Asymmetric Synthesis of (*S*)-5,5,5,5′,5′,5′-Hexafluoroleucine

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(*S*)-5,5,5,5′,5′,5′-Hexafluoroleucine ((*S*)-**13**) of 81% ee is prepared from hexafluoroacetone (**1**) and ethyl bromopyruvate (= ethyl 2-oxopropanoate) in 7 steps with an overall yield of 18% (*Schemes 1* and *2*). Key step in this sequence is the highly enantioselective reduction of the carbonyl group in α-keto ester **4** either by bakers' yeast (91% ee) or by 'catecholborane' **6** utilizing an oxazaborolidine catalyst, yielding hydroxy ester (*R*)-**5** with 99% ee. The absolute configuration was determined by X-ray analysis of the HCl adduct (*S,R*)-**9b** of (2*S*)-*N*-[(*R*)-1-phenylethyl]-5,5,5,5′,5′,5′-hexafluoroleucine ethyl ester.

Introduction. – Replacement of H-atoms by F-atoms in appropriate compounds can lead to drastic changes in the reactivity of pharmacologically and biologically active compounds, while the structural dimensions of these compounds remain almost unchanged. F-Containing compounds have *inter alia* antitumor, antibacterial activity [1] and can act as agonists or antagonists and suicide inhibitors [2] in enzymatic reactions. The profound impact of F-atoms as substituents in organic compounds is also apparent in the pharmacological properties of steroids [3] and in the use of the isotope ^{18}F in the non-evasive positron emission tomography [4]. The unique isotopic purity and the nuclear spin of the F-atom, extremely useful for ^{19}F-NMR investigations of biological phenomena, may be added to this list. The rather small increase of the *van der Waals* radii in the CF_3 groups in comparison with the CH_3 group and the NMR behaviour of the ^{19}F-nucleus have led to a variety of investigations which clearly revealed the potential of this substituent as a unique 'spectator' group.

Considering the presence of an isopropyl group in leucine, it is apparent that its replacement by a hexafluoroisopropyl group would allow the study of the physical, structural and biological properties of this essential amino acid in peptides and depsipeptides. The diastereotopicity of the two CF_3 groups and the large shift range for ^{19}F-NMR spectroscopy are key features for these studies.

Leucine is a constituent of a variety of important proteins like keratine, globulin, and serum albumin. Other important proteins are leucine-enkephaline and the leucine-zipper [5][6]. The importance of leucine as a nonpolar amino acid is further revealed by the fact that there are six codons for it.

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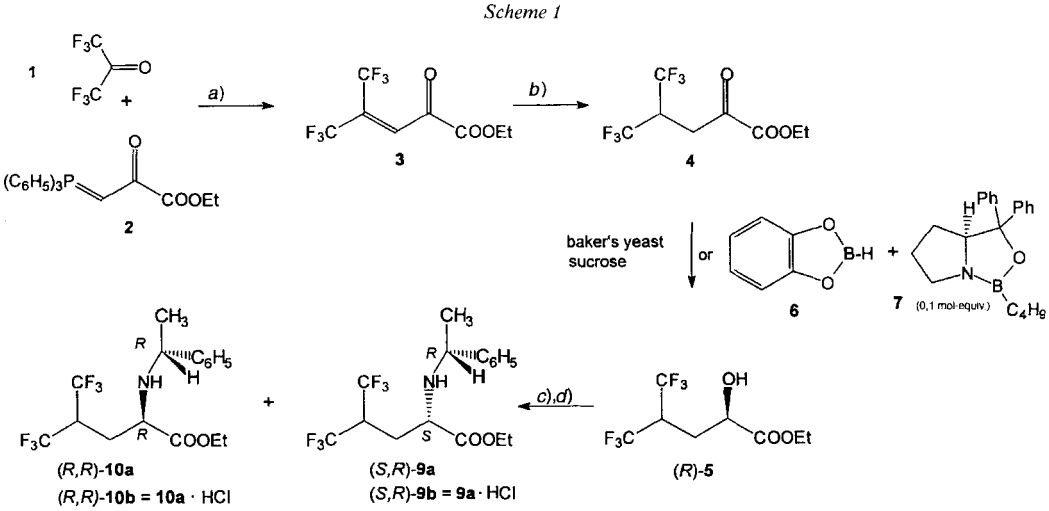
Surprisingly, there is only a single report about racemic 5,5,5,5′,5′,5′-hexafluoroleucine (DL-Leu(F_6)) in the literature [7], and (*S*)- or (*R*)-hexafluoroleucine has hitherto not been described. Thus, its chemistry is essentially nonexistent.

As part of our interest in the physical and biological properties of F-containing compounds [8–13], we have developed an efficient synthesis of (*S*)-5,5,5,5′,5′,5′-hexafluoroleucine (Leu(F_6); (*S*)-**13**) and determined its absolute configuration by the X-ray structure of its *N*-protected ethyl ester hydrochloride, (*S*,*R*)-**9b**.

