Calcd for $C_{26}H_{22}O_2$: C, 85.22; H, 6.05. Found: C, 84.96; H, 6.26.

**Dibenzo-20-crown-6 Hosts (10a-d).**[39] The following procedure for host **10a** is representative. A solution of 1.53 g (2.8 mmol) of pentaethylene glycol ditosylate[4,26] in 60 mL of THF was added to a solution of 0.6 g (2.8 mmol) of diol **9a**[36] and 0.47 g (11 mmol) of NaOH in 130 mL of THF and 8 mL of water. The resulting solution was stirred under $N_2$ and heated under reflux for 72 h and then cooled and acidified (pH 4) with 2 N aqueous HCl. Evaporation of the solvent in vacuo gave a residue, which was distributed between 200 mL of water and 200 mL of ethyl acetate. The organic layer was washed with 200-mL portions of water and saturated aqueous NaCl, dried ($MgSO_4$), and concentrated to dryness under reduced pressure. Gel permeation chromatography of the residue on 100-Å Styragel, followed by gravity chromatography on 75 g of silica gel with ether, gave 0.56 g of host **10a** as a white solid. Recrystallization from 95% ethanol at -20 °C yielded 0.47 g (41%) of **10a** as white crystals: mp 96.5-97.5 °C; MS, $m/e$ 416 ($M^+$); $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 2.299 (s, Ar $CH_3$, 6 H), 3.48-4.17 (m, $CH_2$, 20 H), 6.846 (d, $J$ = 8.3 Hz, Ar H, 2 H), 6.996 (d, $J$ = 2.0 Hz, Ar H, 2 H), 7.065 (dd, $J$ = 2.0, 8.3 Hz, Ar H, 2 H). Anal. Calcd for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 69.20; H, 7.78.

Host **10b** was prepared according to the method described above for **10a** by heating a solution of 3 g (8.1 mmol) of diol **9b**, 1 g (25 mmol) of NaOH, 4.4 g (8.1 mmol) of pentaethylene glycol ditosylate, 600 mL of THF, and 20 mL of water for 120 h. The product was purified by gel permeation chromatography on 100 Å Styragel, followed by flash chromatography[56] on 100 g of silica gel with ether. The resulting light yellow oil was dried at 100 °C in vacuo, yielding 2.6 g (56%) of host **10b**: MS, $m/e$ 574 ($M^+$); $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 2.292 (s, Ar $CH_3$, 6 H), 3.53-3.90 (m, $CH_2$, OH), 7.118 (d, $J$ = 2.2 Hz, Ar H, 2 H), 7.363 (d, $J$ = 2.2 Hz, Ar H, 2 H). Anal. Calcd for $C_{24}H_{30}O_6Br_2$: C, 50.19; H, 5.27. Found: C, 50.13; H, 5.18.

Host **10c** was similarly prepared from 0.23 g (0.63 mmol) of diol **9c**, 0.08 g (2 mmol) of NaOH, and 0.38 g (0.69 mmol) of pentaethylene glycol ditosylate in 40 mL of THF and 1.6 mL of water (reflux time, 48 h). Gel permeation chromatography on 100-Å Styragel, followed by medium-pressure chromatography on silica gel with ether, afforded a yellowish oil, which was dried at 80 °C in vacuo, yielding 0.142 g (40%) of host **10c**: MS, $m/e$ 568 ($M^+$); $^1H$ NMR (60 MHz, $CDCl_3$) $\delta$ 2.36 (s, Ar $CH_3$, 6 H), 3.15-3.75 (m, $CH_2$, 20 H), 7.05-7.70 (m, Ar H, 14 H). Anal. Calcd for $C_{36}H_{40}O_6$: C, 76.03; H, 7.09. Found: C, 76.17; H, 7.08.

Host **10d** was similarly prepared from 1.0 g (4.1 mmol) of diol **9d**,[38] 0.5 g (13 mmol) of NaOH, and 2.5 g (4.5 mmol) of pentaethylene glycol ditosylate in 300 mL of THF and 10 mL of water (reflux time 56 h). Gel permeation chromatography on 100-Å Styragel, followed by gravity chromatography on 50 g of silica gel with ether, gave a yellowish oil, which was dried at 100 °C in vacuo. Thus obtained was 1.23 g (67%) of host **10d**: MS, $m/e$ 444 ($M^+$); $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 2.267 (s, Ar $CH_3$, 6 H), 2.317 (s, Ar $CH_3$, 6 H), 3.45-3.78 (m, $CH_2$, 20 H), 6.945 (d, $J$ = 2.2 Hz, Ar H, 2 H). Anal. Calcd for $C_{26}H_{36}O_6$: C, 70.24; H, 8.16. Found: C, 70.12; H, 8.16.

**Acknowledgment.** Professors J. I. Brauman and D. N. Reinhoudt are thanked for helpful discussions with one of the authors (T.W.B.).

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# Fluorinated Carbohydrates. 2. Selective Fluorination of Gluco- and Mannopyranosides. Use of 2-D NMR for Structural Assignments†

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Methyl and phenyl α-glucosides, or suitably protected derivatives, may be selectively fluorinated with (diethylamino)sulfur trifluoride (DAST) at the 4- or 6-position to afford the corresponding fluorinated galacto- or glucopyranoside. In contrast to the α-glucosides, the β-glucosides underwent ring fluorination at C-3 to give the 3-deoxy-3-fluoro-β-allo derivatives. High yields of primary fluorinated (C-6) products were obtained from both α- and β-glucosides by use of appropriate reaction times. Use of 6-*O*-trityl derivatives of methyl α- and β-glucosides gave methyl 4-deoxy-4-fluoro-α-galactopyranoside (**22**) and methyl 3-deoxy-3-fluoro-β-allopyranoside (**19**), respectively. Use of 2-D NMR (COSY) for structural assignments is also described. Fluorinated *p*-nitrophenyl α- and β-gluco- and -galactopyranosides (such as **15**) have also been prepared by the above DAST reactions. 6-*O*-Pivaloate esters of methyl α-gluco- and α- and β-galactopyranosides have been prepared as an acid and DAST-stable 6-O protecting group. Proof of an intramolecular fluoride-ion delivery mechanism for the $S_N2$ displacement reaction at C-4 in methyl α-D-mannopyranoside is described. Methyl 4-amino-4,6-dideoxy-6-fluoro-α-D-glucopyranoside, methyl 6-amino-3,6-dideoxy-3-fluoro-β-D-allopyranoside, and methyl 6-amino-4,6-dideoxy-4-fluoro-α-D-talopyranoside were also prepared via the above methodology.

The altered hydrogen-bonding properties present in carbohydrates bearing a fluorine atom in place of an hydroxyl group have been exploited in biochemical investigations (enzyme-carbohydrate interactions, lectin-carbohydrate affinities, antibody-carbohydrate binding, etc.).[1-5] The syntheses of fluorinated sugars, however, are both tedious and time consuming because of (1) the protection and deprotection steps required to set up the desired hydroxyl group for the introduction of fluoride, (2) the low nucleophilicity of fluoride ion, and (3) fluoride ion catalyzed elimination reactions.[6,7] As part of a program concerned with the synthesis of modified carbohydrates, we

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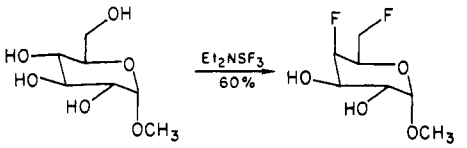
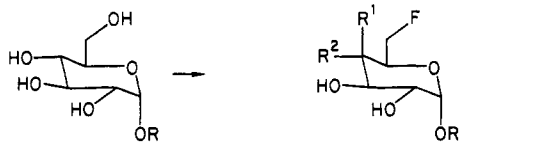
became interested in synthesizing specifically fluorinated carbohydrates from unprotected or only partially protected substrates by use of (diethylamino)sulfur trifluoride (DAST).[8] While DAST has been used to fluorinate sugars,[9,10] only recently have the reactions of DAST with minimally protected derivatives been investigated.[11-13] This paper reports the results of our studies of the reaction of DAST with various gluco- and mannopyranosides.

Somawardhana[11] reported that methyl α-D-glucopyranoside (1) reacts with *neat* DAST to give methyl




1 2

4,6-dideoxy-4,6-difluoro-α-D-galactopyranoside (2) in which both the 4- and 6-hydroxyl groups have been replaced by a fluorine atom. In contrast to this, we recently reported[13] that use of dichloromethane as a reaction solvent allows for the selective monofluorination of 1. Thus, treatment of a suspension of 1 in dichloromethane with excess DAST (6 equiv) afforded methyl 6-deoxy-6-fluoro-α-D-glucopyranoside (3) in 70–88% yield. This simple and selective



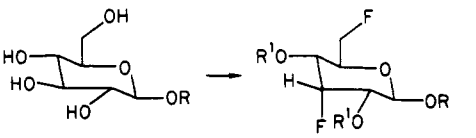

4, R = Ph

3, R = $CH_3$; $R^1$ = H; $R^2$ = OH
5, R = Ph; $R^1$ = H; $R^2$ = OH
13, R = Ph; $R^1$ = F; $R^2$ = H

fluorination of 1 is the method of choice for the preparation of 6-deoxy-6-fluoro-α-glucosides since the previous synthesis[14] was carried out in two steps and in <25% overall yield.

To assess any steric or electronic factors in the DAST reaction, and as a model for the preparation of fluorinated *p*-nitrophenyl glycosides, we also investigated the reaction of phenyl α-D-glucopyranoside (4) with DAST. When a suspension of 4 in dichloromethane was treated with DAST, the monofluorinated α-glucoside 5 was obtained in 58% yield. The position of the fluorine atom in 5 was determined from the chemical shift and coupling constant data in the $^1H$, $^{19}F$, and $^{13}C$ NMR spectra (see Experimental Section).

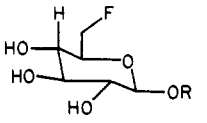
To determine whether the anomeric configuration would affect the outcome of the DAST reaction, as has been demonstrated in the reactions of methyl α- and β-glucopyranosides with sulfuryl chloride,[15] we examined the reaction of DAST with methyl (6) and phenyl (7) β-D-glucopyranoside. In contrast to the results obtained for the α-glucosides 1 and 4, the β-glucosides 6 and 7 in dichloromethane reacted with DAST in a comparable amount of time to afford the difluorinated allopyranosides 8 (51%) and 9 (70%), respectively. The structure of the products follow from their $^1H$, $^{19}F$, and $^{13}C$ NMR spectra. The regio- and stereochemical assignment at C-3 was made after extensive decoupling experiments as well as 2-D NMR spectroscopy (vide infra). The $^{19}F$ NMR spectrum of 8 reveals the presence of a 1° ($\phi$ −234.6) and a 2° ($\phi$ −217.6) fluorine atom. The small $^1H$–$^{19}F$ coupling constant for H-1 ($\delta$ 4.48, $J_{H,F}$ = 1.5 Hz) reveals that the 2° fluorine is not positioned at C-2. H-2 appears ($\delta$ 3.41) as a multiplet with $J_{H,F}$ = 30 Hz, suggesting that the fluorine atom is at C-3 and in an axial orientation. H-3 ($\delta$ 4.88) exhibits a typical geminal $^1H$–$^{19}F$ coupling constant of 54 Hz and proton couplings of <5 Hz, which also suggest that the fluorine atom is in the axial configuration. The $^1H$–$^{19}F$ coupling constant for H-4 ($J$ = 29 Hz) also corroborates the positioning of the 2° fluorine atom at C-3. In addition, H-5 couples with only one fluorine atom (F-6) and thus requires the 2° fluorine atom to be on a carbon atom other than C-4.




6, R = $CH_3$
7, R = Ph

8, R = $CH_3$; $R^1$ = H
9, R = Ph; $R^1$ = H
10, R = $CH_3$; $R^1$ = Bz

The reaction of DAST with β-glucosides can be used for the preparation of monofluorinated products if short reaction times are employed. Thus, methyl 6-deoxy-6-fluoro-β-D-glucopyranoside (11) was obtained in 60% yield




11, R = $CH_3$
12, R = Ph

when the reaction of 6 with DAST was quenched after only 15 min, and phenyl β-*D*-glucoside (7) afforded a 29% yield of 12 after 25 min. The yields of these reactions have not been optimized.

