Facile Methods for the Separation of the *cis*- and *trans*-Diastereomers of Limonene 1,2-Oxide and Convenient Routes to Diequatorial and Diaxial 1,2-Diols

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Abstract: Facile methods are described for accessing four diastereomerically pure products from the commercial mixture of limonene oxide. The use of either an aqueous mercury(II)-mediated or H^+-catalysed hydration, afforded a kinetic separation of (+)-limonene oxide (*cis*- or *trans*-isomer could be respectively recovered) from the commercially available diastereomeric mixture in good recovery yields and high diastereoselectivity (>98% de). The hydrolysed limonene oxide products, either *trans*-diequatorial or *trans*-diaxial diols, are also formed in good conversion yields and high diastereoselectivity (>98% de).

Key words: kinetic separation, diastereomer resolution, limonene oxide, mercury, diols

Optically pure epoxides and their corresponding 1,2-diols are important building blocks in asymmetric synthesis. Limonene oxide (Figure 1) is one such epoxide, which has not only been used in natural product synthesis, but also as a chiral ligand/auxiliary in asymmetric synthesis.[1] The epoxidation of limonene (see Figure 1 for structure) most often leads to a mixture of the *cis*- and *trans*-diastereomers,[2] and although both individual isomers are commercially available, they are expensive, and hence more commonly sold as a diastereomeric mixture (53:47). Efficient methods for separation of these diastereomers are therefore of academic and commercial interest. Physical methods for separation generally involve fractional distillation or chromatography and are expensive and not trivial.[3] The alternative, kinetic separation, which utilises a difference in reactivity of the two diastereomers, has been developed based upon photo-assisted kinetic resolution,[4] hydrolysis with $HClO_4$ or $NaHSO_3$,[5,6] biocatalysis,[7] molybdenum(VI),[8] electrophilic mercuration,[9] amine addition,[10,11] or biotransformation.[12] We have recently described the use of lanthanoid benzoate complexes for the kinetic separation of *cis*/*trans*-limonene oxide.[13]

The hydrolysis of limonene oxide, theoretically, can yield four possible diol stereoisomers, but in practice, predominantly affords the *trans*-diaxial diol **3** and to a much lesser extent, the *trans*-diequatorial diol **4**. Although both have been used in a number of syntheses,[7,10,14,15] they are not commercially available, and there is no selective, high yielding synthesis known for the *trans*-diequatorial diol **4**.

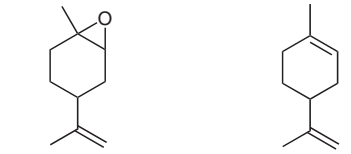

Figure 1 Structure of limonene oxide and limonene

Herein, we describe the results of a two-part study into the stereoselective transformations of *cis*/*trans*-limonene oxide. Firstly, acid hydrolysis at pH 4 (NaOAc buffered solution) yields pure unreacted *trans*-limonene oxide (**2**) and *trans*-diaxial diol **3** which are easily separated. Secondly, in a completely complementary fashion, treatment with $HgCl_2$ at pH 7 yields pure unreacted *cis*-limonene oxide (**1**) and the *trans*-diequatorial diol **4** which are also easily separated. When applied in tandem, these procedures afford both *cis*- and *trans*-limonene oxide (**1** and **2**), and the diaxial and diequatorial diols (**3** and **4**) in excellent recovery yields and diastereoselectivities (Scheme 1).

Acid-Catalysed Separation of *trans*-Limonene Oxide (2)

Previously it has been reported that reaction of both the *cis*- and *trans*-limonene oxide (**1** and **2**), under acidic conditions lead to the same *trans*-diaxial diol **3**.[16] It was reasoned that this occurs due to selective axial nucleophilic attack that can be rationalised by the Fürst–Plattner rule.[2,17] It is therefore postulated that due to steric hindrance and electronic effects, under these conditions, the *cis*-isomer **1** would react at a substantially quicker rate than the *trans*-isomer **2** (Scheme 2). As there is no data on the relative reactivities of the *cis*- and *trans*-isomers under acidic conditions, it was of interest to investigate the reactivity of the *cis*-isomer under these conditions.

