($J_{F,C}$ 10.6 Hz, C-3), 81.46 ($J_{F,C}$ 21.2 Hz, C-2), 76.90 (C-4), 75.36, 74.91, 74.37, 73.55 (4 x CH_2-benzylic), 74.86 ($J_{F,C}$ 7.6 Hz, C-5), 68.41 (C-6). ^1H NMR (300 MHz, C_6D_6): δ 5.15 (dd, 1 H, $J_{1,2}$ 6.3 Hz, $J_{F,1}$ 52.8 Hz, H-1), 3.80 (t, 1 H, $J_{3,4}$ 9.2 Hz, $J_{4,5}$ 9.8 Hz, H-4), 3.52-3.69 (m, 4 H, H-2,3,6a,6b), 3.37 (ddd, 1 H, $J_{5,6a}$ 3.7 Hz, $J_{5,6b}$ 2.1 Hz, H-5). ^{19}F NMR (282 MHz, C_6D_6): δ 24.42 ($J_{F,1}$ 53.1 Hz, $J_{F,2}$ 10.1 Hz, F-1).

Eluted next was material (0.1 g) largely enriched in the slower moving α-fluoride **7** which solidified on concentration. Crystallization from methanol gave **7** exhibiting mp 71-72 °C and $[\alpha]_D$ +11° (*c* 0.9, chloroform), lit.[22] mp 68-69 °C, $[\alpha]_D$ +8.3°. ^{13}C NMR (75 MHz, in $CDCl_3$): δ 105.54 ($J_{F,C}$ 227.8 Hz, C-1), 81.46 (C-3), 79.39 ($J_{F,C}$ 24.2 Hz, C-2), 76.68 (C-4), 75.80, 75.16, 73.52 (2 x 1C, 1 x 2C, 4 x CH_2-benzylic), 72.71 ($J_{F,C}$ 3.9 Hz, C-5), 67.89 (C-6). ^1H NMR (300 MHz, in $CDCl_3$): δ 5.55 (dd, 1 H, $J_{1,2}$ 2.4 Hz, $J_{F,1}$ 53.2 Hz, H-1), 3.98 (t, 1 H, $J_{2,3}$ 9.3 Hz, $J_{3,4}$ 9.3 Hz, H-3), 3.93 (bd, 1 H, $J_{4,5}$ 8.2 Hz, H-5), 3.64-3.78 (m, 3 H, H-4,6a,6b), 3.56 (ddd, 1 H, $J_{2,3}$ 9.% Hz, $J_{F,2}$ 25.3 Hz, H-2). ^{19}F NMR (282 MHz, C_6D_6): δ 12.9 ($J_{F,1}$ 53.5 Hz, $J_{F,2}$ 25.7 Hz, F-1).

Methyl 2,3,4-tri-*O*-benzyl-6-deoxy-fluoro-α-D-glucopyranoside (5).— a) DAST (0.24 mL, 2 mmol) was added dropwise at 0° to a stirred solution of crystalline[23] **4** (0.46 g, 1 mmol) in 1,2-dimethoxyethane (5 mL). The reaction mixture was warmed to and maintained at 60 - 70 °C for 1 h. The mixture was cooled to -10°, methanol (1 mL) was added, and the mixture was neutralized with solid sodium hydrogen carbonate. After concentration, the residue was partitioned between dichloromethane and aqueous, saturated sodium chloride solution. The organic phase was dried, concentrated, and the residue was chromatographed (solvent *C*) to give **5** (0.35 g, 75%) as a viscous, colorless oil: $[\alpha]_D$ +17° (*c* 0.8. chloroform). ^{1}H NMR (300 MHz, C_6D_6): δ 7.40-7.18 (m, 15 H, aromatic protons), 4.68 (ddd, partially overlapped with signals of benzylic protons, $J_{5,6a}$ 3.2 Hz, $J_{6a,F}$ 47.9 Hz, H-6a), 4.62 (d, 1 H, $J_{1,2}$ 3.4 Hz, H-1), 4.39 (ddd, partially overlapped with signals of benzylic protons, $J_{6a,6b}$ 10.2 Hz, $J_{6b,F}$ 48 Hz, $J_{5,6b}$ 1.5 Hz, H-6b), 4.19 (t, 1 H, $J_{3,4}$ ~8.8 Hz, H-3), 3.73 (dddd, 1 H, $J_{5,F}$ 27.9 Hz, H-5), 3.62 (t, 1 H, $J_{4,5}$ 10 Hz, H-4), 3.49 (dd, 1 H, $J_{2,3}$ ~9.5 Hz, H-2), 3.36 (s, 3 H, OMe). ^{13}C NMR (75 MHz, $CDCl_3$): δ 98.27 (C-1), 81.90 ($J_{F,C}$ 173.0 Hz, C-6), 81.89 (C-3), 79.84 (C-2), 76.75 ($J_{F,C}$ 5.8 Hz, C-4), 75.75, 75.20, 73.4 (3 x CH_2-benzylic), 69.76 ($J_{F,C}$ 19.0 Hz, C-5), 55.30 (Me). ^{19}F NMR (282 MHz, C_6D_6): δ -69.8 (dt, $J_{F,6}$ 48.0 Hz, $J_{F,5}$ 28.0 Hz, F-6).

