Syntheses of 5-Deoxy-, 5,4′-Dideoxy-, 5-Deoxy-5-epichloro-, and 5,4′-Dideoxy-5,4′-diepichlorokanamycin A

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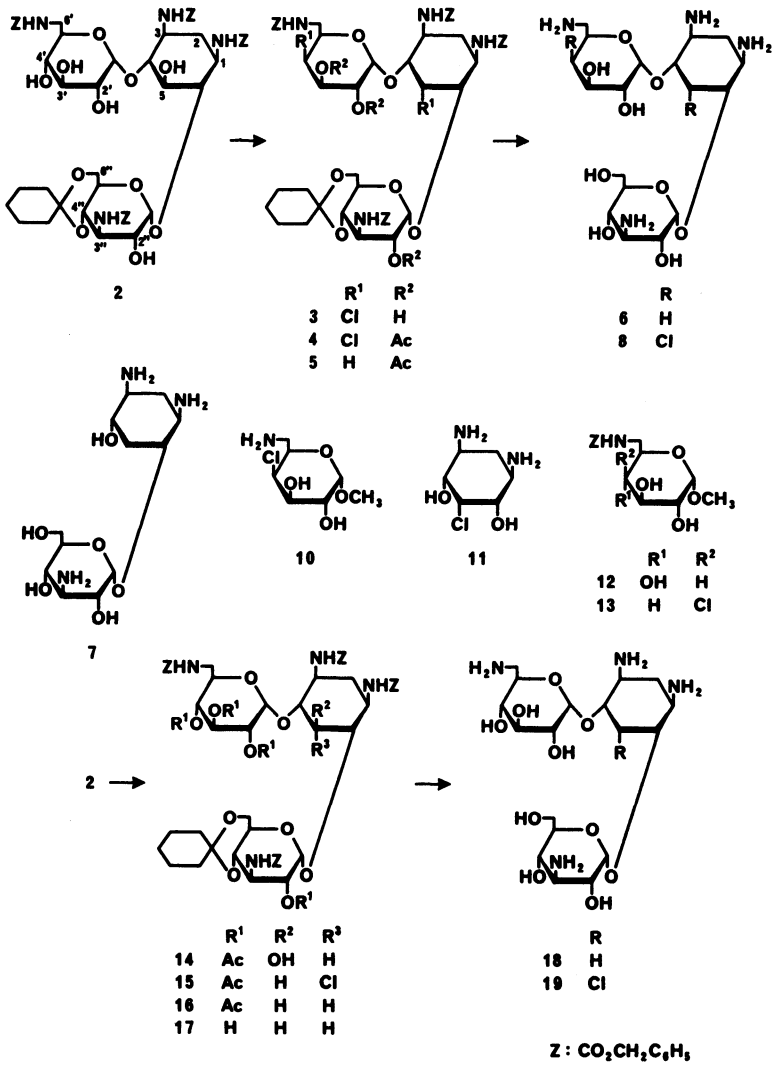
5,4′-Dideoxy-5,4′-diepichlorokanamycin A has been synthesized from 1,3,6′,3″-tetrakis(*N*-benzyloxycarbonyl)-4″,6″-*O*-cyclohexylidenekanamycin A by treatment with sulfuryl chloride, followed by deblocking. Similar treatment of 2′,3′,4′,2″-tetra-*O*-acetyl-1,3,6′,3″-tetrakis(*N*-benzyloxycarbonyl)-4″,6″-*O*-cyclohexylidenekanamycin A gave 5-deoxy-5-epichlorokanamycin A. 5,4′-Dideoxykanamycin A and 5-deoxykanamycin A were synthesized from the corresponding 5,4′-diepichloro and 5-epichloro derivatives by reductive dechlorination with sodium metal in liquid ammonia or tributylstannane. The structures of these derivatives were confirmed by the ^{1}H- and ^{13}C-NMR spectroscopy.

In previous papers[1,2] we reported the syntheses of 4′-deoxykanamycin A and B, which show activities against some kanamycin-resistant strains including *Pseudomonas aeruginosa*. This paper describes the preparation of some chloro and deoxy derivatives of kanamycin A modified at C-5 and C-4′ utilizing sulfuryl chloride.

