A Short and Productive Synthesis of Racemic α-Lipoic Acid

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Racemic α-lipoic acid is synthesized in four steps from the base chemicals vinyl ethyl ether and cyclohexanone. The total yield is 40%.

Results and Discussion

Biochemistry

α-Lipoic acid is involved in central biochemical processes as a protein-bound coenzyme [1]. It occurs, for example, as a cofactor of multienzyme complexes which control energy-producing processes such as aerobic glycolysis and photosynthesis. Scheme 1 shows the biochemical role of lipoic acid in the oxidative decarboxylation of pyruvic acid.

Use

Patients who suffer form diabetes mellitus or the consequences of alcohol abuse have reduced lipoic acid levels. Thus, the supply of the nerve cells with ATP is no longer guaranteed and neurological complications generally occur. The administration of lipoic acid has therefore proven suitable, in particular as a therapy in diabetic and alcoholic polyneuropathy [2].

Together with other biological antioxidants, dihydrolipoic acid has a membrane-stabilizing action and can prevent, for example, oxidative damage in the case of reperfusion after by-pass operations [3].

Synthesis

After the isolation and structural elucidation [4] of α-lipoic acid, numerous syntheses were published in patent specifications and the scientific literature. They can be divided into three categories with respect to the preparation of C_8 precursors which carry functional groups in positions 1, 6 and 8, Scheme 2 [5].

(I) Friedel-Crafts addition of adipic acid monoester chloride to ethylene yields the unsaturated keto ester **2** after spontaneous elimination of hydrogen chloride.

(II) Prins reaction of terminal C_7-olefins affords 1,3-dioxane derivatives **3**.

(III) Baeyer-Villiger oxidation of 2-substituted cyclohexanones **4** leads to the caprolactones **5**.

In addition to the routes (I)–(III), specific processes have also been developed for the preparation of 1, 6, 8-functional intermediates [5].

The introduction of sulfur groups into the intermediates **2, 3** and **5** is carried out either directly by heating with hydrohalic acids and thiourae [6] or in two steps *via* 6,8-dihalides or -disulfonates and reaction with sulfur nucleophiles [7].

Industrial syntheses of racemic α-lipoic acid are based mainly on the Friedel-Crafts route (I). Our process follows the Baeyer-Villiger strategy (III), however. It is different from the variants known from the literature [5, 8], in particular in the first two steps, Scheme 3 [9].

2-(2′-Ethoxyethyl)cyclohexanone (**4**, R_1 = Et) is synthesized in one stage from the base chemicals vinyl ethyl ether and cyclohexanone. Di-*tert*-butyl peroxide is particularly suitable as a catalyst. The reaction is carried out in excess cyclohexanone as a solvent, which can be recovered and recycled during the distillative isolation of **4**. 2-(2′-Acetoxyethyl)cyclohexanone (**4**, R_1 = AC) is analogously formed from vinyl acetate and cyclohexanone in 35% yield.

The subsequent Baeyer-Villiger oxidation can be carried out, for example, using performic acid which is generated in situ from formic acid and 30% aqueous hydrogen peroxide [10]. Before the

