Original Article

Synthesis of (+)-(*S*)-isorobinal together with its antipod, a cyclic monoterpene functioning as the sex pheromone of *Rhizoglyphus setosus* and its distribution among Astigmata*

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Both compounds, (+)-(*S*)- and (−)-(*R*)-4-isopropenyl-3-oxo-1-cyclohexene-1-carbaldehyde [(+)-(*S*)- and (−)-(*R*)-isorobinal, (*S*)- and (*R*)-**1**, $[\alpha]_D^{28}$ +51° (*c*=1.0, CHCl$_3$) and $[\alpha]_D^{25}$ −45° (*c*=1.3, CHCl$_3$), 95% *ee* and 88% *ee*], were synthesized in seven steps starting from (*R*)- and (*S*)-perillyl alcohol [(*R*)- and (*S*)-**2**] available commercially. Isorobinal (**1**) is distributed among seven species of Astigmata among 61 species examined. (*S*)-Isorobinal [(*S*)-**1**], known as the female sex pheromone of *Rhizoglyphus setosus*, was confirmed in two other *Rhizoglyphus* species, while its biological function remained obscure against each species. In the other four species, not only its configuration but also its function has not yet been determined. © Pesticide Science Society of Japan

Keywords: mite, Astigmata, *Rhizoglyphus* sp., isorobinal, 4-isopropenyl-3-oxo-1-cyclohexene-1-carbaldehyde.

Introduction

A total of 88 compounds, classified into 27 compounds with monoterpenoid carbon skeletons, two sesquiterpenes, eight aromatics, and 24 aliphatic compounds (a ketone, aldehydes, fatty acid esters and alkyl formates) together with 27 aliphatic hydrocarbons have been demonstrated as components of the opisthonotal gland secretions from 61 species of mites belonging to ten families of Astigmata in Acari.[1] Parts of the compounds are known to function either as an alarm pheromone, an aggregation pheromone or a sex pheromone in each corresponding species. Among 27 monoterpenoids, ten compounds were first isolated and identified from Astigmata, with the structures unequivocally confirmed by synthesis.[1]

Isorobinal [4-isopropenyl-3-oxo-1-cyclohexene-1-carbaldehyde, **1**], one of such novel cyclic monoterpenes, has been identified from the secretion of the astigmatid mite *Rhizoglyphus* sp. "oki"[2] [its ITS-II (internal transcriptive spacer-II) region consists of 460 bps (code name RH 6, GenBank Accession Number: AB104931)].[3] (*S*)-Isomer of **1** has been demonstrated as the female sex pheromone of the related mite, *Rhizoglyphus setosus* (Acari: Acaridae),[4] using both enantiomers of **1** prepared by a group from Tohoku University[5] and also by us. Herein we report the syntheses of both enantiomers to determine the stereochemistry and the natural distribution of **1** among Astigmata.

Methods and Materials

1. Analytical methods

GC/MS was carried out using a Hewlett Packard HP-5989B gas chromatograph/mass spectrometer operated at 70 eV in the split-less mode, with an HP-5 MS capillary column (0.25 mm in diameter ×30 m in length, 0.25 μm in film thickness). Helium was used as the carrier gas at 1.23 ml/min, at temperatures programmed from 60°C to 290°C at 10°C/min, with an initial 2-min hold at 60°C and then at 290°C for 5 min. ^{1}H- and ^{13}C-NMR spectra were obtained with a Bruker AC300 instrument (^{1}H at 300 MHz, ^{13}C at 75 MHz) in CDCl$_3$ solution with TMS as an internal standard. UV spectra were measured with a Beckman DU-64 spectrophotometer. Optical rotation values were measured with a Jasco DIP-370 spectropolarimeter.

Abbreviations: MCPBA, meta-chloroperbenzoic acid; PCC, pyridinium chlorochromate.

