New Synthesis and Chirality of (−)-4,4,4,4′,4′,4′-Hexafluorovaline

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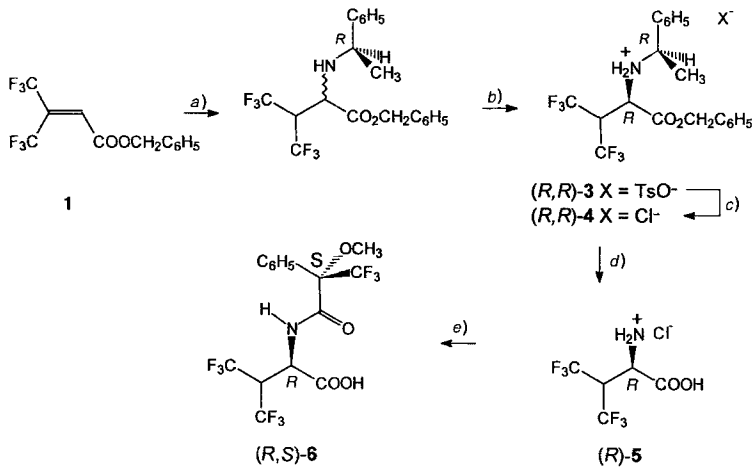
(−)-(*R*)-4,4,4,4′,4′,4′-Hexafluorovaline hydrochloride ((*R*)-**5**) of 98% ee is prepared from *β*,*β*-bis(trifluoromethyl)acrylic acid (= benzyl 4,4,4-trifluoro-3-(trifluoromethyl)but-2-enoate; **1**) in 4 steps with an overall yield of 9.6%. Key step is the separation of the TsOH salts of the diastereoisomers obtained by *anti-Michael* addition of (+)-(*R*)-1-phenylethylamine (**2**) to **1** (→ (*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′,4′-hexafluorovaline hydrochloride.

Introduction. – Earlier we had reported a short and efficient synthesis of methyl 4,4,4,4′,4′,4′-hexafluorovalinate which is based on the *anti-Michael* addition of (+)-(*R*)-1-phenylethylamine to methyl *β*,*β*-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′,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′,4′-hexafluorovaline (Val(F_6)), 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 *β*,*β*-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 $NaHCO_3$ and HCl in the presence of Et_2O. The salt (*R*,*R*)-**3** appears to be rather sensitive towards base, as extensive epimerization was observed when it was treated with aqueous Na_2CO_3 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 pK_a values of (*R*)-**5** are 3.17 and 6.30. Compared to those of (*S*)-valine (pK_a 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′,5′-hexafluoroleucine, where the ammonium group is separated by a CH_2 group from the hexafluoroisopropyl moiety, a 100-fold increase in the acidity of the ammonium group has been found [3].

Scheme



a) (*R*)-MeCH(Ph)NH_2 (**2**) MeOH, −70° → r.t. *b*) TsOH in MeOH. *c*) Et_2O, sat. $NaHCO_3$ soln., HCl in Et_2O. *d*) H_2, Pd/C, MeOH. *e*) (*R*)-*Mosher*'s chloride, H_2O/acetone, $NaHCO_3$.

Absolute Configuration. – As mentioned above, (*S*)-chirality had been assigned to levorotatory 4,4,4,4′,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′,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′,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′,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′,4′-hexa-

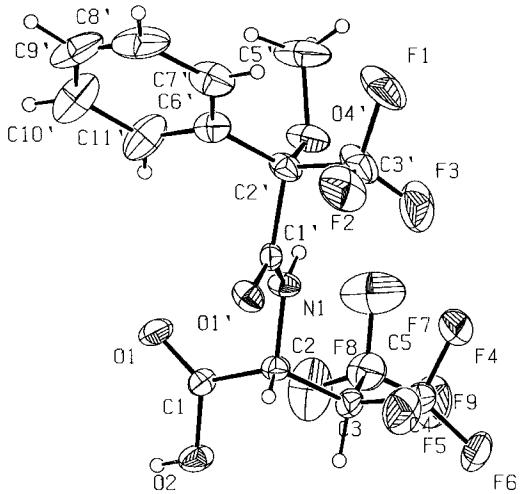


Fig. 1. *A perspective view of* (R,S)-**6**. Arbitrary numbering, thermal ellipoids at 30% probability level. Selected bond angles (°) of residue 2: N(1)–C(2)–C(1) 111.3(5), N(1)–C(2)–C(3) 112.4(5), C(1)–C(2)–C(3) 112.3(5), C(5)–C(3)–C(2) 113.1(7), O(4′)–C(2′)–C(3′) 107.9(5), C(3′)–C(2′)–C(6′) 115.4(5), C(3′)–C(2′)–C(1′) 106.4(5); torsion angles (°) 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).

