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Chinese Chemical Letters 20 (2009) 945–948

CHINESE CHEMICAL LETTERS

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Oxyphyllones A and B, novel sesquiterpenes with an unusual 4,5-secoeudesmane skeleton from *Alpinia oxyphylla*

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Received 3 December 2008

Abstract

Two novel 4,5-secoeudesmane sesquiterpenoids, oxyphyllones A (**1**) and B (**2**) were isolated from the fruits of *Alpinia oxyphylla*. Their structures were established by spectroscopic methods including 1D and 2D NMR spectra. These two compounds are the first example of naturally occurring sesquiterpenoids with a 4,5-secoeudesmane skeleton in the family of Zingiberaceae and oxyphyllone A (**1**) is the first 4,5-secoeudesmane type of 13-norsesquiterpenoid. Compounds **1** and **2** exhibited no cytotoxicities against three cancer cell lines at 10 μg/mL.

Keywords: *Alpinia oxyphylla*; Zingiberaceae; 4,5-Secoeudesmane sesquiterpenoid; Oxyphyllone A; Oxyphyllone B

Alpinia oxyphylla Miq. (Zingiberaceae) distributes widely in South China and is used in folk medicine to treat intestinal disorders, urosis, diuresis, ulceration and dementia [1–3]. Sesquiterpenes, diterpenes, flavonoids, diarylheptanoids in *A. oxyphylla* have been reported previously and some of which showed inhibitory effect on nitric oxide (NO) production in lipopolysaccharide (LPS)-activated mouse peritoneal macrophages [1,2,4,5]. In our study, oxyphyllone A (**1**), a novel 4,5-secoeudesmane 13-norsesquiterpenoid, and a novel 4,5-secoeudesmane sesquiterpenoid oxyphyllone B (**2**) (shown as a 1:1 mixture of diasteroisomers), were found from the fruits of *A. oxyphylla*. This is the first time to find naturally occurring sesquiterpenoids with 4,5-secoeudesmane skeleton in the family of Zingiberaceae. Compound **1** is the first 4,5-secoeudesmane type of 13-norsesquiterpenoid. The cytotoxic activity of compounds **1** and **2** against A549, HT-29 and SGC-7901 cell lines was tested [6]. They showed no cytotoxicities on these cancer cell lines at 10 μg/mL. This paper mainly deals with the isolation and structure elucidation of the novel sesquiterpenoids and a possible biogenetic pathway is also proposed for these compounds.

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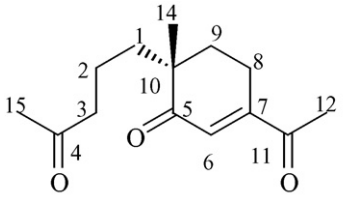
1001-8417/$ – see front matter
doi:10.1016/j.cclet.2009.03.029



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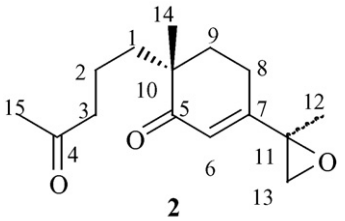
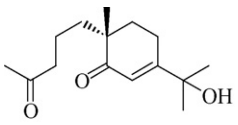


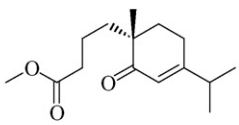
2

The Me_2CO/H_2O (70%) extract of the fruits of *A. oxyphylla* [7] (15 kg) was partitioned in turn with petroleum ether, ethyl acetate, and *n*-butanol against water. Oxyphyllones A (**1**) (8 mg) and B (**2**) (8 mg) were isolated from the ethyl acetate fraction (480 g) by normal-phase column chromatography (silica gel, petroleum ether/acetone 9:1–1:1 and $CHCl_3$/AcOEt 100:1–9:1), and semipreparative HPLC (RP-18, MeOH/H_2O 34:66 and CH_3CN/H_2O 2:8).

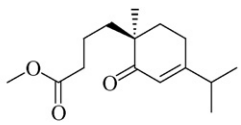
Oxyphyllone A (**1**) [8] was obtained as a colorless oil, $[\alpha]_D^{22.7}$ −18.18 (c 0.55, $CHCl_3$). The molecular formula $C_{14}H_{20}O_3$ was as revealed by HR-ESI-MS (*m/z* 259.1311 $[M+Na]^+$). Its IR spectrum displayed the presence of free ketone and conjugated ketone functions (1714, 1678 cm^{-1}). The ^1H NMR spectrum (Table 1) of **1** exhibited signals for three methyls at δ_H 1.09 (s, 3H), 2.12 (s, 3H) and 2.40 (s, 3H), one olefinic proton at δ_H 6.49 (s, 1H) and five methylenes. The ^{13}C NMR (DEPT) (Table 1) indicated the presence of five quaternary carbons, including a free ketone carbon at δ_C 208.40 and conjugated two ketone carbons at δ_C 200.01 and 205.64. The NMR data of **1** were similar to those of chabrolidione B isolated from Formosan soft coral *Nephthea chabrolii* [9]. Compared with chabrolidione B carefully, a methyl and an oxygenated quaternary carbon signals were absent, whereas a α,β-conjugated ketone signal was present. Besides, the signals due to C-6 (131.40, d) shifted downfield and C-7 (152.68, s) shifted upfield. The above information suggested that **1** could be a 13-norsesquiterpene with a 4,5-secoeudesmane skeleton as shown in Fig. 1. This conclusion was supported by ^1H–^1H COSY, HSQC and HMBC experiments (Fig. 1).