In contrast to the β-glucosides, which undergo rapid ring fluorination at C-3 to give 3-fluoroallopyranosides, the α-glucosides reacted very slowly and afforded 4-fluorogalactopyranosides in moderate yields. Thus, treatment of 1 with DAST over a 72-h period gave methyl 4,6-dideoxy-4,6-difluoro-α-D-galactopyranoside[11] (2) in 40% yield, and 4 gave 13 in 38% yield after 5 days. The assignment of the ring fluorine atom to C-4 follows from the 360-MHz $^1H$ NMR spectrum of 13 in which H-2 ($\delta$ 4.0) is coupled to H-1 ($J$ = 3.5 Hz) and to H-3 ($J$ = 10 Hz), but it is not vicinally coupled to a fluorine atom. In addition, H-3 ($\delta$ 4.2) does exhibit a vicinal coupling ($J$ = 29 Hz) with a fluorine atom, which is therefore at C-4. It is of interest to note that in all the cases we have studied the substitution of a ring hydroxyl group with fluorine via the DAST reagent has occurred with inversion of configuration.[13]

The relative rates of mono- and difluorination of 4 and 7 with DAST were obtained by withdrawing aliquots from the reaction mixture at timed intervals, quenching them in cold methanol, and determining the $^{19}F$ NMR spectra of the crude samples. After 1 h, the only fluorinated derivative present in the reaction of 4 with DAST was 5, and after 2 h, the mono- to difluorinated ratio was 95:5. In contrast, after 1 h the ratio for the reaction of 7 was 37:63

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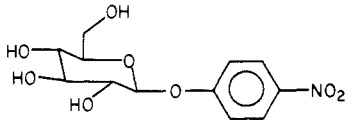
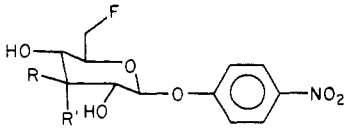
(12/9), and after 2 h only the difluorinated product 9 could be detected. Indeed, the fluorination of C-4 in the α-glucosides is so slow under our conditions that difluorination of 1 required 48–72 h, and the ratio for 4 was still 20:80 (5/13) after a comparable period. No other fluorinated products were detected in any of these experiments.

We also ascribe the lack of reactivity at C-3 in the α-D-glucopyranosides toward the DAST reagent to a steric interaction between the incoming nucleophile and the glycosidic oxygen and aglycon moiety.[15,16]

The utility of *p*-aminophenyl glycosides, for instance in the preparation of immunogenic carbohydrate–protein conjugates,[17] caused us to examine the reaction of *p*-nitrophenyl β-*D*-glucopyranoside[18] (14) with DAST to



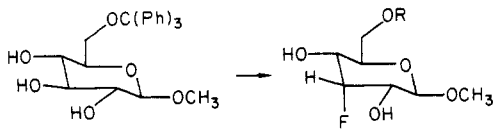
14



15, R = OH; R′ = H
16, R = H; R′ = F

determine whether fluorinated analogues could be readily obtained. As expected from the reactivity of 7, 14 afforded either 15 (55%) after 35 min or 16 (78%) after overnight reaction. *p*-Nitrophenyl α-D-glucopyranoside could also be mono- and difluorinated as per 4, but the fluorinated products appeared to be considerably less stable than 15 and 16 and are not reported here.

The regiospecific preparation of ring-fluorinated sugars is difficult because of the number of protection and deprotection steps required to set up the desired hydroxyl group for the introduction of fluorine.[6,7] The regiospecificity exhibited by the DAST reagent (as shown above and in ref 13) toward gluco- and mannopyranoside rings renders DAST a useful reagent for the regiospecific preparation of ring-fluorinated sugars from only minimally protected carbohydrate derivatives. Thus, treatment of the readily available methyl 6-*O*-trityl-β-D-glucopyranoside (17) with DAST (18 h at room temperature) gave methyl



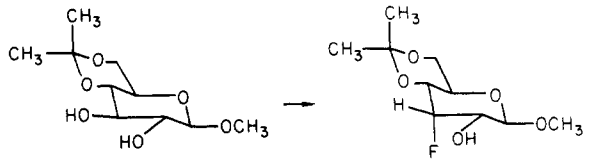
17

18, R = $C(Ph)_3$
19, R = H

3-deoxy-3-fluoro-6-*O*-trityl-β-D-allopyranoside (18) in 50% yield. The assignment of the 3-fluoro allo configuration to 18 follows from its 360-MHz $^1H$ spectrum (see Experimental Section), its 2-D NMR spectrum (vide infra), and X-ray crystallographic analysis.[19]

Detritylation of 18 to give 19 can be effected by either aqueous acetic acid (see Experimental Section) or $CuSO_4$,[20] but we have found the acetic acid method to be more amenable to scaleup. The yield of 19 from 17 is only 22%, but the simplicity and directness of this method make it a useful technique for the preparation of 3-deoxy-3-fluoroallopyranosides.

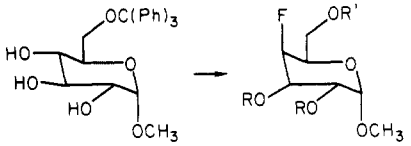
A second method to prepare 3-fluoroallopyranoses with minimal protection steps is to use the readily available methyl 4,6-*O*-isopropylidene-β-D-glucopyranoside[21] (20).



20 21

When 20 was allowed to react with DAST, 21 was obtained in 45% yield. The structure of 21 follows from its 360-MHz $^1H$ NMR spectrum in which H-2 (δ 3.65) exhibits a trans-diaxial coupling with F-3 ($J$ = 27 Hz), thus defining the stereochemistry at C-3.

Methyl 4-deoxy-4-fluoro-D-galactosides have been prepared to study galactoside binding of immunoglobulins[5] and for use as substrates for enzymes such as galactose oxidase.[22] These investigators carried out independent synthesis of methyl 4-deoxy-4-fluoro-β-D-galactopyranoside, with each synthesis consisting of eight steps. Application of the DAST methodology to this problem reduces the synthesis of methyl 4-deoxy-4-fluoro-α-D-galactoside (22) to three steps. Methyl 6-*O*-trityl-α-D-glucopyranoside (23) reacted with DAST to afford 24 in 23% yield. The structure of 24 follows from its 360-MHz 2-D NMR spectrum (vida infra).



23

22, R′ = R = H
24, R′ = $C(Ph)_3$; R = H
25, R′ = R = $COCH_3$

Detritylation of 24 with aqueous acetic acid afforded 22 in 50% yield. The discrepancy between the observed mp for 22 (120–122.5 °C) and that previously reported[23] (102–103 °C) is probably the result of crystalline modifications since both the 2-D NMR spectrum of 24 and the 360-MHz $^1H$ NMR spectrum of triacetate 25 (prepared from 22) firmly support the 4-deoxy-4-fluorogalacto structure.

During large-scale fluorinations of the trityl derivatives such as 17, a significant amount of trityl ether cleavage occurs. This reaction is even more pronounced with the dimethoxytrityl analogue of 17 where only the difluorinated product 8 is obtained. Therefore, we desired to protect the 6-O position with a group that was stable to acid and DAST and that could be specifically introduced at O-6. We have found that pivaloate esters are useful for this purpose. Pivaloate esters have been used to protect the 5′-OH group of nucleosides,[24] but we were unable to

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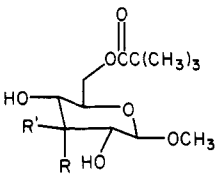
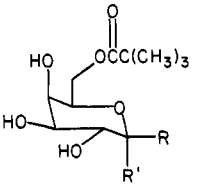
find 6-*O*-pivaloate derivatives of the methyl gluco- and galactopyranosides in the literature. We have found that treatment of **6** in pyridine containing a catalytic amount of 4-(dimethylamino)pyridine with pivaloyl chloride[25] (70 °C, overnight) gave the 6-*O*-pivaloate **26** in 67% yield.



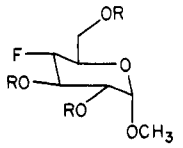


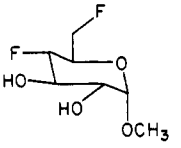
**26**, R = H; R′ = OH
**29**, R = F; R′ = H

**27**, R′ = $OCH_3$; R = H
**28**, R′ = H; R = $OCH_3$

Likewise, methyl α-D-galactopyranoside and methyl β-D-galactopyranoside afforded **27** (70%) and **28** (53%), respectively. Reaction of **26** with DAST gave **29** in 35% yield. The structure of **29** follows from its $^1H$ NMR spectrum where H-2 (δ 3.42) exhibits a large (30 Hz) trans-diaxial coupling with F-3, a large (8 Hz) trans-diaxial coupling with H-1, and a small coupling (2 Hz) with H-3. The yield of this reaction has not been optimized; it is higher than the trityl case, and the fluorinated pivaloate is much easier to handle since it readily crystallizes.

To prepare the gluco analogue of **2**, we debenzoylated **30**[13] with aqueous triethylamine to afford **31**[26] in 74% yield.



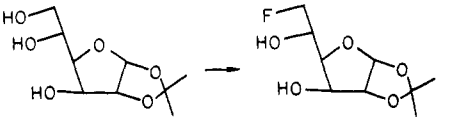


**30**, R = COPh
**31**, R = H

**32**

When **31** was treated with DAST, **32** was obtained in 71% yield. The $^1H$ NMR spectrum of **32** is consistent with its structure. In **32**, H-4 exhibits a large (~9 Hz) coupling with H-3 and H-5, and equatorial H-1 exhibits a five-bond coupling[27] of about 3 Hz with equatorial F-4.

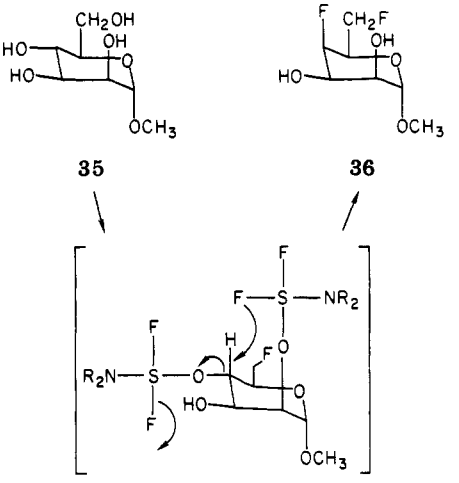
We have also found that D-glucofuranose derivatives may be selectively monofluorinated at C-6 with DAST. Thus, 1,2-*O*-isopropylidene-α-D-glucofuranose (**33**) reacted



**33** **34**

with DAST (90 min, room temperature) to afford 6-deoxy-6-fluoro-1,2-*O*-isopropylidene-α-D-glucofuranose (**34**) in 70% yield. The ease of hydrolysis of the isopropylidene moiety renders this the simplest method for the preparation of 6-deoxy-6-fluoro-D-glucose and certain derivatives.

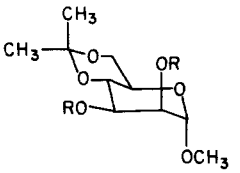
We recently reported[13] that when methyl α-D-mannopyranoside (**35**) was allowed to react with excess DAST in dichloromethane, both the 4- and 6-hydroxyl groups readily reacted to afford methyl 4,6-dideoxy-4,6-difluoro-α-D-talopyranoside (**36**) in 80% yield. The introduction of the fluorine atom at C-4 in **35** is much more facile than in the α- or β-glucopyranosides; in fact, under no circumstances were we able to limit the reaction of **35** with DAST

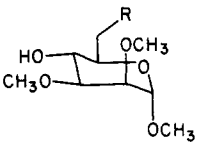


**35** **36**

**37**

to monofluorination. In contrast, monochlorination of **35** was readily achieved,[15] and since $S_N2$-type displacement reactions at C-4 of mannose derivatives are frequently unsuccessful because of the steric hindrance exerted by the axial substituent at C-2,[28] we suggested[13] the possibility of an intramolecular fluoride-ion delivery via an intermediate such as **37** in which an acylated axial substituent at C-2 directs fluoride ion to C-4. To test this hypothesis, we examined the reaction of methyl 2,3-di-*O*-methyl-α-D-mannopyranoside (**38**) with DAST. The presence of the





**39**, R = H
**40**, R = $CH_3$

**38**, R = OH
**41**, R = F

methyl ether at C-2 prevents the formation of an acylated intermediate (such as **37**) and thus should stop the formation of a difluorinated product via intramolecular fluoride-ion delivery. Compound **38** was prepared by methylation of **39**[29,30] (NaH, $CH_3I$) to give **40** (40%) and subsequent hydrolysis ($H_2O$–HOAc) to afford **38** in 96% yield. When **38** was allowed to react with DAST ($CH_2Cl_2$, 1 h, −40 °C → room temperature), a 60% yield of the monofluorinated product **41** was obtained. The structure of **41** follows from its $^1H$, $^{19}F$, and $^{13}C$ NMR spectra. The $^{19}F$ NMR spectra of **41** exhibits only a primary fluorine resonance (φ −233.6). In the 360-MHz $^1H$ NMR spectrum, H-4 (δ 3.84) is coupled only to H-3 and H-5 ($J$'s = 9 Hz) with no geminal fluorine coupling and H-5 (δ 3.72) is coupled to only one fluorine atom (F-6). In addition, the $^{13}C$ NMR spectrum shows C-5 coupling with only one fluorine atom (F-6, $J$ = 17.6 Hz) and C-4 as a doublet ($J_{C-4,F-6}$ = 7.36 Hz) because of long-range coupling with F-6. Thus, the formation of **36** from **35** must involve an intramolecular fluoride-ion delivery to C-4 via an intermediate such as **37**.

