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A synthetic study of methyl 3-deoxy-3-fluoro-α-D-gluco-pyranosides from methyl 2,3-anhydro-α-D-allopyranosides, and synthesis of 3′-deoxy-3′-fluorokanamycin A and 3′-chloro-3′-deoxykanamycin A

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ABSTRACT

Reactions of 4,6-disubstituted 2,3-anhydro-α-D-allopyranosides with potassium hydrogenfluoride (KHF_2) in ethane-1,2-diol gave, by oxirane-ring opening, the corresponding 2-deoxy-2-fluoro-α-D-altro- and 3-deoxy-3-fluoro-α-D-gluco-pyranosyl derivatives, with the latter always in preponderance. The influence of the substituents at C-4 and C-6 on the D-*gluco*–D-*altro* ratio (*r*) have been studied by molecular mechanics, and the discrepancy between the experimental and calculated *r* values has been positively utilized to measure the effects of solvation and hydrogen bonding relative to the C-4 and C-6 substituents. By application of this reaction, 3′-deoxy-3′-fluorokanamycin A has been prepared by treatment of a 2′,3′-anhydro-3′-epikanamycin A derivative (**35**) with KHF_2. 3′-Chloro-3′-deoxykanamycin A was also prepared.

INTRODUCTION

In a preceding paper[1] we described the synthesis of 3′-deoxy-3′-fluorokanamycin A and 3′,4′-dideoxy-3′-fluorokanamycin A by a glycosylation method and reported that these compounds are active against resistant bacteria. Here we describe first the introduction of fluorine into several 2,3-anhydro-α-D-allopyranosides by opening of the oxirane ring to give 3-deoxy-3-fluoro-α-D-glucopyranosyl derivatives, and then the conversion of kanamycin A into 3′-deoxy-3′-fluorokanamycin A, based on this study.

3-Deoxy-3-fluoro-D-glucopyranose and the corresponding glucosides have been prepared[2,3] mainly from 3-deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-D-glucofuranose obtained by deoxyfluorination of 1,2:5,6-di-*O*-isopropylidene-D-allofuranose, and no studies on the displacement of D-allopyranoside 3-sulfonates by fluoride ion have been reported. This may suggest that an SN2 reaction at this position by fluoride ion is difficult. However, in order to prepare 3′-deoxy-3′-fluorokanamycin A from kanamycin A, the conversion of the 6′-amino-6′-deoxy-α-D-glucopyranosyl moiety into 6′-amino-3′,6′-dideoxy-3′-fluoro-α-D-glucopyranosyl structure is essential. As a model for this transformation, we studied the preparation of 3-deoxy-3-fluoro-α-D-glucopyranosides by oxirane-ring opening of 2,3-anhydro-α-D-allopyranosides.

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Cohen *et al.*[4] prepared benzyl 3-deoxy-3-fluoro-β-D-xylopyranoside by treatment of benzyl 2,3-anhydro-β-D-ribopyranoside with potassium fluoride in molten acetamide, or with potassium hydrogenfluoride in diethylene glycol. Methyl 4-*O*-benzyl-3-deoxy-3-fluoro-β-D-xylopyranoside was also prepared[5] (~ 46%) from methyl 2,3-anhydro-4-*O*-benzyl-β-D-ribopyranoside by treatment with potassium hydrogenfluoride in ethane-1,2-diol. In the cases of methyl 2,3-anhydro-4,6-di-*O*-methyl-α-D-allopyranoside[6,7] (**7**) and the corresponding 4,6-diacetate, use of hydrogen tetrafluoroborate in hydrogen fluoride–chloroform gave[7], respectively, the corresponding 2-deoxy-2-fluoro-D-altropyranosyl fluorides (33% for **7**) together with minor proportions of 3-deoxy-3-fluoro-D-glucopyranosyl fluoride.

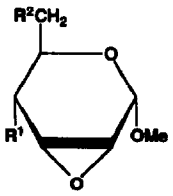
As 2,3-anhydro-D-allopyranosides exist in their ground state in a half-chair[8–10] ($^0H_5$), sofa[11] (E_5), or a hybrid conformation of ^0E and $^0H_5$, nucleophilic oxirane-ring opening of these compounds should give 2-substituted D-altropyranosides, if the reactions occur according to the Fürst–Plattner rule of *trans*-diaxial ring opening. Indeed, when rigid, tricyclic 2,3-anhydro-4,6-*O*-benzylidene-α- and -β-D-allopyranosides were treated with a variety of nucleophiles[12–27], the corresponding 2-substituted D-altropyranosides were produced in preponderance over the 3-substituted D-glucopyranosides. When, however, mobile, bicyclic 2,3-anhydro-D-allopyranosides were treated similarly, the corresponding 3-substituted D-glucopyranosides were mainly formed[28–38] in preference to the 2-substituted D-altropyranosides, although the reverse was true in some cases[12]. This may suggest that the ground state $^0H_5$ (or related) conformation is inverted into the $^5H_0$-like form during the reaction, allowing the incoming nucleophile to avoid electrostatic 1,3-diaxial repulsion by the axial lone-pair

TABLE I

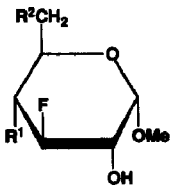
Reaction of 2,3-epoxides with KHF_2 in ethane-1,2-diol[a]

Starting material	*Product*		D-gluco/D-altro (*r*)
	3-Deoxy-3-fluoro-D-gluco	*2-Deoxy-2-fluoro*-D-altro	
2	**13**	**14**	11
3	**15**	**16**	1.36, 1.28
5	**17**	**18**	1.19, 1.17
7	**19**	**20**	2.03, 2.10[b]
8	**21**	**22**	1.66
10	**23**	**24**	2.14, 2.25[b]
11	**25**	**26**	1.80, 1.92
12	**27**	**28**	5.34

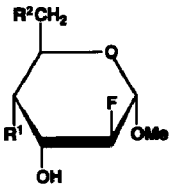
[a] A 1:5 molar mixture of the starting material (~ 100 mg) and KHF_2 in ethane-1,2-diol (130 mg KHF_2 mL^{-1}) was heated for 3 h at 170°. After neutralization with aq. $NaHCO_3$ the fluorinated products were exhaustively extracted with $CHCl_3$ (checked by t.l.c.). The extract was carefully concentrated (some products were volatile), the residue was dissolved in $CDCl_3$, and, in the ^{19}F-n.m.r. spectrum, the strength of the signals of the D-*gluco* (double triplets with ~ 55 Hz) and D-*altro* derivatives (double triplets with ~ 45 Hz) was measured.
[b] After the same reaction as just described, but using ethane-1,2-diol-d_6, a portion of the solution was dissolved in MeOH-d_4, and the ^{19}F-n.m.r. spectrum was recorded.



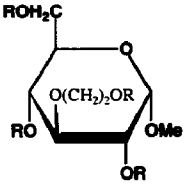
	R^1	R^2
1	PhCHO(O)	
2	OH	OH
3	OMe	OH
4	OMe	OAc
5	OH	OMe
6	OAc	OMe
7	OMe	OMe
8	OMe	F
9	OH	Cl
10	OH	H
11	OMe	H
12	H	H



	R^1	R^2
13	OH	OH
15	OMe	OH
17	OH	OMe
19	OMe	OMe
21	OMe	F
23	OH	H
25	OMe	H
27	H	H



	R^1	R^2
14	OH	OH
16	OMe	OH
18	OH	OMe
20	OMe	OMe
22	OMe	F
24	OH	H
26	OMe	H
28	H	H



29 R = H
30 R = Ac

electrons on the pyranoid-ring oxygen. In 2,3-anhydro-β-D-allopyranosides, lone-pair electrons of the glycosidic oxygen may also operate[39] similarly. However, in the $^5H_0$ form, steric repulsion between the nucleophile approaching at C-3 and the C-5 substituent can be expected.

RESULTS AND DISCUSSION

In contrast to other halo derivatives, 2-deoxy-2-fluoro-D-altropyranosides, once formed by fluorination of 2,3-anhydro-D-allopyranosides, may not revert to the starting oxirane because of the high C–F bond energy; this premise was partly confirmed by the fact that methyl 2-deoxy-2-fluoro-4,6-di-*O*-methyl-α-D-altropyranoside (**20**), once prepared, was stable under further treatment with KHF_2, without conversion into **19** (see Experimental).Therefore, the *gluco–altro* ratio of the reaction products should be a reflection of the populations ([$^0H_5$] and [$^5H_0$]) of the $^0H_5$ and $^5H_0$ forms of the starting 2,3-anhydro-D-allopyranosides in the reaction states, and the fluorination rate constants (k_1 and k_2) for both forms; that is, the product ratio (r, see Table I) will be

expressed* as $k_2[^5H_0]/k_1[^0H_5]$. In our preliminary experiments, methyl 2,3-anhydro-α-D-allopyranoside[6] (**2**), employed as the model compound, was treated with several fluorinating agents such as potassium fluoride–crown ether, spray-dried potassium fluoride[40], potassium hydrogenfluoride (KHF_2), or tetrabutylammonium fluoride, in a solvent chosen from acetonitrile, *N,N*-dimethylformamide (DMF), diglyme, and ethane-1,2-diol. It was found that **2** was best fluorinated when treated with KHF_2 in ethane-1,2-diol at ~ 160° to give methyl 3-deoxy-3-fluoro-α-D-glucopyranoside (**13**) in 48% yield together with trace amounts of methyl 2-deoxy-2-fluoro-α-D-altropyranoside (**14**), methyl 3-*O*-(2-hydroxyethyl)-α-D-glucopyranoside (**29**) and minor by-products; the structure of **29** was confirmed by the ^{1}H-n.m.r. and mass spectra of the per-*O*-acetyl derivative (**30**). Therefore, these conditions were used in the subsequent studies.

When, however, methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside (**1**) was treated similarly, it gave the same products as **2**, because of removal of the benzylidene group in an early stage of the reaction. In the cases of methyl 2,3-anhydro-4-*O*-methyl-α-D-allopyranoside (**3**; prepared by an improved method from that reported[41] and its structure confirmed via the 6-*O*-acetyl derivative **4**), 2,3-anhydro-6-*O*-methyl-α-D-allopyranoside (**5**; structure confirmed by the 4-*O*-acetyl derivative **6**), and 2,3-anhydro-4,6-di-*O*-methyl-α-D-allopyranoside[6,7] (**7**), similar treatments with KHF_2 gave the corresponding D-glucopyranosides (**15**, **17**, and **19**) in only slight preponderance over the D-altropyranosides (**16**, **18**, and **20**). This relatively high proportion of 2-deoxy-2-fluoro-D-altropyranosides (**16**, **18**, and **20**), compared to the case of **2**, was unexpected.

