Derivation of Fluorine-Containing Pyridine Dicarboxylates. II. Elaboration at the 4-Position [1,2]

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In response to the bio-activity found in fluorine-containing 4-alkyl-3,5-pyridinedicarboxylates, a series of novel 4-substituted derivatives, not directly available by Hantzsch sequences, were prepared. Starting 4-alkylpyridines, **1**, were converted *via* enamine **2** to materials **3-8**. Derivatives **9-16** in turn were derived from aldehyde **3**, while acid derivatives **28-36** were prepared from **14**. Addition of oxygen, sulfur, and carbenoids effected conversion of 4-allylpyridine **16** to epoxy and cyclopropyl derivative **16-22**. A number of neighboring group effects were noted, including those forming the fused-ring systems **23-27**.

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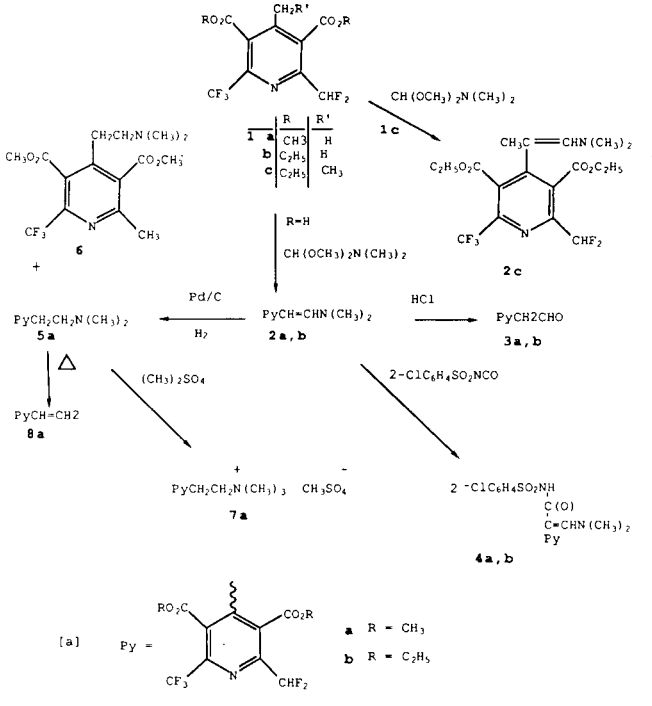
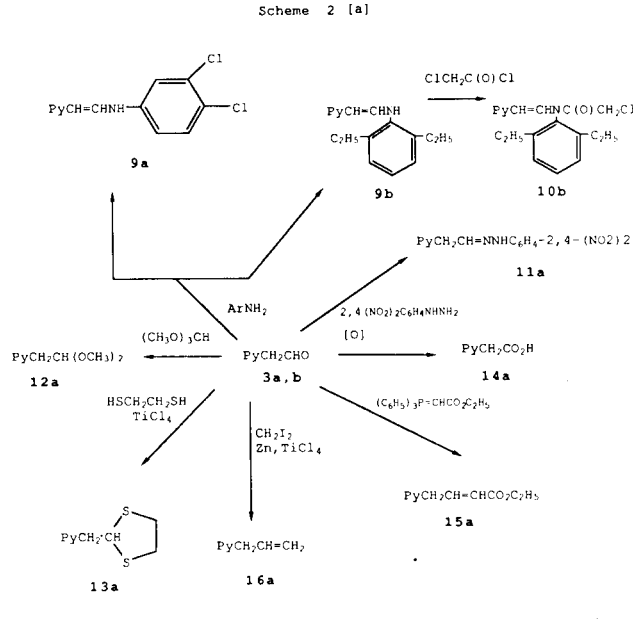
The discovery that 4-alkyl-2-(difluoromethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylates, which are products of certain unique Hantzsch syntheses, possessed commercial level herbicide activity [3], prompted the preparation of a number of further examples. In this and a subsequent report functional elaborations at both the 4-alkyl and 2-(difluoromethyl) substituent were made on the existing pyridine ring system to give a wide range of new and unique materials, not available by the aforementioned Hantzsch routes.

To commence such elaboration, a facile reaction known from both aromatic [4] and heterocyclic [5] chemistry is the formation of enamines by interaction of aminoformals with activated methyl substituents (Scheme 1). Good yields of several derivatives were experienced, with even the 4-ethylpyridine, **1c**, reacting favorably. In like manner orthoformates failed to give the expected vinyl ethers. The enamines **2a,b**, provided convenient routes to further derivation. Hydrolysis of **2a** and **2b** was effected by dissolving them in 37% hydrochloric acid and adding this solution in a thin stream to a ten-fold volume of water, whereby finely divided, solid aldehyde **3a,b** respectively was precipitated. The ^{1}H nmr shows a well defined downfield aldehydic proton as a singlet, while the methylene group integrates for two protons, also as a singlet. The consequent lack of coupling is unexpected (compare with ^{1}H nmr spectra for phenylacetaldehyde), as is the seemingly total lack of enol form (or when wet, of hydrate). Deuterium oxide washes only slowly incorporate this isotope into the *alpha*-methylene group. Presumably the aldehyde **3** can exist well in the unhydrated form without appreciable

Scheme 1 [a]



Scheme 2 [a]



enolization, although the latter must occur to the extent necessary to cause proton exchange, promoting slow deuterium incorporation and lack of A2X coupling.

Enamines **2a,b**, are only weakly basic, and consequently react sluggishly or not at all with normal alkylating or acylating agents at either enamino nitrogen or *beta*-carbon. The latter can be reacted however with sufficiently activated electrophiles such as sulfonyl isocyanates to give, as determined by carbonyl absorption, **4a,b**, (rather than the alternative azetidinones). Reduction of enamines **2a** afforded a saturated amine **5a**, that has restored normal basicity. Minor amounts of the difluoromethyl reduced compound, **6** was also formed. Material **5a** easily dissolved in dilute hydrochloric acid solution, and became quaternized to **7a** with methyl sulfate. It also lost amine on pyrolysis to form the vinyl compound **8a**.

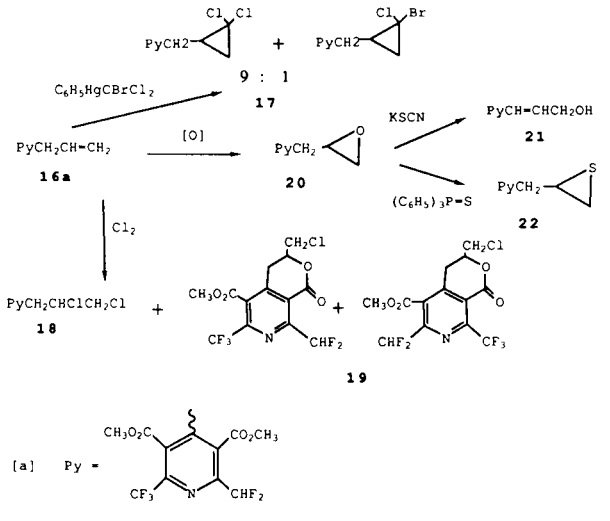
Derivation of aldehydes **3a,b**, are shown in Scheme 2. Additional enamines were quite simply prepared by azeotroping aldehydes **3a,b** with amines. Primary amines gave only the enamine **9**, there being no evidence by ^1H and ^{19}F nmr of mixtures with imine. Moreover these materials in turn can be transformed: chloroacetylation gave **10b**, while classic aldehyde derivation is evident by formation of hydrazone **11a**, acetal **12a**, and thioacetal **13a**. Reaction with Wittig reagents was only successful if the latter were stabilized, to give **15a**; apparently the unstabilized reagents are too basic and cause aldol reactions at the very acidic 4-pyridylmethylene moiety.

4-Allylpyridine **16a**, cannot be derived *via* Hantzsch sequences from the requisite aldehyde due to ready reconjugation to crotonaldehyde. As discussed above, **3** is adversely sensitive to unstabilized Wittig reagents, so **16** was unavailable by that procedure, as were basic variations of the Tebbe reagent. A new modification of the latter [6], wherein the transformation can be carried out under acid conditions, proved equal to the task. Derivations of **16a** are shown in Scheme 3. An attempt to obtain the dichlorocyclopropylmethylpyridine using dichlorocarbene generated by chloroform, caustic and phase transfer catayst resulted in conjugation of the allylic double bond followed by hydrolysis of an ester function. Better results were obtained by thermal generation of dichlorocarbene from the mercury salt, to give the desired product, contaminated however, with bromochloro analog. Chromatographic separation of mixture **17** failed. The formation of the bromochloro side-product was evidently a result of partial conversion of reagent bromodichloro mercury salt to the chlorodibromo salt, made possible by the slow rate of reaction of the carbene with the hindred allylic double bond.

