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TETRAHEDRON: *ASYMMETRY*

Synthesis of (*R*)-4,4,4-trifluoro-2-mercaptobutyric acid

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Abstract

Syntheses of (*R*)-4,4,4-trifluoro-2-mercaptobutyric acid from (*S*)-malic acid via a Mitsunobu reaction and from (*rac*)-thiomalic acid on enzymatic resolution, using *Pseudomonas cepacia* (Amano lipase PS), are described. A new method for direct determination of ees for (*R*)- and (*S*)-4,4,4-trifluoro-2-mercaptobutyric acid derivatives by HPLC on a polysaccharide phase is disclosed.

1. Introduction

Mercapto carboxylic acids are a rare class of natural products. Compounds containing the mercapto or the mercaptoacyl[1] moiety often exhibit strong inhibitory effects on metal-containing enzymes[2] (metallozymes), similar to hydroxamic acids,[3] e.g. some inhibitors of the zinc-containing angiotensine converting enzyme (ACE) possess the α-mercaptoacyl fragment.[4] Fluorinated analogues of naturally occurring biological active compounds often exhibit unique physiological activities.[5] Consequently, there is growing interest in the synthesis of chiral fluorinated building blocks of biological relevance such as amino,[6] hydroxy,[7] keto[8] and mercapto[9] acids and their application to peptide and depsipeptide modification.[10]

In this paper we describe two preparatively simple routes to (*R*)-4,4,4-trifluoro-2-mercaptobutyric acid and some of its derivatives starting from commercially available (*S*)-malic acid via Mitsunobu reaction and from racemic mercapto malic acid on enzymatic resolution of the racemic 2-acetylsulfanyl-4,4,4-trifluorobutyric acid isobutyl ester, using hexafluoroacetone as a protecting and activating agent.

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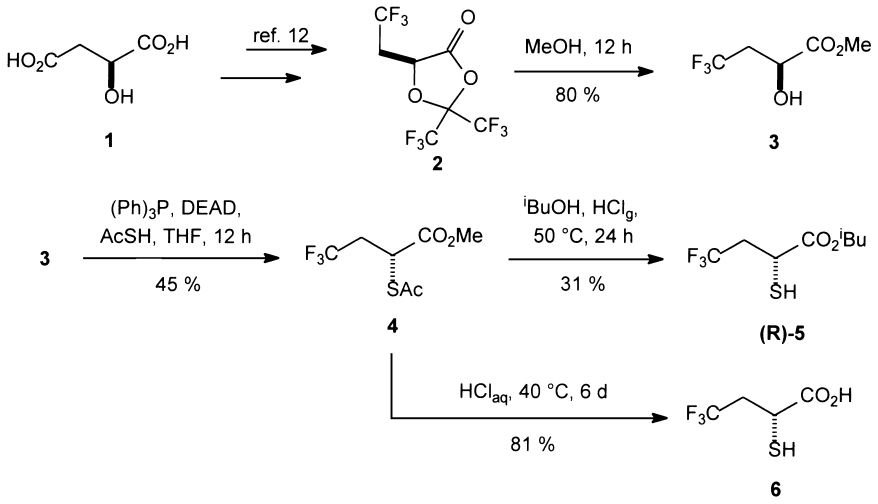
2. Results and discussion

Hexafluoroacetone and α-functionalized alkanoic acids react to give lactones in high yields. This heterocyclization process results in a simultaneous protection of the α-functional group and of the adjacent carboxylic group. In the case of α-functionalized α,ω-dicarboxylic acids the α-carboxylic group is regioselectively activated towards nucleophiles. Since the ω-carboxy group remains unaffected on treatment with hexafluoroacetone, this method can also be applied for regioselective group manipulation at the ω-carboxy group.[11] The transformation of the ω-carboxy group into a trifluoromethyl group (**1**→**2**, **7**→**8**)[12] on treatment with sulfur tetrafluoride[13] is a typical example (Scheme 1). The reaction proceeds in a stereoconservative manner.

