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Short Communication

New sesquiterpenoids from *Petasites japonicus* and *Petasites tricholobus*

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ABSTRACT

Phytochemical investigation of the whole plants of *Petasites japonicus* and *Petasites tricholobus* led to the isolation of five new bakkenolide-type sesquiterpenoids, bakkenolide-Ib (**1**), bakkenolide-IIb (**2**), bakkenolide-IIIb (**3**), bakkenolide-IVb (**4**), and bakkenolide-Vb (**5**), and a new eremophilane-type norsesquiterpenoid, petasindiol (**6**). Their structures were elucidated by NMR and HRESIMS analyses. Petasindiol (**6**) represented the first example of 15-noreremophilane sesquiterpenoid from the genus *Petasites*.

1. Introduction

Species belonging to the genus *Petasites* (Compositae) are known to be a rich source of sesquiterpenoids such as bakkenolide-type and eremophilane-type skeletons (Wu et al., 1999; Sun et al., 2011; Yang et al., 2016; Xu et al., 2016; Dong et al., 2010; Wang et al., 2014). Plants of this genus, comprising approximately 19 species, are herbals mainly distributed in Asia, Europe, and North America, of which six species are present in China (Chen and Nordenstam, 2011). The two title plants have been utilized as folk medicines in China: the rhizomes of *P. japonicus* have been utilized to treat tonsillitis, contusion, and poisonous-snake bite (Yaoita and Kikuchi, 1995), and the flower buds of *P. tricholobus* are reputed for their efficacy to treat coughs, bronchitis, and asthmatic disorders (Xie et al., 2005). A recent preclinical study also showed that petasin, an eremophilane sesquiterpenoid contained in many *Petasites* species, could be useful for the treatment of metabolic diseases, by activating AMPK through the inhibition of mitochondrial respiration (Adachi et al., 2014). As part of a BioBioPha [http://www.chemlib.cn] objective to assemble a large-scale natural product library valuable in the discovery of new drug leads from Nature (Gao et al., 2012, 2015, 2016), phytochemical investigation of the whole plants of *P. japonicus* and *P. tricholobus* led to the isolation of 12 sesquiterpenoids (Fig. 1): bakkenolide-Ib (**1**), bakkenolide-IIb (**2**), bakkenolide-IIIb (**3**), bakkenolide-IVb (**4**), bakkenolide D (Wu et al., 1999), bakkenolide B (Yaoita et al., 1992), bakkenolide III (Jiang et al., 2007), and bakkenolide IIIa (Wang et al., 2009) were isolated from *P. japonicus*, and bakkenolide-Vb (**5**), petasindiol (**6**), bakkenolide D (Wu et al., 1999), 1-oxobakkenolide S (Wu et al., 1999), and bakkenolide Db (Wu et al., 1999) from *P. tricholobus*. Compounds **1–5** were hitherto unreported bakkenolides. Compound **6** represented the first example of 15-noreremophilane sesquiterpenoid from this genus. In this paper, we would like to describe the isolation and structure elucidation of these new compounds.

2. Results and discussion

Compound **1** was isolated as a white powder with a molecular formula of $C_{19}H_{26}O_5S$, as evidenced by HRESIMS at m/z 389.1400 (calcd. 389.1399) and NMR spectroscopic data (Tables 1 and 2), with seven degrees of unsaturation. Obvious in the ^1H NMR spectrum were one characteristic *cis*-3-methylthioacryloyloxy group (Wu et al., 1999) [δ_H 2.40 (3H, s), 5.72 and 7.08 (each 1H, d, J = 10.4 Hz)], three methyl signals [δ_H 0.88 (3H, d, J = 6.8 Hz), 1.08 (3H, s), and 2.40 (3H, s)], two olefinic protons of a terminal double bond [δ_H 5.12 and 5.13 (each 1H, s)]. The ^{13}C NMR and DEPT spectra of **1** showed 19 carbon signals, including five quaternary carbons (δ_C 43.4, 56.5, 149.5, 165.1, and 179.3), six methines (δ_C 36.1, 53.5, 72.2, 83.5, 112.3, and 153.1), five methylenes (δ_C 26.9, 29.4, 45.2, 70.7, and 106.4), and three methyls (δ_C 15.6, 19.8, and 19.2). The ^1H and ^{13}C NMR data indicated that **1** was a bakkenolide sesquiterpenoid similar to bakkenolide D (Wu et al., 1999), except that an acetyl group in bakkenolide D was replaced by a hydroxy group in **1**. The HMBC correlation (Fig. 2) from the proton

