Organic LETTERS

Letter

pubs.acs.org/OrgLett

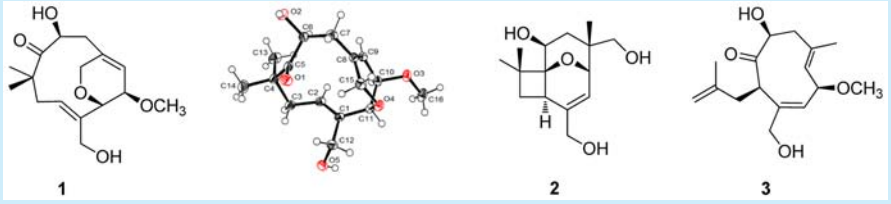
Pestaloporonins: Caryophyllene-Derived Sesquiterpenoids from a Fungicolous Isolate of *Pestalotiopsis* sp.

In Hyun Hwang,[†] Dale C. Swenson,[†] James B. Gloer,*[,†] and Donald T. Wicklow[‡]

[†]Department of Chemistry, University of Iowa, Iowa City, Iowa 52242, United States

[‡]Bacterial Foodborne Pathogens & Mycology Research Unit, Agricultural Research Service, National Center for Agricultural Utilization Research, USDA, Peoria, Illinois 61604, United States

Supporting Information

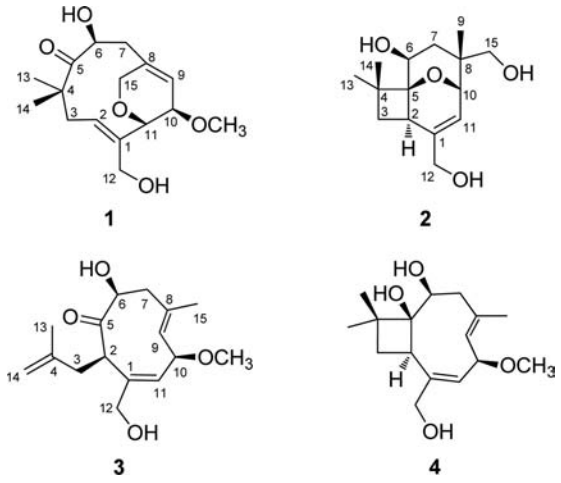


ABSTRACT: Three new sesquiterpenoids (pestaloporonins A–C; **1**–**3**) related to the caryophyllene-derived punctaporonins were isolated from cultures of a fungicolous isolate of *Pestalotiopsis* sp. The structures of **1**–**3** were determined by analysis of NMR and HRMS data, and the structure of **1**, including its absolute configuration, was confirmed by X-ray crystallographic analysis. Compounds **1** and **2** contain new bicyclic and tricyclic ring systems, respectively.

Fungi have contributed significantly to drug discovery as valuable sources of natural products with inspiring novel structures.[1,2] Even so, a large portion of the fungal kingdom remains chemically underexplored.[2,3] Our research continues to focus on studies of targeted fungal niche groups, including mycoparasitic and fungicolous fungi.[4−7] The punctaporonins (originally called punctatins)[8−10] are a series of distinctive caryophyllene/humulene-type metabolites whose first members were reported from *Poronia punctata*. Further punctaporonins and related caryophyllene-type compounds have since been encountered from several other fungal sources, including *Chrysosporium pilosum*,[12] *Cytospora* sp.,[12] *Wallemia sebi*,[13] *Hansfordia sinuosae*,[14] and members of the genus *Pestalotiopsis*.[15−17] These compounds often display intriguing ring system variations that elicit efforts toward total synthesis.[11,18−20] Earlier studies in our laboratory of a fungicolous isolate of *Pestalotiopsis disseminata* (NRRL 36915) afforded several new highly oxidized punctaporonin analogues.[17] In the course of our ongoing studies of fungicolous fungi, three new related analogues having ring systems or skeletons unprecedented among fungal natural products were encountered during chemical investigation of another *Pestalotiopsis* sp. isolate. Details of the isolation and structure elucidation of these metabolites are described here.

