AN EFFICIENT SYNTHESIS OF OFLOXACIN AND LEVOFLOXACIN FROM 3,4-DIFLUOROANILINE

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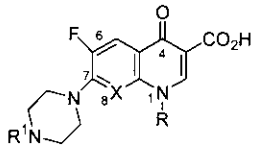
Abstract - The functionalization at either C-2 or C-3 of *N*-(*tert*-butoxycarbonyl)-3,4-difluoroaniline based on its *ortho*-deprotonation under different experimental conditions is described. This kind of products can be readily applied to the synthesis of ofloxacin, levofloxacin and related compounds.

Some quinolones bearing a fluorine atom at C-6 and a piperazine ring at C-7, known as fluoroquinolones, are among the most important antimicrobial agents, showing both a high potency and a broad antibacterial spectrum.[1] Notable examples of clinically significant quinolone antibacterials are shown in Figure 1. Among them ofloxacin has a more complex structure due to its tricyclic skeleton, substitution at C-8, and presence of one stereogenic center. Although ofloxacin is marketed as the racemic mixture, its *(S)*-enantiomer (levofloxacin) shows a higher biological activity and a reduced toxicity than the racemic compound.[2]



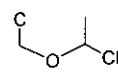
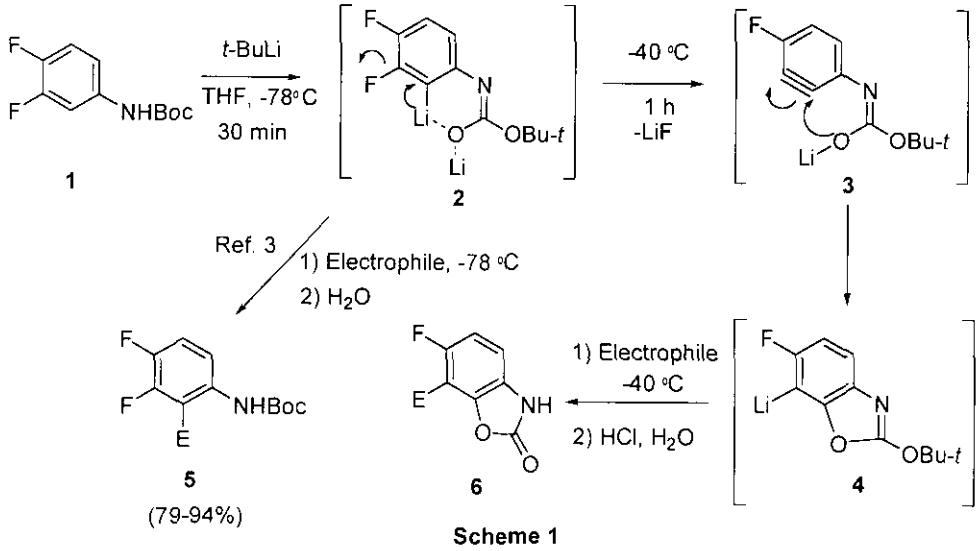
	X	R	R^1
Norfloxacin	CH	CH_2CH_3	H
Perfloxacin	CH	CH_2CH_3	CH_3
Enoxacin	N	CH_2CH_3	H
Ciprofloxacin	CH	c-C_3H_5	H
Amifloxacin	CH	$NHCH_3$	CH_3
Fleroxacin	CF	CH_2CH_2F	CH_3
Ofloxacin			CH_3

Figure 1

A few years ago we reported that the *ortho*-deprotonation of *N*-(*tert*-butoxycarbonyl)-3,4-difluoroaniline (**1**) with *t*-BuLi (2 equiv.) in THF at –78 °C occurred regioselectively at C-2, after quenching of the metalated anion with an electrophile, to give the corresponding 2-substituted products (**5**), which were useful substrates in the synthesis of C-8 substituted bicyclic quinolones.[3] Herein we describe that it is also feasible the clean functionalization at C-3 in compound (**1**), to give carbamates (**6**), simply by performing its metalation reaction at a higher temperature (-40 °C instead of –78 °C) and that both approaches can be applied to the synthesis of ofloxacin or related compounds.

