Tetrahedron Letters,Vol.23,No.1,pp 85-86,1982 0040-4039/82/010085-02$03.00/0
Printed in Great Britain

A NOVEL DEAMINATIVE CYCLIZATION OF AMINOGLYCOSIDE. SYNTHESIS OF A KANAMYCIN B VARIANT HAVING 2-OXA-5-AZABICYCLO[2,2,2]OCT-1,5-DIENE RING

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Abstract: The 3',5'-diene derivative of kanamycin B (2) was obtained from a 4'-ene derivative of kanamycin B (1) by treatment with trimethyl orthoacetate. Formation of the title compound (4) from 2 by deaminative cyclization with sodium methoxide followed by treatment with trifluoroacetic acid was described.

In connection with our interest in development of aminoglycoside antibiotics useful in the treatment of resistant infections[1-3], we have investigated the chemical modification of kanamycin B by conformational change[4,5]. The present paper describes a modification of kanamycin B by bicyclic ring formation in the 4-O-glycoside portion (ring A).

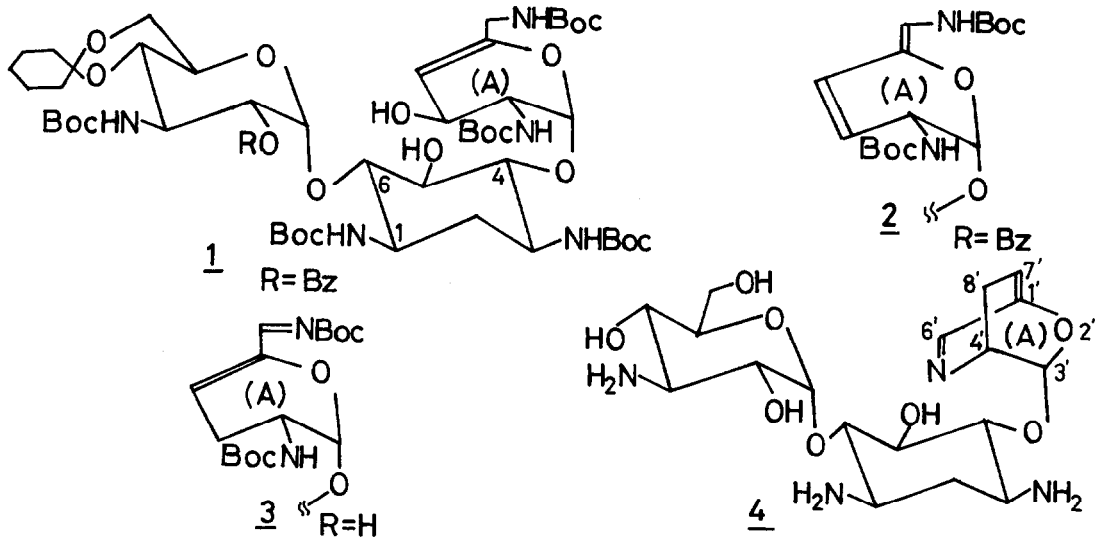
In the preceeding paper, we have reported the formation of a 3',5'-diene kanamycin B derivative (2) which is thought to be formed by deprotonation at 6', as one of two products by treating a kanamycin B derivative (1) containing an allylic alcohol system with $MeCu\cdot BF_3$ "ate" complex[6]. In this paper another synthesis of 2 from 1 by use of trimethyl orthoacetate[7], and a novel transformation of 2 into 2-oxa-5-azabicyclo[2,2,2]oct-1,5-dienyl derivative (4) through an enamine (3) were described.

Treatment of 1 with trimethyl orthoacetate ($H_3CC(OCH_3)_3$, $(CH_3)_3CCOOH$, reflux) gave the 3',5'-diene derivative (2) in 43% yield: $[\alpha]_D^{20}$ +35° (c 0.5, $CHCl_3$); identical with that described[6] previously.

Treatment of 2 with sodium methoxide in methanol gave the enamine derivative (3) with debenzoylation in 67% yield: $[\alpha]_D^{20}$ +5.6° (c 0.54, $CHCl_3$); 100 MHz-PMR ($CDCl_3$) δ6.02 (1H dt) with a small coupling, J=2 and 10 Hz, H-4'); ^{13}C NMR ($CDCl_3$) δ152.49 (C-5'), 109.1 (C-4'), 100.4 (C-1' (?)) and 100.3 (C-1" (?)).

Removal of the t-butoxycarbonyl and cyclohexylidene groups of 3 by treatment with 50% aqueous trifluoroacetic acid followed by resin column chromatography (CG50 (NH_4^+)) gave 4-O-(2-oxa-5-azabicyclo[2,2,2]oct-1,5-diene-3-yl)-6-O-(3-amino-3-deoxy-α-D-glucopyranosyl)-2-deoxystreptamine (4) in 54% yield: $[\alpha]_D^{20}$ +62.9° (c 0.13, H_2O); 250 MHz-PMR (D_2O) δ5.62 (1H d, J=4 Hz, H-1"), 6.01 (1H, d, J=2 Hz, H-3'), 6.03 (1H s, H-7'), 7.96 (1H s, H-6'); ^{13}C-NMR (D_2O)

δ25.0 (C-8'), 35.5 (C-2), 47.1 (C-3), 51.0 (C-1), 55.2 (C-3"), 61.2 (C-6"), 66.6 (C-4'), 69.9 (C-4"), 72.3 (C-3"), 73.1 (C-5"), 76.6 (C-5), 80.8 (C-4), 88.0 (C-6), 99.4 (C-1"), 100.9 (C-3'), 115.8 (C-7'), 146.2 (C-1') and 161.4 (C-6').



1 R=Bz 2 R=Bz 3 R=H 4

To our knowledge, this is the first synthesis of the 2-oxa-5-azabicyclooctadiene ring from a 2,6-diamino-2,6-dideoxy-D-glucoside by deaminative cyclization. It should be noted that in naturally occurring aminoglycoside antibiotics, fortimicin AH, AI[8] and a component of gentamicins[9] have 2-oxa-5-azabicyclo[2,2,2]oct-5-ene ring.

The above methodology may be useful for the synthesis of optically active substituted piperidines as a synthon to alkaloids.

Acknowledgement: We wish to thank Professor H. Umezawa, Institute of Microbial Chemistry, for his discussion on this subject, and Dr. H. Naganawa for his discussion on the 250 MHz PMR and ^{13}C NMR spectra.

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(Received in Japan 9 September 1981)