Synthesis and Structure−Activity Relationships of 5-Amino-6-fluoro-1-[(1*R*,2*S*)-2-fluorocyclopropan-1-yl]-8-methylquinolonecarboxylic Acid Antibacterials Having Fluorinated 7-[(3*R*)-3-(1-Aminocyclopropan-1-yl)pyrrolidin-1-yl] Substituents[1]

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A series of novel 5-amino-6-fluoro-1-[(1*R*,2*S*)-2-fluorocyclopropan-1-yl]-8-methylquinolones bearing fluorinated (3*R*)-3-(1-aminocyclopropan-1-yl)pyrrolidin-1-yl substituents at the C-7 position (**2**−**4**) was synthesized to obtain potent drugs for infections caused by Gram-positive pathogens, which include resistant strains such as methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae* (PRSP), and vancomycin-resistant enterococci (VRE). These fluorinated compounds **2**−**4** exhibited potent antibacterial activity comparable with that of a compound bearing a non-fluorinated (3*R*)-3-(1-aminocyclopropan-1-yl)pyrrolidine moiety at the C-7 position (**1**) and had at least 4 times more potent activity against representative Gram-positive bacteria than ciprofloxacin (CPFX), gatifloxacin (GFLX), or moxifloxacin (MFLX). Among them, the 7-[(3*S*,4*R*)-4-(1-aminocyclopropan-1-yl)-3-fluoropyrrolidin-1-yl] derivative **3** (=DQ-113), which showed favorable profiles in preliminary toxicological and nonclinical pharmcokinetic studies, exhibited potent antibacterial activity against clinically isolated resistant Gram-positive pathogens.

Introduction

Multidrug-resistant Gram-positive pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae* (PRSP), and vancomycin-resistant enterococci (VRE), have become a serious problem in the medical community.[2−5] One particular alarming sign is the acquisition of resistance to vancomycin (VRE and vancomycin-intermediate-resistant staphylococcal strains; VISA), an antibiotic generally regarded as the agent of last resort for serious infections.[2,4−6] In the field of quinolone antibacterial agents, various attempts have been made to obtain potent drugs for resistant Gram-positive bacteria, and trovafloxacin (TVFX),[7] moxifloxacin (MFLX),[8] gemifloxacin (GMFX),[9] and gatifloxacin (GFLX)[10], etc. have been developed and introduced into clinical use over the past several years. Considering that the incidence of Gram-positive bacterial resistance to antibacterial agents has been growing, however, antibacterial activities of these newer quinolones are not potent enough and bacteria resistant to those agents will be problematic in the near future.[11,12] There are a few agents other than quinolones, such as teicoplanin (TEIC),[13] quinupristin/dalfopristin (QPR/DPR),[14] and linezolid,[15] which are now available in clinical use, but they show some problems, e.g., resistance mutations and/or side effects.[5,16] These problems have been the driving force for the development of new antibacterial agents that would be applicable to infections caused by multidrug-resistant Gram-positive pathogens.

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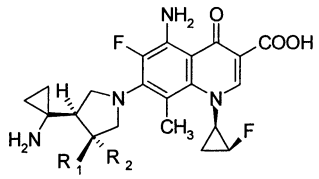

1: R_1 = H, R_2 = H
2: R_1 = H, R_2 = F
3 (= DQ-113): R_1 = F, R_2 = H
4: R_1 = F, R_2 = F

Figure 1.

In our previous paper, we reported that several quinolone derivatives bearing 3-(1-amino-1-substituted-methyl)pyrrolidin-1-yl groups, including the 3-(1-aminocyclopropan-1-yl)pyrrolidin-1-yl substituent, at the C-7 position showed potent antibacterial activity against Gram-positive bacteria.[17] Although 7-{(3*R*)-3-(1-aminocyclopropan-1-yl)pyrrolidin-1-yl}quinolone derivatives exhibit the most potent activity among them, they possess higher genotoxicity than 7-(piperazin-1-yl)- or 7-(3-aminopyrrolidin-1-yl)quinolone derivatives. The high genotoxicity of 7-(3-aminomethylpyrrolidin-1-yl)quinolone derivatives has also been reported by the other groups.[18−21] As a method to reduce the genotoxicity, we reported the usefulness of introducing a (1*R*,2*S*)-2-fluorocyclopropan-1-yl substituent into the N-1 position instead of a cyclopropyl substituent.[22−24] In addition, 5-amino-8-methylquinolone derivatives were reported to exhibit potent antibacterial activity against Gram-positive bacteria and showed reduced chromosomal toxicity in comparison with 8-methylquinolone derivatives.[25−26] Therefore, we initially designed and synthesized 5-amino-1-[(1*R*,2*S*)-2-fluorocyclopropan-1-yl]-8-methylquinolone having the (3*R*)-3-(1-aminocyclopropan-1-yl)pyrrolidin-1-yl substituent at the C-7 position (**1**, Figure 1) to obtain a highly potent compound against

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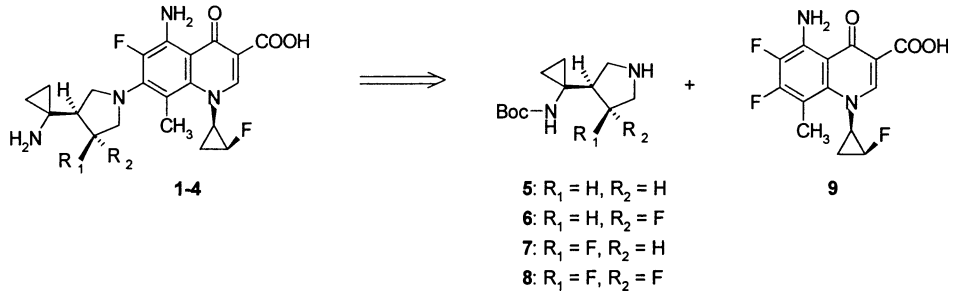
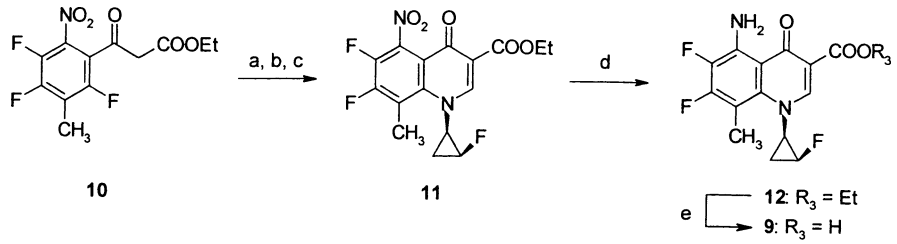
Scheme 1

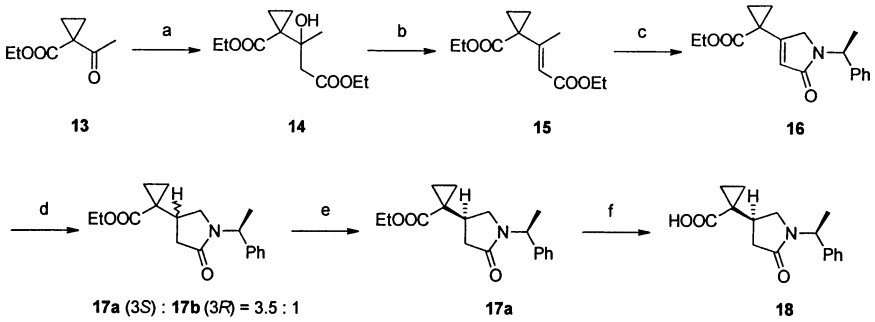


Scheme 2[a]



[a] Reagents: (a) Ac_2O, $CH(OEt)_3$, reflux; (b) (1*R*,2*S*)-2-fluoro-1-cyclopropylamine *p*-toluenesulfonic acid salt, Et_3N/CH_2Cl_2; (c) NaH/1,4-dioxane; (d) H_2, Raney Ni (W-6)/MeOH, 1,4-dioxane; (e) concentrated aqueous HCl, AcOH, reflux.

Scheme 3[a]



[a] Reagents: (a) Zn, $BrCH_2CO_2Et$, cat. I_2/THF, reflux; (b) (1) $SOCl_2$/pyridine, (2) DBU/CH_2Cl_2; (c) (1) NBS, AIBN/CCl_4, (2) (*S*)-1-phenylethylamine, $NaHCO_3$/EtOH, reflux; (d) H_2, PtO_2/MeOH; (e) silica gel column chromatography; (f) aqueous NaOH/EtOH.

Gram-positive bacteria with reduced genotoxicity. As we expected, **1** showed highly potent antibacterial activity but showed a positive response in the micronucleus test and is toxic in the chromosome injuring test.

In addition to the benefit of the (1*R*,2*S*)-2-fluorocyclopropan-1-yl substituent at the N-1 position, we also found that introduction of a fluorine atom into the C-7 pyrrolidine substituent was also effective in reducing genotoxicity.[27] Thus, we planned to introduce this strategy into compound **1** and designed and synthesized three quinolone compounds having the (3*R*,4*R*)-4-(1-aminocyclopropan-1-yl)-3-fluoropyrrolidin-1-yl substituent (**2**), (3*S*,4*R*)-4-(1-aminocyclopropan-1-yl)-3-fluoropyrrolidin-1-yl substituent (**3**), or (4*R*)-4-(1-aminocyclopropan-1-yl)-3,3-difluoropyrrolidin-1-yl substituent (**4**) at the C-7 position.

In this paper, we report the synthesis, the in vitro antibacterial activity, and the toxicity profiles of these 5-amino-1-[(1*R*,2*S*)-2-fluorocyclopropan-1-yl]-8-methylquinolones.

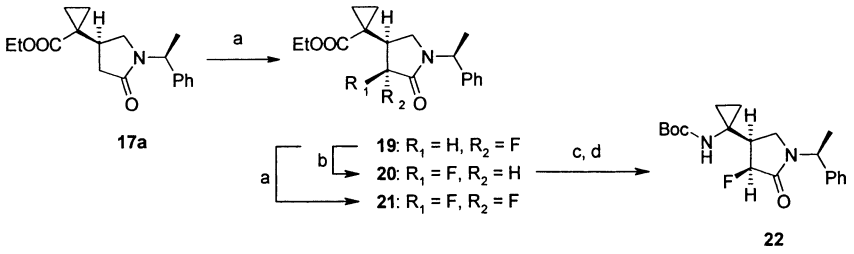
Chemistry

We planned to synthesize those four compounds **1**−**4** by aromatic nucleophilic substitution reaction from 5-amino-6,7-difluoro-1-[(1*R*,2*S*)-2-fluorocyclopropan-1-yl]-8-methylquinolone-3-carboxylic acid **9** and appropriate (3*R*)-3-(1-aminocyclopropan-1-yl)pyrrolidines **5**−**8**, of which the peripheral amino groups were protected by *tert*-butoxycarbonyl groups (Scheme 1).

