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PRACTICAL SYNTHESIS OF DQ-113, A NEW QUINOLONE ANTIBACTERIAL AGENT, BY USING THE INTRAMOLECULAR HORNER-WADSWORTH-EMMONS REACTION

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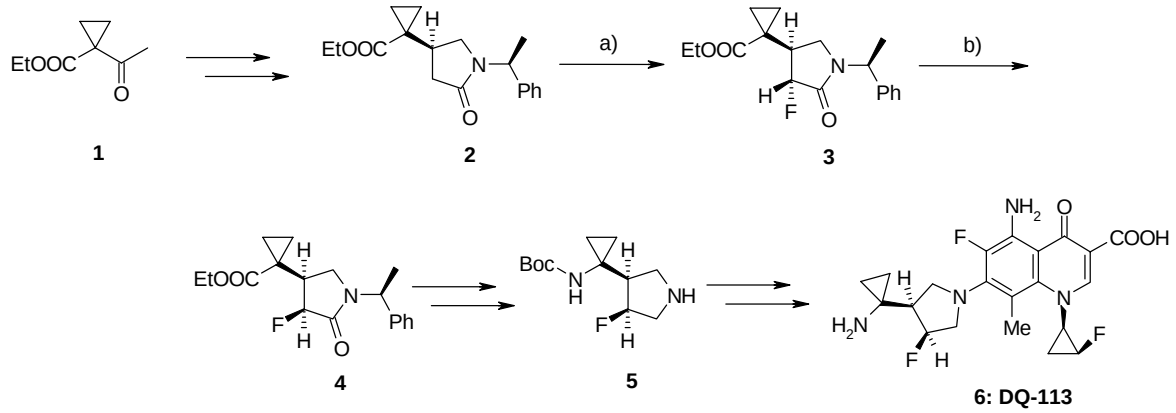
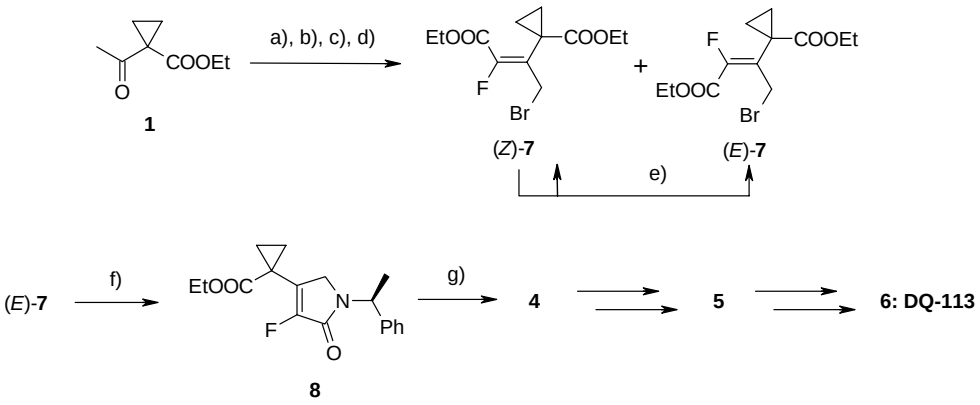
Abstract – A practical route was developed for synthesizing the C-7 substituent of DQ-113 (**6**, 5-amino-7-[(3*S*,4*R*)-4-(1-aminocycloprop-1-yl)-3-fluoro-pyrrolidin-1-yl]-6-fluoro-1-[(1*R*,2*S*)-2-fluorocyclopropan-1-yl]-1,4-dihydro-8-methyl-4-oxoquinolin-3-carboxylic acid), a new quinolone antibacterial agent for serious infections caused by Gram-positive pathogens. The key step was the intramolecular Horner-Wadsworth-Emmons reaction. In addition, the yield of the final aromatic nucleophilic substitution reaction was improved.

