

L-(-)-MENTHOL IN THE SYNTHESIS OF KEY SYNTHONS FOR OPTICALLY ACTIVE METHYL-BRANCHED INSECT PHEROMONES

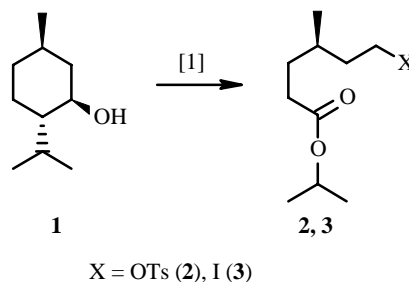
G. Yu. Ishmurov,¹ M. P. Yakovleva,¹ V. A. Ganieva,²
D. V. Amirkhanov,¹ and G. A. Tolstikov¹

UDC 547.223+547.281+547.323
+547.295.226+547.596.2

A synthesis of optically active 4S-methylhexanal, 1-bromo-3S-methylheptane, and 1-bromo-3S-methylundecane, which are key synthons for several methyl-branched insect pheromones, that is based on chemically selective transformations of 6-tosyloxy- and 6-iodoisopropyl-4R-methylhexanoates that are available from L-(-)-menthol was proposed.

Key words: L-(-)-menthol, 6-tosyloxy- and 6-iodoisopropyl-4R-methylhexanoates, 4S-methylhexanal, 1-bromo-3S-methylheptane, 1-bromo-3S-methylundecane, insect pheromones, synthon, synthesis.

We previously reported the synthesis of chiral synthons 6-tosyloxy- (**2**) and 6-iodo- (**3**) isopropyl-4R-methylhexanoates from L-(-)-menthol (**1**) [1]. These were used in the present work to synthesize optically pure 4S-methylhexanal (**5**), 1-bromo-3S-methylheptane (**11**), and 1-bromo-3S-methylundecane (**12**), which are key intermediates for the alarm pheromone of ants of the *Crematogaster* and *Myrmica* genera (**6**), sex pheromones of the peach leafminer *Lyonetia clerkella* (**13**), and pine sawflies of the *Diprion* and *Neodiprion* genera (**14**), respectively. The syntheses of these were also reported [2].

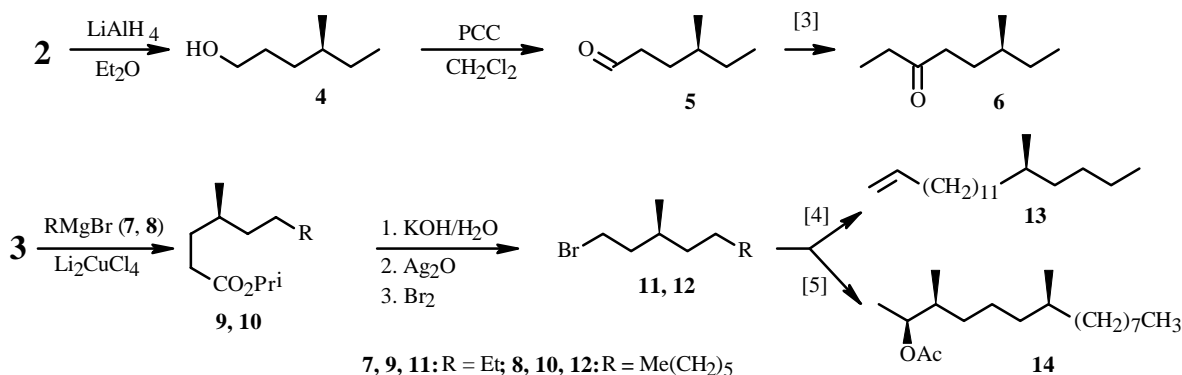


In order to prepare 4S-methylhexanal (**5**), tosyloxyester **2** was converted by hydride reduction, which occurred at both esters, into 4S-methylhexan-1-ol (**4**), which was oxidized further by the Corey method. The resulting aldehyde (**5**) was transformed into the pheromone (**6**) by the literature method [3].

Compounds **11** and **12** were synthesized using catalyzed cross-coupling of the iodoester (**3**) with Grignard reagents **7** and **8**, which were generated from ethyl- or *n*-hexylbromides, to give the isopropyl ester of 4S-methyloctanoic (**9**) or 4S-methyldodecanoic (**10**) acid, respectively. Alkaline hydrolysis of esters **9** and **10** with subsequent Hunsdiecker reaction of the resulting acids produced 1-bromo-3S-methylheptane (**11**), which was converted to the sex pheromone of the peach leafminer (**13**) as before [4], and 1-bromo-3S-methylundecane (**12**), a key synthon for the sex pheromone of pine sawflies (**14**) [5], respectively.