We assume that at –40 °C by elimination of LiF the initially formed *ortho*-metalated lithium species (**2**) evolves into a benzyne intermediate (**3**), that would be intramolecularly trapped by the contiguous carbamate[4] to give a new metalated lithium species (**4**), which interestingly do not evolve into a new benzyne intermediate by a second elimination of LiF.[5] After addition of the electrophile at –40 °C and acid work-up (1M HCl), the carbamates (**6**) were obtained in high yields (71-83% after chromatographic purification) (Scheme 1). The reaction is quite general and a wide variety of electrophiles, such as D_2O, methyl disulfide, methyl iodide, 1,2-dibromoethane or DMF can be used (Table 1).



Scheme 1

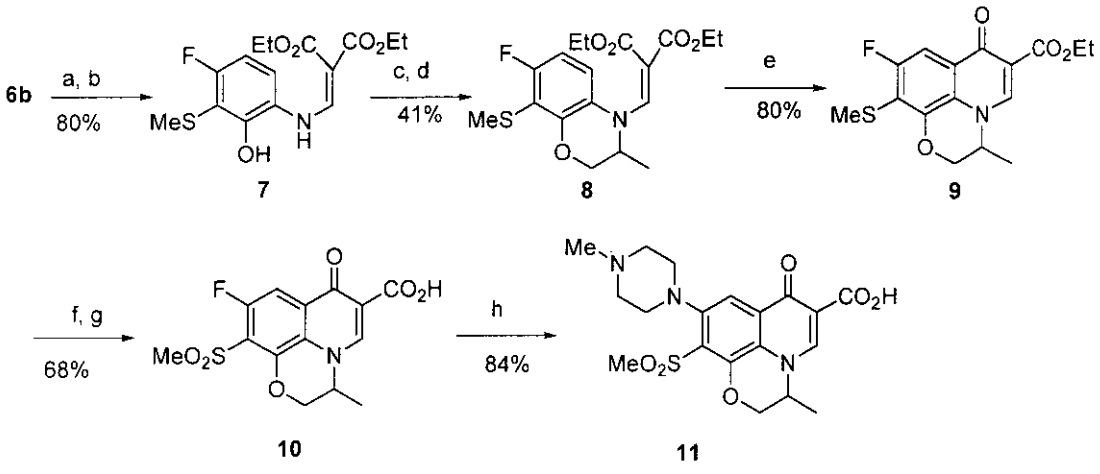
Table 1. C-2 and C-3 functionalization of **1**

Entry	Electrophile	E	**6**	Yield (%)
1	D_2O	D	**6a**	72
2	$(MeS)_2$	SMe	**6b**	82
3	MeI	Me	**6c**	83
4	$BrCH_2CH_2Br$	Br	**6d**	79
5	DMF	CHO	**6e**	71

With intermediates (**5**) and (**6**) in hand we undertook their application to the synthesis of ofloxacin and levofloxacin. For this end cyclic carbamates (**6**) were very appealing substrates due to the presence of the

required oxygenated substitution at C-2. In particular we chose substrate (**6b**) because, at a final stage of the synthetic sequence, the oxidation of the thioether to the corresponding sulfone could allow its further substitution with *N*-methylpiperazine by means of an aromatic nucleophilic substitution, acting the sulfone as leaving group.[6]