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* As $^0H_5$ and $^5H_0$ forms are in rapid equilibrium ($[^5H_0]/[^0H_5] = K$ is constant at a temperature), the reaction rates (under excess F^- ion) as shown in Scheme 1 will be expressed as

$$-\frac{d[^0H_5]}{dt} = k_1[^0H_5] + Kk_2[^0H_5] \quad (1)$$

$$\frac{d[2F]}{dt} = k_1[^0H_5] \quad (2)$$

$$\frac{d[3F]}{dt} = k_2[^5H_0] = Kk_2[^0H_5] \quad (3)$$

As the solution for Eq. *1* is $[^0H_5] = A_0e^{-(k_1+Kk_2)t}$ (A_0 is the concentration of $^0H_5$ at $t = 0$), Eqs. *2* and *3* are described, respectively as

$$\frac{d[2F]}{dt} = A_0k_1e^{-(k_1+Kk_2)t} \text{ and } \frac{d[3F]}{dt} = A_0Kk_2e^{-(k_1+Kk_2)t}.$$

The solutions are (entering the first conditions), respectively,

$$[2F] = \frac{A_0k_1}{k_1+Kk_2}(1-e^{-(k_1+Kk_2)t}) \text{ and}$$

$$[3F] = \frac{A_0Kk_2}{k_1+Kk_2}(1-e^{-(k_1+Kk_2)t}).$$

$$\text{Therefore, } \frac{[3F]}{[2F]} = r = K\frac{k_2}{k_1} = \frac{k_2[^5H_0]}{k_1[^0H_5]} \quad (4)$$

During the study we considered that electron-withdrawing substituents at C-4 or C-6 might increase the proportion of *altro* isomer by decreasing the electron density on the pyranoid-ring oxygen, thereby facilitating the approach of the fluoride ion at C-2 in the $^0H_5$ form. Thus methyl 2,3-anhydro-4,6-di-*O*-acetyl- and -4,6-di-*O*-mesyl-α-D-allopyranosides were prepared and treated similarly. Disappointingly, the diacetate suffered loss of its acetyl groups in an early stage of the reaction giving the same results as **2** or **1**, and the dimesylate gave unknown, degraded products. Therefore, methyl 2,3-anhydro-6-deoxy-6-fluoro-4-*O*-methyl-α-D-allopyranoside (**8**), a compound having the strongly electron-withdrawing fluorine at C-6, was prepared by treatment of **3** with diethylaminosulfur trifluoride (DAST). When **8** was treated similarly with KHF_2, a 3:2 *gluco* (**21**)–*altro* (**22**) mixture was obtained.

As all of these results were based on the yields of products obtained after chromatographic purification of the reaction mixtures, the *gluco*–*altro* ratio (*r*) may not precisely reflect the products actually formed. Therefore, we decided to measure the ratio by ^{19}F-n.m.r. spectroscopy in the samples not subjected to separation procedures (Table I). On this occasion, three 6-deoxy-2,3-epoxides were also prepared, and fluorinated similarly. These compounds were methyl 2,3-anhydro-6-deoxy-α-D-allopyranoside (**10**, prepared from **2** through the 6-chloro-6-deoxy derivative **9**), methyl 2,3-anhydro-6-deoxy-4-*O*-methyl-α-D-allopyranoside (**11**), and methyl 2,3-anhydro-4,6-dideoxy-α-D-*ribo*-hexopyranoside[37] (**12**); treatment of them with KHF_2 gave the 3-deoxy-3-fluoro-D-*gluco* (**23**, **25**, and **27**) and 2-deoxy-2-fluoro-D-*altro* (**24**, **26**, and **28**) derivatives, respectively. The ^{1}H- and ^{19}F-n.m.r. data of the fluoro derivatives are shown in Table II, and the spectroscopically determined product-ratios (*r*) are shown in Table I. It is noteworthy that the 4,6-diol **2** and 4,6-dideoxy compound **12** were two exceptions, giving higher *r* values than the other oxiranes, and that the monohydroxy-mono-*O*-methyl compounds (**3** and **5**) gave lower *r* values (r = 1.2–1.4) than the 4,6-diol (**2**,r = 11) and the 4,6-dimethyl ether **7** (r = 2.07). These results suggest that there may be no regular relationship between *r* and the molecular structure.

In another experiment, ^{1}H-n.m.r. spectra of **2** dissolved in ethane-1,2-diol-d_6 were recorded with or without added of KHF_2 (2%), at various temperatures* (25, 100, and 146°), and a slight decrease in the $J_{4,5}$ value (~ 0.3 Hz) was observed at the highest temperature. This suggests that the ground-state conformation ($^0H_5$) of **2** is not fixed, but moves towards the $^5H_0$ form at high temperature, although the extent is only small.

Considering all of these findings together, we tried to determine the factors that control the *gluco*–*altro* ratio (*r*), in other words, the manner in which the substituents at C-4 and C-6 influence *r*. As *r* is determined by the product of *K* and k_2/k_1 (see Eq. 4 in footnote), evaluation of the latter two terms by molecular mechanics (MM) calculations[42a] was attempted, although the data obtained would be for the vapor state. As *K* is determined by the energy difference of the starting conformers as:

$$\ln K = -(G_2^0 - G_2^0)/RT = -\Delta G_{2\text{-}1}^0/RT \qquad (5)$$

* Measurement at temperatures higher than 146° was not tried for fear of breakage of the n.m.r.-tube by HF.

TABLE II

^{1}H- and ^{19}F-n.m.r. data for the deoxyfluoro compounds **13–28**[a] (δ in p.p.m., J in Hz) in $CDCl_3$

Compound	*H-1*	*H-2*	*H-3*	*H-4$_{ax}$ (H-4$_{eq}$)*	*Other signals*	*F-2*	*F-3*	$J_{1,2}$	$J_{2,3}$	$J_{3,4ax}$ ($J_{3,4eq}$)	$J_{1,F}$	$J_{2,F}$	$J_{3,F}$	$J_{4ax,F}$ ($J_{4eq,F}$)	*Other couplings*
13[b]	4.87 t	~ 3.87	4.57 dt	~ 3.7	3.43 (OMe)		− 199.5 br dt	3.5	9	9	3.5	14	54	14	
14[b]						− 196.1 br dt					~ 10	45	~ 10		
15	4.79 t		4.61 dt				− 196.2 br dt	4	9	9	4	13	54	13	
16	4.83 br d	4.67 ddd				− 196.1 dddd		1.5	4		10	45	7.5	3	
17	4.81 t		4.51 dt		3.42 (OMe × 2)		− 199.8 dddd	3.5	9	9	3.5	13	54	13	
18	4.87 dt	4.67 ddd	3.79 m		3.44 (OMe) 3.48 (OMe)	− 196.6 dddd		1.5	3.5		9	45	8	2.5	$J_{1,3}$ 1.5
19	4.80 t		4.58 dt		3.55d (OMe-4)		− 196.3 br dt	4	9	9	4	13	54	13	$J_{OMe,F}$ 1
20	4.84 br d	4.65 ddd				− 196.2 dddd		1.5	4		10	45	7.5	3	
21[c]	4.81 t						− 196.4 br dt	3.5			3.5	13	54	13	
22[d]	4.85 br d					− 196.1 dddd					10	44.5	7.5	2.5	
23[e]	4.74 t	3.72 ddd	4.46 dt	3.39 dt	1.33d (Me) 3.43 (OMe)		− 199.9 dddd	3.5	9	9	3.5	13	54.5	13	

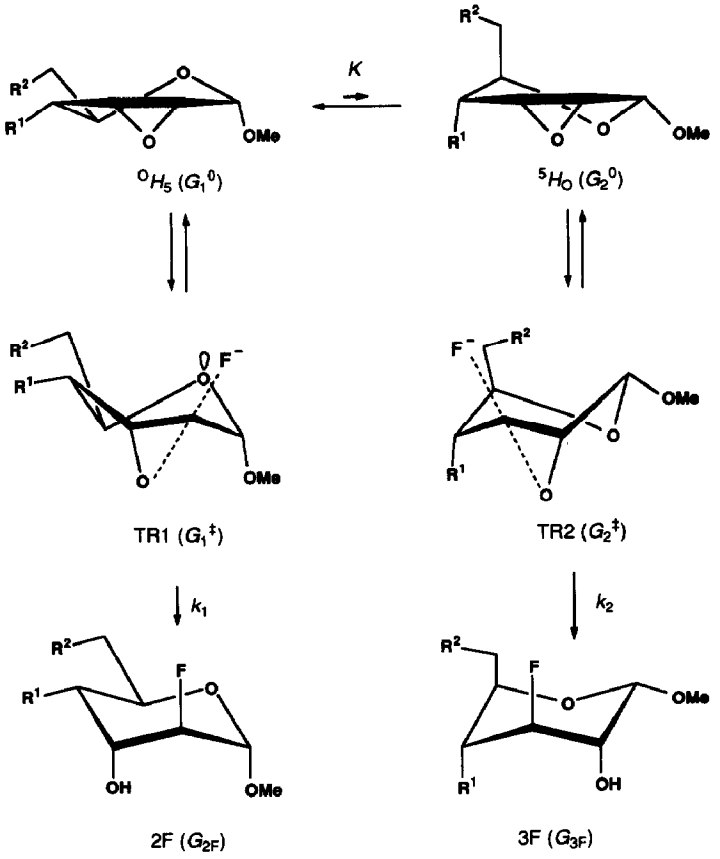
24[e]	4.80 br d	4.66 ddd	4.06 m	3.43 m	1.37d (Me) 3.46 (OMe)	− 196.9 dddd		1.5	3.5		8.5	45	7	2.5	$J_{1,3}$ 1.5 $J_{4,5}$ 10
25[f]	4.71 t	3.71 ddd	4.53 dt	2.95 ddd	1.30d (Me) 2.76 br d (OH) 3.41s (OMe-1) 3.56 d (OMe-4)		− 196.3 br dt	3.5	9	9	4	14	54	13	$J_{4,5}$ 9.5 $J_{OMe,F}$ 1.3
26[e]	4.76 br d	4.65 ddd	4.26 dt	3.15 dt	1.33d (Me) 3.44 (OMe) 3.45 (OMe)	− 196.1 dddd		1.5	3.5	3	10	45	8	3	$J_{4,5}$ 9.8 $J_{OH,F}$ 3
27	4.79 t	3.65 dddd	4.66 dddd	1.54 (2.15)	1.24 (Me) 3.41 (OMe)		− 188.4 m	4	9	11.5 (5.5)	4	13.5	53	~ 12 (~ 5)	$J_{2,OH}$ 9
28	4.85 br d	4.35 dddd	~ 4.4 m	1.81 (1.73)	1.25 (Me) 3.45 (OMe) 3.17 (OH) dd	− 193.6 m		~ 1.5	~ 3		8	45.5	7	3.3 (~ 1)	$J_{3,OH}$ 10.5 $J_{OH,F}$ 2

