SYNTHESIS OF 3*S*-METHYLUNDEC-1-YLBROMIDE, A KEY SYNTHON IN THE SYNTHESIS OF (*S*,*S*,*S*)-DIPRIONYLACETATE, FROM L-(-)-MENTHOL

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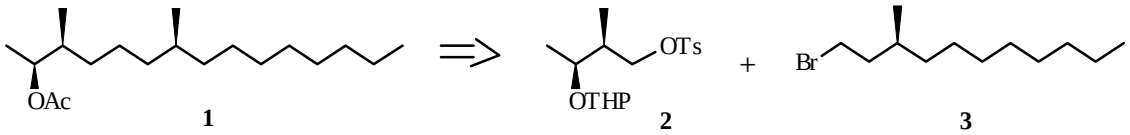
*Three new approaches to the synthesis of 1-bromo-3*S*-methylundecane, a key synthon in the synthesis of (*S,S,S*)-diprionylacetate, a sex pheromone of pine sawflies of the genera* Diprion *and* Neodiprion, *were proposed based on chemo- and stereoselective transformations of L-(-)-menthol derivatives.*

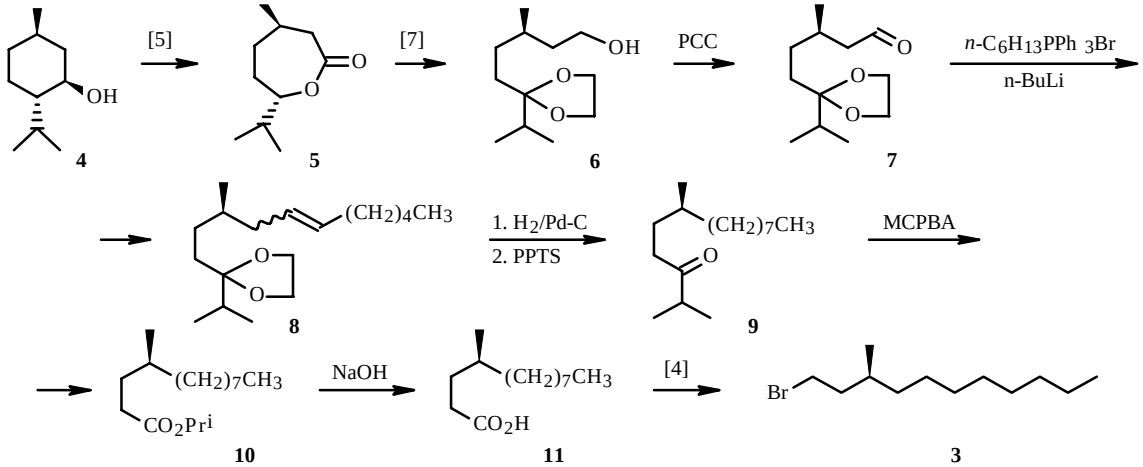
Key words: L-(-)-menthol, 3*R*-dimethyloctan-6*S*-olide (mentholactone), 4*R*-menthenone, 1-bromo-3*S*-methylundecane, 2*S*-acetoxy-3*S*,7*S*-dimethylpentadecane [(*S*,*S*,*S*)-diprionylacetate], synthon, pheromone, synthesis.

Optically active 2*S*-acetoxy-3*S*,7*S*-dimethylpentadecane [(*S*,*S*,*S*-diprionylacetate)] (**1**) is the most preferred attractant for many species of pine sawflies of the genera *Diprion* and *Neodiprion* [1]. All existing synthetic schemes for optically pure (*S*,*S*,*S*)-(**1**) are based on a convergent approach [1-3].



1 **2** **3**

Retrosynthetic analysis and the literature indicate that the optimal synthesis is based on two chiral synthons **2** and **3** [4]. However, the expensive and rare (*R*)-pulegone was used in it as the starting material for preparing optically pure building block **3**. Herein we report the synthesis of 1-bromo-3*S*-methylundecane (**3**) from the relatively inexpensive chiral starting material L-(-)-menthol (**4**). Three approaches were developed, two of which were based on transformations of 3*R*-dimethyloctan-6*S*-olide (mentholactone) (**5**), which was prepared from monoterpene **4** as before [5]. The third involved transformations of 4-menthenone (**15**), which is accessible from **4** by the literature method [6].



