Pheromone Synthesis, CXCI[◇]

Synthesis of the Enantiomers of 8-Hydroxy-2,5,8-trimethyl-4-nonanone, the Myxobacterial Pheromone of *Stigmatella aurantiaca* to Induce the Formation of Its Fruiting Body

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Received May 25, 1998

Keywords: Fruiting body / Ketones / Myxobacterium / Pheromones / *Stigmatella aurantiaca*

The enantiomers of the title compound **1** were synthesized from the enantiomers of citronellol (**2**). Both (*R*)- and (*S*)-**1** induced the formation of the fruiting body of a myxobacterium *Stigmatella aurantiaca* at a concentration of 0.4−1.0 nM.

Myxobacteria are unique procaryotes that undergo multicellular development including swarming and aggregation of their cells and formation of fruiting bodies[1]. For their development, several factors are required such as a large number of myxobacterial cells, depletion of nutrients, etc. In early 1997 Yamanaka, Fudo and their coworkers identified isoeugenitin as a fruiting body inducer for a myxobacterium *Stigmatella aurantiaca*[1]. Isoeugenitin was active at a concentration of 1−40 μM. However, it was not an endogenous signal of *S. aurantiaca* but a metabolite of a soil fungus *Papulaspola* sp.[1]. Subsequently in 1997, Plaga and his coworkers announced the isolation of the genuine pheromone of *S. aurantiaca* to aggregate the starving cells at the beginning of the developmental part of their life cycle[2]. They purified the pheromone by steam distillation followed by chromatography, and clarified its structure on the basis of its IR, ^{1}H- and ^{13}C-NMR and MS analysis. The proposed structure is the simple hydroxy ketone **1** (8-hydroxy-2,5,8-trimethyl-4-nonanone)[2]. Their synthesis of **1** confirmed the correctness of their proposal, because the synthetic **1** showed the spectral and biological properties identical to those of the natural pheromone, which induced the fruiting body formation at a concentration of 1 nM[2]. The absolute configuration of the natural pheromone, however, remained unknown. By the request of Dr. Yamanaka at Ajinomoto Co., we undertook a synthesis of the enantiomers of **1** so as to determine the absolute configuration of the natural **1**.

