Stereoselective Total Synthesis of Natural (*S*)-Bakuchiol and Its Enantiomer

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A practical stereoselective synthesis of (*S*)-bakuchiol (**1**) and its enantiomer is reported. The important intermediate, (*R*)-configured β-siloxy aldehyde **5**, was obtained in three steps from the easily available material geraniol (**2**) *via* the key step of *Yamamoto*'s rearrangement of epoxy silyl ethers. (*S*)-Bakuchiol (**1**) and its enantiomer, (*R*)-bakuchiol (**17**), were finally obtained in different synthetic sequences with overall yields of 51% (ten steps) and 40% (nine steps) from geraniol (**2**), respectively.

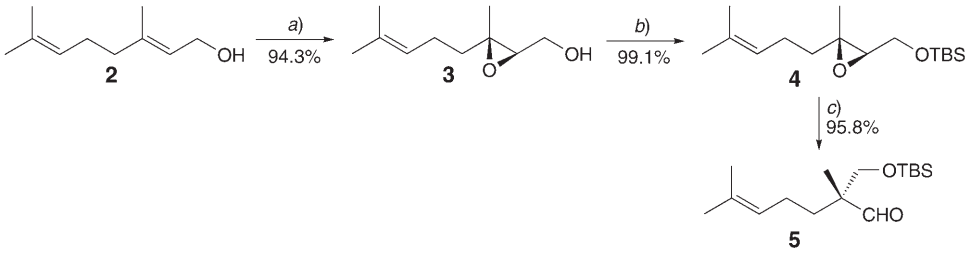
Introduction. – (*S*)-Bakuchiol (**1**), isolated from the seeds of *Psorales corylifolia* LINN, exhibits anti-inflammatory [1], antitumor [2][3], antimicrobial [4][5], and antioxidant [6][7] activities, and it inactivates nuclear transcription factor-κB in RAW 264.7 [8] and inhibits DNA polymerase and topoisomerase II [9]. A recent report [10] about its application for the prevention or treatment of breast cancer especially attracted our attention.

The reported two syntheses [11] of **1** required a chiral starting material and too many steps, which can seriously limit their application to prepare sufficient amounts of the compound for biological studies. Here, we report a practical procedure for the stereoselective preparation of **1** and its (*R*)-enantiomer **17** by routine chemical reactions and in excellent yield.

Results and Discussion. – Geraniol (**2**), which is partly similar in structure to the side chain of **1**, was converted enantioselectively into the chiral intermediate **3** by treatment with *Sharpless* epoxidation reagents (*Scheme 1*) in 94% yield ($[\alpha]_D^{20} = +5.0$ ($c = 1.05$, $CHCl_3$; [12]: $[\alpha]_D^{25} = +5.0$ ($c = 3.0$, $CHCl_3$)). According to the protocol reported by *Yamamoto* and co-workers [13], treating **3** with ^{t}BuMe$_2$SiCl (TBSCl) and 1*H*-imidazole in DMF, followed by rearrangement of silyl ether **4**, catalyzed by methylaluminum bis(4-bromo-2,6-di(*tert*-butyl)phenoxide), the (*R*)-configured β-siloxy aldehyde **5** ($[\alpha]_D^{20} = -6.7$ ($c = 1.30$, $CHCl_3$)) was obtained in 95% overall yield. The *Wittig* reaction of **5** with the ylide prepared from (methyl)(triphenyl)phosphonium iodide should afford **6** with (*S*)-configuration (*cf. Scheme 2*), which is an important intermediate for the synthesis of **1**, while the reaction of **5** with (4-methoxybenzyl)-magnesium chloride should lead to the (3*R*)-configured **12** (*cf. Scheme 3*) as the crucial intermediate for the synthesis of (*R*)-bakuchiol (**17**).

The reaction of **5** with the *Wittig* reagent prepared from (methyl)(triphenyl)phosphonium iodide and BuLi in THF gave **6** (*Scheme 2*) in 90% yield ($[\alpha]_D^{20} = -0.5$ ($c =$

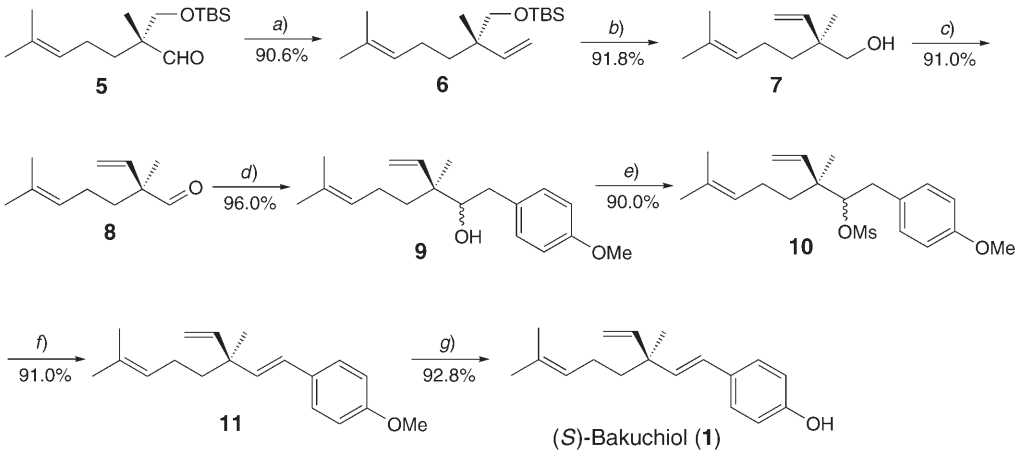
Scheme 1



a) $Ti(O^iPr)_4$, (−)-D-Diisopropyl tartrate ((−)-D-DPT), ^{t}BuOOH, 4-Å molecular sieves. *b*) ^{t}BuMe$_2$SiCl (TBSCl), 1*H*-imidazole. *c*) 1.5 equiv. methylaluminum bis(4-bromo-2,6-di(*tert*-butyl)phenoxide), −78°.

