Note

Synthesis of (S,E)-1-Methyl-9-dodecenyl Acetate, the Sex Pheromone of the Hessian Fly, *Mayetiola destructor*, by Lipase-catalyzed Enantioselective Hydrolysis

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(S,E)-1-Methyl-9-dodecenyl acetate [(S)-8], the sex pheromone of the hessian fly, *Mayetiola destructor*, was synthesized in a highly enantiomerically pure form by *Pseudomonas cepacia* lipase-catalyzed hydrolysis.

There is considerable interest in lipase-catalyzed biotransformations in organic synthesis due to the enantioselective properties that the enzymes exhibit in both aqueous solutions and organic media.1,2) We have very recently shown that the acetates of racemic alkan-2- and 3-ols could be hydrolyzed with good to high enantioselectivity by lipase PS (lipase from *Pseudomonas cepacia*, Amano PS) in an acetone–water solvent system, and that hydrolysis could be utilized in the synthesis of (2R,6R,10R)-6,10,14-trimethyl-2-pentadecan-1-ol, the natural form of the sex pheromone of *Corcyra cephalonica*, and of (R)-sucatinol, an aggregation pheromone of ambrosia beetles.3,4)

The present work was undertaken to extend the usefulness of the enzymatic hydrolysis system with lipase PS, and (S,E)-1-methyl-9-dodecenyl acetate [(S)-8], which is the sex pheromone of the hessian fly (*Mayetiola destructor*), was prepared in a highly enantiomerically pure form of almost 100% e.e. The pheromone acetate, (S)-8, was previously synthesized from (S)-propylene oxide in an enantiomeric purity of about 96.7% e.e.5)

Bromide 10) derived from 1,8-octanediol was treated with lithium acetylide-ethylenediamine to give terminal alkyne 2. Alkyne 2 was then alkylated with n-BuLi and ethyl iodide in the presence of N,N'-dimethylpropyleneurea (DMPU),7) followed by treatment with p-TsOH to yield acetylenic alcohol 4. Alcohol 4 was reduced with LiAlH4 in diglyme, and resulting (E)-alcohol 5 was converted into unsaturated aldehyde 6 by pyridinium chlorochromate (PCC) oxidation. Subsequently, a Grignard reaction of aldehyde 6 with methylmagnesium bromide gave alcohol (±)-7, which led in the usual manner to acetate (±)-8.

To complete the synthesis of (S)-8, acetate (±)-8 was hydrolyzed with lipase PS in an acetone-phosphate buffer. The hydrolysis stopped at ca. 50% conversion, and the unreacted acetate of 95% e.e. was resubmitted to lipase hydrolysis. Pheromone acetate (S)-8 thus obtained showed an enantiomeric purity of almost 100%.

In summary, we synthesized pheromone (S)-8 of 100% e.e. The overall yield was 10.3% in 9 steps from 1.

Experimental

IR spectra were determined with a Fourier transform Perkin Elmer 1720 IR spectrometer. 1H-NMR spectra were obtained with a Fourier transform Hitachi R-1500 (60 MHz) spectrometer, using MeSi as an internal standard. Gas chromatography was carried out on a Hitachi G-3000 chromatograph equipped with a TC-WAX 30 m (60 m) × 0.25 mm capillary column. Optical rotation values were measured with a Horiba SEPA-200 high-sensitivity polarimeter.

**Determination of enantiomeric purity.** The enantiomeric purity of acetate (S)-8 is based on that of alcohol (S)-7 prepared by treating the acetate with K2CO3 in methanol. The e.e. of (S)-7 was determined by a GLC analysis of the diastereomeric ester prepared by treating the alcohol with (S)-2-acetoxypropionyl chloride.5,6) The ester derived from (±)-7 was separated into two equal peaks of tR 24.2 and 25.4 min (column, 60 m TC-WAX; column temperature, 200°C).

