3.1 Introduction

Chiral molecules constitute the fundamental building blocks of much of biology. In general, only one enantiomer of a drug, agrochemical (herbicides, pesticides), flavoring agents, or other molecule, when asymmetric, has the desired biological effect, while the other enantiomer has very different effect or, at least, places a metabolic burden on the body. Industrial companies are concerned about disposing of unwanted compounds and also about the inefficiency and costs involved in the chemical processes. For this reason, asymmetric synthesis to produce only one enantiomer of a molecule for such uses is extremely important. Currently, single-enantiomer drugs account for around a third of the total market and, as such, reliable methods for their synthesis are in even more demand. Thus finding new methods of asymmetric synthesis has in the past twenty or thirty years become a key activity for organic chemists. For despite the spectacular achievements of organic synthesis over the last 50 years, there currently does not exist a collection of reliable synthetic ‘tools’ that would allow chemists to prepare significant
quantities (>10g) of any given molecule with absolute control over chirality in a reasonable amount of time and in high overall yield.

### 3.2 Aims and Objectives

All the methods currently available for asymmetric synthesis of 1,2-diols from olefins involve the use of osmium reagents. Thus 0.2 – 0.4 mol% of osmium reagents added to the reaction mixture either as osmium tetroxide or as the non volatile K₂OsO₂ (OH)₄ are required for most olefinic substrates. From an industrial viewpoint, the high cost of osmium catalyst and chiral ligand as well as the toxicity of osmium tetroxide are the obstacles to large scale application.

It was in this context, we thought it worthwhile to explore the possibility of hydroxylating olefinic compounds to chiral 1,2-diols without using osmium reagents. An exhaustive investigation conducted by Ashcroft has revealed that all structural types of olefins can be hydroxylated using silver succinate and iodine in dry benzene medium. In all cases studied, where stereochemistry is relevant, cis-hydroxylation occurred in agreement with the mechanism discussed in section 1.6.3.3. The aim of the present work was to find whether silver salts of some optically active derivatives of succinic acid can be used in place of silver succinate, along with iodine to achieve enantioselective dihydroxylation of olefinic compounds.

### 3.3 Results and discussion

The starting material selected for preparing optically active derivatives of succinic acid was obviously the naturally occurring optically active dicarboxylic acid, viz., tartaric acid. Tartaric acid is a useful raw material in organic chemistry for the synthesis of other chiral molecules. The naturally
occurring form of the acid is L-(+)-tartaric acid. The mirror image form, D-(-)-
tartaric acid and the achiral form meso tartaric acid can be made artificially.

\[
\text{L-}(+)-\text{tartaric acid} \quad \text{D-}(-)-\text{tartaric acid} \quad \text{meso tartaric acid}
\]

\[\alpha\] = (+)-11.5 – 13.5°

The naturally occurring L-(+)-tartaric acid was esterified and the
hydroxyl groups of diethyl ester were then methylated using silver oxide and
methyl iodide following the method of Purdie and Irvine\textsuperscript{171}. The diethyl
dimethoxy succinate thus obtained was hydrolysed to get the crystalline L-(+)-
dimethoxy succinic acid. The L-(+)-dimethoxy succinic acid was then
converted to silver salt and the L-(+)-silver dimethoxy succinate thus obtained
was used along with iodine for the enantioselective dihydroxylation of olefinic
compounds.

