CHAPTER-II

Enantioselective Synthesis of S-(-)-Methyl-6, 8-dihydroxy-octanoate: A Key Intermediate for the Synthesis of R-(+)-\(\alpha\)-Lipoic acid, using the Novel Retro Henry Cleavage Strategy
Synthesis of Optically Active $\alpha$-Lipoic Acid:

A Review
INTRODUCTION

R-(+)-α-Lipoic acid (1,2-dithiolane-3-valeric acid) 1 is widely distributed among microorganisms, plants and animals. It belongs to the group of co-factors containing sulfur and in nature it couples with thiamin pyrophosphate. However, lipoic acid basically belongs to another class of electron transfer co-factors where the net oxidoreduction function is to produce ATP. The cofactor is needed in fatty acid synthesis and in the metabolism of carbohydrates.

Indeed, it has been recognised for a long time that lipoic acid is an interesting growth factor found in a number of microorganisms. Chemically it can be reduced and the reduced form can be readily reoxidised to lipoic acid. Dihydrolipoic acid is an efficient reducing agent of sulphate ion to sulfite.

![Chemical structure of lipoic acid](image)

(R)-(+)−α-Lipoic acid, 1

α-Lipoic acid was first isolated from processed liver in 1950 by Reed and co-workers. Available evidence suggests that the biological activity of α-lipoic acid is confined only to the naturally occurring 'R' isomer.
BIOLOGICAL ROLE OF \(\alpha\)-LIPOIC ACID.

The well known tricarboxylic acid cycle begins with acetyl coenzyme A, which is obtained either by oxidative decarboxylation of pyruvate available from glycolysis or by oxidative cleavage of fatty acids. Although the acetyl-CoA with which the cycle begins may be derived catabolically from fatty acids or amino acids, the major source in most cells is the pyruvate available from the glycolytic breakdown of carbohydrate. The decarboxylation of carbohydrate is achieved by a complicated sequence of events that is catalysed by a cluster of three enzymes called the pyruvate dehydrogenase complex. In eukariotic cells, this enzyme complex is located in mitochondria, since the glycolytic pathway occurs in the cytosol, it is a pyruvate that the carbon derived from glucose (or other carbohydrates) enters the mitochondria.

In the first step of the conversion, catalysed by pyruvate decarboxylase, a carbon atom from thiaminpyrophosphates adds to the carbonyl carbon of pyruvate. Decarboxylation produces the key reactive intermediate, hydroxyethyl thiamin pyrophosphate (HETPP), which we saw as an intermediate in the conversion of pyruvate to acetaldehyde in the alcoholic fermentation. As shown in Fig-1, ionised ylid form of HETPP is resonance stabilised by the existence of a form without charge separation. The next enzyme, dihydrolipoyl transacetylase, catalyses the transfer of the two carbon moiety to lipoic acid. A nucleophilic attack by HETPP on the
The conversion of pyruvate to acetyl-CoA. The reactions are catalysed by the enzymes of the pyruvate dehydrogenase complex. This complex has three enzymes: pyruvate decarboxylase, dihydrolipoic transacetylase, and dihydrolipoil dehydrogenase. In addition, three coenzymes are required: thiaminpyrophosphate, lipoic acid, and NAD⁺. Lipoic acid is covalently attached to the transacetylase component of the complex by an amide bond between the carboxyl group of lipoic acid and the terminal amino group of a lysine residue of the enzyme.
sulfur atom attached to carbon 6 of oxidised lipoic acid displaces the electrons of the disulphide bond to the sulphur atom attached to carbon 8. The sulphur then picks up a proton from the environment as shown in Fig-1. This simple displacement reaction is also an oxidation reduction reaction, in which the attacking carbon atom is oxidised from aldehyde level in HETPP to the carboxyl level in the lipoic acid derivative. The oxidised (disulphide) form of lipoic acid is converted to the reduced (mercapto) form. The fact that the two carbon moiety has become an acyl group is shown more clearly after dissociation of thiamin pyrophosphate (TPP), which generates acetyl lipoic acid.

