

# Synthesis and Unusual Hydrolysis Products of (1*R*,2*ξ*,5*R*)-2-Ethoxymethylene-4,6,6-trimethylbicyclo-[3.1.1]hept-3-ene\*

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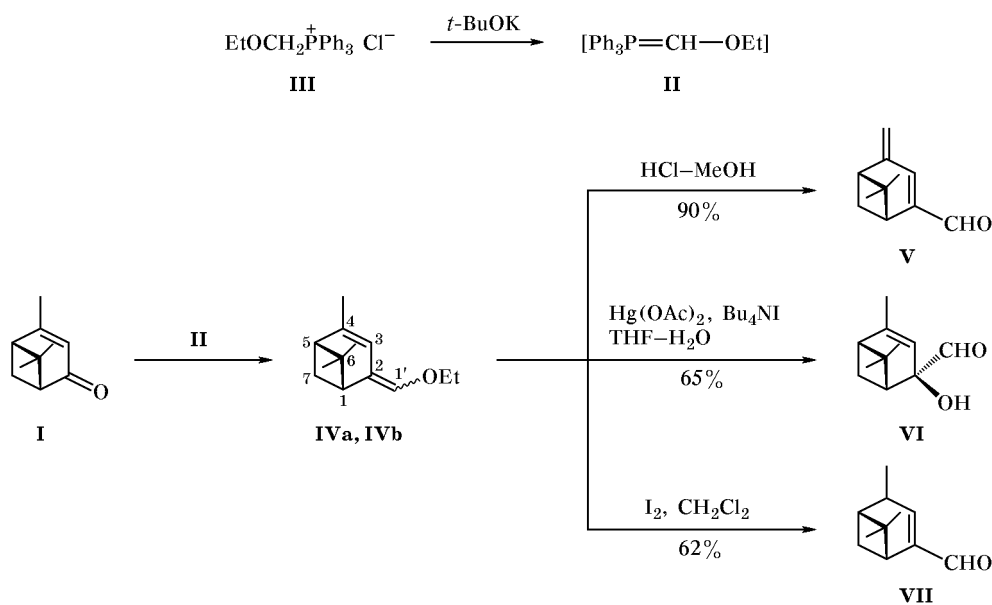
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**Abstract**—The title compound was brought into methanolysis, Hg<sup>2+</sup>-initiated hydrolysis, and electrophilic iodination. In all cases, various aldehydes of the pinane series were obtained.

While searching for new block synthons for taxoids we accomplished olefination of verbenone (**I**) with ylide **II** (20°C, 4 h) and obtained a mixture of *Z,E*-isomeric enol ethers **IVa** and **IVb** in 85% yield (Scheme 1). The *Z:E* ratio was estimated at 3:1 from the intensities of the characteristic 1-H signals in the <sup>1</sup>H NMR spectrum (δ 2.35 and 3.05 ppm for compounds **IVa** and **IVb**, respectively). Further on, we tried to effect addition of isopropyl alcohol to enol

ethers **IVa** and **IVb** using *p*-toluenesulfonic acid as catalyst. We observed slow formation of compound **V** but the reaction did not come to completion. Compound **V** was formed at a high rate and with a very high selectivity when enol ether **IV** was kept for 15 min in a 3% solution of HCl in MeOH at 20°C (yield 90%). The reaction of ether **IV** with I<sub>2</sub> in methylene chloride was also fast, and α,β-unsaturated aldehyde **VII** was thus obtained. Our attempt to

Scheme 1.

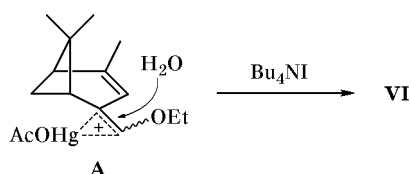


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accomplish hydrolysis of **IV** without migration of the double bond according to the procedure reported in [1] resulted in formation of an unexpected product,  $\alpha$ -hydroxy aldehyde **VI** (Scheme 1).

