Syntheses of α-(*R*)- and α-(*S*)-Lipoic Acid from (*S*)-Malic Acid

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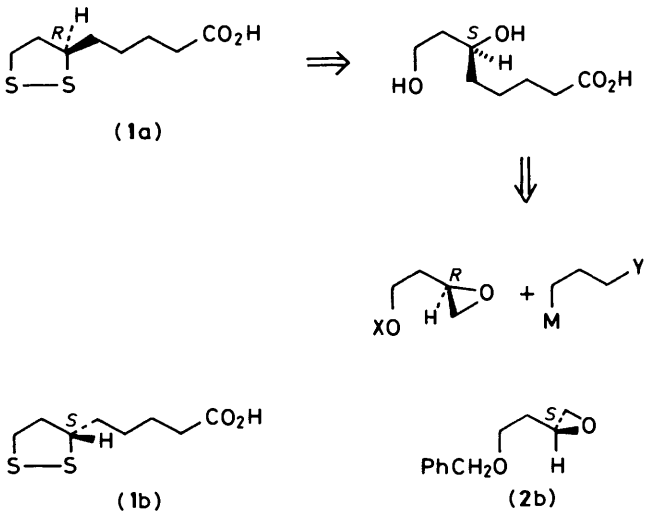
(*S*)-Malic acid has been converted into α-(*R*)- and α-(*S*)-lipoic acid [(**1a**) and (**1b**), respectively] *via* (*R*)- and (*S*)-(2-phenylmethoxyethyl)oxirane [(**2a**) and (**2b**), respectively]. The (*R*)-oxirane (**2a**) was cleaved with but-3-enylmagnesium bromide (cuprate catalysis) to give (*S*)-1-(phenylmethoxy)oct-7-en-3-ol (**4a**). This was converted into methyl (*S*)-6,8-dihydroxyoctanoate (**5a**), the di-*O*-methanesulphonate (**6a**) of which was treated with sodium sulphide and sulphur in dimethylformamide to yield methyl α-(*R*)-lipoate (**7a**), that was saponified to α-(*R*)-lipoic acid (**1a**). The (*S*)-oxirane (**2b**) was similarly converted into α-(*S*)-lipoic acid (**1b**).

We have proved that the absolute configuration of natural α-(+)-lipoic acid is (*R*) [as in structure (**1a**)] by the synthesis of its enantiomer (**1b**) from (*S*)-malic acid.[1] This was achieved by a route that features a single inversion of configuration (displacement of *O*-methanesulphonate by a thiolate nucleophile). α-(*R*)-Lipoic acid is the coenzyme of α-oxo acid dehydrogenases (*e.g.* pyruvate dehydrogenase of *Escherichia coli*) and may participate in other biological reactions.[2] It is available only in very small quantities by extraction from a natural source. Therefore, the synthetic, commercially available racemate has been used for biochemical experiments. It would be preferable to use the pure (*R*)-isomer for such experiments and so we have adapted our route to α-(*S*)-lipoic acid to provide a synthesis of the (*R*)-isomer. Full experimental details are given for this synthesis of (*R*)-lipoic acid, as well as for (*S*)- and (*R*, *S*)-lipoic acid, the syntheses of which were reported in a preliminary communication.[1]

Many syntheses of racemic α-lipoic acid have been described.[3,4] By the resolution of certain intermediates and completion of the synthesis in the manner defined for racemic materials, both optical isomers of α-lipoic acid were obtained.[5,6] However, these methods gave very low (*ca.* 1%) overall yields of the target molecule. Elliott *et al.*[7] have recently accomplished an efficient asymmetric synthesis of α-(*R*)-lipoic acid *via* a chiral acetal template. Arigoni and his co-workers have prepared both enantiomers of α-lipoic acid from 1,3-dithianes derived from menthones.[8] Sutherland has prepared α-(*R*)-lipoic acid by a synthesis incorporating a Sharpless epoxidation.[9] Our syntheses of α-(*R*)- and α-(*S*)-lipoic acid from (*S*)-malic acid, a member of the 'chiral pool', comprise simple experimental procedures which readily provide gram quantities of either enantiomer of α-lipoic acid.

