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Note

Synthesis of Both Enantiomers of Isorobinal, a Novel Cyclic Monoterpene Isolated from the Astigmatid Mite, *Rhizoglyphus* sp.

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Both enantiomers of isorobinal, a cyclic monoterpene isolated from the astigmatid mite (*Rhizoglyphus* sp.), were synthesized from the enantiomers of perillaldehyde in four steps by using PCC-oxidation of a tertiary allylic alcohol intermediate as the key step.

Key words: isorobinal; *Rhizoglyphus;* terpenoid

Astigmatid mites are known to have a pair of opisthonotal glands which contain a set of volatile compounds characteristic to each species. Some of these compounds have been elucidated to function as the alarm pheromone, sex pheromone, or aggregation pheromone.[1] In 1996, Sakata and co-workers isolated a novel monocyclic monoterpene named isorobinal, together with robinal (**5**) and some other compounds from the excretory glands of *Rhizoglyphus* sp. (Astigmata: Rhizoglyphinae) collected in Okinawa prefecture.[2] They identified its structure as that of **1** based on its spectral data, although its absolute configuration and biological function remained unknown. As can be seen from the structures shown in the Figure, the newly identified aldehyde (**1**) is an isomer of robinal (**5**) concerning the double bond position, which had been isolated as an antifungal monoterpenoid produced by the closely related mite, *Rhizoglyphus robini*,[3] and synthesized earlier by us.[4] In this note, we describe the synthesis of both enantiomers of isorobinal, (*R*)-**1** and (*S*)-**1**, from the enantiomers of perillaldehyde, (*S*)-**2** and (*R*)-**2**, respectively.

Our literature survey found compound **4** as a promising precursor of (*S*)-**1**,[5] since allylic rearrangement of the hydroxyl group of **4** and subsequent oxidation of the resulting secondary alcoholic intemediate was considered to afford (*S*)-**1** after releasing the masked aldehyde functionality. We thus attempted the preparation of **4** according to the procedure described by Tius and co-workers.[5] In order to obtain **4**, they treated TBS-enol ether **3**,[5,6] which had been quantitatively derived from (*R*)-perillaldehyde [(*R*)-**2**], with *m*CPBA in a two-phase mixture of ether and saturated aqueous sodium bicarbonate. However, in our hands, the major product obtained under these conditions was a diastereomeric mixture of epoxide **6** instead of desired ring-opened product **4**. Epoxide **6**, itself, had also been prepared by Siegel *et al.*[6] They stated that the *m*CPBA-oxidation of **3** in a two-phase mixture of ether and saturated aqueous sodium bicarbonate initially gave **6**, which was then converted *in situ* into **4** *via* the addition of the *m*-chlorobenzoate anion to **6**, unless the oxidation reaction was immediately stopped after the disappearance of starting enol ether

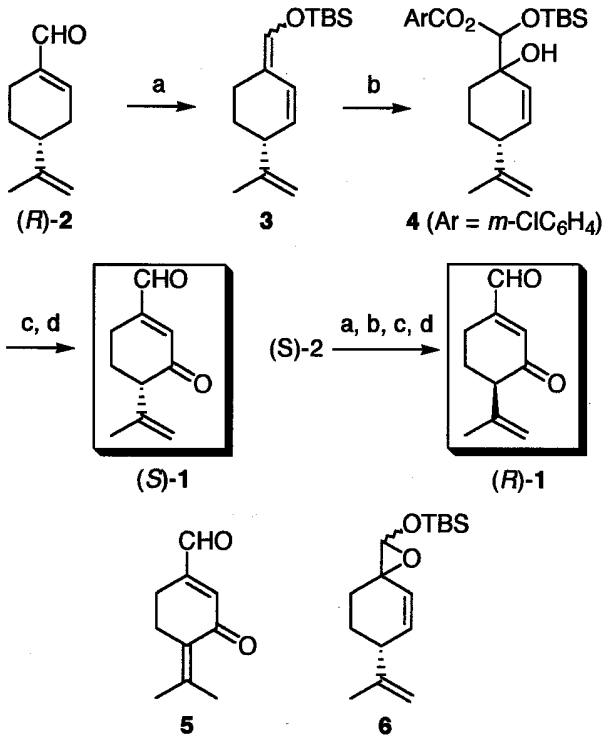

Figure. *Reagents*: a) TBSOTf, Et_3N, CH_2Cl_2 (quant.); b) *m*CPBA, CH_2Cl_2 (86%); c) PCC, 4A MS, CH_2Cl_2 (86%); d) aq. HF, CH_3CN (41%)

