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Enantioselective Synthesis of (+)-Majusculone

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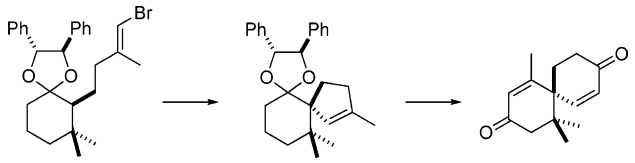
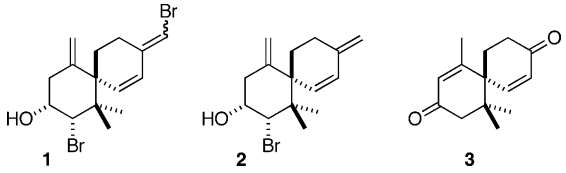


The first enantioselective synthesis of a chamigrane sesquiterpene, (+)-majusculone, has been completed. The quaternary center was generated asymmetrically by alkylidene carbene insertion, with retention of absolute configuration, from a diastereomerically pure ketal.

Introduction

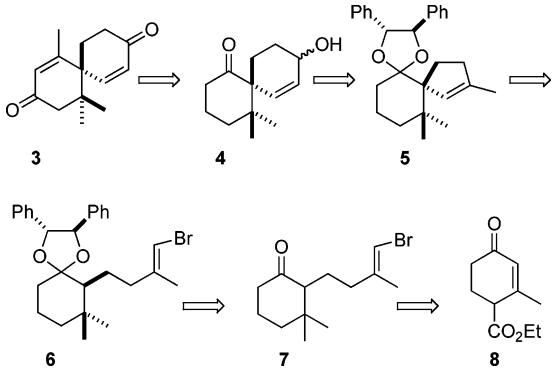
The red algal genus *Laurencia* is regarded as one of the most prolific sources of secondary metabolites, many of which have shown interesting biological activities. For instance, screening of an extract from *Laurencia cartilaginea* led to the isolation of two new closely related bromochamigrenes **1** and **2**. These metabolites showed selective and potent cytotoxicity in the NCI 60 cell antitumor screen, with cytotoxicity profiles that were very similar to one another.[1] They were particularly effective against the colon cancer subpanel. Remarkably, no enantioselective synthesis of a chamigrane has yet been reported. We report a general enantioselective approach to the chamigrane sesquiterpenes, culminating in the first synthesis of majusculone **3**.



Results and Discussion

There have been only a few syntheses of chamigranes reported. In 1986, Martin prepared a chamigrane using intramolecular bromonium induced carbocylization of an exocyclic tetrasubstituted alkene.[2] Iwata in 1988 reported the preparation of 9-(bromomethylene)-1,2,5-trimethylspiro[5.5]undeca-1,7-dien-3-one, using an approach based on the copper-catalyzed cyclization of a diazo ketone.[3] In 1991, Niwa and Yamada reported the synthesis of a bromo chamigrene mixture.[4] Additionally, (±)-α-chamigrene has been prepared independently by Canonne[5] and by Chen.[6]

SCHEME 1



The challenge in the synthesis of the chamigranes is the stereocontrolled assembly of the spiro ring fusion. We envisioned (Scheme 1) that (+)-majusculone **3** could be prepared from the readily available Hagemann's ester **8**. The key step of our retrosynthesis was the construction of the spirocyclic quaternary center by intramolecular C−H insertion with retention of absolute configuration from the diastereomerically pure

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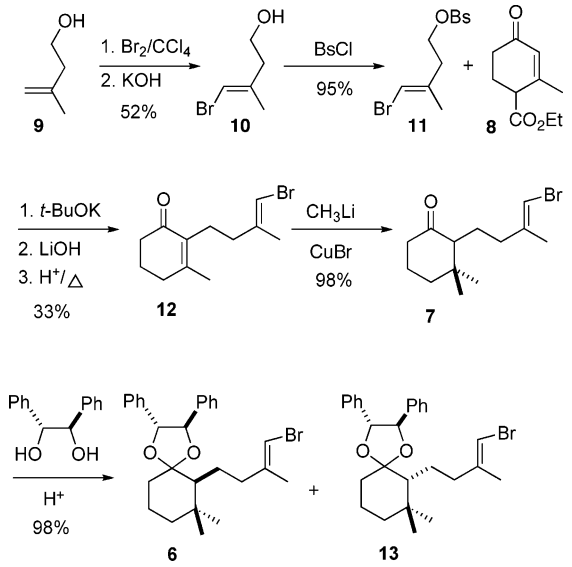
SCHEME 2