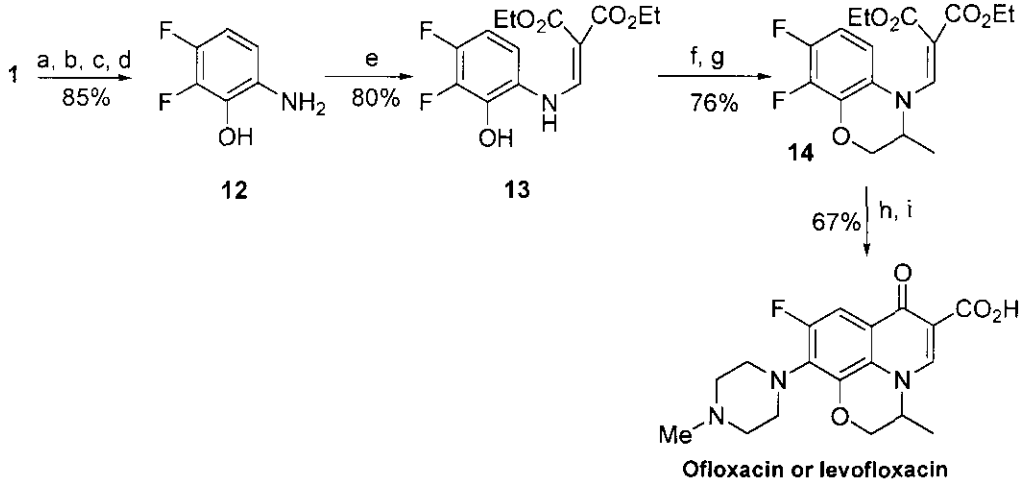
In Scheme 2 is shown the synthetic sequence. Basic hydrolysis of the carbamate moiety of (**6b**) (KOH, EtOH, H_2O, reflux), followed by condensation of the resulting aniline derivative with diethyl ethoxymethylene malonate at 110 °C without solvent afforded the enamine (**7**) (80%).[7] The benzoxazine structure was constructed by *O*-alkylation of the phenolate derived from (**7**) with propylene oxide (NaH cat, $LiClO_4$, THF, 40 °C)[8] and further dehydration with the Mitsunobu reagents (DEAD, PPh_3, THF, rt) to give **8** in 41% overall yield. Intramolecular Friedel-Crafts acylation of **8** was performed by treatment with Ac_2O/H_2SO_4 (1:2) at 50 °C to afford the quinolone ester (**9**) (80%). Its oxidation with Oxone ($KHSO_5$, MeOH, H_2O, 25 °C) and acid hydrolysis of the ester led to the 7-methylsulfonylquinolone (**10**) (68%). Unlike our expectations and the precedents on the use of sulfones as leaving groups in quinolone synthesis,[6] all attempts to substitute the sulfonyl group in **10** (or in its ester precursor) by *N*-methyl piperazine were unsuccessful.[9] In all cases a clean reaction leading to the 6-piperazinyl substituted quinolone (**11**) was observed, showing that the aromatic nucleophilic substitution took place by displacement of the fluorine atom at C-6 instead of the sulfonyl moiety at C-7.[10]



a) KOH, EtOH/H_2O, reflux, 8 d; b) diethyl ethoxymethylenemalonate, 110 °C; c) $LiClO_4$, NaH (cat), propylene oxide, THF, 40 °C, 2 d; d) DEAD, PPh_3, THF, rt, 18 h; e) Ac_2O/H_2SO_4 (1:2), 50 °C, 45 min; f) oxone, MeOH/H_2O, 25 °C; g) HCl(c)/AcOH (1:2), 100 °C, 18 h; h) *N*-methylpiperazine, MeCN, 60 °C, 16 h.

Scheme 2

Taking into account that a fluorine atom at C-7 at the final quinolone appears to be crucial for the introduction of the piperazine, we prepared the difluoroaminophenol (**12**) as the new key starting material. This compound was readily prepared in 85% yield by trapping the metalated anion (**2**) with $(MeO)_3B$ at -78 °C, further oxidation of the formed C-B bond with H_2O_2 in acetic acid and acid hydrolysis.[11] Following an identical synthetic scheme mentioned above, **12** was converted into the enamine (**13**) (80%) and then into the known racemic or enantiomerically pure 1,4-benzoxazine (**14**)[2d,e] (76%), which was transformed into ofloxacin or levofloxacin following reported procedures[2,12] (Scheme 3). Interestingly this approach can be equally applied to the synthesis of both ofloxacin and levofloxacin[13] (being the only difference the use of racemic propylene oxide or its commercially available *(R)*- enantiomer in the *O*-alkylation step). Finally, from a practical point of view it is worth noting that all reactions shown in Scheme 3 have been performed up to a 10-50 gram scale without loss of chemical yield.



