Enzyme Based Chirality Induced Asymmetric Synthesis of *R* (+)-α-Lipoic Acid

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Abstract: In the present work novel and efficient protocol comprise of enzyme based chirality induced asymmetric synthesis of R(+)-α-Lipoic Acid and S(-)-α-Lipoic Acid is proved via lipase catalyzed resolution of a key synthon (±) ethyl 6,8-dihydroxyoctanoate through 51% overall yield

Index terms: *Lopoic Acid, Lipase, Resolution*

1. INTRODUCTION:

Synthesis of optically active compounds is always of immense interest due to their pharmaceutical significance and out of the two; one enantiomer exhibits enhanced therapeutic properties over the other. Hence in vivo activity study of both enantiomers is a prerequisite for regulatory approval and the provision of a single enantiomer is often essential. In the light of this fact we have decided to perform a synthesis of *R*(+)α-Lipoic-acid **(Figure 1).**

α-Lipoic Acid is a yellow coloured organosulfur compound derived from octanoic acid with two sulfur atoms (at C_6 and C_8) connected by a disulfide bond (Figure 1). Hence it is also called as thiooctic acid. The carbon atom at C_6 is chiral center in the molecule and it exists as two enantiomers (R)(+)- α Lipoic acid (**1a**) and (S)(-)- α -Lipoic acid (**1b**) and as a racemic mixture (±)-α-Lipoic Acid (1). Only the (*R*)-(+)-α-Lipoic Acid enantiomer is natural and essential cofactor of four mitochondrial enzyme complexes. Endogenously synthesized (*R*)-(+)-α-Lipoic Acid is essential for aerobic metabolism.

Both *R* and *S* Lipoic Acid are available as over the counter nutritional supplements and have been used nutritionally and clinically since the 1950s for various diseases and under different conditions[1,2].*R*(+)-α-Lipoic Acid has been shown to possess antioxidant activity[3,4] as well as an inhibitory activity against HIV replication and cancer.[5]Interplay between Lipoic Acid and gluathione in the guardian-ship against lipid peroxidation and metal toxicity has also been proved efficient against metal poisoning. Moreover, *R*(+)-α-Lipoic Acid is used to a great extent in the treatment of various diseases such as alcoholic liver diseases,[7,8] food poisoning,[9,10,6]diabetes, and neurodegenerative disorders[11]. This simplicity and broad spectrum pharmaceutical significance of *R*(+)-α-Lipoic Acid have dragged attention of many research groups. Hence various syntheses of (±)-α-Lipoic Acid are reported[23] and still it is molecule of high interest. **(Figure 2)**[12–25]

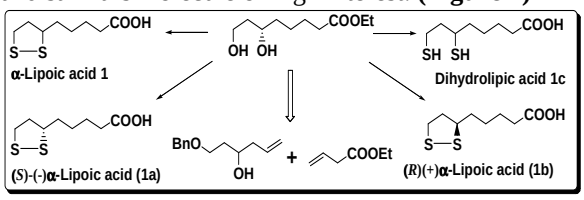

Figure 1: (R)(+)α Lipoic acid (1a) and (S)(-)- α -Lipoic acid (1b)

2. LITERATURE REVIEW:

Reed and co-workers reported the isolation of α-Lipoic Acid in 1951 from liver residue. Although chemical structure of α-Lipoic Acid was determined, its absolute configuration *R* was not known till Golding's synthesis of complementary enantiomer from *S*-malic acid in1983.

From the literature review it is clear that syntheses of (±)-α-Lipoic Acid as well as respective chiral isomers is carried out by chemical as well as chemoenzymatic methods. All of the reported protocols are comprised with either complex sequence of reactions with low overall yield and high cost or toxic reaction conditions **(Figure 2)**

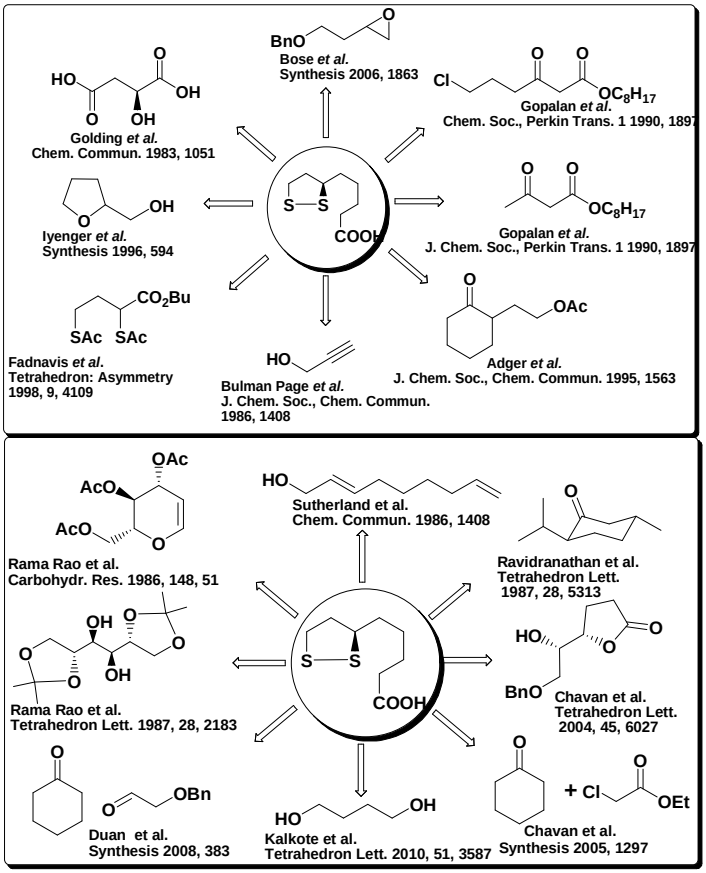

Figure 2: Literature Review

3. PRESENT WORK:

Protocol: (Overall Yield: 39%):