DQ-113 (5-amino-7-[(3*S*,4*R*)-4-(1-aminocycloprop-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, **6**) is a new, potent antibacterial agent for the treatment of infections caused by Gram-positive pathogens, including multi-drug resistant strains, and is presently being developed and prepared for clinical evaluation by Daiichi.[1,2] The C-7 substituent of DQ-113, (3*S*,4*R*)-4-(1-aminocycloprop-1-yl)-3-fluoropyrrolidine, has a complex structure: it has two continuous asymmetric stereo centers, one of which contains a fluorine atom. We previously reported its preparative synthesis, for which the key steps were fluorination of ethyl 1-{(3*S*)-5-oxo-1-[(*S*)-1-phenylethyl]pyrrolidin-3-yl}cyclopropanecarboxylate (**2**) by using lithium diisopropylamide (LDA) and *N*-fluorobenzensulfonimide at –78 °C, and the following isomerization of the resultant *trans*-fluorinated pyrrolidine (**3**) by using LDA and 2,6-di-*tert*-butylphenol at –78 °C (Scheme 1).[1] But this synthetic route included a lot of reaction steps and the total yield was very low. And these two key reactions using the strong base and the expensive fluorinating agent at very low temperature were not suitable for large scale synthesis.



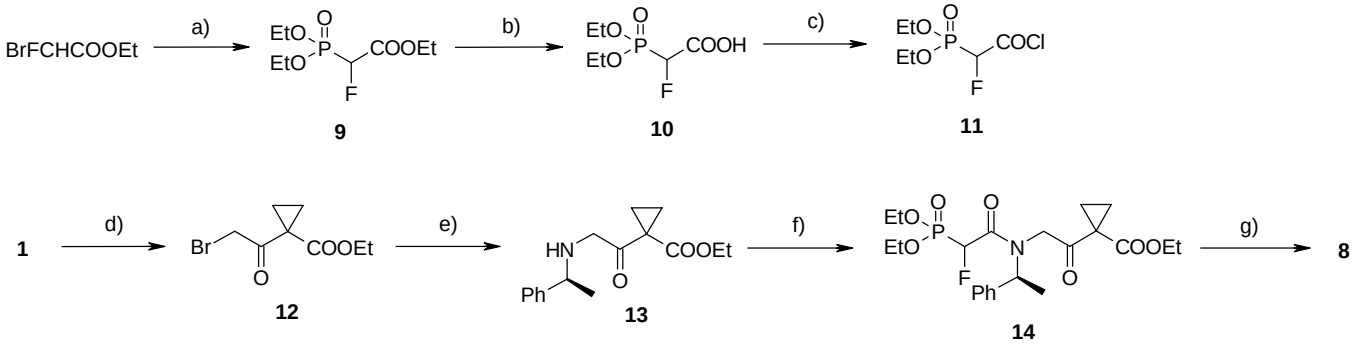
Scheme 1. Preparative synthesis of DQ-113 (fluorination/isomerization strategy): a) LDA (1.3 eq.), $(PhSO_2)_2NF$ (1.6 eq.) / THF, –78°C, 2 h, then rt, 20 min; b) LDA (1.1 eq.), 2,6-di-*tert*-butylphenol (1.2 eq.) / THF, –78°C, 10 min, then rt, 1 h; total yield: 0.6% (16 steps).

Recently, we reported its improved synthesis by using the Reformatsky reaction between ethyl 1-acetylcyclopropanecarboxylate (**1**) and ethyl bromofluoroacetate (Scheme 2), which allowed us to avoid using strong bases or expensive fluorinating agents at low temperature.[3] Nevertheless, the route still requires a multi-step sequence, and the separation of (*E*)-**7** from (*Z*)-**7** and the isomerization of (*Z*)-**7** to (*E*)-**7** was laborious and inadequate for large scale synthesis.