a) *t*-BuLi, THF, -78 °C,1 h; b) $B(OMe)_3$, -78 °C, 5 h; c) H_2O_2, AcOH, rt, 1 h; d) HCl(c), 40 °C, 2 h;
e) diethyl ethoxymethylenemalonate, EtOH, reflux, 1 h; f) $LiClO_4$, NaH(cat), propylene oxide, 40 °C
g) DEAD, PPh_3, AcOEt, rt, 5 h; h) Ac_2O, H_2SO_4 (1:2), 50 °C, 45 min; then H_2O, reflux, 15 h;
i) *N*-methylpiperazine, DMSO, 100 °C, 2 h.

Scheme 3

In summary, it has been described that commercially available 3,4-difluoroaniline is an appropriate starting material for the preparation of ofloxacin, levofloxacin and related quinolones. Key steps in the synthetic sequence are the regioselective functionalization at either C-2 or C-3 of the *N*-(*tert*-butoxycarbonyl)-3,4-difluoroaniline and the construction of the benzoxazine skeleton by *O*-alkylation of the corresponding phenol with propylene oxide.

EXPERIMENTAL

^{1}H-NMR (200 MHz) spectra were recorded on a Bruker WP-200-SY instrument in $CDCl_3$, unless otherwise indicated. Both chemical shifts (ppm downfield from internal tetramethylsilane) and coupling constants (Hz) were obtained by first order analysis of spin patterns. Melting points were measured in unsealed capillary tubes and are uncorrected. IR spectra were recorded on a Philips PU-9716 spectrometer. Elemental analyses were performed on a Perkin-Elmer Model 2400 CHN analyser. HRMS spectra were determined at an ionizing voltage of 70 eV. Analytical thin-layer chromatography was performed on DC-Alufolien 0.2 mm silica gel 60-F plates (MERCK). Visualisation was accomplished with UV light and ethanolic phosphomolybdic acid solution followed by heating. Flash chromatography was performed on silica gel MERCK-60 (230-400 mesh). All reactions involving the use of *tert*-BuLi were carried out under argon atmosphere. All solvents were dried before use. Compounds (**1**) and (**5a-e**) were described in reference 3.

General procedure for the synthesis of the benzoxazolinones (6a-e).

To a solution of (**1**) (100 mg, 0.44 mmol) in THF (15 mL), cooled at –40 °C, was added dropwise *tert*-BuLi (0.6 mL, 1.6 M solution in *n*-hexane, 0.96 mmol, 2.2 equiv.) under an argon atmosphere. After 1 h at –40 °C the corresponding electrophile was added and the reaction was kept at this temperature for the time indicated below for each case. Then, 1 M HCl (2.5 mL) was added, the organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give crude **6a-d** , which were purified by flash chromatography (the eluent was indicated below for each case).

7-Deutero-6-fluoro-2-benzoxazolinone (6a). Electrophile: D_2O (4.40 mmol). Reaction time: 10 min. Eluent: hexane/ethyl acetate 20/1. Yield: 72%. mp 182-184 °C (hexane/ethyl acetate). IR (nujol): 3200, 2990, 1770, 1720, 1615, 1370, 1300, 1230, 1140, 1015 cm^{-1}. ^{1}H-NMR (CF_3CO_2D) δ: 8.59 (br s, 1H), 7.14-6.81 (m, 2H). HRMS *m/z*: Calcd for $C_7H_3DNO_2F$, 154.0288. Found: 154.0285.

6-Fluoro-7-methylthio-2-benzoxazolinone (6b). Electrophile: $(MeS)_2$ (2.20 mmol). Reaction time: 1 h. Eluent: hexane/ethyl acetate 20/1. Yield: 82%. mp 196-198 °C (hexane/ethyl acetate). IR (nujol): 3120, 2915, 2850, 1750, 1715, 1445, 1370, 1300, 1240, 1130, 1010 cm^{-1}. ^{1}H-NMR (CF_3CO_2D) δ: 8.73 (br s, 1H), 7.01-6.94 (m, 2H), 2.59 (d, 3H, *J*= 1.6 Hz). Anal. Calcd for $C_8H_6NO_2FS$: C, 48.24; H, 3.01; N, 7.03. Found: C, 48.32; H, 3.00; N, 6.71.

