Synthesis of 7-Amino-1,4-dihydro-4-oxo-6-(trifluoromethyl)-1,8-naphthyridines. The Use of Methylidenemalonate as an Activating Group and a Sulfur Assisted Cyclization

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2,6-Dichloro-3-(trifluoromethyl)pyridine **3** was used to develop a six-step preparation of 7-amino-4-oxo-6-(trifluoromethyl)naphthyridines. The CF_3 group deactivated the pyridine ring towards both nucleophiles and electrophiles. A new reagent for pyridone annulation, the aminomethylidenemalonate anion, is described, along with several strategies to manipulate the electron density of substituted pyridines.

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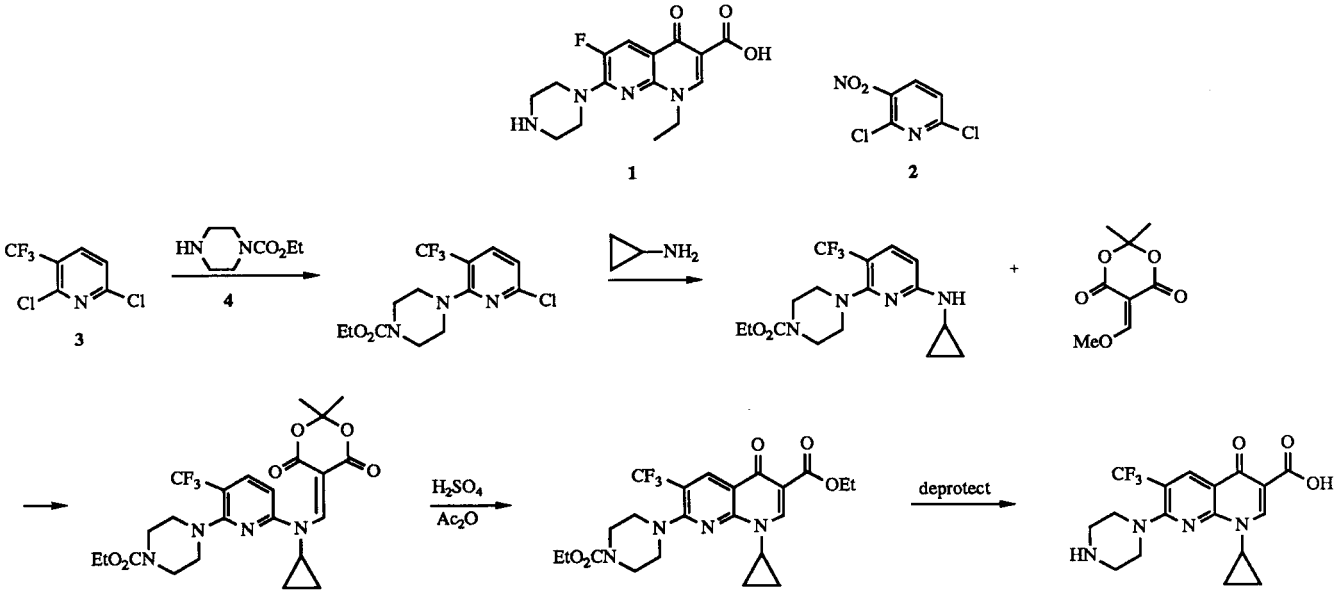
Enoxacin (**1**) is a naphthyridine antibiotic with an excellent spectrum of clinical activity [1]. The 1-cyclopropyl analog can be prepared in several steps from 2,6-dichloro-3-nitropyridine (**2**) by two amine displacements followed by nitro to fluoride conversion, alkylation with diethyl (methoxymethylidene)malonate, cyclization, and deprotection [2]. The ready availability of 2,6-dichloro-3-(trifluoromethyl)pyridine (**3**) suggested that the 6-trifluoromethyl analogues on enoxacin could be made in a simple five-step sequence as shown in Scheme 1 [3]. The timing of the first two steps was open to some question as we were not sure if the CF_3 group would activate the *ortho* or *para* position to a greater extent. Although the inductive effect of the CF_3 group might be expected to be more effective at the proximate position, the CF_3 group causes an upfield shift of the *ortho* signal in the ^{13}C spectra of benzene derivatives [4]. Reaction of the dichloropyridine **3** with *N*-carboxymethylpiperazine (**4**) was rather sluggish requiring heating, unlike the reaction of **4** with the nitro analogue **2**, which is rapid at −20° (Scheme 2). A single product was formed, which had aromatic protons at 7.59 and 6.41 ppm. This highfield position for the H5 proton was suggestive of it being *ortho* rather than *para* to the newly introduced amino function. This would indicate that the 6-chloro substituent had been displaced forming the aminopyridine **5** rather than the desired regioisomer **6**. Therefore, cyclopropylamine was reacted with the dichloropyridine **3** (Scheme 2). Again reaction was rather sluggish, but this time two products **7** and **8** were formed in a 3:1 ratio (93% yield). Unfortunately, both compounds had their H5 resonances at 6.52 ppm, confounding the previous pmr regiochemical assignment. The minor product was the less

Scheme 1

Proposed Synthesis of 6-Trifluoromethyl-1,8-naphthyridines from Dichloride **3**



polar of the two compounds, and reacted slowly when treated with piperazine under forcing conditions. On the other hand, the major component was recovered unchanged under the same conditions. Both of these facts seemed to be more consistent with the minor product being **7**, with the amine being sterically shielded and the chlorine accessible. To prove the regiochemistry of **7** and **8** we used ^{13}C nmr spectra. In Table 1, the aromatic ^{13}C signals for **7** and **8** are given, along with those calculated by using standard aromatic substituent shifts on the pyridine nucleus. For comparison the actual and calculated spectra for the dichloride **3** and the 2,6-diaminopyridine analog **20** are also included. Clearly the fit between the observed and calculated values is reasonable, and **7** is most likely the minor isomer, with the major product coming from displacement of the less hindered 6-chlorine atom. Since the substituted piperazine **4** is bulkier than cyclopropylamine, one would expect it to be more selective sterically, and react to produce the aminopyridine **7**. This regiochemical assignment was confirmed by later synthetic work.

Since cyclopropylamine is low boiling, it was convenient to introduce in onto the less deactivated pyridine nucleus **3** initially. We then under-took to introduce the piperazine **4** into the 2-position. However, even under very forcing conditions (DMF, 100°) there was no reaction between **4** and **8**. The more reactive *N*-methylpiperazine did not react with **8** either.

One possible way of activating the 2-position would be to incorporate a better leaving group there. In electron deficient heteroaromatic systems an ortho sulfonyl substituent if often an excellent leaving group [5]. Therefore, the chloropyridine **8** was reacted with sodium thiophenoxide. However, this excellent nucleophile failed to react with **8**, even under very forcing conditions (HMPA, 130°). This result convinced us that **8** is exceptionally deactivated towards nucleophiles, but the easy formation of the minor product **7** suggested that the 2-position could be activated

