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Total Synthesis of (±)-α-Chamigrene and Brominated Chamigrene[1)]

CHUZO IWATA,* KAZUYUKI MIYASHITA, YASUO KOGA, YASUTAKA SHINOO, MINORU YAMADA, and TETSUAKI TANAKA

Faculty of Pharmaceutical Sciences, Osaka University, 1-6, Yamada-oka, Suita, Osaka 565, Japan

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α-Chamigrene (**1**) and a bromochamigrene derivative, 9-(*Z*)-bromomethylidene-1,5,5-trimethylspiro[5.5]undeca-1,7-dien-3-one (**2a**) were synthesized *via* a useful synthon in the synthesis of chamigrene-type sesquiterpenes, *i.e.*, 1,5,5-trimethylspiro[5.5]undeca-7,10-dien-3-one (**5**), which had been obtained by the copper(II) chloride-catalyzed decomposition of the phenolic α-diazoketone **4**.

Keywords——spirocyclic sesquiterpene; α-chamigrene; brominated chamigrene; spiro[5.5]-undecane; 1,5,5-trimethylspiro[5.5]undeca-7,10-diene-2,9-dione; metal-catalyzed decomposition of phenolic α-diazoketone; copper(II) chloride; regiospecific reduction; allylic oxidation; lithium in liquid ammonia

Spirocyclic sesquiterpenes, which have a spiro[4.5]decane or spiro[5.5]undecane system as the basic skeleton, are attractive targets for total synthesis. We have already developed a new synthetic method for the spiro[4.5]decane skeleton by the metal-catalyzed decomposition of the phenolic α-diazoketone,[2)] and have reported the synthesis of spirovetivane-type sesquiterpenes, solavetivone,[3)] agarospirol and hinesol,[4)] utilizing this method.

Next, we planned the synthesis of another group, a spiro[5.5]undecane series. Although several successful syntheses[5)] of α-chamigrene (**1**),[6)] a characteristic compound in this group, have been reported, little is known concerning the synthesis[7)] of a series of halogenated chamigrenes recently isolated from marine red algae. We wish to report the synthesis of α-chamigrene (**1**) and brominated chamigrane (**2a**),[8)] isolated from *Laurencia majuscula* HARVEY ("Akasozo" in Japanese), *via* the common precursor, 1,5,5-trimethylspiro[5.5]undeca-7,10-diene-2,9-dione (**5**), which was prepared by our spiroannulation method mentioned above.

The phenolic α-diazoketone **4** was prepared from the phenolic carboxylic acid **3**[9)] *via* four steps. Addition of the chloroform solution of **4** to boiling chloroform containing copper(II) chloride gave the spirodienone **5** in 22% yield. Its infrared (IR) spectrum showed the presence of a six-membered ketone (1710 cm^{-1}) and a dienone (1660, 1620 cm^{-1}), and an absorption maximum due to a dienone appeared at 241 nm (ε 17000) in its ultraviolet (UV) spectrum. Sodium borohydride reduction of **5** gave the β-alcohol **6** selectively in 80% yield (α-alcohol <5%). The stereochemistry of **6** was determined by measurement of the ^{1}H-nuclear magnetic resonance (NMR) spectrum; the C_2-proton signal appeared at δ 4.00 as a multiplet with a half-width, $W_{1/2}$, of 8 Hz. Then, catalytic hydrogenation of **6** afforded a saturated ketone **7** in 90% yield, while **6** was reduced regiospecifically by lithium in liquid ammonia to produce the enone **10** [IR 1664, 1617 cm^{-1}; UV 232 nm (ε 10200); ^{1}H-NMR δ 6.65, 6.00] in 89% yield. Similar regiospecific reduction has already been reported by us.[10)]

Synthesis of (±)-α-Chamigrene (1)

The dehydrated product **8** was obtained in 80% yield on heating the mesylate **7** in

dimethyl sulfoxide (DMSO) at 70 °C. The direction of this dehydration is evident from the ^{1}H-NMR and mass spectra (MS): δ 1.82 (allylic methyl proton), 5.52 (one olefinic proton); *m/z* 150 (retro Diels–Alder fission). The ketone **8** gave the alcohol **9** in 99% yield on treatment of methylmagnesium iodide (*ca.* 1 : 1 diastereomeric mixture), and **9** thus obtained, without purification, was treated with *p*-toluenesulfonic acid in dry benzene for four days to give α-chamigrene (**1**) in 59% yield.