1.25, $CHCl_3$)). Treatment of **6** with $Bu_4NF \cdot 3\ H_2O$ (TBAF $\cdot 3\ H_2O$) and 4-Å molecular sieves in THF at room temperature gave the alcohol **7** in 92% yield ($[\alpha]_D^{20} = -16.9$ ($c =$ 1.23, $CHCl_3$)). Subsequently, conversion of **7** to aldehyde **8** ($[\alpha]_D^{20} = +9.7$ ($c = 1.05$, $CHCl_3$)) was accomplished by application of *Collins* oxidation in 91.0% yield. Then, reaction of **8** and (4-methoxybenzyl)magnesium chloride provided alcohol **9** in 96% yield. (*S*)-Bakuchiol methyl ether (**11**; $[\alpha]_D^{20} = +25.6$ ($c = 1.15$, $CHCl_3$)) was obtained through mesylation of **9** with methylsulfonyl chloride (MsCl) and elimination of the MsO group of **10** [14] with ^{t}BuOK in DMSO sequentially, in 89% overall yield. The target compound, (*S*)-bakuchiol (**1**), was obtained *via* demethylation with MeMgI at 180° [15] with 85% ee in 91% yield ($[\alpha]_D^{20} = +25.4$ ($c = 1.12$, $CHCl_3$); natural sample: $[\alpha]_D^{20} = +29.9$ ($c = 1.01$, $CHCl_3$)).

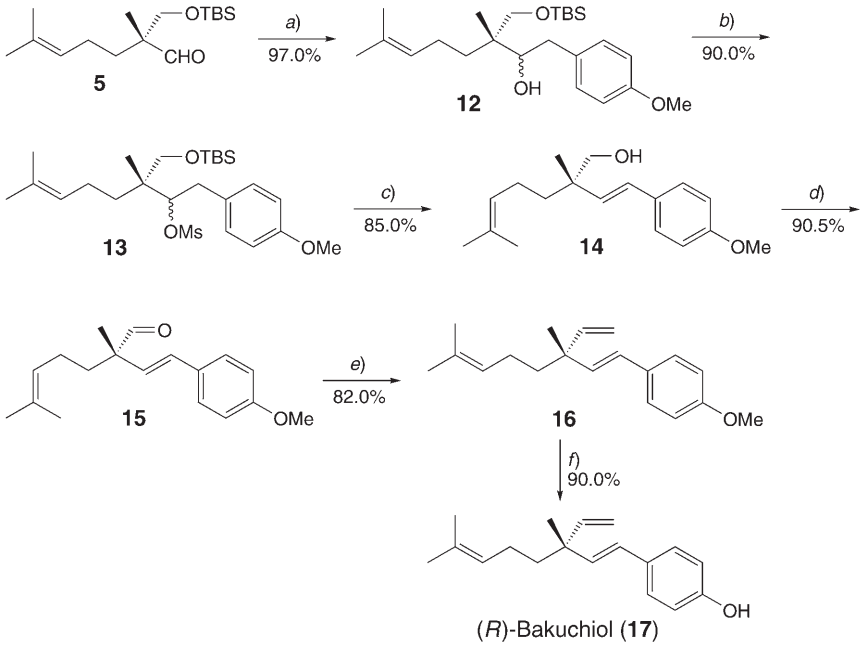
Scheme 2



a) $CH_2{=}PPh_3$, THF. *b*) $Bu_4NF \cdot 3\ H_2O$, THF. *c*) 5.0 equiv. $CrO_3 \cdot 2$ Py, CH_2Cl_2. *d*) 4-(MeO)C_6H_4-CH_2MgCl, THF. *e*) $MeSO_2Cl$, Py. *f*) 2.0 equiv. ^{t}BuOK, DMSO. *g*) MeMgI, 180°.

(*R*)-Bakuchiol (**17**) was synthesized from the key intermediate **5** by another route (*Scheme 3*). Treating **5** with (4-methoxybenzyl)magnesium chloride, followed by mesylation of the residual alcohol **12** with MsCl in dry pyridine, gave methanesulfonate **13** as a colorless oil in 87% overall yield. Treatment of **13** with ^{t}BuOK in DMSO afforded alcohol **14** in 85% yield ($[\alpha]_D^{20} = +27.2$ ($c = 1.04$, $CHCl_3$)). Aldehyde **15** was easily prepared from **14** *via Dess–Martin* oxidation. By the *Wittig* reaction, (*R*)-bakuchiol methyl ether (**16**; $[\alpha]_D^{20} = -25.1$ ($c = 1.39$, $CHCl_3$)) was prepared from aldehyde **15**. The target compound, (*R*)-bakuchiol (**17**) was obtained according to the method mentioned above with 87% ee and in 90% yield ($[\alpha]_D^{20} = -25.4$ ($c = 1.19$, $CHCl_3$)).

Scheme 3



a) 4-(MeO)$C_6H_4CH_2MgCl$, THF. *b*) $MeSO_2Cl$, Py. *c*) 3.0 equiv. ^{t}BuOK, DMSO. *d*) *Dess–Martin* reagent, CH_2Cl_2. *e*) $CH_2{=}PPh_3$, THF. *f*) MeMgI, 180°.

Conclusions. – Starting from the key intermediate **5**, we have synthesized (*S*)-Bakuchiol (**1**) and its enantiomer **17** *via* different synthetic routes. (*S*)-Bakuchiol (**1**) was synthesized in ten steps and 51% overall yield, and (*R*)-bakuchiol (**17**) in nine steps and 40% overall yield, from geraniol (**2**), respectively.

Experimental Part

General. Solvents were distilled from the appropriate drying agents before use. All the reagents were purchased from *Acros*, *Alfa Aesar*, and *National Chemical Reagents Group Co. Ltd*, P. R. China. Column

chromatography (CC): commercial silica gel (*Qingdao Hai Yang Chemical Group Co.*; 200–300 mesh). Spots on the TLC plates (*GF 254*, *Yantai Jiang You Silica R&D Co. Ltd*, P. R. China) were detected under UV light or with I_2. Optical rotation: *Perkin-Elmer 341* polarimeter. ^{1}H- and ^{13}C-NMR spectra: *VARIAN MERCURY-plus* (300 MHz for ^{1}H and 100 MHz for ^{13}C) spectrometer; chemical shifts δ in ppm, with residual $CHCl_3$ (δ (H) 7.26; δ (C) 77.0) as internal standard; *J* in Hz. EI-MS and HR-EI-MS: *Finnigan MAT-95* mass spectrometer; in *m/z*.

