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A Macrocyclic β -Iodoallenolate Intermediate is Key: Synthesis of the ABD Core of Phomactin A

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Abstract

An enantioselective strategy for the synthesis of phomactin natural products is described. The Lewis acid-triggered cyclization of a β -iodoallenolate embedded in a 12-membered macrocycle was used to obtain a highly functionalized bicyclo[9.3.1]pentadecane in good yield and high diastereoselectivity. This iodoenone contains the substituents of the AD ring system of the phomactin family of natural products, appropriate for further functionalization. Synthesis of the oxadecalin core of phomactin A from the AD iodoenone intermediate was achieved. In this unusual strategy, rings A and B are both fashioned within a macrocyclic precursor.

The phomactin natural products (Figure 1) were isolated from *Phoma* sp. [SANK 11486], a marine fungus that grows on the shell of a crab *Chionoecetes opilioi*, off the coast of Fukui prefecture, Japan.¹

Interestingly, the phomactins were found to be platelet-activating factor (1-*O*-alkyl-2(*R*)-(acetylglycerol)-3-phosphorylcholine, PAF) antagonists, inducing platelet aggregation and inhibiting the binding of platelet-activating factor to its receptor.^{2,3} PAF is a highly potent phospholipid, and it is thought to be involved in a number of inflammatory and respiratory diseases.² Phomactin A is the most structurally intricate member of the family, and has thus triggered a variety of creative synthetic strategies over the past decade.⁴ It is characterized by a tetracyclic framework comprised of a bicyclo[9.3.1]pentadecane core, six stereocenters (three of which are quaternary), a reduced furanochroman, and an oxadecalin.

Our synthetic approach was focused on building the oxadecalin core of phomactin A from a macrocyclic precursor. To achieve this task, we intended to employ a β -iodoallenolate cyclization recently developed in our laboratory.⁵ As shown in Scheme 1, 1,4-addition of iodine to alkynone **1** generates β -iodoallenolate intermediate **2**, which can be selectively converted into either cyclohexenyl alcohol **3** or oxadecalin **4**, depending on the Lewis acid.^{6,7} In this communication we describe the execution of this transformation within a carefully crafted 12-membered macrocycle, as a strategy for the synthesis of the framework of members of the phomactin family, including the tricyclic core of phomactin A.

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Supporting Information Available Experimental procedures, characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The synthetic strategy is centered on cyclization of macrocycle **5** to produce target alcohol **6**, which not only contains the framework of the phomactins, but also a vinyl iodide moiety that could act as a versatile linchpin (Scheme 2). An oxy-Michael ring closure of cyclohexenyl alcohol **6** would then give tricycle **7**, containing the ABD ring system of phomactin A. Macrocycle **5** could come from a Nozaki-Hiyama-Kishi reaction with linear precursor **8**, which, in a convergent manner, would come from the β -alkyl Suzuki coupling of vinyl iodide **9** and olefin **10**.

The synthesis of the vinyl iodide **9** commenced with known nerol derived aldehyde **11** (Scheme 3).⁸ Then, using the Ohira-Bestmann⁹ modification of the Seyferth-Gilbert homologation,¹⁰ aldehyde **11** was transformed into terminal alkyne **12**.

Alkylation with methyl iodide followed by regioselective silylcupration afforded vinyl silane **14** in high yield.¹¹ Iododesilylation of vinyl silane **14** was achieved using the conditions developed by Zakarian (*N*-iodosuccinimide (NIS), 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), and 2,6-lutidine).¹² Thus, the desired vinyl iodide **9** was generated in 4 steps and 63% overall yield from aldehyde **11**.

The key challenge for the synthesis of olefin **10** was the diastereoselective installation of the C7 tertiary center adjacent to the C6 all-carbon quaternary center (Figure 1). To achieve this, we relied on the enantioselective palladium-catalyzed cycloisomerization protocol developed by Mikami.¹³ Accordingly, enyne **15** was converted into compound **16**, with excellent yield and enantioselectivity (Scheme 4). Then, conjugate reduction of the α,β -unsaturated ester was accomplished by using Buchwald's procedure to afford compound **17** in 63% yield as a 12:1 mixture of diastereomers.¹⁴ The ester was then reduced and protected as an acetate and the absolute and relative configuration of compound **18** was confirmed by X-ray crystallography of the corresponding *p*-nitrobenzoate derivative.¹⁵ Regioselective opening of the tetrahydrofuran moiety using NaI and AcCl gave rise to iodide **19**.¹⁶ The selectivity can be attributed to iodide attack at the least hindered, more reactive allylic carbon, which is expected to be more favorable than attack at the neopentyl carbon. Radical reduction of the alkyl iodide with *n*-Bu₃SnH and subsequent cleavage of the acetates with K₂CO₃ in methanol provided the diol. Finally, protection of both alcohols with *tert*-butyldimethylchlorosilane (TBSCl) gave the desired olefin **10** in 43% overall yield over 8 steps.