Results and Discussion. – Hexafluoroacetone (= 1,1,1,3,3,3,-hexafluoropropan-2-one; **1**) was used as building block for the introduction of the hexafluoroisopropyl group. The *Wittig* reaction with ethyl (triphenylphosphoranylidene)pyruvate (**2**) [14] gave the α,β-unsaturated keto ester **3** in 86% yield (*Scheme 1*). Hydrogenation over 10% Pd/C yielded the α-keto ester **4** (80%) together with a small amount (6%) of racemic α-hydroxy ester *rac*-**5**. An enantioselective transformation of the carbonyl group in **4** was visualized as key step for the synthesis of Leu(F_6) [15]. Since our attempts to transform **4** by reductive amination directly into the desired amino acid **13** remained unsuccessful, the enantioselective reduction of the carbonyl group was investigated.

Scheme 1



a) Et_2O $-70° \rightarrow$ r.t. *b*) H_2, Pd/C, THF. *c*) $(CF_3SO_2)O$, pyridine, CH_2Cl_2. *d*) (*R*)-MeCH(Ph)NH_2 (**8**).

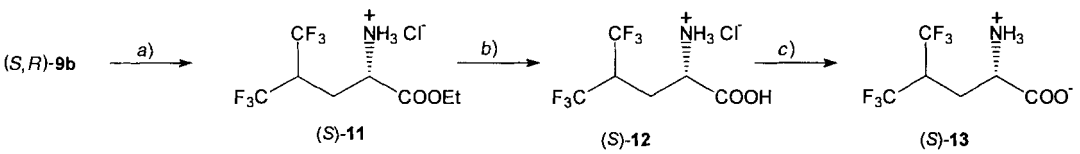
Alpine-borane [16] as well as K-glucoride [17] as reducing agents of **4** gave unsatisfactory results. Variation of the reaction conditions (time, concentration of reagent) and workup procedures led to degradation products rather than to the desired α-hydroxy ester **5**. Therefore, we explored the reduction of α-keto ester **4** with a pyrocatechol (= benzene-1,2-diol)boran derivative using an oxazaborolidine catalyst [18]. Since initial investigations by *Itsuno et al.* [19] had shown that the reaction of α-keto esters with borane in the presence of a homochiral oxazaborolidine gave only a moderate ee, **4** was reduced with catecholborane **6** (= 1,3,2-benzodioxaborole) in the presence of 10 mol-%

of (*S*)-*B*-butyl-oxazaborolidine (= (*S*)-1-butyl-tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]-oxazaborole; **7**). This system had been developed by *Corey* [20] for the reduction of trichloromethyl or trifluoromethyl ketones. The highly enantioselective reduction of **4** was complete after 16 h and gave the dextrorotatory α-hydroxy ester (*R*)-**5** in a chemical yield of 55% and an ee > 98% (for the assignment of chirality, see below). The ee did not change when 20 mol-% of the catalyst was used. Variation of temperature and solvent showed no conversion in the range of −78 to −30° in CH_2Cl_2, and less than 5% of product was formed in toluene (−10°, 72 h). Alternatively, the enantioselective reduction of the α-keto ester **4** was achieved utilizing baker's yeast [21]. With this procedure, the dextrorotatory α-hydroxy ester (*R*)-**5** was obtained in 54% yield with 91% ee.

The α-hydroxy ester (*R*)-**5** obtained by the yeast method was converted into (*S*,*R*)-**9a** by a S_N2 reaction with (*R*)-1-phenylethylamine (**8**) using the triflate protocol [22]. The diastereoisomers (*S*,*R*)-**9a** and (*R*,*R*)-**10a** were separated by chromatography or by crystallization of one of the HCl adducts (*S*,*R*)-**9b** and (*R*,*R*)-**10b**, derived from the diastereoisomer mixture (*S*,*R*)-**9a**/(*R*,*R*)-**10a**.

Hydrogenation of (*S*,*R*)-**9b** gave the dextrorotatory ester (*S*)-**11** with 88% ee (*Scheme 2*). After reflux with 6N HCl for 5 h, the dextrorotatory (*S*)-5,5,5,5′,5′,5′-hexafluoroleucine hydrochloride ((*S*)-**12**) was obtained with a rather low ee of 42%, whereas hydrolysis of (*S*)-**11** in conc. HCl at room temperature for 11 d gave (*S*)-**12** with 81% ee in an analytical assay and with 70% yield on a preparative scale. Treatment of (*S*)-**12** with propylene oxide (2-methyloxirane) in refluxing EtOH yielded the target dextrorotatory hexafluoroleucine (*S*)-**13**. The pK_a values of (*S*)-**12** are 2.79 and 7.51. In comparison with (*S*)-leucine (pK_a 2.61 and 9.71), it is apparent that the acidity of the ammonium group of (*S*)-**12** is affected by the adjacent hexafluoroisopropyl group, leading to a 100 fold decrease in the basicity.

Scheme 2



a) H_2, Pt/C, MeOH. *b*) 6N HCl, reflux. *c*) Propylene oxide, EtOH, reflux.

Absolute Configuration. – (*R*)-Chirality was tentatively assigned to the hydroxy ester (+)-**5** by comparison with (+)-ethyl 2-hydroxy-4-methylpentanoate to which (*R*)-chirality had been assigned [23]. Due to the S_N2 reaction, by which the amino function was introduced, (*S*)-chirality was expected for both (+)-**11** and (+)-**12**.

