Synthesis of 5-Methyl-4-oxo-quinolinecarboxylic Acids

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A series of 5-methyl-4-oxo-3-quinolinecarboxylic acids was prepared in which the eight-position was substituted with fluorine, chlorine, methyl, or hydrogen. These quinolones were synthesized from the appropriate 2-methyl-3,4,6-trifluorobenzoic acids which were derived from oxazolines **8** and **16**. The oxazoline moiety served as both an *ortho*-director (where feasible) and a protecting group; a trimethylsilyl moiety was used to block the most acidic site in the molecule.

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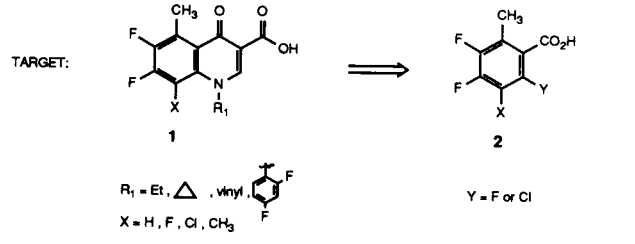
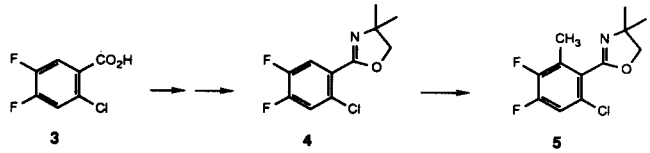
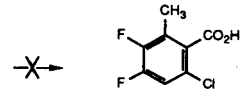
The antibacterial potency of the 4-quinolones is known to be influenced by many factors, several of which have been examined in recent structure-activity studies [1]. While many positions on the quinolone ring have been investigated and optimized, other variables have not been addressed as thoroughly; substitution at the 5-position, for example, has been limited to a few examples of halogen [2,3], amino [4], and alkyl [3]. Although some investigators have suggested that such substitution is deleterious to antibacterial activity [5], recent reports showed that a 5-amino moiety dramatically improves the potency for those quinolones that also contain an 8-fluoro group [4b]. The 5-alkyl quinolones studied previously comprised a very limited data set and did not contain optimized functionalities at other crucial positions on the quinolone ring. As of yet, no expedient synthesis has been described which provides these multifunctionalized quinolones in experimentally useful amounts. This paper describes the construction of several key intermediates in the synthesis of 5-methyl quinolones which possess striking antibacterial potency.

The target quinolones represented by structure 1 could conceivably be prepared from the toluic acids depicted as **2**, where X is a hydrogen, fluorine, chlorine, or methyl and Y is some displaceable group such as fluorine or chlorine. In turn, these acids could theoretically be obtained from an unalkylated precursor such as **4** wherein a masked carboxylic acid serves as an *ortho*-director. This initial strategy, where X is a hydrogen, is shown in Scheme 1. The 2-chloro-4,5-difluorobenzoic acid **3** was converted to the oxazoline **4** in excellent yield using well-established methodology. It was hoped that the proven *ortho*-directing ability of the oxazoline group could then be exploited to introduce the desired methyl group at the 6-position, the least acidic site in the molecule [6]. Indeed, deprotonation with *n*-butyllithium followed by reaction with methyl iodide gave crucial intermediate **5** in good yield with none of the other regioisomer. However, attempts to regenerate the acid functionality *via* acid hydrolysis proved unexpectedly difficult: the oxazoline moiety would not cleave despite refluxing in dilute hydrochloric acid for five days. Other methods reported to cleave oxazoline rings [7] (*i.e.*, treatment with sodium hypochlorite under phase catalysis conditions) were also unsuccessful. Presumably, steric bulk prohibits hydrolysis at this center, since treatment of the unsubstituted, less hindered oxazoline **4** afforded starting acid **3** in quantitative yield.



Scheme 1

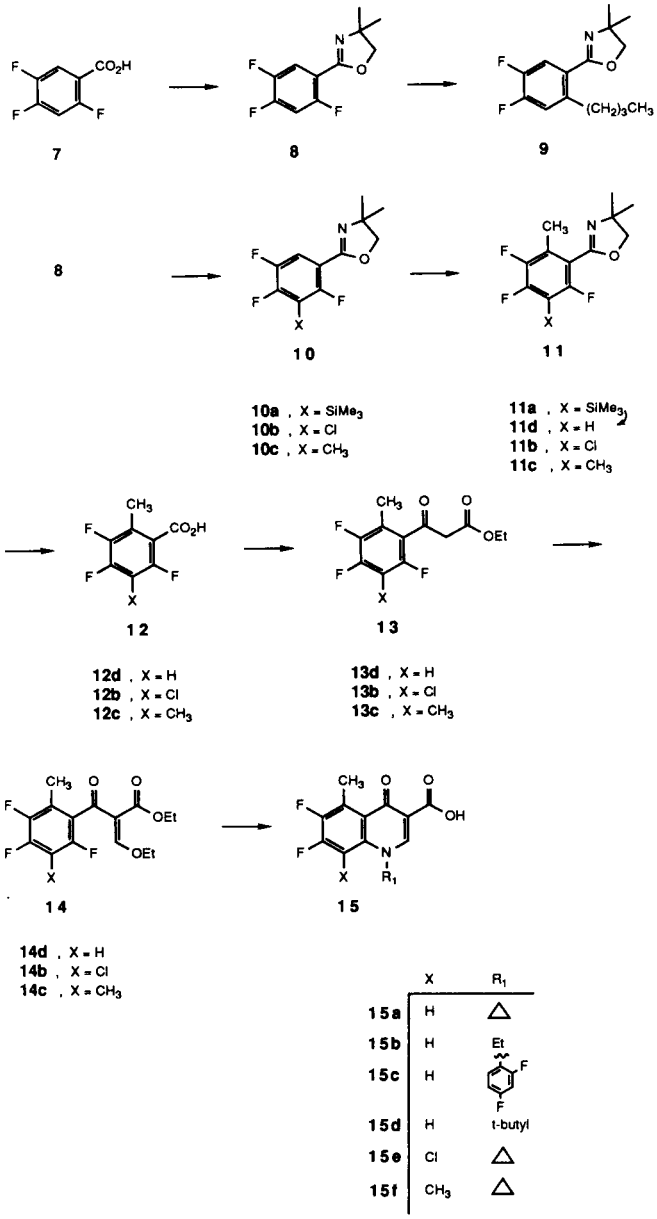




Therefore, a slightly modified approach was implemented as shown in Scheme 2. Oxazoline **8** was synthesized from the analogous acid in a similar fashion as **4**. Since fluorines or methoxy groups *ortho* to oxazolines are easily displaced by alkyl lithium reagents, sequential treatment of **8** with *n*-butyllithium and methyl iodide gave, not surprisingly, 2-(2-*n*-butyl-4,5-difluorophenyl)-4,4-dimethyl-2-oxazoline **9**. Reaction of intermediate **8** with lithium diisopropylamide followed by methyl iodide quench gave compound **10c**, in which the most acidic proton was extracted by the base; unlike the butyllithium, the lithium diisopropylamide did not complex with the oxazoline moiety and

