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Specificity of the Reaction of (–)-1-{(1*S*,2*R*,4*R*)-1-Ethenyl-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-2-yl}ethanone with Ethenylmagnesium Bromide

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Abstract—Ethenylmagnesium bromide (1.5 equiv) forms a chelate with (–)-1-{(1*S*,2*R*,4*R*)-1-ethenyl-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-2-yl}ethanone in THF and promotes its fast primary α-ketol rearrangement into 1-ethenyl-2-hydroxy-2,8,8-trimethylbicyclo[3.2.1]octan-3-one. The latter reacts with excess magnesium reagent (0.5 equiv) according to common 1,2-addition pattern at the carbonyl group and is simultaneously involved in the second α-ketol rearrangement which leads to 1-ethenyl-3-hydroxy-3,8,8-trimethylbicyclo-[3.2.1]octan-2-one as thermodynamically more stable regioisomer.

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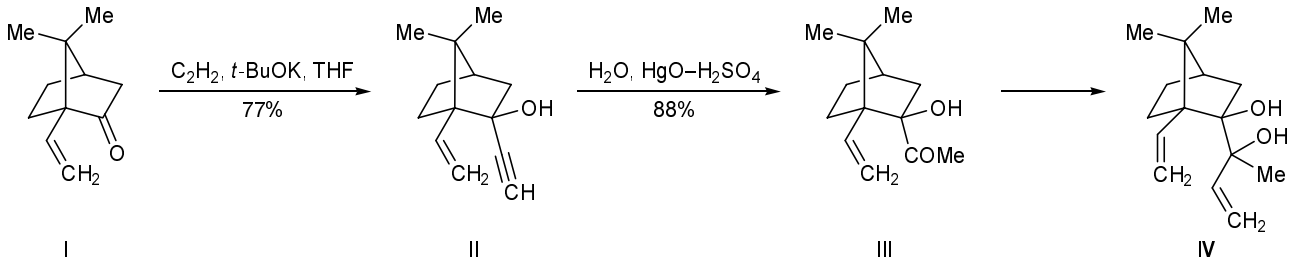
Camphor and its derivatives tend to undergo skeletal rearrangements [1]. We observed a specific example of expansion of the bicyclo[2.2.1]heptane skeleton to bicyclo[3.2.1]octane while studying the reaction with ethenylmagnesium bromide of hydroxy ketone **III** which was synthesized from 10-methylidenecamphor (**I**) [2] through acetylenic alcohol (**II**) [3]. Here, we planned to obtain diol **IV** which was necessary for the subsequent ring closure under the conditions of Grubbs metathesis [4] (Scheme 1).

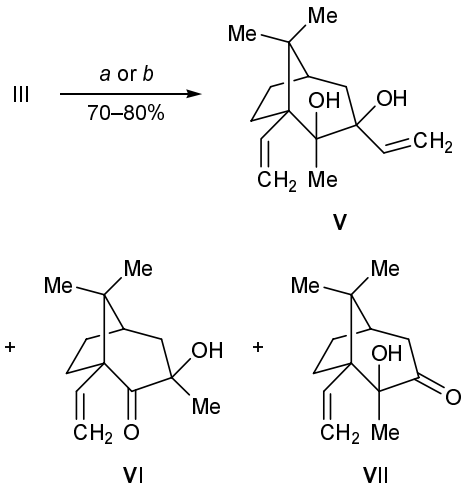
We have found that this reaction is not selective and that it gives a mixture of three products. Under comparable conditions, the amount of one of these was approximately the same, while the ratio of the two other products changed, depending on the reaction time. One of the latter (slightly more polar) was isolated by column chromatography on silica gel. The remaining products (probably isomeric) were characterized by similar R_f values. Their structure was determined after isolation as individual substances in another series of experiments (see below). As a result, we found that the reaction of hydroxy ketone **III** with ethenylmagnesium bromide gives no desired adduct **IV** but leads to the formation of a mixture of ring expansion products **V**–**VII** whose ratio depends on the reaction time (Scheme 2). For example, the ratio of compounds **V**–**VII** was 14:3:10 (according to the intensities of the methyl proton signals in the ^{1}H NMR spectrum) in 3 h; after 12 h, the ratio of regioisomers **VI** and **VII** changed in favor of the former (**V**:**VI**:**VII** = 14:12:4). The absence of diol **IV** in the reaction mixtures was unambiguously proved by chemical transformations. Periodate and lead tetraacetate oxidation of product mixture **V**–**VII** did not produce 10-methylidenecamphor (**I**). Very high stereoselectivity in the addition of the Norman reagent should be

Scheme 1.



