Chemistry of Natural Compounds, Vol. 46, No. 3, 2010

(*R*)-4-MENTHEN-3-ONE IN THE SYNTHESIS OF (3*S*)-METHYLUNDEC- AND (2*S*)-METHYLDEC-1-YLBROMIDES, KEY SYNTHONS FOR (*S*,*S*,*S*)-DIPRIONYLACETATE

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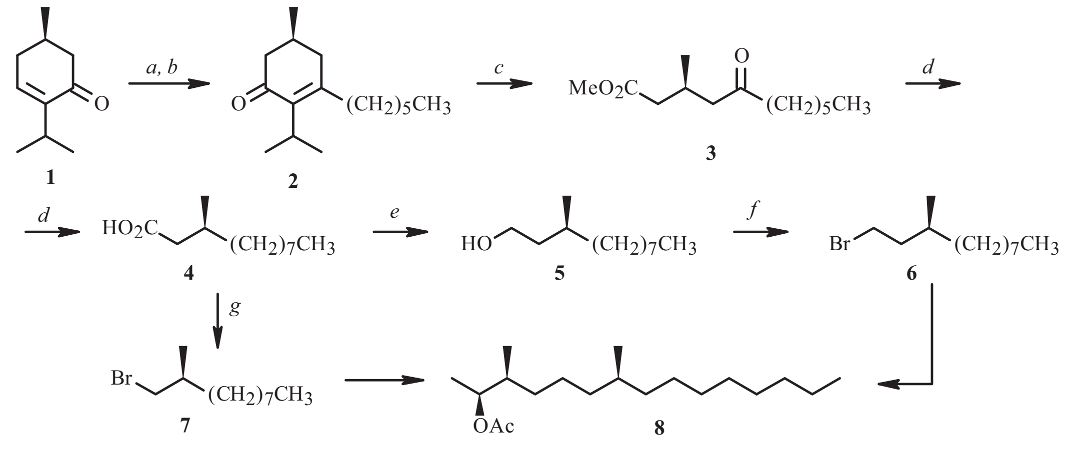
UDC 542.943.5+542.957+547.596

*New capabilities for the synthetic use of (*R*)-4-menthen-3-one were demonstrated using as examples (3*S*)-methylundec- and (2*S*)-methyldec-1-ylbromides, key synthons for (*S,S,S*)-diprionylacetate (sex pheromone of pine sawflies of genera* Diprion *and* Neodiprion*).*

Keywords: (*R*)-4-menthen-3-one, (5*S*)-methyl-2-isopropyl-3-hexyl-2-cyclohexen-1-one, (3*S*)-methyl-5-oxoundecanoic acid methyl ester, (3*S*)-methylundecanoic acid, (3*S*)-methyl-1-undecanol, 1-bromo-3*S*-methylundecane, 1-bromo-2*S*-methyldecane, (*S*,*S*,*S*)-diprionylacetate.

We have previously demonstrated the capabilities for the synthetic use of (*R*)-4-menthen-3-one (**1**), which is available from *l*-menthol, that were connected with the capability of conjugated enones for selective 1,2-addition of organometallic reagents with subsequent rearrangement of the resulting tertiary allyl alcohols through the action of Cr(VI) [3, 4] using as examples (14*S*)-methyloctadec-1-ene [1], a sex pheromone of the peach leafminer moth *Lyonetia clerkella*, and (*R*)-3-methyl-γ-butyrolactone, a synthon for optically active vitamins E and K, in addition to the terpene dolichol and its analogs [2].

