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An Efficient Method of Preparing (*R*)- and (*S*)-4,4,4-Trifluoro-3-hydroxybutanoic Acid: Resolution with (*R*)- or (*S*)-1-Phenylethylamine

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Abstract. Two crystallizations of the *unlike* salts **2** from 4,4,4-trifluoro-3-hydroxybutanoic acid (**1**) and 1-phenylethylamine, followed by recovery of the free acid, lead to the isolation, in *ca.* 30% (60% of the theoretical amount), of the (*R*)- and (*S*)-acid **1** (m.p. 44°) in ⩾ 98% enantiomeric excess. The purity of **1** was determined by *Mosher*'s method, and the sense of chirality (+)-(*R*) and (−)-(*S*) determined by chemical correlation. The resolution procedure leading to enantiomerically pure **1** is compared with the methods using enzymatic or microbial enantioselective reactions.

There is a rapidly increasing interest in organofluorine compounds [1] due to their use as substrates in biological and medicinal studies, which hopefully may lead to further applications as drugs and also for plant protection. In particular, simple, enantiomerically pure fluoro-substituted building blocks are in great demand.

We have found, that *rac*-4,4,4-trifluoro-3-hydroxybutanoic acid (**1**; m.p. 78.4–79.2°), readily available [2] from commercial ethyl trifluoroacetate, can be resolved by crystallization of the *unlike* diastereoisomeric salts **2** with 1-phenylethylamine from abs. EtOH [3]. After one recrystallization of the salt, the acid was recovered and isolated in *ca.* 30% yield with an enantiomeric excess (ee) of ⩾ 98%, as shown by applying *Mosher*'s method [4] to its methyl ester (see **3** in *Fig. 1*).

The enantiomerically pure acid **1** is an extremely hygroscopic, low-melting solid (m.p. 43.8–44.0°). The absolute configuration was determined by esterification with EtOH and comparison of the sense of optical rotation of the ethyl ester with that of an authentic sample [5]. Thus, we assign the (*R*)-configuration to the dextrorotatory acid **1**.

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In an attempt to determine the purity of the diastereoisomeric salts **2**, we applied differential scanning calorimetry (DSC). When a normal heating rate of 5°/min was used, instead of recording the normal melting curve, was measured a distorted curve *(Fig. 2)*, while crystals separated on the cover of the DSC sample holder.

This observation led to the discovery that the diastereoisomeric salts (*R,R*)-**2** and (*R,S*)-**2** sublime with different rates. Thus, when a 1:1 mixture of the two salts was heated in a sublimator at *ca.* 95°/10^{-3} Torr, the sublimate on the cold finger was enriched in the (*R,R*)-**2** isomer, and, correspondingly, the other isomer in the residue. The degree of enrichment can be seen from the data in the *Table*.

Similar results were obtained with the 1-phenylethylammonium salt of the 3-hydroxybutanoic acid, as well as with the 4,4,4-trichloro analogue. We have not investigated the mechanism of this sublimation [6], but we found that the three β-hydroxy-carboxylic acids themselves also sublime readily [7], a property which can be exploited for their purification.