As per depicted in the retro-synthesis; protocol is initiated via mono protection of propane diol to yield

3-(benzyloxy)propan-1-ol (3) which on oxidation provided 3-(benzyloxy)propanal (4). Int 4 is subjected to Barbier allylation to yield Int-5 (benzyloxy) hex-5-en-3-ol which is further converted to ethyl 6,8- dihydroxy ocanoate(7)

With reference to various protocols reported for cross metathesis; H.G. ruthenium catalyst is used in the present protocol for better yield and integrity **(Fig-3).** Further the dihydroxyl intermediate (7) is transformed to (±)-α-Lipoic acid by simple functional group interconvertion. Steps involved in the Cross metathesis are summarized in the **Figure 3** as follows.

Step-1: Tandem cross metathesis and rearrangement.

- Argon bubbling is carried out to activate catalyst and remove radical poisons present in the reaction mass .
- Cross metathesis is carried out by reflux of reaction mass at 80^{o}C and progress of the RM is carried out by GCMS.

Step2: Recovery of solvent: Tandem thermodynamic rearrangement; β-γ to α-β conjugation (Scheme-1/step-d) and recovery of organic solvent are carried out by distillation of solvent EDC.

Step3: Purification: Removal of catalyst and isolation of product from the crude RM is carried out by column chromatography.

- Further standardization of protocol over small scale and implementation over the large scale is carried out.
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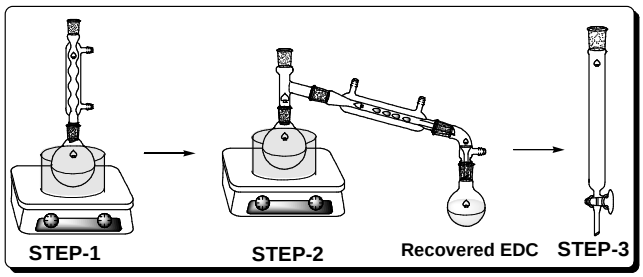
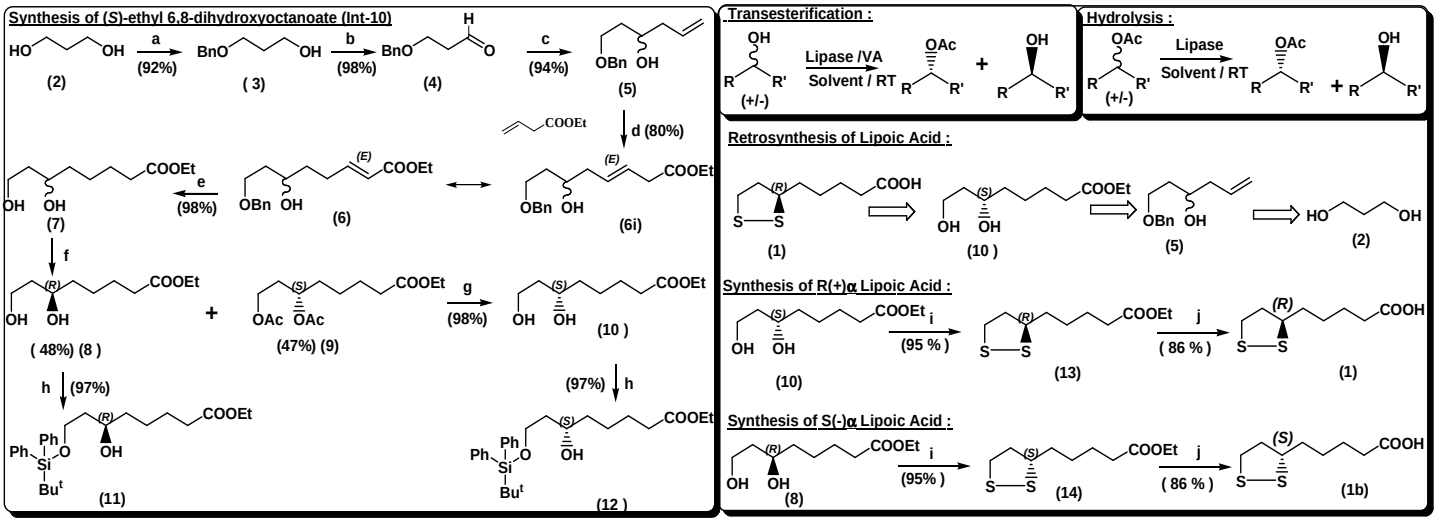


