89. Synthesis and Circular Dichroism of Both Enantiomers of 2-Deuterofluoroacetic Acid (= Fluoro[$^2H_1$]acetic Acid)

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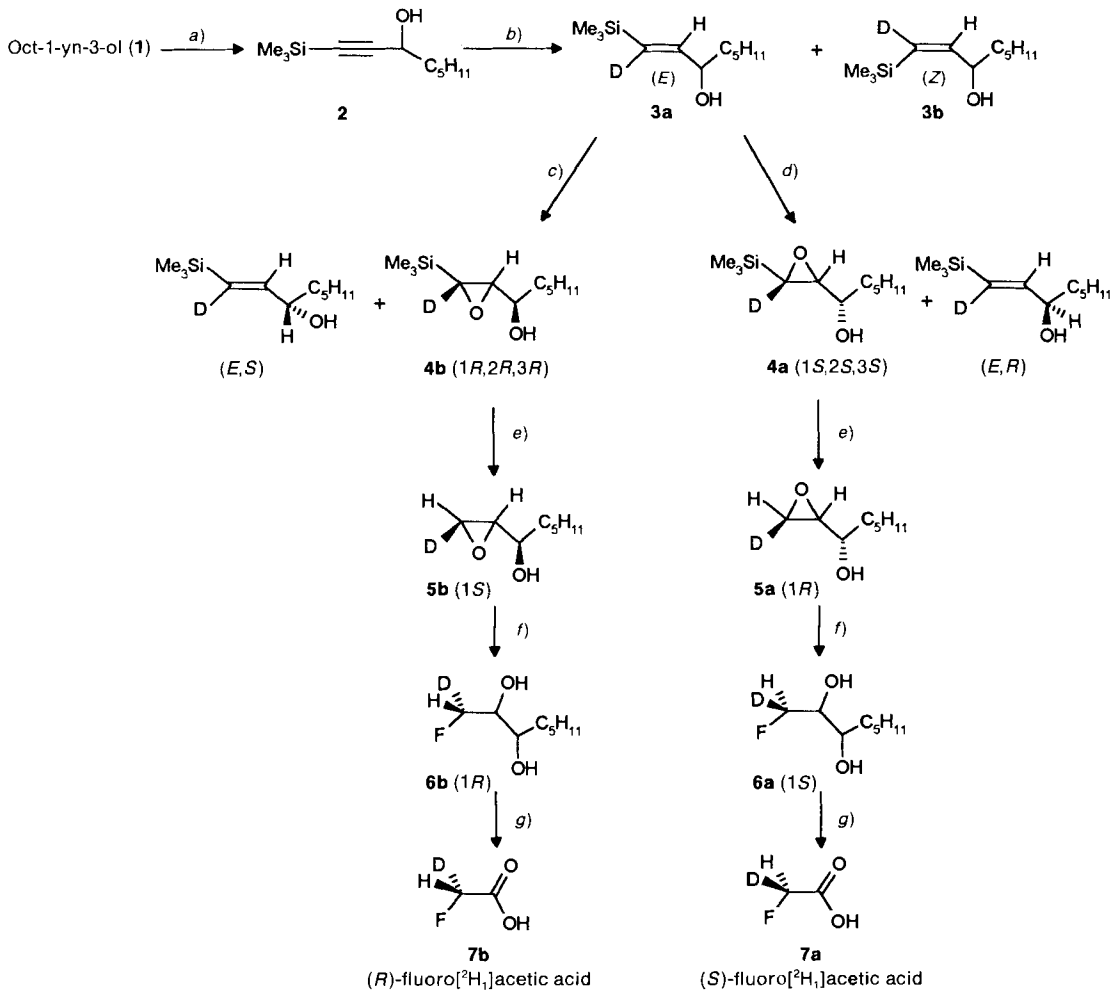
Sharpless epoxidation of (*E*)-1-(trimethylsilyl)[1-$^2H_1$]oct-1-en-3-ol (**3a**) yielded (1*S*,2*S*,3*S*)- and (1*R*,2*R*,3*R*)-1-(trimethylsilyl)-1,2-epoxy[1-$^2H_1$]octan-3-ols (**4a** and **4b**, resp.) which were converted in three steps into (*S*)- and (*R*)-fluoro[$^2H_1$]acetic acid (**7a** and **7b**, resp.) in good yields. Their high isotopic and optical purity was established by ^{1}H- and ^{19}F-NMR, mass, and circular-dichroism spectroscopy.

