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UNIVERSAL APPROACH TO THE SYNTHESIS OF JUVENOID HYDROPRENE AND METHOPRENE FROM 4-METHYLTETRAHYDROPYRAN

G. Yu. Ishmuratov,[1] M. P. Yakovleva,[1] A. V. Galyautdinova,[1] L. V. Faifer,[2] R. Ya. Kharisov,[1] V. V. Zorin,[2] and G. A. Tolstikov[1]

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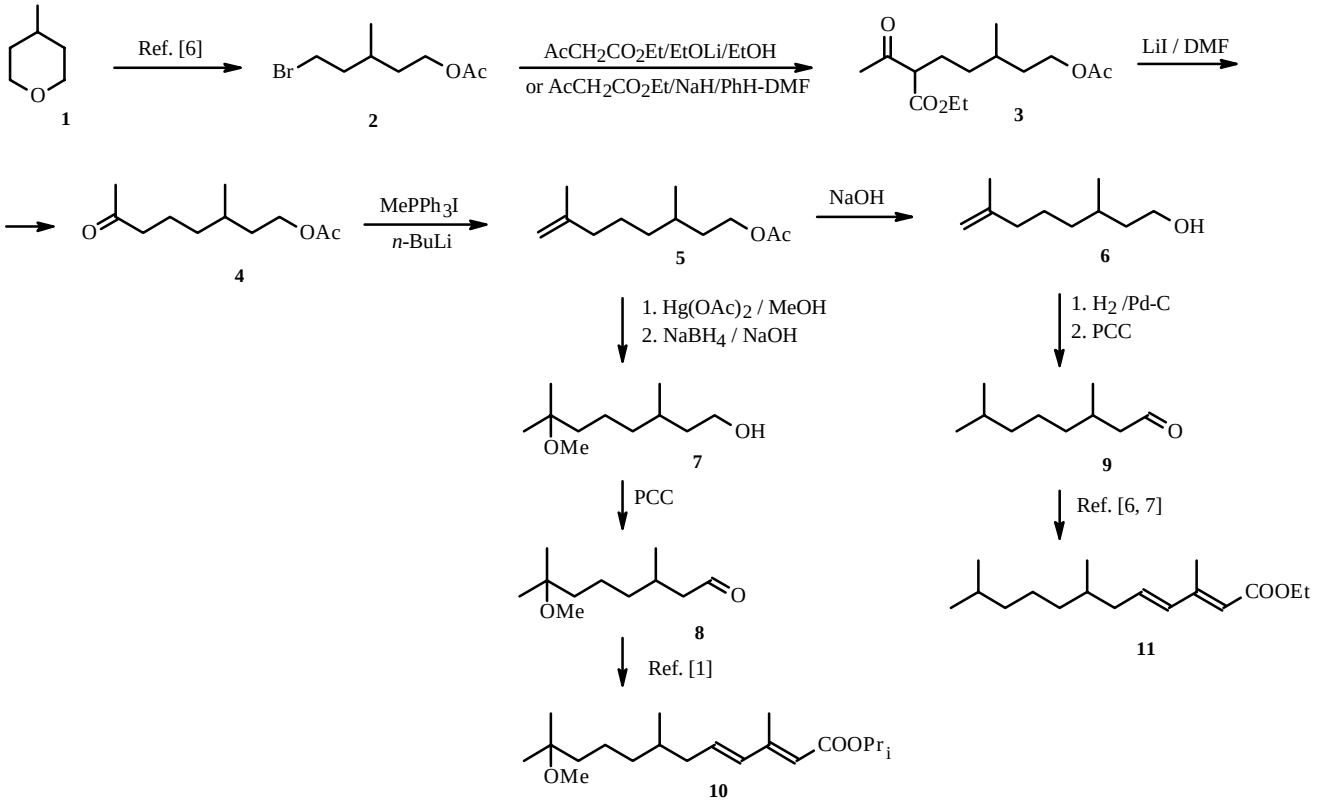
A universal approach to the synthesis of juvenoid hydroprene and methoprene was developed on the basis of monoalkylation of acetoacetate by 1-acetoxy-5-bromo-3-methylpentane, the product of acidic decyclization of 4-methyltetrahydropyran.

Key words: 4-methyltetrahydropyran, alkylation, acetoacetic ester, 1-acetoxy-5-bromo-3-methylpentane, ethyl-2-acetyl-7-acetoxy-5-methylheptanoate, juvenoid hydroprene and methoprene, synthesis.

Several derivatives of 3,7,11-trimethyl-2E,4E-dodecadienoic acid possess high juvenoid activity [1]. Among these, preparations methoprene (**10**) and hydroprene (**11**) are most widely applied in practice. The preparation and properties of these compounds have been reviewed [1, 2].



