was added, and the mixture was stirred for 5 min. The precipitate was removed and washed with ether, and the filtrate was evaporated. Radial chromatography, eluting with 5% and then 10% acetone in cyclohexane, gave **7b** (0.067 g, 92%): IR ($CHCl_3$) 3610, 3450 cm^{-1}; ^1H NMR (300 MHz) δ 0.07 (3 H, s), 0.08 (3 H, s), 0.89 (9 H, s), 0.85–1.32 (5 H, m), 1.44 (1 H, m), 1.50–1.90 (6 H, m), 2.12 (1 H, ddd, J = 14, 9, 2 Hz), 2.24 (1 H, dm, J = 14 Hz), 3.73 (1 H, m), 4.04 (1 H, dd, J = 6, 2 Hz), 4.96 (1 H, m), 5.90 (2 H, m); mass spectrum (EI), m/z 352 [$(M + NH_4)^+$], 334 [$(M + NH_4)^+ - H_2O$], 317 ($MH^+ - H_2O$), 220, 203, 185. Anal. Calcd for $C_{20}H_{34}O_2Si$: C, 71.80; H, 10.24. Found: C, 71.67; H, 9.95.

3-Cyclohexyl-3-(1-ethoxyethoxy)-1-propyne (2c). To a solution of 1-cyclohexyl-2-propyn-1-ol[18] (13.8 g, 100 mmol) and naphthalenesulfonic acid (50 mg, 0.24 mmol) in ether (50 mL) was added ethyl vinyl ether (10.8 g, 14.3 mL, 150 mmol) dropwise at 0 °C. The mixture was warmed to room temperature, stirred overnight, and then diluted with $NaHCO_3$ solution (100 mL) and ether (75 mL). The aqueous phase was separated and extracted with ether (75 mL), and the extracts were dried ($MgSO_4/K_2CO_3$) and evaporated. Kugelrohr distillation (80 °C, ca. 0.1 mmHg) gave **2c** (17.78 g, 85%): IR (liquid film) 3330 cm^{-1}; ^1H NMR (300 MHz) δ 1.00–1.35 (5 H, m), 1.20 and 1.21 (3 H, 2 t, J = 7 Hz), 1.33 and 1.34 (3 H, 2 d, J = 5 Hz), 1.55–1.95 (6 H, m), 2.38 and 2.40 (1 H, 2 d, J = 2 Hz), 3.45–3.85 (2 H, m), 3.94 and 4.15 (1 H, 2 dd, J = 6, 2 Hz), 4.82 and 4.99 (1 H, 2 q, J = 5 Hz). Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.55. Found: C, 74.10; H, 10.59.

***trans*-2-(3-Cyclohexyl-3-(1-ethoxyethoxy)-1-propynyl)-3-cyclopenten-1-ol (3c).** To a solution of **2c** (0.210 g, 1.00 mmol) in hexane (1 mL) was added n-BuLi (0.69 mL of a 1.6 M solution in hexane; 1.1 mmol) dropwise at 0 °C. After 15 min the mixture was cooled to −78 °C and a suspension of **1** (0.205 g, 2.50 mmol) in hexane (0.5 mL) was added dropwise. The mixture was warmed to room temperature, stirred overnight, and diluted with aqueous NaCl (25 mL). The product was extracted with ether, dried ($MgSO_4/K_2CO_3$), concentrated, and chromatographed on silica gel (40 g), eluting with 50% ether in hexane to give **3c** (0.110 g, 38%): ^1H NMR (300 MHz) δ 1.00–1.95 (17 H, m), 2.03 (1 H, br), 2.31 (1 H, m), 2.78 (1 H, m), 3.42 (1 H, m), 3.45–3.80 (2 H, m), 3.92 and 4.12 (1 H, dd, J = 6, 2 Hz), 4.47 (1 H, m), 4.79 and 4.95 (1 H, q, J = 6 Hz), 5.65 (1 H, m), 5.75 (1 H, m).

***cis*-2-(3-((*tert*-Butyldimethylsilyl)oxy)-3-cyclohexyl-1-propynyl)-3-cyclopenten-1-ol (4b).** To a solution of **2b** (0.833 g, 3.30 mmol) in THF (6.0 mL) was added n-BuLi (2.0 mL of a 1.6 M solution in hexane; 3.2 mmol) dropwise at 0 °C. After 15 min Me_2AlCl (3.3 mL of a 1.0 M solution in hexane; 3.3 mmol) was added dropwise, and the mixture was stirred at 0 °C for 50 min and cooled to −20 °C. Epoxide **1** (0.100 g, 1.2 mmol) in THF (0.5 mL) was added dropwise, and the reaction was maintained at this temperature for 2 h and allowed to warm to room temperature overnight. After dilution with saturated NH_4Cl (25 mL), the mixture was filtered through Celite and the residue washed with ether (25 mL). The aqueous phase was extracted with ether (25 mL), and the extracts were dried ($MgSO_4$), concentrated, and chromatographed on silica gel (90 g), eluting with 20% ether in hexane to give **4b** (0.081 g, 20%): IR ($CHCl_3$) 3570 cm^{-1}; ^1H NMR (300 MHz) δ 0.09 (3 H, s), 0.12 (3 H, 2 s), 0.90 (9 H, s), 0.85–1.32 (5 H, m), 1.49 (1 H, m), 1.56–1.91 (5 H, m), 2.19 (1 H, br s, exchanges with D_2O), 2.43 (1 H, dm, J = 15 Hz), 2.58 (1 H, dm, J = 15 Hz), 3.64 (1 H, m), 4.13 (1 H, d, J = 6 Hz), 4.38 (1 H, m), 5.63 (1 H, m), 5.80 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 130.1 (d), 129.1 (d), 87.3 (s), 80.6 (s), 71.5 (d), 67.9 (d), 45.0 (d), 43.6 (d), 40.7 (t), 28.7 (t), 26.6 (t), 26.0 (t), 25.9 (q), 18.2 (s), 4.4 (q), −5.0 (q); mass spectrum (CI), m/z 352 [$(M + NH_4)^+$], 335 (MH^+), 220, 204, 203, 185. Anal. Calcd for $C_{20}H_{34}O_2Si$: C, 71.80; H, 10.24. Found: C, 71.60; H, 10.04.

