Chemistry of Natural Compounds, Vol. 41, No. 6, 2005

SYNTHESIS OF (3*S*,6*RS*)- AND (3*RS*,6*RS*)-ANALOGS OF COMPONENT AI OF THE *Aonidiella aurantii* SEX PHEROMONE BY STEPWISE ALKYLATION OF ACETOACETIC ESTER

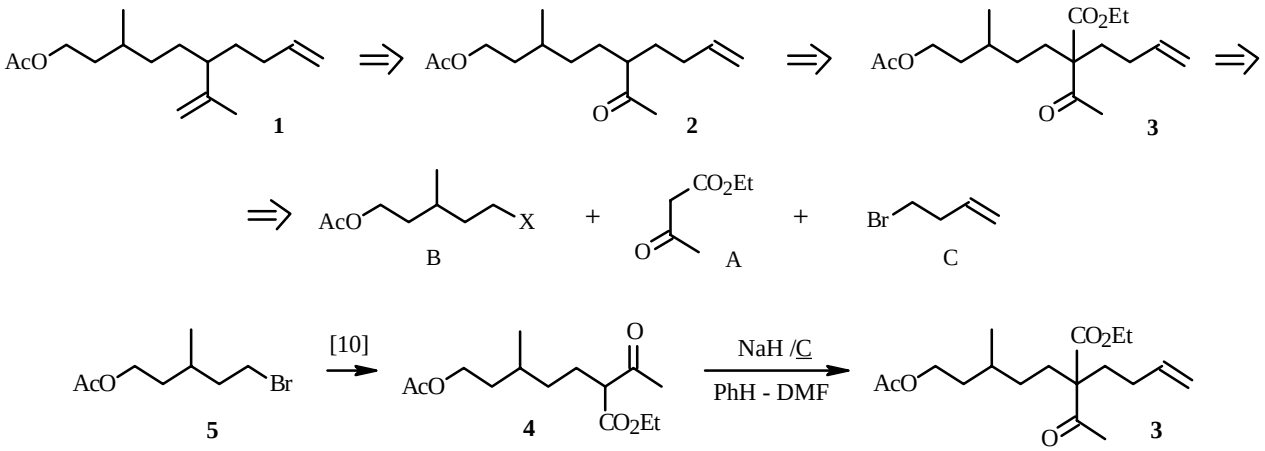
G. Yu. Ishmuratov,[1] R. Ya. Kharisov,[1] M. P. Yakovleva,[1] A. V. Galyautdinova,[1] R. R. Gazetdinov,[1] R. R. Muslukhov,[1] and G. A. Tolstikov[2]

UDC 547.484.4+591.58+632.936.2

Synthetic approaches to (±)- and (3S)-analogs of the AI component of the Aonidiella aurantii *sex pheromone (3S)-methyl-6R-isopropenyldec-9-en-1-ylacetate based on stepwise alkylation of acetoacetic ester by 3-butenylbromide and 1,5-bifunctional 3-methylpentanes were investigated.*

Key words: acetoacetic ester, 1,5-bifunctional 3-methylpentanes, 3-butenylbromide, sex pheromone of California red scale (*Aonidiella aurantii*), ethyl ester of 2-acetyl-7-acetoxy-2-(3-butenyl)-5-methylheptanoic acid, synthesis.

The natural component AI of the California red scale (*Aonidiella aurantii*) citrus pest sex pheromone has been identified as (3*S*)-methyl-(6*R*)-isopropenyldec-9-en-1-ol acetate (**1**) [1]. Biological tests showed that the (*S*)-configuration of asymmetric C-3 is the most important for attractiveness [2]. Known schemes for synthesizing (3*S*)-**1** were developed starting from (*S*)-citronellol [2-5] and (-)-dihydrocarvone [6]. Furthermore, it has been found [2] that enantiomers, which were prepared previously from (±)-citronellol as a diastereomeric mixture of **1** acetates, do not inhibit the biological activity of AI [2, 3, 7-9].



