Synthesis of Mono- and Sesqui-terpenoids. XXI.[1] Synthesis and Absolute Configuration of (*E*)-3-Formyl-(2,6,6-trimethyl-2-cyclohexenyl)-3-pentenal, a Sesquiterpenoid from a Marine Alga, *Caulerpa ashmeadii*

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A six-step synthesis of the enantiomers of (*E*)-3-formyl-(2,6,6-trimethyl-2-cyclohexenyl)-3-pentenal has been achieved, starting from the enantiomers of 2,4,4-trimethyl-2-cyclohexenol. By comparing the sign of the optical rotation of the naturally occurring material isolated from *Caulerpa ashmeadii* with those of the synthetic samples, the (*S*)-absolute configuration was assigned to the natural product.

Dedicated to Professor Lars Skattebøl on the occasion of his 65th birthday.

In 1987, Fenical and his co-workers reported the isolation and identification of (*E*)-3-formyl-(2,6,6-trimethyl-2-cyclohexenyl)-3-pentenal (**1**) from a tropical green alga, *Caulerpa ashmeadii*.[2] This seaweed was least preferred by herbivorous fishes, and the ichthyotoxicity of **1** was thought to act as a chemical defense against grazing fishes.[2] The gross structure of **1** was assigned based on an analysis of spectral data,[2] but the absolute configuration of the natural levorotatory **1** remained unknown. In this paper we describe the first enantioselective synthesis of (*R*)- and (*S*)-**1**, which enables us to assign the (*S*)- absolute configuration to naturally occurring **1**.

Scheme 1 shows our synthetic route leading to **1**. Enzymatic resolution of (±)-**2a**, employing pig-liver esterase, to give (*R*)-**2b** and (*S*)-**2a** was the basis for the synthesis.[3] Both enantiomers of **2b** were purified by recrystallization of the corresponding 3,5-dinitrobenzoate **2c** as reported previously.[3] In the present work, the enantiomeric purity of **2c** was conveniently checked by HPLC analysis on a chiral stationary phase, Chiralcel® OJ [cellulose tris(*p*-methylbenzoate)]. The orthoester Claisen rearrangement[3] of (*R*)-**2b** (ca. 99.0 % e.e.) yielded (*S*)-**3**, the enantiomeric purity of which was estimated to be 97.1 % e.e. by GLC analysis on a permethylated β-cyclodextrin column. The transfer of chirality in the Claisen rearrangement must therefore have taken place in a satisfactory manner. Reduction of (*S*)-**3** with lithium aluminium hydride yielded (*S*)-**4**,[3] which was oxidized under Swern conditions[4] to the aldehyde (*S*)-**5**.

The next step was the olefination reaction of (*S*)-**5** to (*S*)-**6**. When the Horner–Emmons reagent, tetramethyl phosphonosuccinate,[5] was employed, (*S*)-**6** and its *Z*-isomer were obtained in a ratio of 1:1. These two isomers exhibited a characteristic difference in chemical shift values of the olefinic proton of the side-chain [δ = 7.07 in (*S*)-**6** and δ = 6.18 in the *Z*-isomer]. Fortunately, the desired *E*-isomer (*S*)-**6** was the only product, when the olefination was executed with a stable ylide, bis(methoxycarbonyl) ethylidenetriphenylphosphorane.[6]

Reduction of (*S*)-**6** with lithium aluminium hydride smoothly yielded the diol (*S*)-**7**, which was oxidized according to Swern[4] to give the target molecule (*S*)-**1**. The overall yield of (*S*)-**1** was 15 % [based on (*R*)-**2b**; six steps]. Analogously, (*R*)-**1** was prepared from (*S*)-**2a**. The synthetic enantiomers of **1** exhibited IR, ^{1}H NMR and ^{13}C NMR spectra in good accord with those of natural **1**. The enantiomeric purities of the enantiomers of **1** could not be determined directly, but were assumed to be at least 97 % e.e., because none of the steps of the synthesis is likely to cause racemization. Both enantiomers of **1** tasted very hot and exerted a paralyzing effect, when tested on the tongue. The enantiomers of polygodial, an insect antifeedant, have also been reported to taste hot.[7]

