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Three new sesquiterpene lactones from *Carpesium abrotanoides*

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ABSTRACT

Three new sesquiterpene lactones, 5α-hydroxy-4α,15-epoxy-11αH-eudesman-12,8β-olide (**1**), carabrol-4-*O*-palmitate (**2**) and carabrol-4-*O*-linoleate (**3**), along with five known ones, were isolated from the whole plant of *Carpesium abrotanoides*. The structures of new compounds were determined by extensive spectroscopic analysis, and compound **1** was also elucidated by X-ray single-crystal diffraction analysis. The cytotoxic activities of these new compounds against human leukemia cells HL-60 and human breast cancer cells MCF-7 were also evaluated by MTS method.

1. Introduction

The genus *Carpesium* (Asteraceae) comprises approximately 21 species worldwide, and most of them are distributed across Asia and Europe (Yang, 2016). Several of these plants have long been used in traditional medicines for treating various diseases in China, Korea, and Japan (Wu et al., 2016). Previous studies on this genus revealed the presence of monoterpenes, sesquiterpenes, diterpenoids, and phenolic compounds (Gao and Chen, 2012; Gao et al., 2008; Kim et al., 1997; Maruyama et al., 1983, 1995; Shi et al., 1998; Yang et al., 2014), which possess various pharmacological activities including antifungal, antibacterial, anti-inflammatory, anti-plasmodial, anti-tumor, and antioxidant activities (Gao et al., 2007; Lee et al., 2002; Rodriguez et al., 1976; Wang et al., 2006; Zhang et al., 2015). *Carpesium abrotanoides* is a biennial herb, which has been used as Traditional Chinese Medicines. As part of the research on bioactive components from medicinal plants or folk medicines (Dong et al., 2015; Fei et al., 2016; Li et al., 2017; Liu et al., 2017; Zhang et al., 2014, 2018), the chemical constituents of *C. abrotanoides* have been investigated. As a result, three new sesquiterpene lactones named 5α-hydroxy-4α,15-epoxy-11αH-eudesman-12,8β-olide (**1**), carabrol-4-*O*-palmitate (**2**), and carabrol-4-*O*-linoleate (**3**) (Fig. 1), along with five known ones, 4(15)-β-epoxyisotelekin (**4**) (Liu et al., 2010), carabrol (**5**) (Shi et al., 1998), carabrone (**6**) (Maruyama and Omura, 1977), 2-desoxy-4-epi-pulchellin (**7**) (Wang et al., 2009), 4β,10β-dihydroxy-5αH-1,11(13)-guaidien-8α,12-olide (**8**) (Kim et al., 2002) were isolated. Herein, we report the isolation and structure elucidation of the three new compounds. The cytotoxic activities of these new compounds against human leukemia cells HL-60, and human breast cancer cells MCF-7 were also determined.

2. Results and discussion

Compound **1** was isolated as colorless crystals. The molecular formula was determined to be $C_{15}H_{22}O_4$ by HRESIMS (*m/z* 289.1403 $[M + Na]^+$, calcd for $C_{15}H_{22}O_4Na$, 289.1410), accounting for five degrees of unsaturation. Its IR spectrum suggested the presence of hydroxyl (3503 cm^{-1}) and γ-lactone (1752 cm^{-1}) groups. The ^1H NMR spectrum of **1** (Table 1) showed the characteristic signals of an oxygenated methine at δ_H 4.51 (1H, ddd, J = 8.1, 4.8, 4.8 Hz), an oxygenated methylene at δ_H 2.75 (1H, d, J = 4.8 Hz) and 2.80 (1H, d, J = 4.8 Hz), and two methyl groups at δ_H 1.05 (3H, s) and 1.12 (3H, d, J = 7.2 Hz), as well as other complicated signals belonging to other methylenes and methines. There were 15 carbon signals in its ^{13}C NMR (Table 2) and DEPT spectra, including the signals of two methyl groups at δ_C 9.4 and 21.5, six methylenes (one oxygenated carbon at δ_C 54.4), three methines (one oxygenated carbon at δ_C 77.7), and four quaternary carbons (one ester group at δ_C 179.4, two oxygenated carbons at δ_C 74.3, and 61.4). These spectroscopic data indicated that compound **1** should be an eudesmane lactone with an epoxy ring (Liu et al., 2010). Comparing above spectroscopic data with those of **4** (4(15)-β-epoxyisotelekin), it can be found that spectra of compound **1** were very similar to those of compound **4**, the most significant difference in the data was the presence of a methyl group instead of the exocyclic methylene which was attached to C-11 in **4**. The ^1H-^1H COSY spectrum of **1** (Fig. 2) revealed the presence of the two spin systems [$-CH_2(1)-CH_2(2)-CH_2(3)-$ and $-CH_2(6)-CH(7)(-CH$

