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INSECT PHEROMONES AND THEIR ANALOGS.
LX. STEREOCONTROLLED SYNTHESIS OF SEX PHEROMONES OF *Drosophila mulleri* AND *Mayetiola destructor**

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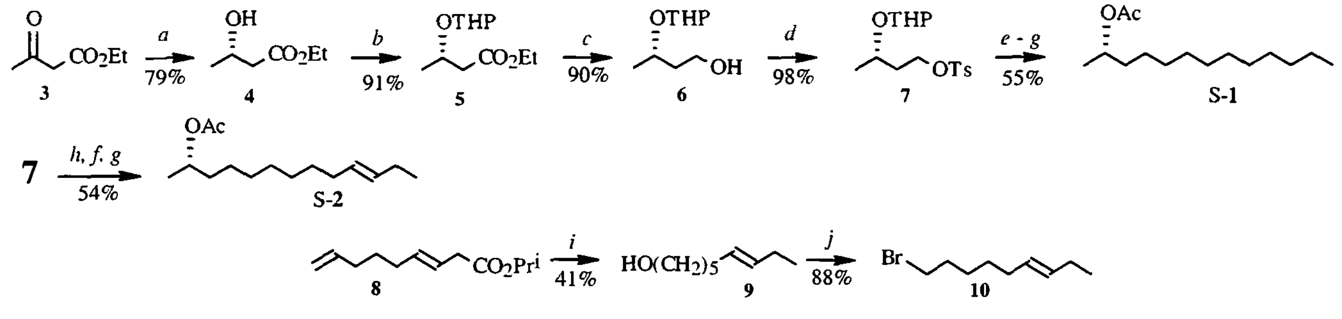
Syntheses are developed for 2S-tridecyl- and 2S-tridec-10E-enylacetates, sex pheromones of the fruit fly Drosophila mulleri *and the Hessian fly* Mayetiola destructor, *respectively, that are based on ethyl-3S-hydroxybutanoate, a product from enzymatic reduction of ethyl acetoacetate by the soil yeast strain "80-1."*

Key words: pheromones, *Drosophila mulleri*, *Mayetiola destructor*, ethyl-3S-hydroxybutanoate, 2S-tridecylacetate, 2S-tridec-10E-enylacetate, synthesis.

Syntheses of 2S-tridecylacetate (**S-1**), the sex pheromone of the fruit fly (*Drosophila mulleri*), have been based on the use of the enantio-differentiating SAMP-reagent [1], deprotonation of 1-dodecanol using (-)-spartein [2], enantio-selective reduction by Baker's yeast of 5-(*p*-tolylsulfonyl)pentan-2-one [3], and enzymatic cleavage of racemic 2-tridecylacetate using lipase catalyst PS (from *Pseudomonas cepacia*) [4].

Preparation of another versatile compound, 2S-tridec-10E-enylacetate (**S-2**), the sex pheromone of the Hessian fly (*Mayetiola destructor*), which causes great damage to winter and spring wheat crops, has used an acetylenic method to construct the E-unsubstituted carbon framework. The chiral center with the S-configuration was introduced using hydrolysis of the racemic analog of the pheromone by lipase PS [5]. Other groups have used the product from enantio-selective (enantiomeric excess 96.4%) reduction by Baker's yeast of an acetoacetic ester, ethyl-3S-hydroxybutanoate [6], and (S)-propylenoxide [7] as the starting compound.



a. strain" 80-1"; *b*. DHP/PPTS; *c*. $LiAlH_4$; *d*. TsCl/Py; *e*. *n*-$C_9H_{19}MgBr/Li_2CuCl_4$;
f. TsOH/MeOH - H_2O; *g*. Ac_2O/Py/DMAP; *h*. **10**/Mg, Li_2CuCl_4; *i*.see Ref. [6]; *j*. PBr_3/Py

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We developed a common synthesis of **S-1** and **S-2** that is based on ethyl-3S-hydroxybutanoate (**4**), which is produced in 97% optical purity by reduction of **3** by soil yeast strain "80-1." Catalyzed cross-combination of chiral tosylate **7**, which is produced by simple transformations of **4** via the route **4** → **7** with the corresponding organomagnesium compounds, is used in the key steps of both syntheses. Unsaturated alcohol **9**, a precursor of the achiral synthon **10** for **S-2**, was prepared according to the literature [8] from isopropyl-3E,8-nonadienoate (**8**). The specific rotations {$[\alpha]_D^{19}$ +4.46° (*c* 0.90, hexane) and $[\alpha]_D^{19}$ +4.20° (*c* 1.02, hexane)} for **S-1** and **S-2**, which were obtained in yields of 35 and 34% based on starting ketoester **3**, respectively, are consistent with full retention of the asymmetric center.

