

Total Synthesis of 1-Hydroxydehydroherbarin and Ascomycones A, B, Naphthoquinone Antibiotics

Wen-Kai Dong,^a Xiong Huang,^a Dong-Cheng Xu,^{*,a} Xin-Sheng Li^a and Jian-Wu Xie^{*,a}

Key Laboratory of the Ministry of Education for Advanced Catalysis Materials,
Department of Chemistry and Life Science, Zhejiang Normal University, 321004, Jinhua, P. R. of China

A primeira síntese total de 1-hidróxi-desidroherbarina e ascomyconas A e B é relatada. As ascomyconas A e B biologicamente interessantes foram obtidas com rendimento total de 18% a partir de 3-cloro-2,5-dimetoxibenzaldeído como bloco de construção.

The first total synthesis of 1-hydroxydehydroherbarin and ascomycones A and B is reported. The biologically interesting ascomycones A and B were obtained in 18% overall yield starting from 3-chloro-2,5-dimethoxybenzaldehyde as building block.

Keywords: pyranonaphthoquinone, 1-hydroxydehydroherbarin, ascomycones A, B, antibiotics, total synthesis

Introduction

The ascomycones A and B (**1** and **2**), two novel heptaketide-derived secondary metabolites, were isolated by Opatz *et al.*¹ in 2008 from cultures of an unknown ascomycete. They exhibited antimicrobial and cytotoxic activities. In addition, ascomycone B (**2**) is an antifungal compound. On the other hand, 1-hydroxydehydroherbarin (**3**) was isolated by Gunatilaka and co-workers in 2007.² To the best of our knowledge, there is no report for the total synthesis of ascomycones A and B, and it is worthwhile to perform their syntheses.³ Moreover, pyranonaphthoquinone antibiotics **4** and **5**⁴ have pronounced biological properties, such as inhibitor of HRV-3C protease, that was discovered by chemists at Merck upon screening the fermentation broths of the fungus *Thysanophora penicilloides*. The interesting biological activity of **4** and **5** has aroused considerable interest among the synthetic community, and many research groups have reported their total synthesis.⁵

Herein we present the first total synthesis of ascomycones A and B (**1** and **2**), as well as the first total synthesis of 1-hydroxydehydroherbarin (**3**).

Results and Discussion

The plan for our synthesis of the pyranonaphthoquinones is shown in Scheme 1. We envisioned that the natural products possessed an acetal or hemiacetal ring, as such a few functional group modifications lead retrosynthetically to the naphthoquinone **6**. This activated intermediate is readily transformed to the naphthoquinone skeleton **7**. A cycloaddition of Brassard's diene with the 2-chloro-1,4-benzoquinone **8** was designed to provide **7**.

The synthesis was initiated with these ideas in mind (Scheme 2). To test the feasibility of our strategy, we first prepared naphthoquinone **7** through a Diels-Alder reaction of 2-chloro-1,4-benzoquinone **8a** with **9** (Scheme 2).⁶⁻¹⁰ Unfortunately, the use of ethylene glycol as protecting group on the compound **8a** resulted in a mixture of naphthoquinone **7a** and **7c** in the Diels-Alder reaction (Scheme 2). On the basis of the experimental observations, a possible mechanism was proposed to explain the formation of compound **7c** from **8a** and **9** (Scheme 3). Firstly, compound **8a** was hydrolyzed slowly to afford aldehyde **I**. Then the intermediate **II** was formed by Diels-Alder reaction of **I** with **9** and the intermediate **IV** was formed through oxidation, hydrolysis and decarboxylation of **III**. Finally, compound **7c** was obtained by aromatization.

We then found that yield and chemoselectivity could be greatly improved by employing 2-chloro-1,4-

