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Agarofuran-, Eudesmane- and Eremophilane-Type Sesquiterpenoids from *Alpinia japonica* (THUNB.) MIQ.

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Three new sesquiterpenoids, 3α,4α-oxidoagarofuran, 3β,4β-oxidoagarofuran and $\Delta^{9(10)}$-eremophilen-11-ol, as well as 10-*epi*-γ-eudesmol, 4α-hydroxydihydroagarofuran, α-agarofuran, dihydroagarofuran and β-eudesmol were isolated from the rhizome of *Alpinia japonica*. Their structures were determined by chemical and spectroscopic methods.

It is interesting from a biogenetic point of view that $\Delta^{9(10)}$-eremophilen-11-ol, β-eudesmol and agarofurans which possess the 10-epimeric eudesmane carbon skeleton were all contained in the same plant.

Keywords——*Alpinia japonica*; Zingiberaceae; sesquiterpene; 3α,4α-oxidoagarofuran; 3β,4β-oxidoagarofuran; $\Delta^{9(10)}$-eremophilen-11-ol; 10-*epi*-eudesmane-type; ^{13}C-NMR; X-ray analysis

Seeds of *Alpinia japonica* (THUNB.) MIQ. (Zingiberaceae) have been used as an aromatic stomachic under the name, "Izu-shukusha" (伊豆縮砂) in Japan. The constituents so far isolated from the seeds are alpinon, izalpinin, kumatakenin, rhamnocitrin, camphor and cineole,[1] and from the rhizome, alpiniol and several sesquiterpenoids.[2] In this work, three new sesquiterpenoids (V, VI and VIII) were isolated together with five known sesquiterpenoids. This paper describes the determination and structural elucidation of the new compounds.

Fresh rhizome was extracted with methanol and the aqueous methanolic extract was treated with petroleum ether. The petroleum ether-soluble fraction was subjected to high-performance liquid chromatography (HPLC) on silica gel and silver nitrate-coated silica gel to give compounds I—VIII.

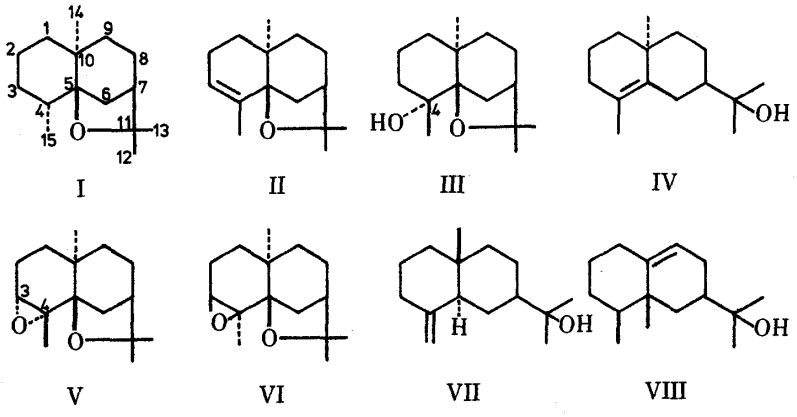


Chart 1

Compound I, $C_{15}H_{26}O$ (*m/z*: 222, M^+), and compound II, $C_{15}H_{24}O$ (*m/z*: 220.1844, M^+), were identified as dihydroagarofuran and α-agarofuran, respectively, by comparison of the spectral data with those reported in the literature.[3]

Compound III was obtained as colorless needles, mp 128.0—129.5 °C, $C_{15}H_{26}O_2$ (*m/z*: 238.1929, M^+), which showed a strong hydroxyl absorption band at 3430 cm^{-1} in the infrared (IR) spectrum. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum ($CDCl_3$) showed four tertiary methyl signals (δ 1.17, 1.21, 1.27, 1.36) and the carbon 13 nuclear magnetic resonance (^{13}C-NMR) spectrum ($CDCl_3$) indicated the presence of an ether linkage (δ 82.1, s; 87.8, s). The molecular formula and the above spectral data suggest that III is 4α-hydroxydihydroagarofuran, a compound which has been isolated from fungus-infected agarowood (*Aquilaria agallocha* ROXB.).[4] Since an authentic sample was not available for comparison, the structure of III was determined by X-ray analysis. Crystallographical data for III: $C_{15}H_{26}O_2$, monoclinic, $P2_1$; $a=8.831$, $b=9.892$, $c=8.299$ (Å), $\beta=108.19°$. A total of 1619 reflections were recorded on a Philips four-circle diffractometer with graphite-monochromated CuK_α radiation. The final *R* value was 0.06.