Further transfer of the acyl group to co-enzyme A is catalysed by the same enzyme. This displacement reaction produces reduced lipoic acid. A third enzyme, dihydrolipoyl dehydrogenase, catalyzes oxidation of this product back to the disulphide form. The electron lost in that oxidation is transferred first to an enzyme bound flavin (not shown in the Fig) and then to NAD$^+$. The overall equation for the conversion catalysed by the pyruvate dehydrogenase complex is

$$\text{Pyruvate} + \text{NAD}^+ + \text{CoA} \rightarrow \text{Acetyl-CoA} + \text{NADH} + \text{CO}_2 + \text{H}^+$$

The standard free energy for this conversion is about -8 kcal/mole.
OTHER BIOLOGICAL AND NONBIOLOGICAL APPLICATIONS OF
\( \alpha \)-LIPOIC ACID.

\( \alpha \)-Lipoic acid is an important factor in vital biochemical processes. It has been shown to have significant physiological and pharmacological properties.\(^3\) It is known to have protective and curative effect in heavy metal poisoning, e.g., from As\(^2\), Pb, Hg\(^4\), Cu\(^5\) and Se in animal tissues. It is found to be very effective in the treatment of liver disorders caused by Amanita phalloides.\(^6\) \( \alpha \)-Lipoic acid is also used for the treatment of persons with chronic toxic persisting hepatitis and chronic toxic active hepatitis, resulting from occupational phosphorous exposure. This effect may be due to its activation of redox process and glycogen synthesis in the liver.\(^7\) It is also shown to have cytoprotective effects on the gastric mucosa against ethanol aggression.\(^8\) One of the most recent important implications of \( \alpha \)-lipoic acid is its ability to control diabetes.\(^9\) Another recent report of this important compound is that it can inhibit HIV-1 replication in T-cells and in HeLa-CD\(^+\) cells at non toxic concentration of 35-70 \( \mu \)g/ml\(^10\).

Besides these pharmacological importances, lipoic acid also finds its use in cosmetic preparations. Skin lotions, ointments and creams containing lipoic acid prevents darkening of the skin\(^11\) and hair preparations containing lipoic acid is shown to control dandruff and stimulate hair growth.\(^12\)
Besides its biochemical functions, lipoic acid also finds applications in photography.\textsuperscript{13} When lipoic acid forms an ingredient of the silver halide emulsion along with other additives and the emulsion coated on a film substrate to form a negative type photographic material, it provides an image with extraordinary hard contrast with good dot quality upon development.

**BIOSYNTHESIS OF LIPOIC ACID**

Although considerable information is available concerning the mechanism of action of lipoic acid, little is known about the biosynthesis of this important compound. In 1964, Reed reported that Octanoic acid 2 serves as a specific precursor of 1 in *Escherichia coli*.\textsuperscript{14}

\[
\text{Octanoic acid } 2 \quad \rightarrow \quad \text{Lipoic acid } 1
\]

Parry\textsuperscript{15} in 1977 proposed that the biosynthesis of lipoic acid may resemble to that of the vitamin (+)-dithiobiotine 4, the pathway is shown in the following scheme.

\[
\text{Dithiobiotine } 4 \quad \rightarrow \quad \text{Lipoic acid } 1
\]
In the first step of their investigation, they verify the observation that (1-$^{14}$C) octanoic acid is specifically incorporated into lipoic acid. Accordingly, sodium (1-$^{14}$C) octanoate was administered to a shake culture of E-Coli and the cell harvested by centrifugation after 16 hr at 32-34°C. The cells were sonicated, radioinactive lipoic acid was added as carrier, and the mixture was then autoclaved in 6N sulphuric acid at 120°C for 2 hr in order to liberate protein bound lipoic acid. The barium carbonate carried 90% of the radioactivity of the lipoic acid and n-heptylamine was radioinactive. The specific incorporation of (1-$^{14}$C) octanoic acid into lipoic acid was therefore confirmed.

