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# Synthesis of 3′-deoxy-3′-fluorokanamycin A* and 3′,4′-dideoxy-3′-fluorokanamycin A

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## ABSTRACT

3′-Deoxy-3′-fluorokanamycin A (**14**) has been prepared by condensation of 6-azido-2,4-di-*O*-benzyl-3,6-dideoxy-3-fluoro-α-D-glucopyranosyl bromide (**8**) and 6-*O*-(2-*O*-acetyl-4,6-*O*-cyclohexylidene-3-deoxy-3-tosylamino-α-D-glucopyranosyl)-2-deoxy-1,3-di-*N*-tosylstreptamine (**10**). Compound **8** was obtained from 3-deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-D-glucofuranose in seven steps. 3′,4′-Dideoxy-3′-fluorokanamycin A (**22**) has been prepared from **12** through selective 4′-chlorodeoxygenation, a key reaction. Both **14** and **22** were more active than 3′-deoxykanamycin A against both sensitive and resistant bacteria.

## INTRODUCTION

Kanamycins are inactivated by enzymes of resistant bacteria phosphorylating or adenylylating the 3′-, 4′-, or 2″-hydroxyl group[2,3]; among these positions, the 3′-hydroxyl group is the most frequently modified. One method for converting kanamycins into derivatives active against resistant bacteria that produce 3′-phosphoryltransferases involves removal of the 3′-hydroxyl group. Synthetic 3′-deoxykanamycin A (ref. 4), 3′,4′-dideoxykanamycin B (ref. 5, dibekacin), and other related 3′-deoxy derivatives successfully inhibit the growth of these resistant bacteria, indicating the validity of this approach. We continue to seek other derivatives more effective than the deoxy derivatives. As fluorine is less bulky than a hydroxyl group, is slightly more negative than oxygen in terms of electron density, and cannot be phosphorylated, substitution of the 3′-hydroxyl group of kanamycin by a fluorine atom may be more satisfactory than deoxygenation for obtaining derivatives having least stereochemical and electronic changes from the parent kanamycin molecule. In other words, the preparation of kanamycin analogs more closely resembling kanamycin than 3′-deoxykanamycins in structure, and not susceptible to phosphorylation, will be of interest from the antibacterial viewpoint. Here we describe the synthesis of 3′-deoxy-3′-fluorokanamycin A and 3′,4′-dideoxy-3′-fluorokanamycin A.

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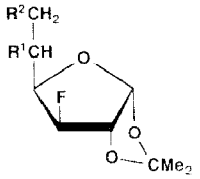
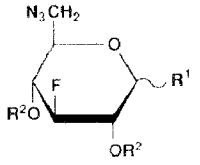
RESULTS AND DISCUSSION

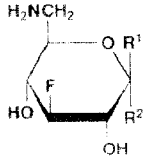
3′-Deoxy-3′-fluorokanamycin A (**14**) is here synthesized by condensation of 6-azido-2,4-di-*O*-benzyl-3,6-dideoxy-3-fluoro-α-D-glucopyranosyl bromide (**8**) and 6-*O*-(2-*O*-acetyl-4,6-*O*-cyclohexylidene-3-deoxy-3-tosylamino-α-D-glucopyranosyl)-2-deoxy-1,3-di-*N*-tosylstreptamine[6] (**10**, a protected kanamycin component). The bromide **8** was prepared from the readily obtainable 3-deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-D-glucofuranose[7] (**1**). Acid-catalyzed partial deprotection of **1** gave the 1,2-*O*-isopropylidene derivative[7] (**2**), and selective 6-*O*-tosylation of **2** (to give **3**) followed by displacement of the tosyloxy group by an azide group gave the 6-azido-3,6-dideoxy-3-fluoro derivative (**4**). Conversion of the furanosyl structure of **4** into the corresponding pyranosyl structure was performed in methanol in the presence of cation-exchange resin to give an anomeric mixture of methyl D-glycopyranosides **5**. Benzylation followed by separation of the resulting anomeric mixture (**6**) gave the syrupy α (**6α**) and crystalline β anomers (**6β**), which, respectively, were converted, by catalytic hydrogenation, into methyl 6-amino-3,6-dideoxy-3-fluoro-α- (**9α**) and -β-D-glucopyranosides (**9β**). Treatment of **6** with acetic anhydride–sulfuric acid gave an anomeric mixture of 1-acetates (**7**), the major one (**7α**) being obtained crystalline. Compound **7** was then converted into the α-1-bromide **8** by treatment with titanium tetrabromide.




| | $R^1$ | $R^2$ |
|---|---|---|
| 1 | $Me_2C(OO)$ | |
| 2 | OH | OH |
| 3 | OH | OTs |
| 4 | OH | $N_3$ |



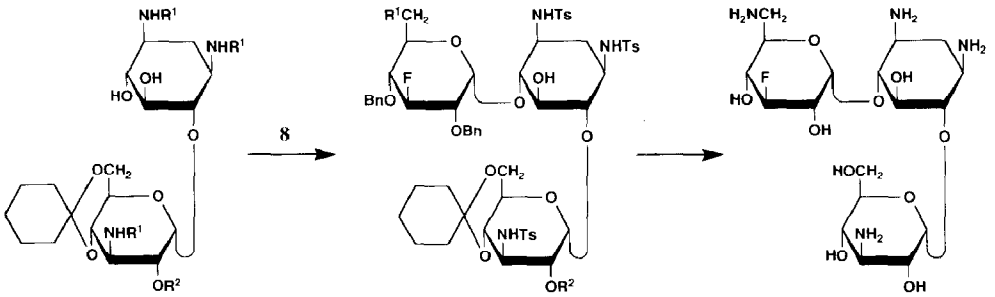

| | $R^1$ | $R^2$ |
|---|---|---|
| 5 | OMe | H |
| 6 | OMe | Bn |
| 7 | OAc | Bn |
| 8 | Br(C) | Bn |




| | $R^1$ | $R^2$ |
|---|---|---|
| 9α | H | OMe |
| 9β | OMe | H |

Coupling of **8** and **10** was performed by a Koenigs Knorr type of reaction [mercury(II) cyanide and molecular sieves in dichloromethane] to give the 4-*O*-α-D-glycoside (**12**) in 44% yield. An isomer, probably the 5-*O*-α-D analog was produced in minor amount, along with two unknown products whose structures were not pursued. The anomeric configuration of **12** was determined by the $J_{H-1,H-2}$ coupling-constant (~4 Hz) and the $J_{H-1,F}$ long-range coupling-constant (~4 Hz). The position (of the 2-deoxystreptamine portion) to which **8** was attached was determined from the coupling between H-4 and H-1′ (similar coupling between H-6 and H-1″ was also observed) in the proton-shift-correlated 2 D spectrum with enhancement of long-range effects, as well as by the $^{13}C$-n.m.r. spectrum of the final product **14**; C-4 of **14** resonated at low field (δ 88.7) indicating attachment of the sugar portion at this position. The final product,

3′-deoxy-3′-fluorokanamycin A (**14**) was prepared from **12** by treatment with sodium in liquid ammonia, followed by deacetylation, and decyclohexylidenation. In this first reaction with sodium, the 6′-azido group was reduced, and the benzyl and tosyl groups were removed simultaneously, but the yield (31%) was low. The reason was not clear, but radical reduction of the 6′-azido group of **12** by sodium was suspected to be the cause. Therefore the azido group was first reduced catalytically and then the benzyl and tosyl groups of the 6′-amino derivative **13** were cleaved with sodium. This modification improved the yield of **14** (from **12**) to 54% (total yield from **10** was 24%). Compound **14** was also prepared[1] through condensation of **8** and 6-*O*-(2-*O*-benzyl-3-benzyloxycarbonylamino-4,6-*O*-cyclohexylidene-3-deoxy-α-D-glucopyranosyl)-1,3-bis(*N*-benzyloxycarbonyl)-2-deoxystreptamine (**11**), but the total yield for this coupling and successive deprotection reactions was only 20%.



