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Preparation of (*R*)- and (*S*)-3-Hydroxy-2-(trifluoromethyl)propionic Acid by Resolution with (*R,R*)- and (*S,S*)-2-Amino-1-phenylpropane-1,3-diol

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Abstract. Racemic 2-trifluoromethyl-3-hydroxypropionic acid (*rac*-**1**) is prepared on a 50 g scale from 3,3,3-trifluoropropene in four steps, the overall yield being 40%. A procedure for the resolution of *rac*-**1** with 2-amino-1-phenylpropane-1,3-diol is described (25 g scale). The acids (*R*)-**1** and (*S*)-**1** are isolated, their enantiomer purities determined by GC analysis of the corresponding methyl esters on a chiral column and their chirality senses assigned from an X-ray crystal structure of the salt formed with phenylethylamine. The non-fluorinated analog of **1** is frequently employed as a chiral synthetic building block ('*Roche* acid').

Readily available, natural, chiral hydroxy acids such as lactic, 3-hydroxybutanoic [2][3], malic and tartaric acid [4] are starting materials which are frequently used for EPC syntheses [4]. They are part of the *pool of chiral building blocks* [5] which has been extended to include other cheap starting materials such as 3-hydroxy-2-methylpropionic acid [6–8] ('*Roche* acid', as it has been used extensively by chemists of this company [6]).

Several years ago, we began to develop methods to provide CF_3 analogs of such acids, which would allow for the synthesis of correspondingly modified target molecules. Thus, 3,3,3-trifluorolactic acid [9] and 4,4,4-trifluoro-3-hydroxybutanoic acid [10][11] (*Fig. 1*) were prepared in enantiomerically pure forms by large scale resolution and were shown to be useful starting materials for a variety of transformations. Alternative methods for preparing these acids, *e.g.* enzymatic and other enantioselective reactions turned out to give less satisfactory results [12]. We now report a synthesis of the racemic 'trifluoro-*Roche* acid' **1** and its resolution on a 25-g scale. As has been shown for the non-fluorinated analog, this acid is especially valuable because suitable functional group manipulations on the enantiotopic branches allow for the synthesis of either enantiomer of a given target structure from the same enantiomer of '*Roche* acid' [6][7] (see *Fig. 1*).

The acid *rac*-**1** was prepared in four steps, keeping fairly close to published procedures [13–16], as outlined in *Scheme 1*: Addition of bromine to 3,3,3-trifluoropropene (→ **2**), HBr elimination to give 2-bromo-3,3,3-trifluoropropene (**3**) and Pd-catalyzed carbonylation with concomitant incorporation of water formed **4**. Its treatment with aqueous sulfuric acid led to *rac*-**1** as a waxy, hygroscopic solid, which can be readily extracted into ether from NaCl-sat. aqueous 2N HCl. The overall yield

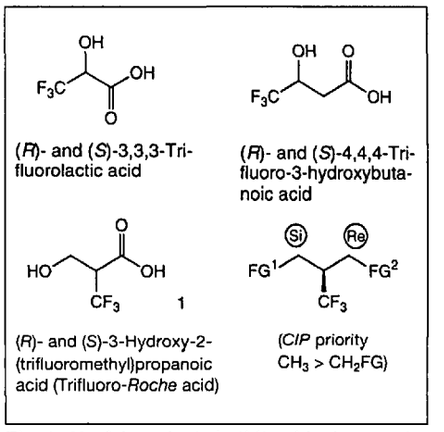
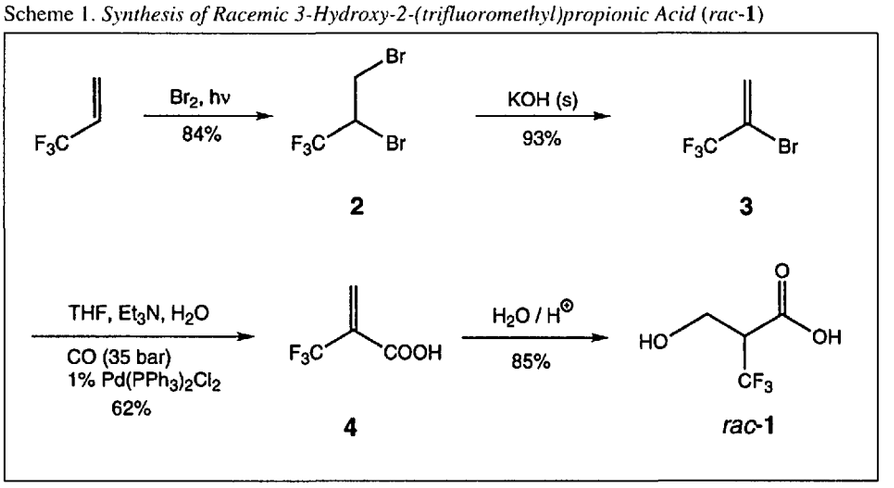


