h, affording 1 (27 mg, 44%) after chromatography (SiO_2, hexane/ether = 10/1).

Thermolysis of 3a. A mixture of **3a** (200 mg, 1.2 mmol) and $KHSO_4$ (40 mg, 0.3 mmol) was heated at 200 °C in an air bath for 30 min and chromatographed (SiO_2, hexane/ether = 5/1) to give 103 mg of a volatile compound, which was found to contain **9** (41%) and **1** (trace) by VPC (NPGS, 3 mm i.d. × 3 m, 120 °C).

Registry No. **1**, 19822-67-4; **3a**, 60047-17-8; **5a**, 29171-20-8; **5b**, 29171-21-9; **6b**, 74026-67-8; **7a**, 87575-35-7; **7b**, 81893-37-0; **7c**, 81253-22-7; **8**, 94617-00-2; **9**, 91056-18-7; **10a**, 97277-67-3; **10b**, 97277-68-4; **11**, 13679-86-2.

L-*threo*- and L-*erythro*-3-Fluoroglutamic Acids. Synthesis by Fluorodehydroxylation and Enzymatic Resolution

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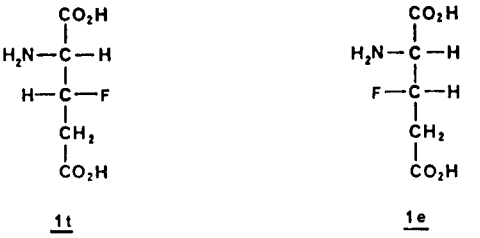
threo- and *erythro*-3-fluoroglutamic acids were prepared by fluorodehydroxylation of *N*-acetyl-3-hydroxyglutamic acids according to Kollonitsch. Following ion exchange column separation of the diastereoisomers, enzymatic deacylation by acylase I afforded optically pure L-isomers of the 3-fluoroglutamic acid. Assignment of structure was achieved by correlation with *cis*- and *trans*-3-fluoropyroglutamic acids. The results indicate predominant inversion of configuration during the fluorodehydroxylation reaction.

Threo and erythro isomers of L-3-fluoroglutamic acid are two potential k_{cat} inhibitors of pyridoxal phosphate dependent enzymes that use glutamic acid as substrate: transaminases, glutamate racemase, and glutamate decarboxylase.[1] However, these acids have not yet been described, even as racemates.

Among the various methods available for synthesis of 3-fluoro amino acids, such as photofluoration,[2] hydroxyl group substitution,[3,4] or aziridine ring opening,[5] we selected the substitution of the hydroxyl group by sulfur tetrafluoride in liquid hydrogen fluoride, a mild and specific method that has been developed by Kollonitsch and coworkers.[6,7]

We report here the synthesis of 3-fluoroglutamic acids (**1e** and **1t**) by fluorodehydroxylation of 3-hydroxyglutamic acid derivatives, the separation of the threo and erythro isomers, and their enzymatic resolution (Chart I).

Chart I. L-*threo*- and L-*erythro*-3-Fluoroglutamic Acids

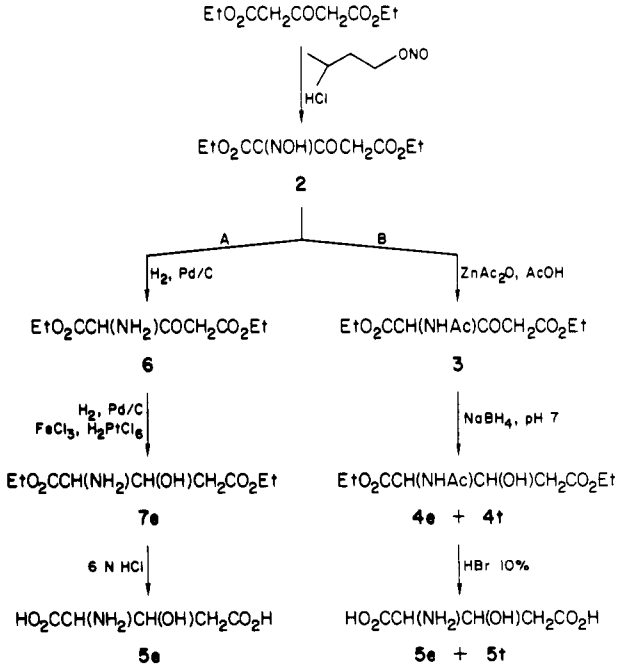


1t **1e**

Results and Discussion

D,L-*erythro*-3-Hydroxyglutamic acid (**5e**) was specifically prepared according to Harington and Randall[8] from diethyl acetonedicarboxylate by catalytic reduction of intermediate diethyl α-aminoacetonedicarboxylate (**6**) (Scheme I, pathway A) whereas a mixture of D,L-*threo*- and -*erythro*-3-hydroxyglutamic acid (**5t** + **5e**) was obtained by reducing diethyl α-acetamidoacetonedicarboxylate (**3**)[9] with sodium borohydride in medium buffered at pH 7 (Scheme I, pathway B) in order to avoid saponification, which we observed, even in ethanol. The high stereoselectivity observed (path A) can be interpreted easily on the basis of Cram's model,[10] if it is assumed that during the catalytic reduction, the reducing agent chelates the carbonyl and the free amino groups and delivers hydrogen to the less hindered face of the chelate (Scheme II).

