Tetrahedron Letters Vol. 22, pp 77 - 80 0040-4039/81/0101-0077$02.00/0

STEREOSPECIFIC TRANSFORMATION OF D-SUGAR TO L-SUGAR IN COMPLEX AMINOGLYCOSIDE. SYNTHESIS OF A KANAMYCIN B ANALOG HAVING 2,6-DIAMINO-2,4,6-TRIDEOXY-L-ARABINO-HEXOPYRANOSE

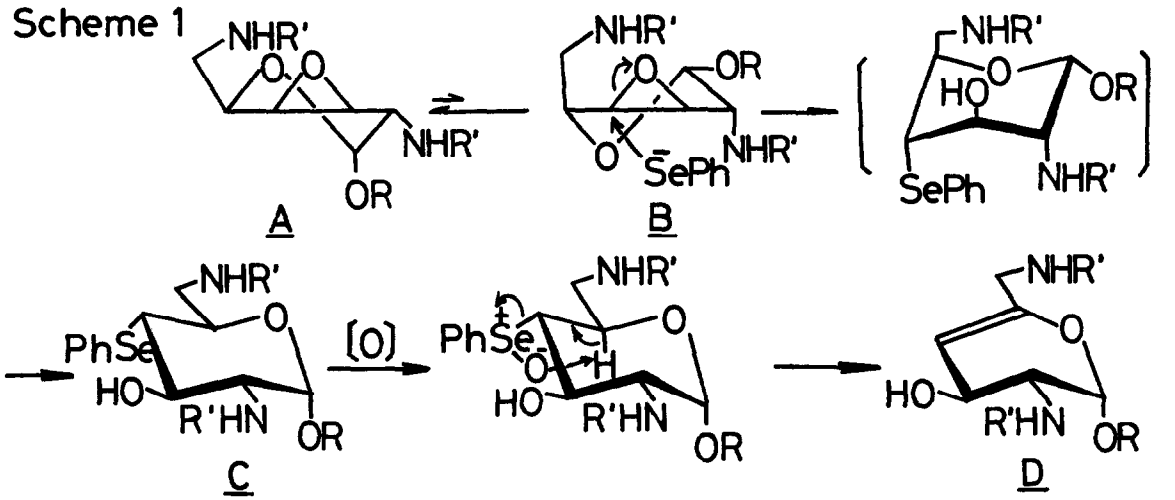
Yoshio Nishimura and Hamao Umezawa
Institute of Microbial Chemistry
14-23, Kamiosaki 3-Chome, Shinagawa-ku, Tokyo, Japan
Sumio Umezawa*
Institute of Bioorganic Chemistry
1614 Ida, Nakahara-ku, Kawasaki-Shi, 211 Japan

Abstract: A 4'-ene derivative of kanamycin B (4) was derived from the epoxide (1) by oxidative elimination of the 4'-phenylseleno group into the allylic alcohol (3). The title compound, O-(2,6-diamino-2,4,6-trideoxy-β-L-arabino-hexopyranosyl)-(1→4)-O-[3-amino-3-deoxy-α-D-gluco-pyranosyl-(1→6)]-2-deoxystreptamine (6) was obtained from 4 by stereospecific hydrogenation followed by removal of the masking groups, changing the D-sugar moiety of the 4-O-glycoside portion into an L-sugar.

In order to develop compounds useful in the treatment of resistant infections, extensive studies have been continued in chemical derivation of kanamycin and structure-activity relationships[1-3]. However, little is known concerning the conformational change of the ring A except for the altered conformations of the ring A due to the 3',4'- or 4',5'-double bond formation as exemplified by 3',4'-unsaturated kanamycin B[1] and sisomicin[4]. The present paper describes a new modification of kanamycin B by the transformation of the ring A (D-sugar) into the L-form. The synthesis involves a novel formation[5] of 4',5'-double bond in the ring A and its dramatic transformation into L-hexopyranoside (ring A') by stereospecific hydrogenation.

