Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 6, pp. 1051-1060, 1994
Elsevier Science Ltd
Printed in Great Britain
0957-4166/94 $7.00+0.00

0957-4166(94)00135-9

Asymmetric Synthesis of α-Trifluoromethyl Substituted Aminoacids *via* 3-Hydroxy-3-trifluoromethyl-2,5-diketopiperazines

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Key words: Methyl trifluoropyruvate; asymmetric synthesis; homochiral α-trifluoromethyl substituted diketopiperazines; homochiral α-trifluoromethyl substituted aminoacids

Abstract: The diastereoselective reaction of organometallic compounds (RMgX, R_2Cd) with *in situ* generated trifluoromethyl substituted cyclic acyl imines representing homochiral α-electrophilic 3,3,3-trifluoroalanine equivalents gives 3-alkyl-3-trifluoromethyl-2,5-diketopiperazines. The corresponding homochiral dipeptide esters are obtained on acidolysis in methanol.

A trifluoromethyl group in α-position of aminoacids exerts considerable polarization effects on neighbouring substituents[3] (pK_a values: Ala-CO_2H: 2.34; (α-TFM)Ala-CO_2H: 1.98; Ala-NH_2: 9.87; (α-TFM)Ala-NH_2: 5.91). This affects the hydrolytic stability of peptides containing α-trifluoromethyl aminoacids[4] and results in increased metabolic stability. The often postulated *quasi*-isosterism between CH_3 and CF_3 groups is still a controversial issue[5]. The van der Waals radii are quite similar (2.0 Å / 2.7 Å), whereas the van der Waals volumes differ significantly (16.8 $Å^3$ / 42.6 $Å^3$)[6]. The steric bulk of a trifluoromethyl group seems to be close to that of an isopropyl group and doubtlessly confers severe conformational restrictions on peptides containing α-trifluoromethyl aminoacids. Furthermore, the lipophilicity is highly increased, as the CF_3 group is probably the most lipophilic substituent known. The site specific incorporation of highly lipophilic amino acids and amino acid analogues into biologically active peptides is a major target in modern peptide chemistry.

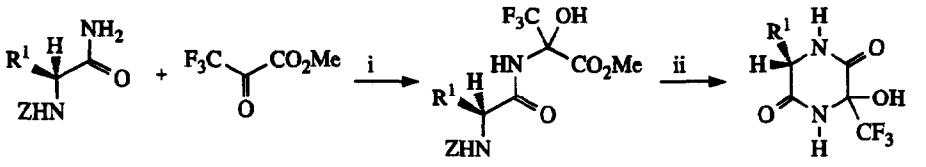
Besides their antibacterial and sometimes antihypertensive properties, α-trifluoromethyl substituted aminoacids gained attention as potent suicide inhibitors of pyridoxalphosphate dependent enzymes (transaminases, decarboxylases)[7,8]. Despite their unique physiological activity[7,9], only few routes to homochiral α-trifluoromethyl α-aminoacids have been reported and these rely on resolution by chemical means[10,11] or by hydrolytic enzymes[12].

Several preparative routes for the synthesis of racemic α-trifluoromethyl aminoacids ((α-TFM)Xaa) have been developed[13]. The most general synthesis proceeds *via* amidoalkylation of carbon nucleophiles with 2-carbamoylimino-3,3,3-trifluoropropionate, an electrophilic synthon for α-trifluoromethyl amino-acids[14-16]. α-Trifluoromethyl aminoacids with unusual side chain substituents are obtained *via* trans-formation of functional groups present in the side chain, *e.g.* isoxazolyl-, pyrazolyl-, and triazolyl-substituted α-trifluoromethylglycine from alkynyl-α-trifluoromethylglycine[17], derivatives of α-trifluoromethyl substituted aspartic acid[18,19], glutamic acid, and α-aminoadipic acid[19], ω-diorgano-phosphinoyl substituted α-trifluoromethyl aminoacids[20].

Results and Discussion

Diketopiperazines are ubiquitous in nature[21] and have received wide attention because of their biological activity or use as model compounds for the structural analyses of peptides[22]. Metallated bislactimethers derived from diketopiperazines are widely used as homochiral nucleophilic templates (homochiral glycine anion equivalents) for the synthesis of non-proteinogenic α-aminoacids[23,24]. Glycine cation equivalents were introduced for instance by Steglich *et al.*[25] or Williams *et al.*[26]. In this paper we report on the synthetic potential of 3-hydroxy-3-trifluoromethyl-2,5-diketopiperazines as homochiral electrophilic synthons for α-trifluoromethyl aminoacids.

Hemiamidal **3** is obtained by addition of a Z-protected aminoacid amide **1** to methyl 3,3,3-trifluoropyruvate **2**[16,27,28]. The adduct **3** is then converted into the corresponding 3-hydroxy-3-trifluoromethyl-2,5-diketopiperazine **4** on removal of the N-protective group by hydrogenation over Pd/C catalyst in methanol.

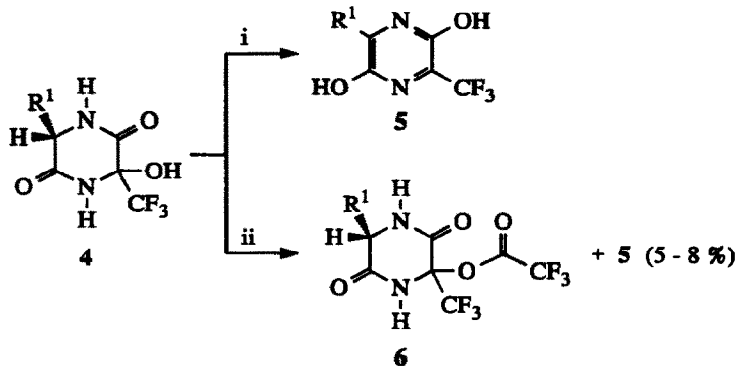


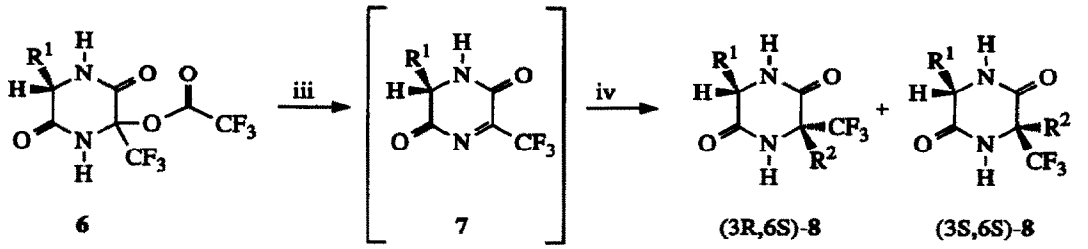
1 **2** **3** **4a**: R^1 = Me **4b**: R^1 = ^{i}Pr **4c**: R^1 = ^{i}Bu **4d**: R^1 = Bzl

i) CH_2Cl_2, r.t.; ii) H_2, Pd/C, MeOH, r.t.

