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Synthesis of kanamycin A analogs containing a 6-amino-6-deoxyglycofuranose moiety

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Abstract

Three kanamycin A analogs containing 6-amino-6-deoxyglycofuranoses have been prepared as candidates for potential activity against resistant bacteria producing 6′-*N*-acetyltransferase. They are 4-*O*-(6-amino-3,5,6-trideoxy-α-D-, -β-D-, and -β-L-*erythro*-hexofuranosyl)-6-*O*-(3-amino-3-deoxy-α-D-glucopyranosyl)-2,5-dideoxy-5-epi-5-fluorostreptamine. Structure–activity relationships of these compounds are discussed.

Keywords: Kanamycin analogs; 6-Amino-3,5,6-trideoxy-D- or -L-*erythro* hexofuranose; 6′-Aminoacetyltransferase

1. Introduction

Kanamycins[1] are aminoglycoside antibiotics having a broad spectrum of antibacterial activities, but they are inactivated by a variety of resistant bacteria that produce phosphoryl-, nucleotidyl-, and acetyl-transferases causing modification of several key functional groups [1]. Such chemically modified kanamycin derivatives as 3′,4′-dideoxykanamycin B (dibekacin) [2], amikacin [3], and arbekacin [4] restore the activity of the parent compounds against most of the resistant bacteria, but for the strains producing 6′-*N*-acetyltransferases, no effective tool to avoid the acetylation has yet been discovered. Past attempts at 6′-*N*-alkylation or 6′-*C*-alkylation of kanamycin and its analogs [5] succeeded in improving this somewhat, but led to lowering of the intrinsic activity. Against this background, we intended to prepare new kanamycin analogs potentially active against the resistant strains by replacing the 6-amino-6-deoxy-D-glucopyranose residue (Glc6N) of kanamycin A with a terminal-aminated sugar designed to avoid the recognition by the 6′-*N*-acetyltransferases of resistant bacteria through changing the conformation adjacent to the 6′-amino group of Glc6N.

This study is an attempt along the foregoing lines, and describes the synthesis of kanamycin A analogs (**29a**,**b**) having a 6-amino-3,5,6-trideoxy-α- or -β-D-*erythro*-hexofuranose group in place of Glc6N, expecting that the pyranose→furanose change might produce some biologically useful change. The reason for the choice of a furanose moiety lacking 3- and 5-hydroxyl groups is based on the expectation that the absence of a 3′-OH

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[1] See structures **20**–**21** as representative kanamycin A derivatives used in this investigation.

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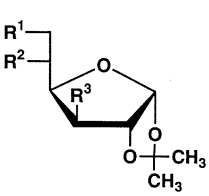
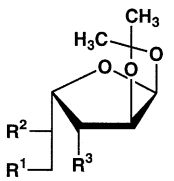
group in the final products **29** may prevent possible 3′-phosphorylation by the resistant bacteria producing 3′-phosphotransferases, and the absence of a 5′-OH group may facilitate the rotation around the C-5′–C-6′ axis, making the 6′-NH_2 group of the new compound approach a suitable position to fit the ribosomal RNA of bacteria [6]. In natural kanamycins, the Glc6N group has the α-D-configuration, but in our synthesis, we prepared both of the α- and β anomeric D- and L-hexofuranoses to examine the activity–structure relationships in more detail.

Forthe6-*O*-(3-amino-3-deoxy-D-glucopyranosyl)-2-deoxystreptamine moiety (3AD), to which the foregoing furanoses were to be coupled, a fluorine atom was introduced with inversion at C-5. One reason for this modification is because the chemical glycosylation of a protected 3AD derivative with a glycosyl halide usually produces undesirable 5-*O*-glycosyl position isomers as by-products [7], making purification of the desired 4-*O*-glycosyl products difficult. Another reason is that the 5-epifluorination sometimes enhances the antibacterial activity, as observed in 5-deoxy-5-epifluoro-amikacin and -arbekacin [8].

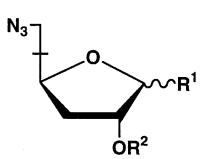
2. Results and discussion

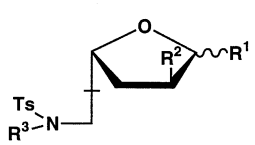
Synthesis of glycosyl donors.—We attempted first a one-step 3,5-dideoxygenation of 1,2-*O*-isopropylidene-3,5-di-*O*-[(methylthio)thiocarbonyl]-6-*O*-trityl-α-D-glucofuranose according to Barton et al. [9], but a complex mixture was obtained; we thus took a stepwise deoxygenation route. We initially attempted to convert a 3-deoxy-6-*O*-tosyl-D-*ribo*-hexofuranose derivative (**6D**) prepared according to Just and Lethe [10,11] by way of **1D**–**5D** into its 5-xanthate by the usual procedure (NaH, CS_2, and MeI), but the undesired 5,6-epoxide was produced by removal of the 6-tosyloxy group. Imidazolylthiocarbonylation under milder basic conditions, however, successfully gave the 5-*O*-thiocarbonyl derivative **7D**. Deoxygenation of **7D** with Bu_3SnH in the presence of AIBN [9] gave the 3,5-dideoxy-6-*O*-tosyl derivative **8D** [12]. After conversion of **8D** into the 6-azido derivative (**9D**), acid-catalyzed methanolysis gave an anomeric mixture of methyl furanosides (**10**). Benzylation (to give **11**), followed by hydrolysis with aq hydrochloric acid–acetic acid (the use of aq hydrochloric acid–THF attempted first gave an undesirable 4-chlorobutyl glycoside) gave a free sugar **12**, which led to the glycosyl chloride **13** by treatment with $SOCl_2$. As **13** was unstable, the stable glycosyl fluoride analog **14** was also prepared from **12** by treatment with Et_2NSF_3 (DAST) [13].





R^1	R^2	R^3		
$OCMe_2$		OCSSMe	**1D**	**1L**
OH	OH	OCSSMe	**2D**	**2L**
OAc	OAc	OCSSMe	**3D**	**3L**
OAc	OAc	H	**4D**	**4L**
OH	OH	H	**5D**	**5L**
OTs	OH	H	**6D**	**6L**
OTs	OCSIm	H	**7D**	
OTs	H	H	**8D**	**8L**
N_3	H	H	**9D**	**9L**

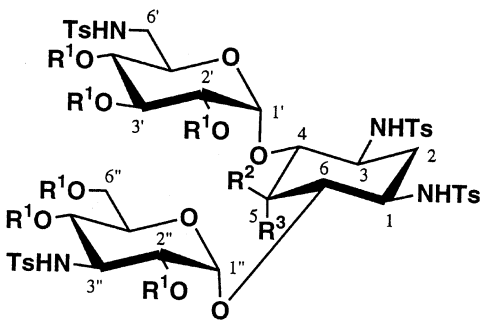




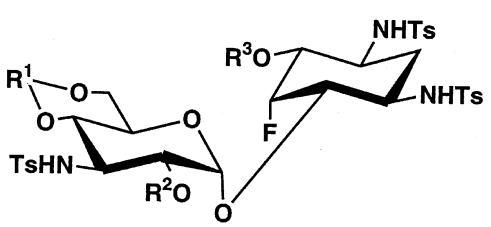
	R^1	R^2		R^1	R^2	R^3
10	OMe	H	**15**	$OCMe_2$		H
11	OMe	Bn	**16**	OMe	OH	H
12	OH	Bn	**17**	OMe	OBn	Bn
13	Cl	Bn	**18**	OH	OBn	Bn
14	F	Bn	**19**	Cl	OBn	Bn

A similar synthesis was applied to the L series. 1,2;5,6-Di-*O*-isopropylidene-α-L-glucofuranose [14] was converted into 3-deoxy-6-*O*-tosyl-L-*ribo*-hexofuranose (**6L**) via six steps (**1L** to **5L**). 5-Thiocarbonylimidazolylation of **6L**, followed by deoxygenation (Bu_3SnH–AIBN) in toluene in one pot gave the dideoxy derivative (**8L**), which led to the 6-azido

derivative (**9L**). As in the D series, the free sugar (**12**) with a 6-azido group was unstable on storage, we attempted conversion of the 6-azido group of **9L** into a tosylamido group by reduction (Raney Ni) and tosylation. The resulting *N*-tosyl derivative (**15**) was successively methanolyzed (to give **16**), benzylated (to give the 2-*O*,6-*N*-dibenzyl derivative **17**), and hydrolyzed to give the free sugar **18**, which, however, was unstable on storage, as with the D analog (**12**). Chlorination of **18** with $SOCl_2$ gave the L-glycosyl donor **19**, which was unstable and was used immediately.



	R^1	R^2	R^3
20	H	OH	H
21	Ac	OH	H
22	Ac	H	F
23	H	H	F



	R^1	R^2	R^3
24	H, H	H	H
25	C_6H_5CH	H	H
26	C_6H_5CH	Ac	H
27	C_6H_5CH	Ac	Ac

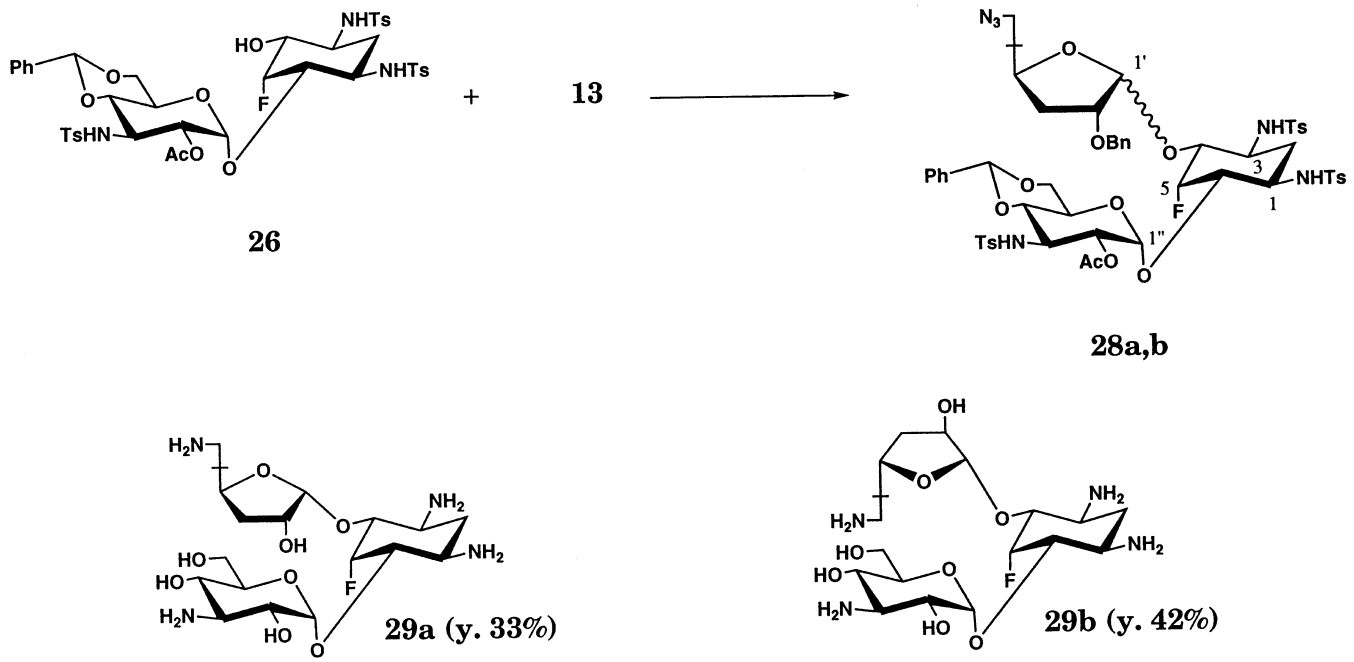
Synthesis of the 3AD acceptor.—Acetylation of tetra-*N*-tosylkanamycin A (**20**) [15] gave the 2′,3′,4′,2″,4″,6″-hexa-*O*-acetyl derivative **21**, with a free HO-5 group (this position resists acetylation or benzoylation [8,16–18]), which was fluorinated with DAST to give the 5-deoxy-5-epifluoro derivative **22** in almost quantitative yield. The axial deposition of fluorine was proven from the large coupling constants [8] ($J_{5,F}$ 50.5 and $J_{4,F} = J_{6,F}$ 26 Hz) in its ^{19}F NMR spectrum. After deacetylation (to give **23**), Smith degradation [19] was performed giving a dialdehyde that was reduced (sodium borohydride) and hydrolyzed (methanolic hydrochloric acid) to give the tri-*N*-tosyl disaccharide **24**. The structure was confirmed by the absence of the 6-tosylamidopyranose moiety. Subsequent benzylidenation of **24** (to give **25**), followed by acetylation (*N*-acetylimidazole in 1:9 pyridine–dimethylsulfoxide [20]) gave the 2′-*O*-acetyl-4-hydroxy derivative **26** (47%) together with the 4,2′-di-*O*-acetyl derivative **27** (50%). Compound **27** could be recycled to **25** after deacetylation.

