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Synthesis of diethyl 3-(trifluoromethyl)glutamate

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Summary — The first synthesis of the two 3-(trifluoromethyl)glutamate chlorhydrates **14** is described. Only the R^*S^* glutamate **15** can be isolated as the pure amino compound; neutralization of the R^*R^* diastereoisomer **14** produces the *trans* 3-(trifluoromethyl)pyroglutamate **4**. The key step of the synthesis is a Michael reaction between 3-chloro-4,4,4-trifluorocrotonate **7** and a glycine derivative.

3-chloro-4,4,4-trifluorocrotonate / Michael substitution / 3-(trifluoromethyl)glutamate *RS* and *SS*

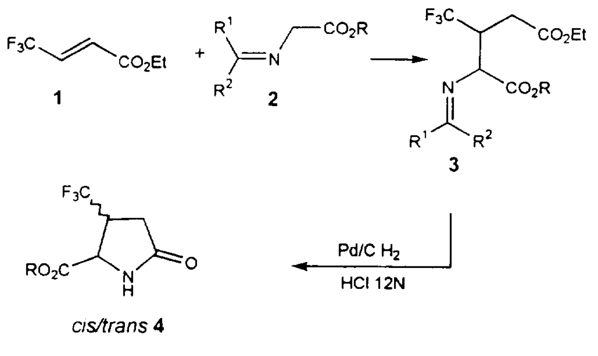
Résumé — Synthèse de 3-(trifluorométhyl)glutamate de diéthyle. *La première synthèse des chlorhydrates* RS *et* SS *des 3-(trifluorométhyl)glutamates de diéthyle **14** est décrite. Seul le glutamate **15** **RS** a été isolé comme aminoacide; la neutralisation du diastéréoisomère **14** fournit le* trans *3-(trifluorométhyl)pyroglutamate d'éthyle 4. L'étape clé de la synthèse est une réaction de Michael entre le 3-chloro-4,4,4-trifluorocrotonate d'éthyle et un dérivé de la glycine.*

3-chloro-4,4,4-trifluoromethyl crotonate / substitution de Michael / 3-trifluoromethyl glutamate de diéthyle *RS* et *SS*

Introduction

Recognition of the wide potential utility of fluorine-containing amino acids has led to their synthesis and biological activity evaluation [1]. The synthesis of unusual fluoroamino acids has continued to produce an incredible range of new compounds [2]. Some of them exhibit high biological activities and are used as chemotherapeutic agents or in studies of the biosynthetic pathways of their corresponding proteinogenic counterparts [3]. Different trifluoromethyl substituted α-amino acids have been synthesized [4]. For example, Burger [5] prepared several α-trifluoromethyl substituted α-amino acids and noticed that 2-(trifluoromethyl)aspartic acid is a stable compound, whereas 2-(trifluoromethyl)glutamic acid undergoes a cyclization leading to a pyroglutamate even at room temperature. This year, Taguchi succeeded in the synthesis of the *trans*-2-(3-carboxy-2,2-difluorocyclopropyl)glycine [6].

In this context, the synthesis of 3-(trifluoromethyl) glutamates has attracted our attention, not only because of their potential use in pharmaceutics but also because of the challenge associated with their preparation. Recently, in an attempt to prepare 3-(trifluoromethyl)glutamic acid, we obtained only the (*cis/trans*)-3-(trifluoromethyl)pyroglutamates (5-oxo-3-(trifluoromethyl)prolinates) [7] (scheme 1).



Scheme 1

As mentioned by Burger [5] for the 2-trifluoromethyl isomer, we were unable to prevent the cyclization of the 3-(trifluoromethyl)glutamate. According to the experimental conditions, the Michael addition gave either exclusively one diastereoisomer of the adduct **3** which produced the (*trans*)-(trifluoromethyl)pyroglutamate **4** or a mixture of the two diastereoisomeric adducts **3** in which the major one was always the precursor of the *trans*-(trifluoromethyl)pyroglutamic acid **4**.

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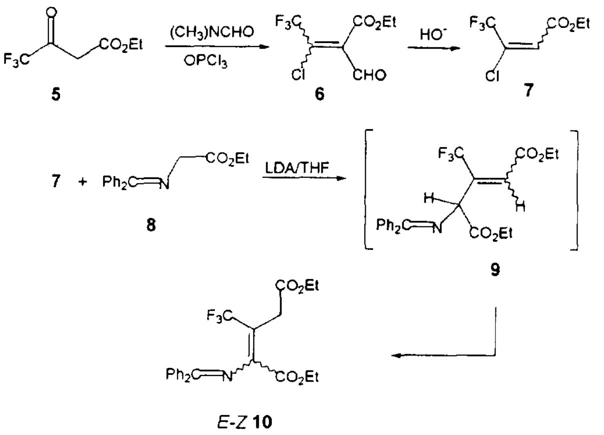
[*] Correspondence and reprints

In order to avoid the cyclization into a pyroglutamate derivative, we studied the synthesis of another precursor. In this paper, we describe our results. Our strategy is based upon a methodology developed by Schöllkopf [8] who described the Michael reaction between methyl β-chlorocrotonate and a glycine derivative.

