SYNTHESIS OF 3′,3″-DIDEOXY-BUTIROSIN

Sir:

Butirosins A and B have similar antibacterial activity against most strains including common and resistant bacteria, but against some strains, there is a difference between the activities of A and B. A similar difference is also found in the activities of 3′-deoxybutirosins A and B and between 5″-amino-5″-deoxybutirosins A and B.[1] Since the difference is thought to be caused by the orientation of the 3″-hydroxyl group in butirosins, we were interested in removing the group in order to see its effect contributing to the activity of butirosins. In this paper we describe the synthesis of 3′,3″-dideoxybutirosin.

The synthesis was carried out by a route which involves methods similar to the ones described in previous papers.[2,3] To a cold solution of methyl 3-deoxy-2,5-*O*-bis(*p*-nitrobenzoyl)-D-*erythro*-pentofuranoside (**1**)[4] in dichloromethane, hydrogen bromide was introduced until saturation and the solution was kept at 4°C overnight. After evaporation, the residual *β*-1-bromide (**2**) (1 mmol) [PMR($CDCl_3$): δ 6.58 (1H s, H-1)] was condensed with 3,2′-*N*-bis (benzyloxycarbonyl)-1-*N* : 6-*O*-carbonyl-4′,6′-*O*-cyclohexylidene-3′-deoxyparomamine[2] (**3**) (0.35 mmol) in dichloromethane in the presence of mercury (II) cyanide and Drierite. Chromatographic separation (silica gel; $CHCl_3$ - EtOH - NEt_3, 10 : 1 : 0.1) of the condensation products gave 5-*O*-*β*-D-pentofuranosyl derivative (**4**) in 37% yield (based on **3**), $[\alpha]_D^{23}+17°$ (*c* 1, $CHCl_3$). Found: C, 58.99, H 5.24, N 6.33%. Calcd. for $C_{54}H_{57}N_5O_{20}$: C 59.17, H 5.24, N 6.39%. Hydrolysis of **4** in dioxane-acetic acid-water (2 : 3 : 1) (60°C, 5 hours) followed by chromatography (silica gel; $CHCl_3$-EtOH, 20:1) gave **5** (90%), $[\alpha]_D^{25}+23°$ (*c* 0.5, $CHCl_3$). Found: C 56.52, H 4.91, N 6.73%. Calcd. for $C_{48}H_{49}N_5O_{20}$: C 56.75, H 4.86, N 6.89%. Selective tosylation of **5** with tosyl chloride (2.5 mol equivalents for **5**) in pyridine (−20°C, 40 hours) gave, after chromatography (silica gel, $CHCl_3$ - EtOH, 50 : 1), 6′-*O*-tosyl derivative (**6**) in 89% yield, $[\alpha]_D^{23}+17°$ (*c* 1, $CHCl_3$). Found: C 56.48, H 4.76, N 6.02, S 2.89%. Calcd. for $C_{55}H_{55}N_5O_{22}S$: C 56.46, H 4.74, N 5.99, S 2.74%.

Treatment of **6** with sodium azide in DMF (60°C, 7 hours under stirring) gave, after chromatography (silica gel, $CHCl_3$ - EtOH, 30 : 1), the 6′-azido derivative (**7**) in 96% yield, $[\alpha]_D^{23}+15°$ (*c* 1, $CHCl_3$). IR (KBr): 2100 cm^{-1} (N_3). Found: C 55.30, H 4.70, N 10.58%. Calcd. for $C_{48}H_{48}N_8O_{19}$: C 55.38, H 4.65, N 10.77%. Simultaneous hydrolysis of the 1,6-carbamate and *p*-nitrobenzoyl groups of **7** with 0.05 M aqueous barium hydroxide-dioxane (1 : 3, v/v) (60°C, 2 hours) followed by coupling with the *N*-hydroxysuccinimide ester[5] of (*S*)-4-benzyloxycarbonylamino-2-hydroxybutyric acid in THF in a manner as