Fig. 1. *Useful synthetic building blocks containing a trifluoromethyl group*

Scheme 1. *Synthesis of Racemic 3-Hydroxy-2-(trifluoromethyl)propionic Acid* (*rac*-**1**)



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starting from 165 g of trifluoropropene is *ca.* 40%.

For the resolution of the 'trifluoro-*Roche* acid', we systematically tested eleven chiral amines, as described previously [9][17]. Combination of the aminodiol (*S,S*)-**5** with *rac*-**1** in a 1:1 ratio resulted in the formation of a salt (*S,S,S*)-**6** (*dr* = 92:8) which is rather insoluble in AcOEt and separated in more than 90% of the theoretical yield. From the residue of the mother liquor, which contained the salt (*S,S,R*)-**6**, the enantiomerically enriched acid (*R*)-**1** was extracted after acidification with 2N HCl and subjected to analogous treatment with the aminodiol (*R,R*)-**5** to give the salt (*R,R,R*)-**6** (*dr* = 95:5) (*Scheme 2*) (for configurational assignment *vide infra*). Recrystallization of the salts from AcOEt/MeOH gave materials of at least 99.5:0.5 *dr* from which (*S*)-**1** ($[\alpha]_D^{r.t.} = +18.9$) and (*R*)-**1** ($[\alpha]_D^{r.t.} = -18.7$) were set free quantitatively; the enantiomerically pure acids are crystalline solids of m.p. = 44° and $pK_a = 3.27$; they are chemically and configurationally stable (in a refrigerator for several months).

For the determination of the enantiomer purity of acid **1**, we used its methyl ester prepared by treatment with diazomethane in ether [20]. This ester can be analyzed by gas chromatography on a cyclodextrin column (*Fig. 2*).

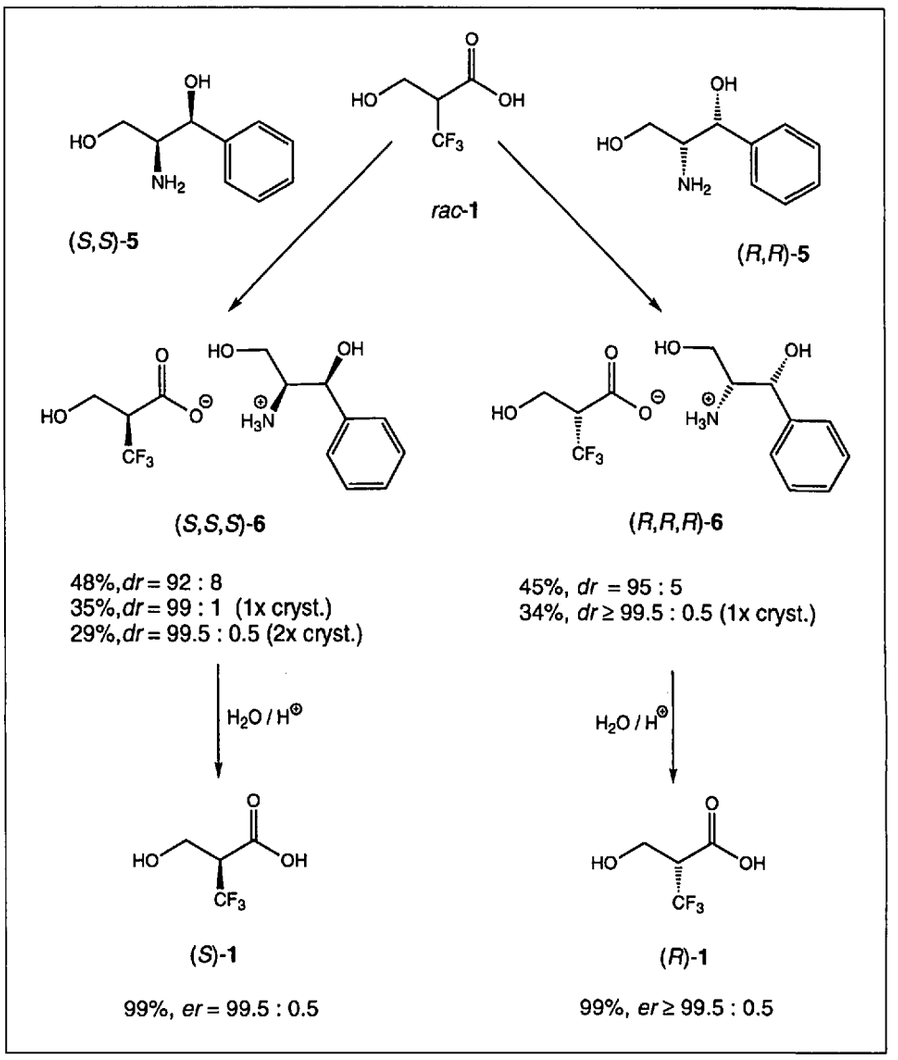
The absolute configuration of **1** was determined by X-ray crystal-structure analysis of the salt formed with (*S*)-1-phenylethylamine. The salt **7** formed from the laevorotatory acid **1** and the (–)-(*S*)-amine [21] gave suitable crystals and turned out to have the relative configuration *unlike* (*Fig. 3*). This result leads to the assignment that the laevorotatory 'trifluoro-*Roche* acid' **1** is of (*R*)- and the dextrorotatory acid is of (*S*)-configuration. It also follows that the methyl ester of **1**, which moves faster on the chiral GC column used for the analysis (*Fig. 2*), is of (*R*)-configuration.

