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Kinetic Separation of *cis*- and *trans*-Limonene Epoxide: Reaction of Diastereomeric Mixture of Limonene Oxides with Secondary Amine and Carbamate

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A simple kinetic separation of (1:1) diastereomeric mixture of limonene oxides was used to purify *cis*- and *trans*-diastereomers of (*R*)-(+)-limonene oxide. The epoxide ring of *trans*-isomer was selectively opened by (*R*)-*N*-methyl-(α-methyl-benzyl)amine. This secondary nucleophilic amine left *cis*-limonene oxide largely unreacted and was obtained up to 90% yield. In a diverse way, (*R*)-*N*-(α-methyl-benzyl)ethyl carbamate, selectively catalyze hydrolysis of *cis*-limonene oxide to 1,2-limonene diol leaving *trans*-limonene oxide largely unreacted. The unreacted *trans*-limonene oxide was recovered in up to 75% yield. HPLC and NMR analyses were used to demonstrate that the isolation of *cis*- and *trans*-diastereomers of (*R*)-(+)-limonene oxide has shown that > 98% were pure. As a result, depending on the realization of the secondary amine or carbamate in the presence of water, either *cis*- or *trans*-limonene oxide may be obtained in high diastereomeric purity.

Keywords: Kinetic separation, Limonene oxide, Diastereomer resolution, Secondary amine, Carbamate.

INTRODUCTION

The ring opening of epoxides with various nucleophiles is a largely used method for the creation of different functional groups on the backbone of organic molecules, which react as multifaceted intermediates for the preparation of various complex molecules [1-5]. The high reactivity of epoxides and directable regioselectivity, generally a base-catalyzed ring opening, will take place at the least hindered carbon atom whereas an acid-catalyzed ring opening occurs at the more substituted carbon atom [6], which makes these epoxides valuable starting compounds for the preparation of biologically active compounds [7,8].

Multiple investigations are carried out for the kinetic resolution of *trans*- and *cis*-oxide limonene from the cheap, commercially available 1:1 mixture of limonene oxides. *cis*- or *trans*-limonene oxide may be, therefore, obtained in high diastereomeric purity and important compounds (β-amino alcool and diol) are, respectively, obtained with a moderate yield. Steiner *et al.* [9] uses the nucleophilic amines like pyrrolidine and piperidine, which selectively open the epoxide ring of *trans*-isomer, leaving *cis*-limonene oxide largely unreacted. Less nucleophilic amines are used, such as triazole or pyrazole, selectively catalyze hydrolysis of *cis*-limonene oxide to 1,2-limonene diol, leaving *trans*-limonene oxide largely unreacted. Blair *et al.* [10] uses either aqueous mercury(II)-mediated or H^+-catalyzed hydration, afforded a kinetic separation of (+)-limonene oxide. Kumar *et al.* [11] uses the nucleophilic addition of methanol in presence of $InCl_3$ was also selective as *cis*-epoxides preferentially reacted leaving behind *trans*-epoxides.

In this work, the kinetic resolution was used as a method in which secondary amine, (*R*)-*N*-methyl-(α-methyl-benzyl) amine, selectively opens the epoxide ring of *trans*-isomer, giving a β-amine alcohol [12] and leaving *cis*-limonene oxide largely unreacted. When the carbamate was used in presence of water, it is observed the selectively catalyzed hydrolysis of *cis*-limonene oxide to 1,2-limonene diol, leaving *trans*-limonene oxide largely unreacted.

This work highlights a facile method to have access to four diastereomerically pure products from the commercially available limonene oxide mixture. These products are β-amino alcohol, diol, *cis*- and *trans*-limonene oxide. A simple, inexpensive

method to isolate both the *cis*- and *trans*-diastereomers of (*R*)-(+)-limonene oxide in high yield and high diastereomeric purity has been shown. Present method is not only useful for the isolation of both diastereomers of limonene oxide, but also for the synthesis of pure β-amino alcohols and *trans*-limonene-1,2-diol.

