An Enantioselective Synthesis of *R*-(+)-α-Lipoic Acid

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R-(+)-α-Lipoic acid (**1**), $[\alpha]_D$ +107°, has been prepared in a six-step enantioselective synthesis from 6-bromohex-1-ene; the enantioselectivity is controlled by a Sharpless asymmetric epoxidation of the intermediate allyl alcohol (**2**).

In 1951, Reed reported the isolation of a crystalline growth-promoting enzyme cofactor from processed insoluble liver residue.[1] This compound was named α-lipoic acid derived from its high lipid solubility and acidic nature (pK_a = 4.7). It was found to display an extremely high level of biological activity, playing a catalytic role in the oxidative decarboxylation of pyruvate to acetate. The chemical structure of lipoic acid was determined in the early 1950s;[2] however, its absolute configuration was unknown until 1983, when Golding synthesised the unnatural enantiomer from (*S*)-malic acid.[3] This confirmed the *R*-configuration of the natural product (**1**).

Since its discovery, lipoic acid has been found to be widely distributed in animal and plant tissue[4] and it plays an important role as a protein-bound transacylating cofactor of several multienzymic α-keto acid dehydrogenase complexes.[5] Evidence that lipoic acid plays an important role in phosphorylation has also been discovered.[6]

Perhaps as a result of the high level of biological activity of lipoic acid, its use in the treatment of various diseases has been investigated. The racemate may be used for treating liver diseases and poisoning;[7] it has been shown to be a potent growth-promoting factor[8] and acts as a radioprotective agent which protects against ionising radiation-induced damage to DNA and its components.[9] The effects of lipoic acid on rats with hepatitis[10] and induced carcinomas[11] have also been investigated with positive results and lipoic acid has in addition been shown to prevent hair loss during chemotherapy in rats[12] and to reduce blood-sugar levels in diabetic rabbits.[13]

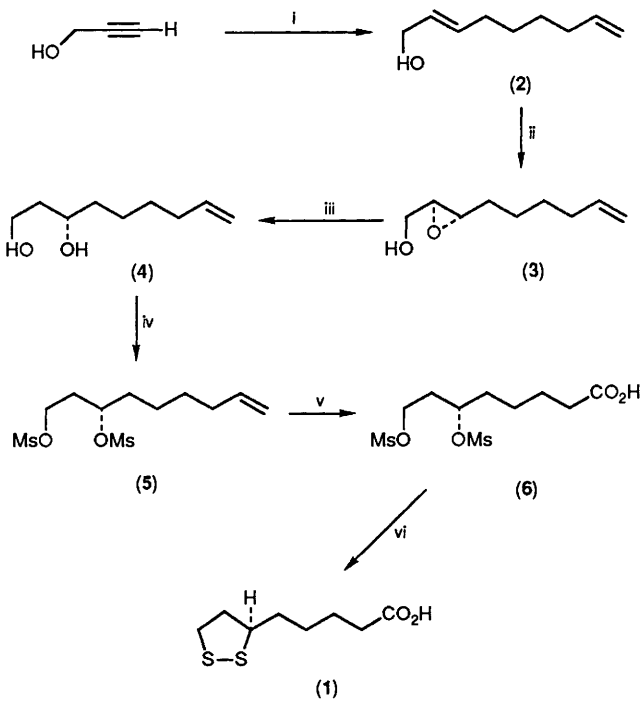
There are indications that the two enantiomeric forms of lipoic acid do not exhibit the same biological activity; in particular the naturally occurring *R*-enantiomer is very much more active than its antipode.[14] It is therefore desirable for any enantioselective synthesis of lipoic acid to provide efficient access to both enantiomers.

Previous syntheses of lipoic acid have suffered from the disadvantages of low overall yields, large numbers of steps, or a need for separation of diastereoisomers or for expensive reagents. Of particular importance are the syntheses of Golding,[15] Johnson,[16] and Arigoni.[17]

We have devised a six step synthesis of lipoic acid which proceeds in an overall yield of 22% from 6-bromohex-1-ene.[18] The route provides easy access to both enantiomeric forms with predictable absolute stereochemistry.