Non-racemic acid **1** has been previously described; it was prepared by enantioselective enzymatic addition of water to 2-(trifluoromethyl)propenoic acid **4**; neither the enantiomer purity nor the absolute configuration of the samples thus obtained had been correctly determined [22][23].

Having both enantiomers of **1** available on a preparative scale, we are now ready to modify the carbon skeleton of this interesting acid and to incorporate its four carbon atoms into natural products or physiologically active compounds.

We gratefully acknowledge Dr. *W.B. Schweizer* (ETH-Zürich) for the determination of the X-ray crystal-structure analysis and *D. Manser* (ETH-Zürich) for the determination of the pK_a of **1**.

Scheme 2. *Resolution of 3-Hydroxy-2-(trifluoromethyl)propionic Acid*



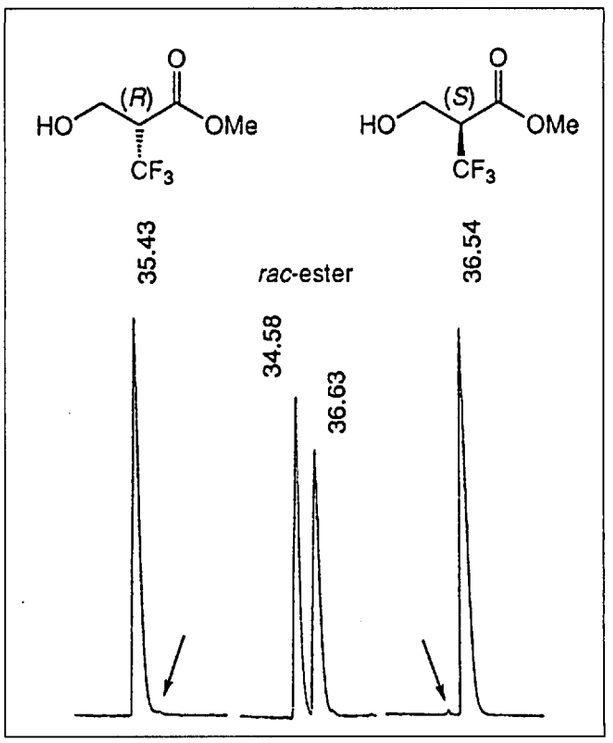


Fig. 2. *Determination of the enantiomer ratio of methyl* (R)- *and* (S)-*3-hydroxy-2-(trifluoromethyl)propionate by GC analysis.* Partial GC chromatogram of the esters of (*R*)-**1**, *rac*-**1**, and (*S*)-**1** on a *FS-Lipodex E* chiral column.

