Chemoenzymatic Synthesis of Methyl (6*S*)-(−)-6,8-Dihydroxyoctanoate: A Precursor to (*R*)-(+)-α-Lipoic Acid[#]

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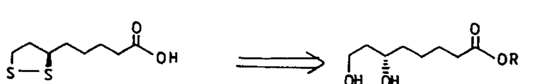
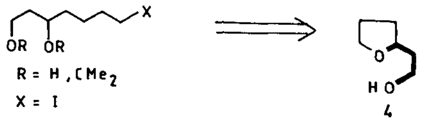
A short synthetic sequence for the preparation of methyl (6*S*)-(−)-6,8-dihydroxyoctanoate, the precursor to (*R*)-(+)-α-lipoic acid is described starting from (2*S*)-(+)-2-(tetrahydro-2-furyl)ethanol.

(*R*)-(+)-α-Lipoic acid (**1**) (thioctic acid; 6,8-dithiooctanoic acid) is an important protein bound coenzyme and growth factor found in animal tissues, plants and microorganisms.[1] The well established biological activity of α-lipoic acid has triggered a burst of efforts towards its synthesis. In general the synthetic routes involved the preparation of the octanoic acid precursors containing halogen, hydroxy or ether groups at C-6 and C-8 positions which on treatment with HI/thiourea or sodium disulfide gave dihydroxylipoic acid followed by oxidation to lipoic acid. The reported methods for the preparation of the above mentioned precursor utilized either Prins reaction[2] or Bayer–Villiger approach[3] to synthesize the dihydroxyoctanoate. The remaining methods also used a multistep approach for the introduction of the 1,3-dihydroxy functionality via several steps.[4] It would be advantageous to build the 1,3-dihydroxy system by a simpler route, with minimum steps and improved yields.



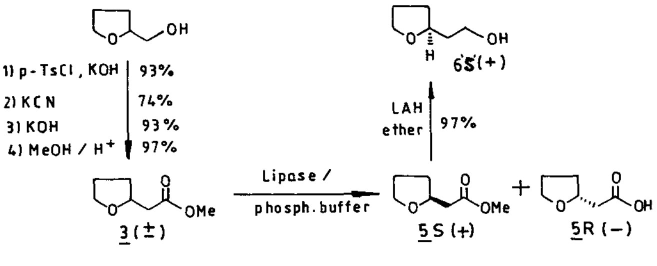
Keeping this in view, a new synthetic strategy for the preparation of 6,8-dihydroxyoctanoate, where the required 1,3-dihydroxy system is generated in a single step, is presented in this communication.

The present strategy consists of a (6 + 2)-approach for the formation of 6,8-dihydroxyoctanoate. The potential 1,3-dihydroxy system present in 2-(tetrahydro-2-furyl)ethanol (**4**) was exploited advantageously to obtain directly the six carbon synthon **7** with the dihydroxy functionality. A suitable two carbon appendage from the appropriate malonate ester should result in the 6,8-dihydroxyoctanoate precursor (Scheme 2).



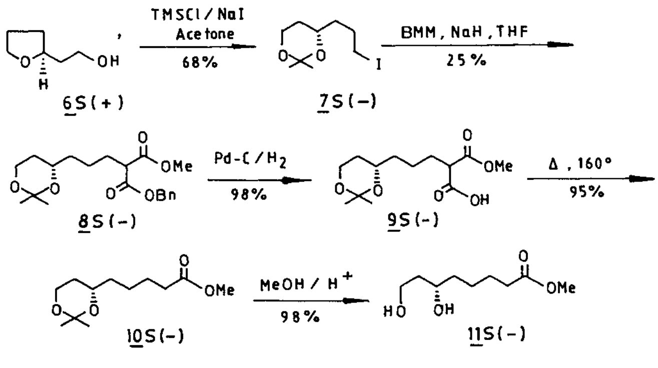
Scheme 1

Preparation of (*R*)-(+)-lipoic acid requires (6*S*)-6,8-dihydroxyoctanoate as the precursor.[7] It should be possible to derive methyl (6*S*)-6,8-dihydroxyoctanoate (**11**) starting from (2*S*)-(+)-(tetrahydro-2-furyl)ethanol (**6**). However, conventional resolution of the racemic 2-(tetrahydro-2-furyl)ethanol (**4**) via the half phthalate ester was reported to give the (*R*)-(−) enantiomer,[5] without any mention of the (*S*)-enantiomer. In the present work, we have adopted kinetic resolution of racemic methyl 2-[tetrahydro-2-furyl]acetate (**3**) with lipase which gave the *S*-ester with high enantiomeric purity and good chemical yield. Thus treatment of the racemic ester **3** with lipase from *Candida cylindracea* [E.C.3.1.1.3] gave (*S*)-(+)-ester **5** in 80 % yield (Scheme 2). (2*S*)-(+)-(Tetrahydro-2-furyl)ethanol (**6**) was obtained by the reduction of (2*S*)-(+)-methyl(tetrahydro-2-furyl)acetate (**5**) with 84 % ee.[9]