### 3.3.1 Preparation of L-(+)-silver dimethoxy succinate

Following the method of S. sugasana\textsuperscript{172}, the naturally occurring L-(+)-
tartaric acid \([\alpha\] = (+)-13.53° (C, 15 in H\textsubscript{2}O) ; reported: (+)-13.10° (C, 15 in}
H₂O) was esterified using ethanol, toluene and concentrated hydrochloric acid to obtain L-(+)-diethyl tartrate \{[\alpha]_D^{20} = (+)-8.194° (C, 15 in MeOH); reported: (+)-7.45°\}. To a solution of L-(+)-diethyl tartrate (0.03 mole) in methyl iodide (0.18 mole) was added silver iodide (0.09 mole) and when the reaction was completed the product was extracted using ether. Removal of the solvent gave diethyl dimethoxy succinate (in 54.3% yield) as a liquid which boiled nearly constantly at 135°C/11mm. The diethyl dimethoxy succinate was subjected to hydrolysis by refluxing with barium hydroxide and the barium salt obtained was subsequently decomposed by calculated amount of sulfuric acid. The L-(+)-dimethoxy succinic acid was collected by crystallisation which showed a specific rotation of (+)-63.558° (C, 1 in H₂O); (reported: (+)-74.74°). The silver salt of L-(+)-dimethoxy succinic acid was prepared by adding silver nitrate solution to a neutral solution of the acid in ammonium hydroxide. On igniting a known weight of the silver salt in a previously weighed silica crucible, it was found to contain 55.55% silver, which is in agreement with the value expected for L-(+)-silver dimethoxy succinate (54.87%).

### 3.3.2 Asymmetric dihydroxylation of octadec-cis-9-enoic acid (oleic acid) using L-(+)-silver dimethoxy succinate and iodine

L-(+)-silver dimethoxy succinate (0.011 mole) in benzene (70ml) was refluxed with iodine (0.01 mole) for about 45 minutes. When boiling stopped, added oleic acid (0.01 mole) and continued refluxing for 6 hrs. Cooled and filtered from silver iodide. Removal of benzene and hydrolysis of the residue using alcoholic potash gave crude dihydroxy acid (51.9%). Recrystallisation of the product from ethanol gave erythro-9, 10-dihydroxy stearic acid (52), melting at 131-132°C. (The reported m.p. is 132°C).
Asymmetric dihydroxylation of olefins using L-(+)-silver dimethoxy succinate and iodine

The $^1$H NMR spectrum of compound (52) showed a triplet of 3 protons at $\delta 0.897 \ (J= 7.0 \text{ Hz})$ for methyl group; a triplet of two protons at $\delta 2.277 \ (J= 7.2 \text{Hz})$ for the $\alpha$-methylene group; a multiplet of 26 protons between $\delta 1.3-1.6$ for the remaining methylene groups; a multiplet of 2 protons centred at $\delta 3.325$ for the methine protons at C-9 and C-10. The $^1$H NMR spectrum of compound (52) was found identical with that reported for erythro-9,10-dihydroxy stearic acid.

The $^{13}$C NMR spectrum of compound (52) showed resonance at $\delta 14.43$ for methyl group, $\delta 23.53$ due to CH$_2$CH$_3$ group (C-17), $\delta 49.01$ due to $\alpha$-methylene carbon atom (CH$_2$COOH), $\delta 75.30$ due to methine carbon atoms at C-9 and C-10, and $\delta 177.72$ due to the carboxyl group. The $^{13}$C NMR spectrum of compound 52 was found identical with that reported for erythro-9, 10-dihydroxy stearic acid.

The IR spectrum of compound (52) showed a broad peak at 3275cm$^{-1}$ due to OH group, a strong, sharp peak at 1695cm$^{-1}$ due to C=O group, and a strong peak at 1072cm$^{-1}$ due to C-O stretching. The IR spectrum of compound (52) was found superimposable with that reported for erythro-9, 10-dihydroxy stearic acid.

Formation of erythro-9, 10-dihydroxy stearic acid (52) from oleic acid corresponds to syn-hydroxylation which is in perfect agreement with the
mechanism proposed\textsuperscript{136} for hydroxylation of olefinic compounds using silver succinate and iodine in benzene.