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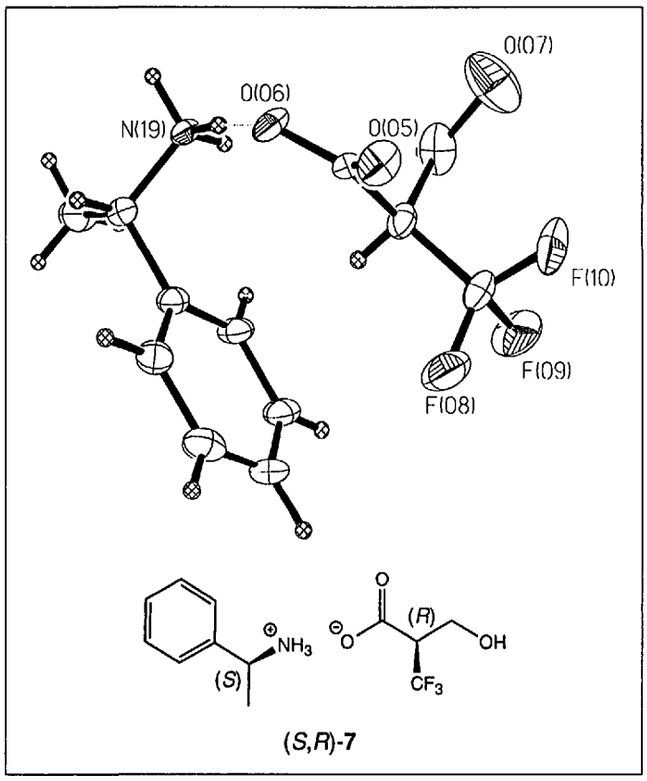

Fig. 3. *Crystal structure of*(S,R)-**7**. The vibrational ellipsoids are drawn to the 25% probability level. The structure was determined by Dr. *W.B. Schweizer*.

Experimental

General. Abbreviations: b.p. (boiling point), *dr* (diastereoisomer ratio), *er* (enantiomer ratio), h.v. (high vacuum, 0.1–0.01 Torr), m.p. (melting point), r.v. (rotary evaporation), t_R (retention time). Commercially available chemicals 3,3,3-trifluoropropene (*Aldrich, PCR Incorp.*), bis(triphenylphosphine)palladium(II) chloride (*Aldrich*), (+)-(1*S*,2*S*)-2-amino-1-phenylpropane-1,3-diol ($[\alpha]_D^{r.t.}$ = +27.5 (*c* = 3.05, MeOH)), (–)-(1*R*,2*R*)-2-amino-1-phenylpropane-1,3-diol ($[\alpha]_D^{r.t.}$ = –26.9 (*c* = 2.99, MeOH), *Boehringer Mannheim, GmbH*), and (–)-(*S*)-1-phenylethylamine ($[\alpha]_D^{r.t.}$ = –38.9 (*c* = neat), *Fluka*) were used as received, all other chemicals were of *p.a.* quality or purified or dried according to standard methods. Photochemical reactions were carried out by irradiating with a 125-W low-pressure Hg-lamp. Capillary gas chromatography (GC): *GHRC* (*Carlo Erba*); column (*Macherey-Nagel*): *FS-Lipodex E*, 50 m x 0.25 mm i.d.; injector temp. 220°, detector temp. 250°, T_0 = 80°/10 min, ΔT = 0.5°/min, p_{carr} = 120 kPa H_2. M.p.: open glass capillaries (uncorrected); *Büchi 510* [24]. $[\alpha]_D^{r.t.}$: *Perkin-Elmer-241* polarimeter, *p.a.* solvents. IR ($CHCl_3$ or KBr unless otherwise stated): *Perkin-Elmer 1600 FT-IR*, $\tilde{\nu}$ in cm^{-1}. NMR Spectra: *Bruker AMX-400* (400 MHz (^1H), 100 MHz (^{13}C)) or *Varian Gemini-300* (282 MHz (^{19}F)); δ in ppm rel. to Me_4Si or $CFCl_3$, *J* in Hz; $CDCl_3$ solns. unless otherwise stated; the multiplicities of ^{13}C signals are based on DEPT measurements. MS: *VG Tribrid* spectrometer; fragment ions in *m/z* with rel. intensities (%) in parentheses. Elemental analyses were performed by the Microanalytical Service of the Laboratorium für Organische Chemie, ETH-Zürich.

