Proof that the Absolute Configuration of Natural α-Lipoic Acid is *R* by the Synthesis of its Enantiomer [(*S*)-(−)-α-Lipoic acid] from (*S*)-Malic Acid

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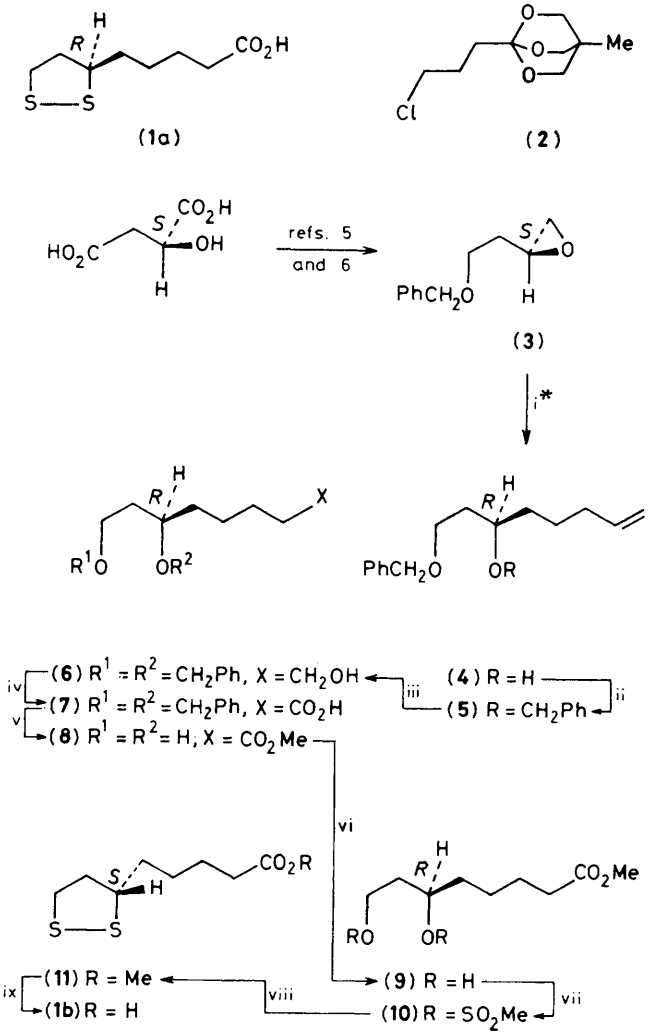
The absolute configuration of natural (+)-α-lipoic acid is confirmed to be *R* by the synthesis of its enantiomer from (*S*)-malic acid.

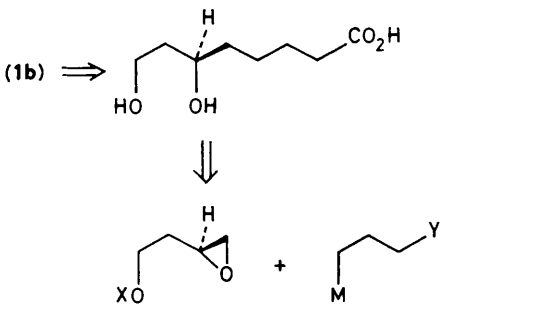
α-(+)-Lipoic acid, the coenzyme for α-ketoacid dehydrogenases,[1] was assigned the (*R*)-configuration (**1a**) by Mislow and Meluch,[2] by comparison of the melting point–composition diagrams for mixtures of (*R*)-(+)-3-methyloctanedioic acid with (+)- and with (−)-3-mercapto-octanedioic acid, respectively. By synthesis, these mercapto-diacids had been correl-



Scheme 1. *Reagents:* i, $CH_2{=}CHCH_2CH_2MgCl$, Li_2CuCl_4 (catalytic), THF; ii, $PhCH_2Br$, NaH, THF; iii, $HBSia_2$, THF, aq. HO_2^-; iv, pyridinium dichromate, DMF; v, MeOH–HCl; vi, Pd/C, H_2; vii, $MeSO_2Cl$, Et_3N; viii, Na_2S, S, DMF; ix, aq. HO^-. THF = tetrahydrofuran; DMF = dimethylformamide; Sia = $Pr^iC(Me)H$–.
* Sequence rule priorities of atoms (groups) at the chiral centre change in this step, although the absolute configuration does not.

