EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

# Accepted Article

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**To be cited as:** Eur. J. Org. Chem. 10.1002/ejoc.201601197

**Link to VoR:** http://dx.doi.org/10.1002/ejoc.201601197

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# A Metathesis Route to (+)-Orientalol F, a Guaiane Sesquiterpene from *Alisma Orientalis*

Martin Zahel,[a] Yuzhou Wang,[a] Anne Jäger,[a] and Peter Metz*[a]

Dedicated to Professor Jürgen Fabian on the occasion of his 80th birthday

**Abstract:** The synthesis of (+)-orientalol F (**1**) commenced with aldehyde **6** that is available from (*R*)-limonene in two steps. Wittig reaction of **6** with unsaturated ylide **7** to give a tetraene and subsequent ring-closing metathesis yielded hydroazulene **4**, selective epoxidation of which provided epoxy ester **3**. After generation of the requisite isopropyl unit and regioselective reductive epoxide opening, the derived dienol **2** was utilized for installation of the oxygen bridge through intramolecular oxymercuration followed by oxidative demercuration. The resultant allylic alcohol epimers **15** and **16** were readily converted to the target natural product **1** by oxidation/reduction sequences.

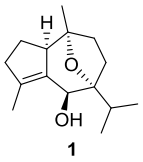


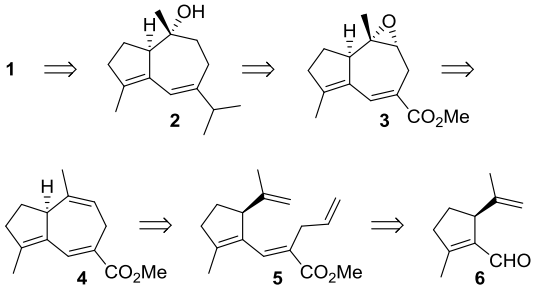

**Figure 1.** Structure of (+)-orientalol F (**1**).

## Introduction

The guaiane (+)-orientalol F (**1**) was isolated from the rhizome of *Alisma orientalis*, which is used in traditional Chinese medicine for the treatment of diabetes and as a diuretic.[1] First syntheses of this sesquiterpene were achieved by the groups of Echavarren[2] as well as Sun and Lin[3] with a maximum ee of 88%. Here we report a concise access to virtually enantiopure (+)-**1** from the commercially available monoterpene (*R*)-limonene.

## Results and Discussion

Scheme 1 depicts our retrosynthetic plan for (+)-orientalol F (**1**). Similar to our recently communicated routes to the guaianes (–)-englerin A[4] and (–)-oxyphyllol,[5] key steps are chemo- and stereoselective oxidation reactions of polyolefins next to a ring-closing metathesis event to generate the carbobicyclic framework. Thus, an oxidative cyclofunctionalization of dienol **2** was envisaged for construction of the oxygen-bridged sesquiterpene **1**. Dienol **2** in turn was traced back to epoxy ester **3**, preparation of which was planned by selective epoxidation of triene **4**. In another key operation, the hydroazulene should be constructed by ring-closing metathesis of tetraene **5**, which was to be assembled through carbonyl olefination from unsaturated aldehyde **6**. This aldehyde is readily accessible according to a published procedure from (*R*)-limonene by chemoselective ozonolysis followed by intramolecular aldol condensation.[6]




**Scheme 1.** Retrosynthetic plan for guaiane **1**.

Gratifyingly, with substrate **6** an efficient and completely stereoselective Wittig reaction with stabilized ylide **7**[7] succeeded in contrast to its saturated cyclopentane analog that was used for the synthesis of (–)-englerin A (Scheme 2).[4] While reflux in toluene was suitable for this process, simply heating the reactants **6** and **7** neat to 100 °C provided an optimum 90% yield of the (*E*)-configured enoate **5**. Using the Grubbs I catalyst **8**, tetraene **5** cyclized smoothly to give hydroazulene **4**, whereas the Grubbs II catalyst was too reactive for selective conversion of **5**.[8] Removal of ruthenium residues by oxidation with small amounts of lead tetraacetate and filtration over silica gel prior to flash chromatography was essential for isolation of **4** in reproducibly high yield.[9,10] Shi epoxidation with catalyst **9**[11] turned out to be the method of choice for chemo- and stereoselective epoxidation of only the isolated olefin of **4**.[12] Optimum conditions involved rigorous exclusion of atmospheric oxygen and running the reaction at ambient temperature in order to avoid formation of overoxidation products. Since we obtained the required α-epoxide **3** at room temperature with the D- (**9**) and with the L-catalyst *ent*-**9** in comparable yields, the diastereoselectivity is completely controlled by the substrate under these conditions. As already applied to the synthesis of englerin A,[4] the ester function in **3** was transformed via a Weinreb amide (**10**) into a methyl ketone (**11**). This compound yielded suitable crystals for X-ray diffraction analysis, through which the stereochemical outcome of the Shi epoxidation was unequivocally proven in retrospect.[13,14]

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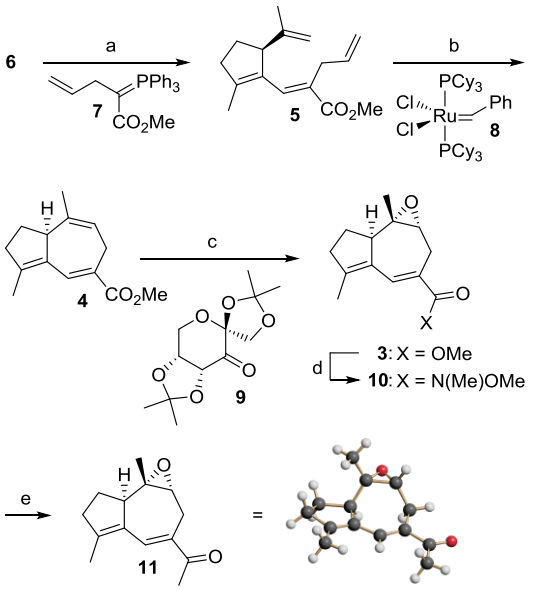
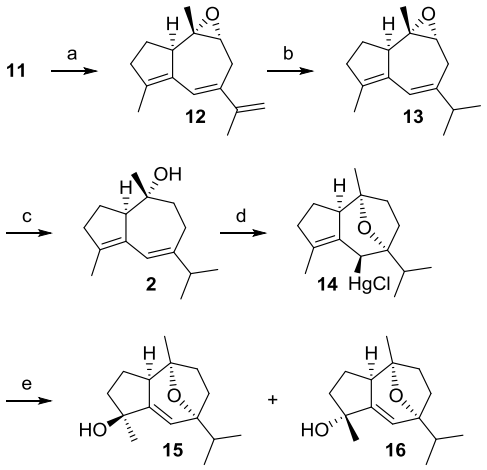


