Chemistry of Natural Compounds, Vol. 39, No. 1, 2003

SYNTHESIS OF (4*R*)-METHYLNONAN-1-OL AND (4*R*,8*RS*)-DIMETHYLDECANAL FROM (*S*)-(+)-3,7-DIMETHYL-1,6-OCTADIENE

G. Yu. Ismuratov, M. P. Yakovleva,
A. V. Galyautdinova, and G. A. Tolstikov

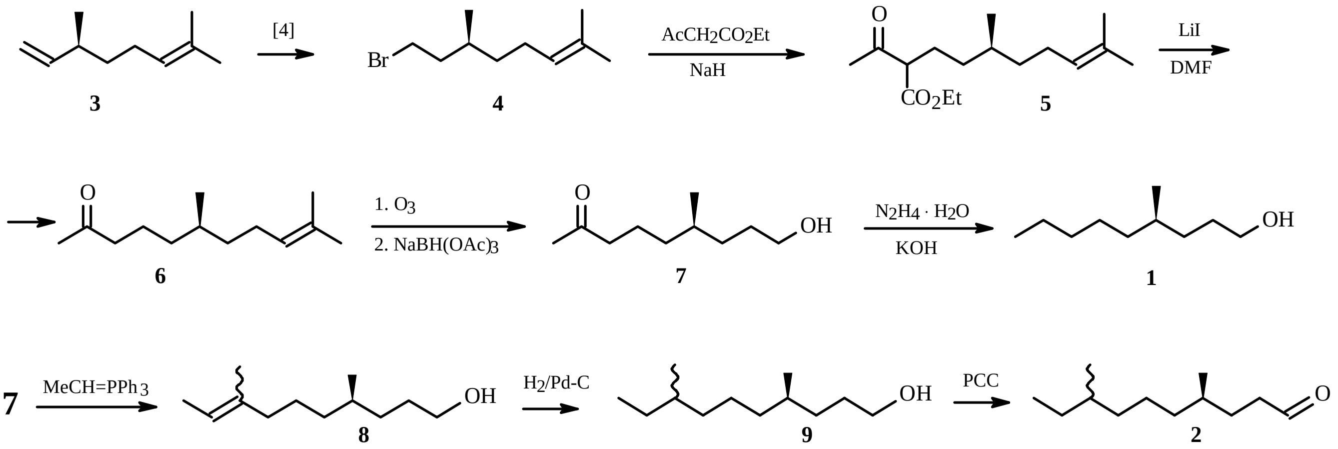
UDC 542.91+547.381+632.936.2

Optically active (4R,8RS)-dimethyldecanal, an analog of the aggregation pheromone of the flour beetles Tribolium confusum *and* T. castaneum, *and (4R)-methylnonan-1-ol, the sex pheromone of the yellow mealworm* Tenebrio molitor *L., are synthesized using ozonolytic transformation of (6R,10)-dimethyl-9-undecen-2-one to (6R)-methyl-9-hydroxynonan-2-one in the key step. The starting compound is available as enantiomerically enriched (ee ~50%) (S)-(+)-3,7-dimethyl-1,6-octadiene.*

Key words: pheromone, (4*R*)-methylnonanol, (4*R*,8*RS*)-dimethyldecanal, (*S*)-(+)-dihydromyrcene, (6*R*,10)-dimethyl-9-yndecen-2-one, (6*R*)-methyl-9-hydroxynonan-2-one, sodium trisacetoxyborohydride, synthesis.

Several syntheses of the optically active stereoisomers of the aggregation pheromone of confused (*Tribolium confusum*) and red flour (*T. castaneum*) beetles, identified as (4*R*,8*R*)-dimethyldecanal [1-3], and (4*R*)-methylnonan-1-ol (**1**), the sex pheromone of the yellow mealworm (*Tenebrio molitor* L.), including from (*S*)-(+)-dihydromyrcene (**3**) [2, 5], are known.