Results and Discussion

Strategy of the Synthesis.—A retrosynthetic analysis for α-(*R*)-lipoic acid is given in Scheme 1. This relates the target molecule to (*R*)-(2-phenylmethoxyethyl)oxirane (**2a**). We have described a synthesis of the (*S*)-isomer (**2b**) from (*S*)-malic acid.[10] Therefore, to obtain the (*R*)-isomer it is either necessary to commence with (*R*)-malic acid or to invert the configuration of an intermediate from (*S*)-malic acid. We adopted the latter course of action, because (*R*)-malic acid is relatively expensive.



Scheme 1. X = protecting group for OH, Y = masked carboxy group, and M = metallic entity

(*R*)-(2-*Phenylmethoxyethyl*)*oxirane.*—Takano *et al.*[11] have reported the stereospecific conversion of (*R*)-3-phenylmethoxypropane-1,2-diol into its antipode by a sequence of mesylation, treatment with potassium acetate in hot acetic anhydride, and finally saponification. The mechanism of the inversion step had already been established.[12] We applied this methodology to (*S*)-4-phenylmethoxybutane-1,2-diol (**3b**) and obtained its (*R*)-isomer (**3a**) in 40% overall yield. The diol was converted into (*R*)-(2-phenylmethoxyethyl)oxirane (**2a**) by the method employed for the (*S*)-isomer (**2b**).[10] The epoxide (**2a**) was pure by h.p.l.c. and was optically pure (n.m.r. analysis by chiral shift reagent).

Conversion of (R)-(2-*Phenylmethoxymethyl*)*oxirane into* α-(R)-*Lipoic Acid.*—Reaction of the epoxide (**2a**) with but-3-enylmagnesium bromide/lithium tetrachlorocuprate[13] gave 6-hydroxy-8-(phenylmethoxy)oct-1-ene (**4a**), which was converted into methyl 6,8-dihydroxyoctanoate (**5a**) by a standard series of reactions (benzylation of the secondary hydroxy group, hydroboration of the vinyl, oxidation of primary hydroxy, esterification, hydrogenolysis of benzyl groups—see Scheme 2). The diol ester (**5a**) was mesylated and the dimethanesulphonate (**6a**) was treated with sodium sulphide nonahydrate and sulphur in

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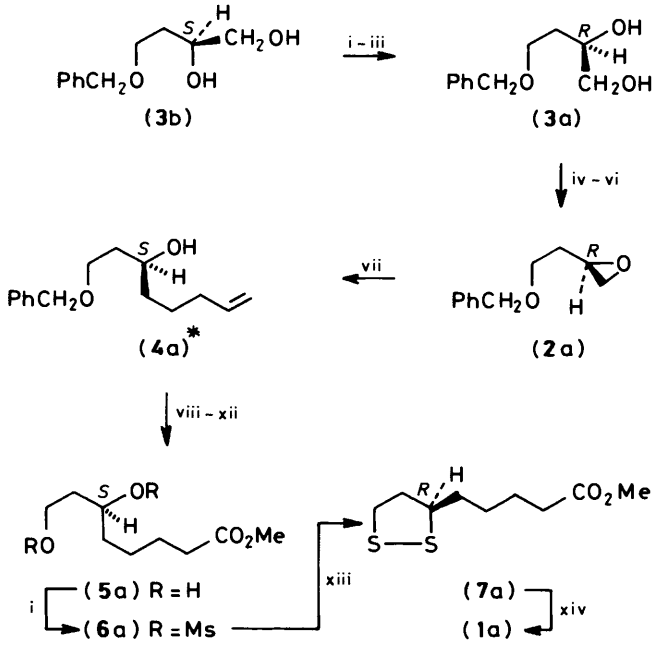

