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A practical synthesis of 3-chloro-2,4-difluoro-5-hydroxybenzoic acid

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Abstract

A new and practical synthesis of 3-chloro-2,4-difluoro-5-hydroxybenzoic acid, a key intermediate for preparing antimicrobial 3-quinolinecarboxylic acid drugs, is synthesized from 2,4-difluoro-3-chlororobenzoic acid. The protocol involves nitration, esterification, reduction of NO_2, diazotization, and hydrolysis with a 70% overall yield. The structures of the synthesized compounds are determined by infrared spectroscopy, nuclear magnetic resonance spectroscopy, and high-resolution electrospray ionization mass spectrometry. The advantages of this developed synthetic strategy include an improved overall yield and readily controllable reaction conditions.

Keywords

3-Chloro-2,4-difluoro-5-hydroxybenzoic acid, 3-quinolinecarboxylic acid derivatives, diazotization, hydrolysis, synthesis

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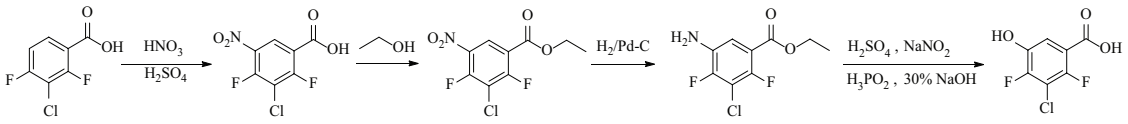

Introduction

Synthetic fluoroquinolone (FQ) antibiotics such as nalidixic acid and piromidic acid are effective antibacterial agents for treating infections caused by Gram-negative microorganisms. As a new generation of FQs, 3-quinolinecarboxylic acid derivatives such as norfloxacin, ofloxacin, moxifloxacin, and besifloxacin are well known for their strong antimicrobial activities and broad spectrum of antibacterial activities, including activity against Gram-positive bacteria.[1,2] Developing new 3-quinolinecarboxylic acid derivatives as novel antimicrobial agents with improved activity, superior pharmacokinetic properties, and satisfactory bacterial resistance is important in pharmaceutical research.[3–7] 1-Cyclopropyl-7-amine-6-hydroxy-8-chloro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid derivatives have been developed for improving antibacterial effects. The novel antibacterial compounds **2** and **3** have been synthesized from 2,4-difluoro-bromobenzene by aromatic chlorination, carboxylation, nitration, and so on with 11 steps in total.[8,9] However, the overall procedure is complicated with many reaction steps, and the carboxylation conditions are harsh requiring *n*-butyllithium below −78 °C. Besides, the reduction of NO_2 and the diazotization of NH_2 afforded impurities in the target final intermediates that made the purification difficult. In this study, compounds **2** and **3** have been synthesized following the route shown in Scheme 1. 3-Chloro-2,4-difluoro-5-hydroxybenzoic acid (**1**) was used as the starting material, followed by benzylation, condensation with diethyl malonate, hydrolysis with *p*-toluenesulfonic acid, condensation with ethyl orthoformate, cyclopropylamine substitution, cyclization, ester hydrolysis, and debenzylation to afford the key quinolone intermediate **1h**. Compounds **2** and **3** were prepared by the condensation of **1h** with cyclic amines. Overall, the syn-

