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SYNTHESIS OF ALL OF THE FOUR POSSIBLE STEREOISOMERS OF 4,8-DIMETHYLDECANAL, THE AGGREGATION PHEROMONE OF THE FLOUR BEETLES†

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Abstract—The four stereoisomers of 4,8-dimethyldecanal were synthesized employing organometallic or electrolytic coupling reactions as the key-step. The response of the red flour beetle, *Tribolium castaneum*, to the (4*R*, 8*R*)-isomer was identical with that to the natural pheromone, while other isomers induced only very weak or no responses. The (4*R*, 8*R*)-isomer is therefore the natural pheromone.

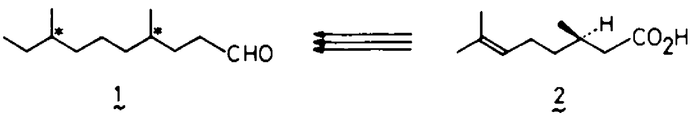
In 1980 Suzuki isolated 760 μg of the aggregation pheromone of the red flour beetle, *Tribolium castaneum*, from 240,000 male equivalents (6000 males × 40 days) and identified it as 4,8-dimethyldecanal **1** on the basis of physicochemical measurements followed by the synthesis of **1** as a diastereomeric mixture.[1,2] This same compound was also found to be the pheromone of the confused flour beetle, *T. confusum*.[1,2] The pheromone activity of his synthetic mixture, however, was less than 1/10 of the natural pheromone, suggesting the importance of the correct stereochemistry at two chiral centers in **1**.[1-3] He later synthesized (4*S*, 8*S*)-**1** and (4*R*, 8*S*)-**1** with unspecified optical purity and found the latter to be far more active than the former.[4]

In order to establish the absolute configuration of the natural pheromone, we decided to synthesize all of the four possible stereoisomers of **1**. Our previous work on the khapra beetle pheromone (trogodermal, 14-methyl-8-hexadecenal) allowed us to assign (*R*)-configuration to its chiral center (C-14) with an ethyl and a methyl branchings like C-8 of **1**.[5] Recently Tumlinson *et al.* also assigned (*R*)-configuration to the chiral center (C-8, Me(Et)CH-) of 8-methyl-2-dodecanol propionate, the pheromone of the western corn rootworm.[6] These, coupled with Suzuki's data indicating the higher activity of (4*R*, 8*S*)-**1** than that of (4*S*, 8*S*)-**1**, made us to assume that the (4*R*, 8*R*)-**1** might be the natural pheromone with the highest activity. This was supported as shown below.

We chose (*R*)-(+)-citronellic acid **2** as our main starting material (Fig. 1) because of its availability in 100% optically pure state.[7] For the synthesis of (4*R*, 8*S*)-**1**, (*S*)-2-methyl-1-butanol was also employed as a starting material whose optical purity was estimated to be about 93% as reported previously.[8] The synthetic strategy was to connect two chiral intermediates in the manner similar to our synthesis of the German cockroach pheromones where the Grignard coupling reaction was used for the connection of the chiral intermediates.[9] In the present case, however, both organometallic and electrolytic coupling reactions were employed to compare their usefulness.

The synthesis of (4*R*, 8*R*)- and (4*R*, 8*S*)-4,8-dimethyldecanal **1** was shown in Fig. 2. The key coupling steps were the aklylation of a sulfone-stabilized carbanion and the Grignard coupling, respectively, (*R*)-(+)-Citronellyl benzyl ether **3b**, prepared in the usual manner from (*R*)-(+)-citronellol **3a**, was converted to an allylic alcohol **4** by Sharpless' procedure.[10,cf7] Ozonolysis of **4** was followed by reductive work-up with $NaBH_4$ to give **5a**. The corresponding tosylate **5b** yielded an iodide **6**, which served as the right-hand half of the target molecule. A phenylsulfone **12** was prepared from the known ester **7**.[7] Ozonolysis of **7** yielded an aldo ester **8**, which was submitted to the Huang Minlon reduction to give an acid **9**. This was treated with I_2 and $Pb(OAc)_4$ under irradiation with a tungsten lamp[11] yielding an iodide **10**. Treatment of **10** with PhSNa afforded a phenyl sulfide **11**. This was oxidized with MCPBA to give the desired sulfone **12**. A carbanion generated from **12** was alkylated with **6** to give a new sulfone **13**. Reduction of **13** with $Li/EtNH_2$ gave (4*R*, 8*R*)-**14a**. For one-carbon elongation, this was converted to a nitrile (4*R*, 8*R*)-**15** via the corresponding tosylate **14b**. Finally treatment of (4*R*, 8*R*)-**15** with DIBAL-H gave (4*R*, 8*R*)-4,8-dimethyldecanal **1**, $[\alpha]_D^{22.5}$-7.37° ($CHCl_3$), in 7.2% overall yield from **3b** or 3.7% over all yield from **7**. Its spectral data were in good accord with the published data of the natural pheromone.[1,2]

Coupling of the tosylate 5**b** with a Grignard reagent prepared from (*S*)-(-)-2-methylbutyl bromide **16**[12] under



1

Four stereoisomers

2

(R)-(+)-Citronellic acid

Fig. 1. Synthetic plan.

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†Pheromone Synthesis-55. Part 54, K. Mori, T. Ito, K. Tanaka, H. Honda and Yamamoto, *Tetrahedron* **39**, 2303 (1983). This work was presented by K. M. as a part of his lecture at Rattanakosin Bicentennial Seminar on Chemistry of Natural Products, Bangkok (Aug. 1982).

