Novel 7-Substituted Quinolone Antibacterial Agents. Synthesis of 7-Alkenyl, Cycloalkenyl, and 1,2,3,6-Tetrahydro-4-pyridinyl-1,8-naphthyridines [1]

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A convergent synthesis of 1,8-naphthyridine antibacterials bearing a carbon-carbon bonded, acyclic or cyclic vinyl substituent at the C-7 position has been achieved. The synthetic methodology is based upon the palladium-catalyzed cross coupling of a 7-chloro-1,8-naphthyridine with an appropriately substituted organotin reagent.

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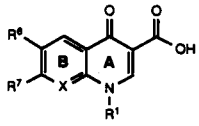
The quinolone antibacterials have emerged as a clinically important class of chemotherapeutic agents [2]. These compounds, represented by **1** (Figure 1), are characterized by the combination of a 1-substituted-1,4-dihydro-4-oxo-3-pyridinecarboxylic acid moiety **A** with a second aromatic or heteroaromatic ring **B** [3].

Figure 1



1

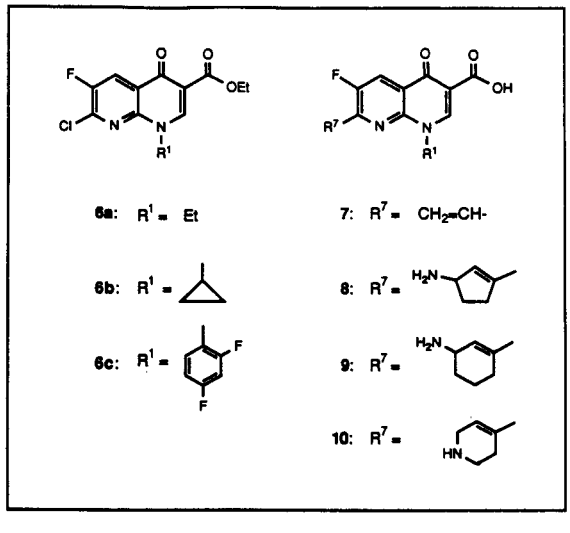
Compound	X	R^1	R^8	R^7
Enoxacin **2**	N	Et	F	1-piperazine
Ciprofloxacin **3**	CH		F	1-piperazine
Tosufloxacin **4**	N		F	3-amino-1-pyrrolidine
Rosoxacin **5**	CH	Et	H	4-pyridine

With the possible exception of N-1, the position of the quinoline or naphthyridine nucleus that has received the greatest attention both in terms of synthesis and SAR is C-7. Medium-sized, nitrogen-containing heterocyclic rings at this position are known to contribute most significantly to the potency and *in vivo* efficacy of these agents [4,5]. Particularly notable are the 1-piperazinyl and the 3-amino-1-pyrrolidinyl groups present in many of the currently relevant quinolones (*e.g.*, enoxacin **2** [6], ciprofloxacin **3** [7], and tosufloxacin **4** [8]).

Although most of the heterocycles that have been evaluated at C-7 are linked to the aromatic nucleus *via* a nitrogen-carbon bond [3,5,9-11], broad spectrum antibacterial activity has been associated mainly with the presence of a basic nitrogen properly positioned within the C-7 substituent (such as the 4-N of the piperazine) [12,13]. The nature of the bonding between the C-7 substituent and the quinoline or naphthyridine nucleus appears to play a less defined role. Rosoxacin **5** [14] is an example of a quinolone possessing an aromatic heterocycle at C-7 not linked through nitrogen. More recently, Culbertson [15] and Domagala [16] have reported on the synthesis of quinolones and naphthyridines bearing other carbon-bonded aromatic heterocycles at C-7, such as 4-thiazolyl, 3- or 4-pyrazolyl, and 4- or 5-pyrimidinyl.

The incorporation of carbon-bonded aliphatic heterocycles or carbocycles at the C-7 position of the quinoline or naphthyridine nucleus, on the other hand, has received less attention [17,18]. In this paper, we wish to present a synthetic strategy that allows the direct attachment of a large variety of unsaturated cyclic, as well as acyclic residues, to a fully functionalized naphthyridine substrate. This methodology has been applied to a convergent syn-

Figure 2



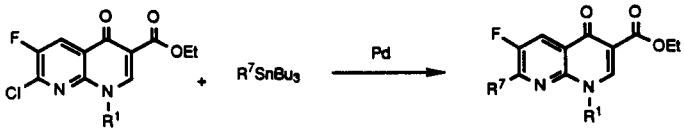
thesis of 1,8-naphthyridine-3-carboxylic acids bearing an ethenyl, a 3-amino-1-cyclopenten-1-yl, a 3-amino-1-cyclohexen-1-yl, or a 1,2,3,6-tetrahydro-4-pyridinyl group at C-7 (**7-10**, Figure 2).

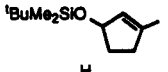
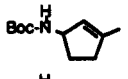
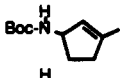
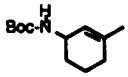
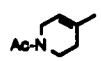
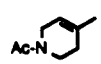
The synthetic approach is based upon Stille's work on the palladium-catalyzed cross coupling reaction of aryl halides with organotin reagents [19-21]. This method offers a number of distinct advantages for the synthesis of carbon-substituted arenes, the most remarkable of which are mild reaction conditions, a high degree of selectivity, and a tolerance of a wide variety of functional groups. We examined the application of this method to 7-chloro-1,8-naphthyridines **6a-c** (Figure 2) [22]. Based on the known reactivity of these compounds towards nucleophilic aromatic substitution at C-7, it was envisioned that a palladium-catalyzed cross coupling with an organotin reagent would provide direct access to novel 7-carbon-substituted derivatives not readily available by more classical methodologies.

Our initial experiments were encouraging. The palladium-catalyzed coupling of **6a** and **6b** with tributylvinyltin proceeded smoothly and with complete chemo- and regioselectivity to give the 7-ethenyl-1,8-naphthyridines **18a** and **18b**, respectively, in very good yields (entries 1 and 2, Table I). The cross-coupling reaction of **6b** with the α-methoxy-substituted vinyltin reagent **14** [23] also occurred in high yield to give the 7-(1-methoxyethenyl) derivative **19** (entry 3). Compounds **18a**, **18b** and **19** are, to our knowledge, the first examples of 6-fluoro-1,8-naphthyridines bearing an unsubstituted or substituted vinyl group at the C-7 position.