For the formation of 4,5-double bond in the ring A it was designed to convert the epoxide (A) into the allylic alcohol (D) by oxidative elimination of 4'-phenylseleno group[6] as shown in Scheme 1. The trans-diequatorial opening of the epoxide was successful by the use of a bulky nucleophile ($PhSe^-$) to give C as expected from literatures[6,7]. The attack of the bulky phenylseleno anion at C-3 is hindered by the anomeric axial group in A, and the less stable conformer B is attacked at C-4 position. An epoxide derivative[8] (1) of kanamycin B was chosen as the starting material.

Scheme 1



Treatment of 1 with sodium phenylselenide generated in situ (PhSeSePh, $NaBH_4$, dimethoxyethane, 60°C) gave 4'-phenylseleno derivative (2) in 68% yield, $[\alpha]_D^{20}$ +58.5° (c 0.8, $CHCl_3$). The regio- and stereochemistry of C-3' and C-4' of 2 were best assigned in the deblocked derivative (7)[9,10] and in the reductive conversion to known 4'-deoxykanamycin B[11]. The derivative 7 was derived from 2 by treatment with sodium methoxide in methanol and then with 50% aqueous trifluoroacetic acid. The deoxy derivative 8 was obtained from 7 by catalytic hydrogenation with Raney Ni. 7: $[\alpha]_D^{20}$ +81.8° (c 0.92, H_2O); PMR (D_2O) δ5.78 (1H d, J=4.0 Hz, H-1'), 5.33 (1H d, J=4.0 Hz, H-1"); ^{13}CNMR (D_2O) δ100.8 (C-1'), 99.7 (C-1"), 72.9 (C-3'), 57.6 (C-4'). 8: $[\alpha]_D^{20}$ +125° (c 1.0, H_2O) [Lit.[11] +122° (c 0.25, H_2O)]; ^{13}CNMR (D_2O) δ101.9 (C-1'), 100.7 (C-1"), 36.81 (C-4'). ^{13}CMR spectrum of 7 shows 13.6 ppm up-field shift for C-4' at δ57.6 compared with that of kanamycin B at δ71.2[12], clearly indicating the presence of phenylseleno group at C-4'. All spectral means (PMR, ^{13}CNMR, IR) and specific rotation of 8 were superimposable to those of authentic sample of 4'-deoxykanamycin B[11], indicating the equatorial hydroxy group at C-3'.

Oxidation of 2 with m-chloroperbenzoic acid (mCPBA) followed by thermal elimination[6] (mCPBA, 4-dimethylaminopyridine, CH_2Cl_2, room temperature, and then reflux in toluene) produced the allylic alcohol (3)[9,10] in 60.6%: $[\alpha]_D^{20}$ +84.5° (c 1.4, $CHCl_3$); ^{13}CNMR ($CDCl_3$) δ147.7 (C-5'), 100 (C-1', C-1"), 101.4 (C-4'); PMR ($CDCl_3$) δ5.6 (1H broad s, H-4').

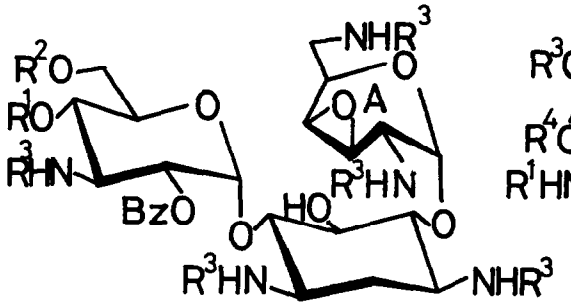
Debenzoylation of 3 with sodium methoxide in methanol gave the triol (4)[9,10] in 99%: $[\alpha]_D^{20}$ +50° (c 1.0, $CHCl_3$); ^{13}CNMR ($CDCl_3$) δ147.5 (C-5'), 101.4 (C-4'), 100 (C-1', C-1").

