Bioactive Constituents of Chinese Natural Medicines. I. New Sesquiterpene Ketones with Vasorelaxant Effect from Chinese Moxa, the Processed Leaves of *Artemisia argyi* LEVL. *et* VANT.: Moxartenone and Moxartenolide

Masayuki YOSHIKAWA,* Hiromi SHIMADA, Hisashi MATSUDA, Johji YAMAHARA, and Nobutoshi MURAKAMI

Kyoto Pharmaceutical University, 5 Nakauchi-cho, Misasagi, Yamashina-ku, Kyoto 607, Japan.
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Two new sesquiterpene ketones, moxartenone and moxartenolide, and three octadecadienoic acids were isolated from Chinese moxa, the processed leaves of *Artemisia argyi* LEVL. *et* VANT., together with two sesquiterpenes, five triterpenes, two phenyl propanoids and three polyoxyflavones. The chemical structures of new sesquiterpenes, moxartenone, moxartenolide, and octadecadienoic acids were determined on the basis of chemical and physicochemical evidence. Moxartenolide was found to inhibit the contractions induced by a high concentration of K^+, by norepinephrine, and by serotonin in isolated aortic strips of rat, while moxartenone showed little activity.

Key words moxa; *Artemisia argyi*; moxartenone; moxartenolide; octadecadienoic acid; vasorelaxant effect

The leaves of *Artemisia argyi* LEVL. *et* VANT. and several related *Artemisia* plants (Compositae) have been used as a Chinese natural medicine, Artemisia Argyi Folium [Gaiyou (艾葉) in Japanese], which is prescribed as a hemostatic and sedative agent in Chinese traditional preparations. The hair and fiber parts of the leaves are called moxa [mogusa (艾) in Japanese] and the preparation of moxa from the fresh leave is an important process in obtaining Artemisia Argyi Folium. Moxa has been particularly used for analgesic purposes in Chinese acupuncture–cautery procedures.

Extensive chemical studies on the leaves of *Artemisia argyi* and related *Artemisia* plants have led to the identification of many compounds, such as monoterpenes, sesquiterpenes, triterpenes, and flavones from the fresh and dry leaves.[1] On the other hand, relatively little is known about the chemical constituents of the processed leaves "moxa," except for some work on the composition of the essential oil.[2]

As a part of our chemical studies on biological active principles of natural medicines,[3] we have isolated two new sesquiterpene ketones designated as moxartenone (**1**) and moxartenolide (**2**) and three octadecadienoic acids (**3**, **4**, **5**) from Chinese moxa, whose botanical origin was identified as *Artemisia argyi* LEVL. *et* VANT.,[4] together with two sesquiterpenes, five triterpenes, two phenyl propanoids, and three polyoxyflavones. This paper deals with the isolation and structure elucidation of those constituents.[5] In addition, we describe the vasorelaxant activity of **1** and **2** on the contractions induced by a high concentration of K^+, by norepinephrine (NE), and by serotonin (5-HT) in isolated aortic strips of rat.

The isolation of the chemical constituents from Chinese moxa was carried out through the procedure shown in Chart 1. The methanolic extract of Chinese moxa was partitioned into an ethyl acetate and water mixture. The ethyl acetate-soluble portion was subjected to repeated ordinary-phase and reversed-phase silica gel column chromatography, preparative thin layer chromatography (preparative TLC) and high-performance liquid chromatography (HPLC) to furnish two sesquiterpene ketones, moxartenone (**1**) and moxartenolide (**2**), three fatty acids, 13-oxo-9(*Z*),11(*E*)-octadecadienoic acid (**3**), 13-oxo-9(*E*), 11(*E*)-octadecadienoic acid (**4**), and 9-oxo-10(*E*),12(*E*)-octadecadienoic acid (**5**), two sesquiterpenes, clovandiol (**6**)[6] and caryophyllene oxide (**7**),[7] five triterpenes, gult-5-en-3β-yl acetate (**8**),[8] dammara-20, 24-dien-3β-yl acetate (**9**),[9] cycloartenyl acetate (**10**),[10] cycloart-23-en-3β,25-diol (**11**),[11] and cycloart-23-en-3β,25-diol monoacetate (**12**),[10] two phenyl propanoids, *trans-o*-coumaric acid (**13**) and scopoletin (**14**),[12] and three flavones, nepetin (**15**),[13] jacesiolin (**16**),[14] and eupatilin (**17**).[11] This is the first time that the two sesquiterpenes (**6**, **7**), five triterpenes (**8**—**12**), two phenyl propanoids (**13**, **14**) and two flavones (**15**, **16**) have been isolated from moxa and the leaves of *Artemisia argyi*.

Moxartenone (1) and Moxartenolide (2) Moxartenone (**1**) was obtained as a white powder. The positive-mode FAB-MS of **1** showed a quasimolecular ion peak at *m/z* 277 $(M+H)^+$ and the molecular formula of **1** was determined to be $C_{17}H_{24}O_3$ from high-resolution MS measurement. The UV spectrum of **1** suggested the presence of an enone function [252 nm ($\log\varepsilon$ 2.34)]. The IR spectrum of **1** showed absorption bands due to ester and enone groups at 1736, 1676, and 1620 cm^{-1}. The ^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR (Table 1) spectra of **1**, which were completely assigned by means of NMR analytical methods,[15] showed the presence of three tertiary methyls [δ 0.90, 0.98, 1.02 (all s)], a vinyl methyl [δ 2.04 (d, J=1.7 Hz)], an acetoxyl (δ 2.08), two methylenes [δ 1.81, 1.83 (both m)], three methines [δ 2.19 (s, 1-H), 2.69 (d, J=6.7 Hz, 2-H), 2.81 (dd, J=1.5, 6.7 Hz, 6-H)], a methine bearing an acetoxyl group [δ 4.73 (dd, J=1.3, 9.9 Hz, 10-H)], and a trisubstituted olefin [δ 5.77 (dq, J=1.5, 1.7 Hz, 4-H)]. The connectivities of the quaternary carbons at the C-3, 5, 7, and 11 positions were clarified by a HMBC experiment with **1**. Namely, HMBC correlations were observed between the following protons

* To whom correspondence should be addressed.