Chlorination of sugars by sulfuryl chloride has been extensively studied.[3] In the case of methyl α-D-glucopyranoside (**1**), Helferich *et al.*[4] observed, in the beginning of the 1920's, the formation of 4,6-dichloro-4,6-dideoxy-α-D-hexoside 2,3-cyclic sulfate by treating **1** with sulfuryl chloride, the correct structure of the product being later determined[5] as a 4,6-dichlorogalactoside derivative formed by inversion of the configuration at C-4. This result indicates that chlorination does not occur at the 2- and 3-hydroxyl groups of a α-D-gluco-



Scheme 1.

pyranoside derivative and, after desulfation (or dechlorosulfation[3]), they are regenerated. Regarding kanamycin A, there are four amino and seven hydroxyl groups in the molecule, and, even if the amino and 4″- and 6″-hydroxyl groups are protected, five reactive hydroxyl groups still remain; among them, the 2′-, 3′-, and 2″-hydroxyl groups are expected not to be replaced by chlorine atoms by treatment with sulfuryl chloride from the above point of view.

We were, therefore, interested in the selective chlorination of a kanamycin A derivative, 1,3,6′,3″-tetrakis(*N*-benzyloxycarbonyl)-4″,6″-*O*-cyclohexylidenekanamycin A[2] (**2**) with sulfuryl chloride. Treatment of **2** with the reagent in dichloromethane–pyridine gave the corresponding 5,4′-diepichloro derivative (**3**) in 45% yield. It should be noted that the 5-epichlorination simultaneously occurred in addition to the 4′-epichlorination, which was unexpected from the steric point of view, because the 5-hydroxyl group of kanamycin derivatives are known to be less reactive among the hydroxyl groups against benzoylation and sulfonylation[2,6,7] due to the bulkiness of the adjacent substituents attached at C-4 and 6. Recently, Suami *et al.*[8] also reported the 5-epichlorination of a protected kanamycin B derivative with sulfuryl chloride.

In order to prepare 5,4′-dideoxykanamycin A (**6**), **3** was treated with sodium metal in liquid ammonia, and the desired **6** was obtained in a low yield (19%) after decyclohexylidenation. As already reported,[9] in the case of methyl 3-chloro-4,6-*O*-cyclohexylidene-2,3-dideoxy-2-(*p*-toluenesulfonamido)-α-D-glucopyranoside,[9] reductive dechlorination smoothly occurred by the same treatment. Treatment of the 2′,3′,2″-tri-*O*-acetyl derivative (**4**) of **3** with sodium in liquid ammonia gave **6** in 27% yield together with 6-*O*-(3-amino-3-deoxy-α-D-glucopyranosyl)-2,5-dideoxystreptamine (**7**). The structure of the latter was confirmed by the paper-chromatography of the acidic hydrolyzates of **7**. Occurrence of the high-degree hydrolysis of a glycoside bond of **4** is somewhat surprising.

In order to improve the yield of **6**, **4** was treated in trial, with tributylstannane in the presence of α,α′-azobis(isobutyronitrile)[10] in 1,4-dioxane, affording 4′-deoxy derivative (**5**) in high yield. Successive deblocking of the acetyl, cyclohexylidene, and benzyloxycarbonyl groups of **5** gave **6** in 77% overall yield from **4**.

Next, to prepare a chloro derivative of kanamycin A, the protecting groups of **3** were removed to give 5,4′-dideoxy-5,4′-diepichlorokanamycin A (**8**). Its structure was determined by the ^{1}H-NMR spectra, which gave double doublets with small spacings (δ=5.10, J=4 and 1 Hz, H-4′) and a narrow triplet (δ=5.63, J=3 Hz, H-5) assignable to the protons attached to the carbon bearing chlorine atom; this indicates that both the chloro atoms are axially attached. The structure of **8** was further confirmed by methanolysis in the presence of Amberlite CG120 (H form) resin at a high temperature according to a reported procedure.[11] Methyl 3-amino-3-deoxy-α-D-glucopyranoside (**9**),[12,13] methyl 6-amino-4-chloro-4,6-dideoxy-α-D-galactopyranoside (**10**), and 2,5-dideoxy-5-epichlorostreptamine (**11**) were obtained after chromatography. The compound **10** was identical with that prepared by a different route. Methyl 6-amino-6-deoxy-α-D-glucopyranoside[14] was successively *N*-benzyloxycarbonylated (to give **12**), and 4′-epichlorinated by the method described for **3** (to give **13**), followed by removal of the *N*-protecting group to give **10**. Its ^{1}H-NMR spectrum showed double doublets assignable to equatorial H-4 (δ=4.98, J=3.2 and 1.0 Hz), the splitting pattern being comparable with that of the corresponding resonances of **8**.