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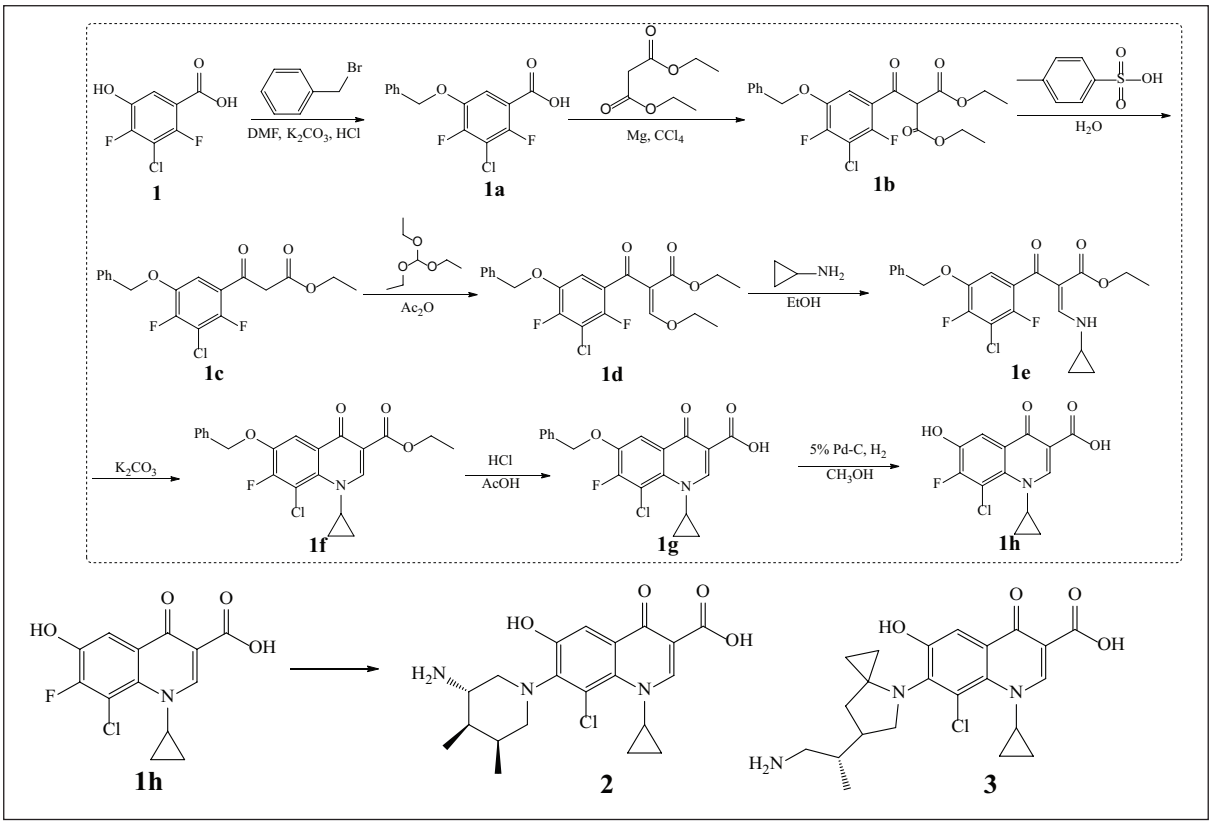
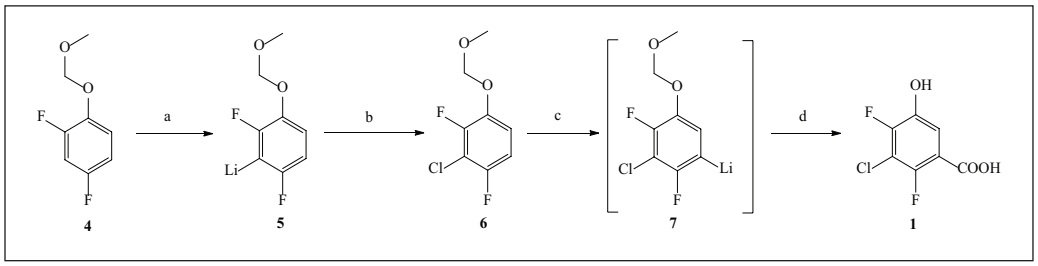


Scheme 1. Synthetic route to compounds **2** and **3** staring from compound **1**.



Scheme 2. Reported synthetic route toward compound **1**.
Reagents and conditions: (a) *sec*-BuLi in THF, −75°C, 2 h, 83%; (b) 1,1,2-trichloro-1,2, 2-trifluoroethane, 82%; (c) LITMP in THF, −75°C, 2 h; and (d) 1—excess dry ice, 2—HCl, 75%.

thetic method is more efficient and does not use *n*-butyllithium (Scheme 1).

