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Study on fluorination of 2,3-dideoxy-2,3-(*N*-tosylepimino)-α-D-allopyranosides, and synthesis of 3′-deoxy-3′-fluorokanamycin B and 3′,4′-dideoxy-3′-fluorokanamycin B *

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ABSTRACT

Reaction of the structurally rigid methyl 2,3-dideoxy-4,6-*O*-isopropylidene-2,3-(*N*-tosylepimino)-α-D-allopyranoside (**6**) with KHF_2 in DMF at 150° gave initially methyl 2,3-dideoxy-2-fluoro-4,6-*O*-isopropylidene-3-tosylamido-α-D-altropyranoside (**10**) by *N*-tosylepimine-ring opening, and **10** was gradually converted into the stable methyl 2,3-dideoxy-3-fluoro-4,6-*O*-isopropylidene-2-tosylamido-α-D-glucopyranoside (**11**). A reversible mechanism involving **6** and **10** has been proposed. In the mobile methyl 2,3-dideoxy-2,3-(*N*-tosylepimino)-α-D-allopyranoside (**7**) and the corresponding 4,6-di-*O*-acetyl (**8**) and -di-*O*-methyl derivatives (**9**), reactions with KHF_2 proceeded comparatively rapidly giving the corresponding 3-deoxy-3-fluoro-α-D-glucopyranosides as the major products. A slightly different reaction mechanism for the mobile compounds has been proposed. By application of this study, 3′-deoxy-3′-fluorokanamycin B was prepared by treatment of 4″,6″-*O*-cyclohexylidene-2′-deamino-3′-deoxy-3′-epi-6′-*N*-methoxycarbonyl-1,3,3″-tri-*N*-tosyl-2′,3′-(*N*-tosylepimino)kanamycin B (**21**) with KHF_2 as the key reaction. 3′,4′-Dideoxy-3′-fluorokanamycin B was also prepared. Both compounds were active against resistant bacteria producing 3′-modifying enzymes.

INTRODUCTION

In preceding papers[1–3] we described the synthesis of 3′-deoxy-3′-fluorokanamycin A obtained by a condensation method[1,2] and by derivation from kanamycin A (ref. 3); 3′-deoxy-3′-fluorokanamycin B was also prepared from kanamycin B. In connection with the former product, we also reported[3] the fluorination of 2,3-anhydro-α-D-allopyranosides with potassium hydrogenfluoride (KHF_2) in ethane-1,2-diol, whereby the corresponding 3-deoxy-3-fluoro-α-D-gluco-

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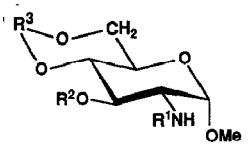
* For a preliminary communication of this work, see ref. 1.

pyranosides were obtained in preponderance over the 2-deoxy-2-fluoro-α-D-altropyranosides. This tendency does not follow the Fürst–Plattner rule, and a mechanism favoring the reaction involving the $^5H_0$ form, rather than the $^0H_5$ form, was proposed[3]. In the structurally rigid 2,3-anhydro-4,6-*O*-benzylidene-D-allopyranosides, however, nucleophiles (no data have been reported for fluorination) generally attack the C-2 position in their $^0H_5$ form to give the 2-substituted D-altropyranosides, in accordance with the Fürst–Plattner rule, possibly because of their inability to adopt the $^5H_0$ form. This paper presents some studies on the fluorination of 2,3-*allo*-epimines by ring-opening. Hough and his coworkers[4], and Baer and Jaworska-Sobiesiak[5] have demonstrated that treatment of rigid methyl 2,3-(*N*-benzoylepimino)-4,6-*O*-benzylidene-2,3-dideoxy-α-D-allopyranoside with tetrabutylammonium fluoride gave the corresponding 3-benzamido-2,3-dideoxy-2-fluoro-α-D-altropyranoside along with a slight amount of the 2-benzamido-2,3-dideoxy-3-fluoro-α-D-glucopyranoside (preponderant formation of the *altro* isomer was also reported[6] in the corresponding benzyl glycoside). In the case of methyl 4,6-*O*-benzylidene-3-diallylamino-3-deoxy-2-*O*-mesyl-α-D-altropyranoside, treatment with $Et_3N \cdot 3HF$ gave[7] exclusively the corresponding 3-diallylamino-2,3-dideoxy-2-fluoro-α-D-altropyranoside through the 2,3-*allo*-aziridinium ion intermediate[8]. These results suggest that the rigid 2,3-*allo*-epimines open the ring according to the Fürst–Plattner rule as encountered in the rigid 2,3-*allo*-epoxides[3]. In the present study we describe the behavior of some rigid and mobile 2,3-*allo*-*N*-tosylepimines with KHF_2. The choice of the *N*-tosylepimine rather than other *N*-substituted epimines was based on the expectation that an *N*-tosyl group will facilitate the epimine-ring opening more strongly than other groups. One of the purposes of this study was to compare the behavior in ring-opening of a 2,3-*allo*-epoxide[3] and the 2,3-*allo*-*N*-tosylepimine with the same fluorinating agent (KHF_2). Based on the results of this study we have prepared 3′-deoxy-3′-fluorokanamycin B from kanamycin B.

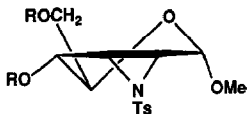
RESULTS AND DISCUSSION

Methyl 2,3-dideoxy-4,6-*O*-isopropylidene-2,3-(*N*-tosylepimino)-α-D-allopyranoside (**6**) and its parent 4,6-diol **7** were chosen as the models of rigid and mobile compounds for fluorination. They were prepared from methyl 2-deoxy-2-(methoxycarbonylamino)-α-D-glucopyranoside (**1**). The 4,6-isopropylidene acetal **2** of **1** was de(methoxycarbonyl)ated to give **3**, which was *N*-tosylated to give **4**, and further tosylated to give the *N*,*O*-ditosyl derivative **5**. This was then converted into the *N*-tosylepimine **6** by treatment with methanolic NaOH. Deacetonation of **6** gave the mobile *N*-tosylepimine **7**.

In preliminary experiments, compound **6** was treated with KHF_2 in solvents such as ethane-1,2-diol[3], acetonitrile, nitromethane, dimethyl sulfoxide, and *N*,*N*-dimethylformamide (DMF) at various temperatures, and it was found that the use of DMF at ~ 150° gave the best yields of deoxyfluoro products. After 5 h under



	R^1	R^2	R^3
1	CO_2Me	H	H, H
2	CO_2Me	H	CMe_2
3	H	H	CMe_2
4	Ts	H	CMe_2
5	Ts	Ts	CMe_2



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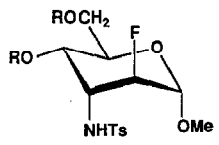
7 R= H
8 R= Ac
9 R= Me



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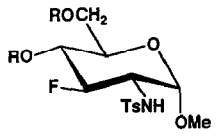
13 R= Ac
15 R= Me



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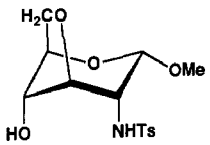
12 R= H
14 R= Ac
16 R= Me



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these conditions, methyl 2,3-dideoxy-2-fluoro-4,6-*O*-isopropylidene-3-tosylamido-α-D-altropyranoside (**10**, 35%) and methyl 2,3-dideoxy-3-fluoro-4,6-*O*-isopropylidene-2-tosylamido-α-D-glucopyranoside (**11**, 10%) were obtained, and 22% of **6** was recovered. The ^{13}C-NMR data of these and related compounds are shown in Table I. After a reaction time of 168 h, however, the starting material was all consumed, and **11** was the major product (33%) whereas **10** had disappeared. In another experiment, the isolated 2-deoxy-2-fluoro-D-altroside **10** was treated similarly with KHF_2 for 6 h at 150°, whereby **6**, **10**, and **11** were obtained in yields of 11, 83, and 3%, respectively, and after a further 145 h, **11** became the major product (35%) and **6** and **10** were no longer detected. These results suggest that the D-altroside **10** was produced first and was then gradually converted into the stable D-glucoside **11**.

To ascertain the mechanism, further experiments were carried out to determine precisely the change of the product ratio (**6** : **10** : **11**) with time, starting from **6** (and also **10**); this was done by measuring the strengths of the *O*-methyl and fluorine signals of the product mixtures in their ^{1}H- and ^{19}F-NMR spectra on the samples obtained after minimum purification-procedures required for the measurements.

