New Stereoconservative Syntheses of β,β,β- and γ,γ,γ-Trifluoro-α-amino, α-Hydroxy, and α-Mercapto Acids and Their Incorporation into a Peptide and Depsipeptide Fragment

Hartmut Schedel,[a] Wojciech Dmowski,[b] Klaus Burger*[a]

[a]Institut für Organische Chemie, Universität Leipzig, Johannisallee 29, 04103 Leipzig, Germany
Fax +49(341)9736599; E-mail: burger@organik.chemie.uni-leipzig.de
[b]Institute of Organic Chemistry of the Polish Academy of Sciences, Kasprzaka St. 44, 01-224 Warsaw, Poland
Received 10 March 2000; revised 28 June 2000

Abstract: Syntheses of β,β,β- and γ,γ,γ-trifluoro-α-amino, α-hydroxy and a-mercapto acids using hexafluoroacetone as protecting and activating reagent are described. The key step of the syntheses is the transformation of an ω-carboxy group into a trifluoromethyl group on treatment with sulfur tetrafluoride. The carboxy activated species obtained are suitable for direct incorporation into peptide and depsipeptide fragments. RP-HPLC experiments and Mosher's TMPA method (^{1}H and ^{19}F) demonstrate that the reaction sequence occurs without racemization.

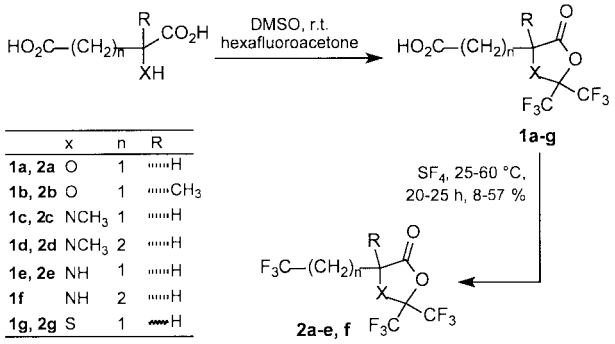
Key words: amino acids, heterocycles, hexafluoroacetone, lactones, peptides, sulfur tetrafluoride

Fluorine is a unique tool for modifying profiles of bioactive compounds.[1] Consequently, there is a growing interest in the synthesis of chiral fluorine containing building blocks. In this context, new synthetic routes to fluorine containing amino,[2] hydroxy,[3] keto[4] and mercapto acids,[5] their incorporation into peptides and depsipeptides, and their application in combinatorial chemistry are of current interest.[6]

Several strategies for the synthesis of trifluoromethyl substituted amino and hydroxy acids using fluorinated building blocks have been developed.[2,3] In most cases racemic mixtures were obtained. Therefore, the development of enzymatic methodology for enantiomeric resolution was necessary.[2a,h] Enantiopure γ-trifluoromethyl α-functionalized acids were obtained on catalytic hydrogenation of chiral fluoro substituted α,β-dehydro amino acid derivatives,[2d] trifluoromethylation of Garner's aldehyde with Ruppert's reagent[2e] and asymmetric synthesis via chiral chromium complexes.[3a] A direct transformation of the ω-carboxy group of hydantoin-protected ω-carboxy-α-amino acids into a trifluoromethyl group on treatment with sulfur tetrafluoride has been described,[7] but hydantoin-protected amino acids are notoriously sensitive to racemization.

Application of hexafluoroacetone as protecting reagent in multifunctional α-amino, α-hydroxy and α-mercapto acid chemistry allows efficient orthogonal functionalization. The functional groups present in the α-position and the adjacent carboxy group are simultaneously protected on reaction with hexafluoroacetone, while the ω-carboxy group remains unaffected. The α-carboxy group incorporated into the five membered heterocyclic system **1** is an activated ester moiety. Consequently, the α-carboxy group can be regioselectively derivatized on reaction with a variety of nucleophiles.[8] On the other hand, the ω-carboxy group in **1** can be selectively activated on transformation into an acid chloride or an isocyanate.[9]

In this paper, we describe a preparative simple two step synthesis of α-carboxy activated ω-trifluoromethyl α-*N*-methylamino, α-hydroxy and α-mercapto alkanoic acids and some of their derivatives starting from the corresponding ω-carboxy substituted α-functionalized alkanoic acids, using hexafluoroacetone as protecting and activating agent. ω-Carboxy substituted α-*N*-methylamino,[10] α-hydroxy and α-mercapto acids are readily transformed into lactones **1** upon reaction with hexafluoroacetone in dimethyl sulfoxide at room temperature.[11]



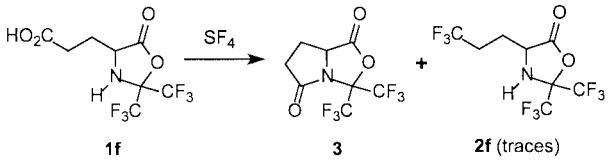
	X	n	R
1a, 2a	O	1	H
1b, 2b	O	1	CH_3
1c, 2c	NCH_3	1	H
1d, 2d	NCH_3	2	H
1e, 2e	NH	1	H
1f	NH	2	H
1g, 2g	S	1	H

Scheme 1

Transformation of the unprotected ω-carboxy group of compounds **1** into a trifluoromethyl group was accomplished in respectable yields on treatment with sulfur tetrafluoride[12] in an autoclave at temperatures between 25-60 °C (Schemes 1,2, Tables 1, 2). At lower temperatures, acid fluorides were the main products, at higher temperatures a mixture of undefined side products is formed. From the reaction mixtures obtained, compounds **2** can be easily separated by distillation.

The yield of the transformation **1e**→ **2e** was low (8%) because of side reactions at the unprotected NH function present in the molecule. When hexafluoroacetone-protected glutamic acid **1f** was treated with sulfur tetrafluoride, the pyroglutamic acid derivative **3** was obtained as

main product. Compound **2f** could only be traced by GCMS and ^{19}F NMR spectroscopy.



Scheme 2

Since compounds **2** are a-carboxy group activated species, deprotection can be achieved under mild conditions. The carboxy group and the functional group in the α-position of compounds **2** are deprotected in one step to give directly the ω-trifluoromethyl α-functionalized acids **4** (Scheme 3, Tables 3, 4). Cleavage of the five-membered lactone can be achieved with various nucleophiles providing a general access to the corresponding esters (**5a**, **5c**), amides (**7**), depsipeptide (**6a**, **6b**) and peptide fragments (**6c**, **6d**). The formation of the alkanoic acid derivatives is always coupled with the deprotection of the functional group

