ELSEVIER

Carbohydrate Research 286 (1996) 107–122

CARBOHYDRATE RESEARCH

Synthesis of kanamycin A analogs containing 6-amino-3-oxa-2,3,4,6-tetradeoxy-D- and -L-*glycero*-hexopyranose

Ryuji Kuwahara, Tsutomu Tsuchiya *

Institute of Bioorganic Chemistry, 1614 Ida, Nakahara-ku, Kawasaki, Japan

Received 27 November 1995; accepted in revised form 5 February 1996

Abstract

6-Azido-3-oxa-2,3,4,6-tetradeoxy-D- and -L-*glycero*-hexopyranoses were synthesized in five steps from (2*S*)- and (2*R*)-1,2-*O*-isopropylideneglycerols, respectively. After conversion into the corresponding ethyl 1-thioglycosides, each was condensed with a protected derivative of 6-*O*-(3-amino-3-deoxy-α-D-glucopyranosyl)-2-deoxystreptamine (**16**). Deprotection and reduction of the azido group of the condensation products gave the title compounds.

Keywords: Kanamycin analog; 6-Azido-3-oxa-2,3,4,6-tetradeoxy-*glycero*-hexopyranose

1. Introduction

A number of kanamycin (or more broadly, aminoglycoside antibiotic) derivatives active against resistant bacteria have been synthesized [1]a and some of them have proved to be of great value in clinical use. However, to develop this kind of drug even further, several shortcomings need to be overcome; for example, renal toxicity, comparatively low transportation into bacterial cells, poor absorption from digestive organs, and ever-increasing resistance of bacteria. In regard to the toxicity, replacement of certain hydroxyl groups in the molecule by a fluorine was found to be useful [2–6]. To increase the transportation into the organs or bacterial cells, a decrease of the number of polar groups in the molecules (hydroxy and amino) is expected to be useful. Concerning the problem of resistance, hindrance of acetylation of the NH_2-6′ group by resistant bacteria

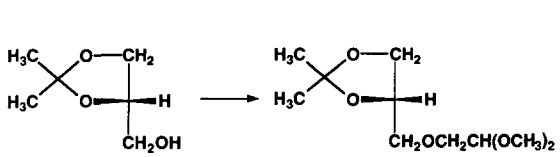
* Corresponding author.

Published by Elsevier Science Ltd.
PII S0008-6215(96)00051-1

is most important, because such strains are ever increasing, possibly because no effective tools to avoid this modification by such bacteria have been discovered. With these drawbacks in mind, we have undertaken to convert the 6-amino-6-deoxy-D-glucose unit of kanamycin A (KMA) into a simpler framework having no polar groups other than an NH_2-6, and having an oxygen atom at position 3, instead of $HOCH_2$-3 [this is the position that is phosphorylated by the resistant bacteria producing APH(3′)]. It was hoped that these changes would provide a derivative with improved absorption and antibacterial activity [especially against the strains producing AAC(6′) [1]c; the biological 6′-*N*-acetylation was expected to be influenced by the slight steric change caused by shortening of the C-2′–C-3′ and C-3′–C-4′ bond lengths in the kanamycin analogue derived by replacement of C-3′ by O-3′]. We describe here the synthesis of 6-azido-3-oxa-2,3,4,6-tetradeoxy-D-*glycero*-hexopyranose and its enantiomer, and their condensation with a protected derivative of 6-*O*-(3-amino-3-deoxy-α-D-glucopyranosyl)-2-deoxystreptamine [7] (3AD), a partially hydrolyzed pseudo-disaccharide of KMA, as key reactions.

2. Results and discussion

The synthesis started with preparation of the 1,4-dioxane derivatives **3a**–**12a**.



1a **2a**

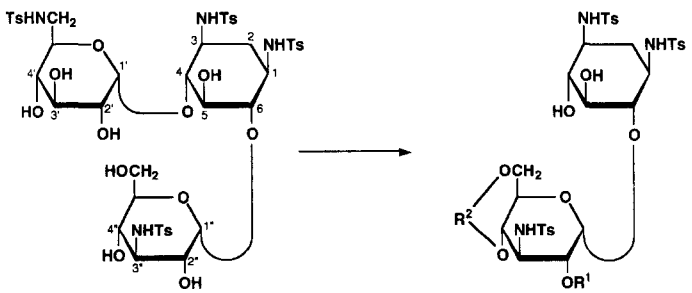
	R^1	R^2	R^3
3a	H	OCH_3	OH
4a	OCH_3	H	OH
5a	H	OCH_3	OTs
6a	OCH_3	H	OTs
7a	H	OCH_3	N_3
8a	OCH_3	H	N_3
9a	H, OH		N_3
10a	H	OAc	N_3
11a	OAc	H	N_3
12a	H, SCH_2CH_3		N_3

Only D-series of compounds are shown

Commercially available (*S*)-glycerol isopropylidene acetal **1a** [8], the optical purity of which was confirmed by HPLC analysis [9] (see Experimental section), was treated with $BrCH_2CH(OCH_3)_2$ [10], and the resulting 2,2-dimethoxyethyl ether **2a** was converted by methanolic HCl into a chromatographically separable mixture (~ 2:1) of methyl 3-oxa-2,3,4-trideoxy-α-D-*glycero*-hexopyranoside **3a** ($[\alpha]_D$ +149°) and its β anomer

4a ($[\alpha]_D$ −96°). Their $^4C_1$ conformation similar to that of D-glucopyranosides was confirmed by the large $J_{4ax,5}$ (**3a** and **4a**) and $J_{1,2ax}$ (**4a**) coupling constants, as well as by NOE effects between H-2*ax*–H-4*ax* [measured in $CDCl_3$, D_2O, and 26% ND_3 in D_2O] (see Experimental section). Introduction of an azido group at C-6 in **3a** and **4a** was smoothly effected through the 6-*O*-tosyl derivatives (**5a** and **6a**). The resulting 6-azido derivatives (**7a** and **8a**) were then hydrolyzed in an acidic medium to give the corresponding free sugar **9a** as an anomeric mixture. The compound was then converted into a derivative suitable for condensation. Initially, 1-halogenation, 1-*O*-sulfonylation, and 1-*O*-trichloroacetimidation were tried using $SOCl_2$–CH_2Cl_2, $SOCl_2$–pyridine–CH_2Cl_2, SO_2Cl_2–CH_2Cl_2, $SOBr_2$–CH_2Cl_2, CH_3SO_2Cl–pyridine–CH_2Cl_2, or Cl_3CCN–K_2CO_3–CH_2Cl_2 (or THF), but in all cases, decomposition occurred without formation of any stable product. Next, 1-*O*-(4-pentenyl)ation [11] was attempted; this time the desired product was obtained in low yield, but condensation of it with the protected 3AD derivative **16** was unsuccessful. Thioglycosylation [12] was attempted next. Acetylation of **9a** with Ac_2O in pyridine followed by chromatography of the resulting anomeric mixture of 1-*O*-acetyl derivatives furnished the α anomer **10a** and the β anomer **11a** in 35 and 60% yields. Treatment of **10a** or **11a** with $C_2H_5SSnBu_3$ in the presence of $CF_3SO_3Si(CH_3)_3$ [13] gave anomeric mixtures of ethyl 1-thioglycosides (**12a**) in good yields.

The L-series of compounds was also synthesized according to the procedures just described, starting from optically pure (*R*)-glycerol isopropylidene acetal **1b** [8]. Compounds thus prepared and characterized are: 2,2-dimethoxyethyl ether **2b**, methyl 3-oxa-2,3,4-trideoxy-α- and -β-L-*glycero*-hexopyranosides (**3b** and **4b**), the 6-*O*-tosyl (**5b** and **6b**) and 6-azido-6-deoxy derivatives (**7b** and **8b**), the free sugar **9b**, the 1-*O*-acetyl derivatives (**10b** and **11b**), and the ethyl 1-thioglycoside **12b**. All of these compounds showed optical rotations of opposite sign with similar magnitudes (within experimental error) and ^1H NMR spectra identical with those for the corresponding D-series of compounds. To confirm the conservation of optical purity, **11a** and **11b** were subjected to HPLC analysis, in which they differed in retention times and showed no contamination by their enantiomers (see Experimental section). It is noteworthy that **9a** tastes bitter, whereas **9b** is tasteless.

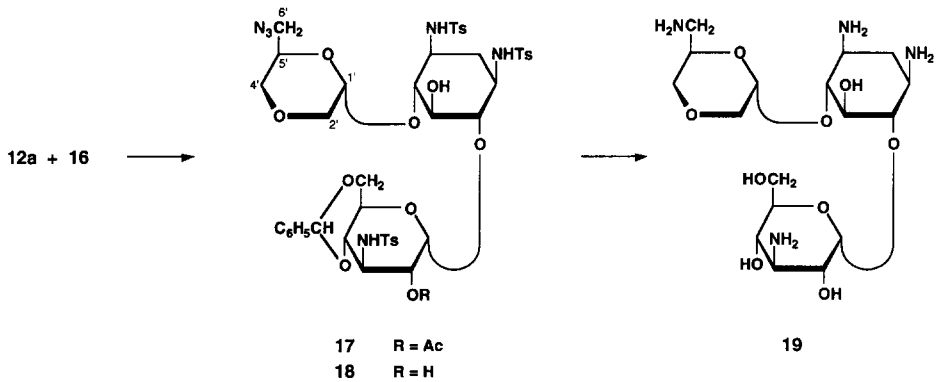


13

	R^1	R^2
14	H	H,H
15	H	C_6H_5CH
16	Ac	C_6H_5CH

The condensation partner, the 3AD derivative **16**, was prepared by selective cleavage of the 6-amino-6-deoxy-D-glucose unit from KMA by treating tetra-*N*-tosylkanamycin A (**13**) with $Pb(OAc)_4$. Incidentally, this method for obtaining 3AD or its derivatives is superior to direct acidic hydrolysis of KMA, in that it avoided the troublesome large-scale chromatography. The tri-*N*-tosyl-3AD was then treated with $C_6H_5CH(OMe)_2$ and the resulting 4″,6″-*O*-benzylidene derivative **15** was partially acetylated to give the 2″-acetate **16** in 43% yield, ready for condensation.