2,3-Dibromo-1,1,1-trifluoropropane (**2**). Prepared according to the procedure of *Henne* and *Nager* [13], from 3,3,3-trifluoropropene (165 g, 1.72 mol). Yield: 370 g (84%). n_D^{25} = 1.429 ([13]: 1.4286). ^1H-NMR: 3.64 (*dd*, *J* = 11.7, 7.9, *H*–C(3)–H); 3.89 (*dd*, *J* = 11.7, 5.5, H–C(3)–*H*); 4.38 (*dqd*, *J* = 7.9, 6.6, 5.5, H–C(2)). ^{19}F-NMR: –70.97 (*d*, *J*(H,F) = 5.7, CF_3).

2-Bromo-3,3,3-trifluoropropene (**3**). Prepared according to the procedure of *Drakesmith et al.* [14], from **2** (245 g, 0.96 mol). Yield: 156 g (93%). B.p. 32–33° ([14]: 33°). n_D^{25} = 1.351 ([13]: 1.3503). ^1H-NMR: 6.03 (*dq*, *J* = 3.0, 1.3, *H*–C(1)–H); 6.51 (*dq*, *J* = 3.0, 1.0, H–C(1)–*H*). ^{19}F-NMR: –69.42 (*s*, [25]).

2-(Trifluoromethyl)propenoic Acid (**4**). Following the procedure of *Fuchikami et al.* [15] **4** was prepared by Pd-catalyzed carbonylation of **3** (140 g, 0.78 mol). Yield: 69 g (63%). M.p. 51.6–52.2° ([14]: 50–51°; [15]: 52.5–53°). ^1H-NMR ($(CD_3)_2CO$, 300 MHz): 6.62 (*q*, [25], *J* = 1.3, *H*–C(3)–H); 6.82 (*q*, [26], *J* = 1.8, H–C(3)–*H*). ^{19}F-NMR ($(CD_3)_2CO$): –65.25 (*S*, [25]).

3-Hydroxy-2-(trifluoromethyl)propionic Acid (*rac*-**1**). Adapting the procedure of *Kawano et al.* [16], a soln. of **4** (50.0 g, 0.357 mol) and conc. H_2SO_4 (4.0 ml) in H_2O (1.0 l) was heated at reflux for 2 d. The aq. soln. was saturated with NaCl and extracted with Et_2O (5 x 300 ml). The combined org. layers were dried ($MgSO_4$). Evaporation of the solvent by r.v. and drying of the resulting waxy solid overnight under h.v. gave the hygroscopic acid *rac*-**1** (48.2 g, 85%). IR: 3300*m* (br.), 1734*s*, 1467*w*, 1323*m*, 1176*s*, 1123*s*, 1040*m*. (The IR spectrum was identical with that reported in [16].)

Resolution of (RS)*-3-Hydroxy-2-(trifluoromethyl)propionic Acid* (*rac*-**1**).