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Abbreviations: *m*CPBA, *meta*-chloroperbenzoic acid; PCC, pyridinium chlorochromate; $Eu(hfc)_3$, europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]

3. Thus, the two-phase reaction mixture was stirred for an additional three hours at room temperature after the disappearance of **3**. However, in this case also, only a small amount of desired product **4** could be detected by a ^{1}H-NMR analysis of the crude product. Contrary to these reports, Hassner *et al.* have reported the conversion of aldehyde-derived silyl enol ethers to hydroxy acetals analogous to **4** by treating with *m*CPBA in dichloromethane either in the presence or absence of *solid* sodium bicarbonate.[7] The application of this non-aqueous procedure to our substrate (**3**) led to the prompt formation of **4** in an 86% yield as a mixture of four stereoisomers, as judged by its ^{1}H-NMR spectrum. These results imply that this transformation proceeded much more efficiently under non-aqueous conditions. With key intermediate **4** in hand, we subjected hydroxy acetal **4** to PCC-oxidation conditions.[8,9] This oxidation, involving concurrent allylic rearrangement of the hydroxyl group, proceeded smoothly to give a protected γ-keto-α,β-unsaturated aldehyde intermediate which, without purification, was deprotected by treating with dilute hydrofluoric acid to afford the target molecule, (*S*)-**1** $\{[\alpha]_D^{22} + 69.6°(c = 1.93$, hexane)$\}$. Although there was the undesirable possibility that the β,γ-double bond of (*S*)-**1** might readily migrate to the α,β-position forming more stable robinal (**5**), (*S*)-**1** could survive the acidic oxidation conditions, while prolonged purification with a silica gel column or standing at room temperature for several weeks brought about isomerization to a substantial extent. The same sequence of reactions was applied to obtain (*R*)-**1** $\{[\alpha]_D^{22} - 67.3°(c = 1.07$, hexane)$\}$ from (*S*)-**2**. The ^{1}H-NMR analyses (300 MHz) of (*S*)-**1** and (*R*)-**1** in the presence of the chiral shift reagent, Eu(hfc)$_3$, revealed the optical purity of each enantiomer to be more than 95%. Synthetic samples are now being investigated by Y. Kuwahara (Kyoto University) to determine the absolute configuration and to identify their biological function

Experimental

(*S*)-Perillaldehyde was purchased from Aldrich Chemical Co., and (*R*)-perillaldehyde was prepared from (+)-limonene oxide according to the literature.[10] IR spectra were measured as films by a Jasco IR Report-100 spectrometer. ^{1}H-NMR (300 MHz) spectra were recorded with TMS as an internal standard in $CDCl_3$ by a Varian Gemini 2000 spectrometer. Optical rotation values were measured with a Horiba Septa-300 polarimeter. Dichloromethane was purified by drying with P_2O_5 and then by distillation from CaH_2. Merck silica gel 60 (70–230 mesh) was used for silica gel column chromatography.

