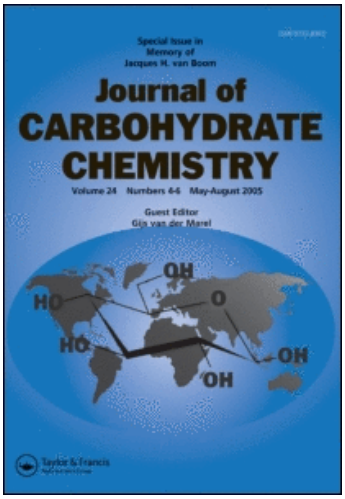

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SYNTHESIS OF 2',3'-DIDEOXY-2'-FLUOROKANAMYCIN A

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ABSTRACT

2',3'-Dideoxy-2'-fluorokanamycin A (23) was prepared by condensation of 6-azido-4-O-benzoyl-2,3,6-trideoxy-2-fluoro-α-D-ribo-hexopyranosyl bromide (13) and a protected disaccharide (19). Methyl 4,6-O-benzylidene-3-deoxy-β-D-arabino-hexopyranoside (5) prepared from methyl 4,6-O-benzylidene-3-chloro-3-deoxy-β-D-allo-hexopyranoside (1) by oxidation with pyridinium chlorochromate followed by reduction with $Na_2S_2O_4$ was fluorinated with the DAST reagent to give methyl 4,6-O-benzylidene-2,3-dideoxy-2-fluoro-β-D-ribo-hexopyranoside (7). Successive treatment of 7 with NBS, NaN_3 and $SOBr_2$ gave 13. The structure of the final product (23) was determined by the ^1H and ^{19}F and shift-correlated 2D NMR spectra.

Kanamycins are inactivated by several kinds of enzymes of resistant bacteria affording phosphonylated, adenylylated, and N-acetylated products. Among them the inactivation by 3'-O-modification occurs most frequently.[1,2] To overcome this biochemical inactivation, one possible and sometimes successful method[1,2] is to remove the hydroxyl group to be phosphonylated

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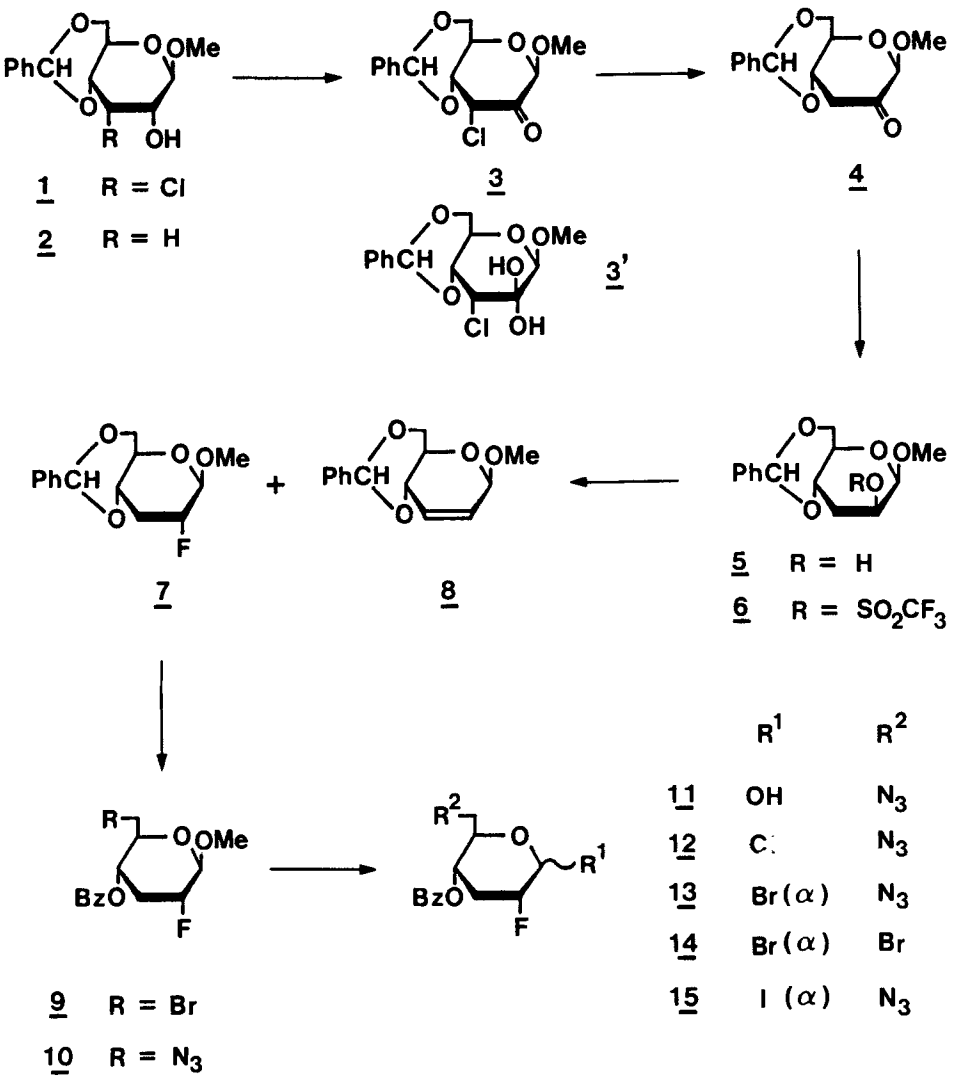
by resistant bacteria, that is, deoxygenation. Recently we reported another kind of promising method which involved replacing the hydroxyl group in question by a fluorine atom. In this manner 3'-deoxy-3'-fluorokanamycin A and B, active against resistant bacteria, were prepared.[3] In this paper we describe the synthesis of 2',3'-dideoxy-2'-fluorokanamycin A (23) performed from another view point. Kanamycin A and B differ in the functional group at C-2'. Since in the periodical table F is located next to O, some linear tendency in biological activities might be expected by changing kanamycin B (NH_2-2') to kanamycin A (OH-2') or 2'-deoxy-2'-fluorokanamycin A. Another aspect which should be of importance is the small van der Waals radius of the fluorine atom, intermediate between the radii of H and OH. Substitution of OH with F is, therefore, not expected to lead to a less active derivative, as does substitution by bulky Cl. 3'-Deoxygenation in addition to 2'-deoxy-fluorination was performed in order to prevent the modification of the OH-3' by resistant bacteria.

2',3'-Dideoxy-2'-fluorokanamycin A (23) was prepared by condensation of 6-azido-4-O-benzoyl-2,3,6-trideoxy-2-fluoro-α-D-ribo-hexopyranosyl bromide (13) and 2'-O-acetyl-4',6'-O-cyclohexylidene-tri-N-tosyl derivative (19) of 6-O-(3-amino-3-deoxy-α-D-glucopyranosyl)-2-deoxystreptamine[4] (3AD). First, methyl 4,6-O-benzylidene-3-deoxy-β-D-arabino-hexopyranoside (5), the key intermediate for the synthesis of 13, was prepared from methyl 4,6-O-benzylidene-3-chloro-3-deoxy-β-D-allopyranoside[5] (1), prepared from methyl 4,6-O-benzylidene-β-D-glucopyranoside with SO_2Cl_2. Reduction of 1 with Raney Ni/H_2 according to Williams et al.,[6] however, gave the 3-deoxy derivative (2) in a low yield (40%). We therefore changed this route and first oxidized the C-2 position. Treatment of 1 with

pyridinium chlorochromate in the presence of molecular sieves gave the 2-keto derivative (3) in high yield. It crystallized in the hydrate form (3') and, in $CDCl_3$, it equilibrated with



the keto form as shown by the ^1H NMR spectrum. The proportion of the keto form was increased by addition of 4Å molecular sieves to the solution. Since the Cl at C-3 in 3 is situated

next to a keto group, it was readily reduced with sodium dithionite[7] ($Na_2S_2O_4$) in DMF to give the 3-deoxy-2-oxo derivative (4) quantitatively. Reduction of 4 with $NaBH_4$ in methanol[6] (reflux, 1 h) or Bu_3SnH/AIBN in dioxane (80°C, 10 h) gave 2 and 5 in equal amounts, but with lithium aluminium hydride (LAH), 5 was the major product. In order to introduce fluorine at C-2 to obtain 2,3-dideoxy-2-fluoro-ribo-hexopyranoside (7), the 2-triflate (6) of 5 was prepared and treated with several kinds of fluorinating agents. By Bu_4NF/silica gel[8] in acetonitrile, 7 was produced in 40% yield along with methyl 4,6-O-benzylidene-2,3-dideoxy-2-eno-β-D-erythro-hexopyranoside[9] (8). With CsF in DMF, even lower yields were obtained. In the case of spray-dried KF[10] in acetonitrile, no reaction was observed; however, by addition of dibenzo-18-crown-6, fluorination occurred to give 7, in a moderate yield, along with 8. The best yield (78%) of 7 was obtained in the reaction of 5 and diethylaminosulfur trifluoride (DAST) in benzene-pyridine. That the fluorine atom was introduced at C-2 in equatorial position was proved by the coupling constants relating to H-1, H-2 and H-3 in the ^1H NMR spectrum of 7 (see Experimental). It is worth mentioning that the H-3ax signals appeared complex when measured in $CDCl_3$ (Fig. 1). Under ^{19}F broad band decoupling, or measured in C_6D_6, the H-3ax signals appeared in the expected pattern. This is interpreted as a strong spin coupling between H-1 and H-2 (lower half) in $CDCl_3$ due to the coincidence of their chemical shifts, thus suggesting the presence of virtual coupling between H-1 and H-3ax.

