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Transformations of (–)-Myrtenal Epoxide over Askanite–Bentonite Clay

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Abstract—Acid-catalyzed transformations of (–)-myrtenal epoxide over askanite–bentonite clay involve skeletal rearrangements of the pinane framework, leading to an optically active dialdehyde (an analog of campholenic aldehyde), aldehydes having a *p*-menthane skeleton, and an unusual optically active aldehyde with a bicyclo[3.2.1]octene skeleton.

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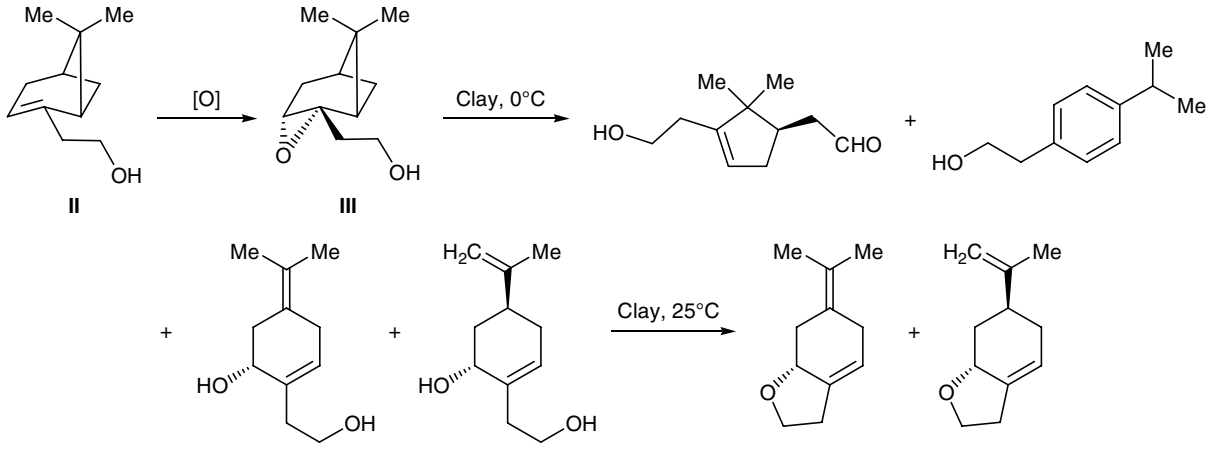
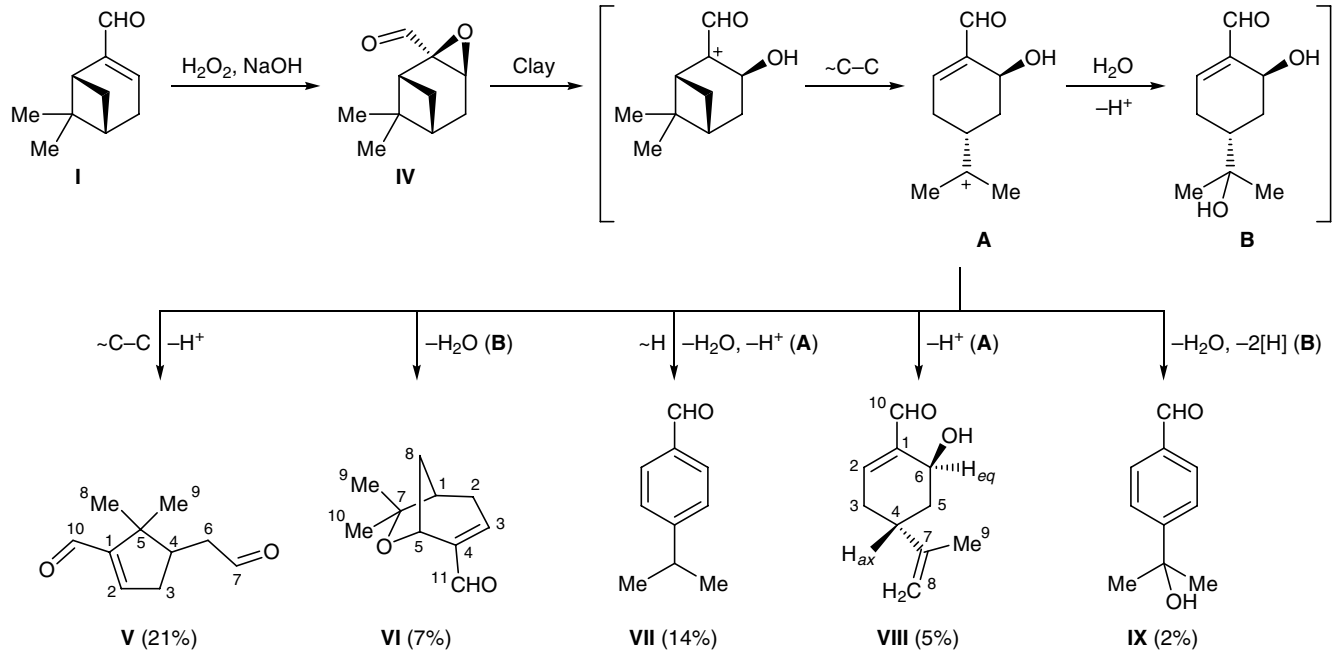
Oxygen-containing monoterpene derivatives of the pinane series are accessible compounds characterized by a high optical purity; they are precursors of biologically active compounds and intermediate products in asymmetric syntheses [1]. As a rule, these compounds readily undergo numerous acid-catalyzed transformations to give complex mixtures of products [2]. We previously showed that in some cases the use of natural montmorillonite, askanite–bentonite clay, and its synthetic analog, K-10 clay, as acid catalyst allows selective preparation of complex compounds, including those having hitherto unknown skeleton, by transformations of pinane terpenoids [3].