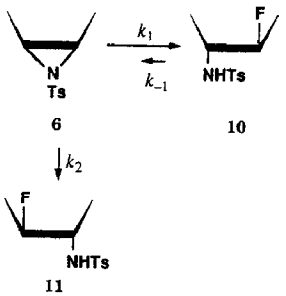
TABLE I

^{13}C-NMR chemical shifts [a] (δ [b], ppm) and coupling constants ($J_{C,F}$, Hz) for **6**, **8**, **9** (in $CDCl_3$) and **10–13** (in pyridine-d_5).

	Compound						
	6	**8**	**9**	**10**	**11**	**12**	**13**
C-1	94.09	93.43	93.62	98.98d	100.84d	100.17d	99.22d
C-2	40.33	41.93	42.57	90.09d	57.50d	57.44d	89.02d
C-3	39.74	38.76	38.39	52.24d	89.99d	94.43d	52.07d
C-4	67.86	64.74	71.02	66.90	73.40d	69.61d	66.10
C-5	61.40	64.70	66.96	60.43	63.33d	73.68d	66.54
C-6	62.34	62.42	70.89	62.63	62.42	61.69	63.10
O*Me*-1	55.78	55.82	55.65	55.04	55.36	55.11	55.42
Ts(*Me*)	21.61	21.59	21.63	21.14	21.18	21.17	21.13
C*Me*$_2$	18.99, 28.84			18.94, 29.10	19.21, 29.26		
*C*Me$_2$	99.96			100.06	100.03		
Other signals		20.27, 20.68 (*Me*CO)	56.70, 59.30 (O*Me*)				20.44, 20.51 (*Me*CO)
$J_{1,F}$				32.8	8.9	9.3	31.6
$J_{2,F}$				176.0	17.2	16.9	178.1
$J_{3,F}$				27.6	189.6	184.5	26.7
$J_{4,F}$					16.7	17.6	
$J_{5,F}$					7.4	7.2	

[a] Confirmed by the ^{13}C–^{1}H correlation method. [b] Internal Me_4Si.

The result (from **6**) obtained (Fig. 1) showed good agreement with calculations based on the assumption that the overall reaction involves reversible and concurrent reactions (see Scheme 1) and not two successive reactions (**6** → **10** and **10** → **11**). The details are described next. Although the reaction rate of **6** and KHF_2 is considered to be proportional to the product of the concentrations of both **6** and the reagent, the concentration of F^- (or HF_2^-) in DMF always remains constant during the reaction period because of saturation of KHF_2 in the solvent due to low solubility (10 mg/mL at 150°), and the system can, therefore, be practically expressed as a mixture of three first-order reactions. (The rate-con-



6 10 11

Scheme 1.

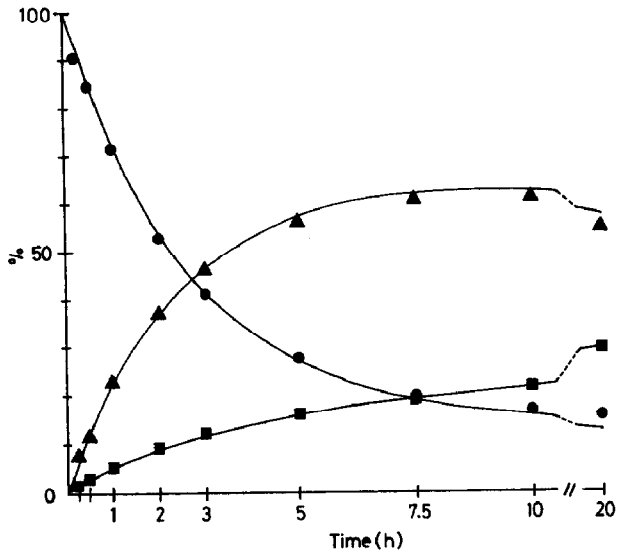


Fig. 1. A solution of **6** (100 mg) and KHF_2 (42 mg) in DMF (2 mL) was heated for a given time at 150° and after cooling, $NaHCO_3$ (230 mg) and water (3.3 mL) were added. Thorough shaking followed by concentration gave a residue that was dissolved in $CHCl_3$ (10 mL), and the solution was washed once with aq satd $NaHCO_3$ solution (5 mL), dried (Na_2SO_4), and concentrated. The residue was dissolved in $CDCl_3$ (0.7 mL) and the ratio of the strength of the OMe-signals (by ^{1}H-NMR) for **6** (δ 3.38), **10** (δ 3.42), and **11** (δ 3.32), and that of the ^{19}F-signals (by ^{19}F-NMR) for **10** (δ −188.5) and **11** (δ −196.6) were measured. Almost no discrepancy was observed for the ratio of **10**:**11** obtained from the ^{1}H- and ^{19}F-NMR spectra. For the yield in this figure, the total yield of the three products were always taken as 100 (%) (that is, $[\mathbf{6}]_0 = 100$ and $[\mathbf{6}]+[\mathbf{10}]+[\mathbf{11}] = 100$) without consideration of by-products. ●, ▲, and ■ are the values for **6**, **10**, and **11** obtained experimentally, and plain lines are the computed lines based on Eqs. *4*, *5*, and *6*, in which k_1, k_{-1}, and k_2 are taken as 0.27, 0.07, and 0.06, respectively.

stants for **6** → **10**, **10** → **6**, and **6** → **11** are denoted as k_1, k_{-1}, and k_2, respectively). Thus the rates of these reactions are

$$-\frac{d[\mathbf{6}]}{dt} = (k_1 + k_2)[\mathbf{6}] - k_{-1}[\mathbf{10}] \quad (1)$$

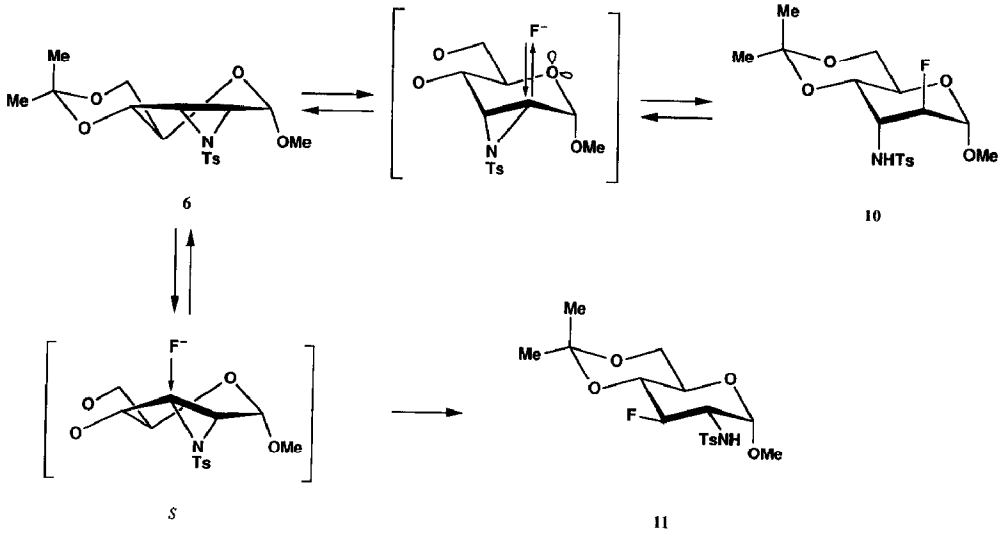
$$\frac{d[\mathbf{10}]}{dt} = k_1[\mathbf{6}] - k_{-1}[\mathbf{10}] \quad (2)$$

$$\frac{d[\mathbf{11}]}{dt} = k_2[\mathbf{6}] \quad (3)$$

Integration utilizing operational calculus with input of the initial conditions (at time $t = 0$: $[\mathbf{6}] = [\mathbf{6}]_0$ and $[\mathbf{10}] = [\mathbf{11}] = 0$) gave solutions for [**6**], [**10**], and [**11**]:

$$[\mathbf{6}] = \frac{[\mathbf{6}]_0}{2R}\left[(R - (k_1 - k_{-1} + k_2))\, e^{pt} + (R + (k_1 - k_{-1} + k_2))\, e^{qt}\right] \quad (4)$$

$$[\mathbf{10}] = \frac{k_1[\mathbf{6}]_0}{R}(e^{pt} - e^{qt}) \quad (5)$$



Scheme 2.

$$[\mathbf{11}] = [\mathbf{6}]_0\left(1 - \frac{R + (k_1 + k_{-1} - k_2)}{2R}e^{pt} - \frac{R - (k_1 + k_{-1} - k_2)}{2R}e^{qt}\right) \qquad (6)$$

where $R = [(k_1 + k_{-1} + k_2)^2 - 4k_{-1}k_2]^{1/2}$, $p = [-(k_1 + k_{-1} + k_2) + R]/2$, $q = [-(k_1 + k_{-1} + k_2) - R]/2$, and t is time (h) (a similar reaction system has been reported[9]).

