Asymmetric Pictet–Spengler Reactions: Synthesis of 1,2,3,4-Tetrahydroisoquinoline Carboxylic Acid (Tic) Chimeras

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Dedicated to Professor Ivar Ugi on the occasion of his 70th birthday

Abstract: A preparatively simple diastereoselective synthesis of the amino acid chimera (1*S*,3*S*)-1,2,3,4-tetrahydroisoquinoline-1,3-dicarboxylic acid from hexafluoroacetone-protected phenylalanine and glyoxylic acid hydrate via Pictet–Spengler reaction is described. The potential of the reaction of hexafluoroacetone-protected phenylalanine with other aldehydes was scrutinized.

Key words: amino acids, cyclizations, diastereoselectivity, heterocycles, quinolines

1,2,3,4-Tetrahydroisoquinolines constitute a class of compounds attracting increasing interest, due to their various biological activities. The broad spectrum of pharmacological properties includes *inter alia* antibacterial and antiplasmodial activity as well as cardiovascular and neuromodulating effects.[1]

Much effort has been devoted to the asymmetric synthesis of optically active 1-substituted 1,2,3,4-tetrahydroisoquinolines, because they are substructures of many naturally occurring alkaloids and their non-natural derivatives.[2] The stereocenter at C-1 can be constructed, *inter alia* via Pictet–Spengler[3] and Bischler–Napieralski[4] reactions. The diastereoselective Pictet–Spengler reaction using tryptamines[5] and tryptophanes[6] and chiral aldehydes as optically active starting materials have been extensively studied, whereas enantioselective reactions are rarely found in literature.[7]

1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid (Tic-3, **1**) is a phenylalanine analog in which the dihedral angle χ (χ^1 = N–C^α–C^β–C^γ, χ^2 = C^α–C^β–C^γ–C^δ) is limited to a very small range because of its bicyclic nature.[8] Tic-3 has been applied in many instances as a replacement of phenylalanine for the design of topographically constrained peptides to study effector/receptor interactions.[9] Likewise, 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (Tic-1, **2**) represents a conformationally rigid phenylglycine analog (Figure 1).

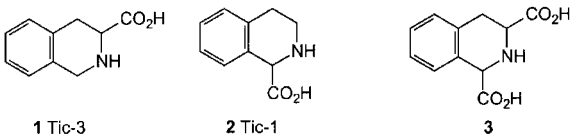
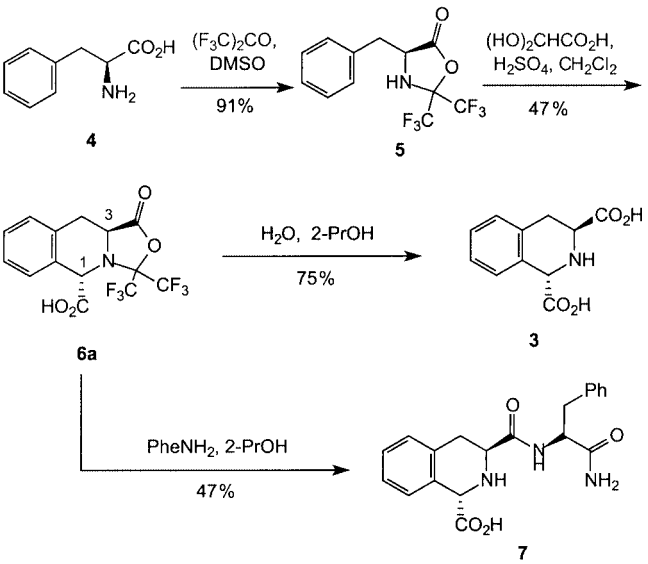


Figure 1 Structures of 1,2,3,4-tetrahydroisoquinoline carboxylic acids **1**–**3**

Recently we described a new access to *N*-methylamino[10] and *N*-ethylamino acids[11] using hexafluoroacetone as a protecting and activating reagent. When we applied the new strategy to hexafluoroacetone (HFA)-protected (*S*)-phenylalanine **5**, we found a preparatively simple synthesis of (1*S*,3*S*)-1,2,3,4-tetrahydroisoquinoline-1,3-dicarboxylic acid (**3**). The diastereoselective condensation reaction of **5** with glyoxylic acid hydrate in the presence of concentrated sulfuric acid at room temperature was successful and gave a single new product. The conversion of the starting material was complete within 3 days (monitored by ^{19}F NMR). Based on the spectroscopic data we ascribe the structure of a HFA-protected 1,2,3,4-tetrahydroisoquinoline-1,3-dicarboxylic acid **6a** to the new compound (Scheme 1).



