

## New Synthesis and Chirality of (–)-4,4,4,4',4'-Hexafluorovaline

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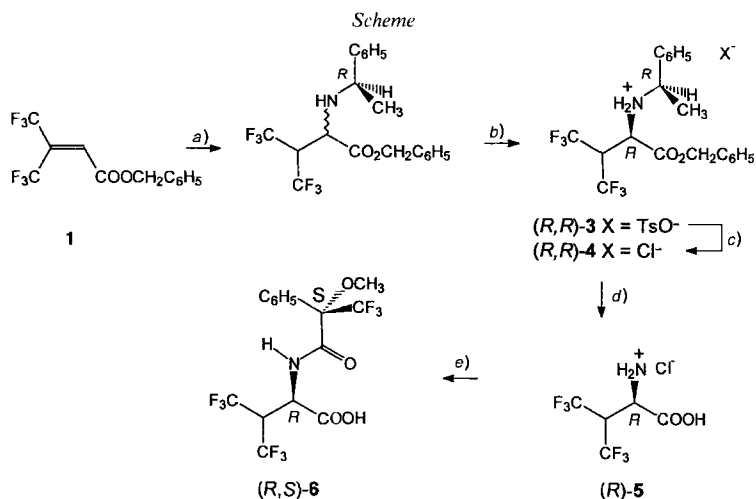
(–)-(*R*)-4,4,4,4',4'-Hexafluorovaline hydrochloride ((*R*)-**5**) of 98% ee is prepared from  $\beta,\beta$ -bis(trifluoromethyl)acrylic acid (= benzyl 4,4,4-trifluoro-3-(trifluoromethyl)but-2-enoate; **1**) in 4 steps with an overall yield of 9.6%. Key step is the separation of the TsOH salts of the diastereoisomers obtained by *anti-Michael* addition of (+)-(*R*)-1-phenylethylamine (**2**) to **1** ( $\rightarrow$  (*R,R*)-**3**). In contrast to the published (*S*)-chirality, the X-ray structure analysis of (*R,S*)-**6** reveals, that (*R*)-chirality has to be assigned to the levorotatory (–)-4,4,4,4',4'-hexafluorovaline hydrochloride.

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**Introduction.** – Earlier we had reported a short and efficient synthesis of methyl 4,4,4,4',4'-hexafluorovalinate which is based on the *anti-Michael* addition of (+)-(*R*)-1-phenylethylamine to methyl  $\beta,\beta$ -bis(trifluoromethyl)acrylate and the separation of the diastereoisomeric HCl salts by crystallization [1]. Extensive racemization of the methyl ester had been observed on cleavage of the ester group, giving hexafluorovaline with disappointing 28% ee. The chirality of (–)-4,4,4,4',4'-hexafluorovaline was assigned by *Eremeev et al.* who compared its CD with that of (*S*)-valine [2]. The extensive racemization in the hydrolysis step and the questionable assignment of chirality led to a new synthesis of homochiral 4,4,4,4',4'-hexafluorovaline (Val(F<sub>6</sub>)), the preparation of a diastereoisomerically pure derivative, and the determination of the chirality by X-ray structure analysis.

**Results and Discussion.** – In an *anti-Michael* reaction of (+)-(*R*)-1-phenylethylamine (**2**) with benzyl  $\beta,\beta$ -bis(trifluoromethyl)acrylate (= benzyl 4,4,4-trifluoro-3-(trifluoromethyl)but-2-enoate; **1**), a mixture of diastereoisomers was formed (*Scheme*). In contrast to our earlier results with the corresponding reaction of the methyl ester [1], addition of HCl to this mixture did not lead to a clean separation of (*R,R*)-**4** (or its (*R,S*)-isomer). However, a crystalline precipitate of the salt (*R,R*)-**3** was obtained on addition of TsOH in MeOH. This salt was readily transformed into (*R,R*)-**4** by consecutive treatment with NaHCO<sub>3</sub> and HCl in the presence of Et<sub>2</sub>O. The salt (*R,R*)-**3** appears to be rather sensitive towards base, as extensive epimerization was observed when it was treated with aqueous Na<sub>2</sub>CO<sub>3</sub> on an attempted conversion to (*R,R*)-**4**. Hydrogenation of (*R,R*)-**4** over Pd/C gave levorotatory (*R*)-**5** in 38% overall yield. An ee of 98% was determined *via* acylation with (*R*)-Mosher's chloride (see below). The p*K*<sub>a</sub> values of (*R*)-**5** are 3.17 and 6.30. Compared to those of (*S*)-valine (p*K*<sub>a</sub> 2.29 and 9.72), the acidity of the

carboxylic acid group of (*R*)-**5** is decreased whereas that of the ammonium group shows a more than 1000fold increase. For (*S*)-5,5,5,5',5'-hexafluoroleucine, where the ammonium group is separated by a CH<sub>2</sub> group from the hexafluoroisopropyl moiety, a 100-fold increase in the acidity of the ammonium group has been found [3].



