Chapter 2

Synthesis of Flavour Important Molecules from Limonene
Section 2.1: Synthesis of flavour molecules from limonene

2.1.1 Introduction

Monoterpene hydrocarbons are the major constituents of essential oils of spices and herbs that are used in flavor and fragrance industry [1]. \( R\)-(+) limonene is a major component of essential oils of more than 300 plants and also in the citrus fruits peel [2]. It has typical citrus flavor, used in creams, products like fruit beverages and ice creams. It has also used in cosmetic formulations such as soaps, perfumes, household cleaning products [3]. It has one chiral center and two double bonds with major reactivity differences. This structural feature of limonene makes it as an ideal substrate for the synthesis of important flavor and perfumery chemicals with the \( p\)-methane skeleton. The important conversions that lead to the formation of several oxygenated of limonene are presented in chapter 1 (Scheme 1.3).

In this section, we report the synthesis of important intermediates and aroma molecule like carvone starting from (+)-limonene. Carvone, an important flavor compound, is a monoterpene by composition and is having additional oxygen in the limonene skeleton. It is naturally found mainly in the essential oil of seeds of caraway and dill [4]. Carvone has a pair of enantiomers with distinguishable odor. \( R\)-(-)-Carvone has spearmint odor whereas other enantiomer \( S\)-(+) -carvone has caraway odor [5]. Though spearmint oil has ~51\% \( R\)-(\( )\)-carvone, its commercial production is by chemical synthesis from limonene. Few important chemical transformations of limonene to carvone are also presented in this chapter.

The \( R\)-(\( )\)-Carvone is prepared from \( R\)-(+) limonene by the addition of nitrosyl chloride followed by oxidation process [6, 7] and bio-oxidation process [8]. Carvone has many applications in flavour and fragrance industry. It acts as an
antimicrobial agent [9] and is used as building block for the synthesis of natural products. It also finds application as a biochemical environmental indicator [10].

We report here the synthesis of \( R-(-)-\)carvone from \( R-(+)-\)limonene \textit{via} its vicinal hydroxy-bromo intermediate (bromohydrins). Bromohydrins are used as intermediates in synthetic organic chemistry, particularly in stereo, regio and chemoselective reactions (Scheme 1.4) [11]. 2-Bromo-1-hydroxy-\( p \)-menth-8-ene (limonene bromohydrin) can be prepared easily from limonene by the addition of –Br and –OH across double bond at position 1,2 using NBS [12]. It was further used to prepare\( \text{trans} \)-limonene oxide, by treating with a base like \( \text{Na}_2\text{CO}_3 \). This is stereo-specific reaction and generates stereo-specific epoxide [12]. There are plenty of reports on the utility of chiral epoxides for the synthesis of many flavors and biologically important compounds [13, 14].

Synthesis of an intermediate such as 2-bromo-1,8-cineole from limonene was also studied. 2-Bromo-1,8-cineole is a key molecule for array of further conversion to aroma molecules. The essential oil of salvia species contains 1,8-cineole, commonly known as eucalyptol, as a major component [15]. It has pleasant spicy aroma and taste, hence used in cosmetics, mouthwash, flavorings, and fragrances. The 1,8-cineole exhibits insecticidal and herbicidal activity [16,17]. Eucalyptol easily forms adducts with phosphoric acid, resorcinol, \( o \)-cresol and halogen acids. The aroma of red wine is mainly due to the presence 1,8-cineole and it can be synthesized from limonene and \( \alpha \)-terpineol [18]. The rhizomes of \textit{Alpinia galanga} willd (greater galangal) has woody, floral odor, and exhibit several medicinal properties. The major aroma components present in the rhizome are isomers of 2-hydroxy-1,8-cineole and 2-acetoxy-1,8-cineole [19]. An exploratory study on the synthetic utility of 2-bromo-1,8-cineole for its conversion to 2-hydroxy-1,8-cineole and 2-oxo-1,8-cineole has
been conducted. It is revealed that the substrate was stable and resistant to further conversions. The intermediate preparation from limonene *via* its bromohydrin derivative is presented in Scheme 2.1.1.

### 2.1.2 Experimental

#### 2.1.2.1 Isolation of *R*-(-)-limonene

In a 250 mL RB flask, cold pressed orange oil was taken and set for fractional distillation under reduced pressure. The fraction that was collected at 64-65 °C at 9 mm Hg was authenticated to be pure *R*-(-)-limonene by NMR, IR, and HRMS spectral studies. The spectral data were in agreement with reference *R*-(-)-limonene.

![Structural formula of *R*-(-)-limonene]

B.p. 55 °C/1Torr $[\alpha]_D^{20} = +126^\circ$, > 98 %, $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 5.42$ (bs, 1H, CH), 4.73 (s, 2H, CH$_2$), 2.04-2.15 (m, 3H, CH$_2$), 1.92-2.00 (m, 2H), 1.82 (m, 1H, CH$_2$), 1.76 (s, 3H, CH$_3$), 1.68 (s, 3H, CH$_3$), 1.49 (ddd, $J_1 = 24.05$ Hz, $J_2 = 11.61$ Hz, $J_3 = 5.61$ Hz, 1H, CH); $^{13}$C NMR (125 MHz,CDCl$_3$): $\delta = 149.9, 133.4, 120.3, 108.0, 40.7, 30.5, 30.2, 27.6, 23.1, 20.4$: HRMS: [M+H]$^+$ for C$_{10}$H$_{17}$, Calculated: 137.1378, found: 137.1372.

#### 2.1.2.2 Preparation of carvomenthene (*p*-menth-1-ene)

In a hydrogenation flask *R*-(-)-limonene (25 g) was taken with ethanol (100 mL). Raney nickel (2.5 g) was added to the flask and set for hydrogenation at 2 atm [20]. Hydrogen pressure was maintained until complete conversion of limonene to carvomenthene. The progress of the reaction was periodically monitored by NMR for the disappearance of olefin proton at 4.76 ppm. After the completion of hydrogenation (4 h), the contents were filtered, and the residue was washed with
ethanol (20 mL). The mixture was transferred to separating funnel, the upper layer $R$- (+)-$p$-menth-1-ene (24 g) was collected. It was subjected to distillation under reduced pressure for further purification.

Yield: 24 g (96%), b.p. 50-51ºC/2 Torr, $[\alpha]_{D}^{20} = +101.5\degree$ (neat), Lit: $[\alpha]_{D}^{20} = +96\degree$ [20]. $^1$H NMR (500MHz, CDCl$_3$): $\delta = 5.40$ (bs, 1H, CH), 1.95-2.03 (m, 3H, CH$_2$), 1.71-1.79 (m, 2H), 1.66 (s, 3H, CH$_3$), 1.49 (octet, $J = 6.59$ Hz, 1H, CH), 1.25 (m, 2H, CH$_2$), 0.91 (t, $J = 6.98$, 6H): $^{13}$C NMR (125 MHz,CDCl$_3$): $\delta = 133.5$, 120.7, 39.7, 31.9, 30.5, 28.6, 26.1, 23.1, 19.6, 19.3: HRMS: [M+H]$^+$ for C$_{10}$H$_{19}$, Calculated: 139.1478, found: 139.1473.