Introduction. – Fluoroacetic acid can replace acetic acid in several enzymatic reactions – sometimes with fatal consequences. *E.g.*, in the 'lethal synthesis', citrate synthase catalyses the condensation of fluoroacetyl CoA with oxaloacetate to form (2*R*,3*R*)-2-fluorocitrate which is a mortal poison for most organisms. Some time ago, our group published a method for the preparation of (*R*)-fluoro[$^2H_1$]acetic acid from (*R*)-[$^2H_1$]glycine using $NaNO_2$/HF/pyridine as reagent [1]. The steric course of this substitution (retention) was determined by analogy to the same reaction with *L*-isoleucine and *D*-alloisoleucine [2]. Since our previous method is tedious, expensive, and unsuitable for obtaining both possible enantiomers of fluoro[$^2H_1$]acetic acid in pure form, we worked out a novel method for its preparation on which we report in the following.

Results. – *Synthesis of (*S*)- and (*R*)-Fluoro[$^2H_1$]acetic Acids* (**7a** and **7b**, resp.). The synthetic route to the enantiomeric fluoro[$^2H_1$]acetic acids is outlined in the *Scheme*. The 1-(trimethylsilyl)oct-1-yn-3-ol (**2**), prepared by reacting of oct-1-yn-3-ol (**1**) first with EtMgBr and then with Me_3SiCl, was reduced with $LiAlH_4$. Workup of the product in deuterium oxide (D_2O) yielded 1-(trimethylsilyl)[1-$^2H_1$]oct-1-en-3-ol (**3**; (*E*)/(*Z*) 5:1) with a high degree of deuteration [3]. The diastereoisomer mixture **3** was epoxidized under *Sharpless* conditions [4] [5] using both enantiomers of diisopropyl tartrate (DIPT) as chirality source. In both reactions, only the (*E*)-isomer **3a** was converted into the epoxide. The resulting (1*S*,2*S*,3*S*)- and (1*R*,2*R*,3*R*)-1-(trimethylsilyl)-1,2-epoxy[1-$^2H_1$]octan-3-ols (**4a** and **4b**, resp.) were obtained with *ca.* 96 and 98% ee, respectively. The unreacted (*Z*)-isomer was separated by chromatography on silica gel. Substitution of the Me_3Si group by a proton occurred with retention of configuration [6] [7]. The substitution reaction was conducted in tetrahydrofuran (THF) by subsequent addition of KO(*t*-Bu), Bu_4NF, and a saturated solution of NH_4Cl, **4a** and **4b** yielding (1*R*,2*S*,3*S*)- and (1*S*,2*R*,3*R*)- 1,2-epoxy[$^2H_1$]octan-3-ols (**5a** and **5b**, resp.) in 93 and 94.4% ee, respectively. For the opening of the oxirane ring, several fluoride reagents were tried [8] [9]. Of those,

Scheme. *Synthesis of the Deuterofluoroacetic Acids* **7a** *and* **7b**



a) EtMgBr, THF, Me_3SiCl; H_2SO_4. *b*) $LiAlH_4$, THF; D_2O. *c*) (−)-DIPT, Ti[O(i-Pr)]$_4$, *t*-BuOOH. *d*) (+)-DIPT, Ti[O(i-Pr)]$_4$, *t*-BuOOH. *e*) Bu_4NF, THF, KO(*t*-Bu). *f*) $Et_3N \cdot 3$ HF. *g*) $RuCl_3$, $NaIO_4$, CCl_4/MeCN/H_2O.

only $Et_3N \cdot 3$ HF [10–12] gave satisfactory results. Starting from **5a** and **5b**, we obtained (1*S*,2*S*)- and (1*R*,2*R*)-1-fluoro[1-$^2H_1$]octane-2,3-diols (**6a** and **6b**, resp.), respectively. Oxidative cleavage of the diols with catalytic amounts of ruthenium trichloride and an excess of sodium metaperiodate [13] yielded the desired enantiomers, **7a** and **7b**, of fluoro[$^2H_1$]acetic acid.