Results and Discussion

The Sharpless asymmetric epoxidation was chosen as the key step and source of enantioselectivity.[28] Introduction of the disulphide moiety of compound (**1**) may be carried out by S_N2 displacement at C-6 and C-8 using the disulphide dianion,[19] resulting in inversion of configuration at C-6; the *S*-configuration is therefore required in the precursor [*e.g.* (6)] in order to give the natural *R*-configuration in the final product. 1,3-Dioxygenated systems are readily available by Red-Al reduction of epoxy alcohols;[20] conversion of the alcohol groups of a suitable 1,3-diol into sulphonate esters gives the required displacement precursor.[21] The synthetic route is outlined in the Scheme.



Scheme. *Reagents:* i, Li, NH_3; 5-bromohex-1-ene; Li, NH_3; ii, 0.62 equiv. L-(+)-DIPT, 0.52 equiv. $Ti(OPr^i)_4$, 1.2 equiv. t-butyl hydroperoxide, CH_2Cl_2, −20 °C, 3 days, 82%; iii, Red-Al, THF, 0 °C, 89%; iv, 2.2 equiv. methanesulphonyl chloride; 2.2 equiv. Et_3N, CH_2Cl_2, −5 °C, 96%; v, $RuCl_3 \cdot 3H_2O$ (catalytic), 4.0 equiv. $NaIO_4$, CCl_4, room temp. 78%; vi, 1.0 equiv. KOH, H_2O; $Na_2S \cdot 9H_2O$, DMF; HCl, 52%. Ms = mesyl (CH_3SO_2).

The first step of the synthesis, alkylation of the lithio dianion of prop-1-yn-3-ol in liquid ammonia with 6-bromohex-1-ene, was followed by *in situ* reduction[22] of the resultant disubstituted acetylene to give the allylic alcohol (**2**) (100% *E* by capillary gas chromatography analysis) in 78% overall yield from the bromide. Catalytic enantioselective epoxidation of the alcohol (**2**) using L-(+)-di-isopropyl tartrate [(+)-DIPT] as the chiral auxiliary[23] gave the 2*S*,3*S*-epoxyalcohol (**3**) in 82% yield. The optical purity of alcohol (**3**) was found to be >96% e.e. by capillary gas chromatography and ^{19}F NMR analysis of

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the ester formed by reaction with (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride,[24] and also by ^{1}H NMR spectroscopy of the acetate ester of alcohol (**3**) in the presence of the optically active lanthanide shift reagent Eu(hfc)$_3$.[25]

Regioselective reduction of compound (**3**) using Red-Al in THF[20] gave the *S*-1,3-diol (**4**) in 89% yield. Mesylation[21] of the diol (**4**) proceeded in excellent yield (96%) and served a dual role – the mesyl groups act both as hydroxyl activating groups for the introduction of the disulphide moiety, and as hydroxyl protecting groups during the next step of the synthesis, the oxidative cleavage of the terminal olefin of compound (**5**) using ruthenium tetroxide.[26] This reaction gave the desired acid (**6**) in 78% yield. The final step of the synthesis, disulphide displacement of the acid dimesylate (**6**),[19] was carried out by initial carboxylate formation using aqueous potassium hydroxide, followed by addition of a suspension of pre-formed disulphide dianion in DMF and heating of the mixture at 80 °C for 24 h. Recrystallisation of the crude product gave a 52% yield of pure (*R*)-(+)-α-lipoic acid (**1**) with all spectral data consistent with that published.[27] The optical rotation of the product ($[\alpha]_D^{28}$ + 107°, *c* = 0.82 in benzene) was consistent with the *R*-configuration of the natural product ($[\alpha]_D^{25}$ +96.7°, *c* = 1.88 in benzene)[2] and the predicted stereochemical outcome of the epoxidation reaction.

The overall yield of this six step synthesis is 22% based on the readily available 6-bromohex-1-ene. The route also provides enantioselective access to the *S*-(−)-enantiomer of compound (**1**) by use of D-(−)-DIPT as the chiral auxiliary in the epoxidation reaction, and to other analogues of compound (**1**), with predictable absolute stereochemistry.