4 **5** **6** **7** **8** **9** **10** **11** **3**

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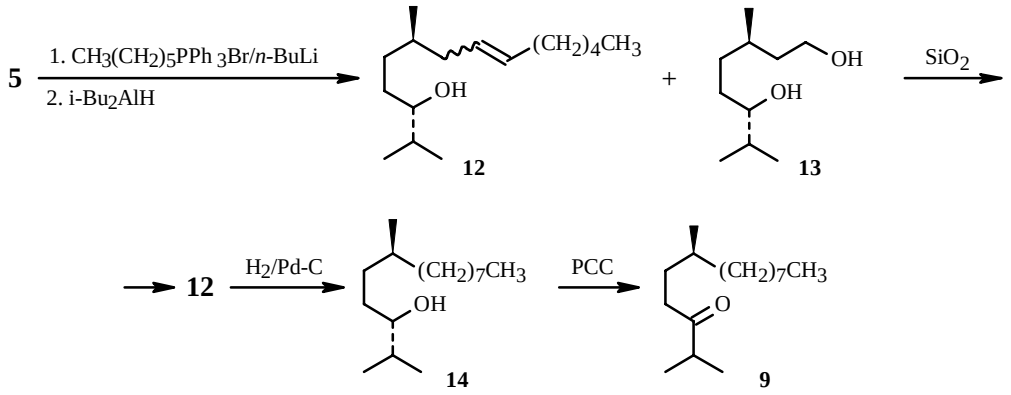
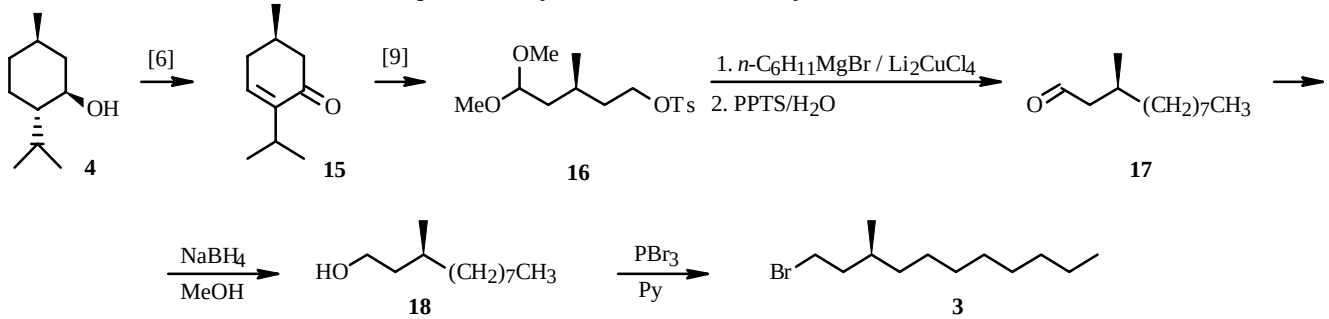
In the first approach, lactone **5** was transformed in four steps by the method previously developed by us [7] into hydroxyketal **6**, which was oxidized to the corresponding aldehyde **7** and converted to the olefin by a Wittig reaction to give (*Z*)-olefin **8** in 86% yield (according to GC and ^{13}C NMR, the content of the main stereoisomer was 78%). Catalytic hydrogenation of **8** and subsequent treatment with acid gave 2,6*S*-dimethyltetradecan-3-one (**9**). The C skeleton of **3** was further constructed using a series of conversions that did not affect the asymmetric center. These were regiospecific Baeyer—Villager oxidation of saturated ketone **9** to the isopropyl ester (**10**), saponification to acid **11**, and conversion of it to the desired bromide **3** using a Hunsdiecker reaction [4]. The overall yield of **3** was 24% calculated from starting **4**.

A shorter pathway for synthesizing **3** consisted of low-temperature reduction of lactone **5** by diisobutylaluminum hydride and conversion to the olefin using *n*-hexylidenetriphenylphosphorane accompanied by partial reduction of **5** into diol **13**. This reduces the yield of the desired unsaturated alcohol **12** to 58%.



Hydrogenation of the resulting (*Z*)-unsaturated alcohol **12** (content of main stereoisomer 75% according to GC and ^{13}C NMR) gave saturated analog **14**, which underwent Corey oxidation to isopropylketone **9**, which was converted to the desired bromide **3** by the transformations described above. The overall yield was 31% calculated for **4**.

The third approach was based on ozonolytic transformation of (*R*)-4-methenone (**15**) into tosyloxyacetal **16** as before [8, 9]. A cuprate catalyzed cross-coupling of **16** and a *n*-hexyl Grignard reagent followed by acid treatment gave aldehyde **17**, standard transformations of which completed the synthesis of **3** in overall yield 20% calculated for **4**.