Fig 3: Schematic presentation of Step-d cross metathesis

After standardization of protocol; *R* and *S* isomers of the (±)-α-Lipoic acid are synthesized by enzymatic resolution of a key precursor (±)ethyl 6,8-dihydroxy octanoate (Int-7) (Table-1). During resolution int-7 is scrutinized under various enzymes along with different reaction conditions and it is observed that trans-esterification by using vinyl acetate and Lipase is the most suitable reaction condition. The versatility of enzymes Lipase is attributed to their 1) high catalytic efficiency 2) high regioselectivity and chiral recognition, 3) high stability, 4) reversible mode of action 5) non-toxicity, and 6) low cost.As described in the **(Table-1)** direct trans-acylation of the chiral and terminal hydroxyl group, instead of etherifying the remote carboxylic group *via*, using a commercially available immobilized lipase CAL is found to be most efficient. Further optical purity of each intermediate obtained is determined by chiral HPLC analysis of respective TBDPS derivative **(Scheme-1)**.

Enzyme	**Time in Hrs**	**Conversion (%)**	**Int-8**		**Int-10**	
			e.e	**% Yield**	**e.e**	**% Yield**
Novazyme	48	47	86	48	86	48
CRL	72	48	81	48	81	48
CCL	24	46	89	47	89	47
PPL	24	48	71	48	71	48
PLE	12	49	79	49	79	49
CAL	**24**	**49**	**99**	**49**	**99**	**49**

Table-1: enzymatic resolution: Int-7+VA +Enzyme at 30±1 ◦C; b: e.e by HPLC Chiracel OD (4.6mm I.d.×25 cm, λ = 254nm,1mL/min. **Reaction Conditions: [(±) ethyl 6,8-dihydroxy octanoate (0.5 g)+Enzyme (0.5 g)+Vinyl Acetate (20 mL)]**



Scheme 1: Reagents and conditions:
(a)NaH, BnBr, THF; (b) PCC, DCM, Celite; (c) Allyl-Br, Zn, THF, aq NH_4Cl; (d) Ru-HG, EDC, Reflux 24hrs; (e) H_2, Pd-C, EtOAc. (f) CAL, Vinyl Acetate; (g) K_2CO_3, MeOH, RT; (h) TBDPS-Cl, Im, DCM, RT; (i) S, Na_2S, DMF, Reflux 2hrs; (j) KOH, EtOH RT.

4. CONCLUSION:

In the present investigative protocol enzyme based chirality induced asymmetric synthesis of *R*(+)-α-Lipoic Acid and *S*(-)-α-Lipoic Acid is achieved from cheap and commercially available propanediol (2) as convenient starting synthon with **51%** yield.

Although enzymatic resolution of diol (7) is the key step in the sequence, tandem cross metathesis and isomerisation of unsaturation; β-γ to α-β conjugation (step-d) conquers the efficiency of protocol. All reactions are operative, simple and can be carried out by using table top reagents with high integrity.

5. EXPERIMENTAL DETAILS:

All physical constants are corrected. Enantiomeric excess (e.e.) were determined by chiral HPLC; performed under the following condition: Chiracel OD (4.6mm I.d.×25 cm] λ = 254 nm, flow rate1 mL/min; mobile phase: hexane:isopropanol 95:05. Pig liver ester-ase (PLE), Porcine Pancreatic Lipase (PPL), Candida Cylindracea Lipase (CCL) Candida Antartica Lipase (CAL); Chirazyme were procured from Sigma; Infrared spectra were recorded with ATIMATT-SON RS-1FT-IR spectro-photometer. 1HNMR and 13CNMR spectra were recorded on Bruker AC 200, TMS as an internal standard.

6. EXPERIMENTAL PROCEDURE:

6.1. Preparation of 3-(benzyloxy) propan-1-ol (3):

To the stirred solution of propanediol (**2)** (25gm, 0.329 mol) in THF (200 mL) sodium hydride (60 %, 16.45 gm, 0.411 mole, 1.25 eq) was added at 0°C and stirred for 30 min. After ½ hour calculated amount of benzyl bromide (70.32 gm, 0.411 mol, and 1.25 eq.) and catalytic amount of TBAI was added and stirring continued further at the same temperature for 6 hr. Progress of the reaction was monitored by TLC. After completion; the reaction was quenched by addition of ice at 0°C and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with water (3 x 10 mL), brine, dried over anhydrous Na_2SO_4 and concentrated on rotary evaporator to get the crude residue. The crude residue was purified by silica gel column chromatography using petroleum ether/ ethyl acetate (8:2) as eluent to afford, 3-(benzyloxy)-propan-1-ol **(3).**

Yield: 50.24 gm (92%); colourless oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.24 (s, 1H), 2.39-2.52 (m, 2H), 3.06 (m, 2H), 4.02 (t, *J*= 6.06 Hz, 2H), 5.00 (s, 2H), 7.83 (bs, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 32.02, 61.24, 68.87, 73.06, 127.53, 128.30, 137.97 ppm; Elemental Anal.Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.30; H, 8.45.

