

M. Bhupathy*, David A. Conlon*, Kenneth M. Wells*,
John R. Nelson, Paul J. Reider, Kai Rossen, Jess W. Sager and R. P. Volante

Merck Research Laboratories, Department of Process Research
P. O. Box 2000, Rahway, NJ 07065-0900, USA

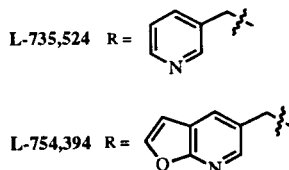
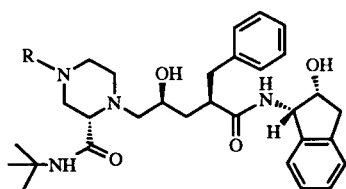
Bruce D. Dorsey, Jacob M. Hoffman, Jr., Sally A. Joseph and Stacey L. McDaniel

Merck Research Laboratories, Department of Medicinal Chemistry
West Point, PA 19486, USA
Received February 10, 1995

A practical synthesis of 5-(chloromethyl)furo[2,3-*b*]pyridine (**10**), the side chain used to incorporate a key pharmacophore of the HIV protease inhibitor, L-754,394, is described. The synthesis was accomplished in ten steps and in 15% overall yield from commercially available methyl 2-furoate.

J. Heterocyclic Chem., **32**, 1283 (1995).

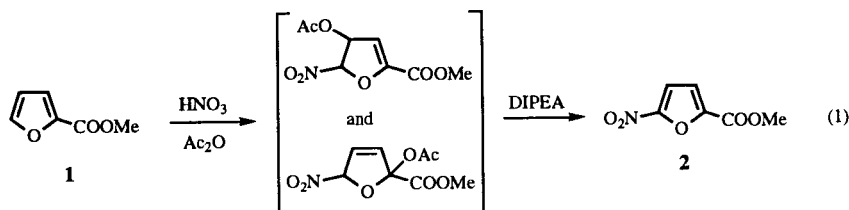
Recent efforts from our laboratories to develop a potent and orally bioavailable HIV protease inhibitor have resulted in the discovery of the current clinical candidate L-735,524 [1,2a]. With an objective to increase bioavailability and improve pharmacokinetics, L-754,394 [2b], a furo[2,3-*b*]pyridine analog of L-735,524 has been identified. The synthesis of L-754,394 has been envisaged following the synthesis of L-735,524 [2,3] using 5-(chloromethyl)furo[2,3-*b*]pyridine (**10**) instead of 3-picolyl chloride for the last coupling step with the piperazine ring of the rest of the molecule.



