

Improved synthesis of DQ-113, a new quinolone antibacterial agent, utilizing the Reformatsky reaction

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Dedicated to Professor Keiichiro Fukumoto on his 70th birthday

(received 25 May 03; accepted 24 July 03; published on the web 30 July 03)

Abstract

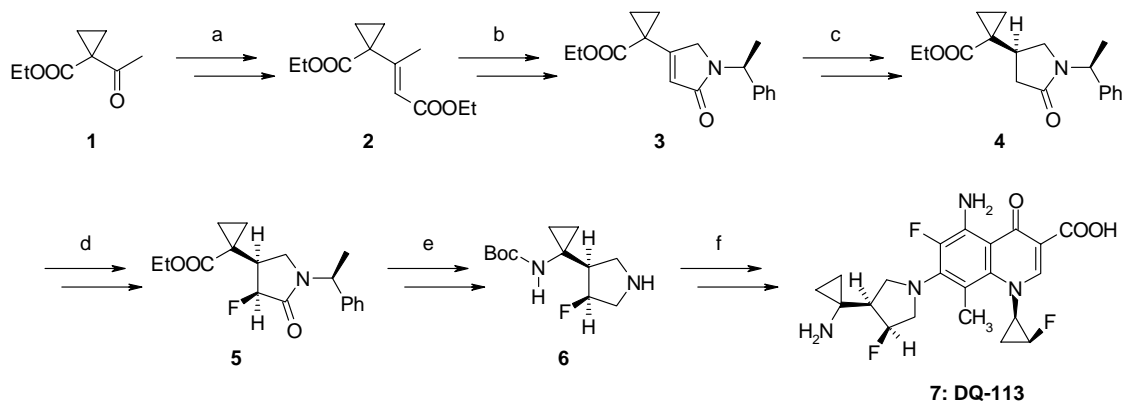
A new improved synthetic route for the C-7 substituent in DQ-113, a new quinolone antibacterial agent for infections caused by Gram-positive pathogens, has been developed which does not use low temperatures and avoids the use of expensive fluorinating agents. The key step is a Reformatsky reaction between ethyl bromofluoroacetate and ethyl 1-acetylcyclopropanecarboxylate.

Keywords: DQ-113, Reformatsky reaction

Introduction

DQ-113, which is 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 (**7**), is a new potent antibacterial agent for infections caused by Gram-positive pathogens including multi-drug resistant strains, and is currently undergoing preclinical evaluation by Daiichi.^{1,2} One of the structural features of DQ-113 is its possession of the *cis*-oriented (3*S*,4*R*)-4-(1-aminocycloprop-1-yl)-3-fluoropyrrolidine moiety as the C-7 substituent, which has been shown to be indispensable for its effective biological properties.¹ Earlier we have reported a preparative synthetic method for the C-7 substituent: (3*S*,4*R*)-4-(1-*tert*-butoxycarbonylamino)cycloprop-1-yl)-3-fluoropyrrolidine (**6**), which have as key steps the fluorination of ethyl 1-[(3*S*)-5-oxo-1-[(*S*)-1-phenylethyl]pyrrolidin-3-yl]cyclopropanecarboxylate (**4**), using lithium diisopropylamide (LDA) and *N*-fluorobenzene-sulfonimide at -78 °C, followed by isomerization of the resultant *trans*-fluorinated pyrrolidine by using LDA and 2,6-di-*tert*-butylphenol at -78 °C (Scheme 1).¹ However, the key steps using LDA and expensive

fluorinating agents at low temperature are not acceptable for large scale synthesis. To produce the intermediate **6** more efficiently than in the initial method, a new synthetic route has been designed and studied, which uses a Reformatsky reaction with ethyl bromofluoroacetate.



