A Concise, Practical Synthesis of the Pyrido[3,2,1-*i,j*]cinnoline Ring System of Potent DNA Gyrase Inhibitors

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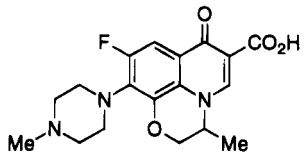
Background

Inhibitors of bacterial DNA gyrase have emerged as extremely effective agents for the treatment of a wide range of bacterial infection.[1] Compounds possessing potent affinity for the bacterial enzyme (a type II topoisomerase), exemplified by the fluoroquinolones, now occupy a position of key importance in the arsenal of the infectious disease practitioner. After the serendipitous discovery of nalidixic acid[2] more than 30 years ago an enormous and unfinished search for more potent analogs has identified the 1,8-bridged tricyclic quinolones as a particularly effective series;[3] ofloxacin[4] (**1**), rufloxacin[5] (**2**), and flumequine[6] (**3**) are compounds that have proven to be especially effective.



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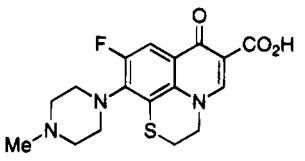

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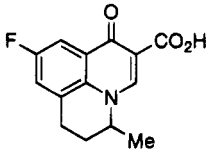

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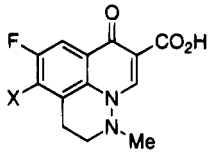

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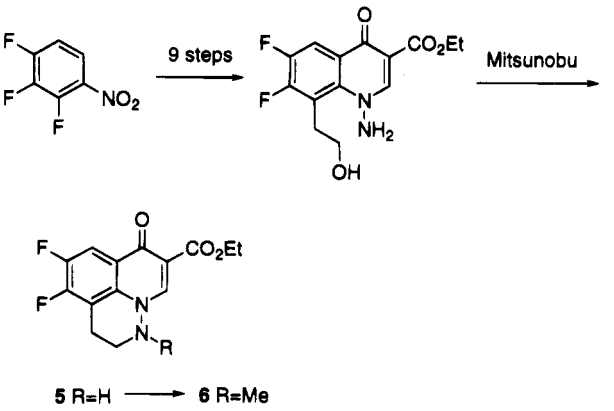
X= secondary amine

Recently, a potent new series of 1,8-bridged tricyclic quinolones **4** based on the pyrido[3,2,1-*i,j*]cinnoline ring system was disclosed, that possessed extremely potent antibacterial activity and excellent oral absorbability.[7]

Scheme 1



The synthetic approach to these compounds involved quinolone ring construction via the well-known Gould–Jacobs cyclization protocol followed by an amination at N-1 with *O*-(mesitylenesulfonyl)hydroxylamine and subsequent intramolecular Mitsunobu cyclization. *N*-Methylation of **5** with dimethyl sulfate at 120 °C then afforded the key intermediate **6** (Scheme 1).[7] For the purposes of full pharmacological and toxicological evaluation of these novel agents we required large quantities of **6**; however, the length, scaleup difficulty, and inconvenience of many of the steps involved (low yields, column purifications, protecting groups) necessitated the development of a short, efficient synthesis that would be amenable to scaleup. Herein we report the results of these studies that led to a novel intramolecular C–C bond formation approach to the tricyclic ring and produced a practical preparation of the key pyrido[3,2,1-*i,j*]-cinnolines.

Results and Discussion

We wish to disclose a novel method for the construction of key intermediate **6**, as well as the corresponding carboxylic acid, via a process that avoids the problems associated with the Mitsunobu route. Our method involves an intramolecular cyclization of a suitably tethered malonate derivative followed by a hydrolysis and double decarboxylation. Our route, shown in Scheme 2, relied upon Michael addition of the weakly basic amino group of readily available 1-(methylamino)quinolone[8,10] (**7**) with di-*tert*-butyl methylenemalonate[9] (**8**), followed by base-mediated cyclization.

