Synthesis of 8,9-Difluoro-2-methyl-6-oxo-1,2-dihydropyrrolo[3,2,1-ij]quinoline-5-carboxylic Acid

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A new and efficient seven-step synthesis of 8,9-difluoro-2-methyl-6-oxo-1,2-dihydropyrrolo[3,2,1-*ij*]-quinoline-5-carboxylic acid (**9**), an important intermediate used in the synthesis of quinolone antibacterials, has been developed beginning with commercially available 2,3,4-trifluoronitrobenzene. Selective displacement of the 2-fluorine of the starting material with the anion of ethyl acetoacetate and subsequent hydrolysis and decarboxylation affords the arylacetone derivative **11**. Reduction of the ketone and nitro groups of **11** followed by condensation with diethyl ethoxymethylenemalonate gives **14**, which is cyclized to the indole derivative **15** by the Mitsunobu procedure. Friedel-Crafts cyclization of **15** and acid hydrolysis gives the title compound **9**.

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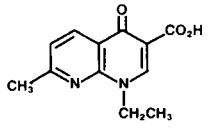
Since the discovery of the prototypical quinolone antibacterial agent, nalidixic acid (**1**) [1], subsequent structural modifications have led to new analogues with dramatically improved antibacterial potency. Common structural features of the more potent, newer generation quinolones norfloxacin (**2**) [2], ciprofloxacin (**3**) [3], A-56620 (**4**) [4], ofloxacin (**5**) [5], and S-25932 (**6**) [6] are a C-6 fluorine and a C-7 cyclic nitrogen-linked group, usually piperazine, that contains a second distal nitrogen.



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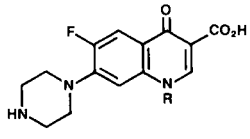
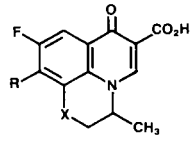
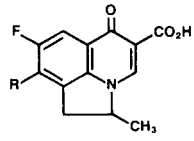


R
2 ethyl
3 cyclopropyl
4 p-fluorophenyl

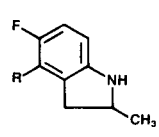


X	R
5 O	N-methylpiperazinyl
6 CH_2	N-imidazolyl

Another series of potent quinolone analogues of interest to us contains the 8-fluoro-2-methyl-6-oxo-1,2-dihydropyrrolo[3,2,1-*ij*]quinoline-5-carboxylic nucleus (**7**), which is structurally related to the tricyclic nuclei of ofloxacin and S-25932. A rather lengthy synthesis of analogues **7** has been described by workers at Otsuka, which involves a blocking-deblocking sequence to effect a regiospecific formation of the indole intermedate **8** [7]. A drawback of this route is that the C-9 amino substituent of **7** is introduced at an early stage of the synthesis, thus making it difficult to vary other substituents at this position. In a revised route, 8,9-difluoro-2-methyl-6-oxo-1,2-dihydropyrrolo-[3,2,1-*ij*]quinoline-5-carboxylic acid (**9**) is prepared as the final intermediate, which undergoes displacement of the C-9 fluorine by an amine to produce analogues **7** directly [8]. Although dihydroindole **10** is mentioned as the precursor to **9** in this revised route, there is no reference given for its synthesis. The unavailability of an efficient synthesis of indole **10**, and the length and lack of flexibility of the original synthesis of analogues **7**, has led us to explore an alternative route to these analogues *via* acid **9**. We describe here a new and efficient synthesis of acid **9** which is outlined in Scheme I.