STEREOCHEMISTRY OF LIPOIC ACID

The five membered ring of lipoic acid is not planar but has a dihedral angle of 26°. Normally disulphides are colourless but lipoic acid is yellow. This property is attributed to the ring strain. This ring strain is caused in part by the repulsion of electron pairs on adjacent sulphur atoms and makes lipoic acid a better oxidising agent than a less strained six membered ring analogue. There is thus a structure function relationship to its biological role.
α-Lipoic acid was assigned the (R)-configuration 1 by Mislow and Meluch,\textsuperscript{16} by comparison of the melting point composition diagrams for mixtures of (R)-(+)\textsuperscript{-}3-methyloctanedioic acid with (+)- and with (-)-3-mercaptooctanedioic acid, respectively. By synthesis these mercapto diacids had been correlated with (-)- and (+)-α-lipoic acid, respectively. Studies of the biosynthesis of 1 by E-Coli have revealed that if α-(+)\textsuperscript{-}lipoic acid has the (R)-configuration, then insertion of sulphur at C-6 of octanoic acid must occur with inversion of configuration.\textsuperscript{17,18} This was proved by Golding et al by the synthesis of (S)-(−)-lipoic acid, the optical antipode, from (S)-malic acid by a route that features a single inversion of configuration at the chiral center.\textsuperscript{19}

SYNTHESIS OF OPTICALLY ACTIVE α-LIPOIC ACID: A REVIEW

Golding\textsuperscript{19} was the first to utilise an asymmetric process for the synthesis of the antipode of the natural isomer. Elliot after a couple of years\textsuperscript{20} synthesised the natural isomer (R)-(+)\textsuperscript{-}α-lipoic acid. The only chiral center of this molecule could be obtained by two modes: (1) by the chiron approach, where the chirality present in a natural product is translated to the desired molecule and (2) by asymmetric induction.

Lipoic acid has been synthesized, employing both the above modes by various groups.
Golding et al. (1983) were the first to synthesize the optical antipode of natural α-lipoic acid. The crucial step in the strategy (Scheme-1) is the opening of the epoxide 3 obtained from S-malic acid 2 with but-3-vinylmagnesium chloride in tetrahydrofuran containing catalytic amount of lithium tetrachlorocuprate to give 6-hydroxy-8-(benzyloxy)-oct-1-ene 4. This was benzylated to give 6,8-bis(benzyloxy)-oct-1-ene 5, which was hydroborated with disimylborane in tetrahydrofuran. The resulting triatyl borane was converted by alkaline hydrogen peroxide into 6,8-bis(benzyloxy)octane-1-ol 6. This was then oxidised by pyridinium dichromate in dimethyl formamide to give 6,8-bis benzyloxyoctanoic acid 7. Esterification of 7 and removal of benzyl groups gave methyl 6,8-dihydroxyoctanoate 9, which was treated with methanesulphonyl chloride and triethylamine in dichloromethane to afford the dimethylsulphonate 10. This was converted to (-)methyllipoate 11 by treatment with sodium sulphide and sulfur in dimethyl formamide. Anaerobic alkaline hydrolysis in darkness gave a crude product from which α-(-)-lipoic acid could be directly crystallised m.p. 45-48°C. Eliel et al. have shown that reaction of Na₂S + S in dimethyl formamide with the ditoluene-p-sulphonates of meso and racemic pentane-2,4-diol, respectively, are processes which affect almost complete inversion at each secondary carbon center. Hence, the α-(-)-lipoic acid obtained by the sequence described
must have the S-configuration, and so the absolute configuration of natural (+)-α-lipoic acid is R.

Scheme 1

(i) CH₂=CHCH₂CH₂MgCl, LiCuCl₄ (catalyst), THF; (ii) PhCH₂Br, NaH, THF; (iii) HB₃Si₂, THF, aq.HO₂⁻; (iv) Pyridinium dichromate, DMF; (v) MeOH-HCl; (vi) Pd/C,H₂; (vii) MeSO₂Cl, Et₃N; (viii) Na₂S, S, DMF; (ix) aq.HO⁻
Then in 1988, Golding et al synthesized the α-(R)-lipoic acid starting from S-malic acid (Scheme-2). This time they first inverted the configuration of an intermediate of S-malic acid to its R antipode and then they follow the same procedure as described in scheme-1 to get the target molecule α-(R)-lipoic acid 1.

\[ \text{Ref 21 & 22} \]

Elliot synthesis\(^\text{20}\)

Elliot et al in 1985 utilised the following scheme (Scheme-3) for the synthesis of R-(+)-α-lipoic acid.
The key step of this reaction is the TiCl₄ mediated diastereoselective coupling of lc and 2 to afford 3c (93% yield, 98:2 diastereoselectivity).