The low nucleophilicity[10] of the secondary amino group of **7** was clearly demonstrated by the complete failure of the reaction with **8** at reflux in 1,2-dichloroethane. Addition of various bases (Et_3N, K_2CO_3, DBN, KF) in a variety of solvents (CH_2Cl_2, $ClCH_2CH_2Cl$, DMF, DMSO) led to complex mixtures composed of starting materials, desired monoadduct **9**, the bis-adduct **10**[11] and, at higher temperatures (60–100 °C), small amounts of the desired tricycle **11**. The best alkaline conditions we could find

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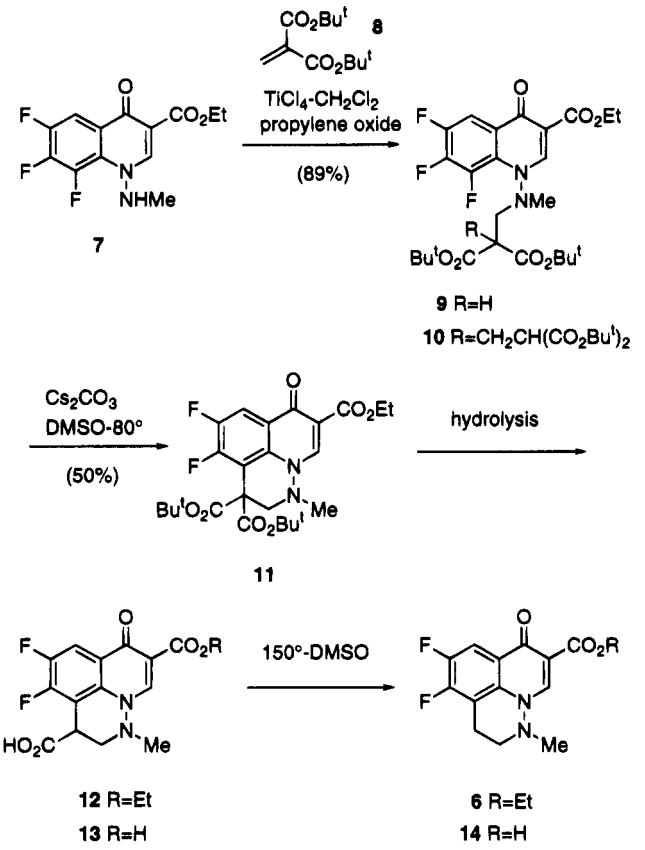
(1) Hooper, D. C.; Wolfson, J. S. *N. Eng. J. Med.* **1991**, *324*, 384.
(2) Lesher, G. Y.; Froelich, E. J.; Gruett, M. D.; Bailey, J. H.; Brundage, R. P. *J. Med. Chem.* **1962**, *5*, 1063.
(3) Chu, D. T. W.; Fernandes, P. B. Recent Developments in the Field of Quinolone Antibacterial Agents. In *Advances in Drug Research*; Testa, B., Ed.; Academic Press: New York, 1991; Vol. 21, pp 39–144.
(4) Hayakawa, I.; Hiramitsu, T.; Tanaka, Y. *Chem. Pharm. Bull.* **1984**, *32*, 4907.
(5) Cecchetti, V.; Fravolini, A.; Fringuelli, R.; Mascellani, G.; Pagella, P.; Palmioli, M.; Segre, G.; Terni, P. *J. Med. Chem.* **1987**, *30*, 465.
(6) Stilwell, G.; Holmes, K.; Turck, M. *Antimicrob. Agents Chemother.* **1975**, *7*, 483.
(7) (a) Yazaki, A. Abstracts of the Tenth Synthetic Organic Chemistry Symposium (SOCS-10), Oct 20–21, 1993, Hiroshima, Japan; pp 41–44. (b) Yokomoto, M.; Yazaki, A.; Hayashi, N.; Hatono, S.; Inoue, S.; Kuramoto, Y. European Patent EP 0470578, 1992. (c) For example, the compound with the 3-amino-4-methyl pyrrolidine side chain showed 8 times greater activity against *P. aeruginosa* compared to ofloxacin.
(8) (a) Anon. *Res. Discl.* **1988**, *291*, 548. *Chem. Abstr.* **1988**, *109*, 211018u. (b) We prepared this amine by reaction of 1-(*tert*-butoxycarbonyl)-1-methylhydrazine with ethyl 2-(2,3,4,5-tetrafluorobenzoyl)-3-ethoxyacrylate followed by cyclization and hydrolysis. See Chu, D. T. W. *J. Heterocycl. Chem.* **1985**, *22*, 1033 for a related process.
(9) (a) Baar, M. R.; Ballesteros, P.; Roberts, B. W. *Tetrahedron Lett.* **1986**, *27*, 2083. (b) Ballesteros, P.; Roberts, B. W.; Wong, J. *J. Org. Chem.* **1983**, *48*, 3603.
(10) Wentland, M. P.; Bailey, D. M.; Cornett, J. B.; Dobson, R. A.; Powles, R. G.; Wagner, R. B. *J. Med. Chem.* **1984**, *27*, 1103.