Synthesis of Brominated Chamigrene (2a)

Dehydration of **10** was performed in a manner similar to that described for **7** to give **11** in 72% yield. The dienone **11** was transformed to the bromomethylidene derivative **12** in 67% yield (*E*:*Z*=3:2 mixture) by means of the Wittig reaction,[11] using bromomethyltriphenylphosphonium bromide and lithium piperidide. The diastereomixture **12** shows signals of an olefinic proton adjacent to the bromine atom at δ 5.81 and 6.04 in its ^{1}H-NMR spectrum. The former corresponds to the *Z* isomer and the latter to the *E* isomer.[8] Although the mixture was inseparable, brominated chamigrenes (**2a** and **2b**) obtained by allylic oxidation of **12** were separated by preparative thin layer chromatography (PTLC). This allylic oxidation was performed by the use of two reagents; one was chromium trioxide-3,5-dimethylpyrazole,[12] and the other was chromium trioxide–pyridine.[13] Compounds **2a** and **2b** were obtained in 12 and 55% yields, respectively, under the former conditions, while **2a** and **2b** were both obtained in 18% yield under the latter conditions with 33% recovery of **12**.

α-Chamigrene (**1**) and brominated chamigrenes (**2a** and **2b**) were identified by comparison of their IR and ^{1}H-NMR spectra with those of authentic samples.

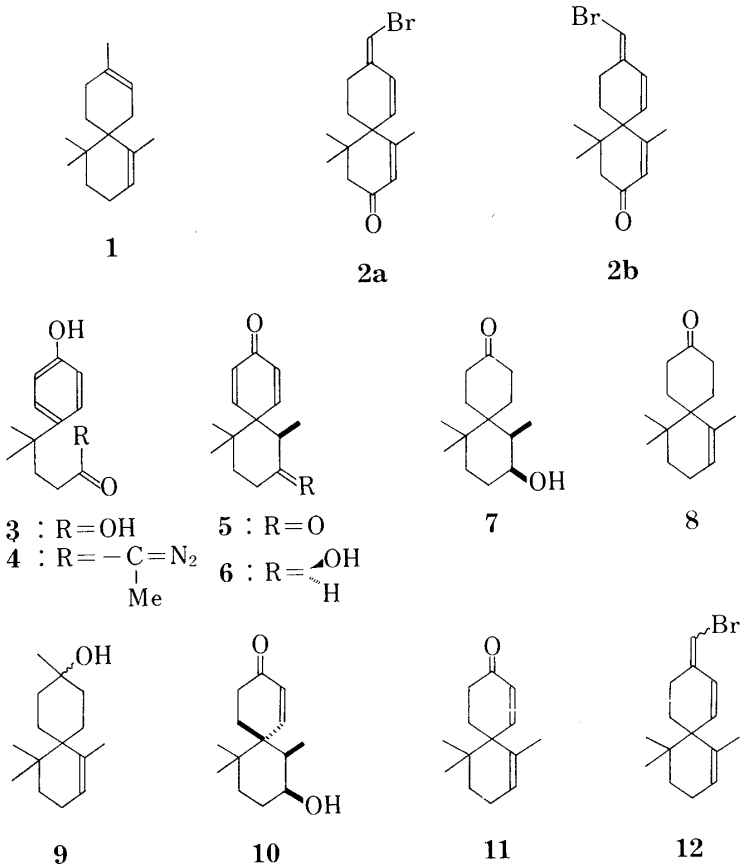

Chart 1

Experimental

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. UV and ^{1}H-NMR spectra were recorded on a Hitachi 124 spectrophotometer and a Hitachi R-22 (90 MHz), respectively. ^{1}H-NMR spectra were obtained with tetramethylsilane as an internal standard, and the following abbreviations are used; s = singlet, d = doublet, m = multiplet, and br = broad. IR spectra were recorded on a Hitachi EPI G-3 and/or a Hitachi 215 spectrometer. MS and high resolution mass spectra (High MS) were obtained with a JEOL JMS-D 300 mass spectrometer. For PTLC and column chromatography Merck Kieselgel PF_{254} and Merck Kieselgel 60 (70—230 mesh) were used, respectively.