The coupling reactions were generally carried out according to Stille's protocol [20], using 1.0-1.5 equivalents of the tin reagent and *ca.* 20 mol% of either bis(triphenylphosphine)dichloropalladium(II) or tetrakis(triphenylphosphine)palladium(0) as the catalyst. In some instances, additional amounts of the corresponding tin reagent and/or the catalyst were added to the reaction mixture to improve the yield of coupled product. The progress of the reaction was monitored by thin-layer chromatography (tlc) or analytical hplc. Once the reaction was determined to be complete, the solvent was evaporated and the residue was re-

Table I



Entry	Substrate	R^1	Organotin	R^7	Conditions [a]	Product	(% Yield)
1	**6a**	Et	**11**	CH_2=CH-	A	**18a**	(70)
2	**6b**		**11**	CH_2=CH-	B	**18b**	(97)
3	**6b**		**12**	CH_2=C(OMe)-	A	**19**	(92)
4	**6b**		**13**		A	**20**	(88)
5	**6b**		**14**		A	**21**	(67)
6	**6b**		**15**		D	**22b**	(43)
7	**6c**		**15**		B	**22c**	(42)
8	**6b**		**16**		B	**23**	(76)
9	**6b**		**17**		C	**24b**	(54)
10	**6c**		**17**		B	**24c**	(83)

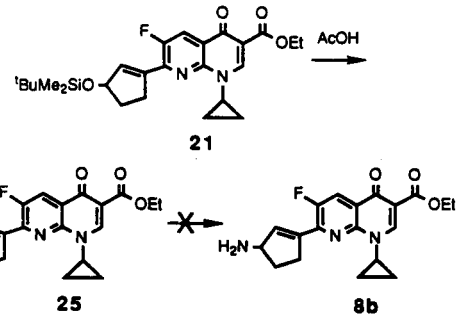
[a] A = $PdCl_2(Ph_3P)_2$ in THF; B = $PdCl_2(Ph_3P)_2$ in DMF; C = $PdCl_2(Ph_3P)_2$ in dioxane; D = $Pd(Ph_3P)_4$ in dioxane

suspended in hexane or cyclohexane, and stirred vigorously for 15-30 minutes. This simple operation allowed the separation of the organotin by-products from the desired 7-substituted-naphthyridine, which was collected by suction-filtration and further purified by column chromatography [24].

The incorporation of a 1-cycloalkenyl group at the C-7 position of the naphthyridine ring was first accomplished by the use of 3-tributylstannyl-2-cyclopentenone **13** [25,26]. The reaction of **6b** with this tin reagent afforded the 7-(3-oxo-1-cyclopenten-1-yl)-1,8-naphthyridine **20** in 88% yield (entry 4). Similarly, the coupling of **6b** with the *O*-silyl-protected 3-tributylstannyl-2-cyclopentenol **14** (entry 5), prepared from **13** by standard procedures, provided the 7-(3-*t*-butyldimethylsilyloxy-1-cyclopenten-1-yl)-1,8-naphthyridine **21**, although in a more modest yield. The lower yield is presumably due to the high steric demands imposed by the presence of the *t*-butyldimethylsily group at the 3-position of cyclopentenylstannane **14** [27].

Compound **21** appeared as a suitable intermediate for the introduction of an amino group at the 3-position of the cyclopentenyl ring. Such an operation would render an isostere of the corresponding 7-(3-amino-1-pyrrolidinyl)-1,8-naphthyridine, in which the pyrrolidine nitrogen has been replaced by an sp^2 carbon. Thus, removal of the silyl protecting group in **21** with acetic acid gave the 7-(3-hydroxy-1-cyclopenten-1-yl)-1,8-naphthyridine **25** (Scheme 1), which was subsequently treated with diphenyl-phosphoryl azide under Mitsunobu's conditions [28]. Unfortunately, a complex mixture of products was obtained. While the cyclopentenyl azide seemed to be the predominant one by proton nmr analysis, several impurities that were present could not be removed. Attempts to carry this material on to the desired amine complicated the mixture further. Alternatively, attempted activation of the hydroxyl group of **25** by reaction with methanesulfonyl chloride and triethylamine in dichloromethane led to extensive decomposition, probably due to the sensitive nature of the intermediate involved.

Scheme I



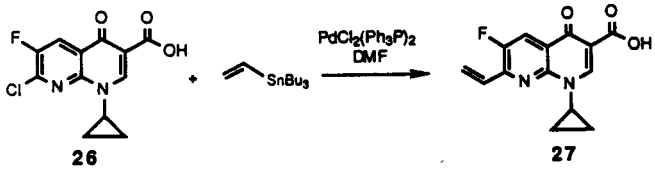
While the palladium-catalyzed cross coupling reaction of 7-chloro-1,8-naphthyridine **6b** with the organotin reagent **14** had been highly chemoselective, the subsequent elaboration of the coupled product into the desired 7-(3-amino-1-cyclopenten-1-yl)-1,8-naphthyridine was not. Clearly, a new approach involving an early introduction of the amino group was required. This approach was successfully carried forward using the *N*-protected-3-amino-1-cycloalkenylstannane **15** [26]. The reaction of 7-chloro-1,8-naphthyridines **6b** and **6c** with **15** provided the coupled products **22b** and **22c**, respectively, in moderate yield (entries 6 and 7). As in the case of cyclopentenylstannane **21**, the presence of a bulky substitutent at the 3-position of **15** most likely had a deleterious effect on the yield of the reaction. The coupling of **6b** with the homologous cyclohexenylstannane **16** [26], on the other hand, gave a sustantially higher yield of product (entry 8). This result may be rationalized in terms of the greater flexibility of the 6-membered ring, which allows adoption of a conformation that relieves the steric bulk at the reaction site.

The last two entries in Table I illustrate the reaction of 7-chloro-1,8-naphthyridines **6b** and **6c** with an heterocycloalkenylstannane, namely, 1-acetyl-4-tributylstannyl-1,2,-3,6-tetrahydropyridine, **17**. This reagent, readily available from *N*-acetyl-4-piperidone [29], allowed the direct introduction of a 1,2,3,6-tetrahydro-4-pyridinyl group at the C-7 position of the naphthyridine nucleus. An earlier approach to quinolones bearing this heterocyclic side chain had involved a nucleophilic attack of 1-lithio-4-bromo-2,5-difluorobenzene onto ethyl 4-oxo-1-piperidinecarboxylate, followed by elimination of the elements of water and subsequent construction of the 1,4-dihydro-4-oxopyridine ring [29]. Notwithstanding the success of this former methodology, the nature of the first step had precluded its extension to the synthesis of the analogous naphthyridines.