*Synthesis of (*S*)-Bakuchiol* (**1**). *(2*R,*3*R*)-3,7-Dimethyl-2,3-epoxyoct-6-en-1-ol* (=*2,3-Epoxygeraniol*; **3**). A mixture of powdered, activated 4-Å molecular sieves (M.S.; 1.2 g) and 15 ml of CH_2Cl_2 was cooled to 0°. (−)-D-Diisopropyl tartrate ((−)-D-DIPT; 0.3 g, 1.2 mmol) and $Ti(O^iPr)_4$ (0.23 g, 0.8 mmol) were added sequentially. After the mixture was cooled to −20°, ^{t}BuOOH in CH_2Cl_2 (10 ml, 25 mmol; 2.5M in CH_2Cl_2) was added, and the resulting mixture was stirred for 20 min, whereupon *geraniol* (**2**; 2.5 g, 16 mmol) was added. Stirring was continued for 45 min. After the mixture was warmed to 0°, the catalyst was destroyed with H_2O (4.6 ml), and the mixture was stirred for 30 min, while allowing it to warm to r.t. Hydrolysis of the tartrate was then effected by adding 2.0 ml of a 30% aq. soln. of NaOH saturated with NaCl under vigorous stirring. After 20 min, a sudden phase separation occurred. The lower org. phase was combined with two 30-ml CH_2Cl_2 extractions of the aq. phase. The combined org. phase was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by CC (silica gel; AcOEt/cyclohexane 1:4) to afford 2.56 g (94.3%) of **3**. Colorless oil. $[\alpha]_D^{20} = +5.0$ ($c = 1.05$, $CHCl_3$; [12]: $[\alpha]_D^{25} = +5.0$ ($c = 3.0$, $CHCl_3$)). ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.29 (*s*, Me−C(3)); 1.40–1.52 (*m*, H−C(4)); 1.60 (*s*, 3 H−C(8)); 1.57–1.72 (*m*, H−C(4)); 1.68 (*s*, Me−C(7)); 2.08 (*q*, *J* = 7.6, 2 H−C(5)); 2.97 (*dd*, *J* = 4.1, 6.7, H−C(2)); 3.63–3.72 (*m*, H−C(1)); 3.78–3.87 (*m*, H−C(1)); 5.08 (*t*, *J* = 7.6, H−C(6)). ^{13}C-NMR ($CDCl_3$, 100 MHz): 16.7, 17.6, 25.6 (3 Me); 23.6 (C(5)); 38.4 (C(4)); 61.2 (C(3)); 61.4 (C(1)); 63.0 (C(2)); 123.2 (C(6)); 132.1 (C(7)). EI-MS: 169 (6, $[M-H]^+$), 153 (17), 135 (13), 125 (16), 109 (65), 95 (25), 81 (32), 69 (100), 55 (22).

*(2*R,*3*R*)-1-[(*tert-*Butyl)dimethylsilyloxy]-3,7-dimethyl-2,3-epoxyoct-6-ene* (**4**). To a soln. of **3** (2.0 g, 11.8 mmol) and 1*H*-imidazole (2.03 g, 29.4 mmol) in 16 ml of DMF was added a soln. of ^{t}BuMe$_2$SiCl (2.0 g, 13.3 mmol) in 10 ml of DMF over a period of 25 min, and the mixture was then stirred at r.t. for 5 h. The reaction was quenched with 5.0 ml of H_2O, and the mixture was stirred for 30 min at r.t. The mixture was then poured into 150 ml of AcOEt. The org. phase was washed with sat. aq. NaCl soln. (3 × 50 ml) and then dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude product was purified by CC (silica gel; AcOEt/cyclohexane 1:100) to afford **4** (3.31 g, 99.1%). Colorless oil. $[\alpha]_D^{20} = +4.9$ ($c = 1.03$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.08 (*s*, Me_2Si); 0.90 (*s*, ^{t}BuSi); 1.25 (*s*, Me−C(3)); 1.38–1.52 (*m*, H−C(4)); 1.60 (*s*, 3 H−C(8)); 1.56–1.71 (*m*, H−C(4)); 1.67 (*s*, Me−C(7)); 2.07 (*q*, *J* = 7.9, 2 H−C(5)); 2.89 (*t*, *J* = 5.3, H−C(2)); 3.72 (*d*, *J* = 5.5, H−C(1)); 3.73 (*d*, *J* = 5.5, H−C(1)); 5.08 (*t*, *J* = 7.4, H−C(6)). ^{13}C-NMR ($CDCl_3$, 100 MHz): −5.3, 18.3, 25.8 (^{t}BuMe$_2$Si); 16.7, 17.6, 25.6 (3 Me); 23.7 (C(5)); 38.5 (C(4)); 60.5 (C(3)); 62.4 (C(1)); 63.1 (C(2)); 123.5 (C(6)); 131.9 (C(7)). EI-MS 283 (1, $[M-H]^+$), 227 (4), 135 (27), 107 (26), 93 (31), 75 (100), 69 (65), 55 (17).

*(*R*)-2-{[(*tert-*Butyl)dimethylsilyloxy]methyl}-2,6-dimethylhept-5-enal* (**5**). To a soln. of methylaluminum bis(4-bromo-2,6-di(*tert*-butyl)phenoxide), which was prepared from 4-bromo-2,6-di(*tert*-butyl)-phenol (3.42 g, 12 mmol) and Me_3Al (6.0 ml, 6.0 mmol; 1.0M in hexane) in 60 ml of CH_2Cl_2 at 0°, was added a soln. of **4** (1.14 g, 4 mmol) at −78° over a period of 30 min. The mixture was then stirred at −78° for 1.5 h. The resulting mixture was treated with NaF (0.5 g, 12 mmol), followed by H_2O (0.3 ml, 18 mmol) at −20°, and then stirred vigorously for 30 min at 0°. The mixture was filtered with the aid of CH_2Cl_2. The filtrate was concentrated under reduced pressure, and the residue was purified by CC (silica gel; AcOEt/cyclohexane 1:200) to afford **5** (1.09 g, 95%). Red liquid. $[\alpha]_D^{20} = -6.7$ ($c = 1.30$, $CHCl_3$; [13]: 95% ee, $[\alpha]_D^{24} = +6.45$ ($c = 1.0$, $CHCl_3$)). ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.03 (*s*, Me_2Si); 0.86 (*s*, ^{t}BuSi); 1.04 (*s*, Me−C(2)); 1.40–1.50 (*m*, H−C(3)); 1.57 (*s*, 3 H−C(7)); 1.54–1.63 (*m*, H−C(3)); 1.67 (*s*, Me−C(6)); 1.90 (*q*, *J* = 8.1, 2 H−C(4)); 3.56 (*d*, *J* = 10.0, 1 H, CH_2O); 3.67 (*d*, *J* = 10.0, 1 H, CH_2O); 5.05 (*t*, *J* = 7.0, H−C(5)); 9.54 (*s*, H−C(1)). ^{13}C-NMR ($CDCl_3$, 100 MHz): −5.7, 18.1, 25.7 (^{t}BuMe$_2$Si); 15.9, 17.6, 25.6 (3 Me); 22.4 (C(4)); 32.4 (C(3)); 51.2 (C(2)); 66.7 (CH_2O); 123.9 (C(5)); 132.1 (C(6)); 206.3 (C(1)). EI-MS: 284 (1, M^+), 283 (1), 267 (2), 243 (2), 227 (9), 202 (7), 185 (6), 171 (5), 157 (9), 135 (35), 107 (24), 93 (27), 75 (100), 69 (32), 55 (14).