In previous papers we described the synthesis of α-trifluoromethyl aminoacids based on nucleophilic addition to acylimines of 3,3,3-trifluoropyruvates[15,16,18,19]. Usually, an acylimine is obtained from the corresponding hemiamidal with trifluoroacetic anhydride/quinoline[29]. However, dehydration of **4** using this method leads to decomposition and no cyclic acylimine is isolated. Therefore, the cyclic hemiamidal is trifluoro-acetylated at low temperatures with trifluoroacetic anhydride without using a base. Trifluoroacetylation at elevated temperatures results in aromatization *via* an enolization/elimination process to give preferentially compounds of type **5**. This process is suppressed at 0 °C; only minor amounts of **5** (5-8 %) are detected.

Starting from **6**, the cyclic acylimine **7** is generated *in situ* at low temperatures *via* base-catalyzed elimination with the organometallic reagent (R^2MgX or R^2_2Cd) acting both as base and as trapping reagent. Compounds **8** are formed stereoselectively in good yields. In general, the diastereoselectivity of the trapping reaction is better with cadmium organyls; however, higher yields are obtained with Grignard reagents. No reaction takes place on application of the standard reaction protocol to compound **4b**.





i) $(CF_3CO)_2O$, THF, reflux; ii) $(CF_3CO)_2O$, THF, 0 °C; iii) R^2M, THF; iv) R^2M, THF, then buffer, pH 7

Table 1. Alkylation of Diketopiperazines **6**

8	M	T	R^1	R^2	d.e. [%][a] (crude)	d.e. [%][b]	isolated yield [%]	config.[c]
aa	MgX	-100 °C→ -35°C	Me	Me	74	54	62	
aa	CdR^2	-20°C → r.t.	Me	Me	80	61	51	
ab	MgX	-100 °C→ -35 °C	Me	Bzl	82	95	35	(3R,6S)
ca	MgX	-100 °C→ -35 °C	iBu	Me	56	>99	51	
ca	CdR^2	-20 °C → r.t.	iBu	Me	72	97	45	
cb	MgX	-100 °C→ -35 °C	iBu	Bzl	70	80	58	(3R,6S)
cc	MgX	-100 °C→ -35 °C	iBu	Allyl	18	5	45	
da	MgX	-100 °C→ -35 °C	Bzl	Me	64	71	62	(3R,6S)
db	MgX	-100 °C→ -35 °C	Bzl	Bzl	67	94	40	(3R,6S)
dc	MgX	-100 °C→ -35 °C	Bzl	Allyl	11	44	47	(3R,6S)

[a] Determined by ^{19}F-NMR analysis of the crude reaction mixture.
[b] D.e. of product after work-up to quoted yield.
[c] Determined by ^1H-NMR analysis (see Table 2).

As in other analogous cases[22,30-32], the configuration at C-3 of the diketopiperazines containing a benzyl group (**8ab**, **8cb**, **8da**, **8db**, **8dc**) is assigned unambiguously by the large upfield shift of the signals in the ^1H-NMR spectrum corresponding to the groups in a *cis* relationship to the benzyl group (Table 2). In all these

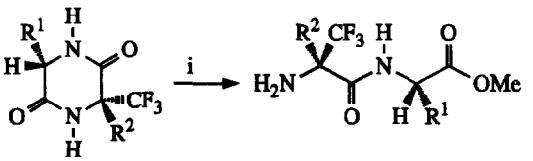
cases, groups R^1 and R^2 in the predominant diastereomer were found to lie *trans* to one another. The observed asymmetric induction can be explained assuming that the reaction proceeds *via* the acylimine **7** in which one of the faces is shielded by R^1. Most of the major diastereomers **(3R,6S)-8** are obtained diastereomerically pure (within the limits of ^{19}F-NMR, > 99 % d.e.) by single recrystallization from ethyl acetate. The optical purity of compound **(3R,6S)-8da** was verified by comparison of the optical rotation index with a sample of the same derivative prepared independently (racemic synthesis of α-trifluoromethylalanine, peptide coupling with Fmoc-L-Phe-Cl, chromatographic resolution of the diastereomers, diketopiperazine formation)[33]. Epimerization at C-6 under the reaction conditions applied can therefore be excluded.

Table 2. Selected Spectroscopic Data of Diketopiperazines **8**

product	$[\alpha]_D^{20}$ (c, solvent)[a]	^{1}H-NMR (D_6-DMSO) δ (ppm)	^{19}F-NMR (D_6-DMSO) δ (ppm)
(3R,6S)-8ca	-11.5 (1.0, DMSO)	1.51 (s, CH_3), 3.87 (m, C*H*-6)	1.5 (s, CF_3)
(3R,6S)-8cb	-25.4 (1.0, DMSO)	0.74, 0.78 (2 d, $(CH_3)_2$CH), 3.18 (m, C*H*-6)	3.1 (s, CF_3)
(3S,6S)-8cb	-	0.46, 0.56 (2 d, $(CH_3)_2$CH), 3.73 (m, C*H*-6)	2.5 (s, CF_3)
(3R,6S)-8da	-15.9 (1.0, DMSO)	1.48 (s, CH_3)	1.3 (s, CF_3)
(3S,6S)-8da	-	0.89 (s, CH_3)	1.0 (s, CF_3)
(3R,6S)-8db	-13.3 (1.0, DMSO)	2.70, 2.94 (dd, PhCH_2C-6), 2.83, 3.31 (d, PhCH_2C-3), 3.33 (m, C*H*-6)	2.8 (s, CF_3)
(3S,6S)-8db	-	2.44, 2,55 (m, PhCH_2C-6) 2.85, 3.40 (d, PhCH_2C-3), 4.19 (m, C*H*-6)	2.4 (s, CF_3)

[a] Determined for recrystallized, optically pure (d.e. > 99 %) material.

Acidolysis of the diketopiperazine ring in alcohol occurs regioselectively to give a dipeptide ester with N-terminal α-trifluoromethyl substituted aminoacid in good yield. The low basicity of the amino group in **9** prevents the formation of diketopiperazines after ring cleavage.



