

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

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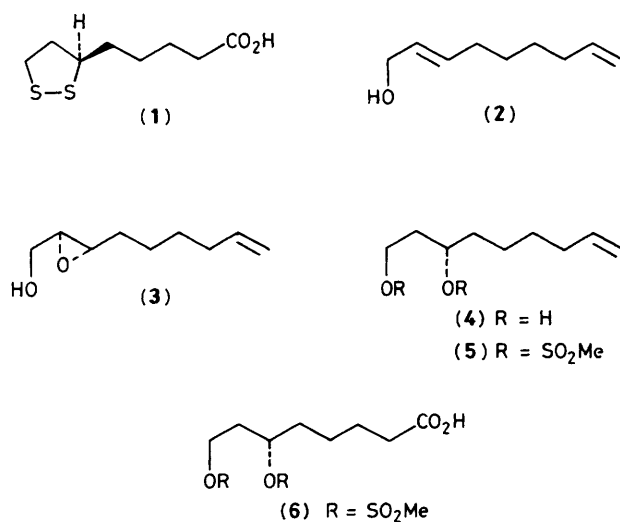
The title compound has been synthesised in an enantioselective manner from achiral precursors using the Sharpless asymmetric epoxidation as the key step in the reaction sequence.

(+)- α -Lipoic acid (+)-(1) is the coenzyme associated with α -ketoacid dehydrogenases.¹ The *R* configuration of (+)-(1) has been confirmed by Golding² by a synthesis of the unnatural (–)-antipode from *S*-malic acid. The first asymmetric synthesis of (+)-(1) was recently reported³ in which the rather expensive (*S,S*)-pentane-2,4-diol was used as the starting material and source of optical activity, but previous syntheses have invariably relied upon resolution of an appropriate racemic precursor.⁴ We report a versatile, efficient, and enantioselective synthesis of (+)-(1) from an achiral precursor using the Sharpless asymmetric epoxidation⁵ to control the absolute configuration at C-3.

Alkylation of the lithio-dianion of propargyl alcohol in liquid ammonia solution with 6-bromohex-1-ene followed by dissolving metal reduction of the resultant disubstituted acetylene⁶ *in situ* gave the allylic alcohol (2) (100% *E* by capillary g.c. analysis) in 78% yield. Catalytic enantioselective epoxidation of alcohol (2) using *L*-(+)-di-isopropyl tartrate [(+)-DIPT] as the chiral auxiliary gave the (2*S*,3*S*)-epoxyalcohol (3) in 82% yield [0.10 equiv. Ti(OPr)₄, 0.12 equiv. (+)-DIPT, 1.2 equiv. *t*-butyl hydroperoxide, CH₂Cl₂, –20 °C, 3 days]. The optical purity of the epoxyalcohol (3) was found to be 96% by capillary g.c. and ¹⁹F n.m.r. analysis of the ester formed by reaction with (*S*)-(–)- α -methoxy- α -trifluoromethylphenyl acetyl chloride.⁷

Reduction of the epoxyalcohol (3) with Red-Al in tetrahydrofuran⁸ resulted in selective formation of the (3*S*)-1,3-diol (4) in 89% yield. Formation of the bis(methanesulphonate) (5) under standard conditions⁹ (96% yield) served the dual role of protection of the alcohol functions during subsequent oxidation of the terminal double bond and provision of a controlling element for introduction of the disulphide linkage at a later stage.

Ruthenium tetroxide oxidation of the terminal double bond of (5) using the catalytic procedure reported by Sharpless¹⁰



resulted in formation of the (3*S*)-acid (6) in 78% yield. Disulphide displacement of the methanesulphonate groups of the potassium salt of the (3*S*)-acid (6) proceeded with inversion of configuration¹¹ at C-3 to give (*R*)-(+)– α -lipoic acid, (+)-(1), m.p. 44–46 °C, [α]_D²⁸ +107° (*c* 0.82, C₆H₆) in 52% yield {lit. values:³ m.p. 43–45 °C, [α]_D²³ +102° (*c* 0.91, C₆H₆)}. The overall yield for this simple six step synthesis is 22%† based on the readily available 6-bromohex-1-ene. Our route

† Compounds (1)–(6) were characterised by ¹H and ¹³C n.m.r. and mass spectrometry, and elemental analysis. The product (1) was purified by recrystallisation from cyclohexane and the m.p., optical rotation, and yield refer to the recrystallised material.

also provides enantioselective access to the (–)-antipode by using D-(–)-isopropyl tartrate as the chiral auxiliary in the epoxidation reaction and to analogues of (1) with predictable absolute stereochemistry.

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References

- 1 L. J. Reed, I. C. Gunsalus, B. G. DeBusk, and C. S. Hornberger, Jr., *Science*, 1951, **114**, 93; 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 M. H. Brookes, B. T. Golding, D. A. Howes, and A. T. Hudson, *J. Chem. Soc., Chem. Commun.*, 1983, 1051. A synthesis of the natural enantiomer has been completed by the same group; we thank Professor Golding for information prior to publication.
- 3 J. D. Elliott, J. Steele, and W. S. Johnson, *Tetrahedron Lett.*, 1985, **26**, 2535.
- 4 E. Walton, A. F. Wagner, F. W. Bachelor, L. H. Peterson, F. W. Holly, and K. Folkers, *J. Am. Chem. Soc.*, 1955, **77**, 5144; D. S. Acker and W. J. Wayne, *ibid.*, 1957, **79**, 6483.
- 5 K. B. Sharpless and T. R. Verhoeven, *Adrichimica Acta*, 1979, **12**, 63; T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, 1980, **102**, 5974; B. E. Rossiter, T. Katsuki, and K. B. Sharpless, *ibid.*, 1981, **103**, 464; K. B. Sharpless, S. S. Woodard, and M. G. Finn, *Pure Appl. Chem.*, 1983, **55**, 1823.
- 6 J. W. Patterson, *Synthesis*, 1985, 337.
- 7 J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543.
- 8 J. M. Finan and Y. Kishi, *Tetrahedron Lett.*, 1982, **23**, 2719.
- 9 R. K. Crossland and K. K. Servis, *J. Org. Chem.*, 1970, **35**, 3195.
- 10 P. H. J. Carlsen, T. Katsuki, V. S. Martin, and K. B. Sharpless, *J. Org. Chem.*, 1981, **46**, 3936.
- 11 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, and A. G. Abatjoglou, *Tetrahedron Lett.*, 1980, 331.