To overcome this rapid intramolecular fluorination and to prepare 6-deoxy-6-fluoro-D-mannopyranosides, we investigated the reaction of methyl 2,3-*O*-isopropylidene-α-D-mannopyranoside[29] (**42**) with DAST. When **42** was treated with DAST for 15 min and then quenched with MeOH, the monofluorinated mannoside **43** was obtained

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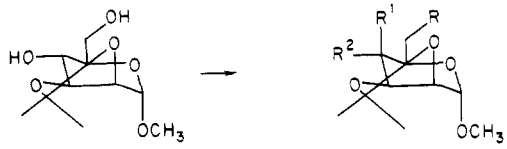
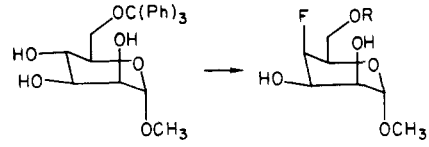


42

43, R = F; $R^1$ = H; $R^2$ = OH
44, R = $OCH_3$; $R^1$ = H; $R^2$ = OH
45, R = F; $R^1$ = F; $R^2$ = H

in only 14% yield. In addition to **43**, methyl ether **44** (12%) was also obtained. Ether **44** must arise via displacement of the DAST intermediate at C-6 with MeOH. However, use of longer reaction times did not increase the yield of **43** and instead the 4,6-difluorinatedtalo derivative **45** was obtained in 23% yield. Hydrolysis of the isopropylidene moiety of **43** afforded methyl 6-deoxy-6-fluoro-α-D-mannopyranoside (**46**) in 87% yield.

We have taken advantage of this rapid intramolecular fluorination reaction to prepare methyl 4-deoxy-4-fluoro-α-D-talopyranoside (**47**). Treatment of methyl 6-*O*-tri-

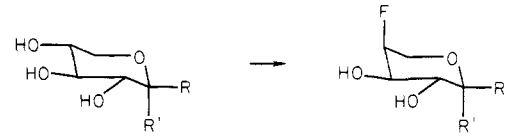


48

49, R = $C(Ph)_3$
47, R = H

tyl-α-D-mannopyranoside (**48**) with DAST afforded the 4-fluoro talo derivative **49** in 40% yield. The stereochemistry at C-4 in **49** was deduced from its 360-MHz $^1H$ NMR spectrum in which H-4 (δ 4.85) couples only with the fluorine atom. Hydrolysis of the trityl ether moiety (aqueous HOAc) gave **47** in 80% yield. Further proof for the structures of **47** and **49** comes from the $^{13}C$ NMR spectrum of **47** in which both C-3 ($J$ = 16.1 Hz) and C-5 ($J$ = 17.6 Hz) couple with F-4.

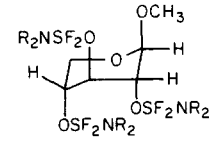
When we examined the reactions of methyl D-xylopyranosides with DAST we found that conformational preferences dictated the site of fluorination. Thus, as expected from the α-glucoside examples, methyl α-D-xylopyranoside (**50**) reacted with DAST overnight at room



50, R = H; R′ = $OCH_3$
52, R = $OCH_3$; R′ = H

51, R = H; R′ = $OCH_3$
53, R = $OCH_3$; R′ = H

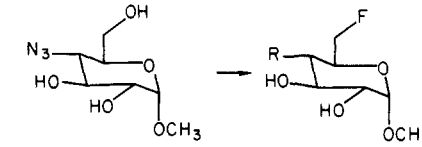
temperature to give methyl 4-deoxy-4-fluoro-α-L-arabinopyranoside (**51**) in low (19%) yield. However, in contrast to the β-glucosides, which underwent fluorination at C-3, methyl β-D-xylopyranoside (**52**) also gave a 4-fluorinated product, methyl 4-deoxy-4-fluoro-β-L-arabinopyranoside (**53**, 52%). The structures of **51** and **53** were assigned on the basis of their $^{13}C$ NMR as well as their 360-MHz $^1H$ NMR spectra, which were analyzed by extensive decoupling experiments. The only logical explanation for the production of **53** from 52 is that **52** reacts in the $^1C_4$ conformation (**54**) in which only C-4 is sterically unhindered



54

toward $S_N2$ displacement. It is well-known[31] that tetraacylated or triacylated derivatives of xylopyranosyl halides predominantly adopt the unusual tetraaxial conformation in solution, and we therefore suggest that this effect is operating here.

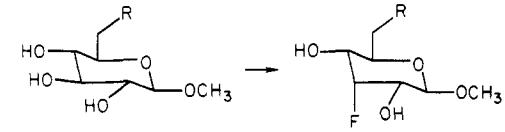
The high percentage of amino sugars in natural systems caused us to investigate the preparation of fluorinated amino sugars. Initial attempts to fluorinate *N*-acetamido derivatives gave mixtures in which, apparently, the *N*-acetamido group was cyclizing onto neighboring carbon atoms to afford oxazoline products. To overcome this problem, we have found that the azido group is stable to DAST. Thus, methyl 4-azido-4-deoxy-α-D-glucopyranoside[32] (**55**) reacted with DAST (18 h, room tem-



55

56, R = $N_3$
57, R = $NH_2$

perature) to give methyl 4-azido-4,6-dideoxy-6-fluoro-α-D-glucopyranoside (**56**) in 68% yield. Catalytic hydrogenation of **56** afforded the fluoro amino sugar **57** (91%). Among similar lines, methyl β-D-glucopyranoside (**6**) was

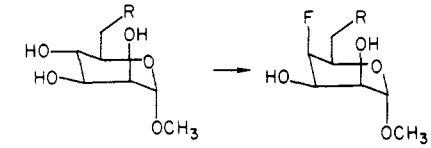


6, R = OH
58, R = $OSO_2C_9H_{11}$
59, R = $N_3$

60, R = $N_3$
61, R = $NH_2$

converted, via the mesitylenesulfonate[33] **58**, into the 6-azido derivative **59**, which reacted with DAST to give methyl 6-azido-3,6-dideoxy-3-fluoro-β-D-allopyranoside **60**. Azide **60** afforded the amino sugar **61** upon catalytic hydrogenation.

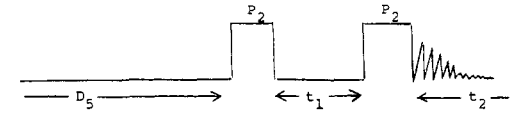
As was described for **6**, methyl α-D-mannopyranoside (**35**) was readily transformed into methyl 6-amino-4,6-dideoxy-4-fluoro-α-D-talopyranoside (**65**).



35, R = OH
62, R = $OSO_2C_9H_{11}$
63, R = $N_3$

64, R = $N_3$
65, R = $NH_2$

**2-D NMR Structural Assignments.** Two-dimensional homonuclear chemical shift correlation (COSY)[34] spectra were obtained on a Nicolet 360 WB spectrometer using the pulse scheme



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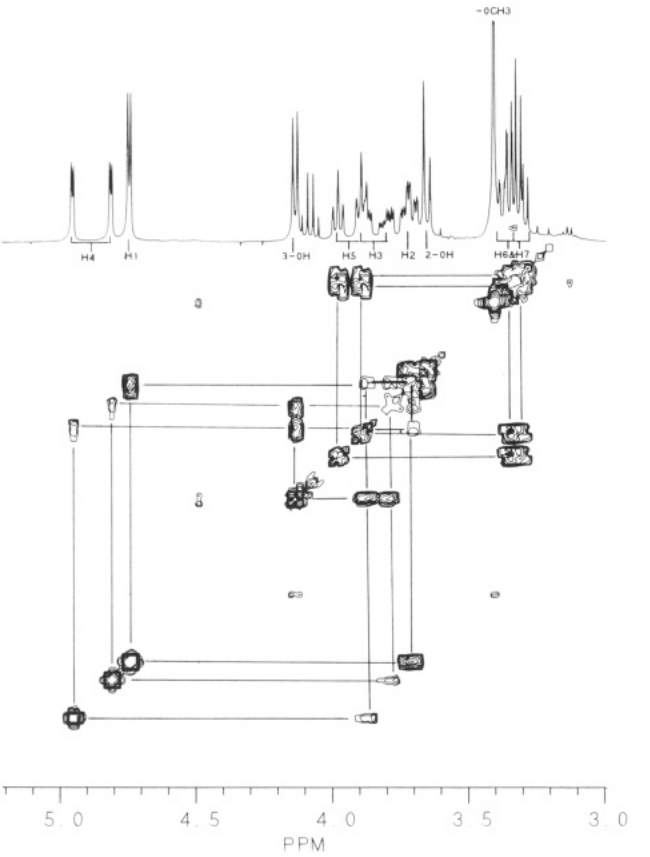


**Figure 1.** (Top) 360-MHz $^1H$ spectrum of **24** in acetone-$d_6$. (Bottom) Proton coupling correlation spectrum of **24**, viewed in the contour mode.

Both 90° pulses as well as the receiver were phase cycled, requiring a minimum of 16 pulses for each spectrum in the $t_1$ dimension. Spectra (512) of 1K points were obtained, giving a 512 × 512 matrix after transformations in the $t_2$ and $t_1$ dimensions. Sine function apodization in the first dimension and both sine function apodization and magnitude calculations in the second dimension were used. Finally, the 2-D data were symmetrized to eliminate any unwanted off-diagonal peaks. An eight-level contour plot of the ring-proton region along with chemical shift connectivities is shown in Figure 1 for compound **24**. The top spectrum is the normal 1-D spectrum, which is reproduced for clarity on the same scale as the 2-D contour plot. Starting with $H_1$ ($\delta$ 4.71), which exhibits only a doublet due to coupling with $H_2$, all remaining protons were assigned by using the contour plot (Figure 1. Assignments for other compounds were made from their COSY 16 contour plots in a similar manner.

The above methodology affords ready access to fluorinated carbohydrates that have previously been difficult to obtain. Application of this methodology to the synthesis of other fluorinated sugars is in progress.

## Experimental Section

**General Methods.** All reactions were performed under a nitrogen atmosphere. Melting points were determined with a Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were determined on a Nicolet 7199 FT-IR spectrometer. Optical rotations were determined on a Perkin-Elmer 241 MC polarimeter. Unless stated otherwise, 360-MHz $^1H$ NMR spectra were obtained in acetone-$d_6$ on a Nicolet NT WB 360 spectrometer and are referenced to internal tetramethylsilane. The $^{19}F$ NMR spectra were obtained on a Varian XL-100 spectrometer and are referenced to internal trichlorofluoromethane. $^{13}C$ NMR spectra were determined on a Bruker WH-90 spectrometer and are referenced to internal tetramethylsilane. Mass spectra were recorded at 70 eV on a VG Micromass 70-70H double-focusing high-resolution spectrometer.

**Methyl 3,6-Dideoxy-3,6-difluoro-$\beta$-D-allopyranoside (8).** DAST was added (7.5 mL, 60 mmol) to a suspension of **6** (1.94 g, 10 mmol) in anhydrous dichloromethane (40 mL) at −40 °C. The cooling bath was removed, and the mixture was allowed to stir overnight at room temperature. The mixture was cooled to −20 °C, quenched via addition of MeOH (40 mL), and then concentrated under reduced pressure. Chromatography of the residue on silica gel (4:1 EtOAc/hexane) afforded 1.01 g (51%) of **8** as a colorless solid; mp 129–130 °C; 360-MHz $^1H$ NMR $\delta$ 2.95 (br m, OH, exchangeable), 3.41 (dm, H-2, $J_{H-2,F-3}$ = 30 Hz), 3.45 (s, 3 H, $OCH_3$), 3.64 (dm, H-4, $J_{H-4,F-3} = J_{C-4,F-6}$ Hz), 3.78 (dm, H-5, $J_{H-5,F-6}$ = 25 Hz, $J_{4,5}$ = 10 Hz), 4.48 (dd, H-1, $J_{1,2}$ = 7, $J_{1,5}$ = 1.5 Hz), 4.5 (m, OH, exchangeable), 4.61 (m, H-6, $J_{H,F-6}$ = 52, $J_{6,6'}$ = 11, $J_{6,5}$ = 4.5 Hz), 4.64 (m, 1 H, H-6′, $J_{H,F-6}$ = 48, $J_{6',5}$ = 2 Hz), 4.88 (dm, H-3, $J_{H-3,F-3}$ = 54 Hz); $^{19}F$ NMR ($^1H$ decoupled) $\phi$ −217.6 (s, F-3), −234.6 (s, F-6); $^{13}C$ NMR $\delta$ 102.0 (d, C-1, $J_{C,F-3}$ = 4.4 Hz), 93.6 (d, C-3, $J_{C-3,F-3}$ = 177.9 Hz), 82.8 (d, C-6, $J_{C-6,F-6}$ = 170 Hz), 73.0 (dd, C-4, $J_{C-4,F-3}$ = 17.6, $J_{C-4,F-6}$ = 2.9 Hz), 70.2 (d, C-2, $J_{C-2,F-3}$ = 17.6 Hz), 66.0 (dd, C-5, $J_{C-5,F-3}$ = 7, $J_{C-5,F-6}$ = 19 Hz), 56.2 (s, $OCH_3$); $[\alpha]_D$ −47.0° ($c$ = 1.03, EtOH).

Anal. Calcd for $C_7H_{12}F_2O_4$: C, 42.43; H, 6.10. Found: C, 42.43; H, 6.15.