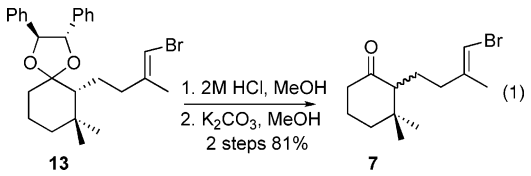


ketal **6**.[7] The efficiency of such a strategy had recently been demonstrated in our group by the enantioselective synthesis of (−)-morphine.[8] A key question was whether the alkylidene carbene derived from **6** would insert efficiently into the very congested target methine.

Preparation of Ketal 6. Our synthesis began with the bromination and subsequent dehydrobromination of 3-methyl-3-buten-1-ol **9** (Scheme 2).[9] The alcohol **10** was then activated by converting the alcohol to the benzenesulfonate ester **11** under phase transfer conditions, to prevent the displacement of the reactive homoallylic benzenesulfonate ester by in situ generated chloride anion. Hagemann's ester **8** was then alkylated with the benzenesulfonate **11**. The product ester was saponified with $LiOH{\cdot}H_2O$ and then decarboxylated to **12** by heating with concentrated HCl in THF.[10] Conjugate addition of Me_2CuLi efficiently produced the ketone **7**, which was quantitatively condensed with (*R*,*R*)-(+)-hydrobenzoin[8] to give the ketals **6** and **13** as a 1:1 mixture.

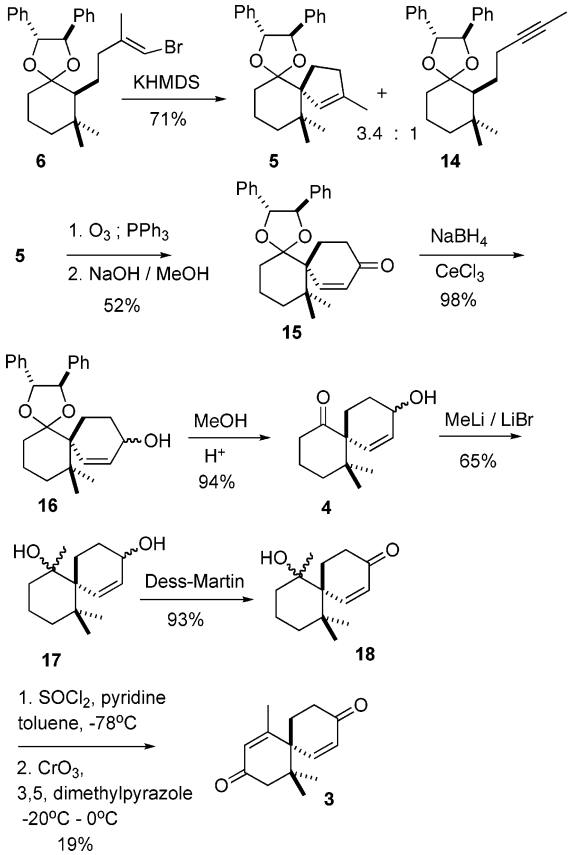
The ketals **6** and **13** were partially separated by column chromatography, using TLC mesh silica gel, to give a 70:30 mix of the diasteromers.[8] Further purification by column chromatography was not efficient, so we investigated crystallization solvents. We found that methanol was particularly effective. The diastereomeric purity of the ketal **6** was established by comparing ^{1}H NMR absorptions at δ 4.75 and δ 4.53 for the methines of the ketal rings of the two diastereomers. The relative configuration of **6** was established by X-ray crystallography.

The mixed ketals enriched in **13** were recycled by heating with 2 M aqueous HCl to give ketone **7**,[11] then epimerizing with K_2CO_3 (eq 1). The resulting racemic ketone was again condensed with (*R*,*R*)-(+)-hydrobenzoin to give back the 1:1 mixture of the diastereomers **6** and **13**.