The synthesis of **9** is illustrated in Scheme 2. Treatment of ketoester **10**, reported by Yoshida,[25] with ethyl orthoformate in acetic anhydride followed by the reaction with (1*R*,2*S*)-2-fluoro-1-cyclopropylamine *p*-toluenesulfonic acid salt in the presence of triethylamine provided crude enaminoketoester. Cyclization of the resultant product with NaH in 1,4-dioxane yielded 5-nitroquinolone-3-carboxylate **11**. Hydrogenation of the nitro group of **11** followed by acidic hydrolysis of the resultant 5-aminoquinolone-3-carboxylate **12** provided quinolonecarboxylic acid **9**.

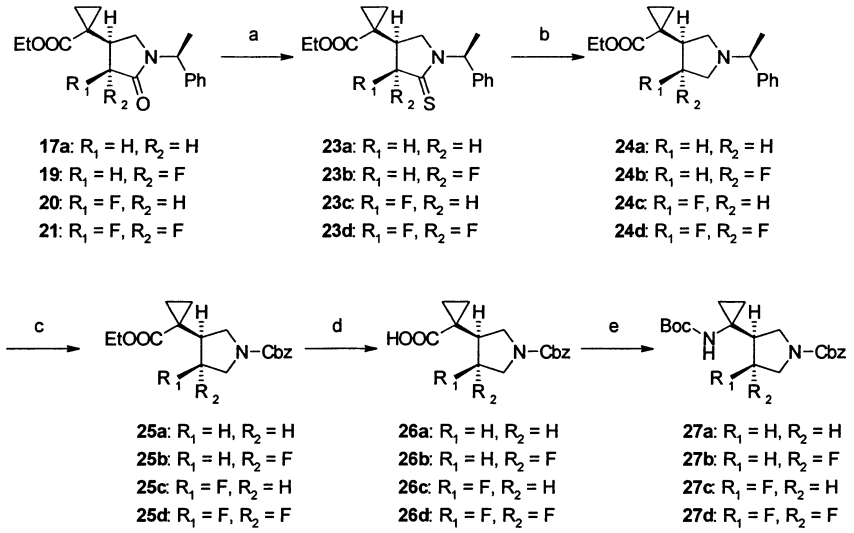
(3*R*)-3-(1-Aminocyclopropan-1-yl)pyrrolidin-1-yl substituents **5**−**8** were synthesized via 1-(5-oxopyrrolidin-3-yl)cyclopropanecarboxylate **17a**. The synthesis of **17a** is illustrated in Scheme 3. The Reformatsky reaction of 1-acetylcyclopropanecarboxylate **13** [28] with ethyl bromoacetate gave hydroxyester **14**. The α,*β*-unsaturated ester **15** was prepared by chlorination of **14** with thionyl chloride/pyridine and the subsequent elimination reaction of the chlorinated product with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). These conditions gave exclu-

Scheme 4[a]



[a] Reagents: (a) LDA, then $(PhSO_2)_2NF$/THF; (b) LDA, then 2,6-di-*tert*-butylphenol/THF; (c) aqueous NaOH/EtOH; (d) diphenylphosphoryl azide, Et_3N/toluene, then *tert*-BuOH.

Scheme 5[a]



[a] Reagents: (a) Lawesson's reagent/benzene; (b) Raney Ni (W-6)/EtOH; (c) Cbz-Cl/CH_2Cl_2; (d) aqueous NaOH/EtOH; (e) diphenylphosphoryl azide, Et_3N/*tert*-BuOH.

sively the (*E*)-isomer. Bromination of the allylic position of **15** with *N*-bromosuccinimide (NBS) catalyzed by azobisisobutyronitrile (AIBN) and treatment of the resultant bromoester with (*S*)-1-phenylethylamine provided cyclized pyrrolinone **16**. Hydrogenation of **16** catalyzed by platinum dioxide gave a mixture of two diastereomers **17a** and **17b**, which were separated by silica gel column chromatography (**17a**/**17b** = 3.5:1). The major isomer **17a** was converted to the carboxylic acid **18** by basic hydrolysis to determine the absolute configuration of the C-3 position. Compound **18** was obtained as prisms, and the absolute configuration was determined to be (3*S*) by X-ray crystallographic analysis.

Incorporation of fluorine atom(s) into the pyrrolidinone ring was achieved as illustrated in Scheme 4. (3*S*)-Oxopyrrolidinylester **17a** was treated with lithium diisopropylamide (LDA) followed by *N*-fluorobenzenesulfonimide to provide *trans*-fluorinated oxopyrrolidinylester **19**. The *cis*-fluorinated compound **20** was synthesized by treatment of **19** with LDA and subsequent quenching with 2,6-di-*tert*-butylphenol. To confirm the configuration of the fluorinated position of the two fluorinated compounds **19** and **20**, **20** was converted to the *tert*-butoxycarbonylamino compound **22** by basic hydrolysis and subsequent Curtius rearrangement reaction using diphenylphosphoryl azide (DPPA) and *tert*-butyl alcohol. Compound **22** was analyzed by X-ray crystallographic analysis, and the configuration of the fluorinated position was determined to be (4*R*). Accordingly, the configuration of the fluorinated position of **19** and **20** was determined to be (4*S*) and (4*R*), respectively. Difluorinated compound **21** was synthesized by treatment of **19** with LDA and *N*-fluorobenzenesulfonimide.

The four oxopyrrolidinylesters **17a**, **19**, **20**, and **21** synthesized above were converted to benzyloxycarbonylpyrrolidine compounds **27a**−**d**, respectively, as shown in Scheme 5. Treatment of the oxopyrrolidinylesters **17a**, **19**, **20**, **21** with Lawesson's reagent afforded thioxopyrrolidinylesters **23a**−**d**, and reduction of the thioxo moieties by Raney nickel gave pyrrolidinylesters **24a**−**d**. The 1-phenylethyl groups of **24a**−**d** were transformed to benzyloxycarbonyl groups using benzyl chloroformate according to the von Braun conditions to provide benzyloxycarbonyl compounds **25a**−**d**. Basic hydrolysis of **25a**−**d** followed by the Curtius rearrangement of the resultant carboxylic acids **26a**−**d** using DPPA and *tert*-butyl alcohol provided **27a**−**d**, respectively.

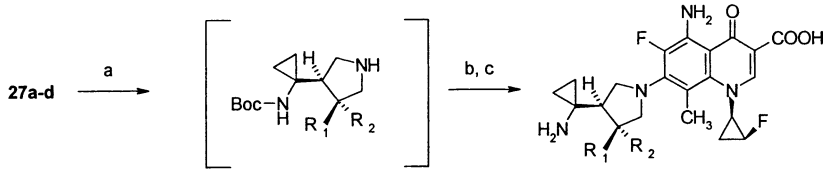
Finally, as illustrated in Scheme 6, the benzyloxycarbonyl groups of **27a**−**d** were deprotected by catalytic hydrogenation, and the resultant crude products of **5**−**8** and quinolonecarboxylic acid **9** were heated with triethylamine in DMSO followed by deprotection of *tert*-butoxycarbonyl groups under acidic condition to give the final products **1**−**4**, respectively.

Reference compounds **30** and **31** were synthesized from **9** and **28** or **29**,[17] respectively, by the same procedure as described for **1**−**4**, as illustrated in Scheme 7.

Results and Discussion

The minimum inhibitory concentrations (MICs) of **1**−**4**, **30**, and **31** against several representative Gram-

Scheme 6[a]

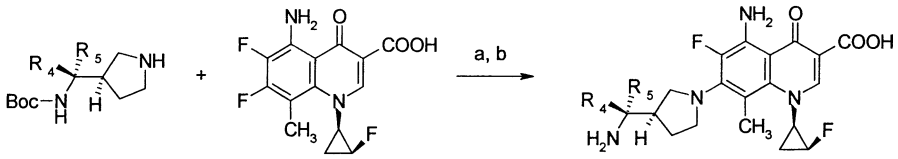


5: R_1 = H, R_2 = H
6: R_1 = H, R_2 = F
7: R_1 = F, R_2 = H
8: R_1 = F, R_2 = F

1: R_1 = H, R_2 = H
2: R_1 = H, R_2 = F (HCl salt)
3 (= DQ-113): R_1 = F, R_2 = H
4: R_1 = F, R_2 = F (HCl salt)

[a] Reagents: (a) H_2, Pd−C/EtOH; (b) **9**, Et_3N/DMSO, heat; (c) concentrated aqueous HCl.

Scheme 7[a]



28: R_4 = H, R_5 = H
29: R_4 = Me, R_5 = H

9

30: R_4 = H, R_5 = H
31: R_4 = Me, R_5 = H

[a] Reagents: (a) Et_3N/DMSO, heat; (b) concentrated aqueous HCl

Table 1. Antibacterial Activities of **1**−**4**, **30**, and **31** and the Reference Compounds

	MIC, μg/mL									
organisms	**1**	**2**	**3**	**4**	**30**	**31**	TVFX[a]	MFLX[a]	GFLX[a]	CPFX[a]
S. aureus FDA 209-P	≤0.003	≤0.003	≤0.003	≤0.003	≤0.003	≤0.003	0.013	0.013	0.05	0.05
S. epidermidis 56500	≤0.003	≤0.003	≤0.003	≤0.003	0.006	≤0.003	0.05	0.1	0.2	0.2
S. pneumoniae J-24	≤0.003	≤0.003	≤0.003	≤0.003	0.013	≤0.003	0.05	0.025	0.2	0.39
S. pyogenes G-36	≤0.003	≤0.003	≤0.003	≤0.003	0.013	≤0.003	0.2	0.2	0.39	1.56
S. mitis IID685	≤0.003	≤0.003	≤0.003	≤0.003	0.006	≤0.003	0.1	0.1	0.2	0.78
E. faecalis ATCC19433	0.013	0.013	0.025	0.013	0.025	0.025	0.2	0.2	0.39	0.78
E. coli NIHJ	≤0.003	≤0.003	≤0.003	≤0.003	0.013	≤0.003	≤0.003	0.006	0.006	≤0.003
K. pneumoniae type II	0.025	0.013	0.013	0.013	0.1	0.025	0.025	0.05	0.05	0.025
P. aeruginosa PAO1	0.1	0.2	0.39	0.2	0.1	0.05	0.2	0.78	0.39	0.05

[a] Abbreviations are as follows: TVFX = trovafloxacin; MFLX = moxifloxacin; GFLX = gatifloxacin; CPFX = ciprofloxacin.

positive and Gram-negative bacteria are summarized in Table 1, along with the data for TVFX, MFLX, GFLX, and ciprofloxacin (CPFX)[29] for comparison. The synthesized compounds **1**−**4**, **30**, and **31** exhibited 2−128 times more potent activity against Gram-positive bacteria than the reference quinolones TVFX, MFLX, GFLX, and CPFX. In particular, 3-(1-amino-1-substituted-methyl)-pyrrolidine derivatives **1**−**4** and **31** were at least 4 times more potent than the newer quinolones TVFX, MFLX, and GFLX, which were designed for Gram-positive infections. Against Gram-negative bacteria, except for *P. aeruginosa*, **1**−**4** and **31** exhibited potency comparable with that of TVFX and CPFX. The compounds possessing fluorinated pyrrolidines at the C-7 position, **2**−**4**, and the non-fluorinated compound **1** showed almost identical antibacterial activities. Thus, introduction of fluorine atom(s) to pyrrolidine substituents did not affect antibacterial activities substantially.