2. HPLC analyses of (+)-(S)-isorobinal and (−)-(R)-isorobinal [(S)-1 and (R)-1]

Compounds (*S*)- and (*R*)-**1** were chromatographed in a chiral HPLC column [Chiralpak AD-H (Daicel Chemical Ind., Ltd.), 250 mm×4.6 mm i.d.], and the column was eluted with hexane–isopropyl alcohol (200 : 1) at a flow rate of 1 ml/min. Peaks were detected by UV at 254 nm using a Jasco UVIDEC-100-H, and recorded with a HP 3390 Integrator. In order to determine the stereochemistry of **1** from three *Rhizoglyphus* species, hexane extracts were prepared by dipping mite bodies in hexane for three minutes. Each mite species, weight of mites and extracted volume of solvent was as follows: *Rhizoglyphus* sp. "oki", 778 mg in hexane 2.6 ml, *Rhizoglyphus* sp. "mori", 579 mg in hexane 2.0 ml, and *R. setosus*, 97 mg in hexane 0.5 ml.

3. Syntheses of (+)-(S)-isorobinal and (−)-(R)-isorobinal [(S)-1 and (R)-1]

3.1. (R)-1,2-Epoxy-8-p-menthen-7-ol [(R)-3]

To a stirred and ice-cooled solution of MCPBA (70%, 1.77 g, 7.20 mmol) in CH_2Cl_2 (30 ml) was added (*R*)-**2** (1.00 g, 6.58 mmol) in CH_2Cl_2 (5 ml). The mixture was stirred overnight at room temperature. It was then quenched with sat. aq. $Na_2S_2O_3$ and the product was extracted with EtOAc. The organic layer was washed with sat. aq. $NaHCO_3$, water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluting with hexane–EtOAc, 2 : 1) to give 1.10 g (quantitative) of (*R*)-**3** as a diastereomeric mixture. GC/MS t_R 11.12 min and 11.25 min; $[\alpha]_D^{25}$ +49° (*c*=1.0, CHCl₃); MS *m/z* (%): 168 (M⁺, 2), 150 (47), 137 (40), 121 (71), 107 (66), 93 (78), 79 (100), 67 (79), 55 (45), 41 (64). MS *m/z* (%): 168 (M⁺, 2), 150 (24), 135 (22), 121 (29), 110 (53), 93 (83), 79 (100), 67 (79), 55 (55), 41 (64); ¹H-NMR δ (CDCl₃) as a diastereomeric mixture: 1.6–2.0 (6H, m), 1.71 (3H, s,=CC$\underline{H}_3$), 2.0–2.2 (1H, m, CH₂C$\underline{H}$CH₂), 3.35 (1H, m, CH₂C$\underline{H}$OC), 3.56–3.76 (2H, m, CH₂OH), 4.68 (1H, s,=CH₂), 4.74 (1H, t-like, *J*=1.4 Hz,=C$\underline{H}_2$); ¹³C-NMR δ (CDCl₃) as a diastereomeric mixture: 20.9 (CH₃), 24.7 (CH₂), 25.9 (CH₂), 30.2 (CH₂), 36.8 (CH), 56.7 (CH), 59.9 (C), 64.1 (CH₂), 109.2 (CH₂), 148.7 (C).

3.2. (S)-1,2-Epoxy-8-p-menthen-7-ol [(S)-3]

In the same manner as described above, (*S*)-**2** (1.00 g, 6.58 mmol) gave (*S*)-**3** (983 mg, 89%) as a mixture of two diastereomers. Its GC/MS, ¹H- and ¹³C-NMR spectra were identical to those of the *R* isomer. $[\alpha]_D^{25}$ −45° (*c*=1.0, CHCl₃).

3.3. (R)-2-(Phenylseleno)-8-p-menthen-1,7-diol [(R)-4]

To a stirred solution of diphenyl diselenide (2.16 g, 6.92 mmol) in dry EtOH (42 ml) was added NaBH₄ (0.524 g, 13.9 mmol) under an N₂ atmosphere. The mixture turned colorless, and (*R*)-**3** (1.10 g, 6.55 mmol) in dry EtOH (6 ml) was then added dropwise. The mixture was refluxed for 2 hr with stirring under N₂ atmosphere. After quenching with 0.5*N*

HCl, the mixture was extracted with EtOAc. The organic layer was washed with sat. aq. $NaHCO_3$, water, brine and dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluting with hexane–EtOAc, 4 : 1) to give (*R*)-**4** (1.23 g, 58%) and the isomer (*R*)-1-(phenylseleno)-8-*p*-menthen-2,7-diol [(*R*)-**5**; 0.32 g, 35%].