Preparation of (+)-Majusculone. We were concerned about the ability of the alkylidene carbene to insert into the very congested methine of **6** (Scheme 3), which is also deactivated by the two electron withdrawing ether oxygens of the ketal. In the event, upon exposure to an excess of KHMDS, prepared by sonicating KH in HMDS in toluene,[12] the carbene generated by α-elimination slowly (12 h at 0 °C to room temperature) inserted into the C−H bond, yielding **5**. We also observe the 1,2-rearrangement product, the alkyne **14**. The power of this approach is that the absolute configuration of the newly generated quaternary center was now locked and could not be altered by the acidic conditions later used to remove the ketal protecting group.

SCHEME 3



Ozonolysis of **5** followed immediately by aldol condensation delivered the enone **15**. Luche reduction[13] followed by the

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deprotection of the chiral ketal in 2 M aqueous HCl[11] gave the allylic alcohol **4** as a mixture of diastereomers. Addition of 1.6 M MeLi/LiBr[14] to the congested ketone was difficult,[15] but with four recycles delivered the tertiary alcohol **17**. Oxidation of the secondary alcohol by the Dess−Martin periodinane gave the enone **18**. Dehydration of the tertiary alcohol with thionyl chloride in toluene[4] formed the endo and exo alkenes in a 3:1 ratio. The alkenes formed were not separable by chromatography. Prolonged exposure to acid did not improve the endo/exo ratio before degradation set in. Other methods for dehydration (e.g., $POCl_3$/pyridine) gave poorer ratios, lower yields, or both. Allylic oxidation of the alkene mixture with chromium trioxide[16] gave enantiopure (+)-majusculone **3**.[17] No other methods for allylic oxidation were investigated.

Conclusion

We have developed a general enantioselective route to the spirocyclic chamigrene sesquiterpene skeleton, and accomplished the first synthesis of (+)-majusculone. The power of intramolecular alkylidene C−H insertion to generate a spirocyclic quaternary center with retention of absolute configuration makes it a valuable tool for the synthesis of natural products of biological interest. We believe that the enantiomerically pure alkene **5** could be a useful intermediate for the preparation of **1** and **2** as well as other chamigrene sesquiterpenes.

Experimental Section

(1*S*,8*R*,9*R*)-1-[(3*E*)-4-Bromo-3-methyl-3-butenyl]-2,2-dimethyl-8,9-diphenyl-7,10-dioxaspiro[6,5]decane (6). *p*-Toluenesulfonic acid (0.28 g, 1.47 mmol) was added in one portion to a mixture of ketone **7** (3.93 g, 14.4 mmol), *R*,*R*-(+)-hydrobenzoin (4.63 g, 22.0 mmol), and trimethylorthoformate (2.00 g, 18.8 mmol) in dry CH_2Cl_2 (72 mL). The reaction mixture was stirred overnight at room temperature. Solid $NaHCO_3$ (1.5 g) was added and the mixture was partitioned between water and CH_2Cl_2. The combined organic layer was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give a 1:1 mixture of ketals (6.37 g, 98% yield) as yellow sticky oil. The mixture (6.37 g, 14.0 mmol) was chromatographed on TLC grade silica eluting with 0.1% Et_2O/PE to give a 70:30 mix of **6** and **13** as a yellowish solid (2.85 g). The 70: 30 mixture (2.85 g, 6.1 mmol) was dissolved in PE (2.0 mL) and concentrated under vacuum. This residue was converted with a minimum amount of methanol (2.0 mL) and the surface of the glass was scratched to initiate crystallization. Once crystallization was initiated, the mixture was allowed to sit in the refrigerator for 24 h. The supernatant was removed by pipet and the procedure was repeated two more times. A mixture of diastereomers **6** and **13** in a ratio of 20:1 was obtained as a white solid (0.70 g, 79% based on ketals not recovered). The purity of the compound was checked by ^{1}H NMR at δ 4.75 and δ 4.53. The mixed ketals **6**/**13** were recovered from the supernatant (5.48 g). For **6**: TLC R_f 0.24 (PE/MTBE 99:1); $[\alpha]^{22}_D$ +23.7 (*c* 0.499, $CHCl_3$); ^{1}H NMR δ 7.36−7.19 (m, 10H), 6.02 (s, 1H), 4.89 (d, 1H, J = 8.6 Hz), 4.75 (d, 1H, J = 8.6 Hz), 2.77 (t, 1H), 2.22−2.18 (m, 2H), 1.93−1.88 (m, 2H), 1.93−1.88 (m, 2H), 1.93 (s, 3H), 1.71 (m, 1H), 1.49−1.57 (m, 4H), 1.31 (m, 1H), 1.0 (s, 6H); ^{13}C NMR[18] δ u 143.1, 139.4, 137.0, 113.1, 41.7, 41.3, 37.3, 36.5, 23.6, 19.8; ^{13}C NMR[18] δ d, 129.1, 129.0, 128.8, 128.2, 127.8, 126.4, 101.7, 87.5, 84.1, 53.6, 31.7, 22.1, 19.9; IR (film) 2949, 1948, 1878,1603 cm^{-1}; mp 71−75 °C; CI *m*/*z* (%) 470 (2), 468 (2), 389 (16), 335 (13), 273 (23), 193 (59),177 (100), 139 (36); HRMS calcd for $C_{27}H_{33}O_2Br$ (M^+) 468.1664, obsd 468.1656.