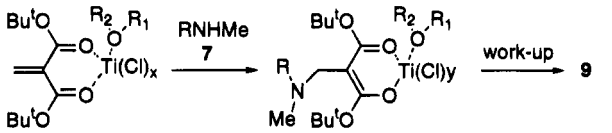
0022-3263/95/1960-3928$09.00/0

Scheme 2



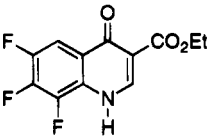
involved treatment with potassium *tert*-butoxide in THF at 0 °C. A 48% yield of **9** was obtained; however, this reaction proved to be somewhat capricious due to the instability of the olefin **8** toward basic reagents and led us to abandon alkaline conditions for this coupling.

Lewis acid-mediated reactions proved to be much more successful. Although no addition occurred using $ZnCl_2$, $MgBr_2$, $MgCl_2$, $BF_3{\cdot}Et_2O$, or $Ti(OEt)_4$ in dichloromethane, smooth Michael addition occurred using the following Lewis acids: $ZnBr_2$ (23%), $SnCl_4$ (43%), $ClTi(OPr^i)_3$ (50%), $TiCl_4$ (55%). In the case of chlorotitanium triisopropoxide, the 3-ethyl ester group was concomitantly transesterified to the corresponding isopropyl ester; use of $Ti(OPr^i)_4$ afforded only transesterification of the starting quinolone **7**. Although use of titanium tetrachloride (0 °C, CH_2Cl_2, 30 min) afforded a 55% yield of **9**, we were surprised to find that extended reaction times, intended to drive the reaction to completion, led to complete disappearance of the product and recovery of the amine **7**.[12] Speculating that a deactivated $TiCl_4$ reagent[13,14] may allow isolation of high yields of product due to suppression of the retro-reaction, we investigated the effect of additives with Lewis basic properties on this Michael reaction. While addition of 1 mol equiv of pyridine completely suppressed reaction, we were encouraged to find that 1.5 equiv of the proton scavenger Amylene (2-methyl-2-butene) led to a 30% isolated yield of **9** along with 49% of recovered **7** (48 h, rt). Better results were obtained when 1 equiv of THF was included (76% isolated yield); however, the optimum additive was the well known acid scavenger propylene oxide. Simply pretreating an ice-cooled solution of **7** and propylene oxide (1 equiv) in dichloromethane with $TiCl_4$ (1 equiv) followed by the olefin **8** (1.5 equiv), led after 20 h at room temperature to *essentially pure* **9** *in 89% isolated yield.* At this stage we cannot emphatically explain the role of the additive in this Michael reaction; however, the presumed activated olefin species **15** is clearly deactivated compared to the additive-free case as evidenced by the time required for complete reaction (20 h vs 30 min). This would tend to suggest a role for propylene oxide as a ligand for titanium in addition to a possible role as an acid scavenger. We propose that the presumed product complex **16** is significantly more stable compared to the additive-free case and this prevents reversion to the amine **7**. In the propylene oxide case, reaction between the $TiCl_4$ and epoxide to give a chlorohydrin–titanium alkoxide species[14] may be ruled out since no transesterification of the ethyl ester group was observed.