[a] The sets of **15** and **16**, **19** and **20**, and **21** and **22** could not be separated because of their having the same respective mobilities and, therefore, they were measured as a mixture. [b] In D_2O. [c] F-6: δ 235.3 dt, $J_{5,F}$ 28, $J_{6,F} = J_{6',F}$ 48 Hz. [d] F-6: δ 235.4 dt, $J_{5,F}$ 27.5, $J_{6,F} = J_{6'F}$ 48 Hz. [e] In $CDCl_3$–D_2O. [f] Irradiation of OMe-4 collapsed the broad dt of ^{19}F to dddd.

where G_1^0 and G_2^0 are the free energies of the ${}^0H_5$ and ${}^5H_0$ forms, respectively, and k_2/k_1 is determined by:

$$\ln(k_2/k_1) = -(\Delta G_2^{\ddagger} - \Delta G_1^{\ddagger})/RT = -\Delta\Delta G_{2-1}^{\ddagger}/RT \quad (6)$$

where $\Delta G_1^{\ddagger}$ is the free-energy difference between the transition state TR1 ($G_1^{\ddagger}$) and the ground state ${}^0H_5$ (G_1^0), and $\Delta G_2^{\ddagger}$ is the free-energy difference between the states of TR2 ($G_2^{\ddagger}$) and ${}^5H_0$(G_2^0) (see Scheme 1), attempts were made to calculate values of G_1^0, G_2^0, $\Delta G_1^{\ddagger}$, and $\Delta G_2^{\ddagger}$. However, as the calculation of the transition-state energy by the MM method is difficult, we made an assumption that $G_1^{\ddagger}$ is composed from three components, that is, (*a*) oxirane-ring breaking energy (G_X), which is expected to be almost equal in magnitude in all oxirane compounds concerned, (*b*) polar, repulsive energy (G_Y) created by interaction between the fluoride ion approaching at C-2 and the pyranoid-ring oxygen, the G_Y being considered almost equal in magnitude for the species producing 2F compounds, because a similar steric environment without influence by the substituents



Scheme 1. The free-energy level of each conformer is given in parentheses.

at C-4 and C-6 is expected in all TR1 states, and (*c*) the free energy (G_{2F}) of the 2F conformer just produced, the G_{2F} being considered to contain all steric and polar, repulsive (or attractive) energies other than those involved in G_X and G_Y. Likewise $G_2^{\ddagger}$ is assumed to be the sum of the G_X and the free energy (G_{3F}) of the 3F conformer produced; in this case the energy corresponding to G_Y is not considered because the polar, repulsive energy created by interaction between the fluoride ion approaching at C-3 and the pyranoid-ring oxygen will be negligible, and the other steric energies caused by interactions between the fluoride ion and several ring substituents will be involved in the G_{3F}. Therefore, the energy difference between $\Delta G_1^{\ddagger}$ and $\Delta G_2^{\ddagger}$ in Eq. *6* may be written as:

$$\begin{aligned}\Delta G_2^{\ddagger} - \Delta G_1^{\ddagger} &= (G_X + G_{3F} - G_2^0) - (G_X + G_Y + G_{2F} - G_1^0) \\ &= \Delta G_{3F-2F} - G_Y - \Delta G_{2-1}^0 \end{aligned} \tag{7}$$

where ΔG_{3F-2F} is the free-energy difference between the 3F [$^1C_4$(D)] and 2F [$^4C_1$(D)] conformers.

Here the conformations of TR1 and TR2 merit discussion. In the usual SN2 reaction, the transition state is a trigonal bipyramid with the nucleophile approaching at C-2 (C-3 for TR2) and the leaving group there occupying an apical position. However, in our fluorinations, the fluoride ion does not approach C-2 (C-3) perpendicularly, but from a direction slightly inclined toward C-1 (C-4) and, as the fluoride ion approaches more to C-2 (C-3), the C-2 (C-3) segment rises up as C-3 (C-2), bearing the quasi-axial oxygen atom, sinks down, giving, in consequence, a conformer similar to the $^4C_1$(D) [$^1C_4$(D)] structure (see Scheme 1). Therefore, it is not so presumptuous to assume that the transition states resemble the products.

As the free energies G^0 and $G^{\ddagger}$ are expressed as $G^0 = H_f^0 - TS^0$ and $G^{\ddagger} = H_f^{\ddagger} - TS^{\ddagger}$, respectively, where H_f^0 and $H_f^{\ddagger}$, and S^0 and $S^{\ddagger}$ are the heats of formation and entropies for the ground and transition-state structures, respectively, attempts were made to evaluate $H_{1,f}^0$, $H_{2,f}^0$, $H_{1,f}^{\ddagger}$, and $H_{2,f}^{\ddagger}$ by the MM method, and S^0 and $S^{\ddagger}$ were calculated[43] based on the equations $S = 2.3\,R \log P$, where P is the number of possible conformers*. The H_f values were actually calculated based on the equation[42b] H_f = SE + BE + $4RT$, where SE is the steric energy for the minimum-energy conformer, BE is the bond enthalpy, and $4RT$ is the adjusting term corresponding to the Bolzmann distribution (3.52 kcal mol^{-1} for the present case). The $(G_1^0)_{MM}$, $(G_2^0)_{MM}$, $(G_{2F})_{MM}$, and $(G_{3F})_{MM}$ values thus calculated are shown in Table III. It is noteworthy that the values of ΔG_{2-1}^0 and ΔG_{3F-2F} for the compounds having an OH-4 group (**2, 5,** and **10**; hereafter denoted as OH-4 compounds) are significantly smaller than those for the compounds having an OMe-4 group (**3, 7, 8,** and **11**; hereafter denoted as OMe-4 compounds), (compare also K_{MM} in Table V). This may be attributed to the presence of the free hydrogen atom at OH-4, which may lower the energy of the higher-energy conformers ($^5H_0$ and $^1C_{4(3F)}$). Inspections of the conformations of the $^5H_0$ and $^1C_{4(3F)}$ forms corre-

* For example, P values of **2, 3, 5,** or **7** for $^0H_5$ and $^5H_0$ forms are 18 and 12, respectively, and those of **13, 15, 17,** or **19** for the $^1C_4$(D) form is 24.

TABLE III

Free energies[a] obtained by MM calculation[b]

Starting compound	$(G_1^0)_{MM}$	$(G_2^0)_{MM}$	ΔG_{2-1}^0	$(G_{2F})_{MM}$	$(G_{3F})_{MM}$	ΔG_{3F-2F}	$\Delta G_{3F-2F} - \Delta G_{2-1}^0$
2	−54.15	−50.93	3.22	−266.40	−261.95	4.45	1.23
3	−48.04	−43.72	4.32	−259.56	−254.10	5.46	1.14
5	−49.67	−46.58	3.09	−261.85	−258.61	3.24	0.15
7	−43.82	−39.42	4.40	−255.14	−250.06	5.08	0.68
8	−54.85	−50.39	4.46	−265.96	−260.08	5.88	1.42
10	−16.85	−14.18	2.67	−228.80	−226.49	2.30	−0.37
11	−11.27	−6.89	4.38	−222.67	−218.09	4.59	0.21
12	21.25	25.01	3.76	−189.35	−186.70	2.65	−1.11

[a] Units: kcal mol^{-1}. [b] Calculations were performed using MM2 UEC (by Yoshiyuki Hase), a modified version based on MM2 (87) by N. L. Allinger, taking into account hydrogen bonding; in this calculation, two lone pairs are attached on every oxygen atom. The SE values of the least minimum and local minima were searched by stepwise tilting (120°) of the O–H, O–Me, and C-6–O bonds of a starting conformer, independently (the *G* values cited here are those based on the least-minimum SE values).

sponding to their calculated energy minima and the local energy minima near the minima show that, for the OH-4 compounds (**2, 5,** and **10**; and **13, 17,** and **23**), the OH-4 hydrogen atom is directed to the inside of the pyranoid ring, suggesting the existence of hydrogen bonding between OH-4 and the inner-side oxygen atoms (the projection angles of H-4–C-4–O–H for the former and the latter groups of compounds are −177° to −178° and +176° to +179°, respectively). As for the OMe-4 compounds (**3, 7, 8,** and **11**; and **15, 19, 21,** and **25**), the OMe-4 methyl and C-5 (or C-3) are in antiperiplanar positions (the projection angles of C-5–C-4–O–Me of the former and the latter groups

TABLE IV

Dipole-energy difference between the $^0H_5$ and $^5H_0$ forms in the least-minimum energy of the methyl 2,3-anhydro-4,6-disubstituted-α-D-allopyranosides

Compound	*Substituent at*		*ΔE ($^5H_0 - {}^0H_5$) kcal mol^{-1}*	*ΔΔE between the respective 4-deoxy compounds*
	C-4	*C-6*		
12	H	H	1.53	
10	OH	H	0.37	−1.16
11	OMe	H	2.51	0.98
	H	OH	0.74	
2	OH	OH	−0.71	−1.45
3	OMe	OH	1.25	0.51
	H	OMe	0.62	
5	OH	OMe	−1.00	−1.62
7	OMe	OMe	1.40	0.78

of compounds are −172° to −174° or −82° to −85°, and −156° to −169° or −82° to −86°, respectively).