***cis*-2-(1-Hexynyl)-3-cyclopenten-1-ol (4d).** The reaction was carried out as above using 1-hexyne (1.00 g, 1.40 mL, 12.2 mmol) with Et_2AlCl (6.77 mL of a 1.8 M solution in toluene; 12.2 mmol) added dropwise followed by toluene (9.5 mL). The mixture was warmed to room temperature, stirred for 1.5 h, and cooled to −20 °C, and **1** (0.492 g, 0.49 mL, 6.0 mmol) was added dropwise. Workup as above and chromatography on silica gel (100 g), eluting with 10% ether in hexane, gave **4d** (0.325 g, 33%): IR ($CHCl_3$) 3550 cm^{-1}; ^1H NMR (300 MHz) δ 0.91 (3 H, t), 1.35–1.56 (4 H, m), 2.23 (2 H, dt, J = 2, 7 Hz), 2.29 (1 H, d, J = 4 Hz, exchanges with D_2O, 2.42 (1 H, dm, J = 15 Hz), 2.58 (1 H, dm, J = 15 Hz), 3.60 (1 H, m), 4.35 (1 H, m), 5.62 (1 H, m), 5.78 (1 H, m); mass spectrum (CI), m/z 182 [$(M + NH_4)^+$], 165 (MH^+). Exact mass (EI), m/z 149.0968 ($M^+ - CH_3$), calcd for $C_{10}H_{13}O$ 149.0966.

***cis*- (4d) and *trans*-2-(1-Hexynyl)-3-cyclopenten-1-ol (3d).** To 1-hexyne (0.688 g, 0.96 mL, 8.4 mmol) in THF (20 mL) was added n-BuLi (4.88 mL of a 1.6 M solution in hexane; 7.8 mmol) at 0 °C. After 15 min the mixture was cooled to −78 °C and **1** (0.492 g, 0.49 mL, 6.0 mmol) was added dropwise over 5 min followed immediately by dropwise addition of $BF_3{\cdot}Et_2O$ (0.852 g, 0.76 mL, 6.0 mmol). After 30 min of stirring at −78 °C, saturated NH_4Cl (50 mL) was added and the mixture was warmed to room temperature. After addition of water to solubilize undissolved salts, the mixture was extracted with ether (3 × 50 mL), and the extracts were dried ($MgSO_4$), evaporated, and chromatographed on silica gel (100 g), eluting with 20% ether in hexane to give **4d** (0.160 g, 16%). Further elution gave **3d** (0.117 g, 12%): IR ($CHCl_3$) 3650, 3470 cm^{-1}; ^1H NMR (300 MHz) δ 0.90 (3 H, t, J = 7 Hz), 1.33–1.53 (4 H, m), 1.96 (1 H, br s, exchanges with D_2O), 2.16 (2 H, dt, J = 2, 7 Hz), 2.29 (1 H, dm, J = 15 Hz), 2.78 (1 H, dm, J = 15 Hz), 3.35 (1 H, m), 4.43 (1 H, m), 5.64 (1 H, m), 5.73 (1 H, m); mass spectrum, m/z 164 (M^+), 146 ($M^+ - H_2O$) 135 ($M^+ - C_2H_5$), 121, 117 ($M^+ - C_2H_5 - H_2O$), 107; exact mass, m/z 164.1180, calcd for $C_{11}H_{16}O$ 164.1201.

***cis*- (4b) and *trans*-2-(3-((*tert*-Butyldimethylsilyl)oxy)-3-cyclohexyl-1-propynyl)-3-cyclopenten-1-ol (3b).** Treatment of **2b** as above furnished **4b** (24%) and **3b** (0.100 g, 25%): IR ($CHCl_3$) 3620 cm^{-1}; ^1H NMR (300 MHz) δ 0.07 (3 H, s), 0.10 (3 H, s), 0.89 (9 H, s), 0.85–1.30 (5 H, m), 1.44 (1 H, m), 1.55–1.95 (6 H, m), 2.30 (1 H, dm, J = 15 Hz), 2.78 (1 H, dm, J = 15 Hz), 3.39 (1 H, m), 4.06 (1 H, dd, J = 6, 2 Hz), 4.47 (1 H, m), 5.65 (1 H, m), 5.74 (1 H, m); ^{13}C NMR δ 129.6 (d), 129.1 (d), 84.2 (s), 83.3 (s), 78.9 (d), 67.9 (d), 45.9 (d), 45.0 (d), 41.0 (t), 28.7 (t), 26.6 (t), 26.1 (t), 25.9 (q), 18.3 (s), −4.4 (q), −5.0 (q); mass spectrum (CI), m/z 352 [$(M + NH_4)^+$], 335 (MH^+), 220, 203, 202, 185. Anal. Calcd for $C_{20}H_{34}O_2Si$: C, 71.80; H, 10.24. Found: C, 71.84; H, 10.49.

Registry No. 1, 7129-41-1; **2b**, 91098-88-3; **2c**, 125974-16-5; **3b**, 125974-19-8; **3c**, 125974-17-6; **3d**, 56268-11-2; **4b**, 125974-12-1; **4d**, 125974-18-7; **5b**, 125974-13-2; **6b**, 125974-14-3; **7b**, 125974-15-4; 1-cyclohexyl-2-propyn-1-ol, 4187-88-6; ethyl vinyl ether, 109-92-2; 1-hexene, 592-41-6.