(3R,6S)-8 **9**

i) HCl, MeOH, ΔT, then propylene oxide

The full scope of the above reactions utilizing **7** as a homochiral electrophilic synthon for the stereoselective synthesis of trifluoromethyl substituted diketopiperazines, dipeptides, and aminoacids is currently under investigation.

Experimental

The organometallic reactions were performed under dry oxygen-free nitrogen atmosphere. Most reagents were commercially available (Fluka, Aldrich, Merck) and of synthetic grade. Ether and tetrahydrofuran were distilled immediately before use from sodium benzophenone ketyl. Analytical TLC plates (Silica gel 60 F_{254} on aluminium foil) were purchased from Merck; Silica gel 60 (32-60 μm, Merck) was used for flash chromatography.

Melting points were determined on a BÜCHI SMP-20 apparatus according to Tottoli and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1600 spectrometer. Optical rotation indexes were measured using a Perkin-Elmer 241 MC polarimeter. NMR spectra were obtained routinely on Bruker AC 200 (^{1}H 200.1 MHz, ^{13}C 50.3 MHz), Bruker AC 250 (^{1}H 250.1 MHz, ^{13}C 62.9 MHz), or Bruker AM 360 (^{1}H 360.1 MHz, ^{13}C 90.6 MHz) spectrometers at 297 K. Chemical shift values are quoted in ppm, coupling constants are given in Hz. The spectra are calibrated internally against residual solvent peaks (^{1}H-NMR: D_6-acetone 2.04 ppm, D_6-DMSO 2.49 ppm, CD_3OD 3.35 ppm, $CDCl_3$ 7.26 ppm; ^{13}C-NMR: D_6-acetone 29.8 ppm, D_6-DMSO 39.5 ppm, CD_3OD 49.3 ppm, $CDCl_3$ 77.0 ppm) or externally (^{19}F-NMR: CF_3CO_2H 0.0 ppm). Mass spectra were obtained using a Varian MAT CH5 spectrometer in EI mode (70 eV). Microanalyses were performed on a Heraeus EA 415/0, Monar System.

General Experimental Procedure for Synthesis of **4**

A mixture of 1.56 g methyl 3,3,3-trifluoropyruvate (10.0 mmol) and Z-protected aminoacid amide (10.0 mmol) in 50 ml abs. dichloromethane is stirred for 24 h at room temperature. The solvent is removed *in vacuo* and the residue is redissolved in 50 ml abs. methanol. 100 mg palladium (10% on activated carbon) are added to the solution and the mixture is stirred under 1 atm of hydrogen for 2 days. The catalyst is removed by filtration and the solvent is evaporated *in vacuo*. The crude product is purified by crystallization from ethyl acetate.

(3RS,6S)-3-Hydroxy-6-methyl-3-trifluoromethylpiperazine-2,5-dione **4a**

Yield: 1.46 g (69 %) diastereomeric mixture. - mp. 253-255 °C. - IR (KBr): ν = 3419, 1689 cm^{-1}. - ^{1}H-NMR (D_6-DMSO): δ= 1.26/1.28 (d/d, $^3J_{HH}$ = 7.2/7.2, 3H, C*H*$_3$); 4.23/4.25 (q/q, $^3J_{HH}$ = 7.2/7.2, 1H, C*H*-6); 6.80, 7.96, 8.33 (br. s, 3H, N*H*, O*H*). - ^{13}C-NMR (D_6-DMSO): δ = 18.05/19.28 (*C*H$_3$); 49.76/50.10 (*C*-6); 78.75/79.05 (q/q, $^2J_{CF}$ = 31.5, *C*-3); 121.35/122.54 (q/q, $^1J_{CF}$ = 287.8, *C*F$_3$); 160.72/161.45 (*C*=O); 168.14/168.41 (*C*=O). - ^{19}F-NMR (D_6-DMSO): δ = -2.8/-2.3 (s/s, *C*F$_3$).- $C_6H_7F_3N_2O_3$ [212.13]. - Calc.: C 33.97, H 3.33, N 13.21; found: C 34.20, H 3.27, N 13.14.

(3RS,6S)-3-Hydroxy-6-isopropyl-3-trifluoromethylpiperazine-2,5-dione **4b**

Yield: 1.85 g (77 %) diastereomeric mixture. - mp. 214-217 °C. - IR (KBr): ν = 3220, 3120, 2980, 1680 cm^{-1}. - ^{1}H-NMR (D_6-DMSO): δ = 0.81/0.84 (d/d, $^3J_{HH}$ = 6.8/6.8, 3H, C*H*$_3$); 0.94/0.97 (d/d, $^3J_{HH}$ = 7.1/7.1, 3H, C*H*$_3$); 2.16/2.26 (m, 1H, C*H*); 3.83 (m, 1H, C*H*-6); 7.96, 8.56/8.61, 9.17 (br. s, 3H, N*H*, O*H*). - ^{13}C-NMR (D_6-DMSO): δ = 17.46/17.94 (*C*H$_3$); 18.81/18.82 (*C*H$_3$); 31.83/32.51 (*C*H); 60.37/60.45 (*C*-6); 79.73 (q, $^2J_{CF}$ = 31.0, *C*-3); 123.00/123.65 (q/q, $^1J_{CF}$ = 287.9/290.0, *C*F$_3$); 162.76/163.19 (*C*=O); 168.07/168.19 (*C*=O). - ^{19}F-NMR (D_6-DMSO): δ = -1.6/-1.3 (s/s, *C*F$_3$). - $C_8H_{11}F_3N_2O_3$ [240.18]. - Calc.: C 40.01, H 4.62, N 11.66; found: C 40.24, H 4.67, N 11.83.

(3RS,6S)-3-Hydroxy-6-isobutyl-3-trifluoromethylpiperazine-2,5-dione **4c**

Yield: 2.18 g (86 %) diastereomeric mixture. - mp. 238-239 °C. - IR (KBr): ν = 3210, 3110, 1700, 1665 cm^{-1}. - ^{1}H-NMR (D_6-DMSO): δ = 0.83-0.88 (m, 6H, C*H*$_3$); 1.47-1.66 (m, 2H, C*H*$_2$CH); 1.79-1.86 (m, 1H, CH$_2$C*H*); 3.86-3.91 (m, 1H, C*H*-6); 7.95, 8.75/8.81, 9.20 (br. s, 3H, N*H*, O*H*). - ^{13}C-NMR (D_6-DMSO): δ = 21.77/22.09 (*C*H$_3$); 22.79/22.88 (*C*H$_3$); 23.43/23.49 (CH$_2$CH); 41.73/43.31 (CH$_2$CH); 53.04/53.20 (*C*-6); 78.91/79.10 (q/q, $^2J_{CF}$ = 31.2/30.9, *C*-3); 122.33/122.76 (q/q, $^1J_{CF}$ = 288.4/289.0, *C*F$_3$); 161.33/161.77

(*C*=O); 168.16/168.57 (*C*=O). - ^{19}F-NMR (D_6-DMSO): δ = -2.4/-2.1 (s/s, CF_3). - MS: m/e= 255 [MH]; 254 [M]; 211 [M-HNCO]; 198 [M-C_4H_8]; 129 [196-CF_3]; 69 [CF_3]; 43 [HNCO]. - $C_9H_{13}F_3N_2O_3$ [254.21].- Calc.: C 42.52, H 5.15, N 11.02; found: C 42.59, H 5.16, N 11.15.

