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# Fluorinated carbohydrates as potential plasma membrane modifiers. Synthesis of 3-deoxy-3-fluoro derivatives of 2-acetamido-2-deoxy-D-hexopyranoses *

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## ABSTRACT

Treatment of benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-allopyranoside with diethylaminosulfur trifluoride or of the 3-*O*-mesyl derivative with tetrabutylammonium fluoride gave the 2,3-unsaturated compound instead of the expected 3-deoxy-3-fluoro derivative. The latter was obtained when benzyl 2-acetamido-4,6-di-*O*-benzyl-2-deoxy-3-*O*-mesyl-α-D-allopyranoside was treated with potassium fluoride. Methyl 2-azido-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranoside was converted into the 2-acetamido- and 2-phthalimido-3-*O*-mesyl derivatives; when treated with fluoride nucleophile, these gave only the 2,3-aziridine derivative. However, treatment of the 2-azido-2-deoxy derivative with diethylaminosulfur trifluoride gave methyl 2-azido-2,3-dideoxy-3-fluoro-α-D-mannopyranoside which, after reduction, deprotection, and acetylation, gave the acetylated derivative of methyl 2-acetamido-2,3-dideoxy-3-fluoro-α-D-mannopyranoside in excellent yield. These acetylated 3-fluoro derivatives exhibited inhibition of cell growth of murine L1210 leukemia cells in culture at micromolar concentrations.

## INTRODUCTION

The modification and inhibition of cell surface glycoconjugates may lead to the alteration of immunogenicity, tumorogenicity, and metastatic potential of cancer cells[1–4]. The preferred target of such molecular modification is the plasma-membrane component, sialic acid[5], and such biosynthetic precursors as 2-acetamido-2-deoxy-D-mannose, the 6-phosphate of which is an obligatory intermediate in the biosynthesis of sialic acid[6,7].

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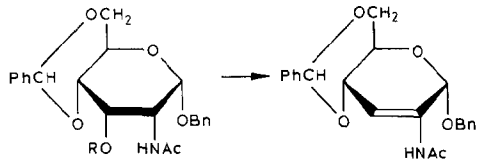
Several derivatives of 2-amino-2,6-dideoxy-6-fluorohexoses were synthesized in our laboratory[8,9], and their biological effects, such as inhibition of cell growth, biosynthetic macromolecular incorporation, and antitumor properties were evaluated. Substitution of the secondary hydroxyl groups by a fluorine atom appears to lead to biochemically effective sugar analogs, since these hydroxyl groups are involved in the oligosaccharide linkage in cell surface glycoconjugates. Substitution of OH-4 by a fluorine atom in 2-acetamido-2-deoxy-D-hexoses[10] gave biologically potent derivatives. Substitution of OH-3 of 2-acetamido-2-deoxy-D-hexoses with a fluorine atom may also give effective inhibitors or modifiers of cell surface glycoconjugates, and their synthesis and biological activity are reported herein.