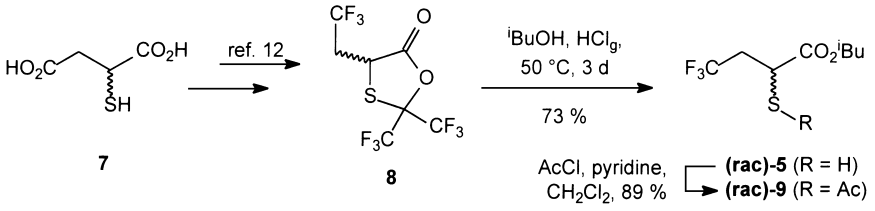


Scheme 1.

The (*S*)-4,4,4-trifluoro-2-hydroxybutyrate **3** was obtained in high yield on methanolysis of the lactone **2** at room temperature. Transformation of the (*S*)-α-hydroxy compound **3** into the mercapto derivative **4** with complete inversion of the configuration can be achieved by a modified Mitsunobu procedure[14] on reaction with thioacetic acid. The *S*-acetylated (*R*)-α-mercapto acid methyl ester **4** formed in acceptable yield can be transformed into the (*R*)-isobutyl ester **(*R*)-5** on stirring with isobutanol at 50°C in the presence of HCl. The fully deblocked (*R*)-4,4,4-trifluoromethyl-2-mercaptobutyric acid **6** was obtained in 81% yield on stirring with HCl_{aq} at 40°C. Compound **(*R*)-5** has been prepared as reference substance to determine the configuration of enzymatic resolution products with an ee value of 61% (±5%). Racemization probably occurs on transformation **4**→**(*R*)-5**. The sensitivity of mercapto bearing carbons adjacent to an electron withdrawing group towards racemization under acidic conditions (10–40% racemization) is described.[14b]

The second approach to (*R*)-4,4,4-trifluoro-2-mercaptobutyric acid derivatives starts from racemic thiomalic acid **7**, which was treated in the hexafluoroacetone-protected form with sulfur tetrafluoride in a steel autoclave to give the fully protected racemic 4,4,4-trifluoro-2-mercaptobutyric acid derivative **8**,[12] which was transformed into the racemic isobutyl ester **(*rac*)-5** (Scheme 2). With neat isobutanol a remarkably stable hemithioketal was formed, but in the presence of HCl at 50°C **(*rac*)-5** was isolated in 73% yield. To obtain the substrate **(*rac*)-9** for the enzymatic

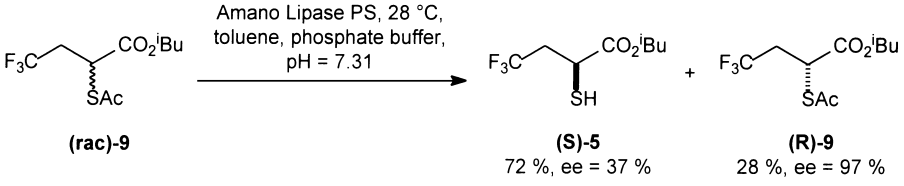
resolution process, **(*rac*)-5** was acetylated with acetyl chloride/pyridine. The sterically demanding isobutyl group was used to make the ester less prone to chemical (non-enzymatic) hydrolysis under the reaction conditions. We assumed that the presence of the isobutyl group had no impact on the fit of the thiolacetyl functionality into the active site of the enzyme.



Scheme 2.

A methodology for the analytical separation of enantiomers of thiolesters and thiols is not described in the literature to the best of our knowledge.[15] Only indirect methods have been described for chiral thiol compounds, based on a derivatization with homochiral reagents.[16] However, this approach would only be suitable to determine the ee values of **5**. Therefore, we developed a direct method to determine the ee values of **5** and **9** in one run, without the solvent (toluene) being a disturbing factor. In the end two types of polysaccharide HPLC phases were found suitable, namely Chiracel OJ and Chiralpak AD. The latter phase gave the best results.