*e-mail: xiejw@zjnu.cn, xu1127@yahoo.com

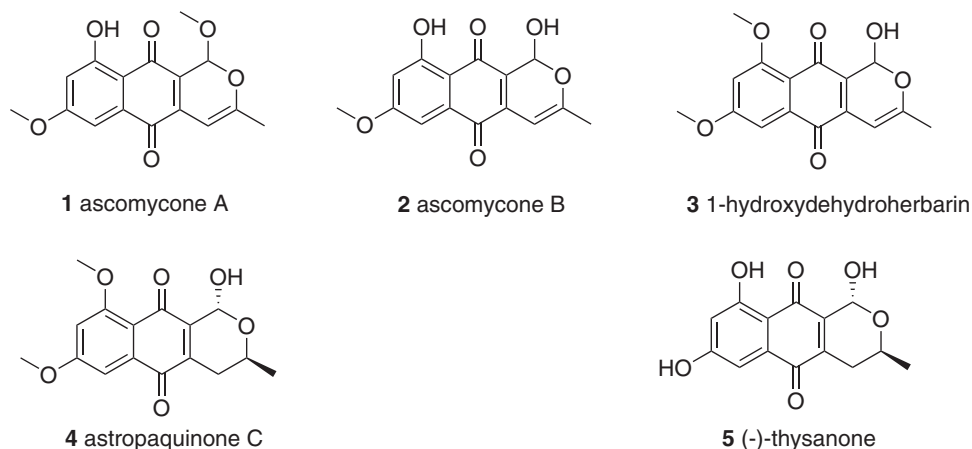
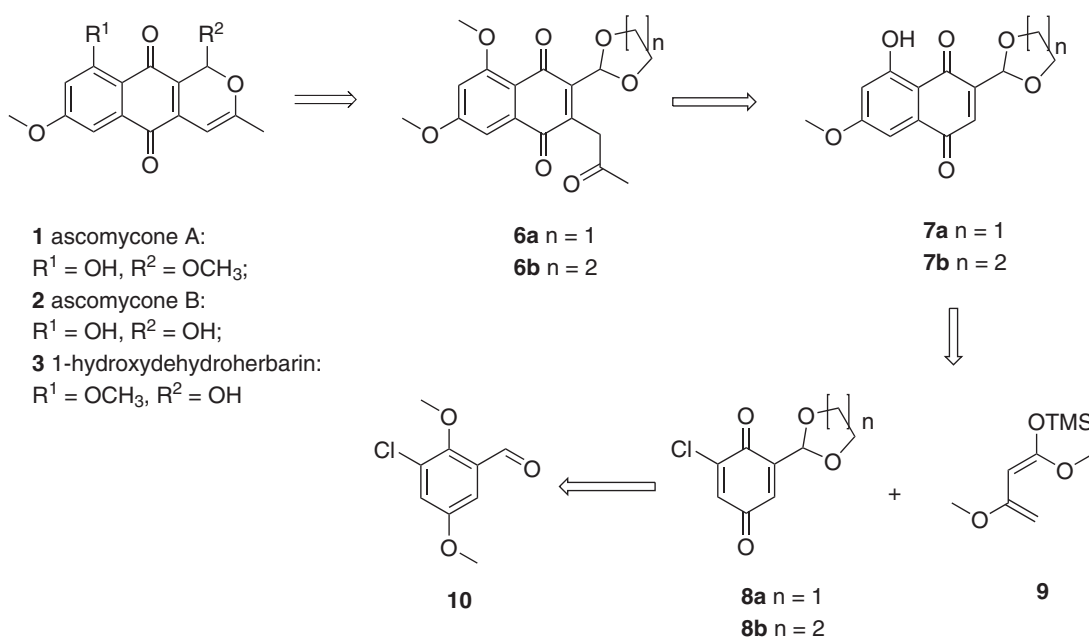
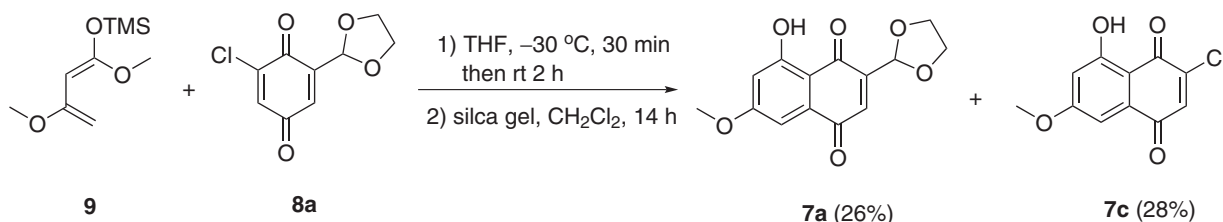


Figure 1. Structures of ascomycones A, B and 1-hydroxydehydroherbarin.



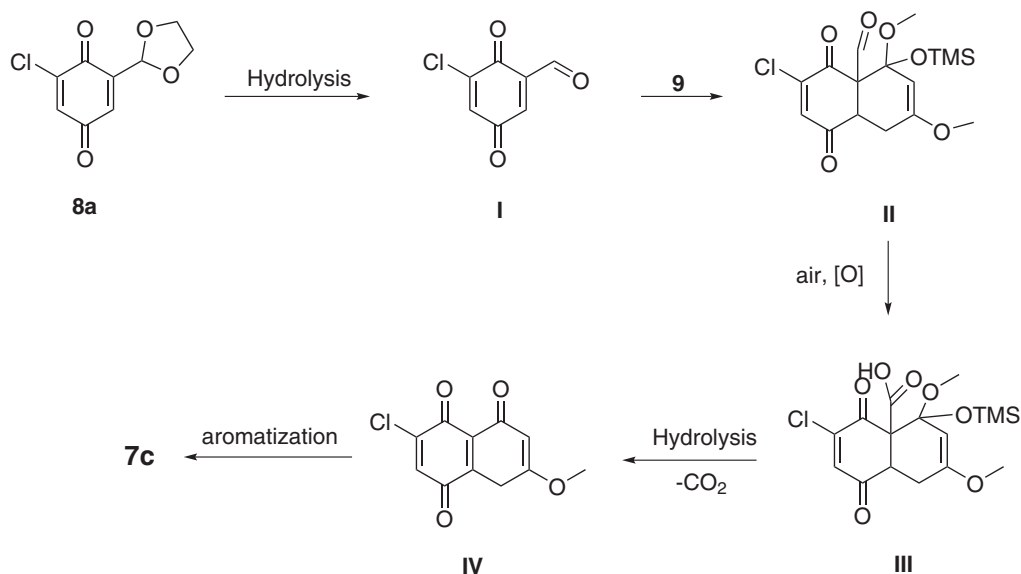
Scheme 1. Retrosynthetic analysis of ascomycones A, B and 1-hydroxydehydroherbarin.