Coupling of **9** and **10** was accomplished by hydroboration of olefin **10** with 9-borabicyclo[3.3.1] nonane (9-BBN) followed by *in situ* β -alkyl Suzuki coupling¹⁷ with vinyl iodide **9** to furnish compound **20** in good yield (Scheme 5). Desilylation of the coupling product followed by selective monoprotection of the primary alcohol with TBSCl gave neopentyl alcohol **21**. Oxidation with pyridinium chlorochromate (PCC) and subsequent homologation with the Ohira-Bestmann reagent produced alkyne **22**. Then, the *p*-methoxybenzyl ether was oxidatively cleaved with DDQ and the terminal alkyne was iodinated with NIS in the presence of silver nitrate. Finally, oxidation with the Dess-Martin periodinane (DMP) gave macrocyclization precursor **8**.

Iodoalkyne **8** was cyclized to afford the corresponding macrocycle *via* an intramolecular Nozaki-Hiyama-Kishi Cr(II)/Ni(II) coupling (Scheme 5).¹⁸ Oxidation of the resulting alcohol with MnO₂ gave the desired ketone **23** in a 3.6:1.0 ratio of *Z* and *E* isomers.¹⁹ Fortunately, these isomers were easily separable *via* flash chromatography. After separation of the *E* and *Z*-isomers, the *Z*-isomer was desilylated using a HF-pyridine solution in tetrahydrofuran. Oxidation of the primary alcohol with the Ley-Griffith reagent²⁰ afforded aldehyde **5** in just 4 steps from iodoalkyne **8**.

Next, we examined the β -iodoallenolate cyclization with aldehyde **5** (Scheme 6). The first attempts with the conditions previously reported ($\text{BF}_3\cdot\text{OEt}_2$ and TiCl_4 ; Scheme 1) failed to provide the corresponding oxadecalin or even the cyclohexenyl alcohol. These conditions gave either complex mixtures or degradation, indicating that these conditions were too harsh. So, we turned our attention to MgI_2 , a milder Lewis acid.^{6e,7b,21} β -Iodoallenolate **24** was then generated in the presence of MgI_2 and cyclized smoothly to afford cyclohexenyl alcohol **6**, in a 60% yield as a single diastereomer. The relative stereochemistry of the alcohol was assigned by nOe analysis.²²

Cyclohexenyl alcohol **6** could serve as an intermediate for the synthesis of multiple members of the phomactin family (Figure 1). This versatility is a notable feature of our synthetic approach to the phomactins. In this study, we focused on generating the tricyclic core of phomactin A.

Mitsunobu inversion of the alcohol with *p*-nitrobenzoic acid using diethyl azocarboxylate (DEAD) and triphenylphosphine generated compound **26**, whose structure was assigned by X-ray crystallography (Scheme 7). Removal of the *p*-nitrobenzoate ester followed by treatment of cyclohexenyl alcohol **25** with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and 2,6-lutidine in toluene triggered an oxy-Michael addition, producing tricycle **7**. This oxadecalin derivative possesses all the stereogenic centers of the A, B and D rings of phomactin A, and was assembled using a highly diastereoselective synthetic strategy.

In summary, we have developed a novel enantioselective approach to the central core of the phomactins, and synthesized the ABD ring system of phomactin A. The strategy features the efficient cyclization of a β -iodoallenolate intermediate, generating the AD ring system of the phomactin skeleton within a 12-membered macrocycle.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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 22. See Supporting Information for nOe data and details concerning the structure assignment of compound **6**.

Figure 1.
Phomactins A, D, and G

Scheme 1.
 β -Iodoallenolate Cyclization

Scheme 2.
Synthetic Strategy

Scheme 3.
Synthesis of Vinyl Iodide **9**

Scheme 4.
Synthesis of Olefin **10**

Scheme 5.
Synthesis of Macrocycle **5**

Scheme 6.
 β -Iodoallenolate Cyclization with Macrocycle **5**

ORTEP drawing for Compound 26:

Scheme 7.
Synthesis of the Core of Phomactin A