Four New Sesquiterpenes from *Petasites formosanus*

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Four new eremophilane-type sesquiterpenes, petasones A (**1**) and B (**2**), *S*-petasitin (**3**), and petasinol (**4**), were isolated from the aerial parts of *Petasites formosanus*. Their structures were elucidated by spectroscopic and chemical methods as 3α-[(*Z*)-3-methylsulfinylacryloxy]-eremophila-7(11),9-dien-8-one; 3α-[(*E*)-3-methylsulfinylacryloxy]eremophila-7(11),9-dien-8-one; 3α-[(*Z*)-3-methylthioacryloxy]-11-hydroxyeremophila-6,9-dien-8-one; and 3α-[(*E*)-3-methylsulfinylacryloxy]-8*β*-hydroxyeremophila-9,11-diene, respectively.

Many sesquiterpenes with the eremophilane skeleton have been isolated from the *Petasites* (Compositae) genus[1−5] and have shown potential antitumor properties[6] or have inhibited peptido-leukotriene biosynthesis.[7,8] *Petasites formosanus* Kitamura is a perennial herb and the only indigenous *Petasites* species in Taiwan.[9] The aerial parts of this plant have been used as a folk drug for treating hypertension and cancer.[10] Chemical investigation on this plant however, has not been previously reported. In this paper, we describe the isolation and structural elucidation of four new eremophilane sesquiterpenes.

Results and Discussion

The EtOAc-soluble fraction from an EtOH extract of the aerial parts of *P. formosanus* was subjected to column chromatography on activated charcoal to obtain fractions that were rich in sesquiterpenes. Further separation of these fractions by MPLC and HPLC on Si gel column led to the isolation of four new eremophilanes, petasone A (**1**), petasone B (**2**), (*S*)-petasitin (**3**), and petasinol (**4**), together with three known compounds, (*S*)-petasin (**5**),[2] (*S*)-isopetasin (**6**),[10] and petasitin (**7**).[11]

Petasone A (**1**) was obtained as a colorless oil, which was shown to have a molecular formula $C_{19}H_{26}O_4S$ by HRMS and ^{13}C NMR spectrum. The IR spectrum showed the presence of α,*β*-unsaturated carbonyl (1660 cm^{-1}), sulfoxide (1050 cm^{-1}), and α,*β*-unsaturated ester (1710 and 1210 cm^{-1}) groups. The ^1H NMR (Table 1) spectrum contained signals due to a (*Z*)-3-methylsulfinylacryloxy moiety: *δ* 2.79 (3H, s, −SOC*H*$_3$), 6.24 and 6.96 (1H each, d, $J = 10.2$ Hz).[5] Without the side ester chain, the parent compound of petasone A is a sesquiterpene. A tertiary methyl group at *δ* 1.04 (s), a secondary methyl group at *δ* 0.93 (d, $J = 6.9$ Hz), and an olefinic proton at *δ* 5.73 (d, $J = 1.5$ Hz), in addition to UV absorption at *λ* 243 nm, showed that the skeleton of petasone A (**1**) is a derivative of 9-eremophilen-8-one.[2] The isopropylidene group linked to C-7 of the eremophilane skeleton was shown by the signals at *δ* 1.82 (3H, s) and 2.04 (3H, d, $J = 1.5$ Hz) and UV absorption band at 276 nm. The characteristic signals of H-6 protons for eremophila-7(11), 9-dien-8-one were present at *δ* 2.91 (1H, d, $J = 13.5$, H$_\beta$-6) and 2.13 (1H, d, $J = 13.5$, 1.5 Hz, H$_\alpha$-6). The latter proton has homoallylic coupling with *H*$_3$-12 (*δ* 2.04, *cis* to carbonyl group). A triplet of doublets at *δ* 4.83 ($J = 11.1$, 4.8 Hz) was assigned to H-3 (*β*-axial orientation) next to the ester group.[11] When comparing ^1H and ^{13}C NMR data between petasone A (**1**) and (*S*)-isopetasin (**6**),[11] we found the only difference to be in the sulfinylmethyl group [*δ* 2.79 (3H, s)] instead of the methylthio group [*δ* 2.41 (3H, s)]. Chemical correlation between **1** and **6** was done as follows. Oxidation of **6** with *m*-chloroperbenzoic acid (*m*-CPBA) in CH_2Cl_2 at room temperature yielded four products: **1** and **8** as a mixture, plus **9** and **10**. Those structures were elucidated by their spectral data. Compound **8** was an epimer of **1** at the sulfur atom,[5] and the ester groups in **9** and **10** were (*E*)-3-methylsulfonylacrylate [υ_{max} 1300, 1150 cm^{-1}; *δ* 3.15 (3H, s, −SO$_2$C*H*$_3$), 6.87 and 7.37 (1H each, d, $J = 15.0$ Hz)] and (*Z*)-3-methylsulfonylacrylate [υ_{max} 1305, 1155 cm^{-1}; *δ* 3.14 (3H, s, −SO$_2$C*H*$_3$), 6.57 and 6.67 (1H each, d, $J = 11.7$ Hz)], respectively. From the above result, the structure of petasone A (**1**) can be assigned as 3α-[(*Z*)-3-methylsulfinylacryloxy]eremophila-7(11), 9-dien-8-one.

