A Short and Productive Synthesis of (R)-α-Lipoic Acid

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Lipoic Acid, Yeast Reduction, Enantioselective Hydrogenation, Regioselective Reduction

(R)-α-Lipoic acid is synthesized in seven steps from the base chemicals methyl acetoacetate or Meldrum’s acid and monomethyl adipate. The key steps are the introduction of the stereogenic center by fermentative or homogeneously catalyzed hydrogenation of 3-oxo-octanedioic acid diester to (3S)-3-hydroxyoctanedioic acid diester and its regioselective reduction to (6S)-6,8-dihydroxyoctanoic acid ester. The overall yield of (R)-α-lipoic acid, starting from 3-oxooctanedioic acid diester, is 40%.

Results and Discussion

(R)-α-Lipoic acid (1) occurs as a protein-bound coenzyme in animal and vegetable tissue and also in microorganisms [1]. (R)- and (S)-α-Lipoic acid differ considerably each other in biochemical and pharmacological investigations [2]. For example, in animal experiments, the (R)-enantiomer mainly has an antiinflammatory action and the (S)-enantiomer mainly an analgesic action. It is therefore sensible to employ α-lipoic acid in enantiomerically pure form.

The (R)-enantiomer of α-lipoic acid (1) can be obtained in various ways, for example by chemical [3] or enzymatic [4] cleavage of the racemic product or of one of its precursors, with the aid of chiral templates [5], from structural units of the chiral pool [6], by enantioselective synthesis [7] and by microbiological transformations [8].

The published syntheses have a number of disadvantages, such as their many reaction steps as well as expensive starting materials and reagents. Consequently they are not carried out industrially. We have developed the synthesis strategy for 1 shown in Scheme 1. The known (6S)-6,8-dihydroxyoctanoic acid ester (2) [9] was planned to be prepared by regioselective reduction of (3S)-3-hydroxyoctanedioic acid diester (3), and this, in turn, should be accessible by enantioselective reduction of 3-oxooctanedioic acid diester (4).

The 3-oxo diesters 4 have not been employed before in lipoic acid syntheses. They can be prepared in good yield and purity in the ways shown in Scheme 2. Acylation of the calcium enolate of methyl acetoacetate with methyl adipoyl chloride yields dimethyl 3-oxooctanedioate (4, R = CH3) [10]. Mixed 3-oxo diesters (4, R = alkyl) are obtained by acylation of Meldrum’s acid and subsequent alcoholysis [11].

Methods have been developed in recent years for the enantioselective reduction of 3-oxo esters which can also be used for the conversion of 4 to 3. The hydrogenation of 4 to 3 is carried out chemically using the catalyst system Ru2Cl4 [(S)-BINAP]2·NET3 [12]. The reaction proceeds particularly smoothly on addition of catalytic amounts of acid [13]. The conversion and enantiomeric excess are 96% and 98% respectively.

The reduction of the 3-oxodiesters 4 also takes place using baker’s yeast. A strong dependence of the radical R is observed here both on the yield and on the enantioselectivity of the reaction. The results achieved with various esters under standard conditions are summarized in Table I. The reduction is preferably carried out with the isobutyl ester (4, R = i-C4H9). After optimization of the reaction conditions, 3 (R = i-C4H9) could be isolated in 75% yield and with an (R/S) enantiomer ratio of 97 to 3 [14]. A further 5% yield of the product is obtained in the form of the free acid (3, R = H). Ethanol has proven suitable as a carbon source and solubilizer in the fermentative reduction [15].

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Table I. Yeast reduction of 4 to 3 under standardized conditions (21 g of dried yeast, 30 g of sucrose and 3 g of 4 in 1 l of water, 24 h, 36 °C).