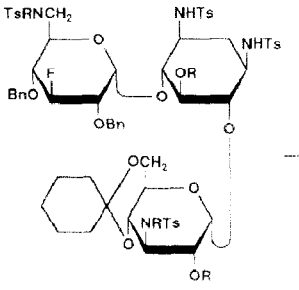

| | $R^1$ | $R^2$ |
|---|---|---|
| **10** | Ts | Ac |
| **11** | Z | Bn |

| | $R^1$ | $R^2$ |
|---|---|---|
| **12** | $N_3$ | Ac |
| **13** | $NH_2$ | H |

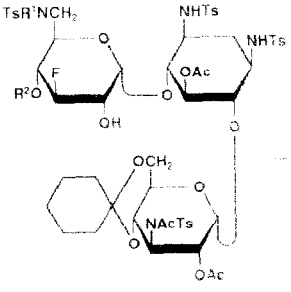
**14**

Z = $CO_2CH_2C_6H_5$
Bn = $CH_2C_6H_5$

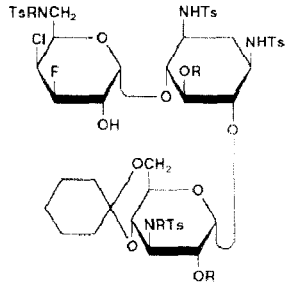
3′,4′-Dideoxy-3′-fluorokanamycin A (**22**) has been prepared in the quest for an analog of **14** active against both kinds of resistant bacteria producing 3′- and 4′-modifying enzymes. Tosylation of **13** gave the tetra-*N*-tosyl derivative **15** and acetylation of **15** with acetic anhydride in pyridine in the presence of 4-dimethylaminopyridine gave the tetraacetyl derivative **16**. As **15** has only two hydroxyl groups, two of the four acetyl groups of **16** should be attached to two of the four *N*-tosyl groups of **15**, and this was confirmed by the i.r. and $^1$H-n.m.r. spectra; the shift-values of H-6′ and H-3″ in the $^1$H-n.m.r. spectrum of **16** lie considerably to low field in comparison with those for **15**, indicating that the two acetyl groups were attached to the 6′- and 3″-amino groups. Catalytic debenzylation of **16** gave the 2′,4′-diol **17**. In this reaction, when crude **16** not purified by column chromatography was used, the catalytic debenzylation sometimes proceeded slowly to give the undesirable 4′-*O*-acetyl derivative (**18**) in large amounts through *N*→*O* acetyl migration. Treatment of **17** with sulfuryl chloride in dichloromethane–pyridine gave the 4′-chloro derivative **19** with inversion of configuration. The



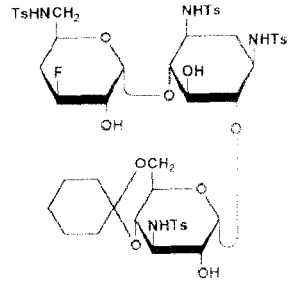

**15** R = H
**16** R = Ac



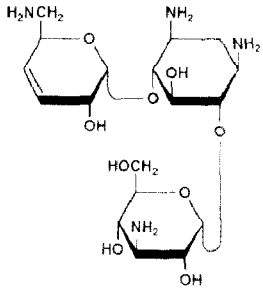

| | $R^1$ | $R^2$ |
|---|---|---|
| **17** | Ac | H |
| **18** | H | Ac |



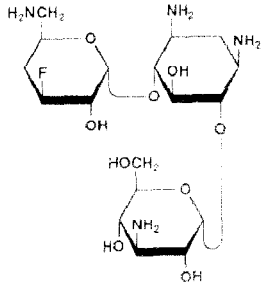

**19** R = Ac
**20** R = H




**21**




**23**




**22**

D-galactosyl structure was confirmed by the $^1$H-n.m.r. spectrum of the deacetyl product **20** (as exemplified by $J_{4',5'}$ 0). Attempts to obtain the 3′,4′-dideoxy-3′-fluoro derivative by treatment of **19** with sodium in liquid ammonia failed, and a 3′,4′-unsaturated compound was formed, together with a disaccharide derivative lacking the 4-*O*-glucose unit; by deblocking, the compounds were, respectively, converted into 3′,4′-dideoxy-3′-enokanamycin A (**23**) and 6-*O*-(3-amino-3-deoxy-α-D-glucopyranosyl)-2-deoxystreptamine[8] (**24**). Compound **20** was therefore first reduced with tributylstannane to give the 3′,4′-dideoxy-3′-fluoro derivative (**21**) in 77% yield, and then this was converted into 3′,4′-dideoxy-3′-fluorokanamycin A (**22**) by treatment with sodium in liquid ammonia in 66% yield. Compound **23** showed much lower antibacterial activity (see Experimental).

3′-Deoxy-3′-fluorokanamycin A (**14**) showed[1] stronger biological activity than did 3′-deoxykanamycin A in inhibiting the growth of both sensitive and resistant bacteria, and 3′,4′-dideoxy-3′-fluorokanamycin A (**22**) showed activies against resistant bacteria producing both 3′-phosphorylating and 4′-adenylylating enzymes.

## EXPERIMENTAL

*General methods.* — Melting points were determined on a Kofler block and are uncorrected. Optical rotations were determined with a Perkin Elmer 241 polarimeter. I.r. spectra were measured with a Jasco A-202 grating spectrophotometer. Mass spectra were measured with a Jeol SX-102 spectrometer. N.m.r. spectra ($^1$H at 250 MHz, $^{13}$C at 62.9 MHz, and $^{19}$F at 235.3 MHz) were recorded in the F.t. mode with a Bruker WM 250 spectrometer. Chemical shifts ($\delta$) for $^1$H, $^{13}$C, and $^{19}$F were measured, respectively, downfield from internal $Me_4Si$, $Me_4Si$ with the aid of 1,4-dioxane ($\delta = \delta_{1,4\text{-dioxane}} + 67.4$), and Freon 11 ($CFCl_3$), unless otherwise stated. The chemical shifts from $^1$H-n.m.r. spectra were confirmed, if necessary, by the $^1$H-shift-correlated 2 D spectra. T.l.c. was performed on Kieselgel 60 $F_{254}$ (Merck), and column chromatography on Wakogel C-200.