(S)-4-Isopropenyl-3-oxo-1-cyclohexene-1-carbaldehyde [(*S*)-**1**]. To a stirred solution of **3** (0.700 g, 2.65 mmol) in dichloromethane (15 ml) was added dropwise a solution of *m*CPBA (70%, 0.654 g, 2.65 mmol) in dichloromethane (10 ml) at *ca.* −10°C. The mixture was stirred at the same temperature for 30 min, poured into sat. aq. $NaHCO_3$, and extracted with chloroform. The extract was successively washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give 0.99 g (86%) of **4**. Judging from the ^{1}H- NMR analysis of the mixture, this product seemed to consist of all of the four possible diastereomers. This mixture was used directly for the next reaction. The major component, however, could be purified by silica gel column chromatography (eluting with hexane-ethyl acetate, 20:1). IR ν_{max} cm^{-1}: 3500 (m), 3090 (w), 3040 (w), 2970 (s), 2950 (s), 2875 (s), 1735 (vs), 1655 (m), 1580 (m), 1480 (m), 1440 (m), 1300 (s), 1270 (vs), 1180 (s), 1120 (s), 1080 (s), 950 (s), 900 (s), 850 (vs); ^{1}H-NMR δ: 0.06 (3H, s, $SiCH_3$), 0.20 (3H, s, $SiCH_3$), 0.92 (9H, s, $Si(CH_3)_3$), 1.70–1.86 (4H, m, CH_2CH_2), 1.74 (3H, s, $=CCH_3$), 2.21 (1H, s, OH), 2.66–2.74 (1H, m, $=CCHC=$), 4.76–4.80 (2H, m, $=CH_2$), 5.77 (1H, dd, $J = 10.3$, 2.5 Hz, C=CH), 5.88 (1H, dd, $J = 10.3$, 2.2 Hz, C=CH), 6.17 (1H, s, OCHO), 7.41 (1H, t, $J = 8.0$ Hz, aromatic-5H), 7.56 (1H, ddd, $J = 8.0$, 2.0, 1.0 Hz, aromatic-4H), 7.95 (1H, ddd, $J = 8$, 1.5, 1.0 Hz, aromatic-6H), 8.04 (1H, dd, $J = 2$, 1.5 Hz, aromatic-2H). To a stirred mixture of PCC (1.08 g, 5.01 mmol) and pulverized 4A molecular sieves (1.0 g) in dichloromethane (20 ml) was added dropwise a solution of **4** (437 mg, 1.00 mmol) in dichloromethane (5 ml) at 0°C, and the mixture was stirred for 4 hours at room temperature. The mixture was diluted with ether and filtered through a pad of Florisil®. The filtrate was concentrated *in vacuo*, and the residue was dissolved in acetonitrile (10 ml). The solution was mixed with a solution of 48% aq. HF (0.5 ml) in water (5 ml), and stirred for 2 hours at room temperature. The mixture was poured into sat. aq. $NaHCO_3$ and extracted with ether. The ethereal solution was successively washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed over silica gel (15 g, petroleum ether-EtOAc, 10:1) to give 67.4 mg (41%) of (*S*)-**1**. $[\alpha]_D^{22} + 69.6°(c = 1.93$, hexane); IR ν_{max} cm^{-1}: 3070 (w), 2920 (s), 2820 (m), 2710 (w), 1690 (vs), 1450 (m), 1420 (m), 1285 (m), 1260 (m), 1110 (s), 1015 (m), 795 (m); ^{1}H-NMR δ: 1.77 (3H, br s, 4-CCH_3), 2.11–2.19 (2H, m, 5-H_2), 2.37–2.50 (1H, m, 6-H), 2.67 (1H, ddt, $J = 18.8$, 4.7, 1.1 Hz, 6-H), 3.13 (1H, t, $J = 7.8$ Hz, 4-H), 4.77 (1H, br s, 4-C=CH), 5.00 (1H, qui, $J = 1.5$ Hz, 4-C=CH), 6.58 (1H, dd, $J = 1.1$, 2.3 Hz, 2-H), 9.79 (1H, s, CHO); MS *m/z* (relative intensity): 165 (13), 164 (M^+, 100), 149 (57), 136 (20), 135 (31), 121 (15), 107 (26), 96 (54), 93 (19), 91 (20), 80 (11), 79 (26), 77 (17), 68 (75), 67 (48), 53 (20), 44 (19), 41 (18), 40 (36), 39 (34); HREIMS

m/z (M^+): calcd. for $C_{10}H_{12}O_2$, 164.0837; found, 164.0840.

(R)-4-Isopropenyl-3-oxo-1-cyclohexene-1-carbaldehyde [(*R*)-**1**]. This compound (322 mg) was synthesized in a 35% overall yield from the enantiomer of **3** in the same manner as that described for (*S*)-**1**. $[\alpha]_D^{22}$ −67.3(*c* = 1.07, hexane); HREIMS *m/z* (M^+): calcd. for $C_{10}H_{12}O_2$, 164.0837; found, 164.0836. The IR, ^{1}H-NMR, and MS data were identical with those of (*S*)-**1**.

Determination of the optical purities of (R)-1 and (S)-1. A solution of (*R*)-**1** (2.0 mg, 12 μmol) and Eu(hfc)$_3$ (8.6 mg, 7.2 μmol) in $CDCl_3$ (1 ml) was prepared and analyzed by ^{1}H-NMR (300 MHz). The proton signal due to 2-H appeared at 7.02 ppm (dd, *J* = 1.1, 2.3 Hz). Exactly the same analysis was conducted with (*S*)-**1**, in which the signal due to 2-H appeared at 6.93 ppm (dd, *J* = 1.1, 2.3 ppm). Each sample hardly showed the signal (less than *ca.* 2%) due to the corresponding enantiomer. In order to ensure the optical purity of each synthetic sample, the two solutions were mixed and similarly analyzed. The ^{1}H-NMR spectrum of the mixed solution showed two signals due to 2-H of each enantiomer. These results enabled the optical purity of each synthetic sample to be evaluated as more than 95%.

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