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Enantioselective Synthesis of the ABC-Tricyclic Core of Phomactin A by a γ-Hydroxylation Strategy

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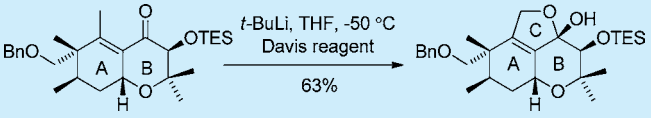
Supporting Information

ABSTRACT: An enantioselective synthesis of the ABC-tricyclic furanochroman core of phomactin A has been accomplished by a γ-hydroxylation approach. The C ring was established by γ-hydroxylation of an α-enone. The regioselectivity was optimized by using a strong base with an oxophilic cation (*t*-BuLi) and a bulky oxygen donor (Davis reagent), which afforded the γ-hydroxylation product selectively in 63% yield.



Phomactins are a new class of bicyclo[9.3.1]pentadecane-containing diterpenoids isolated from a marine fungus *Phoma* sp.[1,2] This class of natural products is a specific platelet activating factor (PAF) antagonist, which exhibits inhibition against PAF-induced platelet aggregation without effecting other platelet aggregation pathways including those induced by adenosine diphosphate, arachidonic acid, and collagen.[1−3] Phomactin A is the structurally most complex member, which contains an ABC-tricyclic furanochroman ring system fused into the bicyclo[9.3.1]pentadecane constituting a unique ABCD-tetracyclic framework (Figure 1).[1] Due to their

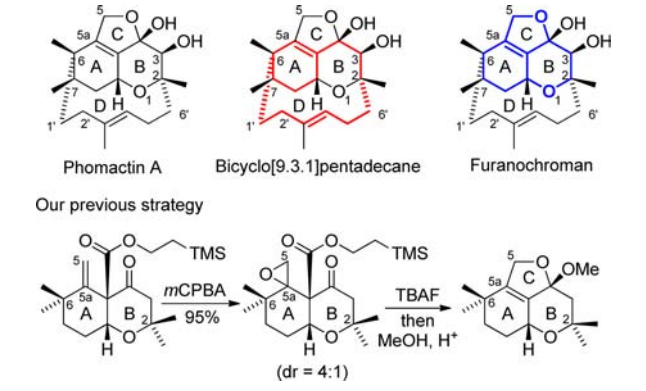


Figure 1. Structure features of phomactin A and our previous strategy for C5-hydroxylation.

intriguing skeletons and unique mode of biological actions, phomactins have attracted a tremendous amount of synthetic efforts,[4,5] including three elegant total syntheses of phomactin A reported by the groups of Pattenden,[6] Halcomb,[7] and Hsung.[8]

In the course of developing a total synthesis of phomactin A, we have previously reported an epoxidation/dealkoxycarbonylation protocol for construction of the ABC-tricyclic furanochroman ring system (Figure 1).[4m] However, Hsung's reports indicated that the challenge in installing the C ring at a late stage was insurmountable in the presence of the D ring since the *E*-alkene of the D ring is sensitive to many strong oxidants such as *m*CPBA and transition metal based oxidants.[8] Thus, the strategies for C5-hydroxylation via epoxidation,[4d,g] including ours,[4m] may not be applicable in the late stage of the synthesis. Therefore, we have decided to explore the possibility for installing the C5-hydroxyl via a γ-hydroxylation strategy. As shown in the model study in Figure 2, deprotonation of α-

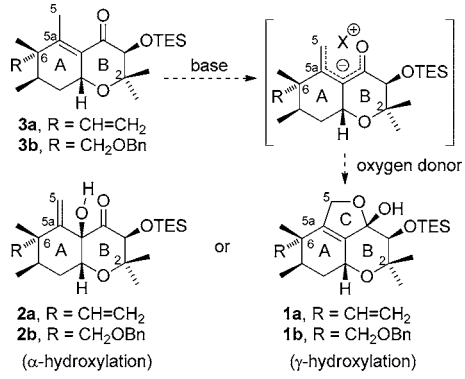


Figure 2. A model study of the C ring formation by γ-hydroxylation at C5.

enones **3** followed by the treatment of an oxygen donor could lead to the γ-hydroxylation products **1** after in situ acetalization. However, successful examples of regioselective γ-hydroxylation of α-enones are still limited.[9] To avoid the formation of the undesired α-hydroxylation products (**2**), we anticipated that an oxophilic counterion could stabilize the electron density at the γ-position of the enolate. Subsequent treatment with a bulky oxygen donor should favor the formation of the less congested

