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SYNTHESIS OF THE JUVENOID (S)-(+)-HYDROPRENE FROM L-(-)-MENTHOL

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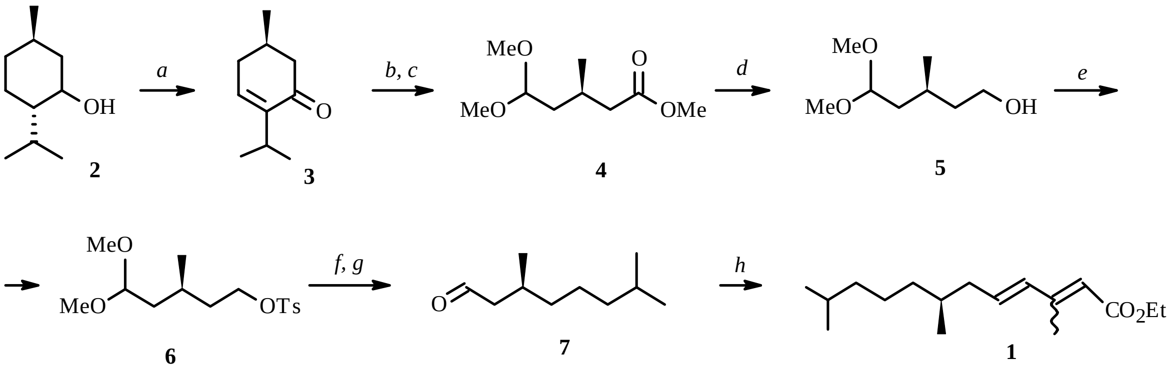
The versatile chiral synthon methyl (R)-5,5-dimethoxy-3-methylpentanoate has been prepared for the first time via ozonolytic decyclization of (R)-4-menthenone, which is available from L-(-)-menthol. The optically pure juvenoid (S)-(+)-hydroprene can be prepared from the synthon.

Key words: (S)-(+)-hydroprene, L-(-)-menthol, (R)-4-menthenone, methyl (R)-5,5-dimethoxy-3-methylpentanoate, ozonolysis, (S)-tetrahydrocitral, juvenoid, synthesis.

The optically active ethyl ester of (S)-3,7,11-trimethyl-2E,4E-dodecadienoic acid [(S)-(+)-hydroprene] (**1**), which is a highly effective analog of an insect juvenile hormone, was previously prepared from (S)-dihydromyrcene [1], (S)-citronellol [2], and racemic dihydrocitronellol with initial separation of it into enantiomers [3].

We propose the synthesis of juvenoid **1** from the readily available optically pure monoterpenoid L-(-)-menthol (**2**), which is isolated from the essential oil of peppermint. We first developed ozonolytic decyclization and used it on the intermediate (R)-4-menthenone (**3**), which is prepared from **2** by a known method, in particular, through (-)-(1R,4S)-menthone via bromination-dehydrobromination of the corresponding enolacetate [4] in 65% yield. Reaction of **3** with an equimolar amount of ozone in cyclohexane (or CCl_4) in the presence of CH_3OH and subsequent treatment of the peroxide products with acidified CH_3OH gives the methyl ester of (R)-5,5-dimethoxy-3-methylpentanoic acid (**4**) in high yield. Reduction of **4** into hydroxyacetal **5** and its tosylation gives tosylate **6**. Cross-linking of **6** with a Grignard reagent catalyzed by dilithiumtetrachlorocuprate and treatment with acid gave (S)-tetrahydrocitral (**7**). Aldehyde **7** was converted to the final juvenoid **1** as a mixture (9:1) of (2E,4E)- and (2E,4Z)-stereoisomers according to the literature method [3] in overall yield of 23% calculated for starting **2**. The specific rotations of **1**, **3-5**, and **7** are consistent with total retention of the optical purity of asymmetric C-1 (1R,3R,4S)-menthol **2** (*ee* > 99%) in all steps.



a. Ref. [4]; *b*. O_3/*c*-C_6H_{12} (or CCl_4)-MeOH; *c*. MeOH/TsOH; *d*. $LiAlH_4$; *e*. TsCl/Py;
f. i-BuMgBr/Li_2CuCl_4; *g*. TS-OH-Py; *h*. Ref. [3]

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EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument as thin layers. NMR spectra were obtained on a Bruker AM-300 spectrometer (working frequency 300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C) in $CDCl_3$ with chloroform internal standard (PMR, δ 7.27 ppm; ^{13}C NMR, average δ 77.00 ppm). Chromatography was performed on a Chrom-5 instrument [1.2 m column, silicon SE-30 (5%) stationary phase on Chromaton N-AW-DMCS (0.16-0.20 mm), working temperature 50-300°C, He carrier gas]. Optical rotations were measured on a Perkin—Elmer 241-MC polarimeter. TLC was carried out on SiO_2 Silufol UV-254 (Czech Rep.) using petroleum ether—ethanol (2:1); chromatography, on SiO_2 (40-100, Chemapol, Czech Rep.) using petroleum ether (40-70°C). For (R)-menthenone (**3**), $[\alpha]_D^{16}$ -67.5° (*c* 5.3, $CHCl_3$) (lit. -67.2°, [5]). IR and PMR spectra of **4**, **5** [6], **1**, and **7** [3] were practically identical to the published ones. Diisopropyl-(3-ethoxy-2-methyl-2-propenyl)phosphonate was graciously supplied by E. P. Serebryakov (N. D. Zelinskii Inst. Org. Chem., Russian Acad. Sci., Moscow).

