Synthesis and Stereochemistry of the Four Himachalene-Type Sesquiterpenes Isolated from the Flea Beetle (*Aphthona flava*) as Pheromone Candidates[‡]

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Both the (1*S*,2*R*) and (1*R*,2*S*) isomers of 2,6,6-trimethylbicyclo[5.4.0]undec-7-en-9-one (**1**) were synthesized by starting from (*S*)- and (*R*)-citronellal (**5**), respectively. The stereochemistry of (1*R*,2*S*)-(–)-**1** was established by an X-ray analysis; it exhibits a CD spectrum similar to that of cholest-4-en-3-one, in agreement with its absolute configuration. The ketones (1*S*,2*R*)- and (1*R*,2*S*)-**1** were converted into the enantiomers of three other himachalene hydrocarbons, 2,2,6-trimethyl-10-methylenebicyclo[5.4.0]undec-1(11)-ene (**2**), 1,1,5,8-tetramethyl-1,2,3,4,5,6,5a-heptahydrobenzo[1,2-*a*]-[7]annulene (**3**), and 1,1,5,8-tetramethyl-1,2,3,4,5-pentahydrobenzo[*a*][7]annulene (*ar*-himachalene, **4**). The stereochemistry of these himachalene-type sesquiterpenes isolated from flea beetles such as *Aphthona flava* and *Phyllotreta cruciferae* as their male-pheromone components was revised to (1*S*,2*R*)-**1**, (6*R*,7*S*)-**2**, (5*R*,5a*S*)-**3**, and (*R*)-**4**.

Introduction

In 2001, Bartelt and co-workers isolated and identified six new himachalene-type sesquiterpenes and the known *ar*-himachalene as the male-specific pheromone candidates of the flea beetle *Aphthona flava*.[1] The same himachalenes were also isolated from another flea beetle, *Phyllotreta cruciferae*.[1] Flea beetles include both agricultural pests like *P. cruciferae* and beneficial species like *A. flava*.

Four out of the seven himachalenes identified by Bartelt et al. are shown in Figure 1. In 2003 they reported the synthesis of racemates of the six new himachalenes.[2] As for the stereochemistry of these compounds, they proposed the absolute configuration opposite to that shown in Figure 1.[1]

In continuation of our work on the synthesis of himachalenes like 3-methyl-α-himachalene, the sex pheromone of *Lutzomyia longipalpis*,[3] we became interested in clarifying the stereochemistry of these new himachalenes. This paper describes the synthesis of the enantiomers of himachalene-type compounds **1**−**4**, starting from the enantiomers of citronellal. The relative stereochemistry of **1** was unambiguously determined by an X-ray analysis of (1*R*,2*S*)-**1**, and the absolute configuration of **1** was assigned on the basis of that of the starting citronellal. Our synthetic and stereochemical studies on **1**−**4** resulted in a revision of the absolute configuration of the naturally occurring **1**−**4**, as shown in Figure 1.

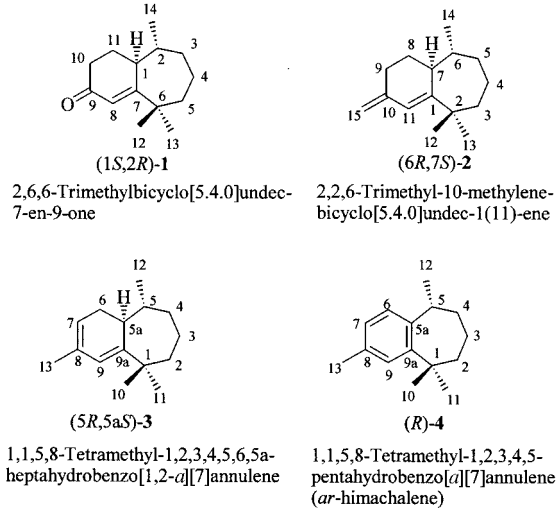

Figure 1. Structures of *Aphthona flava* himachalenes; nomenclature is adopted according to Chemistry 4-D Draw ver. 5.0 (Chem. Innovation Software, Inc.)

Results and Discussion

Because himachalene compounds **2**−**4** are derivable from the ketone **1**, its enantioselective synthesis must be planned

[‡] Pheromone Synthesis, CCXXVI. Part CCXXV: K. Mori, T. Ohtaki, H. Ohrui, D. R. Berkebile, D. A. Carlson, *Eur. J. Org. Chem.* **2004**, 1089−1096.

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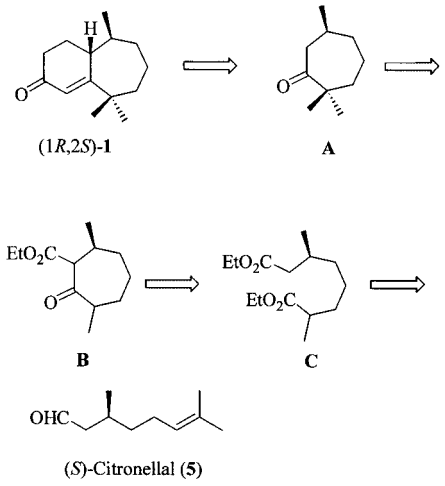
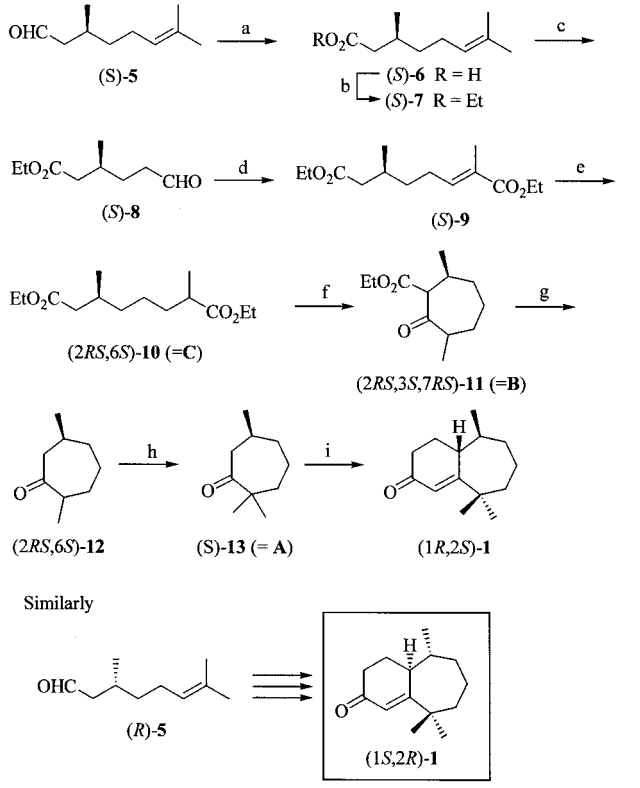
first. Scheme 1 shows the retrosynthetic analysis of (1*R*,2*S*)-**1**. For the construction of (1*R*,2*S*)-**1**, Robinson annulation with (*S*)-2,2,6-trimethylcycloheptanone (**A**) could be performed in analogy with Bartelt's synthesis of (±)-**1**.[2] The ketone **A** was to be prepared via β-oxo ester **B** by Dieckmann condensation of diethyl (2*RS*,6*S*)-2,6-dimethyloctanedioate (**C**). (*S*)-Citronellal (**5**, Takasago, 97% *ee*) serves as an ideal starting material for the preparation of **C**. This plan was realized as detailed below.