1) Institute of Organic Chemistry, Ufa Scientific Center, Russian Academy of Sciences, 450054, prospekt Oktyabrya 71, fax (3472) 5 60 66, kharis@anrb.ru; 2) Ufa State Petroleum Technical University, 450062, ul. Kosmonavtov, 1, fax (3472) 43 19 35. Translated from Khimiya Prirodnykh Soedinenii, No. 5, pp. 413-416, September-October, 2001. Original article submitted October 15, 2001.

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We developed a universal approach to the synthesis of **10** and **11** from readily available 4-methyltetrahydropyran (**1**) [3]. Our research found that the products of ring opening of **1** can be broadly applied to the synthesis of methyl-substituted low-molecular-weight insect bioregulators [4].

The present article expands on the synthetic capabilities of one of these, 1-acetoxy-5-bromo-3-methylpentane (**2**). The versatility is based on monoalkylation of the acetoacetic ester and chemically selective transformations. It should be noted that the yield of the resulting product, ethyl-2-acetyl-7-acetoxy-5-methylheptanoate (**3**), is less than 25% under standard conditions (EtONa/EtOH) after 10 h because cyclization of **2** into starting pyran **1** competes. Replacing EtONa by less basic EtOLi causes the process to proceed slower (~50 h) but without complications, giving **3** in 92% yield. The yield is even higher (96%) if the ketodiester is prepared in a mixture of aprotic solvents, DMF and benzene, and NaH is used as the base.

Further transformations of **3** include decarboxylation by LiI in DMF to the key synthon 8-acetoxy-6-methyloctan-2-one (**4**), formation of the olefin 3,7-dimethyloct-7-en-1-ylacetate (**5**) by a Wittig reaction using methyltriphenylphosphonium, and regioselective methoxylation by $Hg(OAc)_2$ in CH_3OH with subsequent reduction of the intermediate organomercury compound by $NaBH_4$ in the presence of an excess of NaOH in aqueous methanol. The resulting methoxycitronellol **7** can be oxidized by pyridinium chlorochromate in CH_2Cl_2 into methoxycitronellal **8**, which is a valuable fragrance and intermediate in the synthesis of isopropyl 11-methoxy-3,7,11-trimethyl-2E,4E-dodecadienoate (**10**) [1, 5].

Ethyl 3,7,11-trimethyl-2E,4E-dodecadienoate (**11**) of variable stereoisomeric purity was prepared by transformation of unsaturated acetate **5** into 3,7-dimethyloct-7-en-1-ol (**6**), which was then reduced to the saturated analog, oxidized into perhydrocitral **9**, and transformed to **11** according to the previously published method [6, 7].

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 $CDCl_3$ signals as an internal standards (protons of $CHCl_3$ impurity at δ 7.27 ppm in PMR; $CDCl_3$ carbon at δ 77.00 ppm in ^{13}C NMR). Chromatography was performed on a Chrom-5 instrument [column length 1.2 m, silicone SE-30 (5%) on Chromaton N-AW-DMCS (0.16-0.20 mm) stationary phase, 50-300°C, He carrier gas]. Elemental analyses corresponded to those calculated.

Ethyl 2-Acetyl-7-acetoxy-5-methylheptanoate (3). a. A stirred solution of EtONa (Ar, 20°C) prepared from Na (1.55 g, 67.3 mg-atom) in absolute EtOH (34 mL) was treated dropwise with acetoacetic ester (9.42 g, 72.5 mmole), then boiled and treated with 1-acetoxy-5-bromo-3-methylpentane (**2**, 10.00 g, 44.8 mmole) prepared from 4-methyltetrahydropyran (**1**) according to the literature method [6], boiled for 10 h (TLC monitoring), cooled, and filtered through a Schott filter. The solid on the filter was washed with EtOH. The filtrate was evaporated. The solid was chromatographed over a silica-gel column (petroleum ether—diethylether, 5:1) to give **3**, 2.45 g (25%).

IR spectrum (KBr, ν, cm^{-1}): 1755, 1745 (ester C=O), 1718 (ketone C=O), 1245, 1140, 1055 (C–O–C).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.91 (2H, d, J = 6.5, CH_3-5), 1.27 (3H, t, J = 7.0, $C\underline{H}_3CH_2O$), 1.69 (7H, m, H-3-H-6), 2.03 (3H, s, CH_3CO), 2.22 (3H, s, CH_3COO), 3.36 (1H, t, J = 7.0, H-2), 4.08 (2H, m, H-7), 4.19 (2H, q, J = 7.0, $CH_3C\underline{H}_2O$).

