7.03-7.52 (m, 11 H, ArH, TolH); IR (KBr) 3234 (OH), 1023 cm^{-1} (SO); MS (m/z) 354 ($M^+ - O$), 352 ($M^+ - H_2O$); $[\alpha]^{25}_D$ -19.7° (c = 2.0, $CHCl_3$). Anal. Calcd for $C_{21}H_{19}ClO_2S$: C, 68.01; H, 5.16. Found: C, 67.84; H, 5.15. **5c** (major diastereomer): yield 241 mg (62%); mp 134-135 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 2.39 (s, 3 H, CH_3), 3.74 (s, 3 H, OCH_3), 4.87 (br s, 1 H, OH), 6.37 (br s, 1 H, CH), 6.75, 6.86 (ABq, J = 8.6 Hz, 4 H, 2',3',5',6'-ArH), 6.95 (t, J = 7.8 Hz, 1 H, 5-ArH), 7.27 (t, J = 7.8 Hz, 1 H, 4-ArH), 7.28, 7.52 (ABq, J = 8.1 Hz, 4 H, TolH), 7.35 (d, J = 7.8 Hz, 1 H, 3-ArH); IR (KBr) 3326 (OH), 1031 cm^{-1} (SO); MS (m/z) 370 ($M^+ - O$), 368 ($M^+ - H_2O$); $[\alpha]^{25}_D$ -295.8° (c = 2.0, $CHCl_3$). Anal. Calcd for $C_{21}H_{19}ClO_3S$: C, 65.19; H, 4.95. Found: C, 64.76; H, 5.00. **5c** (minor diastereomer): yield 130 mg (34%); mp 122-124 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 2.31 (s, 3 H, CH_3), 3.74 (s, 3 H, OCH_3), 3.90 (br s, 1 H, OH), 6.66 (br s, 1 H, CH), 6.75-7.58 (m, 11 H, ArH, TolH); IR (KBr) 3306 (OH), 1021 cm^{-1} (SO); MS (m/z) 370 ($M^+ - O$), 368 ($M^+ - H_2O$); $[\alpha]^{25}_D$ -21.7° (c = 2.0, $CHCl_3$). Anal. Calcd for $C_{21}H_{19}ClO_3S$: C, 65.19; H, 4.95. Found: C, 64.68; H, 4.92. **5d** (major diastereomer): yield 244 mg (57%); mp 116-117 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 2.37 (s, 3 H, CH_3), 4.65 (br s, 1 H, OH), 6.59 (br s, 1 H, CH), 6.97 (d, J = 7.9 Hz, 1 H, 5-ArH), 6.99, 7.40 (ABq, J = 8.2 Hz, 4 H, 2',3',5',6'-ArH), 7.24, 7.47 (ABq, J = 8.1 Hz, 4 H, TolH), 7.31 (t, J = 7.9 Hz, 1 H, 4-ArH), 7.38 (d, J = 7.9 Hz, 1 H, 3-ArH); IR (KBr) 3330 (OH), 1039 cm^{-1} (SO); MS (m/z) 408 ($M^+ - O$), 406 ($M^+ - H_2O$); $[\alpha]^{25}_D$ -233.8° (c = 2.0, $CHCl_3$). Anal. Calcd for $C_{21}H_{16}F_3ClO_2S$: C, 59.37; H, 3.80. Found: C, 58.90; H, 3.80. **5d** (minor diastereomer): yield 143 mg (34%); mp 101-102 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 2.31 (s, 3 H, CH_3), 4.38 (br s, 1 H, OH), 6.70 (br s, 1 H, CH), 7.10-7.46 (m, 11 H, ArH); IR (KBr) 3372 (OH), 1039 cm^{-1} (SO); MS (m/z) 408 ($M^+ - O$), 406 ($M^+ - H_2O$); $[\alpha]^{25}_D$ -54.9° (c = 2.0, $CHCl_3$). Anal. Calcd for $C_{21}H_{16}F_3ClO_2S$: C, 59.37; H, 3.80. Found: C, 58.89; H, 3.76.