2.1.2.3 Purification of N-Bromosuccinimide (NBS)

The NBS (100 g) was taken in a conical flask and dissolved in distilled water (1L) under boiling temperature. It was filtered, and the resultant clear brown colored filtrate was allowed to cool at room temperature. The colorless crystalline solid separated out was filtered, washed with hot water and suck dried. It was further dried in a desiccator over anhydrous CaCl$_2$ for 12 h. Then pure white crystalline NBS (75 g) obtained was used for the preparation of bromohydrins.

2.1.2.4 Preparation of 2-bromo-1-hydroxy-$p$-menth-8-ene

In a 250 mL RB flask, $R$-(+)-limonene (25 mmol, 3.40 g) was taken with 15% aqueous acetone (30 mL). The reaction mixture was cooled to 0 ºC, and NBS (25 mmol, 4.47 g) was added slowly over 20 minutes. The reaction was stirred at ambient temperature and progress was monitored by TLC analysis. After completion of the reaction (20 min), acetone was evaporated from the mixture and residue was diluted
with water (100 mL). The aqueous solution obtained was then extracted with DCM (15 mL x 3), and combined organic layer was washed with brine solution. It was then dried over anhydrous Na$_2$SO$_4$ and concentrated to get a crude product (5.75 g). The crude product was purified by column chromatography over SiO$_2$ gel (100-200 mesh). Pure product (5.3 g) obtained was characterized by NMR, IR, and HRMS spectral studies.

![Chemical Structure](attachment:image.png)

Yield: 5.3 g, (91.3 %); $[\alpha]_{D}^{20}$ (c = 0.29, CH$_3$OH) = 50.68°, Lit: $[\alpha]_{D}^{20}$ = 59° (neat), b.p. 90 °C/0.6 torr, Lit [12] 95°C/ 1 torr, $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 4.77 (d, $J$ = 11.7 Hz, 2H), 4.18-4.22 (m, 1H), 2.41-2.49 (m, 1H), 2.26 (ddd, $J$ = 14.4, 11.1, 3.3 Hz, 1H), 1.96-2.05 (m, 1H), 1.92-2.01 (m, 1H), 1.74 (s, 3H), 1.55-1.63 (m, 1H), 1.52-1.67 (m, 2H), 1.42 (s, 3H): $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 148.4, 109.5, 71.7, 38.3, 35.7, 33.2, 29.4, 26.1, 21.3: GC-MS ($m/z$): 232(2), 234(2), 217(2), 214(4), 153(2), 135(69), 108(39), 95(13), 93(43), 71(100), 43(73): IR (neat): 2938(s), 3083(m), 3410(broad, s) cm$^{-1}$: HRMS: [M+H]$^+$ for C$_{10}$H$_{18}$BrO, Calculated: 233.0578, found: 233.0569.

2.1.2.5 Preparation of (1S,2S,4R)-2-Bromo-1-hydroxy-p-menthane

In a 250 mL RB flask, $R$-(+)-carvomenthene (25 mmol, 3.45 g) was taken with 15% aqueous acetone (30 mL). The reaction mixture was cooled to 0 °C, and NBS (25 mmol, 4.47 g) was added slowly over 20 minutes. The reaction was stirred at ambient temperature and progress was monitored by TLC analysis. After completion of the reaction (20 min), acetone was evaporated from the mixture and residue was
diluted with water (100 mL). The aqueous solution obtained was then extracted with DCM (15 mL x 3), combined organic layer was washed with brine solution. It was then dried over anhydrous Na$_2$SO$_4$ and concentrated to get crude product (5.75 g). The crude was purified by column chromatography over SiO$_2$ gel (100-200 mesh). Pure product (5.4 g) obtained was characterized by NMR, IR and HRMS spectral studies.

Yield: 5.4 g, (92.3 %); $[\alpha]D^{20}$ (c = 0.33, CH$_3$OH) = 59.35°, b.p. 96 °C/1 torr, $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 4.19 (bs, 1H), 2.04-2.07 (m, 1H), 1.88-1.99 (m, 3H), 1.51-1.60 (m, 4H), 1.41 (s, 3H), 0.91 (d, $J$ = 2.44 Hz, 3H), 0.89 (d, $J$ = 2.5 Hz, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 71.9, 60.8, 37.6, 34.6, 33.2, 31.1, 29.2, 24.3, 20.1, 19.9; GC-MS (m/z): 236(5), 234(5), 218(4), 216(4), 155(21), 137(78), 110(10), 71(100), 43(71); IR (neat): 2872(s), 2958(s), 3410(broad, s) cm$^{-1}$; HRMS: [M+H]$^+$ for C$_{10}$H$_{20}$BrO, Calculated: 235.0678, found: 235.0671.

2.1.2.6 Preparation of trans-limonene oxide

The Limonene bromohydrin (5 mmol, 1.16 g) was taken in 50 mL RB flask and dissolved in CH$_3$CN (20 mL). To this solution, catalytic amount of InCl$_3$ (0.5 mmol, 0.11 g) and NaBH$_4$ (10 mmol, 0.38 g) were added slowly. The contents of the flask were magnetically stirred at room temperature. The progress of the reaction was monitored by TLC analysis. After completion of the reaction (24 h), the mixture was filtered and filtrate was concentrated. The residue was taken in ethyl acetate (20 mL) and washed with water followed by brine solution. Further organic layer was dried
over anhydrous Na$_2$SO$_4$ and flash evaporated to get crude product. Purification was carried out by column chromatography. The product trans–limonene oxide was confirmed by spectral data and in comparison with literature data.

Yield: 0.74 g, (97 %); b. p. 78-80 °C/1.33 kPa, [Lit][21]: 57–59 °C/0.33 kPa; [$\alpha$]$^{D}_{20}$ = +74° (c = 1, MeOH), [Lit][22]: +82°; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 4.66 (s, 2H, -CH$_2$), 2.98 (d, 1H, $J$ = 5.3 Hz, -CH), 2.00-2.05 (m, 2H, -CH$_2$), 1.84-1.89 (m, 1H), 1.68-1.72 (m, 2H, -CH$_2$), 1.66 (s, 3H, -CH$_3$), 1.35-1.39 (m, 2H, -CH$_2$), 1.31 (s, 3H, -CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 148.8, 108.7, 58.9, 57.1, 40.4, 30.4, 29.5, 24.02, 22.7, 19.8; MS (m/z): 152(2), 137(8), 119(9), 108(76), 94(89), 79(51), 67(93), 43(100); HRMS: [M+H]$^+$ for C$_{10}$H$_{17}$O, Calculated: 153.1278, found: 153.1275.

