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SYNTHESIS OF (2*S*, 3*R*, 7*RS*)-STEGOBINONE [2,3-DIHYDRO-2,3,5-TRIMETHYL-6-(1-METHYL-2-OXOBUTYL)-4H-PYRAN-4-ONE] AND ITS (2*R*, 3*S*, 7*RS*)-ISOMER

THE PHEROMONE OF THE DRUGSTORE BEETLE†

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Abstract – Reaction of acetaldehyde with the trianion of 4,6-dimethylnonane-3,5,7-trione followed by acidification yielded a stereoisomeric mixture of stegobinone, the pheromone of *Stegobium paniceum* L. Acylation of the dianion derived from 4-methylheptane-3,5-dione with a mixed anhydride prepared from (2*R*, 3*S*)-3-hydroxy-2-methylbutanoic acid or its enantiomer led to (2*S*, 3*R*, 7*RS*)- or (2*R*, 3*S*, 7*RS*)-stegobinone. The natural pheromone possesses (2*S*, 3*R*)-stereochemistry.

Stegobinone [2,3-dihydro-2,3,5-trimethyl-6-(1-methyl-2-oxobutyl)-4H-pyran-4-one] **1** is the sex pheromone produced by the female drugstore beetle (*Stegobium paniceum* L.).[1,2] Its unusual dihydro-γ-pyrone structure with three chiral centers is particularly attractive as a target of our continuing synthetic studies on chiral insect pheromones, since nothing is known concerning its stereochemistry except that the two *vic*-Me groups are in *cis* relationship.[2] Herein we describe a synthesis of a mixture of two diastereomeric racemates with the plain structure **1** and also a synthesis of (2*S*, 3*R*, 7*RS*)- and (2*R*, 3*S*, 7*RS*)-stegobinone. The latter work enabled us to assign the absolute stereochemistry at C-2 and C-3 of the natural stegobinone to be 2*S*, 3*R*.

A plausible biogenetic precursor of stegobinone **1** is a triketo alcohol **2**. We therefore planned and realized a biomimetic synthesis so as to confirm the proposed plain structure of stegobinone, basing on the recent progress in the chemistry of di- and trianions.[3–6] The usefulness of dianion chemistry in pheromone synthesis was already shown by us in the case of chalcogran.[7] The known diketone **3**[8] was converted to a dianion with 2.6 eq of lithium diisopropylamide (LDA) and the dianion was acylated with a mixed anhydride prepared from propionic acid and methyl chloroformate. The resulting triketone **4** in the mixture was then treated with further 2.2 eq of LDA without isolation, and the generated trianion was quenched with acetaldehyde to give the precursor **2** of the pheromone. This was treated with dil HCl to effect cyclization. The product was purified by chromatography to give the pheromone (±)-**1** in 5.6% yield as a diastereomeric mixture of two racemates. The *trans*-isomer (±)-**1′** was also obtained in 5.8% yield as a diastereomeric mixture. The configurational assignment of the two *vic*-Me groups of (±)-**1** and (±)-**1′** was made possible by inspection of their ^{1}H-NMR spectra: a signal due to the proton at C-2 of (±)-**1** was observed at δ 4.46 as 1 H dq (J = 7 and 3 Hz), while that of (±)-**1′** was observed at δ 4.02 as 1 H dq (J = 14 and 7 Hz). The small J-value (3 Hz) indicated the 2,3-*cis* stereochemistry of (±)-**1**. The IR, UV, NMR and mass spectral data of (±)-**1** were identical with the published data of the natural pheromone.[2] Bioassay of our (±)-**1** on drugstore beetle was carried out by Prof. W. E. Burkholder. Its threshold response level for males was 10^{-4} μg. So the synthetic (±)-**1** was somewhat less active than the natural pheromone whose threshold level was 3×10^{-7} μg. The above biomimetic synthesis thus confirmed the proposed plain structure **1** of stegobinone.[9] Simultaneously but independently, Hassner *et al.* published quite a similar synthesis.[10]

Our subsequent task was a chiral synthesis of optically active stegobinone so as to establish the absolute stereochemistry of the natural pheromone and at the same time to clarify the stereochemistry-pheromone activity relationship. The above described biomimetic synthesis was inadequate for that purpose due to the difficulty in executing asymmetric aldol condensation (**4** → **2**) in addition to the possible equilibration at the chiral centers α to the CO groups. Since the stereo-control at C-7 of the side chain seemed particularly difficult, we decided to start our synthesis from tartaric acid enantiomers so as to determine the absolute stereochemistry of the dihydro-γ-pyrone ring.

