Synthesis of *S*-(+)-hydroprene

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A novel path to *S*-(+)-hydroprene (**1**) starting from the technical grade *S*-(+)-dihydromyrcene (**2**, e.e. ≥50%) is proposed. The latter was selectively transformed into *S*-3,7-dimethyloctanal (**5**) in three steps including hydroalumination. The reactions of **5** with allyl- or methallylmagnesium chloride followed, respectively, either by oxygenation in the presence of $PdCl_2$/CuCl or by ozonolysis, afford *S*,*E*-6,10-dimethyl-3-undecen-2-one (**7**) which was treated with ethoxyethynylmagnesium bromide to give the title juvenile hormone analogue in ~23% overall yield.

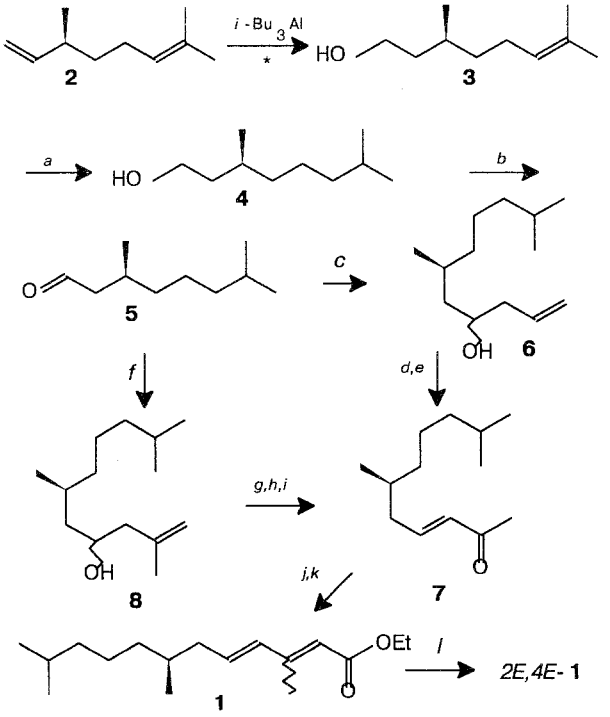
Key words: ethyl *S*-3,7,11-trimethyl-2*E*,4*E*-dodecadienoate, synthesis; *S*-3,7-dimethyl-1,6-octadiene, hydroalumination; *S*-3,7-dimethyloctanal; 6*S*,10-dimethyl-1-undecen-4*R*/*S*-ol; 2,6*S*,10-trimethyl-1-undecen-4*R*/*S*-ol, ozonolysis; *S*,*E*-6,10-dimethyl-3-undecen-2-one.

Juvenile hormone analog *S*-(+)-hydroprene (ethyl *S*-3,7,11-trimethyl-2*E*,4*E*-dodecadienoate, **1**) was obtained earlier[1] by condensing diisopropyl 3-isopropoxycarbonyl-2-methyl-2-propenylphosphonate with *S*-dihydrocitronellal, hydrolyzing the isopropyl dienoate thus formed, and re-esterifying the acid.

Here we report a novel approach to **1**, the final steps of which are similar to those described in our earlier work on the synthesis of racemic hydroprene.[2] Technical grade (+)-dihydromyrcene was used as starting material.[3] Its main component, *S*-(+)-3,7-dimethyl-1,6-octadiene (**2**, e.e. ≥50%) was smoothly transformed into *S*-(−)-citronellol (**3**) by means of hydroalumination.[4,5] Catalytic hydrogenation of **3** followed by oxidation of the resulting saturated alcohol (**4**) afforded *S*-3,7-dimethyloctanal (**5**).

Subsequent transformations of **5** were carried out along two paths converging on the same key intermediate. In one case, aldehyde **5** reacted with allylmagnesium chloride to give 6*S*,10-dimethyl-1-unedecen-4*R*/*S*-ol (**6**) which was then oxygenated according to the Smidt-Moiseev procedure (O_2/$PdCl_2$—CuCl/H_2O—DMF); acidic work-up of the reaction mixture afforded the key α-enone (**7**). In the other case, the transformation of aldehyde **5** into **7** involved the reaction of **5** with methallyl chloride, ozonolysis of the resulting 2,6*S*,10-trimethyl-1-unedecen-4*R*/*S*-ol (**8**), and dehydration. The overall yield of **7** from **5** in the latter case was 54%, in the former — 49%. The *trans*-configuration of the double bond in **7** is evident from the vicinal spin-spin coupling constant of olefinic protons (J = 15 Hz) and the chemical shift of the allylic C(5) atom in its ^{13}C NMR spectrum (δ 39.99).