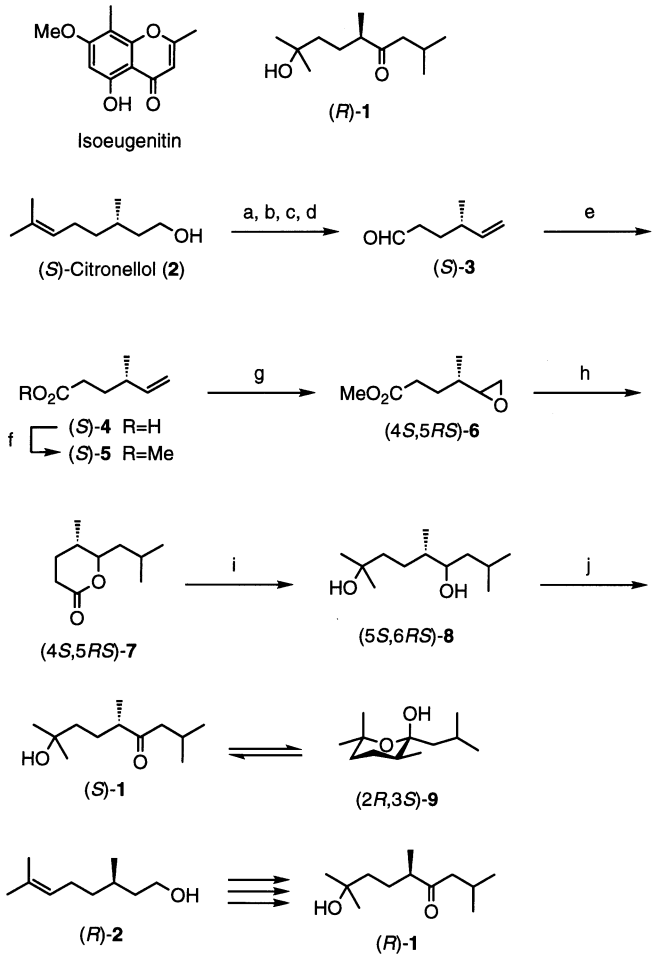
Because the pheromone **1** possesses only one stereogenic center as a methyl branching at C-5, citronellol (**2**) was chosen as the ideal starting material due to the availability of both of its enantiomers. As shown in Scheme 1, (*S*)-citronellol (**2**, 97% e.e.) was converted by the Chugaev reaction to (*S*)-citronellene via the xanthate according to Cernigliaro and Kocienski[3]. Epoxidation of (*S*)-citronellene with *m*-chloroperbenzoic acid (MCPBA) was followed by the periodate cleavage of the resulting epoxide to give the aldehyde (*S*)-**3**[3], which was oxidized with Jones chromic acid to furnish the acid (*S*)-**4**. The corresponding methyl ester (*S*)-**5** was epoxidized with MCPBA in the presence of sodium hydrogen carbonate to afford the epoxy ester (4*S*,5*RS*)-**6**. Treatment of (4*S*,5*RS*)-**6** with isopropylmagnesium chloride in the presence of copper(I) bromide and dimethyl sulfide yielded the lactone (4*S*,5*RS*)-**7**. The ratio of the two isomers of (4*S*,5*RS*)-**7** was 59−63:41−37 by GC analysis, and the enantiomeric purity of one of the isomers of **7** was estimated as 95−98% e.e. by GC analysis on a chiral stationary phase. The enantiomers of the other isomer of **7** could not be separated. The lactone (4*S*,5*RS*)-**7** was treated with an excess of methylmagnesium bromide to give the diol (5*S*,6*RS*)-**8**. Dess-Martin oxidation[4] of (5*S*,6*RS*)-**8** furnished the final product (*S*)-**1**, which was in equilibrium with the cyclic hemiacetal (2*R*,3*S*)-**9** as judged by its ^{1}H- and ^{13}C-NMR spectra. This final product was analyzed by GC on a chiral stationary phase to confirm the high enantiomeric purity (90% e.e.) of (*S*)-**1**. Similarly, the opposite enantiomer (*R*)-**1** (91% e.e.) was synthesized by starting from (*R*)-citronellol (**2**, 97% e.e.). The overall yield of **1** from **2** was 2% (10 steps). Although the final products (*R*)- and (*S*)-**1** were not perfectly pure due to the partial racemization in the final step, we thought them to be pure enough (≥ 90% e.e.) to warrant their biological evaluation.

The bioassay of the enantiomers of **1** was carried out by Drs. R. Fudo and S. Yamanaka, and both the enantiomers induced the formation of the fruiting bodies of *S. aurantiaca* at a concentration of 0.4−1.0 nM. Since both the enantiomers of **1** were equally active, the absolute configu-

[◇] Part CXC: K. Mori, S. Sano, Y. Yokoyama, M. Bando, M. Kido, *Eur. J. Org. Chem*. **1998**, 1135−1141.

  1434−193X/98/1010−2181 $ 17.50+.50/0

Scheme 1. Synthesis of the enantiomers of **1**



Reagents: (a) NaH, CS_2 then MeI. − (b) Heat (45%). − (c) MCPBA, CH_2Cl_2. − (d) $HIO_4{\cdot}2H_2O$, THF/Et_2O. − (e) Jones CrO_3, Me_2CO [45% based on (*S*)-citronellene]. − (f) K_2CO_3, MeI, Me_2CO (89%). − (g) MCPBA, $NaHCO_3$, CH_2Cl_2. − (h) *i*PrMgCl, CuBr·Me_2S, THF (32% based on **5**). − (i) MeMgBr, THF (55%). − (j) Dess-Martin periodinane, C_5H_5N, CH_2Cl_2 (65%).

ration of the natural pheromone could not be determined by the bioassay. A sample of (±)-**1** prepared by mixing the equal amounts of (*R*)- and (*S*)-**1** was as active as the starting enantiomers. Accordingly, the bioactivity of the enantiomers of **1** was neither mutually inhibitory nor synergistic, but merely additive. Our synthetic enantiomers of **1** were then compared chromatographically with the natural **1** isolated by Morikawa et al[5]. Their results indicated the natural pheromone **1** to be an enatiomeric mixture[5].