EXPERIMENTAL

Synthesis of (1*R*,2*R*,4*S*)-1-methyl-2-(*R*)-*N*-methyl-(α-methylbenzyl)amino-4-isopropenyl-cyclohexanol (3) and *cis*-limonene oxide (2): *cis*- and *trans*-Limonene oxide (1:1) (2.4 mmol), water (0.55 mL) and secondary amine ((*R*)-*N*-methyl-(α-methylbenzyl)amine) (5 mmol) were placed in a flask under magnetic stirring at 100 ºC. After 24 h, the product reaction was obtained by column chromatography using as eluent hexane/ether 8:2 β-aminoalcohol (**3**) was obtained in a yield of 60% and *cis*-limonene oxide (**2**) with a yield of 90%.

(1*R*,2*R*,4*S*)-1-Methyl-2-(*R*)-*N*-methyl(α-methylbenzyl)-amino-4-isopropenylcyclohexanol (3): HPLC-MS *m/z*, calcd. for $C_{19}H_{29}NO$ $[M-H]^+$: 288.09636.59372, found: 288.23239, IR (KBr, ν_{max}, cm^{-1}): 3500, 3200, 3050, 1600,710, ^1H NMR (500 MHz, $CDCl_3$): δ 1.28 (3H, d, CH_3), 1.54 (2H, m, CH_2), 1.70 (3H, s, CH_3), 1.72 (3H, s, CH_3), 2.11 (3H, m, CH, CH_2), 2.27 (2H, m, CH_2), 4.05 (1H, q, CH), 4.62 (2H, s, CH_2), 4.69 (1H, s, CH), 7.20-7.28 (5H, m, ArH), ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.20, 23.43, 26.27, 31.50, 33.57, 37.54, 48.85, 57.16, 71.54, 73.96, 109.19, 126.43-129.66, 140.95, 150.

***cis*-Limonene oxide (2):** $[\alpha]_D^{23}$ = +44º (*c* 0.01, $CHCl_3$) (neat), HPLC-MS *m/z*, calcd. for $C_{10}H_{17}O$ $[M-H]^+$: 153.12739, found 153.12691, IR (KBr) (ν_{max}, cm^{-1}): 2900, 1800, 1450, 3050, 850, ^1H NMR (500 MHz, $CDCl_3$): δ 1.37 (s, 3H), 1.60 (m, 2H), 1.68 (s, 3H), 1.69 (m, 2H), 1.86 (m, 2H), 2.05 (m, 1H), 3.06 (t, 1H), 4.68 (d, 2H), ^{13}C NMR (125 MHz, $CDCl_3$): 20.34, 24.40, 26, 28.68, 30.84, 36.30, 57.58, 59.40, 109.21, 149.34.

Synthesis of (1*R*,2*R*,4*R*)-limonene-1,2-diol (4) and *trans*-limonene oxide (1): The 1:1 *cis*- and *trans*-limonene oxide (2.4 mmol), water (0.55 mL) and carbamate (3.5 mmol) were placed in a flask under magnetic stirring at 100 ºC. After 24 h, the reaction product was obtained by column chromatography, using hexane/ether 7:3 as eluent. (1*R*,2*R*,4*R*)-Limonene-1,2-diol was obtained with a yield of 80% and *trans*-limonene oxide (**1**) with a yield of 75%.