Scheme 2

Initial Reactions of 2,6-Dichloro-3-trifluoromethylpyridine (3) with Amines

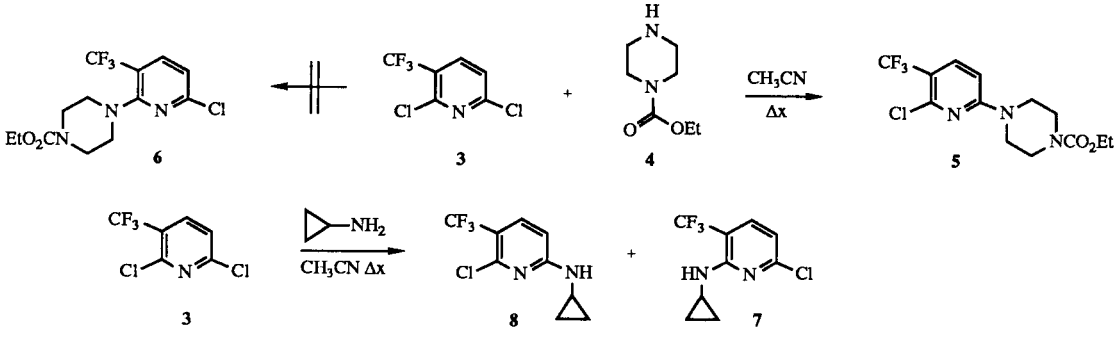


Table 1

^{13}C Assignment of the Regiochemistry to 7 and 8

Compound	Position 2	3	Observed 4 [c]	5[c]	6	7	Calculated [a,b] 2	3	4	5	6
3	148.52	124.24 q J = 33.8 Hz	138.61 q J = 4.8 Hz	122.83	153.53	121.87 q J = 272.6 Hz	149.6	125.7	139.2	123.5	156.1
8	147.69	113.41 q J = 33.3 Hz	137.88 q J = 4.6 Hz	102.99	160.89	123.22 q J = 270.4 Hz [d]	148.1	116.3	138.2	108.1	165
7	155.46	107.01 q J = 32.2 Hz	137.08 q J = 4.8 Hz	111.35	153.43	124.13 q J = 271.1 Hz [e]	158.6	110.3	138.2	114.1	154.6
20	159.38	106.0 q J = 33 Hz	138.77 q J = 4.5 Hz	98.96	160.25	124.9 q J = 270 Hz [f]					

[a] Calculated shifts taken from Ref. [4]. [b] NH_2 values were used for calculating all amine substituents. The effect of a CF_3 group had to be taken from benzene shift tables. [c] Shows NOE ^1H-^{13}C enhancement. [d] Cyclopropyl C; 23.79, 7.75 ppm. [e] Cyclopropyl C; 24.38, 7.37 ppm. [f] Other signals 155.66, 61.32, 50.38, 43.81, 23.82, 14.68, 7.54 ppm.

by some reduction in the aromatic electron density. To achieve this, we attempted to react **8** with acetyl chloride, tosyl chloride, and (methoxymethylidene) Meldrum's acid (**9**). However, the two electron withdrawing groups on the pyridine ring apparently decrease the nucleophilicity of **8** enough for it to be inert towards these electrophiles also. Therefore, we were forced to abandon the idea of two successive aminations of **3** as a synthetic strategy.

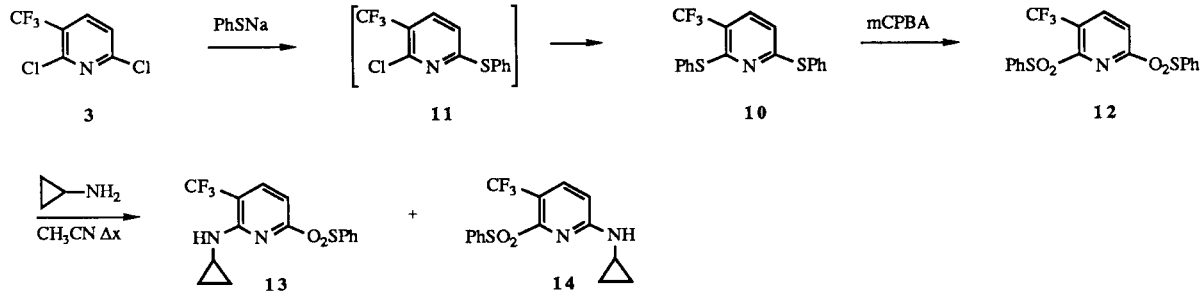
One way of exploring both of the previously described strategies would be to displace both chlorine atoms from **3** with thiophenoxide. The resulting thiol could then be oxidized to the bissulfone for the displacement reactions. When the dichloride **3** was treated with excess sodium thiophenoxide in dimethylformamide at 100° both chlorines were readily displaced to form the bissulfide **10** (Scheme 3). This result was important as it demonstrated that a moderate reduction in aromatic electron density from the aminopyridine **8** to (presumably) the thiopyridine **11** allows for the 2-chlorine to be displaced quite readily. Oxidation of **10** with *m*-chloroperoxybenzoic acid smoothly produced the bissulfone **12**. Reaction of **12** with cyclopropylamine gave a rather low yield of a 3:2 mixture of two displacement products **13** and **14**. The ^{1}H nmr spectra were now consistent with the major product arising from displacement from the 2-position, presumably because the displacement of a bulky sulfonyl group *ortho* to the trifluoromethyl group is sterically accelerated. These unfortunate results meant that this particular approach also was a dead end, since this reversal of regiochemistry could not be exploited. Our previous results had already indicated that the use of a bulkier piperazinyl nucleophile would again lead to 6-displacement predominating. Thus **12** probably represents a case where either order of displacement will lead to the same, undesired, major regiochemistry.

Another way of reducing the electron density of the aromatic ring prior to the second displacement would be to introduce the cyclopropylamine with an electron deficient group already attached to it. This should have the secondary advantage of making the nucleophile bulkier and therefore, more regioselective than cyclopropylamine. Reaction of the dichloropyridine **3** with the sodium salt of *N*-tosylcyclopropylamine (**17a**) gave the tosylaminopyridine **15** (Scheme 4) in 57% yield [6]. The compound which would arise for displacement at the 2-position was not detected. The ^{1}H nmr spectrum of **15** showed that the electron density of the aromatic ring had been considerably reduced, with the H5 proton at 7.42 rather than at 6.52 ppm as was the case in **6**. Pyridine **15** reacted readily with *N*-methylpiperazine to give the protected diaminopyridine **16** in 91% crude yield. The deprotection of **16** was attempted unsuccessfully with sodium hydroxide, alkyl lithium and hydrogen bromide in acetic acid [7].

Rather than attempting further tosylate cleavage reactions, we examined the use of a different prosthetic, the *t*-Boc group. Treatment of cyclopropylamine with di-*t*-butyl dicarbonate gave the desired urethane **17b** quantitatively [8]. The sodium salt derived from **17b** reacted cleanly with the dichloride **3** to give the pyridylurethane **18** in 90% yield (Scheme 5). Unfortunately, the product was contaminated with 10% of the deprotected aminopyridine **8**.

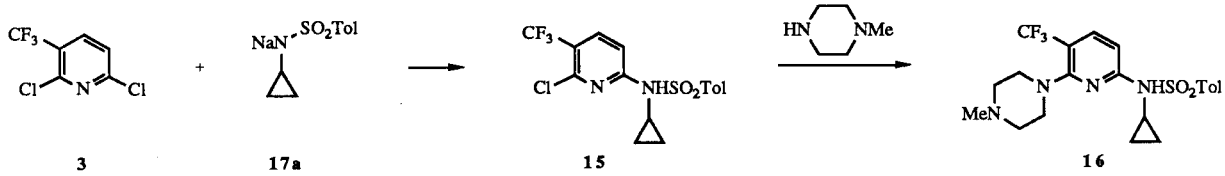
Scheme 3

Preparation and Reaction of the 2,6-Bissulfone



Scheme 4

Reduction of Electron Density of the Pyridine Ring *via* Reaction with *N*-Tosylcyclopropylamine