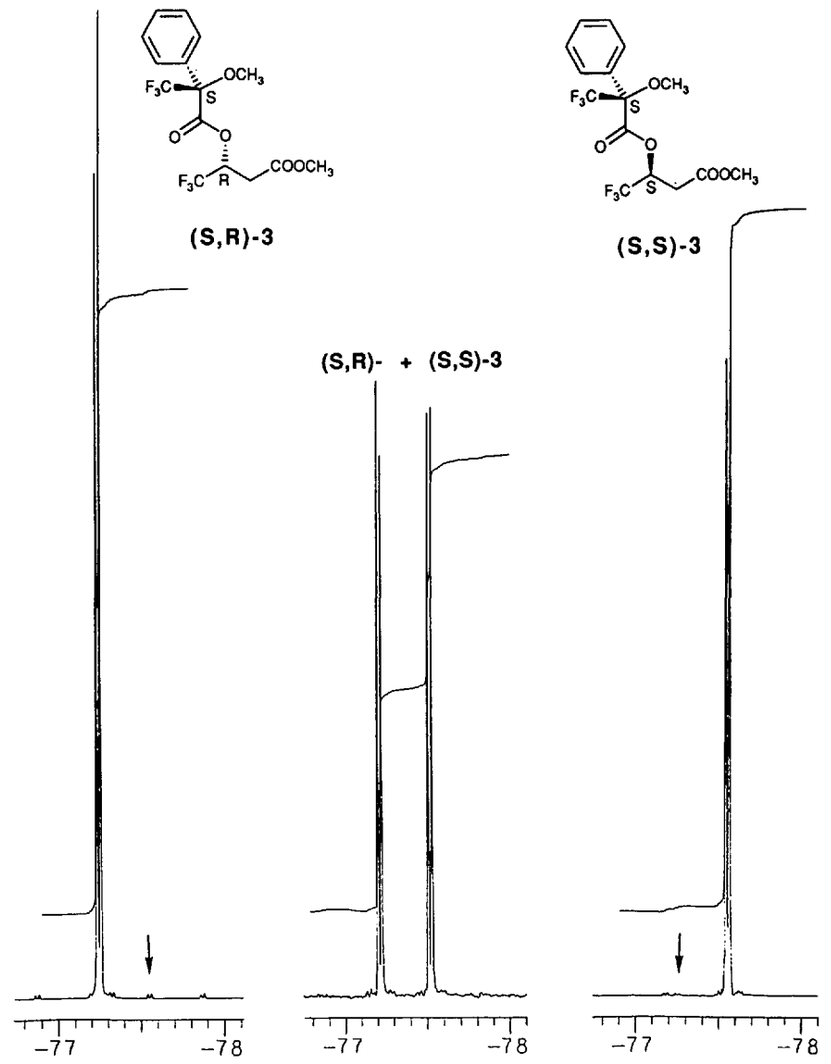
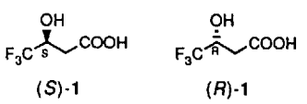
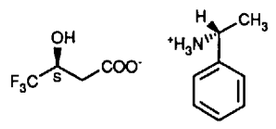
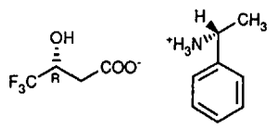
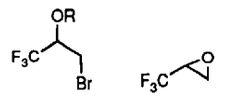


Fig. 1. *Determination of the enantiomeric excess of the (−)-(S)-trifluoro-3-hydroxybutanoic acid* **1**. Partial ^{19}F-NMR spectra of the *Mosher* ester of (*R*)-(+)-**1** *(left)*, *rac*-**1** *(middle)*, and (−)-(*S*)-**1** *(right)* methyl esters.









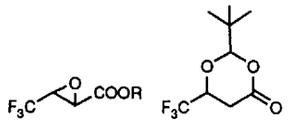


Table. *Diastereoselective Sublimation of the Ammonium Salts Obtained from (+)-(R)-1-Phenylethylamine and the Trifluorohydroxy Acid* **1**. The optical rotations refer to the free acid obtained by hydrolysis of the salt and isolation of the components.

Acid employed	Temp.	Pressure	Sublimate		Residue	
(op [%])	[°C]	[Torr]	Yield [%]	$[\alpha]_D$ (op [%])	Yield [%]	$[\alpha]_D$ (op [%])
rac (0)	100	0.005	31	+ 1.7 (11)	69	− 0.8 (5)
rac (0)	110	0.003	50	+ 1.3 (9)	50	− 1.3 (9)
(+) (11)	90	0.002	41	+ 3.1 (21)	59	+ 0.9 (6)
(−) (5)	90	0.002	42	+ 2.1 (14)	58	− 2.4 (16)
rac (0)	140	760	slow decomposition			

The enantiomer separation of *rac*-**1** with 1-phenylethylamine has previously been mentioned in a patent [8]. The resolution of the trifluoro-hydroxybutanoic acid, as described here, is the most convenient large-scale laboratory method of preparing either enantiomer of this acid. The reported yeast reduction of ethyl 4,4,4-trifluoro-3-oxobutanoate [5] or the kinetic resolution of ethyl 3-acetoxy-4,4,4-trifluorobutanoate by saponification with lipases [9] are more cumbersome procedures for the preparation of derivatives of (+)- or (−)-**1**.

The use of the trifluoro-hydroxy acid for the preparation of other enantiomerically pure CF_3-containing building blocks (see *e.g.* **4**–**7**) will be reported shortly.