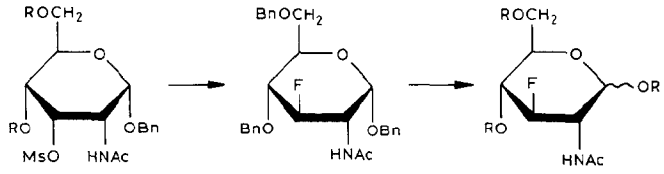
## RESULTS AND DISCUSSION

The usual substitution of OH-3 or OMs-3 on suitably protected 2-acetamido-2-deoxyhexoses through a $S_N2$ displacement reaction by *N*,*N*-diethylaminosulfur trifluoride (DAST) or other fluoride ions did not lead to the target product as expected, but rather yielded the 3-deoxy-2,3-unsaturated derivative. Thus, when benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-mesyl-α-D-allopyranoside[11] (**2**) was treated with tetrabutylammonium fluoride or potassium fluoride, the major product (**3**) was obtained in 75% yield. The same product was obtained when benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-allopyranoside[11] (**1**) was treated with DAST. Compound **2** was hydrolyzed with aqueous acetic acid to give **4**, and benzylation gave benzyl 2-acetamido-4,6-di-*O*-benzyl-2-deoxy-3-*O*-mesyl-α-D-allopyranoside (**6**). Treatment of **6** with potassium fluoride in 1,2-ethanediol led to benzyl 2-acetamido-4,6-di-*O*-benzyl-2,3-dideoxy-3-fluoro-α-D-glucopyranoside (**7**) only in 10% yield. Catalytic hydrogenolysis of **7** gave **8**, which was acetylated into 2-acetamido-1,4,6-tri-*O*-acetyl-2,3-dideoxy-α-D-glucopyranose (**9**). Since a large quantity of the 3-fluoro derivative was needed, we selected an alternative method for the synthesis of the related 2-acetamido-2,3-dideoxy-3-fluorohexose **20**. Benzyl 2-azido-4,6-*O*-benzylidene-2,3-dideoxy-3-fluoro-α-D-mannopyranoside[12] was synthesized in several steps, and a similar, but simplified procedure was used for the synthesis of the 3-azido-2,3-dideoxy-3-fluoro-D-mannose derivative. Methyl 2-azido-4,6-*O*-benzylidene-α-D-altropyranoside[13] (**10**) was treated with DAST in benzene at 80°C to give the 3-deoxy-3-fluoro derivative **16** as the only product isolated. When methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranoside (**11**) was treated with diethylaminosulfur trifluoride, only the aziridine derivative **15** was obtained. This compound was also obtained when the mesyl derivative **12** was treated with tetrabutylammonium fluoride in acetonitrile or with potassium fluoride in 1,2-ethanediol. Again when methyl 2-amino-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranoside[13] was converted to the 2-phthalimido-3-*O*-mesyl derivative[14] **14** and treated with a fluoride nucleophile, only methyl 4,6-*O*-benzylidene-2,3-dideoxy-2,3-imino-β-D-mannopyranoside[15] (**15**) was obtained. Compound **16** was converted by catalytic reduction of the azido group into **17**, which was subsequently



1 R = H
2 R = Ms

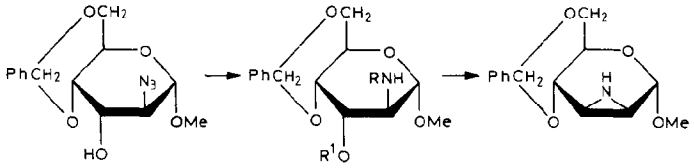
3



4 R = H
5 R = Ac
6 R = Bn

7

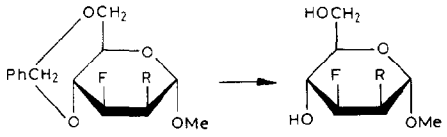
8 R = H
9 R = Ac



10

11 R = Ac; R′ = H
12 R = Ac; R′ = Ms
13 R = Phthaloyl; R′ = H
14 R = Phthaloyl; R′ = Ms

15



16 R = $N_3$
17 R = $NH_2$
18 R = NHAc

19 R = $NH_2$
20 R = NHAc

*N*-acetylated to give **18**. Catalytic hydrogenolysis of **18**, or hydrolysis with aqueous acetic acid afforded **19** in very good yield, and this was acetylated to give methyl 2-acetamido-4,6-di-*O*-acetyl-2,3-dideoxy-3-fluoro-α-D-mannopyranoside (**20**).

