SYNTHESIS OF 3′-DEOXYBUTIROSIN B

Sir:

As reported in a previous paper[1], 3′-deoxyribostamycin exhibits a stronger activity than 3′, 4′-dideoxyribostamycin[2] in inhibiting growth of various bacteria including those which produce kanamycin-neomycin phosphotransferase II[3] (P-ase II). However, it does not inhibit resistant organisms which produce kanamycin-neomycin phosphotransferase I[4] (P-ase I). Butirosin B[5], 1-N-((s)-4-amino-2-hydroxybutyryl) ribostamycin, inhibits resistant organisms with P-ase I but not those with P-ase II. The titled compound, 3′-deoxybutirosin B is, therefore, expected to be active against both resistant organisms.

Tetra-N-benzyloxycarbonyl-3′, 4′;2″, 3″-di-O-cyclohexylidene-5″-O-(1-methoxycyclohexyl) ribostamycin[6] (**1**) was treated with acetone-40 % acetic acid (5:1) at 37°C for 7.5 hours to afford the demethoxycyclohexyl derivative (**2**) in a yield of 63 %, $[\alpha]_D^{20}$ +23° (*c* 2, $CHCl_3$). [Calcd. for $C_{81}H_{74}N_4O_{18}$: C 63.64, H 6.48, N 4.87. Found C 63.51, H 6.47, N 4.85]. Treatment of **2** with NaH in DMF as described in a previous report[7] gave the corresponding 1, 6-carbamate (**3**) in a yield of 65 %, $[\alpha]_D^{20}$ +26° (*c* 1.8, $CHCl_3$); ir (KBr): 1770, 1720, 1535 cm^{-1}. [Calcd. for $C_{54}H_{66}N_4O_{17}$: C 62.18, H 6.38, N 5.37. Found: C 62.07, H 6.44, N 5.50]. Acetylation of **3** followed by selective removal of the 3′, 4′-O-cyclohexylidene group with acetone - 60 % acetic acid (1:1) at 60°C for 1 hour gave the 5″-O-acetyl derivative (**4**) having free 3′, 4′-hydroxyl groups in a yield of 95 % from **3**, $[\alpha]_D^{20}$ +11° (*c* 1.9, $CHCl_3$). [Calcd. for $C_{50}H_{60}N_4O_{18}$: C 59.75, H 6.02, N 5.57. Found C 59.59, H 6.04, N 5.33]. Selective tosylation of **4** in a manner as described previously[8] gave the corresponding 3′-O-tosyl derivative (**5**) in a yield of 76 %. Similar treatment of **4** with *o*-nitrobenzenesulfonyl chloride gave the corresponding 3′-O-(*o*-nitrobenzenesulfonyl) derivative (**6**) in a yield of 55 %, $[\alpha]_D^{14}$ +6.5° (*c* 2.3, $CHCl_3$). [Calcd. for $C_{56}H_{63}N_5O_{22}S$: C 56.51, H 5.34, N 5.88, S 2.69. Found: C 56.25, H 5.40, N 5.75, S 2.88]. Treatment of **6** with NaI in DMF at 100°C for 1.5 hours gave the 3′-iodo derivative (**7**) in a yield of 55 %, mp 108~110°C, $[\alpha]_D^{14}$ +4.6° (*c* 2.7, $CHCl_3$). [Calcd. for $C_{50}H_{59}N_4O_{17}I$: C 53.86, H 5.34, N 5.03, I 11.38. Found: C 54.23, H 5.49, N 5.02,