6-Bromination of 7 was carried out by treatment with N-bromosuccinimide (NBS) according to Hanessian[11] to give 9 in high yield. Treatment of 9 with sodium azide in DMF gave the 6-azido derivative (10) quantitatively. Cleavage of the

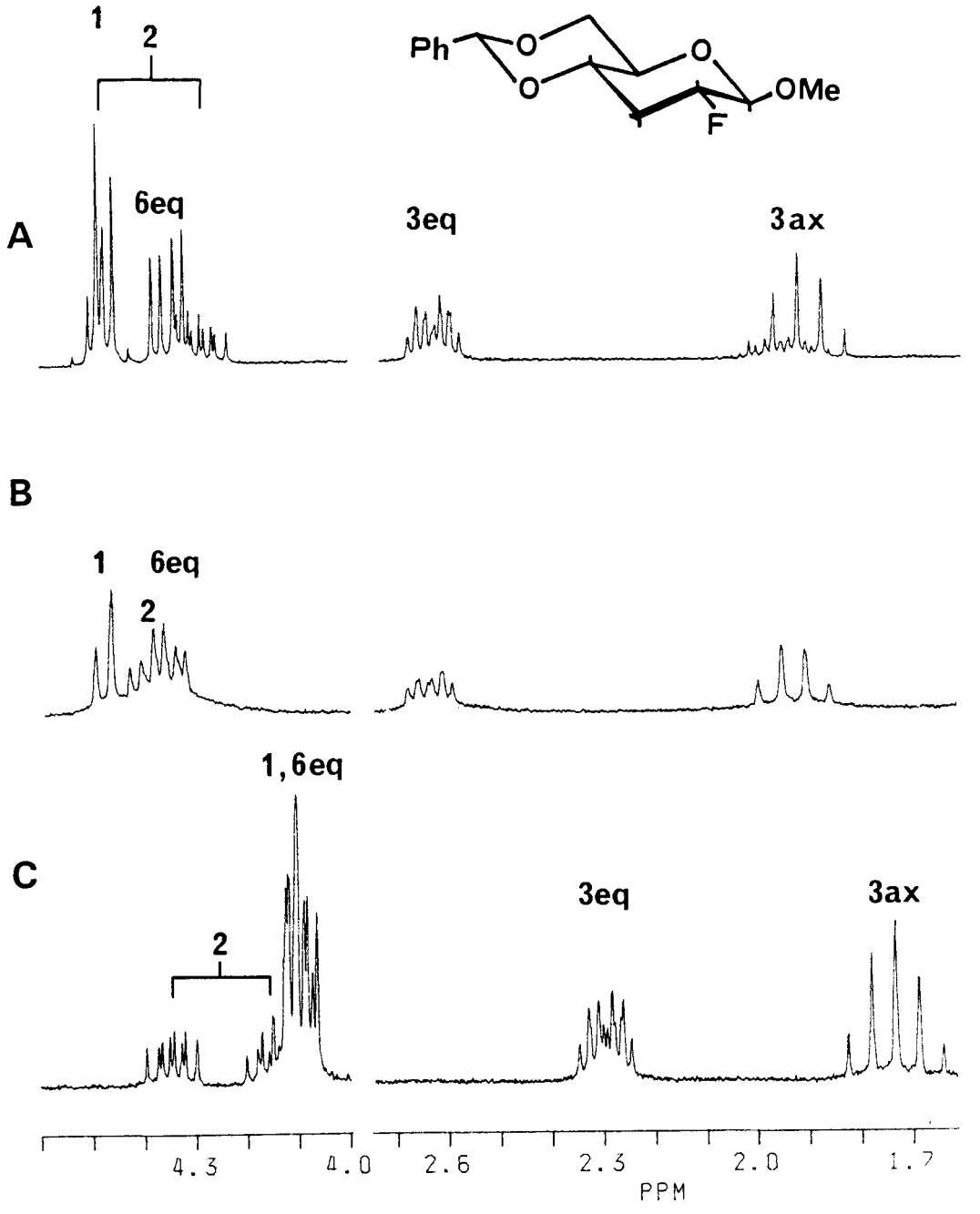


Fig. 1. The 250 MHz ^{1}H NMR spectrum of 7 in $CDCl_3$ (A), under ^{19}F broad band decoupling (B), and in C_6D_6 (C).

glycoside bond of 10 to give the free sugar (11), needed stronger acidic conditions than those used in neutral glycosides suggesting that the presence of a fluorine at C-2 strengthened the glycoside bonding. The sugar (11) was a mixture of α and β-anomers in a ratio of ~1.5:1 and gave a clear ^{1}H NMR spectrum, each signal being properly separated. Chlorination of 11 with thionyl chloride gave a mixture of α- and β-chlorides (12) in a ratio of ~1:2.6. Bromination of 11 with thionyl bromide gave the α-bromide (13) with the 6-bromo-α-bromide (14). Iodination of 13 with sodium iodide gave only the α-iodide (15). Structures of these compounds were confirmed by their ^{1}H NMR spectra (see Experimental). Thus, the β-halogenide was observed only in the chloride 12.

We will discuss here some problems of the coupling constants relating to F-2. The $J_{H-2,F-2}$ values of all compounds prepared were in the range of 47-49 Hz. Comparison of the $J_{H-1,F}$, $J_{H-3ax,F}$ and $J_{H-3eq,F}$ values of 7, 10, 11, 12, 13 and 15 indicated that, in α-D-anomers, $J_{H-1,F}$, $J_{H-3ax,F}$, and $J_{H-3eq,F}$ assumed values of 0-2, 8-9, and ~5 Hz, respectively, and in β-D-anomers (7, 10, 11, 12), $J_{3ax,F}$=11.5-13.5 Hz. However, in the β-D-anomers, the $J_{H-3eq,F}$ values changed from 5 (7), 7 (10), 7 (11) to 15 Hz (12). The large value of 12 may relate to the presence of W-conformation between electron-attractive Cl at C-1 and H-3eq. This suggests that proton-fluorine coupling sometimes is greatly influenced by the electronic environment as well as the stereochemistry.

The ^{1}H NMR spectrum of 10 measured in C_6D_6 showed that H-1 signals appeared fortuitously between those of H-2 widely separated by coupling to F-2 ($J_{H-2,F}$=48 Hz). Since $J_{1,F}$ could not be measured by the first order analysis, it was determined by simulation to be 3.5 Hz. At the same time, $J_{1,F}$ and $J_{2,F}$ were concluded to have the same sign (Fig. 2).

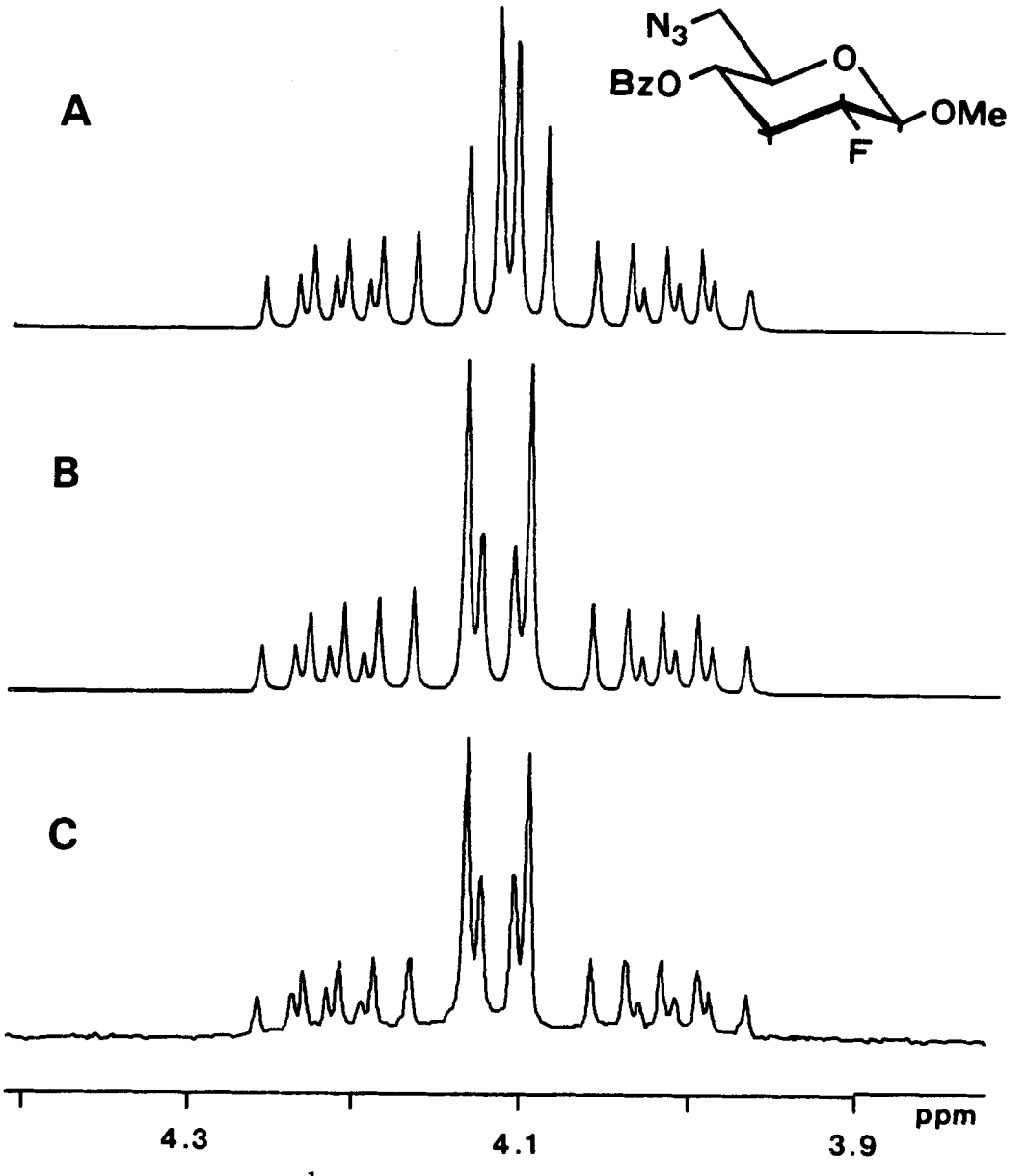
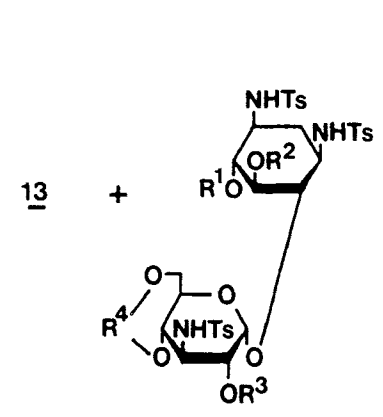


