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TOTAL SYNTHESIS OF (±)-(Z)-9-(BROMOMETHYLENE)-1,5,5-TRIMETHYLSPIRO[5.5]UNDECA-1,7-DIEN-3-ONE, A BROMINATED SESQUITERPENE OF THE CHAMIGRANE TYPE

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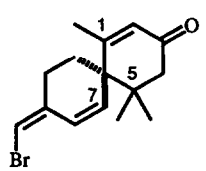
Abstract - (±)-(Z)-9-(Bromomethylene)-1,5,5-trimethylspiro[5.5]undeca-1,7-dien-3-one (**1**), a chamigrane sesquiterpene having a novel bromomethylene group is synthesized from anisole via spiroannelation of 4-(1,1-dimethyl-4-formylbutyl)-3-cyclohexen-1-one (**10**).

A large number of architecturally novel and pharmacologically interesting compounds have been isolated from various marine organisms.[1] In particular, halogenated sesquiterpenes of the chamigrane type are characteristic constituents of the red algae which belong to the genus *Laurencia*.[2] Owing to a variety of the novel structures, the halogenated chamigranes have attracted considerable attention as synthetic targets. While the synthesis of 10-bromo-α-chamigrene (**2**) was reported more than twelve years ago,[3] the only limited number of the halogenated chamigranes such as **1**,[4] **3**-**5**,[5] and **6**[6] have so far been synthesized. Described herein are the full details on our own synthesis of (Z)-9-(bromomethylene)-1,5,5-trimethylspiro[5.5]undeca-1,7-dien-3-one (**1**), isolated from *Laurencia majuscula* HARVEY by Suzuki and Kurosawa,[7] in racemic form.[8]



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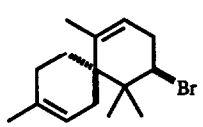

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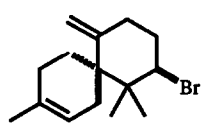

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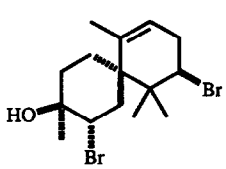

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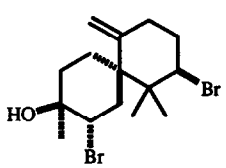

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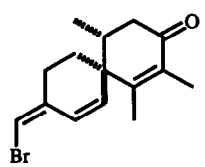

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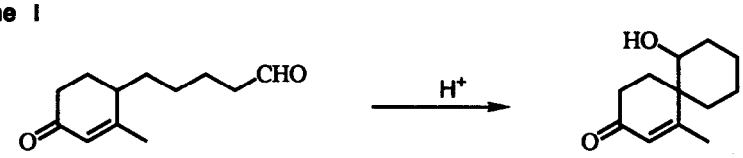
One of the key steps in the present synthesis of (±)-**1** is construction of the spiro[5.5]undecane skeleton. Previously, a novel spiroannelation of a cyclohexenone aldehyde **7** leading to a spiro compound **8** was reported

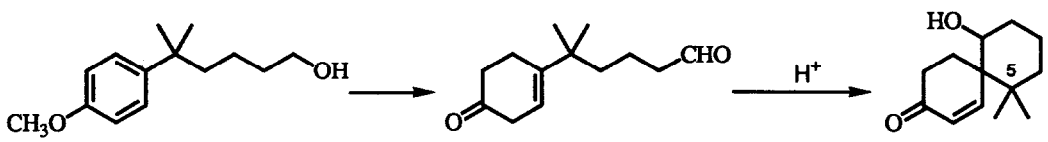
from our laboratory (Scheme I).[9] For the synthesis of (±)-**1**, we required a compound **10** that possesses the geminal dimethyl groups at the position corresponding to the C-5 in **1** (the numbering used for **1**) (Scheme II). The spiroannelation of enone aldehyde **10** may proceed similarly to that of **7** to give the desired spiro compound **11**, which is properly functionalized for the synthesis of (±)-**1**. As the precursor of **10**, one can easily think of an anisole derivative **9**. The first task was therefore focused on the preparation of **9**.

