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Photo-assisted kinetic resolution of diastereomeric limonene and carvomenthene oxides in methanol in the presence of Lewis acids

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Abstract

Photosolvolysis of diastereomeric *R*-(+)-limonene oxide and *R*-(+) carvomenthene oxides in methanol, in the presence of Lewis acid catalysts viz. $ZnCl_2$, $ZnBr_2$ and $InCl_3$ affords resolution of (+)-*trans*-limonene oxide and (+)-*trans*-carvomenthene oxide in excellent yield. Also, the photosolvolyzed products (1*S*, 2*S*, 4*R*) *trans*-1-methoxy-2-hydroxy-*p*-menthane and (1*S*, 2*S*, 4*R*)-*trans*-1-methoxy-2-hydroxy-*p*-menth-8-ene, could be obtained in good purity. The key factor determining the selectivity in solvolysis is the presence of isopropenyl or isopropyl group on the C-4 of limonene or carvomenthene oxides.

Keywords: Photosolvolysis; Kinetic resolution; *cis-/trans*-Limonene oxide; *cis-/trans*-Carvomenthene oxide; Zinc halides; Lewis acid

1. Introduction

Monoterpenes are widely distributed in nature as constituents of essential oils of higher plants. Monoterpene epoxides often serve as starting materials for the synthesis of several fragrances, flavors, herbicides, fungicides and biologically active and therapeutically useful compounds [1]. Enantiopure epoxy-terpenes are valuable building blocks in the asymmetric synthesis of natural products [2,3]. Limonene-1,2-oxide, which occurs naturally in the essential oils of *Cymbopogon densiflorus*, is a typical representative of monocyclic cyclohexene epoxides [4]. Pure diastereomeric epoxides have been synthesized by chemical [5] as well as biological [6] methods. Also, kinetic resolution is an important technique for the production of pure chiral epoxides from the racemic mixtures. Usually, epoxidation of pure limonene results in the formation 1:1 mixture of *cis*- and *trans*-limonene oxides. The diastereomeric *cis*- and *trans*- mixture of limonene oxides is not easily separable [7]. As the diastereomerically pure oxides are useful and their asymmetric synthesis is tough, development of an effective method of kinetic resolution of these epoxides from the commercial mixture is of significant importance.

Hydrolytic kinetic resolution gives pure oxides but needs a specific catalyst [8]. The ring opening of epoxides of limonene and carvomenthene has been used for extensive production of diols; either *cis*- or *trans*-isomer affords the same *trans*-diaxial diol [9]. Their kinetic resolution has been attempted by several methods. Mercury salt induces selective cleavage of *cis*-oxide affording the separation of *trans*-oxide [10]. The method, however, requires an additional step of de-metallation of the mercuric salt of the product from *cis*-oxide. In case of base-induced separation of epoxides, either *cis*- or *trans*-oxide is obtained depending upon the choice of base but the reactions require higher temperatures [11]. Molybdenum complex mediated kinetic separation of *trans*-oxide and conversion of *cis*-oxide to *trans*-diol is reported [12]. Racemic chromium salen complex has been found to effect kinetic resolution in case of monocyclic terpene epoxides containing C-4 substituents in their structure [13]. Photochemical approach to the epoxide ring opening is another attractive strategy for the alcoholysis of the epoxides [14]. Both photo-assisted kinetic stereo-differentiation of addition of methanol to limonene [15] and light-induced ionic addition of methanol to epoxides [16] have been reported. In order to develop a facile and simple procedure for the effective separation of epoxides, the light induced ring cleavage of limonene and carvomenthene oxides in the presence of Lewis acid catalysts was investigated.

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2. Experimental

2.1. General methods

Zinc halides were dried in a drying pistol at 110–115 °C under reduced pressure (0.13 kPa). Gas liquid chromatography (GLC) analyses were carried out on Fisons-8000 gas chromatograph with HP-3380A integrator. GC–MS analyses were carried out on Shimadzu-QP 5000 instrument working with EI (70 eV). PMR spectra were recorded on Bruker AMX-400 NMR spectrometer in $CDCl_3$ solvent

2.2. General procedure

In a typical reaction, a solution of epoxide (mixture of *cis*- and *trans*-isomers, 10 mmol) in dry methanol (150 ml) with the Lewis acid catalyst (5 mol%) was irradiated in a circulating liquid type photo-reactor [17] and the progress of the reaction was monitored by GC. At the end of the reaction, *trans*-oxide [18] and β-hydroxymethyl ether were obtained by usual workup of the product followed by distillation under reduced pressure.

