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

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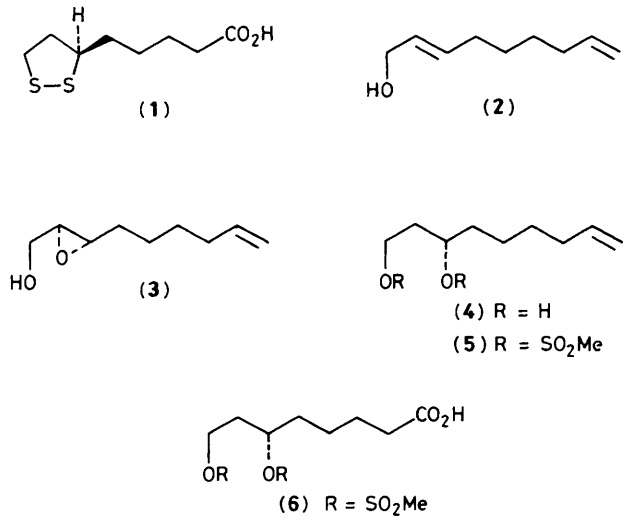
The title compound has been synthesised in an enantioselective manner from achiral precursors using the Sharpless asymmetric epoxidation as the key step in the reaction sequence.

(+)-α-Lipoic acid (+)-(**1**) is the coenzyme associated with α-ketoacid dehydrogenases.[1] The *R* configuration of (+)-(**1**) has been confirmed by Golding[2] by a synthesis of the unnatural (−)-antipode from *S*-malic acid. The first asymmetric synthesis of (+)-(**1**) was recently reported[3] 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 epoxidation[5] 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 acetylene[6] *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. $Ti(OPr^i)_4$, 0.12 equiv. (+)-DIPT, 1.2 equiv. t-butyl hydroperoxide, CH_2Cl_2, −20 °C, 3 days]. The optical purity of the epoxyalcohol (**3**) was found to be 96% by capillary g.c. and ^{19}F 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 tetrahydrofuran[8] resulted in selective formation of the (3*S*)-1,3-diol (**4**) in 89% yield. Formation of the bis(methanesulphonate) (**5**) under standard conditions[9] (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 Sharpless[10]



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 configuration[11] at C-3 to give (*R*)-(+)-α-lipoic acid, (+)-(**1**), m.p. 44—46 °C, $[\alpha]_D^{28}$ +107° (*c* 0.82, C_6H_6) in 52% yield {lit. values:[3] m.p. 43—45 °C, $[\alpha]_D^{23}$ +102° (*c* 0.91, C_6H_6)}.

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 ^{13}C 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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