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Double α-Ketol Rearrangement of (–)-1-{(1*S*,2*R*,4*R*)-1-Ethenyl-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-2-yl}ethan-1-one

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Abstract—The title compound undergoes α-ketol rearrangement by the action of Lewis acids and bases to give the expected and double-rearrangement ring expansion products. Some specific features of the process are discussed.

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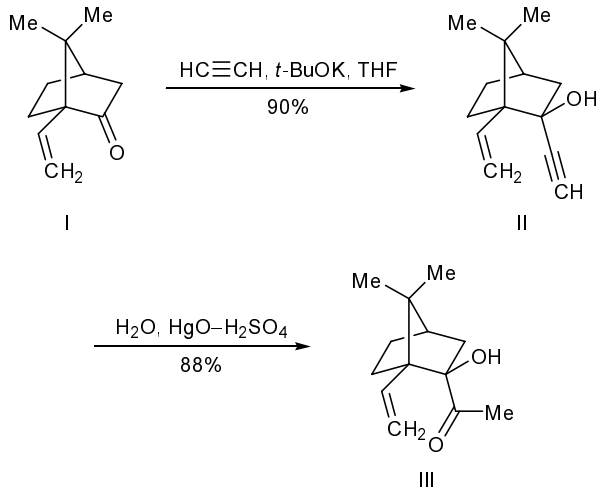
α-Ketol rearrangement is related to acid-catalyzed rearrangements of aldehydes, ketones, and pinacolones and is a classical reaction in organic chemistry [1]. This rearrangement provides an efficient tool for effecting 1,2-migration of a carbonyl group and structural reorganization of ring systems; the corresponding examples can be found in the series of steroidal ketols, precursors of taxoids, etc. [2–6]. Generally α-ketol rearrangement is an equilibrium process which is terminated after one migration; it can be promoted by both acids and basic reagents (for tertiary alcohols) [7].

We have revealed an interesting unusual example of double α-ketol rearrangement (like "domino" reaction) while studying acid- and base-catalyzed transformations of camphor hydroxy ketone **III** which was synthesized from unsaturated ketone **I** [8] through acetylenic derivative **II** [9] (Scheme 1). Treatment of compound **III** with an equimolar amount of boron trifluoride–ether complex ($BF_3 \cdot Et_2O$) in anhydrous methylene chloride at –20°C (resulted in fast and selective formation of tertiary alcohol **IV** (Scheme 2, *a*). The latter can also be obtained in a good yield by heating hydroxy ketone **III** in boiling benzene in the presence of camphorsulfonic acid or *p*-toluenesulfonic acid. Compound **III** was slowly converted into a mixture of isomeric hydroxy ketones **IV** and **V** in the system NaH–THF (*b*) at 20°C; the fraction of **IV** rose as the reaction time increased; correspondingly, the fraction of isomer **V** decreased. Compound **III** was completely converted into a mixture of isomers **IV** and **V** (the former slightly prevailing) in 12 h, and after 24 h, only compound **IV** was detected in the reaction mixture.

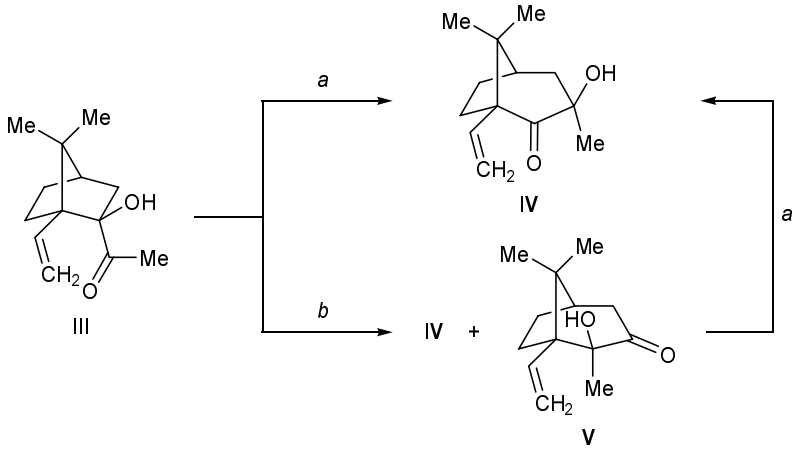
Scheme 1.