6.2. Preparation of 3-(benzyloxy)propanal (4):

To the stirred solution of 3-(benzyloxy)-propan-1-ol **(3)** (40 gm, 0.24 mol) in anhydrous DCM (500 mL); PCC (69.6 g, 0.3 mol, 1.25 eq) was added and reaction mass left for stirring at room temperature for ½ hr. Progress of the reaction was monitored by TLC. After complete conversion; stirring was stopped and the reaction mixture was filtered through celite bed. The celite bed was washed with DCM (50 mL), and collected with filtrate. Combined organic layers were dried over anhydrous sodium sulphate and evaporated over rotary evaporator to afford crude residue. The crude residue was purified by alumina gel column chromatography using petroleum ether/ ethyl acetate (95: 5) as eluent to afford 3-(benzyloxy)-propanal **(4)**.

Yield: 38.72 gm (98%); yellow viscous oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.77-1.90 (m, *J*= 7.08 Hz, 2H), 3.69 (t, *J*= 6.98 Hz, 2H), 4.68 (s, 2H), 7.21 (s, 5H), 9.65 (t, *J*= 1.52 Hz, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 32.02, 68.87, 73.06, 127.53, 128.30, 137.97, 201.49 ppm.

6.3. Preparation of 1-(benzyloxy)-hex-5-en-3-ol (5):
To the stirred solution of aldehyde **4** (30 gm, 0.183 mol) in THF, aq ammonium chloride (30 gm/ 100 ml) and Zn granules (23.42 gm, 0.366 mmol, 2 eq) were added. After ½ hr calculated amount of allyl bromide (43.92gm, 0.366 mol, 2 eq) was added slowly portion wise over 30 min, at 30 °C and stirring was continued further for 6 hrs. Progress of the reaction was monitored by TLC. After completion; the reaction mass extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with water (3X10mL), brine, dried over anhydrous Na_2SO_4 and concentrated on rotary evaporator to get the crude residue. The crude residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate (8:2) as eluent to furnish, 1-(benzyloxy)-hex-5-en-3-ol **(5)**.
Yield: 35,42 gm (94%); yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.65-1.71 (m, *J*= 6.06 Hz, 2H), 2.15 (t, *J*= 6.71 Hz, 2H), 2.88 (s, 1H), .51-3.63 (m, 2H), 3.74-3.80 (m, 1H), 4.43 (s, 2H), 4.97-5.07 (m, 2H), 5.64-5.85 (m, 1H), 7.21-7.25 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 35.82, 41.87, 68.70, 70.06, 73.17, 117.42, 127.54, 127.61, 128.33, 134.78, 137.88 ppm. Elemental Anal.Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.74; H, 8.84.

6.4.Preparation of (E)-ethyl 8-(benzyloxy)-6-hydroxyoct-2-enoate (6): Ethyl but-3-enoate (1.106 gm, 0.0097 mol, 2eq.) was added to stirred solution of 1-(benzyloxy)-hex-5-en-3-ol (5). (1gm,0.00485 mol) in EDC (100 mL) under Argon atmosphere. This is followed by addition of Hoyeda Grubbs catalyst (10%) and the reaction mixture kept on stirring for another 24 hrs at reflux point of solvent. Progress of the reaction was monitored by TLC. During progress of the reaction formation of (E)-ethyl 8-(benzyloxy)-6-hydroxyoct-3-enoate (6i) (β-γ) unsaturated ester which further undergoes *in-situ* rearrangement to yield conjugated isomer. After completion the reaction mixture was filtered through the celite bed, concentrated under vacuum to obtain crude product. The crude residue was purified by silica gel flash column chromatography to afford (E)-ethyl 8-(benzyloxy)-6-hydroxyoct-2-enoate (6).
Yield: 1.13 gm (80%); yellow viscous oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.21 (t, *J*= 7.07 Hz, 3H), 1.30-1.80 (m, 4H), 2.10-2.37 (m, 2H), 3.05 (s, 1H), 3.52-3.82 (m, 3H), 4.10 (q, *J*= 7.20 Hz, 2H), 4.45 (s, 2H), 5.76 (d, *J*= 15.66 Hz, 1H), 6.84-6.99 (m, *J*= 15.66 Hz, 1H), 7.21-7.27 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.22, 28.26, 35.50, 36.39, 60.14, 69.14, 70.68, 73.35, 121.45, 127.65, 128.45, 137.70, 148.86, 166.68 ppm; Elemental Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.89; H, 8.31.

6.5. Preparation of (E)-ethyl-6, 8-dihydroxyoctanoate (7):
To the stirred solution of (E)-ethyl 8-(benzyloxy)-6-hydroxyoct-2-enoate (6) **(**7.00 gm, 0.0183 mol) in ethyl acetate (50 mL) was added 10% Pd/C (100 mg) and stirred under H_2 balloon pressure for 2hrs. Progress of the reaction was monitored by TLC. After completion, the reaction mixture was filtered through a bed of celite, concentrated under vacuum to obtain crude residue. The crude residue was purified by chromatography to afford ethyl 6,8-dihydroxyoctanoate **(7).**
Yield: 4.89 gm (98%); yellow viscous oil; IR ($CHCl_3$) ν_{max} 3020, 2400, 1731, 757 cm^{-1}; ^{1}H NMR (200 MHz,$CDCl_3$): δ 1.18 (t, *J*= 7.20 Hz, 3H), 1.36-1.43 (m, 4H), 1.54-1.69 (m, 4H), 2.25 (t, *J*= 7.30 Hz, 2H), 3.52 (bs, 2H), 3.70-3.84 (m, 3H), 4.05 (q, *J*= 7.21 Hz, 2H); ppm. Elemental Anal.Calcd for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found: C, 58.84; H, 9.92.

