SYNTHESIS OF THE PROMISING CHIRAL SYNTHON ISOPROPYL-4*R*-METHYL-6-IODOHEXANOATE FROM L-(–)-MENTHOL

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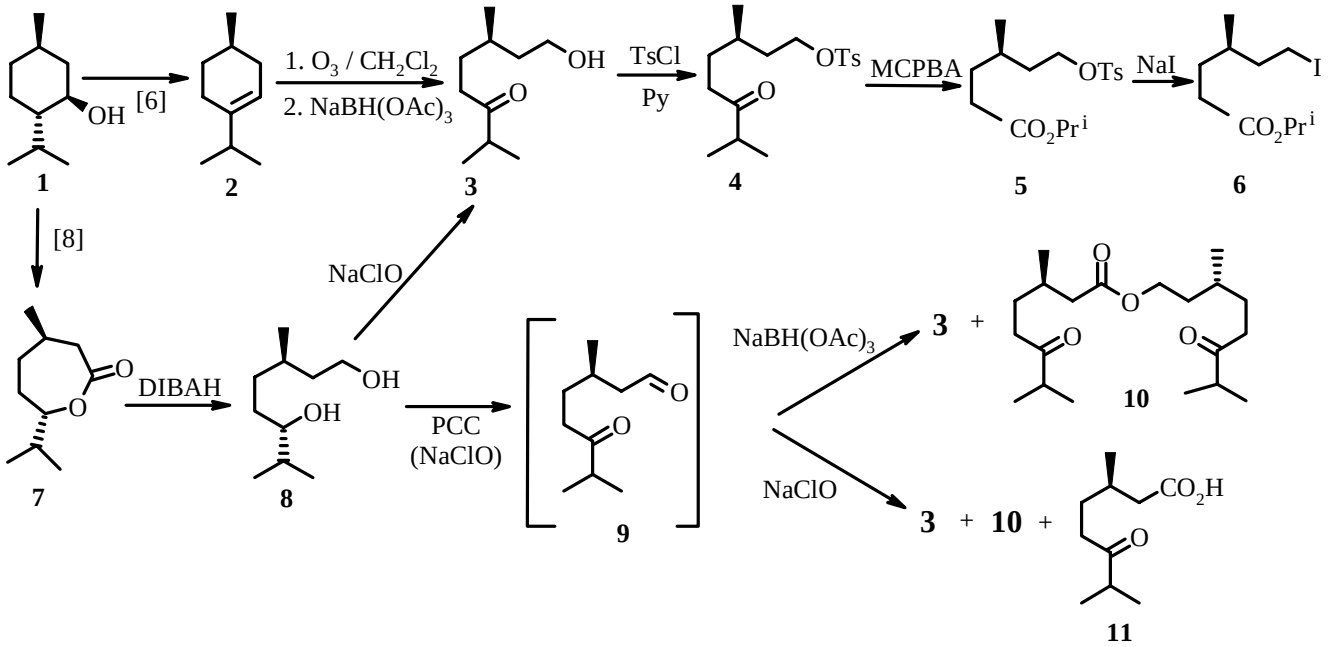
A synthesis of the promising optically pure synthon isopropyl-4R-methyl-6-iodohexanoate based on ozonolytic transformation of the product of regiospecific dehydratation of L-(–)-menthol, (R)-p-menth-3-ene, into 2,6R-dimethyl-8-hydroxyoctan-3-one was proposed.

Key words: L-(–)-menthol, ozonolysis, (*R*)-*p*-menth-3-ene, 2,6*R*-dimethyl-8-hydroxyoctan-3-one, 3*R*,7-dimethyloctan-1,6*S*-diol, 3*R*,7-dimethyl-6-oxooctyl ester of 3*R*,7-dimethyl-6-oxooctanoic acid, 3*R*,7-dimethyl-6-oxooctanoic acid, sodium *tris*-acetoxyborohydride.

We have expanded the synthetic potential of the readily available natural monoterpenoid L-(–)-menthol (**1**) by synthesizing the promising optically pure synthon isopropyl-4*R*-methyl-6-iodohexanoate (**6**), which is a functional analog of methyl-4*R*-methyl-6-iodohexanoate. The last compound is available from (+)-citronellic acid and is used to synthesize biologically active compounds for medicine, agrochemistry, fragrances, and liquid crystals [1]. Furthermore, it was used to synthesize sex pheromones of the smaller tea tortrix moth [2], German cockroach, and pine sawfly [3].



