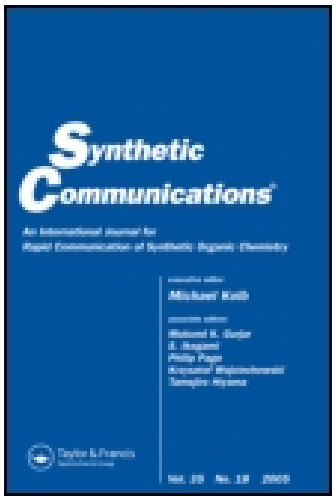

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An Efficient Alternative Synthesis of (+)-(6S,7S)-7-Hydroxy-6,11-cyclofarnes-3(15)-en-2-one, the (S)-Enantiomer of the Antibacterial Sesquiterpene from Premna oligotricha

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An Efficient Alternative Synthesis of (+)-(6*S*,7*S*)-7-Hydroxy-6,11-cyclofarnes-3(15)-en-2-one, the (*S*)-Enantiomer of the Antibacterial Sesquiterpene from *Premna oligotricha*

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ABSTRACT

The title compound has been synthesized from optically active lactone derived from (*S*)-(+)-Wieland–Miescher ketone analogue employing solid-state Baeyer–Villiger reaction.

Key Words: *Premna oligotricha*; Wieland–Miescher ketone; Baeyer–Villiger reaction.

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Premna oligotricha Baker (Verbenaceae) involves several biologically active terpenoids[1,2] and flavonoids,[3] of which some have pronounced antibacterial activity. In 1993, Waterman and his co-workers reported isolation of novel sesquiterpenoid, 7-hydroxy-6,11-cyclofarnes-3(15)-en-2-one **1**[1] from antibiotic fraction of ethanol extract of aerial parts of the plant as a minor constituent (Fig. 1). The compound exhibits weak antibacterial activity against a range of Gram-positive bacteria. The relative stereochemistries of C-6 and C-7 of the natural product **1** were initially assigned by NOESY measurement to be 6*R**,7*S** as shown in the structure **3**. However the proposed relative stereochemistry was corrected by Mori et al.,[4] to be 6*R**,7*R** as shown in the structure **1** by the total synthesis of racemic **1** and **3**. Subsequently, they synthesized the (*S*)-enantiomer **2**, an antipode of the natural product **1**, thereby establishing the absolute stereochemistry of **1** to be 6*R*,7*R*.[5]

Optically pure Wieland–Miescher ketone analogue **7** has been a very useful starting material for numerous natural products[6–10] since our disclosure of an improved synthetic procedure of **7**.[11] Our ongoing efforts in

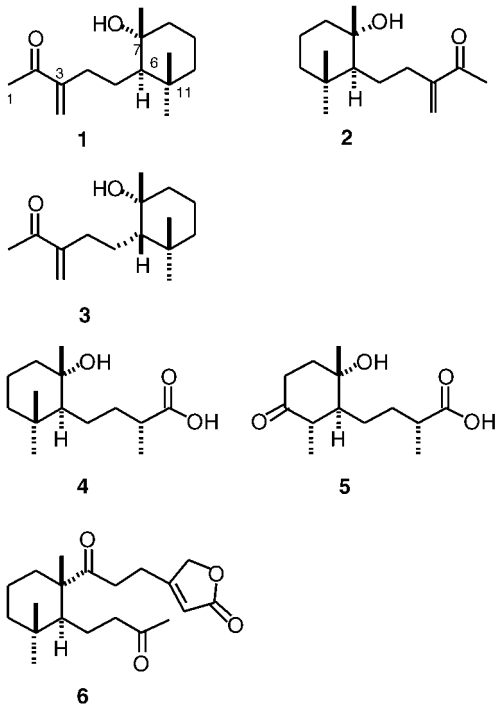

Figure 1.