Scheme 2. Compounds (**4b**)—(**7b**) (not drawn) are the enantiomers of compounds (**4a**)—(**7a**) respectively. *Reagents:* i, $MeSO_2Cl$, Et_3N; ii, KOAc, Ac_2O; iii, K_2CO_3, MeOH; iv, PhCHO, H^+; v, *N*-bromosuccinimide, ClF_2CCCl_2F; vi, NaOH, $HOCH_2CH_2OH$ vii, CH_2 = $CHCH_2CH_2MgBr$, Li_2CuCl_4 (catalytic), THF; ix, $HBSia_2$, THF, aq. HO_2^-; x, pyridinium dichromate, DMF; xi, MeOH–HCl; xii, Pd/C, H_2; xiii, Na_2S, S, DMF; xiv, aq. HO^-. Ac = acetyl; THF = tetrahydrofuran; DMF = dimethylformamide; Sia = $Pr^iC(Me)H^-$

dimethylformamide to give (+)-methyl lipoate (**7a**). This was saponified[14] (anaerobic conditions, in darkness) to yield (+)-α-lipoic acid (**1a**) [22% from (*R*)-(2-phenylmethoxyethyl)oxirane (**3a**)], the chiroptical data of which was identical with that published[15] for natural α-(*R*)-lipoic acid (see Experimental section).

The stereochemical integrity of the synthesis described rests on the presumed inversion of configuration in the conversion of dimethanesulphonate (**6a**) into methyl lipoate. Eliel *et al*[16] have shown that the bistoluene-*p*-sulphonates of *meso*- and *rac*-pentane-2,4-diol react with sodium sulphide and sulphur in dimethylformamide by nearly complete inversion of configuration at each secondary carbon centre. An alternative route to methyl lipoate (**7a**) would have been *via* methyl 6,8-dibromooctanoate, by analogy with the conversion of (*R*)-hexane-1,3-diol into (*R*)-3-propyl-1,2-dithiolane.[17]

Experimental

M.p.s (uncorrected) were recorded using a Reichert Microstage. I.r. spectra were run on a Perkin-Elmer 257 instrument. ^1H N.m.r. spectra were obtained from a Perkin-Elmer R34 (220 MHz) machine using solutions in carbon tetrachloride or deuteriochloroform with tetramethylsilane as internal standard. Mass spectra (e.i. and ammonia c.i.) were determined with a Kratos MS80 machine. Preparative thin layer chromatograms were carried out using Merck Kieselgel 60 PF254. Optical rotations were recorded from a Bendix-N.P.L. automatic polarimeter type 143D. Combustion analyses were performed by E.M.A.L., Beaworthy, Devon. The circular dichroism spectra were measured by Dr. P. M. Scopes, Westfield College, University of London using a Cary 6 instrument.

All solvents and reagents were purified, as required, by literature procedures.[18] An atmosphere of nitrogen, dried where necessary by passage through Drierite, was employed for all reactions.

The syntheses described below were performed in both enantiomeric series and with racemic materials. For 1-phenylmethoxyoct-7-en-3-ol and following compounds a general procedure is described. The spectroscopic data were identical for compounds in both enantiomeric series and the racemic compounds.

(S)-4-*Phenylmethoxybutane*-1,2-*diyl Dimethanesulphonate.*—This compound was obtained from (*S*)-4-phenylmethoxybutane-1,2-diol by following a literature procedure[19] and was isolated as an orange oil (60 g, 79%). It was used directly in the next step; $\delta_H(CDCl_3)$ 1.90 (2 H, m, CH_2CH_2OBn), 2.93 (6 H, s, 2 × CH_3), 3.57 (2 H, m, CH_2OBn), 4.28 (2 H, m, CH_2OMs), 4.36 (2 H, s, CH_2Ph), 4.88 (1 H, m, CHOMs), and 7.18 (5 H, s, Ph).