*3-Deoxy-3-fluoro-1,2-*O*-isopropylidene-6-*O*-tosyl-α-*D*-glucofuranose* (**3**). — To an ice-cold solution of **2** (31.6 g) in dry pyridine (600 mL) was added *p*-toluenesulfonyl chloride (32.5 g, 1.2 mol equivalents for **2**) and the solution was kept overnight at room temperature. Conventional work-up involving column chromatography (developing with 5:1 benzene–EtOAc) gave syrupy **3**; yield 41.4 g (77%), which, on crystallization from benzene–hexane, gave needles, m.p. 84.5–85°, $[\alpha]_D^{19}$ −16° (*c* 1, $CHCl_3$); $^1$H-n.m.r. ($CDCl_3$): $\delta$ 1.32 and 1.47 (each s, 3 H, $Me_2C$), 2.46 [s, 3 H, Ts (*Me*)], 2.62 (d, 1 H, OH-5), ~4.07 (H-4; the upper half signals (dd) were discerned clearly but those for the lower half were overlapped by signals of H-5 and H-6a), 4.67 (dd, 1 H, H-2); 4.97 (d, 0.5 H) and 5.17 (br s, 0.5 H) (H-3); 5.90 (d, 1 H, H-1); $J_{1,2}$ 3.8, $J_{2,3}$ 0, $J_{3,4}$ 2.2, $J_{4,5}$ 9, $J_{5,OH}$ 4.5, $J_{2,F}$ 10.5, and $J_{3,F}$ ~50 Hz; $^{19}$F-n.m.r. ($CDCl_3$): $\delta$ −209.3 (ddd).

*Anal.* Calc. for $C_{16}H_{21}FO_7S$: C, 51.06; H, 5.62; S, 8.52. Found: C, 51.14; H, 5.83; S, 8.62.

*6-Azido-3,6-dideoxy-3-fluoro-1,2-O-isopropylidene-α-D-glucofuranose* (**4**). — A mixture of **3** (33.6 g) and $NaN_3$ (6.96 g) in DMF (600 mL) was stirred for 1 h at 120°, to afford, after purification by column chromatography with 6:1 benzene–EtOAc, syrupy **4**; yield 21.7 g (98%); $[\alpha]_D^{20}$ −27° (*c* 1, $CHCl_3$); i.r. (neat): 2110 $cm^{-1}$ ($N_3$); $^1$H-n.m.r. ($CDCl_3$): $\delta$ 1.35 and 1.52 (each s, 3 H, $Me_2C$), 2.27 (d, 1 H, OH-5), 3.52 (dd, 1 H, H-6a), 3.64 (dd, 1 H, H-6b), 4.13 (ddd, 1 H, H-4), 4.71 (dd, 1 H, H-2), 5.10 (dd, 1 H, H-3), and 5.95 (d, 1 H, H-1); $J_{1,2}$ 3.8, $J_{2,3}$ 0, $J_{3,4}$ 2.2, $J_{4,5}$ 9, $J_{5,6a}$ 6, $J_{5,6b}$ 2.8, $J_{6a,6b}$ 12.5, $J_{2,F}$ 10.5, $J_{3,F}$ 50, and $J_{4,F}$ 28 Hz.

*Anal.* Calc. for $C_9H_{14}FN_3O_4$: C, 43.72; H, 5.71; F, 7.69; N, 17.00. Found: C, 43.81; H, 5.66; F, 7.64; N, 16.74.

*Methyl 6-azido-3,6-dideoxy-3-fluoro-α,β-D-glucopyranoside* (**5**). — A mixture of **4** (21.7 g) and Amberlite CG 120 ($H^+$ form, 200–400 mesh, 108 g) in methanol (650 mL) was refluxed for 40 h. Filtration followed by concentration of the filtrate gave a syrup that was purified by column chromatography (8:1 $CHCl_3$–MeOH), to give syrupy **5** as an anomeric mixture; 19.2 g (99%); $^1$H-n.m.r. ($CDCl_3$): (the ratio of the α and β anomers was ~1:1.8) $\delta$ 3.48 (s, 3 H, OMe for the α anomer), 3.59 [s, 3 H, OMe (β)], 4.26 [dd, 1 H, H-1 (β)], 4.39 [ddd, 1 H, H-3 (β)], 4.50 [ddd, 1 H, H-3 (α)], 4.84 [t, 1 H, H-1 (α)]; *J* values for the α anomer: $J_{1,2}$ 3.5, $J_{2,3}$ 8 or 9, $J_{3,4}$ 9 or 8, $J_{1,F}$ 3.5, and $J_{3,F}$ 54 Hz; β anomer: $J_{1,2}$ 8, $J_{2,3}$ 8.5 or 9, $J_{3,4}$ 9 or 8.5, $J_{1,F}$ < 1, and $J_{3,F}$ 52.5 Hz.

*Anal.* Calc. for $C_7H_{12}FN_3O_4$: C, 38.01; H, 5.47; F, 8.59; N, 19.00. Found: C, 38.26; H, 5.41; F, 8.48; N, 18.75.

*Methyl 6-azido-2,4-di-O-benzyl-3,6-dideoxy-3-fluoro-α-* and *β-D-glucopyranoside* (**6**). — An ice-cold mixture of **5** (17.35 g), benzyl chloride (27 mL), and powdered KOH (21.4 g) in DMF (350 mL) was stirred for 1 h, and then at room temperature for 1 h. T.l.c. of the solution with 1:1 benzene–$CHCl_3$ showed two spots at $R_f$ 0.27 (α anomer) and 0.38 (β anomer). Single column chromatography (1:1 benzene–$CHCl_3$) of the products gave an anomeric mixture (α:β ~1:1.74; determined by the strength of the OMe signals in the $^1$H-n.m.r. spectrum) of **6**, 30.10 g (96%).

Repeated column chromatography of the mixture permitted separation of the anomers. α Anomer (**6α**), syrup, $[\alpha]_D^{19}$ +85° (*c* 1, $CHCl_3$); $^1$H-n.m.r. ($CDCl_3$): $\delta$ 3.37 (s, 3 H, OMe), 3.38 (dd, 1 H, H-6a), 3.48 (br d, 1 H, H-6b), 3.55 (ddd, 1 H, H-4), 3.58 (ddd, 1 H, H-2), 3.75 (ddd, 1 H, H-5), 4.66 (t, 1 H, H-1), and 4.96 (dt, 1 H, H-3); $J_{1,2}$ ~4, $J_{2,3}$ = $J_{3,4}$ 9, $J_{4,5}$ 10, $J_{5,6a}$ 5.5, $J_{5,6b}$ 2.5, $J_{6a,6b}$ 13, $J_{1,F}$ ~4, $J_{2,F}$ 12.5, $J_{3,F}$ 54, and $J_{4,F}$ ~13Hz.

*Anal.* Calc. for $C_{21}H_{24}FN_3O_4$: C, 62.83; H, 6.03; F, 4.73; N, 10.47. Found: C, 62.73; H, 6.15; F, 4.55; N, 10.34.

β Anomer (**6β**), crystals (from hexane), m.p. 60–60.5°, $[\alpha]_D^{19}$ +24° (*c* 0.5, $CHCl_3$); $^1$H-n.m.r. ($CDCl_3$): $\delta$ 3.37 (dd, 1 H, H-6a), 3.47 (ddd, 1 H, H-2), 3.54 (dt, 1 H, H-4), 3.56 (s, 3 H, OMe), 4.32 (d, 1 H, H-1), and 4.65 (dt, 1 H, H-3); $J_{1,2}$ = $J_{3,4}$ = $J_{4,5}$ 8, $J_{2,3}$ 8.7, $J_{5,6a}$ 6.5, $J_{6a,6b}$ 13.5, $J_{1,F}$ 0, $J_{2,F}$ ~12, $J_{3,F}$ 51, and $J_{4,F}$ 15 Hz.