Condensation of the 1-thioglycoside **12a** with **16** was performed according to the standard method [14] using *N*-iodosuccinimide (NIS) in a slightly acidic CH_2Cl_2 solution. Several condensation products that resulted were carefully separated, and the desired 4-*O*-α-D-glycosyl isomer **17** was obtained pure in 30% yield (based on **16**).



17 R = Ac
18 R = H

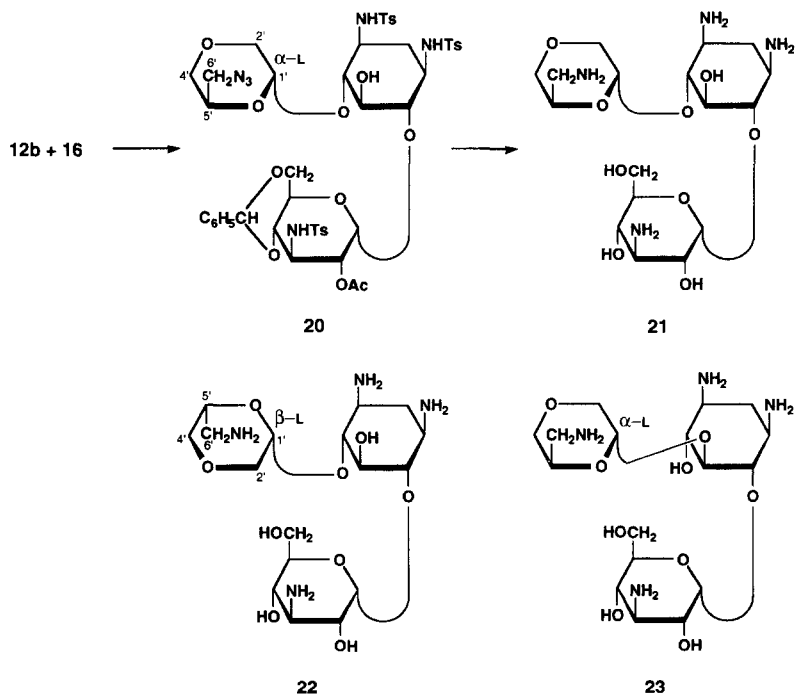
19

Table 1
^{13}C NMR chemical shifts (ppm) of **19**, **21**, **22**, and **23** together with **3a** and **4a** measured in 26% ND_3 in D_2O

	19	21	22	23	3a	4a
C-1	51.28	51.29	51.41	51.24		
C-2	36.28	36.42	36.18	37.65		
C-3	49.94	51.09	49.78	51.31		
C-4	86.81	87.20	88.20	77.19		
C-5	75.25	73.60	74.66	83.30		
C-6	88.62	89.15	88.35	87.49		
C-1′	97.00	96.81	100.23	96.54	96.47	100.23
C-2′	68.91	68.70	68.37	68.84	68.15	68.40
C-4′	68.85	68.95	67.99	68.94	68.00	67.25
C-5′	70.16	69.85	76.68	69.58	68.93	75.42
C-6′	42.02	42.06	41.76	42.09	61.49	61.24
C-1″	100.85	100.88	100.96	101.24		
C-2″	72.39	72.46	72.45	73.32		
C-3″	54.89	54.97	54.99	54.92		
C-4″	69.81	69.95	69.82	69.70		
C-5″	72.69	72.87	72.70	73.82		
C-6″	60.75	60.93	60.75	60.85		

The α-anomeric configuration was verified by the small $J_{1',2'ax}$ value in its ^{1}H NMR spectrum, but the linkage position was not clear at this stage. After deacetylation (to give **18**), the resulting product was treated with sodium in liquid ammonia, which removed the *N*-tosyl and benzylidene groups simultaneously and reduced the azido group, to give the final product **19**. The structure was confirmed by the ^{1}H and ^{13}C NMR spectra (Table 1), and the position to which the oxa sugar was attached (C-4, not C-5) was determined by utilizing a combination of H–H COSY, HETCOR, and HMBC methods. In the ^{1}H NMR spectrum, H-1″ (δ 5.05) is clearly discriminated from H-1′ (δ 5.21) by the splitting patterns; on this basis, C-1″ can then be determined by HETCOR; H-6 is then located by correlation with C-1″ by HMBC (usually discrimination between H-4 and 6 is not easy due to the similar steric situations); once H-6 is determined, H-4 is easy to find from the H–H COSY, and finally H-4 is correlated to C-1′ by the HMBC method. The $^4C_1$ conformation of the attached sugar in **19** was confirmed by observation of NOE effects (by NOESY measurement) between H-2′*ax* and 4′*ax* in 26% ND_3 in D_2O.

Condensation of the α-L enantiomer **12b** with **16** proceeded more readily than that of **12a**, and the 4-*O*-α-L-glycosyl-3AD derivative **20** was isolated in 41% yield.



20 21 22 23

The product, after deacetylation, was treated with sodium in liquid ammonia to give the final product **21**. The structure was confirmed similarly as described for **19**, utilizing the H–H COSY, HETCOR, and HMBC techniques. Two by-products obtained in the condensation were also deprotected to final products. These proved to be the 4-*O*-β-L-

glycosyl-3AD (**22**) and 5-*O*-α-L-glycosyl-3AD (**23**) from their NMR spectra utilizing HMBC; in **23**, a cross peak connecting C-1′ and H-5 was observed. It is worth mentioning that the optical rotations ($[\alpha]_D$ in H_2O) of **19** (+112°), **21** (+36°), **22** (+84°), and **23** (+21°) were reflective of anomeric configurations. The β-L linkage present in **22** was also confirmed by the ^{13}C NMR spectrum (Table 1), in that C-1′ and -5′ resonated at δ 100.23 and 76.68, respectively; these values were close to those for β-L compound **4a**, and different from the values for α-D compounds **3a**, **19**, **21**, and **23**.

Antibacterial activities of **19**, **21**, **22**, and **23** against common bacterial strains were measured, and it was found that **19** showed only slight activity (approximately $1/2^4$ of that of KMA), and **21**–**23** and 3AD were devoid of activity. As KMA, 2′,3′-dideoxy- [15], 2′,3′-dideoxy-2′-fluoro- [16], 3′,4′-dideoxy- [17], and 3′,4′-dideoxy-3′-fluoro-kanamycin A [18] showed activities comparable to each other, the decreased activity of **19** could not be ascribed to the lack of hydroxyl groups at C-2′, 3′, or 4′ but rather to the presence of the ring oxygen-3′. Moreover, the lack of activity of **22**, which is the C-5′ epimer of **19**, suggests that such a C-5′ epimerization of kanamycins [which frequently has been undertaken to obtain derivatives active against resistant bacteria producing AAC(6′)] may produce a derivative of much decreased activity; this supposition was supported by the synthesis of 4-*O*-(2,6-diamino-2,4,6-trideoxy-β-L-*arabino*-hexopyranosyl)-3AD [19], which showed only weak activity. Even so, from the antibacterial spectrum of **19** (see Experimental section) we can draw the following conclusions: (*a*) the lack of HO-3′ and HO-4′ in **19** contributes [1]b to the activity against resistant bacteria producing APH(3′) and AAD(4′), although the extent was only slight (however greater than in KMA), (*b*) replacement of the 6-amino-6-deoxy-D-glucose unit of KMA with a 1,4-dioxane framework does not produce any compound active against resistant bacteria producing AAC(6′). This suggests that the H_2NCH_2-5′ groups of both **19** and KMA have a similar steric situation that is not discriminated by the resistant bacteria. The absence of activity in **21**, having the 1,4-dioxane ring enantiomeric to that for **19** may be explained by the H_2NCH_2-5′ group's occuping the position opposite to that in **19** (that is, the position equal to the C-3′ substituent of KMA), assuming that **21** adopts a conformation similar to that of KMA [20].

3. Experimental

General methods.—The bromoacetaldehyde dimethyl acetal [10] was purchased from Tokyo Chemical Industry Co., Ltd. Optical rotations were determined with a Perkin–Elmer 241 polarimeter. IR spectra were recorded with a Jasco A-202 grating spectrophotometer. Mass spectra were recorded with a Jeol SX-102 spectrometer. NMR spectra (^1H at 250 and 500 MHz, ^{13}C at 125.8 MHz) were recorded with Bruker AC-250P and AMX-500 spectrometers, using Me_4Si as the internal reference. Proton signals were mostly confirmed by the ^1H–^1H COSY. TLC and preparative TLC were performed on Silica Gel 60 F_{254} (Merck 5715 and 5717), and detected under UV light at 254 nm, by charring with aq 50% H_2SO_4, or by 2.5% ammonium molybdate in aq 1.5 M H_2SO_4. Column chromatography was performed on Wakogel C-300. HPLC analysis was accomplished on a column (4.6 × 250 mm) of Chiralcel OB-H (Daicel Chemical

Industries, Japan) using 9:1 (for the benzoates of **1a** and **1b**) and 1:1 (for **11a** and **11b**) hexane–2-propanol in a speed of 0.5 and 0.75 mL min^{-1}, respectively.

(2S)-1,2-O-Isopropylideneglycerol (**1a**).—The benzoate [9] of **1a** was prepared in conventional manner, and subjected to HPLC; the retention time was 15.5 min.

(2R)-1,2-O-Isopropylideneglycerol (**1b**).—The benzoate [9] of **1b** was similarly prepared, and subjected to HPLC; retention time was 22.0 min.

