Simplistic Expedient and Practical Synthesis of (±)-α-Lipoic Acid

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Abstract: Synthesis of α-lipoic acid has been achieved by a simple sequence of reactions. The synthesis highlights the use of α-chloroesters in a Reformatsky reaction. The intermediate keto acid is an intermediate from which both isomers of lipoic acid can be prepared.

Key words: Reformatsky reaction, α-chloroesters, α-lipoic acid, ozonolysis

α-Lipoic acid (1,2-dithiolane-3-pentanoic acid) and its reduced form dihydrolipoic acid (6,8-dimercapto-octanoic acid) are physiologically occurring substances.[1,2]

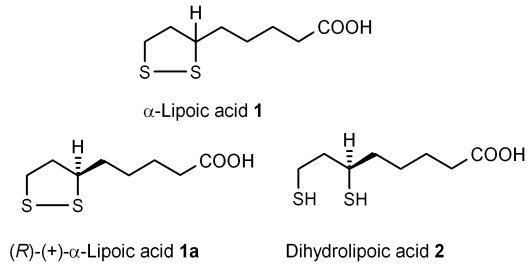
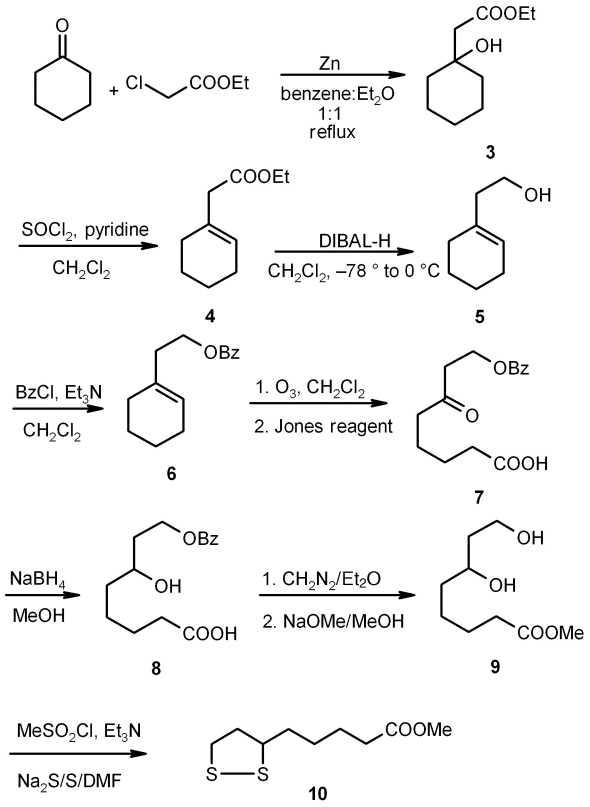


Figure 1

Lipoic acid has been shown to possess antioxidant abilities against attack by free radical[4] as well as an inhibitory effect against HIV replication.[5] Interplay between lipoic acid and gluathione in the guardianship against lipid peroxidation and metal toxicity has also been demonstrated. Moreover, lipoic acid is used to a great extent in the treatment of various diseases such as alcoholic liver diseases,[8] mushroom poisoning,[9] metal poisoning,[6] diabetes, and neurodegenerative disorders.[11] The simplicity and usefulness of lipoic acid have attracted many groups around the world. Several reports have also been published on the biosynthesis of lipoic acid.[23] Still lipoic acid remains a favorite molecule as seen in recent publications.[12–23] Previous syntheses of lipoic acid involve either complex routes, complex intermediates, or harsh reaction conditions.