Glycosylation.—As preliminary couplings of **26** and **13** under some standard conditions gave rise to diverse β:α ratios, conditions for optimization were first examined (Scheme 1). The results (Table 1) showed that the ratio ranged from 1.0 to 7.6, and no clear-cut conditions to produce the α or β anomer selectively were found. As we considered that both the α and β anomers were necessary to examine the antibacterial activities of the final products, the coupling was carried out under the conditions of entry 7 ($\beta:\alpha = 1$), which showed a relatively high yield, and the anomers produced were separated by repeated chromatography.

After Zemplén deacetylation of **28** in 9:1 pyridine–methanol (for **28a**) or 1:1 chloroform–methanol (for **28b**) (both **28a** and **28b** are scarcely soluble even in methanol), the products were deprotected with Na in liquid NH_3–THF (Birch reduction), whereupon the azido (to give an amino group), *N*-tosyl, *O*-benzyl, and *O*-benzylidene groups were removed simultaneously to give the final products **29**; in the case of **28a**, however, reduction of the 6′-azido group (partial debenzylation and debenzylidenation also occurred) was initially carried out prior to the Birch reduction (detosylation) to increase the solubility of the starting material in NH_3.

In the coupling of **26** and **19**, the best conditions among those tested were $Hg(CN)_2$–*s*-collidine in dichloromethane, and **30** was obtained in low yield as an anomeric mixture (β:α ~ 3), from which the β anomer (**30b**) could be separated by chromatography (Scheme 2). Deprotection as described for **28b** gave the final product **32b**. Structural assignments of these synthetic products were performed by NMR spectroscopy (Tables 2 and 3).

Interestingly, in the ^{13}C spectra, compound **32b** with a β-L-glycofuranose moiety, resembles in its chemical shifts, **29a** (α-D structure) in the 2-deoxystreptamine (DST) moiety; on the other hand, **32b** resembles **29b** (β-D struc-

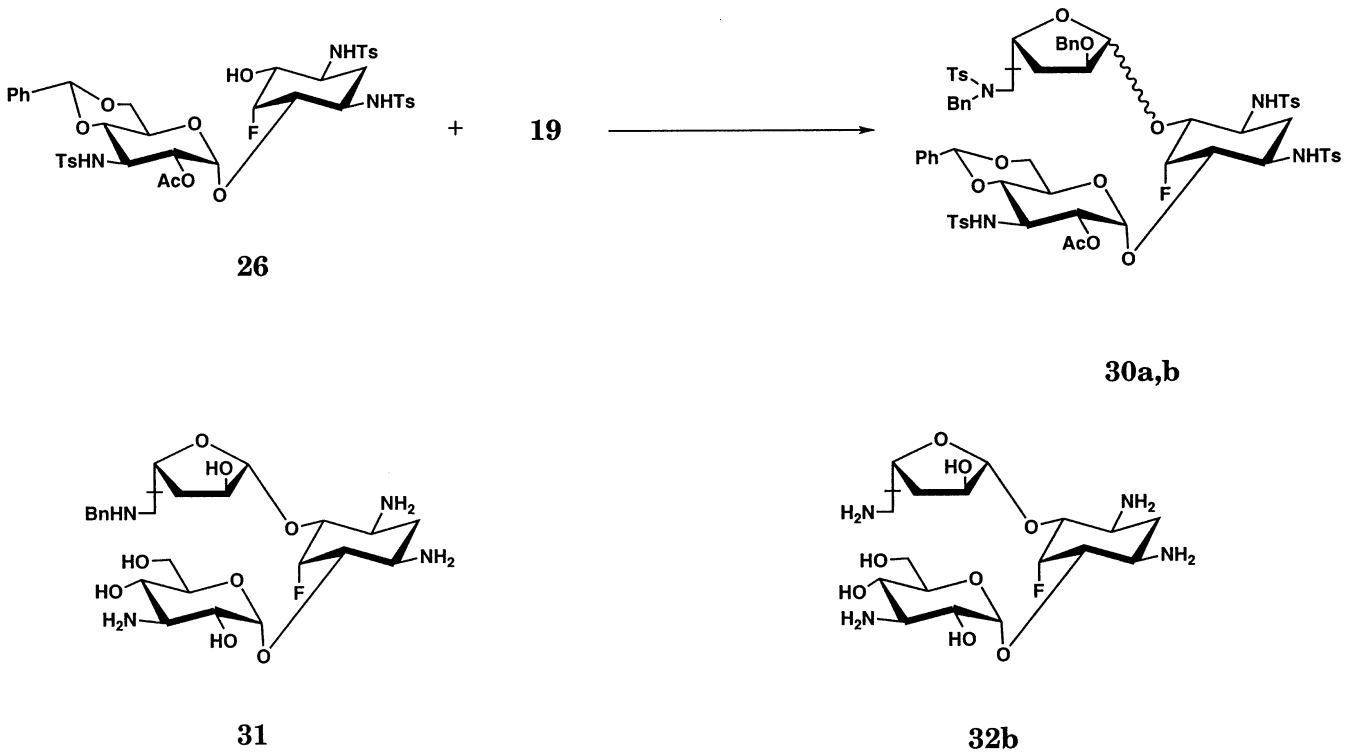


Scheme 1.

Table 1
Glycosylation of **26** with **13** (or **14** [a]) to give **28**

Entry	Reagent (mol equiv [b])	Solvent (v/w [b])	Temperature	Time (h)	Yield (%)	β:α ratio [c]
1	$Hg(CN)_2$ (2.0)	CH_2Cl_2 (5)	rt	1	35	6.0
2	$Hg(CN)_2$ (2.0)	CH_2Cl_2 (10)	rt	1	51	2.7
3	$Hg(CN)_2$ (2.0)	CH_2Cl_2 (10)	−50 → 0 °C	5	no reaction	
4	$Hg(CN)_2$ (2.0)	CH_2Cl_2 (50)	rt	1	45	2.8
5	$Hg(CN)_2$ (2.0)	CH_3CN(10)	rt	1	44	2.4
6	$Hg(CN)_2$ (2.0)	CH_3NO_2 (10)	rt	1	44	2.0
7	$Hg(CN)_2$ (2.0)	THF (10)	rt	1	58	1.0
8	$Hg(CN)_2$ (2.0)–*s*-collidine [d] (4.0)	CH_2Cl_2 (10)	rt	7	53	1.5
9	$HgBr_2$ (2.0)–HgO (4.0)	CH_2Cl_2 (10)	rt	1	55	1.4
10	AgOTf (1.2)–TTBP [e] (1.2)	CH_2Cl_2 (10)	0 °C	1	41	2.1
11	Ag_2CO_3 (2.0)	CH_2Cl_2 (10)	rt	5	47	7.6
12	$AgClO_4$ (3.0)–$SnCl_2$ (3.0)	1:1 CH_2Cl_2–Et_2O (10)	−50 °C	20	41	2.0
13	$CdCO_3$ (2.0)	CH_2Cl_2 (10)	rt	5	51	6.1

[a] Entry 12.
[b] Based on **13** (or **14**).
[c] The anomeric ratios were determined based on the ^1H NMR spectra of **28** (α anomer: H-1′ δ 5.45, $J_{1',2'}$ 4 Hz; β anomer: H-1′ δ 5.63, singlet).
[d] 2,4,6-Trimethylpyridine.
[e] 2,4,6-Tri-*t*-butylpyridine.



Scheme 2.

ture) in the furanose moiety. This suggests that the electronic states for carbons of the DST portions of **32b** and **29a** resemble each other, but differ in the furanose portions, and for the furanose portion, the states of **32b** and **29b** resemble each other.

Antibacterial activity.—The three compounds (**29a**,**b**, and **32b**) synthesized showed no antibacterial activity (MIC > 100 mcg/mL) against normal and resistant strains tested (**32a** cannot be measured due to the small amount obtained).

Discussion.—In order to search for the underlying reason for the inactivity of the products prepared, their energy-minimal conformations (MOPAC with mimic water effect) were calculated and compared with that of kanamycin A. As shown in Fig. 1, where the 6-*O*-(3-amino-3-deoxy-α-D-glucopyranosyl)-2-deoxystreptamine portions of kanamycin A and **29a** (**29b**, **32a**, or **32b**) are brought together to be almost superimposed, the spatial dispositions of the 6-amino-3,5,6-trideoxyfuranose and 6-amino-6-deoxy-D-glucose moieties are considerably deviant. A characteristic feature is the fact that the 6-amino group in each furanose moiety, except for that of **32b**, protrudes from the location of the 6′-amino group of kanamycin A by more than the diameter of one carbon; the β-L isomer **32b** has a short 6′-N(**32b**)–6′-N(KMA) distance (1.02 Å) (see Fig. 1, stereoview). It has been suggested that the position of the 6′-NH_2 group of the kanamycin A molecule is most important for manifesting antibacterial activity [6]. A neamine analog having a 7-amino-7-deoxy sugar moiety (with an α-D-glycopyranose structure) instead of the 6-amino-6-deoxy-D-glucose moiety of kanamycin A, however, retains its antibacterial activity [21], although only weakly. Therefore, the lack of activity of our synthetic products must be ascribed to the steric difference between the pyranose ring (in kanamycin A) and the furanose, suggesting that the latter structure hinders binding of the synthetic products to the ribosomal RNA of bacteria [6].

