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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_2 was proposed. Catalytic activity of TiO_2 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 α-hydroxy ketone.

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 pharmakinetic 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 ($(C_5H_5)_2TiCl$) [13], are known. There are a few examples of epoxides isomerization over heterogeneous catalysts, such as Al_2O_3, ZrO_2 and TiO_2 [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_2 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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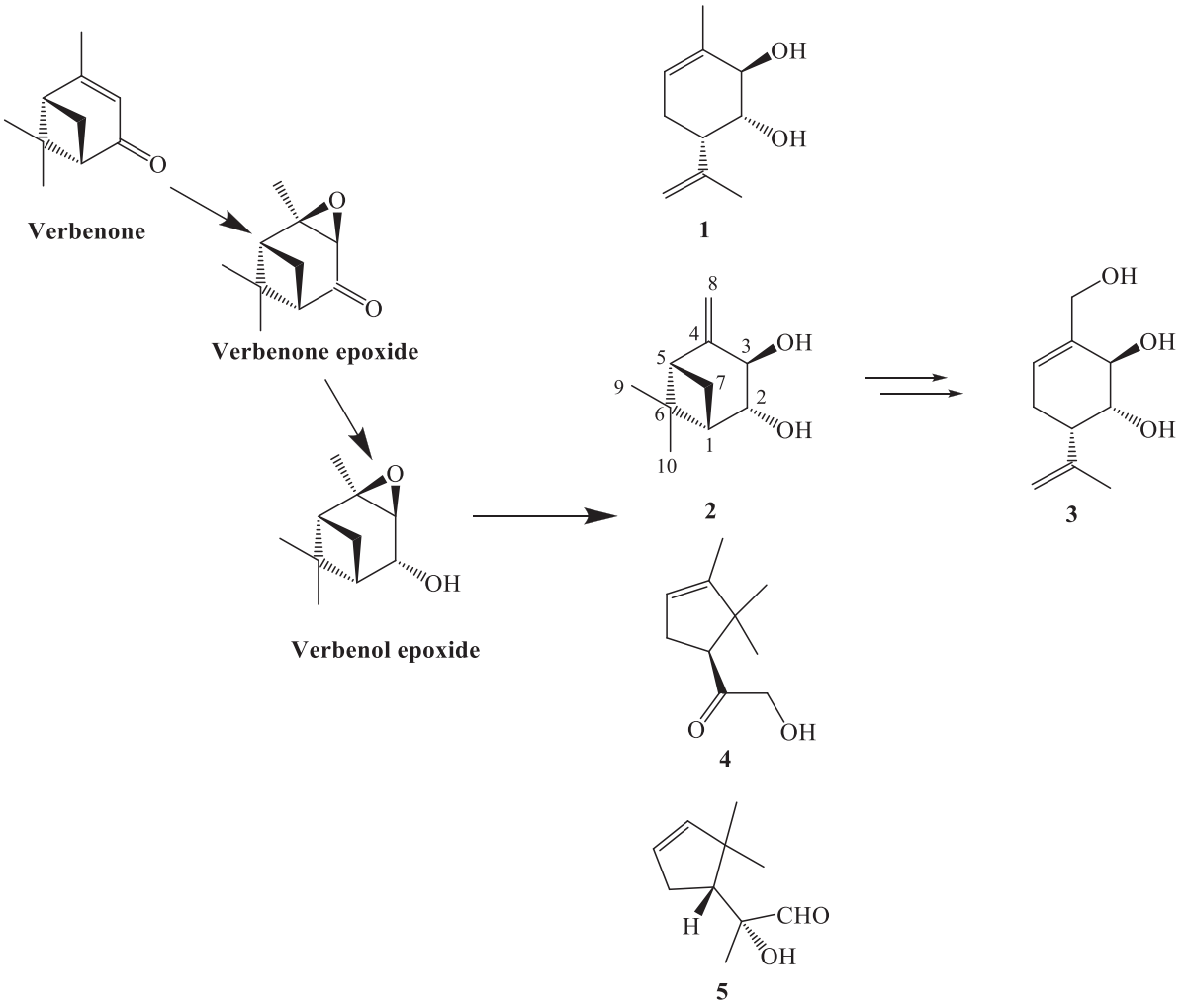


Scheme 1. Isomerization of verbenol epoxide.

