Organic LETTERS

Letter

pubs.acs.org/OrgLett

# Phomopchalasins A and B, Two Cytochalasans with Polycyclic-Fused Skeletons from the Endophytic Fungus *Phomopsis* sp. shj2

Bing-Chao Yan,[†,∥,⊥] Wei-Guang Wang,[†,⊥] Dong-Bao Hu,[§] Xiang Sun,[‡] Ling-Mei Kong,[†] Xiao-Nian Li,[†] Xue Du,[†] Shi-Hong Luo,[†] Yan Liu,[†] Yan Li,[†] Han-Dong Sun,[†] and Jian-Xin Pu*[,†]

[†]State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650201, Yunnan, P. R. China

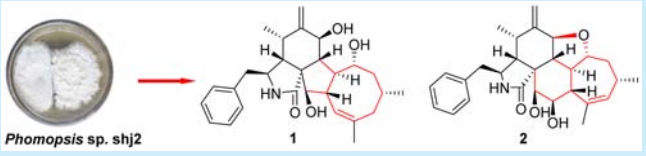
[‡]State Key Laboratory of Mycology, Institute of Microbiology, Chinese Academy of Sciences, Beijing 100190, P. R. China

[§]College of Resource and Environment, Yuxi Normal University, Yuxi 653100, Yunnan, P. R. China

[∥]University of Chinese Academy of Sciences, Beijing 100049, P. R. China

Supporting Information

**ABSTRACT:** Phomopchalasins A (**1**) and B (**2**), two novel cytochalasans with unprecedented carbon skeletons, and phomopchalasin C (**3**), containing a rare hydroperoxyl motif, were obtained from the endophytic fungus *Phomopsis* sp. shj2, which was first isolated from the *Isodon eriocalyx var. laxiflora*. Their structures were elucidated by extensive spectroscopic analyses, electronic circular dichroism (ECD) calculation, and X-ray crystallographic analysis. Notably, **1** possessed an unprecedented 5/6/5/8-fused tetracyclic ring system, and **2** featured a novel 5/6/6/7/5-fused pentacyclic skeleton. The cytotoxic, anti-inflammatory, and antimigratory activities of **1**−**3** were evaluated in vitro.




Cytochalasans comprise a large group of fungal polyketide synthase-nonribosomal peptide synthetase (PKS-NRPS) hybrid metabolites[1] with a wide range of biological activities including cytotoxic,[2] antiviral,[3] immunosuppressive,[4] antiangiogenic effects,[5] and so on. Since the first representatives, cytochalasins A and B, were discovered in 1966,[6] more than 200 cytochalasans have been found from a plethora of fungal genera such as *Phomopsis*, *Penicillium*, *Asperigillus*, and *Chaetomium*, which have also aroused great interest from synthesis and biosynthesis scientists.[7] The complex structures were typically characterized by the presence of a reduced isoindolone nucleus fused to a 9−15-membered macrocyclic ring,[7a] such as periconiasin A[2b] (9-membered), armochaeglobine A[8] (10-membered), cytochalasin J (**4**),[9] and cytochalasins N−S[9b] (11-membered), cytochalasin $Z_7$[2a] (12-membered), chaetoglobosin A[10] (13-membered), and so on.

Our efforts to discover structurally unique and bioactive natural products from the endophytic fungus *Phomopsis* sp. shj2 (GenBank Accession No. KU533636) included, first, isolation from the stems of *Isodon eriocalyx* var. *laxiflora*. It resulted in the isolation of three new cytochalasans, phomopchalasins A−C (**1**−**3**), together with a known one, cytochalasin J (**4**) (Figure 1).

To the best of our knowledge, **1** is the first example of 5/6/5/8-fused tetracyclic 10-phenyl[11]-cytochalasan, and **2** is first reported as a 10-phenyl[11]-cytochalasan bearing a novel 5/6/6/7/5-fused pentacyclic ring system. **3** has a rare hydroperoxyl motif in its structure. Herein, we report the isolation, structure elucidation, and biological evaluation as well as the plausible biosynthetic pathway of **1** and **2**.