The optical activity of the product obtained was measured and compared with the activity of erythro-9,10-dihydroxy stearic acid obtained by dihydroxylation of oleic acid using silver succinate and iodine. The dihydroxy acid obtained by hydroxylation of oleic acid using L-(+)-silver dimethoxy succinate and iodine gave a specific rotation of $+0.312^\circ$ (C, 0.71, MeOH) whereas that produced using silver succinate and iodine was optically inactive. The reported value for d-erythro-9,10-dihydroxy stearic acid is $\pm 0.25^\circ$(MeOH).

### 3.3.3 Asymmetric dihydroxylation of octadec-trans-9-enoic acid (elaidic acid) using L-(+)-silver dimethoxy succinate and iodine

Elaidic acid (0.01 mole) was hydroxylated using L-(+) - silver dimethoxy succinate (0.011 mole) and iodine (0.01 mole) in benzene (70 ml) exactly as given under 3.3.2. Hydrolysis of the resulting product gave crude dihydroxy acid (48.7%) which on repeated crystallisation from ethanol gave threo 9, 10-dihydroxy stearic acid (53), melting at 98$^\circ$C. (The melting point reported for d-threo-9, 10-dihydroxy stearic acid is 99$^\circ$C).

![Image of compound 53](image)

The $^1$H NMR spectrum of compound (53) showed a triplet of 3 protons at $\delta 0.897$ ($J = 6.8$ Hz) for methyl group, a triplet of two protons at $\delta 2.273$ ($J$
Asymmetric dihydroxylation of olefins using L-(+)-silver dimethoxy succinate and iodine

=7.4 Hz) for the α-methylene group; a multiplet of 26 protons between δ1.3-1.6 for the remaining methylene groups; a multiplet of two protons centred at δ3.339 for the methine protons at C-9 and C-10.

The $^{13}$C NMR spectrum of compound (53) showed resonance at δ15.0 for methyl group, δ23.75 due to CH$_2$CH$_3$ group (C-17), δ49.01 due to α-methylene carbon atom (CH$_2$COOH), and at δ75.975 due to methine carbon atoms at C-9 and C-10.

The IR spectrum of compound (53) showed a broad peak at 3339cm$^{-1}$ due to OH group, a strong peak at 1699cm$^{-1}$ due to C=O group, and a strong peak at 1077cm$^{-1}$ due to C-O stretching.

The specific rotation of the product obtained was measured and compared with the activity of threo-9,10-dihydroxy stearic acid formed by hydroxylation of elaidic acid using silver succinate and iodine in benzene medium. The dihydroxy acid obtained by hydroxylation of elaidic acid using L-(+)-silver dimethoxy succinate and iodine showed a specific rotation of (+)-2.3640 (C, 0.73, MeOH) while that formed on using silver succinate and iodine showed no optical activity. The reported value of $[\alpha]_{D}$ for d-threo-9,10-dihydroxy stearic acid is (+)-22.50 (C, 2.81, MeOH).

The appreciable variation in the observed specific rotation of the product may be attributed to its degree of enantiomeric purity. In the last two decades several chiral HPLC techniques have been introduced for the resolution of optically active molecules including 1,2-diols. Enantiomeric characterization of the dihydroxylation product of elaidic acid could not be attempted using such methods since chiral stationary phases capable of resolving 9,10-dihydroxy acids or their esters have not been reported so far. Even though enantiomers of vic-dihydroxy eicosatrienoic acid methyl esters (DHET-Me) could be resolved using chiral columns, such
columns were not effective with vic-dihydroxy stearic acids which lack strong chromophores useful for UV detection during chromatography.

### 3.3.4 Asymmetric dihydroxylation of octadec-6-enoic acid (petroselenic acid)

Petroselenic acid (0.01 mole) was hydroxylated using L-(+)-silver dimethoxy succinate (0.011 mole) and iodine (0.01 mole) in benzene (70ml) exactly as described under 3.3.2. The resulting product on hydrolysis gave crude dihydroxy acid (38.2%) which on crystallisation from ethanol gave erythro-6, 7-dihydroxy stearic acid (54) which melted at 121°C.