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The key intermediate in our proposed synthesis is 2,6*R*-dimethyl-8-hydroxyoctan-3-one (**3**), which was prepared earlier from (+)-citronellol by isomerization of its epoxide [4, 5].

The first approach to **3** was based on ozonolytic transformation of the product of regiospecific dehydratation of **1** by the literature method [6], (*R*)-*p*-menth-3-ene (**2**), under the conditions of the method previously proposed by us for direct reduction of the ozonolysis products of 1-alkylcycloalkenes into ketoalcohols [7].

Further selective transformations of **3** into the desired iodoester **6** included protection of the hydroxyl, Baeyer—Villager oxidation of the intermediate tosyloxyketone (**4**), and exchange of the *p*-toluenesulfonate for iodine.

Another longer and less effective approach to **3** was based on initial transformation of the menthollactone (**7**), which is available from **1** [8], into the corresponding diol (**8**). Oxidation of **8** by sodium hypochlorite, which is widely used to oxidize secondary alcohols in the presence of primary ones, by the literature method [9] at a reagent ratio **8**:NaClO = 1:2.1 was complicated by the formation of significant quantities of other products (according to GC of the resulting reaction mixture): diketoester **10** (61%), the Tishchenko disproportionation product of the side product ketoaldehyde **9**, and ketoacid **11** (23%), from reoxidation of the same aldehyde. Performing the reaction by titration (very slow addition of the oxidant) with a reagent ratio **8**:NaClO = 1:1 produced only hydroxyketone **3** in 87% yield.

Furthermore, **8** underwent exhaustive Corey oxidation to **9**, which was reduced without purification by sodium *tris*-acetoxyborohydride, which selectively reduces an aldehyde in the presence of a ketone [10]. However, this reaction was also accompanied by formation of significant quantities (up to 50%) of **10** according to GC.

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument as thin layers. NMR spectra were recoded on a Bruker AM-300 spectrometer (working frequency 300.13 MHz for PMR and 75.47 MHz for ^{13}C NMR) in $CDCl_3$. The internal standards were impurity protons at δ 7.27 ppm in the deuterated solvent for PMR and the average $CDCl_3$ signal at δ 77.00 ppm for ^{13}C NMR. Signals in the PMR spectra of **3** and **11** were assigned using homonuclear correlation spectroscopy (COSY 90). Spin—spin coupling constants (SSCC) were determined by double resonance. GC was performed in Chrom-5 [column length 1.2 m, stationary phase silicone SE-30 (5%) on Chromaton N-AW-DMCS (0.16-0.20 mm), working temperature 50-300°C] and Chrom-41 [column length 2.4 m, stationary phase PEG-6000, working temperature 50-200°C] instruments with He carrier gas. Column chromatography was carried out over silica gel L (40-100 μm, Czech Rep.). TLC used Silufol UV-254 plates (Czech Rep.). Optical rotation was measured on a Perkin—Elmer-241-MC polarimeter. Elemental analyses of all compounds agreed with those calculated. For chromatography used petroleum ether (40-70°C, PE). An aqueous solution (1 M) of NaClO (Ufakhimprom, Bashkortostan Rep.) was used.

(*R*)-*p*-Menth-3-ene (2). Menthol (**1**, 2.50 g, 14.0 mmol) and triphenylphosphine (PPh_3, 4.20 g, 16.0 mmol) were dissolved in dry CH_3CN (20 mL), heated to boiling, and treated dropwise with CCl_4 (2.50 g, 16.0 mmol). The resulting mixture was boiled until HCl was no longer evolved (~20 h) and then cooled. The resulting solid was filtered off. The solvent was removed at atmospheric pressure using a fractionating column 0.2 m in length. The solid was chromatographed over SiO_2 (pentane) to afford **2** (1.16 g, 60%), $[\alpha]_D^{20}$ +114.88°, lit. [11]. The IR spectrum is practically identical to that described previously [12]; PMR and ^{13}C NMR, [13].

