Synthesis of Mono- and Sesquiterpenoids, XXVI[◇]

Synthesis and Absolute Configuration of Rotundial, a Mosquito Repellent from the Leaves of *Vitex rotundiforia*☆

Hirosato Takikawa, Yuichiro Yamazaki and Kenji Mori*

Department of Chemistry, Faculty of Science, Science University of Tokyo,
Kagurazaka 1−3, Shinjuku-ku, Tokyo 162, Japan
Fax: (internat.) + 81-3/3235-2214

Received October 13, 1997

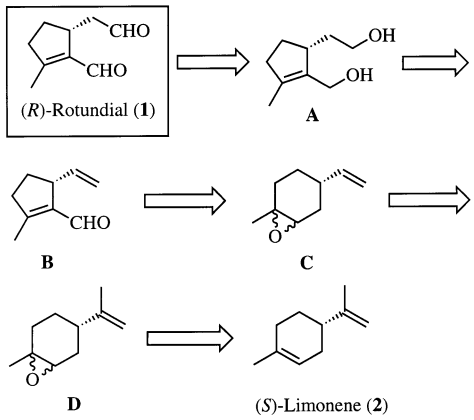
Keywords: Configuration determination / Repellent, mosquito / Rotundial / Terpenoids / *Vitex rotundiforia*

The enantiomers of rotundial (**1**), a mosquito repellent from the leaves of *Vitex rotundiforia*, were synthesized from the enantiomers of limonene oxide (**2**). The absolute configuration of natural rotundial was determined to be *R*.

Vitex rotundiforia has been used as a medicinal plant for a long time[1]. It has also been reported that its leaves and twigs can be used for repelling mosquitos[2]. In 1995, Watanabe et al. isolated and identified a degraded monoterpene dialdehyde, rotundial (**1**), as a new natural mosquito repellent from *V. rotundiforia*[3]. They reported that the mosquito repelling activity of rotundial was superior to that of *N*,*N*-diethyl-*m*-toluamide (Deet®), the active ingredient in almost all the commercial insect-repellent formulations. By comparing the optical rotation of rotundiol (**12**, derived from natural **1**) with that of dehydroiridodiol or isodehydroiridodiol, they deduced the absolute configuration of natural rotundial to be *R*[3]. To confirm the absolute configuration of natural **1**, we undertook a project to synthesize both the enantiomers of **1**. Here, we describe the first synthesis of the enantiomers of **1**.

Our retrosynthetic analysis of **1** is shown in Scheme 1. The target compound **1** is obtained by oxidation of **A**, which is prepared from **B**. The key intermediate **B** is obtainable from **C** by the ring-opening-closure procedure that has been often used in terpenoid synthesis[4][5]. The intermediate **C** is synthesized by starting from (*S*)-limonene oxide (**D**) which is commercially available as the epoxidation product of (*S*)-limonene (**2**).

Scheme 1. Retrosynthetic analysis of rotundial (**1**)

