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Synthesis of (–)-Pyrenophorol†

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Macrodiolide antibiotics, which possess interesting structural and biological properties are found in fungi and marine sponges. These macrodiolides are classified into two groups; one includes homodimers that consist of two identical units, and the other includes heterodimers that consist of two different units. Macrodiolides such as pyrenophorol (**1**),[1] pyrenophorin (**2**),[2] and vermiculine (**3**),[3] which have 16-membered rings are homodimeric macrodiolides, and macrocylic dilactones such as colletallol (**4**)[4] and grahamimycin A1, which have 14-membered rings, are heterodimeric macrolides (Fig. 1). Analogs with various degrees of unsaturation such as tetrahydropyrenophorol (**5**)[5] and dihydropyrenophorin (**6**),[6] have also been reported. These naturally occurring macrodiolides show antifungal and anthelmintic activities. Pyrenophorol (**1**) is isolated from the fungi *Byssochlamys nivea* and *Stemphylium radicinum*. Pyrenophorin (**2**), an analog of pyrenophorol (**1**), is originated from the fungi *Pyrenophora avenae* and *Stemphylium radicinum*.

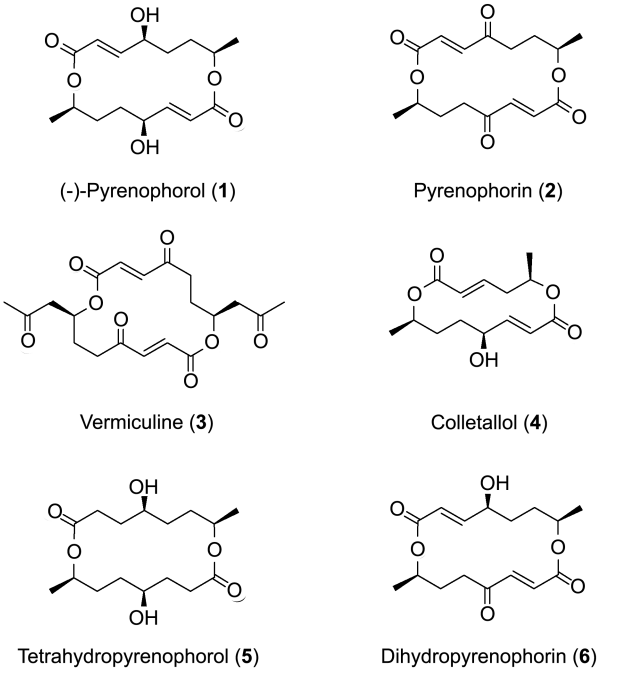


Figure 1. Macrodiolide antibiotics.

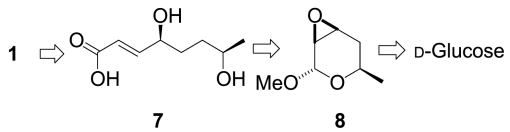
†This paper is dedicated to Professor Eun Lee on the occasion of his honorable retirement.

These macrodiolides have attracted significant attention of synthetic chemists because of their interesting biological properties and structural features. Kibayashi,[7] Zwanenburg,[8] and, recently, Yadav[9] have reported the synthesis of (–)-pyrenophorol. For the preparation of the key intermediate, chiral 4-hydroxy-2-alkenoate, Zwanenburg group exploited the photo-induced rearrangement of the corresponding expoxy diazomethyl ketone. On the other hand, Kibayashi group, synthesized (–)-pyrenophorol using C_2 symmetric (*R,R*)-diepoxide as a chiral building block. Recently, Yadav group synthesized (–)-pyrenophorol employing the hydrolytic kinetic resolution developed by Jacobson and the McMillan α-hydroxylation.

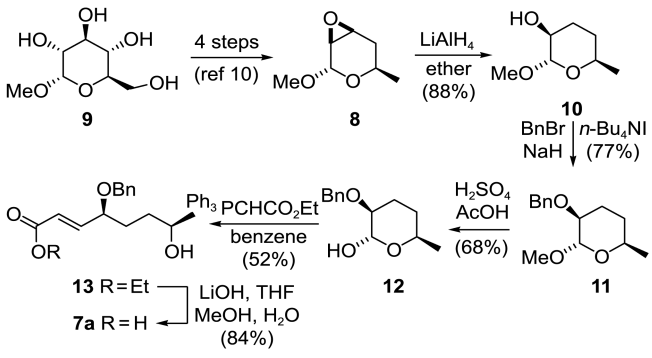
In connection with our interests in the synthesis of natural products, we, herein, report the total synthesis of (–)-pyenophorol (**1**). Our synthetic approach is based on the utilization of a chiral building block **8**, which was used in our previous synthesis of ophiocerins (Scheme 1).[10] The chiral building block **8,** prepared from D-glucose, has the potential to be used as a versatile chiral synthon.