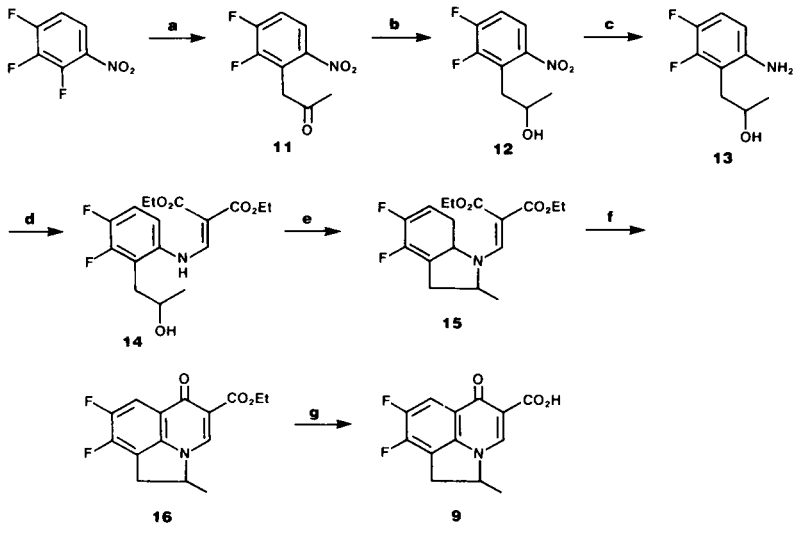
R
7 R'N⟨⟩N–
9 F



R
8 R'N⟨⟩N–
10 F

2,3,4-Trifluoronitrobenzene was considered to be a useful starting material for the synthesis of **9** since it is known to undergo regiospecific displacement of the 2-fluorine with oxygen nucleophiles [9]. As shown in Scheme I, treatment of 2,3,4-trifluoronitrobenzene with the anion of ethyl acetoacetate, followed by hydrolysis and decarboxylation, affords the arylacetone derivative **11** in good yield. The ketone and nitro groups of **11** are reduced successively, *via* intermediate **12**, using sodium borohydride and hydrogenation over Raney-Nickel, respectively, to give anilinoalcohol **13**. Condensation of **13**

SCHEME 1



a) i. ethyl acetoacetate, NaH; ii. HCl(aq.), HOAc, Δ (74%) b) $NaBH_4$ (68%), c) H_2, Ra-Ni (75%), d) diethyl ethoxymethylenemalonate, Δ (100%), e) Ph_3P, DEAD (92%), f) PPA, Δ (82%), g) HCl (aq.), Δ (55%)

with diethyl ethoxymethylenemalonate produces **14**, which is cleanly cyclized by the Mitsunobu procedure [10] to the known dihydroindole **15** [8]. Friedel-Crafts cyclization of **15** according to the literature procedure using polyphosphoric acid [8] then affords tricyclic ester **16**. Finally, acid hydrolysis of **16** gives the desired quinolone intermediate **9**.

In summary, a regiospecific and efficient synthesis of 8,9-difluoro-2-methyl-6-oxo-1,2-dihydropyrrolo[3,2,1-*ij*]-quinoline-5-carboxylic acid (**9**) has been developed. The interesting feature of this route is the selective activation of the 2-fluorine and 3-fluorine of the starting material, 2,3,4-trifluoronitrobenzene, allowing introduction of the pyrrolo ring and amino substituent, respectively. The availability of **9** by this seven-step route allows easy access to the class of quinolone antibacterials **7** containing the 8-fluoro-2-methyl-6-oxo-1,2-dihydropyrrolo[3,2,1-*ij*]quinoline-5-carboxylic acid nucleus.

EXPERIMENTAL

^{1}H-nmr spectra were determined with a Bruker WM-250 or Varian XL300 spectrometer. Chemical shifts are expressed in ppm relative to deuteriochloroform. Significant ^{1}H-nmr data are tabulated in order (number of protons, multiplicity, coupling constant (Hertz)). Mass spectra (ms) were determined with a Finnigan 4510 GSMS mass spectrometer; exact masses were determined on an A.E.I.-MS30 mass spectrometer. Infrared (ir) spectra were determined with a Perkin-Elmer Model 283B infrared spectrophotometer. Elemental analyses were performed by the Pfizer Analytical Chemistry Department. Melting points are uncorrected and were obtained in open capillaries on a Thomas-Hoover melting point apparatus.

Tetrahydrofuran was distilled from sodium/benzophenone prior to use. Other solvents and reagents were commercially available and used directly unless otherwise noted. 2,3,4-Trifluoronitrobenzene was purchased from Asahi Glass Co. Ltd.