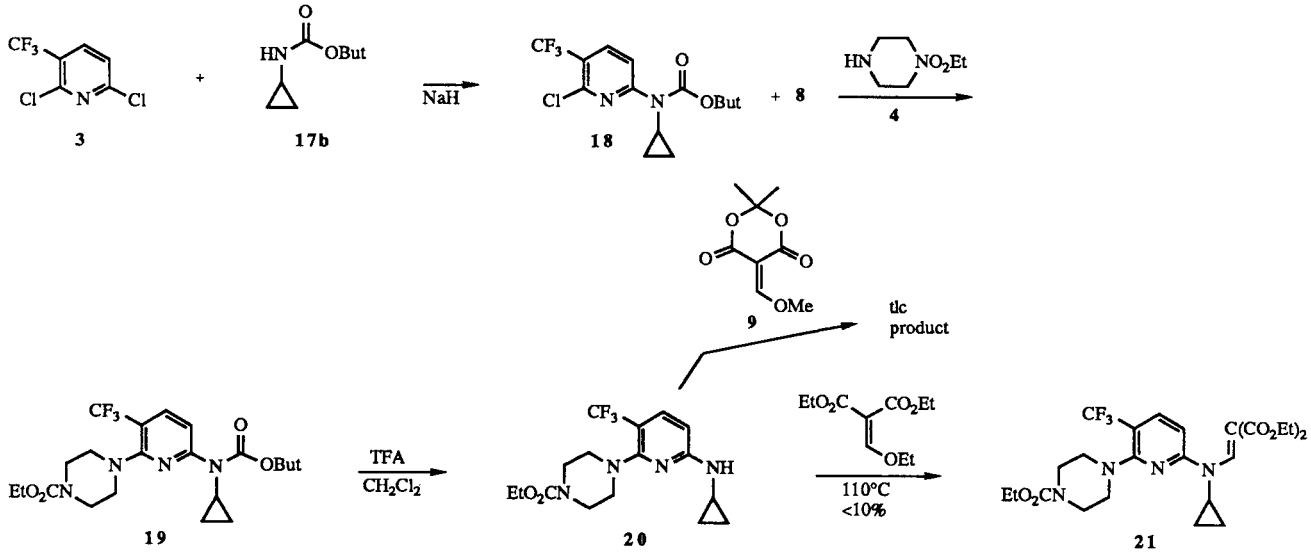


The pyridyl protons in **18** were at 7.81 and 7.50 ppm. As expected from these shift values, the chloropyridine **18** did react with the substituted piperazine **4**, by employing somewhat vigorous conditions, to give the desired protected diamine **19** in 46% yield. Removal of the urethane from **19** to give the diamine **20** was ahieved in 66% yield by using five equivalents of trifluoroacetic acid in dichloromethane at 25° [9].

With the diamine **20** finally in hand the annulation of the pyridone ring was examined. Reaction of **20** with (methoxymethylidene) Meldrum's acid **9** in methanol led to some initial reaction as shown by tlc. However, longer reaction times and an excess of **9** did not force the reaction to completion. Heating the reaction mixture to 45°, on the other hand, caused complete decomposition of the reaction mixture. The use of diethyl 2-(ethoxymethylidene)malonate as the Michael acceptor appeared to give some of the desired product **21** after 66 hours in refluxing toluene [10]. This result is based on an analysis of the pyridyl protons in the nmr spectrum taken on the crude reaction product. All attempts at purification failed. Thus the third step of the original synthesis proceeded poorly at best. No serious attempt was made to optimize the conversion of **20** to **21** because a more attractive option presented itself. The nmr signals assigned to **21** were at 7.74 and 6.82 ppm, whereas the corresponding H4 and H5 signals in **19** occur at 7.66 and 6.40 ppm. This suggested that the methylidene malonate group might be electron withdrawing enough to activate the 2-position for displacement. Reaction of cyclopropylamine with diethyl(ethoxymethylidene)malonate gave the desired reagent **22** quantitatively (Scheme 6). Generation of the anion of **22** with sodium hydride in dimethylsulfoxide, followed by treatment with the dichloride **3** at 50° gave the displacement product **23** in 86% yield. Compound **23** had pyridyl resonances at 7.95 and 7.24 ppm, and was completely consumed when reacted with the piperazine **4** in dimethylsulfoxide at 100° for 16 hours. Approximately 40% of the product was tentatively identified as a 1:1 mixture of the desired displacement product **21** and the demalonylidenylated chloride **8**. Running the reaction for 3 hours provided 65% completion but led to a similar ratio of products. Apparently the cleavage of the side chain is in direct competition with the displacement of the 2-chlorine. Presumably Michael addition to the enedioate system of **23**, followed by expulsion of **8** competes effectively with the sluggish chlorine displacement. To see if a change of nucleophiles would help, piperazine itself was reacted with **23**. The reaction was complete within 1 hour at 25° in dimethyl sulfoxide, but the reaction gave mainly the cleavage product **8**. To circumvent this poor yield, the possibility of cyclizing **23** to the 8-chloronaphthyridine **24** was explored. The EMME adduct **23** reacted rapidly with acetic anhydride/concentrated sulfuric acid at 60°. Isolation and purification provided a 40% yield of a more polar product with the expected single ethyl group and a cyclopropyl group in the ^{1}H nmr spectrum. However, the lowfield spectrum was not consistent with that expected of **24**. Instead of two singlets, it consisted of 3 apparent multiplets. The picture simplified when part of the product crystallized, revealing that the reaction product was a 1:1 mixture of two compounds. They had superimposable highfield nmr resonances and rather similar AB quartets for the H4 and H5 protons, plus singlets for the methylidene protons. The

Scheme 5

Attempted Preparation of EMME Products



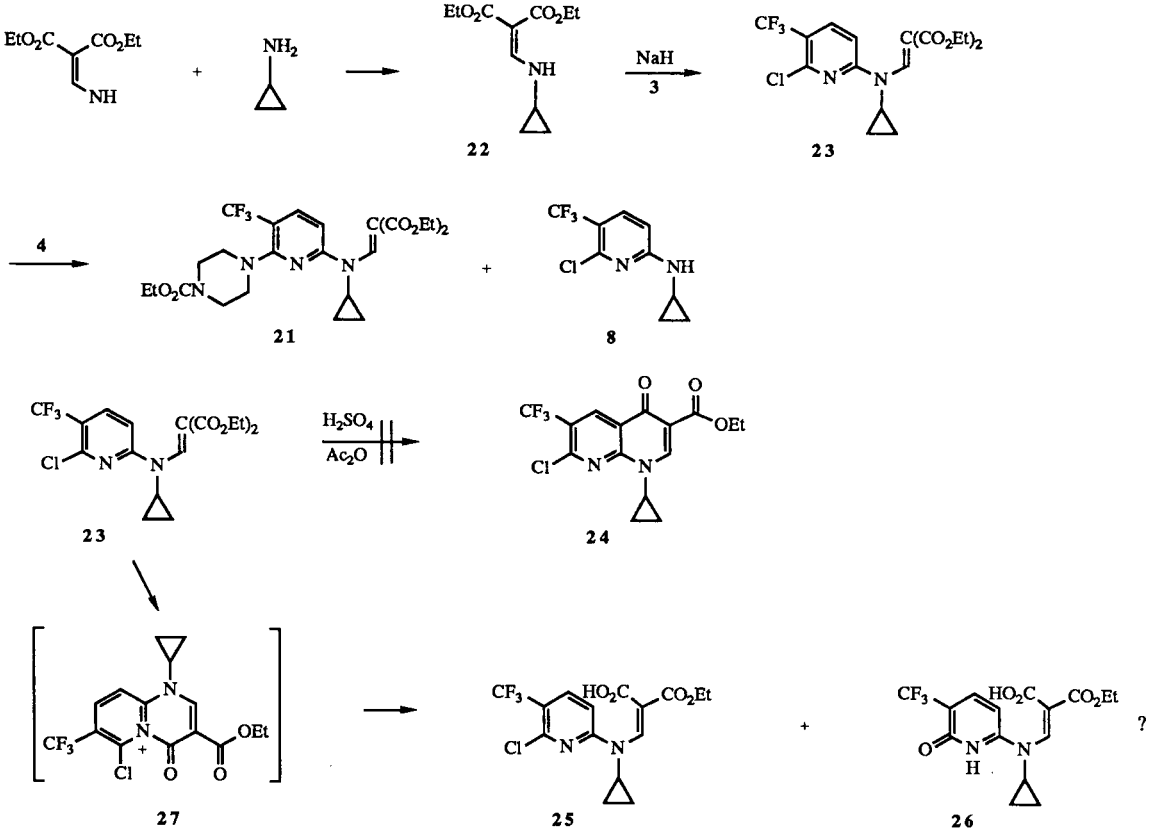
crystalline compound was identified by full spectroscopy as **25**, the simple half acid ester derived from a single hydrolysis of the EMME adduct **23**. The other component was tentatively identified by a fortuitous scan in a time dependent mass spectrum, which gave a molecular ion consistent with pyridone half acid ester **26**. Both of these components would be expected products if **23** initially cyclized onto the nitrogen to give **27** [11]. Hydrolysis could readily give either product, depending on whether water attacked at the carbonyl or the imidoyl chloride first.

