SYNTHESES OF 3-FLUORO
DERIVATIVES OF SPORARICIN A,
3-EPIFLUORO-, 3-FLUORO,
AND 3,3-DIFLUORO-3-
DEMETHOXYSPORARICIN A

Sir:

Sporaricin A and B^{1,2)} are major components isolated from the cultured broth of *Saccharopolyspora hirsuta* subsp. *kobensis*³⁾, and the structures were determined²⁾ as shown below. A variety of chemical modifications⁴⁾ of sporaricin and other related pseudodisaccharide antibiotics have been attempted. This paper concerns the syntheses of three 3-fluoro derivatives of sporaricin A, namely, 3-epifluoro-3-demethoxysporaricin A (1), 3-fluoro-3-demethoxysporaricin A (2), and 3,3-difluoro-3-demethoxysporaricin A (3). The reason why we undertook to introduce fluorine atom at C-3 of sporaricin A is due to our assumption that the strong electron-attracting property of fluorine decreases the basicity of the amino group at C-1, and this decreased basicity may lower the toxicity.

1,2',6'-Tris(*N*-benzyloxycarbonyl)-4-*N*; 5-*O*-carbonyl-3-*O*-demethylsporaricin B⁴⁾ (4) was treated with diethylaminosulfur trifluoride⁵⁾ (DAST reagent) in cold dichloromethane to give the 3-epifluoro derivative (5) by nucleophilic substitution. Selective cleavage of the cyclic carbamate of 5 with aqueous barium hydroxide (to give 6) followed by coupling of *N*-benzyloxycarbonylglycyl residue (by the use of the *N*-hydroxysuccinimide active ester) to the methylamino group at C-4 (to give 7), and removal of the protecting groups with palladium-hydrogen

Fig. 1.

	R ¹	R ²	R ³
Sporaricin A	H	OCH ₃	COCH ₂ NH ₂
Sporaricin B	H	OCH ₃	H
1	F	H	COCH ₂ NH ₂
2	H	F	COCH ₂ NH ₂
3	F	F	COCH ₂ NH ₂

Fig. 2.

	R ¹	R ²
4	H	OH
5	F	H
8	=O	
9	OH	H
10	H	F
11	F	F

	R ¹	R ²	R ³
6	F	H	H
7	F	H	COCH ₂ NHZ

Z: CO₂CH₂C₆H₅

gave the 3-epifluoro compound (1), [α]_D²⁰ +61° (c 1, methanol); *m/z* 378 (M+1); ¹H NMR (D₂O, pD ~ 2): δ 3.29 (3H s, NCH₃), 5.30 (1H broadened d, *J*_{H-3,F} 50 Hz, H-3).

Oxidation of 4 with pyridinium chlorochromate in dichloromethane gave the 3-oxo derivative (8), which was reduced with sodium borohydride to give 3-epihydroxy-3-demethoxysporaricin B (9). Treatment of 9 with diethylaminosulfur trifluoride in a manner as described for 5 gave the 3-fluoro derivative (10). Cleavage of the cyclic carbamate of 10 followed by attachment of the glycyl residue at the methylamino group of 10 in a manner as described above and deblocking the benzyloxycarbonyl groups gave the 3-fluoro compound (2), [α]_D²⁰ +90° (c 1, methanol); *m/z* 378 (M+1); ¹H NMR (D₂O, pD ~ 2): δ 3.19 (3H s, NCH₃), 5.32 (1H ddt, H-3); *J*_{H-3,F} 50, *J*_{2a,3} = *J*_{3,4} 10.5, *J*_{2e,3} 5 Hz.

Reaction of the oxo derivative (8) with diethylaminosulfur trifluoride gave the 3,3-difluoro derivative (11). *Anal.* Found (Calcd. for C₃₉H₄₄F₂N₄O₁₀): C 61.27 (61.09), H 6.05 (5.78), N 7.11 (7.31), F 4.95 (4.96). Attachment of the

glycyl residue after cleavage of the cyclic carbamate, and deblocking as described above, gave the 3,3-difluoro compound (3), $[\alpha]_D^{20} +50^\circ$ (c 1, methanol); m/z 396 (M+1).