Finally, *S*-(+)-hydroprene was obtained upon the reaction of **7** with ethoxyethynylmagnesium bromide[2,6]. The overall yield of **1** from the starting diolefin amounts to 21.5 or 23.9% depending on the adopted path from **5** to **7**. GC-analysis and the ^1H NMR spectrum of *S*-(+)-hydroprene **1** thus obtained show that it contains the 2*Z*,4*E*-stereoisomer as an admixture in a ratio of ~7:3. The individual 2*Z*,4*E*-stereoisomer was isolated by column chromatography on SiO_2.



a. H_2—Pd/C; *b*. PCC; *c*. CH_2=$CHCH_2MgCl$; *d*. O_2/$PdCl_2$—CuCl/H_2O—DMF; *e*. HCl aq; *f*. CH_2=$C(CH_3)CH_2MgCl$; *g*. O_3; *h*. Me_2S; *i*. TsOH/Na_2SO_4; *j*. HC≡COEt/EtMgBr; *k*. H_2SO_4 aq; *l*. Chromatography (SiO_2).

*see ref.[4,5].

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Experimental

IR spectra were recorded on a UR-20 spectrophotometer (neat). ^{1}H NMR spectra were obtained with either Tesla BS-467 (60 MHz, in CCl_4), or Tesla BS-567 instruments (100 MHz, in $CDCl_3$, for **1** and **7** only) using tetramethylsilane as the internal standard. The ^{13}C NMR spectrum of **7** was recorded on a Bruker AM-300 spectrometer (75 MHz, $CDCl_3$). Optical rotations were determined with a Perkin-Elmer 141 polarimeter. GC-analyses were performed on a Chrom-5 gas chromatograph with 5% SE-30 on Chromaton N-AW-DMCS (0.16—0.20 mm) and He as carrier gas, temperature range 50—300°C. TLC-analyses were carried out on Silufol plates.

***S*-3,7-Dimethyloctan-1-ol (4).** Alcohol **3** (25 g, 160 mmol), obtained from **2** according to ref.[4,5] (e.e. ~50%), was dissolved in MeOH (250 ml) and hydrogenated at ~20°C in the presence of 5% Pd/C (2.5 g) until 3.59 l of H_2 were absorbed (50 h). The mixture was filtered and the solution evaporated to give alcohol **4** of 92% purity (GC data), $[\alpha]_D^{23}$ −2.08° (*c* 5.01; $CHCl_3$). Yield 23.50 g (93%). For the optically pure sample of **4** $[\alpha]_D^{25}$ −4.25° (*c* 5.03; $CHCl_3$) was recorded.[7] IR and NMR spectra coincide with those reported earlier.[7]

***S*-(−)-3,7-Dimethyloctanal (5).** To a stirred (20°C, Ar) suspension of PCC (11.62 g, 53.4 mmol) in dry CH_2Cl_2 (120 ml), a solution of **4** (5.70 g, 36.1 mmol) in dry CH_2Cl_2 (30 ml) was added. After 2 h of stirring 200 ml of Et_2O were added and the mixture was filtered through a layer of SiO_2, the precipitate was washed with Et_2O (200 ml) and the combined filtrate was evaporated. The residue was chromatographed on SiO_2 (CH_2Cl_2 as eluent) to give aldehyde **5** of 93% purity (GC data), $[\alpha]_D^{23}$ −6.78° (*c* 5.21; $CHCl_3$). For the *R*-enantiomer of **5** it was recorded:[8] $[\alpha]_D^{25}$ +13.5° (neat). The IR spectrum coincides with that of the racemic sample (cf. [2]). ^{1}H NMR (δ, *J*, Hz): 0.80—1.03 (m, 9 H, CH_3); 1.05—1.67 (m, 8 H, CH_2, CH); 2.00—2.47 (m, 2 H, CH_2C=O); 9.72 (t, 1 H, HCO, *J* = 2).

6*S*,10-Dimethyl-1-undecen-4*R*/*S*-ol (6). To 1.88 g of Mg (78.4 mmol, activated with I_2) in abs. Et_2O (7 ml) few drops of allyl chloride were added. Then a solution of **5** (5.10 g, 32.5 mmol) and CH_2=$CHCH_2Cl$ (5.01 g, 65.5 mmol) in abs. Et_2O (28 ml) was introduced gradually at such a rate as to keep the mixture slowly boiling. This was followed by stirring at 20°C (15 h) and cooling to 5°C. The reaction mixture was treated with a saturated aqueous solution of NH_4Cl (30 ml), stirred for 15 min, and extracted with Et_2O (3x50 ml). The extract was chromatographed on SiO_2 (elution with hexane — Et_2O, 4:1) to give the hydroxyalkene **6** of 95% purity (GC data) with $[\alpha]_D^{25}$ −1.24° (*c* 2.65; $CHCl_3$). Yield 5.19 g (80%). IR and ^{1}H NMR spectra were identical to those reported earlier.[2]

2,6*S*,10-Trimethyl-1-undecen-4*R*/*S*-ol (8). To 1.30 g of Mg (54.2 mmol, activated with I_2) in abs. Et_2O (3 ml) few drops of methallyl chloride were added. Then a solution of **5** (3.38 g, 21.7 mmol) and methallyl chloride (3.52 g, 38.9 mmol) in abs. Et_2O (20 ml) was introduced, and the procedure described above for alcohol **6** was repeated to give its homologue **8**, an oil with $[\alpha]_D^{23}$ −2.03° (*c* 3.49, $CHCl_3$). Yield 3.77 g (82%). Anal. Calc. for $C_{14}H_{28}O$: C 79.11; H 13.31 %. Found: C 79.16; H 13.29 %. IR (ν, cm^{-1}): 888 (=C—H), 1108 (C—O), 1376 and 1460 (CH_3—C), 1644 (C=C), 3072 (=C—H). ^{1}H NMR (δ, *J*, Hz): 0.82—0.92 (m, 9 H, CH_3); 1.02—1.63 (m, 10 H, CH_2 and CH); 1.70 (s, 3 H, CH_3C=C); 1.80—2.13 (m, 3 H, H_2CC=C + OH); 3.35—3.83 (m, 1 H, **H**—C—OH); 4.75 (br.s, 2 H, H_2C=C).