Table 1 Compounds **2a-e, g**, Analytical Data

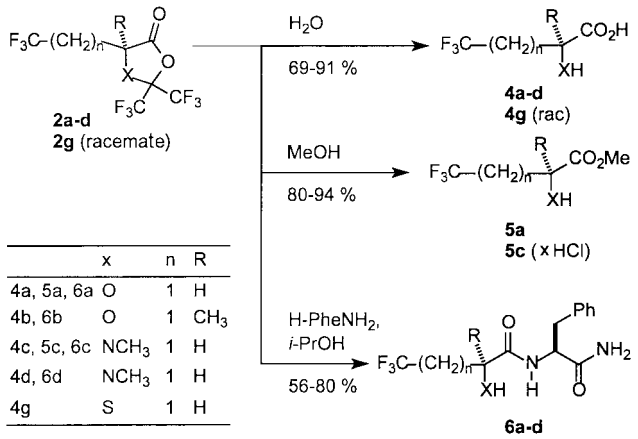
Compound	Conditions (°C) / (h)	Yield [%]	mp / bp (torr) [°C]	$[\alpha]_D$[a]	IR [cm^{-1}]	^1H NMR ($CDCl_3$) δ (ppm), *J* (Hz)	^{19}F NMR ($CDCl_3$) δ (ppm), *J* (Hz)
2a	44 / 24	57	74 (175)	- 8	1861[b]	2.48-2.97 (m, 2 H), 4.93 (dd, 1 H, *J* = 10, 10)	-3.29 (q, $^4J_{FF}$ = 7), -3.08 (q, $^4J_{FF}$ = 7), 13.04 (t, $^3J_{HF}$ = 10)
2b	44 / 23	50	68 (70)	- 8	1850[b]	1.76 (s, 3 H), 2.50-2.80 (m, 2 H)	-3.09 (q, $^4J_{FF}$ = 6), -2.95 (q, $^4J_{FF}$ = 6), 17.18 (t, $^3J_{HF}$ = 9)
2c	60 / 24	44	75-77 (22)[c]	+29	1848[b]	2.50-2.95 (m, 2 H), 2.79 (m, 3 H), 3.81 (dd, 1 H, *J* = 5, 5)	-1,04 (q, $^4J_{FF}$ = 9), 4.39 (q, $^4J_{FF}$ = 9), 14.64 (t, $^3J_{HF}$ = 11)
2d	60 / 25	26	84 (17)[c]	+22	1840[b]	1.90-2.43 (m, 4 H), 2.73 (m, 3 H), 3.73 (m, 1 H)	-0.86 (q, $^4J_{FF}$ = 9), 4.36 (q, $^4J_{FF}$ = 9), 11.28 (t, $^3J_{HF}$ = 11)
2e	25 / 20	8	37 / 75 (104)	+1	1834[b]	2.43 (m, 1 H), 2.81 (m, 1 H), 3.35 (m, 1 H), 4.29 (m, 1 H)	-3.36 (q, $^4J_{FF}$ = 9), -2.31 (q, $^4J_{FF}$ = 9), 12.92 (t, $^3J_{HF}$ = 11)
2g	50 / 22	45	82-84 (70)	–	1824[b]	2.63 (m, 1 H), 3.21 (m, 1 H), 4.40 (dd, 1 H, *J* = 11, 2)	0.92 (q, $^4J_{FF}$ = 9), 1.86 (q, $^4J_{FF}$ = 9), 12.02 (t, $^3J_{HF}$ = 11)

[a] *c* = 2, CH_2Cl_2.
[b] film.
[c] An analytically pure sample was obtained on column chromatography, eluent: petroleum ether/EtOAc (20/1).

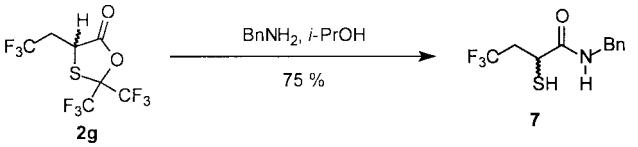
Table 2 Compounds **2a–e, g**, ^{13}C NMR and MS Data

Compound	^{13}C NMR ($CDCl_3$) d (ppm), *J* (Hz)	EI-MS [*m*/*z*]
2a	36.99 (q, $^2J_{CF}$ = 36), 70.15 (q, $^3J_{CF}$ = 4), 98.53 (m), 119.06 (q, $^1J_{CF}$ = 287), 119.73 (q, $^1J_{CF}$ = 287), 124.58 (q, $^1J_{CF}$ = 276), 166.29	287 [2, $(M\text{-}F)^+$], 259 (4), 237 (24), 209 (54), 115 (56), 97 (19), 69 (100)
2b	22.51, 40.96 (q, $^2J_{CF}$ = 31), 78.44 (q, $^3J_{CF}$ = 2), 97.84 (m), 119.10 (q, $^1J_{CF}$ = 278), 119.36 (q, $^1J_{CF}$ = 288), 119.41 (q, $^1J_{CF}$ = 288), 169.15	305 [2, $(M\text{-}CH_3)^+$], 251 (21), 223 (54), 195 (5), 131 (17), 111 (19), 107 (16), 69 (64), 65 (12), 42 (100)
2c	30.86, 35.22 (q, $^2J_{CF}$ = 30), 56.32 (q, $^3J_{CF}$ = 3), 90.15 (m), 120.72 (q, $^1J_{CF}$ = 287), 122.04 (q, $^1J_{CF}$ = 295), 125.18 (q, $^1J_{CF}$ = 277), 168.30	319 (18, M^+), 272 (18), 250 (57), 236 (31), 222 (100), 202 (19), 156 (9), 139 (12), 124 (16), 110 (35), 69 (48)
2d	21.60 (q, $^3J_{CF}$ = 3), 28.04 (q, $^2J_{CF}$ = 28), 33.10 (q, $^4J_{CF}$ = 2), 59.27, 89.90 (m), 120.95 (q, $^1J_{CF}$ = 287), 122.04 (q, $^1J_{CF}$ = 295), 127.06 (q, $^1J_{CF}$ = 276), 169.03	333 (9, M^+), 286 (10), 264 (14), 236 (100), 216 (4), 138 (9), 119 (7), 110 (13), 69 (18)
2e	38.43 (q, $^2J_{CF}$ = 30), 50.12 (q, $^3J_{CF}$ = 3), 88.76 (m), 120.36 (q, $^1J_{CF}$ = 288), 121.43 (q, $^1J_{CF}$ = 287), 125.76 (q, $^1J_{CF}$ = 277), 169.19	305 (<1, M^+), 258 (24), 236 (35), 222 (19), 208 (100), 192 (11), 188 (23), 177 (18), 96 (31), 90 (24), 69 (71)
2g	38.72 (q, $^2J_{CF}$ = 31), 40.18, 83.84 (m), 121.03 (q, $^1J_{CF}$ = 284), 121.66 (q, $^1J_{CF}$ = 285), 125.16 (q, $^1J_{CF}$ = 277), 169.36	322 (30, M^+), 275 (33), 253 (33), 225 (58), 205 (23), 163 (10), 128 (89), 113 (34), 97 (18), 69 (84), 44 (100)

placed in a-position, which can be directly transformed without further manipulation.



	x	n	R
4a, 5a, 6a	O	1	H
4b, 6b	O	1	CH_3
4c, 5c, 6c	NCH_3	1	H
4d, 6d	NCH_3	1	H
4g	S	1	H

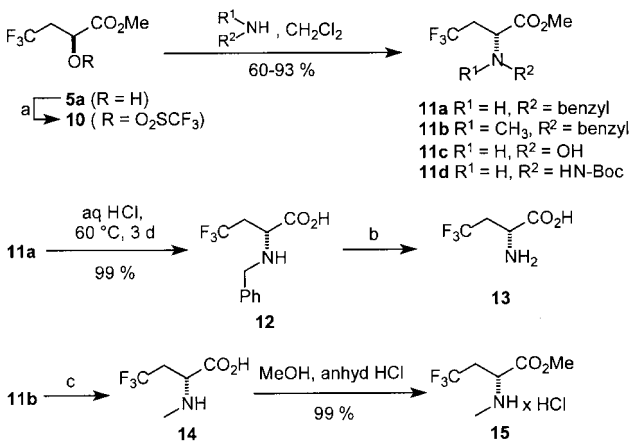


Scheme 3

A variety of *N*-substituted w-trifluoromethyl a-amino acids (**13**, **14**) and some of their derivatives (**11a-d**, **15**) are now available from trifluoromethyl α-hydroxy acid **5a** via triflate[13] **10**. Hydrogenolytic debenzylation of **11b** to give the 4,4,4-trifluoro-2-methylaminobutyric acid (**14**) needs more drastic conditions and was achieved in an autoclave at 13 MPa. We were not able to remove traces of metal ions, dissolved from the autoclave, from compounds **14**, **15**[14] because they form stable complexes. After derivatization, **15**→**17**, they can be removed by extraction with aqueous citric acid.