^{13}C NMR spectrum ($CDCl_3$): 13.81 (q, $\underline{C}H_3CH_2O_2C$), 18.95 (18.89) (q, CH_3-5), 20.68 (q, $\underline{C}H_3CO_2$), 25.23 (t, C-3), 28.54 (q, $\underline{C}H_3CO$), 29.48 (29.43) (d, C-5), 34.08 (34.00) (t, C-4), 34.91 (34.86) (t, C-6), 59.62 (d, C-2), 61.01 (t, $Me\underline{C}H_2COO$), 62.33 (t, C-7), 169.47 (s, C-1), 170.78 (s, $Me\underline{C}O_2$), 202.75 (s, $Me\underline{C}O$).

b. A stirred solution of EtOLi (Ar, 20°C) prepared from Li (0.38 g, 53.8 mg-atom) in absolute EtOH (27 mL) was treated dropwise with acetoacetic ester (9.09 g, 70.0 mmole), then boiled and treated with **2** (10.00 g, 44.8 mmole), boiled for 50 h, and worked up as in **a** to give **3**, 11.17 g (92%), identical to that obtained in the previous synthesis.

c. A stirred dispersion (Ar, 0°C) of NaH (0.88 g, 36.7 mmole) in absolute benzene (37 mL) and dry DMF (37 mL) was treated dropwise with acetoacetic ester (4.77 g, 36.7 mmole) and held at room temperature until the NaH completely dissolved (~3 h). The solution was cooled (0°C), treated dropwise with **2** (7.96 g, 36.7 mmole), held for 11 h at room temperature, boiled for 12 h, treated with water (40 mL), and extracted with benzene (4×40 mL). The combined extracts were washed with water (20 mL), dried over $MgSO_4$, filtered, and evaporated. The solid was chromatographed over a silica-gel column (petroleum ether—ethylacetate, 5:1) to give **3**, 9.58 g (96%), identical to that prepared in **a**.

8-Acetoxy-6-methyloctan-2-one (4). A stirred solution (Ar, 20°C) of **3** (10.00 g, 36.8 mmole) in absolute DMF (104 mL) was treated at once with LiI (12.87 g, 95.5 mmole), boiled until CO_2 evolution ceased (~12 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, and filtered. The solvent was evaporated to give **4**, 5.96 g (81%).

IR spectrum (KBr, ν, cm^{-1}): 1740 (ester C=O), 1720 (ketone C=O), 1250, 1055 (C–O–C).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.88 (3H, d, J = 6.5, CH_3-6), 1.06 (7H, m, H-4-H-7), 2.01 (3H, s, CH_3CO), 2.13 (3H, s, CH_3CO_2), 2.44 (2H, t, J = 7, H-3), 4.05 (2H, m, H-8).

^{13}C NMR spectrum ($CDCl_3$): 18.93 (q, CH_3-6), 20.55 (q, $\underline{C}H_3CO_2$), 20.67, 34.93, 35.85 (all t, C-4, C-5, C-7), 29.30 (q, C-1), 29.44 (d, C-6), 43.33 (t, C-3), 62.34 (t, C-8), 170.58 (s, $CH_3\underline{C}O_2$), 208.32 (s, C-2).

3,7-Dimethyloct-7-en-1-ylacetate (5). A suspension of methyltriphenylphosphonium iodide (19.65 g, 49.0 mmole) in absolute THF (148 mL, Ar, 0°C) was treated dropwise with *n*-butyllithium (1 N, 49 mL, 49 mmole) in hexane. The mixture was stirred at room temperature for 1 h, cooled to 0°C, and treated dropwise with **4** (5.90 g, 29.5 mmole) in absolute THF (21 mL). The reaction mixture was stirred at 0°C for 15 min, left overnight at room temperature, diluted with petroleum ether (200 mL), and filtered through a layer of SiO_2. The solvent was removed. The solid was chromatographed over a silica-gel column (petroleum ether—diethylether, 10:1) to give **5**, 4.95 g (85%). IR spectrum (KBr, ν, cm^{-1}): 3090, 980, 900 (CH_2=C), 1750 (C=C), 1660 (C=C), 1240, 1050 (C–O–C).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.90 (3H, d, J = 6.5, CH_3-3), 1.38 (7H, m, H-2-H-5), 1.69 (3H, s, CH_3C=C), 1.98 (2H, m, H-6), 2.02 (3H, s, CH_3CO_2), 4.04 (2H, m, H-1), 4.66 (2H, d, J = 4.3, CH_2=C).

^{13}C NMR spectrum ($CDCl_3$): 19.38 (q, CH_3-3), 19.42 (q, CH_3-7), 20.97 (q, $\underline{C}H_3COO$), 24.76, 35.42, 36.39, 37.90 (all t, C-2, C-4-C-6), 29.68 (d, C-3), 62.97 (t, C-1), 109.72 (t, C-8), 145.93 (C-7), 171.18 (s, $CH_3\underline{C}OO$).