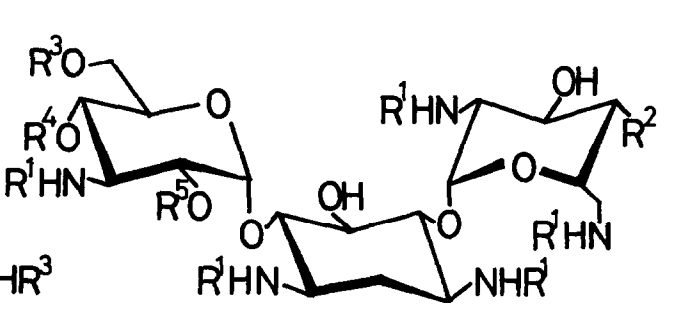
Stereospecific hydrogenation[13] of 4 was best achieved by catalytic hydrogenation with Adams' catalyst in ethanol at room temperature under atmospheric pressure to give 5[9,10] in 89%: $[\alpha]_D^{20}$ +35.7° (c 0.84, $CHCl_3$). ^{13}CNMR spectrum of 5 showed no peak around δ147.5 and 101.4, indicating that 5 has no corresponding double bond.

Finally, removal of the t-butoxycarbonyl and cyclohexylidene groups by treatment with 50% aqueous trifluoroacetic acid at room temperature afforded O-(2,6-diamino-2,4,6-trideoxy-β-L-arabino-hexopyranosyl)-(1→4)-O-[3-amino-3-deoxy-α-D-glucopyranosyl-(1→6)]-2-deoxystreptamine (6) in 77%: $[\alpha]_D^{20}$ +94.5° (c 0.75, H_2O); ^{13}CNMR (D_2O) δ101.0 (C-1', C-1"), 72.7 (C-5"), 30.01

(C-4'); PMR (D_2O) δ5.40 (1H d, $J_{1',2'}$=1.5 Hz, H-1'), 5.36 (1H d, $J_{1'',2''}$=4.0 Hz, H-1''), 3.29 (1H dd, $J_{1',2'}$=1.5, $J_{2',3'}$=3.5 Hz, H-2'). ^{13}CNMR spectrum of 6 showed ~41 ppm up-field shift for C-4' at δ30.06 compared with that of kanamycin B at δ71.2[12], clearly indicating the methylene carbon at C-4'. The small coupling constants of H-1' (d, $J_{1',2'}$=1.5 Hz) and H-2' (dd, $J_{1',2'}$= 1.5 and $J_{2',3'}$=3.5 Hz) suggested that the conformation of 4-O-glycoside portion (ring A') was a skew boat ($B_{4,1}$).

The semisynthetic aminoglycoside 6 was found to have a weak antibacterial activity.





1: R^1,R^2=⟨⟩, R^3=Boc

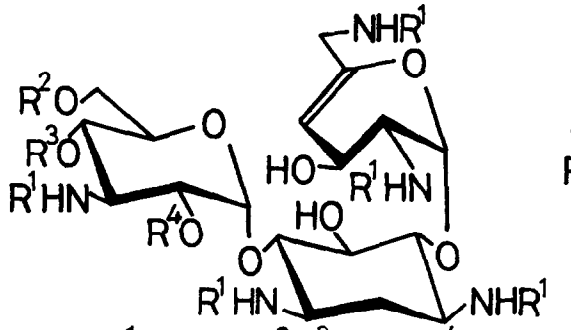
Boc=$COOC(CH_3)_3$

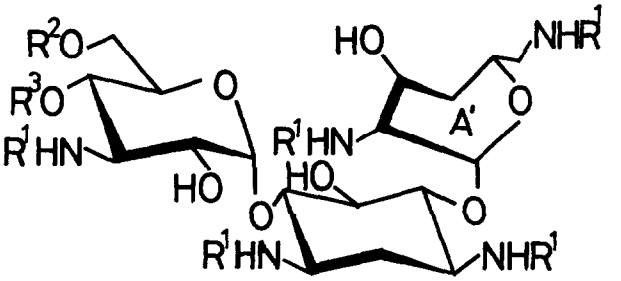
Bz=COC_6H_5

2: R^1=Boc, R^2=SePh, R^3,R^4=⟨⟩, R^5=Bz

7: $R^1=R^3=R^4=R^5$=H, R^2=SePh

8: $R^1=R^2=R^3=R^4=R^5$=H





3: R^1=Boc, R^2,R^3=⟨⟩, R^4=Bz

4: R^1=Boc, R^2,R^3=⟨⟩, R^4=H

5: R^1=Boc, R^2,R^3=⟨⟩

6: $R^1=R^2=R^3$=H

Acknowledgements: We wish to thank Dr. H. Naganawa, Institute of Microbial Chemistry, for PMR spectra and Dr. E. Akita, Central Research Laboratories, Meiji Seika Kaisha Ltd., for his helpful advices and encouragement.

