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Synthesis of New 1,8-Bridged Tricyclic Quinolones by a Novel Intramolecular Arylation of N-1 Tethered Malonamides

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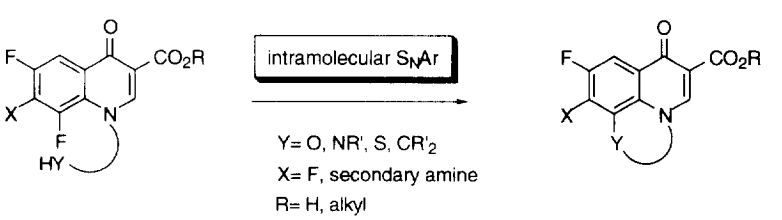
Abstract: An efficient process for the preparation of 2,7-dioxopyrido[3,2,1-*i,j*]cinnolines by a novel intramolecular arylation reaction of N-1 tethered quinolone malonamides is described. The application of this methodology to the synthesis of some novel tricyclic quinolones as potential antibacterial agents is reported.

INTRODUCTION

Recently, interest in compounds bearing a quinolone-type structure, examples of which are extremely potent inhibitors of the bacterial enzyme DNA gyrase[1] as well as the mammalian counterpart, topoisomerase II[2], has been broadened due to potential efficacy in a number of other areas of pharmaceutical interest. The 4-oxoquinoline skeleton is a suitable core from which to design potentially important anticancer[3], antifungal[4], and antiviral agents[5], as well as cell adhesion inhibitors[6] and interleukin-1 release inhibitors.[7] Accordingly, there is a continuing need to construct structurally unique skeletal types and to develop synthetic methods that have the potential to be generally applicable to a variety of ring systems.[8]

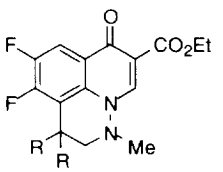
In the 1,8-bridged quinolone series, a particularly effective general method of synthesis involves an intramolecular nucleophilic substitution by an N-1 tethered nucleophile Y, with displacement of, most commonly, a fluorine atom, to generate the third ring (Scheme 1). Whilst heteroatom nucleophiles such as amino[9], alkoxide[10], and thiolate[11] work well in this cyclization, the use of carbanions was unknown until recently. Indeed, the only report, prior to our work, of an N-1 tethered carbanion indicated a preference to

Scheme 1

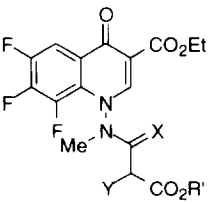


cyclize exclusively to C-2 in a Michael fashion with formation of a 6-membered ring.[12] Clearly it is not obvious that a particular tethered carbanion will cyclize in the desired manner to generate the 1,8-bridged tricycle. We are particularly interested in the factors that govern the selectivity for C-8 versus C-2 cyclization in systems of this kind (hard *versus* soft anions etc).

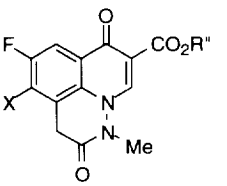
In our recent synthesis[13] of tricyclic quinolone **1**, a key intermediate for the preparation of the pyrido[3,2,1-*i,j*]cinnoline class of potent bacterial DNA gyrase inhibitors[14], we reported the first example of an intramolecular anionic cyclization to the 8-position of 6,7,8-trifluoroquinolones by an N-1 tethered carbon-centered nucleophile. Thus, malonate **3** underwent cyclization in the presence of base to give tricyclic quinolone **2**. To expand the range of suitable carbon-centered nucleophiles in this cyclization with a view to developing efficient synthetic procedures towards novel quinolones is one of the goals of our research. In this paper, we wish to disclose a second example of the afore-mentioned cyclization, namely of the malonamide derivatives **4**, and its application to the synthesis of the novel tricyclic quinolone derivatives **5**, as potential antibacterial agents.



1 R=H
2 R=CO_2Bu^t



3 X=H_2, Y=CO_2Bu^t, R'=Bu^t
4 X=O, Y=H, R'=alkyl, aryl(alkyl)



5 X=amines, F
R"=H, Et

RESULTS AND DISCUSSION

Our interest in compounds of the type **5** arose from a need to explore the structure-activity relationships in the pyrido[3,2,1-*i,j*]cinnoline series in order to investigate the role of conformation of the 1,8-bridging moiety on the biological activity. It was expected that the additional carbonyl group would induce a nearly planar arrangement to the tricyclic ring system, leading to a different and possibly improved biological profile. Additionally, since it is well known that the antibacterial activity and affinity for DNA gyrase are influenced markedly by the steric nature of the N-1 substituent[15], and that some sub-sets of the quinolones are especially toxic due to topoisomerase II inhibition[2], we wished to explore the structure-toxicity relationships within this series.

Our retrosynthetic analysis of these compounds was modeled on our earlier work,[13] and envisaged an intramolecular arylation[16] of a malonamide of the type **4**, followed by hydrolysis and spontaneous decarboxylation. Scheme 2 summarizes the results obtained. Preparation of the cyclization precursors **4** from the amine **6**[13] proceeded smoothly under a variety of conditions. Reaction of the malonic acid half-esters (prepared from Meldrum's acid and the requisite alcohol) with **6** under carbodiimide-mediated coupling conditions produced the derivatives **4b** and **4c** in 45% and 68% yields respectively. Alternatively, the corresponding acid chlorides could be optimally coupled using 1,3-bis (trimethylsilyl) urea as base.[17] The malonamides **4a** and **4b** were thus obtained in 95% and 94% yields respectively.

Preliminary experiments on the cyclization reaction were performed on the ethyl ester **4a** in order to identify the optimal conditions. Exposure of **4a** to a single equivalent of NaH in DMF solution at 100°C for 5hr provided the tricycle **7a** in 31% yield, along with recovered starting material. Since the product has a very acidic proton, it was clear that the failure of the reaction to proceed to completion was related to a competing proton transfer from the product to the starting anion. Increasing to two equivalents gave a 58% yield of **7a**. Reaction solvent was important, since the corresponding reactions in DMI, pyridine, 1,4-dioxane and DMSO gave lower yields (32-43%). In the displacement of aryl halides by malonate-like anions, the beneficial effect of copper salts is well known[18], accordingly the effect on this intramolecular cyclization was examined. For the cyclization of **4a** as the sodium salt, a 57% yield was obtained, indicating no effect, whilst the corresponding potassium salt gave an essentially quantitative conversion when 20 mol% of CuI was included in the reaction in DMSO at 100°C. The allyl ester **4b** and the diphenyl ester **4c** also underwent smooth cyclization under these conditions, however in all three cases, it was difficult to obtain material that was completely free of copper.[19]