Anal. Calcd. for $C_{28}H_{31}FO_5$: C, 72.08; H, 6.69; F, 4.07. Found: C, 72.28; H, 6.85; F, 4.03.

b) To a solution of methyl 6-deoxy-6-fluoro-α-D-glucopyranoside[24] (0.7 g, 3.5 mmol) in 1,2-dimethoxyethane (10 mL) was added sodium hydride (0.43 g, 21.4 mmol) followed by benzyl bromide (2.11 mL, 17.8 mmol), and the mixture was heated at 75 °C with the exclusion of atmospheric moisture and carbon dioxide for 2 h. Additional sodium hydride (0.2 g) and benzyl bromide (1 mL) was added and after another 1 h at 75 °C TLC (solvent *A*) indicated that only traces of underbenzylated material remained. The mixture was cooled (0 °C), methanol added to destroy any excess of the benzylating reagent, and the organic solvents were evaporated. The

material obtained was partitioned between water and dichloromethane and the organic phase was dried and concentrated. The residue obtained was eluted from a column of silica gel to give **5** (1.45 g, 90%).

2,3,4-Tri-*O*-benzyl-6-deoxy-6-fluoro-α- (2) and β-D-glucopyranosyl fluoride (3), and 3,6-anhydro-α-2,4-di-*O*-benzyl-β-D-glucopyranosyl fluoride (11).— a) Compound **1** (0.9 g, 2 mmol) was treated with DAST (1.22 mL, 10 mmol) at 70 °C as described for the conversion **4** → **5**. After work-up, as described above, the crude product was chromatographed (solvent *B*, containing 0.1% of pyridine) to give **2**: (35 mg, 3.8 %), mp 88-89 °C (from ethanol, twice), $[\alpha]_D$ -3.5° (c 0.5, chloroform). CI MS m/z 472 ($[M + NH_4]^+$). ^1H NMR (300 MHz, C_6D_6): δ 7.40 (m, 15 H, aromatic protons), 5.52 (dd, 1 H, $J_{1,2}$ 2.4 Hz, $J_{F,1}$ 53 Hz, H-1), ~4.36 (ddd, partially overlapped with signals of benzylic protons, $J_{F,6a}$ 47.6 Hz, $J_{6a,6b}$ 10.5 Hz, $J_{5,6a}$ 2.4 Hz, H-6a), ~4.31 (ddd, partially overlapped with signals of benzylic protons, $J_{F,6b}$ 47.6 Hz, $J_{5,6b}$ 1.6 Hz, H-6b), 4.06 (t, 1H, $J_{3,4}$ 8.7 Hz, H-3), 3.84 (tdd, 1 H, $J_{F,5}$ 29.7 Hz, H-5), 3.67 (t, 1 H, $J_{4,5}$ 10.3 Hz, H-4), 3.33 (ddd, 1 H, $J_{2,3}$ 9.5 Hz, $J_{F,2}$ 25.3 Hz, H-2). ^{19}F nmr (282 MHz, C_6D_6): δ 13.7 (dd, 1 F, $J_{F,1}$ 53.1 Hz, $J_{F,2}$ 25.5 Hz, F11),-71.8 (td, 1 F, $J_{F,6}$ 47.6 Hz, $J_{F,5}$ 29.1 Hz, F-6). ^{13}C NMR (75 MHz, in $CDCl_3$): δ 105.43 (d, $J_{F,C}$ 227.5 Hz, C-1), 81.19 (d, $J_{F,C}$ 173.8 Hz, C-6), 81.20 (C-3), 79.29 (d, $J_{F,C}$ 24.4 Hz, C-2), 75.39 (d, $J_{F,C}$ 6.1 Hz, C-4), 75.84, 75.72, 73.61 (3 x CH_2-benzylic), 72.23 (dd, $J_{F-6,C}$ 17.1 Hz, $J_{F-1,C}$ 3.6 Hz, C-5).

Anal. Calcd. for $C_{27}H_{28}F_2O_4$: C, 71.34; H, 6.21; F, 8.36. Found: C, 71.54; H, 6.34; F, 8.06.