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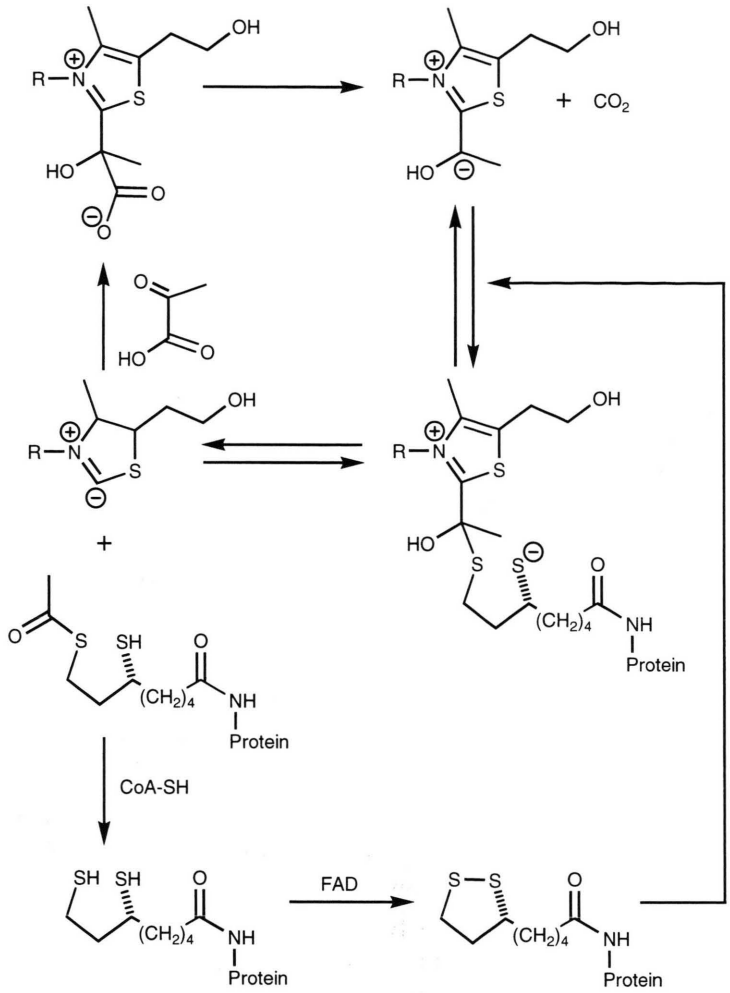
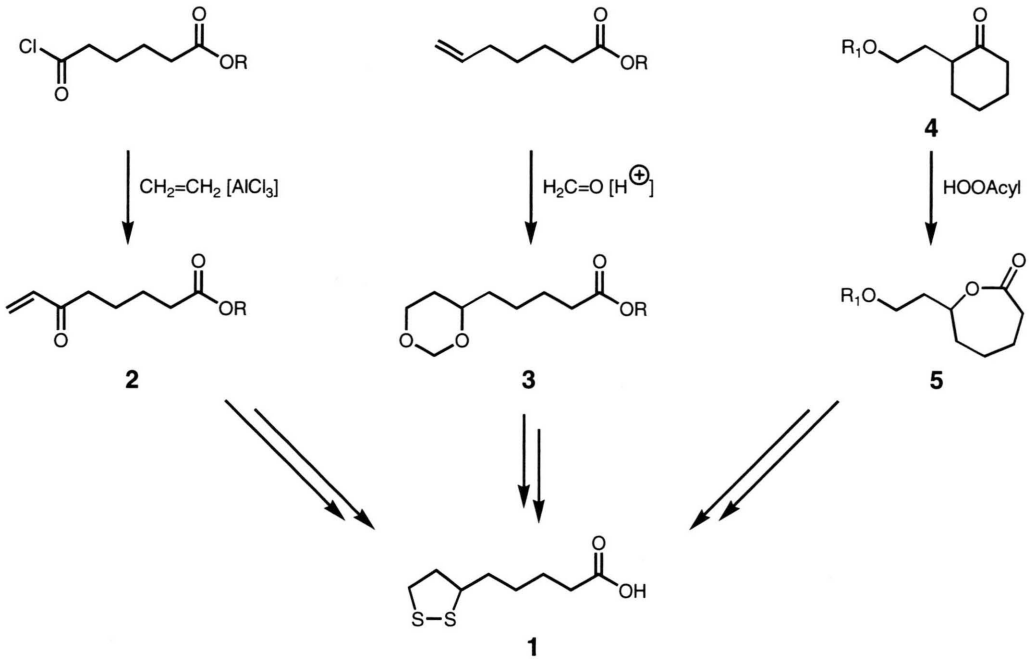


Scheme 1: Lipoic acid as a cofactor of the pyruvate dehydrogenase multienzyme comlex.