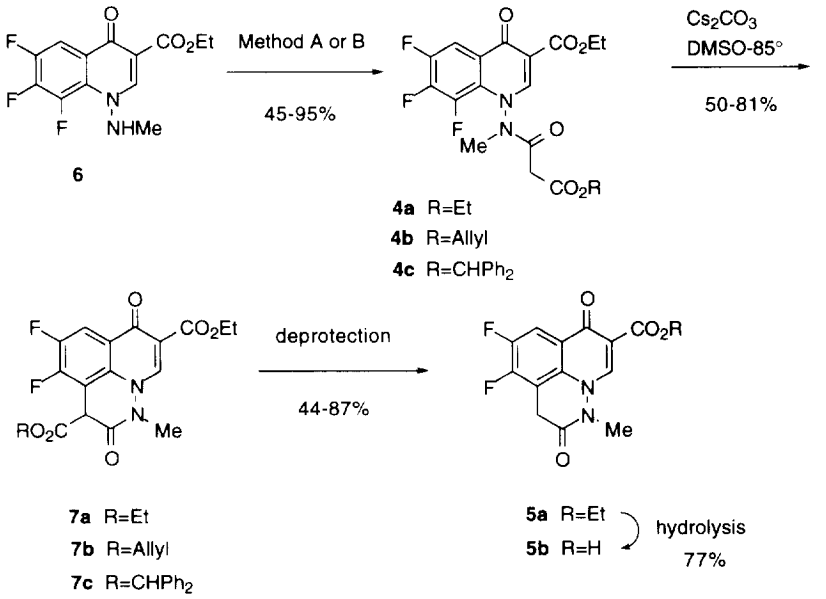
The best conditions from the point of view of operational simplicity, ease of work-up, and product purity were essentially the same as reported in our earlier work.[13] Treatment of the malonamides **4a-c** with 1.1 equivalents of Cs_2CO_3 in DMSO at 85° for 0.5-1hrs followed by AcOH quench and addition of water, gave after filtration, drying and crystallization, *analytically pure* tricyclic malonamide derivatives **7a**, **7b**, **7c** in 50%, 68%, 81% yields respectively. ^1H NMR clearly indicated the tricyclic nature of the products in these reactions. The C3-methine proton of **7a-c** appeared as a singlet at δ 5.37-5.58 ppm, whilst the C6-aromatic proton appeared as a dd at δ 8.11-8.13 ppm (J = 8.3-8.4, 10.3-10.4 Hz), clearly indicating substitution at C8. ^{13}C NMR of **7a** also supported the tricyclic structure: the C4- and C5-carbons appeared as double-doublets due to coupling with the C4- and C5-fluorine atoms and the C3-methine carbon appeared as a singlet at δ 45.2 ppm. Whilst the intramolecular cyclization of the malonate **3** suffered from a competing retro-Michael process[13], in part due to the severe steric constraints associated with the generation of a quaternary center, the derivatives **4** were not susceptible to a competing process and this is reflected in the superior yields.

The utility of the novel tricycles **7a-c** for the synthesis of potentially useful quinolone antibacterial precursors **5a-b** was readily demonstrated. Direct conversion of **7a** and **7b** to acid **5b** was achieved in 80% and 87% yields, respectively (c.HCl-AcOH-reflux). Alternatively, chemoselective hydrolysis of the 3-ethyl ester group of **7a** could be achieved using refluxing TFA containing a trace of water. In this way, ethyl ester **5a** was obtained in 44% yield. We also examined the classical Krapcho conditions[20] with **7a** (NaCl-H_2O-DMSO-140°C; H_2O-DMSO-140°C), but could only obtain tar-like materials that contained only trace quantities of **5a**. Ester **5a** was alternatively produced from diphenyl ester **7c** in 81% yield using TFA, or from allyl ester **7b** in 58% yield using a palladium-catalyzed deprotection.[21]

Since carboxylic acid **5b** was devoid of antibacterial activity we decided to explore the incorporation of amine substituents at C4 since it is well known that such a substitution has a marked effect on the antibacterial efficacy of quinolones[15b] due to a combination of improved DNA gyrase affinity and enhanced cellular penetration. Unfortunately, we were unable to effect coupling of **5a** or **5b** with typical secondary amines, such as piperazine, N-methyl piperazine, BOC-piperazine, and pyrrolidine in polar solvents (CH_3CN, DMF, DMSO) at 80-120°C. We believe that the failure of these reactions is related to the acidic nature of the methylene group adjacent to the phenyl ring leading to deactivation of the 4-fluoro atom towards substitution via deprotonation, and to possible lability of the N-N bond[13] and/or amide moiety. It was clear to us that in

order to prepare our target compounds we would have to incorporate the amine moiety before intramolecular cyclization. Such a process offered a test of the generality of this novel cyclization since the retarding effect of a 7-amino substituent on intramolecular cyclization of alkoxides has been reported previously.[10a,22]

Scheme 2



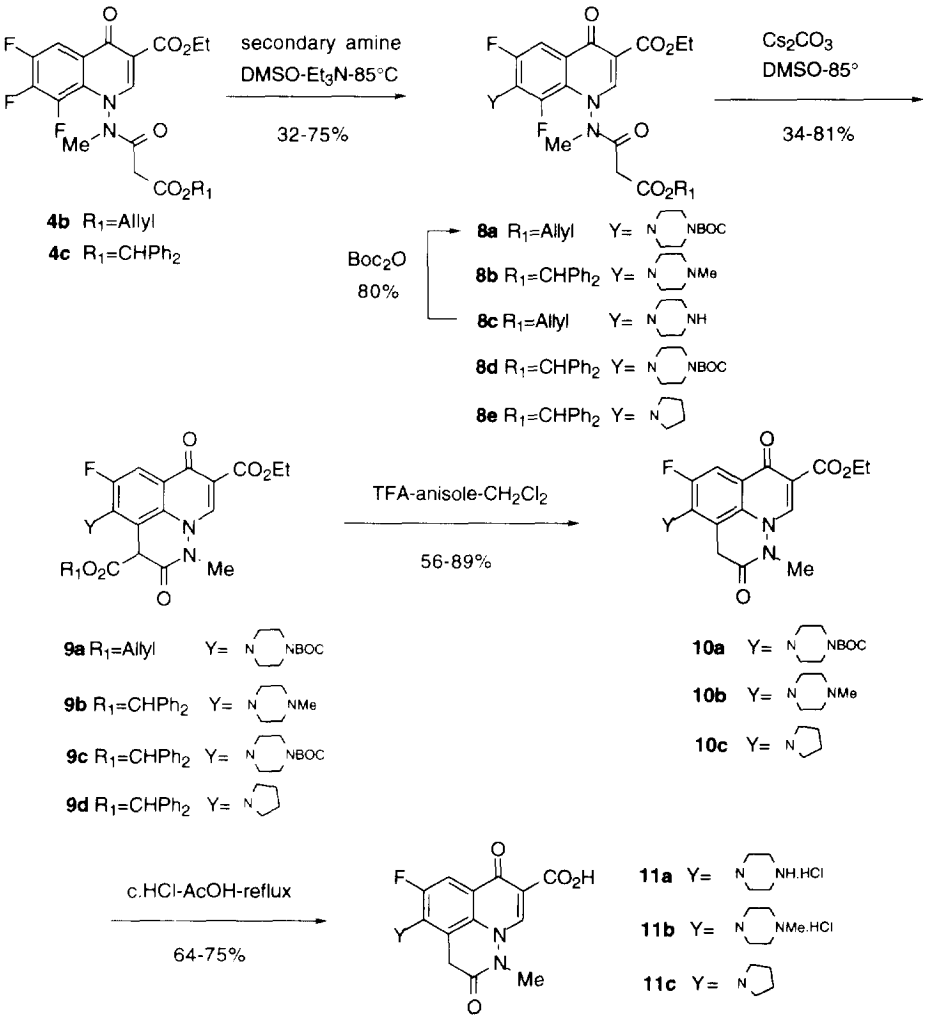
The results summarized in Scheme 3 indicate that this reaction can perform well, and can be applied to the synthesis of novel antibacterial agents. Preparation of the C-7 substituted 6,8-difluoroquinolones **8a-e** was readily accomplished by treatment of the malonamides **4b** and **4c** with the requisite secondary amine and triethylamine in DMSO at 85°C. Thus, N-methyl piperazine derivative **8b** was obtained in 72% yield and BOC-piperazine derivative **8a** was obtained in 56% yield. An alternative preparation of **8a** involved reaction of **4b** with piperazine to give amine **8c** (75%), followed by acylation with di-*tert*-butyl dicarbonate (80%).

Whilst the simple piperazine derivative **8c** failed to afford any cyclization product upon exposure to cesium carbonate, giving intractable mixtures, we were gratified to find that the N-methyl derivative **8b** gave a 34% isolated yield of tricycle **9b**. In contrast to the previous examples, prolonged heating at 85°C was required to drive the reaction to completion indicating clearly that a 7-amino substituent lowers the reactivity of the 8-fluoro towards displacement. The C3-methine ^{1}H NMR signal for **9b** appeared at δ 5.29 ppm as a singlet; this contrasts with δ 5.37-5.58 ppm for the simple tricycles **7a-c**. Presumably the modest upfield shift is a consequence of the lower electronegativity of nitrogen versus fluorine. The BOC-piperazine derivatives **8a** and **8d** underwent cyclization under similar conditions to afford **9a** and **9c** in 51% and 80% yields respectively.