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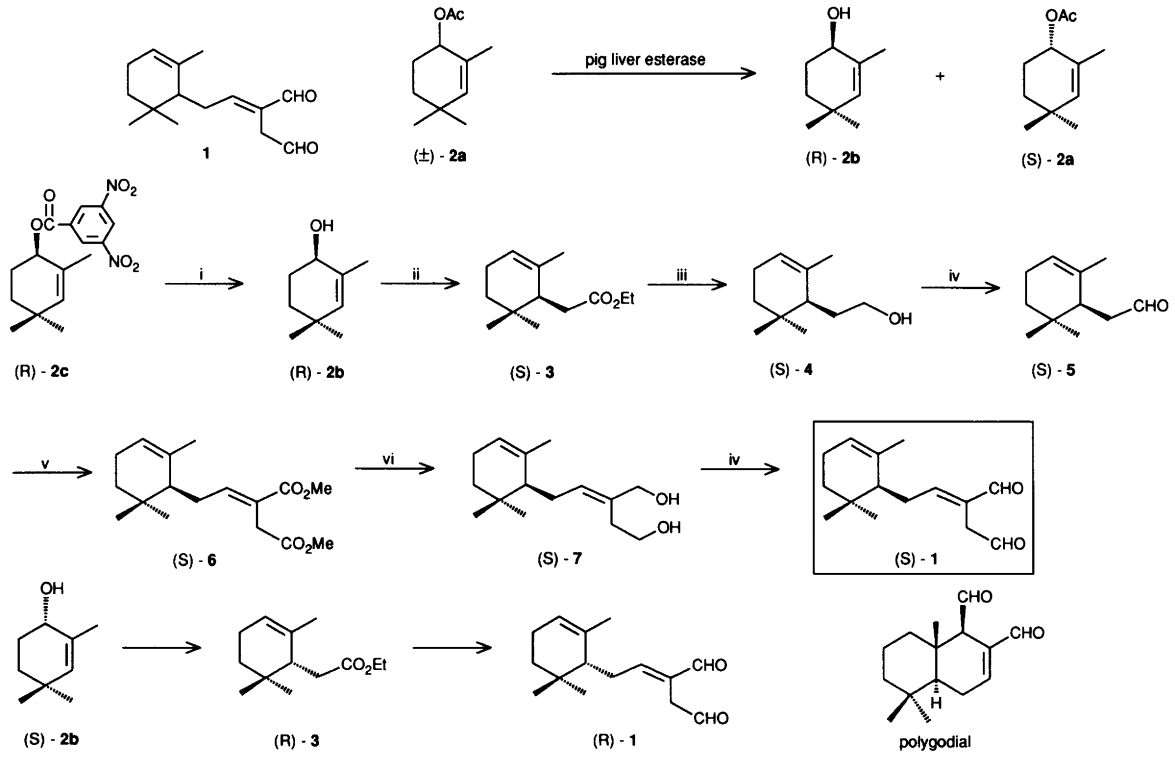

Scheme 1. i, K_2CO_3, $MeOH/CH_2Cl_2$ (95 %); ii, $MeC(OEt)_3$, $EtCO_2H$ (82 %); iii, $LiAlH_4$, THF (85 %); iv, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 (78 % for **4** → **5**; 36 % for **7** → **1**); v, $Ph_3P{=}C(CO_2Me)CH_2CO_2Me$, C_6H_6 (88 %); vi, $LiAlH_4$, Et_2O (82 %).

Finally, the optical rotations of the synthetic samples of **1** were compared with the value reported for naturally occurring **1**: $[\alpha]_D^{25} = -104°$ (chloroform). The specific rotation of (*R*)-**1** was $[\alpha]_D^{21} = +141°$ (chloroform), while that of (*S*)-**1** was $[\alpha]_D^{21} = -138°$ (chloroform). Accordingly, the absolute configuration of the naturally occurring **1** is *S*, although the enantiomeric purity remains obscure. The enantiomers of **1** are now under investigation by Professor M. Hay (University of North Carolina) to determine whether fish can discriminate between the enantiomers.