2-Diazo-6-methyl-6-(4-hydroxyphenyl)-3-heptanone (4)——Acetic anhydride (5.6 ml) was added dropwise to a stirred solution of **3** (9 g) in 1 N NaOH (89 ml) at 0 °C. After being stirred for 1 h, the mixture was adjusted with acetic acid to pH 5, and the resulting mixture was extracted with benzene. The extract was washed, dried, and evaporated to give an acetate. This acetate was transformed to an acid chloride by treatment with thionyl chloride (10 ml) in benzene (100 ml) through a usual procedure. The acid chloride dissolved in dry ether was added to an ether solution of diazoethane (about 5-fold excess) at 0 °C. The mixture was stirred for 3 h, then the solvent was evaporated off under reduced pressure to give the diazoketone. This was dissolved in MeOH (300 ml), then water (225 ml), $NaHCO_3$ (20 g), and Na_2CO_3 (22.5 g) were added. The mixture was stirred overnight at room temperature. After evaporation of most of the MeOH under reduced pressure, the residue was neutralized with sat. oxalic acid, and extracted with benzene. The extract was washed, dried, and evaporated under reduced pressure. The water remaining in the residue was removed azeotropically under reduced pressure with dry benzene (100 ml × 2). The crude phenolic α-diazoketone **4** was obtained (10.7 g) as an unstable yellow oil, and this was used immediately for the annulation without purification. **4**: IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3380 (OH), 2090 (N=N), 1610 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.30 (6H, s, Ar–C–CH_3), 1.90 (3H, s, –C(=N_2)–CH_3), 6.70—7.23 (4H, AA′BB′-type aromatic protons). MS *m/z*: 246 (M^+, 0.4), 218 (10). High MS *m/z*: 218.130 ($M^+ - N_2$ Calcd for $C_{14}H_{18}O_2$: 218.131).

1,5,5-Trimethylspiro[5.5]undeca-7,10-diene-2,9-dione (5)——A chloroform solution (100 ml) of crude **4** (21.1 g) was added dropwise to vigorously boiling chloroform (1.1 l) containing copper(II) chloride (11.6 g) over 20 min, and the reaction mixture was refluxed for a further 5 min. After filtration of the rapidly cooled mixture, the filtrate was washed with water (100 ml × 2), sat. $NaHCO_3$ (100 ml × 3), water (100 ml × 2), and brine (100 ml), then dried, filtered with Florisil (200 g), and evaporated under reduced pressure to give a brown oil, which was purified by silica gel column chromatography (*n*-hexane : ethyl acetate = 3 : 1) to give **5** (4.1 g) in 22% yield. mp 143—144 °C (colorless crystals from ether–petr. ether). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (C=O), 1660, 1620 (C=C–C=O). UV λ_{max}^{EtOH} nm (ε): 241 (17000). ^{1}H-NMR ($CDCl_3$) δ: 0.78 (3H, d, J = 8 Hz, C_1-CH_3), 0.84, 1.47 (each 3H, s, C_5-CH_3), 6.8—7.0 (4H, AA′BB′-type olefinic protons). MS *m/z*: 218 (M^+, 26). *Anal.* Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.33. Found: C, 77.01; H, 8.33.

***cis*-2-Hydroxy-1,5,5-trimethylspiro[5.5]undeca-7,10-dien-9-one (6)**——$NaBH_4$ (20 mg) was added in portions to a stirred solution of **5** (105 mg) in MeOH (10 ml) at 0 °C. After being stirred for 30 min, the reaction mixture was poured into sat. $NaHCO_3$ containing crushed ice, and extracted with ethyl acetate. The extract was washed, dried, and evaporated under reduced pressure. The residue was purified by PTLC (ether : petr. ether = 3 : 1) to give **6** (88 mg) in 83% yield. mp 193—194 °C (colorless plates from ethyl acetate–petr. ether). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3420 (OH), 1660, 1620 (C=C–C=O). ^{1}H-NMR ($CDCl_3$) δ: 0.75, 1.16 (each 3H, s, C_5-CH_3), 0.79 (3H, d, J = 7 Hz, C_1-CH_3), 4.00 (1H, m, $W_{1/2}$ = 8 Hz, C_2-H), 6.23 (2H, br d, J = 11 Hz, C_8- and C_{10}-H), 6.72 (1H, dd, J = 11, 3 Hz, C_7-H), 7.59 (1H, dd, J = 11, 3 Hz, C_{11}-H). UV λ_{max}^{EtOH} nm (ε): 248 (15000). MS *m/z*: 220 (M^+, 7.3). *Anal.* Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.33; H, 9.10.