Scheme I



7 **8**

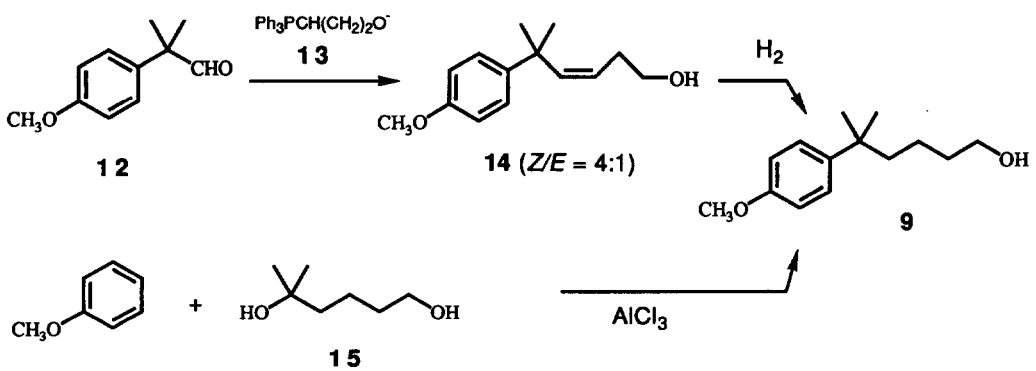
Scheme II



9 **10** **11**

Scheme III shows two routes to the synthesis of the anisole derivative **9**. The known aldehyde **12**[10] was converted into olefin alcohol **14** (*Z*/*E* = 4/1) by Wittig reaction with γ-oxidoylide **13** in 85% yield.[11] Catalytic hydrogenation of **14** on Pd-C gave the desired anisole derivative **9** in 47% yield. This route turned out to be less than satisfactory in practice and the alternative route to **9** was devised. Thus, the desired anisole derivative **9** could be prepared more efficiently by Friedel-Crafts reaction of anisole with 5-methyl-1,5-hexanediol (**15**)[12] in nearly quantitative yield in a single step.[13]

Scheme III

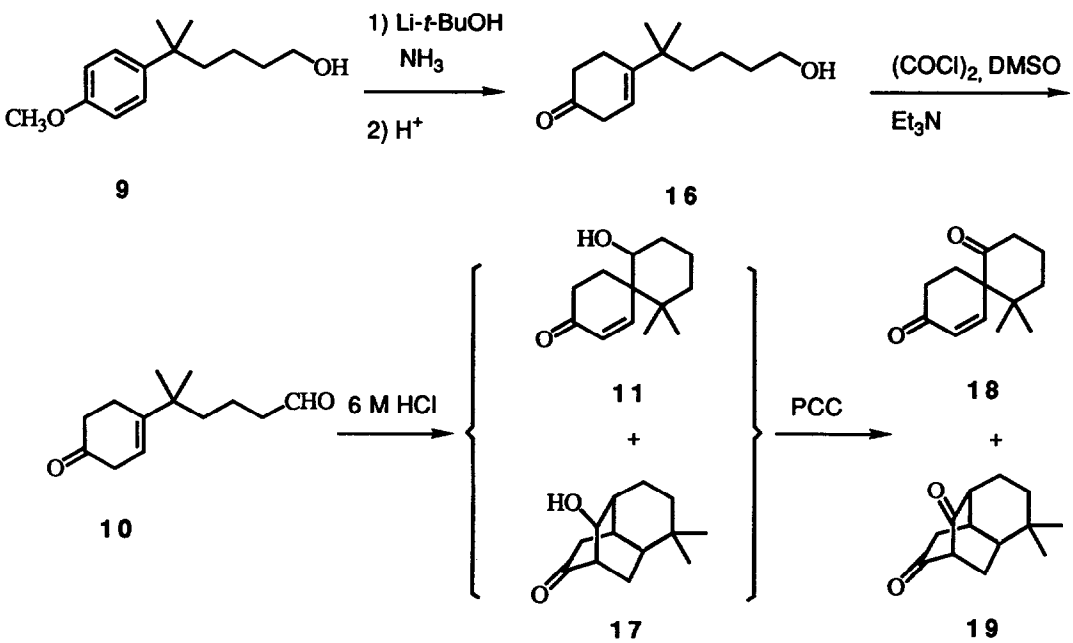


12 **14** (*Z*/*E* = 4:1) **9**

15

Birch reduction (Li, *t*-BuOH, liq. NH_3, ether) of **9** and subsequent hydrolysis [$(COOH)_2$, H_2O-DME] provided enone alcohol **16** in 80% yield (Scheme IV). Swern oxidation[14] of **16** afforded the desired enone aldehyde **10** in 75% yield. On treatment with 6 M HCl in DME at reflux temperature, enone aldehyde **10** underwent cyclization smoothly to give a 5:1 mixture of the desired spiro enone **11**[15a,16] and tricyclic ketone **17**[15b,16] in 97% combined yield. The mixture of **11** and **17** could not be separated at this stage. However, oxidation of this mixture with PCC[17] gave a separable mixture of spiro diketone **18** and tricyclic diketone **19**. Chromatographic separation of the mixture gave pure **18** in 73% yield (from **10**) together with **19** in 14% yield (from **10**).