Hydroxy ketone **III** behaved in a similar way in the system *t*-BuOK–THF, but in this case the rearrangement was faster, and the conversion of **III** into **IV** was complete in ~12 h. Likewise, treatment with BF_3 of isomer mixture **IV**/**V** obtained in system *b* gave exclusively isomer **IV**.

It is seen that the rearrangement of compound **III** in the systems THF–NaH and *t*-BuOK–THF is not regioselective. The formation of isomer mixture **IV**/**V** is accompanied by simultaneous rearrangement of **V** into **IV**. The transformation **V** → **IV** involving methyl

Scheme 2.



a: 1 equiv of $BF_3 \cdot Et_2O$, CH_2Cl_2, –20°C, 0.5 h (yield 86%), or 1 equiv of *p*-TsOH, C_6H_6, Δ, 3 h (78%); *b*: 1 equiv of NaH, THF, 20°C, 12 h (80%), or 1 equiv of *t*-BuOK, THF, 20°C, 4 h (90%).

group migration should also be regarded as ketol rearrangement. The migration of the methyl group is suprasurface, and the methyl group in the final rearrangement product is located at the α-side. An alternative (and seemingly more preferential) version involving migration of the vinyl carbon atom, which leads to sterically strained ketone **III**, does not occur.

The structure of hydroxy ketone **IV** was proved using a combination of one-dimensional ^1H and ^{13}C NMR spectra and two-dimensional correlation techniques. We also performed complete assignment of its NMR signals. The structure of the six-membered cyclic fragment in molecule **IV** was determined on the basis of its heteronuclear correlation spectrum (COLOC, long-range ^{13}C–^1H couplings) which revealed cross peaks between the methylene protons on C^4 resonating at δ 1.95 and 2.2 ppm (δ_{C^4} 42.5 ppm) and

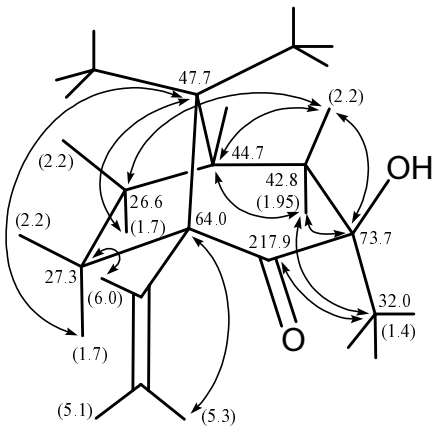


Fig. 1. Scheme of interactions in the heteronuclear correlation spectrum of compound **IV**.

C^3 quaternary carbon atom (δ_C 73.7 ppm) attached to the α-hydroxy group (Fig. 1). Protons in the methyl group on C^3 showed a long-range coupling with the carbonyl carbon atom (δ_C 217.8 ppm). The bridgehead carbon atoms, C^5 (44.7 ppm) and C^1 (δ_C 63.9 ppm) showed cross peaks with the above methylene protons (δ 1.95 and 2.2 ppm) and protons in the vinyl group (δ 5.1 and 5.3 ppm), respectively.