Antibacterial activities of 1, 2, 3 and sporari-

cin A are shown in Table 1. The order of antibacterial activity was 2>sporaricin A>1>3. Their acute toxicities (mice, i.v.) were ca. 100 (for 1), ca. 100 (for 2), >150 (for 3), and 80 mg/kg (sporaricin A). These results indicate, as expect-

Table 1. Minimal inhibitory concentration ($\mu\text{g/ml}$) of 3-epifluoro-(1), 3-fluoro-(2), 3,3-difluoro-3-demethoxysporaricin A(3) and sporaricin A.

	Sporaricin A	1	2	3
<i>Staphylococcus aureus</i> FDA209P	0.78	0.78	0.78	1.56
<i>Staphylococcus aureus</i> Smith	<0.2	<0.2	0.2	0.78
<i>Staphylococcus aureus</i> AP01	0.78	0.78	0.78	6.25
<i>Staphylococcus epidermidis</i> 109	0.39	0.39	0.78	0.78
<i>Micrococcus flavus</i> FDA16	6.25	6.25	3.12	12.5
<i>Micrococcus luteus</i> PCI1001	<0.2	0.39	<0.2	0.78
<i>Bacillus subtilis</i> PCI219	0.39	0.39	0.39	0.78
<i>Bacillus subtilis</i> NRRL B-558	0.39	0.39	0.39	1.56
<i>Corynebacterium bovis</i> 1810	0.78	3.12	1.56	6.25
<i>Escherichia coli</i> K-12	0.78	3.12	0.78	1.56
<i>Escherichia coli</i> K-12 R5	3.12	3.12	1.56	3.12
<i>Escherichia coli</i> K-12 J5 R11-2	3.12	3.12	3.12	6.25
<i>Escherichia coli</i> K-12 ML1629	1.56	3.12	1.56	3.12
<i>Escherichia coli</i> K-12 ML1630	3.12	3.12	3.12	6.25
<i>Escherichia coli</i> K-12 ML1410	3.12	3.12	1.56	6.25
<i>Escherichia coli</i> K-12 ML1410 R81	1.56	3.12	1.56	6.25
<i>Escherichia coli</i> K-12 LA290 R55	1.56	3.12	3.12	3.12
<i>Escherichia coli</i> W677	0.78	1.56	1.56	1.56
<i>Escherichia coli</i> JR66/W677	3.12	3.12	3.12	6.25
<i>Escherichia coli</i> K-12 C600 R135	100	25	12.5	50
<i>Mycobacterium smegmatis</i> ATCC 607	0.39	1.56	0.39	0.78
<i>Klebsiella pneumoniae</i> PCI602	1.56	3.12	1.56	6.25
<i>Klebsiella pneumoniae</i> 22 #3038	6.25	3.12	3.12	12.5
<i>Shigella dysenteriae</i> JS11910	6.25	3.12	3.12	6.25
<i>Salmonella typhi</i> T-63	0.39	0.78	0.39	1.56
<i>Proteus vulgaris</i> OX19	0.39	0.78	0.39	0.78
<i>Proteus rettgeri</i> GN311	0.78	0.78	0.78	1.56
<i>Proteus rettgeri</i> GN466	1.56	1.56	0.78	1.56
<i>Serratia marcescens</i>	3.12	3.12	3.12	6.25
<i>Serratia</i> sp. SOU	>100	100	50	>100
<i>Providencia</i> sp. Pv 16	1.56	1.56	1.56	3.12
<i>Providencia</i> sp. 2991	3.12	3.12	3.12	6.25
<i>Pseudomonas aeruginosa</i> A3	0.78	1.56	0.78	3.12
<i>Pseudomonas aeruginosa</i> No. 12	25	12.5	12.5	25
<i>Pseudomonas aeruginosa</i> H9	12.5	12.5	6.25	25
<i>Pseudomonas aeruginosa</i> TI-13	50	25	25	12.5
<i>Pseudomonas aeruginosa</i> GN315	12.5	12.5	12.5	12.5
<i>Pseudomonas aeruginosa</i> 99	>100	>100	100	>100
<i>Pseudomonas aeruginosa</i> B-13	>100	>100	100	>100
Geometrical mean value ^(a)	2.57	2.76	2.11	5.13

ed, that introduction of fluorine atom(s) at C-3 of sporaricin A decreases the acute toxicity of sporaricin A.

Fluorination of aminoglycoside antibiotics has not been tried very extensively. However, we believe, it will be a promising field of investigation in terms of the biological activities.

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