Organic LETTERS

Letter

pubs.acs.org/OrgLett

Total Synthesis and Structure Revision of (−)-Siphonodictyal B and Its Biomimetic Conversion into (+)-Liphagal

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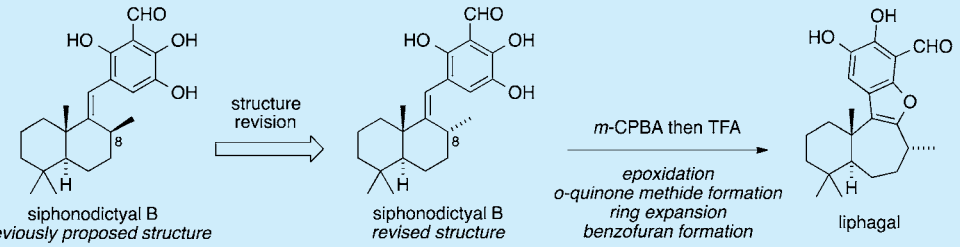
Supporting Information



ABSTRACT: The structure of siphonodictyal B has been reassigned on the basis of the total synthesis of both possible C-8 epimers. The revised structure of siphonodictyal B was converted into liphagal by acid catalyzed rearrangement of a proposed epoxide intermediate. This biomimetic cascade features a succession of four distinct reactions (epoxidation, *o*-quinone methide formation, ring expansion, and benzofuran formation) that occur in a one-pot operation under mild conditions. During these studies we also isolated a surprisingly stable *o*-quinone methide that supports our mechanistic proposal for liphagal biosynthesis.

Siphonodictyal B is a marine sponge derived meroterpenoid with a rather chequered history (Figure 1). Its structure was

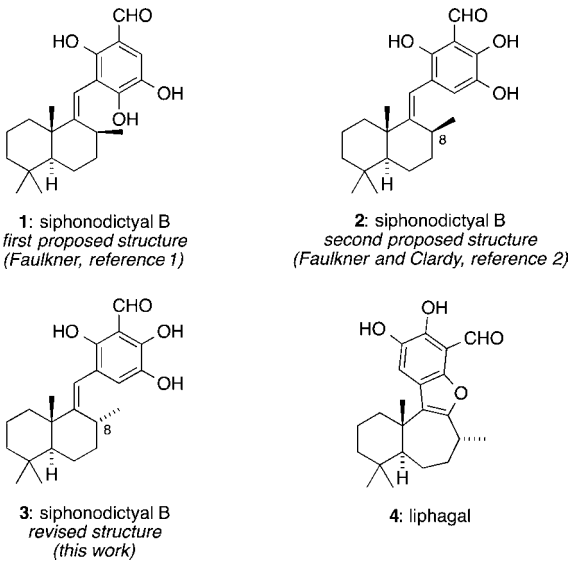


Figure 1. Proposed structures of siphonodictyal B and liphagal.

first reported as **1** by Faulkner and co-workers in 1981, who isolated the compound from *Aka coralliphaga* (otherwise known as *Siphonodictyon coralliphagum*).[1] The structure of siphonodictyal B was then revised to **2** by Faulkner and Clardy in 1986, primarily on the basis of 2D NMR experiments of a dimethoxy derivative that proved the substitution pattern of the aromatic polyketide fragment had been incorrectly assigned in the original report.[2] Siphonodocityal B has also been isolated from *Aka coralliphaga* by Köck and co-workers, alongside some sulfated derivatives, siphonodictyals B1, B2, and B3.[3] However, on the basis of our synthetic work and re-evaluation of published NMR data, we herein demonstrate the correct structure of siphonodictyal B to be **3** (i.e., the C-8 epimer of Faulkner and Clardy's revised structure **2**).

