# OZONOLYTIC TRANSFORMATION OF (S)-(-)-LIMONENE IN HCI–ISOPROPANOL

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Partial ozonolysis of (S)-(-)-limonene (ee 50%) in cyclohexane: isopropanol at 2–4°C formed the 1,2,4-trioxolane as a mixture of diastereomers in a 3:2 ratio. A solution of HCl in i-PrOH acted as a cleaving agent during decomposition of the peroxides and a cyclizing agent during formation of the diastereomeric 1,2,4-substituted cyclohexanes.

Keywords: (S)-(-)-limonene, ozonolysis, isopropanol, HCl.

Monoterpenes are important constituents of essential oils from higher plants. Thus, limonene is broadly distributed in essential oils of many plants but most of all in citrus and turpentine isolated from conifer sap [1]. The exo- and endocyclic double bonds in its structure are responsible for its high synthetic potential, e.g., in ozonolytic transformations. However, only several examples of ozonation of this diene and transformation of its peroxide ozonolysis products were reported. We reported previously [2] that (*S*)-(–)-limonene (1) (*ee* 50%) under partial ozonolysis conditions in cyclohexane:MeOH at 2–4°C formed ozonides **2a** and **2b** as a mixture (2:3) of diastereomers that were 30% transformed into a hemiketal (**3**) after 6 d at room temperature. Furthermore, it was observed that methyl[(1*S*)-2,4-dimethoxy-2,4-dimethylcyclohexyl]acetate (**4**) was formed in 70% yield after 48 h as a single diastereomeric pair in a 3:1 ratio by treating the peroxides (**2a** and **2b**) with semicarbazide hydrochloride. The presence of the hemiketal in **3** explained unambiguously the C-4 methoxy in cyclohexane derivative **4** [2] (Scheme 1).



a. 0.9 eq. O<sub>3</sub>, 2–4°C; b. MeOH–cyclohexane; c. i-PrOH–cyclohexane; d. NH<sub>2</sub>C(O)NHNH<sub>2</sub>·HCl

#### Scheme 1

Herein we present results for the replacement of MeOH by *i*-PrOH during partial ozonolysis of 1, which produced the same ozonides 2a and 2b in a 3:2 ratio. However, their transformation in *i*-PrOH was different. The peroxides (2a and 2b) were converted (70%) after 6 d at room temperature into the ketohemiacetal (5) (Scheme 1).

The different behavior of the intermediate ozonides (2a and 2b) in MeOH and *i*-PrOH apparently had a decisive influence on the structure of the non-peroxide ozonolysis products that were formed by the HCl solution in MeOH or *i*-PrOH.

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Cyclic ester **4** was formed in 60% yield in HCl–MeOH and was entirely identical to that obtained by treatment of the ozonides (**2a** and **2b**) with semicarbazide hydrochloride. However, analogous work up in *i*-PrOH gave a mixture (3:1) of diastereomers of the tri-substituted cyclohexanol (**6**) in 50% yield instead of the proposed isopropyl analog (**7**) of the trimethoxy compound (**4**). The ester of **6** was selectively reduced by DIBAH to give the corresponding primary-tertiary diol (**8**) in order to establish unambiguously the position of the hydroxyl (Scheme 2).



## Scheme 2

We propose that **6** formed according to Scheme 2 upon work up of the ozonides (**2a** and **2b**) with HCl in *i*-PrOH. Initially, unsaturated ketoacid **9** formed upon treatment with HCl and converted to the corresponding isopropyl ester (**10**). Then, the carbonyl was activated by the HCl proton and was attacked by the double bond with simultaneous stabilization by *i*-PrOH.

Thus, (S)-(–)-limonene behaved differently during ozonolysis in *i*-PrOH and MeOH both during transformation into non-peroxide products at room temperature and during treatment with HCl.