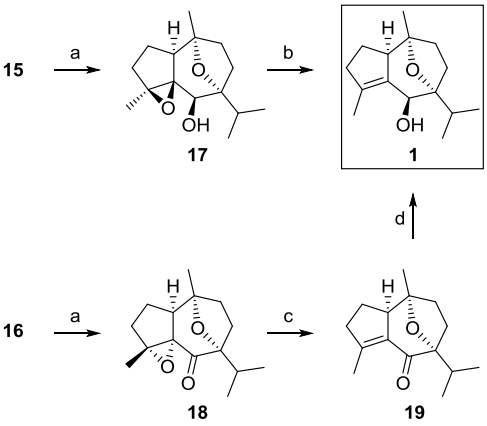

**Scheme 2.** Synthesis of dienone **11**. Reagents and conditions: (a) **7**, 100 °C, 91%; (b) **8** (3 mol-%), $CH_2Cl_2$, room temp., 90%; (c) oxone, **9** (30 mol-%), MeCN, $H_2O$, pH 10.5, room temp., 67%; (d) MeONHMe•HCl, i-PrMgCl, THF, −40 °C to room temp.; (e) MeLi, THF, −40 °C to room temp., 89% (2 steps).

Wittig methylenation of ketone **11** gave conjugated triene **12** (Scheme 3). Hydrogenation of **12** in the presence of the Wilkinson catalyst $(PPh_3)_3RhCl$ enabled a completely chemoselective conversion of only the terminal olefin to afford epoxy diene **13**.[15] Lithium aluminium hydride then effected a regioselective reductive epoxide opening of **13** with formation of tertiary alcohol **2**. Noteworthily, compound **2** was described as a natural product isolated from the soft coral *Nephthea chabrollii*.[16] However, the data of synthetic **2** did not match the values reported in the literature for the naturally occuring sesquiterpene with respect to specific rotation and $^1$H NMR shifts. Thus, revision of the purported structure for this natural product is probably required. After considerable experimentation, intramolecular oxymercuration using mercury trifluoroacetate[17a,b] and subsequent ligand exchange with sodium chloride eventually allowed an efficient cyclofunctionalization to give a single organomercury chloride **14**. Oxidative demercuration[17] of **14** proceeded in high yield, but with complete allylic transposition to furnish a 1.1:1 mixture of epimeric allyl alcohols **15** and **16**. NOESY measurements showed a strong NOE between the angular hydrogen atom and the methyl group at the cyclopentane moiety of **15**, whereas a corresponding NOE was not observed for **16**. The β-hydroxy epimer **15** was found to be identical to a late stage intermediate used in the Echavarren synthesis of orientalol F.[2]




**Scheme 3.** Conversion of dienone **11** into allylic alcohols **15** and **16**. Reagents and conditions: (a) $Ph_3P{=}CH_2$, THF, room temp.; (b) $H_2$, $(PPh_3)_3RhCl$ (10 mol-%), benzene, EtOH, room temp., 92% (2 steps); (c) $LiAlH_4$, $Et_2O$, 20 °C, 72%; (d) $Hg(O_2C\text{-}CF_3)_2$, $CH_2Cl_2$, MeOH, −78 °C, then NaCl, aq. $NaHCO_3$, −78 °C to room temp.; (e) $O_2$, $NaBH_4$, DMF, 0 °C to room temp., 93% (2 steps).

Following the protocol of Echavarren,[2] oxidation of **15** with Collins reagent gave rise to epoxy alcohol **17** (Scheme 4). This compound was subsequently deoxygenated with a lower valent tungsten halide[18] to yield (+)-orientalol F (**1**) for the first time in high enantiomeric purity, i. e. 98% ee as for the starting material (*R*)-limonene. Pleasingly, the novel α-epimer **16** could be converted to the target molecule **1** as well. In this case, oxidation with excess Collins reagent did not stop at the epoxy alcohol stage but led directly to epoxy ketone[19] **18** that was smoothly deoxygenated with molybdenum hexacarbonyl[20] to give the known unsaturated ketone **19**.[2] Again following the protocol of Echavarren,[2] Luche reduction of **19** then provided (+)-orientalol F (**1**).




**Scheme 4.** Completion of the synthesis of (+)-orientalol F (**1**). Reagents and conditions: (a) $CrO_3$•$py_2$, 4 Å sieves, $CH_2Cl_2$, −10 °C to room temp., 60% **17** from **15**, 71% **18** from **16**; (b) $WCl_6$/BuLi (1:2), THF, −78 °C to 45 °C, 73%; (c) $Mo(CO)_6$, DME, reflux, 90%; (d) $NaBH_4$, $CeCl_3$•$7H_2O$, MeOH, room temp., 79% (90% brsm).

## Conclusions

In summary, a highly efficient ring-closing metathesis of tetraene **5** and selective oxidative transformations of polyenes **4** and **2** were used as the key operations in a straightforward synthesis of the guaiane sesquiterpene **1** from (*R*)-limonene.

## Experimental Section

**General Remarks:** THF and DCM were dried and purified by passage through a MB-SPS-800 device using molecular sieves. All commercially available reagents were used as received. Reactions were performed under argon atmosphere. Thin layer chromatography (TLC) was performed on Merck silica gel 60 $F_{254}$ 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm and subsequently developed using anisaldehyde solution as appropriate. Flash column chromatography was carried out using silica gel (Merck, particle size 40-63 microns). Melting points were measured on a Wagner & Munz PolyTherm A and are uncorrected. Optical rotations were measured on a Perkin Elmer 341 LC polarimeter. NMR spectra were recorded on a Bruker DRX500P (500.13 MHz $^1$H, 125.77 MHz $^{13}$C) or else on an Avance-III-600 (600.16 MHz $^1$H, 150.92 MHz $^{13}$C) spectrometer. Chemical shifts ($\delta$) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual proton-containing solvent as internal standard ($CDCl_3$ at 7.27 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q (quartet), spt (septet), br (broad). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Infrared spectra were recorded on a THERMONICOLET Avatar 360 instrument using ATR. Mass spectra were recorded with an Agilent 5973N detector coupled with an Agilent 6890N GC (GC–MS, 70 eV) or else with a Bruker Esquire-LC (direct injection as a methanolic $NH_4OAc$ solution, ESI). HRMS spectra were recorded on a Finnigan MAT 95 (EI, 70 eV) or a Bruker Daltonic "Impact II" (ESI-TOF). Elemental analysis was performed on a Hekatech EA 3000. The X-ray diffraction analysis was carried out with a Bruker Kappa CCD diffractometer.