The absolute configuration of (+)-hexafluoroleucine, determined by X-ray structure analysis of its *N*-protected ethyl ester hydrochloride (+)-**9b**, was assigned by comparison to the known absolute configuration of the (*R*)-PhCH(Me)NH moiety in (+)-**9b** and shown to be (*S*)[3]) (*Fig. 1*). The CF_3 groups and the ester group undergo considerable

[3]) Thus, the reduction of **4** with its hexafluoroisopropyl group by yeast had led to (*R*)-**5**. This is in contrast to non-fluorinated α-keto esters, which were consistently reduced to the (*S*)-enantiomers [24] [21b]. A control experiment with ethyl 2-oxo-4-methylpentanoate proceeded sluggishly and gave (*S*)-2-hydroxy-4-methylpentanoate with 0.6% ee.

thermal motion even at −30°, hence, the bond lengths and angles involving these atoms are rather imprecise. The remaining bond lengths and angles in the molecule are normal within experimental error. Some relevant details are given with *Fig. 1*. In the crystal, the cationic and anionic moieties are linked to one another by H-bonds forming chains extending in the *a* direction (see *Fig. 2* for details).

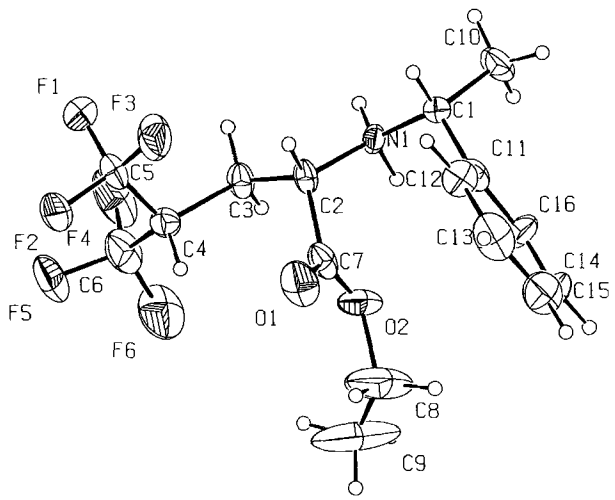


Fig. 1. *A perspective view of the cation of* (S,R)-**9b**. Arbitrary numbering; thermal ellipsoids at 30% probability level. Selected bond angles (°): C(2)–C(3)–C(4) 115.2(8), C(5)–C(4)–C(6) 112.0(1.1), C(5)–C(4)–C(3) 112.9(9), C(6)–C(4)–C(3) 108.3(1.0); torsion angles (°): C(2)–C(3)–C(4)–C(5) 78.9(1.2), C(2)–C(3)–C(4)–C(6) −156.6(1.0), C(2)–N(1)–C(1)–C(10) −173.8(7), C(2)–N(1)–C(1)–C(11) 63.0(9), C(8)–O(2)–C(7)–C(2) 180.0(9).

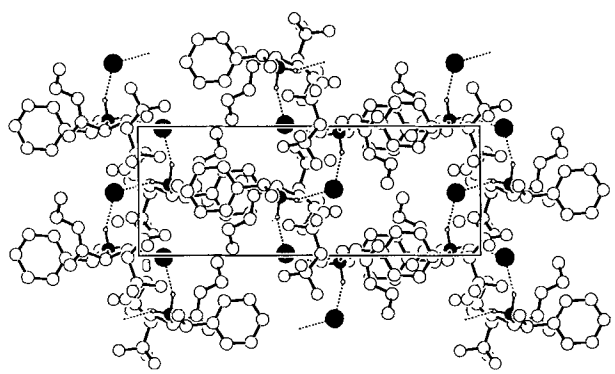


Fig. 2. *Packing diagram of the cation of* (S,R)-**9b** *viewed down the* b *axis showing the H-bonded chains that are formed* (dashed lines) *involving the* N^+-H *atom and the Cl anion.* ● Cl^-, • N^+; H-atoms omitted for clarity, except the N^+-H atoms. Axis *a* vertical, axis *c* horizontal. Hydrogen bonding (D = donor, A = acceptor; Å, °): N(1)–H(21) ··· Cl(1): D–H 1.09(8), H ··· A 2.08(8), D ··· H 3.104(9), D–H ··· A 155(6); N(1)–H(22) ··· Cl(1): D–H 0.97(7), H ··· A 2.23(7), D ··· H 3.125(8), D–H ··· A 154(6).