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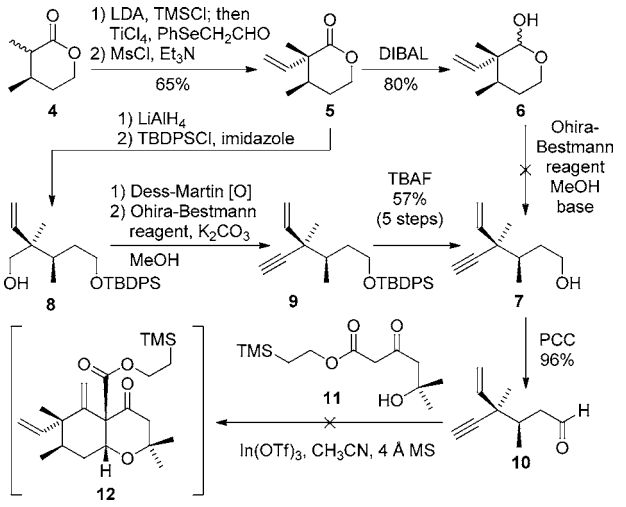
γ-hydroxylation products (**1**). Herein, we reported an enantioselective synthesis of the ABC-tricyclic furanochroman core of phomactin A by this γ-hydroxylation strategy.

The synthesis of the γ-hydroxylation precursor (**3**) began with enantiomerically enriched lactone **4**, which was prepared via enzymatic desymmetrization of 3-methylglutaric anhydride followed by lactonization and α-methylation according to the literature procedures.[10] As shown in Scheme 1, the α-vinyl of **5** was installed via a variation of Clive's protocol.[7,11] Reduction of lactone **5** using DIBAL gave lactol **6** as a mixture of diastereomers in 80% yield. However, treatment of Ohira–Bestmann reagent[12] with a base did not give the expected product **7**, indicating that acetal ring opening of lactol **6** may not be favorable under basic conditions. Lactone **5** was then reduced to the diol using lithium aluminum hydride. After selective silylation of the less hindered alcohol, the free alcohol of **8** was converted to an alkyne via the oxidation/homologation protocol. Deprotection and oxidation provided aldehyde **10**, which was expected to undergo Prins/Conia-ene cascade cyclization with β-keto ester **11** and establish the 1-oxadcalin of **12** in one pot.[4m] Unfortunately, this reaction resulted in a mixture of unidentifiable side products. NMR analysis of the mixture of the crude products showed the disappearance of the terminal alkene, suggesting the terminal alkene of **10** could be more reactive than the alkyne for the Conia-ene reaction.

Scheme 1. An Attempt of Prins/Conia-ene Cascade Cyclization



The terminal alkene of **9** was then converted to a protected alcohol prior to the Prins/Conia-ene cascade cyclization by standard procedures (Scheme 2). Surprisingly, the Prins/Conia-ene cascade cyclization of aldehyde **15** and β-ketoester **11** using $In(OTf)_3$ in CH_3CN resulted in only the Prins cyclization product **16**. The subsequent Conia-ene reaction required ZnI_2 in refluxing toluene for establishing the 1-oxadecalin moiety of **17** (a single diastereomer). The stereochemistry of **17** was characterized unambiguously using 2D NMR experiments.[13] The high diastereoselectivity of the Prins reaction could be rationalized by the chelation transition states (**TS1** and **TS2**), in which the In^{3+} ion is chelating with both the β-keto ester and the benzyl moiety. **TS1** could be more favorable since the less sterically demanding methyl group is pointing toward the ester moiety. This chelation model could also account for the ineffectiveness of $In(OTf)_3$ for the Conia-ene reaction.[14] After installation of the α′-hydroxyl of **18**, dealkoxycarbonylation[4m,15] using TBAF established the enone and TES protection of the α′-hydroxyl finished the synthesis of the γ-hydroxylation precursor **3b**.

With **3b** in hand, a variety of γ-hydroxylation conditions were investigated. As shown in Table 1, deprotonation of **3b** using LDA at −50 °C followed by the treatment of Davis reagent did not give any hydroxylation product (Table 1, entry 1). Switching the base to LiHMDS provided the γ-hydroxylation product **1b** in 3% yield along with 95% recovered starting material (Table 1, entry 2). Increasing the deprotonation temperature with LiHMDS enhanced the yield to 20% (Table 1, entry 3).

With this encouraging result in hand, the effects of a variety of strong bases with different counterions were investigated. Deprotonation with NaHMDS at −50 °C slightly enhanced the yield to 24% (Table 1, entry 4), but KHMDS at −50 °C gave a mixture of α- and γ-hydroxylation **2b** and **1b**, respectively