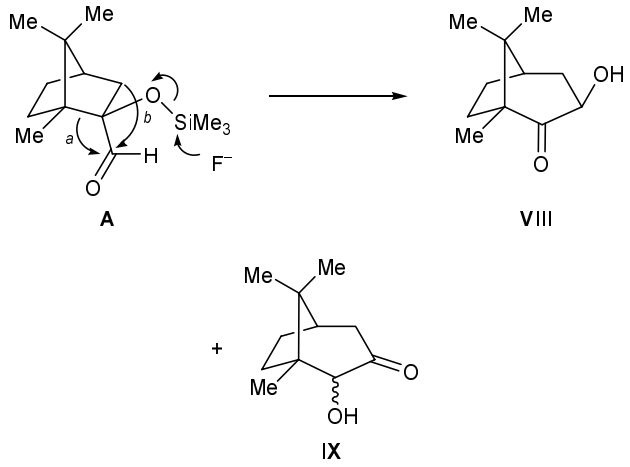
Taking into account that the five-membered cyclic fragment in molecule **IV** is fixed in a rigid *envelope* conformation, indicatory parameters are the dihedral angles between the C–H bonds formed by the *exo*- and *endo*-methylene protons on C^4 and the C^5–C^8 bond connecting the bridgehead and bridging carbon atoms. The *endo*-$H^4C^4C^5C^8$ and *exo*-$H^4C^4C^5C^8$ dihedral angles in an envelope conformation are 150 and 90°, respectively. The corresponding long-range ^{13}C–^1H coupling constant are equal to 6 and 0 Hz, respectively [10]. In fact, this is confirmed by the presence of cross peaks between the quaternary bridgehead carbon atom (δ_C 47.7 ppm) and *endo*-methylene protons (δ 1.7 ppm).

The presence of a bulky methyl group in the *endo* position at C^3 (δ_C 73.7 ppm) is responsible for some flattening of the six-membered cyclic fragment and displacement of conformational equilibrium to the *half-boat* comformer. As a result, a cross peak between *endo*-4-H (δ 1.95 ppm), C^3 (δ_C 73.7 ppm), and methyl carbon atom (δ_C 32.0 ppm) is observed. The position of the C^1 and C^4 signals in the ^{13}C NMR spectra is characteristic for regioisomeric hydroxy ketones **IV** and **V**. Due to deshielding effect of the carbonyl group, the C^1 signal in the spectrum of **IV** and the C^4 signal in the spectrum of **V** are displaced downfield. The

^{1}H NMR spectra of isomers **IV** and **V** showed an appreciable difference in the chemical shifts of protons in the *syn*-methyl groups on C^8. The signal from *syn*-8-Me in **V** is located in a weaker field owing to the presence of spatially close β-hydroxy group [11]. The methylene protons on C^4 in molecule **V** have strongly different chemical shifts and are coupled with each other through a geminal constant ^2J of 17.7 Hz which is typical of such systems.

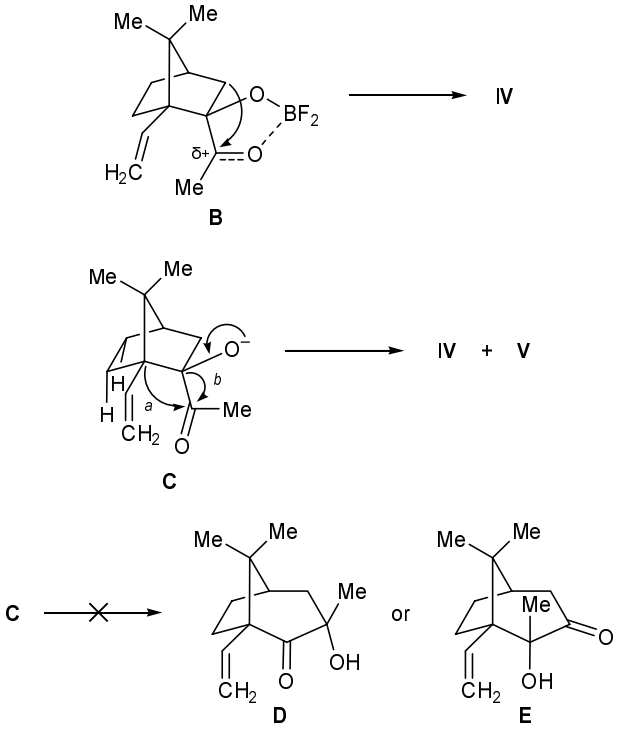
Possible mechanistic aspects of the rearrangement of ketol **III** were also interesting. An "unexpected acyloin rearrangement" like that described in the present work was observed by McIntosh and Cassidy [12] while attempting to effect desilylation of formylisoborneol trimethylsilyl ether **A** (Scheme 3). According to the authors, the rearrangement involves migration of bonds according to path *a* or *b* to give ring expansion products **VIII** and **IX** at a ratio of ~2:1. Analogous results were obtained with the use of boron trifluoride–ether complex.