The reaction mixture (NaOAc buffered solution, pH 4), was analysed by GC analysis over 1.5 hours. It was revealed that the *cis*-epoxide **1** reacted at a quicker rate than the *trans*-epoxide **2** (Figure 2), which is consistent with that *postulated* in the literature. If the reaction was ceased

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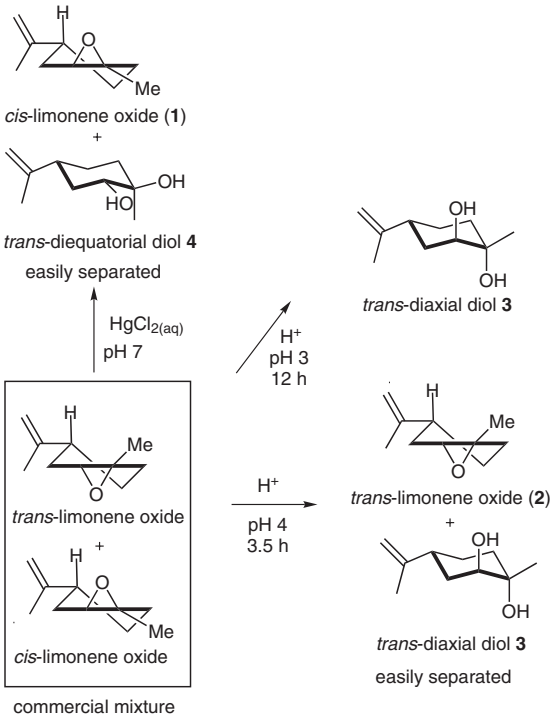
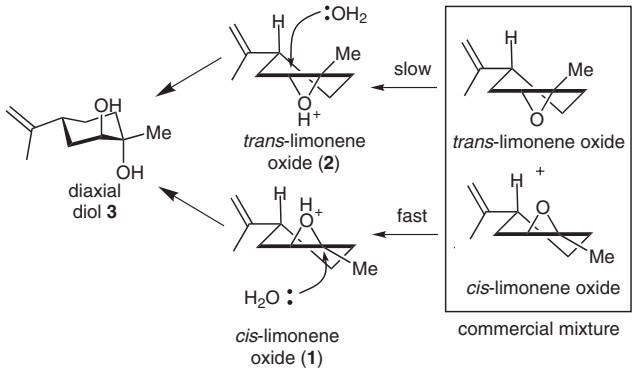


Scheme 1 Separation of diastereomerically pure *cis*- and *trans*-(+)-limonene oxide (**1** and **2**) and the synthesis of the 1,2-*trans*-diols **3** and **4**



Scheme 2 Acid-catalysed hydrolysis of *cis*/*trans*-(+)-limonene oxide (**1** and **2**)

after 3.5 hours (NaOAc buffered solution, pH 4), the unreacted (+)-*trans*-limonene oxide (**2**) could be obtained via extraction of the reaction mixture with hexane [recovery yield based on (+)-*trans*-limonene oxide (**2**) 87%, de >98%]. Subsequent extraction of the reaction mixture with ethyl acetate gave the diaxial diol **3** [76% based on initial amount of (+)-*cis*-limonene oxide, >98% de]. When the mixture was subjected to hydrolysis at pH 3 (KH_2PO_4 buffered aqueous solution, pH 3, 12 h), the diaxial diol **3** was the major hydrolysis product [70% based on the initial amount (+)-limonene oxide, >98% de]. This is consistent with the findings in the literature at pH <1,[9,16] however, we observed only nominal amounts of the diequatorial diol **4**. Thus, this method is a facile method for separation of (+)-*trans*-limonene oxide (**2**) and/or the formation of optically pure diaxial diol **3**.

