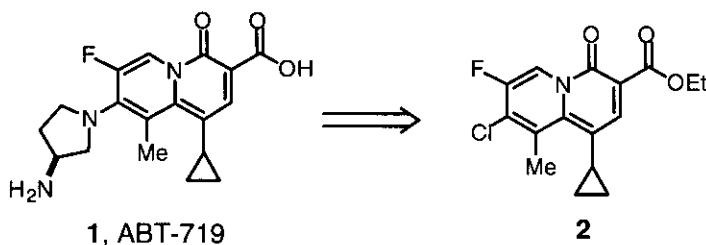


PRACTICAL SYNTHESIS OF 2-PYRIDONE CORE: ETHYL 8-CHLORO-1-CYCLOPROPYL-7-FLUORO-9-METHYL-4-OXO-4H-QUINOLIZINONE-3-CARBOXYLATE

Qun Li,* Thomas Sowin, Akiyo Claiborne, Linda Lijewski, Xiaolin Zhang, Kathleen Raye, Hormoz Mazdiyasi, William Arnold, Laura M. Melcher, Weibo Wang, Lisa Hasvold, Anthony Fung, Daniel T. W. Chu, and J. J. Plattner
Pharmaceutical Product Division, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, Illinois 60064-3500, USA

Abstract - A practical synthesis of the fluoropyridone core (**2**), an important intermediate to ABT-719 and other 2-pyridones, from the commercially available 3-chlorotetrafluoropyridine in 10 to 11 linear transformations with 10-26% overall yield is described.

2-Pyridones¹ are a class of newly discovered and potent broad-spectrum antibacterial agents which exert their activity by inhibiting bacterial DNA gyrase. ABT-719 (**1**)¹ is the first compound of this class which is, among other things, efficacious against resistant organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE). Interest in this area has been increasing rapidly² due to the alarming frequency of bacterial resistance.¹ One very important intermediate to ABT-719 and other fluoropyridones is the fluoropyridone core (**2**). Our original 13 step approach to **2** was cost prohibitive, and involved procedures such as hydrazination, thermal cyclization in Dowtherm A, and multiple chromatography steps, making the approach impractical for large scale synthesis. Therefore, there was a need for a more practical and efficient preparation of **2**. We describe here a concise and practical synthesis of ethyl 8-chloro-1-cyclopropyl-7-fluoro-9-methyl-4-oxo-4H-quinolizine-3-carboxylate (**2**).



The synthesis of **2** is illustrated in Scheme 1. Commercially available regioisomerically impure 3-chlorotetrafluoropyridine (**3**) (70% pure, the remainder is 4-chlorotetrafluoropyridine)³ was reacted with

lithium *tert*-butoxide at $-78\text{ }^{\circ}\text{C}$. The 4-chloro compound remained unreacted and was removed by distillation to give a mixture of the desired 4-*tert*-butoxypyridine (**4**) (80%) and the 2-*tert*-butoxypyridine (**5**) by-product (17%).^{4,5} The mixture was used directly in the next step without further separation. The regiochemistry of products (**4** and **5**) was determined by comparison of ^{19}F chemical shifts with those of starting material (**3**)⁶ (Figure 1).