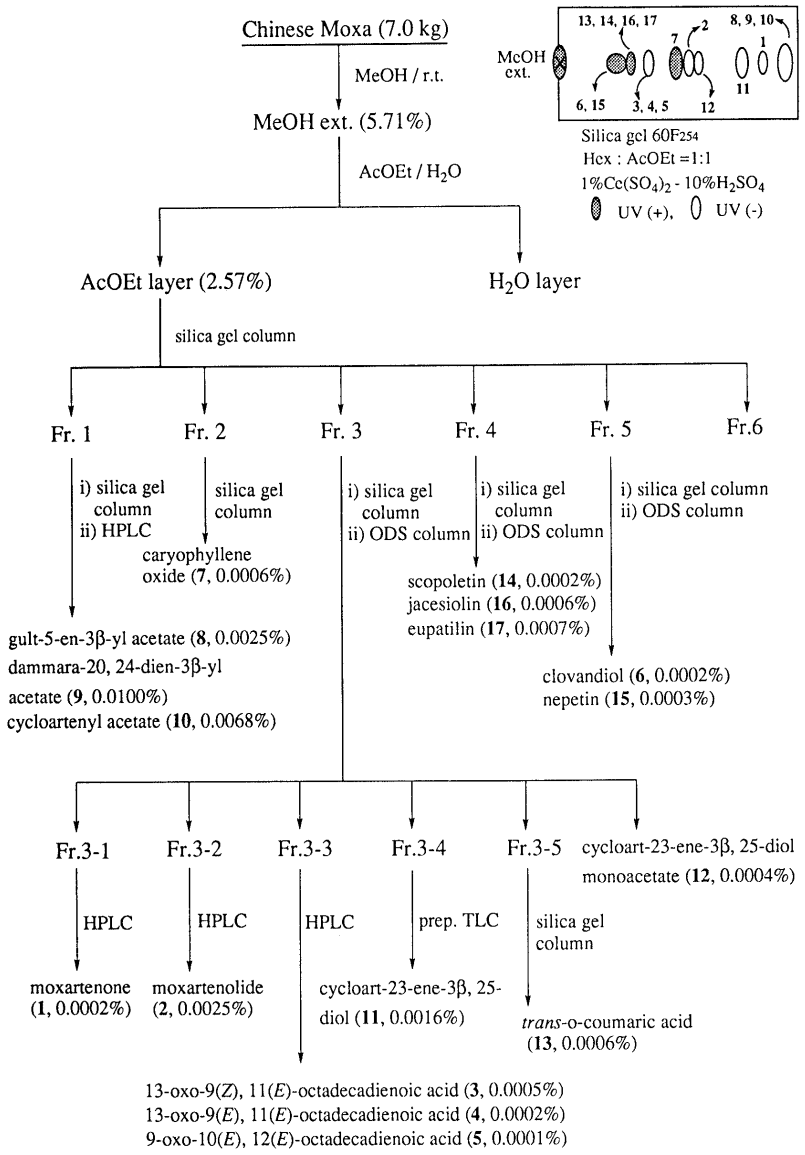

Chart 1

and carbons: 1-H and 7-C; 2-H and 3, 4, 8, 15-C; 6-H and 2, 4, 5, 7-C; 10-H and 1, 11-C, acetyl-C, as shown in Fig 1, so that the longipin-3-en-5-one structure (**1**) having the 10-acetoxyl group was constructed. Comparison of the ^{1}H-NMR and ^{13}C-NMR data for **1** with those for several known longipin-3-en-5-one type sesquiterpenes[16] led us to formulate the 10-acetoxy longipin-3-en-5-one structure of **1**. Furthermore, the stereostructure of **1** was characterized on the basis of a nuclear Overhauser and exchange spectroscopy (NOESY) experiment on **1** (Fig. 2), in which NOE correlations were observed between the following protons; 2-H and 13-CH_3, 15-CH_3; 4-H and 15-CH_3; 6-H and 10-H, 12-CH_3, 14-CH_3; 10-H and 12-CH_3. Finally, the CD spectrum of **1** [$\Delta\varepsilon = +1.56$ (312 nm) (positive maximum), $\Delta\varepsilon = -4.03$ (249 nm) (negative maximum)] was analogous with that of vulgarone B (longipin-3-en-5-one),[16] for which the absolute structure has been determined. Consequently, the absolute stereostructure of moxartenone (**1**) was determined to be 10(*R*)-10-acetoxylongipin-3-en-5-one.