The results of the intravenous single-dose toxicity study and the micronucleus test are summarized in Table 2. Concerning the intravenous single-dose toxicity, compound **1**, which possesses the (3*R*)-3-(1-aminocyclopropan-1-yl)pyrrolidin-1-yl substituent at the C-7 position, was less toxic than compound **30**, which has the (3*R*)-3-(aminomethyl)pyrrolidin-1-yl substituent, and **31**, which has the (3*R*,1′*S*)-3-(1-aminoethyl)pyrrolidin-1-yl substituent. Compounds **2** and **3**, which have monofluorinated pyrrolidines, showed different profiles according to the configuration of their fluorine atoms. Compound **2**, which has *trans*-oriented fluoropyrrolidine, was more toxic than non-fluorinated compound **1**, while *cis*-oriented compound **3** was less toxic than **1**.

Table 2. Intravenous Single-Dose Toxicity and Micronuclei-Forming Toxicity of **1**−**4**, **30**, and **31** in Mice

Intravenous Single-Dose Toxicity

	mortality (dead/tested)					
dose, mg/kg	**1**	**2**	**3**	**4**	**30**	**31**
150	2/2	2/2	0/5	2/2	2/2	2/2
100	0/5	2/2	NT[a]	1/5	2/2	2/2
50	NT[a]	0/5	NT[a]	NT[a]	2/2	1/5

Micronuclei-Forming Toxicity[b]

result (dose, mg/kg)					
1	**2**	**3**	**4**	**30**	**31**
+ (100)	− (50)	− (150)	− (100)	NT[a]	+ (50)

[a] NT = not tested. [b] (+) positive. (−) negative.

Table 3. Solubility of **1**−**4**, **30**, and **31** in Water

solubility, μg/mL					
1	**2**	**3**	**4**	**30**	**31**
39	NT[a]	291	NT[a]	404	95

[a] NT = not tested.

Table 4. Antibacterial Activities of **3** (DQ-113) and Reference Compounds against Clinically Isolated Levofloxacin-Resistant MRSA (LVFX-r MRSA), PRSP, and VRE

	LVFX-r MRSA[a] (74[b])			PRSP[c] (50[b])			VRE (Van A) (33[b])			VRE (Van B) (10[b])		
compds	range, μg/mL	MIC_{50}, μg/mL	MIC_{90}, μg/mL	range, μg/mL	MIC_{50}, μg/mL	MIC_{90}, μg/mL	range, μg/mL	MIC_{50}, μg/mL	MIC_{90}, μg/mL	range, μg/mL	MIC_{50}, μg/mL	MIC_{90}, μg/mL
3 (DQ-113)	≤0.004−4	0.12	0.5	≤0.008−0.015	≤0.008	0.015	0.12−2	0.25	2	0.015−2	0.25	0.25
GFLX[d]	0.12−>128	4	32	0.06−0.5	0.25	0.25	2−64	16	32	0.25−32	2	16
MFLX[d]	0.06−128	4	16	0.06−0.25	0.12	0.25	2−32	16	32	0.12−32	2	8
GMFX[d]	0.06−128	2	32	0.015−0.06	0.03	0.06	1−32	4	32	0.03−16	1	2
ABK[d]	4−128	8	32	4−32	16	32	4−>128	16	64	2−>128	32	>128
VCM[d]	0.5−2	1	2	0.25−0.5	0.5	0.5	>128	>128	>128	8−>128	>128	>128
TEIC[d]	0.06−4	0.5	1	0.12−1	0.25	0.5	8−128	32	64	0.25−2	1	2
QPR/DPR[d]	0.25−1	0.5	0.5	0.5−1	1	1	0.25−16	0.5	8	0.5−16	0.5	8
LNZ[d]	2	2	2	0.25−0.5	0.5	0.5	2	2	2	2	2	2

[a] MIC range of levofloxacin is 0.5−128 μg/mL. [b] No. of strains. [c] MIC range of benzylpenicillin is 1−4 μg/mL. [d] Abbreviations are as follows: GFLX = gatifloxacin; MFLX = moxifloxacin; GMFX = gemifloxacin; ABK = arbekacin; VCM = vancomycin; TEIC = teicoplanin; QPR/DPR = quinupristin/dalfopristin; LNZ = linezolid.

Table 5. Pharmacokinetic Parameters of **3** (DQ-113) Intravenously Administered to Rats at a Dose of 20 mg/kg[30]

	parameters (units)[a]			
tissue	C_{5min} (μg/mL or μg/g)	$t_{1/2}$ (h)	AUC_{0-6h} (μg·h/mL or μg·h/g)	AUC ratio (tissue/serum)
serum	11.1	1.1	9.3	1.0
liver	46.2	1.3	36.0	3.9
kidney	33.7	1.3	34.8	3.7
lung	22.0	0.9	37.9	4.1

[a] Mean values of four animals.

Difluorinated compound **4** showed almost the same toxicity as **1**. Concerning the micronuclei-forming toxicity, the non-fluorinated compounds **1** and **31** showed a positive response, even though they have the 5-amino-8-methyl substituent combination and the (1*R*,2*S*)-2-fluorocyclopropan-1-yl group at the N-1 position, which are reported to reduce genotoxicity.[21−26] Compounds **2**−**4**, which have the fluorinated pyrrolidines, showed negative responses as we expected. The results indicate the advantage of introducing fluorine atom(s) into the pyrrolidine substituent at the C-7 position for reducing micronuclei-forming toxicity as we described before.[27,30]

Table 3 shows the solubility of these compounds in water. The fluorinated compound **3** was more soluble than the non-fluorinated compound **1**. These data indicate that the fluorine atom contributes to improving solubility in water.

The MICs against clinically isolated resistant Gram-positive bacteria of compound **3** (DQ-113), which exhibited the lowest single-dose toxicity and a negative response in the micronucleus test, were determined, and the results are shown in Table 4. Compound **3** exhibited more potent activity than the other quinolone antibacterial agents (GFLX, MFLX, and GMFX), VCM, TEIC, and LNZ, and the activity was comparable with QPR/DPR against levofloxacin-resistant MRSA. Against PRSP, **3** exhibited the most potent activity among the listed compounds. Compound **3** also exhibited the most potent activity against both strains of VRE (Van A strains and Van B strains) among the listed compounds.

The pharmacokinetic profile of compound **3** after intravenous administration (20 mg/kg) to rats is shown in Table 5. Compound **3** exhibited high plasma concentration, and the area under the time−concentration curve (AUC) and showed a good distribution pattern in liver, kidney, and lung.[31]

Conclusion

We synthesized a series of novel 5-amino-6-fluoro-1-[(1*R*,2*S*)-2-fluorocyclopropan-1-yl]-8-methylquinolones bearing fluorinated (3*R*)-3-(1-aminocyclopropan-1-yl)-pyrrolidin-1-yl substituents at the C-7 position. The fluorinated compounds **2**−**4** exhibited potent antibacterial activity comparable with the non-fluorinated compound **1** and at least 4 times more potent activity against Gram-positive bacteria than the reference quinolones. In addition, they showed no micronuclei-forming toxicity. Among the fluorinated compounds, *cis*-oriented derivative **3** (DQ-113) showed reduced intravenous single-dose toxicity in comparison with **1** and a good pharmacokinetic profile in rats and exhibited comparable or greater antibacterial activity against clinically isolated resistant Gram-positive bacteria in comparison with the other quinolones tested, vancomycin, teicoplanin, quinupristin/dalfopristin, and linezolid. Compound **3** has been found to exhibit excellent antibacterial activity against other clinically isolated bacteria[32] in addition to those we describe in this paper and was selected for further preclinical evaluation.

Experimental Section

General. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Melting points were taken on a Yanako MP-500D melting point apparatus and are uncorrected. Optical rotations were measured in a 0.5 dm cell at 25 °C at 589 nm with a HORIBA SEPA-300 polarimeter. ^{1}H NMR spectra were determined on a JEOL JNM-EX400 spectrometer. Chemical shifts are reported in parts per million relative to tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-5-sulfonate as internal standards. Significant ^{1}H NMR data are tabulated in the following order: number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant(s) in hertz. High-resolution mass spectra were obtained on a JEOL JMS-700 mass spectrometer under electron impact ionization conditions (EI), electron spray ionization conditions (ESI), or fast atom bombardment ionization conditions (FAB). Elemental analyses are indicated only by the symbols of the elements; analytical results were within 0.4% of the theoretical values unless otherwise noted. Column chromatography refers to flash column chromatography conducted on Merck silica gel 60, 230−400 mesh ASTM. Thin-layer chromatography (TLC) was performed with Merck silica gel 60 F_{254} TLC plates, and compound visualization was effected with a 5% solution of molybdophosphoric acid in ethanol, UV lamp, iodine, or Wako ninhydrin spray.

In Vitro Antibacterial Activity. The MICs of the compounds tested in this study were determined by the 2-fold

micro broth dilution method using Mueller−Hinton broth (Difco Laboratories, Detroit, MI) with an inoculum size of approximately 10^5 CFU per well. The MIC was defined as the lowest concentration that prevented visible bacterial growth after incubation at 37 °C for 18 h.

Intravenous Single-Dose Toxicity. The test compounds were dissolved in 0.1 N NaOH in saline at different concentrations. The solution was administered intravenously to 5-week-old male Slc:ddY mice at a speed of 0.2 mL/min. The total volume of administration was adjusted to 10 mL/kg of body weight. The number of dead mice was counted on day 7.