#### EXPERIMENTAL

We used equipment at the Khimiya Center for Collective Use, IOC, USC, RAS. IR spectra were recorded from thin layers on an IR Prestige-21 Fourier Transform Spectrophotometer (Shimadzu). NMR spectra were recorded in  $CDCl_3$  with TMS internal standard on high-resolution AM-300 and Avance III 500 spectrometers (operating frequencies 300 and 500 MHz for <sup>1</sup>H and 75.47 MHz for <sup>13</sup>C) (Bruker). Resonances in PMR spectra were assigned and SSCC were determined using double resonance and 2D homo- and heteronuclear COSY (H–H), HSQC, HMBC, and NOESY correlation spectroscopy. Mass spectra were recorded using direct sample introduction into the ion source of a high-resolution MAT 95 XP GC-MS (Thermo Finnigan). The temperature was programmed from 50 to 270°C at 25°C/min and ionizing potential 70 eV. <sup>13</sup>C NMR spectra were recorded with broad-band proton decoupling and in JMOD mode. GC was performed on Chrom-5 [column length 1.2 m, silicone SE-30 (5%) stationary phase on Chromaton N-AW-DMCS (0.16–0.20 mm), operating temperature 50–300°C] and Chrom-41 (column length 2.4 m, PEG-6000 stationary phase, operating temperature 50–200°C) instruments using He carrier gas. TLC monitoring used Sorbfil SiO<sub>2</sub> (Russia), hexane–MTBE eluent, and H<sub>2</sub>SO<sub>4</sub>–anisaldehyde detection. Column chromatography used SiO<sub>2</sub> (70–230) (Lancaster, Great Britain). Optical rotation was measured on a 241-MC polarimeter (PerkinElmer). We used (*S*)-(–)-limonene {97%, *ee* 50%, [ $\alpha$ ]<sub>D</sub><sup>20</sup>–94° (neat)}. Elemental analyses of all compounds corresponded with those calculated. The ozonator output was 40 mmol O<sub>3</sub> per hour.

**Ozonolysis of (S)-(–)-limonene (1).** A solution of **1** (1.1 g, 8.09 mmol, *ee* 50%) in a mixture of distilled cyclohexane (20 mL) and anhydrous alcohol [14.70 mmol, MeOH (0.6 mL) or *i*-PrOH (1.12 mL)] at 2–4°C was purged with an  $O_3/O_2$  mixture until 7.4 mmol of  $O_3$  was absorbed. The mixture was purged with Ar. The cyclohexane layer was decanted.

Stability of Ozonide (2a and 2b). A solution of ozonide (2a and 2b) in *i*-PrOH was held at room temperature for 6 d. <sup>13</sup>C NMR spectra were recorded daily. The ozonide (2a and 2b) was converted (70%) to the hemiacetal (5) in 6 d.

(4*S*)-4-Isopropenyl-1-methyl-7,8,9-trioxabicyclo[4.2.1]nonane (2a and 2b). The <sup>13</sup>C NMR spectrum was identical to that published earlier [2].

(5*S*)-5-(2-Hydroxy-2-isopropoxyethyl)-6-methylhept-6-en-2-one (5). <sup>13</sup>C NMR spectrum (75.47 MHz, *i*-PrOH, C<sub>6</sub>D<sub>6</sub>, δ, ppm): 17.82 (17.95) (q, CH<sub>3</sub>), 26.25 (26.02) (t, C-4), 29.31 (q, C-1), 40.48 (40.42) (t, CH<sub>2</sub>), 41.32 (40.89) (t, C-3), 43.24 (43.08) (d, C-5), 67.69 (67.41) (d, OCH(CH<sub>3</sub>)<sub>2</sub>), 99.68 (99.63) (s, COH)OPr<sup>*i*</sup>), 113.54 (t, C-7, CH<sub>2</sub>=C), 146.15 (145.77) (s, C-6, CH<sub>2</sub>=C), 208.73 (s, C-2, C=O).

**Treatment of Ozonides (2a and 2b) with Alcoholic HCl.** A solution of the ozonides (**2a** and **2b**) was stirred (0°C), treated with alcoholic HCl [25 mL, prepared by bubbling HCl obtained from NaCl (64 g) and  $H_2SO_4$  (conc., 30 mL) through anhydrous MeOH or *i*-PrOH (50 mL)], stirred at room temperature for 24 h, and evaporated. The residue was dissolved in CHCl<sub>3</sub> (100 mL), washed with  $H_2O$  (to pH  $\approx$  7), dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated.

