Structures of New Dinor-eremophilane Derivatives and New Eremophilenolides from the Rhizomes of *Petasites japonicus* MAXIM.[1)]

Yasunori YAOITA and Masao KIKUCHI*

Tohoku College of Pharmacy, 4–4–1 Komatsushima, Aoba-ku, Sendai 981, Japan.
Received March 18, 1996; accepted May 18, 1996

Four new dinor-eremophilane derivatives with a rare skeleton, eremopetasinorone A (1), eremopetasinorone B (2), eremopetasinorol (3) and epoxyeremopetasinorol (4), and three new eremophilenolides, eremosulphoxinolide A (5), eremosulphoxinolide B (6) and 3β,8α-dihydroxy-6β-methoxyeremophil-7(11)-en-12,8β-olide (7), have been isolated from the dried rhizomes of *Petasites japonicus* MAXIM. (Compositae) with 2β-hydroxyeremophil-7(11)-en-12,8α-olide (8), a known synthetic compound. The structures of these compounds were elucidated on the basis of spectral data and chemical transformation.

Key words *Petasites japonicus*; Compositae; dinor-eremophilane derivative; eremophilenolide

The rhizomes of *Petasites japonicus* MAXIM. (fuki in Japanese, Compositae) have been used for the treatment of tonsillitis, contusions and poisonous-snake bite in China.[2)] In previous papers, we reported the structural elucidation of *seco*-eremophilane derivatives,[1)] eremophilenolides,[3)] nor-eremophilane derivative,[4)] triterpenoids,[5)] anthraquinones[5)] and phenolic compounds[6)] from the plant. Here, we report the isolation and structural elucidation of four new dinor-eremophilane derivatives with a rare skeleton, eremopetasinorone A (**1**), eremopetasinorone B (**2**), eremopetasinorol (**3**) and epoxyeremopetasinorol (**4**), and three new eremophilenolides, eremosulphoxinolide A (**5**), eremosulphoxinolide B (**6**) and 3β,8α-dihydroxy-6β-methoxyeremophil-7(11)-en-12,8β-olide (**7**), as well as 2β-hydroxyeremophil-7(11)-en-12,8α-olide (**8**), a known synthetic compound. Extraction and isolation were carried out as described in the Experimental section.

Compound **1** was isolated as a colorless oil, $[\alpha]_D$ −118.0°. The molecular formula was determined to be $C_{13}H_{18}O_2$ by high-resolution (HR)-MS. The IR spectrum suggested the presence of a six-membered ring ketone (1712 cm^{-1}) and an α,β-unsaturated ketone (1666, 1625 cm^{-1}). The UV spectrum also suggested the presence of an α,β-unsaturated ketone (λ_{max}: 235 nm). The ^1H- (Table 1) and ^{13}C-NMR (Table 2) spectra showed signals due to a tertiary methyl group [δ_H 0.67 (s, H-13), δ_C 22.1 (C-13)], a secondary methyl group [δ_H 0.96 (d, J=6.6 Hz, H-12), δ_C 8.8 (C-12)], a methine [δ_H 1.52 (m, H-9), δ_C 44.5 (C-9)], an acetyl group [δ_H 1.97 (s, H-11), δ_C 26.2 (C-11), 195.4 (C-10)], a secondary methyl-bearing methine [δ_H 2.09 (q, J=6.6 Hz, H-4), δ_C 47.7 (C-4)], a methylene [δ_H 2.28 (ddd, J=16.9, 5.5, 1.8 Hz, H-8α), 2.80 (ddd, J=16.9, 8.8, 1.8 Hz, H-8β), δ_C 37.2 (C-8)], a trisubstituted double bond [δ_H 5.99 (dd, J=1.8, 1.8 Hz, H-6), δ_C 147.7 (C-6), 142.8 (C-7)] and a carbonyl group [δ_C 210.4 (C-3)]. These spectral data and molecular formula suggested that compound **1** is a dinor-sesquiterpene derivative. By ^1H–^1H shift correlation spectroscopy (^1H–^1H COSY) and the ^1H-detected heteronuclear multiple bond correlation (HMBC) spectra, the planar structure of **1** was deduced to be as shown in Fig. 1. The relative stereostructure was determined by the nuclear Overhauser effect (NOE) difference spectra, in which