*(*S*)-3-{[(*tert*-Butyl)dimethylsilyloxy]methyl}-3,7-dimethylocta-1,6-diene* (**6**). To a stirred suspension of (methyl)(triphenyl)phosphonium iodide powder (1.53 g, 3.8 mmol) in 20 ml of dry THF at 0° was added BuLi (1.6 ml, 3.7 mmol; 2.3M in hexane) over 15 min, and the mixture was stirred 20 min at 0°. A soln. of **5** (0.6 g, 2.1 mmol) in 5.0 ml of THF was added dropwise over 15 min, and the resulting mixture was stirred at r.t. for 2 h. Acetone (1 ml) was added to the mixture to consume the excess *Wittig* reagent. The mixture was poured into sat. aq. NaCl soln. and extracted with AcOEt (2 × 50 ml). The combined extracts were dried (Na_2SO_4), and then concentrated under reduced pressure. The crude product was purified by CC (silica gel; cyclohexane) to afford **6** (0.54 g, 90.6%). Colorless liquid. $[\alpha]_D^{20} = -0.5$ (c = 1.25, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.01 (*s*, Me_2Si); 0.87 (*s*, ^{t}BuSi); 0.95 (*s*, Me–C(3)); 1.33 (*t*, J = 8.4, 2 H–C(4)); 1.57 (*s*, 3 H–C(8)); 1.66 (*s*, Me–C(7)); 1.86 (*q*, J = 7.3, 2 H–C(5)); 3.30 (*d*, J = 9.5, 1 H, CH_2O); 3.35 (*d*, J = 9.3, 1 H, CH_2O); 4.95 (*d*, J = 17.6, 1 H–C(1)); 5.00 (*d*, J = 10.7, 1 H–C(1)); 5.07 (*t*, J = 7.3, H–C(6)); 5.76 (*dd*, J = 10.9, 17.7, H–C(2)). ^{13}C-NMR ($CDCl_3$, 100 MHz): –5.5, 18.3, 25.9 (^{t}BuMe$_2$Si); 17.6, 20.3, 25.7 (3 Me); 22.7 (C(5)); 37.0 (C(4)); 41.8 (C(3)); 70.3 (CH_2O); 125.2 (C(6)); 130.9 (C(7)); 112.4, 144.8 (C(1), C(2)). EI-MS: 282 (2, M^+), 267 (1), 225 (63), 183 (5), 169 (6), 149 (25), 141 (6), 121 (7), 107 (12), 89 (34), 75 (100), 69 (29), 55 (6).

*(*S*)-2-Ethenyl-2,6-dimethylhept-5-en-1-ol* (**7**). To a soln. of **6** (0.77 g, 2.73 mmol) in 25 ml of dry THF was added 4-Å M.S. (3.0 g) and $Bu_4NF \cdot 3\,H_2O$ (0.95 g, 3.0 mmol) in one portion. The mixture was stirred at r.t. for 3 h. After the completion of the reaction, the org. phase was poured out carefully, and then M.S. was washed with AcOEt (2 × 40 ml). The combined org. phase was washed with sat. aq. NaCl soln. and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude product was purified by CC (silica gel; AcOEt/cyclohexane 1:15) to afford **7** (1.37 g, 91.8%). Colorless oil. $[\alpha]_D^{20} = -16.9$ (c = 1.23, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.03 (*s*, Me–C(2)); 1.33 (*t*, J = 8.6, 2 H–C(3)); 1.59 (*s*, 3 H–C(7)); 1.67 (*s*, Me–C(6)); 1.91 (*q*, J = 7.0, 2 H–C(4)); 3.33 (*d*, J = 10.8, H–C(1)); 3.40 (*d*, J = 10.8, H–C(1)); 5.06 (*d*, J = 17.8, 1 H, CH_2=CH); 5.10 (*t*, J = 7.2, H–C(5)); 5.18 (*d*, J = 10.9, 1 H, CH_2=CH); 5.72 (*dd*, J = 10.8, 17.5, CH_2=C*H*). ^{13}C-NMR ($CDCl_3$, 100 MHz): 17.9, 19.8, 26.0 (3 Me); 22.8 (C(4)); 37.5 (C(3)); 42.7 (C(2)); 70.4 (C(1)); 115.0, 144.3 (CH_2=CH); 124.9 (C(5)); 131.8 (C(6)). EI-MS: 167 (6, $[M-H]^+$), 151 (11), 125 (22), 111 (32), 109 (33), 97 (43), 83 (50), 69 (100), 55 (65).

