SYNTHESIS OF METHYL 6-AMINO-4,6-DIDEOXY-α-D-*XYLO*-HEXOPYRANOSIDE

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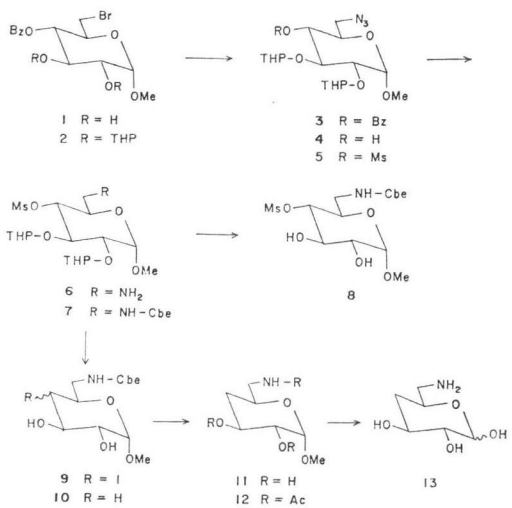
In a previous paper[1] we reported the synthesis of 4′-deoxykanamycin A (Fig. 1) and showed that the compound inhibited kanamycin-resistant organisms that produced aminoglycoside-3′-phosphotransferase II. Since the synthetic 4′-deoxykanamycin A described in the previous paper was characterized mainly by NMR spectroscopy, a definite identification still had not been made for the constitutive new sugar moiety, 6-amino-4,6-dideoxy-D-glucose.* This paper presents the synthesis of methyl 6-amino-4,6-dideoxy-α-D-*xylo*-hexopyranoside (Scheme 1) and its identity with a fragment obtained from the hydrolysis of 4′-deoxykanamycin A.

Two hydroxyl groups of methyl 4-O-benzoyl-6-bromo-6-deoxy-α-D-glucopyranoside[3] (**1**) were protected with a tetrahydropyranyl (THP) group to give **2**. Treatment of **2** with sodium azide in dimethylformamide (DMF) - water afforded the 6-azido derivative (**3**) as a syrup in quantitative yield. IR (liq., cm^{-1}): 2110 (N_3); NMR (DMSO-d_6, δ in ppm): 1.55 (12H, m), 4.5~5.1 (4H, m, anomeric protons & H–4), 7.25~7.95 (5H, m, benzene ring protons). The 4-O-benzoyl group of **3** was removed by treatment with sodium methoxide in dry methanol to give **4** as a syrup in quantitative yield, whose TLC* showed two spots of comparable size at Rf 0.05 and 0.17.

Scheme 1.



Protection of a hydroxyl group with a THP group has been known to yield diastereoisomers in some steroids, sugars and nucleosides[4], and this was found to be the case with compound **4** as evidenced by the following experiments: compound **4** was mesylated to give **5** showing on TLC* two spots at Rf 0.32 and 0.54, which, on separation by silica gel column chromatography, afforded **5a** as prisms (48% from **5**, Rf 0.32) and **5b** as a chromatographically homogeneous syrup (52% from **5**, Rf 0.54). Compound **5a**: m.p. 137.5~138°C, $[\alpha]_D^{26.5}$ −83.3° (*c* 0.5, acetone); IR (KBr): 2100 (N_3), 1180 (SO_2); NMR (acetone-d_6): 1.2~1.9 (12H, m), 3.23 (3H, s, $-SO_2\underline{CH_3}$).

Anal. Calc'd for $C_{18}H_{31}N_3O_9S$: C, 46.44; H, 6.71; N, 9.03; S, 6.89.
Found: C, 46.49; H, 7.03; N, 9.07; S, 7.04.

Compound **5a** was hydrogenated in the presence of palladium on charcoal, and the product (**6a**) was treated with ethyl chloroformate to give **7a**, Rf 0.36**. IR (KBr): 1705 (amide), 1175 (SO_2). Two THP groups of **7a** were removed by treatment with trifluoroacetic acid in aqueous THF to afford **8**, m.p. 129.5~130.5°C, $[\alpha]_D^{27}$ +115° (*c* 0.5, MeOH); NMR (acetone-d_6): 3.25 (3H, s), 4.23 (1H, dd, J=9 & 8.25 Hz, H–4), 4.66 (1H, d, J=3.45 Hz, H–1).