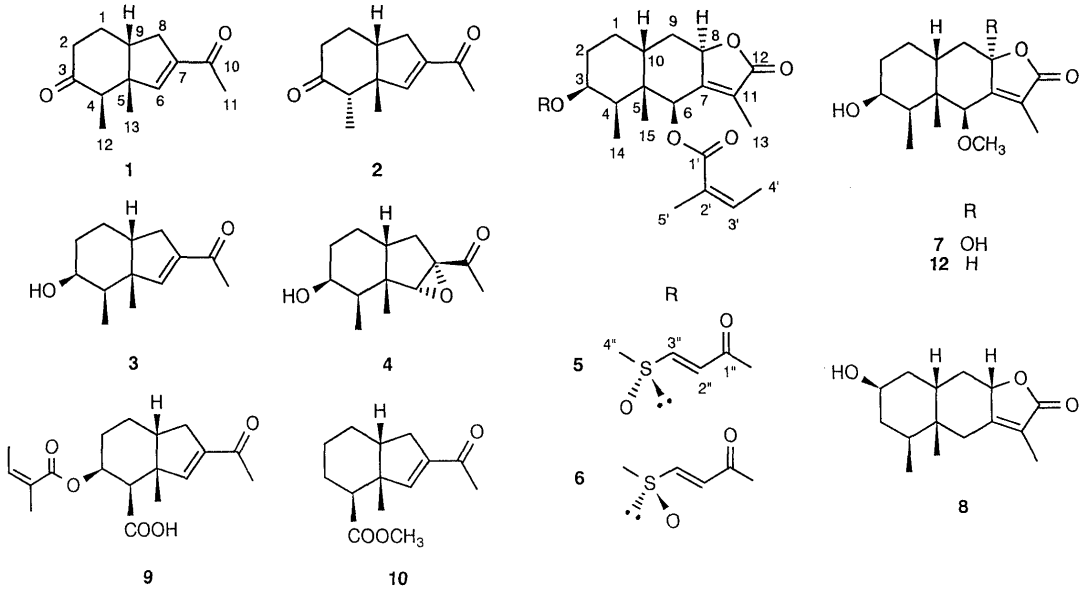

Chart 1

* To whom correspondence should be addressed.

Table 1. ^{1}H-NMR Chemical Shifts of Compounds **1**—**8** (400 MHz)

Proton	**1**[a]	**2**[a]	**3**[a]	**4**[a]	**5**[b]	**6**[b]	**7**[c]	**8**[b]
1							α 2.18 m β 1.75 m	
2							α 1.68 m β 1.52 m	3.83 m
3			3.35 ddd (2.9, 2.9, 2.9)	3.15 br s[d,g]	5.146 ddd (11.7, 4.8, 4.8)	5.146 ddd (11.4, 4.4, 4.4)	4.02 br d (11.7)	α 1.76 dd (11.4, 4.8) β 1.27 ddd (12.8, 12.8, 11.4)
4	2.09 q (6.6)	2.03 q (6.6)	1.11 qd (7.0, 2.9)	0.85 qd (7.0, 2.6)	2.239 m[e]	2.234 m[f]	2.36 m	
6	5.99 dd (1.8, 1.8)	5.96 dd (1.8, 1.8)	6.26 d (2.2)	3.15 br s[d,g]	6.187 br s	6.185 br s	4.47 br s	α 2.90 d (14.3) β 1.92 br d (14.3)
8	α 2.28 ddd (16.9, 5.5, 1.8) β 2.80 ddd (16.9, 8.8, 1.8)	α 2.29 ddd (17.6, 4.4, 1.8) β 2.79 ddd (17.6, 9.5, 1.8)	α 2.37 ddd (16.1, 9.5, 2.2) β 2.60 dd (16.1, 6.6)	α 1.76 dd (13.9, 7.6) β 2.30 dd (13.9, 11.4)	4.923 m	4.913 m		4.60 m
9	1.52 m	1.87 m	1.87 m	1.65 m	α 2.239 m[e] β 1.611 m	α 2.234 m[f] β 1.610 m		β 2.23 ddd (12.8, 6.6, 3.7)
11	1.97 s	1.85 s	2.01 s	1.83 s				
12	0.96 d (6.6)	1.02 d (6.6)	0.87 d (7.0)	0.77 d (7.0)				
13	0.67 s	0.84 s	1.18 s	1.26 s	1.802 dd (1.8, 1.8)	1.802 dd (1.8, 1.8)	1.95 br s	1.81 dd (1.5, 1.5)
14					0.986 d (7.3)	0.992 d (5.9)	0.93 d (7.3)	0.86 d (7.0)
15					0.984 s	0.984 s	0.81 s	1.07 s
3′					6.260 qq (7.3, 1.5)	6.260 qq (7.3, 1.5)		
4′					2.067 dq (7.3, 1.5)	2.067 dq (7.3, 1.5)		
5′					1.998 dq (1.5, 1.5)	1.998 dq (1.5, 1.5)		
2″					6.659 d (15.0)	6.651 d (15.0)		
3″					7.600 d (15.0)	7.591 d (15.0)		
4″					2.703 s	2.711 s		
OCH_3							3.47 s	

Coupling constants (J in Hz) are given in parentheses. *a*) Measurement in C_6D_6. *b*) Measurement in $CDCl_3$. *c*) Measurement in $CDCl_3$ with small amounts of CD_3OD. *d*—*f*) Signals were overlapped. *g*) H-3 and H-6 appeared at δ 3.76 (br s) and δ 3.45 (s), respectively, in $CDCl_3$.