(2S)-3-O-(2,2-Dimethoxyethyl)-1,2-O-isopropylideneglycerol (**2a**).—An ice-cold mixture of **1a** [8] (5 g, 38 mmol), $BrCH_2CH(OMe)_2$ (6.66 mL, 57 mmol), and NaH (60% in mineral oil, 2.27 g, 57 mmol) in DMF (40 mL) was stirred for 6 h. Water (200 mL) was added, and the mixture was extracted with benzene. The organic solution was washed with water, dried (Na_2SO_4), and concentrated. Chromatography of the residual oil with CH_2Cl_2 (300 mL) → 2:1 CH_2Cl_2–EtOAc gave **2** as a syrup, which was thoroughly dried (7.08 g, 85%), $[\alpha]_D^{24}$ +12° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.36 and 1.42 [each s of 3 H, $C(CH_3)_2$], 3.39 (s, 6 H, 2 OCH_3), 3.53 (dd, 1 H, H-3a), 3.54 (dd, 1 H, H-1′a), 3.57 (dd, 1 H, H-1′b), 3.59 (dd, 1 H, H-3b), 3.74 (dd, 1 H, H-1a), 4.05 (dd, 1 H, H-1b), 4.28 (quintet, 1 H, H-2), 4.51 (t, 1 H, H-2′); $J_{1a,1b}$ 8.5, $J_{1a,2} \approx J_{1b,2} \approx J_{2,3a} \approx J_{2,3b}$ 6, $J_{3a,3b}$ 10, $J_{1'a,1'b}$ 11, $J_{1'a,2'} \approx J_{1'b,2'}$ 5 Hz. Anal. Calcd for $C_{10}H_{20}O_5$: C, 54.53; H, 9.15. Found: C, 54.27; H, 9.17.

(2R)-3-O-(2,2-Dimethoxyethyl)-1,2-O-isopropylideneglycerol (**2b**).—Prepared from **1b** [8] (5.0 g) similarly as described for **2a**; a syrup (6.93 g, 83%), $[\alpha]_D^{23}$ −12° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{10}H_{20}O_5$: C, 54.53; H, 9.15. Found: C, 54.80; H, 9.26.

*Methyl 3-oxa-2,3,4-trideoxy-α- and -β-*D-glycero-*hexopyranosides* (**3a** and **4a**).—A solution of **2a** (8.32 g) in methanolic 0.3 M HCl (180 mL) was heated (~ 45 °C) for 1 h, poured into aq $NaHCO_3$ (saturated, 200 mL), and the products were extracted with CH_2Cl_2. Concentration of the organic solution gave a syrup (5.67 g), which showed, in TLC (1:3 hexane–EtOAc), two spots at R_f 0.25 (**3a**) and 0.45 (**4a**). Separation by chromatography with 1:3 → 1:5 hexane–EtOAc gave **3a** (1.85 g, 33%), **4a** (1.50 g, 25%), and a mixture of the two (1.68 g; mainly **3a**), all as syrups. Compound **3a**, $[\alpha]_D^{24}$ +149° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$ and 26% ND_3 in D_2O; δ and *J* values are cited in this order): δ 1.94 (t, 1 H, HO-6 in $CDCl_3$), 3.45, 3.46 (s, 3 H, OCH_3), 3.55, 3.55 (dd, 1 H, H-4*ax*), 3.56, 3.59 (dt, 1 H, H-6a), 3.60, 3.68 (dd, 1 H, H-2*ax*), 3.66, 3.64 (ddd, 1 H, H-6b), 3.75, 3.76 (d, 1 H, H-2*eq*), 3.80, 3.86 (dd, 1 H, H-4*eq*), 4.13, 4.11 (m, 1 H, H-5), 4.58, 4.73 (unresolved s, 1 H, H-1); $J_{1,2ax}$ 2.15, 2.00, $J_{1,2eq}$ 0.00, 0.60, $J_{1,5}$ 0.55, 0.60, $J_{2ax,2eq}$ 11.85, 12.30, $J_{4ax,4eq}$ 11.45, 11.70, $J_{4ax,5}$ 10.60, 10.75, $J_{4eq,5}$ 2.90, 2.75, $J_{5,6a}$ 5.45, 5.50, $J_{5,6b}$ 3.90, 4.05, $J_{6a,6b}$ 11.60, 12.10, $J_{6a,OH} \approx J_{6b,OH}$ 6.0 Hz ($CDCl_3$). NOE experiments in 26% ND_3 in D_2O: irradiation of H-4*ax* caused signal increases of H-2*ax* (3.4%) and H-4*eq* (18.5%), and irradiation of H-2*ax* caused signal increases of H-1 (4.4%), H-2*eq* (20.9%), and H-4*ax* (4.5%); in D_2O: irradiation of H-4*ax* caused signal increases of H-2*ax* (3.8%) and H-4*eq* (18.6%). In $CDCl_3$, however, **3a** showed no NOE between H-2*ax* and H-4*ax*. Anal. Calcd for $C_6H_{12}O_4$: C, 48.64; H, 8.17. Found: C, 48.76; H, 8.11.

Compound **4a**, $[\alpha]_D^{25}$ −96° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$ and 26% ND_3 in D_2O; δ and *J* values are cited in this order): δ 2.07 (t, 1 H, HO-6 in $CDCl_3$), 3.20, 3.22 (dd, 1 H, H-2*ax*), 3.40, 3.37 (dd, 1 H, H-4*ax*), 3.53, 3.56 (s, 3 H, OCH_3), 3.64, 3.64 (dt, 1 H, H-6a), 3.70, 3.81 (dd, 1 H, H-4*eq*), 3.72, 3.68 (ddd, 1 H, H-6b), 3.77, 3.85 (dd, 1 H,

H-2*eq*), 3.83, 3.90 (dddd, 1 H, H-5), 4.56, 4.70 (dd, 1 H, H-1); $J_{1,2ax}$ 8.30, 8.35, $J_{1,2eq}$ 2.60, 2.50, $J_{2ax,2eq}$ 11.30, 11.40, $J_{4ax,4eq}$ 11.50, 11.70, $J_{4ax,5}$ 9.90, 9.85, $J_{4eq,5}$ 2.80, 2.75, $J_{5,6a}$ 5.60, 5.85, $J_{5,6b}$ 3.90, 4.60, $J_{6a,6b}$ 11.80, 12.00, $J_{6a,OH} \approx J_{6b,OH}$ 6.0 Hz ($CDCl_3$). NOE experiments in $CDCl_3$ and in 26% ND_3 in D_2O (signal enhancements are shown in this order): irradiation of H-4*ax* caused increases of H-2*ax* (2.6, 3.4%) and H-4*eq* (12.4, 16.4%), and irradiation of H-2*ax* caused increases of H-2*eq* (12.6, 21.2%) and H-4*ax* (2.4, 3.6%); in D_2O: irradiation of H-2*ax* caused increases of H-4*ax* (4.7%) and H-2*eq* (17.8%). Anal. Calcd for $C_6H_{12}O_4 \cdot 1/2H_2O$: C, 45.85; H, 8.34. Found: C, 46.18; H, 8.28.

*Methyl 3-oxa-2,3,4-trideoxy-α- and -β-*L-glycero-*hexopyranosides* (**3b** and **4b**).—Prepared from **2b** (8.05 g) similarly as described for **3a** and **4a** to give, after chromatography, **3b** (2.80 g, 52%), **4b** (1.36 g, 25%) and a mixture of them (0.24 g) all as syrups. Compound **3b**, $[\alpha]_D^{21}$ −140° (*c* 1, $CHCl_3$). Compound **4b**, $[\alpha]_D^{22}$ +104° (*c* 1, $CHCl_3$). Anal. Calcd for $C_6H_{12}O_4$: C, 48.64; H, 8.17. Found **3b**: C, 48.37; H, 8.10. **4b**: C, 48.43; H, 8.15.

*Methyl 3-oxa-6-*O*-tosyl-2,3,4-trideoxy-α- and -β-*D-glycero-*hexopyranosides* (**5a** and **6a**).—A solution of **3a** (1.72 g, 11.6 mmol) and TsCl (3.34 g, 17.5 mmol) in 1:6.5 pyridine–CH_2Cl_2 (20 mL) was kept for 14 h at room temperature. Water (0.2 mL) was added and, after 1 h, a large amount of CH_2Cl_2 was added, and the solution was washed with aq $NaHCO_3$ (saturated), aq 10% $KHSO_4$, and water, dried (Na_2SO_4), and concentrated. Chromatography of the residue (1:0 → 5:1 $CHCl_3$–EtOAc) gave **5a** as a syrup (2.93 g, 83%), $[\alpha]_D^{23}$ +66° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.45 (s, 3 H, TsCH_3), 3.38 (s, 3 H, OCH_3), 3.41 (dd, 1 H, H-4*ax*), 3.55 (dd, 1 H, H-2*ax*), 3.70 (d, 1 H, H-2*eq*), 3.75 (dd, 1 H, H-4*eq*), 4.00 (dd, 1 H, H-6a), 4.04 (dd, 1 H, H-6b), 4.21 (dddd, 1 H, H-5), 4.49 (unresolved short-range d, 1 H, H-1); $J_{1,2ax}$ 2.0, $J_{1,2eq} \sim 0$, $J_{2ax,2eq}$ 12.0, $J_{4ax,4eq}$ 11.0, $J_{4ax,5}$ 10.0, $J_{4eq,5}$ 3.0, $J_{5,6a} \approx J_{5,6b}$ 5, $J_{6a,6b}$ 10.5 Hz. Anal. Calcd for $C_{13}H_{18}O_6S$: C, 51.64; H, 6.00. Found: C, 51.35; H, 6.07.