6-Fluoro-7-methyl-2-benzoxazolinone (6c). Electrophile: MeI (0.44 mmol). Reaction time: 30 min. Eluent: hexane/ethyl acetate 15/1. Yield: 83%. mp 217-219 °C (hexane/ethyl acetate). IR (nujol): 3140, 2920, 2850, 1750, 1715, 1450, 1370, 1305, 1230, 1130, 1090 cm^{-1}. ^{1}H-NMR (CF_3CO_2D) δ: 8.64 (br s,

1H), 6.96-6.77 (m, 2H), 2.32 (d, 3H, *J*= 1.6 Hz). Anal. Calcd for $C_8H_6NO_2F$: C, 57.49; H, 3.62; N, 8.38. Found: C, 56.93; H, 3.39; N, 8.16.

7-Bromo-6-fluoro-2-benzoxazolinone (6d). Electrophile: 1,2-dibromoethane (1.32 mmol). Reaction time: 1 h. Eluent: hexane/CH_2Cl_2 1/1. Yield: 79%. mp 242-246 °C (hexane/ethyl acetate). IR (nujol): 3120, 2910, 2850, 1750, 1715, 1460, 1410, 1370, 1300, 1240, 1140 cm^{-1}. ^{1}H-NMR (CF_3CO_2D) δ: 8.12 (br s, 1H), 7.14-6.92 (m, 2H). HRMS *m/z*: Calcd for $C_7H_3NO_2BrF$, 230.9331. Found: 230.9329.

6-Fluoro-7-formyl-2-benzoxazolinone (6e). Electrophile: DMF (1.32 mmol). Reaction time: 1 h. In this case the residue was treated with CH_2Cl_2 and filtered to give **6e** (71%). mp 242-243 °C (hexane/ethyl acetate). IR (nujol): 3240, 3070, 2910, 2840, 1750, 1720, 1675, 1640, 1460, 1370, 1180, 1060 cm^{-1}. ^{1}H-NMR (CF_3CO_2D) δ: 10.38 (s, 1H), 9.70 (br s, 1H), 7.53 (m, 1H), 7.20-721 (m, 1H). HRMS *m/z*: Calcd for $C_8H_4FNO_3$, 181.0175. Found: 181.0171.

Diethyl (4-fluoro-2-hydroxy-3-methylthioanilinyl)methylenemalonate (7). To a solution of KOH (0.56 g, 10 mmol) in 1:1 EtOH/H_2O (20 mL) was added **6b** (0.50 g, 2.5 mmol). The resulting mixture was heated under reflux for 8 days. The solution was neutralised by addition of 1M HCl and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to afford 6-amino-3-fluoro-2-methyltiophenol (0.41 g, 94%). ^{1}H-NMR: 6.80-6.30 (m, 3H), 3.68 (br s, 2H), 2.31 (s, 3H). This compound (0.41 g, 2.37 mmol) and diethyl ethoxymethylenemalonate (0.48 mL, 2.37 mmol) were heated at 110 °C for 1 h. The reaction mixture was cooled at rt and treated with hexane. The resulting precipitate was filtered, washed with hexane, and dried to give **7** (0.69 g, 85%). mp 179-180 °C (hexane/ethyl acetate). IR (nujol): 3380, 2975, 1675, 1640, 1590, 1485, 1405, 1290, 1250, 1070, 1010 cm^{-1}. ^{1}H-NMR δ: 11.15 (d, 1H, *J*= 13.9 Hz), 8.48 (d, 1H, *J*= 13.9 Hz), 7.19 (dd, 1H, *J*= 8.9 and 5.1 Hz), 7.09 (s, 1H), 6.72-6.76 (m, 1H), 4.33 (q, 2H, *J*= 7.1 Hz), 4.25 (q, 2H, *J*= 7.1 Hz), 2.35 (s, 3H), 1.38 (t, 3H, *J*= 7.1 Hz), 1.33 (t, 3H, *J*= 7.1 Hz). Anal. Calcd for $C_{15}H_{18}NO_5FS$: C, 52.47; H, 5.28; N, 4.08. Found: C, 52.58; H, 5.23; N, 3.99.

