Synthetic Studies on Diterpenoid Pyrones,
Nalanthalide, Sesquicillin, and Candelalides

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Nalanthalide, isolated from the culture of *Nalanthamala* sp., and candelalides, isolated from the culture broth of *Sesquicillim candelabrum*, were found to be novel blockers of the voltage-gated potassium channel Kv1.3 by Merck research group. In human T cell, blockage of Kv1.3 channels causes the prevention of membrane depolarization, which attenuates intarcellular Ca^{2+} levels for T cell activation and proliferation. Therefore, nalanthalide and candelalides are expected to be promising new leads for the immunosuppressant. A closely related α-pyrone-containig diterpenoid sesquicillin, wherein the γ-pyrone ring of nalanthalide is replaced with an α-pyrone ring, was previously isolated from *Acremonium* sp. It was reported that sesquicillin shows a variety of biological properties such as glucocorticoid antagonist, anticancer and G1 phase arrest activities.

We have accomplished the first total syntheses of nalanthalide and sesquicillin in convergent manner by utilizing coupling reaction of *trans*-decalin segment, prepared through a stereoselective [2,3]-Wittig rearrangement, with γ-pyrone segment. The coupling product consisting of the two segments could be easily converted to nalanthalide via Barton-MacCombie protocol and acetylation of the resulted key intermediate. In addition, transformation of γ-pyrone in the key intermediate to the corresponding α-pyrone under basic conditions led to completion of the synthesis of sesquicillin.

Further synthetic studies on candelalides utilizing similar strategy are now in progress, and the results will be disclosed in the presentation.