Compound **6a** was similarly prepared from **4a** (1.36 g) as a syrup (1.85 g, 67%), $[\alpha]_D^{23}$ −73° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.45 (s, 3 H, TsCH_3), 3.22 (dd, 1 H, H-2*ax*), 3.28 (dd, 1 H, H-4*ax*), 3.44 (s, 3 H, OCH_3), 3.71 (dd, 1 H, H-4*eq*), 3.72 (dd, 1 H, H-2 *eq*), 3.92 (dddd, 1 H, H-5), 4.08 (dd, 1 H, H-6a), 4.12 (dd, 1 H, H-6b), 4.46 (dd, 1 H, H-1); $J_{1,2ax}$ 7.2, $J_{1,2eq}$ 2.5, $J_{2ax,2eq} \approx J_{4ax,4eq}$ 12, $J_{4ax,5}$ 8.5, $J_{4eq,5}$ 3, $J_{5,6a} \approx J_{5,6b}$ 5.5, $J_{6a,6b}$ 11.0 Hz. Anal. Calcd for $C_{13}H_{18}O_6S$: C, 51.64; H, 6.00. Found: C, 51.33; H, 6.08.

*Methyl 3-oxa-6-*O*-tosyl-2,3,4-trideoxy-α- and -β-*L-glycero-*hexopyranosides* (**5b** and **6b**).—Prepared from **3b** (2.59 g) and **4b** (1.15 g) likewise as described for **5a** and **6a**, respectively, to give **5b** (5.28 g, quant.) and **6b** (2.11 g, 97%), both as syrups. Compound **5b**, $[\alpha]_D^{22}$ −64° (*c* 1, $CHCl_3$). Compound **6b**, $[\alpha]_D^{22}$ +79° (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{13}H_{18}O_6S$: C, 51.64; H, 6.00. Found **5b**: C, 51.57; H, 6.02. **6b**: C, 51.28; H, 6.00.

*Methyl 6-azido-3-oxa-2,3,4,6-tetradeoxy-α- and -β-*D-glycero-*hexopyranosides* (**7a** and **8a**).—A mixture of **5a** (2.51 g, 8.3 mmol) and NaN_3 (1.62 g, 25 mmol) in DMF (40 mL) was stirred for 3.5 h at 80 °C. Benzene (400 mL) was added and the organic solution was repeatedly washed with water, dried (Na_2SO_4), and concentrated to give **7a** as a syrup (1.50 g, quant.), TLC (2:1 hexane–EtOAc) R_f 0.4 (cf **5a**: R_f 0.25), $[\alpha]_D^{19}$

+96° (*c* 1, $CHCl_3$), IR (CH_2Cl_2): ν 2120 cm^{-1} (N_3); ^1H NMR ($CDCl_3$): δ 3.24 (dd, 1 H, H-6a), 3.27 (dd, 1 H, H-6b), 3.47 (dd, 1 H, H-4*ax*), 3.47 (s, 3 H, OCH_3), 3.62 (dd, 1 H, H-2*ax*), 3.76 (d, 1 H, H-2*eq*), 3.77 (dd, 1 H, H-4*eq*), 4.23 (m, 1 H, H-5), 4.59 (unresolved d, 1 H, H-1); $J_{1,2ax}$ 2.0, $J_{1,2eq} \sim 0$, $J_{2ax,2eq} \approx J_{4ax,4eq}$ 11.5, $J_{4ax,5}$ 9.5, $J_{4eq,5}$ 2.7, $J_{5,6a}$ 4.5, $J_{5,6b}$ 6.0, $J_{6a,6b}$ 13.0 Hz. Anal. Calcd for $C_6H_{11}N_3O_3$: C, 41.61; H, 6.40; N, 24.27. Found: C, 41.79; H, 6.43; N, 24.32.

Compound **8a** was similarly prepared from **6a** (1.52 g) as a syrup (0.88 g, quant.), TLC (2:1 hexane–EtOAc) R_f 0.6, $[\alpha]_D^{22}$ −119° (*c* 1, $CHCl_3$), IR (CH_2Cl_2): ν 2110 cm^{-1} (N_3); ^1H NMR ($CDCl_3$): δ 3.20 (dd, 1 H, H-6a), 3.23 (dd, 1H, H-2*ax*), 3.29 (dd, 1 H, H-4*ax*), 3.42 (dd, 1 H, H-6b), 3.53 (s, 3 H, OCH_3), 3.68 (dd, 1 H, H-4*eq*), 3.78 (dd, 1 H, H-2*eq*), 3.92 (dddd, 1 H, H-5), 4.56 (dd, 1 H, H-1); $J_{1,2ax}$ 8.5, $J_{1,2eq}$ 2.5, $J_{2ax,2eq} \approx J_{4ax,4eq}$ 11.5, $J_{4ax,5}$ 9.5, $J_{4eq,5}$ 2.5, $J_{5,6a}$ 4.5, $J_{5,6b}$ 7.0, $J_{6a,6b}$ 13.0 Hz. Anal. Calcd for $C_6H_{11}N_3O_3$: C, 41.61; H, 6.40; N, 24.27. Found: C, 41.59; H, 6.40; N, 24.02.

*Methyl 6-azido-3-oxa-2,3,4,6-tetradeoxy-α- and -β-*L-glycero-*hexopyranosides* (**7b** and **8b**).—Prepared from **5b** (4.85 g) and **6b** (2.10 g) likewise as described for **7a** and **8a** to give **7b** (2.80 g, quant.) and **8b** (1.25 g, quant.), respectively, both as syrups. Compound **7b**, $[\alpha]_D^{23}$ −93° (*c* 1, $CHCl_3$). Compound **8b**, $[\alpha]_D^{23}$ +127° (*c* 1.2, $CHCl_3$). Anal. Calcd for $C_6H_{11}N_3O_3$: C, 41.61; H, 6.40; N, 24.27. Found, **7b**: C, 41.67; H, 6.55; N, 23.98. **8b**: C, 41.95; H, 6.63; N, 23.97.

*6-Azido-3-oxa-2,3,4,6-tetradeoxy-*D-glycero-*hexopyranose* (**9a**).—A solution of **7a** (1.04 g) in 1:1 AcOH–aq 1 M HCl (4 mL) was heated for 20 h at 60 °C. Neutralization with powdered $NaHCO_3$, followed by extraction of the product with CH_2Cl_2 and evaporation of the solvents gave a syrup, which was chromatographed (2:1 CH_2Cl_2–EtOAc) to give **9a** as a chromatographically homogeneous syrup (0.83 g, 87%), $[\alpha]_D^{22}$ +18° (*c* 1, $CHCl_3$), IR (CH_2Cl_2): ν 2130 cm^{-1} (N_3); mass spectrum: *m/z* 142.12 (M^+–OH), 160.13 (M^+ +1); Calcd for $C_5H_9N_3O_3$: *m/z* 159.06 for M^+; ^1H NMR ($CDCl_3$) ($\alpha/\beta = 1.2/1$, determined by the strength ratio of the corresponding signals). α Anomer: δ 3.27 (dd, 1 H, H-6a), 3.29 (dd, 1 H, H-6b), 3.49 (dd, 1 H, H-4*ax*), 3.65 (dd, 1 H, H-2*ax*), 3.76 (d, 1 H, H-2*eq*), 3.81 (dd, 1 H, H-4*eq*), 4.37 (dddd, 1 H, H-5), 5.10 (br s, 1 H, H-1); $J_{1,2ax}$ 2.0, $J_{1,2eq} \sim 0$, $J_{2ax,2eq}$ 11.8, $J_{4ax,4eq}$ 11.5, $J_{4ax,5}$ 10.5, $J_{4eq,5}$ 3.0, $J_{5,6a}$ 6.0, $J_{5,6b}$ 4.5, $J_{6a,6b}$ 13.0 Hz. β Anomer: δ 3.18 (dd, 1 H, H-2*ax*), 3.31 (dd, 1 H, H-4*ax*), 3.33 (dd, 1 H, H-6a), 3.38 (dd, 1 H, H-6b), 3.70 (dd, 1 H, H-4*eq*), 3.86 (dd, 1 H, H-2*eq*), 3.93 (dddd, 1 H, H-5), 4.95 (dd, 1 H, H-1); $J_{1,2ax}$ 8.5, $J_{1,2eq}$ 2.5, $J_{2ax,2eq} \approx J_{4ax,4eq}$ 11.5, $J_{4ax,5}$ 10.5, $J_{4eq,5}$ 2.5, $J_{5,6a}$ 4.5, $J_{5,6b}$ 6.0, $J_{6a,6b}$ 13.0 Hz.

Compound **9a** (0.83 g, 87%, $\alpha/\beta = 1.2/1$) was also prepared from **8a** (1.04 g).

*6-Azido-3-oxa-2,3,4,6-tetradeoxy-*L-glycero-*hexopyranose* (**9b**).—Prepared from **7b** (2.47 g) or **8b** (0.80 g) likewise as described for **9a** to give **9b** (1.18 g, 52%) from **7b** and 0.62 g (84%) from **8b** both $\alpha/\beta = 1.2/1$, $[\alpha]_D^{23}$ −19° (*c* 1, $CHCl_3$); mass spectrum: *m/z* 142.13 (M^+–OH), 160.13 (M^+ + 1); Calcd for $C_5H_9N_3O_3$: *m/z* 159.06 for M^+.