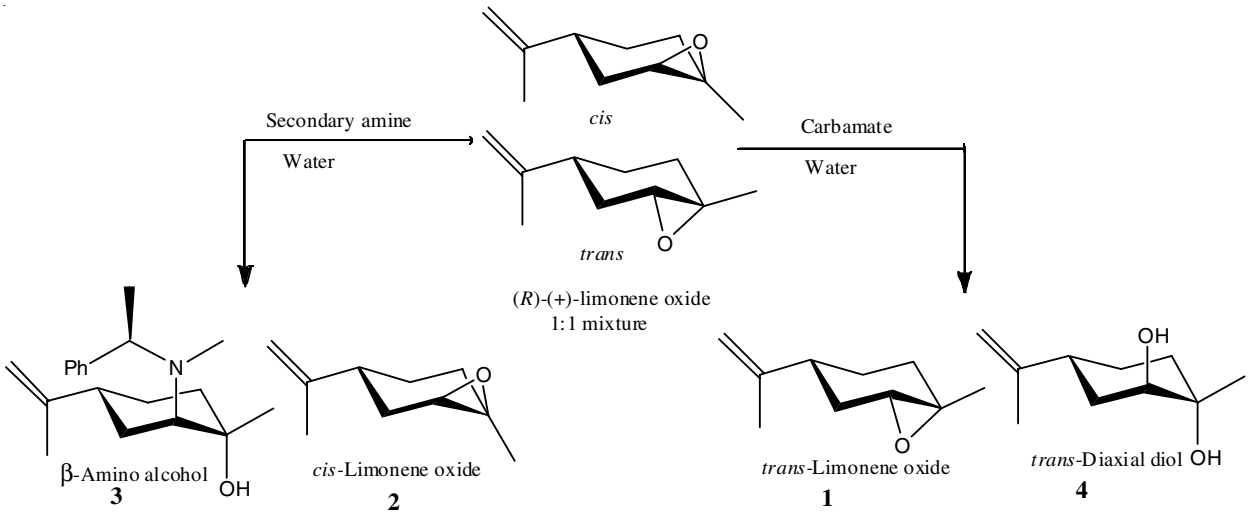
(1*R*,2*R*,4*R*)-Limonene-1,2-diol (4): HPLC-MS *m/z*, calcd. for $C_{10}H_{18}O_2$ $[M-H]^+$: 170.24912, found: 170.80917, IR (KBr, ν_{max}, cm^{-1}): 3500, 2900, 1100,700; ^1H NMR (500 MHz, $CDCl_3$): δ 1.25 (3H, s, CH_3), 1.53-1.59 (4H, m, 2×CH_2), 1.73 (3H, s, CH_3), 1.93 (2H, m, CH_2), 2.27 (1H, m, CH), 3.63 (1H, d, CH), 4.73 (1H, s, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.13, 26.12, 26.32, 33.66, 37.49, 71.54, 73.71, 109.09, 149.28.

***trans*-Limonene oxide (1):** $[\alpha]_D^{23}$ = +78º (*c* 0.01, $CHCl_3$) (neat), HPLC-MS *m/z*, calcd. for $C_{10}H_{17}O$ $[M-H]^+$: 153.12739, found 153.12688, IR (KBr) (ν_{max}, cm^{-1}): 2900, 1800, 1450, 3050, 850, ^1H NMR (500 MHz, $CDCl_3$): δ 1.18 (s, 3 H), 1.22-1.24 (m, 2 H), 1.55 (s, 3H),1.70 (m, 3 H), 1.85 (m, 2 H), 1.95 (m, 2 H), 2.90 (d, 1 H), 4.55 (s, 2 H), ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.18, 23.05, 24.30, 29.85, 30.73, 40.68, 57.34, 59.10, 109.09, 148.97.

RESULTS AND DISCUSSION

Multiple research has been carried out about the previously cited kinetic separations. The *trans*-diastereomer is the only limonene oxide which can be obtained [11,13]. The reaction of secondary amines with a 1:1 mixture of *cis*-**2** and *trans*-limonene oxide (**1**) is as an efficient and easily scalable reaction for the synthesis of limonene β-amino alcohols and the recuperation of *cis*-oxide limonene without reaction [12]. When carbamate with water was used, the obtained product is diol and the recuperation of *trans* limonene is without reaction. Using kinetic resolution, a method to isolate either diastereomer of limonene oxide with > 98% purity in high yield is reported (**Scheme-I**).

The reactions described in **Scheme-I** have demonstrated a clear selectivity of the reactions of *cis*- and *trans*-limonene oxide, which leads to conclude that there is an inherent confor-



