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SOME UNEXPECTED REACTIONS OF 2,2-BIS-(TRIFLUOROMETHYL)-1,3-OXAZOLIDIN-5-ONES**

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Abstract - 2,2-Bis(trifluoromethyl)-1,3-oxazolidin-5-ones and hexafluoroacetone react in dimethyl sulfoxide to give trifluoromethyl substituted 1,3-oxazolidine-4-carboxylate, 3-amino-5,5-bis(trifluoromethyl)-2(5*H*)-furanone and 4-amino-2,2-bis(trifluoromethyl)-1,3-dioxolanes depending on the substituent pattern of the amino acid. All compounds are formed *via* a common intermediate, namely *N*-hexafluoroisopropylidene α-amino acids.

INTRODUCTION

Amino acids and hexafluoroacetone readily react in dimethyl sulfoxide at room temperature to give 2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-ones,[1] which are amino group protected, carboxy group activated amino acid derivatives. Amino group protection and carboxy group activation can be achieved in only one step. Likewise, peptide bond formation on reaction with amino acid esters and deprotection of the *N*-terminal amino group occurs in one step. Consequently, peptide synthesis *via* hexafluoroacetone derivatives of amino acids is an attractive alternative strategy[2] as demonstrated impressively by a two step aspartame synthesis.[3] The main drawback of the method is the lack of reliable reproducibility of the yields. Furthermore, the method can be applied successfully only for certain multifunctional amino acids because of undesired side-reactions. The motivation of the investigations described in this paper was

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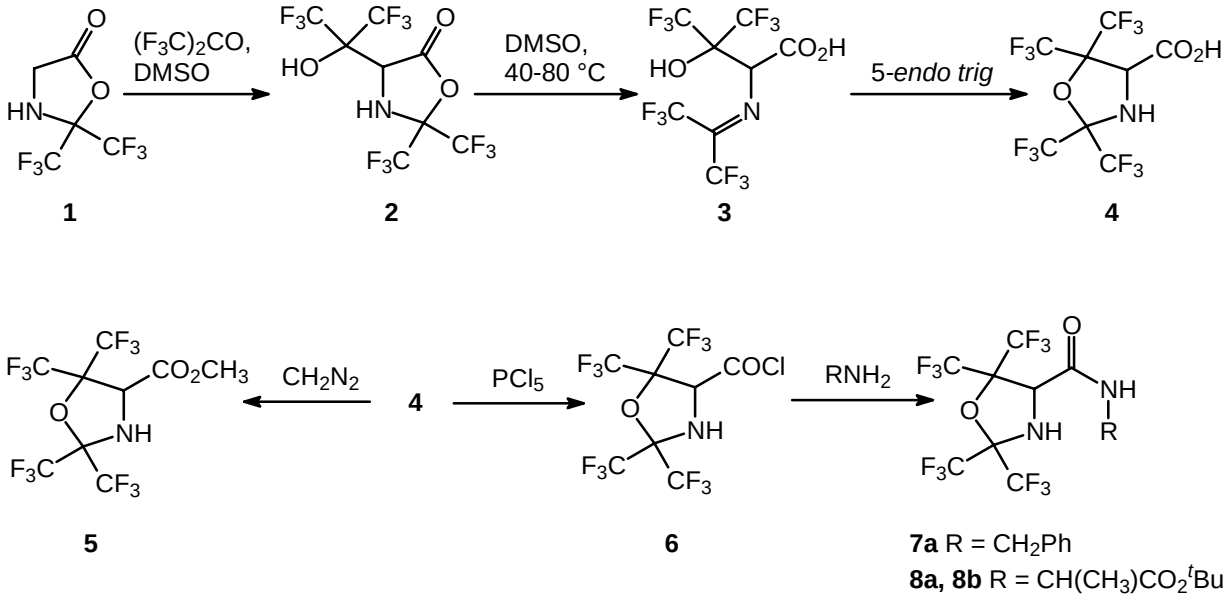
** Dedicated to Prof. A.I. Meyers on the occasion of his 70th birthday.

to study possible side-reactions during formation and aminolysis of 2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-ones, to be able to develop reaction conditions suppressing by-product formation.

RESULTS AND DISCUSSION

Glycine and hexafluoroacetone react at room temperature in DMSO to give 2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (**1**).[1] The yield decreases on heating and on prolonged reaction times. Compound (**1**) turned out to be susceptible to react further with hexafluoroacetone, especially at elevated temperatures to give exclusively 2,2,5,5-tetrakis(trifluoromethyl)-1,3-oxazolidine-4-carboxylic acid (**4**). The structural assignment is based on ^{1}H, ^{13}C and ^{19}F NMR spectral data as well as on a X-Ray structure analysis. The IR spectrum reveals the loss of the lactone moiety (1825 cm^{-1}) and the formation of a carboxylic group (ν = 1752 cm^{-1}). A plausible interpretation of this ring transformation is a two step sequence consisting of a β-elimination followed by an intramolecular ring closure (**2** $\rightarrow$ **3** $\rightarrow$ **4**). The ring closing step can be classified as a 5-*endo-trig* process.[4]



Scheme 1

Compound **4** represents a new type of pseudoproline (ψPro), a class of prolines introduced recently by M. Mutter *et al.*[5-8] **4** is a sterically highly demanding proline surrogate, which should serve as a super lipophilic building block, because of the presence of four trifluoromethyl groups. The recently introduced pseudoproline concept offers an elegant and versatile alternative to the existing chemical methodology of peptide modification. The pseudoprolines described so far have been synthesized from Ser, Thr and Cys. In contrast, **4** is a glycine derivative and represents the first ψPro having perfluoroalkyl substituents. So far, pseudoprolines found applications in providing solubilising, secondary structure disrupting building

blocks for the synthesis of peptidomimetics.[9] More recently, the ψPro concept was extended to targeting *cis*-amide bonds in biologically relevant recognition processes.[10]

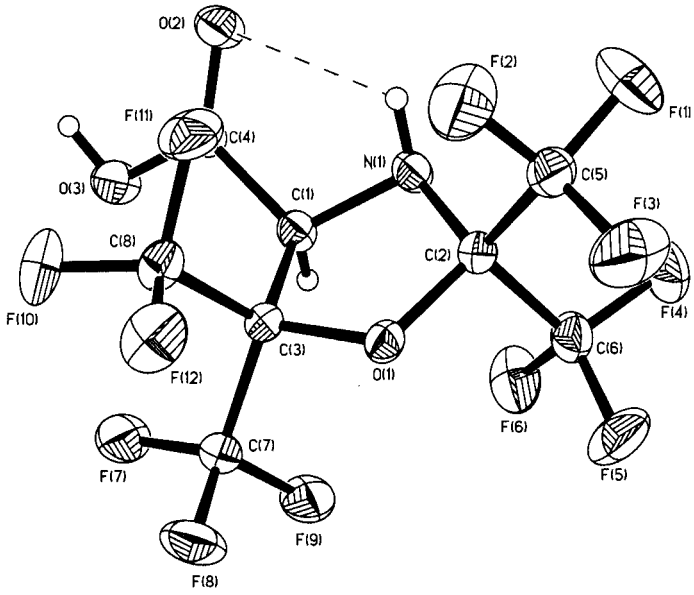


Figure 1. Molecular structure of 2,2,5,5-tetrakis(trifluoromethyl)-1,3-oxazolidine-4-carboxylic acid (**4**) with labeling and displacement ellipsoids at the 50% probability and intramolecular hydrogen bond.

