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: Lipoic 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 C9 and C10) connected by a disulfide bond (Figure 1). Hence it is also called as thiooctic acid. The carbon atom at C9 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 activity3 as well as an inhibitory activity against HIV replication and cancer.3 Interplay between Lipoic Acid and glutathione 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,5,6 food poisoning,9,10,11 diabetes, and neurodegenerative disorders11. 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 reported12 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)](image)

![Figure 2: Literature Review](image)

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). Cross metathesis is carried out by reflux of reagent mass at 80°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.

![Fig 3: Schematic presentation of Step-d cross metathesis](image)

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).

<table>
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<tr>
<th>Enzyme</th>
<th>Time in Hrs</th>
<th>Conversion (%)</th>
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<th>Int-10</th>
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<tr>
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<td>24</td>
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*Table-1: enzymatic resolution: Int-7+VA+Enzyme at 30±1°C; b: e.e by HPLC Chiracel OD (4.6mm l.d.x25 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 NH₄Cl; (d) Ru-HG, EDC, Reflux 24hrs; (e) H₂, Pd-C, EtOAc. (f) CAL, Vinyl Acetate; (g) K₂CO₃, MeOH, RT; (h) TBDPS-Cl, Im, DCM, RT; (i) S, Na₂S, DMF, Reflux 2hrs; (j) KOH, EtOH RT.

**4. CONCLUSION:**

In the present investigational protocol enzyme based chirality induced asymmetric synthesis of \( (+)-\alpha \)-Lipoic Acid and \( (-)-\alpha \)-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 meta-thesis and isomerisation of unsaturation; \( \beta \)-\( \gamma \) to \( \alpha \)-\( \beta \) 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) \( \lambda = 254 \) nm, flow rate1 mL/min; 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 Na₂SO₄ 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-(benzlyoxy)-propan-1-ol (3).

**Yield:** 50.24 gm (92%); colourless oil; \(^1\)H NMR (200 MHz, CDCl₃): \( \delta \) 2.24 (s, 1H), 2.39-2.52 (m, 2H), 3.06 (m, 2H), 5.00 (s, 2H), 7.83 (bs, 5H); \(^13\)C NMR (50 MHz, CDCl₃): \( \delta \) 32.02, 68.87, 73.06, 127.53, 128.30, 137.97 ppm; Elemental Anal.Calcd for C₂₀H₁₄O₂: C, 72.26; H, 8.49. Found: C, 72.30; H, 8.45.

**6.2. Preparation of 3-(benzlyoxy)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 solvent / RT

**Hydrolysis:**

**Synthesis of \( (-)-\) Lipoic Acid:**

**Synthesis of \( (+)-\) Lipoic Acid:**

\[
\begin{align*}
\text{Lipoic Acid} & \quad \text{from (2)} \\
\end{align*}
\]
6.3. Preparation of 1-(benzylthio)-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 (43.92 gm, 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 Na2SO4 and concentrated on rotary evaporator to get crude residue. The crude residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate (8:2) as eluent to furnish, 1-(benzylthio)-5-en-3-ol (5). After completion the reaction mixture was filtered through a bed of celite, washed with MeOH and concentrated on rotary evaporator under H2 balloon pressure for 2hrs. Progress of reaction was monitored by TLC. After 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.

6.4. Preparation of (E)-ethyl 8-(benzylthio)-6-hydroxyoct-2-enoate (6): Ethyl but-3-enoate (1.106 gm, 0.0097 mol, 2eq.) was added to stirred solution of 1-(benzylthio)-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 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-(benzylthio)-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 column chromatography to afford (E)-ethyl 8-(benzylthio)-6-hydroxyoct-2-enoate (6).

Yield: 1.13 gm (80%); yellow viscous oil; 1H NMR (200 MHz, CDCl3): 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, 3H); 13C NMR (125 MHz, CDCl3): 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 C13H12O2: 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-(benzylthio)-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 H2 balloon pressure for 2 hrs. 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 (CHCl3) νmax 3020, 2400, 1731, 757 cm−1; 1H NMR (200 MHz,CDCl3): δ 1.18 (t, J = 7.20 Hz, 3H), 3.61-3.66 (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 C10H16O2: 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) (0.50 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; [α]D= +1.21 (c 2.00, Benzene)[Lit]; [α]D= +1.23 (c 1.62, CHCl3); IR (CHCl3): νmax 3020, 2400, 1731, 757 cm−1; 1H NMR (200 MHz,CDCl3): δ 1.18 (t, J = 7.29 Hz, 3H), 3.33-4.17 (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); 13C NMR (125 MHz, CDCl3): δ 14.23, 27.95, 28.27, 30.51, 35.49, 36.29, 60.14, 69.18, 73.35, 72.95 ppm.; Elemental Anal. Calcd for C10H16O2; 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; [α]D= +12.20 (c 1.00 , CHCl3)[Lit]; [α]D= +12.80 (c 1.00 , CHCl3); 1H NMR (400 MHz,CDCl3): δ 1.24 (t, J = 7.29 Hz, 3H), 1.31-1.35 (m, 2H), 1.39-1.46 (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); 13C NMR (125 MHz, CDCl3): 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 C11H18O4; 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; \([\alpha]_D^{20}= -0.9 (c 2.00, CHCl_3)\); IR (CHCl_3) \(\nu_{max} = 3018, 2934, 1701 \text{ cm}^{-1}\); \(^1^H\) NMR (400 MHz, CDCl_3): \(\delta = 0.97 \text{ (s, 9H)}, 1.18 \text{ (t, } J = 7.15 \text{ Hz, 3H)}, 1.34-1.41 \text{ (m, 4H)}, 1.55-1.62 \text{ (m, 4H)}, 2.24 \text{ (t, } J = 7.40 \text{ Hz, 2H)}, 3.29 \text{ (brs, 1H)}, 3.75-3.84 \text{ (m, 3H)}, 4.05 \text{ (q, } J = 7.4 \text{ Hz, } 2\text{H)}, 7.0. Preparation of (S)-ethyl 8-((tert-butylidiphenylsilyl)-oxy)-6-hydroxyoctanoate (12)