Our strategy involved in the synthesis of lipoic acid is based on a modified Reformatsky reaction that we developed.[24] The synthesis of lipoic acid is to highlight the usefulness of this methodology. Reformatsky reaction on cyclohexanone followed by elimination of hydroxyl group using thionyl chloride and pyridine gave exclusively compound **4**. The reasons as to why the elimination gave exclusively the endocyclic product are under study. DIBAL-H reduction of the ester to alcohol followed by protection using benzoyl chloride gave **6**. The benzoate **6** on ozonolysis followed by Jones oxidation gave ketoacid **7**, which on reduction with $NaBH_4$ in MeOH gave hydroxy acid **8**. The hydroxy acid **8** thus obtained was esterified and treated with sodium methoxide to give diol **9**, which is a key intermediate in the synthesis of lipoic acid. The diol **9** was efficiently converted to lipoic acid following the reported protocol.[12]



Scheme 1

Highlights of this synthesis are the use of ethyl chloroacetate for the Reformatsky reaction using simple conditions. Earlier reports of Reformatsky using chloroacetate involve the use of highly activated zinc[25] or zinc-copper

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couple[26] for the reaction. Another point to be noted here is that enantioselecetive reduction of the carbonyl of **7** can be achieved using Baker's yeast; a similar system has been reported by Gopalan et al.[20]

All solvents were distilled before use. Petroleum ether refers to the fraction boing in the range of 60–80 °C. All melting points and boiling points are uncorrected. IR spectra were recorded on a Perkin-Elmer IR spectrophotometer model 683B or 1605 FTIR. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC 200, MSL 300 and DRX 500 instruments using TMS as an internal standard. Mass spectra were recorded at an ionization energy of 70 eV on a Finnigan MAT-1020 automated GC/MS instrument.

Ethyl (1-Hydroxycyclohexyl)acetate (3)[27]

Zn (830 mg, 12.8 mmol) was placed in a 50-mL two-necked round bottom flask attached with a reflux condenser and septum. The reaction vessel was evacuated and flushed with argon. Anhyd benzene–Et_2O (1:1, 15 mL) was added with vigorous stirring. Ethyl chloroacetate (750 mg, 6.12 mmol) was added dropwise, followed by a crystal of I_2 to initiate the reaction. Cyclohexanone (500 mg, 5.1 mmol) was added dropwise after 15 minutes and the reaction was refluxed at 80 °C. The progress of the reaction was monitored by TLC (EtOAc–petroleum ether, 1:10) and was quenched after 6 h by the addition of HCl (10%, 5 mL). The compound was extracted with Et_2O (2 × 20 mL), washed with dil. HCl (5 mL), and water (2 × 10 mL). The combined organic layers were dried over anhyd Na_2SO_4, filtered, and concentrated under vacuum. Chromatography furnished 616 mg (65%) of **3** as a colorless oil.

IR ($CHCl_3$): 3518, 2934, 2861, 1716, 1447, 1401, 1372, 1332, 1196, 1128, 1031 cm^{-1}.

^{1}H NMR: δ = 1.20 (t, 3 H, *J* = 7 Hz), 1.30–1.80 (m, 10 H), 2.40 (s, 2 H), 3.80 (br, 1 H), 4.10 (q, 2 H, *J* = 7 Hz).

^{13}C NMR: 13.9 (q), 21.7 (2 × t), 25.4 (t), 37.2 (2 × t), 45.4 (t), 59.9 (t), 69.5 (s), 172.1 (s).

Ethyl Cyclohex-1-en-1-ylacetate (4)[28]

Ethyl 1-(hydroxycyclohexyl)acetate (**3**; 2.05 g, 11.07 mmol) in anhyd CH_2Cl_2 (60 mL) was placed in a 100-mL two-necked round bottom flask with an addition funnel and a guard tube attached. Anhyd pyridine (1.050 g, 13.12 mmol) was added and the reaction mixture was cooled to 0 °C using an ice-salt mixture. After 10 min, SO_2Cl_2 (1.447 g, 12.3 mmol) was added dropwise over 10 min. The progress of the reaction was monitored by TLC using EtOAc–petroleum ether (1:19). The reaction mixture was stirred for 30 min, quenched with ice-cold water (5 mL), and CH_2Cl_2 (20 mL) was added. The reaction mixture was washed with dilute HCl (5%, 2 × 15 mL), water (2 × 20 mL), and $NaHCO_3$ (5%, 15mL). The organic layer was dried over anhyd Na_2SO_4, filtered, and concentrated in vacuo. Chromatography (EtOAc–petroleum ether, 1:20) gave 1.60 g (86%) of **4** as a colorless oil.