5-Deoxy and 5-deoxy-5-epichloro derivatives of kanamycin A were further prepared as follows: The protected kanamycin A (**2**) was acetylated and the resulting 2′,3′,4′,2″-tetra-*O*-acetyl derivative (**14**) having a free hydroxyl group at C-5 was treated with sulfuryl chloride in a similar manner as described above to give the 5-deoxy-5-epichloro derivative (**15**). Treatment of **15** with sodium metal in liquid ammonia in a manner as described for **6** followed by deacetylation and decyclohexylidenation gave 5-deoxykanamycin A (**18**) in good yield (69%). The yield was somewhat surprising because **3** or **4** gave poor yields of **6** by the same treatment. The compound **18** was recently synthesized *via* glycosidation by Kavadias *et al.*,[15] or isolated from the fermentation broths of *S. kanamyceticus*.[16] Reduction of **15** with tributylstannane (to give **16**) followed by deprotection also gave **18**. Deprotection of **15** gave the desired 5-deoxy-5-epichlorokanamycin A (**19**).

The ^{13}C-chemical shifts of the final deoxy compounds (**6**, **8**) and kanamycin A are shown in Table 1. Expected downfield shift (2.3 ppm) based on the shift of kanamycin A[2] caused by the 4′-deoxygenation was observed at C-6′ of **6**, which was not observed in the spectrum of **18**. Upfield shifts (4.8 and 5.4 ppm) caused by the 5-deoxygenation were observed at the C-1′ in both **6** and **18**. Similar upfield shifts were reported for 5-

Table 1. The ^{13}C chemical shifts[a] of **6**, **18**, kanamycin A (KMA) measured in D_2O (at pD 9.5)

Carbon	6	18	KMA[e]
1′	95.6	95.0	100.4
2′	73.6	72.0	72.7
3′	68.7[b]	72.0	73.7
4′	36.2	71.8	71.9
5′	67.7[b]	73.5	73.7
6′	44.7	42.1	42.4
1	52.3	52.3	51.2
2	36.2	36.2	36.3
3	53.3	53.3	49.8
4	83.6[c]	83.7[d]	88.2
5	34.4	34.4	74.9
6	77.0[c]	77.3[d]	88.7
1″	101.1	101.1	100.8
2″	72.4	72.5	72.7
3″	55.0	54.9	55.1
4″	70.6	70.6	70.2
5″	73.1	73.1	73.0
6″	61.7	61.7	61.2

a) In ppm downfield from TMS calculated as $\delta^{TMS}=\delta^{dioxane}+67.4$ ppm. b)—d) The values may be reversed. e) Shift assignments were based on the shifts of kanamycin A (pH 9.6) reported.[19]

Table 2. The ^{13}C chemical shifts[a] of **8**, **19**, **10**, kanamycin A (KMA), and methyl 6-amino-6-deoxy-α-D-glucopyranoside (Me 6AG) measured in 20% ND_3 in D_2O

Carbon	**8**	**19**	KMA	**10**	Me 6AG
1′	95.2	94.8	101.0	100.8	100.5
2′	72.1	72.5	73.0	60.2	72.6
3′	69.5[b]	74.5[d]	74.4[f]	71.7[g]	74.2
4′	65.0	72.4	72.3	65.3	72.4
5′	69.0[b]	73.8[d]	74.1[f]	69.7[g]	73.3
6′	43.4	43.0	43.1	43.5	42.8
1	48.8	48.9	51.7		
2	37.0	37.1	36.8		
3	48.1	48.2	50.3		
4	85.2[c]	85.4[e]	88.9		
5	62.2	62.1	75.3		
6	77.9[c]	77.2[e]	89.0		
1″	102.4	102.6	101.2[h]		
2″	72.9	72.9	73.1		
3″	55.4	55.5	55.6		
4″	71.1	71.1	70.6		
5″	74.4	74.0	73.5		
6″	61.6	61.7	61.5		
OCH_3				56.4	56.2

a) In ppm downfield from external TMS. b)—g) The values may be reversed. h) Assigned by selective proton decoupling at H-1″.

deoxykanamycin B [4.3 (as the free base, pD 11)[8] and 4.2 ppm (as the sulfate, pD 7)[17]]. In Table 2, the ^{13}C-chemical shifts of the final chloro compounds (**8**, **19**), **10**, methyl 6-amino-6-deoxy-α-D-glucopyranoside, and kanamycin A are compared. Upfield shifts (7.3 and 7.1 ppm) caused by the 4′(or 4)-epichlorination were observed at C-4′ of **8** and C-4 of **10**, but no obvious difference as experienced in the 4′-deoxy derivatives was observed on the shifts of C-6′ (C-6 in the case of **10**) between the chloro compounds (**8**, **19**, **10**) and kanamycin A. Upfield shifts caused by 5-deoxy-5-epichlorination were observed at C-1′ by 5.8 (**8**) and 6.2 ppm (**19**). Recently a similar upfield shift[18] (4.5 ppm) at C-1′ was observed in 5-epikanamycin B compared with kanamycin B.