Synthesis of 2,4-Dialkoxy-6-(trifluoromethyl)-3,5-pyridinedicarboxylates via a Novel Cyclocondensation of Dialkyl 3-Oxopentanedioates with Trifluoroacetonitrile

Len F. Lee* and Jean E. Normansell

Technology Division, Monsanto, Agricultural Company, A Unit of Monsanto Company, St. Louis, Missouri 63167

Received October 31, 1989

Although 4-alkyl- and 4-aryl-3,5-pyridinedicarboxylates are well-known,[1] the corresponding 2,4-dialkoxy analogues have not been reported. In a continuing effort to synthesize 2-(trifluoromethyl)-3,5-pyridinedicarboxylates as herbicides,[2,3] we decided to prepare 2,4-dialkoxy-6-(trifluoromethyl)-3,5-pyridinedicarboxylates to study the

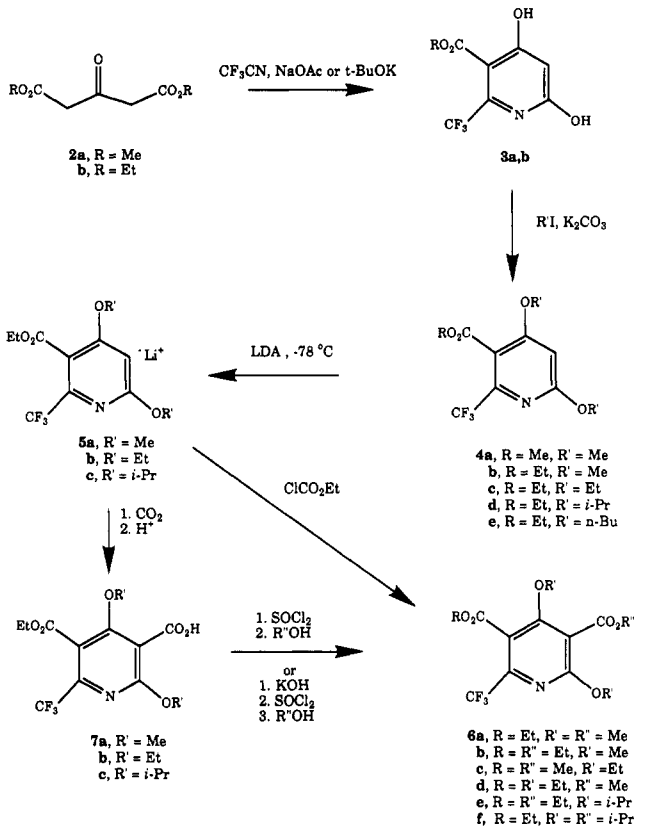
(1) For a review, see: Pollak, P. I.; Windholz, M. In *Pyridine and Its Derivatives*; Abramovitch, R. A., Ed.; *The Chemistry of Heterocyclic Compounds*; Wiley: New York, 1974; Vol. 14, Supplement Part Three, Chapter X.

(2) Lee, L. F. Eur. Pat. Appl. EP 133 612, 1985; U.S. Patent 4 692 184, 1987; *Chem. Abstr.* **1986**, *104*, 19514.

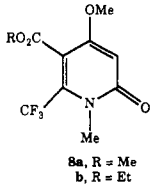
(3) Lee, L. F.; Stikes, G. L.; Normansell, J. E.; Molyneaux, J. M.; Sing, Y. L.; Chupp, J. P.; Woodard, S. S., manuscript submitted for publication in *J. Org. Chem.*

0022-3263/90/1955-2964$02.50/0

Scheme I



structure–activity relationship on this area of chemistry. We have previously reported a one-step synthesis of a 5-cyano-6-(trifluoromethyl)uracil by reaction of ethyl *N*-(cyanoacetyl)urethane with trifluoroacetonitrile (**1**) in the presence of 1 equiv of sodium hydride.[4] We thought the similar reaction of dialkyl 3-oxopentanedioates **2a,b** with **1** might provide the 4,6-dihydroxy-2-(trifluoromethyl)-3-pyridinecarboxylates **3a,b**, the potential intermediates to 2,4-dialkoxy-6-(trifluoromethyl)-3,5-pyridinedicarboxylates **6a–f**, in one step (see Scheme I). In fact, passing gaseous **1** into a solution of **2a,b** in ethanol containing excess aqueous sodium acetate provided **3a,b** in poor to good yields (25–52%) after an acidic workup. We found that the best yields of **3a,b** were obtained by passing **1** into a THF solution of **2a,b** in the presence of 1 equiv of potassium *tert*-butoxide. The yields of **3a,b** were good to excellent (57–95%) by this procedure. Alkylations of **3a,b** with alkyl halides (except methyl iodide) using potassium carbonate as the base gave the 4,6-dialkoxy derivatives **4c–e** as the only products. The reactions with methyl iodide also yielded the pyridones **8a,b** as the minor



products in addition to **4a,b**. The pyridones **8a,b** can be easily distinguished from **4a,b** by ^1H and ^{13}C NMR spectra. Both the *N*-Me protons and carbon of **8a,b** couple with the trifluoromethyl fluorines in the ^1H and ^{13}C NMR spectra. Normally, alkylations of 2-hydroxypyridines with alkyl halides using an alkaline base give the *N*-alkyl-2-pyridones as the major products.[5] In our cases, the sterically bulky and electron-withdrawing trifluoromethyl group may hinder the alkylations at nitrogen, resulting in excellent yields of **4a–e**.

The alkoxy-substituted pyridines are known to form pyridine anions ortho to the alkoxy group upon treatment with a strong base such as lithium diisopropylamide (LDA),[6] an alkyllithium,[7,8] or an aryllithium.[9] In general, metalation with LDA provides the pyridine anion in poor yields due to its equilibration with LDA.[10] In contrast to this report, we found that the pyridine anions **5a–c** can be formed easily with LDA. Treatment of **4b–d** with LDA at −78 °C generated **5a–c**. Quenching **5a,c** with ethyl chloroformate yielded **6b,e**. Although the crude yields of **6b,e** were good, separation of the products from the starting material was difficult, resulting in low isolated yields of **6b,e**. Alternatively, quenching **5a–c** with dry ice followed by an acidic workup gave the acids **7a–c** in good yields without an elaborate purification. Treatment of **7a–c** with thionyl chloride followed by reaction of the resulting acid chlorides with an appropriate alcohol provided the diesters **6a,d,f** in good yield. Hydrolysis of **7b** followed by sequential treatment of the resulting diacid with thionyl chloride and methanol gave **6c**.