Eluted next was the β-fluoride **3** (135 mg, 14.8%), mp 100-101 °C (from ethanol, twice), $[\alpha]_D$ +23° (c 0.8, chloroform). ^1H NMR (300 MHz, C_6C_6): δ 5.08 (dd, 1 H, $J_{1,2}$ 6.3 Hz, $J_{F,1}$ 53.3 Hz, H-1), 4.35 (ddd, 1 H, $J_{6a,F}$ 47.3 Hz, $J_{6a,6b}$ 10.2 Hz, $J_{6a,5}$ 2.1 Hz, H-6a), 4.31 (ddd, 1 H, $J_{6b,F}$ 47.3 Hz, $J_{6b,5}$ 3.5 Hz, H-6b), 3.61 (t, 1 H, $J_{4,5}$ 9,7 Hz, $J_{3,4}$ 9.7 Hz, H-4), 3.46-3.56 (m, 2 H, H-2,3), 3.18 (dddd, 1 H, $J_{5,F}$ 26.2 Hz, H-5). ^{19}F nmr (282 MHz,

C_6D_6): δ 24.8 dd (1 F, $J_{F,1}$ 53.1 Hz, $J_{F,1}$ 10 Hz, F-1), -71.0 (td, 1 F, $J_{F,6}$. 47.8 Hz, $J_{F,5}$ 26.6 Hz, F-6). ^{13}C NMR (75 MHz, $CDCL_3$): δ 109.5 (d, $J_{F,C}$ 216.3 Hz, C-1), 83.22 (d, $J_{F-1,C}$ 9.4 Hz, C-3), 81.33 (d, $J_{F,C}$ 174.9 Hz, C-6), 81.20 (d, $J_{F,C}$ 22.5 Hz, C-2), 75.75 (d, $J_{F-6,C}$ 6.1 Hz, C-4), 75.26, 75.11, 74.34 (3 x CH_2-benzylic), 74.02 (dd, $J_{F-6,C}$ 18.4 Hz, $J_{F-1,C}$ 4.9 Hz, C-5).

Anal. Calcd. for $C_{27}H_{28}F_2O_4$:C, 71.34; H, 6.21; F, 8.36. Found: C, 71.38; H, 6.14; F, 8.23.

Eluted last was the 3,6-anhydro derivative **11** (0.4 g, 44%, mp 83-84 °C (from isopropyl ether, twice), $[\alpha]_D$ -38.5° (c 0.8, benzene). CI MS, m/e 362 ($[M + NH_3]^+$). ^1H NMR (300 MHz, C_6D_6, containing a trace of pyridine-d_5): δ 5.849 (d, 1 H, $J_{F,1}$ 57.4 Hz, $J_{1,2}$ 0.8 Hz, $J_{1,3}$ 1.1 Hz, H-1), 4.244 (dd, $J_{3,4}$ 5.1 Hz, H-3), 4.198 (dd, $J_{6b,6a}$ 10.3 Hz, H-6a), 4.037 (bt, $J_{5,6a}$ not observed, H-5), 3.828 (dd, $J_{F,2}$ 14.7 Hz, $J_{2,3}$ 2.9 Hz, $J_{2,4}$ 0.7 Hz,H-2), 3.492 (bdd, 1 H, $J_{4,5}$ 2.9 Hz, H-4), 3.433 (dd, 1 H, $J_{5,6b}$ 3.2 Hz, H-6b), 4.433, 4.279 (2 x d, ^2J 11.5 Hz, 4-*O*-CH_2), 4.243, 4.152 (2 x d, 2 H, $_2J$ 11.7 Hz, 2-*O*-CH_2). ^{19}F NMR (282 MHz, solvent as above): δ 57.0 (dd, $^2J_{F,1}$ 56.7 Hz, $^3J_{F,2}$ 14.7 Hz, (F-1). ^{13}C NMR (75 Mz, solvent as above): δ 108.51 ($J_{F,C}$ 219.2 Hz, C-1), 80.23 ($J_{F,C}$ 30.5 Hz, C-2), 75.36 (C-4), 73.53 (C-5), 72.91 (2-*O*-CH_2), 72.11 (4-*O*-CH_2), 71.40 (C-3), 70.95 (C-6).

Anal. Calcd. for $C_{20}H_{21}FO_4$: C, 69.75; H, 6.14; F, 5.51. Found: C, 69.68; H, 6.02; F, 5.49.

b) The experiment in a) was repeated in the presence of triethylamine (1 mL). The crude product was chromatographed, to give **2** and **3** in a combined yield of 60%. Compound **11**, which was presumably one of several minor products formed (TLC) was not isolated.

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