Scheme 1. Retrosynthetic analysis of (1*R*,2*S*)-**1**



Scheme 2. Synthesis of **1**; reagents and conditions: (a) PDC, DMF, 0 °C to room temp.; (b) K_2CO_3, EtI, DMF, 0 °C to room temp. (74%, 2 steps); (c) O_3, MeOH, −78 °C; then Me_2S (72%); (d) $(EtO)_2P(O)CHMeCO_2Et$, NaH, THF, −30 °C (96%); (e) H_2, PtO_2, EtOAc, room temp. (quant.); (f) i) *t*BuOK, *m*-xylene, 150 °C; ii) diluted HCl (79%); (g) i) NaOH, MeOH, H_2O, reflux; ii) diluted HCl (85%); (h) *t*BuOK, *t*BuOH, MeI, 0 °C to room temp. (88% based on consumed **12**); (i) LDA, TMSCl, THF, −78 °C; ii) MeLi, CH_2=C(TMS)COMe, THF; iii) NaOMe, MeOH, room temp. (44% based on consumed **13**)

The synthesis of the enantiomers of **1** is summarized in Scheme 2. (*S*)-Citronellal (**5**) was oxidized with pyridinium dichromate (PDC) to give (*S*)-citronellic acid (**6**), which was esterified with ethyl iodide and potassium carbonate to furnish ethyl ester (*S*)-**7**. Ozonolysis of (*S*)-**7** afforded aldehyde (*S*)-**8**, which was subjected to Horner−Wadsworth−Emmons olefination to give diethyl ester (*S*)-**9** [(*E*)/(*Z*) = 87:13 as judged by ^{1}H NMR spectroscopy]. Hydrogenation of (*S*)-**9** over Adams's platinum oxide catalyst yielded saturated ester (2*RS*,6*S*)-**10**, the precursor **C** to be employed in the Dieckmann condensation.

Treatment of **10** with potassium *tert*-butoxide in hot *m*-xylene resulted in ring closure to give the β-oxo ester (2*RS*,3*S*,7*RS*)-**11**,[4,5] which was heated under reflux with sodium hydroxide in aqueous methanol to effect hydrolysis and decarboxylation, furnishing the ketone (2*RS*,6*S*)-**12**. Methylation of **12** with potassium *tert*-butoxide and methyl iodide in *tert*-butyl alcohol gave the trimethyl ketone (*S*)-**13**. Robinson annulation of (*S*)-**13** with 3-trimethylsilyl-3-buten-2-one under Stork's conditions[6−8] afforded bicyclic ketone (1*R*,2*S*)-**1** as colorless rods, m.p. 52.0−53.5 °C, $[\alpha]_D^{22}$ = −62 (hexane). The overall yield of (1*R*,2*S*)-**1** was 13% based on (*S*)-citronellal (9 steps). Similarly, (1*S*,2*R*)-**1**, m.p. 52.0−53.5 °C, $[\alpha]_D^{22}$ = +64 (hexane), was synthesized from (*R*)-citronellal. The specific rotation of the naturally occurring **1** was not reported.[1]

Bartelt et al. obtained (±)-**1** as an oil, and its relative configuration (1*R**,2*S**) was assigned by ^{1}H NMR spectroscopic studies coupled with an ab initio calculation of the lowest-energy conformation of **1**.[2] Because the enantiomers of **1** were nicely crystalline, we were able to carry out an X-ray analysis of (−)-**1**. Figure 2 shows the perspective view of (−)-**1**, which must be (1*R*,2*S*)-**1**, taking into account the (2*S*) configuration of (*S*)-citronellal origin. This X-ray result is in good agreement with the result of the ab initio calculation reported by Bartelt.[2] Further evidence supporting the (1*R*,2*S*) absolute configuration assigned to (−)-**1** was provided by its CD spectrum, which is similar to that of cholest-4-en-3-one in the 300−400 nm region, as shown in Figure 3. The two enantiomers of **1** obviously exhibit spectra that are antipodal to each other.

Scheme 3 summarizes the conversion of the enantiomers of ketone **1** into the enantiomers of himachalene-type hydrocarbons **2**, **3** and **4**. The crystalline ketone (1*R*,2*S*)-**1** was treated with methylenetriphenylphosphorane to give (6*S*,7*R*)-**2**, $[\alpha]_D^{21}$ = −12 (hexane). The specific rotation of the naturally occurring **2** was reported as $[\alpha]_D$ = +1.6 (hexane).[1] Bartelt et al. prepared the naturally occurring **2** by Wittig methylenation of the naturally occurring **1**.[1] The naturally occurring **1** and **2** are therefore (1*S*,2*R*)-**1** and (6*R*,7*S*)-**2**.

Treatment of (6*S*,7*R*)-**2** with hot formic acid caused double-bond migration to give a mixture of (6*S*,7*R*)-**2** and