L-(+)-Tartaric acid **5** was converted into (2*S*, 3*S*)-2,3-epoxybutane **6** as described previously.[11] Lithium diphenylcuprate cleaved the epoxy ring with complete Walden inversion to give a chiral alcohol (2*S*, 3*S*)-**7a**, $[\alpha]_D^{21}$ + 7.41 (ether) in 81% yield. It was shown to be virtually optically pure on the basis of the NMR and glc analyses of its (*S*)-(−)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) ester.[12] After

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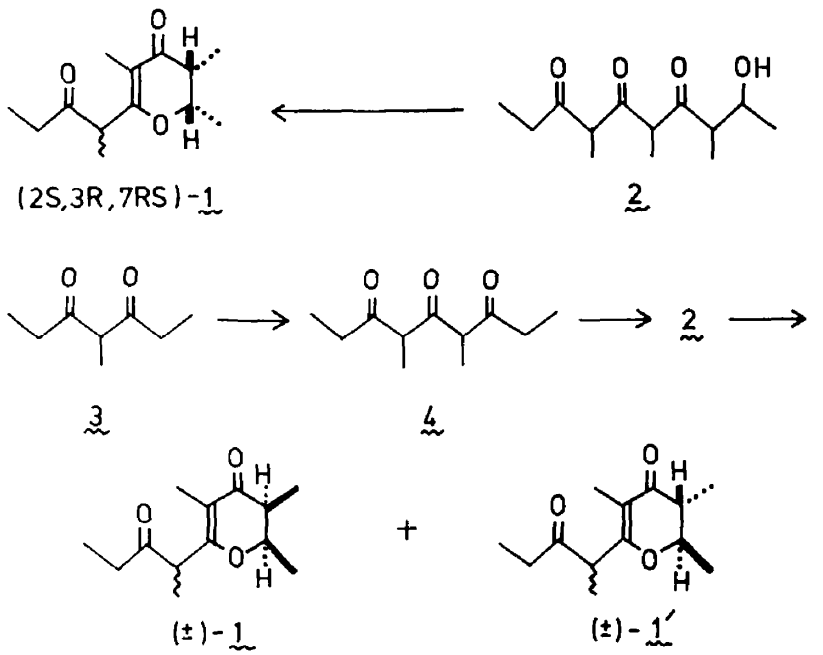
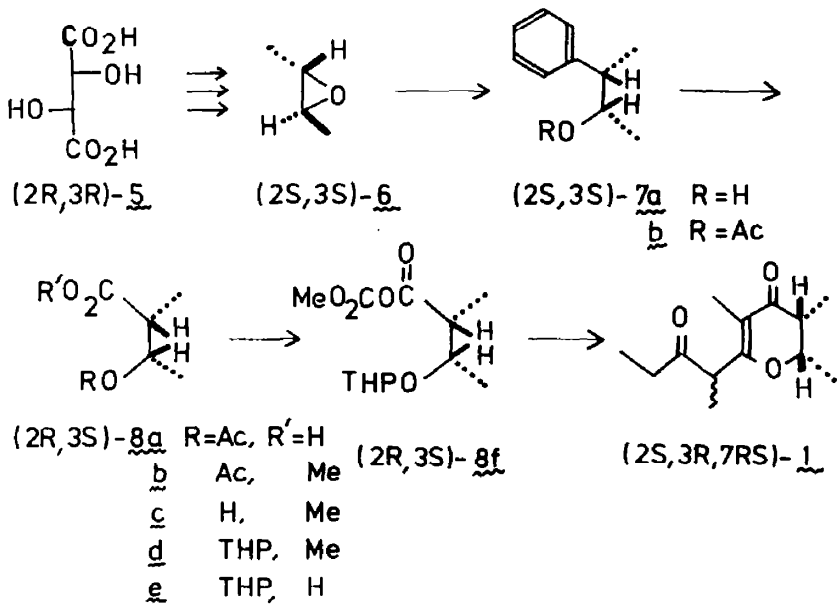
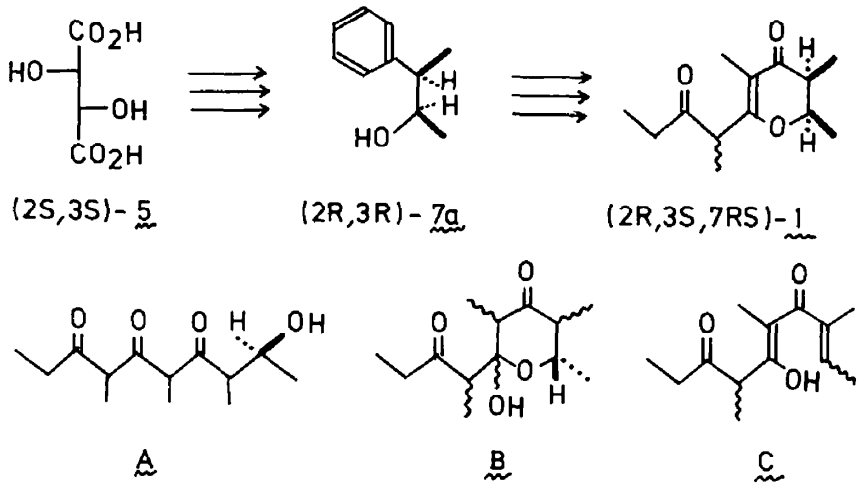


