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INSECT PHEROMONES AND THEIR ANALOGS LVI. CHEMICAL-ENZYMATIC SYNTHESIS OF (S)-(+)-9-HYDROXYDEC-2E-ENOIC ACID, A COMPONENT OF THE QUEEN PHEROMONE OF THE HONEYBEE *Apis mellifera*

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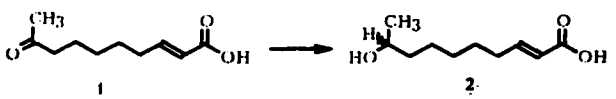
(S,E)-(+)-9-Hydroxydec-2E-enoic acid — a component of the queen pheromones of the honeybee Apis mellifera *— has been synthesized by the enzymatic reduction of 9-oxodec-2E-enoic acid with the aid of bakers' yeast.*

About 20 compounds have been isolated from the submaxillary gland of the honeybee queen. Three of them — 9-oxodec-2E-enoic acid (**1**) and (S)-(+)- and (R)-(−)-9-hydroxydec-2E-enoic acid (**2**) and (**3**) — are responsible for the formation of a bee swarm [1]. It has been established that of the enantiomers of the hydroxy acid in the pheromone of young females the (S)- enantiomer (**2**) predominates, while with increasing age of a queen the level of the (R)- isomer (**3**) rises [2]. Both enantiomers have been synthesized with the use of enantiomerically pure methyloxiranes as chiral synthons [3]. In recent years, ever greater attention of researchers has been attracted by microbiological transformations under the action of lipases [4] and bakers' yeast (BY) [5]. A chemical-enzymatic synthesis of the (S)- and (R)- enantiomers (**2**) and (**3**) has been achieved with the aid of an enantioselective transesterification of racemic ethyl 9-hydroxydec-2-E-enoate catalyzed by porcine pancreatic lipase (PPL) [6]. A microbiological synthesis of the (R,E)- hydroxy acid (**3**) has also been effected by the reduction of the methyl ester of the (E)- keto acid (**1**) with the aid of the culture *Geotrichhum sp.* G 38, while the (SE)- isomer of (**2**) has been obtained by reversal of the configuration of the C-9 atom by Mitsunobu's method [7]. In the same paper it is reported that no biotransformation of the keto ester (**1**) takes place under the action of BY.

We have now shown that when the free acid (**1**) is used as the substrate it is possible with the aid of BY to achieve the enantiospecific reduction of its keto group and to obtain the optically active hydroxy acid (**2**). According to Prelog's rule [8] and in agreement with the results of systematic investigations conducted in the mid-1960s, as a rule the yeast reduction of unsymmetrical ketones leads to the formation of secondary alcohols with the (S)-configuration [9, 10]. In actual fact, the hydroxy acid (**2**) that we isolated showed a positive angle of rotation, which demonstrated the formation of the (S,E)-enantiomer (**2**).

The PMR spectrum of the hydroxy acid (**2**) included characteristic signals — the doublet of a CH_3 group (δ 1.18 ppm, J = 6.1 Hz), the doublet of a vinyl proton at the C-2 atom (δ 5.8 ppm, J = 15.6 Hz), and the doublet of triplet of a vinyl proton at C-3 (δ 7.05 ppm, J = 15.6 and 7.0 Hz). The vicinal constant of the spin−spin coupling of the vinyl protons, 15.6 Hz, witnessed the transoid configuration of the Δ^2 bond. Under the conditions of editing, the ^{13}C NMR spectrum of the hydroxy acid (**2**) performed with the aid of the pulse sequence of a J-modulated spin-echo (the JMOD method). The signals of the carbon atoms of the vinyl, methine, and methyl groups with odd numbers of hydrogen atoms had the opposite phase relative to the signals of the carbon atoms of the carboxylic carbon and of the methyl groups. The position of the signals of the C-4 allyl carbon atom in the 32.24 ppm region corresponded to a *trans*- geometry of the double bond of compound (**2**) [11].



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The initial keto acid (**1**) was synthesized by a scheme that we had proposed previously [12].

EXPERIMENTAL

IR spectra were taken on a Specord-75-IR spectrometer in a thin layer. ^1H and ^{13}C NMR spectra were obtained on a Bruker AM 300 spectrometer with TMS as internal standard and $CDCl_3$ as solvent.

Procedure for Reduction by Bakers' Yeast (BY). A dispersion of 150 g of BY in 500 ml of distilled water was stirred for 1 h, and then 0.5 g of 9-oxodec-2E-enoic acid (**1**) was added and stirring at room temperature was continued for three days, 20 g of fresh BY being added every day. The reaction mixture was extracted with ether (3 × 100 ml) and the ether extract was dried with $MgSO_4$ and evaporated. This gave 0.48 g of a substance containing, according to its PMR spectrum [from the ratio of the intensities of a CH_3 singlet (δ 2.1 ppm) and a CH_3 doublet (δ 1.18 ppm)] approximately equal amounts of the keto acid (**1**) and the hydroxy acid (**2**) [for the mixture obtained, $[\alpha]_D^{25}$ +4.41° (*c* 4.5; MeOH)]. Chromatographic separation (SiO_2, *n*-C_6H_{14}–EtOAc–*n*-PrOH–AcOH (20:20:4:1)) gave 0.2 g (40%) of the keto acid (**1**) (R_f 0.51, mp 53-54°C, see [12], IR and PMR spectra identical with those of an authentic specimen of (**1**)), and 0.2 g (40%) of the hydroxy acid (**2**), R_f 0.34, $[\alpha]_D^{25}$ +8.5° (*c* 4.1; MeOH), see [6].

IR spectrum (ν, cm^{-1}): 1650, 1700, 2400-2700, 2840, 2920, 2950, 3100-3600, 3710, 3800. PMR (300 MHz, $CDCl_3$): 1.18 (3H, d, J = 6.1 Hz, H-10), 1.25-1.7 (8H, m, H-5, H-6, H-7, H-8), 2.3 (2H, m, H-4), 3.8 (1H, m, H-9), 5.8 (1H, d, J = 15.6 Hz, H-2), 7.05 (1H, dt, J_1 = 15.6 Hz, J_2 = 7.0 Hz, H-3), 7.3 (2H, br.s, OH). ^{13}C NMR (75 MHz, $CDCl_3$): 171.59 (C-1), 152.04 (C-3), 120.85 (C-2), 68.23 (C-9), 36.97 (C-8), 32.24 (C-4), 29.13 and 27.86 (C-6/C-5), 25.49 (C-7), 23.32 (C-10).

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