7-Methoxy-3,7-dimethyloctan-1-ol (7). A stirred solution of **5** (1.42 g, 7.0 mmole) in absolute CH_3OH (25 mL, Ar, 5°C) was treated with $Hg(OAc)_2$ (2.09 g, 6.55 mmole), stirred for 1 h at 5°C and 24 h at room temperature, cooled to 0°C, treated dropwise with $NaBH_4$ (0.49 g, 12.7 mmole) and NaOH (1.52 g, 37.8 mmole) in water (1.8 mL), left to stand (0°C, 1 h; 20°C, 2 h), diluted with Et_2O (100 mL), and filtered through a layer of Al_2O_3 on a Schott filter to remove mercury. The filtrate was washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and evaporated. The solid was chromatographed over a silica-gel column (petroleum ether—diethylether, 5:1) to give **6**, 0.64 g (97%).

IR spectrum (KBr, ν, cm^{-1}): 3600-3300 (OH), 1250, 1055 (C–O–C).

PMR spectrum ($CDCl_3$, δ, ppm): 0.89 (3H, d, CH_3-3), 1.11 (6H, s, CH_3-7, H-8), 1.28 (7H, m, H-2-H-5), 1.58 (2H, m, H-6), 2.21 (1H, br.s, OH), 3.14 (3H, s, CH_3O), 3.65 (2H, t, H-1).

^{13}C NMR spectrum ($CDCl_3$): 19.58 (q, CH_3-3), 24.83, 24.91 (both q, CH_3-7, C-8), 21.10, 37.58, 39.85, 39.98 (all t, C-2, C-4-C-6), 29.41 (d, C-3), 48.98 (q, CH_3O), 60.96 (t, C-1), 74.64 (s, C-7).

7-Methoxy-3,7-dimethyloctanal (8). A suspension of pyridinium chlorochromate (0.60 g, 2.8 mmole) in dry CH_2Cl_2 (3 mL) was stirred (Ar, 20°C), treated with **6** (0.70 g, 3.7 mmole) in dry CH_2Cl_2 (1.5 mL), stirred for 2 h, diluted with Et_2O (20 mL), and filtered through a layer of silica gel. The solid was washed with Et_2O (50 mL). The filtrate was evaporated to give **8**, 0.63 g (90%). The IR and PMR spectra were identical to those in the literature [9].

Isopropyl 11-methoxy-3,7,11-trimethyldodeca-2E,4E-dienoate (10) was prepared from **8** in 82% yield according to the literature method [9]. The IR and PMR spectra were identical to those of the authentic compound.

3,7-Dimethyloct-7-en-1-ol (6). Unsaturated acetate (**5**, 3.50 g, 17.7 mmole) was dissolved in CH_3OH (18 mL), treated with KOH (1.04 g, 18.4 mmole), and boiled for 4 h. The CH_3OH was removed. The solid was extracted with Et_2O (3×30 mL). The combined extracts were washed with saturated NaCl solution, dried over Na_2SO_4, filtered, and evaporated to give **7**, 2.49 g (90%).

IR spectrum (KBr, ν, cm^{-1}): 3600-3300 (OH), 3090, 980, 900 (CH_2=C), 1660 (C=C).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.90 (3H, d, J = 6.5, CH_3-3), 1.40 (7H, m, H-2-H-5), 1.70 (3H, s, CH_3C=C), 2.01 (2H, m, H-6), 3.65 (2H, m, H-1), 4.60 (2H, d, J = 4.3, CH_2=C).

^{13}C NMR spectrum ($CDCl_3$): 19.39 (q, CH_3-3), 19.42 (q, CH_3-7), 24.78, 35.44, 36.41, 37.92 (all t, C-2, C-4-C-6), 29.69 (d, C-3), 60.96 (t, C-1), 109.74 (t, C-8), 146.01 (C-7).

3,7-Dimethyloctanal (9). A solution of **7** (2.00 g, 12.7 mmole) in absolute CH_3OH (20 mL) was treated with Pd/C (0.20 g, 5%) with vigorous stirring on a magnetic stirrer and hydrogenated with H_2 (0.28 L, ~5 h). The catalyst was filtered off. The filtrate was evaporated. The solid (1.88 g) was dissolved in dry CH_2Cl_2 (9 mL), stirred, treated with a suspension of pyridinium chlorochromate (3.84 g, 17.8 mmole) in dry CH_2Cl_2 (37 mL, Ar, 20°C), stirred for 2 h, diluted with Et_2O (200 mL),

and filtered through a layer of silica gel. The solid on the filter was washed with Et_2O (200 mL). The filtrate was evaporated to give **9**, 1.69 g (91%). IR and PMR spectra were identical to those in the literature [8].

Ethyl 3,7,11-trimethyldodeca-2E,4E-dienoate (11) was prepared in 43% yield from **9** according to the literature method [6]. IR and PMR spectra were identical to those of authentic compound.

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