Synthesis and Antibacterial Activities of Optically Active Substituted 1,2-Dihydro-6-oxo-6*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylic Acids

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A series of optically active substituted 1,2-dihydro-6-oxo-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylic acids was prepared *via* optically active 2-methyl-4,5-difluoroindoline (10) and tested for antibacterial activities. Among them, (2*S*)-9-[(3*R*,1′*S*)-3-(1′-amino)ethyl-1-pyrrolidinyl]-8-fluoro-1,2-dihydro-2-methyl-6-oxo-6*H*-pyrrolo[3,2,1-*ij*]-quinoline-5-carboxylic acid (19) showed potent activity against gram-positive bacteria and (2*S*)-8-fluoro-1,2-dihydro-2-methyl-9-(3-methyl-1-piperazinyl)-6-oxo-6*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylic acid (16) exhibited well balanced *in vitro* activity, good intravenous efficacy, and high aqueous solubility.

Key words optically active pyrroloquinoline; aqueous solubility; intravenous administration; indoline; antibacterial activity

Quinolone antibacterial agents are an important class of therapeutically useful compounds. In Japan, these agents are given only by the oral route for the treatment of slight and moderate bacterial infections, while in Europe and United States, some of them, ofloxacin (OFLX)[1] and ciprofloxacin (CPFX),[2] are available for parenteral administration.[3] Although their intravenous preparations have already been used clinically, poor aqueous solubility is a problem. Previously, we synthesized nadifloxacin (NDFX),[4] which characteristically exhibits potent antibacterial activity against *Propionibacterium acnes* and possesses chirality. Its (*S*)-isomer shows not only more potent activity than the racemic mixture does,[5] but also better aqueous solubility. However, antibacterial activity