Moxartenolide (**2**), also isolated as a white powder, gave a quasimolecular ion peak at *m/z* 343 $(M+H)^+$ in the positive-mode FAB-MS and the molecular composition was defined as $C_{20}H_{22}O_5$ from the high-resolution FAB-MS analysis. The UV and IR spectra of **2** indicated the presence of γ-lactone, enone, and ester functions. In the ^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR (Table 1) spectra[15] of **2**, it showed signals ascribable to a dienone part [δ 6.21 (d, $J = 1.3$, 3-H), 2.48 (s, 14-CH_3), 2.34 (br s, 15-CH_3); δ_C 133.5 (1-C), 195.0 (7-C), 176.0 (3-C), 169.2 (4-C), 144.8 (10-C)], an α-methylene-γ-lactone moiety [δ 3.74 (dd, $J = 10.2$, 10.2 Hz, 6-H), 3.34 (dddd, $J = 3.0$, 3.3, 10.2, 10.4 Hz, 7-H), 5.64, 6.23 (both d, $J = 2.6$Hz, 13-H_2)] and an angeloyl group [δ 1.93 (dq, $J = 1.3$, 1.7 Hz, 5′-CH_3), 2.04 (dq, $J = 1.3$, 1.7 Hz, 4′-CH_3), 6.24 (dq-like, 3′-H)]. The connectivities of the quaternary carbons in **2** were characterized by a correlation spectroscopy *via* long-range coupling (COLOC) experiment, in which C–H long-range correlations were observed between the following carbons and protons: 1-C and 5-H, 14-CH_3; 2-C and 3-H, 5-H; 3-C and 15-CH_3; 4-C and 15-CH_3, 5-C and 15-CH_3; 10-C and 14-CH_3; 1′-C and 8-H (Fig. 3). Comparison of the ^{1}H-NMR and ^{13}C-NMR data for **2** with those for known 8-*O*-acyl-2-oxoguaia-1(10),3,11(13)-

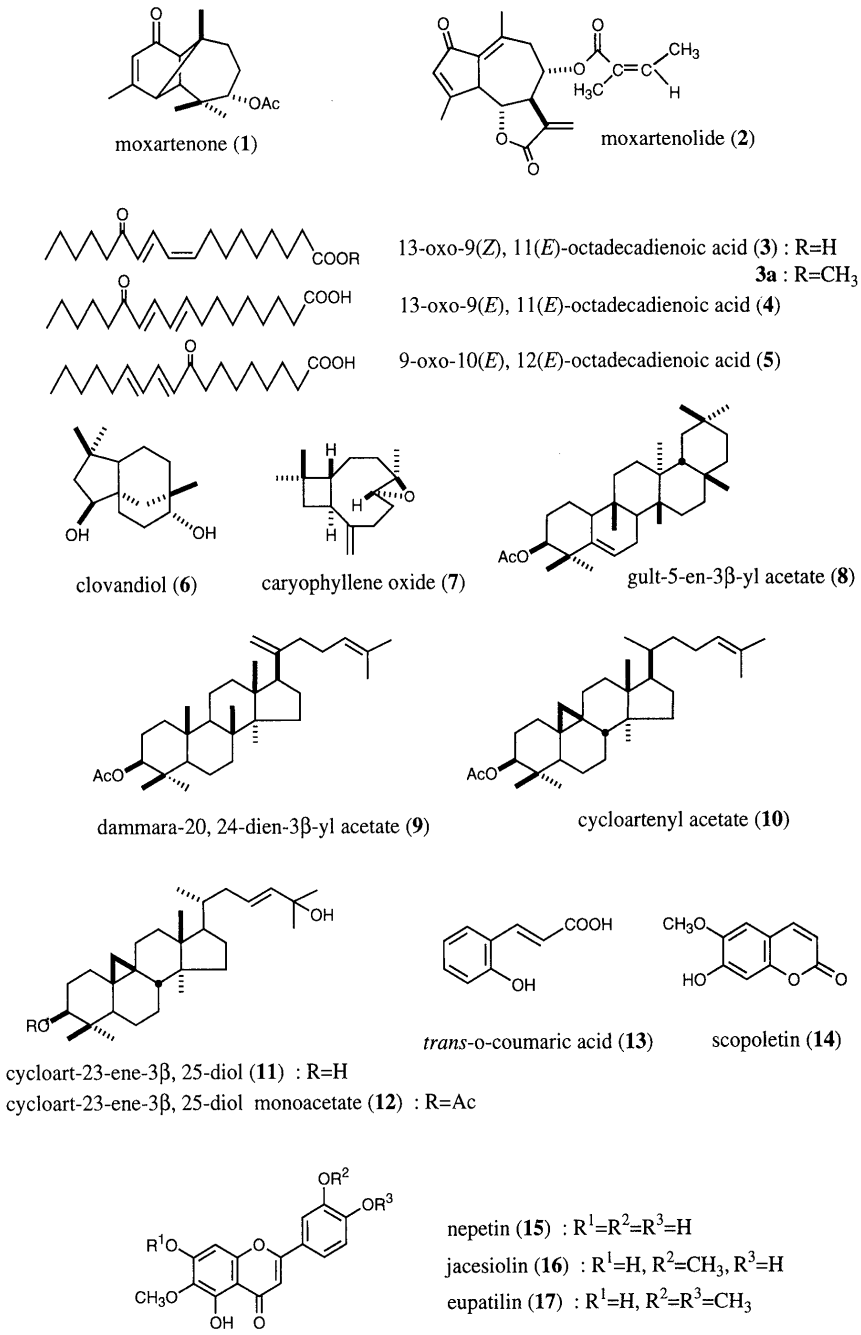

Chart 2

trien-6,12-olides[17] led us to characterize the structure of **2**. Furthermore, NOE correlations were observed between the protons as shown in Fig. 4. Based on the above-mentioned evidence, the structure of moxartenolide was determined to be (5α,6α,8α)-8-angeloxy-2-oxo-guaia-1(10),3,11(13)-trien-12,6-olide (**2**).

