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TETRAHEDRON: *ASYMMETRY*

A facile and efficient method for the kinetic separation of commercially available *cis*- and *trans*-limonene epoxide†

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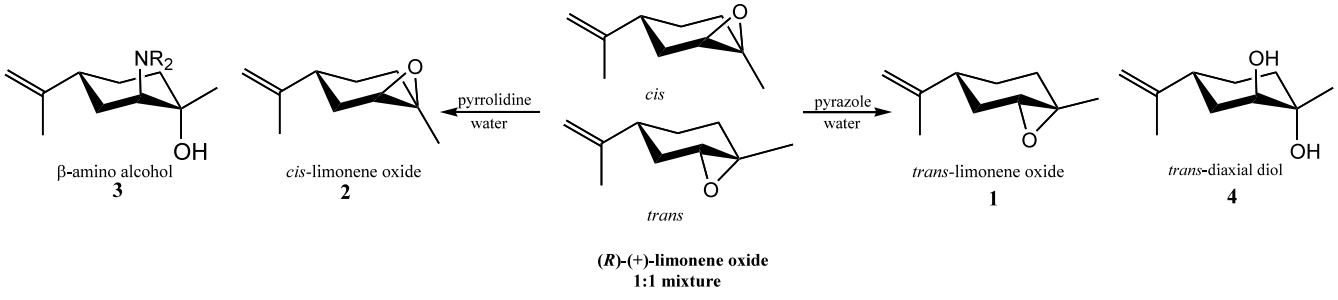
Abstract—*cis*- and *trans*-Diastereomers of (*R*)-(+)-limonene oxide can be purified by simple kinetic separation of the commercially available (1:1) diastereomeric mixture of limonene oxides. Nucleophilic amines, such as pyrrolidine and piperidine, selectively open the epoxide ring of the *trans*-isomer, leaving the *cis*-limonene oxide largely unreacted. The unreacted *cis*-(*R*)-limonene oxide is recovered in up to 88% yield. On the other hand, less nucleophilic amines, such as triazole or pyrazole, selectively catalyze hydrolysis of the *cis*-limonene oxide to 1,2-limonene diol leaving the *trans*-limonene oxide largely unreacted. The unreacted *trans*-limonene oxide is recovered in up to 80% of the theoretical yield by a simple workup procedure. The *cis*- and *trans*-diastereomers of (*R*)-(+)-limonene oxide thus isolated were found to be >98% pure by both GC and NMR analyses. Thus, depending on the choice of amine, either *cis*- or *trans*-limonene oxide may be obtained in high diastereomeric purity by this simple and environmentally friendly method.

1. Introduction

Enantiomerically pure epoxides are synthetically useful for the construction of many chiral non-racemic compounds.[1–5] Both (+)- and (−)-limonene oxide are commercially available and relatively inexpensive, but they are marketed as a 1:1 mixture of the *cis*- and *trans*-epoxides.[6,7] Bacteria, enzymes and yeasts have been used for enantioselective bioconversion of limonene oxide, allowing preferential isolation of one isomer.[8,9] Separation of the diastereomers was also attempted by fractional distillation. However, the result was inefficient, producing only small amounts of the desired products.[10] Due to the difficulty involved in the separation of limonene oxide diastereomers by physical means, synthetic routes to pure limonene oxide have been attempted by many research groups. It has been reported that diastereomerically pure *cis*- and *trans*-isomers[11] of (*R*)-(+)-limonene oxide can be synthesized in moderate yield from the corresponding quaternary ammonium salts derived from limonene amino alcohols.[12,13]



Scheme 1. Kinetic separation of *cis*- and *trans*-limonene oxides.

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† This paper is cordially dedicated to Professor Herbert C. Brown on the occasion of his 90th birthday.