Herein this synthetic approach is expanded using as examples (3*S*)-methylundec-1-ylbromide (**6**) and (2*S*)-methyldec-1-ylbromide (**7**), key synthons [5, 6] for (*S*,*S*,*S*)-diprionylacetate (**8**), a sex pheromone of pine sawflies of the genera *Diprion* and *Neodiprion*.



a. *n*-C_6H_{13}Li, hexane, –78°C; *b*. PCC, CH_2Cl_2; *c*. O_3, MeOH–CH_2Cl_2, 0°C; *d*. $N_2H_4{\cdot}H_2O$; then KOH, Δ; *e*. $LiAlH_4$; *f*. PBr_3/Py; *g*. [5]

Regioselective 1,2-addition of *n*-C_6H_{13}Li to enone **1** at –78°C and further work up of the intermediate enol with pyridinium chlorochromate (PCC) gave (5*S*)-methyl-2-isopropyl-3-hexyl-2-cyclohexen-1-one (**2**). Subsequent ozonolysis of **2** that occurred with loss of the isobutyl moiety and methanolysis led to ketoester **3**. Whereas a large excess of ozone is usually

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0009-3130/10/4603-0370

used for ozonolytic transformations of conjugated enones, an equimolar amount was sufficient for the complete transformation of **2**. Deoxygenation of **3** according to Huang–Minlon that was accompanied by saponification of the ester gave (3*S*)-methylundecanoic acid (**4**), which was converted by the standard method through alcohol **5** to bromide **6** or immediately to bromide **7**.

Thus, we demonstrated new synthetic capabilities of accessible (*R*)-4-menthen-3-one that included chemoselective transformations that did not affect the asymmetric center.

EXPERIMENTAL

IR spectra in thin layers were recorded on a Prestige-21 IR instrument (Shimadzu). NMR spectra in $CDCl_3$ were recorded on a Bruker AM-300 spectrometer (300.13 MHz operating frequency for ^1H; 75.47, ^{13}C). The internal standards were $CDCl_3$ resonances in the PMR spectrum of impurity protons in the deuterated solvent (δ 7.27 ppm); in the ^{13}C NMR spectrum, the average resonance of $CDCl_3$ (δ 77.00 ppm). Chromatography was carried out on Chrom-5 [column length 1.2 m; stationary phase silicone SE-30 (5%) + OV-225 (3%) on Chromaton N-AW-DMCS (0.16–0.20 mm); operating temperature 50–200°C] and GC-9A [Shimadzu, quartz capillary column length 25 m, stationary phase DB-1 (0.25 μm), operating temperature 80–280°C] instruments with He carrier gas. Optical rotation was measured on a Perkin–Elmer 241-MC polarimeter. Column chromatography was performed over silica gel L (60–200 μm, Lancaster, England). TLC used Sorbfil plates (Krasnodar). Mass spectra were obtained on a Shimadzu JCMS 2010 EV under APCI conditions at electron energy 20 eV in positive- and negative-ion modes. The nebulizer gas (N_2) flow rate was 0.05 L/min with $MeOH:H_2O$ (50:50) mobile phase at flow rate 0.03 mL/min.

(5*S*)-Methyl-2-isopropyl-3-hexyl-2-cyclohexen-1-one (2). A stirred solution of **1** (5.00 g, 32.9 mmol) in anhydrous hexane (40 mL, –78°C, Ar) was treated dropwise with a solution of $n\text{-}C_6H_{13}Li$ prepared from Li (1.84 g, 263.2 mg-atom) and $n\text{-}C_6H_{13}Br$ (21.71 g, 131.6 mmol) in anhydrous hexane (80 mL, Δ, Ar). The mixture was stirred for 6 h at –78°C. Then, the temperature was raised to 5°C. Saturated NH_4Cl solution (100 mL) was added. Stirring was continued for 1.5 h. The mixture was extracted with Et_2O (3 × 100 mL). The combined extracts were washed with saturated NaCl solution (until the pH was 7), dried over $MgSO_4$, and evaporated. The crude product [7.69 g; IR spectrum (KBr, ν, cm^{-1}): 3439 (O–H), 1654 (C=C)] was used without further purification in the next step by adding it in anhydrous CH_2Cl_2 (40 mL) with vigorous stirring to a suspension of PCC (14.06 g, 65.1 mmol) in anhydrous CH_2Cl_2 (65 mL, 5 –10°C, Ar). The mixture was stirred for 2 h at room temperature, treated with Et_2O (60 mL), stirred for another 15 min, filtered through a thin layer of Al_2O_3, and washed with Et_2O. The filtrate was evaporated. The solid (7.52 g) was chromatographed over a column of SiO_2 (PE) to afford **2** (5.86 g, 75%), the chemical purity of which according to GC was 99%, R_f 0.68 (PE:MTBE, 3:1), $[\alpha]_D^{21}$ +31.6° (*c* 0.6, CH_2Cl_2). IR spectrum (KBr, ν, cm^{-1}): 1612 (C=C), 1666 (C=O).