15 16

Cyclization of **9** to **11** could be effected by a number of different bases ($NaHCO_3$, K_2CO_3, KF, $KOBu^t$) in polar, aprotic solvents (*N*-methylpyrrolidinone, DMF, dimethylacetamide, DMSO) at elevated temperatures (60–90 °C). Optimum conditions involved exposure of a mixture of **9** and cesium carbonate (0.5 equiv) in dry DMSO at 80 °C for 4 h. Under these conditions **11** was isolated in 50% yield.[15] Varying amounts (5–20%) of the N–N bond cleavage product **17**[16] were also obtained although it was readily removed by crystallization. Although in this reaction the isolated yield is only moderate, HPLC monitoring indicated **11** and **17** as the only observable products, after disappearance of starting material, suggesting a clean process. The ease of isolation and scaleup, however, made this a very practical process for the preparation of large quantities of **11**.[17]



17

Clearly, the well-known tendency of 6,7,8-trifluoroquinolones to undergo 7-fluoro displacement in intermolecular nucleophilic substitution reactions has been overcome by suitable tethering of the nucleophile. Such a process

(11) Data for **10**: ^1H NMR ($CDCl_3$) δ 8.63 (s, 1H), 8.12 (ddd, J = 2.2, 8.2, 10.1 Hz, 1H), 4.39 (q, J = 7 Hz, 2H), 3.61 (s, 2H), 3.13 (t, J = 6 Hz, 1H), 3.02 (s, 3H), 2.51 (d, J = 6 Hz, 2H), 1.47 (s, 9H), 1.44 (t, J = 7 Hz, 3H), 1.42 (s, 9H), 1.41 (s, 9H), 1.33 (s, 9H). FAB MS m/z 757 ($M^+ + H$).

(12) Reaction at 0 °C for 30 min followed by 18 h at rt led after workup only to starting amine **7**.

(13) For the use of $TiCl_4$–XPh_3 (X = P, As, Sb) see (a) Palazzi, C.; Colombo, L.; Gennari, C. *Tetrahedron Lett.* **1986**, *27*, 1735. (b) Suzuki, I.; Yamamoto, Y. *J. Org. Chem.* **1993**, *58*, 4783. (c) Kadota, I.; Miura, K.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 1953.

(14) For the use of $TiCl_4$–DBU in the ring opening of some epoxides see, Spawn, C.-L.; Drtina, G. J.; Wiemer, D. F. *Synthesis* **1986**, 315. The $TiCl_4$–*N*-methylaniline combination is effective in the [3 + 2] cycloaddition of some allylic alcohols, see Ipaktschi, J.; Lauterbach, G. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 354.

(15) The 8-methyl ester was obtained in 57% yield under analogous conditions from the corresponding malonate.

(16) Irikura, T., Koga, H., Murayama, S. Belg. Pat. BE 887574, 1981.

has been reported previously with heteroatom nucleophiles[18,19] but this is the first case to our knowledge involving carbon–carbon bond formation. Elaboration of the tricycle **11** to the target ester **6** was accomplished in good yield by two different procedures. Nonaqueous hydrolysis using TFA at 65 °C yielded acid **12** in 94% yield. Decarboxylation at 150 °C in DMSO then gave ester **6** in 63% yield. Alternatively, acid **13** was produced directly using 6 N HCl in acetic acid at reflux (86%). Chemoselective monodecarboxylation at 150 °C then gave the acid **14** (83% in DMF, 82% in DMSO). Isolation involved simply pouring into water and filtration. Conversion to the ethyl ester was accomplished under standard conditions (K_2CO_3, EtI, DMF, 75 °C, 1.5 h, 94%). Conversion of **6** to potent antibacterial agents via selective displacement of the 4-fluorine atom with amines and ester hydrolysis occurs readily and will be the subject of future publications.

In conclusion, we have developed a concise, efficient process for the preparation of the pyrido[3,2,1-*i,j*]cinnoline system of potent new DNA gyrase inhibitors that enables preparation of large quantities of the key intermediates. Critical to the success of this route was the propylene oxide-modulated $TiCl_4$-mediated Michael reaction between amine **7** and the versatile di-*tert*-butyl methylenemalonate (**8**).

Experimental Section

All melting points are uncorrected. NMR spectra were measured at: ^1H, 200 MHz, ^{13}C, 50.3 MHz. Mass spectra were measured using EI or FAB for ionization.