ortho-direction did not occur. In order to produce the desired isomer, then, the anion generated by lithium diisopropylamide was quenched with trimethylsilyl iodide to afford oxazoline **10a**, which was treated with another equivalent of base and quenched with methyl iodide to give **11a**. Removal of the trimethylsilyl group with cesium fluoride in wet dimethylformamide gave oxazoline **11d**, the 2-fluoro equivalent of the 2-chloro oxazoline **5**. Whereas compound **5** could not be hydrolyzed to the analogous acid, related compound **11d** was converted to acid **12d** in 68% yield. Ketoester **13** was synthesized in the usual fashion, and subsequent elaboration to the desired quinolone acids **15a-d** was achieved using standard methodologies (see Experimental).

Scheme 2



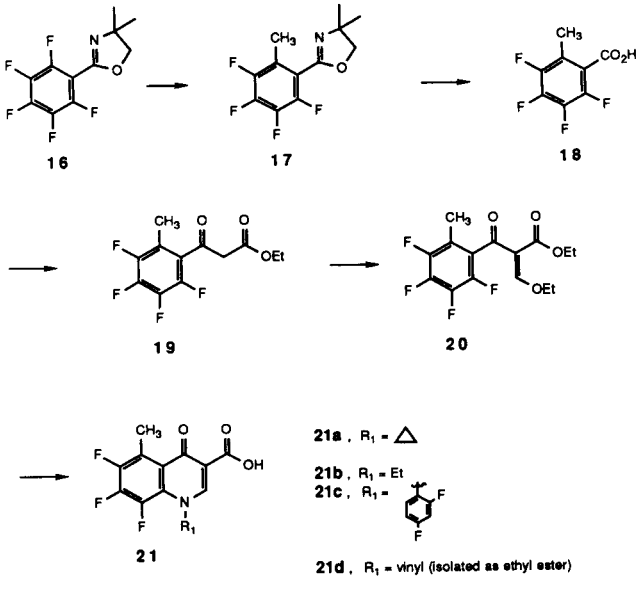
The anion generated from lithium diisopropylamide and **8** could be quenched with other electrophilic agents to provide synthetically useful intermediates. For example, treatment of the anion with hexachloroacetone gave the 3-chloro compound **10b**, which was converted to the methylated derivative **11b** as before. (Originally, we had hoped to convert the silylated compound **11a** to the chloro analogue **11b** *via* an *ipso* substitution on the trimethylsilyl moiety, a well-documented reaction in the chemical literature of aryl silanes [8]; however, attempts to synthesize the desired compound in this manner resulted in the formation of some of the target along with a considerable amount of starting material.) Similarly, reaction of the anion of **8** with methyl iodide gave the 3-methyl derivative **10c** in nearly quantitative yield, and further deprotonation followed by methylation gave intermediate **11c**. In both cases, hydrolysis of the oxazoline group proceeded smoothly to yield the desired acids in good yield - again, the presence of a 2-fluorine group was vital to ensure a successful cleavage reaction. Further elaboration to the respective ketoesters and ultimately to the final quinolone acids **15e-f** was achieved in the usual manner as summarized in Scheme 2.

Although the process outlined in Scheme 2 provided useful amounts of desired product **12d** in good yield, the chromatography required to purify intermediates **8**, **10a** and **11a** was time-consuming on a large scale. Therefore, a conceptually similar but experimentally more expeditious route to benzoic acid **12d** was devised and is shown in Scheme 4. The anion of 1-bromo-2,4,5-trifluorobenzene (**22**) was quenched with chlorotrimethylsilane to give silylated intermediate **23**, which was easily purified *via* distillation. Attempts to alkylate the anion of **23** with methyl iodide resulted in incomplete methylation, so a more potent alkylating agent - methyl trifluoromethanesulfonate - was employed successfully. Surprisingly, the formation of the anion of **23** proceeded slowly: if the anion solution was stirred for less than an hour before the methyl triflate quench, significant quantities of the ethylated product were obtained, presumably from the reaction of excess lithium diisopropylamide with the intermediate methyl compound. Despite these initial drawbacks, the conversion of **23** to **24** proceeded in 73% yield. Elaboration of **24** to benzoic acid **12d** was accomplished *via* metal-halogen exchange with butyllithium, quenching with carbon dioxide, and treatment of penultimate compound **25** with fluoride ion. In all cases, purification was effected using distillation or recrystallization, and overall yields were comparable to those in Scheme 2.

As mentioned previously, a methoxy or fluorine group adjacent to an oxazoline ring will undergo attack by an alkyl lithium reagent, an observation which we then exploited to prepare the 5-methyl-8-fluoroquinolones depicted as **21a-d** (see Scheme 3). It has been reported that

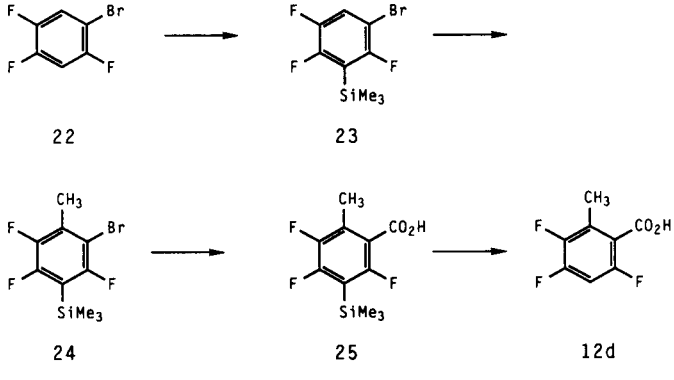
fluorinated oxazoline **16** reacts with methyl grignard to give small amounts of the *ortho*-substituted product [9]; however, we discovered that this same oxazoline reacts cleanly and quantitatively with methyl lithium at low temperatures to give target compound **17**. Hydrolysis of the oxazoline moiety proceeded smoothly to give 2,3,4,5-tetrafluoro-6-methylbenzoic acid **18**. This key intermediate was elaborated into the four different *N*-substituted quinolones shown in Scheme 3.