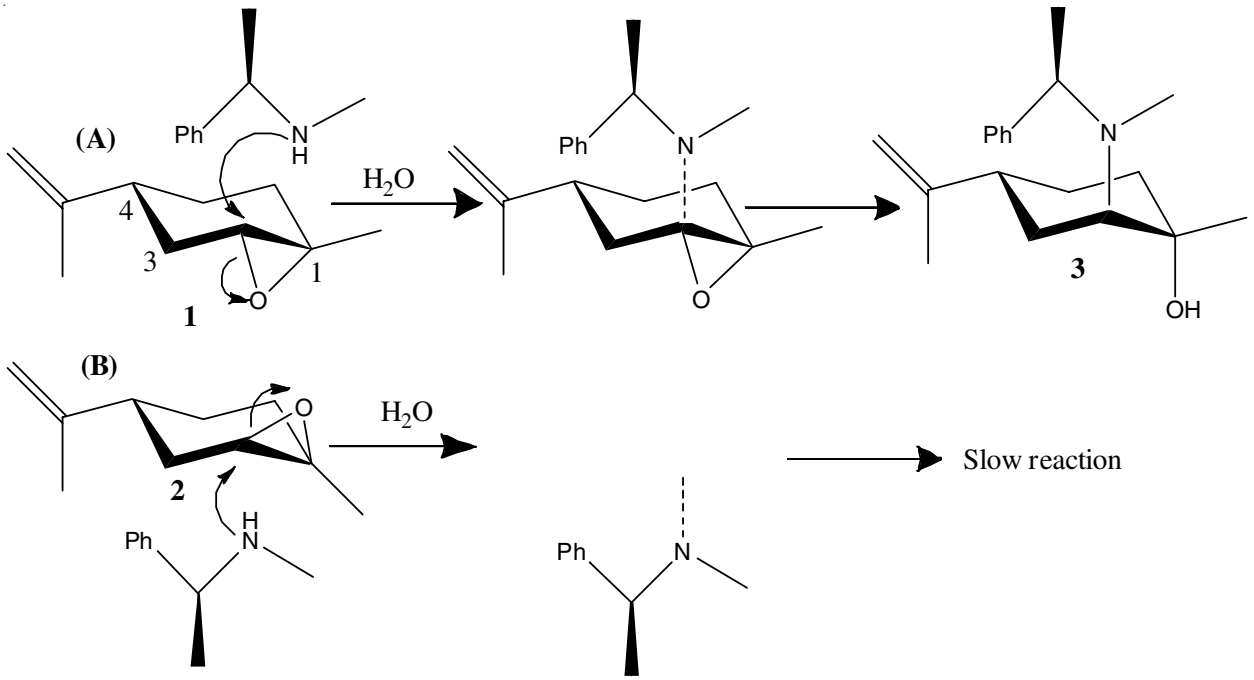
Secondary amine: (*R*)-*N*-methyl- (α-methyl-benzyl)amine
Carbamate: (*R*)-*N*-(α-methyl-benzyl) ethyl carbamate

Scheme-I: Kinetic separation of *cis*-and *trans*-limonene oxide

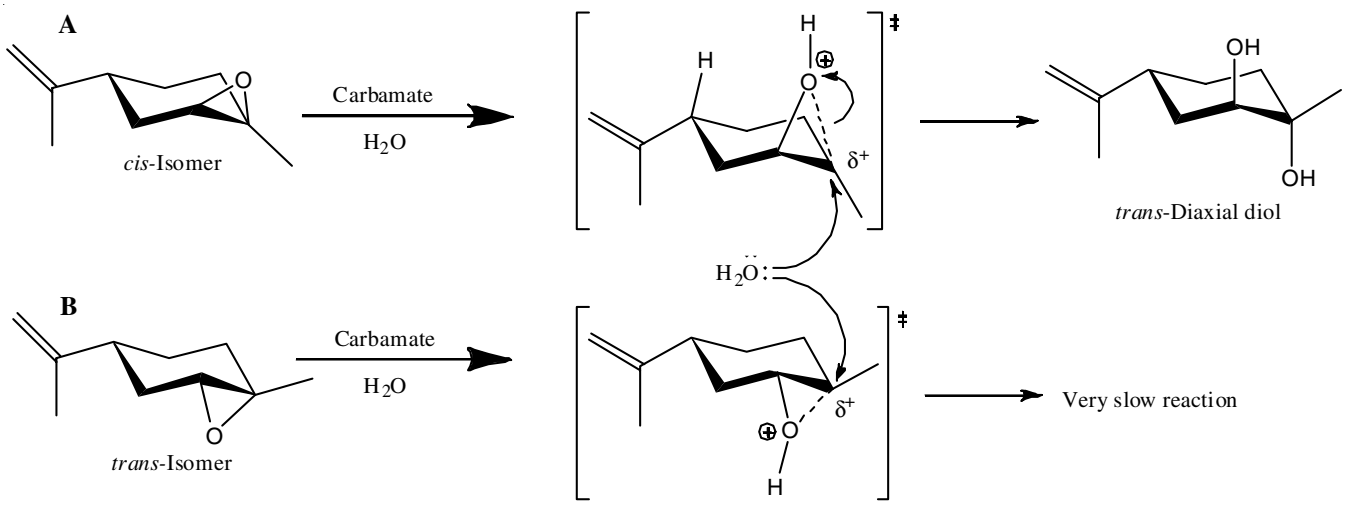
mational differences between them. Steiner *et al.* [9] reported that isopropenyl group prefers the equatorial orientation in both the *cis*-and *trans*-isomers. For *trans*-isomer (**1**), an S_N2-type reaction with a nucleophilic amine (pyrrolidine and piperidine) can be envisioned to occur at the less hindered C-2-carbon through a thermodynamically stable chair-like transition state (**Scheme-IIA**). Steiner *et al.* [9] has also demonstrated that for S_N2-type attack at the C-2-carbon atom to occur, the *cis*-isomer would have to attain the unfavourable, energetically demanding 'boat-like' transition state. As a result, the *cis*-isomer **2** is left largely unreacted (**Scheme-IIB**). Following the same track, in this work, a different nucleophilic amine ((*R*)-*N*-methyl-(α-methyl-benzyl) amine was used (**Scheme-II**).