A fungicolous *Pestalotiopsis* sp. (MYC-709) was obtained from the surface of a polypore collected in Georgia. The acetonitrile-soluble portion of the crude ethyl acetate extract of MYC-709 fermentation cultures was fractionated using silica gel column chromatography. Repeated purification of the resulting fractions by reversed-phase HPLC led to the isolation of compounds **1**–**3**.

Compound **1**[21] crystallized from dichloromethane and was assigned the formula $C_{16}H_{24}O_5$ (five degrees of unsaturation) on the basis of HRESIMS and NMR data. Analysis of the ^1H and ^{13}C



NMR spectra (Table 1) revealed the presence of two trisubstituted olefin units, two isolated oxymethylene groups, three oxygenated methines, a methoxy group, two singlet methyl groups, and a ketone moiety, accounting for three degrees of unsaturation and requiring a bicyclic structure. Although one of the oxymethine signals (H-11) appeared as a broad singlet with no discernible vicinal coupling, COSY correlations of a second oxymethine (H-10) with H-11 and olefinic proton H-9, as well as HMBC correlations (Figure 1) of H-11 with C-9 and C-10, established the C9−C10−C11 unit in **1**. In addition, HMBC correlations from oxymethylene H_2-15 to C-8, C-9, and C-11,

Received: July 20, 2015
Published: August 19, 2015

DOI: 10.1021/acs.orglett.5b02080
Org. Lett. 2015, 17, 4284−4287

Table 1. ^{1}H and ^{13}C NMR Data for Compounds 1 and 2 in Methanol-d_4

	1		2	
no.	δ_C[a]	δ_H, mult. (J in Hz)[b]	δ_C[c]	δ_H, mult. (J in Hz)[b]
1	137.2		141.4	
2	131.0	5.38, br d (12.8)	33.4	2.41, br t (9)
3a	43.9	2.77, t (12.8)	39.3	1.79, dd (9.4, 8.5)
3b		1.98, br d (12.8)		1.59, t (9.4)
4	48.2		39.1[d]	
5	217.1[c]		81.0	
6	73.1	4.61, dd (11.0, 4.7)	70.0	3.84, t (3.0)
7a	34.6	2.37, m	34.2	1.34, d (3.0)
7b		2.08, t (11.0)		
8	140.9		39.0[d]	
9	122.7	6.05, m	23.5	1.40, s
10	74.0	3.91, d (6.5)	76.6	4.09, d (5.0)
11	73.7	4.46, br s	122.5	5.84, dd (5.0, 1.2)
12a	58.1	4.19, d (12.0)	63.9	3.96, d (13.7)
12b		4.00, d (12.0)		3.94, d (13.7)
13	23.5	1.56, s	24.4	1.26, s
14a	29.3	1.20, s	23.1	1.07, s
14b				
15a	65.2	3.82, dd (18.0, 1.8)	71.3	3.20, d (10.7)
15b		3.44, d (18.0)		3.08, d (10.7)
OCH_3	56.4	3.41, s		

[a]Data collected at 150 MHz. [b]Data collected at 600 MHz. [c]Assignments made using HSQC and HMBC data collected at 600 MHz (^{1}H dimension). [d]Assignments are interchangeable.

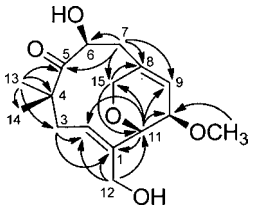


Figure 1. Selected HMBC correlations for **1**.

and from H-11 to C-15, allowed assembly of a six-membered ring via an ether linkage between C-11 and C-15.

The methoxy signal correlated to C-10, thus locating its position. In addition to COSY correlations between oxymethine H-6 and H_2-7, HMBC correlations from H_2-7 to ketone carbon C-5, as well as to C-6, C-8, C-9, and C-15, led to assignment of the C5−C6−C7 unit and its connection to C-8. Linkage of C-5 to quaternary sp^3 carbon C-4, which must bear the two singlet methyl groups, and of C-4 to methylene C-3, was indicated by HMBC correlations of geminal methyl groups H_3-13 and H_3-14 with C-3, C-4, and C-5. HMBC correlations of both C-1/C-2 olefinic carbons with H_2-3 and H-11 required ring closure at C-11 to form a bicyclo[7.2.2] ring system as shown. The second isolated oxymethylene group (CH_2-12) was located at C-1 on the basis of HMBC correlations from H_2-12 to C-1, C-2, and C-11, thereby completing the gross structure of **1**. The carbon skeleton of this new ring system could be envisioned to arise from modification and cyclization of a humulene-type intermediate, a proposed biosynthetic precursor of punctaporonins.[9] A compound with the same carbon skeleton, but lacking the same functionality and the bridging ether linkage (humulane), has been reported from another *Pestalotiopsis* isolate.[16] Given this background, the name pestaloporonin A was proposed for compound **1**.