Petasone B (**2**) was isolated as a colorless oil, which had the same molecular formular ($C_{19}H_{26}O_4S$) as **1** by HRMS and ^{13}C NMR. Comparison of the NMR data (Table 1) of **1** and **2** indicated that both of them have the same skeleton with the exception of a *trans* ester side chain [δ_H 6.67 and 7.62 (1H each, d, $J = 14.7$ Hz), δ_C 126.0 and 151.1][5] in **2** instead of a *cis* form in **1**.

(*S*)-Petasitin (**3**) was isolated as colorless needles, mp 143−144 °C. HRMS and ^{13}C NMR (Table 1) data of **3** suggested a molecular formula $C_{19}H_{26}O_4S$. The IR spectrum showed the presence of a α,*β*-unsaturated carbonyl (1660 cm^{-1}), an ester (1705 and 1210 cm^{-1}), and tertiary alcohol (3520 and 1160 cm^{-1}). ^1H and ^{13}C NMR (Table 1) showed it contains a secondary methyl group [δ_H 0.94 (d, $J = 6.6$ Hz)], three tertiary methyl groups (*δ* 1.08, 1.44, and 1.44), a hydroxyl group [*δ* 4.75 (1H, br s, disappeared after D_2O exchanged)], two olefinic protons [*δ* 6.07 (1H, d, $J = 1.5$ Hz) and 6.88 (1H,

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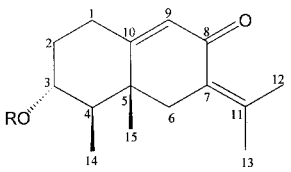
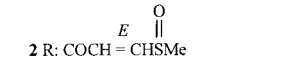
Table 1. ^{1}H and ^{13}C NMR Spectral Data of **1**−**4** (300 and 75 MHz, in $CDCl_3$)