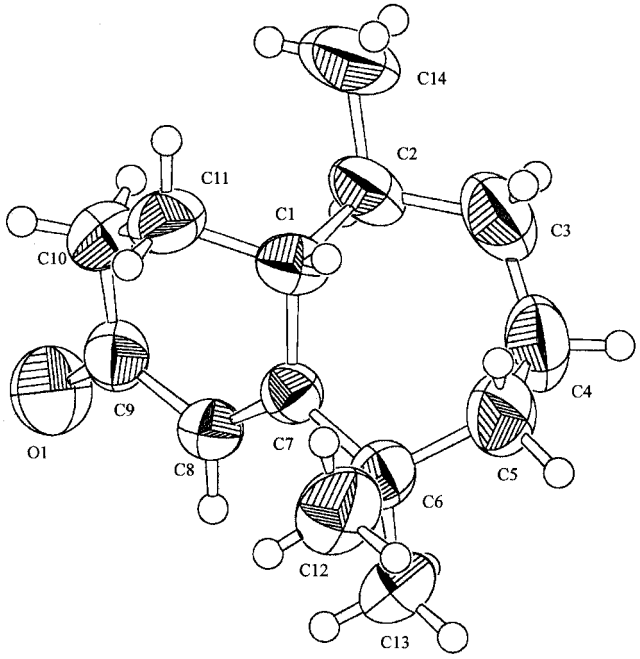


Figure 2. X-ray structure of (1*R*,2*S*)-(−)-**1**

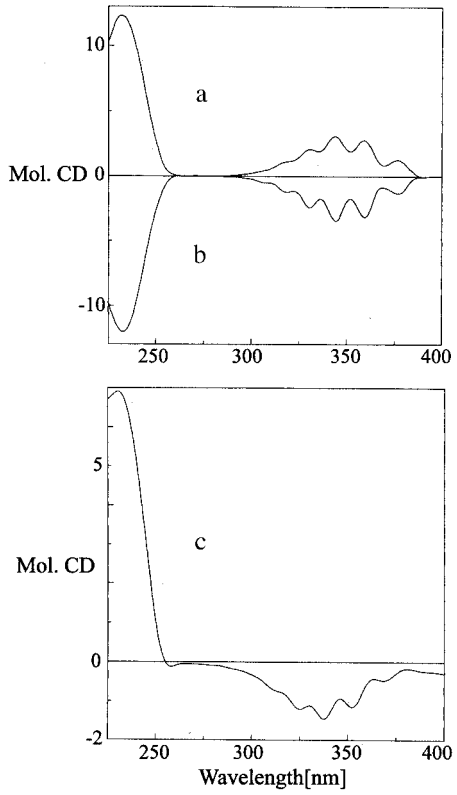
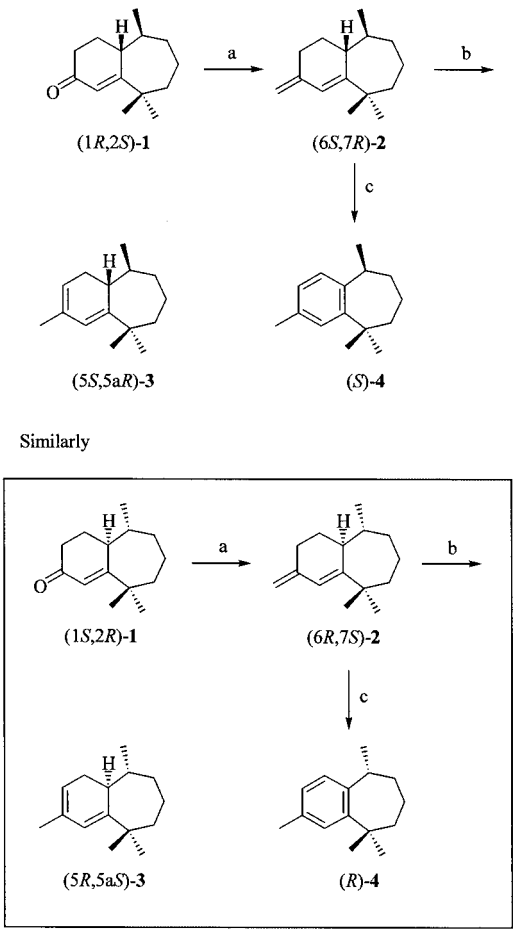


Figure 3. CD spectra of (a) (1*R*,2*S*)-(−)-**1** (1.63 mM in hexane); (b) (1*S*,2*R*)-(+)-**1** (1.33 mM in hexane); and (c) cholest-4-en-3-one (1.67 mM in hexane)

(5*S*,5a*R*)-**3** (17:83), which could be separated by chromatography on silica gel, impregnated with silver nitrate, to furnish (5*S*,5a*R*)-**3**, $[\alpha]_D^{21} = -110$ (hexane). The naturally occurring **3** has an $[\alpha]_D$ value of +82 (hexane),[1] and therefore its configuration is (5*R*,5a*S*)-**3**. Finally, dehydrogenation of (6*S*,7*R*)-**2** with chloranil[1] afforded (*S*)-*ar*-himachalene (**4**), $[\alpha]_D^{26} = -10$ (hexane). *Aphthona flava* produces *ar*-himachalene with $[\alpha]_D < +10$ (hexane),[1] which must therefore be (*R*)-**4**. For the purpose of bioassay, the naturally occurring enantiomers themselves were then synthesized from (1*S*,2*R*)-**1**, giving (6*R*,7*S*)-**2**, (5*R*,5a*S*)-**3** and (*R*)-**4**.



Scheme 3. Synthesis of **2**, **3** and **4**; reagents and conditions: (a) Ph_3PMeBr, *n*BuLi, THF, 0 °C to room temp. (69% based on consumed **1**); (b) HCO_2H, MeOH, room temp. (88% based on consumed **2**); (c) chloranil, C_6H_6, 75 °C (63%)

Our synthesis of (1*R*,2*S*)-(−)-**1** started from (*S*)-(−)-citronellal (**5**), and the relative stereochemistry of (1*R*,2*S*)-**1** was proved by its X-ray analysis. There was therefore no room for error. Accordingly, we conclude that the himachalene-type pheromone candidates isolated from *Aphthona flava* possess the absolute configuration as shown in Figure 1 and the lower part of Scheme 3, opposite to what has been proposed by Bartelt.[1] This conclusion was supported by Dr. Bartelt's GC comparison of our synthetic enantiomers of **1**−**4** with natural **1**−**4** on a chiral stationary phase (CDX-B). It was also ascertained by GC analysis that the European Silver Fir (*Abies alba*) produces (1*R*,2*S*)-**1** and (6*S*,7*R*)-**2**, the opposite enantiomers of the insect materials.[1]

In summary, the male-produced pheromone candidates (1*S*,2*R*)-**1**, (6*R*,7*S*)-**2**, (5*R*,5a*S*)-**3** and (*R*)-**4** of the flea beetle *Aphthona flava* were synthesized from (*R*)-(+)-citronellal. Their enantiomers were also synthesized from (*S*)-(−)-citronellal. These enantiomers will be bioassayed in Hungary, by Dr. M. Tóth, employing the crucifer flea beetle, *Phyllotreta cruciferae*, as the test insect. Finally, it must be added that Pandey and Dev assigned the (*S*) configuration to (+)-*ar*-himachalene in 1968.[9] Our present result is in conflict with theirs. Further investigation is being continued in cooperation with Dr. R. J. Bartelt to solve this stereochemical controversy.

Experimental Section

General: Melting points and boiling points are uncorrected. IR: Jasco FT/IR-410. ^{1}H NMR: Varian Mercury-300 (300 MHz) (TMS at δ = 0.00 or $CHCl_3$ at δ = 7.26 as an internal standard). ^{13}C NMR: Varian Mercury-300 (75 MHz) ($CDCl_3$ at δ = 77.0 as an internal standard). MS: Jeol JMS-SX 102A and Hitachi M-80B. Optical rotation: Jasco DIP-1000. CD spectra: Jasco J-725 spectrometer. Refractive index (n_D): Atago DMT-1. CC: Merck Kieselgel 60 Art 1.07734. TLC: 0.25-mm Merck silica gel plates (60F-254). Microanalyses were performed at the Center for New Materials Research, Science University of Tokyo.