Scheme 3



Quinolones **15a-f** and **21a-d** were reacted with several pyrrolidines and piperazines to give a variety of antibacterial agents which were assayed against representative gram negative and gram positive bacteria. Almost all of these agents were active to some extent, and several showed increased activity *in vivo* and *in vitro* when compared to the unsubstituted parent compounds. These quinolones will be the focus of a future publication investigating the influence of 5-substitution.

Scheme 4



EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. The ^{1}H nmr spectra were recorded on a Varian XL-200 spectrometer with shifts given in ppm downfield from internal tetramethylsilane, and coupling constants are in Hz. Infrared spectra were recorded on a Nicolet FT-IR spectrometer. Mass spectra were obtained on a Finnigan 4500 Mass spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 elemental analyzer. Column chromatography was accomplished with E. Merck silica gel, 70-230 mesh. All solutions were dried over magnesium sulfate, and all concentrations were performed *in vacuo* at 10-30 mm Hz. Butyllithium was purchased from Alfa Chemicals, and diisopropylamine was purchased from Aldrich and was not distilled. Tetrahydrofuran was distilled from sodium; all other solvents were used without purification.

2-(2-Chloro-4,5-difluorophenyl)-4,4-dimethyl-2-oxazoline (**4**).

A solution of 48.1 g (250 mmoles) of 2-chloro-4,5-difluorobenzoic acid (**3**), 34.9 g (275 mmoles) of oxalyl chloride, and 350 ml of dichloromethane was treated with 5 drops of dimethylformamide, and the solution was stirred at room temperature for three hours. The mixture was concentrated, and the residue was dissolved in 200 ml of dichloromethane. This solution was added dropwise to a cold (ice bath) solution of 44.5 g (500 mmoles) of 2-amino-2-methyl-1-propanol in 200 ml of dichloromethane. The suspension was stirred overnight at room temperature. The solids were filtered, and the filtrate was washed with water, 5% sodium bicarbonate solution, and 1 *N* hydrochloric acid. The solution was dried and concentrated to give 59.6 g (90%) of a white solid. The crude material was dissolved in 400 ml of chloroform and treated with 50 ml (685 mmoles) of thionyl chloride, and the reaction mixture was stirred at room temperature for four hours. The solution was concentrated by half, diluted with ether, and filtered. The solids were washed with ether and dissolved in water which was basified to *p*H 8 with 10% sodium hydroxide. The mixture was extracted with chloroform (3 x 250 ml), and the combined extracts were dried and concentrated. The crude product was chromatographed, eluting with 80:20 chloroform:ethyl acetate, to give 39:9 g (72%) of **4** as a clear, colorless oil; pmr (deuteriochloroform): δ 1.40 (s, 6 H, $(CH_3)_2$), 4.13 (s, 2 H, CH_2 on oxazoline ring), 7.28 (m, 1 H), 7.62 (m, 1 H); ir (potassium bromide) 1671, 1518 cm^{-1}.

Anal. Calcd. for $C_{11}H_{10}ClF_2NO$: C, 53.78; H, 4.10; N, 5.70. Found: C, 53.81; H, 4.08; N, 5.66.

2-(6-Chloro-3,4-difluoro-2-methylphenyl)-4,4-dimethyl-2-oxazoline (**5**).

To a solution of 2.46 g (10.0 mmoles) of **4** in 100 ml of dry ether at −5° was added 11.0 ml of 1.0 *M* (11.0 mmoles) of *n*-butyllithium. The solution was stirred at 0° for one hour, then treated with 5.68 g (40.0 mmoles) of methyl iodide. The reaction mixture was stirred at room temperature overnight. Water was added, and the organic layer separated, dried, and concentrated to a dark oil. The product was chromatographed, eluting with 2:1 hexane:ether, to give 2.00 g (72%) of **5**; pmr (deuteriochloroform): δ 1.45 (s, 6 H, $(CH_3)_2$), 2.35 (d, J = 2.5, 3 H, CH_3), 4.20 (s, 2 H, CH_2 in oxazoline ring), 7.15 (m, 1 H).

2-(2,4,5-Trifluorophenyl)-4,4-dimethyl-2-oxazoline (**8**).

Using the same procedure outlined for the synthesis of **4**, the

title compound was prepared from 2,4,5-trifluorobenzoic acid (**7**) in a 72% overall yield, mp 53-54°; pmr (deuteriochloroform): δ 1.39 (s, 6 H, $(CH_3)_2$), 4.11 (s, 2 H, CH_2 in oxazoline ring), 7.05 (m, 1 H), 7.77 (m, 1 H).

Anal. Calcd. for $C_{11}H_{10}F_3NO$: C, 57.64; H, 4.40; N, 6.11. Found: C, 57.47; H, 4.39; N, 6.04.

2-[2,4,5-Trifluoro-3-(trimethylsilyl)phenyl]-4,4-dimethyl-2- oxazoline (**10a**).

A solution of 18.0 ml (128 mmoles) of diisopropylamine in 200 ml of dry tetrahydrofuran was cooled to −78° under argon, treated dropwise with 50.0 ml of 2.05 *M* *n*-butyllithium (102 mmoles), and stirred for 10 minutes. To this solution of lithium diisopropylamide was added a solution of 23.5 g (102.5 mmoles) of **8** in 100 ml of dry tetrahydrofuran, and the dark solution was stirred at −78° for thirty minutes. Trimethylsilyl chloride (33.0 ml, 260 mmoles) was added, and the mixture was allowed to warm to room temperature overnight. Water and ethyl acetate were added. The organic layer was washed with 1 *N* hydrochloric acid, 5% sodium bicarbonate solution, and water and was dried. Concentration gave an off-white solid which was chromatographed, eluting with 2:1 hexane:ether, to give 25.6 g (80%) of **10a** as a pale pink solid, mp 71-72°; pmr (deuteriochloroform, no tetramethylsilane): δ 0.40 (s, 9 H, $Si(CH_3)_3$), 1.40 (s, 6 H, $(CH_3)_2$), 4.09 (s, 2 H, CH_2 on oxazoline ring), 7.71 (m, 1 H); ir (potassium bromide): 1645 cm^{-1}.

Anal. Calcd. for $C_{14}H_{18}F_3NOSi$: C, 55.79; H, 6.02; N, 4.65. Found: C, 55.53; H, 6.02; N, 4.48.

2-(3-Chloro-2,4,5-trifluorophenyl)-4,4-dimethyl-2-oxazoline (**10b**).