The C-1/C-2 olefin of **1** was assigned the *E*-configuration on the basis of a NOESY correlation between H-12a and H-3a. The relative configurations at the three sp^3 stereocenters were assigned based on analysis of further NOESY data (Figure 2)

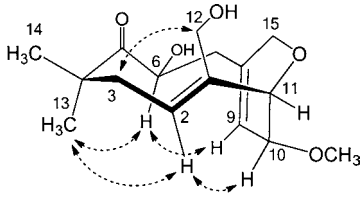


Figure 2. Selected NOESY correlations for **1**.

and later verified by single-crystal X-ray diffraction analysis.[22] Evaluation of the Flack parameter[23] for the X-ray data allowed proposal of the absolute configuration as shown (Figure 3).

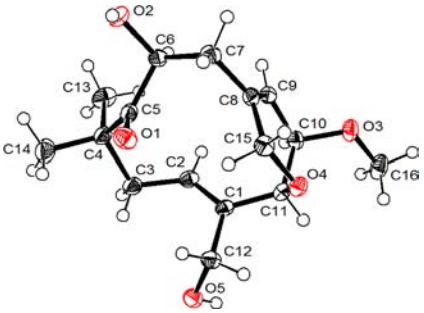


Figure 3. ORTEP representation of **1**.

The molecular formula of compound **2**[24] (pestaloporonin B) was deduced as $C_{15}H_{24}O_4$ (four degrees of unsaturation) by analysis of HRESIMS and NMR data. The ^{1}H NMR spectrum of **2** (Table 1) resembled those of the 6-hydroxypunctaporonins.[10] However, the presence of two isolated oxymethylene units and three upfield singlet methyl groups signaled a skeletal change. HMBC correlations (Figure 4) of geminal methyls H_3-13 and

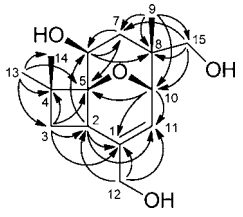


Figure 4. Selected HMBC correlations for **2**.

H_3-14 with C-3, C-4, and C-5, and of H-3a with C-2, C-4, C-5, and C-13, enabled establishment of the C2−C3−C4−C5 unit. The third singlet methyl (H_3-9) correlated with C-7, C-8, C-10, and C-15, forming the C7−C8−C10 unit and linking both CH_3-9 and oxymethylene group CH_2-15 to quaternary carbon C-8. H_2-15 showed correlations to C-7, C-8, C-9, and C-10, reinforcing this connectivity. Correlations observed from H_2-7, a pair of diastereotopic methylene protons that were unresolved in methanol-d_4, to oxygenated quaternary carbon C-5 and oxymethine C-6, and from H-6 to C-7 and C-8, linked the C2−C3−C4−C5 and C7−C8−C10 fragments via C-6. In addition,

DOI: 10.1021/acs.orglett.5b02080
Org. Lett. 2015, 17, 4284−4287

correlations of oxymethine H-10 with olefinic carbons C-1 and C-11 linked C-10 to the C-1/C-11 olefin unit. The second oxymethylene (H_2-12) correlated with C-1, C-2, and C-11, enabling attachment of CH_2-12 to C-1 and resulting in ring closure by linking C-1 and C-2.

Since only one π-bond is present, a tricyclic ring system is required to account for the unsaturation level and was assembled by analysis of further HMBC correlations. A correlation of H-2 with C-6 allowed connection between C-2 and C-5 to form a cyclobutane ring, a feature common to most of the punctaporonins and consistent with the 9.4-Hz geminal coupling for H_2-3.[8,9,17] A strong, key correlation from H-10 to C-5 established the presence of an ether bridge between C-5 and C-10 to complete structure **2**, which represents a second new ring system. A separate set of HMBC data collected in pyridine-d_5 solution were consistent with this assignment.