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\begin{align*}
\text{Br(CH}_2\text{)}_2\text{GOTHP} & \quad \xrightarrow{1} \quad \text{OC} & \quad \text{(CH}_2\text{)}_8\text{GOTHP} & \quad \xrightarrow{2} \quad \text{OC} & \quad \text{(CH}_2\text{)}_8\text{OR} & \quad \xrightarrow{3; \text{R} = \text{OCH}_3} & \quad \text{OC} & \quad \text{(CH}_2\text{)}_8\text{OH} & \quad \xrightarrow{4; \text{R} = \text{H}} & \quad \text{OC} & \quad \text{(CH}_2\text{)}_8\text{CHO} & \quad \xrightarrow{5} & \quad \text{OC} & \quad \text{(CH}_2\text{)}_7\text{OH} & \quad \xrightarrow{6} & \quad \text{OC} & \quad \text{(CH}_2\text{)}_7\text{CHO} & \quad \xrightarrow{\text{lipase PS}} & \quad \text{OC} & \quad \text{(CH}_2\text{)}_7\text{Ac} & \quad \xrightarrow{50\% \text{ conversion}} & \text{OC} & \quad \text{(CH}_2\text{)}_7\text{Ac} & \quad \xrightarrow{14\% \text{ conversion}} & \text{OC} & \quad \text{(CH}_2\text{)}_7\text{Ac} & \quad \xrightarrow{100\% \text{ e.e.}} & \text{OC} \quad \text{(CH}_2\text{)}_7\text{Ac} \\
(\text{S})-7 & \quad 95\% \text{ e.e.} & \quad \text{OC} & \quad \text{(CH}_2\text{)}_7\text{Ac} & \quad \xrightarrow{\text{lipase PS}} & \quad \text{OC} & \quad \text{(CH}_2\text{)}_7\text{Ac} & \quad \xrightarrow{50\% \text{ conversion}} & \text{OC} & \quad \text{(CH}_2\text{)}_7\text{Ac} & \quad \xrightarrow{14\% \text{ conversion}} & \text{OC} & \quad \text{(CH}_2\text{)}_7\text{Ac} & \quad \xrightarrow{100\% \text{ e.e.}} & \text{OC} & \quad \text{(CH}_2\text{)}_7\text{Ac}
\end{align*}
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10-Terahydropranoxyloxy-1-decyn (2). Compound 2 was prepared from bromide 1 in a yield of 87% according to the reported procedure.31

12-Terahydropranoxyloxy-3-decynene (3). To a stirred and cooled (-5°C) solution of alkyne 2 (35 g, 0.15 mol) in dry THF (140 mL) under argon was added 113 mL of 1.6 M n-BuLi in hexane. After the resulting solution had been stirred for 2 h at 0°C, dry DMPO (245 mL) was added, this being followed by the dropwise addition of ethyl iodide (28 g, 0.18 mol). The mixture was then allowed to warm to room temperature while being stirred; stirring was continued overnight, after which the mixture was poured into ice-cooled water and extracted with n-hexane. The usual work-up of the extract gave a yellow liquid, which was purified by column chromatography on silica gel (30 g) with n-hexane-ether (20:1) to give 3 as a colorless liquid (29.6 g, 74%). IR νmax (neat) cm⁻¹: 1137, 1121, 1080, 1034. 1H-NMR (CDCl3) δ: 0.96 (3H, t, J = 7 Hz), 1.34–1.93 (18H, m), 1.99–2.36 (4H, m), 2.39–4.05 (4H, m), 4.57 (1H, broad s).

9-Dodecyn-1-ol (4). Compound 3 (15.5 g, 58.3 mmol) was dissolved in dry methanol (150 mL) containing p-TsOH (0.3 g), and the mixture was heated at 60–65°C for 4 h while stirring. The usual work-up of the mixture gave a yellow liquid, which was purified by column chromatography on silica gel (100 g) with n-hexane-ether (10:1) to give 4 as a colorless liquid (10.5 g, 99%). IR νmax (neat) cm⁻¹: 3338, 1462, 1059. 1H-NMR (CDCl3) δ: 0.96 (3H, t, J = 7 Hz), 1.35–1.66 (13H, m), 1.94–2.32 (4H, m), 3.63 (2H, t, J = 6 Hz).

(E)-9-Dodecen-1-ol (5). A solution of 4 (10.5 g, 57.7 mmol) in dry diglyme (30 mL) was added to a stirred suspension of LiAlH₄ (8.7 g, 0.23 mol) in dry diglyme (125 mL) under nitrogen at room temperature. The mixture was then heated at 120–125°C for 22 h while being stirred. After cooling, the mixture was hydrolyzed with degassed ice-cold water under nitrogen and neutralized with dil. HCl. The usual work-up of the mixture gave a pale yellow liquid, which was purified by column chromatography on silica gel (100 g) with n-hexane-ether (10:1) to give 5 as a colorless liquid (9 g, 84.8%). IR νmax (neat) cm⁻¹: 3338, 1462, 1058, 966. 1H-NMR (CDCl3) δ: 0.97 (3H, t, J = 7 Hz), 1.21–1.56 (12H, m), 1.82–2.18 (5H, m), 3.61 (2H, t, J = 6.5 Hz), 5.41 (2H, m).

(E)-9-Dodecenol (6). A solution of 5 (8.5 g, 46.2 mmol) in dry CH₂Cl₂ (50 mL) was added to a stirred suspension of PCC (22.6 g, 0.105 mol) in dry CH₂Cl₂ (160 mL) at room temperature. The mixture was stirred for 3 h at room temperature and then filtered. The usual work-up of the filtrate gave a brown liquid, which was purified by column chromatography on silica gel (100 g) with n-hexane-ether (10:1) to give 6 as a colorless liquid (6.9 g, 82.1%). IR νmax (neat) cm⁻¹: 2716, 1728, 1462, 967. 1H-NMR (CDCl3) δ: 0.96 (3H, t, J = 7 Hz), 1.21–1.64 (10H, m), 1.83–2.18 (4H, m), 9.77 (1H, t, J = 1.8 Hz).

(±)-(E)-10-Tridecen-2-ol ([±]-7). A stirred solution of 6 (5.8 g, 31.9 mmol) in dry ether (40 mL) was added 3 mL CH₃MgBr (12.8 mL, 38.4 mmol) in ether under nitrogen. The mixture was stirred for 2 h at room temperature and then treated with a 10% NH₄Cl solution. The usual work-up gave a pale yellow liquid, which was purified by column chromatography on silica gel (70 g) with n-hexane-ether (4:1) to give (±)-7 as a colorless liquid (5.5 g, 57%). IR νmax (neat) cm⁻¹: 3338, 1462, 1374, 1125, 966. 1H-NMR (CDCl₃) δ: 0.96 (3H, t, J = 7.5 Hz), 1.18 (3H, d, J = 6.4 Hz), 1.23–1.6 (12H, m), 1.96 (3H, m), 3.82 (1H, m), 3.4 (2H, m).

(±)-(E)-1-Methyl-9-dodecenyl acetate ([±]-8). Alcohol (±)-7 (3.5 g, 17.7 mmol) was treated with acetyl chloride (1.4 g, 17.7 mmol) in dry pyridine (40 mL). The usual work-up of the reaction mixture and subsequent purification by column chromatography on silver nitrate-impregnated silica gel (80 g of SiO₂ and 16 g of AgNO₃ with n-hexane-ether (10:1) gave (±)-8 as a colorless liquid (3.54 g, 83.7%). The IR and 1H-NMR spectra of (±)-8 were identical with those reported.29

(5E,5′E)-1-Methyl-9-dodecenyl acetate ([5S]-8). A mixture of (±)-8 (2 g, 8.33 mmol), lipase PS (0.8 g), 0.1M phosphate buffer (36 mL), and acetone (24 mL) was stirred for 144 h at 30°C. Column chromatography on silica gel (30 g) with n-hexane-ether (15:1) gave ([S]-8) (0.82 g, 41%) of 95% e.e., [α]D20 + 3.88° (c = 1.75, n-pentane) ([α]D20 + 8.48° (c = 2.53, n-pentane) for corresponding alcohol (S)-7. This acetate (0.5 g, 2.08 mmol) was submitted to a second hydrolysis with lipase PS (0.8 g) in a mixture of the 0.1M phosphate buffer (9 mL) and acetone (6 mL). After being stirred for 74 h (14% conversion), the mixture was worked up in the usual way. Column chromatography gave ([S]-8) (0.39 g, 78%) of almost 100% e.e., [α]D20 + 4.33° (c = 2.42, n-pentane) [lit.8 [α]D20 + 0.8° (c = 0.80, CHCl₃)], [α]D20 + 8.9° (c = 1.66, n-pentane) for corresponding alcohol ([S]-7). The IR and 1H-NMR spectra were identical with those of racemic 8. GLC analysis (60 m TC-WAX) showed that ([S]-8) had a chemical and geometrical isomeric purity of at least 98.5%.

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References