	1		**2**		**3**		**4**	
position	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1	NR[a]	29.8	NR	29.9	NR	30.1	NR	29.4
2	NR	31.4	NR	31.4	NR	32.7	NR	33.6
3	4.83 td (11.1,4.8)[b]	75.7	4.92 td (11.1,4.5)	75.1	4.97 td (11.1,4.8)	72.7	4.91 td (11.0,4.8)	76.8
4	NR	45.9	NR	45.9	NR	44.5	NR	42.6
5		42.0		42.1		43.0		39.0
6	2.91 d (13.5)	41.0	2.91 d (13.5)	41.1	6.88 s	147.8	NR	37.2
	2.13 dq (13.5,1.5)		2.18 dq (13.5,1.5)					
7		126.9		126.9		141.3		47.2
8		191.3		191.5		187.6	4.06 d (9.6)	68.8
9	5.73 d (1.5)	126.8	5.77 d (1.2)	126.9	6.07 d (1.5)	125.2	5.43 d (1.2)	123.9
10		164.0		164.4		166.2		145.7[c]
11		143.8		143.7		71.8		144.6[c]
12	2.04 d (1.5)	22.6[c]	2.08 d (1.8)	22.6[c]	1.44 s	28.9[c]	4.72 (br s)	112.8
							4.87 (br s)	
13	1.80 s	22.1[c]	1.84 s	22.1[c]	1.44 s	29.0[c]	1.71 s	19.8
14	0.93 d (6.9)	10.7	0.98 d (6.6)	10.7	0.94 d (6.6)	11.7	0.84 d (6.6)	11.8
15	1.04 s	17.0	1.03 s	17.1	1.08 s	18.5	1.00 s	22.1
1′		163.9		163.4		166.1		163.4
2′	6.24 d (10.2)	124.2	6.67 d (14.7)	126.0	5.79 d (10.5)	112.7	6.64 d (14.7)	126.3
3′	6.96 d (10.2)	159.5	7.62 d (14.7)	151.1	7.07 d (10.5)	152.8	7.57 d (14.7)	150.7
S−Me					2.41 s	19.2		
O‖S–Me	2.79 s	40.6	2.71 s	39.7			2.69 s	39.7
OH					4.75 br s			

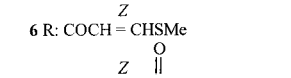
[a] NR: not resolved. [b] Figures in the parentheses are coupling constants in Hz. [c] Assignment may be interchanged.



1 R: COCH = CHSMe (*Z*, 1′ 2′ 3′)

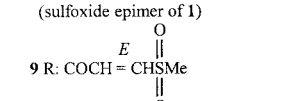


2 R: COCH = CHSMe (*E*)

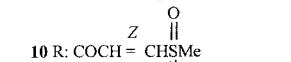


6 R: COCH = CHSMe (*Z*)

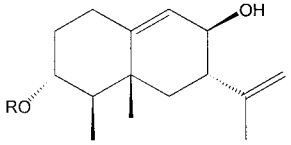
8 R: COCH = CHSMe (*Z*) (sulfoxide epimer of **1**)



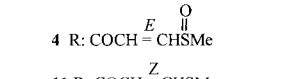
9 R: COCH = CHSMe (*E*)



10 R: COCH = CHSMe (*Z*)

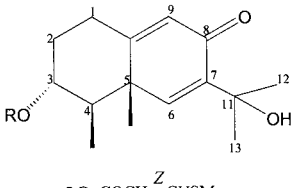


4 R: COCH = CHSMe (*E*)



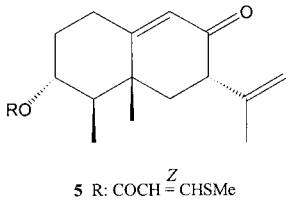
11 R: COCH = CHSMe (*Z*)

12 R: COCH = CHSMe (*Z*)



3 R: COCH = CHSMe (*Z*)

7 R: COCMe = CHMe (*Z*)



5 R: COCH = CHSMe (*Z*)

s)], and a (*Z*)-3-methylthioacrylate [δ_H 2.41 (3H, s), δ_C 19.2; δ_H 5.79 and 7.07 (each 1H, d, J = 10.5 Hz), δ_C 112.7 and 152.8] located at C-3 with α-equatorial orientation, and a methine proton with carbon bearing an ester group [δ_H 4.97 (1H, td, J = 11.1, 4.8 Hz)].

An HMBC experiment revealed the correlations as follows: H-12, 13 (δ 1.44) to C-11 (δ 71.8) and C-7 (δ 141.3); H-15 (δ 1.08) to C-6 (δ 147.8) and C-10 (δ 166.2); and H-6 (δ 6.88) to C-7 (δ 141.3) and C-8 (δ 187.6). This led to structure **3** with the same parent sesquiterpene as petasitin (**7**),[12] and the angeloyl ester moiety in **7** being substituted by (*Z*)-3-methylthioacrylate group in (*S*)-petasitin (**3**). Therefore, the structure of (*S*)-petasitin (**3**) was assigned as 3α-[(*Z*)-3-methylthioacryloxy]-11-hydroxyeremophila-6,9-dien-8-one.