The title compound was prepared from **8**, lithium diisoproylamide, and hexachloroacetone in 67% yield by the same procedure used to prepare **10a**. The crude product was chromatographed, eluting with 90:10 chloroform:ethyl acetate, to give **10b** as an orange oil; pmr (deuteriochloroform): δ 1.40 (s, 6 H), 4.12 (s, 2 H), 7.65 (m, 1 H).

Anal. Calcd. for $C_{11}H_9ClF_3NO$: C, 50.11; H, 3.44; N, 5.31. Found: C, 50.55; H, 3.49; N, 5.19.

2-(2,4,5-Trifluoro-3-methylphenyl)-4,4-dimethyl-2-oxazoline (**10c**).

The title compound was prepared from **8**, lithium diisopropylamide, and methyl iodide in 96% yield by the same procedure used to prepare **10a**. The product was purified *via* chromatography, eluting with 2:1 hexane:ethyl acetate, to give **10c** as a yellow crystal, mp 42-44°; pmr (deuteriochloroform): δ 1.40 (s, 6 H), 2.26 (t, J = 2.2, 3 H), 4.11 (s, 2 H), 7.56 (m, 1 H).

Anal. Calcd. for $C_{12}H_{12}F_3NO$: C, 59.26; H, 4.97; N, 5.76. Found: C, 58.95; H, 4.94; N, 5.66.

2-[2,4,5-Trifluoro-6-methyl-3-(trimethylsilyl)phenyl]-4,4-dimethyl-2-oxazoline (**11a**).

A solution of 5.2 ml (37.1 mmoles) of diisopropylamine in 150 ml of tetrahydrofuran was cooled to −78° under argon, treated dropwise with 14.0 ml of 2.1 *M* *n*-butyllithium (29.4 mmoles), and stirred for ten minutes at −78°. To this solution of lithium diisopropylamide was added a solution of 7.4 g (103 mmoles) of **10a** in 75 ml of tetrahydrofuran. The dark solution was warmed to 0° and stirred at that temperature for thirty minutes. To the solution was added 10.4 g (73.3 mmoles) of methyl iodide, and the solution was allowed to warm to room temperature overnight. The mixture was diluted with water and dichloromethane, and the organic phase was washed with 5% sodium bicarbonate and water. The solution was dried and concentrated to give an oil which was chromatographed (using 2:1 hexane:ethyl acetate as eluent) to yield 5.9 g (77%) of **11a** as a yellow solid, mp 47-49°; pmr (deuteriochloroform, no tetramethylsilane): δ 0.40 (s, 9 H, $Si(CH_3)_3$), 1.43 (s, 6 H, $(CH_3)_2$), 2.35 (d, J = 2, 3 H, CH_3), 4.15 (s, 2 H, CH_2 on oxazoline ring); ir (potassium bromide): 1652 cm^{-1}.

Anal. Calcd. for $C_{15}H_{20}F_3NOSi$: C, 57.12; H, 6.39; N, 4.44. Found: C, 56.74; H, 6.42; N, 4.27.

2-(3-Chloro-2,4,5-trifluoro-6-methylphenyl)-4,4-dimethyl-2-oxazoline (**11b**).

The title compound was prepared from **10b** in 86% yield using the same procedure used to prepare **11a**; purification was accomplished using column chromatography, eluting with 80:20 chloroform:ethyl acetate, to give **11b** as a clear orange oil; pmr (deuteriochloroform): δ 1.4 (s, 6 H), 2.30 (d, 3 H, J = 2.5), 4.15 (s, 2 H).

Anal. Calcd. for $C_{12}H_{11}ClF_3NO$: C, 51.91; H, 3.99; N, 5.04. Found: C, 51.66; H, 3.98; N, 5.04.

2-(2,4,5-Trifluoro-3,6-dimethylphenyl)-4,4-dimethyl-2-oxazoline (**11c**).

The title compound was prepared from **10c**, two equivalents of lithium diisopropylamide, and methyl iodide using the same procedure employed to prepare **11a**. The crude product was chromatographed, eluting with 2:1 hexane:ethyl acetate, to give **11c** as a pale yellow solid, mp 55-57°, in an 86% yield; pmr (deuteriochloroform): δ 1.42 (s, 6 H), 2.19 (m, 3 H, CH_3), 2.30 (d, 3H, CH_3 adjacent to oxazoline ring), 4.12 (s, 2 H); ir (potassium bromide): 1668 cm^{-1}.

Anal. Calcd. for $C_{13}H_{14}F_3NO$: C, 60.69; H, 5.48; N, 5.44. Found: C, 60.91; H, 5.51; N, 5.37.

2-(2,4,5-Trifluoro-6-methylphenyl)-4,4-dimethyl-2-oxazoline (**11d**).

A solution of 11.5 g (36.5 mmoles) of **11a**, 5.70 g (37.5 mmoles) of cesium fluoride, 90 ml of dimethylformamide, and 9 ml of water was stirred overnight at room temperature. The solution was diluted with water and extracted with ethyl acetate. The extract was washed well with water, dried and concentrated to afford 8.75 g (99%) of **11d** as an orange oil; pmr (deuteriochloroform): δ 1.42 (s, 6 H, $(CH_3)_2$), 2.35 (d, J = 2.6, 3 H, CH_3), 4.13 (s, 2 H, CH_2 on oxazoline ring), 6.85 (m, 1 H); ir (potassium bromide): 1671 cm^{-1}.

Anal. Calcd. for $C_{12}H_{12}F_3NO$: C, 59.26; H, 4.97; N, 5.76. Found: C, 59.39; H, 5.18; N, 5.45.

1-Bromo-2,4,5-trifluoro-3-(trimethylsilyl)benzene (**23**).

A solution of 61.0 ml (435 mmoles) of diisopropylamine in 200 ml of dry tetrahydrofuran was cooled to −78° under argon, treated dropwise with 180 ml of 2.2 *M* *n*-butylithium (396 mmoles), and stirred for fifteen minutes. This solution was then transferred *via* catheter to a cold (−78°) solution of 83.6 g (396 mmoles) of 1-bromo-2,4,5-trifluorobenzene (**22**) in 700 ml of dry tetrahydrofuran, adding the base at such a rate that the reaction temperature remained below −70°.

Once addition was complete, the solution was stirred for one hour at −78°. Trimethylsilyl chloride (135 ml, 1060 mmoles) was added all at once, and the mixture was allowed to warm to room temperature. The solution was diluted with water and ethyl acetate, and the organic phase was separated, washed with water, and dried. Concentration gave a yellow liquid which was distilled

at 77-80° (0.1 mm Hg) to give 97.9 g (88%) of a clear colorless liquid; pmr (deuteriochloroform): δ 0.40 (s, 9 H, $Si(CH_3)_3$), 7.37 (m, 1 H).