Scheme 2. Synthesis of the γ-Hydroxylation Precursor 3b

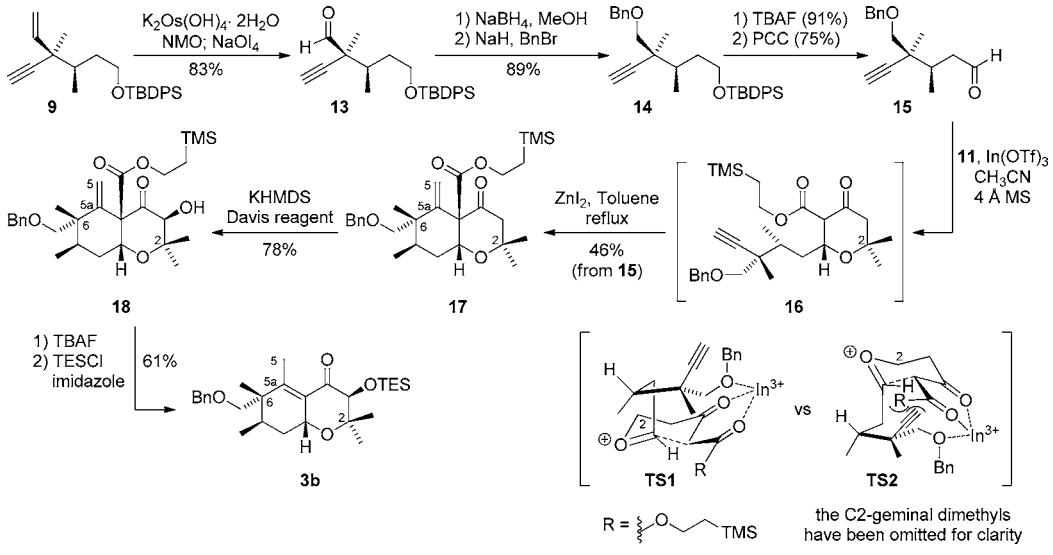


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Table 1. A Study on the Regioselectivity of γ-Hydroxylation of Enone 3b[a]

entry	base	oxygen donor	temp (°C)	γ-hydroxylation product, **1b**[b]	α-hydroxylation product, **2b**[b]	recovered starting material, **3b**[b]
1	LDA	Davis reagent	−50	–	–	88%
2	LiHMDS	Davis reagent	−50	3%	–	95%
3	LiHMDS	Davis reagent	25	20%	–	63%
4	NaHMDS	Davis reagent	−50	24%	–	71%
5	KHMDS	Davis reagent	−50	15%	5%	10%
6	KHMDS/LiCl	Davis reagent	−50	19%	–	–
7	KHMDS	O_2	−50	–	46%	11%
8	*t*-BuLi	Davis reagent	−50	63%	–	–

[a]The general procedures were followed. [b]Isolated yield (%) after silica gel column chromatography.

(Table 1, entry 5). Interestingly, formation of the α-hydroxylation product **2b** was completely suppressed by addition of 1 equiv of LiCl, but only gave a similar level of yield for the γ-hydroxylation product **1b** (Table 1, entry 6). Surprisingly, switching the oxygen donor to molecular oxygen afforded the α-hydroxylation product **2b** selectively in 46% yield (Table 1, entry 7). The structure of **2b** was characterized unambiguously using 2D NMR experiments.[13] These results indicated that using a strong base with an oxophilic counterion and a bulky oxygen donor could enhance the selectivity for the γ-hydroxylation product **1b**. Finally, the conditions for the γ-hydroxylation were optimized by using *t*-BuLi with Davis reagent, which afforded **1b** selectively in 63% yield (Table 1, entry 8). The relative configuration of **1b** was determined by analyzing the NMR data of the corresponding methyl acetal (**19**), which was prepared by treatment of NaH in either THF or DMF followed by methyl iodide (Figure 3).[13]

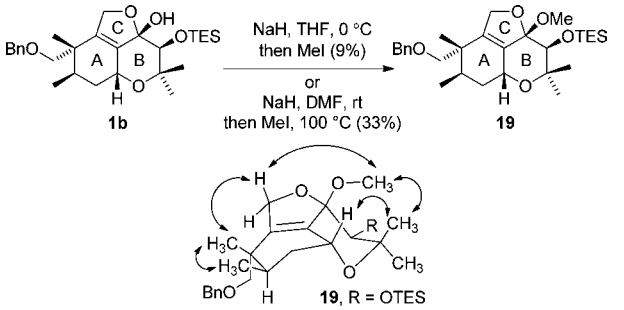

Figure 3. Preparation of methyl acetal **19** and its NOE correlations.

In summary, we have successfully demonstrated a new γ-hydroxylation approach to an enantioselective synthesis of the ABC-tricyclic furanochroman core of phomactin A. The 1-oxadecalin (AB ring) was constructed convergently by a sequential Prins/Conia-ene reaction, and the C ring was established by installing the C5-hydroxyl via γ-hydroxylation of an α-enone. The regioselectivity has been optimized by using a strong base with an oxophilic counterion and a bulky oxygen donor. The optimal selectivity was achieved by using *t*-BuLi with Davis reagent, which resulted in a 63% yield of the γ-hydroxylation product **1b** selectively. The results of this model study provide a promising alternative approach to the C ring, which allows the installation of the C5-hydroxyl in the late stage of the synthesis. The total synthesis of phomactin A based on this γ-hydroxylation approach is still ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds. This material is available free of charge via Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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