Synthesis of Mono- and Sesquiterpenoids, XXVII[◇]

Synthesis of (6*S*,7*S*)-7-Hydroxy-6,11-cyclofarnes-3(15)-en-2-one, the Opposite Enantiomer of the Antibacterial Sesquiterpene from *Premna oligotricha*, and the (*R*) Enantiomer of Ancistrodial, the Defensive Sesquiterpene from *Ancistrotermes cavithorax*

Sayo Horiuchi, Hirosato Takikawa, and Kenji Mori*

Department of Chemistry, Faculty of Science, Science University of Tokyo,
Kagurazaka 1–3, Sinjuku-ku, Tokyo 162-8601, Japan
Fax: (internat.) +81-3/3235-2214

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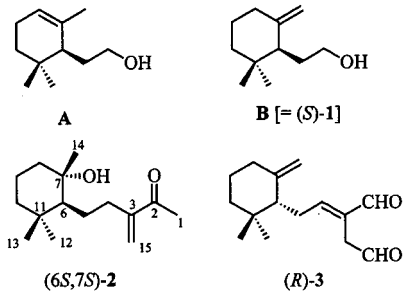
The absolute configuration of the antibacterial sesquiterpene, 7-hydroxy-6,11-cyclofarnes-3(15)-en-2-one (**2**), was determined as (6*R*,7*R*) by the synthesis of its opposite enantiomer (6*S*,7*S*)-**2** from (*S*)-2-(2,2-dimethyl-6-methylenecyclohexyl)ethanol (**1**). This versatile building block (*S*)-**1** was also converted to (*R*)-ancistrodial (**3**).

In 1991, Mori and Puapoomchareon reported a synthesis of the enantiomers of **A** (Scheme 1) employing enzymatic kinetic resolution as the key step[1]. Subsequent works of ours proved the versatile utility of **A** and its enantiomer as the chiral and nonracemic building blocks in sesquiterpene synthesis[2]. It occurred to us that the enantiomers of **B** must be as useful building blocks as the enantiomers of **A**. Accordingly, **B** [= (*S*)-**1**] and its enantiomer were prepared by enzymatic resolution of the corresponding racemate (±)-**B**. Their usefulness was ascertained by the conversion of (*S*)-**1** to (*S*)-γ-coronal, the ambergris fragrance[3]. The present paper reports further confirmation of the usefulness of (*R*)- and (*S*)-**1** as building blocks in terpene synthesis.

Scheme 1. Structures of the building blocks and target molecules



Our first target molecule was (6*S*,7*S*)-7-hydroxy-6,11-cyclofarnes-3(15)-en-2-one (**2**). This sesquiterpene was isolated by Waterman and his coworkers as a new antibacterial compound from the aerial part of *Premna oligotricha*[4]. Its proposed structure, however, was incorrect with regard to the relative stereochemistry. Our synthetic works in 1996 led to the conclusion that the sesquiterpene must be either (6*S*,7*S*)-**2** or its opposite enantiomer[5]. Conversion of (*S*)-**1** to (6*S*,7*S*)-**2** as shown in Scheme 2 proved it to be the opposite enantiomer of the natural product. The synthetic route leading to (6*S*,7*S*)-**2** was essentially the same as that employed for the synthesis of (±)-**2**[5]. Accordingly, the chiral building block (*S*)-**1** was converted to the known iodide (*S*)-**4**[3], with which methyl acetoacetate was alkylated to furnish (2*RS*,1′*S*)-**5**. Epoxidation of **5** with *m*-chloroperbenzoic acid (MCPBA) afforded (2*RS*,1′*S*,2′*RS*)-**6** as a stereoisomeric mixture. Reduction of **6** with lithium aluminum hydride ($LiAlH_4$) was followed by treatment with *N*-bromosuccinimide (NBS) in aqueous 1,2-dimethoxyethane (DME) to give a stereoisomeric mixture of the dihydroxy ketone (2*RS*,1′*S*,2′*RS*)-**7**. Selective tosylation of the primary hydroxy group of **7** yielded the monotosylate (2*RS*,1′*S*,2′*RS*)-**8** as a stereoisomeric mixture. This was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give a mixture of (6*S*,7*S*)-**2** and its stereoisomer (6*S*,7*R*)-**9**. These two products were separated by silica-gel chromatography to afford the oily (6*S*,7*S*)-**2**, whose enantiomeric purity was 97% e.e. as determined by GLC analysis on a chiral stationary phase. The IR, ^{1}H- and ^{13}C-NMR spectra of (6*S*,7*S*)-**2** were identical with those of (±)-**2**[5]. The overall yield of (6*S*,7*S*)-**2** was 15% based on (*S*)-γ-cyclohomogeraniol (**1**, 8 steps). The specific rotation of (6*S*,7*S*)-**2** was $[\alpha]_D^{24} = +6.40$ (c = 0.10, $CHCl_3$). Because the naturally occurring enantiomer of **2** was reported to show $[\alpha]_D = -17$ (c = 0.1, $CHCl_3$), the natural product must be (6*R*,7*R*)-**2**. The reason for the discrepancy between the magnitude of the specific rotation of the natural product and that of (6*S*,7*S*)-**2** is unclear.