**But-3-en-1-yltriphenylphosphonium Bromide:** 4-Bromo-1-butene (0.93 g, 6.89 mmol) and triphenyl phosphine (2.17 g, 8.27 mmol) were dissolved in toluene (30 mL). The mixture was refluxed for 5 d and then cooled to room temperature. The precipitate was filtered off and washed with a small amount of toluene. Drying under vacuum afforded but-3-en-1-yltriphenylphosphonium bromide (1.81 g, 66%) as a colorless solid.[7] M.p. 221 °C. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.86–7.67 (m, 15 H), 5.99 (ddt, *J* = 16.9, 10.2, 6.5 Hz, 1 H), 5.04 (dd, *J* = 17.0, 1.2 Hz, 1 H), 4.98 (d, *J* = 10.2 Hz, 1 H), 3.94 (m, 2 H), 2.47–2.40 (m, 2 H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 135.0 (d, $J_{C,P}$ = 3.0 Hz, CH), 134.9 (d, $J_{C,P}$ = 14.8 Hz, CH), 133.7 (d, $J_{C,P}$ = 10.0 Hz, CH), 130.5 (d, $J_{C,P}$ = 12.6 Hz, CH), 118.1 (d, $J_{C,P}$ = 85.9 Hz, C), 117.4 (s, $CH_2$), 26.6 (d, $J_{C,P}$ = 3.7 Hz, $CH_2$), 22.3 (d, $J_{C,P}$ = 49.4 Hz, $CH_2$) ppm. MS (ESI, positive): *m/z* = 317 $[M–Br^-]^+$.

**Ylide 7:** To a suspension of but-3-en-1-yltriphenylphosphonium bromide (1.00 g, 2.52 mmol) in THF (2 mL) and toluene (4 mL) at 0 °C was added dropwise a solution of NaHMDS in THF (2 M, 2.52 mL, 5.03 mmol). After stirring for 20 min, the mixture was cooled to –78 °C and stirred for another 10 min. Then methyl chloroformate (0.24 g, 2.52 mmol) was added, and the mixture stirred for 1 h. After warming to room temperature the solvents were removed under vacuum, and the residue was taken up in ethyl acetate. Filtration and concentration of the filtrate yielded phosphorus ylide **7** (0.81 g, 86%) as a brown solid.[7] M.p. 137 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 7.61–7.58 (m, 6 H), 7.53–7.51 (m, 3 H), 7.44 (s, 6 H), 5.81–5.79 (m, 1 H), 4.69–4.51 (m, 2 H), 3.58 and 3.12 (s, 3 H), 2.72–2.64 (m, 2 H) ppm. $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ = 170.3 (s, C), 141.0 (s, CH), 133.6 (s, CH), 131.6 (s, CH), 128.4 (d, $J_{C,P}$ = 11.5 Hz, CH), 111.7 (s, $CH_2$), 50.0 and 48.7 (s, $CH_3$), 31.2 (d, $J_{C,P}$ = 137.9 Hz, $CH_2$) ppm, 4-C not visible. MS (ESI, positive): *m/z* = 375 $[M+H]^+$.

**Tetraene 5:** Aldehyde **6**[6] (975 mg, 6.49 mmol) and ylide **7** (4.86 g, 12.9 mmol) were stirred for 3 d at 100 °C. Then the mixture was cooled to room temperature and purified by column chromatography (isohexane/ethyl acetate 10:1) to afford tetraene **5** (1.446 g, 90%) as a colorless oil as a single diastereomer. $[\alpha]_D^{20}$ = +22 (*c* = 1.19, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.37 (s, 1 H), 5.76–5.85 (m, 1 H), 4.92–4.99 (m, 2 H), 4.66–4.69 (m, 1 H), 4.55 (d, *J* = 0.6 Hz, 1 H), 3.73 (s, 3 H), 3.46–3.48 (m, 1 H), 3.00–3.11 (m, 2 H), 2.38–2.48 (m, 1 H), 2.22–2.32 (m, 1 H), 2.00–2.10 (m, 1 H), 1.83 (s, 3 H), 1.64–1.73 (m, 1 H), 1.68 (s, 3 H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 169.1 (C), 147.4 (C), 147.1 (C), 136.5 (CH), 135.1 (CH), 133.8 (C), 127.3 (C), 115.0 ($CH_2$), 110.2 ($CH_2$), 54.4 (CH), 51.8 ($CH_3$), 37.4 ($CH_2$), 31.7 ($CH_2$), 29.2 ($CH_2$), 20.7 ($CH_3$), 15.6 ($CH_3$) ppm. IR (ATR): $\nu$ = 3078 (w), 2950 (m), 2840 (w), 1917 (w), 1844 (w), 1770 (w), 1709 (s), 1651 (m), 1636 (m), 1620 (m), 1435 (m), 1375 (m), 1265 (s), 1208 (s), 1124 (m), 1064 (m), 994 (m), 892 (s), 831 (m), 760 (m), 634 (m) $cm^{-1}$. MS (GC–MS, EI): *m/z* (%) = 246 (5) $[M]^+$, 231 (11) $[M–CH_3]^+$, 215 (6), 205 (89), 187 (26), 171 (35), 157 (17), 145 (100), 131 (51), 119 (39), 105 (31), 91 (46), 77 (29), 59 (12), 41 (21). HRMS: calcd for $C_{16}H_{22}O_2$ $[M]^+$ 246.1620; found 246.1612.