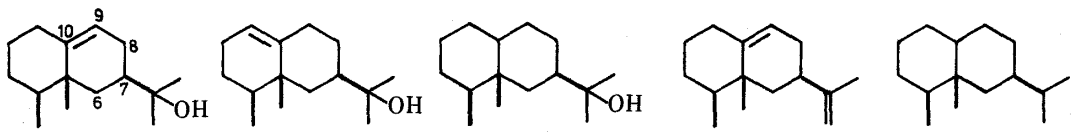
Compound IV was obtained as a colorless oil, $C_{15}H_{26}O$ (*m/z*: 222.1985, M^+). Reaction of IV with *m*-chloroperbenzoic acid gave 4α-hydroxydihydroagarofuran.[5] On the basis of the above reaction as well as the spectral data, IV was identified as 10-*epi*-γ-eudesmol.

Compound V was obtained as a colorless oil, $[\alpha]_D$ −20.8° (*c*=0.39, EtOH); the molecular formula, $C_{15}H_{24}O_2$ was given by the high-resolution mass spectrum (MS), *m/z* 236.1764 (M^+). The ^{1}H-NMR (δ 3.00, 1H, br d) and ^{13}C-NMR (δ 59.9, s and 60.7, d) spectra suggest that this compound is an epoxide of α-agarofuran. Reductive cleavage of the epoxide (V) with lithium aluminum hydride gave colorless needles, identical with III. Accordingly, V was identified as 3α,4α-oxidoagarofuran.

Compound VI was obtained as colorless needles, mp 90.0—91.0 °C, $[\alpha]_D$ −48.2° (*c*=0.36, $CHCl_3$); the molecular formula, $C_{15}H_{24}O_2$, was given by the high-resolution MS, *m/z* 236.1787 (M^+). The IR, ^{1}H- and ^{13}C-NMR spectra of VI suggest that this compound is a stereoisomer of V. It was reported by Maheshwari *et al.*[6] that epoxidation of α-agarofuran with perbenzoic acid yields 3β,4β-oxidoagarofuran, which was identical with VI on the basis of the spectral data and optical rotation.

Compound VII, $C_{15}H_{26}O$, colorless needles, mp 80.5—81.5 °C, was identified as β-eudesmol by comparison of various data with those of an authentic sample.

Compound VIII was obtained as colorless plates, mp 64.0—66.0 °C, $[\alpha]_D$ −14.9° (*c*=0.45, $CHCl_3$); the molecular formula, $C_{15}H_{26}O$, was given by the high-resolution MS, *m/z* 204.1888 (M^+-18, Calcd for $C_{15}H_{24}$: 204.1877). The IR, ^{1}H- and ^{13}C-NMR spectra gave signals due to a tertiary hydroxyl group (3630 cm^{-1}; δ 72.49 (s)), four methyl groups (δ 0.79, 3H, d, *J*=6; 0.91, 3H, s; 1.16, 6H, s; 15.64 (q), 20.92 (q), 26.73 (q), 27.22 (q)) and an olefinic proton (δ 5.33, 1H, br d, *J*=5; 146.75 (s), 117.56 (d)). Compound VIII contained only one double bond, and on catalytic hydrogenation yielded a saturated dihydro derivative (IX),[7] $C_{15}H_{28}O$, $[\alpha]_D$ +26.0°. Dehydration of VIII gave product (X) with no absorption ascribable to a conjugated diene system in the ultraviolet (UV) spectrum. This suggests that the double bond in VIII is present not at C-6 (7) or C-7 (8) but at either C-1 (10) or C-9 (10). Of the two possible structures, VIII and VIIIa, VIIIa was ruled out because our product was not identical