Desulfinylation Reactions of 3a and 5b with Grignard or Organolithium Reagents. In a typical run, to a stirred solution of major diastereomer of sulfoxide **3a** (200 mg, 0.68 mmol) in THF (10 mL) at 0 °C was added 1.0 M EtMgBr (1.36 mL, 1.36 mmol) in THF solution under N_2 at 0 °C for 15 min. Then this mixture was treated with water and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was dried ($MgSO_4$), filtrated, and concentrated under reduced pressure. The crude products were separated by column chromatography (silica gel; eluent hexane/EtOAc = 3/2) to give 96.9 mg (91%) of optically active 1-chloro-3-(1-hydroxyethyl)benzene (**6a**) and 112 mg (98%) of optically active ethyl p-tolyl sulfoxide. **6a**: bp 116-118 °C (20 Torr); ^1H NMR (500 MHz, $CDCl_3$) δ 1.40 (d, J = 6.5 Hz, 3 H, CH_3), 3.00 (br s, 1 H, OH), 4.76 (q, J = 6.5 Hz, 1 H, CH), 7.17-7.27 (m, 3 H, 4,5,6-ArH), 7.33 (s, 1 H, 2-ArH); IR (neat) 3338 cm^{-1} (OH), MS (m/z) 156 (M^+); $[\alpha]^{25}_D$ +38.6° (c = 1.5, acetone). Anal. Calcd for C_8H_9ClO: C, 61.35; H, 5.79. Found: C, 61.20; H, 5.85. **6b**: yield 94.8 mg (89%); bp 116-117 °C (19 Torr); ^1H NMR (500 MHz, $CDCl_3$) δ 1.43 (d, J = 6.5 Hz, 3 H, CH_3), 2.59 (br s, 1 H, OH), 4.80 (q, J = 6.5 Hz, 1 H, CH), 7.14-7.25 (m, 3 H, 4,5,6-ArH), 7.31 (s, 1 H, 2-ArH); IR (neat) 3338 cm^{-1} (OH); MS (m/z) 156 (M^+); $[\alpha]^{25}_D$ -39.0° (c = 1.2, acetone). Anal. Calcd for C_8H_9ClO: C, 61.35; H, 5.79. Found: C, 61.20; H, 5.84. Optical purities of the alcohols **6a** and **6b** were determined by ^1H NMR in $CDCl_3$ using $Eu(tfc)_3$ as a chiral shift reagent. Absolute configurations of the alcohols **6a** and **6b** were determined on the basis of the rotation of optically active 1-phenylethanol, which was obtained by the reaction of alcohol **6a** or **6b** with lithium. Ethyl p-tolyl sulfoxide: ^1H NMR ($CDCl_3$) δ 1.77 (t, J = 7 Hz, 3 H, CH_3), 2.40 (s, 3 H, $TolCH_3$), 2.80 (q, J = 7 Hz, 2 H, CH_2), 7.29, 7.52 (ABq, J = 8 Hz, TolH); $[\alpha]^{25}_D$ -202.1° (c = 1.0, acetone). Optical purity and absolute configuration were 100% and S, respectively. **7a**: yield 117 mg (93%); colorless liquid; ^1H NMR (500 MHz, $CDCl_3$) δ 2.33 (s, 3 H, $TolCH_3$), 5.74 (br s, 1 H, CH), 7.13-7.25 (m, 7 H, 4,5,6-ArH, TolH), 7.39 (s, 1 H, 2-ArH); IR (neat) 3392 cm^{-1} (OH); exact mass calcd for $C_{14}H_{13}ClO$ 232.0655, found 232.0614; $[\alpha]^{25}_D$ +43.1° (c = 2.0, acetone). **7b**: yield 114 mg (91%); colorless liquid; ^1H NMR (500 MHz, $CDCl_3$) δ 2.33 (s, 3 H, $TolCH_3$), 5.74 (br s, 1 H, CH), 7.13-7.26 (m, 7 H, 4,5,6-ArH, TolH), 7.38 (s, 1 H, 2-ArH); IR (neat) 3412 cm^{-1} (OH); exact mass calcd for $C_{14}H_{13}ClO$ 232.0655, found 232.0617; $[\alpha]^{25}_D$ -42.9° (c = 2.0, acetone). Optical purities of the alcohols **7a** and **7b** were determined by the same procedures as **6a** and **6b**.

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Registry No. **1a**, 20268-16-0; **1b**, 135145-16-3; **1c**, 135145-17-4; **2** (isomer 1), 135145-18-5; **2**(isomer 2), 135145-19-6; **3a** (isomer 1), 135145-20-9; **3a** (isomer 2), 135145-21-0; **3b** (isomer 1), 135145-22-1; **3b** (isomer 2), 135145-23-2; **3c** (isomer 1), 135145-24-3; **3c** (isomer 2), 135145-25-4; **4**, 67529-36-6; **5a** (isomer 1), 135145-26-5; **5a** (isomer 2), 135145-27-6; **5b** (isomer 1), 135145-28-7; **5b** (isomer 2), 135145-29-8; **5c** (isomer 1), 135145-30-1; **5c** (isomer 2), 135145-31-2; **5d** (isomer 1), 135145-32-3; **5d** (isomer 2), 135145-33-4; **6a**, 120121-01-9; **6b**, 135145-34-5; **7a**, 135145-35-6; **7b**, 135145-36-7; CH_3CHO, 75-07-0; C_6H_4CHO, 100-52-7; p-$CH_3C_6H_4CHO$, 104-87-0; p-$CH_3OC_6H_4CHO$, 123-11-5; p-$CF_3C_6H_4CHO$, 455-19-6; EtMgBr, 925-90-6; PhMeBr, 100-58-3; n-BuLi, 109-72-8; PhLi, 591-51-5.

Selective Ether Cleavage Reactions of 4,6-Dialkoxy-2-(trifluoromethyl)pyridine Mono- and Dicarboxylates