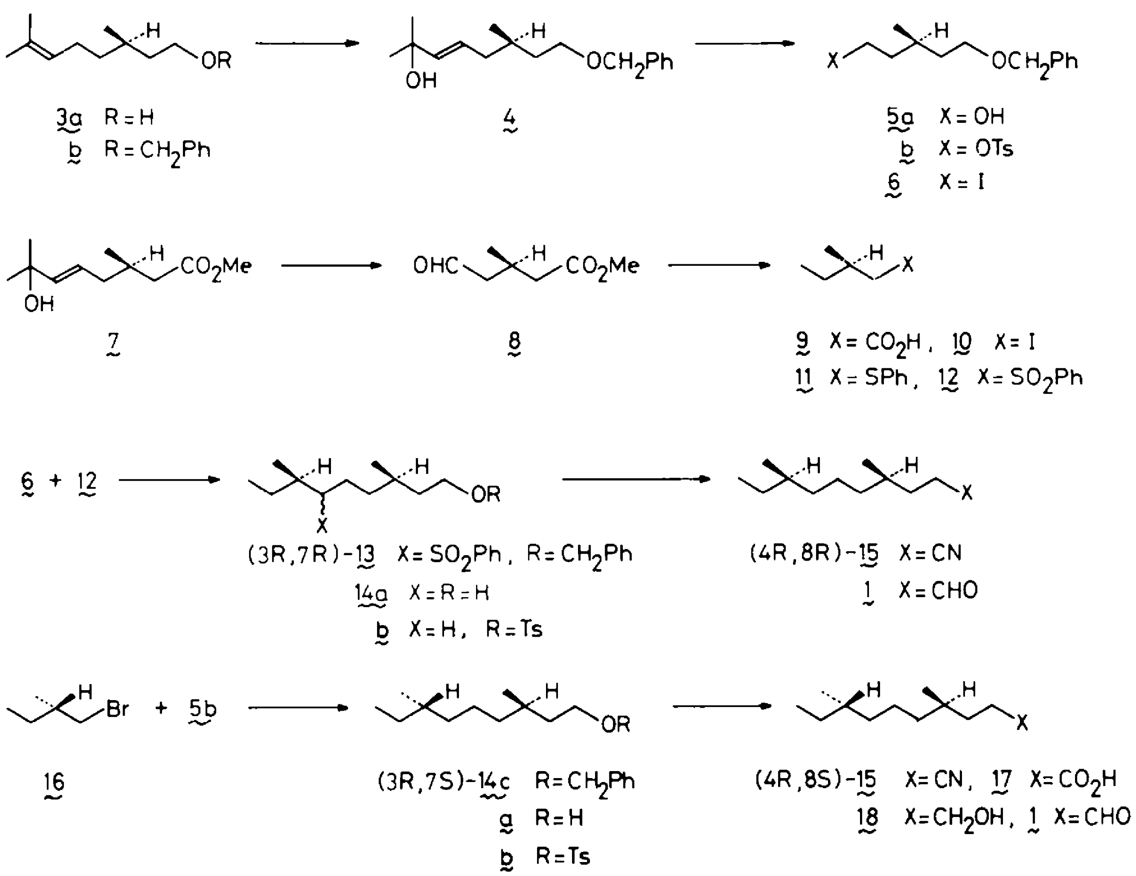

Fig. 2. Synthesis of (4*R*, 8*R*)- and (4*R*, 8*S*)-4,8-dimethyldecanal.

the Schlosser condition[13] yielded (4*R*, 8*S*)-**14c** in 70% yield. Hydrogenolysis of **14c** with H_2/Pd gave an alcohol (4*R*, 8*S*)-**14a**. The corresponding tosylate (4*R*, 8*S*)-**14b** was converted to a nitrile (4*R*, 8*S*)-**15**. This gave (4*R*, 8*S*)-**1**, $[\alpha]_D^{22} + 9.94^c$ ($CHCl_3$), via **17** and **18** in 5.4% overall yield from **3b**.

For the synthesis of (4*S*, 8*R*)- and (4*S*, 8*S*)-isomers of **1**, the Kolbe electrolytic coupling reaction was employed as the key-step (Fig. 3). The well-known Kolbe electrolysis is a simple method for the coupling of two carboxylic acids.[14,15] Schäfer recently reviewed its application in pheromone synthesis.[15] We also had used it for the synthesis of Vitamin E.[16] The mixed Kolbe coupling between the acids **9** and **20** was planned for the synthesis of (4*S*, 8*R*)-**1**. The required acid **20** was prepared by the ozonolysis of (*R*)-(+)-homocitronellic acid **19**[17] followed by acetalization of the resultant aldo acid. A mixture of **9** and **20** (5:1 molar ratio) in NaOMe–MeOH was electrolyzed with Pt electrode to give a mixture of a hydrocarbon, (4*S*, 8*R*)-**21** and a bis-acetal in a ratio of 30:13:1 as revealed by GLC analysis. This was purified by chromatography to give crude (4*S*, 8*R*)-**21**. Hydrolysis of the acetal **21** with 35% $HClO_4$–THF yielded (4*S*, 8*R*)-1, $[\alpha]_D^{22} - 9.92^c$ ($CHCl_3$), after purification by medium pressure liquid chromatography (lc) and distillation. Although the yield of the purified (4*S*, 8*R*)-**1** was only 25% from the acetal acid **20**, the over-all yield of (4*S*, 8*R*)-**1** from citronellol **3a** was 11% compared with 5.4% from **3b** in the case of (4*R*, 8*S*)-**1**. By employing the Kolbe electrolysis, the synthetic sequence was shortened with resultant increase in the overall yield.

The remaining isomer (4*S*, 8*S*)-**1** was synthesized also by employing the mixed Kolbe electrolysis between the acids **22** and **24** as the key-step. The required acid **22** was prepared from (*R*)-(+)-citronellic acid **2** by ozonolysis and acetalization. Another acid **24** was prepared from **23** by the known procedure involving ozonolysis and oxidative work-up.[18,19] A mixture of **22** and **24** (1:5 molar ratio) was electrolyzed yielding a mixture of a hydrocarbon, (4*S*, 8*S*)-**21** and a bis-acetal in a ratio of 24:9:1 (GLC). This was separated by chromatography to give crude (4*S*, 8*S*)-**21**. Its hydrolysis gave the final product as a crude oil which was purified by medium pressure lc to give pure (4S, 8S)-**1**, $[\alpha]_D^{22} + 7.33°$ ($CHCl_3$), in 28% overall yield from (*R*)-(+)-citronellic acid **2**. In this case the Kolbe electrolysis proceeded in 31% yield. The high overall yield realized by the Kolbe routes manifests the merit of simplifying the synthetic design by employing the Kolbe electrolysis.