*Anal.* Found: C, 63.05; H, 6.10; F, 4.62; N, 10.48.

*Methyl 6-amino-3,6-dideoxy-3-fluoro-α-D-glucopyranoside* (**9α**). — A solution of **6α** (298 mg) in 6:1:2 1,4-dioxane–AcOH–water (13.5 mL) was hydrogenated with palladium black under one atmosphere pressure of hydrogen. T.l.c. of the solution with

2:4:5:3 $CHCl_3$–butanol–ethanol–17% aq. ammonia showed a ninhydrin-positive spot at $R_F$ 0.47. Purification of the product on a column of CM Sephadex C 25 ($NH_4^+$ form, 20 mL) with aq. ammonia (0→0.1 M) gave a solid of **9α** as its carbonate; 126 mg (75%); $[\alpha]_D^{22}$ +140° (*c* 1, $H_2O$); $^1$H-n.m.r. (20% $ND_3$ in $D_2O$ at 50°): δ 2.78 (dd, 1 H, H-6a), 3.00 (br d, 1 H, H-6b), 3.43 (s, 3 H, OMe), 3.81 (ddd, 1 H, H-2), 4.54 (dt, 1 H, H-3), and 4.83 (t, 1 H, H-1); $J_{1,2}$ 4, $J_{2,3}$ = $J_{3,4}$ 9, $J_{5,6a}$ 6.5, $J_{6a,6b}$ 13.5, $J_{1,F}$ 4, $J_{2,F}$ 13, and $J_{3,F}$ 54 Hz.

*Anal.* Calc. for $(C_7H_{14}FNO_4)_2 \cdot H_2CO_3$: C, 39.82; H, 6.68; F, 8.40; N, 6.19. Found: C, 40.15; H, 6.92; F, 8.29; N, 5.95.

*Methyl 6-amino-3,6-dideoxy-3-fluoro-β-*D*-glucopyranoside* (**9β**). — Similar treatment of **6β** (396 mg) as described for **6α** gave a solid of **9β** as its carbonate; 167 mg (75%), that had the same mobility (on t.l.c.) as **9α**; $[\alpha]_D^{22}$ −27° (*c* 1, $H_2O$); $^1$H-n.m.r. (20% $ND_3$ in $D_2O$): δ 2.76 (dd, 1 H, H-6a), 3.05 (dd, 1 H, H-6b), 3.38 (ddd, 1 H, H-5), 3.53 (ddd, 1 H, H-2), 3.58 (ddd, 1 H, H-4), 3.59 (s, 3 H, OMe), 4.40 (dt, 1 H, H-3), and 4.41 (d, 1 H, H-1); $J_{1,2}$ 8, $J_{2,3}$ = $J_{3,4}$ 9, $J_{4,5}$ ~ 10, $J_{5,6a}$ 8, $J_{5,6b}$ 2.5, $J_{6a,6b}$ 14, $J_{1,F}$ 0, $J_{2,F}$ 14, $J_{3,F}$ 53, and $J_{4,F}$ ~ 14 Hz.

*Anal.* Calc. for $(C_7H_{14}FNO_4)_2 \cdot H_2CO_3$: C, 39.82; H, 6.68; F, 8.40; N, 6.19. Found: C, 40.19; H, 7.02; F, 8.52; N, 6.27.

*6-Azido-2,4-di-*O*-benzyl-3,6-dideoxy-3-fluoro-*D*-glucopyranosyl acetate* (**7**). — To a cold (−20°) solution of **6** (28.3 g) in $Ac_2O$ (140 mL) was added $H_2SO_4$ (1.4 mL), and the solution was kept overnight at −20°. Chloroform (4 L) was added, and the solution was washed with aq. $NaHCO_3$, dried ($Na_2SO_4$), and concentrated. The resulting syrup was purified by column chromatography with $CHCl_3$ to give syrupy **7**, 25.5 g (84%), which consisted mainly of **7α** (in t.l.c. with $CHCl_3$, **7α** had $R_F$ 0.32, and **7β**, 0.2). Crystallization of the syrup from benzene–hexane gave needles of **7α**, m.p. 56.5–57°, $[\alpha]_D^{19}$ +120° (*c* 0.5, $CHCl_3$); $^1$H-n.m.r. ($CDCl_3$): δ 2.12 (s, 3 H, Ac), 3.46 (dd, 1 H, H-6a), 3.53 (dt, 1 H, H-6b), 3.68 (ddd, 1 H, H-4), 3.71 (ddd, 1 H, H-2), 3.87 (ddd, 1 H, H-5), 4.92 (dt, 1 H, H-3), and 6.31 (t, 1 H, H-1); $J_{1,2}$ 4, $J_{2,3}$ = $J_{3,4}$ 9, $J_{4,5}$ 10, $J_{5,6a}$ 4.5, $J_{5,6b}$ ~ 2, $J_{6a,6b}$ 13, $J_{1,F}$ 4, $J_{2,F}$ 12.5, $J_{3,F}$ 53, $J_{4,F}$ 13.5, and $J_{6b,F}$ ~ 2 Hz.

*Anal.* Calc. for $C_{22}H_{24}FN_3O_5$: C, 61.53; H, 5.63; F, 4.42; N, 9.78. Found: C, 61.48; H, 5.61; F, 4.15; N, 9.58.

*6-Azido-2,4-di-*O*-benzyl-3,6-dideoxy-3-fluoro-α-*D*-glucopyranosyl bromide* (**8**). — A mixture of **7** (8.00 g) and $TiBr_4$ (8.45 g) in 10:1 $CH_2Cl_2$–EtOAc (180 mL) was stirred for 40 h at room temperature. To the resulting deep-brown solution was added toluene (1 L) and anhydrous NaOAc (40 g), and the mixture was stirred for 10 h at room temperature. The resulting pale-yellow mixture was filtered and the filtrate was concentrated. The resulting syrup was purified by column chromatography with $CHCl_3$ to give a colorless syrup of **8**; 5.93 g (71%); $[\alpha]_D^{25}$ +193° (*c* 1, $CHCl_3$); i.r. (neat): 2110 $cm^{-1}$ ($N_3$); $^1$H-n.m.r. ($CDCl_3$): δ 3.48 (dd, 1 H, H-6a), 3.58 (ddd, 1 H, H-6b), 3.60 (ddd, 1 H, H-2), 3.72 (ddd, 1 H, H-4), 4.08 (dt, 1 H, H-5), 4.99 (dt, 1 H, H-3), and 6.31 (t, 1 H, H-1); $J_{1,2}$ 4, $J_{2,3}$ = $J_{3,4}$ 9, $J_{4,5}$ 10, $J_{5,6a}$ 4, $J_{5,6b}$ ~ 3, $J_{6a,6b}$ 13.5, $J_{1,F}$ 4, $J_{2,F}$ 12, $J_{3,F}$ 53, $J_{4,F}$ 14, and $J_{6b,F}$ ~ 2 Hz.

*Anal.* Calc. for $C_{20}H_{21}BrFN_3O_3$: C, 53.34; H, 4.70; Br, 17.75; F, 4.22; N, 9.33. Found: C, 53.39; H, 5.12; Br, 18.31; F, 3.89; N, 9.08.