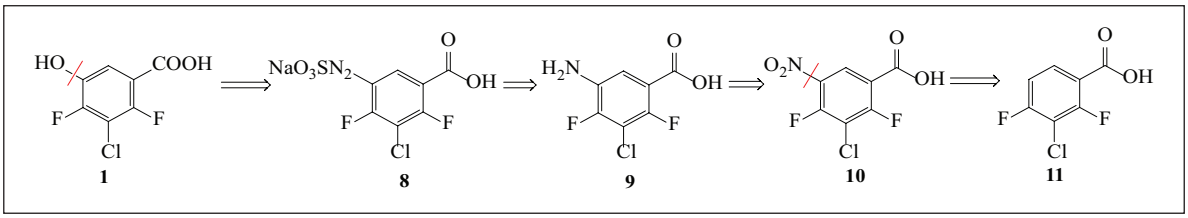
Some FQs are also photolabile compounds which lead to phototoxicity as a side effect. The intrinsic photostability characteristics should be evaluated to demonstrate that light exposure does not result in unacceptable changes.[10] Hydroxylation of FQs at the 6-position is one of the main photodegradation pathways, affording 6-hydroxyciprofloxacin and 6-hydroxysarafloxacin impurities.[11] For quality control of FQ drug substances, it is necessary to synthesize these impurities, which can be prepared from the derivatives of compound **1**.

The synthesis of 3-chloro-2,4-difluoro-5-hydroxybenzoic acid (**1**) was critical for developing new FQs and the quality control of drug substances. However, there is only one reported method for the preparation of the title compound **1** (Scheme 2).[12] 2,4-Difluoro-1-(methoxymethoxy)benzene (**4**) was reacted with *sec*-butyllithium in tetrahydrofuran (THF) at −75°C to give (2,6-difluoro-3-methoxymethoxyphenyl)lithium (**5**) in 83% yield. 2-Chloro-1,3-difluoro-4-methoxymethoxybenzene (**6**) was obtained in 82% yield by treating compound **5** with 1,1,2-trichloro-1,2,2-trifluoroethane. Compound **1** could be prepared through Li-substitution and carboxylation of **6** in 75% yield. However, this method uses dangerous alkyllithium reagents at extremely low temperatures which limits the large-scale preparation using this route. Furthermore, the overall yield for the synthetic route was only 51%.

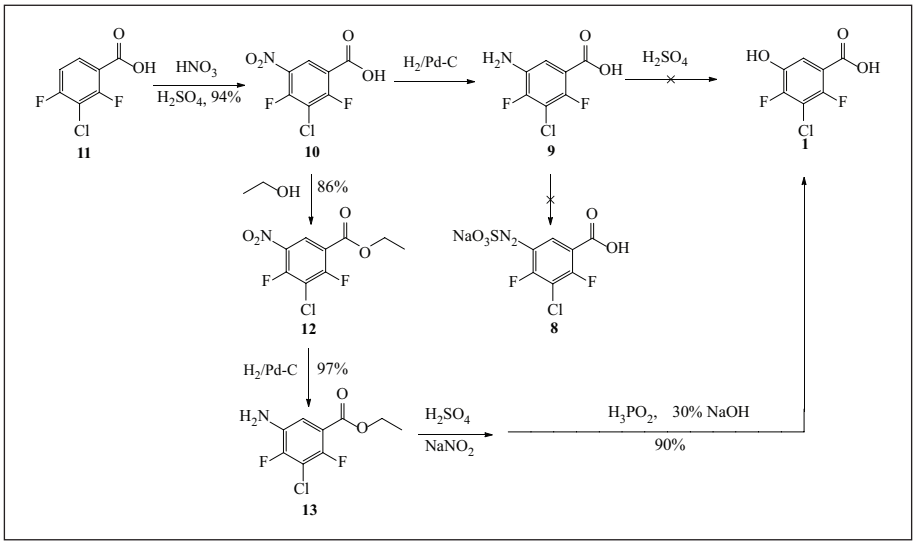
Thus, it is important to develop a more practical and efficient synthetic method for the preparation of compound **1**.

