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Total Synthesis of PDIM A

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Total synthesis of phthiocerol dimycocerosate A (PDIM A), a virulent factor of *Mycobacterium tuberculosis*, has been achieved. Phthiocerol, a component of PDIM A, has been synthesized by subsequent epoxide-opening alkylation reactions with arabinose-derived diepoxide. This route is concise and efficient in supplying PDIM A for biological studies.

Keywords: Phthiocerol dimycocerosate A (PDIM A) | Tuberculosis | Total synthesis

Tuberculosis is a widespread problem, and leather infection disease is caused by *Mycobacterium tuberculosis*. It is estimated that 9.6 million people had fallen ill with tuberculosis in 2014.[1] In 1999, phthiocerol dimycocerosate A (PDIM A, Figure 1) was found to be a virulent factor of *Mycobacterium tuberculosis*.[2] PDIM A is required for further investigation of the infection system of *Mycobacterium tuberculosis*, but only one precedent of total synthesis has been reported by Minnaard group.[3] During the course of synthesizing polyketide compounds in our laboratory,[4] we started the synthesis of PDIM A. PDIM A consists of phthiocerol (**2**) and mycocerosic acid (**3**). Recently, we have achieved the concise synthesis of mycocerosic acid (**3**).[5] Herein, we report the synthesis of phthiocerol (**2**) as well as the total synthesis of PDIM A (**1**).

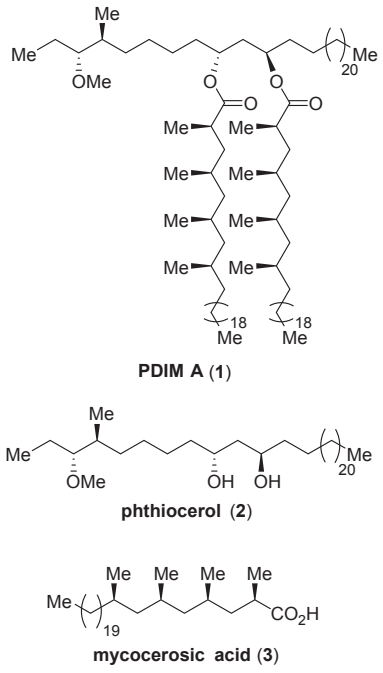
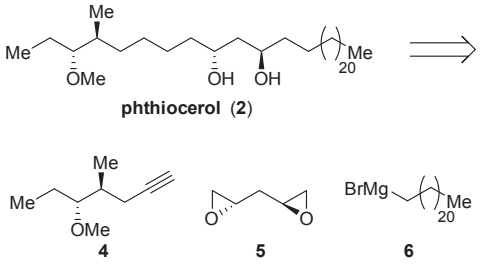


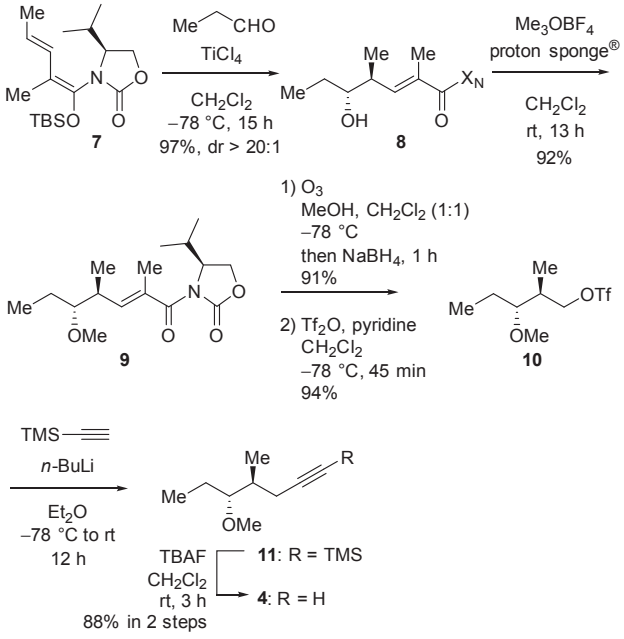
Figure 1. PDIM A and its components.