Oxidation of the secondary alcohol was effected by Jone's reagent. Reduction of 7 to 1,3-diol 8 was achieved by...
BH₃·THF complex, using aqueous KOH to hydrolyse the intermediate cyclic borate ester. Straightforward completion of the synthesis followed essentially the same route as that of Golding.¹⁹

Requisite S, S-acetal was obtained via aldehyde 6 in two steps from cyclohexene using the ozonolytic procedure followed by acetalization with S, S-2,4-pentanediol. Sutherland approach.²³

In this approach, the R- (+)-α-lipoic acid was synthesised in an enantioselective manner from achiral precursors using the Sharpless epoxidation as the key step in the reaction sequence (Scheme-4).

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 in situ gave the allylic alcohol 2. Chiral
catalytic epoxidation of alcohol 2 using L-(+)-diisopropyl-tartarate as the chiral auxiliary gave the (2S, 3S) epoxyalcohol 3. Reduction of the chiral epoxyalcohol 3 with Red-Al in tetrahydrofuran resulted in selective formation of the (3S)-1,3-diol 4. Formation of the bis-methanesulphonate 5 under standard conditions served the dual role of protection of the alcohol function during subsequent oxidation of the terminal double bond and provision of a controlling element for introduction of the disulphide linkage at a latter stage.

Ruthenium tetroxide oxidation of the terminal double bond of 5 using the catalytic procedure resulted in formation of the (3S) acid 6. Disulphide displacement of the methanesulphonate group of the potassium salt of the (3S)-acid 6 proceeded with inversion of configuration.

\[ \text{Scheme-4} \]
A.V. Rama Rao's approach.  

A.V. Rama Rao et al in 1987, reported the synthesis of R-(+)-\( \alpha \)-lipticoic acid starting from readily available 1, 2; 5, 6-di-O-isopropylenedene-D-mannitol(2). Accordingly, 2 was treated with benzoyl chloride-pyridine mixture at room temperature for 3 hr to afford 3, 4-dibenzoate 3. Hydrolysis of the isopropylenedene groups in 3 was achieved with 50% aqueous acetic acid on boiling water bath for 3 hr to give the tetrol which on treatment with methane sulphonyl chloride in pyridine yielded the tetramesylate 4. Reduction of 4 with sodium iodide and zinc dust in refluxing N,N'-dimethylformamide for 2 hr followed by debenzylation with sodium methoxide gave (3R, 4R)-1, 2-divinylglycol 1 (Scheme-5).
The Claisen-ester rearrangement of 7 with excess of triethylorthoacetate and catalytic amount of propionic acid at 145°C gave the diene ester 11. Selective hydroboration-oxidation of the terminal double bond was achieved with 9-BBN and the resulting product 12 was hydroborated with palladised charcoal at normal pressure and room temperature to afford the diol 13. Transformation of 13 into R-(+)-α-lipoic acid was achieved by the procedure of Golding et al.\textsuperscript{19}

\[
\begin{align*}
\text{EtO}_2C & \quad \rightarrow \quad \text{DBz} \\
\text{EtO}_2C & \quad \rightarrow \quad \text{OBn} \\
\text{EtO}_2C & \quad \rightarrow \quad \text{OR} \\
\text{EtO}_2C & \quad \rightarrow \quad \text{OR} \\
\text{HO} & \quad \rightarrow \quad \text{H} \\
\text{HO} & \quad \rightarrow \quad \text{Ms}
\end{align*}
\]

U.T. Bhale Rao's approach.\textsuperscript{25}

In this approach (1990), the synthesis of S-(−)-methyl-6,8-dihydroxyoctanoate was reported. The key step of the synthesis was the assymetric reduction of methyl 8,8-dimethyl-6-oxooctanoate using immobilised baker's yeast as a key step.
R-(+)-α-Lipoic acid

