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Concise route to the key intermediate for divergent synthesis of C7-substituted fluoroquinolone derivatives

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ABSTRACT

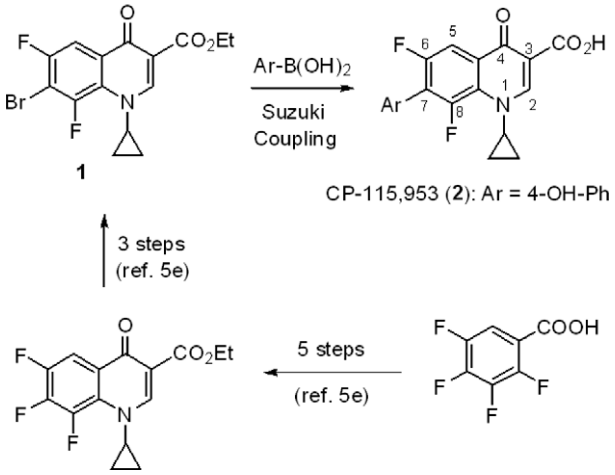
A concise route to ethyl 7-bromo-1-cyclopropyl-6,8-difluoro-4-quinolone-3-carboxylate has been developed. This compound is a key intermediate for divergent synthesis of various C7-substituted fluoroquinolones, a group of potent topoisomerase II inhibitors with promising clinical applications.

DNA topoisomerase II belongs to a class of enzymes that control the topological conformation of DNA, affecting virtually every aspect of nucleic acid physiology. It is crucial to DNA replication and is also involved in transcription, DNA repair, and recombination.[1] All type II topoisomerases are structurally and phylogenetically related. Eukaryotic topoisomerase II is the primary cellular target of a variety of clinically established antitumor agents, while prokaryotic topoisomerase II (DNA gyrase) is the target of antibiotics in treating infections of a wide range of microbial pathogens.[2]

Fluoroquinolone antibiotics are known topoisomerase inhibitors,[3] and hinder bacterial DNA replication through targeting DNA gyrase. As topoisomerase II inhibitors, they also show potential as anticancer agents via stimulating double strand cleavage of DNA. Recently, there has been growing interest of developing quinolone-based ligands for the CB2 cannabinoid receptors. These ligands can be potentially useful in treating alleviating pain, inflammation, cough, dermatitis, and cancers of different origins.[4]

The broad spectrum of fluoroquinolones' activity as topoisomerase II inhibitors in treating bacterial infections, cancers, and other diseases has motivated considerable efforts from the scientific community. Various fluoroquinolone derivatives have been synthesized for structure-activity relationship studies.[3c,e,4a,b,5] Most fluoroqinolones with anticancer activity possess aryl moiety at the C-7 position. Extensive studies focusing on the effect of the substituent group at C7 on activity have been carried out.

Ethyl 7-bromo-1-cyclopropyl-6,8-difluoro-4-quinolone-3-carboxylate (**1**) is the key intermediate for the divergent synthesis of various C7-substituted fluoroquinolone derivatives via convenient Suzuki coupling with different boronic acid compounds (Scheme 1). This compound has previously been synthesized in eight steps from 2,3,4,5-tetrafluorobenzoic acid via the intermediate ethyl 1-cyclopropyl-6,7,8-trifluoro-4-quinolone-3-carboxylate.[5e] Herein, we report our alternative access to compound **1** in six steps under simple reaction conditions. We also exemplify our divergent approach to C7-substituted fluoroquinolone derivatives with the synthesis of CP-115,953 1-cyclopropyl-6,8-di-



Scheme 1. Divergent synthesis of fluoroquinolones.