Anal. Calcd. for $C_9H_{10}BrF_3Si$: C, 38.17; H, 3.56. Found: C, 38.26; H, 3.54.

1-Bromo-2,4,5-trifluoro-6-methyl-3-(trimethylsilyl)benzene (**24**).

A solution of 20.0 ml (143 mmoles) of diisopropylamine in 400 ml of dry tetrahydrofuran was cooled to −78° under argon, treated dropwise with 60.0 ml of 2.2 *M* *n*-butyllithium (132 mmoles), and stirred for fifteen minutes. To this lithium diisopropylamide solution was added a solution of 37.4 g (132 mmoles) of **23** in 100 ml of dry tetrahydrofuran, and the solution was stirred for one hour at −78°. Methyl trifluoromethanesulfonate (40 ml; 353 mmoles) was added all at once. The reaction mixture was allowed to warm to 0°, treated with saturated sodium bicarbonate solution, and extracted with ethyl acetate. The organic phase was washed with water, dried, and concentrated to an orange oil. Distillation of the crude product at 77-79° (0.1 mm Hg) gave 29.4 g (75%) of a slightly cloudy liquid; pmr (deuteriochloroform): δ 0.38 (s, 9 H, $Si(CH_3)_3$), 2.37 (d, J = 2.8, 3 H, CH_3).

Anal. Calcd. for $C_{10}H_{12}BrF_3Si$: C, 40.41; H, 4.07. Found: C, 40.59; H, 4.11.

2,4,5-Trifluoro-6-methyl-3-(trimethylsilyl)benzoic Acid (**25**).

A solution of 29.0 g (97.6 mmoles) of **24** in 400 ml of ether was cooled to −78° under argon, treated dropwise with 42.0 ml of 2.3 *M* *n*-butyllithium (96.6 mmoles), and stirred for five minutes. The solution was then poured into a mixture of dry ice and ether and allowed to warm to room temperature. The mixture was quenched with 6 *M* hydrochloric acid and extracted with ethyl acetate; the organic phase was concentrated to a yellow solid which was suspended in water. The suspension was basified to *p*H 12, washed with ether, acidified to *p*H 2, and extracted with ether. The organic extract was washed with water, dried over magnesium sulfate, and concentrated to give 15.6 g (62%) of white solid; pmr (deuteriochloroform): δ 0.40 (s, 9 H, $Si(CH_3)_3$), 2.43 (d, J = 2.5, 3 H, CH_3). The pmr spectrum showed that some desilylation had occurred in workup, so the material was carried on immediately to the next step without obtaining an elemental analysis.

3,4,6-Trifluoro-2-methylbenzoic Acid (**12d**).

A. From the Oxazoline (Scheme 2).

A solution of 8.7 g (35.7 mmoles) of **11d** in 200 ml of 6 *N* hydrochloric acid was refluxed overnight, then cooled to room temperature. The solution was extracted with ethyl acetate, and the organic layer was dried and concentrated. The crude product was suspended in water which was made basic (*p*H 10) with 10% sodium hydroxide, washed with ether, and acidified to *p*H 2. The mixture was extracted with ethyl acetate, and the extract was washed with water, dried, and concentrated to give 5.4 g (61%) of **12d**, mp 108-110° (hexane); pmr (deuteriochloroform): δ 2.46 (d, J = 2.6, 3 H, CH_3), 6.88 (m, 1 H), 10.5 (br s, 1 H, CO_2H); ir (potassium bromide): 1730 cm^{-1}.

Anal. Calcd. for $C_8H_5F_3O_2$: C, 50.54; H, 2.65. Found: C, 50.36; H, 2.53.

B. From the Silylated Acid (Scheme 4).

A solution of 6.0 g (23.0 mmoles) of **25**, 4.1 g (27 mmoles) of cesium fluoride, and 50 ml of acetonitrile was stirred at room temperature overnight. The solution was diluted with water and extracted with ethyl acetate; the extract was washed with water, dried, and concentrated to give 3.8 g (89%) of **12d**, mp 109-111° (water).

Anal. Calcd. for $C_8H_5F_3O_2$: C, 50.54; H, 2.65. Found: C, 50.47; H, 2.71.

3-Chloro-2,4,5-trifluoro-6-methylbenzoic Acid (**12b**).

Oxazoline **11b** was hydrolyzed to give the title compound, mp 104-106°, in 62% yield following the same procedure used to prepare acid **12d**; pmr (deuteriochloroform): δ 2.45 (d, J = 2.7, 3 H), 9.8 (bs, 1 H, CO_2H); ir (potassium bromide): 1708 cm^{-1}.

Anal. Calcd. for $C_8H_4ClF_3O_2$: C, 42.79; H, 1.79; Cl, 15.78. Found: C, 43.02; H, 1.79; Cl, 15.46.

2,4,5-Trifluoro-3,6-dimethylbenzoic Acid (**12c**).

The title compound was prepared in 73% yield from **11c** following the same procedure used to prepare acid **12d**, giving a white solid, mp 108-110°; pmr (deuteriochloroform): δ 2.24 (m, 3 H, CH_3 *meta* to the acid), 2.42 (d, J = 2.5, 3 H, CH_3 *ortho* to the acid); ir (potassium bromide): 1700 cm^{-1}.

Anal. Calcd. for $C_9H_7F_3O_2$: C, 52.95; H, 3.46. Found; C, 52.80; H, 3.31.

2-(2,3,4,5-Tetrafluoro-6-methylphenyl)-4,4-diemethyl-2-oxazoline (**17**).

To a cold (−35°) solution of 33.2 g (125 mmoles) of 2-(pentafluorophenyl)-4,4-dimethyl-2-oxazoline (**16**) [9] in 250 ml of ether was added 90 ml of 1.4 *M* methyllithium (126 mmoles) dropwise. The cranberry-colored solution was stirred at or below −20° for ninety minutes and was then allowed to warm to room temperature overnight. Water and ethyl acetate were added. The organic layer was washed with water, dried, and concentrated to give 31.0 g (95%) of a pale yellow liquid which was used without purification; pmr (deuteriochloroform): δ 1.44 (s, 6 H, $(CH_3)_2$), 2.33 (m, 3 H, CH_3), 4.16 (s, 2 H, CH_2 on oxazoline ring); ir (potassium bromide): 1671, 1518 cm^{-1}.

Anal. Calcd. for $C_{12}H_{11}F_4NO$: C, 55.17; H, 4.24; N, 5.36. Found: C, 55.16; H, 4.38; N, 5.59.

2,3,4,5-Tetrafluoro-6-methylbenzoic Acid (**18**).