*a)* (*R*)-MeCH(Ph)NH<sub>2</sub> (**2**) MeOH, –70° → r.t. *b)* TsOH in MeOH. *c)* Et<sub>2</sub>O, sat. NaHCO<sub>3</sub> soln., HCl in Et<sub>2</sub>O. *d)* H<sub>2</sub>, Pd/C, MeOH. *e)* (*R*)-Mosher's chloride, H<sub>2</sub>O/acetone, NaHCO<sub>3</sub>.

**Absolute Configuration.** – As mentioned above, (*S*)-chirality had been assigned to levorotatory 4,4,4,4',4'-hexafluorovaline by *Eremeev et al.* [2]. Since F-substituents have a strong influence on the chemical and physical properties of organic compounds, it was questionable whether CD measurements would lead to a conclusive assignment of chirality by comparison of (–)-4,4,4,4',4'-hexafluorovaline with (*S*)-valine itself. Whereas our earlier attempts to prepare crystals of a diastereoisomeric derivative of hexafluorovaline suitable for X-ray structure analysis failed, *N*-acylation of (*R*)-**5** with (*R*)-Mosher's chloride (from (*S*)-Mosher's acid (= (*S*)-α-methoxy-α-(trifluoromethyl)benzeneacetic acid)) gave appropriate crystals of (*R,S*)-**6**. The X-ray structure analysis of (*R,S*)-**6** clearly revealed that (*R*)-chirality has to be assigned to (–)-4,4,4,4',4'-hexafluorovaline hydrochloride (*Fig. 1*).

In the crystal of (*R,S*)-**6**, the molecules are linked by intermolecular H-bonds involving the hydroxy group HO(2) of one residue to the carbonyl O-atom O(1') of the other residue. In this way, helical chains of the molecules extending in the *a* direction are formed (*Fig. 2*).

**Concluding Remarks.** – A short and efficient synthesis of (–)-(*R*)-4,4,4,4',4'-hexafluorovaline hydrochloride ((*R*)-**5**) was developed. It is based on the observation that (*R,R*)-**3** precipitated when the diastereoisomer mixture, formed from benzyl β,β-bis(trifluorodimethyl)acrylate (**1**) and (+)-(*R*)-1-phenylethylamine (**2**) by *anti*-Michael addition, was treated with TsOH. It is obvious, that (+)-(*S*)-4,4,4,4',4'-hexa-

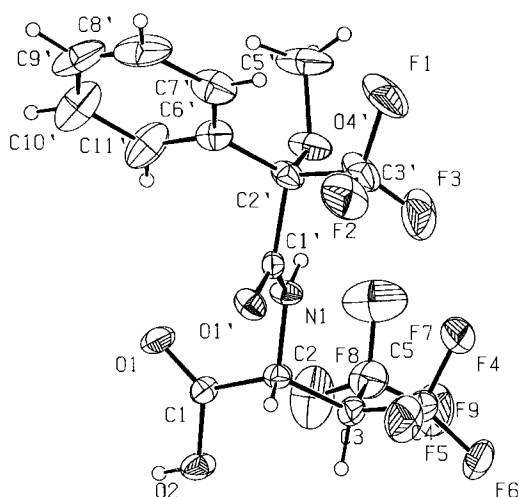


Fig. 1. A perspective view of (R,S)-6. Arbitrary numbering, thermal ellipsoids at 30% probability level. Selected bond angles ( $^{\circ}$ ) of residue 2: N(1)–C(2)–C(1) 111.3(5), N(1)–C(2)–C(3) 112.4(5), C(1)–C(2)–C(3) 112.3(5), C(5)–C(3)–C(2) 113.1(7), O(4')–C(2')–C(3') 107.9(5), C(3')–C(2')–C(6') 115.4(5), C(3')–C(2')–C(1') 106.4(5); torsion angles ( $^{\circ}$ ) in residue 2: N(1)–C(2)–C(3)–C(5):  $-69.5(7)$ , C(1)–C(2)–C(3)–C(5)  $57.0(8)$ , N(1)–C(2)–C(3)–C(4)  $60.3(8)$ , C(1)–C(2)–C(3)–C(4)  $-173.3(6)$ .

