(*R*)-4-Menthenone in the synthesis of optically pure sex pheromone of the peach leafminer moth (*Lyonetia clerkella*)

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The synthesis of (14*S*)-methyloctadec-1-ene, sex pheromone of the peach leafminer moth (*Lyonetia clerkella*), is described to demonstrate a new potential of the synthetic use of (*R*)-4-menthenone.

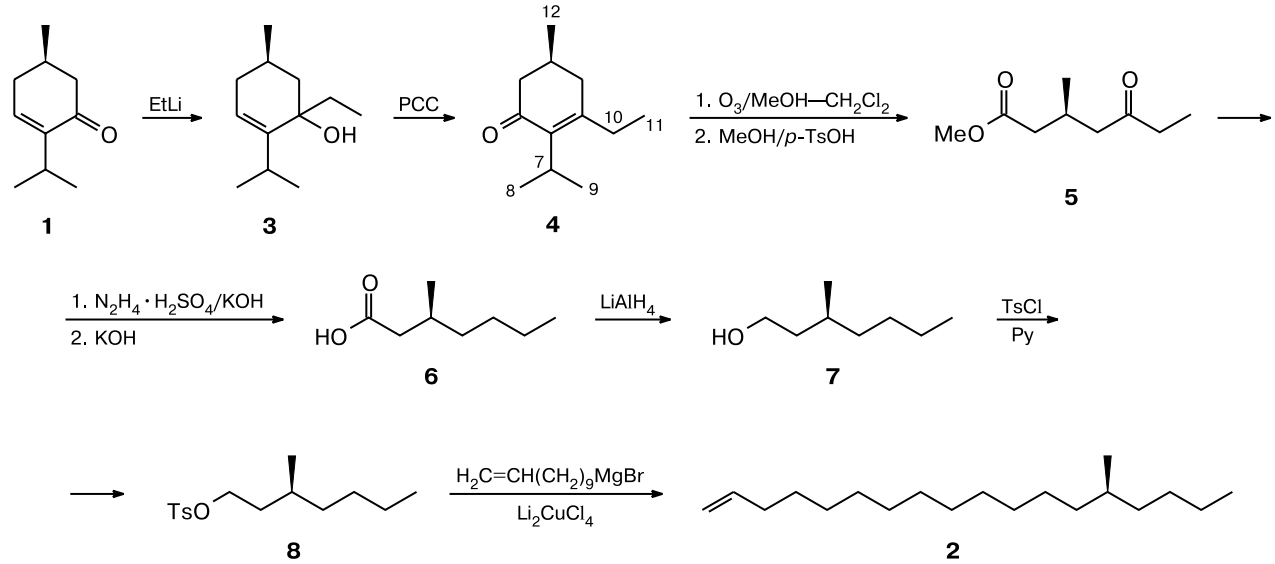
Key words: (−)-menthol, (*R*)-4-menthenone, (5*R*,1*RS*)-1-ethyl-2-isopropyl-5-methylcyclohex-2-enol, (*S*)-3-ethyl-2-isopropyl-5-methylcyclohex-2-enone, methyl (3*S*)-methyl-5-oxoheptanoate, (14*S*)-methyloctadec-1-ene, ozonolysis, Cr^{VI} oxidation, insect pheromones.

Previously,[1—3] we reported ozonolytic transformation of (*R*)-4-menthenone (**1**) prepared from (−)-menthol to give a valuable chiral synthon, namely, methyl (*R*)-5,5-dimethoxy-3-methylpentanoate,[1,2] and the use of this product in the synthesis of optically pure juvenoid, (*S*)-(+)-hydroprene.[3]

In the present study, we report the synthesis of (14*S*)-methyloctadec-1-ene (**2**), the sex pheromone of the peach leafminer moth (*Lyonetia clerkella*), as an example to demonstrate a new potential for the synthetic use of enone **1** related to the ability of conjugated enones to undergo selective 1,2-addition of organometallic reagents followed by oxidative rearrangement of the resulting tertiary allylic alcohols upon treatment with Cr^{VI}.[4,5]

Previously, syntheses of optically pure biologically active (*S*)-isomer **2** have made use of (*R*)-3-hydroxy-2-methylpropionic acid[6] or (*R*)-(+)-pulegone;[7] fractional crystallization of 2-methylhexanoic acid was also used.[8] We proposed to use readily available natural (−)-menthol as the starting compound.