Ethyl 1-[N-{2,2-Bis(*tert*-butoxycarbonyl)ethyl}-N-methylamino]-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (9). To a solution of quinolone **7** (5.00 g, 16.7 mmol) and propylene oxide (1.17 mL, 16.7 mmol) in CH_2Cl_2 (50 mL) at 5 °C was added 1 M $TiCl_4$ in CH_2Cl_2 (16.7 mL) dropwise. After a further 10 min, olefin **8** (5.70 g, 25.0 mmol) was added as neat liquid. After 10 min at 5 °C and 20 h at rt, extractive workup using ethyl acetate provided a solid residue that was triturated with hexane to yield analytically pure **9** (7.80 g, 89%) as an off-white solid: mp 112–115 °C; ^1H NMR ($CDCl_3$) δ 8.63 (s, 1H), 8.10 (ddd, J = 2.2, 8.2, 10.2 Hz, 1H), 4.41 (q, J = 7.1 Hz, 2H), 3.71–3.50 (m, 2H), 3.25 (t, J = 7.1 Hz, 1H), 3.01 (s, 3H), 1.45 (s, 9H), 1.41 (t, J = 7.1 Hz, 3H), 1.38 (s, 9H); IR (KBr) 1745, 1730, 1701 cm^{-1}; MS m/z 528 (M^+). Anal. Calcd for $C_{25}H_{31}F_3N_2O_7$: C, 56.81; H, 5.91; N, 5.30. Found: C, 57.20; H, 6.18; N, 5.30.

Ethyl 3,3-Bis(*tert*-butoxycarbonyl)-4,5-difluoro-2,3-dihydro-1-methyl-7-oxo-1*H*,7*H*-pyrido[3,2,1-*i,j*]cinnoline-8-carboxylate (11). A solution of malonate **9** (3.26 g, 6.17 mmol) in DMSO (33 mL) was treated with Cs_2CO_3 (1.00 g, 3.08 mmol), and the mixture was heated at 80 °C for 4 h. Extractive workup using ethyl acetate yielded an amorphous solid. Addition of CH_2Cl_2 and filtration yielded the byproduct **17**[16] (300 mg, 18%): mp 260–267 °C: ^1H NMR (DMSO-d_6) δ 12.77 (br s, 1H), 8.62 (s, 1H), 7.86 (ddd, J = 2.3, 8.0, 10.4 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H); MS m/z 271 (M^+). Evaporation of the filtrate and purification by SiO_2 chromatography (CH_2Cl_2–EtOAc, 5:1) yielded **11** (1.58 g, 50%). mp 175–177 °C; ^1H NMR ($CDCl_3$) δ 8.55 (s, 1H), 8.29 (dd, J = 8.4, 10.2 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 4.07 (s, 2H), 2.78 (s, 3H), 1.48 (s, 18H), 1.37 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) 172.4, 166.3, 164.7, 152.2 (dd, J = 259, 15.8 Hz), 148.8 (dd, J = 251, 14.2 Hz), 147.2, 129.4 (d, J = 6.1 Hz), 125.4, 115.5 (d, J = 18.8 Hz), 112.2 (d, J = 16.2 Hz), 110.7, 84.4, 61.1, 55.8, 52.6, 45.7, 27.6, 14.4; IR (KBr) 1737, 1693, 1608 cm^{-1}; MS m/z 508 (M^+). Anal. Calcd for $C_{25}H_{30}F_2N_2O_7$: C, 59.05; H, 5.95; N, 5.51. Found: C, 59.37; H, 6.11; N, 5.41.

4,5-Difluoro-2,3-dihydro-1-methyl-7-oxo-8-(ethoxycarbonyl)-1*H*,7*H*-pyrido[3,2,1-*i,j*]cinnoline-3-carboxylic Acid (12). A solution of tricycle **11** (2.00 g, 3.93 mmol) in TFA (4 mL) was heated at 65 °C for 3 h and then allowed to stand at rt overnight and poured into isopropyl ether (iPE)(100 mL). The precipitate was removed by filtration and washed with iPE–hexane to give acid **12** (1.30 g, 94%) as an analytically pure white solid: mp 209–210 °C; ^1H NMR (DMSO-d_6) δ 13.35 (br s, 1H), 8.53 (s, 1H), 8.07 (dd, J = 8.6, 10.6 Hz, 1H), 4.30 (t, J = 5.6 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.84–3.70 (m, 2H), 2.82 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H); IR (KBr) 1728, 1622 cm^{-1}; MS m/z 352 (M^+). Anal. Calcd for $C_{16}H_{14}F_2N_2O_5$: C, 54.55; H, 4.00; N, 7.95. Found: C, 54.19; H, 3.97; N, 7.71.