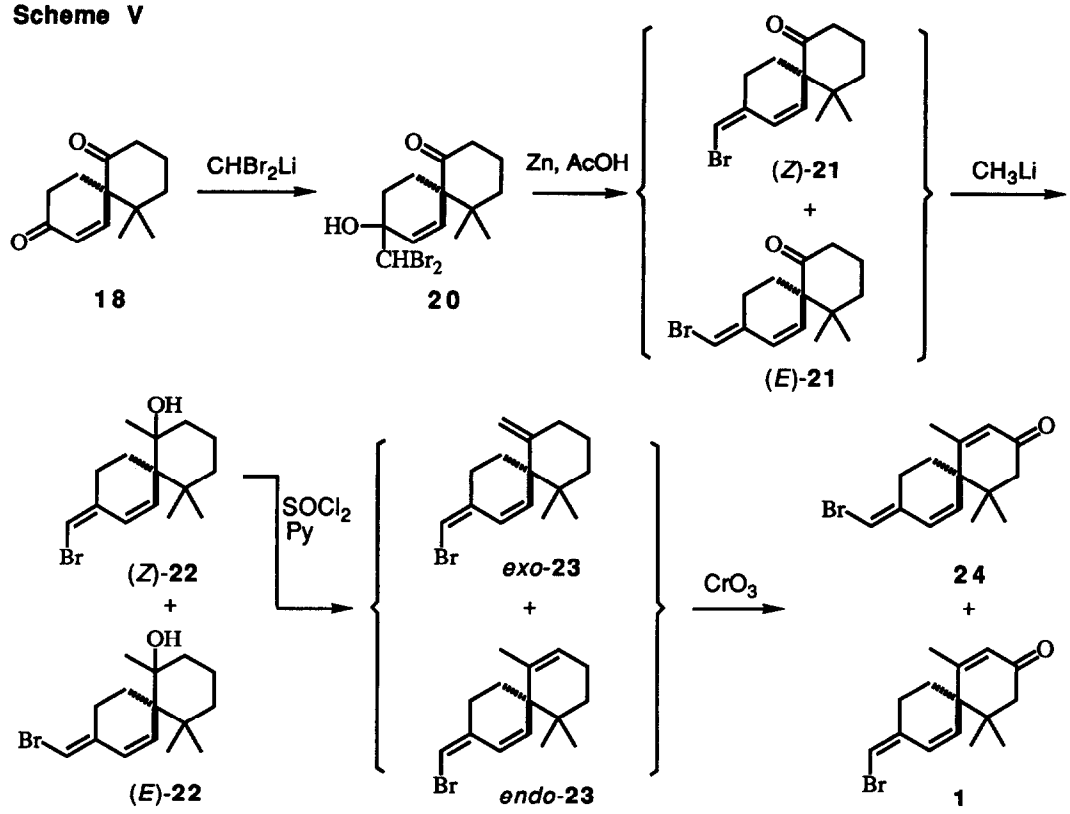
Scheme IV



Thus, we have secured the key intermediate, spiro diketone **18**. Scheme V shows further transformation of **18** and the completion of the synthesis of **1**. Thus, reaction of **18** with dibromomethyllithium[18] in THF at -78 °C provided a single adduct **20**[16] (mp 153-156 °C) in 98% yield. Reduction of **20** with Zn in AcOH and CH_2Cl_2[19] at room temperature yielded an inseparable 1:1 mixture of bromomethylene ketones (*Z*)-**21** and (*E*)-**21** in 70% combined yield. Reaction of this mixture with methyllithium in THF at -78 °C gave (*Z*)-bromomethylene alcohol (*Z*)-**22**[16] and the (*E*)-isomer (*E*)-**22**[16] in 46% and 47% yield, respectively after chromatographic separation. The stereochemistry of the bromomethylene groups in (*Z*)-**22** and (*E*)-**22** was assigned by converting the former isomer to (±)-**1**, since natural **1** has been proven to have (*Z*)-configuration concerning the bromomethylene group.[7] Dehydration of (*Z*)-**22** was effected with $SOCl_2$-pyridine in toluene at -78 °C to give a 3:1 mixture of *endo*-**23** and *exo*-**23** in 99% combined yield. Although the attempts were made to isolate *endo*-**23** in pure form, partial *Z* *E* isomerization of the bromomethylene group in *endo*-**23** was observed to occur.

The final oxidation of the allylic methylene group in **23** was therefore performed without separation of the mixture of *endo*-**23** and *exo*-**23**. Thus, oxidation of the mixture of *endo*-**23** and *exo*-**23** with 3,5-dimethylpyrazole-CrO_3 complex[20] in CH_2Cl_2 at -20 °C furnished (±)-**1** [30% from (*Z*)-**22**] and the (*E*)-isomer **24** [3% from (*Z*)-**22**] along with unreacted *exo*-**23** after chromatographic separation. The spectral properties (IR and ^1H NMR) of the synthetic (±)-**1** were identical with those of natural **1**.