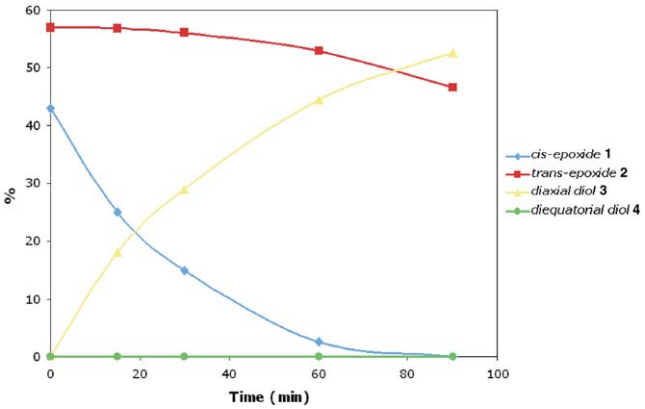
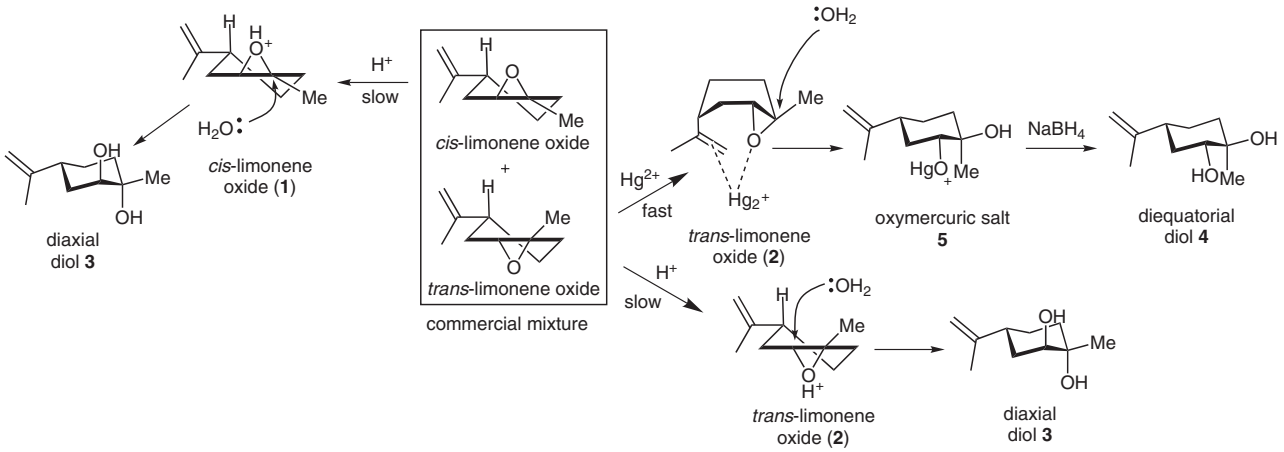


Figure 2 Reaction profile for the kinetic separation of *cis*/*trans*-(+)-limonene oxide in NaOAc buffered solution (pH 4)

$HgCl_2$-Promoted Separation of *cis*-Limonene Oxide (1) and Synthesis of *trans*-Diequatorial Diol 4

The kinetic separation of commercially available *cis*- and *trans*-limonene oxides (**1** and **2**) has been previously described by Van der Werf and co-workers.[9] They report that the optimum conditions [$Hg(OAc)_2$ in 1:1 acetone–50 mM tris buffer, pH 7.0] gives *cis*-limonene oxide (**1**, >98% de) and a mixture of the diequatorial (**4**) and diaxial (**3**) diols in a 7:3 ratio.[9] They concluded that mercuration of *trans*-limonene oxide (**2**) occurs rapidly to give a mixture of diaxial (**3**) and diequatorial (**4**) diols, with water attacking at the tertiary site, to give the diequatorial diol **4** preferentially, after reaction of the oxymercuric salt with $NaBH_4$.[9] From our results obtained with the acid-catalysed separation of limonene oxide, the diaxial diol **3** is a by-product and is formed via acid-catalysed opening of the *cis*-epoxide **1** (Scheme 3). This was most likely due to insufficient buffering capacity, and to prevent this, the buffer concentration was increased from 50 mM to 300 mM. Reaction of *cis*- and *trans*-(+)-limonene oxides (**1** and **2**), with $HgCl_2$ in buffer alone resulted in almost exclusive formation of the diequatorial diol **4**. The use of $Hg(OAc)_2$ in acetone–tris buffer in our hands was unsuccessful, whereas $HgCl_2$ in aqueous conditions afforded reproducible results. The diaxial diol **3** was formed in less than 5% yield according to ^1H NMR spectroscopy and 1% yield as detected by GC. It was also observed that a decrease in pH of the solution was accompanied by an increase in the yield of the diaxial diol **3** (Table 1). This is presumably due to the acid opening of the *cis*-epoxide **1** competing with mercuration of the *trans*-epoxide **2**, and does not occur via formation of a *trans*-oxymercuric salt **5** as previously proposed.[9] Reaction of *cis* and *trans*-(+)-limonene oxides (**1** and **2**) with $HgCl_2$ is summarised in Scheme 3.