(3RS,6S)-3-Hydroxy-6-benzyl-3-trifluoromethylpiperazine-2,5-dione **4d**

Yield: 1.99 g (69 %) diastereomeric mixture. - mp. 247-250 °C. - IR (KBr): ν = 3200, 3100, 1690, 1665 cm^{-1}. - ^{1}H-NMR (D_6-DMSO): δ = 2.94/2.98 (dd/dd, $^2J_{HH}$ = 13.7/14.1, 1H, CH_2); 3.08/3.25 (dd/dd, $^2J_{HH}$ = 13.7/14.1, 1H, CH_2); 4.31/4.34 (m/m, 1H, C*H*-6); 7.12-7.30 (m, 5H, H_{ar}); 7.96/7.97, 8.74/8.88, 9.17/9.31 (br. s, 3H, N*H*, O*H*). - ^{13}C-NMR (D_6-DMSO): δ = 36.56/38.08 (CH_2); 55.13/55.36 (*C*-6); 78.67/79.10 (q/q, $^2J_{CF}$ = 31.4, *C*-3); 121.68/122.86 (q/q, $^1J_{CF}$ = 288.1/289.9, CF_3); 126.41/126.53, 127.81/128.00, 129.70/130.08, 135.48/135.99 (C_{ar}); 161.05/161.90 (*C*=O); 166.77/167.10 (*C*=O). - ^{19}F-NMR (D_6-DMSO): δ = -2.2/-2.9 (s/s, CF_3). - $C_{12}H_{11}F_3N_2O_3$ [288.23]. - Calc.: C 50.01, H 3.85, N 9.72; found: C 49.90, H 3.88, N 9.70.

General Experimental Procedure for Synthesis of **5**

A mixture of **4** (1.04 mmol) and 0.58 g trifluoroacetic anhydride (2.8 mmol) in 10 ml tetrahydrofuran is refluxed for 24 h. The solvent is removed *in vacuo* and the crude product is purified by column chromatography on silica gel using ethyl acetate/hexanes (1:3) as eluent.

2,5-Dihydroxy-6-methyl-3-trifluoromethylpyrazine **5a**

Yield: 0.09 g (45 %). - mp. 310 °C (dec.). - IR (KBr): ν = 3120, 1665 cm^{-1}. - ^{1}H-NMR (D_6-DMSO): δ = 2.29 (s, 3H, CH_3); 11.37 (br. s, 1H, O*H*); 11.58 (br. s, 1H, O*H*). - ^{13}C-NMR (D_6-DMSO): δ = 18.32 (CH_3); 118.86 (q, $^2J_{CF}$ = 34.5, *C*-3); 121.70 (q, $^1J_{CF}$ = 273.1, CF_3); 144.35; 150.78, 150.98 (*C*-2, *C*-5, *C*-6). - ^{19}F-NMR (D_6-DMSO): δ = 14.1 (s, CF_3). - $C_6H_5F_3N_2O_2$ [194.11]. - Calc.: C 37.13, H 2.60, N 14.43; found: C 37.61, H 3.07, N 13.93.

2,5-Dihydroxy-6-isobutyl-3-trifluoromethylpyrazine **5c**

Yield: 0.11 g (46 %). - mp. 218 °C. - IR (KBr): ν = 2960, 1630 cm^{-1}. - ^{1}H-NMR (D_6-DMSO): δ = 0.80 (d, $^3J_{HH}$ = 6.7, 6H, CH_3); 2.03-2.44 (m, 3H, CH_2CH); 11.28 (br. s, 1H, O*H*); 11.55 (br. s, 1H, O*H*). - ^{13}C-NMR (D_6-DMSO): δ = 20.84 (CH_3); 27.06 (*C*H); 38.28 (CH_2); 119.29 (q, $^2J_{CF}$ = 35.33, *C*-3); 121.93 (q, $^1J_{CF}$ = 273.1, CF_3); 147.20; 151.23, 151.38 (*C*-2, *C*-5, *C*-6). - ^{19}F-NMR (D_6-DMSO): δ = 13.9 (s, CF_3). - $C_9H_{11}F_3N_2O_2$ [236.19]. - Calc.: C 45.77, H 4.69, N 11.86; found: C 45.60, H 4.69, N 11.96.

6-Benzyl-2,5-dihydroxy-3-trifluoromethylpyrazine **5d**

Yield: 0.16 g (58 %). - mp. 255 °C. - IR (KBr): ν = 3025, 1630 cm^{-1}. - ^{1}H-NMR (D_6-DMSO): δ = 3.98 (s, 2H, CH_2); 7.21 (m, 5H, H_{ar}); 11.55 (br. s, 1H, O*H*); 11.75 (br. s, 1H, O*H*). - ^{13}C-NMR (D_6-DMSO): δ = 37.43 (CH_2); 119.64 (q, $^2J_{CF}$ = 35.3, *C*-3); 121.49 (q, $^1J_{CF}$ = 273.1, CF_3); 126.13, 128.18, 128.61, 137.39 (C_{ar}); 145.81; 150.75, 151.19 (*C*-2, *C*-5, *C*-6). - ^{19}F-NMR (D_6-DMSO): δ = 13.8 (s, CF_3). - $C_{12}H_9F_3N_2O_2$ [270.21]. - Calc.: C 53.34, H 3.36, N 10.37; found: C 53.41, H 3.45, N 10.14.