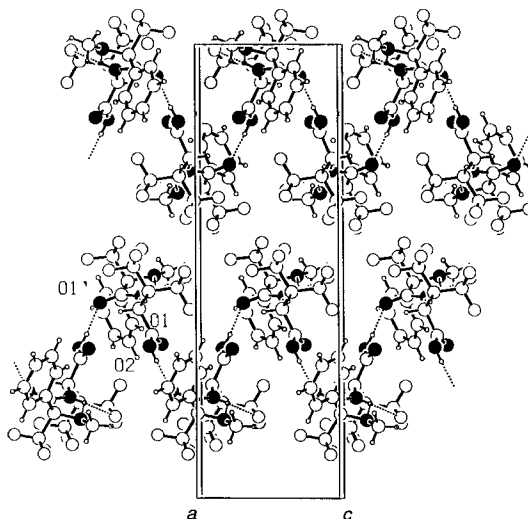


Fig. 2. Packing diagram of (R,S)-6. The two independent molecules are linked by H-bonds to form 'helical' chains extending in the a direction. H-Bonding (D = donor, A = acceptor;  $\text{\AA}$ ,  $^{\circ}$ ): O(2)–H(2\_1)  $\cdots$  O(1'\_2): D–H 0.830, H  $\cdots$  A 1.824, D  $\cdots$  A 2.642, D–H  $\cdots$  A 168.0; O(2)–H(2\_2)  $\cdots$  O(1')H\_1(x + 1, y, z): D–H 0.830, H  $\cdots$  A 1.811, H  $\cdots$  A 1.811, D  $\cdots$  A 2.627, D–H  $\cdots$  A 167.6.

fluorovaline hydrochloride can be prepared using (–)-(S)-1-phenylethylamine as the chiral auxiliary.

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## Experimental Part

General. See [3].

**Benzyl 4,4,4-Trifluoro-3-(trifluoromethyl)but-2-enoate (1)** [4][5]. Treatment of 4,4,4-trifluoro-3-(trifluoromethyl)but-2-enoic acid (3.0 g, 14 mmol) with  $\text{PCl}_5$  (3.0 g, 14 mmol) and benzyl alcohol in the presence of  $\text{Et}_3\text{N}$  gave, after distillation, **1** (3.0 g, 92%). B.p. 96–98°.

**TsOH Adduct of Benzyl 4,4,4-Trifluoro-2-[(R)-1-phenylethyl]amino-3-(trifluoromethyl)butanoate (R,R)-3.** (+)-(R)-1-Phenylethylamine (**2**; 6.9 g, 57 mmol) was slowly added to a soln. of **1** (17.0 g, 57 mmol) in MeOH (50 ml) at –70°. The mixture was allowed to warm to r.t. and kept for 1 h. After addition of a soln. of TsOH (10.5 g, 6.3 mmol) in MeOH (50 ml), most of the solvent was evaporated.  $\text{Et}_2\text{O}$  was added until the salt (R,R)-**3** began to crystallize. When the crystallization was complete, the salt was filtered off: pure (R,R)-**3** (11.1 g, 33%). M.p. 144–147°.  $^1\text{H-NMR}$ : 1.95–2.05 (d, 3 H); 2.4 (s, 3 H); 3.75–3.80 (1 H); 4.5–4.7 (br., 2 H); 5.1–5.3 (dd, 2 H); 7.2–7.45 (m, 14 H); 7.80–7.90 (d, 2 H).

**Benzyl 4,4,4-Trifluoro-2-[(R)-1-phenylethyl]amino-3-(trifluoromethyl)butanoate.** The salt (R,R)-**3** (14.6 g, 24.7 mmol) was added to a mixture of  $\text{Et}_2\text{O}$  (300 ml) and sat.  $\text{NaHCO}_3$  soln. (100 ml). After the evolution of  $\text{CO}_2$  had ceased the mixture was extracted with  $\text{Et}_2\text{O}$  (2 × 300 ml). The org. phase was dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to give 9.8 g (95%) of free amino compound.  $^1\text{H-NMR}$ : 1.35–1.40 (d, 3 H); 1.55–1.70 (1 H); 3.80–3.85 (m, 1 H); 5.2–5.3 (dd, 2 H); 7.2–7.5 (m, 10 H).

**Benzyl 4,4,4-Trifluoro-2-[(R)-1-phenylethyl]amino-3-(trifluoromethyl)butanoate Hydrochloride ((R,R)-4).** The free amino compound (9.8 g, 23.4 mmol) in  $\text{Et}_2\text{O}$  (100 ml) was treated with an  $\text{Et}_2\text{O}$  soln. of HCl gas. Evaporation of the mixture gave (R,R)-**4** (8.64 g, 81%). Solid. M.p. 142–144°.  $^1\text{H-NMR}$ : 1.78–1.84 (d, 3 H); 3.75–3.80 (s, 1 H); 4.2–4.3 (1 H); 4.6–4.8 (1 H); 5.12–5.33 (dd, 2 H); 7.3–7.5 (10 H).  $^{19}\text{F-NMR}$ : 0.57 (q); –1.91 (q).