(*R*)-**4**: GC/MS t_R 21.10 min; $[\alpha]_D^{29}$ +59° (*c*=1.0, CHCl₃); MS *m/z* (%): 326 (M⁺, 18), 308 (5), 169 (32), 151 (100), 133 (42), 123 (41), 107 (53), 93 (48), 81 (50), 67 (52), 55 (45), 41 (41); ¹H-NMR δ (CDCl₃) as a diastereomeric mixture: 1.6–2.4 (7H, m), 1.71 (3H, s,=CC$\underline{H}_3$), 3.3–3.5 (1H, m, CH₂C$\underline{H}$SePh), 3.52 (1H, d, *J*=11.4 Hz, CH₂OH), 3.88 (1H, d, *J*=11.4 Hz, C$\underline{H}_2$OH), 4.73 (2H, s,=C$\underline{H}_2$), 7.2–7.7 (5H, m, Ph); ¹³C-NMR δ (CDCl₃) as a diastereomeric mixture: 21.1 (CH₃), 25.7 (CH₂), 30.0 (CH₂), 33.2 (CH₂), 40.5 (CH), 50.0 (CH), 69.7 (CH₂), 73.8 (C), 109.0 (CH₂), 127.8 (Ph), 129.3 (Ph), 133.9 (Ph), 134.3 (Ph), 149.3 (C).

(*R*)-**5**: GC/MS t_R 19.69 min; $[\alpha]_D^{25}$ +39° (*c*=1.0, CHCl₃); MS *m/z* (%): 308 (M⁺−18, 100), 158 (60), 150 (81), 133 (52), 109 (62), 93 (74), 81 (53), 67 (60), 55 (53), 41 (57); ¹H-NMR δ (CDCl₃) as a diastereomeric mixture: 1.6–2.4 (7H, m), 1.77 (3H, s,=CC$\underline{H}_3$), 3.74 (1H, d, *J*=11.1 Hz, C$\underline{H}_2$OH), 4.09 (1H, d, *J*=11.1 Hz, C$\underline{H}_2$OH), 4.13 (1H, m, CH₂C$\underline{H}$OH), 4.77 (2H, s,=C$\underline{H}_2$), 7.3–7.6 (5H, m, Ph).

3.4. (S)-2-(Phenylseleno)-8-p-menthen-1,7-diol [(S)-4]

In the same manner as described above, (*S*)-**3** (2.56 g, 15.3 mmol) yielded (*S*)-**4** (2.84 g, 57%). Its GC/MS, ¹H- and ¹³C-NMR spectra were identical with those of the *R* isomer. $[\alpha]_D^{29}$ −56° (*c*=1.0, CHCl₃).

3.5. (R)-7-Acetoxy-2-(phenylseleno)-8-p-menthen-1-ol [(R)-6]

Acetic anhydride (3.5 ml) was added to a stirred and ice-cooled solution of (*R*)-**4** (1.23 g, 3.77 mmol) in dry pyridine (5 ml). The mixture was stirred for 4 hr at room temperature, then poured into ice water, and extracted with Et₂O. The ethereal extract was washed successively with 0.5*N* HCl, water, aq. sat. $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluting with hexane–EtOAc, 5 : 1) to give (*R*)-**6** (1.11 g, 80%) as an oil. GC/MS t_R 21.82 min; $[\alpha]_D^{27}$ +33° (*c*=1.0, CHCl₃); MS *m/z* (%): 368 (M⁺, 9), 211 (7), 193 (41), 151 (33), 133 (100), 107 (24), 91 (22), 81 (16), 67 (14), 55 (14), 43 (61); ¹H-NMR δ (CDCl₃): 1.6–2.4 (7H, m), 1.73 (3H, s,=CC$\underline{H}_3$), 1.78 (3H, s, O=CC$\underline{H}_3$), 3.50 (1H, dd, *J*=5.1, 3.0 Hz, CH₂C$\underline{H}$SePh), 4.05 (1H, d, *J*=11.3 Hz, C$\underline{H}_2$OAc), 4.41 (1H, d, *J*=11.3 Hz, C$\underline{H}_2$OAc), 4.74 (2H, s,=C$\underline{H}_2$), 7.3–7.7 (5H, m, Ph); ¹³C-NMR δ (CDCl₃): 20.4 (CH₃), 21.1 (CH₃), 25.3 (CH₂), 30.2 (CH₂), 33.8 (CH₂), 40.6 (CH), 50.6 (CH), 71.5 (CH₂), 73.0 (CH), 109.1 (CH₂), 127.6 (Ph), 129.1 (Ph), 134.3 (Ph), 134.5 (Ph), 149.8 (C), 170.8 (CH₃C=O).