Mass spectrum (*m*/*z*, I_{rel}, %): 237 (100) $[M + H]^+$, 473 (0.6) $[2M + H]^+$, 321 (10.4), 153 (4.6).

PMR spectrum (300.13 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.85 (3H, t, J = 6.6, H-6″), 0.92 (3H, d, J = 6.8, CH_3-5), 1.12 (3H, d, J = 6.5, H-2′), 1.15 (3H, d, J = 6.5, H-3′), 1.15–1.34 (6H, m, H-3″, H-4″, H-5″), 1.30–1.42 (2H, m, H-2″), 1.88 (1H, dd, ^2J = 12.6, ^3J = 3.3, H_a-6), 1.98 (1H, dd, ^2J = 12.6, ^3J = 4.1, H_e-6), 2.03–2.14 (1H, m, H-5), 2.06–2.20 (2H, m, H-1″), 2.18 (1H, dd, ^2J = 12.5, ^3J = 4.3, H_a-4), 2.32 (1H, dd, ^2J = 12.5, ^3J = 2.6, H_e-4), 2.8 (1H, h, J = 6.5, H-1′).

^{13}C NMR spectrum (75.47 MHz, $CDCl_3$, δ): 13.97 (q, C-6″), 20.99 (q, C-2′), 21.16 (q, C-3′, CH_3-5), 22.52 (t, C-5″), 27.31 (d, C-1′), 28.15 (t, C-4″), 29.83 (d, C-5), 30.04 (t, C-3″), 31.62 (t, C-2″), 34.99 (t, C-1″), 40.14 (t, C-4), 47.51 (t, C-6), 139.34 (s, C-2), 157.33 (s, C-3), 199.54 (s, C-1).

(3*S*)-Methyl-5-oxoundecanoic Acid Methyl Ester (3). A solution of **2** (5.80 g, 24.5 mmol) in anhydrous MeOH (25 mL) and anhydrous CH_2Cl_2 (25 mL) at 0°C was purged with an O_3/O_2 mixture (ozonator production 35 mmol O_3/h) until the starting compound disappeared (TLC monitoring). The mixture was purged with Ar before adding TsOH (0.25 g) and anhydrous MeOH (40 mL), stirring at room temperature for 48 h, adding $NaHCO_3$ (3.0 g), and evaporating in vacuo. The solid was treated with Et_2O (200 mL), washed with saturated NaCl solution (until the pH was 7), dried over $MgSO_4$, and evaporated. The solid was chromatographed over a column of SiO_2 (PE) to isolate **3** (4.82 g, 86%), the chemical purity of which according to GC was 99%, R_f 0.53 (PE:MTBE, 3:1), $[\alpha]_D^{21}$ +3.2° (*c* 0.3, CH_2Cl_2). IR spectrum (KBr, ν, cm^{-1}): 1712 (C=O), 1735 (COOMe).

Mass spectrum (*m*/*z*, I_{rel}, %): 229 (100) $[M + H]^+$, 246 (12.3) $[M + H_2O]^+$, 197 (77.1) $[M – OCH_3]^-$, 169 (25.0) $[M – CO_2CH_3]^-$, 227 (76.0) $[M – H]^-$, 196 (100) $[M – H – OCH_3]^-$.

PMR spectrum (300.13 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.82 (3H, t, J = 7.0, H-11), 0.91 (3H, d, J = 6.5, CH_3-3), 1.15–1.28 (16H, m, H-7–H-10), 1.46 (2H, t, J = 7.6, H-6), 2.14 (1H, dd, ^2J = 14.0, ^3J = 7.0, H-2), 2.24 (1H, dd, ^2J = 14.1, ^3J = 7.3, H-4), 2.29 (1H, dd, ^2J = 14.0, ^3J = 7.2, H-2), 2.35–2.43 (1H, m, H-3), 2.42 (1H, dd, ^2J = 14.1, ^3J = 7.3, H-4), 3.6 (3H, s, OCH_3).