Scheme I. Syntheses of D,L-*threo*- and -*erythro*-3-Hydroxyglutamic Acids



Hydrolysis of a mixture of diethyl *N*-acetyl-3-hydroxyglutamates (**4e** + **4t**) afforded *threo*- and *erythro*-3-

(1) Walsh, C. *Tetrahedron* **1982**, *38*, 871.
(2) Kollonitsch, J.; Barash, L. *J. Am. Chem. Soc.* **1976**, *98*, 5591.
(3) Sharts, C. M.; Sheppard, W. A. *Org. React.* **1974**, *21*, 158.
(4) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.
(5) Wade, T. N.; Kheribet, R. *J. Chem. Res. Synop.* **1980**, 210.
(6) Kollonitsch J. *Isr. J. Chem.* **1978**, *17*, 53.
(7) Kollonitsch, J.; Marburg, S.; Perkins, L. M. *J. Org. Chem.* **1979**, *44*, 771.
(8) Harington, C. R.; Randall, S. S. *Biochem. J.* **1931**, *25*, 1917.
(9) Leanza, W. J.; Pfister, K. *J. Biol. Chem.* **1953**, *201*, 377.
(10) Cram, D. J.; Abd Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828.

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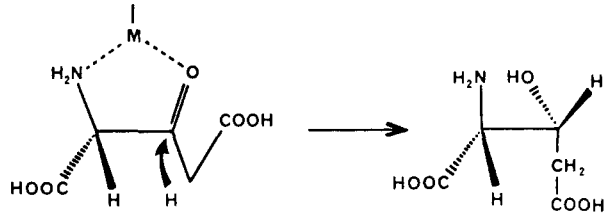
Scheme II. Cram's Model for Catalytic Reduction of 2-Amino-3-ketoglutaric Acid



5e

hydroxyglutamic acids (**5t** + **5e**), which were separated and identified using a cation-exchange column (AG50WX2) according to Lindstedt,[11] the threo isomer (**5t**) being eluted first.

Treatment of D,L-*erythro*-3-hydroxyglutamic acid (**5e**) with sulfur tetrafluoride in liquid hydrogen fluoride at −78 °C yielded exclusively 3-fluoropyroglutamic acid (**8**) which was identified as its methyl ester. We could not conclude whether lactamization occurred prior to or after fluorination. Attempts to regenerate fluoroglutamic acid **1** from the fluoropyroglutamic acid **8** failed; instead 2-oxoglutarate (**10**) was isolated, probably through hydrolysis of the intermediate α,β-didehydroglutamic acid (**9**) (Scheme III).

The undesirable lactam formation which predominated when the unprotected 3-hydroxyglutamic acid was used, could be avoided by lowering the nucleophilicity of the nitrogen atom: treatment of a mixture of *N*-acetyl-3-hydroxyglutamic acids (**11e** + **11t**), prepared according to Scheme IB, with sulfur tetrafluoride in liquid hydrogen fluoride yielded almost quantitatively *N*-acetyl-3-fluoroglutamic acids (**12e** + **12t**) accompanied by only traces of fluoropyroglutamic acids (**8**[12]) (Scheme III).

The D,L-*threo*- and -*erythro*-*N*-acetyl-3-fluoroglutamic acids (**12t** and **12e**) were then separated by using ion-exchange chromatography (Dowex 1-X4 column), and both fractions were deacetylated with acylase I (Scheme III). On the assumption that acylase I is selective for α-acetamido acids of the natural L configuration, we assigned the *R* configuration to the α carbon of the two 3-fluoroglutamic acids (**1e** and **1t**) obtained in this fashion. However, having recently observed lack of selectivity during enzymatic resolutions in the glutamic acid series,[13] we measured the optical purities of **1e** and **1t** by gas chromatography of the *N*-acetyl diisopropyl esters on a chiral column.[14] Compound **1t** proved to be optically pure, whereas the optical purity of **1e** could not be determined directly but was higher than 90%.[15] The order of elution, determined by comparison with the racemates, was consistent with an *R* configuration of the α centers of both isomers. The threo or erythro configuration was assigned to each isomer after lactamization and determination of the cis or trans

Table I. Influence of 18-Crown Ether on the $^3J_{H_2F}$ of 3-Fluoroglutamic Acids

	$^3J_{H_2F}$	$^3J_{H_2F}$ with 18-C-6	$\Delta^3J_{H_2F}$
1t	24.7	24.0	−0.7
1e	27.4	30.7	+3.3

Table II. Stereochemistry of the Fluorodehydroxylation Reaction

compound	% inversion
threonine[7]	92
allothreonine[7]	78
threo-3-hydroxyaspartate[20]	90
erythro-3-hydroxyaspartate[20]	70
5t[a]	94
5e[b]	87

[a] Estimated by fluorodehydroxylation of 79/21 mixture of **5t**/**5e** see Experimental Section. [b] Estimated by fluorodehydroxylation of diastereoisomerically pure **5e**.

structure of both lactams on the basis of analysis of ^{1}H NMR spectra. Coupling constants $J_{H_2H_3}$ of 4.5 Hz and <1 Hz were found for the methyl esters **13c** and **13t**.[16] Such low values have already been observed in the 3-hydroxyproline series and ascribed to considerable puckering of the proline ring.[17] The lactam ring of **13c** and **13t** must thus be also puckered; according to the Karplus equation,[18] $J_{H_2H_3}$ <1 Hz corresponds to an angle close to 90°. This can be achieved only in the trans isomer **13t** (Scheme IV). Furthermore, the J_{H_2F} values, 26.2 Hz for **13c** and 23 Hz for **13t**, are consistent with dihedral angles of 130° and 30° in the conformations depicted in Scheme IV.[19] It follows that the *N*-acetyl-3-fluoroglutamate which is eluted first from the Dowex column corresponds to the threo isomer and the second one to the erythro isomer.