**(–)-(R)-4,4,4,4',4'-Hexafluorovaline Hydrochloride ((R)-5).** A soln. of (R,R)-**4** (8.21 g, 18 mmol) in EtOH (200 ml) was hydrogenated in the presence of 5% Pd/C (1.5 g) until the uptake of  $\text{H}_2$  had stopped (875 ml of  $\text{H}_2$ , calc. 810 ml). The catalyst was filtered off and the soln. evaporated: (R)-**5** (1.78 g, 38%). Solid.  $\text{p}K_a$  (in  $\text{H}_2\text{O}$ ): 3.17, 6.30. M.p. 194–195°.  $[\alpha]_D^{25} = -9.29$  ( $c = 1.625$ ,  $\text{H}_2\text{O}$ ).  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ ): 4.60–4.63 (1 H); 4.70–4.90 (quint., 1 H). Anal. calc. for  $\text{C}_8\text{H}_5\text{F}_6\text{NO}_2 \cdot \text{HCl}$ : C 22.96, H 2.31, N 5.36; found: C 22.75, H 2.41, N 5.26.

**(R)-N-[(S)-3,3,3-Trifluoro-2-methoxy-1-oxo-2-phenylpropyl]-4,4,4,4',4'-hexafluorovaline ((R,S)-6).** The salt (R)-**5** (104 mg, 0.4 mmol) was dissolved in  $\text{H}_2\text{O}$ /acetone 1:1 (32 ml) containing  $\text{NaHCO}_3$  (1 g) and treated with the (–)-(R)-Mosher's chloride (100 mg, 0.4 mmol) and stirred at r.t. overnight. The mixture was evaporated. Conc. HCl soln. (5 ml) was added to the residue and the mixture extracted with  $\text{CH}_2\text{Cl}_2$  (3 ×). The combined extract was dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated and the residue dried under high vacuum: 179 mg of crystalline (R,S)-**6**. M.p. 79–81°.  $^1\text{H-NMR}$  (MeO signals): 3.44 (q,  $J = 1.4$ , 1.1 %); 3.39 (q,  $J = 1.1$ , 98.9 %).  $^{19}\text{F-NMR}$ : 0.52 (q,  $J = 8.9$ , 99 %); –3.19 (q,  $J = 8.9$ , 2 %); –3.26 (q,  $J = 8.9$ , 98 %); –6.31 (s, 1 %); 6.36 (s, 99 %).

**Crystallographic Data for (R,S)-6.** Recrystallization from  $\text{Et}_2\text{O}$ /cyclohexane gave colourless plates suitable for X-ray structure analysis.  $\text{C}_{15}\text{H}_{12}\text{F}_6\text{NO}_4$ , monoclinic, space group  $P2_1$ ,  $a = 7.5235(14)$ ,  $b = 23.660(4)$ ,  $c = 10.3208(14)$  Å,  $\beta = 91.46(1)^\circ$ ,  $V = 1836.6(5)$  Å<sup>3</sup>,  $Z = 4$ ,  $d_{\text{calc}} = 1.596$  Mg/m<sup>3</sup>; 3507 independent reflections were measured and 2592 were considered observed [ $I > 2\sigma(I)$ ], final  $R = 0.0579$ ,  $wR2 = 0.0948$  (obsd. data), goodness of fit 1.159, residual density max./min. 0.265/–0.198 eÅ<sup>–3</sup>. Absorption coefficient  $\mu = 0.173$  mm<sup>–1</sup>; no correction for absorption was applied. Intensity data were collected at 223(2) K on a *Stoe-AED2* 4-circle diffractometer using  $\text{MoK}_\alpha$  graphite monochromated radiation, using  $2\theta/\omega$  scans in the range 4–51° in  $2\theta$ . The structure was solved by direct methods using the programme SHELXS-97 [6]. The refinement and all further calculations were carried out using SHELXL-97 [7]. All of the H-atoms were included in calculated positions and treated as riding atoms. The non-H-atoms were refined anisotropically, using weighted full-matrix least squares on  $F^2$ . The absolute configuration of the molecule was fixed on referring to the absolute configuration of (S)-Mosher's acyl moiety. There are two independent molecules in the asymmetric unit referred to as residues 1 and 2. The bond lengths and angles are normal within experimental error. The molecular structure and crystallographic numbering scheme of (R,S)-**6** is illustrated in the PLATON [8] drawing (Fig. 1). The crystal packing diagram (Fig. 2) was drawn using PLUTON [8]. 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. Further details may be obtained from H. St.-E.

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