Cyclopentene 5. KHMDS in toluene (0.5 M, 11.1 mL, 5.55 mmol) was added dropwise (30 min) to a stirring solution of diastereopure ketal **6** (0.858 g, 1.83 mmol) in 1,4-dioxane (9 mL) at 0 °C. The mixture was stirred overnight at room temperature, and then partitioned between 30% saturated aqueous NH_4Cl and CH_2Cl_2. The combined organic layer was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield cyclopentene **5** (0.391 g, 55% yield) as a colorless sticky oil, followed by alkyne **14** (0.113 g, 16%).

Cyclopentene **5**: TLC R_f 0.37 (PE/Et_2O 98:2), $[\alpha]^{21}_D$ +86.9 (*c* 0.529, $CHCl_3$); ^{1}H NMR δ 7.32−7.29 (m, 7H), 7.21−7.17 (m, 4H), 5.52 (s, 1H), 4.71 (d, 1H, J = 8.8 Hz), 4.55 (d, 1H, J = 8.8 Hz), 2.38 (m, 4H), 1.95−1.87 (m, 3H), 1.76 (s, 3H), 1.49−1.42 (m, 1H), 1.39−1.31 (m, 1H), 1.08 (s, 3H), 0.93 (s, 3H); ^{13}C NMR δ 142.3, 138.2,136.9, 128.3, 128.0, 127.2, 126.8, 126.6, 125.7, 114.2, 85.4, 84.7, 65.3, 38.7, 37.6, 37.1, 37.0, 33.6, 29.7, 28.6, 26.2, 25.2, 19.7, 16.9; ^{13}C NMR (JVERT) δ u 142.2, 138.1, 136.8, 114.0, 65.2, 38.8, 37.5, 36.9, 33.3, 29.7, 28.5, 19.7; ^{13}C NMR (JVERT) δ d 128.4, 127.9, 127.8, 126.9, 126.5, 125.6, 85.4, 85.7, 26.8, 25.2, 16.9; IR (film) 3026, 1948, 1879, 1805, 1452 cm^{-1}; GC/MS *m*/*z* (%) 180 (100), 107 (24), 161 (19), 121 (16), 282 (10), 388 (0.12); HRMS calcd for $C_{27}H_{32}O_2$ (M^+) 387.2324, obsd 387.2324.

(1*S*,8*R*,9*R*)-1-[3-Pentynyl]-2,2-dimethyl-8,9-diphenyl-7,10-dioxaspiro[6,5]decane (14). Colorless oil (0.113 g, 16%); TLC R_f 0.21 (PE/Et_2O 98:2); $[\alpha]^{20}_D$ +44.4 (*c* 0.230, $CHCl_3$); ^{1}H NMR δ 7.34−7.29 (m, 8H), 7.18−7.15 (m, 2H), 4.91 (d, 1H, J = 8.8 Hz), 4.71 (d, 1H, J = 8.8 Hz), 2.61−2.51 (m, 1H), 2.35−2.24 (m, 1H), 2.19 (d, 1H, J = 12 Hz), 2.02−1.87 (m, 2H), 1.84 (t, 3H, J = 2.6 Hz), 1.72−1.45 (m, 6H), 1.03 (s, 3H), 0.98 (s, 3H); ^{13}C NMR δ u 138.9, 136.5, 112.7, 79.9, 75.3, 40.9, 36.8, 35.9, 25.2, 21.45, 19.33; ^{13}C NMR δ d 128.5, 128.4, 128.3, 127.8, 127.5, 125.9, 87.2, 83.8, 52.8, 31.3, 21.6, 3.57; IR (film) 2932, 1950, 1880, 1807, 1605 cm^{-1}; GC/MS *m*/*z* (%) 277 (100), 199 (21), 183 (18), 171 (2.4), 152 (10); HRMS calcd for $C_{27}H_{32}O_2$ (M^+) 388.2402, obsd 388.2396.

