The synthesis study of (±)-subglutinol A and B

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Introduction

Subglutinols were isolated from *Fusarium subglutinanes*, which are traditional chinese medicines, in 1995 (Figure 1, *J. Org. Chem.* **1995**, *60*, 7076.). They have immunosuppressive activity related to IL-2. These natural products contain a dodecahydronaphtho[2, 1-b]furan core and a highly functionalized α-pyrone ring. Total synthesis of subglutinol A and B have reported by Katoh (*Eur. J. Org. Chem.* **2011**, *26*, 5020.) and Hong (*Chem. Asian J.* **2010**, *5*, 1902.). According to their studies, subglutinols were synthesized in 18 or more steps. In this study, we tried to develop more efficient synthetic methods of subglutinol A (**1**) and B (**2**).

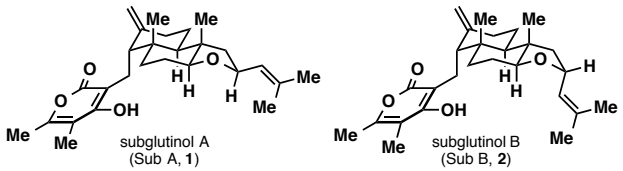

Figure 1. structure of subglutinol A and B

Research plan and results

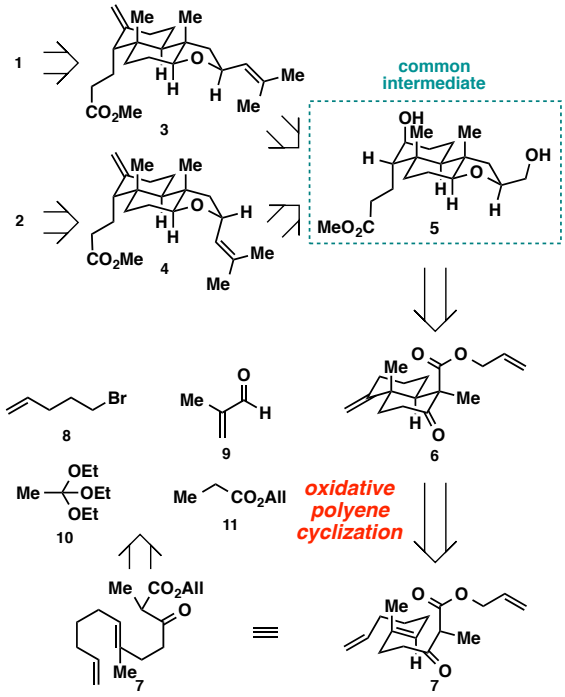

Figure 2. retrosynthetic analyses of subglutinols

A retrosysnthetic analysis of subglutinol A (**1**) and B (**2**) are shown in Figure 2. An α-pyrone moiety is introduced into tricyclic compounds **3** and **4** at the late stage of each synthesis route. The tricyclic compounds **3** and **4** are synthesized from a common intermediate **5**. The common intermediate **5** is afforded from an allyl ester **6**, and the allyl ester **6** is synthesized by oxidative polyene cyclization from a chain compound **7**. This oxidative polyene cyclization allows a effective formation of a dodecahydronaphtho[2, 1-b]fran structure including several asymmetric carbons. The cyclization precursor **7** is made from 5-bromopenten **8**, methacrolein **9**, triehtyl orthoacetate **10** and allyl propionate **11** in a few steps.

The firsts steps was a addition reaction between a Grignard reagent made from 5-bromopenten **8** and methacrolein **9**, followed by Johnson-Claisen rearrangement using triethyl orthoacetate **10** and Craisen condensation with allyl propionate **11** to afford a chain polyene compound **7** in moderate yields. A synthesis of cyclized product **6** was achieved by oxidative polyene cyclization using metal oxidants in electrochemical condition. In electrochemistry, it is possible to decrease an excessive amount of metal oxidants. Moreover, some problems (such as stability of metal oxidants against atmosphere and lack of scalablity in this cyclization) were solved. Decarboxylative allylation and a formation of tetrahydrofuran ring using cyclization product gave a tricyclic compound. The common intermediate **5** was achieved via several steps using the tricyclic compound. A conversion of substituents using common intermediate **5** gave compounds **3** and **4**, which were reported as synthetic intermediate of total synthesis about **1** and **2**. Herein, the effective formal total synthesis of **1** and **2** were completed.

Conclusions

We undertook the development of total synthesis of subglutinol A and B. The formal total synthesis of them were accomplished using oxidative polyene cyclization in electrochemistry.