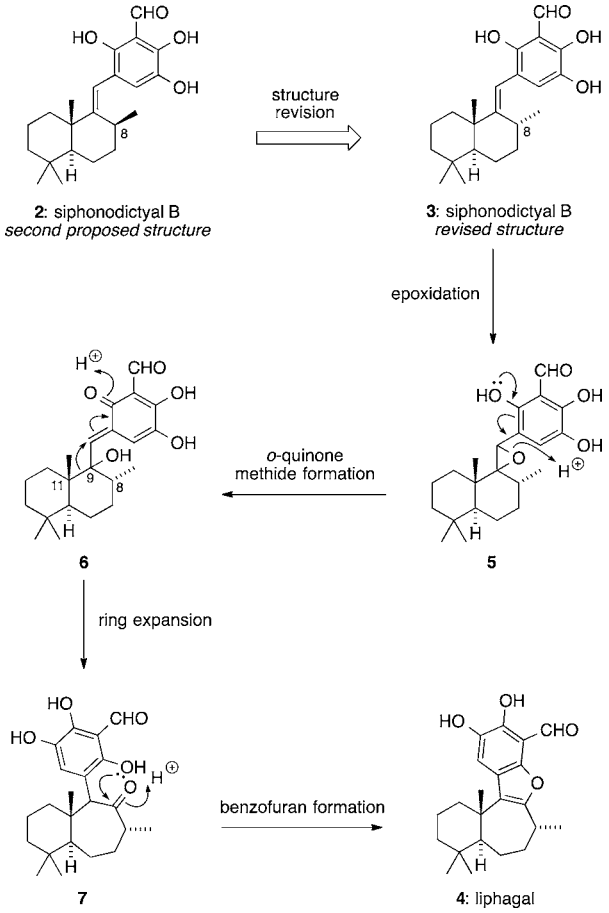
Our interest in the structure of siphonodictyal B stems from speculation on the biosynthesis of liphagal (**4**), a meroterpenoid also isolated from *Aka coralliphaga* by Andersen and co-workers.[4] Liphagal has an unusual 6−7 terpene ring system fused to an electron-rich benzofuran, which Andersen proposed could be formed by two alternative biosynthetic pathways. The first biosynthetic proposal involves a direct cyclization of a benzofuran-polyene to form the 6−7 ring system. This pathway has inspired total syntheses of liphagal by both Andersen[4] and Mehta.[5] The second proposed biosynthesis features a ring expansion of the 6−6 ring system of siphonodictyal B to form the unusual 6−7 ring system of liphagal, as outlined in Scheme 1. We believe that this second hypothesis is more likely as both natural products are produced by the same *Aka coralliphaga* marine sponge. This possible biosynthetic relationship is the first clue that a structure revision of siphonodictyal B (at C-8) might be necessary.

In detail, we believe that the probable biosynthesis of liphagal begins with epoxidation of siphonodictyal B (**3**, the revised structure) to give **5**, which could undergo ring opening to form the *o*-quinone methide **6**. This reactive intermediate could then

Received: July 14, 2015
Published: August 21, 2015

DOI: 10.1021/acs.orglett.5b01973
Org. Lett. 2015, 17, 4228−4231

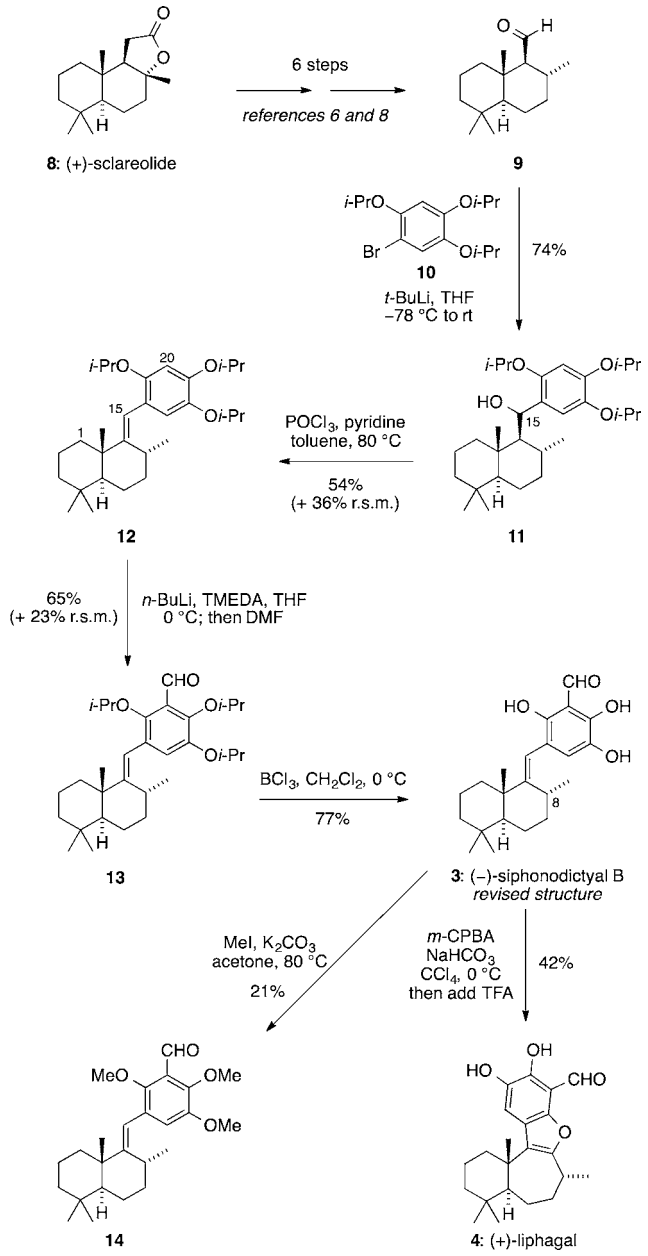
Scheme 1. Proposed Ring Expansion Pathway for the Biosynthesis of Liphagal from Siphonodictyal B