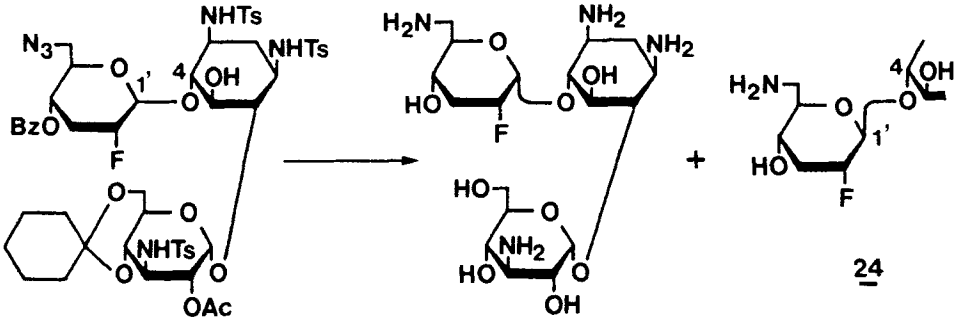
Fig. 2. The 250 MHz ^{1}H NMR spectrum of 10 at the H-1 and H-2 portion measured in C_6D_6 (C), the simulated spectrum (B) in the following parameters: H-1 (δ 4.108), H-2 (4.110), H-3ax (1.47), H-3eq (2.35), H-4 (4.71) and F (10); $J_{1,2}$=7.2, $J_{1,F}$=3.5, $J_{2,F}$= 48.0, $J_{2,3ax}$=10.5, $J_{2,3eq}$=5.2, $J_{3ax,3eq}$=-12, $J_{3ax,F}$=12.5, $J_{3eq,F}$=7.0, $J_{3ax,4}$=10.5 and $J_{3eq,4}$=5.0 Hz (changing the both signs of $J_{1,F}$ and $J_{2,F}$ gave the same pattern), and the spectum (A) by changing the $J_{1,F}$ to -3.5 Hz.

The condensation partner 19 was prepared as follows: N-Tosylation of 3AD[4] gave the tri-N-tosyl derivative (16), which led to the mono 4',6'-O-cyclohexylidene derivative (17) by treating 16 with 1,1-dimethoxycyclohexane in the presence of p-toluenesulfonic acid. Acetylation of 17 with 1-acetylimidazole in dimethylsulfoxide-pyridine gave the 2''-O-acetyl derivative (19) with a small amount of the 4,2''-di-O-acetyl derivative (20). Presence of the 4-O-acetyl group (not 5-O-acetyl) in 20 was proved by the ^{1}H shift-correlated 2D spectrum (see Experimental).

Condensation of 19 and 1-halogenide was first tried with the 1-chloride (12) in dichloromethane in the presence of



	R^1	R^2	R^3	R^4
16	H	H	H	H, H
17	H	H	H	$C(CH_2)_5$
18	$C(CH_2)_5$		H	$C(CH_2)_5$
19	H	H	Ac	$C(CH_2)_5$
20	Ac	H	Ac	$C(CH_2)_5$



21 1' – α

22 1' – β

23

24

mercury(II) cyanide. However, no glycoside formation was observed even at high temperature (100°C, 2h). When the 1-bromide (13) was used, however, 19 was successfully coupled to give α- and β-(1→4) glycoside (21, 22). To raise the yield of α-anomer (21), the Lemieux method[12] by use of 1-iodide (15) was tried, but 21 was scarcely produced. The azido groups in 21 and 22 were reduced and the N-tosyl and acyl groups were removed with sodium in liquid ammonia. The cyclohexylidene groups were then removed by acidic treatment to give the final product, 2',3'-dideoxy-2'-fluorokanamycin A (23) and its 1'-epimer (24). The structure of 23 was proved by the ^{1}H, ^{13}C, and ^{1}H and ^{1}H-^{13}C shift-correlated 2D NMR spectra (Fig. 3 and 4). Anomeric configurations at C-1' of 23 and 24 (α-D and β-D) were determined by the $J_{1',2'}$ values, and on the 1'→4-O linkage of 23, by the 2D spectrum (Fig. 4) and long-range coupling between H-1' and H-4 (Fig. 3). The magnitude of $^{3}J_{C-4',F}$ (12 Hz) also indicated[13] the antiperiplanar relationship between F-2' and C-4', supporting the structure.

Antibacterial activity of 23 was only slightly weaker than that of 3'-deoxykanamycin A. It may be emphasized that the antibacterial activity increased in the series of the following substitution at C-2': F<OH<NH_2. The 1'-epimer (24) had almost no antibacterial activity.

EXPERIMENTAL

Melting points were determined with a Kofler block and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. TLC was carried out on Kieselgel 60 F-254 (E. Merck) silica gel with detection by spraying with 50% H_2SO_4, followed by slight heating. Column chromatography was