General Experimental Procedure for Synthesis of **8**

Protocol A: 1.05 g trifluoroacetic anhydride (5.0 mmol) are added to a solution of **4** (4.7 mmol) in 15 ml tetrahydrofuran at 0 °C. The mixture is stirred at room temperature for 2 h before removing the solvent *in vacuo*. The residue is kept under high vacuum for 4 h in order to remove excess trifluoroacetic anhydride and trifluoroacetic acid. The residual **6** is redissolved in 30 ml tetrahydrofuran and Grignard reagent (solution in tetrahydrofuran, 18.8 mmol) is added dropwise at -100 °C to the stirred solution. The reaction is maintained at -70 °C for 6 h and at -35 °C for 15 h before quenching with phosphate buffer (pH 7, 15 ml). The mixture is extracted with ether (15 ml), followed by ethyl acetate (2 x 30 ml). The combined organic layers are dried, filtered and the solvent is evaporated. The residue is washed with a minimum amount of ether before

crystallizing from ethyl acetate. Compounds **5** are isolated as byproducts with yields of 5 % (**5a**), 6 % (**5c**), and 8 % (**5d**).

Protocol B: 0.63 g trifluoroacetic anhydride (3.0 mmol) are added to a solution of **4** (2.8 mmol) in 15 ml tetrahydrofuran at 0 °C. The mixture is stirred at room temperature for 2 h before removing the solvent *in vacuo*. The residue is kept under high vacuum for 4 h in order to remove excess trifluoroacetic anhydride and trifluoroacetic acid. The residue is dissolved in 20 ml tetrahydrofuran and added at -20 °C to a solution of dimethyl cadmium (5.9 mmol), obtained on reaction of 1.08 g cadmium chloride (5.9 mmol) with methyl magnesium chloride (4.0 ml of a 3M solution in tetrahydrofuran, 12.0 mmol) in 20 ml tetrahydrofuran. The mixture is allowed to warm up and stirred at room temperature for 24 h before quenching with 15 ml phosphate buffer (pH 7). The mixture is extracted with ether (15 ml), followed by ethyl acetate (2 x 30 ml). The combined organic layers are dried, filtered and the solvent is evaporated. The residue is washed with a minimum amount of ether before crystallizing from ethyl acetate.

(3RS,6S)-3,6-Dimethyl-3-trifluoromethylpiperazine-2,5-dione **8aa**

Yield: 0.61 g (62 %, protocol A), 0.30 g (51 %, protocol B) diastereomeric mixture. - mp. 230 °C. - IR (KBr): ν = 3440, 3203, 3092, 1684 cm^{-1}. - major diastereomer: ^{1}H-NMR (D_6-DMSO): δ = 1.24 (d, $^3J_{HH}$ = 7.1, 3H, C*H*$_3$C-6); 1.49 (s, 3H, C*H*$_3$C-3); 3.99 (q, $^3J_{HH}$ = 7.1, 1H, C*H*-6); 8.67 (s, 1H, N*H*); 8.91 (s, 1H, N*H*). - ^{13}C-NMR (D_6-DMSO): δ = 17.44 (*C*H$_3$); 19.76 (*C*H$_3$); 50.40 (*C*-6); 59.71 (q, $^2J_{CF}$ = 27.1, *C*-3); 124.01 (q, $^1J_{CF}$ = 286.7, *C*F$_3$); 160.96 (*C*=O); 167.90 (*C*=O). - ^{19}F-NMR (D_6-DMSO): δ = 1.1 (s, C*F*$_3$). - minor diastereomer: ^{1}H-NMR (D_6-DMSO): δ = 1.24 (d, $^3J_{HH}$ = 7.1, 3H, C*H*$_3$C-6); 1.46 (s, 3H, C*H*$_3$C-3); 4.00 (q, $^3J_{HH}$ = 7.1, 1H, C*H*-6); 8.68 (s, 1H, N*H*); 8.95 (s, 1H, N*H*). - ^{13}C-NMR (D_6-DMSO): δ = 18.18 (*C*H$_3$); 19.13 (*C*H$_3$); 49.38 (*C*-6); 60.26 (q, $^2J_{CF}$ = 27.1, *C*-3); 124.95 (q, $^1J_{CF}$ = 286.7, *C*F$_3$); 162.35 (*C*=O); 168.83 (*C*=O). - ^{19}F-NMR (D_6-DMSO): δ = 1.2 (s, C*F*$_3$). - $C_7H_9F_3N_2O_2$ [210.16]. - Calc.: C 40.01, H 4.32, N 13.33; found: C 39.81, H 4.23, N 13.09.

(3R,6S)-3-Benzyl-6-methyl-3-trifluoromethylpiperazine-2,5-dione **(3R,6S)-8ab**

Yield: 0.47 g (35 %). - $[\alpha]_D^{20}$: -13.7 (c 1.0, DMSO). - mp. 286 °C. - IR (KBr): ν = 3200, 3080, 1685 cm^{-1}. - ^{1}H-NMR (D_6-DMSO): δ = 1.11 (d, $^3J_{HH}$ = 7.1, 3H, C*H*$_3$); 2.85 (d, $^2J_{HH}$ = 13.0, 1H, C*H*$_2$); 3.25 (m, 1H, C*H*-6); 3.37 (d, $^2J_{HH}$ = 13.0, 1H, C*H*$_2$); 7.23 (m, 5H, *H*$_{ar}$); 8.57 (s, 1H, N*H*); 9.00 (s, 1H, N*H*). - ^{13}C-NMR (D_6-DMSO): δ = 20.01 (*C*H$_3$); 36.67 (*C*H$_2$); 49.52 (*C*-6); 64.76 (q, $^2J_{CF}$ = 25.7, *C*-3); 123.83 (q, $^1J_{CF}$ = 287.5, *C*F$_3$); 127.24, 127.92, 130.79, 132.77 (*C*$_{ar}$); 159.84 (*C*=O); 167.87 (*C*=O). - ^{19}F-NMR (D_6-DMSO): δ = 2.8 (s, C*F*$_3$). - $C_{13}H_{13}F_3N_2O_2$ [286.25]. - Calc.: C 54.54, H 4.58, N 9.79; found: C 54.09, H 4.51, N 9.87.