13-Oxo-9(*Z*),11(*E*)-, 13-Oxo-9(*E*),11(*E*)-, and 9-Oxo-10(*E*),12(*E*)-octadecadienoic Acids (3, 4, 5) 13-Oxo-9(*Z*),11(*E*)-octadecadienoic acid (**3**), 13-oxo-9(*E*),11(*E*)-octadecadienoic acid (**4**), and 9-oxo-10(*E*),12(*E*)-octadecadienoic acid (**5**) were each isolated as a white powder. The UV and IR spectra of **3**, **4**, and **5** were very similar and showed absorption bands ascribable to a dienone function [**3**: 278 nm (log ε 4.15), 1709 cm^{-1}; **4**: 276 nm (log ε 4.21), 1709 cm^{-1}; **5**: 276 nm (log ε 4.11), 1719 cm^{-1}]. The electron impact (EI)-MS of **3**, **4**, and **5** showed the same molecular ion peak at *m/z* 294 (M^+) and the molecular composition was defined as $C_{18}H_{30}O_3$ from high-resolution MS measurement in each case.

13- or 9-Oxo-octadecadienoic acids (**3**, **4**, **5**) have been reported as their methyl ester derivatives from the seed oil of *Monnina emarginata* and *Dimorphotheca sinuata*,[18] and from the decomposition product of linoleic acid hydroperoxide.[19] Recently methyl 13-oxo-9(*Z*),11(*E*)-octadecadienoate (**3a**) was isolated, after diazomethane methylation, from the fatty acid fraction obtained from the red alga *Gracilariopsis lemaneiformis*.[20] This time, free fatty acids (**3**, **4**, **5**) were isolated and their structure were confirmed by the following examination.

The ^{1}H-NMR (benzene-d_6) and ^{13}C-NMR (Table 2) spectra[15] of **3** showed the presence of a 9(*Z*),11(*E*)-dien-13-one moiety [δ 5.64 (dt-like, 9-H), 5.99 (dd, *J*=

Table 1. The ^{13}C-NMR Data for Moxartenone (**1**) and Moxartenolide (**2**)

	1	2
C-1	65.5	133.5
2	49.4	195.0
3	172.0	136.0
4	122.4	169.2
5	204.1	51.5
6	57.6	81.4
7	54.7	55.3
8	36.8	68.6
9	26.7	44.5
10	78.1	144.8
11	37.3	136.2
12	26.0	168.4
13	20.6	121.8
14	24.3	21.3
15	23.4	19.9
1′		166.3
2′		126.7
3′		140.9
4′		16.0
5′		20.5
OAc	21.2, 170.4	

The spectra were taken in $CDCl_3$ at 68 MHz.

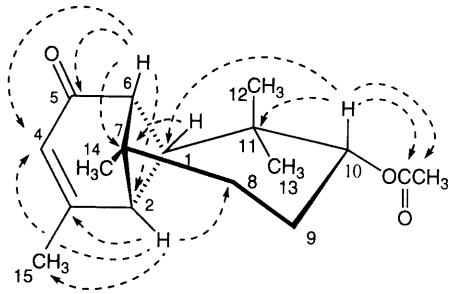

Fig. 1. Long-Range Correlations in the HMBC Spectrum of **1**

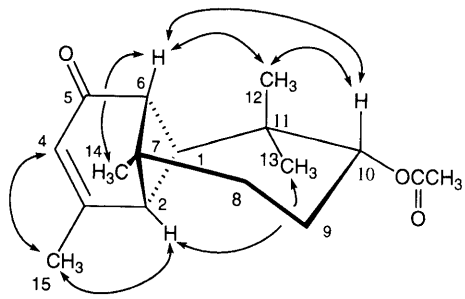

Fig. 2. NOEs Observed in the NOESY Spectrum of **1**

10.7, 11.6 Hz, 10-H), 7.72 (dd, J=11.6, 15.3 Hz, 11-H), 6.05 (d, J=15.3 Hz, 12-H)] together with a methyl [δ 0.83 (t, J=7.3 Hz, 18-CH_3)] and eleven methylenes [δ 2.25 (t, J=7.3 Hz, 2-H_2), 1.47 (tt, J=7.3, 7.3 Hz, 3-H_2), 2.04 (ddt, J=1.5, 7.6, 7.6 Hz, 8-H_2), 2.10 (t, J=7.3 Hz, 14-H_2), 1.61 (tt, J=7.3, 7.4 Hz, 15-H_2), 1.03—1.24 (4—7, 16, 17-H_2)]. The MS of **3** showed fragment ion peaks at m/z 151 (i, 80%), 223 (ii, 46%), and 238 (iii, 24%), together with a molecular ion peak (Fig. 5). Finally, methylation of **3** with diazomethane yielded the methyl ester (**3a**), which was found to be identical with methyl 13-oxo-9(Z),11(E)-octadecadienoate.[20] Consequently, the structure of **3** was