Results

We initially tried to achieve the substitution of the chlorine atom from the ethyl 3-chloro-4,4,4-trifluorocrotonate **7** by the lithium salt of the glycine derivative **8** to obtain the 3-(trifluoromethyl)glutamate skeleton **9** (scheme 2).



Scheme 2

Recently, we reported [9] the synthesis of the β-chlorocrotonate **7** via a Vilsmeier reaction with ethyl 4,4,4-trifluoroacetoacetate **5** followed by a decarbonylation reaction. Using modified reaction conditions, we enhanced the yield of chlorocrotonate **7** to 80%. The (*E*/*Z*)-enimine **10** was obtained by addition, at −78 °C, of (*E*/*Z*)-chlorocrotonate **7** on the anion of ethyl glycinate **8**, followed by hydrolysis and column chromatography. The structure of the enimine **10** has been solved by X-ray analysis which indicates that the crystallized isomer (^{19}F-NMR chemical shift **10** $\delta = -61.8$ ppm) has the *Z* configuration (fig 1). The ^{19}F-NMR chemical shifts of the two stereoisomers ((*E*)-**10**, $\delta = -60.3$ ppm) were in accordance with data previously reported for similar compounds [10]. The (*E*,*Z*)-enimine **10** resulted from isomerization of the imine **9** which was obtained via the substitution reaction. The NMR spectra of the crude product showed the presence of the Schiff base **9**: its ^{19}F-NMR spectrum gave a signal at −64.6 ppm and the ^{1}H-NMR spectrum gave two signals (6.47 and 5.58 ppm) which could be attributed to the vinylic and allylic hydrogens of the imine **9**. When the crude mixture was kept at room temperature for 24 h, the imine **9** was completely isomerized into the enimine **10**. A 1:1 ratio of (*E*/*Z*)-**10** was isolated after column chromatography (yield 72%). Using different experimental conditions, it was possible to direct the reaction towards the formation of either the *E* isomer or the *Z* one. When the column chromatography was performed with an additional 1% of triethylamine to the eluent (petroleum ether/diethyl ether), fairly pure (*E*)-**10** could be obtained from a 7:3 ratio of a **9**/**10** mixture. When the crude mixture was hydrolyzed at low temperature and the residue chromatographed without triethylamine, the formation of the (*Z*)-**10** isomer was favored. When pure (*Z*)-**10** was stirred for 15 h in a mixture of methylene chloride and triethylamine, a 7:3 ratio of (*Z*/*E*)-**10** was obtained as a result of *Z* to *E* isomerization.

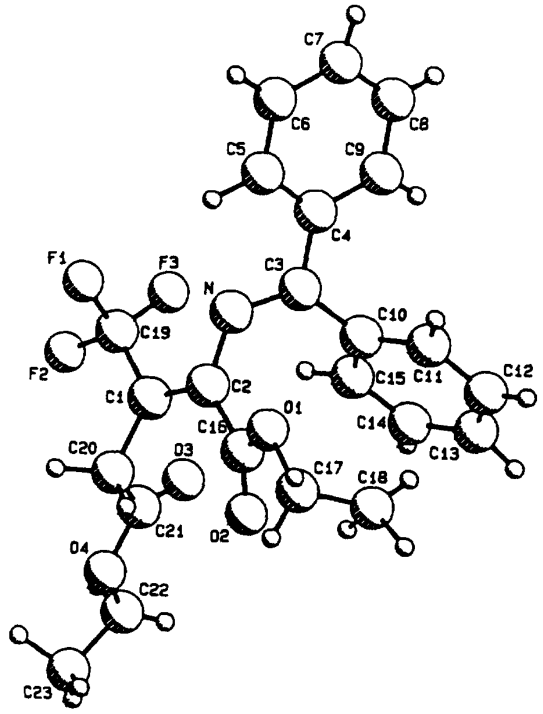
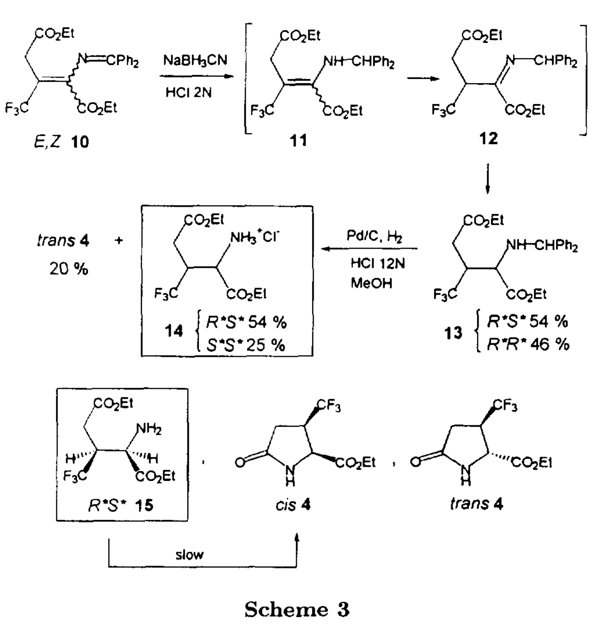


Fig 1. Pluto drawing of the crystallized isomer (*Z*)-**10**.