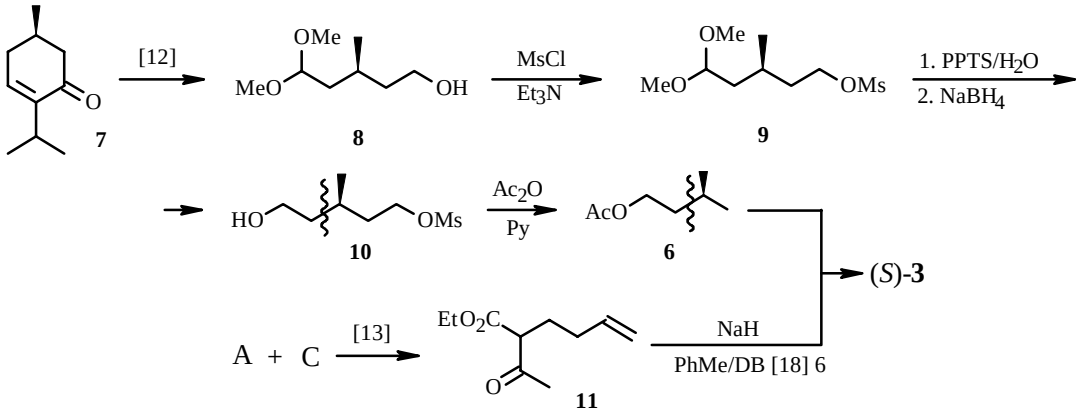
Herein we report synthetic approaches to the acetates of **1** and (3*S*)-**1**. Retrosynthesis of **1** showed that keto-precursor **2** could be prepared by decarbethoxylation of α,α'-disubstituted derivative **3** of acetoacetic ester (A), for which, in turn, the substituting agents are conveniently 1,5-bifunctional 3-methylpentanes (B) and a homoallyl bromide (C).

Key intermediate **3** for the synthesis of optically inert **1** was prepared by condensation of α-substituted acetoacetic ester **4** [10], the product of monoalkylation of the CH-acid A by 1-acetoxy-5-bromo-3-methylpentane (**5**) [11], bromide B.

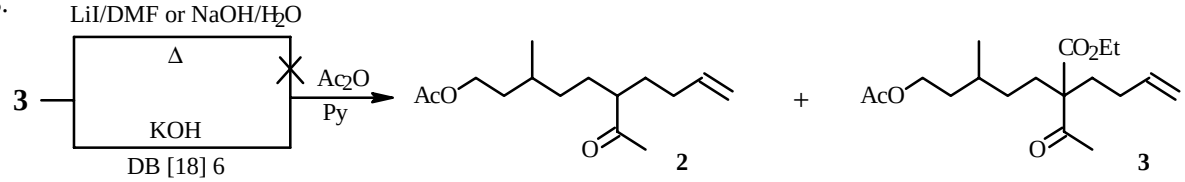
1) Institute of Organic Chemistry, Ufa Scientific Center, Russian Academy of Sciences, 450054, Ufa, pr. Oktyabrya, 71, fax (3472) 35 60 66, e-mail: kharis@anrb.ru; 2) N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Division, Russian Academy of Sciences, 630090, Novosibirsk, pr. Akad. Lavrent′eva, 9. Translated from Khimiya Prirodnykh Soedinenii, No. 6, pp. 589-591, November-December, 2005. Original article submitted February 28, 2005.

0009-3130/05/4106-0715

Chiral acetoxymesylate **6** was used for an entry to (3*S*)-**3** in the approach to optically active (3*S*)-**1**. It was prepared by simple transformations of an acetalalcohol (**8**), which is available from (*R*)-4-menthenone (**7**) [12], by the pathway (**9**) → (**10**) → (**6**). The best result (63%) for linking unsaturated ketoester **11** [13] and **6** was obtained if dibenzo-18-crown-6 (DB18C6) was used as a catalyst.



The high stability of acetoacetic ester **3** made its decarbethoxylation problematical. Thus, whereas this process is usually successfully completed by boiling in DMF in the presence of LiI [14], in our instance even the standard workup in aqueous base [15] was not successful. This was probably due to signficant steric hindrances arising upon hydrolysis of the carbethoxy group. Only the use of KOH under interphase catalysis conditions produced in low yield a difficultly separated mixture (3:2) of **2** and **3** after acylation of the isolated intermediate. An analogous situation was observed for chiral precursor (3*S*)-**3**.



EXPERIMENTAL

General comments have been published [12].

(*S*)-5,5-Dimethoxy-1-mesyloxy-3-methylpentane (9). (*S*)-5,5-Dimethoxy-3-methylpentan-1-ol (**8**, 3.80 g, 20.0 mmol) [12] and absolute Et_3N (4.2 mL) in dry CH_2Cl_2 was stirred (0°C, Ar), treated with MsCl (2.75 g, 24.1 mmol), stirred for 1 h at 0°C, diluted with *t*-BuOMe (100 mL), washed successively with H_2O and saturated $CuSO_4$, $NaHCO_3$, and NaCl solutions, dried over Na_2SO_4, and evaporated to afford **9** (3.43 g, 97%), which was used without further purification.

IR spectrum (ν, cm^{-1}): 1470, 1390 (CH_3–C), 1340, 1185 (S=O), 1128, 1096, 1050, 960 (C–O).