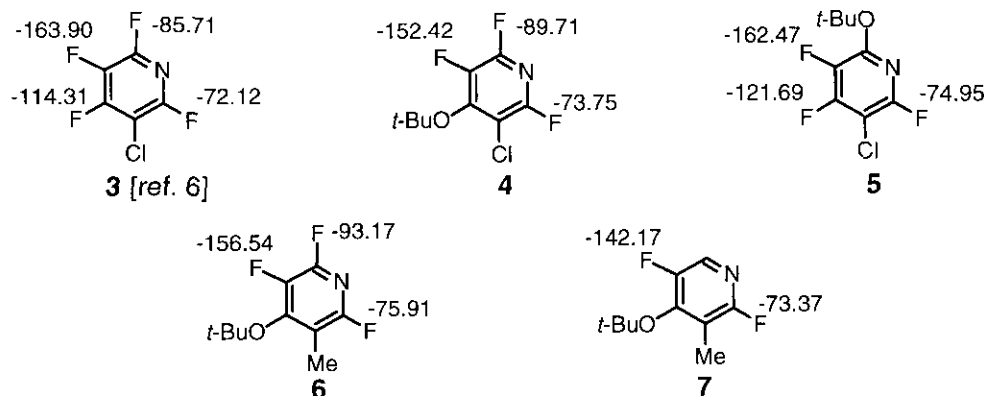
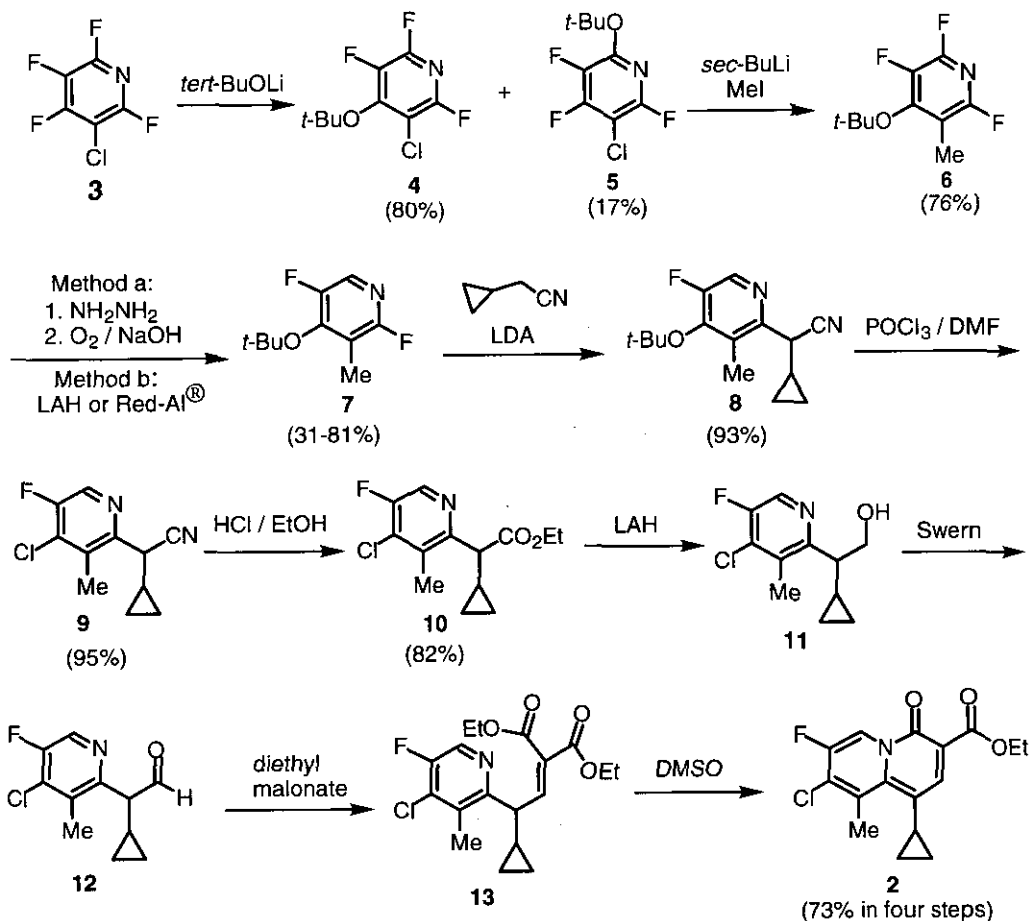


Figure 1. ^{19}F chemical shifts of selected fluoropyridines (ppm)

Attempts to optimize the reaction conditions by changing the *tert*-butoxy protecting group or changing base proved unsuccessful. The use of less hindered groups such as benzyloxy and thiophenoxy proved problematic in the cyclopropylacetonitrile anion reaction. With the less hindered protecting groups, displacement of protecting groups was observed rather than the desired 2-fluorine displacement. The *tert*-butoxy group proved to be the best protecting group. The use of sodium *tert*-butoxide caused the yield of **4** to decrease to 53% and the yield of undesired **5** to increase to 26%.¹