Flash chromatography was performed using 32-63 μm silica gel (Woelm®) according to the method described by Still *et al.* [11] Analytical thin-layer chromatography (tlc) was performed on 250 micron, 2.5 x 10 cm silica gel plates (Analtech) using ultraviolet light or potassium permanganate spray for visualization.

3,4-Difluoro-2-(2-oxopropyl)nitrobenzene (**11**).

Into a 2-ℓ three-necked flask, equipped with thermometer, pressure-equalizing addition funnel, and magnetic stirrer, was placed 10.8 g (0.226 mole) of 50% sodium hydride in mineral oil. The sodium hydride was washed with three portions of hexane and then a solution of 28.6 ml (29.4 g, 0.226 mole) of ethyl acetoacetate in 100 ml of tetrahydrofuran was added dropwise over a 20-minute period as the temperature was maintained at 10-15° using an ice bath. Following additional stirring for 15 minutes, a solution of 20.0 g (0.113 mole) of 2,3,4-trifluoronitrobenzene in 150 ml of tetrahydrofuran was added dropwise at 0° and the mixture was allowed to stir overnight (16 hours) at room temperature. The dark brown mixture was evaporated and the residue was acidified with 400 ml of aqueous 1*N* hydrochloric acid solution. Extraction with ethyl acetate (3 x 500 ml), drying of the extracts (magnesium sulfate), and evaporation of the solvent gave 45 g of a yellow oil which was subjected to hydrolysis without further purification.

The oil was combined with 675 ml of aqueous concentrated hydrochloric acid solution and 675 ml of glacial acetic acid, and the mixture were heated to reflux for 16 hours. The solvent was removed and the residue was partitioned between ethyl acetate (400 ml) and saturated aqueous sodium bicarbonate solution (200 ml). The organic layer was separated, washed with an additional 200 ml portion of saturated aqueous sodium bicarbonate solution, dried (magnesium sulfate), and evaporated to 23 g of a brown oil. Purification of the oil by flash chromatography (12 inches of silica in height, 65 mm diameter) with an ethyl acetate-hexane (1:9) eluant afforded 17.2 g (74%) of 3,4-difluoro-2-(2-oxopropyl)-nitrobenzene (**11**) as a yellow oil which partially solidified as a low melting solid (mp < 30°). The analytical sample was prepared by distillation, bp 115-116°/0.2 Torr: ^{1}H-nmr (deuteriochloroform, 300 MHz): δ 2.30 (3H, s), 4.14 (2H, s), 7.12-7.20 (1H, m), 7.84-7.90 (1H, m); ms: (m/e) 216 (M^+ 1), 173 (base), 156, 125; ir (chloroform) 1728, 1599, 1529, 1485, 1350, 1292, 1161 cm^{-1}.

Anal. Calcd. for $C_9H_7NO_3F_2 \cdot \frac{1}{4} H_2O$: C, 49.20; H, 3.25; N, 6.37. Found:

C, 49.01; H, 3.21; N, 6.33.

3,4-Difluoro-2-(2-hydroxypropyl)nitrobenzene (**12**).

To a 0° solution of 14.5 g (0.0674 mole) of 3,4-difluoro-2-(2-oxopropyl)-nitrobenzene (**11**) in 250 ml of methanol was added 2.80 g (0.0741 mole) of sodium borohydride in portions over a ten minute period. After 20 minutes of stirring at 0°, the mixture was carefully quenched with 200 ml of aqueous 1*N* hydrochloric acid solution. The methanol was removed by rotary evaporation and the mixture was extracted with ethyl acetate (3 x 200 ml). The combined extracts were washed with water (2 x 200 ml), dried (sodium sulfate), and evaporated to 16.8 g of a yellow oil. Distillation of the oil afforded 9.87 g (68%) of 3,4-difluoro-2-(2-hydroxypropyl)-nitrobenzene (**12**) as a yellow liquid, bp 128-130°/1.5 Torr; ^{1}H-nmr (deuteriochloroform, 250 MHz): δ 1.30 (3H, d, J = 7), 1.63 (1H, d J = 7), 3.20 (2H, dd, J = 10 and 2), 4.02-4.20 (1H, m), 7.14-7.26 (1H, m), 7.78-7.89 (1H, m); ir (chloroform): 3591, 1732, 1630, 1597, 1528, 1483, 1448, 1349, 1290 cm^{-1}; ms: (m/e) 173, 156 (base), 128, 101.