***S*,*E*-6,10-Dimethyl-3-undecen-2-one (7).** (*a*) A mixture of $PdCl_2$ (0.15 g, 0.85 mmol), CuCl (0.88 g, 8.98 mmol), DMF (4.58 ml), and water (0.56 ml) was stirred for 1 h under O_2. Then the hydroxyalkene **6** (1.60 g, 7.55 mmol) was added and stirring was continued until 108 ml O_2 was consumed (6 h). The mixture was diluted with 10% hydrochloric acid (4.4 ml), boiled for 1 h, left to cool to ~20°C, and extracted with Et_2O (4x50 ml). The extract was successively washed with saline, aqueous $NaHCO_3$, and saline again, dried (Na_2SO_4), and evaporated. The residue was chromatographed on SiO_2 (hexane — Et_2O, 10:1) to give the α-enone **7** of 95% purity (GC data), $[\alpha]_D^{23}$ −2.44° (*c* 1.00; $CHCl_3$). Yield 0.97 g (61%). IR and ^{1}H NMR spectra coincide with those reported earlier.[2,6] ^{13}C NMR (δ): 19.63 (q, CH_3C-6); 22.56 (q, C-11); 22.65 (q, CH_3C-10); 24.60 (t, C-8); 27.96 (t, C-10); 29.72 (q, C-1); 32.68 (d, C-6); 36.97 (t, C-7); 39.14 (t, C-9); 39.99 (t, C-5); 132.40 (d, C-3); 147.36 (d, C-4); 196.47 (s, C-2).

(*b*) Through a solution of compound **8** (0.85 g, 4.00 mmol) in CH_2Cl_2 (3.4 ml), doped with MeOH (0.3 ml) and cooled to −65°C, a stream of O_3/O_2 was passed until 0.19 g of O_3 (4.00 mmol) was consumed (the output of the ozonator being 20 mmol O_3 per hour). The reaction mixture was flushed with Ar, reduced with Me_2S (2.5 ml), stirred (−60°C, 1 h → −15°C, 1 h → 0°C, 1 h → 20°C, 12 h), and diluted with Et_2O (100 ml). The resulting solution was washed with water (2x25 ml), dried (Na_2SO_4), and evaporated. Benzene (2.8 ml), anhydrous Na_2SO_4 (0.23 g), and a crystal of $TsOH \cdot H_2O$ (2 mg) were added to the residue. This mixture was boiled for 1 h, cooled to ~20°C, diluted with 50 ml of Et_2O, washed with saturated solutions of $NaHCO_3$ and NaCl, dried ($MgSO_4$), and evaporated. The residue was chromatographed on SiO_2 (hexane — AcOEt, 10:1) to afford a sample of **7** which was identical with that obtained from compound **6**. Yield 0.52 g (66%).

Ethyl *S*-(+)-3,7,11-Trimethyl-2*E*,4*E*-dodecadienoate (1). To a stirred solution of ethoxyethynylmagnesium bromide, prepared from 52 mg of Mg (2.2 mmol), 240 mg EtBr (1.9 mmol), and 150 mg EtOC≡CH (2.1 mmol) in abs. Et_2O (1.6 ml),[6] a solution of enone **7** in abs. Et_2O (1.6 ml) was added dropwise (−10°C, under Ar). After 3 h of stirring at this temperature the mixture was warmed up to ~20°C within 1 h, treated with 10% H_2SO_4 (3.5 ml) for 1 h, and diluted with Et_2O (40 ml). The organic layer was separated, washed with saturated aqueous solutions of $NaHCO_3$ and NaCl, dried ($MgSO_4$), and evaporated to give a sample of **1** with the isomer ratio 2*E*,4*E*- : 2*Z*,4*E* ~7 : 3 (GC data). Yield 0.16 g (84%). IR and ^{1}H NMR spectra of the sample coincided with those reported for the corresponding racemate.[6] 100 mg of **1** were chromatographed on SiO_2 (CH_2Cl_2 as eluent) to give 50 mg of pure 2*E*,4*E*-isomer (2*E*,4*E*-**1**), $[\alpha]_D^{28}$ +2.05° (*c* 1.33; $CHCl_3$). For a sample of 2*E*,4*E*-**1** with ~69.6% e.e. recorded:[1] $[\alpha]_D^{25}$ +2.9° (*c* 0.02; MeOH).

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