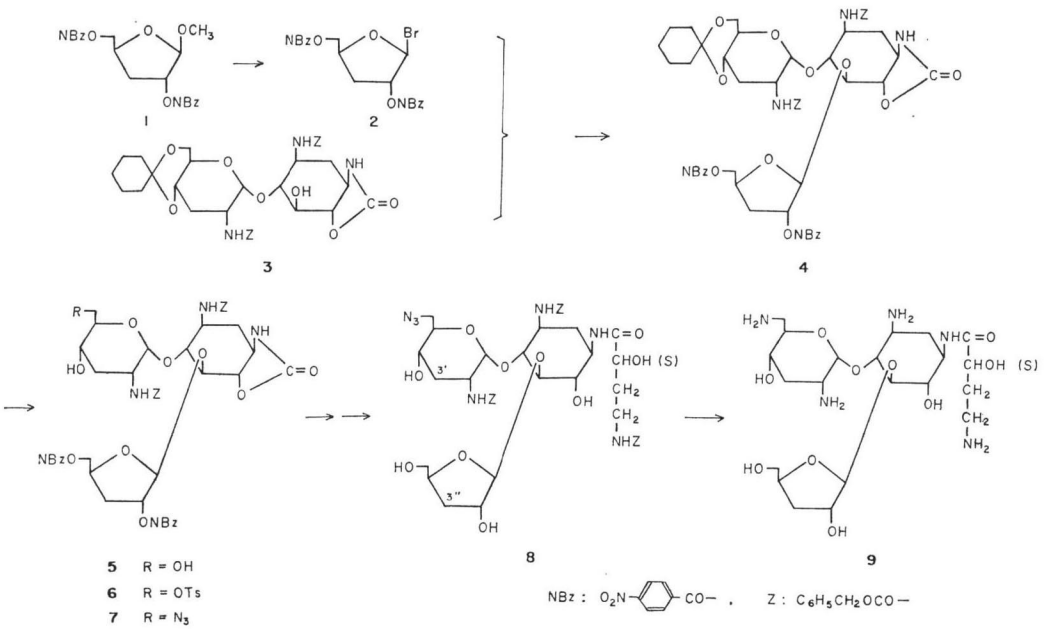

Table 1. Antibacterial spectra of **9**, 3′-deoxybutirosins A and B

Test organisms*	Minimal inhibitory concentration (mcg/ml)		
	9	3′-Deoxy-butirosin A	3′-Deoxy-butirosin B
Staphylococcus aureus FDA 209P	3.12	0.78	0.78
Sarcina lutea PCI 1001	50	6.25	25
Bacillus subtilis NRRL B-558	0.39	<0.2	0.2
Klebsiella pneumoniae PCI 602	0.78	0.39	0.39
〃 type 22 #3038	3.12	1.56	1.56
Salmonella typhi T-63	0.39	0.39	0.2
Escherichia coli NIHJ	1.56	1.56	1.56
〃 K-12	1.56	0.78	0.78
〃 〃 R5	>100	100	>100
〃 〃 ML1629	0.78	0.78	0.78
〃 〃 ML1630	3.12	1.56	1.56
〃 〃 LA290 R55	1.56	1.56	1.56
〃 〃 J5R11-2	0.78	0.78	0.39
〃 〃 W677	0.39	0.78	0.78
〃 〃 JR66/W677	1.56	3.12	3.12
Pseudomonas aeruginosa A3	3.12	3.12	3.12
〃 No. 12	50	25	25
〃 GN315	>100	>100	>100
〃 TI-13	50	25	25
〃 99	25	25	25
Proteus rettgeri GN311	6.25	6.25	6.25
Mycobacterium smegmatis ATCC 607**	0.78	0.78	0.39
Serratia 2019 (Roger Bellon 719)	50	6.25	25
〃 3 (〃 754)	12.5	3.12	12.5
Serratia marcescens GN 6477	3.12	1.56	6.25
〃 GN 6502	100	12.5	100
Enterobacter HEN (Roger Bellon 773)	50	12.5	50
Pyocyanique (〃 743)	100	1.56	6.25
Pyocyanique TAR (〃 771)	50	25	100

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

** 42 hours

previously described[2,3] gave, after chromatography (silica gel, $CHCl_3$ - EtOH, 10 : 1), the 1-*N*-acyl derivative (**8**) in 65% yield, $[\alpha]_D^{23}+15°$ (*c* 1, $CHCl_3$). Found: C 56.34, H 6.18, N 9.84%. Calcd. for $C_{45}H_{57}N_7O_{16}$: C 56.77, H 6.04, N 10.30%. Hydrogenation of **8** with palladium black in aqueous dioxane (2 : 1) in the presence of a small amount of acetic acid removed the benzyloxycarbonyl groups and simultaneously reduced the azido group to afford the desired product. Purification by chromatography on CM-Sephadex C-25 (NH_4^+ form, developed with 0.35 M NH_4OH) gave 3′,3″-dideoxybutirosin (**9**) (63%), $[\alpha]_D^{23}+29°$ (*c* 1, H_2O). IR (KBr): 1545, 1655 cm^{-1}. PMR (in D_2O, at pH 3): δ 5.35 (1H s, H-1″; this shows ($J_{1'',2''}=0$) β-D-pentofuranoside structure), 5.92 (1H d, $J_{1',2'}=3.5$ Hz, H-1′). Found: C 45.72, H 7.70, N 12.36%. Calcd. for $C_{21}H_{41}N_5O_{10}\cdot 1/2H_2CO_3\cdot 1/2H_2O$: C 45.82, H 7.69, N 12.43%.

In vitro tests (Table 1) showed that the 3′,3″-dideoxybutirosin (**9**) has antibacterial activity at a level similar to that of 3′-deoxybutirosin B, but at a slightly lower level than that of 3′-deoxybutirosin A. This result indicates that the presence of C-3″ hydroxyl group in the xylofuranoside moiety enhances the antibacterial activity. It has further been shown that inversion of configuration of the C-3″ hydroxyl group in the ribofuranoside moiety of butirosin B series only slightly enhances the activity (Table 1).

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