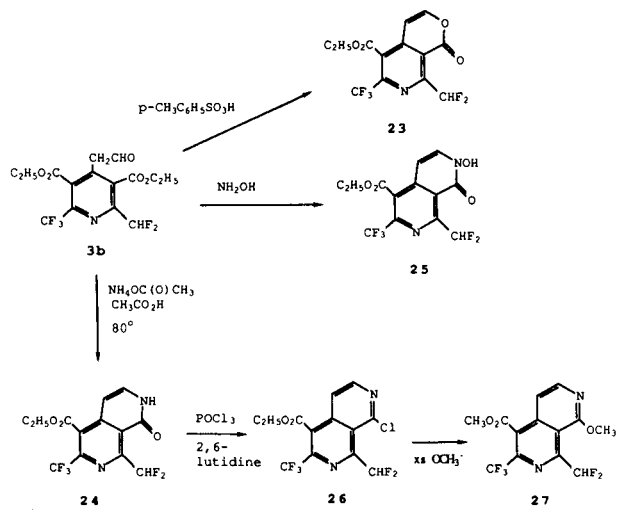
Material **16a** was treated with chlorine to give **18** in part, but the major product isolated was a mixture of chlorolactones **19**, resulting when the carbocation formed after substitution of positive chlorine at the terminal carbon readily combined with the nucleophilic oxygen of the carboxylate group. Oxidation of **16a** with *m*-chloroperbenzoic acid at room temperature slowly gave the epoxide **20**. An attempt to prepare the episulfide from **20** using thiocyanate resulted in the surprising formation of allylic alcohol **21**. Consequently the episulfide **22** was produced under acidic conditions from reaction of **20** with triphenylphosphine sulfide.

In elaborating the 4-substituent, the accessible 3-carboxylate [3] occasionally interacted with the former to produce 3,4-fused ring systems. One such interaction has already been noted in the isolation of **19**. Scheme 4 displays a number of such transformations. Thus **3b** on heating in chlorobenzene with acid catalyst readily gives lactone **23**. Glc/ms parallels this transformation: the dimethyl ester **3a** converts wholly to the lactone, while **3b** only partly does so in these analytical instruments. Likewise, treatment of **3b** with ammonium acetate in acetic acid and hy-

Scheme 3 [a]



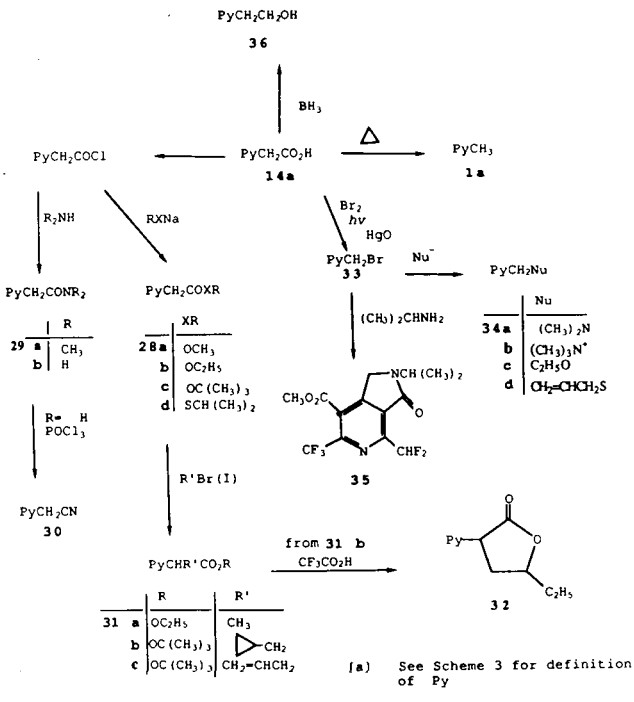
Scheme 4



doxylamine gives **24** and **25** respectively. Single crystal X-ray of **24** confirmed the 3,4 rather than 4,5 orientation of the ring closure reactions. In turn lactam **24** could be converted to fused pyridyl ring systems **26** and **27**. The last compound was formed by both replacement of chlorine and *trans* esterification from **26** with methoxide.

The potential proved as great for derivation of 4-pyridylacetic acid **14a**, Scheme 5, as for 4-pyridylacetaldehyde **3a**, described above. The former material can be derived from the latter by oxidation, preferably Jone's reagent. Care was taken to neutralize the acid oxidation mixture, preventing saponification of 3-pyridinecarboxylate ester. Further, **14** is extremely susceptible to decarboxylation; when **14** was injected into the glc a smooth and probably quantitative decarboxylation took place to **1a**. Derivation of **14** *via* the acid chloride gave esters and thioesters **28a-d**, and amides **29a,b**. The primary amide provided the source through dehydration to nitrile **30**. The esters **28** can be easily alkylated at the *alpha* position to give **31a-c** although attempts to saponify and decarboxylate **31b** under acid conditions to provide homologous 4-alkyl substitution gave the lactone **32** instead.

Scheme 5 [a]



The ready decarboxylation of **14** suggested this material as a candidate for the Hünsdieker reaction. Indeed, light-activated pyrolysis of this material in the presence of bromine and red mercuric oxide (Cristol modification [7]), worked very well to produce the pyridylmethyl bromide, **33**. Neither the Kochi synthesis for alkyl chloride from lead tetraacetate and lithium chloride [8], nor the Patrick modification for alkyl fluoride [9] were successful.

Material **33** reacted well with divalent sulfur nucleophiles to give **34d**, accompanied by minimal reduction to **1a**. Secondary and tertiary amines reacted cleanly, giving **34a,b**. A primary amine spontaneously gave lactam **35**. Metal alcoholates did not give clean ractions since they are basic enough to deprotonate **33**, initiating complex carbanion modes. This feature was overcome by use of neutral alcohol and silver tetrafluoroborate, where good yields of ether **34c** was obtained. Diborane reduction of **14a** gave 4-pyridylethanol **36** although in poor yield.

EXPERIMENTAL

All melting points were determined on a Laboratory Devices Mel-Temp apparatus and are uncorrected. ^1H and ^{19}F nmr spectra were recorded on a Varian EM-360-L(60 MHz), XL300 (300 MHz), or XL400 (400 MHz) instruments referenced to tetramethylsilane and fluorotrichloromethane respectively. Exact ^{19}F chemical shifts were not always recorded, although they were usually in the regions found for CF_3 (-65 ppm) and CHF_2 (-115 ppm); rather, emphasis was given to number and type of multiplicity to confirm sample identity and purity. Mass spectra were measured by a Varian CH7 mass spectrometer with *e.i.* or isobutane chemical ionization (c.i.) expressed as molecular weight (m/e). Liquid chromatography purification was achieved on a Waters Prep 1c, model 500A, with refractive index detector (hplc), or by Chromatotron (rotary tlc). Unless otherwise noted, bp's are recorded as oven temperatures during bulb-to bulb (Kugelrohr) distillations. All microanalysis were performed by Atlantic Microlab Inc., Atlanta, Georgia 30366.

The preparation of materials **1a-c** by Hantzsch sequences from the corresponding trifluoroacetoacetic esters and aldehyde are detailed in reference [3].

Dimethyl 2-(Difluroromethyl)-4-[2-(dimethylamino)vinyl]-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**2a**).

To 6 g (17.7 mmoles) of dimethyl 2-(difluoromethyl)-4-methyl-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**1a**) was added a 10% molar excess of dimethylformamide, dimethyl acetal, and the mixture slowly raised to 115°, with continuous distillation of methanol; after 2 hours at that temperature the reaction, by glc, was complete. The reaction mixture was vacuum treated on a rotary evaporator to 65° (water aspirator) to give 6.1 yellow solid (91%): This material was recrystallized from methylcyclohexane, mp 101-103°; ^1H nmr (deuteriochloroform): δ 2.8 (s, 6H, NCH_3), 3.8 (s, 6H, OCH_3), 4.8 (d, 1H, =CH), 6.4 (t, 1H, CHF_2), 6.75 (d, 1H, =CH); ^{19}F (s, CF_3), (d, CHF_2).

Anal. Calcd. for $C_{15}H_{15}F_5N_2O_4$: C, 47.13; H, 3.96; N, 7.33. Found: C, 47.13; H, 3.95; N, 7.30.

Diethyl 2-(Difluoromethyl)-4-[2-(dimethylamino)vinyl]-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**2b**).