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument as thin layers. PMR spectra were obtained on a Bruker AM-300 (300.13 MHz working frequency) spectrometer in $CDCl_3$ relative to TMS. Chromatographic analysis was performed on a Chrom-5 instrument [column length 1.2 m, stationary phase SE-30 (5%) silicone on Chromaton N-AW-DMCS (0.16-0.20 mm), working temperature 50-300°C] with He carrier gas. Optical rotations were measured on a Perkin—Elmer MC-241 polarimeter.

Biomass preparation. Soil yeast strain "80-1" was obtained from an archive culture of soil organisms in a medium for which the sole source of carbon and energy was ethanol and was inoculated into potato-dextrose agar in Petri dishes at 28-30°C, where it was grown for 48 h. The resulting cells, which had achieved the later logarithmic growth phase, were separated by centrifugation, washed three times with phosphate buffer (pH 7.0, 0.05 M), and used for reduction of the acetoacetic ester (3).

Ethyl-3S-hydroxybutanoate (4). Dry biomass of "80-1" (50.0 g) suspended in phosphate buffer (200 ml, 0.05 M) was treated with **3** (1.25 g, 7.69 mmole) and stirred for 4 h (30°C, pH 7). The reaction mixture was extracted with Et_2O (3×200 ml), dried over Na_2SO_4, and evaporated. Yield of **4**, 1.00 g (79%), $[\alpha]_D^{20}$ +41.0° (*c* 1.00, $CHCl_3$) [9]. IR and PMR spectra are identical to those reported in the literature [10].

Ethyl-3S-(2-tetrahydropyranyloxy)butanoate (5). A solution of **4** (1.00 g, 7.5 mmole) in CH_2Cl_2 (10 ml) was treated with DHP (0.95 g, 11.3 mmole) and PPTS (0.19 g, 8.0 mmole). The mixture was stirred for 3 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (20 ml), washed with Na_2CO_3 (10%) and H_2O, dried over $MgSO_4$, and evaporated. Yield of **5**, 1.50 g (91%). IR and PMR spectra are identical to those reported in the literature [11].

3S-Tetrahydropyranyloxybutan-1-ol (6). A stirred suspension of $LiAlH_4$ (0.22 g, 5.8 mmole) in Et_2O (absolute, 2.7 ml) at 0-5°C under Ar was treated with **5** (1.45 g, 6.7 mmole) in Et_2O (absolute, 17 ml). The reaction mixture was stirred for 3 h at room temperature, cooled to 0°C, treated successively with H_2O (0.2 ml), NaOH (10%), and H_2O, and stirred at room temperature for 1 h. The precipitate was filtered off and washed with Et_2O (20 ml). The filtrate was washed with H_2O, dried over Na_2SO_4, and evaporated. Yield of **6**, 1.05 g (90%), $[\alpha]_D$ +24.0° (*c* 1.00, $CHCl_3$) [10]. IR and PMR spectra are identical to those reported in the literature [10].

3S-Tetrahydropyranyloxy-1-tosyloxybutane (7). A solution of **6** (0.95 g, 5.5 mmole) in dry pyridine (5 ml) at 0°C under Ar was treated with stirring with TsCl (1.50 g, 7.9 mmole). The reaction mixture was stirred (0°C, 5 h), poured into icewater (10 g), and extracted with Et_2O (3×20 ml). The combined extracts were washed successively with H_2O and saturated $CuSO_4$, $NaHCO_3$, and NaCl solutions, dried over $MgSO_4$, and evaporated. Yield of **7**, 1.75 g (98%). The IR spectrum is identical to that reported in the literature [10].

