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SECO-EREMOPHILANE DERIVATIVES FROM RHIZOMES OF *PETASITES JAPONICUS**

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Key Word Index—*Petasites japonicus*; Compositae; rhizomes; *seco*-eremophilane derivatives; secoeremopetasitolide A; secoeremopetasitolide B.

Abstract—Two new *seco*-eremophilane derivatives, secoeremopetasitolides A and B, were isolated from the dried rhizomes of *Petasites japonicus*. The structures of the new compounds were determined by spectroscopic evidence.

INTRODUCTION

The rhizomes of *Petasites japonicus* MAXIM have been used for the treatment of tonsillitis, contusion and poisonous-snake bite in China [1]. In previous papers, we have reported structural elucidation of eremophilenolides [2–5], nor-sesquiterpenoid [6], phenolic compounds [7], triterpenoids and anthraquinones [8] from the dried rhizomes of *P. japonicus*. In continuation of our investigation, we have isolated two new *seco*-eremophilane derivatives, named secoeremopetasitolide A (**1**) and secoeremopetasitolide B (**2**), from a methanolic extract of the dried rhizomes.

RESULTS AND DISCUSSION

Compound **1** was isolated as needles, mp 168–169°, $[\alpha]_D$ −34.7°. The molecular formula $C_{19}H_{26}O_7$ was revealed by HR mass spectrometry. The IR spectrum suggested the presence of a hydroxyl group (3495 cm^{-1}), an α,β-unsaturated γ-lactone (1764 cm^{-1}), a six-membered ring ketone (1703 cm^{-1}) and an α,β-unsaturated ester (1703 and 1645 cm^{-1}). The ^1H and ^{13}C NMR spectra (Table 1), with the aid of ^1H–^1H COSY and HMQC spectra, showed signals due to a secondary methyl group [δ_H 0.95 (6H, *d*, J = 7.3 Hz, H-14), δ_C 10.0/10.2 (C-14)], a tertiary methyl group [δ_H 1.12 (6H, *s*, H-15), δ_C 16.2/16.4 (C-15)], an olefinic methyl group [δ_H 2.11 (6H, *s*, H-13), δ_C 12.9/13.0 (C-13)], a hydroxyl-bearing methine [δ_H 4.56 (2H, *m*, H-3), δ_C 67.1/67.4 (C-3)], an oxygenated methine [δ_H 5.68/5.85 (each 1H, *s*, H-12), δ_C 98.1/98.4 (C-12)], an angeloyloxyl group [δ_H 1.96 (6H, *s*, H-5′), 2.03 (6H, *dq*, J = 7.3 and 1.5 Hz, H-4′), 6.22 (2H, *m*, H-3′), δ_C 16.0 (C-4′), 20.6 (C-5′), 125.8/126.1 (C-2′), 141.8/141.9 (C-3′) 165.7 (C-1′)], an angeloyloxyl-bearing methine [δ_H 6.23 (2H, *s*, H-6), δ_C 69.5/70.1 (C-6)], an α,β-unsaturated-γ-lactone [δ_C 126.2/126.3 (C-7), 160.7/160.8 (C-11), 169.4 (C-8)] and a carbonyl carbon [δ_C 213.3 (C-10)]. These spectral data and the molecular formula suggested that the most likely structure of this compound was **1**. The structure was confirmed further by analysis of the CH long-range correlations from the HMBC spectrum (Fig. 1). The CI mass spectrum showed a $[M + H]^+$ ion at m/z 367 with losses of H_2O (m/z 349), angelic acid (m/z 267), angelic acid and H_2O (m/z 249). The stereostructure was determined by a NOESY spectrum and NOEs were observed between H-3 and H-6, H-14 and H-15 (Fig. 2). The NMR data showed that the material was a mixture of C-12 epimers (Table 1). Thus, secoeremopetasitolide A (**1**) was established as a *seco*-eremophilane-type nor-sesquiterpenoid as depicted in the formula.