Anal. Calcd. for $C_9H_9F_2NO_3$: C, 49.77; H, 4.17; N, 6.44. Found: C, 49.90; H, 4.23; N, 6.40.

3,4-Difluoro-2-(2-hydroxypropyl)aniline (**13**).

A solution of 9.00 g (41.4 mmoles) of 3,4-difluoro-2-(2-hydroxypropyl)-nitrobenzene (**12**) in 100 ml of absolute ethanol was hydrogenated in the presence of 9 g of Raney Nickel on a Parr Shaker Apparatus for 30 minutes. The mixture was filtered and the filtrate was concentrated to a yellow oil which was distilled to afford 5.80 g (75%) of 3,4-difluoro-2-(2-hydroxypropyl)aniline (**13**) as a light yellow oil, bp 128-130°/1.5 Torr; ^{1}H nmr (deuteriochloroform, 250 MHz): δ 1.30 (3H, d, J = 7), 1.90 (1H, broad s), 2.66-2.93 (2H, m), 4.02 (2H, broad s), 4.05-4.25 (1H, m), 6.36-6.42 (1H, m), 6.79-6.91 (1H, m); ir (chloroform): 3594, 3432, 3360, 1619, 1494 cm^{-1}; ms: (m/e) 187 (M$^+$), 143, 142 (base); hrms Calcd. for $C_9H_{11}F_2NO$: 187.0808. Found: 187.0790.

[[(3,4-Difluoro-2-(2-hydroxypropyl)phenyl)amino]methylene]propanedioic Acid Diethyl Ester (**14**).

A mixture of 5.50 g (29.4 mmoles) of 3,4-difluoro-2-(2-hydroxypropyl)-aniline (**13**) and 6.75 ml (7.22 g, 33.4 mmoles) of diethyl ethoxymethylene-malonate was heated to 150-160° for 20 minutes. Upon cooling, the mixture crystallized and was triturated with hexane to afford 10.36 g (100%) of [[(3,4-difluoro-2-(2-hydroxypropyl)phenyl)amino]methylene]propanedioic acid diethyl ester (**14**) as a white solid, mp 87-90°; ^{1}H nmr (deuteriochloroform, 250 MHz): δ 1.26-1.41 (9H, m), 2.03 (1H, d, J = 6), 2.72-3.04 (2H, m), 4.24 (2H, q, J = 7), 4.30 (2H, q, J = 7), 6.92-7.00 (1H, m), 7.05-7.18 (1H, m), 8.26 (1H, d, J = 13), 11.24 (1H, d, J = 13); ms: (m/e) 339 (M$^+$), 129 (base); ir (chloroform): 1687, 1592 cm^{-1}.

Anal. Calcd. for $C_{17}H_{21}F_2NO_5$: C, 57.13; H, 5.92; N, 3.91. Found: C, 57.14; H, 5.91; N, 3.86.

[(4,5-Difluoro-2,3-dihydro-2-methyl-1*H*-indol-1-yl)methylene]propanedioic Acid Diethyl Ester (**15**).

To a mixture of 12.53 g (0.047 mole) of triphenylphosphine and 7.50 ml (8.29 g, 0.047 mole) of diethyl azodicarboxylate in 60 ml of tetrahydrofuran, kept at -20°, was added dropwise a solution of 11.40 g (0.032 mole) of [[3,4-difluoro-2-(2-hydroxypropyl)phenyl)amino]methylene]-propanedioic acid diethyl ester (**14**) in 60 ml of tetrahydrofuran over a 30-minute period. The mixture was then allowed to stir at room temperature for 3 hours at which time 100 ml of water was added. The solvent was removed and the residue was dissolved in 200 ml of ethyl acetate and washed with aqueous 1*N* sodium hydroxide solution (2 x 50 ml) and water (1 x 50 ml). The dried (magnesium sulfate) organic layer was evaporated to a yellow oil which was purified by silica gel chromatography (12 inches in height, 65 mm diameter) using 3:7 to 1:1 hexane-ethyl acetate as eluant to afford 10.00 g (92%) of [(4,5-difluoro-2,3-dihydro-2-methyl-1*H*-indol-yl)methylene]propanedioic acid diethyl ester (**15**) as a light yellow oil which slowly crystallized, mp 50-52° (Rf 0.60, 1:4 ethyl acetate-hexane); ^{1}H-nmr (deuteriochloroform, 250 MHz): δ 1.14 (3H, d, J = 7), 1.27 (3H, t, J = 7), 1.32 (3H, t, J = 7), 2.80 (1H, d, J = 15), 3.38 (1H, dd, J = 9 amd 15), 4.15-4.32 (4H, m), 4.68-4.82 (1H, m), 6.65-6.72 (1H, m), 6.96-7.09 (1H, m), 7.91 (1H, s); ir (chloroform): 1687, 1592 cm^{-1}; ms: (m/e) 339 (M$^+$), 294, 264, 232, 220, 192 (base).