Another energy change supposedly attributable to the OH-4 and OMe-4 groups is that for the dipole energies of the OH-4 and OMe-4 compounds obtained by the MM calculations (see Table IV). The data suggest that the $^5H_0$ form is stabilized by ~ 1.5 kcal mol^{-1} (relative to the 4-deoxy compounds) by hydrogen bonding between OH-4 and the pyranoid ring, oxirane, and/or glycosidic oxygen atoms. Such a hydrogen bond could also be formed in the $^0H_5$ form, but it would be much weaker, if present at all, because of longer H–O distances and unsuitable angles for forming a hydrogen bond. The increased dipole-energy difference of the OMe-4 compounds (Table IV), relative to the 4-deoxy compounds may be attributed to the repulsive interaction between the OMe oxygen and the oxirane, and pyranoid-ring oxygens.

TABLE V

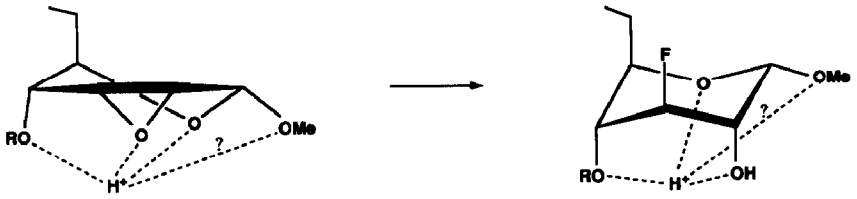
Several parameters[a] derived from the MM calculation (except for *r*)

Starting compound	*Substituents at*		K_{MM}	$(k_2/k_1)'_{MM}$	$r'_{MM} \times 10^3$	r (*mean value*)	$r/(r'_{MM} \times 10^3)$
	C-4	*C-6*					
2	OH	OH	0.026	0.25	6.37	11	1.73
3	OMe	OH	0.007	0.27	2.02	1.32	0.65
5	OH	OMe	0.030	0.84	25.3	1.18	0.05
7	OMe	OMe	0.007	0.46	3.12	2.07	0.66
8	OMe	F	0.006	0.20	5	1.66	1.33
10	OH	H	0.048	1.51	73.0	2.20	0.03
11	OMe	H	0.007	0.80	5.46	1.86	0.34
12	H	H	0.012	3.54	49.2	5.34	0.11

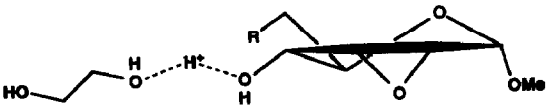
[a] See text.

The K_{MM} and $(k_2/k_1)_{MM}$ values are then calculated using the ΔG values (Table III) based on Eqs *5*, *6*, *7*. However, as G_Y (in Eq. *7*) is unknown (but assusmed to be constant), $(k_2/k_1)_{MM}/e^{G_Y/RT}$ [$\equiv (k_2/k_1)'_{MM}$] is used instead of $(k_2/k_1)_{MM}$, which is equal to $e^{-(\Delta G_{3F-2F}/RT)}$ (see Eq. *8* later). The data obtained are shown in Table V, together with the product of the two terms, $K_{MM} \cdot (k_2/k_1)'_{MM} = r'_{MM}$. The order of the compounds arranged according to the r'_{MM} value is **8<3<7<11<2<<5<12<10.** Comparison of the r'_{MM} values suggest that the OH-4 compounds (except **2**) should give 3F compounds more than 5 times more rapidly than the OMe-4 compounds. But this is not in fact the case; moreover, no relation between the orders by the r'_{MM} values and by the actual *r* values **(5<3<8<11<7<10<12<2)** was observed. This discrepancy between *r* and r'_{MM} may be attributed to the computer program's inability to cope with the solvation effect. However, this discrepancy may itself indicate the degree of solvation or environmental effects and might be quantified by the term r/r'_{MM}; as the value becomes larger, the degree of solvation (and the other actions mediated by solvation) to facilitate the formation of

the 3F compounds will increase. Arrangement of the compounds according to this parameter (Table V) gave the order **10** (OH-4, H-6) < **5** (OH, OMe) < < **12** (H, H) < < **11** (OMe, H) < **3** (Me, OH) ≈ **7** (OMe, OMe) < < **8** (OMe, F) < **2** (OH, OH). As **12** is a compound supposed to be least influenced by solvation as it lacks polar substituents at C-4 and C-6, the fact that **3, 7, 8** and **11** are in a higher region than **12**, and that **5** and **10** are in a lower region than **12** suggests that solvation makes the OMe-4 group work to stabilize the $^{5}H_{0}$ and $^{1}C_{4(3F)}$ conformers, and OH-4, works to stabilize the $^{0}H_{5}$ and $^{4}C_{1(2F)}$ conformers, relative to the respective vapor states. The only exception is **2**. The former description could be reasoned by assuming that hydrogen bonds occur between the OMe-4 and the oxirane, pyranoid-ring, and/or glycosidic oxygens (?) as depicted in I and II (R = Me; some of their hydrogen-bonds may be incomplete). This speculation is analogous to that already described for the OH-4 compounds in terms of hydrogen bonding (see also Table IV). In this instance, however, the OMe-4 group, which is more electron donating than OH-4, can capture a proton from KHF_2 in ethane-1,2-diol and

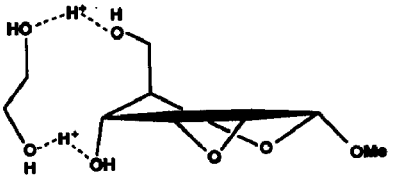


I (R= Me or H) II



III

R= OH



IV

facilitate the formation of polydentate hydrogen bonds (these hydrogen-bonds will be in a rapid equilibrium between each other). The antiperiplanar disposition of the O-Me-4 and C-3 (or C-5) groups, as described in a previous paragraph, will also facilitate the incorporation of the H^+ ion by aligning a lone pair on the methoxyl oxygen in a suitable direction. The fact that reactions with KF (producing no H^+) in ethane-1,2-diol gave no detectable, fluorinated products provides partial support for this assumption. In contrast, the OH-4 group works in the opposite sense. This hydroxyl group may bind to ethane-1,2-diol through an H^+ ion bridging two oxygen atoms, as depicted in III. Formation of a long chain involving a solvent molecule would act to stabilize the equatorial disposition; however, actually the OH-4 compounds will be in an equilibrium between two conformers I (R = H) and III, with the latter in preponderance. The long chain will also be involved in the MeO-4 compounds, however, the O-Me-4 will tend to occupy the least-hindered site, destabilizing the chain. However, when another hydroxyl group is present at C-6 as in **2**, the free hydroxyl end of the solvent-chain should bind, through similar hydrogen-bonding, to OH-6 to form an eleven-membered ring stabilizing the $^5H_0$ form (and $^1C_{4(3F)}$ form) as shown in IV. In the case of **5**, however, the MeO-6 group will hinder the formation of such a ring. This may be the reason why only **2** is in a special position in the rank list by r/r'_{MM}. This kind of ring, however, could also be involved in the $^0H_5$ or $^4C_{1(2F)}$ forms, but in these conformations destabilization by a strong O-4–O-6 electrostatic repulsion (caused by parallel C-4–O and C-6–O bonds as the averaged state) would be expected. This solvent ring may also explain the production of the 3-*O*-(2-hydroxyethyl) compound **29**, which is observed only in the reaction of **2**. Opening of the solvent ring followed by reaction of the freed oxygen atom at C-3 will give **29**. Further, as this solvent ring involves a bridged H^+ ion, this will attract the F^- counter ion, situating it well for attack at C-3. Throughout the study it should be stressed that the C-6 substituents exhibit only a minor effect. However, the reason why **8** has a similar high r/r'_{MM} value as **2** is not clear.

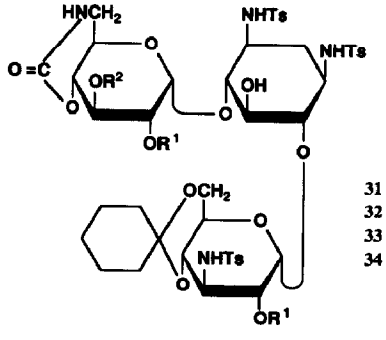
Aside from the hydrogen bonding and solvent effect described here, another prominent feature in these fluorinations is the fact that ΔG_{3F-2F} is positive in all compounds. These conditions favor production of 2F compounds much more than 3F compounds (see Eq. *8* below). But the observed fact is the reverse. Even if the solvation works to greatly lower the ΔG_{3F-2F} values, it may come far from reversing the sign. As r_{MM} can be written as:

$$r_{MM} = e^{\Delta G_{3F-2F}/RT} (= r'_{MM}) \cdot e^{(G_Y/RT)} \qquad (8)$$

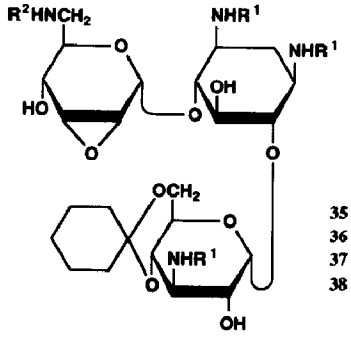
(Eq. *8* is readily derived from Eqs. *5*, *6*, and *7*), G_Y should be large; in other words, approach of the F^- ion to C-2 in TR1 (Scheme 1) would be greatly hindered by axial lone-pair electrons at the pyranoid-ring oxygen. This may be the main reason why 3F compounds are always produced in preponderance over the corresponding 2F compounds.