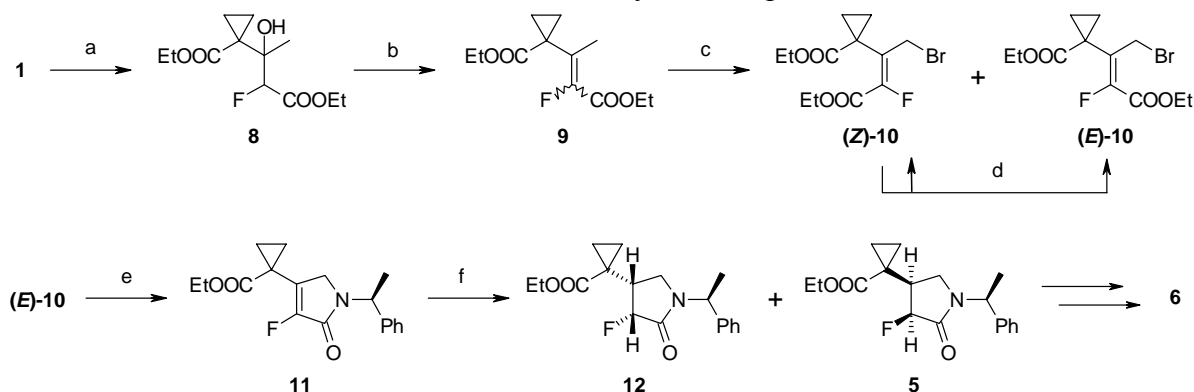
^a Reactions: (a) Reformatsky reaction, elimination; (b) bromination, (*S*)-1-phenylethylamine, cyclization; (c) hydrogenation, separation of diastereomers; (d) fluorination, isomerization; (e) reduction, protecting group conversion, hydrolysis, Curtius rearrangement, deprotection; (f) aromatic nucleophilic substitution with 5-amino-6,7-difluoro-1-[(1*R*,2*S*)-2-fluorocycloprop-1-yl]-1,4-dihydro-8-methyl-4-oxoquinoline-3-carboxylic acid, deprotection.

Scheme 1. ^a The reported synthetic route for DQ-113¹.

Results and Discussion

The new synthetic route for **6** is shown in Scheme 2. The Reformatsky reaction of 1-acetylcyclopropanecarboxylate³ **1** with bromofluoroacetate proceeded under standard conditions to give the fluoro-diester **8**. The crude **8** was then treated with thionyl chloride/pyridine to give a chlorinated product. Treatment of the crude chlorinated product with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave the α -fluoro- α,β -unsaturated ester **9** as a 1:1 mixture of (*E*)- and (*Z*)- isomers in 79% yield from **1**. Bromination of the allylic position of the *E/Z* mixture **9** with *N*-bromosuccinimide (NBS) catalyzed by 2,2'-azo-*bis*-isobutyronitrile (AIBN) gave a 1.35:1 mixture of the (*E*)-bromo-diester (***E***-**10**) and (*Z*)-bromo-diester (***Z***-**10**) in 87% yield, which was separated to give the two isomers (silica gel column chromatography). The (*Z*)-isomer (***Z***-**10**), which could not be converted into the unsaturated lactam **11**, could be converted into the mixture of (***E***-**10**) and (***Z***-**10**) by heating with 0.1 eq. of NBS and 0.1 eq. of AIBN in benzene. After the isomerization process was repeated three times, the collected (*E*)-isomer (***E***-**10**) (83% from **9**) was treated with (*S*)-1-phenylethylamine and sodium hydrogencarbonate in ethanol to give the lactam **11** in 81% yield. Finally, hydrogenation of **11** catalyzed by Raney Nickel gave a 3:1 mixture of the (3*S*,4*S*)-lactam **5** reported before,¹ and the unwanted (3*R*,4*R*)-lactam **12**, in 86% yield, although other conditions using other catalysts lost face-selectivity

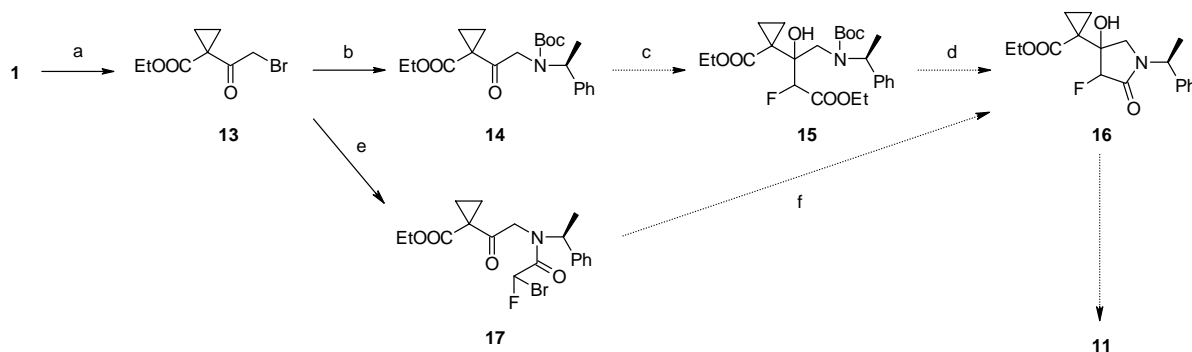
and/or gave more des-fluorine products. The mixture of **5** and **12** could be separated easily into the two isomers by silica gel column chromatography. The (3*S*,4*S*)-lactam **5** obtained by this route could be transformed into **6** in about the same yield as reported before.¹