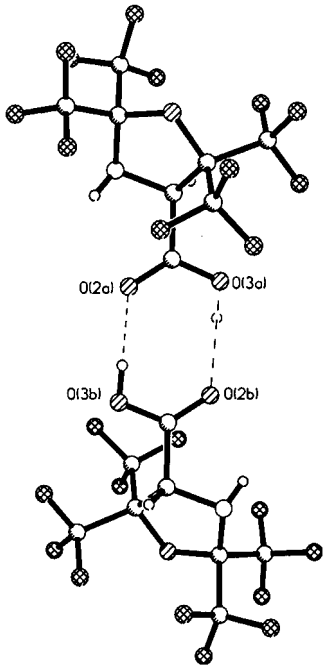


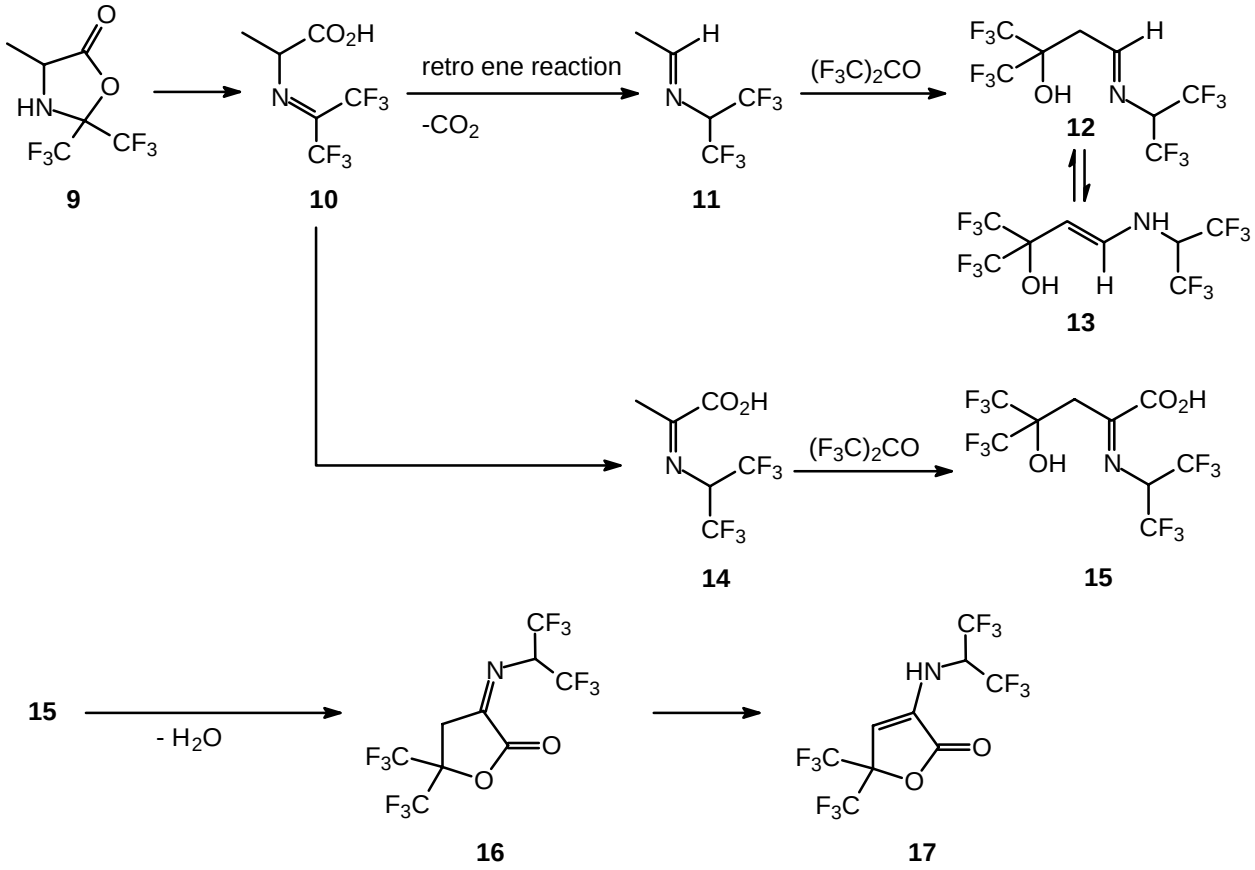
Figure 2. Centrosymmetric dimeric structure arrangement of the carboxylate groups by strong hydrogen bonds of 2,2,5,5-tetrakis(trifluoromethyl)-1,3-oxazolidine-4-carboxylic acid (**4**).

Reactivity of the amino group in **4** is dramatically reduced from sterical (Figure 1) and electronic reasons. Experiments to *N*-acylate compound (**4**) with acetyl chlorid were unsuccessful so far, even in the presence of 4-dimethylaminopyridine. On the other hand, esterification with diazomethane (**4** → **5**) and carboxy group activation *via* acid chloride (**6**) have been performed in high yield. Dipeptide formation (**6** → **8**)

can be achieved without the need of *N*-protection. On reaction with (*L*)-H-Ala-O^{t}Bu a pair of diastereomers (**8a** and **8b**) are formed which can be separated by column chromatography (Scheme 1).

When the hexafluoroacetone derivative of alanine (**9**) is treated with an excess of hexafluoroacetone at elevated temperatures a mixture of compounds is formed. The three main products have been characterized and two of them have been separated in analytically pure form. One of the open-chain products is an imine formed *via* β-elimination, CO_2 elimination (retro ene reaction) and finally aldol addition of hexafluoroacetone (**9** → **10** → **11** → **12**). The imines (**11**) have been synthesized earlier, they are fully characterized and have been used as trifluoromethyl-containing building blocks.[11] The second open-chain compound (**13**) (not isolated) we ascribe an enamine structure based on the NMR spectral data, which were extracted from the mixture of **12**/**13** produced after the tautomerisation of pure **12**. A solution of analytically pure **12** in DMSO contained after standing at room temperature for three days the two tautomers (**12**/**13**) in a 2:1 ratio, after two months in a 2:3 ratio.