Table 2. ^{13}C-NMR Chemical Shifts of Compounds **1**—**8** (100 MHz)

Carbon	**1**[a]	**2**[a]	**3**[a]	**4**[a]	**5**[b]	**6**[b]	**7**[c]	**8**[b]
1	26.6	25.3	19.7	16.8	26.72	26.70	27.1	35.8
2	37.7	35.0	28.9	28.7	25.13	25.14	28.7	66.0
3	210.4	210.7	70.6	70.7	72.57	72.56	68.7	40.0
4	47.7	49.6	39.8	35.9	35.64	35.64	38.1	29.5
5	53.4	54.3	50.1	42.8	45.46	45.45	47.3	39.2
6	147.7	144.9	153.5	70.1	70.78	70.77	79.6	35.6
7	142.8	144.4	143.6	68.4	158.04	158.01	159.4	160.4
8	37.2	36.6	34.0	28.3	77.22	77.20	104.5	80.0
9	44.5	42.0	45.1	38.3	34.24	34.22	38.9	35.9
10	195.4	195.0	195.9	204.7	35.12	35.11	35.1	41.0
11	26.2	26.1	26.0	24.5	122.46	122.45	123.8	121.0
12	8.8	9.4	13.3	13.7	174.00	173.97	172.4	174.7
13	22.1	27.2	21.4	18.0	8.20	8.19	8.2	8.3
14					8.36	8.36	7.6	15.9
15					20.32	20.31	18.9	21.7
1′					166.54	166.50		
2′					126.56	126.54		
3′					141.31	141.31		
4′					15.99	15.98		
5′					20.61	20.60		
1″					162.75	162.67		
2″					126.15	126.22		
3″					150.90	150.77		
4″					39.74	39.70		
OCH_3							59.5	

a) Measurement in C_6D_6. *b*) Measurement in $CDCl_3$. *c*) Measurement in $CDCl_3$ with small amounts of CD_3OD.

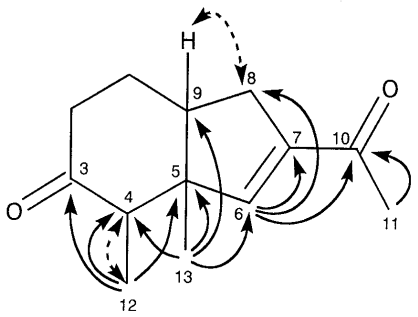

Fig. 1. ^{1}H–^{1}H COSY (←——→) and HMBC (——→) Connections for Compound **1**

NOEs were detected between H-13 and H-6; H-13 and H-9; H-13 and H-12; and H-12 and H-6 (Fig. 2). The absolute stereostructure was determined by a circular dichroism (CD) spectrum. The CD spectrum of **1** showed a negative Cotton effect by a C-3 carbonyl group at 290.5 nm. The application of the octant rule[7] to **1** suggests that the expected sign of the Cotton effect should be negative (Fig. 3). On the basis of the above data, the structure of eremopetasinorone A (**1**) was determined to be as shown in Chart 1.

Compound **2** was isolated as a colorless oil, $[\alpha]_D$ +8.8°. The molecular formula was determined to be $C_{13}H_{18}O_2$ by HR-MS. The IR spectrum suggested the presence of a six-membered ring ketone (1710 cm^{-1}) and an α,β-