<table>
<thead>
<tr>
<th>R</th>
<th>Crude yield (g)</th>
<th>4:3 (HPLC)</th>
<th>(S)-3: (R)-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃</td>
<td>2.8</td>
<td>65:35</td>
<td>85:15</td>
</tr>
<tr>
<td>C₂H₅</td>
<td>1.6</td>
<td>12:88</td>
<td>50:50</td>
</tr>
<tr>
<td>i-C₃H₇</td>
<td>2.2</td>
<td>9:91</td>
<td>60:40</td>
</tr>
<tr>
<td>n-C₃H₇</td>
<td>2.1</td>
<td>18:82</td>
<td>65:35</td>
</tr>
<tr>
<td>i-C₄H₉</td>
<td>2.3</td>
<td>20:80</td>
<td>88:12</td>
</tr>
<tr>
<td>s-C₄H₉</td>
<td>1.8</td>
<td>28:72</td>
<td>65:35</td>
</tr>
<tr>
<td>t-C₄H₉</td>
<td>2.5</td>
<td>30:70</td>
<td>50:50</td>
</tr>
<tr>
<td>(CH₂)₂−CH(CH₃)₂</td>
<td>1.3</td>
<td>35:65</td>
<td>70:30</td>
</tr>
<tr>
<td>n-C₅H₁₁</td>
<td>0.3</td>
<td>Complete hydrolysis</td>
<td></td>
</tr>
<tr>
<td>C₆H₅</td>
<td>1.9</td>
<td>Complete hydrolysis</td>
<td></td>
</tr>
</tbody>
</table>

The regioselective reduction of the 3-hydroxy diester 3 is carried out with sodium borohydride in boiling tetrahydrofuran [16] and yields the enantiomerically pure methyl (6S)-6,8-dihydroxyoctanoate (2) in 90% crude yield [9]. In addition, about 5% of (3S)-octane-1,3,8-triol is found. The high regioselectivity of this reaction is based on the precomplexation of the reductant at the free hydroxyl group of the starting materials 3. Pure 2 of m.p. 51–52 °C and [α]D₂₀ = −4.4 ° (c = 1, dichloromethane) is obtained in 82% yield by crystallization from diisopropyl ether.

The (6S)-dihydroxy ester 2 can be converted into (R)-α-lipoic acid 1 in the ways shown in Scheme 3 via the dimesylate 5 [9] as an intermediate. Reaction of 5 with potassium thioacetate in DMF and cleavage of the (6R)-triester 6 with potassium hydroxide

Scheme 1. Alternative routes to 3-oxooctanedioic acid diester (4).

Scheme 2. Key steps in the synthesis of (R)-lipoic acid (1).
yield (6R)-dihydrolipoic acid (7), which can be reacted to give 1, for example using oxygen and iron(III) chloride as a catalyst [17]. Based on 2, the yield of 1 is 65%. Alternatively, 1 is obtained in two stages, also in 65% yield, specifically by reaction of 5 with sodium disulfide in DMF [5, 18] and base- or lipase-catalyzed hydrolysis of methyl (6R)-α-lipoate (8).

Experimental

Analytical apparatus and equipment: melting point: HWS SGV 500 PLUS, not corrected. – Infrared spectra: Bruker IFS 88. – Nuclear magnetic resonance spectra: Bruker AMX 360 (360 MHz 1H, 90.5 MHz 13C). – Mass spectra: Finnigan MAT 90 (relative intensities of the signals in percent based on the base peak). – Specific rotations: Perkin-Elmer 243 B (25 °C, 1 = 589 nm). – Elemental analyses: C, H, N: Leco 1000; O: Leco RO 478; S: Carlo Erba NA 1500. – Gas chromatography: HP 5890/series II Plus; A: DB 1 701, 30 m, 50 °C → 240 °C (10 °C/min), FID, He 103 kPa, integrator HP 3396 series II; B: CP-SIL/5.50 m, 50 °C → 240 °C (7.5 °C/min), 240 °C → 300 °C (30 °C/min), FID, integrator HP Chem. Station Version A.03.34, He 172 kPa. – Distillation equipment: countercurrent thin-layer evaporator (0.026 m²) with wiper blades and condenser; micro short-path distillation apparatus (Schott/ Mainz) with rotary oil pump. – Thin-layer chromatography: HPTLC aluminum foils silica gel 60 F254 and TLC aluminum foils silica gel 60 F254, both from Merck DA. – Spray reagents: molybdato-phosphoric acid and Cer(IV) sulfate in H2O/H2SO4; anisaldehyde in H2SO4/HOAc/H2O. – Column chromatography: silica gel 0.040–0.063 mm, Merck/DA.

1-O-Isobutyl 8-O-methyl 3-oxooctanedioate (4): 117.6 g (0.8 mol) of Meldrum’s acid and 129 ml (0.16 mol) of pyridine are added at 0 °C to 650 ml of dichloromethane. This solution is treated at 0 °C with 148 g (0.82 mol) of methyl adipoyl chloride in the course of about 90 min and is stirred at room temperature for 4 h. After addition of 150 ml (1.6 mol) of isobutanol, dichloromethane is distilled off to an internal temperature of 60 °C (about 400 ml) and the reaction mixture is then refluxed for 3 h.