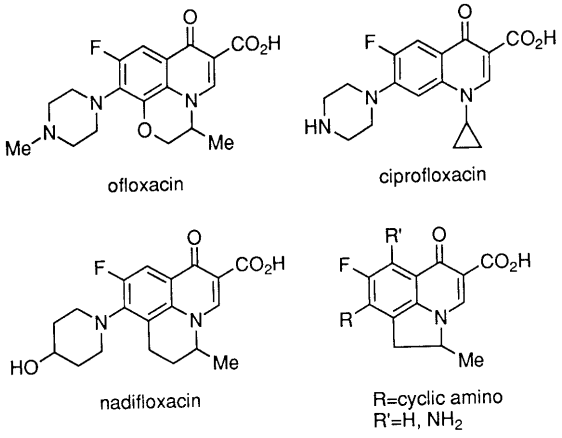

Fig. 1

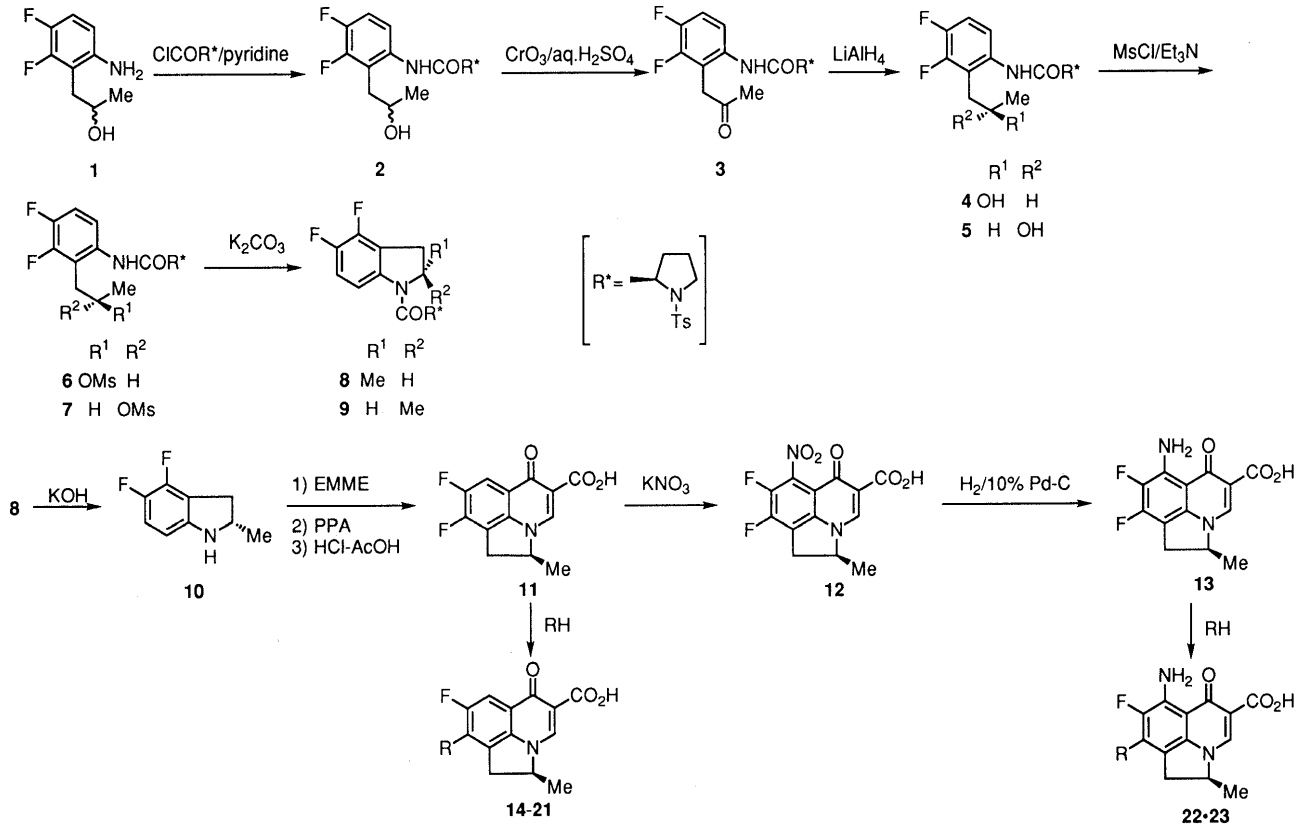

Chart 1

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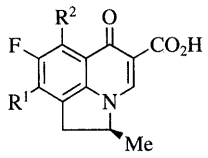
of NDFX against gram-negative bacteria including *Pseudomonas aeruginosa* is rather weak. As a result of a search for compounds with more potent activity against gram-negative bacteria, we found (±)-pyrrolo[3,2,1-*ij*]quinoline carboxylic acids (Fig. 1).[6] Next, we decided to synthesize their (*S*)-isomers because we expected that these isomers would be more active than their racemic mixtures and might have good enough aqueous solubility for parenteral administration. We succeeded in preparing (*S*)-4,5-difluoro-2-methylindoline (**10**), a key intermediate of the (*S*)-isomer.[7] We describe here the synthesis, antibacterial activities, and aqueous solubilities of (*S*)-9-amino-1,2-dihydro-6-oxo-6*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylic acid derivatives.

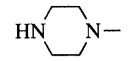
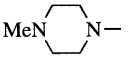
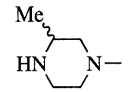
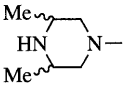
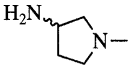
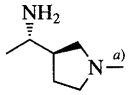
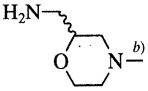
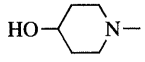
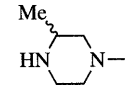
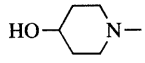
Synthesis

First, compound **10**, a key intermediate of the (*S*)-pyrrolo[3,2,1-*ij*]quinoline carboxylic acids, was prepared. The amino group of the anilinoalcohol (**1**)[8] was acylated with (*R*)-*N*-(*p*-toluenesulfonyl)prolinyl chloride in CH_2Cl_2 in the presence of pyridine at −5°C to afford the anilide (**2**). Oxidation of **2** with chromium(VI) trioxide (CrO_3)/aqueous H_2SO_4 in acetone at room temperature produced the ketone (**3**). Reduction of **3** with lithium aluminum hydride ($LiAlH_4$) in tetrahydrofuran (THF) at −70 °C followed by trituration with 5% iso-PrOH/iso-Pr_2O gave a 91 : 9 mixture of the alcohols (**4**, **5**) in 72% yield from **1**. Sequential processing of **4** and **5** with methanesulfonyl chloride and potassium carbonate (K_2CO_3) followed by recrystallization from acetonitrile (MeCN) furnished *N*-[(*R*)-*N*-*p*-toluenesulfonyl]prolinylindoline (**8**) as almost a single isomer in 70% yield. Hydrolysis of **8** by KOH in a mixture of MeOH and THF provided **10** in 95% yield.

(*S*)-8,9-Difluoropyrroloquinolinecarboxylic acid (**11**) was prepared in 56% yield from **10** in one-pot continuous treatment as follows: condensation of **10** with ethoxymethylenemalonate (EMME) gave an enaminoester compound, which was cyclized with polyphosphoric acid (PPA), followed by hydrolysis with HCl–AcOH. The 7-amino derivative (**13**) was synthesized in 13% yield by

Table 1. Substituted (*S*)-2-Methyl-1,2-dihydro-6-oxopyrrolo[3,2,1-*ij*]quinoline-5-carboxylic Acids



