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REGIOSPECIFIC INTRODUCTION OF A BRANCHED-CHAIN TO KANAMYCIN B AND STEREOSPECIFIC TRANSFORMATION OF THE 2,6-DIAMINO-2,6-DIDEOXY-D-GLUCOPYRANOSYL MOIETY INTO 2,6-DIAMINO-2,3,4,6-TETRADEOXY-3-C-METHYL-L-ARABINO OR LYXO-HEXOPYRANOSYL, OR 2-AMINO-2,3,4,6-TETRADEOXY-5-C-METHYL-L-THREO-HEXOPYRANOSYL

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Abstract: 4-O-(2,6-diamino-2,3,4,6-tetradeoxy-3-C-methyl-β-L-*arabino* and *lyxo*-hexopyranosyl) and 4-O-(2-amino-2,3,4,6-tetradeoxy-5-C-methyl-L-*threo*-hexopyranosyl)-6-O-(3-amino-3-decxy-α-D-glucopyranosyl)-2-deoxystreptamine (6, 7 and 12) were synthesized from a kanamycin B derivative (1) by regiospecific methylation and stereospecific hydrogenation followed by removal of masking groups, converting a D-sugar moiety (4-O-glycoside portion) into L-sugar. The unusual conformations of 6 and 7 were determined as boat and skew by 250 MHz PMR spectra respectively.

Since the biochemical mechanism of resistance of kanamycins was clarified in 1967[1], extensive studies[2-4] have been continued for the synthesis of aminoglycoside derivatives useful in treatment of resistant infections. We have previously reported a new modification of kanamycin B by transformation of a D-sugar into L-sugar[5]. In this paper we wish to report further modification of kanamycin B by 3',4'-dideoxy-3'-C-methylation and 3',4'-dideoxy-5'-C-methylation, converting the ring A (D-sugar) into L-form, and its conformational analysis.

For the syntheses of branched-chain sugars, that is, to introduce 3'-deoxy-3'-C-methyl and 5'-C-methyl group into the ring A, regiospecific alkylation of allylic acetate system with $(CH_3)_2CuLi$ and allylic alcohol system with $CH_3Cu\cdot BF_3$ (S_N2') followed by catalytic hydrogenation have been carried out. To our knowledge this is the first successful application of cuprate and borane "ate" complex reagents to amino sugars.

Acetylation of 1[5] with acetic anhydride in pyridine gave allylic acetate (2) in 98% yield, $[\alpha]_D^{20}$ +87.4° (c 1.26, $CHCl_3$).

Treatment of 2 with lithium dimethylcuprate (Me_2CuLi, Et_2O, -15 → 0°C) afforded a diastereomeric mixture (3) of 3'-C-methyl derivatives in 51% yield: ^{13}C NMR ($CDCl_3$) δ145.8 (C-5'), 103.8 (C-4') and 100 (C-1' and C-1"). The regiochemistry of substitution was clarified by ^{13}C NMR spectra.

Stereospecific hydrogenation of 3 was best achieved with Adams' catalyst in ethanol at room

temperature under atomospheric pressure followed by chromatographic separation to give 4 and 5 in 33 and 52% yield, respectively. 4: $[\alpha]_D^{20}$ +28.6° (c 2.76, $CHCl_3$). 5: $[\alpha]_D^{20}$ +18.3° (c 3.37, $CHCl_3$).

Finally, removal of the t-butoxycarbonyl and cyclohexylidene group of 4 and 5 by treatment with 70% aqueous trifluoroacetic acid at room temperature gave 4-O-(2,6-diamino-2,3,4,6-tetradeoxy-3-C-methyl-β-L-*arabino* and -L-*lyxo*-hexopyranosyl)-6-O-(3-amino-3-deoxy-α-D-glucopyranosyl)-2-deoxystreptamine (6 and 7) in 68 and 70% yield, respectively. 6: $[\alpha]_D^{20}$ +91° (c 0.65, H_2O). 7: $[\alpha]_D^{20}$ +104° (c 1.2, H_2O).