In competition to the retro ene reaction, a 1,3-hydrogen shift may occur, transforming the α-alkyliden-amino into an α-imino function (**10** → **14**). The hydroxy group formed *via* aldol addition reacts with the



Scheme 2

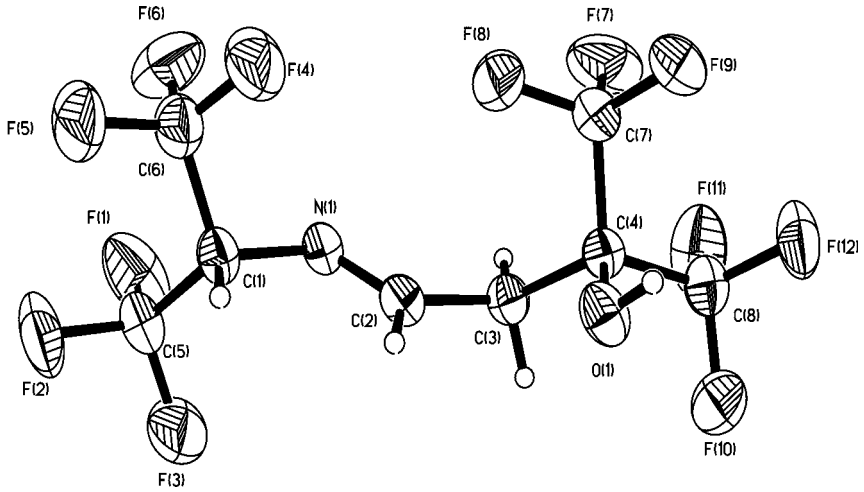


Figure 3. Molecular structure of 1,1,1-trifluoro-2-trifluoromethyl-4-(2,2,2-trifluoro-1-trifluoromethyl-ethylimino)butan-2-ol (**12**) with labeling and displacement ellipsoids at the 50% probability.

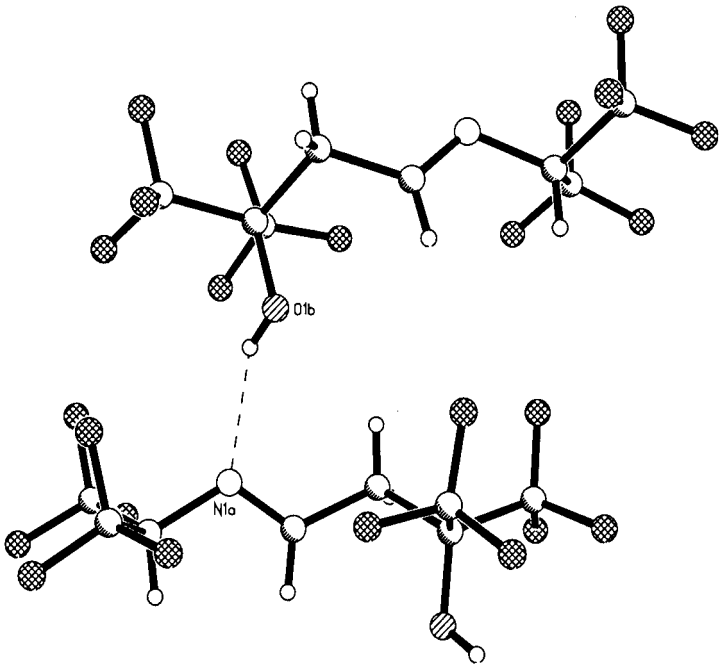
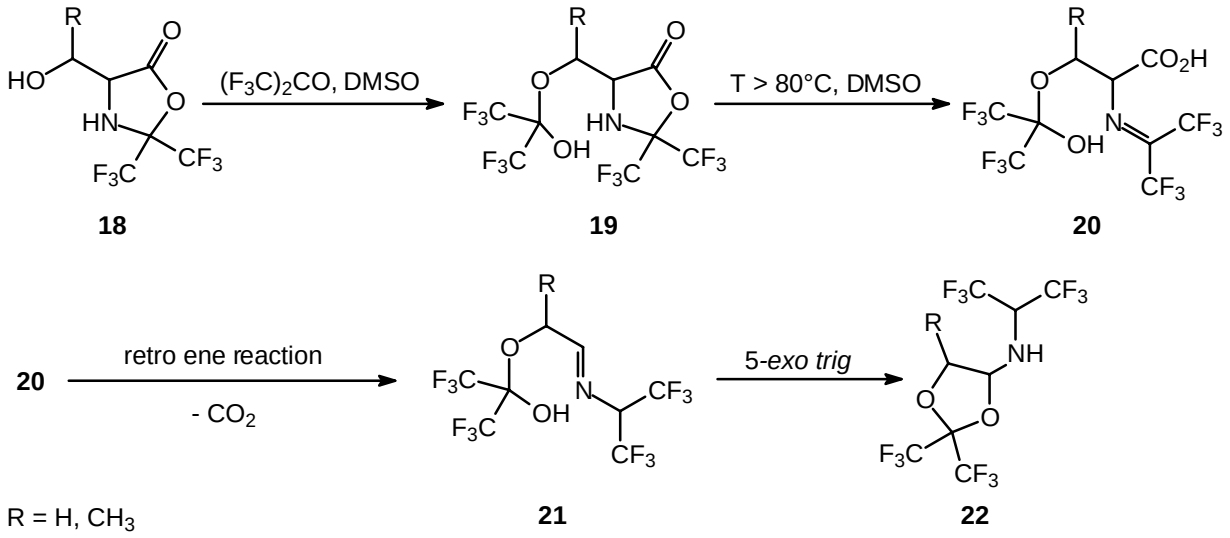


Figure 4. Intermolecular hydrogen bonds of 1,1,1-trifluoro-2-trifluoromethyl-4-(2,2,2-trifluoro-1-trifluoromethyl-ethylimino)butan-2-ol (**12**) generated by a 2_1-screw axis.

carboxylic moiety to form a γ-lactone (**15** → **16**). Finally, the exocyclic double bond migrates into the ring system to give a trifluoromethyl substituted butenolide (**16** → **17**). The synthesis of butenolides with different substitution patterns is an area of current interest due to their broad biological activities. Butenolide-containing compounds are considered as potential insecticides, bactericides, fungicides, antibiotics, anticancer agents, anti-inflammatories, allergy inhibitors, antisoriasis agents, cyclooxygenase inhibitors and phospholipase A_2 inhibitors etc.[12,13] Recently improved access to halobutenolides has been

described.[14] A 3,3,3-trifluoroethyl substituted butenolide displays high selectivity and potency against COX-2.[15]

Multifunctional amino acids, like serine and threonine, react with an excess of hexafluoroacetone in DMSO to give 4-hydroxyalkyl-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-ones (**18a, 18b**).[1] Depending on the molar excess of hexafluoroacetone the hydroxy group in the side-chain is partially blocked as hemi-ketal (**19a**, **19b**). However, the hydroxy group can be deblocked on stirring of a solution of **19** in methylene chloride in the presence of silica gel. When compound (**19a** or **19b**) was stirred in DMSO above 80°C or over a longer period (*ca*. 50 h), even at room temperature, a new type of ring transformation with elimination of CO_2 takes place.