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The inherent difficulty associated with physical separation and the inefficiency of synthetic approaches prompted us to study the kinetic separation of the commercially available 1:1 mixture of limonene oxide for the preparation of pure *cis*- and *trans*-isomers. The isolation of *trans*-limonene oxide **1** by kinetic resolution was first reported using $HClO_4$ in water at pH 4.5.[14] Due to the hazards involved in working with perchloric acid, safer and more efficient methods were explored. For example, *trans*-(+)-limonene oxide **1** was isolated in 24% yield by treating a 1:1 mixture of (*R*)-(+)-limonene oxide with $NaHSO_3$ at a low pH.[15] More recently, a molybdenum catalyst has been shown to selectively hydrolyze *cis*-limonene oxide **2** to form a diol. *trans*-Limonene oxide was left unreacted, however no isolated yield was reported.[16] Similarly, $HgCl_2$ was used, with a pH 7 buffer, to selectively hydrolyze **2**, facilitating the isolation of the *trans*-isomer **1** in 40% yield.[17]

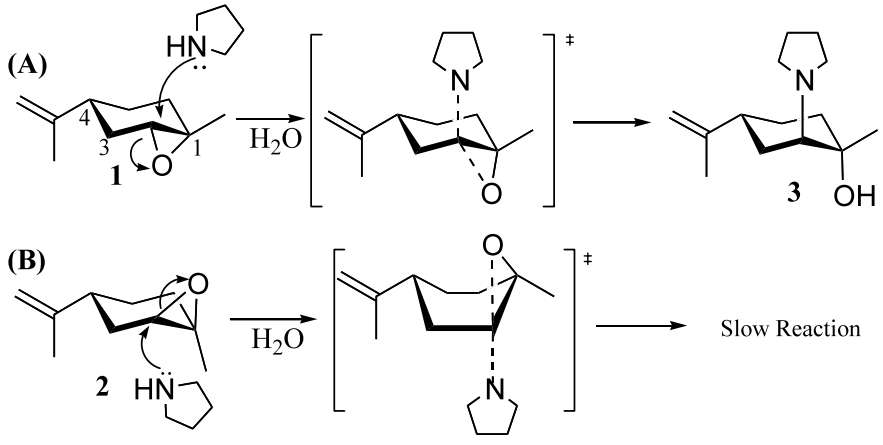
2. Results and discussion

In all of the aforementioned kinetic separations, only the *trans*-diastereomer of limonene oxide can be obtained. Recently, we reported the reaction of secondary amines with a 1:1 mixture of *cis*-**2** and *trans*-limonene oxide **1** as an efficient and easily scalable reaction for the synthesis of limonene based β-amino-alcohols.[18] This reaction and related methods using less nucleophilic amines, such as pyrazole and triazole, have led to the discovery of a new and useful method for the kinetic resolution of *cis*- and *trans*-limonene oxide. We report herein a simple and environmentally friendly method to isolate either diastereomer of limonene oxide with >98% purity in high yield (Scheme 1).

The selectivity observed in these reactions (Scheme 1) can be explained by the inherent conformational differences between *cis*- and *trans*-limonene oxide. Due to the large *A* value, the isopropenyl group prefers the equatorial orientation in both the *cis*- and *trans*-isomers. For the *trans*-isomer **1**, an S_N2-type reaction with a nucleophilic amine can be envisioned to occur at the less hindered C-2-carbon through a thermodynamically stable chair-like transition state (Scheme 2A). In contrast, for S_N2-type attack at the C-2-carbon atom to occur, the *cis*-isomer would have to attain the unfavorable, energetically demanding 'boat-like' transition state. Consequently, the *cis*-isomer **2** is left largely unreacted (Scheme 2B).[19,20]

The epoxide ring opening reaction was carried out using a wide variety of amines, producing structurally interesting β-amino alcohols.[18] *cis*-Limonene oxide **2** is isolated as a by-product in these reactions. For example, the reaction of (*R*)-(+)-limonene oxide with pyrrolidine gave a mixture of the β-amino alcohol **3** and unreacted *cis*-limonene oxide **2**, from which **2** was isolated in 88% theoretical yield with >98% purity (Table 1).

When we attempted to extend this reaction to non-nucleophilic amines, such as triazole and pyrazole, we observed an unexpected result. The reactions involving non-nucleophilic amines catalyzed the selective hydrolysis of *cis*-limonene oxide, leaving *trans*- limonene oxide **1** unreacted. This unexpected result can be rationalized as follows: Triazole and pyrazole activate the epoxide ring by protonation, allowing 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*-