Beguin and co-workers have proposed an empirical rule for identifying the diastereoisomers of 3-fluoroamino acids.[20] This rule relies on the influence of the amino group complexation by 18-crown-6 ether on the chemical shifts and J_{HF} coupling constants. When the crown ether is added, $^3J_{H_2F}$ should increase for the erythro isomer and decrease for the threo isomer.[20] In agreement with Beguin's rule we observed a net increase of $^3J_{H_2F}$ for the *erythro*-3-fluoroglutamate (**1e**) and a very slight decrease ($|\delta\ ^3H_{HF}|$ <1 Hz) for the threo isomer (**1t**) (Table I).

So far, the stereochemical course of the fluorodehydroxylation reaction has been examined in only a few cases. Kollonitsch observed that both isomers of ephedrine yielded the same mixture of fluoro isomers, whereas the reaction occurred with inversion of configuration with threonine and allothreonine;[7] thus he concluded that the mechanism depends on the alcohol, S_N1 for alcohols leading to stable carbocations and S_N2 in other cases (Table II). Beguin and co-workers also observed predominant inversion in the hydroxyaspartic series[20] (Table II).

Our results are in good agreement with these observations since inversion of configuration occurred with both diastereoisomers (Table II). Furthermore, the percentage of inversion is higher with the threo isomer (94%) than

(11) Lindstedt, G. *J. Chromatogr.* **1969**, *40*, 316.

(12) The yield of the reaction and the percentage of lactamization are highly dependent on the relative quantities of **11e** + **11t**, hydrogen fluoride, and sulfur tetrafluoride. Increasing the hydrogen fluoride quantity relative to sulfur tetrafluoride and **11e** + **11t** lowers the lactamization reaction. The yield of reaction, which was almost quantitative when running the reaction on a 50 mg scale, dropped drastically when raising the **11e** + **11t** quantity to the gram scale.

(13) Bory, S.; Dubois, J.; Gaudry, M.; Marquet, A.; Lacombe, L.; Weinstein, S. *J. Chem. Soc., Perkin Trans. 1* **1984**, 475.

(14) König, W. A.; Franke, W.; Benecke, I. *J. Chromatogr.* **1982**, *239*, 227.

(15) The derivatization steps (acetylation and esterification) were straight forward with **1t** but led to complex mixtures with **1e**, precluding direct optical purity determination by gas chromatography. Acylase I is considered as very stereospecific, and the enzymic resolution of **12e** stopped at 50% (as with the threo isomer). Thus **1e** is likely optically pure.

(16) **13c** and **13t** are the methyl esters of lactams **8c** and **8t** derived respectively from the *N*-acetyl-3-fluoroglutamates which were eluted first and second from the Dowex column (Scheme IV).

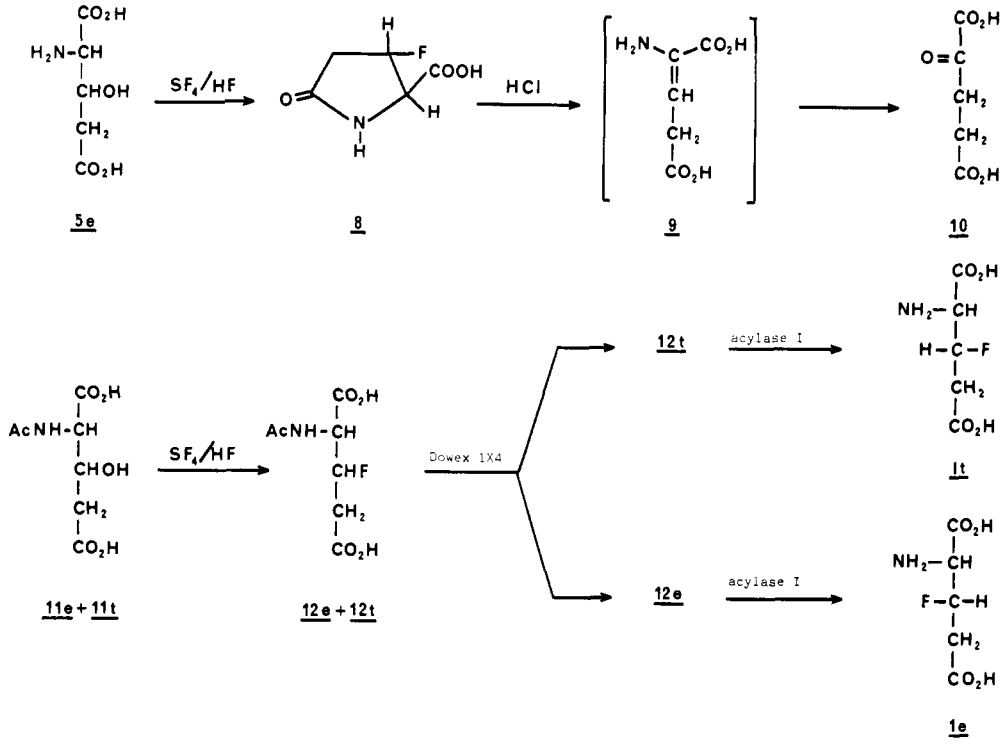
(17) Irreverre, F.; Morita, K.; Robertson, A. V.; Witkop, B. *J. Am. Chem. Soc.* **1963**, *18*, 2824.