3. Experimental

General methods.—Melting points were determined on a Kofler block and are uncorrected. Optical rotations were determined with

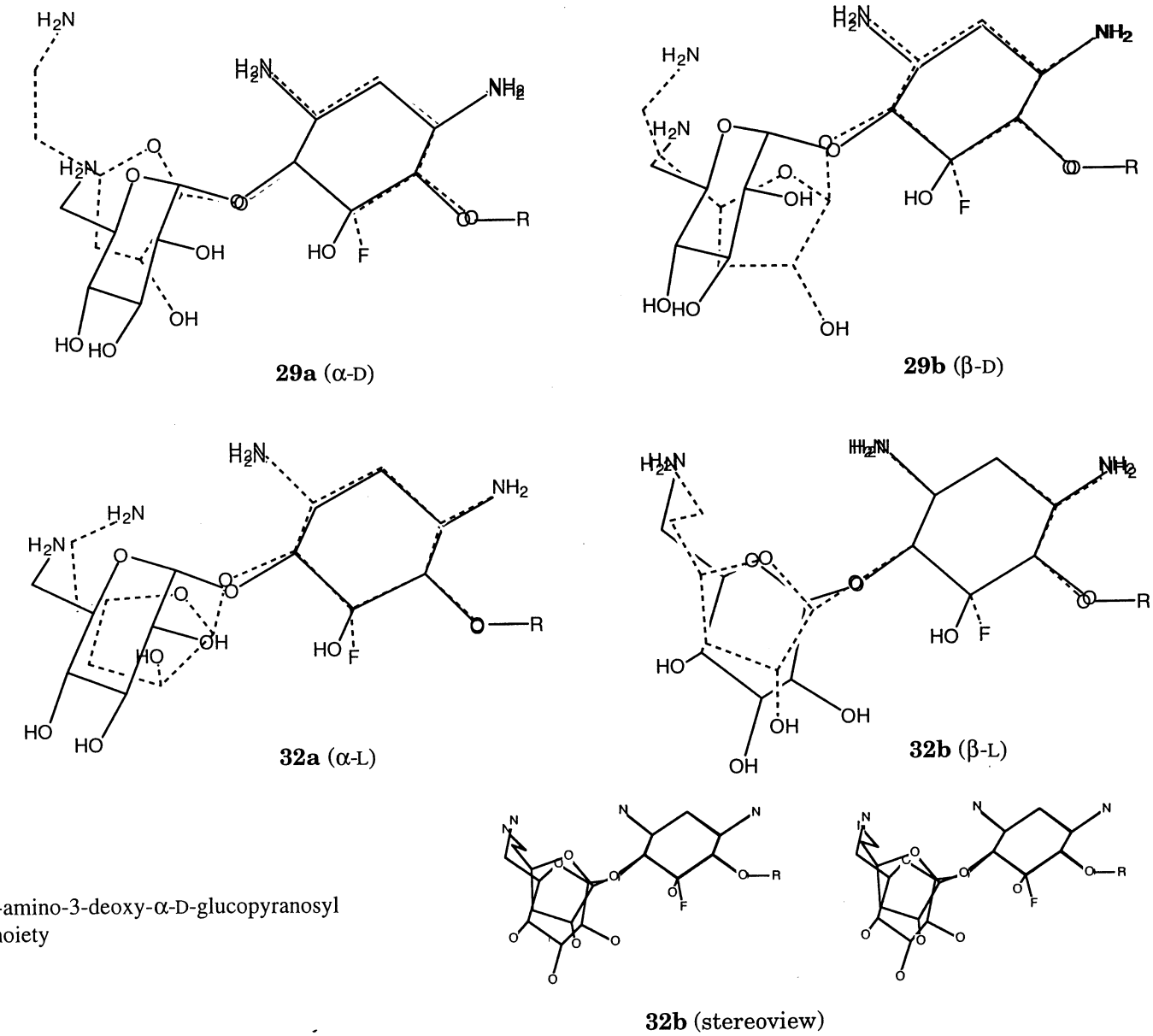


Fig. 1. The energy-minimal conformations of **29a**, **29b**, **32a**, and **32b** computer-calculated (for details, see Section 3) for their glycofuranosyl-DST portions (dotted line), drawn with the 4-*O*-(6-amino-6-deoxy-α-D-glucopyranosyl)-2-deoxystreptamine moiety of kanamycin A (solid line), together with the stereoviews of **32b** and kanamycin A (both solid line) for the corresponding portions.

a Perkin–Elmer 241 polarimeter. IR spectra were recorded with a Jasco A-202 grating spectrophotometer. NMR spectra (^{1}H at 250 and 500 MHz, ^{13}C at 125.8 MHz, and ^{19}F at 235.4 MHz) were recorded with Bruker AC-250P and AMX-500 spectrometers, using Me_4Si and $CFCl_3$ (for ^{19}F) as the internal references, respectively. If necessary, signal assignments were performed by aid of shift-correlated 2D spectra. Asterisks attached after the NMR acronym indicate that only key signals are shown. Thin-layer chromatography (TLC) was performed on Kieselgel 60 F_{254} (E. Merck), high-performance thin layer chromatography (HPTLC) on Kieselgel 60 F_{254} for nano-TLC (E. Merck), and column chro-

Table 2
^{1}H NMR data for compounds **28a**, **28b** (pyridine-d_5) and **29a**, **29b** and **32b** (26% ND_3 in D_2O)

	28a	**28b**	**29a**	**29b**	**32b**
H-1	3.99–4.06m	3.93–4.02m	3.10dddd $J_{1,2ax}$ 12.5, $J_{1,6}$ 10.5, $J_{1,2eq}$ 4.5, $J_{1,F}$ 2	3.09dddd	3.13dddd
H-2$_{ax}$	1.93q $J_{1,2ax} = J_{2ax,2eq} = J_{2ax,3}$ 13	1.96q	1.10q	1.13q $J_{2ax,2eq} = J_{2ax,3}$ 12.5	1.16q
H-2$_{eq}$	2.82dt $J_{1,2eq} = J_{2eq,3}$ 4	2.81dt	2.00dt	2.02dt $J_{2eq,3}$ 4.5	2.05dt
H-3	3.92–3.99m	4.02–4.12m	3.03dddd	2.98dddd	3.01dddd
H-4	4.24ddd $J_{3,4}$ 10.5, $J_{4,5}$ 2, $J_{4,F}$ 28	4.13br dd $J_{3,4}$ 10.5, $J_{4,F}$ 27	3.47ddd $J_{3,4}$ 10.5, $J_{4,5}$ 2, $J_{4,F}$ 29	3.44ddd	3.53ddd
H-5	5.69dt $J_{5,6}$ 2, $J_{5,F}$ 51.5	5.67br d $J_{5,F}$ 51	5.22dt	5.21dt $J_{5,6}$ 2, $J_{5,F}$ 52.5	5.32dt
H-6	4.25ddd $J_{1,6}$ 10.5, $J_{6,F}$ 28	4.27br dd $J_{1,6}$ 10.5, $J_{6,F}$ 27	3.38ddd	3.46ddd $J_{6,F}$ 29	3.45ddd
H-1′	5.45d $J_{1',2'}$ 4	5.63s	5.10d $J_{1',2'}$ 4	5.09s	5.12s
H-2′	4.11dt $J_{2',3'a}$ 8.5, $J_{2',3'b}$ 8.5	4.08d $J_{1',2'}$ 0, $J_{2',3'a}$ 5, $J_{2',3'b}$ 0	4.28dt $J_{2',3'a} = J_{2',3'b}$ 8	4.34d $J_{2',3'a}$ 5	4.28d
H-3′a	1.82ddd $J_{3'a,3'b}$ 12, $J_{3'a,4'}$ 5	1.68ddd $J_{3'a,3'b}$ 13, $J_{3'a,4'}$ 9.5	1.92ddd $J_{3'a,3'b}$ 13, $J_{3'a,4'}$ 5	1.87ddd $J_{3'a,3'b}$ 13, $J_{3'a,4'}$ 10	1.91ddd
H-3′b	2.36dt $J_{2',3'b} = J_{3'b,4'}$ 8.5	2.11dd $J_{3'b,4'}$ 6	2.02dt $J_{3'b,4'}$ 8	2.08dd $J_{3'b,4'}$ 6	2.11dd
H-4′	4.65tt $J_{4',5'a}$ 5, $J_{4',5'b}$ 8.5	4.43–4.52m	4.30m	4.39m	4.42ddt $J_{4',5'a}$ 6, $J_{4',5'b}$ 8
H-5′a	1.65m	1.80dt $J_{4',5'a} = J_{5'a,6'}$ 6, $J_{5'a,5'b}$ 13.5	1.63m	1.72m	1.76m
H-5′b	1.65m	1.91–2.01m	1.63m	1.79m	1.76m
H-6′a	3.27m	3.39t $J_{5'a,6'} = J_{5'b,6'}$ 6	2.59ddd $J_{5'a,6'a}$ 7, $J_{5'b,6'a}$ 8, $J_{6'a,6'b}$ 12.5	2.67ddd	2.70ddd
H-6′b	3.27m	3.39t	2.63ddd	2.71ddd	2.75ddd
H-1″	5.82d $J_{1'',2''}$ 4	5.74d	4.97d $J_{1'',2''}$ 4	5.03d	5.03d
H-2″	5.59dd $J_{2'',3''}$ 10	5.59dd	3.39dd $J_{2'',3''}$ 10	3.43dd	3.46dd
H-3″	4.75dt $J_{3'',4''}$ 10, $J_{3'',NH\text{-}3''}$ 8.5	4.76dt	2.98t $J_{3'',4''}$ 10	3.03t	3.04t
H-4″	4.02t $J_{4'',5''}$ 10	4.03t	3.16t $J_{4'',5''}$ 10	3.33t	3.21t
H-5″	4.51dt $J_{5'',6''a}$ 10, $J_{5'',6''b}$ 5	4.48dt	3.75ddd $J_{5'',6''a}$ 7, $J_{5'',6''b}$ 2	3.72 ddd $J_{5'',6''a}$ 4, $J_{5'',6''b}$ 2	3.82ddd $J_{5'',6''a}$ 7, $J_{5'',6''b}$ 2
H-6″a	3.81t $J_{6''a,6''b}$ 10	3.89t	3.60dd $J_{6''a,6''b}$ 12	3.79dd	3.66dd
H-6″b	4.30dd	4.46dd	3.80dd	3.76dd	3.86dd

Table 3
^{13}C chemical shifts (δ, ppm) and coupling constants ($J_{C,F}$, Hz) for **28a**,**b**, **29a**,**b**, **30a**,**b**, **31**, and **32b**

Solvent C	Pyridine-d_5					26% ND_3 in D_2O		
	28a	**28b**	**30a**	**30b**	**31**	**29a**	**29b**	**32b**
1	51.00d	51.47	51.31d	51.51d	49.35d	48.16d	48.24d	48.12d
	J 4		*J* 4	*J* 4	*J* 4	*J* 4	*J* 4	*J* 3
2	35.13	35.76	34.80	35.26	39.00	36.29	36.31	36.24
3	51.45d	51.47	51.50d	51.00d	48.62d	47.27d	47.82d	47.53d
	J 4		*J* 5	*J* 4	*J* 3	*J* 3	*J* 4	*J* 2.5
4	75.78d	78.80d	77.18d	74.56d	79.86d	79.20d	83.14d	79.34d
	J 17.5	*J* 17	*J* 17	*J* 17	*J* 17	*J* 17	*J* 17	*J* 16
5	90.68d	92.82d	93.03d	89.69d	90.56d	90.95d	93.58d	90.99d
	J 183	*J* 183	*J* 183	*J* 182	*J* 179	*J* 177	*J* 178	*J* 176
6	81.11d	81.15d	81.35d	80.94d	86.18d	84.90d	84.37d	84.97d
	J 17.5	*J* 17.5	*J* 18	*J* 18	*J* 17	*J* 17.5	*J* 17	*J* 17
1′	99.21	108.69	102.89	103.32	106.92	100.01	110.85	106.31
2′	78.61	83.82	78.87	83.94	76.51	71.34	75.75	76.01
3′	34.28	35.63	34.35	35.48	39.26	36.17	37.76	37.95
4′	74.47	78.19	74.53	78.32	79.56	76.44	79.66	79.85
5′	35.63	36.70	35.45	36.26	38.30	38.88	40.29	40.25
6′	48.37	48.91	45.94	46.71	47.41	38.15	38.73	38.90
1″	99.67	99.95	99.61	99.66	103.27	101.83	101.65	101.96
2″	72.16	72.14	72.19	72.12	74.29	72.40	72.43	72.48
3″	54.99	55.03	55.08	55.00	57.25	54.84	54.81	54.95
4″	79.56	79.57	79.54	79.60	72.36	70.52	69.84	70.62
5″	65.11	65.14	65.00	65.10	74.70	73.25	73.11	73.41
6″	68.79	68.71	68.78	68.77	62.97	61.61	60.70	61.70
Ph*C*H_2N			52.64	52.69	54.28			
Ph*C*H_2O	72.05	71.25	72.43	71.21				
Ph*C*H	102.00	102.17	102.11	102.04				

matography on Kieselgel 60 (E. Merck), unless otherwise stated.