The antibacterial activities of the compounds **6**, **8**, **18**, **19**, and kanamycin A are shown in Table 3. It was concluded, by the comparison, that the 4′-epichlorination of kanamycin A caused lack of activity. The 5-deoxygenation of kanamycin A caused lowering of activity in accord with the report by Kavadias *et al.*[15]

Experimental

IR spectra were determined in KBr disks with a Hitachi 285 infrared spectrophotometer. ^1H-NMR spectra were recorded at 90 MHz with a Varian EM-390 spectrometer. ^{13}C-NMR spectra were recorded on a Varian XL-100 spectrometer with a Varian 620-L data processing system (25.2 MHz). Tetramethylsilane ($\delta=0$) was used as the internal standard (in organic solvents), or as the external standard (in deuterium oxide). Thin-layer chromatography (TLC) was carried out on E. Merck precoated silica gel 60 plates with the spray of sulfuric acid or 0.5% ninhydrin in pyridine for detection. Paper chromatography (PPC) was carried out on Toyo-Roshi paper No. 50 with 1-butanol–pyridine–water–acetic acid (6 : 4 : 3 : 1), descending for 7—8 d, unless otherwise stated, and spots were visualized by 0.5% ninhydrin in pyridine. For column chromatography, silica gel (Wakogel C-200) was used, unless otherwise stated.

*1,3,6′,3″-Tetrakis(*N*-benzyloxycarbonyl)-5,4′-dideoxy-5,4′-diepichloro-4″,6″-*O*-cyclohexylidenekanamycin A (3).* To a solution of **2**[2] (504 mg) in a mixture of dry dichloromethane (9 ml) and dry pyridine (3.5 ml), was added sulfuryl chloride (0.55 ml, 15 mol equivalents for **2**) gradually at −78 °C and the solution was kept at the temperature for 30 min, then at room temperature for 1.5 h. A solution of sodium iodide (750 mg) in aqueous pyridine (1 : 2, 7.5 ml) was added to the reaction mixture. The resulting solution showed, on TLC with chloroform–ethanol (10 : 1), spots at R_f 0.4 (**3**, major), 0.25 (**2**, slight), 0.07 (minor), and others. Concentration of the mixture gave a syrup, which was dissolved in chloroform. The solution was washed with water, dried ($MgSO_4$), and concentrated to give a brown solid (405 mg), which was chromatographed on a silica-gel column with chloroform–ethanol = 15 : 1 to give a colorless solid of **3**, 235 mg (45%), $[\alpha]_D^{25}$ +80° (*c* 0.5, *N*,*N*-dimethylformamide).

Found: C, 58.83; H, 5.80; N, 4.72; Cl, 6.41%. Calcd for $C_{56}H_{66}N_4O_{17}Cl_2$: C, 59.10; H, 5.85; N, 4.92; Cl, 6.23%.

*2′,3′,2″-Tri-*O*-acetyl-1,3,6′,3″-tetrakis(*N*-benzyloxycarbonyl)-4″,6″-*O*-cyclohexylidene-5,4′-dideoxy-5,4′-diepichlorokanamycin A (4).* To a solution of **3** (102 mg) in dry pyridine (2 ml) was added acetic anhydride (0.051 ml, 6 mol equivalents for **3**) and the solution was kept at room temperature overnight. After

Table 3. Antibacterial spectra of **6**, **8**, **18**, **19**, and kanamycin A (KMA)

Test Organisms[a]	Minimal inhibitory concentration/μg ml^{-1}				
	6	**8**	**18**	**19**	KMA
Staphylococcus aureus FDA 209P	6.25	>100	6.25	12.5	3.12
Sarcina lutea PCI 1001	25	—	25	100	12.5
Klebsiella pneumoniae PCI 602	12.5	>100	3.12	12.5	1.56
Salmonella typhi T-63	3.12	>100	1.56	6.25	1.56
Escherichia coli K-12	6.25	>100	3.12	12.5	3.12
Escherichia coli K-12 ML1629[b]	>100	>100	>100	>100	>100
Pseudomonas aeruginosa A3	3.12	>100	100	100	25
Pseudomonas aeruginosa No. 12	25	—	>100	>100	>100
Mycobacterium smegmatis ATCC 607[c]	6.25	—	3.12	6.25	1.56

a) Agar dilution streak method (nutrient agar, 37 °C, 18 h). b) This strain phosphorylates the 3′-hydroxyl groups of kanamycins. c) Measured after 48 h.

addition of acetic anhydride (0.025 ml), the solution was heated at 50 °C for 6 h. The solution showed, on TLC with chloroform–ethanol (10 : 1), a single spot at R_f 0.41. Addition of water (0.1 ml) followed by concentration gave a syrup. A chloroform (10 ml) solution of the syrup was washed successively with 5% aqueous sodium hydrogencarbonate solution, and water, dried ($MgSO_4$), and concentrated to give a pale brown solid (110 mg), which was purified by passing through a short column of silica gel with chloroform–2-butanone=3 : 1 to give a colorless solid of **4**, 98.7 mg (87%), $[\alpha]_D^{25}$ +86° (*c* 0.5, chloroform); ^{1}H-NMR ($CDCl_3$): δ=1.73, 2.13, 2.19 (each 3H s, $COCH_3$).