3.6. (S)-7-Acetoxy-2-(phenylseleno)-8-p-menthen-1-ol [(S)-6]

In the same manner as described above, (*S*)-**4** (1.00 g,

3.07 mmol) gave (*S*)-**6** (970 mg, 86%). Its GC/MS, ^{1}H- and ^{13}C-NMR spectra were identical to those of the *S* isomer. $[\alpha]_D^{28}$ −22° (*c*=1.0, CHCl$_3$).

3.7.   (R)-7-Acetoxy-2,8-p-menthadien-1-ol [(R)-7]

To the stirred and ice-cooled solution of (*R*)-**6** (732 mg, 1.99 mmol) in THF (45 ml) was added 30% H$_2$O$_2$ (3.69 ml, 32.4 mmol) dropwise. The resulting solution was stirred for 20 min and then allowed to come to room temperature with stirring for 2 hr. After the addition of water, the mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over Na$_2$SO$_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluting with hexane–EtOAc, 4 : 1) to give (*R*)-**7** (300 mg, 72%) as an oil. GC/MS t_R 13.03 min; $[\alpha]_D^{27}$ +84° (*c*=1.0, CHCl$_3$); MS *m/z* (%): 192 (M$^+$−18, 2), 150 (14), 137 (100), 109 (78), 95 (33), 79 (21), 67 (10), 55 (12), 43 (50); ^{1}H-NMR δ (CDCl$_3$): 1.6–1.9 (4H, m), 1.75 (3H, s,=CC$\underline{H}_3$), 2.12 (3H, s, O=CC$\underline{H}_3$), 2.70 (1H, m, CH$_2$C$\underline{H}$CH=), 4.00 (1H, d, *J*=11.2 Hz, CH$_2$OAc), 4.09 (1H, d, *J*=11.2 Hz, C$\underline{H}_2$OAc), 4.76 (1H, br. s,=C$\underline{H}_2$), 4.80 (1H, t-like, *J*=1.5 Hz,=C$\underline{H}_2$), 5.73 (1H, ddd, *J*=10.2, 2.4, 1.1 Hz, CH=C$\underline{H}$CH), 5.85 (1H, ddd, *J*=10.2, 2.4, 0.6 Hz, CH=C$\underline{H}$CH).

3.8.   (S)-7-Acetoxy-2,8-p-menthadien-1-ol [(S)-7]

In the same manner as described above, (*S*)-**6** (970 mg, 2.64 mmol) yielded (*S*)-**7** (426 mg, 77%). Its GC/MS, ^{1}H- and ^{13}C-NMR spectra were identical to those of the *S* isomer. $[\alpha]_D^{26}$ −70° (*c*=1.0, CHCl$_3$).

3.9.   (S)-7-Acetoxy-3-oxo-1,8-p-menthadiene[(S)-8]