Methyl Ester of (R)-5,5-Dimethoxy-3-methylpentanoic Acid (4). An ozone—oxygen mixture (produced at 40 mmole O_2/h in an ozonator) was bubbled through a solution of **3** (5.00 g, 32.9 mmole) in cyclohexane (35 mL) (or CCl_4) in the presence of absolute CH_3OH (2.82 mL, 65.8 mmole) at 5°C at a ratio of 1.1 mole O_3 per mole of **3**. The reaction mixture was purged with Ar, treated with CH_3OH (50 mL) and TsOH (0.25 g), left at room temperature for 2 d until the peroxide disappeared (starch—I_2 test), treated with $NaHCO_3$ (2.50 g), and evaporated under vacuum. The solid was dissolved in ethanol (100 mL), washed with saturated NaCl solution (until the pH was 7), dried over Na_2SO_4, and evaporated. Yield of **4**, 5.44 g (87%), $[\alpha]_D^{25}$ -1.54° (*c* 4.76, $CHCl_3$) [6].

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 19.48 (q, H_3**C**C-3); 26.14 (d, C-3); 38.38 (t, C-4); 40.78 (t, C-2); 50.56, 51.42, and 52.00 (all t, H_3CO); 102.30 (d, C-5); 172.35 (s, C-1).

(S)-5,5-Dimethoxy-3-methylpentan-1-ol (5). A stirred suspension of $LiAlH_4$ (2.00 g, 52.6 mmole) in absolute ether (60 mL) was treated (0°, Ar) with a solution of **4** (5.00 g, 26.3 mmole) in absolute ether (15 mL). The reaction mixture was heated to ~20°C, stirred for 2 h, cooled to 0°C, treated successively with stirring with H_2O (4 mL) and NaOH solution (1.5 mL, 15%), and stirred for 2 h. The organic layer was separated. The aqueous layer was extracted with ether (3×30 mL). The extracts were combined with the organic layer, washed with saturated NaCl solution (until the pH was 7), dried over Na_2SO_4, and evaporated. Yield of **5**, 3.32 g (78%), $[\alpha]_D^{18}$ +5.72° (*c* 5.21, $CHCl_3$) [6].

(S)-3,7-Dimethyloctanal (7). A solution of **5** (3.30 g, 20.4 mmole) in dry pyridine (6 mL) (0°C, Ar) was treated with stirring with TsCl (4.28 g, 22.5 mmole). The reaction mixture was stirred (0°C, 5 h), left overnight in a refrigerator, treated with icewater (10 g), and extracted with ether (3×30 mL). The combined extracts were treated successively with H_2O and saturated $CuSO_4$, $NaHCO_3$, NaCl solutions; dried over Na_2SO_4; and evaporated. Yield of **6**, 6.32 g. IR spectrum (KBr, ν, cm^{-1}): 960, 1030, 1070, 1110, 1135 (C–O), 1185, 1370 (S=O), 1605 (Ar). The product was used without further purification.

A solution of **6** in absolute THF (25 mL) was added dropwise (-75°C, Ar) to a stirred solution of Grignard reagent prepared from isobutylbromide (3.84 g, 28.0 mmole) and Mg (0.74 g, 30.8 mg-at) in absolute ether (16 mL) and treated with a solution of Li_2CuCl_4 (0.50 mL, 0.2 M) in THF. The reaction mixture was stirred (-70°C, 1 h; -10°C, 2 h; 25°C, 2 h), treated with cold saturated NH_4Cl solution, and extracted with ether (3×50 mL). The combined extracts were washed successively with saturated NaCl, $NaHCO_3$, and NaCl solutions and evaporated. The solid was dissolved in a mixture of acetone (200 mL) and H_2O (0.7 mL), treated successively with pyridine (0.47 g) and TsOH (1.13 g), boiled for 2 h, and evaporated under vacuum. The solid was dissolved in ether (150 mL); treated successively with saturated NH_4Cl, $NaHCO_3$, and NaCl solutions; dried over Na_2SO_4; and evaporated. Yield of **7**, 2.47 g (78%), $[\alpha]_D^{20}$ -13.8° (*c* 5.1, $CHCl_3$) [3].

(S)-(+)-Hydroprene (1). Aldehyde **7** (0.20 g, 1.3 mmole) and diisopropyl-(3-ethoxy-2-methyl-2-propenyl)phosphonate (0.08 g) were reacted according to the literature [3] to give after evaporation of solvent and column chromatography (SiO_2, CH_2Cl_2) **1** (0.23 g, 68%) as a 9:1 mixture of the (2E,4E)- and (2E,4Z)-stereoisomers, $[\alpha]_D^{20}$ -3.43° (*c* 3.1, $CHCl_3$).

REFERENCES

1. V. N. Odinokov, G. Yu. Ishmuratov, R. Ya. Kharisov, E. P. Serebryakov, and G. A. Tolstikov, *Izv. Akad. Nauk, Ser. Khim.*, 110 (1993).
2. C. A. Henrick, R. J. Anderson, G. B. Staal, and G. F. Ludvick, *J. Agric. Food Chem.*, **26**, 542 (1978).

3. G. D. Gamalevich, G. M. Zhdankina, G. V. Kryshtal′, G. I. Nikishin, Yu. N. Ogibin, and E. P. Serebryakov, *Zh. Org. Khim.*, **33**, 525 (1997).
4. W. Treibs and H. Albrecht, *J. Prakt. Chem.*, **13**, 291 (1961).
5. T. Shono, Y. Matsumura, K. Hibino, and S. Miyawaki, *Tetrahedron Lett.*, **14**, 1295 (1974).
6. K. Mori and S. Kuwahara, *Tetrahedron*, **38**, 521 (1982).