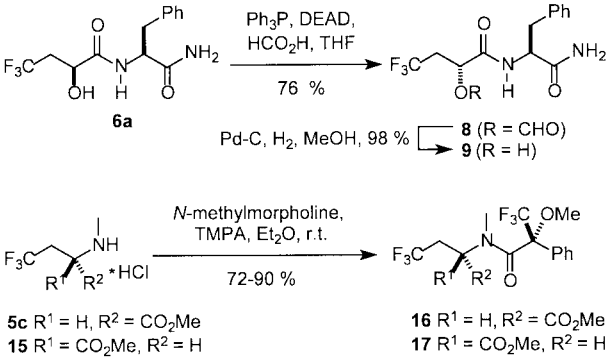
Compounds **5c** and **15** were subjected to a racemization test. For this purpose they were converted into the Mosher derivatives. Derivatization according to the standard protocol using *N*,*N*´-dicyclohexylcarbodiimide failed.[2h,15] Transformation of **5c** into **16**, and **15** into **17** was achieved in good yields with Mosher acid chloride in the presence of *N*-methylmorpholine (Scheme 5). The shift differences of compounds **16** and **17** in their ^1H and ^{19}F NMR spectra are of a size that allows determination of the optical purity. NMR analysis of crude compound **16** proves optical purity. Hence, the multi-step reaction sequence **1c**→**5c** proceeds in a strictly stereoconservative manner. Analysis of crude compound **17** revealed that the sample contained about 10% of **16**. Consequently, partial racemization takes place, during the reaction sequence **5a**→ **15**.

A racemization test was also developed for compound **6a** (Scheme 5). The configuration of the α-hydroxy acid substructure was inverted by a Mitsunobu reaction (**6a**→ **8**→ **9**). Subsequent RP-HPLC experiments revealed



Reagents and conditions: a) $(F_3CSO_2)_2O$, pyridine, 0 °C, 90%; b) 1. MeOH, Pd-C, H_2, 2. EtOH, propene oxide, 87%; c) 1. MeOH, Pd-C, H_2 (13 Mpa), 3 days, 2. aq HCl, 60 °C, 2 days; 3. EtOH, propene oxide, 26%.

Scheme 4



TMPA = (*S*)-a-trifluoromethyl-a-methoxyphenylacetyl chloride

Scheme 5

that the (*S*,*S*) and the (*R*,*S*) configured compounds were nicely separable (Figure). Furthermore, it is possible to identify **6a** and **9** unequivocally on the basis of their

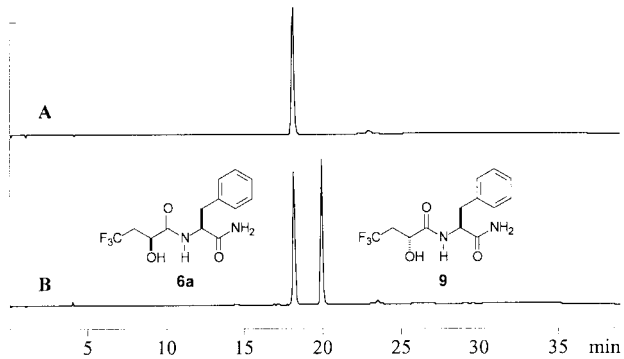


Figure RP-HPLC analysis, with UV detection at λ = 220 nm.
A) Chromatogram: (*S*,*S*) **5a** (crude peptide).
B) Chromatogram: co-injection of (*S*,*S*) **5a** and (*R*,*S*) **9**.

Table 3 Compounds **4a–d, g, 6a–d, 7** Analytical Data

Compound	yield (%)	mp (°C)	$[\alpha]_D$	IR (cm^{-1})	^1H NMR δ (ppm), *J* (Hz)	^{19}F NMR δ =
4a	91	75-77	-4[d]	3067, 1741[e]	(D_2O) 2.32-2.80 (m, 2 H), 4.44 (dd, 1 H, *J* = 9, 4)	(D_2O) 14.37 (t, $^3J_{HF}$ = 11)
4b	70	120-123	11[d]	3430, 1741[e]	(D_2O) 1.36 (s, 3 H), 2.37-2.61 (m, 1 H), 2.63-2.87 (m, 1 H)	(D_2O) 16.28 (t, $^3J_{HF}$ = 11)
4c	70	296[f]	8[g]	1604[e]	(D_2O) 2.62 (s, 3 H), 2.70-2.89 (m, 2 H), 3.75 (dd, 1 H, *J* = 5, 5)	(D_2O) 13.99 (t, $^3J_{HF}$ = 11)
4d	69	304[f]	16[g]	1591[e]	(D_2O / 1% DCl) 1.97-2.34 (m, 4 H), 2.60 (s, 3 H), 3.79 (dd, 1 H, *J* = 7, 7)	(D_2O / 1% DCl) 11.22 (t, $^3J_{HF}$ = 11)
4g	75	66-69	–	3422, 1710[e]	($CDCl_3$) 2.42 (d, 1 H, *J* = 10), 2.57 (m, 1 H), 2.95 (m, 1 H), 3.64 (m, 1 H)	(D_2O) 12.71 (t, $^3J_{HF}$ = 11)
6a	67	159	12[h]	3372, 1657[e]	(DMSO-d_6) 2.00-2.43 (m, 2 H), 2.86 (dd, 1 H, *J* = 14, 8), 3.02 (dd, 1 H, *J* = 14, 5), 4.13 (m, 1 H), 4.48 (m, 1 H), 6.16 (d, 1 H, *J* = 6), 7.15-7.28 (m, 6 H), 7.52 (s, 1 H), 7.81 (d, 1 H, *J* = 9)	(DMSO-d_6) 16.12 (t, $^3J_{HF}$ = 11)
6b	56	160	38[h]	3400, 1663, 1525[e]	(DMSO-d_6) 1.26 (s, 3 H), 2.25-2.70 (m, 2 H), 2.91 (m, 2 H), 4.45 (m, 1 H), 5.94 (s, 1 H), 7.14-7.24 (m, 6 H), 7.46 (s, 1 H), 7.64 (d, 1 H, *J* = 8)	(DMSO-d_6) 18.92 (t, $^3J_{HF}$ = 11)
6c	80	118-120	4[h]	3423, 1654[e]	(DMSO-d_6) 1.84 (s, 3 H), 2.20-2.45 (m, 2 H), 2.75 (dd, 1 H, *J* = 14, 10), 3.02 (dd, 1 H, *J* = 14, 5), 3.20 (dd, 1 H, *J* = 6, 6), 4.52 (m, 1 H), 7.10 (s, 1 H), 7.14-7.23 (m, 5 H), 7.45 (s, 1 H), 8.26 (d, 1 H, *J* = 9)	(DMSO-d_6) 20.97 (t, $^3J_{HF}$ = 11)
6d	71	132-133	8[h]	3433, 1650[e]	(DMSO-d_6) 1.51 (m, 2 H), 1.90-2.20 (m, 2 H), 1.98 (s, 3 H), 2.76 (dd, 1 H, *J* = 14, 10), 2.85 (dd, 1 H, *J* = 6, 6), 3.03 (dd, 1 H, *J* = 14, 4), 4.55 (m, 1 H), 7.08 (s, 1 H), 7.13-7.23 (m, 5 H), 7.52 (s, 1 H), 8.00 (d, 1 H, *J* = 9)	(DMSO-d_6) 13.26 (t, $^3J_{HF}$ = 11)
7	75	87		3274, 1651, 1563[e]	(DMSO-d_6) 2.50-2.76 (m, 1 H), 2.84-3.15 (m, 1 H), 3.45 (s, 1 H), 3.64 (m, 1 H), 4.29 (d, 2 H, *J* = 6), 7.22-7.35 (m, 5 H), 8.70 (dd, 1 H, *J* = 6, 6);	(DMSO-d_6) 14.59 (t, $^3J_{HF}$ = 11);

[d] *c* = 2, H_2O.
[e] KBr.
[f] sealed glass capillary.
[g] *c* = 2, 1N aq HCl.
[h] *c* = 2, DMSO.

chemical shift differences in their ^1H and ^{19}F NMR spectra. Thus, we could demonstrate that crude **6a** did not contain traceable amounts of the diastereomeric compound **9** and vice versa. Likewise, no evidence for racemization could be found in the NMR spectra of crude compound **6d**.

