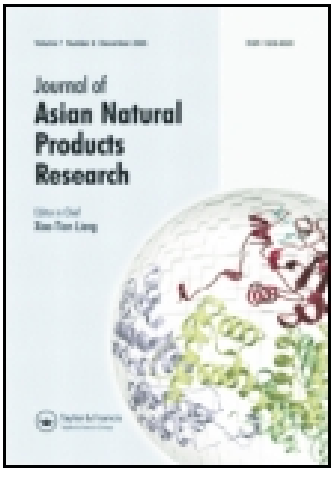

Journal of Asian Natural Products Research
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/ganp20

Three new vibralactone-related compounds from cultures of Basidiomycete Boreostereum vibrans

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Published online: 01 Apr 2014.

To cite this article: Gang-Qiang Wang, Kun Wei, Ling Zhang, Zheng-Hui Li, Qiu-An Wang & Ji-Kai Liu (2014) Three new vibralactone-related compounds from cultures of Basidiomycete Boreostereum vibrans, Journal of Asian Natural Products Research, 16:5, 447-452, DOI: 10.1080/10286020.2014.901312

To link to this article: http://dx.doi.org/10.1080/10286020.2014.901312

Journal of Asian Natural Products Research, 2014
Vol. 16, No. 5, 447–452, http://dx.doi.org/10.1080/10286020.2014.901312

Three new vibralactone-related compounds from cultures of Basidiomycete *Boreostereum vibrans*

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(*Received 8 October 2013; final version received 3 March 2014*)

Three new compounds, named as vibralactones K–M (**1**–**3**), together with vibralactone (**4**) have been isolated from cultures of the Basidiomycete *Boreostereum vibrans*. Their structures were determined on the basis of spectroscopic evidences (1D and 2D NMR, HRMS, UV, and IR data), chemical methods and literature data. None of the compounds was cytotoxic against five human cancer cell lines and showed inhibitory activity on the pancreatic lipase.

Keywords: *Boreostereum vibrans*; Basidiomycete; vibralactone

1. Introduction

The fungus *Boreostereum vibrans* (Berk. & M.A. Curtis; Davydkina & Bondartseva (Aphyllophorales)) belonged to the family of Boreostereaceae [1]. Secondary metabolites vibralactone and vibralactones B–J were isolated from cultures of Basidiomycete *B. vibrans* [2,3], in which vibralactone showed strong inhibitory activity against pancreatic lipase with an IC_{50} value of 0.4 μg/ml [4], while vibralactones D–F showed activity against human and mouse 11β-HSD1 and 11β-HSD2 cell lines [5]. These natural products have attracted great interests of synthetic chemists, vibralactone and vibralactone C have been totally synthesized [6,7]. Recently, vibralactone as a tool to study the activity and structure of the ClpP1P2 complex from *Listeria monocytogenes* has been reported [8]. Zhao et al. [9] reported the biosynthetic pathway for vibralactone in 2013. To find more compounds with the skeleton of vibralactone, the further study was undertaken to investigate the minor constituents of this fungus. Three vibralactones K–M (**1**–**3**) together with vibralactone (**4**) were obtained (Figure 1).

2. Results and discussion

Compound **1** was a colorless oil. Its molecular formula was established as $C_{12}H_{18}O_3$ by the HR-EI-MS at *m/z* 210.1252 $[M]^+$. The IR spectrum exhibited absorption bands for hydroxyl (3431 cm^{-1}) and carbonyl (1754 cm^{-1}) groups. The ^{13}C NMR data (Table 1) revealed 12 carbon signals assigned to a carbonyl, 1 double bond, 4 sp^3 methines (1 oxygenated), 3 sp^3 methylenes, and 2 methyls. The signals at δ_C 25.8 (q, C-11), 17.8 (q, C-12), 29.9 (t, C-8), 121.4 (d, C-9), 133.3 (s, C-10), and δ_H 1.70 (s, H-11), 1.61 (s, H-12), 5.12 (t, H-9) indicated the presence of an isoprenyl moiety.