**Hydroazulene 4:** A solution of tetraene **5** (557 mg, 2.26 mmol) and Grubbs II catalyst **8** (56 mg, 67 μmol) in DCM (55 mL) was stirred for 2 h with occasional short time evaporation for ethylene removal and subsequently treated with $Pb(OAc)_4$ (60 mg, 136 μmol). After stirring overnight, the mixture was filtered over a pad of silica gel and then evaporated. Purification of the residue by column chromatography (isohexane/ethyl acetate 10:1) yielded the air sensitive hydroazulene **4** (444 mg, 90%) as a brown oil. $[\alpha]_D^{20}$ = +43 (*c* = 0.64, MeOH). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.41 (d, *J* = 2.2 Hz, 1 H), 5.62–5.66 (m, 1 H), 4.08 (br s, 1 H), 3.73 (s, 3 H), 3.04–3.28 (m, 2 H), 2.22–2.53 (m, 2 H), 1.92–2.10 (m, 2 H), 1.82 (s, 3 H), 1.74 (d, *J* = 1.3 Hz, 3 H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 169.1 (C), 144.7 (C), 140.7 (C), 133.4 (CH), 132.8 (C), 126.3 (C), 123.2 (CH), 51.9 ($CH_3$), 47.8 (CH), 38.1 ($CH_2$), 25.3 ($CH_2$), 24.7 ($CH_2$), 21.0 ($CH_3$), 14.5 ($CH_3$) ppm. IR (ATR): $\nu$ = 3018 (w), 2948 (w), 2909 (w), 2832 (w), 2056 (w), 1770 (w), 1701 (m), 1653 (m), 1622 (m), 1457 /m), 1433 (m), 1375 (m), 1245 (s), 1196 (s), 1170 (m), 1080 (m), 973 (m), 911 (m), 859 (m), 811 (m), 764 (m), 707 (m), 644 (m) $cm^{-1}$. MS (GC–MS, EI): *m/z* (%) = 218 (41) $[M]^+$, 203 (22 ) $[M–CH_3]^+$, 189 (28), 171 (11), 159 (100), 143 (31), 128 (42), 115 (27), 105 (13), 91 (20), 77 (14), 59 (6), 39 (7). HRMS: calcd for $C_{14}H_{18}O_2$ $[M]^+$ 218.1307; found 218.1299.

**Epoxide 3:** To a solution of ketone **9** (18.1 mg, 70 μmol), substrate **4** (51.0 mg, 234 μmol) and a catalytic amount of tetrabutylammonium hydrogen sulfate in MeCN (2.5 mL) was added 2.5 mL of a buffer (0.05 M $Na_2B_4O_7 \cdot 10\ H_2O$ in $4 \cdot 10^{-4}$ M aqueous $Na_2(EDTA)$). Subsequently were added solutions of oxone (132 mg, 215 μmol in 1 mL of $4 \cdot 10^{-4}$ M aqueous $Na_2(EDTA)$) and $K_2CO_3$ (125 mg, 908 μmol in 1 mL of $4 \cdot 10^{-4}$ M aqueous $Na_2(EDTA)$) simultaneously over 20 min. The mixture was diluted with ethyl acetate and washed with saturated aqueous $NH_4Cl$ solution and brine. Drying over $MgSO_4$ and evaporation of the solvents afforded a residue, that was purified by column chromatography (isohexane/ethyl acetate 5:1) to give epoxide **3** (36.6 mg, 67%) as a colorless solid. M.p. 55 °C. $[\alpha]_D^{20}$ = +93 (*c* = 0.56, $CHCl_3$). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 7.53 (d, *J* = 2.3 Hz, 1 H), 3.78 (s, 3 H), 3.27–3.46 (m, 2 H), 3.07 (dd, *J* = 8.1, 6.6 Hz, 1 H), 2.34–2.64 (m, 3 H), 1.97–2.08 (m, 2 H), 1.89 (s, 3 H), 1.18 (s, 3 H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 168.8 (C), 147.7 (C), 134.9 (CH), 132.8 (C), 123.9 (C), 63.1 (CH), 60.0 (C), 52.1 ($CH_3$), 51.1 (CH), 38.7 ($CH_2$), 27.8 ($CH_2$), 22.2 ($CH_2$), 17.2 ($CH_3$), 15.7 ($CH_3$) ppm. IR (ATR): $\nu$ = 2952 (w), 2900 (w), 2830 (w), 2057

(w), 1844 (w), 1791 (w), 1771 (w), 1734 (w), 1688 (s), 1653 (m), 1624 (m), 1589 (m), 1457 (m), 1432 (m), 1378 (m), 1307 (w), 1245 (s), 1176 (m), 1107 (m), 1062 (m), 949 (m), 888 (m), 846 (m), 787 (m), 754 (m), 695 (m) $cm^{-1}$. MS (GC–MS, EI): *m/z* (%) = 234 (32) $[M]^+$, 219 (6) $[M–CH_3]^+$, 205 (8), 191 (17), 175 (16), 159 (33), 145 (19), 131 (100), 115 (41), 105 (34), 91 (56), 77 (28), 43 (34). HRMS: calcd for $C_{14}H_{18}O_3$ $[M]^+$ 234.1256; found 234.1244.

**Methyl Ketone 11:** To a stirred solution of **3** (885 mg, 3.78 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (1.29 g, 13.23 mmol) in dry THF (50 mL) at –40 °C was added isopropylmagnesium chloride (2 M in THF, 11.3 mL, 22.68 mmol) over 15 min. After stirring for 75 min, the reaction was quenched with saturated aqueous $NH_4Cl$ solution, and the mixture was extracted 3× with ethyl acetate. The combined organic layers were washed with brine and dried over $MgSO_4$. Removal of the solvents under vacuum yielded the crude Weinreb amide **10** as a colorless oil (1.05 g).