6.6. Enzymatic resolution of ethyl 6, 8-dihydroxyoctanoate (7)
To the solution of ethyl 6, 8-dihydroxyoctanoate (**7**) (0.500 gm, 0.0025 mol) in TBME, was added vinyl acetate (0.4365 gm, 0.005 mol) and enzyme CCL and the reaction was stirred for 48 hrs. The progress of the reaction was monitored by TLC. After 50% *trans* acylation (50% consumption of starting material) the reaction was stopped and filtered over celite bed. Celite bed was washed with ethyl acetate and all washings along with filtrate collected together and concentrated under vacuum to get crude residue. Crude residue on flash column chromatography gave **8** and **9**.

(*R*)-Ethyl-6, 8-dihydroxyoctanoate (8)
Yield: 240 mg (48%); yellow viscous oil; $[\alpha]_D$= +1.21 (c 2.00, Benzene){Lit[4] $[\alpha]_D$= +1.23 (c 1.62, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3020, 2400, 1731, 757 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.18 (t, *J*= 7.29 Hz, 3H), 1.33-1.47 (m, 4H), 1.54-1.69 (m, 4H), 2.25 (t, *J*= 7.19 Hz, 2H), 3.52 (bs, 2H), 3.70-3.84 (m, 3H), 4.05 (q, *J*= 7.21 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.23, 27.95, 28.27, 30.51, 35.49, 36.29, 60.14, 69.18, 73.35, 172.95 ppm.; Elemental Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found: C, 58.85; H, 9.91.

(*S*)-Ethyl-6, 8-diacetoxyoctanoate (9)
Yield: 338 mg (48%); yellow solid; mp 48°C; $[\alpha]_D$= +12.20 (c 1.00, $CHCl_3$){Lit.[5]$[\alpha]_D$= +12.80 (c 1.00 , $CHCl_3$)}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, *J*= 7.16 Hz, 3H), 1.31-1.35 (m, 2H), 1.39-146 (m, 4H), 1.52-1.72 (m, 4H), 2.05 (s, 6H), 2.30 (t, *J*= 7.29 Hz, 2H), 4.07-4.41 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.22, 20.98, 24.75, 25.12, 29.67, 34.19, 36.37, 37.01, 60.26, 61.72, 68.35, 171.49, 172.21, 173.71 ppm. Elemental Anal. Calcd for $C_{12}H_{22}O_5$: C, 58.52; H, 9.00; Found: C, 58.49; H, 9.04.

6.7. Preparation of (S) ethyl-6, 8-dihydroxyoctanoate (10)
To the stirred solution of (*S*)-Ethyl-6, 8-diacetoxyoctanoate (9) (0.289 gm, 0.001mole) in methanol; potassium carbonate (0.274 gm, 0.002mole) was added and stirred at room temperature for 3 hrs. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was filtered over celite bed washed with methanol and all washings along with filtrate were concentrated together under vacuum to get crude residue. The resulting residue was purified by using silica gel

column chromatography and ethyl acetate-petroleum ether (25:85) as an eluent, to afford (S) ethyl-6, 8-dihydroxyoctanoate (10).

Yield: 200 mg (98%); yellow viscous liquid; $[\alpha]_D$= -0.9 (c 2.00, $CHCl_3$){Lit.[4] $[\alpha]_D$= -1.23 (c 1.62, $CHCl_3$)}; IR ($CHCl_3$) ν_{max} 3018, 2934, 1701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.18 (t, *J*= 7.29 Hz, 3H), 1.33-1.47 (m, 4H), 1.54-1.69 (m, 4H), 2.25 (t, *J*= 7.19 Hz, 2H), 3.52 (bs, 2H), 3.70-3.84 (m, 3H), 4.05 (q, *J*= 7.21 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.23, 27.95, 28.27, 30.51, 35.49, 36.29, 60.14, 69.18, 73.35, 76.36, 172.95 ppm. Elemental Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found: C, 58.85; H, 9.91.