Anal. Calc'd for $C_{11}H_{21}NO_9S$: C, 38.48; H, 6.16; N, 4.08; S, 9.34.
Found: C, 38.85; H, 5.89; N, 3.75; S, 9.29.

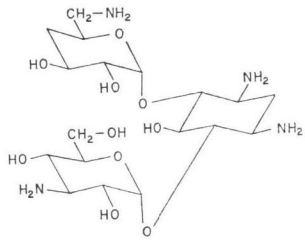
Similarly, **5b** was reduced to give **6b** which was converted to **7b**, Rf 0.45**, IR (KBr): 1725, 1175, and then to **8**, m.p. 130~131°C, $[\alpha]_D^{27}$ +117° (*c* 0.5, MeOH), which was identical with the product derived from **5a**.

In a preparative run, the diastereoisomeric mixture of **7** was reacted with sodium iodide in acetone at 125°C for 32 hours in a sealed tube to give **9** in high yield, indicating that simultaneous

* Preparation of 2,3-di-O-benzyl-4,6-dideoxy-6-ethoxycarbonylamino-α-D-glucose was reported by S. UMEZAWA *et al*[2].

* silica gel TLC, ether - $CHCl_3$ (1:15)
** silica gel TLC, EtOH - $CHCl_3$ (1:30)

Fig. 1. 4′-Deoxykanamycin A



iodination and removal of the THP groups took place as revealed by NMR. Hydrogenation of **9** in the presence of 20% palladium on charcoal and sodium bicarbonate afforded **10** in 94% yield, m.p. 137~139°C, $[\alpha]_D^{24}$ +148° (*c* 0.365, H_2O); IR (KBr): 1695; NMR (D_2O, ppm from HOD): 3.45 (1H, q, J=*ca.* 12 Hz, H–4_{ax}), 2.77 (1H, doublet of double doublets, J_{gem}=12.8 Hz, $J_{3,4}$=4.9 Hz, $J_{4,5}$=2.5 Hz, H–4_{eq}).

Anal. Calc'd for $C_{10}H_{19}NO_6$: C, 48.18; H, 7.68; N, 5.62.
Found: C, 48.30; H, 7.94; N, 5.47.

Hydrolysis of **10** with 1 N sodium hydroxide solution followed by purification of the product on a column of Amberlite CG–50 (NH_4^+) afforded methyl 6-amino-4,6-dideoxy-α-D-glucopyranoside (**11**) in 85% yield, m.p. 88~89°C, $[\alpha]_D^{24}$ +181° (*c* 0.35, H_2O).

Anal. Calc'd for $C_7H_{15}NO_4$: C, 47.45; H, 8.53; N, 7.90.
Found: C, 46.97; H, 8.78; N, 7.72.

The structure of **11** was confirmed by NMR decoupling experiments using the H–O–D signal as an internal reference (Fig. 2). Irradiation of H–1 proton at −0.11 ppm (d, J=3.8 Hz) caused the double doublet signal at 1.26 ppm (J=3.8 and *ca.* 10.5 Hz, H–2) to collapse to a doublet (J=*ca.* 10.5 Hz). Irradiation at the center of 0.7~1.1 ppm (multiplet), which included signals centered at 0.83 ppm (triplet of doublets, J=*ca.* 10.5 and 5 Hz, H–3), resulted in collapse of the doublet-like signal at 2.02 ppm (2H, J=5.6 Hz, H–6) to a singlet, the doublet of double doublets at 2.72 ppm (J=13, 5 and 2 Hz, H–4_{eq}) to a doublet (J=13 Hz) and also the quartet at 3.36 ppm (J=*ca.* 12 Hz, H–4_{ax}) to a doublet (J=13 Hz). Furthermore, irradiation of H–4_{eq} at 2.72 ppm changed the complicated signal of H–3 to a triplet.