Our synthetic plan of phthiocerol (**2**) is shown in Scheme 1. To establish a highly convergent synthesis, phthiocerol (**2**) was divided into three segments, namely, acetylene **4**, diepoxide **5**,[6] and Grignard reagent **6**. C_2-Symmetrical diepoxide **5** would be subsequently alkylated with the carbanion derived from **4** and Grignard reagent **6** to provide an asymmetric chain.[7]

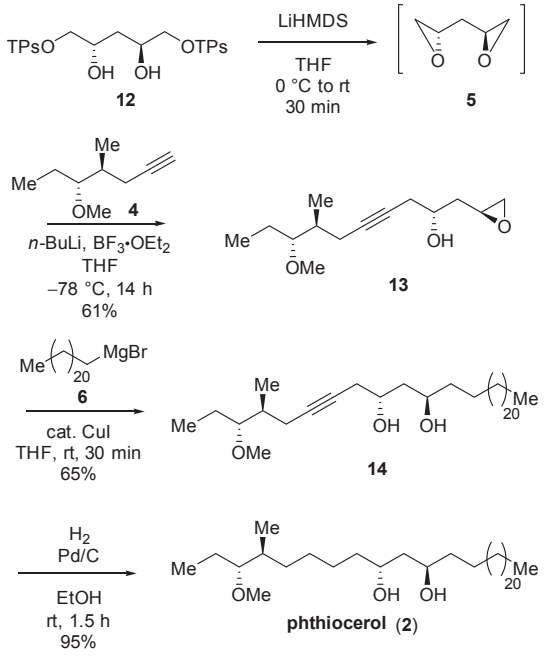
The synthesis of acetylene segment **4** is shown in Scheme 2. The vinylogous Mukaiyama aldol reaction using vinylketene silyl *N*,*O*-acetal **7** with propanal proceeded to give *anti*-adduct **8** in a stereoselective manner.[8] *O*-Methylation with Meerwein's reagent provided methyl ether **9** in good yield. Ozonolysis was followed by reduction to afford the corresponding primary alcohol, and the subsequent sulfonylation gave triflate **10** in good yield. Substitution with lithium acetylide, followed by de-*C*-silylation, provided acetylene segment **4**.



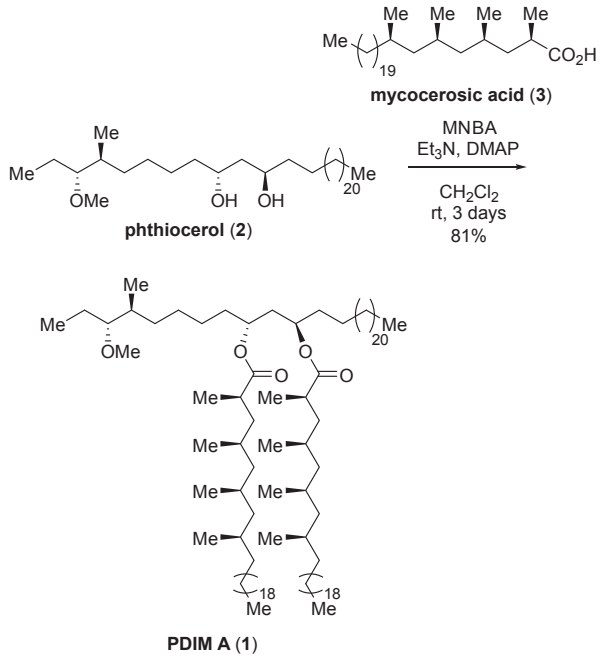
Scheme 1. Synthetic plan of phthiocerol (**2**).



Scheme 2. Synthesis of acetylene **4**.



Scheme 3. Total synthesis of phthiocerol (**2**).



Scheme 4. Total synthesis of PDIM A (**1**).

C_2-Diepoxide **5** was prepared by the Linclau method (Scheme 3).[6d] Treatment of diol **12**[6a] with lithium hexamethyldisilazide (LiHMDS) produced diepoxide **5**, which was reacted with the acetylide anion of **4** in the presence of boron trifluoride diethyl etherate ($BF_3 \cdot OEt_2$)[9] to afford monoalkylated **13** in one pot. Epoxide **13** was exposed to Grignard reagent **6** to afford *anti*-diol **14**. Hydrogenation of the resulting acetylene **14** provided phthiocerol (**2**) in excellent yield.

Finally, condensation of phthiocerol (**2**) and mycocerosic acid (**3**) by using the Shiina reagent (2-methyl-6-nitrobenzoic anhydride, MNBA)[10] afforded PDIM A (**1**) in good yield (Scheme 4). Spectral data of synthetic **1** were consistent with those of reported data.[2a–2c,3b]

In conclusion, we accomplished the total synthesis of PDIM A (**1**), a virulent factor of *Mycobacterium tuberculosis*. Phthiocerol (**2**) was synthesized by subsequent alkylation of C_2-diepoxide **5**. This route is concise and efficient in supplying PDIM A (**1**) for biological studies. Biological studies on PDIM A (**1**) are now in progress.[11]

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Supporting Information is available on http://dx.doi.org/10.1246/cl.160152.

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11 Although the first acylation of diol **2** proceeded non-regioselectively, *O*-protection of **13** would make possible the selective acylation to provide analogs.