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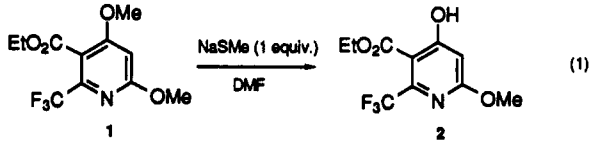
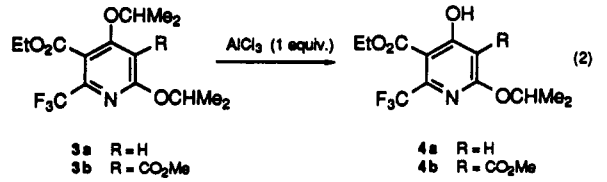
Recent reports from these laboratories have disclosed the synthesis[1,2] and utility[2] of 4,6-dialkoxy-2-(trifluoromethyl)pyridine-3-carboxylates and 4,6-dialkoxy-2-(trifluoromethyl)pyridine-3,5-dicarboxylates as herbicides or herbicide intermediates. Although a variety of 4,6-dialkoxypyridine-3-carboxylates were derived from the corresponding dihydroxypyridines by alkylation with an excess amount of alkyl halides, the methodology permitted the synthesis of only those dialkoxy derivatives wherein the two alkoxy groups are identical. For a complete structure-activity correlation study we required examples of dialkoxypyridines with nonidentical alkoxy groups. In this paper, we describe the regioselective partial ether cleavage reactions of some symmetrical 4,6-dialkoxy-2-(trifluoromethyl)pyridine mono- and dicarboxylates to the corresponding monoalkoxy derivatives and their subsequent elaboration to the unsymmetrical dialkoxypyridines.

The reaction of dimethoxypyridine **1** with 1 equiv of sodium methanethiolate in DMF at 80 °C resulted in clean conversion to the methoxypyridinol **2** in 76% yield (eq 1).



1 2 (1)

Likewise, the diisopropoxypyridines **3a** and **3b** underwent selective cleavage of one of the isopropoxy groups when treated with a stoichiometric amount of anhydrous aluminum chloride at 0 °C to provide isopropoxypyridinols **4a** and **4b** in 83% and 80% yield, respectively (eq 2).[3]

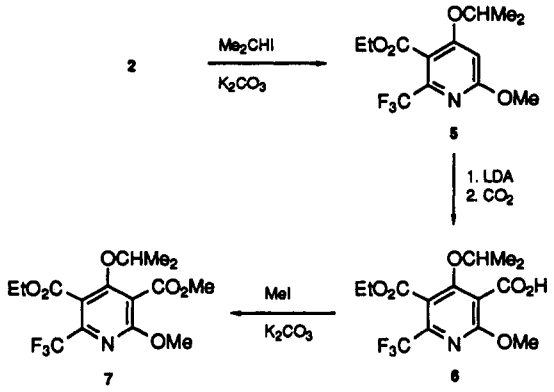


3a R = H
3b R = CO_2Me
4a R = H
4b R = CO_2Me (2)

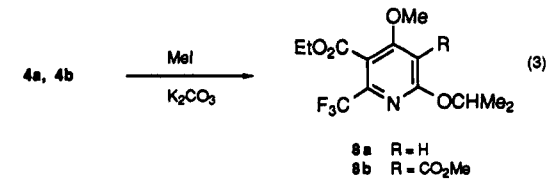
(1) Lee, L. F.; Normansell, J. E. *J. Org. Chem.* 1990, *55*, 2964.
(2) Lee, L. F. Eur. Pat. Appl. EP 181 311, 1986; U.S. Patent 4 609 399, 1986; *Chem. Abstr.* 1986, *105*, 97334.

0022-3263/91/1956-5726$02.50/0

Scheme I



Determining the regiochemistry of ether cleavage from the NMR spectra of **2**, **4a**, and **4b** proved to be tenuous. The structures were determined unambiguously as follows (Scheme I). Alkylation of **2** with isopropyl iodide using potassium carbonate as the base gave **5** in 76% yield. Metalation of **5** with LDA generated the corresponding pyridine anion, which upon quenching with CO_2 and acidic workup provided the crystalline carboxylic acid **6** in 78% yield. Conversion of **6** to the methyl ester **7** was accomplished by alkylation with methyl iodide. X-ray analysis of **6** confirmed the presence of the isopropoxy group in the 4-position and the methoxy group in the 6-position of the pyridine ring (Figure 1, supplementary material), thereby establishing the structures of **2** and **5** and the regiochemistry of ether cleavage depicted in eq 1. In order to determine the structures of pyridinols **4a** and **4b**, they were alkylated with methyl iodide to obtain **8a** and **8b** in 69% and 64% yield, respectively (eq 3). The ^1H NMR spectra



8a R = H
8b R = CO_2Me

of dialkoxypyridines **8a** and **5** were almost identical except for the chemical shift of the isopropyl methine signal (δ 5.28 and 4.51, respectively) indicating that they were regioisomers. Similarly, the regioisomeric nature of **8b** and **7** was ascertained by comparison of their NMR spectra. The possibility of N-methylated structures for **8a** and **8b** could be ruled out based on the fact that the methyl protons and carbon did not show any coupling with the trifluoromethyl fluorines in the ^1H and the ^{13}C spectra.[4] Having determined the structures of **8a** and **8b**, the identity of pyridinols **4a** and **4b** as well as the regiochemistry of ether cleavage depicted in eq 2 were established by extrapolation.

