A Novel Enantiospecific Synthesis of (*S*)-(−)-Methyl 6,8-Dihydroxyoctanoate, a Precursor of (*R*)-(+)-α-Lipoic Acid†

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(*S*)-(−)-Methyl 6,8-dihydroxyoctanoate has been synthesised, with stereocontrolled reduction of methyl 8,8-dimethyl-6-oxo-octanoate using immobilised Bakers yeast as a key step.

The synthesis of (*R*)-(+)-lipoic acid (**8**) has been reported previously, either starting from chiral molecules, using templates, or by the resolution of intermediates.[1] The interesting biological activity of (*R*)-(+)-lipoic acid[2] prompted a synthesis of the enantiomerically pure compound. We now describe a novel, simple, and enantioselective synthesis of (*S*)-(−)-methyl 6,8-dihydroxyoctanoate (**7**) [>99% enantiomeric excess (e.e.)], a precursor of (*R*)-(+)-lipoic acid (Scheme 1). The novelty of the reaction lies in the stereocontrolled reduction of keto acetal (**5**) by Bakers yeast immobilized in calcium alginate beads.[3]‡

Copper catalysed bromoform addition to alkene (**1**)[4] gave methyl 6,8,8-tribromo-octanoate (**2**) (80%) which, on treatment with two equivalents of potassium acetate [18-crown-6, in dimethylformamide (DMF)] resulted in methyl 6-acetoxy-8-bromo-oct-7-enoate (**3**) (85%). Hydrolysis of (**3**) in methanol–K_2CO_3 and oxidation with pyridinium chlorochromate (PCC) gave ketovinyl bromide (**4**) (68%), which was subsequently converted to methyl 8,8-dimethoxy-6-oxo-octanoate (**5**) with *N*-benzyltrimethylammonium hydroxide (Triton B) in methanol. This was enantiospecifically reduced by adding small portions of it in ethanol to a glucose solution (10%) containing Bakers yeast (*Saccharomyces cerevisiae* NCIM 3044) immobilized in calcium alginate beads[5] at pH 4.5—5 over a period of 24 h. The reaction was continued for another 72 h by supplementing the glucose intermittently. During reduction the ester function was hydrolysed, hence the product was extracted from the aqueous medium with diethyl ether, dried, and treated with excess ethereal diazomethane. The crude product, on purification by column chromatography over silica gel, gave (**6**) in 60% yield [based on (**4**)] with >99% e.e. as determined from its Mosher's ester.[6] Compound (**6**), on treatment with H_3PO_4 in acetone followed by $NaBH_4$ reduction, resulted in (**7**) (80%),§ $[\alpha]_D^{25}$ −4.1°