2.1.2.7 Preparation of trans-carvomenthene oxide

The Carvomenthene bromohydrin (5 mmol, 1.17 g) was taken in 50 mL RB flask and dissolved in CH$_3$CN (20 mL). To this solution, catalytic amount of InCl$_3$ (0.5 mmol, 0.11 g) and NaBH$_4$ (10 mmol, 0.38 g) were added slowly. The contents of the flask were magnetically stirred at room temperature. The progress of the reaction was monitored by TLC analysis. After completion of reaction (24 h), the mixture was filtered and filtrate was concentrated. The residue was taken in ethyl acetate (20 mL) and washed with water followed by brine solution. Further organic layer was dried over anhydrous Na$_2$SO$_4$ and flash evaporated to get crude product. Purification was carried out by column chromatography. The product trans–limonene oxide was confirmed by spectral analysis and in comparison with literature data.
Yield: 0.75 g, (96.4%); b. p: 73-75 °C/0.66 kPa, $[\alpha]_D^{20} = +48^\circ$ (c = 1, MeOH); $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 2.96$ (d, 1H, $J = 5.3$ Hz, -CH), 1.91-2.00 (m, 2H, -CH$_2$), 1.61 (ddd, 1H, $J_1 = 14.51$ Hz, $J_2 = 12.21$ Hz, $J_3 = 4.8$ Hz) 1.51 (dd, 1H, $J_1 = 15.0$, $J_2 = 11.62$, -CH$_2$), 1.37 (sept, 1H, $J = 6.73$ Hz, -CH), 1.29 (s, 3H, -CH$_3$), 1.10 (dq, 2H, $J_1 = 12.46$ Hz, $J_2 = 4.16$ Hz, -CH$_2$), 1.01 (ds, 1H, $J_1 = 6.15$ Hz, $J_2 = 2.05$ Hz, -CH ), 0.82 (d, 6H, $J = 6.92$ Hz, -CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 59.2$, 57.4, 38.9, 31.9, 30.6, 27.5, 22.7, 22.1, 19.3, 18.9; MS($m/z$): 154(2), 139(20), 125(13), 111(46), 97(9), 83(20), 69(24), 55(32), 43(100); HRMS:[M+H]$^+$ for C$_{10}$H$_{19}$O, Calculated: 155.1478, found: 155.1476.

### 2.1.2.8 Synthesis of $R$-(-) Carvone

The trans-Limonene oxide (10 mmol, 1.52 g) was taken in a 100 ml RB flask, and 2-butanone (20 mL) was added. The mixture was cooled to 0 °C, the CrO$_3$ dissolved in water (25 mmol, 25 g) was then added slowly. The reaction was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction (3 h), 10 mL isopropanol was added to quench the reaction. The reaction mixture was concentrated to afford residue, and 20 mL pyridine was added to dissolve it. The solution was cooled to 0 °C and SOCl$_2$ (125 mmol, 10 mL) was added slowly and stirred for 1 h at the same temperature. The reaction mixture was then poured into 100 mL water. The resultant precipitate was extracted with DCM (20 mL x 3). The combined organic layer was washed with 5% HCl solution followed by brine solution. It was then evaporated to get crude product. The crude
product was purified by column chromatography over silica gel (100-200 mesh). Pure product \((R-(-)-carvone)\) obtained was characterized by spectral studies. The spectral data obtained were in agreement with the standard \(R-(-)-carvone\) spectral data.

![Structure of R-(-)-carvone](image)

Yield: 1.05 g (70 %), Colorless liquid, b. p. 58-60 °C/ 3.5 Torr. \(^1\)H NMR (500 MHz, CDCl\(_3\)): 1.77 (s, 3H, -CH\(_3\)), 1.80 (m, 3H, -CH\(_3\)), 2.29-2.39 (m, 2H, -CH\(_2\)), 2.43-2.47 (m, 1H,-CH\(_2\)), 2.58-2.62(m, 1H,-CH\(_2\)), 2.68-2.72(m, 4, 1H, -CH), 4.77 (s, 1 H,-CH\(_2\)), 4.82 (s, 1H, -CH\(_2\)), 6.76-6.78 (m, 1H, -CH); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): 15.3, 20.2, 30.9, 42.2, 42.8, 110.1, 135.1, 114.2, 146.4, 199.4; MS (m/z): 150(8), 135 (4), 122 (4), 117(2) 108(29), 94 (6), 93 (33), 91 (12), 82 (100), 79 (17), 54 (42), 41 (19); IR (neat): 1675(s), 2923(s), 3082(s) cm\(^{-1}\); \([\alpha]\)\(_{20}^D\) = -47.17° (c = 0.19, CH\(_3\)OH); HRMS (ESI): [M+H]\(^+\) Calculated for C\(_{10}\)H\(_{15}\)O, 151.1123, found 151.1084.

2.1.2.9 Preparation of 2-Bromo-1,8-cineole

In a 50 mL RB flask, limonene bromohydrin (5 mmol, 1.16 g) was taken and diluted with dichloromethane (20 mL). To this solution Et\(_3\)SiH (10 mmol, 1.16 g) and InCl\(_3\) (0.5 mmol, 0.11g) were added slowly. The reaction mixture was allowed to stir at room temperature till the completion of reaction (20 h). The progress of the reaction was monitored by TLC analysis with 3% PMA staining agent. After completion of the reaction, the mixture was filtered, and the residue was washed with 5 mL dichloromethane. The filtrate thus obtained was flash evaporated and purified
by column chromatography using SiO$_2$ (200-400 mesh size). The pure product (1.08 g, 93\%) was characterized by NMR, IR, and HRMS spectral studies.