Scheme 1

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The relative configuration of **6a** was determined by X-ray structure analysis: Both carboxylic groups are placed *trans* with respect to the bicyclic system. Since the configuration of C-3 is known to be (*S*) [sequence started from (*S*)-phenylalanine] we can assign the (*S*)-configuration to the new stereocenter at C-1. The compound crystallizes in the monoclinic space group $P2_1$ with two independent molecules in the unit cell. The configuration and bonding parameters of both molecules are very similar. Figure 2 shows one of the molecules. Both molecules establish along the b-axis a helical structure with hydrogen bonds between the carboxylic groups (Figure 3).

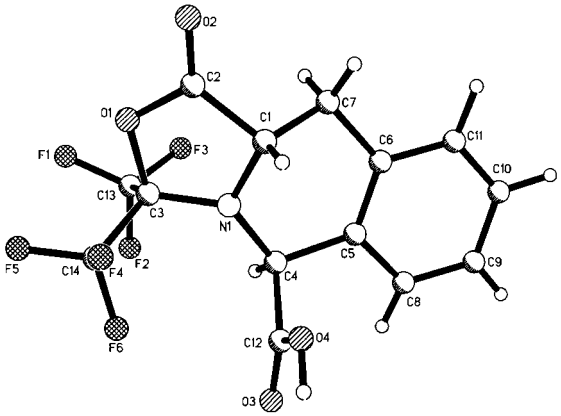


Figure 2 X-ray crystal structure of **6a**

To determine the enantiomeric purity of **6a** we synthesized the enatiomeric reference compound **6b** obtainable from (*R*)-phenylalanine. HPLC experiments revealed that the reaction sequence **4**→ **5**→ **6** occurs without racemization (ee >99.9%).

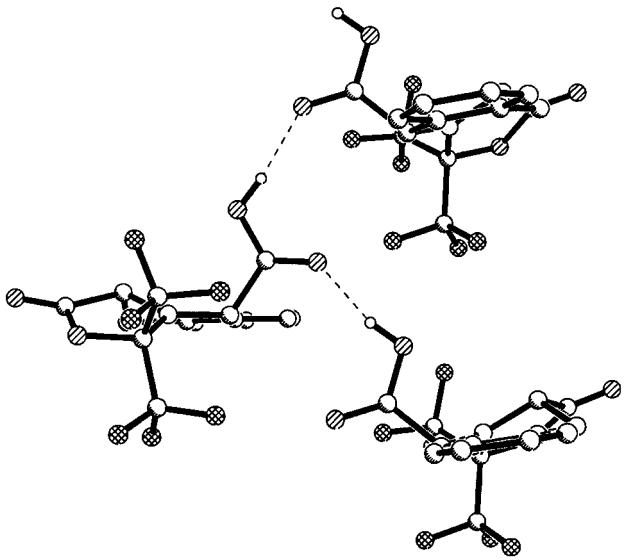
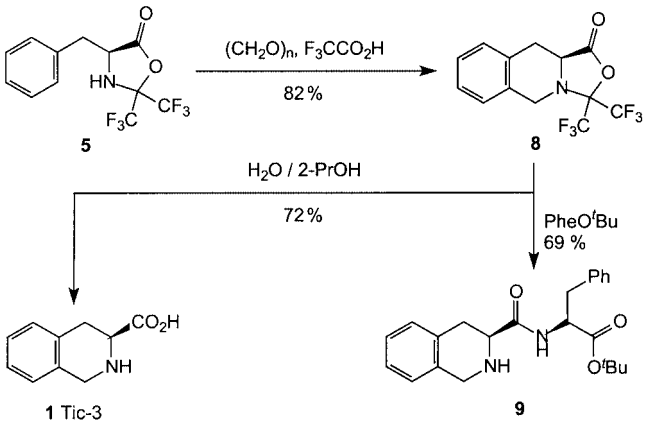


Figure 3 Helical structure along the b-axis in the unit cell of **6a**

The unprotected amino acid **3**, which was unknown to the best of our knowledge, was obtained by hydrolysis of **6a** at room temperature in propan-2-ol–water. It possesses the Tic-3 as well as the Tic-1 substructure. Therefore, it belongs to the class of chimeric amino acids,[12] which are interesting candidates for peptide modification. Furthermore, compound **3** should exhibit potential in the design of secondary structure mimetics and may be applied for inversion of the peptide sequence.