In order to find an appropriate enzyme for the hydrolytic cleavage of the thiolester **(*rac*)-9**, we tested four enzymes.[17] Only the enzyme from *Pseudomonas cepacia* (Amano Lipase PS) showed hydrolytic activity and exclusively on the thiolester and not on the carboxylic ester function (Scheme 3). Therefore, the hydrolytic studies of **(*rac*)-9** were performed with this enzyme. The conversion was monitored by HPLC. Hydrolysis of the thiolester function of **(*rac*)-9** under resolution conditions without enzyme was tested and could be neglected. The relationship between enantiomeric ratio (*E*), conversion, ee value of the substrate and ee value of the product was evaluated according to the literature[18] (Table 1).



Scheme 3.

Work-up was performed after 15 days. The resulting oil was subjected to HPLC analysis. The *E* value for the enantioseparation of **(*rac*)-9** was 8 (at 28°C); consequently, **(*R*)-9** was obtained with an ee value of 97% and a chemical yield of 28%. Comparison experiments by HPLC with the synthesized reference compound **(*R*)-5** revealed that the remaining thiolester is enriched in the (*R*)-isomer, while the hydrolyzed thiol is enriched in the (*S*)-isomer. Therefore, the enzymatic hydrolysis is (*S*)-stereospecific. The reaction time seems rather long in the described experiment, but the process can be accelerated by the addition of higher quantities of the enzyme at the start.

Table 1
Amano Lipase PS catalyzed hydrolysis of (*rac*)-4

time [d]	conversion [%]	ee-value of (R)-9 [%]	ee-value of (S)-5 [%]
3	30	31	71
4	38	42	68
5	44	50	64
6	48	60	64
10	53	66	59
11	62	82	51
12	63	84	50
13	66	90	46
14	69	94	43
15	72	97	37

To the best of our knowledge the reaction described here is the first example of an enzymatic resolution of a fluorosubstituted thiolester.

3. Experimental

3.1. General procedures

Melting points (uncorrected) were determined on a Boëtius heating table. Optical rotations were measured at 589 nm (Na D line); Polartronik, Fa. Schmidt & Haensch was used. ^{1}H NMR spectra were recorded at 200 MHz. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS). ^{13}C NMR spectra were performed at 50 MHz. ^{19}F NMR spectra were recorded at 188 MHz with trifluoroacetic acid (TFA) as external standard. A Varian Gemini 2000 was used. Mass spectra were recorded on a Finnigan MAT 212 electron ionization spectrometer (EI = 70 eV). HR-MS spectras were recorded on an FT-ion-cyclotron-resonance-MS Apex-II Bruker-Daltonics. For preparative column chromatography, silica gel (32–63 μm) was used, with the solvent system given in the text. Organic solvents were dried and distilled prior to use.

3.2. Determination of enantiomeric purity

Enantiomeric excesses were analyzed by HPLC (Gilson 302 pump, a Gilson 231–401 auto-sampling injector and a Waters 481 UV detector at 220 nm) on a Chiralpak AD column (250×4.6 mm, from Daicel Chemical Co., Ltd) at ambient temperature and a mobile phase consisting of 99.2 vol% *n*-hexane and 0.8 vol% isopropanol at a flow rate of 1 ml/min.

3.2.1. (S)-4,4,4-Trifluoro-2-hydroxybutyric acid methyl ester **3**

Compound **2** (13.3 g, 43 mmol) was dissolved in dry methanol (10 ml) and set aside at rt. After 12 h the excess of methanol was removed. The residue was dissolved in CH_2Cl_2 (100 ml) and washed with water (2×50 ml). The separated water phase was extracted with CH_2Cl_2 (4×20 ml).