**Phenyl 6-Deoxy-6-fluoro-$\alpha$-D-glucopyranoside (5).** Phenyl $\alpha$-D-glucopyranoside[18] (**4**, 2.50 g, 9.76 mmol) in dichloromethane (120 mL) at −40 °C was treated with DAST (7.3 mL, 59 mmol) as per the preparation of **8**. After being stirred for 2 h after removal of the low-temperature bath, the mixture was processed as above, and the residue was chromatographed on silica gel (1:1 ETOAc/hexane and subsequently EtOAc) to give **5**: 1.47 g, 58; mp 169.5–171 °C (3:2 EtOAc/hexane); 360-MHz $^1H$ NMR $\delta$ 3.47 (dd, H-3, $J_{2,3}$ = 10, $J_{3,4}$ = 9 Hz), 3.58 (m, H-2, $J_{1,2}$ = 3.5 Hz), 3.83 (dddd, H-5, $J_{5,F}$ = 27, $J_{4,5}$ = 10, $J_{5,6}$ = 2, $J_{5,6'}$ = 4.5 Hz), 3.90 (t, H-4), 4.52 (m, H-6, $J_{6,F}$ = 48, $J_{6,6'}$ = 10 Hz), 4.68 (m, H-6′, $J_{6'F}$ = 48 Hz), 5.51 (d, H-1, $J_{1,2}$ = 3.5), 7.02 (m, 1 H), 7.13 (m, 2 H), 7.3 (m, 2 H); $^{19}F$ NMR ($CD_3OD$) $\phi$ −236.6 (s); $^{13}C$ NMR $\delta$ 157.3 (s, 1 C, aromatic C-1), 129.6 (s, aromatic C-3), 122.4 (s, 1 C, aromatic, C-4), 117.2 (s, aromatic C-2), 98.5 (s, C-1), 82.5 (d, C-6, $J_{C-6,F}$ = 170.6 Hz), 74.2 (s, C-3), 72.5 (s, C-2), 72.0 (d, C-5, $J_{C-5,F}$ = 13.2 Hz), 69.4 (d, C-4, $J_{C-4,F-6}$ = 4.4 Hz); mass spectrum, $m/e$ calcd for $C_{12}H_{15}FO_5$ ($M^+$) 258.0904, found 258.0894; $[\alpha]_D$ +191.7° ($c$ 1.01, EtOH).

Anal. Calcd for $C_{12}H_{15}FO_5$: C, 55.81; H, 5.85. Found C, 55.59; H, 6.01.

**Methyl 2,4-Di-*O*-benzoyl-3,6-dideoxy-3,6-difluoro-$\beta$-D-allopyranoside (10).** A 0 °C solution of **8** (3.96 g, 20 mmol) in pyridine (50 mL) was treated dropwise with benzoyl chloride (7.0 mL, 60 mmol). After being stirred overnight at room temperature, the mixture was poured into saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was dried and concentrated to a yellow oil, which was chromatographed on silica gel (2:1 hexane/ether) and afforded 5.76 g (71%) of **10** as a crystalline solid: mp 91–93 °C; 360-MHz $^1H$ NMR $\delta$ 3.55 (s, 3 H, $OCH_3$), 4.44 (ddm, H-5, $J_{H-5,F-6}$ = 24.5, $J_{4,5}$ = 10.5 Hz), 4.73 ($^1/_2$ of AB, H-6, $J_{H-6,F-6}$ = 47.5, $J_{6,6'}$ = 10.5, $J_{6,5}$ = 4 Hz), 4.76 ($^1/_2$ of AB, H-6′, $J_{H-6',F-6}$ = 47.5, $J_{6',5}$ = 2 Hz), 5.08 (dd, H-1, $J_{1,2}$ = 8, $J_{H-1,F-3}$ = 1.5 Hz), 5.2 (ddd, H-2, $J_{H-2,F-3}$ = 28, $J_{2,3}$ = 2 Hz), 5.33 (ddd, H-4, $J_{H-4,F-3}$ = 27, $J_{3,4}$ = 2, $J_{4,5}$ = 10.5 Hz), 5.5 (dm, H-3, $J_{H,F}$ = 54 Hz), 7.55 (m, 2 H), 7.69 (m, 1 H), 8.07 (m, 2 H); $^{19}F$ NMR $\phi$ −215 (s, $^1H$ decoupled; m, $^1H$ coupled), −234.2 (s, $^1H$ decoupled; ddd, $J$ = 24.5, 48, 47.5 Hz, $^1H$ coupled).

Anal. Calcd for $C_{21}H_{20}F_2O_6$: C, 62.07; H, 4.96. Found: C, 61.69; H, 4.86.

**Phenyl 3,6-Dideoxy-3,6-difluoro-$\beta$-D-allopyranoside (9).** Phenyl $\beta$-D-glucopyranoside[18] (**7**, 6.4 g, 25 mmol) in 50 mL of dichloromethane at −40 °C was treated with DAST (15.6 mL, 125 mmol) as above. After stirring overnight at room temperature, usual processing, and chromatography on silica gel (1:1 EtOAc/hexane), 4.57 g (70%) of **9** was obtained as a colorless solid; mp 129–130.5 ($CHCl_3$); 360-MHz $^1H$ NMR $\delta$ 3.8 (m, 2 H), 4.05 (m, 1 H), 4.67 (m, H-6, $J_{H-6,F-6}$ = 46, $J_{6,6'}$ = 10, $J_{6,5}$ = 4 Hz), 4.72 (m, H-6′, $J_{6',5}$ = 2 Hz), 5.04 (d, H-3, $J_{H,F}$ = 52 Hz), 5.27 (d, H-1, $J_{1,2}$ = 8.5 Hz), 7.01 (m, 1 H, aromatic), 7.09 (m, 2 H, aromatic),

7.29 (m, 2 H, aromatic); $^{19}$F NMR $\phi$ −234.5 ($^1$H decoupled, s; $^1$H coupled, ddd, $J_{F-6,H-5}$ = 25 Hz), −217.7 ($^1$H decoupled, s; $^1$H coupled, ddd, $J_{F-3,H-2}$ = 28, $J_{F-3,H-4}$ = 28 Hz); $^{13}$C NMR $\delta$ 157.9 (s, 1 C, aromatic C-1), 129.5 (s, 2 C, aromatic C-3), 122.5 (s, 1 C, aromatic C-4), 116.7 (s, 2 C, aromatic C-2), 99.0 (d, C-1, $J_{C,F-3}$ = 4.4 Hz), 93.6 (d, C-3, $J_{C-3,F-3}$ = 177.9 Hz), 82.5 (d, C-6, $J_{C-6,F-6}$ = 172 Hz), 73.1 (dd, C-3, $J_{C-3,F-4}$ = 17.6, $J_{C-3,F-6}$ = 2.9 Hz), 70.0 (d, C-2, $J_{C-2,F-3}$ = 17 Hz), 65.8 (dd, C-5, $J_{C-5,F-6}$ = 17.6, $J_{C-5,F-3}$ = 8.0 Hz); $[\alpha]_D$ −79.4° (*c* 1.01, $CHCl_3$).

Anal. Calcd for $C_{12}H_{14}F_2O_4$: C, 55.38; H, 5.42. Found C, 55.14, H, 5.49.

**Methyl 6-Deoxy-6-fluoro-β-D-glucopyranoside (11).** Methyl β-D-glucopyranoside (**6**, 1.94 g, 10 mmol) was treated with DAST as above. After being stirred for 15 min at room temperature, the mixture was produced as usual and chromatographed (EtOAc followed by 9:1 EtOAc/MeOH) to afford 1.18 g (60%) of **11**: mp 125–127 °C (EtOAc); 360-MHz $^1$H NMR $\delta$ 3.19 (m, 1 H), 3.34–3.56 (m, 6 H), 4.23 (d, H-1, $J_{1,2}$ = 8 Hz), 4.61 (m, H-6, $J_{H-6,F-6}$ = 48, $J_{6,6'}$ = 10, $J_{6,5}$ = 5 Hz), 4.68 (m, H-6′, $J_{6',5}$ = 2, $J_{H-6',F-6}$ = 48 Hz); $^{19}$F NMR $\phi$ −233.1 (s; $^1$H decoupled); $^{13}$C NMR $\delta$ 56.1 (s, $OCH_3$), 69.3 (d, C-4 $J_{C-4,F-6}$ = 7.3 Hz), 73.7 (s, C-2), 75.0 (d, C-5, $J_{C-5,F-6}$ = 17.6 Hz), 76.9 (s, C-3), 82.5 (d, C-6, $J_{C-6,F-6}$ = 170.6 Hz), 104.1 (s, C-1); $[\alpha]_D$ +35.4° (*c* 1.0, EtOH).

Anal. Calcd for $C_7H_{13}FO_5$: C, 42.86; H, 6.68. Found: 42.72; H, 6.79.

**Phenyl 6-Deoxy-6-fluoro-β-D-glucopyranoside (12).** A cold (−40 °C) suspension of phenyl β-D-glucopyranoside (**7**, 6.4 g, 25 mmol) in dichloromethane (70 mL) was treated with DAST (15.6 mL, 125 mmol). After stirring for 25 min at room temperature, the reaction was worked up as usual. The residue was chroamtographed (2:1 EtOAc/hexane) and afforded 1.86 g (29%) of **12** as a colorless solid: mp 143–145 °C ($CHCl_3$); 360-MHz $^1$H NMR $\delta$ 3.42–3.62 (m, 3 H), 3.74 (dddd, H-5, $J_{5,F-6}$ = 24, $J_{5,6}$ = 5, $J_{5,6'}$ = 2, $J_{5,4}$ = 10 Hz), 4.63 (m, H-6, $J_{6,F-6}$ = 48, $J_{6,6'}$ = 10 Hz), 4.7 (m, H-6′), 4.75 (br d, OH), 5.03 (d, H-1, $J_{1,2}$ = 8 Hz), 7.0 (m, 1 H), 7.07 (m, 2 H), 7.82 (m, 2 H); $^{19}$F NMR ($^1$H decoupled) −233.0 (s); $^{13}$C NMR $\delta$ 69.1 (d, C-4, $J_{C-4,F-6}$ = 7.35 Hz), 73.7 (s, C-2), 75.2 (d, C-5, $J_{C-5,F-6}$ = 17.6 Hz), 77.0 (s, C-3), 82.5 (d, C-6, $J_{C-6,F-6}$ = 170.6 Hz), 101.0 (s, C-1), 116.8 (s, aromatic C-2)8 122.3 (s, aromatic C-4), 129.5 (s, aromatic C-3), 158.0 (s, aromatic C-1); $[\alpha]_D$ −62.3° (*c* 1.02, EtOH).

Anal. Calcd for $C_{12}H_{15}FO_5$: C, 55.81; H, 5.85. Found: C, 55.66; H, 5.74.

**Methyl 4,6-Dideoxy-4,6-difluoro-α-D-galactopyranoside (2).** Methyl glucoside (**1**; 5.82 g, 30 mmol) was treated with DAST as described above. After 72 h at room temperature, the mixture was processed as usual and chromatographed (EtOAc) to give 2.40 g (40%) of **2**; mp 134–136 °C (lit.[11] mp 135–136 °C).

**Phenyl 4,6-Dideoxy-4,6-difluoro-α-D-galactopyranoside (13).** A −40 °C suspension of phenyl α-D-glucopyranoside (**4**, 2.22 g, 8.6 mmol) in dichloromethane (30 mL) was treated with DAST (6.5 mL, 52 mmol) and the mixture was allowed to stir at room temperature for 5 days. Workup as usual and column chromatography (2:1 EtOAc/hexane) gave 850 mg (38%) of **13** as a colorless solid: mp 154–155 °C; 360-MHz $^1$H NMR $\delta$ 4.0 (m, H-2, $J_{1,2}$ = 3.5, $J_{2,3}$ = 10 Hz), 4.2 (dm, H-3, $J_{H-3,F-4}$ = 29 Hz), 4.34 (m, H-5), 4.44 (m, OH-2), 4.55 (dm, H-6, $J_{H-6,F-6}$ = 43, $J_{6,6'}$ = 9.5, $J_{6,5}$ = 1.2 Hz), 4.6 (br, OH-3), 4.68 (dm, H-6′, $J_{H-6',F-6}$ = 46, $J_{6',5}$ = 4.6 Hz), 4.96 (dd, H-4, $J_{H,F-4}$ = 51, $J$ = 3 Hz), 5.63 (d, H-1, $J_{1,2}$ = 3.5 Hz), 7.06 (m, 1 H), 7.17 (m, 2 H), 7.33 (m, 2 H); $^{19}$F NMR ($^1$H decoupled) $\phi$ −230.7 (s), −219.9 (s).

Anal. Calcd for $C_{12}H_{14}F_2O_4$: C, 55.38; H, 5.42. Found: C, 55.11; H, 5.33.