Found: C, 59.05; H, 5.71; N, 4.39; Cl, 5.87%. Calcd for $C_{62}H_{72}N_4O_{20}Cl_2$: C, 58.91; H, 5.74; N, 4.43; Cl, 5.61%.

2′,3′,2″-Tri-O-acetyl-1,3,6′,3″-tetrakis(N-benzyloxycarbonyl)-4″,6″-O-cyclohexylidene-5,4′-dideoxykanamycin A (5). To a solution of **4** (93.5 mg) in dry 1,4-dioxane (2 ml) were added tributylstannane (0.3 ml) and α,α′-azobis(isobutyronitrile) (10 mg) and the reaction mixture was heated at 80 °C for 2 h under the nitrogen atmosphere. The resulting solution showed, on TLC with chloroform–2-butanone (3 : 1), a single spot at R_f 0.11 (*cf.* **4**, R_f 0.26). The solution was concentrated under reduced pressure to give a solid, which was thoroughly washed with ether and chromatographed on a silica-gel column with chloroform–ethanol=15 : 1 to give a solid of **5**, 78.6 mg (89%), $[\alpha]_D^{25}$ +82° (*c* 0.5, *N,N*-dimethylformamide); ^{1}H-NMR (pyridine-d_5): δ=1.99 (6H) and 2.28 (3H) (each s, $COCH_3$); 1.0—2.8 (25H, C_6H_{10}, $3COCH_3$, CH_2 at C-2,5,4′).

Found: C, 62.07; H, 6.20; N, 4.91%. Calcd for $C_{62}H_{74}N_4O_{20}$: C, 62.30; H, 6.24; N, 4.69%.

5,4′-Dideoxykanamycin A (6). *A) From 5*: To a suspension of **5** (46.2 mg) in dry 1,4-dioxane–methanol (4 : 1, 1 ml) was added 1 M sodium methoxide (1 M=1 mol dm^{-3}) in methanol (0.025 ml), and the mixture was stirred at room temperature for 15 min. The resulting clear solution was neutralized with Dowex 50W×8 resin (H form) pretreated with 1,4-dioxane, filtered, and the filtrate was concentrated to give a solid, 42.0 mg. The deacetyl product was suspended in 80% aqueous acetic acid, and the mixture was stirred at 80 °C for 20 min. The resulting clear solution containing the decyclohexylidenated product was hydrogenated with palladium black under atmospheric pressure of hydrogen for 40 min. The resulting product was purified by chromatography over CM-Sephadex C-25 (NH_4 form, 0→0.3 M aqueous ammonia) to give a solid of **6**, 18.6 mg (86% as the 1.7 carbonate), $[\alpha]_D^{25}$ +130° (*c* 0.5, water); PPC: $R_{f\ \text{kanamycin A}}$ 1.1; TLC (1-butanol–ethanol–chloroform–10 M aqueous ammonia=4 : 7 : 2 : 7): R_f 0.20 (*cf.* kanamycin A, R_f 0.17).

Found: C, 42.42; H, 7.10; N, 10.00%. Calcd for $C_{18}H_{36}N_4O_9 \cdot 1.7\,H_2CO_3$: C, 42.41; H, 7.12; N, 10.04%.

Acidic hydrolysis of **6** (6 M HCl, 100 °C, 50 min) gave three products, on PPC (descending for 2 d), corresponding to 3-amino-3-deoxy-D-glucose ($R_{f\ \text{2-deoxystreptamine (DST)}}$ 2.5), 6-amino-4,6-dideoxy-D-*xylo*-hexose ($R_{f\ \text{DST}}$ 2.0) and 2,5-dideoxystreptamine ($R_{f\ \text{DST}}$ 1.6) (*cf.* 6 amino-6-deoxy-D-glucose, $R_{f\ \text{DST}}$ 1.6).

B) From 3: To a solution of **3** (131 mg) in liquid ammonia (≈35 ml) at −60 °C was added sodium metal (≈260 mg) with stirring, and the resulting deep-blue solution was kept at −50 °C for 2 h. Addition of methanol (5 ml) followed by concentration gave a solid. An aqueous solution of the de(benzyloxycarbonyl)-5,4′-dideoxy intermediate was stirred with Dowex 50W×8 resin (H form, 30 ml), and the resin, after packed in a column and washing it with water, was treated with 1 M aqueous ammonia. The ninhydrin-positive fractions were collected and concentrated. The solid obtained was chromatographed over CM-Sephadex C-25 (NH_4 form, 00.3 M aqueous ammonia) to give a solid of **6**, 12.6 mg (19% as the dicarbonate).