Computation.—All calculations were performed on a Sun SPARC 2 Station with Materia Version 3.2 (Teijin System Technology, Ltd., Hongou, Bunkyo-ku, Tokyo, Japan), using semiempirical MOPAC 93/PM3 [22] according to the MOPAC 93 manual revision Nr. 2 (Fujitsu Ltd., Nakase, Mihama-ku, Chiba, Japan). Geometry optimization was performed by the eigenvector following method. The energy-minimal conformations were searched initially by MM2UEC [23] rotating the glycosidic bond in 15° steps, and the conformations obtained were further optimized with the MOPAC 93 with the COSMO method (setting the dielectric constant as 78.3 to mimic the water effect).

*1,2;5,6-Di-*O*-isopropylidene-3-*O*-(methylthio)thiocarbonyl-α-*D*-glucofuranose* (**1D**).—Prepared according to the procedure reported [10,11], $[\alpha]_D^{24}$ −33° (*c* 1.0, $CHCl_3$), {lit. [24], $[\alpha]_D^{22}$ −15.5° (*c* 2, $CHCl_3$)}.

*1,2;5,6-Di-*O*-isopropylidene-3-*O*-(methylthio)thiocarbonyl-α-*L*-glucofuranose* (**1L**).—1,2;5,6-Di-*O*-isopropylidene-α-L-glucofuranose [14,25] (7.70 g) was xanthated in THF (154 mL) as described above to give a syrup (10.44 g, quant.) $[\alpha]_D^{25}$ +33° (*c* 1.0, $CHCl_3$).

*1,2-*O*-Isopropylidene-3-*O*-(methylthio)thiocarbonyl-α-*D*-glucofuranose* (**2D**).—Compound **1D** (2.44 g) was hydrolyzed as reported [10,11], $[\alpha]_D^{23}$ +40° (*c* 1.0, $CHCl_3$) {lit. [24], $[\alpha]_D^{24}$ −27.8° (*c* 2, 0.025 M HCl in 1:1 water–EtOH)}.

*1,2-*O*-Isopropylidene-3-*O*-(methylthio)thiocarbonyl-α-*L*-glucofuranose* (**2L**).—Compound **1L** (1.38 g) was treated with 0.4 M H_2SO_4 in 7:1 MeOH–water (28 mL) as described for **2D** to give a solid (1.19 g, 97%), $[\alpha]_D^{23}$ −40° (*c* 1.0, $CHCl_3$).

*5,6-Di-*O*-acetyl-1,2-*O*-isopropylidene-3-*O*-

(methylthio)thiocarbonyl - α - D - glucofuranose- (**3D**).—Compound **2D** (1.82 g) was acetylated as described for lit. [10,11] to give a syrup (99%), $[\alpha]_D^{23}$ +11.5° (*c* 1.0, $CHCl_3$) (lit. [11], no data reported).

5,6-Di-O-acetyl-1,2-O-isopropylidene-3-O-(methylthio)thiocarbonyl - α - L - glucofuranose (**3L**).—Syrup (96%), $[\alpha]_D^{23}$ −11° (*c* 1.0, $CHCl_3$).

5,6-Di-O-acetyl-3-deoxy-1,2-O-isopropylidene-α-D-ribo-hexofuranose (**4D**).—Prepared from **3D** according to the method reported [10,11], crystals (84%), mp 57–58 °C, $[\alpha]_D^{24}$ + 19° (*c* 1.0, $CHCl_3$) {lit. [26], $[\alpha]_D^{20}$ +20° (*c* 0.9, $CHCl_3$)}.

5,6-Di-O-acetyl-3-deoxy-1,2-O-isopropylidene-α-L-ribo-hexofuranose (**4L**).—Prepared form **3L** as described above, syrup (93%), $[\alpha]_D^{23}$ −16° (*c* 1.4, $CHCl_3$).

3-Deoxy-1,2-O-isopropylidene-α-D-ribo-hexofuranose (**5D**).—Prepared from **4D** by Zemplén deacetylation, crystals (quant.), mp 76–78 °C, $[\alpha]_D^{21}$ −18° (*c* 1.0, $CHCl_3$) {lit. [27], mp 82 °C, $[\alpha]_D^{21}$ −19.0° (*c* 1.7, $CHCl_3$)}.

3-Deoxy-1,2-O-isopropylidene-α-L-ribo-hexofuranose (**5L**).—Prepared from **4L** (3.96 g) by methanolic NH_3 to give crystals (2.70 g, 96%), mp 78–80 °C, $[\alpha]_D^{23}$ +19° (*c* 1.0, $CHCl_3$).

3-Deoxy-1,2-O-isopropylidene-6-O-tosyl-α-D-ribo-hexofuranose (**6D**).—Prepared from **5D** by selective tosylation (TsCl–pyridine) [10,11] as a syrup (88%), $[\alpha]_D^{26}$ −4° (*c* 1.0, $CHCl_3$) (lit. [11], no data reported).

3-Deoxy-1,2-O-isopropylidene-6-O-tosyl-α-L-ribo-hexofuranose (**6L**).—Prepared from **5L** as described above, syrup (85%), $[\alpha]_D^{23}$ +5° (*c* 1.0, $CHCl_3$).

3-Deoxy-1,2-O-isopropylidene-5-O-(thiocarbonylimidazolyl)-6-O-tosyl-α-D-ribo-hexofuranose (**7D**).—A mixture of **6D** (5.14 g, 14.3 mmol), *N*,*N*′-thiocarbonyldiimidazole (5.10 g, 25.7 mmol), and imidazole (1.95 g, 28.6 mmol) in $(CH_2Cl)_2$ (100 mL) was kept for 30 min at 70 °C. Evaporation of the solvent together with 1,4-dioxane gave a residue, which after agitation in water (1 h), was extracted with CH_2Cl_2. (If 1,4-dioxane was omitted, the residue included a slight amount of thiocarbonyldiimidazole in the $(CH_2Cl)_2$ film adhered to the surface of the solid particle, and this made the decomposition of the reagent incomplete in the next water-treatment giving impure **7D**; addition of 1,4-dioxane corrected the situation.) The organic solution was washed with 5% aq $KHSO_4$, dried (Na_2SO_4), and concentrated to give **7D** as a relatively unstable solid (6.70 g); ^{1}H NMR ($CDCl_3$): δ 1.31, 1.50 [s of 3 H each, $C(CH_3)_2$], 1.79 (ddd, 1 H, $J_{2,3a}$ 4.5, $J_{3a,3b}$ 13.5, $J_{3a,4}$ 11 Hz, H-3a), 2.26 (dd, 1 H, $J_{3b,4}$ 4.5 Hz, H-3b), 2.40 (s, 3 H, Ts-CH_3), 4.37 (dd, 1 H, H-6a), 4.52 (dd, 1 H, H-6b), 4.53 (m, 1 H, H-4), 4.74 (t, 1 H, H-2), 5.77 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 5.82 (dt, 1 H, H-5), 7.03, 7.51, and 8.18 (m of 1 H each, 3 imidazolyl-H), 7.25 and 7.72 (ABq, 4 H, Ph-H of Ts).

3,5-Dideoxy-1,2-O-isopropylidene-6-O-tosyl-α-D-erythro-hexofuranose (**8D**).—To a solution of **7D** (6.60 g) in toluene (268 mL) were added Bu_3SnH (11.5 mL, 43 mmol) and AIBN (235 mg, 1.4 mmol), and the solution was kept under Ar for 30 min at 80 °C. Concentration, followed by chromatography (2:1 *n*-hexane–EtOAc) of the residue gave **8D** as a syrup (3.74 g, 78% based on **6D**), $[\alpha]_D^{22}$ −8° (*c* 1.0, $CHCl_3$), (lit. [12], $[\alpha]_D^{20}$ −2.9° (*c* 1.1, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.29 and 1.47 [s of 3 H each, $C(CH_3)_2$], 1.46 (ddd, 1 H, H-3a), 1.94 (m, 2 H, H-5), 2.09 (dd, 1 H, H-3b), 2.45 (s, 3 H, Ts-CH_3), 4.11 (ddd, 1 H, $J_{5a(5b),6a}$ 6.5 and 8.0, $J_{6a,6b}$ 10.5 Hz, H-6a), 4.17 (ddd, 1 H, $J_{5a(5b),6b}$ 6.0 and 7.5 Hz, H-6b), 4.20 (m, 1 H, H-4), 4.68 (t, 1 H, H-2), 5.73 (d, 1 H, H-1), 7.35 and 7.77 (ABq, 4 H, Ph-H of Ts). Anal. Calcd for $C_{16}H_{22}O_6S$: C, 56.12; H, 6.48; S, 9.36. Found: C, 56.02; H, 6.52; S, 9.38.

3,5-Dideoxy-1,2-O-isopropylidene-6-O-tosyl-α-L-erythro-hexofuranose (**8L**).—A mixture of **6L** (4.53 g, 12.6 mmol), *N*,*N*′-thiocarbonyldiimidazole (2.99 g, 15 mmol) and imidazole (1.03 g, 15 mmol) in toluene (90 mL) was kept under Ar for 30 min at 70 °C. AIBN (207 mg, 1.26 mmol) and Bu_3SnH (16.9 mL, 63 mmol) were added with toluene (180 mL), and the mixture was kept under Ar for 1 h at 80 °C. Concentration of the solution, followed by chromatography (3:1 → 1:1 *n*-hexane–EtOAc) of the residue gave **8L** as a syrup (3.66 g, 85%), $[\alpha]_S^{23}$ +9° (*c* 1.0, $CHCl_3$); Anal. Calcd for $C_{16}H_{22}O_6S$: C, 56.12; H, 6.48; S, 9.36. Found: C, 55.89; H, 6.26; S, 9.08.

6-Azido-1,2-O-isopropylidene-3,5,6-trideoxy-α-D-erythro-hexofuranose (**9D**).—A mixture of **8D** (155 mg, 0.45 mmol) and NaN_3 (294 mg, 4.5 mmol) in DMF (3.1 mL) was stirred for 30 min at 70 °C. Conventional work-up gave, after chromatography (4:1 *n*-hexane–EtOAC), gave **9D** as a syrup (75.3 mg, 78%), $[\alpha]_D^{24}$ −10° (*c* 1.1, $CHCl_3$); IR (KBr): 2100 cm^{-1}. Anal. Calcd for $C_9H_{15}N_3O_3$: C, 50.69; H, 7.09; N, 19.71. Found: C, 50.96; H, 7.14; N, 19.41.

6-Azido-1,2-O-isopropylidene-3,5,6-trideoxy-α-L-erythro-hexofuranose (**9L**).—Compound **8L** (441 mg) in DMF (8.8 mL) was treated similarly as above to give **9L** as a syrup (229 mg, 83%), $[\alpha]_D^{23}$ +10° (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_9H_{15}N_3O_3$: C, 50.69; H, 7.09; N, 19.71. Found: C, 50.93; H, 7.05; N, 19.47.