Ethyl (*S*)-3,7-Dimethyl-6-octenoate [(*S*)-7]: Pyridinium dichromate (PDC; 100 g, 266 mmol) was added to a stirred solution of (*S*)-**5** [$[\alpha]_D^{24}$ = −13.4 (neat), 30.0 g, 195 mmol] in DMF (200 mL) at 0 °C. After stirring at room temperature for 5 h, the reaction mixture was quenched with 1 N aqueous HCl and extracted with Et_2O. The extract was washed three times with 10% aqueous NaOH, the combined alkaline aqueous layer was acidified with concd. HCl, and the separated organic acid was extracted with Et_2O. The extract was washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The crude product **6** (26.0 g) was dissolved in DMF (100 mL), and treated with K_2CO_3 (31.6 g, 229 mmol) and EtI (30.0 g, 192 mmol) at 0 °C. The mixture was stirred overnight at room temperature, quenched with water, and extracted with Et_2O. The extract was successively washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by distillation (b.p. 98−99 °C/6 Torr) to give (*S*)-**7** (28.6 g, 74%), n_D^{24} = 1.4400. $[\alpha]_D^{21}$ = −4.84 (*c* = 1.72, $CHCl_3$). IR (film): $\tilde{\nu}_{max.}$ = 2965 (s, C−H), 1735 (s, C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.6 Hz, 3 H, 3-H), 1.25 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 1.30 (m, 2 H, 4-H), 1.60 (s, 3 H, 7-Me), 1.68 (d, *J* = 1.2 Hz, 3 H, 7-Me), 1.98 (m, 3 H, 3, 5-H), 2.10 (dd, *J* = 14.4, 7.8 Hz, 1 H, 1-H_a), 2.30 (dd, *J* = 14.4, 6.0 Hz, 1 H, 1-H_b), 4.12 (q, *J* = 7.2 Hz, 2 H, OCH_2CH_3), 5.09 (tq, *J* = 7.2, 1.2 Hz, 1 H, 6-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3, 17.6, 19.6, 25.4, 25.7, 30.0, 36.8, 41.9, 60.1, 124.3, 131.5, 173.3 ppm. $C_{12}H_{22}O_2$ (198.3): calcd. C 72.68, H 11.18; found C 72.41, H 11.30.

Ethyl (*R*)-3,7-Dimethyl-6-octenoate [(*R*)-7]: In a similar manner to that described for the preparation of (*S*)-**7**, (*R*)-**5** [$[\alpha]_D^{24}$ = +10.6 (neat), 22.1 g, 144 mmol] gave (*R*)-**7** (16.0 g, 56%) as a colorless oil. Its IR, ^{1}H NMR and ^{13}C NMR spectra are identical to those of (*S*)-**7**. n_D^{23} = 1.4400. $[\alpha]_D^{23}$ = +3.42 (*c* = 1.30, $CHCl_3$). HRMS (EI) [M^+] ($C_{12}H_{22}O_2$): calcd. 198.1620; found 198.1628.

Ethyl (*S*)-3-Methyl-6-oxohexanoate [(*S*)-8]: Ozone was passed through a stirred solution of (*S*)-**7** (1.03 g, 5.20 mmol) in dry methanol (10 mL) at −78 °C at a rate of about 150 mL/min. After stirring at −78 °C for 3 h, the color of the reaction mixture changed to pale blue. O_2 was then passed through to remove the ozone for 30 min, and Me_2S (0.76 mL, 10.3 mmol) was added at −78 °C. The mixture was warmed to room temperature and then concentrated under reduced pressure. The residue was diluted with water and extracted with Et_2O. The extract was washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography (hexane/Et_2O, 10:1) to give (*S*)-**8** (643 mg, 72%) as a colorless oil, n_D^{24} = 1.4325. $[\alpha]_D^{22}$ = −6.64 (*c* = 1.52, $CHCl_3$). IR (film): $\tilde{\nu}_{max.}$ = 2960 (s, C−H), 2720 (m, CHO), 1730 (s, C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 6.6 Hz, 3 H, 3-Me), 1.25 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 1.53 (dddd, *J* = 14.1, 8.1, 8.1, 6.6 Hz, 1 H, 4-H_a), 1.70 (dddd, *J* = 14.1, 8.7, 7.5, 5.7 Hz, 1 H, 4-H_b), 1.99 (dddt, *J* = 7.5, 6.6, 6.3, 5.7 Hz, 1 H, 3-H), 2.16 (dd, *J* = 15.0, 7.5 Hz, 1 H, 2-H_a), 2.28 (dd, *J* = 15.0, 6.3 Hz, 1 H, 2-H_b), 2.46 (m, 2 H, 5-H), 4.13 (q, *J* = 7.2 Hz, 2 H, OCH_2CH_3), 9.77 (t, *J* = 1.5 Hz, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 19.4, 28.5, 29.8, 41.5, 60.3, 172.7, 202.1 ppm. This compound was employed for the next step without further purification.

Ethyl (*R*)-3-Methyl-6-oxohexanoate [(*R*)-8]: In a similar manner to that described for the preparation of (*R*)-**8**, (*S*)-**7** (10.0 g, 46.7 mmol) gave (*R*)-**8** (6.17 g, 69%) as a colorless oil. Its IR, ^{1}H NMR and ^{13}C NMR spectra are identical to those of (*S*)-**8**. n_D^{23} = 1.4338. $[\alpha]_D^{26}$ = +7.19 (*c* = 1.05, $CHCl_3$). This compound was employed for the next step without further purification.

Diethyl (*S*,*E*)-2,6-Dimethyloct-2-enedioate [(*S*)-9]: A solution of triethyl 2-phosphonopropanoate (17.6 g, 73.9 mmol) in dry THF (60 mL) was added dropwise to a stirred suspension of NaH (60% in oil, 2.53 g, 176 mmol) in dry THF (60 mL) at −30 °C under argon. After stirring at −10 °C for 1 h, a solution of (*S*)-**8** (9.08 g, 52.8 mmol) in dry THF (60 mL) was added dropwise at −30 °C, and the mixture was stirred for 30 min. The reaction mixture was quenched with water, and extracted with Et_2O. The extract was successively washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography (hexane/EtOAc, 20:1) to give (*S*)-**9** (12.9 g, 96%) as a colorless oil, n_D^{21} = 1.4560. $[\alpha]_D^{22}$ = −7.12 (*c* = 1.58, $CHCl_3$). IR (film): $\tilde{\nu}_{max.}$ = 2980 (s, C−H), 1735 (s, C=O), 1710 (s, C=O), 1650 (m, C=C) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 6.6 Hz, 3 H, 6-Me), 1.25 (t, *J* = 7.2 Hz, 3 H, OCH_2CH_3), 1.28 (t, *J* = 7.2 Hz, OCH_2CH_3), 1.33 (m, 1 H, 5-H_a), 1.48 (m, 1 H, 5-H_b), 1.83 (tq, *J* = 1.5, 0.9 Hz, 3 H, 2-Me), 1.98 (m, 1 H, 6-H), 2.13 (dd, *J* = 14.7, 7.8 Hz, 1 H, 7-H_a), 2.18 (m, 2 H, 4-H), 2.30 (dd, *J* = 14.7, 6.3 Hz, 1 H, 7-H_b), 4.12 (q, *J* = 7.2 Hz, 2 H, OCH_2CH_3), 4.18 (q, *J* = 7.2 Hz, 2 H, OCH_2CH_3), 6.73 (tq, *J* = 7.5, 1.5 Hz, 1 H, 3-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.3, 14.25, 14.28, 19.5, 26.1, 30.1, 35.3, 41.7, 60.2, 60.4, 128.0, 141.7, 168.2, 172.9 ppm. $C_{14}H_{24}O_4$ (256.3): calcd. C 65.60, H 9.44; found C 65.73, H 9.58.