As the experiments just described indicated that 3-deoxy-3-fluoro-α-D-glucopyranosides may be obtained from 2,3-anhydro-α-D-allopyranosides, albeit in moderate

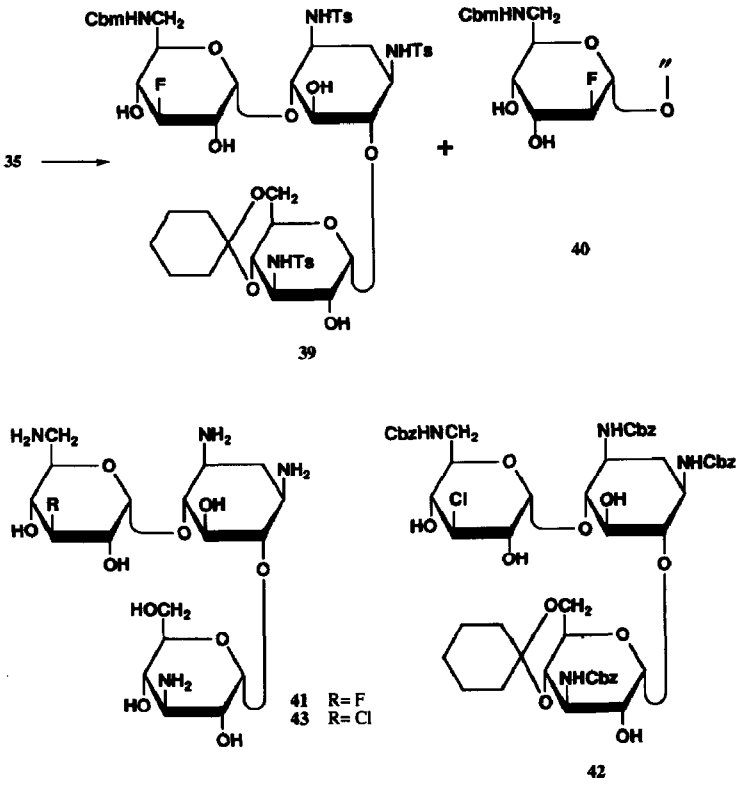
yields, the preparation of 3′-deoxy-3′-fluorokanamycin A was undertaken, starting from a suitably protected kanamycin A derivative having 2′,3′-anhydro-α-D-allopyranosyl structure. 6′-*N*,4′-*O*-Carbonyl-4″,6″-*O*-cyclohexylidene-1,3,3″-tri-*N*-tosylkanamycin A[44] (**31**) was selectively acetylated with *N*-acetylimidazole in 1:10 pyridine–dimethyl sulfoxide to give the 2′,2″-di-*O*-acetyl derivative **32**, which was then benzylsulfonylated with phenylmethanesulfonyl chloride to give the 3′-*O*-sulfonyl derivative **33**. After removal of the acetyl groups (Zemplén), the product **34** was treated with sodium methoxide in methanol to give the 2′,3′-anhydro-D-allopyranosyl derivative **35** bearing an 6′-*N*-methoxycarbonyl group in 75% isolated yield. Treatment of **35** with KHF_2 in ethane-1,2-diol at 160° gave two major products comparatively readily (as compated to **2**, **3**, **5**, and **7**). These were separated by column chromatography in 31 and 16% yields and identified as the 3′-deoxy-3′-fluoro-α-D-*gluco* (**39**) and 2′-deoxy-2′-fluoro-α-D-*altro* (**40**) compounds. Their structures were confirmed by n.m.r. spectroscopy; the large splittings of the H-3′ (55 Hz for **39**) and H-2′ signals (46 Hz for **40**) indicated that the fluorine atoms were introduced at C-3′ and C-2′, respectively; also the large and small proton–proton vicinal couplings relating to the H-3′ and H-2′ atoms indicated that these fluorine atoms were introduced in equatorial and axial dispositions, respectively. Detosylation of **39** with sodium in liquid ammonia, followed by de(methoxycarbonyl)ation (in an alkaline medium) and de(cyclohexyliden)ation (with a cation-ex-



	R^1	R^2
31	H	H
32	Ac	H
33	Ac	SO_2CH_2Ph
34	H	SO_2CH_2Ph



	R^1	R^2
35	Ts	CO_2Me (Cbm)
36	Ts	CO_2CH_2Ph (Cbz)
37	H	H
38	CO_2CH_2Ph	CO_2CH_2Ph



change resin) gave the desired 3′-deoxy-3′-fluorokanamycin A (**41**) in 84% yield. It was identical, in all respects, with a specimen obtained by the glycosylation method[1].

Likewise, 3′-chloro-3′-deoxykanamycin A was prepared by a similar sequence of reactions. However, as the chlorine atom introduced would be reductively removed by sodium in liquid ammonia during detosylation, tosyl groups serving for *N*-protection in **35** were replaced by benzyloxycarbonyl groups, removable by catalytic hydrogenation at a later stage. Thus, the 4′,6′-cyclic carbamate of **34** was transformed into a 6′-*N*-benzyloxycarbonyl group by treatment with sodium benzyloxide in benzyl alcohol, and the product **36** was converted into the 2′,3′-anhydro-4″,6″-*O*-cyclohexylidene derivative **37** having free amino groups by treatment with sodium in liquid ammonia. After *N*-benzyloxycarbonylation, the *N*-protected derivative **38** was treated with LiCl–HCl in DMF, to give the 3′-chloro-3′-deoxy-D-*gluco* derivative **42** in 89% yield. Decyclohexylidenation followed by catalytic de(benzyloxycarbonyl)ation, which did not affect the chloro substituent, furnished 3′-chloro-3′-deoxykanamycin A (**43**) in 85% yield.

The antibacterial activity of **43** was approximately one sixth of that of 3′-deoxy-3′-fluorokanamycin A[45] (**41**), although it was active against resistant bacteria. This result suggests that introduction of the somewhat bulky 3′-chloro atom greatly lowers the activity, in contrast to 3′-deoxygenation or 3′-deoxyfluorination.

EXPERIMENTAL

General methods. — Optical rotations were determined with a Perkin–Elmer 241 polarimeter. ^{1}H- and ^{19}F-n.m.r. spectra were recorded at 250 MHz in the F.t. mode with a Bruker WM 250 spectrometer. Chemical shifts (δ) are recorded downfield from internal Me_4Si and coupling constants (J by Hz) are first order. T.l.c. was performed on Kieselgel 60 F_{254} (Merck), and column chromatography, on Wakogel C-200.

Methyl 2,3-anhydro-4-O-methyl-α-D-allopyranoside (**3**). — A mixture of **2** (300 mg), MeI (0.13 mL), and Ag_2O (1.0 g) in DMF (6 mL) was stirred for 1 h at room temperature. T.l.c. (25:1 $CHCl_3$–MeOH) of the solution showed a single spot at R_F 0.25. Conventional work-up gave **3** as a solid; yield 225 mg (69%), $[\alpha]_D^{18}$ + 197° (*c* 1, $CHCl_3$), lit.[41] $[\alpha]_D^{10}$ + 193.5° (water); ^{1}H-n.m.r. ($CDCl_3$): δ 3.45 and 3.53 (each s, 3 H, OMe × 2), and 4.90 (d, 1 H, $J_{1,2}$ 3 Hz, H-1).

Methyl 6-O-acetyl-2,3-anhydro-4-O-methyl-α-D-allopyranoside (**4**). — Conventional acetylation (Ac_2O in pyridine) of **3** gave a syrup, $[\alpha]_D^{20}$ + 180° (*c* 0.5, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 2.05 (s, 3 H, Ac), 3.47 and 3.51 (each s, 3 H, OMe × 2), ABq centered at 4.27, each signal being split into a doublet (2 H, $J_{5,6}$ 2.5, $J_{5,6'}$ 5, and $J_{6,6'}$ 12 Hz, H-6, 6'); m.s.: calc. for $C_{10}H_{16}O_6$: mol. wt. 232.2, found: *m/z* 233 $(M + H)^+$.

Methyl 2,3-anhydro-6-O-methyl-α-D-allopyranoside (**5**). — A solution of **2** (234 mg) and BzCl (0.16 mL) in pyridine (5 mL) was kept for 15 min at 0°. Addition of water (0.1 mL) followed by standard purification including column chromatography (50:1 $CHCl_3$–MeOH) gave the 6-*O*-benzoyl derivative as a solid; yield 202 mg (54%), $[\alpha]_D^{20}$ + 105° (*c* 1, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 3.45 (s, 3 H, OMe), 3.52 (dd, 1 H, $J_{2,3}$ 3.5 and $J_{3,4}$ 1.5 Hz, H-3), 3.57 (dd, 1 H, H-2), ABq centered at 4.58, each signal being split into a doublet (2 H, $J_{5,6}$ 2.5, $J_{5,6'}$ 5, and $J_{6,6'}$ 12 Hz, H-6, 6'), and 4.91 (d, 1 H, $J_{1,2}$ 3 Hz, H-1); m.s.: calc. for $C_{14}H_{16}O_6$: mol. wt. 280.3, found: *m/z* 281 $(M + H)^+$. A mixture of the derivative (175 mg), 3,4-dihydro-2*H*-pyran (0.5 mL) and *p*-toluenesulfonic acid (5 mg) in $CHCl_3$ (3 mL) was kept for 30 min at room temperature. Neutralization (aqueous $NaHCO_3$) followed by conventional purification gave the 4-*O*-tetrahydropyranyl derivative as a syrup; yield 225 mg (quant.); m.s.: calc. for $C_{19}H_{24}O_7$: mol. wt. 364.4, found: *m/z* 365 $(M + H)^+$. To a solution of the derivative (185 mg) in $CHCl_3$ (5 mL) was added 28% NaOMe in MeOH (0.5 mL) and the solution was kept for 30 min at room temperature. The debenzoyl derivative was obtained as a syrup, 132 mg (quant.); m.s.: calc. for $C_{12}H_{20}O_6$: mol. wt. 260.3, found: *m/z* 261 $(M + H)^+$. To a mixture of the derivative (125 mg) and NaH (25 mg) in DMF (3 mL) was added MeI (0.1 mL) and the mixture was stirred for 15 min at room temperature. The 6-*O*-methyl derivative was obtained as a syrup, 133 mg (quant.); m.s.: calc. for $C_{13}H_{22}O_6$: mol. wt. 274.3, found: *m/z* 275 $(M + H)^+$. To a solution of the derivative (130 mg) in MeCN (4 mL) was added aq. M HCl (1 mL) and the solution was kept for 1 h at room temperature. Standard purification involving column chromatography (50:1 $CHCl_3$–MeOH) gave **5** as a syrup, which gave needles on standing; yield 67.2 mg (75%), m.p. 76–77.5°, $[\alpha]_D^{20}$ + 185° (*c* 1, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 3.41 and 3.46 (each s, 3 H, OMe × 2), 3.48 (dd, 1 H, H-3), 3.50 (dd, 1 H, H-2), 4.01 (dd, 1 H, H-4), and 4.92 (d, 1 H, H-1); $J_{1,2}$ 3, $J_{2,3}$ 4.5, $J_{3,4}$ 1.5, and $J_{4,5}$ 9 Hz.

Anal. Calc. for $C_8H_{14}O_5$: C, 50.22; H, 7.42. Found: C, 50.67; H, 7.45.