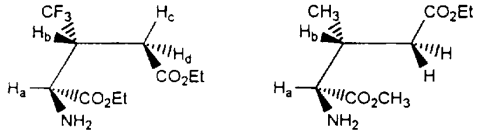


Scheme 3

Reaction of sodium cyanoborohydride with the (E,Z)-enimine **10** in acidic medium afforded a mixture of two diastereoisomers of the glutamate **13** (yield 81%). The ^{19}F-NMR spectrum of the crude mixture showed the presence of the enamine **11** (singlet, $\delta = -59.7$ ppm) which underwent slow isomerization (or quick isomerization on column chromatography) into the imine **12** (doublet, $\delta = -68.2$ ppm)*. A 54:46 ratio of (R^*S^*, R^*R^*)-**13** was obtained. The R^*S^* configuration has been attributed to the major isomer (vide infra). In order to avoid the cyclization of the glutamate **13** into the pyroglutamate, the hydrogenolysis was performed in methanol with hydrochloric acid. A mixture of the two diastereoisomers of the hydrochloride **14** was obtained. This mixture contained about 20% of the (*trans*)-pyroglutamate **4** which was easily identified by its ^{19}F- and ^{1}H-NMR spectra [7]. The ^{19}F-NMR chemical shifts (D_2O) of the hydrochloride derivative **14** were -66.7 ppm for the major isomer (54%) and -67.5 ppm for the minor one (25%). From this mixture it was possible to isolate and recrystallize the major isomer **14**. This pure diastereoisomer was treated with a solution of sodium hydrogen carbonate; this led to the formation of 3-(trifluoromethyl)glutamate **15** which slowly isomerized into (*cis*)-3-(trifluoromethyl)pyroglutamate **4** (several days were required for a total conversion at room temperature). This cyclization reaction allowed the attribution of the (R^*,S^*) configuration to the glutamate **15** and to the corresponding hydrochloride derivative. In another experiment, the mixture of the two diastereoisomers **14** (containing 20% of (*trans*)-pyroglutamate **4**) was neutralized by a 1 M solution of sodium hydrogen carbonate and after the usual work-up, a mixture of compounds was isolated. The ^{19}F-NMR spectrum showed the presence of (R^*,S^*)-glutamate **15** (58%), (*cis*)-pyroglutamate **4** (5%) and (*trans*)-pyroglutamate **4** (37%). This NMR spectrum was recorded again one week later. It showed only a 3:2 ratio of (*cis/trans*)-pyroglutamates **4**. The (R^*,S^*)-glutamate **15** was transformed into (*cis*)-**4**. The rates of the cyclization of the two glutamates **15** are very different for the two isomers: it was possible to isolate the (R^*,S^*) isomer but not the (R^*R^*), which quickly cyclized into the (*trans*)-pyroglutamate **4**.

The cyclization of the (R^*S^*)-**15** diastereoisomer is slower than for the (R^*R^*) one, but it takes place at room temperature, whereas the cyclization of the methyl (RS) compound (CH_3 instead of CF_3) **16** (scheme 4) requires more drastic conditions (140 °C/3 h) [11].

On the basis of hydrogen coupling constants the conformation (R^*S^*)-**15**, described in scheme 4, seems the most likely. The coupling constant between H_a and H_b was found to be 3.7 Hz, which is strongly indicative of a gauche relationship between the two protons. The very different coupling constants between H_b and its neighboring protons H_c and H_d ($J_{H_bH_c} = 4.2$ Hz, $J_{H_bH_d} = 9.2$ Hz) suggest that this conformation is the most probable one; it is also in agreement with the easy cyclization rate at room temperature of the (R^*S^*)-**15** glutamate. Hyperchem molecular modeling shows that this conformation is the most stable one. For the glutamate (RS)-**16**, Viallefont [11] observed a small coupling constant between the two hydrogens H_a, H_b ($J_{ab} = 4.5$ Hz); this value is in agreement with a gauche relationship, but for this compound molecular modeling suggests the conformation (RS)-**16**, described in scheme 4, as the most stable one. These two different conformations, (R^*S^*)-**15** and (RS)-**16**, could explain the difference in their cyclization rates.