Colorless liquid, Yield: 1.08 g (93\%), b. p. 78-80 °C/ 0.7 Torr, $[\alpha]_{20}^D = 8.6^\circ$ (c =3, CH$_3$OH); $^1$H NMR (500MHz, CDCl$_3$): $\delta = 3.88$ (ddd, $J_1 = 10.87$ Hz, $J_2 = 4.85$ Hz, $J_3 = 2.12$ Hz, 1H, CH), 2.52-2.60 (m, 1H, CH$_2$), 2.34 (t, $J = 12$ Hz, 1H, CH$_2$), 2.03 (sept, $J = 6.83$ Hz, 1H, CH), 1.73-1.84 (m, 1H, CH$_2$), 1.67 (t, $J = 6.88$ Hz, 2H), 1.52-1.58 (m, 1H, CH$_2$), 1.46 (s, 3H, CH$_3$), 0.95 (d, 6H, $J = 6.80$ Hz, CH$_3$); $^{13}$C NMR (125 MHz,CDCl$_3$): $\delta = 90.0$, 85.5, 53.3, 43.4, 32.8, 32.4, 31.7, 18.5, 17.5, 17.2; MS ($m/z$): 234(3), 219(3), 191(20), 153(55), 135(10), 55(40), 43(100), 41(95); HRMS (ESI): [M+H]$^+$ Calculated for C$_{10}$H$_{18}$OBr, 233.0578, found 233.0576.
2.1.3 Results and Discussion

The limonene is a clear liquid and exists in two chiral forms ($R$ and $S$). The $R$-enantiomer constitutes about 90-95% of citrus peel oil. The fractional distillation of orange oil, obtained from cold pressed citrus peel, under reduced pressure, affords $R$-$(+)$-limonene at 65-66 °C at 9 mm Hg. The easy, eco-friendly and quantitative availability of $R$-$(+)$-limonene is the main reason to choose it as a starting material for the synthesis of several flavor molecules. In this section, we report a new synthetic protocol for synthesis of molecules of flavor interest. In this direction $R$-$(+)$-limonene was first converted into limonene bromohydrin (2-bromo-1-hydroxy-$p$-menth-8-ene) by treating it with NBS in aqueous acetone (Scheme 2.1.1). It afforded the compound in high (>90%) yield [12]. When limonene bromohydrin treated with NaBH$_4$ in the presence of catalytic amount of Lewis acid InCl$_3$, dehydrohalogenation took place. It resulted in the formation of trans-limonene oxide (Scheme 2.1.2) in excellent yield (96%). The formation of trans-limonene oxide was ascertained by the NMR analysis, which shows proton signal attached to oxirane ring at 2.98 ppm and disappearance of proton attached to carbon containing bromine at 4.20 ppm in the starting material. A similar reaction with NaBH$_4$ in the presence of ZnBr$_2$ also afforded trans-limonene oxide in excellent yield (97%). In yet another reaction with Pd/C in presence of NaOH was resulted in the formation of trans-limonene oxide with yield of 97%.

The carvomenthene, a hydrogenated limonene with saturated double bond at position 8, was also treated with NBS to afford 2-bromo-1-hydroxy-$p$-menthane (carvomenthene bromohydrin). The carvomenthene bromohydrin also undergoes similar cyclization with the elimination of HBr to afford trans-carvomenthene oxide (Scheme 2.1.2). The formation of product was confirmed by the disappearance of
proton attached to carbon containing bromine at 4.19 ppm and appearance of the proton attached to oxirane ring at 2.96 ppm.

![Scheme 2.1.1: Synthesis of 2-bromo-1,8-cineole](image)

The synthetic utility of limonene bromohydrin was then explored to prepare the important flavor compounds of *Alpinia* galanga and grape [18, 19]. The components like (±)-2-hydroxy-1,8-cineole and (±)-2-acetoxy-1,8-cineole are major flavorants of these sources. 2-Bromo-1,8-cineole is an ideal precursor for synthesis of these naturally occurring terpene derivatives. Monoterpene cineoles are well known for their phytotoxic activity [23] and 1,8-cineole, and its natural analogue are known to suppress the growth of several weeds [24]. 2-Bromo-1,8-cineole is synthesized earlier in presence of Lewis acid catalysts, and reactions are carried out in benzene solvent [25].

![Scheme 2.1.2: Synthesis of trans-oxides](image)
Due to limited usage of benzene as a solvent in the organic synthesis, the synthesis of 2-bromo-1,8-cineole with other organic solvents was planned. On reaction of limonene bromohydrin with Et₃SiH in the presence of catalytic quantity of InCl₃ in dichloromethane at room temperature afforded 2-bromo-1,8-cineole. This reaction took place by an internal cyclic addition of hydroxyl group with olefinic bond with net result in the formation of 2-bromo-1,8-cineole (Scheme 2.1.1). It was characterized based on spectral studies. In NMR spectrum broad singlet integrated to single proton appeared at 3.88 ppm indicates it is attached to carbon containing bromine. A singlet peak at 1.46 ppm integrated to three protons indicated that the methyl group and its connection with cyclic ether. The olefinic protons of limonene bromohydrin that appear at 4.77 ppm were absent in the product. In the $^{13}$C NMR, number of carbon signals was found to be ten. Two signals at 90 and 85.5 indicated carbons attachment to oxygen atom and a signal at 53.3 ppm indicated the carbon attached to the bromine atom (Figure 2.1.1). It was further confirmed by 2-D NMR spectral studies. The connectivity of carbon at 53.3 ppm with the proton at 3.88 ppm was confirmed by 2D HSQC experiment. The two quaternary carbons were differentiated based on HMBC correlation (Figure 2.1.2). The peak at 90 ppm presents correlation with isopropyl methyl protons at 0.95 ppm & 0.94 ppm and also with methine proton at 2.03 ppm. Another quaternary carbon resonating at 85.5 ppm shows correlation only from methyl protons at 1.46 ppm (Figure 2.1.1). In the GC-MS spectrum molecular ion [M$^+$] and [M+2]$^+$ peaks appeared at 232 and 234 in the ratio 1:1, which indicated the presence of a bromine confirms the molecular weight of the compound. The preparation of 2-bromo-1,8-cineole was also carried out in chloroform and the presence of various Lewis acid catalysts. The results are summarized in Table 2.1.1.
Figure 2.1.1: HSQC Correlation spectra of 2-bromo-1,8-cineole

Figure 2.1.2: HMBC Correlation spectra of 2-bromo-1,8-cineole
Table 2.1.1: Preparation of 2-bromo-1,8-cineole

<table>
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<th>Yield %</th>
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<td>93</td>
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<tr>
<td>DCM</td>
<td>ZnBr₂</td>
<td>21</td>
<td>90</td>
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From the Table 2.1.1, it is clear that the reaction of limonene bromohydrin with triethyl silane in DCM is more feasible with respect to time and yield (entry 1). In chloroform also excellent yield was realized in optimum reaction time.