chabrolidione B



(*R*)-2-oxo-p-menth-3-ene-1-butyric methyl ester



(*S*)-2-oxo-p-menth-3-ene-1-butyric methyl ester

The absolute configuration of **1** ($[\alpha]_D^{22.7}$ −18.18 (c 0.55, $CHCl_3$)) was established by comparing the analogous compounds with the same chiral carbon at C-10, i.e. chabrolidione B ($[\alpha]_D$ −9.3) [6] and two synthetic enantiomer

Table 1
NMR spectral data of compounds **1**[a], **2a/2b**[a] and chabrolidione B[b].

Position	**1**		**2a/2b**			Chabrolidione B	
	δ_H (*J* in Hz)	δ_c	δ_H (*J* in Hz)	δ_c		δ_H (*J* in Hz)	δ_c
1	1.38 (m); 1.50 (m)	35.34 (t)	1.36 (m); 1.52 (m)	35.30 (t)	35.94 (t)	1.38 (m); 1.55 (m)	35.8
2	1.50 (m)	17.97 (t)	1.52 (m)	18.08 (t)	18.11 (t)	1.51 (m)	18.3
3	2.42 (m)	43.69 (t)	2.42 (m)	43.76 (t)	43.89 (t)	2.42 (m)	44.0
4		208.40 (s)		208.65 (s)	208.72 (s)		208.9
5		205.64 (s)		203.62 (s)	203.65 (s)		204.7
6	6.49 (s)	131.40 (d)	6.02 (s)	124.71 (d)	124.80 (d)	6.04 (s)	121.3
7		152.68 (s)		160.91 (s)	161.00 (s)		168.2
8	2.51 (m)	20.40 (t)	2.29 (m)	21.53 (t)	21.56 (t)	2.42 (m)	22.5
9	1.97 (m) (α); 1.79 (m) (β)	32.36 (t)	1.92 (m) (α); 1.76 (m) (β)	32.60 (t)	32.90 (t)	1.97 (m) (α); 1.77 (m) (β)	33.4
10		44.25 (s)		43.53 (s)	43.53 (s)		43.5
11		200.01 (s)		56.40 (s)	56.43 (s)		72.6
12	2.40 (s)	26.10 (q)	1.52 (s)	19.71 (q)	19.73 (q)	1.41 (s)	28.6
13			2.84 (m)	54.06 (t)	54.09 (t)	1.41 (s)	28.7
14	1.09 (s)	21.36 (q)	1.06 (s)	21.59 (q)	21.65 (q)	1.07 (s)	21.8
15	2.12 (s)	29.86 (q)	2.12 (s)	29.85 (q)	29.85 (q)	2.13 (s)	29.9

[a] ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 and 100 MHz. δ in ppm, *J* in Hz.
[b] ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 500 and 125 MHz from reference [9].

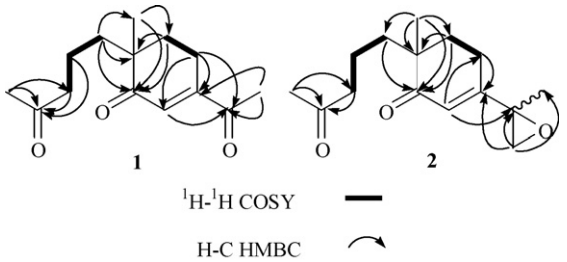


Fig. 1. ^{1}H–^{1}H COSY and Key HMBC correlations for compounds **1** and **2**.