Concluding Remarks. – Based on the topologically selective reduction of the carbonyl group in **4**, achieved by two different methods, an efficient synthesis of (*S*)-5,5,5,5′,5′,5′-hexafluoroleucine ((*S*)-**13**) was developed. Reduction of **4** with 'catecholborane' **6** in the presence of the catalyst **7** gave enantiomerically pure (*R*)-**5**. When the baker's yeast/sucrose protocol was used for reduction, the desired hydroxy ester (*R*)-**5** was obtained with an ee of 91%. Introduction of the amino group *via* the S_N2 reaction of (*R*)-**5** with (*R*)-1-phenylethylamine (**8**) gave a mixture from which the pure amino ester hydrochloride (*S*,*R*)-**9b** was obtained by crystallization. The absolute configuration was established by X-ray analysis of this salt. The hexafluoroleucine ethyl ester hydrochloride (*S*)-**11**, obtained by hydrogenation of (*R*,*S*)-**9b**, was surprisingly sensitive to aqueous HCl solution and racemized partially during hydrolysis to the corresponding acid (*S*)-**12**. An ee of 81% was obtained under mild hydrolytic conditions only. The properties of Leu(F_6) ((*S*)-**13**) in a variety of biologically important compounds can now be investigated on the molecular level.

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Experimental Part

General. Chemicals were purchased from commercial suppliers and used without further purification. CH_2Cl_2 was distilled from P_2O_5, THF from sodium diphenylketyl, Et_2O from $LiAlH_4$. Reactions were normally performed under Ar. Column chromatography (CC): silica gel *60*. TLC: silica gel plates *SILG/UV*$_{254}$ (*Macherey & Nagel*). Flash chromatography (FC): silica gel *60* (230–400 mesh). GC: *Hewlett-Packard-HP-5790* instrument; *Chrompack* capillary *Chirasil-L-val* column (25 m × 0.2 mm); temp. 60°; t_R in min. M.p.: *Büchi-510* melting-point appartus; uncorrected. IR Spectra: *Perkin-Elmer-FTIR-1600* spectrophotometer; in KBr or $CHCl_3$; $\tilde{\nu}$ in cm^{-1}. NMR Spectra: *Bruker-AC-300* (^1H, 300 MHz; ^{13}C, 75 MHz) and *Bruker AM-400* (^{19}F, 376 MHz); in $CDCl_3$, if not mentioned otherwise; δ in ppm rel. to internal $CHCl_3$ (= 7.27 ppm) for ^1H, $CDCl_3$ for ^{13}C, and $PhCF_3$ (= 0 ppm) for ^{19}F. MS: *Varian-MAT-CH7a* (70 eV, EI); *m/z* (rel. %). Elemental analyses were determined by the Laboratoire de Chimie Pharmaceutique, Université de Genève. The pK_a values were measured by the Mikroanalytische Abteilung, Laboratorium für organische Chemie, ETH-Zürich.

Ethyl 5,5,5-Trifluoro-2-oxo-4-(trifluoromethyl)pent-3-enoate (**3**). Anh. hexafluoroacetone (**1**), prepared by warming a mixture of hexafluoroacetone trihydrate (45.4 ml, 330 mmol) and molecular sieves 4 Å (221 g, dried) to 40°, was introduced into a suspension of **2** (41 g, 110 mmol) in Et_2O (150 ml) at −70°. The mixture was stirred at −70° for 5 h and kept at r.t. overnight. The white precipitate was filtered off and washed with pentane. The brownish residue was distilled (70°, 70 Torr): **3** (20.2 g, 70% rel. to **2**) as yellowish oil.

Gaseous **1** (8.0 g, 48.2 mmol) reacted with **2** (22.6 g, 60.0 mmol) in Et_2O (50 ml) to give **3** (10.9 g, 85.7%).

Alternatively a mixture of hexafluoroacetone trihydrate (8.8 g, 40 mmol) and **2** (15.2 g, 40 mmol) was heated in THF (10 ml) in a stoppered flask to 50° (water-bath) until all the solids had dissolved and two layers had been formed. The mixture was slowly heated in an oil-bath to 130–140° at a water aspirator and distilled to give 8.36 g (79%) of **3**. B.p. 65–75° 14 Torr. R_f (hexane/Et_2O 5:1) 0.57. IR (KBr): 1738*s*, 1320*s*, 1280*s*, 988*s*. ^1H-NMR: 7.28 (*m*, 1 H); 4.43 (*q*, 2 H); 1.41 (*t*, 3 H). ^{13}C-NMR: 181.31 (*s*); 158.29 (*s*); 137.08 (*d*); 128.05 (*q*, *J* = 34); 119.80 (*q*, *J* = 275); 119.57 (*q*, *J* = 275); 63.83 (*t*); 13.67 (*q*). MS: 265 (5, $[M + 1]^+$), 246 (3), 237 (6), 226 (11), 217 (100), 198 (30), 191 (95), 181 (29), 172 (92), 163 (96), 144 (45), 123 (16), 115 (30), 97 (25), 75 (56), 69 (62), 50 (20), 29 (65). Anal. calc. for $C_8H_6F_6O_3$: C 36.38, H 2.29; found: C 36.48, H 2.36.

Ethyl 5,5,5-Trifluoro-2-oxo-4-(trifluoromethyl)pentanoate (**4**). Compound **3** (3.0 g, 11.3 mmol) was hydrogenated over 10% Pd/C (550 mg) in THF (15 ml) at r.t. for 2 h (TLC control). After removal of the catalyst and the solvent, CC (hexane/Et_2O 5:1) of the residue gave **4** as a colourless oil (2.4 g, 80%). In addition, *rac*-**5** (200 mg, 6%) was isolated as colourless needles of m.p. 31°.

