博 士 論 文 の 内 容 の 要 旨

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論文題目	Pd-catalyzed hydrogenolysis of activated cyclopropanes and its application to asymmetric total synthesis of bioactive lignans **（Pd 触媒を用いる活性化シクロプロパンの加水素分解反応の開発と生物活性リグナン類の不斉全合成への応用）**

（博士論文の内容の要旨）

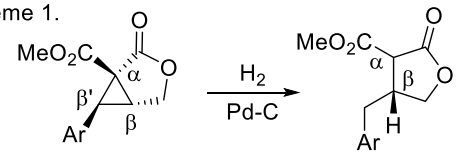
1. As an introduction, Chapter 1 was described the characteristics and properties of cyclopropane which is the key compound in the synthesis of this paper.

Cyclopropanes are an important class of organic compounds due to their synthetic utility and their widespread occurrence in nature. In addition, the rigid conformation of cyclopropanes can be exploited in stereocontrolled syntheses. In particular, donor- acceptor (D- A) cyclopropane has been studied for a long time, and many examples of the use of D-A cyclopropane in synthetic organic chemistry have been reported.

2. Catalytic hydrogenolysis of enantioenriched donor-acceptor cyclopropanes using H_2 and Palladium on charcoal

Lignans are attracting considerable attention due to their widespread distribution in plants and their varied bioactivity. To achieve the total synthesis of these bioactive lignans, I investigated a Pd-catalyzed highly regio- and stereoselective hydrogenolysis of activated cyclopropanes as a key step. In the section 2, I described the hydrogenolysis of activated cyclopropanes, including enantioenriched bicyclic lactones **1** and arylcyclopropanedicarboxylic diesters **3**, using H_2 (1 atm) and a catalytic amount of palladium on charcoal. The present reaction can be used as a new protocol for the asymmetric synthesis of trans-α,β-disubstituted γ-butyrolactones **2** and γ-substituted diesters **4**. As shown in section 2, the synthetic utility of the present reaction was demonstrated by the asymmetric total synthesis of five kind of lignans with high ee and excellent dr.

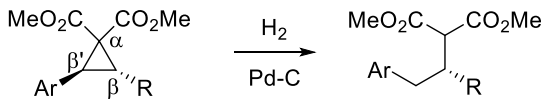
Scheme 1.



1 **2**

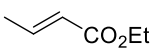
Ar = Ph, dimethoxyphenyl, trimethoxyphenyl, methylenedioxyphenyl, benzyloxymethoxyphenyl, 4-F-C_6H_4-, 4-CO_2Me-C_6H_4-, 4-NO_2-C_6H_4-

Scheme 2.



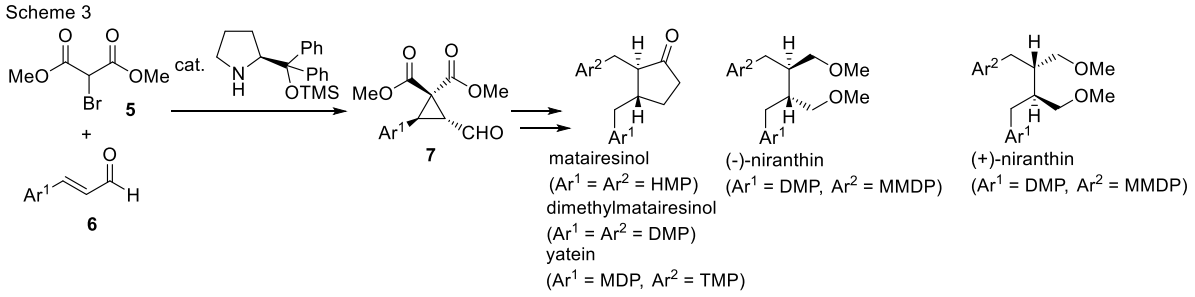
3 **4**

Ar = Ph, R = H

Ar = dimethoxyphenyl, R = CHO, CO_2Me, 

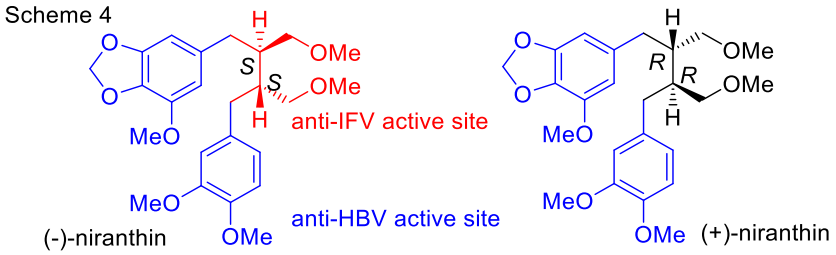
3. Asymmetric total synthesis of five bioactive lignans using Pd-catalyzed highly regio- and stereoselective hydrogenolysis of enantioenriched and activated cyclopropanes.

Using the Pd-catalyzed reductive ring-opening of activated cyclopropanes which is established in section 2, I achieved the asymmetric total synthesis of five bioactive lignans, matairesinol, dimethylmatairesinol, yatein, (-)-niranthin, and (+)-niranthin. Although niranthin exhibits anti-viral activity toward hepatitis B virus (HBV),5b the enantiomeric SAR (structure- activity relationship) for the anti-viral activity of niranthin has not been revealed. To examine the SAR for a pair of enantiomers, we achieved the an alternative asymmetric synthesis of both enantiomers: (-)-niranthin, and (+)-niranthin.



4. HBV and IFV activity of synthesized (-)- and (+)-niranthin

Collaborated with Dr. Noriko Shimazaki of the National Institute of Infectious Diseases, bioassays of the synthesized (-)- and (+)-niranthins using hepatitis B and influenza viruses were carried out to elucidate the relationship between the enantiomeric structure and the anti-viral activity of niranthin. The results indicate that although the anti-HBV activity does not differ significantly between these two enantiomers, the anti-IFV activity of (-)-niranthin is more potent than that of (+)-niranthin. I speculated that the anti-HBV active site of niranthin might be a part of the molecular structure such as aromatic groups which are far from chiral centers. In contrast, anti-IFV active site of niranthin might be closer to the chiral centers (Scheme 4).



In summary, we achieved the asymmetric total syntheses of five bioactive lignans: matairesinol, dimethylmatairesinol, yatein, (-)-niranthin, and (+)-niranthin. Key reactions include the Pd-catalyzed reductive ring-opening reaction of enantioenriched cyclopropanes under a hydrogen atmosphere. Thus, we have achieved the first alternative total synthesis of (-)-niranthin and (+)-niranthin. Using the synthesized niranthin enantiomers, we elucidated the relationship between the enantiomer structure and its anti-viral activity against the hepatitis B virus (HBV) and the influenza virus (IFV). This result may be interpreted in terms of a different recognition of the enantiomeric structure of a bioactive compound among different virus species.