To 2 g (5.4 mmoles) of diethyl 2-(difluoromethyl)-4-methyl-6-(trifluoromethyl)-3.5-pyridinedicarboxylate [3] was added 2 g of dimethylformamide, dimethyl acetal in a magnetically stirred reaction vessel, and heat applied until the temperature reached 130°, with continual distillation of methanol. Following the reaction by glc, the mixture was held between 110-140° for 2 hours when more acetal was added and the mixture heated at 130° for 1

hour. The mixture was then vacuum treated under water pump, and the residue Kugelrohr distilled at 160-180° (0.15 mm Hg) to give 2.17 g (80%) orange oil; ^{1}H nmr (deuteriochloroform): δ 1.4 (t, 6H, OCH_2CH_3), 2.9 (s, 6H, NCH_3), 4.4 (q, 4H, OCH_2CH_3), 4.95 (d, 1H, =CH), 6.67 (t, 1H, CHF_2), 6.98 (d, 1H, =CH); ^{19}F (s, CF_3), (d, CHF_2).

Anal. Calcd. for $C_{17}H_{19}F_5N_2O_4$: C, 49.76; H, 4.67; N, 6.83. Found: C, 49.59; H, 4.52; N, 6.68.

Diethyl 2-(Difluoromethyl)-4-[2-(dimethylamino)-1-methylethenyl]-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**2c**).

Material **1c** (4.07 g, 11.0 mmoles) and 4.0 g of dimethylformamide, diethyl acetal were heated to 165° with continuous takeoff of ethanol. After 8 hours heating, the reaction was 85% complete by glc. The cooled reaction mixture was subjected to vacuum on a rotary evaporator, then the residue distilled through a short path distillation apparatus to give a fraction, 1.5 g (32%) of an oil as the product (93% assay by glc).

Anal. Calcd. for $C_{18}H_{21}F_5N_2O_4$: C, 51.0; H, 4.99; N, 6.60. Found: C, 51.5; H, 5.07; N, 6.70.

Dimethyl 2-(Difluoromethyl)-4-(2-oxoethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**3a**).

Material **2a** (4.9 g, 12.8 mmoles) was dissolved in 20 ml of 37% hydrochloric acid and stirred with a magnetic stirrer for about 2 hours at room temperature. The mixture was then diluted with 200 ml of water, and stirred an additional 4 hours during which time a slurry was formed which became thicker and whiter with time. The slurry was filtered through a medium sintered glass filter funnel, then washed several times with water on the funnel. Air drying of the fine, white solid overnight gave 3.4 g (75%) of product. This material contained *ca* 1 molecular equivalent of hydrated water, although anhydrous aldehyde could easily be obtained by recrystallization from methylcyclohexane, mp 81-82°. Larger quantities could be conveniently prepared by dissolving the enamine in 37% hydrochloric acid and slowly adding this solution immediately in a fine stream to 10x its volume of water with good stirring; ^{1}H nmr (deuteriochloroform): δ 3.85 (s, 8H, OCH_3 and CH_2), 6.6 (t, 1H, CHF_2), 9.52 (s, 1H, CHO); ^{19}F (s, CF_3), (d, CHF_2); ms: glc/c.i. m/e 324 (lactone, see **23** for homolog).

Anal. Calcd. for $C_{13}H_{10}F_5NO_5$: C, 43.96; H, 2.84; N, 3.94. Found: C, 43.93; H, 2.86; N, 3.87.

Diethyl 2-(Difluoromethyl)-4-(2-oxoethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**3b**).

Using the same procedure as described for **3a**, but starting with **2b**, a white solid product was obtained on air drying (as hydrate) in 92% yield. Recrystallization form methylcyclohexane gave crystals, mp 53-55°; ^{1}H nmr (deuteriochloroform): δ 1.4 (t, 6H, CH_2CH_3), 3.90 (s, 2H, CH_2CHO), 4.37 (q, 4H, OCH_2CH_3), 6.72 (t, 1H, CHF_2), 9.58 (s, 1H, CHO); ^{19}F (s, CF_3), (d, CHF_2).

Anal. Calcd. for $C_{15}H_{14}F_5NO_5$: C, 47.01; H, 3.68; N, 3.65. Found: C, 46.87; H, 3.67; N, 3.61.

Dimethyl 4-[1-[[[(2-Chlorophenyl)sulfonyl]amino]carbonyl]-2-(dimethylamino)ethenyl]-2-(difluoromethyl)-6-(trifluoromethyl)-3,5-pyridinecarboxylate (**4a**).

Material **2a** (3 g, 7.9 mmoles) and an equivalent of 2-chlorophenylsulfonyl isocyanate were heated at reflux in toluene for 2 hours, then cooled and filtered to give 3.3 g (56%) yellow solid. Additional purification was achieved by subjecting 1 g of this material to contact with 25 ml 37% hydrochloric acid at 50-60°, whereupon fine, white solid was formed. Filtering through sintered glass, washing with water, and air drying, gave 0.9 g of material, mp 189-192°.

Anal. Calcd. for $C_{22}H_{19}ClF_5N_3O_7S$: C, 44.05; H, 3.19; N, 7.00. Found: C, 44.12; H, 3.21; N, 6.95.

Diethyl 4-[1-[[[(2-Chlorophenyl)sulfonyl]amino]carbonyl]-2-(diethylamino)ethyl]-2-(difluoromethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**4b**).

Material **2b** (2 g, 4.9 mmoles) was mixed with 1 g of 2-chlorophenylsulfonyl isocyanate and heated without solvent at 80-90° for 15 minutes, then cooled to 40-50° and held in this temperature range a further 2 hours. Upon cooling, the glass obtained was crystallized from toluene to give 1.6 g (52%) fine, yellow needles, mp 154-157°.

Anal. Calcd. for $C_{24}H_{23}ClF_5N_3O_7S$: C, 45.90; H, 3.69; N, 6.69. Found: C, 45.62; N, 3.62; N, 6.57.

Dimethyl 2-(Difluoromethyl)-4-[2-(dimethylamino)ethyl]-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**5a**).

Material **2a** (5 g, 13.1 mmoles) was dissolved in 20 ml methanol with 0.1 g of 5% Pd/C and hydrogenated at 55-60 psi in a Parr shaker. To complete the reaction, a second batch of catalyst was substituted for the first. After the hydrogenation was completed, the contents was filtered, and filtrate stripped of methanol and the residue subjected to hplc with elution with 2% ethanol in chloroform. Fraction 3 gave white, waxy solid 1.4 g (28%) with product assaying at 98% by glc, mp 59-61°; ^{1}H nmr (deuteriochloroform): δ 2.2 (s, 6H, NCH_3), 2.2-3.0 (m's, 4H, CH_2CH_2), 3.8 (s, 6H, OCH_3), 6.6 (t, 1H, CHF_2); ^{19}F (s, CF_3), (d, CHF_2).

Anal. Calcd. for $C_{15}H_{17}F_5N_2O_4$: C, 46.88; H, 4.46; N, 7.29. Found: C, 46.75; H, 4.45; N, 7.25.

Material **6** was identified by nmr and glc/ms from fraction 4 above, without further isolation. Upon Kugelrohr distillation of **5a** at 130-170° (2 mm Hg) a portion extruded dimethylamine to give material **8a**, (identified by glc/ms and comparison of glc retention time with an authentic sample of **8a** [3]).

Methyl 2-[2-(Difluoromethyl)-3,5-bis(methoxycarbonyl)-6-(trifluoromethyl)-4-pyridinyl]-*N,N,N*-trimethylethanaminum Sulfate (**7a**).

An 81% assay fraction from hplc in preparation of **5a**, weighing 0.8 g was dissolved in 5 ml of anhydrous diethyl ether, and 0.5 g of dimethyl sulfate added thereto. A white precipitate gradually formed, which was filtered off to give 0.6 g (70%) water soluble salt as fine, white needles, mp 152-153°; ^{1}H nmr (deuterium oxide): δ 2.85 (s, 9H, NCH_3), 3.30 (s, 3H, CH_3OSO_3), 3.70 (s, 6H, OCH_3), 6.67 (t, 1H, CHF_2); ^{19}F (s, CF_3), (d, CF_2H).

Anal. Calcd. for $C_{17}H_{23}F_5N_2O_8S$: C, 40.00; H, 4.54; N, 5.49. Found: C, 39.77; H, 4.40; N, 5.40.

Dimethyl 4-[2-[(3,4-Dichlorophenyl)amino]ethenyl]-2-(difluoromethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**9a**).