*2″-O-Acetyl-6′-azido-2′,4′-di-O-benzyl-4″,6″-O-cyclohexylidene-6′-deamino-3′-deoxy-3′-fluoro-1,3,3″-tri-N-tosylkanamycin A* (**12**). — A mixture of **8** (3.19 g), **10** (4.93 g), $Hg(CN)_2$ (2.90 g), and powdered Drierite (8.06 g), suspended in $CH_2Cl_2$ (8 mL), was stirred for 30 min at 20°, and then for 1 h at 40°. T.l.c. (2:1:2 hexane–$CHCl_3$–acetone) then showed a main spot at $R_f$ 0.55, together with several minor spots [the spot at $R_f$ 0.48 might be the 5-*O*-α-glycosyl isomer, which showed the same $R_f$ value (0.43) as **12** in t.l.c. with 1:1 $CHCl_3$–EtOAc]. Chloroform (300 mL) was added, and the mixture was washed with 5% aq. $NaHCO_3$, dried ($Na_2SO_4$), and concentrated. The residue was purified by column chromatography (2:1:2 hexane–$CHCl_3$–acetone) to give a solid of **12**; 3.03 g (44%); $[\alpha]_D^{21}$ +25° (*c* 0.5, $CHCl_3$); i.r. (KBr): 1740 (CO) and 2110 $cm^{-1}$ ($N_3$); $^1$H-n.m.r. (pyridine-$d_5$): δ 2.22 (3 H), 2.26 (6 H), and 2.43 (3 H) [each s, Ts(*Me*) × 3 and Ac], 3.95 (t, 1 H, H-4″), 4.60 (apparent q, 1 H, H-3″), 5.32 (dt, 1 H, H-3′), 5.63 (dd, 1 H, H-2″), 6.00 (d, 1 H, H-1″), 6.02 (t, 1 H, H-1′), 6.06 (d, 1 H, *J* 5 Hz, OH-5?; disappeared on deuteration), and 9.55 (d, 1 H, NH-3″); $J_{1',2'} \sim 4$, $J_{2',3'} = J_{3',4'}$ 9, $J_{1',2''}$ 3.8, $J_{2',3''}$ 10.5, $J_{3',4'} = J_{3',NH} = J_{4',5'} \sim 10$, $J_{1',F} \sim 4$, and $J_{3',F}$ 55 Hz.

*Anal.* Calc. for $C_{61}H_{73}FN_6O_{17}S_3$: C, 57.35; H, 5.76; N, 6.58; S, 7.53. Found: C, 57.06; H, 5.81; N, 6.64; S, 7.54.

*2′,4′-Di-O-benzyl-4″,6″-O-cyclohexylidene-3′-deoxy-3′-fluoro-1,3,3″-tri-* (**13**) *and -1,3,6′,3″-tetra-N-tosylkanamycin A* (**15**). — To a solution of **12** (1.00 g) in 1,4-dioxane (20 mL) was added M aq. NaOH (20 mL) and the solution was kept for 10 min at room temperature (to give the 2″-deacetyl product). Raney nickel was added and the mixture was stirred for 30 min. One half of the volume of the mixture was withdrawn and processed conventionally to give a ninhydrin-positive, crude solid (**13**, 418 mg).

The residual half of the mixture was filtered, and, to the filtrate, was added *p*-toluenesulfonyl chloride (750 mg) and the solution was kept for 30 min at room temperature to give **15** as a solid; 505 mg (95%); m.p. 248–249° (hexane was added to a solution of **15** in 1:1 benzene–MeOH), $[\alpha]_D^{22}$ +13° (*c* 1, $CHCl_3$); $^1$H-n.m.r. (pyridine-$d_5$): δ 1.75 (q, 1 H, *J* ~13 Hz, H-2*ax*), 2.18, 2.20, 2.26, and 2.31 [each s, 3 H, Ts(*Me*) × 4], 2.77 (br d, 1 H, *J* ~13 Hz, H-2*e*), 3.09 (br t, 1 H, H-1 or 3), ~3.7 (H-3 or 1), ~3.7 (H-6′a), 4.00 (ddd, 1 H, H-6′b), 4.19 (dd, 1 H, H-2″), 4.23 (ddd, 1 H, H-4′), 4.36 (q, 1 H, H-3″), 4.79 and 4.90 (each d, 1 H, *J* 12 Hz, PhC$H_2$O), 5.13 (s, 2 H, *J* 12 Hz, PhC$H_2$O), 5.20 (apparent br d, 1 H, H-5′), 5.31 (d, 1 H, *J* 3.5 Hz, OH-5?; disappeared on deuteration), 5.42 (d, 1 H, H-1″), 5.54 (dt, 1 H, H-3′), 5.96 (t, 1 H, H-1′), 8.77 (dd, 1 H, *J* 3.5 and 9 Hz, NH-6′; disappeared on deuteration), and 9.14 (d, 1 H, NH-3″; disappeared on deuteration); $J_{1',2'} \sim 3.5$, $J_{2',3'} = J_{3',4'}$ 9, $J_{4',5'} \sim 10$, $J_{1',2''}$ 3.8, $J_{2',3''} = J_{3',4'} = J_{3',NH} \sim 9$, $J_{1',F} \sim 3.5$, $J_{3',F}$ 55, and $J_{4',F} \sim 13$ Hz.

*Anal.* Calc. for $C_{66}H_{79}FN_4O_{18}S_4$: C, 58.13; H, 5.84; N, 4.11; S, 9.40. Found: C, 58.00; H, 6.06; N, 4.35; S, 9.50.

*3′-Deoxy-3′-fluorokanamycin A* (**14**). — *(a) From* **12**. Compound **12** was purified by passing it through a column of Sephadex LH 20 with acetone to remove any radical scavenger accompanying the sample. To a solution of the purified sample (800 mg) in liquid $NH_3$ (200 mL) at −50° was added Na (~800 mg) with gentle stirring and, after 5 min, MeOH was added until the solution became colorless. Concentration then gave a