Experimental

General.—Light petroleum (b.p. 40–60 °C and b.p. 60–80 °C) was distilled prior to use. Dichloromethane was dried by distillation from calcium hydride. Diethyl ether was dried by distillation from lithium aluminium hydride. Tetrahydrofuran (THF) was dried by distillation from the sodium benzophenone ketyl radical. Chloroform was dried by distillation from phosphorus pentoxide as required. Dimethylformamide (DMF) was dried by azeotropic removal of water with benzene followed by distillation, and stored over 3 Å molecular sieve.

Commercially available reagents were used as supplied unless otherwise stated. For epoxidation reactions, the tartrate and allylic alcohol were distilled immediately before use. Solutions of t-butylhydroperoxide were prepared according to literature methods.

Reactions requiring rigorously anhydrous conditions were carried out in glassware which had been dried for several hours at 150–200 °C. The apparatus was assembled hot and allowed to cool while a rapid flow of argon was admitted. Reactions were maintained in an atmosphere of argon and reagents and solvents introduced using a syringe or by means of cannula techniques, through a septum cap. Solvents were freshly distilled before use.

Silica-gel refers to Merck 9385 Kieselgel 60 (230–400 mesh). Preparative TLC was performed on 20 × 20 cm glass plates coated with a 1 mm layer of Merck Kieselgel 60 (PF254).

IR spectra were recorded using a Perkin-Elmer 298 IR spectrophotometer and were calibrated against the 1 602 cm^{-1} absorption of polystyrene. ^{1}H NMR spectra were recorded using Perkin-Elmer R 34 (220 MHz) or Bruker WM 250 (250 MHz) spectrometers.

^{13}C NMR spectra were recorded using a Bruker WM 250 spectrometer operating at 62.8 MHz or a JEOL FX 60 Q spectrometer operating at 15.0 MHz. All spectra were recorded using tetramethylsilane as internal standard. ^{19}F Spectra were recorded on a Bruker WM 250 spectrometer operating at 235.8 MHz. Electron impact (EI) and chemical ionisation (CI) mass spectra were recorded on a VG Micromass 7070E instrument.

Capillary gas chromatography was performed on a Dani 3800 gas chromatograph. M.p.s were determined on a Kofler block apparatus and are uncorrected. Microanalyses were carried out by the Department of Chemistry microanalytical service. Optical rotations were determined using Optical Activity AA-1000 or AA-100 polarimeters.

(E)-*Nona*-2,8-*dien*-1-*ol* (**2**).—To a mixture of liquid ammonia (100 ml) and iron(III) nitrate (3 crystals) was added lithium (1.88 g, 0.268 mol) in portions, allowing the blue colour to dissipate between additions. Freshly distilled prop-2-yn-1-ol (7.21 g, 0.129 mol; 7.49 ml) in THF (20 ml) was added dropwise over 25 min and the reaction mixture was allowed to reflux for 90 min. 1-Bromohex-5-ene (14.0 g, 85.8 mmol; 10.86 ml) in THF (30 ml) was added over 30 min and the reaction was allowed to reflux for a further 2.5 h. Lithium (2.05 g, 0.298 mol) was added in portions and the reaction stirred for 60 min. Saturated aqueous ammonium chloride was added until the blue colour dissipated. Most of the ammonia was allowed to evaporate and the reaction mixture was poured onto crushed ice (20 g) and allowed to warm to room temperature overnight. The product was extracted with ether (4 × 100 ml), dried over magnesium sulphate, and filtered. The solvent was removed through a fractionation column and the residue distilled using a Kugelrohr apparatus to give (*E*)-nona-2,8-dien-1-ol (**2**) as a colourless oil (9.30 g, 66.4 mmol, 78%), b.p. 105 °C (0.5 mmHg); ν_{max}(film) 3 350, 3 090, 2 915, 2 860, 1 675, 1 640, 1 460, 1 440, 1 230, 1 090, 1 000, 970, and 910 cm^{-1}; δ(^{1}H, $CDCl_3$) 1.30–1.50 (4 H, m), 1.85 (1 H, br s, removed by D_2O shake), 2.10 (4 H, m), 4.07 (2 H, d, *J* 4.0 Hz), 4.90–5.05 (2 H, m), and 5.50–5.90 (3 H, m); δ(^{13}C, $CDCl_3$) 28.46 (t), 28.60 (t), 32.02 (5), 33.62 (t), 63.74 (t), 114.3 (t), 129.1 (d), 133.1 (d), and 138.7 (d); *m/z* (CI, NH_3), 158 (*M* + NH_4^+), no parent ion observed with EI (Found: C, 77.3; H, 11.5. $C_9H_{16}O$ requires C, 77.09; H, 11.50%).