This undesired pathway is presumably a reflection of the low electron density in the aromatic ring, and might be circumvented by replacing the chlorine with a more efficient electron donating substituent. Therefore, the chloride **23** was reacted with sodium thiophenoxide, which underwent displacement in dimethylformamide at 25° to give the desired sulfide **28** in 89% yield (Scheme 7). More conveniently, it was found that the sequential treatment of a dimethyl sulfoxide solution of the anion of the enamine **22** followed by thiophenoxide produced the sulfide **28** in one pot in 89% crude yield. Surprisingly, **28** did not react at all when treated at 60° with acetic anhydride and sulfuric acid, but at 110° the desired 7-thionaphthyridine **29** was obtained in 45% yield after crystallization. With the ring system in hand, oxidation of the sulfide to a sulfone was the next task. This did not turn out to be straightforward, as the oxidation to the sulfoxide **30** was rapid, but subsequent oxidation to the sulfone **31** was very slow. Unfortunately the sulfoxide was not stable, and on extended reaction time in chloroform, or a few hours in tetrahydrofuran, it rearranged to an unidentified product which did react with piperazine, but did not produce the desired 7-aminonaphthyridine **32**. In the 6-fluoro series the sulfoxide is displaced quite efficiently by amines to give 3:1 mixture of the desired 7-aminonaphthyridines and a 7-oxo by-product in respectable yield [12]. However, treatment of the sulfoxide **30** with piperazine gave no trace of the penultimate ester **32**. Reaction of sulfide **29** with 3 equivalents of *m*-chloroperoxybenzoic acid in refluxing dichloromethane gave over 90% conversion to the sulfone **31** with about 10% rearrangement.

The sulfone **31** reacted rapidly with piperazine in acetonitrile at 25° to give the 7-aminonaphthyridine ester **32** in 49% yield based on the sulfide **29**. Saponification with sodium hydroxide in ethanol gave the desired enoxacin analogue **33** in 60% yield, after isoelectric precipitation. Sub-

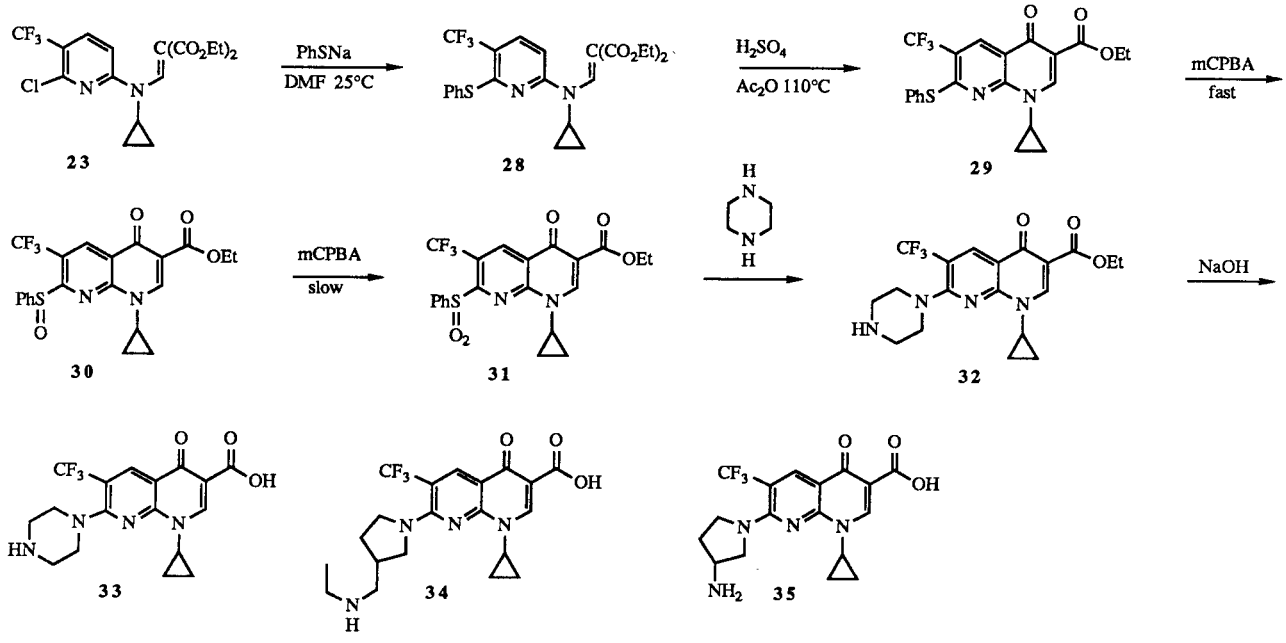
Scheme 6

Preparation and Attempted Ring Closure of EMME Product 23



Scheme 7

Synthetic Route to 6-Trifluoromethyl-1,8-naphthyridines



stitution of 3-(ethylaminomethyl)pyrrolidine for piperazine in this sequence gave the corresponding naphthyridine **34** in 14% yield for the final 3 steps. The 7-(3-amino-1-pyrrolidinyl)naphthyridine **35** was produced from the sulfone **31** by reaction with 3-(*N*-*t*-butoxycarbonylamino)pyrrolidine followed by acid hydrolysis. Compounds **33-35** were tested for inhibition of bacterial gyrase and against a standard battery of microorganisms *in vitro*, and showed about 100-fold less activity than the corresponding 6-fluoronaphthyridine analogues [13].

In conclusion, this paper describes a synthesis of 6-(trifluoromethyl)naphthyridine analogues of enoxacin, one of the "fluoroquinolone" antibiotics. The synthesis is a convergent one, allowing different 7-amino sidechains to be introduced late in the sequence, as shown in Scheme 7. The naphthyridine system was constructed in two steps in 40% yield from a dichloropyridine using a novel methylidene malonate reagent and a thiol substituent to allow the cyclization of the pyridone ring onto the pyridine nucleus. It also illuminates the problems caused by the trifluoromethyl group, which seems to decrease aromatic ring electron density, without appreciably activating ring substituents towards nucleophilic displacement. This property differentiates the CF_3 group from most other electron withdrawing groups, and probably reflects the fact that CF_3 is a very powerful sigma electron acceptor with no appreciable pi component. Our results are consistent with the CF_3 group deactivating the *ortho* position sterically slightly more than it activates it inductively.

EXPERIMENTAL

Melting points were taken on a Hoover capillary melting point apparatus and are uncorrected. Infrared (ir) spectra were determined on a Digilab FTS-14 or Nicolet FT IR SX-20 with 2 cm resolution. Proton magnetic resonance (nmr) spectra were recorded on a Varian EM-390 or an IBM 100 WP100SY spectrometer. Chemical shifts are reported in δ units relative to internal tetramethylsilane. Mass spectra were recorded on either a Finnigan 4500 GCMS or a VG Analytical 7070E/HF with an 11/250 Data System. Solutions were dried over magnesium sulfate and concentrated on a rotary evaporator at 35-40° and pressures of 10-20 mm. All moisture sensitive reactions were carried out under a dry nitrogen atmosphere. Elemental analyses were performed on a Perkin-Elmer 240 elemental analyzer. Column and flash chromatography was performed using E. Merck flash grade silica gel (70-230 mesh). Preparative thick layer chromatography was done on 20 × 20 cm silica gel plates.