The resulting chiral synthon **3** can be used to introduce asymmetric C-7 into (*S*,*S*,*S*)-**1** [4].

Thus, three new approaches to the synthesis of 1-bromo-3*S*-methylundecane, a key synthon in the synthesis of (*S*,*S*,*S*)-diprionylacetate, were proposed based on chemo- and stereoselective transformations of L-(-)-menthol derivatives.

EXPERIMENTAL

General comments have been published [10].

6,6-Ethylenedioxy-3*R*,7-dimethyloctanal (7). A suspension of pyridinium chlorochromate (1.12 g, 5.1 mmol) in dry CH_2Cl_2 (15 mL) was stirred (20°C, Ar), treated with a solution of **6** (0.70 g, 3.3 mmol) prepared from L-(-)-menthol (**4**) as before [5] in dry CH_2Cl_2 (9 mL), stirred for 2 h, diluted with Et_2O (20 mL), and filtered through a layer of SiO_2. The solid on the filter was washed with Et_2O (50 mL). The filtrate was evaporated to afford **8** (0.68 g, 98%), which was used without further purification in the next step. IR spectrum (KBr, ν, cm^{-1}): 2730, 1725 (C=O), 1190, 1105, 1085, 1040 (C–O).

3,3-Ethylenedioxy-2,6*R*-dimethyltetradec-8-ene (8). A suspension of $CH_3(CH_2)_5PPh_3Br$ (1.66 g, 3.9 mmol) in absolute THF (10 mL, -70°C, Ar) was treated dropwise with a solution of *n*-BuLi (6.2 mL, 4.1 mmol, 0.67 M) in hexane, held for 1 h at room temperature, cooled to -70°C, treated dropwise with a solution of **7** (0.67 g, 3.3 mmol) in absolute THF (4 mL), and held at -75°C for 15 min and 20°C for 48 h. The reaction mixture was poured into icewater (15 mL), extracted with Et_2O (3 × 30 mL), dried over $MgSO_4$, filtered, and evaporated. The solid was dissolved in hexane and filtered through a layer of Al_2O_3 to afford **8** (0.80 g, 86%).

IR spectrum (KBr, ν, cm^{-1}): 1640 (C=C).

PMR spectrum (C_6D_6, δ, ppm): 0.92 (12H, m, H-1, CH_3-2, CH_3-6, H-14), 1.40 (13H, m, H-2—H-6, H-11—H-13), 2.00 (4H, m, H-7, H-10), 4.10 (4H, m, $–CH_2–CH_2–$), 5.40 (2H, m, H-8, H-9).

2,6*S*-Dimethyltetradecan-3-one (9): a) Unsaturated ketal (3.50 g, 12.4 mmol) was hydrogenated in THF (95 mL) in the presence of Pd/C (4.8 mmol, 10%) at room temperature for 24 h. The reaction mixture was filtered and evaporated. The solid was dissolved in a mixture of acetone (100 mL) and H_2O (0.35 mL), treated successively with Py (0.23 g) and TsOH (0.57 g), boiled for 2 h, and evaporated in vacuo. The solid was dissolved in Et_2O (100 mL); washed successively with saturated solutions of NH_4Cl, $NaHCO_3$, and NaCl; dried over Na_2SO_4; filtered; and evaporated to afford **9** (2.50 g, 84%), $[\alpha]_D^{21}$ +2.1° (*c* 2.9, $CHCl_3$). IR spectrum (KBr, ν, cm^{-1}): 1717 (C=O).

PMR spectrum ($CDCl_3$, δ, ppm): 0.84 (6H, m, CH_3-6, H-14), 1.02 (6H, m, H-1, CH_3-2), 1.25 (16H, m, H-5, H-7—H-13), 1.95 (1H, m, H-6), 2.40 (1H, m, CH_2CO), 2.58 (1H, m, CHCO);

b) A suspension of PCC (4.16 g, 19 mmol) in dry CH_2Cl_2 (10 mL) at room temperature was treated dropwise with a solution of **14** (3.00 g, 12.4 mmol) in CH_2Cl_2 (6 mL), stirred for 2 h, diluted with Et_2O (10 mL), filtered through a layer of Al_2O_3, and evaporated to afford **9** (2.90 g, 96%) that was identical to that obtained in part **a**.