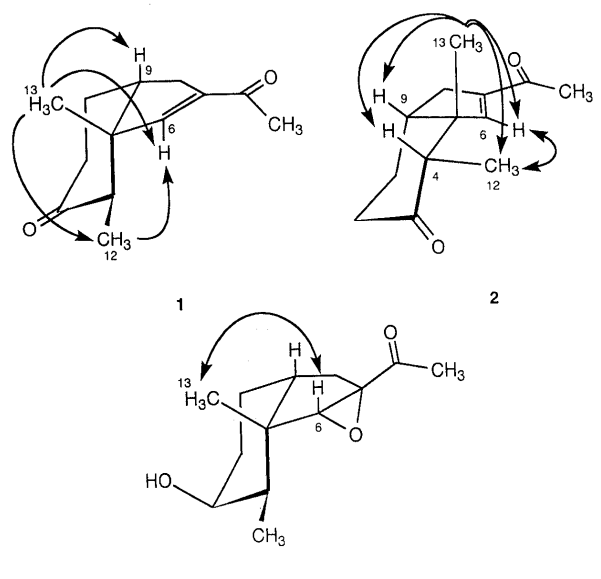

Fig. 2. NOEs Detected for Compounds **1**, **2** and **4**

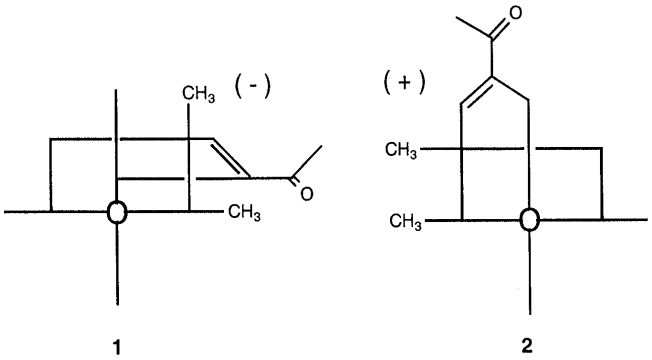

Fig. 3. Back Octant for Compounds **1** and **2**

unsaturated ketone (1666, 1626 cm^{-1}). The ^1H- and ^{13}C-NMR spectra of **2** were similar to those of **1**. A ^1H–^1H COSY correlation was observed between H-8 and H-9. HMBC correlations were observed between H-6 and C-5, C-8 and C-9; H-11 and C-10; H-12 and C-3, C-4 and C-5; and H-13 and C-4, C-5, C-6 and C-9. These data suggested that the planar structure of **2** was identical with that of **1**. The relative stereostructure was determined by NOE difference spectra, in which NOEs were detected between H-6 and H-12; H-12 and H-6; H-13 and H-4; H-13 and H-6; H-13 and H-9; and H-13 and H-12 (Fig. 2). The absolute stereostructure was determined by CD spectrum, in which a positive Cotton effect by the C-3 carbonyl group was shown at 292.5 nm. Application of the octant rule[7] to **2** suggested that the expected sign of the Cotton effect should be positive (Fig. 3). From the above data, the structure of eremopetasinorone B (**2**) was determined to be as shown in Chart 1.

Compound **3** was isolated as a colorless oil, $[\alpha]_D$ −28.4°. The molecular formula was determined to be $C_{13}H_{20}O_2$ by HR-MS. The IR spectrum suggested the presence of a hydroxyl group (3616, 3485 cm^{-1}) and an α,β-unsaturated ketone (1658, 1606 cm^{-1}). The ^1H- and ^{13}C-NMR spectra of **3** were similar to those of **1**, except that the C-3 carbonyl group in **1** was replaced by a hydroxyl group [δ_H 3.35 (ddd, J=2.9, 2.9, 2.9 Hz, H-3), δ_C 70.6 (C-3)] in **3**. The position of this hydroxyl group was determined to be C-3 by ^1H–^1H COSY spectrum. The ^1H–^1H COSY spectrum gave a cross peak between H-8 and H-9. The relative stereostructure was determined by the NOE difference spectra, in which NOEs were detected between H-13 and H-6; H-13 and H-9; H-13 and H-12; H-12 and H-3; and H-12 and H-6. The coupling patterns and constants for H-3 [δ_H 3.35, ddd, J=2.9, 2.9, 2.9 Hz] suggested that the hydroxyl group at C-3 is a β-configuration. Treatment of **3** with pyridinium chlorochromate (PCC)–Al_2O_3 in *n*-hexane gave a ketone which was completely identical with **1** in all respects. From the above data, the absolute structure of eremopetasinorol was determined to be **3**.

Compound **4** was isolated as a colorless oil, $[\alpha]_D$ −10.5°. The molecular formula was determined to be $C_{13}H_{20}O_3$ by HR-MS. The IR spectrum suggested the presence of a hydroxyl group (3630, 3503 cm^{-1}), a carbonyl group (1703 cm^{-1}) and an epoxide (917, 839 cm^{-1}). The ^1H- and ^{13}C-NMR spectra of **4** were closely related to those of **3** except that the 6,7-double bond of **3** was replaced by a 6,7-epoxy functionality. The HMBC spectrum of **4** supported this structure. The relative configuration of the epoxide was determined to be α from the NOE correlation spectroscopy (NOESY) spectrum, in which a cross-peak was seen between H-6β and H-13 (Fig. 2). Treatment of **3** with hydrogen peroxide and NaOH in MeOH gave an epoxide which was completely identical with **4** in all respects. From the above data, the absolute structure of epoxyeremopetasinorol was determined to be **4**. Compounds **1**—**4** are the first dinor-eremophilane derivatives isolated from the genus *Petasites* plants. Naturally occurring dinor-eremophilane derivatives of this class are rare. 2-Acetyl-5β-angeloyloxy-3a,β-methyl-3a,4,5,6,7,7a-hexahydroinden-4β-carboxylic acid (**9**)[8a] and 2-acetyl-3a,β-methyl-3a,4,5,6,7,7a-hexahydroinden-4β-carboxylic acid methyl ester (**10**)[8b] are the only other known members of this class. Compounds **2** and **4** are the first dinor-eremophilane derivatives of this class, with a 4α-methyl group and C_6–C_7 epoxide isolated from natural sources, respectively. A possible mechanism for the formation of **1**—**4** is shown in Fig. 4.[8a] Compounds **1**—**4** are presumably formed from eremopetasidione (**11**), which was isolated from the rhizomes of *Petasites japonicus*.[4]

Compound **5** was isolated as pale yellow oil, $[\alpha]_D$ −13.2°. The molecular formula was determined to be $C_{24}H_{32}O_7S$ by HR-MS. The IR spectrum suggested the presence of an α,β-unsaturated-γ-lactone (1751 cm^{-1}), an α,β-unsaturated ester (1719, 1648, 1623 cm^{-1}) and a sulphoxide (1041 cm^{-1}). The ^1H- and ^{13}C-NMR spectra of **5**, obtained with the aid of ^1H–^1H COSY, ^1H-detected heteronuclear multiple quantum coherence (HMQC) and HMBC spectra, were virtually identical to those of 3β,6β-diangeloyloxyeremophil-7(11)-en-12,8β-olide[3a] except for the presence of an (*E*)-3-methylsulphinylacryloyloxyl group [δ_H 6.659 (d, J=15.0 Hz, H-2″), 7.600 (d, J=15.0 Hz, H-3″), 2.703 (s, H-4″), δ_C 162.75 (C-1″), 126.15 (C-2″), 150.90 (C-3″), 39.74 (C-4″)][9] in place of a C-3β angeloyloxyl group. The stereochemistry of **5** was determined on the basis of a procedure outlined by Naya *et al.*,[10] that is, homoallylic coupling (J=1.0—1.8 Hz) between the olefinic methyl group (H-13) and H-6α found in eremophil-7(11)-en-12,8β-olide derivatives, which had