Scheme 2. Improved synthesis of DQ-113 (the Reformatsky reaction/isomerization strategy): a) $BrFCHCO_2Et$ (1.0 eq.), Zn (3.0 eq.), cat. I_2 / benzene, reflux, 2 h; b) $SOCl_2$ (1.2 eq.) / pyridine, –10°C, 3 h; c) DBU (1.1 eq.) / CH_2Cl_2, rt, 17 h; d) NBS (1.0 eq.), cat. AIBN / $CHCl_3$, reflux, 16 h; e) cat. NBS, cat. AIBN / benzene, reflux, 16 h; f) (*S*)-1-phenylethylamine (1.1 eq.), $NaHCO_3$ (2.5 eq.) / EtOH, reflux, 3 h; g) H_2 (5 kg/cm^2), Raney Ni / EtOH, rt, 3.5 h; total yield: 2.1% (14 steps).

So as not to include such separation or isomerization steps, we designed a new practical synthetic route for the C-7 substituent (**5**) by using the intramolecular Horner-Wadsworth-Emmons (HWE) reaction of fluoroketophosphonate (**14**) (Scheme 3).

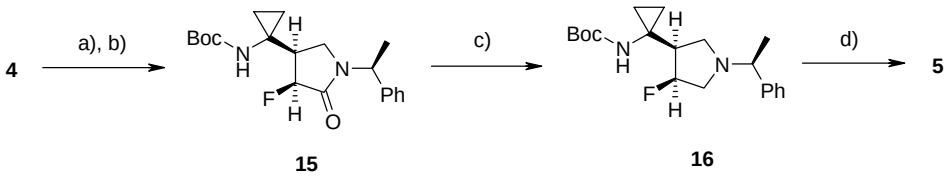


Scheme 3. The new practical synthesis of DQ-113 (intramolecular HWE reaction strategy): a) $P(OEt)_3$ (2.7 eq.), 160°C, 39 h (78%); b) aq. 2 N NaOH (1.2 eq.) / EtOH, rt, 2.5 h (89%); c) $(COCl)_2$ (3.0 eq.), cat. DMF / benzene, rt, 6 h (98%); d) Br_2 (1.3 eq) / EtOH, 30°C, 80 min (quant.); e) (*S*)-1-phenylethylamine (1.0 eq.), Et_3N (1.05 eq.) / MeCN, 0°C, 2 h (77%); f) **11** (1.0 eq), Et_3N (1.0 eq) / THF, 0°C then rt, 12 h (69%); g) *t*-BuOK (1.05 eq.), MS-4A (50% w/w) / toluene, 0°C then rt, 15 h (83%).

In the intramolecular HWE reaction route (Scheme 3), fluoroketophosphonate (**14**), the precursor of the key intermediate (**8**), was planned to be synthesized from amino keto ester (**13**) and acid chloride (**11**). The acid chloride (**11**) was derived from ethyl bromofluoroacetate by an improved method of Coutrot.[4] The amino keto ester (**13**) was synthesized from ethyl 1-acetylcyclopropanecarboxylate (**1**).[5] Bromination of **1** by bromine in ethanol gave α-bromo keto ester (**12**) (quant.). Treatment of the resultant **12** with (*S*)-1-phenylethylamine in acetonitrile in the presence of triethylamine provided the amino keto ester (**13**) (77%). Slow addition of **11** into a solution of **13** and triethylamine in THF below 0°C afforded the condensation product (**14**) in 69% yield as a diastereomixture (*ca*. 1:1 by ^{1}H NMR spectrum). The subsequent intramolecular Horner-Wadsworth-Emmons reaction was proceeded by using potassium *tert*-butoxide and powdered molecular sieves (4A) in toluene below 0°C to yield cyclic fluoro enamide (**8**) (83%). Thus, we succeeded in deriving the key intermediate (**8**) by 4 steps of facile reactions from the known ethyl 1-acetylcyclopropanecarboxylate (**1**) without separation or isomerization of isomers.

