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Synthesis and Structural Revision of Phomopsin B, a Novel Polyketide Carrying a 10-Membered Cyclic-Ether Ring

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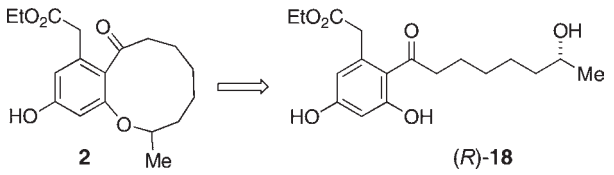
ABSTRACT



Total synthesis of the proposed structure 2 for phomopsin B was achieved by using an intramolecular olefin metathesis as a key step. The spectral data, however, did not match with those of the natural product reported. Re-examination of the reported NMR data led to the structural revision of phomopsin B to known dothiorelone A 18. The *R* configuration of dothiorelone A was determined by total synthesis through a cross-metathesis with a chiral olefin 19.

In 2008, Lin et al. isolated novel aromatic polyketides from the mangrove endophytic fungus, *Phomopsis* sp. ZSU-H76 obtained from the South China Sea, and named them phomopsins A and B.[1] Their structures were elucidated by spectroscopic methods, mainly by the 1D and 2D NMR spectroscopic technique, to be **1** and **2** possessing an oxonine or oxecine ring fused to resorcinol, respectively, as shown in Figure 1. Although there are many macrocyclic lactones such as zearalenone in nature,[2] medium-sized cyclic phenol ethers such as **1** and **2** were virtually unknown.[3] In connection with our studies on heterocyclic natural products,[4] the unique structure stimulated our interest and the total synthesis was planned. Described herein is the first total synthesis of phomopsin B that dictates revision of the formula **2** to **18**.

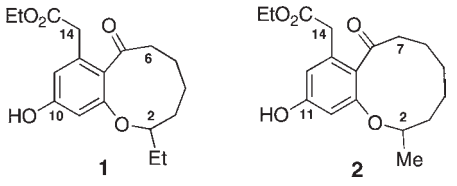


Figure 1. Structures of phomopsins A (**1**) and B (**2**).

In the synthetic study of this unique molecule, construction of the oxecine skeleton[5] fused to ethyl *m*-hydroxyphenylacetate

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(1) Huang, Z.; Cai, X.; Shao, C.; She, Z.; Xia, X.; Chen, Y.; Yang, J.; Zhou, S.; Lin, Y. *Phytochemistry* **2008**, *69*, 1604–1608.

(2) For review, see: (a) Betina, V. *Zearalenone and its Derivatives in Mycotoxins: Chemical, Biological and Environmental Aspects*; Elsevier: Amsterdam, 1989. (b) Shipchandler, M. T. *Heterocycles* **1975**, *3*, 471–520 and references cited therein.

(3) (a) Raduranin A: Asakawa, Y.; Toyota, M.; Takemoto, T. *Phytochemistry* **1978**, *17*, 2005–2010. (b) Helianane: Harrison, B.; Crews, P. *J. Org. Chem.* **1997**, *62*, 2646–2648. (c) Halogenated derivatives of helianane: Martín, M. J.; Berrué, F.; Amade, P.; Fernández, R.; Francesch, A.; Reyes, F.; Cuevas, C. *J. Nat. Prod.* **2005**, *68*, 1554–1555.

(4) (a) Izuchi, Y.; Kanomata, N.; Koshino, H.; Hongo, Y.; Nakata, T.; Takahashi, S. *Tetrahedron: Asymmetry* **2011**, *22*, 246–251. (b) Ye, Y.-Q.; Koshino, H.; Onose, J.; Yoshikawa, K.; Abe, N.; Takahashi, S. *Org. Lett.* **2009**, *11*, 5074–5077. (c) Takahashi, S.; Takahashi, R.; Hongo, Y.; Koshino, H.; Yamaguchi, K.; Miyagi, T. *J. Org. Chem.* **2009**, *74*, 6382–6385. (d) Nishii, Y.; Higa, T.; Takahashi, S.; Nakata, T. *Tetrahedron Lett.* **2009**, *50*, 3597–3601.

(5) Simple medium-sized ring ethers fused to an aromatic ring were prepared by an intramolecular Williamson reaction of a phenol derivative tethering an alkyl chain with a halide atom at the terminal position. However, the method involved a terminal olefin obtained by E_2 elimination as a side product. See: (a) Illuminati, G; Mandolini, L; Masci, B. *J. Org. Chem.* **1974**, *39*, 2598–2600. (b) Mandolini, L.; Masci, B. *J. Org. Chem.* **1977**, *42*, 2840–2843.