Methyl 4-O-acetyl-2,3-anhydro-6-O-methyl-α-D-allopyranoside (**6**). — Conventional acetylation (Ac_2O–pyridine) of **5** gave a syrup, $[\alpha]_D^{20}$ +176° (*c* 0.7, $CHCl_3$); ^{1}H-n.m.r. ($CDCL_3$): δ 2.02 (s, 3 H, Ac), 3.37 and 3.47 (each s, 3 H, OMe × 2), 3.59 (dd, 1 H, H-3), 4.96 (d, 1 H, H-1), and 5.18 (dd, 1 H, H-4); $J_{1,2}$ 3, $J_{2,3}$ 4.5, $J_{3,4}$ 1.5, and $J_{4,5}$ 9 Hz; m.s.: calc. for $C_{10}H_{16}O_6$: mol. wt. 232.2, found: *m/z* 233 $(M + H)^+$.

Methyl 2,3-anhydro-6-deoxy-6-fluoro-4-O-methyl-α-D-allopyranoside (**8**). — To a cold (0–5°) solution of **3** (305 mg) in CH_2Cl_2 (6 mL) and pyridine (0.3 mL) was added DAST (0.65 mL), and the solution was kept for 6 h at room temperature. The solution was washed with aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated to give a residue that was chromatographed with $CHCl_3$ to give needles of **8**; yield 76.5 mg (25%), m.p. 109–111°, $[\alpha]_D^{24}$ +179° (*c* 1, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 3.46 and 3.537 (each s, 3 H, OMe × 2), 3.546 (dd, 1 H, H-2), 3.59 (unresolved d, forming an ABq-like pattern together with the signals of H-2; H-3), 3.69 (dd, 1 H, H-4), 3.87 (dddd, 1 H, H-5), 4.57 and 4.63 (each ddd, 1 H × 2, H-6a and 6b; the signals were separated into two blocks (centered at δ 4.50 and 4.69), the upper and lower ones formed, respectively, a similar ABq-like pattern), and 4.91 (d, 1 H, H-1); $J_{1,2}$ 3.0, $J_{2,3}$ 4.0, $J_{3,4}$ 1.5, $J_{4,5}$ 9.5, $J_{5,6a}$ 2, $J_{5,6b}$ 3.0, $J_{6a,6b}$ 10.5, $J_{5,F}$ 29, $J_{6a,F}$ 48, and $J_{6b,F}$ 47.5 Hz. Irradiation of F-6 collapsed the signals of H-3 to sharp double doublets indicating existence of a small coupling between them. ^{19}F-N.m.r. ($CDCl_3$): δ −235.64 (dt, *J* 29, 47.5, and 48 Hz, F-6); m.s.: calc. for $C_8H_{13}FO_4$: mol. wt. 192.2, found: *m/z* 161 $(M - OMe)^+$.

Methyl 2,3-anhydro-6-deoxy-α-D-allopyranoside (**10**). — A mixture of **2** (245 mg), Ph_3P (500 mg), and CCl_4 (0.5 mL) in pyridine (5 mL) was heated for 3 h at 50°. T.l.c. (25:1 $CHCl_3$–MeOH) of the solution showed a single spot at R_F 0.4 (**2**: R_F 0.12). The product was purified by short-column chromatography [$CHCl_3$ (to remove the remaining Ph_3P) →25:1 $CHCl_3$–MeOH] to give **9** as a solid; yield 226 mg (83%); m.s.: calc. for $C_7H_{11}ClO_4$: mol. wt. 194.6, found: *m/z* 163 $(M - OMe)^+$. To a solution of **9** (435 mg) in toluene (10 mL) was added Bu_3SnH (1.0 g) and 2,2′-azobis(isobutanonitrile) (10 mg), and the mixture was heated for 4 h at 90°. Concentration gave a residue that was chromatographed ($CHCl_3$ → 50:1 $CHCl_3$–MeOH) to give needles of **10**; yield 314 mg (88%), m.p. 99–100°, $[\alpha]_D^{24}$ +165° (*c* 1, $CHCl_3$); ^{1}H-n.m.r. (pyridine-d_5): δ 1.44 (d, 1 H, Me-5), 3.40 (s, 3 H, OMe); 3.55 (unresolved dd, 1 H, H-3), and 3.58 (slightly unsymmetrical dd, 1 H, H-2), forming an ABq-like pattern as a whole; 3.81 (br t, $J \sim 8$ Hz, 1 H, H-4), 4.19 (dq, 1 H, H-5), 4.93 (d, 1 H, H-1), and 7.10 (broad d, $J_{4,OH}$ 7 Hz, OH-4); $J_{1,2}$ 3, $J_{2,3}$ 4, $J_{3,4}$ 1.5, $J_{4,5}$ 9.5, and $J_{5,6}$ 6.5 Hz; m.s.: calc. for $C_7H_{12}O_4$: mol. wt. 160.2, found: *m/z* 129 $(M - OMe)^+$.

Methyl 2,3-anhydro-6-deoxy-4-O-methyl-α-D-allopyranoside (**11**). — To an ice-cold solution of **10** (149 mg) in DMF (3 mL) were added NaH (60% in oil, 41 mg) and MeI (0.18 mL) and the mixture was stirred for 15 min at room temperature. After addition of $CHCl_3$ (30 mL) the solution was washed with water, dried (Na_2SO_4), and concentrated. The residue was chromatographed (toluene → $CHCl_3$ → 50:1 $CHCl_3$–MeOH) to give needles (gradually evaporated under vacuum) of **11**; yield 138 mg (85%), m.p. 80–80.5°, $[\alpha]_D^{20}$ +210° (*c* 1, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 1.23 (d, 1 H, Me-5), 3.24

(dd, 1 H, H-4), 3.44 and 3.51 (each s, each 3 H, OMe × 2), ~ 3.51 (ABq-like signals as a whole, 2 H, H-2, 3), 3.85 (dq, 1 H, H-5), and 4.81 (d, 1 H, H-1); $J_{1,2}$ 3, $J_{3,4}$ 1.5, and $J_{4,5}$ 9.0 Hz; m.s.: calc. for $C_8H_{14}O_4$: mol. wt. 174.2, found: *m/z* 143 $(M - OMe)^+$.

Reaction of **2** *with potassium hydrogenfluoride.* — A mixture of **2** (ref. 6, 200 mg) and KHF_2 (312 mg) in ethane-1,2-diol (distilled, 3 mL) was heated in a pressure tube for 3 h at 160°. T.l.c. (4:1 $CHCl_3$–MeOH) of the solution showed spots of R_F 0.4, 0.48 (**13**), 0.53, and 0.63 (**29**). After cooling, aq. 5% $NaHCO_3$ (1 mL) was added and the mixture, after filtration, was evaporated. The residual syrup was chromatographed with 100:1 → 30:1 $CHCl_3$–MeOH to give **13** as a solid; yield 108 mg (48%), and syrupy **29**; yield ~ 20 mg. Compound **13** had $[\alpha]_D^{22}$ + 188° (*c* 0.7, H_2O).

Anal. Calc. for $C_7H_{13}FO_5 \cdot H_2O$: C, 39.25; H, 7.06; F, 8.87. Found: C, 39.51; H, 6.78; F, 9.10.

*Methyl 3-O-(2-acetoxyethyl)-2,4,6-tri-O-acetyl-α-*D*-glucopyranoside* (**30**). — Conventional acetylation (Ac_2O–pyridine) of **29** gave **30** almost quantitatively as a syrup; $[\alpha]_D^{22}$ + 77° (*c* 1.1, $CHCl_3$); ^{1}H-n.m.r. ($CDCl_3$): δ 2.06, 2.09, 2.10, and 2.14 (each s, 3 H, OAc × 4), 3.40 (s, 3 H, OMe), 3.7–3.9 (m, 4 H, H-3, 5, and $AcOCH_2CH_2O$-), 4.05–4.3 (m, 4 H, H-6, 6′, and $AcOCH_2CH_2O$-), 4.83 (dd, 1 H, H-2), 4.93 (d, 1 H, H-1), and 5.03 (t, 1 H, H-4); $J_{1,2}$ 3.5 and $J_{2,3} = J_{3,4}$ 9 Hz; m.s.: calc. for $C_{17}H_{26}O_{11}$: mol. wt. 406.4, found: *m/z* 406 (M^+).

Reaction of **3** *with potassium hydrogenfluoride.* — A mixture of **3** (53.8 mg) and KHF_2 (155 mg) in ethane-1,2-diol (1 mL) was heated for 3 h at 170°. T.l.c. (25:1 $CHCl_3$–MeOH) of the solution showed a main spot at R_F 0.2 (**15** and **16**). Processing as described for **2** (in column chromatography, 25:1 $CHCl_3$–MeOH was used as the developing solvent) gave a ~ 3:2 mixture of a syrup of **15** and **16**, 25.5 mg (43%).

Anal. Calc. for $C_8H_{15}FO_5$: C, 45.71; H, 7.19; F, 9.04. Found: C, 45.47; H, 7.21; F, 8.88.

Reaction of **5** *with potassium hydrogenfluoride.* — A mixture of **5** (50.2 mg) and KHF_2 (100 mg) in ethane-1,2-diol (1 mL) was heated for 3 h at 170°. T.l.c. (25:1 $CHCl_3$–MeOH) of the solution showed two spots of R_F 0.17 (**17**) and 0.27 (**18**). Neutralization (aq. 5% $NaHCO_3$) followed by evaporation gave a residue, that showed, in the ^{1}H-n.m.r. spectrum, a ~ 1.2:1 mixture of **17** and **18**. The residue was chromatographed with 25:1 $CHCl_3$–MeOH to give **17** as a syrup; yield 23.2 mg (42%) and **18** as a syrup; yield 16.6 mg (30%).

Compound **17** had $[\alpha]_D^{20}$ + 125° (*c* 1, $CHCl_3$).

Anal. Calc. for $C_8H_{15}FO_5$: C, 45.71; H, 7.19; F, 9.04. Found: C, 45.20; H, 7.25; F, 9.45.

Compound **18** had $[\alpha]_D^{20}$ + 126° (*c* 0.7, $CHCl_3$).

Anal. Calc. for $C_8H_{15}FO_5$: C, 45.71; H, 7.19; F, 9.04. Found: C, 45.84; H, 7.45; F, 8.57.

Reaction of **7** *with potassium hydrogenfluoride.* — A mixture of **7** (ref. 6, 120 mg) and KHF_2 (223 mg) in ethane-1,2-diol (1.8 mL) was heated for 3 h at 170°. T.l.c. (2:1 toluene–EtOAc) of the solution showed a main spot at R_F 0.4 (**19** and **20**). Addition of water, followed by extraction of the products with EtOAc and evaporation of the

solvent gave a syrup that was chromatographed with 10:1 toluene–EtOAc to give a ~ 2:1 syrupy mixture of **19** and **20**; yield 77.8 mg (59%).