Scheme 1



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Regioselective 1,2-addition of EtLi to enone **1** and subsequent treatment of the resulting (5*R*,1*RS*)-1-ethyl-2-isopropyl-5-methylcyclohex-2-enol (**3**) with pyridinium chlorochromate yielded (*S*)-ethylmenthenone (**4**) (Scheme 1). The signals for the protons in the ^{1}H NMR spectrum of compound **4** were assigned and the spin-spin coupling constants were determined by means of 2D correlation (COSY-90°) and double resonance techniques. Large vicinal coupling constants, $^3J_{4a,5}$ and $^3J_{6a,5}$, suggest an equatorial orientation of the Me group at C(5).[9] The magnetic nonequivalence of the methyl groups (δ 1.09 and 1.12) in the Pr^i substituent is apparently due to the presence of a barrier to the rotation of the Pr^i group around the C(2)—C(7) bond.

Subsequent ozonolysis of enone **4** accompanied by elimination of the $CCHMe_2$ fragment[2] followed by methanolysis yielded keto ester **5**. The Huang—Minlon deoxygenation of keto ester **5** accompanied by saponification of the ester group gave rise to (3*S*)-methylheptanoic acid (**6**), which was converted, using a standard route *via* alcohol **7** and tosylate **8**, into the target pheromone **2** in an overall yield of 15.4% starting from enone **1**.

Thus, we demonstrated a new potential for the synthetic application of readily available (*R*)-4-menthenone involving chemoselective transformations leaving the asymmetric center intact.

Experimental

IR spectra were recorded on a Specord M-82 spectrometer in thin film. NMR spectra (δ, *J*/Hz) were recorded on a Bruker AM-300 spectrometer (300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C) in $CDCl_3$ relative to Me_4Si. Gas chromatography was carried out on a Chrom-5 instrument (column length 2.4 m; PEG-6000 (5%) on Inerton AW-DMCS (0.125—0.160 mm) as the stationary phase; working temperature 50—200 °C); helium was used as the carrier gas. Optical rotation was measured on a Perkin—Elmer 241-MC polarimeter. Column chromatography was performed on Lancaster silica gel L (60—200 μm) (UK). TLC was carried out using Silufol plates (Czechia); light petroleum with b.p. 40—70 °C was used for chromatography.

The solvents were dried by standard procedures;[10] THF and Et_2O were distilled over DIBAH prior to the reaction. The following commercial reagents were used: TsCl ("pure" grade, produced at the Shostka chemical plant) was recrystallized from $CHC1_3$; $N_2H_4 \cdot H_2SO_4$ ("pure" grade, Reakhim); and $LiAlH_4$ (USSR). Li_2CuCl_4 was prepared by a procedure described previously.[11]

(*S*)-3-Ethyl-2-isopropyl-5-methylcyclohex-2-enone (4). A 1.75 *M* solution of EtLi (45 mL) in anhydrous THF was added dropwise to a stirred solution of menthenone **1**[2,3] (4.00 g, 26.3 mmol) in 30 mL of anhydrous Et_2O (−78 °C, Ar).[12] The reaction mixture was stirred for 1 h, the temperature being gradually raised to ~20 °C. Then the mixture was stirred for an additional 2 h and cooled to 5 °C, a saturated solution of NH_4Cl (40 mL) was added, and the mixture was extracted with Et_2O (3×30 mL). The extract was washed with brine, dried with Na_2SO_4, and concentrated to give 4.74 g of alcohol **3**. IR, ν/cm^{-1}: 916, 994 (H—C=); 1162 (C—O); 1654 (C=C); 3460 (O—H). This product was used in the next step without purification.