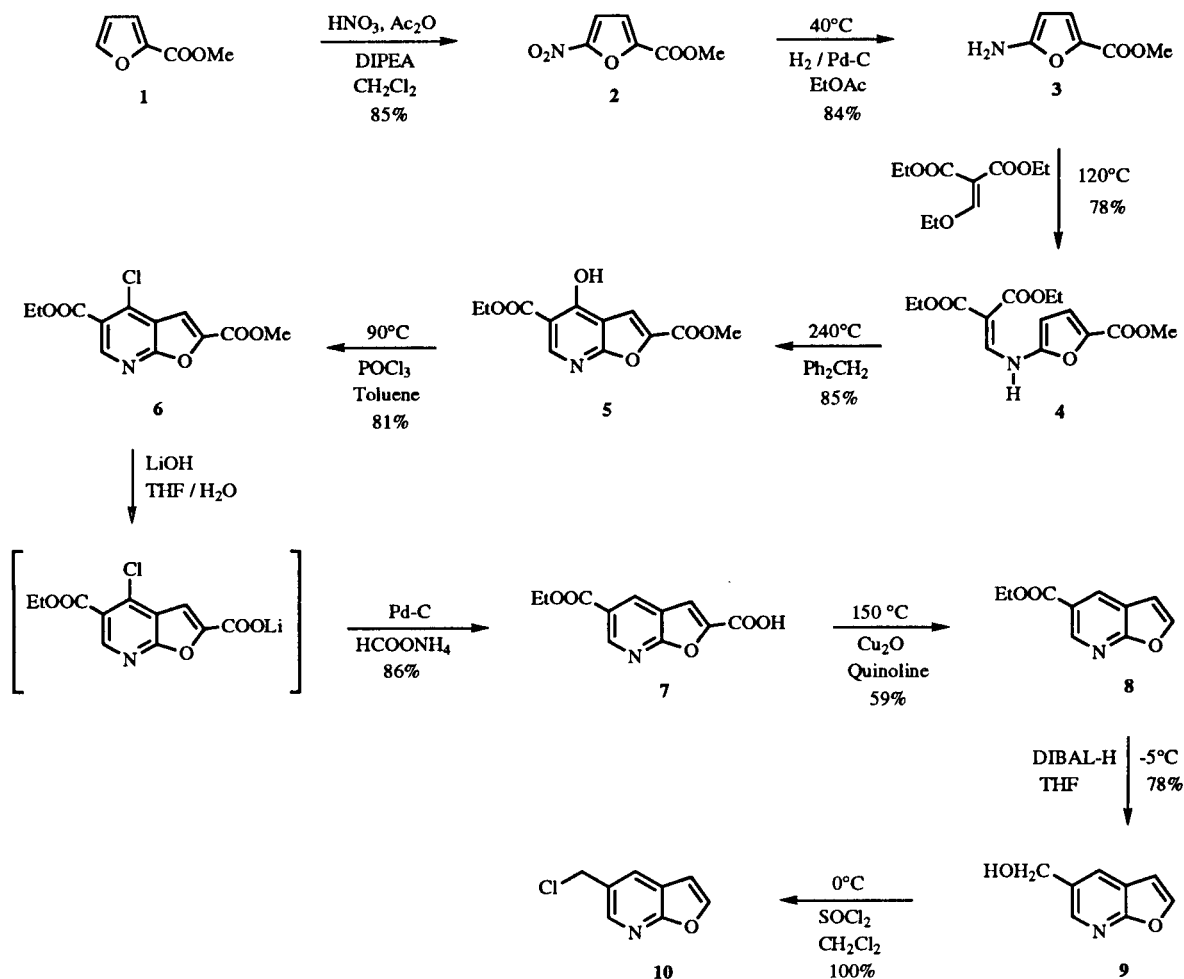
This paper describes a practical synthesis (Scheme I) of kilogram quantities of the key differentiating intermediate **10**. In this approach [4-6], the construction of the furo[2,3-*b*]pyridine was accomplished starting with a precursor containing the furan ring and appending the pyridine ring to it. Although the nitrofuran **2** is commercially available (Lancaster Synthesis Inc.), its limited supply and high cost compelled us to start with the commercially

available, inexpensive methyl 2-furoate (**1**). Nitration of **1** was carried out using acetyl nitrate generated *in situ* with acetic anhydride (3.1 equivalents) and fuming nitric acid (2.0 equivalents) in methylene chloride. In accordance with the observations by Kolb *et al* [7a], as shown by nmr studies, the addition of acetyl nitrate to the furan **1** resulted in the formation of an unstable mixture of 1,2 and 1,4 addition products (equation 1). Following an aqueous work up using a phosphate buffer (pH 7.2) at 0°, the organic layer was treated with *N,N*-diisopropylethylamine (0.98 equivalents) at ambient temperature to eliminate acetic acid and regenerate the furan ring. The nitrofuran **2** was readily isolated as a crystalline material in 85% yield after an aqueous workup followed by vacuum concentration and crystallization from ethanol/water. The current procedure is a vast improvement over the literature procedure [7b] which gave only 20-40% yield of **2**.

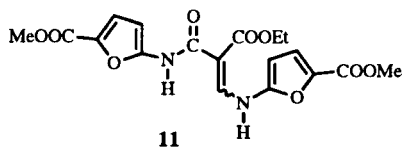
Reduction of the nitro compound **2** to the amine **3** was carried out by catalytic hydrogenation. Initial results were discouraging due to irreproducibility of the reaction. After a careful study varying the solvent (isopropyl acetate, ethyl acetate, methanol, triethylamine combinations), catalyst (palladium on carbon, palladium hydroxide) and catalyst loading (1 to 5 wt%), it was observed that the product **3** was not stable to the reaction conditions and shorter reaction times produced better yields. Hydrogenation of a 0.7 *M* solution of **2** in ethyl acetate using 5 wt% of 5% Pd/C catalyst at 40° for 2 to 3 hours gave the best yield (84%).