Enone 15. A solution of cyclopentene **5** (2.21 g, 5.70 mmol) and a crystal of Sudan III in dry CH_2Cl_2 (11 mL) was ozonized at −78 °C until the red color faded. Nitrogen gas was bubbled for 10 min through the solution at −78 °C. The cool solution was quenched with PPh_3 (1.66 g, 6.30 mmol) and then brought to room temperature. The solution was stirred overnight at room temperature and then concentrated. To the residue in MeOH (95 mL) was added 1 M NaOH (19 mL, 19.0 mmol) and the mixture was stirred overnight at room temperature. The solution was concentrated. The residue was partitioned between 20% saturated aqueous NH_4Cl and CH_2Cl_2. The combined organic layer was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield enone **15** as colorless oil (1.21 g, 52% from **5**). TLC R_f 0.34 (PE/MTBE 85:15); $[\alpha]^{22}_D$ +196.2 (*c* 0.130, $CHCl_3$); ^{1}H NMR δ 7.40−7.30 (m, 7H), 7.24−7.21 (m, 3H), 7.15−7.11 (m, 2H), 6.26 (d, 1H, J = 10.4 Hz), 4.81 (d, 1H, J = 8.8 Hz), 4.63 (d, 1H, J = 8.8 Hz), 2.93−2.84 (m, 1H), 2.53−2.41 (m, 2H), 2.20−2.08 (m, 2H), 2.00−1.94 (m, 1H), 1.84 (quint, 2H, J = 6.2 Hz), 1.53 (m, 1H), 1.16 (s, 3H), 1.08 (s, 3H); ^{13}C NMR δ u 200.0, 137.3, 135.5, 113.4, 49.2, 39.5, 36.3, 35.8, 44.0, 24.1, 19.2; ^{13}C NMR δ d 131.4, 128.5, 128.3, 126.8, 126.4, 85.2, 83.9, 26.7, 26.18; the signals for

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(18) ^{13}C multiplicities were determined with the aid of a JVERT pulse sequence, differentiating the signals for methyl and methine carbons as "d" from methylene and quaternary carbons as "u".

the gem dimethyl, suppressed by JVERT, come at δ 27.2 and δ 26.7 in the non-JVERT ^{13}C NMR spectra; IR (film) 2951, 1952, 1881, 1809, 1680, 1453 cm^{-1}; CI *m/z* (%) 403 (100), 385 (2), 296 (10), 224 (11), 207 (100), 180 (38), 167 (46), 135 (15); HRMS calcd for $C_{27}H_{30}O_3$ (M + H) 403.2273, obsd 403.2257.

Allylic Alcohol 16. $NaBH_4$ (0.150 g, 0.0037 mol) was added over 5 min to a solution of enone **15** (1.21 g, 0.0030 mol) and $CeCl_3 \cdot 7H_2O$ (2.24 g, 0.0060 mol) in an ice-water bath. Water (1 mL) was added after 30 min, then the mixture was concentrated. The residue was diluted with 3 drops of concentrated HCl in water (25 mL), then partitioned with CH_2Cl_2. The combined organic layer was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield allylic alcohol **16** as colorless oil (1.19 g, 98% yield). TLC R_f 0.38 (PE/MTBE 8:2), $[\alpha]^{22}_D$ +95.3 (*c* 0.635, $CHCl_3$); ^{1}H NMR δ 7.28−7.33 (m, 6H), 7.24−7.22 (m, 2H), 7.17−7.14 (m, 2H), 6.36−6.32 (m, 1H), 6.22 (d, J = 10.8 Hz, 1H), 4.77 (d, J = 8.8 Hz, 1H), 4.63 (d, J = 8.8 Hz, 1H), 4.05 (m, 1H), 2.34 (br s, 1H), 2.20−2.12 (m, 1H), 1.99−1.97 (m, 2H), 1.91−1.62 (m, 7H), 1.20 (s, 3H), 0.95 (s, 3H); ^{13}C NMR δ 137.3, 136.1, 133.6, 131.1, 128.4, 128.3, 128.1, 126.6, 114.6, 84.9, 63.3, 48.4, 38.9, 35.7, 32.0, 30.6, 26.9, 24.7, 21.7, 19.5; ^{13}C NMR δ u 137.2, 136.0, 114.6, 48.4, 38.9, 35.6, 32.0, 30.7, 21.7, 19.5; ^{13}C NMR δ d 133.6, 131.1, 128.4, 128.3, 128.1, 126.9, 126.6, 85.0, 84.9, 63.3; the signals for the gem dimethyl, suppressed by JVERT, come at δ 26.9 and δ 24.7 in the non-JVERT; IR (film) 3434, 2971, 2870, 1454 cm^{-1}; CI *m/z* (%) 387 (2), 298 (8), 281 (2), 191 (26), 180 (100), 165 (7), 121 (6); HRMS calcd for $C_{27}H_{32}O_3$ (M − OH) 387.2324, obsd 387.2322.