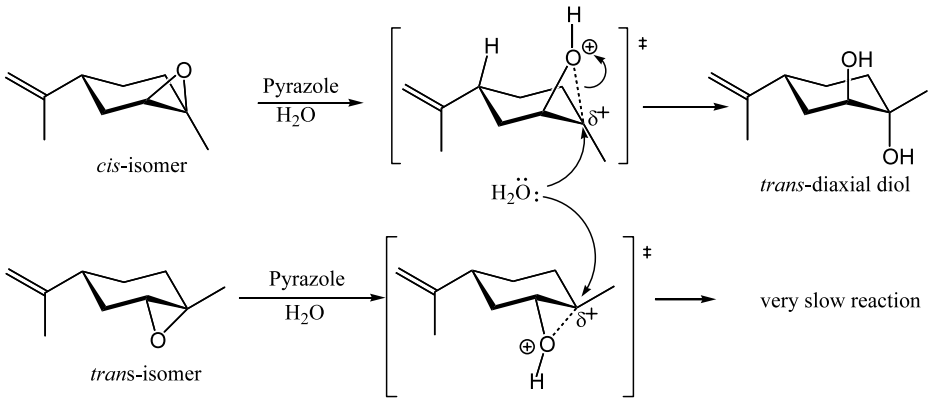


Scheme 2. Selective opening of *trans*-limonene oxide with pyrrolidine.

Table 1. Isolation of *cis*-limonene oxide of high purity by aminolysis-mediated kinetic resolution

Entry	Amine	Time (h)	Amino alcohol yield[a] (%)	%**2** yield[a] (purity)[b]
1	Pyrrolidine	24	85	84 (98)
2	Piperidine	48	89	80 (98)

[a] Isolated yield after distillation.
[b] Determined by ^1H NMR integration. Reactions run at 100°C in an open reflux condenser with constant stirring.



Scheme 3. Selective opening of *cis*-limonene oxide with pyrazole–water.

diaxial limonene diol **4** (Scheme 3A). It should be pointed out that the reaction approaches an S_N1 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. This is in agreement with the results observed previously in the reaction of *cis*-limonene oxide with sodium acetate.[21] In contrast, *trans*-limonene oxide is slow to react with water due 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 sluggishly (Scheme 3B). The unreacted *trans*-limonene oxide can be easily separated from the diol by a simple extraction with cold pentane.

The amount of water used in the reaction is critical, and determines the rate of the reaction and the product ratio. Initially reactions were run with a 1:1 stoichiometric ratio of pyrazole and epoxide with 0.8 equiv. of water. After 2 weeks at reflux temperature, a mixture of pyrazole-derived limonene amino alcohol regioisomers were isolated as the major product, with very little *trans*-limonene oxide. In order to make water the reactive nucleophile in this reaction, a large excess was subsequently used with a catalytic amount of pyrazole. Thus, the reaction of a 1:1 mixture of limonene oxide with 0.15 equiv. of pyrazole and 30 equiv. of water afforded a 77% yield of >98% pure *trans*-limonene oxide **1** after 6 h at 100°C along with the *trans*-diol **4**. A similar result was obtained using triazole as the acid catalyst, resulting in 73% yield of **1** in >98% purity (Table 2).

These observations were further verified by a more detailed study of the reaction stoichiometry with pyrazole. Using a 12-station Bohdan automated synthesizer, reactions were run at 95°C using 2.0, 1.0, and 0.24 equiv. of pyrazole and 30, 10, 1, and 0 equiv. of added water. The results of the three experiments using 30 equiv. of water are shown in Fig. 1. The graphs clearly show that in all three cases, the *cis*-(*R*)-limonene oxide is completely consumed after 4–5 h of reaction time. With 2 equiv. of pyrazole, nearly equal quantities of diols and amines are produced, and *trans*-(*R*)-limonene oxide remains as less than 30 area percent of the mixture.[22] With 0.24 equiv. of pyrazole the major products are the diols, and approximately 43 area percent of the mixture is the *trans*-(*R*)-(+)-limonene oxide.

3. Conclusion

In summary, we have shown a simple and environmentally friendly way to isolate both the *cis*- and *trans*-diastereomers of (*R*)-(+)-limonene oxide in high yield and high diastereomeric purity. The method disclosed herein is inexpensive and uses readily available limonene oxide and a wide variety of secondary amines. Our 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.