Scheme-6

(i) Cu, CHBr₃; (ii) KOAc, 18-Crown-6, DMF; (iii) K₂CO₃/MeOH then PCC; (iv) Triton B/MeOH; (v) immobilised Baker's yeast, pH 4.5-5; (vi) H₃PO₄/MeCOMe then NaBH₄.
Copper catalysed bromoform addition to alkene 1 gave methyl-6,8,8-tribromooctanoate 2 which, on treatment with two equivalents of potassium acetate [18-crown-6, in dimethylformamide], resulted in methyl-6-acetoxy-8-bromooct-7-enolate 3. Hydrolysis of 3 in methanol-K_2CO_3 and oxidation with pyridinium chlorochromate (PCC) gave ketovinyl bromide 4. This was subsequently converted to methyl-8,8-dimethoxy-6-oxooctanoate 5 with N-benzyltrimethyl ammonium hydroxide (triton B) in methanol. This was enatiospecifically reduced by adding small portion of it in ethanol to a glucose solution containing Baker's yeast immobilised in calcium alginate bead at pH 4.5-5 to get 6. This on treatment with H_3PO_4 followed by NaBH_4 reduction resulted in 7. Synthesis of R- (+)-α-lipoic acid 8 from 7 is already known in the literature.19
Results and Discussion
RESULTS AND DISCUSSION

In our approach, we have started the synthesis of this important molecule from 2-Nitrocyclohexanone. The synthetic scheme-7 which we have conceived is given below.

\[
\begin{align*}
\text{NO}_2 & \quad \text{a} \quad \text{NO}_2 \\
\text{64\%} & \quad \text{73\%} \\
2 & \quad \text{trans}(\pm)-3 \\
\text{c} & \quad 4 \\
\text{d} & \quad 7, \text{R}=\text{CH}_3, \text{R'}=\text{OCH}_3 \\
\text{e} & \quad 8, \text{R}=\text{H}, \text{R'}=\text{OCH}_3 \\
\text{R}-(\pm)-\alpha\text{-Lipoic acid, 1}
\end{align*}
\]

Scheme-7

a) MgBr, THF, -30\(^\circ\) to 0\(^\circ\)C; b) anhydrous CuSO\(_4\).SiO\(_2\)/dry Bz, reflux; c) NaOMe, MeOH, H\(_2\)SO\(_4\), -30\(^\circ\) to 0\(^\circ\)C; d) Baker's yeast, glucose, H\(_2\)O, 48h; e) (C\(_4\)H\(_9\)-)\(_4\)N\(^+\)I\(^-\)/BF\(_3\).Et\(_2\)O/CHCl\(_3\).
We have utilised our retro Henry strategy in one of the major steps and to generate the required stereogenic center we used fermenting Bakers' yeast in another step.

Reaction of two equivalents of vinylmagnesium bromide with 2-nitrocyclohexanone 2 as per procedure described by Ballini et al.,27 gave trans (±)-3 in 64% yield.

The product 3 was then refluxed in dry benzene with anhydrous copper sulphate adsorbed on silica gel. A comparatively more polar oily product was formed. Reaction mixture was worked up by the procedure described in the earlier chapter. After purification of the product, obtained after work up and evaporation of the solvent, by preparative thin layer chromatography (1:10, ethyl acetate : petroleum ether) we got an oily product in 73% yield. Its IR spectrum showed sharp peaks at 1675 and 1550 cm⁻¹ indicating the presence of carbonyl and nitro groups respectively. In NMR, a triplet integrating to two protons at 4.15 ppm with J=7Hz and a multiplet integrating to three protons at 5.4-6.3 ppm indicated the presence of -CH₂NO₂ and vinylic protons respectively in the molecule. From these data, following structure 4 has been assigned to the molecule.

\[
\begin{align*}
\text{\(4\)}
\end{align*}
\]
The structure was further supported by its mass spectrum which gave peaks at m/z 171 (M⁺), 144, 125, 111, 97, 83, 69 and 55.