protecting the OH group as an acetate (**7b**), the benzene ring was destroyed by ozonolysis. The ozonide was oxidized with H_2O_2 and the resulting acid (2*R*, 3*S*)-**8a** was esterified with CH_2N_2 to give a Me ester **8b**. Treatment of the acetoxy ester **8b** with MeOH-HCl yielded a hydroxy ester (2*R*, 3*S*)-**8c**, $[\alpha]_D^{22}$-14.1 (MeOH), whose optical purity was shown to be 98% by the glc analysis of its (*S*)-(−)-MTPA ester. The optical rotation of the highly purified (2*S*, 3*R*)-**8c**, obtained by resolution, was reported to be $[\alpha]_D^{20}$ + 14.32 (MeOH).[13] This value is in good accord with ours. The OH group was then protected as a THP ether (**8d**) and the ester group was saponified to give an acid **8e**. This was treated with methyl chloroformate to give a mixed anhydride (2*R*, 3*S*)-**8f**. Acylation of the dianion derived from 4-methylheptane-3,5-dione **3** with the anhydride **8f** was followed by acid treatment to give a complex mixture containing the desired product. This was purified by column chromatography, preparative tlc and preparative glc to give pure (2*S*, 3*R*, 7*RS*)-stegobinone **1**, $[\alpha]_D^{22}$-129° ± 4° ($CHCl_3$), in 2.2% yield from **8c**. Its IR, NMR and mass spectral properties coincided with that of the natural pheromone. In the same manner,





unnatural D-(−)-tartaric acid was converted to (2*R*, 3*R*)-alcohol **7a**, $[\alpha]_D^{22}$ − 7.21 (ether), which was virtually optically pure as determined by the MTPA ester method. The key *erythro*-hydroxy ester (2*S*, 3*R*)-**8c**, $[\alpha]_D^{22}$ + 14.0 (MeOH), was of 98% optical purity. Subsequent transformation yielded (2*R*, 3*S*, 7*RS*)-stegobinone **1**, $[\alpha]_D^{22}$ + 121 ± 3 ($CHCl_3$), in 1.6% yield from **8c**. Hoffmann and Ladner recently reported a synthesis of 65% optically pure (2*R*, 3*S*, 7*RS*)-stegobinone **1** with $[\alpha]_D$ value of 79.8°.[14] Our products **1** with $[\alpha]_D$ value of 121 ~ 129° are therefore highly optically pure at C-2 and C-3 in accord with the 98% optical purity of the starting material **8c**. This retention of configuration at C-2 supports the cyclization mechanism involving intermediates **A** and **B**. If the cyclization were to take place *via* an α,β-unsaturated triketone mono-enol **C** as proposed by Ansell *et al.*[10] complete racemization would result. It therefore seems that the hemiacetal formation from **A** to **B** is followed by dehydration to stegobinone **1**.

The CD spectral data of (2*S*, 3*R*, 7*RS*)- and (2*R*, 3*S*, 7*RS*)-stegobinones are shown in Table 1. Hoffmann's CD data as well as those of the natural pheromone are also listed. The negative extrema due to the enone n → π* chromophore in the 350 nm region indicate that the stereochemistry at C-2 and C-3 of natural stegobinone is same as that of our (2*S*, 3*R*, 7*RS*)-isomer. The CD spectrum of the natural pheromone, however, differs considerably from those of our (2*S*, 3*R*, 7*RS*)-**1** in the 260 to 280 nm region. As suggested by Hoffmann and Ladner,[14] this is probably due to the compensation of the expected exciton couplets in the synthetic 1:1 mixture of C-7 epimers, whereas natural stegobinone seems to be stereochemically homogeneous at C-7.

In conclusion our chiral synthesis allowed the assignment of the absolute configuration of the natural stegobinone to be 2*S*, 3*R*. The configuration at C-7 remains to be determined. The biological activity of our (2*S*, 3*R*, 7*RS*)- and (2*R*, 3*S*, 7*RS*)-stegobinone is under investigation by Prof. W. E. Burkholder, University of Wisconsin.

EXPERIMENTAL

All b.ps were uncorrected. IR spectra refer to films and were determined on a Jasco IRA-1 spectrometer. NMR spectra were recorded as CCl_4 solns 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-4 polarimeter. Glc analyses were performed on a Yanaco G 80 and G 180 gas chromatographs.

