SYNTHESIS OF METHYL 6-AMINO-4,6-DIDEOXY-\(\alpha\)-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-\(\alpha\)-D-glucose.\(^*\) This paper presents the synthesis of methyl 6-amino-4,6-dideoxy-\(\alpha\)-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-\(\alpha\)-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\(\equiv\)); NMR (DMSO-d\(_6\), \(\delta\) in ppm): 1.55 (12H, m), 4.55.1 (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.

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, [\(\alpha\)]\(_{D26.5}\) - 3 - 83.3 (c 0.5, acetone); IR (KBr): 2100 (N\(\equiv\)), 1180 (SO\(_2\)); NMR (acetone-d\(_6\)): 1.2 1.9 (12H, m), 3.23 (3H, s, -SO\(_2\)CH\(_3\)).

Anal. Calc'd for C\(_{18}\)H\(_{31}\)N\(_3\)O\(_9\)S: 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, [\(\alpha\)]\(_{27D}\) + 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\(_9\)S: 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, [\(\alpha\)]\(_{27D}\) + 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

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* Preparation of 2,3-di-O-benzyl-4,6-dideoxy-6-ethoxycarbonylamino-\(\alpha\)-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)
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, \([\alpha]_D^0 +148^\circ\) (c 0.365, H2O); IR (KBr): 1695; NMR (D2O, ppm from HOD): 3.45 (1H, q, J=ca. 12 Hz, H\textsubscript{2}N\textsubscript{ax}), 2.77 (1H, doublet of double doublets, J\textsubscript{1,2} = 12.8 Hz, J\textsubscript{2,3} = 4.9 Hz, J\textsubscript{3,4} = 2.5 Hz, H\textsubscript{4eq}).

Anal. Calc’d for C\textsubscript{10}H\textsubscript{19}NO\textsubscript{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\textsubscript{4}+) afforded methyl 6-amino-4,6-dideoxy-a-D-glucopyranoside (11) in 85% yield, m.p. 88~89°C, \([\alpha]_D^{24} +181^\circ\) (c 0.35, H2O).

Anal. Calc’d for C\textsubscript{7}H\textsubscript{15}N\textsubscript{O}\textsubscript{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\textsubscript{eq}) to a doublet (J=13 Hz) and also the quartet at 3.36 ppm (J=ca. 12 Hz, H–4\textsubscript{eq}) to a doublet (J=13 Hz). Furthermore, irradiation of H–4\textsubscript{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, \([\alpha]_D^{26.8} +141^\circ\) (c 0.5, CH\textsubscript{2}Cl\textsubscript{2}); IR (KBr): 1740, 1650; NMR (CDCl\textsubscript{3}): 1.46 (1H, q, J=ca. 12 Hz, H–4\textsubscript{ax}), 2.15 (1H, d-dd, J\textsubscript{1,2} = ca. 12 Hz, J\textsubscript{3,4} = 5.25 Hz and J\textsubscript{4,5} = 2.25, H–4\textsubscript{eq}), 3.67~4.16 (1H, m, H–5).

Fig. 1. 4’-Deoxykanamycin A

Fig. 2. The NMR spectrum of 11 in D\textsubscript{2}O at 100 MHz
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.

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

<table>
<thead>
<tr>
<th>TLC*</th>
<th>Rf value of hydrolysate</th>
<th>Identification</th>
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<tr>
<td></td>
<td>11</td>
<td>4'-Deoxykanamycin A</td>
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<tr>
<td>System A</td>
<td>0.04</td>
<td>0.04</td>
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<td></td>
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<tr>
<td></td>
<td>0.39</td>
<td>0.39</td>
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<tr>
<td>System B</td>
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<td></td>
<td>0.52</td>
<td>0.52</td>
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</tbody>
</table>

* 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)

References