Although 4,6-dihydroxypyridines have been prepared by cyclocondensation of enamines with carbon suboxide[5] or malonyl chloride,[11] the corresponding 2-(trifluoromethyl) analogues are unknown. The above-described method represents the first example of a novel one-step synthesis of 4,6-dihydroxy-2-(trifluoromethyl)-3-pyridinecarboxylates in high yields from cyclocondensation of dialkyl 3-oxopentanedioates with **1**. Although **1** is commercially available, only a few reports of its utility for the synthesis of trifluoromethylated heterocycles have been published[12–14] prior to our own investigation.[4,15–17] The previous reported syntheses provide the trifluoromethylated heterocycles in poor to modest yields. Recently, a high-yield synthesis of (trifluoromethyl)pyrimidines from **1** was also reported.[18] We found **1** to be very useful for the preparation of a variety of nitrogen-containing heterocycles[19] that otherwise are not easy to synthesize. The synthetic route depicted in Scheme I describes a convenient method for the preparation of novel 2,4-dialkoxy-6-

(4) Sing, Y. L.; Lee, L. F. *J. Org. Chem.* **1985**, *50*, 4642.

(5) For a review, see: Tieckelmann, H. In *Pyridine and Its Derivatives*; Abramovitch, R. A., Ed.; *The Chemistry of Heterocyclic Compounds*; Wiley: New York, 1974; Vol. 14, Supplement Part Three, Chapter XII.

(6) Wada, A.; Kanatomo, S.; Nagai, S. *Chem. Pharm. Bull.* **1985**, *33*, 1016.

(7) Marsais, F.; Le Nard, G.; Quéguiner, G. *Synthesis* **1982**, 235.

(8) Winkle, M. R.; Ronald, R. C. *J. Org. Chem.* **1982**, *47*, 2101.

(9) Comins, D. L.; LaMunyon, D. H. *Tetrahedron Lett.* **1988**, 773.

(10) Trêcourt, F.; Mallet, M.; Marsais, F.; Quéguiner, G. *J. Org. Chem.* **1988**, *53*, 1367 and references cited therein.

(11) Ott, W.; Kollenz, G.; Ziegler, E. *Synthesis* **1974**, 546.

(12) Janz, G. J.; De Crescente, M. A. *J. Org. Chem.* **1958**, *23*, 765.

(13) (a) Banks, R. E.; Thompson, J. *J. Fluorine Chem.* **1983**, *22*, 589. (b) Banks, R. E.; Thompson, J. *Ibid.* **1984**, *26*, 499.

(14) (a) Burger, K.; Hein, F.; Wassmuth, U.; Krist, H. *Synthesis* **1981**, 904. (b) Burger, K.; Wassmuth, U.; Hein, F.; Rottegger, S. *Liebigs Ann. Chem.* **1984**, 991.

(15) (a) Lee, L. F.; Miller, M. L. U.S. Patent 4 698 093, 1987; Eur. Pat. Appl. EP 182 769, 1986; *Chem. Abstr.* **1986**, *105*, 190960. (b) Miller, M. L.; Dolson, M. G.; Lee, L. F. Eur. Pat. Appl. EP 245 230, 1987; *Chem. Abstr.* **1988**, *108*, 131596. (c) Manuscripts in preparation.

(16) Sing, Y. L.; Lee, L. F. *J. Heterocycl. Chem.* **1989**, *26*, 7.

(17) Lee, L. F.; Sing, Y. L., Manuscript accepted for publication in *J. Org. Chem.*

(18) Aizikovich, A. Y.; Zaripova, F. F. *J. Org. Chem. USSR (Engl. Transl.)* **1986**, *22*, 1408; *Zh. Org. Khim.* **1986**, *22*, 1564.

(19) Syntheses of other heterocycles using **1** will be described in several forthcoming communications.

(trifluoromethyl)-3,5-pyridinedicarboxylates which possess herbicidal property.[20]

Experimental Section

Melting points were determined with a Laboratory Devices Mel-Temp apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian T-60 (60 MHz), Varian EM-360 (60 MHz), Varian XL 300 (300 MHz), Bruker AM 360 (360 MHz), or Varian XL 400 (400 MHz) spectrometer. ^{13}C NMR spectra were measured at 25.05 MHz with a JEOL FX-100, at 75.4 MHz with a Varian XL 300, at 90 MHz with a Bruker AM 360, or at 100 MHz with a Varian XL 400 spectrometer. ^{19}F NMR spectra were obtained with a Varian EM-390 (90 MHz) spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ unless otherwise noted and are expressed in parts per million (ppm) downfield from Me_4Si; the coupling constants are expressed as $_nJ$, where n is the number of bonds between carbon and fluorine or carbon and hydrogen, and are in hertz. Unless otherwise noted, ^{19}F NMR spectra were recorded in $CDCl_3$ using benzotrifluoride (δ −63.73) in a sealed capillary as an external standard and are expressed in ppm relative to CCl_3F, with upfield shifts taken as negative. Mass spectra were determined with a Varian MAT 311 A instrument operating in either electron impact (EI) or field ionization (FI) mode. IR spectra were recorded on a Perkin-Elmer 7727 B spectrometer. Gas chromatography (GC) was performed on a Perkin-Elmer gas chromatograph using a 2 ft × 0.25 in. column packed with 10% OV 17 on 80/100 Chromosorb W. Column chromatography (CC) was performed with 60–200-mm silica gel 60 (EM Reagents). Preparative high-performance liquid chromatography (HPLC) was carried out with a Waters PrepLC System 500A on PrepPak silica gel columns. Elemental analysis was performed by Atlantic Microlab, Inc., Atlanta, GA. Unless otherwise noted, the organic layers were dried over $MgSO_4$ and concentrated in vacuo with a Büchi rotary evaporator. The flash distillations were performed with a Kugelrohr distillation apparatus, and the recorded temperature for a specific fraction was the temperature of the Kugelrohr oven.