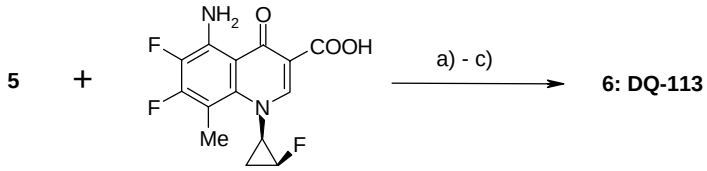
In addition to improving the synthesis of **8**, we improved the synthesis of **5** from **4**. We previously reported that compound (**5**) could be derived from **4** by a series of reactions including thioamidation, desulfurization, benzyloxycarbonylation, and Curtius rearrangement reaction (6 steps, total 51% yield).[1] To decrease the number of reaction steps, we designed a new reaction scheme including a reduction step with the BH_3-THF complex (Scheme 4). *tert*-Butoxycarbonylamino compound (**15**)[1] was derived from **4** in 73% yield by hydrolysis of the ester moiety of **4** and the Curtius rearrangement reaction of the resultant carboxylic acid with diphenylphosphoryl azide (DPPA) and *tert*-butyl alcohol. Reduction of the amide moiety of **15** with the BH_3-THF complex provided *N*-(1-phenylethyl)pyrrolidine derivative (**16**) (99%). Deprotection of the 1-phenylethyl group of **16** by catalytic hydrogenation in ethanol at 40 °C yielded the

C-7 substituent (**5**) in quantitative yield. Thus, we could derive **5** from **4** by 4 reaction steps in total 72% yield.



Scheme 4. The improved synthesis of the C-7 substituent (**5**) from **4**: a) aq. 1 N NaOH (3.0 eq.) / EtOH, 40°C, 6 h; b) DPPA (1.0 eq.), Et_3N (2.0 eq.) / toluene, rt, 1 h, and reflux, 2h, then *tert*-BuOH, reflux, 21 h (73%, 2 steps); c) BH_3-THF (3.5 eq.) / THF, rt, 17 h then Et_3N (5 eq.) / 80% aq. EtOH, reflux, 2.5 h (99%); d) H_2, 10% Pd-C / EtOH, 40°C, 3 h (quant.).

Finally, we improved the final aromatic nucleophilic substitution reaction between the C-7 substituent (**5**) and the quinolone nucleus (**17**). The reaction conditions reported previously (triethylamine / DMSO, 150 °C, 18 h) only gave 12% of **6**.[1] Because some impurities, which were thought to have resulted by a decomposition of **5** or **17**, were observed under these conditions, we explored whether milder conditions would give no impurities. As a result, we found the conditions using 1.0 eq. of **17**, 1.5 eq. of **5**, and 1.2 eq. of *N*-methylpiperidine in DMSO at 75°C for 7 days gave 56% of **6** from **17** (Scheme 5).



Scheme 5. Improved reaction condition of the final aromatic nucleophilic substitution reaction: a) *N*-methylpiperidine (1.2 eq.) / DMSO, 75°C, 7 days; b) conc. HCl, then extraction at pH = 7.4; c) recrystallization from MeOH / *i*-PrOH (56%).

In conclusion, we developed a practical method to synthesize the C-7 substituent (**5**) of DQ-113 (**6**) by using the intramolecular HWE reaction. In addition, we developed improved reaction conditions for the final aromatic nucleophilic substitution reaction between the C-7 substituent (**5**) and the 5-amino-8-methylquinolone nucleus (**17**). Finally, by this method, the total yield for the synthesis of DQ-113 (**6**) from **1** was improved to 11.9% (11 steps). In comparison, the yield for the fluorination/isomerization strategy was 0.6% (16 steps), and that for the Reformatsky reaction/isomerization strategy was 2.1% (14 steps).

EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Optical rotations were measured in a 0.5-dm cell at 589 nm with a HORIBA SEPA-300 polarimeter. ^{1}H NMR spectra and ^{13}C NMR spectra were determined on a JEOL JNM-EX400 spectrometer. Chemical shifts are reported in parts per million relative to tetramethylsilane as internal standard. High-resolution mass spectra were obtained on a JEOL JMS-700 mass spectrometer under electron impact ionization conditions (EI), or fast atom bombardment ionization conditions (FAB).