Good agreement between the experimental and calculated values was observed when comparative rate constants were k_1 0.27, k_{-1} 0.07, and k_2 0.06, determined by computer simulation. Slight deviations from the calculated lines for the values at prolonged times suggest that the decompositions of **6**, **10**, and **11** did not occur proportionally to the fluorination rate-constants.

Compound **10** was also treated similarly, to give an expected time–yield pattern in good accordance with the calculated values *: $t = 0$, **6**:**10**:**11** = 0:100:0; $t = 1$ h, 7:93:0 (calcd: 6:94:0); $t = 5$ h, 13:85:2 (15:82:3); $t = 10$ h, 13:81:6 (16:76:8).

These results suggest that the whole reaction pathway is that shown in Scheme 2. Characteristic features are that (*a*) the fluorine atom is first introduced at C-2 (to give **10**) in spite of the expected, electrostatic repulsion[3] between the fluoride

* $[\mathbf{6}] = \frac{k_{-1}[\mathbf{10}]_0}{R}(e^{pt} - e^{qt})$

$$[\mathbf{10}] = \frac{[\mathbf{10}]_0}{2R}\left[(R + k_1 - k_{-1} + k_2)\,e^{pt} - (k_1 - k_{-1} + k_2 - R)\,e^{qt}\right]$$

$$[\mathbf{11}] = [\mathbf{10}]_0\left(1 - \frac{R + (k_1 + k_{-1} + k_2)}{2R}e^{pt} - \frac{R - (k_1 + k_{-1} + k_2)}{2R}e^{qt}\right)$$

ion approaching at C-2 and the axial lone-pair electrons of the pyranoid-ring oxygen *, (*b*) the D-altroside **10** formed reverts to the starting material **6** under equilibrium, and (*c*) **6** converts gradually into the stable **11**, possibly through the *S* conformation shown. Direct conversion of **10** into **11** does not occur. It is surprising that the supposedly strong C–F bond of **10**, once formed, is split by participation of the neighboring tosylamido group to afford **6**. In this reaction, the presence of an *N*-tosyl group appears to be essential, although the possibility of participation by other groups (such as the *N*-methoxycarbonyl group) is now under study.

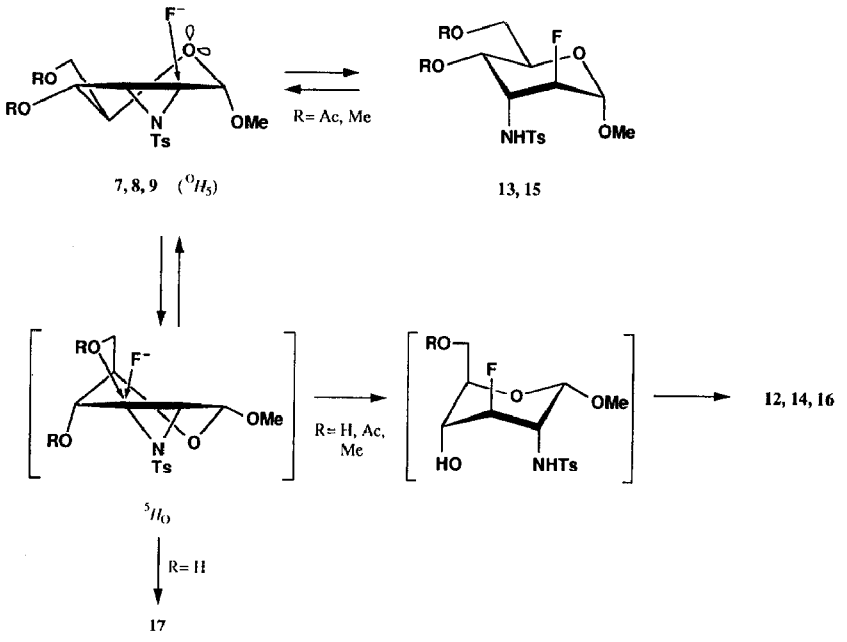
The non-rigid (mobile) *N*-tosylalloepimine **7** was examined next. In this case, **7** was rapidly converted into methyl 2,3-dideoxy-3-fluoro-2-tosylamido-α-D-gluco-pyranoside (**12**) and the 3,6-anhydride **17** within 3 h, and **12** was the only fluorination product observed during the 0.5–3-h reaction period. Rapid formation of **12** and no formation of the corresponding 2-deoxy-2-fluoro-α-D-altropyranoside suggested that the reaction system is slightly different from that of **6**; possibly the products (**12** and **17**) were produced by way of the $^5H_0$ (D) form (see Scheme 3). The structure of **17** was decided on the basis of its NMR spectrum (small $J_{2,3}$ and $J_{4,5}$ values and the presence of coupling between H-2 and N*H*Ts; see Experimental).

Other mobile compounds, methyl 4,6-di-*O*-acetyl-2,3-dideoxy-2,3-(*N*-tosyl-epimino)-α-D-allopyranoside (**8**) and the corresponding 4,6-di-*O*-methyl derivative **9** were also examined. In these cases, slightly longer reaction periods than for **7** were required to complete the reactions, and 3-deoxy-3-fluoro-D-*gluco* derivatives (**14** and **16**) were produced simultaneously with the corresponding 2-deoxy-2-fluoro-D-*altro* derivatives (**13** and **15**). It was further observed that the D-*altro* compound **13** or a 2:3 mixture of **15** and **16** was converted into the D-*gluco* compound **14** or a 1:10 mixture of **15** and **16**, respectively, after a 50-h reaction. These results suggest that the 2-deoxy-2-fluoro-D-*altro* compounds, once formed, are converted into 3-deoxy-3-fluoro-D-*gluco* compounds in a manner similar to that described for **6** (see Scheme 3).

In summary, these studies have shown that *N*-tosyl-2,3-*allo*-epimines, on treatment with KHF_2, give mixtures of 2-deoxy-2-fluoro-α-D-*altro* and 3-deoxy-3-fluoro-α-D-*gluco* compounds, but the former are gradually converted into the latter by way of reversion to the starting epimines. This kind of reversible mechanism was not observed in the structurally related 2,3-*allo*-epoxides[3].

This method of fluorination was then applied for the synthesis of 3′-deoxy-3′-fluorokanamycin B (**23**), a kanamycin analogue which, because of its lack of an

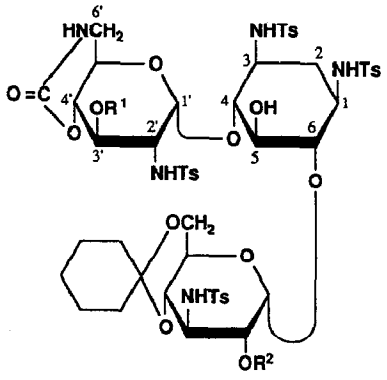
* In an equilibrium system [such as **6** and *S* (Scheme 2), or $^0H_5$ and $^5H_0$ (Scheme 3)], in that the constituting two conformers have no large energy difference but give different products [**6** → **10** and *S* → **11**; or **8** ($^0H_5$) → **13** and **8** ($^5H_0$) → **14**], an electrostatic repulsion created by the interaction of a reagent and the substrate, lying so far toward one conformer, will strongly influence the product ratio; whereas a compound having a stable, rigid conformation generally gives a single product, or no product, wherein the transition energy is very high.



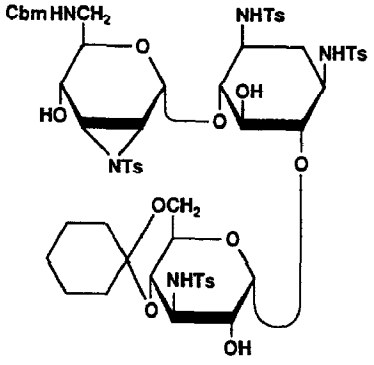
Scheme 3.