Diethyl (*R*,*E*)-2,6-Dimethyloct-2-enedioate [(*R*)-9]: In a similar manner to that described for the preparation of (*S*)-**9**, (*R*)-**8** (2.42 g, 14.1 mmol) gave (*R*)-**9** (3.38 g, 91%) as a colorless oil. Its IR, ^{1}H NMR and ^{13}C NMR spectra are identical to those of (*S*)-**9**. n_D^{26} = 1.4540. $[\alpha]_D^{26}$ = +7.44 (*c* = 1.04, $CHCl_3$). HRMS (EI) [M^+] ($C_{14}H_{24}O_4$): calcd. 256.1675; found 256.1665.

Diethyl (2*RS*,6*S*)-2,6-Dimethyloctanedioate [(*S*)-10]: A solution of (*S*)-**9** (4.22 g, 16.5 mmol) in EtOAc (10 mL) was added to a stirred suspension of PtO_2 (100 mg) in EtOAc (20 mL) at 0 °C under H_2. After stirring at room temperature for 3 h, the mixture was filtered

through Celite and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography (hexane/EtOAc, 20:1) to give (*S*)-**10** (4.28 g, quant.) as a colorless oil. A portion of it was further purified by chromatography to afford an analytical sample. n_D^{21} = 1.4330. $[\alpha]_D^{21}$ = −5.26 (*c* = 1.85, $CHCl_3$). IR (film): $\tilde{\nu}_{max.}$ = 2935 (s, C−H), 1735 (s, C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.6 Hz, 3 H, 6-Me), 1.13 (d, *J* = 6.9 Hz, 3 H, 2-Me), 1.25 (t, *J* = 7.2 Hz, 6 H, OCH_2CH_3), 1.08−1.23 (m, 5 H, 3-H_a, 4, 5-H), 1.64 (m, 1 H, 3-H_b), 1.95 (m, 1 H, 6-H), 2.09 (dd, *J* = 14.4, 8.1 Hz, 1 H, 7-H_a), 2.27 (dd, *J* = 14.4, 6.3 Hz, 1 H, 7-H_b), 2.40 (tq, *J* = 7.2, 6.9 Hz, 1 H, 2-H), 4.12 (q, *J* = 6.9 Hz, 4 H, OCH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3, 17.0, 17.1, 19.59, 19.61, 24.5, 30.17, 30.20, 33.81, 33.82, 36.47, 36.49, 39.5, 41.84, 41.87, 60.1, 173.2, 176.79, 176.81 ppm. $C_{14}H_{26}O_4$ (258.3): calcd. C 65.09, H 10.14; found C 65.27, H 10.36.

Diethyl (2*RS*,6*R*)-2,6-Dimethyloctanedioate [(*R*)-10]: In a similar manner to that described for the preparation of (*S*)-**10**, (*R*)-**9** (2.92 g, 11.4 mmol) gave (*R*)-**10** (3.02 g, quant.) as a colorless oil. Its IR, ^1H NMR and ^{13}C NMR spectra are identical to those of (*S*)-**10**. n_D^{23} = 1.4320. $[\alpha]_D^{26}$ = +4.19 (*c* = 1.06, $CHCl_3$). HRMS (EI) [M^+] ($C_{14}H_{26}O_4$): calcd. 258.1831; found 258.1822.

(2*RS*,3*S*,7*RS*)-2-Ethoxycarbonyl-3,7-dimethylcycloheptanone [(*S*)-11]: A solution of (*S*)-**10** (7.55 g, 29.3 mmol) in *m*-xylene (80 mL) was added dropwise to a stirred solution of *t*BuOK (6.60 g, 58.8 mmol) in *m*-xylene (100 mL) over 2 h at 150 °C. After stirring at 150 °C for 1 h, the reaction mixture was cooled to room temperature, diluted with 1 N aqueous HCl, and extracted with Et_2O. The extract was successively washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography (hexane/EtOAc, 20:1) to give (*S*)-**11** (4.89 g, 79%) as a colorless oil, n_D^{24} = 1.4589. $[\alpha]_D^{24}$ = +43.1 (*c* = 1.96, $CHCl_3$). IR (film): $\tilde{\nu}_{max.}$ = 2930 (s, C−H), 1745 (s, C=O), 1705 (s, C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.01, 1.03, 1.09 and 1.14 (each d, *J* = 7.2, *J* = 6.6, *J* = 6.9 Hz and *J* = 7.2 Hz, total 3 H, 3-Me), 1.23 and 1.25 (each t, each *J* = 6.9 Hz, total 3 H, OCH_2CH_3), 1.44 (d, *J* = 4.8 Hz, 3 H, 7-Me), 1.36−1.95 (m, 5 H), 2.25 (m, 1 H), 2.44 (m, 1 H, 3-H), 2.73 (m, 1 H, 7-H), 3.33, 3.44, 3.75 and 3.84 (each d, *J* = 9.3, *J* = 9.9, *J* = 2.4 Hz and *J* = 2.1 Hz, total 1 H, 2-H), 4.14 and 4.18 (each q, each *J* = 6.9 Hz, total 2 H, OCH_2CH_3) ppm. HRMS (EI) [M^+] ($C_{12}H_{20}O_3$): calcd. 212.1412; found 212.1410.

(2*RS*,3*R*,7*RS*)-2-Ethoxycarbonyl-3,7-dimethylcycloheptanone [(*R*)-11]: In a similar manner to that described for the preparation of (*S*)-**11**, (*R*)-**10** (2.63 g, 10.2 mmol) gave (*R*)-**11** (1.88 g, 87%) as a colorless oil. Its IR and ^1H NMR spectra are identical to those of (*S*)-**11**. n_D^{25} = 1.4580. $[\alpha]_D^{25}$ = −40.3 (*c* = 0.55, $CHCl_3$). HRMS (EI) [M^+] ($C_{12}H_{20}O_3$): calcd. 212.1412; found 212.1413.

