Doctoral Dissertation (Shinshu University)

Pd-catalyzed hydrogenolysis of activated cyclopropanes and its application to asymmetric total synthesis of bioactive lignans

September 2022

Ryotaro Ota

Contents:

Chapter 1

Introduction

Chapter 1 Introduction

1.1 Structure and Properties of Cyclopropane

When four carbons make a bond against the "C", they take the sp^3 hybrid orbital, whose ideal bond angle is 109.5º. However, the carbon-carbon bond angle of cyclopropane is 60º, which does not match the direction of the sp^3 carbon orbital. Adolf von Baeyer suggested that the instability of a compound on the ring correlates with the deviation of its internal angle from the tetrahedral angle, and that the larger the deviation, the greater the bond angle strain the molecule has and the more unstable it becomes[1)]. In other words, the strain caused by shrinking the tetrahedral angle from 109.5º to 60º is very large.

C. A. Coulson and W. A. Moffitt proposed the following model for this binding mode[2)] (Figure 1.1). This carbon-carbon bond is called a bent bond or banana bond, and the orbital overlap is smaller than that of a general σ bond. The overlap of the hybridized orbitals is not symmetrical about the bond axis, resulting in a pseudo σ bond. Therefore, the bond is intermediate between σ and π, and is more easily broken than a normal bond between sp^3 carbons.

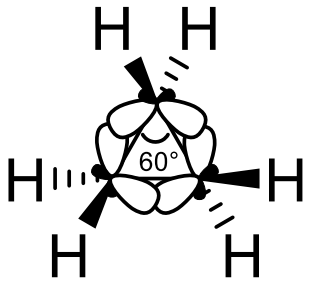


Figure 1.1 Coulson-Moffitt model

In contrast to the Coulson-Moffitt model with bent bonds, Walsh proposed the following model[3)] (Figure 1.2). In this model, the carbon atoms forming cyclopropanes are in sp^2 hybridized orbitals and exist on the same plane. Two of the three sp^2 hybridization orbitals bond to hydrogen atoms. The remaining one overlaps the orbitals in the center of the three-membered ring to form a pseudo σ bond. The remaining p orbital forms a pseudo π bond with a neighboring carbon. In other words, carbons are linked to each other by two types of bonds. The carbon-hydrogen bond is in the perpendicular plane to the cyclopropane ring, and the

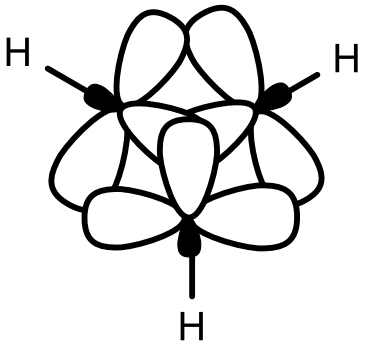
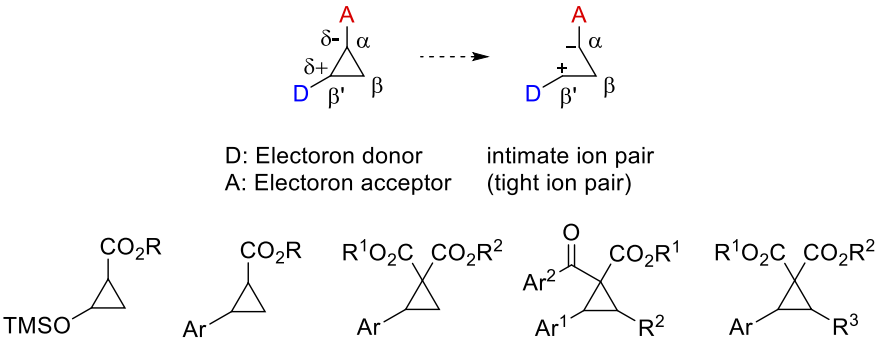


Figure 1.2 Walsh model

HCH bond angle is 120º, which is larger than the HCH bond angle of 109º for sp^3 carbon. The Walsh model also suggests that the carbon-carbon bond in cyclopropane is a bond with σ and π.