Several features of the palladium-catalyzed cross coupling of 7-chloro-1,8-naphthyridines **6a-c** with alkenyl- and cycloalkenylstannanes deserve comment. The reaction is remarkably selective; the coupling takes place exclusively at the C-7 position even in the presence of the C-6 fluorine and of a very reactive α,β-unsaturated ketoester. Most other organometallic reagents would not differentiate so cleanly between the two halogen atoms, and would certainly react at the C-2 position of the naphthyridine ring in a conjugate fashion [30]. The reaction also tolerates a wide arrary of functional groups within the organotin partner, as illustrated by the examples given in Table I. Also noteworthy is the fact that moderate-to-good yields of coupled product are obtained with cyclic, trisubstituted vinylstannanes. While the incorporation of the vinyl unit into a ring does not affect the coupling process (*cf.* entry 4), the presence of a bulky substituent near the reaction site does seem to have a detrimental effect on the yield of the reaction, particularly in conformationally rigid systems (*cf.* entries 5-7).

The naphthyridine esters **22**, **23**, and **24** were hydrolyzed with hydrochloric acid to afford the 7-(3-amino-1-cyclopenten-1-yl, 3 amino-1-cyclohexen-1-yl, and 1,2,3,6-tetrahydro-4-pyridinyl)-1,8-naphthyridine-3-carboxylic acids **8**, **9**, and **10**, respectively (Table II). Attempted hydrolysis of **18a**, however, resulted in extensive decomposition of the substrate. Since it was highly desirable to evaluate the effect of a simple vinyl group at the C-7 position of the naphthyridine ring, the free acid **26** was directly treated with tributylvinyltin in dimethylformamide and in the presence of bis(triphenylphosphine) dichloropalladium(II). The coupling reaction did take place to afford the 7-ethenyl-1,8-naphthyridine-3-carboxylic acid **27** in 30% yield (Scheme 2). It should be mentioned that the first example of a palladium-catalyzed cross coupling of an organostannane with a vinyl iodide bearing a free carboxylic acid group has recently been reported from Stille's laboratories [27].

Scheme II



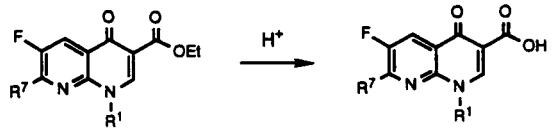
26 **27**

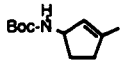
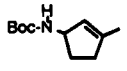
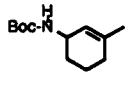
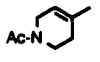
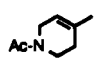
All 7-(ethenyl, 3-amino-1-cycloalkenyl, or 1,2,3,6-tetrahydro-4-pyridinyl)-1,8-naphthyridine-3-carboxylic acids were assayed against Gram positive and Gram negative bacteria using standard microdilution techniques. In general, these compounds displayed activity comparable to their nitrogen-linked counterparts, suggesting that the attachment of the side-chain to the naphthyridine nucleus does not have to be through a nitrogen to maintain potent microbiological activity. A more detailed analysis of the biological data as well as structure-activity relationships including 7-(1-cycloalkenyl)quinolones will be discussed in a future publication.

EXPERIMENTAL

Reactions were carried out in flame-dried glassware under an atmosphere of nitrogen or argon. Tetrahydrofuran was distilled from sodium benzophenone ketyl, dioxane from sodium, and dimethylformamide from calcium hydride. Organic solutions were dried over anhydrous magnesium sulfate and concentrated under reduced pressure on a Büchi rotary evaporator. Thin-layer chromatography (tlc) was carried out on E. Merck silica gel 60 F_{254} pre-coated glass plates (0.25 mm). Flash column chromatography was performed with E. Merck silica gel 60, 230-400 mesh ASTM, according to Still [31]. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra (ir) were recorded on a Nicolet MX-1 FTIR spectrometer. Proton (pmr) and carbon-13 (cmr) magnetic resonance spectra were obtained on either a Varian XL 200 or a Brüker AM 250 spectrometer. Chemical shifts are reported in δ units relative to internal tetramethylsilane. Low (ms) and high resolution (hrms) mass spectra were recorded on either a Finnigan 4500 or a VG analytical 7070E/HF mass spectrometer. Elemental analysis were performed on a CEC 240XA elemental analyzer. The purity of the final products was determined by high-pressure liquid chromatography on a system composed of a

Table II



Entry	Substrate	R^1	R^7	Conditions [a]	Product	(% Yield)
1	**22b**			A	**8b**	(61)
2	**22c**			B	**8c**	(86)
3	**23**			B	**9**	(95)
4	**24b**			B	**10b**	(66)
5	**24c**			C	**10c**	(62)

[a] A = 5N HCl, THF, 50-60°C; B = 5N HCl, H_2O, 65°C; C = 5N HCl, CH_3CN, 60°C

LKB 2150 pump, LKB 2152 controller, and an Applied Biosystems 783A programmable absorbance detector.

Ethyl 7-Ethenyl-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**18a**).

To a suspension of 7-chloro-1,8-naphthyridine **6a** (0.95 g, 3.2 mmoles) in dry tetrahydrofuran (20 ml) was added tri-*n*-butylvinyltin (1.04 g, 3.3 mmoles), bis(triphenylphosphine)palladium(II) chloride (45 mg, 0.06 mmole), and 2,6-di-*t*-butyl-4-methylphenol (2 crystals). The resulting mixture was heated at 65° for 20 hours, cooled to room temperature, and treated with pyridine (1 ml) and pyridinium fluoride (2 ml of a 1.4 *M* solution in tetrahydrofruan). After an additional 12 hours, the mixture was diluted with a small amount of tetrahydrofuran, filtered through a pad of Celite, and poured onto water. The resulting suspension was extracted with chloroform (2 x 100 ml), and the organic extracts were combined, dried, and concentrated. The residue was chromatographed (dichloromethane-methanol 99:1) to give **18a** (0.65 g, 70%); ir (potassium bromide): 1689, 1642, 1610, 1541, 1489, 1097, 807 cm^{-1}; pmr (deuteriochloroform): δ 1.42 (t, 3H, J = 7.1 Hz), 1.54 (t, 3H, J = 7.2 Hz), 4.42 (q, 2H, J = 7.1 Hz), 4.51 (q, 2H, J = 7.2 Hz), 5.81 (dd, 1H, J = 10.8, 1.7 Hz), 6.63 (dd, 1H, J = 17.2, 1.7 Hz), 7.13 (ddd, 1H, J = 17.3, 10.8, 1.4 Hz), 8.40 (d, 1H, J = 9.5 Hz), 8.66 (s, 1H); ms: (ei) m/z 290 (M), 277, 245, 218 (base), 190.