undergo a ring expansion reaction, with selective migration of the more electron-rich C-9−C-11 bond in preference to the C-8−C-9 bond, to give cycloheptanone **7**, followed by benzofuran formation to give liphagal (**4**). Andersen and co-workers proposed a biosynthesis starting from structure **2**, with a late stage C-8 epimerization of the cycloheptanone intermediate required to form liphagal. This attractive biosynthetic proposal has inspired related biomimetic syntheses of liphagal by our group,[6] the Alvarez-Manzaneda group,[7] and the Katoh group.[8] Liphagal has also been synthesized by Stoltz according to a nonbiomimetic strategy,[9] and several synthetic studies toward analogues of liphagal have been reported.[10] In addition to its unusual structure and intriguing biosynthetic origin, liphagal has also attracted synthetic attention due to its potent biological activity as a selective inhibitor of the α isoform of phosphoinositide 3-kinase (PI3Kα).[11]

Our primary aim in this project was to synthesize compound **3** (which we originally considered to be the C-8 epimer of siphonodictyal B) and attempt to convert it directly into liphagal (**4**) via a one-pot cascade reaction following the mechanism delineated in Scheme 1.[12] The Katoh group indirectly achieved a similar transformation via a three step sequence involving a protected substrate.[8] We started our synthesis of **3** (Scheme 2) from (+)-sclareolide (**8**), an inexpensive chiral pool starting material that has found wide application in the synthesis of terpenoid natural products.[13] Conversion of **8** into aldehyde **9** was achieved in six steps according to published procedures.[6,8] Addition of the aryllithium species derived from aryl bromide

Scheme 2. Synthesis of the Revised Structure of Siphonodictyal B and Its Biomimetic Conversion into Liphagal



10[14] to aldehyde **9** then gave benzylic alcohol **11** in 74% yield as a single diastereomer, although the C-15 relative configuration was not determined. Dehydration of **11** by treatment with $POCl_3$ and pyridine gave alkene **12** in 54% yield. The *E* geometry of the alkene of **12** (and all subsequent compounds) was proven by a NOESY interaction between H-1 and H-15. Formation of aldehyde **13** was then achieved by *ortho*-lithiation of **12** at C-20 followed by quenching with DMF. Finally, removal of the isopropyl ether protecting groups was accomplished using BCl_3 to give **3** in 77% yield. We next investigated a biomimetic conversion of **3** into liphagal (**4**), and we were delighted to find that exposure of **3** to *m*-CPBA followed by TFA in CCl_4 at 0 °C gave **4** in 42% yield as the sole isolable product. The use of CCl_4 as solvent was found to significantly increase the yield of this reaction compared to more common solvents such as CH_2Cl_2 and THF.

DOI: 10.1021/acs.orglett.5b01973
Org. Lett. 2015, 17, 4228−4231

Comparison of the ^{1}H and ^{13}C NMR spectra of synthetic **3** with the siphonodictyal B NMR data published by Köck (recorded in DMSO-d_6 and $CDCl_3$) showed excellent agreement,[3] indicating that the structure of siphonodictyal B should be revised to be **3**. The original assignment of the C-8 relative configuration of siphonodictyal B was made by Faulkner via analysis of the coupling constants of H-8, whereas our assignment is secured by clearly observed NOESY correlations between H-8 and Me-14, and between H-1 and H-15 (Figure 2).