Our second target was (*R*)-ancistrodial (**3**). Ancistrodial (**3**) was isolated in 1978 by Baker et. al.[6] as the defensive

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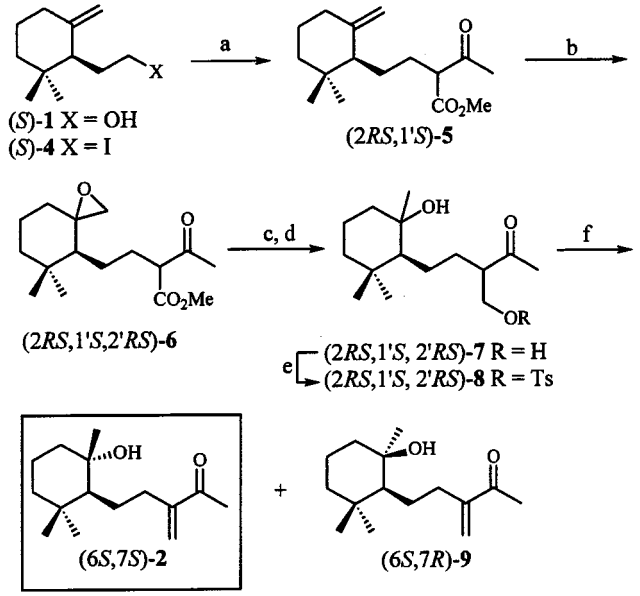
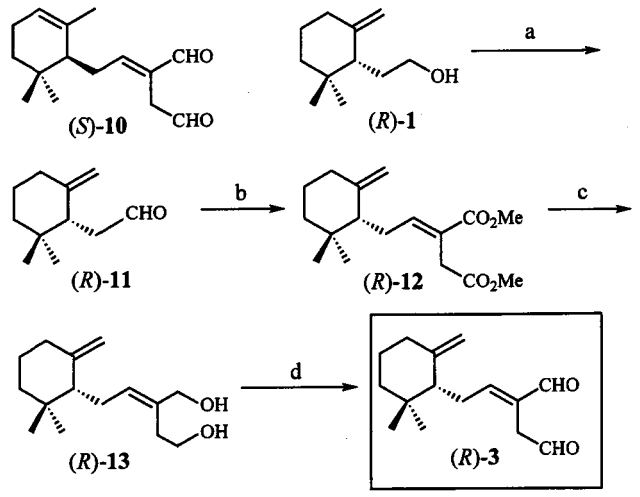
Scheme 2. Synthesis of (6*S*,7*S*)-**2**[a]



[a] Reagents: (a) $MeCOCH_2CO_2Me$, K_2CO_3, Me_2CO/DMF (79%); (b) MCPBA, CH_2Cl_2 (72%); (c) $LiAlH_4$, Et_2O; (d) NBS, DME/H_2O [59% based on (2*RS*,1′S,2′*RS*)-**6**]; (e) TsCl, C_5H_5N (quant.); (f) DBU, toluene, then chromatography [44% for (6*S*,7*S*)-**2**, 44% for (6*S*,7*R*)-**9**].