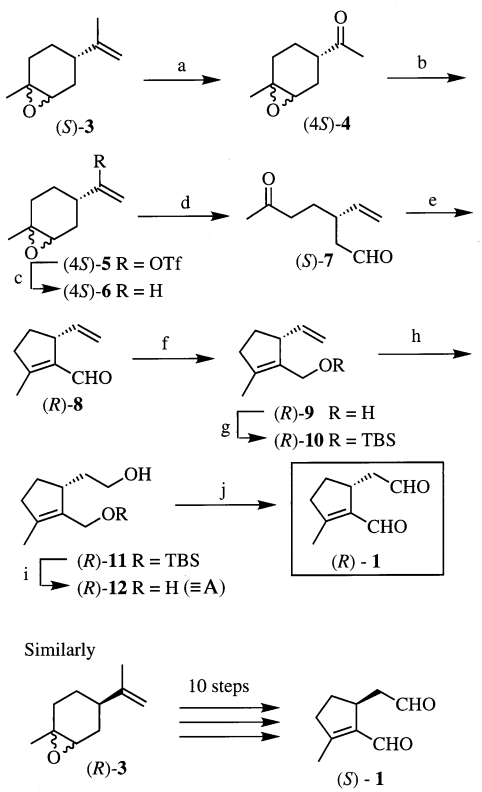


Scheme 2 summarizes the synthesis of the enantiomers of **1**. (*S*)-Limonene oxide (**3**, > 99% e.e., diastereomeric mixture) was converted into the ketone (4*S*)-**4**[6] by ozonolysis followed by reductive workup in 73% yield. The kinetic enolate of (4*S*)-**4**, which was generated with lithium diisopropylamide (LDA), was treated with *N*-phenyltrifluoromethanesulfonimide ($PhNTf_2$) to give the corresponding enol triflate (4*S*)-**5** in 66% yield. Reduction of triflate (4*S*)-**5** with tributyltin hydride (Bu_3SnH) in the presence of tetrakis(triphenylphosphane)palladium [$(Ph_3P)_4Pd$] yielded 75% of (4*S*)-**6**[7]. Periodic acid dihydrate converted (*S*)-**6** to acyclic oxoaldehyde (*S*)-**7**, which was employed for the ring-closure reaction to give (*R*)-**8**[5]. Reduction of (*R*)-**8** with $LiAlH_4$ furnished (*R*)-**9**, whose hydroxy group was protected as the corresponding *tert*-butyldimethylsilyl (TBS) ether to give (*R*)-**10** in 47% yield based on (4*S*)-**6**. Hydroboration-oxidation of (*R*)-**10** with 9-BBN, followed by treatment with alkaline hydrogen peroxide, yielded (*R*)-**11** (quant.), which was deprotected to give (*R*)-**12**, $[\alpha]_D^{23} = -19$ (c = 0.60, $CHCl_3$) {ref.[3] $[\alpha]_D^{25} = -16.6$ (c = 0.60, $CHCl_3$)} in 91% yield. Finally, the diol (*R*)-**12** was oxidized under Swern conditions[8] to give (*R*)-rotundial (**1**) as a colorless oil, $[\alpha]_D^{22} = +108$ (c = 1.00, $CHCl_3$) {ref.[3] $[\alpha]_D^{25} = +39.3$ (c = 1.00, $CHCl_3$)} in 57% yield. The overall yield of (*R*)-**1** over 10 steps based on (*S*)-**3** was 8.8%. The enantiomeric purity of synthetic (*R*)-**1** was estimated to be > 99% e.e. by GLC analysis employing a chiral stationary phase. Similarly, by starting from (*R*)-limonene oxide, (*S*)-rotundial (**1**), $[\alpha]_D^{22} = -107$ (c = 1.02, $CHCl_3$), was synthesized in 10% overall yield. The IR, ^{1}H-NMR, and ^{13}C-NMR spectra of synthetic **1** agreed with those of the natural product.

[◇] Part XXV: A. Yajima, H. Takikawa, K. Mori, *Liebigs Ann. Chem.* **1996**, 891−897.

  1434−193X/98/0202−0229 $ 17.50+.50/0

Scheme 2. Synthesis of rotundial (**1**)



Reagents: (a) O_3, CH_2Cl_2 then PPh_3 (73%). – (b) LDA, THF then $PhNTf_2$ (66%). – (c) $(nBu)_3SnH$, $Pd(PPh_3)_4$, LiCl, THF (75%). – (d) $HIO_4 \cdot 2\,H_2O$, THF/Et_2O. – (e) Pyrrolidine, AcOH, Et_2O. – (f) $LiAlH_4$, Et_2O. – (g) TBSCl, imidazole, DMF [47% based on (4*S*)-**6**]. – (h) 9-BBN, THF then aq. NaOH/aq. H_2O_2. – (i) Bu_4NF, THF [91% based on (*R*)-**10**]. – (j) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2 (81%).

Both synthetic (*R*)-**1** and natural **1** were dextrorotatory, although the rotation value of natural **1** was smaller than that of synthetic (*R*)-**1**, probably due to the impurities in the natural product. There was no big difference between the rotation value of rotundiol (**12**) derived from natural rotundial and that of synthetic (*R*)-**12**. From these results, we conclude that the absolute configuration of natural rotundial is *R* as deduced by Watanabe et al.[3]. As to the bioactivity, a bioassay employing synthetic enantiomers of rotundial (**1**) showed that the two enantiomers are equally bioactive. Therefore, in this case, the absolute configuration of **1** plays no role in its bioactivity as a mosquito repellent.