OH-3′ group, is expected[2] to show antibacterial activity against resistant bacteria producing 3′-phosphoryltransferases. 6′-*N*,4′-*O*-Carbonyl-4″,6″-*O*-cyclohexylidene-1,3,2′,3″-tetra-*N*-tosylkanamycin B[10] (**18**) was selectively acetylated with *N*-acetylimidazole in 1:9 pyridine–dimethyl sulfoxide to give the 2″-*O*-acetyl derivative **19**, which, after 3′-*O*-benzylsulfonylation (to give **20**), was, by treatment with sodium hydroxide in methanol, converted into the 2′,3′-(*N*-tosylepimine) **21** bearing a 6′-*N*-methoxycarbonyl group (created by cleavage of the 4′,6′-cyclic carbamate). Treatment of **21** with KHF_2 in DMF for 2 h at 150° gave one major product (49%), whose structure was proved, by the ^{1}H- and ^{19}F-NMR spectra, to be that of the desired 3′-deoxy-3′-fluorokanamycin B derivative **22**. Efforts to raise its yield were unsuccessful. The ready formation of **22** during a short period suggests that the axial 6′-methoxycarbonylamino group in the $^{5}H_0$ form does not hinder the approach of the fluoride ion to C-3 markedly, and that the HO-4 group plays an important role in producing the 3-deoxy-3-fluoro derivatives *. Detosylation of **22** with sodium in liquid ammonia, followed by deprotection of the other functional groups, gave 3′-deoxy-3′-fluorokanamycin B (**23**). The structure was confirmed by its NMR spectra.

* Both **7** and **21** (having HO-4) gave only the corresponding 3F compounds after a comparatively short reaction time, whereas **8** and **9** gave the 2F and 3F compounds after a longer period. This can be explained if hydrogen bonding as described in 2,3-*allo*-epoxides[3] occurs in **7** and **21**, facilitating formation of the $^{5}H_0$ form. The presence of OAc-4 (in **8**) and OMe-4 (in **9**) will predictably restrict this characteristic.



	R^1	R^2
18	H	H
19	H	Ac
20	$SO_2CH_2C_6H_5$	Ac



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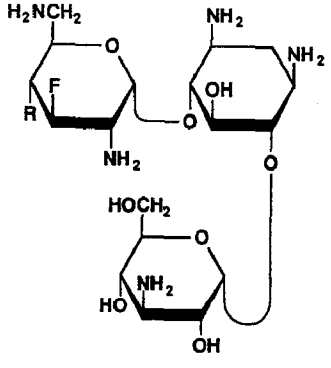
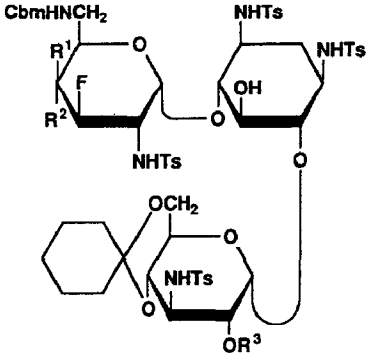


	R
23	OH
28	H



	R^1	R^2	R^3
22	H	OH	H
24	H	OH	Ac
25	H	OSO_2CF_3	Ac
26	Cl	H	Ac
27	H	H	Ac

Cbm = CO_2Me

3′,4′-Dideoxy-3′-fluorokanamycin B was next prepared in order to have a substance active against resistant bacteria producing both 3′- and 4′-modifying enzymes. Treatment of **22** with *N*-acetylimidazole as described for **19** gave the 2″-*O*-acetyl derivative **24**. Sulfonylation of the 4′-hydroxyl group with trifluoromethanesulfonic anhydride (to give **25**), followed by treatment with lithium chloride, gave the 4′-chloro-4′-deoxy derivative **26**. Dechlorination of **26** with tributylstannane gave the 3′,4′-dideoxy-3′-fluoro derivative **27**, which was finally deprotected to 3′,4′-dideoxy-3′-fluorokanamycin B (**28**).

3′-Deoxy-3′-fluorokanamycin B (**23**) showed[1], as expected, inhibitory activities similar to those of 3′-deoxykanamycin B (tobramycin), and 3′,4′-dideoxy-3′-fluorokanamycin B (**28**) was active against resistant bacteria producing both 3′- and 4′-modifying enzymes.

EXPERIMENTAL

General methods.—Optical rotations were determined with a Perkin–Elmer 241 polarimeter. NMR spectra (^{1}H at 250 MHz, ^{13}C at 62.9 MHz, and ^{19}F at 235.3 MHz) were recorded in the FT mode with a Bruker WM 250 spectrometer. Chemical shifts (δ) are reported downfield from internal Me_4Si or Freon 11 ($CFCl_3$, for ^{19}F) and coupling constants (J by Hz) are first-order. TLC was performed on Kieselgel 60 F_{254} (Merck), and column chromatography on Wakogel C-200.

Methyl 2-amino-2-deoxy-4,6-O-isopropylidene-α-D-glucopyranoside (**3**).—To a solution of **2** (4.43 g) in 1,4-dioxane (22 mL) was added aq 2 M NaOH (22 mL) and the mixture was refluxed for 2 h, to give, after usual processing, crystals ($CHCl_3$–diethyl ether) of **3**, 3.19 g (90%), mp 130–131.5°, $[\alpha]_D^{20}$ +124° (*c* 1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 1.45 and 1.55 (each s, 3 H, isopropylidene), 3.45 (s, 3 H, OMe), and 4.70 (d, 1 H, $J_{1,2}$ 4 Hz, H-1).

Anal. Calcd for $C_{10}H_{19}NO_5$: C, 51.49; H, 8.21; N, 6.01. Found: C, 51.58; H, 8.16; N, 6.09.

Methyl 2-deoxy-4,6-O-isopropylidene-2-tosylamido-α-D-glucopyranoside (**4**).—To a solution of **3** (1.45 g) and Na_2CO_3 (0.73 g) in 1:1 1,4-dioxane–water (60 mL) was added *p*-toluenesulfonyl chloride (1.31 g) and the mixture was stirred for 2 h at 0°, to give, after column chromatography (30:1 $CHCl_3$–EtOH), compound **4** as a solid, 2.03 g (84%), $[\alpha]_D^{20}$ +52° (*c* 1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 1.45 and 1.50 (each s, 3 H, isopropylidene), 2.43 [s, 3 H, Ts(*Me*)], 3.25 (s, 3 H, OMe), and 4.28 (d, 1 H, $J_{1,2}$ 4 Hz, H-1).

Anal. Calcd for $C_{17}H_{25}NO_7S$: C, 52.70; H, 6.50; N, 3.62; S, 8.28. Found: C, 52.80; H, 6.46; N, 3.58; S, 8.24.

Methyl 2-deoxy-4,6-O-isopropylidene-3-O-tosyl-2-tosylamido-α-D-glucopyranoside (**5**).—A solution of **4** (2.03 g) and *p*-toluenesulfonyl chloride (5.00 g) in pyridine (40 mL) was kept for 26 h at 90°, to give, after column chromatography (3:1 benzene–EtOAc), compound **5** as a solid, 2.21 g (78%), $[\alpha]_D^{20}$ +54° (*c* 0.5, $CHCl_3$);

^{1}H-NMR ($CDCl_3$): δ 0.92 and 1.20 (each s, 3 H, isopropylidene), 2.42 and 2.45 [each s, 3 H, Ts(*Me*) × 2], 3.37 (s, 3 H, OMe), 4.75 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), and 5.42 (d, 1 H, J 9 Hz, NH).

Anal. Calcd for $C_{24}H_{31}NO_9S_2$: C, 53.22; H, 5.77; N, 2.59; S, 11.84. Found: C, 53.21; H, 5.71; N, 2.61; S, 11.90.

*Methyl 2,3-dideoxy-4,6-*O*-isopropylidene-2,3-(*N*-tosylepimino)-α-*D*-allopyranoside* (**6**).—A solution of **5** (9.34 g) in 0.5 M NaOH in MeOH (200 mL) was kept for 6 h at 40°; near the end of the reaction **6** partly crystallized out. Cooling with ice deposited the crystal, which were filtered, washed with cold MeOH, and dried to give the first crop of **6** (3.51 g). The mother liquor and the washings combined were partly concentrated, cooled, and the second crop (2.86 g) was harvested (total yield, 81%), mp 184–186°, $[\alpha]_D^{20}$ + 102° (*c* 1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 1.26 and 1.44 (each s, 3 H, isopropylidene), 2.44 [s, 3 H, Ts(*Me*)], 3.14 (dd, 1 H, H-3), 3.38 (s, 3 H, OMe), 3.46 (dd, 1 H, H-2), and 4.89 (d, 1 H, H-1); $J_{1,2}$ 4, $J_{2,3}$ 7, and $J_{3,4}$ 2 Hz.

Anal. Calcd for $C_{17}H_{23}NO_6S$: C, 55.27; H, 6.28; N, 3.79; S, 8.68. Found: C, 55.45; H, 6.15; N, 3.90; S, 8.59.