The structure of the compound 4 has two interesting features. Due to the presence of an electron withdrawing nitro group the α-proton is acidic and can be easily removed by a mild base to get a stable carbanion. Again, due to the presence of α,β-unsaturated carbonyl group, the end carbon atom of the chain is susceptible to nucleophilic attack. Our next attempt was to convert nitro group into a carbonyl group by Nef reaction. We tried different reported Nef reactions where we became unsuccessful. Ultimately we got positive results by using Jacobesen's procedure. We modified the reported procedure by increasing the acidity of the system; that increased acidity might hydrolyse the intermediate ketal and oxidise the aldehyde to an ester group. After usual work up, thin layer chromatography indicated the formation of two products, one in major amount and the other one was formed in minor amount. Both the products were purified by preparative thin layer chromatography (solvent system 1:3, ethyl acetate: petroleum ether). The less polar one, which was formed predominantly (80% yield) as an oily product, showed sharp IR bands at 1705 and 1725 cm⁻¹ indicating the presence of a carbonyl and an ester function respectively. Disappearance of the band at 1550 cm⁻¹ gave the proof that the Nef reaction took place, converting nitro function into ester function. In
the NMR spectral data of the product, a singlet integrating to three protons at 3.66 ppm, a triplet integrating to two protons at 3.63 ppm \( (J=6.25 \text{ Hz}) \), a singlet at 3.3 ppm integrating to three protons and a triplet integrating to two protons \( (J=6.2 \text{ Hz}) \) indicated the presence of \((-\text{COOMe}), (-\text{OCH}_2), (-\text{OMe})\) and \((\text{CH}_2\text{COOMe})\) groups respectively. From these data following structure 5 has been proposed for this product.

![Structure 5](image)

Its structure was further supported by its mass spectrum which showed peaks at m/z 203(M+1)+, 170, 139, 111, 59 and 55. The compound 5 was then subjected to sodium borohydride reduction in methanol. Disappearance of the band at 1725 cm\(^{-1}\) and appearance of a new one at 3350 cm\(^{-1}\) in the IR spectrum of the sodium borohydride product gave indication that the carbonyl group has been reduced. Further supportive evidence was provided by its NMR spectrum which showed a singlet at 3.55 ppm integrating to three protons confirming the presence of a \((-\text{COOMe})\) group, a singlet integrating to three protons at 3.35 ppm and a broad peak integrating to one proton at 2.5 ppm gave indication of the presence of a \((-\text{OMe})\) group and a \((-\text{OH})\) group in the molecule respectively. Thus the structure of this reduced product has been assigned as 6a.
Next we tried to characterise the other product which was formed in minor amount (15% yield) as an oil. A sharp IR band at 1705 cm\(^{-1}\) together with a one proton triplet in its NMR spectrum at 9.8 ppm with \(J=2.3\) Hz gave a clear indication of the presence of an aldehydic function in the molecule. Other major peaks, \(\text{viz.}\), a triplet at 3.63 ppm with \(J=6.18\) Hz integrating to two protons, a singlet integrating to three protons at 3.33 ppm, a triplet at 2.6 ppm with \(J=6.18\) Hz integrating to two protons indicated the presence of \((-\text{OCH}_2\)), \((-\text{OMe})\) and \((-\text{CH}_2\text{CO}-)\) respectively. From these data the structure of the resultant product was proposed as 6

![Structure 6a](image)

6a

Its mass spectrum gave major peaks at \(m/z\) 171 (\(M-1\))\(^+\), 139, 111, 97, and 83.

