Total synthesis of (+)-hygrophorone B[12] and its analogues for the development of novel skeletal antimicrobail agents

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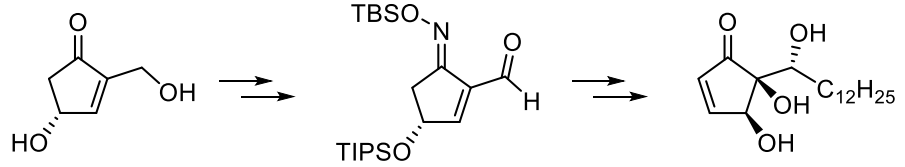
Uncountable numbers of lives have been saved by various antibiotics and other antimicrobial agents so far. However, antimicrobial resistance (AMR) is recently on the rise due to the recent heavy use of antibacterial drugs, and needs urgent action. Additionally, O'Neill has estimated that 10 million lives per year by 2050 may be lost to AMR-related disease due to the current increasing trend of AMR.[1] Therefore, the development and survey of new kinds of antimicrobial agents would certainly be worthwhile to avoid the worst-case scenario. From above the background, we focus on the hygrophorone-B-type, isolated from *Hygrophorus* species,[2] whose consist of a highly substituted cyclopentenone framework with hydroxy groups at two asymmetric centers and a hydrocarbon chain that contains an asymmetric hydroxyl group. These features are not found in existing antimicrobials.

In this presentation, we report the enantioselective total synthesis of (+)-hygrophorone B[12] and its analogues starting from a cyclopentenone **1** prepared from D-glucose.[3] This synthesis involved the following crucial steps: (i) the synthesis of key intermediate **2** by oximation of a ketone to stabilize the requisite aldehyde to install a side chain and (ii) coupling of an aldehyde with a side chain to assemble the desired hydrophorone. In addition, the results of antimicrobial evaluation have revealed that hygrophororne B type compounds are highly effective in preventing the proliferation of chemical-sensitive bacteria and AMR bacteria.



1 from D-glucose　　Key Intermediate **2**　　Hygrophorone B[12]

1) J. O'Neill. Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. The Review on Antimicrobial Resistance. **2016**, 1. 2) T. Lübken, J. Schmidt, A. Porzel, N. Arnold, L. Wessjohann, *Phytochemistry* **2004**, *65*, 1061. 3) a) T. Kamishima, T. Nonaka, T. Watanabe, Y. Koseki, H. Kasai, *Bull. Chem. Soc. Jpn*. **2018**. *91*, 1691; b) Y. Koseki, T. Watanabe, T. Kamishima, E. Kwon, H. Kasai, *Bull. Chem. Soc. Jpn*. **2019**, *92*, 1324.