In the case of the thiomalic acid only the racemate was available for our experiments, therefore compounds **1g**, **2g**, **4g** and **7** are racemates.

In conclusion, we have shown that hexafluoroacetone represents an interesting protecting and activating reagent for stereoconservative orthogonal group transformations of multifunctional α-functionalized alkanoic acids.

Mps (uncorrected) were determined on a Boetius heating table. Optical rotations were measured at 589 nm (Na D line). ^1H NMR spectra were recorded at 200 MHz. Chemical shifts are reported in ppm relative to TMS in $CDCl_3$, D_2O, CD_3OD and DMSO-d_6; *J* values are given in Hz. ^{13}C NMR spectroscopy was performed at 50 MHz. ^{19}F NMR spectra were recorded at 188 MHz with trifluoroacetic acid (TFA) as an external standard. Reactions with sulfur tetrafluoride were carried out in a high-pressure stainless steel autoclave with a needle valve. For flash chromatography, silica gel (32-63 mm) was used with the solvent system given in the text. Analytical HPLC

Table 4 Compounds **4a–d, g, 6a–d, 7** ^{13}C NMR and MS Data

Compound	^{13}C NMR δ (ppm), *J* (Hz)	EI-MS [*m*/*z*]
4a	(D_2O) 37.26 (q, $^2J_{CF}$ = 28), 65.39 (q, $^3J_{CF}$ = 3), 126.40 (q, $^1J_{CF}$ = 277), 176.04 (q, $^4J_{CF}$ = 3)	113 [84, $(M\text{-}CO_2H)^+$], 39 (57), 65 (100)
4b	(D_2O) 29.06, 44.75 (q, $^2J_{CF}$ = 27), 74.37 (q, $^3J_{CF}$ = 3), 128.39 (q, $^1J_{CF}$ = 277), 180.70	127 [31 $(M\text{-}HCO_2)^+$], 111 (11), 91 (5), 69 (6), 63 (20), 42 (100)
4c	(D_2O) 35.00, 35.48 (q, $^2J_{CF}$ = 30), 58.32 (q, $^3J_{CF}$ = 3), 127.83 (q, $^1J_{CF}$ = 277), 171.94	(FAB-MS) 172 [$(M+1)^+$]
4d	(D_2O / 1% DCl) 21.52 (q, $^3J_{CF}$ = 4), 29.12 (q, $^2J_{CF}$ = 30), 31.76, 59.55, 126.78 (q, $^1J_{CF}$ = 276), 170.49	140 [100 $(M\text{-}HCO_2)^+$], 120 (17), 115 (5), 100 (8), 88 (9), 69 (19)
4g	(D_2O) 34.36 (q, $^3J_{CF}$ = 3), 38.86 (q, $^2J_{CF}$ = 27), 125.94 (q, $^1J_{CF}$ = 278), 176.34	174 (44, M^+), 156 (22), 129 (62), 109 (34), 77 (29), 69 (21), 65 (38), 44 (100)
6a	(CD_3OD) 37.88 (q, $^2J_{CF}$ = 28), 38.16, 54.16, 66.68 (q, $^3J_{CF}$ = 3), 126.66 (q, $^1J_{CF}$ = 277), 127.25, 128.79, 129.69, 136.94, 173.78, 175.24	(FAB-MS) 305 [$(M+1)^+$], 327 [$(M+Na)^+$]
6b	(CD_3OD) 27.33, 39.66, 43.50 (q, $^2J_{CF}$ = 27), 55.57, 73.33, 127.45 (q, $^1J_{CF}$ = 277), 129.76, 128.20, 130.74, 138.08, 175.88, 176.89	(FAB-MS) 319 [$(M+1)^+$], 274 [$(M\text{-}CO_2)^+$]
6c	(DMSO-d_6) 33.69, 36.24 (q, $^2J_{CF}$ = 27), 38.75, 54.40, 58.25 (q, $^3J_{CF}$ = 3), 127.18, 127.53 (q, $^1J_{CF}$ = 277), 128.94, 130.19, 138.77, 172.26, 173.82	(FAB-MS) 318 [$(M+1)^+$]
6d	(DMSO-d_6) 25.70, 30.17 (q, $^2J_{CF}$ = 28), 34.57, 38.79, 53.94, 63.04, 127.17, 128.53 (q, $^1J_{CF}$ = 277), 128.98, 130.12, 138.82, 173.43, 174.05	(FAB-MS) 332 [$(M+1)^+$]
7	(CD_3OD) 35.08 (q, $^3J_{CF}$ = 3), 39.77 (q, $^2J_{CF}$ = 28), 43.40, 125.97 (q, $^1J_{CF}$ = 277), 127.46, 127.65, 128.67, 138.55, 172.70	FAB-MS 525 [$(2\times M\text{-}1)^+$], 264 [$(M+1)^+$]

was equipped with a Capcell column (C18, SG 120, 4,6 × 250 mm, 5µm), monitoring at l = 220 nm. Mixtures of MeCN, H_2O and 0.1% TFA were used as the solvent system, with a gradient starting at 95% H_2O, and decreasing to 50% within 30 min. Organic solvents were dried and distilled prior to use. Palladium on carbon (10% Pd-C) was purchased from Aldrich.

Fluorination of Hexafluoroacetone-Protected α-Functional Carboxylic Acids with Sulfur Tetrafluoride; General Procedure A

Autoclaves with a capacity of 30 cm^3 for 15 g of starting material and a capacity of 200 cm^3 for 33-72 g of starting material were used. **1a-g** was placed into an autoclave, the reactor was evacuated, cooled to -70 °C and SF_4 (3 equiv) was condensed into it. The autoclave was heated (25-60 °C/20-25 h) in a rocking muffle furnace, then cooled to r.t., and the gaseous products were released. The remaining liquid was dissolved in CH_2Cl_2 and the organic phase was washed with sat. $NaHCO_3$, and dried ($MgSO_4$). The solvent was removed and the residue was subjected to fractional distillation to give **2a-e**, **g**.

Hydrolysis of 1,3-Dioxolan-4-ones 2a and 2b; General Procedure B

A mixture of **2a** or **2b** (1.0 mmol), *i*-PrOH (5.0 mL), H_2O (1.0 mL) and four drops of concd HCl was stirred at r.t. for 24 h. After removal of the solvent in vacuo, the residue was dissolved in H_2O (25 mL) and lyophilized to give **4a**, **4b**. Lyophilization was repeated until hexafluoroacetone hydrate could not be detected by ^{19}F NMR spectroscopy.

Hydrolysis of 1,3-Oxazolidin-4-ones 2c and 2d; General Procedure C

Compound **2c** or **2d** (1.5 mmol) was dissolved in a mixture of dioxane (10 mL), concd HCl (1.0 mL) and H_2O (1.0 mL). Then the mixture was stirred at 60 °C for 24-84 h (^{19}F NMR analysis). The solvent was removed under reduced pressure and the remaining solid was dissolved in EtOH (4.0 mL), then propene oxide (0.5 mL) was added. The resulting precipitate was collected by filtration and washed with Et_2O to obtain **4c** and **4d**.