Alcohol **3** (4.70 g, 25.8 mmol) in 5 mL of dry CH_2Cl_2 was added to a vigorously stirred suspension of pyridinium chlorochromate (11.98 g, 55.7 mmol) in 20 mL of dry CH_2Cl_2 (5—10 °C, Ar). The reaction mixture was stirred for 2 h at ~20 °C, Et_2O (30 mL) was added, and the mixture was stirred for an additional 15 min and filtered through a layer of Al_2O_3. The precipitate was washed with Et_2O and the filtrate was concentrated. The residue was chromatographed on SiO_2 (using light petroleum as the eluent) to give 2.98 g of compound **4** (63%, based on enone **2**) whose chemical purity, according to GLC, was 97%, R_f 0.62 (light petroleum : Bu^{t}OMe = 2 : 1), $[\alpha]_D^{21}$ +70.9 (*c* 7.23, $CHCl_3$). IR, ν/cm^{-1}: 1612 (C=C); 1666 (C=O). ^{1}H NMR, δ: 1.02 (d, 3 H, H(12), ^3J = 6.0 Hz); 1.08 (t, 3 H, H(11), ^3J = 7.6 Hz); 1.09 and 1.12 (both d, each 6 H, H(8), H(9), ^3J = 7.2 Hz); 1.95—2.01 (m, 1 H, H_{ax}(5)); 2.03 (dd, 1 H, H_{ax}(6), ^2J = 10.2 Hz, ^3J = 10.6 Hz); 2.31 (dd, 1 H, H_{eq}(6), ^2J = 10.2 Hz, ^3J = 2.6 Hz); 2.06 (dd, 1 H, H_{ax}(4), ^2J = 13.7 Hz, ^3J = 12.3 Hz); 2.38 (dd, 1 H, H_{eq}(4), ^2J = 13.7 Hz, ^3J = 3.3 Hz); 2.23 (q, 2 H, H(10), ^3J = 7.6 Hz); 2.83 (sept, 1 H, H(7), ^3J = 7.2 Hz). ^{13}C NMR, δ: 12.23 (q, C(11)); 20.48 (q, C(12)); 20.49 and 21.01 (both q, C(8), C(9)); 26.52 (d, C(7)); 27.16 (t, C(10)); 29.81 (d, C(5)); 39.13 (t, C(4)); 46.65 (t, C(6)); 137.66 (s, C(2)); 158.31 (s, C(3)); 198.08 (s, C(1)). Found (%): C, 79.85; H, 11.12. $C_{12}H_{10}O$. Calculated (%): C, 79.94; H, 11.16.

Methyl (3*S*)-methyl-5-oxoheptanoate (5). An O_3/O_2 mixture (ozonizer productivity 40 mmol of O_3 per h) was passed at 5 °C through a solution of enone **4** (2.90 g, 16.1 mmol) in a mixture of 15 mL of anhydrous MeOH and 15 mL of CH_2Cl_2 until the starting compound disappeared (TLC). The reaction mixture was purged with Ar, TsOH (0.14 g) and anhydrous MeOH (20 mL) were added, the mixture was stirred for 48 h at ~20 °C, $NaHCO_3$ (1.47 g) was added, and the mixture was concentrated *in vacuo*. The residue was diluted with 100 mL of Et_2O, washed with brine to pH 7, dried with Na_2SO_4, concentrated, and chromatographed on SiO_2 (light petroleum as the eluent) to give 2.35 g (85%) of keto ester **5**, whose chemical purity was 98%, according to GLC, R_f 0.3 (light petroleum : Bu^{t}OMe = 2 : 1), $[\alpha]_D^{21}$ +2.8 (*c* 5.76, C_2H_5OH). IR, ν/cm^{-1}: 1114, 1258 (C—O—C); 1714, 1738 (C=O). ^{1}H NMR, δ: 0.89 (d, 3 H, H_3CC(3), ^3J = 6.3 Hz); 0.97 (t, 3 H, H(7), ^3J = 7.3 Hz); 2.14 (dd, 1 H, H(2), ^2J = 14.9 Hz, ^3J = 6.8 Hz); 2.42 (dd, 1 H, H′(2), ^2J = 14.9 Hz, ^3J = 6.8 Hz); 2.26 (dd, 1 H, H(4), ^2J = 13.2 Hz, ^3J = 7.0 Hz); 2.39 (dd, 1 H, H′(4), ^2J = 13.2 Hz, ^3J = 7.0 Hz); 2.25—2.33 (m, 1 H, H(3)); 2.37 (q, 2 H, H(6), ^3J = 7.3 Hz); 3.59 (s, 3 H, H_3CO). ^{13}C NMR, δ: 7.57 (q, C(7)); 19.90 (q, $H_3\underline{C}C$(3),); 26.22 (d, C(3)); 36.19 (t, C(6)); 40.57 (t, C(2)); 48.40 (t, C(4)); 51.29 (q, H_3CO); 172.81 (s, C(1)); 210.29 (s, C(5)). Found (%): C, 62.59; H, 9.31. $C_9H_{16}O_3$. Calculated (%): C, 62.77; H, 9.36.