In the present synthesis there was no step where racemization at chiral centers might take place. Our products should therefore be 100% optically pure in the case of (4*R*, 8*R*)-, (4*S*, 8*R*)- and (4S, 8S)-**1**. In the case of (4*R*, 8*S*)-**1**, the enantiomeric purity at C-4 is 100%, while that at C-8 is 93% due to the use of (*S*)-4-methyl-1-butanol as the building block.

Since no chiroptical data of the natural pheromone were available, we had to rely on the careful comparison of pheromone activity of the four stereoisomers of **1** so as to deduce the absolute configuration of the natural product. According to Dr. T. Suzuki's bioassay, (4*R*, 8*R*)-**1** showed the same pheromone activity against the

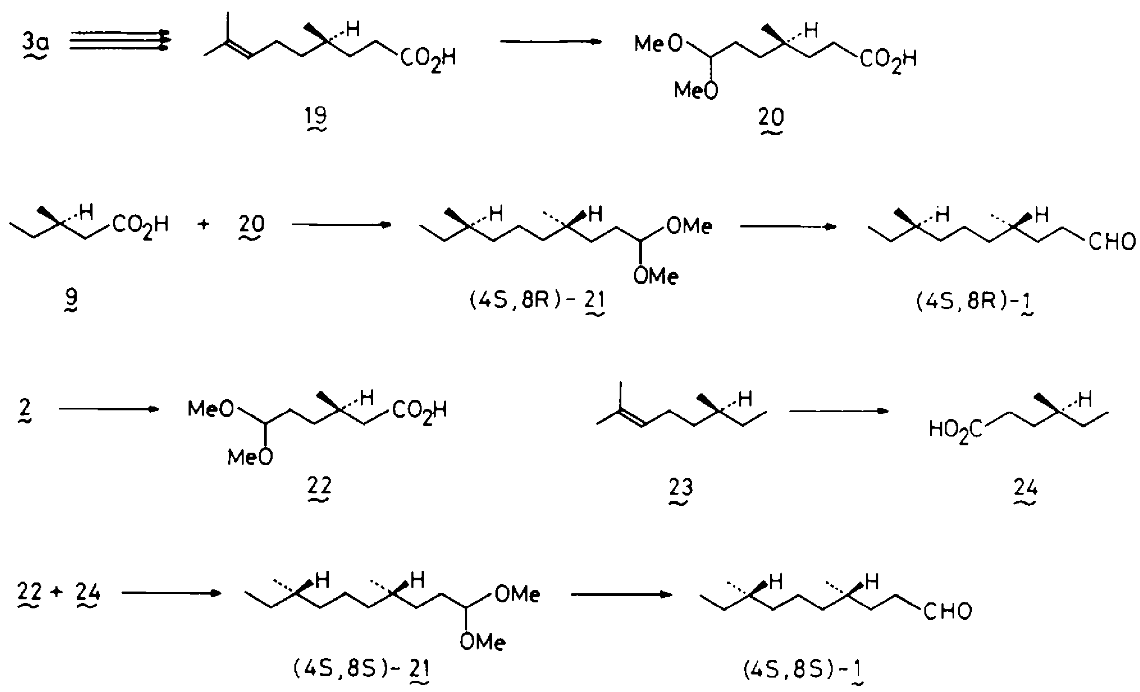

Fig. 3. Synthesis of (4*S*, 8*R*)-and (4*S*, 8*S*)-4,8-dimethyldecanal.

red flour beetle, *Tribolium castaneum*, as that of the natural pheromone even at 1 ng/disc dose (4*R*, 8*S*)-**1** was weakly active [1/50 ~ 1/100 of (4*R*, 8*R*)-**1**], while other two isomers were inactive. The weak activity shown by (4*R*, 8*S*)*a***1** than that of (4*S*, 8*S*)-**1**, made us to assume C-8. The absolute configuration of the natural pheromone was therefore deduced to be (4R, 8R). Prof. H. Z. Levinson also reached to the same conclusion using our samples. These biological results will be published elsewhere in due course.

EXPERIMENTAL

All b.ps were uncorrected. IR spectra were determined as film for oils on a Jasco A–102 spectrometer. NMR spectra were recorded at 60 MHz in CCl_4 with TMS as an internal standard on a Hitachi R-24A spectrometer unless otherwise stated. Optical rotations were measured on a Jasco DIP-140 polarimeter. GLC analyses were performed on a JEOL JGC-20K or Yanaco GCG-550F gas chromatographs.

(R, E)-(+)-7-*Hydroxy-3,7-dimethyl-5-octenyl benzyl ether* **4**. 35% H_2O_2 (8.87 g) was added dropwise to a stirred and ice-cooled soln of Ph_2Se_2 (28. 5 g) in dry CH_2Cl_2 (300 ml). After stirring for 30 min, dry $MgSO_4$ (15.0 g) was added and the mixture was stirred for an additional 30 min. To this was added **3b** [15.0 g, b.p. 123–128°/0.4 mm, n_D^{22} 1.4958; $[\alpha]_D^{22} + 2.67°$ ($c = 3.45$, n-hexane)]. The mixture was stirred for 20 hr at room temp. 70% t-BuOOH (44.7 ml) was added dropwise to the stirred and ice-cooled mixture. The stirring was continued overnight at room temp. The precipitate was filtered off and the filtrate was concentrated *in vacuo*. The residue was diluted with ether. The ether soln was washed with 5% Na_2CO_3 aq, water, 10% $FeSO_4$aq, water, sat $NaHCO_3$ aq, water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography and distillation to give 13.6 g (85%) of **4**, b.p. 140–142°/0.4 mm, n_D^{22} 1.5036; $[\alpha]_D^{22} + 3.22°$ (c=2.92, n-hexane); ν_{max} 1100 (s), 740 (s), 700 (s) cm^{-1}; δ 0.85 (3H, d, J = 6 Hz), 1.20 (6H, s), 1.1–2.4 (5H, m), 3.35 (2H, t, J = 6 Hz), 3.75 (1H, s, -OH), 4.33 (2H, s), 5.25–5.55 (2H, m), 7.11 (5H, s). (Found: C, 77.46; H, 10.13. Calc for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99%).