(3R,6S)-6-Isobutyl-3-methyl-3-trifluoromethylpiperazine-2,5-dione **(3R,6S)-8ca**

Yield: 0.61 g (51 %, protocol A), 0.32 g (45 %, protocol B). - $[\alpha]_D^{20}$: -11.5 (c 1.0, DMSO). - mp. 236-237 °C. - IR (KBr): ν = 3200, 3080, 2980, 1675 cm^{-1}. - ^{1}H-NMR (D_6-DMSO): δ = 0.85 (d, $^3J_{HH}$ = 6.5, 3H, (C*H*$_3$)$_2$CH); 0.87 (d, $^3J_{HH}$ = 6.6, 3H, (C*H*$_3$)$_2$CH); 1.51 (s, 3H, C*H*$_3$); 1.46-1.57 (m, 2H, C*H*$_2$CH); 1.81 (m, 1H, CH$_2$C*H*); 3.87 (m, 1H, C*H*-6); 8.78 (s, 1H, N*H*); 8.93 (s, 1H, N*H*). - ^{13}C-NMR (D_6-DMSO): δ = 20.05 (*C*H$_3$); 21.65 (*C*H$_3$); 23.03 (*C*H$_3$); 23.51 (CH$_2$*C*H); 44.02 (*C*H$_2$CH); 53.32 (*C*-6); 60.05 (q, $^2J_{CF}$ = 27.2, *C*-3); 124.41 (q, $^1J_{CF}$ = 279.4, *C*F$_3$); 161.75 (*C*=O); 167.94 (*C*=O). - ^{19}F-NMR (D_6-DMSO): δ = 1.5 (s, C*F*$_3$). - MS: m/e= 253 [MH]; 252 [M]; 237 [M-CH$_3$]; 209 [M-HNCO]; 196 [M-C$_4$H$_8$]; 127 [196-CF$_3$]; 69 [CF$_3$]; 43 [HNCO]. - $C_{10}H_{15}F_3N_2O_2$ [252.24]. - Calc.: C 47.62, H 5.99, N 11.11; found: C 47.55, H 5.98, N 11.10.

(3S,6S)-6-Isobutyl-3-methyl-3-trifluoromethylpiperazine-2,5-dione **(3S,6S)-8ca**

^{1}H-NMR (D_6-DMSO): δ = 0.81-0.87 (m, 6H, (C*H*$_3$)$_2$CH); 1.48 (s, 3H, C*H*$_3$); 1.40-1.70 (m, 2H, C*H*$_2$CH); 1.82 (m, 1H, CH$_2$C*H*); 3.95 (m, 1H, C*H*-6); 8.62 (s, 1H, N*H*); 8.96 (s, 1H, N*H*). - ^{19}F-NMR (D_6-DMSO): δ = 1.2 (s, C*F*$_3$).

(3R,6S)-3-Benzyl-6-isobutyl-3-trifluoromethylpiperazine-2,5-dione **(3R,6S)-8cb**
Yield: 0.89 g (58 %). - $[\alpha]_D^{20}$: -25.4 (c 1.0, DMSO). - mp. 285 °C. - IR (KBr): ν = 3180, 3080, 2960, 1670 cm^{-1}. - ^{1}H-NMR (D_6-DMSO): δ = 0.74 (d, $^3J_{HH}$ = 6.5, 3H, CH_3); 0.78 (d, $^3J_{HH}$ = 6.6, 3H, CH_3); 1.32-1.49 (m, 2H, CH_2CH); 1.70 (m, 1H, CH$_2$C*H*); 2.91 (d, $^2J_{HH}$ = 12.9, 1H, PhCH_2); 3.18 (m, 1H, C*H*-6); 3.43 (d, $^2J_{HH}$ = 12.9, 1H, PhCH_2); 7.26-7.31 (m, 5H, H_{ar}); 8.68 (s, 1H, N*H*); 9.05 (s, 1H, N*H*). - ^{13}C-NMR (D_6-DMSO): δ = 21.66 (*C*H$_3$); 22.77 (*C*H$_3$); 23.22 (CH$_2$*C*H); 37.18 (PhCH$_2$); 43.57 (*C*H$_2$CH); 52.37 (*C*-6); 64.85 (q, $^2J_{CF}$ = 27.2, *C*-3); 124.03 (q, $^1J_{CF}$ = 279.4, *C*F$_3$); 127.41, 128.09, 130.90, 132.98 (C_{ar}); 160.34 (*C*=O); 167.83 (*C*=O). - ^{19}F-NMR (D_6-DMSO): δ = 3.1 (s, CF_3). - MS: m/e = 328 [M]; 272 [M-C_4H_8]; 237 [M-CH$_2$Ph]; 91 [CH$_2$Ph]. - $C_{16}H_{19}F_3N_2O_2$ [328.34]. - Calc.: C 58.53, H 5.83, N 8.53; found: C 58.19, H 5.75, N 8.70.

(3S,6S)-3-Benzyl-6-isobutyl-3-trifluoromethylpiperazine-2,5-dione **(3S,6S)-8cb**
^{1}H-NMR (D_6-DMSO): δ = 0.46 (d, $^3J_{HH}$ = 6.6, 3H, CH_3); 0.56 (d, $^3J_{HH}$ = 6.6, 3H, CH_3); 1.30-1.50 (m, 2H, CH_2CH); 1.69 (m, 1H, CH$_2$C*H*); 2.85 (d, $^2J_{HH}$ = 12.9, 1H, PhCH_2); 3.43 (d, $^2J_{HH}$ = 12.9, 1H, PhCH_2); 3.73 (m, 1H, C*H*-6); 7.26-7.31 (m, 5H, H_{ar}); 8.56 (s, 1H, N*H*); 8.99 (s, 1H, N*H*). - ^{19}F-NMR (D_6-DMSO): δ = 2.5 (s, CF_3).

(3RS,6S)-3-Allyl-6-isobutyl-3-trifluoromethylpiperazine-2,5-dione **8cc**
Yield: 0.59 g (45 %) diastereomeric mixture. - mp. 247 °C. - IR (KBr): ν = 3200, 3090, 2970, 1685 cm^{-1}. - ^{1}H-NMR (D_6-acetone): δ = 0.89-0.95 (m, 6H, CH_3); 1.58-2.12 (m, 3H, CH_2C*H*); 2.55 (m, 1H, CH_2CH=CH$_2$); 3.03 (m, 1H, CH_2CH=CH$_2$); 4.03/4.12 (m/m, 1H, C*H*-6); 5.21 (m, 2H, CH=CH_2); 5.69 (m, 1H, C*H*=CH$_2$). - ^{13}C-NMR (CD_3OD): δ = 21.87/23.46 (*C*H$_3$); 22.79/23.29 (*C*H$_3$); 25.02/25.06 (CH$_2$*C*H); 36.28/37.50 (*C*H$_2$CH=CH$_2$); 42.52/45.60 (CH$_2$*C*H); 54.31/54.80 (*C*-6); 65.47/65.77 (q/q, $^2J_{CF}$ = 26.5, *C*-3); 122.40/122.58 (CH=*C*H$_2$); 125.12/125.71 (q/q, $^1J_{CF}$ = 285.7/286.5, *C*F$_3$); 130.29/130.65 (*C*H=CH$_2$); 162.96/163.54 (*C*=O); 170.80/171.09 (*C*=O). - ^{19}F-NMR (D_6-acetone): δ = 1.3 (s, CF_3, major diastereomer); 0.8 (s, CF_3, minor diastereomer). - MS: m/e = 278 [M]; 222 [M-C_4H_8]; 209 [M-CF_3]; 181 [222-C_3H_5]; 153 [222-CF_3]. - $C_{12}H_{17}F_3N_2O_2$ [278.27]. - Calc.: C 51.79, H 6.16, N 10.07; found: C 51.78, H 6.13, N 10.16.