(2S,3S)-*Epoxynon*-8-*en*-1-*ol* (**3**).—Dichloromethane (100 ml) was cooled to −25 °C using a thermostatic cold bath. Titanium tetraisopropoxide (2.84 g, 10 mmol; 2.97 ml) was added by syringe followed after 5 min by freshly distilled (+)-diisopropyl tartrate (2.81 g, 12 mmol; 2.52 ml). After a further 5 min, (*E*)-nona-2,8-dien-1-ol (2.72 g, 19.4 mmol) was added, followed, after a further 5 min, by t-butyl hydroperoxide (6.9 ml of 3.39M solution in toluene; 23.4 mmol). The reaction was allowed to stand at −25 °C for 3 days. The flask was then placed in an ice-bath, and saturated aqueous sodium sulphate (10 ml) was added followed by ether (100 ml). The resulting solution was stirred vigorously while reaching room temperature over 1 h. The gelatinous orange precipitate was removed by filtration through a pad of Celite in a sintered glass funnel, and the precipitate was washed with ether (2 × 100 ml) and dried under suction. The combined filtrates were evaporated, the residue dissolved in ether (100 ml), and dimethyl sulphide (2.0 ml) was added. The solution was stirred for 1 h, aqueous sodium hydroxide (1M, 50 ml) was added, and stirring was continued for 3–4 h. The ethereal layer was separated and washed with water (2 × 40 ml), dried over magnesium sulphate, filtered, and the solvent removed under reduced pressure. Distillation using a Kugelrohr apparatus gave (2*S*,3*S*)-epoxynon-8-en-1-ol (**3**) (2.48 g, 15.9 mmol, 82%), b.p. 110 °C (0.5 mmHg); $[\alpha]_D^{25}$ −35.9, (*c* = 5.5 in $CHCl_3$); ν_{max}(film) 3 480, 3 080, 2 980, 2 920, 2 860, 1 645, 1 440, 1 380, 1 240, 1 090, 1 030, 995, 910, 870, 740, 720, and 700 cm^{-1}; δ(^{1}H, $CDCl_3$) 1.35–1.65 (6 H, m), 2.00–2.20 (2 H, m), 2.60 (1 H, br s, removed by D_2O shake), 2.80–3.00 (2 H, m), 3.63 (1 H, dd, *J* 12.0 and 4.0 Hz), 3.87 (1 H, dd, *J* 12.0 and 1.5 Hz), 4.90–5.07 (2 H, m), and 5.68–5.90 (1 H, m); δ(^{13}C, $CDCl_3$) 25.41 (t), 28.63 (t), 31.43 (t), 33.61 (t), 56.05 (d), 58.70 (d), 61.89

(t), 114.6 (t), and 138.6 (d); *m/z* (CI, NH_3), 174 ($M + NH_4^+$), no parent ion observed with EI (Found: C, 69.2; H, 10.1. $C_9H_{16}O_2$ requires C, 69.19; H, 10.32%). Later experiments were carried out in the presence of 4 Å molecular sieves and gave similar results.