Diethyl (7-fluoro-2,3-dihydro-3-methyl-8-methylthio-4*H*-[1,4]benzoxazin-4-yl)methylenemalonate (8): To a solution of **7** (150 mg, 0.44 mmol) in THF (0.5 mL) were sequentially added NaH (60% in mineral oil, 3 mg, 0.09 mmol), $LiClO_4$ (95 mg, 0.88 mmol) and propylene oxide (0.06 mL, 0.88 mmol). The resulting mixture was heated at 40 °C for 48 h. Water was added (3 mL) and the mixture was extracted with CH_2Cl_2 (2 x 3 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate 5/1) to afford 110 mg (62%) of diethyl [4-fluoro-2-(2-hydroxypropyloxy)-3-methylthioanilinyl]methylenemalonate. mp 190-191 °C. ^{1}H-NMR δ: 11.39 (d, 1H, *J*= 13.7 Hz), 8.48 (d, 1H, *J*= 13.7 Hz), 7.25-6.80 (m, 2H), 4.40-3.80 (m, 7H), 2.49 (s, 3H), 1.25-1.45 (m, 9H). IR (nujol): 3555, 2950, 2400, 1630, 1647, 1310, 1230, 1150. Anal. Calcd for $C_{18}H_{24}NO_6FS$: C, 58.51; H, 6.55; N, 3.79. Found: C, 58.91; H, 6.51; N, 3.55.

To a solution of this compound (44 mg, 0.11 mmol) and triphenylphosphine (57 mg, 0.22 mmol) in THF (1.5 mL) were slowly added during 18 h (by means of a perfuser) a solution of DEAD (0.22 mmol) in THF (0.5 mL) at rt. The solvent was evaporated and the residue was treated with Et_2O, the precipitate was filtered (triphenylphosphine oxide and hydrazine coproducts) and the ethereal solution was concentrated. The residue was purified by flash chromatography (hexane/ethyl acetate 5:1) to give **8** (28 mg, 66%). mp 115-117 °C (hexane/ethyl acetate). ^{1}H-NMR δ: 7.67 (s, 1H), 6.98 (dd, 1H, *J*= 9.1 and 5.3 Hz), 6.74-6.76 (m, 1H), 4.50-3.91 (m, 7H), 2.45 (d, 3H, *J*= 1.5 Hz), 1.35 (t, 3H, *J*= 7.1 Hz), 1.34 (t, 3H, *J*= 7.1 Hz), 1.31 (d, 3H, *J*= 6.9 Hz).

Ethyl 9-fluoro-2,3-dihydro-3-methyl-10-methylthio-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate (9): To a solution of **8** (50 mg, 0.13 mmol) in Ac_2O (0.2 mL) a 1:2 mixture of Ac_2O/H_2SO_4 (0.25 mL) was added at 0 °C. The resulting mixture was heated at 50 °C for 45 min. Ice was added and the mixture was stirred until a precipitate appeared, which was filtered and washed with Et_2O to give **9** (32 mg, 80%). ^{1}H-NMR δ: 8.37 (s, 1H), 7.74 (d, 1H, *J*= 9.9 Hz), 4.65-4.31 (m, 3H), 4.40 (q, 2H, *J*= 7.1 Hz), 2.64 (d, 3H, *J*= 1.5 Hz), 1.59 (d, 3H, *J*= 6.9 Hz), 1.59 (t, 3H, *J*= 7.1 Hz).