Material **3a** (3g, 8.5 mmoles) was dissolved in 50 ml of toluene containing 1.4 g (8.7 mmoles) of 3,4-dichloroaniline and heated to reflux for 3 hours in a 250 ml flask fitted with a Dean Stark trap. Upon cooling crystals formed which were filtered off and air dried to give 2 g (47%). A second recrystallization from toluene gave yellow crystals, mp 162-163°; ^{1}H nmr (deuteriochloroform): δ 3.9 (s, 6H, OCH_3), 5.8-7.5 (m's, 5H, ArH and =CH), 6.6 (t, 1H, CHF_2), 9.2 (broad d, 1H, NH).

Anal. Calcd. for $C_{19}H_{13}Cl_2F_5N_2O_4$: C, 45.71; H, 2.62; N, 5.61. Found: C, 45.64; H, 2.67; N, 5.62.

Diethyl 4-[2-[(2,6-Diethylphenyl)amino]ethenyl]-2-(difluoromethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylic Acid (**9b**).

A mixture of 4 g (10.3 mmoles) of aldehyde **2b** was heated at reflux with 1.6 g of 2,6-diethylaniline in toluene with water continuously removed by azeotrope. After 2 hours no more water was evolved and the mixture was cooled, then vacuum treated to remove solvent. The distillate from Kugelrohr distillation proved less pure than the crude collected (100%) as an amber glass; ^{1}H nmr (deuteriochloroform): δ 1.0-1.5 (t's, 12H, CH_3), 2.60 (q, 4H, ArCH_2CH$_3$), 4.2 and 4.3 (2q, 4H, OCH_2CH$_3$), 5.6-5.9 (m, 2H, =CH), 6.65 (t, 1H, CHF_2), 7.2 (m, 3H, ArH); ^{19}F (s, CF_3), (d, CHF_2).

Anal. Calcd. for $C_{25}H_{27}F_5N_2O_4$: C, 58.36; H, 5.29; N, 5.44. Found: C, 57.96; H, 5.10; N, 5.45.

Diethyl 4-[2-[(Chloroacetyl)(2,6-diethylphenyl)amino]ethenyl]-2-(difluoromethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**10b**).

Material **9b** (3g, 5.8 mmoles) was refluxed in toluene with 1.5 g of chloroacetyl chloride for about 2 hours. Solvent was then removed under vacuum, then purified by hplc with elution by 6% ethyl acetate in cyclohexane. The main (second) fraction contained product, which after solvent removal, was recrystallized to give 1.2 g (35%) very light yellow crystals, mp 110-111°; ^{1}H nmr (deuteriochloroform): δ 1.3 (t's, 12H, CH_2CH_3), 2.4 (q, 4H, ArCH_2CH$_3$), 3.7 (s, 2H, $ClCH_2$), 4.3 (2 q's, 4H, OCH_2CH$_3$), 5.18 (d, 1H, =CH), 6.62 (t, 1H, CHF_2), 7.3 (m, 3H, ArH), 8.15 (d, 1H, =CH).

Anal. Calcd. for $C_{27}H_{28}ClF_5N_2O_5$: C, 54.87; H, 4.78; N, 4.74. Found: C, 54.74; H, 4.61; N, 4.72.

Dimethyl 2-(Difluoromethyl)-4-[2-[(2,4-dinitrophenyl)hydrazono]ethyl]-6(trifluoromethyl)-3,5-pyridinedicarboxylate (**11a**).

Aldehyde **3a** (0.4 g, 1.1 mmoles) was dissolved in 10 ml of ethanol and to this solution was added an excess of 2,4-dinitrophenylhydrazine. Almost immediately a yellow precipitate formed which was filtered off after 0.5 hour, washed with ethanol and air dried. The yield of hydrazone was 0.5 g (85%), mp 147-148° (after recrystallization from alcohol).

Anal. Calcd. for $C_{19}H_{14}F_5N_5O_8$: C, 42.63; H, 2.64; N, 13.08. Found: C, 42.55; H, 2.68; N, 13.06.

Dimethyl 2-(Difluoromethyl)-4-(2,2-dimethoxyethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxyate (**12a**).

Aldehyde **3a** (2 g, 5.6 mmoles) was dissolved in 10 ml of methanol with 10 ml of trimethyl orthoformate plus a few drops of thionyl chloride to generate a catalytic amount of hydrogen chloride. After refluxing the mixture for 1 hour, glc indicated complete reaction. The material was cooled and neutralized with solid potassium carbonate. The filtered solution was vacuum treated to remove volatiles, then the 2.1 g remaining oil was Kugelrohr distilled at 140-145° (0.1 mm Hg) to give 1.9 g (85%) yellow oil which solidified. A portion was recrystallized from cold hexane, mp 44-45°; ^{1}H nmr (deuteriochloroform): δ 3.1 (d, 2H, CH_2), 3.19 (s, 6H, OCH_3), 4.9 (s, 6H, OCH_3), 4.4 (t, 1H, CH_2CH), 6.65 (t, 1H, CHF_2).

Anal. Calcd. for $C_{15}H_{16}F_5NO_6$: C, 44.90; H, 4.02; N, 3.49. Found: C, 45.04; H, 4.03; N, 3.42.

Dimethyl 2-(Difluoromethyl)-4-(1,3-dithiolan-2-ylmethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**13a**).

Aldehyde **3a** (3.6 g, 10.1 mmoles) was mixed with 1.0 g of 1,2-ethanedithiol in 10 ml of methylene chloride, cooled to -10° and 0.7 g of titanium tetrachloride added with stirring. The reaction was exothermic, and solid precipitated. The reaction mixture was allowed to stand at room temperature overnight, then treated with 2% sodium hydroxide solution while more methylene chloride was added. The liquid phases were filtered through clay, layers separated, and the organic portion subjected to vacuum removal of solvent. The solid yellow residue was recrystallized from methylcyclohexane to give 2.2 g (51%), mp 103-106°; ^{1}H nmr (deuteriochloroform): δ 3.22 (s, 4H, CH_2S), 3.35 (d, 2H, CH_2CH), 3.95 (s, 6H, OCH_3), 4.7 (t, 1H, $CHCH_2$), 6.72 (t, 1H, CHF_2); ^{19}F (s, CF_3), (d, CHF_2) ms: m/e (high resolution) Calcd. 431.0284; Found: 431.0285.

Anal. Calcd. for $C_{15}H_{14}F_5NO_4S_2$: C, 41.76; H, 3.27; N, 3.25; S, 14.86. Found: C, 42.14; H, 3.27; N, 3.24; S, 14.94.

Dimethyl 4-(Carboxymethyl)-2-(difluoromethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxyate (**14a**).

Chromic oxide (70 mmoles) as Jones reagent (7 g chromic oxide, 50 ml water, and 6.1 ml concentrated sulfuric acid) was added dropwise to 25 g (70 mmoles) of aldehyde **3a** in 200 ml of acetone with stirring and cooling, keeping the temperature below 30°. Fifty minutes after addition, the dark green solid was filtered off through a medium porosity sintered glass funnel. The solid was washed on the filter with more acetone, then the filtrate vacuum treated to remove solvent. The resulting solid was washed with 300 ml water to give 24.5 g (94%) of off-white product, which however was perfectly adequate for further transformation. The material could be further purified by recrystallization from toluene/acetonitrile to give white crystals, mp 156-157°; ^{1}H nmr (deuteriochloroform): δ 3.83 (s, 2H, CH_2), 3.95 (s, 6H, OCH_3), 6.75 (t, 1H, CHF_2); ^{19}F (s, CF_3), (d, CHF_2).

Anal. Calcd. for $C_{13}H_{10}F_5NO_6$: C, 42.06; H, 2.72; N, 3.77. Found: C, 41.97; H, 2.49; N, 3.75.

Dimethyl 4-(4-Ethoxy-4-oxo-2-butenyl)-2-(difluoromethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (*cis* and *trans*) (**15a**).

Aldehyde **3a** (2.4 g, 6.8 mmoles) was dissolved in 50 ml of methylcyclohexane and to this added 2.4 g (6.9 mmoles) of (carbethoxymethylene)triphenylphosphorane, and the mixture heated at 60° for 1 hour. After solvent removal the dark green residue was eluted through an 8 inch long column of silica gel by flash chromatography. After solvent removal the residue was Kugelrohr distilled, then the distillate further purified by elution with 10% ethyl acetate in cyclohexane by Chromatotron to give 0.75 g (26%) as a mixture of *cis*/*trans* isomers, n_D^{25} = 1.4644; ^{19}F nmr (deuteriochloroform): (2s, CF_3), (2d, CHF_2).

Anal. Calcd. for $C_{17}H_{16}F_5NO_6$: C, 48.01; H, 3.79; N, 3.29. Found: C, 47.85; H, 3.78; N, 3.25.

Dimethyl 2-(Difluoromethyl)-4-(2-propenyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxyate (**16a**).