1.2 Donor-acceptor cyclopropane

Cyclopropanes are an important class of organic compounds due to their synthetic utility and their widespread occurrence in nature[4,5]. In addition, the rigid conformation of cyclopropanes as the smallest conceivable [C_3] ring compound can be exploited in stereocontrolled syntheses In particular, cyclopropanes with electron-donating and electron-withdrawing groups are called d-a cyclopropanes, which have attracted considerable attention due to recent synthetic developments[6,7]. Therefore, they can be applied to highly stereoselective synthesis and are highly useful in synthetic organic chemistry (Scheme 1.1).

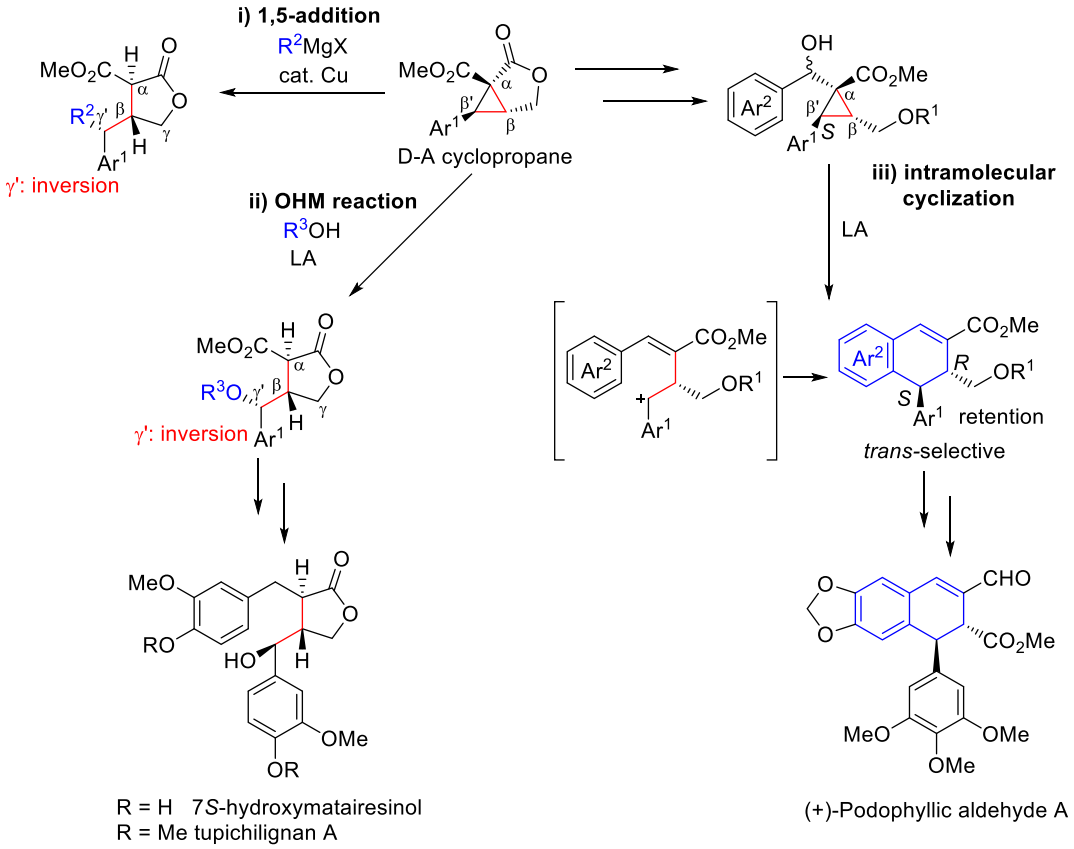


Scheme 1.1 Examples of D-A cyclopropane

The push-pull effect, in which cations are stabilized by electron-donating groups and anions are stabilized by electron-withdrawing groups, causes high polarization of carbon-carbon bonds and thus allows a variety of reactions. In general, D-A cyclopropanes with siloxy or aryl groups as electron-donating groups and carbonyl groups as electron-withdrawing groups have long been studied. In particular, many applications of cyclopropanes with high activity due to the substitution of two carbonyl groups have been reported in synthetic organic chemistry.