(R)-4-*Phenylmethoxybutane* 1,2-*diyl Diacetate.*—The dimesylate was treated with potassium acetate in boiling acetic anhydride using the procedure of Takano *et al.*[11] Distillation of the crude product gave a colourless oil: b.p. 110—120 °C at 0.005 mmHg (19.3 g, 41%); $\delta_H(CCl_4)$ 1.81 (2 H, m, CH_2CH_2OBn), 1.92 (3 H, s, CH_3), 1.96 (3 H, s, CH_3), 3.42 (2 H, m, CH_2OBn), 3.95 (1 H, dd, J_{gem} 17.1 Hz, J_{vic} 4 Hz, HCHOAc), 4.21 (1 H, dd, J_{gem} 17.1 Hz, J_{vic} 5 Hz, HCHOAc), 4.40 (2 H, s, CH_2Ph), 5.12 (1 H, m, CHOAc), and 7.23 (5 H, s, Ph); $\nu_{max.}$ (film) 3 090w, 3 065w, 2 960w, 2 935w, 2 865w, 1 740s, 1 495w, 1 455w, 1 435w, 1 370m, 1 230s, 1 095m, 1 045m, 1 035m, 955w, 735m, and 695m cm^{-1}; *m/z* (e.i. m.s.) 91 (100%), 107 (23), 131 (29), 160 (64), 173 (21), 221 (10), and 280 (7, M^+) [Found: *M*, 280.1313; $C_{15}H_{20}O_5$ requires *M*, 280.1311]; $[\alpha]_D^{23}$ +14.6 (*c* 4.8 in CCl_4) [Found: C, 64.65; H, 7.0. $C_{15}H_{20}O_5$ requires C, 64.25; H, 7.2%].

(R)-4-*Phenylmethoxybutane*-1,2-*diol.*—Methanolysis[11] of the diacetate in the presence of solid potassium carbonate gave the crude diol which was purified by distillation: b.p. 130—135 °C at 0.005 mmHg (12.2 g, 90%); $[\alpha]_D^{22}$ −2.6° (*c* 5.1 in $CHCl_3$) [other data as reported[10] for the (*S*)-isomer].

(R)-2-(*Phenylmethoxyethyl*)*oxirane.*—This compound was synthesised in 60% overall yield from the diol by the method described[10] for obtaining the (*S*)-enantiomer from (*S*)-4-phenylmethoxybutane-1,2-diol: $[\alpha]_D^{25}$ +13.3° (*c* 6.43 in $CHCl_3$).

1-*Phenylmethoxyoct*-7-*en*-3-*ol.*—Magnesium (3 g, 125 mmol), 20 cm^3 of a solution of 4-bromobut-1-ene (16.2 g, 120 mmol) in tetrahydrofuran (100 cm^3), and 3 drops of 1,2-dibromoethane, were gently warmed until reaction commenced. The remainder of the bromoalkene solution was then added over 20 min with stirring. The reaction was cooled to −78 °C and a solution of lithium tetrachlorocuprate (0.18 g, 0.8 mmol) in tetrahydrofuran (5 cm^3) was introduced. After a further 1 h (2-phenylmethoxyethyl)oxirane (6.25 g, 35 mmol) in tetrahydrofuran (50 cm^3) was added dropwise. The mixture was stirred at −78 °C for a further 5 h and was then allowed to warm to room temperature overnight. The contents of the flask were then quenched with cooled (5 °C) saturated aqueous ammonium chloride. The organic phase was subsequently dried (K_2CO_3) and evaporated to give the crude product as a yellow oil (8.0 g, 98%). An analytically pure sample was obtained by preparative t.l.c. [elution with dichloromethane–methanol (9:1)] followed by Kugelrohr distillation: b.p. 110—112 °C at 0.005 mmHg; $\delta_H(CCl_4)$ 1.30—1.55 (4 H, m, 4- and 5-H), 1.62 (2 H, m, CH_2CH_2OBn), 2.02 (2 H, m, CH_2CH=), 2.72 (1 H, br s, OH),