Our next attempt was the asymmetric reduction of the carbonyl function at position 6 of compound 5, to generate a stereogenic center of configuration 'S'. For this purpose we decided to use fermenting Baker's yeast as the best choice.
for this reduction. The use of biological systems (enzymes or microorganisms) to prepare chiral alcohols was a wide spread and very efficient method. The alcohol is obtained by reduction of the corresponding ketone. Most of the organism obey the Prelog's rule and give the enantiomer with 'S' configuration. As per procedure described by Gopalon et al. and Bhale Rao et al., we subjected the compound for Baker's yeast reduction. After usual work up and evaporation of the solvent under reduced pressure, it gave a residue which was purified by preparative TLC using (1:3, ethyl acetate : petroleum ether system) to give an oily product in 50% yield. The IR spectrum of the product showed characteristic band for hydroxy and ester functions at 3350 and 1705 cm⁻¹ respectively. A singlet integrating to three protons at 3.55 ppm in its NMR indicated that the ester function remained intact. Another singlet integrating to three protons at 3.35 ppm and a broad band integrating to one proton at 2.5 ppm were indicative of the presence of (-OMe) and (-OH) protons respectively. The specific rotation of the product was found to be [α]_{D}^{25} = 10.6 (C 0.15 in CHCl₃). Based on these data, structure of the resulting product has been assigned as 7
In the final step the compound 7 was refluxed with n-tetrabutylammoniumiodide in dry chloroform and borontrifluoroethereate. This reagent is known to hydrolyse the O-methoxy group selectively keeping the ester group intact. After usual work up the, product was purified by preparative T.L.C.(1:3 ethyl acetate : petroleum ether solvent system). Its IR spectrum showed sharp bands at 3370, 2940 and 1735 cm\(^{-1}\). Its NMR spectrum consisted of a singlet integrating to three protons at 3.62 ppm, a triplet integrating to two protons (\(J=7.3\) Hz) at 2.25 ppm and a multiplet integrating to three protons at 3.35 ppm indicated the presence of (\(-\text{CO}_2\text{CH}_3\)), (-\(\text{CH}_2\text{CO}_2\text{CH}_3\)), (-\(\text{CH}_2\text{OH} \& -\text{CHOH}\)) protons. From these data the structure of the product has been elucidated to be

![Structure of compound 8](image)

The specific rotation of the compound was found to be \([\alpha]_D^{25} -3.8^\circ\) (CHCl\(_3\)) (Lit.\(^{31}[\alpha]_D^{25} -3.9^\circ\) (CHCl\(_3\)) for 'S' isomer. \[\[77\]
Experimental and References
EXPERIMENTAL SECTION.

Preparation of 1-nitrooct-7-en-6-one, 4:

A mixture of 2-nitroalcohol 3 (0.68g, 3.98mmol), CuSO₄/SiO₂ (3.5g) in dry benzene (25ml) was refluxed for 4h. The reaction was monitored on TLC, filtered the reaction mixture and washed with acetone successively. The combined filtrate was removed under reduced pressure and the product was purified by chromatography (1:10, ethyl acetate:pet. Ether) to give 4 (0.5g, 73%) as an oil.

IR : 1675, 1540 cm⁻¹.

¹H NMR : 5.9 (m, 2H, -HC=CH₂), 5.5 (m, 1H, -CH=CH₂), 4.2 (t, J=7Hz, 2H, -CH₂-NO₂), 2.35 (t, J=6.5Hz, 2H, -CH₂-CO⁻), 1.2 (br, 6H, -CH₂).

MS (m/z) : 171 (M⁺), 144, 125, 111, 97, 83, 69 and 55.

Analysis calculated for C₈H₁₃NO₃ : C, 56.13; H, 7.65; N, 8.18; found C, 56.25; H, 7.50; N, 8.23.

Preparation of Methyl-8-methoxy-6-oxooctanoate, 5:

The compound 4 (0.15g, 0.87 mmol) in 7ml of (0.5N) methanolic sodium methoxide was added dropwise to a solution of 7ml of (9.74N) sulfuric acid in methanol at -35°C. After complete addition of the substrate, dichloromethane was added. The reaction mixture was washed with ice cold water and then with dilute NaOH solution, dried over sodium sulphate and concentrated under reduced pressure. Finally the crude residue was purified by chromatography to obtain 5
(0.12g, 80%) as an oil along with compound 6 (0.023g, 15%). The compound 5 and 6 were eluted with 1:3, ethyl acetate : pet. ether as solvent respectively.

IR (CHCl$_3$) : 1705, 1725 cm$^{-1}$.

$^1$H NMR (300 MHz): 3.66 (s, 3H, -COOMe), 3.63 (t, J=6.25Hz, 2H, -OCH$_2$), 3.3 (s, 3H, -OMe), 2.64 (t, J=6.2Hz 2H, -CH$_2$-COOMe), 2.47 (m, 2H, -COCH$_2$-), 2.33 (m, 2H, -CH$_2$CO-), 1.6 (m, 4H, -CH$_2$-).