2.2.1. *trans-R(+)-Limonene-1,2-oxide [17]*

b.p.57–59 °C/0.33 kPa [4] 78.5–80.5 °C/1.33 kPa $[\alpha]_{20}^{D} = +76.66°$(neat), [Lit] +82°, ^{1}H NMR ($CDCl_3$, J = Hz) δ = 1.31 (s, 3H), 1.69(s, 3H), 1.40–1.50 and 1.70–2.30(m, 7H), 2.98(d, J = 5.2 Hz, 1H), 4.66(s, 2H), MS (*m/z*): 152(2), 137(3), 119(4), 108(20), 94(35), 79(30), 67(70), 43(100).

2.2.2. *(1S, 2S, 4R)-trans-1-Methoxy-2-hydroxy-p-menthan-8(9)-ene*

b.p. 100–102 °C/0.33 kPa, $[\alpha]_{20}^{D} = +40.62°$, ^{1}H NMR ($CDCl_3$, J = Hz) δ = 1.15 (s, 3H), 1.69(s, 3H), 1.40–1.55 and 1.70–2.30(m, 7H), 3.19(s, 3H), 3.60(s, 1H), 4.66(s, 2H), MS (*m/z*): 184(2), 169(5), 152(10), 139(2), 108(15), 85(100), 72(60), 55(50), 43(60).

2.2.3. *trans-R(+)-Carvomenthene-1,2-oxide [17]*

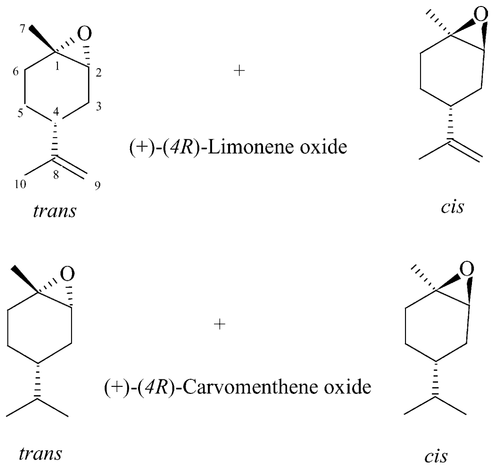
b.p. 58–60 °C/0.33 kPa, $[\alpha]_{20}^{D} = +52.52°$ (neat), ^{1}H NMR ($CDCl_3$, J = Hz) δ = 0.82 (d, J = 6.8, 6H), 1.0–1.15(m, 2H), 1.30(s, 3H), 1.48–1.65(m, 4H) 1.90–2.0(m, 2H), 2.96(d, J = 5.3 Hz, 1H), MS (*m/z*): 154(2), 139(10), 125(8), 111(30), 97(10), 83(15), 69(45), 55(50), 43(100).

2.2.4. *(1S, 2S, 4R)-trans-1-Methoxy-2-hydroxy-p-menthane*

b.p. 96–98 °C/0.27 kPa, $[\alpha]_{20}^{D} = 38.21°$ (neat), ^{1}H NMR ($CDCl_3$, J = Hz) δ = 0.86 (dd, J = 6.7 and 5.0 Hz, 6H), 1.15(s, 3H), 1.18–1.72(m, 6H) 2.16(m, 2H), 3.17(s, 3H), 3.63(s, 1H), MS (*m/z*): 186(3), 171(2), 154(3), 143(15), 125(7), 111(10), 97(4), 83(22), 71(50), 55(30), 43(100).