9-Fluoro-2,3-dihydro-3-methyl-10-methylsulphonyl-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid (10): To a solution of **9** (120 mg, 0.35 mmol) in MeOH (2 mL), cooled at 0 °C, was added a solution of Oxone (640 mg, 1.05 mmol) in H_2O (1.5 mL) at 0 °C. The reaction was stirred at 0 °C for 30 min and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give ethyl 9-fluoro-7-oxo-2,3-dihydro-3-methyl-10-methylsulphonyl-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate (108 mg, 78%). ^{1}H-NMR δ: 8.46 (s, 1H), 7.83 (d, 1H, *J*= 10.4 Hz), 4.70-4.30 (m, 5H), 3.39 (d, 3H, *J*= 1.4 Hz), 1.65 (d, 3H, *J*= 6.9 Hz), 1.42 (t, 3H, *J*= 7.1 Hz).

This compound (100 mg, 0.27 mmol) was dissolved in a 1:4 mixture of concentrated HCl/ AcOH, and the solution was heated at 110 °C for 16 h. The reaction mixture was cooled at rt. The precipitate was filtered off to give **10** (80 mg, 87%). ^{1}H-NMR (CF_3CO_2D) δ: 9.18 (s, 1H), 7.94 (d, 1H, *J*= 10.5 Hz), 5.05-4.59 (m, 3H), 3.55 (d, 3H, *J*= 1.4 Hz), 1.73 (d, 3H, *J*= 6.7 Hz).

2,3-Dihydro-3-methyl-9-(4-methyl-1-piperazinyl)-10-methylsulphonyl-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid (11): To a solution of **10** (15 mg, 0.06 mmol) in MeCN (0.5 mL) was added *N*-methylpiperazine (0.016 mL, 0.15 mmol). The reaction was heated at 60 °C for 14 h. The solvent was evaporated, the residue treated with 10% HCl until neutralization and the precipitate was filtered off to give **11** (19 mg, 84%). ^{1}H-NMR (CF_3CO_2D) δ: 8.94 (s, 1H), 7.83 (d, 1H, *J*= 10.5 Hz), 4.9-4.5 (m, 3H), 3.81-3.32 (m, 8H), 3.55 (s, 3H), 3.08 (s, 3H), 1.72 (d, 3H, *J*= 6.7 Hz).

6-Amino-2,3-Difluorophenol (12): 100 mL of a 1.6 M solution of *tert*-BuLi in pentane (160 mmol) was slowly added to a solution of 18.3 g (79.9 mmol) of **1** in 250 mL of THF, cooled at –78 °C under argon atmosphere. After 1 h at –78 °C, 10 mL (87.9 mmol) of $B(OMe)_3$ was slowly added. The reaction was

stirred at –78 °C for 5 h, and then 7.3 mL of acetic acid was added followed by slow addition of 18.3 mL of H_2O_2 (33% aqueous solution). The reaction was allowed to warm to rt. After 1 h at rt, the lithium salts were filtered and the filtrate was concentrated to the half of its volume. Concentrated HCl (60 mL) was added and the mixture was heated at 40 °C for 2 h and treated with activated carbon. The mixture was filtered and the filtrate was concentrated to the half of its volume. The solution was neutralized to pH 6 by addition of 5.6 M K_2CO_3 and extracted with AcOEt (3 x 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give of phenol (**12**) (9.85 g, 85%). mp 127-129 °C (hexane/ethyl acetate). IR (nujol): 3370, 3326, 3303, 1613, 1507, 1262, 1244, 1036, 968, 889, 806. ^{1}H-NMR δ: 6.54 (m, 1H), 6.42 (ddd, 1H, *J*= 8.8, 4.8 and 1.9 Hz), 4.20 (br s, 2H).