Micronucleus Test. Five-week-old male Slc:ddY mice were used in this test. The test compounds were dissolved in 0.1 N NaOH in saline, and the solution was administered intravenously in each group of mice. At 24 and 48 h after treatment, approximately 5 μL of peripheral blood was collected from a tail blood vessel of each mice. The blood was dropped onto an acridine orange coated glass slide and covered immediately with a coverslip. For each animal, 1000 reticulocytes were examined for micronuclei by fluorescence microscopy, and the frequency of micronucleated reticulocytes (MNRET) was expressed as a percentage. Statistical analysis was performed with the Kastenbaum and Bowman method.[33]

Pharmacokinetic Studies. Seven-week-old male Crj:CD rats ($n = 4$) were used. The animals were administered drug samples in a single intravenous dose (20 mg/kg) as an aqueous solution. The concentrations of the compounds were determined by a microbiological assay (agar well dilution method) using *B. subtilis* ATCC 6051. The mean values of the four rats were shown.

X-ray Crystallographic Study. All measurements were made on a Rigaku AFC7R diffractometer (Cu Kα radiation, $\lambda = 1.541\,78$ Å, graphite monochromator, $\omega-2\theta$ scans, $2\theta_{max} = 120.1°$). The crystal data and parameters are summarized below. The structures were solved by direct methods and refined by full-matrix least-squares and Fourier techniques. The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were refined isotropically ($d_{C-H} = 0.95$ Å), and hydrogen positions were calculated by assuming ideal geometries. The acidic hydrogen atom of **18** was refined with respect to its coordinates. All calculations were performed by using the teXsan crystallographic software package of Molecular Structure Corporation.

Crystal Data and Structure Analysis. For **18**, a colorless prism-shaped crystal was formed from AcOEt: $C_{16}H_{19}NO_3$; FW = 273.33; sample dimensions, 0.30 mm × 0.25 mm × 0.13 mm; orthorhombic, space group $P2_12_12_1$; $a = 11.156(1)$ Å, $b = 20.549(1)$ Å, $c = 6.4714(7)$ Å, $V = 1483.5(2)$ Å^3, $Z = 4$; $d_{calcd} = 1.224$ g/cm^3; $F_{000} = 584$; $\mu = 6.85$ cm^{-1}. The final cycle of full-matrix least squares refinement was based on 1312 observed reflections and 186 variable parameters and converged at $R = 0.042$ ($R_w = 0.107$).

For **22**, a colorless prism-shaped crystal was formed from *n*-hexane/CH_2Cl_2: $C_{20}H_{27}FN_2O_3$; FW = 362.44; sample dimensions, 0.15 mm × 0.25 mm × 0.25 mm; orthorhombic, space group $P2_12_12_1$; $a = 12.186(1)$ Å, $b = 15.8918(9)$ Å, $c = 10.682-(1)$ Å, $V = 2068.7(2)$ Å^3, $Z = 4$; $d_{calcd} = 1.164$ g/cm^3; $F_{000} = 776$; $\mu = 6.92$ cm^{-1}. The final cycle of full-matrix least squares refinement was based on 1595 observed reflections and 237 variable parameters and converged at $R = 0.052$ ($R_w = 0.099$).

Ethyl 6,7-Difluoro-1-[(1*R*,2*S*)-2-fluorocyclopropan-1-yl]-1,4-dihydro-8-methyl-5-nitro-4-oxoquinoline-3-carboxylate (11). A mixture of ethyl 2,4,5-trifluoro-3-methyl-6-nitrobenzoylacetate (**10**) (16.4 g, 53.8 mmol), ethyl orthoformate (17.9 mL, 107.6 mmol), and 29 mL of Ac_2O was heated at 100 °C for 2 h. The mixture was concentrated in vacuo to give a brown oil. To a stirred solution of the brown oil in 200 mL of toluene in an ice bath was added (1*R*,2*S*)-2-fluorocyclopropylamine *p*-toluenesulfonic acid salt (16.0 g, 64.7 mmol), and then a solution of triethylamine (10.9 mL, 78.0 mmol) in 30 mL of toluene was added dropwise. Stirring was continued for 2 h in the ice bath. The mixture was diluted with AcOEt, and the solution was washed with water and brine (2×), dried over Na_2SO_4, and concentrated. To a stirred solution of the residue in 150 mL of 1,4-dioxane on an ice bath was added NaH (60% mineral oil dispersion, 3.23 g, 80.7 mmol) portionwise. The mixture was stirred at ambient temperature for 1 h. After the mixture was poured into ice-cooled 5 N aqueous HCl, the precipitate was collected by filtration and washed with water (3×) to give the crude product. Recrystallization from $CHCl_3$/EtOH gave pure **11** (13.9 g, 70%) as a colorless powder, mp 230−231 °C. ^{1}H NMR ($CDCl_3$): δ 1.35−1.45 (1H, m), 1.38 (3H, t, $J = 7.3$ Hz), 1.58−1.70 (1H, m), 2.75 (3H, d, $J = 3.4$ Hz), 3.85−3.93 (1H, m), 4.37 (2H, q, $J = 7.3$ Hz), 4.80−4.83 and 4.95−4.99 (1H, m), 8.57 (1H, d, $J = 2.9$ Hz). Anal. ($C_{16}H_{13}F_3N_2O_5$) C, H, N. $[\alpha]_D$ −124.0° (*c* 0.325, DMSO).

Ethyl 5-Amino-6,7-difluoro-1-[(1*R*,2*S*)-2-fluorocyclopropan-1-yl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylate (12). 11 (13.9 g, 37.6 mmol) was suspended in 500 mL of methanol and 500 mL of 1,4-dioxane. Raney Ni (200 mL) was added to the suspension, and the suspension was stirred at ambient temperature for 10 min. The suspension was filtered and concentrated in vacuo. The residue was dissolved in 300 mL of $CHCl_3$, filtered through Celite, and concentrated in vacuo to give **12** (12.5 g, 98%) as a yellow powder, mp 187−189 °C. ^{1}H NMR ($CDCl_3$): δ 1.25−1.38 (1H, m), 1.39 (3H, t, $J = 7.3$ Hz), 1.45−1.59 (1H, m), 2.46 (3H, d, $J = 2.4$ Hz), 3.73−3.79 (1H, m), 4.38 (2H, q, $J = 7.3$ Hz), 4.73−4.75 and 4.88−4.92 (1H, m), 6.99 (2H, br s), 8.40 (1H, d, $J = 3.4$ Hz). Anal. ($C_{16}H_{15}F_3N_2O_3$) C, H, N. $[\alpha]_D$ −240.9° (*c* 0.560, DMSO).

5-Amino-6,7-difluoro-1-[(1*R*,2*S*)-2-fluorocyclopropan-1-yl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic Acid (9). A mixture of **12** (10.43 g, 30.6 mmol), 150 mL of AcOH, and 150 mL of concentrated aqueous HCl was heated for reflux for 1 h. After the mixture was cooled, 700 mL of cold water was added and the precipitate was collected by filtration. The resultant solid was washed with water (2×), EtOH, and Et_2O and then dried with a vacuum pump to give **9** (7.52 g, 79%) as a yellow powder, mp 293−297 °C (dec). ^{1}H NMR (0.1 N NaOD/D_2O): δ 1.31−1.42 (1H, m), 1.53−1.68 (1H, m), 2.52 (3H, s), 4.03−4.10 (1H, m), 4.85−4.93 and 5.05−5.10 (1H, m), 8.32 (1H, s). Anal. ($C_{14}H_{11}F_3N_2O_3$) C, H, N. $[\alpha]_D$ −163.0° (*c* 0.460, DMSO).

Ethyl 3-(1-Ethoxycarbonylcyclopropan-1-yl)-3-hydroxybutanoate (14). To a solution of ethyl 1-acetylcyclopropanecarboxylate (**13**) (61.7 g, 0.39 mol) in 500 mL of PhH was added Zn powder (13 g, 0.20 mol) and a catalytic amount of I_2. To the mixture, heated for reflux, a solution of ethyl bromoacetate (56.2 mL, 0.51 mol) in 100 mL of PhH was added dropwise carefully. When the reaction started, the addition was suspended and Zn powder (39 g, 0.61 mol) was added to the reaction vessel portionwise. Then the rest of the ethyl bromoacetate solution was slowly added dropwise and the mixture was heated for reflux for another 2 h. The mixture was cooled to ambient temperature, and 500 mL of 1 N aqueous HCl was added to the mixture. The resultant suspension was filtered through Celite, and the organic layer was separated. The organic solution was washed with brine (2×), dried over Na_2SO_4, and concentrated to give **15** (90.3 g, 95%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.08−1.18 (4H, m), 1.23 (3H, t, $J = 6.8$ Hz), 1.27 (3H, t, $J = 6.8$ Hz), 1.43 (3H, s), 2.91 (1H, d, $J = 15.1$ Hz), 2.98 (1H, d, $J = 15.1$ Hz), 4.09 (2H, q, $J = 6.8$ Hz), 4.19 (2H, q, $J = 6.8$ Hz). High-resolution MS (FAB) calcd for $C_{12}H_{20}O_5$ + H: 245.1389. Found: 245.1382.

Ethyl (*E*)-3-(1-Ethoxycarbonylcyclopropan-1-yl)-2-butenoate (15). To a solution of **14** (90.3 g, 0.37 mol) in pyridine (182 mL, 2.25 mol) at −10 °C, thionyl chloride (35.1 mL, 0.48 mmol) was added dropwise. The mixture was stirred at this temperature for 3 h and then poured into ice water. The mixture was extracted with CH_2Cl_2 (3×), and the combined organic layer was washed with 1 N aqueous HCl and brine and was dried over Na_2SO_4. Then DBU (58 mL, 0.39 mol) was added dropwise to the solution at 0 °C and the mixture was stirred at ambient temperature for 18 h. The resultant solution was washed with 1 N aqueous HCl and brine and was dried over Na_2SO_4, and the residue was purified by column chromatography, eluting with AcOEt/hexane = 1:9 to yield **15** (56.6

g, 68%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.01 (2H, dd, J = 3.9, 6.8 Hz), 1.24 (3H, t, J = 7.3 Hz), 1.28 (3H, t, J = 7.3 Hz), 1.40 (2H, dd, J = 3.9, 6.8 Hz), 2.29 (3H, d, J = 1.5 Hz), 4.13 (2H, q, J = 7.3 Hz), 4.16 (2H, q, J = 7.3 Hz), 5.78 (1H, d, J = 1.0 Hz). High-resolution MS (FAB) calcd for $C_{12}H_{18}O_4$ + H: 227.1283. Found: 227.1283.