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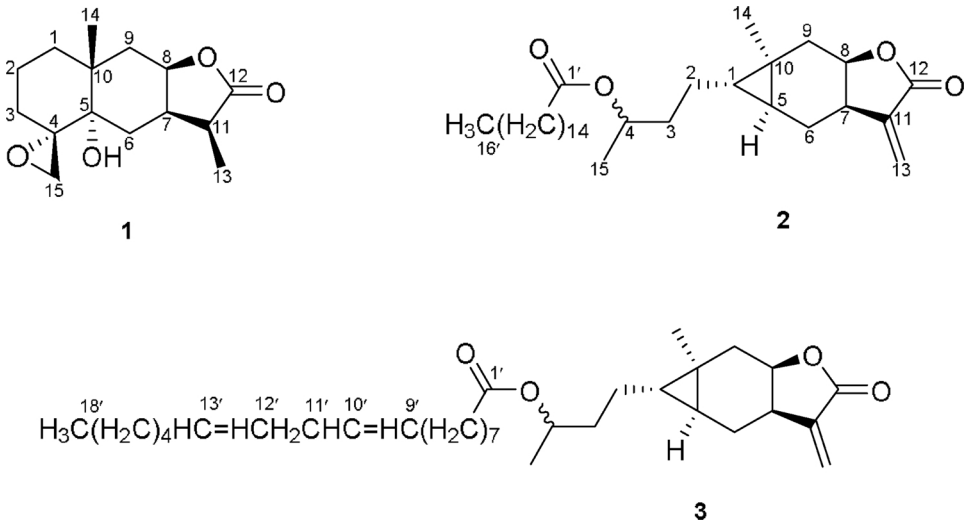

Fig. 1. Structures of compounds **1-3**.

Table 1
^{1}H NMR spectral data for compounds **1-3** ($CDCl_3$, δ in ppm, J in Hz).

position	1	2	3
1	α 1.78 m	0.44 m	0.43 m
	β 1.17 m		
2	α 1.72 m	a 1.62 m	a 1.60 m
	β 1.66 m	b 1.30 m	b 1.28 m
3	α 2.42 m	a 1.69 m	a 1.67 m
	β 1.11 m	b 1.59 m	b 1.55 m
4	–	4.91 m	4.88 m
5	–	0.34 m	0.34 m
6	β 1.42 dd (14.4, 6.0)	α 2.34 dd (14.7, 7.2)	α 2.32 m
	α 1.04 m	β 0.95 m	β 0.92 m
7	2.72 m	3.15 m	3.14 m
8	4.51 ddd (8.1, 4.8, 4.8)	4.78 m	4.76 m
9	α 1.97 dd (15.6, 4.8)	α 2.32 dd (14.1, 7.5)	α 2.30 m
	β 1.85 dd (15.6, 1.2)	β 0.96 m	β 0.95 m
11	2.80 m	–	–
13	1.12 d (7.2)	a 6.23 d (2.4)	a 6.22 d (2.4)
		b 5.54 d (2.4)	b 5.53 d (2.4)
14	1.05 s	1.06 s	1.05 s
15a	2.75 d (4.8)	1.21 d (6.6)	1.19 d (6.6)
15b	2.80 d (4.8)		
2'	–	2.27 t (7.8)	2.24 m
3'	–	1.62 m	1.60 m
4'-7'	–	1.26–1.35 m	1.24–1.36 m
8'	–	1.26–1.35 m	2.03 m
9'	–	1.26–1.35 m	5.37 m
10'	–	1.26–1.35 m	5.34 m
11'	–	1.26–1.35 m	2.77 m
12'	–	1.26–1.35 m	5.34 m
13'	–	1.26–1.35 m	5.37 m
14'	–	1.26–1.35 m	2.03 m
15'	–	1.26–1.35 m	1.24–1.36 m
16'	–	0.88 t (6.6)	1.24–1.36 m
17'	–	–	1.24–1.36 m
18'	–	–	0.86 t (6.6)