Oxazoline **17** was hydrolyzed to give the title compound, mp 80-82°, following the same procedure used to synthesize compound **12d**; pmr (deuteriochloroform); δ 2.12 (d, J = 2.3); ir (potassium bromide): 1709 cm^{-1}.

Anal. Calcd. for $C_8H_4F_4O_2$: C, 46.12; H, 1.94. Found: C, 46.02; H, 1.89.

Ethyl 3,4,6-Trifluoro-2-methyl-β-oxobenzenepropanoate (**13d**).

A solution of 19.3 g (101.5 mmoles) of **12d**, 15.5 g (122 mmoles) of oxalyl chloride, and 200 ml of dichloromethane was treated with five drops of dimethylformamide and stirred for two hours at room temperature. The mixture was concentrated, and the crude acid chloride was used without purification.

A solution of 25.5 g (193 mmoles) of ethyl hydrogen malonate, bipyridyl (catalytic), and 400 ml of tetrahydrofuran was cooled to −35° under argon and treated with 88.0 ml of 2.2 *M* *n*-butyllithium (193 mmoles). The suspension was warmed to −5° and treated with another 88.0 ml of 2.2 *M* *n*-butyllithium (193 mmoles) until a pale pink color persisted for ten minutes. The dianion solution was cooled to −78°, treated with a solution of the acid chloride in 100 ml of tetrahydrofuran, and stirred for one hour at −78°. The reaction mixture was warmed to −35° and

poured into a solution of 6 *M* hydrochloric acid (35 ml) and ice. When the mixture had warmed to room temperature, it was extracted with ethyl acetate; the organic layer was washed with dilute hydrochloric acid, 5% sodium bicarbonate solution, and water then was dried. Concentration gave an orange oil which was chromatographed, eluting with 2:1 hexane:ethyl acetate, to give 24.5 g (93%) of the title compound as a yellow oil; pmr (deuteriochloroform); δ 1.30 (m, 3 H, OCH_2CH_3), 2.34 (d, J = 2.4, 3 H, CH_3), 3.87 (d, 1 H, CH_2CO_2Et of ketone tautomer), 4.20 (m, 2 H, OCH_2CH_3), 5.24 (s, 0.5 H, vinyl proton from enol tautomer), 6.83 (m, 1 H), 12.3 (s, 0.5 H, OH of enol tautomer); ir (liquid film): 1748 cm^{-1}.

Anal. Calcd. for $C_{12}H_{11}F_3O_3$: C, 55.39; H, 4.26. Found: C, 55.65; H, 4.32.

Ethyl 3-Chloro-2,4,5-trifluoro-6-methyl-β-oxobenzenepropanoate (**13b**).

Acid **12b** was converted into the title compound in a 95% yield following the same procedure used to produce ketoester **13d**; pmr (deuteriochloroform): δ 1.25 (t, 3 H), 2.33 (d, J = 2.5, 3 H), 3.8 (d, 1.5 H, CH_2CO_2Et from the keto tautomer), 4.25 (m, 2 H), 5.25 (bs, 0.25 H, vinyl proton from enol tautomer), 10.5 (bs, 0.25 H, OH from the enol tautomer).

Anal. Calcd. for $C_{12}H_{10}ClF_3O_3$: C, 48.91; H, 3.42. Found: C, 48.73; H, 3.26.

Ethyl 2,4,5-Trifluoro-3,6-dimethyl-β-oxobenzenepropanoate (**13c**).

The title compound was prepared from **12c** in 82% yield following the same procedure used to prepare ketoester **13d**; pmr (deuteriochloroform): δ 1.35 (m, 3 H), 2.22 (m, 3 H, CH_3), 2.28 (m, 3 H, CH_3), 3.88 (d, 1 H, CH_2CO_2Et from the keto tautomer), 4.22 (m, 2 H), 5.22 (d, 0.5 H, vinyl proton from enol tautomer), 12.4 (s, 0.5 H, OH from enol tautomer).

Anal. Calcd. for $C_{13}H_{13}F_3O_3$: C, 56.93; H, 4.78. Found: C, 57.08; H, 5.02.

Ethyl 2,3,4,5-Tetrafluoro-6-methyl-β-oxobenzenepropanoate (**19**).

The title compound was prepared from **18** in 89% yield following the same procedure used to prepare ketoester **13d**; pmr (deuteriochloroform): δ 1.25 (m, 3 H), 2.27 (m, 3 H, CH_3), 3.88 (m, 1.5 H, CH_2CO_2Et from the keto tautomer), 4.20 (m, 2 H), 5.25 (s, 0.5 H, vinyl proton of enol tautomer), 12.3 (bs, 0.5 H, OH of enol tautomer).

Anal. Calcd. for $C_{12}H_{10}F_4O_3$: C, 51.81; H, 3.62. Found: C, 52.08; H, 3.60.

Ethyl α-(Ethoxymethylene)-3,4,6-trifluoro-2-methyl-β-oxobenzenepropanoate (**14d**).

A solution of 24.4 g (93.8 mmoles) of **13d**, 23 ml (138 mmoles) of triethyl orthoformate, and 75 ml of acetic anhydride was refluxed for three hours, cooled to room temperature, and concentrated to give 29.2 g (98%) of the title compound as a red oil; pmr (deuteriochloroform): δ 1.25 (m, 6 H, OCH_2CH_3), 2.25 (m, 3 H, CH_3), 4.3 (m, 4 H, OCH_2CH_3), 6.75 (m, 1 H), 7.81 and 7.64 (2 s's, 1 H total, vinyl proton of *E* and *Z* isomers).

Ethyl 3-Chloro-α-(ethoxymethylene)-2,4,5-trifluoro-6-methyl-β-oxobenzenepropanoate (**14b**).

The title compound was synthesized from **13b** in 97% yield following the same procedure used to prepare **14d**; pmr (deuteriochloroform): δ 1.30 (m, 6 H), 2.15 (d, J = 2.5, 3 H), 4.25 (m, 4 H), 7.65 and 7.82 (2 s's, 1 H total, vinyl proton from *E* and *Z* isomers).

Ethyl α-(Ethoxymethylene)-2,4,5-trifluoro-3,6-dimethyl-β-oxobenzenepropanoate (**14c**).

The title compound was prepared from **13c** in 98% yield following the same procedure used to prepare **14d**; pmr (deuteriochloroform): δ 1.25 (m, 6 H), 2.20 (m, 6 H, 2 CH_3 groups), 4.20 (m, 4 H), 7.60 and 7.79 (2 s's, 1 H total, vinyl protons of *E* and *Z* isomers).