Anal. Calc. for $C_9H_{17}FO_5$: C, 48.20; H, 7.64; F, 8.47. Found: C, 47.88; H, 7.46; F, 8.25.

Reaction of a mixture of **19** *and* **20** *with potassium hydrogenfluoride.* — A ~ 2:1 mixture (85 mg) of **19** and **20** prepared from **7** (after chromatography) was heated in ethane-1,2-diol (1.5 mL) with KHF_2 (180 mg) for 5 h at 170°. No change in t.l.c. was observed between the solution and the starting mixture (single spot at R_F 0.4 with 2:1 toluene–EtOAc). Subsequent work-up gave a syrup, 67.5 mg, whose ^{1}H-n.m.r. spectrum was superimposable on that of the starting mixture.

Reaction of **8** *with potassium hydrogenfluoride.* — A mixture of **8** (84.4 mg) and KHF_2 (200 mg) in ethane-1,2-diol (1.6 mL) was heated for 3 h at 170°. Processing as described (**19** from **7**) involving column chromatography (20:1 toluene–butanone as the developer) gave a mixture of **21** and **22** (both compounds had the same R_F value of 0.15 by t.l.c. with 10:1 toluene–butanone; **8**: R_F 0.27), 60.6 mg (65%); m.s.: calc. for $C_8H_{14}F_2O_4$: mol. wt. 212.2, found: *m/z* 212 (M^+).

Reaction of **10** *with potassium hydrogenfluoride.* — A mixture of **10** (40 mg) and KHF_2 (90 mg) in ethane-1,2-diol (0.8 mL) was heated for 3 h at 170°. In t.l.c. (25:1 $CHCl_3$–MeOH), the solution showed two spots of R_F 0.1 (**23**) and 0.2 (**24**). Processing involving column chromatography (25:1 $CHCl_3$–MeOH as the devoloper) gave **23** as a solid; yield 18.2 mg (41%) and **24** as a solid; yield 10.5 mg (24%).

Compound **23** had $[\alpha]_D^{23}$ + 159° (*c* 2, $CHCl_3$), m.s.: calc. for $C_7H_{13}FO_4$: mol. wt. 180.2, found: *m/z* 180 (M^+).

Compound **24** had $[\alpha]_D^{23}$ + 133° (*c* 0.8, $CHCl_3$), m.s.: calc. for $C_7H_{13}FO_4$: mol. wt. 180.2, found: *m/z* 180 (M^+).

Reaction of **11** *with potassium hydrogenfluoride.* — A mixture of **11** (50 mg) and KHF_2 (110 mg) in ethane-1,2-diol (1 mL) was heated for 3 h at 170°. T.l.c. (50:1 $CHCl_3$–MeOH) of the solution gave two spots at R_F 0.25 (**25**) and 0.35 (**26**). After processing as described (**13** from **2**), the products were chromatographed with $CHCl_3$ to give needles of **25**; yield 23.6 mg (42%) and **26** as a syrup; yield 10.8 mg (19%), both compounds being volatile under vacuum.

Compound **25** had m.p. 83–84°, $[\alpha]_D^{24}$ + 194° (*c* 1, $CHCl_3$); m.s.: calc. for $C_8H_{15}FO_4$: mol. wt. 194.2, found: *m/z* 163 (M − OMe)$^+$.

Compound **26** had $[\alpha]_D^{24}$ + 170° (*c* 0.4, $CHCl_3$); m.s.: calc. for $C_8H_{15}FO_4$: mol. wt. 194.2, found: *m/z* 194 (M^+).

Reaction of **12** *with potassium hydrogenfluoride.* — A mixture of **12** (100 mg) and KHF_2 (270 mg) in ethane-1,2-diol (2 mL) was heated for 1 h at 170°. T.l.c. (25:1 $CHCl_3$–MeOH) of the solution gave two spots at R_F 0.3 (**27**) and 0.47 (**28**). After addition of aq. $NaHCO_3$ (saturated, 8 mL), the mixture was extracted with $CHCl_3$ (5 mL × 3). The solution was concentrated, and the residue was chromatographed (10 g silica gel) with 50:1 $CHCl_3$–MeOH to give **27** as a syrup; yield 33.7 mg (30%) and **28** as a syrup; yield 3.0 mg (3%), both compounds being fairly volatile under vacuum.

Compound **27** had $[\alpha]_D^{24}$ + 150° (*c* 1, $CHCl_3$); m.s.: calc. for $C_7H_{13}FO_3$: mol. wt. 164.2, found: *m/z* 133 (M − OMe)$^+$.

Compound **28** had $[\alpha]_D^{23}$ +110° (*c* 1.4, $CHCl_3$); m.s.: calc. for $C_7H_{13}FO_3$: mol. wt. 164.2, found: *m/z* 164 (M^+).

2',2''-Di-O-acetyl-6'-N,4'-O-carbonyl-4'',6''-O-cyclohexylidene-1,3,3''-tri-N-tosylkanamycin A (**32**). — A solution of **31** (450 mg) and *N*-acetylimidazole (188 mg) in dry 1:10 pyridine–Me_2SO (2.23 mL) was kept overnight at room temperature. In t.l.c. (5:1:0.1 $CHCl_3$–MeOH–aq. 28% ammonia), the solution showed a single spot at R_F 0.4 (R_F of **31**: 0.2). Addition of aq. 5% $NaHCO_3$ (30 ml) gave a precipitate, which was filtered off, washed with water and ether, and dried to give **32** as a solid; yield 435 mg (90%), $[\alpha]_D^{25}$ +15° (*c* 0.4, acetone); ^{1}H-n.m.r. (pyridine-d_5): δ 2.22, 2.23, 2.26, 2.27, and 2.47 [each s, 3 H, Ac × 2 and Ts(*Me*) × 3], 5.40 (dd, 1 H, H-2' or -2''), 5.59 (dd, 1 H, H-2'' or -2'), 5.88 (d, 1 H, H-1' or -1''), and 6.02 (d, 1 H, H-1'' or -1'); $J_{1',2'} = J_{1'',2''}$ 4, and $J_{2',3'} = J_{2'',3''}$ 9 Hz.

Anal. Calc. for $C_{50}H_{64}N_5O_{20}S_3 \cdot H_2O$: C, 51.98; H, 5.76; N, 4.85; S, 8.33. Found: C, 51.84; H, 5.50; N, 4.72; S, 8.99.

2',2''-Di-O-acetyl-3'-O-benzylsulfonyl-6'-N,4'-O-carbonyl-4'',6''-O-cyclohexylidene-1,3,3''-tri-N-tosylkanamycin A (**33**). — A solution of **32** (78 mg) and phenylmethanesulfonyl chloride (30 mg) in cold pyridine (0–5°, 1.5 mL) was kept for 10 min. After addition of water (0.1 mL), the solution was concentrated *in vacuo* and the residue extracted with $CHCl_3$. The solution was washed with water, dried ($MgSO_4$), and concentrated to give **33** as a solid; yield 88 mg (quant.), $[\alpha]_D^{20}$ −28° (*c* 1.1, pyridine); ^{1}H-n.m.r. (pyridine-d_5): δ 2.23, 2.25, 2.30, 2.44, and 2.50 [each s, 3 H, Ac × 2 and Ts(*Me*) × 3], 5.10 (s, 2 H, PhCH_2), 5.35 (dd, 1 H, H-2' or -2''), 5.56 (dd, 1 H, H-2'' or -2'), 5.70 (t, 1 H, $J_{2',3'} = J_{3',4'}$ 10 Hz, H-3'), 5.81 (d, 1 H, H-1' or -1''), and 6.06 (d, 1 H, H-1'' or -1'').

Anal. Calc. for $C_{57}H_{70}N_4O_{22}S_4 \cdot 2H_2O$: C, 51.57; H, 5.62; N, 4.22; S 9.65. Found: C, 51.45; H, 5.63; N, 4.33; S, 9.73.

3'-O-Benzylsulfonyl-6'-N,4'-O-carbonyl-4'',6''-O-cyclohexylidene-1,3,3''-tri-N-tosylkanamycin A (**34**). — Zemplén deacetylation of **33** (668 mg) gave **34** as a solid; yield 546 mg (88%), $[\alpha]_D^{21}$ +33° (*c* 1, MeOH); ν_{max} 1705 cm^{-1} (cyclic carbamate); ^{1}H-n.m.r. (pyridine-d_5): δ 2.20, 2.33, and 2.42 [each s, 3 H, Ts(*Me*) × 3], 5.18 (s, 2 H, PhCH_2), 5.45 (d, 1 H, H-1' or -1''), 5.69 (t, 1 H, H-3'), and 5.77 (d, 1 H, H-1'' or -1').

Anal. Calc. for $C_{55}H_{66}N_4O_{20}S_4$: C, 52.72; H, 5.51; N, 4.64; S, 10.62. Found: C, 52.50; H, 5.62; N, 4.58; S, 10.47.

2',3'-Anhydro-4'',6''-O-cyclohexylidene-3'-epi-6'-N-methoxycarbonyl-1,3,3''-tri-N-tosylkanamycin A (**35**). — A solution of **34** (600 mg) in 2% NaOMe in MeOH (12 mL) was kept for 30 min at 45°. In t.l.c. (5:1:0.1 $CHCl_3$–MeOH–aq. 28% ammonia), the solution showed spots of R_F 0.55 (**35**) and 0.53 (trace; 3',4'-anhydro isomer?). After neutralization with methanolic 0.5% HCl, the solution was concentrated and the residue extracted with EtOAc. The products were chromatographed with 50:1 → 10:1 $CHCl_3$–MeOH to give **35** as a solid; yield 400 mg (75%), $[\alpha]_D^{25}$ +4° (*c* 2.3, $CHCl_3$); ^{1}H-n.m.r. (pyridine-d_5): δ 2.20, 2.22, and 2.36 [each s, 3 H, Ts(*Me*) × 3], 3.58 (dd, 1 H, H-3'), 3.63 (dd, 1 H, H-2'), 3.68 (s, 3 H, CO_2Me), 4.44 (dd, 1 H, H-4'), 5.60 (d, 1 H, H-1''), and 5.91 (d, 1 H, H-1'); $J_{1',2'}$ 3, $J_{1'',2''}$ 3.5, $J_{2',3'}$ 4, $J_{3',4'}$ 1, and $J_{4',5'}$ 10 Hz.