Results and discussion

Amino hydrolysis of an aryl amine can be used for preparing phenols.[13–16] As shown in Scheme 3, the retrosynthetic analysis suggests that compound **1** can be synthesized by the



Scheme 3. Retrosynthetic analysis of compound **1**.



Scheme 4. The new synthetic strategy toward compound **1**.

hydrolysis of diazonium salt **8**, which is the typical method for introducing a hydroxy group into an aromatic ring. Compound **8** could be obtained by the diazotization of compound **9**, which occurs rapidly in concentrated sulfuric acid. Compound **9** would be prepared by the reduction of 3-chloro-2,4-difluro-5-nitrobenzoic acid (**10**) with hydrogen in the presence of Pd/C, while **10** can be synthesized by the nitration of commercially available 2,4-difluro-3-chlorobenzoic acid (**11**).

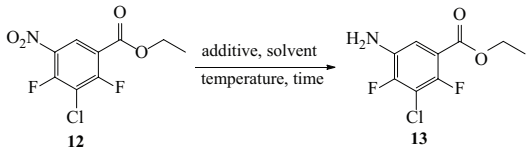
Based on the retrosynthetic analysis of compound **1**, preliminary experiments were performed to verify the feasibility of this scheme. However, the critical intermediate compound **8** could not be separated from water because of its high solubility. Further optimization was achieved by introducing an ester group into benzoic acid to reduce the solubility. The new synthetic strategy is illustrated in Scheme 4. Compound **1** was obtained by the nitration of **11**, which was followed by esterification, reduction of NO_2, diazotization, and hydrolysis of **13**. The structures of the intermediates and products were characterized by infrared (IR) spectroscopy, ^{1}H nuclear magnetic resonance (NMR) spectroscopy, ^{13}C NMR spectroscopy, and mass spectrometry (MS).

In this new synthetic route, compound **11** was treated with concentrated nitric acid to give 3-chloro-2,4-difluoro-5-nitrobenzoic acid (**10**) in 94% yield. The nitration of compound **11** was slow because of the electron-withdrawing effects of the F and COOH groups. The reaction required a high temperature and the inclusion of excess concentrated HNO_3 as an additive. Following esterification of **10**, compound **12** was obtained in a good yield of 86%. The hydrogenation of **12** catalyzed by Pd/C gave ethyl 5-amino-3-chloro-2,4-difluorobenzoate (**13**) in an excellent yield of 97.0%. Finally, compound **13** was converted into the target compound **1** in 90% yield by diazotization and hydrolysis with H_3PO_2/H_2O in one step.

With optimized reaction conditions in hand, we sought to evaluate the suitable conditions for the reduction of compound **12**. 2% Raney Ni and 3 equiv. of hydrazine hydrate (80%) in ethanol were initially used. The result demonstrated low activity, giving a 45% yield of **13** after reaction for 9 h (Table 1, entry 1). The numbers of equivalents of hydrazine hydrate (80%) was increased to 4.0 and the reaction temperature was increased to 78°C; the highest yield was 62%, after reacting for 12 h (entries 2 and 3). By further optimizing the additive (entries 4−6), the yield of compound **13** was significantly improved (entry 6, 82%). Compared to Raney Ni and hydrazine hydrate (80%), using 5% Pd/C (66% water) and H_2 improved the yield to 72% (entry 7). The additive ratios were also optimized, and the highest yield (97%) was obtained (entries 8−11). On increasing the pressure to 0.8−1.0 MPa, the reactions were complete within 5 h, and the highest yield of 97% was obtained.