Compd. No.	R^1	R^2	Recryst. solvent	Yield (%)	mp (°C)	$[\alpha]_D$	Formula	Analysis (%) Calcd (Found) C	H	N
14		H	EtOH–H_2O	30	230—232	+20.6° (*c*=0.68, 1 N NaOH)	$C_{17}H_{18}FN_3O_3 \cdot 1/2H_2O$	59.93 (59.99)	5.63 (5.33)	12.35 (12.26)
15		H	EtOH–H_2O	25	285—290 (dec.)	+10.7° (c=0.87, 1 N NaOH)	$C_{18}H_{20}FN_3O_3 \cdot HCl \cdot H_2O$	54.07 (54.31)	5.79 (5.63)	10.51 (10.62)
16		H	EtOH–H_2O	78	278—283 (dec.)	+27.5° (*c*=0.55, 1 N NaOH)	$C_{18}H_{20}FN_3O_3 \cdot HCl \cdot H_2O$	54.01 (54.28)	5.75 (5.56)	10.50 (10.55)
17		H	EtOH–H_2O	54	288—295 (dec.)	+10.6° (*c*=0.85, 1 N NaOH)	$C_{19}H_{22}FN_3O_3 \cdot HCl \cdot 2H_2O$	52.84 (52.56)	6.30 (6.08)	9.73 (9.47)
18		H	EtOH–H_2O	14	265—271 (dec.)	+119.4° (*c*=0.34, 1 N NaOH)	$C_{17}H_{18}FN_3O_3 \cdot 3H_2O$	52.98 (53.03)	6.28 (6.04)	10.90 (10.80)
19	 [a]	H	EtOH	28	245—247 (dec.)	−157.1° (*c*=0.49, 0.1 N HCl)	$C_{19}H_{22}FN_3O_3 \cdot CF_3CO_2H \cdot 1/3H_2O$	52.61 (52.71)	4.98 (4.82)	8.76 (8.55)
20	 [b]	H	EtOH	30	219—226 (dec.)	+14.0° (*c*=0.43, 0.1 N HCl)	$C_{18}H_{20}FN_3O_4 \cdot CF_3CO_2H \cdot 1/2H_2O$	49.59 (49.79)	4.58 (4.49)	8.68 (8.69)
21		H	DMF–H_2O	77	243—247	+15.5° (*c*=1.11, DMF)	$C_{18}H_{19}FN_2O_4$	62.42 (62.12)	5.53 (5.48)	8.09 (8.14)
22		NH_2	EtOH–H_2O	40	265—270 (dec.)	−20.9° (*c*=0.36, 1 N NaOH)	$C_{18}H_{21}FN_4O_3 \cdot 2HCl \cdot 2H_2O$	48.88 (48.91)	5.47 (5.47)	12.67 (12.77)
23		NH_2	DMF–H_2O	77	274—276 (dec.)	−8.8° (*c*=1.02, DMF)	$C_{18}H_{20}FN_3O_4$	59.83 (59.53)	5.58 (5.54)	11.63 (11.63)

a) Ref. 9. *b*) Ref. 10.

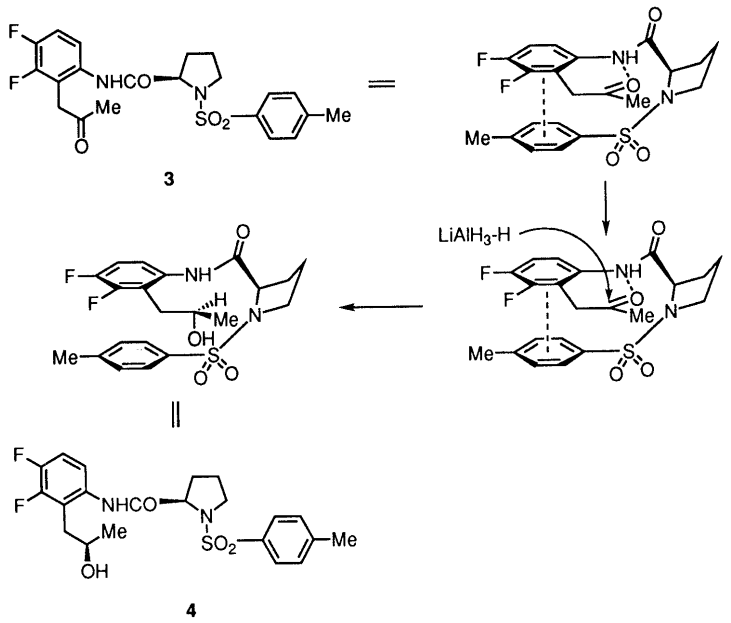


Chart 2

nitration of **11** with potassium nitrate (KNO_3), followed by hydrogenation of the product (**12**) with 10% palladium on carbon (10% Pd–C). Finally, various piperazines, 4-hydroxypiperidine, pyrrolidine derivatives[9] and morpholine derivative[10] were introduced at the 9-position of the acids **11** and **13** in hexamethylphosphoric triamide (HMPA) followed by deprotection, if necessary, to afford the desired compounds (**14**—**23**) (Table 1).