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 $CHCl_3$ solutions. ^1H and ^{13}C NMR spectra were obtained using Bruker DRX-500 apparatus at 500.13 MHz (^1H) and 125.76 MHz (^{13}C) in $CCl_4/CDCl_3$ 1:1 (v/v), chemical shifts δ in ppm were related to residual $CHCl_3$ [δ(H) 7.24, δ(C) 76.90 ppm], J in Hz. The structure of the products was determined by analyzing the ^1H and ^{13}C NMR spectra, ^1H, ^1H double-resonance spectra and ^{13}C, ^1H-type 2D-COSY (J(C,H) = 160 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, α-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 ^1H NMR (CCl_4–$CDCl_3$ (1:1, v/v)). The resulting mixture was separated by column chromatography (SiO_2 (17 g, 60–200 μ; Macherey-Nagel); hexane/Et_2O 100:0 → 0:100). In the case of the kinetic studies the aliquots were taken at appropriate time intervals, filtered and also analyzed by ^1H NMR (CCl_4–$CDCl_3$ (1:1, v/v)).

2.2. Catalyst preparation

The 2 wt.% Au/TiO_2 catalyst was prepared from $HAuCl_4$ aqueous solution (5×10^{-4} M) by deposition-precipitation with urea at 81 °C during 24 h over TiO_2 (Degussa AG, Aerolyst 7708, anatase > 70%, S_{BET} = 45 m^2/g). Obtained slurry was washed with NH_4OH aqueous solution (4 M) and deionized water. Thereafter, the catalyst was dried at 60 °C for 12 h and calcined at 300 °C for 4 h.

Table 1
Verbenol epoxide isomerization over Au/TiO_2 and TiO_2. The reaction conditions: $T = 80\,^{\circ}C$, verbenol epoxide 0.4 mmol, 1,2-dicloroethane 10 ml, catalyst 35 mg.

Catalyst	Conversion (%)	Product selectivity (%)			
		1	**2**	**4**	**5**
Au/TiO_2	100	25	21	43	11
TiO_2 (anatase > 70%)	100	23	40	34	4
TiO_2-a (anatase 100%)	100	20	44	30	6

Table 2
α-Pinene epoxide isomerization over Au/TiO_2 and TiO_2. The reaction conditions: $T = 80\,^{\circ}C$, α-pinene epoxide 0.4 mmol, 1,2-dicloroethane 10 ml, catalyst 35 mg.

Catalyst	Conversion (%)	Product selectivity (%)			
		6	**7**	**8**	**9**
Au/TiO_2	100	32	38	22	8
TiO_2 (anatase > 70%)	100	49	25	17	9
TiO_2-a (anatase 100%)	100	36	36	18	10

3. Results

In the current work, Au/TiO_2 (>70% anatase) catalyst with the Au particle size of *ca.* 2 nm, prepared by deposition-precipitation method with urea, was found to promote the verbenol epoxide isomerization with complete conversion in 15 h. The results of experiments are presented in Fig. 1a.

Verbenol epoxide is transformed into a mixture of compounds **1**, **2**, **4**, **5** (Scheme 1), the hydroxyl ketone **4** being the main product with the selectivity 43% (Table 1). The desired product (**2**) was formed in a yield of 21%. It should be noted that usual products of verbenol epoxide isomerization are only compounds **1**, **4**, **5**, while compound **2** was never found before in the reaction mixtures [5,6].

It was surprisingly observed that titanium oxide *per se*, which was used for the catalyst preparation, also catalyzed the verbenol epoxide isomerization with a comparable reaction rate (Fig. 1b). In the presence of TiO_2 the total conversion of verbenol epoxide was attained for 20 h resulting in the target product (**2**) with selectivity 40% (Table 1), as well as in nearly the same selectivity to hydroxyl ketone **4** and diol **1**.

Unexpectedly the data obtained in the current study did not correlate with that reported in [16], where gold nanoparticles were shown to predominantly catalyze the isomerization of epoxides to corresponding allylic alcohols. However in this case of titania the catalytic activity can strongly depend on its allotropic forms, which was also demonstrated for different reaction types [26–29]. It is well known titanium dioxide occurs in the following main forms: rutile, anatase and brookite. For the gold catalyst preparation TiO_2 powder containing more than 70% of anatase was used in this work (Degussa AG, Aerolyst 7708). In order to specify the eventual influence of titania phase, the 100% anatase form TiO_2 (designated as TiO_2-a) was also tested in the verbenol epoxide isomerization. The anatase form of titania afforded complete conversion giving a similar product distribution as a mixed phase titania (Table 1). Therefore the data obtained demonstrate that TiO_2 activity in epoxides isomerization is unlikely to be strongly connected with its allotropic form.

It is important to note again that although titania *per se* can catalyze rearrangements of verbenol epoxide, the presence of gold nanoparticles supported on titania had an influence on reaction selectivity. For instance primarily hydroxyl ketone **4** was formed over Au/TiO_2, while the reaction over titania *per se* resulted in the corresponding allylic alcohol (**2**) as the major product.