In the $^1$H NMR spectrum of compound (54) the methyl group presented a signal at $\delta$0.895 (t, $J$=6.8 Hz) and the $\alpha$-methylene group resonated as triplet at 2.304 ($J$=6.6 Hz). The remaining methylene groups were visible as a multiplet of 26 protons between $\delta$1.3-1.6 and the methine protons at C-9 and C-10 resonated as a multiplet of 2 protons centered at 3.325.

In the $^{13}$C NMR spectrum, the methyl carbon was visible at $\delta$14.32 and CH$_2$CH$_3$ (C-17) appeared at $\delta$23.74. The spectrum showed resonance at $\delta$49.01 due to $\alpha$-methylene carbon and at $\delta$75.88 due to methine carbon atoms (C-9 and C-10).

The IR spectrum showed a broad peak at 3237 cm$^{-1}$ due to OH group, a strong, sharp peak at 1690 cm$^{-1}$ due to C=O group, and a strong peak at 1072 cm$^{-1}$ due to C-O stretching.
The specific rotation of the product was determined and compared with the optical activity of erythro-6,7-dihydroxy stearic acid (m.p. 121°C) obtained by hydroxylation of petroselenic acid using silver succinate and iodine. The dihydroxy acid obtained from petroselenic acid using L-(+)-silver dimethoxy succinate and iodine gave a specific rotation of (+)-3.482° (C, 0.762, MeOH) whereas that formed on hydroxylation using silver succinate and iodine showed no activity.

### 3.3.5 Summary

The results of the asymmetric dihydroxylation reactions of various olefinic compounds using L-(+)-silver dimethoxy succinate and iodine are given in table I.

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Olefinic compound used</th>
<th>Product</th>
<th>Yield %</th>
<th>m.p. of product</th>
<th>stereochemistry of hydroxylation</th>
<th>Specific rotation</th>
<th>Found</th>
<th>Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Oleic acid</td>
<td>Erythro-9,10-dihydroxy stearic acid</td>
<td>51.9</td>
<td>131° - 132°</td>
<td>syn (+)-0.312 ± 0.25°</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Elaidic acid</td>
<td>Threo-9,10-dihydroxy stearic acid</td>
<td>48.7</td>
<td>98°</td>
<td>syn (+)-2.364° (+)-22.5°</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Petroselenic acid</td>
<td>Erythro-6,7-dihydroxy stearic acid</td>
<td>38.2</td>
<td>121°</td>
<td>syn (+)-3.482° Not reported</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 3.4 Conclusions

The present work reveals that asymmetric dihydroxylation of olefinic compounds can be achieved by the use of silver salts of optically active derivatives of succinic acid and iodine. Thus L-(+)-silver dimethoxy succinate and iodine in benzene is proved to be an effective reagent for accomplishing
asymmetric synthesis of 1, 2-diols by dihydroxylation of olefinic compounds. This assumes significance when we consider the use of chiral 1,2-diols in the fields of medicine and agrochemicals, and the hazardous toxicity and high cost involved in the present methods of osmium catalysed asymmetric dihydroxylation reactions. More investigations are required on methods of ascertaining the enantiomeric purity of 1, 2-diols produced using the new reagent.

The development of L-(+)- silver dimethoxy succinate and iodine as a syn-hydroxylating agent also amounts to yet another modification of the well known Prevost-Woodward methods of hydroxylation of olefinic compounds.

3.5 Experimental

3.5.1 General Procedures

All melting points are uncorrected and were determined on a Neolab melting point apparatus. IR spectra were recorded using AVATAR 370 DTGS FTIR Spectrophotometer. The NMR spectra were recorded on Bruker 400 using MeOD as solvent. The chemical shifts are given in the δ scale with tetramethyl silane as internal standard. Abbreviations used in 1H NMR data are s = singlet, d = doublet, t = triplet, m = multiplet. All optical rotation experiments were done on a Rudolf Autopol IV digital polarimeter and are quoted as degree cm² g⁻¹. Concentration (C) is given in units of g/100 cm³.