Compound **2** was isolated as an oil, $[\alpha]_D$ −5.1°. The molecular formula was determined as $C_{21}H_{30}O_7$ by HR mass spectrometry. The IR spectrum of **2** suggested the presence of a hydroxyl group (3508 cm^{-1}), an α,β-unsaturated-γ-lactone (1766 cm^{-1}) and an α,β-unsaturated ester (1717 and 1645 cm^{-1}). The ^1H and ^{13}C NMR (Table 1) spectra, with the aid of ^1H–^1H and ^{13}C–^1H COSY spectra, were similar to those of **1** and showed signals due to a secondary methyl group [δ_H 1.12 (6H, *d*, J = 7.0 Hz, H-14), δ_C 15.9 (C-14)], a tertiary methyl group [δ_H 1.20 (6H, *s*, H-15), δ_C 16.6 (C-15)], an olefinic methyl group [δ_H 2.12 (6H, *s*, H-13), δ_C 13.1/13.2 (C-13)], a methoxyl group [δ_H 3.38 (6H, *s*), δ_C 54.6], two oxygenated methines [δ_H 3.53 (2H, *dd*, J = 2.6 and 2.6 Hz, H-3), 5.76/5.80 (each

*Part 8 in the series 'Studies on the Constituents of the Rhizomes of *Petasites japonicus* MAXIM.' For part 7 see ref. [5].

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Table 1. ^1H and ^{13}C NMR spectral data for compounds **1** and **2**

	1		**2**	
	^1H	^{13}C	^1H	^{13}C
1	2.52 (2H, *m*), 3.15 (2H, *m*)	36.5/36.8		13.9
2		28.6/28.8		27.3
3	4.56 (2H, *m*)	67.1/67.4	3.53 (2H, *dd*, 2.6, 2.6)	74.8
4	2.47 (2H, *m*)	40.6/40.8	1.58 (2H, *q*, 7.0)	39.1
5		57.1/57.5		42.9
6	6.23 (2H, *s*)	69.5/70.1	5.90 (2H, *br s*)	75†
7		126.2/126.3*		126.6‡
8		169.4		170†
9		—	4.74 (2H, *d*, 2.6)	99.5
10		213.3	1.48 (2H, *br s*)	36.9
11		160.7/160.8		160†
12	5.68 (1H, *s*), 5.85 (1H, *s*)	98.1/98.4	5.76 (1H, *s*), 5.80 (1H, *s*)	97†
13	2.11 (6H, *s*)	12.9/13.0	2.12 (6H, *s*)	13.1/13.2
14	0.95 (6H, *d*, 7.3)	10.0/10.2	1.12 (6H, *d*, 7.0)	15.9§
15	1.12 (6H, *s*)	16.2/16.4	1.20 (6H, *s*)	16.6
1′		165.7		167†
2′		125.8/126.1*		126.6‡
3′	6.22 (2H, *m*)	141.8/141.9	6.17 (2H, *qq*, 7.3, 1.5)	141.1
4′	2.03 (6H, *dq*, 7.3, 1.5)	16.0	2.02 (6H, *dq*, 7.3, 1.5)	15.9§
5′	1.96 (6H, *s*)	20.6	1.99 (6H, *dq*, 1.5, 1.5)	20.7
OCH_3			3.38 (6H, *s*)	54.6

Coupling constants (J in Hz) are given in parentheses.
*Assignments may be reversed.
†These carbons were detected by HMBC and the chemical shift values are approximate.
‡,§Signals were overlapped.

1H, *s*, H-12), δ_C 74.8 (C-3), 97 (C-12)], an acetal group [δ_H 4.74 (2H, *d*, $J = 2.6$ Hz, H-9), δ_C 99.5 (C-9)], an angeloyloxyl group [δ_H 1.99 (6H, *dq*, $J = 1.5$ and 1.5 Hz, H-5′), 2.02 (6H, *dq*, $J = 7.3$ and 1.5 Hz, H-4′), 6.17 (2H, *qq*, $J = 7.3$ and 1.5 Hz, H-3′), δ_C 15.9 (C-4′), 20.7 (C-5′), 126.6 (C-2′), 141.1 (C-3′), 167 (C-1′)], an angeloyloxy-bearing methine [δ_H 5.90 (2H, *br s*, H-6), δ_C 75 (C-6)] and an α,β-unsaturated-γ-lactone [δ_C 126.6 (C-7), 160 (C-11), 170 (C-8)]. These spectral data and the molecular formula suggested that the most likely structure was **2** and this was further confirmed by the HMBC spectrum (Fig. 1). The CI