The lithium-chlorine exchange reaction of the crude mixture⁷ of **4** and **5** (ratio of 4.7:1) using *sec*-butyllithium at $-78\text{ }^{\circ}\text{C}$ went extremely well and the lithium salt precipitated out from the reaction mixture. Subsequent alkylation with methyl iodide afforded the methyl compound (**6**) in 76% yield. As a comparison, when pure **4** was used for the same reaction, the yield of **6** increased to 82%. Attempted metal-halogen exchange using *n*-butyllithium resulted only in nucleophilic displacement of the fluorine. No metal-chloride exchange reaction was observed. Selective cleavage of the 6-fluorine atom was accomplished by two methods. Our original method (method a)¹ was a two step process which involved the replacement of the fluorine with hydrazine and oxidation of the hydrazino product with oxygen to give **7** in high yield (81%). The second method (method b) used reducing agents such as lithium aluminum hydride or Red-Al[®] to provide **7** directly in 31-32% yield. The reported regioselectivity was confirmed by the fact that the 6-fluorine atom, with a ^{19}F chemical shift of -93.17 ppm in **6**, had disappeared in **7** (Figure 1). Reduction of **6** using the hydrazine/oxidation sequence provided higher yields, but is time consuming

and hazardous for large scale synthesis. On the other hand, reduction using either lithium aluminum hydride or Red-Al[®] may be more suitable for large scale operations. The major by-products of the reaction seemed to be the bisdesfluorination compound as well as other more polar products assumed to be associated with the loss of the *tert*-butyl group.



Scheme 1

Reaction of the 2-fluoropyridine (**7**) with 2.5 eq. of the cyclopropylacetonitrile anion provided **8** in 93% yield. Replacing cyclopropylacetonitrile with ethyl cyclopropylacetate in the same reaction failed to provide the desired product, apparently due to decreased nucleophilicity of the latter anion. Our attempts to reduce the cyano group of **8** directly to the aldehyde proved unsuccessful.⁸ Thus, an alternate route was developed which involved deprotection of the *tert*-butyl group followed by conversion of the resulting 4-hydroxypyridine to the chloropyridine (**9**). This conversion was achieved in 95% yield in a single operation using phosphorus oxychloride and *N,N*-dimethylformamide. Refluxing **9** in acidic ethanol afforded the ester (**10**) in 82% yield. The aldehyde (**12**) was obtained by lithium aluminum hydride reduction of the ester (**10**) followed by Swern oxidation of the alcohol (**11**). After condensation of the aldehyde (**12**) with diethyl malonate, the product (**13**) was cyclized in refluxing DMSO to provide the title

compound (**2**). The final four transformations were very convenient, involved no column chromatography, and eliminated the use of the troublesome Dowtherm A.⁹ The overall yield for the four steps was 73%.

In summary, a concise and practical synthesis of the 2-pyridone core from commercially available 3-chlorotetrafluoropyridine in 10 to 11 linear transformations has been described. The present method has fewer steps, higher yield, and simplified operations compared to previous routes. The process is thus applicable to large-scale synthesis and has been used for kilogram scale preparations of **2**. The overall yield for the large-scale synthesis described here ranged from 10% to 26%.

EXPERIMENTAL

General. Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. ¹H NMR spectra were recorded on a General Electric QE300 spectrometer. A Varian Unity 500 spectrometer was used for ¹⁹F NMR spectra. Chemical shifts are reported in parts per million relative to the internal standards Me₄Si for ¹H NMR and CFCl₃ for ¹⁹F NMR. The Desorption Chemical Ionization (DCI/NH₃) MS spectra were measured on a Finningan SSQ 700 instrument. IR spectra were taken on either a Nicolet 5 SXC or a 60 SX FT IR instrument. Flash chromatography refers to flash column chromatography conducted on E. Merck silica gel 60 (230-400 mesh). Anhydrous THF was obtained from Aldrich and used without further purification. All other solvents and reagents were obtained commercially and used without further purification. Unless otherwise specified, all non-aqueous reactions were carried out under a dry nitrogen atmosphere, using oven-dried glassware, and all reaction solvents were removed by rotary evaporator.