Anal. Calcd. for $C_{15}H_{15}FN_2O_3$: C, 62.06; H, 5.21; N, 9.65. Found: C, 61.82; H, 5.22; N, 9.48.

Ethyl 1-Cyclopropyl-7-ethenyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**18b**).

To a suspension of 7-chloro-1,8-naphthyridine **6b** (0.51 g, 1.6 mmoles) in dry dimethylformamide (15 ml) previously purged with nitrogen, were added tri-*n*-butylvinyltin (0.63 g, 2.0 mmoles), bis(triphenylphosphine)palladium(II) chloride (56 mg, 0.08 mmole), and 2,6-di-*t*-butyl-4-methylphenol (3 crystals). The mixture was heated at 45-50° for 5.5 hours, cooled to room temperature, and poured onto ice. The precipitated solids were collected by suction-filtration, resuspended in ethyl acetate and purified by column chromatography (hexane-ethyl acetate 1:1) to yield **18b** (0.47 g, 97%) as a white solid; ir (potassium bromide): 1693, 1645, 1613, 1474, 1399, 1270, 1240, 809 cm^{-1}; pmr (deuteriochloroform): δ 1.05-1.11 (m, 2H), 1.27-1.35 (m, 2H), 1.42 (t, 3H, J = 7.1 Hz), 3.66-3.75 (m, 1H), 4.41 (q, 2H, J = 7.1 Hz), 5.81 (dd, 1H, J = 10.6, 1.9 Hz), 6.70 (dd, 1H, J = 17.2, 1.9 Hz), 7.15 (ddd, 1H, J = 17.3, 10.7, 1.3 Hz), 8.36 (d, 1H, J = 9.5 Hz), 8.69 (s, 1H); cmr (deuteriochloroform): δ 7.63, 14.40, 34.19, 61.08, 111.15, 121.87, 122.15, 124.27, 124.32, 128.21, 149.09, 153.17, 156.62, 165.29, 173.88; ms: (ei) m/z 302 (M), 257, 230, 208, 172, 141, 91 (base).

Anal. Calcd. for $C_{16}H_{15}FN_2O_3 \cdot 0.40\ H_2O$: C, 62.09; H, 4.81; N, 9.05. Found: C, 62.12; H, 4.81; N, 9.05.

Ethyl 1-Cyclopropyl-6-fluoro-1,4-dihydro-7-(1-methoxyethenyl)-4-oxo-1,8-naphthyridine-3-carboxylate (**19**).

To a suspension of **6b** (5.00 g, 16.1 mmoles) in dry tetrahydrofuran (100 ml) were added tri-*n*-butyl(1-methoxy)vinyltin (5.78 g, 16.6 mmoles), bis(triphenylphosphine)palladium(II) chloride (0.21 g, 0.30 mmole), and 2.6-di-*t*-butyl-4-methylphenol (2 crystals). The suspension was slowly warmed to 58°, upon which it became homogeneous. After 47.5 hours additional amounts of the tin reagent (1.40 g, 4.0 mmoles) and the palladium catalyst (0.06 g, 0.08 mmole) were added and stirring continued at 58° for an additional 30 hours. The reaction mixture was then allowed to cool to room temperature and stirred overnight. The precipitated solids were collected by suction-filtration, washed with hexane, and air-dried to give **19** (1.28 g, 24%) as a yellow solid, mp 151-152.5°. The filtrate was concentrated to dryness and the residue was triturated with hexane to afford, after filtration, a second crop of product (3.61 g, 68%); ir (potassium bromide): 1694, 1645, 1614, 1082 cm^{-1}; pmr (deuteriochloroform): δ 1.00-1.23 (m, 2H), 1.23-1.57 (m, 5H), 3.63-3.90 (m, 4H), 4.41 (q, 2H, J = 7.1 Hz), 4.70 (d, 1H, J = 2.6 Hz), 5.25 (d, 1H, J = 2.6 Hz), 8.39 (d, 1H, J = 10.2 Hz), 8.70 (s, 1H); ms: (ei) m/z 332 (M), 317, 303, 287, 260 (base).

Anal. Calcd. for $C_{17}H_{17}FN_2O_4$: C, 61.44; H, 5.16; N, 8.43; F, 5.72. Found: C, 61.67; H, 5.15; N, 8.37; F, 6.13.

Ethyl 1-Cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-(3-oxo-1-cyclopenten-1-yl)-1,8-naphthyridine-3-carboxylate (**20**).

To a suspension of **6b** (5.74 g, 18.5 mmoles) in dry tetrahydrofuran (100 ml) was added a solution of 3-tri-*n*-butylstannyl-2-cyclopentenone (7.10 g, 19.1 mmoles) in tetrahydrofuran (30 ml), followed by bis(triphenylphosphine)palladium(II) chloride (0.27 g, 0.38 mmole), and 2,6-di-*t*-butyl-4-methylphenol (2 crystals). The mixture was heated at 65° for 28 hours and at room temperature for an additional 16 hours. It was then diluted with a small amount of ether and filtered to give **20** (5.78 g, 88%) as a yellow powder, mp 183-184°; ir (potassium bromide): 1726, 1712, 1643, 1611, 1242, 810 cm^{-1}; pmr (deuteriochloroform): δ 1.03-1.18 (m, 2H), 1.27-1.52 (m, 2H), 1.42 (t, 3H, J = 7.1 Hz), 2.53-2.70 (m, 2H), 3.23-3.40 (m, 2H), 3.60-3.83 (m, 1H), 4.42 (q, 2H, J = 7.1 Hz), 7.10 (dd, 1H, J = 4.6, 2.0 Hz), 8.49 (d, 1H, J = 10.3 Hz), 8.75 (s, 1H); ms: (ei) mz 357, 356 (M), 341, 327, 311, 284 (base), 269, 215.