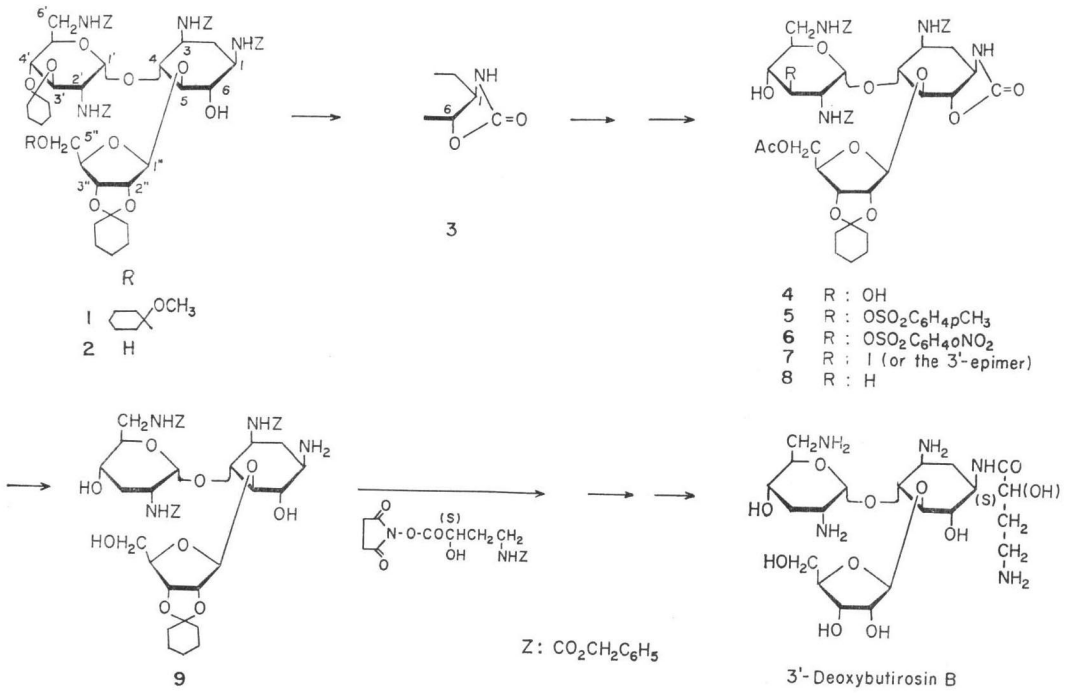

Table 1. Antibacterial spectra of butirosin B and 3′-deoxybutirosin B

Test organisms*	Minimal inhibitory concentration (mcg/ml)	
	Butirosin B	3′-Deoxybutirosin B
Staphylococcus aureus FDA 209P	1.56	0.39
Sarcina lutea PCI 1001	25	25
Bacillus subtilis NRRL B-558	0.2	0.2
Klebsiella pneumoniae PCI 602	0.39	0.39
〃 type 22 #3038	>100	0.78
Salmonella typhosa T-63	0.39	0.39
Escherichia coli NIHJ	0.78	0.78
〃 K-12	0.39	0.2
〃 〃 ML 1629	0.78	0.39
〃 〃 ML 1630	3.12	1.56
〃 〃 ML 1410	0.78	0.78
〃 〃 〃 R 81	3.12	0.78
〃 〃 LA 290 R 55	0.78	0.78
〃 〃 〃 R 56	0.39	0.39
〃 〃 〃 R 64	0.39	0.2
〃 〃 W 677	0.78	0.39
〃 〃 JR 66/W 677	>100	1.56
Pseudomonas aeruginosa A 3	6.25	1.56
〃 〃 No. 12	25	6.25
〃 〃 GN 315	>100	>100
〃 〃 TI-13	12.5	3.12
〃 〃 99	100	12.5
Proteus rettgeri GN 311	6.25	3.12
〃 GN 466	3.12	0.78
Mycobacterium smegmatis ATCC 607**	0.39	0.2

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

I 11.05]. In the iodination, **6** did react with sodium iodide more smoothly than **5**. Hydrogenation of **7** with RANEY nickel in dioxane in the presence of triethylamine gave the 5″-O-acetyl-3, 2′, 6′-tri-N-benzyloxycarbonyl-2″, 3″-O-cyclohexylidene-3′-deoxyribostamycin 1, 6-carbamate (**8**) in a yield of 62 %, $[\alpha]_D^{13}+5°$ (*c* 1, $CHCl_3$). [Calcd. for $C_{50}H_{60}N_4O_{17}$: C 60.72, H 6.11, N 5.66. Found: C 60.35, H 6.20, N 5.52].