***cis*-2-Hydroxy-1,5,5-trimethylspiro[5.5]undecan-9-one (7)**——Compound **6** (161 mg) in ethyl acetate (20 ml) was hydrogenated in the presence of 10% palladium–carbon catalyst (100 mg) at ordinary pressure until the starting material was no longer detectable on thin layer chromatography (TLC). After separation of the catalyst by filtration, the filtrate was evaporated under reduced pressure, and the residue was purified by PTLC (ether : petr. ether = 3 : 2) to give **7** (148 mg) in 90% yield. mp 96—97 °C (colorless crystals from ether–petr. ether). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 0.85, 1.01 (each 3H, s, C_5-CH_3), 1.08 (3H, d, J = 7 Hz, C_1-CH_3), 3.80 (1H, m, C_2-H). MS *m/z*: 224 (M^+, 7.9). *Anal.* Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 75.03; H, 10.79.

1,5,5-Trimethylspiro[5.5]undec-1-en-9-one (8)——Methanesulfonyl chloride (MsCl) (0.3 ml) was added to a solution of **7** (90 mg) in pyridine (5 ml) at 0 °C, and the mixture was stirred for 3 h, then poured into sat. $NaHCO_3$ containing crushed ice and extracted with ethyl acetate. The extract was washed with sat. $NaHCO_3$, cooled 2% HCl, sat. $NaHCO_3$, and brine, then dried, and evaporated below 25 °C under reduced pressure to give the mesylate. This was dissolved immediately in DMSO (3 ml) and warmed at 60—70 °C for 7 h under an Ar atmosphere. The mixture was poured into sat. $NaHCO_3$ containing crushed ice, and extracted with ether. The extract was washed with water, dried, and evaporated. The residue was purified by PTLC (ether : petr. ether = 1 : 3) to give **8** (66 mg) in 80% yield. mp 52—53 °C (colorless crystals from EtOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 0.91 (6H, s, C_5-CH_3),

1.82 (3H, m, C_1-CH_3), 5.25 (1H, m, C_2-H). MS *m/z*: 206 (M^+, 8), 150 (retro Diels–Alder fission, 55). *Anal.* Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.50; H, 10.74.

(±)-α-Chamigrene (1) *via* 9-Hydroxy-1,5,5,9-tetramethylspiro[5.5]undec-1-ene (9)——An ether solution of MeMgI (5-fold molar excess) was added to a solution of **7** (50 mg) in dry ether (2 ml) at 0 °C, and the mixture was stirred for 2 h. Next, ether saturated with water and sat. NH_4Cl were added. The ether extract was washed with sat. $NaHCO_3$ and brine, then dried, and evaporated to give crude **9** (*ca.* 1 : 1 diastereomeric mixture, 53 mg) in 99% yield. A mixture of crude **9** (46 mg), *p*-TsOH (46 mg), and dry benzene (5 ml) was stirred for 4 d at room temperature, washed with sat. $NaHCO_3$ and brine, dried finally evaporated under reduced pressure. The residue was purified by PTLC (*n*-hexane) to give **1** (28.5 mg) in 59% yield.

Birch Reduction of *cis*-2-Hydroxy-1,5,5-trimethylspiro[5.5]undeca-7,10-dien-9-one (6)——A solution of **6** (50 mg) in dry tetrahydrofuran (THF) (7 ml) was added in one batch to a vigorously stirred solution of Li (3.5 mg) in liq. NH_3 (10 ml) at −78 °C, and the mixture was maintained as such for 1 min, then dry powdered NH_4Cl (200 mg) was added. The NH_3 was evaporated off at room temperature, then water and ether were added to the residue. The ether extract was washed with sat. $NaHCO_3$ and brine, dried, and evaporated. The residue was purified by PTLC (ether : petr. ether = 3 : 2) to give **10** (45.3 mg) in 89% yield. mp 155—158 °C (colorless crystals from ether). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1664, 1617 (C=C–C=O). UV λ_{max}^{MeCN} nm (ε): 232 (10200). ^{1}H-NMR ($CDCl_3$) δ: 0.97, 1.03 (each 3H, s, C_5-CH_3), 1.01 (3H, d, *J* = 7 Hz, C_1-CH_3), 3.88 (1H, m, C_2-H), 6.00 (1H, AB d, *J* = 10 Hz, C_8-H), 6.65 (1H, AB d, *J* = 10 Hz, C_7-H). MS *m/z*: 222 (M^+, 6.9). *Anal.* Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.66; H, 9.72.