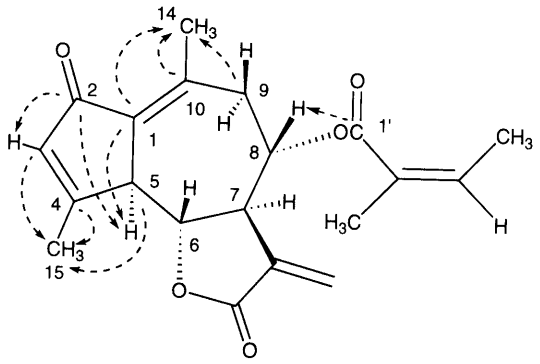

Fig. 3. C–H Long-Range Correlations in the COLOC Spectrum of **2**

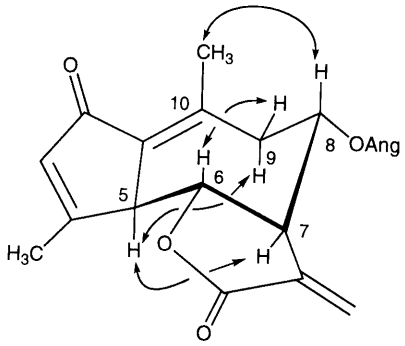

Fig. 4. NOEs Observed in the NOESY Spectrum of **2**

Table 2. The ^{13}C-NMR Data for **3**, **4**, and **5**[a]

	3	4	5
C-1	178.7	179.6	179.7
2	33.9	34.0	34.0
3	24.8	24.9	24.5
4	28.9[b]	28.9[b]	28.7[b]
5	28.9[b]	29.2[b]	29.1[b]
6	28.9[b]	29.3[b]	29.4[b]
7	29.3[b]	33.2[b]	24.9
8	28.2	28.7	40.9
9	142.1	144.4	199.1
10	128.4	129.4	128.4
11	136.4	142.1	142.3
12	129.7	128.5	129.4
13	199.4	199.2	144.8
14	41.8	40.8	33.2
15	24.1	24.3	30.2[b]
16	31.8[b]	31.8[b]	31.6[b]
17	22.8	22.9	22.8
18	14.1	14.2	14.2

a) The spectra were taken in C_6D_6 at 125 MHz; b) The assignments may be interchangeable within the same column.

determined to be as shown.

The carbon and proton signals observed in the ^{1}H-NMR (benzene-d_6) and ^{13}C-NMR (Table 2) spectra[15] of **4** were found to be superimposable on those of **3**, except for the signals due to the 9(E),11(E)-dien-13-one moiety [δ 5.79 (dt, J=7.3, 15.4 Hz, 9-H), 5.97 (dd, J=10.8, 15.4 Hz, 10-H), 7.19 (dd, J=10.8, 15.5 Hz, 11-H), 6.05 (d, J=15.5 Hz, 12-H)]. The MS of **4** showed the molecular ion peak and fragment ion peaks [i (100%), ii (46%), iii (30%)], and the fragmentation pattern was found to be superimposable on that of **3**. Based on the above-

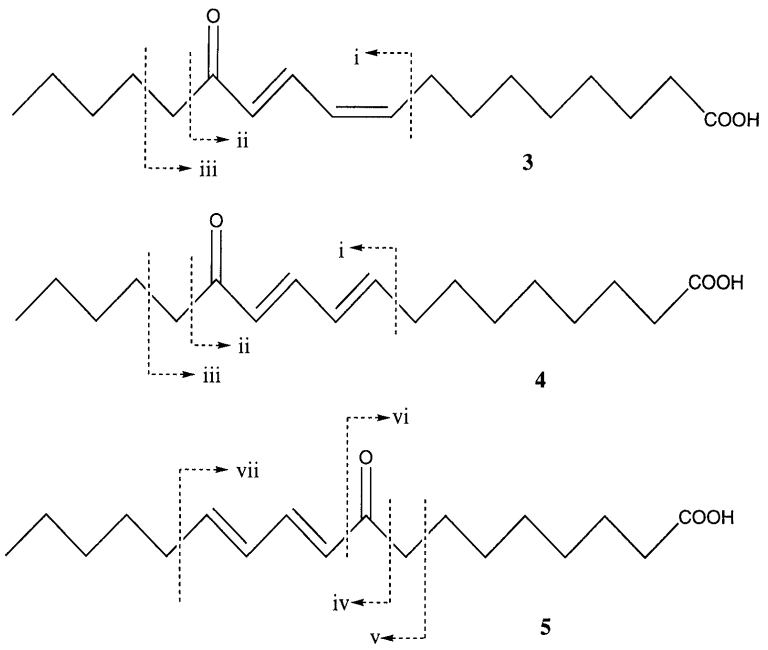

Fig. 5. Fragment Ion Peaks in the EI-MS of **3**, **4**, and **5**

Table 3. Effects of Moxartenone (**1**) and Moxartenolide (**2**) on the Contractions Induced by a High Concentration of K^+, by NE, and by 5-HT in Isolated Thoracic Aorta of Rat

Compound	Inhibition (%)		
	KCl (50 mM)	NE (3×10^{-7} M)	5-HT (10^{-5} M)
Moxartenone (**1**)			
3×10^{-5} M	-0.6 ± 2.7 ($n=4$)	-1.3 ± 4.6 ($n=4$)	-2.0 ± 2.9 ($n=4$)
10^{-4} M	6.7 ± 2.1 ($n=4$)	1.8 ± 3.8 ($n=4$)	8.8 ± 1.1 ($n=4$)
Moxartenolide (**2**)			
3×10^{-6} M	-2.1 ± 2.8 ($n=4$)	0.2 ± 1.0 ($n=4$)	0.3 ± 1.0 ($n=6$)
10^{-5} M	2.8 ± 1.6 ($n=5$)	-1.0 ± 1.9 ($n=5$)	5.4 ± 1.5 ($n=6$)
3×10^{-5} M	24.2 ± 2.7* ($n=5$)	27.5 ± 9.9* ($n=5$)	19.1 ± 2.6* ($n=6$)
10^{-4} M	77.1 ± 2.4* ($n=5$)	84.1 ± 3.7* ($n=5$)	61.4 ± 1.7* ($n=6$)
Nifedipine			
10^{-7} M	98.7 ± 0.3* ($n=4$)	—	—
Nitroprusside			
10^{-7} M	—	86.5 ± 5.0* ($n=4$)	—
Cyproheptadine			
10^{-7} M	—	—	96.5 ± 1.4* ($n=4$)

* Asterisks denote significant differences from the control at $p<0.01$.

mentioned evidence, the structure of **4** was clarified to be as shown.