Ethyl 1-{2,5-Dihydro-5-oxo-1-[(*S*)-1-phenylethyl]-1*H*-pyrrol-3-yl}cyclopropanecarboxylate (16). To a solution of **15** (25.4 g, 0.11 mol) in 300 mL of CCl_4 was added *N*-bromosuccinimide (23.9 g, 0.13 mol) and a catalytic amount of 2,2′-azobisisobutyronitrile, and the mixture was heated to reflux for 5 h. The mixture was filtrated and concentrated in vacuo. The residue was dissolved in 250 mL of EtOH and $NaHCO_3$ (18.8 g, 0.22 mol), and then (*S*)-1-phenylethylamine (15.8 mL, 0.12 mol) was added dropwise at ambient temperature. The mixture was stirred at this temperature for 30 min and then heated to reflux for 4 h. The mixture was concentrated in vacuo, AcOEt was added to the residue, and then the solution was washed with water, 1 N aqueous HCl (2×), and brine (2×) and dried over Na_2SO_4. The residue was purified by column chromatography, eluting with AcOEt/hexane = 1:1 to yield **16** (13.1 g, 39%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.13−1.15 (2H, m), 1.18 (3H, t, J = 6.8 Hz), 1.60 (3H, d, J = 7.3 Hz), 1.61−1.64 (2H, m), 3.80 (1H, d, J = 19.5 Hz), 4.09 (2H, q, J = 6.8 Hz), 4.13 (1H, q, J = 19.5 Hz), 5.56 (1H, q, J = 7.3 Hz), 5.85 (1H, t, J = 1.5 Hz), 7.25−7.37 (5H, m). High-resolution MS (FAB) calcd for $C_{18}H_{21}NO_3$ + H: 300.1600. Found: 300.1609. $[\alpha]_D$ −56.5° (*c* 0.536, $CHCl_3$).

Ethyl 1-{(3*S*)-5-Oxo-1-[(*S*)-1-phenylethyl]pyrrolidin-3-yl}cyclopropanecarboxylate (17a) and Ethyl 1-{(3*R*)-5-Oxo-1-[(*S*)-1-phenylethyl]pyrrolidin-3-yl}cyclopropanecarboxylate (17b). To a solution of **16** (12.1 g, 40.5 mmol) in 300 mL of MeOH was added PtO_2 catalyst (400 mg), and the mixture was stirred at ambient temperature for 18 h under a hydrogen atmosphere. The mixture was filtered and concentrated in vacuo to give a colorless oil. The oil was separated into two diastereomers by column chromatography, eluting with AcOEt/hexane = 2:3. **17a** (9.0 g, 74%) was a pale-yellow oil. ^{1}H NMR ($CDCl_3$): δ 0.63−0.65 (2H, m), 1.13 (3H, t, J = 7.1 Hz), 1.12−1.19 (2H, m), 1.52 (3H, d, J = 7.3 Hz), 2.17 (1H, dd, J = 9.0, 16.8 Hz), 2.46 (1H, dd, J = 9.3, 16.3 Hz), 2.67−2.76 (2H, m), 3.47 (1H, t, J = 8.3 Hz), 3.96−4.11 (2H, m), 5.51 (1H, q, J = 7.3 Hz), 7.26−7.35 (5H, m). High-resolution MS (EI) calcd for $C_{18}H_{23}NO_3$: 301.1678. Found: 301.1684. $[\alpha]_D$ −96.5° (*c* 1.291, $CHCl_3$). **17b** (2.6 g, 21%) was a pale-yellow oil. ^{1}H NMR ($CDCl_3$): δ 0.72−0.76 (2H, m), 1.18−1.24 (2H, m), 1.21 (3H, t, J = 7.1 Hz), 1.52 (3H, d, J = 7.1 Hz), 2.27−2.32 (1H, m), 2.44−2.52 (2H, m), 3.14 (2H, d, J = 8.0 Hz), 4.10 (2H, q, J = 7.1 Hz), 5.50 (1H, q, J = 7.1 Hz), 7.26−7.35 (5H, m).

1-{(3*S*)-5-Oxo-1-[(*S*)-1-phenylethyl]pyrrolidin-3-yl}cyclopropanecarboxylic Acid (18). To a solution of **17a** (10.5 g, 34.9 mmol) in 70 mL of EtOH was added 1 N aqueous NaOH (70 mL, 70.0 mmol) at ambient temperature, and the mixture was stirred at this temperature for 15.5 h and then at 40 °C for 3 h. The reaction mixture was concentrated in vacuo, and the residual aqueous solution was washed with AcOEt. Then the aqueous layer was acidified with concentrated aqueous HCl under ice cooling, and the mixture was extracted with $CHCl_3$ (3×). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo to give **18** (9.4 g, 99%) as a white solid. Recrystallization from AcOEt gave colorless prisms, and the crystals were analyzed by X-ray crystallography. ^{1}H NMR ($CDCl_3$): δ 0.72−0.74 (2H, m), 1.21−1.23 (2H, m), 1.52 (3H, d, J = 7.3 Hz), 2.17 (1H, dd, J = 8.8, 16.8 Hz), 2.48 (1H, dd, J = 9.5, 16.8 Hz), 2.66−2.78 (2H, m), 3.50 (1H, t, J = 9.3 Hz), 5.51 (1H, q, J = 7.3 Hz), 7.25−7.34 (5H, m). High-resolution MS (EI) calcd for $C_{16}H_{19}NO_3$: 273.1365. Found: 273.1361. $[\alpha]_D$ −120.2° (*c* 0.745, $CHCl_3$).

Ethyl 1-{(3*S*,4*R*)-4-Fluoro-5-oxo-1-[(*S*)-1-phenylethyl]-pyrrolidin-3-yl}cyclopropanecarboxylate (19). Under a nitrogen atmosphere, *n*-butyllithium solution (1.68 M in hexane, 18.1 mL, 30.4 mmol) was added dropwise to a stirred solution of diisopropylamine (3.99 mL, 30.4 mmol) in 50 mL of anhydrous THF at −78 °C over 10 min. The mixture was stirred at −10 °C for 20 min and then cooled to −78 °C. To the mixture was added a solution of **17a** (7.05 g, 23.4 mmol) in 30 mL of anhydrous THF dropwise at −78 °C over 15 min. After the mixture was stirred at −78 °C for 1 h, a solution of *N*-fluorobenzenesulfonimide (11.81 g, 37.4 mmol) in 60 mL of anhydrous THF was added dropwise to the mixture at −78 °C over 25 min. The mixture was stirred for 2 h at −78 °C followed by 20 min at room temperature. The reaction was quenched with saturated aqueous NH_4Cl, and the organic layer was separated. The aqueous layer was extracted with diethyl ether (2×), and the organic layers were combined and washed with water (3×), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by silica gel column chromatography, eluting with AcOEt/hexane = 1:3 to yield **19** (5.28 g, 71%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.76−0.81 (1H, m), 0.89−0.93 (1H, m), 1.09 (3H, t, J = 6.8 Hz), 1.24−1.34 (2H, m), 1.58 (3H, d, J = 7.3 Hz), 2.23 (1H, dq, J = 8.3, 28.3 Hz), 2.88−2.93 (1H, m), 3.48 (1H, t, J = 9.3 Hz), 3.92−4.08 (2H, m), 5.14 (1H, dd, J = 7.8, 53.7 Hz), 5.54 (1H, q, J = 7.3 Hz), 7.27−7.34 (5H, m). High-resolution MS (ESI) calcd for $C_{18}H_{22}FNO_3$ + H: 320.3786. Found: 320.3762. $[\alpha]_D$ −103.1° (*c* 0.220, $CHCl_3$).

Ethyl 1-{(3*S*,4*S*)-4-Fluoro-5-oxo-1-[(*S*)-1-phenylethyl]-pyrrolidin-3-yl}cyclopropanecarboxylate (20). Under a nitrogen atmosphere, *n*-butyllithium solution (1.68 M in hexane, 28.1 mL, 47.2 mmol) was added dropwise to a stirred solution of diisopropylamine (7.22 mL, 51.5 mmol) in 100 mL of anhydrous THF at −78 °C over 15 min. The mixture was stirred at 0 °C for 10 min and then cooled to −78 °C. To the mixture was added a solution of **19** (13.72 g, 43.0 mmol) in 40 mL of anhydrous THF dropwise at −78 °C over 20 min. After the mixture was stirred at −78 °C for 20 min, a solution of 2,6-di-*tert*-butylphenol (10.63 g, 51.5 mmol) in 40 mL of anhydrous THF was added dropwise to the mixture at −78 °C over 20 min. The mixture was stirred for 10 min at −78 °C and then warmed to ambient temperature. The reaction was quenched with saturated aqueous NH_4Cl at 0 °C, and the organic layer was separated. The aqueous layer was extracted with diethyl ether (2×), and the organic layers were combined and washed with water (2×), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel column chromatography, eluting with AcOEt/hexane = 1:3 to yield **20** (10.19 g, 74%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.57−0.63 (1H, m), 0.78−0.84 (1H, m), 1.07−1.13 (1H,m), 1.23−1.29 (1H, m), 1.26 (3H, t, J = 7.1 Hz), 1.54 (3H, d, J = 7.3 Hz), 2.59 (1H, t, J = 9.8 Hz), 3.05 (1H, dq, J = 8.3, 28.8 Hz), 3.25 (1H, t, J = 9.8 Hz), 4.00−4.16 (2H, m), 5.15 (1H, dd, J = 6.4, 52.7 Hz), 5.53 (1H, q, J = 7.3 Hz), 7.27−7.38 (5H, m). High-resolution MS (EI) calcd for $C_{18}H_{22}FNO_3$: 319.1584. Found: 319.1579. $[\alpha]_D$ −188.1° (*c* 0.521, $CHCl_3$).

Ethyl 1-{(3*S*)-4,4-Difluoro-5-oxo-1-[(*S*)-1-phenylethyl]-pyrrolidin-3-yl}cyclopropanecarboxylate (21). Following the procedures as described for **19**, the title compound was prepared in 69% yield from **19** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.76−0.82 (1H, m), 0.87−0.94 (1H, m), 1.09 (3H, t, J = 6.8 Hz), 1.23−1.36 (2H, m), 1.58 (3H, d, J = 7.3 Hz), 2.56−2.69 (1H, m), 2.92−2.98 (1H, m), 3.53 (1H, td, J = 2.9, 10.9 Hz), 3.84−3.92 (1H, m), 4.02−4.10 (1H, m), 5.53 (1H, q, J = 7.3 Hz), 7.28−7.35 (5H, m). High-resolution MS (ESI) calcd for $C_{18}H_{21}F_2NO_3$ + H: 338.3690. Found: 338.3702. $[\alpha]_D$ −61.8° (*c* 0.542, $CHCl_3$).