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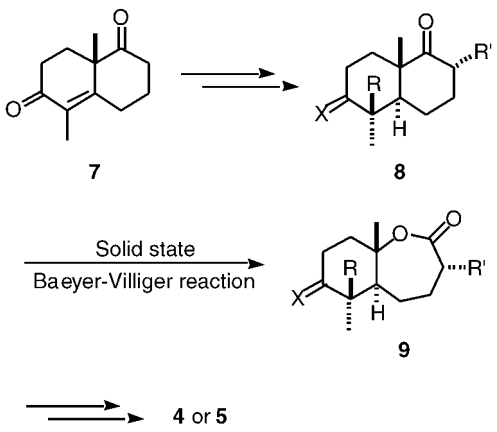
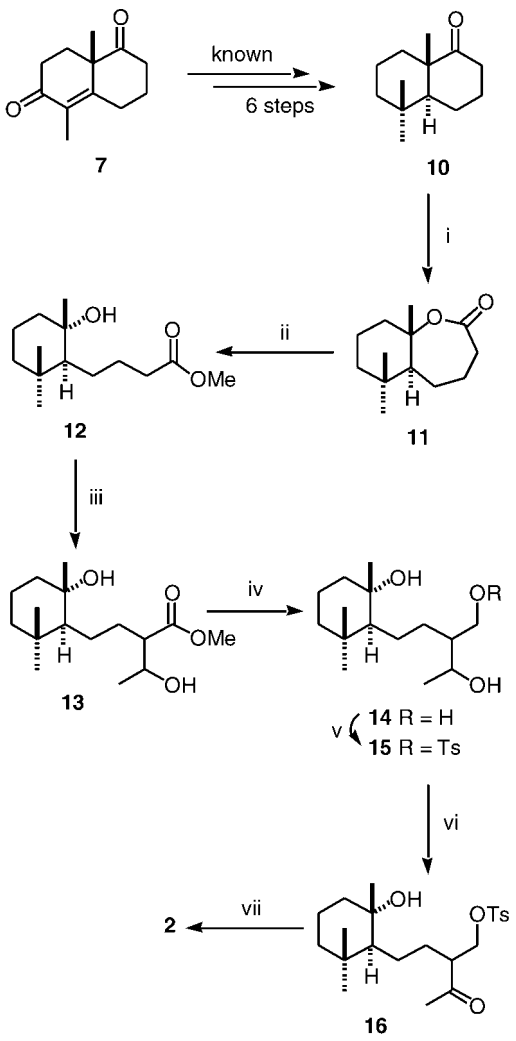


Scheme 1.

enantioselective total syntheses of several terpenoids starting from **7** enabled the first total syntheses of cyclofarnesane sesquiterpenoids, **4** and **5**, employing solid state Baeyer–Villiger reaction as the key reaction[12,13] (Sch. 1). This protocol offered good solution for construction of substituted cyclofarnesane framework which is not enantioselectively accessible by usual means, owing to conformational flexibility of cyclohexane ring. Low optical purity (38% op) of (*S*)-enantiomer **2** in the previous total synthesis by Mori et al.[5] exemplifies such difficulty in enantiocontrol in the synthesis.

Based on our previous synthetic results along with our interest on synthetic study of the constituents of *P. oligotricha*,[14] we delineate herein an alternative enantioselective total synthesis of **2** (Sch. 2).

Synthesis has started from the common precursor **10** for total syntheses of 4-(2′-hydroxy-2′,6′,6′-trimethylcyclohexyl)-2-methylbutanoic acid **4**[13] or chapechoderin A **6**,[15] which was prepared from optically pure (*S*)-(+)-Wieland–Miescher ketone analogue **7** in six steps. Solid state Baeyer–Villiger reaction was achieved in the presence of sodium hydrogencarbonate according to the modified procedure by Uenishi et al.[16] and was found to be accelerated to finish in shorter period of time (1.5 h) to give lactone **11** in slightly better yield (93%) than our previous procedure.[13] Since aldol condensation of enolate of the lactone **11** with acetaldehyde resulted in recovery, the lactone **11** was hydrolysed to afford hydroxy-acid which was treated with diazomethane to give hydroxy-ester **12** quantitatively. Aldol condensation of the ester enolate of **12** with acetaldehyde furnished β-hydroxyester **13** in 74% yield as a mixture of diastereomers. Then, the hydroxy-ester **13** was reduced with lithium aluminum hydride to give in 97%



Scheme 2. Reagents and conditions; (i) MCPBA, $NaHCO_3$, 1.5 h, 93%; (ii) NaOH, EtOH, room temp., 2.3 h then CH_2N_2, quant.; (iii) LDA, THF, HMPA, acetaldehyde, −78°C, 74%; (iv) LAH, Et_2O, 97%; (v) TsCl, DMAP, Et_3N, CH_2Cl_2, 62%; (vi) DMSO, Et_3N, SO_3-pyridine, CH_2Cl_2, 98%; (vii), DBU, toluene, room temp., 86%.