The relative configuration of **2** was assigned by analysis of NOESY data (Figure 5) and NMR *J*-values. H-2 showed a

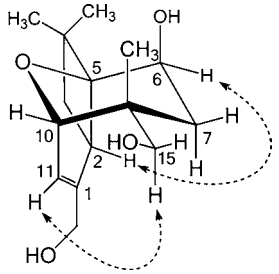


Figure 5. Selected NOESY correlations for **2**.

NOESY correlation to H-6, effectively setting the relative configuration at C-2, C-5, and C-6, requiring a concave arrangement of the two six-membered rings, and placing these two hydrogens on the opposite face relative to the ether bridge. Small vicinal couplings of both C-7 protons with H-6 (J = 3.0 Hz) suggested adoption of a chair conformation for the tetrahydropyran ring as shown in Figure 5, with placement of H-6 in an equatorial orientation. This conformational assignment was fully consistent with energy minimization results (Spartan 10), as well as the NOESY data. A NOESY correlation between olefinic proton H-11 and H-15a allowed assignment of an equatorial orientation for the C-15 oxymethylene group.

The carbon framework of **2** is different from that of **1** and the punctaporonins, requiring a skeletal rearrangement. Caryophyllene itself is susceptible to a variety of skeletal rearrangements.[25] Interestingly, the only prior examples of compounds having this carbon skeleton were reported as major products arising from an apparent Meinwald-type rearrangement of caryophyllene oxide (and dihydrocaryophyllene oxide) observed upon exposure to high temperature in the presence of an acid-washed stationary phase.[26] A mechanistically similar process is envisioned to be involved in formation of **2**. Formation of the C2−C5 bond and rearrangement of the C8−C9−C10 unit in the structure of **2** in a fashion analogous to this literature precedent would give a carbon skeleton identical to that of **1**, and with positions of oxygenation that match. The absolute configuration of **2** was therefore presumed to be analogous to that of **1**.

The molecular formula of compound **3**[27] (pestaloporonin C; $C_{16}H_{24}O_4$) required the same number of unsaturations as **1**, but had one less oxygen atom. ^{13}C NMR data revealed the presence of three olefin units and a ketone carbon, indicating the presence of only one ring in this instance. The ^{1}H NMR spectrum of **3** revealed the absence of the geminal dimethyl groups characteristic of punctaporonin analogues, instead showing signals for a 1,1-disubstituted olefin unit and two olefinic methyl groups. Analysis of COSY and HMBC data enabled recognition of a resemblance to the structure of the known caryophyllene-type metabolite fuscoatrol A (**4**),[28] with data for all positions of the nine-membered ring matching closely except for those associated with C-5. This carbon was clearly a ketone in **3**, as opposed to an oxygenated quaternary sp^3 carbon in **4**, and its location was confirmed by HMBC correlations of ketone carbon C-5 with H-2 and H_2-7. In addition, HMBC correlations of olefinic methyl H_3-13 with the 1,1-disubstituted olefinic carbons (C-14/C-4) and methylene C-3 and COSY correlations between H_2-3 and methine H-2 revealed the presence of a 2-methyl-2-propenyl unit attached to C-2. Thus, **3** differs from fuscoatrol A by cleavage of the C4−C5 bond and the associated four-membered ring characteristic of caryophyllene-type metabolites. Fuscoatrol A (**4**) and its 6-acetyl derivative (pestalotiopsin B)[15] reportedly show two sets of signals due to the presence of conformational isomers in solution,[24] while only a single set of signals was observed for **3**. Presumably, the additional conformational flexibility associated with structure **3** led to this spectroscopic difference. NOESY correlations for the nine-membered ring of **3** match those observed for the major conformer of **4**, suggesting that the relative configurations of these two compounds are analogous. The absolute configuration of **3** was presumed to be analogous to that of **1** as shown. However, disconnection of the cyclobutane unit between C-4 and C-5 is previously undescribed in this class of metabolites, leading to formation of a new carbon skeleton in metabolite **3**. The absolute configurations of other caryophyllene-derived fungal metabolites related to compounds **1**−**3** have been assigned by X-ray crystallographic analysis, Mosher ester analysis, and/or by enantioselective total synthesis, with results in each case being analogous to those assigned here for **1**−**3**.[10,12,17,19]