Scheme 3 Diastereoselective electrophilic mercuration of *cis*/*trans*-(+)-limonene oxide

Table 1 Effect of the pH on the Diastereoselection of the Diols **3** and **4**

Conditions	pH	Yield (%) of diol **4**[a]	Ratio of diols **3**/**4**
330 mM tris–67 mM $HgCl_2$	7	90	1:20
330 mM NaOAc–67 mM $HgCl_2$	5	50	2:3
330 mM KH_2PO_4–67 mM $HgCl_2$	3	33	2:1

[a] After 2 h at 25 °C. Yields of limonene 1,2 diequatorial diol via kinetic separation are calculated from the initial percent composition of *cis*-limonene oxide.

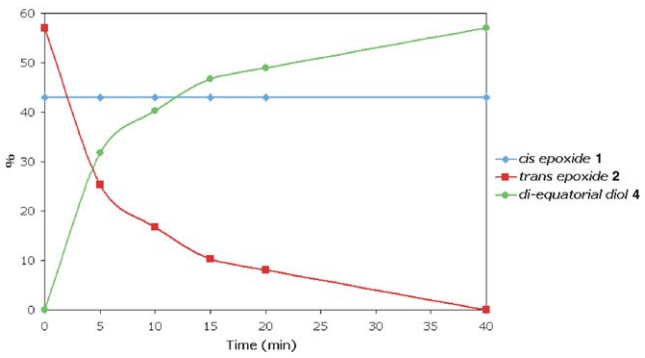


Figure 3 Reaction profile for the kinetic separation of *cis*/*trans*-(+)-limonene oxide, with aq $HgCl_2$. The amount of the diequatorial diol formed was calculated from the disappearance of the *trans*-epoxide, as the oxymercuric intermediate was unable to be detected by GC analysis.

The optimum buffer for the Hg(II) opening of limonene oxide was 330 mM tris buffer. With this information in hand, the reactivities of the *cis*- and *trans*-isomers of (+)-limonene oxide were investigated (Figure 3). It was observed by GC analysis that (+)-*trans*-limonene oxide (**2**) underwent complete conversion to the highly water soluble oxymercuric intermediate in 40 minutes. The unreacted (+)-*cis*-limonene oxide (**1**) was recovered in high yield and diastereoselectivity [96% based on initial (+)-*cis*-limonene oxide, >98% de]. Subsequent reaction of the aqueous solution with $NaBH_4$ gave the diequatorial diol **4** (99% recovery yield, 91% de). Recrystallisation increased the diastereomeric excess to >98%. As a final confirmation of the stereochemistry of **4** an X-ray crystal structure revealed that the *trans*-OH groups and the propenyl group were in equatorial positions (Figure 4).