VIII VIIIa IX X XI

Chart 2

TABLE I. ^{13}C Chemical Shifts of Agarofurans

Carbon No.	I[a]	II	III	V	VI
1	37.6 (t)	32.4 (t)[b]	37.8 (t)[c]	31.8 (t)[d]	28.5 (t)[e]
2	17.0 (t)	22.5 (t)	17.7 (t)	20.7 (t)	22.5 (t)
3	29.5 (t)	127.2 (d)	31.8 (t)	60.7 (d)	60.0 (d)
4	40.5 (d)	132.4 (s)	74.3 (s)	59.9 (s)	58.2 (s)
5	87.8 (s)	84.9 (s)	87.8 (s)	85.0 (s)	84.4 (s)
6	38.4 (t)	34.4 (t)[b]	38.2 (t)[c]	36.9 (t)[d]	34.4 (t)[e]
7	44.6 (d)	44.3 (d)	44.6 (d)	44.3 (d)	44.5 (d)
8	25.1 (t)	24.5 (t)	24.9 (t)	24.3 (t)	24.1 (t)
9	38.1 (t)	32.9 (t)[b]	37.9 (t)[c]	32.1 (t)[d]	33.2 (t)[e]
10	38.4 (s)	37.0 (s)	38.8 (s)	37.5 (s)	36.5 (s)
11	81.2 (s)	80.8 (s)	82.1 (s)	82.3 (s)	80.9 (s)
12	23.6 (q)	22.8 (q)	24.1 (q)	22.7 (q)	22.2 (q)
13	30.6 (q)	30.2 (q)	30.1 (q)	30.0 (q)	30.5 (q)
14	22.9 (q)	21.9 (q)	22.9 (q)	22.7 (q)	21.5 (q)
15	17.7 (q)	19.1 (q)	27.0 (q)	18.6 (q)	21.5 (q)

The measurements were made on a JEOL FX-100 spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as an internal reference and the chemical shifts are expressed in ppm. *a*) The chemical shifts of I are cited from ref. 3. *b*—*e*) The assignments may be reversed.