Table 1. CD spectral data of natural and synthetic stegobinone measured in *n*-hexane

Natural stegobinone[2]		(2S, 3R, 7RS)-1*			(2R, 3S, 7RS)-1	
				ours**		Hoffmann's[14]
λ360nm	Δε−0.42	λ359nm	−0.63	+0.70	λ358.8nm	Δε+0.49
345	−0.87	343.5	−1.39	+1.50	343.4	+1.03
		332	−1.39	+1.55	331.8	+1.06
285	−13.0	283.5	+0.11	−0.19	284.4	−0.23
260	+9.1	260	-	+1.05	260.8	+0.69

* Measured after two weeks' storage as a 0.05% (w/v) soln.

** Measured immediately after purification as a 0.035% (w/v) soln.

A diastereomeric mixture of (±)-2,3-*dihydro*-2,3,5-*trimethyl*-6-(1-*methyl*-2-*oxobutyl*)-4H-*pyran*-4-*one* (±)-**1**

A soln of LDA in THF was prepared by adding n-BuLi (1.4 N in n-hexane, 37.1 ml) to a soln of i-Pr_2NH (7 ml) in dry THF (40 ml) at −60 with stirring under Ar. After 10 min HMPA (20 ml) and 4-methylheptane-3,5-dione **3** (2.84 g) in dry THF (2 ml) were added and the mixture was stirred at −70 ~ −30 for 1 hr. A soln of $EtCO_2CO_2Me$ (2.904 g) in THF (2 ml) was added to the stirred soln at −40 . The mixture was stirred for 1.5 hr at −40 ~ −30 . An LDA soln [prepd. from 1.4 N-n-BuLi in n-hexane (31.4 ml), i-Pr_2NH (3 ml) and THF (10 ml)] was added to the mixture and it was stirred at −40 ~ −30 for 30 min. Then MeCHO (968 mg, 1.24 ml) was added and the stirring was continued for 30 min at −40 ~ −30 . The mixture was poured into 10% HCl–MeCN (1:1, 200 ml), stirred for 17 hr at room temp, and extracted with n-hexane. The extract was washed with $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over silica gel. Elution with n-hexane ~ n-hexane–ether (8:2) gave crude (±)-**1** and (±)-**1′**. These were separately purified by preparative tlc to give (±)-**1** (252 mg, 5.6%) and (±)-**1′** (258 mg, 5.8%). These were further purified by distillation. The *cis*-isomer (±)-**1** boiled at 120 ~ 135 (bath temp)/4 mm, n_D^{22} 1.4849; ν_{max} (film) 2970 (m), 2920 (m), 2860 (m), 1723 (vs), 1660 (vs), 1605 (vs), 1450 (m), 1385 (s), 1363 (m), 1340 (s), 1215 (m), 1145 (s), 1120 (m), 1090 (m), 1050 (m), 1015 (w), 1000 (w), 960 (w), 910 (w), 705 (w) cm^{-1}; δ (60 MHz, $CDCl_3$) 1.05 (3 H, d, J = 7 Hz), 1.06 (3 H, t, J = 7 Hz), 1.30 (6 H, d, J = 7 Hz), 1.79 (3 H, s), 2.1 ~ 2.7 [3 H, m, 2.48 (2 H, q, J = 7 Hz)], 3.67 (1 H, q, J = 7 Hz), 4.46 (1 H, dq, J = 7 and 3 Hz); λ_{max} (EtOH) 273 nm (ε 10,900); MS: *m/e* 224 ($M^+ = C_{13}H_{20}O_3$). The *trans*-isomer (±)-**1′** boiled at 122 ~ 138° (bath temp)/4 mm, n_D^{22} 1.4804; ν_{max} (film) 2970 (m), 2925 (m), 2870 (m), 1725 (s), 1665 (s), 1615 (s), 1455 (m), 1385 (s), 1360 (s), 1343 (m), 1290 (w), 1260 (w), 1195 (s), 1175 (m), 1150 (s), 1080 (m), 1070 (m), 1045 (m), 1012 (m), 990 (w), 958 (m), 915 (w), 860 (w), 850 (w), 805 (w), 780 (w) cm^{-1}; δ (60 MHz, $CDCl_3$) 1.05 (3 H, t, J = 7 Hz), 1.10 (3 H, d, J = 7 Hz), 1.31 (3 H, d, J = 7 Hz), 1.38 (3 H, d, J = 7 Hz), 1.79 (3 H, s), 2.0 ~ 2.7 [3 H, 2.45 (2 H, q, J = 7 Hz)], 3.62 (1 H, q, J = 7 Hz), 4.02 (1 H, dq, J = 14 and 7 Hz); λ_{max} (EtOH) 273 nm (ε 10,800); MS: *m/e* 224.1 (12%), 169.1 (8%), 168.1 (94%), 167.1 (8%), 153.0 (4%), 139.0 (10%), 125.0 (4%), 124.0 (22%), 114.0 (4%), 113.0 (52%), 112.0 (12%), 111.0 (4%), 110.0 (6%), 109.0 (14%), 107.0 (4%), 57.0 (100%).