To work up, the dichloromethane distillate is added again at 25 °C, and the mixture is treated with 700 ml of water and acidified to pH 1.5 using conc. sulfuric acid (about 58 g). The organic phase is washed twice with 300 ml of 5 percent sulfuric acid and twice with 300 ml of water and evaporated under reduced pressure: residue 216.6 g, GC purity [B] 92.5 area% corresponding to 96.9% yield. The crude product is separated from low-boiling and high molecular weight by-products in a countercurrent film evaporator. Degassing: 137 °C, 1 mbar, 150 ml/h; residue 195.3 g. Distillation: 180 °C, 1 mbar, 100 ml/h, distillate 191.8 g. GC [B] 95.5 area% corresponding to 88.9% yield.

Dimethyl 3-oxooctanedioate (4, R=CH3): 233.4 g (3.15 mol) of calcium hydroxide is sus-
pended in 1.6 l of dichloromethane. 348 g (3 mol) of methyl acetoacetate is added within 1 h and the mixture is stirred for 0.5 h. 607.5 g (3.45 mol) of methyl adipoyl chloride is then added within 2 h and the mixture is then refluxed for 2 h. After cooling to 25 °C, a solution of 168.6 g (3.15 mol) of ammonium chloride in 1 l of water is allowed to flow into the reaction mixture which is then adjusted to pH 9 by addition of aqueous ammonia. After 3 h, it is acidified to pH < 1 using concentrated hydrochloric acid. The dichloromethane phase is washed with two portions (1 l) of water and with 0.5 l of 2 N hydrochloric acid and the crude product is isolated by evaporation at reduced pressure: 644 g. GC [B] 81 area% corresponding to 77% yield. Further purification is carried out by distillation in a countercurrent film evaporator; degassing: 110 °C, 0.2 mbar, 150 ml/h, residue 512 g; distillation: 160 °C, 0.2 mbar, distillate 481 g corresponding to 71% yield.

IR (film): ν (cm⁻¹) 1739, 1719. ¹H-NMR (400.1 MHz, DCCl₃): δ = 1.64 (m, 4H), 2.33 (t, J = 7 Hz, 2H), 2.60 (t, J = 7 Hz, 2H), 3.49 (s, 2H), 3.65 (s, 3H), 3.72 (s, 3H); enol form (8%): 5.01 (s, 1H), 12.00 (s, 1H). ¹³C-NMR (100.6 MHz, DCCl₃): δ = 22.9, 24.2, 23.7, 32.5, 49.0 (t, C-5), 6, 7, 4, 2, 51.5 (q, OCH₃) 52.2 (q, OCH₃) 167.8 (s, C-1), 173.7 (s, C-8), 202.5 (s, C-3); enol form: 24.3, 25.7 (2 t, C-5, 6), 33.8, 34.6 (2 t, C-4, 7), 51.1, 51.7 (2 q, 2 OCH₃), 89.0 (d, C-2), 173.1, 173.9 (2 s, C-1, 8), 178.4 (s, C-3). - MS (EI, 70 eV), m/e (%): 217 (15) (MH⁺), 216 (10)(MH⁺), 185 (41)(M⁺-OCH₃), 184 (60)(M⁺-CH₂OH), 153 (42), 143 (67) (M⁺-CH₂CO₂CH₃), 116 (90), 111 (100), 101 (70, 59 (80), 55 (75). 

C₁₅H₁₆O₅ (216.2)
Caled C 55.55 H 7.46 O 36.99%.
Found C 55.20 H 7.80 O 37.20%.

1-O-Isobutyl 8-O-methyl (3S)-3-hydroxyoctanedioate (3): 9.2 l of drinking water is introduced into a 10 l fermenter containing 90 g of sodium chloride and the solution autoclaved at 120 °C for 20 min. 0.3 Vvm of nitrogen are then passed into the fermenter gas space, the temperature is kept at 37 °C and 200 ml of ethanol and 500 g of dried yeast (Gist Brocades) are added at 350 rpm. The pH is kept at 6.0 ± 0.2 using 2 M NaOH. After an initial fermentation phase of 45 min, 300 g of 3 are added and the mixture is stirred for 5–7 days under 0.3 Vvm of nitrogen. The starting material and product concentrations are checked daily by means of GC. The fermentation is stopped at a starting material concentration of <1 g/l.