Scheme 3

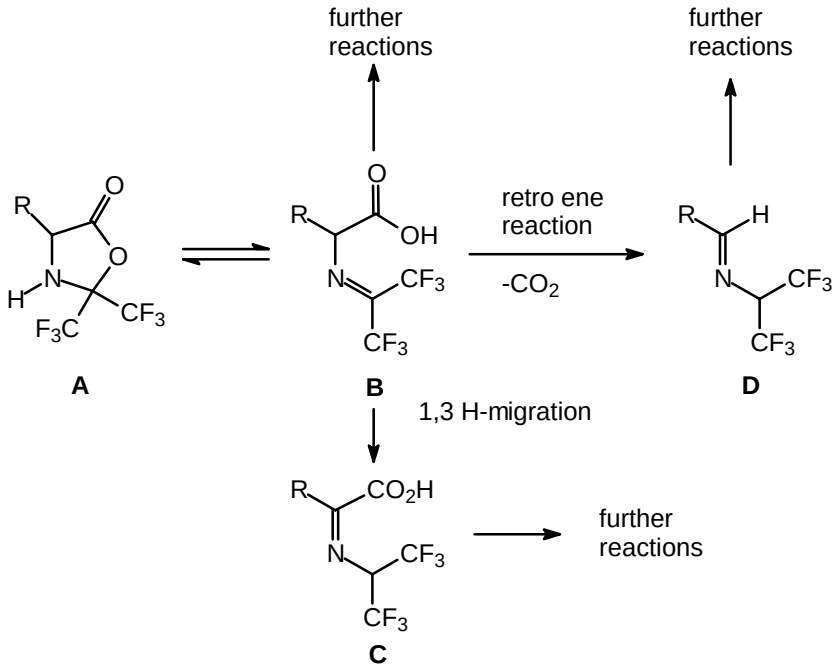
The first step of the ring transformation represents a β-elimination (**19** → **20**). **20** loses CO_2 in a retro ene reaction. Finally, the imine reacts in a 5-*exo*-*trig* process to give the 4-amino-1,3-dioxolane (**21** → **22**).

So far, we found three different reaction types, how 2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-ones can react with hexafluoroacetone (Scheme 4). The reaction starts with a β-elimination to give *N*-hexafluoroisopropylidene α-amino acids (**A**→**B**).

Route 1: The highly reactive C=N double bond of **B** may react further, *i.a.* in an intramolecular cyclization reaction.

Route 2: **B** may undergo an irreversible 1,3-hydrogen migration to give an α-imino carboxylic acid **C**, which may react further.

Route 3: Imines of type **D** are formed *via* retro ene reaction from **B.** Compounds **D** have been isolated and



Scheme 4

fully characterized.[16] They represent versatile trifluoromethyl substituted intermediates.

The reaction pathway very much depends on the substituent pattern of the amino acid. In the case of alanine routes 2 and 3 are competing.

EXPERIMENTAL

IR spectra were obtained on a Genesis ATI Mattson/Unicam FTIR spectrophotometer. ^{1}H NMR spectra were recorded at 300 MHz, 400 MHz and 600 MHz. Chemical shifts were reported in ppm relative to tetramethylsilane (TMS, δ = 0 ppm); *J* values are given in Hertz (Hz). ^{13}C NMR spectroscopy was performed at 75 MHz, 101 MHz and 151 MHz. ^{19}F NMR spectra were recorded at 282 MHz, 376 MHz and 565 MHz with trichlorofluoromethane (δ = 0 ppm) as internal standard. ^{15}N NMR spectra were recorded at 41 MHz with nitromethane (δ = 0 ppm) as internal standard. MS were recorded on a VG 12-250 (Masslab) electron ionization spectrometer (EI = 70 eV) or on a Bruker Daltronics APEX II (7 Tesla) ESI-FT-ICR-MS spectrometer. Optical rotations ($[\alpha]_D$) were measured using a Polatronic polarimeter (Schmidt & Haensch) in a 5 cm cell. Melting points were determined on a Boetius heating table. For C, H, N analyses a CHNO-Rapid-Elemental-Analyser (Hereaus) was used. For flash chromatography, silica gel (32-63 μm) was used with solvent systems given in the text. Compounds were visualized by spraying with ninhydrin (2 mg/mL) in ethanol or with a mixture of ceric(IV) sulfate (0.2 %), ammonium molybdate (5 %) and H_2SO_4 (5 %) in water followed by heating. Organic solvents were dried and distilled prior to use.

2,2,5,5-Tetrakis(trifluoromethyl)-1,3-oxazolidine-4-carboxylic acid (4). *Method A:* A stirred solution of 2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (**1**) (11.15 g, 50 mmol) in DMSO (15 mL) was reacted with an excess of hexafluoroacetone at 80 ^{o}C. The apparatus was equipped with a magnetic stirrer and sealed with a dry-ice condenser. After complete consumption of **1** (^{19}F NMR spectral analysis) the reaction mixture was poured into ice/water and extracted (5x) with CH_2Cl_2. The combined organic layer was washed with water (3x) and dried with $MgSO_4$. Then the solvent was evaporated *in vacuo.* The crude product was purified by sublimation (bath temperature: 50 ^{o}C / $5 \cdot 10^{-2}$ mbar). Yield 50 % (9.34 g). *Method B:* A stirred suspension of glycine (3.75 g, 50 mmol) in DMSO (15 mL) was reacted at rt with an excess of hexafluoroacetone. When the absorption rate of hexafluoroacetone decreased the temperature was gradually rised to 80 ^{o}C and further hexafluoroacetone was added. After completion of the reaction (^{19}F NMR spectral analysis) compound (**4**) was isolated by the above described procedure. Yield 48 % (9.36 g); white crystals, mp. 131 ^{o}C. ^{1}H NMR (600 MHz, DMSO): δ 4.91 (1H, d, ^{3}J = 7 Hz), 6.13 (1H, d, ^{3}J = 7 Hz), 14.3 (1H, br s). ^{13}C NMR (151 MHz, DMSO): δ 62.71, 84.49 (sept, $^{2}J_{CF}$ = 31 Hz), 94.00 (sept, $^{2}J_{CF}$ = 33 Hz), 119.96 (br q, $^{1}J_{CF}$ = 287 Hz), 120.85 (q, $^{1}J_{CF}$ = 288 Hz), 120.90 (br q, $^{1}J_{CF}$ = 285 Hz), 121.18 (q, $^{1}J_{CF}$ = 290 Hz), 164.8. ^{19}F NMR (565 MHz, DMSO): δ -70.3 (3F, qq, $^{4}J_{FF}$ = 8.9 Hz, $^{6}J_{FF}$ = 7.0 Hz), -72.8 (3F, qq, $^{4}J_{FF}$ = 8.9 Hz, $^{6}J_{FF}$ = 6.7 Hz), -76.3 (3F, qq, $^{4}J_{FF}$ = 9.6 Hz, $^{6}J_{FF}$ = 7.0 Hz), -76.6 (3F, qq, $^{4}J_{FF}$ = 9.6 Hz, $^{6}J_{FF}$ = 6.7 Hz). IR (KBr): ν 3600-2800, 3350, 1752 cm^{-1}. Anal. Calcd for $C_8H_3NO_3F_{12}$: C, 24.70; H, 0.78; N 3.60. Found: C, 24.60; H, 0.55; N, 3.73. MS (EI): m/z (%) = 389(4) $[M]^+$, 370(20) $[M\text{-}F]^+$, 344(39) $[M\text{-}CO_2H]^+$, 320(45) $[M\text{-}CF_3]^+$, 274(46), 206(16), 186(26), 158(15), 69(100) $[CF_3]^+$. X-Ray Crystallographic Data: Single crystals were grown from $CHCl_3$. Tetragonal, space group P4/n, T = 220(2) K; a = 16.8617(17) Å, b = 16.8617(17) Å, c = 8.5924(13) Å, V = 2443.0(5) Å^3; Z = 8; D_c = 2.116 Mgm^{-3}; CCD-Diffractometer (BRUKER AXS), 13974 data collected, 2662 independent reflections (R_{int} = 0.0354), structure solution by direct methods, anisotropic refinement[17] for all non-hydrogen atoms, hydrogen atoms refined isotropic, $R1$ = 0.0398, $wR2$ = 0.1030 [I>2σ(I)]; and $R1$ = 0.0504, $wR2$ = 0.1113 for all data.[18]