*(*S*)-2-Ethenyl-2,6-dimethylhept-5-enal* (**8**). To a stirred soln. of pyridine (1.62 ml, 20 mmol) in 24 ml of CH_2Cl_2 was added CrO_3 (1.0 g, 10 mmol) in one portion at 0°. After 1 h, a soln. of **7** (0.34 g, 2 mmol) in 8 ml of CH_2Cl_2 was added dropwise over 5 min at r.t. The mixture was stirred for 13 min, and then filtered through silica gel (200–300 mesh) under reduced pressure. The org. phase was washed with sat. aq. NaCl soln. and dried (Na_2SO_4). The solvent was removed under reduced pressure to give **8** (0.3 g, 91.0%). Colorless liquid. $[\alpha]_D^{20} = +9.7$ (c = 1.05, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.17 (*s*, Me–C(2)); 1.57 (*s*, 3 H–C(7)); 1.60 (*t*, J = 7.8, 2 H–C(3)); 1.66 (*s*, Me–C(6)); 1.91 (*q*, J = 7.7, 2 H–C(4)); 5.07 (*t*, J = 7.2, H–C(5)); 5.12 (*d*, J = 17.7, 1 H, CH_2=CH); 5.26 (*d*, J = 10.8, 1 H, CH_2=CH); 5.80 (*dd*, J = 10.8, 17.4, CH_2=C*H*); 9.38 (*s*, H–C(1)). ^{13}C-NMR ($CDCl_3$, 100 MHz): 17.6, 25.6 (3 Me); 22.6 (C(4)); 35.6 (C(3)); 52.7 (C(2)); 116.5, 138.6 (CH_2=CH); 123.6 (C(5)); 132.3 (C(6)); 202.7 (C(1)). EI-MS: 166 (M^+), 165 (9), 151 (13), 137 (18), 109 (27), 95 (40), 84 (47), 69 (100), 55 (41).

*(2*S*,3*S*)/(2*R*,3*S*)-3-Ethenyl-1-(4-methoxyphenyl)-3,7-dimethyloct-6-en-2-ol* (**9**). To a soln. of **8** (0.17 g, 1 mmol) in 10 ml of THF was added (4-methoxybenzyl)magnesium chloride (4.5 ml, 2.0 mmol, 0.45M in THF) at 0° over 15 min. The mixture was stirred at r.t. for 2 h, and then the reaction was quenched with 5 ml of sat. aq. NH_4Cl soln. The resulting mixture was extracted with AcOEt (3 × 30 ml). The combined org. phase was washed with sat. aq. NaCl soln. and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude product was purified by CC (silica gel; AcOEt/cyclohexane 1:10) to afford **9** (0.27 g, 96.0%). Colorless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.06–1.10 (*m*, Me–C(3)); 1.45–1.60 (*m*, 2 H–C(4)); 1.59 (*s*, 3 H–C(8)); 1.68 (*s*, Me–C(7)); 1.87–1.98 (*m*, 2 H–C(5)); 2.35–2.47 (*m*, H–C(1)); 2.78–2.88 (*m*, H–C(1)); 3.45–3.54 (*m*, H–C(2)); 3.79 (*s*, MeO); 5.04–5.14 (*m*, 1 H, CH_2=CH); 5.07–5.16 (*m*, H–C(6)); 5.17–5.26 (*m*, 1 H, CH_2=CH); 5.78–5.91 (*m*, CH_2=C*H*); 6.85 (*d*, J = 7.4, H–C(3′), H–C(5′)); 7.09–7.17 (*m*, H–C(2′), H–C(6′)). ^{13}C-NMR ($CDCl_3$, 100 MHz): 17.2, 17.4, 17.6, 25.7 (3 Me); 22.6, 22.7 (C(5)); 36.8, 37.4 (C(1)); 37.5 (C(4)); 44.4, 44.7 (C(3)); 55.2 (MeO); 78.3, 78.9 (C(2)); 113.9 (C(3′)); 114.3, 114.8, and 143.6, 143.8 (CH_2=CH); 124.7, 124.8 (C(6)); 130.2 (C(2′)); 131.3, 131.4 (C(1′)); 131.7 (C(7)); 158.1 (C(4′)). EI-MS: 288 (14, M^+), 270 (4), 255 (1), 227 (2), 150 (38), 121 (100), 109 (7), 95 (16), 69 (29), 55(7).

(2S,3S)/(2R,3S)-3-Ethenyl-1-(4-methoxyphenyl)-3,7-dimethyloct-6-en-2-yl Methanesulfonate (**10**). To a soln. of **9** (0.145 g, 0.5 mmol) in 3 ml of dry pyridine was added $MeSO_2Cl$ (63 mg, 0.55 mmol), and the mixture was stirred at r.t. for 10 h. H_2O (0.5 ml) was added, and the product was extracted with Et_2O (3×30 ml). The extracts were washed with H_2O (2×15 ml) and dried (Na_2SO_4). The solvent was removed under reduced pressure to give **10** (0.18 g, 90.0%). Yellow oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.16 (*s*, Me–C(3)); 1.40–1.65 (*m*, 2 H–C(4)); 1.59 (*s*, 3 H–C(8)); 1.67 (*s*, Me–C(7)); 1.82–2.02 (*m*, 2 H–C(5)); 2.09 (*s*, $MeSO_2$); 2.66–2.77 (*m*, H–C(1)); 2.97–3.05 (*m*, H–C(1)); 3.77 (*s*, MeO); 4.82 (*t*, $J = 12.2$, H–C(2)); 5.04–5.15 (*m*, H–C(6)); 5.08–5.17 (*m*, 1 *H*, C*H*$_2$=CH); 5.23–5.30 (*m*, 1 H, C*H*$_2$=CH); 5.77–5.91 (*m*, CH$_2$=C*H*)); 6.84 (*d*, $J = 7.6$, H–C(3′), H–C(5′)); 7.14 (*d*, $J = 7.8$, H–C(2′), H–C(6′)). ^{13}C-NMR ($CDCl_3$, 100 MHz): 17.6 and 17.8, 18.9, 25.6 (3 Me); 22.5, 22.7 (C(5)); 35.6, 35.8 (C(1)); 37.3, 37.5 (C(4)); 38.4 (Ms); 44.4 (C(3)); 55.2 (MeO); 92.0, 92.2 (C(2)); 114.0, 114.2 (C(3′), C(5′)); 115.4, 115.6, and 141.7, 141.9 (C*H*$_2$=CH); 124.3 (C(6)); 130.6 (C(2′), C(6′)); 131.5 (C(7)); 143.6, 143.8 (C(1′)); 158.6 (C(4′)). EI-MS: 366 (2, M^+), 288 (2), 270 (12), 255 (2), 229 (6), 187 (15), 150 (14), 121 (100), 69 (10), 55 (3).