Methyl [(1*S*)-2,4-dimethoxy-2,4-dimethylcyclohexyl]acetate (4).  $R_f$  0.53 (hexane–MTBE, 2:1), a 3:1 pair of diastereomers (according to <sup>13</sup>C NMR). The IR and NMR spectra were identical to those reported earlier [2].

**Isopropyl [(15)- (6a) and (1***R***)- (6b) -4-hydroxy-2-isopropoxy-2,4-dimethylcyclohexyl]acetates** were obtained as a mixture (3:1) of diastereomers (**6a** and **6b**) (1.05 g, 50%) and were separated by chromatography (SiO<sub>2</sub>, hexane–MTBE, 4:1). Light-yellow viscous mass. Mass spectrum, m/z ( $I_{rel}$ , %): 286 (M<sup>+</sup>, 0.1), 252 (2), 225 (5), 169 (60), 167 (20), 165 (10). IR spectrum (KBr, v, cm<sup>-1</sup>): 3475 (OH), 1729 (CO<sub>2</sub>Pr<sup>*i*</sup>), 1080 (C–O–C).

**Compound (6a).** Yield 0.79 g (37%),  $R_f$  0.25 (hexane–MTBE, 2:1). <sup>1</sup>H NMR spectrum (500 MHz, CDCl<sub>3</sub>,  $\delta$ , ppm, J/Hz): 1.08 (3H, s, CH<sub>3</sub>), 1.19 (3H, s, CH<sub>3</sub>), 1.22 (12H, d, J = 6.6, 4CH<sub>3</sub>), 1.38–1.44 (1H, m, H-5), 1.43–1.46 (1H, m, Ha-6), 1.58 (1H, d, J = 15.06, Ha-3), 1.56–1.61 (1H, m, He-6), 1.62 (1H, d, J = 13.7, He-5), 1.79 (1H, dd, J = 15.06, 3.76, He-3), 1.80–1.92 (1H, m, H-1), 1.93 (1H, dd, J = 12.5, 2.1, CHe<sub>2</sub>CO<sub>2</sub>Pr<sup>*i*</sup>), 2.72 (1H, d, J = 12.5, CH<sub>2</sub>CO<sub>2</sub>Pr<sup>*i*</sup>), 3.81 (1H, sept, J = 6.6, CH(CH<sub>3</sub>)<sub>2</sub>), 4.7 (1H, br.s, OH), 5.0 (1H, sept, CO<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>). <sup>13</sup>C NMR spectrum (75.47 MHz, CDCl<sub>3</sub>,  $\delta$ , ppm): 21.88 (q, 2CH<sub>3</sub>), 21.97 (q, 2CH<sub>3</sub>), 25.25 (q, CH<sub>3</sub>), 25.28 (t, C-6), 32.88 (q, CH<sub>3</sub>), 35.28 (t, CH<sub>2</sub>CO<sub>2</sub>Pr<sup>*i*</sup>), 38.56 (t, C-5), 41.95 (d, C-1), 49.24 (t, C-3), 62.51 (d, OCH(CH<sub>3</sub>)<sub>2</sub>), 67.37 (d, CO<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 71.25 (s, C-4), 76.75 (s, C-2), 173.55 (s, CO<sub>2</sub>Pr<sup>*i*</sup>).