To the stirred solution of PCC (1.09 g, 4.95 mmol) in dry CH$_2$Cl$_2$ (22 ml) was added (*R*)-**7** (300 mg, 1.43 mmol) in dry CH$_2$Cl$_2$ (5 ml). The mixture was stirred at room temperature overnight, then diluted with Et$_2$O and filtered through Celite. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (eluting with hexane–EtOAc, 5 : 1) to give (*S*)-**8** (232 mg, 78%) as an oil. GC/MS t_R 14.54 min; $[\alpha]_D^{27}$ +29° (*c*=1.0, CHCl$_3$); MS *m/z* (%): 208 (M$^+$, 7), 193 (3), 166 (5), 148 (22), 133 (10), 120 (9), 105 (5), 98 (100), 43 (28); ^{1}H-NMR δ (CDCl$_3$): 1.76 (3H, s,=CC$\underline{H}_3$), 2.0–2.2 (2H, m, CH$_2$C$\underline{H}_2$CH), 2.14 (3H, s, O=CC$\underline{H}_3$), 2.35 (2H, td, *J*=5.0, 0.7 Hz, CH$_2$C$\underline{H}_2$C=), 3.03 (1H, dd, *J*=10.3, 5.3 Hz, CH$_2$C$\underline{H}$C=O), 4.68 (2H, d, *J*=0.7 Hz, C$\underline{H}_2$OAc), 4.77 (1H, d, *J*=0.5 Hz,=C$\underline{H}_2$), 4.97 (1H, t-like, *J*=1.5 Hz,=C$\underline{H}_2$), 6.05 (1H, t, *J*=1.5 Hz, C=C$\underline{H}$C=O); ^{13}C-NMR δ (CDCl$_3$): 20.6 (CH$_3$), 20.7 (CH$_3$), 25.7 (CH$_2$), 27.4 (CH$_2$), 54.4 (CH), 64.8 (CH$_2$), 113.9 (CH$_2$), 124.6 (CH), 142.9 (C), 157.6 (C), 170.2 (CH$_3$$\underline{C}$=O), 198.9 (C=O).

3.10.   (R)-7-Acetoxy-3-oxo-1,8-p-menthadiene [(R)-8]

In the same manner as described above, (*S*)-**7** (208 mg, 0.99 mmol) gave (*R*)-**8** (158 mg, 77%). Its GC/MS, ^{1}H- and ^{13}C-NMR spectra were identical to those of the *S* isomer. $[\alpha]_D^{26}$ −28° (*c*=1.0, CHCl$_3$).

3.11.   (S)-3-Oxo-1,8-p-menthadien-7-ol [(S)-9]

A catalytic amount of K$_2$CO$_3$ was added to a solution of (*S*)-**8**

(97 mg, 0.47 mmol) in MeOH (20 ml) at −15°C, and stirred for 20 min. After the addition of water, the mixture was neutralized with 0.5 M HCl, then diluted with water, and extracted with EtOAc. The organic layer was washed with brine, dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The residual oily product was purified by silica gel column chromatography (eluting with hexane–Et$_2$O, 1 : 1) to give (*S*)-**9** (66 mg, 85%). GC/MS t_R 13.68 min; $[\alpha]_D^{26}$ +24° (*c*=1.0, CHCl$_3$); MS *m/z* (%): 166 (M$^+$, 33), 151 (40), 135 (32), 121 (7), 107 (9), 98 (100), 91 (14), 67 (36), 55 (19), 42 (31); ^{1}H-NMR δ (CDCl$_3$): 1.75 (3H, s,=CC$\underline{H}_3$), 2.0–2.2 (2H, m, CH$_2$CH$_2$CH), 2.32 (2H, t, *J*=5.7 Hz, CH$_2$CH$_2$C=), 3.02 (1H, dd, *J*=10.0, 5.4 Hz, CH$_2$C$\underline{H}$C=O), 4.26 (2H, s, CH$_2$OH), 4.76 (1H, s,=C$\underline{H}_2$), 4.96 (1H, t-like, *J*=1.5 Hz,=C$\underline{H}_2$), 6.16 (1H, t, *J*=1.6 Hz, C=C$\underline{H}$C=O); ^{13}C-NMR δ (CDCl$_3$): 20.6 (CH$_3$), 25.4 (CH$_2$), 27.6 (CH$_2$), 54.6 (CH), 64.7 (CH$_2$), 113.8 (CH$_2$), 123.2 (CH), 143.1 (C), 163.6 (C), 199.6 (C=O).

3.12.   (R)-3-Oxo-1,8-p-menthadien-7-ol [(R)-9]

In the same manner as described above, (*R*)-**8** (131 mg, 0.63 mmol) yielded (*R*)-**9** (95 mg, 91%). Its GC/MS, ^{1}H- and ^{13}C-NMR spectra were identical to those of the *S* isomer. $[\alpha]_D^{25}$ −25° (*c*=1.0, CHCl$_3$).