(18) Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870.

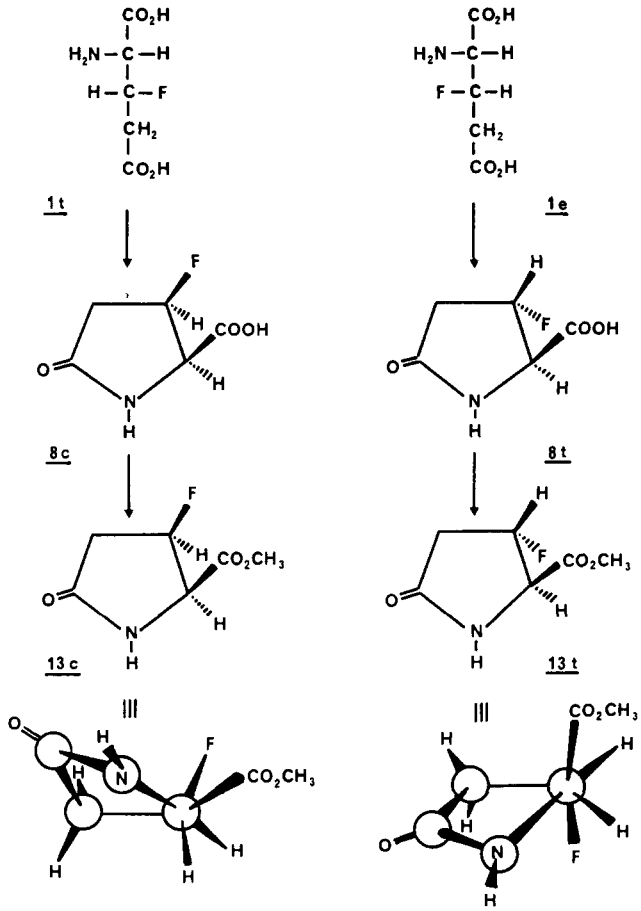
(19) Williamson, K. L.; Li Hsu, Y. F., Hall, F. H., Swager, S., Coulter, M. S. *J. Am. Chem. Soc.* **1968**, *90*, 6717.

(20) Hamman, S.; Salon, M. C.; Beguin, C. *Org. Magn. Reson.* **1982**, *20*, 78.

Scheme III. Syntheses and Resolution of *threo*- and *erythro*-3-Fluoroglutamic Acids



Scheme IV. Lactamization of 3-Fluoroglutamic Acids: Conformation of *cis*- and *trans*-Methyl 5-Oxo-3-fluoropyrrolidine-2-carboxylates



with the erythro isomer (87%). This difference is also consistent with Kollonitsch and Beguin's results; both groups observed a higher percentage of inversion with the threo isomer: 92% for threonine vs. 78% for allothreonine[7] and 90% for *threo*-3-hydroxyaspartate vs. 70% for the erythro isomer.[20] It is probable that the lower percent of inversion, i.e., the larger participation of a S_N1 mechanism for the erythro isomers, originates in less favorable interactions of bulky groups in an S_N2 transition state for the erythro than for the threo isomers.

Experimental Section

General Methods. Melting points were measured using a Kofler hot-stage apparatus and are uncorrected. ^1H NMR and ^{19}F NMR spectra were recorded at 90 MHz on a Jeol FX90Q spectrometer and are reported as follows: (solvent, reference) δ (multiplicity, coupling constants in Hz, number of atoms, group). Optical rotations were determined in a Perkin-Elmer Model 141 polarimeter with 10-cm path length cells. Sulfur tetrafluoride and hydrogen fluoride were handled in a Teflon HF-reaction apparatus (Protection Research Foundation, Minoh, Osaka).

Chemicals. Acetonedicarboxylic acid and isopentyl nitrite were from Prolabo, sulfur tetrafluoride and hydrogen fluoride from Matheson Co., and 18-crown-6 ether was from Borregaard (Norway). AG resins were from Bio-Rad, and Dowex resins were purchased from Fluka. ^2H_2O and $C^2H_3O^2H$ were obtained from C.E.A. (Saclay). All other chemicals were of the highest purity available. Tetrahydrofuran (THF) was dried by refluxing over benzophenone–sodium,[21] and twice distilled water was used for ion-exchange chromatography. Acylase I grade I from porcine kidney (2025 u/mg of protein) was from Sigma Chemical Co.