^a Reagents: (a) BrFCHCO₂Et, Zn, cat. I₂/benzene; (b) SOCl₂/pyridine, then DBU/CH₂Cl₂ (79% from **1**); (c) NBS, cat. AIBN/benzene; (d) 0.1 eq. NBS, 0.1 eq. AIBN/benzene; (e) (*S*)-1-phenylethylamine, NaHCO₃/EtOH (81%, 67% from **9**); (f) H₂, Raney Ni (W-6)/EtOH (**12**: 21%; **5**: 65%).

Scheme 2. ^a The new improved synthetic route for DQ-113 utilizing the Reformatsky reaction with bromofluoroacetate.

In order to avoid the chromatographic separation of (*Z*)-**10** and (*E*)-**10**, and to obtain **11** more efficiently with shorter routes, we tried to develop two new synthetic routes for **11**, shown in Scheme 3. The key step of one route (**1**→**13**→**14**→**15**→**16**→**11**) is a Reformatsky reaction between the amino-ketone **14** and bromofluoroacetate, and of the other (**1**→**13**→**17**→**16**→**11**) is the intramolecular Reformatsky reaction of **17**. However, under standard conditions, both of the Reformatsky reactions gave complex mixtures and did not afford the key intermediates **15** or **16**. Using other reaction conditions, it is possible that these new processes might be achieved in future.



^a Reagent or reaction: (a) Bromination; (b) (1) (*S*)-1-phenylethylamine; (2) Boc₂O; (c) Reformatsky reaction with BrFCHCO₂Et; (d) deprotection and cyclization; (e) (1) (*S*)-1-phenylethylamine; (2) BrFCHCOCl; (f) intramolecular Reformatsky reaction.

Scheme 3. ^a Two possible (unachieved) synthetic routes for **11**.

Conclusions

Thus, we have developed a new synthetic route for **6** utilizing the Reformatsky reaction between the 1-acetylcyclopropanecarboxylate **1** and ethyl bromofluoroacetate. In this route, expensive fluorinating agents or operations at very low temperature were not needed. The total yield from **1** to **5** (6 steps, and 3 times isomerization process) was improved to 41%, from the earlier quoted value of 10% (8 steps).

Experimental Section

General Procedures. Unless otherwise stated, materials were from commercial suppliers were used without further purification. Optical rotations were measured in a 0.5-dm cell at 25°C at 589 nm with a HORIBA SEPA-300 polarimeter. ¹H NMR spectra were determined on a JEOL JNM-EX400 spectrometer. Chemical shifts are reported in ppm relative to tetramethylsilane as internal standard. Significant ¹H NMR data are tabulated in the order: number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q; quartet; m, multiplet), coupling constant(s) in Hz. High-resolution mass spectra were obtained on a JEOL JMS-700 mass spectrometer under electron impact ionization (EI), electron spray ionization (ESI), or fast-atom bombardment conditions (FAB). Column chromatography refers to flash column chromatography using on Merck silica gel 60, 230–400 mesh ASTM. Thin-layer chromatography (TLC) was performed with Merck silica gel 60 F₂₅₄ TLC plates, and compound visualization was effected with a 5% solution of molybdophosphoric acid in ethanol, UV-lamp, iodine, or Wako Ninhydrin Spray.