A new protocol for the synthesis $R$-(-)-carvone from $trans$-limonene oxide was developed. It is a two-step reaction in which the first stage is conversion of limonene to its bromohydrin followed by an easy preparation of $trans$-limonene oxide. The pure diastereo-$trans$-limonene oxide with chromium trioxide in 2-butanone followed by the reaction with thionyl chloride affords $R$-(-)-carvone in excellent yield (70%), (Scheme 2.1.3). The proton signal at 2.98 ppm attached to epoxy carbon was absent, and olefinic signal at 6.77 ppm has appeared. It was further confirmed by the carbonyl and methine carbon signals at 199.4 and 146.4 ppm respectively. It was further analyzed by HRMS and confirmed. The spectral data of synthesized product is in accordance with standard $R$-(-)-carvone.
2.1.4 Conclusion

In conclusion, important flavour molecule like $R$-(-)-carvone, and intermediate trans-limonene oxide were synthesized in a feasible approach. The starting compound $R$-(+)-limonene, is an abundantly available and an inexpensive natural compound. The essential precursor 2-bromo-1,8-cineole was synthesized in an easy approach. This intermediate can further be utilized for the synthesis of aroma compounds like ($\pm$)-2-acetoxy-1,8-cineole, ($\pm$)-2-hydroxy-1,8-cineole, and 1,8-cineole.
References


Section 2.2: Eco-friendly kinetic separation of cis-/trans-limonene and cis-/trans-carvomenthene oxides

2.2.1 Introduction

The chiral epoxides are versatile basic units for the synthesis of biological potential and synthetically useful compounds such as flavours, fragrances, fungicides, and herbicides [1]. They are also used as the precursor for the asymmetric synthesis of natural products [2-4]. The (R)-Limonene oxide is commercially available as a mixture of cis- and trans-mixture (Figure 2.2.1, 1a & 1b) in ~1:1 ratio. Owing to its easy and abundant availability at an economic cost, it is anticipated as the bio-renewable source of chiral epoxide for the synthesis of biodegradable polymers such as polyesters and polycarbonate [5]. A potent anti-Parkinson drug is synthesized from isomerization of chiral verbenol oxide [6]. Epoxides are converted to important compounds like esters, alcohols and carbonyl compounds by reduction, catalytic rearrangement and acid or base catalysed reactions [7]. Pure enantiomeric epoxides are used in the preparation of chiral compounds [4]. Some chiral compounds having cyclohexyl skeleton can be selectively reduced to diastereomers [8]. Limonene-1,2-oxide occurs abundantly in essential oils of Cymbopogon densiflorus is an example of monocyclic epoxide having cyclohexene skeleton [9].

Epoxidation of (+)-4R-carvomenthene (2) also yields cis-/trans-epoxides (2a & 2b) in ~1:1 ratio. The isolation of cis- and trans-epoxides from both carvomenthene and limonene oxide is very difficult by fractional distillation due to their close boiling point range. Also, isolation by column chromatography technique is not practicable because they have very close Rf value and both isomers elute together without separation. Therefore, epoxides are either synthesized by biological
or chemical methods [10, 11]. The best method of isolating the individual epoxides is by kinetic resolution. There are few reports in the literature where one isomer is selectively made to react while the other remains intact. These reactions are conducted either using chiral catalysts or special reagents. The isomer that remained unreactive under the experimental conditions has been isolated by fractional distillation or column chromatography purification.

**Figure 2.2.1:** Structures of 4-\(R\)-(+) -limonene, cis-/trans-limonene oxides, 4-\(R\)-(+) -carvomenthene and cis-/trans-carvomenthene oxides

The selective ring cleavage of epoxides has been carried out by mercury salts, but this method requires an additional de-metallation step [12]. Base-catalysed ring opening of cis- or trans-epoxides yields isolation of either of the epoxide was depending upon base employed in the reaction, but the reactions are usually affected at higher temperatures [13]. Monocyclic terpene epoxides are also kinetically separated using molybdenum complex [14]. Hydrolytic kinetic separation affords pure epoxides but reaction proceeds with particular catalyst and for terminal epoxides [15]. Monocyclic terpene epoxides containing substituent at C-4 position are
kinetically separated using racemic chromium salen complex [16]. There is a report on the kinetic separation of terpene oxides in methanol using Lewis acid as catalysts [17]. The kinetics of the reaction of cis-/trans-oxides depends on the photo-assisted stereo-differentiation in which cleavage of cis-epoxides occurs preferentially to the trans-epoxides. In this case few Lewis acids such as ZnCl₂, ZnBr₂ and ZnI are tested.

In our study, an environmentally benign protocol for separation of cis-/trans-limonene oxide, and cis-/trans-carvomenthene oxide has been planned. Accordingly, green solvents like water, methanol, were considered to react with the mixture of cis-/trans-oxides. Lewis acid catalyst like InCl₃ was selected for the study. The advantage of InCl₃ as a catalyst is, it has high solubility in water and has an excellent tolerance of moisture when compared to other transition metal catalysts [18].

Initially, the reaction of cis-/trans-limonene oxide in water (1a & 1b) in the presence of catalytic amount of Lewis acid InCl₃ (10 mmol) was carried out. It resulted in preferential cleavage of the cis-epoxide whereas trans-epoxide remains intact as shown in Scheme 2.2.1. In next step, the crude product was taken for fractional distillation and the product 1b was separated from product 1d. Hence, in detail study was carried out and it resulted in the development of a new protocol to separate trans-limonene oxide. The protocol also has an advantage since the green solvent water was used in the reaction. The water played a dual role as a nucleophile as well as the solvent. The reaction was further extended to cis-/trans-carvomenthene oxide (2a and 2b) and found it also resulted in the efficient kinetic separation of trans-carvomenthene oxide. In both the cases cis-oxide cleaved to afford diol-product. Both the diol and trans-oxides were separated by fractional distillation. The pure compounds obtained were characterized by NMR, IR and mass spectral analysis. The
physical data such as boiling point and specific optic rotation of the compounds were also recorded and compared with the available literature values.

The above protocol of kinetic separation of trans-epoxides was then tested under similar conditions using methanol as a solvent. It also resulted in the kinetic separation of trans-oxide from both limonene and carvomenthene. Methanol was added preferentially to the cis-oxide and trans-oxide remained unreactive during this time was separated by fractional distillation. The products of the reaction were characterized by NMR, IR and mass spectral analysis. The boiling point and specific rotation data of the compounds were recorded and compared with the literature values.

![Scheme 2.2.1](image)

**Scheme 2.2.1:** Reaction of cis/trans-limonene and carvomenthene oxides in water in the presence of InCl$_3$

### 2.2.2 Experimental

#### 2.2.2.1 Separation of trans-limonene and carvomenthene oxides in water

A mixture of 30 mmol cis-/trans-epoxide was taken in a two neck RB flask along with 50 mL triple distilled water. To the reaction mixture 3 mmol InCl$_3$ was added and contents were stirred at 10-15 °C for limonene oxide and at 25 °C for carvomenthene oxide. Initially the reaction mixture was like an emulsion, slowly it
turned to hazy during course of the reaction. The progress of reaction was monitored by NMR till the disappearance of proton signal at 3.06 and 3.01 ppm, which is attached to epoxide ring at position 2 in compound 1a and 2a respectively. After the complete cleavage of cis-isomer, the reaction mixture was extracted with CH$_2$Cl$_2$ (30 mL×3). The combined organic extracts were again washed with brine solution. The organic layer separated was dried over anhydrous Na$_2$SO$_4$ and concentrated to afford the crude product, which was further purified by fractional distillation under reduced pressure. The physical and spectral data of the pure isolated products is presented below.