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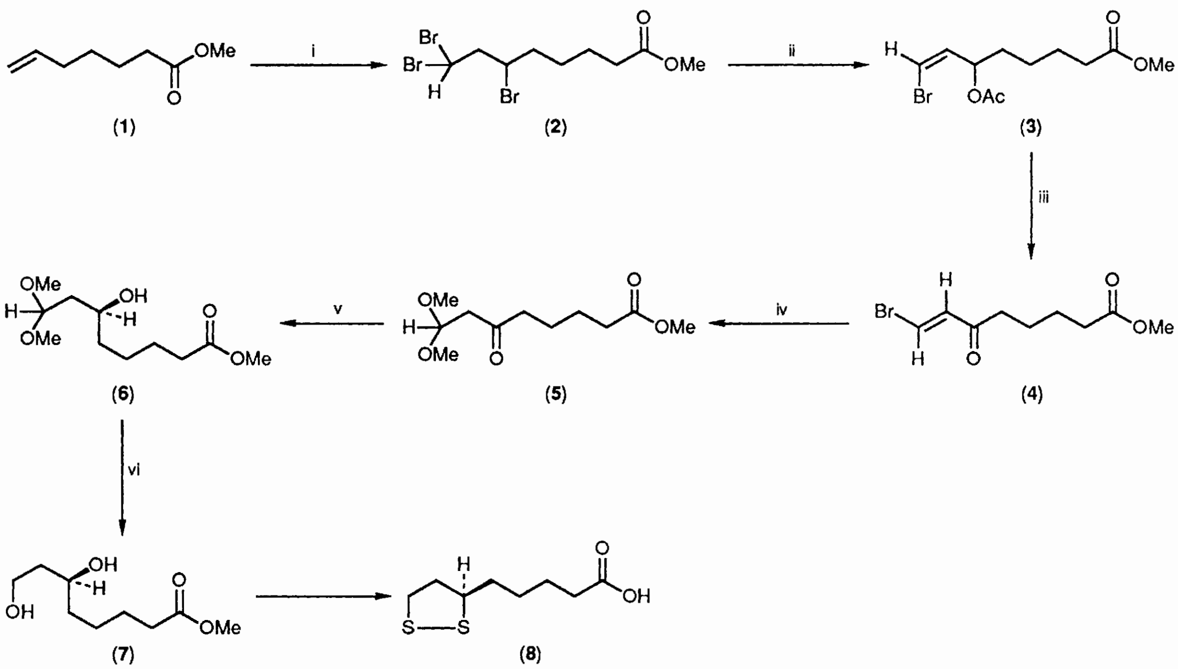
‡ While this manuscript was being prepared another approach based on yeast reduction of a β-ketoester was reported with 82% e.e.[3]

§ All compounds gave satisfactory spectral and analytical data. *Selected ^1H NMR data* ($CDCl_3$, 80 MHz) are as follows. (**3**): δ 1.1—1.2 (m, 6H, 3 × CH_2), 1.9 (s, 3H, $COCH_3$), 2.1 (t, 2H, CH_2–CO_2Me), 3.6 (s, 3H, –CO_2CH_3), 4.9 (m, 1H, *H*–C–OCOMe), 5.9—6.1 (m, 2H, alkenic); (**4**): δ 1.1—1.2 (m, 4H, 2 × CH_2), 2.2 (t, 4H, 2 × CH_2), 3.6 (s, 3H, CO_2CH_3), 6.75 (d, 1H, alkenic HC–CO, *J* 13.5 Hz), 7.5 (d, 1H, alkenic HC–Br, *J* 13.5 Hz); (**5**): δ 1.1—1.2 (m, 4H, 2 × CH_2), 2.2 (t, 4H, 2 × CH_2), 2.8 (d, 2H, HO–C–CH_2–CO), 3.4 (s, 6H, OCH_3), 3.6 (s, 3H, CO_2CH_3), 4.8 (t, 1H, *H*–$COMe_2$); (**6**): δ 1.1—1.2 (m, 6H, 3 × CH_2), 1.5 (br. s, 1H, OH), 2.2 (m, 4H, 2 × CH_2), 2.3 (t, 2H, CH_2–C–OMe), 3.2 (s, 6H, 2 × OCH_3), 3.6 (s, 3H, CO_2CH_3), 3.8 (m, 1H, C*H*OH), 4.7 (t, 1H, *H*–C–OMe); (**7**): 1.1—1.3 (m, 8H, 4 × CH_2), 2.3 (t, 2H, CH_2CO_2Me), 3.6 (s, 3H, CO_2CH_3), 3.6—3.8 (m, 3H, CH_2OH + C*H*OH), 4.7 (br. s, 2H, 2 × OH).



Scheme 1. *Reagents and conditions*: i, Cu, $CHBr_3$; ii, KOAc (2 equiv.), 18-crown-6, DMF; iii, K_2CO_3/MeOH then PCC; iv, Triton B/MeOH; v, immobilised Bakers yeast, pH 4.5—5; vi, H_3PO_4/MeCOMe then $NaBH_4$.

($CHCl_3$) {lit.[1f] $[\alpha]_D^{25}$ −3.9° ($CHCl_3$) for *S*-isomer}. Conversion of (**7**) into (*R*)-(+)-lipoic acid (**8**) has already been achieved by several workers.[1a,b,d—f]

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