Short-term reaction of **6** *with* KHF_2.— A mixture of **6** (100 mg) and KHF_2 (42 mg) in DMF (2 mL) was heated for 5 h at 150°. TLC (40 : 1 $CHCl_3$–acetone) of the solution showed four spots having R_F 0.07 (slight), 0.25 (**11**), 0.3 (**6**), and 0.33 (**10**). After cooling, the solution was poured into aq $NaHCO_3$ (saturated, 8 mL), and the whole mixture was concentrated in vacuo. The residue was extracted with $CHCl_3$ and the solution was washed with water, dried (Na_2SO_4), and concentrated to give a mixture of products. They were separated by twice column chromatography (15 : 1 benzene–EtOAc) to give solids of **10**, 37 mg (35%), **11**, 10.5 mg (10%), and **6**, 22 mg (22%).

Compound **10** had: $[\alpha]_D^{20}$ +62° (*c* 1, $CHCl_3$); ^{1}H-NMR (14 : 1 pyridine-d_5–D_2O): δ 1.30 and 1.36 (each s, 3 H, isopropylidene), 2.25 [s, 3 H, Ts(*Me*)], 3.21 (s, 3 H, OMe), 3.88 (dd, 1 H, H-6a), 3.96 (dd, 1 H, H-6b), 4.24 (ddd, 1 H, H-4), 4.34 (dt, 1 H, H-5), 4.37 (ddd, 1 H, H-3), 4.95 (br. d, 1 H, H-1), and 5.09 (ddd, 1 H, H-2); $J_{1,2}$ 1, $J_{1,F}$ 11, $J_{2,3}$ 3, $J_{2,F}$ 44, $J_{3,4}$ 5, $J_{3,F} = J_{4,5} = J_{5,6a}$ 10, $J_{4,F}$ 3, $J_{5,6b}$ 5.5, and $J_{6a,6b}$ 10.5 Hz; ^{19}F-NMR (pyridine-d_5): δ −185.1 (dt).

Anal. Calcd for $C_{17}H_{24}FNO_6S$: C, 52.43; H, 6.21; N, 3.60. Found: C, 52.31; H, 6.06; N, 3.57.

Compound **11** had: $[\alpha]_D^{20}$ +73° (*c* 1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 1.39 and 1.47 (each s, 3 H, isopropylidene), 2.40 [s, 3 H, Ts(*Me*)], 3.32 (s, 3 H, OMe), 3.54 (dt, 1 H, H-5), 3.64 (dddd, 1 H, H-2), 3.70 (q, 1 H, H-4), 3.74 (t, 1 H, H-6a), 3.85 (ddd, 1 H, H-6b), 4.36 (dt, 1 H, H-3), 4.64 (t, 1 H, H-1), and 5.04 (d, J 10 Hz, 1 H, NH); ^{1}H-NMR (14 : 1 pyridine-d_5–D_2O): δ 1.48 (s, 6 H, isopropylidene), 2.24 [Ts(*Me*)], 3.20 (OMe), 3.78 (H-5), 3.93 (H-6a), 4.01 (dd, 1 H, H-6b), 4.06 (dt, 1 H, H-4), 4.17 (ddd, 1 H, H-2), 4.85 (H-1), and 4.93 (H-3); $J_{1,2} = J_{1,F}$ 3.5, $J_{2,3}$ 10, $J_{2,F}$ 11, $J_{3,4} = J_{4,5}$ 9.5, $J_{4,F}$ 11, $J_{5,6a} = J_{6a,6b}$ 10.5, $J_{5,6b}$ 6, and $J_{3,F}$ 54 Hz; ^{19}F-NMR (pyridine-d_5): δ −195.8 (dt), $J_{2,F} = J_{4,F}$ 11.5 Hz.

Anal. Calcd for $C_{17}H_{24}FNO_6S$: C, 52.43; H, 6.21; N, 3.60. Found: C, 52.78; H, 6.15; N, 3.58.

Longer-term reaction of **6** *with* KHF_2.—A mixture of **6** (100 mg) and KHF_2 (42 mg) in DMF (2 mL) was heated for 168 h at 150°. TLC (40:1 $CHCl_3$–acetone) of the solution showed two spots having R_F 0.25 (**11**) and 0.07. Conventional work-up as described for the short reaction gave **11**, 35 mg (33%) and a mixture of unidentified products (R_F 0.07, 35 mg) containing no fluorine.

*Methyl 2,3-dideoxy-2,3-(*N*-tosylepimino)-α-*D*-allopyranoside* (**7**).—Hydrolysis of **6** (100 mg) with aq 80% AcOH (2 mL) for 15 min at 80° gave crystals (benzene) of **7**, 85 mg (96%), mp 88–88.5°, $[\alpha]_D^{20}$ + 103° (*c* 1, $CHCl_3$); ^{1}H-NMR (pyridine-d_5): δ 2.16 [s, 3 H, Ts(*Me*)], 3.32 (s, 3 H, OMe), 3.66 (dd, 1 H, H-3), 3.75 (dd, 1 H, H-2), 4.08–4.41 (4H, H-4,5,6a,6b), and 5.11 (d, 1 H, H-1); $J_{1,2}$ 4.5, $J_{2,3}$ 7, and $J_{3,4}$ 3 Hz.

Anal. Calcd for $C_{14}H_{19}NO_6S$: C, 51.05; H, 5.81; N, 4.25; S, 9.74. Found: C, 50.85; H, 5.76; N, 4.27; S, 9.72.

Reaction of **7** *with* KHF_2.—A mixture of **7** (97 mg) and KHF_2 (40 mg) in DMF (2 mL) was heated for 3 h at 150°. TLC (10:1 $CHCl_3$–MeOH) of the solution showed two spots having R_F 0.28 (**12**) and 0.43 (**17**) (**7** had R_F 0.36). Similar work-up as described for **10** involving column chromatography (30:1 $CHCl_3$–MeOH) gave solids of **12**, 40 mg (39%) and **17**, 39 mg (40%).

Compound **12** had: $[\alpha]_D^{23}$ +86° (*c* 1, acetone); ^{1}H-NMR (pyridine-d_5); δ 2.20 [s, 3 H, Ts(*Me*)], 3.21 (s, 3 H, OMe), 3.98 (H-5), 4.06 (double quartets, 1 H, H-2), 4.20 (H-4), 4.24–4.34 (H-6a,6b), 4.88 (t, 1 H, H-1), 5.03 (ddd, 1 H, H-3); 7.20 (d, 2 H) and 8.01 (d, 2 H) [Ts(C_6H_4)]; and 10.1 (d, 1 H, NH); $J_{1,2} = J_{1,F}$ 3.5, $J_{2,3}$ 9, $J_{3,4}$ 10.5, $J_{2,F} = J_{2,NH}$ 10, and $J_{3,F}$ 54 Hz; ^{19}F-NMR (pyridine-d_5): δ −193.6 (ddt), $J_{4,F}$ 11 Hz.

Anal. Calcd for $C_{14}H_{20}FNO_6S$: C, 48.13; H, 5.77; N, 4.01. Found: C, 48.01; H, 5.63; N, 3.87.

Compound **17** had: $[\alpha]_D^{20}$ +51° (*c* 1, $CHCl_3$); ^{1}H-NMR (pyridine-d_5): δ 2.21 [s, 3 H, Ts(*Me*)], 3.34 (s, 3 H, OMe), 3.91 (dd, 1 H, H-6a), 4.16 (br., 1 H, H-2), 4.18 (d, 1 H, H-6b), 4.31–4.41 (unresolved m, 3 H, H-3,4,5), and 5.13 (d, 1 H, H-1); ^{1}H-NMR (14:1 pyridine-d_5–D_2O): δ 2.25 [Ts(*Me*)], 3.38 (OMe), 3.94 (H-6a), 4.13 (t, 1 H, H-2), 4.22 (H-6b), 4.31 (dd, 1 H, H-3), 4.37 (dd, 1 H, H-4), 4.46 (t, 1 H, H-5), and 5.17 (H-1); $J_{1,2} = J_{2,3}$ 4, $J_{3,4}$ 5, $J_{4,5} = J_{5,6a}$ 2.5, $J_{5,6b}$ 0, and $J_{6a,6b}$ 10.5 Hz.

Anal. Calcd for $C_{14}H_{19}NO_6S \cdot 0.2H_2O$: C, 50.50; H, 5.87; N, 4.21; S, 9.63. Found: C, 50.50; H, 5.93; N, 4.20; S, 9.35.