3.5.2 Synthesis of L-(+)- silver dimethoxy succinate

3.5.2.1 Preparation of diethyl dimethoxy succinate

L-(+)-diethyl tartrate (6.18g, 0.03 mole) ( [α]D²⁰ = 8.194⁰) was dissolved in methyl iodide (25.56g, 0.18 mole) and silver oxide (20.78g, 0.09 mole) was added in small quantities at a time. The reaction which was spontaneous and at first violent was moderated by dipping the flask in cold
Finally, when spontaneous action has ceased, the reaction was completed by heating the flask on a water bath for 2 hours. The product was then extracted using ether. Removal of the solvent by distillation gave diethyl dimethoxy succinate (3.83g, 54.3% yield) as a liquid which boiled nearly constantly at 135^0/11mm.

3.5.2.2 Preparation of L-(+)-dimethoxy succinic acid

Diethyl dimethoxy succinate (3.83g) was refluxed with barium hydroxide (7.2g) in water (80 ml) for two and a half hours. Filtered and the filtrate was evaporated to dryness on a water bath. Dissolved the residue in water and acidified with calculated amount of 1N sulfuric acid (50ml). Barium sulfate was allowed to settle and filtered off. Concentrated the filtrate and L-(+)-dimethoxy succinic acid (2.51g, 86% yield) was collected by crystallisation, which melted at 151^0C and showed a specific rotation of (+)-53.55^0.

3.5.2.3 Preparation of L-(+)-silver dimethoxy succinate

Dissolved L-(+)-dimethoxy succinic acid (3.1g) in distilled water (100ml) and then added ammonia solution (1:3, 13 ml) till the well-stirred mixture smells of ammonia. Boiled the solution gently until no odor of ammonia could be detected in the steam and until a red litmus paper placed in the steam gave no blue coloration. Then cooled and added silver nitrate solution (10%, 35 ml) with stirring until no further precipitation occurred. Filtered, drained well and washed three times with small quantities of water to remove excess of silver nitrate. Drained thoroughly, transferred to a small evaporating basin, covered with a watch glass and dried in a vacuum desiccator to collect L-(+)-silver dimethoxy succinate (5.46g, 81.5% yield).
3.5.3 Asymmetric dihydroxylation of Octadec-cis-9-enoic acid (oleic acid) using L-(+)-silver dimethoxy succinate and iodine

L-(+)-silver dimethoxy succinate (4.2g, 0.011 mole) in benzene (70 ml) was heated to boil on a water bath. Added iodine (2.54g, 0.01 mole) in three lots during about 20 minutes and refluxed for 30 minutes. When the boiling stopped, added oleic acid (2.82g, 0.01 mole) dissolved in benzene (5 ml) and refluxed for 6 hrs. Cooled to room temperature and filtered from silver iodide. Benzene was removed by distillation from water bath and then on suction pump. The residue was hydrolysed using alcoholic KOH solution (7%, 50 ml). Removed most of the alcohol, diluted with water and acidified with concentrated hydrochloric acid. The crude dihydroxy acid (1.64g, 51.9% yield) was collected, dried in air for some time and triturated with cold petroleum ether (5 ml) to dissolve unreacted oleic acid. Filtered and recrystallised from ethanol to give erythro-9, 10-dihydroxy stearic acid, melting at 131-132\(^0\)C.

\(^1\)H NMR (400 MHz, MeOD):
\[\delta 0.897 \text{ ppm (t, } J=7.0 \text{ Hz, 3H) ; 2.277 (t, } J= 7.2 \text{ Hz, 2H) ; 1.3-1.6 (m, 26 H); 3.25 (m, 2H)}\]

\(^{13}\)C NMR (100 MHz, MeOD):
\[\delta 14.43, 23.74, 26.1, 27.08, 30.21, 30.44, 30.66, 30.86, 33.07, 33.9, 34.97, 49.01, 75.70, 77.72\]

IR (KBr) \(v_{\text{max.}}\): 3275, 2916, 2848, 1695, 1299, 1072, 934, 721 cm\(^{-1}\)

\([\alpha]_D^{30} - (+)-0.312^0\)

Dihydroxylation of oleic acid was carried out using an analogous procedure employing silver succinate in place of L-(+)-silver dimethoxy
succinate. The measurement of optical rotation showed that the product is optically inactive.