**trans-Limonene-oxide (1b):** Yield: 2.40 g, (97 %); b. p. 78-80 °C/1.33 kPa, [Lit][9]: 57–59 °C/0.33 kPa; $[\alpha]_{D}^{20} = +74^\circ$ (c = 1, MeOH), [Lit][19]: +82°; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 4.66 (s, 2H, -CH$_2$), 2.98 (d, 1H, $J = 5.3$ Hz, -CH), 2.00-2.05 (m, 2H, -CH$_2$), 1.84-1.89 (m, 1H), 1.68-1.72 (m, 2H, -CH$_2$), 1.66 (s, 3H, -CH$_3$), 1.35-1.39 (m, 2H, -CH$_2$), 1.31 (s, 3H, -CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 148.8, 108.7, 58.9, 57.1, 40.4, 30.4, 29.5, 24.02, 22.7, 19.8; MS (m/z): 152(2), 137(8), 119(9), 108(76), 94(89), 79(51), 67(93), 43(100)

**trans-Carvomenthene-oxide (2b):** Yield: 2.45 g, (96.4%); b. p. 73-75 °C/0.66 kPa, $[\alpha]_{D}^{20} = +48^\circ$ (c = 1, MeOH); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 2.96 (d, 1H, $J = 5.3$ Hz, -CH), 1.91- 2.00 (m, 2H, -CH$_2$), 1.61 (ddd, 1H, $J_1 = 14.51$ Hz, $J_2 = 12.21$ Hz, $J_3 = 4.8$ Hz ) 1.51 (dd, 1H, $J_1 = 15.0$, $J_2=11.62$, -CH$_2$), 1.37 (sept, 1H, $J = 6.73$ Hz, -CH), 1.29 (s, 3H, -CH$_3$), 1.10 (dq, 2H, $J_1 = 12.46$ Hz, $J_2= 4.16$ Hz, -CH$_2$), 1.01 (ds, 1H, $J_1 = 6.15$ Hz, $J_2= 2.05$ Hz, -CH ), 0.82 (d, 6H, $J = 6.92$ Hz, -CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 59.2, 57.4, 38.9, 31.9, 30.6, 27.5, 22.7, 22.1, 19.3, 18.9; MS(m/z): 154(2), 139(20), 125(13), 111(46), 97(9), 83(20), 69(24), 55(32), 43(100).
(1S,2S,4R)-1-Methyl-4-(prop-1-en-2-yl)cyclohexane-1,2-diol (1d): b.p. 115-117 °C/0.46 kPa; $[\alpha]_{D}^{20} = +42^\circ$ (c = 1, MeOH); Yield: 2.1 g (90 %); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 4.72 (s, 2H, -CH$_2$), 3.61 (t, 1H, $J = 3.12$ Hz, -CH), 2.21-2.29 (m, 1H, -CH), 1.91 (ddd, 1H, $J_1 = 13.99$ Hz, $J_2 = 11.47$ Hz, $J_3 = 2.84$ Hz, -CH$_2$), 1.72-1.77 (m, 1H, -CH$_2$), 1.71 (s, 3H), 1.61-1.66 (m, 1H, -CH$_2$), 1.52-1.56 (m, 2H, -CH$_2$), 1.47-1.52 (m, 1H, -CH$_2$), 1.24 (s, 3H, -CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 148.9, 108.6, 73.5, 71.1, 37.1, 33.6, 33.3, 26.1, 25.8, 20.7; MS (m/z): 170(2), 152(34), 137(21), 111(21), 108(46), 93(40), 82(35), 71(80), 67(46), 55(32), 43(100).

(1S,2S,4R)-4-Isopropyl-1-methylcyclohexane-1,2-diol (2c): b.p. 123-125 °C/0.46 kPa; $[\alpha]_{D}^{20} = +43^\circ$ (c = 1, MeOH); Yield 2 g, (85%); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 3.59 (t, 1H, $J = 3.45$ Hz, -CH), 1.93 (br, 2H, -OH confirmed by D exchange), 1.64-1.74 (m, 2H, -CH$_2$), 1.56-1.61 (m, 1H, -CH$_2$), 1.50-1.53 (m, 1H, -CH$_2$), 1.46-1.50 (m, 2H, -CH$_2$), 1.33-1.38 (m, 2H, -C(4)H and C(5)H$_2$), 1.24 (s, 3H, -CH$_3$), 0.88 (t, 6H, $J = 7.54$ Hz, -CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 73.7, 36.4, 33.4, 32.3, 31.0, 29.3, 25.8, 23.9, 19.7, 19.6; MS (m/z): 172(8), 154(4), 139(11), 111(52), 97(13), 83(28), 71(100), 55(48), 43(91).

### 2.2.2.2 General procedure for separation of trans-limonene and carvomenthene oxides in methanol

A mixture of 30 mmol cis/trans-epoxide in methanol was taken in a two neck RB flask. To this solution, 3 mmol InCl$_3$ was added and the reaction mixture stirred at room temperature. The progress of the reaction was monitored by NMR, till the complete disappearance of proton signal at 3.06 and 3.01 ppm in compound 1a and 2a at position 2 respectively. After completion of the reaction (4 h), methanol was evaporated and the products were extracted into CH$_2$Cl$_2$ (30 mL x 3). The organic layer was washed with water (30 mL x 3), followed by brine solution. The combined
organic layer was dried over anhydrous Na$_2$SO$_4$ and evaporated to get the crude product. Further it was purified by fractional distillation method under reduced pressure to get pure products. The physical and spectral data of products is presented below.

**(**1S,2S,4R)-2-Hydroxy-1-methoxy-p-menthan-8(9)-ene (1c):** Yield: 2.16g, (85%); b.p. 115–117 °C/0.66 kPa; $[\alpha]_{D}^{20} = +39^\circ$; $^1$H NMR (500 MHz, CDCl$_3$): δ = 4.72 (br s, 2H, CH$_2$), 3.68 (s, 1H, CH), 3.19 (s, 3H, OCH$_3$), 2.24 (tt, 1H, $J_1 = 11.70$ Hz, $J_2 = 3.52$ Hz, CH), 1.91 (ddd, 1H, $J_1 = 13.64$ Hz, $J_2 = 12.29$ Hz, $J_3 = 2.69$ Hz, CH$_2$), 1.80 (br, 1H, OH), 1.72 (s, 3H, CH$_3$), 1.70 (dt, 1H, $J_1 = 3.72$ Hz, $J_2 = 1.35$ Hz, CH$_2$ ), 1.62 (m, 1H, CH$_2$), 1.56 (dt, 1H, $J_1 = 13.64$ Hz, $J_2 = 1.77$ Hz, CH$_2$), 1.37-1.51 (m, 2H, CH$_2$), 1.18 (s, 3H, CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$): δ = 149.4, 108.4, 74.8, 72.0, 48.0, 37.1, 33.5, 28.5, 25.7, 20.6, 19.9; MS ($m/z$): 184(2), 169(4), 152(10), 108(15), 85(100), 72(21), 55(19), 43(16).