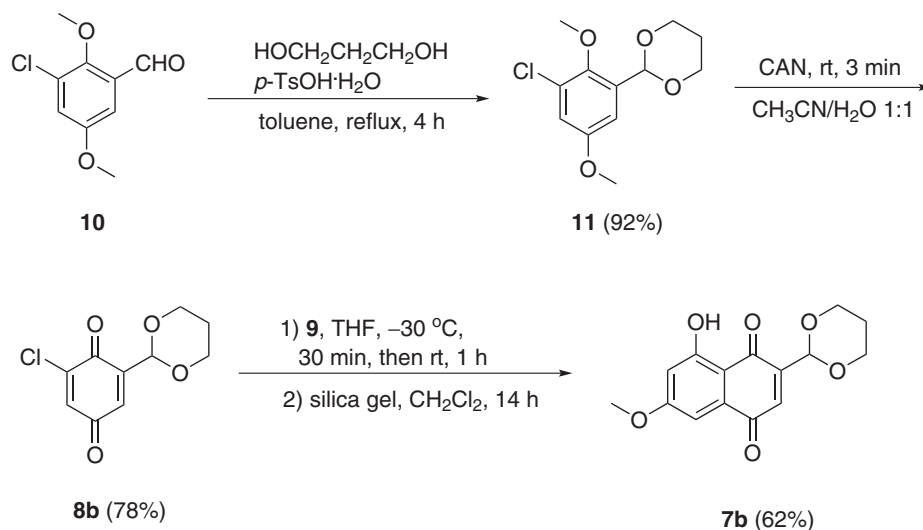
Scheme 2. Diels-Alder reaction of **8a** with **9**.

benzoquinone **8b** which was protected with propanediol, as a dienophile. The procedure for our synthesis of the naphthoquinone skeleton **7b** is shown in Scheme 4. The compound 2-(3-chloro-2,5-dimethoxyphenyl)-1,3-dioxane **11** was accessed in 92% yield from known aldehyde **10**,¹¹ by acetalization under Dean Stark conditions. Several reports on the oxidation of 2-(3-chloro-2,5-dimethoxyphenyl)-1,3-dioxane (**11**)

toward 2-chloro-6-(1,3-dioxan-2-yl)cyclohexa-2,5-diene-1,4-dione (**8b**) with silver(II) dipicolinate, silver(I) oxide, cobalt(III) fluoride, and cerium(IV) ammonium nitrate (CAN) as oxidants are known in the literature.¹³⁻¹⁵ Using CAN the reaction time was minimized to 3 min in order to reduce acetal hydrolysis to obtain 2-chloro-6-(1,3-dioxan-2-yl)cyclohexa-2,5-diene-1,4-dione **8b** in 78% yield (Scheme 4).¹² Then **7b** was obtained in 62% yield



Scheme 3. Possible mechanism for the formation of compound **7c** from **8a** and **9**.



Scheme 4. Preparation of 2-(1,3-dioxan-2-yl)-8-hydroxy-6-methoxynaphthalene-1,4-dione **7b**.