Isopropyl-4*S*-methyldodecanoate (10). A suspension of MCPBA (4.10 g, 11.8 mmol) in dry $CHCl_3$ (30 mL) at room temperature was treated dropwise with a solution of **9** (2.90 g, 12 mmol) in $CHCl_3$ (9 mL); stirred for 48 h; diluted with CH_2Cl_2 (250 mL); washed successively with saturated solutions of $NaHCO_3$, $Na_2S_2O_3$, and NaCl; dried over $MgSO_4$; and evaporated to afford the ester (2.53 g, 82%), $[\alpha]_D^{20}$ +2.50° (*c* 0.4, $CHCl_3$). IR spectrum (KBr, ν, cm^{-1}): 1745 (C=O).

PMR spectrum (C_6D_6, δ, ppm, J/Hz): 0.66 (6H, d, J = 6, H-12, CH_3-4), 1.06 [6H, d, J = 6, $CH(C\underline{H}_3)_2$], 1.31 (17H, m, H-3—H-11), 2.13 (2H, m, H-2), 5.20 [1H, septet, J = 6.2, $C\underline{H}(CH_3)_2$].

^{13}C NMR spectrum (C_6D_6): 19.02 (q, C-12), 20.55 (q, CH_3-4), 21.83 [q, $CH(\underline{C}H_3)_2$], 23.55 (t, C-11), 27.77 (t, C-6), 28.72, 29.32, 29.62 (all t, C-7—C-9), 29.72 (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, $\underline{C}H(CH_3)_2$], 173.85 (s, C-1).

4*S*-Methyldodecanoic Acid (11). A solution of **10** (2.45 g, 9.7 mmol) and KOH (1.30 g, 23 mmol) in MeOH (8 mL) and H_2O (1.2 mL) was boiled for 4 h. The solvent was evaporated. The solid was acidified with H_2SO_4 (10%), extracted with Et_2O (4 × 25 mL), dried over $MgSO_4$, and evaporated to afford **11** (1.85 g, 90%), $[\alpha]_D^{24}$ +0.63° (*c* 7.2, hexane), lit. [4] $[\alpha]_D^{24}$ +0.64° (*c* 5.3, hexane). The IR and PMR spectra were identical to those in the literature [4].

^{13}C NMR spectrum ($CDCl_3$): 14.36 (q, C-12), 19.58 (q, CH_3C-4), 23.28 (t, C-11), 27.61 (t, C-6), 30.04 (t, C-7, C-8), 30.32 (t, C-9), 31.95 (t, C-10), 32.55 (t, C-3, C-5), 32.98 (d, C-4), 37.39 (t, C-2), 175.56 (s, C-1).

1-Bromo-3*S*-methylundecane (3): a) Bromide **3** was prepared from **11** in 85% yield as before [4];

b) A stirred solution of **18** (2.54 g, 29.8 mmol) and dry Py (0.45 mL, 5.5 mmol) in absolute Et_2O (30 mL) was treated dropwise (-15°C, Ar) with PBr_3 (1.0 mL, 10.5 mmol), stirred at -15°C for 2 h and at 20°C for 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 solutions of $NaHCO_3$ and NaCl, dried over $MgSO_4$, and evaporated. The solid was chromatographed over SiO_2 (PE) to afford **3** (2.41 g, 71%), $[\alpha]_D^{20}$ +4.04° (*c* 5.0, hexane), lit. [4] $[\alpha]_D^{20}$ +4.04° (*c* 4.5 hexane). The IR and NMR spectra were identical to those in the literature [4].

2,6*R*-Dimethyltetradec-8-en-3*S*-ol (12) and 3*R*,7-Dimethyl-1,6*S*-octanediol (13). A suspension of $[CH_3(CH_2)_5PPh_3]Br$ (5.74 g, 13.4 mmol) in absolute THF (32 mL, -70°C, Ar) was treated dropwise with a solution of *n*-BuLi (12.3 mL, 1.17 M, 14.5 mmol) in hexane, held for 1 h at room temperature, cooled to -70°C, and treated successively dropwise with **5** (2.00 g, 11.5 mmol) in absolute THF (8 mL) and DIBAH in toluene (9.5 mL, 38.0 mmol, 73%). The reaction mixture was held at -70°C for 1 h and at 20°C for 16 h, decomposed by cold H_2O (38 mL), and filtered through a Schott filter. The filtrate was dried over Na_2SO_4, filtered, and evaporated. The solid was dissolved in MTBE and filtered through a layer of SiO_2 (5 cm). Chromatography over SiO_2 (PE:MTBE, 2:1) afforded **13** (1.60 g, 58%) and **14** (0.96 g, 38%).

2,6*R*-Dimethyltetradec-8-en-3*S*-ol (12). R_f 0.77 (PE:MTBE, 2:1), $[\alpha]_D^{24}$ -15.8° (*c* 1.01, $CHCl_3$).