Experimental

General. IR spectra were measured on neat compounds, unless otherwise indicated, on a Jasco A-102 spectrometer. ^1H NMR spectra were recorded at 90 MHz on a Jeol EX-90 or at 300 MHz on a Bruker AC-300, using either $CDCl_3$ or CCl_4 as the solvent with Me_4Si as an internal standard or C_6H_6 as an external standard. ^{13}C NMR spectra were recorded at 75.5 MHz on a Bruker AC-300, using C_6D_6 as the solvent with C_6H_6 as an internal standard. High resolution mass spectra were obtained on a Jeol DX-303 spectrometer. Optical rotations were determined on a Jasco DIP-140 polarimeter. HPLC analyses were performed on a Shimadzu LC-6A as pump and an SPD-6A as a detector. GLC analyses were performed on a Shimadzu GC-14AD with a flame-ionization detector. CD spectra were recorded on a Jasco J-20C spectropolarimeter. Merck Kieselgel 60 was used for SiO_2 column chromatography. Melting points were taken on a Yanagimoto micro melting point apparatus and are uncorrected. Boiling points are uncorrected.

(R)-*2,4,4-Trimethyl-2-cyclohexenyl 3,5-dinitrobenzoate* (**2c**). To a cooled (5 °C) and magnetically stirred solution of (*R*)-2,4,4-trimethyl-2-cyclohexenol **2b** (6.84 g, 48.9 mmol; prepared by a known method[3]) and 4-(dimethylamino)pyridine (0.48 g, 3.91 mmol) in pyridine (81 ml) was added 3,5-dinitrobenzoyl chloride (13.52 g, 58.6 mmol). After being stirred for 3 h at room temperature, the mixture was cooled to 5 °C, and quenched with water (50 ml). After being stirred for 1 h, the mixture was diluted with water (200 ml) and extracted with dichloromethane (3×100 ml). The organic layer was washed with water (4×100 ml), 2 M hydrochloric acid (4×100 ml), water (2×100 ml), and aqueous sodium hydrogencarbonate (2×100 ml). The extract was dried over anhydrous magnesium sulfate and concentrated *in vacuo* to give crude **2c**. This was recrystallized from diisopropyl ether (200 ml) to give pure **2c**.

Yield 11.2 g (68 %). Light yellow needle-like crystals, m.p. 130.0–131.0 °C [lit.[3] 130–131.5 °C for (*S*)-**2c**]. $[\alpha]_D^{21}$ +122° (*c* 1.04, $CHCl_3$) {lit.[3] $[\alpha]_D^{21}$ −118.5° (*c* 1.04, $CHCl_3$) for (*S*)-**2c**}, Anal. $C_{16}H_{18}N_2O_6$: C, H, N. The IR and ^1H NMR data of (*R*)-**2c** were identical with those reported for (*S*)-**2c**.[3] The enantiomeric purity of **2c** was estimated to be

ca. 99.0 % e.e. by HPLC analysis [column: Chiralcel® OJ [cellulose tris(*p*-methylbenzoate)] 25 cm × 4.6 mm; solvent: *n*-hexane–isopropyl alcohol (60:1); flow rate: 1.0 ml min^{-1}; detected: 254 nm]; t_R 12.1 min (99.5 %) [isomer t_R 17.4 min (0.5 %)].

*Regeneration of (*R*)-2,4,4-trimethyl-2-cyclohexenol* (**2b**) *from* (**2c**). Potassium carbonate (8.63 g, 62.4 mmol) was added to a stirred solution of recrystallized (*R*)-**2c** (11.10 g, 33.2 mmol) in a mixture of methanol (76 ml) and dichloromethane (76 ml). After being stirred for 2 h at room temperature, the mixture was concentrated *in vacuo*. The residue was diluted with water (300 ml) and extracted with diethyl ether (3×150 ml). The organic layer was washed with aqueous sodium hydrogencarbonate (3×150 ml) and brine (150 ml). The extract was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2) to give **2b**.

Yield 4.40 g (95 %). Colorless oil, $[\alpha]_D^{21}$ +94.9 (*c* 1.02, MeOH) {lit.[3] $[\alpha]_D^{21}$ −95.9° (*c* 1.02, MeOH) for (*S*)-**2b**}. The ^1H NMR spectrum of (*R*)-**2b** was identical with that of (*S*)-**2b**.[3]

Ethyl [2,6,6-trimethyl-2-cyclohexenyl]acetate (**3**). (a) (S)-*Isomer*. A solution of (*R*)-**2b** (4.30 g, 30.7 mmol) in distilled triethyl orthoacetate (45 ml) was treated with propanoic acid (0.15 ml). The mixture was stirred and heated at 140–150 °C (bath temperature) with a Dean–Stark trap. After 15.5 h and 22 h of stirring at the same temperature, distilled propanoic acid (0.15 ml each time) was added. Then, after stirring for a further 22 h at the same temperature, the mixture was concentrated *in vacuo*. After dilution with diethyl ether (300 ml), the organic layer was washed with water (2×100 ml), aqueous sodium hydrogencarbonate (100 ml), and brine (100 ml). The extract was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2) to give **3**.