The biomass is separated and washed twice with 21 each of 50 percent ethanol. About 12 l of clear runnings are obtained, which are extracted once with 51 and twice with 2.5 l of ethyl acetate. The ethyl acetate phase is washed with 5.5 l of 2.5 percent sodium hydroxide solution and twice with 4 l portions of water and concentrated on a rotary evaporator (50 °C, 30 mbar). Residue: 285.4 g, GC surface area% (B) after silylation (MSTFA) 80% corresponding to 80% yield.

The crude product is separated from low-boiling and high-boiling impurities by continuous distillation in a countercurrent thin-layer evaporator.

Degassing: 130 °C, 0.2 mbar, distillate I: 6 g, residue: 177 g; distillation: 160 °C, 0.2 mbar, distillation II: 160.8 g, residue: 11 g, GC area% (B) of distillate II: 88.3% corresponding to 71% yield; ee >97% after ¹⁹F-NMR analysis of the Mosher ester.

Dimethyl (3S)-3-hydroxyoctanedioate (3, R = CH₃): All operations are carried out in an argon atmosphere with rigorous exclusion of oxygen. Triethylamine is freshly distilled; methanol and the starting material are saturated with argon before the reaction.

Di[2,2’-bis(diphenylphosphino)-1,1’-binaphthyl]tetrachlororutheniumtriamethylamine adduct (Ru₂Cl₄{(S)-BINAP})₂×Neτ₃: 45.55 mg (0.162 mmol) of di-µ-chloro(p²-1,5-cyclooctadienide)ruthenium(II) (RuCl₂COD)₂, 121.5 mg (0.195 mmol) of (S)-2,2’-bis(diphenylphosphino)-1,1’-binaphthyl-((S)-BINAP) and 0.18 ml (about 1.8 mmol) of triethylamine are dissolved in 7.5 ml of toluene. The solution is refluxed for 3 h, cooled to room temperature and the solvent is evaporated in vacuo (30 °C, 8 mbar).

The residue is taken up in 15 ml of a solution of 216 g (1 mol) of dimethyl 3-oxooctanedioate (4, R = CH₃) in 600 ml of methanol and refluxed for 30 min. After cooling to room temperature, the catalyst solution is added to the remaining solution of the starting material in methanol, 0.25 ml of 1 M sulfuric acid is added and the mixture is hydrogenated in a 2 l stainless steel autoclave having a glass insert (12 h, 80 °C, 30 bar of hydrogen). The autoclave contents are concentrated on a rotary evaporator (50 °C, 30 mbar; residue 233 g).

The crude product can be purified by distillation in a countercurrent film evaporator. Degassing/distillation: heating jacket 120 °C/160 °C, 0.1 mbar; cooling jacket 30 °C/40 °C; residue: 213 g/4 g; distillate 3 g/205 g. According to silylation (MSTFA) and GC analysis (B), a sample of the distillate has a purity of 96%. The enantiomeric purity can be determined by means of ¹H-NMR spectroscopy by complexation with TFAE (OCH₃) and is >96%.
$[\alpha]_D^{25} = +14.3^\circ$ (c = 1.1, dichloromethane). – IR (film) ν = 3507 cm$^{-1}$ (br., O–H), 2952 (m, C–H), 1737 (s, C=O), 1348, 1367, 1257, 1199, 1173, 1097, 1012. – $^1$H-NMR (400 MHz, CDCl$_3$): δ = 1.50 (m, 4H, 5-, 6-CH$_2$), 1.67 (m, 2H, 4-CH$_2$), 2.35 (t, J = 8 Hz, 2H, 7-CH$_2$), 2.47 (m, 2H, 2-CH$_2$), 3.32 (s, 1H, OH), 3.65 (s, 3H, CO$_2$CH$_3$), 3.70 (s, 3H, CO$_2$CH$_2$), 4.01 (m, 1H, 3H). – $^{13}$C-NMR (100 MHz, CDCl$_3$): δ = 24.8, 25.1 (2 t, C-5, 6), 33.9 (t, C-7), 36.2 (t, C-4), 41.4 (t, C-2), 51.5, 51.7 (2 q, 2 OCH$_3$), 67.7 (d, C-3), 173.2, 174.1 (2 s, C-1, 8). – MS (EI, 70 eV), m/e (%): 169 (16, 155 (10), 145 (26), 141 (12), 123 (9), 116 (28), 113 (57), 87 (100); MS (CI, 70 eV), m/e (%): 191 (100) [MH$^+$], 117 (60) [MH$^+$ – H$_2$O].