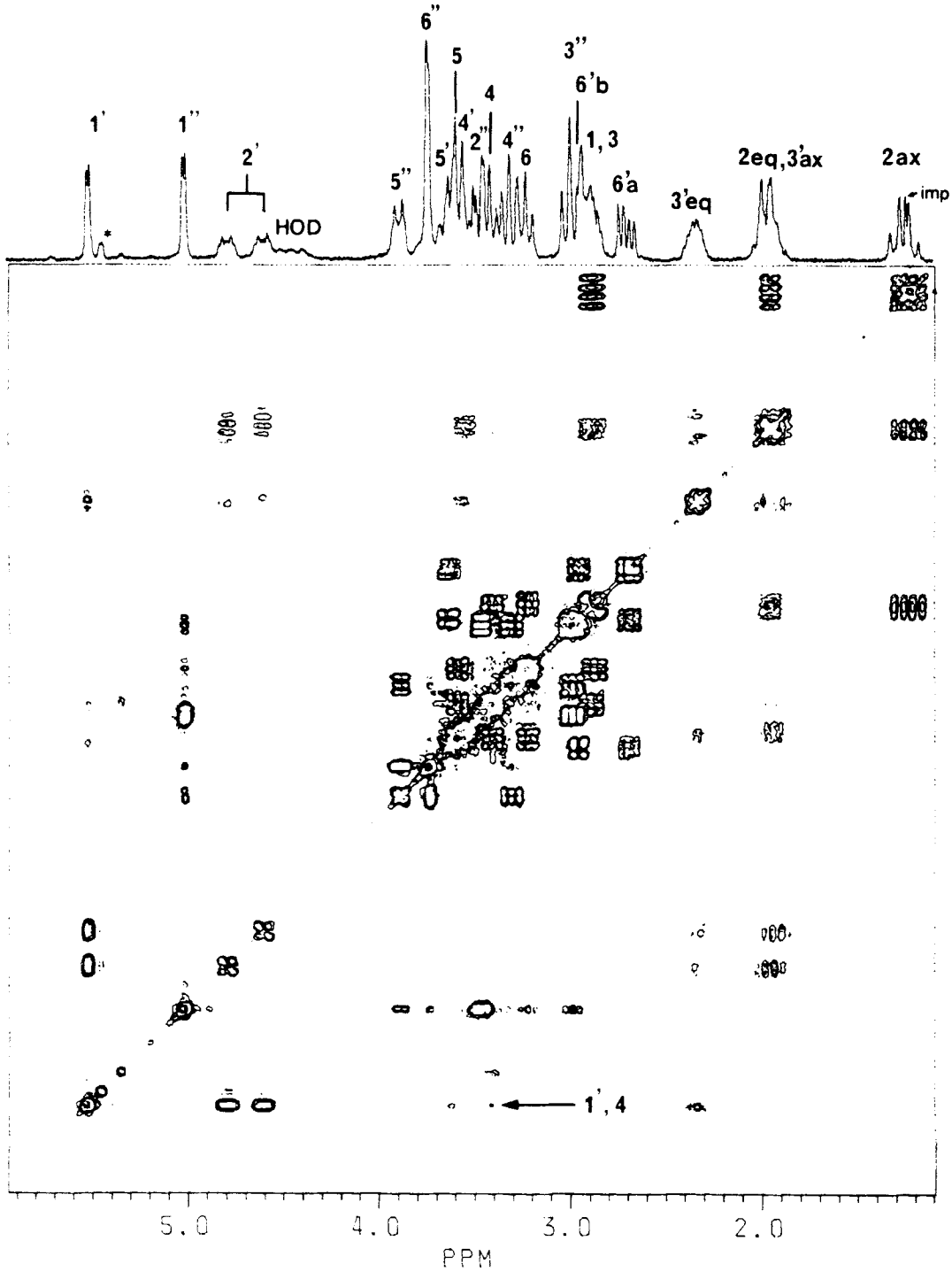


Fig. 3. The 250 MHz ^{1}H shift-correlated 2D spectrum of 2',3'-dideoxy-2'-fluorokanamycin A (23) in 20% ND_3 in D_2O (* originates from the carbonate salt).

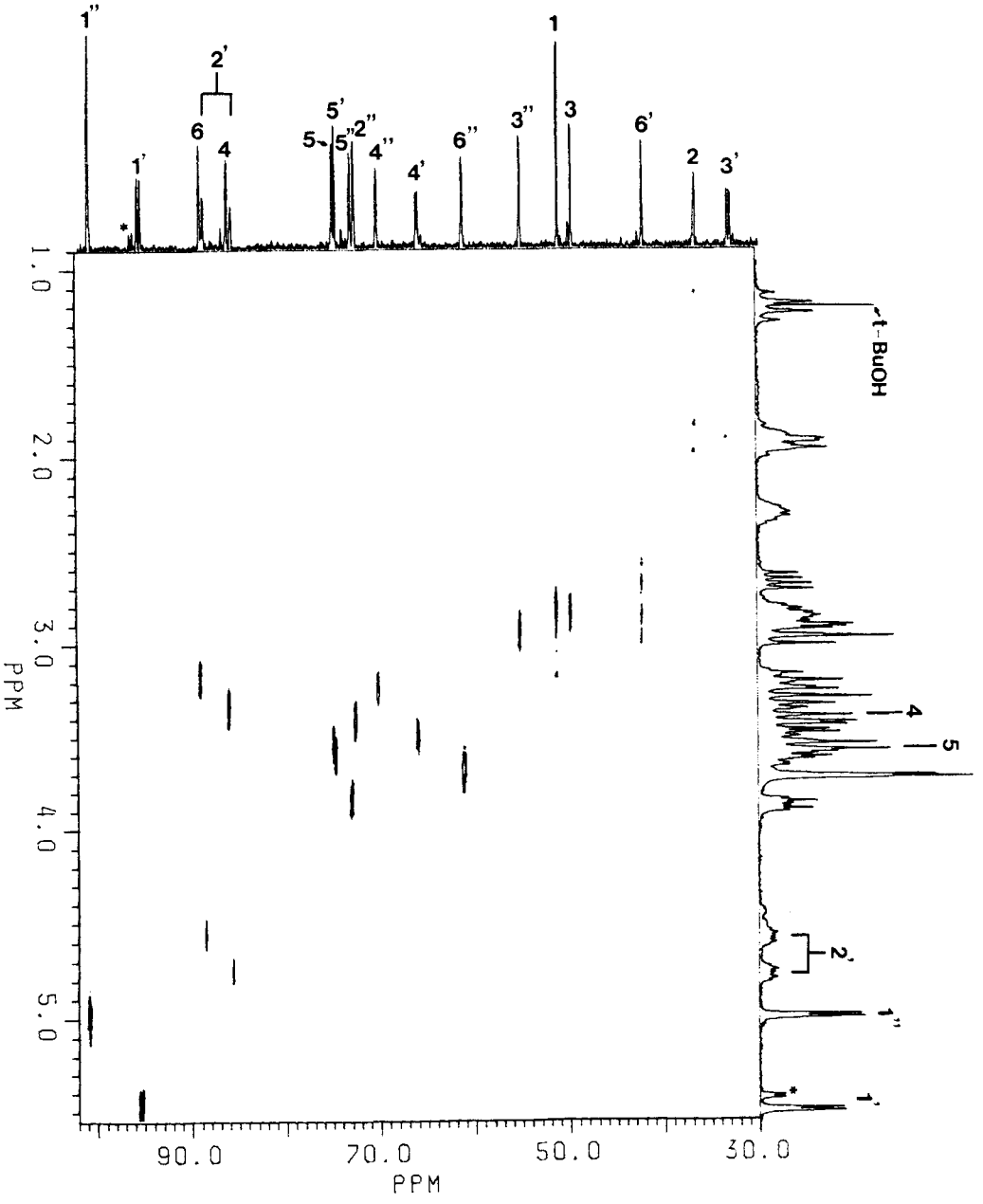


Fig. 4. The 250 MHz ^{1}H-^{13}C shift-correlated 2D spectrum of 23 in 20% ND_3 in D_2O (* originates from the carbonate salt).

performed on Wakogel C-200. IR spectra were measured with a JASCO A-202 grating spectrophotometer. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded at 250, 62.9 and 235.3 MHz respectively in the FT mode with a Bruker WM 250 spectrometer. The chemical shifts (δ by ppm) of ^{1}H, ^{13}C and ^{19}F spectra were measured downfield from internal TMS, TMS with aid of 1,4-dioxane ($\delta = \delta^{dioxane}+67.4$), and Freon 11 ($CFCl_3$) respectively unless otherwise stated.

Methyl 4,6-O-Benzylidene-3-chloro-3-deoxy-β-D-ribo-hexopyranosid-2-ulose (3). A mixture of 1 (5.00 g), pyridinium chlorochromate (10.75 g), 3Å molecular sieves (33.3 g) and dry CH_2Cl_2 (50 mL) was stirred at room temperature for 1 h. Filtration followed by concentration gave a residue, that was twice chromatographed with EtOAc to give needles of 3 as its hydrate form (3'), 4.45 g (85%), mp 93-94°C (from diethyl ether-petr. ether), $[\alpha]_D^{20}$ -32° (c 1, $CHCl_3$); positive Beilstein test for halogen. IR(KBr): no peak was observed near 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ ~3.2 (s, one of OHs at C-2 of 3'), 3.63 (s, 3H, OMe), 3.81 (hydrate form) and 3.85 (keto form) (each t, H-6ax), 4.07 and 4.30 (each dt, H-5), 4.21 and 4.09 (each dd, H-4), 4.40 and 4.52 (each dd, H-6eq), 4.45 and 4.70 (each d, H-3), 4.77 and 5.36 (each s, H-1), 5.50 and 5.53 (each s, $C_6H_5\underline{C}H$); the ratio of the hydrate and keto forms just dissolved in $CDCl_3$ was 1.5-4:1 (it seemed to change by concentration and humidity of the solvent); $J_{3,4}$=3.5 (hydrate form) and 4.0 Hz (keto form), $J_{4,5}$=9.5~10, $J_{5,6ax}=J_{6ax,6eq}$=10, $J_{5,6eq}$=5 Hz. Proton assignments were confirmed by the ^{1}H shift-correlated 2D spectrum.

Anal. Calcd for $C_{14}H_{17}ClO_6$: C, 53.09; H, 5.41; Cl, 11.19. Found: C, 53.14; H, 5.42; Cl, 11.16.

Methyl 4,6-O-Benzylidene-3-deoxy-β-D-erythro-hexopyranosid-2-ulose (4). To an ice-cold aqueous mixture (460 mL) of sodium

sodium dithionite ($Na_2S_2O_4$, 6.84 g) and $NaHCO_3$ (16.5 g) was added 2 (6.10 g) in DMF (460 mL) under nitrogen atmosphere and the mixture was stirred at room temperature for 3.5 h. TLC ($CHCl_3$-acetone=5:1) showed that a spot of R_f 0.32 (3) disappeared and R_f 0.4 (4) appeared. Concentration was followed by extraction of the residue with $CHCl_3$. The solution was washed with water, dried (Na_2SO_4), and concentrated to give needles of 4, 5.00 g (98%), mp 158-159°C (from $CHCl_3$-diethyl ether), lit.[6] 153-155°C, $[\alpha]_D^{20}$ -30° (c 1, $CHCl_3$), lit.[6] -30° ($CHCl_3$); IR(KBr): 1725 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 2.62 (dd, 1H, H-3ax), 3.04 (dd, 1H, H-3eq), 3.52 (s, 3H, OMe), 3.99 (ddd, 1H, H-4); $J_{3ax,3eq}$=15.5, $J_{3ax,4}$=12, $J_{3eq,4}$=5.5, $J_{4,5}$=9.0 Hz.