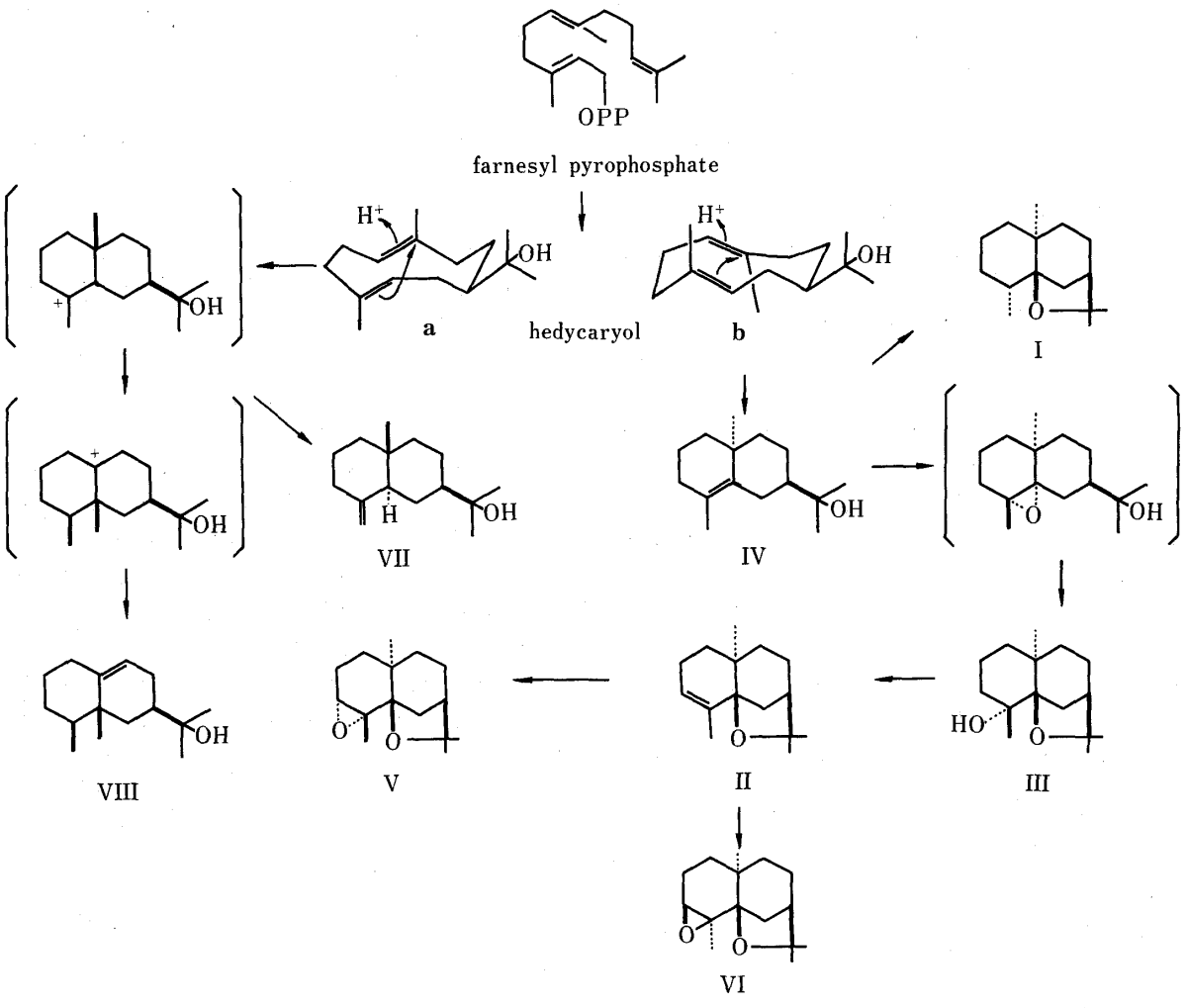


Chart 3

with a sample of VIIIa provided by Ishii.[7] Accordingly the structure was determined to be VIII. Catalytic hydrogenation of X produced a saturated liquid hydrocarbon (XI),[7] $C_{15}H_{28}$, $[\alpha]_D$ +19.3°. The spectral data and specific rotation of XI were identical with those of 7β-eremophilane.

The ^{13}C-NMR spectra of the agarofurans have been tentatively assigned and are summarized in Table I.

The probable biogenetic relationships of the sesquiterpenoids isolated from *Alpinia japonica* are shown in Chart 3. From the biogenetic point of view, these sesquiterpenoids were classified into two groups. One of them includes β-eudesmol (VII) and $\Delta^{9(10)}$-eremophilen-11-ol (VIII), which could be biosynthesized from the conformer (**a**) of the precursor, hedycaryol. The other group, including agarofurans (I, II, III, V and VI) and 10-*epi*-γ-eudesmol (IV), which possess 10-*epi*-eudesmane skeleton, could be supposed to be derived from hedycaryol in the conformation (**b**). The results of molecular mechanics calculations favor the biogenetic hypothesis in Chart 3, because the conformers **a** and **b** are the more stable types of hedycaryol with energy minima among the four conformers.[8] On the other hand, it was also reported that acid cyclization of *E,E*-hedycaryol and *E,Z*-hedycaryol gave only eudesmane and 10-*epi*-eudesmane type products respectively, and *Z,E*- and *Z,Z*-hedycaryol gave both of them.[9] However, it is noteworthy that these two types of sesquiterpene were found in the same plant. A few similar instances have been reported recently.[10,11]

Experimental

All melting points were recorded on a Yanagimoto micro melting point apparatus and are uncorrected. Spectral data were obtained on the following instruments; optical rotation on a JASCO DIP-4, IR on a JASCO IRA-1 and JASCO A-302, UV on a Hitachi 557, ^{1}H-NMR on a JEOL JNM-PS 100 and Varian EM 390, ^{13}C-NMR on a JEOL FX-100 in $CDCl_3$ solution, mass spectra (MS) on a Hitachi RMU-7L and Hitachi M-80. HPLC was carried out on a CIG column system (Kusano Scientific Co., Tokyo) with IATROBEADS (60 μ silica gel, IATRON Co., Tokyo) as the stationary phase.