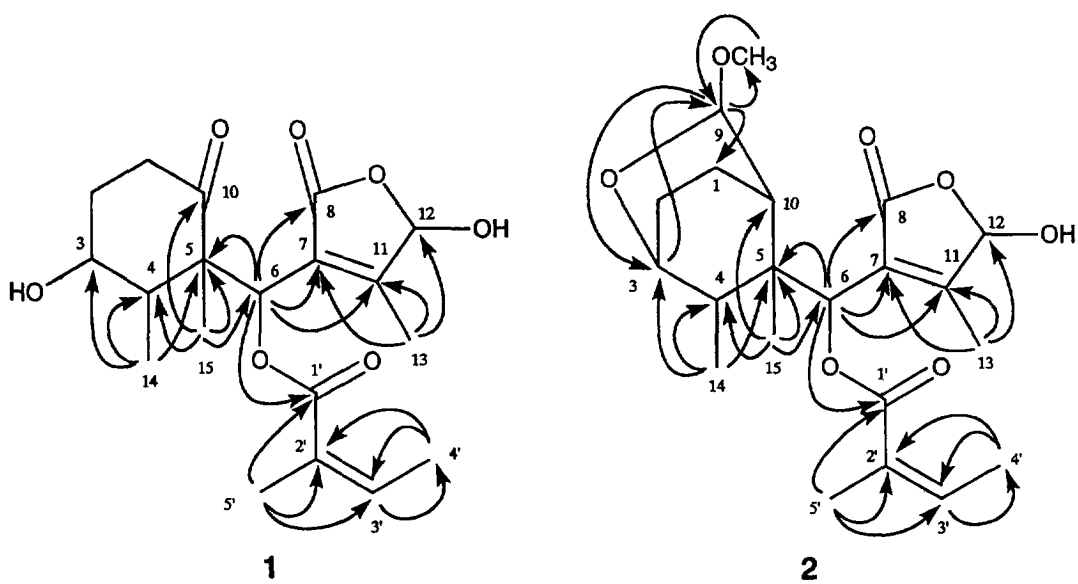


Fig. 1. Long-range correlations detected by HMBC of **1** and **2**.

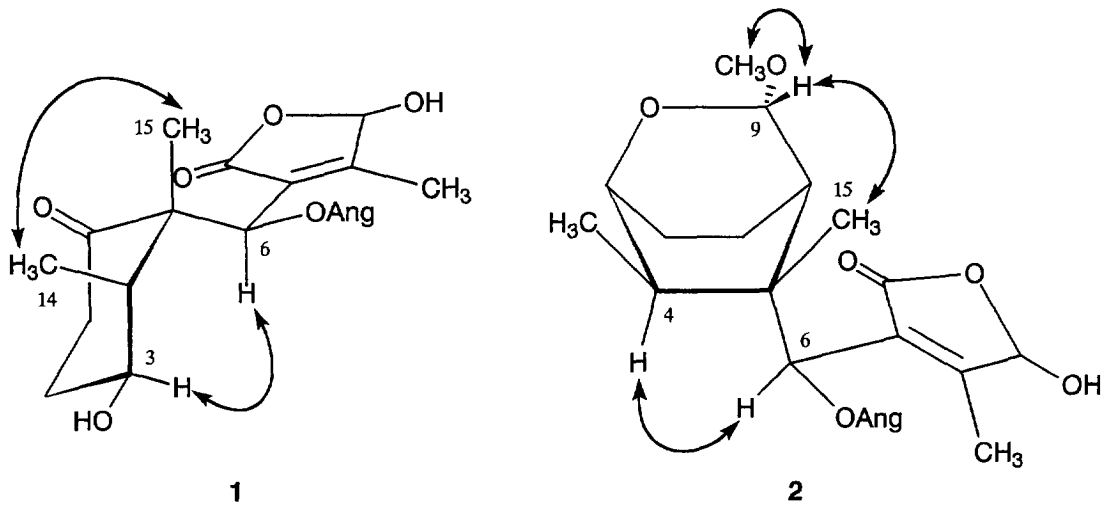


Fig. 2. NOEs detected for **1** and **2**.