References and Notes

1) S. Umezawa, Advan. Carbohyd. Chem. Biochem., 30, 111-182 (1974).

2) H. Umezawa, Advan. Carbohyd. Chem. Biochem., 30, 183-225 (1974).

3) D. A. Cox, K. Richardson, B. C. Ross, in P. G. Sammes (Ed.) Topics in Antibiotic Chemistry, Vol. 1, Ellis Horwood, Chichester, England, 1977, pp. 5-90.

4) M. Kugelman, A. K. Mallams, H. F. Vernay, J. Antibiot., 26, 394 (1973).

5) Little is known concerning the 4,5-unsaturation of hexopyranoside. For the formation of the 4,5-double bond by β-elimination of the 6-aldehyde derivative of a glycoside, see S. Hanessian, G. Rancourt, Can. J. Chem., 55, 1111 (1977).

6) K. B. Sharpless, R. F. Lauer, J. Am. Chem. Soc., 95, 2697 (1973).

7) K. Capek, J. Nemec, J. Jary, Collect. Czech. Chem. Commun., 33, 1758 (1968).

8) T. Yoneta, S. Shibahara, T. Matsuno, S. Tohma, S. Fukatsu, S. Seki, H. Umezawa, Bull. Chem. Soc. Jpn, 52, 1131 (1979).

9) This compound has been fully characterized by spectral means and elemental composition determined by mass spectroscopy and elemental analysis.

10) 3: ^{13}CNMR δ166.21, 157.37, 155.41, 155.23, 147.66, 133.51, 130.10, 129.20, 128.58, 101.35, 100.01, 99.08, 97.86. 4: ^{13}CNMR δ157.61, 156.15, 155.39, 147.50, 101.41, 100.03, 99.78, 99.29; mass spectrum (FD) m/e 1045. 5: ^{13}CNMR δ154.62, 154.33, 153.96, 153.64, 97.44, 96.92, 96.67. 6: 100 MHz-NMR δ5.40 (1H d, J=1.5 Hz), 5.36 (1H d, J=4.0 Hz), 3.83 (1H dd, J=4.0, 10 Hz), 3.29 (1H dd, J=1.5, 3.5 Hz), 2.31 (1H dt, J=4.0, 13 Hz), 1.4-2.1 (3H m); ^{13}CNMR δ100.96, 88.47, 87.18, 74.96, 73.44, 72.69, 70.03, 61.01, 55.03, 53.26, 51.52, 49.97, 45.71, 36.28, 30.06. 7: 100 MHz-NMR δ8.05 (2H m), 7.78 (3H m), 5.78 (1H d, J=4.0 Hz), 5.32 (1H d, J=4.0 Hz); ^{13}CNMR δ138.08, 130.34, 130.26, 124.78, 100.76, 99.67, 88.97, 84.08, 75.66, 72.93, 72.58, 70.29, 70.08, 61.14, 57.56, 55.04, 51.14, 50.15, 48.10, 43.82, 35.92. 8: 80 MHz-NMR δ5.65 (1H d, J=4.0 Hz), 5.35 (1H d, J=4.0 Hz); ^{13}CNMR δ101.89, 100.70, 88.75, 87.27, 75.35, 72.92, 72.64, 70.70, 70.14, 68.89, 61.18, 57.64, 55.05, 51.18, 50.16, 45.42, 36.81, 36.31.

11) Y. Abe, S. Nakagawa, K. Fujisawa, T. Naito, H. Kawaguchi, J. Antibiot., 30, 1001 (1977).

12) K. F. Koch, J. A. Rhoades, E. W. Hagaman, E. Wenkert, J. Am. Chem. Soc., 96, 3300 (1974).

13) Hydrogenation occurred only from sterically less hindered side (β-side).

(Received in Japan 15 September 1980)