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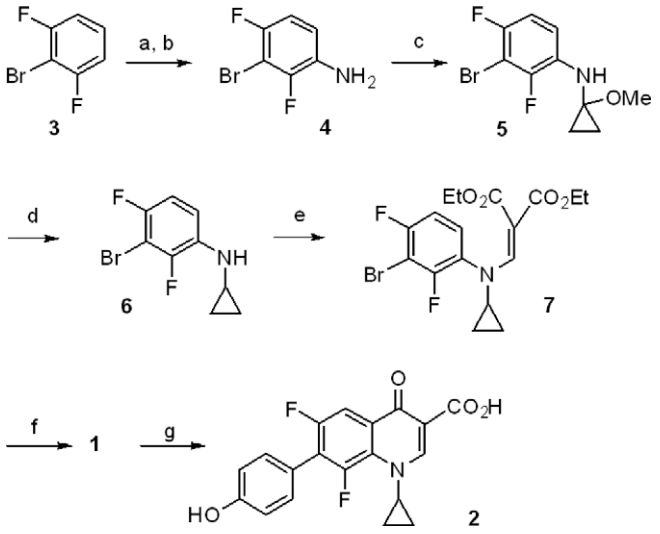

Scheme 2. Reagents and conditions: (a) HNO_3/H_2SO_4, 0–25 °C, 2 h, 91%; (b) $SnCl_2{\cdot}2H_2O$, HCl (conc.), 60 °C, 40 min, 82%; (c) (1-ethoxycyclopropoxy)trimethylsilane, AcOH, MeOH, 67–69 °C, 3 h; (d) (i) $NaBH_4$, $BF_3{\cdot}Et_2O$, THF, 5 °C, 1 h; (ii) **5**, THF, 5–10 °C, 25 °C for 5 h, reflux for 2 h, 68% from **4** to **6**; (e) diethyl ethoxymethylenemalonate, Py, 150 °C, 7.5 h, 77%; (f) polyphosphoric acid, hexane, 120 °C, 3.5 h, 37%; (g) (i) 4-hydroxyphenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, THF, 110 °C (sealed), 8 h, 64%; (ii) HCl (10% aq), THF, 70 °C, 1 h, 89%.

fluoro-7-(4-hydroxyphenyl)-4-quinolone-3-carboxylic acid (**2**), one of the most investigated quinolones.

The synthesis began with the commercially available compound 2-bromo-1,3-difluorobenzene (**3**) (Scheme 2). Nitration of **3** with nitric acid/sulfuric acid provided the corresponding nitro compound 2-bromo-1,3-difluoro-4-nitrobenzene in 91% yield. Subsequent reduction with tin (II) chloride in concentrated HCl at 60 °C produced the 3-bromo-2,4-difluoroaniline **4** in 81% yield. Installation of the cyclopropyl group onto the aniline nitrogen was accomplished with a two-step sequence. First, the aniline **4** reacted with (1-ethoxycyclopropoxy)trimethylsilane in acetic acid/methanol at 67 °C. The obtained intermediate **5** was treated with sodium borohydride ($NaBH_4$) in the presence of trifluoroborane etherate ($BF_3{\cdot}OEt_2$) to provide the desired 3-bromo-*N*-cyclopropyl-2,4-difluoroaniline (**6**) in 68% yield over two steps.[6] Reaction of **6** and diethyl ethoxymethylenemalonate at 150 °C led to **7** in 77% yield. Cyclization of **7** to **1** proved to be challenging. Neither heating **7** in diphenyl ether in the range 250–280 °C[3c] nor reactions of **7** in oleum or chlorosulfonic acid could generate **1**.[7] Eventually, this key intermediate **1** was obtained in 37% yield from the reaction carried out in polyphosphoric acid at 120 °C. From compound **1**, CP-115,953 was conveniently obtained in 57% yield from Suzuki reaction with 4-hydroxyphenylboronic acid followed by hydrolysis of the C3 ethyl ester moiety in dilute hydrochloric acid.[8] (Scheme 2)

In summary, the intermediate **1**, crucial for divergent synthesis of various C7-substituted fluoroquinolone compounds for extensive SAR studies, has been synthesized in six steps with a 14% overall yield. Although the overall yield is lower than that of the eight-step sequence in the literature (i.e., 31%),[5e] this synthesis provides a convenient and simple alternative access to the target compound.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.077.

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