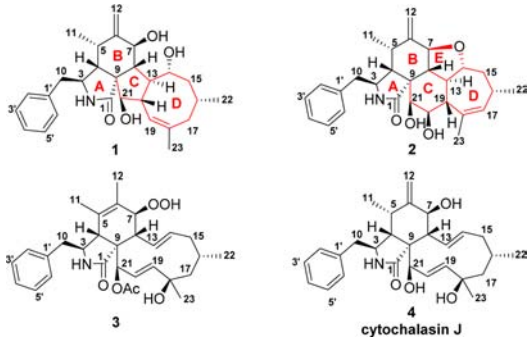



**Figure 1.** Structures of compounds **1**−**4**.

Phomopchalasin A (**1**) was isolated as colorless needles with the molecular formula $C_{28}H_{37}NO_4$ which was determined by its HRESIMS data ($[M + Na]^+$, $m/z$ 474.2619, calcd for 474.2615), corresponding to 11 degrees of unsaturation. The $^1$H NMR spectrum (Table 1) showed typical signals assignable to one tertiary methyl at $\delta_H$ (1.73, 3H, s), two secondary methyl groups at $\delta_H$ (0.96, 3H, d, $J$ = 6.3 Hz; 0.98, 3H, d, $J$ = 7.0 Hz), an olefinic methylene group (exocyclic double bond) at $\delta_H$ (4.98 and 5.14, 2H, both s), three oxygenated methine groups at $\delta_H$ (4.26, 1H, d, $J$ = 9.0 Hz; 3.41, 1H, overlap; 3.53, 1H, br s), and one single-substituted phenyl at $\delta_H$ (7.19−7.32, 5H). The $^{13}$C NMR (Table 2) and DEPT spectra of **1** displayed resonances for 28 carbons, ascribed to three methyls, four methylenes (including one

**Received:** January 22, 2016
**Published:** February 16, 2016

ACS Publications © 2016 American Chemical Society



DOI: 10.1021/acs.orglett.6b00214
*Org. Lett.* 2016, 18, 1108−1111

Table 1. $^1$H NMR Data for Compounds 1−3[a] ($\delta$ in ppm, $J$ in Hz)