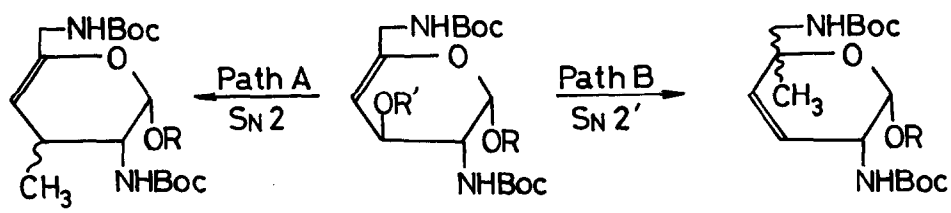
Treatment of 1 with MeCu·BF_3 generated in situ (MeCu, $BF_3 \cdot Et_2O$, Et_2O, -75° ⟶ RT) followed by column chromatography afforded 5'-C-methyl derivative (8), 3',5'-diene derivative (9) and the starting material (1) in 14, 18 and 52% yield, respectively. 8: $[\alpha]_D^{20}$ +79.4° (c 0.42, $CHCl_3$); 80 MHz-PMR ($CDCl_3$) δ5.75 (2H broad s, H-3' and H-4'). 9: $[\alpha]_D^{20}$ +37.14 (c 1.3, $CHCl_3$); 80 MHz-PMR ($CDCl_3$) δ6.0 (2H m, H-3' and H-4').

Debenzoylation of 8 with sodium methoxide in methanol gave the corresponding alcohol (10) in 95% yield: $[\alpha]_D^{20}$ +56° (c 0.25, $CHCl_3$); 80 MHz-PMR ($CDCl_3$) δ5.75 (2H broad s, H-3' and 4').

Removal of the t-butoxycarbonyl and cyclohexylidene groups of 10 by the similar treatment above mentioned gave the free base (11) in 78% yield: $[\alpha]_D^{20}$ +69.76° (c 0.74, H_2O); 250 MHz-PMR (D_2O) δ1.82 (3H s, 5'-CH_3), 5.52 (1H d, J=4 Hz, H-1"), 5.54 (1H d, J=2.5 Hz, H-1'), 6.28 (1H d, J=10 Hz, H-4') and 6.46 (1H dd, J=10 and 5.5 Hz, H-3').

Catalytic hydrogenation of 11 with Adams' catalyst in water afforded 4-O-(2-amino-2,3,4,6-tetradeoxy-5-C-methyl-L-*threo*-hexopyranosyl)-6-O-(3-amino-3-deoxy-α-D-glucopyranosyl)-2-deoxystreptamine (12) in 91% yield: $[\alpha]_D^{20}$ +85.5° (c 0.54, H_2O); 250 MHz-PMR (H_2O) δ1.76 (3H s, 5'-CH_3), 5.47 (1H d, J=2 Hz, H-1') and 5.54 (1H d, J=4 Hz, H-1").

In the sequence of reactions described above, interesting problems of regiospecificity (path A and path B) and stereospecificity (configuration at 3'-C and 5'-C) are involved.

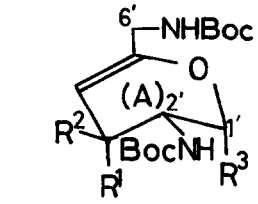


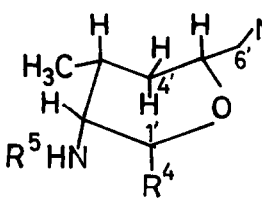
R = H or Ac

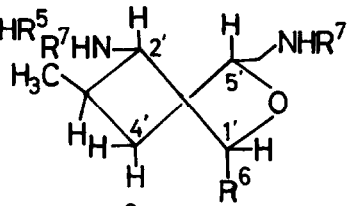
The dialkylcopper-lithium "ate"[6] complexes are known to give substituted products generally by both fashions of direct displacement (S_N2) and allylic rearrangement (S_N2') in the case of γ-unsubstituted allylic substrates, and, in cyclic allylic acetate, substitution generally occurs stereoselectively on the side of the ring opposite to the replaced acetate group[7,8]. However, these regio- and stereoselectivities are controlled by various factors. The regiospecific direct displacement (path A) and loss of stereospecificity shown in our case may be caused by some steric reason of 1'-aglycon (X_2) and electronic reason of the neighbouring 2'- and 6'-t-butoxycarbonylamido groups and ring oxygen to give the products.

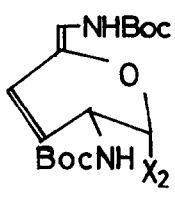
On the other hand, little is known about the γ-alkylation of γ-substituted allylic substrates[9,10]. The regiospecific substitution of allylic alcohol with complete allylic rearrangement (S_N2', path B) was successful with MeCu·BF_3 "ate" complex. The stereospecificity

of substituent was also shown in this case[11]. The novel diene (9) is thought to be formed by deprotonation at 6' with rearrangement of the double bond.