(1S,2S)-2-Hydroxy-1-(hydroxymethyl)-2-phenylethylammonium (S)-3-Hydroxy-2-(trifluoromethyl)propionate ((*S,S,S*)-**6**): A warm suspension (*ca.* 60°) of (+)-(1*S*,2*S*)-2-amino-1-phenylpropane-1,3-diol ((*S,S*)-**5**) (26.4 g, 0.158 mol) in AcOEt (420 ml) was added with stirring to a warm soln. (65–70°) of *rac*-**1** (25.0 g, 0.158 mol) in AcOEt (320 ml). The product (*S,S,S*)-**6** precipitated after a few seconds from the clear solution. After heating under reflux for 15 min, the mixture was allowed to cool to r.t. and stirred overnight. Filtration and drying of the resulting solid under h.v. gave the ammonium salt (*S,S,S*)-**6** (24.9 g, 48% (max. = 50%)). (The *er* (*S*)-**1**/(*R*)-**1** = 92:8 was determined by the method described below.) Dissolving (*S,S,S*)-**6** in boiling MeOH (36 ml) and subsequent dropwise addition of AcOEt (215 ml) led to spontaneous crystallization. Cooling to r.t. and stirring overnight, filtering and drying of the resulting solid under h.v. gave the ammonium salt (*S,S,S*)-**6** (18.0 g, 35% from *rac*-**1**, containing 8.7 g of the acid (*S*)-**1**, *er* = 99:1). A further recrystallization with MeOH (25 ml) and AcOEt (165 ml) gave (*S,S,S*)-**6** (15.0 g, 29% from *rac*-**1**, containing 7.3 g of the acid (*S*)-**1**, *er* = 99.5:0.5, $[\alpha]_D^{r.t.}$ = +18.9). (*S,S,S*)-**6**: M.p. 144.2–144.4°. $[\alpha]_D^{r.t.}$ = +27.7 (*c* = 1.31, EtOH). IR: 3280*s* (br.), 2965*s*, 2769*w*, 2687*w*, 2615*w*, 1638*s*, 1570*m*, 1541*m*, 1406*m*, 1372*m*, 1324*s*, 1240*s*, 1214*m*, 1170*s*, 1122*s*, 1038*s*. ^1H-NMR (CD_3OD): 3.11 (*qdd*, *J* = 9.5, 6.7, 5.7, H–C(CF_3)); 3.27–3.32 (*m*, *H*–C(NH_3^+)); 3.41 (*dd*, *J* = 11.7, 6.1, H_a–C–C(NH_3^+)); 3.54 (*dd*, *J* = 11.7, 3.7, H_b–C–C(NH_3^+)); 3.88 (*dd*, *J* = 11.2, 5.7, H_a–C–C(CF_3)); 3.95 (*dd*, *J* = 11.2, 6.7, H_b–C–C(CF_3)); 4.74 (*d*, *J* = 8.8, *H*–C(OH)(C_6H_5)); 7.31–7.44 (*m*, 5 arom. H). ^{13}C-NMR (CD_3OD): 172.8 (*s*); 142.1 (*s*, arom. C); 129.8 (*d*, 2 arom. C); 129.6 (*d*, arom. C); 128.0 (*d*, 2 arom. C); 127.0 (*q*, *J*(C,F) = 279.2, CF_3); 72.3 (*d*); 60.4 (*d*); 60.2 (*t*); 59.9 (*t*); 56.3 (*dq*, *J*(C,F)) = 23.8, *C*(CF_3)). ^{19}F-NMR (CD_3OD): –65.9 (*d*, *J*(H,F) = 10.0, CF_3). MS: 168 (<1), 141 (<1), 136 (2), 128 (10), 118 (5), 108 (5), 91 (21), 77 (12), 71 (3), 60 (100), 51 (5). Anal. calc. for $C_{13}H_{18}F_3NO_5$ (325.28): C 48.00, H 5.58, N 4.31; found: C 47.97, H 5.59, N 4.34.

(1R,2R)-2-Hydroxy-1-hydroxymethyl-2-phenylethylammonium (R)*-3-Hydroxy-2-(trifluoromethyl)propionate* ((*R,R,R*)-**6**): The collected filtrates from the isolation of (*S,S,S*)-**6** were concentrated by r.v. and the resulting solid (37.7 g) was dissolved in 2N HCl (250 ml), which was then saturated with NaCl and extracted with Et_2O (5 x 100 ml). The combined org. layers were dried ($MgSO_4$), filtered and concentrated to give **1** (16.7 g, 0.106 mol) which was dissolved in AcOEt (215 ml) at 60° and treated as described above with a suspension of (–)-(1*R*,2*R*)-2-amino-1-phenylpropane-1,3-diol ((*R,R*)-**5**) (17.6 g, 0.106 mol) in AcOEt (280 ml), leading to precipitation of the ammonium salt (*R,R,R*)-**6** (23.2 g, 45% from *rac*-**1**, containing 11.2 g of (*R*)-**1**, *er* = 95:5). Recrystallization of the remaining salt from MeOH (33 ml) and AcOEt (200 ml) gave (*R,R,R*)-**6** (17.7 g, 34% from *rac*-**1**, containing 8.6 g of (*R*)-**1**, *er* ≥ 99.5:0.5, $[\alpha]_D^{r.t.}$ = –18.7). (*R,R,R*)-**6**: M.p. 145.6–146.0°. $[\alpha]_D^{r.t.}$ = –27.5 (*c* = 1.32, EtOH).