Ethyl (*E/Z*)-3-(1-ethoxycarbonylcycloprop-1-yl)-2-fluoro-2-butenolate (9**).** To a solution of ethyl 1-acetylcyclopropanecarboxylate (**1**) (124.5 g, 0.797 mol) in 1.5 L of PhH was added Zn powder (156.4 g, 2.393 mol) and a catalytic amount of I₂. To the mixture, heated under reflux, a solution of ethyl bromofluoroacetate (94.2 ml, 0.797 mol) in 200 mL of PhH was added dropwise over 1 h, and the mixture was heated under reflux for another 1 h. The mixture was cooled on an ice bath, and 1 L of aqueous 1 M HCl solution was added. After stirring for 1 h, the organic layer was separated. The organic solution was washed with aqueous 1 M HCl solution, water, brine, dried over Na₂SO₄, and concentrated *in vacuo* to give crude **8**. To the crude **8** in pyridine (387 mL, 4.78 mol) was added thionyl chloride (69.8 mL, 0.957 mol) at –10 °C, and the mixture was stirred for 3 h at the same temperature. The resultant mixture was poured into 2 L of ice cold aqueous 1 M HCl solution, and was extracted with 1.5 L of AcOEt. The organic layer was washed with aqueous 1 M HCl solution, water, brine, dried over Na₂SO₄, and concentrated *in vacuo* to give the crude chlorinated product. To this, in 0.5 L of CH₂Cl₂, was added DBU (131 mL, 0.877 mol) at 0°C, and the mixture was stirred for 17 h at ambient temperature. The reaction mixture was partitioned between 1 L of CHCl₃ and 2 L of aqueous 1 M HCl solution,

and the organic layer was washed with brine, dried over Na₂SO₄, and concentrated *in vacuo* to give crude **9**. This was purified by silica gel chromatography, eluting with AcOEt:hexane = 1:4 to yield **9** as an *E/Z* mixture (152.8 g, 79%, *E/Z* = 1/1, by ¹H NMR) as a colorless oil. This *E/Z* mixture was used for the next reaction without separation of isomers. ¹H NMR (CDCl₃) δ 0.96–0.98 (0.5 × 2H, m), 1.04–1.07 (0.5 × 2H, m), 1.20–1.38 (6H, m), 1.50–1.56 (2H, m), 1.93 (0.5 × 3H, *J* = 4.9 Hz), 2.16 (0.5 × 3H, *J* = 3.4 Hz), 4.10–4.16 (2H, m), 4.24–4.31 (2H, m).

Ethyl (Z)-4-bromo-3-(1-ethoxycarbonylcycloprop-1-yl)-2-fluoro-2-butenate [(Z)-10] and ethyl (E)-4-bromo-3-(1-ethoxycarbonylcycloprop-1-yl)-2-fluoro-2-butenate [(E)-10]. To a solution of ethyl (*E/Z*)-3-(1-ethoxycarbonylcycloprop-1-yl)-2-fluoro-2-butenate (**9**) (152.8 g, 0.625 mol) in 1.5 L of CHCl₃ was added NBS (111.3 g, 0.625 mol) and a catalytic amount of AIBN, and the mixture was heated under reflux for 16 h. After cooling to ambient temperature, the mixture was concentrated *in vacuo*. 0.3 L of benzene was added to the residue, and the resultant suspension was filtered. The filtrate was concentrated *in vacuo*, and the resultant crude product was separated into two isomers by silica gel chromatography. (**E**)-**10** (100.5 g, 50%) was obtained as a pale yellow oil, eluting with AcOEt:hexane = 1:4. ¹H NMR (CDCl₃) δ 1.23 (3H, t, *J* = 7.1 Hz), 1.38 (3H, t, *J* = 7.1 Hz), 1.52–1.62 (4H, m), 4.11 (2H, q, *J* = 7.1 Hz), 4.35 (2H, q, *J* = 7.1 Hz), 4.54 (2H, s). High-resolution MS (FAB) Calcd. for C₁₂H₁₇O₄F⁷⁹Br+H: 323.0294. Found: 323.0261. Calcd. for C₁₂H₁₇O₄F⁸¹Br+H: 325.0275. Found: 325.0273. Further elution with AcOEt:hexane = 1:2 afforded (**Z**)-**10** (75.0 g, 37%) as a pale yellow oil. ¹H NMR (CDCl₃) δ 1.21 (3H, t, *J* = 7.1 Hz), 1.32 (3H, t, *J* = 7.1 Hz), 1.52–1.62 (4H, m), 4.11 (2H, q, *J* = 7.1 Hz), 4.13 (2H, s), 4.29 (2H, q, *J* = 7.1 Hz). High-resolution MS (FAB) Calcd. for C₁₂H₁₇O₄F⁷⁹Br+H: 323.0294. Found: 323.0309. Calcd. for C₁₂H₁₇O₄F⁸¹Br+H: 325.0275. Found: 325.0296.