Ethyl α-(Ethoxymethylene)-2,3,4,5-tetrafluoro-6-methyl-β-oxobenzenepropanoate (**20**).

The title compound was prepared from **19** in 99% yield following the procedure used to synthesize **14d**; pmr (deuteriochloroform): δ 1.30 (m, 6 H), 2.22 (m, 3 H, CH_3), 4.3 (m, 4 H), 7.73 and 7.87 (2 s's, 1 H total, vinyl protons of *E* and *Z* isomers).

Preparation of 1-Cyclopropyl-6,7-difluoro-1,4-dihydro-5-methyl-4-oxo-3-quinolinecarboxylic Acid (**15a**).

General Method A.

A solution of 8.27 g (26.1 mmoles) of **14d** in 30 ml of absolute ethanol was cooled to 5° and treated dropwise with 1.64 g (28.7) of cyclopropylamine. The mixture was stirred at 5-15° for ninety minutes and at room temperature for two hours. The mixture was concentrated to an oil which was triturated with hexane to give a tan solid. This material was dissolved in dry tetrahydrofuran and treated with 1.1 g (27.5 mmoles, 1.05 equivalents) of 60% sodium hydride. The reaction mixture was stirred at room temperature overnight, then concentrated to a solid which was partitioned between 1 *N* hydrochloric acid and dichloromethane. The organic layer was washed with brine, dried, and concentrated. The residue was refluxed in 50 ml of 6 *M* hydrochloric acid for 3 hours and cooled to room temperature. The solids were filtered, washed with water and ether, and dried to give 3.86 g (53% from **14d**) of white powder, which was recrystallized from dichloromethane:-*n*-hexane, mp >300°; pmr (deuteriodimethyl sulfoxide): δ 1.20 (m, 4 H, cyclopropyl), 2.82 (d, J = 3, 3 H, CH_3 at C-5), 3.77 (m, 1 H, cyclopropyl), 8.23 (m, 1 H, C-8 proton), 8.72 (s, 1 H, C-2 proton); ir (potassium bromide): 1726, 1623 cm^{-1}.

Anal. Calcd. for $C_{14}H_{11}F_2NO_3$: C, 60.22; H, 3.97; N, 5.02. Found: C, 59.96; H, 3.95; N, 4.87.

1-Ethyl-6,7-difluoro-1,4-dihydro-5-methyl-4-oxo-3-quinolinecarboxylic Acid (**15b**).

The title compound was prepared from **14d** and ethylamine following the procedure used to prepare **15a**; quinolone **15b** was isolated in 45% yield from **14d** as a white powder, mp >300°; pmr (deuteriodimethyl sulfoxide): δ 1.25 (t, 3 H, NCH_2CH_3), 2.80 (d, J = 3, 3 H, CH_3 at C-5), 4.25 (m, 2 H, NCH_2CH_3), 8.10 (m, 1 H, C-8 proton), 9.05 (s, 1 H, C-2 proton); ir (potassium bromide): 1711, 1620 cm^{-1}.

Anal. Calcd. for $C_{13}H_{11}F_2NO_3$: C, 58.43; H, 4.15; N, 5.24. Found: C, 58.20; H, 3.90; N, 4.89.

1-(2,4-Difluorophenyl)-6,7-difluoro-1,4-dihydro-5-methyl-4-oxo-3-quinolinecarboxylic Acid (**15c**).

Ethoxyacrylate **14d** was reacted with 2,4-difluoroaniline using the same procedure outlined for **15a**; the adduct obtained was chromatographed (eluting with 2:1 hexane:ethyl acetate) prior to treatment with sodium hydride. Compound **15c** was isolated as an off-white powder in 66% yield from **14d**, mp 282-284°; pmr

(deuteriodimethyl sulfoxide): δ 2.87 (bs, 3 H, CH_3 at C-5), 7.21 (m, 1 H, C-8 proton), 7.42 (m, 1 H, *N*-phenyl), 7.72 (m, 1 H, *N*-phenyl), 7.85 (m, 1 H, *N*-phenyl), 8.90 (s, 1 H, C-2 proton); ir (potassium bromide): δ 1720, 1622 cm^{-1}.

Anal. Calcd. for $C_{17}H_9F_4NO_3 \cdot 0.5$ HCl: C, 55.26; H, 2.59; N, 3.70. Found: C, 55.13; H, 2.42; N, 3.57.

8-Chloro-1-cyclopropyl-6,7-difluoro-1,4-dihydro-5-methyl-4-oxo-3-quinolinecarboxylic Acid (**15e**).

The title compound **15e** was synthesized from ethoxyacrylate **14b** in 52% overall yield following the same procedure used to prepare **15a** and was isolated as a pale yellow solid, mp 212-214°; pmr (deuteriodimethyl sulfoxide): δ 1.05 (m, 2 H, cyclopropyl), 1.20 (m, 2 H, cyclopropyl), 2.77 (d, J = 2.7, 3 H, CH_3 at C-5), 4.40 (m, 1 H, cyclopropyl), 8.85 (s, 1 H, C-2 proton); ir (potassium bromide): 1735, 1619 cm^{-1}.

Anal Calcd. for $C_{14}H_{10}ClF_2NO_3$: C, 53.60; H, 3.21; N, 4.46. Found: C, 53.48; H, 3.33; N, 4.21.

1-Cyclopropyl-6,7-difluoro-1,4-dihydro-5,8-dimethyl-4-oxo-3-quinolinecarboxylic Acid (**15f**).

The title compound **15f** was synthesized from ethoxyacrylate **14c** in 46% yield following the same procedure used to prepare **15a** and was isolated as an off-white solid, mp 228-229°; pmr (deuteriodimethyl sulfoxide); δ 0.92 (m, 2 H, cyclopropyl), 1.18 (m, 2 H, cyclopropyl), 2.70 (m, 3 H, CH_3 at C-8), 2.74 (m, 3 H, CH_3 at C-5), 4.36 (m, 1 H, cyclopropyl), 8.81 (s, 1 H, C-2 proton); ir (potassium bromide): 1723, 1624 cm^{-1}.

Anal. Calcd. for $C_{15}H_{13}F_2NO_3$: C, 61.43; H, 4.47; N, 4.78. Found: C, 61.40; H, 4.50; N, 4.65.

1-Cyclopropyl-6,7,8-trifluoro-1,4-dihydro-5-methyl-4-oxo-3-quinolinecarboxylic Acid (**21a**).