The configuration of C<sup>2</sup> in hydroxy aldehyde **VI** follows from the mechanism of Hg<sup>2+</sup>-initiated hydration of enol ether **IV**. It is known that approach of a reagent to the verbenone molecule is favored from the sterically unhindered  $\alpha$ -side [2–4]. Therefore, diene **IV** (which is isosteric to ketone **I**) initially gives rise to cation **A**, and the latter undergoes *trans*-attack by hydroxide ion OH<sup>-</sup> from the  $\beta$ -side (Scheme 2). Product **VII** is an individual stereoisomer.

Scheme 2.



The formation of aldehydes **V** and **VII** from enol ethers **IVa** and **IVb** under the above conditions seems to be surprising, and possible reaction mechanisms are not clear.

## EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer from samples prepared as thin films. The <sup>1</sup>H and <sup>13</sup>C NMR spectra were obtained on a Bruker AM-300 instrument at 300 and 75.47 MHz, respectively; chloroform-*d* was used as solvent, and tetramethylsilane, as internal reference. Silufol plates were used for thin-layer chromatography. The optical rotations were measured on a Perkin–Elmer 241 MC instrument. Verbenone (**I**) [2] with  $[\alpha]_D^{20} = +107.3^\circ$  was used.

**(+)-(1R,5R)-2-Ethoxymethylene-4,6,6-trimethylbicyclo[3.3.1]hept-3-ene (IVa/IVb).** Potassium *tert*-butoxide, 2.5 g (22.44 mmol), was added under argon to a solution of 8 g (22.44 mmol) of ethoxymethyl-(triphenyl)phosphonium chloride (**III**) in 40 ml of anhydrous THF, and the mixture was stirred for 30 min at 20°C. A solution of 0.56 g (3.74 mmol) of verbenone (**I**) in 10 ml of THF was added to the resulting solution of ylide **II**. When the reaction was complete (TLC), the mixture was treated with 10 ml of a saturated aqueous solution of NH<sub>4</sub>Cl, THF was removed under reduced pressure, 50 ml of ethyl acetate was added to the residue, the organic phase

was separated, and the aqueous phase was extracted with ethyl acetate (3 × 25 ml). The combined extracts were dried over MgSO<sub>4</sub> and evaporated, and the residue was subjected to chromatographic purification on silica gel to isolate 500 mg (71%) of an oily mixture of *Z* and *E* isomers **IVa** and **IVb**; *R*<sub>f</sub> 0.63 (hexane–ethyl acetate, 9:1).

**Isomer IVa.** <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: 0.86 s (3H, CH<sub>3</sub>), 1.23 t (3H, CH<sub>3</sub>), 1.35 m (1H, 7-H), 1.45 s (3H, CH<sub>3</sub>), 1.73 d (3H, CH<sub>3</sub>, *J* = 1.4 Hz), 2.08 m (1H, 5-H), 2.45 m (1H, 7-H), 3.05 m (1H, 1-H), 3.75 q (2H, OCH<sub>2</sub>, *J* = 7.0 Hz), 5.56 t (1H, 3-H, *J* = 1.4 Hz), 5.9 s (1H, 1'-H). <sup>13</sup>C NMR spectrum,  $\delta_C$ , ppm: 15.18 (CH<sub>3</sub>), 21.94 (CH<sub>3</sub>), 22.84 (CH<sub>3</sub>), 26.01 (CH<sub>3</sub>), 33.55 (C<sup>7</sup>), 41.22 (C<sup>6</sup>), 42.13 (C<sup>1</sup>), 48.62 (C<sup>5</sup>), 67.67 (OCH<sub>2</sub>), 116.89 (C<sup>3</sup>), 123.16 (C<sup>2</sup>), 138.34 (C<sup>1'</sup>), 142.18 (C<sup>4</sup>).