Ethyl 1-(Bromoacetyl)cyclopropanecarboxylate (12): To a solution of ethyl 1-acetylcyclopropane-carboxylate (**1**, 1.199 kg, 7.68 mol) in EtOH (6 L) was added Br_2 (516 mL, 10.00 mol) dropwise over 160 min in an ice bath. After the solution was warmed at 25-30 °C for 80 min, water (6 L) was added and the lower layer (organic layer) was separated. The upper layer was concentrated in vacuo, and extracted with AcOEt (3 ×). The organic layers were combined and washed with aqueous 10% $Na_2S_2O_3$ solution (2 ×), saturated aqueous $NaHCO_3$ solution, and brine. The washed organic solution was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give **12** (1.857 kg, quant.) as a colorless oil. **12** was used for the next reaction without further purification. ^{1}H NMR ($CDCl_3$): δ 1.30 (3H, t, *J* = 6.6 Hz), 1.58-1.65 (4H, m), 4.23 (2H, q, *J* = 7.1 Hz), 4.50 (2H, s). ^{13}C NMR ($CDCl_3$): δ 13.9, 21.0, 35.0, 53.5, 60.5, 170.2, 197.4. High-resolution MS (FAB) Calcd for $C_8H_{12}O_3{}^{79}$Br+H: 234.9970. Found: 234.9959. Calcd for $C_8H_{12}O_3{}^{81}$Br+H: 234.9950. Found: 236.9948.

Ethyl 1-{*N*-[(*S*)-1-Phenylethyl]aminoacetyl}cyclopropanecarboxylate (13): To a solution of ethyl 1-(bromoacetyl)cyclopropanecarboxylate (**12**, 302.3 g, 1.286 mol) in acetonitrile (1.3 L) was added (*S*)-1-phenylethylamine (164 mL, 1.286 mol) dropwise over 15 min below 0 °C, and then triethylamine (188 mL, 1.350 mol) was added dropwise over 25 min below 0°C. After stirring the solution for 2 h at 0 °C, water (0.65 L) was added, and the solution was concentrated in vacuo. Then diisopropyl ether (0.8 L) was added to the concentrated solution, and the organic layer was separated. An aqueous 2 N HCl solution (0.8 L) was added to the organic solution in order to change the desired amine compound to its hydrochloride salt, and the aqueous layer including the salt was separated. The aqueous layer was alkalified with an aqueous 2 N NaOH solution (*ca*. 0.8 L), and the resultant solution was extracted with AcOEt (2 ×). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo to give **13** (273.1 g, 77%) as a red-brown oil. **13** was used for the next reaction without further purification. ^{1}H NMR ($CDCl_3$): δ ^{1}H NMR ($CDCl_3$): δ 1.17 (3H, t, *J* = 7.2 Hz), 1.38 (3H, d, *J* = 6.6 Hz), 1.47 (4H, s), 3.72 (1H, q, *J* = 6.6 Hz), 3.83-3.88 (2H, m), 4.10 (2H, q, *J* = 7.2 Hz), 7.22-7.38 (5H, m). ^{13}C NMR ($CDCl_3$): δ 13.8, 19.78, 19.83, 24.2, 33.6, 56.9, 57.9, 61.2. 126.6, 127.0, 128.4, 144.9, 170.4, 204.2.