Reaction of **10** *with* KHF_2.—*Short-term reaction*. A mixture of **10** (20 mg) and KHF_2 (8.4 mg) in DMF (0.4 mL) was heated for 6 h at 150°. Separation of the products by column chromatography as described for the reaction of **6** with KHF_2 gave solids of **6**, 2.1 mg (11%), **10**, 16.6 mg (83%), and **11**, 0.6 mg (3%).

Long-term reaction. Similar reaction of **10** (44 mg) and KHF_2 (18 mg) in DMF (0.9 mL) for 145 h at 150° gave **11**, 16 mg (35%) and a mixture of non-fluorinated products (22 mg), the major components of the latter seem to be the 4,6-*O*-isopropylidene derivatives of methyl 2-deoxy-2-tosylamido-α-D-glucopyranoside and

methyl 3-deoxy-3-tosylamido-α-D-altropyranoside in a ratio of 5 : 13, as indicated by the ^{1}H-NMR spectrum.

Methyl 4,6-di-O-acetyl-2,3-dideoxy-2,3-(N-tosylepimino)-α-D-allopyranoside (**8**).—A solution of **7** (700 mg) and Ac_2O (2.2 mL) in pyridine (14 mL) was kept for 2 h at room temperature. Standard purification gave **8** as a solid, 835 mg (95%), $[\alpha]_D^{25}$ +150° (*c* 1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$); δ 1.71 and 2.05 (each s, 3 H, OAc × 2), 2.45 [s, 3 H, Ts(*Me*)], 3.35 (dd, 1 H, H-3), 3.41 (s, 3 H, OMe), 3.54 (dd, 1 H, H-2), 3.96 (ddd, 1 H, H-5); 4.095 (1 H, H-6a) and 4.105 (1 H, H-6b) forming an ABq-like pattern together; 4.81 (dd, 1 H, H-4), and 4.98 (d, 1 H, H-1); $J_{1,2}$ 4, $J_{2,3}$ 7, $J_{3,4}$ 3, $J_{4,5}$ 10, $J_{5,6a}$ 4, $J_{5,6b}$ 3 , and $J_{6a,6b}$ 11.5 Hz.

Anal. Calcd for $C_{18}H_{23}NO_8S$: C, 52.29; H, 5.61; N, 3.39; S, 7.76. Found: C, 52.18; H, 5.49; N, 3.41; S, 7.56.

Reaction of **8** *with* KHF_2.—A mixture of **8** (50 mg) and KHF_2 (19 mg) in DMF (1 mL) was heated for 8 h at 150°. TLC (40 : 1 $CHCl_3$–acetone) of the solution showed spots of 0.03, 0.2 (**14**), 0.28 (**8**), and 0.35 (**13**). Similar work-up as described for **10** involving column chromatography (40 : 1 $CHCl_3$–acetone) gave **13** as a syrup, 4.9 mg (9.3%) **14** as a solid, 18.8 mg (36%), and **8**, 9.4 mg (19%).

Compound **13** had: $[\alpha]_D^{22}$ +65° (*c* 1, $CHCl_3$); ^{1}H-NMR (pyridine-d_5): δ 1.86 and 1.99 (each s, 3 H, OAc × 2), 2.19 [s, 3 H, Ts(*Me*)], 3.27 (s, 3 H, OMe), 4.47 (dd, 1 H, H-6a), ~ 4.5 (m, 1 H, H-5), 4.57 (dd, 1 H, H-6b), 4.67 (tt, 1 H, H-3), 4.90 (ddd, 1 H, H-2), 5.01 (br. d, 1 H, H-1), and 5.51 (ddd, 1 H, H-4); $J_{1,2}$ 2, $J_{1,F}$ 10.5, $J_{2,F}$ 46, $J_{2,3} = J_{3,4}$ 4.5, $J_{3,NH} = J_{3,F}$ 9, $J_{4,F}$ 2, $J_{4,5}$ 8.5, $J_{5,6a}$ 2, $J_{5,6b}$ 5.5, and $J_{6a,6b}$ 12.5 Hz; ^{19}F-NMR (pyridine-d_5): δ − 188.2 (dt).

Anal. Calcd for $C_{18}H_{24}FNO_8S$: C, 49.88; H, 5.58; N, 3.23. Found: C, 49.71, H, 5.70; N, 3.11.

Compound **14** had: $[\alpha]_D^{22}$ +98° (*c* 1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 2.04 and 2.08 (each s, 3 H, OAc × 2), 2.41 [s, 3H, Ts(*Me*)], 3.32 (s, 3 H, OMe), 3.65 (ddt, 1 H, H-2), 3.81 (ddd, 2 H, H-5), 4.06 (dt, 1 H, H-6a), 4.22 (dd, 1 H, H-6b), 4.45 (ddd, 1 H, H-3), 4.66 (t, 1 H, H-1), 5.06 (ddd, 1 H, H-4), and 5.27 (d, 1 H, NH); $J_{1,2}$ 3.5, $J_{2,3}$ 10, $J_{3,4}$ 9, $J_{4,5}$ 10, $J_{5,6a}$ 2, $J_{5,6b}$ 5, $J_{6a,6b}$ 12.5, $J_{1,F}$ 3.5, $J_{2,F}$ 12, $J_{3,F}$ 53, $J_{4,F}$ 12.5, $J_{6a,F}$ 2, and $J_{2,NH}$ 10 Hz; ^{1}H-NMR (14 : 1 pyridine-d_5–D_2O; ^{19}F-broadband decoupling): δ 2.01 and 2.06 (each OAc), 2.20 [Ts(*Me*)], 3.26 (OMe), 4.03 (ddd, H-5), 4.25 (dd, H-2), 4.34 (dd, H-6a), 4.49 (dd, H-6b), 4.89 (d, H-1), 5.03 (dd, H-3), and 5.53 (dd, H-4); ^{19}F-NMR ($CDCl_3$): δ −196.6 (apparent dt with small splittings in each signal).

Anal. Calcd for $C_{18}H_{24}FNO_8S$: C, 49.88; H, 5.58; N, 3.23. Found: C, 49.67; H, 5.63; N, 3.18.

Reaction of **13** *with* KHF_2.—A mixture of **13** (23 mg) and KHF_2 (8.4 mg) in DMF (0.5 mL) was heated for 21 h at 150°. Separation of the products by column chromatography (20 : 1 $CHCl_3$–acetone) gave **8**, 3.5 mg (16%), **13**, 8.1 mg (35%), and **14**, 3.2 mg (14%).

Methyl 2,3-dideoxy-4,6-di-O-methyl-2,3-(N-tosylepimino)-α-D-allopyranoside (**9**).—A mixture of **7** (100 mg), dimethyl sulfate (0.37 mL), BaO (180 mg), and

$Ba(OH)_2 \cdot 8H_2O$ (60 mg) in DMF (3 mL) was stirred for 3 h at room temperature. Addition of aq 28% ammonia followed by evaporation gave a residue, that was extracted with $CHCl_3$, and the solution was washed with water and concentrated to give a syrup. The latter was purified by column chromatography (5:1 benzene–EtOAc) to give **9** as a syrup, 67 mg (62%), $[\alpha]_D^{22}$ +157° (*c* 1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 2.43 [s, 3 H, Ts(*Me*)], 3.26, 3.34, and 3.36 (each s, 3 H, OMe × 3), 3.34 (dd, 1 H, H-3), 3.48 (dd, 1 H, H-2), 3.51 (t, 2 H, H-6a, 6b), 3.61 (dd, 1 H, H-4), 3.71 (dt, 1 H, H-5), and 4.93 (d, 1 H, H-1); $J_{1,2}$ 4.5, $J_{2,3}$ 7, $J_{3,4}$ 3, $J_{4,5}$ 10, and $J_{5,6a} = J_{5,6b}$ 3 Hz.

Anal. Calcd for $C_{16}H_{23}NO_6S$: C, 53.77; H, 6.49; N, 3.92; S, 8.97. Found: C, 53.69; H, 6.50; N, 3.66; S, 8.92.

Reaction of **9** *with* KHF_2.—A mixture of **9** (21.1 mg) and KHF_2 (9.2 mg) in DMF (0.4 mL) was heated for 20 h at 150°. TLC (5:1 benzene–EtOAc) of the solution showed two spots having R_F 0.08 and 0.3 (**15** and **16**) with disappearance of the spot (R_F 0.23) for **9**. Concentration gave a residue that was purified by column chromatography (2:1 benzene–EtOAc) to give a mixture of **15** and **16**: 12.3 mg (55%), and the product having R_F 0.08, 6.3 mg; mass spectrum of the mixture of **15** and **16**; Calcd for $C_{16}H_{24}FNO_6S$: mol. wt. 377.4, Found: *m/z* 378 $(M + H)^+$; ^{19}F-NMR ($CDCl_3$): δ −190.9 (apparent dt with small splittings in each signal, 0.4 F, $J_{1,F} = J_{3,F} \sim 9$ and $J_{2,F}$ 45 Hz, F-2 of **15**) and −193.3 (apparent dt with small splittings in each signal, 0.6 F, $J_{2,F} = J_{4,F} \sim 12.5$ and $J_{3,F}$ 53 Hz, F-3 of **16**).