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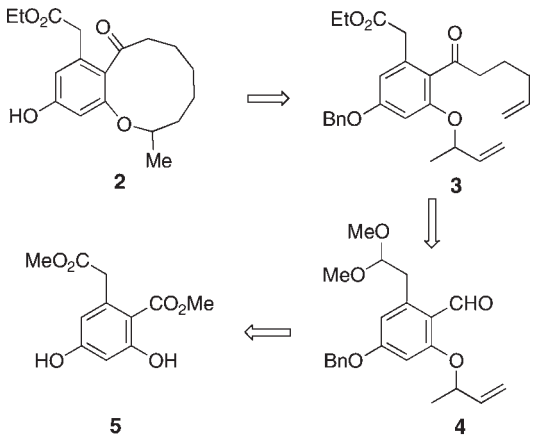
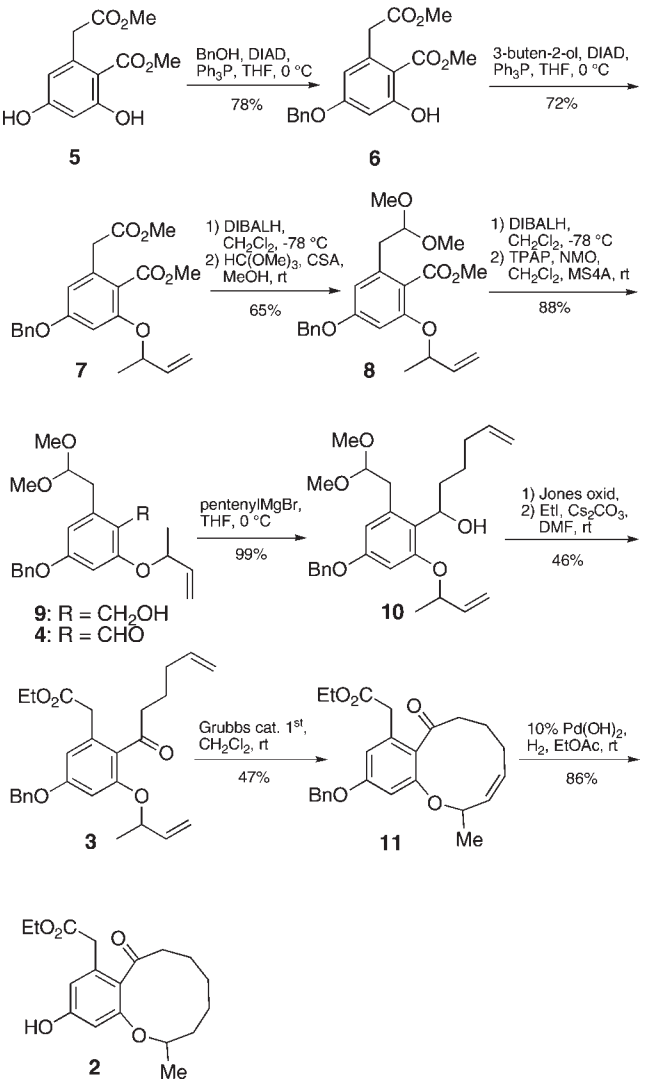
is the main problem throughout the synthetic course. We planned to utilize an intramolecular olefin metathesis reaction[6] as a key step to build up the skeleton and designed a synthetic strategy as shown in Scheme 1. Cleavage of the 10-membered ring in the target molecule leads to the tetrasubstituted benzene **3**. Releasing the pentenyl group and changing the oxidation level can revert **3** back to the benzaldehyde derivative **4**. This would be synthesized from methyl benzoate derivative **5**[7] through an *O*-protection and selective reduction. These retrosynthetic analyses allowed us to prepare a real structure **18** of phomopsin B by exchanging the *O*-alkyl group at the C-2 position of **5**.