3. Results and discussion

Epoxidation of limonene and carvomenthene with peracetic acid (~40%) produces a mixture of *cis*- and *trans*-oxides in nearly equal quantities (Scheme 1). Pure *trans*-epoxides of limonene and carvomenthene were prepared from the corresponding bromohydrins as per the reported method [18]. The photoreaction of carvomenthene oxide conducted in methanol without any catalysts was found to be very slow as only a small amount of *cis*-oxide reacted even after irradiation at 240–366 nm for 24 h. However, the same reaction, when conducted in the presence of 5 mol% $ZnCl_2$, led to the consumption of the *cis*-oxide with the *trans*-oxide remaining un-reacted. After 8 h of irradiation, when all the *cis*-oxide reacted, the product after aqueous workup was subjected to fractional distillation under reduced pressure. The fraction, which distilled at 58–60 °C/0.33 kPa, was identified as *trans*-carvomenthene oxide, based on its PMR spectrum wherein the proton attached to epoxide appeared at 2.96 ppm as doublet (5.3 Hz). Its identity was further confirmed by co-elution on GC with an authentic sample of *trans*-oxide. The other fraction, which distilled at 96–98 °C/0.27 kPa, was identified as (1*S*, 2*S*, 4*R*)-*trans*-1-methoxy-2-hydroxy-*p*-menthane. The presence of two singlets at 3.17 and 3.63 ppm for three and one proton respectively, indicated the methoxy and hydroxyl groups in the product. The hydroxyl and methoxy groups were assigned *trans*-stereochemistry as arising from the effective diaxial ring opening of the *cis*-oxide according to Furst-Plattner rule [19a,b]. Here, the 4-alkyl substituents have been shown to determine the conformation in which the *cis*- and *trans*-1,4-substituted cyclohexene-1,2-epoxides react with acidic reagents. Similarly, when the photoreaction was carried out in the presence of 5 mol% of $ZnBr_2$ or $InCl_3$, identical results were obtained. The reaction was also carried out at room temperature and under reflux condition in the presence of 5 mol% Lewis acid catalysts. It was observed that the reactions at ambient temperature were very slow and hence unsuitable for the kinetic separation whereas those run under reflux conditions were fast and non-selective as some amount of *trans*-oxide also was found to react, giving mixtures of products. The results of these various experiments are summarized in Table 1.



Scheme 1.

Table 1
Reaction of carvomenthene oxide with methanol in presence of 5 mol% Lewis acid catalysts

Lewis acid	Time (h)	% *trans*-Carvomenthene-oxide[a]	% *cis*-Carvomenthene-oxide[a]	% *trans*-1-Methoxy-2-hydroxy-*p*-menthane[a]
$InCl_3$				
A	20	45	0	48
B	5	49	0	47
C	1.5	30	0	43
$ZnCl_2$				
A	96	54	25	15
B	8	52	0	44
C	1	45	9	35
$ZnBr_2$				
A	96	50	23	25
B	5	54	0	45
C	1	45	13	40

A: Stirring (25 °C), B: light (240–366 nm) at 25 °C, C: reflux.
[a] Yield determined by GC.