*R*S** **15** *RS* **16**

Scheme 4

Crystal structure analysis of (Z)-10

The configuration of the isomer (Z)-**10** has been evidenced by X-ray diffraction analysis. Colorless crystals were obtained from a pentane solution. A crystal of 0.5 × 0.6 × 0.6 mm was mounted on a Nonius CAD-4 diffractometer at 20 °C, using Cu$K\alpha$ radiation (graphite monochromator). The unit cell parameters were refined from setting angles of 25 selected reflections ($9.5 < \theta < 37.8°$). The crystals are monoclinic, space group $P2_1/c$ with $a = 9.811(1)$, $b = 21.969(2)$, $c = 13.334(2)$ Å, $\beta = 128.08(1)°$, $V = 2\,262.3(8)$ Å^3, $M = 433.4$ for $C_{23}H_{22}O_4F_3N$, $D_x = 1.273$ g.cm^{-3}, $Z = 4$, $\mu(\lambda \mathrm{Cu}K\alpha) = 9$ cm^{-1}. Intensity data were collected using $\omega - 4/3\theta$ scan. The 8 811 reflections for half a limiting sphere were measured, leading to 4 507 independent reflections. Among them, 3 222 with $I > 3\sigma(I)$ were used for the structure solution and refinement. The structure was solved using Multan and refined by full-matrix least squares based on F. All the hydrogen atoms were located from ΔF syntheses and assigned with an isotropic thermal parameter of 6. The final agreement index was $R = 0.075$. All the calculations were carried out on a DEC MicroVax 3100-80 computer using the Enraf Nonius SDP [12] system. Atomic coordinates and equivalent isotropic thermal parameters are given in table I and main bond lengths and angles in tables II and III. Lists of anisotropic thermal parameters and H-atom coordinates are available from the authors on request. Figure 1 is a Pluto drawing [13] showing the configuration of **10**.

Experimental section

NMR spectra were recorded in $CDCl_3$ unless otherwise noted, at 200 MHz (^{1}H), 56.4 MHz (^{19}F) and 75.47 MHz (^{13}C). TMS was used as an internal standard for ^{1}H- and ^{13}C-NMR and $CFCl_3$ for ^{19}F-NMR. Chemical shifts are

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* The enimine **10** could be converted into glutamate by catalytic hydrogenation followed by hydrogenolysis. Hydrogenation of (E)-**10** over Pd/C, for 20 h, resulted in the production of a mixture of imine **12** (16%) and (*trans*)-3-(trifluoromethyl)pyroglutamate **4** (60%). A study of this reaction allowed us to point out that the imine **12** was formed quickly. The double bond of compound **12** was slowly hydrogenated and the cyclization into the pyroglutamate occurred very quickly.

Table I. Atomic coordinates and equivalent isotropic displacement parameters (Å^2).

$B_{eq} = 4/3\Sigma_i\Sigma_j\beta_{ij}a_ia_j$

	x	y	z	B_{eq}
F1	0.0141(2)	0.07190(9)	0.6429(1)	6.59(4)
F2	−0.2334(2)	0.1091(1)	0.4979(1)	7.57(4)
F3	−0.0072(2)	0.16188(7)	0.5740(1)	6.57(4)
O1	0.2567(2)	0.02956(9)	0.4143(1)	5.40(4)
O2	−0.0080(2)	0.0597(1)	0.2490(2)	6.86(6)
O3	−0.3083(3)	0.16179(9)	0.2479(2)	8.01(8)
O4	−0.4888(3)	0.0870(1)	0.1282(2)	7.39(7)
N	0.2439(2)	0.09540(8)	0.5808(1)	3.90(4)
C1	−0.0629(2)	0.08074(9)	0.4369(2)	3.98(5)
C2	0.0909(2)	0.08048(9)	0.4606(2)	3.67(4)
C3	0.3538(2)	0.13500(9)	0.5992(2)	3.63(4)
C4	0.5134(2)	0.1421(1)	0.7309(2)	4.02(5)
C5	0.5572(3)	0.0977(1)	0.8223(2)	5.71(7)
C6	0.7035(4)	0.1039(2)	0.9466(3)	7.4(1)
C7	0.8107(4)	0.1530(2)	0.9834(3)	7.4(1)
C8	0.7696(4)	0.1972(1)	0.8956(3)	6.72(9)
C9	0.6216(3)	0.1924(1)	0.7700(2)	5.24(6)
C10	0.3252(2)	0.1732(1)	0.4954(2)	4.06(5)
C11	0.4542(3)	0.1771(1)	0.4812(2)	5.16(5)
C12	0.4250(3)	0.2099(2)	0.3806(2)	6.83(7)
C13	0.2712(4)	0.2395(1)	0.2965(2)	7.16(7)
C14	0.1435(4)	0.2362(1)	0.3098(3)	6.64(8)
C15	0.1699(3)	0.2025(1)	0.4087(2)	5.15(6)
C16	0.1048(3)	0.0561(1)	0.3613(2)	4.56(5)
C17	0.2782(3)	0.0006(2)	0.3254(3)	7.34(8)
C18	0.3231(4)	0.0440(2)	0.2720(3)	10.4(1)
C19	−0.0721(3)	0.1060(1)	0.5372(2)	4.75(5)
C20	−0.2297(3)	0.0585(1)	0.3191(2)	4.69(6)
C21	−0.3433(3)	0.1092(1)	0.2297(2)	5.19(6)
C22	−0.6174(5)	0.1309(2)	0.0327(4)	10.8(2)
C23	−0.7799(8)	0.1023(4)	−0.0518(7)	16.8(3)

Table II. Main bond lengths (Å).