**Isomer IVb.** <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: 0.87 s (3H, CH<sub>3</sub>), 1.24 t (3H, CH<sub>3</sub>, *J* = 7.0 Hz), 1.35 m (1H, 7-H), 1.45 s (3H, CH<sub>3</sub>), 1.70 m (1H, 7-H), 1.78 d (3H, CH<sub>3</sub>, *J* = 1.4 Hz), 2.08 m (1H, 7-H), 2.35 m (1H, 1-H), 2.45 m (1H, 7-H), 3.75 q (2H, OCH<sub>2</sub>, *J* = 7.0 Hz), 5.70 s (1H, 3-H), 6.12 d (1H, 1'-H, *J* = 1.0 Hz). <sup>13</sup>C NMR spectrum,  $\delta_C$ , ppm: 15.18 (CH<sub>3</sub>), 21.84 (CH<sub>3</sub>), 23.02 (CH<sub>3</sub>), 26.14 (CH<sub>3</sub>), 34.55 (C<sup>7</sup>), 41.88 (C<sup>6</sup>), 46.64 (C<sup>1</sup>), 48.75 (C<sup>5</sup>), 67.58 (OCH<sub>2</sub>), 114.10 (C<sup>3</sup>), 121.42 (C<sup>2</sup>), 135.30 (C<sup>1</sup>), 144.70 (C<sup>4</sup>).

**(+)-(1R)-6,6-Dimethyl-4-methylenebicyclo[3.3.1]hept-2-ene-2-carbaldehyde (V).** Enol ether **IV**, 50 mg (0.26 mmol), was added to 15 ml of a 3% solution of hydrogen chloride in methanol, and the mixture was stirred for 15 min and neutralized with a saturated aqueous solution of NaHCO<sub>3</sub>. Methanol was distilled off, and the aqueous residue was extracted with ethyl acetate (3 × 5 ml). The extracts were dried over MgSO<sub>4</sub> and evaporated under reduced pressure, and the residue was subjected to chromatography on silica gel to isolate 38 mg (90%) of aldehyde **V** as an oily substance. *R*<sub>f</sub> 0.44 (hexane–ethyl acetate, 9:1);  $[\alpha]_D^{20} = -14.6^\circ$  (*c* = 0.5, CHCl<sub>3</sub>). IR spectrum,  $\nu$ , cm<sup>-1</sup>: 1620, 1690. <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: 0.7 s (3H, CH<sub>3</sub>), 1.35 m (1H, *endo*-7-H, *J* = 9.1 Hz), 1.40 s (3H, CH<sub>3</sub>), 2.62 d.t (1H, *exo*-7-H, *J* = 9.1, 5.6 Hz), 2.75 t (1H, 1-H, *J* = 5.6 Hz), 2.96 t (1H, 5-H, *J* = 5.6 Hz), 5.15 s (1H) and 5.23 s (1H) (=CH<sub>2</sub>), 6.85 s (1H, 3-H), 9.52 s (1H, CHO). <sup>13</sup>C NMR spectrum,  $\delta_C$ , ppm: 21.85 (CH<sub>3</sub>), 25.60 (CH<sub>3</sub>), 34.66 (C<sup>7</sup>), 39.01 (C<sup>1</sup>), 42.74 (C<sup>6</sup>), 51.18 (C<sup>5</sup>), 116.89 (=CH<sub>2</sub>), 143.66 (C<sup>3</sup>), 149.04 (C<sup>2</sup>), 149.37 (C<sup>4</sup>), 191.27 (CHO).