Scheme 3.

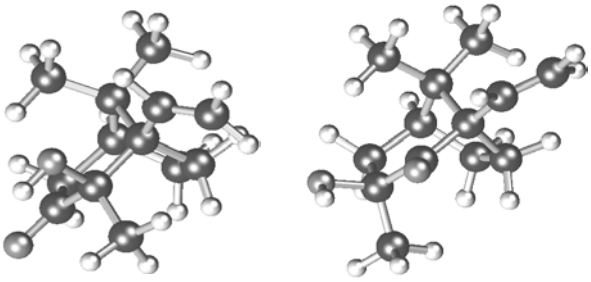


In our case, the rearrangement of ketone **III** promoted by BF_3 is regio- and stereoselective. No isomer **IV** was detected by TLC monitoring of the reaction course. Presumably, the reaction catalyzed by BF_3 involves formation of intermediate complex **B** in which the five-membered boradioxolane ring is fixed in a conformation ensuring antiperiplanar orientation of the C=O and C^2–C^3 bonds (Scheme 4). Therefore, the C^2–C^3 bond undergoes migration, and hydroxy ketone **IV** is formed in a regio- and stereoselective fashion. An alternative transition state with antiperiplanar orientation of the C=O and C^1–C^2 is unfavorable for steric reasons (repulsion between spatially close *endo*-6-H and methyl group). The stereoselectivity of the rearrangement **III**→**IV** originates exclusively from complex formation in the transition state, for migration of any of the nearest bonds in intermediate **B** should lead to alcohols having only α-configuration (**IV** and **V**). On the other hand, we do not rule out the possibility for formation of some amount of compound **V** via the BF_3-catalyzed rearrangement; in this case, the rearrangement **V**→**IV** should be so fast that compound **V** could not accumulate in a TLC-detectable amount. Under the conditions of thermodynamic control (in the presence of *p*-TsOH), hydroxy ketone **III** is converted into compound **IV**, and no isomer **V** could be detected by TLC.

Scheme 4.



Interesting results were obtained in the NaH-promoted anionotropic rearrangement of hydroxy ketone **III**. In keeping with published data related to the chemistry of steroids, the reaction should involve intermediate **C** with antiperiplanar orientation of the oxido (O^-) and carbonyl (C=O) groups due to their mutual repulsion. Migration of any bond in anion **C** could give rise to structures **D** and **E** which are isomeric to **IV** and **V**. However, the reaction does not follow this path. Probably, the rearrangement through anionic intermediate **C** is hindered for the following reason. The C=O bond in the predominant rotamers is likely to be configured in the antiperiplanar mode with respect to the C^1–C^2 and C^2–C^3 (*gauche* or *synclinal* conformation).



IV V

Fig. 2. Structures of isomeric hydroxy ketones **IV** and **V**, simulated by the AM1 method. Enthalpies of formation: –82.6 (**IV**) and –78.4 kcal/mol (**V**).

The process is favored by *trans*-antiperiplanar orientation of the migrating C–C bond and the π-carbonyl bond to be broken; as a result, only the corresponding β-hydroxy alcohol is formed. For example, bond migration in intermediate **C** according to path *a* gives hydroxy ketone **IV**, while pathway *b* leads to compound **V** (Scheme 4).