Reaction of **8a** with KO^{t}Bu-CuI in DMSO at 100°C gave a 32% isolated yield of **10a** as the only identifiable product. The higher temperature combined with the presence of iodide ion presumably leading to a Krapcho-like dealkylative hydrolysis and decarboxylation affording **10a**. Deprotection of the allyl ester of **9a** under palladium-catalyzed conditions[21] did not afford any **10a**, although it could be produced in 67% yield from tricycle **9c** by treatment with TFA followed by reacylation with di-*tert*-butyl dicarbonate. Conversion of **10a** and **10b** into potential antibacterial agents was accomplished readily by acidic hydrolysis. Compounds

11a and **11b** were thus produced in 69% and 64% yields respectively. Alternatively, ester **9a** could be exhaustively deprotected under the same conditions to give **11a** in 75% yield. The acidic nature of the C3-methylene group was clearly indicated by the lack of a signal in the ^1H NMR spectra of **11a** and **11b** in D_2O, although the corresponding signals could be observed in DMSO-d_6. We also examined the compatibility of a pyrrolidine substituent in this novel cyclization reaction, since pyrrolidine substituents are also known to be potent enhancers of antibacterial activity in quinolones.[1] Cyclization precursor **8e** was obtained by the same method used for preparation of **8a-d**. Cesium carbonate-mediated cyclization proceeded uneventfully to furnish **9d** in 78% yield. TFA-deprotection produced the tricycle **10c** in 89% yield. However, acid hydrolysis of **10c** under the standard conditions gave mixtures in which **11c** was a minor component.[23]

Scheme 3



Single Crystal X-Ray Structural Analysis of 10a

Unequivocal assignment of the tricyclic nature of the products obtained in this study was achieved by X-ray crystallographic analysis of compound **10a**. Figure 1 shows the molecular structure of **10a**. Overall, bond lengths and other geometric parameters were in general agreement with standard values. The most striking feature of this structure was the observation that the N-Me group is almost co-planar with the 4-oxoquinoline moiety. In the reported crystal structure of the related tricyclic quinolone, nadifloxacin the analogous methyl group is almost perpendicular to the quinolone ring.[24] Additionally, calculations have shown that the favored position of the methyl group in ofloxacin is similarly positioned.[15c] Since compounds **11a** and **11b** showed weak antibacterial activity,[25] indicating that the extra carbonyl group has a detrimental influence (the corresponding 2,3-tetrahydro compounds are very potent),[14] we propose that enolization of the methylene group probably leads to poor affinity for the bacterial DNA gyrase by inhibition of quinolone-quinolone self-association[1] or to poor intracellular penetration.

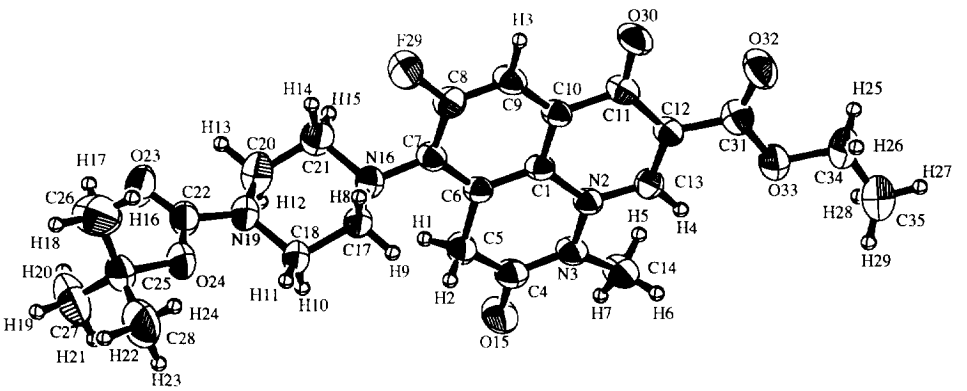
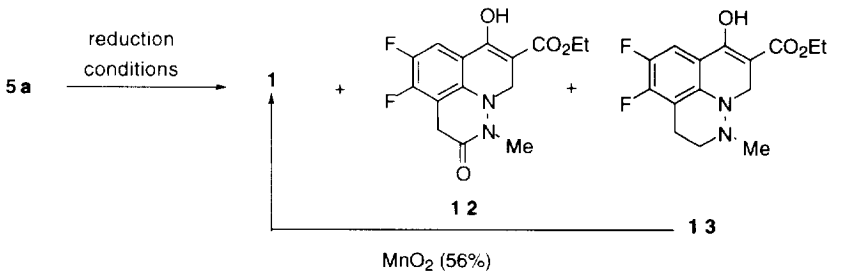


Figure 1. ORTEP drawing (41%-ellipsoids) of **10a** with crystallographic numbering scheme. Selected bond lengths (Å), bond angles (deg), and torsion angles (deg): N(2)-N(3)=1.421(4), N(3)-C(4)=1.365(4), C(4)-O(15)=1.214(4), C(4)-C(5)=1.492(6), C(5)-C(6)=1.492(5), C(7)-N(16)=1.418(4), C(8)-F(29)=1.356(4), C(12)-C(13)=1.365(5); N(2)-N(3)-C(14)=117.0(3), N(2)-N(3)-C(4)=122.6(3), N(3)-C(4)-O(15)=120.3(4), C(4)-C(5)-C(6)=115.6(4); N(3)-N(2)-C(1)-C(6)=11.3(5), C(1)-N(2)-N(3)-C(14)=163.3(4), O(15)-C(4)-N(3)-C(14)=5.2(7), C(13)-N(2)-N(3)-C(14)=-12.5(6).

We briefly examined the utility of the ester **5a** as an intermediate towards the potent pyridocinnoline class of gyrase inhibitors.[13,14] This objective required the chemoselective reduction of the 2-oxo group in the presence of the keto and ester moieties,[26] however, all of the conditions examined gave mixtures and suffered from poor mass balance and low isolated yields. We had anticipated potential problems since the doubly activated unsaturated olefin of quinolones is known to be susceptible to reduction[27] and indeed, with $NaBH_4$-THF, β-keto ester **12** was the only identifiable product (58%). We examined reaction with $NaBH_4$-TFA[28], diborane[29], $NaBH_4$-pyridine[30], and $POCl_3$-$NaBH_4$.[31] Complex mixtures containing **1** (2-10%), **12** (6-

13%), and **13** (0-13%) as well as other very minor components derived from further reactions of the β-keto ester moiety were obtained. Including an oxidation step[32] (DDQ) in the work-up procedure did not improve yields of **1**. Since control experiments[33] indicated that the olefin bond of **5a** was very reactive to reduction with $NaBH_4$ we presume that **12** is the primary product and that the lack of chemoselectivity results from poor differentiation between the reactivity of the amide and β-keto ester moieties.[34] Overall, **1** was obtained from **6** in 4 steps and a maximum yield of only 5%. This contrasts with 26% (4 steps) by our previously reported method.[13]

Scheme 4



CONCLUSIONS

In this paper we have described an efficient synthetic approach to 2,7-dioxopyrido[3,2,1-*i,j*] cinnolines by developing a second example of anionic cyclization by a soft carbon-centered nucleophile tethered to the N-1 position of a quinolone, to the C-8 position. Whilst a C-7 amino substituent has a retarding effect on the rate of cyclization in comparison to a fluoro substituent, the reaction nevertheless proceeds smoothly to give the corresponding tricyclic compound. We believe that the potential applications of this novel cyclization in the quinolone area for the design and synthesis of novel agents of pharmaceutical interest make it a useful addition to the methodology for constructing multiple ring systems. These results, coupled with earlier reports[12,13] suggest that hard carbanions cyclize exclusively to C-2 whilst soft carbanions cyclize only to C-8,[35] leading to an interesting dichotomy. We are currently extending this cyclization methodology to other skeletal types.