In the fourth step, concentrated sulfuric acid was first employed as the solvent for the hydrolysis of compound **13**; however, the reaction did not occur. Further experiments showed that compound **1** could be afforded by diazotization with $NaNO_2$ and hydrolysis with 50% H_3PO_2 to give **13**. For

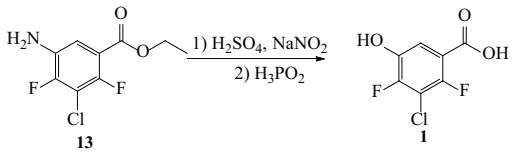
Table 1. Optimization of the reduction reaction conditions.



Entry	Additive (w/w, equiv., H_2 pressure)[a]	Solvent	Temperature (°C)	Time (h)	Yield (%)[b]
1	Raney Ni (0.02), NH_2NH_2 (3.0)	Ethanol	60	9	45
2	Raney Ni (0.02), NH_2NH_2 (4.0)	Ethanol	70	9	53
3	Raney Ni (0.03), NH_2NH_2 (4.0)	Ethanol	78	12	62
4	5% Pd-C (0.02), NH_2NH_2 (3.0)	Ethanol	60	9	63
5	5% Pd-C (0.02), NH_2NH_2 (3.0)	Methanol	68	9	75
6	5% Pd-C (0.03), NH_2NH_2 (4.0)	Methanol	68	9	82
7	5% Pd-C (0.02), H_2 (0.1 MPa)	Ethanol	60	9	72
8	5% Pd-C (0.03), H_2 (0.1 MPa)	Ethanol	78	6	85
9	5% Pd-C (0.02), H_2 (0.5 MPa)	Methanol	30	5	93
10	5% Pd-C (0.02), H_2 (0.8 MPa)	Methanol	40	5	97
11	5% Pd-C (0.03), H_2 (1 MPa)	Methanol	40	5	97

[a]Entries 1–3: Raney Ni (w/w); entries 4–11: 5% Pd-C (dry weight/w).
[b]Isolated yield.

Table 2. Optimization of the diazotization and hydrolysis reaction conditions.[a]



Entry	$NaNO_2$ (equiv.)	H_2SO_4 (equiv.)	Temperature (°C)	Time (h)	Yield (%)[b]
1	1.0	2.5	10	4	48
2	1.0	3.0	10	3	50
3	1.2	3.0	5	3	57
4	1.25	3.0	5	3	63
5	1.25	4.0	0	2	89
6	1.25	4.0	0	2.5	90

[a]Compound **13** (10 mmol), H_2O (50 mL), 50% H_3PO_2 (30 mmol).
[b]Isolated yield.

optimizing the reaction conditions, the equivalents of $NaNO_2$ and H_2SO_4 were studied (Table 2). Equivalents of $NaNO_2$ from 1.0 to 1.25 were screened and the results showed that $NaNO_2$ equivalents below 1.2 gave only moderate yields (Table 1, entries 1−3). Subsequently, by decreasing the reaction temperature from 10°C to 0°C, it was found that 1.25 equiv. of $NaNO_2$ in 4.0 equiv. of H_2SO_4 successfully improved the yield from 57% to 90% (Table 2, entries 4−6).

Conclusion

In summary, a novel and practical process for the synthesis of 3-chloro-2,4-difluoro-5-hydroxybenzoic acid (**1**), a key intermediate for preparing antimicrobial 3-quinolinecarboxylic acid derivatives, has been developed. The synthetic strategy involved the nitration of 2,4-difluoro-3-chlororobenzoic acid (**11**), esterification, reduction of NO_2, diazotization, and hydrolysis. Hazardous alkyllithium reagents and low reaction temperatures are avoided to decrease the formation of byproducts. In addition, this new synthetic route has the advantages of readily available reagents and a high overall yield of 70%. The described strategy is also suitable for the synthesis of derivatives of compound **1**.