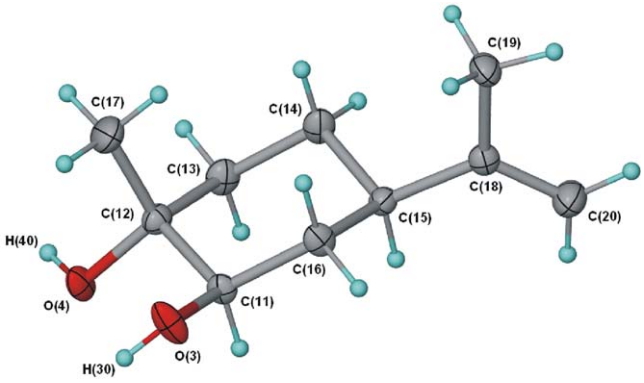


Figure 4 X-ray crystal structure of the *trans*-diequatorial diol **4**

In conclusion, it has been demonstrated that *cis*- and *trans*-limonene oxide hydrolyse at very different rates in a dilute acid solution, and therefore can be exploited to provide one of the most efficient and simple methods for the kinetic separation of the *trans*-diastereomer. In a complementary fashion, it was found that an adequately buffered $HgCl_2$ solution allows complete separation of the *cis*-epoxide, and exclusive formation of the diequatorial diol **4**, in excellent yield and diastereoselectivity (>98% de).

This work highlights a facile method for accessing four diastereomerically pure products from the commercially available limonene oxide mixture.

Chemical shifts are expressed in parts per million (δ). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 300 spectrometer at 300 and 75 MHz, respectively. Melting points were recorded on a Kofler hot stage apparatus and are uncorrected. Mass spectrometry (ESI) was performed on a Micromass Platform QMS spectrometer. IR spectra were recorded on a Bruker Equinox 55 ATR spectrometer. GC analyses were performed on a Varian 3700 with a SGE 30 QC5 BPX5 (1.0 μm column of internal diameter, 0.53 mm × 30m) (He carrier gas, 85 °C for 3 min, then ramped to 280 °C at 8 °C/min). Optical rotations were obtained using a PolAAR 2001 automatic polarimeter, using a 1 dm cell with $CHCl_3$ as solvent, at a wavelength of 589 nm (sodium D line). (+)-Limonene oxide (*cis*/*trans* mixture, 53:47, Aldrich) was used as received.

(1*S*,2*S*,4*R*)-1-Methyl-4-(prop-1-en-2-yl)cyclohexane-1,2-diol (3)

(+)-Limonene oxide (*cis*/*trans* isomers **1** and **2**, 1.0 g, 6.57 mmol) was added to a solution of NaOAc (200 mL, 100 mM, pH 4). Stirring was continued until total consumption of the *cis*-epoxide occurred (ca. 3.5 h) as detected by GC analysis. The mixture was neutralised with aq sat. $NaHCO_3$, extracted with hexane (3 × 100 mL), dried (Na_2SO_4) and concentrated in vacuo to afford the unreacted *trans*-epoxide **2** [373 mg, 87% recovery yield based on initial (+)-*trans*-limonene oxide, de >98%, yields of *cis*- or *trans*-limonene oxide via kinetic separation are calculated from the initial percent composition (i.e., 53:47)]. The residual aqueous phase was extracted EtOAc (3 × 100 mL), dried (Na_2SO_4) and concentrated under reduced pressure to afford the diaxial diol **3** [487 mg, 76% based on initial (+)-*cis*-limonene oxide, >98% de].

Mp 68–70 °C; $[\alpha]_D^{20}$ +18.1 (*c* 0.01, $CHCl_3$); t_R = 10.81 min (SGE 30 QC5 BPX5).

IR (solid sample): 3354, 3081, 2931, 2235, 1644, 1448, 1371, 1240 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.26 (s, 3 H), 1.54–1.61 (m, 4 H), 1.62–1.68 (m, 1 H), 1.71–1.74 (m, 3 H), 1.87–98 (m, 1 H), 2.22–2.28 (m, 1 H), 3.61–3.64 (m, 1 H), 4.72–4.73 (m, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.3, 26.45, 26.9, 33.9, 34.3, 37.7, 71.5, 74.2, 109.2, 149.6.

Spectral data was consistent to that previously reported.[10]

(+)-*trans*-Limonene Oxide (2)

$[\alpha]_D^{20}$ +78 (neat) {Lit.[4] $[\alpha]_D$ +77 (neat)}; t_R = 7.46 min (SGE 30 QC5 BPX5).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.34 (s, 3 H), 1.35–1.40 (m, 2 H), 1.66–1.67 (m, 3 H), 1.69–1.70 (m, 2 H), 1.84–1.87 (m, 2 H), 2.98 (d, *J* = 4.0 Hz, 1 H), 4.65–4.67 (m, 2 H).

