Communications to the editor

SYNTHESIS OF 1-N-((s)-4-AMINO-2-HYDROXYBUTYRYL)-3′, 4′-DIDEOXYNEAMINE

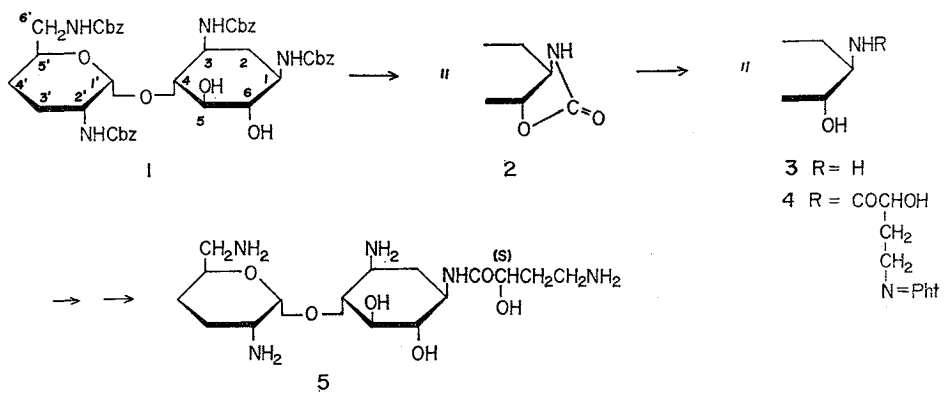
Sir:

As reported in a previous paper[1], we have accomplished the synthesis of butirosin B[2] starting from ribostamycin[3] *via* a cyclic carbamate intermediate. Butirosin B is active against most of organisms resistant to ribostamycin. This unique activity can be ascribed to the presence of an (s)-4-amino-2-hydroxybutyryl residue which prevents the binding of the neamine moiety to the enzyme phosphorylating the 3′-hydroxyl group. Recently the 1-N-((s)-4-amino-2-hydroxybutyryl) derivative of kanamycin was reported by KAWAGUCHI *et al.*[4] to be strongly antibacterial both to kanamycin-sensitive and resistant bacteria. Therefore, to prove the contribution of the residue attached to the amino group at C-1 of deoxystreptamine, we undertook to synthesize the title compound starting from 3′, 4′-dideoxyneamine[5].

The four amino groups of 3′, 4′-dideoxyneamine were protected with benzyloxycarbonyl chloride in 70% methanol to give tetra-N-benzyloxycarbonylneamine (**1**) in a yield of 80%, $[\alpha]_D^{25}$+45.4° (*c* 2, chloroform), which was then treated with sodium hydride as described in a previous paper[1]. Compound **1** was dissolved in dry DMF and after displacement of the air in the reaction vessel with nitrogen, 3 molecular equivalents of sodium hydride were added, and the mixture was agitated in an ice bath for 4 hours. The resulting clear solution was neutralized with acetic acid and poured into a mixture of a large amount of chloroform-water. The crude product obtained from the organic layer was purified by column chromatography with silica gel and chloroform-ethanol (20:1) to give tri-N-benzyloxycarbonyl-3′, 4′-dideoxyneamine-1, 6-carbamate (**2**) in a yield of 62%, mp 107~110°C, $[\alpha]_D^{25}$+58° (*c* 1.9, chloroform). ir: 1765 cm^{-1} (trans-fused cyclic carbamate[6]). [Calcd. for $C_{37}H_{42}N_4O_{11}$: C 61.83, H 5.89, N 7.80; Found: C 61.92, H 5.99, N 7.67].

Selective hydrolysis of the cyclic carbamate to the free aminol was effected with barium hydroxide in aqueous dioxane as described in a previous paper[1], and the resulting ninhydrin-positive product, 3, 2′, 6′-tri-N-benzyloxycarbonyl-3′, 4′-dideoxyneamine (**3**) was condensed with (s)-2-hydroxy-4-phthalimido-butyric acid by the method described in a previous paper[1] and 3, 2′, 6′-tri-N-benzyloxycarbonyl-3′, 4′-dideoxy-1-N-((s)-2-hydroxy-4-phthalimidobutyryl) neamine (**4**) was obtained in a yield of 62% from **2**, mp 228~230°C (recrystallized from methanol), $[\alpha]_D^{22}$+32° (*c* 1.5, chloroform), ir: 1705, 1690, 1655, 1535 cm^{-1}. [Calcd. for $C_{48}H_{53}N_5O_{14}\cdot H_2O$: C 61,20, H 5.89, N 7.43; Found: C 61.34, H 5.93, N 7.39].