C$_{10}$H$_8$O$_4$ (218.2)

Calcd C 55.03 H 8.31 O 36.65%.
Found C 54.50 H 8.30 O 36.70%.

**Methyl (6S)-6,8-dihydroxoctanoate (2):** A solution of 218 g (1 mol) of dimethyl (3S)-3-hydroxyoctanoate (3, R = CH$_3$) in 1.251 of tetrahydrofuran is introduced into a 31 high-grade steel reactor (stirrer, thermometer, distillation attachment), treated with 23.6 g (0.6 mol) of sodium borohydride. After cooling to room temperature, the reaction mixture is acidified by metering in a 1 M solution of hydrogen chloride in methanol to pH 5. 11 of solvent mixture is then distilled off at 45–50 °C, 300 mbar. After addition of 11 of methanol each time, this distillation is repeated a further two times*.

1.21 of ethyl acetate and 150 ml of ethyl acetate phase from the preceding batch are added to the residue and the solution is washed twice with 300 ml of water. Small amounts of 2 are isolated from the aqueous phases by washing with 150 ml of ethyl acetate and added to the following batch after washing with water.

The ethyl acetate solution is evaporated and the residue is taken up in 660 ml of diisopropyl ether with warming to 50 °C. After cooling to 25 °C and addition of seed crystals, the temperature is reduced to 20 °C. After warming to 50 °C. After cooling to 25 °C and addition of seed crystals, the temperature is reduced to 20 °C. After warming to 50 °C.

In the same manner, 3 (R = t-C$_4$H$_9$) can also be reduced to 2 using sodium borohydride. To determine the purity of the ethyl acetate solution a sample is evaporated and analyzed by gas chromatography (B) using an internal standard: 89% 2, 5% 2-isobutyl ester. The yield of crystalline 2 is 72%.

(R)-**Dihydrolipoic acid (7):** 29.5 g (150 mmol) of methyl (6S)-6,8-dihydroxoctanoate (2) and 60.6 g (600 mmol) of triethylamine in 400 ml of dichloromethane are dissolved in a 31 high-grade steel reactor (thermometer, dropping funnel, distillation attachment with 20 cm packed column) and 51.6 g (450 mmol) of methanesulfonyl chloride are added at 0 °C within 1.5 h. The mixture is allowed to react at 0 °C for 1 h, 300 ml of water are added and the lower phase is separated off. The aqueous phase is re-extracted with 150 ml of dichloromethane. The combined dichloromethane phases are washed twice with 150 ml of 1 M hydrochloric acid and twice with 150 ml of water and dried by azeotropic distillation. The residual dichloromethane is distilled off with simultaneous addition of 300 ml of cyclohexane up to a transition temperature of 80 °C.

A sample of the cyclohexane solution is evaporated in vacuo for determining the purity of and characterization [6] of the methyl (6S)-6,8-dimethylsulfonyloxyoctanoate: crude yield quantitative, yellow oil. $[\alpha]_D^{25} = +17.6^\circ$ (c = 1.2, dichloromethane). – $^1$H-NMR (250 MHz, CDCl$_3$): δ = 1.30–1.88 (m, 6 H, 3-, 4-, 5-, 6-, 7-CH$_2$), 2.09 (m, 2H, 7-CH$_2$), 2.30 (t, J = 7 Hz, 2H, 2-CH$_2$), 3.05 (s, 3H, CH$_3$SO$_2$), 3.10 (s, 3H, CH$_3$SO$_3$), 3.57 (s, 3H, CO$_2$CH$_3$), 4.32 (t, J = 7 Hz, 2H, 8-CH$_2$), 4.85 (m, 1H, 6-H).

150 ml of dimethylformamide and 22.3 g (200 mmol) of potassium thioacetate are introduced into a 11 high-grade steel reactor (thermometer, dropping funnel, distillation attachment) and treated at 50 °C/200 mbar with 35 ml (about 75 mmol) of a so-

* The last portions of distillate are free from trimethyl borate according to GC analysis (B).
olution of methyl (6S)-6,8-dimethanesulfonyloxyoctanoate in cyclohexane. Cyclohexane largely distills off during this procedure.