2S-Acetoxytridecane (S-1). A stirred solution of the Grignard reagent prepared from *n*-nonylbromide (0.68 g, 3.3 mmole) and Mg (0.097 g, 3.6 mg-atom) in Et_2O (absolute, 3 ml) was treated at -75°C and dropwise under Ar with **7** (0.75 g, 2.3 mmole) in THF (absolute, 4 ml) and then Li_2CuCl_4 (0.13 ml, 0.2 M) in THF. The reaction mixture was stirred (-70°C, 1 h; -10°C, 2 h; 25°C, 2 h), poured into a cooled saturated solution of NH_4Cl, and extracted with Et_2O (3×25 ml). The combined extracts were washed successively with saturated NaCl, $NaHCO_3$, and NaCl solutions and evaporated. The solid was dissolved in MeOH (4 ml), treated with TsOH (0.03 g), and left overnight. The solvent was evaporated under vacuum. The solid was dissolved in Et_2O (30 ml), washed successively with saturated $NaHCO_3$ and NaCl solutions, dried over Na_2SO_4, and evaporated. The solid was treated with 4-dimethylaminopyridine (DMAP, 20 mg) and a Ac_2O—Py mixture (2:3, 2.6 ml) and stirred for 24 h. The volatiles were removed. The solid was dissolved in CH_2Cl_2 (50 ml), washed with HCl (5%), H_2O, and saturated NaCl solution, dried over $MgSO_4$, and evaporated. The crude product was chromatographed on silica gel (eluent petroleum ether:Et_2O, 5:1). Yield of **S-1**, 0.30 g (55%), $[\alpha]_D^{19}$ +4.46° (*c* 0.90, hexane) [1]. IR and PMR spectra are identical to those reported in the literature [1].

1-Bromonon-6E-ene (10). A solution of **9** (0.85 g, 6.0 mmole) and pyridine (0.15 ml) in Et_2O (absolute, 6 ml) was treated with stirring under Ar at -10°C with PBr_3 (0.74 ml, 0.72 g, 2.7 mmole), stirred for 20 h, cooled to 0°C, treated with saturated NH_4Cl solution, and extracted with Et_2O (3×50 ml). The extracts were successively washed with saturated NH_4Cl and NaCl solutions, dried over $MgSO_4$, and evaporated. The solid was chromatographed (silica gel, pentane). Yield of **10**, 0.95 g (88%), n_D^{20} 1.4705 [12]. IR spectrum (KBr, ν, cm^{-1}): 570 and 650 (C–Br), 975 (CH=). PMR spectrum (300.13 MHz, $CDCl_3$, ppm, J, Hz): 0.89 (3H, t, J = 7, CH_3), 1.18-1.49 (6H, m, CH_2), 1.73-2.10 (4H, m, CH_2C=), 3.33 (2H, t, J = 6.5, CH_2Br), 5.22-5.50 (2H, m, HC=).

2S-Acetoxytridec-10E-ene (S-2). A stirred solution of the Grignard reagent prepared from **10** (0.90 g, 4.4 mmole) and Mg (0.13 g, 4.7 mg-atom) in Et_2O (absolute, 4 ml) was treated at -75°C and dropwise under Ar with a solution of **7** (1.00 g, 3.0 mmole) in THF (absolute, 5 ml) and then Li_2CuCl_4 (0.17 ml, 0.2 M). The reaction mixture was stirred (-70°C, 1 h; -10°C, 2 h; 25°C, 2 h), poured into cold saturated NH_4Cl solution, and extracted with Et_2O (3x25 ml). The combined extracts were washed successively with saturated NaCl, $NaHCO_3$, and NaCl solutions and evaporated. The solid was dissolved in MeOH (4 ml), treated with TsOH (0.03 g), and left overnight. The solvent was evaporated under vacuum. The solid was dissolved in Et_2O (30 ml), treated successively with saturated $NaHCO_3$ and NaCl solutions, dried over Na_2SO_4, and evaporated. The solid was treated with DMAP (20 mg) and a mixture of Ac_2O and pyridine (2.6 ml, 2:3) and stirred for 24 h. Volatiles were evaporated under vacuum. The solid was dissolved in CH_2Cl_2 (50 ml), washed with HCl (5%), H_2O, and saturated NaCl solution, dried over $MgSO_4$, and evaporated. The crude product was chromatographed on silica gel (eluent petroleum ether:Et_2O, 5:1). Yield of **S-2**, 0.29 g (54%), $[\alpha]_D^{19}$ +4.20° (*c* 1.02, hexane) [5]. IR and PMR spectra are identical to those reported in the literature [6].

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