Hydrogenation of **3** (3.0 g, 11.3 mmol) over 5% Pd/C (400 mg) in EtOH at r.t. for 1.5 h gave 60% of **4**. R_f (hexane/Et_2O 5:1) 0.53. IR (KBr): 2924*w*, 1734*s*, 1314*s*, 1264*s*. ^1H-NMR: 4.35 (*q*, 2 H); 3.84 (*m*, 1 H); 3.32 (*d*, *J* = 5.6, 2 H); 1.38 (*t*, 3 H). ^{13}C-NMR: 187.57 (*s*); 159.57 (*s*); 123.26 (*q*, *J* = 280); 123.21 (*q*, *J* = 280);

63.37 (*t*); 42.67 (*m*, *J* = 30); 33.27 (*t*); 13.83 (*q*). MS: 266 (25, M^+), 238 (11), 219 (24), 199 (47), 193 (99), 173 (35), 145 (100), 123 (62), 113 (13), 95 (26), 77 (41), 69 (52), 56 (40), 29 (66). Anal. calc. for $C_8H_8F_6O_3$: C 36.10, H 3.03; found: C 36.38, H 3.09.

(R)-Ethyl 5,5,5-Trifluoro-2-hydroxy-4-(trifluoromethyl)pentanoate ((*R*)-**5**). *Method A*. A mixture of (*S*)-α,α-diphenylprolinol (18.8 mg, 0.074 mmol) and butylboronic acid (8.8 mg, 0.088 mmol) in toluene (12 ml) under Ar was refluxed for 12 h in a *Dean-Stark* apparatus containing 4-Å molecular sieves in the side arm and was then evaporated (→ **7**). After addition of **4** (200 mg, 0.74 mmol) in CH_2Cl_2 (0.6 ml), 1,3,2-benzodioxaborole (**6**; 116 µl, 1.12 mmol) was added dropwise at 0° within 10 min under vigorous stirring. After completion of the reaction (TLC control), the mixture was diluted with CH_2Cl_2 (3 ml) and MeOH (0.5 ml) and extracted with 0.1M HCl (5 ml). The org. layer was washed with 1N NaOH (5 × 10 ml) until colourless and with H_2O (2 × 5 ml), dried ($MgSO_4$), and evaporated, and the oily residue submitted to CC (hexane/Et_2O 5:1): (*R*)-**5** (110 mg, 55%). Colourless needles. $[\alpha]_D^{23} = +19.3$ (*c* = 1.0, MeOH). GC (chiral column): t_R 10.67; ee > 99%.

Method B: *Reduction with Baker's Yeast*. A mixture of **4** (0.77 g, 2.89 mmol), sucrose (5.0 g, 14.6 mmol), and baker's yeast (4.0 g) in tap water (100 ml) was stirred at 30° for 4 h and extracted with pentane (3 × 50 ml). The combined org. layer was washed with sat. NaCl soln. (3 × 50 ml); dried (Na_2SO_4), and evaporated and the crude product (490 mg) submitted to CC (hexane/Et_2O 4:1): (*R*)-**5** (420 mg, 54.5%). Colourless needles. $[\alpha]_D^{23} = +17.3$ (*c* = 1.0, MeOH). GC (chiral column): t_R 15.84 and 17.43 (ratio 95.9:4.1); 91.8% ee. M.p. 35°. R_f (hexane/Et_2O 5:1) 0.20. IR (KBr): 1738*s*, 1398*s*, 1296*s*, 1256*s*. ^{1}H-NMR: 4.28 (*m*, 1 H); 4.28 (*q*, 2 H); 3.43 (*m*, *J* = 3, 1 H); 2.96 (*d*, 1 H); 2.31 (*ddd*, 1 H); 2.01 (*m*, *J* = 4.0, 1 H); 1.32 (*t*, 3 H). ^{13}C-NMR: 173.56 (*s*); 123.74 (*q*, *J* = 278); 123.70 (*q*, *J* = 278); 66.85 (*d*); 62.51 (*t*); 43.79 (*m*, *J* = 28); 28.40 (*d*); 13.99 (*q*). MS: 269 (**4**, $[M+1]^+$), 225 (11), 195 (100), 181 (15), 175 (74), 155 (87), 127 (68), 103 (25), 75 (32), 44 (16), 29 (35). Anal. calc. for $C_8H_{10}F_6O_3$: C 35.81, H 3.76; found: C 36.05, H 3.99.