(2*RS*,6*S*)-2,6-Dimethylcycloheptanone [(*S*)-12]: A solution of NaOH (0.50 g, 12.5 mmol) in water (10 mL) was added to a stirred solution of (*S*)-**11** (1.09 g, 5.14 mmol) in MeOH (2.0 mL) at room temperature. After refluxing for 4 h, the reaction mixture was cooled to room temperature, diluted with 1 N aqueous HCl, and extracted with Et_2O. The extract was successively washed with water and brine, dried with $MgSO_4$, and concentrated carefully under reduced pressure in order not to lose the low-boiling product. The residue was purified by chromatography (hexane/Et_2O, 30:1) to give (*S*)-**12** (612 mg, 85%) as a colorless oil, n_D^{24} = 1.4540. $[\alpha]_D^{24}$ = −54.2 (*c* = 1.10, $CHCl_3$). IR (film): $\tilde{\nu}_{max.}$ = 2925 (s, C−H), 1700 (s, C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.98 and 0.99 ppm(each d, each *J* = 6.6 Hz, total 3 H, 6-Me), 1.05 and 1.07 (each d, *J* = 7.2 Hz and *J* = 6.9 Hz, total 3 H, 2-Me), 1.18 (m, 1 H), 1.36 (m, 2 H), 1.59 (m, 1 H), 1.81 (m, 3 H), 2.30−2.60 (m, 3 H, 2, 7-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.5, 18.0, 22.6, 23.2, 23.9, 28.0, 31.70, 31.78, 31.80, 33.5, 38.4, 38.9, 46.4, 47.4, 49.8, 50.2, 215.4, 216.3 ppm. HRMS (EI) [M^+] ($C_9H_{16}O$): calcd. 140.1201; found 140.1208.

(2*RS*,6*R*)-2,6-Dimethylcycloheptanone [(*R*)-12]: In a similar manner to that described for the preparation of (*S*)-**12**, (*R*)-**11** (2.73 g, 12.9 mmol) gave (*R*)-**12** (1.29 g, 72%) as a colorless oil. Its IR, ^1H NMR and ^{13}C NMR spectra are identical to those of (*S*)-**12**. n_D^{23} = 1.4548. $[\alpha]_D^{23}$ = +59.5 (*c* = 1.15, $CHCl_3$). HRMS (EI) [M^+] ($C_9H_{16}O$): calcd. 140.1201; found 140.1204.

(*S*)-2,2,6-Trimethylcycloheptanone [(*S*)-13]: A solution of (*S*)-**12** (1.41 g, 10.0 mmol) in *t*BuOH (5.0 mL) was added to a stirred solution of *t*BuOK (3.36 g, 29.9 mmol) in *t*BuOH (15 mL) at room temperature. After stirring for 30 min, MeI (3.0 mL, 48.2 mmol) was added at 0 °C. The mixture was warmed to room temperature over 2 h, filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was diluted with water, and extracted with Et_2O. The extract was washed with brine, dried with $MgSO_4$, and concentrated carefully under reduced pressure in order not to lose the low-boiling product. The residue was purified by chromatography (hexane/Et_2O, 50:1) to give (*S*)-**13** [994 mg, 88% based on consumed (*S*)-**12**] as a colorless oil, n_D^{24} = 1.4546. $[\alpha]_D^{24}$ = −51.7 (*c* = 1.03, $CHCl_3$). IR (film): $\tilde{\nu}_{max.}$ = 2925 (s, C−H), 1700 (s, C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.99 (d, *J* = 6.6 Hz, 3 H, 6-Me), 1.07 (s, 6 H, 2-Me), 1.20 (m, 2 H), 1.72 (m, 5 H), 2.23 (ddd, *J* = 10.8, 2.1, 1.5 Hz, 1 H, 7-H_a), 2.63 (dd, *J* = 11.1, 10.8 Hz, 1 H, 7-H_b) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.4, 23.5, 23.8, 27.4, 33.5, 39.4, 39.5, 47.61, 47.64, 217.3 ppm. HRMS (EI) [M^+] ($C_{10}H_{18}O$): calcd. 154.1358; found 154.1359.

(*R*)-2,2,6-Trimethylcycloheptanone [(*R*)-13]: In a similar manner to that described for the preparation of (*S*)-**13**, (*R*)-**12** (1.28 g, 9.14 mmol) gave (*R*)-**13** [636 mg, 55% based on the consumed (*R*)-**12**] as a colorless oil. Its IR, ^1H NMR and ^{13}C NMR spectra are identical to those of (*S*)-**13**. n_D^{23} = 1.4520. $[\alpha]_D^{23}$ = +45.6 (*c* = 1.21, $CHCl_3$). HRMS (EI) [M^+] ($C_{10}H_{18}O$): calcd. 154.1358; found 154.1357.

(1*R*,2*S*)-2,6,6-Trimethylbicyclo[5.4.0]undec-7-en-9-one [(1*R*,2*S*)-1]: *n*BuLi (1.58 M in hexane, 2.26 mL, 3.57 mmol) was added to a stirred solution of diisopropylamine (0.60 mL, 4.28 mmol) in THF (8.0 mL) at 0 °C under argon. After stirring for 30 min, a solution of (*S*)-**13** (500 mg, 3.25 mmol) in THF (3.0 mL) was added at −78 °C. The mixture was stirred at −78 °C for 30 min, and TMSCl (0.80 mL, 6.48 mmol) was added dropwise at −78 °C. After stirring at −78 °C for 1 h, the mixture was diluted with hexane and saturated aqueous NH_4Cl, and extracted with Et_2O. The extract was washed with water, saturated aqueous $NaHCO_3$ and brine, dried with K_2CO_3, and concentrated under reduced pressure. The residue was diluted with THF (10 mL), and MeLi (2.2 M in Et_2O, 1.47 mL, 3.23 mmol) was added at 0 °C under argon. The mixture was stirred and refluxed for 1 h, and then cooled to −78 °C. A solution of 2-trimethylsilyl-1-buten-3-one (500 mg, 3.52 mmol) in THF (3.0 mL) was added, and the mixture was warmed to room temperature. After stirring overnight, the reaction was quenched with water, and extracted with Et_2O. The extract was washed with brine, dried with K_2CO_3, and concentrated under reduced pressure. A solution of 10% NaOMe in methanol (10 mL) was added at room temperature to a solution of the crude residue in MeOH (4.0 mL). After refluxing for 6 h, the mixture was diluted with 1 N aqueous HCl, and extracted with Et_2O. The extract was washed with water, saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated

under reduced pressure. The residue was purified by chromatography (hexane/Et_2O, 10:1) to give (1*R*,2*S*)-**1** [294 mg, 44% based on consumed (*S*)-**13**] as colorless prisms, m.p. 52.0−53.5 °C. $[\alpha]_D^{22}$ = −62 (*c* = 0.51, hexane). CD (*c* = 0.00163, hexane): Δε = +12.3 (232 mm), −2.43 (331), −3.46 (345), −3.14 (360), −1.33 (377). IR (KBr): $\tilde{\nu}_{max.}$ = 2925 (s, C−H), 1670 (s, C=O), 1610 (C=C), 1455 (m), 1340 (m), 1255 (m) cm^{-1}. ^1H NMR (300 MHz, C_6D_6): δ = 0.71 (d, *J* = 6.6 Hz, 3 H, 2-Me), 0.80 (s, 3 H, 6-Me), 0.93 (s, 3 H, 6-Me), 0.81−1.11 (m, 2 H), 1.15−1.58 (m, 6 H), 1.63 (m, 1 H), 1.79 (ddd, *J* = 9.6, 3.9, 2.7 Hz, 1 H, 1-H), 2.24 (ddd, *J* = 17.4, 7.2, 3.0 Hz, 1 H, 10-H_a), 2.30 (ddd, *J* = 17.4, 12.6, 4.8 Hz, 1 H, 10-H_b), 6.05 (s, 1 H, 8-H) ppm. ^{13}C NMR (75 MHz, C_6D_6): δ = 20.7, 22.4, 26.0, 27.7, 30.9, 32.7, 36.0, 37.6, 39.6, 39.7, 40.0, 123.6, 176.2, 197.9 ppm. EI MS (70 eV): *m*/*z* (%) = 206 (39) [M^+], 191 (18), 178 (50), 163 (53), 150 (71), 135 (100), 121 (41), 109 (46), 93 (52), 79 (40), 67 (29), 55 (38), 41 (67). These spectroscopic data are identical with those reported for (±)-**1**.[2] $C_{14}H_{22}O$ (206.3): calcd. C 81.50, H 10.75; found C 81.28, H 10.60.

(1*S*,2*R*)-2,6,6-Trimethylbicyclo[5.4.0]undec-7-en-9-one [(1*S*,2*R*)-1]: In a similar manner to that described for the preparation of (1*R*,2*S*)-**1**, (*R*)-**13** (400 mg, 2.60 mmol) gave (1*S*,2*R*)-**1** [182 mg, 44% based on consumed (*R*)-**13**] as colorless prisms. m.p. 52.0−53.5 °C. Its IR, ^1H NMR and ^{13}C NMR spectra are identical to those of (1*R*,2*S*)-**1**. $[\alpha]_D^{23}$ = +64 (*c* = 0.79, hexane). CD (*c* = 0.00133, hexane): Δε = −12.1 (232 mm), +2.07 (331), +3.09 (344), +2.79 (359), +1.27 (377). $C_{14}H_{22}O$ (206.3): calcd. C 81.50, H 10.75; found C 81.34, H 10.85.

(6*S*,7*R*)-2,2,6-Trimethyl-10-methylenebicyclo[5.4.0]undec-1(11)-ene [(6*S*,7*R*)-2]: *n*BuLi (1.58 M in hexane, 0.17 mL, 0.27 mmol) was added to a stirred suspension of methyltriphenylphosphonium bromide (104 mg, 0.291 mmol) in dry THF (5 mL) at 0 °C under argon and the mixture was then warmed to room temperature. After stirring for 3 h, a solution of (1*R*,2*S*)-**1** (49 mg, 0.24 mmol) in dry THF (1 mL) was added to the resulting mixture at 0 °C. The mixture was stirred at room temperature for 1.5 h, diluted with water, and extracted with Et_2O. The extract was washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography (20% $AgNO_3$, SiO_2; hexane/Et_2O, 50:1) to give (6*S*,7*R*)-**2** [13 mg, 69% based on consumed (1*R*,2*S*)-**1**] as a colorless oil, n_D^{24} = 1.5200. $[\alpha]_D^{23}$ = −12 (*c* = 0.85, hexane). IR (film): $\tilde{\nu}_{max.}$ = 2925 (s, C−H), 1625 (m, C=C), 1455 (s), 1360 (m), 1200 (w) cm^{-1}. ^1H NMR (300 MHz, C_6D_6): δ = 0.87 (d, *J* = 6.6 Hz, 3 H, 6-Me), 0.99 (s, 3 H, 2-Me), 1.06 (m, 2 H), 1.16 (s, 3 H, 2-Me), 1.30 (m, 2 H), 1.49 (m, 3 H), 1.72 (m, 2 H), 1.96 (m, 1 H, 7-H), 2.26 (m, 1 H, 9-H_a), 2.45 (m, 1 H, 9-H_b), 4.88 (s, 1 H, 10-C$H_a$$H_b$), 4.97 (s, 1 H, 10-C$H_a$$H_b$), 6.20 (s, 1 H, 11-H) ppm. ^{13}C NMR (75 MHz, C_6D_6): δ = 20.0, 22.6, 25.3, 26.8, 27.8, 31.8, 36.4, 37.2, 38.8, 39.3, 40.7, 109.4, 122.8, 143.9, 154.5 ppm. EI MS (70 eV): *m*/*z* (%) = 204 (100) [M^+], 189 (63), 175 (8), 161 (72), 147 (37), 133 (89), 119 (72), 105 (70), 91 (68), 79 (31), 69 (26), 55 (36), 41 (46). HRMS (EI) [M^+] ($C_{15}H_{24}$): calcd. 204.1878; found 204.1884.

(6*R*,7*S*)-2,2,6-Trimethyl-10-methylenebicyclo[5.4.0]undec-1(11)-ene [(6*R*,7*S*)-2]: In a similar manner to that described for the preparation of (6*S*,7*R*)-**2**, (1*S*,2*R*)-**1** (100 mg, 0.485 mmol) gave (6*R*,7*S*)-**2** [77 mg, 82% based on consumed (1*S*,2*R*)-**1**] as a colorless oil. Its IR, MS, ^1H NMR and ^{13}C NMR spectra are identical to those of (6*S*,7*R*)-**2**. n_D^{26} = 1.5222. $[\alpha]_D^{26}$ = +6.0 (*c* = 0.90, hexane). HRMS (EI) [M^+] ($C_{15}H_{24}$): calcd. 204.1878; found 204.1872.