Scheme 2

Regioselective opening of **6** with iodotrimethylsilane in acetone[6] gave (4*S*)-(−)-2,2-dimethyl-4-(3′-iodopropyl)-1,3-dioxane (**7**), the desired 6 carbon synthon with a protected diol system in a single step. Alkylation of benzyl methyl malonate (BMM) with **7** gave (4*S*)-(−)-2,2-dimethyl-4-[4′-benzyloxycarbonyl, 4′-methoxycarbonyl)-butyl]-1,3-dioxane (**8**). Sequential debenzylation, decarboxylation and hydrolysis of **8** gave (6*S*)-(−)-methyl 6,8-dihydroxyoctanoate (**11**) with 71 % enantiomeric excess (Scheme 3). The ^{1}H NMR of **11** was in complete agreement with those reported in the literature.[8] The conversion of **11** to (*R*)-(+)-α-lipoic acid is well established in the literature.[4] Thus synthesis of the (6*S*)-(−)-6,8-dihydroxyoctanoate precursor for the preparation of (*R*)-(+)-α-lipoic acid was achieved by a new and shorter route.



Scheme 3

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All solvents were distilled or dried according to the standard laboratory procedures prior to use. Chlorotrimethylsilane was distilled over zinc dust. NMR spectra were recorded on Varian Gemini 200 MHz spectrometer. Mass spectra were recorded on VG micromass 7070H spectrometer. IR spectra were recorded on Perkin-Elmer 221 spectrometer. Lipase was obtained from Sigma Chemicals. All the new compounds were analyzed satisfactorily.

(Tetrahydro-2-furyl)methyl p-Toluenesulfonate: The *p*-toluenesulfonyl derivative was obtained from tetrahydro-2-furylmethanol (51 g, 0.5 mol), *p*-toluenesulfonyl chloride (96 g, 0.503 mol) and KOH (56 g, 1.0 mol) following the reported procedure;[10] yield: 120 g (93%); mp 38 °C (Lit.[10] mp 38–39 °C).

^{1}H NMR ($CDCl_3$): $\delta = 1.70$ (1 H, m), 1.90 (3 H, m), 2.50 (3 H, s), 3.75 (2 H, m), 4.00 (2 H, d, $J = 5$ Hz), 4.05 (1 H, q, $J = 6$ Hz), 7.35 (2 H, d, $J = 8$ Hz), 7.80 (2 H, d, $J = 8$ Hz).

2-(Tetrahydro-2-furyl)acetonitrile:

(Tetrahydro-2-furyl)methyl *p*-toluenesulfonate (62 g, 0.242 mol), KCN (44 g, 0.676 mol) and EtOH (500 mL) were refluxed under stirring for 10 h. The mixture was evaporated in vacuo at 50 °C. The residue was washed with brine (200 mL), water (40 mL) and finally extracted with Et_2O (400 mL). After separation, the aqueous layer was extracted further with Et_2O (3 x 100 mL). The combined ether extracts were washed with brine (2 x 100 mL), dried (Na_2SO_4) evaporated in vacuo and finally vacuum distilled; bp 92 °C to 93 °C/15 Torr (Lit.[10] bp 90 °C–93 °C/15 Torr) to give 2-(tetrahydro-2-furyl)acetonitrile as a colorless liquid; yield: 20 g (93%).

^{1}H NMR ($CDCl_3$): $\delta = 1.75$ (1 H, m), 2.00 (3 H, m), 2.15 (1 H, m), 2.55 (2 H, d, $J = 7$ Hz), 3.98 (2 H, m), 4.10 (1 H, q, $J = 6$ Hz).

IR ($CHCl_3$): $\nu = 2945$, 2870, 2240, 1450, 1410, 1360, 1290, 1070, 960, 920 cm^{-1}.

2-(Tetrahydro-2-furyl)acetic Acid: The acid was obtained by hydrolysis of 2-(tetrahydro-2-furyl)acetonitrile (10 g, 0.090 mol) with KOH (12 g, 0.25 mol) as described in the literature;[10] yield: 10 g (97%).