3.55 (2 H, m, CH_2OBu), 3.63 (1 H, m, CH), 4.43 (2 H, s, CH_2Ph), 4.93 (2 H, dd, J_{cis} 9 Hz, J_{trans} 16 Hz, CH_2=CH), 5.74 (1 H, m, CH=), and 7.21 (5 H, s, Ph); $\nu_{max.}$(film) 3 430br, 3 065w, 2 930s, 2 875m, 1 640m, 1 495w, 1 455w, 1 360w, 1 205w, 1 090s, 1 025w, 990w, 905m, 730m, and 695m cm^{-1}; *m/z* (c.i. m.s.) 91 (100%), 107 (81), 131 (20), 159 (49), 181 (19), and 235 [53, $(M + 1)^+$]; $[\alpha]_D^{25}$ +6.0° (*S*-isomer, *c* 4.9 in CCl_4), $[\alpha]_D^{23}$ −6.5° (*R*-isomer, *c* 5.2 in CCl_4) (Found: C, 77.1; H, 9.6. $C_{15}H_{22}O_2$ requires C, 77.9; H, 9.45%).

6,8-*Diphenylmethoxyoct*-1-*ene*.—This compound was prepared using the benzylation procedure of Czernecki *et al.*[20] The residue from the work-up was redissolved in pentane and allowed to percolate through anhydrous magnesium sulphate to remove the catalyst and other impurities. After re-evaporation, the product was further purified by heating to 80 °C at 0.005 mmHg for 5 h to remove traces of benzyl bromide. The dibenzyl ether was thus obtained as a yellow oil (10.23 g, 95%).

An analytically pure sample was isolated by preparative t.l.c. (elution with dichloromethane) followed by Kugelrohr distillation: b.p. 170—175 °C at 0.003 mmHg; $\delta_H(CCl_4)$ 1.52 (4 H, m, 4- and 5-H), 1.77 (2 H, m, CH_2CH_2OBn), 2.04 (2 H, m, CH_2CH=), 3.50 (2 H, m, CH_2OBn), 3.53 (1 H, m, CH), 4.40 (2 H, s, 1 CH_2Ph), 4.41 (1 H, d, *J* 8.3 Hz, 2 CH*H*Ph), 4.45 (1 H, d, *J* 8.3 Hz, 2 C*H*HPh), 4.95 (2 H, dd, J_{cis} 9 Hz, J_{trans} 16 Hz, CH_2=CH), 5.75 (1 H, m, CH=), and 7.22 (10 H, s, 2 × Ph); $\nu_{max.}$(film) 3 060m, 3 025w, 2 925s, 2 850s, 1 640w, 1 600w, 1 495w, 1 452m, 1 360m, 1 305m, 1 205m, 1 085s, 1 065s, 1 025w, 990w, 905m, 730m, and 690m cm^{-1}; *m/z* (c.i. m.s.) 91 (100%), 107 (15), 127 (8), 181 (8), 215 (2), 233 (18), and 325 [11, $(M + 1)^+$] (Found: *M*, 325.2161. Calc. for $C_{22}H_{29}O_2$: *M*, 325.2168); $[\alpha]_D^{23}$ +21.3° (*S*-isomer, *c* 5.6 in CCl_4), $[\alpha]_D^{25}$ −22° (*R*-isomer, *c* 5.0 in CCl_4) (Found: C, 81.05; H, 8.8. $C_{22}H_{28}O_2$ requires C, 81.45; H, 8.7%).