The compounds synthesized were tested as inhibitors of growth of murine L1210 leukemia cells in culture. Compounds **9** and **20** were found to reduce tumor cell growth by 50% at 2.7 and $4.3 \cdot 10^{-5}$ M, respectively ($ID_{50}$). In the preclinical therapeutic evaluation in vivo, these compounds were found to be relatively inactive with only a nominal increase in life span (14% ILS at 100 mg $kg^{-1}$)[16] in DBA/2J mice with L1210 leukemia. However, the peracetylated derivative **9** caused a specific dose dependent decrease in [$^3$H]glucosamine incorporation. At a concentration of 0.1 mM, incorporation of [$^3$H]glucosamine in L1210 leukemia cell was decreased by 41%, and that of [$^3$H]thymidine by only 7%[17]. These results suggest a specific inhibitory action on glycoconjugate biosynthesis.

## EXPERIMENTAL

*General methods.*—Melting points (uncorrected) were determined by the capillary method. Optical rotations were measured for a 10-cm cell with a Perkin-Elmer 141 Polarimeter. IR spectra were recorded with a Perkin–Elmer model 457 spectrometer and $^1$H NMR spectra (δ values) with Varian 390 and XL100 instruments, the latter operating in the FT mode. $^{13}$C NMR and $^{19}$F NMR spectra were recorded with a Varian XL100 instrument. Column chromatography was performed on Silica Gel Bio-Sil (100–200 mesh; Bio-Rad) and TLC on an Analtech Uniplate Silica Gel GF-250. The spots were detected with 10% $H_2SO_4$ in MeOH at 100°C.

*Benzyl 2-acetamido-4,6-O-benzylidene-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside* (**3**).—A solution of benzyl 2-acetamido 4,6-*O*-benzylidene-2-deoxy-3-*O*-mesyl-α-D-allopyranoside[11] (**2**; 1 g) in acetonitrile (20 mL) containing tetrabutylammonium fluoride (3 g) was heated under reflux for 4 h. The deep-red solution was concentrated, the residue taken up in benzene, and poured onto a column of silica gel. After elution of the fast-moving impurities with petroleum ether, the product was eluted with ether. It crystallized from $CHCl_3$–ether (820 mg, 70%); mp 200–201°C; $[\alpha]_D^{20} + 60°$ (*c* 1, $CHCl_3$); $\nu_{max}^{KBr}$ 3250 (NH), 1650 and 1540 (C=O, amide), and 700 $cm^{-1}$ (arom.); $^1$H NMR ($CDCl_3$): δ 1.98 (s, 3 H, N Ac), 5.55 (s, H, H-1), 6.65 (m, 1 H, H-3), 7.35 (m, 10 H, arom.). Anal. Calcd for $C_{22}H_{23}NO_5$: C, 69.28; H, 6.08; N, 3.67. Found: C, 69.03; H, 6.30; N, 3.55.

*Benzyl 2-acetamido-2-deoxy-3-O-mesyl-α-D-allopyranoside* (**4**).—To a hot solution of **2** (1.2 g) in AcOH (20 mL) at 90°C was added water (7 mL) slowly, with stirring. After 1 h, the solution was cooled and concentrated to give an oily residue. Benzaldehyde was removed from the residue by washing with ether and the residue was chromatographed on a silica gel column. The column was eluted with $CHCl_3$ to remove impurities and the product eluted with 9:1 $CHCl_3$–MeOH

to give **4** as an amorphous hygroscopic solid (720 mg, 85%); mp 114°C (dec); $[\alpha]_D^{22}$ +67° (*c* 1, $CHCl_3$); $\nu_{max}^{KBr}$ 3500–3200 (NH, OH), 1650 (C=O, amide), 1180 and 1345 $cm^{-1}$ ($SO_2$). Anal. Calcd for $C_{16}H_{23}NO_8S$: C, 49.36; H, 5.95; N, 3.60; S, 8.22. Found: C, 49.08; H, 6.04; N, 3.25; S, 8.18.