yield triol **14** which was transformed into tosylate **15** in 62% yield. An attempt of selective oxidation of secondary alcohol of the triol **14** by NBS failed.[4] Oxidation of the tosylate **15** by SO_3-pyridine complex afforded keto-tosylate **16** in 98% yield. β-Elimination of tosyloxy group was observed partially on

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prolonged treatment to give target compound **2**. Then the keto-tosylate **16** was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to complete enantioselective total synthesis of **2** in 86% yield. The spectral data were completely identical with those reported in the literature except sign of optical rotational value $[\alpha]_D + 18.4$ (c 0.15, $CHCl_3$) {lit.[1] $[\alpha]_D - 17$ (c 0.1, $CHCl_3$)}.

In summary, we have completed enantioselective total synthesis of **2**, in 7 steps in 35% overall yield from the known decalone **10** in better enantioselectivity and overall yield than previous work.[5]

EXPERIMENTAL

General

Mp was determined with a Yanaco MP hot-stage apparatus and is uncorrected. IR spectra were recorded on a Shimadzu FT/IR-4200 spectrophotometer in carbon tetrachloride unless otherwise indicated. ^{1}H-NMR spectra were obtained for solutions in deuteriochloroform with Varian Gemini 200H (200 MHz) and Unity 500 plus (500 MHz) instruments with tetramethylsilane as internal standard. *J*-values are in Hz. ^{13}C-NMR spectra were obtained for solutions in deuteriochloroform with Varian Gemini 200H (50 MHz) and Unity 500 plus (125 MHz) instruments. Mass spectral data were obtained with a JEOL GC-Mate spectrometer. Specific rotations were measured with a Horiba SEPA-200 spectrophotometer for solutions in methanol unless otherwise indicated. Medium pressure LC (MPLC) were carried out on Hitachi LC system.

(1*S*,7*S*)-1,8,8-Trimethyl-2-oxabicyclo[5.4.0]undecan-3-one (11). To a solution of ketone **10** (81 mg, 0.42 mmol) and MCPBA (80%; 183 mg, 0.85 mmol) in CH_2Cl_2 (1 cm^3) was added finely ground $NaHCO_3$ (56 mg, 0.66 mmol) and then the suspension was evaporated to dryness at room temperature in 1.5 h. The resulting mixture was dissolved in ethyl acetate and the organic layer was washed successively with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness. MPLC purification of the residue (ethyl acetate-*n*-hexane 2 : 1) gave lactones **11** (82 mg, 93%) as a white solid; $[\alpha]_D^{20} - 72.1$ (c 0.62); m.p. 40 $\sim$ 42°C; ν_{max}/cm^{-1} 2960, 2870, 1779, 1725 and 1551; δ (200 MHz) 0.81 (3H, s), 0.99 (3H, s), 1.51 (3H, s), 1.1–1.8 (8H, m), 1.88–2.08 (3H, m), 2.56 (1H, dd like) and 2.75 (1H, dd like); δ_C (50 MHz) 19.5 (t), 21.3 (q), 21.8 (q), 23.9 (t), 25.8 (t), 32.6 (q), 35.3 (s), 37.0 (t), 41.6 (t), 42.4 (t), 54.3 (d), 85.6 (s) and 175.4 (s); m/z (EI) 210.1615 (3.2%, M^+, $C_{13}H_{22}O_2$ requires 210.1620), 195 (14), 58 (31) and 43 (100).

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Methyl 4-[(1*S*,2*S*)-2-hydroxy-2,6,6-trimethylcyclohexyl]butanoate (12). A solution of the lactone **11** (85 mg, 0.40 mmol) in EtOH (9.9 cm^3) and 2N aq. sodium hydroxide (2.0 cm^3) was stirred at room temperature for 2.3 h. The reaction was quenched by addition of dil. aq. hydrochloric acid. After extraction with ethyl acetate (×3), the combined organic layer was washed with brine (×1) and water and dried over anhydrous Na_2SO_4. Evaporation of the solvent provided crude carboxylic acid (114 mg).