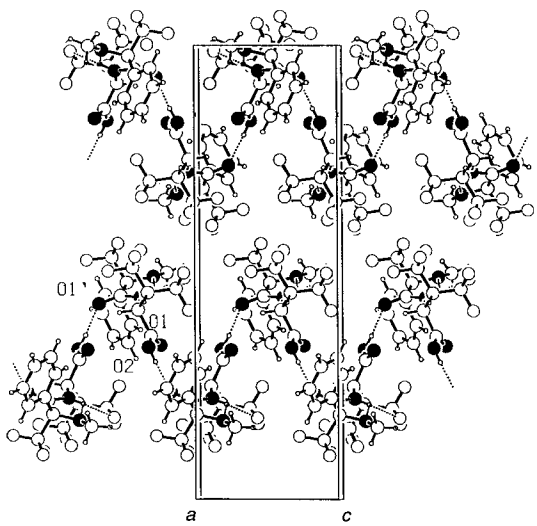


Fig. 2. *Packing diagram of* (R,S)-**6**. The two independent molecules are linked by H-bonds to form 'helical' chains extending in the a direction. H-Bonding (D = donor, A = acceptor; Å, °): O(2)–H(2_1) ··· O(1′_2): D–H 0.830, H ··· A 1.824, D ··· A 2.642, D–H ··· A 168.0; O(2)–H(2_2) ··· O(1′)H_1($x+1,y,z$): D–H 0.830, H ··· A 1.811, H ··· A 1.811, D ··· A 2.627, D–H ··· 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 PCl_5 (3.0 g, 14 mmol) and benzyl alcohol in the presence of Et_3N 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. Et_2O 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}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 Et_2O (300 ml) and sat. $NaHCO_3$ soln. (100 ml). After the evolution of CO_2 had ceased the mixture was extracted with Et_2O (2 × 300 ml). The org. phase was dried (Na_2SO_4) and evaporated to give 9.8 g (95%) of free amino compound. ^{1}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 Et_2O (100 ml) was treated with an Et_2O soln. of HCl gas. Evaporation of the mixture gave (*R,R*)-**4** (8.64 g, 81%). Solid. M.p. 142–144°. ^{1}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}F-NMR: 0.57 (*q*); −1.91 (*q*).

(−)-(R)-4,4,4,4',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 H_2 had stopped (875 ml of H_2, calc. 810 ml). The catalyst was filtered off and the soln. evaporated: (*R*)-**5** (1.78 g, 38%). Solid. pK_a (in H_2O): 3.17, 6.30. M.p. 194–195°. $[\alpha]_D^{rt.} = -9.29$ (*c* = 1.625, H_2O). ^{1}H-NMR (CD_3OD): 4.60–4.63 (1 H); 4.70–4.90 (*quint.*, 1 H). Anal. calc. for $C_5H_5F_6NO_2 \cdot HCl$: 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',4'-hexafluorovaline ((*R,S*)-**6**). The salt (*R*)-**5** (104 mg, 0.4 mmol) was dissolved in H_2O/acetone 1:1 (32 ml) containing $NaHCO_3$ (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 CH_2Cl_2 (3 ×). The combined extract was dried (Na_2SO_4) and evaporated and the residue dried under high vacuum: 179 mg of crystalline (*R,S*)-**6**. M.p. 79–81°. ^{1}H-NMR (MeO signals): 3.44 (*q*, *J* = 1.4, 1.1%); 3.39 (*q*, *J* = 1.1, 98.9%). ^{19}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 Et_2O/cyclohexane gave colourless plates suitable for X-ray structure analysis. $C_{15}H_{12}F_9NO_4$, monoclinic, space group $P2_1$, a = 7.5235(14), b = 23.660(4), c = 10.3208(14) Å, β = 91.46(1)°, V = 1836.6(5) Å^3, Z = 4, d_{calc} = 1.596 Mg/m^3; 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^{-3}. Absorption coefficient μ = 0.173 mm^{-1}; no correction for absorption was applied. Intensity data were collected at 223(2) K on a *Stoe-AED2* 4-circle diffractometer using MoK_α graphite monochromated radiation, using $2\theta/\omega$ scans in the range 4–51° in 2θ. 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.*

REFERENCES

[1] R. Keese, C. Hinderling, *Synthesis* **1996**, 695.

[2] A. Eremeev, I. Solodin, F. Polyak, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.* **1985**, *3*, 345.

[3] C. Zhang, C. Ludin, M. K. Eberle, H. Stoeckli-Evans, R. Keese, *Helv. Chim. Acta* **1998**, *81*, 174.
[4] I. L. Knunjants, Yu. A. Cherbukov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* (Engl. Transl.) **1960**, *12*, 2007.
[5] K. Hsieh, P. Needleman, G. R. Marshall, *J. Med. Chem.* **1987**, *30*, 1097.
[6] G. M. Sheldrick, 'SHELXS-86 Program for Crystal Structure Determination', *Acta Crystallogr., Sect. A* **1990**, *46*, 467.
[7] G. M. Sheldrick, 'SHELXL-93', Universität Göttingen, Göttingen, Germany, 1993.
[8] A. L. Speck, 'PLATON/PLUTON', *Acta Crystallogr., Sect. A* **1990**, *46*, C34.

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