6.8. Preparation of (R) ethyl 8-((tert-butyldiphenylsilyl)-oxy)-6-hydroxyoctanoate (11)

To the stirred solution of (R) ethyl-6, 8-dihydroxyoctanoate **(8)** (200 mg, 0.009798 mol) in dry DCM (20 mL) was added imidazole (133 mg, 0.0195 mol, 2 eq) at 0°C. After stirring for 30 min, TBDPS-Cl (268 mg, 0.0097 mol, 0.27ml, 1 eq) was added portion wise with syringe and further stirring was continued for 12 hr at the same temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with cold water at 0°C and extracted with DCM (40 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get the crude residue. The crude residual oil was purified by silica gel column chromatography using petroleum ether/ ethyl acetate (75:25) as eluent to furnish (R)-ethyl 8-((tert-butyldiphenylsilyl)oxy)-6-hydroxyoctanoate **(11).**

Yield: 366 mg (97 %); yellow viscous oil; ^1H NMR (400 MHz, $CDCl_3$): δ 0.97 (s, 9H), 1.18 (t, *J*= 7.15 Hz, 3H), 1.34-1.41 (m, 4H), 1.55-1.62 (m, 4H), 2.24 (t, *J*= 7.40 Hz, 2H), 3.29 (brs, 1H), 3.75-3.84 (m, 3H), 3.99-4.10 (q, *J*= 7.16 Hz, 2H), 7.25-7.37 (m, 5H), 7.58-7.62 (m, 5H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.22, 18.97, 24.95, 25.11, 26.76, 34.29, 37.09, 38.23, 60.18, 63.66, 71.68, 127.76, 129.83, 132.82, 132.92, 135.53, 173.77 ppm.

6.9. Preparation of (S)-ethyl 8-((tert-butyldiphenylsilyl)-oxy)-6-hydroxyoctanoate (12)

To the stirred solution of (S) ethyl-6, 8-dihydroxyoctanoate **10** (192 mg, 0.009412 mol) in dry DCM (20 mL) was added imidazole (128 mg, 0.018824 mol, 2 eq) at 0 °C. After stirring for 30 min, TBDPS-Cl (258 mg, 0.009412 mmol, 0.25 ml, and 1eq) was added portion wise with syringe and stirred further for 12 hr at the same temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with cold water at 0°C and extracted with DCM (2X20mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get the crude residue. The crude residual oil was purified by silica gel column chromatography using petroleum petrolium ether / ethyl acetate (75:25) as eluent to furnish (S) ethyl 8-((tert-butyldiphenylsilyl)oxy)-6-hydroxyoctanoate **12.**

Yield: 366 mg (97 %); yellow viscous oil; ^1H NMR (400 MHz, $CDCl_3$): δ 0.97 (s, 9H), 1.18 (t, *J*= 7.15 Hz, 3H), 1.34-1.41 (m, 4H), 1.55-1.62 (m, 4H), 2.24 (t, *J*= 7.40 Hz, 2H), 3.29 (brs, 1H), 3.75-3.84 (m, 3H), 3.99-4.10 (q, *J*= 7.16 Hz, 2H), 7.25-7.37 (m, 5H); 7.58-7.62 (m, 5H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.22, 18.97, 24.95, 25.11, 26.76, 34.29, 37.09, 38.23, 60.18, 63.66, 71.68, 127.76, 129.83, 132.82, 132.92, 135.53, 173.77 ppm.

7.0. Preparation of (5*R*)-ethyl-5-(1, 2-dithiolan-3-yl)-pentanoate or (*R*)-ethyl Lipoate (13)

To the stirred solution of ethyl 6, 8-dihydroxyoctanoate **8** (200 mg, 0.49 mmol) in anhydous CH_2Cl_2 (5 mL) was added Et_3N (319 mg, 0.98 mmol) at 0°C and $MeSO_2Cl$ (463 mg, 0.98 mmol) dropwise. Progress of the reaction was monitored by TLC. After completion, the reaction was quenched with water (5 mL) and the organic layer was washed with aq $NaHCO_3$ (2%, 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator to get crude compound. The crude compound was utilized directly in the next reaction. The solution of crude mesylate, finely ground $Na_2S\cdot H_2O$ (410 mg, 0.6 mmol) and sulfur (54 mg, 0.6 mmol) in anhyd DMF (5 mL) was heated at 80°C for 24 hr and then stirred at room temperature for 1hr. The reaction mixture was poured into ice-cold water (15 mL) and was extracted with EtOAc (3×20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and evaporated on rotaryevaporator to furnish crude residue. The crude residue purified by silica gel column chromatography using petroleum ether/ ethyl acetate (9:1) to furnish **13** as yellow oil.

Yield: 217 mg (95%); yellow oil; $[\alpha]_D^{25}$ = +54.31°(*c* 1.00, $CHCl_3$) {Lit.[11] $[\alpha]_D$= +61° (*c* 1.00, $CHCl_3$)}; IR ($CHCl_3$): ν_{max} 3020, 2400, 1731, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, *J* = 7.22 Hz, 3H), 1.45-1.51 (m, 2H), 1.61-1.70 (m, 4H), 1.84-1.93 (m, 1H), 2.30 (t, *J* = 7.46 Hz, 2H), 2.40-2.53 (m, 1H), 3.03-3.20 (m, 2H), 3.49-3.62 (m, 1H), 4.11 (q, *J* = 7.20 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.20, 24.64, 28.70, 34.06, 34.54, 38.43, 40.16, 56.29, 60.25, 173.50 ppm.