(R)-(−)-3-*Methyl-1,5-pentanediol monobenzyl ether* **5a**. $NaHCO_3$ (2.0 g) was added to a soln of **4** (11.5 g) in CH_2Cl_2–MeOH (1 : 1, 150 ml). O_3 was bubbled into the stirred and cooled mixture at −70°. After checking the disappearance of **4** by TLC, $NaBH_4$ (6.64 g) was added portionwise to the stirred and cooled mixture. Then the temp was gradually raised to room temp while the stirring was continued overnight. The mixture was concentrated *in vacuo*. The residue was neutralized with dil HCl and extracted with ether. The ether extract was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 7.32 g (80%) of **5a**, b. p. 126–129°/0.3 mm, n_D^{22} 1.5042; $[\alpha]_D^{22} - 4.11°$ (c = 4.21, n-hexane): ν_{max} 3400 (m), 1100 (s), 1075 (s), 740 (s), 700 (s) cm^{-1}; δ 0.86 (3H, d, J = 5 Hz), 1.1–1.9 (5H, m), 2.78 (1H, s, -OH), 3.38 (2H, t, J = 6 Hz), 3.44 (2H, t, J = 6 Hz), 4.34 (2H, s), 7.13 (5H, s). (Found: C, 74.75: H, 9.70. Calc for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68%).

(S)-3-*Methyl-1,5-pentanediol monotosylate monobenzyl ether* **5b** *p*-TsCl (5.37 g) was added to a stirred and ice-cooled soln of **5a** (2.93 g) in dry C_5H_5N (28 ml). The stirring was continued for 5 hr at 0–5°. The mixture was poured into ice-dil HCl and extracted with ether. The ether soln was washed with dil HCl, water, sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 5.72 g of crude **5b**. ν_{max} 1595 (w), 1360 (s), 1190 (s), 1175 (s), 1095 (s), 940 (s) cm^{-1}. This was directly used for the next step.

(S)-5-*Iodo-3-methylpentyl benzyl ether* **6**. NaI (5.92 g) was added to a soln of **5b** (5.72 g) in dry acetone (40 ml). The mixture was stirred and heated under reflux for 1.5 hr and then stirred overnight at room temp. It was poured into ice-water and extracted with ether. The ether soln was washed with 10% $Na_2S_2O_3$ aq, water, sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (Merck Kieselgel 60, Art 7734, 70 g; elution with n-hexane-ether) to give 4.31 g (96%) of **6**. ν_{max} 1100 (s), 735 (s), 700 (s) cm^{-1}; δ 0.87 (3H, d, J = 5 Hz), 1.2–2.1 (5H, m), 3.08 (2H, dd, J_1 = 7 Hz, J_2 = 6 Hz), 3.35 (2H, t, J = 6 Hz), 4.32 (2H, s), 7.09 (5H, s). This was employed for the next step without further purification.

Methyl (*R*)-3-*methyl-5-oxopentanoate* **8**. $NaHCO_3$ (3 g) was added to a soln of **7** (15.6 g) in CH_2Cl_2–MeOH (1 : 1, 170 ml). O_3 was bubbled into the stirred and cooled mixture at −50°. After checking the disappearance of **7**, the excess O_3 was removed by bubbling N_2. Me_2S (15 ml) was then added dropwise to the stirred and cooled mixture. The temp was gradually raised to room temp. The stirring was continued overnight. The mixture was concentrated *in vacuo*. The residue was diluted with water and extracted with ether. The ether soln was washed with water and brine, dried (Na_2SO_4) and concentrated *in vacuo* to give 10.9 g of crude **8**. This was directly employed for the next step.

(R)-(−)-3-*Methylpentanoic acid*. **9**. 80% $N_2H_4 \cdot H_2O$ (17.13 g) was added to a soln of **8** (9.9 g) in diethylene glycol (50 ml) and the mixture was heated under reflux for 1 hr. KOH aq (15.45 g in 15.5 ml water) was then added to the soln and it was heated under reflux for 2 hr. The excess $N_2H_4 \cdot H_2O$ was distilled off and the mixture was stirred and heated at 195–200° for 2 hr. After cooling, the mixture was diluted with water and extracted with C_6H_6 to remove neutral impurities. The aq layer was acidified with 6N HCl and 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 5.40 g (60%) of **9**, b.p. 73 ~ 77°/5 mm, n_D^{23} 1.4117, $[\alpha]_D^{23} - 6.42°$ ($c = 4.03$, $CHCl_3$); ν_{max} ~ 3000 (br), 1710 (s), 940 (m) cm^{-1}; δ 0.6–1.1 (6H, seemingly d, J = 6 Hz), 1.1–2.0 (3H, m), 2.0–2.5 (2H, m), 11.80 (1H, s). (Found: C, 62.00; H, 10.33. Calc for $C_6H_{12}O_2$: C, 62.04; H, 10.41%).

(R)-(−)-2-*Methylbutyl iodide* **10**. Pb $(OAc)_4$ (6.27 g) was added to a soln of **9** (1.2 g) in CCl_4 (100 ml). The mixture was stirred and heated under reflux under Ar. I_2 (2.7 g) was added portionwise to the mixture which was kept under irradiation with a tungsten lamp (185 W). At the end of the reaction the red color of I_2 persisted. After cooling, the mixture was filtered and the filtrate was washed with 10% $Na_2S_2O_3$ aq and sat $NaHCO_3$ aq, dried ($MgSO_4$) and concentrated to give 2.0 g of crude **10**. An analytical sample of **10** was obtained by distillation, b.p. 59–60°/38 mm, n_D^{23} 1.4930; $[\alpha]_D^{23}$ −5.57° (neat, d_4^{22} 1.53); ν_{max} 1190 (s) cm^{-1}; δ 0.65–1.15 (6H, m), 1.15–1.7 (3H, m), 3.06 (2H, d, J = 5 Hz). (Found: C, 30.60: H, 5.57. Calc for $C_5H_{11}I$: C, 30.32; H, 5.60%).