Drying of the combined organic phase with $MgSO_4$, evaporation of the solvent and distillation in vacuo afforded **3**: yield 5.9 g (80%), colourless liquid, bp 48°C/4.0 mmHg; $[\alpha]_D^{21} = -3$ (*c* 2, CH_2Cl_2); anal. calcd for $C_5H_7F_3O_3$ (found) C, 34.89 (34.40); H, 4.10 (4.15); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.44 (m, 1H, CH_2), 2.68 (m, 1H, CH_2), 3.04 (d, J = 5 Hz, 1H, OH), 3.84 (s, 3H, CH_3), 4.48 (m, 1H, CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 38.61 (q, $^2J_{CF} = 29$ Hz, CH_2), 53.70 (CH_3), 65.98 (q, $^3J_{CF} = 3$ Hz, CH), 126.02 (q, $^1J_{CF} = 277$ Hz, CF_3), 173.63 (CO); ^{19}F NMR (188 MHz, $CDCl_3$) δ 14.14 (t, $^3J_{HF} = 9$ Hz, CF_3); IR (film) ν_{max} 3446, 1747 cm^{-1}; MS *m*/*z* (%) 172 (2, M$^+$), 144 (3), 135 (4), 113 (87), 93 (61), 89 (11), 69 (14), 65 (100), 59 (42).

3.2.2. (R)-2-Acetylsulfanyl-4,4,4-trifluorobutyric acid methyl ester **4**

To an efficiently stirred solution of triphenylphosphine (5.8 g, 22.0 mmol) in tetrahydrofuran (30 ml) at –10°C under an argon atmosphere diethyl azodicarboxylate (3.8 g, 22.0 mmol) was added. A white precipitate resulted. Tetrahydrofuran was added to get a mushy mixture. A solution of thioacetic acid (1.7 g, 22.0 mmol) and **3** (3.0 g, 17.4 mmol) in tetrahydrofuran (10 ml) was added dropwise. The stirred mixture was allowed to warm up to rt. A clear yellow solution resulted. After 12 h the solvent was distilled off. The residue was refluxed with light petroleum (250 ml) for 20 min. The solution was filtered, and set aside at –30°C overnight. After filtration and evaporation of the solvent, the oily residue was subjected to chromatography with light petroleum:ethyl acetate (10:1) to afford **4**: yield 1.8 g (45%), pale yellow, oily liquid; $[\alpha]_D^{21} = +90$ (*c* 2, CH_2Cl_2); anal. calcd for $C_7H_9F_3O_3S$ (found) C, 36.52 (36.70); H, 3.94 (3.90); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.40 (s, 3H, CH_3), 2.52 (m, 1H, CH_2), 2.96 (m, 1H, CH_2), 3.76 (s, 3H, OCH_3), 4.42 (dd, J = 8, 6 Hz, 1H, CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 30.39 (CH_3), 36.87 (q, $^2J_{CF} = 30$ Hz, CH_2), 39.33 (q, $^3J_{CF} = 3$ Hz, CH), 53.63 (OCH_3), 125.64 (q, $^1J_{CF} = 278$ Hz, CF_3), 170.51 (CO), 192.65 (SCO); ^{19}F NMR (188 MHz, $CDCl_3$) δ 12.71 (t, $^3J_{HF} = 11$ Hz, CF_3); IR (film) ν_{max} 1743, 1709 cm^{-1}; MS *m*/*z* (%) 230 (22, M$^+$), 199 (11), 188 (2), 171 (3), 156 (4), 59 (16), 42 (100).