IR ($CHCl_3$): 3411, 2936, 1736, 1457, 1370, 1300, 1159, 1032 cm^{-1}.

^{1}H NMR: δ = 1.21 (t, 3 H, *J* = 7 Hz), 1.32–2.11 (m, 8 H), 2.90 (s, 2 H), 4.10 (q, 2 H, *J* = 7 Hz), 5.51 (m, 1 H).

2-Cyclohex-1-en-1-ylethanol (5)[29]

Ethyl cyclohex-1-en-1-ylacetate (**4**; 2.84 g, 17 mmol) was placed in a 100-mL dry two-necked round bottom flask with a two-way stopcock and a septum. The round bottom flask was flushed with argon, anhyd CH_2Cl_2 (50 mL) was added, and the mixture was cooled to –78 °C in a cryostat. DIBAL-H (3 M, 17 mL, 51.0 mmol) was added dropwise with constant stirring and stirring was continued for 3 h and then a further 2 h at 0 °C. The reaction was monitored by TLC and reaction was quenched with a sat. solution of potassium sodium tartrate. The temperature of the reaction mixture was allowed to rise to r.t. It was filtered through celite, concentrated in vacuo, and purified by flash column chromatography to furnish 1.75 g (81%) of **5** as a colorless liquid; bp 85 °C (7 torr) [lit. 85 °C (7 torr)].

IR (neat): 3350, 2924, 1439 cm^{-1}.

^{1}H NMR: δ = 1.2–2.0 (m, 8 H), 2.25 (t, 2 H, *J* = 6 Hz), 3.6 (t, 2 H, *J* = 6 Hz), 5.5 (m, 1 H).

^{13}C NMR: δ = 22.5 (t), 23.0 (t), 25.4 (t), 28.3 (t), 41.3 (t), 60.4 (t), 123.7 (d), 134.3 (s).

2-Cyclohex-1-en-1-ylethyl Benzoate (6)

2-Cyclohex-1-en-1-ylethanol (**5**; 1.00 g, 8.0 mmol) was placed in a 100 mL round bottom flask with a guard tube and addition funnel attached. Anhyd CH_2Cl_2 (40 mL) was added followed by Et_3N (962 mg, 9.6 mmol). The reaction was cooled to 0 °C in an ice-bath. BzCl (1.226 mg, 8.8 mmol) was added dropwise. The reaction was quenched with water (5 mL) and the product was extracted with CH_2Cl_2 (2 × 20 mL). The organic phase was washed with $NaHCO_3$ solution (2%, 3 × 20 mL). The organic phase was dried, filtered, and concentrated in vacuo to furnish 680 g (92%) of **6** as a colorless oil.

IR (neat): 3063, 2930, 2672, 1685, 1595, 1419 cm^{-1}.

^{1}H NMR: δ = 1.2–2 (m, 8 H), 2.25 (t, 2 H, *J* = 6 Hz), 4.2 (t, 2 H, *J* = 6 Hz), 5.5 (m, 1 H), 7.38–7.52 (m, 3 H), 8.00–8.05 (m, 2 H).

^{13}C NMR: δ = 22.2 (t), 22.8 (t), 25.2 (t), 28.4 (t), 37.1 (t), 63.3 (t), 123.7 (d), 129.3 (d), 129.4 (d), 132.4 (d), 133.6 (s), 146.5 (s), 166.0 (s).

MS: *m*/*z* = 230 (M^+).