Methyl 6-azido-3,5,6-trideoxy-D-erythro-hexofuranoside (**10**).—Methanolysis (1.5 h at room temperature (rt)) of **9D** (1.23 g, 5.76 mmol) in 1:5 aq 12 M HCl–MeOH (25 mL), followed by neutralization ($NaHCO_3$) and subsequent chromatography (1:1 *n*-hexane–EtOAc) gave **10** as a syrup (813 mg, 75%), TLC (2:1 *n*-hexane–EtOAc): R_f 0.17 (α anomer), 0.2 (β anomer) (*cf.* **9D**: R_f 0.7); ^1H NMR* ($CDCl_3$): δ 2.21 (br s, 1 H, OH-2), 3.34 (s, 2.6 H, β-OCH_3), 3.49 (s, 0.4 H, α-OCH_3), 4.24 (br s, 1 H, H-2), 4.78 [s, 0.86 H, H-1(β)], 4.87 [d, 0.14 H, $J_{1,2}$ 4.5 Hz, H-1(α)]. Anal. Calcd for $C_7H_{13}N_3O_3$: C, 44.91; H, 7.00; N, 22.45. Found: C, 44.44; H, 7.17; N, 22.22.

Methyl 6-azido-2-O-benzyl-3,5,6-trideoxy-D-erythro-hexofuranoside (**11**).—An anomeric mixture of **10** (701 mg, 3.74 mmol) and NaH (60% in mineral oil, 450 mg, 11.2 mmol) in DMF (7.0 mL) was vigorously stirred for 5 min at 0 °C, BnBr (0.67 mL, 5.6 mmol) was added, and the mixture was stirred for a further 45 min. After addition of water, the product was extracted with benzene and subjected to chromatography (5:1 *n*-hexane–EtOAc) to give **11α** (133 mg, 13%) and **11β** (868 mg, 84%) as syrups.

Compound **11α**: $[\alpha]_D^{21}$ +100° (*c* 1.0, $CHCl_3$); ^1H NMR* ($CDCl_3$): δ 3.41 (s, 3 H, OCH_3), 3.98 (dt, 1 H, $J_{1,2}$ 4, $J_{2,3a} = J_{2,3b}$ 8.5 Hz, H-2), 4.81 (d, 1 H, H-1). Anal. Calcd for $C_{14}H_{19}N_3O_3$: C, 60.63; H, 6.91; N, 15.15. Found: C, 60.64; H, 6.95; N, 15.18.

Compound **11β**: $[\alpha]_D^{23}$ −25° (*c* 1.2, $CHCl_3$); ^1H NMR* ($CDCl_3$): δ 3.33 (s, 3 H, OCH_3), 3.99 (br d, 1 H, $J_{2,3a}$ 5 Hz, H-2), 4.92 (s, 1 H, H-1). Anal. Calcd for $C_{14}H_{19}N_3O_3$: C, 60.63; H, 6.91; N, 15.15. Found: C, 60.67; H, 6.86; N, 15.05.

6-Azido-2-O-benzyl-3,5,6-trideoxy-D-erythro-hexofuranose (**12**).—An anomeric mixture of **11** (514 mg, 1.85 mmol) in 1:11 aq 12 M HCl–aq 80% AcOH (10 mL) was kept for 6 h at rt. Concentration with occasional additions of toluene and water gave a residue, which was chromatographed (4:1 *n*-hexane–EtOAc) to give **12** as a syrup (353 mg, 72%) together with **11** recovered (94 mg, 18%). ^1H NMR ($CDCl_3$): δ 1.65–1.95 (m, 3 H, H-3a,5a,5b), 2.16 (ddd, 1 H, H-3b, $J_{2,3b}$ 1, $J_{3a,3b}$ 13.5, $J_{3b,4}$ 6 Hz), 3.4 (m, 2 H, H-6a,6b), 4.13 (m, 1 H, H-2), 4.34 (m, 1 H, H-4), 4.55 [s, $C_6H_5CH_2$ (β)], 4.61 [d, *J* 4 Hz, $C_6H_5CH_2$ (α)], 5.36 [d, 0.18 H, *J* 4 Hz, H-1(α)], 5.40 [d, 0.82 H, *J* 3 Hz, H-1(β)]. Anal. Calcd for $C_{13}H_{17}N_3O_3$: C, 59.30; H, 6.51; N, 15.95. Found: C, 59.12; H, 6.53; N, 15.74.

6-Azido-2-O-benzyl-3,5,6-trideoxy-D-erythro-hexofuranosyl chloride (**13**).—A mixture of **12** (251 mg, 0.95 mmol) and $SOCl_2$ (2.5 mL) was kept for 3.5 h at rt. Concentration of the solution gave **13** as a syrup (292 mg, quant), which was used without purification; ^1H NMR ($CDCl_3$): δ 4.22 [dt, 0.1 H, $J_{1,2}$ 3.5, $J_{2,3a} = J_{2,3b}$ 9 Hz, H-2(α)], 4.38 [dd, 0.9 H, $J_{2,3a(3b)}$ 0.5 and 4 Hz, H-2(β)], 6.17 [s, 0.9 H, H-1(β)], 6.25 [d, 0.1 H, H-1(α)].

6-Azido-2-O-benzyl-3,5,6-trideoxy-D-erythro-hexofuranosyl fluoride (**14**).—To an ice-cooled solution of **12** (63.4 mg, 0.24 mmol) in CH_2Cl_2 (1.3 mL) was added DAST (64 μL, 0.48 mmol) and the solution was kept for 20 min at that temperature. After addition of excess CH_2Cl_2 and aq $NaHCO_3$ (satd, 1 mL), followed by stirring for 30 min, the mixture was washed with water, dried (Na_2SO_4), and concentrated to give, after chromatography (7:1 *n*-hexane–EtOAc), **14α** (12.2 mg, 19%) and **14β** (42.3 mg, 66%) as syrups.

Compound **14α**: TLC (2:1 *n*-hexane–EtOAc): R_f 0.5; ^1H NMR ($CDCl_3$): δ 1.76 (m, 2 H, H-5a,5b), 1.93 (ddd, 1 H, $J_{2,3a}$ 9, $J_{3a,3b}$ 12.5, $J_{3a,4}$ 4 Hz, H-3a), 2.24 (dt, 1 H, $J_{2,3b}$ =

$J_{3b,4}$ 9 Hz, H-3b), 3.38 (dt, 2 H, H-6a,6b), 4.05 (ddt, 1 H, $J_{1,2}$ 3, $J_{2,F}$ 19.5 Hz, H-2), 4.52 (m, 1 H, H-4), 4.62 (ABq, 2 H, PhCH_2), 5.68 (dd, 1 H, $J_{1,F}$ 65 Hz, H-1); ^{19}F NMR ($CDCl_3$): δ −136.22 (dd, $J_{1,F}$ 65, $J_{2,F}$ 19.5 Hz, F-1).

Compound **14β**: TLC (2:1 *n*-hexane–EtOAc): R_f 0.55; ^{1}H NMR ($CDCl_3$): δ 1.81 (dddd, 1 H, $J_{2,3a}$ 4.5, $J_{3a,3b}$ 13.5, $J_{3a,4}$ 3, $J_{3a,F}$ 9 Hz, H-3a), 1.86 (q, 2 H, $J_{4,5} = J_{5,6a} = J_{5,6b}$ 7 Hz, H-5a,5b), 2.20 (dd, 1 H, $J_{3b,4}$ 6.5 Hz, H-3b), 3.44 (m, 2 H, H-6a,6b), 4.15 (dd, 1 H, $J_{2,F}$ 3.5 Hz, H-2), 4.51 (m, 1 H, H-4), 4.56 (s, 2 H, PhCH_2), 5.73 (d, 1 H, $J_{1,F}$ 64 Hz, H-1); ^{19}F NMR ($CDCl_3$): δ −114.31 (ddd, $J_{1,F}$ 64, $J_{2,F}$ 3.5, $J_{3a,F}$ 9 Hz, F-1).

*1,2-*O*-Isopropylidene-6-tosylamido-3,5,6-trideoxy-α-*L-erythro-*hexofuranose* (**15**).—A mixture of **9L** (385 mg, 1.80 mmol) and Raney Ni in 2:1 THF–water (12 mL) was stirred under H_2 for 1 h at rt. Filtration through a bed of Celite, followed by concentration gave a residue, which was treated with TsCl (412 mg, 2.2 mmol) and Na_2CO_3 (230 mg, 2.2 mmol) in 2:1 CH_2Cl_2–water (10 mL) under vigorous stirring for 1 h. The product was chromatographed (3:2 *n*-hexane–EtOAc) to give **15** as a syrup (532 mg, 87%), $[\alpha]_D^{23}$ +8° (*c* 1.1, $CHCl_3$); ^{1}H NMR* ($CDCl_3$): δ 1.30, 1.46 [s of 3 H each, C(CH_3)$_2$], 2.42 [s, 3 H, Ts(CH_3)], 5.20 (br dd, 1 H, TsN*H*-6), 5.76 (d, 1 H, $J_{1,2}$ 4 Hz, H-1). Anal. Calcd for $C_{16}H_{23}NO_5S$: C, 56.29; H, 6.79; N, 4.10; S, 9.39. Found: C, 56.03; H, 6.96; N, 4.27; S, 9.24.

*Methyl 6-tosylamido-3,5,6-trideoxy-*L-erythro-*hexofuranoside* (**16**).—Compound **15** (1.60 g, 4.68 mmol) was methanolyzed in 1:5 aq 12 M HCl–MeOH (32 mL) for 1 h at rt and the product was chromatographed (30:1 $CHCl_3$–MeOH) to give an anomeric mixture of **16** as a syrup (1.44 g, 97%).

*Methyl 2-*O*-benzyl-6-*N*-benzyl-6-tosylamido-3,5,6-trideoxy-*L-erythro-*hexofuranoside* (**17**).—Compound **16** (1.10 g) was benzylated as described for **11** to give **17** as a syrup (1.75 g, quant). Analytical samples of the α and β anomers were obtained by chromatography (4:1 → 2:1 *n*-hexane–EtOAc).

α Anomer: TLC (2:1 *n*-hexane–EtOAc): R_f 0.4, $[\alpha]_D^{24}$ −54° (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.47–1.55 (m, 2 H, H-3a,5a), 1.60 (ddd, 1 H, $J_{4,5b}$ 4.5, $J_{5a,5b}$ 12.5, $J_{5b,6a}$ 9 Hz, H-5b), 1.98 (dt, 1 H, $J_{2,3b} = J_{3b,4}$ 8.5, $J_{3a,3b}$ 12 Hz, H-3b), 2.43 [s, 3 H, Ts(CH_3)], 3.10 (ddd, 1 H, $J_{5a,6a}$ 6, $J_{6a,6b}$ 14 Hz, H-6a), 3.19 (ddd, 1 H, $J_{5a,6b}$ and $J_{5b,6b}$: 6.5 and 9 Hz, H-6b), 3.34 (s, 3 H, OCH_3), 3.82 (dt, 1 H, $J_{1,2}$ 4, $J_{2,3a}$ 8.5 Hz, H-2), 3.97 (tt, 1 H, H-4), 4.30 (ABq, 2 H, $C_6H_5CH_2$), 4.52 (s, 2 H, $C_6H_5CH_2$), 4.69 (d, 1 H, H-1). Anal. Calcd for $C_{28}H_{33}NO_5S$: C, 67.85; H, 6.71; N, 2.83; S, 6.47. Found: C, 67.59; H, 6.63; N, 2.74; S, 6.68.