Scheme V



Experimental

Melting points and boiling points are uncorrected. IR spectra were taken on a JASCO IR-810 spectrophotometer. ^1H NMR spectra were recorded on a JEOL FX-90QE (90 MHz) spectrometer: Chemical shifts (δ) are reported in ppm downfield from internal tetramethylsilane and coupling constants in Hz. Low-resolution mass spectra (EIMS) and high-resolution mass spectra (HREIMS) were measured on a JEOL JMS-LG-2000 instrument. Fuji-Davison silica gel BW-820 MH was used for column chromatography. Merck precoated silica gel 60 F_{254} plates, 0.25 mm thickness were used for analytical thin layer chromatography (TLC) and Merck silica gel PF_{254} for preparative TLC. Ether, tetrahydrofuran (THF), and dimethoxyethane (DME) were distilled from sodium-benzophenone ketyl under nitrogen. Dichloromethane (CH_2Cl_2), *t*-butyl alcohol (*t*-BuOH), pyridine, and triethylamine (Et_3N) were distilled from calcium hydride under nitrogen. Toluene was distilled from sodium under nitrogen. Unless otherwise stated, the organic solutions obtained by extractive workup were washed with saturated aqueous NaCl, dried over anhydrous sodium sulfate (Na_2SO_4) and concentrated under reduced pressure by a rotary evaporator.

5-Methyl-1,5-hexanediol (15). To a mechanically stirred solution of CH_3MgI (prepared from 120.0 g of CH_3I and 19.5 g of Mg) in ether (540 ml) was added a solution of δ-valerolactone (20.0 g, 0.2 mol) in ether (40 ml) at 0 °C under nitrogen over a period of 30 min. The mixture was then heated under reflux for 4 h and cooled to 0 °C. To the cooled, vigorously stirred reaction mixture was added saturated aqueous NH_4Cl (350 ml). The mixture was filtered through a glass filter. The residue was washed thoroughly with ethyl acetate (EtOAc) (300 ml). The filtrate and the washings were combined and the organic layer was separated. The aqueous layer was extracted with EtOAc (8 x 100 ml). The combined organic layers were washed with saturated aqueous NaCl, dried, and concentrated to give an oily residue, distillation of which provided **15** (14.5 g, 55%): bp 95-97 °C (1.5 mmHg) [Lit.[12a] 93 °C (0.5 mmHg)]; IR ($CHCl_3$) 3600 and 3400 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.22 (6 H, s), 1.4-1.6 (6 H, m), and 3.67 (2 H, t, J = 6.4 Hz); EIMS *m/z* (relative intensity) 117 [$(M-15)^+$, 9] and 99 (100).

5-Methyl-5-(4-methoxyphenyl)-1-hexanol (9). Anisole (75 ml, 690 mmol) was placed in a 300-ml three necked flask fitted with a thermometer, a dropping funnel, and a $CaCl_2$ tube. The flask was cooled with an ice bath until the temperature of anisole reached below 3 °C. To anisole was added anhydrous $AlCl_3$ (3.92 g, 29.4 mmol) and the mixture was stirred until $AlCl_3$ dissolved. From the dropping funnel a suspension of 5-methyl-1,5-hexanediol (**15**) (3.52 g, 26.5 mol) in anisole (15 ml, 138 mmol) was added at such a rate that the reaction temperature could be maintained below 6 °C. The addition required 45 min. Additional $AlCl_3$ (3.97 g, 29.8 mmol) was added and the reaction mixture was stirred at 2 °C for 3.5 h and then at room temperature for 39 h. The reaction mixture was poured into 60 ml of 6 M HCl and extracted with ether (4 x 45 ml). The combined ether extracts were washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried , and concentrated. The oily residue was purified by column chromatography on silica gel (60 g) with 2:1 hexane-ether to give **9** (5.90 g, 99%) as a colorless oil: bp 114-118 °C (0.1 mmHg); IR ($CHCl_3$) 3620, 3450 (broad), 3010, 1610, 1580, 1515, 1040, and 830 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.26 (6 H, s), 1.0-1.7 (7 H, m), 3.56 (2 H, t, J = 6.7 Hz), 3.80 (3 H, s), 6.84 (2 H, m), and 7.25 (2 H, m); MS *m/z* (relative intensity) 222 (M^+, 17), 207 (2), 149 (100), 121 (15), and 109 (8) [HREIMS. Found: 222.1595 (M^+). $C_{14}H_{22}O_2$ requires: 222.1620].