secretion of the west African termite *Ancistrotermes cavithorax*. The absolute configuration of ancistrodial[6] still remains unknown due to the scarcity of the isolated material, although Vidari et. al.[7] recently reported a synthesis of (*R*)-**3**. As shown in Scheme 3, a short synthesis of (*R*)-**3** was achieved by employing (*R*)-**1** as the starting material. The synthesis followed a similar route to that employed in our 1992 synthesis of the marine sesquiterpene (*S*)-**10**[8]. Swern oxidation of (*R*)-**1**[3] gave the corresponding aldehyde (*R*)-**11**. The olefination reaction of (*R*)-**11** with 1,2-bis(methoxycarbonyl)ethylidenetriphenylphosphorane furnished the diester (*R*)-**12**, which was reduced with $LiAlH_4$ to afford the diol (*R*)-**13**. Finally, treatment of (*R*)-**13** with Dess−Martin periodinane[9] gave the desired product, (*R*)-ancistrodial (**3**), $[\alpha]_D^{24} = -22.0$ (*c* = 0.70, CH_2Cl_2). The overall yield of (*R*)-**3** was 46% based on (*R*)-**1** (5 steps).

Scheme 3. Synthesis of (*R*)-**3**[a]



[a] Reagents: (a) $(COCl)_2$, DMSO, CH_2Cl_2; Et_3N (89%); (b) $Ph_3P{=}C(CO_2Me)CH_2CO_2Me$, C_6H_6 (62%); (c) $LiAlH_4$, Et_2O; (d) Dess−Martin periodinane, C_5H_5N/CH_2Cl_2 [83% based on (*R*)-**12**].

In conclusion, short and efficient syntheses of both (6*S*,7*S*)-**2** and (*R*)-**3** were achieved by starting from the chiral building block (*S*)- or (*R*)-**1**. The absolute (6*R*,7*R*) configuration was assigned to the sesquiterpene **2** of *Premna oligotoricha*.

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Experimental Section

General: IR: Hitachi Perkin−Elmer 1640. − ^{1}H NMR: Jeol JNM-EX 90A (90 MHz), Bruker DPX 300 (300 MHz), TMS at $\delta_H = 0.00$ or $CHCl_3$ at $\delta_H = 7.26$ as an internal standard. − ^{13}C NMR: Bruker DPX 300 (75.5 MHz), $CDCl_3$ at $\delta_C = 77.0$ as an internal standard. − MS: Jeol JMS-SX 102A and Hitachi M-80B. − Optical rotation: Jasco DIP-1000. − CC: Merck Kieselgel 60 Art 1.07734.