Isomerization of (Z)-10 to a mixture of (Z)-10 and (E)-10. A mixture of ethyl (**Z**)-4-bromo-3-(1-ethoxycarbonylcycloprop-1-yl)-2-fluoro-2-butenate (**Z**)-**10**, 0.1 eq. of NBS, and 0.1 eq. of AIBN was dissolved in benzene, and heated under reflux under nitrogen for 12–16 h. After the solvent was evaporated, the remaining residue was purified and separated by silica gel chromatography, eluting with AcOEt:hexane = 1:20 → 1:10 → 1:4 → 1:2 to give (**E**)-**10** and a mixture of (**E**)-**10** and (**Z**)-**10**. Using the mixture of (**E**)-**10** and (**Z**)-**10**, the same isomerization procedure was repeated three times to give total 89% of (**E**)-**10** from (**Z**)-**10**.

Ethyl 1-{4-fluoro-2,5-dihydro-5-oxo-1-[(S)-1-phenylethyl]-1H-pyrrol-3-yl}cyclopropane-carboxyl-ate (11**)**. To a solution of ethyl (**E**)-4-bromo-3-(1-ethoxycarbonylcycloprop-1-yl)-2-fluoro-2-butenate [(**E**)-**10**] (46.2 g, 0.143 mol) in 1 L of EtOH was added NaHCO₃ (30.1 g, 0.358 mol), and then (*S*)-1-phenylethylamine (20.3 mL, 0.158 mol), dropwise at ambient temperature. After heating under reflux for 3 h, the mixture was cooled to ambient temperature and filtered through Celite. The filtrate was concentrated *in vacuo*, and purified by silica gel chromatography, eluting with AcOEt:hexane = 1:2 to yield **11** (37.0 g, 81%) as a colorless oil. ¹H NMR (CDCl₃): δ 1.16 (3H, t, *J* = 7.1 Hz), 1.22–1.30 (2H, m), 1.55–1.59 (2H, m), 1.62 (3H, d, *J* = 7.3 Hz), 3.60 (1H, dd, *J* = 18.1, 5.4 Hz), 3.92 (1H, dd, *J* = 18.1, 5.4 Hz), 4.08 (2H, q, *J* = 7.1 Hz), 5.56 (1H, q, *J* = 7.3 Hz), 7.25–7.37 (5H, m). High-resolution MS (EI) Calcd. for C₁₈H₂₀NO₃F: 317.1427. Found: 317.1414. [α]_D –37.9° (c 1.594, CHCl₃).

Ethyl 1-((3*R*,4*R*)-4-fluoro-5-oxo-1-[(*S*)-1-phenylethyl]pyrrolidin-3-yl)cyclopropane-carboxylate (12) and ethyl 1-((3*S*,4*S*)-4-fluoro-5-oxo-1-[(*S*)-1-phenylethyl]pyrrolidin-3-yl)-cyclopropane-carboxylate (5). To a solution of ethyl 1-{4-fluoro-2,5-dihydro-5-oxo-1-[(*S*)-1-phenylethyl]-1*H*-pyrrol-3-yl}cyclopropane-carboxylate (**11**) (587 mg, 1.85 mmol) in 5 mL of EtOH was added Raney Nickel (W-6) (2 mL), and the mixture was stirred vigorously under 5 kg/cm² of hydrogen atmosphere at ambient temperature for 1 h. After more Raney Nickel (W-6) (3 mL) was added to the mixture, the mixture was reacted 2.5 h further under the conditions mentioned above. The resultant mixture was filtered (Celite), and the filtrate was concentrated *in vacuo*. The residue was separated into two isomers by silica gel chromatography; **5** (382 mg, 65%) was obtained as a colorless oil, eluting with AcOEt:hexane = 1:3. The spectroscopic data of **5** were identical to those reported.¹ Compound **12** (101 mg, 21%) was obtained as a colorless oil, eluting with AcOEt:hexane = 1:3. ¹H NMR (CDCl₃) δ 0.66–0.71 (1H, m), 0.97–1.02 (1H, m), 1.25–1.35 (1H, m), 1.22 (3H, t, *J* = 7.2 Hz), 1.19–1.26 (1H, m), 1.32–1.36 (1H, m), 1.57 (3H, d, *J* = 7.1 Hz), 2.76–2.88 (1H, m), 2.92–3.03 (2H, m), 4.12 (2H, q, *J* = 7.2 Hz), 5.15 (1H, dd, *J* = 52.7, 6.3 Hz), 5.53 (1H, q, *J* = 7.0 Hz), 7.27–7.37 (5H, m). High-resolution MS (EI) Calcd. for C₁₈H₂₂NO₃F: 319.1584. Found: 319.1585, [α]_D –31.4° (*c* 0.793, CHCl₃).

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