Synthesis of a Novel Tricyclic 4-Quinolone. Incorporation of a Spiro-cyclopropyl Group at N1 by Bridging to C2

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An important pharmacophore in many quinolone antiinfectives is the N1 cyclopropane. By incorporating the cyclopropane into a N1 to C2 bridge, the first quinolone substrate incorporating a spiro fused cyclopropane, 8,9,10-trifluoro-2,3,4,6-tetrahydro-6-oxospiro[1*H*-benzo[*c*]quinolizine-1,1'-cyclopropane]-5-carboxylic acid, ethyl ester (**8**), was prepared.

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In the realm of new antiinfective agents, compounds containing a 1-substituted-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid **2** are of great interest [1]. These "quinolones", such as ciprofloxacin (**2a**) [2] possess outstanding Gram positive and Gram negative activity and are usually prepared by condensing the appropriate substrate **1**, with an amine (Figure 1) [3].

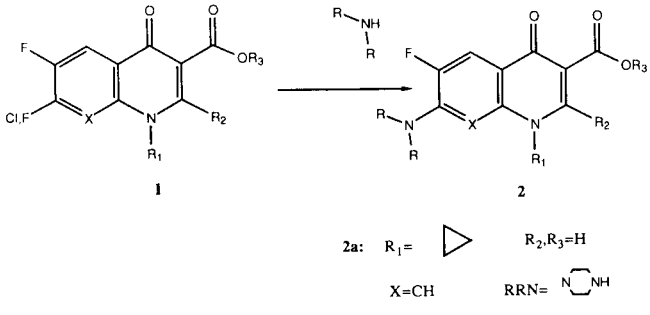


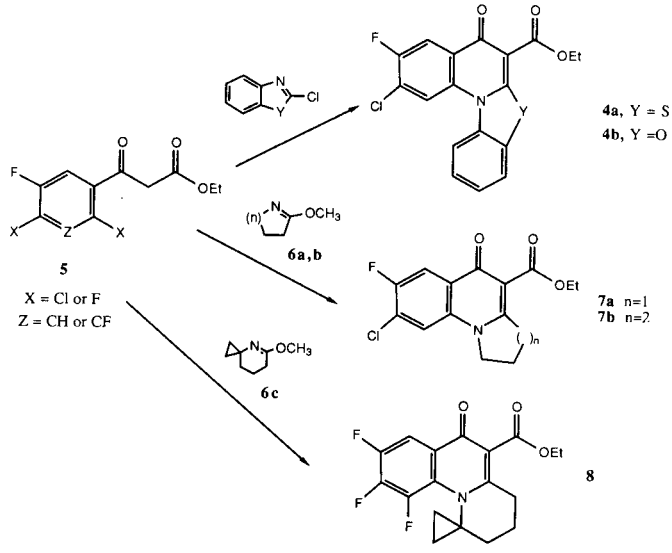
Figure 1

The structure activity relationship of substitution at N1 of the quinolone ring has been reported [3]. In particular, cyclopropane at N1 has been shown to dramatically increase *in vitro* and *in vivo* potency [3]. We wished to prepare a novel quinolone substrate, which would restrict the possible conformations of the cyclopropane moiety, allowing us to gain insight into the spatial requirements of the cyclopropane attached at N1. This could be accomplished by bridging the N1 substituent to C8 [4] or to C2.

Substituents bridging N1 to the C2 position are known but are limited primarily to aryl, such as benzothiazoloquinoline **4a** [5a] and benzoxazolo-quinoline **4b** [5b] or alkyl, *via* carbon chains **7a,b** [5c] (Scheme 1). While C2 substitution in general leads to loss of antibacterial potency [6,9a], bridging the N1 substituent to C2 may not be detrimental to activity [5a].

The known substrates **4a**, **4b**, **7a** and **7b** were prepared by condensing the anion of β-keto ester **5** with electrophiles; chlorobenzothiazoles [5a], chlorobenzoxazoles [5b] or iminoethers **6a** or **6b** [5c], respectively. By analogy to this method, preparation of **8**, a quinolone containing a spirofused cyclopropane, would require iminoether **6c**. While one may devise several routes to **6c**, we opted for an alternate approach utilizing methodology developed in our laboratory where the key step is intramolecular Grignard addition to the C2 position.