We thank Emeritus Prof. *S. Marumo* (Nagoya University), Drs. *S. Yamanaka* and *R. Fudo* (Ajinomoto Co., Inc., Kawasaki), and Prof. *A. Isogai* and Dr. *S. Takayama* (Nara Institute of Science and Technology) for discussion. Drs. *S. Yamanaka* and *R. Fudo* are thanked for the bioassay. GC analysis on a chiral stationary phase was kindly carried out by Mr. *S. Tamogami* (T. Hasegawa Co., Ltd., Kawasaki). Our thanks are due to *Takasago International Corporation* for the gift of citronellol enantiomers. This work was financially supported by *Ajinomoto Co., Inc.*

Experimental Section

Boiling points: uncorrected values. − IR: Jasco A-102. − ^{1}H NMR: Jeol JNM-EX 90A (90 MHz) and Jeol JNM-EX 270L (270 MHz) and Bruker DPX 300 (300 MHz) ($CHCl_3$ at δ = 7.26 as an internal standard). − ^{13}C NMR: Jeol JNM-EX 270L (67.5 MHz) and Bruker DPX 300 (75.5 MHz) ($CDCl_3$ at δ = 77.0 as an internal standard). − Optical rotation: Jasco DIP-1000. − MS: Jeol JMS-SX102A.

(S)-4-Methyl-5-hexenoic Acid [(*S*)-**4**]: To a stirred and cooled solution of (*S*)-**3** (crude 20 g)[3] in acetone (400 ml), Jones reagent (2.69 M, 83 ml, 223 mmol) was added dropwise at 0°C. After stirring for 1 h at 0°C, the reaction was quenched with 2-propanol. Water and diethyl ether were added to the reaction mixture. The organic phase was separated and the aqueous phase was extracted with diethyl ether. The combined organic phase was extracted with 15% sodium hydroxide solution. The resulting aqueous phase was acidified with dilute HCl, and extracted with diethyl ether. The extract was washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by distillation to give 11.7 g [20% from (*S*)-**2**] of (*S*)-**4** as a colorless oil, b.p. 105−106°C/10 Torr. n_D^{24} = 1.4357. − $[\alpha]_D^{22}$ = +15.5 (*c* = 1.16, $CHCl_3$). − IR(film): ν_{max} = 2970 cm^{-1} (s, O−H), 1710 (s, C=O), 1640 (m, C=C), 1215 (s, C−O), 995 (m), 915 (s). − ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.02 (d, *J* = 6.8 Hz, 3 H, 4-Me), 1.40−1.77 (m, 2 H, 3-H_2), 1.86−2.45 (m, 3 H, 2-H_2, 4-H), 4.83−5.12 (m, 2 H, 6-H_2), 5.66 (ddd, *J* = 18 Hz, *J′* = 9.9 Hz, *J″* = 7.2 Hz, 1 H, 5-H); due to the broadening of the signal, a proton of the carboxyl group could not be detected clearly. − $C_7H_{12}O_2$ (128.2): calcd. C 65.60, H 9.44; found C 65.71, H 9.13.

(R)-Methyl-5-hexenoic Acid [(*R*)-**4**]: In the same manner as described above, (*R*)-**3** was converted to (*R*)-**4** [4.37 g, 13% from (*R*)-**2**], b.p. 105−106°C/10 Torr. n_D^{24} = 1.4382. − $[\alpha]_D^{22}$ = −16.1 (*c* = 1.04, $CHCl_3$). − Its IR and ^{1}H-NMR spectra were identical with those of the (*S*)-isomer.