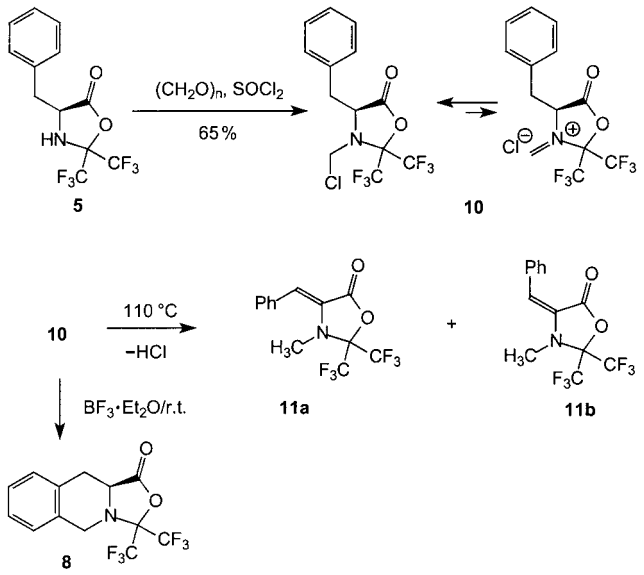
The 3-carboxy group of **6a** can be regioselectively functionalized on reaction with various nucleophiles. With amino acid amides for example dipeptide amides are formed (**6a** → **7**).

We tested the reaction of HFA-protected phenylalanine **5** with a series of aldehydes and ketones. However, only paraformaldehyde reacted with compound **5** in the presence of trifluoroacetic acid to give the Pictet–Spengler product **8** in good yields (Scheme 2). Compound **8** represents a carboxy group activated derivative of Tic-3. Therefore, it can be hydrolyzed under mild conditions (propan-2-ol–water, r.t.) to give Tic-3 (**1**). Comparison of the optical rotation measured for Tic-3 (**1**) ($[\alpha]_D$ –134) obtained via **5** → **8** → **1** with the value cited in literature ($[\alpha]_D$ –139)[13] reveals that the product is optically pure. On reaction with amino acid esters dipeptide esters are formed (**8** → **9**) (Scheme 2).



Scheme 2

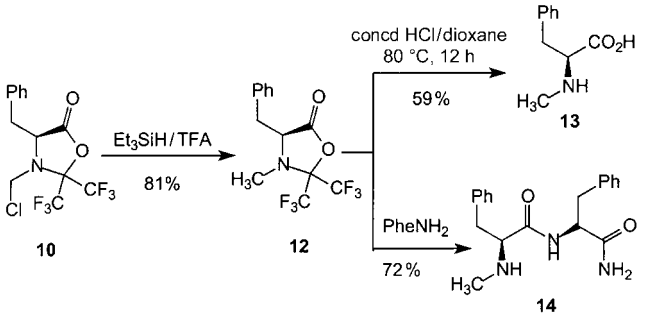
When **5** was reacted with paraformaldehyde in the presence of thionyl chloride *N*-chloromethylation was observed. The *N*-chloromethyl compound **10** is stable at room temperature. On distillation in vacuo, at about 110 °C, HCl elimination occurs (Scheme 3). However, the Pictet–Spengler product could not be isolated. The formation of *E/Z* olefins **11a** and **11b**, which can be separated by distillation (Vigreux column) under reduced pressure, should be the result of a thermal induced 1,3-HCl elimination. The azomethine ylide[14] formed first undergoes a sigmatropic 1,4-H shift to give a mixture of **11a** and **11b**.



Scheme 3

Compounds of type **10** with a Cl–CH_2–N< moiety belong to the class of 1-halogenalkylamines which exist in an equilibrium with the resonance-stabilized alkylidene iminium salts.[15] Equilibria of this type have been studied by ^{13}C NMR spectroscopy.[16] For example *N*,*N*-dimethyl(methylene)iminium chloride gives rise to four resonance signals at δ = 38.7 (s), 49.4 (t), 79.0 (s) and 168.1 (t) in the ^{13}C NMR spectrum (solvent: CH_2Cl_2/SO_2) demonstrating that there exists an equilibrium between 1-halogenalkylamine and the alkylidene iminium salt in solution. Introduction of electron-withdrawing substituents like trifluoromethyl groups results in a stabilization of the 1-halogenalkylamine form. The ^{13}C NMR spectra of all *N*-chloromethyl[10], *N*-bromomethyl[17], *N*-iodomethyl[18], and *N*-trifluoroacetoxy[19] compounds of type **10** recorded so far give rise only to a single resonance signal for the *N*-methylene carbon atom in the region of 30–73 ppm. No resonance absorption could be detected in the region of 160 ppm. From these findings we conclude that *N*-halogenmethyl-2,2-bis(trifluoromethyl)oxazolidin-5-ones exist mainly in the 1–halogenalkylamine form, with the halogen covalently bound. This could be the reason that olefins **11a** and **11b** are formed on heating compound **10**, and not the Pictet–Spengler product, which should be generated via the methyleneiminium salt. In agreement with this assumption, compound **8** was obtained from **10** upon treatment with boron trifluoride etherate at room temperature.

On treatment with triethylsilane in the presence of trifluoroacetic acid compound **10** readily gave the HFA-protected *N*-methylphenylalanine **12**. Transformation into the unprotected *N*-methylphenylalanine **13** can be accomplished on heating (80 °C) in a dioxane–concd HCl mixture (Scheme 4). Compound **12** as activated species can be directly subjected to peptide synthesis (**12** → **14**).