(R)-(−)-2-*Methylbutyl phenyl sulfide* **11**. PhSH (1.34 g) was added to a soln of NaOEt (from 0.28 g of Na) in EtOH (25 ml) at room temp under Ar. The soln was further stirred at room temp for 15 min. A soln of crude **10** (2.0 g) in EtOH (5 ml) was added dropwise to the stirred soln and the stirring was continued for 3 hr at room temp. The mixture was poured into water and extracted with pet. ether. The extract was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 1.02 g (55%) of **11**, b.p. 92–93°/1.3 mm, n_D^{22} 1.5380; $[\alpha]_D^{22.5} - 24.9°$ (c = 1.24, $CHCl_3$); ν_{max} 1590 (m), 1090 (m), 740 (s), 690 (s) cm^{-1}; δ 0.7–1.2 (6H, m), 1.2–1.9 (3H, m), 2.41–3.02 (2H, m), 6.8–7.3 (5H, m). (Found: C, 73.26; H, 8.95. Calc for $C_{11}H_{16}S$: C, 73.28; H, 8.94%).

(R)-2-*Methylbutyl phenyl sulfone* **12**. 85% MCPBA (6.0 g) was added portionwise to a stirred and ice cooled soln of **11** (2.39 g) in dry CH_2Cl_2 (90 ml). The mixture was stirred for 2 hr at room temp. MCBA was filtered off. The filtrate was washed with 5% $NaHSO_3$ aq, 5% Na_2CO_3 aq and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 2.93 g of **12**, ν_{max} 1590 (w), 1305 (s), 1150 (s) cm^{-1}; δ 0.80 (3H, t, J = 7 Hz), 1.00 (3H, d, J = 6 Hz), 1.15–1.65 (2H, m), 1.65–2.25 (1H, m), 2.50–3.15 (2H, m), 7.23–7.58 (3H, m), 7.58–7.92 (2H, m). This was employed for the next step without further purification.

(3R, 7R)-3,7-*Dimethyl-6-benzenesulfonylnonyl benzyl ether* **13**. A soln of n-BuLi in n-hexane (1.62 N, 9.3 ml) was added dropwise to a stirred and cooled soln of **12** (2.77 g) in dry THF (30 ml) and dry HMPA (10 ml) at −70° under Ar. After the addition the mixture was stirred for 15 min at −30°. It was then cooled to −70°. A soln of **6** (4.15 g) in THF (10 ml) was added dropwise to the stirred soln. The reaction temp was gradually raised to room temp during 2 hr. The mixture was poured into ice–NH_4Cl aq and extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 5.36 g of an oil. This was chromatographed over SiO_2 (100 g). Elution with n-hexane-ether gave 4.95 g of **13**, ν_{max} 1590 (w), 1500 (w), 1305 (s), 1150 (s), 1100 (s), 1085 (s), 730 (s), 695 (s) cm^{-1}; δ 0.6–1.1 (9H, m), 1.1–1.2 (10H, m), 2.50–2.82 (1H, m) 3.24 (2H, t, J = 6 Hz), 4.26 (2H, s), 7.03 (5H, s), 7.2–7.45 (3H, m), 7.45–7.8 (2H, m). This was used for the next step without further purification.

(3R, 7R)-(−)-3,7-*Dimethyl*-1-*nonanol* (3R, 7R)-**14a**. Li wire (2.31 g) was added portionwise to stirred and cooled $EtNH_2$ (420 ml) at −55° under N_2. The mixture was stirred for 1 hr at −55° to dissolve Li. A soln of (3*R*, 7*R*)-**13** (4.45 g) in dry THF (35 ml) was added dropwise to the stirred and cooled blue soln of Li in $EtNH_2$ at −65 ~ −60°. The mixture was stirred for 45 min at −65°. 1,3-Butadiene was bubbled into the soln to destroy excess Li. Then MeOH (50 ml) and water (50 ml) were added to the mixture. It was concentrated *in vacuo*. The residue was diluted with water and extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, 25 g) and distillation to give 0.582 g (30%) of **14a**, b.p. 88–89°/4 mm, n_D^{23} 1.4375; $[\alpha]_D^{23} - 4.95°$ ($c = 4.38$, $CHCl_3$); ν_{max} 3350 (m), 1055(m) cm^{-1}; δ 0.6–1.05 (9H, m), 1.05–1.9 (12H, m), 2.48 (1H, s, -OH), 3.50 (2H, deformed t, J = 6 Hz). (Found: C, 76.84; H, 13.92. Calc for $C_{11}H_{24}O$: C, 76.67; H, 14.04%).

(3R, 7R)-3,7-*Dimethylnonyl tosylate* **14b**. *p*-TsCl (1.2 g) was added to a stirred and ice-cooled soln of **14a** (0.55 g) in dry C_5H_5N (5.5 ml). The mixture was stirred for 3 hr at 0–5°. It was then poured into ice-dil HCl and extracted with ether. The ether soln was washed with dil HCl, water, sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 1.5 g of crude **14b**, ν_{max} 1600 (m), 1380 (s), 1365 (s, sh), 1190 (s), 1175 (vs), 945 (s), 810 (s), 655 (s) cm^{-1}. This was directly used for the next step without purification.

(4R, 8R)-4,8-*Dimethyldecanenitrile* (4R, 8R)-**15**. NaCN (0.4 g) was added to a soln of **14b** (1.5 g) in DMSO (10 ml). The mixture was stirred overnight at 60–65°. It was then poured into water and 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 0.477 g (82%) of **15**, b.p. 100–101°/9 mm, n_D^{21} 1.4350; $[\alpha]_D^{21} - 5.03°$ ($c = 3.79$, $CHCl_3$); ν_{max} 2250 (w) cm^{-1}; δ 0.6–1.05 (9H, m), 1.05–1.9 (12H, m), 2.20 (2H, t, J = 6 Hz). (Found: C, 79.67; H, 12.70; N, 7.81. Calc for $C_{12}H_{23}N$: C, 79.49; H, 12.79; N, 7.73%).