Reports of bioactivity for members of this class of compounds have been limited. Pestalotiopsin B shows immunosuppressive and cytotoxic activity,[15] while various punctaporonin analogues show modest antibacterial activity and the recently reported punctaporonin K was found to reduce triglycerides and total cholesterol in a cellular assay.[14,17] Compounds **1**−**3** were tested in disk assays[29,30] against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Candida albicans* at 50 μg/disk, but showed no effects in these assays.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02080.

General experimental procedures, details regarding fungal material, extraction, and isolation, ECD spectra for **1** and **3**, X-ray data for **1**, tabulated ^{1}H and ^{13}C NMR data for **3**, and ^{1}H NMR, ^{13}C NMR, and HMBC spectra for **1**−**3** (PDF)

Crystallographic data for **1** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: james-gloer@uiowa.edu.

Notes

The authors declare no competing financial interest.

DOI: 10.1021/acs.orglett.5b02080
Org. Lett. 2015, 17, 4284−4287

■ ACKNOWLEDGMENTS

Financial support was provided by a grant from the National Science Foundation (CHE-1011847). Crystallographic data were collected through the SCrALS (Service Crystallography at Advanced Light Source) program at the Small-Crystal Crystallography Beamline 11.3.1 at the Advanced Light Source (ALS), Lawrence Berkeley National Laboratory. The ALS is supported by the U.S. Department of Energy, Office of Energy Sciences Materials Sciences Division, under Contract DE-AC02-05CH11231.