Methyl (2RS,1′S)-2-[2-(2,2-Dimethyl-6-methylenecyclohexyl)-ethyl]-3-oxobutanoate [(2*RS*,1′*S*)-**5**]**:** To a solution of (*S*)-**4** (1.17 g, 6.11 mmol) in dry acetone (50 ml) was added potassium carbonate (2.38 g, 17.2 mmol), and the mixture was stirred vigorously. Then methyl acetoacetate (1.00 g, 8.61 mmol) was added followed by *N*,*N*-dimethylformamide (2 ml). After the addition, the reaction mixture was heated at 68°C for 20 h, then cooled to room temp., diluted with water and extracted several times with diethyl ether. The combined ethereal extracts were washed with water and a saturated aqueous ammonium chloride solution, and dried with anhydrous magnesium sulfate. After concentration in vacuo, the residue was chromatographed on silica gel (15.0 g, hexane/ethyl acetate, 80:1) to give a mixture of (2*RS*,1′*S*)-**5** and *O*-alkylation product (1.41 g). To this mixture was added a solution of 3% *p*-toluenesulfonic acid in methanol (30 ml). The mixture was heated at 55°C for 50 min, subsequently cooled to room temp., diluted with water and extracted several times with diethyl ether. The combined ethereal extracts were washed with a saturated aqueous sodium hydrogen carbonate solution and dried with anhydrous magnesium sulfate. After concentration of the solution in vacuo, the residue was chromatographed on silica gel (20 g, hexane/ethyl acetate, 80:1) to give 238 mg (14%) of (*S*)-**1** and 1.29 g (79%) of (2*RS*, 1′*S*)-**5** as a colorless oil. − $n_D^{23} = 1.4775$. − $[\alpha]_D^{24} = +5.2$ (*c* = 0.98, $CHCl_3$). − IR (film): $\tilde{\nu} = 1745$ cm^{-1} (s, C=O), 1715 (s, C=O), 1640 (m). − ^{1}H NMR ($CDCl_3$, 90 MHz): $\delta = 0.80$ (s, 3 H, 2″-CH_3), 0.88 (s, 3 H, 2″-CH_3), 1.13−2.14 (m, 11 H, 1′, 2′, 3″, 4″, 5″-H_2, 1″-H), 2.21 (s, 3 H, CH_3C=O), 3.40 (m, 1 H, 2-H), 3.73 (s, 3 H, CH_3O), 4.58 (br. d, *J* = 2.0 Hz, 1 H, C=CH_aH_b), 4.81 (br. s, 1 H, C=CH_aH_b). − $C_{16}H_{23}O_3$ (266.4): calcd. C 72.14, H 9.84; found C 71.58, H 9.50.

Methyl (2RS,1′R,2′RS)-2-[2-(2-Epoxymethylene-6,6-dimethylcyclohexyl)ethyl]-3-oxobutanoate [(2*RS*,1′*R*,2′*RS*)-**6**]: MCPBA (80%, 1.46 g, 7.75 mmol) was added carefully to a stirred and ice-cooled solution of (2*RS*,1′*S*)-**5** (966 mg, 3.63 mmol) in dry dichloromethane (20 ml). The reaction mixture was allowed to warm to room temp., stirred for 6 h, diluted with a saturated aqueous sodium hydrogen carbonate solution, and extracted several times with diethyl ether. The combined ethereal extracts were washed with 0.06 M sodium hydroxide and a saturated aqueous sodium

hydrogen carbonate solution, and dried with anhydrous magnesium sulfate. After concentration of the solvent in vacuo, the residue was chromatographed on silica gel (18 g, hexane/ethyl acetate, 50:1) to afford 820 mg (80%) of (2*RS*,1′*R*,2′*RS*)-**6** as a colorless oil. − n_D^{24} = 1.4773. − $[\alpha]_D^{24}$ = −3.8 (*c* = 0.98, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 1745 cm^{-1} (vs, C=O), 1715 (vs, C=O). − ^1H NMR ($CDCl_3$, 90 MHz): δ = 0.80, 0.91, 1.00 and 1.10 (s × 4, total 6 H, 6″-CH_3), 1.10−2.02 (m, 11 H, 1′, 2′, 3″, 4″, 5″-H_2, 1″-H), 2.22 (s, 3 H, CH_3C=O), 2.47−2.65 (m, 2 H, CH_2O), 3.30−3.60 (m, 1 H, 2-H), 3.65−3.94 (m, 3 H, CH_3O). − $C_{16}H_{26}O_4$ (282.4): calcd. C 68.06, H 9.28; found C 67.70, H 9.46.