Optical Purity and Circular Dichroism of the Enantiomeric Fluoro[$^2H_1$]acetic Acids. Samples of both enantiomers **7a** and **7b** of fluoro[$^2H_1$]acetic acid were esterified with methyl (−)-(*R*)-mandelate to yield the corresponding diastereoisomeric derivatives. Purification by HPLC afforded pure samples which were examined by ^{1}H-NMR spectros-

copy. The protons at the C^1H^2HF groups gave *dt*'s at 5.03/4.84 and 5.09/4.91 ppm for the methyl mandelate derivatives of (2*R*)- and (2*S*)-fluoro[$^2H_1$]acetic acids, respectively. Integration of the corresponding signals indicated that the enantiomer purity of the samples was better than 93%. On the other hand, the degree of deuteration could be best determined by the ^{19}F-NMR spectra. The ^{19}F signals for the methyl mandelate derivatives of the fluoro[$^2H_1$]acetic acids were observed at −231.79 and 231.95 ppm (*dt*), whereas the signal of the unlabelled derivative was found at −230.97 ppm (*t*). Integration of the signals revealed a degree of deuteration which was above 97%.

The circular-dichroism spectra were measured between 190 and 240 nm in 5 mM *Tris* · HCl (pH 7.4) and in a CF_3CH_2OH solution. The resulting spectra are shown in the *Figure* and exhibited the expected mirror images for the two investigated enantiomers. The extrema of the CD spectra were found at 206 and 208 nm for the fluoro[$^2H_1$]acetic acid solutions in *Tris* · HCl and CF_3CH_2OH, respectively.

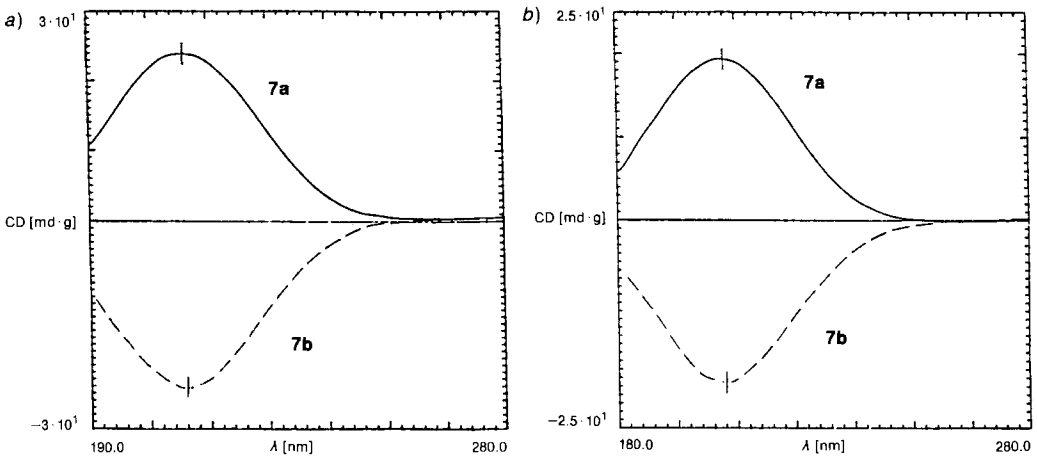


Figure. *Circular-dichroism spectra of (S)- and (R)-fluoro[$^2H_1$]acetic acids* (**7a** and **7b**, resp.), a) *in* Tris · *HCl buffer* (5 mM, pH 7.4; extrema at 206 nm, $\Phi = \pm 2.41 \cdot 10^1$) *and* b) *in* CF_3CH_2OH (extrema at 208 nm, $\Phi = \pm 1.95 \cdot 10^1$). (*S*)-Enantiomer **7a**: ——, (*R*)-enantiomer **7b**: – – –.

Discussion. – Previously prepared samples of (*R*)-fluoro[$^2H_1$]acetic acid (**7b**) were characterized only by ^{1}H- and ^{19}F-NMR spectroscopy and by the behavior of their coenzyme A esters in the citrate and malate synthase reactions [1]. Although these tests unambiguously defined their deuterium content and their absolute configuration, the original method was too expensive and tedious to prepare both enantiomers of fluoro-[$^2H_1$]acetic acid in high purity and in quantities enough for further characterization.