The mixture is stirred at 50 °C for 4 h, 600 ml of water are added and it is extracted three times with 200 ml of n-hexane. The hexane phases are washed with 200 ml of water and concentrated in a counter-current film evaporator (200 mbar, 50 °C); the crude yield of methyl (6R)-6,8-diacetyldihydrolipoate is quantitative.

A sample is purified by column chromatography for characterization (silica gel, hexane/methyl t-butyl ether 4/1): colorless liquid. \([\alpha]_D = -6.16 (c = 0.62, \text{dichloromethane})\). – IR (film): \(v = 2930 \text{ cm}^{-1} (\text{w, C-H}), 1738 (\text{s, C=O}), 1691 (\text{s, C=O}), 1355, 1700, 1628, 1436, 1355, 1197, 1173, 1135, 1114, 952, 630.\) – 1H-NMR (400 MHz, CDCl3): \(\delta = 1.40 (m, 2H, CH_2), 1.62 (m, 4H, CH_2-CH_2), 1.80 (m, 1H, 7-H), 1.86 (m, 1H, 8-H), 2.32 (m, 8H, 2S-\text{CO-CH}_3), 2.90 (m, 2H, 8-CH_2), 3.56 (s, 3H, \text{OCH}_3), 13C-NMR (100 MHz, CDCl3): \(\delta = 24.6 (t, \text{C-3}), 26.2 (t, \text{C-4}), 30.5, 30.7 (2 q, 2 \text{S-CO-CH}_3), 33.8 (t, \text{C-2}), 34.4 (t, \text{C-5}), 34.7 (t, \text{C-5}), 43.4 (d, \text{C-6}), 51.4 (q, \text{OCH}_3), 173.8 (s, \text{C-1}), 195.3, 195.4 (2 s, 2 \text{S-\text{CO-CH}_3}).\) – MS (El, 70 eV), \(m/e (\%): 263 (57) [M+-\text{CO-CH}_3], 233 (10), 221 (30), 189 (75), 43 (100); MS (CI, 70 eV), \(m/e (\%): 307 (100) [\text{MH}^+], 247 (19).\)

\(\text{C}_{13}\text{H}_{22}\text{O}_4\text{S}_2 (306.4)\)

Calcd C 50.95 H 7.24 O 20.88 S 20.93%
Found C 50.80 H 7.30 O 20.90 S 20.90%

46 g (about 140 mmol) of crude methyl (6R)-6,8-diacetyldihydrolipoate and 160 g (about 1.4 mol) of 50% strength potassium hydroxide solution are intensively stirred for 6 h in a 11 high-grade steel reactor at room temperature with rigorous exclusion of oxygen and the mixture is then diluted with 500 ml of water. The mixture is acidified while cooling with concentrated hydrochloric acid (pH 1) and the product is extracted three times with 200 ml portions of dichloromethane. The dichloromethane phases are washed twice with 200 ml of water and concentrated on a rotary evaporator (50 °C, 50 mbar). 32.5 g of crude (R)-dihydrolipoic acid (7) is obtained as a residue.

The crude product can be purified by short-path distillation: degassing/distillation: heating jacket 100 °C/100 °C, cooling jacket 20 °C/40 °C, pressure 1 mbar/0.03 mbar, distillate 1.5 g/28.1 g, residue 29.1 g/0.8 g. Purity according to GC 97%, 0.2% (R)-a-lipoic acid; ee (MSTFA) 99.6%. The yield of (R)-dihydrolipoic acid (7) is 85.7% based on methyl (6S)-6,8-dihydroxyoctanoate.

\([\alpha]_D = -15.3 (c = 0.91, \text{dichloromethane})\). – IR (film): \(v = 2934 \text{ cm}^{-1} (\text{m, C-H}), 2860 (\text{w, C-H}), 1706 (\text{s, C=O}), 1412, 1284, 1089, 937, 742.\) – 1H-NMR (400 MHz, CDCl3): \(\delta = 1.33 (d, J = 10 \text{ Hz}, 1\text{H, CH-SH}), 1.40 (t, J = 8 \text{ Hz}, 1\text{H, CH}_2\text{SH}), 1.45-1.70 (m, 6H, 3-8, 4-5-CH_2), 1.77 (m, 1H, 7-H), 1.90 (m, 1H, 7-H), 2.40 (t, J = 6 \text{ Hz}, 2-CH_2), 2.71 (m, 2H, 8-CH_2), 2.94 (m, 1H, 6-H), 11.02 (1H, \text{CO}_2\text{H}).\) – 13C-NMR (100 MHz, CDCl3): \(\delta = 22.3 (t, \text{C-8}), 24.2 \text{ and } 26.4 (1 \text{t, C-3 and C-4}), 33.9 (t, \text{C-2}), 38.6 (t, \text{C-5}), 39.2 (d, 6\text{C-6}), 42.7 (t, \text{C-7}), 180 (s, \text{C-1}).\) – MS (El, 70 eV), \(m/e (\%): 208 (70) [\text{M}^+], 206 (15) [\text{M}^+-2\text{H}], 95 (82), 87 (85), 81 (100), 73 (70), 67 (55), 55 (54) [\text{C}_4\text{H}_7]^+, 45 (54), 41 (65) [\text{C}_3\text{H}_5]^+.\)