6,8-*Diphenylmethoxyoctan*-1-*ol*.—The dibenzylated alkene was hydroborated with di-isopentylborane prepared *in situ* at 0 °C[21] in tetrahydrofuran. After work-up the crude product was isolated as a colourless oil (9.41 g, 89%). An analytically pure sample was obtained by preparative t.l.c. (1,1,1-trichloromethane–methanol, 17:3) followed by Kugelrohr distillation: b.p. 178—186 °C at 0.005 mmHg; $\delta_H(CCl_4)$ 1.27—1.60 (6 H, m, 3 × CH_2), 1.73 (2 H, m, CH_2CH_2OBn), 2.80 (1 H, br s, OH), 3.46 (5 H, m, CH_2OH + CH_2OBn + CHOBn), 4.39 (2 H, s, 8-OCH_2Ph), 4.41 (1 H, d, *J* 8.3 Hz, 6-OCH*H*Ph), 4.44 (1 H, d, *J* 8.3 Hz, 6-OC*H*HPh), and 7.25 (10 H, s, 2 × Ph); $\nu_{max.}$(film) 3 410br, 3 090w, 3 070w, 3 030w, 2 930s, 2 860s, 1 495w, 1 455m, 1 365m, 1 205m, 1 090s, 1 070s, 1 025m, 910w, 735s, and 695s cm^{-1}; *m/z* (c.i. m.s.; NH_3) 18 (100%), 91 (61), 108 (6), 127 (39), 145 (4), 181 (6), 235 (10), and 343 [41, $(M + 1)^+$]; $[\alpha]_D^{23}$ +23.3° (*S*-isomer, *c* 4.7 in CCl_4); $[\alpha]_D^{20}$ −22.0° (*R*-isomer, *c* 5 in CCl_4) (Found: C, 76.8; H, 8.65. $C_{21}H_{28}O_3$ requires C, 77.15; H, 8.85%).

Methyl 6,8-*diphenylmethoxyoctanoate*.—6,8-Diphenylmethoxyoctan-1-ol (9.2 g, 26.9 mmol) in dimethylformamide (50 cm^3) was added dropwise to a stirred solution of pyridinium dichromate (50 g, 141 mmol) in dimethylformamide (150 cm^3) at 0 °C. After being left for 24 h at room temperature, the mixture was poured into 10 volumes of water. Extraction with light petroleum (b.p. 40—60 °C)–ether (1:1; 4 × 250 cm^3), drying (Na_2SO_4) and removal of solvent under reduced pressure gave crude 6,8-diphenylmethoxyoctanoic acid. This was esterified by dissolution in 3% methanolic HCl (150 cm^3) and stirring overnight. Evaporation under reduced pressure gave the impure methyl ester which was purified by filtration under suction through a pentane/$MgSO_4$ slurry. The filtrate was evaporated to give the title compound as an oil (7.58 g, 76%). A small sample was further purified by preparative t.l.c. (1,1,1-trichloroethane–methanol, 9:1) followed by Kugelrohr distillation: b.p. 230—240 °C at 0.005 mmHg (almost colourless oil); $\delta_H(CCl_4)$ 1.25—1.60 (6 H, m, 3 × CH_2), 1.73 (2 H, m, CH_2CH_2OBn), 2.19 (2 H, t, *J* 7.3 Hz, CH_2CO_2Me), 3.47 (3 H, m, CHOBn + CH_2OBn), 3.67 (3 H, s, OCH_3), 4.41 (2 H, s, 8-OCH_2Ph), 4.42 (1 H, d, *J* 8.3 Hz, 6-OCH*H*Ph), 4.45 (1 H, d, *J* 8.3 Hz, C*H*HPh), and 7.21 (10 H, s, 2 × Ph); $\nu_{max.}$(film) 3 090w, 3 060w, 3 030w, 2 940s, 2 860m, 1 735s, 1 495w, 1 455m, 1 435w, 1 360m, 1 250w, 1 205w, 1 160w, 1 155w, 1 090s, 1 065m, 1 025w, 730s, and 695s cm^{-1}; *m/z* (e.i. m.s.) 91 (100%), 108 (11), 141 (28), 181 (13), 264 (8), and 371 [6 $(M + 1)^+$] (Found: *M*, 370.2150. $C_{23}H_{30}O_4$ requires *M*, 370.2144); $[\alpha]_D^{23}$ +22° (*S*-isomer, *c* 5.1 in CCl_4); $[\alpha]_D^{18}$ −23° (*R*-isomer, *c* 6.3 in CCl_4) (Found: C, 74.9; H, 8.05. $C_{23}H_{30}O_4$ requires C, 74.55; H, 8.15%).