residue that was dissolved in water and neutralized with Amberlite CG 120 resin ($H^+$ form, 10 g). The resin was packed onto a column that, after washing with water, was eluted with M aq. ammonia. Ninhydrin-positive fractions were concentrated and the residue was treated with 80% aq. AcOH (20 mL; 30 min, 80°) to remove the cyclohexylidene group. The resulting product was then purified on a column of CM-Sephadex C 25 with aq. ammonia (0→0.15 M) to give **14** as a solid, as a monocarbonate; 108 mg (31%); $[\alpha]_D^{22}$ +121° (*c* 1, $H_2O$); $^1$H-n.m.r. (20% $ND_3$ in $D_2O$): $\delta$ 1.22 (q, 1 H, H-2*ax*), 1.96 (dt, 1 H, H-2*e*), 2.78 (dd, 1 H, H-6′a), ~2.9 (2 H, H-1,3), 3.00 (dd, 1 H, H-6′b), 3.01 (t, 1 H, H-3″), 3.24 (t, 1 H, H-6), 3.32 (t, 1 H, H-4″), 3.33 (t, 1 H, H-4), 3.48 (dd, 1 H, H-2″), 3.60 (ddd, 1 H, H-4′), 3.65 (t, 1 H, H-5), ~3.75 (2 H, H-6″), ~3.8 (1 H, H-5′), 3.86 (ddd, 1 H, H-2′), ~3.9 (1 H, H-5″), 4.58 (dt, 1 H, H-3′), 5.02 (d, 1 H, H-1″), and 5.38 (t, 1 H, H-1′); $J_{1,2ax}$ 12.5, $J_{1,2e}$ 4, $J_{1,6}$ 9.5, $J_{2ax,2e} = J_{2ax,3}$ 12.5, $J_{2e,3}$ 4, $J_{3,4} = J_{4,5} = J_{5,6}$ 9.5, $J_{1',2'}$ 4, $J_{2',3'} = J_{3',4'}$ 9, $J_{4',5'}$ 10, $J_{5',6'a}$ 7, $J_{5',6'b}$ 2.5, $J_{6'a,6'b}$ 14, $J_{1'',2''}$ 3.8, $J_{2'',3''} = J_{3'',4''} = J_{4'',5''}$ 10, $J_{1',F}$ 4, $J_{2',F}$ 13, $J_{3',F}$ 54, and $J_{4',F}$ 13.5 Hz; $^{13}$C-n.m.r. (20% $ND_3$ in $D_2O$): $\delta$ 36.8 (C-2), 42.5 (C-6′), 50.0 (C-3), 51.4 (C-1), 55.4 (C-3″), 61.5 (C-6″), 70.3, (d, C-4′), 70.5 (C-4″), 71.4 (d, C-2′), 72.9 (C-2″), 73.4 (C-5″), 73.6 (d, C-5′), 75.1 (C-5), 88.7 (C-4), 89.0 (C-6), 96.2 (d, C-3′), 100.7 (d, C-1′), and 101.0 (C-1″); $J_{C-1',F}$ 11, $J_{C-2',F}$ 17, $J_{C-3',F}$ 179, $J_{C-4',F}$ 17, and $J_{C-5',F}$ 7 Hz; $^{19}$F-n.m.r. (20% $ND_3$ in $D_2O$; Freon 11 as external reference) $\delta$: −199.2 (ddt, $J_{1',F}$ ~3.5, $J_{2',F}$ 13, $J_{3',F}$ 54.5, and $J_{4',F}$ 13 Hz, F-3′).

*Anal.* Calc. for $C_{18}H_{35}FN_4O_{10}\cdot H_2CO_3$: C, 41.60; H, 6.80; F, 3.46; N, 10.21. Found: C, 41.78; H, 7.13; F, 3.35; N, 10.34.

*(b) From* **13**. To a solution of **13** (126 mg) in liquid $NH_3$ (12 mL) at −55° was added Na (~120 mg), and the solution was stirred for 5 min at the temperature, and then the mixture was treated as described for (*a*) to give **14**, as a monocarbonate; yield 35 mg (54% based on **12**).

*(c) From condensation of* **8** *and* **11**. A mixture of **8** (520 mg), **11** (500 mg), $Hg(CN)_2$ (600 mg), and Drierite (1.36 g) suspended in $CH_2Cl_2$ (7 mL) was stirred overnight at 100° in a glass pressure-bottle. T.l.c. (3:1 $CHCl_3$–EtOAc) then showed several spots including $R_F$ 0.28. Successive work-up as described for **12** gave the condensation product having expected $R_F$ value; 228 mg (32%). The product (83.5 mg) was dissolved in 80% aq. AcOH (10 mL) and heated for 1 h at 80°. The decyclohexylidenated product was then hydrogenolyzed with palladium black in 20:10:1 1,4-dioxane–water–AcOH (30 mL) under one atmosphere pressure of hydrogen, and the resulting product was purified by chromatography with CM-Sephadex C 25, to give **14** as a monocarbonate; 22 mg (61%), identical with that obtained through route (*a*).

*6′,3″-Di-*N*-acetyl-5,2″-di-*O*-acetyl-2′,4′-di-*O*-benzyl-4″,6″-*O*-cyclohexylidene-3′-deoxy-3′-fluoro-1,3,6′,3″-tetra-*N*-tosylkanamycin A* (**16**). — To a solution of **15** (860 mg) in pyridine (17 mL) were added $Ac_2O$ (0.70 mL, 12 mol equivalents for **15**) and 4-dimethylaminopyridine (77 mg, 1 mol equivalent for **15**), and the solution was kept for 5 h at room temperature. T.l.c. (4:1 $CHCl_3$–EtOAc) of the solution showed one major spot at $R_F$ 0.5 together with weak spots at $R_F$ 0.36 and 0.58. Concentration gave a syrup, that was dissolved in $CHCl_3$, and the solution was washed with 5% aq. $NaHCO_3$, dried ($Na_2SO_4$), and concentrated. The residue was chromatographed with 5:1 $CHCl_3$–EtOAc

to give **16** as a slightly crude solid; 957 mg (99%); an analytical sample was prepared by further chromatography; $[\alpha]_D^{22}$ +52° (*c* 0.5, $CHCl_3$); i.r. (KBr): 1700 (NAc) and 1750 $cm^{-1}$ (OAc); $^1$H-n.m.r. (pyridine-$d_5$): $\delta$ 2.19, 2.21, 2.23, 2.27, 2.28, 2.38, 2.44, and 2.50 [each s, 3 H, Ts (*Me*) × 4 and Ac × 4], ~3.68 and ~3.82 (each 1 H, H-1 and 3), 4.08 and 4.33 (each t, 1 H, H-4 and 6), 4.53 (dd, 1 H, H-6'a), 4.70 (dd, 1 H, H-6'b), 5.00 (apparent t, 1 H, $J$ ~10 Hz, H-4''), 5.30 (dt, 1 H, H-3'), 5.33 (t, 1 H, H-3''), 5.56 (t, 1 H, H-5), 5.76 (d, 1 H, H-1''), 5.78 (t, 1 H, H-1'), 6.30 (dd, 1 H, H-2''), 7.48 (d, 1 H, $J$ 8 Hz, NH-1 or 3), and 7.76 (d, 1 H, $J$ ~4 Hz, NH-3 or 1); $J_{1,6} = J_{3,4} = J_{4,5} = J_{5,6} = 9$, $J_{1,2}$ 3.5, $J_{2,3} = J_{3,4}$ 9, $J_{5,6'a}$ 8, $J_{5,6'b}$ 3.5, $J_{6'a,6'b}$ 15.5, $J_{1',2'}$ 3.8, $J_{2',3'} = J_{3',4'}$ 10.5, $J_{3',4'}$ 3.5, and $J_{3',F}$ 54.5 Hz.

*Anal.* Calc. for $C_{74}H_{87}FN_4O_{22}S_4$: C, 58.02; H, 5.73; N, 3.66; S, 8.37. Found: C, 58.24; H, 5.87; N, 3.66; S, 8.22.

*6',3''-Di-*N*-acetyl-5,2''-di-*O*-acetyl-4'',6''-*O*-cyclohexylidene-3'-deoxy-3'-fluoro-1,3,6',3''-tetra-*N*-tosylkanamycin A* (**17**). — Compound **16** (410 mg) in 1,4-dioxane (25 mL) was hydrogenolyzed with palladium black under one atmosphere of hydrogen for 2 h at room temperature. The product was purified by chromatography (1:1 $CHCl_3$–EtOAc) to give **17** as a solid; 292 mg (80% based on **15**), $[\alpha]_D^{23}$ +38° (*c* 0.5, $CHCl_3$).

*Anal.* Calc. for $C_{60}H_{75}FN_4O_{22}S_4$: C, 53.32; H, 5.59; N, 4.15; S, 9.49. Found: C, 53.14; H, 5.86; N, 4.18; S, 9.61.

