Synthesis of 1'-Epi-stegobinone

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1'-Epi-stegobinone [(2*S*,3*R*,1'*S*)-2,3-dihydro-2,3,5-trimethyl-6-(1'-methyl-2'-oxobutyl)-4H-pyran-4-one], an inhibitor of stegobinone, which is the sex pheromone of drugstore beetle (*Stegobium paniceum* L.), was synthesized by stereocontrol at C-2 and C-1' starting from ethyl (*R*)-3-hydroxybutanoate and methyl (*R*)-3-hydroxypentanoate.

The drugstore beetle (*Stegobium paniceum* L.) is known as a devastating pest of stored food and crops. The sex pheromone of this insect, stegobinone (**1**) was isolated by Kuwahara *et al.*,¹⁾ and very recently, stegobiol (**2**) has been isolated by Kodama *et al.*²⁾ Previously, we reported the synthesis of both the pheromones in a stereoselective manner and confirmed the absolute stereochemistry of the natural pheromone to be (2*S*,3*R*,1'*R*)-**1**³⁾ and (2*S*,3*R*,1'*S*,2'*S*)-**2**,⁴⁾ respectively. Our chemical studies on the sex pheromone of drugstore beetle revealed the biologically interesting fact that (2*S*,3*R*,1'*RS*)-**1** had no pheromone activity against the drugstore beetle in contrast with (2*S*,3*R*,1'*R*)-**1**.³⁾ This fact suggested that (2*S*,3*R*,1'*S*)-**3** inhibited the pheromone activity of (2*S*,3*R*,1'*R*)-**1** (stegobinone). Very recently, Kodama *et al.* also reported the inhibition of the male response of drugstore beetle against racemic stegobinone (**1**) by its racemic 1'-epimer (**3**).⁵⁾ It is very rare case that one of the diastereomers, and not an enantiomer, inhibits an other's pheromone activity. Only one example has been reported about this type of inhibition to data.⁶⁾ Moreover, very recently Kodama's investigation suggested another interesting fact. That is, (2*S*,3*R*,1'*R*,2'*R*)-**4** inhibited the activity of (2*S*,3*R*,1'*S*,2'*S*)-**2** (stegobiol).⁷⁾ In order to clarify the stereochemistry-inhibitory activity

relationship, we became interested in synthesizing these two compounds in an optically pure state.

As shown in Fig. 1, our synthetic strategy for **3** and **4** was the same as that employed previously for stegobinone (**1**)³⁾ and stegobiol (**2**).⁴⁾ An intramolecular acylation (**10**→**3**) was the key-step, the starting materials being ethyl (*R*)-3-hydroxybutanoate (**5**)⁸⁾ and methyl (*R*)-3-hydroxypentanoate (**7**). These esters were readily available in quantity by microbial processes and were employed by us for natural product synthesis.^{3,4,10)}

The 13-step conversion of **5** to hydroxy ketone **6** was carried out as reported previously by us in a 27.0% overall yield.³⁾ The chemical purity of **6** was shown to be >97% with an optical purity of 100%. Another key intermediate (**9**) was derived from **7** via **8a**. The 3-step conversion of **7** to **8a** was carried out as reported previously in a 12.3% overall yield.¹¹⁾ Both the chemical and optical purities of **8a** were shown to be 100%. Silylation of **8a** with *t*-butyldimethylsilyl chloride (TBDMS Cl) gave **8b** in a 90.0% yield. This ester **8b** was saponified with KOH aq. to give **9** in a 95.2% yield. Esterification of **9** with **6** was carried out under Yamaguchi conditions,¹²⁾ but using commercially available 2,6-dichlorobenzoyl chloride instead of the 2,4,6-trichlorobenzoyl chloride of the original procedure,^{3,4,10b)} to

Fig. 1. Structures of the Target Molecules and Their Syntheses.

give **10** in an 89.7% yield. Treatment of **10** with 2 eq. of lithium hexamethyldisilazide, which was followed by acidification with monochloroacetic acid and deprotection with hydrogen fluoride, afforded **4**, $[\alpha]_D^{23} -100^\circ$ (CHCl_3), in a 13.8% yield after purification by preparative TLC. The IR, NMR and mass spectral properties supported the structure of **4**. Subsequent oxidation of **4** under Swern conditions gave **3** as crystals (mp $47-48^\circ\text{C}$; in lit.¹³⁾ mp $46-48^\circ\text{C}$), $[\alpha]_D^{23} +8.1^\circ$ (CHCl_3) in a 63.0% yield after purification by preparative TLC. The stereochemical homogeneity at C-1' of our synthetic **3** was confirmed to be $>99\%$ by 500 MHz ^1H -NMR measurement and also by HPLC analysis.