| no. | 1 | 2 | 3 |
|---|---|---|---|
| 2 | – | 7.85 (s) | 5.62 (s) |
| 3 | 3.42 (overlap) | 3.22 (dd, 4.6, 4.5) | 3.33 (br t, 7.5) |
| 4 | 2.49 (m) | 2.40 (t, 4.5) | 2.49 (br s) |
| 5 | 2.65 (m) | 2.69 (m) | – |
| 7 | 4.26 (d, 9.0) | 3.76 (d, 13.0) | 4.16 (d, 10.3) |
| 8 | 2.55 (t, 13.0) | 2.32 (t, 12.8) | 3.06 (d, 10.2) |
| 10 | 2.79 (dd, 13.3, 5.4) | 2.76 (dd, 13.5, 5.4) | 3.00 (dd, 13.4, 6.7) |
| | 2.76 (m) | 2.62 (dd, 13.5, 4.6) | 2.96 (dd, 13.4, 8.7) |
| 11 | 0.96 (d, 6.3) | 0.90 (d, 6.7) | 1.45 (s) |
| 12 | 5.14 (s), 4.98 (s) | 5.11 (s), 5.02 (s) | 1.75 (s) |
| 13 | 2.72 (m) | 1.39 (ddd, 12.4, 10.0, 9.5) | 6.06 (dd, 15.7, 10.2) |
| 14 | 3.41 (overlap) | 3.46 (ddd, 12.0, 9.4, 3.2) | 5.42 (ddd, 15.5, 10.6, 4.8) |
| 15 | 1.87 (m), 1.53 (br d, 14.0) | 1.72 (dd, 10.8, 3.0), 1.07 (dd, 22.7, 11.4) | 2.05 (dd, 12.2, 4.7), 1.85 (dd, 12.2, 3.8) |
| 16 | 2.08 (m) | 2.00 (m) | 1.80 (m) |
| 17 | 2.63 (m), 1.75 (m) | 5.13 (s) | 1.88 (dd, 10.7, 3.5), 1.56 (br d, 3.0) |
| 19 | 5.47 (d, 7.5) | 2.09 (t, 9.6) | 5.55 (dd, 16.5, 2.2) |
| 20 | 2.43 (m) | 4.38 (ddd, 9.6, 8.1, 3.5) | 5.71 (dd, 16.5, 2.1) |
| 21 | 3.53 (br s) | 3.11 (t, 3.5) | 5.81 (s) |
| 22 | 0.98 (d, 7.0) | 1.03 (d, 6.1) | 1.05 (d, 6.8) |
| 23 | 1.73 (s) | 1.86 (s) | 1.37 (s) |
| 2′, 6′ | 7.19 (d, 7.0) | 7.21 (d, 7.0) | 7.19 (d, 7.2) |
| 3′, 5′ | 7.32 (t, 7.0) | 7.30 (t, 7.3) | 7.32 (t, 7.5) |
| 4′ | 7.27 (t, 7.0) | 7.23 (t, 7.3) | 7.25 (overlap) |
| 21-OAc | – | – | 2.29 (s) |
| 20-OH | – | 4.30 (d, 8.1) | – |
| 21-OH | – | 4.77 (d, 3.9) | – |

[a] **1** and **3** were recorded at 600 MHz in $CDCl_3$; **2** was recorded at 500 MHz in DMSO-$d_6$; assignments were based on DEPT, HSQC, COSY, HMBC, and ROESY experiments.

Table 2. $^{13}$C NMR Data of Compounds 1−3 ($\delta$ in ppm)[a]

| no. | 1 | 2 | 3 |
|---|---|---|---|
| 1 | 179.5 | 175.2 | 175.0 |
| 3 | 52.9 | 53.0 | 60.7 |
| 4 | 43.2 | 44.8 | 50.5 |
| 5 | 31.5 | 36.3 | 128.8 |
| 6 | 150.0 | 150.3 | 131.6 |
| 7 | 71.5 | 75.4 | 83.5 |
| 8 | 51.3 | 42.5 | 44.8 |
| 9 | 57.1 | 48.5 | 51.8 |
| 10 | 43.2 | 42.9 | 45.0 |
| 11 | 13.0 | 14.7 | 17.5 |
| 12 | 113.6 | 111.9 | 14.2 |
| 13 | 51.7 | 43.0 | 129.4 |
| 14 | 76.8 | 88.1 | 135.6 |
| 15 | 43.9 | 39.2 | 43.2 |
| 16 | 31.2 | 28.8 | 28.3 |
| 17 | 37.8 | 133.1 | 54.1 |
| 18 | 134.8 | 140.7 | 74.6 |
| 19 | 128.1 | 41.1 | 138.5 |
| 20 | 53.4 | 70.0 | 125.8 |
| 21 | 81.9 | 73.5 | 75.3 |
| 22 | 24.8 | 23.9 | 26.6 |
| 23 | 26.7 | 22.5 | 30.7 |
| 1′ | 137.5 | 136.8 | 137.6 |
| 2′, 6′ | 129.6 | 130.4 | 129.3 |
| 3′, 5′ | 128.6 | 128.1 | 129.1 |
| 4′ | 126.9 | 126.4 | 127.2 |
| 21-OAc | – | – | 170.6, 21.2 |

[a] **1** and **3** were recorded at 150 MHz in $CDCl_3$; **2** was recorded at 125 MHz in DMSO-$d_6$; assignments were based on DEPT, HSQC, COSY, HMBC, and ROESY experiments.