Ethyl 4,5-Difluoro-2,3-dihydro-1-methyl-7-oxo-1*H*,7*H*-pyrido[3,2,1-*i,j*]cinnoline-8-carboxylate (6). A solution of acid **12** (1.00 g, 2.84 mmol) in DMSO (10 mL) was heated to 135–165 °C for 5.5 h and then cooled to rt. Extractive workup using ethyl acetate followed by trituration with Et_2O–hexane gave analytically pure ester **6** (550 mg, 63%) as an off-white solid: mp 220–224 °C; ^1H NMR (DMSO-d_6) δ 8.53 (s, 1H), 7.95 (dd, J = 8.8, 10.9 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.48 (t, J = 6 Hz, 2H), 3.06 (t, J = 6 Hz, 2H), 2.81 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H); IR (KBr) 1726 cm^{-1}; MS m/z 308 (M^+). Anal. Calcd for $C_{15}H_{14}F_2N_2O_3 \cdot 0.1H_2O$: C, 58.10; H, 4.62; N, 9.03. Found: C, 57.73; H, 4.45; N, 8.71.

4,5-Difluoro-2,3-dihydro-1-methyl-7-oxo-1*H*,7*H*-pyrido-[3,2,1-*i,j*]cinnoline-3,8-dicarboxylic Acid (13). A solution of the tricycle **11** (1.52 g, 2.99 mmol) in AcOH (7.6 mL) was treated with 6 N HCl (7.6 mL) and warmed to reflux. After 4 h the solution was cooled to rt and poured into water (90 mL). The white precipitate was filtered, washed thoroughly with water, and dried to yield the diacid **13** (833 mg, 86%) as an analytically pure solid: mp 235–237 °C; ^1H NMR (DMSO-d_6) δ 14.68 (br s, 1H), 13.49 (br s, 1H), 8.83 (s, 1H), 8.31 (dd, J = 8.6, 10.3 Hz, 1H), 4.40 (t, J = 6 Hz, 1H), 3.85 (d, J = 6Hz, 2H), 2.89 (s, 3H); IR (KBr) 1732, 1705, 1622 cm^{-1}; MS m/z 324 (M^+). Anal. Calcd for $C_{14}H_{10}F_2N_2O_5 \cdot H_2O$: C, 49.13; H, 3.53; N, 8.18. Found: C, 49.01; H, 3.72; N, 8.09.

4,5-Difluoro-2,3-dihydro-1-methyl-7-oxo-1*H*,7*H*-pyrido-[3,2,1-*i,j*]cinnoline-8-carboxylic Acid (14). A solution of the diacid **13** (775 mg, 2.39 mmol) in DMSO (15.5 mL) was placed in a preheated oil bath at 150 °C for 30 min and then cooled to rt and poured into water (150 mL). The precipitate was filtered, washed with water, and dried to yield analytically pure acid **14** (550 mg, 82%): mp 261–263 °C; ^1H NMR (DMSO-d_6) δ 14.80 (br s, 1H), 8.82 (s, 1H), 8.17 (dd, J = 8.5, 10.5 Hz, 1H), 3.54 (t, J = 6 Hz, 2H), 3.14 (t, J = 6Hz, 2H), 2.89 (s, 3H); IR (KBr) 1709, 1622 cm^{-1}; MS m/z 280 (M^+). Anal. Calcd for $C_{13}H_{10}F_2N_2O_3$: C, 55.72; H, 3.60; N, 10.00. Found: C, 55.45; H, 3.52; N, 10.00.

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(17) Concerning the pathway for formation of the cleavage product **17**, HPLC analysis revealed the intermediacy of the amine **7** in the early stages of the reaction, but this was gradually replaced by the quinolone **17**, suggesting a competing retro-Michael process as the source of moderate yields. In a control experiment, the amine **7** was almost completely degraded by exposure to the cyclization reaction conditions, indicating the weakness of the N–N bond.

(18) For intramolecular alkoxy anion cyclizations see (a) Dax, S. L.; Wei, C.-C. *J. Org. Chem.* **1992**, *57*, 744. (b) Kiely, J. S., Schroeder, M. C., Sosnie, J. C. *J. Med. Chem.* **1988**, *31*, 2004.

(19) For a thiolate cyclization see, Okada, T., Tsuji, T., Tsushima, T., Ezumi, K., Yoshida, T., Matsuura, S. *J. Heterocycl. Chem.* **1991**, *28*, 1067.