I II III IV

Scheme 2.

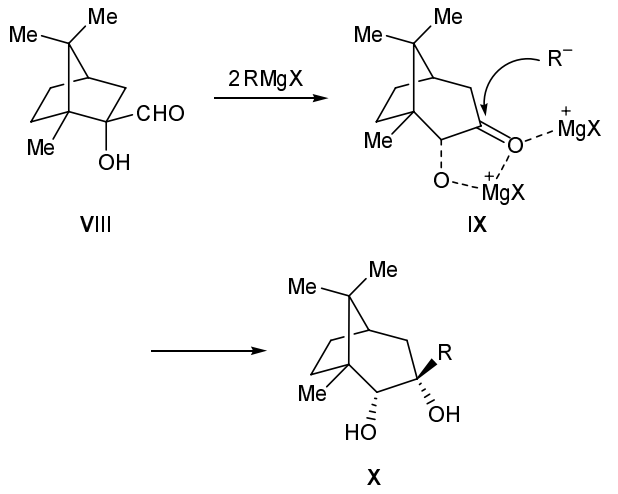


a: CH_2=CHMgBr (1.5 equiv.), THF, 20°C, 3 h;
b: CH_2=CHMgBr (1.5 equiv.), THF, 20°C, 12 h.

noted: in both cases, we detected no alternative stereoisomer of **V**.

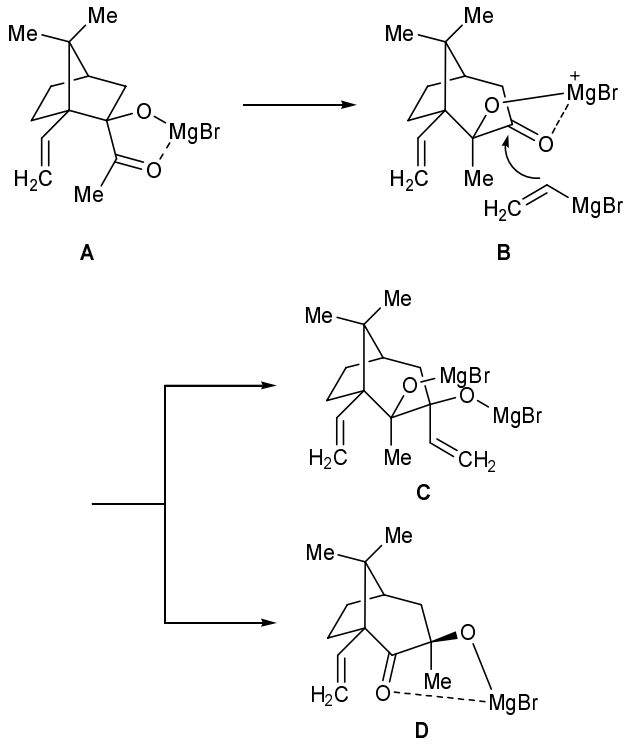
As concerns interpretation of the results, the following must be noted. While the present article was under preparation, Yang et al. [5] reported on the reactions of 2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]-heptane-2-carbaldehyde (**VIII**) with Grignard compounds; the authors showed that the process involves rearrangement of a chelate formed by the Grignard compound and hydroxy aldehyde **VIII** into ketol **IX** which then takes up the second Grignard reagent molecule to give the corresponding alkylated bicyclo-[3.2.1]octanediols **X** (Scheme 3).

Scheme 3.



Obviously, in our case the reaction of ethenylmagnesium bromide with α-ketol **III** follows an analogous scheme (Scheme 4). Initial formation of chelate **A** promotes fast ring expansion according to the α-ketol rearrangement pattern with exclusive migration of the ethenyl-substituted quaternary carbon atom. Chelate **B** thus formed reacts with the second ethenylmagnesium bromide molecule whose attacks is directed at the carbonyl carbon atom from the less sterically hindered α-side to give adduct **C** with high stereoselectivity; hydrolysis of the latter yields diol **V**.