8-(Benzoyloxy)-6-oxooctanoic Acid (7)

2-Cyclohex-1-en-1-ylethyl benzoate (**6**; 500 mg, 2.2 mmol) was placed in a 100-mL round bottomed flask. Anhyd CH_2Cl_2 (30 mL) was added and the reaction mixture was cooled to –78 °C and O_3 was bubbled through until the blue color persisted indicating the end of the reaction. O_2 was passed through the mixture for an additional 10 min, followed by N_2 for a further 10 min. Me_2S (2 mL) was added and the temperature of the reaction mixture was allowed to reach r.t. H_2O (10 mL) was added to the reaction mixture and the organic layer was separated, dried, filtered, and concentrated under vacuum. The crude product thus obtained was subjected to the Jones oxidation at 0 °C in acetone (10 mL). The reaction was quenched with *i*-PrOH (4 mL) and filtered through celite and concentrated in vacuo to furnish 488 mg (85%) of **7** as a white solid; mp 57.5–58 °C.

IR ($CHCl_3$): 3438, 3020, 2956, 1713, 1414 cm^{-1}.

^{1}H NMR: δ = 1.65 (m, 4 H), 2.4 (t, 2 H, *J* = 7 Hz), 2.51 (t, 2 H, *J* = 7 Hz), 2.87 (t, 2 H, *J* = 6 Hz), 4.59 (t, 2 H, *J* = 6 Hz), 7.4–7.6 (m, 3 H), 8.0 (d, 2 H, *J* = 8 Hz).

^{13}C NMR: δ = 23.1(t), 24.3 (t), 33.9 (t), 41.7 (t), 42.9 (t), 60.1 (t), 128.5 (d), 129.8 (d), 130.24 (s), 133.2 (d), 166.5 (s), 179.1 (s), 207.3 (s).

Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.75; H, 6.47. Found: C, 64.60; H, 6.49.

8-(Benzoyloxy)-6-hydroxyoctanoic Acid (8)[30]

8-(Benzoyloxy)-6-oxooctanoic acid (**7**; 500 mg, 1.9 mmol) was placed in a single neck round bottom flask. MeOH (10 mL) was added and reaction mixture was cooled to 0 °C in an ice-bath. $NaBH_4$ (135 mg, 3.6 mmol) was added slowly. The progress of the reaction was monitored by TLC (EtOAc–petroleum ether, 3:7). The reaction was quenched by the addition of a sat. solution of NH_4Cl (2 mL). The solution was filtered and the product extracted with

EtOAc (2 × 20 mL). The organic layer was dried over anhyd Na_2SO_4, filtered, and concentrated in vacuo. Chromatography furnished 453 mg (90%) of **8**.

IR ($CHCl_3$): 3446, 2934, 1711, 1599 cm^{-1}.

^1H NMR: δ = 1.25–2.01 (m, 8 H), 2.30 (t, 2 H, *J* = 6 Hz), 3.75 (m, 1 H), 4.34–4.57 (m, 2 H), 7.07 (br s, 1 H), 7.40–7.60 (m, 3 H), 8.00 (d, 2 H, *J* = 8 Hz).

^{13}C NMR: δ = 24.8 (t), 25.2 (t), 34.1 (t), 36.5 (t), 37.1 (t), 62.4 (t), 68.6 (t), 128.5 (d), 129.8 (d), 130.4 (s), 133.1 (d), 167.1 (s), 178.7 (s).

Methyl 6,8-Dihydroxyoctanoate (9)[12]

8-(Benzoyloxy)-6-hydroxyoctanoic acid (**8**; 500 mg, 1.9 mmol) was dissolved in Et_2O (10 mL) and cooled to 0 °C. Diazomethane (ca. 7 equiv) in Et_2O was added to the compound and the reaction mixture was left over-night. The reaction mixture was then concentrated and the crude product was placed in a 50-mL 2-neck round bottom flask with a two-way stopcock and a stopper attached. Anhyd MeOH (10 mL) was added to the compound followed by NaOMe (15 mg). The reaction was left for 3–4 h and then quenched with acidic resin (IR 120) till the reaction medium was neutral. The reaction mixture was then filtered and concentrated in vacuo. After chromatography 340 mg (91%) of **9** was obtained as a colorless oil.