In the ^1H–^1H COSY spectrum, the significant correlations between H-2 and H-6, H-3 and H-4/H-2, H-5 and H-4, H-6 and H-5, H-7 and H-6 were observed as

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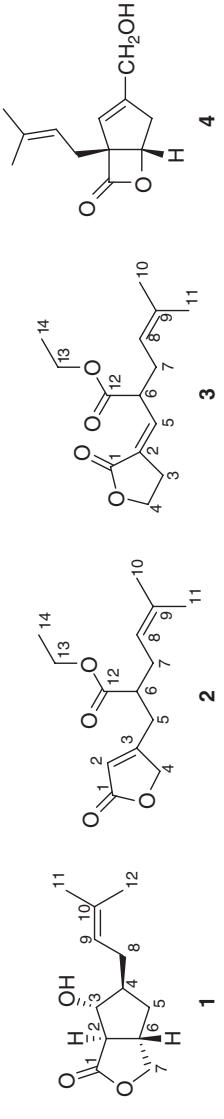


Figure 1. Structures of compounds **1**–**4**.

shown in Figure 1. The heteronuclear multiple bond connectivity (HMBC) correlations of H-7 at δ_H 4.53 (1H, t, $J = 9.0$ Hz) and 4.10 (1H, dd, $J = 3.2$, 9.2 Hz) with C-1 at δ_C 178.7 established a γ-lactone ring. In addition, the HMBC correlations of H-8 with C-3 and C-5 suggested that the isoprenyl group was attached at C-4 (Figure 2).

To establish the relative configuration of compound **1**, a rotating frame Overhauser enhancement spectroscopy (ROESY) experiment was exerted. The ROESY correlations between H-3 and H-8β, and H-6, and between H-7α and H-2 suggested H-8, H-6, and H-3 at β-orientation, while H-7 and H-2 at α-orientation. Therefore, the structure of compound **1** was established and named as vibralactone K.

Compound **2** was obtained as a colorless oil and possesses a molecular formula $C_{14}H_{20}O_4$ as established by the HR-EI-MS at *m/z* 252.1362 $[M]^+$. IR absorption bands at 1782 and 1750 cm^{-1} revealed the presence of two carbonyl groups. The ^{13}C NMR data (Table 1) revealed 14 carbon signals assigned to 2 carbonyls, 4 olefinic, 1 methine, 4 methylenes (1 oxygenated), and 3 methyls. The NMR data of **2** were closely similar to those of vibralactone J, and comparison of the ^1H and ^{13}C NMR spectral data of **2** with those of vibralactone J revealed that **2** had one more ethyl group (δ_C 60.9, 14.2; δ_H 4.12, 1.23). In addition, the HMBC correlations of H-14 at δ_H 4.12 (2H, m) with C-12 at δ_C 173.8 (s), and H-15 at δ_H 1.23 (3H, t, $J = 7.1$ Hz) with C-14 at δ_C 60.9 (t) suggested that the ethyl group was connected to C-12 via oxygen (Figure 1). Thus, the structure of compound **2** was established as shown in Figure 1 and named vibralactone L.

Compound **3** was a colorless oil and its molecular formula was found to be $C_{14}H_{20}O_4$ by the HR-EI-MS at *m/z* 252.1367 $[M]^+$. Its IR spectrum showed the presence of carbonyl groups (1761,

Table 1. ^{1}H and ^{13}C NMR spectral data of **1**–**3** (δ in ppm, *J* in Hz).