β Anomer: TLC (2:1 *n*-hexane–EtOAc): R_f 0.55, $[\alpha]_D^{24}$ +17° (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.55–1.68 (m, 3 H, H-3a,5a,5b), 1.96 (ddd, 1 H, $J_{2,3b}$ 0.5, $J_{3a,3b}$ 13, $J_{3b,4}$ 6 Hz, H-3b), 2.42 [s, 3 H, Ts(CH_3)], 3.13–3.19 (m, 1 H, H-6a), 3.16 (s, 3 H, OCH_3), 3.29 (ddd, 1 H, $J_{5a,6b}$ and $J_{5b,6b}$: 5.5 and 10.5, $J_{6a,6b}$ 14 Hz, H-6b), 3.88 (br d, 1 H, $J_{2,3a}$ 4.5 Hz, H-2), 4.10 (m, 1 H, H-4), 4.32 (ABq, 2 H, $C_6H_5CH_2$), 4.48 (s, 2 H, $C_6H_5CH_2$), 4.79 (s, 1 H, H-1). Anal. Calcd for $C_{28}H_{33}NO_5S$: C, 67.85; H, 6.71; N, 2.83; S, 6.47. Found: C, 67.93; H, 6.78; N, 2.88; S, 6.41.

*2-*O*-Benzyl-6-*N*-benzyl-6-tosylamido-3,5,6-trideoxy-*L-erythro-*hexofuranose* (**18**).—Hydrolysis of **17** (1.75 g) as described for **12**, followed by chromatography (20:1 $CHCl_3$–MeOH) gave **18** as a syrup (1.47 g, 86%). ^{1}H NMR ($CDCl_3$): δ 1.41–1.75 (m, 3 H, H-3a,5a,5b), 1.96 (m, 1 H, H-3b), 2.42 [s, 3 H, Ts(CH_3)], 2.60 (br s, 0.6 H, OH-1), 3.06–3.37 (m, 2 H, H-6a,6b), 3.86–4.15 (m, 2 H, H-2,4), 4.29, 4.54 (ABq, 4 H, $C_6H_5CH_2$), 4.48 (s, 2 H, $C_6H_5CH_2$), 5.27 (m, 1 H, H-1). Anal. Calcd for $C_{27}H_{31}NO_5S{\cdot}0.7H_2O$: C, 65.61; H, 6.61; N, 2.83. Found: C, 65.42; H, 6.28; N, 2.80.

*2-*O*-Benzyl-6-*N*-benzyl-6-tosylamido-3,5,6-trideoxy-*L-erythro-*hexofuranosyl chloride* (**19**).—A mixture of **18** (484 mg, 1.01 mmol) and $SOCl_2$ (4.8 mL) was kept for 3 h at rt. Careful concentration gave **19** as an unstable syrup (528 mg, quant), which was used without purification.

*2′,3′,4′,2″,4″,6″-Hexa-*O*-acetyl-1,3,6′,3″-tetra-*N*-tosylkanamycin A* (**21**).—An ice-cold mixture of 1,3,6′,3″-tetra-*N*-tosylkanamycin A (**20**) [15] (5.00 g, 4.54 mmol) and AcCl (2.26 mL, 31.8 mmol) in pyridine (100 mL) was

kept for 6 h at rt. After addition of water (1.2 mL), followed by standing for 1 h, the solution was concentrated to give a residue, which, after dissolving in $CHCl_3$, was washed with aq $NaHCO_3$ (satd), aq 5% $KHSO_4$, and water, dried (Na_2SO_4), and concentrated to give **21** as an amorphous solid (6.06 g, 99%). An analytical sample was prepared by chromatography (3:1 $CHCl_3$–acetone), $[\alpha]_D^{24}$ +48° (*c* 1.0, $CHCl_3$); ^{1}H NMR* (pyridine-d_5): δ 1.90, 1.91, 2.04, 2.07, 2.08, 2.17, 2.17, 2.30, 2.31, 2.37 [s of 3 H each, 4 Ts(CH_3) and 6 Ac], 3.6–4.0 (m, 7 H, H-1,3,4,5,6,6′a,6′b), 4.71 (q, 1 H, $J_{2'',3''} = J_{3'',4''} = J_{3'',NH\text{-}3''}$ 10 Hz, H-3″), 6.01 (d, 1 H, $J_{1',2'}$ 4 Hz, H-1′), 6.03 (d, 1 H, $J_{1'',2''}$ 4 Hz, H-1″), 6.61 (d, 1 H, O*H*-5); 8.52, 9.01 (d of 1 H each, TsN*H*-1,3), 8.72 (m, 1 H, TsN*H*-6′), 10.08 (d, 1 H, *J* 7 Hz, TsN*H*-3″). Anal. Calcd for $C_{58}H_{72}N_4O_{25}S_4$: C, 51.47; H, 5.36; N, 4.14; S, 9.47. Found: C, 51.17; H, 5.59; N, 4.39; S, 9.09.

2′,3′,4′,2″,4″,6″-Hexa-O-*acetyl-5-deoxy-5-epi-5-fluoro-1,3,6′,3″-tetra*-N-*tosylkanamycin A* (**22**).—To a cold (−20 °C) solution of **21** (5.91 g, 4.37 mmol) in CH_2Cl_2 (120 mL), DAST (2.89 mL, 22 mmol) was added, and the solution was kept for 2.5 h at 0 °C. Aqueous $NaHCO_3$ (satd, 400 mL) was added under vigorous stirring, and the product was extracted with $CHCl_3$ to give **22** as an amorphous solid (6.93 g, quant). An analytical sample was prepared by chromatography (20:1 $CHCl_3$–MeOH); HPTLC (20:1 $CHCl_3$–MeOH), R_f 0.6 (*cf.* **21**: R_f 0.52), $[\alpha]_D^{23}$ +56.5° (*c* 1.0, $CHCl_3$); ^{1}H NMR* (500 MHz, pyridine-d_5): δ 1.96, 1.99, 2.017, 2.024, 2.04, 2.16, 2.17, 2.20, 2.31, 2.35 [s of 3 H each, 4 Ts(CH_3) and 6 Ac], 3.62 (ddd, 1 H, $J_{5',6'a}$ 2.5, $J_{6'a,6'b}$ 13.5, $J_{6'a,NH\text{-}6'}$ 5 Hz, H-6′a), 3.70 (ddd, 1 H, $J_{5',6'b}$ 3.5, $J_{6'b,NH\text{-}6'}$ 8 Hz, H-6′b), 3.85 (ddt, 1 H, $J_{1,2ax} = J_{1,6}$ 10.5, $J_{1,2eq}$ 4.5, $J_{1,NH\text{-}1}$ 7 Hz, H-1), 4.04 (m, 1 H, H-3), 4.13 (dd, 1 H, $J_{6,F}$ 27.5 Hz, H-6), 4.26 (dd, 1 H, $J_{3,4}$ 11, $J_{4,F}$ 27.5 Hz, H-4), 4.55 (br d, 1 H, $J_{6''a,6''b}$ 13.5 Hz, H-6″a), 4.64 (dd, 1 H, $J_{5'',6''b}$ 4 Hz, H-6″b), 4.75 (m, 1 H, H-3″), 4.90 (dd, 1 H, $J_{1',2'}$ 4, $J_{2',3'}$ 10.5 Hz, H-2′), 5.45 (dd, 1 H, $J_{1'',2''}$ 4, $J_{2'',3''}$ 10.5 Hz, H-2″), 5.46 (br d, 1 H, $J_{5,F}$ 51.5 Hz, H-5), 5.59 (d, 1 H, H-1″), 5.85 (d, 1 H, H-1′), 7.86 (d, 1 H, TsN*H*-1), 8.69 (dd, 1 H, TsN*H*-6′), 9.30 (d, 1 H, $J_{3,NH\text{-}3}$ 9 Hz, TsN*H*-3), 10.03 (br d, 1 H, $J_{3'',NH\text{-}3''}$ 7 Hz, TsN*H*-3″). The H-1, 3, and 4, 6 signals were assigned by ^{1}H–^{1}H COSY, HMQC, and HMBC spectra. ^{19}F NMR (pyridine-d_5): δ −213.39 (dt, $J_{4,F} = J_{6,F}$ 26, $J_{5,F}$ 50.5 Hz, F-5). Anal. Calcd for $C_{58}H_{71}FN_4O_{24}S_4 \cdot H_2O$: C, 50.72; H, 5.36; N, 4.08; S, 9.34. Found: C, 50.63; H, 5.33; N, 4.25; S, 9.17.

5-Deoxy-5-epi-5-fluoro-1,3,6′,3″-tetra-N-*tosylkanamycin A* (**23**).—A solution of **22** (monohydrate, 332 mg, 0.25 mmol) in 0.5% NaOMe in MeOH (6.6 mL) was kept for 30 min at rt. Conventional purification gave **23** as an amorphous solid (268 g, 99%), TLC (2:1:1 $CHCl_3$–MeOH–aq 28% NH_3): R_f 0.1; $[\alpha]_D^{24}$ +50° (*c* 1.0, DMF); ^{1}H NMR* (500 MHz, pyridine-d_5): δ 2.09, 2.15, 2.21, 2.26 [s of 3 H each, 4 Ts(CH_3)], 3.71 (dt, 1 H, H-1), 3.82 (m, 2 H, H-6′a,6′b), 4.02 (dd, 1 H, $J_{1,6}$ 11, $J_{6,F}$ 26.5 Hz, H-6), 4.08 (m, 1 H, H-3), 4.19 (dd, 1 H, $J_{3,4}$ 11, $J_{4,F}$ 26.5 Hz, H-4), 4.46 (t, 1 H, H-3″), 5.45 (d, 1 H, H-1″), 5.48 (d, 1 H, H-1′), 5.99 (d, 1 H, $J_{5,F}$ 51.5 Hz, H-5), 8.44 (br s, 1 H, TsN*H*-1), 8.61 (br t, 1 H, $J_{6'a(6'b),NH\text{-}6'}$ 6 Hz, TsN*H*-6′), 8.96 (br d, 1 H, $J_{3,NH\text{-}3}$ 7 Hz, TsN*H*-3), 9.41 (br s, 1 H, TsN*H*-3″); ^{19}F NMR (pyridine-d_5): δ −212.05 (dt, $J_{4,F} = J_{6,F}$ 27.5, $J_{5,F}$ 51.5 Hz, F-5); ^{13}C NMR (pyridine-d_5): δ 21.14, 21.29, 21.35, 21.45 [4 Ts(*C*H$_3$)], 34.68 (C-2), 45.08 (C-6′), 50.94 (d, *J* 4 Hz, C-3), 51.80 (d, *J* 4 Hz, C-1), 61.67 (C-3″), 62.11 (C-6″), 69.99 (C-4″), 72.25 (C-2″), 72.39 (C-4′,5′), 73.47 (C-2′), 74.60 (C-3′), 75.43 (C-5″), 77.40 (d, *J* 17 Hz, C-4), 82.58 (d, *J* 17 Hz, C-6), 90.82 (d, *J* 182 Hz, C-5), 98.67 (C-1′), 103.66 (C-1″). The H-1, 3, 4, 6 signals were assigned by ^{1}H–^{1}H COSY, HMQC, and HMBC spectra. Anal. Calcd for $C_{46}H_{59}FN_4O_{18}S_4$: C, 50.08; H, 5.39; N, 5.08; S, 11.62. Found: C, 50.04; H, 5.56; N, 5.02; S, 11.32.