Methyl 6,8-*Dihydroxyoctanoate*.—Methyl 6,8-diphenylmethoxyoctanoate (7.3 g, 19.7 mmol) in methanol (75 cm^3) was added to a suspension of 5% palladium on charcoal (0.3 g) in methanol (25 cm^3). This mixture was placed in a Parr apparatus and hydrogenation (initially 30 p.s.i. hydrogen) was allowed to proceed overnight. Filtration through Celite, and removal of solvent and toluene under reduced pressure left a viscous residue. This was taken up in ether (250 cm^3), dried (sodium sulphate), and re-evaporated to give the dihydroxy ester as a colourless oil (3.53 g, 95%).

An analytically pure sample was obtained by double Kugelrohr distillation: b.p. 120—125 °C at 0.005 mmHg (lit.,[4] b.p. 110—115 °C at 10^{-4} mmHg); $\delta_H(CDCl_3)$ 1.51 (8 H, m, 4 × CH_2); 2.28 (2 H, t, *J* 7.3 Hz, CH_2CO_2Me), 3.62 (3 H, s, OCH_3), 3.35 (3 H, m, CH_2OH + CHOH), and 4.53 (2 H, s, 2 × OH); $\nu_{max.}$(film) 3 370br, 2 940s, 2 870m, 1 735s, 1 460w, 1 435m, 1 420w, 1 363m, 1 195m, 1 175m, 1 150w, 1 095m, 1 055m, 1 001m, and 970m cm^{-1}; *m/z* (c.i. m.s.; NH_3) 130 (3%), 141 (22), 163 (10), 173 (18), and 191 [100, $(M + 1)^+$]; $[\alpha]_D^{22.5}$ −3.9° (*S*-isomer, *c* 2.3 in $CHCl_3$); $[\alpha]_D^{18}$ +4.2° (*R*-isomer, *c* 5.2 in $CHCl_3$) (Found: C, 56.7; H, 9.7. $C_9H_{18}O_4$ requires C, 56.3; H, 9.55%).

Methyl 6,8-*Dimethylsulphonyloxyoctanoate*.—This compound was prepared from methyl 6,8-dihydroxyoctanoate by a standard mesylation procedure[19] and was isolated as a brown oil (5.92 g, 98%): $\delta_H(CDCl_3)$ 1.32—1.87 (6 H, m, 3 × CH_2), 2.07 (2 H, m, CH_2CH_2OMs), 2.28 (2 H, t, *J* 7.3 Hz, CH_2CO_2Me), 3.04 (3 H, s, CH_3SO_2), 3.07 (3 H, s, CH_3SO_2), 3.55 (3 H, s, OCH_3), and 4.32 (2 H, t, *J* 7 Hz, CH_2OMS) and 4.85 (1 H, m, CHOMs); $\nu_{max.}$(film) 3 030m, 2 940s, 2 870m, 1 735s, 1 630w, 1 460w, 1 445m, 1 415w, 1 345s, 1 250w, 1 170s, 1 095m, 970s, 905s, 780s, 765m, 765m, and 725m cm^{-1}.

Methyl Lipoate.—Finely ground sodium sulphide nonahydrate (4.1 g, 17 mmol) and sulphur (0.54 g, 17 mmol) were dissolved in dimethylformamide (40 cm^3). The stirred mixture was heated to 80 °C for 1 h after which the above dimesylate (5.92 g, 17.1 mmol) in dimethylformamide (40 cm^3) was added dropwise. The reaction mixture was maintained at 80 °C for 67 h and then for 17 h at room temperature. The product was isolated by pouring the whole into water (800 cm^3), extracting with light petroleum (b.p. 40—60 °C; 3 × 100 cm^3), drying the combined extracts ($MgSO_4$) and then evaporating the latter under reduced pressure to leave a yellow oil (2.57 g, 68%).