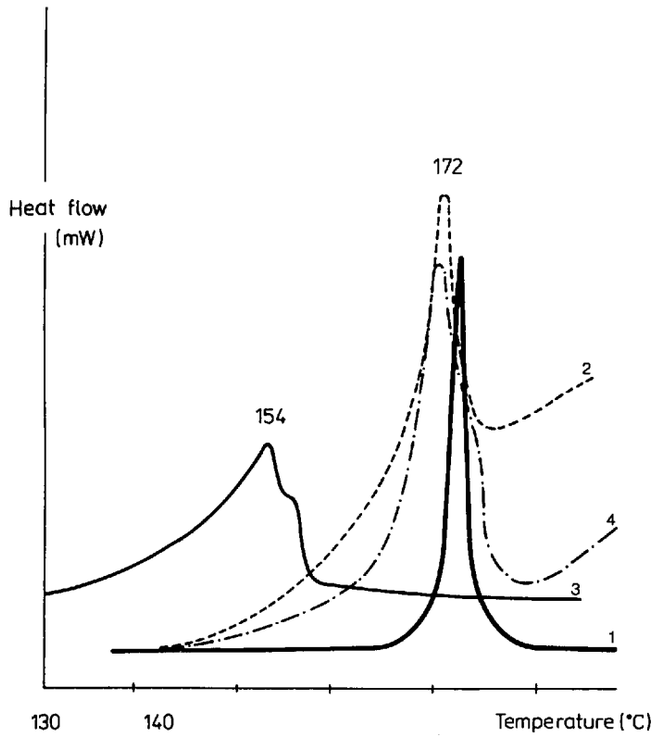


Fig. 2. *DSC Curves of* (R,R)-**2** *recorded at various heating rates*. Deviation from the nearly ideal curve (*1*) (recorded for the benzylammonium salt of the racemic acid at a heating rate of 5°/min) indicates the possibility of sublimation. Using a higher heating rate of 15°/min (*2*), the melting procedure of (*R,R*)-**2** is also accompanied by sublimation. At 2°/min (*3*) an endothermic effect is observed more than 20° below the melting point of (*R,R*)-**2**, whereupon there is no further uptake of heat. The curve (*4*) was obtained with a heating rate of 5°/min. The DSC-curves were recorded by a *Mettler FP 84 DSC* apparatus supplied by an *FP 800* control unit.

Experimental

rac-*4,4,4-Trifluoro-3-hydroxybutanoic Acid* (*rac*-**1**). The racemic acid **1** is prepared by following the procedures of *Grillot et al.* and *McBee et al.* [2] on a 100-g scale with an overall yield of 85% starting from the β-keto ester. M.p. = 78.4–79.2° ([2b]: 78–79°).

Resolution. To a warm soln. (*ca.* 50°) of 100.0 g (0.63 mol) of *rac*-**1** in 1 l of abs. EtOH is slowly added with stirring a warm soln. (*ca.* 50°) of 76.6 g (0.63 mol) of (+)-(*R*)-1-phenylethylamine in 760 ml of abs. EtOH. After the addition is completed, crystals of the ammonium salt precipitate. The mixture is allowed to cool to r.t. and stirred for another 2.5 h. Filtration and washing with *ca.* 80 ml of cold EtOH yield, after drying *in vacuo*, 64.5 g of the ammonium salt *A* (containing 36.5 g of the acid with an $[\alpha]_D = -13.7$, ee = 91% [10]).

The filtrate is evaporated to dryness (112.1 g), dissolved in *ca.* 380 ml of 2N HCl (pH ≤ 1), and extracted 4 times with 150 ml of Et_2O. The combined org. layers are washed with brine and dried (anh. $MgSO_4$). Evaporation of the solvent yields 63 g of the acid which is dissolved in 630 ml of EtOH and treated with a soln. of 48.6 g of (−)-(*S*)-1-phenylethylamine in 480 ml of EtOH. In this way, 64.2 g of the ammonium salt *B* (containing 36.3 g of the acid with an $[\alpha]_D = +13.5$, ee = 90% [10]) are isolated.

Enantiomerically pure material is obtained by dissolving 61.9 g of the crystal fraction *A* in hot EtOH and cooling to r.t. Stirring for 3 h, filtering, and drying *in vacuo* yields 47.4 g (77%, 28% calculated from *rac*-**1**) of the salt *C* (containing 26.8 g of the acid with an $[\alpha]_D = -15.0$, ee ≥ 98% [10]).

Recrystallization of 5.0 g of the salt fraction (*B*) in 50 ml of EtOH yields 4.0 g (80%) of salt *D* (containing 2.3 g of the acid with an $[\alpha]_D = +15.1$, ee ≥ 98% [10]).

*Isolation of (+)- or (−)-***1**. The ammonium salt **2** is dissolved in 2N HCl and the pH of the soln. adjusted to ≤ 1. Extraction with Et_2O (4 ×) followed by drying of the combined org. layers ($MgSO_4$) and evaporation of the solvent yields the hygroscopic acid quantitatively.