7.1. Preparation of (5*S*)-ethyl-5-(1, 2-dithiolan-3yl)-pentanoate [(*S*)-ethyl lipoate] (14)

To the stirred solution of ethyl (*R*) 6, 8-dihydroxyoctanoate **(8)** (200 mg, 0.49 mmol) in anhydous CH_2Cl_2 (5 mL) was added Et_3N (319 mg, 0.98 mmol) at 0°C and $MeSO_2Cl$ (463 mg, 0.98 mmol) dropwise. Progress of the reaction was monitored by TLC. After completion, the reaction was quenched with water (5 mL) and the organic layer was washed with aq $NaHCO_3$ (2%, 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated on rotary evaporator to get crude residue. The crude compound was utilized directly in the next reaction. The solution of crude mesylate, finely ground $Na_2S\cdot H_2O$ (410 mg, 0.6 mmol) and sulfur (54 mg, 0.6

mmol) in anhyd DMF (5 mL) was heated at 80°C for 24 hr and then stirred at room temperature for 1hr. The reaction mixture was poured into ice-cold water (15 mL) and was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and evaporated on rotary evaporator to furnish crude residue. The crude residue purified by silica gel chromatography using petroleum ether/ ethyl acetate (9:1) to furnish **13b** as yellow oil.

Yield: 217 mg (95%); yellow oil; $[\alpha]_D^{25}$ = -50.92^o (*c* 1.00, $CHCl_3$) {Lit.[11] $[\alpha]_D$= -61^o(*c* 1.00, $CHCl_3$)}; IR ($CHCl_3$): ν_{max} 3020, 2400, 1731, 757 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, *J* = 7.22 Hz, 3H), 1.45-1.48 (m, 2H), 1.61-1.70 (m, 4H), 1.88-1.94 (m, 1H), 2.30 (t, *J* = 7.48 Hz, 2H), 2.43-2.49 (m, 1H), 3.08-3.20 (m, 2H), 3.49-3.62 (m, 1H), 4.11 (q, *J* = 7.20 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.20, 24.64, 28.70, 34.06, 34.54, 38.43, 40.16, 56.29, 60.25, 173.50 ppm.

7.2. Preparation of (*R*)-5-(1, 2-dithiolan-3-yl)-pentanoic acid or (*R*)(+)-α-lipoic acid (1a)

To the stirred solution of **13** (110 mg, 0.4694 mmol) in EtOH (5 mL) was added aqueous KOH (0.1 M, 4 mL) and stirred at r. t. for 24 h. After completion of reaction EtOH was evaporated on rotavapor and the reaction mixture was washed with Et_2O (2 x 10 mL) and the aqueous layer was acidified carefully with 6N HCl to pH 2. The product was extracted with Et_2O (2 x 10 mL) and the combined organic phases were dried over Na_2SO_4, filtered and concentrated on a rotary evaporator under reduced pressure to afford crude residue. The resulting residue was purified by silica gel column chromatography using EtOAc-petroleum ether (15:85) as an eluent, to afford **1a** as yellow solid.

Yield: 83 mg (86%); yellow solid; mp 44°C, **(**Lit.[12] mp 44°C**)** ; $[\alpha]_D^{25}$ = +103.18^o (*c* 0.88, Benzene){Lit.[12] $[\alpha]_D$= +102^o(*c* 0.88, Benzene)}; IR ($CHCl_3$): ν_{max} 3021, 2928, 1709, 1409, 1216, 758 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41-1.49 (m, 2H), 1.55-1.75 (m, 4H), 1.81-1.96 (m, 1H), 2.36 (t, *J* = 7.33 Hz, 2H), 2.40-2.53 (m, 1H), 3.03-3.24 (m, 2H), 3.49-3.63 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.35, 28.63, 33.74, 34.55, 38.47, 40.18, 56.25, 179.46 ppm; Elemental Anal. Calcd for $C_8H_{14}O_2S_2$: C, 46.57; H, 6.84; S, 31.80. Found: C, 46.48; H, 6.90; S, 31.82; LCMS: 204.93 $(M-1)^+$.

7.3. Preparation of (*S*)-5-(1, 2-dithiolan-3-yl)-pentanoic acid or
(*S*) (-)-α-Lipoic acid (1b)

To the stirred solution of **14** (100 mg, 0.4267 mmol) in EtOH (10 mL) was added aqueous KOH (0.1 M, 4 mL) and stirred at r. t. for 24 h. MeOH was evaporated on rotavapour and the reaction mixture was washed with Et_2O (2 x 10 mL) and the aqueous layer was acidified carefully with 6N HCl to pH 2. The product was extracted with Et_2O (2 x 10 mL) and the combined organic phases were dried over Na_2SO_4, filtered and concentrated on a rotavapor to afford crude residue. The resulting residue was purified by flash column chromatography (silica gel) using petroleum ether/ ethylacetate (85:15) as an eluent, to afford **1b** as yellow solid.

Yield: 83 mg (86%); yellow solid; mp 44^{o}C, **(**Lit.[12] mp 44°C**)**; $[\alpha]_D^{25}$ = -101.4^o(*c* 0.85, Benzene){Lit.[12] $[\alpha]_D$= -104.4^o (*c* 0.85, Benzene)}; IR ($CHCl_3$): ν_{max} 3021, 2928, 1709, 1409, 1216, 758 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41-1.55 (m, 2H), 1.59-1.75 (m, 4H), 1.81-1.98 (m, 1H), 2.36 (t, *J* = 7.32 Hz, 2H), 2.40-2.53 (m, 1H), 3.03-3.24 (m, 2H), 3.49-3.63 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.35, 28.63, 33.74, 34.55, 38.47, 40.18, 56.25, 179.46 ppm. Elemental Anal. Calcd for $C_8H_{14}O_2S_2$: C, 46.57; H, 6.84; S, 31.80. Found: C, 46.49; H, 6.89; S, 31.79; LCMS: 204.93$(M-1)^+$.