3.2.3. (R)-4,4,4-Trifluoro-2-mercaptobutyric acid isobutyl ester (R)-5

Compound **4** (500 mg, 2.0 mmol) was dissolved in isobutanol (6 ml), isobutanol saturated with hydrogen chloride (20 drops) was added and stirred at 50°C. After 24 h the solvent was distilled off and the residue was subjected to chromatography with light petroleum:ethyl acetate (12:1) to afford **(*R*)-5**: yield 143 mg (31%), pale yellow, oily liquid; $[\alpha]_D^{21} = +31$ (*c* 2, CH_2Cl_2); ee = 61±5% (HPLC); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.95 (d, J = 7 Hz, 6H, $2CH_3$), 1.99 (m, 1H, CH), 2.32 (d, J = 10 Hz, 1H, SH), 2.55 (m, 1H, CH_2), 2.99 (m, 1H, CH_2), 3.62 (m, 1H, SCH), 3.96 (d, J = 7 Hz, 2H, OCH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.39 ($2CH_3$), 28.15 (CH), 34.79 (q, $^3J_{CF} = 3$ Hz, SC), 40.38 (q, $^2J_{CF} = 29$ Hz, CH_2), 72.62 (OCH_2), 125.46 (q, $^1J_{CF} = 278$ Hz, CF_3), 172.02 (CO); ^{19}F NMR (188 MHz, $CDCl_3$) δ 12.19 (t, $^3J_{HF} = 11$ Hz, CF_3); IR (film) ν_{max} 2963, 1677 cm^{-1}; MS *m*/*z* (%) 230 (< 1, M$^+$), 156 (7), 129 (50), 109 (12), 65 (10), 57 (100).

3.2.4. (R)-4,4,4-Trifluoro-2-mercaptobutyric acid (**6**)

To **4** (500 mg, 2.0 mmol) hydrochloric acid (3 ml, 20%) was added and stirred vigorously at 40°C for 6 days. Then the mixture was diluted with water (15 ml) and extracted with diethyl ether (5×10 ml). The combined extracts were dried over $MgSO_4$ and the solvent was distilled off. The resulting residue crystallizes. Recrystallization from light petroleum gave **6**: yield 284 mg (81%), colourless needles, mp 68–70°C; $[\alpha]_D^{21} = +4$ (*c* 2, CH_2Cl_2); anal. calcd for $C_4H_5F_3O_2S$ (found) C, 27.59 (27.60); H, 2.89 (3.25); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.42 (d, J = 9 Hz, 1H, SH), 2.52 (m, 1H, CH_2), 2.97 (m, 1H, CH_2), 3.63 (ddd, J = 10, 9, 5 Hz, 1H, CH), 9.66 (bs, 1H, OH); ^{13}C NMR

(50 MHz, $CDCl_3$) δ 34.41 (q, $^3J_{CF}=3$ Hz, CH), 39.79 (q, $^2J_{CF}=30$ Hz, CH_2), 125.38 (q, $^1J_{CF}=278$ Hz, CF_3), 177.39 (CO); ^{19}F NMR (188 MHz, $CDCl_3$) δ 12.26 (t, $^3J_{HF}=11$ Hz, CF_3); IR (KBr) ν_{max} 3013, 2576, 1710 cm^{-1}; MS *m*/*z* (%) 174 (77, M^+), 156 (41), 129 (82), 109 (38), 77 (28), 69 (13), 65 (32), 44 (100).