Petasinol (**4**) was obtained as an amorphous solid. HRMS showed that **4** had the molecular formula $C_{19}H_{28}O_4S$. The IR spectrum indicated the presence of hydroxyl (3440 cm^{-1}) and an α,β-unsaturated carbonyl group (1710, 1625, 1220 cm^{-1}). Compound **4** had a (*E*)-3-methylsulfinylacryloxy side chain as in **2**: δ 2.69 (3H, s, −SOC*H*$_3$), 6.64, and 7.57 (1H each, d, J = 14.7 Hz). The ^{1}H NMR spectrum of **4** (Table 1) also revealed an isopropenyl group [δ 1.71 (3H, s), 4.72, and 4.87 (1H each, br s)], singlet and doublet methyl groups [δ 1.00 (3H, s) and 0.84 (3H, d, J = 6.6 Hz)], and a methine proton with triplet of doublets linked to ester [δ 4.91 (1H, td, J = 11.0, 4.8 Hz, H-3)]. An olefinic proton at higher field [δ 5.43 (1H, d, J = 1.2 Hz, allylic coupling with H-1 axial)] than the corresponding protons in **1**, **2**, and **3** showed that the C-9−C-10 olefin group was not conjugated. No ketone group was observed in its spectra, but a methine proton signal bearing a hydroxyl group was present at δ 4.06. This methine proton's coupling constant (J = 9.6 Hz) indicated that it was in quasi-axial orientation. The relatively lower field position of this proton at δ 4.06 showed that it was allylic. The structure of petasinol (**4**) was elucidated as 3α-[(*Z*)-3-methylsulfinylacryloxy]-8β-hydroxyeremophila-9,11-diene from HMBC correlations (Figure 1). The reduction of (*S*)-petasin (**5**) with $NaBH_4$ in MeOH yielded **11** [υ_{max} 3420, 1030 cm^{-1}; δ 4.05 (1H, d, J = 9.6 Hz, H-8)], which was subsequently oxidized with *m*-CPBA in CH_2Cl_2 at 0−5 °C and afforded compound **4** and a

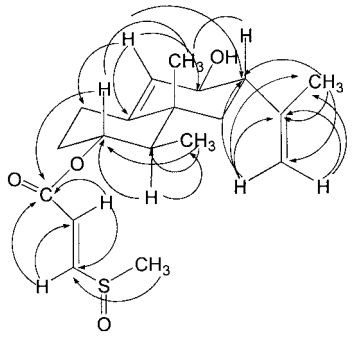


Figure 1. NOESY (curved line) and HMBC (curved arrow) correlations observed for **4**.

mixture of **12** and its epimer. The epimer of **4** was not observed from the oxidative products.

Experimental Section

General Experimental Procedures. Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were run on a Perkin−Elmer 781 spectrophotometer. UV spectra were taken on a Hitachi U-3200 spectrophotometer. NMR experiments were run on Bruker AC-300 and DMX-300 instruments with $CDCl_3$ as solvent. MS were recorded in EI mode (70 eV) on a Finnigan TSQ-46C MS spectrometer. HREIMS were recorded on a JEOL SX-102A. Optical rotations were obtained on a JASCO DIP-370 polarimeter. MPLC were run on a Buchi 688 chromatography pump (Kiesel gel 18−32 μm). Preparative HPLC was performed on a Hitachi L-6000 pump and used Lichrosorb Si 60 (7μm) 250 × 10 mm column with ERC-7525 RI detector.

Plant Material. The aerial parts of *P. formosanus* were collected from Ali mountain (endemic altitude at 1500−2500 m in northern and southern mountains) in May 1997. It was identified by comparison with a voucher specimen, which has been deposited at the Herbarium of the Department of Botany of National Taiwan University (no: TAI 197973, collected on March 21, 1985).