***p*-Nitrophenyl 6-Deoxy-6-fluoro-β-D-glucopyranoside (15).** *p*-Nitrophenyl β-D-glucopyranoside (**14**,[18] 3.91 g, 13 mmol) was treated with DAST as described above. After being stirred for 35 min at room temperature, the solution was cooled to −40 °C and quenched via addition of MeOH. Concentration under reduced pressure and chromatography (EtOAc) afforded 2.16 g (55%) of **15** as a colorless solid: mp 186–189 °C (EtOAc/hexane); 360-MHz $^1$H NMR $\delta$ 3.03 (br, m, 2 H, OH), 3.46–3.65 (m, 3 H), 3.86 (dddd, H-5, $J_{4,5}$ = 10, $J_{5,6}$ = 2, $J_{5,6'}$ = 5, $J_{5,F-6}$ = 24 Hz), 4.55–4.8 (m, 3 H), 5.27 (d, H-1, $J_{1,2}$ = 8 Hz), 7.27 (d, 2 H, $J$ = 10 Hz), 8.23 (d, 2 H, $J$ = 10 Hz); $^{19}$F NMR $\phi$ −233.5 (s, $^1$H decoupled; $^1$H coupled, ddd $J_{F-6,H-6}$ = 48 Hz); $^{13}$C NMR $\delta$ 68.9 (d, C-4, $J_{C-4,F-6}$ = 7.36 Hz), 73.6 (s, C-2), 75.5 (d, C-5, $J_{C-5,F-6}$ = 17.6 Hz), 76.9 (s, C-3), 82.2 (d, C-6, $J_{C-6,F-6}$ = 170.6 Hz), 100.5 (s, C-1), 110.1 (s, aromatic), 116.8 (s, aromatic), 125.6 (s, aromatic), 162.7 (s, aromatic).

Anal. Calcd for $C_{12}H_{14}FNO_7$: C, 47.53; H, 4.65. Found: C, 47.55; H, 4.58.

***p*-Nitrophenyl 3,6-Dideoxy-3,6-difluoro-β-D-allopyranoside (16).** *p*-Nitrophenyl β-D-glucopyranoside (**14**,[18] 3.91 g, 13 mmol) was suspended in dichloromethane (75 mL) at −40 °C, and 9.75 mL (78 mmol) DAST was added. After stirring overnight at room temperature, processing as usual, and concentration under reduced pressure, a brown residue was obtained. Chromatography (1:1 EtOAc/hexane followed by 2:1) afforded 3.08 g (78%) of a colorless solid: mp 158–160 °C (EtOAc/hexane); 360-MHz $^1$H NMR $\delta$ 3.04 (br m, 1 H, OH), 3.86 (dm, H-2, $J_{1,2}$ = 8, $J_{H-2,F-3}$ = 28 Hz), 3.89 (dm, H-4, $J_{H-4,F-3}$ = 29 Hz), 4.15 (ddd, H-5, $J$ = 28, 10, 4 Hz), 4.67 (m, H-6, $J_{6,F-6}$ = 48 Hz, $J_{6,6'}$ = 10, $J_{6,5}$ = 4 Hz), 4.74 (m, H-6′), 4.98 (br m, OH, exchangeable), 5.07 (d, H-3, $J_{H-3,F-3}$ = 52 Hz), 5.46 (d, H-1, $J_{1,2}$ = 8 Hz), 7.32 (d, 2 H, $J$ = 10 Hz), 8.22 (d, 2 H, $J$ = 10 Hz); $^{19}$F NMR (MeOH) $\phi$ −235.5 (s, F-6), −217.9 (s, F-4).

Anal. Calcd for $C_{12}H_{13}F_2NO_6$: C, 47.22; H, 4.29; N, 4.59. Found: C, 46.68; H, 4.22; N, 4.76.

**Methyl 3-Deoxy-3-fluoro-6-*O*-trityl-β-D-allopyranoside (18).** A −40 °C solution of **17** (2.18 g, 5 mmol) in dichloromethane (25 mL) was treated with DAST (2.8 mL, 22.5 mmol), and the resulting mixture was allowed to stir overnight at room temperature. Workup as above and chromatography on silica gel (1:1 EtOAc/hexane) afforded 1.0 g (50%) of **18** as a colorless solid: mp 84–86 °C; 360-MHz $^1$H NMR (acetone-$d_6$) $\delta$ 3.17 (br, OH), 3.33 (dd, H-6, $J_{6,6'}$ = 10, $J_{6,5}$ = 5.4 Hz), 3.50 (dd, H-6′, $J_{6,6'}$ = 10, $J_{6',5}$ = 2.2 Hz), 3.55 (dm, H-2), 3.80 (ddd, H-4, $J_{H-4,F-3}$ = 28.0, $J_{H-4,H-5}$ = 8.0, $J_{H-4,H-3}$ = 1.5 Hz), 3.87 (m, H-5), 4.4 (br, OH), 4.62 (dd, H-1, $J_{1,2}$ = 8.0, $J_{1,F-3}$ = 1.5 Hz), 4.94 (dt, H-3, $J_{3,F-3}$ = 53, $J$ = 2.1 Hz), 7.22–7.33 (m, 9 H), 7.43–7.48 (m, 6 H); $^{19}$F NMR (acetone-$d_6$) $\phi$ ($^1$H decoupled) −217.4 (s).

Anal. Calcd for $C_{26}H_{27}FO_5$: C, 71.22; H, 6.21. Found: C, 71.34; H, 6.02.

**Methyl 3-Deoxy-3-fluoro-β-D-allopyranoside (19).** Glycoside **18** (6.85 g, 15.6 mmol) was detritylated as per **24**. Chromatography on silica gel (9:1 EtOAc/MeOH) afforded 1.32 g (43%) of **19** as a colorless solid: mp 124–125 °C (EtOAc); 360-MHz $^1$H NMR $\delta$ 3.40 (ddd, H-2, $J_{H-2,F-3}$ = 29, $J_{1,2}$ = 8, $J_{2,3}$ = 2 Hz), 3.43 (s, 3H, $OCH_3$), 3.6–3.88 (m, 5 H), 4.44 (m, 1 H, OH), 4.48 (dd, H-1, $J_{1,2}$ = 8, $J_{1,F-3}$ = 2 Hz), 4.86 (dm, H-3, $J_{H-3,F-3}$ = 53, $J$ = 2 Hz); $^{19}$F NMR ($CH_3OH$) $\phi$ −217.2 (s); $^{13}$C NMR $\delta$ 56.1 (s, $OCH_3$), 62.0 (s, C-6), 67.4 (d, C-2, $J_{C-2,F-3}$ = 16.1 Hz), 70.3 (d, C-4, $J_{C-4,F-3}$ = 16.1 Hz), 74.5 (s, C-5), 93.7 (d, C-3, $J_{C-3,F-3}$ = 176 Hz), 102 (d, C-1, $J_{C-1,F-3}$ = 2.9 Hz).

Anal. Calcd for $C_7H_{13}FO_5$: C, 42.85; H, 6.68. Found: C, 43.12; H, 6.51.

**Methyl 3-Deoxy-3-fluoro-4,6-*O*-isopropylidene-β-D-allopyranoside (21).** Ketal **20**[21] (4.68 g, 20 mmol) was treated with excess DAST as described above. Usual processing and column chromatography (1:1 EtOAc/hexane) gave **21** (45%) as an off-white solid: mp 85.5–87.5 °C (ether/hexane); 360-MHz $^1$H NMR ($CDCl_3$) $\delta$ 1.46 (s, 3 H), 1.50 (s, 3 H), 2.53 (br d, 1 H, OH), 3.53 (dm, H-4, $J_{H,F-3}$ = 27 Hz), 3.58 (s, 3 H, $OCH_3$), 3.65 (dm, H-2, $J_{H,F-3}$ = 28, $J_{1,2}$ = 8 Hz), 3.78 (m, 2 H), 4.01 (m, 1 H), 4.53 (d, H-1), 4.97 (dm, H-3, $J_{H,F}$ = 54 Hz); $^{19}$F NMR $\phi$ −217.4 (s, $^1$H decoupled).

Anal. Calcd for $C_{10}H_{17}FO_5$: C, 50.84; H, 7.25. Found: C, 50.88; H, 7.37.

**Methyl 4-Deoxy-4-fluoro-6-*O*-trityl-α-D-galactopyranoside (24).** A suspension of **23** (5.98 g, 13.7 mmol) in $CH_2Cl_2$ (50 mL) at −40 °C was treated with DAST (7.8 mL, 62 mmol). After stirring at room temperature for 72 h, usual workup afforded a yellow solid. Column chromatography (EtOAc) gave **24** (1.39 g, 23%) as colorless needles: mp 161.5–162.5 °C (EtOAc); 360-MHz $^1$H NMR $\delta$ 3.28 ($^1/_2$ of AB, H-6, $J_{6,6'}$ = 9, $J_{6,5}$ = 6.5 Hz), 3.34 ($^1/_2$ of AB, H-6′, $J_{6',5}$ = 6.5 Hz), 3.38 (s, 3 H, $OCH_3$), 3.62 (br m, OH-2), 3.68 (m, H-2), 3.81 (dm, H-3, $J_{3,F-4}$ = 29 Hz), 3.91 (dt, H-5, $J_{5,F-4}$ = 30), 4.41 (d, H-1, $J_{1,2}$ = 3.5 Hz), 4.85 (dd, H-4, $J_{H,F}$ = 51, $J_{3,4}$ = 2.5 Hz), 7.27 (m, 3 H), 7.34 (m, 6 H), 7.49 (m, 6 H); $^{19}$F NMR $\phi$ −219.9 (s, $^1$H decoupled).

Anal. Calcd for $C_{26}H_{27}FO_5$: C, 71.22; H, 6.21. Found: C, 71.10; H, 6.40.

**Methyl 4-Deoxy-4-fluoro-α-D-galactopyranoside (22).** A solution of **24** (8.90 g, 20.3 mmol) in 80 mL of AcOH–$H_2O$ (4:1)

was heated at 70 °C for 5 h. The mixture was partitioned between ether/water, and the aqueous layer was concentrated to give a colorless solid. Colum chromatography (9:1 EtOAc/MeOH) afforded 1.93 g (50%) of **22**: mp 120–122.5 °C (EtOAc) (lit. mp 102–103 °C); $^{19}$F NMR (acetone-$d_6$/$CD_3OD$) $\phi$ −220.9 (s, $^1$H decoupled); $^{13}$C NMR (acetone-$d_6$/$D_2O$) $\delta$ 55.9 (s, $OCH_3$), 60.76 (d, C-6, $J_{F-4,C-6}$ = 5.9 Hz), 69.27 (d, C-5, $J_{C-5,F-4}$ = 17.6 Hz), 69.4 (s, C-2), 70.5 (d, C-3, $J_{C-3,F-4}$ = 17.6 Hz), 90.9 (d, C-4, $J_{C-4,F-4}$ = 177.9 Hz), 100.6 (s, C-1); $[\alpha]_D$ +159.8° (*c* 1.03, MeOH) (lit $[\alpha]_D$ +144.5° (*c*, 1.7, MeOH).

Anal. Calcd for $C_7H_{13}FO_5$: C, 42.86; H, 6.68. Found: C, 42.65; H, 6.55.

**Methyl 4-Deoxy-4-fluoro-2,3,6-*tri*-*O*-acetyl-α-D-galactopyranoside (25).** A solution of **22** (830 mg, 4.2 mmol)in pyridine (13 mL) was treated dropwise with acetic anhydride (3 mL). After being stirred overnight at room temperature, the mixture was poured into $H_2O$ and extracted with EtOAc. The organic layer was washed with 10% HCl and saturated $NaHCO_3$, dried, and concentrated to a colorless solid. Recrystallization from hexane/ether gave **25**: mp 92–94 °C; 360-MHz $^1$H NMR ($CDCl_3$) $\delta$ 2.0 (s, 3 H), 2.09 (s, 3 H), 2.12 (s, 3 H), 3.41 (s, 3 H), 4.06 (dt, H-5, $J_{5,F-4}$ = 29, $J_{5,6}$ = 6.5 Hz), 4.23 (m, H-6, $J_{5,6}$ = 6.5, $J_{6,6'}$ = 11.5 Hz), 4.31 (m, H-6′, $J_{6',5}$ = 7, $J_{6,6'}$ = 11.5 Hz), 4.92 (dd, H-4, $J_{3,4}$ = 2.5, $J_{4,F-4}$ = 51 Hz), 5.01 (d, H-1, $J_{1,2}$ = 3.5 Hz), 5.20 (m, H-2), 5.28 (ddd, H-3, $J_{3,F-4}$ = 25.5, $J_{2,3}$ = 10.5, $J_{3,4}$ = 2.5 Hz); $^{19}$F NMR $\phi$ −219.7 (s, $^1$H decoupled).

Anal. Calcd for $C_{13}H_{19}FO_8$: C, 48.45; H, 5.94. Found: C, 48.68; H, 5.76.