The CD spectral data of stegobiol (**2**) and its (2*S*,3*R*,1'*R*,2'*R*)-isomer (**4**) are listed in Table I, and those of stegobinone (**1**) and 1'-epi-

Table I. CD SPECTRAL DATA OF **2** AND **4**

2		4	
λ (nm)	$\Delta\epsilon$	λ (nm)	$\Delta\epsilon$
355	-0.80	355	-0.46
341	-1.64	340	-0.98
329	-1.69	329	-1.20
282	+0.25	285	-0.08
254	-0.82	255	-0.94

stegobinone (**3**) in Table II. As can be seen from Table I, compounds **2** and **4** showed almost the same CD spectral properties. On the other hand, the CD spectral data of **1** and **3** had very significant differences in the 250 to 300 nm region. It was apparent that these differences were caused by the perturbation of the C-2' carbonyl group.

Table II. CD SPECTRAL DATA OF 1 AND 3

1		3	
λ (nm)	$\Delta\epsilon$	λ (nm)	$\Delta\epsilon$
360	-0.46	360	-0.88
345	-0.86	345	-2.18
332	-0.69	331	-2.34
290	-12.9	285	+13.4
262	+8.8	261	-10.9

In conclusion, 1'-epi-stegobinone (**3**) was synthesized *via* (2*S*,3*R*,1'*R*,2'*R*)-stegobiol (**4**). The overall yield was 2.1% in 18 steps from **5**, or 0.8% in 10 steps from **7**. Biological studies on our synthetic **3** and **4** are now underway.

Experimental

All bp and mp data are uncorrected. IR spectra were measured as films 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 rotations 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 spectro-polarimeter.

*Methyl (2*R*,3*R*)-3-*t*-butyldimethylsilyloxy-2-methylpentanoate (8b)*. Imidazole (300 mg, 4.41 mmol) and TBDMS Cl (443 mg, 2.94 mmol) were added to a stirred solution of **8a** (326 mg, 2.23 mmol) in dry DMF (5 ml). The mixture was stirred overnight at room temp., before being poured into an ice-water mixture and extracted with ether. The ether solution was washed with water and brine, dried (MgSO₄) and concentrated *in vacuo*. The residue was distilled to give 522 mg (90.0%) of **8b**, bp 87–88°C (5 mmHg); n_D^{23} 1.4278; $[\alpha]_D^{23}$ -38.0° (c =0.79, CHCl₃); IR $\nu_{\max}$ cm⁻¹ 2980 (m), 2960 (m), 2910 (m), 2880 (m), 1745 (s), 1465 (m), 1260 (m), 1120 (m), 840 (s); NMR δ (CCl₄) 0.04 (6H, s), 0.81 (3H, t, J =7 Hz), 0.84 (9H, s), 1.02 (3H, d, J =7 Hz), 1.09–1.70 (2H, m), 2.51 (1H, dq, J =7 and 7 Hz), 3.54 (3H, s), 3.6–4.0 (1H, m). *Anal.* Found: C, 59.63; H, 10.64. *Calcd.* for C₁₃H₂₈O₃Si: C, 59.95; H, 10.84%.

*(2*R*,3*R*)-3-*t*-Butyldimethylsilyloxy-2-methylpentanoic acid (9)*. To a stirred solution of **8b** (502 mg, 1.93 mmol) in MeOH (6 ml) was added dropwise 1*N* KOH aq. (3 ml, 3 mmol). The mixture was stirred for 6 hr under reflux, and after cooling, was concentrated *in vacuo* to remove MeOH. The residue was extracted with ether, and the aq. layer was acidified (pH 5) by the addition of AcOH. This was then

extracted with ether. The ether solution was washed with water, dried (MgSO₄) and concentrated *in vacuo* to give 452 mg (95.2%) of **9**, IR $\nu_{\max}$ cm⁻¹ 3000 (br.), 2960 (s), 2940 (s), 2900 (m), 2860 (m), 1720 (s), 1460 (m), 835 (s), 775 (s). This was employed in the next step without further purification.