*1-O-Acetyl-6-azido-3-oxa-2,3,4,6-tetradeoxy-α- and -β-*D-glycero-*hexopyranoses* (**10a** and **11a**).—A mixture of **9a** (480 mg) and Ac_2O (0.67 mL) in pyridine (5 mL) was kept for 5 h at room temperature. Methanol (0.3 mL) was added and, after 2 h, the mixture was diluted with CH_2Cl_2, and the solution was washed successively with aq $NaHCO_3$ (saturated), aq 10% $KHSO_4$, and water, dried (Na_2SO_4), and concentrated. Chromatog-

raphy (2:1 hexane–EtOAc) of the residue gave **10a** (214 mg, 35%; R_f 0.4 in TLC with 2:1 hexane–EtOAc) and **11a** (361 mg, 60%; R_f 0.5), both as syrups. Compound **10a**, $[\alpha]_D^{24}$ +54° (*c* 1.1, $CHCl_3$), IR (CH_2Cl_2): ν 1745 (C = O), 2110 cm^{-1} (N_3); ^1H NMR ($CDCl_3$): δ 2.16 (s, 3 H, Ac), 3.28 (dd, 1 H, H-6a), 3.32 (dd, 1 H, H-6b), 3.55 (dd, 1 H, H-4*ax*), 3.72 (dd, 1 H, H-2*ax*), 3.82 (d, 1 H, H-2*eq*), 3.85 (dd, 1 H, H-4*eq*), 4.27 (dddd, 1 H, H-5), 5.98 (unresolved d, 1 H, H-1); $J_{1,2ax}$ 2.0, $J_{1,2eq} \sim 0$, $J_{2ax,2eq} \approx J_{4ax,4eq}$ 12, $J_{4ax,5}$ 11.0, $J_{4eq,5}$ 3.0, $J_{5,6a}$ 5.5, $J_{5,6b}$ 5.0, $J_{6a,6b}$ 13.0 Hz. Anal. Calcd for $C_7H_{11}N_3O_4$: C, 41.79; H, 5.51; N, 20.89. Found: C, 41.51; H, 5.48; N, 21.00. Compound **11a**, HPLC: 57.2 min (retention time), $[\alpha]_D^{24}$ −57° (*c* 1, $CHCl_3$), IR (CH_2Cl_2): ν 1750, 1765, 2110 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.12 (s, 3 H, Ac), 3.41 (dd, 1 H, H-6a), 3.47 (dd, 1 H, H-2*ax*), 3.495 (dd, 1 H, H-4*ax*), 3.505 (dd, 1 H, H-6b), 3.77 (dd, 1 H, H-4*eq*), 3.81 (dd, 1 H, H-2*eq*), 3.96 (m, 1 H, H-5), 5.85 (dd, 1 H, H-1); $J_{1,2ax}$ 6.8, $J_{1,2eq}$ 2.5, $J_{2ax,2eq} \approx J_{4ax,4eq}$ 11.5, $J_{4ax,5}$ 8.0, $J_{4eq,5}$ 3.0, $J_{5,6a}$ 5.5, $J_{5,6b}$ 6.0, $J_{6a,6b}$ 13.0 Hz. Anal. Calcd for $C_7H_{11}N_3O_4$: C, 41.79; H, 5.51; N, 20.89. Found: C, 41.97; H, 5.51; N, 20.68.

*1-O-Acetyl-6-azido-3-oxa-2,3,4,6-tetradeoxy-α- and -β-*L-glycero-*hexopyranoses* (**10b** and **11b**).—Prepared from **9b** (1.03 g) as described for **10a** and **11a** gave **10b** (190 mg, 15%), $[\alpha]_D^{24}$ −49° (*c* 1, $CHCl_3$) and **11b** (710 mg, 54%), HPLC: 20.5 min (retention time), $[\alpha]_D^{24}$ +57° (*c* 1, $CHCl_3$) and a mixture of **10b** and **11b** (360 mg, 28%). Anal. Calcd for $C_7H_{11}N_3O_4$: C, 41.79; H, 5.51; N, 20.89. Found, **10b**: C, 41.83; H, 5.65; N, 21.05. **11b**: C, 41.58; H, 5.47; N, 20.90.

*Ethyl 6-azido-3-oxa-2,3,4,6-tetradeoxy-1-thio-*D-glycero-*hexopyranose* (**12a**).—To a solution of **11a** (201 mg, 1.0 mmol) in 1,2-dichloroethane (2 mL), $EtSSnBu_3$ (375 μL, 1.2 mmol) and $CF_3SO_3SiMe_3$ (178 μL, 1.0 mmol) were added, and the solution was kept for 15 min at room temperature. After dilution with the same solvent (12 mL), the solution was washed with aq $NaHCO_3$ (saturated) and aq NaCl (saturated), dried (Na_2SO_4), and concentrated. The residue was chromatographed with 5:1 hexane–EtOAc to give **12a** ($\alpha/\beta \sim 1/1$) as a syrup (149 mg, 73%), $[\alpha]_D^{26}$ +34° (*c* 1, $CHCl_3$), IR (neat, KBr): ν 2100 cm^{-1} (N_3); ^1H NMR ($CDCl_3$): δ 1.31 and 1.32 (each t of equal 1.5 H strength, SCH_2CH_3), 2.6–2.85 (m, 2 H, SCH_2CH_3), 3.15–3.5 (3.5 H), 3.7–3.9 (2.5 H), 3.93 [m, 0.5 H, H-5(β)], 4.55 [m, 0.5 H, H-5(α)], 4.76 [dd, 0.5 H, H-1(β)], 5.18 [sl. br d, 0.5 H, H-1(α)]; $J_{1,2ax}(\alpha) \sim 3$, $J_{1,2ax}(\beta)$ 10.5, $J_{1,2eq}(\beta)$ 2.5 Hz. Anal. Calcd for $C_7H_{13}N_3O_2S$: C, 41.36; H, 6.45; N, 20.67; S, 15.78. Found: C, 41.33; H, 6.50; N, 20.12; S, 15.48.

Compound **12a** was prepared likewise from **10a** (150 mg) as a syrup (107 mg, 71%).

*Ethyl 6-azido-3-oxa-2,3,4,6-tetradeoxy-1-thio-*L-glycero-*hexopyraose* (**12b**).—Prepared from **10b** (144 mg) or **10b** + **11b** (500 mg) as described for **12a** gave 86 mg (60%) and 320 mg (63%), respectively, $[\alpha]_D^{26}$ −25° (*c* 1, $CHCl_3$), which showed the same ^1H NMR spectrum as that from **10a**.

*Tetra-*N*-tosylkanamaycin A* (**13**).—To a solution of KMA sulfate (5.0 g, 780 mg g^{-1} potency, 8.0 mmol) in 1:2.5 1,4-dioxane–H_2O (70 mL), TsCl (4.0 g, 20 mmol) and Na_2CO_3 (1.9 g, 18 mmol) were added and the mixture was stirred for 4.5 h, and then TsCl (2.1 g), Na_2CO_3 (1.9 g), and 1,4-dioxane (20 mL) were added, and stirring was continued for further 1 h; additional Na_2CO_3 (1.9 g) was added, and treated similarly for further 3 h. Aqueous 28% NH_3 (2 mL) was added, and stirring was continued for 20 h

to decompose the excess of TsCl. The mixture was concentrated and the residue was shaken with water. The resulting precipitate was filtered, and its solution in MeOH was passed through a column of Dowex 50W-X2 with MeOH and concentrated, to give **13** as a solid (5.77 g, 64%), $[\alpha]_D^{25}$ +18° (*c* 1, MeOH); ^{1}H NMR (pyridine-d_5): δ 2.06, 2.10, 2.29, and 2.34 [each s of 3 H, 4 Ts(CH_3)], 5.42 and 5.51 (each d of 1 H, *J* ~ 3 Hz, H-1′, 1″). Anal. Calcd for $C_{46}H_{60}N_4O_{19}S_4 \cdot H_2O$: C, 49.36; H, 5.58; N, 5.00; S, 11.46. Found: C, 49.10; H, 5.65; N, 5.22; S, 11.33.

*2-Deoxy-6-O-(3-deoxy-3-tosylamido-α-*D*-glucopyranosyl)-1,3-di-*N*-tosylstreptamine* (**14**).—A mixture of **13** hydrate (11 g, 9.83 mmol) and $Pb(OAc)_4$ (8.8 g, 20 mmol) in pyridine (100 mL) was kept for 3 h at room temperature. Ethylene glycol (2.2 mL) was added, and after 20 h, the mixture was poured into water (1 L). The resulting precipitate was filtered over a bed of Celite, and the mass obtained was dissolved in MeOH. To the solution, $NaBH_4$ (7.6 g, 200 mmol) was added, and after 3.5 h, acetone (150 mL) was added. The mixture was kept for 14 h and then aq 3 M HCl (360 mL) was added and the slightly turbid solution was stirred for 7.5 h. Excess aq $NaHCO_3$ was then added and the mixture was concentrated. The residue was thoroughly washed with water, and the insoluble matter was dissolved in MeOH. The solution was filtered and concentrated to give **14** as a solid (3.4 g, 44%). For an analytical sample, it was chromatographed (5:1 $CHCl_3$–MeOH) to give a pure solid, $[\alpha]_D^{23}$ +25° (*c* 1, DMF) [lit. [16] $[\alpha]_D^{22}$ +21° (*c* 1, DMF)]; ^{1}H NMR (pyridine-d_5): δ 1.93 (q, 1 H, H-2*ax*), 2.06, 2.21, and 2.29 [each s of 3 H, 3 Ts(CH_3)], 5.53 (d, 1 H, *J* 3.5 Hz, H-1″). Anal. Calcd for $C_{33}H_{43}N_3O_{13}S_3 \cdot 1/2H_2O$: C, 49.86; H, 5.58; N, 5.29. Found: C, 49.69; H, 5.64; N, 5.53.

*6-O-(4,6-O-Benzylidene-3-deoxy-3-tosylamido-α-*D*-glucopyranosyl)-2-deoxy-1,3-*N*-tosylstreptamine* (**15**).—To a solution of **14** hemihydrate (500 mg, 0.63 mmol) in DMF (6 mL), anhydrous TsOH (21 mg, 0.12 mmol) and $C_6H_5CH(OMe)_2$ (105 μL, 0.7 mmol) were added, and the mixture was stirred for 6 h under reduced pressure (~ 35 Torr); during the period, a portion of the solvent (~ 0.5 mL) was evaporated off together with the liberated MeOH. Another 50 μL of $C_6H_5CH(OMe)_2$ was added and the reaction was continued for 1.5 h. The mixture was poured into water (20 mL), and the resulting precipitate was washed with water, and dried to give **15** as a solid (540 mg, 95%), $[\alpha]_D^{24}$ +21° (*c* 0.5, acetone); ^{1}H NMR (pyridine-d_5): δ 1.93 (q, 1 H, *J* 13 Hz, H-2*ax*), 2.08, 2.20, and 2.27 [each s of 3 H, 3 Ts(CH_3)], 3.13 (dt, 1 H, *J* 4, 4, 13 Hz, H-2*eq*), 4.35 (dd, 1 H, $J_{1'',2''}$ 3.5, $J_{2'',3''}$ 10 Hz, H-2″), 5.50 (s, 1 H, C*H*Ph), 5.66 (d, 1 H, H-1″). Anal. Calcd for $C_{40}H_{47}N_3O_{13}S_3 \cdot 1.5H_2O$: C, 53.32; H, 5.59; N, 4.66. Found: C, 53.26; H, 5.54; N, 4.27.