Anal. Calcd. for $C_{19}H_{17}FN_2O_4$: C, 64.04; H, 4.81; N, 7.86. Found; C, 63.68; H, 4.46; N, 8.01.

Ethyl 1-Cyclopropyl-7-[3-[(1,1-dimethylethyl)dimethylsiloxy]-1-cyclopenten-1-yl]-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**21**).

To a suspension of **6b** (7.00 g, 22.5 mmoles) in dry tetrahydrofuran (150 ml) was added a solution of **14** (12.0 g, 24.6 mmoles) in tetrahydrofuran (50 ml), followed by bis(triphenylphosphine)palladium(II) chloride (0.35 g, 0.5 mmole), and 2,6-di-*t*-butyl-4-methylphenol (2 crystals). The resulting mixture was heated at 65° for 26 hours and at room temperature for an additional 12 hours. A small amount of water was added and the layers were separated. The aqueous layer was extracted twice with dichloromethane, the extracts were combined with the organic layer, dried, and concentrated. The residue was triturated with hexane and filtered to give 8.36 g of a 4:1 mixture of **21** (7.18 g, 67%) and starting 7-chloro-1,8-naphthyridine, which was used as is for the preparation of **25** (*vide infra*). A small sample of the product was obtained by suspending the above material in 100 ml of hot hexane, filtering the slurry, and allowing it to cool slowly to room temperature. The crystals that formed were filtered and air-dried to give **21**; pmr (deuteriochloroform): δ 0.17 (s, 6H), 0.93 (s, 9H), 1.00-1.13 (m, 2H), 1.20-1.38 (m, 2H), 1.43 (t, 3H, J = 7.3 Hz), 1.73-1.98 (m, 1H), 2.27-2.50 (m, 1H), 2.70-2.95 (m, 1H), 3.06-3.32 (m, 1H), 3.57-3.73 (m, 1H), 4.43 (q, 2H, J = 7.3 Hz), 5.13-5.25 (m, 1H), 6.81-6.92 (m, 1H), 8.36 (d, 1H, J = 11.3 Hz), 8.68 (s, 1H).

Ethyl 1-Cyclopropyl-7-[3-[[(1,1-dimethylethoxy)carbonyl]amino]-1-cyclopenten-1-yl]-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**22b**).

To a suspension of 7-chloro-1,8-naphthyridine **6b** (1.90 g, 6.1 mmoles) in dry dioxane (40 ml) previously purged with nitrogen, were added 1,1-dimethylethyl-[3-(tri-*n*-butylstannyl)-2-cyclopenten-1-yl]carbamate, **15**, (2.83 g, 6.0 mmoles), tetrakis(triphenylphosphine)palladium(0) (140 mg, 0.12 mmole), and 2,6-di-*t*-butyl-4-methylphenol (5 crystrals). The mixture was heated at gentle reflux for 40 hours and it was then concentrated to dryness. The residue was resuspended in cyclohexane (100 ml) and the suspension stirred vigorously for 20-30 minutes. The solids were collected by suction-filtration, washed with cyclohexane (2 x 5 ml), and recrystallized from dichloromethane-hexane to afford a mixture of starting material and product, which were separated by column chromatography (dichloromethane-methanol 25:1) to afford **6b** (0.98 g, 52% recovery) and **22b** (1.20 g, 43%) as a light pink solid; ir (potassium bromide): 1701, 1641, 1613, 1242, 1171, 1033, 809 cm^{-1}; pmr (deuteriochloroform): δ 1.02-1.08 (m, 2H), 1.24-1.32 (m, 2H), 1.41 (t, 3H, J = 7.1 Hz), 1.48 (s, 9H), 1.65-1.78 (m, 1H), 2.44-2.63 (m, 1H), 2.83-2.98 (m, 1H), 3.04-3.20 (m, 1H), 3.56-3.70 (m, 1H), 4.41 (q, 2H, J = 7.1 Hz), 4.62-4.79 (m, 1H), 4.92-5.12 (m, 1H), 6.80-6.84 (m, 1H), 8.34 (d, 1H, J = 10.5 Hz), 8.68 (s, 1H); ms: (ci, methane) m/z 486 (M + 29), 458 (M + 1, base), 402, 311, 185, 87.

Anal. Calcd. for $C_{24}H_{28}FN_3O_5$: C, 63.01; H, 6.17; N, 9.18. Found: C, 62.70; H, 6.41; N, 9.24.

Ethyl 1-(2,4-Difluorophenyl)-7-[3-[[(1,1-dimethylethoxy)carbonyl]-amino]-1-cyclopenten-1-yl]-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**22c**).

To a suspension of 7-chloro-1,8-naphthyridine **6c** (2.70 g, 7.0 mmoles) in dry dioxane (45 ml) previously purged with nitrogen, were added 1,1-dimethylethyl-[3-(tri-*n*-butylstannyl)-2-cyclopenten-1-yl]carbamate, **15**, (3.31 g, 7.0 mmoles), tetrakis(triphenylphosphine)palladium(0) (404 mg, 0.35 mmole), 2,6-di-*t*-butyl-4-methylphenol (5 crystals). The mixture was heated at gentle reflux for 55 hours and it was then concentrated to dryness. The residue was recrystallized from dichloromethane-hexane to give a mixture of starting material and product which were separated by column chromatography (dichloromethane-methanol 25:1 to 15:1) to give **6c** (1.59 g, 59% recovery) and **22c** (1.56 g, 42%) as an off-white solid; ir (potassium bromide): 1702, 1645, 1615, 1514, 1173, 809 cm^{-1}; pmr (deuteriochloroform): δ 1.41 (t, 3H, J = 7.2 Hz), 1.46 (s, 9H), 1.75-1.90 (m, 1H), 2.30-2.48 (m, 2H), 2.50-2.60 (m, 1H), 4.41 (q, 2H, J = 7.2 Hz), 4.50-4.70 (m, 1H), 4.83-5.00 (m, 1H), 6.70-6.80 (m, 1H), 7.05-7.17 (m, 1H), 7.40-7.51 (m, 2H), 7.62-7.72 (m, 1H), 8.38 (d, 1H, J = 10.4 Hz), 8.60 (s, 1H); ms: (fab, xenon-thioglycerol) m/z 637 (M + 108), 553 (M + 23), 530 (M + 1); hrms: Calcd. for $C_{27}H_{27}F_3N_3O_5$ (M + 1): 530.1903. Found: 530.1880.