(3R,6S)-6-Benzyl-3-methyl-3-trifluoromethylpiperazine-2,5-dione **(3R,6S)-8da**
Yield: 0.83 g (62 %). - $[\alpha]_D^{20}$: -15.9 (c 1.0, DMSO). - mp. 263 °C. - IR (KBr): ν = 3200, 3070, 1670 cm^{-1}. - ^{1}H-NMR (D_6-DMSO): δ = 1.48 (s, 3H, CH_3); 2.99 (m, 2H, CH_2); 4.27 (m, 1H, C*H*-6); 7.07-7.30 (m, 5H, H_{ar}); 8.64 (s, 1H, N*H*); 8.87 (s, 1H, N*H*). - ^{13}C-NMR (D_6-DMSO): δ = 20.42 (*C*H$_3$); 39.01 (*C*H$_2$); 55.91 (*C*-6); 60.09 (q, $^2J_{CF}$ = 27.1, *C*-3); 123.90 (q, $^1J_{CF}$ = 286.7, *C*F$_3$); 126.57, 128.10, 129.84, 130.33 (C_{ar}); 161.73 (*C*=O); 166.36 (*C*=O). - ^{19}F-NMR (D_6-DMSO): δ = 1.3 (s, CF_3). - MS: m/e = 286 [M]; 91 [CH$_2$Ph]. - $C_{13}H_{13}F_3N_2O_2$ [286.25]. - Calc.: C 54.55, H 4.58, N 9.79; found: C 54.60, H 4.67, N 10.00.

(3S,6S)-6-Benzyl-3-methyl-3-trifluoromethylpiperazine-2,5-dione **(3S,6S)-8da**
^{1}H-NMR (D_6-DMSO): δ = 0.89 (s, 3H, CH_3); 2.91 (m, 1H, CH_2); 3.10 (m, 1H, CH_2); 4.37 (m, 1H, C*H*-6); 7.07-7.30 (m, 5H, H_{ar}); 8.78 (s, 1H, N*H*); 8.87 (s, 1H, N*H*). - ^{19}F-NMR (D_6-DMSO): δ = 1.0 (s, CF_3).

(3R,6S)-3,6-Dibenzyl-3-trifluoromethylpiperazine-2,5-dione **(3R,6S)-8db**
Yield: 0.68 g (40 %). - $[\alpha]_D^{20}$: -13.3 (c 1.0, DMSO). - mp. 300 °C. - IR (KBr): ν = 3200, 3080, 1680 cm^{-1}. - ^{1}H-NMR (D_6-DMSO): δ = 2.70 (dd, $^2J_{HH}$ = 13.7, 1H, CH_2C-6); 2.83 (d, $^2J_{HH}$ = 12.9, 1H, CH_2C-3); 2.94 (dd, $^2J_{HH}$ = 13.7, 1H, CH_2C-6); 3.31 (d, $^2J_{HH}$ = 12.9, 1H, CH_2C-3); 3.33 (m, 1H, C*H*-6); 7.03-7.30 (m, 10H, H_{ar}); 8.62 (s, 1H, N*H*); 8.92 (s, 1H, N*H*). - ^{13}C-NMR (D_6-DMSO): δ = 37.81 (*C*H$_2$); 38.56 (*C*H$_2$); 54.55 (*C*-6); 64.83 (q, $^2J_{CF}$ = 25.5, *C*-3); 123.48 (q, $^1J_{CF}$ = 288.9, *C*F$_3$); 126.53, 127.49, 127.91, 128.14, 129.85, 130.76, 132.80, 135.40 (C_{ar}); 160.42 (*C*=O); 166.25 (*C*=O). - ^{19}F-NMR (D_6-DMSO): δ = 2.8 (s, CF_3). - MS: m/e =

362 [M]; 271 [M-CH_2Ph]; 91 [CH_2Ph]. - $C_{19}H_{17}F_3N_2O_2$ [362.35]. - Calc.: C 62.98, H 4.73, N 7.73; found: C 62.99, H 4.73, N 7.88.

(3S,6S)-3,6-Dibenzyl-3-trifluoromethylpiperazine-2,5-dione **(3S,6S)-8db**

^{1}H-NMR (D_6-DMSO): δ = 2.44 (m, 1H, CH_2C-6); 2.55 (m, 1H, CH_2C-6); 2.85 (d, $^2J_{HH}$ = 13.4, 1H, CH_2C-3); 3.40 (d, $^2J_{HH}$ = 13.4, 1H, CH_2C-3); 4.19 (m, 1H, C*H*-6); 6.88-7.35 (m, 10H, H_{ar}); 8.59 (s, 1H, N*H*); 9.09 (s, 1H, N*H*). - ^{19}F-NMR (D_6-DMSO): δ = 2.4 (s, CF_3).