Scheme I



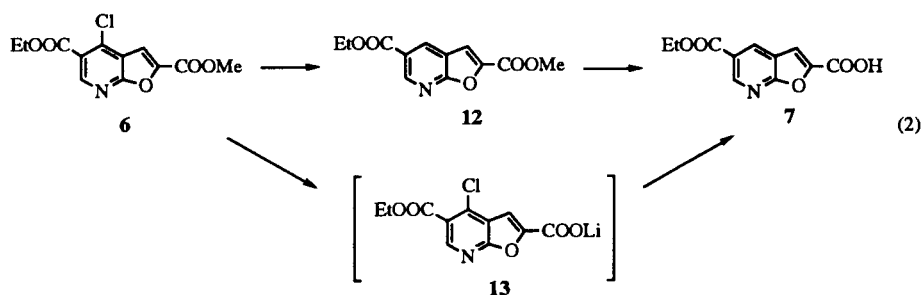
The reaction was followed by gc assay and at the end of the reaction, the catalyst was removed by filtration. The filtrate containing the product 3 was immediately used in the next step.



Michael addition of the amine 3 with diethyl ethoxymethylenemalonate gave the desired adduct 4, along with an impurity 11 [8]. In a control experiment, when the pure compound 4 was heated with the amine 3, the impurity amide 11 was not formed. This indicated that the amide 11 was formed by competing 1,2 addition before the Michael addition or production of 4. It was also observed that the amount of 11 formed depended on the tempera-

ture of the reaction, $\leq 1\%$ at 120° and about 14% at 150° . Under the optimized conditions, the amine 3 in ethyl acetate was concentrated and turned over to diethyl ethoxymethylenemalonate (1.3 equivalents) under vacuum at $\leq 90^\circ$, then heated to 120° and aged for ~ 2.5 hours. The desired product 4 was isolated in 78% yield by crystallization from 2-propanol.

The intramolecular Friedel-Crafts cyclization of 4 was carried out at 240° in diphenylmethane to produce the furo[2,3-*b*]pyridine 5. The reaction mixture was cooled and diluted with toluene to isolate the crystalline product in 85% yield. The literature protocol [5] for the conversion of the hydroxypyridine 5 to the chloropyridine 6 was modified by a) decreasing the number of equivalents of phosphorus oxychloride from 12.5 equivalents to 3 equivalents b) using toluene as a cosolvent for the reaction at 90° instead of carrying out the reaction neat at 100° and c) replacing the tedious aqueous workup with a crystallization procedure to isolate the product. These improvements resulted in the isolation of crystalline chlorofuro[2,3-*b*]pyridine 6 in 81% yield.



Initially the intermediate **6** was dechlorinated under catalytic hydrogenation conditions (equation 2). The resulting diester **12** was isolated and subjected to a selective hydrolysis to give the ester-acid **7**. In this approach, dechlorination of **6** suffered from low volumetric productivity (0.04 M) and a possible reduction of the sensitive furan ring. A solution to these problems was found when the order of the steps was reversed and the milder transfer hydrogenation was used for dechlorination.

The hydrolysis and dechlorination steps were carried out in a single pot. Selective hydrolysis of the methyl ester in the diester **6** occurred in aqueous tetrahydrofuran with lithium hydroxide, the reaction was completely selective as seen by ^1H nmr. The resulting solution of the carboxylate **13** was subsequently treated at room temperature with 1.2 to 1.5 equivalents of ammonium formate and 5% Pd/C. Under these conditions, dechlorination readily occurred without any reduction of the furan ring. Crystallization of the product **7** was accomplished after removal of tetrahydrofuran by concentration and pH adjustment of the solution to 1-2 by the addition of aqueous 2N hydrochloric acid. The ester-acid **7** was obtained in 86% yield for the two steps.