Methyl 2,2,5,5-tetrakis(trifluoromethyl)-1,3-oxazolidine-4-carboxylate (5). To a solution of **4** (1.95 g, 5 mmol) in ether (10 mL) an excess of diazomethane in ether was added. After 30 min the excess of diazomethane and the solvent were evaporated *in vacuo*. The remaining liquid was distilled under reduced pressure. Yield 79% (1.60 g); colorless liquid, bp 85 ^{o}C / 16 mbar. ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.91 (3H, s), 4.14 (1H, d, ^{3}J = 10.7 Hz), 4.60 (1H, d, ^{3}J = 10.7 Hz). ^{13}C NMR (151 MHz, $CDCl_3$): δ 54.39, 63.73, 85.90 (sept, $^{2}J_{CF}$ = 32 Hz), 96.76 (sept, $^{2}J_{CF}$ = 34 Hz), 120.49 (br q, $^{1}J_{CF}$ = 287 Hz), 121.44 (br q, $^{1}J_{CF}$ = 286 Hz), 121.46 (q, $^{1}J_{CF}$ = 288 Hz), 121.48 (q, $^{1}J_{CF}$ = 288 Hz), 164.85. ^{19}F NMR (565 MHz, $CDCl_3$): δ -72.8 (3F, qq, $^{4}J_{FF}$ = 9.6 Hz, $^{6}J_{FF}$ = 8.5 Hz), -74.0 (3F, qq, $^{4}J_{FF}$ = 9.6 Hz, $^{6}J_{FF}$ = 7.5 Hz), -76.9

(3F, qq, $^{4}J_{FF}$ = 9.8 Hz, $^{6}J_{FF}$ = 8.5 Hz), -78.8 (3F, qq, $^{4}J_{FF}$ = 9.8 Hz, $^{6}J_{FF}$ = 7.5 Hz). IR (film): ν 3340, 1765 cm^{-1}. Anal. Calcd for $C_9H_5NO_3F_{12}$: C, 26.81; H, 1.25; N, 3.48. Found: C, 26.91; H, 1.26; N, 3.72. MS (EI): m/z (%) = 403(4) $[M]^+$, 384(9) $[M - F]^+$, 344(100) $[M - CO_2CH_3]^+$, 334(34) $[M - CF_3]^+$, 324(11), 274(24), 206(14), 185(14), 69(41) $[CF_3]^+$.

2,2,5,5-Tetrakis(trifluoromethyl)-1,3-oxazolidine-4-carbonyl chloride (6). **4** (3.0 g, 7.71 mmol) and an excess of PCl_5 were mixed in an glass apparatus equipped with a condenser. After 12 h of heating at 130°C (oil bath) the reaction mixture was poured into ice/water and extracted (3x) with $CHCl_3$. The combined organic layer was washed (3x) with water and dried with $MgSO_4$. The solvent was evaporated *in vacuo*. The remaining liquid was distilled under reduced pressure. Yield 75 % (2.35 g); colorless liquid, bp 42°C / 18 mbar. ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.17 (1H, d, ^{3}J = 9.6 Hz), 4.96 (1H, d, ^{3}J = 9.6 Hz). ^{13}C NMR (151 MHz, $CDCl_3$): δ 71.96, 86.48 (sept, $^{2}J_{CF}$ = 32 Hz), 96.04 (sept, $^{2}J_{CF}$ = 34 Hz), 120.46 (br q, $^{1}J_{CF}$ = 287 Hz), 121.30 (overl. q, $^{1}J_{CF}$ = 286 Hz, $^{1}J_{CF}$ = 288 Hz), 121.46 (q, $^{1}J_{CF}$ = 288 Hz), 167.27. ^{19}F NMR (565 MHz, $CDCl_3$): δ -71.6 (3F, qq, $^{4}J_{FF}$ = 9.3 Hz, $^{6}J_{FF}$ = 8.5 Hz), -73.3 (3F, qq, $^{4}J_{FF}$ = 9.3 Hz, $^{6}J_{FF}$ = 7.7 Hz), -77.2 (3F, qq, $^{4}J_{FF}$ = 9.7 Hz, $^{6}J_{FF}$ = 8.5 Hz), -78.7 (3F, qq, $^{4}J_{FF}$ = 9.7 Hz, $^{6}J_{FF}$ = 7.7 Hz). IR (film): ν 3967-3348, 1784 cm^{-1}. MS (EI): m/z (%) = 360(10), 344(100) $[M - COCl]^+$, 324(13), 274(23), 206(23), 186(19), 158(14), 117(13), 97(11), 69(67) $[CF_3]^+$. MS (ESI): m/z (calcd) = 407.96539 (407.96552) $[M+H^+]^+$.

***N*-Benzyl-2,2,5,5-tetrakis(trifluoromethyl)oxazolidine-4-carboxamide (7)**. Benzylamine (263 mg, 2.45 mmol) was added slowly to the ice cooled, stirred solution of **6** (350 mg, 0.86 mmol) in CH_2Cl_2 (15 mL). After 3 h the solvent was evaporated *in vacuo* and the crude product was purified by column chromatography using $CHCl_3$ as eluent. Yield 62% (254 mg); colorless oil crystallized on standing, mp 77 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.39 (1H, br d, ^{3}J = 10.5 Hz), 4.44 (1H, dd, ^{2}J = 14.6 Hz, ^{3}J = 5.6 Hz), 4.45 (1H, br. d, ^{3}J = 10.5 Hz), 4.51 (1H, dd, ^{2}J = 14.6 Hz, ^{3}J = 5.6 Hz), 6.20 (1H, br t, ^{3}J = 6 Hz), 7.22-7.37 (5H, m). ^{13}C NMR (151 MHz, $CDCl_3$): δ 44.98, 64.12, 85.35 (sept, $^{2}J_{CF}$ = 31 Hz), 96.55 (sept, $^{2}J_{CF}$ = 34 Hz), 120.10 (q, $^{1}J_{CF}$ = 287 Hz), 120.89 (q, $^{1}J_{CF}$ = 288 Hz), 121.12 (q, $^{1}J_{CF}$ = 288 Hz), 121.51 (q, $^{1}J_{CF}$ = 286 Hz), 128.14, 128.40, 129.13, 136.23, 160.95. ^{19}F NMR (565 MHz, $CDCl_3$): δ -72.1 (3F, $^{4}J_{FF}$ = 9.5 Hz, $^{6}J_{FF}$ = 8.9 Hz), -73.5 (3F, qq, $^{4}J_{FF}$ = 9.5 Hz, $^{6}J_{FF}$ = 7.8 Hz), -76.9 (3F, qq, $^{4}J_{FF}$ = 9.7 Hz, $^{6}J_{FF}$ = 8.9 Hz), -78.7 (3F, qq, $^{4}J_{FF}$ = 9.7 Hz, $^{6}J_{FF}$ = 7.8 Hz). IR (KBr) ν = 3923-3336, 1720, 1697, 1562 cm^{-1}. Anal. Calcd for $C_{15}H_{10}N_2O_2F_{12}$: C, 37.67; H, 2.11; N, 5.86. Found: C, 37.8; H, 2.29; N, 5.88. MS (ESI): m/z = $[M+H]^+$ 479.06328 (479.06234), $[M+Na]^+$ 501.04498 (501.04429).