4-(1,1-Dimethyl-5-hydroxypentyl)-3-cyclohexen-1-one (16). To a stirred solution of **9** (4.98 g, 22.4 mmol) in a mixture of ether (22.5 ml), *t*-BuOH (8.5 ml), and liq. NH_3 (125 ml) were added freshly cut lithium pieces (670 mg, 97.1 mmol) in portions over a period of 1 h. After the reaction mixture was stirred for 3 h at -33 °C, NH_4Cl (50 g) was added cautiously in portions. The mixture was continuously stirred while ammonia was removed by spontaneous evaporation. The residue was diluted with saturated aqueous NH_4Cl (75 ml) and the mixture was extracted with CH_2Cl_2 (3 x 250 ml). The combined extracts were washed, dried, and concentrated to give an oil of an enol ether (5.37 g). A mixture of the crude enol ether (5.37 g), DME (125 ml), and saturated aqueous oxalic acid (25 ml) was vigorously stirred ar room temperature for 25 h. After the reaction mixture was cooled to 0°C, saturated aqueous NH_4Cl (75 ml) was added and the mixture was extracted with ether (4 x 100 ml). The combined organic layers were washed with saturated aqueous NaCl, dried, and concentrated to leave an oil. Purification by column chromatography on silica gel (100 g) with hexane-EtOAc (8:1-1:1) provided **16** (3.78 g, 80% from **9**) as a colorless oil: IR ($CHCl_3$) 3620, 3450 (broad), and 1710 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.05 (6H, s), 1.1-1.8 (6 H, m), 1.72 (1 H, br s, OH), 2.41 (4 H, s), 2.88 (2 H, d, J = 3.7 Hz), 3.62 (2 H, t, J = 6.3 Hz), and 5.48 (1 H, t, J = 3.7 Hz); EIMS *m/z* (relative intensity) 210 (M^+, 14), 195 (3), 137 (100), and 109 (13) [HREIMS. Found: 210.1640 (M^+). $C_{13}H_{22}O_2$ requires: 210.1620].

4-(1,1-Dimethyl-4-formylbutyl)-3-cyclohexen-1-one (10). To a stirred solution of oxalyl chloride (0.5 ml, 5.7 mmol) in CH_2Cl_2 (13 ml) cooled to -65 °C under nitrogen was added a solution of dimethyl sulfoxide (0.85 ml, 12 mmol) in CH_2Cl_2 (3 ml) over a period of 5 min. After the mixture was stirred at -65 °C for 10 min, a solution of **16** (802 mg, 3.81 mmol) in CH_2Cl_2 (7 ml) was added over a period of 5 min. After 15 min, Et_3N (4.0 ml, 29 mmol) was added over a period of 5 min at -65 °C. The reaction mixture was allowed to warm to room temperature and water (15 ml) was added. The mixture was extracted with 1:1 hexane-ether (5 x 30 ml). The combined organic layers were washed with water and saturated aqueous NaCl, dried, and concentrated. The residual oil was purified by column chromatography on silica gel (20 g) with 2:1 hexane-ether to give **10** (599 mg, 75%) as a colorless oil: IR ($CHCl_3$) 2730 and 1720 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.07 (6 H, s), 1.2-1.6 (4 H, m), 2.42 (4 H, m), 2.2-2.5 (2 H, m), 2.89 (2 H, d, J = 3.7 Hz), 5.51 (1 H, t, J = 3.7 Hz), and 9.75 (1 H, t, J = 1.7 Hz); EIMS *m/z* (relative intensity) 208 (M^+, 22), 137 (100), and 109 (20) [HREIMS. Found: 208.1463 (M^+). $C_{13}H_{20}O_2$ requires: 208.1463].

5,5-Dimethylspiro[5.5]undec-7-ene-1,9-dione (18) and 6,6-dimethyltricyclo[5.3.1.$0^{3,8}$]undeca-2,10-dione (19). A mixture of **10** (599 mg, 2.88 mmol) and 6 M HCl (2.4 ml) in DME (24 ml) was heated under reflux for 1 h.