Anal. Calcd. for $C_{17}H_{19}F_2NO_4$: C, 60.17; H, 5.64; N, 4.12. Found: C, 60.17; H, 5.69; N, 4.08.

8,9-Difluoro-2-methyl-6-oxo-1,2-dihydropyrrolo[3,2-*ij*]quinoline-5-carboxylic Acid Ethyl Ester (**16**).

A mixture of 560 mg (1.65 mmoles) of [(4,5-difluoro-2,3-dihydro-2-methyl-1*H*-indol-1-yl)methylene]propanedioic acid diethyl ester (**15**) and 1.6 g of polyphosphoric acid was heated at 40° for 30 minutes. The yellow mixture was cooled and 100 ml of water was added. The resulting white solid was collected by filtration, dissolved in chloroform, and dried (magnesium sulfate). Filtration and evaporation of the solvent afforded 400 mg (82%) of 8,9-difluoro-2-methyl-6-oxo-1,2-dihydropyrrolo[3,2,1-*ij*]-quinoline-5-carboxylic acid ethyl ester (**16**), mp 220-222°; ^{1}H-nmr (deuteriochloroform, 300 MHz): δ 1.40 (3H, t, J = 7), 1.69 (3H, d, J = 7), 3.17 (1H, dd, J = 5 and 15), 3.79 (1H, dd, J = 8 and 15), 4.37 (2H, q, J = 7), 4.83-4.97 (1H, m), 7.78-7.85 (1H, m), 8.47 (1H, m), 8.47 (1H, s); ir (chloroform): 1726, 1687, 1649, 1606, 1552, 1471 cm^{-1}; ms: (m/e) 293 (M$^+$), 248, 221 (base), 206.

8,9-Difluoro-2-methyl-6-oxo-1,2-dihydropyrrolo[3,2,1-*ij*]quinoline-5-carboxylic Acid (**9**).

A suspension of 200 mg (0.682 mmole) of 8,9-difluoro-2-methyl-6-oxo-1,2-dihydropyrrolo[3,2,1-*ij*]quinoline-5-carboxylic acid ethyl ester (**16**) in 30 ml of aqueous 1*N* hydrochloric acid solution was heated to reflux for 3 hours. The solvent was removed and the white solid residue was triturated in ether to afford 100 mg (55%) of 8,9-difluoro-2-methyl-6-oxo-1,2-dihydropyrrolo[3,2,1-*ij*]quinoline-5-carboxylic acid (**9**), mp 285-290°. The analytical sample was prepared by recrystallization from methanol, mp 300-302°, (lit 296-297°) [8]: ^{1}H-nmr (deuteriodimethyl sulfoxide-d_6, 300 MHz): δ 1.60 (3H, d, J = 7), 3.82 (1H, dd, J = 8 and 15), 5.04-5.22 (1H, m), 7.84-7.96 (1H, m), 9.08 (1H, s); ms: (m/e) 265 (M$^+$), 220, 205 (base); ir (potassium bromide): 1712 cm^{-1}.

Anal. Calcd. for $C_{13}H_9F_2NO_3$: C, 58.87; H, 3.42; N, 5.27. Found: C, 58.59; H, 3.26; N, 5.16.

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