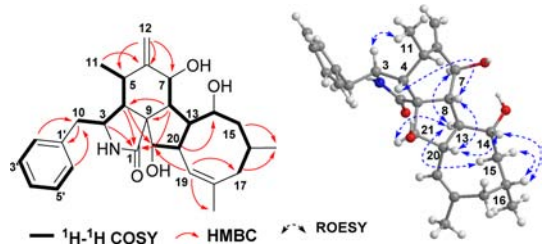



**Figure 2.** Key $^1$H−$^1$H COSY, HMBC, and ROESY correlations of **1**.

exocyclic carbon−carbon double bond), 11 methines (one olefinic), four quaternary carbons (two olefinic groups and one amide carbonyl), and six other signals assignable to the single-substituted phenyl group. Thus, the above-mentioned results indicated that **1** should be a novel pentacyclic cytochalasan including a benzene ring, which was greatly different from the cytochalasan skeletons reported previously.

Analyses of the NMR data of **1** with those of cytochalasin J (**4**)[9b] indicated their structural similarities for the phenylalanine moiety (rings A and B) and the manifest differences of the substructures of rings C and D in **1** from those of **4**. And the complete structure of **1** was established by extensive analysis of its 2D NMR spectra.

The proton spin system of H-7/H-8/H-13/H-20/H-21 deduced by the $^1$H−$^1$H COSY and HSQC spectra of **1** (Figure 2), along with HMBC correlations from H-8 ($\delta_H$ 2.55, t, 13.0 Hz) to C-1, C-4, C-9 and H-4 ($\delta_H$ 2.49, m) to C-21, established a five-membered ring C, which was fused to ring B via C-8 and C-9. Additionally, an unusual eight-membered carbon ring D was elucidated by the $^1$H−$^1$H COSY correlations of H-13/H-14/H-15/H-16/H-17 and HMBC correlations from H-19 ($\delta_H$ 5.47, d, 7.5 Hz) to C-17, C-21, and C-23 and from H-15b ($\delta_H$ 1.53, br d, 14.0 Hz) and H-17 ($\delta_H$ 1.75, m; 2.63, m) to C-22.

The relative configurations of **1** in rings A and B were determined to be the same as those of **4** by analysis of the ROESY spectrum. The NOE correlations of H-8/H-20, H-20/H-14, and H-14/H-16 implied that they were cofacial and assigned as $\beta$-orientated. In contrast, the NOE correlations of H-7/H-13 and H-13/H-21 suggested that H-7, H-13, and H-21 were on the same side with an $\alpha$-orientation. The structure including its relative configuration was confirmed by single-crystal X-ray diffraction analysis of **1** (CCDC 1440709) as shown in Figure 3.

The calculated ECD spectra for **1** were performed using time-dependent density-functional theory (TDDFT) at the B3LYP/6-31++G(d,p) level in the gas phase[11] in order to determine its absolute configuration. We found that the calculated ECD spectrum of the conformers of **1** with 3*S*, 4*R*, 5*S*, 7*S*, 8*R*, 9*R*, 13*R*, 14*R*, 16*R*, 20*S*, 21*R* (Figure S44, Supporting Information (SI)) is in good accordance with the experimental spectrum (Figure 4). Consequently, the absolute configuration of **1** was unambiguously assigned.

Phomopchalasin B (**2**) was obtained as a colorless gum and gave an HRESIMS ion peak at $m/z$ 450.2641 $[M + H]^+$ (calcd for