(*rac*)-4,4,4-Trifluoro-2-mercaptobutyric Acid (4g)

Compound **2g** (1.0 g, 3.1 mmol) was dissolved in dioxane (4.0 mL), H_2O (6.0 mL), concd HCl (1.0 mL) and stirred at r.t. for 50 h. H_2O (15 mL) was added and the mixture was extracted with Et_2O (4 × 10 mL). The organic layer was dried ($MgSO_4$) and the solvent evaporated. Recrystallization from light petroleum afforded **4g** as colorless crystals.

Peptides and Amides (6a-d, 7); General Procedure D

To a solution of the nucleophile, L-phenylalanine amide (468 mg, 2.9 mmol) or benzylamine (216 mg, 2 mmol) in *i*-PrOH (7.0 mL), the hexafluoroacetone protected derivative **2a-d** (2.0 mmol) or **2g** (500 mg, 1.6 mmol) was added with stirring at r.t. After completion of the reaction (^{19}F NMR analysis), the solvent was evaporated in vacuo. The resulting crude product was purified by column chromatography (CH_2Cl_2/MeOH, for **6b**, **6c**, 20:1; **6d**, 8:1; and **7**, 10:1). Compound **6a** crystallizes from the mixture, the crystalline solid was collected by filtration. Stirring with Et_2O (15 mL) for 24 h and filtration gave the pure product.

(*S*)-4,4,4-Trifluoro-2-hydroxybutyric Acid Methyl Ester (5a)

Compound **2a** (13.3 g, 43 mmol) was dissolved in neat MeOH (10 mL) and kept at r.t. After 12 h the excess of MeOH was removed.

The residue was dissolved in CH_2Cl_2 (100 mL) and washed with H_2O (2 × 50 mL). The water phase was extracted with CH_2Cl_2 (4 × 20 mL). Drying of the combined organic phase ($MgSO_4$), evaporation of the solvent, and distillation in vacuo gave **5a** (5.9 g, 80%) as a colorless liquid; bp = 48 °C (4.0 torr); $[\alpha]^{21}_D$ = -3 (*c* 2, CH_2Cl_2).

IR (film): ν = 3446, 1747 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.44 (m, 1H), 2.68 (m, 1H), 3.04 (d, 1H, *J* = 5), 3.84 (s, 3H), 4.48 (m, 1H).

^{13}C NMR ($CDCl_3$): δ = 38.61 (q, $^2J_{CF}$ = 29), 53.70, 65.98 (q, $^3J_{CF}$ = 3), 126.02 (q, $^1J_{CF}$ = 277), 173.63.

^{19}F NMR ($CDCl_3$): δ = 14.14 (t, $^3J_{HF}$ = 9).

EI-MS: *m/z* (%) = 172 (2, M^+), 144 (3), 135 (4), 113 (87), 93 (61), 89 (11), 69 (14), 65 (100), 59 (42).

(*S*)-4,4,4-Trifluoro-2-methylaminobutyric Acid Methyl Ester Hydrochloride (5c)

Compound **2c** (200 mg, 0.63 mmol) was dissolved in MeOH (5 mL). The solution was saturated with anhyd HCl and kept at r.t. After 24 h, the excess of MeOH was removed in vacuo and the residue was stirred with Et_2O (5 mL). Filtration after 24 h gave **5c** (130 mg, 94%) as a white crystalline product; mp = 154-155 °C; $[\alpha]^{21}_D$ = 9 (*c* 2, MeOH).

IR (KBr): ν = 1747 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 2.60 (s, 3H), 3.00-3.25 (m, 2H), 3.78 (s, 3H), 4.42 (dd, 1H, *J* = 7, 5), 9.90 (br s, 2H).

^{13}C NMR (CD_3OD): δ = 32.04, 33.03 (q, $^2J_{CF}$ = 31), 53.44, 55.42 (q, $^3J_{CF}$ = 3), 125.52 (q, $^1J_{CF}$ = 277), 167.50.

^{19}F NMR (DMSO-d_6): δ = 15.92 (t, $^3J_{HF}$ = 11).

EI-MS: *m/z* (%) = 185 [4, $(M-HCl)^+$], 126 (100), 102 (9), 62 (7).

(1*R*)-Formic Acid 1-(1*S*)-1-Carbamyl-2-phenylethylcarbamoyl-3,3,3-trifluoropropyl Ester (8)

THF (40 mL) was added to a mixture of **6a** (600 mg, 1.97 mmol), Ph_3P (629 mg, 2.40 mmol), and HCO_2H (184 mg, 4.0 mmol). Diethyl azodicarboxylate (418 mg, 2.40 mmol) was added dropwise to the stirred and cooled (-5 °C) suspension over 20 min. A clear yellow solution resulted and was stirred at r.t. for additional 15 h. The solution was evaporated and purified by column chromatography (light petroleum/CH_2Cl_2/EtOAc/*i*-PrOH, 16:16:7:1) and recrystallized from $CHCl_3$/EtOAc to give **8** (500 mg, 76%) as a white crystalline product; mp = 140-142 °C; $[a]_D$ = +4 (*c* 2, DMSO).

IR (KBr): ν = 1739, 1672, 1647 cm^{-1}.

^1H NMR (DMSO-d_6): d = 2.30-2.65 (m, 2H), 2.75 (dd, 1H, *J* = 14, 10), 3.02 (dd, 1H, *J* = 14, 5 Hz), 4.47 (m, 1H), 5.28 (dd, 1H, *J* = 9, 4), 7.10-7.30 (m, 6H), 7.48 (s, 1H), 8.28 (s, 1H), 8.54 (d, 1H, *J* = 9).

^{13}C NMR (DMSO-d_6): d = 35.72 (q, $^2J_{CF}$ = 29), 38.48, 54.62, 67.04 (q, $^3J_{CF}$ = 3), 126.56 (q, $^1J_{CF}$ = 276), 127.29, 128.95, 130.19, 138.69, 161.86, 167.14, 173.37.

^{19}F NMR (DMSO-d_6): d = 15.75 (t, $^3J_{HF}$ = 11).

FAB-MS: *m/z* = 333 $[(M+1)^+]$, 355 $[(M+Na)^+]$.

(1*R*)-*N*-[(1*S*)-1-Carbamoyl-2-phenylethyl]-4,4,4-trifluoro-2-hydroxybutyramide (9)

To **8** (300 mg, 0.90 mmol) dissolved in MeOH (10 mL) were added MeOH saturated with anhyd HCl (10 drops) and Pd-C (50 mg). The mixture was stirred under H_2 (normal pressure) at r.t. for 48 h. The catalyst was removed by filtration and the solvent was evaporated in vacuo. Recrystallization from $CHCl_3$/EtOAc gave **9** (269 mg, 98%) as a white powder; mp = 140-141 °C; $[\alpha]_D$ = +38 (*c* 2, DMSO).

IR (KBr): ν = 3325, 3188, 1686, 1639 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 2.19-2.65 (m, 2H), 2.90 (dd, 1H, *J* = 14, 8), 3.06 (dd, 1H, *J* = 14, 5 Hz), 4.14 (m, 1H), 4.52 (m, 1H), 6.16 (d, 1H, *J* = 7), 7.16-7.32 (m, 6H), 7.54 (s, 1H), 7.93 (d, 1H, *J* = 9).

^{13}C NMR (CD_3OD): δ = 39.34 (q, $^2J_{CF}$ = 28), 39.54, 55.55, 67.84 (q, $^3J_{CF}$ = 3), 128.07 (q, $^1J_{CF}$ = 276), 128.20, 129.80, 130.67, 138.33, 174.58, 175.91.