(3RS,1′S,2′RS)-3-Hydroxymethyl-5-(2-hydroxy-2,6,6-trimethylcyclohexyl)-2-pentanone [(3*RS*,1′*S*,2′*RS*)-**7**]: A solution of (2*RS*,1′*R*,2′*RS*)-**6** (810 mg, 2.82 mmol) in dry diethyl ether (15 ml) was added dropwise to a stirred and ice-cooled suspension of $LiAlH_4$ (280 mg, 7.18 mmol) in dry diethyl ether (15 ml) at 0°C over 2 h. Then the reaction mixture was allowed to warm to room temp. and heated under reflux. After stirring for 2 h, it was cooled to 0−5°C, and the excess reagent was destroyed by cautious addition of water (0.3 ml), 15% aqueous sodium hydroxide solution (0.3 ml), and water (0.9 ml). The mixture was filtered through a Celite pad. The filter cake was washed with tetrahydrofuran. Evaporation of the solvent of the combined filtrate and washings in vacuo gave 510 mg of the diol (quant.). − IR (film): $\tilde{\nu}$ = 3380 cm^{-1} (br. s, OH). This was dissolved in DME containing 10% of water (15 ml). To this solution, NBS (530 mg, 2.98 mmol) was added, and the reaction mixture was stirred for 19 h at room temp. After the addition of a small amount of sodium hydrogen carbonate, the mixture was concentrated in vacuo, and the residue was diluted with water. The solution was extracted several times with ethyl acetate. The combined extracts were washed with diluted hydrochloric acid and a saturated aqueous sodium hydrogen carbonate solution, and dried with anhydrous magnesium sulfate. After concentration of the solvent in vacuo, the residue was chromatographed on silica gel (6.0 g, hexane/ethyl acetate, 5:1) to afford 426 mg (59%) of (2*RS*,3*RS*,1′*S*,2′*RS*)-**7** as a colorless oil. − n_D^{24} = 1.4999. − $[\alpha]_D^{24}$ = +6.90 (*c* = 1.03, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3440 cm^{-1} (br. s, OH), 1715 (s, C=O). − ^1H NMR ($CDCl_3$, 90 MHz): δ = 0.80, 0.85, 0.98 and 1.10 (s × 4, total 6 H, 6′-CH_3), 1.10−1.24 (m, 3 H, 2′-CH_3), 1.25−2.05 (m, 13 H, 3′, 4′, 4, 5′, 5-H_2, CH_2OH, 6′-OH, 1′-H), 2.23 (s, 3 H, CH_3C=O), 2.59−2.92 (m, 1 H, 3-H), 3.80 (br. d, 2 H, *J* = 7.0 Hz, CH_2O). − This was employed in the next step without further purification.

(3RS,1′S,2′RS)-5-(2-Hydroxy-2,6,6-trimethylcyclohexyl)-3-tosyloxymethyl-2-pentanone [(3*RS*,1′*S*,2′*RS*)-**8**]: To an ice-cooled solution of (2*RS*,3*RS*,1′*S*,2′*RS*)-**7** (270 mg, 1.05 mmol) in dry pyridine (20 ml) was added *p*-toluenesulfonyl chloride (270 mg, 1.58 mmol), and the reaction mixture was stirred at 0−4°C for 17 h. It was then diluted with water and extracted several times with diethyl ether. The combined ethereal extracts were washed with water, a saturated aqueous copper sulfate solution, water and brine, and dried with anhydrous magnesium sulfate. After concentration of the solvent in vacuo, the residue was chromatographed on silica gel (4.0 g, hexane/ethyl acetate, 5:1) to give 483 mg (quant.) of (2*RS*,3*RS*,1′*S*,2′*RS*)-**8** as a colorless oil. − IR (film): $\tilde{\nu}$ = 3540 cm^{-1} (br. m, OH), 1715 (s, C=O), 1365 (s,O=S=O), 1180 (vs, O=S=O). − ^1H NMR ($CDCl_3$, 90 MHz): δ = 0.78−0.98 (m, total 6 H, 6″-CH_3), 1.10−1.92 (m, 15 H, 2′-CH_3, 4, 5, 3′, 4′, 5′-H_2, 1′-H, 2′-OH) 2.05 and 2.18 (s × 2, 3 H, CH_3C=O), 2.34 and 2.45 (s × 2, 3 H, C*H*$_3$-Ar), 2.75−3.04 (m, 1 H, 2-H), 4.04−4.63 (m, 2 H, CH_2O), 7.38 (br. d, *J* = 8.4 Hz, 2 H, *H*-Ar), 7.78 (br. d, *J* = 8.4 Hz, 2 H, *H*-Ar). − This was employed in the next step without further purification.