A sample of **4** (750 mg) was acetylated with $Ac_2O$ (2 mL) and pyridine (4 mL) to give **5** as a crystalline solid (800 mg, 84%); mp 84–85°C; $[\alpha]_D^{22}$ +104° (*c* 1, $CHCl_3$); $\nu_{max}^{KBr}$ 3350 (NH), 1780 (C=O, Ac), 1660 and 1540 (C=O, amide), 1350 and 1180 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 2.1 (s, 3 H, NAc), 2.25 (s, 6 H, 2 OAc), 3.20 (s, 3 H, Ms), 5.35 (d, 1 H, *J* 3.50 Hz, H-1), 6.2 (d, 1 H, NH), 7.5 (s, 5 H, arom.). Anal. Calcd for $C_{20}H_{27}NO_{10}S$: C, 50.74; H, 5.70; N, 2.95, S, 6.76. Found: C, 50.69, H, 5.49; N, 2.83; S 7.03.

*Benzyl 2-acetamido-4,6-di-*O*-benzyl-3-*O*-mesyl-α-*D*-allopyranoside* (**6**).—A mixture of **4** (2.5 g), BaO (4.4 g), $Ba(OH)_2$ (1.1 g) in *N*,*N*-dimethylformamide (35 mL) containing benzyl bromide (5 mL) was stirred at room temperature for 24 h. The mixture was diluted with $CHCl_3$, cooled in an ice-bath, neutralized with aq formic acid (10%), and extracted with $CHCl_3$. The extract was washed with water, dried ($Na_2SO_4$), and concentrated. The oily residue was taken up in benzene and poured onto a column of silica gel. The column was eluted with petroleum ether to remove the fast-moving impurities and then with EtOAc to give a syrup which crystallized from ether–petroleum ether (3.9 g, 89%); mp 70–71°C; $[\alpha]_D^{22}$ +93° (*c* 1, $CHCl_3$); $\nu_{max}^{KBr}$ 3325 (NH), 1610 and 1535 (C=O, amide), 1349 and 1170 ($SO_2$), and 700 $cm^{-1}$ (arom.); $^1H$ NMR ($CDCl_3$): $\delta$ 2.15 (s, 3 H, NAc), 3.50 (s, 3 H, OMs); 5.50 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 7.34 (m, 15 H, arom.). Anal. Calcd for $C_{30}H_{35}NO_8S$: C, 63.26; H, 6.19, N, 2.46, S, 5.61. Found: C, 63.39; H, 6.39; N, 2.41; S, 5.90.

*Benzyl 2-acetamido-4,6-di-*O*-benzyl-2,3-dideoxy-3-fluoro-α-*D*-glucopyranoside* (**7**). —To a hot (210°C) solution of anhyd KF (7 g) in 1,2-ethanediol (50 mL) was added a solution of **6** (5 g) in 1,2-ethanediol (10 mL). The mixture was heated with stirring at 200–210°C for 15 min and the colored solution was poured onto ice and extracted with $CHCl_3$. The extract was washed with water, dried ($Na_2SO_4$), and concentrated. The residue was chromatographed on a silica gel column. After elution with $CHCl_3$ to remove some fast-moving impurities, the product was eluted with EtOAc as a syrup (1 g); it crystallized from ether–petroleum ether; mp 136–137°C; $[\alpha]_D^{22}$ +84° (*c* 1, $CHCl_3$); $\nu_{max}^{KBr}$ 3300 (NH), 1645 and 1545 (C=O, and amide), 730–710 $cm^{-1}$ (arom); $^1H$ NMR ($CDCl_3$): $\delta$ 1.95 (s, 3 H, N Ac); 4.92 (d, 1 H, $J_{1,2}$ 3.91 Hz, H-1), 5.65 (d, 1 H, *J* 10.2 Hz, NH), 7.35 (m, 15 H, arom.); $^{13}C$ NMR ($CDCl_3$): $\delta$ 23.3 (s, 3 H, NAc), 51.6 (d, C-2), 68.12, 70.06 (m, C-5), 70.50, 73.35 (d), 75.6, 94.50 (d, $J_{C,F}$ 185.10 Hz, C-3), 127.80 (m, arom.), 136.5, 137.60, and 137.80 (quartern. arom. C), and 169.71 (C=O); $^{19}F$ NMR ($CDCl_3$–$CFCl_3$): $\delta$ −195.30 (complex d, $J_{F,H-3}$ 54.30 Hz). Anal. Calcd for $C_{29}H_{32}FNO_5$: C, 70.59; H, 6.49, N, 2.83; F, 3.85. Found: C, 70.70; H, 6.64; N, 3.16; F, 3.68.