(4R, 8R)-(−)-4,8-*Dimethyldecanal* (4R, 8R)-**1**. A soln of DIBAL-H in n-hexane (1.7 ml of 25(w/v)% soln) was added to a stirred and cooled soln of **15** (0.274 g) in dry n-hexane (15 ml) at −70° under Ar. After the addition, the cooling bath was removed and the stirring was continued for 25 min. HCO_2Et (0.24 ml) was added dropwise and the mixture was stirred for 1 hr at room temp. It was then poured into sat NH_4Cl aq. The mixture was stirred for 30 min, acidified with 5% H_2SO_4 aq (15 ml) and extracted with ether. The ether soln was washed with water, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2, 14 g) and distillation to give 129 mg (46%) of (4*R*, 8*R*)-**1**, b.p. 65°/2.5 mm, n_D^{22} 1.4336; $[\alpha]_D^{22.5} - 7.37°$ ($c = 2.04$, $CHCl_3$); ν_{max} 2970 (s), 2940 (s), 2875 (s), 2820 (m, sh), 2710 (m), 1730 (s), 1465 (m), 1410 (w), 1380 (m), 1130 (w), 1020 (w), 970 (w), 765 (w), 730 (w) cm^{-1}; δ 0.6–1.0 (9H, m), 1.0–1.9 (12H, m), 2.28 (2H, dt, J_1 = 1.8 Hz, J_2 = 6 Hz), 9.49 (1H, t, J = 1.8 Hz): GLC (Column, 3% SE-30, 1.5 m × 2 mm at 115°: Carrier gas. N_2, 0.9 kg/cm^2) Rt 5.06 min (95%). (Found: C, 77.73; H, 13.01. Calc for $C_{12}H_{24}O$: C, 78.19; H, 13.13%).

(3R, 7S)-(+)-3,7-*Dimethylnonyl benzyl ether* (3R, 7S)-**14c**. The bromide **16**, b. p. 110–112°, n_D^{21} 1.4406; $[\alpha]_D^{21} + 3.48°$ (neat d_4^{18} 1.20), was prepared as described in Ref. 12 from (*S*)-2-methyl-1-butanol, $[\alpha]_D^{21} - 5.54°$ (neat, d_4^{20} 0.82). A Grignard reagent was prepared as usual from **16** (2.06 g) and Mg (0.33 g) in dry ether (10 ml). To this was added a soln of **5b** (3.20 g) in dry THF (15 ml) with stirring and cooling at −70° under Ar. A soln of Li_2CuCl_4 in THF (0.1 M, 0.5 ml) was added dropwise to the stirred and cooled soln and the reaction temp was gradually raised. The stirring was continued overnight at room temp. The mixture was then poured into ice-dil H_2SO_4 and extracted with ether. The ether soln was washed with water, sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed (SiO_2) and distilled to give 1.67 g (70%) of (3*R*, 7*S*)-**14c**, b.p. 130–133°/0.5 mm, n_D^{22} 1.4783; $[\alpha]_D^{22} + 10.18°$ (c = 3.49, n-hexane); ν_{max} 1100 (s), 700 (s) cm^{-1}; δ 0.6–1.05 (9H, m), 1.05–1.9 (12H, m), 3.32 (2H, t, J = 6 Hz), 4.30 (2H, s), 7.04 (5H, s). (Found: C, 82.86; H, 11.42. Calc for $C_{18}H_{30}O$: C, 82.38; H, 11.52%).

(3R, 7S)-3,7-*Dimethyl-l-nonanol* (3R, 7S)-**14a**. 5 Pd-C (1.0 g) was added to a soln of (3*R*, 7*S*)-**14c** (1.60 g) in EtOH (30 ml) and the mixture was shaken under H_2. At the end of the H_2 uptake, the catalyst was filtered off. The filtrate was concentrated *in vacuo* to give 0.91 g of (3*R*, 7*S*)-**14a**, ν_{max} 3350 (m), 1055 (m) cm^{-1}. This was used for the next step without further purification.

(3R, 7S)-3,7-*Dimethylnonyl tosylate* (3R, 7S)-**14b**. *p*-TsCl (1.20 g) was added to a stirred and ice-cooled soln of (3*R*, 7*S*)-**14a** (0.90 g) in dry C_5H_5N (10 ml). The mixture was stirred overnight at 0–5°. It was then poured into ice-water and extracted with ether. The ether soln was washed with dil HCl, water and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 1.7 g of (3*R*, 7*S*)-**14b**, ν_{max} 1600 (m), 1500 (w), 1365 (s), 1190 (s), 1180 (s), 945 (s) cm^{-1}. This was directly used for the next step.

(4R, 8S)-(+)-4,8-*Dimethyldecanenitrile* (4R, 8S)-**15**. NaCN (0.3 g) was added to a soln of (3R, 7S)-**14b** (1.6 g) in DMSO (10 ml). The mixture was stirred overnight at 50–60°. It was then poured into ice-water and 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 0.45 g (44% from **14c**) of (4*R*, 8*S*)-**15**, b.p. 100–103°/1.0 mm, n_D^{22} 1.4349; $[\alpha]_D^{22}$ + 13.6° (*c* = 1.12, n-hexane); ν_{max} 2250 (w) cm^{-1}; δ 0.6–1.05 (9H, m), 1.05–1.9 (12H, m), 2.21 (2H, t, J = 6 Hz). (Found: C, 79.47; H, 13.07; N, 7.67. Calc for $C_{12}H_{23}N$: C, 79.49; H, 12.79; N, 7.73%).

(4R, 8S)-4,8-*Dimethyldecanoic acid* **17**. NaOH aq (1.8 g in 2.5 ml) was added to a soln of (4R, 8S)-**15** (0.42 g) in 95% EtOH (6 ml). The mixture was heated under reflux for 2 days and concentrated *in vacuo*. The residue was diluted with water, acidified with dil HCl and extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 0.33 g of crude **17**, ν_{max} ~ 3000 (m, br), 1710 (s), 940 (w) cm^{-1}.