Scheme 4

Solvents were purified and dried prior to use. Reagents were used as purchased. TLC was performed on alumina plates coated with Merck silica gel $60F_{254}$. Compounds were visualized by spraying with a mixture of ceric(IV) nitrate, ammonium molybdate and H_2SO_4 followed by heating. Column chromatography was carried out on silica gel (32–63 μm). For the determination of enantiomeric excess in **6a**/**6b**, a Chiralpak AD column (Daicel Chemical Co. Ltd.) 25 × 0.46 cm, and as eluent system hexane–propan-2-ol–trifluoroacetic acid (90:10:0.05%, v/v), UV-detection (210 nm) and an injection volume of 20 μL were used. Under these conditions the enantiomers **6a** and **6b** eluted at 4.6 and 5.9 min, respectively. Melting points were determined with a Boëtius heating table. Optical rotations ($[\alpha]_D$) were measured using a Polartronic polarimeter (Schmidt & Haensch) in a 5 cm cell. For C, H, N analyses a CHNO-Rapid-Elemental-Analyser (Hereaus) was used. Mass spectra were recorded on a VG 12–250 (Masslab) electron ionization spectrometer (EI = 70 eV) or by VG ZAB-HSQ FAB spectrometer. ESI-FT-ICR-MS spectra were recorded on a Bruker Daltronics APEX II spectrometer (7 Tesla). IR spectra were obtained by using a FTIR spectrometer (Genesis ATI Mattson). ^1H (200.041 or 300.075 MHz), ^{13}C (50.305 or 75.462 MHz) and ^{19}F NMR (188.205 or 282.380 MHz) spectra were recorded on a Varian Gemini 200 or a Varian Gemini 300 spectrometer. Tetramethylsilane was used as reference standard for ^1H and ^{13}C NMR spectra (internal) and trifluoroacetic acid for ^{19}F NMR spectra (external). Abbreviations used are: Phe = phenylalanine, TFA = trifluoroacetic acid.

(4*S*)-4-Benzyl-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (5)
Compound **5** was obtained[20] from **4** (16.5 g, 100 mmol) as a solid. Yield: 28.5 g (91%); mp 53–54 °C; $[\alpha]_D^{25}$ –44 (*c* = 1.6, $CHCl_3$).

^1H NMR (300 MHz, $CDCl_3$): δ = 2.98 (2 H, m, NH, CH_2), 3.25 (1 H, m, CH_2), 4.18 (1 H, m, CH), 7.23–7.41 (5 H, m, C_6H_5).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.5 (CH_2), 56.0 (CH), 88.4 [m, $C(CF_3)_2$], 120.1 (q, *J* = 284 Hz, CF_3), 121.1 (q, *J* = 287 Hz, CF_3), 127.8, 129.2, 129.3, 135.0 (C_6H_5), 170.6 (CO).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –2.77 [m, $C(CF_3)_2$].

IR (KBr): ν = 1827 (C=O) cm^{-1}.

MS (EI): *m*/*z* (%) = 313 (36) $[M]^+$, 266 (16), 216 (12), 91 (100).

Anal. Calcd for $C_{12}H_9F_6NO_2$: C, 46.02; H, 2.90; N, 4.47. Found: C, 46.06; H, 2.87; N, 4.53.

(5*S*,10a*S*)-3,3-Bis(trifluoromethyl)-1-oxo-(1,2,3,4-tetrahydroisoquinolino)[2,3-*c*]oxazolidin-5-carboxylic Acid (6a)
To a solution of oxazolidinone **5** (3.1 g, 10 mmol) and glyoxylic acid monohydrate (1.8 g, 20 mmol) in CH_2Cl_2 (30 mL) was added concd H_2SO_4 (4 mL) and stirred in a flask equipped with a bubbler at r.t. for several days. After consumption of the starting material (reaction control by ^{19}F NMR), CH_2Cl_2 (60 mL) was added and then poured into a mixture of ice and aq NaOAc solution. After separation, the organic phase was washed with H_2O (2 × 50 mL), dried

($MgSO_4$) and evaporated. Triturating with pentane gave a crystalline powder, which was washed with pentane (2 × 30 mL). Filtration and drying in vacuo gave **6** as a white crystalline powder. Yield: 1.74 g (47%); mp 183–186 °C; $[\alpha]_D^{25}$ –101.8 (*c* = 1.0, $CHCl_3$); ee >99.9% (HPLC).

^{1}H NMR (200 MHz, acetone-d_6): δ = 3.05 (1 H, m, CH_2), 3.24 (1 H, m, CH_2), 5.04 (1 H, m, CH), 5.11 (1 H, s, C*H*CO_2H), 7.29–7.58 (4 H, m, C_6H_4).