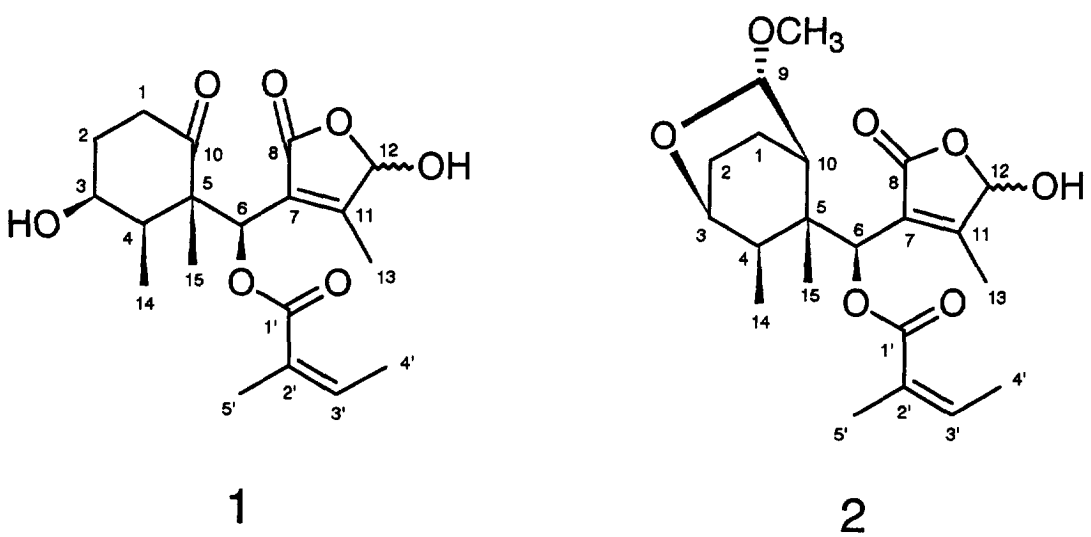
mass spectrum of **2** showed a $[M + H]^+$ ion at *m/z* 395 with losses of H_2O (*m/z* 377), CH_3OH (*m/z* 363), angelic acid (*m/z* 295), angelic acid and CH_3OCHO (*m/z* 235). The stereostructure was determined by the NOESY spectrum, in which NOEs were observed between H-4 and H-6, H-9 and H-15, and H-9 and the methoxyl group. The material was an epimeric mixture at C-12, as was clearly indicated by the NMR spectral data (Table 1). Thus, **2** was established as a *seco*-eremophilane-type sesquiterpenoid as depicted in the formula. This is the first example of a *seco*-eremophilane derivative having a six-membered acetal ring formed between C-3 and C-9. A possible mechanism for the formation of **1** and **2** is shown in Scheme 1. Compounds **1** and **2** are presumably formed via the endoperoxide, the product of a reaction of the corresponding furanoeremophilane such as **3** and singlet oxygen [9]. Compounds **1** and **2** are the first *seco*-eremophilane derivatives isolated from the genus *Petasites*.