^1H NMR: δ = 1.2–1.75 (m, 8 H), 2.32 (t, *J* = 6 Hz, 2 H), 2.9 (m, 1 H), 3.73 (s, 3 H), 3.76–3.87 (m, 2 H).

^{13}C NMR: δ = 24.4 (t), 24.7 (t), 33.6 (t), 37.0 (t), 38.1 (t), 51.1 (t), 71.3 (d), 173.7 (s).

Methyl Lipoate (10)[12]

Methyl 6,8-dihydroxyoctanoate (**9**; 300 mg, 1.58 mmol) was placed in a two-necked round bottom flask with a two-way stopcock and a septum attached. Anhyd CH_2Cl_2 (10 mL) was added followed by Et_3N (319 mg, 3.16 mmol). The reaction was cooled to 0 °C. $MeSO_2Cl$ (463 mg, 3.16 mmol) was added dropwise. The progress of the reaction was monitored by TLC. The reaction was quenched with water (5 mL) and the organic layer was washed with aq $NaHCO_3$ (2%, 10 mL). The organic layer was dried over anhyd Na_2SO_4, filtered, and concentrated under vacuum. The crude compound was used directly in the next reaction. Finely ground $Na_2S{\cdot}H_2O$ (410 mg, 1.7 mmol) and sulfur (54 mg, 1.7 mmol) were dissolved in anhyd DMF (5 mL). The mixture was heated at 80 °C for 24 h and then stirred at r.t. for 1 h. The reaction mixture was poured into ice-cold water (15 mL) and was extracted with EtOAC (3 × 20 mL) The combined organic extracts were dried over anhyd Na_2SO_4, filtered, and evaporated under reduced pressure to furnish 257mg (74%) of **10** as a yellow oil.

IR ($CHCl_3$): 2932, 1735, 1435 cm^{-1}

^1H NMR: δ = 1.3–1.7 (m, 6 H), 1.75–1.8 (m, 1 H), 2.23 (t, 2 H, *J* = 8 Hz), 2.35–2.50 (m, 1 H), 3.03–3.22 (m, 2 H), 3.43–3.60 (m, 1 H), 3.57 (s, 3 H).

^{13}C NMR: δ = 24.63 (t), 28.71 (t), 33.75 (t), 34.6 (t), 38.45 (t), 40.1 (t), 51.4 (q), 56.2 (d), 173.5 (s).

Lipoic Acid (1)[12]

Aq KOH (0.1 M, 12 mL) was added to methyl lipoate (**10**; 0.220 g, 1 mmol) in MeOH (5 mL) and the mixture was stirred at r.t. in the dark for 24 h. The MeOH was evaporated, the mixture was washed with Et_2O (15 mL) and the aq layer was acidified carefully with HCl (6 N) to pH 2. The product was extracted with Et_2O (2 × 20 mL), the combined organic layers were dried over anhyd Na_2SO_4, filtered and concentrated. The purification of the residue by chromatography over silica gel (petroleum ether–EtOAc, 8:1) gave 0.120 g (70%) of **1**.

^1H NMR: δ = 1.30–1.98 (m, 7 H), 2.37 (t, 2 H, *J* = 6.8 Hz), 2.42–2.55 (m, 1 H), 3.04–3.22 (m, 2 H), 3.48–3.60 (m, 1 H), 8.10 (br s, 1 H).

^{13}C NMR: δ = 24.2 (t), 28.5 (t), 33.7 (t), 34.4 (t), 38.3 (t), 40.0 (t), 56.1 (d), 180.0 (s).

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