The chirality-generating step in the present synthesis was a *Sharpless* epoxidation [4] [5] of allyl alcohol **3a**. Essential for a high stereoselectivity was the introduction of a Me_3Si substituent which in the chiral oxiranes **4a** and **4b** could be replaced by proton with complete retention of configuration [6] [7]. Opening the oxirane ring by F^- took place with complete inversion of configuration, thus generating the C^1H^2HF group with known sense of chirality in the diols **6a** and **6b**. Oxidative degradation led finally to the enantio-

meric fluoro[$^2H_1$]acetic acids **7a** and **7b**, whose high enantiomer purity could be established by ^{1}H-NMR spectroscopy of their methyl (−)-(*R*)-mandelate. Their CD curves showed perfect mirror images (*Fig.*). The absolute configuration of the enantiomeric fluoro[$^2H_1$]acetic acids were also confirmed by the behavior of their coenzyme A esters in the citrate synthase reaction [1].

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Experimental Part

1. *General.* $Bu_4NF \cdot 3\ H_2O$, ruthenium(III) chloride hydrate, sodium (meta)periodate($NaIO_4$), oct-1-yn-3-ol (**1**), titanium tetraisopropoxide, (+)-diisopropyl tartrate, (−)-diisopropyl tartrate, *tert*-butyl hydroperoxide (anh. in isooctane), Me_3SiCl, *N,N'*-dicyclohexylcarbodiimide, KO(*t*-Bu), (−)-(*S*)-malic acid, 4-(dimethylamino)-pyridine, and (−)-(*R*)-methyl mandelate were products of *Fluka Chemicals*, Switzerland. Bromoethane and THF were from *Janssen Chimica* and $Et_3N \cdot 3$ HF from *Merck*, Darmstadt. All solvents were freshly distilled and dried prior to use. HPLC: *Merck-Hitachi-L-6210* pump, *L4000* UV detector, *D–2500* chromato-integrator, silical gel *100-C8*, (15–30 μm) and *Hewlett-Packard-1050 C18* (3–60 mm), prep. columns. TLC: *Macherey & Nagel* silica gel *254* plastic plates; solvent systems *A:* hexane/AcOEt 7:3; *B:* CH_2Cl_2/AcOEt 40:1; detection by heating after treatment with 3% ethanolic phosphomolybdenic acid. Prep. column chromatography (CC) was used for analysing the intermediates. M.p.: *Büchi* capillary m.p. instrument; uncorrected. NMR Spectra: *Bruker-WM-250* spectrometer for ^{1}H, ^{13}C, and DEPT; *Bruker-AM-400* spectrometer for ^{1}H and ^{19}F; $CDCl_3$ solns. containing Me_4Si as internal standard unless otherwise stated.

2. *1-(Trimethylsilyl)oct-1-yn-3-ol* (**2**). To the stirred suspension of Mg (7.3 g, 300 mmol) in dry THF (125 ml) under N_2, bromoethane (24.5 ml, 300 mmol) was added dropwise at 50°. After complete addition, the temp. was kept at 50° for 1 h, and then the mixture was cooled to 5°. A soln. of oct-1-yn-3-ol (13.63 g, 108 mmol) in THF was cautiously added dropwise, and the suspension was stirred overnight. Then the soln. was cooled to 5° on ice, and Me_3SiCl (38.1 ml, 300 mmol) was added dropwise while maintaining the temp. at 25°. Then the mixture was refluxed for 2 h. After cooling, 2M aq. H_2SO_4 (50 ml) was added dropwise and the aq. phase extracted with Et_2O. The Et_2O layers were washed with H_2O and brine, dried ($MgSO_4$), and evaporated. The residue was purified by distillation. B.p. 90°/10 Torr. Yield: 20.92 g (106 mmol, 98%). ^{1}H-NMR: 0.06 (*t*, Me_3Si); 0.8 (*t*, Me(8)); 1.2–1.76 (*m*, 4 CH_2); 4.2 (*t*, C*H*OH). ^{13}C-NMR: 106.92 (C(1)); 89.27 (C(2)); 62.91 (CHOH); 37.64 (CH_2); 31.37 (CH_2); 24.49 (CH_2); 22.49 (CH_2); 13.94 (Me); −0.13 (Me_3Si).