This crude product (1.05 g) was dissolved in dry THF (50 mL) and cooled to –40 °C. A solution of methylmagnesium bromide (3 M in diethyl ether, 3.8 mL, 11.34 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 1 h. Then it was poured into saturated aqueous $NH_4Cl$ solution, extracted 3× with DCM, and the combined organic layers were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (isohexane/ethyl acetate 5:1) to afford methyl ketone **11** (730 mg, 89%, 2 steps) as a colorless solid. M.p. 102 °C. $[\alpha]_D^{20}$ = +58 (*c* = 0.46, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): δ = 7.34 (s, 1 H), 3.55 (dd, *J* = 15.4, 6.3 Hz, 1 H), 3.37 (br s, 1 H), 2.97 (dd, *J* = 8.2, 6.3 Hz, 1 H), 2.42–2.59 (m, 2 H), 2.39 (s, 3 H), 2.29 (dd, *J* = 15.6, 8.4 Hz, 1 H), 1.99–2.07 (m, 2 H), 1.90 (s, 3 H), 1.16 (s, 3 H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 198.7 (C), 148.4 (C), 135.4 (CH), 133.6 (C), 133.2 (C), 63.0 (CH), 59.8 (C), 51.2 (CH), 38.9 ($CH_2$), 25.6 ($CH_2$), 25.4 ($CH_3$), 22.2 ($CH_2$), 17.2 ($CH_3$), 14.8 ($CH_3$) ppm. IR (ATR): ν = 2966 (m), 2926 (w), 2834 (w), 1734 (w), 1697 (w), 1653 (m), 1618 (m), 1583 (m), 1517 (w), 1474 (m), 1423 (m), 1379 (s), 1344 (m), 1307 (m), 1282 (m), 1245 (s), 1180 (s), 1151 (m), 1106 (m), 1054 (m), 998 (m), 968 (m), 886 (s), 821 (s), 745 (m), 638 (m), 616 (s) $cm^{-1}$. MS (GC–MS, EI): *m/z* (%) = 218 (17) $[M]^+$, 203 (3) $[M–CH_3]^+$, 189 (5), 175 (31) $[M–CH_3CO]^+$, 157 (8), 133 (21), 115 (17), 105 (22), 91 (4), 77 (15), 65 (8), 43 (100) $[CH_3CO]^+$. HRMS: calcd for $C_{14}H_{18}O_2$ $[M]^+$ 218.1307; found 218.1306.

**Isopropyl Derivative 13:** Methyltriphenylphosphonium bromide (2.39 g, 6.69 mmol) was suspended in dry THF (15 mL), and NaHMDS (2 M in THF, 3.0 mL, 6.02 mmol) was added. After 5 min ketone **11** (730 mg, 3.34 mmol) in dry THF (15 mL) was added dropwise to the above mixture. After stirring for 5 min, the reaction was quenched with saturated aqueous $NH_4Cl$ solution, and the mixture was extracted 3× with DCM. The combined organic layers were dried over $MgSO_4$ and filtered over a pad of silica gel (elution with isohexane/ethyl acetate 5:1) to yield the crude triene **12** (733 mg) as a colorless solid.

The above crude triene **12** (733 mg) and $(PPh_3)_3RhCl$ (304 mg, 0.33 mmol) were dissolved in ethanol (15 mL) and benzene (15 mL). The resulting mixture was stirred under hydrogen (1 atm) for 2 h and adsorbed on silica subsequently. Column chromatography (isohexane/ethyl acetate 10:1) yielded the isopropyl derivative **13** (646 mg, 91%, 2 steps) as a colorless solid. M.p. 57 °C. $[\alpha]_D^{20}$ = +108 (*c* = 1.32, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): δ = 6.06 (s, 1 H), 3.29 (br s, 1 H), 2.97 (dd, *J* = 8.4, 6.5 Hz, 1 H), 2.59 (dd, *J* = 15.4, 8.2 Hz, 1 H), 2.48 (dd, *J* = 15.1, 6.3 Hz, 1 H), 2.37–2.44 (m, 1 H), 2.27–2.37 (m, 2 H), 1.93–2.01 (m, 2 H), 1.74 (s, 3 H), 1.18 (s, 3 H), 1.05 (d, *J* = 6.6, 3 H), 1.02 (d, *J* = 6.6 Hz, 3 H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 141.3 (C), 135.3 (C), 133.0 (C), 118.8 (CH), 63.9 (CH), 60.4 (C), 51.7 (CH), 38.1 ($CH_2$), 37.8 (CH), 30.6 ($CH_2$), 22.3 ($CH_2$), 21.2 ($CH_3$), 21.1 ($CH_3$), 17.3 ($CH_3$), 14.0 ($CH_3$) ppm. IR (ATR): ν = 2952 (m), 2926 (m), 2834 (m), 1440 (w), 1379 (m), 1362 (w), 1329 (w), 1297 (w), 1269 (w), 1231 (w), 1206 (w), 1179 (w), 1106 (w), 1057 (m), 1015 (m), 907 (w), 883 (s), 823 (s), 749 (s), 716 (w), 677 (w), 629 (w) $cm^{-1}$. MS (GC–MS, EI): *m/z* (%) = 218 (56) $[M]^+$, 203 (19) $[M–CH_3]^+$, 189 (33), 175 (47) $[M–C(CH_3)_2]^+$, 157 (39), 147 (67), 131 (71), 119 (54), 105 (98), 91 (100), 77 (51), 65 (23), 55 (28), 43 (66) $[C(CH_3)_2]^+$. HRMS: calcd for $C_{15}H_{22}O$ $[M]^+$ 218.1671; found 218.1669.

**Tertiary Alcohol 2:** $LiAlH_4$ (43 mg, 1.15 mmol) was suspended in diethyl ether (2.5 mL). A solution of epoxide **13** (50.0 mg, 229 μmol) in diethyl ether (2.5 mL) was added dropwise at 0 °C, and the mixture warmed to 20 °C (not room temperature!) and stirred for 3 d at this temperature. Afterwards Glauber's salt (750 mg) was added, and the suspension was stirred for another 30 min. Subsequently the mixture was filtered through a glass sintered funnel, and the filtrate was concentrated under vacuum. Column chromatography (isohexane/ethyl acetate 2:1) of the residue yielded alcohol **2** (36.2 mg, 72%) as a colorless oil. $[\alpha]_D^{20}$ = –164 (*c* = 0.36, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): δ = 6.01 (s, 1 H), 3.04 (br s, 1 H), 2.42–2.53 (m, 1 H), 2.17–2.41 (m, 3 H), 1.84–2.03 (m, 3 H), 1.79–1.83 (m, 2 H), 1.73 (d, *J* = 1.3 Hz, 3 H), 1.09 (s, 3 H), 1.04 (d, *J* = 6.6 Hz, 3 H), 1.03 (d, *J* = 6.6 Hz, 3 H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 148.2 (C), 136.6 (C), 133.2 (C), 117.8 (CH), 75.7 (C), 57.9 (CH), 44.3 ($CH_2$), 38.1 (CH), 37.3 ($CH_2$), 25.5 ($CH_2$), 24.2 ($CH_2$), 22.4 ($CH_3$), 21.6 ($CH_3$), 21.4 ($CH_3$), 14.4 ($CH_3$) ppm. IR (ATR): ν = 3356 (w), 2958 (s), 2922 (s), 2871 (m), 2838 (m), 1458 (m), 1438 (m), 1373 (m), 1333 (w), 1291 (m), 1196 (m), 1093 (s), 1006 (m), 976 (w), 961 (w), 901 (s), 865 (m), 843 (m), 808 (w), 762 (w) $cm^{-1}$. MS (GC–MS, EI): *m/z* (%) = 220 (48) $[M]^+$, 202 (26) $[M–H_2O]^+$, 187 (40) $[M–H_2O–CH_3]^+$, 177 (24), 159 (76), 147 (49), 131 (40), 119 (59), 105 (61), 91 (88), 79 (46), 55 (24), 43 (100) $[C(CH_3)_2]^+$. HRMS: calcd for $C_{15}H_{24}O$ $[M]^+$ 220.1827; found 220.1826.