3.2.5. (rac)-4,4,4-Trifluoro-2-mercaptobutyric acid isobutyl ester (rac)-5

Compound **8** (7.7 g, 23.7 mmol) was dissolved in isobutanol (10 ml). The solution was saturated with hydrogenchloride and warmed up to 50°C. After 3 days the excess of alcohol was removed in vacuo. Distillation of the residue afforded **(*rac*)-5**: yield 4.0 g (73%), colourless, slightly pungent smelling, oily liquid, bp 45°C/0.9 mmHg; HR-MS *m*/*z* calcd for $C_8H_{13}F_3O_2S$ (found) 230.0583 (230.0583); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.95 (d, J = 7 Hz, 6H, $2CH_3$), 1.99 (m, 1H, CH), 2.32 (d, J = 10 Hz, 1H, SH), 2.55 (m, 1H, CH_2), 2.96 (m, 1H, CH_2), 3.59 (m, 1H, SCH), 3.96 (d, J = 7 Hz, 2H, OCH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.26 ($2CH_3$), 28.04 (CH), 34.68 (q, $^3J_{CF}=3$ Hz, SC), 40.27 (q, $^2J_{CF}=29$ Hz, CH_2), 72.57 (OCH_2), 125.48 (q, $^1J_{CF}=278$ Hz, CF_3), 172.12 (CO); ^{19}F NMR (188 MHz, $CDCl_3$) δ 12.19 (t, $^3J_{HF}=11$ Hz, CF_3); IR (film) ν_{max} 2966, 1740 cm^{-1}; MS *m*/*z* (%) 230 (2, M^+), 174 (4), 156 (4), 129 (14), 109 (4), 89 (4), 57 (100).

3.2.6. (rac)-2-Acetylsulfanyl-4,4,4-trifluorobutyric acid isobutyl ester (rac)-9

Isobutyl ester **(*rac*)-5** (3.5 g, 15.0 mmol) and dry pyridine (1.6 g, 20.0 mmol) were dissolved in CH_2Cl_2 (10 ml). A solution of acetylchloride (1.6 g, 20.0 mmol) in CH_2Cl_2 (20 ml) was added with stirring. After 2 h the mixture was washed with water (2×10 ml) and $NaHCO_3$ solution (2×10 ml). Drying over $MgSO_4$, evaporation of the solvent and distillation in vacuo afforded **(*rac*)-9**: yield 3.6 g (89%), colourless, slightly smelling, oily liquid, bp 63°C/0.4 mmHg; HR-MS *m*/*z* calcd for $C_{10}H_{15}F_3O_3S$ (found) 272.0689 (272.0717); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.92 (d, J = 7 Hz, 6H, $2CH_3$), 1.95 (m, 1H, CH), 2.38 (s, 3H, $OCCH_3$), 2.55 (m, 1H, CH_2), 2.93 (m, 1H, CH_2), 3.93 (d, J = 7 Hz, 2H, OCH_2), 4.41 (dd, J = 8, 5 Hz, 1H, SCH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.34 ($2CH_3$), 28.08 (CH), 30.52 (CH_3), 36.96 (q, $^2J_{CF}=30$ Hz, CH_2), 39.76 (q, $^3J_{CF}=3$ Hz, SCH), 72.79 (OCH_2), 125.67 (q, $^1J_{CF}=278$ Hz, CF_3), 169.92 (CO), 192.63 (SCO); ^{19}F NMR (188 MHz, $CDCl_3$) δ 12.81 (t, $^3J_{HF}=11$ Hz, CF_3); IR (film) ν_{max} 2966, 1741, 1710 cm^{-1}; MS *m*/*z* (%) 272 (3, M^+), 230 (29), 217 (21), 199 (21), 171 (11), 156 (4), 128 (11), 56 (29), 42 (100).

3.2.7. Enzymatic resolution of (rac)-2-acetylsulfanyl-4,4,4-trifluorobutyric acid isobutyl ester (rac)-9

The substrate **(*rac*)-9** (103 mg, 0.37 mmol) was dissolved in toluene (2 ml), aqueous phosphate buffer (2 ml, 250 mM, pH 7.31) and sodium bisulfite (0.4 wt% of mixture) was added. The mixture was agitated in an orbital shaker (180 rpm) at 28°C for 15 min. Subsequently, enzyme (35 mg, Amano Lipase PS, from *Pseudomonas cepacia*) was added and the mixture was agitated again. At various time intervals a sample was taken and analyzed, and additional portions of enzyme were added after 4 days (18 mg) and 6 days (20 mg). Results and notes are given in Table 1. After 15 days, the toluene phase was separated and evaporated in vacuo to give an oil which was analyzed by HPLC.

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