Yield 5.29 g (82 %). Colorless oil, b.p. 146–148 °C/3.3 kPa [lit.[3] b.p. 106–108 °C/1.1 kPa for (*R*)-**3**], n_D^{20} 1.4653, $[\alpha]_D^{22}$ −79.7° (*c* 1.22, MeOH). Anal. $C_{13}H_{22}O_2$: C, H. ^1H NMR ($CDCl_3$): δ 0.84 (3 H, s, CH_3-6′), 0.92 (3 H, s, CH_3-6), 1.00–1.52 (2 H, m, H-5), 1.26 (3 H, t, *J* 7.2 Hz, $CO_2CH_2CH_3$), 1.58–1.72 (3 H, m, CH_3-2), 1.80–2.15 (3 H, m, H-1, 4), 2.15–2.55 (2 H, m, H-2), 4.14 (2 H, q, *J* 7.2 Hz, $CO_2CH_2CH_3$), 5.34 (1 H, br s, H-3). IR: 3040 (w), 2970 (s), 2920 (s), 1735 (s), 1450 (s), 1370 (m), 1350 (m), 1150 (m), 825 (w) cm^{-1}. These spectral data are in good accord with those reported for (*R*)-**3**.[3] The enantiomeric purity of **3** was estimated to be 97.1 % e.e. by GLC analysis [column: PMBCD-TH (permethylated β-cyclodextrin); 50 m×0.25 mm; carrier gas: H_2, inlet pressure: 0.8 kg cm^{-2}; injection temp.: 250 °C; column temp.: 70 °C to 180 °C; program rate: 1 °C min^{-1}], t_R 72.8 min (98.55 %); t_R 74.9 min [1.45 %, (*R*)-isomer]. The enantiomeric purity of (*S*)-**3** was therefore 97.1 % e.e.

(b) (R)-*Isomer*. This compound was prepared by a known method.[3] n_D^{22} 1.4629 (lit.[3] n_D^{22} 1.4641), $[\alpha]_D^{24}$ +80.9° (*c* 1.31, MeOH) {lit.[3] $[\alpha]_D^{21}$ +79.6° (*c* 1.44, MeOH)}. The enantiomeric purity was determined in the same manner as described above. t_R 74.9 min [99.7 %], t_R 72.8 min [0.3 %, (*S*)-isomer]. The enantiomeric purity of (*R*)-**3** was therefore 99.4 % e.e.

2-[(S)-2,6,6-Trimethyl-2-cyclohexenyl]ethanol (**4**). To a cooled (5 °C) and magnetically stirred solution of (*S*)-**3** (3.01 g, 14.3 mmol) in anhydrous tetrahydrofuran (30 ml) was added lithium aluminium hydride (353 mg, 9.30 mmol). After 13.5 h at 25 °C, an additional amount of lithium aluminium hydride (41 mg, 1.08 mmol) was added to the mixture which was stirred for a further 2.5 h at 25 °C. The mixture was cooled to 5 °C, and quenched carefully with water (2.0 ml). Anhydrous magnesium sulfate was added, the solids were filtered off, and the filtrate was concentrated. The residual oil was diluted with dichloromethane (70 ml), washed with brine (20 ml), and dried over anhydrous magnesium sulfate. Following solvent removal, 2.21 g (92 %) of the crude product was purified by column chromatography (SiO_2) to give **4**.