**Formation of the Ether Bridge:** Diene **2** (50.0 mg, 227 μmol) was dissolved in DCM (10 mL), and methanol (25.0 mg) was added. Then $Hg(O_2CCF_3)_2$ (116 mg, 272 μmol) was added at –78 °C in one portion, and the mixture was stirred for 15.5 h at this temperature. Thereafter saturated aqueous solution of $NaHCO_3$ (10 mL) and brine (10 mL) were added, and the mixture was warmed to room temperature and stirred for another 3.5 h. Afterwards the layers were separated and the aqueous layer was extracted 3× with diethyl ether. The combined organic layers were dried over $MgSO_4$ and evaporated to yield the crude organomercurial **14** (113.2 mg) as an off-white solid.

A solution of $NaBH_4$ (48 mg, 1.27 mmol) in DMF (15 mL) was cooled to 0 °C. Oxygen was bubbled through this solution for 30 min, and a solution of the above crude organomercurial **14** (113.2 mg) in DMF (3 mL) was added dropwise over 1 h. The mixture was warmed to room temperature and stirred for another 30 min (oxygen bubbling was continued until workup). Subsequently 1 N aqueous HCl was added, and the suspension was filtered through a plug of celite (elution with DCM). The filtrate was diluted with DCM and washed with brine, dried over $MgSO_4$ and concentrated under vacuum. Flash chromatography (isohexane/ethyl acetate 3:1) of the residue afforded the allylic alcohols **15**[2] and **16** (50.2 mg, 94%) as a 1.1:1 diastereomeric mixture.

**Allylic Alcohol 15:** $[\alpha]_D^{20}$ = –27 (*c* = 0.28, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): δ = 5.74 (d, *J* = 2.8 Hz, 1 H), 2.70–2.79 (m, 1 H), 1.88–1.96 (m, 2 H), 1.66–1.85 (m, 5 H), 1.42–1.49 (m, 1 H), 1.37 (s, 3 H), 1.36 (s, 3 H), 1.34–1.39 (m, 1 H), 0.98 (d, *J* = 7.3 Hz, 3 H), 0.98 (d, *J* = 7.3 Hz, 3 H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 150.1 (C), 119.1 (CH), 85.8 (C), 82.4 (C), 77.5 (C), 51.1 (CH), 41.3 ($CH_2$), 38.6 ($CH_2$), 34.0 (CH), 30.5 ($CH_2$), 28.0 ($CH_3$), 26.0 ($CH_3$), 23.8 ($CH_2$), 18.1 ($CH_3$), 17.8 ($CH_3$) ppm. IR (ATR): ν = 3430 (w), 2960 (m), 2872 (m), 1917 (w), 1844 (w), 1780 (s), 1727 (s), 1684 (w), 1651 (m), 1473 (m), 1441 (m), 1684 (w), 1651 (m),

1472 (m), 1441 (m), 1373 (m), 1164 (s), 1122 (s), 1053 (m), 1018 (m), 999 (m), 951 (m), 904 (m), 862 (m), 753 (m), 663 (m), 623 (m) $cm^{-1}$. MS (GC–MS, EI): *m/z* (%) = 218 (10) $[M–H_2O]^+$, 203 (5) $[M–H_2O–CH_3]^+$, 193 (8), 175 (10), 160 (43), 147 (50), 135 (16), 119 (19), 105 (33), 91 (37), 77 (21), 55 (14), 43 (100) $[C(CH_3)_2]^+$.

**Allylic Alcohol 16:** $[\alpha]_D^{20}$ = –49 (*c* = 0.91, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): δ = 5.67 (d, *J* = 2.5 Hz, 1 H), 3.02–3.10 (m, 1 H), 1.64–1.97 (m, 7 H), 1.41–1.48 (m, 1 H), 1.39 (s, 3 H), 1.36 (s, 3 H), 1.18–1.25 (m, 1 H), 0.98 (d, *J* = 6.9 Hz, 3 H), 0.98 (d, *J* = 6.9 Hz, 3 H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 147.6 (C), 119.6 (CH), 85.6 (C), 82.5 (C), 77.2 (C), 50.2 (CH), 41.1 ($CH_2$), 38.4 ($CH_2$), 34.0 (CH), 30.5 ($CH_2$), 26.1 ($CH_3$), 25.6 ($CH_3$), 23.1 ($CH_2$), 18.1 ($CH_3$), 17.9 ($CH_3$) ppm. IR (ATR): ν = 3391 (w), 2962 (s), 2928 (s), 2871 (m), 1666 (w), 1486 (w), 1458 (w), 1374 (m), 1304 (w), 1268 (w), 1224 (w), 1181 (m), 1121 (m), 1086 (s), 1055 (m), 1022 (m), 996 (w), 953 (w), 908 (m), 861 (m), 776 (w), 623 (w) $cm^{-1}$. MS (GC–MS, EI): *m/z* (%) = 236 (3) $[M]^+$, 218 (7) $[M–H_2O]^+$, 203 (6) $[M–H_2O–CH_3]^+$, 193 (6), 175 (12), 160 (32), 147 (40), 133 (17), 119 (14), 105 (30), 91 (34), 77 (21), 55 (11), 43 (100) $[C(CH_3)_2]^+$. HRMS: calcd for $C_{15}H_{24}O_2$ $[M]^+$ 236.1776; found 236.1784.