(1E,3S)-3-Ethenyl-1-(4-methoxyphenyl)-3,7-dimethylocta-1,6-diene (=*(S)-Bakuchiol Methyl Ether*; **11**). To a soln. of **10** (0.37 g, 1 mmol) in 3 ml of dry DMSO was added ^{t}BuOK (0.224 g, 2 mmol) in one portion, and the mixture was stirred at r.t. for 5 h. The mixture was poured into 15 ml of H_2O, and the product was extracted with Et_2O (3×35 ml). The combined org. phase was washed with sat. aq. NaCl soln. and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude product was purified by CC (silica gel; petroleum ether) to afford **11** (0.246 g, 91.0%). Colorless oil. $[\alpha]_D^{20} = +25.6$ ($c = 1.15$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.19 (*s*, Me–C(3)); 1.40–1.60 (*m*, 2 H–C(4)); 1.58 (*s*, 3 H–C(8)); 1.67 (*s*, Me–C(7)); 1.84–2.02 (*m*, 2 H–C(5)); 3.80 (*s*, MeO); 5.01 (*d*, $J = 17.9$, 1 H, C*H*$_2$=CH); 5.03 (*d*, $J = 10.4$, 1 H, C*H*$_2$=CH); 5.10 (*t*, $J = 7.4$, H–C(6)); 5.88 (*dd*, $J = 10.6$, 17.0, CH$_2$=C*H*); 6.06 (*d*, $J = 16.6$, H–C(2)); 6.26 (*d*, $J = 16.6$, H–C(1)); 6.84 (*d*, $J = 8.9$, H–C(2′), H–C(6′)); 7.29 (*d*, $J = 8.5$, H–C(3′), H–C(5)). ^{13}C-NMR ($CDCl_3$, 100 MHz): 17.6, 23.3, 25.7 (3 Me); 23.2 (C(5)); 41.3 (C(4)); 42.5 (C(3)); 55.3 (MeO); 111.8, 146.0 (CH$_2$=CH); 113.8 (C(3′), C(5′)); 124.8 (C(6)); 126.5 (C(2)); 127.1 (C(2′), C(6′)); 130.6 (C(1′)); 131.3 (C(7)); 135.7 (C(1)); 158.7 (C(4′)). EI-MS: 270 (16, M^+), 255 (2), 227 (8), 187 (100), 172 (12), 159 (12), 121 (22), 69 (6), 55 (7).

4-[(1E,3S)-3-Ethenyl-3,7-dimethyloct-1,6-dienyl]phenol (=*(S)-Bakuchiol*; **1**). To a soln. of **11** (0.27 g, 1.0 mmol) in 5 ml of Et_2O was added a soln. of MeMgI in Et_2O (6.0 ml, 0.25M). The solvent was removed under reduced pressure, and the residue was heated under Ar at 185° for 10 min. The mixture was cooled to r.t., and the reaction was quenched with 1 ml of sat. aq. NH_4Cl soln. The product was extracted with Et_2O (3×50 ml). The combined org. phase was washed with sat. aq. NaCl soln. and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude product was purified by CC (silica gel; AcOEt/cyclohexane 1:10) to afford **1** with 85% ee (0.23 g, 92.8%). $[\alpha]_D^{20} = +25.4$ ($c = 1.12$, $CHCl_3$; natural: $[\alpha]_D^{20} = +29.9$ ($c = 1.01$, $CHCl_3$)). ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.20 (*s*, Me–C(3′)); 1.46–1.54 (*m*, 2 H–C(4′)); 1.59 (*s*, 3 H–C(8′)); 1.68 (*s*, Me–C(7′)); 1.91–2.02 (*m*, 2 H–C(5′)); 5.02 (*d*, $J = 17.5$, 1 H, C*H*$_2$=CH); 5.04 (*d*, $J = 10.7$, 1 H, C*H*$_2$=CH); 5.12 (*t*, $J = 7.5$, H–C(6′)); 5.89 (*dd*, $J = 10.8$, 17.4, CH$_2$=C*H*); 6.06 (*d*, $J = 16.3$, H–C(2′)); 6.26 (*d*, $J = 16.2$, H–C(1′)); 6.78 (*d*, $J = 8.5$, H–C(2), H–C(6)); 7.25 (*d*, $J = 8.2$, H–C(3), H–C(5)). ^{13}C-NMR ($CDCl_3$, 100 MHz): 17.6, 23.3, 25.7 (3 Me); 23.2 (C(5′)); 41.2 (C(4′)); 42.5 (C(3′)); 111.8, 145.9 (CH$_2$=CH); 115.3 (C(3), C(5)); 124.7 (C(6′)); 126.4 (C(2′)); 127.3 (C(2), C(6)); 130.7 (C(1)); 131.3 (C(7′)); 135.7 (C(1′)); 154.6 (C(4)). EI-MS: 256 (24, M^+), 241 (5), 227 (2), 213 (16), 199 (4), 185 (7), 173 (100), 145 (30), 107 (36), 69 (8), 55 (12). HR-EI-MS: 256.1829 ($C_{18}H_{24}O^+$; calc. 256.1827).

Synthesis of (R)-Bakuchiol (**17**). *(2S,3R)/(2R,3R)-3-{[(*tert*-Butyl)dimethylsilyloxy]methyl}-1-(4-methoxyphenyl)-3,7-dimethyloct-6-en-2-ol* (**12**). Compound **5** (0.57 g, 2 mmol) was subjected to the *Grignard* reaction according to the procedure described for the preparation of **9** in 20 ml THF with 8.9 ml of (4-methoxybenzyl)magnesium chloride (4.5 ml, 2.0 mmol, 0.45M in THF) at 0°. After workup, the solvent was removed under reduced pressure, and the crude product was purified by CC (silica gel; AcOEt/cyclohexane 1:15) to afford **12** (0.79 g, 97.0%). Colorless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.07 (*s*, Me_2Si); 0.90 (*s*, ^{t}BuSi); 0.88–0.93 (*m*, Me–C(3)); 1.23–1.42 (*m*, H–C(4)); 1.49–1.67 (*m*, H–C(4)); 1.61 (*s*, 3 H–C(8)); 1.69 (*s*, Me–C(7)); 1.89–2.05 (*m*, 2 H–C(5)); 2.47–2.59 (*m*, H–C(1)); 2.73–2.86 (*m*, H–C(1)); 3.50 (*m*, H–C(2)); 3.62–3.72 (*m*, CH_2O); 3.78 (*s*, MeO); 5.08–5.16 (*m*, H–C(6)); 6.84

(*d*, *J* = 7.3, H–C(3′), H–C(5′)); 7.14 (*d*, *J* = 7.1, H–C(2′), H–C(6′)). ^{13}C-NMR ($CDCl_3$, 100 MHz): –5.7, 18.1, 25.8 (^{t}BuMe$_2$Si); 17.6 and 17.7, 19.2, 25.7 (3 Me); 32.1 (C(4)); 35.5, 37.7 (C(1)); 40.8, 40.9 (C(3)); 55.2 (MeO); 69.7, 69.9 (CH_2O); 78.2, 80.2 (C(2)); 113.6, 113.8 (C(3′), C(5′)); 124.8 (C(6)); 130.1 (C(2′), C(6′)); 131.2, 131.3 (C(1′)); 132.4 (C(7)); 157.9 (C(4′)). EI-MS: 406 (4, M^+), 285 (5), 267 (7), 242 (13), 153 (6), 135 (25), 121 (100), 89 (12), 75 (10), 69 (8), 55 (2).