F1–C19	1.339(3)	C1–C2	1.338(3)	C8–C9	1.388(3)
F2–C19	1.326(3)	C1–C19	1.500(4)	C10–C11	1.393(4)
F3–C19	1.329(3)	C1–C20	1.488(2)	C10–C15	1.378(3)
O1–C16	1.327(3)	C2–C16	1.509(4)	C11–C12	1.387(4)
O1–C17	1.471(5)	C3–C4	1.472(2)	C12–C13	1.367(4)
O2–C16	1.196(2)	C3–C10	1.490(3)	C13–C14	1.371(6)
O3–C21	1.187(3)	C4–C5	1.404(4)	C14–C15	1.390(5)
O4–C21	1.313(3)	C4–C9	1.391(3)	C17–C18	1.413(6)
O4–C22	1.470(5)	C5–C6	1.375(3)	C20–C21	1.505(3)
N–C2	1.401(2)	C6–C7	1.369(5)	C22–C23	1.411(7)
N–C3	1.285(3)	C7–C8	1.375(5)		

reported in ppm. Infrared (IR) spectra were recorded on a Perkin-Elmer 297. Mass spectra were recorded using a Nermag R10-10^5 instrument operated at 70 eV. Melting points are uncorrected. Merck 60 (0.063–0.200 mm), Merck 60H silica gels and EGA-Chemie basic alumina gel were used for column chromatography. All reactions involving air-sensitive materials were conducted under a nitrogen atmosphere.

Preparation of ethyl 3-chloro-4,4,4-trifluorocrotonate **7**

To a solution of potassium hydroxide (2.55 g, 45.5 mmol) in water (40 mL) cooled to 5 °C was added the aldehyde **6** (6.16 g, 26.7 mmol). The reaction mixture was left stirring for 1 h and then an aqueous solution of hydrochloric acid 3×10^{-3} M (40 mL) was added. This aqueous phase was extracted with diethylether (4×50 mL). The combined organic layers were washed twice with brine (50 mL) and dried over magnesium sulfate. The solvent was evaporated in vacuo to afford a 4:1 ratio of (E/Z)-**7** (4.38 g, 21.6 mmol); yield 80%. Analytical and spectroscopic data are in accordance with those described in the literature [9].

Diethyl N-(diphenylmethylene)-3-(trifluoromethyl)-3,4-dehydroglutamate **10**

- *General procedure*

A solution of LDA (5.0 mmol) in THF (3 mL) was cooled to −78 °C. A solution of *N*-(diphenylmethylene)glycine ethyl ester **8** (1.5 g, 5.6 mmol) in THF (5 mL) was added and the resulting mixture was stirred for 45 min. Then a solution of **7** (1.0 g, 4.9 mmol) in THF (3 mL) was added dropwise and the reaction was left stirring for several hours at various temperatures. An aqueous solution of 2.5 N hydrochloric acid (25 mL) was added. The aqueous layer was saturated with sodium chloride and extracted with diethyl ether (3 x 50 mL). The organic layer was washed with water (2 x 25 mL) and dried over magnesium sulfate. The solvent was evaporated in vacuo and the resulting residue was purified by chromatography on silica gel or on a basic alumina gel.

- When the reaction mixture was left stirring for 2 h at −78 °C, the ^{19}F-NMR spectrum of the crude product (2.08 g) showed 32% of 88:12 ratio of (Z/E)-**10** and 42% of **9** (**9**, ^{1}H-NMR, δ = 6.47, 5.58 ppm, ^{19}F −64.6 ppm). The crude product was purified by chromatography on silica gel (petroleum ether/methylene chloride, 85:15) to afford an 88:12 ratio of (Z/E)-**10** (1.20 g, 2.78 mmol), yield 56%.

Table III. Main bond angles (°).

C16–O1–C17	115.7(2)	C5–C4–C9	118.1(2)	O1–C16–O2	124.3(3)
C21–O4–C22	117.1(3)	C4–C5–C6	120.8(3)	O1–C16–C2	111.6(2)
C2–N–C3	123.9(2)	C5–C6–C7	120.6(3)	O2–C16–C2	124.1(2)
C2–C1–C19	118.0(2)	C6–C7–C8	119.6(2)	O1–C17–C18	111.0(3)
C2–C1–C20	126.4(2)	C7–C8–C9	120.9(3)	F1–C19–F2	105.6(2)
C19–C1–C20	115.5(2)	C4–C9–C8	120.1(3)	F1–C19–F3	106.2(2)
N–C2–C1	121.7(2)	C3–C10–C11	119.7(2)	F1–C19–C1	112.7(2)
N–C2–C16	118.3(2)	C3–C10–C15	121.3(3)	F2–C19–F3	106.3(2)
C1–C2–C16	119.6(2)	C11–C10–C15	118.9(2)	F2–C19–C1	112.3(2)
N–C3–C4	116.7(2)	C10–C11–C12	120.0(2)	F3–C19–C1	113.1(2)
N–C3–C10	123.2(1)	C11–C12–C13	120.3(3)	C1–C20–C21	112.8(2)
C4–C3–C10	120.1(2)	C12–C13–C14	120.3(3)	O3–C21–O4	124.4(2)
C3–C4–C5	119.6(2)	C13–C14–C15	119.9(2)	O3–C21–C20	125.4(2)
C3–C4–C9	122.3(2)	C10–C15–C14	120.5(3)	O4–C21–C20	110.2(2)
O4–C22–C23	110.0(5)				

(*Z*)-**10** mp 82.5–83 °C.