Ethyl 1-Cyclopropyl-7-[3-[[(1,1-dimethylethoxy)carbonyl]amino]-1-cyclohexen-1-yl]-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**23**).

A solution of 1,1-dimethylethyl-[3-(tri-*n*-butylstannyl)-2-cyclohexen-1-yl]carbamate, **16**, (3.15 g, 6.5 mmoles) in dry dimethylformamide (20 ml) was added dropwise, over a 3 hour period, to a solution of 7-chloro-1,8-naphthyridine **6b** (1.86 g, 6.0 mmoles), bis(triphenylphosphine)palladium(II) chloride (84 mg, 0.12 mmole), and 2,6-di-*t*-butyl-4-methylphenol (1 crystal) in dimethylformamide (10 ml) at 85°. The resulting mixture was stirred at 80-85° for 15 hours, at 100° for 7 hours, and at room temperature for 65 hours. An additional amount (40 mg) of the catalyst was then added and the mixture stirred at 100° for 9 hours and at 70° for 15 hours. The suspension was allowed to cool to room temperature, poured into hexane (20 ml) and stirred vigorously for 20-30 minutes. The dimethylformamide layer was decanted, washed with hexane, and concentrated. The precipitated solids were filtered, washed with hexane and ether, and air-dried, to give **23** (2.14 g, 76%) as a white solid; ir (potassium bromide): 1700, 1641, 1613, 1241, 1167, 808 cm^{-1}; pmr (deuteriochloroform): δ 1.01-1.08 (m, 2H), 1.24-1.32 (m, 2H), 1.41 (t, 3H, J = 7.2 Hz), 1.48 (s, 9H), 1.78-1.92 (m, 2H), 1.97-2.13 (m, 1H), 2.59-2.67 (m, 2H), 3.60-3.68 (m, 1H), 4.40 (q, 2H, J = 7.2 Hz), 4.40-4.50 (m, 1H), 4.68-4.77 (m, 1H), 6.76-6.80 (m, 1H), 8.33 (d, 1H, J = 10.9 Hz), 8.67 (s, 1H); ms: (ei) m/z 472 (M + 1), 415 (base), 371, 343, 57.

Anal. Calcd. for $C_{25}H_{30}FN_3O_5 \cdot 0.60\ H_2O$: C, 62.25; H, 6.52; N, 8.71. Found: C, 62.46; H, 6.49; N, 8.32.

Ethyl 7-(1-Acetyl-1,2,3,6-tetrahydro-4-pyridinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**24b**).

To a suspension of 7-chloro-1,8-naphthyridine **6b** (4.40 g, 15 mmoles) in dry dioxane (80 ml), were added stannane **17** (7.00 g, 17 mmoles), bis(triphenylphosphine)palladium(II) chloride (1.00 g, 1.40 mmoles), and 2,6-di-*t*-butyl-4-methylphenol (5 crystals). The mixture was heated at reflux for 3 hours, at room temperature for an additional 12 hours and it was then concentrated to dryness. The residue was chromatographed (dichloromethane-methanol 99:1 to 95:5) to give a mixture of **6b** and product. Recrystallization of this material from tetrahydrofuran provided **24b** (2.18 g, 37%). The mother liquor was concentrated and rechromatographed to give **6b** (1.75 g, 40% recovery) and a second crop of product (1.00 g, 17%); ir (potassium bromide): 1723, 1647, 1610, 1540, 1292, 1234, 1166, 809 cm^{-1}; pmr (deuteriochloroform): δ 1.05-1.15 (m, 2H), 1.27-1.35 (m, 2H), 1.41 (t, 3H, J = 7.2 Hz), 2.18 and 2.20 (2xs, 3H), 2.75-2.96 (m, 2H), 3.58-3.67 (m, 1H), 3.72 (apparent t, 1H, J = 5.7 Hz), 3.89 (apparent, 1H, J = 5.7 Hz), 4.20-4.30 (m, 1H), 4.35-4.41 (overlapping q, 2H, J = 7.2 Hz, and m, 1H), 6.95-7.05 (m, 1H), 8.35 and 8.36 (2xd, 1H, J = 11.0 Hz), 8.68 (s, 1H). **Note**: Variable temperature pmr experiments caused the acetyl singlets at 2.18 and 2.20 ppm to collapse into a single peak, and the H-5 doublets at 8.35 and 8.36 to collapse into a single doublet; ms: (ei) m/z 399 (M, base), 356, 327, 310, 284, 268, 243, 82.

Anal. Calcd. for $C_{21}H_{22}FN_3O_4$: C, 63.15; H, 5.55; N, 10.52; F, 4.76. Found: C, 62.81; H, 5.48; N, 10.37; F, 4.79.

Ethyl 7-(1-Acetyl-1,2,3,6-tetrahydro-4-pyridinyl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylate (**24c**).

To a suspension of 7-chloro-1,8-naphthyridine **6c** (2.50 g, 6.5 mmoles) in dry dimethylformamide (30 ml) previously purged with nitrogen, were added 1-acetyl-1,2,5,6-tetrahydro-4-(tri-*n*-butylstannyl)pyridine, **17**, (2.80 g, 6.7 mmoles), bis(triphenylphosphine)palladium(II) chloride (91 mg, 0.13 mmole), and 2,6-di-*t*-butyl-4-methylphenol (5 crystals). The mixture was heated at gentle reflux for 7 hours and it was then concentrated to dryness. The residue was resuspended in cyclohexane (20 ml) and the suspension was stirred vigorously for 15-20 minutes. The solids were collected by suction-filtration, washed with cyclohexane (2 x 5 ml), and chromatographed (dichloromethane-methanol 25:1) to afford **24c** (2.53 g, 83%) as a light yellow solid; ir (potassium bromide): 1731, 1677, 1616, 1514, 808 cm^{-1}; pmr (deuteriochloro-

form): δ 1.41 (t, 3H, J = 7.1 Hz), 2.14 (s, 3H), 2.28-2.45 (m, 2H), 3.50-3.61 (m, 1H), 3.65-3.78 (m, 1H), 4.17-4.34 (m, 2H), 4.41 (q, 2H, J = 7.1 Hz), 6.79-6.90 (m, 1H), 7.03-7.18 (m, 2H), 7.27-7.55 (m, 1H), 8.39 (d, 1H, J = 11.0 Hz), 8.59 (s, 1H); ms: (ei) m/z 471 (M), 443, 428, 399, 382, 269, 82 (base); hrms: Calcd. for $C_{24}H_{20}F_3N_3O_4$ (M): 471.1406. Found: 471.1395.