C) From 4: **4** (60.2 mg) was treated with sodium metal (≈140 mg) in liquid ammonia (≈20 ml) as described for B). Deacetylation of the resulting product was carried out by treating it with 1 M aqueous sodium hydroxide at 50 °C for 30 min. Purification in a manner as described above gave a solid of **6** (6.7 mg, 27% as the 1.2 carbonate) and that of **7** (10.1 mg, 60% as the 0.7 carbonate).

6: Found: C, 43.75; H, 7.18; N, 10.53%. Calcd for $C_{18}H_{36}N_4O_9 \cdot 1.2H_2CO_3$: C, 43.76; H, 7.35; N, 10.63%.

7: $[\alpha]_D^{25}$ +72° (*c* 1, water); PPC: $R_{f\ \text{kanamycin A}}$ 2.3; TLC (1-butanol–ethanol–chloroform–10 M aqueous ammonia=4 : 7 : 2 : 7): R_f 0.28; ^{1}H-NMR (D_2O): δ=1.5—2.4 (2H m, H-2ax and 5ax), 2.4—3.2 (2H m, H-2eq and 5eq), 5.53 (1H d, J 4 Hz, H-1′).

Found: 43.52; H, 7.55; N, 11.78%. Calcd for $C_{12}H_{25}N_3O_6 \cdot 0.7H_2CO_3$: C, 43.49; H, 7.59; N, 11.98%.

PPC of the acidic hydrolyzates of **7** (6 M HCl, 100 °C, 30 min; descending for 2 d): $R_{f\ \text{2-deoxystreptamine (DST)}}$ 2.6 (3-amino-3-deoxy-D-glucose) and 1.6 (2,5-dideoxystreptamine).

5,4′-Dideoxy-5,4′-diepichlorokanamycin A (8). A suspension of **3** (161 mg) in 80% aqueous acetic acid was stirred at 90 °C for 45 min. The resulting clear solution was hydrogentated with palladium black under atmospheric pressure of hydrogen at room temperature for 20 min. The crude product was chromatographed over CM-Sephadex C-25 (NH_4 form, 0→0.1 M aqueous ammonia) to give a solid of **8**, 71.5 mg (84% as the monocarbonate monohydrate), $[\alpha]_D^{25}$ +146° (*c* 1, water); PPC: $R_{f\ \text{kanamycin A}}$ 2.5; TLC (1-butanol–ethanol–chloroform–10 M aqueous ammonia=4 : 7 : 2 : 7): R_f 0.32 (*cf.* kanamycin A, R_f 0.18); ^{1}H-NMR (as the HCl salt, in D_2O): δ=5.10 (1H dd, $J_{3',4'}$ 4 Hz, $J_{4',5'}$ 1 Hz, H-4′), 5.63 (1H t, $J_{4,5}=J_{5,6}$ 3 Hz, H-5).

Found: C, 38.21; H, 6.19; N, 9.25; Cl, 12.05%. Calcd for $C_{18}H_{34}N_4O_9Cl_2 \cdot H_2CO_3 \cdot H_2O$: C, 37.94; H, 6.36; N, 9.32; Cl, 11.79%.

Methanolysis of 8. To a suspension of **8** (56.8 mg, as the 0.8 carbonate) in dry methanol (4 ml) was added Amberlite CG120 resin (H form, 200—400 mesh, dried *in vacuo* at 60 °C), and the mixture was stirred in a sealed tube at 100 °C for 4.5 h. The mixture was filtered, and the solid was washed with 1 M aqueous ammonia. The filtrate and washings combined were concentrated to give a solid (46.7 mg). The solid showed, on TLC with 1-butanol–ethanol–chloroform–10 M ammonia (4 : 7 : 2 : 7), spots at R_f 0.60 (**10**), 0.58 (minor), 0.55 (**9**), and 0.42 (**11**). The solid was chromatographed over CM-Sephadex C-25 (NH_4 form, 0→0.1 M aqueous ammonia) to give solids of **9** (16.2 mg, 82% as the 0.1 carbonate), **10** (8.0 mg, 38% as the free base), and **11** (10.2 mg, 50% as the 0.3 carbonate) (cited in order of elution).

9: $[\alpha]_D^{25}$ +116° (*c* 1, water) (lit,[12] +144°, lit,[13] +136°); ^{1}H-NMR (20% ND_3 in D_2O): δ=3.93 (3H s, OCH_3), 5.25 (1H d, $J_{1,2}$ 3.8 Hz, H-1).