(*S*)-1-Mesyloxy-3-methylpentan-5-ol (10). A solution of **9** (3.43 g, 14.3 mmol) in acetone (130 mL) and H_2O (3.8 mL) was treated successively with Py (0.29 g) and TsOH (0.66 g), boiled for 2 h, and evaporated in vacuo. The solid was dissolved in Et_2O (100 mL), washed successively with saturated NH_4Cl, $NaHCO_3$, and NaCl solutions, dried over Na_2SO_4, and evaporated. The solid was dissolved in MeOH (27 mL), treated with $NaBH_4$ (0.44 g, 11.6 mmol), held at <20°C, and stirred for 3 h. Solvent was evaporated in vacuo. The solid was treated successively with *t*-BuOMe (75 mL) and AcOH (3 mL, 10%). The aqueous layer was separated. The organic layer was washed with saturated NaCl solution, dried over K_2CO_3, and evaporated to afford **10** (2.26 g, 81%).

IR spectrum (ν, cm^{-1}): 3400 (O–H), 1114, 1048 (C–O), 1470, 1390 (CH_3–C), 1348, 1174 (S=O).

(*S*)-5-Acetoxy-1-mesyloxy-3-methylpentane (6). A mixture of **10** (2.26 g, 11.6 mmol), Ac_2O (21 mL), and Py (31.5 mL) was stirred for 3 h at 20°C, stored for 48 h, diluted with Et_2O (150 mL), washed successively with HCl (3%) and saturated $NaHCO_3$ and NaCl solutions, dried over Na_2SO_4, and evaporated to afford **6** (2.44 g, 88%).

IR spectrum (ν, cm^{-1}): 1745 (C=O), 1470, 1390 (CH_3–C), 1345, 1185 (S=O), 1250 (C–O–C), 1130 (C–O).

Ethyl Ester of 2-Acetyl-7-acetoxy-2-(3-butenyl)-5-methylheptanoic Acid (3). A suspension of NaH (0.34 g, 14.2 mmol) in absolute benzene (15 mL) and absolute DMF (15 mL) was stirred (Ar, 0°C), treated dropwise with ketodiester **4** (3.86 g, 14.2 mmol) [10], held at room temperature until the NaH compeltely dissolved (~3 h), cooled to 0°C, treated dropwise with bromide C (1.91 g, 14.2 mmol) stirred at room temperature for 11 h, boiled for 12 h, treated with H_2O (5 mL), and extracted with benzene (3 × 50 mL). The combined extracts were washed with H_2O, dried over $MgSO_4$, and evaporated. The solid was chromatographed (PE:Et_2O 5:1) to afford **3** (2.59 g, 56%).

IR spectrum (ν, cm^{-1}): 3080, 3020 (=C–H), 1745 (C=O), 1705 (C=O), 1630 (C=C), 1470, 1390 (CH_3–C), 1250 (C–O–C), 990, 920 (C=C).

PMR spectrum (δ, ppm, J/Hz): 0.90 (3H, m, CH_3C-5), 1.01-2.00 (11H, m, CH_2CH_2C=, H-3—H-6), 1.25 (3H, t, J = 7.1, $C\underline{H}_3CH_2O$), 2.03 (3H, s, CH_3CO), 2.12 (3H, s, CH_3CO_2), 4.00-4.16 (2H, m, H-7), 4.19 (2H, q, J = 7.1, $CH_3C\underline{H}_2O$), 4.92 (1H, d, J = 10.1, *cis*-H_2C=), 5.02 (1H, d, J = 17.4, *trans*-H_2C=), 5.65-5.85 (1H, m, HC=).

^{13}C NMR spectrum (δ, ppm): 13.98 (q, $\underline{C}H_3CH_2O$), 19.34 (q, $\underline{C}H_3$C-5), 20.90 (q, $\underline{C}H_3CO_2$), 26.56 (d, C-5), 28.01 (t, $\underline{C}H_2C$=), 28.37 (t, C-3), 29.65 (q, $\underline{C}H_3CO$), 30.73 (t, C-6), 31.44 (t, $\underline{C}H_2CH_2CH$=), 39.34 (t, C-4), 60.03 (s, C-2), 60.65 (t, C-7), 62.99 (t, $CH_3\underline{C}H_2O$), 114.98 (t, H_2C=), 137.43 (d, HC=), 170.99 (s, $CH_3\underline{C}O_2$), 172.35 (s, C-1), 205.25 (s, $CH_3\underline{C}O$).

Ethyl Ester of 2-Acetyl-7-acetoxy-2-(3-butenyl)-(5*S*)-methylpentanoic Acid (*S*)-(3). A suspension of NaH (0.45 g, 8.8 mmol) and DB18C6 (0.45 g, 1.5 mmol) in absolute toluene (13.5 mL) was stirred, treated dropwise with **11** (1.62 g, 8.8 mmol) [13] in absolute toluene (6 mL), stirred for 1 h at 20°C, treated with **6** (2.10 g, 8.8 mmol) in absolute toluene (6 mL), boiled with stirring for 17 h, and evaporated. The solid was dissolved in Et_2O (100 mL), washed with saturated KCl solution, dried over Na_2SO_4, and evaporated. The solid was chromatographed (PE:Et_2O 1:1) to afford (*S*)-**3** (1.80 g, 62.7%), the spectral characteristics of which were practically identical to those published for **3**.

