

## Rearrangements of verbenol epoxide in supercritical fluids

Konstantin P. Volcho,<sup>a\*</sup> Irina V. Il'ina,<sup>a</sup> Nariman F. Salakhutdinov,<sup>a</sup> and Vladimir I. Anikeev<sup>b</sup>

<sup>a</sup>Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, Prosp. Akad. Lavrent'eva 9, Novosibirsk 630090, Russian Federation

<sup>b</sup>Boreskov Institute of Catalysis, Siberian Branch of the Russian Academy of Sciences, Prosp. Akad. Lavrent'eva 5, Novosibirsk 630090, Russian Federation

E-mail: [volcho@nioch.nsc.ru](mailto:volcho@nioch.nsc.ru)

Dedicated to Professor Usein M. Dzhemilev on the occasion of his 65<sup>th</sup> birthday

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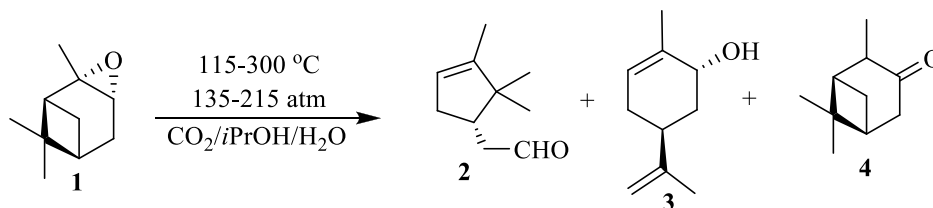
### Abstract

Transformations of verbenol epoxide in a supercritical mixture of CO<sub>2</sub>, isopropyl alcohol, and water were studied. The main identified products were similar to those obtained in the presence of Montmorillonite clays, but with much shorter contact times and without an acid catalyst. The reactivity of verbenol epoxide in supercritical media differs dramatically from the behavior of this epoxide in the presence of Lewis acid ZnBr<sub>2</sub>. In contrast to studies of  $\alpha$ -pinene epoxide transformations, the presence of water caused no essential changes in product distribution. The presence of triethylamine suppressed the rearrangements; obviously the reaction has cationic character.

**Keywords:** Verbenol epoxide, supercritical carbon dioxide, isopropyl alcohol, isomerization, terpenoid

### Introduction

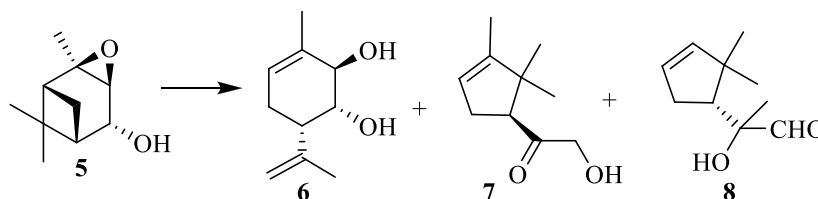
We showed earlier<sup>1</sup> that rearrangements of  $\alpha$ -pinene epoxide **1** in mixtures of supercritical CO<sub>2</sub>, lower alcohols (ethanol, isopropyl alcohol) and water differ considerably from products of its conventional thermolysis or its reaction with acid catalysts (Scheme 1).



**Scheme 1.** Reactivity of  $\alpha$ -pinene epoxide **1** in a mixture of supercritical CO<sub>2</sub>, *i*-PrOH and H<sub>2</sub>O.

In the presence of ethanol, the conversion of  $\alpha$ -pinene epoxide **1** was noticeably higher than with isopropyl alcohol, but the selectivity for campholenic aldehyde **2** decreased considerably. Moreover, it was shown that the main products obtained from  $\alpha$ -pinene epoxide **1** in a solvent containing water were campholenic aldehyde **2** and carveol **3**, and in the absence of water campholenic aldehyde **2** and pinocamphone **4**, their total content in the reaction mixture attaining 80%.

The present paper reports the results of study of the transformations of verbenol epoxide **5** in supercritical media. Conversion products of this monoterpenoid are of great interest mainly due to their high biological activity, for example, compound **6** (Scheme 2) which can be obtained from verbenol epoxide **5** using Montmorillonite clays<sup>2,3</sup> demonstrates high antiepileptic<sup>4</sup> and antiparkinsonian<sup>5</sup> activities. Application of a flow technique for transformations of labile terpenoids such as compound **5** helps to avoid the use of acid catalysts and the inevitable difficulties associated with the catalyst separation, and may also improve the rate and selectivity of the transformations<sup>6</sup>.