IR (cm^{-1}): 1 730, 1 630, 1 200–1 160.

^{1}H-NMR δ: 1.08 (t, $J = 7.1$ Hz, 3H), 1.24 (t, $J = 7.1$ Hz, 3H), 3.53 (s, 2H), 3.88 (q, $J = 7.1$ Hz, 2H), 4.15 (q, $J = 7.1$ Hz, 2H), 7.50 (m, 10H).

^{13}C-NMR δ: 13.74, 14.14, 33.23 (q, $^3J_{CF} = 2.5$ Hz), 61.02, 61.66, 115.10 (q, $^2J_{CF} = 29.5$ Hz), 124.01 (q, $^1J_{CF} = 275.3$ Hz), 128.20 (4C), 129.43 (4C), 130.71 (4C), 145.17 (q, $^3J_{CF} = 2.8$ Hz), 163.19, 169.69, 171.16 (q, $^5J_{CF} = 1.4$ Hz).

^{19}F-NMR δ: −61.81 (s).

MS (*m*/*z*): 434 (M$^+$ + H), 29 (Et, 100%).

Anal calc for $C_{23}H_{22}F_3NO_4$: C, 63.74; H, 5.08; N, 3.23. Found: C, 63.49; H, 5.28; N, 3.37.

(*E*)-**10**: ^{1}H-NMR δ: 1.02 (t, $J = 7.2$ Hz, 3H), 1.17 (t, $J = 7.2$ Hz, 3H), 3.48 (s, 2H), 3.74 (q, $J = 7.2$ Hz, 2H), 4.09 (q, $J = 7.1$ Hz, 2H), 7.50 (m, 10H).

^{13}C-NMR δ: 13.37, 14.02, 32.75 (q, $^3J_{CF} = 2.6$ Hz), 61.15, 61.68, 114.14 (q, $^2J_{CF} = 32.3$ Hz), 123.40 (q, $^1J_{CF} = 272.2$ Hz), 128.20 (4C), 128.29 (2C), 128.41 (2C), 128.44 (2C), 131.41, 136.75, 146.50 (q, $^3J_{CF} = 4.32$ Hz), 163.98, 169.56, 172.64.

^{19}F-NMR δ: −60.06 (s).

- The reaction mixture was left stirring for 2 h at −78 °C, then was slowly warmed to room temperature and stirred for 25 h. The ^{19}F-NMR spectrum of the crude product (2.33 g) showed 100% of a 1:1 ratio of (*Z*/*E*)-**10**. The crude product was purified by chromatography on basic alumina gel (petroleum ether/methylene chloride, 7:3) to afford a 1:1 ratio of (*Z*/*E*)-**10** (1.57 g, 3.63 mmol); yield 74%.

Hydrogenation of compound 10

To a mixture of palladium on activated charcoal (0.05 g) and ethanol (5 mL) was added a solution of **10** (0.49 g, 1.1 mmol) in ethanol (5 mL). The reaction mixture was stirred under a hydrogen atmosphere for 20 h. After filtration over celite, ethanol was evaporated in vacuo. The residue (0.47 g) was purified by chromatography on silica gel. A mixture of petroleum ether/diethyl ether (12:1) afforded the imine **12** (0.08 g, 0.2 mmol, 16%). A mixture of methylene chloride/methanol (1:1) afforded the *trans* isomer of **4** (0.16 g, 0.7 mmol, 61%).

12: IR (cm^{-1}): 1 730, 1 655, 1 180–1 110.

^{1}H-NMR δ: 1.08 (t, $J = 7.1$ Hz, 3H), 1.30 (t, $J = 7.1$ Hz, 3H), 2.74 (dd, $^2J = 16.9$ Hz, $J = 3.8$ Hz, 1H), 3.30 (dd, $^2J = 16.9$ Hz, $J = 10.9$ Hz, 1H), 3.90 (m, 2H), 4.33 (2 × dq, $^2J = 10.9$ Hz, $J = 7.3$ Hz, 2H), 4.10–4.40 (m, 1H), 6.15 (s, 1H), 7.10–7.40 (m, 10H).

^{13}C-NMR δ: 13.77, 13.89, 30.85 (q, $^3J_{CF} = 2.2$ Hz), 45.86 (q, $^2J_{CF} = 26.8$ Hz), 60.91, 61.92, 69.76, 125.20 (q, $^1J_{CF} = 281.0$ Hz), 126.96, 126.98 (2C), 127.13, 127.49 (2C), 128.29 (4C), 142.66, 142.73, 153.41 (q, $^3J_{CF} = 2.7$ Hz), 161.39, 169.91.

^{19}F- NMR δ: −68.2 (d, $^3J_{HF} = 8.3$ Hz).