ated with (−)- and (+)-α-lipoic acid, respectively. Studies of the biosynthesis of (**1**) by *Escherichia coli* have revealed that if α-(+)-lipoic acid has the (*R*)-configuration, then insertion of sulphur at C-6 of octanoic acid must occur with inversion of configuration.[3,4] We now report a synthesis of (*S*)-α-(−)-lipoic acid (**1b**) from (*S*)-malic acid (Scheme 1) by a route that features a *single inversion* of configuration at the chiral centre. Thus, Mislow and Meluch[2] were right and the conclusions[3,4] from biosynthetic studies about the stereochemistry of sulphur insertion are validated.

Our strategy to (*S*)-α-(−)-lipoic acid is shown in Scheme 2. Initially, we planned to treat (*S*)-(2-benzyloxyethyl)oxirane (**3**) [prepared from (*S*)-malic acid[5,6]] with an organometallic derivative of 1-(3-chloropropyl)-4-methyl-2,6,7-trioxabicyclo-[2.2.2]octane (**2**).[7] However, neither a Grignard reagent nor an organolithium derivative could be prepared from the orthoester (**2**). Therefore, the epoxide (**3**) was treated (−78 °C, 3 h → room temp., overnight) with but-3-enylmagnesium chloride (3 mol. equiv.) in tetrahydrofuran containing 10 mol % (based on epoxide) of lithium tetrachlorocuprate[8,9] to give



Scheme 2. X = protecting group for OH; Y = masked carboxy-group; M = metallic entity.

6-hydroxy-8-(benzyloxy)oct-1-ene (**4**).† This was benzylated[10] to give 6,8-bis(benzyloxy)oct-1-ene (**5**),† which was hydroborated with di-siamylborane in tetrahydrofuran.[11] The resulting trialkylborane was converted by alkaline hydrogen peroxide[11] into 6,8-bis(benzyloxy)octan-1-ol (**6**),† which was oxidised by pyridinium dichromate in dimethylformamide[12] to give 6,8-bis(benzyloxy)octanoic acid (**7**). Esterification (MeOH–HCl) of (**7**) [→ ester (**8**)†] and removal of benzyl groups (Pd/C, H_2) gave methyl 6,8-dihydroxyoctanoate (**9**),† which was treated with methanesulphonyl chloride and triethylamine in dichloromethane[13] to afford the dimethanesulphonate (**10**). This was converted into (−)-methyl lipoate (**11**)† by treatment with sodium sulphide nonahydrate and sulphur in dimethylformamide.[14] Anaerobic alkaline hydrolysis (0.1 M aq. KOH, room temp., 20 h)[15] in darkness gave a crude product from which α-(−)-lipoic acid could be directly crystallised: m.p. 45—48 °C (lit.[16] m.p. 46—48 °C), $[\alpha]_D^{22}-117°$ (*c* 1.8 in benzene) {lit.[16] $[\alpha]_D^{20}$ − 113° (*c* 1.8 in benzene)}. The circular dichroism of this sample showed $\Delta\epsilon$ − 0.075 (λ 262 nm), +0.075 (312 nm), and −0.12(9) (355 nm) (in 2,2,4-trimethylpentane at 29 °C), which is essentially the mirror image of data published[17] for natural α-lipoic acid. Eliel *et al*,[14] have shown that reactions of Na_2S + S in dimethylformamide with the ditoluene-*p*-sulphonates of *meso*- and *rac*-pentane-2,4-diol, respectively, are processes which effect almost complete inversion at each secondary carbon centre. Hence, the α-(−)-lipoic acid obtained by the sequence described must have the *S*-configuration, and so the absolute configuration of natural (+)-α-lipoic acid is *R*.

It is notable that for the 9-step route described converting the epoxide (**3**) into (−)-α-lipoic acid *none of the intermediates was chromatographed, distilled, or crystallised.*‡ The overall yield from (**3**) to (**11**) was *ca.* 25%. The poorest step in the synthesis is the hydrolysis of the ester (**11**) which proceeded in 53% yield [of twice recrystallised (−)-α-lipoic acid]. Previous syntheses of optically active α-lipoic acids have all relied on resolution of a racemic intermediate.[16,18] Our synthesis shows how one member of the 'chiral pool'[19] of cheap optically pure natural products can be used to make (*S*)-(−)-α-lipoic acid. For the synthesis of (*R*)-(+)-lipoic acid,

† An analytical sample of this compound was obtained by preparative layer chromatography (silica gel PF_{254}) and kugelrohr distillation (where applicable). The compound showed ^1H n.m.r. and i.r. spectra, and an electron impact mass spectrum (including exact mass measurement of M^+), in accord with the assigned structure.