1.3 Research on D-A cyclopropane in our laboratory

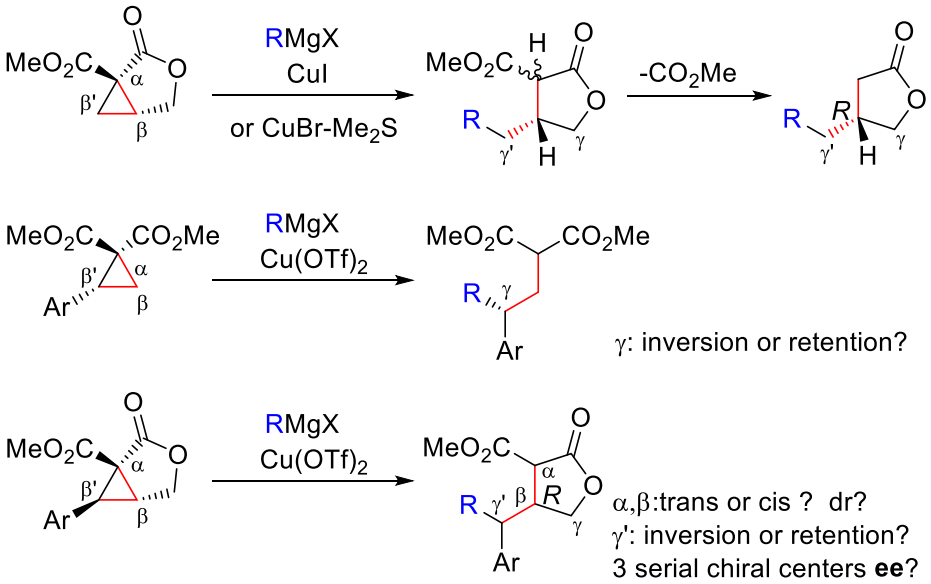
Recently, our laboratory has been developing asymmetric synthesis of polysubstituted D-A cyclopropanes and highly stereoselective synthetic methods involving ring cleavage of these cyclopropanes[8,9]. Tetrasubstituted D-A cyclopropanes were synthesized by the method of Wang et al.[10] using a Hayashi-Jørgensen catalyst[11]. The synthesized tetrasubstituted D-A cyclopropanes were also used for 1) 1,5-addition reaction,[9f] in which the reaction proceeds highly stereoselectively with ring cleavage upon nucleophilic attack, 2) oxyhomo Michael (OHM) reaction[9e] and total synthesis of tupichilignan and 7S-hydroxymatairesinol with lignan lactone skeleton,[9i] 3) intramolecular ring-opening-cyclization reaction[9h,g] capable of highly stereoselective construction of dihydronaphthalene skeleton from cyclopropylcarbinol and total synthesis of podophyllic aldehyde A was achieved (Scheme 1.2).



Scheme 1.2 Highly stereoselective ring cleavage reactions and their applications.

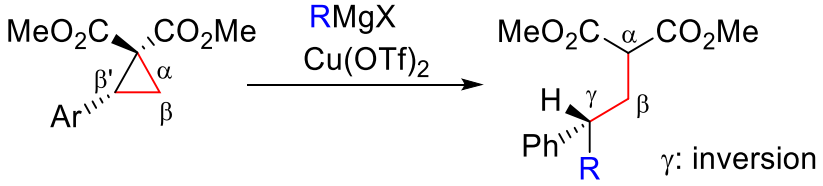
1.3.1 1,5-addition reaction

Asymmetric 1,4-conjugate addition using a Grignard reagent with a copper catalyst is one of the most useful protocols for enantioselective carbon–carbon bond formation in organic synthesis[12]. As an extension of this method, Lee and co-workers have reported the 1,5-addition[13] of a Grignard reagent to an enantioenriched bicyclic cyclopropane in their asymmetric synthesis of β-substituted γ-butyrolactones[14] (Scheme 1.3). However, due to the absence of an aryl substituent on the β'-carbon, there are no data for the stereoselectivity at the γ'-position of the ring-opened product.