Extraction and Isolation——The fresh rhizomes (16.7 kg) of *Alpinia japonica* were extracted three times with methanol. The methanol extract was partitioned with petroleum ether (bp 40—60 °C), and the petroleum ether layer was concentrated to give a yellow oil (18.1 g). The petroleum ether extract was subjected to column chromatography on silica gel with an *n*-hexane–ethyl acetate gradient system. Repeated chromatography of each fraction (HPLC, benzene–ethyl acetate system, *n*-hexane–ethyl acetate system; $AgNO_3$-HPLC, the same system) afforded I (50 mg), II (200 mg), III (470 mg), IV (900 mg), V (70 mg), VI (100 mg), VII (1.2 g) and VIII (130 mg). Compounds III and VI were recrystallized from *n*-hexane, and VII and VIII were purified by sublimation.

Compound I (Dihydroagarofuran): A colorless oil, $[\alpha]_D$ −79.4° (*c*=0.75, $CHCl_3$). MS *m/z* (%): 222 (M^+, 10), 207 (100), 189 (24), 164 (16), 149 (28), 137 (68), 109 (42). IR (neat) cm^{-1}: 2930, 1457, 1385, 1363, 1300, 1232, 1157, 1147, 1118, 1090, 1062, 1015, 963, 885. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, d, *J*=8.0 Hz), 1.07 (3H, s), 1.14 (3H, s), 1.33 (3H, s).

Compound II (α-Agarofuran): A colorless oil, $[\alpha]_D$ +32.3° (*c*=0.16, EtOH). MS *m/z* (%): 220 (M^+, 74, Calcd for $C_{15}H_{24}O$, 220.1827; Found 220.1844), 205 (25), 202 (18), 147 (28), 123 (33), 82 (100). IR (neat) cm^{-1}: 2920, 1455, 1385, 1235, 1150, 1080, 1010, 885. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, s), 1.23 (3H, s), 1.36 (3H, s), 1.71 (3H, d, *J*=1.5 Hz), 5.60 (1H, br s).

Compound III (4α-Hydroxydihydroagarofuran): Colorless needles, mp 128.0—129.5 °C, $[\alpha]_D$ −71.6° (*c*=0.16, EtOH). MS *m/z* (%): 238 (M^+, 100, Calcd for $C_{15}H_{26}O_2$, 238.1933; Found 238.1929), 223 (87), 162 (47), 125 (58), 109 (74), 95 (79). IR (KBr) cm^{-1}: 3430, 2920, 1455, 1380, 1365, 1200, 1155, 1085, 1000, 875. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, s), 1.21 (3H, s), 1.27 (3H, s), 1.36 (3H, s).

Compound IV (10-*epi*-γ-Eudesmol): A colorless oil, $[\alpha]_D$ −30.8° (*c*=0.16, EtOH). MS *m/z* (%): 222 (M^+, 5, Calcd for $C_{15}H_{26}O$, 222.1983; Found 222.1985), 204 (67), 189 (100), 175 (9), 161 (72), 147 (25), 133 (51), 105 (33), 91 (37), 59 (9). IR (neat) cm^{-1}: 3420, 2920, 1455, 1370, 1135, 925, 755. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (3H, s), 1.21 (3H, s), 1.25 (3H, s), 1.66 (3H, s), 1.96 (1H, s, disappeared on addition of D_2O), 2.63 (1H, br s), 2.77 (1H, br s). ^{13}C-NMR ($CDCl_3$) δ: 19.0 (t), 19.6 (q), 22. 5 (t), 25.3 (t), 26.0 (q), 27.8 (q), 29.6 (q), 32.7 (t), 34.4 (s), 38.1 (t), 39.4 (t), 44.2 (d), 74.3 (s), 125.7 (s), 134.9 (s).