4. Experimental

Reactions were carried out in oven-dried glassware under an inert atmosphere. *cis*/*trans*-(+)-Limonene oxide and amines were supplied by the Aldrich Chemical Company and used as received. ^1H and ^{13}C NMR spectra were recorded on a Varian 500 MHz system. Optical rotations were recorded on a Jasco DIP-371

Table 2. Isolation of *trans*-limonene oxide of high purity by hydrolysis-mediated kinetic resolution

Entry	Amine	Water:amine (equiv.)[a]	Time (h)	Diol **4** yield[b] (%)	%**1** yield[b] (purity)[c]
1	None	30:0	7	100	61 (96)
2	Pyrazole	30:1.5	6	55	27
3	Pyrazole	9:0.05	24	85	48 (98)
4	Pyrazole	30:0.15	5	71	77 (98)
5	Triazole	30:0.15	5.5	71	73 (97)

[a] One equiv. of limonene oxide is used in all reactions.
[b] Isolated yield after distillation.
[c] Determined by ^1H NMR integration.

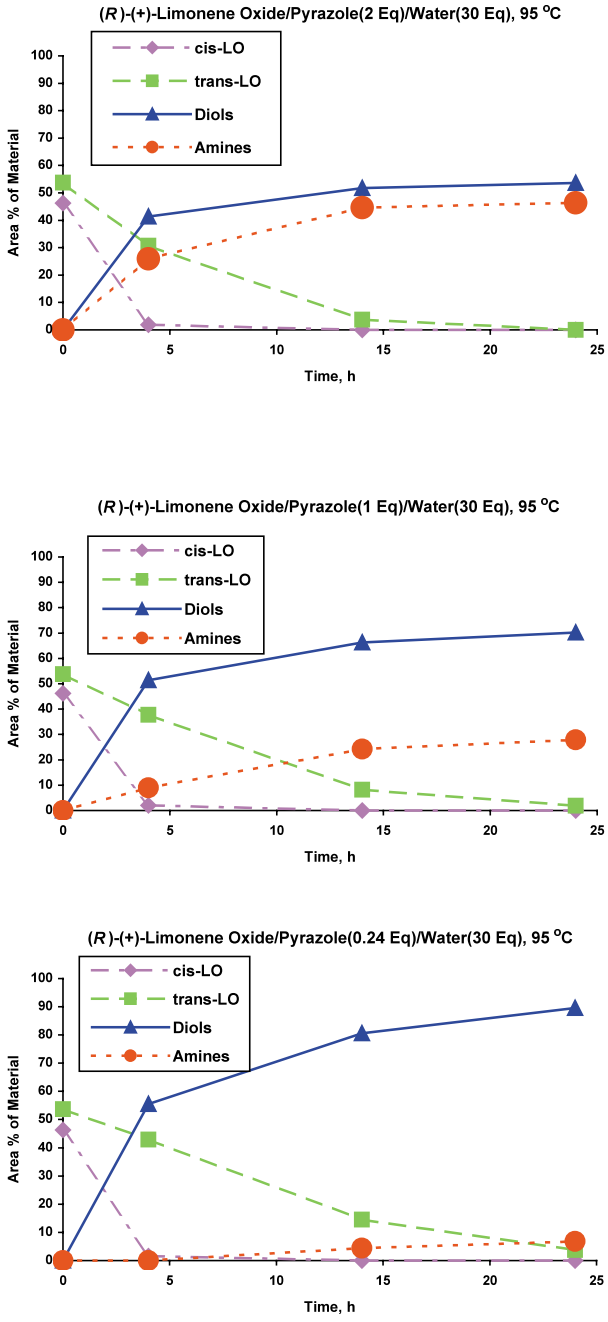


Figure 1. Reaction profiles of the reaction of (*R*)-(+)-limonene oxide with 30 equiv. of water in the presence of 2.0, 1.0, and 0.24 equiv. of pyrazole (capillary GC area%).

polarimeter diluted in spectral grade methanol. High resolution mass spec. was done on a PerSeptive Biosystems, Mariner TOF mass spectrometer using positive ionization.