Initially the decarboxylation was carried out at 250° with one equivalent of copper powder and quinoline. Even after chromatographic isolation of the product, a considerable amount of residual copper was observed. To circumvent these problems, alternative procedures were examined. Decarboxylation of **7** occurred cleanly in 1-methylnaphthalene with a catalytic amount of basic copper carbonate at 240° in ~30 minutes. The product, in this case, could be purified by column chromatography. To avoid the chromatography step and to lower the reaction temperature, another procedure was developed based on the observations by Cohen *et al.* [9]. Decarboxylation of **7** was readily carried out using 5-10 wt% of cuprous oxide in quinoline at 150° in 2-5 hours. After dilution of the reaction mixture with toluene, filtration through a bed of Solka-Floc® and an aqueous workup, crystalline ethyl ester **8** was obtained in 59-65% yield.

Reduction of the ester **8** to the alcohol **9** was not straightforward due to competitive reduction of the furan ring. Of the borohydride and aluminum hydride reagents

explored, the best results were obtained using lithium aluminum hydride and DIBAL-H. In addition, use of commercial solutions of DIBAL-H in tetrahydrofuran was inferior to neat DIBAL-H due to problems associated with the degradation of the commercial solutions on storage. The reaction was carried out in tetrahydrofuran and after aqueous workup, the product was isolated in 78-83% yield by crystallization from isopropyl acetate/hexanes. Both aluminum and copper levels were <10 ppm in the isolated alcohol **9**.

Conversion of the alcohol **9** to the chloride **10** was accomplished using thionyl chloride in methylene chloride. A cold sodium bicarbonate wash and solvent removal resulted in the production of **10** in quantitative yield.

EXPERIMENTAL

The ^1H and ^{13}C -nmr spectra were obtained on a Bruker AM-250 instrument (^1H -nmr at 250 MHz, ^{13}C -nmr at 63 MHz). Spectra are referenced to the solvent (chloroform $\delta = 7.27$ ppm; methanol $\delta = 3.30$ ppm; dimethyl sulfoxide $\delta = 2.49$ ppm). All coupling constants are reported in hertz (Hz).

Capillary gas chromatography (gc) was performed on a Hewlett Packard 5890 Series II chromatograph equipped with a 7673 GC/SFC Injector, 3396 Series II Integrator and a 30 m HP 50+ column (0.52 mm i.d. x 1 μ m film). A Hewlett Packard Series 1050 equipped with an autosampler, variable wavelength detector and a Zorbax RX C-8 column (4.6 mm x 25 cm) was used for hplc assays. The output from the detector was connected to a Vectra 486/66xm computer which operated the HP Chem Station.

Melting points were determined on a Haake Buchler melting point apparatus and are uncorrected. Microanalysis was performed by Quantitative Technologies, Inc. Yields for non-isolated intermediates were determined with an external standard. The yields for isolated compounds are corrected for weight percent purity using an external standard.

Reagents and solvents were purchased from either Aldrich Chemical Co. or Fisher Scientific. Solvents were dried over molecular sieves.

5-Nitro-2-furancarboxylic Acid Methyl Ester (2) [10].

A stirred and cooled (-11 to -5°) solution of acetic anhydride (5 L, 5.4 Kg, 53 moles) in dry methylene chloride was treated with 90% nitric acid (1.48 L, 2.1 Kg, 33.3 moles) over 1.5 hour. After allowing to stir for 2 hours at -5°, this solution was treated