2,6*R*-Dimethyl-8-hydroxyoctan-3-one (3). An ozone—oxygen mixture (ozonator productivity 40.0 mmol O_3/h) was bubbled through a solution of **2** (0.90 g, 6.5 mmol) and glacial AcOH (0.78 g, 13.0 mmol) in CH_2Cl_2 (18 mL) with stirring at -4 to -2°C until 6.7 mmol of ozone was absorbed. The reaction mixture was purged with Ar, diluted with CH_2Cl_2 (9 mL), stirred (10°C), and treated with a previously prepared suspension of $NaBH(OAc)_3$ [prepared by adding a solution of glacial AcOH (5.34 g, 89.0 mmol) in CH_2Cl_2 (9 mL) to a suspension of $NaBH_4$ (1.13 g, 29.7 mol) in CH_2Cl_2 (45 mL) with subsequent stirring for 2 h]. The reaction mixture was heated to room temperature, stirred for 3 h, cooled to 10°C, and treated with a solution of NaOH (2.03 g) in water (45 mL). The organic layer was separated. The aqueous layer was extracted with CH_2Cl_2, successively washed with saturated NH_4Cl solution and water, dried over Na_2SO_4, and evaporated to produce **3** (0.89 g, 78%), $[\alpha]_D^{20}$ +8.64° (*c* 0.3, $CHCl_3$), R_f 0.42 (PE:ethylacetate = 7:3). IR spectrum (KBr, ν, cm^{-1}): 3200-3600, 1055 (OH), 1708 (C=O).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.89 (3H, d, J = 6.7, CH_3C-6), 1.06 (6H, d, J = 6.7, CH_3C-2, H-8), 1.40-1.55 (2H, m, H-4, H-7), 1.59-1.73 (2H, m, H-4, H-7), 1.75-1.92 (1H, m, H-6), 2.43-2.52 (2H, m, H-4), 2.53 (1H, septet, ^{3}J = 6.9, H-2), 4.07 (2H, dd, ^{2}J = 9.1, ^{3}J = 6.9, H-8).

^{13}C NMR spectrum ($CDCl_3$): 18.27 (q, CH_3C-2), 19.08 (q, CH_3C-6), 27.67 (d, C-6), 30.03 (t, C-5), 37.80 (t, C-4), 40.61 (d, C-2), 41.61 (t, C-7), 62.49 (t, C-8), 214.38 (s, C-3).

3*R*,7-Dimethyloctan-1,6*S*-diol (8). A solution of **7** (23.5 mmol) prepared as before [8] in dry CH_2Cl_2 (80 mL) was treated dropwise (Ar, -15°C) with a toluene solution (12.5 mL, 73%) of diisobutylaluminium hydride (DIBAH) in dry CH_2Cl_2 (10 mL), stored (-15°C, 1 h; 20°C, 12 h), and treated successively with THF (11 mL) and H_2O (25 mL). The resulting solid was filtered off with a sintered-glass filter. The organic layer was dried over $MgSO_4$, filtered, and evaporated to afford **8** (3.33 g, 83%), R_f 0.10 (PE:ethylacetate = 7:3), $[\alpha]_D^{20}$ -10.3° (*c* 2.43, $CHCl_3$). IR spectrum (KBr, ν, cm^{-1}): 3200-3600, 1100, 1055 (OH).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.75-0.95 (9H, ddd, J = 6.7, CH_3C-3, CH_3C-7, H-8), 1.10-1.70 (9H, m, H-2—H-7), 2.50 (2H, br.s, OH), 3.50-3.75 (2H, m, H-1).

^{13}C NMR spectrum ($CDCl_3$): 16.99 and 18.81 (q, CH_3C-7, C-8), 19.74 (q, CH_3C-3), 29.54 (d, C-3), 31.20 (t, C-5), 32.77 (t, C-4), 33.37 (d, C-7), 39.58 (t, C-2), 60.13 (t, C-1), 76.67 (d, C-6).

2,6*R*-Dimethyl-8-hydroxyoctan-3-one (3), 3,7-Dimethyl-6-oxooctyl Ester of 3,7-Dimethyl-6-oxooctanoic Acid (10), and 3*R*,7-Dimethyl-6-oxooctanoic Acid (11).

a. A solution of **8** (1.18 g, 6.8 mmol) and glacial AcOH (5 mL) at room temperature was treated dropwise with aqueous NaClO (7.2 mL, 1 M) and then after 30 min with another portion (7.2 mL) of the same solution, stirred for 12 h until the peroxide disappeared (iodine—starch test), diluted with ethylacetate (50 mL), washed successively with saturated solutions of $NaHCO_3$ and NaCl, dried over Na_2SO_4, filtered, and evaporated to produce a mixture (1.01 g) consisting according to GC of **3** (16%), **10** (61%), and **11** (23%), which was separated chromatographically over SiO_2 (PE:ethylacetate = 7:3).