Thus, the proposed synthesis of optically pure 4S-methylhexanal, 1-bromo-3S-methylheptane, and 1-bromo-3S-methylundecane, which are key synthons for several methyl-branched insect pheromones, is based on chemically selective transformations of 6-tosyloxy- and 6-iodoisopropyl-4R-methylhexanoates, which are available from L-(-)-menthol.

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) Birk State Social-Pedagogical Academy, 452320, RF, Birk, ul. Internatsional'naya, 10. Translated from *Khimiya Prirodnikh Soedinenii*, No. 6, pp. 592-593, November-December, 2005. Original article submitted July 29, 2005.



EXPERIMENTAL

General comments have been published [1].

4S-Methylhexan-1-ol (4). A solution of **2** (4.00 g, 11.7 mmol), which was prepared as before [1], in absolute Et₂O (24 mL, Ar, 0°C) was treated with LiAlH₄ (1.32 g, 34.7 mmol), stirred at the same temperature for 1 h, decomposed with H₂O (4 mL), diluted with Et₂O (120 mL), and filtered. The filtrate was washed with saturated NaCl solution, dried over MgSO₄, and evaporated to afford **4** (0.98 g, 72%), $[\alpha]_D^{20} +8.54^\circ$ (*c* 5.3, CDCl₃), lit. [6] $[\alpha]_D^{20} +8.62^\circ$ (*c* 3.7, CDCl₃). IR and PMR spectra were identical to those in the literature [7].

4S-Methylhexanal (5). A suspension of PCC (2.89 g, 13.4 mmol) in dry CH₂Cl₂ (31 mL, Ar, 20°C) was treated in one portion with a solution of **4** (0.95 g, 9.1 mmol) in dry CH₂Cl₂ (7 mL), held at the same temperature for 1.5 h, diluted with Et₂O (40 mL), and filtered through a layer of Al₂O₃ (5 cm). The filtrate was evaporated to afford **5** (0.86 g, 92%). The IR and NMR spectra were identical to those in the literature [3].

Isopropyl-4S-methyloctanoate (9). A solution of **3** (7.70 g, 25.8 mmol), prepared as before [1], was treated (Ar, -10°C) with Li₂CuCl₄ in absolute THF (10 mL, 0.1 M) and Grignard reagent **7**, which was generated from EtBr (5.30 g, 49 mmol) and Mg (1.30 g, 54 mg-at) in absolute THF (90 mL), held at the same temperature for 6 h, decomposed by saturated NH₄Cl solution (50 mL), extracted with Et₂O (3 × 70 mL), washed with saturated NaCl solution, dried over MgSO₄, and evaporated. The solid was chromatographed over SiO₂ (PE:MTBE 20:1) to afford **9** (2.18 g, 54%), $[\alpha]_D^{20} +4.13^\circ$ (*c* 2.6, CHCl₃).

IR spectrum (KBr, *v*, cm⁻¹): 1740 (C=O).

PMR spectrum (CDCl₃, δ , ppm, J/Hz): 0.84 (3H, t, J = 6, H-8), 0.90 (3H, d, J = 6, CH₃-4), 1.19 [6H, d, J = 6, CH(CH₃)₂], 1.50 (9H, m, H-3—H-7), 2.25 (2H, m, H-2), 4.97 [1H, septet, J = 6.3, CH(CH₃)₂].

¹³C NMR spectrum (CDCl₃): 19.10 (q, C-8), 21.03 (q, CH₃-4), 21.67 [q, CH(CH₃)₂], 29.53 (d, C-4), 31.28, 31.85, 32.33, 35.22 (all t, C-3, C-5—C-7), 62.73 (t, C-2), 67.51 [d, CH(CH₃)₂], 173.30 (s, C-1).

1-Bromo-3S-methylheptane (11). A solution of **9** (2.40 g, 12.0 mmol) and KOH (1.60 g, 29.0 mmol) in MeOH (10 mL) and H₂O (2 mL) was boiled and evaporated. The solid was dissolved in H₂O (23 mL) and treated with a solution of AgNO₃ (2.04 g, 12.0 mmol) in hot H₂O (60°C, 8 mL). The solid was filtered off and dried in vacuo (10-15 mm Hg) at 100°C to produce the silver salt (2.52 g), which was suspended in CCl₄ (15 mL), treated dropwise with stirring with Br₂ (1.82 g, 11.5 mmol) in CCl₄ (4 mL), held at room temperature for 2 h, and then boiled (until CO₂ evolution was complete). The solid was filtered off. The filtrate was evaporated. The solid was chromatographed (SiO₂, hexane) to afford **11** (1.66 g, 83%), $[\alpha]_D^{21} +7.42^\circ$ (*c* 3.7, CHCl₃), lit. [4] $[\alpha]_D^{21} +3.71^\circ$ (*c* 3.3, CHCl₃) (ee ~50%). IR and PMR spectra were identical to those in the literature [4].