Extraction and Isolation. The dried aerial parts of *P. formosanus* (5 kg) were extracted with 95% EtOH (50 L × 3). The EtOH extract was evaporated *in vacuo* to yield a black residue (295 g), which was taken up in H_2O and partitioned successively with EtOAc and *n*-BuOH. The EtOAc fraction (146 g) showed cytotoxicity and was fractionated by chromatography on an activated charcoal column, eluted with a 10% EtOAc−hexane−EtOAc gradient. Fractions rich in sesquiterpenes (20−70% EtOAc−hexane) were further separated by MPLC and HPLC on Si gel columns, leading to the isolation of seven eremophilanes: petasone A (**1**) (41 mg), petasone B (**2**) (15 mg), (*S*)-petasitin (**3**) (86 mg), and petasinol (**4**) (12 mg), together with (*S*)-petasin (**5**) (3.4 g), (*S*)-isopetasin (**6**) (1.2 g), and petasitin (**7**) (25 mg).

Petasone A (1): colorless oil; $[\alpha]^{25}_D$ +40° (*c* 1.0, MeOH); UV (MeOH) λ_{max} (log ϵ) nm 243 (4.47), 276 (3.22); IR (KBr) ν_{max} 3040, 1710, 1660, 1635, 1210, 1150, 1050, 815 cm^{-1}; ^{1}H and ^{13}C NMR ($CDCl_3$, 300 and 75 MHz), see Table 1; EIMS *m/z* 350 $[M]^+$ (5), 334 (8), 216 (100), 201 (54), 161 (100), 54 (70); HREIMS *m/z* 350.1560, (calcd for $C_{19}H_{26}O_4S$, 350.1553).

Petasone B (2): colorless oil; $[\alpha]^{25}_D$ −28° (*c* 1.0, MeOH); UV (MeOH) λ_{max} (log ϵ) nm 241 (4.56), 276 (3.43); IR (KBr) ν_{max} 3040, 1725, 1710, 1660, 1625, 1220, 1145, 1060, 995, 890 cm^{-1}; ^{1}H and ^{13}C NMR ($CDCl_3$, 300 and 75 MHz), see Table 1; EIMS *m/z* 350 $[M]^+$ (12), 216 (72), 161 (100), 148 (32), 55 (32); HREIMS *m/z* 350.1562, (calcd for $C_{19}H_{26}O_4S$, 350.1553).

***S*-Petasitin (3):** colorless needles (from EtOH); mp 143−144 °C; $[\alpha]^{25}_D$ −15° (*c* 1.0, MeOH); UV (MeOH) λ_{max} (log ϵ) nm 240 (4.43); IR (KBr) ν_{max} 3520, 3020, 1705, 1660, 1620, 1575, 1210, 1160, 1010, 800 cm^{-1}; ^{1}H and ^{13}C NMR ($CDCl_3$, 300 and 75 MHz), see Table 1; EIMS *m/z* 350 $[M]^+$ (8), 335 (45), 214 (100), 199 (38), 160 (35); HREIMS *m/z* 350.1558 (calcd for $C_{19}H_{26}O_4S$, 350.1553).

Petasinol (4): colorless amorphous solid; $[\alpha]^{25}_D$ +25° (*c* 1.0, MeOH); UV (MeOH) λ_{max} (log ϵ) nm 261 (4.19); IR (KBr) ν_{max} 3440, 3020, 1710, 1650, 1625, 1220, 1150, 1050, 890 cm^{-1}; ^{1}H and ^{13}C NMR ($CDCl_3$, 300 and 75 MHz), see Table 1; EIMS *m/z* 352 $[M]^+$ (4), 335 (10), 278 (20), 216 (22), 200 (100), 185 (72), 150 (96), 145 (82); HREIMS *m/z* 352.1705 (calcd for $C_{19}H_{28}O_4S$, 352.1709).