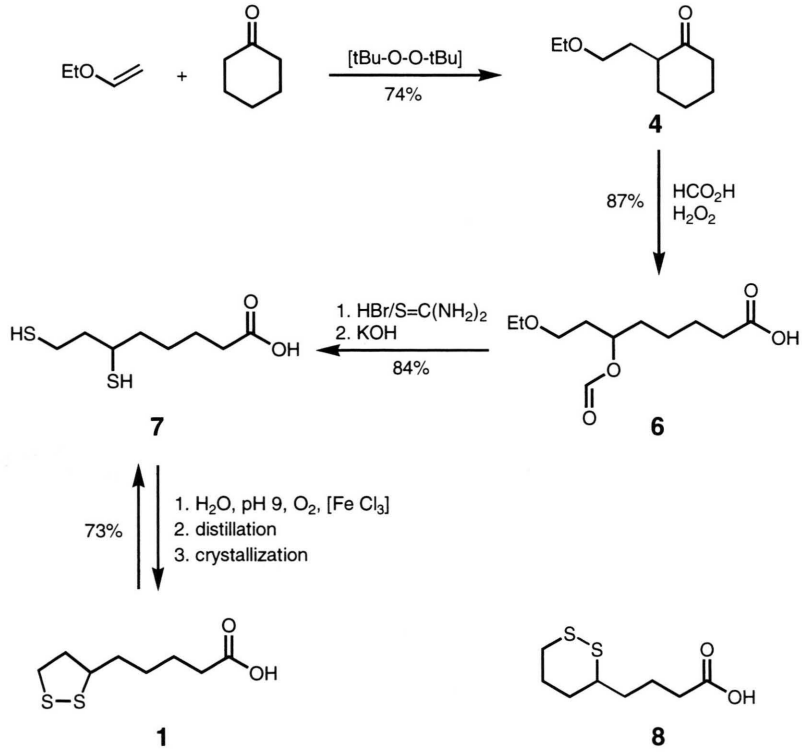
distillative work-up, excess oxidant is decomposed to carbon dioxide and water at 90 °C. Here also, the formic acid employed in excess as a solvent can be removed as a water azeotrope and recycled. 8-Ethoxy-6-formyloxyoctanoic acid (**6**) is obtained as the main product of this variant of the Baeyer-Villiger oxidation, accompanied by small amounts of the 6-hydroxy compound, of the corresponding lactone and of a dimeric formyloxy ester. The mixture of these components can be used directly for the further reaction to give dihydrolipoic acid (**7**).

To introduce sulfur into positions 6 and 8, the crude product from the Baeyer-Villiger oxidation is heated with concentrated hydrohalic acid in the presence of thiourea [6]. 62% hydrobromic acid has proven particularly suitable in this context. Hydrolysis of the initially formed 6,8-bis-isothiuronium bromide with potassium hydroxide yields **7**. In addition, the 5,8-dithiol results in a small amount as a result of a rearrangement. Pure dihydrolipoic acid (**7**) is obtained by reduction of **1** with sodium borohydride.

Dehydrogenation of **7** with oxygen and catalytic amounts of iron(III) chloride yields crude **1**, which is separated from oligomeric disulfides by continuous vacuum distillation. Small amounts of the



Scheme 2. Classical synthesis of racemic α-lipoic acid.



Scheme 3. New synthesis of racemic α-lipoic acid.

secondary component **8** [11] are separated off by crystallization from diisopropyl ether. Based on cyclohexanone and vinyl ethyl ether, the yield of R,S-α-lipoic acid (**1**) is about 40%.

Experimental Section

The preparative work was carried out by C. T. Wolfgang Kriegl, C. L. Markus Niebel and C. L. Ursula Schäfer.

2-(2'-Ethoxyethyl)cyclohexanone (**4**, R_1 = Et): 1140 g (12 mol) of cyclohexanone are introduced into a 2 l glass reactor (stirrer, thermometer, reflux condenser, two submerged inlets) and heated to 155 °C. When this temperature is reached, 86.4 g (1.2 mol) of vinyl ethyl ether and a solution of 35 g (0.24 mol) of di-*tert*-butyl peroxide in 51.4 g of cyclohexanone are added synchronously in the course of 8 h using two balance-controlled pumps. During the reaction, the temperature in the reactor falls to about 148 °C. About 1 h after completion of the addition, the mixture is cooled to room temperature.

The reflux condenser is exchanged for a packed column having about two theoretical plates, a vacuum of about 25 mbar is applied and about 120 g/h of cyclohexanone is distilled off while slowly increasing the temperature of the heating jacket to 130 °C; total amount 1100 g. 220 g of crude product is obtained as a residue, which is transferred to a 500 ml round-bottomed flask and purified by distillation over a bridge: main run 80–83 °C, 3 mbar; 159 g of **4** (R_1 = Et) having a purity of 95% ≅ 74.8% yield, as determined by gas chromatography.

^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.15 (t, J = 7.6 Hz, 3H, $-CH_3$), 2.34 (2H, $-CH_2-CO-$), 2.48 (1H, $>CH-CO-$), 3.41 (m, 4H, $-CH_2-O-$).

$C_{10}H_{16}O_2$ (168.23)
Calcd. C 71.40 H 9.59%,
Found C 71.50 H 9.70%.

8-Ethoxy-6-formyloxyoctanoic acid (**6**). 70.7 g (0.4 mol) of **4** (R_1 = Et) is dissolved in 276 g (6 mol) of formic acid in a 1 l glass reactor (stirrer, thermometer, reflux condenser, dropping funnel) and treated with 68 g (0.6 mol) of 30% aqueous hydrogen peroxide in the course of abouth 0.4 h. The internal temperature is kept at 45 ± 5 °C during this time; the evolution of heat is particularly high at the start of the reaction. After addition of the oxidant, the mixture is stirred at 45 °C for 1 h.

