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Total synthesis of (−)-phaeosphaeride B by a biomimetic conversion from (−)-phaeosphaeride A

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ABSTRACT

We have accomplished the first total synthesis of STAT3 inhibitory (−)-phaeosphaeride A and its stereoisomer (−)-phaeosphaeride B. This work confirms the configurational assignment of these natural products. Notably, TFA-mediated dehydrative stereoinversion of phaeosphaeride A afforded phaeosphaeride B, based on our hypothesis of the biosynthesis mechanism of phaeosphaeride B from phaeosphaeride A.

1. Introduction

Phaeosphaerides A (proposed structure **1**) and B (**2**) are nitrogen-containing bicyclic natural products that were isolated from the endophytic fungus FA39 (*Phaeosphaeria avenaria*) by Clardy and co-workers in 2006 (Fig. 1).[1] Phaeosphaeride A is an inhibitor of STAT3-DNA binding with an IC_{50} of 0.61 mM and also inhibits cell growth in STAT3-dependent U266 multiple myeloma cells with an IC_{50} of 6.7 μM *in vitro*, whereas its stereoisomer phaeosphaeride B (**2**) has no STAT3 inhibitory activity.

In 2011 and 2012, our group[2] and Sarli's group[3] independently demonstrated the total synthesis of the proposed structure of phaeosphaeride A (**1**), which revealed that the structure of phaeosphaeride A was misassigned. Stereochemical considerations suggested that the correct structure of phaeosphaeride A is C-7 epimer **3** of the originally proposed structure (**1**) or its enantiomer (**4**). The first total synthesis of **3** was achieved by our group in 2015, providing a corrected configuration (**4**) for phaeosphaeride A,[4] and this result was supported by the X-ray crystal structure of natural phaeosphaeride A reported by Abzianidze et al.[5]

During the course of these studies, Sarli and colleagues and Abzianidze et al. also conducted biological studies of their synthetic compounds.[3,6,7] Sarli and colleagues synthesized and biologically evaluated the stereoisomers of phaeosphaeride A, which suggested that these compounds are upstream inhibitors of a tyrosine kinase in the JAK/STAT pathway.[6] Abzianidze et al. prepared the C-6 acyl derivatives from the isolated natural phaeosphaeride A, and a chloroacetyl derivative exhibited more potent cytotoxicity (EC_{50} = 33 ± 7 μM) against A549 cancer cells than natural phaeosphaeride A (EC_{50} = 46 ± 5 μM).[7] Their studies highlighted phaeosphaeride A as a potential seed compound for STAT3 inhibitors in anti-cancer drug discovery,[8] and further screening of unnatural phaeosphaeride A derivatives may provide compounds that are more biologically active. Furthermore, the ambiguous biosynthetic pathway for phaeosphaerides A and B was expected to be clarified. Based on the structures of the phaeosphaeride family, we assumed that proton-mediated biosynthetic conversion occurred between phaeosphaerides A and B (Scheme 1).

In this paper, we describe the total synthesis of (−)-phaeosphaeride B (**2**) by a hypothetical biomimetic conversion from (−)-phaeosphaeride A through a TFA-mediated stereoinversion.

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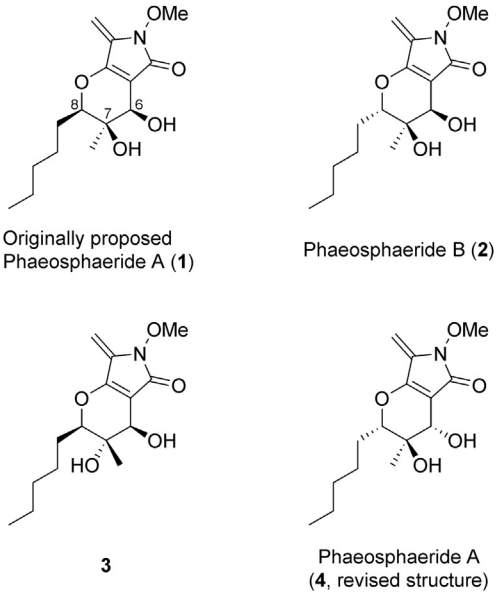
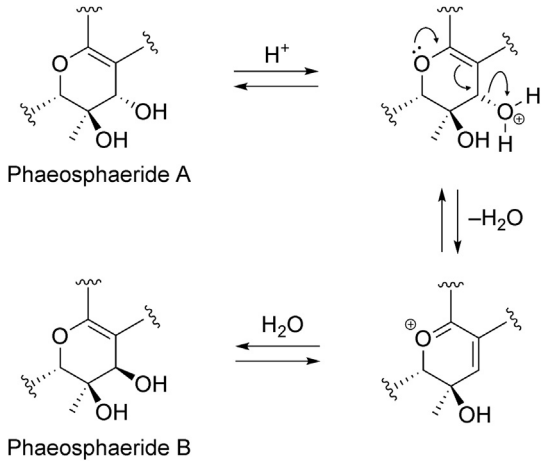


Fig. 1. Structures of phaeosphaerides.