EXPERIMENTAL SECTION

All melting points were measured on a Thomas-Hoover apparatus and are uncorrected. IR spectra were recorded on a Horiba Spectradesk FT-210 or a Hitachi IR-408 spectrometer. NMR spectra were measured on a Brucker AC200P (^1H, 200 MHz, ^{13}C, 50.3 MHz). Chemical shifts are given in parts per million, and tetramethylsilane was used as the internal standard for spectra obtained in DMSO-d_6, $CDCl_3$, and CF_3CO_2D. DSS was used for spectra run in D_2O. Mass spectra were measured on a Hitachi Model M-80 mass spectrometer using EI for ionization. Elemental analyses were carried out on a Perkin Elmer 2400 CHN Elemental Analyzer. Reagents and solvents were used as obtained from commercial suppliers without further purification. Column chromatography was performed using silica-gel, and the progress of reactions was

determined by tlc analysis on silica-gel coated glass plates. Preparative tlc (PTLC) was performed using Merck kieselgel 60 F_{254} coated glass plates.

General Procedures for Preparation of Malonamides 4. Method A: To a solution of amine **6** (27.45 g, 91.43 mmol) in CH_2Cl_2 (275 mL) was added 1,3-bis(trimethylsilyl)urea (10.28 g, 50.29 mmol) and the mixture stirred at ambient temperature for 30 minutes. Ethyl malonyl chloride (12.81 mL, 115.8 mmol) was added and the mixture stirred 2 hours. CH_2Cl_2 was added and the solution washed with water, saturated sodium hydrogen carbonate solution and brine, dried ($MgSO_4$), evaporated and the residue crystallized from Me_2CO-isopropyl ether(iPE) to give 35.89 g (95%) of **4a** as a white solid.

Ethyl 1-{N-(Ethoxycarbonyl)acetyl-N-methylamino}-6,7,8-trifluoro-1,4-dihydro-4-oxo quinoline-3-carboxylate (4a). mp 149-151°C; ^{1}H NMR (DMSO-d_6)(3:2 mixture of amide rotational isomers) δ 8.81 (s, 0.6H), 8.72 (s, 0.4H), 8.05-7.96 (m, 1H), 4.26, 4.25, 4.15, 3.98 (each q, 4H total, J = 7.1 Hz), 3.83 and 3.74 (each d, 1.2H, AB system, J = 16.5 Hz), 3.59 (s, 1.8H), 3.52 and 3.43 (each d, 0.8H, AB system, J = 10 Hz), 3.37 (s, 1.2H), 1.29, 1.26, 1.22, 1.11 (each t, 6H total, J = 7.1 Hz). IR(KBr) 1745, 1736, 1709, 1689, 1655, 1628 cm^{-1}; MS *m/z* 415 (MH^+); Anal. Calcd for $C_{18}H_{17}F_3N_2O_6$: C, 52.18 ; H, 4.13 ; N, 6.76. Found: C, 52.01; H, 3.96 ; N, 6.73%.

Method B: To a solution of amine **6** (3.00 g, 9.99 mmol) and malonic acid monodiphenylmethyl ester (2.70 g, 9.99 mmol) in CH_2Cl_2 (60 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.30 g, 12.00 mmol) under ice-cooling. After 30 minutes at 0-5°C and 1 hour at room temperature the mixture was poured into water (60 mL). The organic layer was washed with water (60 mL), saturated sodium chloride solution (60 mL), dried ($MgSO_4$), evaporated, and the crude product purified by silica-gel chromatography (50 g, 99:1 $CHCl_3$-MeOH elution) and crystallized from Me_2CO-iPE-hexane to give 3.73 g (68%) of **4c** as a white powder.

Ethyl 1-{N-(Diphenylmethyloxycarbonyl)acetyl-N-methylamino}-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (4c). mp 160-161°C; ^{1}H NMR (DMSO-d_6)(3:2 mixture of amide rotational isomers) δ 8.85 (s, 0.4H), 8.73 (s, 0.6H), 8.05-7.96 (m, 1H), 7.43-7.25 (m, 10H), 6.88 (s, 0.6H), 6.75 (s, 0.4H), 4.26 and 4.23 (each q, 2H total, J = 7.1 and 7.1 Hz), 4.07 and 3.91 (each d, 1.2H total, AB system, J = 16.2 Hz), 3.70 (s, 0.8H), 3.60 and 3.44 (each s, 3H total), 1.28 (t, 3H, J = 7.1 Hz). IR (KBr) 1739, 1699, 1658, 1630 cm^{-1}; MS *m/z* 553 (MH^+); Anal. Calcd for $C_{29}H_{23}F_3N_2O_6$: C, 63.04 ; H, 4.20 ; N, 5.07. Found: C, 62.70 ; H, 4.07 ; N, 4.99%.

Ethyl 1-{N-(Allyloxycarbonyl)acetyl-N-methylamino}-6,7,8-trifluoro-1,4-dihydro-4-oxo quinoline-3-carboxylate (4b). Method A: Yield: 8.01 g (94%). Method B: Yield: 320 mg (45%) as a white powder. mp 124-126°C; ^{1}H NMR (DMSO-d_6) (3:2 mixture of amide rotational isomers) δ 8.83 (s, 0.6H), 8.73 (s, 0.4H), 8.07-7.97 (m, 1H), 6.00-5.72 (m, 1H), 5.41-5.15 (m, 2H), 4.66-4.63 (m, 1.2H), 4.50-4.48 (m, 0.8H), 4.26 and 4.25 (each q, 2H total, J = 7.1 and 7.1 Hz), 3.91 and 3.80 (each d, 1.2H total, AB system, J = 16.1 Hz), 3.60 (s, 1.8H), 3.58 and 3.52 (each d, 0.8H total, AB system, J = 16.1 Hz), 3.37 (s, 1.2H), 1.29 (t, 3H, J = 7.1 Hz); IR(KBr) 1747, 1734, 1709, 1687, 1655, 1626 cm^{-1}; MS *m/z* 427 (MH^+); Anal. Calcd for $C_{19}H_{17}F_3N_2O_6$: C, 53.53 ; H, 4.02 ; N, 6.57. Found: C, 53.28; H, 3.78 ; N, 6.49%.

General Procedure for Preparation of Malonamides 8a-e. A solution of malonamide **4b** (1.84 g, 4.32 mmol) in DMSO (18 mL) was treated with Et_3N (1.31 g, 13.0 mmol) and 1-*tert*-butoxycarbonylpiperazine (964 mg, 5.18 mmol) and the mixture heated at 85°C for 4 hours then cooled to

ambient temperature. Water was added and the mixture extracted with ethyl acetate. The organic layer was washed with water, saturated sodium chloride solution, dried ($MgSO_4$), filtered, evaporated and the residue purified by silica-gel chromatography (150 g, 99:1 $CHCl_3$-MeOH elution) then crystallized from Me_2CO-iPE to give 1.43 g (56%) of **8a** as a white powder.

Ethyl 1-{N-(Allyloxycarbonyl)acetyl-N-methylamino}-7-(4-*tert*-butoxycarbonyl-1-piperazinyl)-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (8a). mp 143-144°C; ^{1}H NMR (DMSO-d_6)(1:1 mixture of amide rotational isomers) δ 8.68 (s, 0.5H), 8.58 (s, 0.5H), 7.75-7.69 (m, 1H), 6.00-5.74 (m, 1H), 5.40-5.14 (m, 2H), 4.65-4.62 and 4.48-4.46 (each m, 2H total), 4.24 and 4.23 (each q, 2H total, J = 7 Hz), 3.88 and 3.78 (each d, 1H total, AB system, J = 16 Hz), 3.57 and 3.34 (each s, 3H total), 3.56 and 3.45 (each d, 1H total, AB system, J = 16 Hz), 3.45 (br s, 4H), 3.23 (br s, 4H), 1.43 (s, 9H), 1.29 (t, 3H, J = 7 Hz); IR(KBr) 1739, 1695, 1649, 1620 cm^{-1}; MS *m/z* 593 (MH^+); Anal. Calcd for $C_{28}H_{34}F_2N_4O_8$: C, 56.75 ; H, 5.78 ; N, 9.45. Found: C, 56.62 ; H, 5.72 ; N, 9.29%.