Methyl 4,6-O-Benzylidene-3-deoxy-β-D-arabino-hexo-pyranoside (5). A mixture of 4 (1572 mg) and LAH (114 mg) in oxolane (75 mL) was refluxed for 1 h. TLC ($CHCl_3$-acetone=5:1) showed two spots of R_f 0.45 (2) and 0.53 (5). Powdered $Na_2SO_4 \cdot 10H_2O$ (1.94 g) was added and, after stirring for 30 min, water (5 mL) was added and the resulting precipitate was removed by centrifugation. The precipitate was repeatedly extracted with oxolane and the combined organic solutions were concentrated. The residue was column-chromatographed with $CHCl_3$-acetone (10:1) to give needles of 2, 545 mg (34%), and 5, 985 mg (62%).

5: mp 168-169°C (from $CHCl_3$-diethyl ether), lit.[6] 171-172°C, $[\alpha]_D^{20}$ -66° (c 1, $CHCl_3$), lit.[6] -66.3° ($CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.78 (dddd, 1H, H-3ax), 2.38 (ddd, 1H, H-3eq), 2.45 (t, 1H, OH), 3.44 (dt, 1H, H-5), 3.57 (s, 3H, OMe), 3.84 (t, 1H, H-6ax), 4.31 (dd, 1H, H-6eq), 4.49 (d, 1H, H-1); $J_{1,2}$=1.2, $J_{2,3ax}$=3, $J_{2,3eq}$=4, $J_{3ax,3eq}$=13.5 Hz.

2: mp 168-169°C, lit.[14] 168-169°C, $[\alpha]_D^{20}$ -61° (c 1, $CHCl_3$), lit.[14] -60.5° ($CHCl_3$).

Methyl 4,6-O-Benzylidene-3-deoxy-2-O-trifluoromethylsulfonyl-β-D-arabino-hexopyranoside (6). To a cold (-15°C) solution

of 5 (53.3 mg) in CH_2Cl_2 (2 mL) were added pyridine (0.091 mL), and trifluoromethanesulfonic anhydride (0.05 mL) in CH_2Cl_2 (0.5 mL), and the solution was gradually warmed to room temperature (ca 1h). The solution was poured into an aqueous 5% $NaHCO_3$ and extracted with $CHCl_3$. The pale yellow solid obtained by evaporation was purified by short-column chromatography with $CHCl_3$ to give unstable needles of 6, 76.6 mg (96%), mp 102-103°C (decomp), $[\alpha]_D^{22}$ -48° (c 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 2.07 (ddd, 1H, H-3ax), 2.54 (ddd, 1H, H-3eq), 4.59 (d, 1H, H-1), 5.09 (unresolved m, 1H, H-2); $J_{1,2}$=1, $J_{2,3ax}$=3, $J_{2,3eq}$=3.5 Hz.

Anal. Calcd for $C_{15}H_{17}F_3O_7S$: C, 45.23; H, 4.30; S, 8.05. Found: C, 45.23; H, 4.41; S, 8.32.

Methyl 4,6-O-Benzylidene-2,3-dideoxy-2-fluoro-β-D-ribo-hexopyranoside (7). From 5. To an ice-cold solution of the DAST (1.1 mL) in dry pyridine-dry C_6H_6 (3:50, 27 mL) was added 5 (500 mg), and the mixture stirred at the temperature for 30 min, then at 60°C for 3h. TLC (toluene-EtOAc=5:1) showed two spots of R_f 0.55 (minor, 8) and 0.61 (7) (cf 5: R_f 0.16). The solution, after cooling, was poured into a cold aqueous $NaHCO_3$ (saturated) and, after agitation for 30 min (to destroy the DAST), the mixture was extracted with C_6H_6. The syrup (490 mg) obtained by evaporation was chromatographed with $CHCl_3$ to give needles of 7, 391 mg (78%) and 8, 28 mg (6%).

7: mp 134-135°C (from $CHCl_3$-petr. ether), $[\alpha]_D^{20}$ -57°(c 1, $CHCl_3$); ^1H NMR (C_6D_6) (see also Fig. 1): δ 1.74 (quintet, 1H, H-3ax), 2.30 (dddd, 1H, H-3eq), 2.93 (dddd, 1H, H-4), 3.05 (dt, 1H, H-5), 3.25 (s, 3H, OMe), 3.40 (t, 1H, H-6ax), 4.095 (dd, 1H, H-6eq), 4.100 (dd, 1H, H-1), 4.253 (dddd, 1H, H-2), 5.17 (s, 1H, $C_6H_5\underline{CH}$); $J_{1,2}$=7.5, $J_{2,3ax}$=11.3, $J_{3ax,3eq}$=$J_{3ax,4}$=11.5, $J_{2,3eq}$=5.5, $J_{3eq,4}$=4, $J_{4,5}$=9, $J_{5,6ax}$=$J_{6ax,6eq}$=10, $J_{5,6eq}$=4.7; $J_{1,F}$=3.5, $J_{2,F}$=49, $J_{3ax,F}$=11.5, $J_{3eq,F}$=5.0, $J_{4,F}$=1.5 Hz. The $J_{1,2}$, $J_{1,F}$, $J_{2,F}$, $J_{3,F}$, and $J_{2,3}$ were confirmed by the simulation method and ^{19}F spectrum.

Anal. Calcd for $C_{14}H_{17}FO_4$: C, 62.67; H, 6.39; F, 7.08. Found: C, 62.85; H, 6.21; F, 6.86.

8: mp 94.5-95.5°C, lit.[9] 94-95°C; $[\alpha]_D^{22}$ +36° (c 1, $CHCl_3$), lit.[15] $[\alpha]_D^{22}$ +37°; ^1H NMR ($CDCl_3$): δ 5.28 (apparently narrow quintet, 1H, J=1.5, 1.5, and 2.5 Hz, H-1) 5.69 (ddd, 1H, J=1.5, 2.5, and 10.5 Hz, H-3 or 2), 6.16 (unresolved d, 1H, H-2 or 3). Irradiation of H-1 collapsed the signals at δ 5.69 to double doublets (J=2.5 and 10.5 Hz).

From 6 and Bu_4NF-silica gel. A mixture of 6 (52.3 mg), Bu_4NF on silica gel (ca 1 mmol/g, 700 mg, Alfa Products, U.S.A.), and CH_3CN (3 mL) was stirred at room temperature for 8 h. TLC (C_6H_6) showed three spots of R_f 0.2 (8), 0.26 (7), and 0.31 (6). The mixture was extracted with $CHCl_3$ and the solution was washed with aqueous 5% $NaHCO_3$, and water, dried (Na_2SO_4), and concentrated. The residue was twice chromatographed with $CHCl_3$ to give needles of 7, 14 mg (40%), 8, 8.8 mg (27%), and 6 (14 mg) recovered.

From 6 and Spray-dried KF[10]. A mixture of 6 (52.1 mg), spray-dried KF (31 mg) and dry CH_3CN (2 mL) was refluxed for 1.5 h. TLC (C_6H_6) showed two spots of R_f 0.31 (6) and 0. Work-up in a previous manner including one chromatography gave 6, recovered, 23 mg.

From 6, Spray-dried KF, and 2,3,11,12-Dibenzo-1,4,7,10,13,16-hexaoxacyclooctadeca-2,11-diene (Dibenzo-18-crown-6). A mixture of spray-dried KF (24.0 mg), dibenzo-18-crown-6 (145 mg), and dry CH_3CN (2.5 mL) was refluxed for 10 min to give a clear solution. Compound 6 (34.5 mg) was added, and refluxing was continued for 1 h. TLC (C_6H_6) showed two spots of R_f 0.2 (8) and 0.26 (7). Work-up as described previously gave 7, 11.1 mg (48%) and 8, 8.0 mg (37%).

From 6 and CsF. A mixture of 6 (50.9 mg), CsF (130 mg, dried over CaH_2, 100°C, 3 h), and dry DMF (1 mL) was stirred at 130°C for 30 min. TLC (C_6H_6) showed spots of R_f 0.2 (8), 0.26

(7) and 0-0.1. Concentration, extraction of the residue with $CHCl_3$ and work-up as described above gave 7, 3.7 mg (11%), 8, 6.5 mg (21%), and 2, 9.3 mg (27%).

Methyl 4-O-Benzoyl-6-bromo-2,3,6-trideoxy-2-fluoro-β-D-ribo-hexopyranoside (9). A mixture of 7 (391 mg), NBS (285 mg), $BaCO_3$ (474 mg) and CCl_4 (20 mL) was refluxed for 1 h. Concentration and extraction of the residue with $CHCl_3$ gave a crude product, that was chromatographed with toluene-EtOAc (20:1) to give needles of 9, 469 mg (93%), mp 141-142°C (from $CHCl_3$-diethyl ether), $[\alpha]_D^{20}$ +5° (c 1, $CHCl_3$); positive Beilstein test for halogen; IR(KBr): 1715 cm^{-1} (ester); ^1H NMR ($CDCl_3$, under ^{19}F irradiation): δ 1.93 (q, 1H, H-3ax), 2.76 (dt, 1H, H-3eq), 3.47 (dd, 1H, H-6a), 3.60 (dd, 1H, H-6b), 3.89 (ddd, 1H, H-5), 4.45 (ddd, 1H, H-2), 4.54 (d, 1H, H-1), 5.02 (ddd, 1H, H-4); $J_{1,2}$=7.5, $J_{2,3ax}$=$J_{3ax,3eq}$=$J_{3ax,4}$=11, $J_{2,3eq}$=5 Hz; $J_{2,F}$=48 Hz.