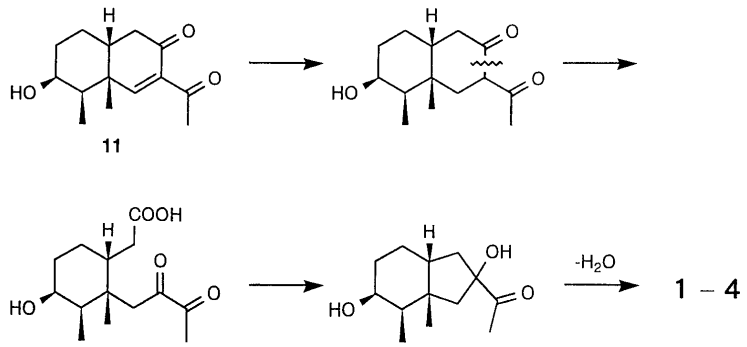

Fig. 4. Possible Formation of Compounds **1**—**4**

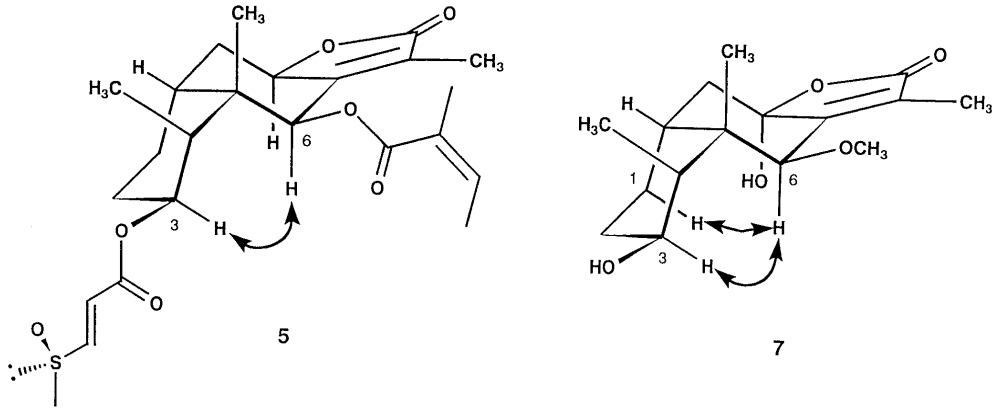

Fig. 5. NOEs Detected for Compounds **5** and **7**

a non-steroidal conformation, while this long-range coupling was absent in eremophil-7(11)-en-12,8α-olide derivatives, which had a steroidal conformation. The sign of the specific rotation of eremophil-7(11)-en-12,8β-olide derivatives was negative, and that of eremophil-7(11)-en-12,8α-olide derivatives was positive. The ^{1}H-NMR spectrum of **5** showed homoallylic coupling ($J=1.8$ Hz) of the olefinic methyl group (H-13) with H-6α. In the NOESY spectrum, NOE was seen between H-3α and H-6α. The sign of the specific rotation of **5** was negative. These data indicated that **5** is an eremophil-7(11)-en-12,8β-olide derivative which has a non-steroidal conformation (Fig. 5). The configuration of the acyl groups at C-3 and C-6 were shown to be β, respectively, by the NOESY spectrum, giving a cross-peak between H-3α and H-6α (Fig. 5). Compound **5** has UV absorption at 270 nm (shoulder), which corresponds to an (*E*)-3-methylsulphinylacryloyloxyl moiety. The CD spectrum of **5** showed a positive Cotton effect at 273.5 nm ($\Delta\varepsilon=+1.29$), indicating that the absolute configuration of sulphoxide group should be *R*.[11] Based on this evidence, the structure of eremosulphoxinolide A (**5**) was determined to be as shown in Chart 1.

Compound **6** was isolated as pale yellow oil, $[\alpha]_D$ −77.6°. The molecular formula was determined to be $C_{24}H_{32}O_7S$ by HR-MS. The IR spectrum suggested the presence of an α,β-unsaturated-γ-lactone (1751 cm^{-1}), an α,β-unsaturated ester (1720, 1644, 1623 cm^{-1}) and a sulphoxide (1041 cm^{-1}). The ^{1}H- and ^{13}C-NMR spectra of **6**, obtained with the aid of ^{1}H–^{1}H, ^{13}C–^{1}H COSY and HMBC spectra, resembled the data of **5**, except for the chemical shift differences of the C-3β(*E*)-3-methylsulphinylacryloyloxyl moiety. The CD spectrum of **6** showed a negative Cotton effect at 279.5 nm ($\Delta\varepsilon=-2.09$), indicating that the absolute configuration of a sulphoxide group should be *S*. From the above data, the strucuture of eremosulphoxinolide B (**6**) was determined to be the epimer of **5** at the sulphur atom. Compounds **5** and **6** are the first eremophilenolide derivatives with an (*E*)-3-methylsulphinylacryloyloxyl group isolated from natural sources, respectively.