**Methyl 6-*O*-Pivaloyl-β-D-glucopyranoside (26).** A solution of **6** (3.88 g, 20 mmol) in 25 mL of pyridine containing a catalytic amount of 4-(dimethylamino)pyridine was treated dropwise with pivaloyl chloride[26] (3.6 mL, 30 mmol), and the resulting mixture was heated at 70 °C overnight. Removal of the volatiles under reduced pressure and chromatography on silica gel (EtOAc followed by 9:1 EtOAc/MeOH) gave 3.73 g (67%) of **26**: mp 114–116.5 °C; 360-MHz $^1$H NMR ($CDCl_3$) $\delta$ 1.21 (s, 9 H), 3.36 (m, 2 H), 3.53 (m, 5 H), 4.21 (d, H-1, $J_{1,2}$ = 8 Hz), 4.25 (m, 1 H), 4.48 (m, 3 H), 5.08 (br, 1 H, OH); IR (KBr) 3390, 1730 cm$^{-1}$; $^{13}$C NMR $\delta$ 26.7, 38.6; 55.9 ($OCH_3$) 63.7 (C-6), 70.8 (C-4), 73.9, 74.1, 77.0 (C-5), 104.1 (C-1), 177.6 (ester C=O); $[\alpha]_D$ −38.1° (*c* 1.01, $CHCl_3$).

Anal. Calcd for $C_{12}H_{22}O_7$: C, 51.79; H, 7.96. Found: C, 51.76; H, 7.86.

**Methyl 6-*O*-Pivaloyl-α-D-galactopyranoside (27).** A solution of methyl α-D-galactopyranoside (9.7 g, 50 mmol) in 65 mL of pyridine containing a catalytic amount of 4-(dimethylamino)-pyridine was treated dropwise with pivaloyl chloride (9 mL, 75 mmol). After complete addition, the mixture was heated at 70 °C for 24 h. Removal of the pyridine under reduced pressure and chromatography on silica gel (EtOAc and subsequently 9:1 EtOAc/MeOH) gave 9.73 g (70%) of **27**: mp 151–153 °C (EtOAc/hexane); 360-MHz $^1$H NMR $\delta$ 1.1 (s, 9 H), 3.36 (s, 3 H), 3.73 (m, 2 H), 3.93 (m, 2 H), 4.21 (m, H-6, $J_{6,6'}$ = 12, $J_{6,5}$ = 5 Hz), 4.27 (m, H-6′, $J_{6',5}$ = 8 Hz), 4.67 (br s, H-1).

Anal. Calcd for $C_{12}H_{22}O_7$: C, 51.79; H, 7.96. Found: C, 51.51; H, 7.71.

**Methyl 6-*O*-Pivaloyl-β-D-galactopyranoside (28).** Methyl β-D-galactopyranoside (14.55 g, 75 mmol) in pyridine (100 mL) and a catalytic amount of 4-(dimethylamino)pyridine were treated with pivaloyl chloride (13.5 mL, 112 mmol) and then heated at 70 °C for 24 h. Workup and chromatography as described for **27** afforeded 10.94 g (53%) of **28**: mp 105–107 °C (EtOAc/hexane); 360-MHz $^1$H NMR $\delta$ 1.09 (s, 9 H), 2.97 (br d, 2 H, OH), 3.44 (s, 3 H), 3.54 (m, 2 H), 3.75 (m, 1 H), 3.86 (m, 1 H), 4.13 (d, H-1, $J_{1,2}$ = 8 Hz), 4.18–4.35 (m, 3 H); $^{13}$C NMR $\delta$ 26.7 (s, $-C(CH_3)_3$), 38.5 (s, $-C(CH_3)_3$), 55.6 (s, $OCH_3$), 63.5 (s, C-6), 68.9 (s), 71.3 (s), 72.6 (s), 73.7 (s), 104.6 (s, C-1), 177.5 (s, carboxyl); IR (KBr) 3380, 1725 cm$^{-1}$.

Anal. Calcd for $C_{12}H_{22}O_7$: C, 51.79; H, 7.96. Found: C, 51.72; H, 8.03.

**Methyl 3-Deoxy-3-fluoro-6-*O*-pivaloyl-β-D-allopyranoside (29).** Methyl 6-*O*-pivaloyl-β-D-glucopyranoside (**26**; 6.04 g, 21.7 mmol) was treated with DAST as above. After being stirred overnight at room temperature, the mixture was processed as usual and the residue was chromatographed on silica gel (1:1 EtOAc/hexane) to give 2.12 g (35%) of **29**: mp 104.5–106 °C (ether); 360-MHz $^1$H NMR $\delta$ 1.22 (s, 9 H), 3.42 (ddd, H-2, $J_{H-2,F-3}$ = 30, $J_{1,2}$ = 8, $J_{2,3}$ = 2 Hz), 3.43 (s, 3 H, $OCH_3$), 3.67 (dm, H-4, $J_{H-4,F-3}$ = 28 Hz), 3.86 (m, H-5), 4.21 (dd, H-6, $J_{6,6'}$ = 11.5, $J_{6,5}$ = 6 Hz), 4.44 (dd, H-6′, $J_{6',5}$ = 2 Hz), 4.62 (br m, 1 H, OH), 4.92 (dt, H-3, $J_{H-3,F-3}$ = 53, $J$ = 2 Hz); $^{19}$F NMR $\phi$ −217.4 (s, $^1$H decoupled; dt, $^1$H coupled, $J$ = 53, 28 Hz); $^{13}$C NMR $\delta$ 26.7 (s, $-C(CH_3)_3$), 38.6 (s, $-C(CH_3)_3$), 55.9 (s, $OCH_3$), 63.7 (s, C-6), 67.4 (d, C-2, $J_{C-2,F-3}$ = 17.6 Hz), 70.2 (d, C-4, $J_{C-4,F-3}$ = 16.1 Hz), 72.0 (d, C-5, $J_{C-5,F-3}$ = 2.9 Hz), 93.4 (d, C-3, $J_{C-3,F-3}$ = 177.9 Hz), 101.8 (d, C-1, $J_{C-1,F-3}$ = 3 Hz), 177.5 (s, carboxyl); $[\alpha]_D$ −48.8° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_{12}H_{21}FO_6$: C, 51.42; H, 7.55. Found: C, 51.32; H, 7.53.

**Methyl 4-Deoxy-4-fluoro-α-D-glucopyranoside (31).** Tribenzoate **30**[13] (2.54 g, 5 mmol) was dissolved in 125 mL of $MeOH/H_2O/Et_3N$ (5:4:1), and the mixture was refluxed overnight. Concentration under reduced pressure and flash chromatography (EtOAc) afforded 720 mg (74%) of **31**: mp 125–127.5 °C (1:1 EtOAc/acetone) (lit.[2] mp 129–130 °C); $^{19}$F NMR (MeOH) $\phi$ −198.0 (s, $^1$H decoupled; $^1$H coupled, ddm, $J_{H-4,F-4}$ = 50, $J_{H,F-4}$ = 17 Hz); 360-MHz $^1$H NMR $\delta$ 3.47 (m, 2 H), 3.55 (m, 2 H), 3.64 (ddd, H-3, $J_{H-3,F-4}$ = 16.5, $J_{3,4}$ = 9, $J_{2,3}$ = 9 Hz), 4.0 (ddd, H-4, $J_{H-4,F-4}$ = 50, $J_{4,5}$ = 9, $J_{3,4}$ = 9 Hz), 4.47 (t, H-1, $J_{1,2}$ = 3.5, $J_{H-1,F-4}$ = 3.5 Hz).

**Methyl 4,6-Dideoxy-4,6-difluoro-α-D-glucopyranoside (32).** Glycoside **31** (5.0 g, 25.5 mmol) was treated with DAST as above. After stirring overnight at room temperature, usual processing and chromatography (1:1 EtOAc/hexane) afforded 3.58 g (71%) of **32**: mp 93–94 °C (EtOAc/hexane); 360-MHz $^1$H NMR $\delta$ 3.06 (br, 1 H, OH), 3.36–3.47 (m, 4 H), 3.8–3.95 (m, 2 H), 4.14 (br m, 1 H, OH), 4.27 (ddd, H-4, $J_{H-4,F-4}$ = 50, $J$ = 8, 9 Hz), 4.62 (dm, 2 H, H-6 and H-6′, $J_{H,F}$ = 46 Hz), 4.72 (t, H-1, $J$ = 3 Hz); $^{19}$F NMR ($^1$H decoupled $\phi$ −235.6 (s, F-6), −198.8 (s, F-4); $^{13}$C NMR $\delta$ 55.0 (s, $OCH_3$), 68.2 (dd, C-5, $J$ = 17, 19 Hz), 71.9 (s, C-2), 72.0 (d, C-3, $J_{C-3,F-4}$ = 15 Hz), 81.7 (d, C-6, $J_{C-6,F-6}$ = 171 Hz), 88.8 (dd, C-4, $J_{C-4,F-4}$ = 181, $J_{C-4,F-6}$ = 7.3 Hz), 100.0 (s, C-1); $[\alpha]_D$ +142.0° (*c* 1.02, $CHCl_3$).

Anal. Calcd for $C_7H_{12}F_2O_4$: C, 42.42; H, 6.10. Found: C, 42.17; H, 6.11.

**6-Deoxy-6-fluoro-1,2-*O*-isopropylidene-α-D-glucofuranose (34).** A suspension of 1,2-*O*-isopropylidene-α-D-glucofuranose[35] (**33**, 11 g, 50 mmol) in dichloromethane (100 mL) at −40 °C was treated with DAST (25 mL, 200 mmol). After stirring for 90 min at room temperature, the reaction was quenched with MeOH (200 mL) and concentrated to a viscous yellow residue. Chromatography on silica gel (3:2 EtOAc/hexane) gave 7.8 g (70%) of **34** as a colorless syrup: bp (Kugelrohr) 149–155 °C (0.03 mmHg); 360-MHz $^1$H NMR ($CDCl_3$) $\delta$ 1.32 (s, 3 H), 1.49 (s, 3 H), 3.67 (br s, 2 H, OH), 4.1 (dd, H-4, $J_{3,4}$ = 2.5, $J_{4,5}$ = 8 Hz), 4.18 (dm, H-5, $J_{5-f}$ = 25 Hz), 4.37 (d, H-3), 4.54 (d, H-2, $J_{1,2}$ = 4 Hz, collapses upon irradiation at $\delta$ 5.9), 4.57 (m, H-6, $J_{6,6'}$ = 10, $J_{6,5}$ = 5, $J_{H-6,F-6}$ = 48 Hz), 4.67 (m, H-6′, $J_{6',5}$ = 3, $J_{6',F-6}$ = 48 Hz), 5.95 (d, H-1); $^{19}$F NMR ($CDCl_3$, $^1$H decoupled)$\phi$ −233.6 (s); $[\alpha]_D$ −9.8° (*c* 1.02, $CHCl_3$).

Anal. Calcd for $C_9H_{15}FO_5$: C, 48.64; H, 6.80. Found: C, 48.59; H, 6.69.

**Methyl 4,6-*O*-Isopropylidene-2,3-di-*O*-methyl-α-D-mannopyranoside (40).** A solution of **39**[30,31] (19.5 g, 83 mmol) in DMF (500 mL) was treated with excess sodium hydride. After 1 h of stirring at room temperature, methyl iodide (31 mL) was gradually added, and the mixture was kept overnight at room temperature. MeOH was added dropwise to quench the excess NaH, and the mixture was poured into water and extracted with ether. The ether layer was dried ($MgSO_4$) and concentrated to a colorless residue. Chromatography (3:1 hexane/EtOAc) afforded 8.5 (40%) of **40** as a solid: mp 74–76 °C; 360-MHz $^1$H NMR ($CDCl_3$) $\delta$ 1.43 (s, 3 H), 1.53 (s, 3 H), 3.37 (s, 3 H), 3.49 (s, 3 H), 3.52 (s, 3 H), 3.54–3.64 (m, 3 H), 3.84 (m, 2 H), 4.06 (dd, 1 H, $J$ = 10 Hz), 4.76 (d, H-1, $J_{1,2}$ = 2 Hz); $[\alpha]_D$ +57.9° (*c* 1.01, $CHCl_3$).

Anal. Calcd for $C_{12}H_{22}O_6$: C, 54.95; H, 8.45. Found: C, 54.88; H, 8.35.

**Methyl 2,3-Di-*O*-methyl-α-D-mannopyranoside (38).** Acetonide **40** (7.36 g, 28 mmol) was dissolved in 400 mL of 3:1 $H_2O$/HOAc, and the mixture was heated at 75 °C for 90 min. Concentration under reduced pressure and chromatography (9:1 EtOAc/MeOH) afforded 5.96 g (96%) of **38** as a colorless syrup:

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360-MHz $^1$H NMR ($CDCl_3$) $\delta$ 3.35–3.57 (m, 13 H), 3.61 (m, 1 H), 3.85 (m, 3 H), 4.8 (d, H-1, $J_{1,2}$ = 1.8 Hz).