DOI: 10.1021/acs.orglett.6b00214
*Org. Lett.* 2016, 18, 1108−1111

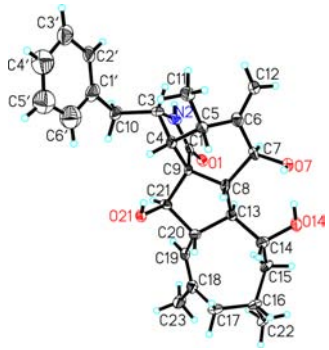



**Figure 3.** X-ray structure of **1**.

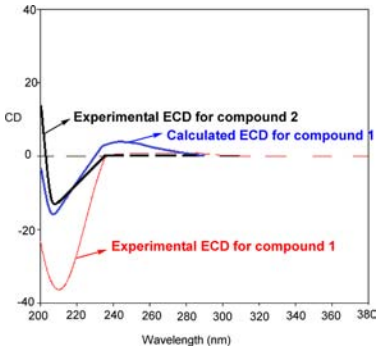



**Figure 4.** Experimental and calculated ECD spectra of **1**.

450.2639), which corresponded to a molecular formula of $C_{28}H_{35}NO_4$ with 12 degrees of unsaturation. A comparison of its corresponding $^{13}C$ and $^1H$ NMR data (Tables 1 and 2) with those of **1** indicates that these two compounds are closely related. The major structural difference between the two compounds is that the 5/8-rings C and D in **1** were changed to the 6/7-rings C and D in **2**. Additionally, a new five-membered epoxy unit (ring E) was formed by the dehydration reaction between 7-OH and 14-OH.

The gross structure of **2** was established by analyses of the NMR spectra (Tables 1 and 2). The phenylalanine moiety (rings A and B) of **2** was elucidated based on the HMBC correlations from H-2 ($\delta_H$ 7.85, s) to C-1, C-3, C-4, and C-9, from H-8 ($\delta_H$ 2.32, t, 12.8 Hz) to C-1, C-6, and C-9, from $H_2$-10 ($\delta_H$ 2.76, dd, 13.5, 5.4 Hz; 2.62, dd, 13.5, 4.6 Hz) to C-1′, C-2′, and C-6′, from $H_3$-11($\delta_H$ 0.90, d, 6.7 Hz) to C-4, C-5, and C-6, and from $H_2$-12 ($\delta_H$ 5.11, s; 5.02, s) to C-5, C-6, and C-7, along with $^1H-^1H$ COSY correlations of $H_2$-10/H-3/H-4/H-5/$H_3$-11 and H-7/H-8.

Furthermore, a six-membered ring C and a seven-membered ring D in **2** varied greatly from the 11-membered ring in **4**, which was determined by the HMBC correlations from H-8 to C-13, C-14, and C-21, from H-13 ($\delta_H$ 1.39, ddd, 12.4, 10.0, 9.5 Hz) to C-7, C-8, C-14, C-15, and C-18, from H-19 ($\delta_H$ 2.09, t, 9.6 Hz) to C-13, C-14, C-17, C-18, and C-20, from H-20 ($\delta_H$ 4.38, ddd, 9.6, 8.1, 3.5 Hz) to C-18 and C-19, from 21-OH ($\delta_H$ 4.77, d, 3.9 Hz) to C-9, from $H_3$-22 ($\delta_H$ 1.03, d, 6.1 Hz) to C-15, C-16, and C-17, and from $H_3$-23 ($\delta_H$ 1.86, s) to C-17, C-18, and C-19, along with the $^1H-^1H$ COSY correlations of H-8/H-13/H-19/H-20/H-21 and H-13/H-14/H-15/H-16($H_3$-22)/H-17 (Figure 5).

Another oxygen-containing five-membered ring E was deduced by the analysis of its HRESIMS and NMR data. Four oxygenated methines were located at C-7, C-14, C-20, and C-21 based on the HSQC spectra, of which C-20 and C-21 were,