Found: C, 42.28; H, 7.44; N, 6.81%. Calcd for $C_7H_{15}NO_5 \cdot 0.1H_2CO_3$: C, 42.75; H, 7.68; N, 7.06%.

10: $[\alpha]_D^{25}$ +208° (*c* 1, water); ^{1}H-NMR (20% ND_3 in D_2O): δ=4.98 (1H dd, $J_{3,4}$ 3.3 Hz, $J_{4,5}$ 1 Hz, H-4), 5.33 (1H d, $J_{1,2}$ 3.8 Hz, H-1).

Found: C, 39.54; H, 6.50; N, 6.34; Cl, 16.54%. Calcd for $C_7H_{14}NO_4Cl$: C, 39.72; H, 6.67; N, 6.62; Cl, 16.75%.

11: ^{1}H-NMR (20% ND_3 in D_2O): δ=5.03 (1H t, $J_{4,5}=J_{5,6}$ 3.3 Hz, H-5).

Found: C, 37.99; H, 6.63; N, 13.64%. Calcd for $C_6H_{13}N_2O_2Cl \cdot 0.3H_2CO_3$: C, 37.98; H, 6.88; N, 14.06%.

Methyl 6-Amino-4-chloro-4,6-dideoxy-α-D-galactopyranoside (10) Obtained from 13. A solution of **13** (55.0 mg) in 1,4-dioxane–

methanol (2 : 1, 1 ml) was hydrogenated with palladium black in the usual manner to give a solid of **10**, 28.9 mg (86% as the base).

Methyl 6-Benzyloxycarbonylamino-6-deoxy-α-D-glucopyranoside (12). A mixture of methyl 6-amino-6-deoxy-α-D-glucopyranoside[14] (530 mg), benzyl chloroformate (0.46 ml) and anhydrous sodium carbonate (293 mg) in aqueous acetone (1 : 1, 10 ml) was stirred at room temperature for 45 min. Usual work-up gave a solid of **12**, 835 mg (93%), $[\alpha]_D^{25}$ +40° (*c* 0.5, chloroform); IR: 1700, 1560 cm^{-1}.

Found: C, 55.14; H, 6.41; N, 4.28%. Calcd for $C_{15}H_{21}NO_7$: C, 55.04; H, 6.47; N, 4.28%.

Methyl 6-Benzyloxycarbonylamino-4-chloro-4,6-dideoxy-α-D-galactopyranoside (13). To a solution of **12** (516 mg) in dry dichloromethane (15.5 ml)–dry pyridine (0.7 ml) was added sulfuryl chloride (0.47 ml, 4 mol equivalents for **12**) at −78 °C. Successive workup as described for **3** gave a syrup, which was recrystallized from ethanol to give needles of **13**, 329 mg (60%), mp 126—128 °C; $[\alpha]_D^{25}$ +129° (*c* 1, chloroform); TLC (chloroform–ethanol, 8 : 1): R_f 0.37 (*cf.* **12**, R_f 0.23); ^{1}H-NMR (pyridine-d_5–D_2O, 20 : 1): δ=4.90 (1H dd, *J* 1 and 3 Hz, H-4).

Found: C, 52.36; H, 5.89; N, 3.85; Cl, 10.34%. Calcd for $C_{15}H_{20}NO_6Cl$: C, 52.10; H, 5.83; N, 4.05; Cl, 10.25%.

2',3',4',2''-Tetra-O-acetyl-1,3,6',3''-tetrakis(N-benzyloxycarbonyl)-4'',6''-O-cyclohexylidenekanamycin A (14). To a solution of **2** (519 mg) in dry pyridine (10 ml) was added acetic anhydride (0.36 ml) and the solution was kept at room temperature overnight, then more acetic anhydride (0.36 ml) was added and the solution was heated at 50 °C for 4 h. The reaction mixture was then worked up as described for **4** to give a solid of **14**, 537 mg (90%), $[\alpha]_D^{25}$ +76° (*c* 0.5, chloroform); IR: 1240 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ=1.87 (3H), 2.02 (6H), and 2.07 (3H) (each s, $COCH_3$).

Found: C, 60.35; H, 5.99; N, 4.40%. Calcd for $C_{64}H_{76}N_4O_{23}$: C, 60.56; H, 6.04; N, 4.41%.