The absolute configurations of **4** and **5** were determined by X-ray analysis.[7] A plausible mechanism of this asymmetric reduction is depicted in Chart 2. Owing to π–π interaction and hydrogen bonding, the downside of the ketone carbonyl group is blocked by the *N*-(*p*-toluenesulfonyl)proline moiety. Consequently, hydride ion attacks the carbonyl group from the upper side to give the (*R*)-alcohol **4** predominantly.

Biological Results and Aqueous Solubility

Compounds **14**—**23** were evaluated for *in vitro* antibacterial activities against gram-positive (*Staphylococcus aureus* 209P and *Enterococcus faecalis* ATCC-21212) and gram-negative bacteria (*Escherichia coli* NIHJ JC-2 and *Pseudomonas aeruginosa* ATCC-10145) by using a two-fold agar dilution method.[11] The results are summarized in Table 2. The antibacterial activities of racemic mixtures of **14**, **15**, **21**, **23**,[6] and OFLX are also given.

(*S*)-Pyrroloquinoline derivatives (**14**, **15**, **21**, **23**) had more potent activity against *S. aureus* than the corresponding racemic mixtures by 2- to 4-fold. Substitution of the hydrogen of the piperazinyl group (**14**) by a methyl group (**15**) brought about an increase of activity against all bacteria examined. Introduction of the methyl group at the 3-position (**16**) of the piperazinyl group (**14**) caused enhancement of the activity against *S. aureus*, but the introduction of two methyl groups at the 3- and 5-positions (**17**) decreased the activity against most bacteria compared with **16**. The replacement of the piperazine side chain (**14**) by 3-aminopyrrolidine (**18**) increased the activity against *S. aureus* and *Ps. aeruginosa*, but decreased the activity against *E. coli*. Compound **19** with a (3*R*,1′*S*)-3-(1′-amino)ethylpyrrolidine moiety at the 9-position exhibited excellent activity against gram-positive bacteria. The displacement of the piperazine side chain (**14**) by 3-aminomethyl morpholine (**20**) diminished the activity against gram-negative bacteria. Compound **22** bearing an amino group at the 7-position on the pyrroloquinoline skeleton showed more potent antibacterial activity against gram-positive bacteria than did the un-

Table 2. *In Vitro* Antibacterial Activity [Minimum Inhibitory Concentration (*MIC*) (μg/ml), Inoculum Size: 10^6 Cells/ml]

Compd. No.	*S. aureus* FDA 209p	*E. faecalis* ATCC-21212	*E. coli* NIHJ JC-2	*P. aeruginosa* ATCC 10145
14	0.39	3.13	0.05	0.78
(±)-**14**[a]	1.56	—	0.1	0.78
15	0.2	1.56	0.025	0.39
(±)-**15**[a]	0.39	—	0.05	1.56
16	0.2	3.13	0.05	0.78
17	0.39	3.13	0.1	1.56
18	0.2	3.13	0.1	0.39
19	0.012	0.012	0.1	0.39
20	0.78	1.56	1.56	6.25
21	0.05	0.78	0.39	3.13
(±)-**21**[a]	0.2	—	0.39	3.13
22	0.1	0.78	0.05	0.78
23	0.05	1.56	0.39	3.13
(±)-**23**[a]	0.2	—	0.39	6.25
OFLX	0.2	1.56	0.1	1.56

a) Ref. 6.

Table 3. Aqueous Solubility of **15**, **16**, and Their Racemic Mixtures

Compound[a]	Solubility (mg/ml)
15	230
(±)-**15**	12
16	385
(±)-**16**	29

a) All compounds are hydrochlorides.

Table 4. Efficacy against Systemic Infections by Parenteral Administration in Mice

Test organism	Compound	*MIC* (μg/ml)[a]	Challenge dose (cells/mouse)	ED_{50} (mg/kg)
S. aureus SMITH	**16**	0.39	4.80×10^5	0.795 (0.534—1.149)[b]
	OFLX	0.39	4.80×10^5	1.399 (1.144—1.759)
E. coli No. 29	**16**	0.024	2.60×10^6	0.180 (0.141—0.220)
	OFLX	0.05	2.60×10^6	0.230 (0.169—0.334)
Ps. aeruginosa E-2	**16**	0.78	1.65×10^6	2.641 (1.939—4.373)
	OFLX	3.13	1.65×10^6	7.473 (6.257—8.627)

a) Inoculum size: 10^6 cells/ml. *b*) 95% confidence limit.

substituted compound (**16**).

The aqueous solubilities of **15**, **16**, and corresponding racemic mixtures are shown in Table 3. The data indicate that each (*S*)-isomer has higher aqueous solubility than the racemic mixture, by 19- and 13-fold, respectively.

Finally, **16** and OFLX were tested by parenteral administration on systemic infections due to *S. aureus* SMITH, *E. coli* No. 29 and *Ps. aeruginosa* E-2 in mice. The results are listed in Table 4. Compound **16** was superior to OFLX.

In summary, compound **16** exhibited well balanced *in vitro* activity, good intravenous efficacy, and excellent aqueous solubility, and appears to be available as a parenteral agent.

Experimental

Melting points were taken on a Yanaco MP-500D apparatus and are uncorrected. Proton nuclear magnetic resonance (NMR) spectra were recorded with a Hitachi (90 MHz) spectrometer. The chemical shifts are reported in δ downfield from tetramethylsilane as an internal standard. The elemental analyses were run on a Yanaco CHN corder MT-3.

3′,4′-Difluoro-2′-(2-hydroxypropyl)-[*N*-*p*-toluenesulfonyl-(*R*)-prolin]-anilide (2) Pyridine (106.8 ml, 1.3 mol) and (*R*)-*N*-*p*-toluenesulfonylprolinyl chloride (379.8 g, 1.3 mol) were added to a stirred solution of a racemic anilinoalcohol (**1**)[8] (224.6 g, 1.20 mol) in CH_2Cl_2 (2.4 l) at −5°C. The mixture was stirred for 30 min, washed successively with 10% HCl, water, 5% aqueous solution of $NaHCO_3$ and water, and then dried over $MgSO_4$. Removal of the solvent gave **2** (526.2 g, 100%) as a brown solid (mp 161—164 °C), which was used in the next reaction without further purification. NMR ($CDCl_3$) δ: 1.26, 1.47 (1.5, 1.5H, each d, J=6.3 Hz), 1.55—2.34 (4H, m), 2.48 (3H, s), 2.55—3.36 (4H, m), 3.43—3.80 (1H, m), 4.01—4.55 (2H, m), 7.08 (1H, q, J=8.8 Hz), 7.40 (2H, d, J=8.0 Hz), 7.40—7.70 (1H, m), 7.78 (2H, d, J=8.0 Hz), 10.21, 10.38 (0.5, 0.5H, each br s).

3′,4′-Difluoro-2′-(2-oxopropyl)-[*N*-*p*-toluenesulfonyl-(*R*)-prolin]anilide (3) A solution of CrO_3 (95.5 g, 0.96 mol) in 30% aqueous H_2SO_4 (357.5 ml) was added to a stirred solution of **2** (521.8 g, 1.19 mol) in acetone (4.8 l) and the resulting mixture was stirred for 45 min at room temperature. After addition of iso-PrOH (91.9 ml, 1.2 mol), the mixture was filtered and the filtrate was evaporated. The residue was dissolved in a mixture of CH_2Cl_2 and water. The aqueous phase was extracted twice with CH_2Cl_2, and the combined organic extracts were washed twice with water, then dried over $MgSO_4$. Evaporation of the solvent afforded **3** (519.4 g, 100%) as a brown solid (mp 149—152 °C), which was used in the next reaction without further purification. NMR ($CDCl_3$) δ: 1.50—2.40 (4H, m), 2.43 (3H, s), 2.48 (3H, s), 3.04—3.39 (1H, m), 3.60—3.90 (1H, m), 3.95—4.36 (3H, m), 7.15 (1H, q, J=8.8 Hz), 7.41 (2H, d, J=7.5 Hz), 7.41—7.67 (1H, m), 7.75 (2H, d, J=7.5 Hz), 9.06 (1H, br s).

3′,4′-Difluoro-2′-[(*R*)-2-hydroxypropyl]-[*N*-*p*-toluenesulfonyl-(*R*)-prolin]anilide (4) and 3′,4′-Difluoro-2′-[(*S*)-2-hydroxypropyl]-[*N*-*p*-toluenesulfonyl-(*R*)-prolin]anilide (5) $LiAlH_4$ (26.6 g, 0.7 mol) was added carefully in portions to a stirred solution of **3** (510.7 g, 1.17 mol) in THF (2.4 l), with cooling so as to keep the temperature bellow −70 °C. The mixture was stirred for 1 h, then poured into 10% HCl and ice-water, and the aqueous layer was extracted twice with CH_2Cl_2. The combined extracts were washed twice with water and dried over $MgSO_4$. After evaporation of the solvent, the resulting solid was triturated with 5% iso-PrOH/iso-Pr_2O to give a 91 : 9 mixture of **4** and **5** (369.9 g, 72%) as a pale yellow solid, mp 172—173 °C, $[\alpha]_D^{25}$ +164.3° (c=1.00, $CHCl_3$). NMR ($CDCl_3$) δ: 1.26, 1.47 (0.27, 2.73 H, each d, J=6.3 Hz), 1.55—2.34 (4H, m), 2.48 (3H, s), 2.55—3.36 (4H, m), 3.43—3.80 (1H, m), 4.01—4.55 (2H, m), 7.08 (1H, q, J=8.8 Hz), 7.40 (2H, d, J=8.0 Hz), 7.40—7.70 (1H, m), 7.78 (2H, d, J=8.0 Hz), 10.21 (1H, br s). *Anal.* Calcd for $C_{21}H_{24}F_2N_2O_4S$: C, 57.52; H, 5.52; N, 6.39. Found: C, 57.68; H, 5.33; N, 6.22.

