Synthesis and Absolute Configuration of Serricorole and Serricorone, Sex Pheromone Components of Cigarette Beetle[†]

Takashi EBATA and Kenji MORI*

Department of Agricultural Chemistry, The University of Tokyo,
1-1-1 Yayoi, Bunkyo-ku, Tokyo 113, Japan

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(2*S*,3*R*,1'*S*,2'*S*)-Serricorole (**1**) and (2*S*,3*R*,1'*R*)-serricorone (**2**), sex pheromone components of the cigarette beetle (*Lasioderma serricorne* F.), were synthesized, starting from the enantiomers of methyl 3-hydroxypentanoate. The stereochemistry of the naturally occurring **1** was determined to be 2*S*,3*R*,1'*S*,2'*S*, and that of **2** to be 2*S*,3*R*,1'*R**S* by comparing between the CD spectra of the natural and synthetic samples.

Serricorole (**1**) [2,3-dihydro-3,5-dimethyl-2-ethyl-6-(1-methyl-2-hydroxybutyl)-4*H*-pyran-4-one] and serricorone (**2**) [2,3-dihydro-3,5-dimethyl-2-ethyl-6-(1-methyl-2-oxobutyl)-4*H*-pyran-4-one] were isolated by Chuman *et al.* as

FIG. 1. Structures of the Target Molecules and Related Compounds.

new components of the sex pheromone produced by females of the cigarette beetle, *Lasioderma serricorne* F.¹⁾ This insect is known as a serious pest of cured tobacco leaves and almost all dry foodstuffs. Previously, Chuman *et al.* also reported the isolation of serricornin **3** as the major component of the sex phero-

none of the cigarette beetle.²⁾ The proposed structures of serricorole (**1**) and serricorone (**2**) have been confirmed by the synthesis of their racemic and diastereomeric mixtures.¹⁾ It is noteworthy that these pheromones have almost the same structures as those of stegobiol (**4**)³⁾ and stegobinone (**5**),⁴⁾ the sex pheromone of the drugstore beetle (*Stegobium paniceum* L.) belonging to the same Anobiidae. However, nothing is known about the absolute stereochemistry of natural serricorole (**1**) and serricorone (**2**). We therefore became interested in the stereocontrolled synthesis of serricorole (**1**) and serricorone (**2**) to clarify both the absolute stereochemistry of natural compounds and their actual role in the sex pheromone activity against the cigarette beetle in comparison with serricornin (**3**). As our synthetic targets, we chose (2*S*, 3*R*, 1'*S*,2'*S*)-serricorole (**1**) and (2*S*, 3*R*, 1'*R*)-serricorone (**2**) as shown in Fig. 1. The choice was made on the basis of the established stereochemistry of stegobiol (**4**) and stegobinone (**5**).

As shown in Fig. 2, our synthetic strategy for serricorole (**1**) and serricorone (**2**) was same as that employed previously for stegobiol (**4**)⁵⁾

[†] Pheromone Synthesis. Part 103. For Part 102, see T. Kitahara, M. Mori and K. Mori, *Tetrahedron*, **43**, 2689 (1987).

* Address correspondence to this author.

FIG. 2. Syntheses of Serricorole (1) and Serricorone (2).

and stegobinone (5).⁶ An intramolecular acylation (9→1) was the key-step. The starting materials were the (*R*)- and (*S*)-isomers of methyl 3-hydroxypentanoate. Both the enantiomers of this ester were readily available in quantity by microbial processes^{7,8} and were employed by us for natural product synthesis.⁹