(4R, 8S)-4,8-*Dimethyldecanol* **18**. A soln of crude **17** (0.33 g) in dry ether (4 ml) was added to a stirred and ice-cooled suspension of LAH (0.2 g) in dry ether (8 ml). After the addition, the mixture was stirred for 1.5 hr at room temp. Subsequent work-up gave 0.3 g of an oil. This was purified by chromatography (SiO_2, 9 g). Elution with n-hexane–ether yielded 0.246 g of **18**, ν_{max} 3340 (m), 1055 (m) cm^{-1}; δ 0.6–1.05 (9H, m), 1.05–1.8 (14H, m), 2.48 (1H, s, -OH), 3.43 (2H, t, J = 6 Hz). This was employed for the final step without further purification.

(4R, 8S)-4,8-*Dimethyldecanal* (4R, 8S)-**1**. CrO_3 (0.925 g) was added portionwise to a stirred and ice-cooled soln of C_5H_5N (1.47 g) in dry CH_2Cl_2 (18 ml). The mixture was stirred for 70 min at room temp. To this was added a soln of **18** (0.264 g) in dry CH_2Cl_2 (7 ml) with stirring. The stirring was continued for 3.5 hr. The mixture was diluted with dry ether and filtered through a short column of florisil. The filtrate was concentrated *in vacuo*. The residue was chromatographed (SiO_2, 27 g) and distilled to give 0.11 g (26% from **15**) of (4*R*, 8*S*)-**1**, b.p. 60°/3 mm, n_D^{22} 1.4325, $[\alpha]_D^{22}$ + 9.94° (*c* = 2.40, $CHCl_3$); ν_{max} 2970 (s), 2940 (s), 2875 (s), 2820 (m, sh), 2720 (m), 1735 (s), 1465 (m), 1415 (w), 1380 (m), 1135 (w), 1020 (w), 970 (w), 765 (w), 730 (w) cm^{-1}; δ 0.6–1.0 (9H, m), 1.0–1.95 (12H, m), 2.27 (2H, dt, J_1 = 1.8 Hz, J_2 = 6 Hz), 9.54 (1H, t, J = 1.8 Hz); GLC (Column, 3% SE–30, 1.5 m × 2 mm at 115°; Carrier gas, N_2, 0.92 kg/cm^2) Rt 4.92 min (93%). (Found: C, 77.84; H, 13.14, Calc for $C_{12}H_{24}O$: C, 78.19; H, 13.13%).

(R)-7,7-*Dimethoxy-4-methylheptanoic acid* **20**. O_3 was bubbled into a stirred and cooled soln of **19** (3.50 g) in MeOH (35 ml) for 40 min at −60°. After confirming the disappearance of **19** by TLC, excess O_3 was removed by bubbling N_2. Me_2S (3 ml) was added and the temp was gradually raised to 0° during 70 min. *p*-TsOH (0.1 g) was then added and the mixture was stirred for 1 hr at 0–5°. It was diluted with ether (*ca.* 300 ml). The ether soln was washed with $NaHCO_3$–NaCl aq, dried (Na_2SO_4) and concentrated *in vacuo* to give 4.3 g of crude **20**. This was purified by chromatography (SiO_2, 65 g). Elution with n-hexane–ether (2:1) gave 2.05 g (53%) of **20**, ν_{max} ($CHCl_3$) ~ 3000 (m, br), 1710 (vs), 1125 (s), 1050 (m), 960 (m) cm^{-1}; δ($CDCl_3$) 0.75 − 1.0 (3H), 1.05 − 1.8 (7H, m), 2.28 (2H, t, J = 7 Hz), 3.22 (6H, s), 4.24 (1H, t, J = 5 Hz), 10.81 (1H, s); MS: *m/z* 173 (M^+ − 31), 172 (M^+ − 32).

(4S, 8R)-4,8-*Dimethyldecanal dimethylacetal* (4S, 8R)-**21**. A soln containing **9** (5.11 g), **20** (1.80 g) and NaOMe (from 0.025 g of Na) in MeOH (28 ml) was electrolyzed with Pt electrodes for 130 min at 20–30° (0.8 ~ 1.2A, ~ 24V) until the final pH of the soln reached 8–9. The mixture was diluted with sat $NaHCO_3$ aq and extracted with ether. The ether soln was washed with water and brine, dried (K_2CO_3) and concentrated. The crude extract was analyzed by GLC (Column, 3% SE–30, 1.5 m × 2 mm at 56° + 5°/min; Carrier gas, N_2, 0.8 kg/cm^2) Rt. 4.14 min (hydrocarbon): Rt 18.74 min (**21**): Rt 30.58 min (bis-acetal) = 30:13:1. The crude extract was further concentrated *in vacuo* to give an oil (3.77 g). This was chromatographed over SiO_2 (150 g). Elution with n-hexane–ether gave 1.15 g of (4S, 8R)-**21**. ν_{max} 1120 (s), 1055 (s) cm^{-1}; δ 0.6–1.05 (9H, m), 1.05–1.8 (14H, m), 3.12 (6H, s), 4.13 (1H, t, J = 5 Hz). This was directly used for the final step.

(4S, 8R)-(−)-4,8-*Dimethyldecanal* (4S, 8R)-**1**. A soln of 35% $HClO_4$ (3.2 ml) in THF (6 ml) was added to a stirred and ice-cooled soln of (4S, 8R)-**21** (1.15 g) in THF (4 ml). The mixture was stirred for 30 min at room temp. It was then poured into sat $NaHCO_3$ aq and extracted with ether. The ether soln was washed with water and brine, dried (Na_2SO_4) and concentrated *in vacuo* to give 0.887 of an oil. This was purified by medium pressure lc (Merck Lobar column, n-hexane-ether = 30:1). The crude (4*S*, 8*R*)-**1** was distilled (b.p. 75°/1 mm) to give 0.407 g (25%) of pure (4*S*, 8*R*)-**1**. n_D^{21} 1.4330: $[\alpha]_D^{22}$ − 9.92° (c = 2.51. $CHCl_3$), GLC (5% PEG 20 M, 2 m × 4 mm at 115°; Carrier gas, N_2, 1.1 kg/cm^2) Rt 5.66 min (98%). (Found: C, 78.24: H, 13.09; Calc for $C_{12}H_{24}O$: C, 78.19; H, 13.13%). The IR and NMR spectra were identical with those of (4*R*, 8*S*)-**1**.