4-*tert*-Butoxy-3-chloro-2,5,6-trifluoropyridine (**4**)¹

A solution of *tert*-BuOLi (75.0 g, 0.937 mol) in THF (750 mL) was cooled to -78 °C in a dry-ice / acetone bath. A solution of 2,4,5,6-tetrafluoro-3-chloropyridine (225 g, 0.849 mol, from Aldrich, 70% pure, the remainder: 2,3,5,6-tetrafluoro-4-chloropyridine) in THF (450 mL) was added dropwise. After the addition, the reaction was stirred for 2 h at -78 °C, then at ambient temperature overnight. The mixture, which was a reddish brown syrup, was concentrated with a bath temperature at ~30 °C. Hexane (1 L) and Celite® (~50 g) were added, and the mixture was stirred for 30 min. The solid was removed by filtration and the filtrate was concentrated with a bath temperature at 30-35 °C. Distillation under reduced pressure yielded a colorless liquid (194 g, 96%) as a mixture of **4** (4-butoxy, desired) and **5** (6-butoxy) (ratio (by NMR): 4.7:1), bp 50-75 °C (4 mmHg). This material was carried on as a mixture of **4** and **5**. The two compounds can be separated by flash chromatography eluting with 6% ethyl acetate/hexane. **4**: ¹H NMR (CDCl₃) δ 1.52 (d, *J*=2 Hz, 9H); ¹⁹F NMR (CDCl₃) δ -73.75 (dd, *J*₁=14.2, *J*₂=23.2 Hz, 1F), -89.71

(dd, $J_1=14.2$, $J_2=21.9$ Hz, 1F), -152.42 (apparent t, $J=22$ Hz, 1F); MS(DCI/NH₃): 238, 240 (M+H); **5**: ¹H NMR (CDCl₃) δ 1.61 (s, 9H); ¹⁹F NMR (CDCl₃) δ -74.95 (dd, $J_1=9.0$, $J_2=24.5$ Hz, 1F), -121.69 (dd, $J_1=9.0$, $J_2=18.1$ Hz, 1F), -162.47 (dd, $J_1=18.1$, $J_2=24.5$ Hz, 1F); MS(DCI/NH₃): 238, 240 (M+H).

4-*tert*-Butoxy-3-methyl-2,5,6-trifluoropyridine (**6**)¹

A 3L three-necked flask equipped with a mechanical stirrer, a graduated addition funnel and a digital thermometer was charged with a mixture of **5** and **6** (4.7:1, 294 g, 82.5% pure, 1.01 mol) and THF (900 mL). The internal temperature of the mixture was cooled to -70 °C using a dry-ice / acetone bath. A solution of *sec*-BuLi (960 mL, 1.3 M in cyclohexane, 1.25 mol) was transferred *via* cannula to an addition funnel and was added to the above stirred solution over a period of 1.5 h. The speed of addition was adjusted as to maintain an internal temperature between -61 to -70 °C. After the addition was complete, stirring was continued for an additional 1 h in a dry-ice / acetone bath. MeI (95 mL, 1.53 mol) was added over ~15 min, the lithium salt dissolved and the internal temperature rose quickly to -39 °C. The mixture was stirred for 1 h at ambient temperature. The reaction was quenched with saturated aqueous NH₄Cl (300 mL) and extracted with 1 L of ether. The extract was washed with water (1x), brine (2x), dried over MgSO₄, and concentrated to give the crude product (284 g). This material was distilled under reduced pressure to give **6** (168 g, 76%) as a pale yellow liquid, bp 75-81 °C (7.5 mmHg). It was carried on without further purification. ¹H NMR (CDCl₃) δ 1.47 (m, 9H), 2.12 (m, 3H); ¹⁹F NMR (CDCl₃) δ -75.91 (apparent dd, $J_1=15.0$, $J_2=22.1$ Hz, 1F), -93.17 (apparent dd, $J_1=15.0$, $J_2=22.1$ Hz, 1F), -156.54 (m, 1F); MS (DCI/NH₃): 220 (M+H).