IR spectrum (KBr, ν, cm^{-1}): 3500-3200 (OH), 1645 (C=C).

PMR spectrum ($CDCl_3$, δ, ppm): 0.90 (12H, m, H-1, CH_3-2, $C\underline{H}_3$-6, H-14), 1.44 (12H, m, H-2, H-4—H-6, H-11—H-13), 2.00 (4H, m, H-7, H-10), 3.33 (1H, m, H-3), 5.18 (1H, s, OH), 5.42 (2H, m, H-9, H-10).

3*R*,7-Dimethyl-1,6*S*-octanediol (13). R_f 0.10 (PE:ethylacetate, 7:3), $[\alpha]_D^{20}$ -10.3° (*c* 2.43, $CHCl_3$). IR, PMR, and NMR spectra were identical to those in the literature [10].

2,6*S*-Dimethyltetradecan-3*S*-ol (14). Unsaturated alcohol **13** (3.30 g, 13.8 mmol) was hydrogenated in absolute THF (105 mL) in the presence of Pd/C (5.3 mmol, 10%) for 24 h. The reaction mixture was filtered. The filtrate was evaporated to afford **13** (3.00 g, 91%).

IR spectrum (KBr, ν, cm^{-1}): 3500-3200 (OH).

PMR spectrum ($CDCl_3$, δ, ppm): 0.90 (12H, m, H-1, CH_3C-2, CH_3C-6, H-14), 1.26 (18H, m, H-4, H-5, H-7—H-13), 1.48 and 1.66 (2H, m, H-6, H-2), 3.30 (1H, br.s, OH), 3.48 (1H, m, H-3).

^{13}C NMR spectrum ($CHCl_3$, δ, ppm): 14.13 (q, C-14), 16.99, 19.01 (both q, C-1, CH_3-2), 19.82 (q, CH_3-6), 22.74 (t, C-13), 27.12 (t, C-8), 29.43, 29.75, 30.07 (all t, C-9—C-11), 31.77, 32.00, 33.04 (all t, C-4, C-5, C-12), 33.30, 33.41 (both d, C-2, C-6), 37.00 (t, C-7), 65.88 (d, C-3).

(*S*)-3-Methylundecanal (17). A solution of **16** that was prepared from L-(-)-menthol as before [6, 8, 9] in absolute THF (25 mL) was added dropwise (-75°C, Ar) to a stirred solution of Grignard reagent prepared from *n*-hexylbromide (4.56 g, 28.0 mmol) and Mg (0.74 g, 30.8 mg-at) in absolute Et_2O (16 mL). A solution of Li_2CuCl_4 in THF (0.50 mL, 0.2 M) was added. The reaction mixture was stirred at -70°C for 1 h, at -10°C for 2 h, and at 25°C for 2 h, poured into a cold solution of saturated NH_4Cl, and extracted with Et_2O (3 × 50 mL). The combined extracts were washed successively with saturated solutions of NaCl, $NaHCO_3$, and NaCl, and evaporated. The solid was dissolved in a mixture of acetone (200 mL) and H_2O (0.7 mL) and treated successively with Py (0.47 g) and TsOH (1.13 g). The reaction mixture was boiled for 2 h and evaporated in vacuo. The solid was dissolved in Et_2O (150 mL); washed successively with saturated solutions of NH_4Cl, $NaHCO_3$, and NaCl; dried over Na_2SO_4; and evaporated to afford **17** (2.93 g, 78%), $[\alpha]_D^{20}$ -13.80° (*c* 5.1, $CHCl_3$).

IR spectrum (KBr, ν, cm^{-1}): 2730 (H–CO), 1725 (C=O).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.91 (6H, m, CH_3), 1.35 (15H, m, CH_2, CH), 2.23 (2H, m, CH_2CO), 9.72 (1H, t, J = 2.0, CHO).

(*S*)-3-Methylundecanol (18). A solution of **17** (2.93 g, 15.9 mmol) in MeOH (35 mL) was stirred, treated with $NaBH_4$ (0.60 g, 15.9 mmol), held below 20°C, and stirred for 3 h at room temperature. The MeOH was evaporated. The solid was dissolved in MTBE and H_2O acidified with several drops of AcOH, washed with saturated NaCl solution, dried over Na_2SO_4, and evaporated to afford **18** (2.54 g, 87%), $[\alpha]_D^{20}$ -3.45° (*c* 5.4, hexane), lit. [11] $[\alpha]_D^{20}$ -3.50° (*c* 5.1, hexane). IR and NMR spectra were practically identical to those in the literature [11].

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