2',3',4',2''-Tetra-O-acetyl-1,3,6',3''-tetrakis(N-benzyloxycarbonyl)-4'',6''-O-cyclohexylidene-5-deoxy-5-epichlorokanamycin A (15). To a solution of **14** (201 mg) in dry dichloromethane (2 ml)–dry pyridine (0.4 ml) was added sulfuryl chloride (0.06 ml, 5 mol equivalents for **14**) at −78 °C, and the solution was kept at the temperature for 30 min, then at room temperature for 1.5 h. The solution showed, on TLC with chloroform–2-butanone (3 : 2), a single spot at R_f 0.45 (*cf.* **14**, R_f 0.31). The reaction mixture was then worked up as described for **3** omitting the treatment with sodium iodide to give a solid of **15**, 170 mg (83%), $[\alpha]_D^{25}$ +74° (*c* 0.5, *N,N*-dimethylformamide).

Found: C, 59.44; H, 5.87; N, 4.30; Cl, 3.01%. Calcd for $C_{64}H_{75}N_4O_{22}Cl$: C, 59.69; H, 5.87; N, 4.35; Cl, 2.75%.

2',3',4',2''-Tetra-O-acetyl-1,3,6',3''-tetrakis(N-benzyloxycarbonyl)-4'',6''-O-cyclohexylidene-5-deoxykanamycin A (16). Compound **15** (112 mg) was treated with tributylstannane similarly as described for **5** to give a solid of **16**, 96.8 mg (89%), $[\alpha]_D^{25}$ +84° (*c* 0.5, chloroform), ^{1}H-NMR ($CDCl_3$): δ=1.83, 2.00, 2.03, 2.13 (each 3H s, $COCH_3$), 1.0—2.4 (26H, C_6H_{10}, 4$COCH_3$, CH_2 at C-2,5).

Found: C, 61.53; H, 6.22; N, 4.52%. Calcd for $C_{64}H_{76}N_4O_{22}$: C, 61.33; H, 6.11; N, 4.47%.

1,3,6',3''-Tetrakis(N-benzyloxycarbonyl)-4'',6''-O-cyclohexylidene-5-deoxykanamycin A (17). Compound **16** (52.1 mg) was deacetylated as described for **6** (A) to give a solid of **17**, 42.2 mg (93%), $[\alpha]_D^{25}$ +66° (*c* 0.5, *N,N*-dimethylformamide).

Found: C, 60.93; H, 6.28; N, 4.93%, Calcd for $C_{56}H_{68}N_4O_{18}\cdot H_2O$: C, 60.97; H, 6.40; N, 5.08%.

5-Deoxykanamycin A (18). *A) From 17*: The protecting groups of **17** (98.5 mg) were removed as described for **6** (A) to give a solid of **18**, 21.5 mg (42% as the 1.5 carbonate), $[\alpha]_D^{25}$ +124° (*c* 0.5, water) [lit,[15] +101.8° (free base)]; PPC: $R_{f\ kanamycin\ A}$ 0.9; TLC (1-butanol–ethanol–chloroform–10 M aqueous ammonia=4 : 7 : 2 : 7): R_f 0.13; ^{1}H-NMR (D_2O): δ=1.6—3.4 (4H, CH_2 at C-2,5); 5.55 (1H d, *J* 4 Hz, H-1' or 1''), 5.65 (1H d, *J* 3 Hz, H-1'' or 1').

Found: C, 41.94; H, 7.03; N, 9.75%. Calcd for $C_{18}H_{36}N_4O_{10}\cdot 1.5H_2CO_3$: C, 41.71; H, 7.00; N, 9.98%.

PPC of the acidic hydrolyzates of **18** (6 M HCl, 100 °C, 50 min; descending for 2 d): $R_{f\ 2\text{-deoxystreptamine}}$ 2.5 (3-amino-3-deoxy-D-glucose) and 1.6 (6-amino-6-deoxy-D-glucose and 2,5-dideoxystreptamine).

B) From 15: **15** (54.6 mg) was treated with sodium metal in liquid ammonia as described for **6** (B) to give a solid of **18**, 16.0 mg (69% as the 1.3 carbonate).

Found: C, 42.22; H, 7.00; N, 10.26%. Calcd for $C_{18}H_{36}N_4O_{10}\cdot 1.3H_2CO_3$: C, 42.21; H, 7.09; N, 10.20%.

5-Deoxy-5-epichlorokanamycin A (19). Compound **15** (252 mg) was treated as described for **6** (A) to give a solid of **19**, 81.4 mg (75% as the 0.8 carbonate), $[\alpha]_D^{25}$ +128° (*c* 1, water); PPC: $R_{f\ kanamycin\ A}$ 1.0; ^{1}H-NMR (20% ND_3 in D_2O) δ=5.6 (3H m, H-5,1', 1'').

Found: C, 41.01; H, 6.96; N, 9.98; Cl, 6.32%. Calcd for $C_{18}H_{35}N_4O_{10}Cl\cdot 0.8H_2CO_3$: C, 40.86; H, 6.68; N, 10.14; Cl, 6.42%.

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