3-*Phenylbutan*-2-*ol* **7a**

(a) (2*S*, 3*S*)-(+)-*Isomer*. A soln of PhLi in ether was prepared from PhBr (27.2 g) and Li (4.5 g) in dry ether (200 ml) under Ar. The filtered soln was added dropwise at 0 ~ 10 to a suspension of CuI (10.6 g) in dry ether (50 ml) with stirring. The mixture was stirred for 1 hr at 0 . A soln of (2*S*, 3*S*)-**6** (640 mg) in dry ether (2 ml) was added to the Ph_2CuLi soln at 0 ~ 3 under ice-salt cooling. The mixture was stirred for 1 hr at −5 ~ 0 and then for 13 hr at 5 . Subsequently it was poured into cold NH_4Cl aq., filtered to remove solid ppt, and extracted with ether. The ether soln was washed with brine, dried (K_2CO_3) and concentrated *in vacuo*. The residual oil (4.42 g) was chromatographed over silica gel (Merck Kieselgel 60, 60 g). Elution with n-hexane–ether (20:1 ~ 5:1) gave **7a**. This was distilled to give 1.08 g (81.2%) of pure **7a**, b.p. 82 ~ 84 /7 mm, n_D^{22} 1.5162; $[\alpha]_D^{21}$ + 7.41 (*c* = 1.85, ether); ν_{max} ~ 3340 (br), 3070 (w), 3050 (w), 3010 (m), 2960 (s), 2920 (m), 2880 (m), 1600 (m), 1580 (w), 1495 (s), 1455 (s), 1415 (w), 1375 (m), 1310 (br. w), 1250 (br. w), 1200 (w), 1185 (w), 1150 (m), 1110 (m), 1085 (s), 1045 (m), 1025 (w), 1010 (s), 995 (m), 970 (m), 910 (s), 775 (w), 760 (s), 740 (w), 705 (s) cm^{-1}; δ 1.01 (3 H, d, J = 6 Hz), 1.30 (3 H, d, J = 7 Hz), 1.63 (1 H, br. s), 2.33 ~ 2.90 (1 H, m), 3.50 ~ 4.03 (1 H, m), 7.20 (5 H, s); MS: *m/e* 150 (M^+), 135, 132, 105, 91, 77; GLC (Column, Thermon 1000, 30 m × 0.3 mm. at 120°; Carrier gas, N_2, 40 ml/min): Rt 17.1 min (100%). (Found: C, 79.39; H, 9.41. $C_{10}H_{14}O$ requires: C, 79.96; H, 9.39%).

(b) (2*R*, 3*R*)-(−)-*Isomer*. This was prepared from (2*R*, 3*R*)-**6** (1.80 g) in 80.5% yield (3.02 g), b.p. 98 ~ 102 /13 mm, n_D^{22} 1.5168; $[\alpha]_D^{22}$ − 7.21 (*c* = 2.03, ether).

Acetic ester **7b** *of* 3-*phenylbutan*-2-*ol*

(a) (2*S*, 3*S*)-*Isomer*. Ac_2O (10 ml) was added to a soln of **7a** (4.18 g) in C_5H_5N (20 ml) and the mixture was stirred for 14 hr at room temp. Then it was poured into ice-water and extracted with ether. The ether extract was washed with $CuSO_4$ soln, water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 5.22 g (97.6%) of **7b**, b.p. 86 ~ 91 /6 mm, n_D^{22} 1.4878; ν_{max} 1730 (s), 1595 (w), 1575 (w), 1370 (s), 1240 (s), 1020 (sh), 1010 (s), 700 (s) cm^{-1}; δ 1.00 (3 H, d, J = 6 Hz), 1.26 (3 H, d, J = 7 Hz), 1.99 (3 H, s), 2.50 ~ 3.08 (1 H, m), 4.71 ~ 5.31 (1 H, m), 7.19 (5 H, s). (Found: C, 74.69; H, 8.33. $C_{12}H_{16}O_2$ requires: C, 74.97; H, 8.39%).

(b) (2*R*, 3*R*)-*Isomer*. This was prepared from (2*R*, 3*R*)-**7a** (2.15 g) in 99.3% yield (2.73 g), b.p. 82 ~ 86 /5 mm; n_D^{22} 1.4876.