4-*tert*-Butoxy-2,5-difluoro-3-methylpyridine (**7**)¹

Method a. A solution of **6** (168 g, 0.766 mol) and hydrazine monohydrate (>98%, 93 mL, 1.92 mol) in methanol (300 mL) was refluxed for 9 h. The methanol was removed and the residue was dissolved in methylene chloride (~400 mL) and washed with water (2x). The orange colored residue (169 g) was redissolved in methanol (850 mL). To this was added aqueous sodium hydroxide (20%, 450 mL). Air was passed through the solution for 6 days with vigorous stirring. The methanol was removed with a bath temperature of 30-35 °C. The residue was dissolved in ether (1.5 L), which was washed with water (1x), 10% HCl (1x), saturated brine (1x), and dried over MgSO₄. The solvent was removed and the residue was distilled under reduced pressure to give **7** (125 g, 81%) as a colorless liquid, bp 50-60 °C (1.0 mmHg). ¹H NMR (CDCl₃) δ 1.43 (d, $J=1.5$ Hz, 9H), 2.18 (d, $J=1.5$ Hz, 3H), 7.85 (br, 1H); ¹⁹F NMR (CDCl₃) δ -73.37 (d, $J=24.5$ Hz, 1F), -142.17 (d, $J=24.5$ Hz, 1F), MS(DCI/NH₃): 202 (M+H).

Method b-1. Lithium aluminum hydride reduction. Lithium aluminum hydride (56.7 g, 1.49 mol) was added to THF (6 L), and the suspension was cooled to 0 to -5 °C. To this solution 477 g (2.17 mol) of **6** in THF (750 mL) was added in a stream *via* cannula over a 15 min period. The mixture was stirred at rt for

16 h, then hexane (500 mL) was added. The reaction was then quenched while maintaining an internal temperature of 10-20 °C by adding H₂O (57 mL), 15% NaOH solution (57 mL) and H₂O (171 mL), sequentially. The mixture was filtered, and the solid was washed with THF and hexane. The filtrate was concentrated with a bath temperature of 35 °C. The residue was purified by flash chromatography, eluting with hexane and 5% ethyl acetate/hexane to afford 141 g of **7** (32%).

Method b-2. Red-Al[®] reduction. A solution of **6** (477 g, 2.17 mol) in THF (6 L) was cooled to 0 to 5 °C. A solution of sodium bis(2-methoxyethoxy)aluminum hydride (3.4 M in toluene, 750 mL, 2.5 mol) was added dropwise over 1 h. The reaction was stirred at rt for 16 h. After the addition of hexane (500 mL), the reaction was quenched with water (500 mL) slowly to maintain the internal temperature of <25 °C. The organic layer was decanted, and the solid was washed thoroughly with hexane. The combined organic layers were concentrated and the residue was purified by flash chromatography, eluting with hexane and 5% ethyl acetate/hexane to give 138 g of **7** (31%).

2-(4-tert-Butoxy-5-fluoro-3-methyl-2-pyridinyl)-2-cyclopropylacetonitrile (8)

LDA was formed by adding *n*-BuLi (2.5 M in hexanes, 300 mL, 0.750 mol) dropwise to a stirred solution of diisopropylamine (103 mL, 0.735 mol) in THF (300 mL) at -78 °C. The reaction was allowed to stir at 0 °C for 15 min and then recooled to -78 °C with a dry-ice / acetone bath. Cyclopropylacetonitrile (60.0 g, 0.740 mol) in anhydrous THF (150 mL) was added over a period of 15 min to the above solution of LDA, keeping the internal temperature between -51 and -67 °C. The mixture was stirred for an additional 35 min at the same temperature. To the above solution, **7** (60.0 g, 0.298 mol) in THF (150 mL) was added over 20 min maintaining an internal temperature of -65 to -71 °C. The cooling bath was removed and stirring was continued for 30 min. When the temperature reached -30 °C, an exothermic reaction was observed and the temperature rose quickly to 17 °C. The reaction was quenched with saturated aqueous NH₄Cl (200 mL) and was extracted with ether (1 L). The extract was washed with saturated brine, dried over MgSO₄ and concentrated. The excess cyclopropylacetonitrile was removed at 40-45 °C at 0.2 mmHg. The residue was purified by flash chromatography eluting with 5% ethyl acetate/hexane to give **8** (73.0 g, 93%) as a colorless liquid which solidified on standing. mp 52-54 °C. ¹H NMR (CDCl₃) δ 0.50 (m, 2H), 0.63 (m, 1H), 0.73 (m, 1H), 1.60 (m, 1H), 1.43 (d, *J*=2 Hz, 9H), 2.29 (s, 3H), 3.76 (d, *J*=8 Hz, 1H), 8.30 (d, *J*=3 Hz, 1H); IR (neat) ν 2240, 1580, 1470 cm⁻¹. MS (DCI/NH₃): 263 (M+H). Anal. Calcd for C₁₅H₁₉N₂OF: C, 68.68; H, 7.30; N, 10.68. Found: C, 68.71; H, 7.22; N, 10.75.