■ REFERENCES

(1) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2012**, *75*, 311−335 and earlier reports in the series.
(2) Gloer, J. B. Applications of Fungal Ecology in the Search for New Bioactive Natural Products. In *The Mycota*, Vol. *IV*, 2nd ed.; Kubicek, C. P., Druzhinina, I. S., Eds.; Springer-Verlag: New York, 2007; pp 257−283.
(3) Schmit, J. P.; Mueller, G. M. *Biodiversity Conserv.* **2007**, *16*, 99−111.
(4) Neff, S. A.; Lee, S. U.; Asami, Y.; Ahn, J. S.; Oh, H.; Baltrusaitis, J.; Gloer, J. B.; Wicklow, D. T. *J. Nat. Prod.* **2012**, *75*, 464−472.
(5) Greshock, T. J.; Grubbs, A. W.; Jiao, P.; Wicklow, D. T.; Gloer, J. B.; Williams, R. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3573−3577.
(6) Sy, A. A.; Swenson, D. C.; Gloer, J. B.; Wicklow, D. T. *J. Nat. Prod.* **2008**, *71*, 415−419.
(7) Shim, S. H.; Swenson, D. C.; Gloer, J. B.; Wicklow, D. T. *Org. Lett.* **2006**, *8*, 1225−1228.
(8) Poyser, J. P.; Edwards, R. L.; Anderson, J. R.; Hursthouse, M. B.; Walker, N. P.; Sheldrick, G. M.; Whalley, A. J. *J. Antibiot.* **1986**, *39*, 167−169.
(9) Anderson, J. R.; Edwards, R. L.; Poyser, J. P.; Whalley, A. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 823−831.
(10) Sugimura, T.; Paquette, L. A. *J. Am. Chem. Soc.* **1987**, *109*, 3017−3024.
(11) Yang, S. W.; Chan, T. M.; Terracciano, J.; Boehm, E.; Patel, R.; Chen, G.; Loebenberg, D.; Patel, M.; Gullo, V.; Pramanik, B.; Chu, M. *J. Nat. Prod.* **2009**, *72*, 484−487.
(12) Li, Y.; Li, C.-W.; Cui, C.-B.; Liu, Z.-Z.; Che, Y.-S. *Nat. Prod. Bioprospect.* **2012**, *2*, 70−75.
(13) Frank, M.; Kingston, E.; Jeffery, J. C.; Moss, M. O.; Murray, M.; Simpson, T. J.; Sutherland, A. *Tetrahedron Lett.* **1999**, *40*, 133−136.
(14) Wu, Z.; Liu, D.; Proksch, P.; Guo, P.; Lin, W. *Mar. Drugs* **2014**, *12*, 3904−3916.
(15) Pulici, M.; Sugawara, F.; Koshino, H.; Uzawa, J.; Yoshida, S.; Lobkovsky, E.; Clardy, J. *J. Org. Chem.* **1996**, *61*, 2122−2124.
(16) Pulici, M.; Sugawara, F.; Koshino, H.; Okada, G.; Esumi, Y.; Uzawa, J.; Yoshida, S. *Phytochemistry* **1997**, *46*, 313−319.
(17) Deyrup, S. T.; Swenson, D. C.; Gloer, J. B.; Wicklow, D. T. *J. Nat. Prod.* **2006**, *69*, 608−611.
(18) Kende, A. S.; Kaldor, I.; Aslanian, R. *J. Am. Chem. Soc.* **1988**, *110*, 6265−6266.
(19) Takao, K.; Hayakawa, N.; Yamada, R.; Yamaguchi, T.; Saegusa, H.; Uchida, M.; Samejima, S.; Tadano, K. *J. Org. Chem.* **2009**, *74*, 6452−6461.
(20) Fleck, M.; Bach, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 6189−6191.
(21) Pestaloporonin A (**1**): colorless crystals (CH_2Cl_2); mp 151−153 °C; $[\alpha]^{22}_D$ −120 (*c* 0.08, MeOH); CD (211 μM, MeOH) λ_{max} ($\Delta\varepsilon$) 213 (−239), 243 (+6), 313 (−4), and 351 (+1); ^{1}H and ^{13}C NMR data, see Table 1; HMBC data: H-2 → C-11, 12; H-3a → C-1, 2, 4, 13, 14; H-3b → C-1, 2, 4, 5; H-6 → C-7; H-7a → C-5, 6, 8, 9, 15; H-7b → C-5, 6, 8, 9, 15; H-9 → C-7, 11, 15; H-10 → C-8, 9, 11, OCH_3; H-11 → C-1, 2, 9, 10, 12, 15; H-12a → C-1, 2, 11; H-12b → C-1, 2, 11; H_3-13 → C-3, 4, 5, 14; H_3-14 → C-3, 4, 5, 13; H-15a → C-8, 9, 11; H-15b → C-8, 9; NOESY data: H-2 ↔ H-10, 13; H-3a ↔ H-3b, 12a, 14; H-3b ↔ H-3a, 13; H-6 ↔ H-7a, 9, 13; H-7a ↔ H-6, 7b, 9; H-7b ↔ H-7a, 15a; H-9 ↔ H-6, 7a, 10, OCH_3; H-10 ↔ H-2, 9, 11, OCH_3; H-11 ↔ H-10, 12b, OCH_3; H-12a ↔ H-3a, 12b; H-12b ↔ H-11, 12a, 15b; H_3-13 ↔ H-2, 3b, 6; H_3-14 ↔ H-3a; H-15a ↔ H-7b, 15b; H-15b ↔ H-12b, 15a; HRESIMS *m*/*z* 295.1533 $[M - H]^-$ (calcd for $C_{16}H_{23}O_5$, 295.1545).