3. *1-(Trimethylsilyl)[1-$^2H_1$]octan-3-ol* (**3**). A soln. of **2** (20 g, 100 mmol) in THF (50 ml) was added dropwise to a suspenson of $LiAlH_4$ (6 g, 160 mmol) in THF (250 ml) at 0°. The mixture was stirred overnight under N_2 at r.t. After the reaction was complete, D_2O (15 ml) was added. The insoluble materials were filtered and washed with Et_2O. The combined org. layers were dried ($MgSO_4$) and evaporated. The resulting product **3** (19.29 g, 96 mmol, 96%) was used without further purification. ^{1}H-NMR (250 MHz, $CDCl_3$): 0.06 (*s*, Me_3Si (*E*)); 0.13 (*s*, Me_3Si (*Z*)); 0.87 (*t*, Me(8)); 1.28–1.72 (*m*, 4 CH_2); 4.02 (*m*, C*H*OH (*E*)); 4.19 (*m*, C*H*OH (*Z*)); 5.98 (*m*, J = 18.2, H–C(2) (*E*)); 6.16 (*d*, J = 13.4, H–C(2) (*Z*)). ^{13}C-NMR: 150.11 (C(2) (*Z*)); 148.57 (C(2) (*E*)); 131.14 (*t*, J = 20.2, C(1) (*Z*)); 128.72 (*t*, J = 20.8, C(1) (*E*)); 74.63 (CHOH); 36.85 (CH_2); 31.72 (CH_2); 25.08 (CH_2); 22.56 (CH_2); 13.98 (Me(8)); 0.41 (Me_3Si (*Z*)); −1.33 (Me_3Si (*E*)).

4. *1-(Trimethylsilyl)-1,2-epoxy[1-$^2H_1$]octan-3-ols* (= *α-Pentyl-3-(trimethylsilyl)[3-$^2H_1$]oxirane-2-methanol;* **4a** *and* **4b**). To a mixture of Ti[O(i-Pr)]$_4$ (18 g, 60 mmol, 1 equiv.) in CH_2Cl_2 (300 ml) and molecular sieve, a soln. of (+)-L-DIPT (16.86 g, 72 mmol, 1.2 equiv.) in CH_2Cl_2 (5 ml) was added under Ar. The resulting mixture was stirred for 10 min at −20°. After addition of **3** (12 g, 60 mmol, 1 equiv.), the resulting soln. was stirred for an additional 15 min, *t*-BuOOH (26 ml, 1.3 equiv.; 3M soln. in anh. isooctane) was added slowly, and the mixture was stirred for 5 h. Subsequently, Me_2S (2 ml, 1 equiv.) was added, and the mixture was stirred for 30 min at −20°. Then 10% aq. tartaric acid soln. (20 ml), Et_2O (150 ml), NaF (20 g), and *Celite* (10 g) were successively added. The mixture was stirred for 1 h at. r.t. and filtered. The precipitate was washed with Et_2O, the combined filtrate dried ($MgSO_4$) and evaporated and the residue chromatographed (Et_3N-deactivated silica gel, CH_2Cl_2/AcOEt 40:1). Yield: 3.68 g (17 mmol, 28% calc. for the mixture of **3a** and **3b**) **4a.** ^{1}H-NMR: 0.07 (*t*, J = 3.2, Me_3Si); 0.89 (*t*, J = 6.8, Me(8));

1.29–1.57 (*m*, 4 CH_2); 1.87 (br. *s*, J = 1.76, OH); 2.86 (*d*, J = 3.1, H–C(2)); 3.86 (*m*, J = 3.1, 2.3, *CH*OH). ^{13}C-NMR: −3.70 (Me_3Si); 14.03 (Me); 22.57 (CH_2); 24.90 (CH_2); 31.90 (CH_2); 33.57 (CH_2); 47.30 (*t*, ^1J(C,D) = 23.4, C(1)); 58.33 (C(2)); 68.89 (CHOH).

Enantiomer **4b** was prepared according to the same procedure using (−)-D-DIPT.

5. *1,2-Epoxy[1-$^2H_1$]octan-3-ols* (= *α-Pentyl[3-$^2H_1$]oxirane-2-methanols*; **5a** *and* **5b**). To an ice-cooled soln. of **4a** (0.866 g, 3.9 mmol) in THF (20 ml), KO(*t*-Bu) (0.47 g, 4.2 mmol, 1.1 equiv.) was added, and the soln. was stirred for 2 min. Then Bu_4NF (1.63 g, 5 mmol, 1.4 equiv.) in THF (5 ml) was added. After another 10 min. sat. NH_4Cl soln. (5 ml) was added and the mixture extracted with Et_2O. The Et_2O layers were dried ($MgSO_4$) and evaporated, and the residue was chromatographed (silica gel, hexane/AcOEt 7:3). Yield: 0.275 g (1.9 mmol, 49%) **5a.** ^{1}H-NMR: 0.87 (*t*, J = 6.8, Me(8)); 1.29–1.55 (*m*, 4 CH_2); 1.88 (br. *s*, OH); 2.7 (*d*, J = 3.9, H–C(1)); 2.99 (*t*, J = 3.4, 3.7, H–C(2)); 3.82 (*m*, *CH*OH). ^{13}C-NMR: 13.90 (Me(8)); 22.44 (CH_2); 24.86 (CH_2); 31.74 (CH_2); 35.31 (CH_2); 43.01 (*t*, J = 26.9, C(1)); 54.41 (C(2)); 68.31 (CHOH).