***N*-[(1-Ethoxycarbonylcycloprop-1-yl)carbonylmethyl]-*N*-[(*S*)-1-phenylethyl]-2-(diethoxy-phosphoryl)-2-fluoroacetamide (14):** To a solution of ethyl 1-{*N*-[(*S*)-1-phenylethyl]aminoacetyl}-cyclopropanecarboxylate (**13**, 212.3 g, 0.771 mol) in THF (1.2 L) was added a solution of diethoxyphophorylfluoroacetyl chloride (**11**, 176.2 g, 0.771 mol) in THF (0.2 L) dropwise over 20 min below 0 °C, and then triethylamine (108 mL, 0.771 mol) solution in THF (0.1 L) was added dropwise over 20 min below 0 °C. After stirring the solution for 12 h at ambient temperature, the solution was filtered through Celite, diluted with AcOEt, and washed with aqueous 1 N HCl solution, water, aqueous saturated $NaHCO_3$ solution, and brine. The resultant solution was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by silica gel column chromatography, eluting with AcOEt/hexane = 2:1 to yield **14** (244.8 g, 69%, *ca*. 1:1 diastereomixture) as a red-orange oil. ^{1}H NMR ($CDCl_3$): δ 1.09-1.73 (16H, m), 4.00-4.46 (7H, m), 4.57-4.98 (1H, m), 5.07-5.31 (0.5H, m), 5.50-5.70 (1H, m), 5.99-6.11 (0.5H, m), 7.23-7.42 (5H, m). ^{13}C NMR ($CDCl_3$): δ 13.75, 13.78, 13.82, 15.8, 15.9, 16.17, 16.21, 17.7, 17.9, 18.6, 18.7, 19.0, 19.9, 20.18, 20.21, 20.5, 32.8, 33.0, 33.51, 33.54, 51.8 51.9, 52.16, 52.19, 52.3, 52.46, 54.51, 54.62, 54.68, 54.79, 54.84, 61.06, 61.10, 61.4, 61.5, 64.10, 64.14, 64.26, 64.37, 64.44, 64.5, 64.6, 83.9, 84.6, 85.5, 85.9, 86.2, 86.5, 87.4, 88.1, 126.7, 127.39, 127.45, 127.48, 127.65, 127.68, 128.0, 128.2, 128.4, 128.6, 138.9, 139.7, 170.1, 170.6, 197.5, 197.7, 200.1, 200.5. High-resolution MS (EI) Calcd for $C_{22}H_{31}NO_7FP$: 471.1822. Found: 471.1838.

Ethyl 1-{4-Fluoro-2,5-dihydro-5-oxo-1-[(*S*)-1-phenylethyl]-1*H*-pyrrol-3-yl}cyclopropanecarboxylate (8): To a suspension of *N*-[(1-ethoxycarbonylcycloprop-1-yl)carbonylmethyl]-*N*-[(*S*)-1-phenylethyl]-2-(diethoxyphosphoryl)-2-fluoroacetamide (**14**, 244.8 g, 0.519 mol) and powdered molecular sieves 4A (123 g) in toluene (1.1 L) was added potassium *tert*-butoxide (61.2 g, 0.545 mol) portionwise over 1 h below 0 °C. After the solution was stirred for 15 h at ambient temperature, an aqueous 10% citric acid solution was added dropwise to the solution at 0 °C. The resultant suspension was diluted with AcOEt and filtered through Celite, and then the organic layer of the filtrate was separated and washed with water and brine. The resultant solution was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by silica gel column chromatography, eluting with AcOEt/hexane = 1:2 to yield **8** (135.8 g, 83%) as a red-yellow oil. The spectral data of **8** obtained by this procedure were identical to those reported.[3]

(3*S*,4*R*)-4-[1-(*tert*-Butoxycarbonylamino)cycloprop-1-yl]-3-fluoro-1-[(*S*)-1-phenylethyl]pyrrolidine (16): To a solution of (3*S*,4*R*)-4-[1-(*tert*-butoxycarbonylamino)cycloprop-1-yl]-3-fluoro-2-oxo-1-[(*S*)-1-phenylethyl]pyrrolidine (**15**, 122.8 g, 0.339 mol) in THF (2.4 L) was added a 1 N BH_3-THF complex solution in THF (1.2 L, 1.200 mol) dropwise over 1.5 h in an ice-salt cooling bath. After the solution was stirred for 17 h at ambient temperature, the solvent was evaporated off. Water (0.5 L), EtOH (2 L), and triethylamine (0.25 L) were added to the residue, and the mixture was heated for reflux for 2.5