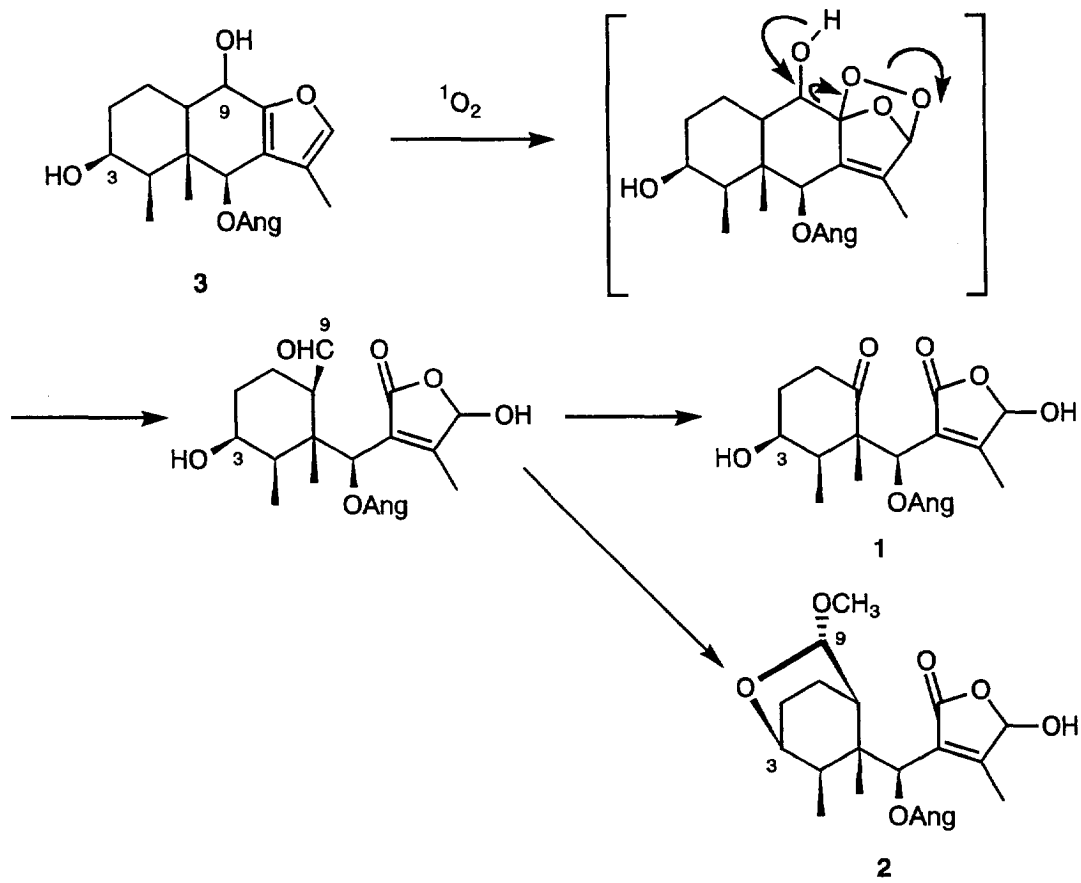
EXPERIMENTAL

General. Mps: uncorr. ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively (in $CDCl_3$ soln, TMS as int. standard); CC: Kieselgel 60 (230–400 mesh, Merck); HPLC: pump, CCPD; detector, UV-8011 (Tosoh).

Plant material. The dried and chopped rhizomes of *P. japonicus* were purchased from Tochimoto Tenkaido Co. (Osaka, Japan) in 1990.

Extraction and isolation. The dried and chopped rhizomes of *P. japonicus* (3.0 kg) were extracted with MeOH at room temp. for 2 weeks. The MeOH extract was concd under red. pres. and the residue was suspended in a small excess of H_2O. This residue was





Scheme 1. Possible formation of **1** and **2**.

extracted, successively, with $CHCl_3$, Et_2O, EtOAc and *n*-BuOH. The $CHCl_3$-soluble fr. was concd under red. pres. to afford a residue (112.5 g). This residue (60.0 g) was subjected to CC on silica gel using C_6H_6–EtOAc (9:1, 4:1, 7:3) and $CHCl_3$–MeOH (4:1), and the eluate was sepd into 4 frs (1–4). Fr. 4 was rechromatographed on a silica gel column using C_6H_6–EtOAc (3:2, 1:1, 2:3, 3:7) and $CHCl_3$–MeOH (9:1, 4:1), and the eludate was separated into 4 frs (frs 1′–4′). Fr. 2′ was rechromatographed on a silica gel column using *n*-hexane–Me_2CO (5:4, 5:5, 4:5, 3:6) and Me_2CO, and the eluate was separated into 5 frs (1″–5″). Fr. 4″ was sepd by prep. 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^{-1}; UV detector, 220 nm) into 10 frs (frs 4″-1–4″-10). Fr. 4″-3 was sepd by prep. HPLC (column, TSK gel ODS-120T, 21.5 mm i.d. × 30 cm; mobile phase, MeOH–H_2O (1:2); column temp., 40°; flow rate, 4.0 ml min^{-1}; UV detector, 220 nm) into 3 frs (frs 4″-3-1–4″-3-3). Fr. 4″-3-2 was purified by prep. HPLC (column, TSK gel ODS-120T, 7.8 mm i.d. × 30 m; mobile phase, MeOH–H_2O (1:3); column temp., 40°C; flow rate, 2.5 ml min^{-1}; UV detector, 220 nm) to give **1** (2.9 mg). Fr. 5″ was purified by prep. HPLC (column, TSK gel ODS-120T, 21.5 mm i.d. × 30 cm; mobile phase, MeOH–H_2O (1:1); column temp., 40°; flow rate, 4.5 ml min^{-1}; UV detector, 220 nm) to give **2** (3.9 mg).

Secoeremopetasitolide A (**1**). Needles ($CHCl_3$–MeOH). Mp 168–169°. $[\alpha]_D^{26}$ −34.7° (MeOH; *c* 0.3). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3495, 1764, 1703, 1645. UV λ_{max}^{MeOH} nm (log ε): 213 (4.2). ^1H and ^{13}C NMR: Table 1. HR-MS: *m/z*: 366.1704 ($[M]^+$, calc. for $C_{19}H_{26}O_7$: 366.1678). CI-MS: *m/z* 367 $[M+H]^+$, 349, 267, 249.

Secoeremopetasitolide B (**2**). Oil. $[\alpha]_D^{26}$ −5.1° (MeOH; *c* 0.4). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3508, 1766, 1717, 1645. UV λ_{max}^{MeOH} nm (log ε): 210 (4.1). ^1H and ^{13}C NMR: Table 1. HR-MS: *m/z* 394.2004 ($[M]^+$, calc. for $C_{21}H_{30}O_7$: 394.1992). CI-MS: *m/z* 395 $[M+H]^+$, 377, 363, 295, 235.

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