The 13-step conversion of (*R*)-6 to (4*R*,5*S*)-sitophilure (7), the aggregation pheromone of the rice weevil and the maize weevil, was carried out as reported previously by us in a 2.0% overall yield.⁹ The chemical purity of 7 was shown to be >98% with an optical purity of 100%. Another key intermediate (8) was prepared from (*S*)-6 in an 11% overall yield via a 5-step conversion as previously reported by us.⁵ Both the chemical and optical purities of 8 were shown to be 100%.⁵ Esterification of 8 with 7 was carried out under the Yamaguchi condition,¹⁰ using commercially available 2,6-dichlorobenzoyl chloride^{5,6} instead of 2,4,6-trichlorobenzoyl chloride in the original procedure, to give 9 in a 92% yield. Treatment of 9 with 2 eq of lithium hexamethyldisilazide followed by acidification with monochloroacetic acid and deprotection with hydrogen fluoride afforded (2*S*,3*R*,1'*S*,2'*S*)-serricorole (1) in an 18% yield after purification by preparative

TLC. Our synthetic serricorole (1) showed NMR and mass spectral properties identical to those of the natural pheromone. The overall yield of (2*S*,3*R*,1'*S*,2'*S*)-1 was 0.3% in 17 steps from (*R*)-6 or 1.8% in 9 steps from (*S*)-6. Subsequent oxidation of serricorole (1) under the Swern condition¹¹ gave serricorone (2) in a 65% yield after purification by preparative TLC. The mass spectral properties of our synthetic (2*S*,3*R*,1'*R*)-serricorone (2) coincided with those reported for the natural pheromone. The stereochemical homogeneity at C-1' of our synthetic 2 was confirmed to be >99% by its 500 MHz ¹H NMR measurement and also by its HPLC analysis.

As shown in Table I, the CD spectral data of our synthetic (2*S*,3*R*,1'*S*,2'*S*)-serricorole (1) were in good accord with those of natural 1. The absolute configuration of natural serricorole was thus assigned as 2*S*,3*R*,1'*S*,2'*S*. The CD spectral data of our (2*S*,3*R*,1'*R*)-serricorone (2) and natural 2 are listed in Table II. The negative extrema due to the enone n→π* chromophore in the 350 nm region indicate the stereochemistry at C-2 and C-3 of

TABLE I. CD SPECTRAL DATA OF SYNTHETIC AND NATURAL SERRICOROLE

Wavelength (nm)	$\Delta\epsilon$	
	Natural	Synthetic
355	-0.62	-0.70
342	-1.31	-1.42
331	-1.25	-1.37
289	+0.15	+0.18
259	-1.60	-1.33

TABLE II. CD SPECTRAL DATA OF SYNTHETIC AND NATURAL SERRICORONE

Wavelength (nm)	$\Delta\epsilon$	
	Natural	Synthetic
360	-0.49	-0.54
344	-0.75	-0.84
331	-0.74	-0.54
289	+1.17	-13.7
262	-2.05	+8.95

TABLE III. CD SPECTRAL DATA OF SYNTHETIC (2*S*,3*R*,1'*RS*) AND (2*S*,3*R*,1'*R*)-STEGOBINONE

Wavelength (nm)	$\Delta\epsilon$
Natural	
359	-0.61
343.5	-1.39
332	-1.39
283.5	+0.11
258	-0.82
Synthetic	
360	-0.46
345	-0.86
332	-0.69
290	-12.9
262	+8.8

natural serricorone to be 2*S*,3*R*. However, in the 260 to 280 nm region, the CD data of (2*S*,3*R*,1'*R*)-**2** were considerably different from those of natural **2**. Previously, we observed almost the same differences in CD data between (2*S*, 3*R*,1'*R*)-stegobinone (**5**) and (2*S*,3*R*,1'*RS*)-**5**⁽¹²⁾ as shown in Table III. Thus, the natural serricorone (**2**) seems to have been stereochemically heterogeneous at C-1'. This fact was also confirmed by its 500 MHz ¹H NMR measurement. Consequently, the absolute stereochemistry of the natural pheromone **2** was 2*S*,3*R*,1'*RS*. It is a very rare case that the natural pheromone was isolated as an epimeric mixture, if this epimerization had not been caused during the isolation procedure.