(–)-Myrtenal (**I**) is a well known and accessible optically active compound of the pinane series; except for thermal isomerization to aldehydes having a cyclohexane or *p*-menthane skeleton [4], reactions of **I** do not involve rearrangements of the pinane skeleton. On the other hand, pinenes and their oxygen-containing derivatives have found wide application in industry just due to their ability to undergo acid-catalyzed skeletal rearrangements [5]. We have found that (–)-myrtenal (**I**) remains unchanged on keeping over askanite–bentonite clay. According to the results of our previous studies [3, 6], epoxidation of the double bond in α- and β-pinenes and their derivatives essentially changes the reactivity of terpenoids in the presence of clays, giving rise to unusual structures. For example, nopol (**II**) remains unchanged on keeping over askanite–bentonite clay at 0°C, while at 20°C it undergoes slow tarring with formation of a mixture of many products. On the

Scheme 1.



Scheme 2.

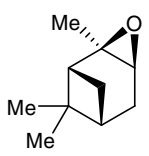


other hand, in the presence of askanite–bentonite clay nopol oxide **III** is converted into a variety of products (Scheme 1) whose composition and ratio depend on the temperature. In the cold, the major isomerization products are hydroxy aldehyde analogous to campholenic aldehyde and *p*-menthane diols; the latter are transformed at room temperature into partially hydrogenated 1-benzofuran derivatives [6].

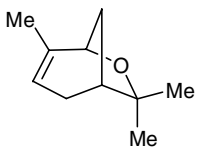
Taking the above data into account, in the present work we synthesized (–)-myrtenal epoxide **IV** and examined for the first time its behavior under acidic conditions. *trans*-Epoxy derivative **IV** was obtained in 74% yield by oxidation of (–)-myrtenal (**I**) with hydrogen peroxide in the presence of alkali according to the procedure described in [7]. A solution of compound **IV** in methylene chloride was stirred over askanite–bentonite clay for 2 h at room temperature. As a result, a mixture of the following compounds was formed (Scheme 2): dialdehyde **V** (21%), bicyclic aldehyde **VI** (7%), and *p*-menthane aldehydes **VII** (14%), **VIII** (5%), and **IX** (2%) (the yields were calculated on the reacted epoxide **IV**, its conversion being 85%).

Compounds **V**, **VI**, and **VIII** are optically active, and they were not reported previously. Aldehyde **VII** (cuminaldehyde, cuminal) is a component of many essential oils, and it exhibits biological activity [8].