Compound **7** was isolated as an amorphous powder, $[\alpha]_D$ −164.8°. The molecular formula was determined to be $C_{16}H_{24}O_5$ by HR-MS. The IR spectrum suggested the presence of a hydroxyl group (3529, 3233 cm^{-1}) and an α,β-unsaturated-γ-lactone (1727, 1683 cm^{-1}). The ^{1}H- and ^{13}C-NMR spectra of **7** were virtually identical to those of 3β-hydroxy-6β-methoxyeremophil-7(11)-en-12,8β-olide (**12**),[3b] except that **7** contained one more hydroxyl group. The ^{13}C-NMR spectrum of **7** showed a signal due to a hemi-ketal carbon [δ_C 104.5 (C-8)], suggesting that the hydroxyl group was attached to C-8.[3] The NOESY spectrum gave cross-peaks between H-1α and H-6α, and between H-3α and H-6α. A Dreiding model showed that an 8α-hydroxyl group was the only possible structure which could account for this NOE (Fig. 5). On the basis of this evidence, the structure of **7** was determined to be 3β,8α-dihydroxy-6β-methoxyeremophil-7(11)-en-12,8β-olide.

Compound **8** was isolated as a colorless oil, $[\alpha]_D$ +106.6°. The molecular formula was determined to be $C_{15}H_{22}O_3$ by HR-MS. The IR spectrum suggested the presence of a hydroxyl group (3606, 3475 cm^{-1}) and an α,β-unsaturated-γ-lactone (1746, 1688 cm^{-1}). The ^{1}H- and ^{13}C-NMR spectra of **8**, obtained with the aid of ^{1}H–^{1}H, ^{13}C–^{1}H COSY and HMBC spectra, were in accord with those of 2β-hydroxyeremophil-7(11)-en-12,8α-olide.[12]

Thus, compound **8** was as shown in Chart 1. Compound **8** was isolated from a natural source for the first time, although **8** has already been synthesized by Kitahara *et al.*[12]

Experimental

General Procedures Optical rotations were determined using a JASCO DIP-360 digital polarimeter. CD spectra were performed on a JASCO J-720 spectropolarimeter. IR spectra were recorded with a Perkin-Elmer FT-IR 1725X infrared spectrophotometer and UV spectra with a Beckman DU-64 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded with a JEOL JNM-GSX 400 (400 and 100 MHz, respectively) spectrometer. Chemical shifts were given on a δ (ppm) scale with tetramethylsilane as an internal standard (s, singlet; br s, broad singlet; d, doublet; br d, broad doublet; dd, double doublet; ddd, double double doublet; dq, double quartet; q, quartet; qd, quartet doublet; qq, quartet quartet; m, multiplet). The EI-MS and HR-MS were recorded on a JEOL JMS-DX 303 mass spectrometer. Column chromatography was carried out on Kieselgel 60 (Merck; 230—400 mesh). Preparative HPLC was carried out on a Tosoh HPLC system (pump, CCPD; detector, UV-8011 or RI-8010) using a TSK gel ODS-120T column (Tosoh).

Plant Material Dried and chopped rhizomes of *Petasites japonicus* were purchased from Tochimoto Tenkaido Co., Ltd. in 1990.