*6-O-(2-O-Acetyl-4,6-O-benzylidene-3-deoxy-3-tosylamido-α-*D*-glucopyranosyl)-2-deoxy-1,3-*N*-tosylstreptamine* (**16**).—To a solution of **15** sesquihydrate (219 mg, 0.24 mmol) in 9:1 $(CH_3)_2SO$–pyridine (1.1 mL), *N*-acetylimidazole (55 mg, 0.50 mmol) was added and the solution was kept for 54 h at room temperature. During the period, additional *N*-acetylimidazole (55 and 28 mg) was added after 6 and 30 h from the beginning, respectively. The final mixture was poured into water, and the resulting precipitate was washed thoroughly with water and then with Et_2O. Chromatography (15:1 $CHCl_3$–MeOH) of the powder obtained gave **16** (R_f 0.17 in TLC with 15:1 $CHCl_3$–MeOH) as a solid (99.2 mg, 43%) together with diacetyl product(s) (71 mg, R_f 0.25) and **15** (25 mg, R_f 0.1). Compound **16**, $[\alpha]_D^{25}$ 0° (*c* 1, $CHCl_3$); ^{1}H NMR

(pyridine-d_5): δ 1.75 (q, 1 H, H-2*ax*), 2.13, 2.22, and 2.26 [each s of 3 H, 3 Ts(CH_3)], 2.54 (s, 3 H, Ac), 2.60 (dt, 1 H, H-2*eq*), 5.62 (s, 1 H, C*H*Ph), 5.74 (dd, 1 H, H-2″), 6.32 (d, 1 H, H-1″). Anal. Calcd for $C_{42}H_{49}N_3O_{14}S_3 \cdot 1.5H_2O$: C, 53.49; H, 5.56; N, 4.46. Found: C, 53.22; H, 5.60; N, 4.31.

*6-O-(2-O-Acetyl-4,6-O-benzylidene-3-deoxy-3-tosylamido-α-*D*-glucopyranosyl)-4-O-(6-azido-3-oxa-2,3,4,6-tetradeoxy-α-*D*-*glycero*-hexopyranosyl)-2-deoxy-1,3-di-*N*-tosylstreptamine* (**17**).—To a solution of **12a** (initially 91 mg, and then 45 mg each after 0.5 and 1 h; total 0.9 mmol) and **16** sesquihydrate (275 mg, 0.29 mmol) in CH_2Cl_2 (3 mL), NIS (168 mg, 0.75 mmol), molecular sieves 4A (90 mg), and a trace amount of CF_3SO_3H (60 μL of 0.09 M CH_2Cl_2 solution) were added, and the mixture was stirred for 2.5 h at room temperature. After dilution with CH_2Cl_2 (20 mL), the solution was washed with aq $NaHCO_3$ (saturated), aq 10% $Na_2S_2O_3$, aq NaCl (saturated), and dried (Na_2SO_4). In TLC (15:1 $CHCl_3$–MeOH), the solution showed several spots at R_f 0.4 (A), 0.35 (B), 0.32 (C), 0.28 (D), 0.22 (E) and 0.18 (**16**). Concentration gave a residue, which was chromatographed (20:1 $CHCl_3$–MeOH) to give A (12 mg), a mixture of A–C (255 mg), a mixture of D, E (61 mg), and **16** (40 mg). Preparative TLC (20:1 $CHCl_3$–MeOH) of the second fraction gave A (43 mg), B (95 mg), and C (35 mg). Similar TLC of the third fraction gave D (29 mg), but the product, following further column chromatography (1:2 CH_2Cl_2–EtOAc), was separated into D-1 (11 mg) and D-2 (22 mg). Product A was unstable in pyridine and not pursued further. Product C was a mixture of two products and was also not pursued. Product D-1 and D-2 seemed, by their ^{1}H NMR spectra, 5-*O*-α-D-glycosyl and 4-*O*-β-D-glycosyl derivatives, respectively, but as they were still contaminated with other products, the structural study was abandoned. Product B was found to be **17** (30% based on **16**), $[\alpha]_D^{25}$ +7° (*c* 1, $CHCl_3$), IR (KBr): ν 2110 cm^{-1} (N_3); ^{1}H NMR (pyridine-d_5): δ 1.67 (q, 1 H, H-2*ax*), 2.15, 2.27, and 2.29 [each s of 3 H, 3 Ts(CH_3)], 2.39 (dt, 1 H, H-2*eq*), 2.49 (s, 3 H, Ac), 3.31 (dd, 1 H, H-6′a), 3.49 (dd, 1 H, H-6′b), 3.63 (dd, 1 H, H-4′*ax*), 3.69 (dd, 1 H, H-2′*ax*), 3.70 (d, 1 H, H-6″a), 3.72–3.76 [2 H, H-3(or 1),4′*eq*], 3.87 (t, 1 H, H-4″), 3.89 (t, 1 H, H-4 or 6), 3.91 (dd, 1 H, H-2′*eq*), 3.97 (m, 1 H, H-5), 4.06 (t, 1 H, H-6 or 4), 4.12 (m, 1 H, H-1 or 3), 4.36 (dd, 1 H, H-6″b), 4.74 (dt, 1 H, H-3″), 4.81 (m, 1 H, H-5′), 5.15 (dt, 1 H, H-5″), 5.57 (sl. br s, 1 H, H-1′), 5.59 (s, 1 H, C*H*Ph), 5.68 (dd, 1 H, H-2″), 6.26 (d, 1 H, H-1″), 7.84 (d, 1 H, HO-5), 8.22 (d, 1 H, NH-3 or 1), 8.73 (d, 1 H, NH-1 or 3), 9.70 (d, 1 H, NH-3″); $J_{1',2'ax}$ 2.5, $J_{1',2'eq}$ ~ 1, $J_{2'ax,2'eq}$ 12.0, $J_{1'',2''}$ 3.7 Hz. Anal. Calcd for $C_{47}H_{56}N_6O_{16}S_3 \cdot 2H_2O$: C, 51.63; H, 5.53; N, 7.69; S, 8.79. Found: C, 51.26; H, 5.47; N, 7.58; S, 8.86.

*4-O-(6-Azido-3-oxa-2,3,4,6-tetradeoxy-α-*D*-glycero-hexopyranosyl)-6-O-(4,6-O-benzylidene-3-deoxy-3-tosylamido-α-*D*-glucopyranosyl)-2-deoxy-1,3-di-*N*-tosylstreptamine* (**18**).—To a solution of **17** (76.9 mg, 0.073 mmol) in MeOH (1.4 mL), 0.1% NaOMe in MeOH (0.4 mL) was added and the solution was kept for 3 h at room temperature. Concentration followed by washing the residue with water gave **18** as a solid (72.5 mg, quant.), $[\alpha]_D^{25}$ +19° (*c* 1, $CHCl_3$), IR (KBr): ν 2110 cm^{-1} (N_3); ^{1}H NMR (pyridine-d_5): δ 1.82 (q, 1 H, H-2*ax*), 2.08, 2.19, and 2.33 [each s of 3 H, 3 Ts(CH_3)], 2.90 (dt, 1 H, H-2*eq*), 3.34 (m, 1 H, H-3 or 1), 3.38 (dd, 1 H, H-6′a), 3.65 (dd, 1 H, H-6′b), 3.67–3.74 (m, 3 H, H-2′*ax*,4′*ax*,6″a), 3.80–3.94 [m, 6 H, H-1(or 3),4,5,6,4′*eq*,4″], 4.00 (d, 1 H, H-2′*eq*), 4.32 (dd 1 H, H-6″b), 4.33 (dd, 1 H, H-2″), 4.51 (t, 1 H, H-3″), 4.57

(dt, 1 H, H-5″), 5.24 (m, 1 H, H-5′), 5.43 (s, 1 H, C*H*Ph), 5.59 (d, 1 H, H-1″), 5.60 (br s, 1 H, H-1′). Anal. Calcd for $C_{45}H_{54}N_6O_{15}S_3 \cdot H_2O$: C, 52.31; H, 5.46; N, 8.14; S, 9.30. Found: C, 52.47; H, 5.36; N, 8.40; S, 9.63.