^{1}H NMR ($CDCl_3$): $\delta = 1.50$ (1 H, m), 1.85 (2 H, m), 2.05 (1 H, m), 2.50 (2 H, m), 3.75 (2 H, m), 4.15 (1 H, q, $J = 6$ Hz), 8.78 (1 H, br).

IR ($CHCl_3$): $\nu = 3400–2800$, 1710, 1400, 1280, 1200, 1160, 1060 cm^{-1}.

Methyl 2-(tetrahydro-2-furyl)acetate (3):

To a solution of 2-(tetrahydro-2-furyl)acetic acid (7 g, 0.058 mol) in MeOH (30 mL) was added conc. H_2SO_4 (1 drop) and this was refluxed for 5 h. The mixture was concentrated under reduced pressure at r.t., diluted with CH_2Cl_2 and washed with water. The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure at r.t. to give **3** as a colorless liquid; yield: 7.5 g (91%).

^{1}H NMR ($CDCl_3$): $\delta = 1.55$ (1 H, m), 1.90 (2 H, m), 2.50 (2 H, m), 3.70 (3 H, s), 3.80 (2 H, m), 4.25 (1 H, q, $J = 7$ Hz).

IR ($CHCl_3$): $\nu = 2940$, 2880, 1730, 1430, 1380, 1200, 1160, 1060, 1010, 980, 820 cm^{-1}.

Enzymatic Hydrolysis of Methyl 2-(Tetrahydro-2-furyl)acetate (3):

Into a phosphate buffer (0.01 M, 0.01 M NaCl, 100 mL), lipase from *Candida cylindracea* [EC 3.1.1.3] (0.100 g) was added under stirring, followed by a methanolic solution of **3** (4.0 g in 10 mL). Stirring was continued at r.t. while adjusting the pH to 7.00 with intermittent addition of 0.1 N NaOH solution. The reaction was terminated after 50% hydrolysis indicated by the consumption of alkali. The reaction mixture was extracted with EtOAc (3 x 50 mL) after adjusting the pH to 8.0. The combined organic extracts were dried (Na_2SO_4), the residue obtained after evaporation was purified by column chromatography (silica gel, benzene/hexane, 9 : 1) to give (2*S*)-methyl(tetrahydro-2-furyl) acetate (**5**); yield: 1.60 g (80%); $[\alpha]_D$ 3.8 ($c = 2$, $CHCl_3$).

The aqueous layer was acidified with conc. HCl, extracted with EtOAc (3 x 35 mL) and purified by column chromatography (hexane/EtOAc, 7 : 3) to give (2*R*)-2-(tetrahydro-2-furyl)acetic acid [(R)-**5**]; yield: 1.75 g (97%); $[\alpha]_D$ -8.1 ($c = 2$, $CHCl_3$).

(2*S*)-(Tetrahydro-2-furyl)ethanol (6):

To a suspension of $LiAlH_4$ (0.700 g, 0.019 mol) in anhyd Et_2O (40 mL) was added a solution of (*S*)-**5** (1.2 g, 0.008 mol) in anhyd Et_2O (5 mL) at -40 °C. The mixture was stirred for 4 h and then quenched by cautious addition of brine (over a period of 30 min). The mixture was stirred for 10 min and the Et_2O layer decanted from the white slurry. The slurry was extracted thoroughly with Et_2O (3 x 50 mL). The combined Et_2O extracts were dried (Na_2SO_4) and evaporated under vacuo to give **6** as a colorless liquid; yield: 1.0 g (97%); $[\alpha]_D$ -4.9 ($c = 2.0$, $CHCl_3$).

^{1}H NMR ($CDCl_3$): $\delta = 1.55$ (1 H, m), 1.76 (2 H, m), 1.95 (3 H, m), 2.70 (1 H, br), 3.75 (3 H, m), 3.85 (2 H, m).

(4*S*)-2,2-Dimethyl-4-(3′-iodopropyl)-1,3-dioxane (7):

To a solution of NaI (2.019 g, 0.012 mol) and **6** (0.726 g, 0.006 mol) in anhyd acetone (25 mL), was added $ClSiMe_3$ (1.731, 0.012 mol) dropwise at 0 °C. The reaction mixture was stirred for 2 h at r.t. and concentrated under vacuo. The residue was taken in Et_2O and washed with 20% $Na_2S_2O_4$ solution (2 x 5 mL) dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by column chromatography over silica gel (hexane/ethyl acetate, 9 : 1) to give **7** as a colorless liquid; yield: 1.2 g (68%); $[\alpha]_D$ -3.5 ($c = 2.0$, $CHCl_3$).

