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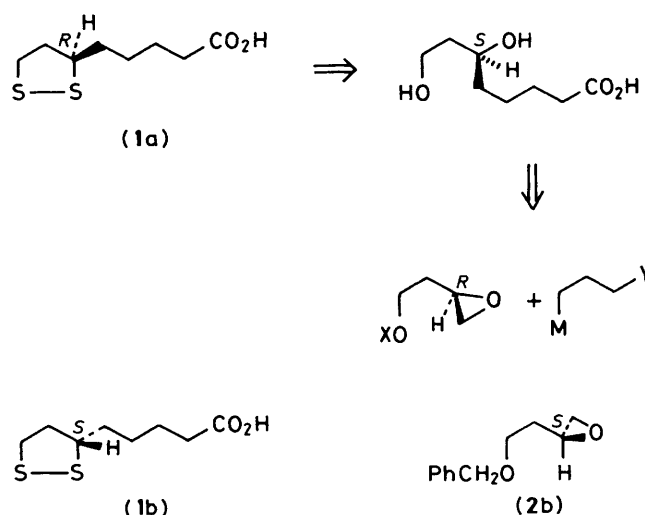
Scheme 1. X = protecting group for OH, Y = masked carboxy group, and M = metallic entity

(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
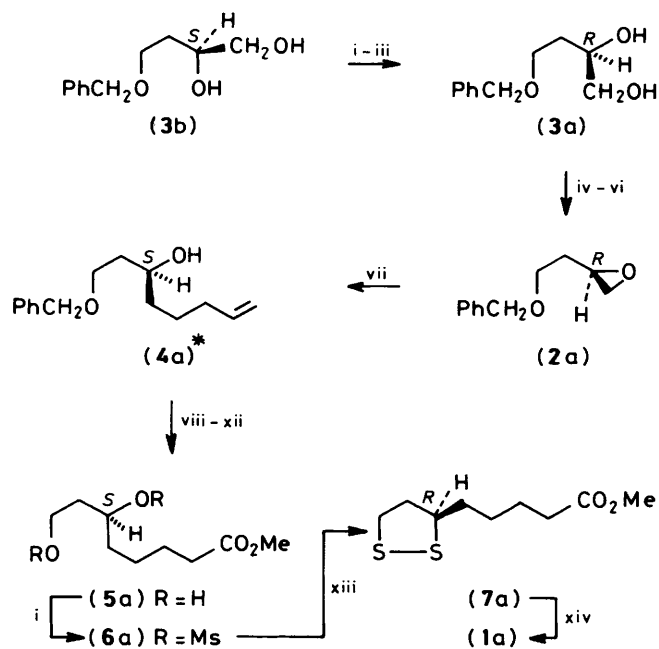
Scheme 2. Compounds (**4b**)—(**7b**) (not drawn) are the enantiomers of compounds (**4a**)—(**7a**) respectively. *Reagents:* i, MeSO$_2$Cl, Et$_3$N; ii, KOAc, Ac$_2$O; iii, K$_2$CO$_3$, MeOH; iv, PhCHO, H$^+$; v, *N*-bromosuccinimide, ClF$_2$CCCl$_2$F; vi, NaOH, HOCH$_2$CH$_2$OH vii, CH$_2$ = CHCH$_2$CH$_2$MgBr, Li$_2$CuCl$_4$ (catalytic), THF; ix, HBSia$_2$, THF, aq. HO$_2$$^-$; x, pyridinium dichromate, DMF; xi, MeOH–HCl; xii, Pd/C, H$_2$; xiii, Na$_2$S, S, DMF; xiv, aq. HO$^-$. Ac = acetyl; THF = tetrahydrofuran; DMF = dimethylformamide; Sia = Pr^{i}C(Me)H$^-$

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-dibromo-octanoate, 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 Micro-stage. I.r. spectra were run on a Perkin-Elmer 257 instrument. [1]H 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-phenyl-methoxyoct-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-phenylmethoxy-butane-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; δ$_H$(CDCl$_3$) 1.90 (2 H, m, C*H*$_2$CH$_2$OBn), 2.93 (6 H, s, 2 × CH$_3$), 3.57 (2 H, m, C*H*$_2$OBn), 4.28 (2 H, m, C*H*$_2$OMs), 4.36 (2 H, s, C*H*$_2$Ph), 4.88 (1 H, m, C*H*OMs), and 7.18 (5 H, s, Ph).

(*R*)-4-*Phenylmethoxybutane* 1,2-*diyl Diacetate.*—The di-mesylate 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%); δ$_H$(CCl$_4$) 1.81 (2 H, m, C*H*$_2$CH$_2$OBn), 1.92 (3 H, s, CH$_3$), 1.96 (3 H, s, CH$_3$), 3.42 (2 H, m, C*H*$_2$OBn), 3.95 (1 H, dd, J_{gem} 17.1 Hz, J_{vic} 4 Hz, HC*H*OAc), 4.21 (1 H, dd, J_{gem} 17.1 Hz, J_{vic} 5 Hz, *H*CHOAc), 4.40 (2 H, s, C*H*$_2$Ph), 5.12 (1 H, m, C*H*OAc), and 7.23 (5 H, s, Ph); ν$_{max.}$ (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]; [α]$_D$^{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%); [α]$_D$^{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: [α]$_D$^{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-phenylmethoxy-ethyl)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$_2$CO$_3$) 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; δ$_H$(CCl$_4$) 1.30—1.55 (4 H, m, 4- and 5-H), 1.62 (2 H, m, C*H*$_2$CH$_2$OBn), 2.02 (2 H, m, C*H*$_2$CH=), 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; δ_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° CHHPh), 4.45 (1 H, d, J 8.3 Hz, 2° CHHPh), 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 850m, 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; δ_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-OCHHPh), 4.44 (1 H, d, J 8.3 Hz, 6-OCHHPh), and 7.25 (10 H, s, 2 × Ph); $\nu_{max.}$(film) 3 410br, 3 090w, 3 070w, 3 030w, 2 930s, 2 860m, 1 495w, 1 455m, 1 365m, 1 205m, 1 090s, 1 070s, 1 025w, 910w, 735s, and 695s cm^{-1}; m/z (c.i. m.s.; NH$_3$) 18 (100%), 91 (61), 108 (6), 127 (39), 145 (4), 163 (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$_2$SO$_4$) 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); δ_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-OCHHPh), 4.45 (1 H, d, J 8.3 Hz, CHHPh), 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 250m, 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); δ_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$_9$H$_{18}$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%): δ_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$_3$SO$_2$), 3.07 (3 H, s, CH$_3$SO$_2$), 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 940m, 2 870m, 1 735s, 1 630w, 1 460w, 1 445m, 1 415w, 1 345s, 1 250m, 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; δ_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, HCHCH$_2$S), 3.05 (2 H, m, CH$_2$S), 3.47 (1 H, m,

CHS), and 3.60 (3 H, s, OCH$_3$); ν_{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$_2$SO$_4$) 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; δ_H(CCl$_4$) 1.52 (2 H, m, CH$_2$), 1.68 (6 H, m, 3 × CH$_2$), 1.87 (1 H, m, HCHCH$_2$S), 2.35 (2 H, t, J 7.3 Hz, CH_2CO$_2$H), 2.93 (1 H, m, HCHCH$_2$S), 3.08 (2 H, m, CH$_2$S), 3.48 (1 H, m, CHS), and 12.06 (1 H, br s, OH); ν_{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$_8$H$_{18}$O$_2$S$_2$: 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]

Acknowledgements

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