After cooling to 0 °C, the reaction mixture was neutralized by the addition of $NaHCO_3$ and the mixture was extracted with ether (3 x 30 ml). The combined organic layers were washed with saturated aqueous NaCl, dried, and concentrated. The oily residue was purified by column chromatography on silica gel (100 g) with 3:1 hexane-EtOAc to give an oil (582 mg), which was found to be an inseparable 5:1 mixture of the desired **11** and the side product **17** by ^1H NMR analysis. The inseparable mixture of **11** and **17** was oxidized with PCC. To a stirred solution of the mixture of **11** and **17** (582 mg) in CH_2Cl_2 (6 ml) was added PCC (814 mg, 3.78 mmol) and the reaction mixture was stirred at room temperature. After 2 h, additional PCC (164 mg, 0.76 mmol) was added and the stirring was continued for additional 2 h. The reaction mixture was diluted with ether (30 ml). The precipitates were triturated and the mixture was passed through a column packed with Florisil. The column was washed with EtOAc (100 ml). The filtrate and washings were combined and concentrated to leave an oily residue. Purification by column chromatography on silica gel (50 g) with 7:1 hexane-EtOAc provided **18** (435 mg, 73% from **10**) as a colorless oil and **19** (84 mg, 14% from **10**) as colorless prisms. **18**: IR ($CHCl_3$) 1710, 1690, and 1680 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.93 (3 H, s), 1.00 (3 H, s), 1.4-2.9 (10 H, m), 6.06 (1 H, dd, J = 0.9, 10.5 Hz), and 7.09 (1 H, dd, J = 1.7, 10.5 Hz); EIMS *m/z* (relative intensity) 206 (M^+, 100), 191 (5), 188 (3), 178 (3), 173 (3), 163 (12), 150 (16), 138 (99), and 135 (76) [HREIMS. Found: 206.1339 (M^+). $C_{13}H_{18}O_2$ requires: 206.1307]. **19**: mp 78.5-80.0 °C (hexane-benzene); IR ($CHCl_3$) 1735 and 1715 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.91 (3 H, s), 1.09 (3 H, s), 1.1-2.2 (7 H, m), 2.28 (1 H, m), 2.41 (2 H, m), 2.60 (1H, dt, J = 2.9, 5.7 Hz), and 3.16 (1 H, t, J = 2.9 Hz); EIMS *m/z* (relative intensity) 206 (M^+, 100), 191 (8), 178 (15), 163 (17), 135 (15), and 109 (51). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.69; H, 9.15.

9-(Dibromomethyl)-9-hydroxy-5,5-dimethylspiro[5.5]undec-7-en-1-one (20). A mixture of **18** (131 mg, 0.633 mmol) and dibromomethane (0.10 ml, 1.4 mmol) in THF (3.0 ml) was cooled to -78 °C under nitrogen. To the cooled, vigorously stirred mixture was added a 0.53 M solution of lithium dicyclohexylamide in THF (2.4 ml, 1.3 mmol) over a period of 10 min. After the reaction mixture was stirred at -78 °C for 1 h, saturated aqueous NH_4Cl (5 ml) was added. The mixture was warmed to room temperature with vigorous stirring and extracted with EtOAc (4 x 20 ml). The combined organic layers were washed successively with saturated aqueous $CuSO_4$ and saturated aqueous NaCl, dried, and concentrated. The oily residue was purified by column chromatography on silica gel (5.0 g) with 10:1 $CHCl_3$-ether to give **20** (236 mg, 98%) as colorless needles. The product **20** was found to consist of a single diastereomer by ^1H NMR analysis. **20**: mp 153-156 °C (hexane-CH_2Cl_2); IR ($CHCl_3$) 3560, 3390 (broad), and 1710 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.87 (3 H, s), 0.93 (3 H, s), 1.0-2.8 (10 H, m), 2.44 (1 H, br s, OH), 5.74 (1 H, s), 5.99 (1 H, dd, J = 1.4, 10.5 Hz), and 6.18 (1 H, dd, J = 0.9, 10.5 Hz); EIMS *m/z* (relative intensity) 382 [$(M+4)^+$, 0.5], 380 [$(M+2)^+$, 1], 378 (M^+, 0.5), 301 (11), 299 (11), 283 (1.5), 281 (1.5), 219 (34), 207 (100), and 123 (19). Anal. Calcd for $C_{14}H_{20}O_2Br_2$: C, 44.23; H, 5.30. Found: C, 43.83; H, 5.34.

(Z)-9-(Bromomethylene)-5,5-dimethylspiro[5.5]undec-7-en-1-one [(Z)-21] and (E)-9-(bromomethylene)-5,5-dimethylspiro[5.5]undec-7-en-1-one [(E)-21]. To a solution of **20** (59.2 mg, 0.156 mmol) in CH_2Cl_2 (2.0 ml) were added acetic acid (0.10 ml) and zinc dust (101 mg, 1.54 mmol). After vigorous stirring for 2 h at room temperature, the reaction mixture was filtered through a cotton plug to remove precipitates. The precipitates were washed with ether (ca. 2 ml). The filtrate and washings were combined and washed with saturated aqueous $NaHCO_3$ (3 ml). The aqueous layer was extracted with ether (3 x 5 ml). The combined organic layers were washed with saturated aqueous NaCl, dried, and concentrated to give an oily residue. Purification by column chromatography on silica gel (15 g) with 50:1 hexane-ether followed by preparative TLC with 4:1 hexane-ether provided an inseparable 1:1 mixture[21] of (*Z*)-**21** and (*E*)-**21** (30.8 mg, 70%) as a colorless oil along with over-reduction product, 5,5-dimethyl-9-methylenespiro[5.5]undec-7-en-1-one (5.3 mg, 17%). (*Z*)-**21** and (*E*)-**21**: IR ($CHCl_3$) 1705 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.88 and 0.89 (total 3 H, s each), 0.94 (3 H, s) 1.0-2.7 (10 H, m), 5.92 and 6.15 (total 1 H, s each), 5.98 and 6.21 (total 1 H, d each, J = 11.0 Hz), 6.21 and 6.64 (total 1 H, d each, J = 11.0 Hz); EIMS *m/z* (relative intensity) 284 [$(M+2)^+$, 100], 282 (M^+, 100), 215 (64), and 213 (69) [HREIMS. Found: 282.0611 (M^+). $C_{14}H_{19}O^{79}Br$ requires: 282.0619]. 5,5-Dimethyl-9-methylenespiro[5.5]undec-7-en-1-one: IR ($CHCl_3$) 3080, 1700, 1635, 1590, and 890 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.84 (3 H, s), 0.90 (3 H, s), 1.2-2.7 (10 H, m), 4.80 (2 H, br s), 5.95 (1 H, d, J = 9.8 Hz), and 6.26 (1 H, d, J = 9.8 Hz); EIMS *m/z* (relative intensity) 204 (M^+, 87), 135 (75), and 91 (100) [HREIMS. Found: 204.1543 (M^+). $C_{14}H_{20}O$ requires: 204.1514].