3′,4′-Difluoro-2′-[(*R*)-2-methylsulfonyloxypropyl]-[*N*-*p*-toluenesulfonyl-(*R*)-prolin]anilide (6) and 3′,4′-Difluoro-2′-[(*S*)-2-methylsulfonyloxypropyl]-[*N*-*p*-toluenesulfonyl-(*R*)-prolin]anilide (7) Methanesulfonyl chloride (83.6 ml, 1.08 mol) and triethylamine (185.4 ml, 1.33 mol) were added to a stirred solution of a mixture of **4** and **5** (364.4 g, 0.83 mol) in CH_2Cl_2 (1.6 l) at 0 °C. The reaction mixture was stirred for 3 h, and poured into 10% HCl. The organic layer was washed with water and dried over $MgSO_4$. Evaporation of the solvent furnished a mixture of **6** and **7** (428.8 g, 100%) as a pale yellow solid, which was used in the next reaction without further purification. mp 63—66 °C. NMR ($CDCl_3$) δ: 1.72 (3H, d, J=6.3 Hz), 1.80—2.35 (4H, m), 2.48 (3H, s), 2.85 (3H, s), 2.90—3.55 (3H, m), 3.60-3.93 (1H, m), 4.05—4.31 (1H, m), 4.76—5.15 (1H, m), 7.14 (1H, q, J=8.8 Hz), 7.40 (2H, d, J=8.0 Hz), 7.40—7.63 (1H, m), 7.83 (2H, d, J=8.0 Hz), 9.12 (1H, br s).

(2*S*)-4,5-Difluoro-2-methyl-1-[*N*-*p*-toluenesulfonyl-(*R*)-prolyl]indoline (8) A suspension of a mixture of **6** and **7** (423.6 g, 0.82 mol) and K_2CO_3 (170.0 g, 1.23 mol) in acetone (9.8 l) and water (40 ml) was refluxed for 1 h. After evaporation of the solvent, the residue was dissolved with CH_2Cl_2 and water. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed twice with water, dried over $MgSO_4$, and evaporated. The residue was added to MeCN (2 l) and the resulting mixture was refluxed for 30 min, then cooled. The precipitates were collected by filtration to afford **8** (241.1 g, 70%) as a single isomer, colorless needles, mp 237—238 °C, $[\alpha]_D^{25}$ +71.4° (c=1.02, $CHCl_3$). NMR ($CDCl_3$) δ: 1.53 (3H, d, J=6.3 Hz), 1.76—2.38 (4H, m), 2.45 (3H, s), 2.65—3.00 (1H, m), 3.20—3.65 (3H, m), 4.36—4.70 (1H, m), 4.70—4.92 (1H, m), 7.02 (1H, q, J=8.8 Hz), 7.31 (2H, d, J=8.0 Hz), 7.65—7.95 (1H, m),7.82 (2H, d, J=8.0 Hz). *Anal.* Calcd for $C_{21}H_{22}F_2N_2O_3S$: C, 59.99; H, 5.27; N, 6.66. Found: C, 59.86; H, 5.33; N, 6.60.

(*S*)-4,5-Difluoro-2-methylindoline (10) A solution of **8** (236.1 g, 0.56 mol) in THF (1.2 l) was added to a stirred solution of KOH (184.8 g, 2.8 mol) in MeOH (1.2 l), and the resulting mixture was refluxed for 2.5 h. After evaporation of the solvent, the residue was dissolved in a mixture of toluene (1.2 l) and water (1.2 l). The organic layer was washed with water (× 3) and dried over Na_2SO_4. Evaporation of the solvent and distillation gave **10** (89.6 g, 95%) as a colorless oil, bp 90 °C (4 mmHg). NMR ($CDCl_3$) δ: 1.29 (3H, d, J=6.3 Hz), 2.66 (1H, dd, J=7.6, 15.8 Hz), 3.21 (1H, dd, J=7.6, 15.8 Hz), 3.60 (1H, br s), 3.90—4.17 (1H, m), 6.24 (1H, dd, J=3.2, 8.8 Hz), 6.78 (1H, q, J=8.8 Hz). *Anal.* Calcd for $C_9H_9F_2N$: C, 63.90; H, 5.38; N, 8.28. Found: C, 63.72; H, 5.35; N, 8.42. The optical purity of this compound was determined to be 100% ee by HPLC analysis.[12]