Another structural aspect of pyridinols **2**, **4a**, and **4b** deals with the possibility of hydroxypyridine–pyridone tautomerism. Ultraviolet and infrared spectroscopy have been extensively used to assess the qualitative nature of such prototropic equilibria.[5-7] The IR spectra of alkoxypyridinols **2**, **4a**, and **4b** in neat form and in CCl_4 solutions exhibited broad OH bands. In addition, their C=O bands were shifted by 60–75 cm^{-1} to the lower frequencies relative to the C=O bands of the corresponding dialkoxypyridines[8] **1**, **3a**, and **3b**, respectively, indicating intramolecular hydrogen bonding.[9] In addition, the UV spectra of **2**, **4a**, and **4b** resembled very closely those of **1**, **3a**, and **3b** in ethanol solutions.[8] Although the appropriate N-alkylated pyridones were not available for more complete UV studies, the IR and UV data, in conjunction, lead us to believe that the pyridinols **2**, **4a**, and **4b** exist predominantly in the hydroxypyridine form in undiluted state as well as in ethanol and CCl_4 solutions.[10] Strongly electron-withdrawing substituents α to the pyridine nitrogen are known to shift the equilibrium to favor the hydroxypyridine tautomer by lowering the basicity of the nitrogen atom.[11] Furthermore, intramolecular hydrogen bonding can preferentially stabilize the hydroxypyridine structure. Although both of these factors may be operative in the pyridinols at hand, the latter must be relatively less important since the hydroxypyridine tautomer predominates even in a protic solvent such as ethanol.

The selectivities depicted in eqs 1 and 2 may be explained by invoking an initial complexation of the thiolate or aluminum chloride with the carboxylic ester group, thereby causing a preferential cleavage of the ether linkage in the near vicinity. Such directing effects of neighboring carbonyl substituents have been documented previously in the demethylation of polymethoxybenzene derivatives with several Lewis acids[12,13] as well as thiolates.[14-16] Our results demonstrate that the selectivity observed in the aromatic series is readily translated to the cleavage of 4,6-dialkoxy-2-(trifluoromethyl)pyridine mono- and dicarboxylates. Previous reports indicate that simple 2,4-dialkoxypyridine derivatives generally undergo ether cleavage in the 2-position when treated with acidic reagents such as HCl and HBr.[17] Likewise, 2,4-dimethoxyquinoline derivatives are selectively demethylated in the 2-position by HBr.[18] The selective cleavages of **3a** and **3b** with

(3) Both of the isopropoxy groups in **3b** were cleaved upon treatment with 2.5 equiv of aluminum chloride in methylene chloride at room temperature for 4 h.

(4) For examples of *N*-methyl-6-(trifluoromethyl)-2-pyridones and the long-range ^1H and ^{13}C coupling of *N*-Me protons and carbon with the trifluoromethyl fluorines, see ref 1.

(5) For a comprehensive review, see: Elguero, J.; Marzin, C.; Katritzky, A. R.; Linda, P. *The Tautomerism of Heterocycles*. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1976; Supplement 1.

(6) (a) Haller, R. *Tetrahedron Lett.* **1965**, 3175. (b) Muller, E.; Haller, R.; Merz, K. W. *Chem. Ber.* **1966**, *99*, 445.

(7) Kitagawa, T.; Mizukami, S.; Hirai, E. *Chem. Pharm. Bull.* **1978**, *26*, 1403.

(8) The IR and UV data of **1** and **3a** are as follows: **1** IR (Nujol) C=O 1735, (CCl_4) C=O 1750 cm^{-1}; UV (EtOH) λ_{max} 203 nm (ϵ 21 000), 266 (900); **3a** IR (Neat) C=O 1740, (CCl_4) C=O 1745 cm^{-1}; UV (EtOH) λ_{max} 205 nm (ϵ 31 200), 268 (1500).

(9) Compound **4b** exhibited two carbonyl bands in the IR spectrum: a hydrogen-bonded ester group (1665 cm^{-1} in neat form and in CCl_4) and a nonchelated ester group (1745 cm^{-1} in neat form and 1740 cm^{-1} in CCl_4).

(10) Although the major absorption bands in the UV spectra of **3b** and **4b** are identical, the differences seen in the absorption bands with relatively low extinction coefficients may be indicative of a small contribution of the pyridone tautomer of **4b**.

(11) (a) Gordon, A.; Katritzky, A. R.; Roy, S. K. *J. Chem. Soc. B* **1968**, 556. (b) Katritzky, A. R.; Rowe, J. D.; Roy, S. K. *J. Chem. Soc. B* **1967**, 758.

(12) Paul, E. G.; Wang, P. S. *J. Org. Chem.* **1979**, *44*, 2307 and references cited therein.

(13) Bhatt, M. V.; Kulkarni, S. U. *Synthesis* **1983**, 249 and references cited therein.

(14) Hansson, C.; Wickberg, B. *Synthesis* **1976**, 191.

(15) Asker, W.; Shalaby, A. F. A. M.; Zayed, S. M. A. D. *J. Org. Chem.* **1985**, *23*, 1781.

(16) Evers, M. *Chem. Scr.* **1986**, *26*, 585 and references cited therein.

(17) den Hertog, H. J.; Burrman, D. J. *Recl. Trav. Chim. Pay-Bas.* **1956**, *75*, 257 and references cited therein.

(18) Narasimhan, N. S.; Joag, S. D. *Ind. J. Chem., Sect. B* **1981**, *20B*, 543.

aluminum chloride represent a reversal of the general trend and further substantiate the regiodirecting influence of a carboxylate group.