Scheme 1

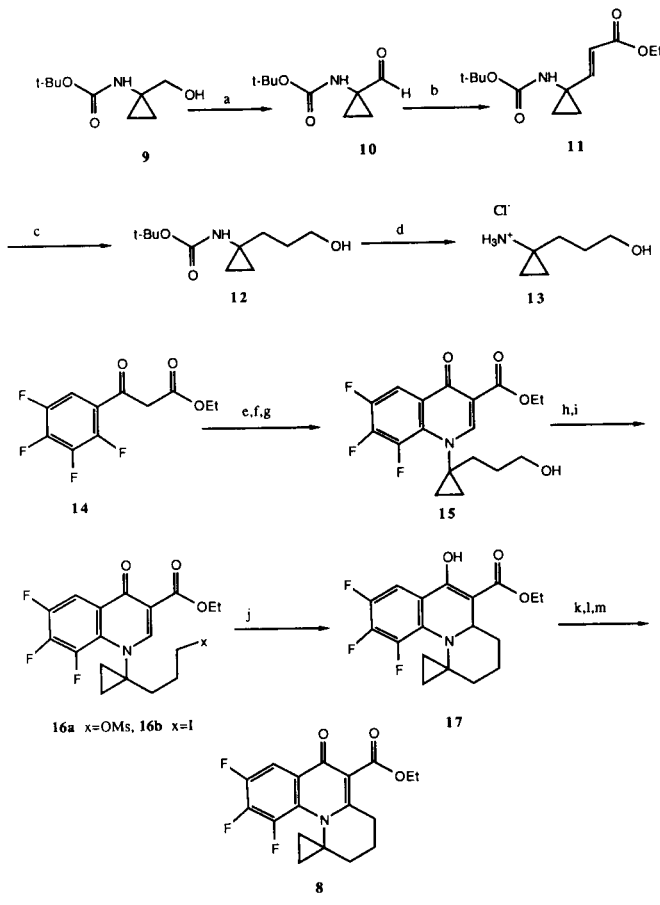


Below we report the synthesis of the novel quinolone **8** which contains the cyclopropane of ciprofloxacin fused to a six membered ring bridging N1 and C2.

1,1-Dimethylethyl [1-(hydroxymethyl)cyclopropyl]carbamate (**9**) [7] was oxidized in excellent yield using the method of Swern [8] (see Scheme 2). The resulting aldehyde **10** was added to the anion of triethylphosphonoacetate, formed from addition of the Wittig-Horner reagent to sodium hydride. The resulting α,β-unsaturated ester **11** was obtained in 70% yield.

We initially viewed the reduction of **11** as a two step process, reduction of the ester followed by catalytic reduction of the double bond or *vice versa*. However, treatment of the ester with lithium borohydride in tetrahydrofuran gave the saturated alcohol **12** directly in 34% yield after chromatography. Treatment of **12** with gaseous hydrogen

Scheme 2



a) ClCOCOCl, CH_2Cl_2, DMSO, Et_3N b) NaH, THF, $(EtO)_2POCH_2CO_2Et$ c) $LiBH_4$, THF d) HCl, CH_2Cl_2 e) $(EtO)_3CH$, Ac_2O f) KOtBu, tBuOH g) KOtBu h) Et_3N, MsCl, THF i) NaI, acetone j) Mg, CuI, THF k)NaH, THF l) PhSeCl m)H_2O_2

chloride in methylene chloride gave the amino alcohol **13** as its hydrochloride salt.

This cyclopropylamine hydrochloride **13** was condensed under standard conditions with ethyl 2,3,4,5-tetrafluoro-β-oxobenzenepropanoate (**14**) [3] giving quinolone **15**. Conversion of the alcohol **15** into an iodide was accomplished in two steps. First treatment of the alcohol with methanesulfonyl chloride and triethylamine in tetrahydrofuran gave the mesylate **16a** which was isolated and used without purification. The mesylate **16a** was refluxed with sodium iodide in acetone to give the iodide **16b**.

Facile 1,4 addition of simple Grignard and alkyl lithium reagents to the C2 position of quinolones is known to occur in good yield [9]. Model experiments showed that reaction of preformed butylmagnesium chloride/copper(1) iodide/tetrahydrofuran at −70° gave 94% (crude yield) of butylation at C2 after 2 hours. *In situ* formation of the Grignard using chlorobutane/magnesium metal under similar conditions at 25° was slow and gave only traces of product after 24 hours at reflux. However, bromobutane/magnesium metal gave a 2:1 ratio of C2 substitution to starting material after 26 hours at 25°.