Methyl 4,6-Dihydroxy-2-(trifluoromethyl)-3-pyridinecarboxylate (3a). (a) Using NaOAc as Base. Into a well-stirred mixture of 84.4 g (0.484 mol) of dimethyl 3-oxopentanedioate, 200 mL of saturated sodium acetate, and 400 mL of ethanol at 70 °C was passed 49 g (0.52 mol) of trifluoroacetonitrile over 4 h. The reaction mixture was cooled and poured into a mixture of 100 mL of concentrated hydrochloric acid and 1 kg of ice. The precipitate was collected to give 28.7 g (25%) of product, mp 235–238.5 °C dec. Recrystallization from acetone–chloroform gave the pure product, mp 240–242.5 °C; ^{1}H NMR (Me_2SO-d_6) δ 11.68 (s, 2 H, OH), 6.33 (s, 1 H), 3.80 (s, 3 H). Anal. Calcd for $C_8H_6F_3NO_4$: C, 40.56; H, 2.55; N, 5.91. Found: C, 40.55; H, 2.59; N, 5.88.

(b) Using *t*-BuOK as Base. Into a mechanically stirred mixture of 11.2 g (0.1 mol) of *t*-BuOK and 120 mL of THF was added 17.4 g (0.1 mol) of dimethyl 3-oxopentanedioate at such a rate that the reaction temperature was maintained below 60 °C. After complete addition of dimethyl 3-oxopentanedioate, 39 (0.38 mol) of trifluoroacetonitrile was passed into the reaction mixture. The reaction mixture was concentrated, and the residue was dissolved in 100 mL of water and poured into a mixture of 50 mL of concentrated hydrochloric acid and 400 mL of water. The solid precipitate was collected to give 19.3 g of a solid, mp 223–230 °C dec. This solid was heated with 100 mL of chloroform and filtered to give 13.6 (57%) of a white solid, mp 237–241 °C dec.

Ethyl 4,6-Dihydroxy-2-(trifluoromethyl)-3-pyridinecarboxylate (3b). (a) Using NaOAc as Base. Into a mechanically stirred solution of 201 g (1.0 mol) of diethyl 3-oxopentanedioate, 95 g (1.2 mol) of NaOAc, 100 mL of water, and 200 mL of ethanol at 55 °C was passed 89 g (0.94 mol) of trifluoroacetonitrile over 15 h. The reaction temperature was raised to 70 °C and an additional 15 g (0.16 mol) of trifluoroacetonitrile was passed into the reaction mixture over 15 h. The reaction mixture was poured into a mixture of 100 mL of concentrated hydrochloric acid and 600 mL of water. The precipitate was collected and recrystallized from acetone–chloroform to give 130 g (52%) of a solid, mp 217–220 °C; IR (Nujol) 3450, 3200–2500, 1730, 1680, 1610 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 11.60 (s, 2 H, OH), 6.33 (s, 1 H), 4.3 (q, J = 7, 2 H), 1.30 (t, J = 7, 3 H); ^{13}C NMR (Me_2SO-d_6) δ 165.30, 165.04, 164.95, 141.74 (q, $^2J_{CF}$ = 33.7), 121.31 (q, $^1J_{CF}$ = 275.5), 112.74 (q, $^3J_{CF}$ = 1.5), 97.85, 61.87, 13.89; ^{19}F NMR δ −63.8; MS m/z = 251 (M^+). Anal. Calcd for $C_9H_8F_3NO_4$: C, 43.03; H, 3.21; N, 5.58. Found: C, 43.01; H, 3.22; N, 5.55.

(b) Using *t*-BuOK as Base. Into a mechanically stirred mixture of 335 g (2.98 mol) of *t*-BuOK and 1.25 L of THF was added 575 g (2.84 mol) of diethyl 3-oxopentanedioate at such a rate that the reaction temperature was maintained below 60 °C. After complete addition of diethyl 3-oxopentanedioate, 484 g (5.09 mol) of trifluoroacetonitrile was passed into the reaction mixture. The reaction mixture was concentrated, and the residue was poured into a mixture of 300 mL of concentrated hydrochloric acid and 1.8 L of water. The solid precipitate was collected to give 727 g (95%) of a solid, mp 208.5–210.5 °C, which was the monohydrate of **3b**; ^{1}H NMR (Me_2SO-d_6) δ 6.32 (s, 1 H), 5.09 (br, 4 H, OH), 4.22 (q, J = 7, 2 H), 1.22 (t, J = 7, 3 H). Anal. Calcd for $C_9H_8F_3NO_4 \cdot H_2O$: C, 40.16; H, 3.74; N, 5.20. Found: C, 40.02; H, 3.56; N, 5.37.

General Procedure A for the Preparation of 4a–e. A mixture of **3a,b**, 2 equiv of K_2CO_3, and an excess of an alkyl iodide in 100–300 mL of acetone was held at reflux for 18–72 h and filtered. The acetone solution was concentrated, and the residue was dissolved in ether, washed with 10% NaOH, dried ($MgSO_4$), and concentrated. The residue was either Kugelrohr distilled in vacuo or chromatographed on silica gel to give the products.