Extraction and Isolation The dried rhizomes of *Petasites japonicus* (3.0 kg) were extracted three times with MeOH at room temperature for 2 weeks. The MeOH extract was concentrated under reduced pressure and the residue was suspended in a small excess of water. This suspension was extracted with $CHCl_3$, Et_2O, AcOEt and *n*-BuOH, successively. The $CHCl_3$-soluble fraction was concentrated under reduced pressure to afford a residue (112.5 g). This residue (60.0 g) was chromatographed on a silica-gel column using benzene–AcOEt (9 : 1, 8 : 2, 7 : 3) and $CHCl_3$–MeOH (8 : 2), to afford 4 fractions (frs. 1—4). Fraction 4 was rechromatographed on a silica-gel column using benzene–AcOEt (6 : 4, 5 : 5, 4 : 6, 3 : 7) and $CHCl_3$–MeOH (9 : 1, 8 : 2), to afford 4 fractions (frs. 1′—4′). Fraction 2′ was rechromatographed on a silica-gel column using *n*-hexane–acetone (5 : 4, 5 : 5, 4 : 5, 3 : 6) and acetone, to afford 5 fractions (frs. 1″—5″). Fraction 2″ was rechromatographed on a silica gel column using benzene–AcOEt (3 : 2) to afford 7 fractions (frs. 1‴—7‴). Fraction 2‴ was purified by preparative HPLC (Column, TSK gel ODS-120T, 7.8 mm i.d. × 30 cm; mobile phase, MeOH–H_2O (2 : 3); column temperature, 40 °C; flow rate, 1.0 ml/min; UV detector, 220 nm) to give **1** (3.2 mg), **3** (10.9 mg) and a mixture of **2** and **4**. The mixture of **2** and **4** was purified by preparative HPLC (Column, TSK gel ODS-120T, 7.8 mm i.d. × 30 cm; mobile phase, MeOH–H_2O (4 : 7); column temperature, 40 °C; flow late, 1.0 ml/min; refractive index (RI) detector) to give **2** (1.1 mg) and **4** (1.0 mg). Fraction 4″ was separated by preparative HPLC (Column, TSK gel ODS-120T, 21.5 mm i.d. × 30 cm; mobile phase, MeOH–H_2O (1 : 1); flow rate, 4.0 ml/min; UV detector, 220 nm) to give a mixture of **7** and **8**. The mixture of **7** and **8** was separated by preparative HPLC (Column, TSK gel ODS-120T, 21.5 mm i.d. × 30 cm; moble phase, MeOH–H_2O (1 : 2); column temperature, 40 °C; flow rate, 4.0 ml/min; UV detector, 220 nm) to give pure **7** (10.6 mg) and crude **8**. The crude **8** was purified by preparative HPLC (Column, TSK gel ODS-120T, 7.8 mm i.d. × 30 cm; mobile phase, MeOH–H_2O (1 : 3); column temperature, 40 °C; flow rate, 2.5 ml/min; UV detector, 220 nm) to give pure **8** (2.0 mg). Fraction 5″ was purified by preparative HPLC (Column, TSK gel ODS-120T, 21.5 mm i.d. × 30 cm; mobile phase, MeOH–H_2O (1 : 1); column temperature, 40 °C; flow rate, 4.5 ml/min; UV detector, 220 nm) to give **5** (3.8 mg) and **6** (4.5 mg).

Eremopetasinorone A (1) Colorless oil. $[\alpha]_D^{18}$ −118.0° (c=0.3, MeOH). CD ($c=1.54\times10^{-4}$, MeOH) $\Delta\varepsilon$ (nm): −6.08 (290.5), +7.61 (242.5), −2.2 (208). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1712, 1666, 1625. UV λ_{max}^{MeOH} nm (log ε): 235 (3.8). HR-MS m/z: 206.1305 (M$^+$, Calcd for $C_{13}H_{18}O_2$; 206.1307). ^{1}H-NMR: see Table 1. ^{13}C-NMR: see Table 2.

Eremopetasinorone B (2) Colorless oil. $[\alpha]_D^{18}$ +8.8° (c=0.1, MeOH). CD ($c=1.38\times10^{-4}$, MeOH) $\Delta\varepsilon$ (nm): +0.55 (292.5), +0.35 (230), −0.62 (213). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710, 1666, 1626. UV λ_{max}^{MeOH} nm (log ε): 228 (3.8). HR-MS m/z: 206.1320 (M$^+$, Calcd for $C_{13}H_{18}O_2$; 206.1307). ^{1}H-NMR: see Table 1. ^{13}C-NMR: see Table 2.

Eremopetasinorol (3) Colorless oil. $[\alpha]_D^{24}$ −28.4° (c=1.1, MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3616, 3485, 1658, 1606. UV λ_{max}^{MeOH} nm (log ε): 241 (3.9). HR-MS m/z: 208.1456 (M$^+$, Calcd for $C_{13}H_{20}O_2$; 208.1463). ^{1}H-NMR: see Table 1. ^{13}C-NMR: see Table 2.

Epoxyeremopetasinorol (4) Colorless oil. $[\alpha]_D^{20}$ −10.5° (c=0.1, MeOH). IR $\nu_{max}^{CHCl_3}$cm^{-1}: 3630, 3507, 1703, 917, 839. HR-MS m/z: 224.1435 (M$^+$, Calcd for $C_{13}H_{20}O_3$; 224.1413). ^{1}H-NMR: see Table 1. ^{13}C-NMR: see Table 2.

Eremosulphoxinolide A (5) Pale yellow oil. $[\alpha]_D^{24}$ −13.2° (c=0.4, $CHCl_3$). CD ($c=3.77\times10^{-5}$, MeOH) $\Delta\varepsilon$ (nm): +1.29 (273.5), −4.77 (216.0). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1751, 1719, 1648, 1623, 1041. UV λ_{max}^{MeOH} nm (log ε): 216 (4.3), 270 sh (3.6). HR-MS m/z: 464.1833 (M$^+$, Calcd for $C_{24}H_{32}O_7S$; 464.1869). ^{1}H-NMR: see Table 1. ^{13}C-NMR: see Table 2.

Eremosulphoxinolide B (6) Pale yellow oil. $[\alpha]_D^{24}$ −77.6° (c=0.5, $CHCl_3$). CD ($c=4.48\times10^{-5}$, MeOH) $\Delta\varepsilon$ (nm): −2.09 (279.5), −7.76 (218.5). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1751, 1720, 1644, 1623, 1041. UV λ_{max}^{MeOH} nm (log ε): 215 (4.3), 270 sh (3.6). HR-MS m/z: 464.1896 (M$^+$, calcd for $C_{24}H_{32}O_7S$; 464.1869). ^{1}H-NMR: see Table 1. ^{13}C-NMR: see Table 2.