with methyl 2-furoate (**1**) (2.05 Kg, 16.8 moles) over an hour. The reaction mixture was slowly warmed to room temperature and aged at this temperature for 5 hours. The cooled (-5°) reaction mixture was washed sequentially with 26 L of water and 20 L of phosphate buffer solution (pH 7.2). The separated organic layer was treated with *N,N*-diisopropylethylamine (2.76 L, 2.05 Kg, 15.8 moles) and warmed to room temperature with stirring overnight. The reaction mixture was cooled to -5° and washed sequentially with 1*N* hydrochloric acid (40 L), water (40 L), and saturated sodium bicarbonate (40 L). The separated organic layer was concentrated at $<25^{\circ}$ and the solvent was turned over to ethanol. Addition of water resulted in the crystallization of **2** which was isolated by filtration. The product (2.4 Kg) was obtained as a light orange solid (ethanol/water) in 85% yield, mp $80.4-80.7^{\circ}$, (lit $79-80^{\circ}$ [10]); ^1H nmr (deuteriochloroform): δ 7.34 (d, $J = 3.8$ Hz, 1H, 4-H), 7.28 (d, $J = 3.8$ Hz, 1H, 3-H), 3.94 (s, 3H, CO_2CH_3).

5-Amino-2-furancarboxylic Acid Methyl Ester (**3**) [10].

A mixture of methyl 5-nitro-2-furoate (**2**) (1.4 Kg, 8.2 moles) and 5% Pd/C (70 g) in ethyl acetate (11 L) was heated to 40° under 40 psi of hydrogen for about two hours. The reaction was followed by gc assay (retention time for **2** was 16.6 minutes and for **3** was 17.7 minutes). At the end of reaction, the reaction mixture was cooled to room temperature and filtered through a bed of Solka-Floc[®]. The product solution was immediately used in the next step. The yield of **3**, determined by gc assay, was 971 g (84%), ^1H nmr (deuteriochloroform): δ 7.08 (d, $J = 3.7$ Hz, 1H, 3-H), 5.25 (d, $J = 3.5$ Hz, 1H, 4-H), 4.47 (bs, 2H, NH_2), 3.79 (s, 3H, CO_2CH_3).

((5-(Methoxycarbonyl)-2-furanyl)amino)methylene)propane-dioic Acid Diethyl Ester (**4**).

The solution of **3** (622 g, 4.4 moles) from the hydrogenation reaction was concentrated *in vacuo* at room temperature and treated with diethyl ethoxymethylenemalonate (1.16 L, 1.24 Kg, 5.73 moles). The distillation was continued *in vacuo* until the pot temperature reached 90° . The reaction flask was flushed with nitrogen and the mixture was heated to 120° for 3.25 hours. The cooled reaction mixture was diluted with 2-propanol (2.75 L), seeded and stirred at room temperature overnight. The product was isolated as a white solid by filtration and dried *in vacuo* to obtain 1.07 Kg (78%) of **4**, mp $96.9-97.9^{\circ}$; ^1H nmr (deuteriochloroform): δ 11.27 (d, $J = 12.8$ Hz, 1H, NH), 8.34 (d, $J = 12.8$ Hz, 1H, $=\text{CHN}$), 7.15 (d, $J = 3.6$ Hz, 1H, 3-H), 5.84 (d, $J = 3.6$ Hz, 1H, 4-H), 4.25 (m, 4H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.86 (s, 3H, CO_2CH_3), 1.32 (m, 6H, $\text{CO}_2\text{CH}_2\text{CH}_3$); ^{13}C nmr (deuteriochloroform): δ 168.4 (CO_2Et), 164.7 (CO_2Et), 158.5 (CO_2Me), 150.5 (2), 149.3 ($=\text{CHN}$), 138.6 ($(\text{EtO}_2\text{C})_2\text{C}=\text{}$), 121.0 (3), 96.9 (5), 92.7 (4), 60.9 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 60.5 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 51.8 (CO_2CH_3), 14.3 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 14.2 ($\text{CO}_2\text{CH}_2\text{CH}_3$).

Anal. Calcd. for $\text{C}_{14}\text{H}_{17}\text{NO}_7$ (311.29): C, 54.01; H, 5.51; N, 4.50. Found: C, 54.01; H, 5.43; N, 4.46.

4-Hydroxyfuro[2,3-*b*]pyridine-2,5-dicarboxylic Acid 5-Ethyl 2-Methyl Ester (**5**).