**(+)-(1R,2R)-2-Hydroxy-4,6,6-trimethylbicyclo[3.3.1]hept-3-ene-2-carbaldehyde (VI).** Mercury(II)

acetate, 780 mg (2.44 mmol), was added with stirring to a solution of 100 mg (0.52 mmol) of compound **IV** in a mixture of 8 ml of THF and 0.8 ml of water. When the reaction was complete (according to TLC), 3 g (8.06 mmol) of Bu<sub>4</sub>NI was added, and the mixture was stirred for 2 h and treated with 40 ml of a saturated solution of NH<sub>4</sub>Cl. The aqueous phase was extracted with ethyl acetate (3 × 25 ml), the combined extracts were dried over MgSO<sub>4</sub> and evaporated, and the residue was subjected to chromatography on silica gel to isolate 61 mg (65%) of compound **VI** as an oily substance. *R*<sub>f</sub> 0.4 (hexane–ethyl acetate, 1:1), [α]<sub>D</sub><sup>20</sup> = –39.5° (*c* = 1.0, CHCl<sub>3</sub>). IR spectrum, ν, cm<sup>–1</sup>: 1620, 1660, 1680, 3400. <sup>1</sup>H NMR spectrum, δ, ppm: 0.82 s (3H, CH<sub>3</sub>), 1.38 d (1H, *endo*-7-H, *J* = 9.9 Hz), 1.41 s (3H, CH<sub>3</sub>), 1.45 s (3H, CH<sub>3</sub>), 1.98 br.s (1H, OH), 2.11 d.d.d (1H, 5-H, *J* = 5.6, 2.7, 5.4 Hz), 2.49 d.t (1H, *exo*-7-H, *J* = 9.9, 5.6 Hz), 2.87 d.d.d (1H, 1-H, *J* = 5.6, 5.4, 1.1 Hz), 6.43 d.d (1H, 3-H, *J* = 1.1, 2.1 Hz), 9.52 s (1H, CHO). <sup>13</sup>C NMR spectrum, δ<sub>C</sub>, ppm: 23.56 q (CH<sub>3</sub>), 25.47 q (CH<sub>3</sub>), 26.85 q (CH<sub>3</sub>), 31.99 t (C<sup>7</sup>), 39.13 d (C<sup>1</sup>), 46.23 s (C<sup>6</sup>), 53.46 d (C<sup>5</sup>), 73.24 s (C<sup>2</sup>), 148.28 d (C<sup>3</sup>), 150.10 s (C<sup>4</sup>), 192.09 d (CHO).

**(+)-(1*R*)-4,6,6-Trimethylbicyclo[3.3.1]hept-2-ene-2-carbaldehyde (VII)**. A solution of 66 mg (0.52 mmol) of I<sub>2</sub> in 100 ml of dry methylene chloride was added with stirring to a solution of 100 mg (0.52 mmol) of compound **IV** in 20 ml of the same solvent. When the reaction was complete (the initially dark red mixture turned green), the mixture was treated with 20 ml of a saturated solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>,

the organic phase was separated, and the aqueous phase was extracted with ethyl acetate (3 × 30 ml). The extracts were combined with the organic phase, dried over MgSO<sub>4</sub>, and evaporated, and the residue was subjected to chromatography on silica gel to isolate 53 mg (62%) of aldehyde **VII** as an oily substance. *R*<sub>f</sub> 0.46 (hexane–ethyl acetate, 9:1), [α]<sub>D</sub><sup>20</sup> = +28.2° (*c* = 0.5, CHCl<sub>3</sub>). IR spectrum, ν, cm<sup>–1</sup>: 1650, 1690. <sup>1</sup>H NMR spectrum, δ, ppm: 0.83 s (3H, CH<sub>3</sub>), 1.15 d (1H, *endo*-7-H, *J* = 9.2 Hz), 1.23 d (3H, *exo*-4-CH<sub>3</sub>, *J* = 7.7 Hz), 1.36 s (3H, CH<sub>3</sub>), 2.10 t.t.t (1H, 5-H, *J* = 2.0, 3.8, 5.7 Hz), 2.55 d.t (1H, *exo*-7-H, *J* = 9.2, 5.7 Hz), 2.80–2.90 m (2H, 1-H and 4-H), 6.63 br.s (1H, 3-H), 9.45 s (1H, CHO). <sup>13</sup>C NMR spectrum, δ<sub>C</sub>, ppm: 17.55 (CH<sub>3</sub>), 23.05 (CH<sub>3</sub>), 26.48 (CH<sub>3</sub>), 33.90 (C<sup>7</sup>), 38.38 (C<sup>1</sup>), 40.69 (C<sup>4</sup>), 47.57 (C<sup>5</sup>), 149.44 (C<sup>2</sup>), 152.76 (C<sup>3</sup>), 191.64 (CHO).

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