Experimental

2,4-Difluoro-3-chlororobenzoic acid (**11**) was purchased from Aladdin (Shanghai) with 98% purity. Unless otherwise mentioned, all solvents, reagents, and materials were purchased from commercial suppliers and used without further purification. All reactions were monitored by thin-layer chromatography (TLC) on silica gel plates (GF-254; Qingdao Ocean Chemical Company, China) and products were purified by silica gel column chromatography (200−300 mesh; Qingdao Marine Chemical Industry

Corporation, China). Melting points (m.p.) were determined on a YRT-3 melting point apparatus using the capillary method without correction. IR spectra were obtained on an Avatar 330FT-IR (Thermo Nicolet) spectrometer, using the attenuated total reflectance (ATP) method. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance DPX 300 MHz instrument in $CDCl_3$ or DMSO-d_6 with tetramethylsilane (TMS) as an internal reference. Chemical shifts (δ) are reported in parts per million (ppm). High-resolution mass spectra (HRMS) were obtained from Agilent 1100 LC/MS Spectrometry Services.

3-Chloro-2,4-difluoro-5-nitrobenzoic acid (*10*)

A solution of concentrated HNO_3 (65%, 15.0 g) and H_2SO_4 (98%, 8.0 g) was added dropwise to 2,4-difluoro-3-chlorobenzoic acid (**11**) (15.0 g, 78.13 mmol) and concentrated H_2SO_4 (98%, 32.0 g) at ice-bath temperature. The temperature was kept below 20°C during the addition process. After the addition was complete, the mixture was stirred for 2 h at 70–75°C until TLC (40% ethyl acetate in hexane) showed the starting materials had disappeared. The mixture was cooled to room temperature, poured into ice-water (180 g), stirred for another 1 h at 0–5°C, filtered, and washed with water to afford a gray solid. The crude product was purified by recrystallization from hexane to afford **10** as a white solid (17.38 g, 94%); m.p. 122.3–124.1°C, (123–124°C);[17] IR (KBr)/cm^{-1}: 3269, 3055, 1692, 1533, 1322, 891; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 13.67 (br s, 1 H, D_2O exchangeable), 8.52–8.57 (m, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 161.9 (d, *J* = 3.8 Hz), 160.3 (dd, *J* = 268.4, 2.7 Hz), 154.4 (dd, *J* = 268.1, 3.7 Hz), 133.9, 127.4, 116.8 (dd, *J* = 12.1, 4.1 Hz), 113.2 (t, *J* = 22.5 Hz); HRMS (ESI): *m*/*z* $[M-H]^-$ calcd for $C_7HClF_2NO_4$: 235.9562; found: 235.9559.

Ethyl 3-chloro-2,4-difluoro-5-nitrobenzoate (*12*)

A mixture of compound **10** (12.0 g, 50.6 mmol), ethanol (200 mL), and H_2SO_4 (98%, 7.5 g) was stirred under reflux for 3 h until the starting materials had disappeared (TLC detection, 10% ethyl acetate, 90% hexane). After cooling, the solvent was removed under reduced pressure, the residue cooled to 5 °C, and the pH value was adjusted to neutral with 10% sodium carbonate solution (70 mL). The mixture was extracted twice with ethyl acetate (60 mL × 2) and the combined organic layer was dried with Na_2SO_4. The solvent was removed on a rotary evaporator, and the crude product was purified by column chromatography using 5% ethyl acetate:9% petroleum ether as an eluent. The solvent was removed under reduced pressure to afford **12** as a light yellow solid (11.5 g, 86%); m.p. 127–129 °C; IR (KBr)/cm^{-1}: 3145, 3081, 2967, 2875, 1716, 1534, 1327, 901; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.68 (t, *J* = 7.2 Hz, 1 H), 4.47 (q, *J* = 7.1 Hz, 2 H), 1.45 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9 (d, *J* = 3.4 Hz), 161.1 (dd, *J* = 204.2, 2.2 Hz), 155.1 (dd, *J* = 272.3, 3.8 Hz), 134.0, 127.3 (t, *J* = 2.2 Hz), 116.3 (dd, *J* = 11.7, 4.5 Hz), 114.6 (dd, *J* = 22.3, 20.0 Hz), 62.8, 14.1; HRMS (ESI): *m*/*z* $[M+H]^+$ calcd for $C_9H_7ClF_2NO_4$: 266.0032; found: 266.0049.