Methyl (S)-4-Methyl-5-hexenoate [(*S*)-**5**]: To a stirred solution of (*S*)-**4** (11.5 g, 90.0 mmol) in acetone (250 ml), potassium carbonate (16.2 g, 117 mmol) and methyl iodide (38.3 g, 270 mmol) were added at room temperature. The mixture was stirred for 1 d. Diethyl ether and brine were added to the mixture, and the organic phase was separated. The aqueous phase was extracted with diethyl ether. Combined organic phase was washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by distillation to give 11.4 g (89%) of (*S*)-**5** as a colorless oil, b.p. 84−86°C/67 Torr. n_D^{23} = 1.4233. − $[\alpha]_D^{21}$ = +14.1 (*c* = 1.07, $CHCl_3$). − IR(film): ν_{max} = 3080 cm^{-1} (m, olefinic C−H), 1740 (s, C=O), 1640 (m, C=C), 1170 (s, C−O), 1000 (s), 915 (s, olefinic C−H). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.99 (d, *J* = 6.7 Hz, 3 H, 4-Me), 1.51−1.71 (m, 2 H, 3-H_2), 2.05−2.17 (m, 1 H, 4-H), 2.25 (ddd, *J* = 15.5 Hz, *J′* = 8.4 Hz, *J″* = 7.1 Hz, 1 H, 1 of 2-H), 2.31 (ddd, *J* = 15.5 Hz, *J′* = 8.4 Hz, *J″* = 7.1 Hz, 1 H, 1 of 2-H), 3.64 (s, 3 H, COOMe), 4.93 (ddd, *J* = 10.3 Hz, *J′* = 1.8 Hz, *J″* = 0.8 Hz, 1 H, *trans* 6-H), 4.96 (ddd, *J* = 17.2 Hz, *J′* = 1.8 Hz, *J″* = 1.2 Hz, 1 H, *cis*-6-H), 5.62 (ddd, *J* = 17.2 Hz, *J′* = 10.3 Hz, *J″* = 7.8 Hz, 1 H, 5-H). − HRMS [$C_8H_{14}O_2$]: calcd. 142.0994; found 142.0992. − Due to the volatility of the ester, correct elemental analytical data could not be obtained.

Methyl (R)-4-Methyl-5-hexenoate [(*R*)-**5**]: In the same manner as described above, (*R*)-**4** (4.21 g, 32.8 mmol) was converted to (*R*)-**5** (3.12 g, 69%), b.p. 95−96°C/78 Torr. n_D^{23} = 1.4230. − $[\alpha]_D^{22}$ = −14.5 (*c* = 1.16, $CHCl_3$). − Its IR and ^{1}H-NMR spectra were

identical with those of the (*S*) isomer. – HRMS [$C_8H_{14}O_2$]: calcd. 142.0994; found 142.0986. – Due to the volatility of the ester, correct elemental analytical data could not be obtained.

Methyl (S)-5,6-Epoxy-4-methylhexanoate [(*S*)-**6**]: To a stirred solution of (*S*)-**5** (5.00 g, 35.2 mmol) in dichloromethane (100 ml), sodium hydrogen carbonate (5.91 g, 70.3 mmol) and MCPBA (12.1 g, 70.3 mmol) were added at 0°C. After the addition, the reaction temperature was raised to room temp. and the mixture was stirred for 4 d. The reaction mixture was poured into water, and the organic phase was separated and the aqueous phase was extracted with dichloromethane. The combined organic phases were washed with saturated aqueous sodium thiosulfate solution, water, saturated aqueous sodium hydrogen carbonate solution and brine, dried with $MgSO_4$, and concentrated in vacuo to give 3.77 g (68%) of (*S*)-**6** as a colorless oil. The crude oil was used for the next step without further purification. – IR(film): ν_{max} = 1740 cm^{-1} (s, C=O), 1175 (s, C–O). – ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.85–1.96 (m, 6 H, 3-H_2, 4-H, 4-Me), 2.26–2.83 (m, 5 H, 2-H_2, 5-H, 6-H_2), 3.66 (s, 3 H, COOMe).

Methyl (R)-5,6-Epoxy-4-methylhexanoate [(*R*)-**6**]: In the same manner as described above, (*R*)-**5** (3.00 g, 21.1 mmol) was converted to (*R*)-**6** (2.37 g, 71%). – Its IR and ^{1}H-NMR spectra were identical with those of the (*S*) isomer.