We thank Drs. *K. Watanabe*, *N. Matsuo*, and their colleagues at *Sumitomo Chemical Co.* (Takarazuka, Japan) for the copies of the IR, ^{1}H- and ^{13}C-NMR spectra of natural rotundial and also for the bioassay.

Experimental Section

General: Boiling points and melting points: uncorrected value. – IR: Jasco IRA-102. – ^{1}H NMR: Jeol JNM-EX 90A (90 MHz) and Bruker DPX 300 (300 MHz, TMS at $\delta_H = 0.00$ or $CHCl_3$ at $\delta_H = 7.26$ as internal standard). – ^{13}C NMR: Bruker DPX 300 (75.5 MHz), ($CDCl_3$ at $\delta_C = 77.0$ as internal standard). – MS: Shimadzu GCMS-QP 2000A and Jeol JMS-SX 102A. – Optical rotation: Jasco DIP-1000. – CC: Merck Kieselgel 60 Art 1.07734 and Merck Kieselgel 60 Art 1.15111. – TLC: 0.25 mm Merck silica-gel plates (60F-254).

4-Acetyl-1,2-epoxy-1-methylcyclohexane (**4**). – (i) (4*S*) *Isomer:* Ozone gas was bubbled into a stirred and cooled solution of (4*S*)-**3** (40.0 g, 263 mmol) in CH_2Cl_2 (400 ml) at −78°C until saturation. After flashing off the excess O_3 with O_2 gas, Ph_3P (120 g, 0.46 mol) was added portionwise. The mixture was allowed to warm to room temp. with stirring for 12 h. After removal of the solvent, diethyl ether was added to the residue. The precipitated Ph_3PO was filtered off, and then the filtrate was concentrated in vacuo. This procedure was repeated three times, and the residue was distilled to give 29.6 g of (4*S*)-**4** (73%), colorless oil, b.p. 80−82°C/1 Torr, $n_D^{24} = 1.4667$, $[\alpha]_D^{24} = -80.3$ ($c = 1.09$, $CHCl_3$). – $C_9H_{14}O_2$ (154.2): calcd. C 70.10, H 9.15; found C 69.80, H 9.50. – IR (film): $\tilde{\nu}_{max} = 1715$ cm^{-1} (s, C=O). – ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.28, 1.31 (each s, total 3 H, 1-Me), 1.42−2.23 (m, 7 H, 3-, 4-, 5-, 6-H), 2.11, 2.12 (each s, total 3 H, *Me*−C=O), 2.99−3.06 (m, 1 H, 2-H). – The ^{1}H-NMR spectrum suggested that this product was a mixture of two diastereomers [(1*R*,2*S*,4*S*)/(1*S*,2*R*,4*S*) ≈ 1:1].

(ii) (4*R*) *Isomer:* In the same manner as described above, (4*R*)-**3** (40.0 g, 263 mmol) was converted into 30.0 g of (4*R*)-**4** (74%), b.p. 72−80°C/1 Torr, $n_D^{24} = 1.4644$, $[\alpha]_D^{23} = +78.0$ ($c = 1.20$, $CHCl_3$). – $C_9H_{14}O_2$ (154.2): calcd. C 70.10, H 9.15; found C 69.79, H 9.30. – Its IR and ^{1}H-NMR spectra were identical with those of (4*S*)-**4**.