^{19}F NMR (DMSO-d_6): δ = 16.25 (t, $^3J_{HF}$ = 12).

FAB-MS: *m/z* = 327 $[(M+Na)^+]$, 305 $[(M+1)^+]$.

(*S*)-4,4,4-Trifluoro-2-(trifluoromethanesulfonyloxy)butyric Acid Methyl Ester (10)

Compound **5a** (1.0 g, 6.0 mmol) and anhyd pyridine (554 mg, 7.0 mmol) was dissolved in light petroleum (10 mL) and CH_2Cl_2 (1 mL) and added dropwise to a stirred, ice-cold solution of trifluoromethanesulfonic acid anhydride (1.97 g, 7.0 mmol) in light petroleum (20 mL) and stirred for additional 10 min. Filtration from the precipitated salt and evaporation in vacuo afforded **10** (1.59 g, 90%) as slightly yellow liquid (stable at 0 °C for long time); $[\alpha]^{21}_D$ = -54 (*c* 2, CH_2Cl_2).

IR (film): ν = 1766, 1428 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.75-3.00 (m, 2H), 3.91 (s, 3H), 5.36 (dd, 1H, *J* = 8, 4).

^{13}C NMR ($CDCl_3$): δ = 36.65 (q, $^2J_{CF}$ = 31), 54.55, 76.63 (q, $^3J_{CF}$ = 3), 118.70 (q, $^1J_{CF}$ = 310), 124.63 (q, $^1J_{CF}$ = 269), 166.16.

^{19}F NMR ($CDCl_3$): δ = 2.82 (s), 13.28 (m).

EI-MS: *m/z* (%) = 285 [4, $(M-F)^+$], 245 (11), 235 (26), 207 (14), 79 (92), 69 (79), 59 (100).

(*R*)-2-Benzylamino-4,4,4-trifluorobutyric Acid Methyl Ester (11a)

To benzylamine, (707 mg, 6.6 mmol) dissolved in CH_2Cl_2 (40 mL), **10** (1.0 g, 3.3 mmol) in CH_2Cl_2 (10 mL) was added dropwise with stirring at r.t. After an additional 30 min, the solvent was distilled off and the residue was subjected to column chromatography (light petroleum/EtOAc, 7:1) to give **11a** (782 mg, 90%) as colorless, oily liquid.

$[\alpha]^{21}_D$ = +44 (*c* 2, CH_2Cl_2).

IR (film): ν = 1742 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.92 (br s, 1H), 2.30-2.70 (m, 2H), 3.59 (dd, 1H, *J* = 6, 6), 3.68 (d, 1H, *J* = 13), 3.76 (s, 3H), 3.84 (d, 1H, *J* = 13), 7.26-7.34 (m, 5H).

^{13}C NMR ($CDCl_3$): δ = 37.83 (q, $^2J_{CF}$ = 33), 52.25, 52.72, 55.65 (q, $^3J_{CF}$ = 3), 126.18 (q, $^1J_{CF}$ = 277), 127.84, 128.72, 128.98, 139.54, 174.06.

^{19}F NMR ($CDCl_3$): δ = 14.08 (t, $^3J_{HF}$ = 11).

EI-MS: *m/z* (%) = 261 (6, M^+), 202 (37), 107 (36), 92 (100), 65 (5).

(*R*)-2-(Benzylmethylamino)-4,4,4-trifluorobutyric Acid Methyl Ester (11b)

In analogy to **11a**, benzylmethylamine (933 mg, 6.6 mmol) and **10** (1.0 g, 3.3 mmol) gave, after column chromatography (light petroleum/EtOAc, 10:1), **11b** (690 mg, 76%) as a colorless, oily liquid.

$[a]^{21}_D$ = +88 (*c* 2, CH_2Cl_2).

IR (film): n = 1737 cm^{-1}.

^1H NMR ($CDCl_3$): d = 2.23 (s, 3H), 2.40-2.60 (m, 1H), 2.65-2.85 (m, 1H), 3.60-3.77 (m, 3H), 3.80 (s, 3H), 7.26-7.34 (m, 5H).

^{13}C NMR ($CDCl_3$): d = 34.66 (q, $^2J_{CF}$ = 28), 37.81, 52.07, 59.60, 60.43 (q, $^3J_{CF}$ = 3), 126.65 (q, $^1J_{CF}$ = 277), 127.78, 128.84, 129.15, 138.98, 171.08.

^{19}F NMR ($CDCl_3$): d = 13.69 (t, $^3J_{HF}$ = 11).

EI-MS: *m/z* (%) = 275 (5, M^+), 216 (12), 91 (100).

(*R*)-4,4,4-Trifluoro-2-hydroxyaminobutyric Acid Methyl Ester (11c)

In analogy to **11a** (THF as solvent), hydroxylamine (436 mg, 50% aq solution, 6.6 mmol) and **10** (1.0 g, 3.3 mmol) gave, after column chromatography (CH_2Cl_2/EtOAc, 7:1), **11c** (370 mg, 60%) as a white, crystalline solid (decomposition to a brown oil at r.t. within weeks); mp = 73-74 °C; $[\alpha]^{21}_D$ = +27 (*c* 2, MeOH).

IR (KBr): ν = 3435, 3260, 1741 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.50-2.74 (m, 2H), 3.66 (s, 3H), 3.69 (dd, 1H, *J* = 13, 7), 6.10 (dd, 1H, *J* = 7, 3), 7.72 (d, 1H, *J* = 3).

^{13}C NMR (DMSO-d_6): δ = 33.40 (q, $^2J_{CF}$ = 28), 52.86, 60.00 (q, $^3J_{CF}$ = 3), 127.28 (q, $^1J_{CF}$ = 277), 172.78.

^{19}F NMR (DMSO-d_6): δ = 15.70 (t, $^3J_{HF}$ = 12).

EI-MS: *m/z* (%) = 187 (7, M^+), 128 (100), 108 (34), 90 (9), 72 (6).

(*R*)-4,4,4-Trifluoro-2-[2-(*tert*-butoxycarbonyl)hydrazino]butyric Acid Methyl Ester (11d)

Hydrazinecarboxylic acid *tert*-butyl ester (Boc-hydrazine) (1.0 g, 6.6 mmol) and **10** (1.0 g, 3.3 mmol) were dissolved in CH_2Cl_2 (50 mL) and refluxed during 6 days to give, after column chromatography (light petroleum/EtOAc, 5:1), **11d** (941 mg, 93%) as a white, crystalline solid; mp = 75-78 °C; $[\alpha]^{21}_D$ = 29 (*c* 2, CH_2Cl_2).

IR (KBr): ν = 3374, 3244, 1743, 1696 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.45 (s, 9H), 2.40-2.79 (m, 2H), 3.78 (s, 3H), 3.95 (m, 1H), 4.52 (m, 1H), 6.17 (m, 1H).

^{13}C NMR ($CDCl_3$): δ = 28.60, 35.20 (q, $^2J_{CF}$ = 29), 53.11, 58.03, 81.68, 126.19 (q, $^1J_{CF}$ = 277), 156.96, 171.64.

^{19}F NMR ($CDCl_3$): δ = 14.22 (t, $^3J_{HF}$ = 11).

EI-MS: *m/z* (%) = 286 (1, M^+), 271 (2), 230 (16), 213 (6), 186 (25), 171 (24), 153 (11), 127 (64), 57 (100).

(*R*)-2-Benzylamino-4,4,4-trifluorobutyric Acid Hydrochloride (12)

Compound **11a** (416 mg, 1.6 mmol) was dissolved in a mixture of aq HCl (4 mL, 20%) and dioxane (1 mL) and stirred for 3 days at 60 °C. Evaporation of the solvent in vacuo gave **12** (447 mg, 99%) as slightly brown crystals; mp = 250 °C (dec.); $[\alpha]^{21}_D$ = 0 (*c* 2, 1 N aq HCl).