(6S,7S)-7-Hydroxy-6,11-cyclofarnes-3(15)-en-2-one [(6*S*,7*S*)-**2**]: To an ice-cooled solution of (2*RS*,3*RS*,1′*S*,2′*RS*)-**8** (483 mg, 1.05 mmol) in toluene (15 ml) was added DBU (110 mg, 1.17 mmol) , and the reaction mixture was stirred at room temp. for 18 h. Then it was diluted with water and extracted several times with diethyl ether. The combined ethereal extracts were washed with a saturated aqueous sodium hydrogen carbonate solution and brine, and dried with anhydrous magnesium sulfate. After concentration of the solvent in vacuo, the residue was chromatographed on silica gel (10 g, hexane/ethyl acetate, 20:1→5:1) to furnish 123 mg (44%) of (6*S*,7*S*)-**9** and 123 mg (44%) of (6*S*,7*R*)-**2** as colorless oils. − (6*S*,7*S*)-**2**: − n_D^{24} = 1.4984. − $[\alpha]_D^{24}$ = +6.40 (*c* = 0.10, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3475 cm^{-1} (br. m, OH), 2930 (vs, C−H), 2865 (s), 1680 (vs, C=O), 1625 (s), 1460 (m), 1365 (s). − ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.87 (s, 3 H, 12-CH_3), 0.94 (s, 3 H, 13-H_2), 1.20 (s, 3 H, 14-CH_3), 1.31−1.80 (m, 9 H, 5, 8, 9, 10-H_2, 6-H), 2.33 (s, 3 H, CH_3C=O), 2.16−2.50 (m, 2 H, 4-H_2), 5.81 (s, 1 H, C=CH_aH$_b$), 6.00 (s, 1 H, C=C$H_a$$H_b$). − ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 20.4 (C-9), 21.2 (C-12), 23.3 (C-14), 25.5 (C-5), 25.9 (C-1), 32.7 (C-13), 34.2 (C-4), 35.3 (C-11), 41.4 (C-10), 43.0 (C-8), 56.9 (C-6), 74.1 (C-7), 125.3 (C-15), 149.7 (C-3), 200.3 (C-2). − $C_{15}H_{26}O_2$ (238.4): calcd. C 75.58, H 11.00; found C 75.70, H 10.95. (6*S*,7*R*)-**9**: ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.77 (s, 3 H, 12-CH_3), 0.94 (s, 3 H, 13-H_2), 1.16 (s, 3 H, 14-CH_3), 1.21−1.60 (m, 9 H, 5, 8, 9, 10-H_2, 6-H), 2.33 (s, 3 H, CH_3C=O), 2.25−2.60 (m, 2 H, 4-H_2), 5.80 (s, 1 H, C=CH_aH$_b$), 5.99 (s, 1 H, C=C$H_a$$H_b$). − ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 18.2 (C-9), 21.4 (C-12), 25.0 (C-14), 25.8 (C-5), 30.7 (C-1), 32.0 (C-13), 34.2 (C-4), 34.7 (C-11), 41.2 (C-10), 41.7 (C-8), 53.8 (C-6), 73.0 (C-7), 124.9 (C-15), 149.6 (C-3), 199.7 (C-2).

