Supporting Information

Title: **A Novel Synthesis of (S)-5,5,5,5',5',5'-Hexafluoroleucine**

Authors: Xuechao Xing, Alfio Fichera and Krishna Kumar*

Department of Chemistry, Tufts University
62 Talbot Avenue, Medford, MA 02155-5813

General Procedures. Melting points were determined in open capillaries on a MEL-TEMP II apparatus (Laboratory Devices, Inc., Holliston, MA) and are uncorrected. All reactions requiring non-aqueous conditions were performed in oven-dried glassware under positive pressure of argon. Flash column chromatography was performed by forced flow of solvent using Kieselgel 60 SiO_2 (230-240 mesh) gel (EM Science) packed into glass columns using standard litertaure procedures.[1] Analytical thin layer chromatography was performed using E. Merck silica gel Kieselgel 60 F_{254} (0.25 mm) plates. Compounds were visualized by UV light, exposure to iodine vapour or by staining with a ninhydrin solution followed by heating. Reagents and solvents were of reagent grade or better and were obtained from Aldrich Chemical Co., Fluka Chemie AG, Lancaster Synthesis or Novabiochem Corp. Deuterated solvents were obtained from Cambridge Isotope Laboratories.

Infra-red spectra were obtained on a Mattson 1000 FT–IR instrument with a 4 cm^{-1} bandpass. Spectra of solid samples were obtained as solid thin-films or dissolved in thin layers of organic solvents between NaCl plates. Mass Spectra were obtained on a Hewlett Packard GC–MS (Model 5988A) with a dip-probe using conditions as indicated. Nuclear magnetic resonance spectra were recorded on a Bruker AM–300 or a Bruker

DPX–300 instrument in standard deuterated solvents. Optical rotations were measured using an AUTOPOL IV digital polarimeter (Rudolph Research Analytical, NJ).

Bis-trifluoromethyl olefin (2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70 (d, 1H, J = 8.7 Hz), 4.81 (bs, 1H), 4.23 (dd, 1H, J = 6.9 Hz, 9.3 Hz), 3.79 (dd, 1H, J = 3.9 Hz, 9.3 Hz), 1.65 (s, 3H), 1.56 (s, 3H), 1.42 (s, 9H); ^{19}F NMR (282.6 MHz, $CDCl_3$/$CFCl_3$) δ –65.01 (d, 3F, J = 5.9 Hz), –58.44 (d, 3F, J = 5.9 Hz); FT–IR (film, ν_{max}, cm^{-1}) 2983m, 2935m, 2885w, 1713s, 1479w, 1460w, 1379s, 1230s, 1165s, 1110m, 971m; $[\alpha]_D^{26.1}$ = + 12.3 ° (c 1.7, $CHCl_3$); GC-MS (CI, CH_4): 364 (1, $[M+1]^+$), 336 (18), 308 (100), 288 (98), 264 (37), 102 (2), 57 (9).

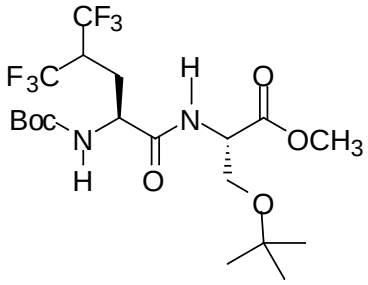
Oxazolidine (3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.23 (4.05) (m, 1H), 4.00 (dd, 1H, J = 5.4 Hz, 9.3 Hz), 3.73 (d, 1H, J = 9.3 Hz), 3.58 (3.05) (m, 1H), 2.18 (2.01) (m, 2H), 1.62 (1.58) (s, 3H), 1.48 (br. s, 12H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 153.22 (151.51) (C=O), 123.89 (q, 2 × CF_3, $^{1}J_{CF}$ = 284.0), 94.47 (94.03) (C), 80.85 (80.73) (C), 67.26 (66.65) (CH_2), 55.58 (55.12) (CH), 45.44 (45.12) (quintet, CH, $^{2}J_{CF}$ = 27.2 Hz), 28.98 (28.00) (CH_2), 28.25 (3 × CH_3), 27.58 (26.90) (CH_3), 24.15 (22.86) (CH_3); ^{19}F NMR (282.6 MHz, $CDCl_3$/$CFCl_3$) δ –67.68 - –68.42 (m); FT–IR (film, ν_{max}, cm^{-1}): 2984m, 2941m, 2884w, 1704s, 1457m, 1393s, 1258s, 1168s, 1104s, 847m; $[\alpha]_D^{22.4}$= +17.5 ° (c 0.4, $CHCl_3$); GC-MS (CI, CH_4): 366 (4, $[M+1]^+$), 338 (16), 310 (100), 290 (48), 266 (48), 57 (8).

***N*–Boc-5,5,5,5',5',5'-(*S*)-hexafluoroleucinol (4)**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.03 (d, 1H, J = 8.1 Hz), 3.84 (m, 1H), 3.70 (m, 2H), 3.20 (m, 1H), 3.10 (br. s, 1H), 1.98 (m, 2H), 1.45 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 156.57 (C=O), 124.00 (q, 2 × CF_3, $^{1}J_{CF}$ = 284.0 Hz), 80.58 (C), 66.08 (CH_2), 50.57 (CH), 45.09 (m, CH, $^{2}J_{CF}$ = 28.1 Hz), 28.38 (3 × CH_3), 26.44 (CH_2); ^{19}F NMR (282.6 MHz, $CDCl_3$/$CFCl_3$) δ –67.96 (m), –68.46 (m);

FT–IR (KBr pellet, ν_{max}, cm^{-1}) 3397s (br), 3253s, 3068m, 2981s, 2948m, 1686s, 1552s, 1369s, 1289s, 1174s, 1145s, 1055s; $[\alpha]_D^{22.9} = -14.4°$ (*c* 1.0, CH_3OH); GC-MS (CI, CH_4): 326 (8, $[M+1]^+$), 298 (14), 270 (100), 226 (20), 57 (2); m.p. = 114-115 °C.

***N*–Boc-5,5,5,5',5',5'-(S)-hexafluoroleucine (5)**. ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (5.21) (d, 1H, *J* = 6.3 Hz), 4.41 (m, 1H), 3.37 (m, 1H), 2.43-2.11 (br. m, 2H), 1.47 (s, 9H); ^{19}F NMR (282.6 MHz, $CDCl_3/CFCl_3$) δ −67.87 - −68.23 (m); FT–IR (KBr pellet, ν_{max}, cm^{-1}) 3358-2500m (br.), 3245s, 3107m, 2989s, 2980m, 1725s, 1712s, 1657s, 1477s, 1458s, 1404s, 1296s, 1277s, 1258s, 916m; $[\alpha]_D^{21.8} = -23.0°$ (*c* 1.0, CH_3OH); GC-MS (CI, CH_4): 340 (21, $[M+1]^+$), 312 (7), 284 (100), 264 (16), 240 (19), 57 (39).

Dipeptide (8). ^1H NMR (300 MHz, $CDCl_3$) δ 6.68 (d, 1H, *J* = 8.1 Hz), 5.21 (d, 1H, *J* = 8.1 Hz), 4.64 (m, 1H), 4.40 (m, 1H), 3.86 (dd, 1H, *J* = 2.7 Hz, 9.3 Hz), 3.76 (s, 3H), 3.56 (dd, 1H, *J* = 3.3 Hz, 9.3 Hz), 3.50 (m, 1H), 2.33-2.10 (br. m, 2H), 1.45 (s, 9H), 1.14 (s, 9H).



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References

(1) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.