IR (KBr): ν = 3420, 1746 cm^{-1}.

^{1}H NMR (D_2O): d = 2.71-2.92 (m, 2H), 4.06 (s, 2H), 4.13 (dd, 1H, *J* = 5, 5), 7.17 (m, 5H).

^{13}C NMR (CD_3OD): δ = 33.62 (q, $^2J_{CF}$ = 31), 51.03, 54.19 (q, $^3J_{CF}$ = 3), 125.47 (q, $^1J_{CF}$ = 277), 129.44, 130.12, 130.62, 130.84, 168.16.

^{19}F NMR (DMSO-d_6) δ = 16.16 (t, $^3J_{HF}$ = 11).

FAB-MS: *m/z* = 248 [(M-HCl)$^+$].

(*R*)-2-Amino-4,4,4-trifluorobutyric Acid (13)

Compound **12** (300 mg, 1.1 mmol) was dissolved in MeOH (7 mL) and HOAc (1 drop), the catalyst (Pd-C) was added and the mixture was stirred in an H_2 atm. After 2 days, the solvent was distilled off, and the residue was dissolved in a small amount of EtOH (~2-3 mL) and treated with propene oxide (0.5 mL). The precipitate was filtered off and washed with Et_2O to give **13** (145 mg, 87%) as a white powder; mp = 244-247 °C (Lit.[2d] (*S*)-enantiomer): mp = 244 °C; $[\alpha]^{21}_D$ = -4 (*c* 2, 1 N aq HCl), [Lit.[2d] (*S*)-enantiomer: $[\alpha]_D$ = +3.4 (*c* 1, 5% aq HCl)].

IR (KBr): ν = 3443, 1641 cm^{-1}.

^{1}H NMR (D_2O): d = 2.43-2.82 (m, 2H), 4.06 (dd, 1H, *J* = 8, 4).

^{13}C NMR (D_2O): d = 33.62 (q, $^2J_{CF}$ = 30), 47.70 (q, $^3J_{CF}$ = 3), 125.39 (q, $^1J_{CF}$ = 277), 169.77.

^{19}F NMR (D_2O): d = 13.65 (t, $^3J_{HF}$ = 11).

FAB-MS: *m/z* = 158 [(M+1)$^+$].

(*R*)-4,4,4-Trifluoro-2-methylaminobutyric Acid (14)

Compound **11b** (1.2 g, 4.2 mmol) was dissolved in MeOH (50 mL). The catalyst (Pd-C, 150 mg) and anhyd HCl (until pH of the solution < 7) were added and the mixture was stirred in an autoclave at r.t. under 13 MPa H_2 pressure for 3 days. After releasing the pressure, the catalyst was removed by filtration, and the solution evaporated. The residue was dissolved in aq HCl (8 mL, 20%) and stirred at 60 °C for 2 days. After evaporation, the resulting solid was dissolved in EtOH and treated with propene oxide (0.5 mL). The precipitate was collected by filtration. Washing with Et_2O gave **14** (185 mg, 26%) as a pale brown powder.

Mp = 214-216 °C; $[\alpha]^{21}_D$ = -6 (*c* 2, 1 N aq HCl).

IR (KBr): n = 3435, 1604 cm^{-1}.

^{1}H NMR (D_2O/1% DCl): d = 2.58 (s, 3H), 2.75-3.00 (m, 2H), 4.17 (dd, 1H, *J* = 5, 5).

^{13}C NMR (D_2O/1% DCl): d = 34.99, 35.45 (q, $^2J_{CF}$ = 31), 58.27, 127.64 (q, $^1J_{CF}$ = 247), 172.08.

^{19}F NMR (D_2O/1% DCl): d = 16.78 (t, $^3J_{HF}$ = 11).

FAB-MS: *m/z* = 172 [(M+1)$^+$].

(*R*)-4,4,4-Trifluoro-2-methylaminobutyric Acid Methyl Ester Hydrochloride (15)

Compound **14** (100 mg, 0.58 mmol) was dissolved in MeOH (4 mL) saturated with anhyd HCl and kept overnight at r.t. Evaporation of the solvent in vacuo and storing over P_2O_5 gave **15** (129 mg, 99%) as a pale green, crystalline solid; mp = 151 °C; $[\alpha]^{21}_D$ = -4 (*c* 2, MeOH).

IR (KBr): ν = 3433, 1746 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 2.59 (s, 3H), 3.07-3.25 (m, 2H), 3.78 (s, 3H), 4.43 (dd, 1H, *J* = 7, 5), 9.91 (br s, 2H).

^{13}C NMR (DMSO-d_6): δ = 33.14, 34.04 (q, $^2J_{CF}$ = 30), 54.50, 56.45, 126.45 (q, $^1J_{CF}$ = 277), 168.44.

^{19}F NMR (DMSO-d_6): δ = 20.12 (t, $^3J_{HF}$ = 12).

EI-MS: *m/z* (%) = 185 [3, (M-HCl)$^+$], 126 (100), 103 (6), 62 (4).

(*S*)-4,4,4-Trifluoro-2-[(3,3,3-trifluoro-(*R*)-2-methoxy-2-phenylpropionyl)amino]butyric Acid Methyl Ester (16)

Compound **5c** (90 mg, 0.40 mmol) was suspended in Et_2O (5 mL), *N*-methylmorpholine (45 mg, 0.45 mmol) was added and the mixture was sonificated for 15 min. (*S*)-a-Trifluoromethyl-a-methoxyphenylacetyl chloride (114 mg, 0.45 mmol) was added and the mixture stirred for 1 day. The mixture was diluted with EtOAc (30 mL) and washed with $NaHCO_3$ solution (3 × 10 mL), aqueous citric acid (3 × 10 mL, 5%) and brine (3 × 10 mL). Drying ($MgSO_4$) and removing of the solvents gave **16** (91 mg, 72%) as colorless crystals; mp = 104-106 °C; $[\alpha]^{21}_D$ = -120 (*c* 2, CH_2Cl_2).

IR (KBr): ν = 1759, 1647 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.70-3.20 (m, 2H), 2.77 (s, 3H), 3.73 (q, 3H, $^5J_{HF}$ = 2), 3.82 (s, 3H), 4.42 (dd, 1H, *J* = 10, 2), 7.37-7.44 (m, 3H), 7.50-7.73 (m, 2H).

^{13}C NMR ($CDCl_3$): δ = 32.97 (q, $^2J_{CF}$ = 29), 36.25, 53.33, 55.97, 57.61 (q, $^3J_{CF}$ = 3), 84.90 (q, $^2J_{CF}$ = 26), 123.93 (q, $^1J_{CF}$ = 290), 126.50 (q, $^1J_{CF}$ = 276), 127.31, 128.65, 129.95, 133.38, 166.88, 169.12.

^{19}F NMR ($CDCl_3$): δ = 7.17 (br s), 13.26 (t, $^3J_{HF}$ = 12).

FAB-MS: *m/z* = 424 [$(M+Na)^+$], 402 [$(M+1)^+$], 370 [$(M-OCH_3)^+$].

(*R*)-4,4,4-Trifluoro-2-[(3,3,3-trifluoro-(*R*)-2-methoxy-2-phenylpropionyl)amino]butyric Acid Methyl Ester (17)

In analogy to **16**, compound **15** (55 mg, 0.25 mmol) was derivatized with *N*-methylmorpholine (27 mg, 0.27 mmol) and (*S*)-α-trifluoromethyl-α-methoxyphenylacetyl chloride (70 mg, 0.28 mmol) to give **17** (90 mg, 90%) as colorless crystalline solid (contains approx. 10% **16**, ^{1}H and ^{19}F NMR analysis).