*2″-*O*-Acetyl-6′-*N*,4′-*O*-carbonyl-4″,6″-*O*-cyclohexylidene-1,3,2′,3″-tetra-*N*-tosyl-kanamycin B* (**19**).—A solution of **18** (ref. 10, 1.58 g) and *N*-acetylimidazole (0.78 g) in dry 1:9 pyridine–Me_2SO (7.9 mL) was kept overnight at room temperature. TLC (10:1 $CHCl_3$–MeOH) of the solution showed a single spot at R_F 0.25 (cf. **18**: R_F 0.15). Addition of aq $NaHCO_3$ (satd, 160 mL) gave a precipitate that was filtered off and washed with water and diethyl ether to give **19** as a solid, 1.63 g (quant.), $[\alpha]_D^{20}$ −23° (*c* 1, MeOH); ^{1}H-NMR (pyridine-d_5): δ 2.14 (s, 3 H, Ac), 2.24, 2.32, 2.35, and 2.36 [each s, 3 H, Ts(*Me*) × 4], 5.50 (dd, 1 H, H-2″), 5.60 (d, 1 H, H-1″), and 5.75 (d, 1 H, H-1′); $J_{1',2'}$ 3.5, $J_{1'',2''}$ 3.5, and $J_{2'',3''}$ 10.5 Hz.

Anal. Calcd for $C_{55}H_{69}N_5O_{20}S_4$: C, 52.91; H, 5.57; N, 5.61; S, 10.27. Found: C, 52.97; H, 5.73; N, 5.27; S, 9.97.

*2″-*O*-Acetyl-3′-*O*-benzylsulfonyl-6′-*N*,4′-*O*-carbonyl-4″,6″-*O*-cyclohexylidene-1,3,2′,3″-tetra-*N*-tosylkanamycin B* (**20**).—To a cold (−20°) solution of **19** (1.62 g) in pyridine (32 mL) was added phenylmethanesulfonyl chloride (270 mg, and 50 mg after 3.5 h) and the solution was kept for 4.5 h at −20°. Water (0.15 mL) was added and, after 10 min at room temperature, the solution was concentrated. The residue was extracted with $CHCl_3$ and the solution was washed with aq $NaHCO_3$ (satd), aq 5% $KHSO_4$, and water, dried ($MgSO_4$), and concentrated to give **20** as a solid, 1.78 g (98%), $[\alpha]_D^{20}$ −34° (*c* 1, MeOH); IR (KBr): 1730 cm^{-1}; ^{1}H-NMR (pyridine-d_5): δ 2.08 (s, 3 H, Ac), 2.24, 2.386, 2.396, and 2.404 [each s, 3 H, Ts(*Me*) × 4], 5.03 (s, 2 H, PhCH_2SO_2), 5.52 (dd, 1 H, H-2″), 5.59 (d, 1 H, H-1″),

5.64 (t, 1 H, H-3′), and 5.98 (d, 1 H, H-1′); $J_{1',2'}$4, $J_{2',3'} = J_{3',4'}$ 10, $J_{1'',2''}$ 4, and $J_{2'',3''}$ 10 Hz.

Anal. Calcd for $C_{62}H_{75}N_5O_{22}S_5 \cdot H_2O$: C, 52.42; H, 5.46; N, 4.93; S, 11.29. Found: C, 52.33; H, 5.41; N, 5.25; S, 11.24.

4″,6″-O-Cyclohexylidene-2′-deamino-3′-deoxy-3′-epi-6′-N-methoxycarbonyl-1,3,3″-tri-N-tosyl-2′,3′-(N-tosylepimino)kanamycin B (**21**).—A solution of **20** (1.82 g) in 0.5 M NaOH in MeOH (36 mL) was kept for 4 h at room temperature. Conventional work-up gave **21** as a solid, 1.46 g, (92%), $[\alpha]_D^{20}$ +35° (*c* 1, MeOH); IR (KBr): 1700 cm^{-1}; ^{1}H-NMR (pyridine-d_5): δ 2.19, 2.21, 2.34, and 2.36 [each s, 3 H, Ts(*Me*) × 4], 3.61 (dd, 1 H, H-2′), 3.63 (s, 3 H, CO_2Me), 3.73 (dd, 1 H, H-3′), 5.37 (d, 1 H, H-1″), and 5.83 (d, 1 H, H-1′); $J_{1',2'}$ 3.5, $J_{2',3'}$ 7, $J_{3',4'}$ 3, and $J_{1'',2''}$ 3.5 Hz.

Anal. Calcd for $C_{54}H_{69}N_5O_{19}S_4 \cdot 2H_2O$: C, 51.62; H, 5.86; N, 5.57; S, 10.21. Found: C, 51.94; H, 6.03; N, 5.63; S; 10.38.

4″,6″-O-Cyclohexylidene-3′-deoxy-3′-fluoro-6′-N-methoxycarbonyl-1,3,2′,3″-tetra-N-tosylkanamycin B (**22**).—A mixture of **21** (116 mg) and KHF_2 (15 mg) in dry DMF (2.3 mL) was stirred for 2 h at 150°. TLC (10:1 $CHCl_3$–MeOH) of the solution showed a main spot at R_F 0.45 (**21**: R_F 0.4) along with several weak spots. The solution, after cooling, was poured into aq $NaHCO_3$ (satd, 50 mL), and the precipitate was subjected to column chromatography (30:1 $CHCl_3$–MeOH) to give **22** as a solid, 58 mg (49%), $[\alpha]_D^{20}$ −20° (*c* 1, MeOH); ^{1}H-NMR (pyridine-d_5): δ 2.14, 2.18, and 2.36 (6 H) [each s, Ts(*Me*) × 4], 3.58 (s, 3 H, CO_2Me), 5.22 (dt, 1 H, H-3′), 5.27 (d, 1 H, H-1″), and 5.85 (br. s, 1 H, H-1′); $J_{2',3'} = J_{3',4'}$9, $J_{3',F}$ 54, and $J_{1'',2''}$ 4 Hz; ^{19}F-NMR (pyridine-d_5): δ −193.6 (dt); $J_{2',F} = J_{4',F}$ 11.5 Hz.

Anal. Calcd for $C_{54}H_{70}FN_5O_{19}S_4$: C, 52.29; H, 5.69; N, 5.65; S, 10.34. Found: C, 52.17; H, 5.39; N, 6.00; S, 10.10.

3′-Deoxy-3′-fluorokanamycin B (**23**).—To a solution of **22** (75.7 mg) in liquid NH_3 (~ 10 mL) at −50° was added Na (~ 100 mg), and the deep-blue solution was kept for 5 min at −50°. After addition of MeOH until the solution became colorless, NH_3 was gradually evaporated under warming and the aqueous solution (strongly basic) of the residue was heated for 1 h at 80° (to remove the methoxycarbonyl group). After cooling, Dowex 50W-X2 resin (H^+ form, 200–400 mesh, 10 mL) was added, and the mixture was kept overnight at room temperature (to remove the cyclohexylidene group). The treated resin was poured into a column containing the same fresh resin (H^+ form, 3 mL) and, after washing the column with water, the product was eluted with aq M NH_3. The product was further purified by column chromatography of CM-Sephadex C-25 (35 mL) with aq 0 → 0.15 M NH_3 to give **23** (ref. 1) as its carbonate, 15.1 mg (42%), $[\alpha]_D^{20}$ +127° (*c* 0.6, H_2O); ^{1}H-NMR (20% ND_3 in D_2O): δ 4.47 (dt, 1 H, H-3′), 5.03 (d, 1 H, H-1″), and 5.34 (t, 1 H, H-1′); $J_{1',2'} = J_{1',F}$ 4, $J_{2',3'} = J_{3',4'}$ 10, $J_{3',F}$ 54, and $J_{1'',2''}$ 4 Hz; ^{13}C-NMR (20% ND_3 in D_2O): δ 36.6 (C-2), 42.3 (C-6′), 50.2 [C-3 (or 1)], 51.0 [C-1 (or 3)], 55.0 (d, $J_{2',F}$ 18 Hz, C-2′), 55.1 (C-3″), 61.2 (C-6″), 70.2 (C-4″), 70.4 (d, $J_{4',F}$ 16 Hz, C-4′), 72.6 (C-2″), 73.2 (C-5″), 73.3 (d, $J_{5',F}$ 7.5 Hz, C-5′), 75.2

(C-5), 87.8 [C-4 (or 6)], 89.0 [C-6 (or 4)], 96.5 (d, $J_{3',F}$ 178 Hz, C-3'), 100.6 (C-1''), and 101.5 (d, $J_{1',F}$ 11 Hz, C-1'); ^{19}F-NMR (20% ND_3 in D_2O): δ −196.9 (ddt), $J_{2',F} = J_{4',F}$ 12 Hz.