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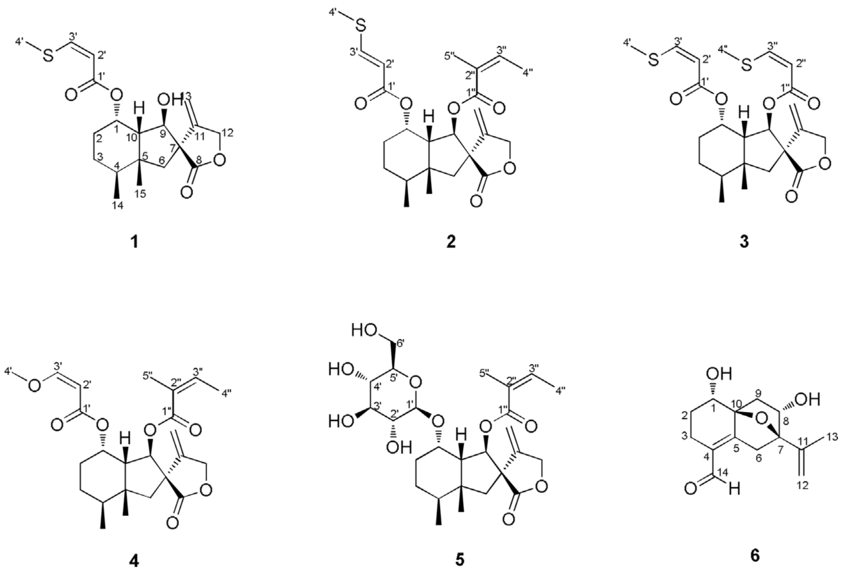

Fig. 1. The structures of compounds **1–6**.

Table 1
^{1}H NMR Spectroscopic Data for **1–5** (δ in ppm, *J* in Hz).