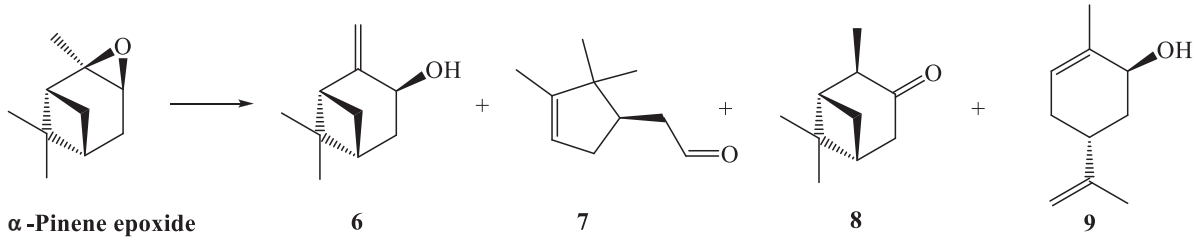
In order to explore the role of gold in the epoxide transformations, gold on titania and titania *per se* were evaluated in the isomerization of terpene epoxides with different molecular structures such as α-pinene epoxide which was used in [16] as one of the substrate as well as verbenone epoxide. *trans*-Pinocarveol (**6**), campholenic aldehyde (**7**) and pinocamphone (**8**) were found to be the products of α-pinene epoxide isomerization in the presence of gold on titania in a ratio 65:25:10 [16]. In our experiments α-pinene epoxide was transformed to *trans*-pinocarveol (**6**), campholenic aldehyde (**7**), pinocamphone (**8**) and *trans*-carveol (**9**) as shown in Scheme 2.

Similar types of products as for verbenol epoxide were observed in the case of α-pinene epoxide for both Au catalyst and TiO_2 (Table 2).

The activity of Au/TiO_2 was comparable with TiO_2. Au/TiO_2 catalyst was shown to promote mainly formation of campholenic aldehyde (**7**) with selectivity of 38% and pinocarveol (**6**) with selectivity of 32%. At the same time TiO_2 containing more than 70% of anatase resulted in pinocarveol (**6**) with 49% selectivity, while in the presence of 100% anatase form of titania (TiO_2-a) the equal amounts (36% each) of pinocarveol (**6**) and campholenic aldehyde (**7**) were obtained. These experiments confirm that Au nanoparticles play a minor role in the formation of the corresponding allylic alcohol, and titania as such can be applied in transformations of verbenol and α-pinene epoxides. It should be noted that at the present moment it is too premature to assume applicability of pristine titania for transformations of other epoxides to allylic alcohols. This would require a special study with a broader base of polycyclic terpene epoxides.

It is interesting that verbenone epoxide reacted neither over Au/TiO_2 nor TiO_2 and its conversion was zero after 20 h. At the moment, it can be only speculated that the peculiarities of molecule coordination on the catalyst surface or the effect of the functional group are responsible for these results.

Based on these results in the presence of TiO_2 the concerted mechanism of the epoxides isomerization, presented in the Fig. 2 for verbenol epoxide, can be envisaged. The epoxide molecule is coordinated first to the catalyst Lewis sites following by the rapid proton transfer. In the case of Au/TiO_2 catalyst the mechanism of the epoxide isomerization was proposed to be initiated by the coordination of oxygen atom in the epoxide to the $Au^{\delta+}$ species, inducing



Scheme 2. Isomerization of α-pinene epoxide.

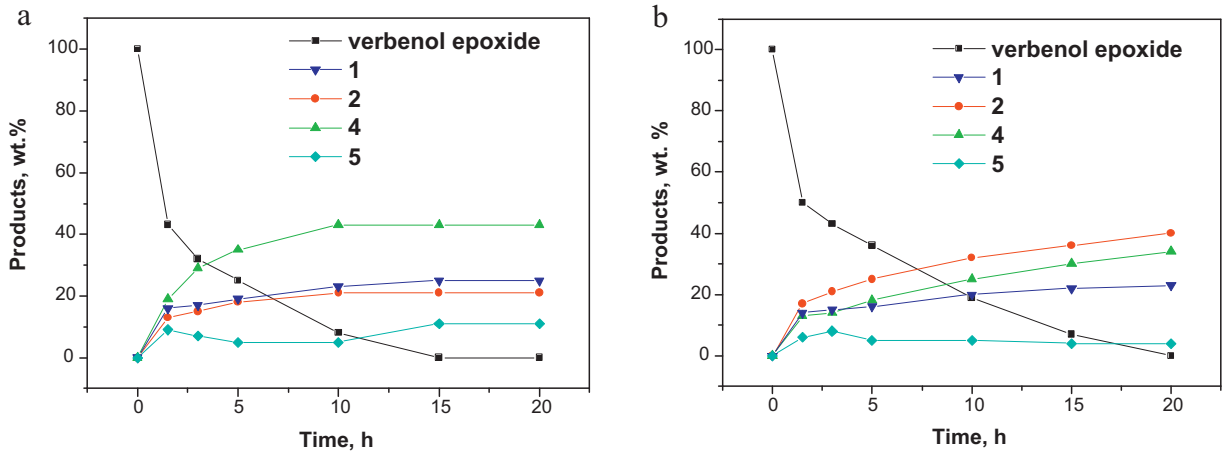


Fig. 1. Product distribution as a function of the reaction time during verbenol epoxide isomerization over Au/TiO_2 (a) and TiO_2 (b). The reaction conditions: $T = 80\,^{\circ}C$, verbenol epoxide 0.4 mmol, 1,2-dicloroethane 10 ml, catalyst 35 mg.