As might be expected by analogy with the transformations of nopol oxide **III** in the presence of clay, the major product was a campholenic aldehyde analog, dialdehyde **V**. On the other hand, the formation of bicyclic aldehyde **VI** was surprising. In fact, we know only two examples of the transformation of α-pinene oxide (**X**) and its derivatives into compounds having a 6-oxabicyclo[3.2.1]octane skeleton. Motherwell et al. [9] isolated pinol (**XI**, 4,7,7-trimethyl-6-oxabicyclo-[3.2.1]oct-3-ene) as a minor product of the isomerization of compound **X** over specially prepared acidic molecularly imprinted polymers (which may be regarded as a set of pockets with a definite size containing acid catalysts). The same compound (**XI**), but probably another enantiomer, was obtained by transformation of epoxide **X** in superacidic medium (HSO_3F–SO_2FCl) at –120°C [10]. Therefore, the formation of aldehyde **VI** in the transformation of epoxide **IV** over ordinary askanite–bentonite clay at room temperature rather than under special conditions or in the presence of specific catalysts ensuring conformational control seemed to be quite unusual. Bicyclic aldehyde **VI** cannot be formed directly by cyclization of cation **A**, for the hydroxy and isopropenyl groups in the latter are arranged *trans* (Scheme 2). Most probably, compound **VI** is formed as a result of



X



XI

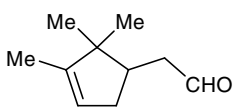
intramolecular dehydration of intermediate **B**. This transformation is likely to be favored by specific mode of fixing of epoxide **IV** (or intermediates derived therefrom) in a definite conformation upon adsorption on the clay.

Compound **IX** was synthesized previously by reaction of *p*-bromobenzaldehyde dimethyl acetal with acetone in the presence of butyllithium [11]. In order to rationalize the formation of **IX** from epoxide **IV**, we presumed that opening of the protonated epoxide ring in **IV** is followed by skeletal rearrangement to give *p*-menthane carbocation **A** which takes up water molecule and then undergoes dehydrogenation; analogous processes were observed by us previously in the transformations of terpenes catalyzed by askanite–bentonite clay [12].

Like nopol oxide (**III**) [6] but in contrast to α-pinene oxide (**X**) [3], myrtenal oxide **IV** failed to react with aldehydes (such as acrolein, salicylaldehyde, and butyraldehyde) in the presence of askanite–bentonite clay. Under these conditions, the products were exclusively those formed by isomerization of **IV**.

Thus we were the first to examine the behavior of (–)-myrtenal oxide (**IV**) under acidic conditions. We found that transformations of compound **IV** over askanite–bentonite clay involve rearrangements of the pinane skeleton, leading to optically active aldehyde **V** (an analog of campholenic aldehyde), aldehydes **VII**–**IX** having a *p*-menthane skeleton, and an unusual product, optically active bicyclic aldehyde **VI**.

The structure of the isolated compounds was proved by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. The carbonyl carbon signal and signals from methylene carbon atoms in the ^{13}C NMR spectrum of **V** were assigned using LRJMD technique: irradiation at a frequency corresponding to resonance of the olefinic 2-H proton (δ 6.64 ppm) gave rise to doublet signals at δ_C 188.78 and 44.46 ppm in the LRJMD spectrum; they were assigned to C^{10} and C^4, respectively; in addition, a singlet at δ_C 45.39 ppm (C^5) and a triplet at δ_C 36.78 ppm (C^3) were observed. The quartets at δ_C 20.34 and 25.45 ppm in the ^{13}C NMR spectrum were assigned to the β- and α-methyl groups, respectively, by analogy with published data for structurally related compound **XII** [13].



XII

Compound **VIII** showed in the ^{1}H NMR spectrum small (less than 5 Hz) vicinal coupling constants between 6-H and protons in the neighboring methylene group; therefore, the 6-H proton was assigned pseudo-equatorial orientation; large coupling constants for the axial 5-H_{ax} and 3-H_{ax} protons with 4-H ($J_{5\text{-}ax,4}$ = 12, $J_{3'\text{-}ax,4}$ = 11.5 Hz) indicated axial orientation of the latter. These data suggest that the substituents on C^4 and C^6 in molecule **VIII** are arranged *trans* with respect to each other.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer (400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C) using $CDCl_3$–CCl_4 (~1:1, by volume) as solvent; the chemical shifts were measured relative to the solvent signals ($CHCl_3$, δ 7.24 ppm; $CDCl_3$, δ_C 76.90 ppm). The high-resolution mass spectra were obtained on a Finnigan MAT-8200 instrument. The specific optical rotations $[\alpha]_{580}$ were determined on a Polamat A spectropolarimeter from solutions in $CHCl_3$. The purity of the initial reactants and reaction products was checked by GLC on a Model 3700 chromatograph equipped with a flame ionization detector and a VC-30 quartz capillary column (15000× 0.22 mm); carrier gas helium, inlet pressure 1 atm.