Isopropyl-4S-methyldodecanoate (10). A solution of **3** (5.77 g, 15 mmol), which was prepared as before [1], was treated (Ar, -10°C) with Li₂CuCl₄ in absolute THF (0.8 mL, 0.1 M) and Grignard reagent, which was generated from *n*-hexylbromide (6.06 g, 37 mmol) and Mg (0.98 g, 40 mg-at) in absolute THF (67 mL), held at the same temperature for 6 h, decomposed with saturated NH₄Cl solution (40 mL), extracted with Et₂O (4 × 50 mL), washed with saturated NaCl solution, dried over MgSO₄, and evaporated. The solid was chromatographed over SiO₂ (PE:MTBE 20:1) to afford **10** (1.61 g, 42%), $[\alpha]_D^{20} +2.50^\circ$ (*c* 0.4, CHCl₃).

IR spectrum (KBr, ν , cm^{-1}): 1745 (C=O).

PMR spectrum (C_6D_6 , δ , ppm, J/Hz): 0.69 (6H, m, CH_3 -4, H-12), 1.06 [6H, d, $J = 6$, $\text{CH}(\text{CH}_3)_2$], 1.31 (17H, m, H-3—H-11), 2.13 (2H, m, H-2), 5.20 [1H, septet, $J = 6.2$, $\text{CH}(\text{CH}_3)_2$].

^{13}C NMR spectrum (C_6D_6): 19.02 (q, C-12), 20.55 (q, CH_3 -4), 21.83 [q, $\text{CH}(\text{CH}_3)_2$], 23.55 (t, C-11), 27.77 (t, C-6), 28.72, 29.32, 29.62 (all t, C-7—C-9), 29.82 (d, C-4), 31.72, 32.04, 32.30 (all t, C-2, C-3, C-10), 35.45 (t, C-5), 67.27 [d, $\text{CH}(\text{CH}_3)_2$], 173.85 (s, C-1).

1-Bromo-3S-methylundecane (12). A solution of **10** (1.60 g, 6.3 mmol) and KOH (0.85 g, 15 mmol) in MeOH (10 mL) and H_2O (1 mL) was boiled for 4 h and evaporated. The solid was dissolved in H_2O (16 mL) and treated with AgNO_3 (1.07 g, 6.3 mmol) in hot water (60°C , 7 mL). The solid was filtered off and dried in vacuo (10–15 mm Hg) at 100°C to produce the silver salt (1.80 g), which was suspended in CCl_4 (11 mL), treated dropwise with stirring with Br_2 (0.90 g, 6.0 mmol) in CCl_4 (3 mL), and worked up as above for **11**. The solid was chromatographed (SiO_2 , hexane) to afford **12** (1.18 g, 85%), $[\alpha]_{\text{D}}^{23} +4.02^\circ$ (c 4.4, hexane), lit. [5] $[\alpha]_{\text{D}}^{21} +4.04^\circ$ (c 4.5, hexane). IR and PMR spectra were identical to those in the literature [5].

REFERENCES

1. G. Yu. Ishmurov, M. P. Yakovleva, V. A. Ganieva, R. R. Muslukhov, and G. A. Tolstikov, *Khim. Prir. Soedin.*, 33 (2005).
2. G. Yu. Ishmurov, M. P. Yakovleva, R. Ya. Kharisov, and G. A. Tolstikov, *Usp. Khim.*, 1095 (1997).
3. Y. Naoshima, D. Hayashi, and M. Ochi, *Agric. Biol. Chem.*, **52**, 1605 (1988).
4. V. N. Odinkov, G. Yu. Ishmurov, R. Ya. Kharisov, E. P. Serebryakov, and G. A. Tolstikov, *Khim. Prir. Soedin.*, 714 (1992).
5. T. Kikukawa, M. Imaida, and A. Tai, *Bull. Chem. Soc. Jpn.*, **57**, 1954 (1984).
6. K. Mori, S. Kuwahara, H. Z. Levinson, and A. R. Levinson, *Tetrahedron*, **38**, 2291 (1982).
7. K. Mori, T. Suguro, and M. Uchida, *Tetrahedron*, **34**, 3119 (1978).