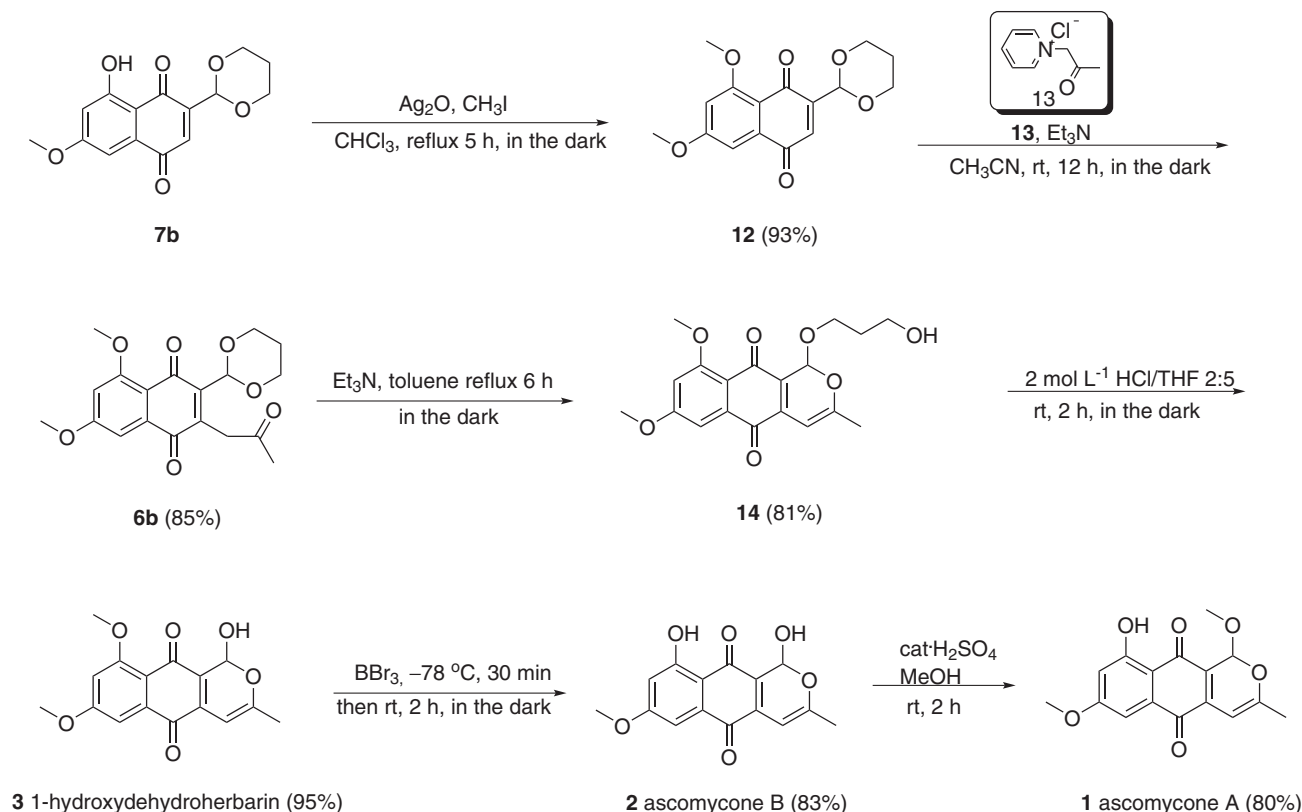
by the regioselective cycloaddition of **8b** with **9**, without isolating the intermediate **7c**.

To avoid the formation of the anthraquinone side product,¹⁶ the 8-hydroxyl group of compound **7b** was protected by *O*-methylation using iodomethane and silver(I) oxide (Scheme 5). Reaction of **12** with acetylpyridinium chloride (**13**) and 1.2 equiv. of triethylamine gave the **6b** as the sole product in a yield of 85%.^{16,17} Thus, upon treatment of this acylmethyl substituted naphthoquinone (**6b**) with triethylamine, it cyclized selectively to the pyranonaphthoquinone dehydroherbarin (**14**) in 81% yield.^{12,17} For the synthesis of **1-3**, **14** needed to be further deprotected. Therefore, compound **14** was first treated with excess hydrochloric acid in tetrahydrofuran at room temperature to give 1-hydroxydehydroherbarin (**3**) in 95%

yield (Scheme 4). Then the most active antifungal compound ascomycone B (**2**) was obtained in 83% yield when **3** was treated with excess boron tribromide in dichloromethane at -78 °C to give selective *O*-demethylation at the *peri*-position.¹⁷ In addition, ascomycone A (**1**) was cleanly obtained when ascomycone B was stirred in methanol. Our synthetic ascomycones B and 1-hydroxydehydroherbarin display ¹H and ¹³C NMR, IR, and MS spectra identical to those reported for the natural samples.

Conclusions

In summary, we have developed an efficient total synthesis of the biologically interesting ascomycones A and B in 9 steps and 18% overall yield starting from



Scheme 5. Completion of the total syntheses of ascomycones A and B (**1**, **2**) and 1-hydroxydehydroherbarin (**3**).

3-chloro-2,5-dimethoxybenzaldehyde (**10**) as building block. Notably, 1-hydroxydehydroherbarin was obtained in more than 21% yield. Key features of our synthetic approach include an efficient method on the oxidation of **11** toward **8b** with CAN. The efficient approach and rapid synthetic route reported here should be easily applied to the synthesis of analogues for further biological testing, which will be reported in due time.

Supplementary Information

Supplementary data are available free of charge as a pdf file at <http://jbc.sbg.org.br>.

Acknowledgments

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