Starting from the enantiomerically enriched (ee ~50%) diene (**3**), we propose an alternate approach to optically active 4,8-diemthyldecanal (**2**) as a mixture of the (4*R*,8*RS*)-diastereomers and the methyl-branched alcohol (**1**).



The definitive step in the synthetic scheme of **1** and **2** is ozonolytic cleavage of the intermediate (6*R*,10)-dimethyl-9-undecen-2-one (**6**). The use of sodium trisacetoxyborohydride as reductant can selectively [6] transform the peroxidic products into the hydroxy derivatives without affecting existing or formed ketones and can produce exclusively the key intermediate (6*R*)-methyl-9-hydroxynonan-2-one (**7**) in high yield. Also, unsaturated ketone (**6**) was prepared by known transformations [7, 8] and those modified by us of citronellyl bromide (**4**), which is available from dihydromyrcene (**3**).

Institute of Organic Chemistry, Ufa Scientific Center, Russian Academy of Sciences 450054, Ufa, pr. Oktyabrya, 71, fax (3472) 35 60 66, e-mail: kharis@anrb.ru. Translated from Khimiya Prirodnykh Soedinenii, No. 1, pp. 27-29, January-February, 2003. Original article submitted February 11, 2003.

0009-3130/03/3901-0031$25.00

The final steps in the synthesis of **2** are olefination by ethylidenetriphenylphosphorane, hydrogenation of the intermediate unsaturated alcohol (**8**), and subsequent oxidation; for **1**, Huang—Minlon reduction of the carboxylic acid [9].

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument in thin layers; NMR spectra, on a Bruker AM-300 spectrometer (working frequency 300.13 MHz for ^1H and 75.47 MHz for ^{13}C) in $CDCl_3$ using the $CDCl_3$ signals as standards (protons of the deuterated solvent with δ 7.27 ppm; average ^{13}C $CDCl_3$ NMR signal with δ 77.00 ppm). GC was performed in Chrom-5 [stationary phase silicone SE-30 (5%) on Chromaton N-AW-DMCS (0.16-0.20 mm), column length 1.2 m, working temperature 50-300°C] and Chrom-41 (stationary phase PEG-6000, column length 2.4 m, working temperature 50-200°C) instruments with He carrier gas. Column chromatography was carried out over silica gel L (Czech. Rep., 40-100 μm); TLC, on Silufol UV-254 plates (Czech. Rep.). Optical rotation was measured on a Perkin—Elmer 241-MC polarimeter.

Ethyl Ester of 2-Acetyl-5*S*,9-dimethyl-8-decenoic Acid (5). A stirred suspension of NaH (0.36 g, 15.2 mmole) in absolute benzene (15 mL) and DMF (15 mL) was treated dropwise under Ar at 0°C with acetoacetic ester (1.98 g, 15.2 mmole), held at room temperature until the reaction mixture was completely homogeneous (~3 h), cooled to 0°C, treated dropwise with (*S*)-citronellyl bromide (**4**, 3.32 g, 15.2 mmole, prepared as before [4]), held at room temperature for 11 h, boiled for 12 h, treated with water (15 mL), and extracted with benzene (4×50 mL). The combined extracts were washed with water (10 mL), dried over $MgSO_4$, filtered, and evaporated. The solid was chromatographed over SiO_2 (PE:Et_2O, 4:1) to give **5** (3.63 g, 89%), $[\alpha]_D^{22}$ +1.66° (*c* 6.44, $CHCl_3$). IR and PMR spectra were identical to those in the literature [7]. ^{13}C NMR ($CDCl_3$): 13.93 (q, $\underline{C}H_3CH_2$), 17.49 (q, *cis*-C-10), 18.68 (19.26) (q, CH_3-5), 25.17 (t, C-7), 25.56 (q, *trans*-C-10), 27.73 (t, C-3), 36.41 (t, C-4), 36.54 (t, C-6), 31.16 (32.09) (d, C-5), 59.98 (d, C-2), 61.18 (61.07) (t, $Me\underline{C}H_2$), 124.27 (d, C-8), 135.50 (s, C-9), 166.98 (169.75) (s, C-1), 203.14 (201.50) (s, $Me\underline{C}O$).