A solution of the carboxylic acid (114 mg) in diethyl ether (2.5 cm^3) was treated with an ethereal solution of diazomethane at 0°C until the yellow colour persisted. Evaporation of diethyl ether followed by MPLC purification of the residue (ethyl acetate-*n*-hexane 2 : 1) provided ester **12** (97 mg, 100% in two steps) as a colourless oil; $[\alpha]_D^{20} + 9.8$ (*c* 0.60); ν_{max}/cm^{-1} 2950, 1742, 1366 and 1379; δ (200 MHz) 0.80 (3H, s), 0.94 (3H, s), 1.16 (3H, s), 1.1–1.9 (12H, m), 2.34 (2H, t, *J* 7.1) and 3.67 (3H, s); δ_C (50 MHz) 20.5 (t), 21.3 (q), 23.4 (q), 25.8 (t), 27.9 (t), 32.8 (q), 34.5 (t), 35.4 (s), 41.5 (t), 43.3 (t), 51.5 (q), 57.2 (d), 74.1 (s) and 174.4 (s) ; *m*/*z* (EI) 224.1775 (29.5%, $M^+ - H_2O$, $C_{14}H_{24}O_2$ requires 224.1776), 209 (100), 168 (94), 123 (80) and 109 (78).

Methyl 2-[2-(1*S*,2*S*)-(2-hydroxy-2,6,6-trimethylcyclohexyl)ethyl]-3-hydroxybutanoate (13). To a stirred solution of diisopropylamine (0.69 cm^3, 4.9 mmol) in THF (1.0 cm^3) was added an *n*-hexane solution (1.57 M) of *n*-butyllithium (3.1 cm^3, 4.9 mmol) at 0°C under nitrogen atmosphere. After being stirred for 30 min, a solution of ester **12** (118 mg, 0.49 mmol) in THF (1.0 cm^3) was added at −78°C and stirring was continued for 30 min. Subsequently, HMPA (0.34 cm^3, 2.0 mmol) was added at −78°C. After being stirred at for 30 min, acetaldehyde (0.14 cm^3, 2.5 mmol) was added at −78°C and the resulting solution was stirred at −78°C for 2.5 h. The reaction was quenched by addition of aq. ammonium chloride and product was extracted with ethyl acetate (× 3). The combined organic layer was washed with water and brine. After drying over anhydrous Na_2SO_4, evaporation of the solvent followed by MPLC purification of the residue (ethyl acetate-*n*-hexane 3 : 1) gave diastereomeric diols, **13-1** and **13-2** as an inseparable mixture (67 mg, 48%), **13-3** (18 mg, 13%) and **13-4** (19 mg, 14%) as colourless oil in the order of elution.

Diols **13-1** and **13-2** had (200 MHz) 0.78 (3H, s), 0.916 and 0.925 (total 3H, s), 1.15 and 1.17 (total 3H, s), 1.19 and 1.22 (total 3H, d, *J* 6.5 and 6.6), 1.00–2.01 (13H, m), 2.45 (1H, m), 3.72 and 3.73 (total 3H, s), and 4.00 (1H, m); δ_C(50 MHz) 20.4 (t), 20.7 (q), 21.2 (q), 21.4 (q), 23.4 (q), 23.5 (t), 23.7 (t), 30.4 (t), 31.6 (t), 32.7 (q), 35.3 (s), 35.4 (s), 41.4 (t), 41.5 (t), 43.2 (t), 43.5 (t), 51.6 (q), 52.7 (d), 53.1 (d), 56.8 (d), 67.8 (d), 68.1 (d), 74.1 (s), 74.4 (s), 175.4 (s) and 175.9 (s).

Diol **13-3** had $[\alpha]_D^{20} + 43.1$ (*c* 0.126); ν_{max}/cm^{-1} 3616, 3360, 2950, 1736, 1366 and 1379; δ_H(200 MHz) 0.79 (3H, s), 0.93 (3H, s), 1.15 (3H, s),

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1.19 (3H, d, *J* 6.3), 1.00–1.90 (13H, m), 2.45 (1H, m), 3.73 (3H, s) and 3.98 (1H, m)

Diol **13-4** had $[\alpha]_D^{20}$ + 80.2 (*c* 0.096); ν_{max}/cm^{-1} 3603, 3400, 2951, 1721 and 1379; δ(200 MHz) 0.79 (3H, s), 0.91 (3H, s), 1.15 (3H, s), 1.23 (3H, d, *J* 6.3), 1.00–1.90 (13H, m), 2.43 (1H, m), 3.73 (3H, s) and 3.93 (1H, m); m/z (EI) 268.2041 (4.8%, $M^+ - H_2O$, $C_{16}H_{28}O_3$ requires 268.2038), 123 (100), 95 (86), 81 (97) and 79 (74).