A mixture of 5.0 g (75 mmoles) of zinc dust, 3.4 ml (42 mmoles) of diiodomethane, and 80 ml of anhydrous tetrahydrofuran was stirred at room temperature for 1 hour. A solution of 1.1 ml (9 mmoles) of titanium tetrachloride in 8 ml of methylene chloride was added cautiously to this mixture controlling the initial exotherm below 70° with an ice bath. The reaction mixture was held at 20° for 30 minutes, then a solution of 3.9 g (98.4 mmoles) **3a** in 10 ml tetrahydrofuran was added. After 1 hour stirring at room temperature, the mixture was treated with dilute hydrochlo-

ric acid and ether. The crude product was isolated by evaporation of the organic phase, then successively Kugelrohr distilled, further purified by Chromatotron purification (40% methylene chloride in cyclohexane), and finally another Kugelrohr distillation to afford 1.05 g (35%) of water white oil, mp 125-135° (1.5 mm Hg), n_D^{25} = 1.4537; ^{1}H nmr (deuteriochloroform): δ 3.65 (d, (with secondary coupling), 2H, $CH_2CH=$), 4.05 (s, 6H, OCH_3), 4.95-6.2 (m's, 3H, = CH), 6.9 (t, 1H, CHF_2); ^{19}F δ -64.98 (s, CF_3), -115.98 (d, CHF_2); ms: glc/c.i. m/e 353.

Anal. Calcd. for $C_{14}H_{12}F_5NO_4$: C, 47.60; H, 3.42; N, 3.96. Found: C, 47.68; H, 3.43; N, 3.96.

Dimethyl 4-[(2-Bromo-2-chlorocyclopropyl)methyl]-2-(difluoromethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate, Mixture with Dimethyl 4-[(2,2-Dichlorocyclopropyl)methyl]-2-(difluoromethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**17**).

Material **16a** (1.3 g, 3.6 mmoles) and 3.5 g (7.9 mmoles) of (bromodichloromethyl)phenyl mercury in 10 ml of benzene was refluxed for 2 hours. After this time another 1.4 g of fresh mercury reagent was added, and the mixture refluxed another hour. The cooled mixture was filtered, and the filtrate purified by Chromatotron to give 6.71 g (45%) of water white oil, bp 160-170° (1 mm Hg), n_D^{25} = 1.4756; ^{1}H nmr (deuteriochloroform): δ 1.1-1.3 (m's, 3H, cyclopropyl H), 2.5-3.6 (m's, 2H, CH_2), 3.9 (s, 6H, OCH_2), 6.65 (t, 1H, CHF_2); ^{19}F δ -64.80 (s, CF_3), -115.73 (d, CHF_2); ms: glc/c.i. m/e 435 (90%), 479 (10%).

Anal. Calcd. for $C_{15}H_{12}Cl_2F_5NO_4$ (90%), and $C_{15}H_{12}BrClF_5NO_4$ (10%): C, 40.92; H, 2.75; N, 3.17. Found: C, 40.46; H, 2.72; N, 3.13.

Dimethyl 4-(2,3-Dichloropropyl)-2-(difluoromethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**18**).

Excess chlorine gas was bubbled into a solution of 2.2 g (6.2 mmoles) **16a** in 20 ml of chloroform. The solution was stirred for 18 hours at room temperature, then the reaction mixture filtered (see below) and the filtrate evaporated, with the residue purified by Chromatotron with 10% ethyl acetate in cyclohexane. After Kugelrohr distillation the product (0.43 g, 16%) was collected as a water white oil, bp 160-170° (1.3 mm Hg) that solidified, mp 54-56°; ^{1}H nmr (deuteriochloroform): δ 3.39-3.87 (8 d's, 4H, $2CH_2$- (prochiral and coupled to methane H), 4.3 (m, 1H, methine H), 6.80 (t, 1H, CHF_2); ^{19}F (s, CF_3), (2d, prochiral CHF_2).

Anal. Calcd. for $C_{14}H_{12}Cl_2F_5NO_4$: C, 39.64; H, 2.85; N, 3.30. Found: C, 39.78; H, 2.89; N, 3.29.

Methyl 3-(Chloromethyl)-6-(difluoromethyl)-3,4-dihydro-1-oxo-8-(trifluoromethyl)-1*H*-pyrano[3,4-*c*]pyridine-5-carboxylate, Mixture with Methyl 3-(Chloromethyl)-8-(difluoromethyl)-3,4-dihydro-1-oxo-6-(trifluoromethyl)-1*H*-pyrano[3,4-*c*]pyridine-5-carboxylate (**19**).

The solid filtered off in the preparation of **18** weighed 1.58 g (68%), mp 155-162°, and by glc/ms and nmr was the mixture as indicated (inseparable by hplc); ^{1}H nmr (deuteriodimethylsulfoxide): δ 3.6-3.85 (m's and d's, 2H, CH_2), 4.34-4.48 (m's and d's, 2H, CH_2), 4.49 (s, 3H, OCH_3), 5.37 (m, 1H, methine *H*), 7.5 and 8.0 (2t, 1H, 60% CHF_2 and 40% CHF_2); ms: glc/c.i. m/e 373 (1 Cl) (60%), 373 (1 Cl) (40%).

Anal. Calcd. for $C_{13}H_9ClF_5NO_4$: C, 41.78; H, 2.42; N, 3.74. Found: C, 41.80; H, 2.46; N, 3.73.

Dimethyl 2-(Difluoromethyl)-4-(oxiranylmethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**20**).

A mixture of 2.45 g (6.9 mmoles) of **16a** and 3.7 g (17 mmoles) in 35 ml of methylene chloride was stirred at room temperature for 72 hours. The mixture was filtered, and the filtrate washed with dilute sodium carbonate and sodium thiosulfate solution. Upon workup the product was purified by Chromatotron (45% methylene chloride in cyclohexane) and Kugelrohr distilled to give 1.95 g (76% yield) of water white liquid, bp 150-160° (1.4 mm Hg), n_D^{25} = 1.4630; ^{1}H nmr (deuteriochloroform): δ 2.4 (q, 1H), 2.77 (t, 1H), 3.12 (m's, 3H), 4.00 and 4.02 (2s, 6H, OCH_3), 6.8 (t, 1H, CHF_2); ^{19}F δ -64.73 (s, CF_3), -116.06, -116.23 (2d, prochiral CHF_2).

Anal. Calcd. for $C_{14}H_{12}F_5NO_5$: C, 45.54; H, 3.27; N, 3.79: Found: C, 45.56; H, 3.19; N, 3.75.

Dimethyl 2-(Difluoromethyl)-4-(3-hydroxy-1-propenyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**21**).

A mixture of 0.6 g (1.6 mmoles) **20** and 0.32 g (3.2 mmoles) of potassium thiocyanate in 10 ml of methanol was stirred at room temperature for 4 hours. The mixture was quenched in water, then extracted with ether. Purification by Chromatotron afforded 0.17 g (28%) of water white oil, n_D^{25} = 1.4772; ^{1}H nmr (deuteriochloroform): δ 3.9 (2s, 6H, OCH_3), 4.31 (broad s, 2H, CH_2), 6.27 (2t, 1H, =CH), 6.68 (d, 1H, J = 14 Hz (*trans* coupling), =CH), 6.75 (t, 1H, CHF_2).

Anal. Calcd. for $C_{14}H_{12}F_5NO_5$: C, 45.54; H, 3.27; N, 3.79. Found: C, 45.28; H, 3.35; N, 3.85.

Dimethyl 2-(Difluoromethyl)-4-(thiiranylmethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**22**).

To a solution of 1.0 g (3.7 mmoles) of **20** and 1.5 g (5.0 mmoles) of triphenylphosphine sulfide in 20 ml of benzene was added 0.6 g (5.0 mmoles) of trifluoroacetic acid and the mixture stirred at room temperature for 0.5 hour. The mixture was filtered, the filtrate vacuum treated to remove solvent and the residue then purified by Chromatotron (4% ethyl acetate in cyclohexane) to afford 0.85 g (59%) of white solid, mp 59-61°; ^{1}H nmr (deuteriochloroform): δ 2.29 and 2.49 (2 d's (with fine splitting), 2H, cyclopropyl H), 3.02-3.21 (m's, 3H, CH_2 and cyclopropyl H), 4.0 (2s, 6, OCH_3), 6.28 (t, 1H, CHF_2); ms/c.i. m/e 385.

Anal. Calcd. for $C_{14}H_{12}F_5NO_4S$: C, 43.64; H, 3.14; N, 3.64. Found: C, 43.88; H, 3.19; N, 3.55.