Scheme 1.3 Copper-catalyzed 1,5-additions of grignard reagents to enantioenriched donor–acceptor cyclopropanes.

In the 1,5-addition of alkyl groups by dialkyl copper catalyst, enantioenriched cyclopropanes with substituents at the β' position were used to investigate three items: whether the addition of alkyl groups proceeds by inversion or retention, enantioselectivity and diastereoselectivity. As a result, it was concluded that the reaction proceeds in a highly enantioselective manner and the addition of alkyl groups proceeds by inversion (Scheme 1.4).

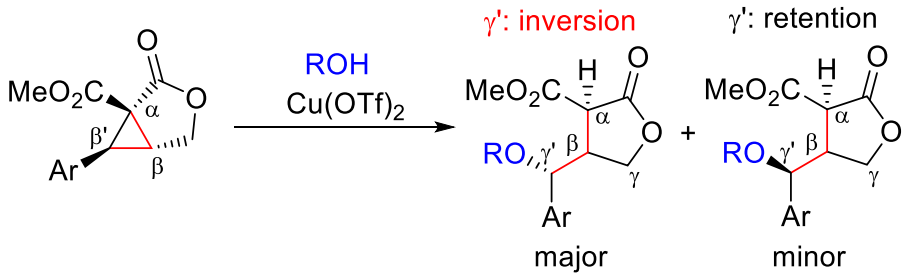


Scheme 1.4　1,5-Additions of alkyl groups to enantioenriched cyclopropane.