Ethyl (2S)-5,5,5-Trifluoro-2-{[(R)-1-phenylethyl]amino}-4-(trifluoromethyl)pentanoate ((*S,R*)-**9a**) *and Diastereoisomer (R,R)*-**10a**. To a soln. of $(CF_3SO_2)_2O$ (310 mg, 1.10 mmol) in dry CH_2Cl_2 (2 ml), a mixture of (*R*)-**5** (268 mg, 1.00 mmol) and pyridine (87 mg, 1.10 mmol) in dry CH_2Cl_2 (2 ml) was added at 0°. The mixture was stirred at 0° for 30 min and filtered through a short silica-gel column with dry CH_2Cl_2. After evaporation, the triflate of (*R*)-**5** (400 mg, 100%) was obtained as a colourless oil which was used in the next step. To a soln. of (*R*)-1-phenylethylamine (**8**; 357 mg, 3.0 mmol) in dry CH_2Cl_2 (2 ml), a soln. of the crude triflate (400 mg, 1.0 mmol) in dry CH_2Cl_2 (2 ml) was added at 0°. After 30 min, the mixture was evaporated and the residue extracted with pentane. Filtration through a short silica-gel column with pentane/Et_2O 10:1 gave (*S,R*)-**9a**/(*R,R*)-**10a** 19:1 (330 mg, 88.9%) as a colourless oil. Addition of a sat. HCl/soln. in Et_2O (10 ml) to this mixture, dissolved in Et_2O (40 ml), gave pure (*S,R*)-**9b** (300 mg) as colourless needles. Treatment of the mother liquor (containing (*R,R*)-**10b**) with 1.0N NaOH (10 ml) and extraction with Et_2O (3 × 10 ml) gave, after workup, pure (*R,R*)-**10a** (15 mg) as a colourless oil. Following the same procedure, pure (*S,R*)-**9a** was obtained from (*S,R*)-**9b** as a colourless oil.

(*S,R*)-**9a**: R_f (hexane/Et_2O 4:1) 0.56. $[\alpha]_D^{23} = -10.0$ (*c* = 1.0, MeOH). IR ($CHCl_3$): 2955*w*, 1730*s*, 1455*m*, 1395*m*, 1375*m*, 1290*s*, 1250*s*, 1165*s*, 1125*s*, 1090*s*, 1025*m*. ^{1}H-NMR: 7.29 (*m*, 5 H); 4.05 (*m*, 2 H); 3.72 (*q*, 1 H); 3.68 (*m*, 1 H); 3.40 (*dd*, 1 H); 2.12 (*ddd*, 1 H); 1.87 (*m*, 2 H); 1.35 (*d*, 3 H); 1.22 (*t*, 3 H). ^{13}C-NMR: 174.02 (*s*); 144.85 (*s*); 128.52 (*d*); 127.37 (*d*); 126.61 (*d*); 124.13 (*q*, *J* = 279); 123.93 (*q*, *J* = 279); 61.28 (*t*); 56.55 (*d*); 55.98 (*d*); 44.04 (*m*, *J* = 28); 27.53 (*t*); 22.39 (*q*); 14.05 (*q*). MS: 370 (4, $[M-1]^+$), 356 (50), 298 (100), 282 (10), 194 (29), 120 (38), 105 (80). Anal. calc. for $C_{16}H_{19}F_6NO_2$: C 51.75, H 5.16, N 3.77; found: C 51.51, H 5.14, N 3.68.

(*R,R*)-**10a**: R_f (hexane/Et_2O 4:1) 0.56. $[\alpha]_D^{23} = +99.8$ (*c* = 1.05, MeOH). IR ($CHCl_3$): 2960*s*, 2930*s*, 2875*m*, 1735*s*, 1455*m*, 1325*m*, 1295*s*, 1255*s*, 1125*s*, 1090*s*, 1020*w*. ^{1}H-NMR 7.29 (*m*, 5 H); 4.24 (*m*, 2 H); 3.75 (*q*, 1 H); 3.50 (*m*, 1 H); 3.07 (*dd*, 1 H); 2.04 (*ddd*, 1 H); 1.80 (*m*, 2 H); 1.37 (*d*, Me); 1.30 (*t*, 3 H). ^{13}C-NMR: 174.43 (*s*); 143.91 (*s*); 128.50 (*d*); 127.47 (*d*); 126.98 (*d*); 123.90 (*q*, *J* = 279); 123.83 (*q*, *J* = 279); 61.26 (*t*); 56.70 (*d*); 55.86 (*d*); 43.93 (*m*, *J* = 28); 27.53 (*t*); 24.78 (*q*); 14.18 (*q*). MS: 371 (12, M^+), 356 (75), 298 (100), 282 (36), 194 (85), 149 (17), 120 (63), 105 (95), 77 (16). Anal. calc. for $C_{16}H_{19}F_6NO_2$: C 51.75, H 5.16, N 3.77; found: C 51.50, H 5.17, N 3.68.

(*S,R*)-**9b**: M.p. 228–230°. $[\alpha]_D^{23} = +12.4$ (*c* = 1.0, MeOH). IR (KBr): 3640–3200*m* (br.), 3060–2500*m* (br.), 1745*s*, 1370*w*, 1340*w*, 1310*m*, 1275*s*, 1240*s*, 1155*s*. ^{1}H-NMR (CD_3OD): 7.45 (*m*, 5 H); 4.57 (*q*, 1 H); 4.20 (*m*, 2 H); 4.05 (*dd*, 1 H); 3.78 (*m*, 1 H); 2.57 (*m*, 1 H); 2.32 (*m*, 1 H); 1.70 (*d*, 3 H); 1.25 (*t*, 3 H). ^{13}C-NMR (CD_3OD): 168.27 (*s*); 136.81 (*s*), 131.13 (*d*); 130.58 (*d*); 129.11 (*d*); 125.02 (*q*, *J* = 279); 124.79 (*q*, *J* = 279); 64.84 (*t*); 59.64 (*d*); 56.84 (*d*); 45.49 (*m*, *J* = 29); 24.85 (*t*); 19.12 (*q*); 14.09 (*q*). ^{19}F-NMR (CD_3OD): −5.88 (*q*, *J* = 10); −6.58 (*q*, *J* = 10). MS: 372 (5, $[M-Cl]^+$), 370 (10), 356 (87), 298 (97), 282 (56), 194 (100), 120 (68), 105 (90). Anal. calc. for $C_{16}H_{20}ClF_6NO_2$: C 47.12, H 4.94, N 3.44; found: C 47.07, H 4.92, N 3.40.