(5*S*,5a*R*)-1,1,5,8-Tetramethyl-1,2,3,4,5,6,5a-heptahydrobenzo[1,2-*a*][7]-annulene [(5*S*,5a*R*)-3]: Formic acid (0.15 mL, 3.98 mmol) was added to a stirred solution of (6*S*,7*R*)-**2** (33 mg, 0.16 mmol) in MeOH (1 mL) at room temperature. The mixture was stirred at room temperature overnight, diluted with water, and extracted with hexane. The extract was washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography (20% $AgNO_3$, SiO_2; hexane) to give (5*S*,5a*R*)-**3** [22 mg, 88% based on consumed (6*S*,7*R*)-**2**] as a colorless oil, n_D^{24} = 1.5010. $[\alpha]_D^{21}$ = −110 (*c* = 0.85, hexane). IR (film): $\tilde{\nu}_{max.}$ = 2925 (s, C−H), 1655 (w, C=C), 1455 (m), 1365 (m), 1200 (m), 785 (m) cm^{-1}. ^1H NMR (300 MHz, C_6D_6): δ = 0.85 (d, *J* = 6.6 Hz, 3 H, 5-Me), 0.90−1.20 (m, 2 H), 1.06 (s, 3 H, 1-Me), 1.11 (s, 3 H, 1-Me), 1.53 (m, 4 H), 1.72 (m, 2 H), 1.73 (m, 3 H, 8-Me), 2.09 (dddt, *J* = 16.8, 6.2, 3.0, 3.0 Hz, 1 H, 6-H_a), 2.27 (ddd, *J* = 16.8, 6.3, 1.2 Hz, 1 H, 6-H_b), 5.25 (m, 1 H, 9-H), 5.57 (s, 1 H, 7-H) ppm. ^{13}C NMR (75 MHz, C_6D_6): δ = 21.2, 22.4, 23.1, 26.7, 28.1, 32.6, 34.3, 37.6, 38.6, 39.9, 41.0, 116.1, 119.7, 132.7, 153.6 ppm. EI MS (70 eV): *m*/*z* (%) = 204 (57) [M^+], 189 (16), 161 (27), 147 (8), 133 (100), 119 (72), 105 (54), 91 (21), 77 (11), 69 (13), 55 (17), 41 (19). HRMS (EI) [M^+] ($C_{15}H_{24}$): calcd. 204.1878; found 204.1876.

(5*R*,5a*S*)-1,1,5,8-Tetramethyl-1,2,3,4,5,6,5a-heptahydrobenzo[1,2-*a*]-[7]annulene [(5*R*,5a*S*)-3]: In a similar manner to that described for the preparation of (5*S*,5a*R*)-**3**, (6*R*,7*S*)-**2** (25 mg, 0.12 mmol) gave (5*R*,5a*S*)-**3** [20 mg, 95% based on consumed (6*R*,7*S*)-**2**] as a colorless oil. Its IR, MS, ^1H NMR and ^{13}C NMR spectra are identical to those of (5*S*,5a*R*)-**3**. n_D^{25} = 1.5059. $[\alpha]_D^{25}$ = +115 (*c* = 0.55, hexane). HRMS (EI) [M^+] ($C_{15}H_{24}$): calcd. 204.1878; found 204.1873.

(*S*)-1,1,5,8-Tetramethyl-1,2,3,4,5-pentahydrobenzo[*a*][7]annulene [(*S*)-4, (*S*)-*ar*-Himachalene]: Chloranil (60 mg, 0.24 mmol) was added to a stirred solution of (6*S*,7*R*)-**2** (24 mg, 0.12 mmol) in dry benzene (2 mL) at room temperature. After stirring at 75 °C for 5 h, the mixture was cooled to room temperature, diluted with water, and extracted with hexane. The extract was successively washed with water and brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography (hexane) to give (*S*)-**4** (15 mg, 63%) as a colorless oil, n_D^{24} = 1.5272. $[\alpha]_D^{26}$ = −10 (*c* = 0.65, hexane). IR (film): $\tilde{\nu}_{max.}$ = 2925 (s, C−H), 1610 (w, C=C), 1460 (m), 1360 (m), 810 (m) cm^{-1}. ^1H NMR (300 MHz, C_6D_6): δ = 1.31 (d, *J* = 6.6 Hz, 3 H, 5-Me), 1.34 (s, 3 H, 1-Me), 1.42 (s, 3 H, 1-Me), 1.28−1.78 (m, 6 H, 2, 3, 4-H), 2.27 (d, *J* = 0.6 Hz, 3 H, 8-Me), 3.26 (m, 1 H, 5-H), 7.03 (ddt, *J* = 7.8, 1.5, 0.6 Hz, 1 H, 7-H), 7.21 (d, *J* = 7.8 Hz, 1 H, 6-H), 7.31 (d, *J* = 1.5 Hz, 1 H, 9-H) ppm. ^{13}C NMR (75 MHz, C_6D_6): δ = 21.1, 21.3, 24.2, 34.1, 36.8, 39.5, 41.3, 125.8, 126.9, 135.1, 141.1, 147.6 ppm. EI MS (70 eV): *m*/*z* (%) = 202 (53%) [M^+], 187 (100), 159 (15), 145 (56), 131 (31), 119 (10), 105 (10), 91 (7), 41 (7). HRMS (EI) [M^+] ($C_{15}H_{22}$): calcd. 202.1721; found 202.1730.

(*R*)-1,1,5,8-Tetramethyl-1,2,3,4,5-pentahydrobenzo[*a*][7]annulene [(*R*)-4, (*R*)-*ar*-Himachalene]: In a similar manner to that described for the preparation of (*S*)-**4**, (6*R*,7*S*)-**2** (25 mg, 0.12 mmol) gave (*R*)-**4** (18 mg, 72%) as a colorless oil. Its IR, MS, ^1H NMR and ^{13}C NMR spectra are identical to those of (*S*)-**4**. n_D^{25} = 1.5288. $[\alpha]_D^{25}$ = +7.8 (*c* = 0.45, hexane). HRMS (EI) [M^+] ($C_{15}H_{22}$): calcd. 202.1721; found 202.1713.

X-ray Analysis of (1*R*,2*S*)-1: Crystal Data: $C_{14}H_{22}O$, *M* = 206.33, orthorhombic, space group $P2_12_12_1$, *a* = 10.86(1) Å, *b* = 12.056(7) Å, *c* = 9.634(7) Å, *V* = 1261(2) $Å^3$, *Z* = 4, $D_{calcd.}$ = 1.087 $Mg·m^{-3}$, *F*(000) = 456, μ(Mo-K_α) = 0.660 cm^{-1}. The crystal used for data

collection was a colorless prism with the approximate dimensions 0.80 × 0.50 × 0.50 mm. All data were obtained with a Rigaku AFC-5S automated four-circle diffractometer with graphite-monochromated Mo-K_α radiation. Unit cell parameters were determined by least-squares refinement of the optimized setting angles of 25 reflections in the range $13.2° < \theta < 14.8°$. The intensities were measured using the $\omega/2\theta$ scan technique up to 55°. Three standard reflections were monitored every 150 measurements. The data were corrected for Lorentz and polarization factors. An absorption correction (ψ-scan,[10] transmission factor = 0.945−0.999), but no decay correction, was applied. Of the 1617 independent reflections collected, all reflections were used for structure determination and refinement. The structure was solved by direct methods using the TEXSAN crystallographic software package.[11] All non-H atoms were found in the Fourier map. The refinement of the atomic parameters were carried out by the full-matrix least-squares refinement, using anisotropic temperature factors for all non-H atoms. All H-atoms were located geometrically and not refined. The final refinement converged with $R = 0.058$ and $Rw = 0.134$ {$R1 = 0.044$ and $R_W1 = 0.120$ calculated by 965 reflections with $I > [2\sigma(I)]$ for 138 parameters}. Atomic scattering factors were taken from "International Tables for X-ray Crystallography".[12] CCDC-218493 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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