From these model reactions, we anticipated that the Grignard of iodide **16b** would add in an intramolecular fashion to the C2 position of the quinolone giving the desired spiro fused cyclopropane ring system. As expected, addition of the iodide **16b** to a suspension of magnesium metal and copper(I) iodide in tetrahydrofuran initiated Grignard formation and subsequent cyclization gave the enol ester **17** in good yield. Treatment of the enol **17** with sodium hydride and phenylselenium chloride followed by oxidation and *in situ* elimination produced the desired substrate **8** in 61% yield [10].

Although there have been several compounds synthesized which restrict the rotation of the quinolone N1 substituent by bridging to C2, none include cyclopropane, a potent contributor to antibacterial efficacy. The synthesis outlined above is the first preparation of the novel substrate **8**.

When the substrate **8** was coupled with piperazine and hydrolyzed to the carboxylic acid, MICs greater than 25 μg/ml were obtained.

EXPERIMENTAL

Melting points were taken on a Hoover capillary melting point apparatus and are uncorrected. Infrared (ir) spectra were determined on a Nicolet Ft IR SX-20 with 2 cm^{-1} resolution. Proton magnetic resonance (^{1}H-nmr) were recorded on a Varian XL-200 spectrometer. Chemical shifts are reported in delta units relative to tetramethylsilane. Mass spectra were recorded on either a Finnigan 4500 GCMS or a VG Analytical 7070E/HF with a 11/250 data system. Column chromatography was performed with W. R. Grace silica gel 60, 230-400. Solutions were dried over magnesium sulfate. All concentrations of solutions were performed under reduced pressure on a Buchi rotary evaporator. The CHN elemental analyses were performed on either a Control Equipment Corp. Model 240XA or a Carlo-Erba Model 1106 Elemental Analyzer and halogen determinations were performed by the closed flask combustion method, employing a titrimetric determination. All new products and intermediates had analytical results within +/− 0.4% of theoretical values. The hplc purity of the final products was performed on reverse phase C18 columns using 20% THF/80% 0.05 *M* ammonium phosphate buffer (*p*H 3.0) mobile phase at 1.0 ml/minute with product detection by absorbance at 287 nm.

1,1-Dimethylethyl (1-Formylcyclopropyl)carbamate (**10**).

A solution of oxalyl chloride (7.52 g, 59.2 mmoles) in methylene chloride (135 ml) was cooled to −60°. Dry dimethyl sulfoxide (10.1 g, 129 mmoles) in methylene chloride (25 ml) was added over 5 minutes followed by stirring for an additional 10 minutes. A solution of **9** (10.1 g, 53.8 mmoles) in methylene chloride (55.0 ml) was added over 7 minutes. The reaction was stirred for another 15 minutes followed by addition of triethylamine (27.2 g, 269 mmoles). The ice bath was removed and the reaction was warmed to room temperature. The reaction was diluted with water (160 ml), and stirred 10 minutes. The resulting layers were separated and the aqueous layer was extracted twice with methylene chloride. The organic layers were combined, dried and concentrated. The residue was triturated with diethyl ether and the resulting white solid isolated by filtration giving **10**, 9.98 g, 99%, mp 76.5-78.5°; ^{1}H-nmr (deuteriochloroform): 1.25-1.40 (m, 2H), 1.42-1.60 (m, 1H), 5.17 (br s, 1H), 9.2 (s, 1H); ir (potassium bromide): 3332, 3014, 1714, 1687, 1520, 1166, 972, 630 cm^{-1}; ms: (ei$^+$) m/z 129 (M^+ - *t*-butyl), 57 (*t*-butyl, base).

Anal. Calcd. for $C_9H_{15}NO_3 \cdot 0.17$ water: C, 57.41; H, 8.21; N, 7.44. Found: C, 57.41; H, 8.26; N, 7.09.

Ethyl 3-[1-[[(1,1-Dimethylethoxy)carbonyl]amino]cyclopropyl]-2-propenate (**11**).