^{1}H NMR ($CDCl_3$): δ = 2.70-3.20 (m, 2H), 2.74 (s, 3H), 3.76 (s, 3H), 3.77 (s, 3H), 4.58 (dd, 1H, *J* = 10, 2), 7.38-7.54 (m, 5H).

^{19}F NMR ($CDCl_3$): δ = 7.09 (br s), 13.40 (t, $^3J_{HF}$ = 11).

Acknowledgement

We gratefully acknowledge financial support by Deutsche Forschungsgemeinschaft and Bayer AG. We wish to thank Dipl. Chem. Sven Tust for RP-HPLC analyses, Mr. Adam Wolniewicz (Inst. of Org. Chem. of the Polish Academy of Sciences) for assistance with GC analyses and helpful advice.

References

(1) *Biomedical Frontiers of Fluorine Chemistry;* Ojima, I.; McCarthy, J. R.; Welch, J. T., Eds.; ACS Symposium Series 639; American Chemical Society: Washington, DC, 1996.
Biomedical Aspects of Fluorine Chemistry; Filler, R.; Kobayashi, Y., Eds.; Kodansha Ltd.; Tokyo and Elsevier Biomedical: Amsterdam, 1982.
Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry;* Wiley & Sons: New York, 1991.

(2) a) Tsushima, T.; Kawada, K.; Ishihara, S.; Uchida, N.; Shiratori, O.; Higaki, J.; Hirata, M. *Tetrahedron* **1988**, *44*, 5375.
b) Kukhar, V. P.; Soloshonok, V. A. *Fluorine-containing Amino Acids, Synthesis and Properties*; Wiley & Sons: New York, 1995.
c) Sting, A. R.; Seebach, D. *Tetrahedron* **1996**, *52*, 279.
d) Seebach, D.; Bürger, H. M.; Schickli, C. P. *Liebigs Ann. Chem.* **1991**, 669.
e) Qing, F. -L.; Peng, S.; Hu, C. -M. *J. Fluorine Chem.* **1998**, *88*, 79.
f) Uneyama, K.; Nanbu, H. *J. Org. Chem.* **1988**, *53*, 4598.
g) Walborsky, H. M.; Baum, M.; Loncrini, D. F. *J. Am. Chem. Soc.* **1955**, *77*, 3637.
h) Ojima, I.; Kato, K.; Nakahashi, K. *J. Org.Chem.* **1989**, *54*, 4511.

(3) a) Solladié-Cavallo, A.; Quazzotti, S. *Synthesis* **1991**, 177.
b) von dem Bussche-Hünnefeld, C.; Cescato, C.; Seebach, D. *Chem. Ber.* **1992**, *125*, 2795.
c) Sato, Y.; Watanabe, S.; Uneyama, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1840.
d) Konovalova, I. V.; Burnaeva, L. A.; Loginova, I. V.; Pudovik, A. N. *J. Gen. Chem. USSR* (Engl. Transl.) **1991**, *61*, 2298; *Zh. Obshch. Khim.* **1991**, *61*, 2476.
e) Uneyama, K.; Watanabe, S.; Tokunaga, Y.; *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1976.

(4) Knunyants, I. L.; Shokina, V. V.; Tyuleneva, V. V. *Dokl. Akad. Nauk. SSSR* **1966**, *169*, 594.
Sianesi, D.; Pasetti, A.; Tarli, F. *J. Org. Chem.* **1966**, *31*, 2312.
Osipov, S. N.; Golubev, A. S.; Sewald, N.; Michel, T.; Kolomiets, A. F.; Fokin, A. V.; Burger, K. *J. Org. Chem.* **1996**, *61*, 7521.

(5) Hrib, N. J.; Jurcak, J. G.; Bregna, D. E.; Burgher, K. L.; Hartman, H. B.; Kafka, S.; Kerman, L. L.; Kongsamut, S.; Roehr, J. E.; Szewczak, M. R.; Woods-Kettelberger, A. T.; Corbett, R. *J. Med. Chem.* **1996**, *39*, 4044;
Ishizaki, Masahiko (Tokuyama Soda Kk) Jpn. Kokai, Tokyo, Koho, JP 06122671, *Chem. Abstr.* **1994**, *121*, 179098;
Hrib, Nicholas J.; Jurcak, J. G. (Hoechst-Roussel Pharmaceuticals, Inc.) U.S. US 5229388, *Chem. Abstr.* **1994**, *120*, 270452.
Hrib, Nicholas J.; Jurcak, J. G. (Hoechst-Roussel Pharmaceuticals, Inc.) U.S. US 4933453, *Chem. Abstr.* **1991**, *114*, 81887.
Enomoto, M.; Kojima, A.; Komuro, Y.; Morooka, S.; Aono, S.; Sanemitsu, Y.; Mizutani, M.; Tanabe, Y. (Sumitomo Pharmaceuticals Co., Ltd.) Eur. Pat. Appl. EP 292305, *Chem. Abstr.* **1989**, *110*, 144829.

(6) Ojima, I.; Kato, K.; Jamieson, F. A.; Conway, J.; Nakahashi, K.; Hagiwara, M.; Miyamae, T.; Radunz, H. E. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 219.
Ojima, I.; Jameison, F. A.; Pete, B.; Radunz, H. E.; Schittenhelm, C.; Lindner, H. J.; Emith, A. E. *USA Drug Des. Discovery* **1994**, *11*, 91.
Koksch, B.; Sewald, N.; Jakubke, H. -D.; Burger, K. In *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I.; McCarthy, J. R.; Welch, J. T., Eds.; *ACS Symposium Series* 639; American Chemical Society: Washington, DC **1996**, 42.
Winkler, D.; Sewald, N.; Burger, K.; Chung, N. N.; Schiller, P. W. *J. Peptide Sci.* **1998**, *4*, 496.
Dal Pozzo, A.; Muzi, L.; Moroni, M.; Rondanin, R.; de Castiglione, R.; Bravo, P.; Zanda, M. *Tetrahedron* **1998**, *54*, 6019.

(7) Babb, R. M.; Bollinger, F. W. *J. Org. Chem.* **1970**, *35*, 1438.

(8) Spengler, J.; Burger, K. *Synthesis* **1998**, 67.
Spengler, J.; Burger, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, *1*, 2091.
Rudolph, M.; Burger, K. *Chem.-Ztg.* **1990**, *114*, 251.

(9) Hydroxy Acids: Burger, K.; Pires, R.; Windeisen, E. *J. Org. Chem.* **1995**, *60*, 7641.
Pires, R.; Burger, K. *Tetrahedron* **1997**, *53*, 9213.
Amino Acids: Winkler, D.; Burger, K. *Synthesis* **1996** 1419.
Mercapto Acids: Pires, R.; Burger, K. *Tetrahedron Lett.* **1996**, *37*, 8159.

(10) For synthesis of *N*-methyl aspartic and glutamic acid, see: Spengler, J.; Burger, K. *Eur. J. Org.* **2000**, 199.

(11) Pires, R.; Fehn, S.; Golubev, A.; Winkler, D.; Burger, K. *Amino Acids* **1996**, *11*, 301.

(12) For a review on the sulfur tetrafluoride fluorination technique, see: Dmowski, W. In *Houben-Weyl*, Vol E10a; Thieme Stuttgart: 1999.

(13) Effenberger, F.; Burkhard, U.; Willfahrt, J. *Angew. Chem.* **1983**, *95*, 50.

(14) Different chemical shifts, mps, and analyses of the enantiomers **4c**/**14** and **5c**/**15** were observed because of unremovable metal ion traces in **14** and **15**.

(15) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

Article Identifier:
1437-210X,E;2000,0,12,1681,1688,ftx,en;H01700SS.pdf