MS (m/z) : 203([M+1]$^+$), 170, 139, 111, 59 and 55. Analysis calculated for C$_{16}$H$_{18}$O$_4$: C, 59.39, H, 8.97; found, C, 59.45, H, 8.85.

8-Methoxy-6-Oxooctanal, 6:

Yield : 15% ; Oil.

IR (CHCl$_3$) : 1705 cm$^{-1}$.

$^1$H NMR (300 MHz): 9.8 (t, J=2.3Hz, -CHO), 3.63 (t, J=6.18Hz, 2H, -OCH$_2$-), 3.33 (s, 3H, -OMe), 2.6 (t, J=6.18Hz, 2H, -CH$_2$CO-), 2.46 (m, 4H, -COCH$_2$- and -CH$_2$-CHO), 1.2 (m, 4H, -CH$_2$).

MS (m/z) : 171 ([M-1]$^+$), 139, 111, 97 and 83. Analysis calculated for C$_9$H$_{16}$O$_3$: C, 62.77, H, 9.63; found C, 62.69, H, 9.45.

Preparation of S-(-)-Methyl-6-hydroxy-8-methoxyoctanoate, 7:

A suspension of bakers' yeast (128.28g) and D- glucose (6.5g) in 2.3 ml water was stirred for 30 minutes at 32°C. A solution of compound 5 (0.1g, 0.49 mmol) in 2ml of methanol
was then added. The reaction mixture was allowed to stand at room temperature for 48h, filtered through celite pad and washed with ethyl acetate (150ml).

the filtrate was acidified with 2N hydrochloric acid to bring pH 1 and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, evaporated and finally purified by preparative TLC (1:3, ethyl acetate : pet. ether) to give 6 (0.05g, 50%) as an oil.

IR (CHCl$_3$) : 3350, 1705 cm$^{-1}$.

$^1$H NMR (300 MHz): 3.55 (s, 3H, -COOCH$_3$), 3.4 (m, 2H, -OCH$_2$), 3.35 (s, 3H, -OMe), 2.5 (br, 1H, -OH), 2.3 (t, J=7.4Hz, 2H, -CH$_2$COOMe), 1.55 (q, J=5.4Hz, 7H, -CH$_2$-CH(OH)-CH$_2$-), 1.4 (m, 2H, -CH$_2$-).

MS (m/z) : 205 ([M+1]$^+$), 187, 171, 155, 139, 113, and 87.

Analysis calculated for C$_{10}$H$_{20}$O$_4$ : C, 58.80, H, 9.87; found C, 58.94, H, 9.82.

$\left[\alpha\right]_{D}^{25}$ : $-10.6^\circ$ (c 0.15 in CHCl$_3$).

S-(-)-Methyl-6,8-dihydroxyoctanoate, 8 :

To a mixture of compound [(S)-7] (0.05g, 0.26mmol) and n-tetrabutylammonium iodide (0.1g, 0.27mmol) in dry chloroform (5ml) was added boron trifluoride etherate (0.04g, 0.27 mmol) and the mixture was refluxed for 4h. The reaction mixture was then treated with saturated sodium hydrogen carbonate solution (50ml) and extracted chloroform. The organic layer was washed with aqueous sodium thiosulfate
solution (20ml) followed by water (50ml), dried over anhydrous sodium sulfate. The solvent was removed in vacuo and purified by preparative TLC (1:3, ethyl acetate : pet. ether) to furnish the pure diol 8 (0.04g, 80%) as an oil.

IR (CHCl₃) : 3370, 2940, 1735, 1460 cm⁻¹.

$^1$H NMR : 1.51 (m, 8H, -CH₂⁻), 2.25 (t, J=7.3Hz, 2H, -CH₂CO₂Me), 3.35 (m, 3H, -CH₂OH & -CHOH), 3.62 (s, 3H, -OCH₃), 4.53 (s, 2H, -OH).

MS (m/z) : 191 ([M+1]⁺), 173, 163, 141, 130.

$[\alpha]_D^{25}$ : -3.8° (CHCl₃) (lit. 31° -3.9° (CHCl₃) for S isomer).
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