(3*S*,4*R*)-4-[1-(*tert*-Butoxycarbonylamino)cyclopropan-1-yl]-3-fluoro-2-oxo-1-[(*S*)-1-phenylethyl]pyrrolidine (22). To a solution of **20** (12.6 g, 39.3 mmol) in 120 mL of EtOH was added 1 N aqueous NaOH (120 mL, 120.0 mmol) at ambient temperature, and the mixture was stirred at 40 °C for 6 h. The reaction mixture was concentrated in vacuo, and the residual aqueous solution was washed with $CHCl_3$ (2×). Then the aqueous layer was acidified with 1 N aqueous HCl under ice cooling, and the mixture was extracted with $CHCl_3$ (2×) and Et_2O. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo to give colorless needles (10.2 g). To a solution of the colorless needles (3.66 g) in 100 mL of

toluene was added triethylamine (3.50 mL, 25.1 mmol) followed by diphenylphosphoryl azide (2.71 mL, 12.6 mmol) dropwise at ambient temperature. The mixture was stirred at ambient temperature for 1 h and then heated to reflux for 2 h. To the mixture was added 100 mL of *tert*-butyl alcohol, and the mixture was heated to reflux for another 21 h. The solvent was removed in vacuo, and the residue was purified by silica gel column chromatography, eluting with AcOEt/hexane = 1:1 to yield **22** (3.30 g, 73%) as a colorless oil. Recrystallization from *n*-hexane/CH_2Cl_2 gave colorless prisms, and the crystals were analyzed by X-ray crystallography. ^{1}H NMR ($CDCl_3$): δ 0.58−0.66 (1H, m), 0.70−0.82 (2H, m), 0.88−0.96 (1H, m), 1.31 (9H, s), 1.54 (3H, d, J = 7.3 Hz), 2.36−2.52 (1H, m), 2.86 (1H, t, J = 8.3 Hz), 3.32 (1H, t, J = 8.3 Hz), 4.99 (1H, dd, J = 6.4, 52.7 Hz), 4.99 (1H, s), 5.46 (1H, q, J = 7.3 Hz), 7.27−7.42 (5H, m). High-resolution MS (FAB) calcd for $C_{20}H_{27}FN_2O_3$ + Na: 385.1903. Found: 385.1914. $[\alpha]_D$ −167.4° (*c* 0.608, $CHCl_3$).

Ethyl 1-{(3*S*)-1-[(*S*)-1-Phenylethyl]-5-thioxopyrrolidin-3-yl}cyclopropanecarboxylate (23a). To a solution of **17a** (4.05 g, 13.4 mmol) in 100 mL of anhydrous benzene was added Lawesson's reagent (6.53 g, 16.1 mmol), and then the mixture was heated to reflux for 3 h under nitrogen atmosphere. The solvent was removed in vacuo, and the residue was purified by silica gel column chromatography, eluting with AcOEt/hexane = 1:3 to yield **23a** (4.18 g, 98%) as a colorless amorphous product. ^{1}H NMR ($CDCl_3$): δ 0.63 (2H, m), 1.11 (2H, m), 1.14 (3H, t, J = 7.1 Hz), 1.59 (3H, d, J = 7.1 Hz), 2.65−2.72 (1H, m), 2.79 (1H, m), 3.00−3.13 (2H, m), 3.77 (1H, dd, J = 8.5, 11.5 Hz), 4.02 (2H, m), 6.40 (1H, q, J = 7.1 Hz), 7.30−7.36 (5H, m). High-resolution MS (EI) calcd for $C_{18}H_{23}NO_2S$: 317.1450. Found: 317.1446.

Ethyl 1-{(3*S*,4*R*)-4-Fluoro-1-[(*S*)-1-phenylethyl]-5-thioxopyrrolidin-3-yl}cyclopropanecarboxylate (23b). Following the procedures as described for **23a**, the title compound was prepared in 89% yield from **19** as a pale-yellow oil. ^{1}H NMR ($CDCl_3$): δ 0.75−0.82 (1H, m), 0.88−0.93 (1H, m), 1.11 (3H, t, J = 7.3 Hz), 1.25−1.34 (2H, m), 1.64 (3H, d, J = 7.3 Hz), 2.28 (1H, dq, J = 8.3, 26.9 Hz), 3.12−3.18 (1H, m), 3.72 (1H, dd, J = 9.3, 11.2 Hz), 3.92−4.08 (2H, m), 5.22 (1H, dd, J = 7.8, 53.2 Hz), 6.33 (1H, q, J = 7.3 Hz), 7.28−7.38 (5H, m). High-resolution MS (ESI) calcd for $C_{18}H_{22}FNO_2S$ + H: 335.4442. Found: 335.4459.

Ethyl 1-{(3*S*,4*S*)-4-Fluoro-1-[(*S*)-1-phenylethyl]-5-thioxopyrrolidin-3-yl}cyclopropanecarboxylate (23c). Following the procedures as described for **23a**, the title compound was prepared in 90% yield from **20** as a pale-yellow oil. ^{1}H NMR ($CDCl_3$): δ 0.59−0.66 (1H, m), 0.86−0.92 (1H, m), 1.08−1.15 (1H, m), 1.20 (3H, t, J = 7.3 Hz), 1.24−1.31 (1H, m), 1.60 (3H, d, J = 7.3 Hz), 2.85 (1H, dd, J = 9.3, 11.2 Hz), 3.16 (1H, qd, J = 8.3, 30.3 Hz), 3.50 (1H, dd, J = 9.3, 11.2 Hz), 4.04−4.15 (2H, m), 5.32 (1H, dd, J = 5.4, 52.7 Hz), 6.28−6.34 (1H, m), 7.30−7.41 (5H, m). High-resolution MS (EI) calcd for $C_{18}H_{22}FNO_2S$: 335.1355. Found: 335.1354.

Ethyl 1-{(3*S*)-4,4-Difluoro-1-[(*S*)-1-phenylethyl]-5-thioxopyrrolidin-3-yl}cyclopropanecarboxylate (23d). With the procedures as described for **23a**, the title compound was prepared in 76% yield from **21** as a pale-yellow oil. ^{1}H NMR ($CDCl_3$): δ 0.85−0.95 (2H, m), 1.10 (3H, t, J = 6.8 Hz), 1.24−1.32 (2H, m), 1.64 (3H, d, J = 7.3 Hz), 2.69−2.81 (1H, m), 3.20 (1H, ddd, J = 2.9, 6.8, 11.7 Hz), 3.73 (1H, td, J = 2.5, 10.3 Hz), 3.84−3.92 (1H, m), 4.02−4.11 (1H, m), 6.31 (1H, q, J = 7.3 Hz), 7.32−7.38 (5H, m). High-resolution MS (ESI) calcd for $C_{18}H_{21}F_2NO_2S$ + H: 354.4346. Found: 354.4320.

Ethyl 1-{(3*S*)-1-[(*S*)-1-Phenylethyl]pyrrolidin-3-yl}-cyclopropanecarboxylate (24a). To a solution of **23a** (3.75 g, 11.8 mmol) in 40 mL of EtOH was added Raney nickel catalyst (W-6, 20 mL), and then the mixture was heated to reflux for 6 h. After the mixture was cooled to ambient temperature, the catalyst was removed by filtration through Celite and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography, eluting with MeOH/CH_2Cl_2 = 1:20 to yield **24a** (3.07 g, 91%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.68−0.76 (2H, m), 1.06−1.12 (2H, m), 1.19 (3H, t, J = 7.2 Hz), 1.35 (3H, d, J = 6.6 Hz), 1.36−1.42 (1H, m), 1.95−2.02 (2H, m), 2.31−2.37 (1H, m), 2.60−2.68 (2H, m), 2.80−2.86 (1H, m), 3.16 (1H, q, J = 6.6 Hz), 4.06 (2H, q, J = 7.1 Hz), 7.19−7.32 (5H, m). High-resolution MS (EI) calcd for $C_{18}H_{25}NO_2$: 287.1885. Found: 287.1848.

Ethyl 1-{(3*S*,4*R*)-4-Fluoro-1-[(*S*)-1-phenylethyl]pyrrolidin-3-yl}cyclopropanecarboxylate (24b). To a solution of **23b** (4.40 g, 13.1 mmol) in 150 mL of EtOH was added Raney nickel catalyst (W-6, 13 mL), and then the mixture was stirred for 1 h at ambient temperature. With the purification procedures as described for **24a**, the title compound (3.79 g, 95%) was prepared as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.66−0.71 (1H, m), 0.83−0.88 (1H, m), 1.19 (3H, t, J = 7.3 Hz), 1.28−1.44 (2H, m), 1.37 (3H, d, J = 6.8 Hz), 2.02 (1H, dm, J = 29.3 Hz), 2.10 (1H, q, J = 9.3 Hz), 2.67 (1H, ddd, J = 5.4, 11.2, 33.2 Hz), 2.80 (1H, t, J = 7.8 Hz), 3.17 (1H, q, J = 6.8 Hz), 3.33 (1H, dd, J = 11.2, 23.0 Hz), 4.06 (2H, q, J = 7.3 Hz), 5.16 (1H, dd, J = 3.4, 56.7 Hz), 7.21−7.34 (5H, m). High-resolution MS (ESI) calcd for $C_{18}H_{24}FNO_2$ + H: 306.3951. Found: 306.3962.

Ethyl 1-{(3*S*,4*S*)-4-Fluoro-1-[(*S*)-1-phenylethyl]pyrrolidin-3-yl}cyclopropanecarboxylate (24c). Following the procedures as described for **24b**, the title compound was prepared in 86% yield from **23c** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.54−0.60 (1H, m), 0.95−1.08 (2H, m), 1.22 (3H, t, J = 7.3 Hz), 1.25−1.32 (1H, m), 1.35 (3H, d, J = 6.4 Hz), 1.99 (1H, t, J = 9.3 Hz), 2.42 (1H, t, J = 8.3 Hz), 2.63 (1H, ddd, J = 2.0, 11.7, 33.2 Hz), 2.99 (1H, dm, J = 28.3 Hz), 3.25−3.37 (2H, m), 4.03−4.16 (2H, m), 5.33 (1H, dm, J = 55.7 Hz), 7.21−7.36 (5H, m). High-resolution MS (EI) calcd for $C_{18}H_{24}FNO_2$: 305.1791. Found: 305.1760.

Ethyl 1-{(3*S*)-4,4-Difluoro-1-[(*S*)-1-phenylethyl]pyrrolidin-3-yl}cyclopropanecarboxylate (24d). With the procedures as described for **24b**, the title compound was prepared in 96% yield from **23d** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.67−0.89 (2H, m), 1.19 (3H, t, J = 7.3 Hz), 1.27−1.46 (2H, m), 1.38 (3H, d, J = 7.3 Hz), 2.49−2.62 (2H, m), 2.69−2.97 (2H, m), 3.20 (1H, q, J = 7.3 Hz), 3.48−3.52 (1H, m), 3.94−4.09 (2H, m), 7.28−7.34 (5H, m). High-resolution MS (ESI) calcd for $C_{18}H_{23}F_2NO_2$ + H: 324.3855. Found: 324.3829.