**Scheme 2.** Isomerization of verbenol epoxide **5**.

## Results and Discussion

The rearrangements of verbenol epoxide **5** were studied in a flow reactor using a mixture of supercritical CO<sub>2</sub> and isopropyl alcohol. Our previous studies<sup>1</sup> of  $\alpha$ -pinene epoxide **1** transformations in a mixture of supercritical CO<sub>2</sub>, ethanol or isopropyl alcohol and water formed the basis of the temperature and pressure variation intervals we chose.

Experimental data on the transformations of verbenol epoxide **5** are presented in Table 1. Hydroxy ketone **7** and diol **6** (Scheme 2) are the main reaction products; quantitative conversion of verbenol epoxide **5** occurred at 292 °C (Table 1, exp. 1). Additionally, a very small amount of  $\alpha$ -hydroxy aldehyde **8** was formed, as in earlier studies in the presence of Montmorillonite clay.<sup>3</sup> In considering how **8** could form, the authors<sup>3</sup> suggested a quite complex multi-step scheme which assume compound **8** to form from verbenol epoxide **5** via specific adsorption of the latter on the catalyst surface, though a comparable explanation cannot apply here.

Heating verbenol epoxide **5** in this way gave a large amount of unidentified products, making up about half of the reaction products; the main by-product did not exceed 5% of this. As the CO<sub>2</sub> flow rate was increased from 2.5 to 4.0 ml/min (Table 1, exp. 2), the fraction of unidentified products decreased considerably, most likely because the contact time was shorter.

Concentrating and column-chromatographic separation of the reaction mixture in exp. 2 (Table 1) allowed preparative isolation of compound **6** being 18% of the total reaction products, and in agreement with GLC-MS measurements. The enantiomeric compositions of verbenone (*ee* 72%), from which verbenol epoxide **5** was synthesized, and compound **6** (*ee* 72%) by GLC-MS method using a chiral column, revealed that no decrease of optical purity occurred during the transformations, that is, isomerization of compound **5** proceeded stereospecifically.

As the reaction temperature was decreased to 197 °C (Table 1, exp. 3), the product mixture contained more of compound **6** than at 292 °C. Conversion of epoxide **5** at 197 °C proceeded quantitatively, whereas in our experiments with  $\alpha$ -pinene epoxide **1**, conversion did not exceed 60% at temperatures below 212 °C.<sup>1</sup>

When 1.5% of water was added to the reaction mixture (Table 1, exp. 4), the fraction of unidentified products decreased; as a result, the proportion of compounds **6-8** in the reaction mixture increased.

Decreasing the reaction temperature to 140 °C (Table 1, exp. 5) increased the content compounds **6** and **7** to 29.9 and 44.2%, respectively, and decreased the proportion of both hydroxy aldehyde **8** and the unidentified products. Addition of water (Table 1, exp. 6) decreased of the proportion of unidentified compounds to 17.5% and also produced more of the compounds with a cyclopentane skeleton (**7** and **8**), however, not all of starting epoxide **5** was consumed. Addition of water had a smaller effect on the course of verbenol epoxide **5** transformations compared to those of  $\alpha$ -pinene epoxide **1**.<sup>1</sup>

Studies of the effect of the supercritical CO<sub>2</sub> concentration (which is varied by changing its flow rate) on the product distribution showed (Figure 1) that as the CO<sub>2</sub> flow rate was increased from 2.5 to 4.0 ml/min, the verbenol epoxide **5** conversion remained unchanged. Further increase of CO<sub>2</sub> flow rate caused a considerable decrease of verbenol epoxide **5** conversion, because residence time became shorter. However, varying the CO<sub>2</sub> flow rate produced an insignificant effect on selectivity; it influenced only the proportion of hydroxy ketone **7** in the product mixture.

**Table 1.** Isomerization of verbenol epoxide **5** in a flow reactor using supercritical CO<sub>2</sub> and *i*-PrOH: products distribution