Ethyl 1-{N-(Diphenylmethyloxycarbonyl)acetyl-N-methylamino}-7-(4-methyl-1-piperazinyl)-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (8b). Prepared from **4c** (2.00 g). Yield: 1.64 g (72%) as a light yellow powder. mp 174-174.5°C; ^{1}H NMR (DMSO-d_6)(1:1 mixture of amide rotational isomers) δ 8.69 (s, 0.5H), 8.56 (s, 0.5H), 7.73-7.66 (m, 1H), 7.39-7.30 (m, 10H), 6.87 (s, 0.5H), 6.75 (s, 0.5H), 4.23 and 4.20 (each q, 2H total, J = 7.1 and 7.1 Hz), 4.03 and 3.90 (each d, 1H total, AB system, J = 16 Hz), 3.69 and 3.56 (each d, 1H total, AB system, J = 16.2 Hz), 3.56 and 3.33 (each s, 3H total), 3.22 (br s, 4H), 2.38 (br s, 4H), 2.20 (s, 3H), 1.27 (t, 3H, J = 7.1 Hz); IR(KBr) 1732, 1684, 1616 cm^{-1}; MS *m/z* 633 (MH^+); Anal. Calcd for $C_{34}H_{34}F_2N_4O_6$: C, 64.55 ; H, 5.42 ; N, 8.86. Found: C, 64.32 ; H, 5.36 ; N, 8.66%.

Ethyl 1-{N-(Allyloxycarbonyl)acetyl-N-methylamino}-7-(1-piperazinyl)-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (8c). Prepared from **4b** (5.00 g). Yield: 4.32 g (75%) as an amorphous glass. ^{1}H NMR ($CDCl_3$)(4.4:1 mixture of amide rotational isomers) δ 8.32 and 8.22 (each s, 1H total), 7.93 (dd, 1H, J = 1.9, 11.6 Hz), 5.90-5.74 (m, 1H), 5.44-5.21 (m, 2H), 5.58-5.55 and 4.74-4.71 (each m, 2H total), 4.39 (q, 2H, J = 7.1 Hz), 3.61 and 3.44 (each s, 3H total), 3.60-3.40 (m, 7H), 3.10-2.90 (m, 4H), 1.40 (t, 3H, J = 7.1 Hz) ; IR($CHCl_3$) 1735, 1695, 1640, 1620 cm^{-1}; MS *m/z* 493 (MH^+). Satisfactory analytical data could not be obtained for this material.

Ethyl 1-{N-(Diphenylmethyloxycarbonyl)acetyl-N-methylamino}-7-(4-*tert*-butoxycarbonyl-1-piperazinyl)-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (8d). Prepared from **4c** (3.00 g). Yield: 1.65 g (42%) as a white powder. mp 188-190°C; ^{1}H NMR (DMSO-d_6)(1:1 mixture of amide rotational isomers) δ 8.72 (s, 0.5H), 8.59 (s, 0.5H), 7.75-7.69 (m, 1H), 7.39-7.30 (m, 10H), 6.86 (s, 0.5H), 6.74 (s, 0.5H), 4.24 and 4.20 (each q, 2H total, J = 7 and 7 Hz), 4.05 and 3.87 (each d, 1H total, AB system, J = 16.2 Hz), 3.70 and 3.57 (each d, 1H total, AB system, J = 16.5 Hz), 3.56 and 3.33 (each s, 3H total), 3.38 (br s, 4H), 3.15 (br s, 4H), 1.42 (s, 9H), 1.27 (t, 3H, J = 7 Hz); IR(KBr) 1734, 1691, 1649, 1618 cm^{-1}; MS *m/z* 719 (MH^+); Anal. Calcd for $C_{38}H_{40}F_2N_4O_8$: C, 63.50 ; H, 5.61 ; N, 7.79. Found: C, 63.93 ; H, 5.73 ; N, 7.73%.

Ethyl 1-{N-(Diphenylmethyloxycarbonyl)acetyl-N-methylamino}-7-(1-pyrrolidinyl)-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (8e). Prepared from **4c** (5.40 g). Yield: 1.90 g (32%) as a white powder. mp 193.5-195°C; ^{1}H NMR (DMSO-d_6)(1:1 mixture of amide rotational isomers) δ 8.61 (s, 0.5H), 8.48 (s, 0.5H), 7.60 (dd, 1H, J = 1.7, 14 Hz), 7.42-7.20 (m, 10H), 6.86 (s, 0.5H), 6.75 (s,

0.5H), 4.22 and 4.19 (each q, 2H total, J = 7 and 7 Hz), 4.00 and 3.56 (each d, 1H total, AB system, J = 16 Hz), 3.74-3.49 (m, 5H), 3.54 and 3.31 (each s, 3H total), 1.81 (br s, 4H), 1.26 (t, 3H, J = 7 Hz); IR(KBr) 1749, 1693, 1647, 1620 cm^{-1}; MS *m/z* 604 (MH^+); Anal. Calcd for $C_{33}H_{31}F_2N_3O_6$: C, 65.66 ; H, 5.18 ; N, 6.96. Found: C, 65.86 ; H, 5.33 ; N, 6.87%.

Alternative Preparation of 8a. A solution of malonamide **8c** (4.25 g, 8.63 mmol) and Et_3N (1.45 mL, 10.40 mmol) in CH_2Cl_2 (17 mL) was treated with di-*tert*-butyl dicarbonate (2.00 g, 9.16 mmol) and the mixture stirred one hour at ambient temperature, concentrated under reduced pressure and the residue purified by silica-gel chromatography (60 g, $CHCl_3$-MeOH 99:1 elution) to give 4.06 g (80%) of **8a** as a white powder.

General Procedure for Cesium Carbonate-Mediated Cyclizations. A solution of **4c** (2.00 g, 3.62 mmol) in DMSO (20 mL) was treated with Cs_2CO_3 (1.30 g, 3.99 mmol) and the mixture heated at 85°C for 30 minutes then cooled to ambient temperature. AcOH (10 mL) and water (250 mL) were added. After stirring 5 minutes, the solid was collected, washed thoroughly with water, dried and crystallized from Me_2CO-iPE to give 1.56 g (81%) of **7c** as a white powder.

Ethyl 3-(Diphenylmethoxycarbonyl)-4,5-difluoro-2,3-dihydro-1-methyl-2,7-dioxo-1*H*,7*H*-pyrido[3,2,1-*i*,*j*]cinnoline-8-carboxylate (7c). mp 171.5-173°C; ^1H NMR (DMSO-d_6) δ 8.93 (s, 1H), 8.13 (dd, J = 8.3, 10.4 Hz, 1H), 7.30-7.18 (m, 10H), 6.78 (s, 1H), 5.58 (s, 1H), 4.28 (q, 2H, J = 7.1 Hz), 3.74 (s, 3H), 1.31 (t, 3H, J = 7.1 Hz); IR (KBr) 1741, 1722, 1687, 1616 cm^{-1}; MS *m/z* 533 (MH^+); Anal. Calcd for $C_{29}H_{22}F_2N_2O_6$: C, 65.41 ; H, 4.16 ; N, 5.26 . Found: C, 65.31 ; H, 4.07 ; N, 5.18%.

Ethyl 3-(Ethoxycarbonyl)-4,5-difluoro-2,3-dihydro-1-methyl-2,7-dioxo-1*H*,7*H*-pyrido[3,2,1-*i*,*j*]cinnoline-8-carboxylate (7a). Prepared from ester **4a** (600 mg)(0.5 hr reaction time). Yield: 284 mg (50%) as a white powder. mp 174-174.5°C; ^1H NMR (DMSO-d_6) δ 8.90 (s, 1H), 8.11 (dd, 1H, J = 8.4, 10.4 Hz), 5.37 (s, 1H), 4.27 (q, 2H, J = 7.1 Hz), 4.15 (q, 2H, J = 7.1 Hz), 3.73 (s, 3H), 1.30 (t, 3H, J = 7.1 Hz), 1.15 (t, 3H, J = 7.1 Hz); ^{13}C NMR (DMSO-d_6) δ 169.8 (s), 165.4 (s), 163.7 (s), 157.5 (s), 149.4 (dd, J = 255.7, 16 Hz), 148.0 (dd, J = 249.5, 13.1 Hz), 140.2 (s), 129.6 (d, J = 6.9 Hz), 123.4 (dd, J = 4.8, 2.5 Hz), 113.2 (d, J = 18.7 Hz), 110.4 (d, J = 18.4), 109.7 (s), 62.6 (s), 60.3 (s), 45.8 (s), 34.2 (s), 14.1 (s), 13.6 (s); IR (KBr) 1747, 1730, 1711, 1693, 1624, 1604 cm^{-1}; MS *m/z* 395 (MH^+); Anal. Calcd for $C_{18}H_{16}F_2N_2O_6$: C, 54.83 ; H, 4.09 ; N, 7.10. Found: C, 54.66 ; H, 3.95 ; N, 7.02%.