(R)-2-(2,2-Dimethyl-6-methylenecyclohexyl)ethanal [(*R*)-**11**] : To a cooled and stirred solution of oxalyl chloride (0.27 ml, 3.03 mmol) in dry dichloromethane (3 ml) was added dropwise dimethyl sulfoxide (0.36 ml, 5.06 mmol) at −60°C. After 5 min at −60°C, a solution of (*R*)-**1** (340 mg, 2.02 mmol) in dry dichloromethane (2 ml) was added dropwise over 5 min. The mixture was stirred at the same temp. for 30 min. Triethylamine (1.10 ml, 10.1 mmol) was then added dropwise. The mixture was warmed to 0°C over 1 h, diluted with water, and extracted several times with dichloromethane. The combined extracts were washed with 1 M hydrochloric acid, water, a saturated aqueous sodium hydrogen carbonate solution and brine, and dried with anhydrous magnesium sulfate. After concentration in vacuo, the residue was chromatographed on silica gel (6.0 g, hexane/ethyl acetate, 50:1) to afford 273 mg (83%) of (*R*)-**11** as a colorless oil. −n_D^{24} = 1.4774. − $[\alpha]_D^{24}$ = −44.6 (*c* = 1.05, CH_2Cl_2). − IR (film): $\tilde{\nu}$ = 2715 cm^{-1} (w, CHO), 1725 (s, C=O), 1645 (m, C=C). − ^1H NMR ($CDCl_3$, 90 MHz): δ = 0.79 (s, 3 H, 2′-CH_3), 0.98 (s, 3 H, 2′-CH_3), 1.04−2.24 (m, 7 H, 3′, 4′, 5′-H_2, 1′-H), 2.48 (d, *J* = 1.5 Hz, 2 H, CH_2C=O), 4.52 (br. s, 1 H, C=CH_aH$_b$), 4.80 (br. s, 1 H, C=C$H_a$$H_b$), 9.62 (t, *J* = 2.0 Hz, 1 H, CHO). − This was employed in the next step without further purification.

Methyl (3E,1′R)-5-(2,2-Dimethyl-6-methylenecyclohexyl)-3-methoxycarbonyl-3-pentenoate [(3*E*,1′*R*)-**12**]: To a solution of (*R*)-**11** (273 mg, 1.64 mmol) in benzene (15 ml) was added 1,2-bis(methoxycarbonyl)ethylidenetriphenylphosphorane (2.0 g, 5.30 mmol) at room temp., and the reaction mixture was refluxed for 12 h under Ar. Then it was diluted with ethyl acetate and filtered. The filtrate was washed with water and brine. The organic layer was dried with anhydrous magnesium sulfate. After evaporation of the solvent in vacuo, the residue was chromatographed on silica gel (6.0 g, hexane/ethyl acetate, 150:1) to afford 300 mg (62%) of (3*E*,1′*R*)-**12** as a colorless oil. − n_D^{24} = 1.4980. − $[\alpha]_D^{24}$ = −18.2 (*c* = 1.00,

CH_2Cl_2). – IR (film): $\tilde{\nu}$ = 2865 cm^{-1} (m, C=H), 1745 (s, C=O), 1715 (s, C=O), 1645 (m, C=C), 1260 (s). – ^1H NMR ($CDCl_3$, 90 MHz): δ = 0.83 (s, 3 H, 2-CH_3), 0.95 (s, 3 H, 2-CH_3), 1.25–2.42 (m, 9 H, 5, 3′, 4′, 5′-H_2, 1′-H), 3.36 (s, 3 H, 2-H_2), 3.69 and 3.73 (s × 2, 6 H, OCH_3 × 2), 4.52 (br. s, 1 H, C=C$H_a$$H_b$), 4.80 (s, 1 H, C=C$H_a$$H_b$). – $C_{17}H_{26}O_4$ (294.4) : calcd. C 69.36, H 8.90; found C 69.52, H 9.35.