^{1}H NMR ($CDCl_3$): $\delta = 1.30$ (6 H, s), 1.65 (3 H, m), 1.95 (3 H, m), 3.20 (2 H, t, $J = 7$ Hz), 3.70 (1 H, t, $J = 2$ Hz), 4.10 (1 H, dd, $J = 12$ Hz), 4.65 (1 H, q, $J = 5$ Hz).

(4*S*)-2,2-Dimethyl-4-[(4′-benzyloxycarbonyl,4′-methoxycarbonyl)butyl]-1,3-dioxane (8):

To a stirred suspension of NaH (50% suspension in mineral oil, 0.210 g, 0.004 mol) in anhyd THF (50 mL) was added dropwise benzyl methyl malonate (0.828 g, 0.004 mol) and the mixture was stirred for 30 min. The mixture was cooled to -5 °C and the iodide **7** (1.2 g, 0.004 mol) in anhydr. THF (5 mL) was added dropwise. The mixture was stirred further for 24 h, the solvent was removed under reduced pressure and the residue treated with water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under vacuo. The crude product was purified by column chromatography over silica gel (hexane/EtOAc, 9 : 1) to give **8** as a colorless liquid; yield: 0.384 g (25%); $[\alpha]_D$ -2.4 ($c = 2.0$, $CHCl_3$).

^{1}H NMR ($CDCl_3$): $\delta = 1.25$ (6 H, s), 1.45 (6 H, m), 1.90 (2 H, q, $J = 7$ Hz), 3.40 (1 H, *t*, $J = 8$ Hz), 3.70 (4 H, s), 4.00 (1 H, dd, $J = 12$ Hz), 4.60 (1 H, q, $J = 6$ Hz), 5.20 (2 H, s), 7.35 (5 H, s).

MS: $m/z = 273$ ($M^+ - 91$).

(4*S*)-2,2-Dimethyl-4-[(4′-carboxy,4′-methoxycarbonyl)butyl]-1,3-dioxane (9):

To a solution of **8** (0.812 g, 3 mmol) in absolute EtOH (10 mL) was added Pd/C (5%) (0.010 g) and the mixture was stirred under H_2 atmosphere for 24 h. The mixture was filtered and evaporated under vacuo to give **9** as a colorless liquid; yield: 0.10 g (98%); $[\alpha]_D$ -2.9 ($c = 2.0$, $CHCl_3$).

^{1}H NMR ($CDCl_3$): $\delta = 1.25$ (6 H, m), 1.50 (6 H, m), 3.40 (1 H, t, $J = 8$ Hz), 3.75 (4 H, m), 4.10 (1 H, dd, $J = 12$ Hz), 4.70 (1 H, q, $J = 6$ Hz), 6.80 (1 H, br).

MS: m/z 273 ($M^+ - 1$).

(4*S*)-2,2-Dimethyl-4-[(4′-methoxycarbonyl)butyl]-1,3-dioxane (10):

Compound **9** (0.100 g, 0.4 mmol) was taken in a 5 mL round bottomed flask and stirred at 160 °C for 4 h. The residue was purified by column chromatography over silica gel (hexane/EtOAc, 9 : 1) to give **10** as a colorless liquid; yield: 0.080 g (95%); $[\alpha]_D$ -1.7 ($c = 1.0$, $CHCl_3$).

^{1}H NMR ($CDCl_3$): $\delta = 1.25$ (3 H, s), 1.26 (3 H, s), 1.50 (8 H, m), 2.35 (2 H, *t*, $J = 7$ Hz), 3.70 (4 H, m), 4.10 (1 H, dd, $J = 12$ Hz), 4.60 (1 H, q, $J = 6$ Hz).

^{13}C NMR ($CDCl_3$): $\delta = 21.24$, 24.56, 24.86, 31.15, 34.17, 35.66, 54.05, 66.38, 76.22, 98.88, 173.28.

MS: $m/z = 215$ ($M^+ - 15$).

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(6*S*)-Methyl 6,8-Dihydroxyoctanoate (11):

The ester **10** (0.050 g, was dissolved in MeOH (5 mL), a drop of conc. H_2SO_4 was added and the mixture refluxed for 4 h. EtOH was removed under reduced pressure, the residue was taken into CH_2Cl_2, dried (Na_2SO_4) and concentrated to give **11** as a colorless liquid with 71 % ee; yield: 0.075 g (98 %); $[\alpha]_D - 2.8$ ($c = 0.8$, $CHCl_3$) [Lit.[8] $[\alpha]_D - 3.8$].