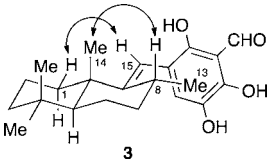
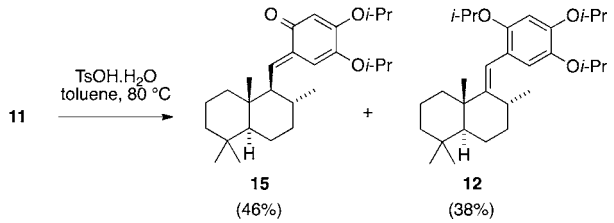


Figure 2. Key NOESY correlations of the revised structure of siphonodictyal B.

Furthermore, the direct conversion of **3** into liphagal is good evidence that our assignment of the C-8 configuration of **3** is correct. Unfortunately, our ^{1}H NMR data for siphonodictyal B did not quite agree with the originally published data of Faulkner (which consists only of partial ^{1}H NMR data in CD_3OD).[1] However, methylation of **3** according to Faulkner's procedure gave the trimethoxy derivative **14**, which perfectly matched the ^{1}H and ^{13}C NMR data of the corresponding derivative synthesized from natural siphonodictyal B. The optical rotation of naturally occurring siphonodictyal B has not previously been reported. However, we predict that our synthetic (−)-siphonodictyal B is the natural enantiomer as it has the same absolute configuration as (+)-liphagal, which is coisolated from the same *Aka coralliphaga* marine sponge.

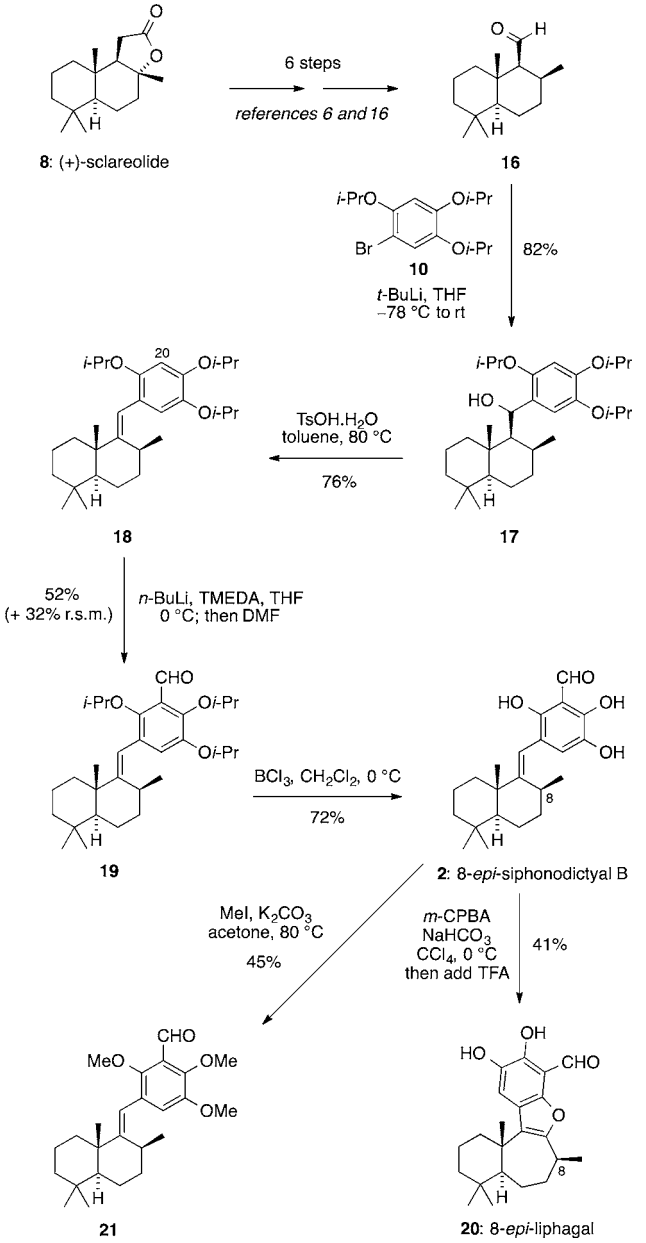
During the course of optimizing dehydration conditions for the conversion of **11** into **12**, we often observed the formation of a stable *o*-quinone methide **15** (Scheme 3).[15] The unusual stability of this compound suggests that a similar intermediate could be involved in liphagal biosynthesis, as we proposed in Scheme 1.