Analytical Data

M.p.: *Büchi 510* apparatus; not corrected. $[\alpha]_D$: *Perkin-Elmer 241* polarimeter. IR spectra: *Perkin Elmer 983* or *Perkin Elmer 782*. ^{1}H-, ^{13}C-, and ^{19}F-NMR spectra: *Bruker WM 300* or *Varian XL 300* spectrometer. MS: *VG Tribrid* spectrometer.

(S)-1-Phenylethylammonium (R)-4,4,4-Trifluoro-3-hydroxybutanoate ((*R,S*)-**2**): M.p. 194.2–194.6°. $[\alpha]_D = +2.3$ (*c* = 1.29, EtOH). IR (KBr): 3290, 2970, 2190, 1560, 1525, 1405, 1275, 1170, 1115. ^{1}H-NMR (CD_3OD, 300 MHz): 7.47–7.35 (*m*, C_6H_5); 4.43 (*q*, *J* = 6.9, $CH(CH_3)$); 4.34 (*ddq*, $J_1 = 3.8$, $J_2 = 8.8$, $J(H,F) = 7.2$, $CH(CF_3)$); 2.50 (*dd*, $J_1 = 15.4$, $J_2 = 3.8$, CH_AH_B); 2.37 (*dd*, $J_1 = 15.4$, $J_2 = 8.8$, CH_AH_B); 1.62 (*d*, *J* = 6.9, CH_3). ^{13}C-NMR (CD_3OD, 75 MHz): 177.5 (*s*); 140.2 (CH); 130.3 (CH); 130.0 (CH); 127.7 (CH); 127.0 (*q*, $J(C,F) = 281$, CF_3); 69.3 (*q*, $J(C,F) = 31$, CH); 52.3 (CH); 38.6 (CH_2); 21.0 (CH_3). ^{19}F-NMR (CD_3OD, 282 MHz, Ref. $CFCl_3$): −79.5 (*d*, $J(H,F) = 7.1$). MS: 141 (15), 120 (22), 106 (100), 89 (59), 79 (66), 71 (67), 69 (26), 43 (80). Anal. calc. for

$C_{12}H_{16}NO_3F_3$: C 51.61, H 5.78, N 5.02, O 17.19, F 20.41; found: C 51.69, H 5.92, N 5.24, F 20.38.

(R)-1-Phenylethylammonium (S)-4,4,4-Trifluoro-3-hydroxybutanoate ((*S,R*)-**2**): $[\alpha]_D = -2.3$ ($c = 1.09$, EtOH).

(R)-4,4,4-Trifluoro-3-hydroxybutanoic Acid ((+)-**1**): M.p. 43.8–44.0°. $[\alpha]_D = +15.1$ ($c = 7.27$, EtOH). IR (KBr): 3460, 3180, 1735, 1275, 1180, 1130. ^{1}H-NMR (CD_3OD, 300 MHz): 4.40 (*ddq*, $J_1 = 3.3$, $J_2 = 9.7$, $J(H,F) = 7.1$, $CH(CF_3)$); 2.67 (*dd*, $J_1 = 16.0$, $J_2 = 3.3$, CH_AH_B); 2.50 (*dd*, $J_1 = 16.0$, $J_2 = 9.7$, CH_AH_B). ^{13}C-NMR (CD_3OD, 75 MHz): 173.1 (*s*); 126.7 (*q*, $J(C,F) = 281$, CF_3); 68.2 (*q*, $J(C,F) = 32$, CH); 36.6 (CH_2). ^{19}F-NMR (CD_3OD, 282 MHz, Ref. $CFCl_3$): −79.9 (*d*, $J(H,F) = 7.2$). MS: 159 (54), 141 (84), 120 (49), 89 (86), 71 (95), 69 (42), 43 (100). Anal. calc. for $C_4H_5O_3F_3$: C 30.39, H 3.19, O 30.36, F 36.05; found: C 30.16, H 3.23, F 36.0.

(S)-4,4,4-Trifluoro-3-hydroxybutanoic Acid ((−)-**1**): $[\alpha]_D = -15.0$ ($c = 6.58$, EtOH).

