Synthesis of *S*-(+)-methoprene

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An optically active juvenile hormone analogue, *S*-(+)-methoprene (**1**), is synthesized in six steps from technical grade *S*-(+)-3,7-dimethyl-1,6-octadiene ("(+)-dihydromyrcene", e.e. ~50%) by a novel procedure which begins with selective hydroalumination-oxidation to give *S*-(−)-citronellol. This alcohol is oxidized to give *S*-(−)-citronellal which on reaction with allylmagnesium chloride affords 6*S*,10-dimethyl-1,9-undecadien-4*R*/*S*-ol (**5**). Smidt-Moiseev oxygenation of **5** followed by dehydration leads to 6*S*,10-dimethyl-3*E*,9-undecadien-2-one. The latter on treatment with isopropoxyethynylmagnesium bromide is transformed into isopropyl 3,7*S*,11-trimethyl-2*E*/*Z*,4*E*,10-dodecatrienoate which upon Brown solvomercuration-reduction in MeOH gives **1** in 14% overall yield.

Key words: *S*-(+)-methoprene, synthesis; *S*-(+)-3,7-dimethyl-1,6-octadiene, hydroalumination; 6*S*,10-dimethyl-1,9-undecadien-4*R*/*S*-ol, Smidt oxygenation; isopropyl 3,7*S*,11-trimethyl-2*E*/*Z*,4*E*,10-dodecatrienoate, methoxylation at C(11).

Optically active isopropyl 11-methoxy-3,7*S*,11-trimethyl-2,4-dodecatrienoate [*S*-(+)-methoprene, **1**], a potent juvenile hormone analogue, was earlier obtained by the Horner-Emmons reaction of dialkyl 3-isopropoxycarbonyl-2-methyl-2-propenylphosphonates with *S*-(−)-methoxycitronellal of varying optical purity,[1,2] prepared from *S*-(−)-pulegone,[1] *S*-(−)-citronellol,[1,2] and *S*-(+)-3,7-dimethyl-1,6-octadiene (**2**).[3]

We propose an alternative route to **1** starting from the industrially available [4] hydrocarbon **2**. Its reaction with triisobutylalane takes place chemo- and regioselectively at the terminal double bond to give, on subsequent oxidation of the resulting hydroalumination product, *S*-(−)-citronellol (**3**) (*cf.*[5,6]) which is further oxidized to *S*-(−)-citronellal (**4**) with pyridinium chlorochromate. The addition of allylmagnesium chloride to **4** affords 6*S*,10-dimethyl-1,9-undecadien-4*R*/*S*-ol (**5**), a novel intermediate for the synthesis of *S*-(+)-methoprene. This diolefin is subjected to Smidt-Moiseev oxygenation of the terminal double bond ($O_2/PdCl_2$—CuCl/H_2O—DMF) and the resulting β-hydroxy ketone (**6**) is dehydrated, without isolation, to give 6*S*,10-dimethyl-3*E*,9-undecadien-2-one (**7**). The structure of **7** follows from characteristic absorbtion at 1690 and 1710 cm^{-1} in its IR spectrum and from the signals in the ^1H NMR spectrum at δ 2.06 (s, 3 H, CH_3CO), 5.87 (d, 1 H, $J_{3,4}$ = 16 Hz, H—C(3)), and 6.58 (dt, 1 H, $J_{3,4}$ = 16 Hz, $J_{4,5}$ = 8 Hz, H—C(4)), revealing the presence of an *E*-configured —CH=CH—COMe grouping.

In analogy to ref.[7], enone **7** on treatment with isopropoxyethynylmagnesium bromide followed by acid-catalyzed transposition is transformed into isopropyl 3,7*S*,11-trimethyl-2,4,10-dodecadienoate (**8**). This product consists of two geometric isomers (2*E*,4*E* and 2*Z*,4*E*) in ~7:3 ratio (GC data), the 2*E*,4*E*-isomer prevailing. This is evident from the ratio of integral intensities of the singlets due to the Me—C(3) groups at δ 2.26 and 1.98 (2*E*- and 2*Z*-isomers, respectively).[8] Methoxylation of compound **8** by means of solvomercuration in MeOH followed by reductive demercuration occurs selectively at the isolated Δ^{10} bond and, in accordance with ref.[8], affords *S*-(+)-methoprene (**1**). The overall yield of **1** from **2** by this route amounts to 14%.

Experimental

IR spectra were recorded with a UR-20 spectrophotometer (in films). ^1H NMR spectra were obtained at 60 MHz with a Tesla BS-467 (in CCl_4, for compounds **4**, **6**), or at 100 MHz with a Tesla BS-567 instrument (in $CDCl_3$, for compounds **1**, **5**, **7**, **8**). Chemical shifts are reported in ppm downfield from tetramethylsilane as the internal standard. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. GC-analyses were performed with a Chrom-5 instrument using an SE-30 (5%)/Chromaton N-AW-DMCS (0.16—0.20 mm) column (helium as carrier gas, temperature range from 50 to 300°C). For TLC analyses Silufol plates with fixed SiO_2 layer were used.