4-[6-Chloro-5-(trifluoromethyl)-2-pyridinyl]-1-piperazinecarboxylic Acid Ethyl Ester (**5**).

To a 0° solution of 0.43 g (2.0 mmoles) of 2,6-dichloro-3-(trifluoromethyl)pyridine (**3**), 0.22 g (2.2 moles) of triethylamine and 5 ml of dichloromethane was added 0.32 g (2.0 mmoles) of *N*-carbethoxyethylpiperazine (**4**). The reaction mixture was allowed to warm to room temperature where it was stirred for 48 hours. After washing with 10 ml of water which was back extracted with dichloromethane (2 × 10 ml), the combined organic layers were washed with saturated sodium chloride solution (brine), dried and concentrated *in vacuo* to give 0.65 (96%) of **5** as a yellow oil which solidified upon standing. A sample recrystallized from hexane had mp 87-89°; ^{1}H nmr (deuteriochloroform): δ 1.20 (t, J = 7 Hz, 3H, CH_3), 3.43-3.63 (m, 4H), 4.10 (q, J = 7.1 Hz,

2H, OCH_2), 6.41 (d, J = 8.85 Hz, 1H, H5), 7.59 (d, J = 8.85 Hz, 1H, H4).

Anal. Calcd. for $C_{13}H_{15}ClF_3N_3O_2$: C, 46.23; H, 4.48; N, 12.44. Found: C, 46.01; H, 4.11; N, 12.21.

6-Chloro-*N*-cyclopropyl-5-(trifluoromethyl)-2-pyridinamine (**8**) 6-Chloro-*N*-cyclopropyl-3-(trifluoromethyl)-2-pyridinamine (**7**).

A solution of 2.16 g (10.0 mmoles) of **3**, 2.28 g (40 mmoles) of cyclopropylamine and 50 ml of acetonitrile was heated at reflux for 20 hours. The solvent was removed *in vacuo* and the residue was partitioned between ether and water (30 ml each). The ether layer was separated and the aqueous layer was reextracted with ether (20 ml). The combined ether layers were washed with water (2 × 20 ml), brine (20 ml) and dried. The solvent was removed *in vacuo* to give 2.20 g (94%) of a 3:1 mixture of **8** and **7**, established by ^1H and ^{13}C nmr.

2,6-Bis(phenylthio)-3-(trifluoromethyl)pyridine (**10**).

To a suspension of 0.20 g (5 mmoles) of hexane washed 60% sodium hydride-mineral oil in 4 ml of hexamethylphosphoramine was added 0.55 g (5 mmoles) of thiophenol. The reaction mixture was stirred at 25° until gas evolution ceased (approximately 10 minutes) and the light yellow turbid solution was treated with 0.43 g (2.0 mole) of **3**. A vigorous exotherm with a transient orange-red color was followed by a heavy yellow precipitate. The reaction mixture was heated at 100° for one hour, cooled to 25° and poured into 25 ml of 0.5 *N* sodium hydroxide. After extracting with ether (2 × 20 ml), the combined ether layers were washed with water (3 × 20 ml), brine, dried and concentrated *in vacuo* to give 0.70 g (96%) of **10** as a pale yellow oil; ^1H nmr (deuteriochloroform): δ 6.54 (d, J = 8 Hz, 1H, H5), 7.05-7.55 (m, 11H, Ar + H4).

Anal. Calcd. for $C_{18}H_{12}F_3NS_2$: C, 59.49; H, 3.33; N, 3.86. Found: C, 59.53; H, 3.52; N, 4.08.

2,6-Bis(phenylsulfonyl)-3-(trifluoromethyl)pyridine (**12**).

To a solution of 2.0 g (10 mmoles) of 85% *m*-chloroperoxybenzoic acid in 10 ml of dichloromethane was added 0.73 g (2.0 mmoles) of **10**. After an initial exotherm, the reaction mixture was stirred at 25° for 24 hours. The mixture was cooled to 0° and the precipitate was removed by filtration. The filtrate was washed with 50 ml of an 0.2 *M* solution of dipotassium acid phosphate (K_2HPO_4), water, brine (20 ml each), dried and the solvent removed *in vacuo* to give 0.83 g (97%) of **12** as a white waxy semisolid; ^1H nmr (deuteriochloroform): δ 7.3-8.1 (m, 11H, Ar + H4), 8.33 (d, J = 8 Hz, 1H, H5).

Anal. Calcd. for $C_{18}H_{12}F_3NO_4S_2$: C, 50.58; H, 2.83; N, 3.28; S, 15.00. Found: C, 50.43; H, 2.96; N, 3.19; S, 14.82.

N-Cyclopropyl-6-(phenylsulfonyl)-3-(trifluoromethyl)-2-pyridinamine (**13**) and *N*-Cyclopropyl-(6-phenylsulfonyl)-5-(trifluoromethyl)-2-pyridinamine (**14**).

To a 0° solution of 1.0 g (2.0 mmoles) of **12** in 10 ml of dichloromethane was added a solution of 0.30 g (3.0 mmoles) of triethylamine and 0.12 g (2.0 mmoles) of cyclopropylamine. The solution was allowed to come to 25° where it was stirred for 8 hours. An additional 0.23 g (4.0 mmoles) of cyclopropylamine was added and the reaction mixture was stirred at reflux for 90 hours. The reaction mixture was diluted with dichloromethane (20 ml), washed with water (2 × 10 ml), brine (10 ml), dried and the solvent removed *in vacuo* to give 0.68 g of a mixture of **13** and **14** as a viscous orange oil. Preparative thick layer chromatography eluting with chloroform afforded 0.30 g of **13** (Rf = 0.55) as a light yellow oil; ^1H nmr (deuteriochloroform): δ 0.28-0.70 (m, 4H, cyclopropyl), 2.15-2.46 (m, 1H), 5.45 (broad s, 1H, NH), 6.68 (1H, J = 9 Hz, H5), 7.25-7.60 (m, 3H, Ar), 7.71 (d, J = 9 Hz, 1H, H4), 7.90 (dd, J = 9 and 2.5 Hz, 2H, *ortho* to SO_2).

Anal. Calcd. for $C_{15}H_{13}F_3N_2O_2S$: C, 52.62; H, 3.83; N, 8.19. Found: C, 52.73; H, 3.71; N, 8.01.

Elution also afforded 0.13 g of **14** (Rf = 0.31) as a light yellow gum; ^1H nmr (deuteriochloroform): δ 0.28-0.53 (m, 2H, cyclopropyl), 0.55-0.85 (m, 2H, cyclopropyl), 2.52-2.80 (m, 1H), 5.25 (broad s, 1H, NH), 7.37-7.60 (m, 4H), 7.76 (d, J = 8 Hz, 1H, H4), 8.05 (dd, J = 8 and 2.5 Hz, 1H, *ortho* to SO_2).

Anal. Calcd. for $C_{15}H_{13}F_3N_2O_2S$: C, 52.62; H, 3.83; N, 8.19. Found: C, 52.40; H, 3.56; N, 8.02.

N-Cyclopropyl-4-methylbenzenesulfonamide (**17a**).

To a 0° solution of 1.71 g (30 mmoles) of cyclopropylamine, 3.03 g (30 mmoles) of triethylamine and 25 ml of dichloromethane was added portionwise (over 5 minutes) 4.75 g (25 mmoles) of solid *p*-toluenesulfonyl chloride. After the initial exotherm had subsided, the reaction mixture was stirred at 25° for 14 hours and poured onto 50 ml of water. The aqueous layer was extracted with dichloromethane (25 ml) and the combined organic layers were washed with 20 ml of a 1.0 *M* solution of disodium hydrogen phosphate (Na_2HPO_4), water (25 ml), brine (25 ml), dried and the solvent removed *in vacuo* to give 3.79 g (72%) of **17a** mp 74-76°; ^1H nmr (deuteriochloroform): δ 0.5-0.7 (m, 4H, cyclopropyl), 2.1-2.35 (m, 1H), 2.38 (s, 3H, CH_3), 5.11 (broad s, 1H, NH), 7.25 (d, J = 8 Hz, 2H), 7.74 (d, J = 8 Hz, 2H).