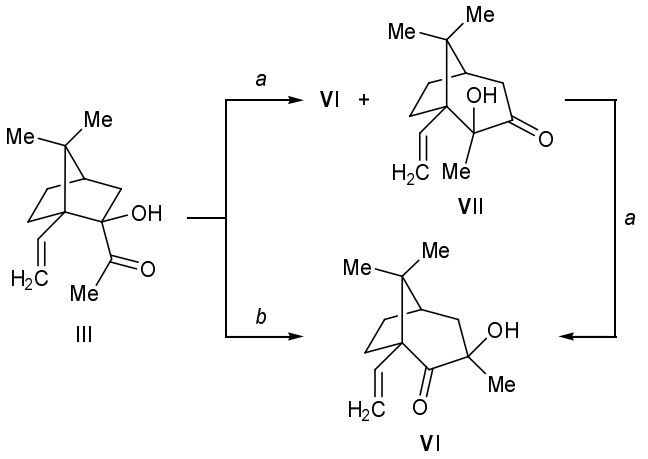
Scheme 4.



Analogous stereocontrol is impossible in the reaction with compound **III** which possesses a conformationally labile exocyclic acetyl group. After complete consumption of CH_2=CHMgBr (1.5 equiv), coordination compound **B** undergoes rearrangement into thermodynamically more favorable isomer **D** which is precursor of **VII**.

Regioisomeric ketols **VI** and **VII** were isolated as individual substances by treatment of compound **III** under standard conditions for the α-ketol rearrangement (Scheme 5). Anhydrous $MgBr_2$ in THF did not promote rearrangement, while $BF_3 \cdot Et_2O$ in CH_2Cl_2 induced fast and selective transformation of **III** into ketol **VI**. Using NaH in THF we obtained a mixture of ketols **VI** and **VII**. These results and stereochemical aspects of the observed rearrangement will be discussed in a separate publication.

Scheme 5.



a: $BF_3 \cdot Et_2O$ (1 equiv.), CH_2Cl_2, –20°C, 0.5 h, 86%;
b: NaH (1 equiv.), THF, 20°C, 12 h, 80%.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrophotometer from samples prepared as thin films or dispersed in Nujol. The ^1H and ^{13}C NMR spectra were measured from solutions in $CDCl_3$ on a Bruker AM-300 spectrometer at 300 and 75.47 MHz, respectively. The optical rotations were measured on a Perkin–Elmer 241-MC polarimeter. The mass spectra (electron impact, 70 eV) were obtained on an MKh-1320 instrument (ion source temperature 80–90°C). Silufol plates were used for thin-layer chromatography.

(–)-1-{(1*S*,2*R*,4*R*)-1-Ethenyl-2-hydroxy-7,7-dimethylbicyclo[2.2.1]hept-2-yl}ethanone (III). A solution of 0.10 g (0.53 mmol) of acetylenic alcohol **II** in 5 ml of acetone was mixed with a solution of 0.01 g (0.05 mmol) of HgO in 20 ml of 5% sulfuric acid, and the mixture was heated for 0.5 h at the boiling point. The mixture 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 and dried over Na_2SO_4, and the solvent was distilled off under reduced pressure. The residue was purified by chromatography to isolate 0.08 g (77%) of hydroxy ketone **III**, $[\alpha]_D^{20}$ = –53° (*c* = 1.0, $CHCl_3$), mp 80–82°C. ^1H 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; H 9.68.

Reaction of hydroxy ketone III with ethenylmagnesium bromide. Compound **III**, 0.100 g (0.48 mmol), was dissolved in 4 ml of anhydrous THF, and 4 ml (0.60 mmol) of a 0.15 M solution of ethenylmagnesium bromide was added dropwise under argon. The mixture was stirred for 12 h and treated with 2 ml of a saturated solution of NH_4Cl. Tetrahydrofuran was distilled off, the residue was extracted with methylene chloride (3×5 ml), the extracts were combined and dried over Na_2SO_4, and the solvent was distilled off under reduced pressure. Analysis of the residue by ^1H NMR spectroscopy showed the ratio **V**:**VI**:**VII** to be 14:12:4. By chromatography we isolated 0.041 g (38%) of compound **V** and 0.041 g (41%) of a mixture of hydroxy ketones **VI** and **VII**.