**Methyl 6-Deoxy-2,3-di-*O*-methyl-6-fluoro-α-D-mannopyranoside (41).** A −40 °C solution of **38** (1.11 g, 5 mmol) in dichloromethane (20 mL) was treated with DAST (1.9 mL, 15 mmol). After stirring for 1 h at room temperature, usual processing afforded a colorless syrup. Chromatography (EtOAc) gave 670 mg (60%) of **41** as a syrup: 360-MHz $^1$H NMR ($CDCl_3$) $\delta$ 2.87 (br, 1 H, OH), 3.40 (s, 3 H), 3.44–3.5 (m, 7 H), 3.63 (m, 1 H, H-2), 3.72 (dm, H-5, $J_{H-5,F-6}$ = 22 Hz), 3.84 (t, H-4, $J$ = 9 Hz), 4.66 (dm, H-6 and H-6′, $J_{H,F}$ = 48 Hz), 4.84 (d, H-1, $J_{1,2}$ = 1.5 Hz); $^{19}$F NMR ($CDCl_3$) $\phi$ −233.6 (s, $^1$H decoupled); $^{13}$C NMR $\delta$ 54.3 (s, $OCH_3$), 56.7 (s, $OCH_3$), 58.4 (s, $OCH_3$), 65.4 (d, C-4, $J_{C-4,F-6}$ = 7.36 Hz), 72.3 (d, C-5, $J_{C-5,F-6}$ = 17.6 Hz), 76.4 (s, C-2), 81.6 (s, C-3), 82.8 (d, C-6, $J_{C,F}$ = 170.6 Hz), 98.9 (s, C-1); mass spectrum, *m/e* calcd for $C_8H_{14}FO_4$ ($M^+$ − $OCH_3$) 193.0876, found 193.0869.

**Methyl 6-Deoxy-6-fluoro-2,3-*O*-isopropylidene-α-D-mannopyranoside (43) and Methyl 2,3-*O*-Isopropylidene-6-*O*-methyl-α-D-mannopyranoside (44).** A solution of **42**[30] (3.51 g, 15 mmol) in $CH_2Cl_2$ (30 mL) at −40 °C was treated with DAST (5.7 mL, 45 mmol), and the resulting mixture was stirred at room temperature for 15 min and then cooled to −20 °C and quenched with MeOH (50 mL). Usual processing and column chromatography (2:1 ether/hexane) afforded two fractions.

**43**: 480 mg (14%), bp (Kugelrohr) 150–155 °C (0.01 mmHg); 360-MHz $^1$H NMR (acetone-$d_6$) $\delta$ 1.30 (s, 3 H), 1.42 (s, 3 H), 3.36 (s, 3 H), 3.55–3.7 (m, 2 H), 4.03 (t, 1 H, $J$ = 6 Hz), 4.08 (d, 1 H, $J$ = 6 Hz), 4.61 (m, H-6, $J_{6,6'}$ = 10, $J_{6,5}$ = 4, $J_{6,F}$ = 48 Hz), 4.67 (d, 1 H, $J$ = 6 Hz), 4.68 (m, H-6′, $J_{6',5}$ = 2, $J_{6',F}$ = 48 Hz), 4.87 (s, H-1); $^{13}$C NMR $\delta$ 54.9 (s, $OCH_3$), 68.6 (d, C-4, $J_{C,F}$ = 7.3 Hz), 70.1 (d, C-5, $J_{C,F}$ = 17.6 Hz), 76.5 (s, C-3), 79.9 (s, C-2), 83.4 (d, C-6, $J_{C,F}$ = 170.6 Hz), 99.1 (C-1), 109.7 (s); $^{19}$F NMR ($CDCl_3$) $\phi$ −235.0 (s).

Anal. Calcd for $C_{10}H_{17}FO_5$: C, 50.84; H, 7.25. Found: C, 51.01; H, 7.41.

**44**: 460 mg (12%) as a colorless semisolid: bp (Kugelrohr) 155–160 °C (0.01 mmHg); 360-MHz $^1$H NMR ($CDCl_3$) $\delta$ 1.35 (s, 3 H), 1.53 (s, 3 H), 3.17 (br, 1 H, OH), 3.41 (s, 3 H), 3.43 (s, 3 H), 3.67 (m, 3 H), 4.13 (m, 2 H, $H_{6,6'}$), 4.91 (s, H-1); $^{13}$C NMR (acetone-$d_6$) $\delta$ 53.2 (s, $OCH_3$), 57.7 (s, $OCH_3$), 68.5 (s, 1 C), 68.7 (s, 1 C), 71.5 (s, 1 C), 75.0 (s, 1 C), 78.4 (s, 1 C), 97.5 (s, C-1), 107.9 (s, 1 C).

Anal. Calcd for $C_{11}H_{20}O_6$: C, 53.21; H, 8.12. Found: C, 52.94; H, 7.85.

**Methyl 4,6-Dideoxy-4,6-difluoro-2,3-*O*-isopropylidene-α-D-talopyranoside (45).** A −40 °C solution of **42** (3.51 g, 15 mmol) in dichloromethane (30 mL) was treated with DAST (5.7 mL, 45 mmol). After stirring at room temperature for 24 h, the reaction was quenched via addition of saturated aqueous $NaHCO_3$. The organic layer was dried, concentrated, and chromatographed on silica gel (4:1 hexane/ether) to give 810 mg (23%) of **45** as a colorless oil: $^{19}$F NMR $\phi$ −235.1 (s, $^1$H decoupled; dt, $J$ = 48, 25 Hz, $^1$H coupled), −196.9 (s, $^1$H decoupled; dd, $^1$H coupled, $J$ = 25, 52 Hz); mass spectrum, *m/e* calcd for $C_9H_{13}F_2O_4$ ($M^+$ − $CH_3$) 223.0782, found 223.0790, *m/e* calcd for $C_9H_{13}F_2O_3$ ($M^+$ − $OCH_3$) 207.0833, found, 207.0817.

**Methyl 6-Deoxy-6-fluoro-α-D-mannopyranoside (46).** A solution of **43** (1.99 g, 8.4 mmol) in 3:1 $H_2O$/AcOH (120 mL) was heated at 70 °C for 90 min. Removal of the volatiles under reduced pressure and flash chromatography (19:1 EtOAc/MeOH) gave 1.43 g (87%) of **46** as a colorless solid: mp 112–114 °C; 360-MHz $^1$H NMR (acetone-$d_6$) $\delta$ 3.1 (br s, 1 H, OH), 3.33 (s, 3 H, $OCH_3$), 3.56–3.7 (m, 3 H), 3.82 (m, 1 H), 4.12 (m, 1 H), 4.32 (m, 1 H), 4.5–4.59 (m, 1 H), 4.64–4.73 (m, 2 H); $^{19}$F NMR $\phi$ −232.1 (s, $^1$H decoupled; $^1$H coupled dt, $J$ = 25.5, 49 Hz); $^{13}$C NMR $\delta$ 54.8 (s, $OCH_3$), 67.3 (d, C-4, $J_{C-4,F-6}$ = 7.35 Hz), 71.5 (s, C-3), 72.5 (d, C-5, $J_{C-5,F-6}$ = 19.1 Hz), 72.6 (s, C-2), 83.5 (d, C-6, $J_{C-6,F-6}$ = 170.6 Hz), 102.2 (s, C-1); $[\alpha]_D$ +88.4° (*c* 0.99, MeOH).

Anal. Calcd for $C_7H_{13}FO_5$: C, 42.86; H, 6.68. Found: C, 43.07; H, 6.61.

**Methyl 4-Deoxy-4-fluoro-6-*O*-trityl-α-D-talopyranoside (49).** Using the standard DAST procedure and a 2-h reaction period, 80 g (185 mmol) of **48** afforded 32.4 g (40%) of **49** as a colorless solid foam: 360-MHz $^1$H NMR ($CDCl_3$) $\delta$ 2.2 (m, 1 H, OH), 3.12 (m, 1 H, OH), 3.37 (m, 4 H), 3.45 (m, 1 H), 3.72 (m, 2 H), 3.82 (m, 1 H), 4.79 (s, H-1), 4.85 (d, H-4, $J_{H,F}$ = 49 Hz), 7.2–7.32 (m, 9 H), 7.72–7.47 (m, 6 H); $^{19}$F NMR ($CDCl_3$, $^1$H decoupled) $\phi$ −215 (s).

Anal. Calcd for $C_{26}H_{27}FO_5$: C, 71.22; H, 6.21. Found: C, 71.00; H, 6.46.

**Methyl 4-Deoxy-4-fluoro-α-D-talopyranoside (47).** A solution of **49** (21.65 g, 51 mmol) in 4:1 HOAc/$H_2O$ (200 mL) was heated at 70 °C for 4 h and then concentrated under reduced pressure. The residue was triturated with ether, and the ether layer was discarded. Chromatography of the residue on silica gel (9:1 EtOAc/MeOH) afforded 8.03 g (80%) of **47** as a colorless solid: mp 91–93 °C; 360-MHz $^1$H NMR $\delta$ 3.28 (s, 3 H, $OCH_3$), 3.75–3.88 (m, 3 H), 3.92–3.98 (m, 2 H), 4.74 (s, H-1), 4.77 (dd, H-4, $J_{H-4,F-4}$ = 49, $J$ = 2 Hz); $^{19}$F NMR ($^1$H decoupled) $\phi$ −217.05 (s); $^{13}$C NMR $\delta$ 54.5 (s, $OCH_3$), 60.5 (d, C-6, $J_{C-6,F-4}$ = 7.35 Hz), 66.7 (d, C-3, $J_{C-3,F-4}$ = 16.1 Hz), 69.9 (s, C-2), 70.0 (d, C-5, $J_{C-5,F-4}$ = 17.6 Hz), 90.0 (d, C-4, $J_{C-4,F-4}$ = 179 Hz), 102.0 (s, C-1); mass spectrum, *m/e* calcd for $C_6H_{10}FO_4$ ($M^+$ − $OCH_3$) 165.0563, found 165.0568; $[\alpha]_D$ +88.8° (*c* 0.99, $H_2O$).

Anal. Calcd for $C_7H_{13}FO_5$: C, 42.85; H, 6.67. Found: C, 43.08; H, 6.69.

**Methyl 4-Deoxy-4-fluoro-α-L-arabinopyranoside (51).** Treatment of methyl α-D-xylopyranoside (**49**, 6.46 g 39.4 mmol) in dichloromethane (80 mL) at −40 °C with DAST (22 mL, 177 mmol) as above afforded a brown residue. Chromatography on silica gel (EtOAc) gave **51** (1.24 g, 19%) as a colorless solid: mp 139–141 °C ($CHCl_3$); 360-MHz $^1$H NMR $\delta$ 3.37 (s, 3 H, $OCH_3$), 3.68–3.86 (m, 5 H), 4.68 (d, H-1, $J_{1,2}$ = 3.5 Hz), 4.74 (d, H-4, $J_{H,F}$ = 50 Hz); $^{19}$F NMR ($^1$H decoupled)$\phi$ −201.5 (s); $^{13}$C NMR ($D_2O$) $\delta$ 99.4 (s, C-1), 90.3 (d, C-4, $J_{C-F}$ = 173.5 Hz), 67.9 (s, C-2), 67.5 (d, C-3, $J_{C-3,F-4}$ = 19.1 Hz), 60.1 (d, C-5, $J_{C-5,F-4}$ = 19.1 Hz), 55.0 (s, $OCH_3$); $[\alpha]_D$ +222.5° (*c* 1.03, $H_2O$).

Anal. Calcd for $C_6H_4FO_4$: C, 43.37; H, 6.67. Found: C, 43.23; H, 6.54.

**Methyl 4-Deoxy-4-fluoro-β-L-arabinopyranoside (53).** A suspension of methyl β-D-xylopyranoside (**52**, 8.2 g, 50 mmol) in dichloromethane (100 mL) at −40 °C was treated with DAST (28 mL, 225 mmol). After being stirred overnight at room temperature, the reaction mixture was quenched and concentrated as above. Chromatography on a column of silica gel (9:1 EtOAc/MeOH) afforded 4.28 g (52%) of **53** as a colorless solid: mp 120–122 °C ($CHCl_3$); 360-MHz $^1$H NMR $\delta$ 3.5 (s, 3 H, $OCH_3$), 3.61 (ddd, H-5 ax, $J_{H,F}$ = 33, $J_{5,5'}$ = 13, $J_{5,4}$ = 1 Hz), 3.66 (m, H-2), 3.68 (dm, H-3, $J_{3,F}$ = 31 Hz), 4.1 (ddd, H-5 eq, $J_{H,F}$ = 26, $J_{5,4}$ = 3 Hz), 4.18 (dd, H-1, $J_{1,2}$ = 7, $J_{H,F}$ = 1.5 Hz), 4.74 (m, H-4, $J_{H,F}$ = 49, $J_{3,4}$ = 2 Hz); $^{19}$F NMR ($^1$H decoupled) $\phi$ −205.9 (s); $^{13}$C NMR $\delta$ 104.6 (s, C-1), 89.4 (d, C-4, $J_{C,F}$ = 177.9 Hz), 72.2 (d, C-3, $J_{C,F}$ = 22 Hz), 71.7 (s, C-2), 64.0 (d, C-5, $J_{C,F}$ = 20.6 Hz), 55.9 (s, $OCH_3$); $[\alpha]_D$ −5.2° (*c* 1.0, $CHCl_3$).

Anal. Calcd for $C_6H_{11}O_4F$: C, 43.37; H, 6.67. Found: C, 43.09; H, 6.61.