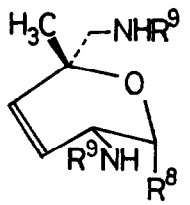


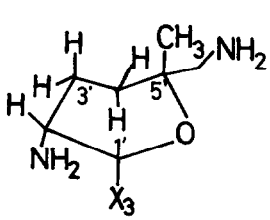
1 R^1=H, R^2=OH, R^3=X_2
2 R^1=H, R^2=OAc, R^3=X_2
3 R^1, R^2=H, CH_3, R^3=X_1

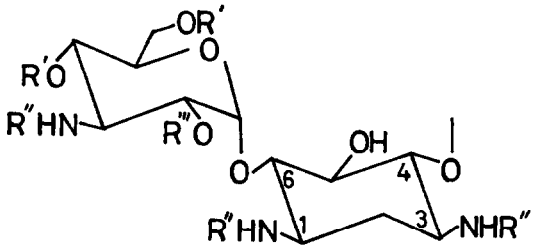
4 R^4=X_1, R^5=Boc
6 R^4=X_3, R^5=H

5 R^6=X_1, R^7=Boc
7 R^6=X_3, R^7=H

9







8 R^8=X_2, R^9=Boc
10 R^8=X_1, R^9=Boc
11 R^8=X_3, R^9=H

12

X_1 R'=⬡, R''=Boc, R'''=H
X_2 R'=⬡, R''=Boc, R'''=Bz
X_3 R'=R''=R'''=H

Either 1C or $B_{4,1}$ conformation was supposed from the coupling patterns and constants of the 1'- and 4'-protons of compound 6[12]. The unusual large coupling constant between 3' and 4'quasi ax protons suggested a boat conformation ($B_{4,1}$)[13] of the pyranose ring (A) of 6.

The coupling patterns and constants concerning the 4'quasi ax, 4'quasi eq and 1'-protons of compound (7)[12] suggested an abnormal skew conformation (S^5_1) of the pyranose ring (A) of 7. The higher chemical shift of 4'-equatorial proton than that of 4'-axial proton, and the difference in coupling constants between 5'-4'quasi eq (2.3 Hz) and 3'-4'quasi ax (5.5 Hz) protons supported the above conclusion[13]. A number of articles on the skew conformations of fused ring systems in carbohydrates[14] have been published. However, to our knowledge, the compound 7 is a rare instance of skew conformation of an unprotected glycoside.

A small coupling constant (J=2 Hz) between 1' and 2'-proton of compound (12) suggested that the pyranose ring (A) has either 1C or boat conformation. However, no NOE was observed between twos of the 5'-CH_3, 1' and 3'-protons, suggesting a boat conformation.

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11) The stereochemistry at 5' could not be clarified by PMR or ^{13}C NMR spectra, or specific rotation. Methylation must have occurred from sterically less hindered side (β-side)[9].

12) 6: 250 MHz-PMR (D_2O) δ1.53 (3H d, J=7.5 Hz, 3'-CH_3), 1.70 (1H q, J=12.8 Hz, H-4'quasi ax), 1.78 (1H q, J=13.0 Hz, H-2ax), 1.95 (1H broad dt, $J_{3',4'quasi\ eq}$=4, $J_{4'quasi\ eq,5'}$= 3 and $J_{4'quasi\ ax,4'quasi\ eq}$=12.8 Hz, 4'quasi eq), 2.52 (1H dt, J=5.0 and 13.0 Hz, H-2eq), 5.34 (1H d, J=1.5 Hz, H-1') and 5.55 (1H d, J=4.0 Hz, H-1").
7: 250 MHz-PMR (D_2O) δ1.62 (3H d, J=7.5 Hz, 3'-CH_3), 1.73 (1H q, J=13.0 Hz, H-2ax), 1.80 (1H dt, $J_{3',4'quasi\ eq}$=$J_{4'quasi\ eq,5'}$=2.3 and $J_{4'quasi\ ax,4'quasi\ eq}$=13.6 Hz, H-4'quasi eq), 2.16 (1H dq, $J_{3',4'quasi\ ax}$=5.5, $J_{4'quasi\ ax,5'}$=12.8 and $J_{4'quasi\ ax,4'quasi\ eq}$=13.6 Hz, H-4'quasi ax), 2.48 (1H dt, J=4.5 and 13.0 Hz, H-2eq), 5.53 (1H d, J=3.5 Hz, H-1") and 5.54 (1H d, J=$\sim$1 Hz, H-1').

13) No NOE between twos of the 1', 3' and 5' protons also supported this conclusion.

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