1,2-Epoxy-1-methyl-4-(1-trifluoromethanesulfonyloxyvinyl)cyclohexane (**5**). – (i) (4*S*) *Isomer:* A solution of LDA was prepared by the addition of an *n*BuLi solution (1.60 M, 82 ml, 0.13 mol) to a stirred and cooled solution of $(iPr)_2NH$ (20 ml, 0.14 mol) in dry THF (160 ml) at 0°C under Ar. The mixture was stirred at 0°C for 20 min. To the stirred and cooled solution of LDA, a solution of (4*S*)-**4** (18.0 g, 0.12 mol) in dry THF (160 ml) was added dropwise at −78°C. After stirring for 40 min, Tf_2NPh (50 g, 0.14 mol) was added portionwise. This mixture was stirred at −78°C for 30 min and allowed to warm to −40°C over 4 h. It was then poured into water and extracted with diethyl ether. The organic layer was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography on SiO_2 (360 g, elution with hexane/ethyl acetate = 80:1) to give 22.0 g of (4*S*)-**5** (66%), colorless oil. – IR (film): $\tilde{\nu}_{max} = 1670$ cm^{-1} (s, C=C), 1200 (s, sulfonate), 1150 (s, sulfonate). – ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.33, 1.34 (each s, total 3 H, 1-Me), 1.59−2.60 (m, 7 H, 3-, 4-, 5-, 6-H), 2.95−3.15 (m, 1 H, 2-H), 4.92 (br. d, J = 4 Hz, 1 H, C=C*H*^{a}H^b), 5.09, 5.14 (each d, J = 4 Hz, total 1 H, C=CH^a*H*^{b}). – This was employed for the next step without further purification.

(ii) (4*R*) *Isomer:* In the same manner as described above, (4*R*)-**4** (9.80 g, 64 mmol) was converted into 16.0 g of (4*R*)-**5** (88%). Its IR and ^{1}H-NMR spectra were identical with those of (4*S*)-**5**. This was employed for the next step without further purification.

1,2-Epoxy-1-methyl-4-vinylcyclohexane (**6**). – (i) (4*S*) *Isomer:* To a mixture of LiCl (0.59 g, 14 mmol), $Pd(PPh_3)_4$ (0.10 g, 0.087 mmol) in dry THF (25 ml), a solution of (4*S*)-**5** (1.24 g, 4.2 mmol) in dry THF (10 ml) was added at room temp. under Ar. After stirring for 10 min, $(nBu)_3SnH$ (1.2 ml, 4.6 mmol) was added dropwise to this mixture. It was stirred for 30 min and diluted with pentane (30 ml). This pentane solution was washed with water, an aqueous NH_3 solution (10%), water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography on SiO_2 (25 g, elution with hexane/ethyl acetate = 70:1) to give 450 mg of (4*S*)-**6** (75%). An analytical sample was obtained by distillation, colorless oil, b.p. 73−76°C/40 Torr, $n_D^{24} = 1.4600$, $[\alpha]_D^{23} = -86.8$ ($c = 1.05$, $CHCl_3$). – IR (film): $\tilde{\nu}_{max} = 3070$ cm^{-1}

(m, C=CH_2), 1640 (m, C=C). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.31, 1.32 (each s, total 3 H, 1-Me), 1.33−2.25 (m, 7 H, 3-, 4-, 5-, 6-H), 3.00 (m, 1 H, 2-H), 4.80−5.10 (m, 2 H, C=CH_2), 5.50−5.95 (m, 1 H, C−CH=C). − HR MS; *m/z*: found 138.1051 [M^+], calcd. for $C_9H_{14}O$ 138.1044.

(ii) (4*R*) *Isomer:* In the same manner as described above, (4*R*)-**5** (15.7 g, 54.8 mmol) was converted into 3.98 g of (4*R*)-**6** (53%), b.p. 72−73°C/23 Torr, n_D^{24} = 1.4593, $[\alpha]_D^{23}$ = +78.3 (*c* = 1.06, $CHCl_3$). − HR MS; *m/z*: found 138.1043 [M^+]; calcd. for $C_9H_{14}O$ 138.1044. − Its IR and ^{1}H-NMR spectra were identical with those of (4*S*)-**6**.

6-Oxo-3-vinylheptanal (**7**) − (i) (*S*) *Isomer:* To an ice-cooled suspension of periodic acid dihydrate (13.3 g, 58.3 mmol) in diethyl ether (100 ml), a solution of (4*S*)-**6** (7.20 g, 52.1 mmol) in THF (75 ml) was added dropwise. This mixture was stirred at 0°C for 2.5 h and then filtered through Celite. The filtrate was diluted with a satd. aqueous $Na_2S_2O_3$ solution, and extracted with diethyl ether. The organic layer was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo to give 11.4 g of crude (*S*)-**7** (quant.). − IR (film): $\tilde{\nu}_{max}$ = 3090 cm^{-1} (m, C=CH_2), 2730 (m, aldehyde C−H), 1725 (s, aldehyde), 1715 (s, ketone), 1640 (m, C=C). − This was employed for the next step without further purification.