Tert-Butyl *N*-[(2,2,5,5-tetrakis(trifluoromethyl)oxazolidine-4-carbonyl)]alaninate (8a and 8b). A mixture of (*L*)-H-Ala-O^{t}Bu × HCl (187 mg, 1.03 mmol) and *N*-ethyldiisopropylamine (266 mg, 2.06 mmol) in CH_2Cl_2 (10 mL) was added slowly to an ice cooled, stirred solution of **6** (350 mg, 0.86 mmol) in CH_2Cl_2 (10 mL). After 3 h the solvent was evaporated *in vacuo.* The purification of the crude product was achieved by column chromatography using $CHCl_3$ as eluent giving **8a** and **8b** as two diastereomers.

Diastereomer 1 (eluted first, **8a**): Yield 33% (145 mg); colorless crystals, mp 121 °C. $[\alpha]_D$ = -46.0 ^{o} (c = 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.40 (3H, d, ^3J = 7.1 Hz), 1.49 (9H, s), 4.44 (2H, overl. br s), 4.51 (1H, dq, ^3J = 7 Hz, ^3J = 7 Hz), 6.61 (1H, br d, ^3J = 6 Hz). ^{13}C NMR (151 MHz, $CDCl_3$): δ 17.74, 27.93, 49.76, 64.00, 83.35, 85.32 (sept, $^2J_{CF}$ = 32 Hz), 96.62 (sept, $^2J_{CF}$ = 34 Hz), 120.50 (q, $^1J_{CF}$ = 286 Hz), 120.90 (q, $^1J_{CF}$ = 288 Hz), 121.06 (q, $^1J_{CF}$ = 288 Hz), 121.50 (q, $^1J_{CF}$ = 286 Hz), 159.90, 171.34. ^{19}F NMR (565 MHz, $CDCl_3$): δ -72.0 (3F, $^4J_{FF}$ = 9.5 Hz, $^6J_{FF}$ = 8.6 Hz), -73.5 (3F, qq, $^4J_{FF}$ = 9.5 Hz, $^6J_{FF}$ = 7.8 Hz), -76.9 (3F, qq, $^4J_{FF}$ = 9.7 Hz, $^6J_{FF}$ = 8.6 Hz), -78.8 (3F, qq, $^4J_{FF}$ = 9.7 Hz, $^6J_{FF}$ = 7.8 Hz). ^{15}N NMR (41 MHz, $CDCl_3$): δ -254, -325. IR (KBr) ν = 3888-3210, 1676, 1547 cm^{-1}. Anal. Calcd for $C_{15}H_{16}N_2O_4F_{12}$: C, 34.90; H, 3.12; N, 5.43. Found: C, 34.9; H, 2.73; N, 5.43. MS (ESI): m/z = $[M+Na]^+$ 539.08203 (539.08107), $[M+K]^+$ 555.05427 (555.05500), $[2M+Na]^+$ 1055.17195 (1055.17236).

Diastereomer 2 (eluted second, **8b**): Yield 33% (147 mg); colorless oil. $[\alpha]_D$ = +18.0 ^{o} (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (3H, d, ^3J = 7.0 Hz), 1.48 (9H, s), 4.45 (2H, overl. br s), 4.48 (1H, dq, ^3J = 7 Hz, ^3J = 7 Hz), 6.76 (1H, br d, ^3J = 6 Hz). ^{13}C NMR (101 MHz, $CDCl_3$): δ 18.50, 27.88, 49.94, 64.01, 83.29, 85.41 (sept, $^2J_{CF}$ = 32 Hz), 96.31 (sept, $^2J_{CF}$ = 34 Hz), 120.10 (q, $^1J_{CF}$ = 287 Hz), 120.86 (q, $^1J_{CF}$ = 288 Hz), 121.12 (q, $^1J_{CF}$ = 288 Hz), 121.44 (q, $^1J_{CF}$ = 286 Hz), 160.18, 170.84. ^{19}F NMR (565 MHz, $CDCl_3$): δ -72.2 (3F, $^4J_{FF}$ = 9.5 Hz, $^6J_{FF}$ = 8.8 Hz), -73.6 (3F, qq, $^4J_{FF}$ = 9.5 Hz, $^6J_{FF}$ = 7.8 Hz), -77.0 (3F, qq, $^4J_{FF}$ = 9.7 Hz, $^6J_{FF}$ = 8.8 Hz), -78.7 (3F, qq, $^4J_{FF}$ = 9.7 Hz, $^6J_{FF}$ = 7.8 Hz). ^{15}N NMR (41 MHz, $CDCl_3$): δ -254, -325. IR (film) ν = 3388-2987, 1732, 1685 cm^{-1}. Anal. Calcd for $C_{15}H_{16}N_2O_4F_{12}$: C, 34.90; H, 3.12; N, 5.43. Found: C, 34.9; H, 3.19; N, 5.42. MS (ESI): m/z = 539.08220 (539.08107) $[M+Na]^+$, 555.05650 (555.05500) $[M+K]^+$, 1055.17526 (1055.17236) $[2M+Na]^+$.

1,1,1-Trifluoro-2-trifluoromethyl-4-(2,2,2-trifluoro-1-trifluoromethyl-ethylimino)butan-2-ol (12). A stirred suspension of L-alanine (8.9 g, 100 mmol) in DMSO (30 mL) was reacted at rt with an excess of hexafluoroacetone. When the absorption rate of hexafluoroacetone decreased the temperature was gradually rised to 140 ^{o}C and further hexafluoroacetone was added. After completion of the reaction (^{19}F NMR spectral analysis), the reaction mixture was poured into ice/water and extracted (5x) with CH_2Cl_2. The combined organic layer was washed with water (3x) and dried with $MgSO_4$. Then the solvent was evaporated *in vacuo.* From the crude product **12** and **17** were isolated by column chromatography using $CHCl_3$ as eluent. Yield for **12** (eluted second) 13 % (4.63 g), colorless crystals, mp 70 °C. ^{1}H NMR (400