Methyl 4,6-Dimethoxy-2-(trifluoromethyl)-3-pyridinecarboxylate (4a) and Methyl 1,6-Dihydro-4-methoxy-1-methyl-6-oxo-2-(trifluoromethyl)-3-pyridinecarboxylate (8a). A mixture of 14.5 g (0.061 mol) of **3a**, 16.8 g (0.122 mol) of K_2CO_3, 59 g (0.416 mol) of methyl iodide, and 100 mL of acetone was reacted for 17 h and worked up according to general procedure A. The crude product was chromatographed on 250 g of silica gel and eluted with EtOAc–cyclohexane (1:4 (v/v)) to give 10.5 g (65%) of **4a** in the first fraction, mp 85–87.5 °C; IR ($CHCl_3$) 1730, 1610 cm^{-1}; ^{1}H NMR δ 6.33 (s, 1 H), 3.96, 3.90, 3.86 (3 overlapping s, total 9 H). Anal. Calcd for $C_{10}H_{10}F_3NO_4$: C, 45.28; H, 3.80; N, 5.28. Found: C, 45.42; H, 3.83; N, 5.24.

The second fraction, obtained by eluting with 1 L of EtOAc, was 2.71 g (17%) of **8a**, mp 104.5–106 and 112 °C; IR ($CHCl_3$) 1730, 1660, 1610 cm^{-1}; ^{1}H NMR δ 6.07 (s, 1 H), 3.86, 3.83 (2 overlapping s, total 6 H), 3.57 (q, $^5J_{HF}$ = 2); ^{13}C NMR δ 163.26, 162.53, 162.50, 132.41 (q, $^2J_{CF}$ = 33.6), 119.53 (q, $^1J_{CF}$ = 275.0), 111.04 (q, $^3J_{CF}$ = 3.7), 99.37, 56.27, 52.90, 31.61 (q, $^4J_{CF}$ = 4.4); ^{19}F NMR δ −60.83 (q, $^5J_{HF}$ = 2). Anal. Calcd for $C_{10}H_{10}F_3NO_4$: C, 45.28; H, 3.80; N, 5.28. Found: C, 45.28; H, 3.81; N, 5.24.

Ethyl 4,6-Dimethoxy-2-(trifluoromethyl)-3-pyridinecarboxylate (4b) and Ethyl 1,6-Dihydro-4-methoxy-1-methyl-6-oxo-2-(trifluoromethyl)-3-pyridinecarboxylate (8b). A mixture of 50.2 g (0.2 mol) of **3b**, 45.2 g (0.4 mol) of K_2CO_3, 114 g (0.8 mol) of methyl iodide, and 200 mL of acetone was reacted for 3 days and worked up according to general procedure A. The crude product was chromatographed on silica gel. The first 2 L of eluate (1:4 (v/v) EtOAc–cyclohexane) was 41 g of a solid, which was recrystallized from hexane to give 36 g (65%) of **4b**, mp 78.5–80.5 °C; ^{1}H NMR δ 6.33 (s, 1 H), 4.40 (q, J = 7, 2 H), 3.96 (s, 3 H), 3.86 (s, 3 H), 1.36 (t, J = 7, 3 H); ^{19}F NMR δ −67.46; ^{13}C NMR δ 165.32, 165.25, 164.14, 141.90 (q, $^2J_{CF}$ = 34.9), 120.9 (q, $^1J_{CF}$ = 274.8), 114.45, 94.73, 61.79, 55.96, 53.69, 13.46. Anal. Calcd for $C_{11}H_{12}F_3NO_4$: C, 47.31; H, 4.33; N, 5.02. Found: C, 47.51; H, 4.37; N, 4.99.

The second fraction, obtained by eluting with 2 L of EtOAc, was 10.6 g (19%) of **8b**, mp 97–99 °C; IR ($CHCl_3$) 1730, 1660, 1610 cm^{-1}; ^{1}H NMR δ 6.1 (s, 1 H), 4.33 (q, J = 7, 2 H), 3.83 (s, 3 H), 3.60 (q, $^5J_{HF}$ = 2, 3 H), 1.33 (t, J = 7, 3 H); ^{13}C NMR δ 162.31, 162.26, 162.06, 131.82 (q, $^2J_{CF}$ = 33.5), 119.37 (q, $^1J_{CF}$ = 275.7), 111.09 (q, $^3J_{CF}$ = 3.3), 99.06, 61.75, 55.92, 31.14 (q, $^4J_{CF}$ = 4.3), 13.15; ^{19}F NMR δ −60.63 (q, $^5J_{HF}$ = 2). Anal. Calcd for $C_{11}H_{12}F_3NO_4$: C, 47.31; H, 4.33; N, 5.02. Found: C, 47.35; H, 4.36; N, 5.03.

Ethyl 4,6-Diethoxy-2-(trifluoromethyl)-3-pyridinecarboxylate (4c). One equivalent of **3b**, 2 equiv of K_2CO_3, and excess ethyl iodide were reacted in acetone for 18 h and worked

(20) Lee, L. F. Eur. Pat. Appl. EP 181 311, 1986; U.S. Patent 4 609 399, 1986; *Chem. Abstr.* **1986**, *105*, 97334.

up according to general procedure A to give **4c** in 83% yield, n^{25}_D 1.4534;: ^{1}H NMR δ 6.30 (s, 1 H), 4.40, 4.37, and 4.10 (3 overlapping q, total 6 H), 1.2–1.6 (m, 9 H). Anal. Calcd for $C_{13}H_{16}F_3NO_4$: C, 50.82; H, 5.24. Found: C, 50.79; H, 5.27.

Ethyl 4,6-Diisopropoxy-2-(trifluoromethyl)-3-pyridinecarboxylate (4d). A mixture of 37.3 g (0.148 mol) of **3b**, 41 g (0.36 mol) of K_2CO_3, 99 g (0.58 mol) of 2-iodopropane, and 300 mL of acetone was reacted for 21 h and worked up according to general procedure A. The crude product was Kugelrohr distilled at 165 °C (0.7 Torr) to give 48.8 g (98%) of an oil, n^{25}_D 1.4491; IR ($CHCl_3$) 1730, 1610 cm^{-1}; ^{1}H NMR δ 6.27 (s, 1 H), 5.35 (h, J = 6, 1 H), 4.2–4.8 (a h at δ 4.60 overlapped with a q at δ 4.33, total 3 H), 1.2–1.6 (m, 15 H). Anal. Calcd for $C_{15}H_{20}F_3NO_4$: C, 53.72; H, 6.01; N, 4.18. Found: C, 53.77; H, 6.02; N, 4.15.