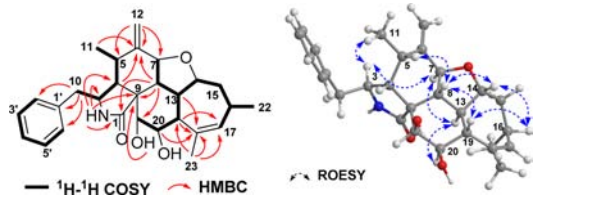



**Figure 5.** Key $^1H-^1H$ COSY, HMBC, and ROESY correlations of **2**.

respectively, connected with a hydroxyl group ($\delta_{HO\text{-}20}$ 4.30, d, $J$ = 8.1 Hz; $\delta_{HO\text{-}21}$, 4.77, d, $J$ = 3.9 Hz, Table 1). In addition, the chemical shifts of C-7 ($\delta_C$ 76.0 in $CDCl_3$ and 75.4 in DMSO-$d_6$) and C-14 ($\delta_C$ 89.3 in $CDCl_3$ and 88.1 in DMSO-$d_6$) in **2** were significantly shifted downfield compared with C-7 ($\delta_C$ 71.5 in $CDCl_3$) and C-14 ($\delta_C$ 76.8 in $CDCl_3$) in **1**. Thus, the connection from C-7 to C-14 via an oxygen atom was deduced no doubt by the above evidence.

The relative configurations of **2** in rings A and B were determined to be the same as those of **1** and **4**[9b] by analysis of the ROESY spectra. The NOE correlations of H-3/$H_3$-11, H-7/H-13, and H-13/H-20, along with the small coupling constant between H-20 and H-21 ($J_{20/21}$ = 3.5 Hz), implied that they were cofacial and $\alpha$-oriented, whereas the NOE correlations of H-8 with H-5, H-14, and H-19 and of H-16 with H-14 and H-19 suggested that H-5, H-8, H-14, H-16, and H-19 have the same $\beta$-orientations.

Considering the almost complete consistent CD spectra of **1** and **2** (Figure 4), the absolute configuration of **2** was determined as 3*S*, 4*R*, 5*S*, 7*S*, 8*R*, 9*R*, 13*R*, 14*R*, 16*S*, 19*R*, 20*R*, 21*S*.

Phomopchalasin C (**3**), with a molecular formula of $C_{30}H_{39}NO_6$ and 12 degrees of unsaturation, was determined by its HRESIMS. The ion peak at $m/z$ 478 ($[M-O_2+H]^+$) in the positive ESIMS/MS (Figure S43, SI) suggested that **3** should possess a hydroperoxyl group. X-ray crystallographic analysis of **3** confirmed the above deduction. The Flack parameter 0.15(9) and Hooft parameter of 0.16(11) for 1966 Bijvoet pairs[12] allows an explicit assignment of the absolute structure as 3*S*, 4*R*, 7*S*, 8*R*, 9*R*, 16*S*, 18*R*, 21*R* with a probability of 1.000 (Figure 6) (CCDC 1439969).

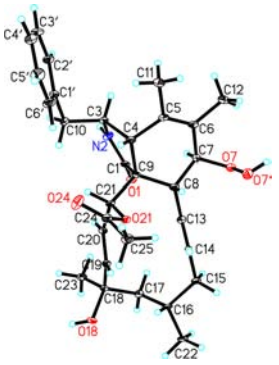
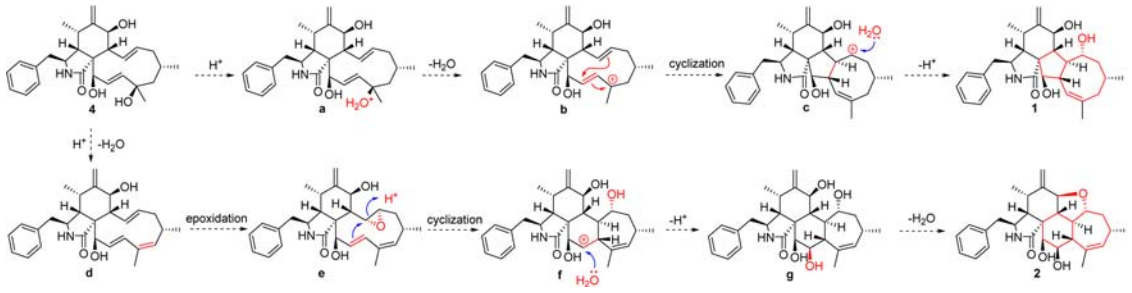