\(\text{C}_9\text{H}_{16}\text{O}_{12}\text{S}_2 (280.3)\)

Calcd C 46.12 H 7.74 O 15.36 S 30.78%
Found C 45.40 H 7.60 O 15.40 S 30.60%

(R)-a-Lipoic acid (1): 520 ml of water and 11 g (about 50 mmol) of crude (R)-dihydrolipoic acid are introduced into a 11 high-grade steel reactor (thermometer, gas inlet tube, 20 cm packed column with distillation attachment) with exclusion of light and treated with 2 M sodium hydroxide solution (about 33 g) to pH 9. 0.3 ml of a 10% Fe(III) chloride solution is added, and the solution is gassed intensively with air until the color changes from gray-black to yellow-green (about 3 h) and acidified with concentrated hydrochloric acid to pH 1. It is extracted twice with 200 ml of dichloromethane, the combined phases are washed twice with 200 ml of water and the dichloromethane solution is dried by azeotropic distillation. The residual dichloromethane is distilled off with simultaneous addition of 200 ml of cyclohexane up to a transition temperature of 80 °C. The hot cyclohexane solution is filtered through 15 g of silica gel and the filtrate is cooled to 5 °C in the course of 6 h in the reactor after seeding with 1. The crystals are filtered off with suction, washed with cold cyclohexane and dried in a vacuum drying oven (30 mbar, 30 °C). 8.5 g of 1 of m.p. 49–50 °C are obtained, GC purity (B) 98%. The yield is 74% based on methyl (6S)-6,8-dihydroxyoctanoate (2).

\([\alpha]_D = +117 (c = 1.81, \text{benzene}, [6]).\) – IR (KBr): \(v = 3032 \text{ cm}^{-1} (\text{br., O-H}), 2926 (m, \text{C-H}), 1701 (s, \text{C-O}), 1425, 1409, 1305, 1286, 1248, 1205, 932.\) – 1H-NMR (360 MHz, CDCl3): \(\delta = 1.50 (m, 2 \text{H, CH}_2), 1.69 (m, 4 \text{H, CH}_2-\text{CH}_2), 1.92 (m, 1 \text{H, 7-H}), 2.38 (t, J = 7 \text{ Hz}, 2 \text{H, 2-CH}_3), 2.47 (m, 1 \text{H, 7-H}), 3.15 (m, 2 \text{H, 8-CH}_2), 3.58 (m, 1 \text{H, 6-H}), 11.55 (1 \text{H, CO}_2\text{H}).\) – 13C-NMR (90.6 MHz, CDCl3): \(\delta = 24.3\)
(t, C-3), 28.6 (t, C-4), 33.8 (t, C-2), 34.5 (t, C-5), 38.5 (t, C-8), 40.2 (t, C-7), 56.2 (d, C-6), 180.1 (s, C-1).

- MS (EI, 70 eV), m/e (%): 206 (100) [M+], 173 (15) [M+-SH], 141 (9) [M+-SH-S], 123 (59) [M+-SH-S-H2O], 105 (17), 95 (60), 81 (73), 55 (37), 41 (40).

C₈H₁₄O₂S₂ (206.3)
Calcd C 46.57 H 6.84 O 15.51 S 31.08%,
Found C 46.60 H 6.80 O 15.30 S 30.90%.

[1] a) F. Balkenhohl, J. Paust, preceding publication and references given therein;
    b) C. V. Natraj, V. M. Gandhi, K. K. G. Menon, J. Bioscience 6, 37 (1984);


    b) M. H. Brookes, B. T. Golding, J. Chem. Soc. Perkin 1, 9–12 (1990);