MHz, DMSO): δ 3.06 (2H, br d, ^3J = 5.2 Hz), 5.49 (1H, sept, $^3J_{HF}$ = 7.1 Hz), 8.25 (1H, br t, ^3J = 5.2 Hz), 8.58 (1H, s). ^{13}C NMR (101 MHz, DMSO): δ 36.77, 68.15 (sept, $^2J_{CF}$ = 29 Hz), 74.75 (sept, $^2J_{CF}$ = 30 Hz), 121.63 (overl. q, $^1J_{CF}$ = 280 Hz), 122.72 (q, $^1J_{CF}$ = 288 Hz), 122.75 (q, $^1J_{CF}$ = 289 Hz), 172.96. ^{19}F NMR (376 MHz, DMSO): δ -69.8 (6F, d, $^2J_{HF}$ = 7 Hz), -75.5 (6F, s). IR (KBr) ν = 3404, 1670 cm^{-1}. MS (EI): m/z (%) = 359 $[M]^+$, 340(27) $[M\text{-}F]^+$, 290(84) $[M\text{-}CF_3]^+$, 178(100), 124(31), 69(61) $[CF_3]^+$. X-Ray Crystallographic Data: Single crystals were grown from CH_2Cl_2. Monoclinic, space group P2(1)/n, T = 220(2) K; a = 11.5359(12) Å, b = 9.4117(9) Å, c = 12.3420(12) Å, β = 116.174(2)°; V = 1202.6(2) Å^3; Z = 4; D_c = 1.984 Mgm^{-3}; CCD-Diffractometer (BRUKER AXS), 6985 data collected, 2600 independent reflections (R_{int} = 0.0277), structure solution by direct methods, anisotropic refinement[17] for all non-hydrogen atoms, hydrogen atoms refined isotropic, $R1$ = 0.0410, $wR2$ = 0.1045 [I>2σ(I)]; and $R1$ = 0.0599, $wR2$ = 0.1189 for all data.[18]

1,1,1-Trifluoro-2-trifluoromethyl-4-(2,2,2-trifluoro-1-trifluoromethylethylamino)but-3-en-2-ol (13). The compound (**13**) has not been isolated in analytically pure form, but it was characterized spectroscopically from an analytically pure mixture of the two tautomers (**12/13**). ^{1}H NMR (600 MHz, DMSO): δ 4.79 (1H, d, ^3J = 14.8 Hz), 5.59 (1H, dsept, ^3J = 10.6 Hz, $^3J_{HF}$ = 7 Hz), 6.61 (1H, dd, ^3J = 13.7 Hz, ^3J = 9.0 Hz), 7.01 (1H, br t, ^3J = 9.8 Hz). ^{13}C NMR (151 MHz, DMSO): δ 57.07 (sept, $^2J_{CF}$ = 30 Hz), 74.99 (sept, $^2J_{CF}$ = 32 Hz), 87.55 (s), 122.25 (overl. q, $^1J_{CF}$ = 280 Hz), 122.90 (overl. q, $^1J_{CF}$ = 289 Hz), 139.92. ^{19}F NMR (376 MHz, DMSO): δ -70.9 (6F, d, $^2J_{HF}$ = 7 Hz), -76.7 (6F, s).

5,5-Bis(trifluoromethyl)-3-(2,2,2-trifluoro-1-trifluoromethylethylamino)-2(5*H*)-furanone (17). Preparation and purification as described for **12**. Yield 15 % (5.84 g), colorless crystals, mp 38 °C. ^{1}H NMR (400 MHz, DMSO): δ 5.78 (1H, dsept, ^3J = 10.3 Hz, $^3J_{HF}$ = 7.2 Hz), 6.80 (1H, s), 8.70 (1H, d, ^3J = 10.3 Hz). ^{13}C NMR (101 MHz, DMSO): δ 56.69 (sept, $^2J_{CF}$ = 32 Hz), 80.79 (sept, $^2J_{CF}$ = 31 Hz), 100.83, 120.42 (q, $^1J_{CF}$ = 287 Hz), 121.74 (overl. q, $^1J_{CF}$ = 284 Hz), 121.79 (q, $^1J_{CF}$ = 284 Hz), 139.19, 163.92. ^{19}F NMR (376 MHz, DMSO): δ -70.0 (6F, d, $^2J_{HF}$ = 7 Hz), -74.9 (6F, s). IR (KBr) ν = 3362, 1821, 1677 cm^{-1}. MS (EI): m/z (%) = 385(25) $[M]^+$, 338(36), 316(52) $[M\text{-}CF_3]^+$, 288(100), 238(51), 218(69), 190(31), 170(26), 69(85) $[CF_3]^+$. MS (ESI): m/z = 383.99027 (383.98994) $[M\text{-}H^+]^-$, 768.98677 (768.98771) $[2M\text{-}H^+]^-$.

4-(2,2,2-Trifluoro-1-trifluoromethylethylamino)-2,2-bis(trifluoromethyl)-1,3-dioxolane (22a). A stirred suspension of L-serine (15.5 g, 147 mmol) in DMSO (50 mL) was reacted with an excess of hexafluoroacetone in an glass apparatus equipped with a dry-ice condenser. Hexafluoroacetone was added in such a rate that a slightly exothermic reaction takes place. After completion of the reaction (^{19}F NMR

spectral analysis) the mixture was stirred in the presence of an excess of hexafluoroacetone at rt for 50 h. Then the reaction mixture was poured into ice/water and extracted with CH_2Cl_2 (5x). The organic layer was washed with water (3x), then the solvent was distilled off *in vacuo*. The remaining liquid was purified by distillation. Yield 48% (26.4 g); colorless liquid, bp 59 °C / 1 mbar. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.77 (1H, br t, ^3J = 9 Hz), 3.90 (1H, dd, ^2J = 9 Hz, ^3J = 6 Hz), 3.99 (1H, dsept, ^3J = 8 Hz; $^3J_{HF}$ = 7 Hz), 4.49 (1H, dd, ^2J = 9 Hz, ^3J = 6 Hz), 5.50 (1H, dt, ^3J = 9 Hz, ^3J = 6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 59.89 (sept, $^2J_{CF}$ = 32 Hz), 71.11, 92.84, 100.63 (sept, $^2J_{CF}$ =34 Hz), 120.74 (q, $^1J_{CF}$ = 290 Hz), 122.11 (q, $^1J_{CF}$ = 282 Hz), 122.37 (overl. q, $^1J_{CF}$ = 282 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ -71.2 (3F, dq, $^4J_{FF}$ = 9 Hz, $^3J_{HF}$ = 7 Hz), -72.6 (3F, dq, $^4J_{FF}$ = 9 Hz, $^3J_{HF}$ = 7 Hz), -79.8 (3F, q, $^4J_{FF}$ = 8 Hz), -80.4 (3F, q, $^4J_{FF}$ = 8 Hz). IR (film): ν = 3420 cm^{-1}. Anal. Calcd for $C_8H_5NO_2F_{12}$: C, 25.62; H, 1.34; N, 3.73. Found: C, 25.50; H, 1.29; N, 3.53. MS (EI) m/z (%): 375(5) $[M]^+$, 306(70), 209(100), 192(82), 142(28), 128(38), 69(77) $[CF_3]^+$, 28(33).