Experimental Section

Melting point are uncorrected. All NMR spectra were recorded in $CDCl_3$ unless noted. ^1H NMR spectra were measured at either 400 or 300 MHz; ^{13}C spectra and ^{19}F spectra were measured at 75 and 282 MHz, respectively. ^1H and ^{13}C NMR shifts are expressed in parts per million (ppm) downfield from TMS; 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 Hz. ^{19}F NMR spectra were recorded 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. UV and IR spectra were recorded on standard analytical instruments. Preparative high-performance liquid chromatography (HPLC) was carried out with a Waters PrepLC System 500A on PrePak silica gel columns. Radial chromatography was performed with a Harrison Research Model 7924 chromatotron. 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. Elemental analysis was performed by Atlantic Microlab, Inc., Atlanta, GA.

Compounds 1 and **3a** were obtained according to the procedures described in the literature.[1]

Ethyl 4-Hydroxy-6-methoxy-2-(trifluoromethyl)-3-pyridinecarboxylate (2). A solution of 14.0 g (0.05 mol) of 1 and 3.5 g (0.05 mol) of sodium methanethiolate in 25 mL of dry DMF was heated at 80 °C for 28 h. The reaction mixture was cooled to room temperature, diluted with water (150 mL), and washed with ether (2 × 100 mL). The aqueous layer was acidified with 10% HCl and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated. Purification of the residue by chromatography (preparative HPLC, SiO_2, 10% ethyl acetate/hexane) gave 10.1 g (76%) of **2** as a colorless liquid: IR (neat) OH 3050–3400 (br), C=O 1675, (CCl_4) OH 3050–3450 (br), C=O 1675 cm^{-1}; UV (EtOH) λ_{max} 204 nm (ϵ 21 600), 266 (1500); ^1H NMR δ 1.32 (t, J = 7.2 Hz, 3 H), 3.88 (s, 3 H, OCH_3), 4.35 (q, J = 7.2 Hz, 2 H), 6.3 (s, 1 H, ArH), 11.18 (br s, 1 H, OH); ^{13}C NMR δ 13.35, 54.18, 62.73, 98.75, 117.45, 121.7 (q, $^1J_{CF}$ = 265 Hz), 147.05 (q, $^2J_{CF}$ = 34.5 Hz), 165.3, 168.33, 169.46; ^{19}F NMR δ -65.38. Anal. Calcd for $C_{10}H_{10}F_3N_1O_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.47; H, 7.65; N, 4.68.

5-Ethyl 3-Methyl 2,4-Bis(1-methylethoxy)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (3b). A solution of 22.7 g (0.06 mol) of 5-(ethoxycarbonyl)-2,4-diisopropoxy-6-(trifluoromethyl)-3-pyridinecarboxylic acid[1] and 14.2 g (0.1 mol) of methyl iodide in 100 mL of dry DMF was added to 13.8 g (0.1 mol) of anhydrous K_2CO_3. The resulting slurry was vigorously stirred at room temperature overnight and then filtered to remove insoluble salts. The filtrate was diluted with water (200 mL) and extracteed with ether (3 × 200 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated. Purification of the residue by Kugelrohr distillation (0.5 mm, 125–130 °C) of the crude product gave 20.4 g (87%) of **3b** as a colorless oil: IR (neat) C=O 1745, (CCl_4) C=O 1740 cm^{-1}; UV (EtOH) λ_{max} 207 nm (ϵ 25 400), 277 (2300); ^1H NMR δ 1.22 (d, J = 6 Hz, 6 H, $(CH_3)_2$), 1.28 (d, J = 6 Hz, 6 H, $(CH_3)_2$), 1.30 (t, J = 7.2 Hz, 3 H), 3.86 (s, 3 H, CO_2CH_3), 4.31 (q, J = 7.2 Hz, 2 H), 4.47 (h, J = 6 Hz, 1 H), 5.30 (h, J = 6 Hz, 1 H); ^{13}C NMR δ 13.80, 21.71, 22.27, 52.69, 62.13, 71.06, 78.01, 112.18, 117.86, 120.61 (q, $^1J_{CF}$ = 273.6 Hz), 142.95 (q, $^2J_{CF}$ = 35.03 Hz), 161.1, 161.74, 164.18, 164.7; ^{19}F NMR δ -67.47. Anal. Calcd for $C_{17}H_{22}F_3N_1O_6$: C, 51.91; H, 5.64; N, 3.56. Found: C, 52.00; H, 5.64; N, 3.53.

Ethyl 4-Hydroxy-6-(1-methylethoxy)-2-(trifluoromethyl)-3-pyridinecarboxylate (4a). To a solution of 16.8 g (0.05 mol) of **3a** in 200 mL of methylene chloride at 0 °C was added 6.7 g (0.05 mol) of anhydrous aluminum chloride in small portions. After 2 h at 0 °C, 100 mL of 20% HCl solution was added and the mixture was stirred for an additional 30 min. The methylene chloride layer was separated, washed with brine, dried ($MgSO_4$), and evaporated. Purification of the residue by chromatography (preparative HPLC, SiO_2, 10% ethyl acetate/hexane) gave 12.2 g (83%) of **4a** as a colorless liquid: IR (neat) OH 3000–3450 (br), C=O 1680, (CCl_4) OH 3050–3450 (br), C=O 1675 cm^{-1}; UV (EtOH) λ_{max} 204 nm (ϵ 25 100), 267 (1800); ^1H NMR δ 1.25 (d, J = 6.2 Hz, 6 H, $(CH_3)_2$), 1.31 (t, J = 7.16 Hz, 3 H), 4.33 (q, J = 7.16 Hz, 2 H), 5.25 (h, J = 6.2 Hz, 1 H), 6.25 (s, 1 H, ArH),11.15 (br s, 1 H, OH); ^{13}C NMR δ 13.38, 21.77, 62.6, 70.05, 99.22, 104.86, 120.9 (q, $^1J_{CF}$ = 273.5 Hz), 147.29 (q, $^2J_{CF}$ = 35.2 Hz), 165.06, 168.38, 169.48; ^{19}F NMR δ -65.41. Anal. Calcd for $C_{12}H_{14}F_3N_1O_4$: C, 49.15; H, 4.81; N, 4.78. Found: C, 49.22; H, 4.80; N, 4.75.