Anal. Calcd for $C_{14}H_{16}BrFO_4$: C, 48.43; H, 4.65; Br, 23.02; F, 5.47. Found: C, 48.63; H, 4.85; Br, 23.32; F, 5.14.

Methyl 6-Azido-4-O-benzoyl-2,3,6-trideoxy-2-fluoro-β-D-ribo-hexopyranoside (10). A mixture of 9 (449 mg), NaN_3 (112 mg), and DMF (10 mL) was heated at 100°C for 30 min. TLC (C_6H_6) showed a single spot at R_f 0.35 (10) (cf 9: R_f 0.33). Concentration, followed by extraction of the residue with C_6H_6 gave a crude product, that was purified by column chromatography with $CHCl_3$ to afford a syrup of 10, 388 mg (97%), $[\alpha]_D^{20}$ -20° (c 1, $CHCl_3$); negative Beilstein test for halogen; IR(neat): 1725, 2110 cm^{-1} (N_3).

Anal. Calcd for $C_{14}H_{16}FN_3O_4$: C, 54.36; H, 5.22; F, 6.14; N, 13.59. Found: C, 54.24; H, 4.96; F, 6.17; N, 13.89.

6-Azido-4-O-benzoyl-2,3,6-trideoxy-2-fluoro-D-ribo-hexopyranose (11). A solution of 10 (128 mg) in a mixture (2.6 mL) of CF_3CO_2H and 12 N aqueous HCl (1:1) was heated at 50°C

for 1 h. TLC (toluene-EtOAc=6:1) of the solution showed a single spot (R_f 0.36). Neutralization with $NaHCO_3$ (3.0 g) followed by extraction with $CHCl_3$ gave a product, that was purified by column chromatography (toluene-EtOAc=6:1) to give a syrup of 11, 110 mg (90%), $[\alpha]_D^{20}$ +98° (c 1, $CHCl_3$); IR(neat): 1725, 2110 cm^{-1}.

^1H NMR($CDCl_3$): (the ratio of the α and β anomers was ~1.5:1) δ 1.91 (dddd, apparently quintet, 1H, H-3ax for the β-anomer), 2.25 (dq, 1H, H-3ax for the α-anomer), 2.59 [apparently sextet, 1H, H-3eq(α)], 2.81[ddt, 1H, H-3eq(β)], 3.14[d, 1H, OH-1(α)], 3.31-3.50 [two kinds of ABq, 2H in total, H-6,6'(α and β)], 3.88 [ddd, 1H, H-5(β)], 4.30 [ddd, 1H, H-5 (α)], 4.31 and 4.51 [each ddd, 0.5H, H-2(β)], 4.61 and 4.80 [each ddd, 0.5H, H-2(α)], 4.93 [ddd, 1H, $J_{1,OH}$=5 Hz, H-1(β)], 5.02 [dddd, 1H in total, H-4(α and β)], 5.44 [t, 1H, H-1(α)]; J values for the α-anomer: $J_{1,2}$=3.8, $J_{1,OH}$=3.5, $J_{2,3ax}$=12, $J_{2,3eq}$=$J_{3eq,4}$=5, $J_{3ax,3eq}$=$J_{3ax,4}$=11.5, $J_{4,5}$=10 Hz; $J_{1,3eq}$≦0.3 Hz; $J_{1,F}$=~1, $J_{2,F}$=48, $J_{3ax,F}$=9, $J_{3eq,F}$=5.5, $J_{4,F}$=1.2 Hz. J values for the β-anomer: $J_{1,2}$=7, $J_{2,3ax}$=11, $J_{3ax,4}$=11.5, $J_{2,3eq}$=$J_{3eq,4}$=5, $J_{3ax,3eq}$=12, $J_{4,5}$=10 Hz; $J_{1,F}$=3 (measured from the ^{19}F spectrum), $J_{2,F}$=49, $J_{3ax,F}$=12, $J_{3eq,F}$=7, $J_{4,F}$=1.2 Hz. Above J values were confirmed by the ^1H spectrum under ^{19}F broad band decoupling.

^{19}F NMR ($CDCl_3$): δ -190.07 and -190.27 [each ddd of equal strength, J=3, 7, 12 Hz, F-2(β-anomer)], -190.38 and -190.58 [each dd (with small splittings) of equal strength, J=5.5, 9 Hz, F-2(α-anomer)].

Anal. Calcd for $C_{13}H_{14}FN_3O_4$: C, 52.88; H, 4.78; F, 6.43; N, 14.23. Found: C, 53.05; H, 5.04; F, 6.50; N, 14.09.

6-Azido-4-O-benzoyl-2,3,6-trideoxy-2-fluoro-D-ribo-hexopyranosyl Chloride (12). A mixture of 11 (50.2 mg) and $SOCl_2$ (1 mL) was kept at room temperature overnight. TLC

(C_6H_6) of the solution showed a single spot (R_f 0.6). After evaporation, the resulting syrup was purified by column chromatography (C_6H_6) to give a syrup of 12, 48.8 mg (92%); IR(neat): 1720, 2110 cm^{-1}(N_3).

^1H NMR ($CDCl_3$): (the ratio of the α and β anomers was ~1:2.6) δ 2.03 (ddt, 1H, H-3ax for the β-anomer), 2.31 (dq, 1H, H-3ax for the α-anomer), 2.66 [ddt, 1H, H-3eq(α)], 2.88 [ddt, 1H, H-3eq(β)], 3.36-3.62 (H-6,6'), 4.00 [ddd, 1H, H-5(β)], 4.31 [ddd, apparently octet, 1H, H-5(α)], 4.55 and 4.74 [each ddd, 0.5 H, H-2(β)], 4.76 and 4.95 [each ddd, 0.5H, H-2 (α)], 5.11 [dddd, 1H, H-4(α)], 5.16 [dddd, 1H, H-4 (β)], 5.55 [dd, 1H, H-1(β)], 6.25 [d, 1H, H-1(α)]; J values for the α-anomer: $J_{1,2}$=3.8, $J_{2,3ax}$=12, $J_{2,3eq}$=$J_{3eq,4}$=5, $J_{3ax,3eq}$=$J_{3ax,4}$=11.5, $J_{4,5}$=10, $J_{5,6}$=5, $J_{5,6'}$=3 Hz; $J_{1,3eq}$≦0.5 Hz; $J_{1,F}$=0, $J_{2,F}$=48, $J_{3ax,F}$=8.5, $J_{3eq,F}$=5, $J_{4,F}$=1.5 Hz. J values for the β-anomer: $J_{1,2}$=6.5, $J_{2,3ax}$=$J_{3ax,4}$=9, $J_{2,3eq}$=$J_{3eq,4}$=5, $J_{3ax,3eq}$=13.5, $J_{4,5}$=8 Hz; $J_{1,F}$=4.5, $J_{2,F}$=48, $J_{3ax,F}$=13.5, $J_{3eq,F}$=15, $J_{4,F}$≦1 Hz.

^1H NMR under ^{19}F broad band decoupling: δ 2.03 [dt, J=9, 9, 13.5 Hz, H-3ax(β)], 2.31 [q, J=11.5, 11.5, 12 Hz, H-3ax(α)], 2.66 [dt, J=5, 5, 12 Hz, H-3eq(α)], 2.88 [dt, J=5, 5, 13.5 Hz, H-3eq(β)], 4.65 [ddd, H-2(β)], 4.85 [ddd, J=4, 5, 12 Hz, H-2 (α)], 5.55 [d, J=6.5 Hz, H-1(β)], 6.25 [d, J=3.8 Hz, H-1(α)].

6-Azido-4-O-benzoyl-2,3,6-trideoxy-2-fluoro-α-D-ribo-hexopyranosyl Bromide (13). To a solution of 11 (8.70 g) in CH_2Cl_2 (175 mL) was added $SOBr_2$ (11 mL), and the solution was kept at 30°C for 15 h. TLC (C_6H_6) showed two spots at R_f 0.6 (13) and 0.65 (slight, 14). Gradual addition of $NaHCO_3$ (200 g) followed by agitation for 1 h and extraction (CH_2Cl_2) gave a product mixture, which was subjected to column chromatography (C_6H_6) to give a syrup of 13, 6.15 g (58%) and needles of 14, 1.19 g (10%). 13: $[\alpha]_D^{20}$ +186° (c 1, $CHCl_3$); IR(neat): 1725, 2110 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 2.32 (dq, 1H, H-3ax), 2.64 (ddddd, 1H, H-3eq), AB part signals of an ABX system centered at 3.49 (2H, H-6,6'), 4.28 [ddd with small splittings ($J_{1,5} \leq 0.3$ Hz), 1H, H-5], 4.55 and 4.74 (each ddd, 0.5 H, H-2), 5.14 (dddd, 1H, H-4), 6.61 (d, 1H, H-1); $J_{1,2}$=3.8, $J_{2,3ax}$=$J_{3ax,3eq}$=$J_{3ax,4}$=11.5, $J_{2,3eq}$=4.7, $J_{3eq,4}$=5, $J_{4,5}$=10, $J_{5,6}$=5, $J_{5,6'}$=2.7, $J_{6,6'}$=13.5 Hz; $J_{1,3eq}$=1.3 Hz; $J_{1,F}$=0, $J_{2,F}$=47.5, $J_{3ax,F}$=8.3, $J_{3eq,F}$=5, $J_{4,F}$=1.4 Hz; Irradiation of H-1 sharpened all signals of H-5. ^{1}H NMR under ^{19}F broad band decoupling: δ 5.14 (ddd, 1H, J=5, 10, 11.5 Hz, H-4).