	1[a]		**2**[a]		**3**[b]	
No.	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
1	178.7, s		174.2, s		171.7, s	
2	47.1, d	3.11 (t, 8.9)	116.1, d	5.84 (br, s)	127.6, s	
3	77.6, d	3.99–3.96 (m)	168.1, s		25.3, t	2.98–2.96 (m) 2.94–2.86 (m)
4	46.3, d	1.82–1.78 (m)	73.2, t	4.73 (s)	65.3, t	4.41 (t, 7.4)
5	35.3, t	1.82–1.78 (m)	29.8, t	2.72–2.70 (m)	136.8, d	6.78–6.76 (m)
		1.69–1.67 (m)		2.51 (br, d, $J = 13.5$)		
6	35.5, d	2.96–2.94 (m)	44.0, d	2.69–2.63 (m)	47.6, d	3.23–3.21 (m)
7α	75.5, t	4.53 (t, 9.0);	31.0, t	2.40–2.35 (m)	30.6, t	2.58–2.56 (m)
7β		4.10 (dd, 3.2, 9.2)		2.29–2.24 (m)		2.39–2.37 (m)
8α	29.9, t	2.35–2.32 (m);	119.6, d	5.06–5.04 (m)	119.5, d	5.07–5.05 (m)
8β		1.94–1.87 (m)				
9	121.4, d	5.12 (t, 7.2)	135.3, s		135.2, s	
10	133.3, s		25.8, q	1.70 (s)	25.7, q	1.71 (s)
11	25.8, q	1.70 (s)	17.8, q	1.60 (s)	17.8, q	1.64 (s)
12	17.8, q	1.61 (s)	173.8, s		170.7, s	
13			60.9, t	4.18–4.08 (m)	61.1, t	4.18 (q, 7.1)
14			14.2, q	1.23 (t, 7.1)	14.1, q	1.28 (t, 7.1)

[a] At 400 and 100 MHz, resp., in $CDCl_3$.
[b] At 500 and 125 MHz, resp., in $CDCl_3$.

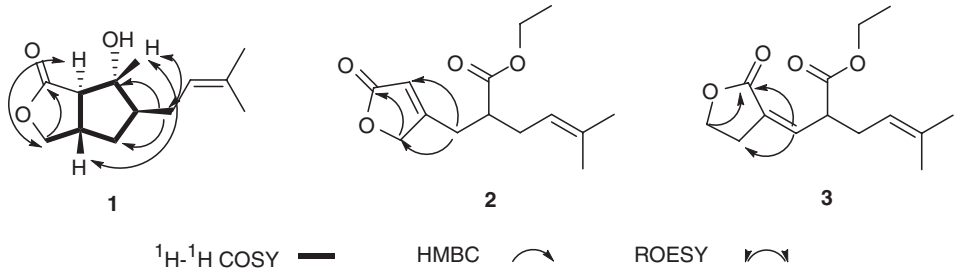
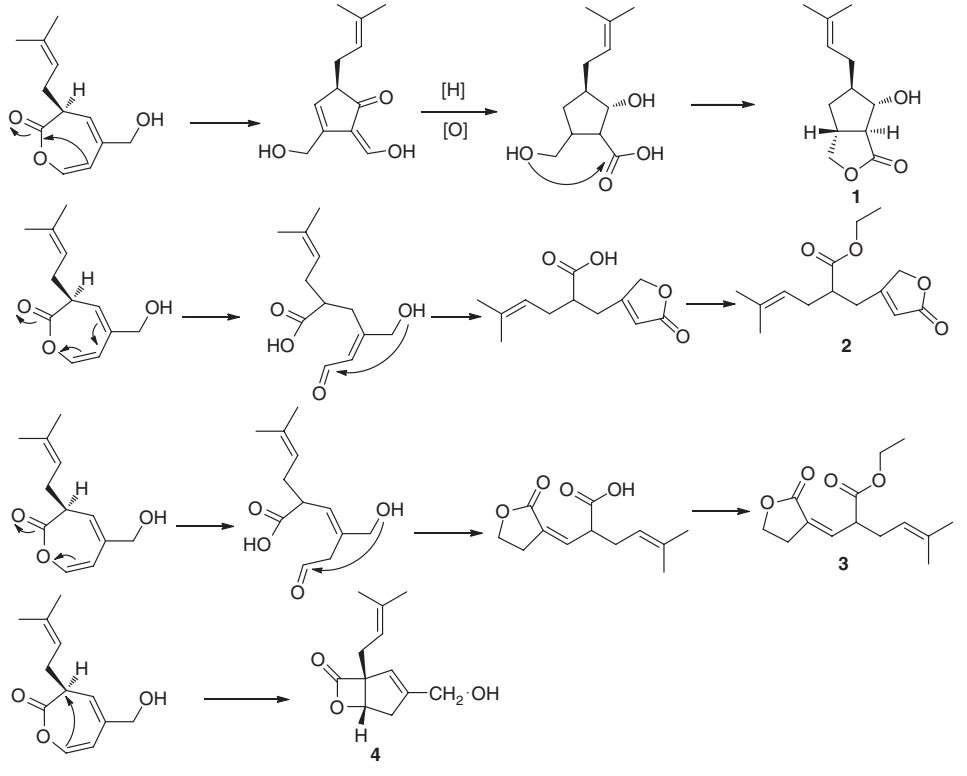