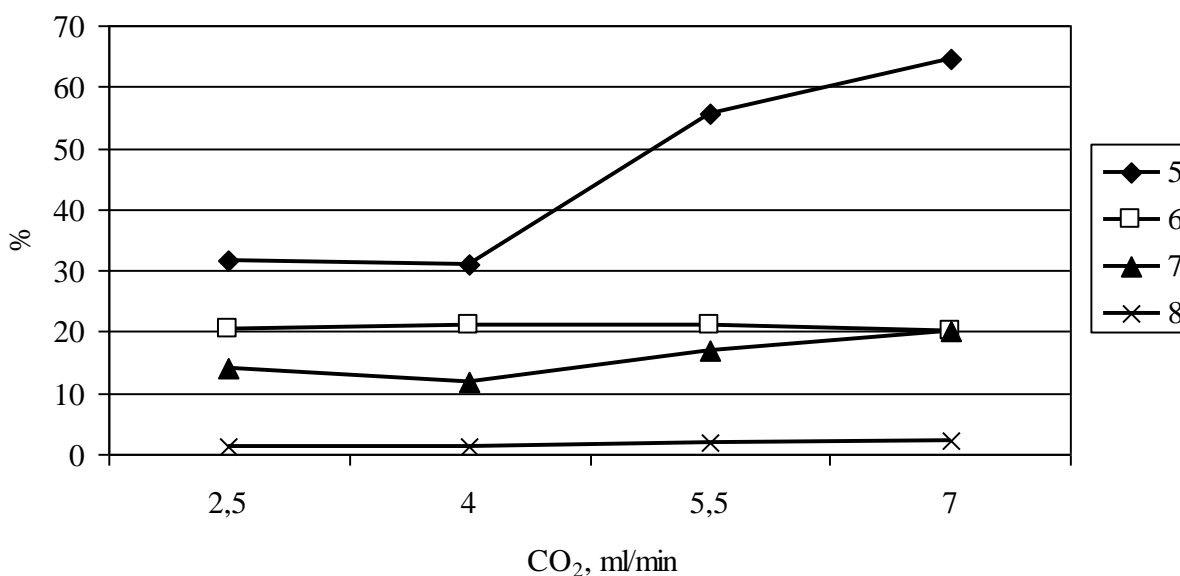
N	Supercritical solvent <sup>a</sup>	T, °C	P, atm (psi)	Content (%), according to GLC-MS data				
				<b>5</b>	<b>6</b>	<b>7</b>	<b>8</b>	Other products
1	<i>i</i> -PrOH/CO <sub>2</sub>	292	165 (2420)	-	12.6	38.5	0.4	48.5
2	<i>i</i> -PrOH/CO <sub>2</sub> <sup>b</sup>	292	175 (2570)	-	19.6	42.9	2.8	34.7
3	<i>i</i> -PrOH/CO <sub>2</sub>	197	165 (2420)	-	23.3	30.5	2.8	43.4
4	<i>i</i> -PrOH/CO <sub>2</sub> /H <sub>2</sub> O <sup>c</sup>	197	165 (2420)	-	25.8	37.9	4.3	32.0
5	<i>i</i> -PrOH/CO <sub>2</sub>	140	160 (2350)	-	29.9	44.2	1.6	24.3
6	<i>i</i> -PrOH/CO <sub>2</sub> /H <sub>2</sub> O <sup>c</sup>	140	160 (2350)	7.6	23.9	48.7	2.3	17.5

<sup>a</sup>2.5 ml/min. <sup>b</sup>4 ml/min. <sup>c</sup>*i*-PrOH/H<sub>2</sub>O = 93.5/6.

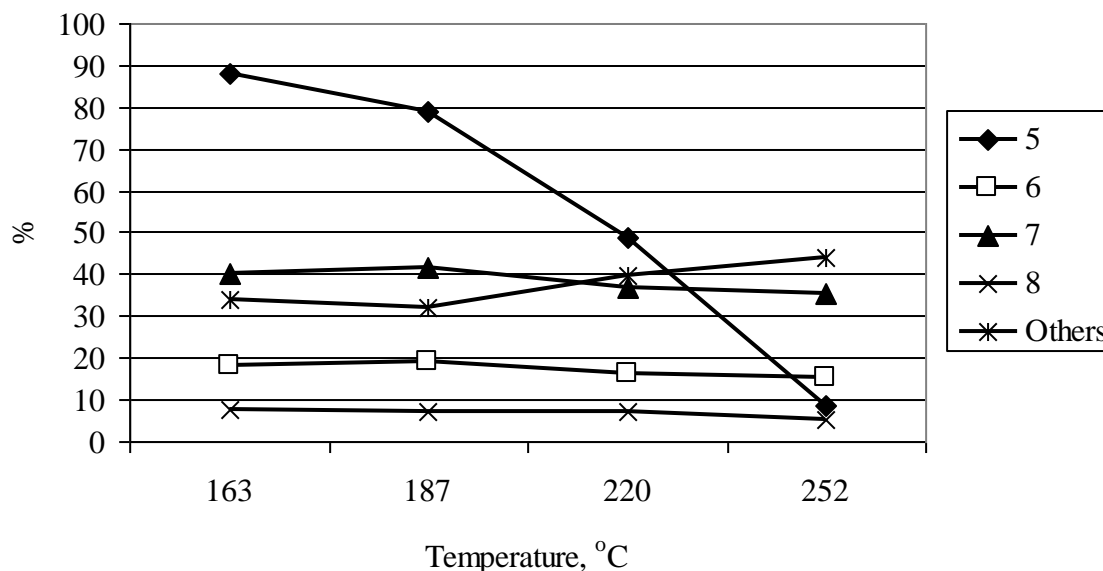
In our earlier studies<sup>1</sup> of  $\alpha$ -pinene epoxide **1** transformations, we suggested that the transformations had a “cationic” character, judging by the structure of main product **2**, and could be explained by the high acidity of the system isopropyl alcohol – CO<sub>2</sub> in supercritical state, more so in the presence of water. The suggestion was supported by product distributions which depended on water concentration; in the absence of water, the proportion of other products which can be formed by thermal isomerization increased considerably.