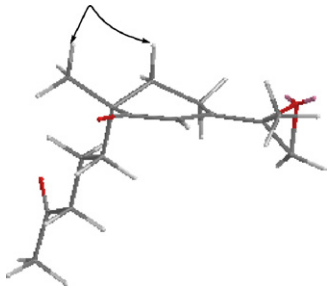
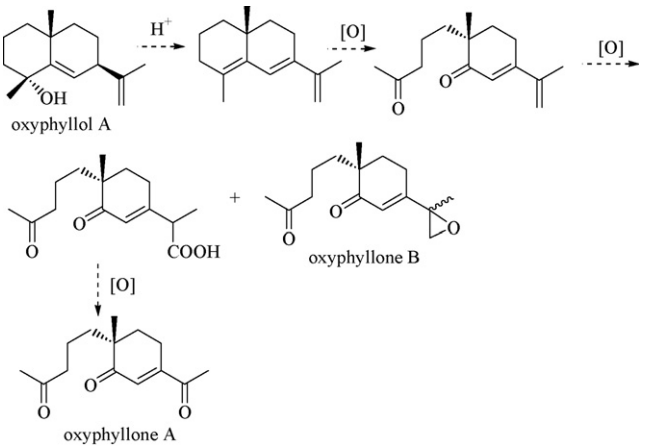


Fig. 2. Key ROESY correlation of compounds **2a/2b**.

compounds, (*R*)-2-oxo-p-menth-3-ene-1-butyric methyl ester ($[\alpha]_D$ −4.6) and (*S*)-2-oxo-p-menth-3-ene-1-butyric methyl ester ($[\alpha]_D$ +5.5) arising from β-eudesmol and valeranone, respectively [10]. Hikino et al. (1965) determined the absolute configuration of C-10 in valeranone by comparing the optical rotation value of (*S*) and (*R*)-2-oxo-p-menth-3-ene-1-butyric methyl ester [10], and the absolute configuration of chabrolidione B was determined to be 10*R* because of the similar structure and the same sign of optical rotation to (*R*)-2-oxo-p-menth-3-ene-1-butyric methyl ester [9]. Thus, compound **1** was inferred to be 10*R* following this similarity.

Oxyphyllone B (**2**) [11] (isolated as a 1:1 mixture of diasteroisomers) was obtained as a colorless oil, $[\alpha]_D^{27.3}$ −13.64° (c 0.11, $CHCl_3$). Its molecular formula $C_{15}H_{22}O_3$ was provided by HR-ESI-MS (*m/z* 273.1462 $[M+Na]^+$). The ^{1}H and ^{13}C NMR spectral data of compounds **2a/2b** was similar to those of chabrolidione B [9] and oxyphyllone A (**1**). The main differences in ^{13}C NMR spectrum were that the signals corresponding to C-11 (56.40/56.43, s) shifted upfield, and C-13 (54.06/54.09, t) shifted downfield in compounds **2a/2b** compared with chabrolidione B, which suggest the presence of epoxy ring at C-11 and C-13. The structure of **2** as shown in Fig. 1 with 4,5-secoeudesmane



Scheme 1. A possible biogenetic pathway proposed for compounds **1** and **2a/2b**.

skeleton was determined by ^{1}H–^{1}H COSY, HSQC and HMBC experiments. The relative configuration of 10-CH_3 was β orientation from the ROESY correlation between H-14 with H-9β (Fig. 2) [9].

Although the absolute stereochemistry of **2** was not established, this compound and **1** were presumed to originate from the same precursor, oxyphyllol A [2] (Scheme 1). Therefore, compounds **2a/2b** are diasteroisomers and the absolute configuration of C-10 could be *R*.

Acknowledgments

This work was supported by the grant from The National Natural Science Foundation of China (No. 30725048), National Basic Research Program of China (No. 2009CB522303) and the Foundation of Chinese Academy of Sciences (West Light Program). The authors are grateful to the staff of analytical group at the State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences for the spectral data.

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[6] P. Skehan, R. Storeng, D. Scudiero, et al. J. Natl. Cancer Inst. 82 (13) (1990) 1107, A549 = lung cancer cell line, HT-29 = colon cancer cell line, SGC-7901 = gastric cancer cell line.
[7] The fruit of *Alpinia oxyphylla* were bought from Kunming medicinal market, Kunming, Yunnan Province, People's Republic of China, in August 2006. The sample was identified by Professor Ning-Hua Tan.
[8] Oxyphyllone A (**1**): colorless oil; $[\alpha]_D^{22.7}$ −18.18 (c 0.55, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 244 (3.83) nm; IR (KBr) ν_{max} 2926, 1714, 1678 cm^{-1}; HR-ESI-MS $[M+Na]^+$ *m/z*: 259.1311 (calcd. for $C_{14}H_{20}O_3Na^+$, 259.1310); ^{1}H and ^{13}C NMR, see Table 1.
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[11] Oxyphyllone B (**2a/2b**): colorless oil; $[\alpha]_D^{27.3}$ −13.64 (c 0.11, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 238 (4.02) nm; IR (KBr) (ν_{max} 3436, 2959, 2934, 1714, 1668 cm^{-1}; HR-ESI-MS $[M+Na]^+$ *m/z*: 273.1462 (calcd. for $C_{15}H_{22}O_3Na^+$, 273.1466). ^{1}H and ^{13}CNMR, see Table 1.