(22) Crystallographic data for compound **1** have been deposited with the Cambridge Crystallographic Data Centre (deposition number CCDC 1017886). Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: + 44-(0) 1223-336033; or e-mail: deposit@ccdc.cam.ac.uk).
(23) Flack, H. D.; Bernardinelli, G. *Chirality* **2008**, *20*, 681−690.
(24) Pestaloporonin B (**2**): white amorphous solid; $[\alpha]^{22}_D$ −9 (*c* 0.07, MeOH); ^{1}H and ^{13}C NMR data, see Table 1; HMBC data: H-2 → C-1, 3, 6, 11, 12; H-3a → C-2, 4, 5, 6*, 13; H-3b → C-1, 2, 4, 14; H-6 → C-7, 8; H_2-7 → C-5, 6, 8, 9, 10; H-9 → 7, 8, 10, 15; H-10 → C-1, 5, 7, 8, 9, 11; H-11 → C-2, 10, 12; H_2-12 → C-1, 2, 11; H_3-13 → C-3, 4, 5, 14; H_3-14 → C-3, 4, 5, 13; H-15a → C-7, 8, 9, 10; H-15b → C-7, 8, 9, 10; *Four-bond correlation; NOESY data: H-2 ↔ H-3a, 6, 12, 13; H-3a ↔ H-2, 3b; H-3b ↔ H-3a, 14; H-6 ↔ H-2, 7; H_2-7 ↔ H-6; H-9 ↔ H-10; H-10 ↔ H-9, 11; H-11 ↔ H-10, 12, 15a; H_2-12 ↔ H-2, 11; H_3-13 ↔ H-2; H_3-14 ↔ H-3b; H-15a ↔ H-11, 15b; H-15b ↔ H-15a; HRESIMS *m*/*z* 291.1564 $[M + Na]^+$ (calcd for $C_{15}H_{24}O_4Na$, 291.1572).
(25) Collado, I. G.; Aleu, J.; Macias-Sanchez, A. J.; Hernandez-Galan, R. *J. Nat. Prod.* **1994**, *57*, 738−746.
(26) Nigam, I. C.; Levi, L. *J. Org. Chem.* **1965**, *30*, 653−654.
(27) Pestaloporonin C (**3**): white amorphous solid; $[\alpha]^{22}_D$ +86 (*c* 0.14, MeOH); CD (MeOH) λ_{max} ($\Delta\varepsilon$) 205 (−119), 240 (+11), 259 (+6), and 296 (+21); ^{1}H and ^{13}C NMR data, see Table S2; HMBC data: H-2 → C-1, 3, 4, 5, 11, 12; H_2-3 → C-1, 2, 4, 5, 13, 14; H-6 → C-7; H-7a → C-5, 6, 8, 9, 15; H-7b → C-5, 6, 8, 9, 15; H-9 → 7, 10, 11, 15; H-10 → C-8, 11, OCH_3; H-11 → C-2, 12; H-12a → C-1, 11; H-12b → C-1, 2, 11; H_3-13 → C-3, 4, 14; H-14a → C-3, 4, 13; H-14b → C-3, 4, 13; H_3-15 → C-7, 8, 9; OCH_3 → C-10; NOESY data: H-2 ↔ H-3, 6, 10, 13, 14b, 15; H_2-3 ↔ H-2, 12a, 13, 14b; H-6 ↔ H-2, 7a; H-7a ↔ H-6, 7b, 15; H-7b ↔ H-7a, 9; H-9 ↔ H-7b, 10, OCH_3; H-10 ↔ H-2, 9, 11, 15, OCH_3; H-11 ↔ H-10, 12b; H-12a ↔ H-3, 12b; H-12b ↔ H-11, 12a; H_3-13 ↔ H-2, 3, 14a; H-14a ↔ H-13, 14b; H-14b ↔ H-2, 3, 14a; H_3-15 ↔ H-2, 7a, 10, OCH_3; OCH_3 ↔ H-9, 10, 15; HRESIMS *m*/*z* 303.1564 $[M + Na]^+$ (calcd for $C_{16}H_{24}O_4Na$, 303.1572), 583.3232 $[2\ M + Na]^+$ (calcd for $C_{32}H_{48}O_8Na$, 583.3247).
(28) Smetanina, O. F.; Kuznetsova, T. A.; Gerasimenko, A. V.; Kalinovsky, A. I.; Pivkin, M. V.; Dmitrenok, P. C.; Elyakov, G. B. *Russ. Chem. Bull.* **2004**, *53*, 2643−2646.
(29) Bauer, A. W.; Kirby, W. M. M.; Sherris, J. C.; Turck, M. *Am. J. Clin. Pathol.* **1966**, *45*, 493−496.
(30) Wagenaar, M. M.; Clardy, J. *J. Nat. Prod.* **2001**, *64*, 1006−1009.

DOI: 10.1021/acs.orglett.5b02080
Org. Lett. 2015, 17, 4284−4287