Diethyl [(5-carbomethoxy-2-furylamino)methylene]malonate (**4**) (2.5 Kg, 8.0 moles) and diphenyl methane (10 L) were heated to 240° , cooled and diluted with toluene (5 L). Compound **5** was isolated by filtration and dried *in vacuo* at 40° . The yield was 1.8 Kg (85%), mp $197.3-197.8^{\circ}$; ^1H nmr (deuterio-

chloroform): δ 12.01 (s, 1H, OH), 8.89 (s, 1H, 6-H), 7.64 (s, 1H, 3-H), 4.48 (q, $J = 7.1$ Hz, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.97 (s, 3H, CO_2CH_3), 1.44 (t, $J = 7.1$ Hz, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$); ^{13}C nmr (deuteriochloroform): δ 169.8 (4), 165.6 (CO_2Et), 164.6 (7a), 159.0 (CO_2Me), 150.9 (6), 143.8 (2), 111.1 (3), 108.6 (5), 106.5 (3a), 62.3 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 52.6 (CO_2CH_3), 14.2 ($\text{CO}_2\text{CH}_2\text{CH}_3$).

Anal. Calcd. for $\text{C}_{12}\text{H}_{11}\text{NO}_6$ (265.22): C, 54.34; H, 4.18; N, 5.28. Found: C, 54.35; H, 4.13; N, 5.20.

4-Chlorofuro[2,3-*b*]pyridine-2,5-dicarboxylic Acid 5-Ethyl 2-Methyl Ester (**6**) [11].

A slurry of **5** (2.8 Kg, 10.5 moles) in toluene (11 L) was heated to 95° and treated with phosphorus oxychloride (2.7 L, 29.3 moles). The temperature was maintained at 100° for 1.5 hours at which time the solution became homogeneous. Toluene (20 L) was slowly added while maintaining the reaction temperature at 95° . The reaction temperature was increased and 20 L of distillate was removed. Heptane (3 L) was added at 90° resulting in the precipitation of a dark waxy solid. The reaction solution was decanted from this solid and diluted with heptane (27 L). The reaction solution was seeded and allowed to cool with stirring overnight. The resulting slurry was cooled to -5° and filtered. The isolated solid was dried *in vacuo* to give 2.4 Kg (81%) of **6**, mp $136.1-136.7^{\circ}$; ^1H nmr (deuteriochloroform): δ 9.00 (s, 1H, 6-H), 7.66 (s, 1H, 3-H), 4.45 (q, $J = 7.1$ Hz, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 4.00 (s, 3H, CO_2CH_3), 1.42 (t, $J = 7.1$ Hz, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$); ^{13}C nmr (deuteriochloroform): δ 163.6 (CO_2Et), 162.5 (7a), 158.6 (CO_2Me), 150.8 (6), 146.2 (2), 140.3 (4), 122.6 (5), 120.2 (3a), 111.8 (3), 62.1 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 52.9 (CO_2CH_3), 14.2 ($\text{CO}_2\text{CH}_2\text{CH}_3$).

Anal. Calcd. for $\text{C}_{12}\text{H}_{10}\text{ClNO}_5$ (283.66): C, 50.81; H, 3.55; Cl, 12.50; N, 4.94. Found: C, 50.80; H, 3.49; Cl, 12.29; N, 4.83.

Furo[2,3-*b*]pyridine-2,5-dicarboxylic Acid 5-Ethyl Ester (**7**).

A solution of lithium hydroxide monohydrate (319 g, 7.6 moles) in water (2.5 L) was added to a solution of **6** (1.65 Kg, 5.81 moles) in water (6.6 L) and tetrahydrofuran (49 L). After allowing the reaction mixture to stand overnight at room temperature, ammonium formate (660 g, 10.5 moles), 5% palladium on carbon (115 g), and water (8.8 L) were added and the mixture was allowed to stand at room temperature for 6 hours. The reaction mixture was filtered and the tetrahydrofuran was removed by distillation. The concentrate was treated with 2*N* hydrochloric acid (12 L) and the resulting solid was isolated by filtration. This solid was slurried in water (36 L), filtered and dried *in vacuo* at 50° to yield 1.2 Kg (86%) of **7** as an off white solid, mp $>265^{\circ}$; ^1H nmr (methanol- d_4): δ 9.01 (d, $J = 2.1$ Hz, 1H, 6-H), 8.78 (d, $J = 2.1$ Hz, 1H, 4-H), 7.58 (s, 1H, 3-H), 4.43 (q, $J = 7.2$ Hz, 2H, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.42 (t, $J = 7.1$ Hz, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$); ^{13}C nmr (dimethyl- d_6 sulfoxide): δ 164.3 (CO_2Et), 163.0 (7a), 159.4 (CO_2H), 148.3 (6), 146.8 (2), 134.4 (4), 122.9 (5), 119.1 (3a), 112.9 (3), 61.2 ($\text{CO}_2\text{CH}_2\text{CH}_3$), 14.0 ($\text{CO}_2\text{CH}_2\text{CH}_3$).