Anal. Calcd. for $C_{10}H_{13}NO_2S$: C, 56.85; H, 6.20; N, 6.63. Found: C, 56.58; H, 6.05; N, 6.42.

N-Cyclopropyl-4-methyl-*N*-[6-chloro-5-(trifluoromethyl)-2-pyridinyl]benzenesulfonamide (**15**).

To an 80° suspension of 0.50 g (12.5 mmoles) of hexane washed 60% sodium hydride-mineral oil in 20 ml of dimethylformamide was added, in small portions, 2.11 g (10 mmoles) of **17a**. After the addition was complete, the mixture was stirred at 80° for 10 minutes and treated with 2.16 g (10 mmoles) of **3**. After 1 hour at 80°, the reaction mixture was allowed to cool to 20° and poured into 100 ml of an 0.1 molar solution of sodium dihydrogen phosphate (NaH_2PO_4). The mixture was extracted with ether (3 × 30 ml) and the combined ether layers were washed with water (2 × 50 ml), brine (50 ml), dried and the solvent evaporated *in vacuo* to give 3.51 g of **15** as a thick brown oil. Purification by flash chromatography on silica gel (200 g) eluting with 5% ethyl acetate in hexane (600 ml) and 10% ethyl acetate in hexane (1.4 l), collecting fractions based on tlc afforded 2.29 g (59%) of pure **15** as a clear colorless syrup; ^1H nmr (deuteriochloroform): δ 0.77-1.01 (m, 4H, cyclopropyl), 2.40 (s, 3H, CH_3), 2.59-2.82 (m, 1H), 7.25 (d, J = 8 Hz, Ar), 7.42 (d, J = 8 Hz, H5), 7.65 (d, J = 8 Hz, Ar), 7.92 (d, J = 8 Hz, H4).

Anal. Calcd. for $C_{16}H_{15}ClF_3N_2O_2S$: C, 49.04; H, 3.86; N, 7.15; S, 8.18. Found: C, 48.89; H, 3.95; N, 7.03; S, 8.02.

N-Cyclopropyl-4-methyl-*N*-[6-(4-methyl-1-piperazinyl)-5-(trifluoromethyl)-2-pyridinyl]benzenesulfonamide (**16**).

A solution of 2.29 g (5.90 mmoles) of **15** and 1.20 g (12.0 mmoles) of *N*-methylpiperazine in 6 ml of dimethylformamide was heated at 100° for 15 hours. The reaction mixture was diluted with 30 ml of water and extracted with ether (3 × 20 ml). The combined ether layers were washed with water (2 × 30 ml),

brine (30 ml), dried and the solvent evaporated *in vacuo* to give 2.49 g of impure **16** as a light yellow gum. Purification by column chromatography eluting with chloroform provided 2.31 g (86%) of **16** (Rf = 0.65) as a colorless waxy solid, mp 88-92°; ^{1}H nmr (deuteriochloroform): δ 0.77-1.02 (m, 4H, cyclopropyl), 2.40 (s, 3H, CH_3), 2.59-2.82 (m, 1H), 7.25 (d, J = 8 Hz, 2H), 7.42 (d, J = 8 Hz, 1H, H5), 7.65 (d, J = 8 Hz, 2H), 7.92 (d, J = 8 Hz, 1H, H4).

Anal. Calcd. for $C_{22}H_{25}F_3N_4O_2S$: C, 55.51; H, 5.51; N, 12.33; S, 7.05. Found: C, 55.32; H, 5.63; N, 12.00; S, 7.33.

Cyclopropylcarbamic Acid *t*-Butyl Ester (**17b**).

A solution of 2.39 g (42 mmole) of cyclopropylamine in 60 ml of dichloromethane was added dropwise, over 30 minutes to a solution of 8.72 g (40 mmole) of di-*t*-butyl dicarbonate in 40 ml of dichloromethane. After 2 hours at 25°, the solvent was removed *in vacuo* at 50° to give 6.24 g (99%) of **17b** as a white waxy solid, mp 61-63°; ^{1}H nmr (deuteriochloroform): δ 0.4-0.8 (m, 4H, cyclopropyl), 1.41 (m, 9H, *t*-butyl), 2.36-2.66 (s, 1H), 4.4-5.0 (broad s, 1H, NH).

Anal. Calcd. for $C_8H_{15}NO$: C, 61.12; H, 9.62; N, 8.91. Found: C, 60.98; H, 9.91; N, 8.72.

[6-Chloro-5-(trifluoromethyl)-2-pyridinyl]cyclopropylcarbamic Acid *t*-Butyl Ester (**18**).

To a suspension of 0.50 g (12.5 mmoles) of hexane washed 60% sodium hydride-mineral oil in 10 ml of dimethylformamide was added 1.57 g (10 mmoles) of **17b**. After the initial exotherm, the reaction was allowed to cool to 25° over 20 minutes and was then treated with 2.16 g (10 mmoles) of **3**. After the initial exotherm had ceased, the reaction mixture was stirred at room temperature for 2 hours, and poured into 100 ml of saturated sodium bicarbonate. The mixture was extracted with ether (2 × 50 ml), and the combined ether layers were washed with water (3 × 50 ml), brine (50 ml), dried and the solvent evaporated *in vacuo* to give 3.62 g of **18** as a clear tan oil; ^{1}H nmr (deuteriochloroform): δ 0.45-0.55 (m, 2H, cyclopropyl), 0.94-1.02 (m, 2H, cyclopropyl), 1.45 (s, 9H, *t*-butyl), 3.06 (septet, J = 3.8 Hz, 1H, cyclopropyl), 7.49 (d, J = 8.5 Hz, 1H, H4).

Anal. Calcd. for $C_{14}H_{16}ClF_3N_2O_2$: C, 49.93; H, 4.79; N, 8.32. Found: C, 50.11; H, 4.90; N, 8.16.

4-{6-[(*t*-Butoxycarbonyl)cyclopropylamino]-3-(trifluoromethyl)-2-pyridinyl}-1-piperazinecarboxylic Acid Ethyl Ester (**19**).

A solution of 3.02 g (9 mmoles) of **18** 1.42 g (9 mmoles) of *N*-carboxyethylpiperazine (**4**), 3.03 g (10 mmoles) of triethylamine and 5 ml of dimethylformamide was heated at 140° for 20 hours. After cooling to 25°, the solid reaction mixture was added to 100 ml of water and extracted with ether (3 × 50 ml). The combined ether layers were washed with water (3 × 50 ml), brine (50 ml), dried and solvent evaporated *in vacuo* to give 3.08 g of crude **19** as a dark brown viscous oil. The crude product was purified by flash chromatography eluting with chloroform to give 1.89 g (46%) of **19** as a golden syrup; ^{1}H nmr (deuteriochloroform): δ 0.45-0.55 (m, 2H, cyclopropyl), 0.9-1.0 (m, 2H, cyclopropyl), 1.28 (t, J = 7.2 Hz, 3H, CH_3), 1.53 (s, 9H, *t*-butyl), 2.95 (septet, J = 3.8 Hz, 1H, cyclopropyl), 3.15-3.25 (m, 4H, piperazine), 3.55-3.65 (m, 4H, piperazine), 4.17 (q, J = 7 Hz, 2H, OCH_2), 7.23 (d, J = 8.5 Hz, 1H, H3), 7.77 (d, J = 8.5 Hz, 1H, H4).

Anal. Calcd. for $C_{21}H_{29}F_3N_4O_4$: C, 55.01; H, 6.38; N, 12.22. Found: C, 55.34; H, 6.22; N, 12.16.

4-[6-(Cyclopropyl)amino-3-(trifluoromethyl)-2-pyridinyl]-1-piperazinecarboxylic Acid Ethyl Ester (**20**).