Scheme 3. Synthesis of a Stable *o*-Quinone Methide



To add further evidence in favor of the structure revision of siphonodictyal B, we also synthesized the proposed structure of Faulkner and Clardy,[2] i.e., compound **2** (Scheme 4). Aldehyde **16** was synthesized in six steps from (+)-sclareolide (**8**) according to previously published procedures.[6,16] Treatment of **16** with the aryllithium species derived from aryl bromide **10** gave **17** as an inseparable mixture of two diastereomers. Dehydration of **17** then gave alkene **18**, which was formylated at C-20 to give aldehyde **19**. Deprotection of **19** using BCl_3 then gave **2**. NMR data for **2** did not agree with the published siphonodictyal B data of Faulkner[1] or Köck,[3] and neither did the NMR data of the trimethoxy derivative **21** match the data for the trimethoxy

Scheme 4. Synthesis of the Previously Proposed Structure of Siphonodictyal B and Its Conversion into 8-*epi*-Liphagal



derivative of siphonodictyal B published by Faulkner.[1] This adds further weight to our revision of the true structure of siphonodictyal B to compound **3**. We also converted **2** (which we now refer to as 8-*epi*-siphonodictyal B) into 8-*epi*-liphagal (**20**) using our established ring expansion conditions.

Comparison of the ^{1}H NMR spectra of siphonodictyal B (**3**) and 8-*epi*-siphonodictyal B (**2**) with the related marine sponge meroterpenoids deoxyspongiaquinol[17] (**22**) and wiedendiol[18] (**23**) indicates that the configuration at C-8 strongly influences the chemical shift of Me-13 (Figure 3). The equatorial Me-13 group of **3** is more shielded by the adjacent aromatic ring and has a chemical shift of 0.77 ppm, whereas the axial Me-13 groups of **2**, **22**, and **23** appear in the range 1.03−1.16 ppm. This trend, which is followed in all our synthetic intermediates, also suggests that the C-8 configuration of the sulfated natural products siphonodictyals B1, B2, and B3 (coisolated with siphonodictyal B from

DOI: 10.1021/acs.orglett.5b01973
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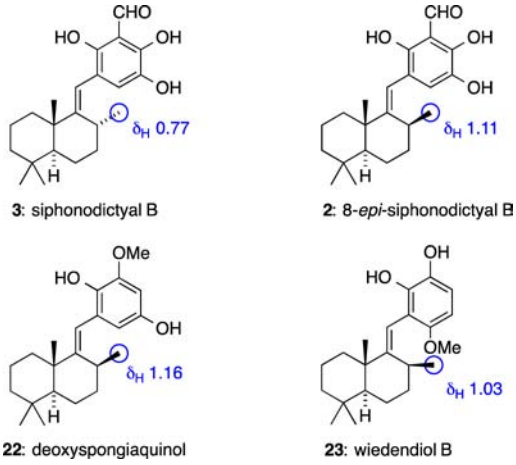

Figure 3. Comparison of the chemical shift of the methyl group attached to C-8 of related meroterpenoid natural products (^{1}H spectra in $CDCl_3$).

Aka coralliphaga by Köck and co-workers[3]) should be reinvestigated.

In conclusion, we have synthesized the two possible C-8 epimers of the marine sponge meroterpenoid siphonodictyal B, and on the basis of NMR data we conclude that the true structure of the natural product is **3**, rather than the previously proposed **2**. This neatly correlates with our proposal that structure **3** is the biosynthetic precursor of liphagal (**4**), an unusual natural product found in the same *Aka coralliphaga* marine sponge as siphonodictyal B. This biosynthetic relationship was further strengthened by our direct, biomimetic conversion of siphonodictyal B (**3**) into liphagal (**4**) in a one-pot cascade reaction that occurs under simple reaction conditions. Overall, this project shows the value of biosynthetic speculation both in guiding the structure revision of natural products and in the development of novel cascade reactions.[19]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01973.

Experimental procedures and full characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Australian Research Council for financial support in the form of a Discovery Project (DP130101827) and a Discovery Early Career Researcher Award (DE130100689) to J.H.G.