Yield 2.05 g (85 %). Colorless oil, b.p. 139–140 °C/3.6 kPa [lit.[3] b.p. 76–78 °C/0.40 kPa for (*R*)-**4**], n_D^{21} 1.4852, $[\alpha]_D^{22}$ −115° (*c* 1.03, MeOH) {lit.[3] $[\alpha]_D^{21}$ +115.1° (*c* 1.03, MeOH) for (*R*)-**4**}. Anal. $C_{11}H_{20}O$: C, H. ^1H NMR ($CDCl_3$): δ 0.88 (3 H, s, CH_3-6′), 0.91 (3 H, s, CH_3-6′), 0.97–1.79 (5 H, m, H-2, 5′, OH), 1.69 (3 H, m, $W_{1/2}$ 5.0 Hz, CH_3-2′), 1.79–2.12 (3 H, m, H-1′, 4′), 3.68 (2 H, t, *J* 7.3 Hz, H-1), 5.31 (1 H, br s, H-3′). IR: 3340 (s), 2975 (s), 2925 (s), 1660 (w), 1470 (m), 1455 (s), 1385 (m), 1365 (m), 1040 (s), 820 (m) cm^{-1}. These spectral data are in good accord with those reported for (*R*)-**4**.

2-(2,6,6-Trimethyl-2-cyclohexenyl)ethanal (**5**). (a) (S)-*Isomer*. To a cooled (−60 °C) and magnetically stirred solution of oxalyl chloride (0.31 ml, 3.55 mmol) in anhydrous dichloromethane (5 ml) was added dropwise dimethyl sulfoxide (0.51 ml, 7.19 mmol). After 5 min at −60 °C, a solution of (*S*)-**4** (500 mg, 2.98 mmol) in anhydrous dichloromethane (5 ml) was added dropwise over 5 min. The mixture was stirred at the same temperature for 30 min. Triethylamine (2.07 ml, 14.9 mmol) was then added dropwise. The mixture was warmed to 0 °C over 1 h and quenched with water. After dilution with dichloromethane (30 ml), the organic layer was separated and washed with 1 M hydrochloric acid (15 ml), water (2×15 ml), aqueous sodium hydrogencarbonate (15 ml), and brine (15 ml). The extract was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2) to give (*S*)-**5**.

Yield 384 mg (78 %). Colorless oil, n_D^{22} 1.4785, $[\alpha]_D^{21}$ −99.0° (*c* 1.04, $CHCl_3$), Anal. $C_{11}H_{18}O$: C, H. HRMS: Found M^+ 166.1347.Calc. for $C_{11}H_{18}O$ 166.1358. ^1H NMR ($CDCl_3$): δ 0.82 (3 H, s, CH-6′), 0.93 (3 H, s, CH_3-6′), 1.00–1.48 (2 H, m, H-5′), 1.52–1.71 (3 H, m, CH_3-2′), 1.78–2.11 (2 H, m, H-4′), 2.13–2.39 (1 H, m, H-1′), 2.28 (1

H, ddd, *J* 17.6, 7.3, 2.0 Hz, H-2), 2.52 (1 H, ddd, *J* 17.6, 7.3, 2.0 Hz, H-2), 5.39 (1 H, br s, H-3′), 9.83 (1 H, t, *J* 2.0 Hz, CHO). IR: 3040 (w), 2970 (s), 2920 (s), 2720 (m), 1720 (s), 1450 (m), 1385 (m), 1365 (m), 820 (m) cm^{-1}.

(b) (R)-*Isomer*. In the same manner as described above, (*R*)-**4** (1.000 g, 5.95 mmol) gave (*R*)-**5**.

Yield 485 mg (49%). Colorless oil, n_D^{21} 1.4785, $[\alpha]_D^{21}$ +100° (*c* 1.04, $CHCl_3$), Anal. $C_{11}H_{18}O$: C, H. HRMS: Found M^+ 166.1371. Calc. for $C_{11}H_{18}O$ 166.1358. Its NMR and IR spectra were indistinguishable from those of (*S*)-**5**.

Methyl 3-methoxycarbonyl-5-(2,6,6-trimethyl-2-cyclohexenyl)-3-pentenoate (**6**). (a) (S)-*Isomer*. To a solution of (*S*)-**5** (290 mg, 1.75 mmol) in benzene (6 ml) was added 1,2-bis-(methoxycarbonyl)ethylidenetriphenylphosphorane (2.128 g, 5.24 mmol) at room temperature, and then the mixture was refluxed for 11 h under an atmosphere of Ar. The mixture was diluted with ethyl acetate (6 ml) and filtered. The filtrate was washed with water (2×5 ml) and brine (5 ml). The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residual oil was purified by column chromatography (SiO_2) to give (*S*)-**6**.