(4S,5RS)-4,7-Dimethyl-5-octanolide [(*S*)-**7**]: Isopropylmagnesium chloride (2.0 M in tetrahydrofuran, 33 ml, 66 mmol) was added to copper(I) bromide–dimethyl sulfide (274 mg 1.34 mmol) at 0°C under Ar, and the mixture was cooled to –78°C. To this mixuture, a solution of (*S*)-**6** (3.52 g, 22.3 mmol) in tetrahydrofuran (50 ml) was added at –78°C. After stirring for 4 h, saturated aqueous ammonium chloride solution was added and the temperature was gradually raised to room temperature. The reaction mixture was filtered through Celite, the organic phase was separated, and the aqueous phase was extracted with diethyl ether. The combined organic phases were washed with water and brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography on silica gel (80 g, hexane/ethyl acetate, 10:1) to give 1.77 g [32% from (*S*)-**5**] of (*S*)-**7** as a colorless oil, n_D^{24} = 1.4616. – $[\alpha]_D^{22}$ = –15.8 (*c* = 1.21, $CHCl_3$). – IR(film): ν_{max} = 1730 cm^{-1} (s, C=O), 1240 (s, C–O), 1205(s). – ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.76–1.08 (m, 9 H, 4-Me, 7-Me, 8-H_3), 1.10–2.17 (m, 6 H, 3-H_2, 4-H, 6-H_2, 7-H), 2.41–2.63 (m, 2 H, 2-H_2), 3.97 (dt, *J* = 4 Hz, *J′* = 9 Hz, 0.4 H, 5-H). 4.28-4.49 (m, 0.6 H, 5-H). – HRMS [$C_{10}H_{18}O_2$]: calcd. 170.2282; found 170.1309. – $C_{10}H_{18}O_2$ (170.2): calcd. C 70.55, H 10.66; found C 70.88, H 9.85. GC [column: 3-*O*-acetyl-2,6-di-*O*-pentyl-ß-cyclodextrin, T. Hasegawa, 0.25 mm × 50 m, 70–140°C (+0.7°C/min); carrier gas: N_2, pressure 0.8 kg/cm^2, flow rate 0.8 ml/min]: t_R = 105.70 min [minor isomer of (4*S*, 5*RS*)-**7**, 37%], 115.27 [major isomer of (4*S*, 5*RS*)-**7**, 63%], 115.96 (opposite enantiomer of the major isomer, major isomer/opposite enantiomer = 97.5:2.5); the enantiomeric purity of the major isomer of (4*S*, 5*RS*)-**7** was 95% e.e.

(4R,5RS)-4,7-Dimethyl-5-octanolide [(*R*)-**7**]: In the same manner as described above, (*R*)-**6** (2.15 g, 13.6 mmol) was converted to (*R*)-**7** (1.32 g, 37% from (*R*)-**5**), n_D^{24} = 1.4594. – $[\alpha]_D^{23}$ = +12.5 (*c* = 1.14, $CHCl_3$). – Its IR and ^{1}H-NMR spectra were identical with those of the (*S*) isomer. – HRMS [$C_{10}H_{18}O_2$]: calcd. 170.2282; found 170.1580. – $C_{10}H_{18}O_2$ (170.2): calcd. C 70.55, H 10.66; found C 69.82, H 10.10. – This lactone **7** was slightly volatile and the results of its combustion analysis fluctuated. – GC [under the same condition as for the analysis of (4*S*, 5*RS*)-**7**]: t_R = 105.37 min [minor isomer of (4*R*, 5*RS*)-**7**, 41%], 114.09 (opposite enantiomer of the major isomer; major isomer/opposite enantiomer = 99:1), 116.49 [major isomer of (4*R*, 5*RS*)-**7**, 59%]; the enantiomeric purity of the major isomer of (4*R*, 5*RS*)-**7** was 98% e.e.

(5S,6RS)-2,5,8-Trimethyl-2,6-nonanediol [(*S*)-**8**]: To a stirred solution of (*S*)-**7** (700 mg, 4.11 mmol) in tetrahydrofuran (20 ml), a solution of methylmagnesium bromide (0.92 M in tetrahydrofuran, 45 ml, 41 mmol) was added at 0°C under Ar. After stirring for 5 h at 0°C, the reaction mixture was poured into water. The organic phase was separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography on silica gel (10 g, hexane/ethyl acetate, 5:1) to give 456 mg (55%) of (*S*)-**8** as a colorless oil, n_D^{23} = 1.4559. – $[\alpha]_D^{20}$ = –11.3 (*c* = 0.29, $CHCl_3$). – IR(film): ν_{max} = 3400 cm^{-1} (s, O–H). – ^{1}H NMR (90 MHz, $CDCl_3$): δ = 0.81–0.98 (m, 9 H, 5-Me, 8-Me, 9-H_3), 1.02–1.70 (m, 9 H, 3, 4, 7-H_2, 5, 6, 8-H), 1.21 (s, 6 H, 1-H_3, 2-Me), 3.59 (br., 1 H, OH). – This oil was employed for the next step without further purification.

(5R,6RS)-2,5,8-Trimethyl-2,6-nonanediol [(*R*)-**8**]: In the same manner as described above, (*R*)-**7** (309 mg, 1.81 mmol) was converted to (*R*)-**8** (232 mg, 63%), n_D^{24} = 1.4544. – $[\alpha]_D^{20}$ = +10.7 (*c* = 0.32, $CHCl_3$). – Its IR and ^{1}H-NMR spectra were identical with those of the (*S*) isomer.