2-(4-Chloro-5-fluoro-3-methyl-2-pyridinyl)-2-cyclopropylacetonitrile (9)

To a solution of **8** (45.5 g, 0.173 mol) and DMF (68.0 mL, 0.878 mol) in anhydrous methylene chloride (370 mL), POCl₃ (63.5 mL, 0.681 mol) was added slowly with an ambient temperature bath cooling since there was a delayed exothermic reaction. The solution was stirred overnight before being poured into crushed ice. (Caution: make sure POCl₃ is consumed before doing the extraction!). The mixture was extracted with methylene chloride (2x). The combined extracts were washed with water (1x), saturated

aqueous NaHCO_3 (1x), water (2x), dried over MgSO_4 , and concentrated. The product was purified by flash chromatography, eluting with 20% ethyl acetate / hexane to yield **9** as a pale yellow solid (36.8 g, 95%). mp 43-44 °C. ^1H NMR (CDCl_3) δ 0.48 (m, 1H), 0.58 (m, 1H), 0.66 (m, 1H), 0.77 (m, 1H), 1.50 (m, 1H), 2.49 (s, 3H), 3.80 (d, $J=8$ Hz, 1H), 8.39 (s, 1H); MS (DCI/NH_3): 225, 227 (M+H). *Anal.* Calcd for $\text{C}_{11}\text{H}_{10}\text{N}_2\text{ClF}$: C, 58.81; H, 4.49; N, 12.47. Found: C, 58.80; H, 4.38; N, 12.38.

Ethyl 2-(4-chloro-5-fluoro-3-methyl-2-pyridinyl)-2-cyclopropylacetate (10)

A solution of **9** (136 g, 0.604 mol) in ethanol (90 mL) was added to a solution of ethanol (1.0 L) saturated with HCl gas (~400 g) at 0 °C. The reaction was stirred for 3 h at 0 °C. To this solution was added H_2O (90 mL). The reaction was heated at 80 °C for 2 h. The mixture was poured over ice to give a total volume of 4 L. The solution was neutralized with 50% NaOH to pH 8 while maintaining a temperature less than 0 °C. The solid was filtered, redissolved in CH_2Cl_2 , and the residual water layer removed. The organic layer was dried over MgSO_4 and evaporated to provide **10** as a pure tan solid (134 g, 82%). mp 64-65 °C. ^1H NMR (CDCl_3) δ 0.12 (m, 1H), 0.38 (m, 1H), 0.53 (m, 1H), 0.76 (m, 1H), 1.20 (t, $J=7$ Hz, 3H), 1.67 (m, 1H), 2.40 (s, 3H), 3.23 (d, $J=9$ Hz, 1H), 4.16 (q, $J=7$ Hz, 2H), 8.36 (s, 1H); MS (DCI/NH_3): 272, 274 (M+H). *Anal.* Calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_3\text{ClF}$: C, 57.47; H, 5.56; N, 5.15. Found: C, 57.54; H, 5.45; N, 5.08.

2-(4-Chloro-5-fluoro-3-methyl-2-pyridinyl)-2-cyclopropylethanol (11)

A solution of **10** (98.5 g, 0.363 mol) in anhydrous THF (400 mL) was cooled to -78 °C in a dry-ice / acetone bath. LiAlH_4 (11.7 g, 0.31 mol) was added to the solution *via* a powder dispensing funnel over 15 min. The speed of addition was adjusted to maintain the internal temperature between -20 °C and 10 °C. The resulting mixture was stirred at 0-10 °C for 2.5 h. The reaction was quenched carefully with water (12 mL), followed by 15% NaOH (12 mL) and water (35 mL). The solid was then filtered and washed with ether until no product could be detected in the washings. The filtrate (total volume of 2 L) was washed with saturated brine (1x), dried over MgSO_4 , and concentrated to give **11** as an off-white solid (85.1 g), which was carried on without further purification. ^1H NMR (CDCl_3) δ 0.21 (m, 2H), 0.44 (m, 1H), 0.60 (m, 1H), 1.21 (m, 1H), 2.39 (s, 3H), 2.56 (m, 1H), 3.52 (br s, 1H), 4.02 (m, 2H), 8.31 (s, 1H); MS (DCI/NH_3): 230, 232 (M+H). *Anal.* Calcd for $\text{C}_{11}\text{H}_{13}\text{NOClF}$: C, 57.52; H, 5.71; N, 6.10. Found: C, 57.82; H, 5.54; N, 5.91.

