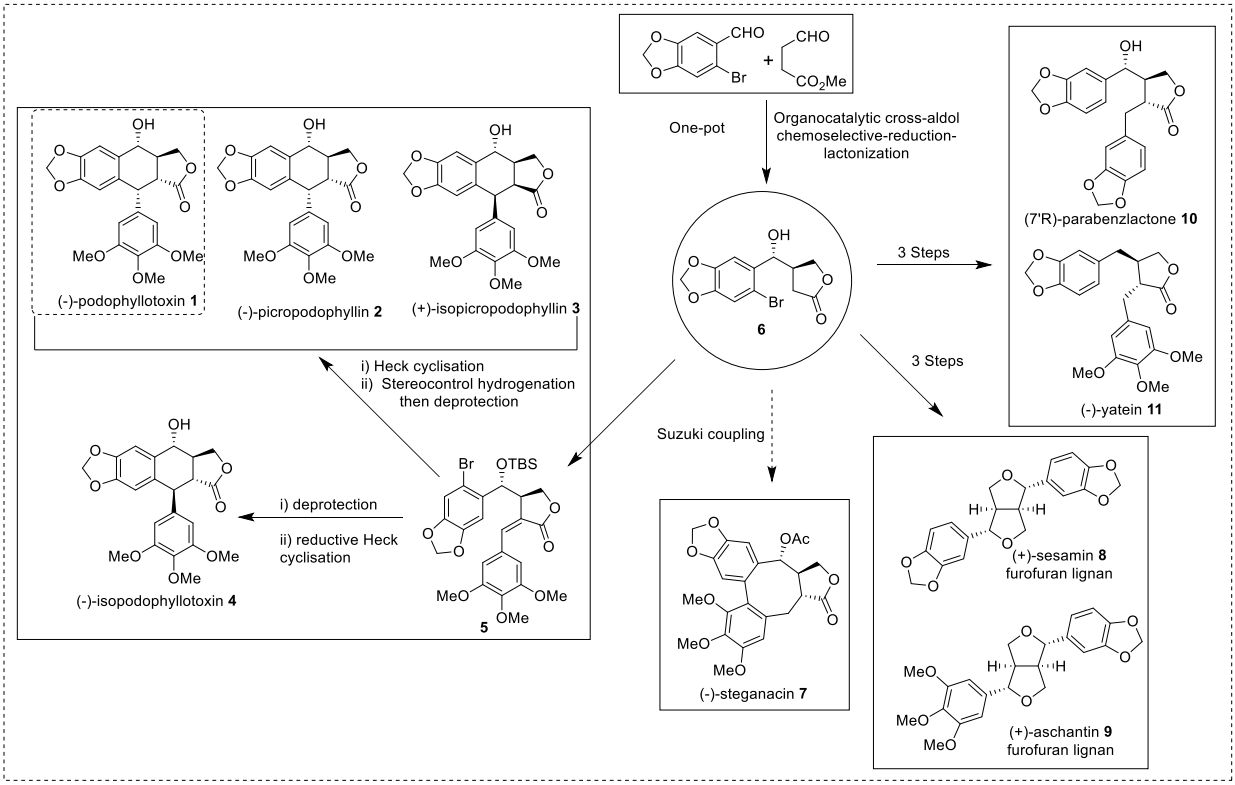
Abstract

Lignans, generated by a β-β' linkage of two cinnamyl units, are the diversely oriented natural products with potent bioactivities. Either γ-butyrolactone or tetrahydrofuran moiety with different oxy-functionalized arenescan be found as a common structural unit in thousands of the naturally occurring lignans. Among the oxyarenes, 3,4-methelenedioxyarene is a very important structural motif found in many bioactive lignans. (-)-Podophyllotoxin**1** is not only in the central position of these lignans but also in whole lignan family. As this molecule itself is used for the treatment of genital warts and serves as a synthetic precursor for the chemotherapeutic drugs etoposide and teniposide. In addition, the natural isomeric lignans of podophyllotoxin exhibit important bioactivities. Thus these attracted considerable attention towards synthetic chemists for the asymmetric total synthesis of these molecules for the last sixty years. However, a method for the catalytic enantioselective concise total synthesis was still an unmet challenge. Our focus was on that synthetic challenge, where we optimized an organocatalytic aldol route to access a lactone intermediate **6**.This lactone intermediate **6** serves as the precursor for the synthesis of (-)-podophyllotoxin **1**, it's stereoisomeric analogousand other allied lignans. An intramolecular Heck cyclisation of benzylidene lactone **5** and subsequent distal stereocontrol catalytic transfer hydrogenation (CTH) completed the total synthesis of (-)-podophyllotoxin **1** in five steps. Stereoisomeric derivatives of (-)-podophyllotoxin such as (-)-picropodophyllin **2**, (+)-isopicropodophyllin **3**, formal synthesis (+)-podophyllotoxin (**ent-1**) and (-)-isopodophyllotoxin **4** were synthesized using different hydrogenation and reductive-Heck reaction, respectively. The synthesized lactone intermediate **6** was utilized for the study of Suzuki cross coupling and Stille coupling reactions towards the synthesis of (-)-steganacin **7**. Short scalable total synthesis of furofuranlignanssuch as (+)-sesamin**8**, (+)-aschantin**9** and dibenzylbutyrolactone lignans (7′R)-parabenzlactone **10**, (-)-yatein **11** were accomplished using the synthesized lactone intermediate **6** (Scheme 1).

Abstract



Scheme 1: Unified asymmetric total synthesis of (-)-podophyllotoxin, its stereoisomers,and other lignans

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Keywords: (-)-Podophyllotoxin, Organocatalytic cross aldol reaction, Intramolecular Heck cyclisation, Reductive Heck cyclisation, Catalytic transfer hydrogenation (CTH), Distal stereocontrol hydrogenation.