3.13.   (1)-(S)-Isorobinal [(S)-1]

To a solution of (*S*)-**9** (66 mg, 0.40 mmol) in anhydrous CH$_2$Cl$_2$ (20 ml), Dess-Martin periodinane (296 mg, 0.70 mmol) and 3 drops of pyridine were added at 0°C. The mixture was stirred for 15 min, and then diluted with Et$_2$O. After the addition of sat. aq. NaHCO$_3$ and Na$_2$S$_2$O$_3$ to the mixture under vigorously stirring, the resulting solution was extracted with Et$_2$O, and the ethereal solution of the product was successively washed with water and brine, dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The residue was chromatographed on a silica gel column (eluting with hexane–Et$_2$O, 3 : 1) to give (*S*)-**1** (44 mg, 68%). GC/MS t_R=10.97 min; $[\alpha]_D^{28}$ +51° (*c*=1.0, CHCl$_3$); UV (Hexane): λmax nm (log ε)=240 (4.08), 306 (2.27); MS *m/z* (%): 164 (M$^+$, 77), 149 (93), 135 (41), 121 (12), 107 (26), 96 (53), 79 (16), 68 (100), 67 (69), 53 (18), 41 (17); ^{1}H-NMR δ (CDCl$_3$): 1.78 (3H, s,=CCH$_3$), 2.16 (2H, m, CH$_2$CH$_2$CH), 2.45 (1H, dtd, *J*=18.9, 7.5, 2.3 Hz, CH$_2$CH$_2$C=), 2.65 (1H, dtd, *J*=18.9, 4.8, 1.0 Hz, CH$_2$CH$_2$C=), 3.13 (1H, t, *J*=7.6 Hz, CH$_2$CHC=O), 4.77 (1H, br. s,=CH$_2$), 5.00 (1H, dq, *J*=1.4, 1.4 Hz,=CH$_2$), 6.58 (1H, dd, *J*=2.3, 1.2 Hz, C=CHC=O), 9.79 (1H, s, CHO); ^{13}C-NMR δ (CDCl$_3$): 20.6 (CH$_3$), 21.0 (CH$_2$), 27.0 (CH$_2$), 55.5 (CH), 114.3 (CH$_2$), 139.2 (CH), 142.1 (C), 153.8 (C), 194.2 (CHO), 200.5 (C=O).

3.14.   (−)-(R)-Isorobinal [(R)-1]

In the same manner as described above, (*R*)-**9** (95 mg, 0.57 mmol) gave (*R*)-**1** (67 mg, 71%). Its GC/MS, ^{1}H- and ^{13}C-NMR spectra were identical to those of the *S* isomer. $[\alpha]_D^{25}$ −45° (*c*=1.3, CHCl$_3$).

Results and Discussion

1.   Synthesis of both isomers

Our synthetic route is summarized in Fig. 1. Commercially available (*R*)-perillyl alcohols [(*R*)-**2**] were separately epoxidized with MCPBA to give corresponding diastereomeric mixtures of (*R*)-**3**. The phenylselenide anion opened the mixture of (*R*)-**3** to the hydroxy selenide (*R*)-**4** and (*R*)-**5**,[6] which could be separated by silica gel column chromatography. The primary hydroxy group of hydroxy selenide (*R*)-**4** was protected by acetylation and the resulting acetate (*R*)-**6** was oxidized by excess hydrogen peroxide to effect the oxidative elimination reaction,[6] giving the desired (*R*)-**7**. Oxidation of the allylic tertiary alcohol (*R*)-**7** with 5 equivalent of PCC afforded the transposed α,β-unsaturated ketone (*S*)-**8**.[7,8] Finally, the ketone (*S*)-**8** was hydrolyzed with potassium carbonate at $-15°$C to give the primary alcohol (*S*)-**9**. The alcohol (*S*)-**9** was subsequently oxidized with Dess-Martin periodinane[9,10] to give the target molecule **1**. The overall yield of (+)-(*S*)-isorobinal $\{(S)$-**1**, $[\alpha]_D^{28} +51°$ $(c=1.0,$ CHCl$_3)\}$ was 17% based on (*R*)-perillyl alcohol (*R*)-**2**. In the same manner, (−)-(*R*)-isorobinal $\{(R)$-**1**, $[\alpha]_D^{25} -45°$ $(c=1.3,$ CHCl$_3)\}$ was synthesized from (*S*)-perillyl alcohol (*S*)-**2** with similar overall yield. The GC/MS and ^{1}H-NMR spectra of (*S*)- and (*R*)-**1** were identical with that of the natural **1** reported by Sakata *et al.*[2]