*3''-*N*-Acetyl-5,4',2''-tri-*O*-acetyl-4'',6''-*O*-cyclohexylidene-3'-deoxy-3'-fluoro-1,3,6',3''-tetra-*N*-tosylkanamycin A* (**18**). — $[\alpha]_D^{24}$ +35° (*c* 1, $CHCl_3$); $^1$H-n.m.r. (pyridine-$d_5$): $\delta$ 1.99 (3 H), 2.19 (6 H), 2.27 (3 H), 2.33 (3 H), 2.37 (6 H), and 2.50 (3 H) [each s, Ts (*Me*) × 4 and Ac × 4], 5.24, (dt, 1 H, H-3'), 5.26 (br d, 1 H, H-5'), 5.31 (t, 1 H, H-3''), 5.54 (t, 1 H, H-1'), 5.56 (d, 1 H, H-1''), 5.70 (t, 1 H, H-5), 5.79 (q, 1 H, H-4'), 6.28 (dd, 1 H, H-2''), and 8.52 (1 H, t, $J$ ~6 Hz, NH-6''); $J_{4,5} = J_{5,6}$ 9.5, $J_{1',2'}$ ~4, $J_{2',3'} = J_{3',4'} = J_{4',5'}$ ~10, $J_{1',2}$ 3.8, $J_{2',3'} = J_{3',4'}$ 10.5, $J_{1',F}$ ~4, $J_{3',F}$ 54.5, and $J_{4',F}$ ~10 Hz.

*Anal.* Calc. for $C_{60}H_{75}FN_4O_{22}S_4$: C, 53.32; H, 5.59; N, 4.15; S, 9.49. Found: C, 52.98; H, 5.70; N, 4.30; S, 9.33.

*6',3''-Di-*N*-acetyl-5,2''-di-*O*-acetyl-4'-chloro-4'',6''-*O*-cyclohexylidene-3',4'-dideoxy-4'-epi-3'-fluoro-1,3,6',3''-tetra-*N*-tosylkanamycin A* (**19**). — To a cold solution (dry ice–acetone) of **17** (1.51 g) in 2:1 $CH_2Cl_2$–pyridine (45 mL) was added $SO_2Cl_2$ (0.223 mL) and the solution was gradually warmed to room temperature (30 min) and kept for 5 h at that temperature. Addition of NaI (750 mg) in 2:1 pyridine–water (9 mL), followed by concentration gave a residue that was dissolved in $CHCl_3$ and the solution was washed with 5% aq. $NaHCO_3$, dried ($Na_2SO_4$), and concentrated to give **19** as a slightly crude solid; 1.40 g (~92%). Attempted purification by column chromatography on silica gel was unsuccessful.

*4'-Chloro-4'',6''-*O*-cyclohexylidene-3',4'-dideoxy-4'-epi-3'-fluoro-1,3,6',3''-tetra-*N*-tosylkanamycin A* (**20**). — To a solution of **19** (1.40 g) in 1,4-dioxane (20 mL) was added M aq. NaOH (20 mL) and the solution was kept overnight at room temperature. Neutralization (with aqueous HCl), concentration of the solution, extraction of the residue with EtOAc, washing the solution with water, drying, and concentration gave a residue that was purified by column chromatography with 15:1 $CHCl_3$–MeOH to give **20** as a solid; 920 mg (75%); $[\alpha]_D^{24}$ −9° (*c* 0.5, MeOH); $^1$H-n.m.r. (pyridine-$d_5$): $\delta$ 1.78 (q, 1

H, *J* 12.5 Hz, H-2*ax*), 2.16, 2.19, 2.29, and 2.38 [each s, 3 H Ts, (*Me*) × 4], 2.74 (br d, 1 H, *J* ~13 Hz, H-2*e*), 3.10 (br t, 1 H, *J* ~10.5 Hz, H-1 or 3), 4.18 (dd, 1 H, H-2″), ~4.36 (1 H, H-5″), 4.40 (q, 1 H, H-3″), 4.70 (dt, 1 H, H-2′), 5.14 (t, 1 H, H-4″), ~5.43 (1 H, H-5′), 5.44 (d, 1 H, H-1″), 5.46 (ddd, 1 H, H-3′), 5.86 (t, 1 H, H-1′), 6.36 (d, 1 H, *J* 3 Hz, OH-5?), 8.01 (br t, 1 H, *J* ~6 Hz, NH-6′), and 9.14 (d, 1 H, NH-3″); $J_{1',2'}$ 4, $J_{2',3'}$ 10, $J_{3',4'}$ 4, $J_{4',5'}$ 0, $J_{1'',2''}$ ~4, $J_{2'',3''} = J_{3'',4''} = J_{3'',NH}$ ~10, $J_{1',F}$ 4, $J_{2',F}$ ~10, $J_{3',F}$ 50, and $J_{4',F}$ 4 Hz.

*Anal.* Calc. for $C_{52}H_{66}ClFN_4O_{17}S_4$: C, 51.97; H, 5.54; Cl, 2.95; N, 4.66; S, 10.67. Found: C, 52.09; H, 5.77; Cl, 2.89; N, 4.71; S, 10.45.

*4″,6″-O-Cyclohexylidene-3′,4′-dideoxy-3′-fluoro-1,3,6,3″-tetra-*N*-tosylkanamycin A* (**21**). — Reduction of a solution of **20** (760 mg) in 1,4-dioxane (20 mL) with two additions of $Bu_3SuH$ (0.55 mL × 2) and α,α′-azobis(isobutyronitrile) (15 mg × 2; the second batches of both reagents were added after 1 h from the first addition) for 2 h at 80° gave a crude product that was purified by column chromatography by elution with $CHCl_3$ (to remove the resulting tributyltin oxide and other side products) and then with 15:1 $CHCl_3$–MeOH to give **21** as a solid; 565 mg (77%); $[\alpha]_D^{24}$ −10° (*c* 1, MeOH); $^1$H-n.m.r. (pyridine-$d_5$): δ ~2.14 (1 H, *J* ~12 Hz, H-4′*ax*), 2.16, 2.18, 2.28, and 2.35 [each s, 3 H, Ts (*Me*) × 4], 3.95 (dt, 1 H, H-2′), 5.10 (br d, 1 H, *J* 11 Hz, H-5′), 5.28 (m, 1 H, H-3′; on decoupling of $^{19}$F, the m collapsed to an imcomplete dt), 5.45 (d, 1 H, *J* 3.8 Hz, H-1″), and 5.67 (t, 1 H, H-1′); $J_{1',2'}$ ~4, $J_{2',3'} = J_{3',4'ax}$ ~10, $J_{3',4'e}$ ~6, $J_{1',F}$ ~4, $J_{2',F}$ ~10, $J_{3',F}$ ~52, and $J_{4'ax,F}$ ~12 Hz.

*Anal.* Calc. for $C_{52}H_{67}FN_4O_{17}S_4$: C, 53.50; H, 5.79; N, 4.80; S, 10.99. Found: C, 53.45; H, 5.79; N, 4.59; S, 11.02.