(*trans*)-**4**: ^{1}H-NMR δ: 1.32 (t, $J = 7.1$ Hz, 3H), 2.51 (dd, $^2J = 17.9$ Hz, $J = 4.1$ Hz, 1H), 2.70 (dd, $^2J = 17.8$ Hz, $J = 10.1$ Hz, 1H), 3.43 (m, 1H), 4.25 (q, $J = 7.1$ Hz, 2H), 4.31 (d, $J = 4.0$ Hz, 1H), 7.04 (m, 1H).

^{13}C-NMR δ: 14.03, 29.53, 41.04 (q, $^2J_{CF} = 30.6$ Hz), 55.35, 62.67, 131.64 (q, $^1J_{CF} = 277.5$ Hz), 169.68, 174.48.

^{19}F-NMR δ: −73.66 (d, $^3J_{HF} = 11.2$ Hz).

MS (*m*/*z*): 225 (M$^+$, 6%), 152 (M$^+$-CO_2Et, 100%).

- *Diethyl-*N*-(diphenylmethyl)-3-(trifluoromethyl) glutamate* **13**

To a solution of **10** (0.60 g, 1.37 mmol) in THF (1.3 mL) and methanol (2.6 mL) was added bromophenol blue. Aqueous 2N hydrochloric acid was added dropwise until a yellow coloration was obtained (pH ≈ 3). Sodium cyanoborohydride (0.36 g, 5.7 mmol) was added protionwise over 0.5 h. The reaction mixture was stirred for 0.5 h at room temperature. The yellow coloration was maintained by a dropwise addition of 2 N HCl. Chloroform (10 mL) was added. The layers were separated and the organic phase was washed successively with a solution of 1N $NaHCO_3$ (3 × 5 mL), water (3 × 5 mL) and brine (5 mL). The dried organic layer was evaporated in vacuo. The residue (0.66 g) was purified by chromatography on silica gel (petroleum ether/methylene chloride, 3:2) to afford a 54:46 ratio of (R^*S^*/R^*R^*)-**13** (0.59 g, 1.34 mmol); yield 81%.

(R^*S^*)-**13**: IR (cm^{-1}): 3 330, 1 750, 1 220–1 110.

^{1}H-NMR δ: 1.18 (t, $J = 7.2$ Hz, 3H), 1.27 (t, $J = 7.1$ Hz, 3H), 2.40 (d, $J = 12.0$ Hz, 1H), 2.62 (dd, $^2J = 17.6$ Hz, $J = 4.0$ Hz, 1H), 2.97 (dd, $^2J = 17.6$ Hz, $J = 9.2$ Hz, 1H), 3.25–3.40 (m, 1H), 3.49 (dd, $J = 12.0$ Hz, $J = 3.5$ Hz, 1H), 3.90 and 4.02 (2 × dq, $J = 10.7$ Hz, $J = 7.1$ Hz, 2H), 4.13–4.33 (m, 2H), 4.88 (s, 1H), 7.16–7.45 (m, 10H).

^{13}C-NMR δ: 14.02 (2C), 30.34 (q, $^3J_{CF} = 2.5$ Hz), 42.66 (q, $^2J_{CF} = 25.5$ Hz), 56.88 (q, $^3J_{CF} = 1.4$ Hz), 61.06, 61.57, 65.48, 126.81 (q, $^1J_{CF} = 280.0$ Hz), 127.05–128.67 (10C), 142.18, 143.91, 170.53, 172.80.

^{19}F-NMR δ: −66.98 (d, $^3J_{HF} = 11.4$ Hz).

(R^*R^*)-**13**: ^{1}H-NMR δ: 1.26 (t, $J = 7.1$ Hz, 3H), 1.28 (t, $J = 7.1$ Hz, 3H), 2.25 (dd, $J = 12.0$ Hz, $J = 2.0$ Hz, 1H), 2.58 (dd, $^2J = 16.8$ Hz, $J = 4.2$ Hz, 1H), 2.75 (dd, $^2J = 16.7$ Hz, $J = 7.7$ Hz, 1H), 3.32 (dd, $^2J = 11.0$ Hz, $J = 2.0$ Hz, 1H), 3.33 (m, 1H), 3.95 (m, 2H), 4.17 (m, 2H), 7.17–7.45 (m, 10H).

^{13}C-NMR δ: 14.15 (2C), 31.22 (q, $^3J_{CF} = 2.4$ Hz), 43.19 (q, $^2J_{CF} = 27.0$ Hz), 57.67 (q, $^3J_{CF} = 2.1$ Hz), 61.23, 61.57, 65.48, 126.48 (q, $^1J_{CF} = 280.0$ Hz), 127.05–128.67 (10C), 141.79, 143.60, 171.11, 172.36.

^{19}F-NMR δ: −69.38 (d, $^3J_{HF} = 6.9$ Hz).