(ii) (*R*) *Isomer*: In the same manner as described above, (4*R*)-**6** (3.98 g, 28.8 mmol) was converted into 4.61 g of crude (*R*)-**7** (quant.). Its IR spectrum was identical with that of (*S*)-**7**. This was employed for the next step without further purification.

(2-Methyl-5-vinyl-1-cyclopenten-1-yl)methanol (**9**). − (i) (*R*) *Isomer:* To a solution of crude (*S*)-(**7**) (11.4 g, ca. 52.1 mmol) in diethyl ether (70 ml), pyrrolidine (0.7 ml) and acetic acid (0.7 ml) were added successively. It was then stirred at room temp. for 1 h. This solution was washed with dil. hydrochloric acid, a satd. aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo to give 7.0 g of crude (*R*)-**8** [99% based on (4*S*)-**6**, in 2 steps]. A solution of (*R*)-**8** (7.0 g, 51 mmol) in diethyl ether (30 ml) was added dropwise to a stirred and ice-cooled suspension of $LiAlH_4$ (1.5 g, 40 mmol) in diethyl ether (20 ml). The mixture was stirred at 0°C for 30 min. It was then ice-cooled and the excess $LiAlH_4$ was destroyed by the successive addition of water (1.5 ml), an aqueous NaOH solution (15%, 1.5 ml) and water (4.5 ml). The mixture was filtered through Celite. The filtrate was dried ($MgSO_4$) and concentrated in vacuo to give 8.1 g of (*R*)-**9** [quant. based on (4*S*)-**6**, 3 steps]. Thus obtained (*R*)-**9** was found to contain inseparable impurities. Its purification was so difficult that it was employed for the next step without further purification. However, a small amount of the purified TBS ether [(*R*)-**10**] was deprotected by treatment with Bu_4NF to give an analytical sample of (*R*)-**9**, colorless oil, n_D^{23} = 1.4937, $[\alpha]_D^{22}$ = −182 (*c* = 0.35, $CHCl_3$). − IR (film): $\tilde{\nu}_{max}$ = 3350 cm^{-1} (s, O−H), 3100 (m, C=CH_2), 1640 (m, C=C). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.25 (br. s, 1 H, OH), 1.40−1.80 (m, 1 H, 4-H^a), 1.73 (br. s, 3 H, Me), 1.84−2.26 (m, 3 H, 3-H, 4-H^b), 3.20−3.55 (m, 1 H, 5-H), 4.06 (br. d, 1 H, *J* = 12 Hz, −C*H*^{a}H^b−O), 4.18 (br. d, 1 H, *J* = 12 Hz, −CH^a*H*^{b}−O), 4.96 (1 H, dd, *J* = 9 Hz, *J′* = 2 Hz, −C=C*H*^{a}H^b), 5.08 (1 H, dd, *J* = 17 Hz, *J′* = 2 Hz, −C=CH^a*H*^{b}), 5.76 (1 H, ddd, *J* = 17 Hz, *J′* = 9 Hz, *J″* = 9 Hz, −CH=C). − HR MS; *m/z*: found 138.1048 [M^+]; calcd. for $C_9H_{14}O$ 138.1044.

(ii) (*S*) *Isomer:* In the same manner as described above, (*S*)-**7** (4.60 g, ca. 28.9 mmol) was converted into 3.89 g of crude (*S*)-**9** [98% based on (4*R*)-**6**, 3 steps]. This was employed for the next step without further purification. A small amount of the purified corresponding TBS ether [(*S*)-**10**] was deprotected by treatment with Bu_4NF to give an analytical sample, colorless oil, n_D^{23} = 1.4923, $[\alpha]_D^{23}$ = +199 (*c* = 0.55, $CHCl_3$). − HR MS; *m/z*: found 138.1044 [M^+]; calcd for $C_9H_{14}O$ 138.1044. − Its IR and ^{1}H-NMR spectra were identical with those of (*R*)-**9**.