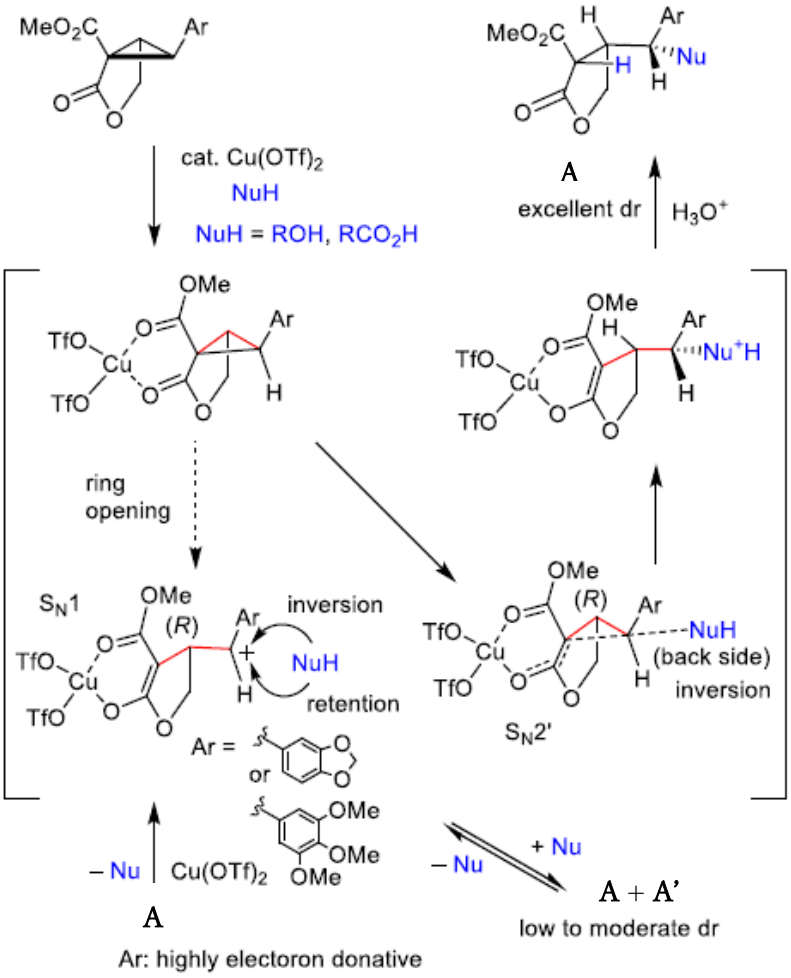
1.3.2　Oxy-homo-Michael (OHM) reaction

The intermolecular stereoinductive oxy-homo-Michael (OHM) addition of nucleophiles to donor–acceptor (D–A) cyclopropane has also been studied[6,15,16]. Most of the reactions proceed with inversion manner on the benzyl position. However, the synthesis of fused-ring γ-butyrolactones involves the OHM addition of water to racemic cyclopropane and sequential lactonization to furnish bislactone as the major product with retention mode[16]. Recently, the asymmetric OHM addition of alcohols or water to racemic D–A cyclopropanes using kinetic and dynamic kinetic resolution in the presence of a Cu-catalyst with chiral ligands has been reported[6]. Although the mechanisms of similar processes have been proposed[17,18,19], the mechanism of the OHM reaction remains ambiguous. Taking these previous studies into account, we focus on the stereoselectivity and mechanisms of the OHM reaction of enantioenriched bicyclic D–A cyclopropanes.

The results of the study showed that the reaction proceeds in a highly stereoselective and highly asymmetric propagation with a reaction mode similar to S_N2', and the β' position of cyclopropane is inverted (Scheme 1.5). Diastereoselectivity is also found to be reduced when the aryl group on the D-A cyclopropane ring is a highly electron-donating substrate (Scheme 1.6).

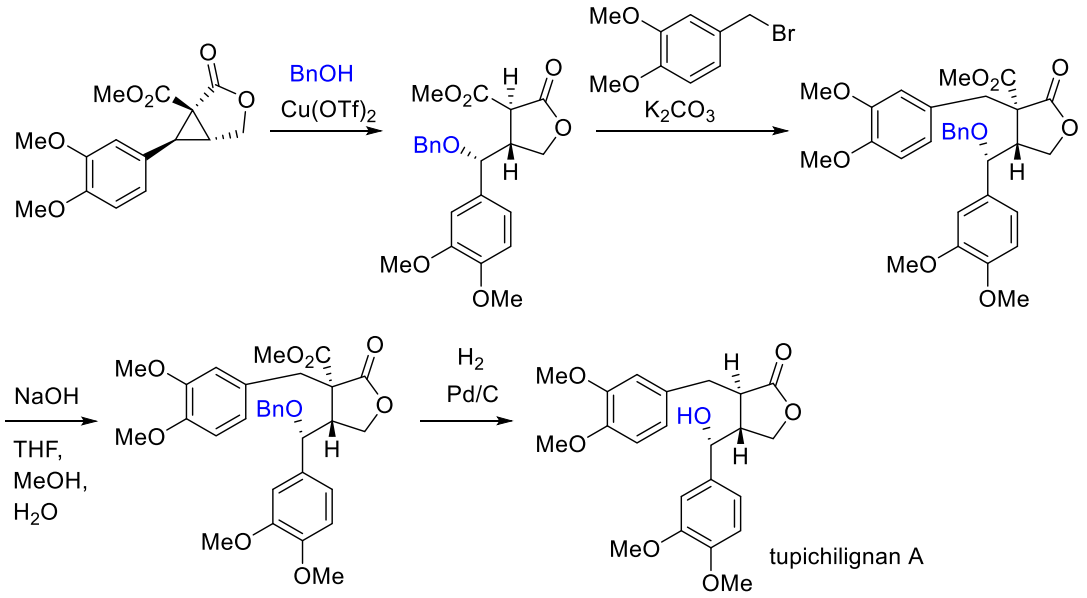


Scheme 1.5　Oxy-homo-Michael reaction

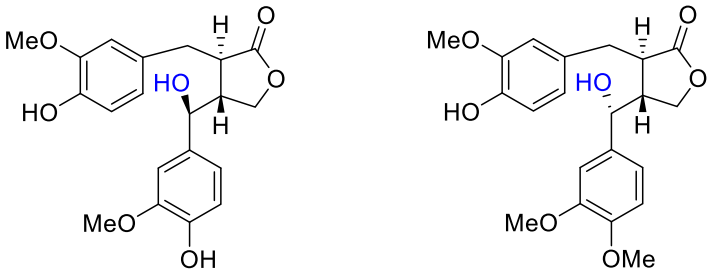


Scheme 1.6 Proposed reaction mechanism.