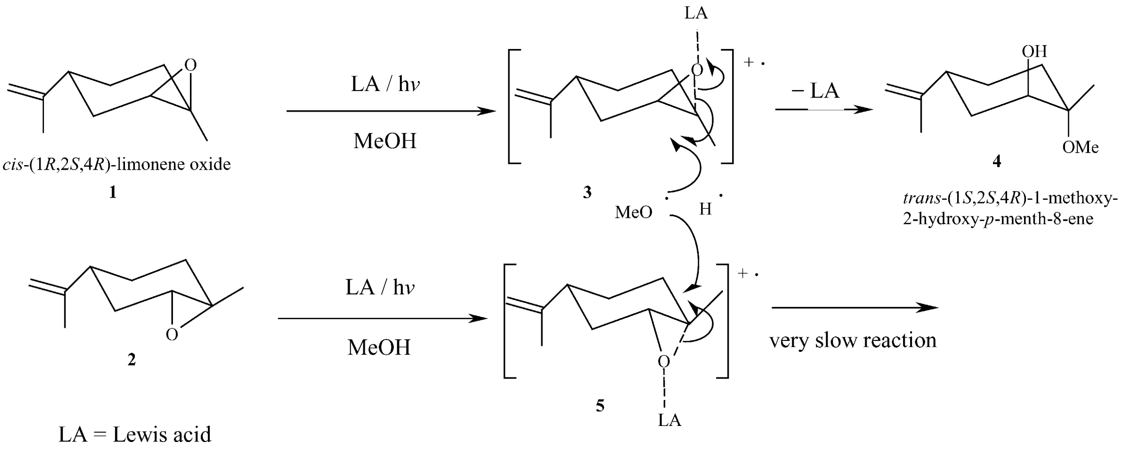
Under the standardized conditions, photo-irradiation of limonene-1,2-oxide was studied in methanol in the presence of 5 mol% Lewis acid catalyst. On irradiation in the presence of 5 mol% $ZnCl_2$, methanol added preferentially to *cis*-limonene oxide leaving behind the *trans*-oxide unreacted. After aqueous workup, the product was subjected to fractional distillation under reduced pressure. The fraction, which distilled at 57–59 °C/0.33 kPa was identified as *trans*-limonene-1,2-oxide based on the its PMR spectrum wherein the proton attached to epoxide appeared at 2.98 ppm as doublet (5.3 Hz). Its identity was further confirmed by co-elution on GC with an authentic sample of *trans*-oxide. The compound, which distilled at 100–102 °C/0.33 kPa, had a PMR spectrum which clearly showed the presence of methoxy group at 3.19 ppm and hydroxyl at 3.60 ppm and was identified as (*1S*, *2S*, *4R*)-*trans* 1-methoxy-2-hydroxy-*p*-menth-8-ene based on other signals. Using the optimized conditions, with 5 mol% of Lewis acid and in methanol, the reaction was carried out under different conditions and results are summarized in Table 2.

The mechanism of photo-assisted selective addition of methanol to 4-alkyl substituted cyclohexene oxides under the influence of light in the presence of Lewis acid catalysts is illustrated and explained with *cis*- and *trans*-limonene oxides (**1** and **2**) in Scheme 2. Initially photo-assisted cleavage of C_1–O bond takes place, which was influenced by the presence of Lewis acid. In case of **1**, Lewis acid can easily make association with the axially oriented epoxide oxygen to form radical cation **3**. In this case C-4 substituent oriented equatorially offers less hindrance for the approach of Lewis acid. Whereas this is difficult in case of **2**, because of the equatorial orientation of epoxide oxygen and also hindrance to the approach of Lewis acid due to the presence of isopropenyl group at C-4 position. Formation of **4** from **3** is fast, as the methoxy and proton radicals generated in the presence of light quickly add to the intermediate **3**. Hence it appears that the presence of substituent at C-4 position plays an important role in determining the difference in the reactivity of the diastereomeric epoxides. Thus, light induces the selectivity in respect of preferential cleavage of *cis*-oxide leaving be-

Table 2
Reaction of (+)-limonene-1,2-oxide with methanol in presence of 5 mol% Lewis acid catalysts

Lewis acid	Time (h)	% *trans*-Limonene-oxide[a]	% *cis*-Limonene-oxide[a]	% *trans*-1-Methoxy-2-hydroxy-*p*-menth-8-ene[a]
$InCl_3$				
A	12	54	0	41
B	3	48	0	41
C	0.5	35	0	40
$ZnCl_2$				
A	96	56	25	16
B	20	55	0	40
C	2	41	0	35
$ZnBr_2$				
A	96	55	20	22
B	10	52	0	42
C	1	40	0	36

A: stirring (25 °C), B: light (240–366 nm) at 25 °C, C: reflux.
[a] Yield determined by GC.



Scheme 2.

hind the pure *trans*-oxide (>98%). The present strategy of kinetic resolution can be utilized as a simple and convenient method for the preparation of pure diastereomeric epoxides.

4. Conclusions

In conclusion, we found that light promotes kinetic stereodifferentiation in Lewis acid catalyzed ring cleavage of terpene epoxides in methanol. The method would be not only useful as a new synthetic tool for the production of pure *trans*-epoxides, but also for the synthesis of *trans*-β-hydroxy methyl ethers.

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