2-(4-Chloro-5-fluoro-3-methyl-2-pyridinyl)-2-cyclopropylacetaldehyde (12)

A solution of DMSO (62.0 mL, 0.874 mol) in anhydrous methylene chloride (700 mL) was cooled with a dry-ice / acetone bath. To this solution, oxalyl chloride (2.0 N in CH_2Cl_2 , 220 mL, 0.440 mol) was added dropwise over a period of 20 min. The mixture was stirred for an additional 20 min. A solution of **11** (from above, ~0.363 mol) in methylene chloride (300 mL) was added dropwise to the above solution over

15 min. The solution was stirred for 30 min, and triethylamine (250 mL, 1.79 mol) was added over 7 min while the internal temperature rose to -36 °C. Stirring was continued without a cooling bath for 10 min. The reaction was quenched with water, and transferred to a separatory funnel. The organic layer was separated, washed with water (2x), and dried over MgSO₄. The solvent was removed to give **12** (93.2 g, theory: 82.5 g) as a colorless oil, which was carried on without purification. ¹H NMR (CDCl₃) δ 0.24 (m, 1H), 0.35 (m, 1H), 0.60 (s, 1H), 0.76 (m, 1H), 1.53 (m, 1H), 2.38 (s, 3H), 3.19 (dd, *J*=3, 9 Hz, 1H), 8.37 (s, 1H), 9.86 (d, *J*=3 Hz, 1H); MS (DCI/NH₃): 228, 230 (M+H).

Ethyl 4-(4-chloro-5-fluoro-3-methyl-2-pyridinyl)-4-cyclopropyl-2-ethoxycarbonyl-2-butenate (13)

Diethyl malonate (270 mL, 1.78 mol), piperidine (35 mL), and acetic acid (35 mL) were added to a solution of **12** (from above, ~0.363 mol) in ethanol (1 L). The solution was heated at reflux for 8 h. The reaction was concentrated and the residue was dissolved in ether (1 L), washed with water (1x) and saturated brine (1x), dried over MgSO₄, and concentrated and the diethyl malonate was distilled off at 50-75 °C under 0.2 mmHg. The remaining yellow oil **13** (136 g, theory: 134 g) was taken directly on to the next step. MS (DCI/NH₃): 270, 272 (M+H).

Ethyl 8-chloro-1-cyclopropyl-7-fluoro-4H-9-methyl-4-oxo-quinolizine-3-carboxylate (2)

A solution of **13** (from above, ~0.363 mol) in anhydrous DMSO (300 mL) was heated to reflux. Once reflux was reached (30 min), heating was continued for 1 h. The reaction, after cooling to about 50 °C (before the product precipitated out) was poured into water (2 L). The solid was filtered and washed thoroughly with water and hexane and dried under vacuum at 65 °C overnight to give the title compound as a yellow crystalline solid (85.1 g, 73% over four steps). mp 143-144 °C (EtOAc / Hexane). ¹H NMR (CDCl₃) δ 0.75 (m, 2H), 1.07 (m, 2H), 1.42 (t, *J*=7 Hz, 3H), 2.31 (m, 1H), 3.08 (s, 3H), 4.42 (q, *J*=7 Hz, 2H), 8.40 (s, 1H), 9.44 (d, *J*=6 Hz, 1H); MS (DCI/NH₃): 324, 326 (M+H). *Anal.* Calcd for C₁₆H₁₅NO₃ClF: C, 59.36; H, 4.67; N, 4.33; Cl, 10.95. Found: C, 59.56; H, 4.52; N, 4.21; Cl, 10.70.