*6-O-(3-Amino-3-deoxy-α-*D*-glucopyranosyl)-4-O-(6-amino-3-oxa-2,3,4,6-tetradeoxy-α-*D*-*glycero*-hexopyranosyl)-2-deoxystreptamine* (**19**).—To a solution of **18** (58.6 mg, 0.057 mmol) in liquid NH_3 (~ 8 mL) at −55 °C, was added Na (~ 5 mg), and the deep-blue solution was kept for 3 min at the same temperature. MeOH was added until the solution became colorless, then NH_3 was gradually evaporated under warming, and the aqueous solution of the residue was neutralized with Dowex 50W-X2 resin (H^+ form, 200–400 mesh, 2 mL). The resin was poured into a column containing the same fresh resin (H^+ form, 3 mL) and, after washing the column with water, products were eluted with aq 0.5 M NH_3 to give **19** as its carbonate hemihydrate (10.9 mg, 38%), together with 3AD (5.5 mg). **19**: $[\alpha]_D^{24}$ +112° (*c* 0.5, H_2O); ^{1}H NMR (26% ND_3 in D_2O): δ 1.25 (q, 1 H, H-2*ax*), 1.99 (dt, 1 H, H-2*eq*), 2.68 (dd, 1 H, H-6′a), 2.70 (dd, 1 H, H-6′b), 2.85 (ddd, 1 H, H-3), 2.90 (ddd, 1 H, H-1), 3.03 (t, 1 H, H-3″), 3.26 (t, 1 H, H-6), 3.35 (t, 1 H, H-4″), 3.38 (t, 1 H, H-4), 3.49 (dd, 1 H, H-4′*ax*), 3.51 (dd, 1 H, H-2″), 3.52 (t, 1 H, H-5), 3.73 (dd, 1 H, H-2′*ax*), 3.77 (2 H, H-6″a,6″b), 3.87–3.91 (2 H, H-2′*eq*,4′*eq*), 3.91 (dt, 1 H, H-5″), 4.18 (m, 1 H, H-5′), 5.05 (d, 1 H, H-1″), 5.21 (sl. br s, 1 H, H-1′); $J_{1,2ax} \approx J_{2ax,2eq} \approx J_{2ax,3}$ 12, $J_{1,2eq} \approx J_{2eq,3}$ 4, $J_{3,4} \approx J_{4,5} \approx J_{5,6} \approx J_{6,1}$ 9, $J_{1',2'ax} \sim 2$, $J_{1',2'eq} \sim 0$, $J_{2'ax,2'eq}$ 12.0, $J_{4'ax,4'eq}$ 11.0, $J_{4'ax,5'}$ 10.0, $J_{4'eq,5'} \sim 3$, $J_{5',6'a}$ 6.5, $J_{5',6'b}$ 4.0, $J_{6'a,6'b}$ 13.0, $J_{1'',2''}$ 4.0, $J_{2'',3''} \approx J_{3'',4''} \approx J_{4'',5''}$ 9 Hz. Anal. Calcd for $C_{17}H_{34}N_4O_9 \cdot H_2CO_3 \cdot 0.5H_2O$: C, 42.43; H, 7.32; N, 10.99. Found: C, 42.09; H, 7.31; N, 10.84.

*6-O-(2-O-Acetyl-4,6-O-benzylidene-3-deoxy-3-tosylamido-α-*D*-glucopyranosyl)-4-O-(6-azido-3-oxa-2,3,4,6-tetradeoxy-α-*L*-glycero-hexopyranosyl)-2-deoxy-1,3-di-*N*-tosylstreptamine* (**20**).—To a solution of **12b** (91 mg, 0.45 mmol) and **16** sesquihydrate (275 mg, 0.29 mmol) in CH_2Cl_2 (3 mL), NIS (168 mg, 0.75 mmol), molecular sieves 4A (90 mg) and a trace amount of CF_3SO_3H (60 μL of 0.09 M solution in CH_2Cl_2) were added, and after the mixture was stirred for 30 min, another 23 mg (0.11 mmol) of **12b** was added, and the reaction was continued for a further 1 h. Processing as described for **17** gave a syrup (397 mg), which showed, in TLC (3:1 $CHCl_3$–acetone), three spots of R_f 0.3 (A), 0.25 (**20**), and 0.18 (B). Column chromatography (silica gel 25 g, 3:1 $CHCl_3$–acetone) of the syrup gave A + **20** (54 mg), **20** (81 mg), and **20** + B (93 mg). Rechromatography (silica gel 5.4 g, 3:1 $CHCl_3$–acetone) of the first mixture gave another 37 mg of **20**. Preparative TLC (using the same solvent system) of the last mixture gave **20** (11 mg) and **20** + B (75 mg). A total of 129 mg (41%) of **20** was thus obtained as a solid, $[\alpha]_D^{24}$ −25° (*c* 1, $CHCl_3$), IR (KBr): ν 2110 cm^{-1} (N_3); ^{1}H NMR (pyridine-d_5): δ 1.68 (q, 1 H, H-2*ax*), 2.16, 2.23 and 2.28 [each s of 3 H, 3 Ts(CH_3)], 2.26 (dt, 1 H, H-2*eq*), 2.49 (s, 3 H, Ac), 3.09 (dd, 1 H, H-6′a), 3.14 (dd, 1 H, H-6′b), 3.43 (t, 1 H, H-4′*ax*), 3.52 (dd, 1 H, H-2′*ax*), 3.62 (dd, 1 H, H-4′*eq*), 3.77 (t, 1 H, H-6″a), 3.79–3.86 [3 H, H-3(or 1),6(or 4),2′*eq*], 3.93 (t, 1 H, H-4″), 4.0–4.08 [3 H, H-1(or 3),4(or 6),5], 4.49 (dd, 1 H, H-6″b), 4.82 (dt, 1 H, H-3″), 5.12 (m, 1 H, H-5′), 5.24 (dt, 1 H, H-5″), 5.64 (s, 1 H, C*H*Ph), 5.67 (sl. br s, 1 H, H-1′), 5.70 (dd, 1 H, H-2″), 6.21 (d, 1 H, H-1″), 8.60 (d, 1 H, NH-1 or 3), 9.23 (d, 1 H, NH-3 or 1), 9.75 (d, 1 H, NH-3″); $J_{1',2'ax}$ 2.5, $J_{1',2'eq} \sim 0$, $J_{2'ax,2'eq}$ 11.5, $J_{1'',2''}$ 3.8 Hz. Anal. Calcd for

$C_{47}H_{56}N_6O_{16}S_3 \cdot H_2O$: C, 52.50; H, 5.44; N, 7.82; S, 8.95. Found: C, 52.86; H, 5.73; N, 8.14; S, 8.82.

6-O-(3-Amino-3-deoxy-α-D-glucopyranosyl)-4-O-(6-amino-3-oxa-2,3,4,6-tetradeoxy-α-L-glycero-hexopyranosyl)-2-deoxystreptamine (**21**).—Compound **20** (95.1 mg, 0.088 mmol) was deacetylated as described for **18** and the well-dried product (87.8 mg; chromatographically homogeneous) was treated with Na (~ 30 mg in ~ 8 mL NH_3, at −55 °C, 15 min) as described for **19** to give a crude product (36.4 mg), which showed, in TLC (2:4:7:7 $CHCl_3$–PrOH–EtOH–aq 17% NH_3), two spots of R_f 0.3 (**21**) and 0.2 (3AD). Separation by a column of CM Sephadex C-25 (NH_4^+ form) using 0 → 0.15 M aq NH_3 as eluent gave **21** as a solid (15.7 mg, 39%) together with 3AD (8.1 mg); **21**: $[\alpha]_D^{25}$ +36° (*c* 1, H_2O); ^{1}H NMR (26% ND_3 in D_2O): δ 1.19 (q, 1 H, H-2*ax*), 1.90 (dt, 1 H, H-2*eq*), 2.60 (dd, 1 H, H-6′a), 2.62 (dd, 1 H, H-6′b), 2.80 (ddd, 1 H, H-3), 2.86 (ddd, 1 H, H-1), 2.98 (t, 1 H, H-3″), 3.21 (t, 1 H, H-6), 3.28 (t, 1 H, H-4″), 3.29 (t, 1 H, H-4), 3.445 (t, 1 H, H-4′*ax*), 3.453 (dd, 1 H, H-2″), 3.475 (t, 1 H, H-5), 3.66 (dd, 1 H, H-2′*ax*), 3.71 (dd, 1 H, H-6″a), 3.725 (dd, 1 H, H-6″b), 3.82 (dd, 1 H, H-4′*eq*), 3.88 (d, 1 H, H-2′*eq*), 3.89 (m, 1 H, H-5″), 4.29 (m, 1 H, H-5′), 5.00 (sl. br s, 1 H, H-1′), 5.005 (d, 1 H, H-1″); $J_{1,2ax} \approx J_{2ax,2eq} \approx J_{2ax,3}$ 12, $J_{1,2eq} \approx J_{2eq,3}$ 4, $J_{3,4} \approx J_{4,5} \approx J_{5,6} \approx J_{6,1}$ 9, $J_{1',2'ax} \sim 2$, $J_{1',2'eq} \sim 0$, $J_{2'ax,2'eq}$ 12.0, $J_{4'ax,4'eq}$ 11.0, $J_{4'ax,5'}$ 10.0, $J_{4'eq,5'}$ 3.0, $J_{5',6'a}$ 6.0, $J_{5',6'b}$ 2.5, $J_{6'a,6'b}$ 13.0, $J_{1'',2''}$ 4.0, $J_{2'',3''} \approx J_{3'',4''} \approx J_{4'',5''}$ 9, $J_{5'',6''a}$ 4.0, $J_{5'',6''b}$ 2.5, $J_{6''a,6''b}$ 12.0 Hz. Anal. Calcd for $C_{17}H_{34}N_4O_9 \cdot H_2O$: C, 44.73; H, 7.95; N, 12.27. Found: C, 44.62; H, 7.98; N, 12.28.