Complete Conversion of *cis*/*trans*-Limonene Oxide Mixture to (1*S*,2*S*,4*R*)-1-Methyl-4-(prop-1-en-2-yl)cyclohexane-1,2-diol (3)

(+)-Limonene oxide (*cis*/*trans* isomers **1** and **2**, 5.0 g, 32.9 mmol) in potassium phosphate buffer (200 mL, 200 mM, pH 3) was stirred at r.t. for 12 h. During this time the product, the diaxial diol, precipitated. The diaxial diol **3** was removed by filtration and the aqueous solution was concentrated to a quarter of its original volume. The solution was allowed to stand overnight at 5 °C to afford a second crop of diaxial diol **3** [3.93 g, 70% based on initial (+)-limonene oxide, >98% de]. The spectroscopic data of the title compound **3** was identical to that obtained when NaOAc was the buffer.

(1*R*,2*R*,4*R*)-1-Methyl-4-(prop-1-en-2-yl)cyclohexane-1,2-diol (4)

To a solution of $HgCl_2$ (250 mL, 67 mM in 330 mM tris buffer, pH 7) was added (+)-limonene oxide (*cis*/*trans* epoxides **1** and **2**, 4.0 g, 26.3 mmol) dropwise. The mixture was stirred at r.t. and the progress of the reaction was followed by GC. Aliquots (1 mL) were diluted with aq sat. $NaHCO_3$ (1 mL) followed by extraction with EtOAc (2 mL). The samples were then analysed by GC analysis. After 40 min, the *trans*-epoxide **2** was completely consumed. The mixture was extracted with hexane (3 × 70 mL), to remove unreacted *cis*-(+)-limonene oxide (**1**; 1.64 g, maximum theoretical yield 96%, >98% de) and $NaBH_4$ (3.20 g, 84.6 mmol) was subsequently added to the aqueous phase. After stirring at r.t. for 3 h, the mixture was extracted with EtOAc (3 × 100 mL), dried (Na_2SO_4), and concentrated in vacuo to afford a white crystalline solid [2.52 g, 99% based on starting *trans*-(+)-limonene oxide, yields of *cis*- or *trans*-limonene oxide via kinetic separation are calculated from the initial percent composition (i.e., 53:47)]. A mixture of the diequatorial and diaxial diols (20:1) was observed by ^{1}H NMR spectroscopy. Recrystallisation from water afforded the diastereomerically pure diequatorial diol **4** (68%, >98% de).

Mp 74–76 °C; $[\alpha]_D^{20}$ –5.5 (*c* 0.01, $CHCl_3$); t_R = 11.03 min (SGE 30 QC5 BPX5).

IR (solid sample): 3330, 3251, 3075, 2981, 2864, 1697, 1644, 1434, 1374 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.20 (s, 3 H), 1.21–1.26 (m, 2 H), 1.29–145 (m, 2 H), 1.67 (s, 3 H), 1.72 (dt, *J* = 2.4, 9.6 Hz, 1 H) 1.85–1.95 (m, 2 H), 2.05 (tt, *J* = 2.9, 9.3 Hz, 1 H), 2.91 (s, 1 H), 3.20 (s, 1 H), 3.56 (dd, *J* = 3.3, 9.0 Hz, 1 H), 4.71 (s, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 18.9, 20.8, 28.7, 36.1, 38.5, 43.6, 74.0, 77.2, 109.1, 148.5.

X-ray Data

For X-ray crystal data of **4**, please see ref. 18.

(+)-*cis*-Limonene Oxide (1)

$[\alpha]_D^{20}$ +48.1 (*c* 0.01, $CHCl_3$) {Lit.[10] $[\alpha]_D$ +44 (neat)}; t_R = 7.40 min (SGE 30 QC5 BPX5).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.30 (s, 3 H), 1.45–1.68 (m, 3 H), 1.69–1.72 (m, 3 H), 1.80–1.96 (m, 2 H), 1.85–1.95 (m, 2 H), 2.10–2.20 (m, 1 H), 3.04–3.06 (m, 1 H), 4.65–4.67 (m, 1 H), 4.67–4.73 (m, 1 H).

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