As mentioned above, the effect of water additive on the transformations of verbenol epoxide **5** is less than on the transformations of  $\alpha$ -pinene epoxide **1**. This may be attributed to a lower stability of verbenol epoxide **5** in weakly acidic medium. That is, the acidity of system isopropyl alcohol – CO<sub>2</sub> is sufficient to catalyze verbenol epoxide **5** transformations. To check this suggestion, we added triethylamine, to neutralize acidity, and in experiments at 163 °C we found the conversion of verbenol epoxide **5** to be insignificant (Figure 2), which can be compared with the quantitative conversion of **5** in the absence of triethylamine and at a lower temperature (140 °C) (Table 1, exp. 5). We conclude that the rearrangements of verbenol epoxide **5** in the present conditions have mainly cationic character. Note, although triethylamine caused a strong decrease in verbenol epoxide **5** conversion, its influence on the product distribution was insignificant.

As the temperature increased, the conversion of verbenol epoxide **5** increased as well (Figure 2), while the selectivity remained almost unchanged; only a small adjustment of product distribution towards unidentified products occurred. Since the formation of compounds with cyclopentane skeleton **7** and **8** by thermal isomerization seems unlikely,<sup>11</sup> even residual acidity of supercritical media in the presence of triethylamine appears sufficient for initiation of verbenol epoxide **5** transformations.



**Figure 1.** Dependencies of starting material **5** and products **6-8** proportions on the CO<sub>2</sub> flow rate (conditions: *i*-PrOH–CO<sub>2</sub>, 257 °C, 150 atm).



**Figure 2.** Dependencies of the verbenol epoxide **5** and isomerization products **6-8** content on the reaction temperature in the presence of  $\text{NEt}_3$  (conditions: *i*-PrOH– $\text{CO}_2$  (2.5 ml/min), 0.7%  $\text{NEt}_3$ , 167 atm).

In the presence of  $\text{ZnBr}_2$  verbenol epoxide **5** transforms into compound **7**,<sup>12</sup> while in the presence of Montmorillonite clay the main product is compound **6** (44% yield); compounds with cyclopentane skeleton **7** and **8** are formed in smaller quantities (16 and 10%, respectively).<sup>3</sup> Our results in this flow system are more similar to those on clays than to those catalyzed by  $\text{ZnBr}_2$ .

## Experimental Section

Verbenol epoxide **5** has been synthesized by means of two-stage synthesis from (*S*)-(-)-verbenone (Aldrich, ee 72%) via verbenone epoxide according to known procedures (epoxidation of verbenone with hydrogen peroxide in the presence of  $\text{NaOH}$ ;<sup>7</sup> reduction of verbenone epoxide with  $\text{LiAlH}_4$ )<sup>2</sup>; the purity epoxide **5** was not less than 98.0%. The  $^1\text{H}$  NMR spectra of compounds **5** coincided with those given in the literature.<sup>2</sup> Isopropyl alcohol contains no less than 99.8 wt. % of the main substance and no more than 0.05 wt.% of water.  $\text{CO}_2$  was a stated purity of 99.9 vol. % and contained no more than 0.02 vol.% water.