2-[2-((1*S*,2*S*)-2-Hydroxy-2,6,6-trimethylcyclohexyl)ethyl]butane-1,3-diol (14). To a solution of the diols **13-1** and **13-2** (29 mg, 0.10 mmol) in anhydrous diethyl ether (10 cm^3) was added lithium aluminium hydride (23 mg, 0.60 mmol) at 0°C under nitrogen atmosphere. After being stirred for 2 h, the reaction mixture was quenched by cautious addition of aq. ammonium chloride. Filtration through anhydrous Na_2SO_4 followed by evaporation of diethyl ether provided triol **14** an inseparable diastereomeric mixture (26 mg, 97%) as a colourless oil.

Compound **14** had ν_{max}/cm^{-1} 3312, 2992, 2896, 1091, 1075 and 918; δ(200 MHz) 0.77 (3H, s), 0.88 (3H, s), 1.17 and 1.19 (total 3H, s), 1.16 and 1.32 (total 3H, d, *J* 5.6 and 6.5), 0.53–1.90 (11H, m), 1.94–2.50 (1H, m), 3.60–4.30 (3H, m) and 4.68–5.60 (3H, br m); δ_C(50 MHz) 20.0 (q), 20.4 (t), 20.5 (t), 21.0 (q), 21.4 (q), 22.3 (q), 22.5 (q), 23.3 (t), 23.5 (t), 26.5 (t), 32.2 (q), 34.3 (t), 35.7 (s), 41.2 (t), 42.4 (t), 42.7 (t), 45.2 (d), 45.4 (d), 58.4 (d), 58.7 (d), 59.8 (t), 65.1 (t), 73.5 (d), 73.6 (d) and 74.4 (s); m/z (EI) 240.2090 (1.2%, $M^+ - H_2O$, $C_{15}H_{28}O_2$ requires 240.2089), 123 (38), 109 (100), 95 (48) and 81 (58).

2-[2-((1*S*,2*S*)-2-Hydroxy-2,6,6-trimethylcyclohexyl)ethyl]-3-hydroxybutyl 4-methylbenzenesulfonate (15). To a solution of the triols **14** (9 mg, 0.03 mmol) in anhydrous dichloromethane (1 cm^3), was added anhydrous triethylamine (0.12 cm^3) and *p*-toluenesulfonyl chloride (34 mg, 0.18 mmol) at room temperature. After being stirred at room temperature for 13 h, the organic layer was diluted with ethyl acetate and passed through a short column of silica-gel. Evaporation of the solvent followed by MPLC purification of the residue (ethyl acetate) gave a diastereomeric tosylates **15-1** (4 mg, 30%) and **15-2** (5 mg, 32%) as colourless oils in the order of elution.

Less polar tosylate **15-1** had $[\alpha]_D^{20}$ − 6.3 (*c* 0.511); ν_{max}/cm^{-1} 3568, 3440, 2944, 1599 and 1462; δ(200 MHz) 0.77 (3H, s), 0.89 (3H, s), 1.14 (3H, s), 1.16 (3H, d, *J* 7.12), 1.05–1.80 (14H, m), 2.45 (3H, s), 3.83 (1H, quint, *J* 6.24), 4.13 (1H, dd, *J* 9.85 and 4.76), 4.21 (1H, dd, *J* 9.85 and 4.52), 7.34 (2H, d, *J* 8.06) and 7.80 (2H, d, *J* 8.34); δ_C(125 MHz) 20.4 (t), 20.8 (q), 21.2 (q), 21.6 (q), 23.4 (t), 23.4 (q), 29.8 (t), 32.7 (q), 35.4 (s), 41.5 (t), 43.4 (t), 45.4 (d), 56.9 (d), 67.6 (d), 70.0 (t), 74.2 (s), 127.9 (d), 129.8 (d), 132.9 (s) and 144.7 (s); m/z (EI) 412.2271 (0.3%, M^+, $C_{22}H_{36}O_5S$ requires 412.2283), 109 (98), 95 (92), 91 (100) and 81 (98).