^{13}C NMR (50 MHz, acetone-d_6): δ = 30.2 (CH_2), 49.7 (CH), 56.4 (*C*HCO$_2$H), 89.5 [m, *C*$(CF_3)_2$], 120.3 (q, *J* = 286 Hz, CF_3), 121.5 (q, *J* = 294 Hz, CF_3), 127.6, 127.9, 128.5, 129.4, 130.7, 131.5 (C_6H_4), 169.8 (CO), 177.1 (CO_2H).

^{19}F NMR (188 MHz, acetone-d_6): δ = 0.43 (q, *J* = 8.6 Hz, CF_3), 1.32 (q, *J* = 8.6 Hz, CF_3).

IR (KBr): ν = 1838 (C=O), 1725 cm^{-1}.

MS (EI): *m*/*z* (%) = 369 (4) $[M]^+$, 324 (33) $[M - CO_2H]^+$, 302 (5), 226 (10), 130 (100).

Anal. Calcd for $C_{14}H_9F_6NO_4$: C, 45.54; H, 2.46; N, 3.79. Found: C, 45.14; H, 2.79; N, 3.78.

X-ray Crystallographic Data: Single crystals were grown from $CHCl_3$–hexane. Monoclinic, space group $P2_1/c$, T = 223 K; a = 13.391(1) Å, b = 7.009(1) Å, c = 15.627(1) Å, β = 93.77(1)°; V = 1464.5(2) Å^3; Z = 4; D_c = 1.676 gcm^{-3}; CCD-Diffractometer (BRUKER AXS), ω-scans (0.3°), 7982 data collected, 5260 independent reflections (R_{int} = 0.037), structure solution by direct methods,[21] anisotropic refinement[22] for all nonhydrogen atoms, hydrogen atoms refined isotropic, *R*1 = 0,0476; *wR*2 = 0,1232 [I >2σ(I)]; and *R*1 = 0,0647; *wR*2 = 0.1398 for all data.[23]

(5*R*,10a*R*)-3,3-Bis(trifluoromethyl)-1-oxo-(1,2,3,4-tetrahydroisoquinolino)[2,3-*c*]oxazolidin-5-carboxylic Acid (6b)

Compound **6b** was prepared analogous to **6a** starting from (*R*)-phenylalanine. $[\alpha]_D^{25}$ +110 (*c* = 1, $CHCl_3$); ee >99.9% (HPLC). Other characteristic data are in agreement with compound **6a**.

(1*S*,3*S*)-1,2,3,4-Tetrahydroisoquinoline-1,3-dicarboxylic Acid (3)

Compound **6a** (0.74 g, 2 mmol) was dissolved in a mixture of propan-2-ol (2 mL)–H_2O (2 mL) and stirred for several days. After consumption of the starting material (reaction control by ^{19}F NMR or TLC) the solvents were removed in vacuo. Recrystallization from EtOH–H_2O gave **3** as a white solid. Yield: 0.33 g (75%); mp 209–211 °C (dec.); $[\alpha]_D^{25}$ –27 (*c* = 3, DMSO).

^{1}H NMR (200 MHz, D_2O): δ = 3.04 (1 H, m, CHC*H*$_2$), 3.22 (1 H, m, CHC*H*$_2$), 4.01 (1 H, m, CH), 5.07 (1 H, s, C*H*CO_2H), 7.11–7.39 (4 H, m, C_6H_4).

^{13}C NMR (DMSO-d_6): δ = 29.3 (CH*C*H$_2$), 51.9 (CH_2*C*H), 57.2 (CH), 126.1, 127.1, 128.1, 128.6, 130.0, 132.0 (C_6H_4), 170.1, 171.4 (2 CO_2H).

MS (EI): *m*/*z* (%) = 221 (5) $[M]^+$, 176 (59) $[M - CO_2H]^+$, 130 (100).

Anal. Calcd for $C_{11}H_{11}NO_4 \cdot 1.5H_2O$: C, 57.38; H, 5.25; N, 6.08. Found: C, 57.20; H, 5.01; N, 5.77.

(2*S*)-*N*$^{\alpha}$-[(1*S*,3*S*)-3-(1-Carboxy-1,2,3,4-tetrahydroisoquinolyl)-carbonyl]phenylalanine Amide (7)

Compound **6a** (0.74 g (2 mmol) and (*S*)-phenylalanine amide (0.48 g, 3 mmol) were dissolved in propan-2-ol (4 mL) and stirred for several days. After consumption of the starting material (reaction control by ^{19}F NMR or TLC) the precipitate was filtered and recrystallized (EtOH–H_2O) to give **7**. Yield: 0.34 g (47%); mp 218–221 °C; $[\alpha]_D^{25}$ –43 (*c* = 0.8, DMSO).