Methyl 3-*acetoxy*-2-*methylbutyrate* **8b**

(a) (2*R*, 3*S*)-*Isomer*. Ozone was bubbled into a soln of (2*S*, 3*S*)-**7b** (5.17 g) in AcOH (30 ml) with stirring at room temp for 24 hr. Then 35% H_2O_2 (20 ml) was added and the mixture was stirred for 14 hr at room temp. The excess H_2O_2 was destroyed by the addition of a small amount of Pt black. After 4 hr stirring, Pt was filtered off and the filtrate was concentrated *in vacuo* to give crude **8a**. This was treated with ethereal CH_2N_2. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed over silica gel (Kieselgel 60, 60 g). Elution with pentane–ether (20:1 ~ 5:1) gave **8b**. This was distilled to give 2.47 g (52.7%) of pure **8b**, b.p. 71 ~ 75 /7 mm, n_D^{23} 1.4180; ν_{max} 2980 (m), 2940 (m), 2870 (w), 2840 (w), 1740 (s), 1460 (m), 1435 (m), 1370 (m), 1315 (m), 1260 (sh), 1250 (sh), 1240 (s), 1200 (m), 1170 (w), 1135 (w), 1125 (w), 1080 (m), 1030 (m), 1020 (sh), 990 (sh), 970 (w), 940 (m), 880 (m), 850 (m), 815 (w), 760 (m), 700 (m); δ 1.13 (3 H, d, J = 7 Hz), 1.20 (3 H, d, J = 6 Hz), 1.99 (3 H, s), 2.26 ~ 2.88 (1 H, m), 3.65 (3 H, s), 4.78 ~ 5.36 (1 H, m). (Found: C, 54.71; H, 7.90. $C_8H_{14}O_4$ requires: C, 55.15; H, 8.10%).

(b) (2*S*, 3*R*)-*Isomer*. This was prepared from (2*R*, 3*R*)-**7b** (2.72 g) in 56.5% yield (1.39 g), b.p. 74 ~ 76 /9 mm; $n_D^{22.5}$ 1.4171.

Methyl 3-*hydroxy*-2-*methylbutyrate* **8c**

(a) (2*R*, 3*S*)-*Isomer*. A sat soln of HCl gas in MeOH (5 ml) was added to a soln of (2*R*, 3*S*)-**8b** (2.36 g) in MeOH (10 ml). The mixture was stirred for 5 hr at room temp. Then it was neutralized with $NaHCO_3$ aq and concentrated *in vacuo* to remove MeOH. The residue was extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 1.25 g (69.8%) of **8c**, b.p. 73 ~ 77 /12 mm, n_D^{22} 1.4230; $[\alpha]_D^{22}$ − 14.1 (*c* = 1.90, MeOH); ν_{max} 3400 (m), 2940 (m), 2860 (m), 1730 (s), 1710 (s), 1450 (m), 1430 (m), 1405 (w), 1370 (m), 1350 (m), 1305 (w), 1265 (m), 1200 (s), 1170 (s), 1150 (sh), 1105 (sh), 1080 (s), 1060 (m), 1030 (m), 990 (m), 970 (w), 905 (m), 850 (m), 825 (w), 750 (w) cm^{-1}; δ 1.14 (3 H, d, J = 6 Hz), 1.18 (3 H, d, J = 7 Hz), 2.10 ~ 2.85 [2 H, m, 2.56 (1 H, s)], 3.56 ~ 4.18 (1 H, m), 3.69 (3 H, s); GLC (Column, Thermon-1000, 30 m × 0.3 mm at 80 ; Carrier gas, N_2, 50 ml/min): Rt 12.2 min (100%). (Found: C, 54.29; H, 9.14. $C_6H_{12}O_3$ requires: C, 54.51; H, 9.15%).

(b) (2*S*, 3*R*)-*Isomer*. This was prepared from (2*S*, 3*R*)-**8b** (650 mg) in 61.5% yield (303 mg), b.p. 80–95 (bath temp.)/15 mm, n_D^{22} 1.4232; $[\alpha]_D^{22}$ + 14.0 (*c* = 1.45, MeOH).

Methyl 2-*methyl*-3-*tetrahydropyranyloxybutyrate* **8d**

(a) (2*R*, 3*S*)-*Isomer*. Dihydropyran (458 mg) and *p*-TsOH (50 mg) were added to a soln of (2*R*, 3*S*)-**8c** (480 mg) in dry ether (5 ml) and the mixture was stirred for 18 hr at room temp. Then it was washed with sat $NaHCO_3$ aq, dried (K_2CO_3) and concentrated *in vacuo* to give 893 mg (quantitative) of **8d**, ν_{max} 2930 (s), 2860 (m), 1740 (s), 1205 (s), 1180 (m), 1160 (m), 1125 (s), 1075 (s), 1030 (s), 1020 (s), 980

(m), 970 (s) cm^{-1}. This was employed for the next step without further purification.

(b) (2*S*, 3*R*)-*Isomer*. This was prepared from (2*S*, 3*R*)-**8c** (303 mg) in quantitative yield (810 mg).