Yield 451 mg (88%). Colorless oil, n_D^{21} 1.4945, $[\alpha]_D^{22}$ −117° (*c* 1.03, $CHCl_3$). Anal. $C_{17}H_{26}O_4$: C, H. ^{1}H NMR ($CDCl_3$): δ 0.86 (3 H, s, CH_3-6′), 0.89 (3 H, s, CH_3-6′), 1.05–2.17 (5 H, m, H-1′, 4′, 5′), 1.66 (3 H, m, $W_{1/2}$ 5.0 Hz, CH_3-2′), 2.31 (2 H, dd, *J* 7.3, 5.1 Hz, H-5), 3.37 (2 H, s, H-2), 3.68 (3 H, s, CO_2CH_3-3), 3.75 (3 H, s, CO_2CH_3-1), 5.39 (1 H, br s, H-3′), 7.07 (1 H, t, *J* 3.3 Hz, H-4). IR: 3040 (w), 2970 (s), 2920 (s), 2880 (s), 1740 (s), 1715 (s), 1645 (m), 1435 (s), 830 (m) cm^{-1}.

(b) (R)-*Isomer*. In the same manner as described above, (*R*)-**5** (480 mg, 2.89 mmol) gave (*R*)-**6**.

Yield 782 mg (92%). Colorless oil, n_D^{21} 1.4945, $[\alpha]_D^{20}$ +120° (*c* 1.03, $CHCl_3$), Anal. $C_{17}H_{26}O_4$: C, H. Its NMR and IR spectra were indistinguishable from those of (*S*)-**6**.

3-Hydroxymethyl-5-(2,6,6-trimethyl-2-cyclohexenyl)-3-penten-1-ol (**7**). (a) (S)-*Isomer*. To a cooled (5 °C) and magnetically stirred solution of methyl (*S*)-**6** (350 mg, 1.19 mmol) in anhydrous diethyl ether (7 ml) was added lithium aluminium hydride (69 mg, 1.82 mmol). After being stirred for 2 h at 24 °C, the mixture was cooled to 0 °C and quenched carefully with water (1.0 ml). The mixture was diluted with ethyl acetate (50 ml). The organic layer was washed with 2 M hydrochloric acid (10 ml), water (2×10 ml), aqueous sodium hydrogencarbonate (10 ml), and brine (10 ml). The extract was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2) to give (*S*)-**7**.

Yield 227 mg (82%). Colorless oil, n_D^{22} 1.5101, $[\alpha]_D^{21}$ −120° (*c* 0.97, $CHCl_3$), Anal. $C_{15}H_{26}O_2$: C, H. ^{1}H NMR ($CDCl_3$): δ 0.88 (6 H, s, CH_3-6′), 1.00–1.77 (3 H, m, H-1′, 5′), 1.66 (3 H, m, $W_{1/2}$ 5.6 Hz, CH_3-2′), 1.80–2.10 (2 H, m, H-4′), 2.18 (2 H, dd, *J* 7.0, 6.2 Hz, H-5), 2.43 (2 H, t, *J* 5.9 Hz, H-2), 2.69 (2 H, br s, OH), 3.72 (2 H, t, *J* 5.9 Hz, H-1), 4.03 (2 H, br s, CH_2OH-3), 5.27–5.42 (1 H, br s, H-3′), 5.63 (1 H, t, *J* 7.0 Hz, H-4). IR: 3325 (s), 3040 (w), 2970 (s), 2930 (s), 2880 (s), 1450 (s), 1380 (m), 1360 (m), 1045 (s), 815 (w) cm^{-1}.

(b) (R)-*Isomer*. In the same manner as described above, (*R*)-**6** (502 mg, 1.71 mmol) gave (*R*)-**7**.

Yield 388 mg (82%). Colorless oil, n_D^{22} 1.5094, $[\alpha]_D^{22}$ +122° (*c* 0.98, $CHCl_3$). Anal. $C_{15}H_{26}O_2$: C, H. Its NMR and IR spectra were indistinguishable from those of (*S*)-**7**.