Diethyl 2-Nitroso-3-ketoglutarate (2). 2 was obtained in 66% yield from ethyl acetonedicarboxylate and isopentyl nitrite according to Harington and Randall.[8] ^1H NMR (C^2HCl_3, Me_4Si): δ 4.33 (q, J = 7, 2 H, CH_2CH_3); 4.17 (q, J = 7, 2 H, CH_2CH_3); 3.78 (s, 2 H, $COCH_2$); 1.35 (t, J = 7, 3 H, CH_2CH_3); 1.27 (t, J = 7, 3 H, CH_2CH_3).

Diethyl 2-Acetamido-3-ketoglutarate (3). 2 (2.3 g, 10 mmol) in dry acetic acid (2.8 mL) was added dropwise in 30 min to a stirred suspension of zinc dust (3.5 g) in a mixture of acetic anhydride and dry acetic acid (1:2 (v/v), 8.5 mL) cooled at 10 °C. After 3 h of stirring at room temperature, filtration, and removal of the solvents, the oily residue was dissolved in chloroform, washed successively with 10% sodium bicarbonate and water and

(21) Seyferth, D.; Spohn, R. J. *J. Am. Chem. Soc.* **1969**, *91*, 3037.

dried. Elimination of solvent under vacuum yielded **3** (1.7 g, 65%, mp 54–55 °C, ether–acetone), R_f 0.46 (ethyl acetate).

^{1}H NMR (C^2HCl_3, Me_4Si): δ 6.8 (m, 1 H, NH); 5.41 (d, J = 6.8, 1 H, CH-N); 4.26 (q, J = 7, 2 H, CH_2CH_3); 4.22 (q, J = 7, 2 H, CH_2CH_3); 3.74 (s, 2 H, CH_2CO); 2.08 (s, 3 H, CH_3CO); 1.32 (t, J = 7, 3 H, CH_2CH_3); 1.28 (t, J = 7, 3 H, CH_2CH_3).

Diethyl *N*-Acetyl-3-hydroxyglutamate (4e + 4t). **3** (9 g, 34.7 mmol) in THF (60 mL) was added to a solution of sodium borohydride (1.28 g, 34.7 mmol) in potassium phosphate buffer (100 mL, 0.1 M, pH 7). After 15 min, extraction with methylene chloride yielded **4** (9 g, 100%) as a 1:1 mixture of the two diastereoisomers. Both isomers could be separated by column chromatography (silica gel, eluent ethyl acetate–hexane, 1:1).

Isomer 1 (R_f 0.29, ethyl acetate–hexane, 1:1) ^{1}H NMR (C^2HCl_3, Me_4Si): δ 7.96 (m, 1 H, N*H*); 4.68 (m, 1 H, CHN); 4.60 (m, 1 H, C*H*OH; 4.19 (q, J = 7, 2 H, CH_2CH_3); 4.15 (q, J = 7, 2 H, CH_2CH_3); 3.94 (m, 1 H, OH); 2.51 (m, 2 H, CH_2COO); 2.03 (s, 3 H, $COCH_3$); 1.24 (t, J = 7, 3 H, CH_2CH_3); 1.22 (t, J = 7, 3 H, CH_2CH_3).

Isomer 2 (R_f 0.16, ethyl acetate–hexane, 1:1) ^{1}H NMR (C^2HCl_3, Me_4Si): δ 6.59 (broad d, 1 H, NH); 4.63 (d of d, J_{H_1NH} = 7.2, $J_{H_1H_2}$ = 4, 1 H, CHN); 4.30 (m, 1 H, C*H*OH); 4.24 (q, J = 7, 2 H, CH_2CH_3); 4.06 (q, J = 7, 2 H, CH_2CH_3); 3.93 (m, 1 H, OH); 2.60 (m, 2 H, CH_2COO); 2.01 (s, 3 H, CH_3CO); 1.27 (t, J = 7, 3 H, CH_2CH_3); 1.23 (t, J = 7, 3 H, CH_2CH_3).

***N*-Acetyl-3-hydroxyglutamic Acid (11e + 11t).** **4e + 4t** (14.5 g, 55 mmol) were saponified for 45 min at room temperature in 1 N sodium hydroxide. The crude mixture was poured on top of a Dowex 1-X4 column (200–400 mesh, 40 × 5.5 cm, formate form). After the mixture was washed with water, elution with 0.5 N formic acid yielded quantitatively **11e + 11t** between 1.3 and 2.6 L.

***N*-Acetyl-3-fluoroglutamic Acid (12e + 12t).** In a typical run, anhydrous liquid hydrogen fluoride (80 mL) and sulfur tetrafluoride (15 mL) were condensed at −196 °C on **11e + 11t** (2 g, 9.75 mmol). After stirring at −78 °C for 1 h, the mixture was taken to dryness under vacuum, dissolved in water, and lyophilized.

The crude products of five experiments were combined and purified on a Dowex 1 × 4 column (200–400 mesh, 52 × 3.6 cm, formate form). After the column was washed with water and 0.5 N formic acid, elution with 1 N formic acid yielded **12t** (460 mg, 2.70–3.30 L) and **12e** (540 mg, 3.37–4 L).

12t ^{1}H NMR (sodium salt ^2H_2O, Me_4Si external): δ 5.37 (m, J_{HF} = 45.5, J_{HH} = 2.2, 1 H, CHF); 4.39 (d of d, J_{HF} = 34.6, J_{HH} = 2.2, 1 H, CHN); 2.49 (m, 2 H, CH_2COO); 2.07 (s, 3 H, CH_3CO).