2-Methyl-3-tetrahydropyranyloxybutyric acid **8e**

(a) (2*R*, 3*S*)-*Isomer*. A soln of KOH (611 mg) in water (5 ml) was added to a soln of (2*R*, 3*S*)-**8d** (893 mg) in MeOH (5 ml). The mixture was stirred for 16 hr at room temp and then concentrated *in vacuo* to remove MeOH. NaCl was added to the residue and the mixture was extracted with ether to remove neutral impurities. Then the aq layer was acidified to pH 4 ~ 5 with AcOH and thoroughly extracted with ether. The ether soln was dried (Na_2SO_4) and concentrated *in vacuo* to give 687 mg of crude **8e**, ν_{max} ~ 2940 (s), ~2610 (m), 1710 (vs), 1290 (s), 1270 (s), 1250 (s), 1135 (s), 1120 (s), 1075 (s), 1020 (s) cm^{-1}. This was employed for the next step without further purification.

(b) (2*S*, 3*R*)-*Isomer*. This was prepared from (2*S*, 3*R*)-**8d** (810 mg) yielding 592 mg of crude **8e**.

2-Methyl-3-tetrahydropyranyloxybutyric methylcarbonic anhydride **8f**

(a) (2*R*, 3*S*)-*Isomer*. A soln of $ClCO_2Me$ (413 mg) in dry ether (5 ml) was added to a soln of (2*R*, 3*S*)-**8e** (687 mg) in dry ether (20 ml). To this soln was added Et_3N (515 mg) in dry ether (10 ml) with stirring at $-6 \sim -4$ (ice-salt bath). After the addition, the mixture was stirred for 2 hr at $-8 \sim -5$. The ppt (Et_3NHCl) was filtered off. The filtrate was washed with water and brine, dried (Na_2SO_4) and concentrated *in vacuo* to give 881 mg of crude **8e**, ν_{max} 2960 (m), 2850 (m), 1820 (vs), 1770 (s), 1255 (s), 1140 (s), 1080 (s), 1030 (s), 1020 (s), 1010 (s), 990 (s) cm^{-1}. This was used for the next step without further purification.

(b) (2*S*, 3*R*)-*Isomer*. This was prepared from (2*S*, 3*R*)-**8e** (592 mg) yielding 584 mg of crude **8f**.

(2*S*, 3*R*, 7*RS*)-(−)-*Stegobinone* **1**

A soln of LDA was prepared from n-BuLi (1.62 N in hexane, 8.48 ml) and i-Pr_2NH (1.5 ml) in THF (5 ml) at −60 with stirring under Ar. After stirring for 15 min, HMPA (5.4 ml) was added dropwise and the temp was raised to −25° to make a homogeneous soln. Then the mixture was cooled to −60 and a soln of **3** (780 mg) in dry THF (2 ml) was added dropwise. The mixture was stirred for 15 min to ensure the dianion formation. Then a soln of (2*R*, 3*S*)-**8f** (881 mg) in dry THF (2 ml) was added and the mixture was stirred at $-60 \sim -5$ for 4 hr. Subsequently it was poured into 10% HCl-MeCN (1:1, 50 ml), stirred for 14 hr at room temp and extracted with ether. The ether soln was washed with $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 1.82 g of an oil. This was chromatographed over silica gel (Merck Kieselgel 60, 20 g, n-hexane–ether = 40: 1 ~ 2:1). The fraction containing **1** was further purified by preparative tlc (Kieselgel 60, F_{254}, double development with n-hexane–ether = 4:3; R_f 0.32) to give 55 mg (6.8% yield) of **1** with 90% purity as checked by glc. The final purification was carried out by glc (Column 5% PEG 20 M, 2 m × 6 mm at 200°; Carrier gas, N_2, 0.5 kg/cm^2; Rt 8.8 min) yielding 18 mg (2.2% from **8c**) of pure **1**, $[\alpha]_D^{24}$ − 129° ± 4° (*c* = 0.22, $CHCl_3$); ν_{max} 2970 (m), 2930 (m), 2870 (m), 1725 (s), 1665 (s), 1610 (s), 1460 (sh), 1455 (m), 1415 (w), 1385 (s), 1365 (m), 1345 (s), 1305 (w), 1290 (w), 1265 (w), 1245 (w), 1215 (m), 1185 (w), 1170 (m), 1145 (s), 1120 (m), 1095 (m), 1070 (sh), 1050 (m), 1015 (m), 1000 (m), 955 (m), 910 (w), 860 (w), 835 (w), 805 (w), 780 (w), 760 (w), 710 (m) cm^{-1}; δ (100 MHz, $CDCl_3$) 1.07 (3 H, d, J = 7 Hz), 1.09 (3 H, t, J = 7 Hz), 1.31 (3 H, d, J = 6 Hz), 1.32 (3 H, d, J = 6 Hz), 1.80 (3 H, s), 2.26 ~ 2.67 (3 H, m), 3.65 (1 H, q, J = 7 Hz), 4.42 (1 H, m); MS: *m/e* 224.1428 (M^+, $C_{13}H_{20}O_3$ requires: 224.1412), 168, 139, 124, 113, 112, 111, 109, 97, 57; glc (Column, 5% OV-17, 2 m × 4 mm at 161°, Carrier gas, N_2, 28 ml/min): Rt 10.4 min (>96%).