Recorded at 600 MHz.

Table 2
^{13}C NMR spectral data for compounds **1-3** ($CDCl_3$, δ in ppm).

position	1	2	3
1	34.3	34.8	34.8
2	19.3	25.0	25.0
3	29.6	36.0	36.0
4	61.4	70.3	70.4
5	74.3	22.9	22.9
6	22.8	30.8	30.8
7	36.8	37.8	37.8
8	77.7	75.6	75.6
9	36.1	37.4	37.4
10	37.2	17.1	17.1
11	41.0	139.1	139.1
12	179.4	170.4	170.4
13	9.4	122.4	122.4
14	21.5	18.2	18.2
15	54.4	19.9	19.9
1'	–	173.5	173.4
2'	–	34.7	34.7
3'	–	25.1	25.1
4'-7'	–	29.1–29.7	29.4–29.7
8'	–	29.1–29.7	27.2
9'	–	29.1–29.7	130.0
10'	–	29.1–29.7	128.0
11'	–	29.1–29.7	25.6
12'	–	29.1–29.7	128.0
13'	–	29.1–29.7	130.2
14'	–	31.9	27.2
15'	–	22.6	29.4–29.7
16'	–	14.1	32.5
17'	–	–	22.7
18'	–	–	14.1

Recorded at 150MHz.

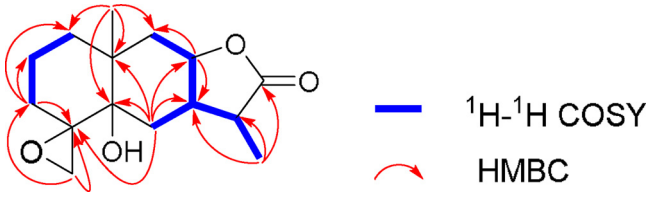

Fig. 2. Key ^{1}H-^{1}H COSY and HMBC correlations of **1**.

(8) – CH_2(9)–) – CH(11) – CH_3(13) (Fig. 2)]. The HMBC spectrum (Fig. 2) showed the key correlations of H_3-14 with C-1 (δ_C 34.3), C-5 (δ_C 74.3), C-9 (δ_C 36.1) and C-10 (δ_C 37.2), H_2-6 with C-4 (δ_C 61.4), C-5, C-7 (δ_C 36.8), C-8 (δ_C 77.7) and C-10, and H_2-15 with C-4, which further confirmed the location of the hydroxyl group at C-5, and the epoxy ring between C-4 and C-15. Hence, the planar structure of **1** was proposed to be 5-hydroxy-4(15)-epoxyeudesman-12,8-olide.

The NOESY spectrum and an X-ray diffraction study were used to confirm the stereochemistry of **1**. In the NOESY spectrum (Fig. 3), the key correlations of H_3-14/H_2-15, H_3-14/H-6β and H_3-13/H-6β revealed that these protons were β-oriented. The correlations from H-8 to H-7, H-7 to H-6α and H-11 to H-7 suggested the α-orientations of H-8, H-7, and H-11. Fortunately, we got the single crystal of compound **1**, and we