Sodium hydride (60%, 6.22 g, 156 mmoles), washed free of oil with hexane, was suspended in dry tetrahydrofuran (100 mℓ). The suspension was cooled to 0° with an ice/water bath and a solution of triethyl phosphonoacetate (30.5 g, 136 mmoles) in dry tetrahydrofuran (80 mℓ) was added over 30 minutes. The reaction was cooled to −78° and **10** (12.0 g, 643.8 mmoles) in dry tetrahydrofuran (70 mℓ) was added to the solution over 15 minutes. The cold bath was removed and the reaction was allowed to warm to room temperature. After stirring 2.5 hours the reaction was quenched with saturated ammonium chloride solution (60 mℓ) then concentrated. The residue was partitioned between ethyl acetate and water. The layers were separated and the aqueous phase was washed three times with ethyl acetate. The organic layers were combined and washed three times with saturated sodium bicarbonate solution then three times with saturated sodium chloride solution. After drying, the organics were concentrated giving 20.3 g of crude material. Flash chromatography (silica gel/ethyl acetate) gave **11** as a tan solid, 11.5 g, 70%, mp 78.0-79.0°; ^{1}H-nmr (deuteriochloroform): 1.07-1.23 (m, 2H), 1.23-1.38 (m, 5H), 1.45 (s, 9H), 4.18 (q, J = 7.1 Hz, 2H), 4.85-5.20 (m, 1H), 5.85 (d, J = 15.5 Hz, 1H), 6.49 (d, J = 15.5 Hz, 1H); ir (potassium bromide): 3291, 1706, 1690 cm^{-1}; ms: (fab) m/z 511 (2 x M$^+$), 256 (M$^+$ + 1), 273 (base).

Anal. Calcd. for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49. Found: C, 60.95; H, 8.32; N, 5.30.

1,1-Dimethylethyl [1-(3-Hydroxypropyl)cyclopropyl]carbamate (**12**).

Lithium borohydride (9.85 g, 452 mmoles) was suspended in dry tetrahydrofuran (300 mℓ) and a solution of **11** (32.8 g, 128 mmoles) in dry tetrahydrofuran (300 mℓ) was added over 45 minutes. The reaction was stirred at room temperature overnight, then quenched with an equal volume of saturated ammonium chloride solution (vigorous foaming). The mixture was evaporated and the residue was partitioned with ethyl acetate (350 mℓ). The layers were separated and the aqueous phase was washed with ethyl acetate (3 x 350 mℓ). The organic layers were combined, dried and concentrated to give 18.4 g of crude material. Chromatography (silica gel/ethyl acetate) gave **12** as a white solid, 9.60 g, 34%, mp 53.5-56.5°; ^{1}H-nmr (deuteriochloroform): 0.53-0.67 (m, 2H), 0.68-0.82 (m, 2H), 1.42 (s, 9H), 1.51-1.80 (m, 4H), 1.87 (br s, 1H), 3.60-3.77 (m, 2H), 4.93 (br s, 1H); ir (potassium bromide): 3435 cm^{-1}; ms: (ci + CH_4, 0.5 torr) m/z 216 (M$^+$ + 1), 160 (M$^+$ - *t*-butyl, base).

Anal. Calcd. for $C_{11}H_{21}NO_3 \cdot 0.28$ water: C, 59.96; H, 9.86; N, 6.36. Found: C, 59.97; H, 10.00; N, 6.11.

1-Aminocyclopropanepropanol Monohydrochloride (**13**).

Hydrogen chloride gas was bubbled into a solution of **12** (8.70 g, 40.4 mmoles) in methylene chloride (70 mℓ) for 10 minutes. The reaction became cloudy after 5 minutes and a residue formed. After stirring 1 hour at room temperature, tlc indicated the reaction was incomplete. Additional hydrogen chloride gas was passed into the reaction for 15 minutes followed by stirring for 2 hours. The reaction was concentrated, the residue was triturated with diethyl ether, and the resulting solid was filtered off giving **13** as a white solid, 5.58 g, 90%, mp 72-80° dec; (deuteriomethyl sulfoxide + deuterium oxide): 0.60-0.77 (m, 2H), 0.83-1.00 (m, 2H), 1.45-1.77 (m, 4H), 3.44 (t, J = 5.8 Hz, 2H); ir (potassium bromide): 3435, 3205, 2905, 1529, 1020 cm^{-1}; ms: (ci + CH_4, 0.6 torr) m/z 156 (M$^+$ + C_3H_5), 144 (M$^+$ + C_2H_5), 116 (M$^+$ + 1, base), 98 (M$^+$ - OH).

Anal. Calcd. for $C_6H_{14}ClNO \cdot 0.08$ water: C, 47.08; H, 9.32; N, 9.15. Found: C, 47.07; H, 9.31; N, 9.12.

6,7,8-Trifluoro-1,4-dihydro-1-[1-(3-hydroxypropyl)cyclopropyl]-4-oxo-3-quinolinecarboxylic Acid, Ethyl Ester (**15**).