^{13}C NMR spectrum (75.47 MHz, $CDCl_3$, δ): 14.00 (q, C-11), 20.00 (q, CH_3-3), 22.46 (t, C-10), 26.27 (d, C-3), 31.56 (t, C-7 –C-9), 40.72 (t, C-6), 43.26 (t, C-4), 48.89 (t, C-2), 56.46 (q, OCH_3), 172.99 (s, C-1).

(3*S*)-Methylundecanoic Acid (4). Ketoester **3** (4.75 g, 20.8 mmol) was dissolved in diethyleneglycol (20 mL), treated dropwise with $N_2H_4 \cdot H_2O$ (3.94 g, 63.0 mmol, 80%) at 15°C, stirred for 2.5 h, left for 16 h at room temperature, treated with KOH (5.89 g, 105.3 mmol), and refluxed for 2 h. Water and the excess of hydrazine hydrate were distilled off by heating to 195°C and holding for another 4 h at this temperature. The mixture was cooled to room temperature and extracted with CH_2Cl_2 (3 × 50 mL). The aqueous layer was acidified with H_2SO_4 (10%) and extracted with CH_2Cl_2 (3 × 50 mL). The resulting extract was dried over $MgSO_4$ and evaporated to afford **4** [3.40 g; IR spectrum (KBr, ν, cm^{-1}): 1705, 3200-3600 (COOH)], which was used without further purification in the next step.

(3*S*)-Methyl-1-undecanol (5). A suspension of $LiAlH_4$ (0.76 g, 20.0 mmol) in anhydrous Et_2O (20 mL) was stirred at 0°C under Ar, treated with a solution of **4** (2.00 g, 10.0 mmol) in anhydrous Et_2O (10 mL), stirred for 2 h at room temperature, cooled to 0°C, treated with NaOH solution (4 mL, 7.5%), and stirred for 2 h. The organic layer was separated. The aqueous layer was extracted with Et_2O (3 × 30 mL). The extracts were combined with the organic layer, washed with saturated NaCl solution (until the pH was 7), dried over $MgSO_4$, and evaporated to afford **5** (1.70 g, 91%), $[\alpha]_D^{20}$ –3.45° (*c* 5.4, hexane) {lit. $[\alpha]_D^{20}$ –3.45° (*c* 5.4, hexane}. The IR and NMR spectra were identical with those reported earlier [6].

1-Bromo-3*S*-methylundecane (6). A stirred solution of **5** (1.65 g, 8.8 mmol) and dry Py (0.14 mL, 1.7 mmol) in anhydrous Et_2O (15 mL) was treated dropwise (–15°C, Ar) with PBr_3 (0.30 mL, 3.1 mmol), stirred (–15°C, 2 h; 20°C, 15 h), diluted with MTBE (100 mL), poured into icewater (40 mL), and extracted with MTBE (3 × 100 mL). The combined extracts were washed successively with saturated $NaHCO_3$ and NaCl solutions (until the pH was 7), dried over $MgSO_4$, and evaporated. The solid was chromatographed over SiO_2 (PE) to afford **6** (1.87 g, 85%), $[\alpha]_D^{20}$ +4.04° (*c* 5.0, hexane) {lit. $[\alpha]_D^{20}$ +4.04° (*c* 5.0, hexane)}. The IR and NMR spectra were identical to those reported earlier [5].

1-Bromo-2*S*-methyldecane (7). Acid **4** (1.35 g, 6.8 mmol) was used to prepare **7** (1.17 g, 87%), $[\alpha]_D^{20}$ +0.29° (lit. $[\alpha]_D^{20}$ +0.29°) according to the literature method [5]. The IR and NMR spectra were identical to those reported earlier [7].

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