(S)-3-Hydroxy-2-(trifluoromethyl)propionic Acid ((*S*)-**1**). The ammonium salt (*S,S,S*)-**6** (5.0 g, 15.4 mmol) was dissolved in 2N HCl (30 ml), which was then saturated with NaCl and extracted with Et_2O (5 x 20 ml). The combined org. layers were dried ($MgSO_4$), evaporated by r.v. and dried under h.v. to give the hygroscopic acid (*S*)-**1** (2.43 g, 99%, *er* = 99.5:0.5). M.p. 43.8–44.2°. $[\alpha]_D^{r.t.}$ = +18.9 (*c* = 1.29, MeOH). pK_a = 3.27 [27]. IR: 3030*m* (br.), 1734*s*, 1467*w*, 1323*w*,

1125*m*, 1040*m*. ^{1}H-NMR ($(CD_3)_2CO$): 3.55 (*qdd*, *J* = 9.0, 6.7, 5.2, H–C(2)); 4.04 [28] (*dd*, *J* = 11.1, 5.2, *H*–C(3)–H); 4.07 [28] (*dd*, *J* = 11.1, 6.7, H–C(3)–*H*). ^{13}C-NMR ($(CD_3)_2CO$): 167.58 (*s*); 125.5 (*q*, *J*(C,F) = 279.2, CF_3); 58.96 (*t*); 53.27 (*dq*, *J*(C,F) = 25.5, *C*(CF_3)). ^{19}F-NMR ($(CD_3)_2CO$): –65.9 (*d*, *J*(H,F) = 9.2, CF_3). MS: 159 (27) ([*M*+H]$^+$), 141 (45), 128 (71), 109 (39), 108 (39), 91 (100), 89 (50), 88 (35), 82 (5), 77 (9), 71 (22), 69 (20), 63 (6), 51 (4). Anal. calc. for $C_4H_5F_3O_3$ (158.07): C 30.39, H 3.19; found: C 30.28, H 3.29.

(R)-3-Hydroxy-2-(trifluoromethyl)propionic Acid ((*R*)-**1**). The ammonium salt (*R,R,R*)-**6** (2.01 g, 6.18 mmol) was treated as described above, yielding hygroscopic (*R*)-**1** (0.97 g, 99%, *er* ≥ 99.5:0.5). M.p. 43.8–44.2°. $[\alpha]_D^{rt}$ = –18.7 (*c* = 1.30, MeOH) ([29]: –8.55 (*c* = 1.38, MeOH)).

Esterification of the Acids rac-**1**, (R)-**1** *and (S)-***1** *to the Methyl Esters for Determination of the* er *by GC Analysis.* The enantiomer ratios of the resolved acids (*R*)-**1** and (*S*)-**1** were determined in the following way: 50 mg of the corresponding ammonium salts (*S,S,S*)-**6** or (*R,R,R*)-**6** were dissolved in 2N HCl (1 ml) and extracted with Et_2O (10 ml). The organic layer was dried ($MgSO_4$) and filtered. Esterification of the acid was achieved by the addition of an ethereal soln. of diazomethane [30] to an ethereal soln. of the acid until the soln. remained yellow. After decomposition of the excess CH_2N_2 with a small amount of AcOH, the resulting soln. was used directly for GC analysis (t_R((–)-(*R*)-methyl ester) = 34.6 min and t_R((+)-(*S*)-methyl ester) = 36.6 min, column and conditions see *General*).

Determination of the Absolute Configuration of (–)-3-Hydroxy-2-(trifluoromethyl)propionic Acid.