*6-*O*-(3-Deoxy-3-tosylamido-α-*D*-glucopyranosyl)-2,5-dideoxy-5-epi-5-fluoro-1,3-di*-N-*tosylstreptamine* (**24**).—To a solution of **23** (1.00 g, 0.91 mmol) in MeOH (100 mL) was added $NaIO_4$ (1.94 g, 9.07 mmol), and the mixture was stirred for 2 h at rt. Ethylene glycol (0.5 mL) was added, and after stirring for 30 min, the solution was concentrated. The residue was shaken with water and the insolu-

ble matter was collected, and dried. To a MeOH solution (20 mL) of the solid was added $NaBH_4$ (858 mg, 22.7 mmol), and the mixture was kept for 2.5 h at rt. After acetone (6.67 mL) had been added, followed by stirring (30 min), the mixture was neutralized with aq 1 M HCl. After concentration, the residue dissolved in 1.5 M HCl in MeOH (20 mL) was kept for 5 h at rt. Concentration of the solution gave a residue, which was thoroughly washed with water and dried to give **24** as a practically pure solid (639 mg, 87%), TLC (1.5:1:1 $CHCl_3$–MeOH–aq 28% NH_3): R_f 0.33 (*cf.* **23**: R_f 0.2), $[\alpha]_D^{19}$ +25° (*c* 1.0, DMF); ^{1}H NMR* (pyridine-d_5): δ 2.08, 2.18, 2.22 [s of 3 H each, 3 Ts(CH_3)], 5.57 (d, 1 H, $J_{1',2'}$ 4 Hz, H-1′), 5.71 (br d, 1 H, $J_{5,F}$ 52 Hz, H-5), 8.45 (br s, 1 H, TsN*H*-1 or 3), 9.27 (br d, 1 H, TsN*H*-3 or 1), 9.43 (br d, 1 H, TsN*H*-3′); ^{19}F NMR (pyridine-d_5): δ −211.66 (dt, $J_{4,F} = J_{6,F}$ 30, $J_{5,F}$ 52 Hz, F-5). Anal. Calcd for $C_{33}H_{42}FN_3O_{12}S_3 \cdot H_2O$: C, 49.18; H, 5.50; N, 5.21. Found: C, 48.96; H, 5.43; N, 5.10.

6-O-*(4,6*-O-*Benzylidene-3-deoxy-3-tosylamido-α*-D-*glucopyranosyl)-2,5-dideoxy-5-epi-5-fluoro-1,3-di*-N-*tosylstreptamine* (**25**).—A mixture of **24** (986 mg, 1.25 mmol), $C_6H_5CH(OMe)_2$ (0.38 mL, 2.50 mmol), and anhyd *p*-toluenesulfonic acid (43 mg) in DMF (10 mL) was stirred for 1 h under vacuum (35 mmHg) at 60 °C, whereupon removal of the MeOH liberated occurred. After pouring the solution into aq $NaHCO_3$ (satd), the precipitate was washed thoroughly with water, dried, and chromatographed (10:1 $CHCl_3$–MeOH) to give **25** as an amorphous solid (1.08 g, quant), $[\alpha]_D^{21}$ +8° (*c* 1.0, $CHCl_3$); ^{1}H NMR (pyridine-d_5): δ 2.07, 2.14, 2.22 [s of 3 H each, 3 Ts(CH_3)], 5.44 (s, 1 H, C_6H_5CH), 5.54 (br. d, 1 H, $J_{5,F}$ 53 Hz, H-5), 5.57 (d, 1 H, $J_{1',2'}$ 3.5 Hz, H-1′), 6.8–8.4 [17 H, 3 Ts(C_6H_4), C_6H_5CH], 8.39 (s), 9.35 (d), 9.57 (d) (1 H each, TsN*H*-1,3,3′); ^{19}F NMR (pyridine-d_5): δ −211.18 (dt, $J_{4,F} = J_{6,F}$ 27.5, $J_{5,F}$ 51 Hz, F-5). Anal. Calcd for $C_{40}H_{46}FN_3O_{12}S_3$: C, 54.84; H, 5.29; N, 4.80; S, 10.98. Found: C, 54.43; H, 5.41; N, 4.89; S, 10.96.

6-O-*(2*-O-*Acetyl-4,6*-O-*benzylidene-3-deoxy-3-tosylamido-α*-D-*glucopyranosyl)-2,5-dideoxy-5-epi-5-fluoro-1,3-di*-N-*tosylstreptamine* (**26**) *and 6*-O-*(2*-O-*acetyl-4,6*-O-*benzylidene-3-deoxy-3-tosylamido-α*-D-*glucopyranosyl)-4*-O-*acetyl-2,5-dideoxy-5-epi-5-fluoro-1,3-di*-N-*tosylstreptamine* (**27**).—To a solution of **25** (691 mg, 0.79 mmol) in 9:1 dry Me_2SO–pyridine [20] (6.9 mL) was added *N*-acetylimidazole (174 mg, 1.58 mmol), and the solution was kept for 65 h at rt. Water was added, and after stirring for 30 min, the precipitate obtained was filtered, dried, and chromatographed (15:1 $CHCl_3$–MeOH) to give **26** (342 mg, 47%) and **27** (380 mg, 49%) as amorphous solids. Compound **27** could be converted into **25** by deacetylation, as described for **23**.

Compound **26**: TLC (7:1 $CHCl_3$–MeOH): R_f 0.45 (*cf.* **25**: R_f 0.25); $[\alpha]_D^{23}$ −14° (*c* 1.0, $CHCl_3$); ^{1}H NMR* (pyridine-d_5): δ 2.35 (s, 3 H, AcO-2′), 5.56 (s, 1 H, C_6H_5CH), 5.58 (dd, 1 H, $J_{1',2'}$ 4, $J_{2',3'}$ 11 Hz, H-2′), 5.59 (dt, 1 H, $J_{4,5} = J_{5,6}$ 1.5, $J_{5,F}$ 52 Hz, H-5), 5.83 (d, 1 H, H-1′); ^{19}F NMR (pyridine-d_5): δ −211.93 (dt, $J_{4,F} = J_{6,F}$ 29, $J_{5,F}$ 52 Hz, F-5). Anal. Calcd for $C_{42}H_{48}FN_3O_{13}S_3$: C, 54.95; H, 5.27; N, 4.58; S, 10.48. Found: C, 54.62; H, 5.47; N, 4.71; S, 10.74.

Compound **27**: TLC (7:1 $CHCl_3$–MeOH): R_f 0.65; $[\alpha]_D^{22}$ +10° (*c* 1, $CHCl_3$); ^{1}H NMR* (pyridine-d_5): δ 1.83 (s, 3 H, AcO-4), 2.33 (s, 3 H, AcO-2′), 4.07 (m, 1 H, H-1), 4.20 (m, 1 H, H-3), 5.45 (ddd, 1 H, $J_{3,4}$ 11, $J_{4,5}$ 2, $J_{4,F}$ 28 Hz, H-4), 5.57 (s, 1 H, C_6H_5CH), 5.58 (dd, 1 H, $J_{1',2'}$ 4, $J_{2',3'}$ 10.5 Hz, H-2′), 5.62 (br d, 1 H, $J_{5,F}$ 52 Hz, H-5), 5.81 (d, 1 H, H-1′); ^{19}F NMR (pyridine-d_5): δ −211.50 (dt, $J_{4,F} = J_{6,F}$ 28.5, $J_{5,F}$ 52.5 Hz, F-5). Anal. Calcd for $C_{44}H_{50}FN_3O_{14}S_3 \cdot H_2O$: C, 54.03; H, 5.63; N, 4.30; S, 9.83. Found: C, 54.33; H, 5.31; N, 4.33; S, 9.72.

6-O-*(2*-O-*Acetyl-4,6*-O-*benzylidene-3-deoxy-3-tosylamido-α*-D-*glucopyranosyl)-4*-O-*(6-azido-2*-O-*benzyl-3,5,6-trideoxy-α*-D- (**28a**) *and -β*-D-erythro-*hexofuranosyl)-2,5-dideoxy-5-epi-5-fluoro-1,3-di*-N-*tosylstreptamine* (**28b**).—A mixture of **26** (430 mg, 0.47 mmol), **13** (110 mg, 0.39 mmol), and $CaSO_4$ (Drierite, 530 mg), in THF (1.1 mL) was stirred for 30 min. Then $Hg(CN)_2$ (197 mg, 0.78 mmol) was added, and stirring was continued for 1 h at rt in the dark. After filtration through a bed of Celite and CH_2Cl_2, the organic solution was washed with aq $NaHCO_3$ (satd) and water, dried (Na_2SO_4), and concen-

trated. Chromatography (1:1 → 2:3 *n*-hexane–EtOAc, changed gradually) of the residue gave **28** as an anomeric mixture (α:β = 1:1, 264 mg, 58% based on **13**) together with **26** recovered (180 mg). Pure anomers were prepared by repeated chromatographys (2:1 → 1:1 toluene–EtOAc).

Compound **28a**: TLC (1:2 *n*-hexane–EtOAc): R_f 0.35; $[\alpha]_D^{25}$ +46° (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, pyridine-d_5; see Table 2 for the signals not included below): δ 2.14, 2.21, 2.24 [s of 3 H each, 3 Ts(CH_3)], 2.33 (s, 3 H, Ac), 4.67 (ABq, 2 H, $C_6H_5CH_2$), 5.57 (s, 1 H, C_6H_5CH), 8.09, 8.72 (d of 1 H each, *J* 6 Hz, TsN*H*-1,3), 9.83 (d, 1 H, *J* 8 Hz, TsN*H*-3″); ^{19}F NMR (pyridine-d_5): δ −211.83 (dt, $J_{4,F} = J_{6,F}$ 27.5, $J_{5,F}$ 52 Hz, F-5); ^{13}C NMR (pyridine-d_5; see Table 3 for other signals): δ 21.08, 21.21, 21.25, 21.28 [3 Ts(*C*H_3) and *C*H_3CO]. Anal. Calcd for $C_{55}H_{63}FN_6O_{15}S_3 \cdot 0.5H_2O$: C, 56.35; H, 5.50; N, 7.17; S, 8.20. Found: C, 56.40; H, 5.74; N, 7.31; S, 8.19.

Compound **28b**: TLC (1:2 *n*-hexane–EtOAc): R_f 0.5; $[\alpha]_D^{25}$ −1.5° (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, pyridine-d_5; see Table 2 for the signals not included below): δ 2.14, 2.20, 2.30 [s of 3 H each, 3 Ts(CH_3)], 2.34 (s, 3 H, Ac), 4.61 (s, 2 H, $C_6H_5CH_2$), 5.63 (s, 1 H, C_6H_5CH), 8.03 (d, 1 H, TsN*H*-1), 9.28 (d, 1 H, $J_{3,NH\text{-}3}$ 7 Hz, TsN*H*-3), 9.85 (d, 1 H, *J* 8 Hz, TsN*H*-3″); ^{19}F NMR (pyridine-d_5): δ −212.76 (dt, $J_{4,F} = J_{6,F}$ 27, $J_{5,F}$ 51 Hz, F-5); ^{13}C NMR (pyridine-d_5; see Table 3 for the signals not included below): δ 21.09, 21.23, 21.27 (two overlapped signals), [3 Ts(*C*H_3) and *C*H_3CO]. Anal. Calcd for $C_{55}H_{63}FN_6O_{15}S_3$: C, 56.79; H, 5.46; N, 7.22; S, 8.27. Found: C, 57.05; H, 5.49; N, 7.18; S, 8.27.