Then, using this OHM reaction as a key reaction, they achieved the total synthesis of bioactive substances with lignan lactone skeleton, which is used as a therapeutic agent for rheumatic diseases and snakebite (Scheme 1.7). The lignan lactone skeleton was formed by the action of benzyl alcohol on enantioenriched bicyclolactone by OHM reaction, followed by the introduction of a benzyl group at the α-position of the carbonyl group. Then, through decarboxylation and debenzylation, the synthesis of tupichilignan A was achieved. *7S*-hydroxymatairesinol and *7S*-hydroxyartigenin were also achieved by the same synthetic route.



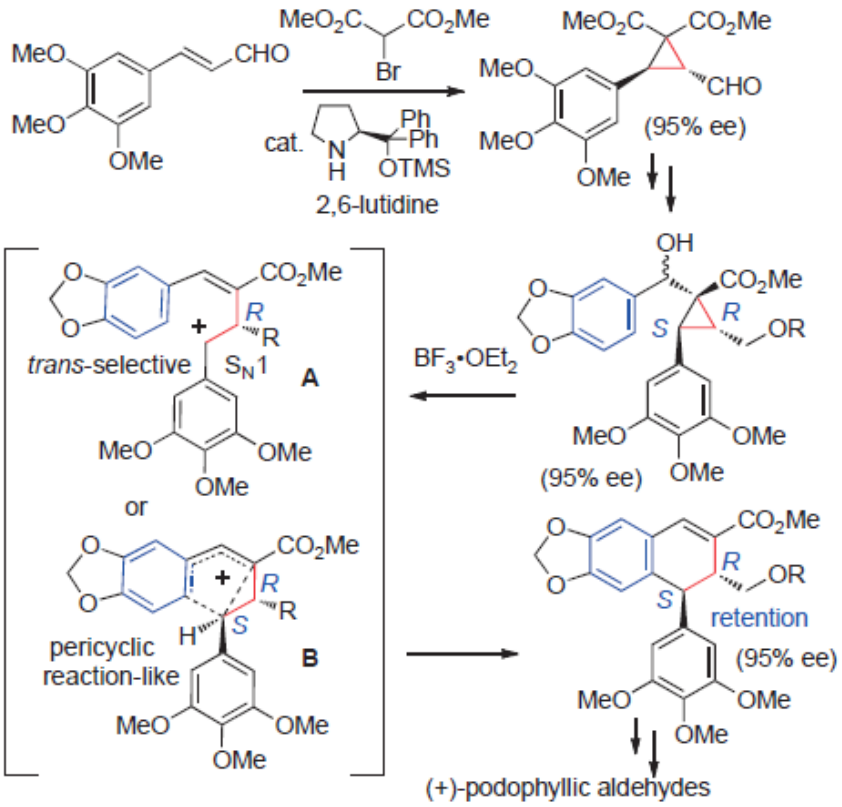
Scheme 1.7 Asymmetric total synthesis of tupichilignan A.