6*R*,10-Dimethyl-9-undecen-2-one (6). A stirred (20°C) solution of **5** (3.50 g, 13 mmole) in absolute DMF (38 mL) was treated in portions with LiI (4.52 g, 33.7 mmole), boiled until CO_2 evolution ceased (~5 h), cooled, and extracted with Et_2O (4×50 mL). The combined extracts were washed successively with saturated $Na_2S_2O_3$ and NaCl solutions, dried over Na_2SO_4, filtered, and evaporated to give unsaturated ketone **6** (2.22 g, 87%), $[\alpha]_D^{17}$ -0.23° (*c* 2.2, $CHCl_3$). IR and PMR spectra were identical to those in the literature [7].

9-Hydroxy-6-methyl-2-nonanone (7). An ozone—oxygen mixture (ozonator, 40 mmole O_3/h) was bubbled through a solution of **6** (2.00 g, 10.2 mmole) and glacial AcOH (1.22 g, 20.4 mmole) in dry CH_2Cl_2 (29 mL) at -4 to -2°C until 10.5 mmoles of O_3 were absorbed. The reaction mixture was purged with Ar, diluted with CH_2Cl_2 (14 mL), stirred (10°C), added to a previously prepared suspension of $NaBH(OAc)_3$ [prepared by adding glacial AcOH (8.42 g, 140.2 mmole) in CH_2Cl_2 (14 mL) to a suspension of $NaBH_4$ (1.78 g, 46.8 mmole) in CH_2Cl_2 (71 mL) with subsequent stirring for 2 h], heated to room temperature, stirred for 3 h, cooled to 10°C, and added to NaOH solution (3.2 g in 71 mL H_2O). The organic layer was separated, washed successively with saturated NH_4Cl solution and water, dried over Na_2SO_4, and evaporated to give **7** (1.56 g, 89%), $[\alpha]_D^{17}$ -0.28° (*c* 2.5, $CHCl_3$). IR and PMR spectra were identical to those in the literature [9].

4*R*-Methylnonan-1-ol (1). Ketoalcohol **5** (0.50 g, 2.8 mmole) was dissolved in diethyleneglycol (2 mL), treated with $N_2H_4 \cdot H_2O$ (0.71 g, 80%), boiled for 1 h, cooled, treated with KOH solution (0.63 g in 0.6 mL H_2O), and boiled for 2 h. The water and excess of hydrazine were distilled off until the still temperature was 195°C. The mixture was refluxed for another 4 h at 195-200°C, cooled, diluted with H_2O (2 mL), and extracted (3×20 mL) with methyl-*t*-butylether (MTBE). The extract was dried over Na_2SO_4 and evaporated to give **1** (0.28 g, 63%), $[\alpha]_D^{20}$ +0.63° (*c*, $CHCl_3$). IR and PMR spectra were identical to those in the literature [5, 10].