*(2*S*,3*R*)/(2*R*,3*R*)-3-{[(*tert*-Butyl)dimethylsilyloxy]methyl}-1-(4-methoxyphenyl)-3,7-dimethyloct-6-en-2-yl Methanesulfonate* (**13**). To a soln. of **12** (0.41 g, 1 mmol) in 3 ml of dry pyridine was added MsCl (0.13 g, 1.1 mmol) dropwise, and the mixture was stirred at r.t. overnight. H_2O (1 ml) was added, and the product was extracted with Et_2O. The extracts were washed with H_2O and dried (Na_2SO_4). The solvent was removed under reduced pressure to give **13** (0.44 g, 90.0%). ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.07 (*s*, Me$_2$Si); 0.93 (*s*, ^{t}BuSi); 0.94–1.06 (*m*, Me–C(3)); 1.16–1.60 (*m*, 2 H–C(4)); 1.62 (*s*, 3 H–C(8)); 1.69 (*s*, Me–C(7)); 1.73–2.05 (*m*, 2 H–C(5)); 2.05–2.09 (*m*, $MeSO_2$); 2.74–2.97 (*m*, H–C(1)); 2.97–3.14 (*m*, H–C(1)); 3.45–3.58 (*m*, CH_2O); 3.78 (*s*, MeO); 5.02–5.10 (*m*, H–C(2)); 5.07–5.16 (*m*, H–C(6)); 6.86 (*d*, *J* = 8.7, H–C(3′), H–C(5′)); 7.16 (*d*, *J* = 8.6, H–C(2′), H–C(6′)). ^{13}C-NMR ($CDCl_3$, 100 MHz): –5.6, 18.2, 25.8 (^{t}BuMe$_2$Si); 17.6, 18.1 and 18.8, 25.7 (3 Me); 22.1, 22.2 (C(5)); 32.9 (C(4)); 35.2, 35.4 (C(1)); 38.2 (Ms); 42.3, 42.4 (C(4)); 55.2 (MeO); 65.9, 67.1 (CH_2O); 90.8, 91.4 (C(2)); 113.9 (C(3′), C(5′)); 124.5 (C(6)); 130.1, 130.3 (C(1′)); 130.6 (C(2′), C(6′)); 131.3, 131.5 (C(7)); 158.6 (C(4′)). EI-MS: 484 (1, M^+), 388 (1), 331 (5), 267 (4), 243 (14), 153 (12), 135 (7), 121 (100), 73 (11).

*(2*S*)-2-[(*E*)-2-(4-Methoxyphenyl)ethenyl]-2,6-dimethylhept-5-en-1-ol* (**14**). To a soln. of **13** (0.485 g, 1 mmol) in 3 ml of dry DMSO was added ^{t}BuOK (0.336 g, 3 mmol) in one portion, and the mixture was stirred at r.t. for 3 h. The mixture was poured into 15 ml of H_2O, and the product was extracted with AcOEt (3 × 35 ml). The combined org. phase was washed with sat. aq. NaCl soln. and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude product was purified by CC (silica gel; AcOEt/cyclohexane 1:8) to afford **14** (0.233 g, 85.0%). White solide (M.p. 42–46°). $[\alpha]_D^{20} = +27.2$ (*c* = 1.04, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.13 (*s*, Me–C(2)); 1.36–1.49 (*m*, 2 H–C(3)); 1.58 (*s*, 3 H–C(7)); 1.67 (*s*, Me–C(6)); 1.87–2.05 (*m*, 2 H–C(4)); 3.40 (*d*, *J* = 10.8, 1 H–C(1)); 3.47 (*d*, *J* = 10.6, 1 H–C(1)); 3.80 (*s*, MeO); 5.11 (*t*, *J* = 6.9, H–C(5)); 5.97 (*d*, *J* = 16.4, CH=C*H*–C(2)); 6.35 (*d*, *J* = 16.4, C*H*=CH–C(2)); 6.85 (*d*, *J* = 7.2, H–C(2′), H–C(6′)); 7.31 (*d*, *J* = 6.8, H–C(3′), H–C(5′)). ^{13}C-NMR ($CDCl_3$, 100 MHz): 17.6, 20.2, 25.7 (3 Me); 22.6 (C(4)); 37.8 (C(3)); 41.9 (C(2)); 55.2 (MeO); 70.6 (C(1)); 113.9 (C(3′), C(5′)); 124.7 (C(5)); 127.2 (C(2′), C(6′)); 129.0 (CH=*C*H–C(2)); 130.1 (C(1′)); 131.4 (C(6)); 133.4 (*C*H=CH–C(2)); 158.9 (C(4′)). EI-MS: 274 (28, M^+), 259 (1), 243 (86), 187 (16), 161 (33), 149 (32), 121 (94), 109 (21), 91 (10), 81 (28), 69 (100), 55 (6).