1,5,5-Trimethylspiro[5.5]undeca-1,7-dien-9-one (11)——Compound **11** was prepared in a manner similar to that described for compound **8** from **10** (506 mg), pyridine (10 ml), MsCl (1.2 ml), and DMSO (7 ml) in 73% yield as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1665, 1612 (C=C–C=O). ^{1}H-NMR ($CDCl_3$) δ: 0.94, 0.99 (each 3H, s, C_5-CH_3), 1.67 (3H, br s, C_1-CH_3), 5.51 (1H, m, C_2-H), 6.11 (1H, AB d, *J* = 10 Hz, C_8-H), 6.67 (1H, AB d, *J* = 10 Hz, C_7-H). MS *m/z*: 204 (M^+, 7.9), 148 (retro Diels–Alder fission, 32). High MS *m/z*: 204.151 (M^+, Calcd for $C_{14}H_{20}O$: 204.151).

9-(*Z*)-Bromomethylidene-1,5,5-trimethylspiro[5.5]undeca-1,7-dien-3-one (2a) and Its Isomer 2b *via* Bromomethylidene Derivative (12)——Lithium piperidide solution [prepared from piperidine (0.26 ml) and *n*-butyllithium (1.6 ml, 15% in hexane) in dry THF (2 ml) at −78 °C followed by stirring for 5 min at 0 °C under N_2] was added to a stirred mixture of bromomethyltriphenylphosphonium bromide (1.37 g) and dry THF (5 ml) at 0 °C. The mixture was stirred for 10 min, then **11** (168 mg) in dry THF (2 ml) was added, and the whole was stirred for 6—7 h at room temperature. Water and ether were added. The ether extract was washed with water, dried, and evaporated. The residue was purified by PTLC (*n*-hexane) to give **12** (150 mg) as a colorless oil in 67% yield (*E* : *Z* = 3 : 2 from ^{1}H-NMR and HPLC analysis). ^{1}H-NMR ($CDCl_3$) δ: 5.81 (1H, br s, $=\!\!<^{H}_{Br}$, *Z* isomer), 6.04 (1H, br s, $=\!\!<^{H}_{Br}$, *E* isomer). The geometric mixture **12** was subjected to the next oxidation without further purification.

Oxidation of **12** with Chromium Trioxide–3,5-Dimethylpyrazole (3,5-DMP): 3,5-DMP (197.6 mg) was added in one batch to a vigorously stirred mixture of chromium trioxide (205.6 mg) and dry CH_2Cl_2 (3 ml) at −20 °C under N_2. Compound **12** (*E* : *Z* = 3 : 2 mixture, 35.4 mg) in CH_2Cl_2 (1 ml) was added dropwise to the mixture. The mixture was stirred for 3 h at 0 °C, then water (3 ml) was added, and stirring was continued for 30 min. The mixture was extracted with ether, and the extract was washed, dried, and evaporated. The residue was purified by PTLC (ether : petr. ether = 3 : 2) to give **2a** (*Rf* = 0.4, 4.4 mg) in 12% yield and **2b** (*Rf* = 0.5, 20.9 mg) in 55% yield.

Oxidation of **12** with Chromium Trioxide–Pyridine: A stirred mixture of pyridine (0.72 ml) and dry CH_2Cl_2 (20 ml) was treated with chromium trioxide (445 mg) at 0 °C under N_2, and the mixture was stirred for 5 min at 0 °C, then for 10 min at room temperature. Compound **12** (*E* : *Z* = 3 : 2 mixture, 83.3 mg) in dry CH_2Cl_2 (1 ml) was added. The whole was stirred for 36 h at room temperature, then water and ether were added, and the mixture was extracted with ether. The extract was washed with water, dried, and evaporated. The residue was purified by PTLC (ether : petr. ether = 3 : 2) to give **2a** (15.7 mg) in 18% yield and **2b** (15.4 mg) in 18% yield with recovery of **12** (27.5 mg, 33%).

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