To the stirred solution of (S) ethyl-6,8-dihydroxyoctanoate (12) was purified by silica gel column chromatography using petroleum ether/ethyl acetate (25:85) as an eluent, to afford (S) ethyl 8-((tert-butylidiphenylsilyl)oxy)-6-hydroxyoctanoate 12.

**Yield:** 366 mg (97%); yellow viscous oil; \(^1^H\) NMR (400 MHz, CDCl_3): \(\delta = 0.97 \text{ (s, 9H)}, 1.18 \text{ (t, } J = 7.15 \text{ Hz, 3H)}, 1.34-1.41 \text{ (m, 4H)}, 1.55-1.62 \text{ (m, 4H)}, 2.24 \text{ (t, } J = 7.40 \text{ Hz, 2H)}, 3.29 \text{ (brs, 1H)}, 3.75-3.84 \text{ (m, 3H)}, 4.05 \text{ (q, } J = 7.2 \text{ Hz, } 2\text{H)}, 7.25-7.37 \text{ (m, 5H)}, 7.58-7.62 \text{ (m, 5H)} \text{ ppm}; \(^1^C\) NMR (50 MHz, CDCl_3): \(\delta = 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 \text{ ppm.}

7.0. Preparation of (SR)-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 anhydrous 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 evaporated 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-H_2O (410 mg, 0.6 mmol) and sulfur (54 mg, 0.6 mmol) in anhydrous CH_2Cl_2 (5 mL) was heated at 60°C for 24 hr and then stirred at room temperature for 1 hr. 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 column chromatography using petroleum ether/ethyl acetate (75:25) as eluent to furnish (R)-ethyl 8-((tert-butylidiphenylsilyl)oxy)-6-hydroxyoctanoate 13 as yellow oil.

**Yield:** 217 mg (95%); yellow oil; \([\alpha]_D^{25} = +54.31 (c 1.00, \text{CHCl}_3)\) \(\{\text{Lit.} \ [\alpha]_D^{25} = +61 (c 1.00, \text{CHCl}_3)\}\); IR (CHCl_3) \(\nu_{max} = 3030, 2400, 1731, 757 \text{ cm}^{-1}\); \(^1^H\) NMR (400 MHz, CDCl_3): \(\delta = 1.24 \text{ (t, } J = 7.22 \text{ Hz, 2H)}, 1.45-1.51 \text{ (m, 2H)}, 1.61-1.70 \text{ (m, 4H)}, 1.84-1.93 \text{ (m, 1H)}, 2.30 \text{ (t, } J = 7.46 \text{ Hz, 2H)}, 2.40-2.53 \text{ (m, 1H)}, 3.03-3.20 \text{ (m, 2H)}, 3.49-3.62 \text{ (m, 1H)}, 4.11 \text{ (q, } J = 7.20 \text{ Hz, } 2\text{H)}, 7.25-7.37 \text{ (m, 5H)}, 7.58-7.62 \text{ (m, 5H)} \text{ ppm}; \(^1^C\) NMR (50 MHz, CDCl_3): \(\delta = 14.20, 24.64, 28.70, 34.06, 34.54, 38.43, 40.16, 56.29, 60.25, 173.50 \text{ ppm.}

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

To the stirred solution of ethyl (R) 6, 8-dihydroxyoctanoate 8 (200 mg, 0.49 mmol) in anhydrous 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-H_2O (410 mg, 0.6 mmol) and sulfur (54 mg, 0.6 mmol) in anhydrous CH_2Cl_2 (5 mL) was heated at 60°C for 24 hr and then stirred at room temperature for 1 hr. 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 get crude residue. The crude residue purified by silica gel column chromatography using petroleum ether/ethyl acetate (75:25) as eluent to furnish (S)-ethyl 8-((tert-butylidiphenylsilyl)oxy)-6-hydroxyoctanoate 14.
mmol) in anhyd DMF (5 mL) was heated at 80°C for 24 hr and then stirred at room temperature for 1 hr. The reaction mixture was poured into ice-cold water (15 mL) and was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over anhydrous Na2SO4, 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; [α]D25 = -50.92° (c 1.00, CHCl3) [Lit.11 [α]D25 = -61°(c 1.00, CHCl3)]; IR (CHCl3); νmax 3021, 2928, 1709, 1409, 1216, 758 cm⁻¹; 1H NMR (400 MHz, CDCl3); δ 1.41-1.49 (m, 2H), 1.59-1.75 (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, 3H), 3.49-3.63 (m, 1H); 13C NMR (50 MHz, CDCl3); δ 24.35, 28.63, 33.74, 34.55, 38.47, 40.18, 56.25, 179.46 ppm. Elemental Anal. Calcd for C14H23O2S: C, 46.48; H, 6.90; S, 31.82; LCMS: 204.93 (M-1)°.

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REFERENCES AND NOTES: