**Note**

Preparation of Both the Enantiomers of 3-Octanol, the Pheromone of Various Species of Ants, by Enantioselective Hydrolysis with *Pseudomonas cepacia* Lipase

Makoto KAMEZAWA,** Takao RAKU,* Hojun TACHIBANA,** Takehiko OHTANI,** and Yoshinobu NAOSHIMA*.†

*Department of Biochemistry, Faculty of Science, Okayama University of Science, 1-1 Ridai-cho, Okayama 700, Japan**
**Konan Chemical Industry Co., Ltd., 5-21 Nakagawa-cho, Takatsuki, Osaka 569, Japan

Received October 20, 1993

The two enantiomers of 3-octanol (3), the pheromone of a number of species of ants, were synthesized with a high enantiomeric purity of almost 100% e.e. via an enzymatic two-step hydrolysis catalyzed by *Pseudomonas cepacia* lipase in an acetone-water solvent system.

A number of species of the myrmicine ant secrete 3-octanol (3) from the mandibular glands; the two species of *Crematogaster, C. castanea* and *C. liengmei*, use (S)-3 as their pheromone.13 Cammaerts and Mori have recently found that the ants of the *Myrmica* species (*M. scabrinodis* and *M. rubra*) specifically respond only to (R)-3 and that, for *M. scabrinodis*, the naturally produced mixture of (R)-3 and (S)-3 (9:1) was more active than enantiomerically pure (R)-3.2 The enantiomers of 3 have been prepared by several chemical or biochemical methods. An enzymatic resolution of (±)-3 yielded (S)-3 with 65% e.e.,3,4 while Brand et al. prepared (S)-3 with 86-90% e.e. and (R)-3 with 75-80% e.e. by the microbial reduction of 3-octanone.5 The two enantiomers of 3 with >99% e.e. have been synthesized from methyl (R)- and (S)-3-hydroxypropionate, each of 100% e.e.6 A more recent synthesis of (R)- and (S)-3 was based upon the Sharpless epoxidation of (±)-1-octen-3-ol and subsequent hydrogenation.6

In the course of our continuing research on the chemo-enzymatic synthesis of optically active natural products, the enzyme-mediated hydrolysis of unsaturated substrates with lipase PS (*Pseudomonas cepacia* lipase, Amano PS) was found to show higher enantioselectivity than that of the saturated analogs.7 In the present work, the enzymatic resolution method has been successfully utilized to prepare a chiral acyclic alcohol, and both the enantiomers of pheromone 3 were synthesized with almost 100% e.e. by lipase-catalyzed hydrolysis of unsaturated acetate 2 in an acetone-water solvent system.

For the synthesis of (R)-3, unsaturated acetate 2 prepared from (±)-7-octen-3-ol (1) was hydrolyzed with lipase PS in an acetone-phosphate buffer to give (R)-alcohol 1 of 94% e.e. in a 30% conversion. Alcohol 1 was converted into its acetate, and the latter was resubmitted to lipase hydrolysis. The resulting (R)-alcohol 1 of 100% e.e. was hydrogenated over a 5% Pd/C catalyst to yield (R)-pheromone 3 with almost 100% e.e.; no appreciable racemization had occurred during the hydrogenation step. For (S)-3, the same hydrolysis of (±)-2 stopped at about 50% conversion, and remaining acetate (S)-2 with 94% e.e. was submitted to the second hydrolysis with lipase PS. The (S)-acetate thus obtained was converted by alkaline hydrolysis into (S)-unsaturated alcohol 1 having an enantiomeric purity of 100% e.e. This alcohol was hydrogenated as already described to yield (S)-pheromone 3 with ca. 100% e.e. The overall yields of (R)- and (S)-3 were respectively 15% and 28% in five steps from (±)-1.

The present synthesis used accessible materials and employed simple and facile reactions. The method can be expected to facilitate the preparation of optically active natural products possessing chiral alkan-3- or -2-ol skeletons.

**Experimental**

IR spectra were determined with a Fourier transform Perkin Elmer 1720 IR spectrometer. 1H-NMR spectra were obtained with a Fourier transform...
form Hitachi R-1500 (60 MHz) spectrometer or a Bruker AMX-R400 spectrometer, using Me$_3$Si as an internal standard. $^1$C-NMR spectra were obtained with a Bruker AMX-R400 spectrometer. Gas chromatography was carried out on a Hitachi G-5000 chromatograph equipped with a TC-WAX 30 m x 0.25 mm capillary column, using He as the carrier gas. Optical rotation values were measured with a Horiba SEPA-200 high-sensitivity polarimeter. The starting material, $(\pm)$-7-oxan-3-ol (1), was prepared by a Grignard reaction of propionaldehyde with 4-penten-1-yl magnesium bromide in dry ether. IR $\nu_{\text{max}}$(neat) cm$^{-1}$: 3367, 3078, 2964, 2934, 2878, 1641, 1460, 992, 911; $^1$H-NMR (CDCl$_3$) $\delta$: 0.93 (3H, t, J = 6.5 Hz), 1.27 1.70 (7H, m), 1.95 2.15 (2H, m), 3.53 (1H, m), 4.86 5.12 (2H, m), 5.52 6.08 (1H, m).

**Determination of enantiomeric purity:** The enantiomeric purity of alcohols (R)- and (S)-1 and (R)- and (S)-3 was determined by a GLC analysis of the diastereomeric propionates prepared by treating each of these alcohols with (S)-2-acetoxypropionyl chloride. The diastereomeric esters derived from (±)-1 and (±)-3 were each separated into two equal peaks of $\nu_g$ 13.2 and 13.6 min for (±)-1, and $\nu_g$ 8.6 and 8.9 min for (±)-3 (column temperature, 120 °C). The e.e. of chiral acetate (S)-2 is based on that of the corresponding alcohol.

$(\pm)$-1-Ethyl-5-hexenyl acetate [(±)-2]. Racemic unsaturated alcohol 1 (5.51 g, 43 mmol) was treated with acetic anhydride (8.87 g, 86 mmol) in dry CH$_2$Cl$_2$ (70 ml) in the presence of 4-pyridilpyridopinidine (1 g). After being stirred for 5 h, the mixture was poured into ice-cooled water and extracted with CH$_2$Cl$_2$. The usual work-up of the extract gave a pale yellow liquid, which was purified by column chromatography on silica gel (140 g) with n-hexane ether (30:1) to give (±)-2 as a colorless liquid (6.94 g, 95%). IR $\nu_{\text{max}}$(neat): 3079, 2971, 2941, 2881, 1738, 1642, 1460, 1373, 1245, 993, 954, 912. $^1$H-NMR (CDCl$_3$) $\delta$: 0.89 (3H, t, J = 5 Hz), 1.27 1.69 (6H, m), 1.91 2.21 (5H, s at 2.04), 4.66 5.11 (3H, m), 5.52 6.08 (1H, m).

**Preparation of (R)-7-oxan-3-ol [(R)-1].** A mixture of (±)-2 (2.5 g, 14.7 mmol), lipase PS (1 g), acetone (30 ml), and a 0.1 M phosphate buffer (45 ml) was stirred for 26 h at 30 °C (30% conversion). Column chromatography of the product on silica gel with n-hexane ether (30:1) gave (R)-1 (0.51 g, 27%) with 94% e.e. (3.66, n-pentane). This alcohol was recovered into corresponding acetate (R)-2 (96% yield), and the latter (0.5 g, 2.94 mmol) was added to a mixture of lipase PS (0.2 g), acetone (6 ml), and the 0.1 M phosphate buffer (9 ml). The mixture was stirred for 27 h at 30 °C, GLC showing a conversion of about 70%, Column chromatography as already described gave (R)-1 (0.25 g, 66.4%) with 100%, e.e. (3.66, n-pentane). The IR and $^1$H-NMR spectra of (R)-1 were identical with those of (±)-1.

(R)-3-Octanol [(R)-3]. Hydrogenation of (R)-1 (0.2 g, 1.56 mmol) with 100% e.e. in dry MeOH was carried out in the presence of 5% Pd/C (0.1 g). Distillation of the product gave (R)-3 (0.196 g, 96.5%), bp 85-87 °C (24 mmHg), $[\alpha]_D^{20}$ = 9.93 (c = 0.78, n-pentane), $[\alpha]_D^{10}$ = 10.03 (c = 1.47, CHCl$_3$) [lit.$^7$] $[\alpha]_D^{10}$ = 9.7° (c = 0.93, CHCl$_3$). The enantiomeric purity of (R)-3 was estimated to be 100%. The IR and $^1$H-NMR spectra were identical with those reported.$^9$

**Preparation of (S)-7-oxan-3-ol [(S)-1].** A mixture of (±)-2 (2.5 g, 14.7 mmol), lipase (1 g), acetone (30 ml), and a 0.1 M phosphate buffer (45 ml) was stirred for 180 h at 30 °C (50% conversion). Column chromatography as already described gave acetate (S)-2 (1.05 g, 43%) with 94% e.e. $[\alpha]_D^{10}$ = 6.77° (c = 4.43, n-pentane). This acetate (0.8 g, 4.7 mmol) was submitted to a second hydrolysis with lipase PS (0.64 g) in a mixture of acetone (9.6 ml) and the 0.1 M phosphate buffer (14.4 ml). After being stirred for 72 h (2% conversion), the mixture was worked up in the usual way. Column chromatography gave (S)-2 (0.61 g, 76%), $[\alpha]_D^{10}$ = 7.24° (c = 3.01, n-pentane). Acetate (S)-2 (0.5 g, 2.94 mmol), in turn, was treated with KOH in methanol (15 ml). Distillation of the product yielded (S)-1 (0.36 g, 95.5%) with 100% e.e., bp 72-74 °C (12 mmHg), $[\alpha]_D^{10}$ = 11.54° (c = 3.74, n-pentane).

**S-(3-Octanol [(S)-3].** As described for (R)-1, catalytic hydrogenation of (S)-1 (0.25 g, 1.95 mmol) gave (S)-3 (0.244 g, 96%), bp 88-90 °C (30 mmHg), $[\alpha]_D^{10}$ = 9.71° (c = 2.34, n-pentane), $[\alpha]_D^{10}$ = 9.99° (c = 1.6, CHCl$_3$) [lit.$^9$] $[\alpha]_D^{10}$ + 10.1° (c = 0.82, CHCl$_3$). The e.e. of (S)-3 was estimated to be 100%. The IR and $^1$H-NMR spectra of (S)-3 were identical with those of (R)-3. $^1$C-NMR (CDCl$_3$) $\delta$: 73.26, 36.88, 31.89, 30.08, 25.29, 22.60, 13.97, 9.80.

GLC analysis showed that (R-) and (S)-3 had a chemical purity of almost 100%.

**References**