



## Isomerization of bicyclic terpene epoxides into allylic alcohols without changing of the initial structure



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### ABSTRACT

A novel method of (1*S*,2*R*,3*R*,5*R*)-6,6-dimethyl-4-methylenebicyclo[3.1.1]heptane-2,3-diol synthesis, which is a valuable intermediate in the synthesis of a perspective potent anti-Parkinson drugs, in the presence of TiO<sub>2</sub> was proposed. Catalytic activity of TiO<sub>2</sub> in the bicyclic terpene epoxides isomerization to corresponding allylic alcohols without changing of the initial structure was demonstrated, contrary to titania-supported Au catalysts which promoted rearrangement with predominant formation of a cyclopentene  $\alpha$ -hydroxy ketone.

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### 1. Introduction

The development of new effective medications for the medical correction of the most common diseases is a challenging topic in pharmaceutical industry. Terpenes represent a large and diverse class of organic compounds that possess biological activity and are widely used in the development of new drugs and vitamins. Recently the compound (**1**) in Scheme 1 synthesized from naturally derived verbenone was demonstrated to exhibit high anti-Parkinson's activity in the *in vivo* experiments in combination with low acute toxicity [1,2].

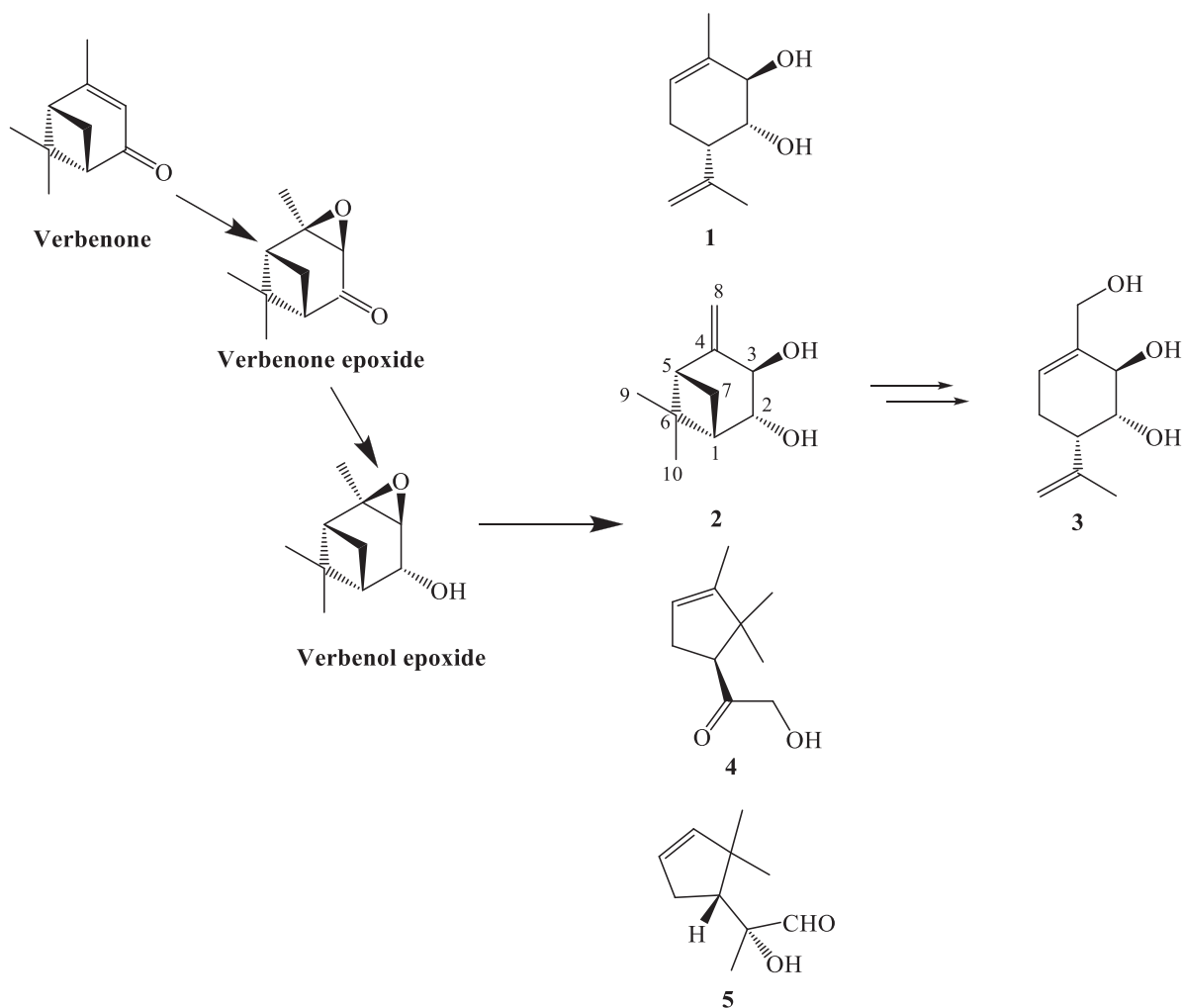
At the same time a set of the most probable metabolites of this compound is of great interest for the further pharmacokinetic examination, particularly triol **3**. The effective way leading to compound **3** starts from two steps transformation of available verbenone to verbenol epoxide. The key step of the triol **3** synthesis is verbenone epoxide isomerization to compound **2** which is a valuable intermediate. According to the published earlier results for this reaction type selectivity to products can be affected by the presence of Lewis and Brønsted acid sites as well as the reaction conditions such as polarity and basicity of the solvent [3,4]. The application of different

montmorillonite clays were actively studied for the synthesis of the diol **1** [5,6], while the highest recently reported yield of this compound (79%) was obtained using Fe-modified zeolite [7].