Synthesis of diethyl 3-(trifluoromethyl)glutamate hydrochloride 14

To a solution of a 54:46 ratio of (R^*S^*/R^*R^*)-**13** (0.18 g, 0.40 mmol) in methanol (3.0 mL) was added an aqueous solution of 12 N HCl (0.1 mL) and palladium on activated charcoal (0.04 g). The reaction mixture was stirred at room temperature for 4 h under a hydrogen atmosphere. After filtration over celite, the residue was washed successively with methanol (3 × 10 mL) and water (2 × 5 mL). The filtrate was evaporated in vacuo to remove the methanol. The residue was taken up twice with petroleum ether (to remove the benzophenone). The ^{19}F-NMR spectrum of the solid residue (0.09 g) showed 79% of a 7:3 ratio of (R^*S^*/R^*R^*)-**14** and 20% of (*trans*)-**4**. Recrystallization in ethyl acetate afforded (R^*S^*)-**14** as a white solid. Mp 109.5–110 °C.

^{1}H-NMR (D_2O) δ: 1.27 (t, J = 7.1 Hz, 3H), 1.32 (t, J = 7.2 Hz, 3H), 2.93 (dd, ^2J = 17.9 Hz, J = 8.0 Hz, 1H), 3.04 (dd, ^2J = 17.9 Hz, J = 5.4 Hz, 1H), 3.80 (m, 1H), 4.23 (q, J = 7.2 Hz, 2H), 4.35 (q, J = 7.2 Hz, 2H), 4.60 (d, J = 3.8 Hz, 1H).

^{13}C-NMR (D_2O) δ: 13.52, 13.69, 30.48 (q, $^3J_{CF}$ = 2.3 Hz), 40.55 (q, $^2J_{CF}$ = 27.7 Hz), 51.85 (q, $^3J_{CF}$ = 1.9 Hz), 63.25, 64.96, 125.98 (q, $^1J_{CF}$ = 280.1 Hz), 167.87, 172.07.

^{19}F-NMR δ: −66.71 (d, $^3J_{HF}$ = 10.1 Hz).

(R^*R^*)-**14**: ^{19}F-NMR (D_2O) δ: −67.53 (d, $^3J_{HF}$ = 9.4 Hz).

Ethyl 3-(trifluoromethyl)pyroglutamate **4**

To a solution of the above crude mixture (0.09 g) in water was added dropwise an aqueous solution of 1N $NaHCO_3$ to reach a neutral pH. The solution was extracted with methylene chloride (3 × 10 mL). The organic extracts were dried over magnesium sulfate and evaporated in vacuo to afford a white solid (0.06 g). The ^{19}F-NMR spectrum showed 58% of (R^*S^*)-**15** and 42% of a 12:88 ratio of (*cis/trans*)-**4**. The derivative **15** was not stable, and 7 days later the ^{19}F-NMR spectrum showed only a 3:2 ratio of (*cis/trans*)-**4**.

(*cis*)-**4**: IR (cm^{-1}): 3 420, 1 745, 1 720, 1 125.

^{1}H-NMR δ: 1.30 (t, J = 7.3 Hz, 3H), 2.53 (dd, ^2J = 16.7 Hz, J = 9.0 Hz, 1H), 2.67 (dd, ^2J = 16.7 Hz, J = 10.5 Hz, 1H), 3.43 (m, 1H), 4.25 (q, J = 7.1 Hz, 2H), 4.40 (d, J = 8.0 Hz, 1H), 7.00 (m, 1H).

^{13}C-NMR δ: 13.81, 29.70, 44.77 (q, $^2J_{CF}$ = 30.6 Hz), 55.13, 62.40, 124.87 (q, $^1J_{CF}$ = 277.5 Hz), 169.14, 175.17.

^{19}F-NMR δ: −69.04 (d, $^3J_{HF}$ = 7.8 Hz).

MS (m/z): 225 (M^+, 3%); 152 (M^+–CO_2Et, 100%).

Synthesis of diethyl 3-(trifluoromethyl)glutamate **15**

To a solution of (R^*S^*)-**14** (0.16 g, 0.52 mmol) in water (5–10 mL) was added dropwise an aqueous solution of 1 N $NaHCO_3$ to reach a neutral pH. After a classical work-up, the organic layer was dried over magnesium sulfate. The solvent was evaporated in vacuo to afford (R^*S^*)-**15** (0.11 g, 0.40 mmol); yield 78%.

^{1}H-NMR δ: 1.29 (t, J = 7.1 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.61 (s, 2H), 2.66 (dd, ^2J = 17.1 Hz, J = 4.2 Hz, 1H), 2.96 (dd, ^2J = 17.1 Hz, J = 9.2 Hz, 1H), 3.41 (m, 1H), 3.73 (d, J = 3.7 Hz, 1H), 4.12–4.30 (m, 4H).

^{13}C-NMR δ: 13.99, 14.05, 30.35 (q, $^3J_{CF}$ = 2.3 Hz), 42.68 (q, $^2J_{CF}$ = 25.3 Hz), 53.05, 61.13, 61.63, 126.76 (q, $^1J_{CF}$ = 281.3 Hz), 170.86, 173.45.

^{19}F-NMR δ: −67.13 (d, $^3J_{HF}$ = 8.9 Hz).

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