**Epoxy Alcohol 17:** Pyridine (353 μl, 4.37 mmol) was added dropwise to a suspension of chromium trioxide (218.6 mg, 2.18 mmol) and molecular sieves 4 Å (330 mg) in dichloromethane (15 mL) cooled to –10 °C. The mixture was warmed to room temperature and stirred for 1 h. After cooling the mixture to –10 °C, a solution of allyl alcohol **15** (129.0 mg, 0.546 mmol) in dichloromethane (3 mL) was added, and the mixture was warmed to room temperature and stirred for 6.5 h. The mixture was diluted with diethyl ether (10 mL) and filtered over a pad of silica gel. Following removal of the solvents under vacuum, the residue was purified by flash chromatography (pentane/diethyl ether 8:2) to give epoxy alcohol **17**[2] (82.6 mg, 60%) as a colorless oil. $[\alpha]_D^{23}$ = –33.9 (c = 1.02, $CH_2Cl_2$). $^1$H NMR (600 MHz, $CDCl_3$): δ = 4.09 (dd, *J* = 10.5, 1.1 Hz, 1 H), 2.25 (d, *J* = 10.5 Hz, 1 H), 2.07–2.12 (m, 1 H), 1.93–2.04 (m, 2 H), 1.86–1.92 (m, 2 H), 1.67 (tdd, *J* = 12.8, 3.8, 1.1 Hz, 1 H), 1.50 (s, 3 H), 1.47–1.55 (m, 1 H), 1.34–1.42 (m, 1 H), 1.21 (s, 3 H), 1.04 (d, *J* = 6.4 Hz, 3 H), 1.03 (d, *J* = 6.4 Hz, 3 H), 0.97–1.06 (m, 1 H) ppm. $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 87.6 (C), 82.9 (C), 71.2 (C), 67.2 (CH), 65.0 (C), 50.3 (CH), 33.3 (CH), 32.9 ($CH_2$), 31.4 ($CH_2$), 28.1 ($CH_2$), 24.3 ($CH_3$), 20.1 ($CH_2$), 18.2 ($CH_3$), 17.3 ($CH_3$), 15.2 ($CH_3$) ppm. IR (ATR): ν = 3484 (br w), 2963 (m), 2926 (m), 2876 (w), 1473 (m), 1456 (m), 1379 (m), 1314 (w), 1260 (m), 1230 (w), 1187 (m), 1111 (m), 1076 (s), 1057 (s), 1019 (s), 1007 (s), 935 (s), 871 (s), 782 (s), 768 (s), 702 (m), 653 (m), 606 (s) $cm^{-1}$. MS (ESI, positive): 270.1 $[M+NH_4]^+$, 522.2 $[2M+NH_4]^+$.

**Epoxy Ketone 18:** Pyridine (401 μl, 4.96 mmol) was added dropwise to a suspension of chromium trioxide (247.8 mg, 2.48 mmol) and molecular sieves 4 Å (370 mg) in dichloromethane (18 mL) cooled to –10 °C. The mixture was warmed to room temperature and stirred for 1 h. After cooling the mixture to –10 °C, a solution of allyl alcohol **16** (117 mg, 0.495 mmol) in dichloromethane (3 mL) was added, and the mixture was warmed to room temperature and stirred for 24 h. The mixture was diluted with diethyl ether (10 mL) and filtered over a pad of silica gel. Following removal of the solvents under reduced pressure, the residue was purified by flash chromatography (pentane/diethyl ether 8:2) to give epoxy ketone **18** (88.0 mg, 71%) as a colorless oil. $[\alpha]_D^{23}$ = –0.73 (*c* = 1.23, $CH_2Cl_2$). $^1$H NMR (600 MHz, $CDCl_3$) δ = 2.76 (d, *J* = 9.4 Hz, 1 H), 2.16 (spt, *J* = 7.2 Hz, 1 H), 2.03–2.12 (m, 2 H), 1.85–1.95 (m, 2 H), 1.69–1.77 (m, 1 H), 1.61–1.70 (m, 1 H), 1.50–1.56 (m, 1 H), 1.41–1.50 (m, 1 H), 1.35 (s, 3 H), 1.32 (s, 3 H), 0.99 (d, *J* = 6.8 Hz, 3 H), 0.98 (d, *J* = 6.8 Hz, 3 H) ppm. $^{13}$C NMR (150 MHz, $CDCl_3$) δ = 202.0 (C), 90.9 (C), 84.5 (C), 74.9 (C), 71.4 (C), 55.3 (CH), 32.6 ($CH_2$), 32.0 ($CH_2$), 30.5 ($CH_2$), 24.7 ($CH_3$), 23.2 ($CH_2$), 17.5 ($CH_3$), 17.2 ($CH_3$), 14.9 ($CH_3$) ppm. IR (ATR): ν = 2979 (m), 2961 (m), 2929 (m), 2899 (w), 2877 (w), 1724 (s), 1699 (w), 1684 (w), 1450 (w), 1389 (m), 1368 (m), 1305 (w), 1273 (w), 1183 (w), 1097 (m), 1070 (m), 1034 (m), 970 (m), 952 (m), 923 (w), 877 (s), 838 (m), 777 (m), 735 (m), 706 (w) $cm^{-1}$. MS (ESI, positive): 268.2 $[M+NH_4]^+$, 518.2 $[2M+NH_4]^+$. HRMS: calcd for $C_{15}H_{26}NO_3$ $[M+NH_4]^+$ 268.1907; found 268.1913.