Askanite–bentonite clay used as catalyst was prepared by acid activation of bentonite clay from Askan deposit according to TU (technical specification) 113-12-86-82. The catalyst was calcined for 3 h at 110°C just before use. The solvent was dried by passing through a column charged with calcined Al_2O_3. The reaction mixtures were separated by column chromatography on silica gel (70–230 μm, Merck); gradient elution with hexane–diethyl ether (0 to 100% of the latter) and then with ethyl acetate.

trans-Epoxide **IV**, $[\alpha]_{580}^{18}$ = –114.5° (*c* = 2.3) {published data [14]: $[\alpha]_D^{20}$ = –89.4° ($CHCl_3$)} was synthesized in 74% yield from (1*R*)-(–)-myrtenal (**I**) {Aldrich, 98%, $[\alpha]_D^{22}$ = –15° (neat)} according to the procedure described in [7].

Transformation of myrtenal epoxide IV over askanite–bentonite clay. A solution of 0.340 g of compound **IV** in 6 ml of methylene chloride was added to a suspension of 2.5 g of askanite–bentonite clay in 10 ml of methylene chloride. The mixture was stirred for 2 h at 20°C and diluted with 5 ml of diethyl ether, the catalyst was filtered off, the filtrate was evaporated, and the residue was subjected to column chromatography on silica gel (10 g) to isolate 0.041 g of

compound **V**, 0.030 g of a mixture of aldehydes **V** and **VII** (2.2:1, according to the ^{1}H NMR data), 0.077 g of a mixture of **IV** and **VII** (2:1, ^{1}H NMR), 0.019 g of **VI**, and 0.020 g of a mixture of aldehydes **VIII** and **IX** (2:1, ^{1}H NMR).

5,5-Dimethyl-4-(2-oxoethyl)cyclopent-1-ene-1-carbaldehyde (V). $[\alpha]_{580}^{20}$ = +20.7° (*c* = 8.2). ^{1}H NMR spectrum, δ, ppm: 0.93 s (C^9H_3), 1.21 s (C^8H_3), 2.05 d.d.d (3-H, $J_{3,3'}$ = 18.5, $J_{3,4}$ = 9, $J_{3,2}$ = 2.5 Hz), 2.33 d.d.d (6-H, $J_{6,6'}$ = 10, $J_{6,4}$ = 10, $J_{6,7}$ = 2.0 Hz), 2.36 m (4-H), 2.55 m (6'-H), 2.74 d.d.d (3'-H, *J* = 18.5, $J_{3',4}$ = 7.5, $J_{3',2}$ = 3 Hz), 6.64 d.d (2-H, $J_{2,3'}$ = 3, $J_{2,3}$ = 2.5 Hz), 9.61 s (10-H), 9.75 d.d (7-H, $J_{7,6}$ = 2, $J_{7,6'}$ = 1.5 Hz). ^{13}C NMR spectrum, δ_C, ppm: 153.90 s (C^1), 150.49 d (C^2), 36.78 t (C^3), 44.46 d (C^4), 45.39 s (C^5), 43.85 t (C^6), 200.34 d (C^7), 25.45 q (C^8), 20.34 q (C^9), 188.78 d (C^{10}). Found: $[M]^+$ 166.09956. $C_{10}H_{14}O_2$. Calculated: *M* 166.09937.