1-tert-Butyldimethylsilyloxymethyl-2-methyl-5-vinyl-1-cyclopentene (**10**) − (i) (*R*) *Isomer:* To a solution of (*R*)-**9** (8.1 g, ca 52 mmol) in DMF (80 ml), imidazole (7.5 g, 0.11 mol) and TBSCl (7.5 g, 50 mmol) were added. After stirring at room temp. for 1.5 h, it was diluted with water and extracted with diethyl ether. The organic layer was washed with water, a satd. aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by chromatography on SiO_2 (80 g, elution with hexane/ethyl acetate = 200:1) to give 6.18 g of (*R*)-**10** [47% based on (4*S*)-**6**, 4 steps], colorless oil, n_D^{25} = 1.4739, $[\alpha]_D^{22}$ = −102 (*c* = 1.10, $CHCl_3$).− IR (film): $\tilde{\nu}_{max}$ = 3100 cm^{-1} (m, C=CH_2), 1640 (m, C=C), 1260 (s, Si−Me), 1065 (s, Si−O). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.05 (s, 6 H, Si−Me), 0.90 (s, 9 H, *t*Bu), 1.40−1.75 (m, 1 H, 4-H^a), 1.70 (br. s, 3 H, 2-Me), 1.85−2.45 (m, 3 H, 3-H, 4-H^b), 3.20−3.55 (m, 1 H, 1-H), 4.03 (br. d, *J* = 12 Hz, 1 H, C*H*^{a}H^b−O), 4.25 (d, *J* = 12 Hz, 1 H, −CH^a*H*^{b}−O), 4.91 (dd, *J* = 10 Hz, *J′* = 2 Hz, 1 H, −C=C*H*^{a}H^b), 5.00 (dd, *J* = 17 Hz, *J′* = 2 Hz, 1 H, −C=CH^a*H*^{b}), 5.71 (ddd, *J* = 17 Hz, *J′* = 10 Hz, *J″* = 8 Hz, −CH=C). − $C_{15}H_{28}OSi$ (252.5): calcd. C 71.36, H 11.18; found C 70.81, H 11.14.

(ii) (*S*) *Isomer:* In the same manner as described above, (*S*)-**9** (3.89 g, 28.1 mmol) was converted into 3.58 g of crude (*S*)-**10** [49% based on (4*R*)-**6**, 4 steps], colorless oil, n_D^{24} = 1.4614, $[\alpha]_D^{24}$ = +95.0 (*c* = 1.04, $CHCl_3$). Its IR and ^{1}H-NMR spectra were identical to those of (*R*)-**10**. − $C_{15}H_{28}OSi$ (252.5): calcd. C 71.36, H 11.18; found C 71.16, H 10.70.

2-(2′-tert-Butyldimethylsilyloxymethyl-3′-methyl-2′-cyclopenten-1′-yl)ethanol (**11**). − (i) (*R*) *Isomer:* The solution of (*R*)-**10** (5.00 g, 19.8 mmol) in THF (40 ml) was added dropwise to a stirred and ice-cooled solution of 9-BBN (0.5 M in THF, 120 ml, 0.06 mol) at 0°C under Ar. It was stirred at room temp. for 25 h and then cooled to 0°C. To this cooled solution, water (20 ml), an aqueous NaOH solution (3 M, 120 ml) and an aqueous H_2O_2 solution (34%, 120 ml) were carefully added. After stirring at room temp. for 1.5 h, it was extracted with diethyl ether. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was filtered through SiO_2 to give 6.02 g of crude (*R*)-**11** (quant.). This was employed for the next step without further purification. A small amount of crude (*R*)-**11** was purified by chromatography on SiO_2 (hexane/ethyl acetate = 40:1) to give an analytical sample, colorless oil, n_D^{24} = 1.4739, $[\alpha]_D^{22}$ = −7.6 (*c* = 0.65, $CHCl_3$). − IR (film): $\tilde{\nu}_{max}$ = 3350 cm^{-1} (s, O−H), 1255 (s, Si−Me), 1060 (s, Si−O). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.05, 0.07 (each s, total 6 H, Si−Me), 0.90 (s, 9 H, *t*Bu), 1.25−2.38 (m, 7 H, 2-, 1′-, 4′-, 5′-H, OH), 1.66 (br. s, 3 H, 3′-Me), 2.83 (m, 1 H, 1′-H), 3.69 (dt, 2 H, *J* = 2 Hz, *J′* = 7 Hz, CH_2−OH), 4.23 (br. s, 2 H, 2-H). − $C_{15}H_{30}O_2Si$ (270.5): calcd. C 66.61, H 11.18; found C 66.14, H 10.96.