3.5.4 Asymmetric dihydroxylation of octadec-9-enoic acid (elaidic acid)

Iodine (2.54g, 0.01 mole) was refluxed with L-(+)-silver dimethoxy succinate (4.2g, 0.011 mole) in benzene (70 ml) for about 45 minutes. When the boiling stopped, added elaidic acid (2.82g, 0.01 mole) dissolved in benzene (5 ml) and continued heating for 6 hrs. Cooled and filtered from silver iodide. Removed the solvent by distillation and hydrolysed the residue using alcoholic KOH solution. Removed most of the ethanol, diluted with water and acidified with concentrated hydrochloric acid. The crude dihydroxy acid (1.54g, 48.7% yield) was collected, dried and then triturated with petroleum ether to dissolve the unreacted elaidic acid. Filtered and recrystallised from ethanol to get threo-9, 10-dihydroxy stearic acid, melting at 98°C.

$^1$H NMR (400 MHz, MeOD)

$\delta$ 0.897 ppm (t, $J= 6.8$ Hz, 3H); 2.273 (t, $J= 7.4$ Hz, 2H); 1.3-1.6(m, 26 H); 3.339(m, 2H)

$^{13}$C NMR (100 MHz, MeOD)

$\delta$ 15.0,23.75,26.12, 26.98, 30.23, 30.45, 30.68, 30.88,33.07, 33.61, 34.99,49.01, 75.96

IR (KBr) $\nu_{max}$: 3339,2915, 2848,1699,1297, 1077, 923, 721cm$^{-1}$

$[\alpha]_{D}^{20} = (+)2.364^0$ (C, 0.73, MeOD)

Elaidic acid was hydroxylated using an analogous procedure employing silver succinate in place of L-(+)-silver dimethoxy succinate. Measurement
of the optical rotation showed that the threo-9, 10-dihydroxy stearic acid formed is optically inactive.

3.5.5 Asymmetric dihydroxylation of octadec-cis-6-enoic acid (Petroselenic acid)

Petroselenic acid (2.82g, 0.01 mole) was hydroxylated using L-(+)-silver dimethoxy succinate (4.2g, 0.011 mole) and iodine (2.54g, 0.01 mole) in benzene (70 ml) exactly as described under 3.5.3. The resulting product was hydrolysed using alcoholic KOH solution to collect crude dihydroxy acid (1.2g, 38.2%). Recrystallisation of the product from ethanol, after petroleum ether treatment, gave erythro-6, 7-dihydroxy stearic acid, melting at 121°C.

\[\begin{align*}
\text{H NMR (400 MHz, MeOD)} & \\
\delta & 0.895\text{ppm (t, } J = 6.8 \text{ Hz, 3H); 2.304 (t, } J = 6.6 \text{ Hz, 2H); 1.3-1.6 (m, 26H); 3.325 (m, 2H)} \\
\text{C NMR (100 MHz, MeOD)} & \\
\delta & 14.32, 23.74, 26.22, 27.04, 30.48, 30.77, 30.88, 33.08, 33.67, 35.02, 49.01, 75.88 \\
\text{IR (KBr) } \nu & \text{max. } 3237, 2914, 2848, 1690, 1274, 1072, 942, 719 \\
\text{[α]} & \text{D}^0 = (+)-3.482^\circ \text{ (C, 0.762, MeOD)}
\end{align*}\]

Hydroxylation of petroselenic acid using silver succinate in place of L-(+)-silver dimethoxy succinate gave a product which showed no optical activity.