*3′,4′-Dideoxy-3′-fluorokanamycin A* (**22**). — Compound **21** (550 mg) was treated as described for **14** to give solid **22** as a monocarbonate; 170 mg (66%); $[\alpha]_D^{23}$ +122° (*c* 0.5, $H_2O$); $^1$H-n.m.r. (20% $ND_3$ in $D_2O$): δ 1.22 (q, 1 H, H-2*ax*), 1.61 (quintet, 1 H, H-4′*ax*), 1.96 (dt, 1 H, H-2*e*), 2.23 (dddd, 1 H, H-4′*e*), ~2.75 (2 H, H-6′), 2.80–2.95 (2 H, H-1, 3), 3.01 (t, 1 H, H-3″), 3.25 and 3.30 (each t, 1 H, H-4,6), 3.31 (t, 1 H, H-4″), 3.48 (dd, 1 H, H-2″), 3.63 (t, 1 H, H-5), ~3.75 (2 H, H-6″), 3.78 (ddd, 1 H, H-2′), 3.90 (dt, *J* 3.5, 3.5, and 10 Hz, H-5″), 4.03 (m, 1 H, H-5′), 4.85 (dddd, 1 H, H-3′), 5.02 (d, 1 H, H-1″), and 5.39 (t, 1 H, H-1′); $J_{1',2'}$ 4, $J_{2',3'}$ 9.5, $J_{3',4'ax}$ 11.5, $J_{3',4'e}$ 5.5, $J_{4'ax,4'e} = J_{4'ax,5'}$ 11.5, $J_{4'e,5'}$ ~1.5, $J_{1',F}$ 4, $J_{2',F}$ 13, $J_{3',F}$ 52.5, $J_{4'ax,F}$ 11.5, and $J_{4'e,F}$ ~5 Hz; $^{13}$C-n.m.r. (20% $ND_3$ in $D_2O$): δ 34.7 (d, C-4′), 37.0 (C-2), 45.9 (C-6′), 50.3 (C-3), 51.6 (C-1), 55.6 (C-3″), 61.6 (C-6″), 70.7 (C-4″), 70.8 (d, C-5′), 73.1 (C-2″), 73.2 (d, C-2′), 73.6 (C-5″), 75.4 (C-5), 89.1 (C-4 and 6), 91.8 (d, C-3′), 101.1 (C-1″), and 102.0 (d, C-1′); $J_{C-1',F}$ 11, $J_{C-2',F}$ 17, $J_{C-3',F}$ 175, $J_{C-4',F}$ 18, and $J_{C-5',F}$ ~11 Hz; $^{19}$F-n.m.r. (20% $ND_3$ in $D_2O$; Freon 11 as external reference): δ −187.4 (br d, $J_{3',F}$ 52.5 Hz, F-3′).

*Anal.* Calc. for $C_{18}H_{35}FN_4O_9 \cdot H_2CO_3 \cdot H_2O$: C, 41.45; H, 7.14; F, 3.45; N, 10.18. Found: C, 41.45; H, 7.17; F, 3.20; N, 9.94.

*Reduction of* **20** *with sodium in liquid ammonia.* — Treatment of **20** (98.2 mg), with Na in liquid $NH_3$ as described for **14** gave solid **23** as a monocarbonate (14.7 mg) and **24** as a monocarbonate; 7.1 mg. **23**: $^1$H-n.m.r. (20% $ND_3$ in $D_2O$): δ 1.23 (q, 1 H, H-2*ax*), 1.97 (dt, 1 H, H-2*e*), 2.74 (dd, 1 H, H-6′a), 2.80 (dd, 1 H, H-6′b), 2.85 (m, 1 H, H-3 or 1), 2.88 (ddd, 1 H, H-1 or 3), 3.01 (t, 1 H, H-3″), 3.26 (t, 1 H, H-6 or 4), 3.32 (t, 1 H, H-4″),

3.36 (t, 1 H, H-4 or 6), 3.48 (dd, 1 H, H-2″), 3.56 (t, 1 H, H-5), 3.73 (dd, 1 H, H-6″a), 3.75 (dd, 1 H, H-6″b), 3.90 (ddd, 1 H, H-5″), 4.32 (dd, 1 H, H-2′), 4.37 (ddd, 1 H, H-5′), 5.03 (d, 1 H, H-1″), 5.35 (d, 1 H, H-1′), and 5.85 (s, 2 H, H-3′,4′); $J_{1,2a}$ 12.5, $J_{1,2e}$ 4, $J_{1,6}$ 9.5, $J_{2a,2e} = J_{2a,3}$ 12.5, $J_{2e,3}$ 4, $J_{3,4} = J_{4,5} = J_{5,6}$ 9.5, $J_{1',2'}$ 3.8, $J_{2',3'} = J_{4',5'} \sim 0$, $J_{2',5'}$ 3, $J_{5',6'a}$ 6, $J_{5',6'b}$ 4, $J_{6'a,6'b}$ 13.5, $J_{1'',2''} = 3.8$ $J_{2'',3''} = J_{3'',4''} = J_{4'',5''}$ 10, $J_{5'',6''a}$ 4.5, $J_{5'',6''b}$ 2.5, and $J_{6''a,6''b}$ 12.5 Hz. F.a.b. mass spectrum: *m/z* 451 $(M + H)^+$.

*Minimal inhibitory concentration (μg/mL) of* **14, 21,** *and* **23.** Performed on Mueller–Hinton agar for 18 h at 37°; *Staphylococcus aureus* FDA 209P: 6.25, 6.25, and 50, in the foregoing order: *S. aureus* Ap01: 12.5, 6.25, and 100; *S. epidermidis* 109: 100, 25, and >100; *Bacillus subtilis* PCI219: 1.56, 1.56, and 12.5; *Escherichia coli* K-12: 1.56, 1.56, and 50; *E. coli* K-12 ML 1629: 3.12, 6.25, and >100; *E. coli* W677: 3.12, 3.12, and 50; *E. coli* JR66/W677: 100, >100, and >100; *Klebsiella pneumoniae* PCI602: 3.12, 3.12, and 100; *Proteus rettgeri* GN311: 1.56, 1.56, and 50; *Serratia marcescens*: 25, 50, and >100; *Pseudomonas aeruginosa* A3: 0.39, 1.56, and 25; *P. aeruginosa* H9: 3.12, 6.25, and >100.

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REFERENCES

1 T. Tsuchiya, Y. Takahashi, Y. Kobayashi, S. Umezawa, and H. Umezawa, *J. Antibiot.*, 38 (1985) 1287–1290.
2 S. Umezawa, *Adv. Carbohydr. Chem. Biochem.*, 30 (1974) 111–182.
3 H. Umezawa, *Adv. Carbohydr. Chem. Biochem.*, 30 (1974) 183–225.
4 S. Umezawa, T. Tsuchiya, R. Muto, Y. Nishimura, and H. Umezawa, *J. Antibiot.*, 24 (1971) 274–275.
5 H. Umezawa, S. Umezawa, T. Tsuchiya, and Y. Okazaki, *J. Antibiot.*, 24 (1971) 485–487; S. Umezawa, H. Umezawa, Y. Okazaki, and T. Tsuchiya, *Bull. Chem. Soc. Jpn.*, 45 (1972) 3624–3628.
6 T. Tsuchiya, Y. Takahashi, M. Endo, S. Umezawa, and H. Umezawa, *J. Carbohydr. Chem.*, 4 (1985) 587–611.
7 A. B. Foster, R. Hems, and J. M. Webber, *Carbohydr. Res.*, 5 (1967) 292–301; U. Reichman, K. A. Watanabe, and J. J. Fox, *Carbohydr. Res.*, 42 (1975) 233–240.
8 K. Maeda, M. Murase, H. Mawatari, and H. Umezawa, *J. Antibiot.*, 11 (1958) 163–165.