(3E,1′R)-5-(2,2-Dimethyl-6-methylenecyclohexyl)-3-hydroxymethyl-3-penten-1-ol [(3*E*,1′*R*)-**13**]: A solution of (3*E*,1′*R*)-**12** (200 mg, 0.68 mmol) in dry diethyl ether (5 ml) was added dropwise to an ice-cooled suspension of $LiAlH_4$ (3.0 mg, 0.81 mmol) in dry diethyl ether (5 ml) at 0–5°C. The reaction mixture was allowed to warm to room temp. and stirred for 2 h. It was then cooled to 0–5°C, and the excess reagent was destroyed by cautious addition of water (1 ml). The mixture was filtered through a Celite pad. The filter cake was washed with tetrahydrofuran. The reaction mixture was diluted with ethyl acetate. The organic layer was washed with 1 M hydrochloric acid, water and brine, and dried with anhydrous magnesium sulfate. After evaporation of the solvent in vacuo, the residue was chromatographed on silica gel (5.0 g, hexane/ethyl acetate, 5:1) to afford 150 mg (93%) of (3*E*,1′*R*)-**13** as a colorless oil. – n_D^{24} = 1.4774. – $[\alpha]_D^{24}$ = –18.9 (*c* = 0.60, CH_2Cl_2). – IR (film): $\tilde{\nu}$ = 3320 cm^{-1} (br. s, OH), 1645 (w, C=C). – ^1H NMR ($CDCl_3$, 90 MHz): δ = 0.84 (s, 3 H, 2′-CH_3), 0.94 (s, 3 H, 2′-CH_3), 1.18–2.49 (m, 13 H, 2, 5, 3′, 4′, 5′-H_2, 1′-H, 2 × OH), 3.73 (t, *J* = 7.0 Hz, 2 H, 2-H_2), 4.02 (s, 2 H, CH_2OH), 4.52 (br. s, 1 H, C=C$H_a$$H_b$), 4.76 (br. s, 1 H, C=C$H_a$$H_b$), 5.48 (t, *J* = 6.8 Hz, 1 H, 4-H). – This was employed in the next step without further purification.

(3E,1′R)-5-(2,2-Dimethyl-6-methylenecyclohexyl)-3-formyl-3-pentenal: [(*R*)-**3**]: To a solution of (3*E*,1′*R*)-**13** (67.0 mg, 0.28 mmol) in dry dichloromethane (5 ml), a solution of Dess–Martin periodinane (143 mg, 0.33 mmol) and pyridine (0.1 ml) in dry dichloromethane (5.0 ml) was added, and the reaction mixture was stirred at room temp. for 15 min. Then it was diluted with diethyl ether and 1:1 mixture of a saturated aqueous sodium hydrogen carbonate solution and a saturated aqueous sodium thiosulfate solution, and extracted several times with diethyl ether. The combined extracts were washed with a saturated aqueous sodium hydrogen carbonate solution and brine, and dried with anhydrous magnesium sulfate. After concentration in vacuo, the residue was chromatographed on silica gel (1.2 g, hexane/ethyl acetate, 20:1) to afford 60 mg (92%) of (*R*)-**3** as a colorless oil. – n_D^{23} = 1.4118. – $[\alpha]_D^{24}$ = –22.0 (*c* = 0.70, CH_2Cl_2) {ref.[7]: $[\alpha]_D^{20}$ = –15.83 (*c* = 0.6, CH_2Cl_2)}. – IR (film): $\tilde{\nu}$ = 3070 cm^{-1} (w, C=CH), 2930 (vs, C–H), 2865 (vs, C–H), 2720 (w, CHO), 1730 (s, CHO), 1680 (s, CHO), 1645 (m, C=C), 1450 (m), 1385 (m), 1365 (m), 1155 (m), 890 (m). – ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.86 (s, 3 H, 2′-CH_3), 0.97 (s, 3 H, 2′-CH_3), 1.21–1.36, 1.42–1.60, 1.94–2.17 (m, 7 H, 3′, 4′, 5′-H_2, 1′-H), 2.33–2.54 (m, 2 H, , 2-H_2), 3.40 (dd, *J* = 1.5, *J* = 7.5 Hz, 2 H, 2-H_2), 4.52 (s, 1 H, C=C$H_a$$H_b$), 4.82 (s, 1 H, C=C$H_a$$H_b$), 6.74 (t, *J* = 7.0 Hz, 1 H, 4-H), 9.41 (s, 1 H, CH_2CHO), 9.61 (s, 1 H, CH_2CHO). – ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 23.9, 25.4, 27.2, 28.9, 33.6, 35.6, 37.5, 39.7, 53.8, 110.4, 135.4, 148.4, 159.3, 194.0, 197.8. – EIMS; *m/z* (%): 234 (18) [M^+], 205 (22), 190 (19), 147 (15), 123 (95), 95 (44), 81 (100), 41 (87), 27 (25). – HRMS: found [M^+] 234.1592; calcd. for $C_{15}H_{22}O_2$: 234.1619. – These spectral data are in good accord with those reported[7].

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