Ethyl 8-(Difluoromethyl)-1-oxo-6-(trifluoromethyl)-1*H*-pyrano-[3,4-*c*]pyridine-5-carboxylate (**23**).

Aldehyde **3b** (3 g, 7.8 mmoles) was dissolved in 200 ml of chlorobenzene with 0.1 g of *p*-toluenesulfonic acid, and refluxed for 3 hours under a soxhlet extractor filled with 10 g 4A molecular sieve. The cooled reaction mixture was washed with sodium bicarbonate solution, organic solvent removed under vacuum, and the residue recrystallized from methylcyclohexane/ethyl acetate mixture using decolorizing charcoal to give 1.5 g (57%) of white crystals, mp 114-115°; ^{1}H nmr (deuteriochloroform): δ 1.4 (t, 3H, OCH_2CH_3), 4.4 (q, 2H, OCH_2CH_3), 6.52 and 7.45 (2d, 2H, =CH), 7.52 (t, 1H, CHF_2); ^{19}F (s, CF_3), (d, CHF_2).

Anal. Calcd. for $C_{13}H_8F_5NO_4$: C, 46.31; H, 2.39; N, 4.15. Found: C, 46.03; H, 2.54; N, 3.93.

Ethyl 1-(Difluoromethyl)-7,8-dihydro-8-oxo-3-(trifluoromethyl)-1,2,7-naphthyridine-4-carboxylate (**24**).

Aldehyde **3b** (5 g, 13 mmoles) was mixed with 20 ml of glacial acetic acid containing 5 g of ammonium acetate. The mixture was heated at 80° with stirring for 3 hours. After cooling, the mixture

was poured into 200 g of ice/water to give 3.9 g of crude solid. Recrystallization from toluene gave 2.0 g (46%). A second recrystallization from toluene/ethyl acetate furnished the analytical sample, mp 238-241°; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 1.4 (t, 3H, CH_2CH_3), 4.35 (q, 2H, CH_2CH_3), 6.35 and 7.28 (2d, 2H, =CH), 7.82 (t, 1H, CHF_2), 11.0 (b, 1H, NH); ^{19}F (s, CF_3), (d, CHF_2). X-ray crystal structure of **24**: Formula $C_{13}H_9F_5N_2O_3$, MW = 336.22, crystallized as colorless plates, size 0.6 x 0.5 x 0.1 mm crystal used, space group $P2_1/n$, cell dimensions, a = 8.471 (2), b = 15.828 (4), c = 10.651 (2) A, β = 100.72 (2)°, and V = 1403.1 (5) A^3, Z = 4, μ = 13.7 cm^{-1}, SYNTEX P2, diffractometer with graphite-monochromated CuK_α radiation (λ = 1.5418Å) was used. Data were collected using θ-2θ scan method with variable scan rates. Of total 2047 unique reflections collected up to 2θ = 120°, 1378 with $I > 2.33\ \delta_I$ are considered to be observed. The structure was solved by direct methods using the MULTAN system. The hydrogen atoms were found in the successive difference Fourier maps. In the final cycles of full-matrix least squares refinement, the non-hydrogen atoms were refined with anisotropic temperature factors and the hydrogen atoms refined with isotropic temperature factors. Refinement converged at R = 0.073 and R = 0.102 for 1378 observed reflections. The difference map at this stage showed no peaks greater than 0.3 eA^{-3}.

Anal. Calcd. for $C_{13}H_9F_5N_2O_3$: C, 46.44; H, 2.70; N, 8.33. Found: C, 46.43; H, 2.73; N, 8.32.

Ethyl 1-(Difluoromethyl)-7,8-dihydro-7-hydroxy-8-oxo-3-(trifluoromethyl)-2,7-naphthyridine-4-carboxylate (**25**).

Aldehyde **3b** (2.5 g, 6.5 mmoles) was mixed with 3 g of hydroxylamine hydrochloride and 10 ml of ethanol, then heated at 80° for 3 hours, and cooled. The material was vacuum treated to remove alcohol, washed with acidified water, then extracted with ether. The ether was washed with 1% sodium hydroxide, filtered through clay, and the aqueous portion of the filtrate acidified with hydrochloric acid. The solid was filtered off, washed with water, and air dried, mp 175-178°; ^{1}H nmr (deuteriochloroform): δ 1.4 (t, 3H, CH_2CH_3), 4.45 (q, 2H, CH_2CH_3), 6.45 and 7.8 (2d, 2H, =CH), 7.98 (t, 1H, CHF_2); ^{19}F (s, CF_3), (d, CHF_2).

Anal. Calcd. for $C_{13}H_9F_5N_2O_4$: C, 44.33; H, 2.58; N, 7.95. Found: C, 43.90; H, 2.60; N, 7.70.

Ethyl 8-Chloro-1-(difluoromethyl)-3-(trifluoromethyl)-2,7-naphthyridine-4-carboxylate (**26**).

Material **24** (2.2 g, 6.5 mmoles) was placed in 25 ml of phosphorus oxychloride with 1 g of 2,6-lutidine and heated to boiling. After 3 hours the mixture was cooled, poured into 10% hydrochloric acid, extracted with ether, and the latter washed with water. After drying over magnesium sulfate, filtering and solvent evaporation, the solid residue was recrystallized from methylcyclohexane to give 2.1 g (91%), mp 95-96.5°; ^{1}H nmr (deuteriochloroform): δ 1.45 (t, 3H, CH_2CH_3), 4.45 (q, 2H, CH_2CH_3), 7.6 (t, 1H, CHF_2), 7.70 and 8.56 (2d, 2H, =CH); ^{19}F (s, CF_3), (d, CHF_2).

Anal. Calcd. for $C_{13}H_8ClF_5N_2O_2$: C, 44.02; H, 2.27; N, 7.90. Found: C, 44.07; H, 2.30; N, 7.86.

Methyl 1-(Difluoromethyl)-8-methoxy-3-(trifluoromethyl)-2,7-naphthyridine-4-carboxylate (**27**).

Material **26** (0.8 g, 2.3 mmoles) was dissolved in methanol and to this with stirring was added a molar excess of sodium methoxide in methanol. After stirring overnight, the mixture was poured into water to give after air drying, 0.5 g (65%) of white solid; mp (methylcyclohexane) 144-146°; ^{1}H nmr (deuteriochloroform): δ 4.02 and 4.18 (2s, 6H, OCH_3), 7.24 and 8.32 (2d, 2H, =CH), 7.54 (t, 1H, CHF_2); ^{19}F (s, -67.12, CF_3), (d, -121.04, CHF_2); ms: m/e 336.

Anal. Calcd. for $C_{13}H_9F_5N_2O_3$: C, 46.44; H, 2.70; N, 8.33. Found: C, 46.43; H, 2.73; N, 8.32.

Dimethyl 2-(Difluoromethyl)-4-(2-methoxy-2-oxoethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**28a**).

The acid **14a** was boiled 1.5 hours in excess thionyl chloride as solvent. Crude acid chloride was quantitatively obtained upon evaporation of thionyl chloride, and served as starting material for the transformations described below: Acid chloride, 1.8 g, (4.6 mmoles) in 10 ml of methanol was contacted with 13 ml of 0.373 *N* sodium methoxide in methanol. The mixture was stirred 1 hour, then poured into 5% hydrochloric acid solution (containing some salt). The precipitate was filtered, washed on the filter with water, then air dried overnight to give 1.8 g (100%). Recrystallization from methylcyclohexane gave a white solid, mp 84-84.5°; ^{1}H nmr (deuteriochloroform): δ 3.7 (s, 3H, OCH_3), 3.87 (s, 2H, CH_2), 3.95 (s, 6H, OCH_3), 6.80 (t, 1H, CHF_2).

Anal. Calcd. for $C_{14}H_{12}F_5NO_6$: C, 43.65; H, 3.14; N, 3.64. Found: C, 43.53; H, 3.14; N, 3.61.

Materials **28b-29b** were prepared in like fashion, as follows:

Dimethyl 2-(Difluoromethyl)-4-(2-ethoxy-2-oxoethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**28b**).

Sodium ethoxide in ethanol furnished a white solid (92%), mp 81-82°; ^{1}H nmr (deuteriochloroform): δ 1.2 (t, 3H, CH_2CH_3), 3.9 (s, 2H, CH_2), 3.98 (s, 6H, OCH_3), 4.15 (q, 1H, CH_2CH_3), 6.89 (s, 1H, CHF_2).

Anal. Calcd. for $C_{15}H_{14}F_5O_6$: C, 45.12; H, 3.53; N, 3.51. Found: C, 45.20; H, 3.55; N, 3.49.

Dimethyl 2-(Difluoromethyl)-4-[2-(1,1-dimethylethoxy)-2-oxoethyl]-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**28c**).