Diethyl (3,4-difluoro-2-hydroxyanilinyl)methylenemalonate (13): To a solution of **12** (50 g, 0.34 mmol) in EtOH (150 mL) was added diethyl ethoxymethylenemalonate (69.5 g, 0.34 mmol). The mixture was heated at reflux for 1 h. The solvent was evaporated and the mixture was cooled at 0 °C. The precipitate was filtered and washed with EtOH to give **13** (86.5 g, 80%). mp 185-187 °C (hexane/ethyl acetate). IR (nujol): 2990, 1673, 1507, 1476, 1435, 1370, 1292, 1154, 1101, 1044 cm^{-1}. ^{1}H-NMR δ: 11.07 (d, 1H, *J*= 13.8 Hz), 8.47 (d, 1H, *J*= 13.8 Hz), 6.92-6.96 (m, 1H), 6.72-6.74 (m, 1H), 6.60 (s, 1H), 4.33 (q, 2H, *J*= 7.1 Hz), 4.26 (q, 2H, *J*= 7.1 Hz), 1.38 (t, 3H, *J*= 7.1 Hz), 1.33 (t, 3H, *J*= 7.1 Hz). Anal. Calcd For $C_{14}H_{15}NO_5F_2$: C, 53.34; H, 4.80; N, 4.44. Found: C, 53.12; H, 4.81; N, 4.21.

Diethyl (7,8-difluoro-2,3-dihydro-3-methyl-4*H*-[1,4]benzoxazin-4-yl)methylenemalonate (14): To a solution of **13** (32.7 g, 0.1 mol) in propylene oxide (48 mL) were added NaH (60% suspension in mineral oil, 0.9 g, 0.2 mol) and $LiClO_4$ (12.15 g, 0.11 mol). The mixture was heated at 40 °C for 18 h. The excess of propylene oxide was recovered by distillation at atmospheric pressure. Water was added (60 mL) and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give diethyl [3,4-difluoro-2-(2-hydroxypropyloxy)anilinyl]methylenemalonate (36.9 g, 95%). mp 171-172 °C (hexane/ethyl acetate). IR (nujol): 3324, 2984, 1684, 1647, 1593, 1512, 1493, 1428, 1387, 1348, 1242, 1098 cm^{-1}. ^{1}H-NMR δ: 11.44 (d, 1H, *J*= 13.8 Hz), 8.47 (d, 1H, *J*= 13.8 Hz), 7.11-6.80 (m, 2H), 4.41-3.90 (m, 7H), 1.37 (t, 3H, *J*= 7.1 Hz), 1.35 (t, 3H, *J*= 7.2 Hz), 1.27 (d, H, *J*= 6.7 Hz).

To a solution of this compound (36.9 g, 0.99 mol) and triphenylphosphine (28.56 g, 0.11 mol) in ethyl acetate (240 mL) was slowly added (addition time 5 h) a solution of DEAD (17.13 mL, 0.11 mol) in ethyl acetate (60 mL) at rt. The reaction mixture was cooled at 0 °C and stirred for 2 h. The solid was filtered (triphenylphosphine oxide and the hydrazine coproducts) and the solution was concentrated. The resulting oil was treated with *i*-Pr_2O, the solid was filtered (triphenylphosphine oxide and the hydrazine byproducts) and the solution was concentrated to give **14** (28.1 g, 80%) which shows a reasonable purity by ^{1}H-NMR. Pure **14** can be obtained by flash chromatography (hexane/ ethyl acetate 5:1). mp 202-203 °C

(hexane/ethyl acetate). ^{1}H-NMR δ: 7.75 (s, 1H), 6.80-6.72 (m, 2H), 4.51-3.90 (m, 7H), 1.37 (t, 3H, *J*= 7.1 Hz), 1.34 (t, 3H, *J*= 7.1 Hz), 1.31 (d, 3H, *J*= 7.0 Hz). MS *m/z*: 355 (M^+, 100), 310 (27), 282 (51), 264 (84), 208 (40). HRMS m/z: Calcd for $C_{17}H_{19}NO_5F_2$: 355.1227. Found: 355.1219.

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10. Likely in compound (**10**) the presence at C-7 of the highly electron-withdrawing sulfonyl group greatly activates the substitution of the fluorine atom at C-6. For a recent publication on regioselective substitutions in 6-fluoro-7-chloroquinolone acids, see: I. Hermecz, L. Vasvari-Debreczy, B. Podanyi, G. Kereszturi, M. Balogh, A. Horvath, and P. Varkonyi, *Heterocycles*, 1998, **48**, 1111.

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