(2*R*, 3*S*, 7*RS*)-(+)-*Stegobinone* **1**

This was prepared from (2*S*, 3*R*)-**8f** (582 mg) yielding 41 mg (8.0% yield) of 92% pure **1**, which was further purified by glc to give 8 mg (1.6%) of pure **1**, $[\alpha]_D^{22}$ + 121 ± 3 (*c* = 0.20, $CHCl_3$). We could not isolate the *trans*-isomer **1′** in pure state even after GLC purification. A trace amount of a three-component mixture containing **1′** was obtained which could not be separated.

Determination of the optical purity of **7a**

(a) (2*S*, 3*S*)-*Isomer*. (2*S*, 3*S*)-**7a** was converted to its MTPA ester in the usual manner. The ester (48 mg) and Eu $(fod)_3$ (15 mg) were dissolved in CCl_4 (0.2 ml) and submitted to the NMR measurement: δ 4.40 (OMe, 3 H, s). Glc analyses with four different columns (3% SE-30, 5% PEG 20 M, 5% OV-17 and Thermon 1000) proved the homogeneity of the ester. The optical purity was virtually 100%.

(b) (2*R*, 3*R*)-*Isomer*. The MTPA ester of (2*R*, 3*R*)-**7a** (48 mg) and Eu $(fod)_3$ (15 mg) were dissolved in CCl_4 (0.2 ml) and submitted to the NMR measurement: δ 4.11 (OMe, 3 H, s). Glc analyses with four different columns (3% SE-30, 5% PEG 20 M, 5% OV-17 and Thermon 1000) proved the homogeneity of the ester. The optical purity was virtually 100%.

Determination of the optical purity of **8c**

(a) (2*R*, 3*S*)-*Isomer*. (2*R*, 3*S*)-**8c** was converted to its MTPA ester in the usual manner. It was proved to be pure by NMR measurement. The ester (31 mg) and Eu$(fod)_3$ (33 mg) were dissolved in CCl_4 (0.2 ml) and submitted to the analysis: δ 5.65 (OMe, 3 H, s). However, by glc 1% contamination of the ester derived from (2*S*, 3*R*)-**8c** could be detected. Glc (Column, Thermon 1000, 30 m × 0.3 mm at 172°; Carrier gas, N_2, 40 ml/min): Rt 21.2 min (99%); 21.8 min (1%). The optical purity was therefore 98%.

(b) (2*S*, 3*R*)-*Isomer*. The MTPA ester of (2*S*, 3*R*)-**8c** (42 mg) and Eu$(fod)_3$ (48 mg) were dissolved in CCl_4 (0.2 ml) and submitted to the NMR analysis: δ 5.18 (OMe, 3 H, s). By glc, the optical purity was shown to be 98%. The analytical condition was as described for the (2*R*, 3*S*)-isomer: Rt 20.9 min (1%), 21.9 min (99%).

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REFERENCES

[1]Y. Kuwahara, H. Fukami, S. Ishii, F. Matsumura and W. E. Burkholder, *J. Chem. Ecol.* **1**, 413 (1975).
[2]Y. Kuwahara, H. Fukami, R. Howard, S. Ishii, F. Matsumura and W. E. Burkholder, *Tetrahedron* **34**, 1769 (1978).
[3]T. T. Howarth, G. P. Murphy and T. M. Harris, *J. Am. Chem. Soc.* **91**, 517 (1969).
[4]T. M. Harris and G. P. Murphy, *Ibid.* **93**, 6708 (1971).
[5]S. N. Huckin and L. Weiler, *Ibid.* **96**, 1082 (1974).
[6]S. N. Huckin and L. Weiler, *Can. J. Chem.* **52**, 1343 (1974).
[7]K. Mori, M. Sasaki, S. Tamada, T. Suguro and S. Masuda, *Tetrahedron* **35**, 1601 (1979).
[8]J. D.v. Mikusch-Buchberg and A. N. Sagredos, *Liebigs Ann. Chem.* **681**, 118 (1965).
[9]Preliminary communication: M. Sakakibara and K. Mori, *Tetrahedron Letters* 2401 (1979).
[10]J. M. Ansell, A. Hassner and W. E. Burkholder, *Ibid.* 2497 (1979).
[11]K. Mori and S. Tamada, *Tetrahedron* **35**, 1279 (1979).
[12]J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.* **95**, 512 (1973).
[13]A. Tai and M. Imaida, *Bull. Chem. Soc. Japan* **51**, 1114 (1978).
[14]R. W. Hoffman and W. Ladner, *Tetrahedron Letters* 4653 (1979).