Anal. Calcd for $C_{13}H_{13}BrFN_3O_3$: C, 43.59; H, 3.66; Br, 22.31; F, 5.30; N, 11.73. Found: C, 43.29; H, 3.80; Br, 22.34; F, 5.02; N, 11.80.

14: mp 112-112.5°C, $[\alpha]_D^{22}$ +161° (c 1, $CHCl_3$); IR(KBr): no peak was observed near 2110 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.33 (H-3ax), 2.66 (H-3eq), 3.58 (2H, H-6,6'), 4.33 (H-5), 4.55 and 4.74 (each 0.5H, H-2), 5.16 (H-4), 6.61 (H-1).

Anal. Calcd for $C_{13}H_{13}Br_2FO_3$: C, 39.42; H, 3.30; Br, 40.35; F, 4.80. Found: C, 39.60; H, 3.15; Br, 40.62; F, 4.93.

6-Azido-4-O-benzoyl-2,3,6-trideoxy-2-fluoro-α-D-ribo-hexopyranosyl Iodide (15). A mixture of 13 (10 mg), NaI (21 mg) and dry acetone (0.2 mL) was stirred at room temperature for 3 h in the dark. To the resulting suspension (ppt will be NaBr) was added CH_2Cl_2 (1 mL) and the mixture was filtered. Concentration of the filtrate gave an unstable syrup of 15, having the same R_f value (0.6) on TLC (C_6H_6) with that of 13, 11.8 mg (95%). ^{1}H NMR ($CDCl_3$): δ 2.20 (dq, J=8.5, 11.5, 11.5, 11.5 Hz, H-3ax), 2.57 (ddddd, J=1.3, 5, 5, 5, 11.5 Hz, H-3eq), AB part signals of an ABX system centered at 3.49 (H-6,6'), 3.84 and 4.03 (apparently dt, J=4, 4.5, 11.5 Hz, H-2), 4.04 (apparently octet, H-5), 5.16 (dddd, H-4), 7.05 (m, H-1); On ^{19}F broad band decoupling, H-1 signals appeared as a dd

indicating $J_{1,2}$=4, $J_{1,3eq}$=1.5 and $J_{1,F}$=~2 Hz. All J values except for those relating to H-1 and H-2 were almost the same as those of 13.

2-Deoxy-6-O-(3-deoxy-3-tosylamino-α-D-glucopyranosyl)-1,3-di-N-tosylstreptamine (16). To an ice-cold solution of 3AD[4] base (15.0 g) and anhydrous Na_2CO_3 (10.0 g) in aqueous dioxane (1:1, 300 mL) was added p-toluenesulfonyl chloride (27.7 g) in small portions, and the mixture was stirred at the temperature for 2 h, then kept at room temperature overnight. Concentration gave a residue that was extracted with EtOAc. The organic solution was washed with water, dried (Na_2SO_4), and concentrated to give a solid of 16, 29.5 g (81%), $[\alpha]_D^{22}$ +21° (c 1, DMF; reprecipitated from aqueous MeOH=1:10 by addition of diethyl ether).

Anal. Calcd for $C_{33}H_{43}N_3O_{13}S_3$: C, 50.43; H, 5.51; N, 5.35; S, 12.24. Found: C, 50.42; H, 5.43; N, 5.39; S, 11.95.

6-O-(4,6-O-Cyclohexylidene-3-deoxy-3-tosylamino-α-D-glucopyranosyl)-2-deoxy-1,3-di-N-tosylstreptamine (17). To a solution of 16 (25.0 g) in DMF (300 mL) were added 1,1-dimethoxycyclohexane (5.3 mL) and p-toluenesulfonic acid (1.1 g) and the solution was stirred at 60°C for 1 h under reduced pressure (~20 mm Hg; to remove the MeOH liberated as much as possible). The solution was poured into aqueous 5% $NaHCO_3$ (2 L) and the precipitate was filtered, washed with water and dried (23.6 g). TLC ($CHCl_3$-MeOH=5:1) of the solid showed spots at R_f 0.09 (slight, 16), 0.47 (17) and 0.6 (4,5:4",6"-di-O-cyclohexylidene isomer, 18). Column chromatography ($CHCl_3$-MeOH=8:1) gave solids of 17, 16.1 g (57%) and 18, 5.7 g (19%).

17: mp 177-178°C (crystals from MeOH-H_2O), $[\alpha]_D^{23}$ +28° (c 1, DMF); ^1H NMR (pyridine-d_5): δ 2.19, 2.22, and 2.28 [each s, 3H, Ts(Me)×3], 4.22 (dd, 1H, $J_{2',3'}$=10 Hz, H-2'), 4.47 (q, 1H, H-3'), 4.58 (dt, 1H, H-5'), 5.60 (d, 1H, $J_{1',2'}$=3.8 Hz, H-1').

Anal. Calcd for $C_{39}H_{51}N_3O_{13}S_3 \cdot H_2O$: C, 52.99; H, 6.04; N, 4.75; S, 10.88. Found: C, 53.07; H, 5.92; N, 4.74; S, 10.93.

18: $[\alpha]_D^{20}$ +55° (c 1, $CHCl_3$).

Anal. Calcd for $C_{45}H_{59}N_3O_{13}S_3$: C, 57.13; H, 6.29; N, 4.44; S, 10.17. Found: C, 57.10; H, 6.31; N, 4.39; S, 9.91.

6-O-(2-O-Acetyl-4,6-O-cyclohexylidene-3-deoxy-3-tosylamino-α-D-glucopyranosyl)-2-deoxy-1,3-di-N-tosylstreptamine (19) and 4-O-Acetyl-6-O-(2-O-acetyl-4,6-O-cyclohexylidene-3-deoxy-3-tosylamino-α-D-glucopyranosyl)-2-deoxy-1,3-di-N-tosylstreptamine (20). To a solution of 17 (14.4 g) in DMSO-pyridine (9:1, 70 mL) was added 1-acetylimidazole (3.70 g, 2 mol equiv for 17) and the solution was kept at room temperature for 27 h. The solution was poured into aqueous $NaHCO_3$ (saturated, 2L) and the precipitate was washed with water, then with diethyl ether, and dried (14 g). TLC ($CHCl_3$-MeOH=8:1) of the solid showed three spots at R_f 0.2 (17), 0.32 (19), and 0.52 (20). Column chromatography ($CHCl_3$-MeOH=10:1) gave 19, 10.10 g (67%), 20, 3.70 g (23%), and 17, 1.28 g (9%).

19: $[\alpha]_D^{22}$ +68° (c 1, DMF), +4° (c 1, $CHCl_3$). ^1H NMR (pyridine-d_5): δ 2.20, 2.23, and 2.26 [each s, 3H, Ts(Me)×3], 2.44 (s, 3H, Ac), 4.70 (q, 1H, $J_{2',3'}=J_{3',4'}=J_{3',NH}=\sim$10 Hz, H-3'), 5.19 (dt, 1H, J=5.5, 10, 10 Hz, H-5'), 5.66 (dd, 1H, $J_{1',2'}=3.8$, $J_{2',3'}=10.5$ Hz, H-2'), 6.24 (d, 1H, H-1').

Anal. Calcd for $C_{41}H_{53}N_3O_{14}S_3$: C, 54.23; H, 5.88; N, 4.63; S, 10.59. Found: C, 53.94; H, 5.86; N, 4.35; S, 10.49.

20: $[\alpha]_D^{22}$ +69°(c 1, DMF), +2° (c 0.5, $CHCl_3$). ^1H NMR (pyridine-d_5): δ 1.71 (q, 1H, J=12.5, 12.5, 12.5 Hz, H-2ax), ~2.25 (H-2eq), 1.98 and 2.47 (each s, 3H, Ac×2), 2.22, 2.25, and 2.30 [each s, 3H, Ts(Me)×3], 3.73 (t, 1H, J=10, 10 Hz, H-6'ax), 3.82-4.01 (4H, H-3,5,4',6'eq), 4.06 (t, 1H, J=9.5, 9.5 Hz, H-6), 4.2 (m, 1H, H-1), 4.67 (q, 1H, H-3'), 5.05 (dt, 1H, J=5, 10, 10 Hz, H-5'), 5.34 (apparantly t, 1H, J=10, 10.5 Hz,

H-4), 5.63 (dd, 1H, $J_{1',2'}$=3.8, $J_{2',3'}$=11.5 Hz, H-2'), 6.18 (d, 1H, H-1').