4*R*,8-Dimethyl-8*Z*/*E*-decen-1-ols (8). A suspension of ethyltriphenylphosphonium bromide (13.0 g, 35 mmole) in absolute benzene (29 mL, Ar, 75°C) was stirred, treated with $NaN(SiMe_3)_2$ in benzene (35 mL, 1 N) over 30 min, and cooled to room temperature. The resulting ylide was treated dropwise with **7** (1.50 g, 8.7 mmole) in absolute benzene (15 mL), stirred for 3 h, acidified with HCl (0.5 N) until the pH was 7, and extracted with Et_2O (4×50 mL). The combined extracts were washed with saturated NaCl solution, dried over $MgSO_4$, and evaporated. The solid was chromatographed over SiO_2 (PE:Et_2O, 10:1) to give a mixture of alcohols **8** (0.75 g, 70%). IR spectrum (ν, cm^{-1}): 3450-3300 (OH), 1650 (C=C).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.91 [d, 3H, $H_3C(4)$, J = 6.5], 1.29 [br.s, 8H, H(2), H(3), H(5), H(6)], 1.56 and 1.65 [both s, 1.5 H each, $H_3C(8)$], 1.54 [s, 3H, H(10)], 1.61-1.67 [m, 1H, H(4)], 1.87 [t, 2H, H(7), J = 7], 3.53 (br.s, 1H, OH), 3.79 [t, 2H, H(1), J = 6.5], 5.15-5.25 [m, 1H, H(9)].

4*R*,8*RS*-Dimethyldecanal (2). A solution of **8** (0.73 g, 4 mmole) in absolute CH_3OH (7 mL) was treated with Pd/C (0.60 g, 5%) and stirred vigorously on a magnetic stirrer during hydrogenation until 88 mL of H_2 were absorbed (~5 h). The catalyst was filtered off. The filtrate was evaporated to give **9** (0.72 g, 98%). IR and PMR spectra were identical to those in the literature [11]. Alcohol **9** (0.70 g, 3.8 mmole) was dissolved in dry CH_2Cl_2 (5 mL), stirred, added to a suspension of pyridinium chlorochromate (1.43 g, 6.6 mmole) in dry CH_2Cl_2 (14 mL, 20°C, Ar), stirred for 2 h, treated with Et_2O (100 mL), and filtered through a layer of SiO_2. The precipitate on the filter was washed with Et_2O (100 mL). The filtrate was evaporated to give **2** (0.55 g, 78%), $[\alpha]_D^{23}$ -0.50° (*c* 4.5, EtOH). IR and PMR spectra were identical to those in the literature [4, 10].

REFERENCES

1. K. Mori, *Tetrahedron*, **45**, 3233 (1989).
2. G. Yu. Ishmuratov, M. P. Yakovleva, R. Ya. Kharisov, and G. A. Tolstikov, *Usp. Khim.*, 1095 (1997).
3. N. S. Akhaev, G. A. Zakladnoi, M. V. Mavrov, A. M. Moiseenkov, N. K. Khao, E. P. Serebryakov, and B. A. Cheskis, *Bioorg. Khim.*, **14**, 243 (1988).
4. V. N. Odinokov, G. Yu. Ishmuratov, R. Ya. Kharisov, M. P. Yakovleva, R. M. Sultanov, E. P. Serebryakov, U. M. Dzhemilev, and G. A. Tolstikov, *Khim. Prir. Soedin.*, 571 (1991).
5. V. N. Odinokov, G. Yu. Ishmuratov, O. V. Sokolʹskaya, M. P. Yakovleva, R. Ya. Kharisov, E. P. Serebryakov, and G. A. Tolstikov, *Khim. Prir. Soedin.*, 711 (1992).
6. K. Mori, S. Kuwahara, and H. Udea, *Tetrahedron*, **39**, 2439 (1983).
7. R. Azerad and M.-O. Cyrot, *Bull. Chim. France*, 3740 (1965).
8. K. Mori and K. Igarashi, *Liebigs Ann. Chem.*, 717 (1988).
9. G. Yu. Ishmuratov, R. Ya. Kharisov, M. P. Yakovleva, O. V. Botsman, R. R. Muslukhov, and G. A. Tolstikov, *Zh. Org. Khim.*, **37**, 49 (2001).
10. A. Carpita, E. De Magistris, and R. Rossi, *Gazz. Chim. Ital.*, **119**, 99 (1989).
11. R. S. Randad and G. H. Kulkarni, *Indian J. Chem., Sect. B*, **25**, 296 (1986).