We performed quantum-chemical calculations of the low-energy conformers of compounds **IV** and **V**. The results (Fig. 2) indicated that irreversible catalytic rearrangement of hydroxy ketone **V** into isomer **IV** is possible. Here, the driving force is the gain in the enthalpy of formation in going to compound **IV** (ΔH = 4.2 kcal/mol). By contrast, the selectivity in the transformations **III**→**IV** and **III**→**V** does not depend on thermodynamic parameters but is determined by structural specificity of the initial compound and catalyst nature.

To conclude, it should be noted that the original β-orientation of the hydroxy group is retained in the rearrangement products, regardless of the catalyst nature, and that the NaH-catalyzed transformation **V**→**IV** and the transformation sequence **III**→**V**→**IV** may be regarded as a rare example of double α-ketol rearrangement.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer at 300 and 75.47 MHz, respectively, using $CDCl_3$ as solvent and tetramethylsilane as reference. Thin-layer chromatography was performed on Silufol plates. The optical rotations were measured on a Perkin–Elmer polarimeter. The mass spectra (electron impact, 70 eV) were run on an MKh-1320 instrument with direct sample admission into the ion source (ion source temperature 60–90°C).

Quantum-chemical calculations were performed using GAMESS software [13]. The equilibrium structures were simulated by the AM1 semiempirical method with full geometry optimization. The relative stability of isomers **IV** and **V** was estimated by the calculated enthalpies of formation.

(–)-1-{(1*S*,2*R*,4*R*)-1-Ethenyl-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-2-yl}ethan-1-one (III). A mixture of 0.10 g (0.53 mmol) of ethynyl derivative **II** in 5 ml of acetone and 0.01 g (0.05 mmol) of HgO in 20 ml of 5% H_2SO_4 was heated for 0.5 h under reflux. The solution was cooled to room temperature, neutralized to pH 7 with a saturated solution of $NaHCO_3$, and extracted with chloroform (3×5 ml). The extracts were combined, dried over Na_2SO_4, and evaporated under reduced pressure, and the residue was purified by chromatography. Yield 0.08 g (77%), $[\alpha]_D^{20}$ = –53° (*c* = 1.0, $CHCl_3$), mp 80–82°C. ^{1}H NMR spectrum, δ, ppm: 0.77 s (CH_3), 0.90 m (1H), 1.18–1.25 m (1H), 1.20 s (CH_3), 1.65–1.90 m (4H), 2.18 s (3H, CH_3), 2.45 d (1H, 3-H, *J* = 13.0 Hz), 2.60 s (1H, OH), 5.07 d.d (1H, *J* = 17.8, 1.7 Hz), 5.45 d.d (1H, CH_2=, *J* = 11.0, 1.7 Hz), 6.20 d.d (1H, =CH, *J* = 11.0, 17.8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 20.37 (CH_3), 21.15 (CH_3), 25.11 (C^6), 25.62 (C^5), 26.93 (CH_3), 40.62 (C^3), 45.76 (C^4), 52.00 (C^7), 57.50 (C^1), 89.50 (C^2), 117.73 and 135.09 (CH_2=CH), 209.5 (CO). Found, %: C 75.24; H 9.79. $C_{13}H_{20}O_2$. Calculated, %: C 74.96; N 9.68.

Rearrangement of hydroxy ketone III in the system CH_2Cl_2–$BF_3 \cdot Et_2O$. Boron trifluoride–ether complex, 0.068 g (0.48 mmol), was added to a solution of 0.100 g (0.48 mmol) of compound **III** in 3 ml of anhydrous methylene chloride, cooled to –20°C. The mixture was stirred for 0.5 h and decomposed by treatment with 2 ml of a saturated solution of $NaHCO_3$. The products were extracted into methylene chloride (3×5 ml), the extract was dried over Na_2SO_4 and evaporated under reduced pressure, and the residue was purified by chromatography on silica gel to isolate 0.086 g (86%) of compound **IV**.