The ^{1}H-NMR (benzene-d_6) and ^{13}C-NMR (Table 2) spectra[15] of **5** showed signals due to the 10(*E*),12(*E*)-dien-9-one moiety [δ 6.04 (d, $J=15.5$ Hz, 10-H), 7.19 (dd, $J=10.9$, 15.5 Hz, 11-H), 5.97 (dd, $J=10.9$, 15.0 Hz, 12-H), 5.79 (dt, $J=7.3$, 15.0 Hz, 13-H)]. The EI-MS of **5** showed the molecular ion peak and fragment ion peaks at *m/z* 151 (iv, 100%), 166 (v, 98%), 171 (vi, 8%) and 223 (vii, 88%). Comparison of the spectral data for **5** with those for **3** and **4** led us to formulate the structure of **5**.

Vasorelaxant Effect of Moxartenone (1) and Moxartenolide (2) Vasorelaxant effects of **1** and **2** were examined by using a bioassay to test the inhibitory activity on the contraction induced by a high concentration of K^+ (high-K^+), by NE, and by 5-HT in isolated aortic strips of rat. Two sesquiterpene ketones, **1** and **2**, had no effect on the resting tension at 3×10^{-6} to 10^{-4} M concentration. As shown in Table 3, **2** inhibited the contraction induced by high-K^+, NE, and 5-HT in a concentration-dependent manner (10^{-5}—10^{-4} M), while **1** showed slight activity at 10^{-4} M concentration. The vasorelaxant effect of **2** may be beneficial and the anti-serotonin effect of **2** may also be related to the analgesic effect of this natural medicine.

Experimental

The following instruments were used to obtain physical data: melting points, Yanagimoto micro-melting point apparatus MP-500D (values are uncorrected); specific rotations, Horiba SEPA-300 digital polarimeter ($l=5$ cm); UV spectra, Shimadzu UV-1200 spectrometer; IR spectra, Shimadzu FTIR-8100 spectrometer; ^{1}H-NMR spectra, JEOL EX-270 (270 MHz) and JNM-LA500 (500 MHz) spectrometer; ^{13}C-NMR spectra, JEOL EX-270 (68 MHz) and JNM-LA500 (125 MHz) spectrometers with tetramethylsilane as an internal standard; MS and high-resolution MS, JEOL JMS-SX 102A mass spectrometer; HPLC, Shimadzu LC-10AS chromatograph.

The following experimental conditions were used for chromatography: ordinary-phase column chromatography; Silica gel BW-200 (Fuji Silysia Chemical Ltd., 150—350 mesh), Chromatorex ODS DM1020T (Fuji Silysia Chemical Ltd., 100—200 mesh): TLC, pre-coated TLC plates with Silica gel $60F_{254}$ (Merck, 0.25 mm) (ordinary-phase) and Silica gel RP-18 $60F_{254}$ (Merck, 0.25 mm) (reversed-phase); HPTLC, pre-coated TLC plates with Silica gel RP-18 $60WF_{254s}$ (Merck, 0.25 mm) (reversed-phase). Detection was done by spraying 1% $Ce(SO_4)_2$–10% aqueous H_2SO_4, followed by heating.

Extraction and Isolation Chinese moxa (7 kg, obtained from Nippon Chugoku Onkyu Co., Ltd., Kobe, in 1994) was extracted with MeOH for 24 h at room temperature three times. After removal of the solvent from the MeOH solution under reduced pressure, the extract (400 g) was partitioned into an AcOEt–H_2O (1 : 1) solution. Removal of the solvent *in vacuo* from the AcOEt-soluble portion gave the AcOEt extract (164.3 g). The AcOEt extract (150 g) was subjected to ordinary-phase silica gel column chromatography [2 kg, *n*-hexane–AcOEt (10 : 1—1 : 1), AcOEt, $CHCl_3$–MeOH–H_2O (10 : 3 : 1, lower layer)] to give six fractions [fr. 1 (7.5 g), fr. 2 (1.8 g), fr. 3 (40.3 g), fr. 4 (12.9 g), fr. 5 (8.3 g), fr. 6 (6.4 g)]. Fraction 1 (7.5 g) was purified by repeated ordinary-phase silica gel column chromatography [i) 380 g, *n*-hexane–AcOEt; ii) 310 g, *n*-hexane–CH_2Cl_2] and finally HPLC [YMC-pack SIL (YMC Co., Ltd.), *n*-hexane–AcOEt] separation to afford **8**[8] (173.3 mg), **9**[9] (731.0 mg), and **10**[10] (474.4 mg). Ordinary-phase silica gel column chromatography