In conclusion, (2*S*, 3*R*,1'*S*,2'*S*)-serricorole (**1**) and (2*S*,3*R*,1'*R*)-serricorone (**2**) were synthesized. This work allowed us the assignment of the (2*S*,3*R*,1'*S*,2'*S*)-absolute configuration to the natural pheromone **1** and (2*S*,3*R*,1'*RS*)-stereochemistry to the natural pheromone **2**. Biological studies on our synthetic **1** and **2** are now under way by Dr. Chuman of Japan Tobacco Inc.

EXPERIMENTAL

IR spectra were measured as films for oils on a JASCO A-102 spectrometer. ¹H-NMR spectra were recorded at 60 MHz with TMS as an internal standard on a Hitachi R-24A spectrometer, unless otherwise stated. Optical ro-

tations were measured on a JASCO DIP-140 polarimeter. Mass spectra were recorded at 70 eV on a JEOL DX-300 spectrometer. CD spectra were recorded on a JASCO J-20 automatic spectropolarimeter.

(1'*S*,2'*R*)-1'-Ethyl-2'-methyl-3-oxopentyl (2*S*,3*S*)-3-*t*-butyldimethylsilyloxy-2-methylpentanoate (**9**). 2,6-Dichlorobenzoyl chloride (577 mg, 2.76 mmol) was added to a mixture of **8** (678 mg, 2.76 mmol) and Et₃N (306 mg, 3.03 mmol) in dry THF (14 ml) under Ar. The mixture was stirred overnight at room temperature. After the removal of Et₃N·HCl by filtration, the filtrate was concentrated under N₂, and the residue was dissolved in dry benzene (10 ml). To this solution were added a solution of **7** (397 mg, 2.76 mmol) in dry benzene (3 ml) and DMAP (370 mg, 3.03 mmol) in dry benzene (3 ml) at 0°C under Ar. The resulting mixture was stirred for 5 hr at 0°C. It was then diluted with ether (15 ml), successively washed with 1 N HCl, water and saturated NaHCO₃ solution, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by chromatography over SiO₂ (Merck Kieselgel 60, 15 g). Elution with *n*-hexane-ether (20:1) gave 929 mg (90.2%) of **9**, IR $\nu_{\max}$ cm⁻¹ 2980 (s), 2950 (s), 2885 (m), 2860 (m), 1735 (s), 1720 (s), 1255 (s), 1185 (s), 1110 (s), 1050 (s), 1015 (s), 835 (s), 775 (s); NMR δ (CCl₄) 0.07 (6H, s), 0.6~0.8 (28H, m, containing at 0.89, 9H, s), 2.2~3.0 (4H, m), 3.82 (1H, dt, *J*=5 Hz, 5 Hz), 5.02 (1H, dt, *J*=5 Hz, 6 Hz).

(2*S*,3*R*,1'*S*,2'*S*)-Serricorole (**1**). To a solution of **9** (100 mg, 0.27 mmol) in dry THF (5 ml) and TMEDA (1 ml) was slowly added dropwise a solution of lithium hexamethyldisilazide in dry THF (0.34 M, 0.80 ml, 0.27 mmol) with stirring at -70°C under Ar. The reaction temperature was gradually raised to 0°C over 2 hr. The reaction mixture was then cooled (-70°C) again, and to it was added dropwise a solution of lithium hexamethyldisilazide in dry THF (0.34 M, 0.80 ml, 0.27 mmol). The mixture was poured into 10% ClCH₂CO₂H aq. (255 ml) and THF (25 ml). After stirring overnight at room temperature, the solution was concentrated *in vacuo* to remove THF. The residue was next extracted with ether. The ether solution was washed with water, saturated NaHCO₃ aq. and brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was dissolved in MeCN (2 ml). To this solution were added 5 drops of 46% HF aq. After stirring for 5 hr at room temperature, the mixture was diluted with ether (10 ml). The ether solution was washed with water, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by preparative TLC (Merck Kieselgel 60 F₂₅₄, *n*-hexane-ether=1:3, *R*_f=0.25) to give 11.6 mg (18.0%) of **1**, [α]_D²⁴ -113±3° (*c*=0.15, CHCl₃); IR $\nu_{\max}$ cm⁻¹ 3470 (m), 2970 (s), 2940 (s), 2880 (m), 1660 (s), 1605 (s), 1455 (m), 1385 (m), 1370 (m), 1365 (m), 1350 (m), 1190 (m), 1150 (m), 1140 (m), 1110 (m), 1070 (m), 1025 (m), 970 (m); NMR δ (500 MHz, CDCl₃) 1.00 (3H, t, *J*=7.4 Hz), 1.01 (3H, t, *J*=7.4 Hz), 1.02 (3H, d, *J*=7.4 Hz), 1.19 (3H, d,