Ethyl 5-amino-3-chloro-2,4-difluorobenzoate (*13*)

Compound **12** (10. 0 g, 37.73 mmol), Pd/C (10%, 0.2 g), and methanol (100 mL) were placed in an autoclave (250 mL). H_2 was purged into the autoclave three times to remove air, and the reaction mixture was stirred at 40°C for 5 h under a pressure between 0.8 and 1.0 MPa. After the reaction was complete, the resulting mixture was transferred to a tube and filtered to recycle the catalyst. The solvent was removed under reduced pressure to afford **13** as a gray solid (8.6 g, 97%); m.p. 115.2–115.9°C; IR (KBr)/cm^{-1}: 3431, 3410, 3351, 3216, 3072, 3011, 2972, 1713, 1496, 1284, 1018, 779; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 (m, 1 H), 4.37 (q, *J* = 7.1 Hz, 2 H), 3.76 (s, 2 H, D_2O exchangeable), 1.38 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.4 (d, *J* = 4.3 Hz), 150.9 (d, *J* = 253.5 Hz), 149.9 (d, *J* = 248.9 Hz), 131.3 (dd, *J* = 12.8, 3.1 Hz), 115.8 (d, *J* = 5.4 Hz), 115.3 (dd, *J* = 10.9, 3.7 Hz), 111.2 (dd, *J* = 22.9, 18.6 Hz), 61.6, 14.0; HRMS (ESI): *m*/*z* $[M-H]^-$ calcd for $C_9H_7ClF_2NO_2$: 234.0133; found: 234.0128.

3-Chloro-2,4-difluoro-5-hydroxybenzoic acid (*1*)

A mixture of compound **13** (2.35 g, 10 mmol) and H_2O (45 mL) was cooled to 0°C, concentrated sulfuric acid (98%, 4.0 g) was added dropwise, and the temperature was kept below 5°C. A white solid precipitated during the process, and the mixture was stirred for 30 min. To this emulsion, a solution of $NaNO_2$ (0.86 g, 12.5 mmol) in H_2O (5.0 mL) was added dropwise to the cooled reaction mixture. Stirring was continued for another 30 min during which the reaction mixture became a clear solution. A solution of 50% hypophosphorous acid (3.96 g, 30 mmol) was added dropwise below 0°C, and the mixture was stirred at 0°C for 2.5 h. Then, the pH of the reaction mixture was adjusted to 9–10 with 30% NaOH and stirred for another 1 h at 50°C (the reaction was monitored by TLC (25% ethyl acetate, 5% acetic acid in hexane)). The reaction mixture was cooled to room temperature and extracted with dichloromethane (2 × 300 mL), and the combined organic phases were decolorized with activated charcoal and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford a white solid. The crude product was washed with a mixture of hexane (10 mL) and ethyl acetate (2 mL), and then dried between 50 and 55°C for 5 h. The product was obtained as a white solid (1.87 g, 90%); m.p. 194.7–195.9°C, (195–197°C);[12] IR (KBr)/cm^{-1}: 3566, 3506, 3257, 3048, 1698, 1597, 1495, 1459, 1088, 932; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 13.47 (br, s, 1 H, D_2O exchangeable), 10.66 (br, s, 1 H, D_2O exchangeable), 7.43 (dd, *J* = 9.09, 7.32 Hz, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 163.6 (d, *J* = 3.6 Hz), 150.2 (d, *J* = 252.9 Hz), 149.7 (d, *J* = 252.4 Hz), 141.8 (dd, *J* = 11.6, 2.9 Hz), 117.1 (d,

J=4.3 Hz), 115.5 (dd, J=11.1, 3.8 Hz), 110.4 (dd, J=22.9, 18.4 Hz); ^{19}F NMR (376 MHz, DMSO-d_6): δ=−122.5, −127.6; HRMS (ESI): m/z $[M-H]^-$ calcd for $C_7H_2ClF_2O_3$: 206.9661; found: 206.9672.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplemental material

Supplemental material for this article is available online.

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