Figure 2. Key 2D NMR correlations of **1**–**3**.

1732 cm^{-1}). The ^{1}H and ^{13}C NMR data of **3** were very similar to those of **2** (Table 1). The difference between **3** and **2** was the connection location of the γ-lactone. In the HMBC spectrum of **3**, the significant correlations from H-5 at δ_H 6.77 (m) to C-1 at δ_C 170.7 (s), C-3 at δ_C 25.3 (t) were observed, which suggested that C-5 at δ_C 136.8 (d) was connected to C-2 at δ_C 127.6 (s) (Figure 2). Detailed analysis of other 2D NMR data (HSQC, HMBC, ^{1}H–^{1}H COSY, and ROESY) suggested that other parts were the same as those of **2**. Therefore, compound **3** was established as depicted, and named as vibralactone M. A possible biogenetic pathway of compounds **1**–**3** is proposed (Scheme 1).

Compounds **1**–**3** were evaluated for its cytotoxicity against five human cancer cell lines, SK-BR-3 breast, SMMC-7721



Scheme 1. Plausible biogenetic synthetic pathway of vibralactones of **1**–**4**.

hepatocellular carcinoma, HL-60 myeloid leukemia, PANC-1 pancreatic cancer, and A-549 lung cancer, using the MTT method reported previously [9] with minor revision. Unfortunately, no significant activity was detected ($IC_{50} > 40$ μm). Compounds **1**–**3** were also evaluated on the activity of pancreatic lipase, and none of them showed inhibitory activity.

3. Experimental

3.1 General experimental procedures

Optical rotations were measured with a Horiba SEPA-300 polarimeter (Horiba, Kyoto, Japan). UV spectra were obtained using a Shimadzu UV-2401A spectrophotometer (Shimadzu, Kyoto, Japan). A Tenor 27 spectrophotometer was used for scanning IR spectroscopy (Bruker Optics GmbH, Ettlingen, Germany) using KBr pellets. 1D and 2D spectra were run on Avance III 600, Bruker DRX-500, and AM-400 spectrometers (Bruker BioSpin GmbH, Rheinstetten, Germany) with TMS as an internal standard. Chemical shifts (δ) were expressed in ppm with reference to the solvent signals. HR-EI-MS were performed on an API-Qstar-Pulsar-1 spectrometer (MDS Sciex, Concord, ON, Canada). Column chromatography was performed on Silica gel (200–300 mesh; Qingdao Haiyang Chemical Co. Ltd, Qingdao, China) and RP-18 (20–45 μm; Fuji Silysia Chemical Ltd, Aichi, Japan). Fractions were monitored by TLC (GF 254; Qingdao Haiyang Chemical Co., Ltd), and spots were visualized by heating silica gel plates sprayed with 10% H_2SO_4. Preparative HPLC was performed on an Agilent 1100 series with a Zorbax SB-C18 (5 mm, 9.4 mm × 150 mm) column.