Enantiomer **5b** was prepared according to the same procedure using **4b**.

6. *1-Fluoro[1-$^2H_1$]octane-2,3-diols* (**6a** and **6b**). A soln. of **5a** (0.6 g, 4.1 mmol) and $Et_3N \cdot 3$ HF (10 ml, 5.5 mmol) was stirred for 4 h at 80° under N_2. After cooling, CH_2Cl_2 (20 ml) was added and the mixture cautiously washed with sat. $NaHCO_3$ and aq. NaCl soln. The org. phase was dried ($MgSO_4$) and evaporated and the residue chromatographed (silica gel, hexane/AcOEt 7:3): **6a.** White solid. TLC: R_f 0.22. M.p. 85°. Yield: 0.25 g (1.5 mmol, 38%). ^{1}H-NMR: 0.88 (*t*, J = 6.6, Me(8)); 1.26–1.58 (*m*, 4 CH_2); 1.96 (*d*, J = 5.1, OH); 2.44 (*d*, J = 5.1, OH); 3.72–3.82 (*m*, ^3J(H,F) = 19.2, 2 *CH*OH); 4.46–4.68 (*dd*, ^2J(H,F) = 46.8, H–C(1)). ^{13}C-NMR: 14.00 (Me(8)); 22.54, 25.45, 31.69 (CH_2); 32.52 (*t*, CH_2); 72.15 (*d*, ^3J(C,F) = 6.9, CHOH); 72.9 (*d*, ^2J(C,F) = 17.8, CHOH); 83.61, 85.25 (*d*, ^1J(C,F) = 165.5, C(1)). ^{19}F-NMR: −235.38 to −235.49 (*dm*, ^1J(F,H) = 47.9, ^2J(F,H) = 19.4, ^1J(F,H) = 7.1); 1.5% of non-deuterated substance (signals at −234.66 to −234.96 (*dt*)).

Enantiomer **6b** was prepared according to the same procedure using **5b**.

7. *Fluoro[2-$^2H_1$]acetic Acids* (**7a** and **7b**). To a soln. of CCl_4/MeCN/H_2O 2:2:3 **6a** (0.189 g, 1.1 mmol) was added. To the resulting biphasic mixture, sodium metaperiodate (1 g, 4.6 mmol, 4.1 equiv.) and a catalytic amount of ruthenium trichloride hydrate (6.9 mg 2.5%) were added, and the mixture was stirred vigorously for 2 h at r.t. Then, CH_2Cl_2 (5 ml) was added and the aq. phase extracted with CH_2Cl_2 (3 × 10 ml) to remove hexanoic acid. After the addition of 7% aq. H_2SO_4 soln., the aq. phase was extracted with Et_2O (5 × 30 ml). The Et_2O extract was dried ($MgSO_4$) and cautiously evaporated. Thus a yellow liquid was obtained which upon cooling to 0° yielded a white crystalline residue **7a** (0.066 g, 0.8 mmol, 72%). ^{1}H-NMR: 4.81–4.99 (*dt*, ^2J(F,H) = 46.9, ^2J(H,D) = 2.4, H–C(2)); 9.07 (br. *s*, COOH). ^{13}C-NMR (CD_2Cl_2): 78.91–76.03 (*dt*, ^1J(C,F) = 180, ^1J(C,D) = 23.6, C(2)); 173.4 (*d*, ^2J(C,F) = 21.9, COOH). ^{19}F-NMR (D_2O buffer, pD 6.5): −217.9 to −218.1 (*dt*, ^1J(F,H) = 48.0, ^1J(F,D) = 6.6).

Enantiomer **7b** was prepared according to the same procedure, starting from **6b**.

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