Compound **4** was then treated with 4% hydrazine hydrate in 80% ethanol-dioxane (1:1) at 60°C for 2 hours to remove the phthaloyl group and then with palladium black and hydrogen in aqueous dioxane (1:1) to remove the benzyloxycarbonyl groups to give the final product, which was purified by a column of CM-Sephadex C-25 (NH_4^+ form) with ammonia



1 2 3 R= H 4 R = COCHOH CH2 CH2 N=Phf 5

Table 1. Antibacterial spectra of **5**, 3′, 4′-dideoxyneamine and neamine

Test organisms*	Minimal inhibitory concentration (mcg/ml)		
	5	3′, 4′-Dideoxy-neamine	Neamine
Staphylococcus aureus FDA 209P	3.12	6.25	6.25
Sarcina lutea PCI 1001	25	50	>100
Bacillus subtilis NRRL B-558	<0.39	0.39	0.78
Klebsiella pneumoniae PCI 602	6.25	25	12.5
〃 type 22 #3038	12.5	25	>100
Salmonella typhosa T-63	1.56	3.12	3.12
Escherichia coli NIHJ	3.12	12.5	12.5
〃 K-12	3.12	6.25	6.25
〃 〃 R-5	50	50	>100
〃 〃 ML 1629	3.12	12.5	>100
〃 〃 ML 1630	3.12	12.5	>100
〃 〃 ML 1410	3.12	6.25	12.5
〃 〃 〃 R 81	12.5	25	>100
〃 〃 LA 290 R 55	3.12	6.25	6.25
〃 〃 〃 R 56	3.12	6.25	12.5
〃 〃 〃 R 64	3.12	12.5	6.25
〃 〃 C 600 R 135	12.5	12.5	12.5
〃 〃 W 677	3.12	6.25	6.25
〃 〃 JR 66/W 677	12.5	25	>100
〃 J 5 R 11-2	6.25	6.25	>100
Pseudomonas aeruginosa A 3	6.25	25	>100
〃 No. 12	6.25	25	>100
〃 GN 315	>100	>100	>100
〃 TI-13	6.25	25	>100
〃 99	25	50	>100
Proteus rettgeri GN 311	25	50	100
〃 GN 466	12.5	25	25
Mycobacterium smegmatis ATCC 607**	6.25	25	12.5

* Agar dilution streak method (nutrient agar, 37°C, 18 hours).
** 48 hours.

(0~0.5 N). At the concentration of 0.4 N ammonia, the desired product was eluted, and further treatment gave 1-N-((s)-4-amino-2-hydroxybutyryl)-3′, 4′-dideoxyneamine (**5**) as a monohydrate in a yield of 53 % from **4**, $[\alpha]_D^{22}+38°$ (*c* 0.85, water), ir: 1650, 1560 cm^{-1}. $Rf_{3',4'\text{-dideoxyneamine}}$ 0.47 (on peper chromatography with 1-butanol-pyridine-wate-acetic acid (6:4:3:1)). [Calcd. for $C_{16}H_{33}N_5O_6 \cdot H_2O$: C 46.93, H 8.62, N 17.10; Found: C 46.92, H 8.52, N 17.24].

Retention of configuration at C-2 of the side residue in **5** was confirmed by acidic hydrolysis of the compound. By treatment of **5** as described in the literature[2] for butirosins A and B, (s)-4-amino-2-hydroxybutyric acid, $[\alpha]_D^{20}-27°$ (*c* 1, water) (lit.[2] −28.2°) was isolated.

The synthetic 3′, 4′-dideoxyneamine derivative (**5**) showed stronger antibacterial activity (Table 1) than that of the parent substance, 3′,-4′-dideoxyneamine, against both sensitive and resistant bacteria.

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References

1) IKEDA, D.; T. TSUCHIYA, S. UMEZAWA & H. UMEZAWA: Synthesis of butirosin B. J. Antibiotics 25 : 741-742, 1972

2) a) WOO, P.W.K.; H.W. DION & Q.R. BARTZ: Butirosins A and B, aminoglycosidic antibiotics. I. Structural units. Tetrahedron Letters 1971: 2617~2620, 1971

b) WOO, P.W.K.: Butirosins A and B, aminoglycosidic antibiotics. II. Mass spectrometric study. Tetrahedron Letters 1971: 2621~2624, 1971

c) WOO, P.W.K.; H.W. DION & Q.R. BARTZ: Butirosins A and B. aminoglycosidic antibiotics. III. Structure. Tetrahedron Letters 1971: 2625~2628, 1971

3) AKITA, E.; T. TSURUOKA, N. EZAKI &. T. NIIDA: Studies on antibiotic SF-733, a new antibiotic. II. J. Antibiotics 23 : 173~183, 1970

4) KAWAGUCHI, H.; T. NAITO, S. NAKAGAWA & K. FUJISAWA: BB-K8, A new semisynthetic aminoglycoside antibiotic. J. Antibiotics 25 : 695~708, 1972

5) UMEZAWA, S.; T. TSUCHIYA, T. JIKIHARA & H. UMEZAWA: Synthesis of 3′, 4′-dideoxyneamine active against kanamycin-resistant *E. coli* and *P. aeruginosa*. J. Antibiotics 24 : 711~712, 1971

6) UMEZAWA, S.; Y. TAKAGI & T. TSUCHIYA: Studies on aminosugars. XXVI. A new method for the simultaneous protection of amino and hydroxyl groups in aminosugars and aminocyclitols. Bull. Chem. Soc. Japan 44 : 1411~1415, 1971