Scheme 1



Synthesis of the proposed structure **2** began with selective *O*-alkylation of 2,4-dihydroxybenzoic acid derivative **5** (Scheme 2). Thus, **5** was initially treated with 1.0 equiv of benzylalcohol in the presence of diisopropyl azodicarboxylate (1.0 equiv)[8] and triphenylphosphine (1.0 equiv) to afford 4-*O*-benzyl derivative **6**. Second *O*-alkylation into the 2-position of **6** was performed by using 3-buten-2-ol in the presence of a large amount of Mitsunobu reagent to provide **7** in good yield. For our purpose, a chain elongation at the unsaturated carbonyl group was required. However, discrimination of the two carbonyl group in **7** by conventional methods was difficult. For example, MnO_2 or $BaMnO_4$ oxidation of a diol obtained from DIBALH reduction of **7** resulted in a mixture of a desired hydroxy aldehyde, its cyclized hemiacetal, and the corresponding lactone in a variety of ratios. Attempts to prepare[9] the corresponding homophthalic anhydride or isocoumarin derivative from **7** and their use for the chain elongation reaction also gave unsatisfactory results. Therefore, the saturated carbonyl was tentatively reduced and

Scheme 2



the formyl group in the resulting unstable compound was protected as dimethylacetal to give **8**. This was transformed into **4** via **9** through a reduction−oxidation process. The chain elongation reaction from **4** was performed by the action of a Grignard reagent prepared from 4-pentenyl bromide to provide alcohol **10** in good yield. Jones oxidation of **10** was accompanied by hydrolysis of the dimethylacetal moiety, and upon ethylation the resulting carboxylic acid led to ethyl ester **3**. An intramolecular olefin metathesis of **3** was affected by the action of a first generation Grubbs catalyst (20 mol %) in dichloromethane under diluted conditions (4 mM) at rt to give oxecine **11**[10] in 47% yield along with open-chain dimers (21%).[12] Although more diluted conditions were utilized,

(6) (a) Grubbs, R. H. *Handbook of Metathesis*, Vols. 1−3; Wiley-VCH: 2003. (b) Synthesis of (±)-helianane with a 8-membered ring via olefin metathesis was reported. See: Stefinovic, M.; Snieckus, V. *J. Org. Chem.* **1998**, *63*, 2808–2809.

(7) Langer, P.; Kracke, B. *Tetrahedron Lett.* **2000**, *41*, 4545–4547.

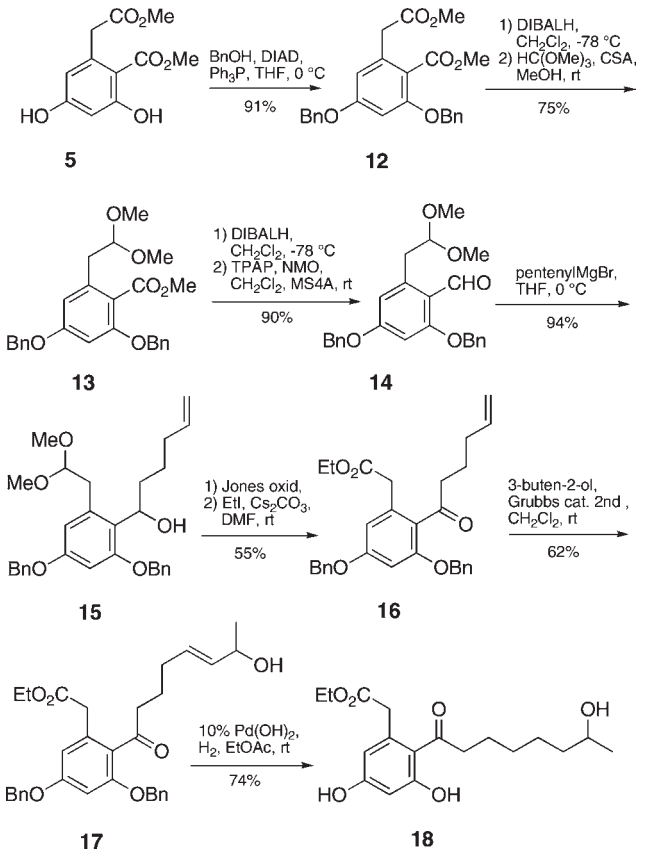
(8) Mitsunobu, O. *Synthesis* **1981**, 1–28.

(9) (a) Watanabe, M.; Date, M.; Furukawa, S. *Chem. Pharm. Bull.* **1989**, *37*, 292–297. (b) Kim, S.; Fan, G.-J.; Lee, J.; Lee, J. J.; Kim, D. *J. Org. Chem.* **2002**, *67*, 3127–3130. (b) Bauta, W. E.; Lovett, D. P.; Cantrell, W. R.; Burke, B. D. *J. Org. Chem.* **2003**, *68*, 5967–5973.