3-Hydroxy-11,11-dimethyl[6,6]spiroundec-1-en-7-one (4). To a solution of allylic alcohol **16** (1.44 g, 3.56 mmol) in dry MeOH (20 mL) was added 2 M aqueous HCl (6.00 mL, 12 mmol). The mixture was heated to 50 °C. The reaction was monitored by TLC. The reaction was over in 6.5 h. The mixture was partitioned between 10% saturated $NaHCO_3$ and CH_2Cl_2. The combined organic layer was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield ketone **4** as a colorless oil (0.700 g, 94% yield). TLC R_f 0.12 (PE:MTBE 70:30), $[\alpha]^{22}_D$ +19.0 (*c* 0.690, $CHCl_3$); ^{1}H NMR δ 5.94 (m, 2H), 4.10 (m, 1H), 2.60−2.52 (m, 1H), 2.80−2.20 (m, 1H), 2.17−2.13 (m, 1H), 2.09−1.75 (m, 4H), 1.52−1.31 (m, 4H), 0.90 (s, 3H), 0.80 (s, 3H); ^{13}C NMR δ u, 212.1, 41.8, 38.2, 35.2, 30.8, 28.7, 22.9, 22.7; ^{13}C NMR δ d 135.6, 128.6, 67.28, 24.8, 22.8; IR (film) 3391, 1702, 1461, 1057 cm^{-1}; CI *m/z* (%) 208 (17), 147 (13), 138 (21), 129 (34), 121 (100); HRMS cacld for $C_{27}H_{30}O_3$ (M^+) 207.1385, obsd 207.1379.

7,11,11-Trimethyl[6,6]spiroundec-1-en-3,7-diol (17). To a mixture of LiBr (0.109 g, mmol) and ketone **4** (120 mg, 0.576 mmol) in dry Et_2O at −78 °C was added 1.5 M MeLi (1.15 mL, 1.725 mmol) dropwise (5 min). The solution was stirred at −78 °C for 1 h and then allowed to reach room temperature. The mixture was partitioned between water and Et_2O. The combined organic layer was dried (Na_2SO_4) and concentrated. The residue was recycled three more times and then was chromatographed to yield tertiary alcohol **17** as colorless oil (56 mg, 65% yield) and recovered ketone **4** (34 mg). For **17**: TLC R_f 0.20 (CH_2Cl_2/MTBE 8:2); $[\alpha]^{20}_D$ −24.8 (*c* 1.515, $CHCl_3$); ^{1}H NMR δ 5.84 (d, J = 10.4 Hz, 1H), 5.75 (d, J = 10.8 Hz, 1H), 4.10 (s, 1H), 1.97−2.13 (m, 2H), 1.89−1.74 (m, 2H), 1.63−1.34 (m, 8H), 1,19 (s, 3H), 1.11 (s, 3H), 0.77 (s, 3H); ^{13}C NMR δ d 132.9, 132.8, 66.5, 30.6, 28.7, 24.3; ^{13}C NMR δ u 75.2, 46.3, 37.8, 37.1, 36.9, 32.4, 21.1, 18.3; IR (film) 3377, 2936, 1464, 1327 cm^{-1}; CI *m/z* (%) 223 (12), 207 (100), 189 (81), 121 (75), 119 (49); HRMS (M − H) calcd 223.1698, obsd 223.1698.