Anal. Calcd. for $\text{C}_{11}\text{H}_9\text{NO}_5$ (235.19): C, 56.17; H, 3.86; N, 5.96. Found: C, 51.19; H, 3.87; N, 5.83 [12].

Ethyl Furo[2,3-*b*]pyridine-5-carboxylate (**8**).

A mixture of furo[2,3-*b*]pyridine-2,5-dicarboxylic acid 5-ethyl ester (**7**) (1.16 Kg, 4.9 moles), copper(I) oxide (113.5 g) and quinoline (1.7 L) was heated at 150° for two hours. The thick slurry was cooled to 120° , diluted with toluene (15.3 L) and filtered through a bed of Solka-Floc[®]. The filtrate was washed with 2*N* hydrochloric acid (3 x 5 L) and water (2 x 7 L). The toluene was removed *in*

vacuo, the resulting thick oil diluted with heptane (*ca* 4.5 L) and warmed to 50°. The homogenous solution was seeded and cooled to room temperature. The resulting solid was isolated by filtration and dried to give 550 g (59%) of **8**, mp 73.9-75.8°; ¹H nmr (deuteriochloroform): δ 8.95 (d, *J* = 2.0 Hz, 1H, 6-H), 8.53 (d, *J* = 2.0 Hz, 1H, 4-H), 7.73 (d, *J* = 2.5 Hz, 1H, 2-H), 6.81 (d, *J* = 2.5 Hz, 1H, 3-H), 4.38 (q, *J* = 7.1 Hz, 2H, CO₂CH₂CH₃), 1.37 (t, *J* = 7.1 Hz, 3H, CO₂CH₂CH₃); ¹³C nmr (deuteriochloroform): δ 165.4 (CO₂Et), 163.9 (7a), 146.4 (6), 146.1 (2), 132.0 (4), 122.6 (5), 118.9 (3a), 106.4 (3), 61.3 (CO₂CH₂CH₃), 14.3 (CO₂CH₂CH₃).

Anal. Calcd. for C₁₀H₉NO₃ (191.18): C, 62.82; H, 4.74; N, 7.33. Found: C, 62.64; H, 4.64; N, 7.27.

Furo[2,3-*b*]pyridine-5-methanol (**9**).

Neat diisobutylaluminum hydride (1.1 L, 6.2 moles) was added to a solution of ethyl furo[2,3-*b*]pyridine-5-carboxylate (**8**) (548 g, 2.86 moles) in dry tetrahydrofuran (12.9 L) while keeping the temperature below -5°. The reaction solution was cautiously quenched with saturated aqueous sodium potassium tartarate solution (8 L) while maintaining the reaction temperature below -4°. The batch was heated to reflux and the separated organic layer was diluted with isopropyl acetate (12 L). The organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, treated with activated carbon (30 g), filtered through silica gel and concentrated *in vacuo*. The product **9** was isolated from isopropyl acetate/hexanes (3 L/7.5 L) and dried *in vacuo* at room temperature to give 738 g (78%) of **9**, mp 56.0-56.7°; ¹H nmr (deuteriochloroform): δ 8.25 (d, *J* = 2.0 Hz, 1H, 6-H), 7.96 (d, *J* = 2.2 Hz, 1H, 4-H), 7.68 (d, *J* = 2.5 Hz, 1H, 2-H), 6.74 (d, *J* = 2.6 Hz, 1H, 3-H), 4.80 (d, *J* = 2.6 Hz, 2H, CH₂OH), 2.91 (bs, 1H, OH); ¹³C nmr (deuteriochloroform): δ 161.3 (7a), 145.3 (6), 143.2 (2), 132.5 (5), 129.6 (4), 119.3 (3a), 106.0 (3), 62.3 (CH₂OH).