As summarized in Scheme 2, the key starting chiral building block **8** was prepared from methyl α-D-glucopyranoside (**9**), which was prepared from α-D-glucose, in four steps.[10]

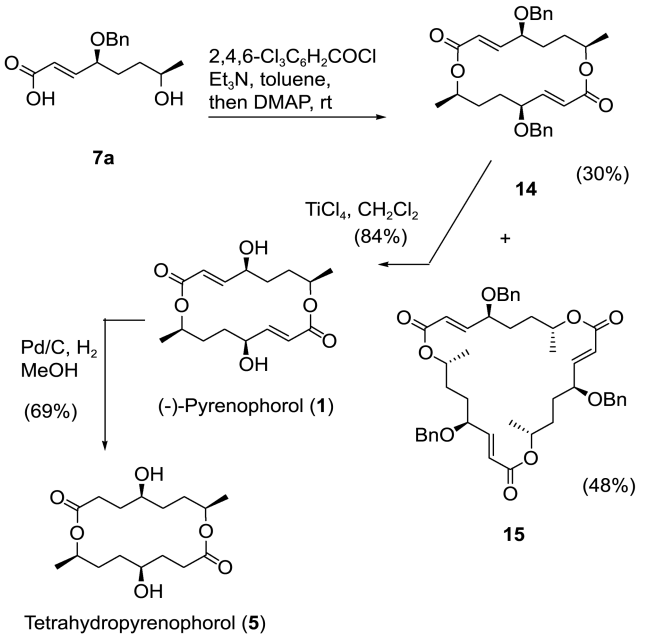
Regioselective reductive opening of the epoxide ring in **8** was the key step to establish the required stereocenter.



Scheme 1. Retrosynthetic analysis of (–)-pyrenophorol.



Scheme 2. Synthesis of hydroxy ester **7a**.



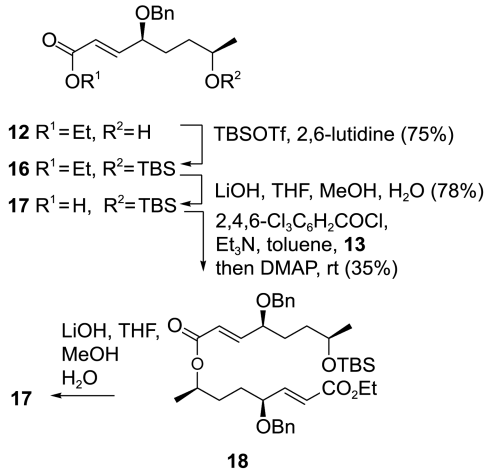
Scheme 3. Synthesis of (–)-pyrenophorol(**1**) and tetrahydropyrenophorol (**5**).

Opening was easily achieved in good yield by hydride attack ($LiAlH_4$, ether)[11] to provide **10**, which was subjected to protection. The resultant hydroxyl group was protected as a benzyl ether. Initial protection as a TBS ether turned out to be problematic as it did not survive the acidic conditions in the next step.

Hydrolysis of the methyl acetal under acidic conditions provided **12**, which was subjected to the Wittig olefination (Ph_3PCHCO_2Et, benzene) to yield hydroxy ester **13**. Hydrolysis of the hydroxy ester **13** afforded hydroxy acid **7a**.

The end game synthesis of (–)-pyrenophorol (**1**) is summarized in Scheme 3. The Yamaguchi esterification of **7a** afforded the desired dimeric product **14** in 30% yield, along with substantial amount of a byproduct. We suspect this undesired byproduct is trimer **15** based on its molecular weight and NMR spectra. Unfortunately, our efforts to minimize the formation of the trimeric product **15** were in vain even under the diluted conditions. The yield reached an optimum value when the concentration of **7a** was about 0.02 M. Higher or lower concentrations gave lower yields. In order to increase the yield of the dimeric product **14**, we tried sequential esterification (Scheme 4). The ζ-hydroxy group was first protected as a TBS ether. Hydrolysis of the ester (LiOH, THF, MeOH, H_2O) yielded acid **17** which was subjected to the coupling reaction with hydroxy ester **13** under the Yamaguchi conditions to provide the desired ester **18**. Hydrolysis of the ethyl ester and removal of the TBS group followed by lactonization would complete the synthesis. However, attempted hydrolysis of the ethyl ester resulted in the cleavage of both ester groups to furnish **17**. As we were not able to find the conditions enabling selective hydrolysis of the terminal ethyl ester group, we decided to discard the sequential esterification route.

The isolated lactone **14** was then debenzylated first under



Scheme 4. Sequential esterification for the synthesis of (–)-pyrenophorol.

the conventional DDQ protocol. The overnight treatment of **14** with DDQ indeed provided the desired (–)-pyrenophorol (**1**), but as a mixture with the monobenzylated product. We finally discovered that **14** can be cleanly debenzylated when treated with $TiCl_4$ in CH_2Cl_2 (Scheme 3).[12] Finally, tetrahydropyrenophorol was also prepared by reducing the double bond. The spectroscopic data of our (–)-pyrenophorol (**1**) and tetrahydropyrenophorol (**5**) are identical to those reported in the literature.[9]

In summary, we found that epoxide **8** is a useful intermediate for the synthesis of (–)-pyrenophorol (**1**). Epoxide **8** could be prepared from readily available D-glucose in a few steps. Regioselective reductive epoxide opening reaction successfully installed the desired stereocenter.

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