*2-Acetamido-1,4,6-tri-*O*-acetyl-2,3-dideoxy-3-fluoro-*D*-glucopyranose* (**9**).—Benzyl 2-acetamido-4,6-di-*O*-benzyl-3-fluoro-α-*D*-glucopyranoside (**7**, 1 g) was hydrogenolyzed in AcOH (25 mL) in the presence of Pd–C (1.1 g, 10%) for 48 h, to

give 2-acetamido-2,3-dideoxy-3-fluoro-D-glucopyranose (**8**) as a thick syrup (310 mg, 70%); $[\alpha]_D^{22}$ +52.5° (*c* 1, MeOH); $\nu_{max}^{KBr}$ 3200–3500 (OH, NH), 1630 and 1550 (C=O, amide); $^{13}C$ NMR ($D_2O$): δ 21.20 and 21.60 (d, $CH_3$, NAc, α and β anomers), 92.15 (d, $J_{C,F}$ 9.9 Hz, C-1α); 94.01 (d, $J_{C,F}$ 181.3 Hz, C-3), 95.2 (d, $J_{C,F}$ 10.1 Hz, C-1β), 175.2 (C=O); $^{19}F$ NMR ($D_2O$–$CFCl_3$ ext.): δ −195.07 (2m, $J_{F,H-3}$ 54.10 Hz).

Compound **8** (310 mg) was acetylated with $Ac_2O$ (4 mL) and pyridine (7 mL) overnight. After addition of ice–water, the solution was concentrated to dryness and pyridine and AcOH were removed by coevaporation with toluene. The residue was chromatographed on a short column of silica gel and the product was eluted with EtOAc as a foamy solid (410 mg 82%); $[\alpha]_D^{22}$ +59.5° (*c* 1, $CHCl_3$); $\nu_{max}^{KBr}$ 3200 (NH), 1780 (C=O, OAc), 1640 and 1520 (C=O, amide); $^{19}F$ NMR ($CDCl_3$–$CFCl_3$): δ −194.7 (complex d, $J_{F,H-3}$ 52.50 Hz). Anal. Calcd for $C_{14}H_{20}FNO_8 \cdot H_2O$: C, 45.79; H, 5.99; N, 3.81; F, 5.18. Found: C, 45.98; H, 6.02; N, 4.01; F, 5.46.

*Methyl 2-acetamido-4,6-O-benzylidene-2-deoxy-α-D-altropyranoside* (**11**).—A solution of methyl 2-amino-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranoside[13] (1 g) in abs MeOH (40 mL) was treated with $Ac_2O$ (4 mL) at 0°C for 1 h, and then at room temperature for 5 h. The mixture was treated with ice–water and, after 10 min, concentrated to dryness. The solid crystallized from MeOH–ether (940 mg, 88%); mp 192–193°C, $[\alpha]_D^{22}$ +79.5° (*c* 1, MeOH); $\nu_{max}^{KBr}$ 3450 (OH), 330 (NH) 1660 and 1545 (C=O, amide), and 705 $cm^{-1}$ (arom.); $^1H$ NMR ($CDCl_3$): δ 1.95 (s, 3 H, NAc), 3.65 (s, 3 H, $OCH_3$), 5.65 (s, 1 H, H-1), and 7.35 (m, 5 H, arom). Anal. Calcd for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33. Found: C, 59.53; H, 6.32; N, 4.14.

*Methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-mesyl-α-D-altropyranoside* (**12**).—To a solution of **11** (900 mg) in pyridine (7 mL) was added methanesulfonyl chloride (2 mL) at 0°C and left stirring at 0–5°C for 18 h. The deep-red solution was poured into ice–water and extracted with $CHCl_3$. The extract was washed with water, dried ($Na_2SO_4$), and concentrated. The residue was chromatographed on a column of silica gel and eluted with EtOAc. After colored impurities the product was eluted in later fractions as a white solid, which crystallized from $CHCl_3$–ether–petroleum ether (600 mg, 62%); mp 132–135°C; $[\alpha]_D^{22}$ +67° (*c* 1, $CHCl_3$); $^1H$ NMR ($CDCl_3$): δ 2.05 (s, 3 H, NAc), 3.05 (s, 3 H, Ms), 3.35 (s, 3 H, $OCH_3$), 4.95 (s, 1 H, $CHC_6H_5$), 6.25 (d, 1 H, *J* 7.9 Hz, NH). Anal. Calcd for $C_{17}H_{23}NO_8S$: C, 50.87; H, 5.78; N, 3.49, S, 7.97. Found: C, 50.58; H, 6.04; N, 3.35; S, 8.05.

*Methyl 4,64l-O-benzylidene-2-deoxy-2-phthalimido-α-D-altropyranoside* (**13**).—A mixture of methyl 2-amino-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranoside[13] (1 g), phthalic anhydride (602 mg), triethylamine (0.4 mL), and toluene (50 mL) was heated to reflux with continuous separation of water for 2 h. The solution was concentrated to remove the solvent and the residue was chromatographed on a silica gel column. The product was eluted with EtOAc as a dry foam; it crystallized from ether–petroleum ether (1.1 g, 75%); mp 80–81°C; $[\alpha]_D^{22}$ +4° (*c* 1, $CHCl_3$); $\nu_{moll}^{KBr}$ 3500 (OH), 1710 (C=O, amide), 710 $cm^{-1}$ (arom.); $^1H$ NMR ($CDCl_3$): δ 3.40 (s, 3 H, $OCH_3$), δ 4.80 (d, 1 H, *J* 2.5 Hz, H-1), 4.71 (s, 1 H, $CHC_6H_5$), 7.35 (m, 5

H, arom.), and 7.80 (m, 4 H, arom.). Anal. Calcd for $C_{22}H_{21}NO_7$: C, 64.23; H, 5.15; N, 3.40. Found: C, 64.56; H, 5.39; N, 3.18.

*Methyl 4,6-O-benzylidene-2-deoxy-3-O-mesyl-2-phthalimido-α-D-altropyranoside* (**14**).—A solution of **13** (500 mg) in anhyd pyridine (2 mL) was treated with a solution of methanesulfonyl chloride (1 mL) in pyridine (1 mL) at 0°C and left at 0–5°C for 18 h. It was then poured into ice–water and extracted with $CHCl_3$; the extract was concentrated and dried to a dry foam. It was chromatographed on a column of silica gel and **14** was eluted with 4:1 $CHCl_3$–EtOAc as a solid (510 mg, 78%); mp 95–98°C; $[\alpha]_D^{22}$ +1° (*c* 1, $CHCl_3$); $^1$H NMR ($CDCl_3$): δ 2.90 (s, 3 H, OMs), 3.35 (s, 3 H, $OCH_3$), 5.20 (t, 1 H, H-1), 5.65 (s, 1 H, C*H*$C_6H_5$), 7.35 (m, 5 H, arom), 7.80 (m, 4 H, arom.). Anal. Calcd for $C_{23}H_{23}NO_9S \cdot 0.5H_2O$: C, 55.37; H, 4.81; N 2.81; S, 6.41. Found: C 55.56; H, 5.18; N, 2.82; S, 6.27.