*(1'*S*,2'*S*)-1',2'-Dimethyl-3-oxopentyl (2*R*,3*R*)-3-*t*-butyldimethylsilyloxy-2-methylpentanoate (10)*. 2,6-Dichlorobenzoyl chloride (852 mg, 4.07 mmol) and Et₃N (452 mg, 4.48 mmol) in dry THF (20 ml) under Ar. The mixture was stirred overnight at room temp. After the removal of Et₃N-HCl by filtration, the filtrate was concentrated under N₂, and the residue was dissolved in dry C₆H₆ (15 ml). To this solution were added a solution of **6** (529 mg, 4.07 mmol) in dry C₆H₆ (5 ml) and DMAP (546 mg, 4.48 mmol) in dry C₆H₆ (15 mmol) at 0° under Ar. The resulting mixture was stirred for 5 hr at 0°C. It was then diluted with ether (20 ml), successively washed with 1*N* HCl, water, saturated NaHCO₃ aq. and brine, dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by chromatography over SiO₂ (Kieselgel 60, 25 g). Elution with *n*-hexane-ether (20:1) gave 1.31 g (89.7%) of **10**, IR $\nu_{\max}$ cm⁻¹ 2980 (s), 2950 (s), 2900 (m), 2870 (m), 1735 (s), 1720 (s), 1265 (s), 1175 (s), 1120 (s), 1080 (s), 1050 (s), 1015 (s), 835 (s), 775 (s); NMR δ (CCl₄) 0.03 (6H, s), 0.6–1.7 (26H, m, containing 0.87, 9H, s), 2.2–2.9 (2H, m), 3.65–4.0 (1H, m), 4.8–5.3 (1H, m).

*(2*S*,3*R*,1'*R*,2'*R*)-Stegobiol (4)*. To a solution of **10** (300 mg, 0.84 mmol) in dry THF (15 ml) and TMEDA (13 ml) was slowly added dropwise a solution of lithium hexamethyldisilazide in dry THF (0.34*M*, 2.47 ml, 0.84 mmol) with stirring at -70°C under Ar. The reaction temp. was gradually raised to 0°C over 2 hr. Then, the reaction mixture was cooled (-70°C) again, and to it was added dropwise a solution of lithium hexamethyldisilazide in dry THF (0.34*M*, 2.47 ml, 0.84 mmol). The reaction temp. was gradually raised again to 0°C over 2 hr, before the mixture was poured into 10% ClCH₂CO₂H aq (80 ml) and THF (80 ml). After stirring overnight at room temp, the solution was concentrated *in vacuo* to remove the THF. The residue was extracted with ether. The ether solution was successively washed with water, saturated NaHCO₃ aq. and brine, dried (MgSO₄) and concentrated *in vacuo*. The residue was dissolved in MeCN (5 ml), to this solution were added 7 drops of 46% HF aq. After stirring for 5 hr at room temp., the mixture was diluted with ether (20 ml). The ether solution was washed with water, dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by preparative TLC (Merck Kieselgel 60 F₂₅₄, *n*-hexane-ether=1:3, R_f =0.23) to give 26 mg (13.8%) of **4**, $[\alpha]_D^{23}$ -80.0° (c =0.1, CHCl₃); IR $\nu_{\max}$ cm⁻¹ 3420 (br.), 2990 (m), 2940 (m), 2890 (m), 1650 (s), 1600 (s), 1455 (m), 1380 (s), 1345 (m), 1215 (m), 1145 (s), 1115 (s), 975 (m); NMR δ (CDCl₃, 500 MHz) 1.00 (3H, t, J =7.4 Hz), 1.07

(3H, d, $J=7.3$ Hz), 1.17 (H, d, $J=7.1$ Hz), 1.35 (3H, d, $J=6.6$ Hz), 1.4–1.5 (1H, m), 1.5–1.6 (1H, m), 1.75 (3H, s), 1.92 (1H, d, $J=7$ Hz), 2.32 (1H, dq, $J=3.2$ and 7.3 Hz), 2.84 (1H, dq, $J=7.1$ and 7.1 Hz), 3.54–3.63 (1H, m), 4.43 (1H, dq, $J=3.2$ and 6.6 Hz). CD ($\Delta\epsilon$ in *n*-hexane) -0.94 (255 nm), -0.08 (285 nm), -1.20 (329 nm), -0.98 (340 nm), -0.46 (355 nm). MS (m/z) 227 ($M^+ + 1$, 5%), 226 (M^+ , 30%), 168 (72%), 124 (22%), 113 (80%), 112 (100%), 109 (21%), 83 (61%), 59 (30%), 57 (27%), 56 (23%), 55 (30%). Found: MS (m/z) 226.1559 (M^+). Calcd. for $C_{13}H_{22}O_3$: 226.1569.