Acetylation of **11** with acetic anhydride in pyridine gave **12** in 84% yield, m.p. 125~126°C, $[\alpha]_D^{26.8}$ +141° (*c* 0.5, $CHCl_3$); IR (KBr): 1740, 1650; NMR ($CDCl_3$): 1.46 (1H, q, J=*ca.* 12 Hz, H–4_{ax}), 2.15 (1H, d-dd, J_{gem}=*ca.* 12 Hz, $J_{3,4}$= 5.25 Hz and $J_{4,5}$=2.25, H–4_{eq}), 3.67~4.16 (1H, m, H–5).

Fig. 2. The NMR spectrum of **11** in D_2O at 100 MHz

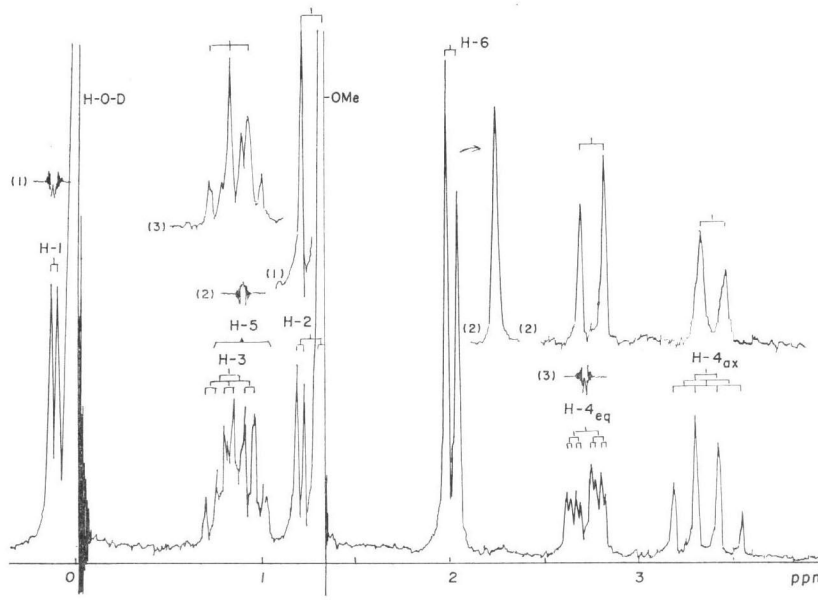


Table 1. Thin-layer chromatography on acid hydrolysates of **11**, 4′-deoxykanamycin A and kanamycin A

TLC*	Rf value of hydrolysate			Identification
	11	4′-Deoxy-kanamycin A	Kanamycin A	
System A		0.04	0.04	Deoxystreptamine
		—	0.29	6-Amino-6-deoxyglucose
	0.33	0.33	—	6-Amino-4,6-dideoxyglucose (**13**)
		0.39	0.39	3-Amino-3-deoxyglucose
		—	0.54	A degradation product of 6-amino-6-deoxyglucose
System B		0.34	0.34	Deoxystreptamine
		—	0.38	6-Amino-6-deoxyglucose
		0.45	0.45	3-Amino-3-deoxyglucose
	0.52	0.52	—	6-Amino-4,6-dideoxyglucose (**13**)

* TLC plate: Merck, silica gel 60 F_{254} (0.25 mm); Detection: ninhydrin.
System A: *n*-Propanol - pyridine - acetic acid - water (51: 20: 6: 24)
System B: chloroform - methanol - 28% aq.ammonia (1: 3: 2)

Anal. Calc'd for $C_{13}H_{21}NO_7$: C, 51.48; H, 6.98; N, 4.62.
Found: C, 51.30; H, 7.16; N, 4.51.

4′-Deoxykanamycin A[1] and kanamycin A were hydrolyzed in 4 N HCl and the hydrolysis product examined by two TLC systems. Compound **11** was also treated under the same condition to give **13**, whose solution was used as a reference in the TLC assay. As shown in Table 1, the hydrolysate of 4′-deoxykanamycin A gave three ninhydrin-positive spots which were identified as deoxystreptamine, 6-amino-4,6-dideoxyglucose (**13**) and 3-amino-3-deoxyglucose, while the hydrolysate of kanamycin A showed TLC spots for 6-amino-6-deoxyglucose and its degradation product but lacked the spot of **13**.

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