(S)-8-Hydroxy-2,5,8-trimethyl-4-nonanone [(*S*)-**1**]: To a stirred solution of Dess-Martin reagent (4.43 g, 10.5 mmol) in dichloromethane (50 ml) and pyridine (10 ml), a solution of (*S*)-**8** (423 mg, 2.09 mmol) in dichloromethane (10 ml) was added at room temp. under Ar. After stirring for 2.5 h, the reaction mixture was poured into a mixture of saturated aqueous sodium thiosulfate solution and saturated aqueous sodium hydrogen carbonate solution (1:1). The organic phase was separated, and the aqueous phase was extracted with dichloromethane. The combined organic phases were washed with water, dilute HCl, water, saturated aqueous sodium hydrogen carbonate and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography on silica gel (10 g, hexane/ethyl acetate, 10:1) to give 274 mg (65%) of (*S*)-**1** as a colorless oil, n_D^{23} = 1.4485. – $[\alpha]_D^{22}$ = +7.63 (*c* = 0.51, $CHCl_3$). – IR: (film) ν_{max} = 3450 cm^{-1} (s, O–H), 2960, 2870, 1710 (s, C=O), 1455, 1365, 1215, 1170 (m, C–O), 1035, 950, 920, 905. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.6 Hz, 3 H, 1-H_3), 0.91 (d, *J* = 6.6 Hz, 3 H, 2-Me), 1.07 (d, *J* = 7.0 Hz, 3 H, 5-Me), 1.20 (s, 6 H, 8-Me, 9-H_3), 1.35–1.46 (m, 3 H, 7-H_2, -OH), 1.67–1.86 (m, 2 H, 6-H_2), 2.10–2.20 (m, 1 H, 2-H), 2.28–2.33 (m, 2 H, 3-H_2), 2.43–2.49 (m, 1 H, 5-H). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 16.5, 22.6, 22.7, 24.2, 26.5, 27.3, 29.2, 41.2, 46.8, 50.3, 70.7, 214.5). – The following signals were assigned to be those due to the cyclic hemiacetal **9**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 6.5 Hz, 6 H, 3′-Me, 4′-H_3), 1.17 (s, 6 H, 5-Me × 2), 1.54–1.58 (m, 7 H, 3-H_2, 3′-H, 2-Me, OH), 1.88–1.93 (m, 5 H, 2′, 4-H_2, 2-H). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 17.9, 22.4, 25.1, 26.8, 29.2, 33.5, 39.5, 71.9, 100.4). – HRMS [$C_{12}H_{24}O_2$ – H_2O]: calcd. 182.1671; found 182.1663. – GC [column: 2,3-di-*O*-methyl-6-*O*-pentyl-ß-cyclodextrin, T. Hasegawa, 0.25 mm × 50 m, 70–140°C (+0.5°C/min); carrier gas: N_2, pressure 0.8 kg/cm^2, frow rate 0.8 ml/min]: t_R = 112.06 min [(*R*)-**1**, 5%], 113.34 [(*S*)-**1**, 95%]; the enantiomeric purity of (S)-**1** was 90% e.e. – This hydroxy ketone **1** was sometimes, presumably in the presence of a trace amount of acid inpurity, unstable to give an anhydro compound via cyclic hemiacetal **9**, and correct combustion analytical data could not be obtained.

(R)-8-Hydroxy-2,5,8-trimethyl-4-nonanone [(*R*)-**1**]: In the same manner as described above, (*R*)-**8** (232 mg, 1.15 mmol) was converted to (*R*)-**1** (161 mg, 70%), $n_D^{24} = 1.4447$. − $[\alpha]_D^{22} = -7.85$ ($c = 0.53$, $CHCl_3$). − Its IR, ^1H- and ^{13}C-NMR spectra were identical with those of the (*S*) isomer. − HRMS [$C_{12}H_{24}O_2$]: calcd. 200.1777; found 200.1775. − GC [under the same condition as for the analysis of (S)-**1**]: $t_R = 112.55$ min [(*R*)-**1**, 95.5%], 113.56 [(*S*)-**1**, 4.5%]; the enantiomeric purity of (*R*)-**1** was 91% e.e.

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[O98234]