Decarboxylation Method. A mixture of **3** (0.50 g, 1.5 mmol), KOH (0.09 g, 1.6 mmol), DB18C6 (0.45 g, 1.5 mmol), EtOH (0.75 mL), and benzene (15 mL) was boiled with stirring for 48 h, cooled, treated with Et_2O (50 mL), washed with saturated KCl solution, dried over Na_2SO_4, and evaporated. The solid was treated with Ac_2O (5 mL) and Py (7.5 mL), stirred at room temperature for 24 h, diluted with Et_2O (50 mL), washed successively with HCl (3%) and saturated $NaHCO_3$ and NaCl solutions, dried over Na_2SO_4, and evaporated to afford a mixture of **3** and **2** (0.21 g, 3:2 ratio according to GC) that was difficult to separate by chromatography.

IR spectrum (ν, cm^{-1}): 3080 (H–C=), 1745 (C=O), 1630 (C=C), 1470, 1390 (CH_3–C), 1255 (C–O–C), 990, 920 (C=C).

The ^{13}C NMR spectrum of **2** was obtained from the mixture with **3** (δ, ppm): 20.33 (q, $\underline{C}H_3$C-3), 21.02 (q, $\underline{C}H_3CO_2$), 26.82 (t, C-5), 27.96 (d, C-3), 29.68 (t, C-4), 30.31 (q, $\underline{C}H_3CO$), 31.75 (t, C-8), 32.75 (t, C-7), 35.19 (t, C-2), 52.42 (d, C-6), 62.80 (t, C-1), 115.04 (t, H_2C=), 137.89 (d, HC=), 172.46 (s, $CH_3\underline{C}CO_2$), 203.42 (s, $CH_3\underline{C}O$).

Decarboxylation of (*S*)-**3** proceeded analogously.

ACKNOWLEDGMENT

The work was supported financially by the Complex Program of the RAS Presidium "Directed Synthesis of Compounds with Given Properties and Creation of Functional Materials Based on Them" State Contract No. 36.

REFERENCES

1. W. L. Roelofs, M. J. Gieselmann, A. M. Carde, H. Tashiro, D. S. Moreno, C. A. Henrick, and R. J. Anderson, *Nature (London)*, **267**, 698 (1977).
2. R. J. Anderson, K. G. Adams, H. R. Chinn, and C. A. Henrick, *J. Org. Chem.*, **45**, 2229 (1980).
3. B. Snider and D. Rodini, *Tetrahedron Lett.*, 1399 (1978).
4. N. Carnieri, D. R. Kelly, W. Kugler, and A. A. Marcondes, *Agric. Biol. Technol.*, **36**, 421 (1993).
5. K. Panagiotis and N. Ragoussis, *Synthesis*, 644 (1995).
6. R. Baudouy and C. Maliverney, *Tetrahedron*, **44**, 471 (1988).
7. U. S. Pat. No. 4158096 (1979); *Chem. Abstr.*, **91**, 210909 (1979).
8. B. B. Snider and G. B. Phillips, *J. Org. Chem.*, **48**, 464 (1983).

9. V. A. Dragan, V. V. Veselovskii, and A. M. Moiseenkov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1143 (1989).
10. G. Yu. Ishmuratov, M. P. Yakovleva, A. V. Galyautdinova, L. V. Faifer, R. Ya. Kharisov, V. V. Zorin, and G. A. Tolstikov, *Khim. Prir. Soedin.*, 413 (2001).
11. V. N. Odinokov, G. Yu. Ishmuratov, R. Ya. Kharisov, S. I. Lomakina, and G. A. Tolstikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1923 (1989).
12. R. Ya. Kharisov, R. R. Gazetdinov, G. Yu. Ishmuratov, and G. A. Tolstikov, *Khim. Prir. Soedin.*, 122 (2001).
13. A. A. Vasil′ev, A. L. Vlasyuk, G. V. Kryshtal′, and E. P. Serebryakov, *Izv. Akad. Nauk, Ser. Khim.*, 2026 (1995).
14. G. A. Tolstikov, M. S. Miftakhov, and F. A. Valeev, *Zh. Org. Khim.*, **17**, 1441 (1981).
15. V. N. Odinokov, G. Yu. Ishmuratov, L. P. Botsman, R. R. Vakhidov, I. M. Ladenkova, T. A. Kargapol′tseva, and G. A Tolstikov, *Khim. Prir. Soedin.*, 423 (1992).