From acid chloride, *t*-butyl alcohol, and a mixture of triethylamine and 4-(dimethylamino)pyridine was obtained (from methylcyclohexane) 7 g of white solid (82%), mp 63.5-67°; ^{1}H nmr (deuteriochloroform): δ 1.35 (s, 9H, $(CH_3)_3C$), 3.80 (s, 2H, CH_2), 3.98 (s, 6H, OCH_3), 6.78 (t, 1H, CHF_2).

Anal. Calcd. for $C_{17}H_{18}F_5NO_6$: C, 47.78; H, 4.25; N, 3.28. Found: C, 47.55; H, 4.05; N, 3.33.

Dimethyl 2-(Difluoromethyl)-4-[2-[(1-methylethyl)thio]-2-oxoethyl]-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**28d**).

Reaction from acid chloride and isopropyl mercaptan was neutralized with an equivalent of potassium *t*-butoxide, and gave after hplc with 3.5% ethyl acetate in cyclohexane, and crystallization from cold hexane, white needles (35%), mp 69-70°; ^{1}H nmr (deuteriochloroform): δ 1.2 (d, 6H, $CH(CH_3)_2$), 3.95 (s, 6H, OCH_3), 4.12 (s, 2H, CH_2), 6.7 (t, 1H, CHF_2); ms: m/e Calcd. 429.0669; Found: 429.0684.

Anal. Calcd. for $C_{16}H_{16}F_5NO_5S$: N, 3.26; S, 7.47. Found: N, 3.12; S, 7.26.

Dimethyl 2-(Difluoromethyl)-4-[2-(dimethylamino)-2-oxoethyl]-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**29a**).

Acid chloride in methylene chloride with dimethylamine gave after recrystallization from toluene and methylcyclohexane 1.8 g (59%), mp 137-138.5°; ^{1}H nmr (deuteriochloroform): δ 2.95 (d,

6H, NCH_3), 3.90 (s, 6H, OCH_3), 3.95 (s, 2H, CH_2), 6.70 (t, 1H, CHF_2).

Anal. Calcd. for $C_{15}H_{15}F_5N_2O_5$: C, 45.24; H, 3.80; N, 7.03. Found: C, 45.32; H, 3.80; N, 7.01.

Dimethyl 4-(Aminocarbonylmethyl)-2-(difluoromethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**29b**).

Acid chloride in 50 ml of methylene chloride and 10 ml of aqueous concentrated ammonia yielded after recrystallization twice from toluene, 2.0 g (54%); mp 160-163°, ^1H nmr (deuteriochloroform): δ 3.80 (s, 2H, CH_2), 4.0 (s, 6H, OCH_3), 6.80 (t, 1H, CHF_2); ^{19}F (s, CF_3), (d, CHF_2).

Anal. Calcd. for $C_{13}H_{11}F_5N_2O$: C, 42.17; H, 2.99; N, 7.57. Found: C, 42.06; H, 2.76; N, 7.51.

Dimethyl 4-(Cyanomethyl)-2-(difluoromethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**30**).

Material **29b** (3.4 g, 9.2 mmoles) was refluxed 2.5 hours in 20 ml of phosphorus oxychloride. After vacuum treatment of the reaction mixture to remove volatiles, the material was treated with 100 ml of water and 3.0 g of solid filtered off. The latter was recrystallized from a mixture of toluene and methylcyclohexane to give 2.5 g (77%) of light buff crystals, mp 137-139°; ^1H nmr (deuteriochloroform): δ 3.90 (s, 2H, CH_2), 4.00 (s, 6H, OCH_3), 6.75 (t, 1H, CHF_2); ^{19}F (s, CF_3), (d, CHF_2).

Anal. Calcd. for $C_{13}H_9F_5N_2O_4$: C, 44.33; H, 2.58; N, 7.95. Found: C, 44.31; H, 2.59; N, 7.93.

Dimethyl 2-(Difluoromethyl)-4-(2-ethoxy-1-methyl-2-oxoethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**31a**).

Material **28b** (2 g, 5 mmoles) was dissolved in 30 ml of dimethylformamide and 2 g (excess) of methyl iodide with 2 g of potassium carbonate was added and the mixture stirred overnight. Glc indicated a single component. The material was treated with 2.5% hydrochloric acid, extracted with ether, and the latter washed once again with dilute hydrochloric acid, then dried over magnesium sulfate. After solvent removal under vacuum the 2.0 g of the crude was Kugelrohr distilled at 140-145° (0.1 mm Hg) to give 1.5 g (73%) of yellow oil, n_D^{25} = 1.4566; ^1H nmr (deuteriochloroform): δ 1.2 (t, 3H, OCH_2CH_3), 1.52 (d, 3H, CCH_3), 3.95 (s, 6H, OCH_3), 3.8-4.3 (m's, 3H, methine *H* and OCH_2CH_3), 6.70 (t, 1H, CHF_2): ^{19}F (s, CF_3), (d, CHF_2).

Anal. Calcd. for $C_{16}H_{16}F_5NO_6$: C, 46.50; H, 3.90; N, 3.39. Found: C, 46.50; H, 3.90; N, 3.38.

Dimethyl 4-[1-[(Cyclopropyl)methyl]-2-(1,1-dimethylethoxy)-2-oxoethyl]-6-(difluoromethyl)-2-(trifluoromethyl)-3,5-pyridinedicarboxylate (**31b**).

In like manner to the preparation of **31a**, 2.15 g (5.0 mmoles) of **28d** with 2 g of cyclopropylmethyl bromide gave a crude product which was purified by hplc with 4% ethyl acetate in cyclohexane to give, after Kugelrohr distillation at 160-170° (0.2 mm Hg), 1.6 g (67%) of a very viscous colorless oil: ^1H nmr (deuteriochloroform): δ -0.2-0.7 (m's, cyclopropyl *H*), 1.40 (s, 9H, $(CH_3)_3C$), 4.05 (s, 6H, OCH_3), 6.9 (t, 1H, CHF_2); ^{19}F (s, CF_3), (2d, prochiral CHF_2).

Anal. Calcd. for $C_{21}H_{24}F_5NO_6$: C, 52.39; H, 5.02; N, 2.91. Found: C, 52.40; H, 5.04; N, 2.85.

Dimethyl 2-(Difluoromethyl)-4-[1-[(1,1-dimethylethoxy)carbonyl]-3-butenyl]-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**31c**).

The material was prepared in like manner to that described for **31a** from **28c** and 3-bromopropene. Purification by hplc with 4% ethyl acetate in cyclohexane gave 1.5 g (48%) after Kugelrohr distillation at 145-160° (0.15 mm Hg); ^1H nmr (deuteriochloroform): δ 1.30 (s, 9H, $(CH_3)_3C$), 2-3 (m's, 2H, CH_2), 3.75 (m, 1H, methine *H*), 4.7-5.7 (m's, 3H, =CH), 6.7 (t, 1H, CHF_2); ^{19}F (s, CF_3), (2d, prochiral CHF_2); ms: glc/c.i. m/e 367.

Anal. Calcd. for $C_{20}H_{22}F_5NO_6$: C, 51.40; H, 4.74; N, 3.00. Found: C, 51.44; H, 4.76; N, 2.98.

Dimethyl 2-(Difluoromethyl)-4-(5-ethyl-2-oxo-3-tetrahydrofuranyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**32**).

Material **31b** (0.4 g, 0.83 mmole) was dissolved in 2 ml of trifluoroacetic acid and refluxed for 36 hours, after which time the *t*-butyl group was scarcely discernable in the ^1H nmr spectra of the reaction solution. The mixture was poured into methylene chloride, washed 3x with water, and once with sodium bicarbonate solution. After vacuum removal of the solvent the residue was recrystallized from methylcyclohexane to give 0.22 g (62%) of white solid, mp 101-102°; ^1H nmr (deuteriochloroform): δ 1.02 (t, 3H, CH_2CH_3), 2.78 and 2.88 (2 heptets, 2H, prochiral CH_2CH_3), 2.53 and 2.70 (q and m, 2H, CH_2), 4.96 (s, 6H, OCH_3), 4.98 (t, 1H, methine *H*), 4.45 (m, 1H, methine *H*), 6.82 (t, 1H, CHF_2); ms: m/e 425.

Anal. Calcd. for $C_{17}H_{16}F_5NO_6$: C, 48.01; H, 3.79; N, 3.29. Found: C, 48.14; H, 3.82; N, 3.26.

Dimethyl 4-(Bromomethyl)-2-(difluoromethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**33**).