**Figure 6.** X-ray structure of **3**.

Both **1** and **2** might rationally share the same biosynthetic precursor **4** originating from a polyketide chain (octaketide) and an amino acid (phenylalanine) (Scheme 1).[7a] **4** might subsequently involve dehydration, intramolecular rearrangement, and hydroxylation to produce the 5/6/5/8-fused tetracyclic skeleton of **1**. In another pathway, **4** undergoes dehydration, epoxidation, intramolecular nucleophilic addition,


DOI: 10.1021/acs.orglett.6b00214
*Org. Lett.* 2016, 18, 1108−1111

**Scheme 1. Plausible Biosynthetic Pathway of 1 and 2**




and hydroxylation to yield the 5/6/6/7 tetracyclic intermediate **g**. The subsequent intramolecular dehydration affords a tetrahydrofuran ring and leads to the formation of **2**, which possesses a 5/6/6/7/5-fused pentacyclic ring system.

Compounds **1**−**3** were evaluated for in vitro cytotoxicity (*cis*-platin as the positive control), anti-inflammatory (MG132 as the positive control), and antimigratory (cytochalasin D as the positive control) activities (Tables S1−S3 in the SI). **3** displayed moderate cytotoxicity against HL-60, SMMC-7721, and A-549 cell lines ($IC_{50}$s, 14.9, 22.7, and 21.1 $\mu$M, respectively) and inhibitory activity against NO production in LPS-activated RAW 264.7 macrophages with an $IC_{50}$ value of 11.2 $\mu$M. Both **2** and **3** exhibited an antimigratory effect against MDA-MB-231 in vitro with $IC_{50}$ values of 19.1 and 12.7 $\mu$M, respectively.

In summary, phomopchalasins A (**1**) and B (**2**) represent the first examples of cytochalasans featuring unprecedented 5/6/5/8-fused tetracyclic and 5/6/6/7/5-fused pentacyclic skeletons, implying that **1** and **2** are the representatives of two new subclasses of the cytochalasan family with an 11-membered carbocyclic ring. Additionally, **3** possesses a rare peroxide functionality,[8] distinguished from other cytochalasins. Notably, their complex structures with the shared biosynthetic intermediate shed new light on the biosynthesis diversity of the complex cytochalasans, which implied the diversity of the endophytic fungal secondary metabolites from the medicinal plant *I. eriocalyx* var. *laxiflora*.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00214.

Experimental procedures, 1D and 2D NMR, MS, IR, UV, and ECD spectra for compounds **1**−**3** (PDF)
ITS region DNA sequence of *Phomopsis* sp. shj2 (TXT)
X-ray crystal structure for compound **1** (CIF)
X-ray crystal structure for compound **3** (CIF)

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: pujianxin@mail.kib.ac.cn.

### Author Contributions

⊥B.-C.Y. and W.-G.W. contributed equally.


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This project was supported financially by the NSFC-Joint Foundation of Yunnan Province (U1302223), the National Natural Science Foundation of China (Nos. 21322204 and 21402213), the Youth Innovation Promotion Association, and the West Light Foundation of the CAS. (W.-G. Wang).

## ■ REFERENCES


(1) Schumann, J.; Hertweck, C. *J. Am. Chem. Soc.* **2007**, *129*, 9564−9565.

(2) (a) Liu, R.; Gu, Q. Q.; Zhu, W. M.; Cui, C. B.; Fan, G. T.; Fang, Y. C.; Zhu, T. J.; Liu, H. B. *J. Nat. Prod.* **2006**, *69*, 871−875. (b) Zhang, D. W.; Ge, H. L.; Dan, X.; Chen, R. D.; Zou, J. H.; Tao, X. Y.; Dai, J. G. *Org. Lett.* **2013**, *15*, 1674−1677.