^{1}H NMR (200 MHz, DMSO-d_6): δ = 2.68 (1 H, m, CH_{2Phe}), 2.93 (3 H, m, CHC*H*$_2$, CH_{2Phe}), 4.14 (1 H, m, CH), 4.47 (1 H, m, CH_{Phe}), 4.55 (1 H, s, C*H*CO_2H), 7.00–7.43 (10 H, m, C_6H_4, C_6H_5 and $CONH_2$), 7.67 (1 H, s, $CONH_2$), 8.58 (1 H, m, CONH).

^{13}C NMR (50 MHz, DMSO-d_6): δ = 30.2 (CH*C*H$_2$), 37.6 (CH_{2Phe}), 52.3 (CH), 54.0 (CH_{Phe}), 57.7 (*C*HCO$_2$H), 126.0, 126.5, 127.0, 128.0, 128.2, 128.4, 129.3, 131.8, 132.4, 137.9 (C_6H_4 and C_6H_5), 170.8, 171.3, 173.0 (CONH, $CONH_2$, CO_2H).

MS (ESI+): *m*/*z* = 368.1607 ($[M + H]^+$ requires 368.1605).

(10a*S*)-3,3-Bis(trifluoromethyl)-1-oxo-(1,2,3,4-tetrahydroisoquinolino)[2,3-*c*]oxazolidine (8)

Compound **5** (1.56 g, 5 mmol) and paraformaldehyde (0.3 g, 10 mmol) were dissolved in $CHCl_3$ (2 mL)–TFA (2 mL). After 30 min (reaction control by ^{19}F NMR or TLC) the solvents were removed in vacuo. Recrystallization from hexane gave **8** as a solid. Yield: 1.33 g (82%); mp 81–82 °C; $[\alpha]_D^{25}$ –114.3 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.07 (1 H, m, CHC*H*$_2$), 3.20 (1 H, m, CHC*H*$_2$), 3.89 (1 H, m, CH), 4.32 (1 H, m, CH_2), 4.43 (1 H, m, CH_2), 7.12–7.28 (4 H, m, C_6H_4).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.2 (C*H*$_2$CH), 47.3 (CH_2), 54.1 (CH), 89.7 [m, *C*$(CF_3)_2$], 120.5 (q, *J* = 285 Hz, CF_3), 121.7 (q, *J* = 293 Hz, CF_3), 126.6, 127.1, 127.4, 129.8, 131.2, 131.8 (C_6H_4), 168.6 (CO).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –0.26 (q, *J* = 8.7 Hz, CF_3), 3.76 (q, *J* = 8.7 Hz, CF_3).

IR (KBr): ν = 1820 (C=O) cm^{-1}.

MS (EI): *m*/*z* (%) = 325 (46) $[M]^+$, 278 (6), 256 (7), 228 (39), 104 (100).

Anal. Calcd for $C_{13}H_9F_6NO_2$: C, 48.01; H, 2.79; N, 4.31. Found: C, 47.94; H, 2.84; N, 4.23.

(3*S*)-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic Acid (1)

Compound **8** (0.65 g, 2 mmol) was dissolved in a mixture of propan-2-ol (2 mL)–H_2O (2 mL) and stirred for several days. After consumption of the starting material (reaction control by ^{19}F NMR or TLC) the solvents were removed in vacuo. Recrystallization from EtOH–H_2O gave **1** as a white solid. Yield: 0.25 g (72%); mp 304–310 °C (Lit.[1] mp 325 °C); $[\alpha]_D^{25}$ –134 (*c* = 1.0, 0.1 N HCl) (Lit.[13] $[\alpha]_D^{25}$ –139 (*c* = 1.0, 0.1 N HCl).

MS (EI): *m*/*z* (%) = 177 (7) $[M]^+$, 132 (100) $[M - CO_2H]^+$).

(2*S*)-*N*$^{\alpha}$-[(3*S*)-3-(1,2,3,4-tetrahydroisoquinolyl)carbonyl]-phenylalanine *tert*-Butyl Ester (9)

Compound **8** (0.65 g, 2 mmol) and (*S*)-phenylalanine *tert*-butyl ester (0.67 g, 3 mmol) were dissolved in Et_2O (4 mL) and stirred for several days. After consumption of the starting material (reaction control by ^{19}F NMR or TLC) the precipitate was filtered and stirred vigorously with Et_2O to give **9** as a white powder. Yield: 0.53 g (69%); mp 142–145 °C; $[\alpha]_D^{25}$ –5.3 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.45 [9 H, s, C$(CH_3)_3$], 2.73 (1 H, m, CH_{2Phe}), 3.00–3.24 (3 H, m, CHC*H*$_2$, CH_{2Phe}), 3.56 (1 H, m, CH_{Phe}), 3.85 (1 H, m, CH_2), 3.96 (1 H, m, CH_2), 4.79 (1 H, m, CH), 7.04–7.27 (9 H, m, C_6H_4, C_6H_5), 7.70 (1 H, m, CONH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.5 [C(*C*H$_3)_3$], 31.4 (CH*C*H$_2$), 38.6 (CH_{2Phe}), 47.6 (CH_2), 53.6 (CH_{Phe}), 56.7 (CH), 82.7 [*C*$(CH_3)_3$], 126.0, 126.7, 127.1, 127.4, 128.8, 129.5, 130.0, 134.8, 136.7, 136.8 (C_6H_4, C_6H_5), 171.2 (CONH), 173.2 (*C*O$_2$Bu-*t*).