(2*S*)-8,9-Difluoro-1,2-dihydro-2-methyl-6-oxo-6*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylic Acid (11) A mixture of **10** (86.3 g, 0.51 mol) and EMME (102.3 ml, 0.51 mol) was heated at 120 °C for 2 h. PPA prepared from P_2O_5 (289.6 g, 2.04 mol) and H_3PO_4 (289.6 g, 2.96 mol) was added at 130 °C and the whole was heated at the same temperature for 1.5 h. It was poured into water and the resulting precipitates were collected by filtration. This crude ester was added to a mixture of AcOH

(470 ml) and concentrated HCl (235 ml) and heated under reflux for 4 h. After evaporation of the solvent, the resulting solid was washed successively with water (×3) and EtOH (×3). Recrystallization from *N*,*N*-dimethylformamide (DMF) gave **11** (75.7 g, 56%) as colorless prisms, mp 293—294 °C, $[\alpha]_D^{23}$ +39.6° (*c*=1.06, DMF). NMR (DMSO-d_6) δ: 1.66 (3H, d, *J*=6.6 Hz), 3.31 (1H, dd, *J*=8.3, 17.1 Hz), 3.88 (1H, dd, *J*=8.1, 17.1 Hz), 5.10—5.35 (1H, m), 7.96 (1H, dd, *J*=7.0, 10.6 Hz), 9.17 (1H, s). *Anal.* Calcd for $C_{13}H_9F_2NO_3$: C, 58.87; H, 3.42; N, 5.28. Found: C, 58.97; H, 3.14; N, 5.31.

(2*S*)-8,9-Difluoro-1,2-dihydro-2-methyl-7-nitro-6-oxo-6*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylic Acid (12) A solution of **11** (12.0 g, 45 mmol) in concentrated H_2SO_4 (120 ml) was treated with KNO_3 (17.7 g, 0.17 mol), and the resulting mixture was heated at 70 °C for 2 h. After cooling, the reaction mixture was poured into ice-water and the resulting precipitates were collected by filtration. Recrystallization from DMF afforded **12** (2.9 g, 21%) as pale yellow prisms, mp 257—262 °C (dec.), $[\alpha]_D^{21}$ +42.2° (*c*=0.63, DMF). NMR (DMSO-d_6) δ: 1.66 (3H, d, *J*=6.6 Hz), 3.32 (1H, dd, *J*=3.6, 18.0 Hz), 3.95 (1H, dd, *J*=9.0, 18.0 Hz), 5.04—5.49 (1H, m), 9.24 (1H, s), 15.6 (1H, br s). *Anal.* Calcd for $C_{13}H_8F_2N_2O_5$: C, 50.33; H, 2.60; N, 9.03. Found: C, 50.08; H, 2.74; N, 8.85.

(2*S*)-7-Amino-8,9-difluoro-1,2-dihydro-2-methyl-6-oxo-6*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylic Acid (13) A mixture of **12** (1.8 g, 5.8 mmol) and 10% Pd–C (0.3 g) in DMF (80 ml) was stirred at room temperature under 5 kg/cm^2 pressure of hydrogen for 16 h. The mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was triturated with EtOH and the precipitates were collected by filtration. Recrystallization from DMF gave **13** (1.02 g, 63%) as yellow needles, mp 270—273 °C (dec.), $[\alpha]_D^{24}$ +5.2° (*c*=0.37, DMF). NMR (DMSO-d_6) δ: 1.59 (3H, d, *J*=6.6 Hz), 3.03 (1H, dd, *J*=4.5, 16.2 Hz), 3.67 (1H, dd, *J*=9.0, 16.2 Hz), 4.87—5.32 (1H, m), 7.11 (2H, br s), 8.91 (1H, s), 14.86 (1H, br s). *Anal.* Calcd for $C_{13}H_{10}F_2N_2O_3$: C, 55.72; H, 3.60; N, 10.00. Found: C, 55.43; H, 3.54; N, 9.95.