Ethyl 1-[(3*S*)-1-Benzyloxycarbonylpyrrolidin-3-yl]cyclopropanecarboxylate (25a). Under a nitrogen atmosphere, benzyl chloroformate (2.72 mL, 19.0 mmol) was added to a solution of **24a** (2.74 g, 9.52 mmol) in 50 mL of anhydrous CH_2Cl_2 at ambient temperature, and then the mixture was stirred at 40 °C for 15 h. After the solvent was removed in vacuo, the residue was purified by silica gel column chromatography, eluting with AcOEt/hexane = 1:2 to yield **25a** (2.68 g, 89%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.74−0.80 (2H, m), 1.18−1.25 (5H, m), 1.41−1.56 (1H, m), 1.84−1.97 (1H, m), 2.72−2.83 (1H, m), 2.93 (1H, dd, J = 10.2, 18.3 Hz), 3.30 (1H, dt, J = 6.8, 10.7 Hz), 3.53−3.62 (1H, m), 3.66−3.70 (1H, m), 4.08−4.13 (2H, m), 5.12 (2H, m), 7.28−7.36 (5H, m). High-resolution MS (FAB) calcd for $C_{18}H_{23}NO_4$ + H: 318.1705. Found: 318.1694.

Ethyl 1-[(3*S*,4*R*)-1-Benzyloxycarbonyl-4-fluoropyrrolidin-3-yl]cyclopropanecarboxylate (25b). With the procedures as described for **25a**, the title compound was prepared in 89% yield from **24b** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.71−0.78 (1H, m), 0.90−0.95 (1H, m), 1.23 (3H, t, J = 6.8 Hz), 1.19−1.25 (1H, m), 1.28−1.32 (1H, m), 2.48 (1H, dm, J = 28.3 Hz), 3.27 (1H, t, J = 10.3 Hz), 3.67 (1H, dd, J = 13.2, 23.9 Hz), 3.80−3.92 (2H, m), 4.11 (2H, q, J = 6.8 Hz), 5.14 (2H, s), 5.17 (1H, br d, J = 55.2 Hz), 7.29−7.35 (5H, m). High-resolution MS (ESI) calcd for $C_{18}H_{22}FNO_4$ + H: 336.3780. Found: 336.3761.

Ethyl 1-[(3*S*,4*S*)-1-Benzyloxycarbonyl-4-fluoropyrrolidin-3-yl]cyclopropanecarboxylate (25c). With the procedures as described for **25a**, the title compound was prepared in 89% yield from **24c** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.71−0.78 (1H, m), 1.11−1.23 (2H, m), 1.24 (3H, t, J = 6.8 Hz), 1.29−1.37 (1H, m), 2.93−3.00 (1H, m), 3.10 (1H, dm, J = 34.7 Hz), 3.54−3.84 (3H, m), 4.09−4.18 (2H, m), 5.14 (2H, s), 5.34 (1H, ddm, J = 16.6, 53.7 Hz), 7.29−7.38 (5H, m). High-

resolution MS (FAB) calcd for $C_{18}H_{22}FNO_4$ + H: 336.1611. Found: 336.1616.

Ethyl 1-[(3*S*)-1-Benzyloxycarbonyl-4,4-difluoropyrrolidin-3-yl]cyclopropanecarboxylate (25d). With the procedures as described for **25a**, the title compound was prepared in 83% yield from **24d** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.97−1.05 (1H, m), 1.07−1.16 (1H, m), 1.20−1.30 (1H, m), 1.22 (3H, t, J = 7.3 Hz), 1.32−1.42 (1H, m), 2.93−3.07 (2H, m), 3.36−3.44 (1H, m), 3.77−3.84 (1H, m), 3.93 (1H, t, J = 10.7 Hz), 4.12 (2H, dq, J = 1.5, 7.3 Hz), 5.14 (2H, s), 7.28−7.35 (5H, m). High-resolution MS (ESI) calcd for $C_{18}H_{21}F_2NO_4$ + H: 354.3684. Found: 354.3693.

1-[(3*S*)-1-Benzyloxycarbonylpyrrolidin-3-yl]cyclopropanecarboxylic Acid (26a). To a solution of **25a** (4.34 g, 12.9 mmol) in 50 mL of EtOH was added 1 N aqueous NaOH (50 mL, 50 mmol) at 0 °C, and then the mixture was stirred at 40 °C for 3 h. After the mixture was concentrated in vacuo, water was added to the resultant solution and the aqueous solution was washed with CH_2Cl_2 (2×). The aqueous layer was acidified with concentrated aqueous HCl at 0 °C and extracted with $CHCl_3$ (2×). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to yield **26a** (4.11 g, quantitative) as a colorless amorphous product. ^{1}H NMR ($CDCl_3$): δ 0.80−0.90 (2H, m), 1.23−1.31 (2H, m), 1.43−1.60 (1H, m), 1.85−2.00 (1H, m), 2.69−2.78 (1H, m), 2.95 (1H, dd, J = 10.0, 19.3 Hz), 3.30 (1H, dt, J = 6.8, 10.6 Hz), 3.54−3.63 (1H, m), 2.95 (1H, dd, J = 7.9, 10.4 Hz), 5.12 (2H, s), 7.29−7.36 (5H, m). MS (EI) m/z: 289 (M^+).

1-[(3*S*,4*R*)-1-Benzyloxycarbonyl-4-fluoropyrrolidin-3-yl]cyclopropanecarboxylic Acid (26b). With the procedures as described for **26a**, the title compound was prepared in 98% yield from **25b** as a colorless amorphous product. ^{1}H NMR ($CDCl_3$): δ 0.84−0.89 (1H, m), 0.99−1.07 (1H, m), 1.32−1.42 (2H, m), 2.37−2.56 (1H, m), 3.26−3.31 (1H, m), 3.58−3.67 (1H, m), 3.82−3.88 (2H, m), 5.13 (2H, s), 5.20 (1H, br d, J = 55.0 Hz), 7.30−7.34 (5H, m). MS (ESI) m/z: 308 ($M + H^+$).

1-[(3*S*,4*S*)-1-Benzyloxycarbonyl-4-fluoropyrrolidin-3-yl]cyclopropanecarboxylic Acid (26c). With the procedures as described for **26a**, the title compound was prepared in 92% yield from **25c** as a colorless amorphous product. ^{1}H NMR ($CDCl_3$): δ 0.79−0.89 (1H, m), 1.18−1.35 (2H, m), 1.37−1.47 (1H, m), 2.90−3.18 (2H, m), 3.50−3.84 (3H, m), 5.13 (2H, s), 5.31 (1H, ddm, J = 15.1, 53.2 Hz), 7.26−7.42 (5H, m). MS (FAB) m/z: 308 ($M + H^+$).

1-[(3*S*)-1-Benzyloxycarbonyl-4,4-difluoropyrrolidin-3-yl]cyclopropanecarboxylic Acid (26d). With the procedures as described for **26a**, the title compound was prepared in 93% yield from **25d** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.08−1.14 (1H, m), 1.19−1.28 (1H, m), 1.37−1.42 (1H, m), 1.44−1.49 (1H, m), 2.93−3.09 (1H, m), 3.37−3.46 (1H, m), 3.76−3.85 (2H, m), 3.92−4.00 (1H, m), 5.14 (2H, s), 7.29−7.34 (5H, m). MS (ESI) m/z: 348 ($M + Na^+$), 326 ($M + H^+$).

(3*R*)-1-Benzyloxycarbonyl-3-[1-(*tert*-butoxycarbonylamino)cyclopropan-1-yl]pyrrolidine (27a). To a solution of **26a** (289 mg, 1.00 mmol) in 10 mL of *tert*-butyl alcohol was added triethylamine (0.24 mL, 1.60 mmol) and diphenylphosphoryl azide (0.28 mL, 1.30 mmol), and the mixture was stirred at ambient temperature for 2 h and then heated to reflux for 18 h. The solvent was removed in vacuo, and the residue was purified by silica gel column chromatography, eluting with AcOEt/hexane = 1:4 to yield **27a** (263 mg, 73%) as a colorless amorphous product. ^{1}H NMR ($CDCl_3$): δ 0.65−0.85 (4H, m), 1.41 (9H, m), 1.57−1.72 (1H, m), 1.88−1.97 (1H, m), 2.17−2.32 (1H, m), 3.07−3.13 (1H, m), 3.26−3.33 (1H, m), 3.51−3.65 (2H, m), 4.88 (1H, br d, J = 10.5 Hz), 5.12 (2H, m), 7.25−7.36 (5H, m). High-resolution MS (FAB) calcd for $C_{20}H_{28}N_2O_4$ + H: 361.2127. Found: 361.2126. $[\alpha]_D$ +8.8° (c 0.345, $CHCl_3$).

(3*R*,4*R*)-1-Benzyloxycarbonyl-4-[1-(*tert*-butoxycarbonylamino)cyclopropan-1-yl]-3-fluoropyrrolidine (27b). With the procedures as described for **27a**, the title compound was prepared in 65% yield from **26b** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.64−0.70 (1H, m), 0.79−0.83 (1H, m), 0.86−1.09 (2H, m), 1.39 (9H, s), 2.21 (1H, dm, J = 21.5 Hz), 3.44 (1H, dd, J = 2.9, 11.2 Hz), 3.59−3.76 (3H, m), 4.91 (1H, br s), 5.14 (2H, s), 5.40 (1H, br d, J = 52.7 Hz), 7.28−7.33 (5H, m). High-resolution MS (ESI) calcd for $C_{20}H_{27}FN_2O_4$ + H: 379.4458. Found: 379.4439. $[\alpha]_D$ +12.9° (c 0.622, MeOH).

(3*S*,4*R*)-1-Benzyloxycarbonyl-4-[1-(*tert*-butoxycarbonylamino)cyclopropan-1-yl]-3-fluoropyrrolidine (27c). With the procedures as described for **27a**, the title compound was prepared in 81% yield from **26c** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.65−0.74 (1H, m), 0.77−0.84 (1H, m), 0.85−1.00 (2H, m), 1.42 (9H, s), 2.21 (1H, dm, J = 36.1 Hz), 3.08−3.24 (1H, m), 3.48−3.84 (3H, m), 5.02 (1H, br s), 5.13 (2H, s), 5.15 (1H, br d, J = 53.7 Hz), 7.28−7.38 (5H, m). High-resolution MS (FAB) calcd for $C_{20}H_{27}FN_2O_4$ + H: 379.2033. Found: 379.2000. $[\alpha]_D$ −9.3° (c 0.381, $CHCl_3$).