Anal. Calcd for $C_{18}H_{36}FN_5O_9 \cdot H_2CO_3 \cdot 0.2\ H_2O$: C, 41.41; H, 7.02; N, 12.71; F, 3.45. Found; C, 41.28; H, 7.24; N, 12.54; F, 3.59.

2''-O-Acetyl-4'',6''-O-cyclohexylidene-3'-deoxy-3'-fluoro-6'-N-methoxycarbonyl-1,3,2',3''-tetra-N-tosylkanamycin B (**24**).—Compound **22** (244 mg) was treated with *N*-acetylimidazole (87 mg) in 1:9 pyridine–Me_2SO (1.2 mL) for 72 h at room temperature, and worked up as described for **19** to give **24** as a solid, 250 mg (99%), $[\alpha]_D^{20}$ +9° (*c* 1, MeOH); ^{1}H-NMR (pyridine-d_5): δ 5.20 (dt, 1 H, H-3'), 5.52 (dd, 1 H, H-2''), 5.65 (d, 1 H, H-1''), and 5.86 (t, 1 H, H-1'); $J_{1',2'} = J_{1',F}$ 4, $J_{2',3'} = J_{3',4'}$ 9, $J_{3',F}$ 54, $J_{1'',2''}$ 3.5, and $J_{2'',3''}$ 10.5 Hz.

Anal. Calcd for $C_{56}H_{72}FN_5O_{20}S_4$: C, 52.45; H, 5.66; N, 5.46; S, 10.00. Found: C, 52.21; H, 5.57; N, 5.70; S, 9.90.

2''-O-Acetyl-4'',6''-O-cyclohexylidene-3',4'-dideoxy-3'-fluoro-6'-N-methoxycarbonyl-1,3,2',3''-tetra-N-tosylkanamycin B (**27**).—A mixture of **24** (250 mg), trifluoromethanesulfonic anhydride (0.13 mL), and pyridine (0.12 mL) in cold (−20°) CH_2Cl_2 (5 mL) was kept for 2.5 h. Water (0.07 mL) was added, and the solution was warmed to room temperature. After dilution with $CHCl_3$ (20 mL), the solution was washed with water, and concentrated to give crude solid **25**; 288 mg. A mixture of the solid (250 mg) and LiCl (75 mg) in DMF (5 mL) was stirred for 5 min at 50°. TLC (10:1 $CHCl_3$–MeOH) of the solution showed a main spot at R_F 0.4 (compare **25**, R_F 0.37) along with two minor spots. Addition of water (95 mL) gave a precipitate that was thoroughly washed with water to give the slightly unstable **26** as a crude solid, 218 mg; ^{1}H-NMR (pyridine-d_5): δ 4.74 (m, 1 H, H-2'), 5.06 (dt, 1 H, H-4'), 5.34 (m, 1 H, H-5'), 5.40 (dm, 1 H, H-3'), and 6.17 (m, 1 H, H-1'); $J_{3',F}$ 49 and $J_{4',F}$ 4 Hz; ^{19}F NMR (pyridine-d_5): δ −189.0 (br. d, *J* 49 Hz).

To a solution of **26** (72.4 mg) in 1,4-dioxane (1.5 mL) were added tributylstannane (80 mg; additional 80 mg after 5 min), and 2,2'-azobis(isobutyronitrile) (4.5 mg; additional 4.5 mg after 5 min), and the solution was heated for 35 min at 80° under N_2. TLC (2:1 $CHCl_3$–acetone) of the solution showed a main spot at R_F 0.4 (compare **26**, R_F 0.5). Concentration gave a residue, that was chromatographed with $CHCl_3$, and then with 2:1 $CHCl_3$–acetone to give **27** as a solid, 48.5 mg (66% based on **24**), $[\alpha]_D^{20}$ +27° (*c* 1, MeOH); ^{1}H-NMR (pyridine-d_5): δ 3.62 (s, 3 H, CO_2Me), 5.04 (m, 1 H, H-5'), 5.17 (m, 1 H, H-3'), 5.55 (dd, 1 H, H-2''), 5.65 (d, 1 H, H-1''), and 5.96 (t, 1 H, H-1'); $J_{1',2'} = J_{1',F}$ 3.5, $J_{1'',2''}$ 3.5, and $J_{2'',3''}$ 10.5 Hz; ^{19}F-NMR (pyridine-d_5): δ −182.2 (br. d) and $J_{3',F}$ 52 Hz.

Anal. Calcd for $C_{56}H_{72}FN_5O_{19}S_4$: C, 53.11; H, 5.73; N, 5.53; S, 10.13. Found: C, 52.86; H, 5.81; N, 5.82; S, 10.16.

3',4'-Dideoxy-3'-fluorokanamycin B (**28**).—To a solution of sodium (~ 80 mg) in liquid NH_3 (~ 15 mL) at −50° was added dropwise a solution of **27** (48.5 mg) in oxolane (1.5 mL). After 10 min at the temperature (the *N*-tosyl groups were removed), ice-cold MeOH was added until the solution became colorless, and,

after the NH_3 had been evaporated by gentle warming, the solution was concentrated to dryness. An aqueous solution (strongly basic, 3.5 mL) of the residue was heated for 2 h at 80° (the acetyl and methoxycarbonyl groups were removed), and, after cooling, the solution was neutralized with Dowex 50W-X2 resin (H^+ form, 200–400 mesh, 6 mL; removal of Na^+ ions), and the mixture was kept overnight at room temperature (removal of the cyclohexylidene group). The treated resin was poured into a column containing the same fresh resin (2 mL), and the column was washed thoroughly with water. Elution of the product with aq M NH_3, followed by purification of the resulting product on a column of CM–Sephadex C-25, developed with 0 → 0.15 M aq NH_3, gave a solid of **28** as its carbonate, 10.4 mg (51%), $[\alpha]_D^{20}$ +123° (*c* 1, H_2O); ^{1}H-NMR (20% ND_3 in D_2O): δ 1.65 (quintet, 1 H, H-4′*ax*), 2.27 (dddd, 1 H, H-4′*eq*), 4.80 (ddt, 1 H, H-3′), 5.08 (d, 1 H, H-1″), and 5.43 (t, 1 H, H-1′); $J_{1',2'}$ 4, $J_{2',3'}$ 11, $J_{3',4'ax} = J_{4'ax,4'eq} = J_{4'ax,5'}$ 11.5, $J_{3',4'eq}$ 5, $J_{4'eq,5'}$ 5.5, and $J_{1'',2''}$ 4 Hz; ^{13}C-NMR (20% ND_3 in D_2O): δ 34.8 (d, $J_{4',F}$ 17 Hz, C-4′), 36.8 (C-2), 45.7 (C-6′), 50.3 (C-3), 51.1 (C-1), 55.2 (C-3″), 56.4 (d, $J_{2',F}$ 18 Hz, C-2′), 61.3 (C-6″), 70.3 (C-4″), 70.5 (d, $J_{5',F}$ 13 Hz, C-5′), 72.6 (C-2″), 73.2 (C-5″), 75.3 (C-5), 87.9 (C-4), 89.0 (C-6), 92.2 (d, $J_{3',F}$ 170 Hz, C-3′), 100.6 (C-1″), and 102.5 (d, $J_{1',F}$ 11 Hz, C-1′); ^{19}F-NMR (20% ND_3 in D_2O): δ −185.9 (dt), $J_{1',F}$ 4, $J_{2',F}$ 11.5, $J_{4',F}$ 52, $J_{4'ax,F}$ 11.5, and $J_{4'eq,F}$ 2 Hz.

Anal. Calcd for $C_{18}H_{36}FN_5O_8 \cdot H_2CO_3$: C, 42.93; H, 7.21; N, 13.18; F, 3.57. Found: C, 43.18; H, 7.47; N, 12.91; F, 3.67.

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