Ethyl 3-(Allyloxycarbonyl)-4,5-difluoro-2,3-dihydro-1-methyl-2,7-dioxo-1*H*,7*H*-pyrido[3,2,1-*i*,*j*]cinnoline-8-carboxylate (7b). Prepared from ester **4b** (2.00 g)(1 hr reaction time). Yield: 1.30 g (68%) as a white powder. mp 160-162°C; ^1H NMR (DMSO-d_6) δ 8.90 (s, 1H), 8.12 (dd, 1H, J = 8.4, 10.3 Hz), 5.95-5.76 (m, 1H), 5.46 (s, 1H), 5.25-5.16 (m, 2H), 4.65-4.62 (m, 2H), 4.27 (q, 2H, J = 7.1 Hz), 3.73 (s, 3H), 1.30 (t, 3H, J = 7.1 Hz) ; IR (KBr) 1749, 1730, 1712, 1693, 1624, 1606 cm^{-1}; MS *m/z* 407 (MH^+); Anal. Calcd for $C_{19}H_{16}F_2N_2O_6$: C, 56.16 ; H, 3.97 ; N, 6.89. Found: C, 56.01; H, 3.78 ; N, 6.85%.

Ethyl 3-(Allyloxycarbonyl)-4-(4-*tert*-butoxycarbonyl-1-piperazinyl)-5-fluoro-2,3-dihydro-1-methyl-2,7-dioxo-1*H*,7*H*-pyrido[3,2,1-*i*,*j*]cinnoline-8-carboxylate (9a). Prepared from ester **8a** (1.41 g)(8 hr reaction time). Yield: 1.10 g (81%) as a light yellow powder. mp 149-151°C(dec.); ^1H NMR (DMSO-d_6) δ 8.87 (s, 1H), 7.91 (d, 1H, J = 12.2 Hz), 5.92-5.76 (m, 1H), 5.30 (s, 1H), 5.26-5.17 (m, 2H), 4.62 (d, 2H, J = 4.4 Hz), 4.26 (q, 2H, J = 7 Hz), 3.73 (s, 3H), 3.30-2.60 (m, 8H), 1.43 (s, 9H), 1.30

(t, 3H, J = 7Hz); IR(KBr) 1736, 1693, 1620 cm^{-1}; MS *m/z* 573 (MH^+); Anal. Calcd for $C_{28}H_{33}FN_4O_8$: C, 58.73 ; H, 5.81 ; N, 9.78. Found: C, 58.33 ; H, 5.69 ; N, 9.85%.

Ethyl 3-(Diphenylmethoxycarbonyl)-5-fluoro-2,3-dihydro-4-(4-methyl-1-piperazinyl)-1-methyl-2,7-dioxo-1*H*,7*H*-pyrido[3,2,1-*i*,*j*]cinnoline-8-carboxylate (9b). Prepared from ester **8b** (540 mg)(8 hr reaction time, extractive work-up). Yield: 180 mg (34%) as a light yellow powder. mp 175-179°C; ^1H NMR (DMSO-d_6) δ 8.88 (s, 1H), 7.91 (d, 1H, J = 12.3 Hz), 7.27-7.13 (m, 10H), 6.76 (s, 1H), 5.29 (s, 1H), 4.27 (q, 2H, J = 7 Hz), 3.72 (s, 3H), 3.09 (br m, 4H), 2.27 (br m, 4H), 2.05 (s, 3H), 1.31 (t, 3H, J = 7 Hz); IR (KBr) 1739, 1689, 1637, 1622 cm^{-1}; MS *m/z* 613 (MH^+); Anal. Calcd for $C_{34}H_{33}FN_4O_6$: C, 66.66 ; H, 5.43 ; N, 9.14. Found: C, 66.36 ; H, 5.59 ; N, 8.83%.

Ethyl 3-(Diphenylmethoxycarbonyl)-5-fluoro-2,3-dihydro-4-(4-*tert*-butoxycarbonyl-1-piperazinyl)-1-methyl-2,7-dioxo-1*H*,7*H*-pyrido[3,2,1-*i*,*j*]cinnoline-8-carboxylate (9c). Prepared from ester **8d** (1.00 g)(10 hr reaction time). Yield: 779 mg (80%) as a light yellow powder. mp 213-214°C; ^1H NMR (DMSO-d_6) δ 8.89 (s, 1H), 7.91 (d, 1H, J = 12.1 Hz), 7.13-7.26 (m, 10H), 6.78 (s, 1H), 5.36 (s, 1H), 4.28 (q, 2H, J = 7 Hz), 3.73 (s, 3H), 3.40-2.80 (br m, 8H), 1.41 (s, 9H), 1.31 (t, 3H, J = 7 Hz); IR (KBr) 1732, 1689, 1639, 1622 cm^{-1}; MS *m/z* 699 (MH^+); Anal. Calcd for $C_{38}H_{39}FN_4O_8$: C, 65.32 ; H, 5.62 ; N, 8.02. Found: C, 65.05 ; H, 5.76 ; N, 7.94%.

Ethyl 3-(Diphenylmethoxycarbonyl)-5-fluoro-2,3-dihydro-4-(1-pyrrolidinyl)-1-methyl-2,7-dioxo-1*H*,7*H*-pyrido[3,2,1-*i*,*j*]cinnoline-8-carboxylate (9d). Prepared from ester **8e** (1.00 g)(15 hr reaction time). Yield: 750 mg (78%) as a white powder. mp 188-190.5°C; ^1H NMR (DMSO-d_6) δ 8.80 (s, 1H), 7.84 (d, 1H, J = 13.4 Hz), 7.35-7.08 (m, 10H), 6.73 (s, 1H), 5.34 (s, 1H), 4.27 (q, 2H, J = 7 Hz), 3.70 (s, 3H), 3.50-3.40 (m, 2H), 2.97-2.83 (m, 2H), 1.95-1.60 (m, 4H), 1.31 (t, 3H, J = 7 Hz); IR (KBr) 1732, 1680, 1622 cm^{-1}; MS *m/z* 584 (MH^+); Anal. Calcd for $C_{33}H_{30}FN_3O_6$: C, 67.91 ; H, 5.18 ; N, 7.20. Found: C, 68.13; H, 5.24; N, 7.18%.

Ethyl 4-(4-*tert*-Butoxycarbonyl-1-piperazinyl)-5-fluoro-2,3-dihydro-1-methyl-2,7-dioxo-1*H*,7*H*-pyrido[3,2,1-*i*,*j*]cinnoline-8-carboxylate (10a). A suspension of ester **8a** (1.00 g, 1.68 mmol), cuprous iodide (64 mg, 0.34 mmol), and potassium *tert*-butoxide (398 mg, 3.55 mmol) in DMSO (5 mL) was heated at 50-55°C for 30 minutes and at 100-105°C for 6 hours. After cooling, glacial acetic acid (0.11 mL) was added to the reaction mixture followed by water (25 mL). The precipitate was collected by filtration , dried, purified by silica-gel chromatography (10 g, $CHCl_3$-MeOH, 99:1 elution) and triturated with iPE to give **10a** (260 mg, 32%) as a light yellow powder. mp 171-175°C; ^1H NMR ($CDCl_3$) δ 8.71 (s, 1H), 7.99 (d, 1H, J = 12.2 Hz), 4.42 (q, 2H, J = 7.1 Hz), 3.99 (s, 2H), 3.74 (s, 3H), 3.80-3.30 (br m, 4H), 3.07 (br s, 4H), 1.50 (s, 9H), 1.42 (t, 3H, J = 7.1 Hz); IR(KBr) 1724, 1691, 1624 cm^{-1}; MS *m/z* 489 (MH^+); Anal. Calcd for $C_{24}H_{29}FN_4O_6 \cdot 2H_2O$: C, 54.95 ; H, 6.34 ; N, 10.68. Found: C, 54.84 ; H, 6.16 ; N, 10.53%.