■ REFERENCES

(1) Sullivan, B.; Djura, P.; McIntyre, D. E.; Faulkner, D. J. *Tetrahedron* **1981**, *37*, 979.
(2) Sullivan, B. W.; Faulkner, D. J.; Matsumoto, G. K.; He, C.-H.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 4568.
(3) (a) Grube, A.; Assmann, M.; Lichte, E.; Sasse, F.; Pawlik, J. R.; Köck, M. *J. Nat. Prod.* **2007**, *70*, 504. (b) Gothel, Q.; Köck, M. *Beilstein J. Org. Chem.* **2014**, *10*, 613.
(4) Marion, F.; Williams, D. E.; Patrick, B. O.; Hollander, I.; Mallon, R.; Kim, S. C.; Roll, D. M.; Feldberg, L.; Van Soest, R.; Andersen, R. J. *Org. Lett.* **2006**, *8*, 321.
(5) Mehta, G.; Likhite, N. S.; Kumar, C. S. A. *Tetrahedron Lett.* **2009**, *50*, 5260.
(6) George, J. H.; Baldwin, J. E.; Adlington, R. M. *Org. Lett.* **2010**, *12*, 2394.
(7) Alvarez-Manzaneda, E.; Chahboun, R.; Alvarez, E.; Cano, M. J.; Haidour, A.; Alvarez-Manzaneda, R. *Org. Lett.* **2010**, *12*, 4450.
(8) Kamishima, T.; Kikuchi, T.; Narita, K.; Katoh, T. *Eur. J. Org. Chem.* **2014**, *2014*, 3443.
(9) Day, J. J.; McFadden, R. M.; Virgil, S. C.; Kolding, H.; Alleva, J. L.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 6814.
(10) (a) Zhang, Y.; Oblak, E. Z.; Bolstad, E. S. D.; Anderson, A. C.; Jasinski, J. P.; Butcher, R. J.; Wright, D. L. *Tetrahedron Lett.* **2010**, *51*, 6120. (b) Pereira, A. R.; Strangman, W. K.; Marion, F.; Feldberg, L.; Roll, D.; Mallon, R.; Hollander, I.; Andersen, R. J. *J. Med. Chem.* **2010**, *53*, 8523. (c) Pepper, H. P.; Kuan, K. K. W.; George, J. H. *Org. Lett.* **2012**, *14*, 1524. (d) Zhang, J.; Li, L.; Wang, Y.; Wang, W.; Xue, J.; Li, Y. *Org. Lett.* **2012**, *14*, 4528. (e) Laplace, D. R.; Verbraeken, B.; Van Hecke, K.; Winne, J. M. *Chem. - Eur. J.* **2014**, *20*, 253.
(11) For a review of PI3K inhibitors, see: Sundstrom, T. J.; Anderson, A. C.; Wright, D. L. *Org. Biomol. Chem.* **2009**, *7*, 840.
(12) For previous studies towards the synthesis of siphonodictyal B and related compounds, see: Bernet, A.; Seifert, K. *Helv. Chim. Acta* **2006**, *89*, 784.
(13) For a review of the use of (+)-sclareolide in the synthesis of terpenoid natural products, see: Frija, L. M. T.; Frade, R. F. M.; Afonso, C. A. M. *Chem. Rev.* **2011**, *111*, 4418.
(14) Pla, D.; Albericio, F.; Alvarez, M. *Eur. J. Org. Chem.* **2007**, *2007*, 1921.
(15) For examples of similar stable *o*-quinone methides, see: (a) Armstrong, V.; Barrero, A. F.; Alvarez-Manzaneda, E. J.; Cortes, M.; Sepulveda, B. *J. Nat. Prod.* **2003**, *66*, 1382. (b) Laube, T.; Bernet, A.; Dahse, H.-M.; Jackson, I. D.; Seifert, K. *Bioorg. Med. Chem.* **2009**, *17*, 1422.
(16) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R. *Tetrahedron Lett.* **1997**, *38*, 8101.
(17) (a) Göhl, M.; Seifert, K. *Eur. J. Org. Chem.* **2014**, *2014*, 6975. (b) Urban, S.; Capon, R. J. *Aust. J. Chem.* **1996**, *49*, 611.
(18) Coval, S. J.; Conover, M. A.; Mierzwa, R.; King, A.; Puar, M. S.; Phife, D. W.; Pai, J.-K.; Burrier, R. E.; Ahn, H.-S.; Boykow, G. C.; Patel, M.; Pomponi, S. A. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 605.
(19) For further recent examples of biosynthetically guided structure revisions of natural products, see: (a) Spence, J. T. J.; George, J. H. *Org. Lett.* **2011**, *13*, 5318. (b) Brown, P. D.; Willis, A. C.; Sherburn, M. S.; Lawrence, A. L. *Angew. Chem., Int. Ed.* **2013**, *52*, 13273. (c) Calvert, M. B.; Sperry, J. *Chem. Commun.* **2015**, *51*, 6202.

DOI: 10.1021/acs.orglett.5b01973
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