4.1. General procedure for *cis*-(+)-limonene oxide, 2

Pyrrolidine (8.35 mL, 0.10 mol), (*R*)-(+)-limonene oxide (16.4 mL, 0.10 mol), and deionized water (1.5 mL, 0.08 mol) were added to a 50 mL round-bottom flask equipped with a magnetic stir bar and a reflux condenser. The reaction mixture was heated to reflux, 100°C, and stirred under reflux for 24 h. The contents of the round-bottom were transferred to a separatory funnel with pentane (50 mL). The organic solution was extracted with deionized water (2×50 mL). The pentane layer was dried with anhydrous magnesium sulfate and gravity filtered into a 100 mL, round-bottom flask. The pentane was removed in vacuo (rotary evaporator). The *cis*-(*R*)-(+)-limonene oxide was then distilled at reduced pressure, bp 68°C (18 Torr) giving product (5.49 g). $\alpha_D^{23} = +44°$ (neat), *d* 0.931 (Fluka), HRMS calcd for $C_{10}H_{17}O(M^+)$ *m*/*z* 153.12739, found 153.12666, ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.55 (m, 2H), 1.71 (s, 3H), 1.74 (m, 2H), 1.86 (m, 2H), 2.14 (m, 1H), 3.07 (t, 1H), 4.70 (d, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.145, 24.334, 25.998, 28.689, 30.805, 36.280, 57.371, 60.576, 109.121, 149.017.

4.2. (1*R*,2*R*,4*S*)-1-Methyl-4-(1-methylethenyl)-2-(1-pyrrolidino)cyclohexanol[18]

Bp 128–131°C (3.0 Torr), $\alpha_D^{23} = -34.9$ (*c*, 4.0, methanol), HRMS calcd for $C_{14}H_{26}NO$ (M^+) *m*/*z* 224.20226, found 224.20089, IR (neat): 3460.5, 2873.4, 2795.2, 1640.9, 1455, 1368.8, 1123.8, 1089.5 cm^{-1}, ^{1}H NMR (250 MHz, DMSO-d_6): $\delta = 1.25$ (s, 3H), 1.37–1.68 (m, 9H), 1.68 (s, 3H), 1.90 (m, 1H), 2.25 (m, 1H), 2.54 (m, 2H), 2.68 (m, 2H), 3.94 (m, 1H), 4.79 (s, 2H). ^{13}C NMR (62.5 MHz, DMSO-d_6) $\delta = 21.59$, 23.50, 24.01, 25.73, 26.98, 29.29, 36.14, 52.80, 66.47, 71.88, 109.56, 148.86.

4.3. General procedure for preparation of *trans*-(*R*)-(+)-limonene oxide, 1

A 50 mL, round-bottom flask equipped with a magnetic stir bar and a reflux condenser was charged with (*R*)-(+)-limonene oxide (4.57 g, 0.03 mol), pyrazole (0.34 g, 0.005 mol), and deionized water (16.2 mL). The mixture was heated to 100°C (reflux) and heated under reflux for 5 h. The reaction mixture was placed in a water bath heated to approximately 80°C. The mixture was then transferred to a separatory funnel and extracted with warm (80°C) deionized water (2×30 mL) to remove the diol. The aqueous layer was then placed in a refrigerator wherein the diol precipitated upon cooling. Excess pentane was then added to the open separatory funnel containing the organic layer and a slurry of white solid formed immediately. The mixture was vacuum filtered to remove the solid and further solid formed upon evaporative cooling from the vacuum. The mixture was filtered for a second time removing the remainder of 1,2-limonene diol. The pentane remained clear and was dried over anhydrous magnesium sulfate and gravity filtered into a 100 mL, round-bottom flask. The pentane was removed in vacuo (rotary evaporator) leaving *trans*-*R*-(+)-limonene oxide (2.01 g). $\alpha_D^{23} = +82°$ (neat), *d* 0.930 (Fluka),[7] HRMS calcd for $C_{10}H_{17}O(M^+)$ *m*/*z* 153.12739, found 153.12666, ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.31$ (s, 3H), 1.39 (m, 2H), 1.69 (s, 3H), 1.69–1.72 (m, 2H), 1.84–1.88 (m, 2H), 2.06 (m, 1H), 2.98 (d, 1H), 4.66 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 20.274$, 23.163, 24.412, 29.949, 30.836, 40.806, 57.574, 59.331, 109.167, 149.204.

4.4. (1*S*,2*S*,4*R*)-Limonene-1,2-diol

^{1}H NMR (500 MHz, $CDCl_3$): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.26$ (s, 3H), 1.51–1.68 (m, 4H), 1.73 (s, 3H), 1.93 (m, 2H), 2.27 (m, 1H), 3.63 (d, 1H), 4.73 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 21.161$, 26.294, 26.760, 33.791, 34.118, 37.555, 71.417, 74.030, 109.089, 149.391. Correlates to previously reported preparation, Ref. 23.

Acknowledgements

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