Ethyl 1-Cyclopropyl-1,4-dihydro-6-fluoro-4-oxo-7-(3-hydroxy-1-cyclopenten-1-yl)-1,8-naphthyridine-3-carboxylate (**25**).

To a suspension of **21** (1.0 g, 2.1 mmoles) in water (15 ml) was added glacial acetic acid (30 ml). The mixture was stirred at room temperature overnight, and then partitioned between water and dichloromethane. The aqueous layer was decanted and extracted with dichloromethane. The organic layer and extracts were combined, washed successively with saturated sodium bicarbonate and sodium chloride solutions, dried, and concentrated. The residue was chromatographed (dichloromethane-methanol 98:2) to afford **25** (0.34 g, 45%); ir (potassium bromide): 3340-3536, 1724, 1613, 1469, 1428, 1237 cm^{-1}; pmr (deuteriochloroform): δ 1.01-1.09 (m, 2H), 1.26-1.30 (m, 2H), 1.42 (t, 2H, J = 7.2 Hz), 1.80-2.07 (two overlapping m, 2H), 2.39-2.55 (m, 1H), 2.81-2.96 (m, 1H), 3.10-3.24 (m, 1H), 3.59-3.67 (m, 1H), 4.41 (q, 2H, J = 7.2 Hz), 5.13-5.20 (m, 1H), 6.91-6.97 (m, 1H), 8.32 (d, 1H, J = 10.7 Hz), 8.68 (s, 1H); ms: (ei) m/z 360, 359, 358 (M), 343, 313, 286 (base), 215, 83.

Anal. Calcd. for $C_{19}H_{19}FN_2O_4 \cdot 0.15\ H_2O$: C, 63.20; H, 5.39; N, 7.76. Found: C, 63.19; H, 5.20; N, 7.64.

7-(3-Amino-1-cyclopenten-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid (**8b**).

To a solution of **22b** (1.20 g, 2.6 mmoles) in tetrahydrofuran (50 ml) was added dropwise 5*N* hydrochloric acid (10 ml). The resulting solution was stirred at room temperature for 48 hours. The precipitated solid was filtered, washed with cold methanol and ether, and dried *in vacuo* to give **8b** as the hydrochloride salt (0.52 g, 61%); ir (potassium bromide): 3350-3550, 1726, 1615, 1501, 1032, 813 cm^{-1}; pmr (hexadeuteriodimethyl sulfoxide): δ 1.10-1.23 (m, 4H), 1.82-2.00 (m, 1H), 2.41-2.50 (m, 1H), 2.95-3.10 (m, 1H), 3.20-3.40 (m, 1H), 3.79-3.84 (m, 1H), 4.55-4.61 (m, 1H), 6.80-6.92 (m, 1H), 8.10-8.30 (m, 3H), 8.57 (d, 1H, J = 10.5 Hz), 8.87 (s, 1H), 14.35-14.50 (m, 1H); ms: (ci, methane) m/z 370 (M+41), 358 (M+29), 330 (M+1, base), 312, 85; hrms: Calcd. for $C_{17}H_{17}FN_3O_3$ (M+1): 330.1254. Found: 330.1255.

7-(3-Amino-1-cyclopenten-1-yl)-6-fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid (**8c**).

To a solution of **22c** (1.56 g, 2.9 mmoles) in tetrahydrofuran (50 ml) and water (40 ml) was added dropwise 5*N* hydrochloric acid (40 ml). The resulting solution was stirred at 40-50° for 24 hours and at room temperature for an additional 75 hours. The precipitated solid was filtered, washed with cold methanol and ether, and dried *in vacuo* to give **8c** as the hydrochloride salt (0.90 g, 77%). The filtrate and washings were concentrated to afford a second crop of product (110 mg, 9%); ir (potassium bromide): 3350-3550, 1734, 1618, 1511, 812 cm^{-1}; pmr (hexadeuteriodimethyl sulfoxide): δ 1.70-1.85 (m, 1H), 2.19-2.30 (m, 1H), 2.60-2.80 (m, 1H), 4.37-4.55 (m, 1H), 6.77 (br s, 1H), 7.30-7.45 (m, 1H), 7.58-7.70 (m, 1H), 7.78-7.97 (m, 1H), 8.20-8.40 (m, 3H, NH_3^+), 8.64 (d, 1H, J = 10.4 Hz), 9.13 (s, 1H), 14.03-14.20 (m, 1H); ms: (ei) m/z 401 (M), 356, 276, 243, 113, 82 (base).

Anal. Calcd. for $C_{20}H_{14}F_3N_3O_3 \cdot HCl \cdot H_2O$: C, 52.70; H, 3.76; N, 9.22. Found: C, 52.69; H, 3.61; N, 8.95.

7-(3-Amino-1-cyclohexen-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid (**9**).

To a suspension of **23** (1.20 g, 2.5 mmoles) in water (20 ml) was added dropwise 5*N* hydrochloric acid (50 ml). The resulting mixture was stirred at 60-65° for 19 hours and then cooled to 0°. The precipitated solid was filtered, washed with water, cold methanol, and ether, and dried *in vacuo* to give **9** as the hydrochloride salt (0.92 g, 95%); ir (potassium bromide): 3300-3550, 1726, 1618, 1502, 1418, 813 cm^{-1}; pmr (hexadeuteriodimethyl sulfoxide): δ 1.10-1.18 (m, 2H), 1.20-1.40 (m, 2H), 1.60-1.87 (m, 2H), 1.94-2.17 (m, 2H), 2.60-2.76 (m, 2H), 3.75-3.88 (m, 1H), 4.00-4.14 (m, 1H), 6.90-6.97 (br s, 1H), 8.32-8.50 (m, 3H), 8.52 (d, 1H, J = 10.9 Hz), 8.85 (s, 1H), 14.30-14.43 (m, 1H); ms: (ei) m/z 343 (M), 299, 284, 205, 96 (base), 82.