5-Ethyl 3-Methyl 4-Hydroxy-2-(1-methylethoxy)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (4b). Treatment of 2.95 g (0.0075 mol) of **3b** with 1 g (0.0075 mol) of anhydrous aluminum chloride as above and purification of the crude product by chromatography (preparative HPLC, SiO_2, 10% ethyl acetate/hexane) gave 2.1 g (80%) of **4b** as a colorless oil: IR (neat) OH 3050–3300 (br), C=O 1745, C=O 1665, (CCl_4) OH 3100–3350 (br), C=O 1740, C=O 1665 cm^{-1}; UV (EtOH) λ_{max} 207 nm (ϵ 21 800), 253 (3700), 292 (2800); ^1H NMR δ 1.19 (t, J = 7.2 Hz, 3 H), 1.24 (d, J = 6.1 Hz, 6 H, $(CH_3)_2$), 3.83 (s, 3 H, CO_2CH_3), 4.26 (q, J = 7.15 Hz, 2 H), 5.32 (h, J = 6.1 Hz, 1 H), 12.65 (br s, 1 H, OH); ^{13}C NMR δ 13.5, 21.38, 52.68, 62.02, 71.24, 99.09, 112.51, 120.34 (q, $^1J_{CF}$ = 273.9 Hz), 145.11 (q, $^2J_{CF}$ = 35.03 Hz), 162.3, 163.58, 169.24, 169.96; ^{19}F NMR δ -68.48. Anal. Calcd for $C_{14}H_{16}F_3N_1O_6$: C, 47.87; H, 4.59; N, 3.99. Found: C, 47.76; H, 4.60; N, 3.95.

Ethyl 6-Methoxy-4-(1-methylethoxy)-2-(trifluoromethyl)-3-pyridinecarboxylate (5). A solution of 8.74 g (0.033 mol) of **2** and 17 g (0.1 mol) of isopropyl iodide in 200 mL of acetone was added to 13.8 g (0.1 mol) of anhydrous K_2CO_3. The resulting slurry was vigorously stirred and heated at reflux for 24 h. After being cooled to room temperature, the mixture was filtered to remove insoluble salts and the filtrate was evaporated. The residue was diluted with water (100 mL) and extracted with chloroform (100 mL). The organic layer was washed with brine, dried ($MgSO_4$), and evaporated. Purification of the residue by Kugelrohr distillation (0.5 mm, 90–95 °C) afforded 7.7 g (76%) of **5** as a colorless liquid: ^1H NMR δ 1.25 (d, J = 6 Hz, 6 H, $(CH_3)_2$), 1.26 (t, J = 7.2 Hz, 3 H), 3.85 (s, 3 H, OCH_3), 4.28 (q, J = 7.2 Hz, 2 H), 4.51 (h, J = 6 Hz, 1 H), 6.23 (s, 1 H, ArH); ^{13}C NMR δ 13.89, 21.38, 53.96, 61.77, 72.22, 94.9, 96.04, 121.01 (q, $^1J_{CF}$ = 273.1 Hz), 142.2 (q, $^2J_{CF}$ = 34.5 Hz), 163.98, 164.56, 165.25; ^{19}F NMR δ -67.38. Anal. Calcd for $C_{13}H_{16}F_3N_1O_4$: C, 50.82; H, 5.25; N, 4.56. Found: C, 50.74; H, 5.27; N, 4.53.

2-Methoxy-4-(1-methylethoxy)-6-(trifluoromethyl)-3,5-pyridinedicarboxylic Acid, 5-Ethyl Ester (6). To a -78 °C solution of LDA, prepared from 1.52 g (0.015 mol) of diisopropylamine, 0.015 mol of n-butyllithium, and 10 mL of THF, was added 4.6 g (0.015 mol) of **5** in 20 mL of THF. After 3.5 h at -78 °C, excess dry ice was added and the reaction mixture was slowly warmed to room temperature. The reaction mixture was diluted with water (200 mL) and washed with ether (2 × 100 mL). The aqueous layer was acidified with 10% HCl and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated. Recrystallization of the residue from hexane afforded 4.1 g (78%) of **6** as a white solid: mp 110–111 °C; ^1H NMR δ 1.29 (d, J = 6 Hz, 6 H, $(CH_3)_2$), 1.34 (t, J = 7.2 Hz, 3 H), 4.02 (s, 3 H, OCH_3), 4.38 (q, J = 7.2 Hz, 2 H), 4.77 (h, J = 6 Hz, 1 H), 11.2 (br s, 1 H, CO_2H); ^{13}C NMR δ 14.11, 22.43, 53.26, 55.11, 62.80, 78.79, 113.95, 121.62 (q, $^1J_{CF}$ = 272.25 Hz), 142.53 (q, $^2J_{CF}$ = 34.9 Hz), 162.10, 162.31, 164.35, 164.83; ^{19}F NMR δ -62.58. Anal. Calcd for $C_{14}H_{16}F_3N_1O_6$: C, 47.87; H, 4.59; N, 3.99. Found: C, 47.70; H, 4.66; N, 3.90.