The title compound was synthesized in 62% yield from ethoxyacrylate **20** following the procedure used to prepare **15a** and was isolated as a white solid, mp 234-235°; pmr (deuteriodimethyl sulfoxide): δ 1.25 (m, 4 H, cyclopropyl), 2.77 (d, J = 2.5, 3 H, CH_3 at C-5), 4.15 (m, 1 H, cyclopropyl), 8.73 (s, 1 H, C-2 proton); ir (potassium bromide): 1731, 1625 cm^{-1}.

Anal. Calcd. for $C_{14}H_{10}F_3NO_3$: C, 56.57; H, 3.39; N, 4.71. Found: C, 56.82; H, 3.17; N, 4.39.

1-Ethyl-6,7,8-trifluoro-1,4-dihydro-5-methyl-4-oxo-3-quinolinecarboxylic Acid (**21b**).

Ethoxyacrylate **20** was reacted sequentially with anhydrous ethylamine, sodium hydride, and 6 *N* hydrochloric acid as outlined for the synthesis of **15a**. The acid **21b** was isolated in 52% yield from **20** as a grainy white solid, mp 199-201°; pmr (deuteriodimethyl sulfoxide): δ 1.43 (t, 3 H, NCH_2CH_3), 2.78 (m, 3 H, CH_3 at C-5), 4.60 (m, 2 H, NCH_2CH_3), 9.00 (s, 1 H, C-2 proton); ir (potassium bromide): 1714, 1621 cm^{-1}.

Anal. Calcd. for $C_{13}H_{10}F_3NO_3$: C, 54.74; H, 3.53; N, 4.91. Found: C, 54.79; H, 3.65; N, 4.78.

1-(2,4-Difluorophenyl)-6,7,8-trifluoro-1,4-dihydro-5-methyl-4-oxo-3-quinolinecarboxylic Acid (**21c**).

Ethoxyacrylate **20** was reacted with 2,4-difluoroaniline in the same procedure used to prepare **15a**, and the product obtained was chromatographed (eluting with 2:1 hexane:ethyl acetate) prior to treatment with sodium hydride. After ring closure and hydrolysis, compound **21c** was obtained as a yellow powder (64% from **20**), mp 218-219° pmr (deuteriodimethyl sulfoxide): δ 2.82 (d, J = 2, 3 H, CH_3 at C-5), 7.36 (m, 1 H, *N*-phenyl), 7.57 (m, 1 H, *N*-phenyl), 7.94 (m, 1 H, *N*-phenyl), 8.77 (s, 1 H, C-2 proton); ir (potassium bromide): 1726, 1626 cm^{-1}.

Anal. Calcd. for $C_{17}H_8F_5NO_3$: C, 55.30; H, 2.18; N, 3.79. Found: C, 55.63; H, 1.96; N, 3.68.

Preparation of 1-(*t*-Butyl)-6,7-difluoro-1,4-dihydro-5-methyl-4-oxo-3-quinolinecarboxylic Acid (**15d**).

General Method B.

A solution of 9.7 g (30.7 mmoles) of **14d** in 25 ml of ethanol was cooled to −15° and treated with 4.5 ml (61.6 mmoles) of *t*-butylamine. The mixture was allowed to warm to room temperature overnight, then concentrated to a thick oil. This residue was dissolved in 100 ml of dry dioxane, treated with 1.45 g (36.2 mmoles) of 60% sodium hydride, and stirred overnight at room temperature. The suspension was concentrated to a solid which was partitioned between dichloromethane and 1 *N* hydrochloric acid. The organic phase was washed with brine, dried, and concentrated. The crude ester was suspended in 13 ml of 1 *N* sodium hydroxide (one equivalent) and 100 ml of ethanol, and the reaction mixture was stirred at room temperature for ten hours. The suspension was concentrated to a paste which was partitioned between dichloromethane and water. The aqueous phase was acidified to *p*H 3, and the solids that formed were filtered and washed with water and ether. Upon air-drying, 3.4 g (55% from **14d**) of **15d** were obtained as a white solid, mp 264-265°; pmr (deuteriodimethyl sulfoxide): δ 1.85 (s, 9 H, *t*-butyl group), 2.84 (d, J = 2.5, 3 H, CH_3 at C-5), 8.23 (m, 1 H, C-8 proton), 9.00 (s, 1 H, C-2 proton); ir (potassium bromide): 1725, 1617 cm^{-1}.

Anal. Calcd. for $C_{15}H_{15}F_2NO_3$: C, 61.01; H, 5.12; N, 4.74. Found: C, 60.69; H, 5.03; N, 4.53.

Preparation of Ethyl 1-Ethenyl-6,7,8-trifluoro-1,4-dihydro-5-methyl-4-oxo-3-quinolonecarboxylate (**21d**).

General Method C.

A cold (ice bath) solution of 4.35 g (13.0 mmoles) of **20**, 3.20 g (15.6 mmoles) of bromoethylamine hydrochloride, and 100 ml of ethanol was treated with 1.44 g, (14.3 mmoles) of triethylamine, stirred at 5-10° for one hour, and warmed to room temperature overnight. The solution was concentrated to a gold solid which was dissolved in dichloromethane. The solution was washed with water, dried and concentrated to a yellow solid. This residue was dissolved in 150 ml of dry *t*-butyl alcohol and treated portionwise with 1.06 g (9.48 mmoles) of potassium *t*-butoxide. The mixture was stirred at room temperature overnight, then concentrated. The residue was partitioned between dichloromethane and 1 *N* hydrochloric acid; the organic layer was washed with water, dried, and concentrated. The crude product was dissolved in 5 ml of dimethylformamide and treated with 6.2 g (45 mmoles) of freshly ground potassium carbonate. The suspension was heated at 80° for three hours under argon, then cooled to room temperature and concentrated under high vacuum. The oil that remained was dissolved in dichloromethane, and the solution was washed with water, dried, and concentrated to give 1.5 g (37% from **20**) of title compound **21d** as a complex with dimethylformamide (pale orange solid, mp 150-152°); pmr (deuteriodimethyl sulfoxide): δ 1.42 (t, 3 H, OCH_2CH_3), 2.83 (m, 3 H, CH_3 at C-5), 3.40 (d, 6 H, $N(CH_3)_2$ from dimethylformamide), 4.38 (q, 2 H, OCH_2CH_3), 5.10 (m, 1 H, vinyl proton), 5.37 (m, 1 H, vinyl proton, 7.28 (m, 1 H, vinyl proton), 8.59 (s, 1 H, C-2 proton); ir (potassium bromide):

1726, 1618 cm^{-1}.

Anal. Calcd. for $C_{13}H_8F_3NO_3 \cdot C_3H_7NO$: C, 53.93; H, 4.24; N, 7.86. Found: C, 53.58; H, 4.08; N, 7.66.

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