(5*R*),(4*S*)-(2,2,2-Trifluoro-1-trifluoromethylethylamino)-5-methyl-2,2-bis(trifluoromethyl)-1,3-dioxolane (22b). L-Threonine (5.96 g, 50 mmol) was reacted with an excess of hexafluoroacetone in DMSO (15 mL). The gas was added in such a rate that an exothermal reaction occurred. When the reaction was complete (^{19}F NMR spectral analysis) the temperature was rised to 90 °C and the mixture stirred till CO_2 elimination occurred. The product was isolated by extraction with CH_2Cl_2 (see above) then purified with column chromatography using $CHCl_3$ as eluent. Yield (for the crude diastereomeric mixture **22b**/**22c**) 78 % (15.16 g) with *de* = 90 %; colorless liquid. The determination of the absolute configuration at C-4 was established by NMR spectrometry, and is based on the known absolute configuration of C-5 (*R)* and by ^{1}H{^{1}H} homonuclear and ^{1}H{^{19}F} heteronuclear NOE measurements. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.45 (3H, d, ^3J = 6.1 Hz), 2.68 (1H, br t, ^3J = 10 Hz), 3.93 (1H, dsept, ^3J = 8.4 Hz, $^3J_{HF}$ = 6.5 Hz), 4.03 (1H, br dq, ^3J = 6 Hz, ^3J = 6 Hz), 4.88 (1H, dd, ^3J = 10.9 Hz, ^3J = 7.6 Hz). ^{13}C NMR (151 MHz, $CDCl_3$) δ 16.23, 59.80 (sept, $^2J_{CF}$ = 32 Hz), 78.86, 97.88, 99.38 (sept, $^2J_{CF}$ = 35 Hz), 120.76 (overl. q, $^1J_{CF}$ = 288 Hz), 122.15 (overl. q, $^1J_{CF}$ = 283 Hz). ^{19}FNMR (565 MHz, $CDCl_3$) δ -72.7 (3F, dq, $^4J_{FF}$ = 9.7 Hz, $^3J_{HF}$ = 6.5 Hz); -74.0 (3F; dq, $^4J_{FF}$ = 9.7 Hz, $^3J_{HF}$ = 6.5 Hz), -81.4 (3F, q, $^4J_{FF}$ = 8.1 Hz), -82.0 (3F, q, $^4J_{FF}$ = 8.1 Hz). IR ($CHCl_3$) ν = 3402, 1231, 1224 cm^{-1}. Anal. Calcd for $C_9H_7NO_2F_{12}$: C, 27.78; H, 1.81; N, 3.60. Found: C, 27.91; H, 1.86; N, 3.68.

(5*R*),(4*R*)-(2,2,2-Trifluoro-1-trifluoromethylethylamino)-5-methyl-2,2-bis(trifluoromethyl)-1,3-dioxolane (22c). **22c** has been characterized spectroscopically from an analytically pure diastereomeric mixture of **22b** and **22c**, as the minor component. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.37 (3H, d, ^3J = 6.5 Hz), 2.56 (1H, br t, ^3J = 10 Hz), 3.89 (1H, dsept, ^3J = 8.4 Hz, $^3J_{HF}$ = 6.6 Hz), 4.66 (1H, br dq, ^3J = 6 Hz,

^{3}J = 6 Hz), 5.28 (1H, dd, ^{3}J = 12.3 Hz, ^{3}J = 6.0 Hz). ^{13}C NMR (151 MHz, $CDCl_3$) δ 14.54, 60.95 (sept, $^{2}J_{CF}$ = 32 Hz), 77.60, 93.47, 99.67 (sept, $^{2}J_{CF}$ = 33 Hz), 120.52 (overl. q, $^{1}J_{CF}$ = 288 Hz), 122.10 (overl. q, $^{1}J_{CF}$ = 286 Hz). ^{19}FNMR (565 MHz, $CDCl_3$) δ -72.5 (3F, dqq, $^{4}J_{FF}$ = 9.9 Hz, $^{3}J_{HF}$ = 6.4 Hz, $^{8}J_{FF}$ = 2.6 Hz); -74.2 (3F; dq, $^{2}J_{FF}$ = 9.9 Hz, $^{3}J_{HF}$ = 6.6 Hz), -80.9 (3F, br q, $^{4}J_{FF}$ = 8.6 Hz), -81.1 (3F, qq, $^{4}J_{FF}$ = 8.6 Hz, $^{8}J_{FF}$ = 2.5 Hz).

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REFERENCES

1. F. Weygand, K. Burger, and K. Engelhardt, *Chem. Ber.*, 1966, **99**, 1461.
2. K. Burger, M. Rudolph, S. Fehn, A. Worku, and A. Golubev, *Amino Acids*, 1995, 195.
3. K. Burger and M. Rudolph, *Chem.-Ztg.*, 1990, **114**, 249.
4. J. E. Baldwin, J. Chem. Soc., *Chem. Commun.*, 1976, 734; 738.
5. T. Haack and M. Mutter, *Tetrahedron Lett.*, 1992, **33**, 1589; T. Wöhr, F. Wahl, A.; Nefzi, B. Rohwedder, T. Sato, X. Sun, and M. Mutter, *J. Am. Chem. Soc.*, 1996, **118**, 9218.
6. A. Mutter, A. Nefzi, T. Sato, X. Sun, F. Wahl, and T. Wöhr, *Peptide Res.*, 1995, **8**, 145.
7. P. Dumy, M. Keller, D. E. Ryan, B. Rohwedder, T. Wöhr, and M. Mutter, *J. Am. Chem. Soc.*, 1997, **119**, 918; M. Keller, C. Sager, P. Dumy, M. Schutkowski, G. Fischer, and M. Mutter, *J. Am. Chem. Soc.*, 1998, **120**, 2714; T. Rückle, P. de Lavallaz, M. Keller, P. Dumy, and M. Mutter, *Tetrahedron*, 1999, **55**, 11281.
8. A. Wittelsberger, M. Keller, L. Scarpellino, A. Patiny, H. Acha – Orbea, and M. Mutter, *Angew. Chem.*, 2000, **112**, 1153; *Angew. Chem., Int. Ed.*, 2000, **39**, 1111.
9. M. Keller, T. Wöhr, P. Duny, L. Patiny, and M. Mutter, *Chemistry*, 2000, **23**, 4358.
10. M. Mutter, T. Wöhr, S. Gioria, and M. Keller, *Biopolymers*, 1999, **51**, 121.
11. K. Burger, G. Dirnsteiner, and J. Fehn, *Liebigs Ann. Chem.*, 1971, **747**, 45.
12. Y. S. Rao, *Chem. Rev.*, 1964, **64**, 353; Y. S. Rao, *Chem. Rev.*, 1976, **76**, 625; D.W. Knight, *Contemp. Org. Synth. I*, 1994, 287; S. Ma and Z. Shi, *J. Org. Chem.*, 1998, **63**, 6387; S. Ma, Z. Shi, and Z. Yu, *Tetrahedron Lett.*, 1999, **40**, 2393.
13. S. S. Kindermann and B. L. Ferringa, *Tetrahedron Asymm.*, 1998, **9**, 1215.
14. S. Ma, Z. Shi, and Z. Yu, *Tetrahedron*, 1999, **55**, 12137.
15. L. Tan, C. Y. Chen, R. D. Larsen, T. R. Verhoeven, and P. J. Reider, *Tetrahedron Lett.*, 1998, **39**, 3961.
16. K. Burger and E. Burgis, *Liebigs Ann.*, 1970, **741**, 39.
17. G. M. Sheldrick, *SHELXS 97, Program Used to Solve and to Refine Structure*; University of Göttingen: Germany, 1997.
18. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre, CCDC No. 179733 for **4** and CCDC No. 179734 for **12**. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1233 336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).