To work up the reaction, the mixture is heated to 100 °C in approximately 1 h, excess performic acid decomposing with evolution of carbon dioxide. The reflux condenser is then exchanged for a bridge and water and formic acid are distilled off at a bath temperature of 100 °C by reducing the pressure. The residue (88 g) consists to about 90% of **6**, according to HPLC analysis.

To characterize **6**, 10 g of the crude product is continuously degassed (130 °C, 0.5 mbar) and distilled (130 °C, 0.05 mbar) in a film evaporator [12]. 9.1 g of distillate with a purity of 97% is obtained, as – determined by gas chromatography. This corresponds to a yield of about 65% for **6**.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.17 (t, J = 8.3 Hz, 3H, $-CH_3$), 2.36 (t, J = 7.9 Hz, 2H, CH_2-CO_2H), 3.42 (3H, $-CH_2-O-$), 5.12 (1H, $-CH-O-CH=O$), 8.10 (s, 1H, $-O-CH=O$). – ^{13}C NMR ($DCCl_3$): δ = 15.06, 24.41, 24.63, 33.82, 33.99, 34.23, 66.37, 66.61, 71.80 ($>CH-O-CH=O$), 161.08 ($-O-CH=O$), 179.27 ($-CO_2H$).

$C_{11}H_{20}O_5$ (232.27)
Calcd C 56.88 H 8.67%
Found C 57.00 H 8.90%.

6-R,S-Dihydrolipoic acid (**7**): 274 g (2.1 mol) of 62 percent hydrobromic acid, 182.4 g (2.4 mol) of thiourea and 72 g of crude product from the Baeyer-Villiger oxidation (about 0.3 mol of useful product) are introduced into a 1 l glass reactor (stirrer, thermometer, reflux condenser). The mixture is refluxed for 20 h (internal temperature 116 °C).

960 g (6 mol) of 35 percent aqueous potassium hydroxide solution is introduced into a 2 l glass reactor (stirrer, thermometer, reflux condenser, gas inlet tube) and heated to boiling. The solution of the bisisothiuronium bromide is allowed to flow from reactor 1 into reactor 2 in the course of about 0.5 h and is refluxed for a further 3 h. During this phase, heating is carried out with extensive exclusion of light and a gentle stream of nitrogen is passed through the reaction mixture. The volatile constituents (ethyl mercaptan, ammonia, carbon dioxide) are absorbed in a scrubber filled with sodium hydroxide solution and sodium hypochlorite solution.

The reactor contents are then cooled to room temperature, acidified to pH 1 with conc. hydrochloric acid (about 320 ml) and the crude dihydrolipoic acid (**7**) is isolated by extracting three times with 400 ml each of methyl *tert*-butyl ether. After the evaporation of the MTB solution, **7** is obtained as a pale yellow oil (65.5 g). For determination of the yield and characterization, 10 g of the crude product is separated from solvent residues and nonvolatile constituents by continuous distillation in a film evaporator [12] (150 °C,

0.1 mbar). Distillate 8.4 g, purity according to GC: 90% **6**, 5% α-lipoic acid **1**; yield **7** + **1** about 84%.

R,S-Dihydrolipoic acid (**7**) *by hydrogenation of R,S-α-lipoic acid* (**1**): A solution of 51.5 g (0.25 mol) of **1**, m.p. 60–61 °C and 21 g (0.25 mol) of sodium bicarbonate in 1 l of water is treated in portions with 12.8 g (0.32 mol) of 85% sodium borohydride in the course of 0.5 h while cooling with an ice bath. The raction can be monitored by thin-layer chromatography (cover the acidified sample with a layer of ethyl acetate; silica gel, eluent ethyl acetate/*n*-Hex = 2/1).

Stirring is continued at 5 °C for 0.5 h and the disired product is taken up in ethyl acetate after acidifying to pH 1 with conc. hydrochlorid acid. After concentration in a rotary evaporator, 50.4 g of crude product **7** is obtained, which is purified by distillation as described above: 47.3 g (91%) of **7**, colorless oil, purity according to GC 99.1%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.34 (d, J = 10 Hz, 1H, >CH–S*H*), 1.41 (t, J = 8 Hz, 1H, –CH_2–S*H*), 2.37 (t, J = 5.5 Hz, –CH_2–CO_2H), 2.70 (m, 2H, –CH_2–SH), 2.90 (m, 1H, >C*H*–SH). – ^{13}C NMR ($CDCl_3$): δ = 22.25, 24.21, 26.39, 33.89, 38.61, 39.23, 42.68, 48.47, 56.22, 180.12.