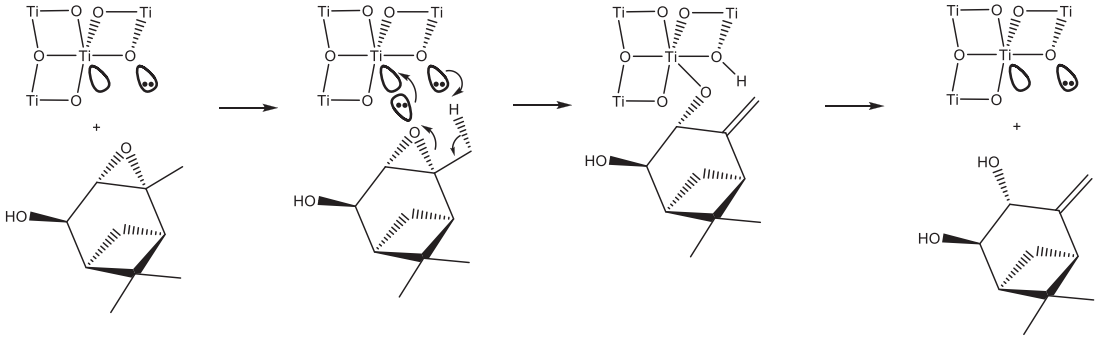


Fig. 2. Proposed mechanism for the isomerization of verbenol epoxide over TiO_2.

the ring opening and followed by subsequent or concerted alkyl shifts.

4. Conclusions

A novel method of (1*S*,2*R*,3*R*,5*R*)-6,6-dimethyl-4-methylenebicyclo[3.1.1]heptane-2,3-diol (**1**) synthesis in the presence of TiO_2 was proposed. It was demonstrated that titania can be used as an effective heterogeneous catalyst in the isomerization of epoxides to corresponding allylic alcohols without changing of the initial structure. The main product has a bicyclic non-isomerized pinene structure. Gold nanoparticles supported on titania being not critical in epoxide transformation promote rearrangement of the initial epoxide with predominant formation of a monocyclic isomer with cyclopentene structure.

Appendix A. Appendix 1. Product analysis NMR

(1S,2R,3R,5R)-6,6-dimethyl-4-methylenebicyclo[3.1.1]heptane-2,3-diol (**2**).

$[\alpha]_D^{25} = +9.30$ (*c* 0.667, $CHCl_3$). ^1H NMR (CCl_4–$CDCl_3$ (1:1, v/v)): 0.89 (s, C^9H_3); 1.17 (d, H^{7anti}, ^2J 10.4 Hz), 1.28 (s, $C^{10}H_3$), 2.19 (ddd, H^1, $J_{1,7syn}$ 6.6, $J_{1,5}$ 5.4, $J_{1,2}$ 3.5 Hz), 2.43 (ddd, H^{7syn}, ^2J 10.4, $J_{7syn,1}$ 6.6, $J_{7syn,5}$ 5.6 Hz), 2.53 (dd, H^5, $J_{5,7syn}$ 5.6, $J_{5,1}$ 5.4 Hz), 2.50 br. s. and 2.59 br. s. – 2OH, 4.06 (dd, H^{2e}, $J_{2e,1}$ 3.5, $J_{2e,3e}$ 2.7 Hz), 4.47 (ddd, H^{3e}, $J_{3e,2e}$ 2.7, $J_{3e,8}$ 1.7, $J_{3e,8'}$ 1.7 Hz), 4.91 (dd, H^8, $J_{8,3e}$ 1.7, ^2J 1.2 Hz), 5.08 (dd, $H^{8'}$, $J_{8',3e}$ 1.7, ^2J 1.2 Hz). ^{13}C NMR: 47.51 (d, C^1), 80.55 (d, C^2), 75.53 (d, C^3), 153.74 (s, C^4), 51.44 (d, C^5), 39.08 (s, C^6), 28.32 (t, C^7), 110.48 (t, C^8), 23.87 (q, C^9), 26.55 (q, C^{10}). Calculated for $C_{10}H_{16}O_2$ *M* 168.1147, found *M* 168.1145.

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