(3*S*)-Methylheptanoic acid (6). Keto ester **5** (0.60 g, 3.5 mmol) and diethylene glycol (3.5 mL) were added dropwise with stirring at 15 °C to a solution of $N_2H_4 \cdot H_2SO_4$ (1.36 g, 10.5 mmol) in 13 mL of 10% aqueous KOH. The mixture was stirred at this temperature for 2.5 h and allowed to stand for 16 h. Potassium hydroxide (1.00 g, 17.4 mmol) was added, the mixture was refluxed for 2 h, and water and excess hydrazine hydrate were distilled off until the reaction temperature reached

195 °C. The mixture was heated for an additional 4 h at 195 °C, cooled, diluted with 4 mL of water, and extracted with CH_2Cl_2 (3×20 mL). The aqueous layer was acidified with 10% H_2SO_4 and extracted with CH_2Cl_2 (3×20 mL). The extract was dried with $MgSO_4$ and concentrated. The residue was chromatographed on SiO_2 ($CHCl_3$ as the eluent) to give 0.31 g (61%) of acid **6**, R_f 0.67 (light petroleum : ethyl acetate = 2 : 1), $[\alpha]_D^{18}$ −4.15 (*c* 3.99, benzene) (*cf.* Ref. 13). The parameters of the IR spectrum were virtually identical to those reported previously:[14] ^{1}H NMR, δ: 0.89 (t, 3 H, H(7), ^3J = 6.5 Hz); 0.97 (d, 3 H, $H_3CC(3)$, ^3J = 6.6 Hz); 1.15—1.44 (m, 6 H, H(4)—H(6)); 1.88—2.05 (m, 1 H, H(3)); 2.15 (dd, 1 H, H(2), ^2J = 14.9 Hz, ^3J = 8.2 Hz); 2.36 (dd, 1 H, H′(2), ^2J = 14.9 Hz, ^3J = 5.9 Hz); 11.15 (br.s, H—O). (*cf.* Ref. 14).

(3*S*)-Methylheptan-1-ol (7). A solution of acid **6** (0.30, 2.1 mmol) in 2 mL of anhydrous Et_2O was added (0 °C, Ar) to a stirred suspension of $LiAlH_4$ (0.16 g, 4.2 mmol) in 4 mL of anhydrous Et_2O. Then the reaction mixture was heated to ~20 °C, stirred for 2 h, and cooled to 0 °C, and 0.3 mL of water and 0.12 mL of a 15% solution of NaOH were added successively with stirring. The reaction mixture was stirred for 2 h, the organic layer was separated, and the aqueous layer was extracted with Et_2O (3×15 mL). The extracts were combined with the organic layer, washed with brine (to pH 7), dried with Na_2SO_4, and concentrated to give 0.23 g (75%) of alcohol **7**, $[\alpha]_D^{18}$ −2.73 (*c* 2.96, $CHCl_3$) (*cf.* Ref. 15). Parameters of the IR and ^{1}H NMR spectra were almost identical to those reported previously.[16]

(3*S*)-Methyl-1-tosyloxyheptane (8). Tosyl chloride (0.28 g, 1.5 mmol) was added in small portions to a solution of alcohol **7** (0.20 g, 1.4 mmol) in 4.5 mL of anhydrous pyridine at 0 °C and the mixture was left for 16 h in a refrigerator. Then the mixture was dissolved in 20 mL of Et_2O, washed successively with brine, saturated solutions of $CuSO_4$ and $NaHCO_3$, and brine, dried with Na_2SO_4, and concentrated to give 0.39 g of tosylate **8**. IR, ν/cm^{-1}: 1180, 1350 (S=O); 1600 (Ar). The product was used in the next step without further purification.

(14*S*)-Methyloctadec-1-ene (2). A solution of tosylate **8** (0.39 g, 1.4 mmol) in 10 mL of anhydrous THF was added dropwise (−75 °C, Ar) to a stirred solution of the Grignard reagent prepared from undec-10-enyl bromide[17] (0.36 g, 1.5 mmol) and Mg (0.04 g, 1.7 mmol) in 5 mL of anhydrous THF. A 0.2 *M* solution of Li_2CuCl_4 (0.40 mL) in anhydrous THF was added. The reaction mixture was stirred for 1 h at −70 °C, for 2 h at −10 °C, and for 2 h at 25 °C, poured into a cooled saturated solution of NH_4Cl, and extracted with Et_2O (3×20 mL). The combined extract was washed successively with brine, a saturated solution of $NaHCO_3$, and brine, dried with $MgSO_4$, and concentrated. The residue was chromatographed on SiO_2 (using light petroleum as the eluent) to give 0.23 g (63%) of olefin **1**, $[\alpha]_D^{18}$ +1.18 (*c* 5.1, $CHCl_3$) (*cf.* Ref. 7). Parameters of the IR and NMR spectra were almost identical to those reported previously.[17]

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