*Methyl 4,6-O-benzylidene-2,3-dideoxy-2,3-epimino-α-D-mannopyranoside*[15] (**15**).—A solution of **14** (250 mg) was refluxed with tetrabutylammonium fluoride (2 g) in dry acetonitrile (10 mL) for 20 h. Most of the solvent was evaporated and the residue was taken up in $CHCl_3$, washed with water, and dried ($Na_2SO_4$). The solvent was removed, and the residue was chromatographed on a silica gel column. The product was eluted with EtOAc to give a crystalline solid from ether–petroleum ether (110 mg, 84%); mp 145–146°C (lit.[15] 145–146°); $[\alpha]_D^{22}$ +107° (*c* 1, $CHCl_3$) (lit.[15] +105°); $^1$H NMR ($CDCl_3$): δ 0.95 (s, 1 H, NH), 2.50 (d, 2 H, H-2,3), 3.42 (s, 3 H, $OCH_3$) 4.75 (s, 1 H, H-1) 5.49 (s, 1 H, C*H*$C_6H_5$), and 7.40 (m, 5 H, arom.).

*Methyl 2-azido-4,6-O-benzylidene-2,3-dideoxy-3-fluoro-α-D-mannopyranoside* (**16**).—To a mixture of **10** (2.0 g) in anhyd benzene (20 mL) at 0°C was added a solution of DAST (4 mL) in benzene (10 mL) with stirring. After stirring for 30 min at −10°C, anhyd pyridine (3.5 mL) was added and heated at 70–80°C for 2 h. The grey-colored solution was cooled to −20°C, abs EtOH (4 mL) and, after 20 min, ice–water (4 mL) were added, and the mixture was extracted with $CH_2Cl_2$. The extract was poured onto a column of silica gel and eluted with $CH_2Cl_2$ as one fraction. After evaporation of the solvent, the residue was purified by rechromatography on a silica gel column. The product eluted with $CH_2Cl_2$ (1.8 g, 85%) crystallized from ether–petroleum ether; mp 131–132°C; $[\alpha]_D^{22}$ +49.5° (*c* 1, $CHCl_3$); $\nu_{max}^{KBr}$ 2100 ($N_3$) and 700 $cm^{-1}$ (arom.); $^1$H NMR ($CDCl_3$): δ 3.40 (S, 3 H, $OCH_3$); 5.35 (m, 1 H, H-1), 5.60 (s, 1 H, $CHC_6H_5$), and 7.35 (m, 5 H, arom.); $^{19}$F NMR ($CDCl_3$–$CFCl_3$): δ −201.85 (complex d, $J_{F,H-3}$ 50.10 Hz). Anal. Calcd for $C_{16}H_{20}FNO_5$: C, 59.07; H, 6.20, N; 4.31; F, 5.84. Found: C, 59.24; H, 6.42; N, 4.15; F, 5.75.

*Methyl 2-amino-4,6-O-benzylidene-2,3-dideoxy-3-fluoro-α-D-mannopyranoside* (**17**).—A solution of **16** (1.9 g) in abs EtOH (75 mL) was hydrogenolyzed in the presence of Pd–C (500 mg, 10%) for 3 h. After the usual workup, the residue, after evaporation of the solvent, separated from MeOH–ether as a solid (1.5 g, 89%); mp 147–49°C (dec); $[\alpha]_D^{22}$ +93° (*c* 1, $CHCl_3$); $\nu_{max}^{KBr}$ 3400 ($NH_2$) and 700 $cm^{-1}$ (arom); $^1$H NMR ($CDCl_3$): δ 1.51 (br s, 2 H, $NH_2$), 3.42 (s, 3 H, $OCH_3$), 5.40 (m, 1

H, H-1), 5.61 (s, 1 H, $CH_6H_5$), and 7.52 (m, 5 H, arom.). Anal. Calcd for $C_{14}H_{18}FNO_4$: C, 59.36; H, 6.40; N, 4.94; F, 6.71. Found: C, 59.14; H, 6.25; N, 4.72; F, 6.69.