(2*S*,3*R*,1'*S*)-*Stegobinone* (3). To a cooled (-70°C) and stirred solution of oxalyl chloride (39.4 mg, 0.31 mmol) in CH_2Cl_2 (3 ml) was added dropwise a solution of DMSO (32.3 mg, 0.41 mmol) in dry CH_2Cl_2 (0.6 ml) under Ar. The mixture was stirred for 2 min at -70°C , and then a solution of **4** (46.8 mg, 0.21 mmol) in dry CH_2Cl_2 (0.6 ml) was added dropwise with stirring. After 50 min at -70°C , Et_3N (105 mg, 1.04 mmol) was added dropwise, and the stirring was continued for 15 min at this temp. The mixture was allowed to warm to 0°C , stirred for 20 min at this temp., and partitioned between a mixture of C_6H_6 -ether (4:1, 6 ml) and water (6 ml). The organic layer was washed with brine, dried (MgSO_4) and concentrated *in vacuo*. The residue was purified by preparative TLC (Merck, Kieselgel 60 F_{254} , *n*-hexane-ether = 1:1, $R_f=0.42$) to give 29.2 mg (63%) of **3**, mp $47\text{--}48^\circ\text{C}$, $[\alpha]_D^{23} +8.1^\circ$ ($c=0.11$, CHCl_3); IR $\nu_{\text{max}} \text{ cm}^{-1}$ 2995 (s), 2950 (s), 2890 (m), 1725 (s), 1665 (s), 1610 (s), 1455 (s), 1385 (s), 1345 (s), 1215 (s), 1145 (s), 1120 (s), 1095 (m), 1050 (s), 955 (m), 915 (m), 705 (m); NMR δ (CDCl_3 , 500 MHz), 1.05 (3H, d, $J=7.3$ Hz), 1.07 (3H, t, $J=7.3$ Hz), 1.29 (3H, d, $J=7.1$ Hz), 1.30 (3H, d, $J=6.7$ Hz), 1.80 (3H, s), 2.31–2.56 (3H, m), 3.65 (1H, q, $J=7.1$ Hz), 4.43 (1H, dq, $J=3.4$ and 6.7 Hz). CD ($\Delta\epsilon$ in *n*-hexane) -10.9 (261 nm), $+13.4$ (288 nm), -2.34 (331 nm), -2.18 (345 nm), -0.88 (360 nm). MS (m/z) 224 (M^+ , 21%), 169 (13%), 168 (100%), 139 (13%), 124 (17%), 112 (14%), 109 (15%), 83 (20%), 57 (81%), 55 (13%). HPLC (column, Nucleosil 50-5, 25 cm $\times$ 4.6 mm; solvent,

n-hexane-THF-MeOH = 6000:100:2; flow rate, 1.0 ml/min) R_t 2.18 hr (99.5%), 2.31 hr (0.5%). Found: MS (m/z) 224.1450 (M^+). Calcd. for $C_{13}H_{20}O_3$: 224.1412.

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References

- 1) Y. Kuwahara, H. Fukami, R. Howard, S. Ishii, F. Matsumura and W. E. Burkholder, *Tetrahedron*, **34**, 1769 (1978).
- 2) H. Kodama, M. Ono, M. Kohno and A. Ohnishi, *J. Chem. Ecol.*, **13**, 1871 (1987).
- 3) K. Mori and T. Ebata, *Tetrahedron*, **42**, 4413 (1986).
- 4) K. Mori and T. Ebata, *Tetrahedron*, **42**, 4685 (1986).
- 5) H. Kodama, K. Mochizuki, M. Kohno, A. Ohnishi and Y. Kuwahara, *J. Chem. Ecol.*, **13**, 1859 (1987).
- 6) M. Mori, K. Mochizuki, M. Kohno, T. Chuman, A. Ohnishi, H. Watanabe and K. Mori, *J. Chem. Ecol.*, **12**, 83 (1986).
- 7) Kodama's personal communication to T. E.
- 8) T. Sugai, M. Fujita and K. Mori, *Nippon Kagaku Kaishi (J. Chem. Soc. Jpn.)*, **1983**, 1315.
- 9) J. Hasegawa, S. Hamaguchi, M. Ogura and K. Watanabe, *J. Ferment. Technol.*, **59**, 257 (1981).
- 10) a) K. Mori and T. Ebata, *Tetrahedron*, **42**, 4421 (1986).
b) T. Ebata and K. Mori, *Agric. Biol. Chem.*, **51**, 2925 (1987).
- 11) M. Kato and K. Mori, *Agric. Biol. Chem.*, **49**, 3073 (1985).
- 12) J. Inanaga, K. Hirata, H. Saeki, T. Katsuki and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, **52**, 1989 (1979).
- 13) R. W. Hoffmann, W. Ladner, K. Steinbach, W. Massa, R. Schmidt and G. Snatzke, *Chem. Ber.*, **114**, 2786 (1981).