Alternative Preparation of 10a from Ester 9c. A solution of ester **9c** (318 mg, 0.456 mmol) in CH_2Cl_2 (4 mL) was treated with anisole (0.4 mL) and TFA (0.8 mL). After 2 hours at room temperature, the solution was evaporated, redissolved in THF (4 mL) and treated with Et_3N (0.317 mL, 2.28 mmol) and di-*tert*-butyl dicarbonate (149 mg). After 3 hours, the solution was diluted with EtOAc, washed with 0.1N hydrochloric acid (3x), brine, dried ($MgSO_4$), evaporated and crystallized from Me_2CO-iPE-hexane to give **10a** (150 mg, 67%), identical by ^1H NMR, IR, and MS with the sample obtained from **8a**.

Ethyl 4,5-Difluoro-2,3-dihydro-1-methyl-2,7-dioxo-1*H*,7*H*-pyrido[3,2,1-*i,j*]cinnoline-8-carboxylate (5a). Method A: A solution of diphenylmethyl ester **7c** (21.41 g, 40.21 mmol) in a mixture of anisole (10.7 mL) and TFA (214 mL) was stirred at ambient temperature for one hour. The mixture was evaporated under reduced pressure and purified by silica-gel chromatography (30g, CH_2Cl_2-MeOH, 99-1 to 98-1 elution) to give 10.47 g (81%) of ester **5a** as a light yellow powder. An analytical sample was obtained by recrystallization from EtOH. mp 247-250°C(dec.); ^{1}H NMR (DMSO-d_6) δ 8.83 (s, 1H), 7.99 (dd, 1H, J = 8.5, 10.5 Hz), 4.26 (q, 2H, J = 7.1 Hz), 4.05 (s, 2H), 3.68 (s, 3H), 1.30 (t, 3H, J = 7.1 Hz); IR (KBr) 1728, 1687, 1628, 1603 cm^{-1}; MS *m/z* 323 (MH^+); Anal. Calcd for $C_{15}H_{12}F_2N_2O_4$: C, 55.90 ; H, 3.75 ; N, 8.69. Found: C, 55.53 ; H, 3.61; N, 8.65%. **Method B:** To a solution of palladium acetate (11 mg, 0.05 mmol) and triphenylphosphine (26 mg, 0.1 mmol) in a mixture of dimethylformamide (2 mL) and THF (10 mL) was added a mixture of formic acid (0.09 mL) and Et_3N (0.41 mL) in THF (1 mL) at ambient temperature. To the mixture was added allyl ester **7b** (410 mg, 1 mmol) and the mixture stirred at ambient temperature for 4 hours. The resulting precipitate was collected by filtration and dried to give **5a** (148 mg, 58%). **Method C:** A solution of diethyl ester **7a** (100 mg, 0.254 mmol) in a mixture of water (0.05 mL) and TFA (1.0 mL) was heated under reflux for 3 hours. After evaporation, the residue was purified by preparative TLC, developing with ethyl acetate to give **5a** (36 mg, 44%).

4,5-Difluoro-2,3-dihydro-1-methyl-2,7-dioxo-1*H*,7*H*-pyrido[3,2,1-*i,j*]cinnoline-8-carboxylic Acid (5b). A solution of quinolone **5a** (1.00 g, 3.1 mmol) in a mixture of concentrated hydrochloric acid (1 mL) and glacial acetic acid (10 mL) was refluxed for 5 hours. After cooling, water was added to the mixture and the solid collected by filtration then washed thoroughly with water and dried. The solid was suspended in 1:1 acetone-methanol, stirred 5 minutes, filtered and dried to give **5b** (700 mg, 77%) as a light-grey analytically pure powder. mp 280-285°C; ^{1}H NMR (DMSO-d_6) δ 14.69 (s, 1H), 9.06 (s, 1H), 8.23 (dd, 1H, J = 8.3, 10.2 Hz), 4.16 (s, 2H), 3.77 (s, 3H); IR (KBr) 1739, 1678, 1626 cm^{-1}; MS *m/z* 295 (MH^+); Anal. Calcd for $C_{13}H_8F_2N_2O_4$: C, 53.07 ; H, 2.74 ; N, 9.52. Found: C, 52.70 ; H, 2.50 ; N, 9.41 %. By the same procedure, **5b** (287 mg, 80%) was obtained from **7a** (510 mg). Similarly, **5b** (135 mg, 87%) was obtained from **7b** (214 mg).

5-Fluoro-2,3-dihydro-1-methyl-2,7-dioxo-4-(1-piperazinyl)-1*H*,7*H*-pyrido[3,2,1-*i,j*]cinnoline-8-carboxylic Acid Hydrochloride (11a). By the same procedure used for preparation of **5b**, **11a** (104 mg, 75%) was obtained from **9a** (200 mg) as an off-white solid. mp 305-310°C(dec.); ^{1}H NMR (DMSO-d_6) δ 9.05 (br s, 2H), 9.03 (s, 1H), 8.02 (d, 1H, J = 12 Hz), 4.14 (s, 2H), 3.76 (s, 3H), 3.34 (br s, 8H); ^{1}H NMR (D_2O) δ 8.59 (s, 1H), 7.95 (d, 1H, J = 12.6 Hz), 3.60-3.00 (m, 8H), 2.81 (s, 3H); IR(KBr) 1720, 1676, 1630, 1606 cm^{-1}; MS *m/z* 361 (MH^+, free); Anal. Calcd for $C_{17}H_{17}FN_4O_4$·HCl·0.5H_2O : C, 50.31 ; H, 4.72 ; N, 13.80. Found: C, 50.71 ; H, 4.53 ; N, 13.40%. Similarly, **11a** (101 mg, 69%) was obtained from **10a** (200 mg).

Ethyl 4-(4-Methyl-1-piperazinyl)-5-fluoro-2,3-dihydro-1-methyl-2,7-dioxo-1*H*,7*H*-pyrido[3,2,1-*i,j*]cinnoline-8-carboxylate (10b). A solution of ester **9b** (122 mg, 0.20 mmol) in CH_2Cl_2 (3 mL) was treated with anisole (0.2 mL) followed by TFA (1.5 mL). After 45 minutes the solution was evaporated then diluted with ethyl acetate and washed with saturated sodium hydrogen carbonate solution. The aqueous layer was extracted with ethyl acetate (4x). The dried ($MgSO_4$) combined organic layers were evaporated and the residue crystallized from Me_2CO-iPE to give 45 mg (56%) of **10b** as a light yellow powder. mp 197-202°C; ^{1}H NMR (DMSO-d_6) δ 8.79 (s, 1H), 7.73 (d, 1H, J = 12.6 Hz), 4.25 (q, 2H, J =

7.1 Hz), 3.95 (s, 2H), 3.65 (s, 3H), 3.09 (br s, 4H), 2.50 (br s, 4H), 2.27 (s, 3H), 1.29 (t, 3H, J = 7.1 Hz); IR (KBr) 1687br, 1631 cm^{-1}; MS m/z 403 (MH^+); Anal. Calcd for $C_{20}H_{23}FN_4O_4 \cdot 0.7H_2O$: C, 57.88 ; H, 5.92 ; N, 13.50. Found: C, 57.95 ; H, 5.76 ; N, 13.38%.