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REFERENCES AND NOTES:

(1) Herbert, A. A.; Guest, J. R. *Arch. Microbiol.* **1975**, *106*, 259.
(2) Reed, L. J. *Compr. Biochem.* **1966**, *14*, 99.
(3) Reed, L. J.; Hackert, M. L. *J. Biol. Chem.* **1990**, *256*, 8971.
(4) Bast, A.; Haenen, G. R. M. M. *Biochim. Biophys. Acta* **1988**, *963*, 558.
(5) Baur, A.; Harrer, T.; Jahn, G.; Kalden, J. R.; Fleckenstein, B. *Klin. Wochenschr.* **1991**, *69*, 722.
(6) Muller, L.; Menzel, H. *Biochim. Biophys. Acta* **1990**, *1052*, 386.
(7) Podda, M.; Tritschler, H. J.; Ulrich, H.; Packer, L. *Biochem.Biophys. Res. Commun.* **1994**, *204*, 98.
(8) Marshell, A. W.; Graul, R. S.; Morgan, M. Y.; Sherlock, S. *Gut* **1982**, *23*, 1088.
(9) Plotzker, R.; Jensen, D.; Payne, J. A. *Am. J. Med. Sci.* **1979**, 283.
(10) Gandhi, V. M.; Wagh, S. S.; Natraj, C. V.; Menon, K. K. G. *J. Biosci.* **1985**, *9*, 117.
(11) Alterkrich, H.; Stoltenburg D. G.; Wagner, H. M.; Herrmann, J. *Neurotoxicol. Tetratol.* **1990**, *12*, 619.
(12) (a) Brookes, M. H.; Golding, B. T.; Howes, D. A.; Hudson, A. T. *J. Chem. Soc., Chem. Commun.* **1983**, 1051. (b) Brookes, M. H.; Golding, B. T.; Hudson, A. T. *J. Chem. Soc., Perkin Trans. 1* **1988**, 9.
(13) Rao, A. V. R.; Gurjar, M. K.; Garyali, K.; Ravindranathan, T. *Carbohydr. Res.* **1986**, *148*, 51.
(14) Rao, A. V. R.; Punrandare, A. V.; Reddy, E. R.; Gurjar, M. K. *Synth. Commun.* **1987**, *17*, 1095.
(15) Rao, A. V. R.; Mysorekar, S. V.; Gurjar, M. K.; Yadav, J. S. *Tetrahedron Lett.* **1987**, *28*, 2183.
(16) Rao, A. V. R.; Mysorekar, S. V.; Yadav, J. S. *Synth. Commun.* **1987**, *17*, 1339.
(17) Elliott, J. D.; Steele, J.; Johnson, W. S. *Tetrahedron Lett.* **1985**, *26*, 2535.
(18) Page, P. C. B.; Rayner, C. M.; Sutherland, I. O. *J. Chem. Soc., Chem. Commun.* **1986**, 1408.
(19) Menon, R. B.; Kumar, M. A.; Ravindranathan, T. *Tetrahedron Lett.* **1987**, *28*, 5313.

(20) Gopalan, A. S.; Jacobs, H. K. *J. Chem. Soc., Perkin. Trans.1* **1990**, 1897.
(21) Laxmi, Y. R. S.; Iyengar, D. S. *Synthesis* **1996**, 594.
(22) Rao, B. V.; Rao, A. S. *Synth. Commun.* **1995**, *25*, 1531.
(23) (a) Adger, B.; Bes, M. T.; Grogan, G.; McCaque, R.;Pedragosa, M. S.; Roberts, S. M.; Villa, R.; Wan, P. W. H.; Willetts, A. *J. Bioorg. Med. Chem.* **1997**, *5*, 253. (b) Chavan, S. P.; Praveen, C.; Ramakrishna, G.; Kalkote, U. R. *Tetrahedron Lett.* **2004**, *45*, 6027. (c) Panchgalle, S. P.; Gogdand, G. F.; Kalkote, U. R. *Tetrahedron Lett.* **2010**, *51*, 3587.
(24) Chavan, S. P.; Shivasankar, K.; Sivappa, R. *J. Chem. Res.* **2004**, 406.
(25) Rieke, R. D.; Uhm, S. J. *Synthesis* **1975**, 452.
(26) Santaniello, E.; Manzocchi, A. *Synthesis* **1977**, 698.
(27) Picotin, G.; Miginiac, P. *J. Org. Chem.* **1987**, *52*, 4796.
(28) Das, J.; Chandrasekaran, S. *Tetrahedron* **1994**, *40*, 11709.
(29) Jackson, A. C.; Goldman, B. E.; Snider, B. B. *J. Org. Chem.* **1984**, *49*, 3988.(30) Lewis, B. A.; Raphael, R. A. *J. Chem. Soc.* **1962**, 42