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More polar tosylate **15-2** had $[\alpha]_D^{20}$ − 6.2 (*c* 1.052); ν_{max}/cm^{-1} 3408, 2934, 1599 and 1462; δ(200 MHz) 0.76 (3H, s), 0.88 (3H, s), 1.14 (3H, s), 1.15 (3H, d, *J* 6.4), 1.05–1.80 (14H, m), 2.45 (3H, s), 3.88 (1H, quint like), 4.04 (1H, dd, *J* 5.29 and 9.81), 4.13 (1H, dd, *J* 6.05 and 9.78), 7.35 (2H, d, *J* 8.06) and 7.80 (2H, d, *J* 8.34); δ_C(50 MHz) 20.5 (t), 20.5 (q), 21.2 (q), 21.7 (q), 22.9 (t), 23.4 (q), 29.2 (t), 32.7 (q), 35.3 (s), 41.4 (t), 43.4 (t), 45.1 (d), 57.2 (d), 67.1 (d), 70.6 (t), 74.4 (s), 127.9 (d), 129.9 (d), 132.8 (s) and 144.8 (s).

2-[2-((1*S*,2*S*)-2-Hydroxy-2,6,6-trimethylcyclohexyl)ethyl]-3-oxobutyl 4-methylbenzenesulfonate (16). To a solution of the less polar tosylate **15-2** (16 mg, 0.039 mmol) in anhydrous dichloromethane (1.4 cm^3), DMSO (0.20 cm^3, 2.8 mmol) and triethylamine (0.077 cm^3, 0.55 mmol) were added at room temperature. Subsequently SO_3-Py (54 mg, 0.34 mmol) was added at 0°C and the reaction mixture was stirred at room temperature for 0.7 h. The resulting mixture was diluted with ethyl acetate and the organic layer was washed successively with water and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by MPLC purification of the residue (ethyl acetate) provided **16** (16 mg, 98%) as a colourless oil which had $[\alpha]_D^{20}$ + 9.5 (*c* 1.140); ν_{max}/cm^{-1} 3540, 2944, 1721, 1599, 1460, 1372, 1190, 1179, 1100, 970 and 666; δ(200 MHz) 0.75 (3H, s), 0.87 (3H, s), 1.12 (3H, s), 1.00–1.80 (12H, m), 2.18 (3H, s), 2.45 (3H, s), 2.93 (1H, quint like), 4.09 (1H, dd, *J* 9.4 and 5.3), 4.17 (1 H, dd, *J* 9.2 and 7.3), 7.35 (2H, d, *J* 8.5) and 7.77 (2H, d, *J* 8.4); δ_C(50 MHz) 20.5 (t), 21.1 (q), 21.7 (q), 23.0 (t), 23.4 (q), 29.8 (q), 30.8 (t), 32.7 (q), 35.4 (s), 41.4 (t), 43.8 (t), 51.8 (d), 57.0 (d), 69.5 (t), 74.1 (s), 127.9 (d), 129.8 (d), 132.5 (s), 144.9 (s) and 208.8 (s); *m/z* (EI) 392.1951 (0.11%, $M^+ - H_2O$, $C_{22}H_{32}O_4S$ requires 392.2021), 150 (60), 94 (64), 81 (63) and 43 (100).

(+)-(6*S*,7*S*)-7-Hydroxy-6,11-cyclofarnes-3(15)-en-2-one = 3-[2-((2*S*)-2-hydroxy-2,6,6-trimethylcyclohexyl)ethyl]but-3-en-2-one (2). To a solution of **16** (16 mg, 0.038 mmol) in toluene (0.45 cm^3), DBU (0.0068 cm^3, 0.045 mmol) was added 0°C, and the reaction mixture was stirred at room temperature for 4.5 h. The solution was diluted with ethyl acetate and passed through a short column of silica-gel (ethyl acetate). Evaporation of the solvent followed by MPLC purification of the residue (ethyl acetate) gave enone **2** (7.8 mg, 86%) as a colourless oil which had $[\alpha]_D^{20}$ + 18.4(*c* 0.152, $CHCl_3$){lit.[1] $[\alpha]_D$ − 17 (*c* 0.1, $CHCl_3$)}; ν_{max}/cm^{-1} 3517, 2963, 1680, 1462, 1366 and 1101; δ(500 MHz) 0.78 (3H, s), 0.95 (3H, s), 1.17 (3H, s), 1.18–1.61 (8H, m), 1.75 (1H, m), 1.85 (1H, br s), 2.34 (3H, s), 2.35 (1H, m), 2.46 (1H, dddd, *J* 14.2, 10.8, 4.9 and 1.2), 5.82 (1H, s) and 6.00 (1H, s); δ_C(125 MHz) 20.4, 21.2, 23.4, 25.5, 25.9, 32.7, 34.2, 35.4, 41.5, 43.0, 56.9, 74.1, 125.3, 149.8 and 200.3.

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