(130 g, *n*-hexane–AcOEt) of fraction 2 (1.8 g) furnished **7**[7] (39.9 mg). Fraction 3 (40.3 g) was subjected successively to ordinary-phase (2 kg, *n*-hexane–AcOEt) and reversed-phase silica gel column chromatographies (450 g, MeOH–H_2O) to give **12** (105.0 mg) and five fractions (frs. 3-1—3-5). Fractions 3-1 and 3-2 were purified by HPLC [YMC-pack R&D (YMC Co., Ltd.), MeOH–H_2O (70:30)] separation to give **1** (13.5 mg) and **2** (159.8 mg), respectively. HPLC [YMC-pack R&D (YMC Co., Ltd.), CH_3CN–H_2O (75:25)] separation of fr. 3-3 furnished **3** (31.1 mg), **4** (9.3 mg), and **5** (6.8 mg). Fraction 3-4 was subjected to preparative TLC [benzene–AcOEt (2:1)] to afforded **11** (22.2 mg). Fraction 3-5 was separated successively by ordinary-phase (benzene–AcOEt) and reversed-phase (MeOH–H_2O) silica gel column chromatography to give **13** (146.6 mg). Fraction 4 (12.9 g) was purified by ordinary-phase (690 g, *n*-hexane–AcOEt) and reversed-phase silica gel column chromatographies (75 g, MeOH–H_2O) to afford **14** (2.8 mg), **16** (39.1 mg) and **17** (45.9 mg). By ordinary-phase silica gel column chromatography (427 g, benzene–acetone) of fr. 5 (8.3 g) followed by reversed-phase silica gel column chromatography (168 g, MeOH–H_2O), **6** (15.4 mg) and **15** (18.3 mg) were isolated. Two known compounds (**13**, **14**) were identified by comparison of TLC behavior and IR, ^{1}H-NMR, and ^{13}C-NMR spectra with those of authentic samples and other known compounds (**6—12**, **15—17**) were identified by comparison of their physical data ($[\alpha]_D$, ^{1}H-NMR, and ^{13}C-NMR) with reported values.[6-11]

Moxartenone (**1**): A white powder, $[\alpha]_D^{28}$ +51.6° (c=0.4, MeOH). High-resolution positive-mode FAB-MS: Calcd for $C_{17}H_{25}O_3$ $(M+H)^+$: 277.1844; Found: 277.1827. CD (c=0.002, MeOH): $\Delta\varepsilon$=+1.56 (312) (positive maximum), $\Delta\varepsilon$=0 (282), $\Delta\varepsilon$=−4.03 (249) (negative maximum). UV λ_{max}^{MeOH} nm (log ε): 252 (2.34). IR (KBr): 2829, 1736, 1676, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz), δ: 0.90 (3H, s, 12-H_3), 0.98 (3H, s, 14-H_3), 1.02 (3H, s, 13-H_3), 1.81 (2H, m, 8-H_2), 1.83 (2H, m, 9-H_2), 2.04 (3H, d, J=1.7 Hz, 15-H_3), 2.08 (3H, s, OAc), 2.19 (1H, s, 1-H), 2.69 (1H, d, J=6.7 Hz, 2-H), 2.81 (1H, dd, J=1.5, 6.7 Hz, 6-H), 4.73 (1H, dd, J=1.3, 9.9 Hz, 10-H), 5.77 (1H, dq, J=1.5, 1.7 Hz, 4-H). ^{13}C-NMR: as given in Table 1. Positive-mode FAB-MS m/z: 277 $(M+H)^+$.

Moxartenolide (**2**): A white powder, $[\alpha]_D^{28}$ +119.9° (c=1.1, $CHCl_3$). High-resolution positive-mode FAB-MS : Calcd for $C_{20}H_{23}O_5$ $(M+H)^+$: 343.1546; Found: 343.1545. UV λ_{max}^{MeOH} nm (log ε): 256 (4.14), 212 (4.20). IR (KBr): 1775, 1719, 1692, 1644, 1619 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 270 MHz), δ: 1.93 (3H, dq, J=1.3, 1.7 Hz, 5′-H_3), 2.04 (3H, dq, J=7.3, 1.7 Hz, 4′-H_3), 2.34 (3H, br s, 15-H_3), 2.48 (3H, s, 14-H_3), 2.52 (1H, dd, J=2.3, 13.5 Hz, 9β-H), 2.76 (1H, dd, J=10.7, 13.5 Hz, 9α-H), 3.34 (1H, dddd, J=3.0, 3.3, 10.2, 10.4 Hz, 7-H), 3.74 (1H, dd, J=10.2, 10.2 Hz, 6-H), 5.03 (1H, ddd, J=2.3, 10.4, 10.7 Hz, 8-H), 5.64, 6.23 (2H, both d, J=2.6 Hz, 13-H_2), 6.21 (1H, d, J=1.3 Hz, 3-H), 6.24 (1H, dq-like, 3′-H). ^{13}C-NMR: as given in Table 1. Positive-mode FAB-MS m/z: 343 $(M+H)^+$.

13-Oxo-9(Z),11(E)-octadecadienoic Acid (**3**): A white powder. High-resolution EI-MS: Calcd for $C_{18}H_{30}O_3$ $(M)^+$: 294.2195; Found: 294.2213. UV λ_{max}^{MeOH} nm (log ε): 278 (4.15). IR (KBr): 2930, 1709 cm^{-1}. ^{1}H-NMR (C_6D_6, 500 MHz) δ: 0.83 (3H, t, J=7.3 Hz, 18-H_3), 1.03-1.24 (12H, m, 4, 5, 6, 7, 16, 17-H_2), 1.47 (2H, tt, J=7.3, 7.3 Hz, 3-H_2), 1.61 (2H, tt, J=7.3, 7.4 Hz, 15-H_2), 2.04 (2H, ddt, J=1.5, 7.6, 7.6 Hz, 8-H_2), 2.10 (2H, t, J=7.3 Hz, 14-H_2), 2.25 (2H, t, J=7.3 Hz, 2-H_2), 5.64 (1H, dt-like, 9-H), 5.99 (1H, dd, J=10.7, 11.6 Hz, 10-H), 6.05 (1H, d, J=15.3 Hz, 12-H), 7.72 (1H, dd, J=11.6, 15.3 Hz, 11-H). ^{13}C-NMR: as given in Table 2. EI-MS m/z (%): 294 (M^+, 43), 238 (24), 223 (46), 151 (80), 95 (65), 81 (100), 67 (68), 53 (38), 39 (19).