Compound V (3α,4α-Oxidoagarofuran): A colorless oil, $[\alpha]_D$ −20.8° (*c*=0.39, EtOH). MS *m/z* (%): 236 (M^+, 100, Calcd for $C_{15}H_{24}O_2$, 236.1766; Found 236.1764), 221 (58), 135 (58), 125 (82), 123 (56), 109 (79), 95 (79). IR

(neat) cm^{-1}: 2920, 1390, 1155, 1145, 1010, 970, 895. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H, s), 1.25 (3H, s), 1.31 (3H, s), 1.37 (3H, s), 3.00 (1H, br d).

Compound VI (3β,4β-Oxidoagarofuran): Colorless needles, mp 90.0—91.0 °C, $[\alpha]_D$ −48.2° (c=0.36, $CHCl_3$). MS m/z (%): 236 (M^+, 5, Calcd for $C_{15}H_{24}O_2$, 236.1766; Found 236.1787), 221 (100), 178 (20), 163 (25), 125 (30), 55 (15). IR (CCl_4) cm^{-1}: 2925, 1460, 1380, 1115, 1020, 895, 675. ^{1}H-NMR (CCl_4) δ: 0.81 (3H, s), 1.17 (3H, s), 1.23 (3H, s), 1.30 (3H, s), 2.73 (1H, br s).

Compound VII (β-Eudesmol): Colorless needles, mp 80.5—81.5 °C (sublim.), $[\alpha]_D$ +51° (c=0.09, EtOH). MS m/z (%): 222 (M^+, 3, Calcd for $C_{15}H_{26}O$, 222.1983; Found 222.1957), 204 (5), 189 (6), 164 (32), 149 (42), 135 (11), 123 (19), 109 (24), 59 (100). IR (KBr) cm^{-1}: 3260, 2920, 1640, 1375, 1190, 1135, 880. ^{1}H-NMR ($CDCl_3$) δ: 0.71 (3H, s), 1.20 (6H, s), 4.46 (1H, br s), 4.73 (1H, br s). ^{13}C-NMR ($CDCl_3$) δ: 16.3 (q), 22.4 (t), 23.4 (t), 25.0 (t), 27.1 (q×2), 35.9 (s), 36.9 (t), 41.1 (t), 41.9 (t), 49.5 (d), 49.8 (d), 72.9 (s), 105.3 (t), 151.1 (s).

Compound VIII ($\Delta^{9(10)}$-Eremophilen-11-ol): Colorless plates, mp 64.0—66.0 °C (sublim.), $[\alpha]_D$ −14.9° (c=0.45, $CHCl_3$). MS m/z (%): 204 (M^+ − 18, 47, Calcd for $C_{15}H_{24}$, 204.1877; Found 204.1888), 189 (32), 161 (83), 147 (34), 105 (100), 91 (26), 59 (29). IR (CCl_4) cm^{-1}: 3630, 2970, 2930, 2860, 1465, 1440, 1380, 1370. ^{1}H-NMR ($CDCl_3$) δ: 0.79 (3H, d, J=6.0 Hz), 0.91 (3H, s), 1.16 (6H, s), 5.33 (1H, br d, J=5.0 Hz). ^{13}C-NMR ($CDCl_3$) δ: 15.6 (q), 20.9 (q), 26.7 (q), 27.2 (q), 27.6 (t), 29.4 (t), 31.3 (t), 32.1 (t), 35.6 (t), 38.5 (d), 39.5 (s), 41.3 (d), 72.5 (s), 117.6 (d), 146.8 (s).