A pure sample for analysis was obtained by preparative t.l.c. (dichloromethane) followed by Kugelrohr distillation: 125—135 °C at 0.9 mmHg; $\delta_H(CCl_4)$ 1.75—1.39 (6 H, m, 3 × CH_2), 1.85 (1 H, m, HCHCH$_2$S), 2.24 (2 H, t, *J* 7.3 Hz, CH_2CO_2Me), 2.40 (1 H, m, HC*H*CH$_2$S), 3.05 (2 H, m, CH$_2$S), 3.47 (1 H, m,

CHS), and 3.60 (3 H, s, OCH_3); $\nu_{max.}$(film) 2 925s, 2 830m, 1 735s, 1 460m, 1 435m, 1 365w, 1 250m, 1 195w, 1 170s, 1 105w, 1 075w, 1 020w, and 885w cm^{-1}; *m/z* (e.i. m.s.) 81 (28%), 87 (6), 95 (30), 113 (9), 123 (46), 155 (26), 189 (22), and 220 (100) (M^+); $[\alpha]_D^{20}$ −103° (*S*-isomer, *c* 1.9 in benzene); $[\alpha]_D^{23}$ +97° (*R*-isomer, *c* 1.8 in benzene).

Lipoic Acid.—Methyl lipoate (2.0 g, 9.1 mmol) was suspended in 0.1M KOH (300 cm^3) which had been saturated with nitrogen. Hydrolysis was achieved over 24 h in the dark with good stirring. After extraction with ether (2 × 50 cm^3) to remove lipophilic impurities, the aqueous phase was acidified to pH 1 by addition of 1M sulphuric acid. The lipoic acid so liberated, was extracted into fresh ether (3 × 50 cm^3). These combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give a yellow oil which solidified with time. This was taken up in boiling pentane and left to crystallize at 5 °C to afford yellow leaflets of lipoic acid (1.01 g, 54%) [22% overall from (*R*)-(2-phenylmethoxyethyl)oxirane]. An analytically pure sample was obtained by a further recrystallisation from pentane: m.p. 46—48.5 °C; $\delta_H(CCl_4)$ 1.52 (2 H, m, CH_2), 1.68 (6 H, m, 3 × CH_2), 1.87 (1 H, m, $HCHCH_2S$), 2.35 (2 H, t, *J* 7.3 Hz, CH_2CO_2H), 2.93 (1 H, m, $HCHCH_2S$), 3.08 (2 H, m, CH_2S), 3.48 (1 H, m, CHS), and 12.06 (1 H, br s, OH); $\nu_{max.}(CCl_4)$ 3 420—2 300br, 2 930s, 2 860m, 1 760w, 1 710s, 1 460w, 1 435w, 1 415m, 1 280m, 1 250brm, 1 115brw, and 930vw cm^{-1}; *m/z* (e.i. m.s.) 81 (100%), 95 (7), 105 (27), 123 (67), 155 (17), 173 (14), and 206 (72, M^+) [Found: (*R*-isomer): 46.8; H, 6.9; S, 31.15. Calc. for $C_8H_{18}O_2S_2$: C, 46.55; H, 6.85; S, 31.1%]; $[\alpha]_D^{23}$ 106° (*R*-isomer, *c* 1.86 in benzene); $[\alpha]_D^{22}$ −117° (*S*-isomer, *c* 2.13 in benzene).

C.D. Spectrum.—Temperature 26.8 °C, 27.4 °C respectively. (*R*)-Isomer +0.076 at 261 nm, −0.074 at 310 nm, +0.132 at 355 nm; concentration 15.9 mg in 10 cm^3 2,2,4-trimethylpentane.

(*S*)-Isomer −0.075 at 261 nm, +0.075 at 312 nm, −0.129 at 355 nm; concentraton 14.2 mg in 5 cm^3 2,2,4-trimethylpentane.

The chiroptical data given are in excellent agreement with the literature values for both enantiomers of α-lipoic acid.[5,15]

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