Ethyl 4,6-Di-*n*-butoxy-2-(trifluoromethyl)-3-pyridinecarboxylate (4e). A mixture of 22.6 g (0.09 mol) of **3b**, 99 g (0.54 mol) of *n*-butyl iodide, 25 g (0.22 mol) of K_2CO_3, and 250 mL of acetone was reacted for 26 h and worked up according to general procedure A. The crude product was Kugelrohr distilled at 0.3 Torr to give 32.5 g (99%) of an oil, n^{25}_D 1.4543; IR ($CHCl_3$) 1730, 1610 cm^{-1}; ^{1}H NMR δ 6.33 (s, 1 H), 4.2–4.6 (a q overlapped with a t, total 4 H), 4.03 (t, J = 7, 2 H), 0.7–2.0 (m, 17 H). Anal. Calcd for $C_{17}H_{24}F_3NO_4$: C, 56.19; H, 6.66; N, 5.02. Found: C, 56.26; H, 6.66; N, 3.84.

General Procedure B for the Preparation of 7a–c. To a −78 °C solution of 1–2.5 equiv of lithium diisopropylamide (LDA), prepared from *n*-butyllithium and diisopropylamine in 1,2-dimethoxyethane (DME), was added 1 equiv of **4b–d**. The resulting dark color solution was stirred for 30 min at −78 °C. To the above solution was added excess dry ice. The reaction mixture was stirred at −78 °C for 15 min and warmed to room temperature over 1 h. The reaction mixture was poured into ice water (100 mL) and extracted with ether. The aqueous layer was acidified with concentrated hydrochloric acid. The oily precipitate was extracted with ether. The ether extract was dried ($MgSO_4$) and concentrated in vacuo to give the desired products **7a–c**.

4,6-Dimethoxy-2-(trifluoromethyl)-3,5-pyridinedicarboxylic Acid 3-Ethyl Ester (7a). This crude acid was obtained in 95% yield as a solid from 0.465 mol of LDA and 0.105 mol of **4b** according to general procedure B and was used without further purification; ^{1}H NMR δ 9.66 (s, 1 H, OH), 4.40 (q, J = 7, 2 H), 4.07 (s, 6 H), 1.38 (t, J = 7, 3 H).

4,6-Diethoxy-2-(trifluoromethyl)-3,5-pyridinedicarboxylic Acid 3-Ethyl Ester (7b). The crude acid was obtained in 96% yield as a syrup from 0.427 mol of LDA and 0.146 mol of **4c** according to general procedure B. After crystallization from hexane a solid was obtained in 67% yield and was used without further purification, mp 76–82 °C; ^{1}H NMR δ 10.10 (s, 1 H, OH), 4.1–4.7 (m, 6 H), 1.0–1.6 (m, 9 H). Anal. Calcd for $C_{14}H_{16}F_3NO_6$: C, 47.87; H, 4.59; N, 3.91. Found: C, 47.29; H, 4.64;, N, 3.94.

4,6-Diisopropoxy-2-(trifluoromethyl)-3,5-pyridinedicarboxylic Acid 3-Ethyl Ester (7c). This material was obtained in 51% yield from 0.072 mol of LDA and 0.056 mol of **4d** according to general procedure B as a solid, mp 63–65 °C; ^{1}H NMR δ 9.16 (s, 1 H, OH), 5.40 (h, J = 6, 1 H), 4.2–5.0 (a h at δ 4.66 overlapped with a q at δ 4.40, total 3 H), 1.2–1.6 (m, 15 H). Anal. Calcd for $C_{16}H_{20}F_3NO_6$: C, 50.56; H, 5.31. Found: C, 50.93; H, 5.29.

General Procedure C for the Preparation of 6a,d,f. The acid **7a–c** (5.0 g) was held at reflux with excess thionyl chloride until the reaction was complete. Excess thionyl chloride was removed in vacuo. The residual acid chloride was held at reflux with an excess of an appropriate alcohol for 2–4 h and concentrated. The residue was dissolved in ether and washed with 10% K_2CO_3, dried ($MgSO_4$), and concentrated. The residue was further purified by either Kugelrohr distillation or HPLC separation.

5-Ethyl 3-Methyl 2,4-Dimethoxy-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (6a). (a) By General Procedure C. This material was obtained from **7a** and methanol in 42% yield according to general procedure C as an oil, n^{25}_D 1.4615; ^{1}H NMR δ 4.40 (q, J = 7, 2 H), 4.03, 3.97, 3.93 (3 overlapping s, total 9 H), 1.37 (t, J = 7, 3 H); ^{13}C NMR δ 164.42, 163.62, 162.90, 161.72, 142.64 (q, $^2J_{CF}$ = 35.5), 120.44 (q, $^1J_{CF}$ = 274.7), 114.96, 109.67, 62.19, 60.56, 54.69, 52.84, 13.56; ^{19}F NMR δ −67.62. Anal. Calcd for $C_{13}H_{14}F_3NO_6$: C, 46.30; H, 4.18; N, 4.15. Found C, 46.32; H, 4.24; N, 3.96.

(b) Alkylation of 7a with Methyl Iodide. A mixture of crude **7a** (prepared from 0.121 mol of **4b**), 20 g (0.15 mol) of K_2CO_3, 38 mL (0.61 mol) of methyl iodide, and 200 mL of acetone was stirred at reflux for 24 h and concentrated. The residue was dissolved in ether, washed with water, dried, and concentrated. The residue was Kugelrohr distilled at 0.4 Torr (95-100 °C) to give 34.9 g (85% from 4b) of 6a, n^{25}_D 1.4618.