MS (EI): *m*/*z* (%) = 380 (20) $[M]^+$, 324 (71), 132 (100).

Anal. Calcd for $C_{23}H_{28}N_2O_3$: C, 72.60; H, 7.42; N, 7.36. Found: C, 72.84; H, 7.29; N, 7.72.

(4*S*)-4-Benzyl-2,2-bis(trifluoromethyl)-3-chloromethyl-1,3-oxazolidin-5-one (10)
Compound **10** was obtained[10] from **5** (6.27 g, 20 mmol) by Kugelrohr distillation as an oil. Yield: 4.70 g (65%); bp 90–100 °C (Kugelrohr)/0.7 Torr; $[\alpha]_D^{25}$ +9.7 (*c* = 1.2, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 3.22 (2 H, m, CH_2), 4.53 (1 H, m, CH), 5.01 (1 H, m, CH_2Cl), 5.26 (1 H, m, CH_2Cl), 7.19–7.38 (5 H, m, C_6H_5).

^{13}C NMR ($CDCl_3$): δ = 35.9 (CH_2), 56.1 (CH), 59.1 (m, CH_2Cl), 90.1 [m, $C(CF_3)_2$], 120.4 (q, *J* = 287 Hz, CF_3), 121.0 (q, *J* = 290 Hz, CF_3), 128.4, 129.4, 129.8, 134.1 (C_6H_5), 168.2 (CO).

^{19}F NMR ($CDCl_3$): δ = –0.43 (q, *J* = 8.6 Hz, CF_3), 3.73 (q, *J* = 9.1 Hz, CF_3).

IR (film): ν = 1845 (C=O) cm^{-1}.

MS (EI): *m*/*z* (%) = 361 (7) $[M]^+$, 326 (30) $[M - Cl]^+$, 132 (25), 91 (100).

Anal. Calcd for $C_{13}H_{10}ClF_6NO_2$: C, 43.18; H, 2.79; N, 3.87. Found: C, 43.20; H, 2.73; N, 4.08.

(*Z*)-4-Benzylidene-2,2-bis(trifluoromethyl)-3-methyloxazolidin-5-one (11a)
Compound **10** was stirred at 145 °C until the gas evolution (HCl) ceased (ca 1 h). The mixture of both isomers (**11a/11b**, 1:1) was separated by distillation over a Vigreux column (20 cm) in vacuo. Colorless oil; yield: 1.4 g (22%); bp 84 °C/1.0 Torr.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.87 (3 H, m, CH_3), 6.64 (1 H, s, CH), 7.26–7.44 (5 H, m, C_6H_5). The olefinic proton gave no NOE with the *N*-methyl group.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 33.8 (CH_3), 84.0 [m, $C(CF_3)_2$], 110.0 (CH), 120.8 (q, *J* = 255 Hz, 2 CF_3), 126.2 (C), 128.7, 129.9, 130.1, 132.9 (C_6H_5), 162.7 (CO).

^{19}F NMR (188 MHz, $CDCl_3$): δ = 1.10 [s, $C(CF_3)_2$].

IR (film): ν = 1823 (C=O), 1641 cm^{-1}.

MS (EI): *m*/*z* (%) = 325 (57) $[M]^+$, 256 (36), 228 (64), 132 (11), 131 (100).

Anal. Calcd for $C_{13}H_9F_6NO_2$: C, 48.01; H, 2.79; N, 4.31. Found: C, 48.05; H, 2.76; N, 4.54.

(*E*)-4-Benzylidene-2,2-bis(trifluoromethyl)-3-methyloxazolidin-5-one (11b)
Distillation of the reaction mixture from **11a** gave as second fraction **11b**. Yield: 1.8 g (28%); slowly crystallizing colorless oil; mp 44 °C; bp ~100 °C/1.0 Torr.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.09 (3 H, m, CH_3), 5.99 (1 H, s, CH), 7.26–7.36 (3 H, m, C_6H_5), 7.55–7.59 (2 H, m, C_6H_5). The olefinic proton gave a NOE with the *N*-methyl group.

^{13}C NMR (50 MHz, $CDCl_3$): δ = 31.1 (CH_3), 88.2 [m, $C(CF_3)_2$], 112.6 (CH), 120.9 (q, *J* = 292 Hz, 2 CF_3), 126.2 (C), 128.6, 128.7, 130.2, 132.7 (C_6H_5), 160.0 (CO).