***S*-(−)-3,7-Dimethyl-6-octenal (4).** To a stirred suspension of pyridinium chlorochromate (9.27 g, 43 mmol) in 100 ml of abs. CH_2Cl_2 (20°C, under Ar) a solution of alcohol **3** (prepared from **2** according to ref.[6], 4.50 g, 28.8 mmol) in 21 ml of abs. CH_2Cl_2 was added. After 2 h of stirring, the reaction mixture was diluted with 280 ml of Et_2O and filtered through a layer of SiO_2. The precipitate on the filter was washed with Et_2O (300 ml) and the combined filtrates were evaporated. The residue was chromatographed (SiO_2, CH_2Cl_2 as eluent) to afford aldehyde **4**, $[\alpha]_D^{21}$ −6.47° (*c* 7.1, EtOH) (*cf.* [9]). Yield 3.77 g (85%). IR and H^1 NMR spectra are identical to those reported earlier.[10]

6*S*,10-Dimethyl-1,9-undecadien-4*R*/*S*-ol (5). To 1.05 g of magnesium (43.8 mmol, activated with I_2) in 3 ml of abs. Et_2O a few droplets of allyl chloride were added. Then a solution of aldehyde **4** (2.82 g, 18.3 mmol) and CH_2=$CHCH_2Cl$ (2.80 g, 36.6 mmol) in abs. Et_2O (18 ml) was slowly introduced at a rate sufficient to keep the reaction mixture boiling slightly. After 15 h of stirring at 20°C it was cooled to 5°C, quenched with saturated aqueous NH_4Cl (10 ml), stirred for 15 min, and extracted with Et_2O (3×100 ml). The extract was washed with saline, dried (Na_2SO_4), and evaporated. The residue was chroma-

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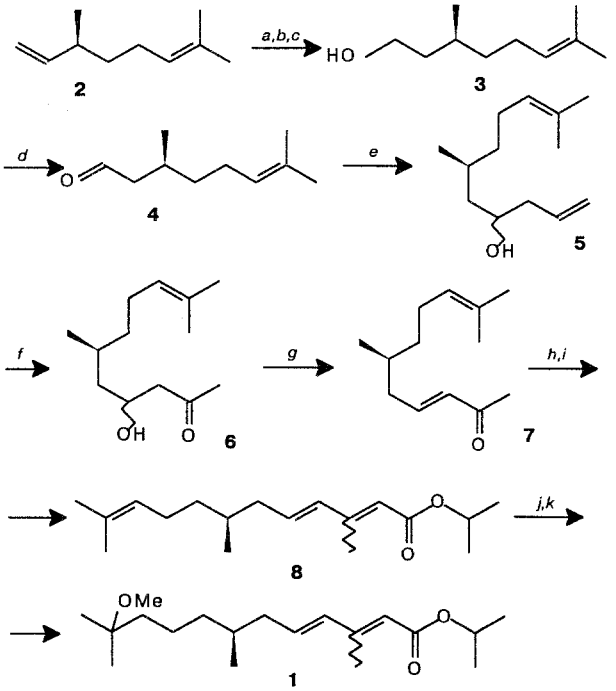
tographed on SiO_2 (elution with hexane — Et_2O, 4:1) to give compound **5**, n_D^{21} 1.4671, $[\alpha]_D^{21}$ +2.83° (*c* 8.00, $CHCl_3$). Yield 3.01 g (79%). Found: C 79.52; H 12.34. Calcd. for $C_{13}H_{24}O$: C 79.53; H 12.32%. IR spectrum (ν, cm^{-1}): 840, 930, 1010 (=C—H), 1060 (C—O), 1645 (C=C), 3090 (=C—H). ^1H NMR spectrum (δ, CCl_4, *J*, Hz): 0.91 (d, 3H, *J* = 6); 1.04—1.55 (m, 5H, CH_2, CH); 1.60 and 1.67 (s, 6H, CH_3C=C); 1.83—2.14 (m, 4H, H_2CC=C); 3.62—4.00 (m, 1H, H—C—O); 5.00—5.35 (m, 3H, H_2C-1 and HC-9); 5.65—6.20 (m, 1H, HC-2).