b. A solution of **8** (1.00 g, 6.0 mmol) in glacial AcOH (3 mL) at room temperature was treated dropwise over 1 h with aqueous NaClO (6.0 mL, 1 M, 6.0 mmol), extracted with CH_2Cl_2 (3 × 30 mL), washed successively with saturated solutions of $NaHCO_3$ and NaCl, dried over Na_2SO_4, filtered, and evaporated to produce **3** (0.86 g, 87%).

c. A suspension of pyridinium chlorochromate (PCC, 5.02 g, 23.3 mmol) in dry CH_2Cl_2 (8 mL) (Ar, 20°C) was treated dropwise with **8** (1.30 g, 7.5 mmol) in dry CH_2Cl_2 (5 mL), stored for 2 h, diluted with Et_2O (20 mL), and filtered through SiO_2 (20 g) on a sintered-glass filter. The filtrate was evaporated. The solid 3*R*,7-dimethyloctan-6-on-1-al (**9**, 1.25 g, R_f 0.50, PE:ethylacetate = 7:3) was dissolved in dry CH_2Cl_2 (10 mL), stirred (10°C), and treated with a previously prepared suspension of $NaBH(OAc)_3$ [prepared by adding a solution of glacial AcOH (6.20 g, 103.0 mmol) in CH_2Cl_2 (10 mL) to a suspension of $NaBH_4$ (1.30 g, 34.4 mmol) in CH_2Cl_2 (50 mL) with subsequent stirring for 2 h]. The reaction mixture was heated to room temperature, stirred for 3 h, cooled to 10°C, and treated with a solution of NaOH (2.34 g, 58.5 mmol) in water (50 mL). The organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) washed successively with saturated solutions of NH_4Cl and water, dried over Na_2SO_4, and evaporated to produce a mixture (1.15 g) consisting according to GC of **3** (50%) and **10** (50%), which was separated chromatographically over SiO_2 (PE:ethylacetate = 7:3).

The IR spectra, PMR spectra, and ^{13}C NMR spectra of **3** prepared by methods **a**-**c** were practically identical to those described above.

3*R*,7-Dimethyl-6-oxooctyl Ester of 3*R*,7-Dimethyl-6-oxooctanoic Acid (10), R_f 0.57 (PE:ethylacetate = 7:3), $[\alpha]_D^{20}$ +13.6° (*c* 1.73, $CHCl_3$). IR spectrum (KBr, ν, cm^{-1}): 1735, 1705 (C=O), 1030 (C–O–C).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.98 (6H, d, J = 6.7, CH_3C-3, CH_3C-3′), 1.07 (12H, d, ^{3}J = 7.0, CH_3C-7, CH_3C-7′, H-8, H-8′), 1.33-1.49 (3H, m, H-2′, H-4, H-4′), 1.51-1.68 (3H, m, H-2′, H-4, H-4′), 1.90-2.25 (2H, m, H-3, H-3′), 2.09 (1H, dd, ^{2}J = 15.2, ^{3}J = 7.4, H-2), 2.25 (1H, dd, ^{2}J = 15.2, ^{3}J = 6.0, H-2), 2.40-2.48 (4H, m, H-5, H-5′), 2.60-2.75 (2H, m, H-7, H-7′), 4.03 (2H, t, J = 6.6, H-1′).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 18.10 (q, CH_3C-7, C-8, CH_3C-7′, C-8′), 18.95 (q, CH_3C-3), 19.29 (q, CH_3C-3′), 29.27 (d, C-3′), 29.74 (d, C-3), 30.02 (t, C-4), 30.26 (t, C-4′), 35.08 (t, C-7), 37.53 (t, C-2′, C-5′), 40.53 (d, C-7, C-7′), 42.25 (t, C-2), 62.27 (t, C-1′), 172.65 (s, C-1), 214.13 (s, C-6′), 214.42 (s, C-6).