(2*S*)-8-Fluoro-1,2-dihydro-2-methyl-9-(3-methyl-1-piperazinyl)-6-oxo-6*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylic Acid (16) 2-Methylpiperazine (3.4 g, 34 mmol) was added to a solution of **11** (3.0 g, 11 mmol) in HMPA (30 ml) and the resulting mixture was heated at 120 °C for 1 h. After removal of the solvent *in vacuo*, AcOEt was added to the residue. The resulting precipitates were collected by filtration and suspended in water. A 1 N NaOH solution was added to this suspension to adjust the pH to 8, and then 10% HCl was added to make pH 1. After treatment with active charcoal, the mixture was concentrated and the residue was recrystallized from EtOH–H_2O to furnish **16** (3.28 g, 78%) as pale yellow prisms. NMR (DMSO-d_6) δ: 1.32 (3H, d, *J*=5.1 Hz), 1.64 (3H, d, *J*=6.2 Hz), 3.21—3.78 (8H, m), 3.94 (1H, dd, *J*=9.0, 18.0 Hz), 4.90—5.35 (1H, m), 7.72 (1H, d, *J*=12.6 Hz), 9.05 (1H, s), 9.47 (2H, br s), 18.65 (1H, br s). The melting point, optical rotation and elemental analysis data are given in Table 1.

Compounds **14**, **15**, **17** and **21**—**23** were obtained similarly; the yield, melting point, optical rotation and elemental analysis data are given in Table 1.

(2*S*)-9-(3-Amino-1-pyrrolidinyl)-8-fluoro-1,2-dihydro-2-methyl-6-oxo-6*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylic Acid (18) A mixture of **11** (7.0 g, 26 mmol), 3-aminopyrrolidine dihydrochloride (21 g, 0.13 mol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (40 ml, 0.26 mol) in HMPA (70 ml) was heated at 120 °C for 2 h. After evaporation of the solvent, the residue was dissolved in 2% HCl (100 ml). Insoluble material was filtered off and the filtrate was concentrated. The resulting solid was recrystallized from EtOH–H_2O and dissolved in water. A saturated solution of $NaHCO_3$ was added to adjust the pH to 8. The resulting precipitates were collected by filtration to afford **18** (1.4 g, 14%) as pale green prisms. NMR (DMSO-d_6) δ: 1.60—2.32 (2H, m), 1.61 (3H, d, *J*=6.3 Hz), 2.90—4.55 (9H, m), 4.76—5.25 (1H, m), 7.56 (1H, d, *J*=14.4 Hz), 8.90 (1H, s), 15.81 (1H, br s). The melting point, optical rotation and elemental analysis data are given in Table 1.

(2*S*)-9-[(3*R*,1′*S*)-3-(1′-Amino)ethyl-1-pyrrolidinyl]-8-fluoro-1,2-dihydro-2-methyl-6-oxo-6*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylic Acid (19) A mixture of **11** (0.53 g, 2.0 mmol), (3*R*,1′*S*)-3-[1′-(*N*-*tert*-butoxycarbonyl)amino]ethylpyrrolidine[9] (0.64 g, 3.0 mmol) and pyridine (0.49 ml, 6.0 mmol) in HMPA (5.5 ml) was stirred at 110 °C for 2 h. After removal of the solvent *in vacuo*, the residue was treated with AcOEt and water. The resulting precipitates were collected by filtration to furnish the *tert*-butoxycarbonylamine compound, which was added to trifluoroacetic acid (10 ml) and anisole (2 ml). This mixture was stirred at room temperature for 1 h, Et_2O was added, and the resulting precipitates were collected by filtration and recrystallized from EtOH to give **19** (265 mg, 28%) as a yellow powder. NMR (DMSO-d_6) δ: 1.27 (3H, d, *J*=6.3 Hz), 1.59 (3H, d, *J*=6.4 Hz), 1.60—2.50 (4H, m), 2.63—4.23 (6H, m), 4.73—5.20 (1H, m), 7.50 (1H, d, *J*=15.1 Hz), 8.01 (3H, br s), 8.84 (1H, s), 15.73 (1H, br s). The melting point, optical rotation and elemental analysis data are given in Table 1.

Compound **20** was obtained by the same method as described for **19**; the yield, melting point, optical rotation, and elemental analysis data are given in Table 1.

Aqueous Solubility Measurements A known excess weight of each compound was shaken overnight at room temperature (23 °C) with a known volume of water for injection. The contents were filtered through 0.45-μ membrane filter, and the clear filtrate was diluted with mobile phase and analyzed by HPLC.

***In Vivo* Efficacy on Systemic Infections** Test bacteria were inoculated into the peritoneal cavity of ICR male mice with 5% mucin and the test compounds were administered intravenously 1 h after infection. The ED_{50} values were calculated by the probit method using the survival rate at 7 d after infection.

Acknowledgment We thank gratefully Mr. S. Toyama for his many valuable suggestions. We also thank Mr. K. Ohmori and Miss K. Ohguro for biological data.

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12) HPLC: Yanaco L-4000S pump; M-315 detector set at 254 nm, connected to a Shimadzu C-R6A CHROMATOPAC; CHIRALCEL OD column, 4.6 i.d. × 250 mm; solvent system (v/v), *n*-hexane : EtOH = 99 : 1; flow rate, 0.5 ml/min.