*(2*S*)-2-[(*E*)-2-(Methoxyphenyl)ethenyl]-2,6-dimethylhept-5-enal* (**15**). To a soln. of **14** (0.275 g, 1.0 mmol) in 12 ml of CH_2Cl_2 was added *Dess–Martin* reagent (0.51 g, 1.2 mmol) in one portion at r.t. The mixture was stirred for 2 h, and the reaction was quenched with 2.0 ml of sat. aq. sodium thiosulfate. The resulting mixture was extracted with AcOEt (3 × 20 ml). The extracts were washed with sat. aq. NaCl soln. and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude product was purified by CC (silica gel; AcOEt/cyclohexane 1:20) to afford **15** (0.247 g, 90.5%). Colorless oil. $[\alpha]_D^{20} = -9.8$ (*c* = 1.25, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.28 (*s*, Me–C(2)); 1.58 (*s*, 3 H–C(7)); 1.68 (*s*, Me–C(6)); 1.71 (*t*, *J* = 8.3, 2 H–C(3)); 1.88–2.07 (*m*, 2 H–C(4)); 3.81 (*s*, MeO); 5.10 (*t*, *J* = 6.8, H–C(5)); 6.00 (*d*, *J* = 16.3, CH=C*H*–C(2)); 6.38 (*d*, *J* = 16.6, C*H*=CH–C(2)); 6.86 (*d*, *J* = 8.0, H–C(2′), H–(6′)); 7.31 (*d*, *J* = 8.0, H–C(3′), H–C(5′)); 9.42 (*s*, H–C(1)). ^{13}C-NMR ($CDCl_3$, 100 MHz): 17.6, 18.3, 25.6 (3 Me); 22.8 (C(4)); 36.0 (C(3)); 52.1 (C(2)); 55.3 (MeO); 114.0 (C(3′), C(5′)); 123.7 (C(5)); 127.4 (C(2′), C(6′)); 127.8 (CH=*C*H–C(2)); 129.6 (*C*H=CH–C(2)); 130.9 (C(1′)); 132.3 (C(6)); 159.3 (C(4′)), 202.2 (C(1)). EI-MS: 272 (14, M^+), 243 (48), 229 (4), 199 (13), 175 (29), 161 (38), 135 (83), 121 (63), 109 (22), 81 (20), 69 (100), 55 (8).

*(1*E*,3*R*)-3-Ethenyl-1-(4-methoxyphenyl)-3,7-dimethylocta-1,6-diene* (=*(*R*)-Bakuchiol Methyl Ether*; **16**). To a stirred suspension of powdered (methyl)(triphenyl)phosphonium iodide (0.8 g, 2.0 mmol) in 15 ml of dry THF was added BuLi (0.85 ml, 1.9 mmol; 2.3M in hexane) at 0° over 15 min, and then the mixture was stirred for 20 min at 0°. A soln. of **15** (0.33 g, 1.2 mmol) in 4.0 ml of THF was added dropwise over 10 min, and the resulting mixture was stirred for 4 h at r.t. Acetone (1 ml) was added to the mixture to consume the excess *Wittig* reagent. The mixture was poured into sat. aq. NaCl soln. and extracted with Et_2O (2 × 50 ml). The combined extracts were dried (Na_2SO_4), and then

concentrated under reduced pressure. The crude product was purified by CC (silica gel; petroleum ether) to afford **16** (0.265 g, 82.0%). Colorless oil. $[\alpha]_D^{20} = -25.1$ ($c = 1.39$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.19 (*s*, Me–C(3)); 1.45–1.53 (*m*, 2 H–C(4)); 1.58 (*s*, 3 H–C(8)); 1.68 (*s*, Me–C(7)); 1.89–2.01 (*m*, 2 H–C(5)); 3.80 (*s*, MeO); 5.01 (*d*, $J = 17.5$, 1 H, CH_2=CH); 5.04 (*d*, $J = 10.7$, 1 H, CH_2=CH); 5.11 (*t*, $J = 7.0$, H–C(6)); 5.88 (*dd*, $J = 10.9, 17.6$, CH_2=CH); 6.07 (*d*, $J = 16.2$, H–C(2)); 6.27 (*d*, $J = 16.4$, H–C(1)); 6.84 (*d*, $J = 8.6$, H–C(2′), H–C(6′)); 7.30 (*d*, $J = 8.6$, H–C(3′), H–C(5′)). ^{13}C-NMR ($CDCl_3$, 100 MHz): 17.6, 23.3, 25.7 (3 Me); 23.2 (C(5)); 41.3 (C(4)); 42.5 (C(3)); 55.3 (MeO); 111.8, 146.0 (CH_2=CH); 113.8 (C(3′), C(5′)); 124.8 (C(6)); 126.5 (C(2)); 127.1 (C(2′), C(6′)); 130.6 (C(1′)); 131.3 (C(7)); 135.7 (C(1)); 158.7 (C(4′)). EI-MS: 270 (17, M^+), 255 (2), 244 (4), 227 (8), 187 (100), 172 (12), 159 (12), 135 (8), 121 (23), 69 (7), 55 (6).

*4-[(1*E*,3*R*)-3-Ethenyl-3,7-dimethylocta-1,6-dienyl]phenol* (=*(*R*)-Bakuchiol*; **17**). The target compound **17** was obtained according to the procedure described for the preparation of (*S*)-*bakuchiol* (**1**) with 87% ee. $[\alpha]_D^{20} = -25.4$ ($c = 1.19$, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.20 (*s*, Me–C(3′)); 1.46–1.58 (*m*, 2 H–C(4′)); 1.60 (*s*, 3 H–C(8′)); 1.69 (*s*, Me–C(7′)); 1.90–2.02 (*m*, 2 H–C(5′)); 5.03 (*d*, $J =$ 17.1, 1 H, CH_2=CH); 5.05 (*d*, $J = 10.8$, 1 H, CH_2=CH); 5.12 (*t*, $J = 7.5$, H–C(6′)); 5.90 (*dd*, $J = 10.6$, 17.4, CH_2=CH); 6.07 (*d*, $J = 16.7$, H–C(2′)); 6.27 (*d*, $J = 16.8$, H–C(1′)); 6.78 (*d*, $J = 7.9$, H–C(2), H–C(6)); 7.26 (*d*, $J = 8.0$, H–C(3), H–C(5)). ^{13}C-NMR ($CDCl_3$, 100 MHz): 17.6, 23.3, 25.7 (3 Me); 23.2 (C(5′)); 41.2 (C(4′)); 42.5 (C(3′)); 111.8, 145.9 (CH_2=CH); 115.3 (C(3), C(5)); 124.7 (C(6′)); 126.4 (C(2′)); 127.3 (C(2), C(6)); 130.7 (C(1)); 131.3 (C(7′)); 135.7 (C(1′)); 154.6 (C(4)). EI-MS: 256 (19, M^+), 241 (4), 230 (9), 213 (16), 187 (6), 173 (100), 145 (37), 121 (12), 107 (43), 83 (11), 69 (15), 55 (13). HR-EI-MS: 256.1817 ($C_{18}H_{24}O^+$; calc. 256.1827).

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