**Methyl 4-Azido-4,6-dideoxy-6-fluoro-α-D-glucopyranoside (56).** Azide **55**[32] (6.02 g, 27.5 mmol) was suspended in dichloromethane (130 mL), cooled to −40 °C, and treated with DAST (15.4 mL, 123 mmol). After stirring overnight at room temperature, usual processing and column chromatography (1:1 EtOAc/hexane) gave 4.13 g (68%) of **56** as a colorless solid: mp 147–148 °C ($CHCl_3$); IR (KBr) 3430 (OH), 2120 ($N_3$) cm$^{-1}$; 360-MHz $^1$H NMR $\delta$ 3.4 (m, 4 H, $OCH_3$), 3.5 (dd, H-2, $J_{1,2}$ = 3.5, $J_{2,3}$ = 10 Hz), 3.6 (ddm, H-5, $J_{5,F}$ = 26, $J$ = 10 Hz), 3.81 (t, 1 H, $J$ = 9 Hz), 4.6 (dm, H-6 and H-6′, $J_{H,F}$ = 46 Hz), 4.74 (d, H-1, $J_{1,2}$ = 3.5 Hz); $^{13}$C NMR $\delta$ 55.0 (s, $OCH_3$), 61.7 (d, C-4, $J$ = 5.9 Hz), 69.2 (d, C-5, $J_{C,F}$ = 17.6 Hz), 72.8 (s, C-2), 73.5 (s, C-3), 82.7 (d, C-6, $J_{C,F}$ = 172 Hz), 100.5 (s, C-1); $^{19}$F NMR $\phi$ −234.1 (s, $^1$H decoupled); $[\alpha]_D$ +257.4° (*c* 0.99, EtOH).

Anal. Calcd for $C_7H_{12}FN_3O_4$: C, 38.01; H, 5.47; N, 19.00. Found: C, 37.89; H, 5.39; N, 18.73.

**Methyl 4-Amino-4,6-dideoxy-6-fluoro-α-D-glucopyranoside (57).** Azide **56** (4.12 g, 18.6 mmol) in EtOH (110 mL) was hydrogenated at ~1 atm of $H_2$ over a catalytic amount of 10% Pd/C. Filtration through Celite and removal of the solvent under reduced pressure gave 3.29 g (90.7%) of **57** as an off-white solid: mp 113–115 °C (EtOH); IR (KBr) 3420, 1065, 1040 cm$^{-1}$; 360-MHz $^1$H NMR (acetone-$d_6$) $\delta$ 3.33–3.49 (m, 5 H), 3.72 (t, 1 H, $J$ = 9.5 Hz), 3.92 (dddd, H-5, $J_{H-5,F-6}$ = 28.5, $J_{4,5}$ = 10, $J_{5,6}$ = 4, $J_{5,6'}$ = 1.5 Hz), 4.25 (d of ABX, H-6, $J_{6,6'}$ = 10, $J_{6,F-6}$ = 48 Hz), 4.33 (d of ABX, H-6′, $J_{6',F-6}$ = 48.5 Hz), 4.7 (d, H-1, $J_{1,2}$ = 4 Hz); $^{19}$F NMR

$\phi$ −233.8 (s, $^1$H decoupled; $^1$H coupled gave ddd, $J$ = 48, 28, 48.5 Hz); $[\alpha]_D$ +151.1° ($c$ 1.03, MeOH).

Anal. Calcd for $C_7H_{14}FNO_4$: C, 43.07; H, 7.23; N, 7.18. Found: C, 43.28; H, 7.45; N, 6.93.

**Methyl 6-Azido-6-deoxy-β-D-glucopyranoside (59).** Sulfonate **58**[33] was converted into **59** (98.5%) as is described for **62**: IR (KBr) 3400, 2110 cm$^{-1}$; $^{13}$C NMR (acetone-$d_6$) $\delta$ 99.4 (C-1), 72.4, 72.0, 69.9, 61.5, 60.7, 53.8; $[\alpha]_D$ +241.7° ($c$ 1.02, EtOH).

Anal. Calcd for $C_7H_{13}N_3O_5$: C, 38.35; H, 5.97; N, 19.17. Found: C, 38.26; H, 5.88; N, 19.04.

**Methyl 6-Azido-3,6-dideoxy-3-fluoro-β-D-allopyranoside (60).** A −40 °C suspension of azide **59** (12.16 g, 55.5 mmol) in dichloromethane (200 mL) was treated with DAST (31 mL, 249 mmol). After 3 h at room temperature, usual workup and flash chromatography (EtOAc) afforded 3.39 g (28%) of **60** as a colorless solid: mp 80–82 °C (ether/hexane); 360-MHz $^1$H NMR $\delta$ 3.47 (dm, H-2, $J_{H\text{-}2,F\text{-}3}$ = 29, $J_{1,2}$ = 8.5, $J_{2,3}$ = 2 Hz), 3.48 (m, 5 H, H-6, and H-6′, and $OCH_3$), 3.61 (dm, H-4, $J_{4,F\text{-}3}$ = 28, $J_{4,5}$ = 10, $J_{3,4}$ = 2 Hz), 3.84 (m, H-5), 4.47 (m, 2 H, OH), 4.52 (dd, H-1, $J_{1,F\text{-}3}$ = 2, $J_{1,2}$ = 8.5 Hz), 4.89 (ddd, H-3, $J_{H,F}$ = 53, $J_{2,3}$ = $J_{3,4}$ = 2 Hz); $^{19}$F NMR $\phi$ −217.4 ($^1$H decoupled, s; $^1$H coupled, ddd, $J$ = 29, 53, 29 Hz); IR (KBr) 3320 (OH), 2110 ($N_3$) cm$^{-1}$; $^{13}$C NMR $\delta$ 52.0 (s, $-CH_2N_3$), 56.2 (s, $OCH_3$), 68.2 (d, C-4, $J_{C\text{-}4,F\text{-}3}$ = 18 Hz), 70.4 (d, C-2, $J_{C\text{-}2,F\text{-}3}$ = 17 Hz), 73.8 (d, C-5, $J_{C\text{-}5,F\text{-}3}$ = 3 Hz), 93.5 (d, C-3, $J_{C,F}$ = 177.7 Hz), 102.0 (d, C-1, $J_{C\text{-}1,F\text{-}3}$ = 3.4 Hz); $[\alpha]_D$ −100.8° ($c$ = 1.0, $CHCl_3$).

Anal. Calcd for $C_7H_{12}FN_3O_4$: C, 38.01; H, 5.47; N, 19.00. Found: C, 38.29; H, 5.64; N, 18.73.

**Methyl 6-Amino-3,6-dideoxy-3-fluoro-β-D-allopyranoside (61).** A solution of **60** (2.94 g, 13.3 mmol) in EtOH (100 mL) was hydrogenated at ~1 atm of $H_2$ over a catalytic amount of 1.0% Pd/C. Removal of the solvent under reduced pressure gave 2.46 g (95%) of **61** as a colorless solid: mp 179.5–183.5 °C dec (EtOH); IR (KBr) 3430 cm$^{-1}$; $[\alpha]_D$ −40.1° ($c$ 1.0, $H_2O$).

Anal. Calcd for $C_7H_{14}FNO_4$: C, 43.07; H, 7.23; N, 7.18. Found: C, 42.78; H, 7.16; N, 7.30.

**Methyl 6-Azido-4,6-dideoxy-4-fluoro-α-D-talopyranoside (64).** A solution of **35** (9.7 g, 50 mmol) in 200 mL of pyridine was treated 2-mesitylenesulfonyl chloride (11 g, 50 mmol), and the mixture was stirred at room temperature. After 66 h, the reaction was poured into ice-water, dried, and concentrated by using toluene to help remove the last traces of pyridine. Column chromatography (EtOAc) gave 9.0 g (48%) of **62** as a colorless hygroscopic solid: 360-MHz $^1$H NMR $\delta$ 2.3 (s, 3 H), 2.6 (s, 6 H), 3.32 (s, 3 H, $OCH_3$), 3.4 (s, 1 H, OH), 3.7–3.93 (m, 6 H), 4.22 (m, 2 H), 4.67 (s, 1 H, H-1), 6.96 (s, 2 H, aromatic).

A solution of **62** (11.3 g, 30 mmol) in 110 mL of DMF at 80 °C was saturated with $NaN_3$ and then kept at 80 °C for 4 h. The DMF was removed under reduced pressure, and the residue was dissolved in $CH_2Cl_2$, filtered through Celite, and concentrated to a milky residue. The residue was chromatographed on $SiO_2$ (9:1 $CHCl_3$/MeOH) and afforded 4.56 g (69%) of **63**[36] as a colorless syrup: IR (neat) 3300 (OH), 2100 ($N_3$) cm$^{-1}$.

Azide **63** (2.19 g, 10 mmol) was treated with DAST (45 mmol) as described above. After 1 h at room temperature, usual processing and column chromatography (19:1 $CHCl_3$/MeOH) afforded 1.24 g (56%) of **64** as a colorless solid: mp 96–98 °C (EtOAc/hexane); 360-MHz $^1$H NMR ($CDCl_3$) $\delta$ 2.33 (br m, 1 H, OH), 3.26 (br m, 1 H, OH), 3.35 (dd, H-6, $J_{6,6'}$ = 12, $J_{6,5}$ = 5 Hz), 3.44 (s, 3 H), 3.68 (ddd, H-6′, $J_{6,6'}$ = 12, $J_{6',5}$ = 8, $J_{6',F\text{-}4}$ = 2 Hz), 3.77 (br, 2 H), 3.93 (dm, H-5, $J_{5,F\text{-}4}$ = 30 Hz), 4.70 (d, H-4, $J_{H,F}$ = 51 Hz), 4.87 (s, H-1); $^{19}$F NMR $\phi$ −216.1 ($^1$H decoupled, s; $^1$H coupled, dt, $J$ = 30, 51 Hz); IR (KBr) 3400 (OH), 2100 ($N_3$) cm$^{-1}$.

Anal. Calcd for $C_7H_{12}FN_3O_4$: C, 38.01; H, 5.47; N, 19.00. Found: C, 38.31; H, 5.59; N, 19.17.

**Methyl 6-Amino-4,6-dideoxy-4-fluoro-α-D-talopyranoside (65).** Azide **64** (2.33 g, 10.5 mmol) was dissolved in EtOH (100 mL) and hydrogenated at ~1 atm of $H_2$ over a catalytic amount of 10% Pd/C. Removal of the solvent under reduced pressure gave 2.02 g (98%) of **65** as a colorless solid: mp 140–142.5 °C; IR (KBr) 3400 cm$^{-1}$; 360-MHz $^1$H NMR $\delta$ 3.33 (s, 3 H, $OCH_3$), 3.37 (m, 2 H, H-6 + H-6′), 3.64 (m, H-2), 3.68 (dm, H-3, $J_{H\text{-}3,F\text{-}4}$ = 32 Hz), 3.90 (dt, H-5, $J_{H\text{-}5,F\text{-}4}$ = 31, $J$ = 7 Hz), 4.67 (d, H-4, $J_{H,F}$ = 51 Hz), 4.69 (s, H-1); $^{19}$F NMR $\phi$ −217 (s, $^1$H decoupled); $[\alpha]_D$ +91.9° ($c$ 1.01, $H_2O$).

Anal. Calcd for $C_7H_{14}FNO_4$: C, 43.07; H, 7.23; N, 7.18. Found: C, 43.06; H, 7.27; N, 6.97.

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**Registry No.** **1**, 709-50-2; **2**, 79291-95-5; **4**, 4630-62-0; **5**, 87638-52-6; **6**, 709-50-2; **7**, 1464-44-4; **8**, 87585-90-8; **9**, 87585-92-0; **10**, 87585-91-9; **11**, 87585-93-1; **12**, 67010-02-0; **13**, 87585-94-2; **14**, 2492-87-7; **15**, 87585-95-3; **16**, 87585-96-4; **17**, 67412-01-5; **18**, 87585-97-5; **19**, 87585-98-6; **20**, 16802-97-4; **21**, 87585-99-7; **22**, 32934-07-9; **23**, 18311-26-7; **24**, 87586-00-3; **25**, 32934-08-0; **26**, 87586-01-4; **27**, 87586-02-5; **28**, 85542-09-2; **29**, 87586-03-6; **30**, 84065-98-5; **31**, 56926-53-5; **32**, 87586-04-7; **33**, 18549-40-1; **34**, 87586-05-8; **35**, 617-04-9; **38**, 27299-05-4; **39**, 63167-67-9; **40**, 87586-06-9; **41**, 87586-07-0; **42**, 63167-69-1; **43**, 87586-08-1; **44**, 28140-06-9; **45**, 87586-09-2; **46**, 87586-10-5; **47**, 87586-12-7; **48**, 20231-36-1; **49**, 87586-11-6; **50**, 91-09-8; **51**, 87586-13-8; **52**, 1824-97-1; **53**, 87586-14-9; **55**, 4181-01-5; **56**, 87586-15-0; **57**, 87586-22-9; **58**, 53914-56-0; **59**, 87586-16-1; **60**, 87586-17-2; **61**, 87586-18-3; **62**, 87586-20-7; **63**, 66224-56-4; **64**, 87586-19-4; **65**, 87586-21-8; DAST, 38078-09-0; methyl α-D-galactopyranoside, 3396-99-4; methyl β-D-galactopyranoside, 1824-94-8.

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