7,7-Dimethyl-6-oxabicyclo[3.2.1]oct-3-ene-4-carbaldehyde (VI). $[\alpha]_{580}^{20}$ = +29.8 (*c* = 9.4). ^{1}H NMR spectrum, δ, ppm: 1.18 s and 1.22 s (C^9H_3, $C^{10}H_3$), 1.69 d (*syn*-8-H, ^2J = 11 Hz), 2.23 m (1-H, $J_{1,8\text{-}anti}$ = 5, $J_{1,2}$ = 4, $J_{1,2'}$ = 2.5 Hz), 2.33 d.d.d (*anti*-8-H, ^2J = 11, $J_{8\text{-}anti,1}$ = 5, $J_{8\text{-}anti,5}$ = 5 Hz), 2.53 d.d.d (2-H, $J_{2,2'}$ = 20, $J_{2,1}$ = 4, $J_{2,3}$ = 3 Hz), 2.62 d.d.d.d (2'-H, *J* = 20, $J_{2',3}$ = 4, $J_{2',1}$ = 2.5, *J* = 1 Hz), 4.81 br.d (5-H, $J_{5,8\text{-}anti}$ = 5 Hz) 6.54 m (3-H, $J_{3,2'}$ = 4, $J_{3,2}$ = 3, $J_{3,5}$ = 1 Hz), 9.34 s (11-H). ^{13}C NMR spectrum, δ_C, ppm: 42.15 d (C^1), 31.82 t (C^2), 148.13 d (C^3), 146.52 s (C^4), 67.31 d (C^5), 82.99 s (C^7), 33.89 t (C^8), 25.57 q and 30.38 q (C^9, C^{10}), 189.99 d (C^{11}). Found: $[M]^+$ 166.09949. $C_{10}H_{14}O_2$. Calculated: *M* 166.09937.

The ^{1}H and ^{13}C NMR spectra of hydroxy aldehyde **VIII** and benzaldehyde **IX** were recorded from their ~2:1 mixture.

6-Hydroxy-4-isopropenylcyclohex-1-ene-1-carbaldehyde (VIII). ^{1}H NMR spectrum, δ, ppm: 1.51 d.d.d (5-H_{ax}, $J_{5\text{-}ax,5\text{-}eq}$ = 13.5, $J_{5\text{-}ax,4\text{-}ax}$ = 12, $J_{5\text{-}ax,6'\text{-}eq}$ = 4.5 Hz), 1.75 br.s (C^9H_3), 2.00 d.d.d.d (5-H_{eq}, *J* = 13.5, $J_{5\text{-}eq,4\text{-}ax}$ = 2.5, $J_{5\text{-}eq,6'\text{-}eq}$ = 2.5, $J_{5\text{-}eq,3'\text{-}eq}$ = 1.5 Hz), 2.15 d.d.d.d (3'-H_{ax}, $J_{3'\text{-}ax,3'\text{-}eq}$ = 20.5, $J_{3'\text{-}ax,4\text{-}ax}$ = 11.5, $J_{3'\text{-}ax,2}$ = 2.5, $J_{3'\text{-}ax,6'\text{-}eq}$ = 1.2 Hz), 2.46–2.57 m (3'-H_{eq}, 4-H_{ax}), 4.60 d.d.d (6'-H_{eq}, $J_{6'\text{-}eq,5\text{-}ax}$ = 4.5, $J_{6'\text{-}eq,5\text{-}eq}$ = 2.5, $J_{6'\text{-}eq,3'\text{-}ax}$ = 1.2 Hz), 4.71 br.s (8-H), 4.76 d.q (8'-H, $J_{8',8}$ = 1.5, $J_{8',9}$ = 1.2 Hz), 6.89 d.d (2-H, $J_{2,3'\text{-}eq}$ = 5.5, $J_{2,3'\text{-}ax}$ = 2.5 Hz), 9.42 s (10-H). ^{13}C NMR spectrum, δ_C, ppm: 142.37 s (C^1), 151.94 d (C^2), 31.94 t (C^3), 35.32 d (C^4), 34.47 t (C^5), 61.03 d (C^6), 147.46 s (C^7), 110.05 t (C^8), 20.90 q (C^9), 193.66 d (C^{10}).

4-(1-Hydroxy-1-methylethyl)benzaldehyde (IX). The chemical shifts of protons and carbon nuclei in the ^{1}H and ^{13}C NMR spectra of compound **IX** were similar to those reported in [9].

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