3.2 Fungal material and cultivation

Boreostereum vibrans was provided and fermented by Engr Zheng-Hui Li, Kunming Institute of Botany. A voucher specimen (No. 20120920B) was deposited in the Herbarium of Kunming Institute of Botany, Chinese Academy of Sciences, and identified by Engr Zheng-Hui Li. The culture medium consisted of glucose 5%, peptone 0.15%, yeast 0.5%, KH_2PO_4 0.05%, and $MgSO_4$ 0.05% in 1 l of deionized water (pH 6.5 before autoclaving). The fungus was grown in Erlenmeyer flasks (500 ml with 300 ml of medium). Fermentation was carried out in a rotary shaker at 22°C and 200 rpm for 26 days.

3.3 Extraction and isolation

The whole culture broth (25 l) of *B. vibrans* was extracted three times with EtOAc (20 l) after filtration. The organic layer was concentrated under reduced pressure to give a crude extract (10 g). The residue was subjected to column chromatography over silica gel (200–300 mesh, 6 × 40 cm), eluted with a petroleum ether/EtOAc (20:1, 15:1, 10:1, 5:1, 1:1, 0:1 v/v) gradient, to afford fractions A–E. Fraction B (1.03 g) eluted with petroleum ether/EtOAc (4:1) to give five major fractions 1–5, and fraction 4 (21 mg) was separated repeatedly by reversed-phase RP-18 ($MeOH/H_2O$, 30% → 80%) column chromatography, followed by Sephadex LH-20 (acetone) column chromatography to give **1** (4 mg). Fraction C (0.81 g) was separated by silica gel eluted with petroleum ether/EtOAc (2:1) to give three major fractions 1–3, and fractions 2 (19 mg) and 3 (27 mg) were, respectively, purified by preparative HPLC using CH_3CN/H_2O (from 20% to 40%, 20 min) as mobile phase (flow rate: 10 ml/min), then separated by Sephadex LH-20 (acetone) column chromatography to afford compounds **2** (4 mg) and **3** (13 mg).

3.3.1 Vibralactone K (1)

Colorless oil. $[\alpha]_D^{25}$ − 5.3 (*c* 0.29, MeOH). IR (KBr) ν_{max} cm^{-1}: 3431, 2966, 2923, 1817, 1754, 1382, 1190. For ^1H (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectral data, see Table 1. HR-EI-MS *m/z*:

210.1252 $[M]^+$ (calcd for $C_{12}H_{18}O_3$, 210.1256).

3.3.2 Vibralactone L (**2**)

Colorless oil. $[\alpha]_D^{25} + 3.8$ (*c* 0.34, MeOH). IR (KBr) ν_{max} cm^{-1}: 2979, 2919, 1782, 1750, 1446, 1174, 1029. For ^1H (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) spectral data, see Table 1. HR-EI-MS *m/z*: 252.1362 $[M]^+$ (calcd for $C_{14}H_{20}O_4$, 252.1362).

3.3.3 Vibralactone M (**3**)

Colorless oil. $[\alpha]_D^{24} - 22.1$ (*c* 0.17, MeOH/$CHCl_3$, (1:1)). UV (MeOH) λ_{max} nm (log ε): 235 (2.91). IR (KBr) ν_{max} cm^{-1}: 2978, 2918, 1761, 1732, 1382, 1185, 1028. For ^1H (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) spectral data, see Table 1. HR-EI-MS *m/z*: 252.1367 $[M]^+$ (calcd for $C_{14}H_{20}O_4$, 252.1362).

Acknowledgments

This project was financially supported by National Natural Science Foundation of China (Nos 81102348 and 21302194) and Hunan Province Innovation Foundation for Postgraduate (CX2012B160).

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