To a solution of 1.83 g (4 mmoles) of **19** in 10 ml of dichloromethane was added 9.12 g (80 mmoles) of trifluoroacetic acid. The reaction mixture was stirred at 25° for 3 hours. After diluting with 50 ml of dichloromethane, the reaction mixture was stirred with saturated sodium carbonate (2 × 50 ml) separating the organic layer between washes. After drying, the solvent was removed *in vacuo* to give 1.39 g (66%) of **20** as a light brown oil. Purification by flash chromatography eluting with 10%, 15% and, 20% ethyl acetate in hexane (1.5 ℓ, 0.5 ℓ, and 0.5 ℓ respectively) afforded analytically pure **20**, mp 82-84°; ^{1}H nmr (deuteriochloroform): δ 0.4-1.0 (m, 4H, cyclopropyl), 1.24 (t, J = 7.0 Hz, 3H, CH_3), 2.35-2.60 (m, 1H), 3.00-3.30 (m, 4H, piperazine), 3.40-3.72 (m, 4H, piperazine), 4.07 (q, J = 7 Hz, 2H, OCH_2), 6.28 (d, J = 9 Hz, 1H, H5), 7.55 (d, J = 9 Hz, 1H, H4).

Anal. Calcd. for $C_{16}H_{21}F_4N_4O_2$: C, 53.63; H, 5.87; N, 15.64; F, 15.92. Found: C, 53.79; H, 5.98; N, 15.70; F, 16.26.

[(Cyclopropylamino)methylene]propanedioic Acid Diethyl Ester (**22**).

To a 0° solution of 10.8 g (50 mmoles) of diethyl (ethoxymethylidene) malonate in 50 ml of methanol was added 2.85 g (50 mmoles) of cyclopropylamine. After 15 minutes at 0°, the solvent was removed *in vacuo* at 45° to give 11.4 g (100%) of **22** as a pale yellow oil; ^{1}H nmr (deuteriochloroform): δ 0.6-0.9 (m, 4H, cyclopropyl), 1.29 (t, J = 6 Hz, 3H, CH_3), 1.32 (t, J = 6 Hz, 3H, CH_3), 2.63-2.93 (m, 1H), 4.10 (q, J = 6 Hz, 2H, OCH_2), 4.13 (q, J = 6 Hz, 2H, OCH_2), 8.00 (d, J = 14 Hz, 1H, vinyl), 9.10 (broad d, J = 14 Hz, 1H, NH).

Anal. Calcd. for $C_{11}H_{17}NO_4$: C, 58.13; H, 7.54; N, 6.17. Found: C, 57.88; H, 7.76; N, 6.02.

[[Cyclopropyl[6-chloro-5-(trifluoromethyl)-2-pyridinyl]amino]-methylene]propanedioic Acid Diethyl Ester (**23**).

To a suspension of 0.88 g (22 mmoles) of hexane washed 60% sodium hydride-mineral oil in 10 ml of dimethyl sulfoxide was added a solution of 4.54 g (20 mmoles) of **22** in 20 ml of dimethyl sulfoxide. After an initial exotherm, the reaction mixture was stirred at 25° until gas evolution ceased (30 minutes). The resulting solution was treated dropwise with 4.32 g (20 mmoles) of **3** and heated to 50° for 4 hours. After stirring an additional 15 hours at 25°, the reaction mixture was poured into 100 ml of water and extracted with ether (3 × 25 ml). The combined ether extracts were washed with water (2 × 50 ml), brine (50 ml), dried and the solvent evaporated *in vacuo* to give 7.01 g of impure **23**. Column chromatography eluting with 2% methanol in chloroform afforded analytically pure **23**, mp 103-108°; ^{1}H nmr (deuteriochloroform): δ 0.78 (m, 2H), 1.04 (m, 2H), 1.32 (t, J = 7.0 Hz, 3H, CH_3), 1.36 (t, J = 7.1 Hz, 3H, CH_3), 2.97 (m, 1H, NH), 4.27 (q, J = 7.0 Hz, 2H, OCH_2), 4.29 (q, J = 7.1 Hz, 2H, OCH_2), 7.24 (d, J = 8.6 Hz, 1H, H3), 7.95 (d, J = 8.6 Hz, H4), 8.80 (s, 1H, vinyl).

Anal. Calcd. for $C_{17}H_{18}ClF_3N_2O_4$: C, 50.18; H, 4.43; N, 6.89; Cl, 8.73; F, 14.02. Found: C, 50.36; H, 4.35; N, 6.71; Cl, 9.06; F, 14.35.

[[Cyclopropyl[6-(phenylthio)-5-(trifluoromethyl)-2-pyridinyl]-amino]methylene)propanedioic Acid Diethyl Ester (**28**).

To a suspension of 1.12 g (28 mmoles) of hexane washed 60% sodium hydride-mineral oil in 20 ml of dimethyl sulfoxide was added a solution of 5.68 g (25 mmoles) of **22** in 10 ml of dimethyl

sulfoxide. After an initial exotherm, the reaction mixture was stirred at 25° until gas evolution ceased (20 minutes) and 5.40 g (25 mmoles) of **3** was added dropwise. The light orange-brown slurry was heated to 50° for 4.5 hours, cooled to 25° and treated with a solution of sodium thiophenoxide {prepared from 1.12 g (28 mmoles) of hexane washed 60% sodium hydride and 3.3 g (30 mmoles) of thiophenol in 20 ml of dimethylsulfoxide}, dropwise, over 15 minutes. The reaction was stirred at 25° for 2.5 hours and 200 ml of water was added to the solidified reaction mixture. The light brown precipitate which formed was removed by filtration, washed with water (100 ml) and dried *in vacuo* at 40° to give 10.7 g (89%) of **28**. An analytical sample was obtained by recrystallizing from methanol and had, mp 123-125°; ^{1}H nmr (deuteriochloroform): δ 0.62-0.70 (m, 2H), 0.86-0.96 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H, CH_3), 1.32 (t, J = 7.1 Hz, 3H, CH_3), 2.81 (septet, J = 4 Hz, 1H, cyclopropyl), 4.21 (q, J = 7.1 Hz, 2H, OCH_2), 4.24 (q, J = 7.1 Hz, 2H, OCH_2), 7.00 (d, J = 8.6 Hz, 1H, H3), 7.41-7.46 (m, 3H, Ar), 7.57-7.62 (m, 2H, Ar), 7.81 (d, J = 8.6 Hz, 1H, H4), 8.12 (s, 1H, vinyl).

Anal. Calcd. for $C_{23}H_{23}F_3N_2O_4S$: C, 57.50; H, 4.79; N, 5.83; S, 6.67. Found: C, 57.29; H, 4.76; N, 5.82; S, 6.56.

1-Cyclopropyl-1,4-dihydro-4-oxo-7-(phenylthio)-6-(trifluoromethyl)-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester (**29**).

To a suspension of 10.3 g (21.5 mmoles) of **28** in 50 ml of acetic anhydride was added dropwise, over 15 minutes, 20 ml of concentrated sulfuric acid. The reaction was exothermic to reflux and after the addition, the mixture was stirred until the temperature reached 35° (30 minutes). The reaction mixture was poured into 200 ml of ice water and stirred for 30 minutes diluting with an additional 100 ml of water. The initial gummy precipitate crystallized with stirring and it was removed by filtration, washed with water and dried *in vacuo* at 50° to give 6.99 g of crude **29**. One recrystallization from acetone afforded the analytical sample, 4.17 g (45%), mp 204-206°; ^{1}H nmr (deuteriochloroform): δ 0.53-0.61 (m, 2H), 0.62-0.72 (m, 2H), 1.38 (t, J = 7 Hz, 3H, CH_3), 2.92-3.01 (m, 1H), 4.36 (q, J = 7 Hz, 2H, OCH_2), 7.40-7.52 (m, 3H, Ar), 7.60-7.65 (m, 2H, Ar), 8.47 (s, 1H, H5), 8.82 (s, 1H, H2).