5-Ethyl 3-Methyl 2-Methoxy-4-(1-methylethoxy)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (7). A solution of 2.53 g (0.0075 mol) of **6** and 1.42 g (0.01 mol) of methyl iodide in 15 mL of dry DMF was added to 2 g (0.015 mol) of anhydrous K_2CO_3. The resulting slurry was vigorously stirred at room temperature overnight and then filtered to remove insoluble salts. The filtrate was diluted with water (100 mL) and extracted with ether (3 × 100 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated. Purification of the residue by Kugelrohr distillation (0.5 mm, 120 °C) afforded 2.4 g (88%) of **7** as a colorless oil: ^1H NMR δ 1.21 (d, J = 6 Hz, 6 H, $(CH_3)_2$), 1.28 (t, J = 7.2 Hz, 3 H), 3.86 (s, 3 H, OCH_3), 3.93

(s, 3 H, OCH_3), 4.30 (q, J = 7.2 Hz, 2 H), 4.44 (h, J = 6 Hz, 1 H); ^{13}C NMR δ 13.87, 22.32, 52.98, 54.88, 62.27, 78.27, 111.81, 118.56, 120.57 (q, $^1J_{CF}$ = 273.75 Hz), 143.09 (q, $^2J_{CF}$ = 35.2 Hz), 161.62, 161.93, 164.09, 164.65; ^{19}F NMR δ −67.36. Anal. Calcd for $C_{15}H_{18}F_3N_1O_6$: C, 49.32; H, 4.97; N, 3.83. Found: C, 49.37; H, 5.03; N, 3.79.

Ethyl 4-Methoxy-6-(1-methylethoxy)-2-(trifluoromethyl)-3-pyridinecarboxylate (8a). A solution of 5 g (0.017 mol) of **4a** and 4.26 g (0.03 mol) of methyl iodide in 100 mL of acetone was added to 4.14 g (0.03 mol) of anhydrous K_2CO_3. The resulting suspension was vigorously stirred and heated at reflux for 24 h. After being cooled to room temperature, the mixture was filtered to remove insoluble salts and the filtrate was evaporated. The residue was diluted with water (50 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated. Purification of the residue by chromatography (preparative HPLC, SiO_2, 10% ethyl acetate/hexane) afforded 3.6 g (69%) of **8a** as a colorless oil: ^1H NMR δ 1.25 (d, J = 6.2 Hz, 6 H, $(CH_3)_2$), 1.31 (t, J = 7.16 Hz, 3 H), 4.33 (q, J = 7.16 Hz, 2 H), 5.25 (h, J = 6.2 Hz, 1 H), 6.25 (s, 1 H, ArH), 11.15 (br s, 1 H, OH); ^{13}C NMR δ 13.85, 21.75, 56.23, 62.08, 69.7, 95.44, 114.16, 121.0 (q, $^1J_{CF}$ = 273.2 Hz), 142.35 (q, $^2J_{CF}$ = 35.05 Hz), 164.58, 164.69, 165.48; ^{19}F NMR δ −67.33. Anal. Calcd for $C_{13}H_{16}F_3N_1O_4$: C, 50.82; H, 5.25; N, 4.56. Found: C, 50.98; H, 5.31; N, 4.50.

5-Ethyl 3-Methyl 4-Methoxy-2-(1-methylethoxy)-6-(trifluoromethyl)-3,5-pyridinedicarboxylate (8b). Treatment of 1.2 g (0.0034 mol) of **4b** and 1.42 g (0.01 mol) of methyl iodide in 100 mL of acetone with 1.38 g (0.01 mol) of anhydrous K_2CO_3 as above and purification of the crude product by radial chromatography (SiO_2, 10% ethyl acetate/hexane) gave 0.8 g (64%) of **8b** as a colorless oil: ^1H NMR δ 1.19 (t, J = 7.2 Hz, 3 H), 1.24 (d, J = 6.1 Hz, 6 H, $(CH_3)_2$), 3.83 (s, 3 H, CO_2CH_3), 4.26 (q, J = 7.15 Hz, 2 H), 5.32 (h, J = 6.1 Hz, 1 H), 12.65 (br s, 1 H, OH); ^{13}C NMR δ 13.79, 21.58, 52.87, 60.68, 62.29, 71.18, 110.17, 116.53, 120.57 (q, $^1J_{CF}$ = 273.52 Hz), 142.86 (q, $^2J_{CF}$ = 34.95 Hz), 161.31, 162.88, 163.98, 164.8; ^{19}F NMR δ −67.55. Anal. Calcd for $C_{15}H_{18}F_3N_1O_6$: C, 49.32; H, 4.97; N, 3.83. Found: C, 49.40; H, 4.99; N, 3.82.

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Supplementary Material Available: ORTEP diagram (Figures 1 and 2) and tables of crystallographic data, fractional coordinates, bond distances and angles, isotropic and anisotropic thermal parameters, and hydrogen atom coordinates for 6 (19 pages). Ordering information is given on any current masthead page.