Oxidation of IV with *m*-Chloroperbenzoic Acid——A solution of IV (55 mg) and *m*-chloroperbenzoic acid (109 mg) in CH_2Cl_2 was kept for 4.5 h at room temperature, then washed with 10% $Na_2S_2O_3$, saturated $NaHCO_3$ solution and brine, dried and evaporated. The residue was subjected to HPLC (*n*-hexane : ethyl acetate = 17 : 3) to give colorless needles, III (29 mg).

Reduction of V with Lithium Aluminum Hydride——An ether solution of V (23 mg) was treated with lithium aluminum hydride (100 mg) in dry Et_2O under a nitrogen atmosphere for 3 h at room temperature. After work-up in the usual way, the product was subjected to HPLC (*n*-hexane : ethyl acetate = 17 : 3) to give colorless needles, III (16 mg).

Hydrogenation of VIII——A solution of VIII (20 mg) in $CHCl_3$ (5 ml) was stirred with PtO_2 (5 mg) for 13 h at room temperature under an H_2 atmosphere, then the catalyst was removed by filtration and the filtrate was evaporated to give a colorless oil (IX), eremophilan-11-ol (19 mg): $[\alpha]_D$ +26.0° (c=0.2, $CHCl_3$). MS m/z (%): 209 (M^+ − 15, 5), 191 (15), 166 (50), 109 (27), 95 (28), 81 (20), 59 (100). IR (neat) cm^{-1}: 3370, 2900, 2840, 1470, 1450, 1380, 1150, 940, 910, 800. ^{1}H-NMR ($CDCl_3$) δ: 0.73 (3H, d, J=6.5 Hz), 0.87 (3H, s), 1.14 (6H, s).

Dehydration of VIII——Thionyl chloride (0.33 ml) was added to a cooled solution of VIII (100 mg) in pyridine (3 ml) and the reaction mixture was left for 1.5 h at 0 °C. The mixture was poured into ice-water and extracted with ether, and the ether layer was washed with saturated $NaHCO_3$ solution and saturated NaCl solution, then dried (Na_2SO_4) and evaporated, leaving a colorless oil (53 mg). This was purified by HPLC (*n*-hexane) to give a colorless oil (X), $\Delta^{9(10),11(12)}$-eremophilene (44 mg): $[\alpha]_D$ −11.1° (c=0.18, $CHCl_3$), MS m/z (%): 204 (M^+, 13), 189 (11), 161 (21), 133 (19), 121 (22), 105 (100), 91 (42), 79 (24), 55 (24). IR (CCl_4) cm^{-1}: 3085, 2970, 2925, 2850, 1640, 1460, 1440, 1370, 1050, 885. ^{1}H-NMR ($CDCl_3$) δ: 0.79 (3H, d, J=6.0 Hz), 0.92 (3H, s), 1.73 (3H, s), 4.70 (2H, br s), 5.37 (1H, m). ^{13}C-NMR ($CDCl_3$) δ: 15.75 (q), 20.76 (q), 21.04 (q), 29.23 (t), 31.37 (t), 31.48 (t), 32.29 (t), 37.71 (d), 38.69 (d), 39.44 (s), 39.67 (t), 108.17 (t), 117.85 (d), 146.28 (s), 150.14 (s).

Hydrogenation of X——A solution of X (18 mg) in $CHCl_3$ (5 ml) was stirred with PtO_2 (5 mg) for 13 h at room temperature under an H_2 atmosphere, then the catalyst was removed by filtration and the filtrate was evaporated to give a colorless oil (XI), 7β-eremophilane (16 mg): $[\alpha]_D$ +19.3° (c=0.12, $CHCl_3$). MS m/z (%): 208 (M^+, 53, Calcd for $C_{15}H_{28}$, 208.2190; Found 208.2190), 193 (48), 165 (88), 109 (78), 95 (100), 81 (91), 55 (76). IR (CCl_4) cm^{-1}: 2960, 2950, 2875, 1470, 1450, 1380, 1370. ^{1}H-NMR ($CDCl_3$) δ: 0.71 (3H, d, J=6.0 Hz), 0.83 (3H, s), 0.84 (6H, d, J=6.0 Hz).

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