3β,8α-Dihydroxy-6β-methoxyeremophil-7(11)-en-12,8β-olide (7) Amorphous powder. $[\alpha]_D^{19}$ −164.8° (c=1.1, MeOH). IR ν_{max}^{KBr} cm^{-1}: 3529, 3233, 1727, 1683. UV λ_{max}^{MeOH} nm (log ε): 219 (4.0). HR-MS m/z: 296.1649 (M$^+$, Calcd for $C_{16}H_{24}O_5$; 296.1624). ^{1}H-NMR: see Table 1. ^{13}C-NMR: see Table 2.

2β-Hydroxyeremophil-7(11)-en-12,8α-olide (8) Colorless oil. $[\alpha]_D^{25}$ +106.6° (c=0.2, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3606, 3475, 1746, 1688. UV λ_{max}^{MeOH} nm (log ε): 220 (4.0). HR-MS m/z: 250.1560 (M$^+$, Calcd for $C_{15}H_{22}O_3$; 250.1569). ^{1}H-NMR: see Table 1. ^{13}C-NMR: see Table 2.

Oxidation of Eremopetasinorol (3) To a solution of compound **3** (5 mg) in *n*-hexane (10 ml), PCC–Al_2O_3 (120 mg) was added and the mixture was stirred for 2 h at room temperature. The reaction mixture was filtered and the filtrates were evaporated. The product was purified by preparative HPLC (Column, TSK gel ODS-120T, 7.8 mm i.d. × 30 cm; mobile phase, MeOH–H_2O (1 : 1); column temperature, 40 °C; flow rate, 1.0 ml/min; UV detector, 241 nm) to give **1** (2.5 mg).

Epoxidation of Eremopetasinorol (3) To a solution of compound **3** (1.9 mg) in MeOH (1 ml), 10% NaOH (25 μl) and 30% hydrogen peroxide (25 μl) were added. The reaction mixture was allowed to stand at 0 °C for 96 h, water (2 ml) was added, and the mixture was extracted with $CHCl_3$. After work-up, the product was purified by preparative HPLC (Column, TSK gel ODS-120T, 7.8 mm i.d. × 30 cm; moble phase, MeOH–H_2O (1 : 1); column temperature, 40 °C; flow rate, 1.0 ml/min; RI detector) to give **4** (0.8 mg).

Acknowledgements The authors are grateful to Dr. S. Suzuki, Dr. K. Hisamichi and Mr. S. Sato (Tohoku College of Pharmacy) for their measurements of mass spectra and NMR spectra.

References

1) Part IX in a series of studies on the constituents of the rhizomes of *Petasites japonicus* Maxim., Part VIII: Yaoita Y., Kikuchi M., *Phytochemistry*, **42**, 751—755 (1996).
2) Shanghai Scientific Technological Publishers and Shougakukan (eds.), "Dictionary of Chinese Materia Medica," Vol. 4, Shougakukan, Tokyo, 1985, p. 2386.
3) *a*) Yaoita Y., Nagata K., Suzuki N., Kikuchi M., *Chem. Pharm. Bull.*, **40**, 3277—3279 (1992); *b*) Yaoita Y., Kikuchi M., *ibid.*, **42**, 1944—1947 (1994); *c*) *Idem*, *ibid.*, **43**, 1738—1743 (1995); *d*) *Idem*, *Nat. Med.*, **50**, 49—53 (1996).
4) Yaoita Y., Kikuchi M., *Phytochemistry*, **37**, 1765—1766 (1994).
5) Yaoita Y., Kikuchi M., *Tohoku Yakka Daigaku Kenkyu Nempo*, **40**, 111—114 (1993).
6) Yaoita Y., Kikuchi M., *Phytochemistry*, **37**, 1773—1774 (1994).
7) Moffitt W., Woodward R. B., Moscowitz A., Klyne W., Djerassi C., *J. Am. Chem. Soc.*, **83**, 4013—4018 (1961).
8) *a*) Bohlmann F., Zdero C., Grenz M., *Chem. Ber.*, **107**, 3928—3945 (1974); *b*) Zhao Y., Jia Z., Peng H., *J. Nat. Prod.*, **58**, 1358—1364 (1995).
9) Wu T., Chang F., Wu P., *Phytochemistry*, **39**, 1453—1457 (1995).
10) *a*) Naya K., Kanazawa R., Sawada M., *Bull. Chem. Soc. Jpn.*, **48**, 3220—3225 (1975); *b*) Naya K., Nogi N., Makiyama Y., Takashina H., Imagawa T., *ibid.*, **50**, 3002—3006 (1977); *c*) Naya K., Shimizu M., Nishio H., Takada M., Oka S., Hirota K., *ibid.*, **64**, 1071—1080 (1991).
11) Ikegami F., Sekine T., Duangteraprecha S., Matsushita N., Matsuda N., Ruangungsi N., Murakoshi I., *Phytochemistry*, **28**, 881—882 (1989).
12) Kitahara Y., Maeda S., Ueno M., Funamizu M., Kata T., Novotny L., Herout V., Sorm F., *Chem. Lett.*, **1977**, 1031—1034.