**(**1S,2S,4R)-2-Hydroxy-1-methoxy-p-menthane (2d):** Yield: 2.17 g, (86.8 %); b.p. 102–104 °C/0.33 kPa; $[\alpha]_{D}^{20} = 33^\circ$ (c = 1, MeOH); $^1$H NMR (500MHz, CDCl$_3$): δ = 3.62 (s, 1H, CH), 3.17 (s, 3H, CH$_3$), 2.40 (br, 1H, OH), 1.63-1.72 (m, 2H, -C(3)H$_2$ and -C(6)H$_2$), 1.52-1.59 (m, 1H, -CH$_2$), 1.50 (dd, 1H, $J_1 = 12.95$ Hz, $J_2 = 3.59$ Hz, -CH$_2$), 1.43-1.47 (m, 1H, -CH), 1.40-1.43 (m, 1H, -CH$_2$), 1.32-1.38 (m, 1H, -CH), 1.18-1.22 (m, 1H, -CH$_2$), 1.15 (s, 3H, -CH$_3$), 0.87 (t, 6H, $J = 6.67$ Hz, -CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$): δ = 75.2, 72.2, 48.0, 36.2, 32.0, 31.5, 28.6, 23.7, 19.8, 19.7, 19.5; MS ($m/z$): 186(6), 171(4), 154(4), 143(4), 136(11), 125(2), 111(10), 97(2), 85(100), 83(4), 72(20), 55(17), 43(13).
2.2.2.3 Preparation and estimation of peracetic acid

a) Concentration of hydrogen peroxide

In a 2 L round-bottom socket joint flask equipped with inner T-joint, which carries an air leak and a bent to the condenser, commercially available H\textsubscript{2}O\textsubscript{2} was taken (30\%, 1000 mL). Distillation under reduced pressure (30 mm Hg) was carried out at the constant rate maintaining the water bath temperature at 50 °C. Using iodometric method concentrated H\textsubscript{2}O\textsubscript{2} (300 mL) was estimated.

b) Estimation of hydrogen peroxide [20]

Reagents required: 2N H\textsubscript{2}SO\textsubscript{4} solution, 0.1N Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} solution, 3\% Ammonium molybdate solution, 10 \% v/v KI solution

In a conical flask, diluted hydrogen peroxide (25 mL, 1 mL of ~95 \% H\textsubscript{2}O\textsubscript{2} in 100 mL H\textsubscript{2}O) was taken, to the mixture 2N H\textsubscript{2}SO\textsubscript{4} solution (100mL), KI solution (10 mL) and 2-3 drops of ammonium molybdate were added. The liberated iodine was titrated with the standard sodium thiosulfate taken in a burette.

1 mL of 1N Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} = 0.01701 g H\textsubscript{2}O\textsubscript{2}

The concentration of H\textsubscript{2}O\textsubscript{2} was found to be ~ 98 \%.

c) Preparation of peracetic acid [20]

In a 2 L conical flask, glacial acetic acid (40 mL) and concentrated H\textsubscript{2}SO\textsubscript{4} (0.4 mL) were taken and the flask was cooled to about 15 °C. Keeping the temperature at 15-20 °C with occasional shaking, concentrated H\textsubscript{2}O\textsubscript{2} (28 mL, 98 \%) was added slowly over a period of 20-30 minutes. The mixture was kept overnight at ambient temperature and taken for estimation of peracetic acid.

2.2.2.4 Preparation of epoxides

The p-Menth-1-ene (0.05 mol, 6.9 g) was taken in a 100 mL RB flask, to this 20 mL DCM was added and cooled to 0 °C. Peracetic acid (9.0 g, 38 \%) saturated
with sodium acetate was added slowly under stirring at 0 °C. The progress of the reaction was monitored for the disappearance of the olefin signal by NMR. After completion of reaction (4 h), the mixture was poured into water (20 mL) and the organic layer was separated. Further the aqueous layer was extracted with DCM (10 mL × 2) and the combined organic layer was washed with water followed by brine. The clear organic layer was flash evaporated to get crude carvomenthene oxide. This was further purified by distillation under reduced pressure and taken for kinetic resolution.

2.2.2.5 Catalyst recyclability test

The catalytic action of InCl$_3$ was checked by carrying out reaction consecutively over for ten cycles. In each cycle the kinetic separation reaction was carried out on 10 mmol scale, the progress of the reaction was monitored by NMR, after completion of the reaction, the usual work up yielded the mixture of 1d and trans-epoxide. The aqueous layer separated during work up process was taken for next cycle reaction as it contains catalyst InCl$_3$. The same procedure was followed and repeated for 10 times. The efficiency of the catalyst decreased for each consecutive cycle and confirmed by monitoring the reaction time for each cycle. The data of ratio of cis- and trans-epoxide for ten cycles is given in Table 2.2.1. It was found that in every cycle, the ratio of cis- and trans-epoxide was different, which shows the catalytic role of InCl$_3$ in water. From the data presented in Table 2.2.1, it is clear that the catalytic activity of InCl$_3$ was intact for first two cycles and gradually decreases up to the fifth cycle. But from sixth cycle onwards the catalytic activity decreased further as the reaction took more time. However, the effect of the catalytic activity of InCl$_3$ was retained up to 10 cycles and can be reused efficiently for kinetic separation.


2.2.3 Results and Discussion

The commercially available limonene oxide containing \textbf{1a} and \textbf{1b} in the ratio ~1:1 was taken for the kinetic separation reaction in the presence of catalyst InCl$_3$ (10 mol\%) in water (Scheme 2.2.1). The progress of ring cleavage reaction was monitored by NMR. When the reaction was carried out at room temperature both the epoxide underwent ring cleavage and yielded a mixture of diaxial diol products. Since the reaction was fast no selectivity was observed. However, at low temperature the reaction was selective, and preferential cleavage of \textit{cis}-epoxide was noticed. During this time, \textit{trans}-oxide remains unreactive. The temperature condition was optimized and at 10-15 °C, \textit{trans}-epoxide did not take part in the reaction whereas \textit{cis}-epoxide reacted with the nucleophile to afford ring opened diaxial product.