6*S*,10-Dimethyl-3*E*,9-undecadien-2-one (7). A mixture of $PdCl_2$ (0.17 g), CuCl (1.01 g), DMF (5.2 ml), and water (0.66 ml) was stirred for 1 h under O_2. Then diolefin **5** (1.84 g, 9.39 mmol) was added and the stirring was continued until 125 ml of O_2 was consumed. The mixture was diluted with 50 ml of Et_2O and acidified with 10% hydrochloric acid (6.5 ml). The organic layer was separated, the aqueous phase was thoroughly extracted with Et_2O (3×100 ml), the organic layer and extracts were combined, washed successively with saline, $NaHCO_3$, and saline again, then dried ($MgSO_4$), and evaporated. The residue (1.59 g), characterized as hydroxy ketone **6** by its IR and ^1H NMR spectra [ν 840 (=C—H), 1050 (C—O), 1640 (C=C), 1720 (C=O), 3400 cm^{-1} (OH); δ (CCl_4) 0.84 (d, 3H, CH_3C(6), *J* = 6); 1.01—1.38 (m, 5H, CH_2 and CH); 1.53 and 1.60 (s, 6H, CH_3C=C); 1.83—2.14 m (2H, H_2C—C=C); 2.05 (s, 3H, CH_3CO); 2.36 (d, 2H, CH_2CO, *J* = 6); 2.67 (br.s, 1H, OH); 3.70—4.13 (m, 1H, HC—O); 4.87 (t, 1H, HC=C, *J* = 7)], without further purification was dissolved in 7 ml of benzene. Anhydrous Na_2SO_4 (0.72 g) and TsOH (6 mg) were added to this solution and the resulting mixture was stirred and boiled for 1 h, then cooled to ~20°C, diluted with 300 ml of Et_2O, washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated. The residue upon chromatography on SiO_2 (elution with hexane—AcOEt 9:1) afforded enone **7**, n_D^{15} 1.4795, $[\alpha]_D^{22}$ +1.41° (*c* 5.60; $CHCl_3$). Yield 1.09 g (60%). Found: C 80.23; H 11.34. Calcd. for $C_{13}H_{22}O$: C 80.35; H 11.41%. IR spectrum (ν, cm^{-1}): 840, 990 (=C—H), 1640, 1690 (C=C), 1710 (C=O).



a. *i*-Bu_3Al, 100°C; *b*. O_2; *c*. H_2SO_4 aq; *d*. PCC; *e*. CH_2=$CHCH_2MgCl$; *f*. $O_2/PdCl_2$—$CuCl/H_2O$—DMF; *g*. $TsOH/Na_2SO_4$; *h*. *i*-PrOC≡CH/EtMgBr; *i*. $Hg(OAc)_2$/MeOH; *j*. $NaBH_4$.

^1H NMR spectrum (δ, CCl_4, *J*, Hz): 0.84 (d, 3H, CH_3C(6), *J* = 6); 1.00—1.37 (m, 3H, H_2C(7), HC(6)); 1.51 and 1.59 (s, 6H, CH_3C=C); 1.83—2.14 (m, 4H, H_2CC=C); 2.06 (s, 3H, CH_3CO); 4.95 (t, 1H, HC(9)); 5.87 (d, 1H, HC(3), $J_{3,4}$ = 16); 6.58 (dt, 1H, HC(4), $J_{3,4}$ = 16, $J_{4,5}$ = 8).

Isopropyl 3,7*S*,11-trimethyl-2*E*/*Z*,4*E*-dodecatrienoate (8). To a stirred solution of isopropoxyethynylmagnesium bromide, prepared from Mg (0.21 g, 8.75 mmol), ethyl bromide (1.00 g, 9.17 mmol), isopropoxyethyne [11] (0.74 g, 8.8 mmol) and abs. Et_2O (6 ml), a solution of enone **7** (0.56 g, 2.88 mmol) in abs. Et_2O (7 ml) was added dropwise at −10°C, under Ar. After 3 h of stirring at this temperature the reaction mixture was left to warm to 20° (1h) and acidified with 10% H_2SO_4 (15 ml, dropwise). The stirring was continued for 1 h, the mixture was diluted with 160 ml of Et_2O, the organic layer was separated, washed successively with saturated aqueous $NaHCO_3$ and NaCl, dried ($MgSO_4$), and evaporated. The residue was chromatographed on SiO_2 (elution with CH_2Cl_2) to give ester **8** that displayed the same IR and ^1H NMR spectra as its racemic analogue (*cf.* [8]). Yield 0.64 g (80%).

Isopropyl 11-methoxy-3,7*S*,11-trimethyl-2*E*/*Z*,4*E*-dodecatrienoate (1). To a solution of the isopropyl trienoate **8** (0.42 g, 1.44 mmol) in abs. MeOH (4.7 ml) mercuric acetate (0.307 g) was added (5°C, under argon). The reaction mixture was stirred for 1 h at 5°C, then warmed to ~20°C and kept for 24 hr. Then it was cooled to 0°C and a solution of $NaBH_4$ (2.2 g) and NaOH (0.60 g) in water (7.6 ml) was added dropwise with stirring to precipitate mercury. The supernatant was filtered through a short column of SiO_2 and extracted with Et_2O (3×50 ml). The ethereal extract was washed with saline, dried ($MgSO_4$), and evaporated. The residue was chromatographed on SiO_2 (hexane—AcOEt, 9:1) to afford *S*-(+)-methoprene (**1**) of ~70% geometrical purity (GC and ^1H NMR data), $[\alpha]_D^{23}$ +2.29° (*c* 0.48; $CHCl_3$). Yield 0.31 g (70%). Its IR and ^1H NMR spectra coincide with those reported for the corresponding racemate.[12]

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