(Z)-9-(Bromomethylene)-1-hydroxy-1,5,5-trimethylspiro[5.5]undec-7-ene [(Z)-22] and (E)-9-(bromomethylene)-1-hydroxy-1,5,5-trimethylspiro[5.5]undec-7-ene [(E)-22]. A 1:1 mixture of (*E*)-**21** and

(Z)-**21** (200 mg, 0.668 mmol) was dissolved in THF (6.0 ml) under nitrogen. To the solution cooled to -78 °C was added a 1.25 M solution of CH_3Li in hexane (0.70 ml, 0.88 mmol). After the reaction mixture was stirred at -78 °C for 1 h, saturated aqueous $NaHCO_3$ (5 ml) was added at -78 °C. The mixture was gradually warmed to room temperature with vigorous stirring and extracted with ether (3 x 10 ml). The organic layers were combined, washed with saturated aqueous NaCl, dried, and concentrated. The oily residue was purified by column chromatography on silica gel (20 g) with 15:1 hexane-ether to give (Z)-**22** (91.7 mg, 46%) and (*E*)-**22** (93.2 mg, 47%) as colorless oils, respectively. The ^1H NMR analyses of the two products indicated that each product consisted of a single diastereomer. (Z)-**22**: IR ($CHCl_3$) 3600 and 3300 (broad) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78 (3 H, s), 1.16 (6 H, s), 1.0-2.6 (10 H, m), 5.87 (1 H, m), 6.00 (1 H, dd, *J* = 1.1, 10.6 Hz), and 6.56 (1 H, dd, *J* = 0.4, 10.6 Hz); EIMS *m/z* (relative intensity) 300 [$(M+2)^+$, 0.6], 298 (M^+, 0.6), 284 (1.2), 282 (2.4), 280 (1.2), 123 (13), 117 (40), and 99 (100) [HREIMS. Found: 280.0822 (M^+-H_2O). $C_{15}H_{21}{}^{79}Br$ (M-H_2O) requires: 280.0827]. (*E*)-**22**: IR ($CHCl_3$) 3600, and 3300 (broad) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.76 (3 H, s), 1.13 (3 H, s), 1.16 (3 H, s), 1.0-2.7 (11 H, m), 5.78 (1 H, d, *J* = 10.4 Hz), 6.08 (1 H, s), and 6.14 (1 H, d, *J* = 10.4 Hz); EIMS *m/z* (relative intensity) 300 [$(M+2)^+$, 0.8], 298 (M^+, 0.8) , 284 (8), 282 (9), 280 (1.6), 127 (39), and 109 (100) [HREIMS. Found: 280.0800 (M^+-H_2O). $C_{15}H_{21}{}^{79}Br$ (M^+-H_2O) requires: 280.0827].