7-Hydroxy-7,11,11-trimethyl[6,6]spiroundec-1-en-3-one (18). To the tertiary alcohol **17** (13.9 mg, 0.063 mmol) in dry CH_2Cl_2 was added Dess−Martin reagent (28 mg, 0.066 mmol). The mixture was stirred for 1 h at room temperature, and then the mixture was partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. The combined organic layer was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give enone **18** as a colorless oil (12.8 mg, 93% yield). TLC R_f 0.31 (CH_2Cl_2:MTBE 8:2); $[\alpha]^{22}_D$ +11.3 (*c* 0.300, $CHCl_3$); ^{1}H NMR δ 6.91 (d, 1H, J = 12.0 Hz), 6.08 (d, 1H, J = 12.0 Hz), 2.64−2.46 (m, 2H), 2.42−2.37 (m, 1H), 2.14−2.08 (m, 1H), 1.94−1.83 (tt, 1H), 1.80−1.67 (dd, 1H), 1.25 (s, 3H), 1.22 (s, 3H), 0.85 (s, 3H); ^{13}C NMR δ u 154.6, 130.1, 30.5, 30.2, 25.4; ^{13}C NMR δ d 199.9, 75.7, 47.9, 38.6, 38.5, 38.0, 36.7, 22.9, 18.5; IR (film) 3457, 2942, 1666, 1462, 1243 cm^{-1}; GC/MS *m/z* (%) 222 (4), 204 (2), 148 (4), 137 (100), 121 (3); HRMS calcd for $C_{14}H_{22}O_2$ (M + H) 223.1698, obsd 223.1688.

(+)-Majusculone (3). To enone **18** (36 mg, 0.162 mmol) in toluene (3 mL) was added pyridine (70 μL, 0.865 mmol) at −78 °C. The mixture was stirred for 5 min at −78 °C. Thionyl chloride (50 μL, 0.685 mmol) was added dropwise (2 min) to the chilled mixture, and stirring was continued for 30 min at −78 °C. The mixture was partitioned between ether and, sequentially, ice water and saturated aqueous $NaHCO_3$. The combined organic layer was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield a mixture of alkenes. This was then added to a mixture of CrO_3 (0.286 g, 2.86 mmol) and 3,5-dimethylpyrazole (0.275 g, 2.86 mmol) in dry CH_2Cl_2 (3 mL) at −20 °C. The mixture was stirred for 4 h at 0 °C, then partitioned between water and Et_2O. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield a clear colorless oil (17 mg). TLC R_f 0.22 (CH_2Cl_2/MTBE 95:5). The oil was dissolved in 3 mL of ethanol and diluted 1000-fold. Quantitative UV (lit.[17a] λ_{max} 241 nm, ϵ = 19 900, EtOH) was used to determine that the actual amount of (+)-majusculone was 6.7 mg (19% from **18**). $[\alpha]^{20}_D$ 147.2 (*c* 0.338, $CHCl_3$) (lit. $[\alpha]^{19}_D$ = 145 (*c* 0.965, $CHCl_3$)); ^{1}H NMR δ 6.77 (d, 1H, J = 10.8 Hz), 6.29 (d, 1H, J = 10.8 Hz), 5.98 (s, 1H), 2.68−2.30 (m, 6H), 2.14−2.06 (m, 1H), 1.98 (s, 3H), 1.11(d, 6H, J = 4.4 Hz); ^{13}C NMR δ 197.6, 197.4, 163.0, 149.8, 131.9, 127.4, 48.6, 47.3, 40.9, 35.1, 27.5, 25.5, 25.0, 23.0; ^{13}C NMR δ u 197.7, 197.5, 48.5, 40.9, 35.0, 29.6; ^{13}C NMR δ d 149.8, 131.9, 127.4, 25.0, 23.1; IR (film) 3017, 2126, 1666, 1375 cm^{-1}; CI *m/z* (%) 162 (100), 134 (9), 119 (19), 105 (19), 91 (63); HRMS calcd for $C_{14}H_{18}O_2$ (M + H) 219.1385, obsd 219.1381.

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Supporting Information Available: General experimental procedures, preparation of **11**, procedure for racemization, procedure for KHMDS preparation, X-ray crystal data for ketal **6**, and ^{1}H and ^{13}C NMR spectra for all new compounds and (+)-majusculone **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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