Crystals of (*S,R*)-**9b** suitable for X-ray analysis were grown from $CHCl_3$: colourless rods.

(S)-5,5,5,5',5',5'-Hexafluoroleucine Ethyl Ester Hydrochloride ((*S*)-**11**). (*S,R*)-**9b** (240 mg) was hydrogenated over 10% Pt/C (240 mg), in MeOH (10 ml) at r.t. for 24 h. The crude product (190 mg) was recrystallized from AcOEt: (*S*)-**11** (120 mg, 67.1%). Colourless needles. M.p. 204–206°. $[\alpha]_D^{23} = +5.0$ ($c = 1.0$, MeOH); 86.6–88.8% ee (see below). IR (KBr): 3200–2700*m* (br.), 1745*m*, 1290*s*, 1270*s*, 1245*m*, 1205*m*, 1165*m*, 1105*m*, 1085*m*. ^{1}H-NMR (CD_3OD): 4.32 (*q*, 2 H); 4.20 (*dd*, 1 H); 3.91 (*m*, 1 H); 2.45 (*ddd*, 1 H); 2.31 (*dt*, 1 H); 1.31 (*t*, 3 H). ^{13}C-NMR (CD_3OD): 168.58 (*s*); 124.80 (2*q*, $J = 277$); 64.20 (*t*); 51.26 (*d*); 45.29 (*m*, $J = 29$); 25.35 (*t*); 13.93 (*q*). ^{19}F-NMR (CD_3OD): −6.23 (*q*, $J = 10$); −6.54 (*q*, $J = 10$). MS: 268 (5, $[M - Cl]^+$), 194 (100), 174 (49), 154 (68), 134 (35), 85 (14). Anal. calc. for $C_8H_{12}ClF_6NO_2$: C 31.64, H 3.98, N 4.61; found: C 31.15, H 3.93, N 4.53.

(S)-5,5,5,5',5',5'-Hexafluoroleucine Hydrochloride ((*S*)-**12**). A soln. of (*S*)-**11** (120 mg) was refluxed in 6N HCl (10 ml) for 16 h. The mixture was evaporated and the residue recrystallized from AcOEt: (*S*)-**12** (90 mg, 82.6%). Colourless crystals. p*K*: 2.79, 7.51. M.p. 198–200°. $[\alpha]_D^{23} = +10.5$ ($c = 1.0$, MeOH); 39.2–45.4% ee (see below). IR (KBr): 3650–3300*w*, 3250–2300*s* (br.), 1740*s*, 1600*m*, 1520*m*, 1495*m*, 1395*m*, 1355*m*, 1325*s*, 1175*s*, 1145*m*, 1110*m*, 1085*s*. ^{1}H-NMR (CD_3OD): 4.04 (*dd*, 1 H); 3.86 (*m*, 1 H); 2.36 (*ddd*, 1 H); 2.22 (*dt*, 1 H). ^{13}C-NMR (CD_3OD): 170.36 (*s*); 125.30 (2*q*, $J = 276$); 51.64 (*d*); 45.94 (*m*, $J = 29$); 26.02 (*t*). ^{19}F-NMR (CD_3OD): −6.19 (*q*, $J = 10$); −6.67 (*q*, $J = 10$). MS: 240 (3, $[M - Cl]^+$), 194 (100), 174 (54), 154 (82), 134 (68), 85 (29), 36 (54). Anal. calc. for $C_6H_8ClF_6NO_2$: C 26.15, H 2.93, N 5.08; found: C 26.16, H 2.97, N 5.06.

For hydrolysis at r.t., (*S*)-**11** (15 mg) was hydrolyzed in 37% HCl soln. for 11 d at r.t. The soln. was added to $NaHCO_3$ (3 g) in H_2O (4 ml), treated with acetone (4 ml) followed by (*S*)-*Mosher*'s chloride (8 µl) and stirred at r.t. overnight. The org. phase, obtained after acidification with conc. HCl and extraction with CH_2Cl_2 (4×), was dried (Na_2SO_4) and evaporated to give *(S)-N-[(R)-3,3,3-trifluoro-2-methoxy-1-oxo-2-phenylpropyl]-5,5,5,5',5',5'-hexafluoroleucine* (22 mg). ^{1}H-NMR: 3.49 (9.2%), 3.39 (90.8%) (2*q*, $J = 1.8$, MeO); 81.6% ee.