3*R*,7-Dimethyl-6-oxooctanoic Acid (11), R_f 0.25 (PE:ethylacetate = 7:3), $[\alpha]_D^{20}$ +9.90° (*c* 0.25, $CHCl_3$). IR spectrum (KBr, ν, cm^{-1}): 1705, 1725 (C=O).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.98 (3H, d, ^{3}J = 6.7, CH_3C-3), 1.10 (6H, d, ^{3}J = 7.0, CH_3C-7, H-8), 1.49 (1H, dtd, ^{2}J = 14.8, ^{3}J = 5.7, ^{3}J = 3.9, H-4), 1.67 (1H, dtd, ^{2}J = 14.8, ^{3}J = 7.7, ^{3}J = 8.7, H-4), 1.90-2.20 (1H, m, H-3), 2.18 (1H, dd, ^{2}J = 15.1, ^{3}J = 7.9, H-2), 2.34 (1H, dd, ^{2}J = 15.1, ^{3}J = 6.0, H-2), 2.43-2.52 (2H, m, H-5), 2.61 (1H, septet, ^{3}J = 7.0, H-7), 8.9 (1H, br.s, OH).

^{13}C NMR spectrum ($CDCl_3$): 18.30 (q, CH_3C-7, C-8), 18.87 (q, CH_3C-3), 29.61 (d, C-3), 30.07 (t, C-4), 37.60 (t, C-5), 40.67 (d, C-7), 41.16 (t, C-2), 178.40 (s, C-1), 214.69 (s, C-6).

3*R*,7-Dimethyl-1-tosyloxyoctan-6-one (4). A solution of *p*-toluenesulfonyl chloride (TsCl, 0.76 g, 3.96 mmol) in dry Py (5 mL) (Ar, 0°C) was treated with **3** (0.57 g, 3.30 mmol), held at that temperature for 12 h, diluted with Et_2O (50 mL), washed successively with HCl (10%) and saturated solutions of $NaHCO_3$ and NaCl, dried over $MgSO_4$, filtered, and evaporated to produce **4** (0.84 g, 78%). IR spectrum (KBr, ν, cm^{-1}): 1715 (C=O), 1600 (Ar), 1370, 1180 (S–O).

Isopropyl-4*R*-methyl-6-tosyloxyhexanoate (5). A suspension of *m*-chloroperbenzoic acid (MCPBA, 0.40 g, 50%) in dry $CHCl_3$ (1 mL) (20°C) was treated dropwise with a solution of **4** (0.40 g, 1.2 mmol) in dry $CHCl_3$ (3 mL), stirred for 5 h, diluted with CH_2Cl_2 (5 mL), washed successively with saturated solutions of $Na_2S_2O_3$ and NaCl, dried over $MgSO_4$, filtered, and evaporated to produce **5** (0.40 g, 96%). IR spectrum (KBr, ν, cm^{-1}): 1735 (C=O), 1590 (Ar), 1370, 1180 (S–O).

Isopropyl-4*R*-methyl-6-iodohexanoate (6). A solution of **5** (0.40 g, 1.1 mmol) and NaI (0.42 g, 2.8 mmol) in dry acetone (4 mL) was boiled for 1.5 h, left in the dark for 24 h, diluted with icewater (3 mL), extracted with Et_2O (3 × 15 mL), washed successively with saturated solutions of $Na_2S_2O_3$, $NaHCO_3$, and NaCl, dried over $MgSO_4$, filtered, and evaporated. The solid was chromatographed over SiO_2 (PE:ethylacetate = 5:1) to produce **6** (0.40 g, 92%), $[\alpha]_D^{20}$ -6.1° (*c* 4.10, $CHCl_3$), R_f 0.47 (PE:ethylacetate = 5:1). IR spectrum (KBr, ν, cm^{-1}): 1735 (C=O), 500 (C–J).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.85 (3H, d, CH_3C-4, J = 6.2), 1.21 [6H, d, $CH(C\underline{H}_3)_2$, J = 6.3], 1.50-1.70 (2H, m, H-5), 1.48-1.65 (2H, m, H-3), 1.65-1.80 (1H, m, H-4), 2.20-2.35 (2H, m, H-2), 3.13 (2H, t, H-6, J = 7.5), 4.96 [1H, st, $C\underline{H}(CH_3)_2$, J = 6.3].

^{13}C NMR spectrum ($CDCl_3$): 4.47 (t, C-6), 18.25 (q, CH_3C-4), 21.77 [q, $CH(\underline{C}H_3)_2$], 31.02 (t, C-2), 32.08 (t, C-3), 40.43 (t, C-5), 67.41 [d, $\underline{C}H(CH_3)_2$], 173.01 (s, C-1).

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