Ethyl 2,3,4,5-tetrafluoro-β-oxobenzenepropanoate (**14**) [3] (2.61 g, 9.89 mmoles), acetic anhydride (2.42 g, 23.7 mmoles) and triethyl orthoformate (2.20 g, 14.8 mmoles) were combined and warmed to reflux (oil bath temperature = 158°) for 2.5 hours. The oil bath was cooled to 80° and the volatiles were removed under reduced pressure (approximately 0.10 mm Hg). The oil bath was further cooled to 45° and a suspension of **13** (1.50 g, 9.89 mmoles) and potassium *t*-butoxide (1.11 g, 9.89 mmoles) in *t*-butyl alcohol (52 mℓ) was added to the reaction. After stirring 3 hours at 45°, a second equivalent of potassium *t*-butoxide (1.11 g, 9.89 mmoles) was added to the reaction. The reaction was stirred overnight, quenched with 1.00 mℓ acetic acid and the solvents evaporated. The residue was partitioned between water (100 mℓ) and methylene chloride (100 mℓ). The layers were separated and the aqueous phase was extracted with methylene chloride (2 x 100 mℓ). The organic layers were combined and concentrated to give a viscous orange oil. Chromatography (silica gel/-6:3:1-chloroform:hexane:isopropyl alcohol) gave **15** as a yellow foam, 2.23 g, 60%, mp 59° dec; ^{1}H-nmr (deuteriochloroform): 1.13-1.47 (m, 6H), 1.47-1.87 (m, 5H), 2.37-2.62 (m, 1H), 3.57-3.58 (m, 2H), 4.39 (q, J = 7.1 Hz, 2H), 8.07-8.23 (m, 1H), 8.61 (s, 1H); ir (potassium bromide): 3456, 2960, 1733, 1699, 1624, 1483, 803 cm^{-1}; ms: (ei) m/z 370 (M$^+$ + 1), 369 (M$^+$) 53 (base).

Anal. Calcd. for $C_{18}H_{18}F_3NO_4 \cdot 0.24$ water: C, 57.86; H, 4.98; N, 3.75; F, 15.25. Found: C, 57.86; H, 4.87; N, 3.54; F, 15.13.

6,7,8-Trifluoro-1,4-dihydro-1-[1-(3-iodopropyl)cyclopropyl]-4-oxo-3-quinolinecarboxylic Acid, Ethyl Ester (**16b**).

The quinolone alcohol **15** (6.70 g, 18.1 mmoles) was dissolved in dry tetrahydrofuran (300 mℓ), triethylamine (2.75 g, 27.2 mmoles) was added and the reaction was cooled to 0°. Methanesulfonyl chloride (3.12 g, 27.2 mmoles) in tetrahydrofuran (25 mℓ) was added dropwise over 5 minutes and the reaction was stirred 100 minutes at 0° before the reaction was concentrated under reduced pressure. The residue was partitioned between water (50 mℓ) and methylene chloride (50 mℓ), the layers were separated and the aqueous phase was washed with methylene chloride (2 x 50 mℓ). The organic layers were combined, dried and concentrated to give 9.35 g of crude material. Proton nmr indicated this crude material to be the mesylate **16a**.

The crude mesylate was dissolved in acetone (650 mℓ) and sodium iodide (24.4 g, 163 mmoles) was added. The reaction was refluxed for 1.5 hours, cooled to room temperature, and concentrated. The residue was dissolved in methylene chloride (150 mℓ) and washed with water (3 x 75 mℓ) followed by 50% (w/w) sodium thiosulfate solution (2 x 50 ml). The organic layer was dried and concentrated to a solid. Recrystallization (hexane/ethyl acetate) of the crude solid gave **16b** as light yellow crystals; 7.37 g, 85%, mp 148-150°; ^{1}H-nmr (deuteriochloroform): 1.15-1.47 (m, 7H), 1.47-1.67 (m, 1H); 1.70-2.10 (m, 2H), 2.37-2.60 (m, 1H), 3.03-3.30 (m, 2H), 4.40 (q, J = 7.1 Hz, 2H), 8.10-8.27 (m, 1H); ir (potassium bromide): 3467, 1730, 1689, 1623, 1482, 803 cm^{-1}; ms: (ei$^+$) m/z 480 (M$^+$ + 1, base).

Anal. Calcd. for $C_{18}H_{17}F_3NO_3$: C, 45.11; H, 3.57; N, 2.92; I, 26.48. Found: C, 44.92; H, 3.43; N, 2.74; I, 26.51.