(S)-5,5,5,5',5',5'-Hexafluoroleucine ((*S*)-**13**). Crude (*S*)-**12**, obtained by hydrolysis of (*S*)-**11** (160 mg, 0.527 mmol), was dissolved in EtOH (2 ml), and 2-methyloxirane (1 ml) was added [25]. After reflux for 15 min, the product was filtered off, washed with EtOH (3 × 1 ml), and dried at 0.1 Torr for 20 h: 100 mg (79.4%) of (*S*)-**13**. M.p. 264–266°. $[\alpha]_D^{23} = +9.6$ ($c = 1.0$, MeOH). IR (KBr): 1610*s*, 1500*m*, 1410*m*, 1395*m*, 1360*s*, 1330*s*, 1310*s*, 1275*s*, 1255*s*, 1160*s*, 1080*s*. ^{1}H-NMR (CD_3OD): 4.15 (*m*, 1 H); 3.60 (*dd*, 1 H); 2.27 (*ddd*, 1 H); 2.13 (*ddd*, 1 H). ^{13}C-NMR (CD_3OD): 172.32 (*s*); 52.92 (*d*); 45.89 (*m*, $J = 28$); 26.59 (*t*). MS: 240 (1, $[M + 1]^+$), 194 (100), 174 (26), 154 (48), 134 (27). Anal. calc. for $C_6H_7F_6NO_2$: C 30.14, H 2.95, N 5.86; found: C 29.89, H 3.10, N 5.71.

*Enantiomeric Excess of (S)-***11** *and (S)-***12**. To a mixture of the ester hydrochloride (*S*)-**11** (15 mg) and $NaHCO_3$ (500 mg) in H_2O/acetone 1:1 (8 ml) (*S*)- and (*R*)-acyl chloride of (*R*)- and (*S*)-*Mosher*'s acid (= α-methoxy-α-(trifluoromethyl)benzeneacetic acid; *Fluka*; 99.5% ee; 10 µl), resp., was added. After stirring overnight, the acetone was evaporated, the aq. phase extracted 3 time with CH_2Cl_2, the org. phase dried (Na_2SO_4), and evaporated, and the residue dried under high vacuum at r.t. The derivatives of (*S*)-**12** were prepared similarly, except that the aq. solns. were acidified with conc. HCl (1 ml) prior to extraction. The ee was obtained for both diastereoisomers, prepared from (*S*)- and (*R*)-*Mosher*'s chloride, resp., by integration of the ^{1}H-NMR signals (*q*, $^5J(FH) = 1.1$ Hz); for the MeO group. ^{1}H-NMR from (*S*)-**11**: with (*S*)-acid 3.521 (94.4%, (*S,S*)) and 3.398 (5.6%, (*S,R*)); with (*R*)-acid; 3.521 (6.7%, (*R,R*)), 3.398 (93.3%, (*R,S*)). ^{1}H-NMR from (*S*)-**12**: with (*S*)-acid: 3.487 (72.2%, (*S,S*)) and 3.386 (27.8%, (*S,R*)); with (*R*)-acid: 3.480 (30.4%, (*R,R*)) and 3.383 (69.6%, (*R,S*)); similar area ratios were obtained from the CF_3 groups of *Mosher*'s acid derivatives in the ^{19}F-NMR spectra.

Crystallographic Data for Ethyl (2S)-5,5,5-Trifluoro-2-{[(R)-1-phenylethyl]amino}-4-(trifluoromethyl)-pentanoate Hydrochloride ((*S,R*)-**9b**). Intensity data were collected at 243 K on a *Stoe-AED2* 4-circle diffractometer using MoK_α graphite monochromated radiation ($\lambda = 0.71073$ Å) with $\omega/2\theta$ scans in the 2θ range 5–50°. $C_{16}H_{19}F_6NO_2 \cdot HCl$, orthorhombic, space group $P2_12_12_1$, $a = 7.006(2)$, $b = 14.752(3)$, $c = 18.694(4)$ Å, $Z = 4$; 2538 reflections were measured at 243 K, 2217 independent reflections ($R_{int} = 0.0287$), with only 1313 observed reflections [$I > 2\sigma(I)$]; final $R1 = 0.0877$, $Rw2 = 0.1226$, goodness of fit 1.183, residual density max./min. 0.264/−0.246 e Å^{-3}. Absorption coefficient $\mu = 0.263$ mm^{-1}; no correction for absorption was applied. The structure was solved by direct methods using the program SHELXS-86 [26]. The refinement and all further calculations were carried out using SHELXL-93 [27]. The majority of the H-atoms were included in calculated positions and allowed to ride on the corresponding C-atom. The nitrogen H-atoms at N were located from difference maps and allowed to refine isotropically. The non-H-atoms were refined anisotropically, using weighted full-matrix least squares on F^2. The molecular structure and crystallographic numbering scheme for (*S,R*)-**9b** are illustrated in *Fig. 1*, drawn using PLATON [28]. The packing diagram (*Fig. 2*) was drawn using the program PLUTON [28]. Further details may be obtained from *H. St.-E.* Full tables of atomic parameters and bond lengths and angles may be obtained from the *Cambridge Crystallographic Data Centre*, 12 Union Road, Cambridge CB2 1EZ, U.K, on quoting the full journal citation.

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