(ii) (*S*) *Isomer:* In the same manner as described above, (*S*)-**10** (3.0 g, 12 mmol) was converted into 4.8 g of crude (*S*)-**11** (quant.), n_D^{24} = 1.4723, $[\alpha]_D^{24}$ = +6.6 (*c* = 0.69, $CHCl_3$). − $C_{15}H_{30}O_2Si$ (270.5): calcd. C 66.61, H 11.18; found C 66.72, H 11.27. − Its IR and ^{1}H-NMR spectra were identical with those of (*R*)-**11**.

2-(2′-Hydroxymethyl-3′-methyl-2′-cyclopenten-1′-yl)ethanol (Rotundiol, **12**) − (i) (*R*) *Isomer:* To a solution of (*R*)-**11** (5.76 g, ca. 19 mmol) in THF (50 ml), Bu_4NF solution (1 M in THF, 40 ml, 40 mmol) was added dropwise. It was stirred at room temp. for 2 h, poured into brine, and extracted with diethyl ether. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated in

vacuo. The residue was purified by chromatography on SiO_2 (115 g, elution with $CHCl_3$/MeOH = 50:1) to give 2.70 g of (*R*)-**12** [91% based on (*S*)-**10**, 2 steps]. An analytical sample was further purified by recrystallization (from hexane/diethyl ether) to give colorless plates, m.p. 52−53°C (ref.[3] oil), $[\alpha]_D^{23} = -19$ (*c* = 0.60, $CHCl_3$). − IR (KBr): $\tilde{\nu}_{max}$ = 3300 cm^{-1} (s, O−H), 1065 (m), 1015 (m), 1000 (m). − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.45 (m, 2 H, 5′-H^a, 2-H^a), 1.69 (s, 3 H, 3′-Me), 1.91 (m, 1 H, 2-H^b), 2.03 (m, 1 H, 5′-H^b), 2.27 (m, 2 H, 4′-H), 2.90 (br. s, 1 H, 1′-H), 3.14 (br. s, 2 H, OH), 3.69 (m, 2 H, 1-H), 4.13 (br. d, *J* = 12.2 Hz, 1 H, 2-C*H*^{a}H^b−OH), 4.21 (d, *J* = 12.2 Hz, 1 H, 2-CH^a*H*^{b}−OH). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.0, 28.6, 36.5, 37.1, 42.6, 57.1, 61.2, 136.6, 136.9. − $C_9H_{16}O_2$ (156.2): calcd. C 69.19, H 10.32; found C 69.02, H 10.31.

(ii) (*S*) *Isomer:* In the same manner as described above, (*S*)-**11** (3.93 g, ca. 9.8 mmol) was converted into 1.41 g of (*S*)-**12** [93% based on (*S*)-**10**, 2 steps], m.p. 53−54°C, $[\alpha]_D^{23} = +18$ (*c* = 0.60, $CHCl_3$). − $C_9H_{16}O_2$ (156.2): calcd. C 69.19, H 10.32; found C 69.05, H 10.16. − Its IR, ^1H-NMR and ^{13}C-NMR spectra were identical with those of (*R*)-**12**.