(–)-(S)-1-Phenylethylammonium (R)-3-Hydroxy-2-(trifluoromethyl)propionate ((*S,R*)-**7**). (–)-(*S*)-1-Phenylethylamine (0.134 ml, 1.053 mmol) was added to a stirred soln. of (–)-(*R*)-3-hydroxy-2-(trifluoromethyl)propionic acid (162 mg, 1.024 mmol) in EtOH (1.0 ml) in a 15 ml sample vial. After removing the magnetic stirring bar, the soln. was kept at r.t. and the solvent was allowed to evaporate slowly. After 3 d, suitable crystals for X-ray crystal-structure analysis were obtained. The crystal structure (*Fig. 3*) showed the absolute configuration of (–)-**1** to be (*R*) [31]. For further analysis of **7**, the remaining crystals were dried under h.v. for 2 d. M.p. 127.2–127.6°. $[\alpha]_D^{rt}$ = –5.34 (*c* = 1.34, MeOH). IR: 3429*w* (br.), 2939*m* (br.), 1636*w*, 1582*s*, 1390*m*, 1282*m*, 1148*m*, 1109*s*, 1051*w*, 858*w*, 769*w*, 703*m*, 683*w*. ^{1}H-NMR: 1.62 (*d*, *J* = 6.9, C*H*$_3$–C(NH_3^+)); 3.11 (*qdd*, *J* = 9.6, 6.7, 5.8, H–C(CF_3)); 3.88 (*dd*, *J* = 11.2, 5.8, *H*–C(OH)–H); 3.94 (*dd*, *J* = 11.2, 6.7, H–C(OH)–*H*); 4.44 (*q*, *J* = 6.9, *H*–C(NH_3^+)); 7.37–7.47 (*m*, 5 arom. H). ^{13}C-NMR: 172.76 (*s*); 139.98 (*s*); 130.31 (*d*, 2 arom. C), 130.12 (*d*, arom. C); 127.70 (*d*, 2 arom. C); 127.07 (*q*, *J*(C,F) = 279.2, CF_3); 60.19 (*t*); 56.30 (*qd*, *J*(C,F) = 23.7, *C*(CF_3)); 52.53 (*d*); 20.88 (*q*). ^{19}F-NMR: –65.94 (*d*, *J*(H,F) = 9.1, CF_3). MS: 141 (<1), 128 (10), 120 (5), 106 (100), 91 (19), 79 (27), 77 (20), 69 (5), 51 (14). Anal. calc. for $C_{12}H_{16}F_3NO_3$ (279.26): C 51.61, H 5.77, N 5.02; found: C 51.64, H 5.92, N 5.04.

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[1] Part of the projected Dissertation of *S.P.G.*, ETH-Zürich.

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[20] For non-analytical purposes, *i.e.* for the *preparation* of the ester, it is important to use a CH_2N_2 soln. which has not been stored over KOH, as the ester is prone to racemization, especially under basic conditions. When pure, it may be stored in a refrigerator for longer periods of time.

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[26] The geminal coupling constant is <1 Hz.

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[28] Spectrum of higher order, the given shift value corresponds to the center of the multiplet.

[29] For the first description of the determination of the abs. configuration of (*S*)-3-hydroxy-2-(trifluoromethyl)propionic acid ((*S*)-**1**) see [23] (the *er* and the abs. configuration of the sample described therein are incorrect).

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[31] To make sure that the crystal used for X-ray analysis actually contained the (*R*)-acid and the (*S*)-amine it was analyzed after completion of the refraction data collection: it was dissolved in 2N HCl (0.1 ml), the acid was extracted into Et_2O (0.7 ml) and converted into the methyl ester as described above. Analysis by GC confirmed that no epimerization of the (–)-3-hydroxy-2-(trifluoromethyl)propionic acid ((–)-(*R*)-**1**) had taken place. The aq. layer was then made basic (pH > 11) with a small pellet of NaOH and the 1-phenylethylamine was extracted into Et_2O (1 ml). After drying ($MgSO_4$) and filtration, the solvent was evaporated under an argon flow. The amine was dissolved in CH_2Cl_2 (250 µl) and trifluoroacetic anhydride (50 µl) was added. The solution was allowed to stand at r.t. for 4 h, after which the solvent was evaporated under an argon flow overnight. After dissolving in Et_2O (0.25 ml), the sample was directly analyzed by GC (FS permabond *L-Chirasil Val*, *Macherey-Nagel*, 25 m x 0.25 mm, *p* = 60 kPa, *T* = 75° isotherm) confirming (–)-(*S*)-1-phenylethylammonium as the cationic part of the crystal (t_R((*S*)-2,2,2-trifluoro-*N*-(1-phenylethyl)acetamide) = 24.95 min, t_R((*R*)-2,2,2-trifluoro-*N*-(1-phenylethyl)acetamide) = 24.19 min) [21].