Methyl (R)-4,4,4-Trifluoro-3-hydroxybutanoate: $[\alpha]_D = +21.0$ ($c = 4.78$, $CHCl_3$). IR (film): 3460, 2960, 1730, 1440, 1275, 1170, 1130. ^{1}H-NMR ($CDCl_3$, 300 MHz): 4.51–4.40 (*m*, $CH(CF_3)$); 3.77 (*s*, CH_3O); 2.75 (*dd*, $J_1 = 16.8$, $J_2 = 4.2$, CH_AH_B); 2.68 (*dd*, $J_1 = 16.8$, $J_2 = 8.2$, CH_AH_B). ^{13}C-NMR ($CDCl_3$, 75 MHz): 171.3 (*s*); 124.5 (*q*, $J(C,F) = 281$, CF_3); 67.3, (*q*, $J(C,F) = 32$, CH); 52.5 (CH_3); 34.7 (CH_2). ^{19}F-NMR ($CDCl_3$, 282 MHz, Ref. $CFCl_3$): −80.4 (*d*, $J(H,F) = 7.1$). MS: 173 (0.5), 141 (48), 103 (40), 69 (26), 59 (40), 43 (100), 28 (78), 15 (66). Anal. calc. for $C_5H_7O_3F_3$: C 34.90, H 4.10, O 27.89, F 33.11; found: C 34.77, H 4.27, F 32.9.

Methyl *(S)-4,4,4-Trifluoro-3-hydroxybutanoate:* $[\alpha]_D = -20.9$ ($c = 2.11$, $CHCl_3$).

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[1] The attention paid to this class of compounds is illustrated by the number of contributions about this topic in the *International Chemical Congress of Pacific Basin Societies* (12% of the presentations in the Organic Division!): *Pacifichem '89*, Honolulu, Hawaii, 17.–22.12.1989.

[2] a) G.F. Grillot, S. Aftergut, S. Marmor, F. Carrock, *J. Org. Chem.* **1958**, *23*, 386; b) E.T. McBee, O.R. Pierce, D.D. Smith, *J. Am. Chem. Soc.* **1954**, *76*, 3722.

[3] With this amine, the 4,4,4-trichloro-3-hydroxybutanoic acid has been resolved a long time ago: D. Borrmann, R. Wegler, *Chem. Ber.* **1967**, *100*, 1575.

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[5] D. Seebach, P. Renaud, W.B. Schweizer, M. Züger, M.-J. Brienne, *Helv. Chim. Acta* **1984**, *67*, 1843; see also J. Ehrler, D. Seebach, *ibid.* **1989**, *72*, 793. For the first description of the yeast reduction of the trifluoro-ketoester yielding the trifluoro-hydroxyester, of which the %ee was incorrectly determined, see: T. Kitazume, N. Ishikawa, *Chem. Lett.* **1983**, 237.

[6] Salt molecules or the dissociated components in the gas phase? *Cf.* C.G. de Kruif, *J. Chem. Phys.* **1982**, *77*, 6247.

[7] At 0.001 Torr, the CH_3, CCl_3, and CF_3 derivatives start subliming at 40, 40, and 20°, respectively.

[8] Japanese Patent Application Jpn. Kokai Tokkyo Koho JP 6403,154, S. Mihashi, H. Kondo (*CA:* **1989**, *111*, 31747p).

[9] T. Kitazume, J.T. Lin, *J. Fluorine Chem.* **1987**, *34*, 461; T. Kitazume, N. Okamura, T. Ikeya, T. Yamazaki, *ibid.* **1988**, *39*, 107; T. Kitazume, *Bio. Ind.* **1988**, *5*, 733.

[10] Determined by esterification with CH_2N_2 and ^{19}F-NMR spectroscopy of the *Mosher* ester [4] **3**.

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Groupe d'Analyse Chimique Interdisciplinaire de l'EPFL, GACHI*: 10e Journée d'Analyse: ICP-MS

Raymond Houriet**

The 10th meeting was hold on November 28, 1989, sponsored by Perkin-Elmer *and* VG Instruments. *Its topic was the coupling between emission spectroscopy and mass spectrometry: ICP-MS. The state of the art in the method was introduced by Prof.* Mermet. *Recent developments were described by the manufacturers and applications were presented by users of the method, including contributions of three (out of the four) swiss laboratories equipped with the method. Three articles discuss the limits of detection in emission* vs. *ICP-MS* (E. Poussel *and* J.M. Mermet), *the applications of ICP-MS in an industrial analytical center* (H. Baumann)*** *and the impact of ICP-MS on studies in groundwater typology* (A. Parriaux *and* J.D. Dubois)***.

* For further information, see *Chimia* **1988**, *42*, 398.

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*** See one of the forthcoming issues.