^1H NMR ($CDCl_3$): $\delta = 1.2-1.7$ (8 H, m), 2.35 (2 H, *t*, $J = 7$), 2.70 (2 H, br), 3.70 (3 H, s), 3.85 (3 H, m).

IR ($CHCl_3$): $v = 3405$, 2926, 1734, 1437, 1200, 1176, 1105, 1057 cm^{-1}.

MS (CI): *m/z* 191 ($M^+ + 1$).

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(1) Yadav, J.S.; Sudha, V.M.; Kamini, G. *J. Sci. Ind. Res.* **1990**, *49*, 400, and references cited therein.

(2) Braude, E.A.; Linstead, R.P.; Woolridge, K.R.H. *J. Chem. Soc.* **1956**, 3074.
Lüttringhaus, A.; Hagele, K. U.S. Patent 2915563; *Chem. Abstr.* **1960**, *54*, 5473.

(3) Serge, A.; Viterbo, R.; Parisi, G. *J. Am. Chem. Soc.* **1957**, *79*, 3503.
Ohara, M.; Yamamoto, K.; Deguchi, Y.; Endo, Y. Japanese Patent 15029; *Chem. Abstr.* **1965**, *63*, 16355.
Lewis, B.A.; Raphael, R.A. *J. Chem. Soc.* **1962**, 4263.

(4) Bullock, M.W.; Brockmann, J.A.; Patterson, E.L.; Pierce, J.V.; von Saltza, M.H.; Sanders, F.; Stokstad, E.L.R. *J. Am. Chem. Soc.* **1954**, *76*, 1828.
Brookes, M.H.; Goldring, B.T.; Howes, D.A.; Hudson, A.T. *J. Chem. Soc., Chem. Commun.* **1983**, 1051.
Rao, A.V.R.; Gurjar, M.K.; Garyali, K.; Ravindranathan, T. *Carbohydr. Res.* **1986**, *148*, 51.
Menon, R.B.; Kumar, M.A.; Ravindranathan, T. *Tetrahedron Lett.* **1987**, *28*, 5313.
Elliot, J.D.; Steele, J.; Johnson, W.S. *ibid.* **1985**, *26*, 2535.
Page, P.C.B.; Rayner, C.M.; Sutherland, I.O. *J. Chem. Soc., Chem. Commun.* **1986**, 1408.
Gopalan, A.S.; Jacobs, H.K. *ibid.* **1989**, *30*, 5705, and references cited in 1.

(5) Hacksell, U.; Stevenson, U.; Nilsson, J.L.G.; Hjorth, S.; Carlsson, A.; Wikstrom, H.; Lindberg, Per.L.; Sachez, D. *J. Med. Chem.* **1979**, *22*, 1481.

(6) Analogous reaction of trimethylsilyl iodide in acetone with (tetrahydro-2-furyl)methanol was first reported to give a protected 1,2-diol system:
Amouroux, R.; Jatczak, M.; Chastreete, M. *Bull. Soc. Chim. Fr.* **1987**, 505.
Amouroux, R.; Jatczak, M.; Chastreete, M. *Tetrahedron Lett.* **1985**, *26*, 2315.

(7) The conversion of (6*S*)-6,8-dihydroxyoctanoate to (*R*)-(+)-lipoic acid involved inversion of configuration at C-6 as reported by White:
White, R.H. *J. Am. Chem. Soc.* **1980**, *102*, 6605.

(8) Dasaradhi, L.; Fadnavis, N.W.; Bhalerao, U.T. *J. Chem. Soc., Chem. Commun.* **1990**, 729.

(9) Jarvest, R.L.; Barnes, R.D.; Earshaw, D.L.; O'Toole, K.J.; Sime, J.T.; Vere Hodge, R.A. *J. Chem. Soc., Chem. Commun.* **1990**, 555.
We thank Dr. N.W. Fadnavis for supplying the enzyme lipase and for helpful discussions. The configuration of **5** was established based on the sign of rotation [Lit.[5] (*R*)-(+) alcohol: $[\alpha]_D - 5.8$]. Ee of the alcohol was calculated based on the above value.

(10) Barger, G.; Robinson, R.; Smith, L.R. *J. Chem. Soc.* **1937**, 718.

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