Opening[7] of the cyclic carbamate with barium hydroxide gave the ninhydrin-positive product (**9**) quantitatively, which was then coupled with (s)-4-benzyloxycarbonylamino-2-hydroxybutyric acid[9] in THF by the active ester method using N-hydroxysuccinimide and DCC to give the corresponding 1-N-acyl derivative (**10**) in a yield of 40 %, $[\alpha]_D^{18}+2.5°$ (*c* 1, $CHCl_3$). [Calcd. for $C_{59}H_{73}N_5O_{19}\cdot 2H_2O$: C 59.44, H 6.51, N 5.87. Found: C 59.44, H 6.21, N 5.87]. Hydrogenolysis of **10** with Pd black followed by hydrolysis with hydrochloric acid gave the 3′-deoxybutirosin B, which was purified by chromatography on a column of CM Sephadex C-25 with linear gradient ammonia (0~0.4 M); $[\alpha]_D^{24}+27°$ (*c* 2, H_2O); ir (KBr): 1640, 1560 cm^{-1}. [Calcd. for $C_{21}H_{41}N_5O_{11}\cdot H_2CO_3$: C 43.92, H 7.20, N 11.64. Found: C 43.44, H 7.26, N 11.45].

The synthetic 3′-deoxybutirosin B shows a strong antibacterial activity (Table 1) and inhibits resistant organisms with P-ase I (*E. coli* K-12 ML 1629 and 1630) and P-ase II (*E. coli* K-12 JR66/W 677). The activity against sensitive organisms is stronger than those of butirosin B and 3′,4′-dideoxybutirosin B[10].

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References

1) Ikeda, D.; T. Tsuchiya, S. Umezawa & H. Umezawa: Synthesis of 3′-deoxyribostamycin. J. Antibiotics 26: 799~801, 1973
2) Umezawa, S.; T. Tsuchiya, D. Ikeda & H. Umezawa: Syntheses of 3′, 4′-dideoxy and 3′, 4′, 5″-trideoxyribostamycin active against kanamycin-resistant *E. coli* and *P. aeruginosa*. J. Antibiotics 25: 613~616, 1972
3) Yagisawa, M.; H. Yamamoto, H. Naganawa, S. Kondo, T. Takeuchi & H. Umezawa: A new enzyme in *Escherichia coli* carrying R-factor phosphorylating 3′-hydroxyl of butirosin A, kanamycin, neamine and ribostamycin. J. Antibiotics 25: 748~750, 1972
4) Umezawa, H.; H. Yamamoto, M. Yagisawa, S. Kondo, T. Takeuchi & Y.A. Chabbert: Kanamycin phosphotransferase I: Mechanism of cross resisistance between kanamycin and lividomycin. J. Antibiotics 26: 407~411, 1973
5) Woo, P.W.K.; H.W. Dion & Q.R. Bartz: Butirosins A and B, aminoglycoside antibiotics. I. Structural units. Tetrahedron Letters 1971: 2617~2620, 1971; III. Structure. *ibid.* 1971: 2625~2628, 1971
6) Ikeda, D.; T. Suzuki, T. Tsuchiya, S. Umezawa & H. Umezawa: Syntheses of 3′, 4′-dideoxy- and 3′, 4′, 5″-trideoxyribostamycin. Bull. Chem. Soc. Japan 46: 3210~3213, 1973
7) Ikeda, D.; T. Tsuchiya, S. Umezawa & H. Umezawa: Synthesis of butirosin B and its 3′, 4′-dideoxy derivative. Bull. Chem. Soc. Japan 47: 3136~3138, 1974
8) Takagi, Y.; T. Miyake, T. Tsuchiya, S. Umezawa & H. Umezawa: Synthesis of 3′-deoxykanamycin B. J. Antibiotics 26: 403~406, 1973
9) Kawaguchi, H.; T. Naito, S. Nakagawa & K. Fujisawa: BB-K8, a new semisynthetic aminoglycoside antibiotic. J. Antibiotics 25: 695~708, 1972
10) Ikeda, D.; T. Tsuchiya, S. Umezawa, H. Umezawa & M. Hamada: Synthesis of 3′, 4′-dideoxybutriosin B. J. Antibiotics 26: 307~309, 1973