Material **14a** (10 g, 27 mmoles) was mixed with 3.7 g (17.1 mmoles) of red mercuric oxide in 50 ml v/v of 1,2-ethylene dichloride and carbon tetrachloride. As the temperature was increased towards reflux, 4.5 g (28 mmoles) of bromine in 20 ml of the mixed solvent was added, while a 150 watt flood light was used to illuminate the flask. Slightly more bromine was added after 15 minutes reflux until the bromine color persisted. After 0.5 hour the mixture was allowed to cool and the solution decanted from the heavy white precipitate with additional washing of the latter with more mixed solvent. The organic solution was then washed with sodium bicarbonate solution, and the whole mixture filtered through clay prior to separating the lower organic layer. This phase was vacuum treated to give 10.5 g (96%) oily product with only traces of suspended mercury salts. The oil solidfied to a hard white solid. This material could be used directly, while analytical material was produced by two recrystallizations from methanol, mp 65-67.5°; ^1H nmr (deuteriochloroform): δ 4.02 (s, 6H, OCH_3), 4.57 (s, 2H, CH_2), 6.75 (t, 1H, CHF_2); ^{19}F (s, CF_3), (d, CHF_2).

Anal. Calcd. for $C_{12}H_9BrF_5NO_4$: C, 35.49; H, 2.23; Br, 19.68; N, 3.45. Found: C, 35.55; H, 2.32; Br, 19.70; N, 3.43.

Dimethyl 2-(Difluoromethyl)-4-[(dimethylamino)methyl]-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**34a**).

To a solution of 2.95 g (7.4 mmoles) of **33** in 35 ml of ether was added 1.6 g (36 mmoles) dimethylamine in 10 ml of ether. After stirring 0.5 hour at room temperature the reaction mixture was washed with water, then extracted with 1% hydrochloric acid. The combined aqueous acid extracts were treated with excess 10% sodium hydroxide, then extracted with ether. The ether extracts were dried over magnesium sulfate, filtered and solvent removed. The residue was distilled by Kugelrohr distillation to give 1.91 g (69%) of light yellow oil, bp 130-140° (0.1 mm), n_D^{25} = 1.4524; ^1H nmr (deuteriochloroform): δ 2.20 (s, 6H, NCH_3),

3.60 (s, 2H, CH_2), 4.00 (s, 6H, OCH_3), 6.82 (t, 1H, CHF_2); ^{19}F δ -64.56 (s, CF_3), -115.81 (d, J = 54 Hz, CF_2H).

Anal. Calcd. for $C_{14}H_{15}F_5N_2O_4$: C, 45.41; H, 4.08; N, 7.57. Found: C, 45.39; H, 4.06; N, 7.54.

2-(Difluoromethyl)-3,5-bis(methoxycarbonyl)-*N,N,N*-trimethyl-6-(trifluoromethyl)-4-pyridinemethanaminium Bromide (**34b**).

Material **33** (2.0 g, 5.9 mmoles) was dissolved in 10 ml of ether and placed in a capped bottle containing 4.1 g of trimethyl amine dissolved in 100 ml of ether. The whole solution turned dark and deposited a dark gray solid. This was filtered off and triturated with ether to give 1.5 g (55%), mp 149-152°; ^1H nmr (deuterium oxide): δ 3.05 (s, 9H, NCH_3), 3.95 (s, 6H, OCH_3), 4.78 (s, 2H, CH_2), 7.0 (t, 1H, CHF_2).

Anal. Calcd. for $C_{15}H_{18}BrF_5N_2O_4$: C, 38.73; H, 3.90; Br, 17.18; N, 6.02. Found: C, 38.76; H, 3.92; Br, 17.27; N, 6.00.

Dimethyl 2-(Difluoromethyl)-4-(ethoxymethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**34c**).

A mixture of 1.9 g (4.7 mmoles) of **33** and 1.2 g (6.1 mmoles) of silver tetrafluoroborate was dissolved in 10 ml of anhydrous ethanol, then heated and held at reflux for 4 hours. The cooled reaction mixture after filtering and solvent evaporation was taken up in 100 ml of methylene chloride and washed twice with 1% sodium chloride/1% sodium bicarbonate solution, then dried over magnesium sulfate. After filtration and solvent removal the material was purified by silica gel hplc followed by Kugelrohr distillation to afford 1.18 g (67%) of light yellow oil, bp 140-150° (0.1 mm Hg) n_D^{25} = 1.4483, which crystallized on standing, mp 31-33°; ^1H nmr (deuteriochloroform): δ 1.22 (t, 3H, CH_2CH_3), 3.55 (q, 2H, CH_2CH_3), 4.15 (s, 6H, OCH_3), 4.75 (s, 2H, CH_2), 6.95 (t, 1H, CHF_2); ^{19}F δ -64.50 (s, CF_3), -115.89 (d, J = 54 Hz, CF_2H).

Anal. Calcd. for $C_{14}H_{14}F_5NO_5$: C, 45.29; H, 3.80; N, 3.77. Found: C, 45.34; H, 3.81; N, 3.74.

Dimethyl 2-(Difluoromethyl)-4-[(2-propenylthio)methyl]-6-(trifluoromethyl)-3,5-pyridinecarboxylate (**34d**).

A mixture of 1.88 g (4.6 mmoles) of **33**, 1.0 g (10 mmoles) of 2,6-lutidine, and 1.5 ml (12 mmoles) of allylthiol were refluxed together in 10 ml of tetrahydrofuran for 18 hours. The cooled reaction mixture was vacuum treated to remove solvent, then the residue taken up in 150 ml of methylene chloride and washed with 100 ml of 1% sodium chloride. After further washing the organic solution with 0.5% hydrochloric acid, it was dried over magnesium sulfate, filtered and stripped. The residue was purified by hplc followed by Kugelrohr distillation to give 0.35 g (18%) of colorless oil, bp 160-170° (0.5 mm Hg), n_D^{25} = 1.4855; ^1H nmr (deuteriochloroform): δ 3.31 (d, 2H, CH_2CH), 4.10 (s, 2H, CH_2), 4.26 (s, 6H, OCH_3), 5.1-6.3 (m's, 3H, =CH), 7.12 (t, 1H, CHF_2); ^{19}F -64.89 (s, CF3), -115.39 (d, J = 54 Hz, CF_2H).

Anal. Calcd. for $C_{15}H_{14}F_5NO_4S$: C, 45.11; H, 3.53; N, 3.51. Found: C, 45.07; H, 3.55; N, 3.63.

Ethyl 4-(Difluoromethyl)-2,3-dihydro-2-(1-methylethyl)-3-oxo-6-(trifluoromethyl)-1*H*-pyrrolo[3,4-*c*]pyridine-7-carboxylate (**35**).

In like manner to the procedure described for the preparation of **34a**, crude product was obtained from **33** and isopropylamine to give 2.5 g of solid, which was Kugelrohr distilled, bp 170-185° (2 mm Hg), then recrystallized from methylcyclohexane to give 1.81 g (69%), mp 140-143°; ^1H nmr (deuteriochloroform): δ 1.27 (d, 6H, $CH(CH_3)_2$), 3.98 (s, 3H, OCH_3), 4.52 (s, 2H, CH_2), 4.58 (heptet, 1H, CH), 7.62 (t, 1H, CHF_2); ms/c.i. m/e 352.

Anal. Calcd. for $C_{14}H_{13}F_5N_2O_3$: C, 47.74; H, 3.72; N, 7.95. Found: C, 47.74; H, 3.73; N, 7.92.

Dimethyl 2-(Difluoromethyl)-4-(2-hydroxyethyl)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (**36**).

Material **14a** (3.7 g, 100 mmoles) was dissolved in 100 ml of tetrahydrofuran and 20 ml (20 mmoles) of borane solution added. The material was stirred, then permitted to stand 5 days when 4% hydrochloric acid was added dropwise with gas evolution (This was done after evaporation of most of the tetrahydrofuran on a rotary evaporator). Diethyl ether was added, the material was shaken with more dilute hydrochloric acid, followed by a water wash. After drying over magnesium sulfate the material was vacuum treated to remove solvent to give 4 g of viscous oil. The material was recrystallized from methylcyclohexane/ethyl acetate to give 1.5 g (50%) of waxy solid, mp 61-63°. ^1H nmr (deuteriochloroform): δ 2.42 (s (broad), 1H, OH), 3.0 (t, 1H, CH_2), 3.8 (m, 2H, CH_2OH), 3.95 (s, 6H, OCH_3), 6.7 (s, 1H, CHF_2).

Anal. Calcd. for $C_{13}H_{12}F_5NO_5$: C, 43.71; H, 3.39; N, 3.92. Found: C, 43.70; H, 3.43; N, 3.90.

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