Singaram *et al.* [14-16] and Christman *et al.* [17] have shown that the addition of secondary amines to *cis*- and *trans*-limonene oxide has produced interesting β-amino alcohols. *cis*-Limonene oxide (**2**) was isolated as a unreacted product. In this work, the addition of (*R*)-*N*-methyl-(α-methylbenzyl)-amine to (*R*)-(+)-limonene oxide produced β-amino alcohol (**3**) and unreacted *cis*-limonene oxide (**2**). In this reaction, *cis*-isomer **2** was isolated in 90% theoretical yield with > 98% purity.

When carbamate was used with water, a reaction is come up which involved carbamate, catalyzes the selective hydrolysis of *cis*-limonene oxide, leaving *trans*-limonene oxide (**1**) unreacted. This reaction leads us to an unexpected result. In other words, carbamate activates the epoxide ring by protonation, which allows water to selectively react with *cis*-limonene oxide (**2**) at the C-1-carbon atom, through a chair-like transition state, to form the *trans*-diaxial limonene diol (**4**) (**Scheme-IIIA**). Moreover, the reaction approaches an S_N1-



Scheme-II: Selective opening of *trans*-limonene oxide with (*R*)-*N*-methyl-(α-methyl-benzyl) amine



Carbamate: (*R*)-*N*-(α-methyl-benzyl)ethyl carbamate

Scheme-III: Selective opening of *cis*-limonene oxide with carbamate-water

type mechanism based on the electronic state of the C-1-carbon atom, but still retains the S_N2 characteristics and gives inversion of configuration at the C-1 center. The same results has been previously shown in the reaction of *cis*-limonene oxide with sodium acetate [18]. Conversely, *trans*-limonene oxide slowly reacts with water thanks to the conformation of the ring and the stereoelectronics of the system; the C-1-carbon atom forcing water to react at the C-2-carbon atom inactively (**Scheme-IIIB**). The unreacted *trans*-limonene oxide can be easily separated from the diol by column chromatography using as eluent hexane/ether 8:2.

If water is used without carbamate, a reaction (1 equivalent of 1:1 mixture of limonene oxides and an excess of water (12.5 equivalent)) was produced after 6 h at 100 ºC. As a result, *trans*-axial diol was obtained with a yield of 95% and *trans*-limonene oxide with a yield of 60%. Otherwise, if the reaction with 1 equivalent of 1:1 mixture of limonene oxides and 2.2 equivalent of carbamate and an excess of water (12.5 equiv.) was carried out after 24 h at 100 ºC, 75% yield of > 98% pure *trans*-limonene oxide (**1**) along with *trans*-diol (**4**) 80% was obtained,

Conclusion

In conclusion, a kinetic resolution was used as a simple, inexpensive method to have access to two pure products from the commercially available limonene oxide mixture. These products were *cis*- and *trans*-diastereomers of (*R*)-(+)-limonene oxide in high yield and high diastereomeric purity using a secondary amine and carbamate with water.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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