Anal. Calc. for $C_{47}H_{62}N_4O_{18}S_3 \cdot 1/2H_2O$: C, 52.45; H, 5.85; N, 5.20; S, 8.93. Found: C, 52.54; H, 5.78; N, 5.04; S, 8.92.

2′,3′-Anhydro-6′-N-*benzyloxycarbonyl-4″,6″*-O-*cyclohexylidene-3′-epi-1,3,3″-tri*-N-*tosylkanamycin A* (**36**). — To a solution of **34** (2.43 g) in $CHCl_3$ (50 mL) was added 2M sodium benzyloxide in benzyl alcohol (10 mL) and the mixture was stirred for 0.5 min at 45°. The resulting mixture was washed with water, dried ($MgSO_4$), and concentrated. The residue was chromatographed with 20:0 → 20:1 $CHCl_3$–MeOH to give **36** as a solid; yield 2.64 g (89%), $[\alpha]_D^{24}$ +2° (*c* 0.5, $CHCl_3$); ^{1}H-n.m.r. (pyridine-d_5): δ 2.19, 2.22, and 2.29 [each s, 3 H, Ts(*Me*) × 3], 5.10 (ABq, 2 H, *J* 13 Hz, CO_2CH_2Ph), 5.57 (d, 1 H, $J_{1″,2″}$ 3 Hz, H-1″), and 5.92 (br s, 1 H, H-1′).

Anal. Calc. for $C_{53}H_{66}N_4O_{18}S_3$: C, 55.68; H, 5.82; N, 4.90; S, 8.41. Found: C, 55.33; H, 5.91; N, 4.65; S, 8.08.

3′-Deoxy-3′-fluoro-6′-N-*methoxycarbonyl-1,3,3″-tri*-N-*tosylkanamycin A* (**39**) *and 2′-deoxy-2′,3′-diepi-2′-fluoro-6′*-N-*methoxycarbonyl-1,3,3″-tri*-N-*tosylkanamycin A* (**40**). — A mixture of **35** (174 mg) and KHF_2 (90.2 mg, dried *in vacuo* for 8 h at 100°) in ethane-1,2-diol (3 mL, dried over molecular sieves 4A, and then distilled *in vacuo*) was heated in a pressure tube for 3.5 h at 150–160°. In t.l.c. (3:1:0.1 $CHCl_3$–MeOH–aq. 28% ammonia), the solution showed spots of R_F 0.5 (**40**), 0.37 (**39**), 0.3 (minor), and 0. After addition of EtOAc, the mixture was washed with aq. 5% $NaHCO_3$, dried ($MgSO_4$), and concentrated to give a residue that was chromatographed with 30:1 → 5:1 $CHCl_3$–MeOH to give solids of **39**, 51.4 mg (31%) and **40**, 26 mg (16%).

Compound **39** had $[\alpha]_D^{21}$ +3° (*c* 1.3, MeOH); ^{1}H-n.m.r. (pyridine-d_5): δ 2.07, 2.31, and 2.37 [each s, 3 H, Ts(*Me*) × 3], 3.62 (s, 3 H, CO_2Me), 5.33 (dt, 1 H, H-3′), 5.38 (d, 1 H, H-1″), and 5.62 (t, 1 H, H-1′); $J_{1′,2′} = J_{1′,F}$ 3, $J_{1″,2″}$ 4, $J_{2′,3′} = J_{3′,4′}$ 10, and $J_{3′,F}$ 55 Hz.

Anal. Calc. for $C_{41}H_{55}FN_4O_{18}S_3 \cdot 1/2H_2O$: C, 48.46; H, 5.55; N, 5.51. Found: C, 48.37; H, 5.48; N, 5.48.

Compound **40** had $[\alpha]_D^{21}$ +4° (*c* 1.1, MeOH); ^{1}H-n.m.r. (pyridine-d_5): δ 2.07, 2.28, and 2.33 [each s, 3 H, Ts(*Me*) × 3] 3.62 (s, 3 H, CO_2Me), 5.10 (br d, 1 H, H-2′), 5.39 (d, 1 H, H-1″), and 6.00 (br d, 1 H, H-1′); $J_{1″,2″}$ 3, $J_{1′,F}$ 10, and $J_{2′,F}$ 46 Hz.

Anal. Calc. for $C_{41}H_{55}FN_4O_{18}S_3$: C, 48.90; H, 5.50; N, 5.56. Found: C, 48.58; H, 5.35; N, 5.38.

3′-Deoxy-3′-fluorokanamycin A (**41**). — To a solution of **39** (45.7 mg) in liquid ammonia (~ 3 mL) at −50° was added Na (~ 50 mg); the deep-blue solution was kept for 5 min at −50°, then diluted with MeOH until colorless, and concentrated gradually by warming to room temperature and finally under diminished pressure. An aqueous solution of the resulting syrup was heated for 15 min at 50° and then mixed with Dowex 50W–X2 (H^+ form, 3 mL), which was then packed into a column containing the same resin (NH_4^+ form, 4 mL), washed with water, and eluted with 0.5M ammonia, to give **41** as its hemicarbonate; yield 20.1 mg (84%), $[\alpha]_D^{20}$ +123° (*c* 1.5, H_2O); ^{1}H-n.m.r. (20% ND_3 in D_2O): δ 4.65 (dt, 1 H, H-3′), 5.10 (d, 1 H, H-1″), and 5.45 (t, 1 H, H-1′); $J_{1′,2′} = J_{1″,2″} = J_{1′,F}$ 4, $J_{2′,3′} = J_{3′,4′} = 10$, and $J_{3′,F}$ 51 Hz.

Anal. Calc. for $C_{18}H_{35}FN_4O_{10} \cdot 0.5H_2CO_3 \cdot H_2O$: C, 41.49; H, 7.15; N, 10.46; F, 3.55. Found: C, 41.22; H, 6.88; N, 10.34; F, 3.77.

2′,3′-Anhydro-4″,6″-O-*cyclohexylidene-3′-epikanamycin A* (**37**). — Compound **36** (340 mg) was treated with Na (~300 mg) in liquid NH_3 (~35 mL) in the manner

described for **41**, to give **37**; yield 88 mg (54%), $[\alpha]_D^{22}$ +97° (*c* 0.4, H_2O); ^{1}H-n.m.r. (20% ND_3 in D_2O): δ 1.3–1.9 (m, 10 H, cyclohexylidene), 3.58 (dd, 1 H, H-3′), 3.74 (dd, 1 H, H-2′), 3.87 (dd, 1 H, H-4′), 5.04 (d, 1 H, H-1″), and 5.50 (d, 1 H, H-1′); $J_{1',2'}$ 3, $J_{1'',2''}$ 3.5, $J_{2',3'}$ 4.5, $J_{3',4'}$ 1.5, and $J_{4',5'}$ 9.5 Hz.

Anal. Calc. for $C_{24}H_{42}N_4O_{10}\cdot 2H_2O$: C, 49.47; H, 7.27; N, 9.62. Found: C, 49.38; H, 7.34; N, 9.85.

*2′,3′-Anhydro-1,3,6′,3″-tetrakis(*N*-benzyloxycarbonyl)-4″,6″-*O*-cyclohexylidene-3′-epikanamycin A* (**38**). — To an ice-cold suspension of **37** (120 mg) and anhydrous Na_2CO_3 (180 mg) in 2:1 1,4-dioxane–water (30 mL) was added benzyl chloroformate (0.18 mL), and the mixture was stirred for 3 h at 0–5°. After concentration, admixture of the residue with water (30 mL) gave a precipitate, which was filtered off, and washed with water and ether to give, after drying, **38** as a solid; yield 216 mg (91%), $[\alpha]_D^{22}$ +39° (*c* 2, pyridine).

Anal. Calc. for $C_{56}H_{66}N_4O_{18}$: C, 62.10; H, 6.14; N, 5.17. Found: C, 61.95; H, 5.97; N, 5.03.

*1,3,6′,3″-Tetrakis(*N*-benzyloxycarbonyl)-3′-chloro-4″,6″-*O*-cyclohexylidene-3′-deoxykanamycin A* (**42**). — To a solution of **38** (44.4 mg) in DMF (1 mL) were added LiCl (16.9 mL) and 0.4M HCl in DMF (0.1 mL), and the mixture was kept for 1 h at 120°. After concentration *in vacuo* at room temperature, admixture of the residue with water gave a precipitate, which was thoroughly washed with water to give, after drying, **42** as a solid; yield 40.5 mg (89%), $[\alpha]_D^{22}$ +69° (*c* 1.7, pyridine); ^{1}H-n.m.r. (pyridine-d_5): δ 5.43 (t, 1 H, $J_{2',3'} = J_{3',4'}$ 9 Hz, H-3′).

Anal. Calc. for $C_{56}H_{67}ClN_4O_{18}$: C, 60.07; H, 6.03; N, 5.00; Cl, 3.17. Found: C, 59.85; H, 5.95; N, 4.91; Cl, 2.89.

3′-Chloro-3′-deoxykanamycin A (**43**). — A solution of **42** (45.2 mg) in aq. 80% AcOH (1 mL) was heated for 1 h at 90°. The decyclohexylidenated product in 20:1:2 1,4-dioxane–AcOH–water (2.3 mL) was then hydrogenolyzed with palladium black under one atmosphere pressure of hydrogen. The crude product obtained by conventional processing was purified on a column of CM–Sephadex C–25 (NH_4^+ form, 5 mL) with aq. ammonia (0 → 0.5M). Ninhydrin-positive fractions were collected, and concentrated to give solid **43** as its carbonate; yield 17.5 mg (85%), $[\alpha]_D^{22}$ +115° (*c* 0.3, H_2O); ^{1}H-n.m.r. (20% ND_3 in D_2O): δ 4.04 (t, 1 H, H-3′), 5.03 (d, 1 H, H-1″), and 5.35 (d, 1 H, H-1′); $J_{1',2'} = J_{1'',2''}$ 4, and $J_{2',3'} = J_{3',4'}$ 9 Hz.

Anal. Calc. for $C_{18}H_{35}ClN_4O_{10}\cdot 0.5H_2CO_3\cdot 0.5H_2O$: C, 40.92; H, 6.87; N, 10.32; Cl, 6.54. Found: C, 40.77; H, 6.81; N, 10.51; Cl, 6.65.

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