Anal. Calcd. for C₈H₇NO₂ (149.14): C, 64.42; H, 4.73; N, 9.39. Found: C, 64.29; H, 4.76; N, 9.28.

5-(Chloromethyl)furo[2,3-*b*]pyridine (**10**).

A solution of furo[2,3-*b*]pyridine-5-methanol (**9**) (780 g, 4.8 moles) in dry methylene chloride (15 L) at 0° was treated with thionyl chloride (386 ml, 5.3 moles). Aqueous saturated sodium bicarbonate (20 L) was added and the layers were separated. The separated organic layer was dried with anhydrous sodium sulfate (1 Kg) and treated with activated carbon (40 g). Filtration and solvent removal *in vacuo* gave 851 g (100%) of the product **10**, mp 56.0-60.0°; ¹H nmr (deuteriochloroform): δ 8.32 (d, *J* = 2.1 Hz, 1H, 6-H), 7.97 (d, *J* = 2.2 Hz, 1H, 4-H), 7.72 (d, *J* = 2.5 Hz, 1H, 2-H), 6.76 (d, *J* = 2.4 Hz, 1H, 3-H), 4.69 (s, 2H, CH₂Cl); ¹³C nmr (deuteriochloroform): δ 161.8 (7a), 145.8 (6), 144.5 (2), 130.6 (4), 129.2 (5), 119.4 (3a), 106.0 (3), 43.6 (CH₂Cl).

Anal. Calcd. for C₈H₆ClNO (167.59): C, 57.33; H, 3.61; Cl, 21.15; N, 8.36. Found: C, 57.24; H, 3.47; Cl, 21.08; N, 8.24.

Diethyl Furo[2,3-*b*]pyridine-2,5-dicarboxylate (**14**) [5,12].

To a solution of furo[2,3-*b*]pyridine-2,5-dicarboxylic acid 5-ethyl ester (**7**) (1 g, 4.25 mmoles) in absolute ethanol (10 ml) was added 2 ml of sulfuric acid. The resulting solution was heated at reflux for 2 hours, cooled and evaporated to dryness. The reaction product was chromatographed on silica gel (2:1 ethyl acetate:hexanes) to give 0.75 g (67%) of the diester **14**, mp 89.9-90.9° (lit 90-91° [5]); ¹H nmr: (deuteriochloroform): δ 9.11

(d, *J* = 2.0 Hz, 1H, 6-H), 8.67 (d, *J* = 2.1 Hz, 1H, 4-H), 7.54 (s, 1H, 3-H), 4.43 (m, 4H, CO₂CH₂CH₃), 1.40 (t, *J* = 7.1 Hz, 6H, CO₂CH₂CH₃); ¹³C nmr: δ 164.7 (5-CO₂Et), 163.5 (7a), 158.5 (2-CO₂Et), 149.5 (2), 146.5 (6), 133.9 (4), 123.5 (5), 118.8 (3a), 112.6 (3), 62.0 (CO₂CH₂CH₃), 61.6 (CO₂CH₂CH₃), 14.2 (CO₂CH₂CH₃), 14.1 (CO₂CH₂CH₃).

Anal. Calcd. for C₁₃H₁₃NO₅ (263.24): C, 59.29; H, 4.97; N, 5.32. Found: C, 59.21; H, 4.93; N, 5.28.

Acknowledgments.

The authors are grateful to J. J. Bergan and D. R. Sidler for help with the large scale experiments, to A. L. Houck and C. Bazalal for carrying out the hydrogenation experiments and to Lisa M. DiMichelle for help with the nmr spectral assignments.

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- [11] The chloro compound **6** is shock sensitive and should be handled carefully.
- [12] The ester-acid **7** was converted to the known diethyl ester **14** [5] for further structural confirmation.