$J=7.2$ Hz), 1.37~1.47 (1H, m), 1.53~1.64 (2H, m), 1.75 (3H, s), 1.79~1.89 (2H, m), 2.37 (1H, dq, $J=3.4$ Hz, 7.4 Hz), 2.88 (1H, dq, $J=7.2$ Hz, 6.7 Hz), 3.55~3.62 (1H, m), 4.15~4.19 (1H, m). MS (m/z) 241 ($M^+ + 1$, 4%), 240 (M^+ , 19%), 183 (13%), 182 (95%), 153 (23%), 141 (13%), 125 (19%), 124 (31%), 113 (88%), 112 (100%), 109 (30%), 83 (45%), 70 (19%), 69 (20%), 59 (26%), 57 (26%), 55 (26%). Found: MS (m/z) 240.1698 (M^+). Calcd. for $C_{14}H_{24}O_3$: 240.1726.

(2*S*,3*R*,1'*R*)-Serricorone (2). To a cooled (-70°C) and stirred solution of oxalyl chloride (10.3 mg, 0.08 mmol) in dry CH_2Cl_2 (0.7 ml) was added dropwise a solution of dimethyl sulfoxide (8.4 mg, 0.11 mmol) in dry CH_2Cl_2 (0.2 ml) under Ar. The mixture was stirred for 2 min at -70°C , and then a solution of **1** (13 mg, 0.05 mmol) in dry CH_2Cl_2 (0.2 ml) was added dropwise with stirring. After 50 min at -70°C , Et_3N (27.3 mg, 0.27 mmol) was added dropwise and the stirring was continued for 20 min this temperature. The mixture was allowed to warm to 0°C , stirred for 20 min at this temperature, and partitioned between a mixture of benzene-ether (4:1, 2 ml) and water (2 ml). The organic layer was washed with brine, dried over MgSO_4 and concentrated *in vacuo*. The residue was purified by preparative TLC (Merck, Kieselgel 60 F_{254} , *n*-hexane-ether = 1:1, $R_f=0.44$) to give 8.4 mg (65.1%) of **2**, $[\alpha]_D^{24} -269 \pm 4^\circ$ ($c=0.11$, CHCl_3); IR ν_{max} cm^{-1} 2980 (m), 2940 (m), 2880 (m), 1725 (s), 1665 (s), 1615 (s), 1450 (m), 1380 (m), 1365 (m), 1350 (m), 1185 (m), 1150 (m), 1140 (m), 1070 (m), 1050 (m); NMR δ (500 MHz, CDCl_3) 0.95 (3H, t, $J=7.4$ Hz), 1.02 (3H, d, $J=7.3$ Hz), 1.06 (3H, t, $J=7.2$ Hz), 1.32 (3H, d, $J=6.9$ Hz), 1.48~1.57 (1H, m), 1.74~1.84 (4H, m, containing at 1.79, 3H, s), 2.34~2.52 (3H, m), 3.65 (1H, q, $J=6.9$ Hz), 4.09~4.15 (1H, m). MS (m/z) 239 ($M^+ + 1$, 4%), 238 (M^+ , 18%), 183 (13%), 182

(100%), 153 (10%), 124 (27%), 113 (45%), 109 (14%), 83 (16%), 57 (79%), 55 (13%). Found: MS (m/z) 238.1562 (M^+). Calcd. for $C_{14}H_{22}O_3$: 238.1567.

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