Stereoselective Synthesis of 3-Alkylated Glutamic Acids: Application to the Synthesis of Secokainic Acid

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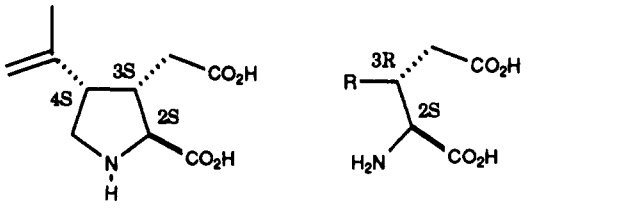
Recently great effort has been devoted to elucidating the physiological role of glutamic acid. Several glutamic receptor subtypes have been identified as a result of biochemical experimentation with natural and synthetic glutamic acids. A physiological function has been tentatively attributed to each subtype.[1] Kainic acid (1) exerts a powerful neuroexcitatory effect on glutamate receptors, but its neurotoxicity has prohibited pharmacological application.[2] After noting that kainic acid and glutamic acid are structurally similar, we addressed the following question: do acyclic analogues of kainic acid like the methallyl- or benzyl-substituted glutamic acids 2 and 3 display the desirable biochemical activity of kainic acid but not the toxic side effects?

Scheme I



1 Kainic acid 2 R = methallyl (seco-kainic acid) 3 R = benzyl

As a first step toward answering this question, we decided to prepare homochiral β-substituted glutamic acids in a stereoselective manner, one that would generate in 2 and 3 the same absolute configuration about C(2) and C(3) that exists in kainic acid, i.e., S and R, respectively (Scheme I).[3] The Michael type addition of the synthetic equivalent of an N-protected glycine anion to enoates can, in theory, provide access to β-substituted glutamates. However, such additions are apparently possible with only a few enoates, and the regeneration of the amino acid functionality in the final products is rather tedious.[4,5] This knowledge prompted us to study the 1,4-addition of lithium dialkylcuprates to oxazolidine 5. The amino-substituted allylic carbon atom of 5 is incorporated into an oxazolidine derived from (R)-serine.[6] Although the stereochemical outcome of conjugate additions to enoates that bear γ-alkyl or γ-alkoxy substituents has been intensively investigated,[7] only a few examples of such additions of

(1) For excellent reviews, see: (a) Watkins, J. C.; Krogsgaard-Larsen, P.; Honorê, T. *Trends Pharmacol. Sci.* **1990**, *11*, 25. (b) Lodge, D.; Johnson, K. M. *Trends Pharmacol. Sci.* **1990**, *11*, 81. (c) Young, B. A.; Fagg, G. E. *Trends Pharmacol. Sci.* **1990**, *11*, 126. (d) Johnson, R. L.; Koerner, J. F. *J. Med. Chem.* **1988**, *31*, 2057.

(2) McGeer, E. G., Olney, J. W., McGeer, P. L., Eds.; *Kainic acid as a Tool in Neurobiology*; Raven Press: New York, 1978.

(3) The absolute stereochemistry of the C(3) carbon is, according to the Cahn–Ingold–Prelog rules, S in kainic acid (1) and R in secokainic acid (2).

(4) (a) El Achqar, A.; Boumzebra, M.; Roumestant, M. L.; Viallefont, P. *Tetrahedron* **1988**, *44*, 5319. (b) Kanemasa, S.; Tatsukawa, A.; Wada, E.; Tsuge, O. *Chem. Lett.* **1989**, 1301. (c) Yamagushi, M.; Torisu, K.; Minami, T. *Chem. Lett.* **1990**, 377.

(5) (a) Schöllkopf, U.; Pettig, D.; Busse, U. *Synthesis* **1986**, 737. (b) Hartwig, W.; Born, L. *J. Org. Chem.* **1987**, *52*, 4357. (c) Pettig, D.; Schöllkopf, U. *Synthesis* **1988**, 173. (d) Schöllkopf, U.; Pettig, D.; Schulze, E.; Klinge, M.; Egert, E.; Benecke, B.; Noltemeyer, M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1194.

(6) (a) Garner, P. *Tetrahedron Lett.* **1984**, *25*, 5855. (b) Garner, P.; Park, J. M. *J. Org. Chem.* **1990**, *55*, 3772.

(7) For selected examples, see: (a) Kruger, D.; Sopchick, A. E.; Kingsbury, C. A. *J. Org. Chem.* **1984**, *49*, 778. (b) Yamamoto, Y.; Nishii, S.; Ibuka, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1572. (c) Leonard, J.; Ryan, G. *Tetrahedron Lett.* **1987**, *28*, 2525. (d) Heathcock, C. H.; Kiyooka, S.; Blumenkopf, T. *J. Org. Chem.* **1984**, *49*, 4214. (e) Yamamoto, Y.; Nishii, S.; Ibuka, T. *J. Chem. Soc., Chem. Commun.* **1987**, 464. (f) Fronza, G.; Fuganti, C.; Grasselli, P. *J. Chem. Soc., Perkin Trans. 1* **1982**, 885. (g) For an ab initio study, see: Dorigo, A. E.; Morokuma, K. *J. Am. Chem. Soc.* **1989**, *111*, 6524. (h) For a molecular mechanics study, see: Bernardi, A. E.; Capelli, A. M.; Gennari, C.; Scolastico, C. *Tetrahedron: Asymmetry* **1990**, *1*, 21.

0022-3263/91/1956-5729$02.50/0