(4*R*)-1-Benzyloxycarbonyl-4-[1-(*tert*-butoxycarbonylamino)cyclopropan-1-yl]-3,3-difluoropyrrolidine (27d). With the procedures as described for **27a**, the title compound was prepared in 60% yield from **26d** as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.83−0.92 (2H, m), 1.40 (9H, s), 1.34−1.55 (2H, m), 2.38−2.51 (1H, m), 3.47 (1H, t, J = 9.3 Hz), 3.67−3.84 (3H, m), 4.99 (1H, br s), 5.13 (2H, s), 7.29−7.35 (5H, m). High-resolution MS (FAB) calcd for $C_{20}H_{26}F_2N_2O_4$ + H: 397.4362. Found: 397.4388. $[\alpha]_D$ +10.0° (c 0.410, MeOH).

5-Amino-7-[(3*R*)-3-(1-aminocyclopropan-1-yl)pyrrolidin-1-yl]-6-fluoro-1-[(1*R*,2*S*)-2-fluorocyclopropan-1-yl]-1,4-dihydro-8-methyl-4-oxoquinolin-3-carboxylic Acid (1). To a solution of **27a** (649 mg, 1.80 mmol) in 20 mL of MeOH was added 5% Pd/C (200 mg, containing 55.6% water), and the mixture was heated by a lamp with vigorous shaking under hydrogen (atmospheric pressure) for 2 h. The catalyst was filtered off, and the filtrate was concentrated in vacuo. The residue was mixed with **9** (312 mg, 1.00 mmol), 2 mL of triethylamine, and 20 mL of DMSO, and the mixture was heated at 150 °C for 18 h under nitrogen atmosphere. The solvent was removed in vacuo, the residue was dissolved with $CHCl_3$, and the solution was washed with 10% aqueous citric acid and brine. The resultant solution was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. To the residue was added 10 mL of concentrated aqueous HCl at 0 °C, and the mixture was stirred for 1 h at ambient temperature. The solution was washed with CH_2Cl_2 and made alkaline with saturated aqueous NaOH at 0 °C, and then the pH of the solution was adjusted to 7.4 with concentrated aqueous HCl and dilute aqueous HCl. The resultant solution was extracted with chloroform (4×), and the combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by semiseparable TLC, eluting with an underlayer solution of $CHCl_3$/MeOH/water = 7:3:1 to give the crude product. The crude product was recrystallized from $CHCl_3$/diisopropyl ether to yield **1** (102 mg, 24%) as a yellow powder, mp 215−216 °C. ^{1}H NMR (0.1 N NaOD/D_2O): δ 0.55 (4H, m), 1.09−1.18 (1H, m), 1.45−1.57 (1H, m), 1.61−1.74 (1H, m), 1.95−2.05 (1H, m), 2.16−2.25 (1H, m), 2.27 (3H, s), 3.24−3.37 (2H, m), 3.45−3.57 (1H, m), 3.68−3.80 (1H, m), 3.89−3.98 (1H, m), 4.85−4.91, 5.02−5.07 (1H, m), 8.26 (1H, d, J = 2.9 Hz). $[\alpha]_D$ −407.0° (c 0.115, 0.1 N aqueous NaOH). Anal. ($C_{21}H_{24}F_2N_4O_3 \cdot 0.5H_2O$) C, H, N.

5-Amino-7-[(3*R*,4*R*)-4-(1-aminocyclopropan-1-yl)-3-fluoropyrrolidin-1-yl]-6-fluoro-1-[(1*R*,2*S*)-2-fluorocyclopropan-1-yl]-1,4-dihydro-8-methyl-4-oxoquinolin-3-carboxylic Acid Hydrochloride (2). To a solution of **27b** (758 mg, 2.00 mmol) in 80 mL of MeOH was added 5% Pd/C (800 mg, containing 55.6% water), and the mixture was shaken vigorously under 4.5 kg/cm^2 of hydrogen for 7 h at ambient temperature. The catalyst was filtered off, and the catalyst was concentrated in vacuo. The residue was mixed with **9** (405 mg, 1.30 mmol), 3 mL of triethylamine, and 8 mL of DMSO, and the mixture was heated at 120 °C for 4 days under nitrogen atmosphere. The solvent was removed in vacuo, the residue was dissolved in $CHCl_3$, and the solution was washed with 10% aqueous citric acid (2×) and brine. The resultant solution was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. To the residue was added 10 mL of concentrated aqueous HCl at 0 °C, and the mixture was stirred

for 15 min at ambient temperature. After 10 mL of water was added to the solution, the solution was washed with CH_2Cl_2 (4×) and made alkaline with saturated aqueous NaOH at 0 °C. Then the pH of the solution was adjusted to 7.4 with concentrated aqueous HCl and dilute aqueous HCl, and the resultant solution was extracted with $CHCl_3$ (4×). The combined extract was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by semiseparable TLC, eluting with an underlayer solution of $CHCl_3$/MeOH/water = 7:3:1. To a solution of the crude product in 20 mL of EtOH was added 1.5 mL of 1 N aqueous HCl dropwise at 0 °C. The solution was stirred for 5 min at 0 °C and concentrated in vacuo. The residue was recrystallized from EtOH/diisopropyl ether to yield **2** (142 mg, 22%) as a yellow powder, mp 220−225 °C. ^{1}H NMR (0.1 N NaOD/D_2O): δ 0.58−0.68 (4H, m), 1.11−1.25 (1H, m), 1.52−1.59 (1H, m), 2.39−2.49 (1H, m), 2.41 (3H, s), 3.39 (1H, t, J = 9.3 Hz), 3.58−3.67 (1H, m), 3.71−3.83 (2H, m), 3.88−3.99 (1H, m), 4.96 (1H, dm, J = 65.9 Hz), 5.49 (1H, br d, J = 54.7 Hz), 8.27 (1H, d, J = 3.4 Hz). $[\alpha]_D$ −342.0° (*c* 0.444, H_2O). Anal. ($C_{21}H_{23}F_3N_4O_3$·HCl·H_2O) C, H, N.

5-Amino-7-[(3*S*,4*R*)-4-(1-aminocyclopropan-1-yl)-3-fluoropyrrolidin-1-yl]-6-fluoro-1-[(1*R*,2*S*)-2-fluorocyclopropan-1-yl]-1,4-dihydro-8-methyl-4-oxoquinolin-3-carboxylic Acid (3 = DQ-113). With the procedures as described for **1**, the title compound was prepared in 12% yield from **9** and **27c** as a yellow powder, mp 199−201 °C. ^{1}H NMR (0.1 N NaOD/D_2O): δ 0.55−0.71 (4H, m), 1.10−1.21 (1H, m), 1.46−1.58 (1H, m), 2.30 (3H, s), 2.21−2.35 (1H, m), 3.32 (1H, t, J = 8.8 Hz), 3.49 (1H, dd, J = 12.2, 25.9 Hz), 3.85−3.97 (2H, m), 4.11 (1H, ddm, J = 12.5, 40.8 Hz), 4.97 (1H, dm, J = 70.3 Hz), 5.49 (1H, br d, J = 55.2 Hz), 8.27 (1H, d, J = 3.4 Hz). $[\alpha]_D$ −488.3° (*c* 0.985, 0.1 N aqueous NaOH). Anal. ($C_{21}H_{23}F_3N_4O_3$) C, H, N, F.

5-Amino-7-[(4*R*)-4-(1-aminocyclopropan-1-yl)-3,3-difluoropyrrolidin-1-yl]-6-fluoro-1-[(1*R*,2*S*)-2-fluorocyclopropan-1-yl]-1,4-dihydro-8-methyl-4-oxoquinolin-3-carboxylic Acid Hydrochloride (4). With the procedures as described for **2**, the title compound was prepared in 20% yield from **9** and **27d** as a yellow powder, mp 211−215 °C. ^{1}H NMR (0.1 N NaOD/D_2O): δ 0.59−0.71 (4H, m), 1.08−1.20 (1H, m), 1.48−1.57 (1H, m), 2.25−2.33 (1H, m), 2.30 (3H, s), 3.37−3.54 (1H, m), 3.88 (1H, t, J = 9.3 Hz), 3.90−3.95 (2H, m), 3.97−4.04 (1H, m), 4.96 (1H, dm, J = 65.9 Hz), 8.25 (1H, d, J = 2.9 Hz). $[\alpha]_D$ −410.0° (*c* 0.220, H_2O). Anal. ($C_{21}H_{22}F_4N_4O_3$·HCl·1.5H_2O) C, H, N.

5-Amino-7-[(3*S*)-3-(aminomethyl)pyrrolidin-1-yl]-6-fluoro-1-[(1*R*,2*S*)-2-fluorocyclopropan-1-yl]-1,4-dihydro-8-methyl-4-oxoquinolin-3-carboxylic Acid (30). With the procedures as described for **1**, the title compound was prepared in 51% yield from **9** and **28** as a yellow powder, mp 159−160 °C. ^{1}H NMR (0.1 N NaOD/D_2O): δ 1.04−1.15 (1H, m), 1.44−1.59 (2H, m), 2.08−2.12 (1H, m), 2.23−2.34 (4H, m), 2.69 (2H, d, J = 6.8 Hz), 3.25−3.34 (3H, m), 3.65−3.71 (1H, m), 3.88−3.93 (1H, m), 4.85−5.10 (1H, m), 8.27 (1H, s). $[\alpha]_D$ −334.4° (*c* 0.340, 0.1 N aqueous NaOH). Anal. ($C_{19}H_{22}F_2N_4O_3$·0.75H_2O) C, H, N.

5-Amino-7-[(3*R*,1′*S*)-3-(1-aminoethyl)pyrrolidin-1-yl]-6-fluoro-1-[(1*R*,2*S*)-2-fluorocyclopropan-1-yl]-1,4-dihydro-8-methyl-4-oxoquinolin-3-carboxylic Acid (31). With the procedures as described for **1**, the title compound was prepared in 29% yield from **9** and **29** as a yellow powder, mp 225−226 °C. ^{1}H NMR (0.1 N NaOD/D_2O): δ 1.11−1.19 (4H, m), 1.48−1.59 (2H, m), 2.09−2.13 (2H, m), 2.29 (3H, s), 2.80−2.88 (1H, m), 3.25−3.34 (1H, m), 3.37−3.46 (1H, m), 3.47−3.58 (1H, m), 3.73−3.82 (1H, m), 3.89−3.99 (1H, m), 4.85−5.10, (1H, m), 8.26 (1H, s). $[\alpha]_D$ −305.1° (*c* 0.276, 0.1 N aqueous NaOH). Anal. ($C_{20}H_{24}F_2N_4O_3$·2H_2O) C, H, N.

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Supporting Information Available: Crystal structures and crystallographic details for **18** and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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