12e ^{1}H NMR (sodium salt ^2H_2O, Me_4Si external): δ 5.22 (m, J_{HF} = 42.5, J_{HH} = 4.4, 1 H, CHF); 4.51 (d of d, J_{HF} = 18.4, J_{HH} = 4.4, 1 H, CHN); 2.52 (m, 2 H CH_2COO); 2.04 (s, 3 H, CH_3CO).

L-3-Fluoroglutamic Acid (1t). **12t** (450 mg, 2.17 mmol) in water (30 mL, pH 7.0) was incubated with acylase I (182 250 units, potassium phosphate buffer (80 mM, pH 7.0, 30 mL)) for 26 h at 25 °C. The crude mixture was poured on top of a Dowex 1 × 4 column (200–400 mesh, 43.5 × 3.8 cm, formate form). After the mixture was washed with water, elution with 0.25 N formic acid yielded **1t** (100 mg, 56%, 0.98–1.3 L): $[\alpha]^{20}_D$ 4.1° (*c* 1, H_2O); $[\alpha]^{20}_D$ 8.5° (*c* 1, 1 N HCl). ^{1}H NMR (sodium salt, ^2H_2O, Me_4Si external): δ 5.38 (d of m, J_{HF} = 45, 1 H, CHF); 3.91 (d of d, J_{HF} = 26.3, J_{HH} = 3.9, 1 H, CHN); 3.10–2.53 (m, 2 H, CH_2COO). ^{19}F NMR (sodium salt, ^2H_2O, CF_3COO^-) δ −154 (12 lines).

Further elution with 1 N formic acid yielded unreacted **12t**.

L-3-Fluoroglutamic Acid (1e). **12e** (540 mg, 2.60 mmol) was resolved as above with acylase I (202 500 units) for 26 h. The Dowex 1 × 4 column (200–400 mesh, 40.5 × 3.5 cm, formate form) yielded **1e** (87 mg, 40%, 0.92–1.25 L of 0.25 N formic acid): $[\alpha]^{20}_D$ 8° (*c* 1, H_2O); $[\alpha]^{20}_D$ 21.9° (c 1, 1 N HCl) ^{1}H NMR (sodium salt, ^2H_2O, Me_4Si external): δ 5.31 (d of m, J_{HF} = 47, 1 H, CHF); 4.06 (d of d, J_{HF} = 20.5, J_{HH} = 2.6, 1 H, CHN); 2.88–2.30 (m, 2 H, CH_2COO). ^{19}F NMR (sodium salt, ^2H_2O, CF_3COO^-) δ −156 (17 lines).

Further elution with 1 N formic acid yielded unreacted **12e**.

Diethyl 3-Hydroxyglutamate (7e). **2** (10 g, 43.2 mmol) was hydrogenated in the presence of palladium over carbon (10%, 4 g) in hydrogen chloride saturated absolute ethanol (125 mL). After absorption of 2 equiv of hydrogen (3 h), the catalyst was filtered and washed with ethanol. The ethanol was evaporated and the residue dissolved in water (150 mL). The original catalyst was added, along with 5 mL of a solution containing chloroplatinic acid (10%) and ferric chloride (0.5%). Hydrogenation was continued till 1 equiv of hydrogen was absorbed (3 h). After filtration and washing of the catalyst with hot water, elimination of water yielded **7e** (6.8 g).

***erythro*-3-Hydroxyglutamic Acid (5e).** Crude **7e** (6.8 g) was refluxed in 6 N hydrochloric acid (200 mL) for 1.5 h. Following elimination of hydrochloric acid under vacuum, the crude product was purified on a Dowex 1 × 4 column (200–400 mesh, 54 × 3.4 cm, acetate form). Washing with water followed by an elution with a linear gradient of acetic acid (0.2 N → 0.5 N, 2 L) yielded **5e** (0.6–1.1 L), which was crystallized from water (2.18 g, 31%), mp 72 °C (loss of water). ^{1}H NMR (^2H_2O, Me_4Si external): δ 4.54 (m, 1 H, C*H*OH); 3.94 (d, J = 3.6, 1 H, CHN); 2.71 (m, 2 H, CH_2–COO).

***erythro*-*N*-Acetyl-3-hydroxyglutamic Acid (11e).** **5e** (1.6 g, 9.8 mmol) was stirred at room temperature for 2.5 h in methanol (50 mL) containing acetic anhydride (1.8 mL). Following evaporation of solvents, the starting material was eliminated by using AG 50W resin (H^+ form) batchwise. (After washing with water, starting material **5e** could be eluted with 3 N ammonium hydroxide.) Crude **11e** was purified on a Dowex 1 × 4 column (200–400 mesh, 50 × 3.8 cm, formate form). Elution with 0.5 N formic acid afforded **11e** (1.7 g, 85%, 1.87–2.74 L), mp 175–177 °C. ^{1}H NMR (C^2H_3OD, Me_4Si): δ 4.58 (d, J = 5, 1 H, CH-N); 4.37 (q, 1 H, C*H*OH); 2.62 (d, 2 H, CH_2COO); 2.04 (s, 3 H, CH_3CO).