Experimental studies on rearrangement of verbenol epoxide **5** were performed in the laboratory-scale set-up described earlier,<sup>8</sup> using a tubular flow-type reactor with a length of ca. 3 m and inside diameter 1.75 mm (reactor volume ca. 7.2  $\text{cm}^3$ ). The reaction mixture was fed to the reactor as two streams. The first stream – supercritical  $\text{CO}_2$  – was delivered by syringe pump to a mixer mounted at the reactor inlet, through a heat exchanger where it was heated to the reaction temperature. The

CO<sub>2</sub> flow rate varied from 2.5 to 7.0 ml/min. The second stream – a mixture of verbenol epoxide **5** with the solvent (pure alcohol or alcohol with water) – was fed to the same mixer by piston pump. The molar ratio of epoxide/alcohol or epoxide/alcohol/water in the stream was 0.6:99.4 and 0.5:93.5:6, respectively. The ratio was chosen on the basis of our previous work.<sup>9</sup> The mixture was fed to the reactor at a flow rate of 1 ml/min.

The products of reaction were cooled at the reactor outlet, separated into gas and liquid phases, and analyzed. Composition of the reaction products in the liquid phase was determined by gas chromatography-mass spectrometry (GC-MS) using a Hewlett-Packard 5890/II gas chromatograph equipped with a quadrupole mass spectrometer HP MSD 5971 as a detector. Quartz column HP-5 (copolymer 5%–diphenyl–95%–dimethylsiloxane) of length 30 m, internal diameter 0.25 mm and stationary phase film thickness 0.25 μm was used for the analysis.

Qualitative analysis was performed by comparing retention indices of components and their complete mass spectra with the corresponding data for pure compounds. The percentage composition of mixtures was calculated from the surface areas of chromatographic peaks using no correction coefficients.

The reaction mixture residence time  $\tau$  was 120 s at 2.5 ml/min flow rate and was calculated as a ratio of reactor volume  $V_R$  (cm<sup>3</sup>) to the inlet volume consumption of mixture  $Q$  (cm<sup>3</sup>/s). The temperature and pressure intervals used for thermolysis of verbenol epoxide **5** were  $T = 140\text{--}292$  °C and  $P = 140\text{--}175$  atm (2060–2570 psi).

In order to determine the reaction conditions (temperature and pressure) providing a homogeneous state of reaction mixture in the reactor, thermochemical calculations were used to construct a phase diagram for the initial composition of the mixture, and the critical values  $T_{cr}$  and  $P_{cr}$  were found. The calculations were based on techniques developed earlier using the Redlich–Kwong–Soave equation of state.<sup>10</sup>

Since the total proportion of CO<sub>2</sub> and alcohol in the initial mixture exceeds 0.95 and remains virtually constant in the course of reaction, one can suggest that position of the critical point will change only slightly during the isomerization of the epoxide.

Chirospecific GLC-MS: 6890N gas chromatograph (Agilent Tech., USA); 5973 INERT mass-selective detector (Agilent Tech., USA); Cyclosil-B capillary column (30 m × 0.32 mm × 0.25 μm, Agilent Tech., USA); the temperature of the column thermostat was 50 °C/2min; temperature gradient from 2 °C/min to 220 °C/5 min; evaporator and interface temperature 250 °C; He as carrier gas (flow rate 2 ml/min, flow division 99:1); sweep from  $m/z$  29 to  $m/z$  500; 1 μl sample. <sup>1</sup>H NMR (300 MHz) spectra were recorded in CDCl<sub>3</sub>.

### Compound (6) preparation

For the isolation of compound **6** on a preparative scale, a sample of reaction mixture (72 ml) obtained in experiment 2 (Table 1) was concentrated to give 0.430 g of products. The residue was separated on 9 g SiO<sub>2</sub> (60–200 mesh, Macherey-Nagel; 10–100% gradient ethyl acetate/hexane as an eluent) to give (1*R*,2*R*,6*S*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol **6** (0.077 g, 18%). The <sup>1</sup>H NMR spectrum of compound **6** was the same as the spectrum given in the literature.<sup>7</sup>

## Conclusions

This paper describes the first study of the behavior of verbenol epoxide **5** in a flow reactor at high temperature and in a mixture of supercritical carbon dioxide and isopropyl alcohol with, in some case, water. The main products were similar to those obtained in the presence of Montmorillonite clays, but with much shorter contact times and without any acid catalysts. The reactivity of epoxides **5** in these conditions differs dramatically from their behavior in the presence of  $ZnBr_2$ . Preparative isolation of compound **6** followed by analysis by chiral GLC-MS proved that the isomerization of verbenol epoxide **5** to **6** proceeded stereospecifically. In contrast to earlier studies of  $\alpha$ -pinene epoxide **1** transformations, the presence of water caused no essential changes in product distribution. In the presence of triethylamine, a sharp decrease of conversion was observed, so the reaction has cationic character.

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