(3S)-*Non*-8-*en*-1,3-*diol* (**4**).—To a stirred solution of epoxy alcohol (**3**) (0.61 g, 3.91 (mmol) in THF (100 ml) at 0 °C was added Red-Al (2.0 ml of 3.4M solution in toluene, 6.8 mmol). The resulting solution was stirred at 0 °C for 3 h and allowed to reach room temperature overnight. Aqueous sodium hydroxide (1M; 5 ml) was cautiously added and the resulting solution was stirred for 1 h. The organic phase was separated and the aqueous layer extracted with ether (2 × 30 ml). The combined extracts were washed with saturated aqueous sodium chloride solution, dried over magnesium sulphate, filtered, and the solvent removed under reduced pressure. The crude product mixture was passed through a short column of silica gel and the fractions containing the diol (**4**) were combined and evaporated. Kugelrohr distillation gave (3*S*)-non-8-en-1,3-diol (**4**) as a waxy solid (0.54 g, 3.42 mmol, 89%), m.p. 20 °C; b.p. 130 °C (0.5 mmHg); ν_{max}(film) 3 360, 3 100, 2 940, 1 640, 1 470, 1 440, 1 420, 1 380, 1 330, 1 200, 1 090, 1 040, 1 000, 915, and 735 cm^{-1}; $\delta(^1H, CDCl_3)$ 1.25–1.82 (8 H, m), 2.00–2.15 (2 H, m), 3.73–3.97 (3 H, m), 3.85–4.05 (2 H, br s, removed by D_2O shake), 4.90–5.10 (2 H, m), and 5.70–5.95 (1 H, m); $\delta(^{13}C, CDCl_3)$ 25.05 (t), 28.90 (t), 33.67 (t), 37.67 (t), 38.40 (t), 61.60 (t), 71.97 (d), 114.4 (t), and 138.7 (d); *m/z* (CI, NH_3) 176 ($M + NH_4^+$) (Found: C, 68.0; H, 11.7. $C_9H_{18}O_2$ requires C, 68.31; H, 11.47%).

(3S)-*Non*-8-*en*-1,3-*diol Dimesylate* (**5**).—To a solution of diol (**4**) (0.51 g, 3.2 mmol) in dichloromethane (50 ml) at −5 °C was added methanesulphonyl chloride (0.55 ml; 7.10 mmol). Triethylamine (1.0 ml; 7.10 mmol) was added dropwise using a syringe and the solution was stirred for 3 h after which time the solvent was removed under reduced pressure. Ether (50 ml) was added and the solution was washed with water (20 ml), dilute hydrochloric acid (20 ml), water (10 ml), saturated aqueous sodium hydrogen carbonate (20 ml), and saturated aqueous sodium chloride (10 ml). The organic layer was dried over magnesium sulphate, filtered, and solvent removed under reduced pressure to give (3*S*)-non-8-en-1,3-diol dimesylate (**5**) (0.97 g, 3.1 mmol, 96%) which could be used without further purification. An analytical sample was obtained by flash column chromatography on silica gel; ν_{max}(film) 3 080, 3 030, 2 980, 2 940, 2 860, 1 640, 1 465, 1 440, 1 415, 1 355, 1 175, 975, 915, 825, 785, 750, 742, 735, 720, 710, and 703 cm^{-1}; $\delta(^1H, CDCl_3)$ 1.32–1.55 (4 H, m), 1.65–1.85 (2 H, m), 1.95–2.25 (4 H, m), 3.05 (6 H, s), 3.35 (2 H, t, *J* 5 Hz), 4.80–4.95 (1 H, m), 4.95–5.10 (2 H, m), and 5.70–5.90 (1 H, m); $\delta(^{13}C, CDCl_3)$ 24.03 (t), 28.35 (t), 33.34 (t), 33.85 (t), 34.60 (t), 37.23 (q), 38.55 (q), 65.98 (t), 79.11 (d), 114.8 (t), and 138.4 (d); *m/z* (CI, NH_3) 332 ($M + NH_4^+$) and 236. No parent ion observed with EI (Found: C, 41.8; H, 7.1. $C_{11}H_{22}S_2O_6$ requires C, 42.02; H, 7.05%).