Oxidation of (*S*)-isopetasin (6) with *m*-CPBA. (*S*)-Isopetasin (**6**) (50 mg) and *m*-CPBA (46 mg) were dissolved in CH_2Cl_2 (2 mL), and the mixture was stirred at room temperature for 40 min. The mixture was diluted with CH_2Cl_2 (5 mL) and washed with aqueous $NaHSO_3$, then brine. After evaporation *in vacuo*, the mixture was purified on Si gel by HPLC (33% EtOAc−hexane), and yielded a mixture of **1** (2 mg) and **8** (9 mg) [colorless oil; υ_{max} 3020, 1705, 1665, 1145 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.98 (3H, d, J = 6.6 Hz), 1.01 (3H, s), 1.82 (3H, s), 2.06 (3H, d, J = 1.5 Hz), 2.15 and 2.89 (1H each, d, J = 13.8 Hz), 2.70 (3H, s), 4.97 (1H, td, J = 11.3, 4.7 Hz), 5.75 (1H, s), 6.24 and 6.98 (1H each, d, J = 10.2 Hz)]; **9** (3 mg)[colorless oil; υ_{max} 3020, 1715, 1665, 1630, 1300, 1150 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.94 (3H, d, J = 6.9 Hz), 1.02 (3H, s), 1.84 (3H, s), 2.08 (3H, d, J = 1.5 Hz), 2.17 and 2.91 (1H each, d, J = 13.8 Hz), 3.15 (3H, s), 4.95 (1H, td, J = 11.3, 4.7 Hz), 5.79 (1H, s), 6.87 and 7.37 (1H each, d, J = 15.0 Hz)]; and **10** (11 mg) [colorless oil; υ_{max} 3030, 1720, 1665, 1630, 1305, 1155 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.97 (3H, d, J = 6.6 Hz), 1.01 (3H, s), 1.82 (3H, s), 2.06 (3H, d, J = 1.5 Hz), 2.16 and 2.90 (1H each, d, J = 13.5 Hz), 3.14 (3H, s), 4.96 (1H, td, J = 11.3, 4.7 Hz), 5.75 (1H, s), 6.57 and 6.67 (1H each, d, J = 11.7 Hz)].

Reduction of (*S*)-Petasin (1) with $NaBH_4$. Excess $NaBH_4$ was added in small portion to a solution of (*S*)-petasin (68 mg) in MeOH (2 mL), and the mixture was stirred for 2 h in ice-bath, then poured into H_2O (10 mL). The aqueous solution was extracted with EtOAc (20 mL × 3) and purified on Si gel column chromatography to yield **11** (41 mg) [colorless oil; υ_{max} 3420, 3020, 1710, 1630, 1580, 1210, 1030, 890 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84 (3H, d, J = 6.9 Hz), 1.03 (3H, s), 1.70 (3H, s), 2.36 (3H, s), 4.05 (1H, d, J = 9.6 Hz), 4.85 and 4.91 (1H each, br s), 4.89 (1H, td, J = 11.0, 4.6 Hz), 5.42 (1H, d, J = 1.3 Hz), 5.78 and 6.71 (1H each, d, J = 10.9 Hz).

Oxidation of 11 by *m*-CPBA. Compound **11** (41 mg) was oxidized with *m*-CPBA (29.7 mg) in 3 mL of CH_2Cl_2 at 0−5 °C for 30 min and yielded three products, **4** (3 mg) and **12** (mixture of two epimers) (14.9 mg) [colorless oil; IR (KBr) ν_{max} 3460, 3020, 1710, 1630, 1210, 1150, 1050, 898 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.83 (3H, d, J = 6.6 Hz), 1.02 (3H, s), 1.71 (3H, s), 2.69 (3H, s), 4.06 (1H, d, J = 9.8 Hz), 4.86 and 4.90 (1H each, br s),

4.86 (1H, td, J = 11.3, 4.7 Hz), 5.39 (1H, s), 6.22 and 6.98 (1H each, d, J = 10.2 Hz)]; other epimer δ 0.84 (3H, d, J = 6.6 Hz), 1.02 (3H, s), 1.71 (3H, s), 2.71 (3H, s), 4.06 (1H, d, J = 9.8 Hz), 4.86 and 4.90 (1H each, br s), 4.86 (1H, td, J = 11.3, 4.7 Hz), 5.39 (1H, s), 6.24 and 7.00 (1H each, d, J = 10.2 Hz).

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References and Notes

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