h. The solvent was evaporated off, and saturated aqueous $NaHCO_3$ solution was added to the residue. The resultant mixture was extracted with $CHCl_3$ (3 ×), and the combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel column chromatography, eluting with AcOEt/hexane = 1:1 to yield **16** (116.3 g, 99%) as a colorless gum. ^{1}H NMR ($CDCl_3$): δ 0.55-0.60 (1H, m), 0.71-0.95 (3H, m), 1.34 (3H, d, *J* = 6.3 Hz), 1.42 (9H, s), 2.28-2.43 (2H, m), 2.52 (1H, t, *J* = 7.8 Hz), 2.69 (1H, dd, *J* = 32.7, 11.5 Hz), 3.00-3.12 (1H, m), 3.28 (1H, q, *J* = 6.3 Hz), 5.07 (0.8H, br s), 5.13 (1H, dm, *J* = 56.2 Hz), 7.20-7.29 (5H, m). ^{13}C NMR ($CDCl_3$): δ 12.0, 12.8, 22.7, 28.3, 30.7 (d, *J* = 7.5 Hz), 48.3 (d, *J* = 17.6 Hz), 52.4, 59.1 (*J* = 22.6 Hz), 65.1, 79.0, 94.9 (*J* = 178.1 Hz), 127.0, 127.1, 128.3, 144.8, 155.6. High-resolution MS (EI) Calcd for $C_{20}H_{29}N_2O_2F$: 348.2213. Found: 348.2218. $[\alpha]_D$ -57.3° (*c* 0.908, $CHCl_3$).

5-Amino-7-[(3*S*,4*R*)-4-(1-aminocycloprop-1-yl)-3-fluoropyrrolidin-1-yl]-6-fluoro-1-[(1*R*,2*S*)-2-fluorocycloprop-1-yl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic Acid (3 = DQ-113): To a solution of (3*S*,4*R*)-4-[1-(*tert*-butoxycarbonylamino)cycloprop-1-yl]-3-fluoro-1-[(*S*)-1-phenylethyl]-pyrrolidine (**16**, 523 mg, 1.50 mmol) in EtOH (15 mL) was added 10% Pd/C (520 mg, containing 50.2% water), and the suspension was stirred vigorously at 40 °C for 3 h under hydrogen atmosphere. The catalyst was filtered off, and the filtrate was concentrated in vacuo to give a crude of **7** (366 mg, quant.) as a colorless gum. The crude **5** was used for the next reaction without further purification.

The crude **5** (366 mg, 1.50 mmol), 5-amino-6,7-difluoro-1-[(1*R*,2*S*)-2-fluorocycloprop-1-yl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid (**17**, 312 mg, 1.00 mmol), *N*-methylpiperidine (0.146 mL, 1.20 mmol), and DMSO (1.7 mL) were mixed and the mixture was heated at 75 °C for 7 days under nitrogen atmosphere. The solvent was removed in vacuo, and the residue was dissolved with $CHCl_3$, and the solution was washed with aqueous 10% citric acid solution. The resultant solution was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The obtained crude Boc-DQ-113 was roughly purified by silica gel chromatography, eluting with $CHCl_3$/MeOH = 10:1 to give 520 mg of Boc-DQ-113.

To the roughly purified Boc-DQ-113 (520 mg) was added concentrated aqueous HCl solution (10 mL) at 0 °C, and the mixture was stirred for 20 min at ambient temperature. The solution was washed with $CHCl_3$, then alkalified with saturated aqueous NaOH solution at 0 °C, and the solution was washed with CH_2Cl_2. After the pH of the solution was adjusted to 7.4 with concentrated aqueous HCl solution and aqueous 1 N HCl solution, the aqueous solution was extracted with $CHCl_3$ (2 ×), and the combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The obtained crude product was purified by recrystallization from MeOH/*i*-PrOH to yield **6** (= **DQ-113**, 243 mg, 56%) as a yellow powder. The spectral data of **6** obtained by this procedure were identical to those reported.[1]

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