6-O-(3-Amino-3-deoxy-α-D-glucopyranosyl)-4-O-(6-amino-3-oxa-2,3,4,6-tetradeoxy-β-L-glycero-hexopyranosyl)-2-deoxystreptamine (**22**) *and 6-O-(3-amino-3-deoxy-α-D-glucopyranosyl)-5-O-(6-amino-3-oxa-2,3,4,6-tetradeoxy-α-L-glycero-hexopyranosyl)-2-deoxystreptamine* (**23**).—The crude syrup (75 mg) obtained in the preparation of **20** was deacetylated as described for **18**, and the well-dried product-mixture (70 mg) was treated with Na (~ 30 mg in ~ 8 mL NH_3, at −55 °C, 15 min) as described for **19** (including the resin treatment) to give a crude mixture of final products (29.3 mg; R_f 0.3 in TLC with 2:4:7:7 $CHCl_3$–PrOH–EtOH–aq 17% NH_3) along with 3AD (5.5 mg, R_f 0.2). Separation of the mixture with a column of CM Sephadex as described for **21** gave 3AD (6.9 mg), **21** (5.7 mg, ~ 18%), **22** (5.3 mg, ~ 17%), and **23** (6.4 mg, ~ 20%) all as solids, eluted in this order. Compound **22**, $[\alpha]_D^{25}$ +84° (*c* 0.5, H_2O); mass spectrum: *m/z* 439.37 ($M^+ + 1$); Calcd for $C_{17}H_{34}N_4O_9$: *m/z* 438.23 for M^+; ^{1}H NMR (26% ND_3 in D_2O): d 1.16 (q, 1 H, H-2*ax*), 1.92 (dt, 1 H, H-2*eq*), 2.63 (dd, 1 H, H-6′a), 2.67 (dd, 1 H, H-6′b), 2.70 (ddd, 1 H, H-3), 2.82 (ddd, 1 H, H-1), 2.96 (t, 1 H, H-3″), 3.15 (dd, 1 H, H-2′*ax*), 3.18 (t, 1 H, H-6), 3.20 (t, 1 H, H-4′*ax*), 3.29 (t, 1 H, H-4″), 3.34 (t, 1 H, H-4), 3.39 (t, 1 H, H-5), 3.44 (dd, 1 H, H-2″), 3.69–3.74 (3 H, H-4′*eq*,6″a,6″b), 3.76 (m, 1 H, H-5′), 3.86 (dt, 1 H, H-5″), 3.90 (dd, 1 H, H-2′*eq*), 4.90 (dd, 1 H, H-1′), 4.98 (d, 1 H, H-1″); $J_{1,2ax} \approx J_{2ax,2eq} \approx J_{2ax,3}$ 12, $J_{1,2eq} \approx J_{2eq,3}$ 4, $J_{3,4} \approx J_{4,5} \approx J_{5,6} \approx J_{6,1}$ 9, $J_{1',2'ax}$ 9, $J_{1',2'eq}$ 2.5, $J_{2'ax,2'eq}$ 11.0, $J_{4'ax,4'eq}$ 11.5, $J_{4'ax,5'}$ 10.0, $J_{4'eq,5'}$ 2.2, $J_{5',6'a}$ 7.0, $J_{5',6'b}$ 4.0, $J_{6'a,6'b}$ 13.0, $J_{1'',2''}$ 4.0, $J_{2'',3''} \approx J_{3'',4''} \approx J_{4'',5''}$ 9, $J_{5'',6''a} \approx J_{5'',6''}$ ~ 4 Hz.

Compound **23**, $[\alpha]_D^{25}$ +21° (*c* 0.6, H_2O); mass spectrum: *m/z* 439.37 ($M^+ + 1$); Calcd for $C_{17}H_{34}N_4O_9$: *m/z* 438.23 for M^+; ^{1}H NMR (26% ND_3 in D_2O): d 1.19 (q, 1 H, H-2*ax*), 1.93 (dt, 1 H, H-2*eq*), 2.60 (dd, 1 H, H-6′a), 2.62 (dd 1 H, H-6′b), 2.65 (ddd, 1 H, H-3), 2.81 (ddd, 1 H, H-1), 2.97 (t, 1 H, H-3″), 3.17 (t, 1 H, H-4), 3.27 (t, 1

H, H-4″), 3.34 (dd, 1 H, H-2″), 3.40 (t, 1 H, H-6), 3.42 (t, 1 H, H-4′*ax*), 3.51 (t, 1 H, H-5), 3.60 (ddd, 1 H, H-5″), 3.65 (dd, 1 H, H-2′*ax*), 3.67 (dd, 1 H, H-6″a), 3.71 (dd, 1 H, H-6″b), 3.82 (dd, 1 H, H-4′*eq*), 3.87 (d, 1 H, H-2′*eq*), 4.33 (dddd, 1 H, H-5′), 5.06 (sl. br s, 1 H, H-1′), 5.11 (d, 1 H, H-1″); $J_{1,2ax} \approx J_{2ax,2eq} \approx J_{2ax,3}$ 12, $J_{1,2eq} \approx J_{2eq,3}$ 4.5, $J_{3,4} \approx J_{4,5} \approx J_{5,6} \approx J_{6,1}$ 9, $J_{1',2'ax} \sim 2$, $J_{1',2'eq} \sim 0$, $J_{2'ax,2'eq}$ 12.0, $J_{4'ax,4'eq} \approx J_{4'ax,5'}$ 11, $J_{4'eq,5'}$ 3.0, $J_{5',6'a} \approx J_{5',6'b} \sim 5.5$, $J_{6'a,6'b}$ 13.0, $J_{1'',2''}$ 3.2, $J_{2'',3''} \approx J_{3'',4''} \approx J_{4'',5''}$ 9, $J_{5'',6''a} \sim 2$, $J_{5'',6''b}$ 4.0, $J_{6''a,6''b}$ 12.0 Hz.

Minimal inhibitory concentration (μg mL^{-1}) of KMA and **19**.—This assay was performed on Mueller–Hinton agar for 18 h at 37 °C. *Staphylococcus aureus* FDA 209 P: 1.56 and 12.5 in the above compound order; *S. aureus* Ap 01 [AAD(4′)]: 25, > 100; *S. epidermidis* 109 [AAD(4′)]: 100, 25; *Bacillus subtilis* PCI 219: 0.39, 12.5; *Escherichia coli* K-12: 1.56, 25; *E. coli* K-12 ML1629 [APH(3′)-I]: > 100, 50; *E. coli* K-12 R5 [AAC(6′)]: 100, > 100; *E. coli* J5R11-2 [APH(3′)-I]: > 100, 25; *E. coli* JR66/W677 [AAD(2″), APH(3′)-II]: > 100, > 100; *Klebsiella pneumoniae* PCI 602: 3.12, 50; *Proteus rettgeri* GN 311: 0.39, 12.5; *Serratia marcescens*: 3.12, 50; *Pseudomonas aeruginosa* A3: 25, 12.5; *P. aeruginosa* H9 [APH(3′)-II]: > 100, 100.

Acknowledgements

The authors are grateful to Drs. Hiroshi Naganawa, Masa Hamada, and Ms. Hiroko Hino of Institute of Microbial Chemistry for measurements of mass spectra, antibacterial bioassay, and elemental analysis, respectively. We also thank to Ms. Yoshiko Koyama of our Institute for measurements of 500 M Hz NMR spectra.

References

[1] H. Umezawa and I.R. Hooper (Eds.), *Aminoglycoside Antibiotics*, Springer Verlag, Berlin, 1982. (a) pp 37–110, 111–203, (b) pp 205–220, (c) pp 267–292.
[2] T. Tsuchiya, T. Torii, S. Umezawa, and H. Umezawa, *J. Antibiot.*, 35 (1982) 1245–1247; T. Tsuchiya, T. Torii, Y. Suzuki, and S. Umezawa, *Carbohydr. Res.*, 116 (1983) 277–287.
[3] T. Shitara, Y. Kobayashi, T. Tsuchiya, and S. Umezawa, *Carbohydr. Res.*, 232 (1992) 273–290.
[4] E. Umemura, T. Tsuchiya, Y. Koyama, and S. Umezawa, *Carbohydr. Res.*, 238 (1993) 147–162.
[5] T. Tsuchiya, T. Shitara, S. Umezawa, T. Takeuchi, M. Hamada, N. Tomono, and E. Umemura, *Carbohydr. Res.*, 240 (1993) 307–312.
[6] Y. Takahashi, C. Ueda, T. Tsuchiya, and Y. Kobayashi, *Carbohydr. Res.*, 249 (1993) 57–76.
[7] K. Maeda, M. Murase, H. Mawatari, and H. Umezawa, *J. Antibiot.*, 11 (1958) 163–165.
[8] M.E. Jung and T.J. Shaw, *J. Am. Chem. Soc.*, 102 (1980) 6304–6311.
[9] Y. Terao, K. Tsuji, M. Murata, K. Achiwa, T. Nishio, N. Watanabe, and K. Seto, *Chem. Pharm. Bull.*, 37 (1989) 1653–1655.
[10] Catalog No. 24,250-0 in: Catalog Handbook of Fine Chemicals, Aldrich, 1994–1995.
[11] B. Fraser-Reid, U.E. Udodong, Z. Wu, H. Ottosson, J.R. Merritt, C.S. Rao, C. Roberts, and R. Madsen, *Synlett*, (1992) 927–942.
[12] P. Sinaÿ, *Pure and Appl. Chem.*, 63 (1991) 519–528; related references are cited therein.
[13] T. Ogawa, K. Beppu, and S. Nakabayashi, *Carbohydr. Res.*, 93 (1981) C6–C9.
[14] G.H. Veeneman, S.H. van Leeuwen, and J.H. van Boom, *Tetrahedron Lett.*, 31 (1990) 1331–1334.

[15] Y. Kobayashi, T. Tsuchiya, S. Umezawa, T. Yoneta, S. Fukatsu, and H. Umezawa, *Bull. Chem. Soc. Jpn.*, 60 (1987) 713–720.
[16] T. Tsuchiya, Y. Takahasyhi, M. Endo, S. Umezawa, and H. Umezawa, *J. Carbohydr. Chem.*, 4 (1985) 587–611.
[17] T. Tsuchiya, T. Jikihara, T. Miyake, S. Umezawa, M. Hamada, and H. Umezawa, *J. Antibiot.*, 32 (1979) 1351–1353.
[18] Y. Takahashi, T. Tsuchiya, S. Umezawa, and H. Umezawa, *Carbohydr. Res.*, 210 (1991) 221–232.
[19] Y. Nishimura, H. Umezawa, and S. Umezawa, *Tetrahedron Lett.*, 22 (1981) 77–80.
[20] G. Koyama and Y. Iitaka, *Tetrahedron Lett.*, (1968) 1875–1879.