13-Oxo-9(E),11(E)-octadecadienoic Acid (**4**): A white powder. High-resolution EI-MS: Calcd for $C_{18}H_{30}O_3$ $(M)^+$: 294.2195; Found : 294.2177. UV λ_{max}^{MeOH} nm (log ε): 276 (4.21). IR (KBr): 2930, 1709 cm^{-1}. ^{1}H-NMR (C_6D_6, 500 MHz) δ: 0.85 (3H, t, J=7.0 Hz, 18-H_3), 1.07—1.36 (12H, m, 4, 5, 6, 7, 16, 17-H_2), 1.49 (2H, tt, J=7.5, 7.6 Hz, 3-H_2), 1.64 (2H, tt, J=7.3, 7.3 Hz, 15-H_2), 1.88 (2H, dt, J=7.3, 7.3 Hz, 8-H_2), 2.10 (2H, t, J=7.5 Hz, 2-H_2), 2.29 (2H, t, J=7.3 Hz, 14-H_2), 5.79 (1H, dt, J=7.3, 15.4 Hz, 9-H), 5.97 (1H, dd, J=10.8, 15.4 Hz, 10-H), 6.05 (1H, d, J=15.5 Hz, 12-H), 7.19 (1H, dd, J=10.8, 15.5 Hz, 11-H). ^{13}C-NMR: as given in Table 2. EI-MS m/z (%): 294 (M^+, 47), 238 (30), 223 (46), 151 (100), 95 (66), 81 (78), 67 (41).

9-Oxo-10(E),12(E)-octadecadienoic Acid (**5**): A white powder. High-resolution EI-MS: Calcd for $C_{18}H_{30}O_3$ $(M)^+$: 294.2195; Found: 294.2181. UV λ_{max}^{MeOH} nm (log ε): 276 (4.11). IR (KBr): 2930, 1719 cm^{-1}. ^{1}H-NMR (C_6D_6, 500 MHz) δ: 0.86 (3H, t, J=7.3 Hz, 18-H_3), 1.06—1.40 (12H, m, 4, 5, 6, 15, 16, 17-H_2), 1.46 (2H, tt, J=7.5, 7.5 Hz, 3-H_2), 1.58 (2H, tt, J=7.3, 7.3 Hz, 7-H_2), 1.89 (2H, dt, J=7.3, 7.3 Hz, 14-H_2), 2.07 (2H, t, J=7.5 Hz, 2-H_2), 2.27 (2H, t, J=7.5 Hz, 8-H_2), 5.79 (1H, dt, J=7.3, 15.3 Hz, 13-H), 5.97 (1H, dd, J=10.9, 15.3 Hz, 12-H), 6.04 (1H, d, J=15.5 Hz, 10-H), 7.19 (1H, dd, J=10.9, 15.5 Hz, 11-H). ^{13}C-NMR: as given in Table 2. EI-MS m/z (%): 294 (M^+, 30), 223 (88), 171 (8), 166 (98), 151 (100), 95 (85), 81 (88).

Diazomethane Methylation of 3 A solution of **3** (0.8 mg) in MeOH (0.5 ml) was treated with ethereal diazomethane (*ca.* 0.7 ml) until the yellow color persisted. The solution was stirred for 10 min, then the solvent was removed under reduced pressure to furnish **3a** (0.9 mg), which was identified by comparison of the physical data with reported values.[20]

Bioassay Methods for the Inhibitory Effect on the Concentration Induced by KCl, NE, and S 5-HT in Isolated Thoracic Aorta Male Wistar rats weighing about 250—450 g were exsanguinated by severing both carotid arteries. The thoracic aorta was removed, cut into helical strips (2—3×15 mm) and mounted in a Magnus bath containing 15 ml of Krebs–Henseleit solution. To investigate the isometric contractile responses, helical strips of aorta were subjected to an initial load of about 1 g. Contractions were recorded isometrically *via* a force displacement transducer (Type 45196A, NEC San-ei Instruments Ltd., Tokyo, Japan). Composition of Krebs–Henseleit solution: NaCl 118.0, KCl 4.7, KH_2PO_4 1.2, $MgSO_4$ 1.2, $CaCl_2$ 2.5, $NaHCO_3$ 25.0 and glucose 10.0 (mM).

1) Effects on High-K^+-Induced Contraction: After equilibration of the preparation for 1 h, 50 mM KCl was added to the bath. The tissues were washed 3 times and re-equilibrated after the contraction had reached the maximum level. This procedure was repeated, and a second contraction was obtained. Tissues were exposed for 10 min to each test compound and then 50 mM KCl was applied to obtain a third contraction. In order to minimize variability between tissues, the contraction ratio of the third response to the second response was used. The mean contraction ratio in the control was taken to be 100%.

2) Effects on the NE-Induced Contraction: *dl*-NE hydrochloride at 3×10^{-7} M was applied instead of 50 mM KCl described above.

3) Effects on the Serotonin-Induced Contraction: Serotonin-creatinine sulfate (5-HT) at 10^{-5} M was used instead of 50 mM KCl described above.

Statistical analysis was performed by Dunnett's method.[21] Results are expressed as the mean±S.E.

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