^{19}F NMR (188 MHz, $CDCl_3$): δ = 0.76 [s, $C(CF_3)_2$].

IR (film): ν = 1823 (C=O), 1657 cm^{-1}.

MS (EI): *m*/*z* (%) = 325 (70) $[M]^+$, 278 (9), 256 (51), 228 (7), 131 (100).

Anal. Calcd for $C_{13}H_9F_6NO_2$: C, 48.01; H, 2.79; N, 4.31. Found: C, 47.96; H, 2.81; N, 4.39.

(4*S*)-4-Benzyl-2,2-bis(trifluoromethyl)-3-methyl-1,3-oxazolidin-5-one (12)
Compound **12** was obtained[10] from **5** (6.27 g, 20 mmol) via **10** (see above) as a colorless oil. Yield: 5.3 g (81%); bp 63–65 °C/0.7 Torr; $[\alpha]_D^{25}$ +14.6 (*c* = 3.6, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.64 (3 H, m, CH_3), 3.04 (1 H, m, CH_2), 3.18 (1 H, m, CH_2), 3.84 (1 H, m, CH), 7.19–7.38 (5 H, m, C_6H_5).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 33.8 (br, CH_3), 36.7 (CH_2), 62.3 (CH), 90.0 [m, $C(CF_3)_2$], 120.8 (q, *J* = 285 Hz, CF_3), 122.1 (q, *J* = 294 Hz, CF_3), 127.8, 129.0, 130.3, 135.2 (C_6H_5), 169.7 (CO).

^{19}F NMR (188 MHz, $CDCl_3$): δ = –1.69 (q, *J* = 8.1 Hz, CF_3), 4.32 (q, *J* = 8.1 Hz, CF_3).

IR (film): ν = 1842 (CO) cm^{-1}.

MS (EI): *m*/*z* (%) = 327 (60) $[M]^+$, 280 (25), 258 (7), 236 (64), 91 (100).

Anal. Calcd for $C_{13}H_{11}F_6NO_2$: C, 47.70; H, 3.36; N, 4.28. Found: C, 47.44; H, 3.28; N, 4.47.

(2*S*)-*N*-Methylphenylalanine (13)
Compound **12** (0.65 g, 2 mmol) was dissolved in dioxane (3 mL)–concd HCl (3 mL) and stirred at 80 °C for 12 h. The solution was evaporated to dryness and the residue dissolved in EtOH (1 mL). Stirring with propylene oxide (3 mL) and drying the precipitate gave **13** as a white powder. Yield: 0.21 g (59%); mp 233–241 °C (Lit.[24] mp 243–246 °C); $[\alpha]_D^{25}$ +19.0 (*c* = 0.5, 5 N HCl) {Lit.[24] $[\alpha]_D^{25}$ +7.6 (*c* = 0.5, 5 N HCl}.

Analytical data are identical with the literature data.[24]

(2*S*)-*N*$^{\alpha}$-[(2*S*)-*N*-Methylphenylalanyl]phenylalanine Amide (14)
Compound **12** (0.65 g, 2 mmol) and (*S*)-phenylalanine amide (0.48 g, 3 mmol) were dissolved in propan-2-ol (4 mL) and stirred for several days. After consumption of the starting material (reaction control by ^{19}F NMR or TLC) the solvent was evaporated and the residue purified by flash chromatography (R_f 0.25) (eluent: light petroleum–$CHCl_3$–MeOH, 3:7:1) and recrystallization (EtOH–H_2O) to give **14** as needles. Yield: 0.49 g (72%); mp 79–81 °C; $[\alpha]_D^{25}$ +8.4 (*c* = 1.5, $CHCl_3$ + 5% TFA).

^{1}H NMR (300 MHz, $CDCl_3$ + 5% TFA): δ = 2.71 (3 H, s, CH_3), 2.74 (1 H, m, CH_{2Phe}), 2.92 (1 H, m, CH_{2Phe}), 3.15 (2 H, m, CH_2), 4.26 (1 H, m, CH), 4.85 (1 H, m, CH_{Phe}), 6.16 (1 H, s, $CONH_2$), 6.90 (1 H, s, $CONH_2$), 7.01–7.30 (10 H, m, 2 C_6H_5), 7.65 (1 H, m, CONH).

^{13}C NMR (75 MHz, $CDCl_3$ + 5% TFA): δ = 32.9 (CH_3), 37.6 (CH_2), 38.8 (CH_{2Phe}), 55.4 (CH_{Phe}), 63.3 (CH), 128.5, 129.5, 129.7, 129.8, 130.2, 132.6, 135.4 (2 C_6H_5), 168.1 (CONH), 175.4 ($CONH_2$).

MS (ESI+): *m*/z = 326.18607 ($[M + H]^+$ requires 326.1863).

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