4-O-*(6-amino-3,5,6-trideoxy-α*-D-erythro-*hexofuranosyl)-6*-O-*(3-amino-3-deoxy-α*-D-*glucopyranosyl)-2,5-dideoxy-5-epi-5-fluoro-streptamine* (**29a**).—A solution of **28a** (218 mg, 0.187 mmol) in 0.5% NaOMe in 9:1 pyridine–MeOH (4.4 mL) was kept for 1 h at rt. The mixture was poured into aq 5% $KHSO_4$ (440 mL) under vigorous stirring, and the precipitate was filtrated, washed with water, and dried, which was hydrogenated with palladium black in 1:1 DMF–aq 80% AcOH (21 mL) for 4 h under hydrogen bubbling (reduction of N_3 with partial debenzylation and debenzylidenation). After filtration, the solvent was evaporated azeotropically with the aid of toluene and water. To the residue in liquid NH_3 (~40 mL) at −50 °C, sodium (~200 mg) was added, and after 1 h (detosylation, debenzylation, and debenzylidenation occurred during this operation) MeOH was added until the blue color disappeared. Excess NH_3 was removed by gradually raising the temperature to rt. The residue dissolved in water, after neutralization with Dowex 50W-X2 resin (H^+ form), was chromatographed with the same resin with aq 1 M NH_4OH. The ninhydrin-positive fractions were collected, concentrated, and again chromatographed with CM-Sephadex C-25 (0.05 → 0.2 M NH_4OH, gradual change) to give **29a** as a solid (30.5 mg, 33% as $0.7H_2CO_3$ salt; it is generally difficult to obtain aminoglycoside antibiotics as the free base due to their absorbing CO_2 readily from the air during the isolation process; the situation was the same with **29b** and **32b**), $[\alpha]_D^{25}$ +154° (*c* 0.9, water); ^{19}F NMR (26% ND_3 in D_2O): δ −213.10 (dt, $J_{4,F} = J_{6,F}$ 29, $J_{5,F}$ 52.5 Hz, F-5). Anal. Calcd for $C_{18}H_{35}FN_4O_8 \cdot 0.7H_2CO_3$: C, 45.11; H, 7.37; N, 11.25; F, 3.82. Found: C, 45.23; H, 7.65; N, 11.04; F, 3.50.

4-O-*(6-Amino-3,5,6-trideoxy-β*-D-erythro-*hexofuranosyl)-6*-O-*(3-amino-3-deoxy-α*-D-*glucopyranosyl)-2,5-dideoxy-5-epi-5-fluoro-streptamine* (**29b**).—A solution of **28b** (697 mg, 0.60 mmol) was deacetylated (0.1% NaOMe in 1:1 $CHCl_3$–MeOH) and, after neutralization [Dowex 50W-X2 resin (H^+ form, stored in MeOH)], was deprotected with sodium (~670 mg) in 10:1 liquid NH_3–THF (~140 mL) as described for **29a** to give **29b** as a solid (121 mg, 42% as $0.7H_2CO_3$ salt), $[\alpha]_D^{25}$ +46° (*c* 0.8, water); ^{19}F NMR (26% ND_3 in D_2O): δ −212.68 (dt, $J_{4,F} = J_{6,F}$ 29, $J_{5,F}$ 52 Hz, F-5). Anal. Calcd for $C_{18}H_{35}FN_4O_8 \cdot 0.7H_2CO_3$: C, 45.11; H, 7.37; N, 11.25; F, 3.82. Found: C, 45.24; H, 7.65; N, 11.17; F, 3.58.

6-O-*(2*-O-*Acetyl-4,6*-O-*benzylidene-3-deoxy-3-tosylamido-α*-D-*glucopyranosyl)-4*-O-*(2*-O-*benzyl-6*-N-*benzyl-6-tosylamido-3,5,6-trideoxy-*L-erythro-*hexofuranosyl)-2,5-dideoxy-5-epi-5-fluoro-1,3-di*-N-*tosylstreptamine* (**30**).

—A mixture of **26** (541 mg, 0.59 mmol), **19** (246 mg, 0.49 mmol), and 4 Å molecular sieves (246 mg) in CH_2Cl_2 (2.5 mL) was stirred for 30 min at rt. Then $Hg(CN)_2$ (248 mg, 0.98 mmol) and *s*-collidine (0.26 mL, 1.96 mmol) were added, and the mixture was stirred for 16 h at rt in the dark. After filtration through a bed of Celite and CH_2Cl_2, the solution was washed with aq $NaHCO_3$ (satd), aq 5% $KHSO_4$, and water, dried (Na_2SO_4), and concentrated. Chromatography (2:1 toluene–EtOAc) of the residue gave **30b** (β anomer, 153 mg) as a solid and a mixture of the anomers (**30a**,**b**, 62 mg) (32% in total). An analytical sample of **30a** was obtained by repeated chromatographys (3:1 → 1:1 toluene–EtOAc with gradual change).

30a: TLC (1:1 toluene–EtOAc): R_f 0.4, $[\alpha]_D^{19}$ +1° (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, pyridine-d_5): δ 1.56–1.70 (m, 3 H, H-3′a,5′a,5′b), 1.89 (q, 1 H, H-2ax), 2.10 (m, 1 H, H-3′b), 2.14, 2.22, 2.26, 2.27 [s of 3 H each, 4 Ts(CH_3)], 2.28 (s, 3 H, Ac), 2.82 (dt, 1 H, H-2eq), 3.36 (m, 2 H, H-6′a,6′b), 3.82 (t, 1 H, H-6″a), 3.86 (m, 1 H, H-1), 3.93–4.02 (m, 3 H, H-3,2′,4″), 4.17–4.36 (m, 4 H, H-4,6,4′,6″b), 4.41 (ABq, 2 H, $C_6H_5CH_2$-6′), 4.45 (m, 1 H, H-5″), 4.87 (ABq, 2 H, $C_6H_5CH_2$-2′), 4.74 (m, 1 H, H-3″), 5.56 (dd, 1 H, H-2″), 5.59 (s, 1 H, C_6H_5CH), 5.60 (d, 1 H, $J_{1',2'}$ 4 Hz, H-1′), 5.65 (br d, 1 H, $J_{5,F}$ 51.5 Hz, H-5), 5.76 (d, 1 H, $J_{1'',2''}$ 4 Hz, H-1″), 8.00 (d, 1 H, $J_{1,NH\text{-}1}$ 6 Hz, TsN*H*-1), 8.59 (d, 1 H, $J_{3,NH\text{-}3}$ 7.5 Hz, TsN*H*-3), 9.82 (d, 1 H, $J_{3'',NH\text{-}3''}$ 8.5 Hz, TsN*H*-3″); ^{19}F NMR (pyridine-d_5): δ −212.09 (dt, $J_{4,F} = J_{6,F}$ 28, $J_{5,F}$ 51.5 Hz, F-5). Anal. Calcd for $C_{69}H_{77}FN_4O_{17}S_4$: C, 59.98; H, 5.62; N, 4.06. Found: C, 59.88; H, 5.62; N, 3.90.

30b: TLC (1:1 toluene–EtOAc): R_f 0.55, $[\alpha]_D^{19}$ +8° (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, pyridine-d_5): δ 1.66 (ddd, 1 H, $J_{2',3'a}$ 5, $J_{3'a,3'b}$ 13, $J_{3'a,4'}$ 10 Hz, H-3′a), 1.84–2.00 (m, 3 H, H-2ax,3′b,5′a), 2.12 (m, 1 H, H-5′b), 2.14, 2.21, 2.24, 2.28 [s of 3 H each, 4 Ts(CH_3)], 2.31 (s, 3 H, Ac), 2.72 (dt, 1 H, $J_{1,2eq} = J_{2eq,3}$ 4.5, $J_{2ax,2eq}$ 13.5 Hz, H-2eq), 3.29 (ddd, 1 H, $J_{5'a(5'b),6'a}$ 6.5 and 8.5, $J_{6'a,6'b}$ 14 Hz, H-6′a), 3.56 (ddd, 1 H, $J_{5'a(5'b),6'b}$ 5 and 9 Hz, H-6′b), 3.81 (t, 1 H, $J_{5'',6''a} = J_{6''a,6''b}$ 10.5 Hz, H-6″a), 3.96 (br d, 1 H, $J_{2',3'a}$ 5 Hz, H-2′), 3.98–4.07 (m, 2 H, H-1,3), 4.03 (t, 1 H, $J_{3'',4''} = J_{4'',5''}$ 10.5 Hz, H-4″), 4.18–4.32 (m, 4 H, H-4,6,4′,6″b), 4.41 (ABq, 2 H, $C_6H_5CH_2$-6′), 4.47 (ABq, 2 H, $C_6H_5CH_2$-2′), 4.48–4.55 (m, 1 H, H-5″), 4.77 (dt, 1 H, $J_{2'',3''}$ 10.5, $J_{3'',NH\text{-}3''}$ 9 Hz, H-3″), 5.52 (s, 1 H, H-1′), 5.58 (dd, 1 H, $J_{1'',2''}$ 4 Hz, H-2″), 5.59 (s, 1 H, C_6H_5CH), 5.75 (br d, 1 H, $J_{5,F}$ 52 Hz, H-5), 5.81 (d, 1 H, H-1″); 8.25, 8.31 (br d of 1 H each, TsN*H*-1,3), 9.82 (d, 1 H, TsN*H*-3″); ^{19}F NMR (pyridine-d_5): δ −212.56 (dt, $J_{4,F} = J_{6,F}$ 26, $J_{5,F}$ 52 Hz, F-5). Anal. Calcd for $C_{69}H_{77}FN_4O_{17}S_4 \cdot H_2O$: C, 59.21; H, 5.69; N, 4.00. Found: C, 59.32; H, 5.60; N, 3.98.

*4-*O*-(6-Amino-3,5,6-trideoxy-β-*L*-erythro-hexofuranosyl)-6-*O*-(3-amino-3-deoxy-α-*D*-glucopyranosyl)-2,5-dideoxy-5-epi-5-fluoro-streptamine* (**32b**).—Compound **30b** (363 mg, 0.263 mmol) was deacetylated as described for **29a** and the product was deprotected with sodium in liquid ammonia as described for **29b** to give the 6′-*N*-benzyl derivative **31** (152 mg); ^{1}H NMR* (500 MHz, pyridine-d_5): δ 1.90 (dt, 1 H, *J* 7, 7, 14 Hz, H-5′a), 2.03 (ddd, 1 H, $J_{2',3'a}$ 4.5, $J_{3'a,3'b}$ 13, $J_{3'a,4'}$ 10 Hz, H-3′a), 2.11 (dt, 1 H, *J* 7, 7, 14 Hz, H-5′b), 2.24 (dd, 1 H, $J_{3'b,4'}$ 6 Hz, H-3′b), 2.84 (m, 2 H, H-6′a,6′b), 3.81 (s, 2 H, $C_6H_5CH_2$-6′), 4.69 (d, 1 H, H-2′), 4.81 (m, 1 H, H-4′), 5.46 (d, 1 H, $J_{1'',2''}$ 4 Hz, H-1″) 5.76 (s, 1 H, H-1′), 7.25–7.49 (5 H, $C_6H_5CH_2$-6′); ^{19}F NMR (pyridine-d_5): δ −211.08 (dt, $J_{4,F} = J_{6,F}$ 29, $J_{5,F}$ 53 Hz, F-5). Compound **31** (142 mg) dissolved in 80% aq AcOH (10 mL) was hydrogenated with palladium black under bubbling of hydrogen as described for **29a** to give, after chromatography (CM-Sephadex C-25, aq 0.05 → 0.2 M NH_4OH), **32b** as a solid (20.4 mg, 15% based on **30b** as H_2CO_3 salt) with **31** recovered (80 mg), $[\alpha]_D^{19}$ +127° (*c* 0.5, water); ^{19}F NMR (26% ND_3 in D_2O): δ −213.13 (dt, $J_{4,F} = J_{6,F}$ 29, $J_{5,F}$ 52.5 Hz, F-5). Anal. Calcd for $C_{18}H_{35}FN_4O_8H_2CO_3 \cdot H_2O$: C, 42.69; H, 7.35; N, 10.48. Found: C, 42.61; H, 7.55; N, 10.54.

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