Abstract

Podophyllotoxin is a naturally occurring lignan with a wide range of biological activities, including anti-cancer and anti-viral properties. Total synthesis of podophyllotoxin has been a long-standing challenge in organic synthesis due to its complex and highly functionalized structure. In this work, we present our approach toward the total synthesis of podophyllotoxin using a fully stereoselective strategy.

Our approach involves the enantioselective vinylation of 2-bromo-piperonal followed by a stereoselective conjugate addition reaction combined with the addition of methylene unit and a metathesis reaction, that provides starting material for another conjugate addition, which could lead to the target. The key step of our synthesis is the stereoselective conjugate addition of an organolithium to an α,β-unsaturated ester, which leads to the formation of a chiral quaternary center with high selectivity and metathesis that successfully joins parts into the desired cycle.

Despite the success of our strategy in achieving the desired stereoselectivity, we encountered some challenges in the subsequent steps of the synthesis, which prevented us from completing the total synthesis of podophyllotoxin. However, our results demonstrate the potential of enantioselective vinylation and stereoselective conjugate addition reactions in the total synthesis of complex natural products.

Future studies will focus on optimizing the reaction conditions and developing new strategies to overcome the remaining challenges in the total synthesis of podophyllotoxin. Overall, our work provides valuable insights into the development of new methods for reaching not only podophyllotoxin, but also the synthesis of complex natural products and will inspire new directions for future research in this field.