Determination of the Specificity of the Fluorodehydroxylation Reaction. Fluorination of 11e. **11e** was fluorinated according to the procedure previously described for **11e + 11t**. After lyophilization and esterification with diazomethane of the crude mixture of **12t** and **12e**, the methyl esters were separated by high-performance liquid chromatography using a μPorasil column (25 × 0.39 cm, ethyl acetate solvent, UV detection at 210 nm) indicating a **12t/12e** composition of 87/13.

Fluorination of 11t. A mixture of **4t** and **4e** (0.77 g, 2.95 mmol) was refluxed for 2 h in 10% hydrobromic acid (5.5 mL). The crude product was taken to dryness and purified on a AG50WX2 column (100–200 mesh, H^+ form). Following washing with water, elution of **5t + 5e** was achieved with 0.1 N hydrochloric acid. Chromatography of **5t** and **5e** was performed on a AG50WX2 column (100–200 mesh, 110 × 1.8 cm, H^+ form) with 0.07 N hydrochloric acid. A fraction enriched in **5t** was eluted first (2.28–2.56 L) before **5e** (2.72–3.2 L). The free amino group was obtained on an AG1X2 column (100–200 mesh, 24 × 2.3 cm, acetate form, linear gradient 0.2 N → 0.5 N acetic acid) followed by lyophilization (235 mg, 49%). ^{1}H NMR (^2H_2O, Me_4Si external): δ 4.51 (m, 1 H, C*H*OH); 3.83 (d, J = 5, 1 H, C*H*N); 2.74 (m, 2 H, CH_2COO).

Acetylation with acetic anhydride in methanol as previously described yielded a mixture of **11t + 11e** whose composition (**11t/11e** = 79/21) was determined by NMR.

Fluorination of this mixture (50 mg) as previously (hydrogen fluoride 8 mL, sulfur tetrafluoride 1 mL) yielded a crude mixture whose composition was determined as above by HPLC on a μ Porasil column: **12e/12t** = 78/22.

Lactamization of 1t and 1e. Methyl *cis*-3-Fluoro-5-ketopyrrolidine-2-carboxylate (13c). **1t** (15 mg, 0.09 mmol) in water (3 mL, pH adjusted to 5 with 0.1 N sodium hydroxide) was heated at 75–80 °C for 60 h. Unreacted **1t** was eliminated by using an AG50W column, and the crude product was esterified with diazomethane and purified on silica gel (3.5 g, ethyl acetate–methanol, 10:0.5), yielding **13c**. ^{1}H NMR (C^2HCl_3, Me_4Si): δ 5.44 (bd, J_{HF} = 51, 1 H, CHF); 4.47 (dd, J_{HF} = 26.2, J_{HH} = 4.6, 1 H, CHN); 3.88 (s, 3 H, OCH_3); 2.67 (dm, 2 H, CH_2).

Methyl *trans*-3-Fluoro-5-ketopyrrolidine-2-carboxylate (13t). **1e** (11.5 mg, 0.07 mmol) in water (3 mL, pH adjusted to 5 with 0.1 N sodium hydroxide) was treated as above, yielding **13t**. ^{1}H NMR (C^2HCl_3, Me_4Si): δ 5.40 (bd, J_{HF} = 52, 1 H, CHF); 4.40 (bd, J_{HF} = 23, J_{HH} < 1, 1 H, CHN); 3.82 (s, 3 H, OCH_3); 2.65 (dm, 2 H, CH_2).

Influence of 18-Crown-6 Ether on the NMR Spectra of 3-Fluoroglutamic Acids 1t and 1e. After the spectrum of *threo*- or *erythro*-3-fluoroglutamic acid (0.2 N in $C^2H_3O^2H$ containing a trace of Me_4Si and acidified with 8 μL of 7.7 N ^2HCl) was recorded, 18-crown-6 ether was added (final concentration 0.4 N), and a second spectrum was recorded with a special pulse sequence

(irradiation after the acquisition time) in order to minimize the crown ether signals.

Optical Purity Determinations. 1t (4 mg, 25 μmol) was acetylated in dry methanol (100 μL) with acetic anhydride (4 μL) at room temperature for 2 h. Following elimination of solvent under vacuum, the crude product was esterified by refluxing for 30 min in dry 2-propanol–hydrogen chloride (1.5 mol/L; 100 μL). Following elimination of solvent under vacuum, the crude product was analyzed by gas chromatography on a Chrompack-fused silica capillary column (50 m × 0.25 mm) coated with XE60-S–Valine (*S*)-phenylethylamide (175 °C helium (1.5 bar)).