*Methyl 2-acetamido-4,6-O-benzylidene-2,3-dideoxy-3-fluoro-α-D-mannopyranoside* (**18**).—To a solution of **17** (1 g) in abs MeOH (25 mL) was added $Ac_2O$ at 0°C, and the mixture was stirred at room temperature for 2 h. The solution was cooled to 0°C, ice–water added, and concentrated to give a syrupy residue. This was then taken up in $CHCl_3$, washed with water, dried ($Na_2SO_4$), and concentrated. Chromatography on a silica gel column eluted with EtOAc gave a colorless, foamy solid (920 mg, 80%); $[\alpha]_D^{22}$ +76.5° (*c* 1, $CHCl_3$); $\nu_{max}^{KBr}$ 3290 (NH), 1650 (C=O, amide), 750 and 700 $cm^{-1}$ (arom.); $^1H$ NMR ($CDCl_3$): δ 2.05 (s, 3 H, NAc), 3.31 (s, 3 H, $OCH_3$), 4.80 (m, 1 H, H-1), 5.55 (s, 1 H, $CHC_6H_5$), 6.15 (d, 1 H, *J* 9.5 Hz, 1 H), 7.40 (m, 5 H, arom); $^{19}F$ NMR ($CDCl_3$–$CFCl_3$): δ −201.5 (complex d, $J_{F,H-3}$ 49.80 Hz). Anal. Calcd for $C_{16}H_{20}FNO_5$: C, 59.07; H, 6.20; N, 4.15; F, 5.75. Found: C, 59.25; 4, 6.42; N, 4.15; F, 5.75.

*Methyl 2-acetamido-2,3-dideoxy-3-fluoro-α-D-mannopyranoside* (**19**).—To a hot solution of **18** (1.1 g) in AcOH (20 mL) at 60–70°C was added water (10 mL) and the mixture heated with stirring at 70–75°C for 2 h. The clear solution was concentrated to dryness in a vacuum. The residue was taken up in MeOH, diluted with $CHCl_3$, and poured onto a column of silica gel, and the product was eluted with 1:9 MeOH–$CHCl_3$ (TLC, 1:9 MeOH–$CHCl_3$; $R_f$ 0.30) as a glassy solid (650 mg, 80%); $[\alpha]_D^{22}$ +31.5° (*c* 1, MeOH); $\nu_{max}^{KBr}$ 3200–3400 (NH, OH), 1650 and 1520 (C=O, amide). Anal. Calcd for $C_8H_{16}FNO_5 \cdot H_2O$: C, 42.35, H, 7.11, N, 5.49; F, 7.44. Found C, 42.55; H, 7.24; N, 5.52, F, 7.21.

*Methyl 2-acetamido-4,6-di-O-acetyl-2,3-dideoxy-3-fluoro-α-D-mannopyranoside* (**20**).—Compound **19** (620 mg) was acetylated with $Ac_2O$ (4 mL) and anhyd pyridine (7 mL) for 18 h. After treatment with ice–water, the solution was concentrated to a syrupy residue, and pyridine and AcOH were removed by coevaporation with toluene. The residue was chromatographed on a silica gel column and the product eluted with EtOAc to give an amorphous solid (600 mg, 74%); $[\alpha]_D^{22}$ +24° (*c* 1, $CHCl_3$); $\nu_{max}^{KBr}$ 3300 (NH), 1750 (C=O, OAc), 1650 and 1545 $cm^{-1}$ (C=O, amide); $^1H$ NMR ($CDCl_3$): δ 2.1 (m, 9 H, NAc and OAc), 3.35 (s, 3 H, $OCH_3$), 5.15 (m, 1 H, H-1), and 6.25 (d, 1 H, *J* 9.5 Hz, NH); $^{19}F$ NMR ($CDCl_3$–$CFCl_3$); δ −201.50 (complex d, $J_{F,H-3}$ 50.12 Hz). Anal. Calcd for $C_{13}H_{20}FNO_7 \cdot 0.5H_2O$: C, 47.27; H, 6.41; N, 4.24; F, 5.75. Found: C, 47.01; H, 6.52; N, 4.05; F, 5.54.

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