2-(2′-Formyl-3′-methyl-2′-cyclopenten-1′-yl)acetaldehyde (Rotundial, **1**) − (i) (*R*) *Isomer:* To a stirred and cooled solution of $(COCl)_2$ (0.37 ml, 4.2 mmol) in dry CH_2Cl_2 (3 ml), DMSO (0.59 ml, 8.3 mmol), and a solution of (*R*)-**12** (300 mg, 1.92 mmol) in dry CH_2Cl_2 (2.5 ml) were successively added, dropwise at −78°C under Ar. It was then stirred at −78°C for 30 min. Et_3N (2.65 ml, 19.0 mmol) was added to the reaction mixture, and it was then allowed to warm to room temp. with stirring. This mixture was poured into water and extracted with diethyl ether. The organic layer was washed with a satd. aqueous $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on SiO_2 (5 g, elution with hexane/ethyl acetate = 40:1) to give 168 mg of (*R*)-**1** (57%), colorless oil, $n_D^{23} = 1.5120$, $[\alpha]_D^{22} = +108$ (*c* = 1.00, $CHCl_3$). − IR (film): $\tilde{\nu}_{max}$ = 3450 cm^{-1} (w), 3300 (w), 2950 (m, C−H), 2840 (s, C−H), 2730 (m, aldehyde C−H), 1725 (s, C=O), 1665 (s, C=O), 1635 (m, C=C), 1430 (m), 1385 (m), 1355 (m), 1295 (w), 1255 (m), 1190 (m). − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.53 (m, 1 H, 5′-H^a), 2.17 (s, 3 H, 3′-Me), 2.18 (m, 1 H, 5′-H^b), 2.37 (ddd, *J* = 16.8 Hz, *J*′ = 9.2 Hz, *J*″ = 2.2 Hz, 1 H, 2-H^a), 2.56 (m, 2 H, 4-H), 2.94 (ddd, *J* = 16.8 Hz, *J*′ = 4.2 Hz, *J*″ = 1.5 Hz, 1 H, 2-H^b), 3.42 (m, 1 H, 1′-H), 9.76 (dd, *J* = 1.5 Hz, *J*″ = 1.5 Hz, 1 H, 1-H), 9.98 (s, 1 H, 2-CHO). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.4, 28.1, 38.1, 39.0, 47.8, 138.9, 164.2, 187.9, 201.9. − HR MS; *m/z*: found 152.0845 [M^+]; calcd. for $C_9H_{12}O_2$ 152.0838. − Rotundial (**1**) was rather unstable and therefore correct elemental analytical data could not be obtained.

(ii) (*S*) *Isomer:* In the same manner as described above, (*S*)-**12** (302 mg, 1.93 mmol) was converted into 188 mg of (*S*)-**1** (64%), colorless oil, $n_D^{24} = 1.4993$, $[\alpha]_D^{22} = -107$ (*c* = 1.02, $CHCl_3$). − HR MS; *m/z*: found 152.0848 [M^+]; calcd. for $C_9H_{12}O_2$ 152.0838. − Its IR, ^1H- and ^{13}C-NMR spectra were identical with those of (*R*)-**1**.

Determination of the Enantiomeric Purity of Rotundial (**1**): GLC (column: Chirasil DEX-CB®, 0.25 mm × 25 m, 100°C 1 min, +1°C/min; carrier gas: He, press 110 kPa).

(i) (*R*) *Isomer:* t_R = 58.9 [(*S*)-**1**, < 0.5%], t_R = 59.2 [(*R*)-**1**, > 99.5%]. The enantiomeric purity of (*R*)-**1** was therefore > 99%.

(ii) (*S*) *Isomer:* (*S*)-Rotundial (**1**) was also thought to be of > 99% e.e., and the peak due to (*R*)-**1** could not be observed in the GLC trace due to the tailing of (*S*)-**1**.

☆ Dedicated to Professor *M. Matsui* on the occasion of his 80th birthday.

[1] Y. Kimura, M. Takido, Y. Hiwatashi, *Yakugaku Zasshi* (in Japanese), **1967**, *87*, 1429−1430; *Chem. Abstr.* **1967**, *68*, 62627x.
[2] O. Okuda, *Koryo Kagaku Soran* (in Japanese), Hirokawa Shoten, Tokyo, **1967**, p. 310−311.
[3] K. Watanabe, Y. Takada, N. Matsuo, H. Nishimura, *Biosci. Biotech. Biochem.* **1996**, *59*, 1979−1980.
[4] J. Wolinsky, W. Barker, *J. Am. Chem. Soc.* **1960**, *82*, 636−638.
[5] J. Wolinsky, M. R. Slebaugh, T Gibson, *J. Org. Chem.* **1964**, *29*, 3740−3742.
[6] W. Knöll, C. Tamm, *Helv. Chim. Acta* **1975**, *58*, 1163−1171.
[7] W. J. Scott, J. K. Stille, *J. Am. Chem. Soc.* **1986**, *108*, 3033−3040.
[8] A. J. Mancuso, S.-L. Huang, D. Swern, *J. Org. Chem.* **1978**, *43*, 2480−2482.

[97308]