(10) The *Z*-geometry was determined by the coupling constant value (J = 11 Hz) of two olefinic protons in the ^{1}H NMR spectra in C_6D_6 not in $CDCl_3$.[11]

the yield of the desired product was not improved.[13] The use of a second generation Grubbs catalyst provided **11** and a cyclic dimer[12] in 25 and 23% yield, respectively. The structure of **11** was confirmed by NMR and MS analyses. The oxecine **11** was hydrogenated over 10% $Pd(OH)_2$ under a hydrogen atmosphere to give the proposed structure **2** in good yield.

Scheme 3



As shown in Table 1S,[14] ^1H and ^{13}C NMR data of **2** did not match with those of the natural product in the literature.[1] In particular, the splitting pattern of protons adjacent to carbonyl carbons was quite different. Thus, H-7 of natural phomopsin B was reported to be δ 2.84 as a triplet (J = 7.5 Hz) whereas that of a synthetic sample was observed at 2.59 and 2.88 ppm as dt (J = 14.2 and 5.5 Hz) and ddd (J = 14.2, 10.0, and 5.9 Hz), respectively. In general, such protons on the ring of a simple cycloalkenone with a chiral center did not seem to be equivalent, thus resulting in a pair of complicated signals with different chemical shifts in the ^1H NMR spectra. Therefore, the data of the natural product are likely to be those of an acyclic compound. The singlet signal at 3.79 ppm derived from H-14 of the natural product also reflects that the circumstance around the isolated methylene protons is equal, suggesting the side chain including the ketone group is not cyclic. Based on the results and the fact that phomopsin C[1] with an acyclic chain was isolated from the same origin, we estimated that the real structure of natural phomopsin B may be phenol **18** with an acyclic chain. Although the molecular formula of the natural product was determined to be $C_{18}H_{24}O_5$ by HR-EIMS at m/z 320.1613 (calcd 320.1618), the data would be explained by those of the corresponding dehydration product. By using the CAS database, we found that our proposed structure was a known compound named dothiorelone A. Su et al.[15,16] had isolated it[17] from a similar mangrove endophytic fungus, *Dothiorella* sp. HTF3 in 2004. Subsequently, Lin et al. and Lin, Wu, and Proksch et al. reported its isolation from *Phomopsis* sp. ZSU-H76[16−18] and *Rhizophora mucronata*,[17,19] respectively. Recently, this natural product was also isolated from *Cytospora* sp. by Abreu et al.[16,17,20] An exact comparison of the data, however, was impossible since the NMR spectra of dothiorelone A were measured in DMSO-d_6 or acetone-d_6. For confirmation of our hypothesis, we synthesized **18** as follows (Scheme 3). The phenol **5** was benzylated under the Mitsunobu conditions to give **12**.[9b] According to the method described above, this compound was transformed into aldehyde **14** via **13**. Reaction of **14** with pentenylmagnesium bromide gave **15**, which was oxidized by a Jones reagent, affording **16** after esterfication. Cross metathesis of **16** with 3-buten-2-ol in the presence of a second generation Grubbs catalyst afforded **17** in good yield. Reductive debenzylation of **17** with $Pd(OH)_2$ in ethyl acetate gave **18** in good yield. The ^1H and ^{13}C NMR data in the several solvents reported and MS data of **18** were well matched with those of the natural product cited in the literature.[21] Therefore, the proposed structure of phomopsin B was revised to be **18**, showing that phomopsin B is identical to dothiorelone A.[22]

(11) Takahashi, S.; Satoh, H.; Hongo, Y.; Koshino, H. *J. Org. Chem.* **2007**, *72*, 4578–4581.

(12) For the structures of open-chain and cyclic dimers and their structural determination, see Supporting Information.

(13) Grubbs−Hoveyda catalysts first and second generation were also employed for the metathesis. However, the desired product was obtained in a low yield (4−10%).

(14) See Supporting Information.

(15) Xu, Q.; Wang, J.; Huang, Y.; Zheng, Z.; Song, S.; Zhang, Y.; Su, W. *Acta Oceanolog. Sin.* **2004**, *23*, 541–547.

(16) No $[\alpha]_D$ value was denoted.

(17) Its absolute configuration is not shown.

(18) Huang, Z.; Guo, Z.; Yang, R.; Yin, X.; Li, X.; Luo, W.; She, Z.; Lin, Y. *Chem. Nat. Compd.* **2009**, *45*, 625–628.