(3RS,6S)-3-Allyl-6-benzyl-3-trifluoromethylpiperazine-2,5-dione **8dc**

Yield: 0.68 g (47 %) diastereomeric mixture. - mp. 231 °C. - IR (KBr): ν = 3210, 3100, 1690 cm^{-1}. - major diastereomer: ^{1}H-NMR (D_6-DMSO): δ = 2.37 (dd, $^2J_{HH}$ = 13.3, 1H, CH_2CH=CH_2); 2.77 (dd, $^2J_{HH}$ = 13.3, 1H, CH_2CH=CH_2); 2.77 (m, 1H, CH_2Ph); 2.94 (m, 1H, CH_2Ph); 4.25 (m, 1H, C*H*-6); 5.22 (m, 2H, CH=CH_2); 5.58 (m, 1H, C*H*=CH_2); 7.13-7.27 (m, 5H, H_{ar}); 8.58 (s, 1H, N*H*); 8.86 (s, 1H, N*H*). - ^{13}C-NMR (D_6-DMSO): δ = 35.96 (*C*H_2CH=CH_2); 38.48 (*C*H_2Ph); 55.12 (*C*-6); 63.11 (q, $^2J_{CF}$ = 27.0, *C*-3); 121.50 (CH=*C*H_2); 123.11 (q, $^1J_{CF}$ = 291.2, *C*F_3); 126.30, 127.76, 129.10, 129.58, 135.43 (*C*H=CH_2, C_{ar}); 160.10, 166.34 (*C*=O). - ^{19}F-NMR (D_6-DMSO): δ = 2.4 (s, CF_3). - minor diastereomer: ^{1}H-NMR (D_6-DMSO): δ = 2.17 (dd, $^2J_{HH}$ = 13.9, 1H, CH_2CH=CH_2); 2.57 (dd, $^2J_{HH}$ = 13.9, 1H, CH_2CH=CH_2); 2.88 (dd, $^2J_{HH}$ = 13.8, $^3J_{HH}$ = 5.0, 1H, CH_2Ph); 3.24 (dd, $^2J_{HH}$ = 13.8, $^3J_{HH}$ = 3.0, 1H, CH_2Ph); 4.39 (m, 1H, C*H*-6); 4.56 (m, 1H, C*H*=CH_2); 4.66 (d, $^3J_{HH}$ = 8.0, 1H, CH=CH_2); 4.88 (d, $^3J_{HH}$ = 15.3, 1H, CH=CH_2); 7.13-7.27 (m, 5H, H_{ar}); 8.88 (s, 1H, N*H*); 8.89 (s, 1H, N*H*). - ^{13}C-NMR (D_6-DMSO): δ = 34.06 (*C*H_2CH=CH_2); 36.51 (*C*H_2Ph); 54.27 (*C*-6); 63.11 (q, $^2J_{CF}$ = 27.0, *C*-3); 119.81 (CH=*C*H_2); 123.11 (q, $^1J_{CF}$ = 291.2, *C*F_3); 127.59, 128.57, 130.08, 135.14, (*C*H=*C*H_2, C_{ar}); 166.63 (*C*=O). - ^{19}F-NMR (D_6-DMSO): δ = 1.8 (s, CF_3,). - MS: m/e = 313 [MH]; 312 [M]; 91 [CH_2Ph]. - $C_{15}H_{15}F_3N_2O_2$ [312.29]. - Calc.: C 57.69, H 4.84, N 8.97; found: C 57.39, H 4.82, N 9.17.

Illustrative Experimental Procedure for Synthesis of **9**

A solution of 35 mg **8ca** (0.13 mmol) and 0.7 ml conc. hydrochloric acid in 15 ml methanol is refluxed for 48 h, before the solvent is removed *in vacuo*. The residue is co-evaporated with 10 ml toluene and the crude residue stirred with 5 ml propylene oxide for 1h at room temperature. The solution is evaporated *in vacuo* to give after crystallization from chloroform 23 mg (58 %) of **9a** as white solid.

Methyl (R)-2-Trifluoromethylalanyl-(S)-leucinate R-(α-TFM)Ala-S-Leu(OMe) **9a**

Yield: 23 mg (58 %). - mp. 215 °C. - $[\alpha]_D^{20}$ = -16.2 (c 0.65, MeOH). - IR (KBr): ν = 3432, 2962, 1741, 1677 cm^{-1}. - ^{1}H-NMR ($CDCl_3$): δ = 0.90 (d, $^3J_{HH}$ = 6.8, 6H, (CH_3)$_2$CH); 1.47 (s, 3H, CH_3); 1.53-1.66 (m, 3H, CH_2C*H*); 2.17 (br. s, 2H, NH_2); 3.69 (s, 3H, OCH_3); 4.55 (m, 1H, Leu-H_α); 7.64 (br. d, 1H, N*H*) - ^{13}C-NMR ($CDCl_3$): δ = 20.40 (q, $^3J_{CF}$ = 1.6, *C*H$_3$); 21.19 ((CH$_3$)$_2$CH); 22.20 ((*C*H$_3$)$_2$CH); 24.33 (CH$_2$*C*H); 40.66 (*C*H$_2$CH); 50.03 (Leu-C$_\alpha$); 51.75 (OCH$_3$); 60.16 (q, $^2J_{CF}$ = 27.3, *C*-CF$_3$); 125.05 (q, $^1J_{CF}$ = 284.3, *C*F$_3$); 168.44 (*C*=O); 172.48 (*C*=O). - ^{19}F-NMR ($CDCl_3$): δ = -0.5 (s, CF_3). - $C_{11}H_{19}F_3N_2O_3$ [284.28]. Calc.: C 46.48, H 6.74, N 9.85; found: C 45.86, H 6.40, N 10.21.

Methyl (R)-2-Trifluoromethylalanyl-(S)-phenylalaninate R-(α-TFM)Ala-S-Phe(OMe) **9b**

In analogy to the procedure given for **9a**, 0.16 g (46 %) of **9b** are obtained as colourless oil from 0.23 g **8da** (0.8 mmol). - $[\alpha]_D^{20}$ = -9.1 (c 1.35, MeOH). - IR (Film): ν = 3390, 2940, 1755, 1685 cm^{-1}. - ^{1}H-NMR ($CDCl_3$): δ = 1.45 (s, 3H, CH_3); 2.55 (br. s, 2H, NH_2); 3.14 (m, 2H, CH_2); 3.73 (s, 3H, OCH_3); 4.81 (m, 1H, Phe-H_α); 7.08-7.28 (m, 5H, H_{ar}); 7.74 (br. s, 1H, N*H*). - ^{13}C-NMR ($CDCl_3$): δ = 20.30 (q, $^3J_{CF}$ = 1.6, *C*H$_3$); 36.96 (*C*H$_2$); 51.85 (Phe-C$_\alpha$); 52.49 (OCH$_3$); 60.12 (q, $^2J_{CF}$ = 27.3, *C*-CF$_3$); 125.03 (q, $^1J_{CF}$ = 284.5, *C*F$_3$); 126.66, 128.02, 128.61, 135.02 (C_{ar}); 168.24 (*C*=O); 170.98 (*C*=O). - ^{19}F-NMR ($CDCl_3$): δ = -0.3 (s, CF_3). - $C_{14}H_{17}F_3N_2O_3$ [318.30]. - Calc.: C 52.83, H 5.38, N 8.80; found: C 52.47, H 5.30, N 8.08.

Acknowledgment

Generous support from the Royal Society of Chemistry (postdoctoral research fellowship to L.C.S.), Deutscher Akademischer Austauschdienst (postdoctoral research fellowship to S.N.O.), Deutsche Forschungsgemeinschaft (Bu 277/14-1, and Habilitandenstipendium to N.S.), and HOECHST AG is gratefully acknowledged.

References and Notes

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(*Received* 18 *March* 1994)