(1*S*,3*R*,5*R*)-1-Ethenyl-3-hydroxy-3,8,8-trimethylbicyclo[3.2.1]octan-2-one (IV). Colorless crystals, mp 36–38°C, $[\alpha]_D^{20}$ = –13° (*c* = 1.0, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm: 0.80 s (CH_3), 0.88 s (CH_3), 1.36 s (CH_3), 1.70 m (2H, *endo*-6-H, *endo*-7-H), 1.95 m (2H, 4α-H, 5-H), 2.20 m (3H, *exo*-6-H, *exo*-7-H, 4β-H), 3.45 s (1H, OH), 5.10 d.d (1H, *J* = 1.2, 17.6 Hz), 5.30 d.d (1H, *J* = 1.2, 11.0 Hz), 6.00 d.d (1H,

J = 11.0, 17.6 Hz) (CH=CH_2). ^{13}C NMR spectrum, δ_C, ppm: 20.58 (CH_3), 23.76 (CH_3), 26.64 (C^6), 27.31 (C^7), 32.06 (CH_3), 42.85 (C^4), 44.78 (C^5), 47.79 (C^8), 64.00 (C^1), 73.76 (C^2), 116.27 and 135.09 (CH=CH_2), 217.96 (CO). Mass spectrum, m/z (I_{rel}, %): 208 $[M]^+$ (19), 179 $[M - C_2H_5]^+$ (13), 165 $[M - C_3H_7]^+$ (10), 147 (16), 137 (26), 122 (63), 120 (65), 111 (25), 102 (100), 92 $[C_7H_8]^+$ (90), 79 (65), 65 (68), 43 $[C_3H_7]^+$ (100), 29 $[C_2H_5]^+$ (66).

In an analogous rearrangement of hydroxy ketone **III** in boiling benzene containing 1 equiv of *p*-toluenesulfonic acid (reaction time 3 h) we isolated compound **IV** in 78% yield.

Rearrangement of hydroxy ketone III in the system THF–NaH. Sodium hydride (a 65% suspension in oil), 0.024 g (0.65 mmol), was added to a solution of 0.100 g (0.48 mmol) of ketone **III** in 4 ml of THF. The mixture was stirred for 12 h, 4 ml of a saturated solution of sodium chloride was added, and the aqueous phase was extracted with ethyl acetate (3 × 5 ml), the extracts were dried over Na_2SO_4 and evaporated, and the residue was subjected to chromatography on silica gel to isolate 0.034 g (34%) of compound **IV** and 0.046 g (46%) of its isomer **V**.

(1*S*,2*S*,5*R*)-1-Ethenyl-2-hydroxy-2,8,8-trimethylbicyclo[3.2.1]octan-3-one (V). Oily substance, $[\alpha]_D^{20}$ = –28° (c = 1.0, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm: 0.82 s (CH_3), 1.20 s (CH_3), 1.28 s (CH_3), 1.50–2.10 m (5H), 2.25 d.d (1H, 4α-H, J = 1.3, 17.7 Hz), 3.03 d.d.d (1H, 4β-H, J = 1.3, 3.6, 17.7 Hz), 5.05 d.d (1H, J = 1.3, 17.7 Hz), 5.25 d.d (1H, J = 1.3, 11.0 Hz) and 6.10 d.d (1H, J = 11.0, 17.7 Hz) (CH=CH_2). ^{13}C NMR spectrum, δ_C, ppm: 20.59 (CH_3), 21.63 (CH_3), 25.32 (CH_3), 27.12 and 27.20 (C^6, C^7), 44.04 (C^5), 44.66 (C^4), 47.79 (C^8), 56.46 (C^1), 79.59 (C^2), 115.84 and 137.44 (CH=CH_2), 213.94 (CO). Found, %: C 75.11; H 9.53. $C_{13}H_{20}O_2$. Calculated, %: C 74.96; H 9.68.

Likewise, the rearrangement of hydroxy ketone **III** in the system *t*-BuOK–THF (reaction time 4 h) gave a mixture of compounds **IV** and **V**; after 12 h, only isomer **IV** was present in the reaction mixture.

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