(3) (a) Jayasuriya, H.; Herath, K. B.; Ondeyka, J. G.; Polishook, J. D.; Bills, G. F.; Dombrowski, A. W.; Springer, M. S.; Siciliano, S.; Malkowitz, L.; Sanchez, M. *J. Nat. Prod.* **2004**, *67*, 1036−1038. (b) Rochfort, S.; Ford, J.; Ovenden, S.; Wan, S. S.; George, S.; Wildman, H.; Tait, R. M.; Meurer-Grimes, B.; Cox, S.; Coates, J.; Rhodes, D. *J. Antibiot.* **2005**, *58*, 279−283.

(4) Hua, C. Y.; Yang, Y. H.; Sun, L.; Dou, H.; Tan, R. X.; Hou, Y. Y. *Immunobiology* **2013**, *218*, 292−302.

(5) (a) Udagawa, T.; Yuan, J.; Panigrahy, D.; Chang, Y. H.; Shah, J.; D'Amato, R. J. *J. Pharmacol. Exp. Ther.* **2000**, *294*, 421−427. (b) Lee, J.; Yi, J. M.; Kim, H.; Lee, Y. J.; Park, J. S.; Bang, O. S.; Kim, N. S. *Biol. Pharm. Bull.* **2014**, *37*, 6−12.

(6) (a) Rothweiler, W.; Tamm, C. *Experientia* **1966**, *22*, 750−752. (b) Aldridge, D. C.; Armstrong, J. J.; Speake, R. N.; Turner, W. B. *Chem. Commun.* **1967**, 26−27.

(7) (a) Scherlach, K.; Boettger, D.; Remme, N.; Hertweck, C. *Nat. Prod. Rep.* **2010**, *27*, 869−886. (b) Zhu, H. C.; Chen, C. M.; Xue, Y. B.; Tong, Q. Y.; Li, X. N.; Chen, X. T.; Wang, J. P.; Yao, G. M.; Luo, Z. W.; Zhang, Y. H. *Angew. Chem., Int. Ed.* **2015**, *54*, 13374−13378.

(8) Chen, C. M.; Zhu, H. C.; Li, X. N.; Yang, J.; Wang, J. P.; Li, G. T.; Li, Y.; Tong, Q. Y.; Yao, G. M.; Luo, Z. W.; Xue, Y. B.; Zhang, Y. H. *Org. Lett.* **2015**, *17*, 644−647.

(9) (a) Patwardhan, S. A.; Pandey, R. C.; Dev, S.; Pendse, G. S. *Phytochemistry* **1974**, *13*, 1985−1988. (b) Izawa, Y.; Hirose, T.; Shimizu, T.; Koyama, K.; Natori, S. *Tetrahedron* **1989**, *45*, 2323−2335.

(10) (a) Sekita, S.; Yoshihira, K.; Natori, S.; Kuwano, H. *Tetrahedron Lett.* **1973**, *14*, 2109−2112. (b) Silverton, J. V.; Akiyama, T.; Kabuto, C.; Sekita, S.; Yoshihira, K.; Natori, S. *Tetrahedron Lett.* **1976**, *17*, 1349−1350.

(11) (a) Bringmann, G.; Bruhn, T.; Maksimenka, K.; Hemberger, Y. *Eur. J. Org. Chem.* **2009**, *2009*, 2717. (b) Berova, N.; Di Bari, L.; Pescitelli, G. *Chem. Soc. Rev.* **2007**, *36*, 914−931.

(12) (a) Flack, H. D. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **1983**, *39*, 876−881. (b) Hooft, R. W. W.; Straver, L. H.; Spek, A. L. *J. Appl. Crystallogr.* **2008**, *41*, 96−103.




DOI: 10.1021/acs.orglett.6b00214
*Org. Lett.* 2016, 18, 1108−1111