Three reaction steps from PCC oxidation of (*R*)- and (*S*)-**7** involving the concurrent allylic rearrangement of the hydroxy
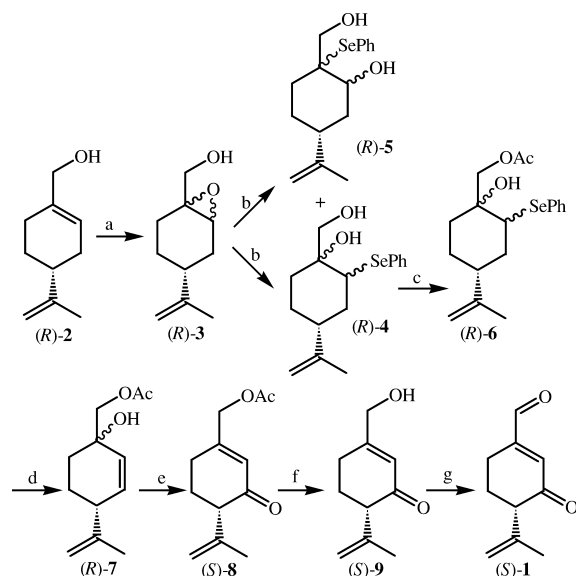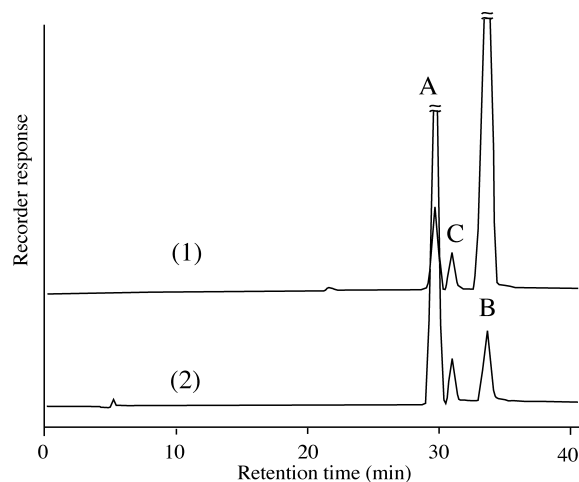
Fig. 2.   Typical separation of (*R*)- and (*S*)-isorobinal by HPLC using a chiral column. (1) Preparation of (−)-(*R*)-isorobinal, (2) Preparation of (+)-(*S*)-isorobinal.
A: (+)-(*S*)-Isorobinal, B: (−)-(*R*)-Isorobinal, C: Robinal

group to (*S*)- and (*R*)-**1**, *via* hydrolysis and Dess-Martin periodinane oxidation, proceeded successfully to give 50% yield, possibly because all reactions were carried out in nearly neutral conditions. On the other hand, the reported two step reactions involving the same PCC oxidation resulted in 38% yield, because the next deprotection step by aq. HF in acetonitrile resulted in a poor yield (41%).[5]

2.   Enatiomeric purities and stability of isorobinal

Enantiomeric purities of (*S*)- and (*R*)-**1**, determined by HPLC analyses using a chiral column (Chiralpak AD-H), were 95% *ee* and 88% *ee*, respectively, corresponding to slightly lower $[\alpha]_D^{25}$ values than those reported.[5] At present, it remains obscure why such a fairly large difference in *ee* values is observed between two enantiomers. It is possible that the optical purity of each starting perillyl alcohol [(*S*)- and (*R*)-**2**] was different, although their *ee* values were not determined.