In the reaction of **III** with ethenylmagnesium bromide under analogous conditions (reaction time 3 h), the ratio **V**:**VI**:**VII** was 14:3:10.

(1*S*,2*R*,3*R*,5*R*)-1,3-Bis(ethenyl)-2,8,8-trimethylbicyclo[3.2.1]octane-2,3-diol (V). Colorless crystals, mp 122°C. $[\alpha]_D^{20}$ = +33° (*c* = 1.0, $CHCl_3$). ^1H NMR spectrum, δ, ppm: 0.75 s (CH_3), 1.20 s (CH_3), 1.30 s (CH_3), 1.60–1.90 m (6H), 2.60 s (1H, OH), 5.04 d.d (1H, *J* = 2.0, 17.2 Hz) and 5.20 d.d (1H, =CH_2, *J* = 2.0, 11.1 Hz), 5.14 d.d (1H, *J* = 1.3, 10.8 Hz) and 5.30 d.d (1H, =CH_2, *J* = 1.3, 17.3 Hz), 6.15 d.d (1H, =CH, *J* = 11.1, 17.3 Hz), 6.21 d.d (1H, =CH, *J* = 10.8, 17.3 Hz). ^{13}C NMR spectrum, δ_C, ppm: 20.34 (CH_3), 22.29 (CH_3), 24.45 (C^6), 25.20 (CH_3), 25.79 (C^7), 40.78 (C^4), 45.73 (C^5), 52.53 (C^8), 58.89 (C^1), 78.84 (C^3), 85.03 (C^2), 113.99 and 143.16 (CH_2=CH), 117.75 and 137.61 (CH_2=CH). Found, %: C 76.11; H 10.06. $C_{15}H_{24}O_2$. Calculated, %: C 76.23; H 10.24.

Rearrangement of hydroxy ketone III in the system CH_2Cl_2–$Et_2O \cdot BF_3$. Compound **III**, 0.100 g (0.48 mmol), was dissolved in 3 ml of anhydrous methylene chloride, the solution was cooled to –20°C, 0.068 g (0.48 mmol) of $Et_2O \cdot BF_3$ was added, and the mixture was stirred for 0.5 h. The mixture was then decomposed by adding 2 ml of a saturated solution of $NaHCO_3$, the aqueous phase was extracted with methylene chloride (3×5 ml), the extract was dried over sodium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by chromatography on silica gel to isolate 0.086 g (86%) of ketone **VI**.

(1*S*,3*R*,5*R*)-1-Ethenyl-3-hydroxy-3,8,8-trimethylbicyclo[3.2.1]octan-2-one (VI). Colorless crystals,

mp 36–38°C, $[\alpha]_D^{20}$ = –13° (*c* = 1.0, $CHCl_3$). ^1H 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 (19) $[M]^+$, 179 (13), 165 (10), 147 (16), 137 (26), 122 (63), 120 (65), 111 (25), 102 (100), 92 (90), 79 (65), 65 (68), 43 (100), 29 (66).

Rearrangement of hydroxy ketone III in THF–NaH. Sodium hydride, 0.024 g (0.65 mmol) (a 65% suspension in oil), was added to a solution of 0.100 g (0.48 mmol) of compound **III** in 4 ml of THF. The mixture was stirred for 12 h, treated with 4 ml of a saturated solution of NaCl, and extracted with ethyl acetate (3 × 5 ml), the extract was dried over Na_2SO_4, the solvent was distilled off under reduced pressure, and the residue was subjected to column chromatography on silica gel to isolate 0.034 g (34%) of hydroxy ketone **VI** and 0.046 g (46%) of ketone **VII**.

(1*S*,2*S*,5*R*)-1-Ethenyl-2-hydroxy-2,8,8-trimethylbicyclo[3.2.1]octan-3-one (VII). Oily substance, $[\alpha]_D^{20}$ = –28° (*c* = 1.0, $CHCl_3$). ^1H 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), 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), 44.66 (C^4), 44.04 (C^5), 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.

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