(R)-6,6-*Dimethoxy-3-methylhexanoic acid* **22**. O_3 was bubbled into the stirred and cooled soln of **2** (15 g) in MeOH (150 ml) for 2 hr at −60 ~ −65°. After confirming the disappearance of **2** by TLC, excess O_3 was removed by bubbling N_2. Me_2S (15 ml) was added dropwise to the stirred and cooled soln. The temp was gradually raised to 0°. *p*-TsOH (0.2 g) was added and the stirring was further continued for 1 hr at 0–5°. The mixture was poured into ether (*ca* 700 ml). The ether soln was washed with $NaHCO_3$–NaCl aq, dried (Na_2SO_4) and concentrated *in vacuo* to give 28 g of an oil. This was chromatographed over SiO_2 (280 g). Elution with n-hexane–ether (2:1) gave 14.88 g (89%) of **22**, ν_{max} ($CHCl_3$) ~ 3000 (m, br), 1710 (vs), 1125 (s), 1050 (s), 940 (w) cm^{-1}; δ ($CDCl_3$) 0.96 (3H, d, J = 6 Hz), 1.1-2.05 (5H, m), 2.05–2.5 (2H, m), 3.23 (6H, s), 4.27 (1H, t, J = 5 Hz): MS: *m/z* 159 (M^+ −31), 158 M^+ − 32).

Methyl (R)-2,6-*dimethoxy-3-methylhexanoate*. A portion of the oily **22** was esterified with CH_2N_2 and the product was distilled to give the corresponding ester, b.p. 57–58°/0.3 mm, ν_{max} 1740 (s), 1195 (s), 1160 (s), 1135 (s), 1060 (s) cm^{-1}; δ 0.92 (3H, d, J = 6 Hz), 1.1–2.0 (5H, m), 2.0–2.4 (2H, m), 3.15 (6H, s), 3.54 (3H, s), 4.18 (1H, t, J = 5 Hz). (Found: C, 58.55; H, 9.73. Calc for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87%).

(S)-(+)-4-*Methylhexanoic acid* **24**. O_3 was bubbled into a stirred and cooled soln of **23** [9.15 g, $[\alpha]_D^{23}$ + 12.3° (*c* = 1.69, Et_2O)] in acetone (190 ml) at −60°. After checking the disappearance of **23** by TLC, excess O_3 was removed by bubbling N_2. Jones CrO_3 reagent (54 ml) was added dropwise with stirring and cooling at − 60 ~ −65°. After the addition, the temp was gradually raised to 0°. MeOH (10 ml) was added dropwise to the stirred and ice-cooled soln to destroy excess CrO_3. The mixture was diluted with water and concentrated. The residue was extracted with ether. The ether soln was shaken thoroughly with 5% NaOH aq. The aq layer was separated, acidified with conc HCl and extracted with ether. The ether soln was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 6.64 g (78%) of **24**, b.p. 88–90°/4.5 mm, n_D^{22} 1.4203; $[\alpha]_D^{22.5}$ + 10.3° (*c* = 2.14, $CHCl_3$); ν_{max} ~ 3000 (m, br), 1710 (s), 940 (m) cm^{-1}; δ 0.7–1.1 (6H, seemingly s, br), 1.1–2.0 (5H, m), 2.30 (2H, t, J = 7 Hz), 12.02 (1H, s). (Found: C, 64.17; H, 10.74. Calc for $C_7H_{14}O_2$: C, 64.58; H, 10.84%).

(4S, 8S)-4,8-*Dimethyldecanal dimethylacetal* (4S, 8S)-**21**. A soln of **22** (2.0 g), **24** (6.8 g) and NaOMe (from 0.03 g of Na) in MeOH (35 ml) was electrolyzed with Pt electrodes at 30° for 2 hr (1.3 ~ 1.5A, ~ 24V) until the final pH value reached to 8–9. The mixture was poured into sat $NaHCO_3$ aq and extracted with ether. The ether soln was washed with water, $NaHCO_3$ aq and brine, dried (K_2CO_3) and concentrated a little. The remaining soln was analyzed by GLC (Column, 3% SE–30, 1.5 m × 2 mm, 56° +

5°/min; Carrier gas, N_2, 0.8 kg/cm^2) Rt 9.40 min (hydrocarbon): Rt 18.66 min (**21**): Rt 26.36 min (bis-acetal) = 24:9:1. The extract was further concentrated *in vacuo*. The residue (5.43 g) was chromatographed over SiO_2 (150 g). Elution with n-hexane-ether gave 1.45 g of crude (4S, 8S)-**21**, ν_{max} 1120 (m), 1055 (m) cm^{-1}; δ 0.6–1.05 (9H, m), 1.05–1.8 (14H, m), 3.13 (6H, s), 4.15 (1H, t, J = 5 Hz). This was employed for the final step without further purification.

(4*S*, 8*S*)-(+)-4,8-*Dimethyldecanal* (4S, 8S)-**1**. A soln of 35% $HClO_4$ (4 ml) in THF (7.5 ml) was added to a stirred and ice-cooled soln of (4*S*, 8*S*)-**21** (1.45 g) in THF (5 ml). After stirring for 30 min at room temp, the mixture was poured into sat $NaHCO_3$ soln and extracted with ether. The ether soln was washed with water and brine, dried (Na_2SO_4) and concentrated *in vacuo* to give 1.20 g of an oil. This was purified by medium pressure lc (Merck Lobar column). Elution with n-hexane–ether (30:1) gave pure (4*S*, 8*S*)-**1** which was distilled to give 0.601 g (31%) of oily **1**, b.p. 72°/1 mm, n_D^{22} 1.4326; $[\alpha]_D^{22}$ + 7.33° (c = 3.42, $CHCl_3$); GLC (Column, 5% PEG 20 M, 2 m × 4 mm at 115°; Carrier gas, N_2, 1.2 kg/cm^2)Rt 5.63 min (98%). (Found: C, 78.05; H, 13.21. Calc for $C_{12}H_{24}O$: C, 78.19; H, 13.13%). The IR and NMR spectra were identical with those of (4*R*, 8*R*)-**1**.

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