(6S)-6,8-*Dihydroxyoctanoic Acid Dimesylate* (**6**).—To a vigorously stirred solution of alkene (**5**) (2.10 g, 6.7 mmol) in a mixture of carbon tetrachloride (15 ml), acetonitrile (15 ml), and water (23 ml) was added sodium periodate (5.87 g, 27.4 mmol) and two crystals of ruthenium(III) chloride hydrate. The resulting two-phase mixture was stirred for 3 h at room temperature after which dichloromethane (100 ml) was added and the organic layer separated, dried over magnesium sulphate, and filtered through a thin pad of Celite to remove any inorganic residues. Removal of solvent under reduced pressure gave a white solid which was recrystallised from ether to give (6*S*)-6,8-dihydroxyoctanoic acid dimesylate (**6**) (1.73 g, 5.21 mmol, 78%), mp 54–55 °C; $\nu_{max}(CCl_4)$, 3 700–2 300, 3 030, 2 940, 2 870, 1 730, 1 705, 1 460, 1 410, 1 340, 1 170, 1 090, 970, 915, 825, 785, and 735 cm^{-1}; $\delta(^1H, CDCl_3)$ 1.30–1.55 (2 H, m), 1.55–1.83 (4 H, m), 2.00–2.15 (2 H, m), 2.41 (2 H, t, *J* 6 Hz), 3.05 (6 H, s), 4.33 (2 H, t, *J* 5 Hz), 4.77–4.94 (1 H, m), and 10.30 (1 H, br s, removed by D_2O shake); $\delta(^{13}C, CDCl_3)$ 24.13 (t), 33.57 (t), 33.97 (t), 34.51 (t), 37.39 (q), 38.64 (q), 65.66 (t), 78.52 (d), and 179.2 (s) (one signal missing due to overlap); *m/z* (CI, NH_3), 350 ($M + NH_4^+$) and 254 (Found: C, 36.2; H, 6.0. $C_{10}H_{20}O_8S_2$ requires C, 36.13; H, 6.06%).

(R)-(+)-α-*Lipoic Acid* (**1**).—To a stirred solution of potassium hydroxide (0.23 g, 4.16 mmol) in water (5 ml) was added acid (**6**) (1.38 g, 4.16 mmol), which dissolved over *ca.* 5 min. Most of the water was then removed under reduced pressure (temperature < 40 °C). A slurry of $Na_2S \cdot 9H_2O$ (1.10 g, 4.57 mmol) and flowers of sulphur (0.146 g, 4.57 mmol) in DMF (10 ml) was added to the crude potassium salt and the resulting mixture was heated under reflux for 24 h at 80 °C with vigorous stirring. The reaction mixture was poured into ice water (20 g), acidified (3M HCl; *ca.* 5 ml), and extracted with chloroform (4 × 50 ml). The organic phase was washed with water (4 × 10 ml), dried over magnesium sulphate, and solvent removed under reduced pressure. The residue was extracted with hot light petroleum (2 × 10 ml) and the solvent was removed under reduced pressure to give a yellow solid which was recrystallised from cyclohexane to yield (*R*)-(+)-α-lipic acid (**1**) (0.44 g, 2.16 mmol, 52%) as yellow platelets, m.p. 44–46 °C, $[\alpha]_D^{28}$ +107° (*c* = 0.82 in benzene); $\nu_{max}(CH_2Cl_2)$ 3 700–2 300, 2 930, 2 850, 1 705, 1 410, 1 260, 1 120, 930, 735, and 700 cm^{-1}; $\delta(^1H, CDCl_3)$ 1.38–1.72 (6 H, m), 1.70–1.90 (1 H, m), 2.36 (2 H, t, *J* 7.0 Hz), 2.40–2.50 (1 H, m), 3.10–3.20 (2 H, m), 3.51–3.61 (1 H, m), and 11.00 (1 H, br s); $\delta(^{13}C, CDCl_3)$ 24.40 (t), 28.68 (t), 33.87 (t), 34.61 (t), 38.52 (t), 40.23 (t), 56.28 (d), and 180.0 (s); *m/z* (EI) 206 (M^+) (Found: C, 46.4; H, 6.9. $C_8H_{14}O_2S_2$ requires C, 46.57; H, 6.84%).

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