**Compound (6b).** Yield 0.26 g (12%),  $R_f$  0.22 (hexane–MTBE, 2:1).  $[\alpha]_D^{20}$  +4.6° (CH<sub>2</sub>Cl<sub>2</sub>, 1.15). <sup>1</sup>H NMR spectrum (500 MHz, CDCl<sub>3</sub>,  $\delta$ , ppm, J/Hz): 1.03 (3H, s, CH<sub>3</sub>), 1.18 (12H, d, J = 6.6, 4CH<sub>3</sub>), 1.25 (3H, s, CH<sub>3</sub>), 1.30 (1H, dd, J = 9.5, 3.0, Ha-5), 1.40 (1H, d, J = 14.1, Ha-3), 1.41–1.45 (1H, m, Ha-6), 1.54–1.59 (1H, m, He-6), 1.58 (1H, d, J = 9.5, He-5), 1.74 (1H, d, J = 14.1, He-3), 1.80–1.92 (1H, m, H-1), 2.03 (1H, ddd, J = 15.5, 9.3, 1.3, CHe<sub>2</sub>CO<sub>2</sub>Pr<sup>*i*</sup>), 2.52 (1H, dd, J = 15.5, 4.1, CHa<sub>2</sub>CO<sub>2</sub>Pr<sup>*i*</sup>), 3.76 (1H, sept, J = 6.6, CH(CH<sub>3</sub>)<sub>2</sub>), 4.7 (1H, br.s, OH), 4.92 (1H, sept, CO<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>). <sup>13</sup>C NMR spectrum (75.47 MHz, CDCl<sub>3</sub>,  $\delta$ , ppm): 21.79 (q, 2CH<sub>3</sub>), 21.88 (q, 2CH<sub>3</sub>), 24.79 (q, CH<sub>3</sub>), 25.09 (t, C-6), 25.88 (q, CH<sub>3</sub>), 34.78 (t, CH<sub>2</sub>CO<sub>2</sub>Pr<sup>*i*</sup>), 38.14 (t, C-5), 43.18 (d, C-1), 47.86 (t, C-3), 63.44 (d, OCH(CH<sub>3</sub>)<sub>2</sub>), 67.32 (d, CO<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>), 70.80 (s, C-4), 75.78 (s, C-2), 173.46 (s, CO<sub>2</sub>Pr<sup>*i*</sup>).

(4*S*)-4-(2-Hydroxyethyl)-3-isopropoxy-1,3-dimethylcyclohexanol (8). A solution of **6** (0.14 g, 0.5 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (20 mL) at 0°C was stirred, treated with *i*-Bu<sub>2</sub>AlH (73%, 1.0 mL) in toluene, stirred at room temperature for 2 h (TLC monitoring), treated with H<sub>2</sub>O (2 mL, 0°C), and filtered. The filtrate was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to afford diastereomers (3:1) **8** (0.80 g, 70%) (according to GC and <sup>13</sup>C NMR) as a light-yellow viscous mass,  $R_f$  0.10 (hexane-MTBE, 2:1), [α]<sub>D</sub><sup>20</sup> +11.4° (CH<sub>2</sub>Cl<sub>2</sub>, 0.523). IR spectrum (v, cm<sup>-1</sup>): 3359 (OH), 1073 (C–O–C). <sup>1</sup>H NMR spectrum (300 MHz, CDCl<sub>3</sub>, δ, ppm, J/Hz): 1.15 (6H, d, J = 4.8, 2CH<sub>3</sub>), 1.25 (3H, s, CH<sub>3</sub>), 1.28 (3H, s, CH<sub>3</sub>), 1.30–1.36 (1H, m, Ha-6), 1.36–1.39 (1H, m, Ha-5), 1.39 (2H, m, CH<sub>2</sub>CH<sub>2</sub>OH), 1.40–1.49 (1H, m, He-6), 1.44–1.52 (1H, m, H-1), 1.71–1.79 (1H, m, He-5), 1.95 (1H, dd, J = 13.5, 2.3, H-3), 2.10 (1H, dd, J = 13.5, 2.2, H-3), 3.50–3.62 (1H, m, CH<sub>2</sub>OH), 3.69–3.78 (1H, m, CH<sub>2</sub>OH), 3.96 (1H, sept, OCH(CH<sub>3</sub>)<sub>2</sub>), 4.40 (1H, br.s, OH), 4.80 (1H, br.s, OH). <sup>13</sup>C NMR spectrum (75.47, CDCl<sub>3</sub>, δ, ppm): 19.09 (18.88) (q, CH<sub>3</sub>), 25.86 (24.84) (q, CH<sub>3</sub>), 27.30 (25.86) (t, C-6), 32.72 (30.79) (q, CH<sub>3</sub>), 34.55 (32.72) (t, CH<sub>2</sub>CH<sub>2</sub>OH), 38.98 (38.93) (t, C-5), 44.01 (44.54) (d, C-1), 49.74 (53.42) (t, C-3), 61.39 (61.83) (t, CH<sub>2</sub>OH), 63.03 (63.71) (d, CH(CH<sub>3</sub>)<sub>2</sub>), 70.72 (70.59) (s, C-4), 78.29 (76.88) (s, C-2).

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