Anal. Calcd. for $C_{21}H_{17}F_3N_2O_3S$: C, 58.06; H, 3.92; N, 6.45. Found: C, 58.15; H, 3.94; N, 6.36.

1-Cyclopropyl-1,4-dihydro-4-oxo-7-(phenylsulfonyl)-6-(trifluoromethyl)-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester (**31**).

A solution of 2.17 g (5.0 mmoles) of **29**, 3.0 g (15 mmoles) of 85% *m*-chloroperoxybenzoic acid and 100 ml of dichloromethane was heated at reflux for 3.5 hours. The reaction mixture was allowed to cool to 25°, poured into 100 ml of saturated sodium carbonate and layers separated. The aqueous layer was extracted with 50 ml of dichloromethane and the combined organic layers were washed with saturated sodium carbonate (50 ml). After drying, the solvent was removed *in vacuo* to give 2.54 g (quantitative yield) of **31** as a yellow foam; ^{1}H nmr (deuteriochloroform): δ 0.71-0.76 (m, 4H, cyclopropyl), 1.36 (t, J = 7 Hz, 3H, CH_3), 3.91-4.15 (m, 1H), 4.26 (q, J = 7 Hz, 2H, OCH_2), 7.40-7.72 (m, 3H, Ar), 7.85-8.08 (m, 2H, Ar), 8.48 (s, 1H, H5), 9.04 (s, 1H, H2).

Anal. Calcd. for $C_{21}H_{17}F_3N_2O_5S$: C, 54.07; H, 3.68; N, 6.01. Found: C, 54.25; H, 3.76; N, 6.25.

1-Cyclopropyl-1,4-dihydro-4-oxo-7-(1-piperazinyl)-6-(trifluoromethyl)-1,8-naphthyridine-3-carboxylic Acid (**33**).

A solution of 0.70 g (8 mmoles) of piperazine, 0.46 g (1 mmole) of **31** and 20 ml of acetonitrile was stirred at 25° for 30 minutes. The reaction mixture was poured into 50 ml of water and extracted with ethyl acetate (2 × 50 ml). The combined organic layers were washed with water (2 × 50 ml), brine (25 ml), dried and the solvent evaporated *in vacuo*. The residue was suspended in a solution of 0.05 g (1.25 mmoles) of sodium hydroxide in 5 ml of ethanol and the mixture stirred at room temperature for 8 hours. The solvent was removed *in vacuo* and the residue was dissolved in 6 ml of water and the *p*H adjusted to 7.3 with 1.0 *M* hydrochloric acid. The yellow-brown solid was collected by filtration, washed with water (2 × 5 ml), and dried *in vacuo* at 70° to give 0.14 g (37%) of **33**, mp 234-238°; ^{1}H nmr (trifluoroacetic acid): δ 1.33-1.42 (m, 2H, cyclopropyl), 1.5-1.65 (m, 1H, cyclopropyl), 3.75-3.95 (m, 4H, piperazine), 4.10-4.25 (m, 1H), 4.35-4.65 (m, 4H, piperazine), 9.17 (s, 1H, H5), 9.43 (s, 1H, H2).

Anal. Calcd. for $C_{17}H_{17}F_3N_4O_3 \cdot 0.33H_2O$: C, 52.58; H, 4.55; N, 14.43; F, 14.69. Found: C, 52.54; H, 4.41; N, 14.38; F, 14.66.

1-Cyclopropyl-7-[3-[(ethylamino)methyl]-1-pyrrolidinyl]-1,4-dihydro-4-oxo-6-(trifluoromethyl)-1,8-naphthyridine-3-carboxylic Acid (**34**).

A solution of 0.38 g (3.0 mmoles) of (*N*-ethyl-3-pyrrolidine)-methanamine, 0.50 g (5 mmoles) of triethylamine, 1.27 g (2.5 mmoles) of **31** and 20 ml of acetonitrile was stirred at room temperature for 30 minutes. The reaction mixture was poured into 50 ml of water and extracted with ethyl acetate (2 × 25 ml). The combined organic layers were washed with water (2 × 25 ml), brine (25 ml), dried and the solvent evaporated *in vacuo*. The residue was dissolved in a solution of 0.20 g (5 mmoles) of sodium hydroxide in 15 ml of ethanol. After stirring at 25° for 3 hours, the solvent was removed *in vacuo*, the residue was dissolved in water (30 ml) and washed with ethyl acetate (2 × 20 ml). The aqueous layer was adjusted to *p*H 7.4 with 1.0 *M* hydrochloric acid and the resulting gummy precipitate was heated in the aqueous mixture at 60° until a yellow, free-flowing precipitate developed. The precipitate was removed by filtration, washed with water (2 × 15 ml) and dried *in vacuo* at 70° for 4 hours to give 0.14 g (14%) of **34**, mp 210-212°; ^{1}H nmr (trifluoroacetic acid): δ 1.25-1.45 (m, 2H, cyclopropyl), 1.50 (t, J = 7.3 Hz, 3H, CH_3), 1.57 (d, J = 10 Hz, 2H, cyclopropyl), 1.95-2.20 (m, 1H, cyclopropyl), 2.45-2.65 (m, 1H), 2.90-3.12 (m, 1H), 3.31-3.72 (m, 4H), 3.81 (t, J = 10 Hz, 1H, NCH), 4.01-4.20 (m, 2H, CH_2N), 7.10-7.45 (broad s, 2H, NH_2), 9.03 (s, 1H, H5), 9.29 (s, 1H, H2).

Anal. Calcd. for $C_{20}H_{22}F_3N_4O_3 \cdot 0.20\ H_2O$: C, 56.13; H, 5.24; N, 13.10; F, 13.33. Found: C, 55.94; H, 5.47; N, 12.97; F, 13.70.

7-[3-Amino-1-pyrrolidinyl]-1-cyclopropyl-1,4-dihydro-4-oxo-6-(trifluoromethyl)-1,8-naphthyridine-3-carboxylic Acid (**35**).

A suspension of 3-(*N*-*t*-butoxycarbonylamino)pyrrolidine, 0.51 g (5 mmoles) of triethylamine, 1.27 g (2.5 mmoles) of **31** and 20 ml of acetonitrile was stirred at room temperature for 1 hour. The reaction mixture was poured into 100 ml of water and the resulting yellow-brown precipitate was collected by filtration, washed with water (2 × 15 ml) and dried *in vacuo* to give 1.32 g (98%) of protected product. This material was refluxed in a solution of 5 ml of 6.0 *M* hydrochloric acid and 5 ml of ethanol for 3 hours. The solvent was removed *in vacuo* and the residue was dissolved in water. The *p*H was adjusted to 13.0 with 1.0 *N* sodium hydroxide and the resulting solution was rewashed with ethyl acetate (2 × 20 ml). The aqueous layer was adjusted to *p*H 7.1 with 1.0 *M* hydrochloric acid and the mixture was allowed to stand at 4° for 16 hours. The resulting precipitate was removed by filtration,

washed with water (10 ml), ethanol (2 ml), ether (20 ml) and dried *in vacuo* at 70° for 16 hours to give 0.30 g (32%) of **35** as a yellow solid, mp 262-263°; ^{1}H nmr (trifluoroacetic acid): δ 0.60-0.82 (m, 2H, cyclopropyl), 0.85-1.03 (m, 2H, cyclopropyl), 1.93-2.25 (m, 2H), 3.35-3.50 (m, 1H, NCH), 3.61-4.02 (m, 5H), 8.46 (s, 1H, H5), 8.70 (s, 1H, H2).

Anal. Calcd. for $C_{17}H_{17}F_3N_4O_3 \cdot 0.33\ H_2O$: C, 52.58; H, 4.55; N, 14.43; F, 14.69. Found: C, 52.35; H, 4.48; N, 14.23; F, 14.76.

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