ACKNOWLEDGMENT

The authors wish to thank Ms. Beth Steiner and Dr. Curt Cooper for helpful discussions. We also acknowledge the support from the Structural Chemistry Department for analysis of the compounds.

REFERENCES

1. Q. Li, D. T. Chu, A. Claiborne, C. S. Cooper, C. M. Lee, K. Raye, K. B. Berst, P. Donner, W. Wang, L. Hasvold, A. Fung, Z. Ma, M. Tufano, R. Flamm, L. L. Shen, J. Baranowski, A. Nilius, J. Alder, J. Meulbroek, K. Marsh, D. Crowell, Y. Hui, L. Seif, L. M. Melcher, R. Henry, S. Spanton,

- R. Faghih, L. L. Klein, S. K. Tanaka, and J. J. Plattner, *J. Med. Chem.*, 1996, **39**, 3070, and references therein.
2. For other 2-pyridone related papers, see: (a) Q. Li, W. Wang, K. B. Berst, A. Claiborne, L. Hasvold, K. Raye, M. Tufano, A. Nilius, L. L. Shen, R. Flamm, J. Alder, K. Marsh, D. Crowell, D. T. W. Chu, and J. J. Plattner, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 1953. (b) Z. Ma, D. T. W. Chu, Q. Li, L. L. Shen, A. Fung, C. S. Cooper, W. Wang, S. Wang, R. K. Flamm, A. Nilius, J. D. Alder, S. K. Tanaka, Y. Or, and J. J. Plattner, *37th Interscience Conference on Antimicrobial Agents and Chemotherapy*, 1997, Abstract F169. (c) T. Park, K. Nam, Y. Ha, Y. Choi, Y. Choi, J. Kong, and Y. Kim, *37th Interscience Conference on Antimicrobial Agents and Chemotherapy*, 1997, Abstract 173. (d) L. L. Klein, D. A. DeGoey, S. A. Thomas, C. M. Yeung, C. L. Leone, D. J. Grampovnik, D. T. Chu, and P. A. Lartey, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 1167. (e) R. K. Flamm, C. Vojtko, D. T. Chu, D. Q. Li, J. Beyer, D. Hensey, N. Ramer, J. J. Clement, and S. K. Tanaka, *Antimicrob. Agents Chemother*, 1995, **39**, 964. (f) G. M. Eliopoulos, C. B. Wennersten, G. Cole, D. Chu, D. Pizzuti, and R. C. Moellering, Jr., *Antimicrob. Agents Chemother*, 1995, **39**, 850. (g) J. Alder, J. Clement, J. Meulbroek, N. Shipkowitz, M. Mitten, K. Jarvis, A. Oleksijew, T. Hutch, Sr., L. Paige, R. Flamm, D. Chu, and K. Tanaka, *Antimicrob. Agents Chemother*, 1995, **39**, 971. (h) R. A. Fromtling, *Drugs Fut.*, 1995, **20**, 1103.
 3. R. D. Chambers, J. Hutchinson, and W. K. R. Musgrave, *J. Chem. Soc.*, 1964, 3573. The 70% pure **3** was available from Aldrich. The pure **3** is now available from both Fluorochem and Aldrich.
 4. Repeating the same reaction starting with the 99% pure 3-chlorotetrafluoro-pyridine (**3**) gave 4-*tert*-butoxypyridine **4** in 75% yield on a kilogram scale.
 5. R. D. Chambers, D. Close, W. K. R. Musgrave, J. S. Waterhouse, and D. L. H. Williams, *J. Chem. Soc., Perkin Trans II*, 1977, 1774.
 6. R. D. Chambers, J. Hutchinson and W. K. R. Musgrave, *J. Chem. Soc.*, 1964, 5634.
 7. Separation of **4** and **5** is not necessary. However, when pure **4** was used, the overall yield from **4** to **7** increased to 67%.
 8. Recently, Park and his colleagues claimed at the 37th Interscience Conference on Antimicrobial Agents and Chemotherapy that they were able to reduce **9** directly to the aldehyde using DIBAL as a reducing agent. Our reduction attempts using DIBAL under several different conditions were unsuccessful. See ref. 2c.
 9. Dowtherm A is a mixture of biphenyl and diphenyl ether (23:77).