**Enone 19:** A solution of epoxy ketone **18** (90.0 mg, 0.36 mmol) and molybdenum hexacarbonyl (109.2 mg, 0.414 mmol) in 1,2-dimethoxyethane (3.5 mL) was stirred at 90 °C for 16 h. After removal of the solvent under vacuum, the residue was purified by flash chromatography (pentane/diethyl ether 20:1) to yield enone **19**[2,3] (75.7 mg, 90%) as a colorless oil. $[\alpha]_D^{23}$ = –27.8 (*c* = 0.96, $CH_2Cl_2$). $^1$H NMR (500 MHz, $CDCl_3$) δ = 3.15–3.25 (m, 1 H), 2.39–2.58 (m, 1 H), 2.23–2.33 (m, 1 H), 2.17 (spt, *J* = 6.9 Hz, 1 H), 1.94–2.08 (m, 5 H), 1.84–1.92 (m, 1 H) 1.57–1.64 (m, 1 H), 1.42–1.50 (m, 1 H), 1.33–1.41 (m, 1 H), 1.31 (s, 3 H), 1.01 (d, *J* = 6.9 Hz, 3 H), 1.00 (d, *J* = 6.9 Hz, 3 H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$) δ = 199.8 (C), 154.4 (C), 131.9 (C), 91.0 (C), 84.3 (C), 57.8 (CH), 38.8 ($CH_2$), 33.2 ($CH_2$), 30.5 (CH), 30.0 ($CH_2$), 25.9 ($CH_2$), 24.6 ($CH_3$), 18.4 ($CH_3$), 17.3 ($CH_3$), 15.9 ($CH_3$) ppm. IR (ATR): ν = 2964 (m), 2926 (m), 2876 (m), 1734 (w), 1716 (w), 1688 (s), 1652 (m), 1625 (s), 1457 (m), 1434 (m), 1375 (m), 1268 (m), 1176 (w), 1143 (w), 1115 (m), 1076 (s), 1034 (m), 1005 (m), 975 (m), 929 (m), 900 (w), 883 (m), 800 (m), 769 (m) $cm^{-1}$. MS (ESI, positive): 235.3 $[M+H]^+$.

**(+)-Orientalol F (1) from Epoxy Alcohol 17:** To a suspension of tungsten hexachloride (365.0 mg, 0.92 mmol) in THF (10 mL) cooled to –78 °C was added BuLi (2.2 M in hexane, 0.84 mL, 1.84 mmol). After warming the mixture to room temperature over 1 h, it was cooled to 0 °C and treated with a solution of epoxy alcohol **17** (116.0 mg, 0.46 mmol) in THF (4 mL). The mixture was stirred for 30 min at room temperature and 30 min at 45 °C, and then the reaction was quenched by addition of an aqueous solution of sodium potassium tartrate (1.5 M, 8 mL) and NaOH (2 N, 8 mL). Following extraction with diethyl ether (3×), the combined organic layers were washed with brine and dried over $MgSO_4$. Removal of the solvents under vacuum and purification by flash chromatography (pentane/ethyl acetate 15:1) afforded (+)-orientalol F[1-3] (**1**, 79.3 mg, 73%) as a white solid.

**(+)-Orientalol F (1) from enone 19:** To a mixture of enone **19** (83.0 mg, 0.367 mmol) and cerium trichloride heptahydrate (136.7 mg, 0.367 mmol) in methanol (7 mL) was added sodium borohydride (14.0 mg, 0.367 mmol). After stirring for 24 h at room temperature, the reaction was quenched by addition of brine. The mixture was extracted with diethyl ether (3×), the combined organic layers were washed with brine and dried over $MgSO_4$, and the solvents were removed under vacuum. Flash chromatography (pentane/diethyl ether 8:2) provided (+)-orientalol F[1-3] (**1**, 66.5 mg, 79%, 90% based on recovered starting material) as a white solid and unreacted enone **19** (10.1 mg).

**(+)-Orientalol F (1):** M.p. 38.2–39.5 °C. $[\alpha]_D^{23}$ = +13.7 (c = 0.57, $CH_2Cl_2$) from epoxy alcohol **17** and $[\alpha]_D^{23}$ = +13.5 (*c* = 0.52, $CH_2Cl_2$) from enone **19**; ref [2]: $[\alpha]_D^{25}$ = +12.2 (*c* = 0.5, $CH_2Cl_2$) for **1** with 88% ee, ref [3]: $[\alpha]_D^{23}$ = –7.88 (*c* = 0.5, $CH_2Cl_2$) for *ent*-**1** with 67% ee. $^1$H NMR (600 MHz, $CDCl_3$): δ = 4.40–4.45 (m, 1 H), 2.64–2.70 (m, 1 H), 2.28–2.36 (m, 1 H), 2.17–2.24 (m, 1 H), 1.94 (spt, *J* = 7.0 Hz, 1 H), 1.88 (s, 3 H), 1.76–1.82 (m, 2 H), 1.66–1.72 (m, 1 H), 1.59–1.64 (m, 1 H), 1.44 (d, *J* = 7.5 Hz, 1 H), 1.26–1.32 (m, 1 H), 1.17–1.25 (m, 1 H), 1.18 (s, 3 H), 1.03 (d, *J* = 7.0 Hz, 3 H), 1.01 (d, *J* = 7.0 Hz, 3 H) ppm. $^{13}$C NMR (150 MHz, $CDCl_3$): δ = 133.5 (C), 133.0 (C), 86.6 (C), 84.4 (C), 73.9 (CH), 57.6 (CH), 39.0 ($CH_2$), 31.7 (CH), 31.6 ($CH_2$), 28.6 ($CH_2$), 24.0 ($CH_2$), 23.9 ($CH_3$), 18.1 ($CH_3$), 17.2 ($CH_3$), 14.6 ($CH_3$) ppm. IR (ATR): ν = 2964 (m), 3450 (w), 3401 (w), 2965 (m), 2924 (m), 2878 (w), 2836 (w), 1473 (w), 1374 (m), 1313 (w), 1254 (w), 1176 (m), 1108 (m), 1066 (m), 1008 (s), 975 (w), 931 (m), 901

(m), 871 (w), 799 (m), 769 (w) $cm^{-1}$. MS (ESI, positive): 237.5 $[M+H]^+$, 219.5 $[M+H-H_2O]^+$.

**Keywords:** Asymmetric synthesis • Metathesis • Natural products • Oxidation • Terpenoids

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## Entry for the Table of Contents

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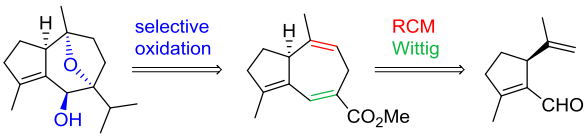


(+)-orientalol F

A highly efficient ring-closing metathesis of a tetraene and selective oxidative transformations of polyenes were used as the key operations in a straightforward synthesis of the title guaiane sesquiterpene from (*R*)-limonene.

**Hydroazulene Synthesis**

*Martin Zahel, Yuzhou Wang, Anne Jäger, Peter Metz**

***Page No. – Page No.***

**A Metathesis Route to (+)-Orientalol F, a Guaiane Sesquiterpene from *Alisma Orientalis***