Diethyl 2,4-Dimethoxy-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (6b). To a −78 °C solution of LDA, prepared from 4.6 mL (0.033 mol) of diisopropylamine, 0.034 mol of *n*-butyllithium, and 40 mL of DME, was added a solution of 8.37 g (0.03 mol) of **4b** in 29 mL of DME. The orange solution was stirred at −78 °C for 1 h and treated with 10 mL (0.129 mol) of ethyl chloroformate. After stirring at −78 °C for 15 min, the reaction mixture was poured into a mixture of 20 mL of concentrated hydrochloric acid and 100 mL of ice water. The mixture was extracted with ether (2 × 200 mL). The ether extract was dried ($MgSO_4$) and concentrated to give 5.5 g of an oil which was Kugelrohr distilled at 80–120 °C (0.1 Torr) to give 5.0 g of an oil which was primarily **6b** contaminated with 10% **4b**. This oil was distilled through a short-path still at 0.1 Torr to give 1.9 g (18%) of pure **6b** as an oil, bp 132–133 °C; n^{25}_D 1.4386; ^{1}H NMR δ 4.43, 4.40 (2 overlapped q, J = 7, total 4 H), 4.00, 3.97 (2 s, total 6 H), 1.37, 1.33 (2 overlapped t, J = 7, total 6 H); ^{13}C NMR δ 163.85, 163.61, 162.69, 161.71, 142.46 (q, $^2J_{CF}$ = 35.5), 120.44 (q, $^1J_{CF}$ = 275.1), 117.13 (q, $^3J_{CF}$ = 1.0), 110.12, 62.16, 62.10, 60.60, 54.59, 13.57, 13.42; ^{19}F NMR δ −67.66. Anal. Calcd for $C_{14}H_{16}F_3NO_6$: C, 47.87; H, 4.59; N, 3.99. Found: C, 47.83; H, 4.59; N, 3.99.

Dimethyl 2,4-Diethoxy-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (6c). A mixture of 9.01 g (0.161 mol) of 85% KOH, 11.84 g (0.037 mol) of **7b**, 150 mL of ethanol, and 10 mL of water was held at reflux for 24 h and poured into 250 mL of water containing 50 mL of concentrated hydrochloric acid. The mixture was extracted with ether. The ether extract was dried ($MgSO_4$) and concentrated to give 11.84 g of a solid. A portion (8.0 g) of this solid was held at reflux with 150 mL of thionyl chloride for 3 h and concentrated. The residue was held at reflux with 150 mL of methanol and concentrated to given an oil which was purified by HPLC using 5% EtOAc–cyclohexane as eluent to give 3.03 g (34.8%) of an oil, n^{25}_D 1.4566; ^{1}H NMR δ 4.47 (q, J = 7, 2 H), 4.17 (q, J = 7, 2 H), 3.93, 3.90 (2 overlapping s, total 6 H), 1.37, 1.33 (2 overlapping t, J = 7, total 6 H). Anal. Calcd for $C_{14}H_{16}F_3NO_6$: C, 47.87; H, 4.59; N, 3.99. Found: C, 47.87; H, 4.76; N, 3.81.

3-Ethyl 5-Methyl 4,6-Diethoxy-2-(trifluoromethyl)-3,5-pyridinedicarboxylate (6d). This material was obtained from **7b** and methanol in 73% yield according to general procedure C as a solid, mp 46–48 °C; ^{1}H NMR δ 4.1–4.8 (m, 6 H), 4.00 (s, 3 H), 1.2–1.6 (m, 9 H). Anal. Calcd for $C_{15}H_{18}F_3NO_6$: C, 49.32; H, 4.97; N, 3.83. Found: C, 49.62; H, 4.93; N, 3.83.

Diethyl 2,4-Diisopropoxy-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (6e). To a −78 °C solution of 0.021 mol of LDA in 30 mL of DME was added a solution of 4.65 g (0.014 mol) of **4d** in 20 mL of DME. The resulting solution was stirred for 10 min and treated with 2.7 mL (0.035 mol) of ethyl chloroformate. After stirring at −78 °C for 30 min, the reaction mixture was warmed to room temperature over 30 min and poured into 50 mL of water. The mixture was extracted with ether. The ether extract was washed with 10% K_2CO_3, dried over $CaSO_4$, and concentrated. The residue was Kugelrohr distilled at 55 °C (0.15 Torr) to remove low-boiling material (1.08 g) and then at 164–173 °C (0.15 Torr) to give 1.95 g (34.5%) of an oil; ^{1}H NMR δ 5.33 (h, J = 6, 1 H), 4.1–4.8 (m, 5 H), 1.1–1.6 (m, 18 H). Anal. Calcd for $C_{18}H_{24}F_3NO_6$: C, 53.07; H, 5.94. Found: C, 53.14; H, 5.96.

3-Ethyl 5-Isopropyl 4,6-Diisopropoxy-2-(trifluoromethyl)-3,5-pyridinedicarboxylate (6f). This material was obtained in 70% yield from **7c** and isopropyl alcohol according to general procedure C as an oil, n^{25}_D 1.4508; ^{1}H NMR δ 5.0–5.6 (m, 2 H), 4.1–4.8 (m, 3 H), 1.0–1.6 (m, 21 H). Anal. Calcd for $C_{19}H_{26}F_3NO_6$: C, 54.15; H, 6.22. Found: C, 53.81; H, 6.08.

Registry No. **2a**, 1830-54-2; **2b**, 105-50-0; **3a**, 103900-78-3; **3b**, 103900-77-2; **4a**, 103900-79-4; **4b**, 103900-80-7; **4c**, 103900-83-0; **4d**, 103900-82-9; **4e**, 103900-81-8; **6a**, 103900-91-0; **6b**, 103900-96-5; **6c**, 103900-92-1; **6d**, 103900-94-3; **6e**, 103900-97-6; **6f**, 103900-95-4; **7a**, 103900-88-5; **7b**, 103900-90-9; **7c**, 103900-89-6; **8a**, 125734-72-7; **8b**, 125734-73-8; CF_3CN, 353-85-5.