3-Formyl-5-(2,6,6-trimethyl-2-cyclohexenyl)-3-pentenal (**1**). (a) (S)-*Isomer*. To a cooled (−60 °C) and magnetically stirred solution of oxalyl chloride (0.24 ml, 2.73 mmol) in anhydrous dichloromethane (5 ml) was added dropwise a solution of dimethyl sulfoxide (0.39 ml, 5.46 mmol) in anhydrous dichloromethane (2 ml). After 5 min at −60 °C, a solution of (*S*)-**7** (213 mg, 0.91 mmol) in anhydrous dichloromethane (3 ml) was added dropwise over 5 min. The mixture was stirred at the same temperature for 30 min. Triethylamine (1.27 ml, 9.10 mmol) was then added dropwise. The mixture was warmed to 0 °C over 1 h and quenched with water (2 ml). After dilution with dichloromethane (30 ml), the organic layer was washed with 2 M hydrochloric acid (10 ml), water (10 ml), aqueous sodium hydrogencarbonate (10 ml), and brine (10 ml). The extract was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2; repeated twice) to give (*S*)-**1**.

Yield 76 mg (36%). Oil, n_D^{21} 1.5195, $[\alpha]_D^{21}$ −138° (*c* 1.01, $CHCl_3$) {Lit.[2] $[\alpha]_D^{25}$ −104° (*c* 1.0, $CHCl_3$)}, CD (*c* 0.02, EtOH) λ_{ext} 311 nm (Δε −0.19). Anal. $C_{15}H_{22}O_2$: C, H. HRMS: Found M^+ 234.1619. Calc. for $C_{15}H_{22}O_2$ 234.1619. ^{1}H NMR (300 MHz, CCl_4): δ 0.88 (3 H, s, CH_3-6′), 0.91 (3 H, s, CH_3-6′), 1.08–1.47 (2 H, m, H-5′), 1.68 (3 H, br d, *J* 1.6 Hz, CH_3-2′), 1.74–1.85 (1 H, m, H-1′), 1.94–2.09 (2 H, m, H-4′), 2.37–2.47 (2 H, m, H-5), 3.27 (1 H, d, *J* 16.0 Hz, H-2), 3.37 (1 H, d, *J* 16.0 Hz, H-2), 5.41 (1 H, br s, H-3′), 6.77 (1 H, t, *J* 7.0 Hz, H-4), 9.38 (1 H, s, CHO-3), 9.52 (1 H, t, *J* 1.6 Hz, CHO-1). ^{13}C NMR (C_6D_6): δ 23.2, 23.5, 27.5 (×2), 30.5, 31.8, 32.7, 39.4, 49.3, 122.4, 134.7, 135.0, 157.9, 192.9, 196.2. IR (CCl_4): 3045 (w), 2975 (s), 2930 (s), 2875 (s), 2720 (m), 1735 (s), 1690 (s), 1640 (m), 1450 (m), 1385 (m), 1365 (m), 1160 (m) cm^{-1}.

(b) (R)-*Isomer*. In the same manner as described above, (*R*)-**7** (331 mg, 1.39 mmol) gave (*R*)-**1**.

Yield 81 mg (25%). Oil, n_D^{20} 1.5194, $[\alpha]_D^{21}$ +141° (*c* 1.04, $CHCl_3$), CD (*c* 0.03, EtOH) λ_{ext} 311 nm (Δε +0.14). Anal. $C_{15}H_{22}O_2$: C, H. HRMS: Found M^+ 234.1621. Calc. for $C_{15}H_{22}O_2$ 234.1619. Its NMR and IR spectra were indistinguishable from those of (*S*)-**1**. The spectral data of both (*R*)- and (*S*)-**1** were in good accord with those of naturally occurring **1**.

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References

1. Part XX. Kitahara, T., Kiyota, H., Kurata, H. and Mori, K. *Tetrahedron 47* (1991) 1649.
2. Paul, V. J., Littler, M. M., Littler, D. S. and Fenical, W. *J. Chem. Ecol. 13* (1987) 1171.
3. Mori, K. and Puapoomchareon, P. *Liebigs Ann. Chem.* (1991) 1053.
4. Mancuso, A. J., Huang, S.-L. and Swern, D. *J. Org. Chem. 43* (1978) 2480.
5. Harvey, R. G. *Tetrahedron 22* (1966) 2561.
6. Cameron, A. F., Duncanson, F. D., Freer, A. A., Armstrong, V. W. and Ramage, R. *J. Chem. Soc., Perkin Trans. 2* (1975) 1030.
7. Mori, K. and Watanabe, H. *Tetrahedron 42* (1986) 273.

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