$C_8H_{16}O_2S_2$ (208.35)
Calcd C 46.12 H 7.75 S 30.78%,
Found C 46.27 H 7.55 S 30.90%.

R,S-α-Lipoic acid (**1**): 1700 ml of water and 52 g (about 0.2 mol) of crude dihydrolipoic acid (**7**) are introduced into a 3 l glass reactor (aerating stirrer, pH probe, dropping funnel, waste gas tube) and treated with 2 N sodium hydroxide solution at room temperatur to pH 8.8 (about 130 ml ≅ 0.24 mol). 1.2 ml of 10 percent iron (III) chloride solution is added and the mixture is gassed with air until the color changes from black-gray to yellow (about 2 l/min, 2.5 h). The pH rises in the course of this to about 11.5.

After addition of 200 ml of dichloromethane, the mixture is adjusted to pH 1 with concentrated hydrochloric acid. The phases are separated, the aqueous phase is extracted with a further 100 ml of dichloromethane, the dichloromethane solutions are concentrated and the crude product is purified by continuous distillation in a film evaporator at 150 °C, 0.05 mbar; distillate 41.6 g, residue 7 g.

The distillate is dissolved in 250 ml of diisopropyl ether at 55 °C. The solution is filtered through 10 g of silica gel, cooled to 15 °C and seeded; after a few minutes crystallization starts. After about 15 min, the mixture is cooled to –15 °C, the product is isolated after 30 min by filtering off with suction, and the crystals washed with 40 ml of cold diisopropyl ether and dried at room temperature in a stream of nitrogen; 32.2 g, m.p. 57–59 °C, purity according to GC 96%, 3% side product **8** (Hewlett-Packard 5880, 30 m DB 5, 100 → 250 °C).

A further crystallization from diisopropyl ether yields 30.1 g of pure **1**, m.p. 60–61 °C, GC purity 99%, 0.3% side product **8**.

^{1}H NMR ($CDCl_3$, 360 MHz): δ = 1.50 (2H, CH_2), 1.68 (4H, 2CH_2), 1.92 and 2.46 (1H + 1H, S–CH–CH_2–CH_2–S), 2.37 (t, J = 3.6 Hz, CH_2–CO_2H), 3.14 (2H, CH_2–S), 3.57 (1H, C*H*–S). – ^{13}C NMR ($CDCl_3$): 24.34, 28.60, 33.84, 34.53, 38.48, 40.19, 56.25, 180.13.

$C_8H_{14}O_2S_2$ (206.33)
Calcd C 46.57 H 6.84 S 31.08%,
Found C 46.72 H 6.68 S 31.18%.

The by-product **8** was identified by GC comparison with a preparation synthesized according to literature details [10].

5,8-Dimercaptooctanoic acid: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.40 (2H, S*H*), 1.57 (2H), 1.62–1.90 (4H), 2.40 (t, J = 5.5 Hz, 2H, CH_2–CO_2H), 2.57 (2H, CH_2–SH), 2.79 (H, C*H*–SH). – ^{13}C NMR ($CDCl_3$): δ = 22.17, 24.33, 31.33, 33.66, 33.66, 37.48, 38.26, 40.26, 179.65.

$C_8H_{16}O_2S_2$ (208.35)
Calcd C 46.12 H 7.75 S 30.78%,
Found C 46.30 H 7.51 S 30.90%.

$C_8H_{16}O_2S_2$ (208.35)
Calcd C 46.12 H 7.75 S 30.78%
Found C 46.30 H 7.51 S 30.91%.

4-(1,2-Dithian-3-yl)butyric acid (**8**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.50–1.76 (4H), 1.83 (2H), 2.10 (2H), 2.40 (t, J = 5.5 Hz, 2H, CH_2–CO_2H), 2.70–2.93 (3H, CH_2–S). – ^{13}C NMR ($CDCl_3$): δ = 21.86, 27.63, 32.97, 33.68, 34.28, 34.56, 45.85, 179.78.

$C_8H_{14}O_2S_2$ (206.33)
Calcd. C 46.57 H 6.84 S 31.08%,
Found C 46.42 H 6.80 S 31.08%.

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