(Z)-9-(Bromomethylene)-1,5,5-trimethylspiro[5.5]undeca-1,7-diene (endo-23) and (Z)-9-(bromomethylene)-1-methylene-5,5-dimethylspiro[5.5]undec-7-ene (exo-23). To a solution of (Z)-**22** (20.7 mg, 0.0692 mmol) in toluene (2 ml) cooled to -78 °C under nitrogen were added pyridine (1.0 ml) and thionyl chloride (0.05 ml, 0.7 mmol). The reaction mixture was stirred at -78 °C for 20 min, and then a small piece of ice was added. The mixture was warmed to 0 °C with vigorous stirring, diluted with saturated aqueous $NaHCO_3$, and extracted with ether (3 x 5 ml). The combined organic layers were washed successively with saturated aqueous $CuSO_4$, water, and saturated aqueous NaCl, dried, and concentrated. The oily residue was purified by column chromatography on silica gel (2.0 g) with hexane to give a 3:1 mixture[21] of *endo*-**23** and *exo*-**23** (19.3 mg, 99% combined yield) as a colorless oil: IR ($CHCl_3$) 3075, 1635, 1580 and 905 cm^{-1}; EIMS *m/z* (relative intensity) 282 [$(M+2)^+$, 14], 280 (M^+, 14), 226 (63), 224 (63), 211 (6), 209 (6), 201 (3), and 145 (100) [HREIMS. Found: 280.0855 (M^+). $C_{15}H_{21}{}^{79}Br$ requires 280.0827]. ^1H NMR of the major *endo*-**23** (90 MHz, $CDCl_3$): δ 0.89 (6 H, s), 1.3-2.1 (6 H, m), 1.60 (3 H, d, *J* = 1.3 Hz), 2.42 (2 H, dt, *J* = 1.1, 7.6 Hz), 5.40 (1 H, m), 5.80 (1 H, dd, *J* = 1.5, 9.5 Hz), 5.86 (1 H, s), and 6.63 (1 H, d, *J* = 9.5 Hz).

(±)-(Z)-9-(Bromomethylene)-1,5,5-trimethylspiro[5.5]undeca-1,7-dien-3-one [(±)-1] and (±)-(E)-9-(bromomethylene)-1,5,5-trimethylspiro[5.5]undeca-1,7-dien-3-one (24). To a suspension of CrO_3 (120 mg, 1.20 mmol) in CH_2Cl_2 (2 ml) cooled to -20 °C under nitrogen was added 3,5-dimethylpyrazole (117 mg, 1.22 mmol). The mixture was stirred stirred at -20 -- -10 °C for 20 min. To the mixture was added a solution of a 3:1 mixture of *endo*-**23** and *exo*-**23** (19.3 mg, 0.0686 mmol) in CH_2Cl_2 (1.5 ml). After the reaction mixture was stirred at -20 °C for 1 h, 5 M NaOH (1 ml) was added to the reaction mixture. After vigorous stirring for 15 min, the mixture was extracted with ether (5 x 5 ml). The combined organic layers were washed successively with saturated aqueous $CuSO_4$, water, and saturated aqueous NaCl, dried, and concentrated to give an oily residue. Purification by column chromatography on silica gel (5 g) with 3:1 hexane-ether provided (±)-**1** [6.1 mg, 30% from (Z)-**22**] and **24** [0.6 mg, 3% from (Z)-**22**] along with unreacted *exo*-**23** (3.3 mg). (±)-**1**: colorless oil; IR (neat) 3080, 1665, 1615, and 1585 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.00 (3 H, s), 1.04 (3 H, s), 1.88 (3 H, d, *J* = 1.1 Hz), 1.0-2.6 (6 H, m), 5.88 (1 H, br d, *J* = 10.8 Hz), 5.89 (1 H, br s), 6.00 (1 H, br s), and 6.82 (1 H, dd, *J* = 1.0, 10.8 Hz); EIMS *m/z* (relative intensity) 296 [$(M+2)^+$, 8], 294 (M^+, 8), 240 (100), 238 (100), 159 (31) [HRMS. Found: 296.0626 $(M+2)^+$. $C_{15}H_{19}{}^{81}BrO$ requires: 296.0600]. **24**: colorless oil; IR ($CHCl_3$) 3070, 1665, and 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (6 H, s), 1.87 (3 H, d, J = 1.0 Hz), 1.0-2.7 (6 H, m), 5.66 (1 H, d, *J* = 10.6 Hz), 5.88 (1 H, q, *J* = 1.0 Hz), 6.23 (1 H, br s), and 6.38 (1 H, d, *J* = 10.6 Hz); EIMS *m/z* (relative intensity) 296 [$(M+2)^+$, 9], 294 (M^+, 9), 240 (100), 238 (100), 159 (34), 149 (31), and 91 (34) [HREIMS. Found: 294.0590 (M^+). $C_{15}H_{19}{}^{79}BrO$ requires: 294.0620]. *exo*-**23**: colorless oil; IR ($CHCl_3$) 3080, 1635, and 900 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 0.84 (3 H, s), 0.97 (3 H, s), 1.2-2.3 (10 H, m), 4.57 (1 H, br d, J = 2.2 Hz), 4.85 (1 H, br s), 5.83 (1 H, br s), 6.04 (1 H, d, *J* = 10.4 Hz), and 6.58 (1 H, d, *J* = 10.4 Hz); EIMS *m/z* (relative intensity) [282 $(M+2)^+$, 5], 280 (M^+, 5), 213 (5), 211 (5), 200 (52), 185 (70), 157 (45), 144 (100), and 129 (83) [HREIMS. Found: 280.0855 (M^+). $C_{15}H_{21}{}^{79}Br$ requires: 280.0827].

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