Position	1[a]	2[a]	3[a]	4[a]	5[b]
1	5.28 (dt, 11.0, 5.3)	5.12 (dt, 11.0, 5.1)	5.14 (dt, 11.2, 5.1)	5.09 (dt, 11.9, 4.8)	3.95 (dt, 12.2, 4.8)
2	1.63[c]	1.83[c]	1.79 (dddd, 17.1, 13.3, 13.3, 3.9)	1.75 (dddd, 16.8, 13.0, 13.0, 3.7)	1.83 (dddd, 17.1, 13.0, 13.0, 3.9)
	1.99 (m)	1.83[c]	1.83 (m)	1.85 (m)	2.00 (m)
3	1.36 (dddd, 16.5, 14.0, 14.0, 2.3)	1.38 (dddd, 17.4, 13.2, 13.2, 4.0)	1.34 (dddd, 17.1, 13.3, 13.3, 3.9)	1.36 (dddd, 17.4, 13.0, 13.0, 3.7)	1.31 (dddd, 17.1, 13.0, 13.0, 3.9)
	1.63[c]	1.69 (dddd, 17.4, 4.5, 3.2, 3.2)	1.66 (dddd, 17.1, 3.9, 3.4, 3.4)	1.65 (m)	1.67 (m)
4	1.49 (m)	1.61 (m)	1.57 (m)	1.58 (m)	1.62 (m)
6	1.89 (d, 14.5),	1.96 (d, 14.1)	1.94 (d, 14.4)	1.94 (d, 14.5)	2.15 (d, 14.2)
	2.16 (d, 14.5)	2.26 (d, 14.1)	2.22 (d, 14.4)	2.23 (d, 14.5)	2.01 (d, 14.2)
9	4.54 (d, 10.5)	5.91 (d, 11.2)	5.84 (d, 11.0)	5.87 (d, 11.2)	5.92 (d, 11.2)
10	2.54 (dd, 10.5, 4.7)	2.82 (dd, 11.2, 5.1)	2.74 (dd, 11.0, 5.0)	2.75 (dd, 11.2, 5.0)	2.84 (dd, 11.2, 4.8)
12	4.91 (d, 12.4),	4.64 (br d, 13.0)	4.63 (d, 12.8)	4.63 (d, 12.7)	4.64 (dt, 13.1, 1.7)
	4.74 (d, 12.4)	4.68 (br d, 13.0)	4.66 (d, 12.8)	4.66 (d, 12.7)	4.78 (dt, 13.1, 2.6)
13	5.12 (s)	5.17 (s)	5.14 (s)	5.15 (s)	5.25 (s)
	5.13 (s)	5.22 (s)	5.19 (s)	5.20 (s)	5.26 (s)
Me-14	0.88 (d, 6.8)	0.92 (d, 6.7)	0.89 (d, 6.7)	0.89 (d, 6.7)	0.91 (d, 6.5)
Me-15	1.08 (s)	1.12 (s)	1.10 (s)	1.10 (s)	1.07 (s)
1′					4.21 (d, 7.8)
2′	5.72 (d, 10.4)	5.35 (d, 15.0)	5.53 (d, 10.2)	4.52 (d, 7.1)	2.92 (dd, 9.2, 7.8)
3′	7.08 (d, 10.4)	7.55 (d, 15.0)	6.93 (d, 10.2)	6.32 (d, 7.1)	3.27 (t, 9.2, 9.2)
4′					3.13 (dd, 9.2, 8.4)
5′					3.19 (ddd, 8.4, 6.0, 2.2)
6′					3.57 (dd, 12.1, 6.0)
					3.78 (dd, 12.1, 2.2)
Me-4′	2.40 (s)	2.21 (s)	2.35 (s)	3.83 (s)	
2″			5.81 (d, 10.2)		
3″		6.19 (q, 7.5)	7.09 (d, 10.2)	6.15 (q, 7.1)	6.15 (q, 7.2)
Me-4″		2.01 (dd, 7.5, 1.3)	2.39 (s)	2.00 (d, 7.1)	1.96 (d, 7.2)
Me-5″		1.84 (br s)		1.84 (s)	1.85 (s)

[a] Recorded in $CDCl_3$.
[b] Recorded in CD_3OD.
[c] Overlapped signals.

signal at δ_H 5.28 to the carbonyl signal at δ_C 165.1 (C=O of the *cis*-3-methylthioacryloyloxy group), indicated the presence of the *cis*-3-methylthioacryloyloxy group at C-1.

The relative configuration of compound **1** was established using information from ROESY spectrum (Fig. 2) and by comparison of its spectroscopic data with those of bakkenolide sesquiterpenoids (Wu et al., 1999). The observed cross-peaks of H-13 ↔ H-9, H-13 ↔ H-4, H-4 ↔ H-9, H-4 ↔ H-2α, H-10 ↔ Me-15, Me-15 ↔ Me-14, and H-1 ↔ H-10 in the ROESY spectrum suggested a conformation for **1** as depicted in Fig. 2. The lactone ring was perpendicular to the central five-membered ring, while the latter moiety, in an envelope conformation, was *cis*-fused to the six-membered ring adopting a chair conformation. Consequently, the structure of **1** was assigned as shown and named bakkenolide-Ib.

Compound **2** was obtained as a white powder. Its molecular formula, $C_{24}H_{32}O_6S$, was determined by the $[M + Na]^+$ ion peak in the