Ethyl 4-(1-Pyrrolidinyl)-5-fluoro-2,3-dihydro-1-methyl-2,7-dioxo-1*H*,7*H*-pyrido[3,2,1-*i,j*]cinnoline-8-carboxylate (10c). By the same procedure used for preparation of **10b**, **10c** (370 mg, 89%) was obtained from **9d** (650 mg) as a yellow powder. mp 144-148°C(dec.); ^1H NMR (DMSO-d_6) δ 8.76 (s, 1H), 7.69 (d, 1H, J = 13.4 Hz), 4.25 (q, 2H, J = 7.1 Hz), 3.92 (s, 2H), 3.64 (s, 3H), 3.39-3.25 (m, 4H), 1.96-1.89 (m, 4H), 1.29 (t, 3H, J = 7.1 Hz); IR (KBr) 1728, 1685, 1626 cm^{-1}; MS m/z 374 (MH^+); Anal. Calcd for $C_{19}H_{20}FN_3O_4 \cdot 0.5H_2O$: C, 59.68 ; H, 5.53; N, 10.91. Found: C, 59.50 ; H, 5.14 ; N, 10.57%.

5-Fluoro-2,3-dihydro-1-methyl-2,7-dioxo-4-(4-methyl-1-piperazinyl)-1*H*,7*H*-pyrido[3,2,1-*i,j*]cinnoline-8-carboxylic Acid Hydrochloride (11b). By the same procedure used for preparation of **5b**, **11b** (130 mg, 64%) was obtained from **10b** (200 mg) as a yellow powder. mp 215-218°C(dec.); ^1H NMR (DMSO-d_6) δ 14.83 (br s, 1H), 10.54 (br s, 1H), 9.03 (s, 1H), 8.02 (d, 1H, J = 12 Hz), 4.13 (s, 2H), 3.76 (s, 3H), 3.58-3.45 (m, 8H), 2.85 (s, 3H); ^1H NMR (D_2O) δ 8.96 (s, 1H), 7.91 (d, 1H, J = 11.9 Hz), 3.81 (s, 3H), 3.73-3.57 (m, 4H), 3.48-3.38 (m, 4H), 3.02 (s, 3H); IR (KBr) 1720, 1680, 1631, 1608 cm^{-1}; MS m/z 375 (MH^+, free); Anal. Calcd for $C_{18}H_{19}FN_4O_4 \cdot HCl \cdot 1.5H_2O$: C, 49.38 ; H, 5.29; N, 12.79. Found: C, 49.02 ; H, 5.44 ; N, 12.45%.

X-Ray Crystallographic Analysis of 10a.

Yellow prismatic crystals of **10a** ($C_{24}H_{29}FN_4O_6$, Calcd: C, 59.01; H, 5.98; N, 11.47. Found: C, 59.45; H, 5.91; N, 11.45%) were grown from acetone solution. Diffraction measurements were performed on a Rigaku AFC-5R diffractometer using graphite-monochromatized CuK α radiation (λ = 1.54178 Å). Crystal data: $C_{24}H_{29}FN_4O_6$, Mr = 488.51, monoclinic, $C2/c$ (no.15), a = 33.186 (2) Å, b = 9.507 (2) Å, c = 15.622 (2) Å, β = 100.528 (9)°, V = 4585 (1) $Å^3$, Z = 8, D_{calc} = 1.339 gcm^{-3}, μ = 8.59 cm^{-1}, $F(000)$ = 2064, T = 297K. A total of 4500 reflections (4414 unique reflections) were collected using the ω-2θ scan technique within a 2θ range of 130.2°. The structure was solved by a direct method and refined by a full-matrix least-squares method using 2771 reflections ($Io > 3.0\ \sigma(I)$). The final refinement converged to R = 0.060 and R_w = 0.052.

Reduction Reactions of Amide 5a.

(a) $NaBH_4$-TFA: A suspension of $NaBH_4$ (60 mg, 1.59 mmol) in dioxane (1 mL) was treated with a solution of TFA (181 mg, 1.59 mmol) in dioxane (0.2 mL) below 10°C. To this mixture was added **5a** (100 mg, 0.31 mmol) and the mixture heated at 100°C for 5 hours then cooled. The insoluble material was removed and the evaporated filtrate purified by PTLC (EtOAc elution) to give 13.4 mg (13%) of ethyl 4,5-difluoro-2,3,8,9-tetrahydro-1-methyl-2,7-dioxo-1*H*,7*H*-pyrido[3,2,1-*i,j*]cinnoline-8-carboxylate (**12**) as an amorphous yellow glass. ^1H NMR ($CDCl_3$) δ 12.11 (br s, 1H), 7.40 (dd, 1H, J = 8.3, 10.1 Hz), 4.34 (q, 2H, J = 7.1 Hz), 4.19 (s, 2H), 3.70 (s, 2H), 3.37 (s, 3H), 1.37 (t, 3H, J = 7.1 Hz); IR (KBr) 1657, 1601 cm^{-1}; MS m/z 324 (M^+)(satisfactory analytical data could not be obtained for this compound); and 9.4 mg (10%) of ethyl 4,5-difluoro-2,3-dihydro-1-methyl-7-oxo-1*H*,7*H*-pyrido[3,2,1-*i,j*]cinnoline-8-carboxylate (**1**)[13]. Compound **12** (235 mg, 58%) was also obtained from **5a** (400 mg) by $NaBH_4$ reduction in THF(18hr, rt).

(b) NaBH4-Pyridine: A suspension of **5a** (300 mg, 0.931 mmol) in pyridine (2 mL) was treated with NaBH4 (100 mg, 2.64 mmol) and then refluxed for 8 hours. The solid was removed and the filtrate evaporated under reduced pressure to give a syrup. The syrup was purified by PTLC, eluting with ethyl acetate to give 37 mg (13%) of ethyl 4,5-difluoro-2,3,8,9-tetrahydro-1-methyl-7-oxo-1*H*,7*H*-pyrido[3,2,1-*i*,*j*]cinnoline-8-carboxylate (**13**) as an amorphous yellow glass. ^{1}H NMR ($CDCl_3$)(1:1 mixture of keto-enol tautomers) δ 12.16 (s, 0.5 H), 7.60 (dd, 0.5 H, *J* = 9, 10.4 Hz), 7.29 (dd, 0.5 H, *J* = 8.8, 10.8 Hz), 4.31-4.18 (m, 3.5 H), 4.02-3.58 (m, 1H), 3.13-3.00 (m, 2H), 2.86-2.69 (m, 2H), 2.56 and 2.52 (each s, 3H total), 1.32 and 1.27 (each t, 3H total, *J* = 7.1 and 7.1 Hz); IR (nujol) 1658, 1630 cm^{-1}; MS *m/z* 310 (M^+)(satisfactory analyses were not obtained for this compound); and 5.6 mg (2%) of **1**.[13]

(c) $POCl_3$-NaBH4: To phosphoryl chloride (0.35 mL) was added ester **5a** (100 mg, 0.31 mmol) at room temperature and the mixture stirred 1.5 hours then evaporated. The dark oil was dried under vacuum for 30 minutes then dissolved in ethylene glycol dimethyl ether (5 mL), cooled with ice and treated with NaBH4 (36 mg, 0.93 mmol) with vigorous stirring. After 1 hour at room temperature 1N-HCl (1 mL) was added dropwise. The mixture was evaporated and water (3 mL) added. The collected precipitate was then purified by PTLC (EtOAc elution) to give **1**[13](10 mg, 10%).

Oxidation of β-Ketoester 13 with MnO_2. To a solution of **13** (20 mg, 0.064 mmol) in EtOAc (1 mL) was added activated MnO_2 (30 mg) and the mixture stirred at ambient temperature for 2 days. After removal of insoluble material, the evaporated filtrate was purified by PTLC (EtOAc elution) to give 11.2 mg (56%) of **1**, identical by ^{1}H NMR with an authentic sample.[13]

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33. For example, in a control experiment (500 mg scale, 0.3M in EtOH, $NaBH_4$ (1.1 equiv)), TLC analysis indicated complete consumption of **5a** within 15 minutes at room temperature.

34. Attempts to mask the β-keto ester of **12**, for example, by *O*-alkylation prior to amide reduction, followed by oxidative deprotection were unsuccessful.

35. Other research in our group indicates that other hard anions also give exclusive C-2 cyclization products with no closure to C-8 even at elevated temperatures (manuscript in preparation).

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