Anal. Calcd. for $C_{18}H_{18}FN_3O_3 \cdot HCl \cdot 0.5\ H_2O$: C, 55.60; H, 5.18; N, 10.81. Found: C, 55.65; H, 4.92; N, 10.81.

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1,2,3,6-tetrahydro-4-pyridinyl)-1,8-naphthyridine-3-carboxylic Acid (**10b**).

A solution of **24b** (0.80 g, 2.0 mmoles) in 6*N* hydrochloric acid (30 ml) was heated at very gentle reflux for 3 hours, cooled to room temperature, and concentrated to give a yellow solid. This crude material was redissolved in 6*N* hydrochloric acid and the solution cooled in an ice bath. The precipitated solid was filtered and dried *in vacuo* to give **10b** as the hydrochloride salt (0.48 g, 66%); ir (potassium bromide): 1724, 1616, 1457, 1422, 1283, 811 cm^{-1}; pmr (hexadeuteriodimethyl sulfoxide): δ 1.13-1.20 (m, 2H), 1.20-1.31 (m, 2H), 2.93-2.98 (m, 2H), 3.30-3.50 (m, 1H), 3.80-3.95 (m, 1H), 3.95-4.00 (m, 2H), 6.95-7.10 (m, 1H), 8.53 (d, 1H, J = 11.0 Hz), 8.86 (s, 1H), 9.30-9.60 (m, 2H), 14.20-14.60 (m, 1H); ms: (ei) m/z 329 (M, base), 285, 270, 256, 242, 227, 215, 203, 82.

Anal. Calcd. for $C_{17}H_{16}FN_3O_3 \cdot HCl \cdot 1.25\ H_2O$: C, 52.58; H, 5.06; N, 10.82; Cl, 9.13. Found: C, 52.57; H, 4.86; N, 10.76; Cl, 9.40.

6-Fluoro-1-(2,4-difluorophenyl)-1,4-dihydro-7-(1,2,3,6-tetrahydro-4-pyridinyl)-4-oxo-1,8-naphthyridine-3-carboxylic Acid (**10c**).

To a suspension of **24c** (0.86 g, 1.8 mmoles) in acetonitrile (10 ml) was added 5*N* hydrochloric acid (2 ml). The resulting orange solution was stirred at room temperature for 163 hours. The precipitated solid was filtered, washed with ether, and dried to give the *N*-acetyl derivative of **10c** (0.54 g, 68%); ir (potassium bromide): 3350-3600, 1735, 1619, 1494, 811 cm^{-1}; pmr (hexadeuteriodimethyl sulfoxide): δ 2.01 and 2.04 (2xs, 3H), 2.18-2.41 (m, 2H), 3.45-3.62 (m, 2H), 4.11-4.31 (m, 2H), 6.81-6.96 (m, 1H), 7.31-7.47 (m, 1H), 7.58-7.73 (m, 1H), 7.80-7.95 (m, 1H), 8.56 (d, 1H, J = 10.9 Hz), 9.10 and 9.11 (2xs, 1H); ms: (ei) m/z 444 (M+1, base), 426, 401, 356, 82.

Anal. Calcd. for $C_{22}H_{16}F_3N_3O_4 \cdot 1.60\ H_2O$: C, 55.96; H, 4.10; N, 8.90; F, 12.07. Found: C, 55.63; H, 3.77; N, 9.05; F, 11.96.

A suspension of the above material (0.50 g, 1.1 mmoles) in 5*N* hydrochloric acid (30 ml) was heated at 50-60° for 24 hours, and then concentrated under reduced pressure. The solid was filtered, washed successively with cold methanol and ether, and dried *in vacuo* to give **10c** (0.40 g, 91%) as a beige solid; ir (potassium bromide): 3350-3550, 1739, 1612, 1423 cm^{-1}; pmr (hexadeuteriodimethyl sulfoxide): δ 2.38-2.45 (m, 2H), 3.17-3.28 (m, 2H), 3.75-3.85 (m, 2H), 6.84-6.92 (m, 1H), 7.33-7.45 (m, 1H), 7.60-7.72 (m, 1H), 7.80-7.93 (m, 1H), 8.62 (d, 1H, J = 10.9 Hz), 9.11 (s, 1H),

9.30-9.44 (m, 1H); ms: (ci, methane) m/z 402 (M + 1), 356, 203, 123, 107 (base), 91.

Anal. Calcd. for $C_{20}H_{14}F_3N_3O_3 \cdot 2\,HCl \cdot H_2O$: C, 49.07; H, 3.38; N, 8.58. Found: C, 49.06; H, 3.56; N, 8.36.

1-Cyclopropyl-7-ethenyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic Acid (**27**).

To a suspension of **26** (0.51 g, 1.8 mmoles) in dry dimethylformamide (15 ml) were added tri-*n*-butylvinyltin (0.70 g, 2.2 mmoles), bis(triphenylphosphine)palladium(II) chloride (63 mg, 0.09 mmole), and 2,6-di-*t*-butyl-4-methylphenol (3 crystals). The mixture was heated at 45-50° for 5.5 hours, and at room temperature for an additional 64 hours. It was then poured onto ice and stirred for 15-20 minutes. The precipitated solid was collected by suction-filtration, resuspended in cyclohexane, and the suspension stirred vigorously for 20-30 minutes. The resulting greenish solid was filtered and recrystallized from chloroform to give **27** (0.15 g, 30%) as a yellow solid; ir (potassium bromide): 3300-3550, 1732, 1617, 815 cm^{-1}; pmr (deuteriochloroform): δ 1.11-1.18 (m, 2H), 1.34-1.39 (m, 2H), 3.80-3.89 (m, 1H), 5.91 (dd, 1H, J = 10.8, 1.7 Hz), 6.79 (dd, 1H, J = 17.2, 1.7 Hz), 7.19 (ddd, 1H, J = 17.2, 10.6, 1.3 Hz), 8.39 (d, 1H, J = 9.0 Hz), 8.95 (s, 1H), 14.2 (br s, 1H); cmr (deuteriochloroform): δ 7.07, 35.28, 107.86, 120.86, 121.14, 126.32, 127.75, 146.45, 147.73, 149.68, 152.62, 156.07, 165.15, 177.67; ms: (ei) m/z 275 (M + 1), 257, 230 (base), 215, 107; hrms: Calcd. for $C_{14}H_{12}FN_2O_3$ (M + 1): 275.0832. Found: 275.0815.

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