The chemical structures of both (*S*)- and (*R*)-**1** contained acid- and base-sensitive β,γ-double bond easily convertible to the more stable α,β-position, and, therefore, both compounds seemed to be labile to give robinal (3-oxo-4-isopropylidene-1-cyclohexene-1-carboxaldehyde).[11] As indicated in Fig. 2, a small amount of robinal is always accompanied with (*S*)- and (*R*)-**1** preparations.

3.   Determination of stereochemistry and its distribution among related mites

The chiral HPLC profiles (Fig. 3) of both enantiomers will enable us to determine the absolute configuration of natural **1** of the other mite. Compound **1** is known to be distributed in the following seven species belonging to the family Acaridae among 61 species consisting of 10 families of Astigmata examined; *Rhizoglypus robini*, *R. stosus*, *Rhizoglyphus* sp. "oki", *Rhizoglyphus* sp. "mori" [447 bps (code name RH 34,
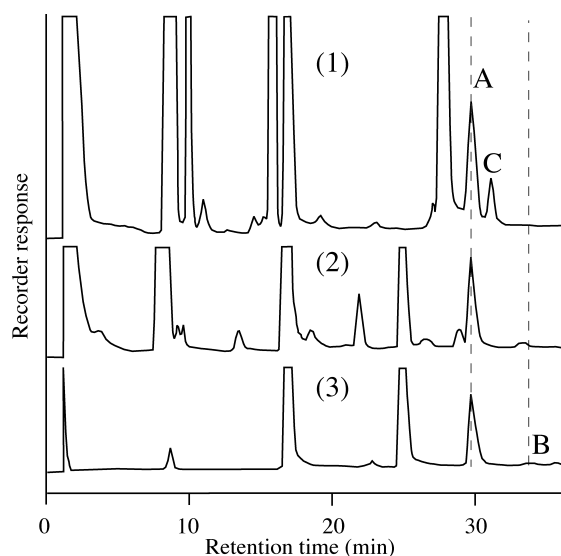
Fig. 1.   Synthetic procedure of (+)-(*S*)-isorobinal [(*S*)-**1**]] from (*R*)-perillyl alcohol [(*R*)-**2**].
Reagents: (a) MCPBA, CH$_2$Cl$_2$, (b) Ph$_2$Se$_2$, NaBH$_4$, EtOH, (c) Ac$_2$O, pyridine, (d) 30% H$_2$O$_2$, THF, H$_2$O, (e) PCC, CH$_2$Cl$_2$, (f) K$_2$CO$_3$, MeOH, (g) Dess-Martin periodinane, CH$_2$Cl$_2$. Following the same procedure, (−)-(*R*)-isorobinal [(*R*)-**1**] was prepared from (*S*)-perillyl alcohols [(*S*)-**2**].

Fig. 3.   Stereochemistry of natural isorobinal present in three *Rhizoglyphus* species. (1) *Rhizoglyphus* sp. "mori", (2) *Rhizoglyphus* sp. "oki", (3) *R. setosus*.
A: (+)-(*S*)-Isorobinal, B: (−)-(*R*)-Isorobinal, C: Robinal

GenBank Accession Number: AB104969)],[3] *Tyrophagus similis*, *Tyroborus lini*, and *Schwiebea araujoae*.[1] Distribution, therefore, seems to be restricted only among species belonging to the family Acaridae.

As mentioned in the Introduction, compound (**1**) has been identified from the unidentified *Rhizoglyphus* sp. "oki",[2] without any biological activity, and was then re-identified as the sex pheromone of *R. setosus*, together with its *S* stereochemistry.[4] In this study, the stereochemistry of **1** present in each corresponding extract of two species, the unidentified *Rhizoglyohus* sp. "oki" and *Rhizoglyohus* sp. "mori", was determined to be *S*, though the possible presence of a minute amount of (*R*)-**1** was not excluded, as indicated in Fig. 3.

In the case of *R. robini*, the content of **1** was too low to ob-

tain a reliable peak by chiral HPLC analysis, and its stereochemistry remained obscure (data not indicated). Likewise, in the other three species, *Tyrophagus similis*, *Tyroborus lini*, and *Schwiebea araujoae*, their GC responses of **1** were too low, and no attempts were made to determine their stereochemistry.

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