At the same time to the best of our knowledge, the compound **2** as well as the method of its synthesis has never been described in the literature. Generally the rearrangement of epoxides to corresponding allylic alcohols is an attractive approach which has been thoroughly investigated. Different methods, including reaction with alkylamide bases [8–11], use of organoselenium chemicals [12] and a radical pathway ((C<sub>5</sub>H<sub>5</sub>)<sub>2</sub>TiCl) [13], are known. There are a few examples of epoxides isomerization over heterogeneous catalysts, such as Al<sub>2</sub>O<sub>3</sub>, ZrO<sub>2</sub> and TiO<sub>2</sub> [14,15]. However, the reaction in the presence of these catalysts mainly proceeds extremely slow or requires elevated temperature to form small amounts of allylic alcohol. Recently gold catalysts were shown to be highly active in the selective isomerization of terpene epoxides to the corresponding allylic alcohols in contrast to TiO<sub>2</sub> that was found to be inactive without Au [16].

Nowadays special attention in the literature is deservedly devoted to utilization of gold catalysts for fine chemical synthesis due to its unique activity for transformations of organic compounds. Many review articles concerning application of nano-gold catalysis in organic reactions were published, including those by Hashmi and Hutchings in 2006 [17], Corma and Garcia in 2008 [18], Stratakis and Garcia [19] and Zhang et al. in 2012 [20]. Renewable

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**Scheme 1.** Isomerization of verbenol epoxide.

monoterpenes conversion in the presence of gold nanoparticles is one of the promising directions in transformation of biomass. Some examples of unusual high activity of nanosized gold catalyst in monoterpenes transformations were also described recently in [21–23].

Ultimately, the main aim of this work was to synthesize (1*S*,2*R*,3*R*,5*R*)-6,6-dimethyl-4-methylenebicyclo[3.1.1]heptane-2,3-diol (**2**), which is a valuable intermediate in the synthesis of a perspective potent anti-Parkinson compounds **3**, from verbenone epoxide using gold catalysts.

## 2. Experimental

### 2.1. Catalytic experiment

Reagents and solvents were purchased from commercial suppliers and used as received. Dry solvents were obtained according to the standard procedures. Optical rotation was measured using polAAR 3005 spectrometer in  $\text{CHCl}_3$  solutions.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were obtained using Bruker DRX-500 apparatus at 500.13 MHz ( $^1\text{H}$ ) and 125.76 MHz ( $^{13}\text{C}$ ) in  $\text{CCl}_4/\text{CDCl}_3$  1:1 (v/v), chemical shifts  $\delta$  in ppm were related to residual  $\text{CHCl}_3$  [ $\delta(\text{H})$  7.24,  $\delta(\text{C})$  76.90 ppm],  $J$  in Hz. The structure of the products was determined by analyzing the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra,  $^1\text{H}$ ,  $^1\text{H}$  double-resonance spectra and  $^{13}\text{C}$ ,  $^1\text{H}$ -type 2D-COSY ( $J(\text{C},\text{H}) = 160\text{ Hz}$ ). For high resolution mass spectrometry DFS

Thermo Scientific spectrometer was used in a full scan mode (15–500  $m/z$ , 70 eV electron impact ionization, direct sample administration).

The epoxides isomerization was carried out at atmospheric pressure in a glass reactor equipped with an electromagnetic stirrer and a reflux condenser. The (-)-*cis*-verbenol,  $\alpha$ -pinene and verbenone epoxides were synthesized as reported previously [5,24,25]. The catalysts were additionally calcined before the reaction. After 20 h the reaction mixture was filtered and the solvent was removed under vacuum for identification of products composition by  $^1\text{H}$  NMR ( $\text{CCl}_4\text{-CDCl}_3$  (1:1, v/v)). The resulting mixture was separated by column chromatography ( $\text{SiO}_2$  (17 g, 60–200  $\mu$ ; Macherey-Nagel); hexane/ $\text{Et}_2\text{O}$  100:0  $\rightarrow$  0:100). In the case of the kinetic studies the aliquots were taken at appropriate time intervals, filtered and also analyzed by  $^1\text{H}$  NMR ( $\text{CCl}_4\text{-CDCl}_3$  (1:1, v/v)).

### 2.2. Catalyst preparation

The 2 wt.%  $\text{Au}/\text{TiO}_2$  catalyst was prepared from  $\text{HAuCl}_4$  aqueous solution ( $5 \times 10^{-4}\text{ M}$ ) by deposition-precipitation with urea at 81 °C during 24 h over  $\text{TiO}_2$  (Degussa AG, Aerolyst 7708, anatase > 70%,  $S_{\text{BET}} = 45\text{ m}^2/\text{g}$ ). Obtained slurry was washed with  $\text{NH}_4\text{OH}$  aqueous solution (4M) and deionized water. Thereafter, the catalyst was dried at 60 °C for 12 h and calcined at 300 °C for 4 h.

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