‡ The route described has also been used to prepare in similar overall yield *rac*-α-lipoic acid, m.p. 59.5—62 °C (not depressed on admixture with commercial *rac*-α-lipoic acid, m.p. 59—61 °C) from *rac*-(2-benzyloxyethyl)oxirane [obtained in two steps (benzylation, epoxidation) from but-3-en-1-ol].

among the approaches being studied is the use of (*R*)-but-1-ene-3,4-diol [from (*R*,*R*)-tartaric acid][5] as starting material for the preparation of (*R*)-(**3**).

Added in proof. D. Arigoni and P. Berta have recently independently confirmed that the configuration of natural α-lipoic acid is *R* (D. Arigoni, personal communication).

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References

1 Reviews: U. Schmidt, P. Grafen, K. Altland, and H. W. Goedde, *Adv. Enzymol.*, 1969, **32**, 423; H. Sigel, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 389.
2 K. Mislow and W. C. Meluch, *J. Am. Chem. Soc.*, 1956, **78**, 5920.
3 R. H. White, *Biochemistry*, 1980, **19**, 15; *J. Am. Chem. Soc.*, 1980, **102**, 6605.
4 R. J. Parry and D. A. Trainor, *J. Am. Chem. Soc.*, 1978, **100**, 5243.
5 D. A. Howes, M. H. Brookes, D. Coates, B. T. Golding, and A. T. Hudson, *J. Chem. Res.*, 1983, (*S*), 9; (*M*), 217.
6 J. Mulzer and P. De Lasalle, *J. Chem. Res.* (*S*), 1983, 10.
7 M. P. Atkins, B. T. Golding, D. A. Howes, and P. J. Sellars, *J. Chem. Soc., Chem. Commun.*, 1980, 207 (for a recent application of a 2,6,7-trioxabicyclo[2.2.2]octane as a masked carboxy-group see E. J. Corey and K. Shimoji, *J. Am. Chem. Soc.*, 1983, **105**, 1662).
8 G. Forquet and M. Schlosser, *Angew. Chem., Int. Ed. Engl.*, 1974, **13**, 82.
9 M. P. Atkins, B. T. Golding, A. Bury, M. D. Johnson, and P. J. Sellars, *J. Am. Chem. Soc.*, 1980, **102**, 3630.
10 S. Czernecki, C. Georgoulis, and C. Provelenghiou, *Tetrahedron Lett.*, 1976, 3535.
11 H. C. Brown, S. U. Kulkarni, and C. G. Rao, *Synthesis*, 1980, 151.
12 E. J. Corey and G. Schmidt, *Tetrahedron Lett.*, 1979, 399.
13 R. K. Crossland and K. L. Servis, *J. Org. Chem.*, 1970, **35**, 3195.
14 E. L. Eliel, V. S. Rao, S. Smith, and R. O. Hutchins, *J. Org. Chem.*, 1975, **40**, 524; see also E. L. Eliel, W. H. Pearson, L. M. Jewell, A. G. Abatjoglou, and W. R. Kenan, *Tetrahedron Lett.*, 1980, 331.
15 C. S. Hornberger, R. F. Heitmiller, I. C. Gunsalus, G. H. F. Schnakenberg, and L. J. Reed, *J. Am. Chem. Soc.*, 1953, **75**, 1273.
16 E. Walton, A. F. Wagner, F. W. Bachelor, L. H. Peterson, F. W. Holly, and K. Folkers, *J. Am. Chem. Soc.*, 1955, **77**, 5144.
17 L. A. Neubert and M. Carmack, *Tetrahedron Lett.*, 1974, 3543.
18 D. S. Acker and W. J. Wayne, *J. Am. Chem. Soc.*, 1957, **79**, 6483.
19 D. Seebach and E. Hungerbühler, 'Modern Synthetic Methods,' ed. R. Scheffold, Salle & Sauerländer, Frankfurt am Main, vol. 2, 1980, p. 91.