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Action of Diazomethane on Methyl (*Z*(or *E*))-2-(Acylamino)cinnamates. A New Route to Methyl (*Z*)-2-(Acylamino)-3-methylcinnamates

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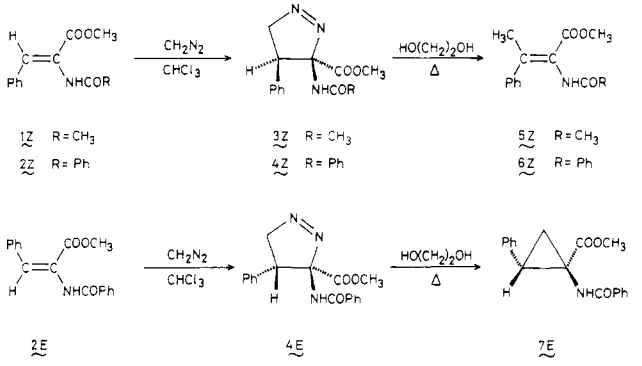
Diazomethane reacts with methyl (*Z*(or *E*))-2-acetamido(or benzamido)cinnamates (**1**, **2**) to afford regio- and stereospecifically (*Z*(or *E*))-4-phenyl-3-acetamido(or benzamido)-3-carbomethoxy-Δ^1-pyrazolines (**3**, **4**). **3Z** and **4Z** undergo pyrolysis to afford stereoselectively methyl (*Z*)-2-acetamido(or benzamido)-3-methylcinnamates (**5Z** and **6Z**). **4E** undergoes pyrolysis to afford stereoselectively methyl (*E*)-2-phenyl-1-benzamidocyclopropane-1-carboxylate (**7E**).

It has recently been reported[1] that ethyl *N*-acetyl-α,β-dehydroalaninate reacts with some 1,3-dipoles in 1,3-dipolar cycloadditions which have proved to proceed regiospecifically regardless of the presence of the acetamido group which exercises a strong directing effect on the addition of electrophilic reagents to the double bond,[2] to afford geminally functionalized heterocyclic amino carboxylic acids.

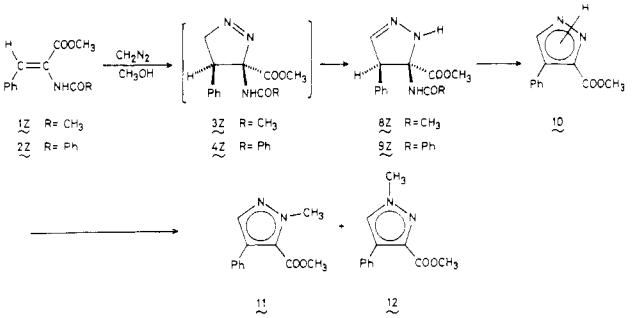
We have now tested the action of diazomethane on methyl (*Z*(or *E*))-2-acetamido(or benzamido)cinnamates[3] (**1**, **2**) and the pyrolysis of the pyrazolines obtained because of our interest in synthesizing prochiral enamides containing tetrasubstituted alkene moieties[4] in order to hydrogenate them.

We have found that diazomethane reacts regiospecifically with methyl (*Z*(or *E*))-2-acetamido(or benzamido)-cinnamates (**1**, **2**) in 1,3-dipolar cycloadditions to afford (*Z*(or *E*))-4-phenyl-3-acetamido(or benzamido)-3-carbomethoxy-Δ^1-pyrazolines (**3**, **4**) in quantitative yields without noticeable influence of the solvent polarity[5] on the cycloaddition rate,[6] as pointed out by Huisgen and others[7] (Scheme I). Furthermore, these cycloadditions have been shown to proceed stereospecifically, as expected,[8] since *Z* olefins gave *Z* pyrazolines and the *E* olefin gave *E* pyrazoline, as we verified by NOE by the irradiation of the hydrogen in the acylamino group in **3Z**, **4Z**, and **4E**.

Scheme I



Scheme II



Cycloaddition occurred without noticeable influence of the solvent polarity on the reaction rate to afford Δ^1-pyrazolines (**3**, **4**), but when methanol was used as a solvent the initially formed Δ^1-pyrazolines (**3**, **4**) underwent sub-

(1) Horikawa, H.; Nishitani, T.; Iwasaki, T.; Inoue, I. *Tetrahedron Lett.* **1983**, *24*, 2193.

(2) See for example: Love, A. L.; Olsen, R. K. *J. Org. Chem.* **1972**, *37*, 3431.

(3) Stereochemistry of all products was unambiguously determined by ^{13}C NMR couplings and NOE: (a) Cutolo, M.; Fiandanese, V.; Naso, F.; Sciacovelli, O. *Tetrahedron Lett.* **1983**, *24*, 4603. (b) Prokofev, E. P.; Karpeiskaya, E. I. *Tetrahedron Lett.* **1979**, 737. (c) Shimohigashi, Y.; Nitz, T. J.; Stammer, C. H. *Tetrahedron Lett.* **1982**, *23*, 3235.

(4) Oro, L. A.; Cabeza, J. A.; Cativiela, C.; Díaz de Villegas, M. D.; Meléndez, E. *J. Chem. Soc., Chem. Commun.* **1983**, 1383.

(5) We tested chloroform, tetrahydrofuran, and dimethylformamide, and for synthetic purposes we chose chloroform because it dissolves a great amount of the product in a few milliliters and it is easily removable.

(6) Although kinetics were not performed, a simultaneous experiment in the same conditions for the three solvents did not show noticeable differences in the disappearance of the departure products (tested by TLC). In all cases the reaction took place in about three days.

(7) See for example: Huisgen, R. *J. Org. Chem.* **1968**, *33*, 2291.

(8) Elguero, J. "Comprehensive Heterocyclic Chemistry"; Katritzky, A. R., Ed.; Pergamon Press: Oxford, 1984; Vol. 5, pp 277–284.

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