The reaction was further continued to test the reactivity of \textit{trans}-oxide (\textbf{1b}) for 24 h. It was found that \textit{trans}-epoxide did not react under this condition. The optimized condition was diastereo-differentiating between \textit{cis}- and \textit{trans}-epoxides. During the reaction at 5 h, \textit{cis}-epoxide was almost completely reacted with hydroxyl nucleophile to afford \textit{trans}-diaxial diol (\textbf{1d}), whereas \textit{trans}-epoxide remains unreacted. The un-reacted \textit{trans}-epoxide was separated by fractional distillation under reduced pressure since diol and \textit{trans}-epoxide have a difference in their boiling range. After the separation of the \textit{trans}-epoxide, it was confirmed by comparing it with spectral data of standard \textit{trans}- limonene oxide (NMR).
Table 2.2.1: Reaction of cis/trans-limonene oxide in water in presence of 10% InCl₃

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<tr>
<th>Cycle No.</th>
<th>% oxide in 5 h</th>
<th>Time(h)ᵃ</th>
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<td>cis-oxide</td>
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ᵃTime taken for complete conversion of cis-oxide

The standard trans-limonene oxide was synthesized by treating limonene with NBS in aqueous acetone. The product 2-bromo-1-hydroxy-p-menth-8-ene (section 2.1, limonene bromohydrin) was then reacted with Na₂CO₃ in aqueous ethanol [21]. The product afforded was identified as trans-limonene oxide by NMR and confirmed by comparison with literature data. In NMR, a doublet proton signal appeared at 2.98 ppm, which indicates a proton attached to epoxide ring (1b), the corresponding proton of cis-oxide appeared at 3.01 ppm as singlet (Figure 2.2.4). This difference was utilized as a tool to monitor the reaction progress by periodic measurement of proton integration ratio. Once the complete consumption of cis-oxide (integration of singlet proton signal reaches close to zero) was found, the reaction was stopped and taken up.
for workup and purification. The reaction kinetics with respect to time as measured by NMR is given in **Figure 2.2.2**

![Figure 2.2.2: Kinetics of the reaction of cis/trans-limonene and carvomenthene oxides in water in the presence of InCl₃](image)

The reaction was then checked using different protic solvents such as methanol, ethanol and isopropyl alcohol. The best result in respect of selective cleavage of *cis*-epoxide was found in methanol. In ethanol and isopropyl alcohol, the stereoselectivity was not observed as both the stereoisomers reacted at the almost same rate. The reaction of *cis*-/trans-limonene oxide in methanol is presented in **Scheme 2.2.2**. It was found that 1a reacted at a faster rate and yielded the ring opened product 1c leaving behind 1b intact. Compounds 1b and 1c were then separated by fractional distillation under reduced pressure. In **Figure 2.2.3** the progress of the kinetic separation reaction of *cis*-/trans-limonene oxide & *cis*-/trans-carvomenthene oxide in methanol is presented.
Scheme 2.2.2: Reaction of cis/trans-limonene and carvomenthene oxides in methanol in the presence of InCl₃.

Figure 2.2.3: Kinetics of the reaction of cis/trans-limonene oxide and cis/trans-carvomenthene oxide in methanol in the presence of InCl₃.

Next, the reaction of cis-/trans-carvomenthene oxide under the same condition was taken up (Schemes 2.2.1 and 2.2.2). R-(+)-limonene was taken for hydrogenation reaction of in the presence of Raney nickel to afford carvomenthene. It was purified by fractional distillation under reduced pressure. Carvomenthene epoxide was
prepared by oxidation of carvomenthene using 30% peracetic acid. In GC analysis, it was found that the cis-trans-carvomenthene oxides are not well resolved. The ratio of cis- and trans-carvomenthene oxides was checked by NMR analysis. The integration of proton attached to epoxide ring at 2nd position in cis-epoxide exhibited as broad singlet at 3.01 ppm and it integrated to 0.45 whereas trans-epoxide shows doublet at 2.95 ppm and it integrated to 0.55 (Figure 2.2.5), hence the percentage ratio of cis- to trans-epoxide was taken as 45:55. The pure trans-carvomenthene oxide was also prepared via its β-bromo-tert-alcohol intermediate. Compound 2-bromo-1-hydroxy-\(\beta\)-menthane obtained by treating carvomenthene with NBS. This was followed by the addition of \(\text{Na}_2\text{CO}_3\) in aqueous ethanol [21].

The reaction of cis/trans-carvomenthene oxides in water in the presence of \(\text{InCl}_3\) catalyst was tested at 25 °C. It was found that the reaction took 4 h for complete consumption of cis-epoxide. Compound 2b remains unaffected during this time (Scheme 2.2.1). The kinetics of the reaction is presented in Figure 2.2.2. The same reaction when carried out at temperature 5-10 °C and 10-15 °C was found to cleave the cis oxide selectively but at a slower rate.

When the reaction was carried out for cis/trans-carvomenthene oxide using methanol as a solvent, cis-oxide reacted selectively to afford a ring opened product (1-methoxy-2-hydroxy-\(\beta\)-menthane), whereas trans-carvomenthene oxide remain unaffected (Scheme 2.2.2). The mixture of un-reacted trans-carvomenthene oxide and ring opened chiral product 2d were separated by fractional distillation as they have different boiling range. The graph showing rate of reaction versus time is shown in Figure 2.2.3.
Figure 2.2.4: Monitoring of oxirane ring proton of limonene oxide by NMR

Figure 2.2.5: Monitoring of oxirane ring proton of carvomenthene oxide by NMR
2.2.4 Reaction mechanism

A plausible mechanism for the kinetic resolution of trans-limonene oxide and trans-carvomenthene oxide in water and methanol using InCl$_3$ as a catalyst is presented in Figure 2.2.6. The isopropenyl moiety occupies an equatorial position in both cis-oxide and trans-oxide because of inherent conformational differences [13]. The interaction of InCl$_3$ with epoxide oxygen followed by its opening takes place at a faster rate in case of cis-oxide. The nucleophilic substitution takes place at more substituted carbon atom (C-1) because it has more $S_N$1 character. Whereas the interaction of InCl$_3$ with oxygen in trans-oxide is comparatively slower and according to Furst-Plattner rule, its cleavage with nucleophile leading to diaxial product takes place with nucleophile sitting on carbon atom C-2 [13]. Hence, this divergence in reactivity of cis-oxide and trans-oxide with Lewis acid towards nucleophilic substitution reaction helps the kinetic resolution of trans-oxide over cis-oxide by stopping the reaction at an appropriate time.

Figure: 2.2.6: InCl$_3$-Catalyzed solvolysis of cis-/trans-limonene oxide
2.2.5 Conclusion

In conclusion, we have developed a new, facile and eco-friendly kinetic separation method for cis-/trans-limonene and cis-/trans-carvomenthene oxides. An easily available and inexpensive Lewis acid InCl$_3$ was used as a catalyst to achieve the kinetic separation of trans-oxides in a simple experimental protocol. The catalytic activity of InCl$_3$ was found to be efficient up to ten cycles. When compared to the existing literature methods for kinetic separation, the protocol is superior in affording separation of terpene epoxides in high yield. The present methodology also works well and affords high yield of trans-oxides in the presence of protic solvent methanol.
References