8,9,10-Trifluoro-2,3,4,4a-tetrahydro-6-hydroxyspiro[1*H*-benzo[c]quinolizine-1,1′-cyclopropane]-5-carboxylic Acid, Ethyl Ester (**17**).

A suspension of magnesium metal (1.32 g, 54.3 mmoles) in dry tetrahydrofuran (4.00 mℓ) was activated by adding several drops of 1,2-dibromoethane. Copper(I) iodide (0.15 g, 0.81 mmole) was added to the magnesium/tetrahydrofuran slurry, followed by dropwise addition of **16b** (1.30 g, 2.71 mmoles) in dry tetrahydrofuran (40.0 mℓ). The green solution was stirred for 6 hours. The mixture was filtered and the filtrate was quenched with saturated ammonium chloride solution (20.0 mℓ). The filtrate was evaporated and the residue was extracted with methylene chloride. The organic layers were combined, washed with saturated ammonium chloride solution followed by saturated sodium chloride solution, dried and concentrated to give 0.91 g of crude yellow solid. Chromatography (silica gel/methylene chloride) gave **17** as a yellow solid, 0.55 g, 57%, mp 134-137°; ^{1}H-nmr (deuteriodimethyl sulfoxide): 0.58-0.82 (m, 2H) 0.82-1.19 (m, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.43-1.88 (m, 4H), 1.93-2.23 (m, 1H), 4.12-4.53 (m, 3H), 7.23-7.41 (m, 1H), 12.06 (s, 1H); ir (potassium bromide): 3459, 1660, 1639, 1596, 1507, 1408, 1270, 1031, 827 cm^{-1}; ms: (ei$^+$) m/z 353 (M$^+$), 307 (M$^+$ - OEt), 288 (base).

Anal. Calcd. for $C_{18}H_{18}F_3NO_3 \cdot 0.27$ water: C, 60.36; H, 5.22; N, 3.91; F, 15.91. Found: C, 60.36; H, 5.17; N, 3.89; F, 15.55.

8,9,10-Trifluoro-2,3,4,6-tetrahydro-6-oxospiro[1*H*-benzo[c]quinolizine-1,1'-cyclopropane]-5-carboxylic Acid, Ethyl Ester (**8**).

Sodium hydride (34.0 mg, 0.85 mmole, 60% oil suspension) was washed free of oil, suspended in dry tetrahydrofuran (3.00 m*l*) and cooled to 0-5°. A solution of **17** (200 mg, 0.57 mmole) in dry tetrahydrofuran (7.00 m*l*) was added over approximately 10 minutes. The reaction was stirred for an additional 10 minutes followed by rapid addition of phenylselenium chloride (120 mg, 0.62 mmole) in dry tetrahydrofuran (5 m*l*). The reaction was stirred 10 minutes then partitioned between methylene chloride (25 m*l*) and saturated sodium bicarbonate solution (25 m*l*). The layers were separated and the aqueous phase was washed with methylene chloride (2 x 25 m*l*). The organic layers were combined, dried and concentrated. The residual yellow oil was dissolved in methylene chloride (10 m*l*) and added dropwise into a solution of hydrogen peroxide (160 mg, 1.4 mmoles, 30% aqueous solution) and water (5 m*l*). The two phase reaction mixture was stirred at room temperature for 3 hours then partitioned between 10% sodium carbonate solution (25 m*l*) and methylene chloride (25 m*l*). The layers were separated and the aqueous phase was washed with methylene chloride (2 x 25 m*l*). The combined organic layers were dried and concentrated to give 246 mg of crude material. Chromatography (silica gel/70:30-ethyl acetate:hexane) gave **8**, 124 mg, 61%; ^{1}H-nmr (deuteriochloroform): 0.63-1.31 (m, 4H), 1.38 (t, J = 7.1 Hz, 3H), 1.78-2.55 (m, 4H), 3.13 (t, J = 6.5 Hz, 2H), 4.39 (q, J = 7.1 Hz, 2H), 7.85-8.02 (m, 1H); ir (potassium bromide): 3459, 1729, 1610, 1486 cm^{-1}; ms: (ei$^+$) m/z 351 (M$^+$), 286 (base).

Anal. Calcd. for $C_{18}H_{16}F_3NO_3 \cdot 0.38$ water: C, 60.36; H, 4.72; N, 3.91; F, 15.91. Found: C, 60.35; H, 4.56; N, 3.81; F, 15.92.

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