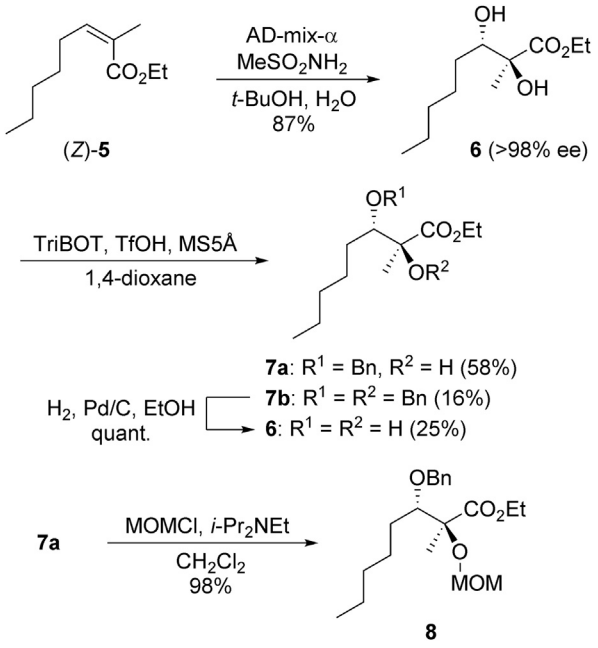
Scheme 1. Possible biosynthetic conversion between phaeosphaerides A and B.

2. Results and discussion

2.1. Synthesis of (−)-phaeosphaerides A

To synthesize (−)-phaeosphaeride B (**2**) from (−)-phaeosphaeride A (**4**) by a hypothetical stereoinversion at C-6, we first prepared (−)-phaeosphaeride A (**4**) by following our synthetic path to *ent*-phaeosphaeride A (**3**).[4] The synthesis of (−)-phaeosphaerides A (**4**) began with Sharpless asymmetric dihydroxylation of known (*Z*)-**5**,[4] synthesized by the *Z*-selective Horner–Wadsworth–Emmons reaction (Scheme 2).[9] Ester (*Z*)-**5** was dihydroxylated to (2*S*,3*S*)-diol **6**, an enantiomer of the known diol,[4] by Sharpless asymmetric dihydroxylation using AD-mix-α[10] in high yield (87%) and enantioselectivity (98% ee, determined by modified Mosher's method).[11]

According to our synthetic scheme for **3**, diol **6** was converted to ester **8**. The two hydroxy groups in **6** were protected with a Bn group[12] for the secondary alcohol and a MOM group for the tertiary alcohol to obtain **8** in 57% yield (two steps).



Scheme 2. Synthesis of ester **8**.

Ester **8** was reduced with DIBALH to provide the alcohol in 86% yield, which was then protected to give the TIPS ether in quantitative yield (Scheme 3). Removal of the Bn group by hydrogenation using catalytic Pd/C produced desired secondary alcohol **9** in 99% yield. Oxa-Michael addition of alcohol **9** to **10** using catalytic *n*-BuLi gave (*E*)-**11** in 86% yield. TIPS ether (*E*)-**11** was then converted to aldehyde **12** by desilylation with HF-pyridine to give an alcohol, followed by Dess-Martin oxidation. To construct a dihydropyran ring, aldehyde **12** was subjected to a sodium hexamethyldisilazide-mediated vinyl anion aldol reaction to generate desired product **13a** (56%), its TMS ether **13b** (4%), and C-6 diastereomer byproduct **13c** (15%). During this reaction, alcohol **13a** and TMS ether **13b** appeared to be stereoselectively formed through the transition state shown in parentheses in Scheme 3.[13] W-type long-range coupling[14] between H-6 and H-8 in **13a** and **13b** was observed to confirm the required *S* configuration at the C-6 stereocenter.

Without protection of the C-6 alcohol in **13a**, exposure of diester **13a** to 1 M aqueous NaOH in MeOH caused regioselective hydrolysis of one of the two ester groups to afford a mono acid,[15] which was immediately subjected to amidation with $MeONH_2$ (**14**) to give maleimide derivative **15** with spontaneous cyclization in 48% yield, accompanied by amide **16** in 22% yield (Scheme 4). Amide **16** was easily converted to **15** in 81% yield by treating with Et_3N in DMF at 50 °C. Total synthesis of **4** was achieved by exo-methylene formation through methylation by using MeMgBr and dehydration mediated by HCl in 1,4-dioxane. The ^1H and ^{13}C NMR spectra of synthetic **4** matched the literature data[1] for natural phaeosphaeride A, and the optical rotation of **4** ($[\alpha]_D^{25}$ −98.6 (*c* 0.85, CH_2Cl_2)) was the same sign as the natural product ($[\alpha]_D^{25}$ −93.6 (*c* 2.0, CH_2Cl_2)). Thus, we identified the structure of natural phaeosphaeride A as compound **4** through its total synthesis.[5]

2.2. Hypothetical biosynthetic pathway from phaeosphaeride A to phaeosphaeride B

With synthetic phaeosphaeride A (**4**) in hand, our next challenge was preparing and assigning the configuration of phaeosphaeride B.[1,6,16] We assumed that a biosynthetic transformation