SUMMARY OF Ph.D. DISSERTATION

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Title

Synthetic Studies of Biologically Active Alkaloids Based on the Claisen Rearrangement and Its Cascade Version

Abstract

Claisen rearrangement, a well known [3,3]sigmatropic rearrangement reaction with thermal supra-supra facial chirality transfer, is a very useful method for natural product synthesis. Despite its usefulness, reported examples which applied this reaction for the construction of benzylic quaternary carbon center were limited. Moreover, cascade version of Claisen rearrangement that could form two asymmetric carbon centers from the corresponding vicinal diol substrate in one-pot operation was rarely reported. In this thesis, *de novo* natural product syntheses toward galanthamine and morphine utilizing Claisen rearrangement for the construction of sterically hindered benzylic quaternary carbon center and its application to the cascade reaction, starting from carbohydrate, are described.

Galanthamine, an *Amaryllidaceae* alkaloid, is clinically used as the medicine for Alzheimer's disease. 2-Nitrophenol-catalyzed Johnson-Claisen rearrangement of cyclohexenol possessing *o*-substituted phenyl group, prepared from **D**-glucose using Ferrier's carbocyclization, afforded the rearranged product in high yield. The dibenzofuran skeleton was effectively constructed by a bromonium ion-mediated cyclization. After introduction of a carbon-carbon double bond, the Pictet-Spengler type cyclization, followed by reduction of the amide function, completed the chiral and non-biomimetic synthesis of galanthamine.

In the opium alkaloid morphine synthesis, **D**-glucal was converted into a cyclohexene diol possessing a cathecol moiety using the Ferrier's carbocyclization and Suzuki-Miyaura coupling as the key transformations. The cascade Claisen rearrangement of the diol in the presence of 2-nitrophenol successfully provided the double-rearranged product in moderate yield. The epoxide-mediated dibenzofuran formation, followed by intramolecular Friedel-Crafts reaction, afforded desired tetracyclic substrate. Introduction of a methylamine function and Birch reduction provided (–)-dihydroisocodeine, representing the formal synthesis of (-)-morphine.