^{1}H shift-correlated 2D spectrum: (arrow indicates the sequence of the coupled protons as determined by the cross peaks, not overlapped with other ones) H-1' → H-2' → H-3' → H-4' (δ=~3.9); H-4 (δ=5.34) → H-3,5 (δ=~3.9) ← 2ax,2eq → H-1. If it is assumed that the triplet at δ 5.34 is not the resonance of H-4, but H-5 (and therefore, OH-5 was acetylated), the centers of the signals of both H-4 and H-6 should come near δ 3.9. Since, however, the center of the signals of H-3 or H-1 locates at δ ~3.9 (as determined by the above sequence), and only four proton signals (including those of H-4' and H-6'eq) were found at around δ 3.9, the above assumption is concluded to be incorrect from oversaturation.

Anal. Calcd for $C_{43}H_{55}N_3O_{15}S_3$: C, 54.36; H, 5.84; N, 4.42; S, 10.12. Found: C, 54.60; H, 5.87; N, 4.31; S, 9.81.

2''-O-Acetyl-6'-azido-4'-O-benzoyl-4'',6''-O-cyclohexylidene-6'-deamino-2',3'-dideoxy-2'-fluoro-1,3,3''-tri-N-tosylkanamycin A (21) and the 1'-Epimer (22). A mixture of 13 (1.00 g), 19 (845 mg), $Hg(CN)_2$ (1.06 g), Drierite ($CaSO_4$, 2.27 g), and dry CH_2Cl_2 (2 mL) was stirred at 40°C for 49 h in the dark. TLC (C_6H_6-EtOAc=5:4) of the mixture showed major spots at R_f 0.5 (21) and 0.3 (22) with other minor spots. Addition of $CHCl_3$ (200 mL) followed by filtration with aid of Celite gave a pale brown solution, which was washed with aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated. The residue was chromatographed (C_6H_6-EtOAc=10:9) to give solids of 21, 447 mg (41%) and 22, 384 mg (34%, each based on 19).

21: $[\alpha]_D^{20}$ +5° (c 1, $CHCl_3$); IR(KBr): 1160, 1720, 2110 cm^{-1} (N_3); ^{1}H NMR (pyridine-d_5): δ 2.22, 2.27, 2.32, 2.42 (each s, 3H, Ts(Me)×3 and Ac), 5.65 (dd, 1H, $J_{1'',2''}$=3.8, $J_{2'',3''}$=10.5 Hz, H-2''), 6.12 (d, 1H, H-1''), 6.35 (d, 1H, $J_{1',2'}$=3.5 Hz, H-1').

Anal. Calcd for $C_{54}H_{65}FN_6O_{17}S_3$: C, 54.72; H, 5.53; N, 7.09; S, 8.11. Found: C, 55.11; H, 5.67; N, 6.94; S, 7.83.

22: $[\alpha]_D^{20}$ +24° (c 0.5, $CHCl_3$); IR(KBr): 1160, 1725, 2100 cm^{-1}; ^1H NMR (pyridine-d_5): δ 2.21, 2.27, 2.34, 2.45 (each s, 3H, Ts(Me)×3 and Ac), 5.52 (dd, 1H, H-1'), 5.65 (dd, 1H, H-2"), 6.22 (d, 1H, H-1"); $J_{1',2'}$=7, $J_{1',F}$=3.5, $J_{1",2"}$=3.8, $J_{2",3"}$= 10.5 Hz.

Anal. Calcd for $C_{54}H_{65}FN_6O_{17}S_3 \cdot H_2O$: C, 53.90; H, 5.61; N, 6.98; S, 7.99. Found: C, 54.00; H, 5.57; N, 6.98; S, 7.79.

2',3'-Dideoxy-2'-fluorokanamycin A (23). A solution of 21 (549 mg) in acetone was passed through a column of Sephadex LH-20 (50 mL, prewashed with acetone) with acetone, and concentrated to give pure 21. To a solution of the thoroughly dried 21 in liquid ammonia (~100 mL, -50°C) was added sodium (~700 mg) and the deep blue solution was kept at the temperature for 10 min. Addition of methanol (4 mL) until the blue color diappeared was followed by concentration. To an aqueous solution of the residue was added Amberlite CG-120 (H^+) resin (13 g). The resin, after standing at room temperature for 30 min (the cyclohexylidene group was removed), was packed in a column, washed with water, and treated with 1 N aqueous ammonia. The ninhydrin-positive fractions were concentrated to give a pale-yellow solid. An aqueous solution of the solid was chromatographed on a CM-Sephadex C-25 column (40 mL, 0→0.15 N aqueous NH_3) to afford a solid of 23 as the carbonate, 63 mg (27%), $[\alpha]_D^{20}$ +106° (c 0.5, H_2O).

^1H NMR (20% ND_3 in D_2O): δ 1.25 (q, 1H, J=12.5, 12.5, 12.5 Hz, H-2ax), 1.9-2.05 (2H, H-2eq,3'ax), 2.34 (m, 1H, H-3'eq), 2.71 (dd, 1H, J=7, 13.5 Hz, H-6'a), 2.83-2.98 (2H, H-1,3), 2.97 (dd, 1H, J=2.5, 13.5 Hz, H-6'b), 3.00 (t, 1H, J=~10, ~10 Hz, H-3"), 3.24 (t, 1H, J=9.5, 9.5 Hz, H-6), 3.32 (t, 1H, J=10, 10 Hz, H-4"), 3.43 (t, 1H, J=~9.5, ~9.5 Hz, H-4), 3.48 (dd, 1H,

J=3.8, 10.5 Hz, H-2"), 3.57 (m, 1H, H-4'), 3.61 (t, 1H, J=9.5, 9.5 Hz, H-5), 3.66 (ddd, 1H, J=2.5, 7, 9.5 Hz, H-5'), 3.75 (d, 2H, J=3.5 Hz, H-6"a,b), 3.90 (dt, 1H, J=~3.5, ~3.5, 10 Hz, H-5"), 4.62 and 4.81 (each dt, 0.5H, J=~4, ~4, 11 Hz, H-2'), 5.03 (d, 1H, $J_{1",2"}$=3.8 Hz, H-1"), 5.54 (d, 1H, $J_{1',2'}$=3.7 Hz, H-1'). Above data were confirmed by the ^{1}H shift-correlated 2D spectrum.

^{13}C NMR (20% ND_3 in D_2O; proton decoupled): δ C-1 (51.31), C-2 (36.84), C-3 (49.87), C-4 (86.31), C-5 (75.08), C-6 (89.17), C-1' (95.54, d), C-2' (87.30, d), C-3' (33.195 d), C-4' (66.155, d), C-5' (74.83), C-6' (42.35), C-1" (100.85), C-2" (72.81), C-3" (55.26), C-4" (70.45), C-5" (73.24), C-6" (61.35); $^{2}J_{C-1',F}$=20.1, $^{1}J_{C-2',F}$=182.4, $^{2}J_{C-3',F}$=17.0, $^{3}J_{C-4',F}$=120 Hz.

^{19}F NMR (20% ND_3 in D_2O; measured from Freon 11 as external reference): δ -187.79 (apparently dt, $J_{1,F}$=0, $J_{2,F}$=47.5, $J_{3ax,F}$=~8, $J_{3eq,F}$=~6 Hz, F-2).

Anal. Calcd for $C_{18}H_{35}FN_4O_9 \cdot 0.5\ H_2CO_3$: C, 44.31; H, 7.24; F, 3.79; N, 11.17. Found: C, 44.41; H, 7.40; F, 3.43; N, 10.91.

2',3'-Dideoxy-1'-epi-2'-fluorokanamycin A (24). Compound 22 (536 mg) was treated similarly as described for 23 to give a solid of 24 as the carbonate, 89 mg (39%), $[\alpha]_D^{20}$ +70° (c 0.5, H_2O).

^{1}H NMR (20% ND_3 in D_2O): δ 1.22 (q, 1H, H-2ax), 1.79 (quintet, 1H, $J_{2',3'ax}=J_{3'ax,3'eq}=J_{3'ax,4'}=J_{3'ax,F}$=11.5 Hz, H-3'ax), 1.95 (dt, 1H, J=4.0, 4.0, 12.5 Hz, H-2eq), 2.57 [apparently sextet, 1H, J=~5, ~5, ~5(=$J_{3'eq,F}$), 11.5 Hz, H-3'eq] 2.69 (dd, 1H, J=7.7, 13.8 Hz, H-6'a), 4.32 and 4.52 (each m, 0.5 H, H-2'), 4.79 (dd, 1H, $J_{1',2'}$=7.6, $J_{1',F}$=2.2 Hz, H-1'), 5.03 (d, 1H, J=3.9 Hz, H-1"); $J_{2',F}$=~50 Hz.

Anal. Calcd for $C_{18}H_{35}FN_4O_9 \cdot 0.5\ H_2CO_3 \cdot 0.5\ H_2O$: C, 43.52; H, 7.31; F, 3.72; N, 10.97. Found: C, 43.78; H, 7.55; F, 3.38; N, 10.98.

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