(19) Xu, J.; Kjer, J.; Sendker, J.; Wray, V.; Guan, H.; Edrada, R.; Mueller, W. E. G.; Bayer, M.; Lin, W.; Wu, J.; Proksch, P. *Bioorg. Med. Chem.* **2009**, *17*, 7362–7367. In this paper, the erroneous name "dothiorelone B" is used for dothiorelone A.

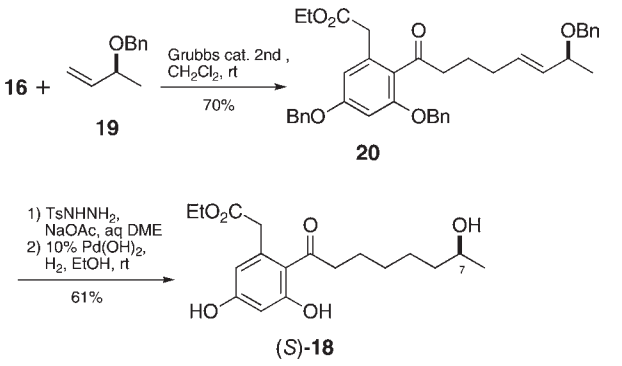
(20) Abreu, L. M.; Phipps, R. K.; Pfenning, L. H.; Gotfredsen, C. H.; Takahashi, J. A.; Larsen, T. O. *Tetrahedron Lett.* **2010**, *51*, 1803–1805.

(21) We found that some signals around aromatic and carbonyl groups in **18** are sensitive to dissolved solvent or additive trace solvent in $CDCl_3$ solution. Complete NMR assignments in $CDCl_3$, $CDCl_3$ with water or MeOH, DMSO-d_6, and acetone-d_6 are summarized in Tables 2S and 3S; see Supporting Information.

(22) The sign of $[\alpha]_D$ of both natural products was reported to be negative although there was a discrepancy with their magnitude between refs 1 and 19.

(23) (a) Laughton, C. A.; Bradshaw, T. D.; Gescher, A. *Int. J. Cancer* **1989**, *44*, 320–324. (b) Evans, P. A.; Leahy, D. K. *J. Am. Chem. Soc.* **2002**, *124*, 7882–7883. (c) Reddy, G. V.; Kumar, R. S. C.; Sreedhar, E.; Babu, K. S.; Rao, J. M. *Tetrahedron Lett.* **2010**, *51*, 1723–1726.

Scheme 4



In order to determine the absolute configuration of dothiorelone A, a cross metathesis with chiral olefin **19**[23] was also performed, giving **20** (Scheme 4). Reduction of **20** under the same conditions that were used for **17** caused a partial cleavage of an allylic benzyl ether moiety. Hence, the double bond in **20** was initially reduced with diimide and then the resulting compound underwent hydrogenolysis, giving (*S*)-**18** $\{[\alpha]_D^{22} +3.4\,(c = 0.50, \text{methanol})\}$. The sign of its $[\alpha]_D$ was opposite to those of the natural phomopsin B[1] and dothiorelone A {lit.[19] $[\alpha]_D$ −6 (c = 0.1, methanol)}. Therefore, the absolute configuration of dothiorelone A was determined to be *R*.

Structural revision of phomopsin B then focused our attention on the proposed structure of phomopsin A and made us re-examine the ^{1}H and ^{13}C NMR data of the natural product. We found that the methylene protons at C-6 and C-14 in the ^{1}H NMR spectra of **1** showed a triplet at 2.85 ppm and singlet at δ 3.76, respectively, and concluded that the structure of natural phomopsin A also would not be the oxonine derivative reported but an ethyl phenylacetate derivative carrying a long side chain with a secondary alcohol. The compound was identified as dothiorelone B[15,18] by the CAS database. Taking into account the origin and the spectral data, it is likely that the structure of phomopsin A should be revised to be dothiorelone B. The ^{13}C NMR data of phomopsin A,[1] however, are not completely identical to those of dothiorelone B.[15,18] We suggest that reinvestigation of the assignments of dothiorelone B is necessary; see Supporting Information.

In summary, we achieved the first total synthesis of the proposed structure **2** for phomopsin B and *ent*-dothiorelone A (*S*)-**18**, thus leading to the conclusion that phomopsin B is identical to dothiolerone A. The *R* configuration of natural dothiolerone A was determined by chiral synthesis.

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Supporting Information Available. Experimental procedures, NMR spectra of **2**−**4**, **6**−**18**, **20**, and dimers. This material is available free of charge via the Internet at http://pubs.acs.org.