Scheme 1.8 7S-hydroxymatairesinol and 7R-hydroxyarctigenin

1.3.3 Intramolecular ring-opening-cyclization reaction

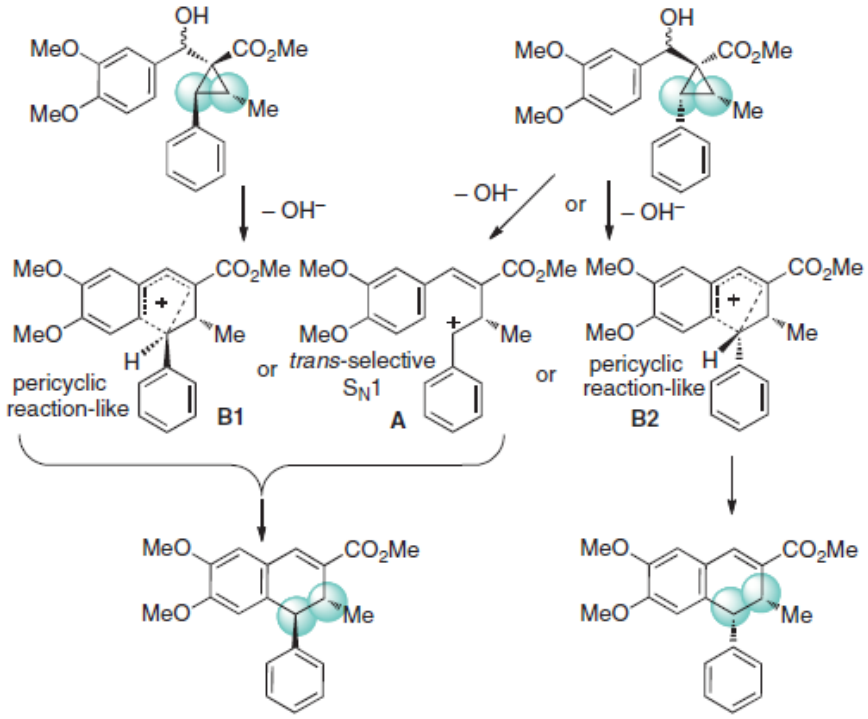
Cyclization reactions of donor-acceptor (D-A) cyclopropanes are recognized as versatile protocols for the syntheses of carbocyclic and heterocyclic scaffolds[20,21]. As a part of a program of synthetic studies using cyclopropropane moieties[9], we achieved the first asymmetric total synthesis of (+)-podophillic aldehydes using the highly stereoselective Lewis acid-mediated ring-opening cyclization of D-A cyclopropylcarbinols to afford 1-aryl-1,2-dihydronaphthalene with retention of stereochemistry and high enantiomeric excess (Scheme 1.9)[9c].



Scheme 1.9 7S-hydroxymatairesinol and 7R-hydroxyarctigenin

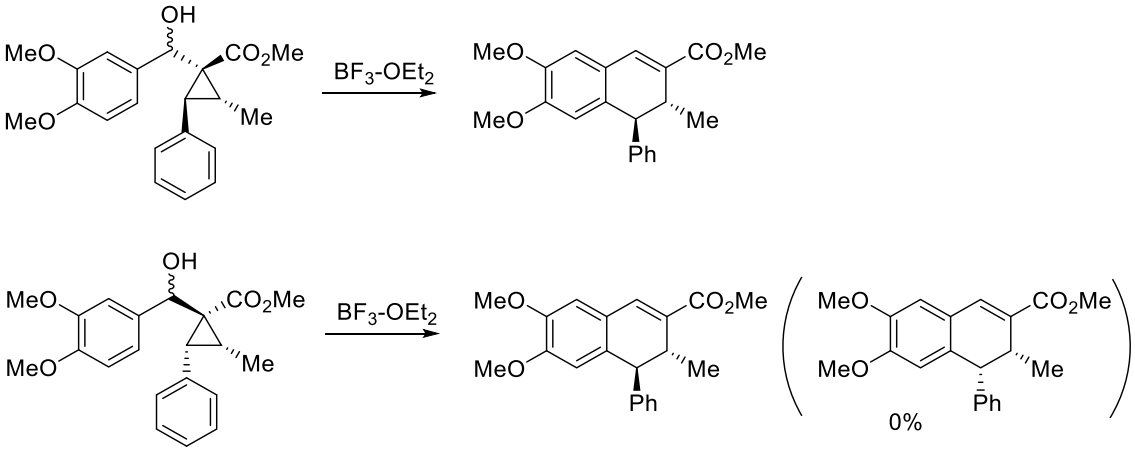
Meanwhile, the mechanism of the reaction has not been revealed, and two plausible mechanisms can be proposed. One is the Friedel-Crafts-type attack of the aromatic ring to the benzyl cation to furnish the *trans*-product based on the neighboring chiral center (*trans*-selective S_N1 pathway via cation A).

The other is the pericyclic reaction-like mechanism via transition state B with retention of stereochemistry of the cyclopropane. (Scheme 1.10)

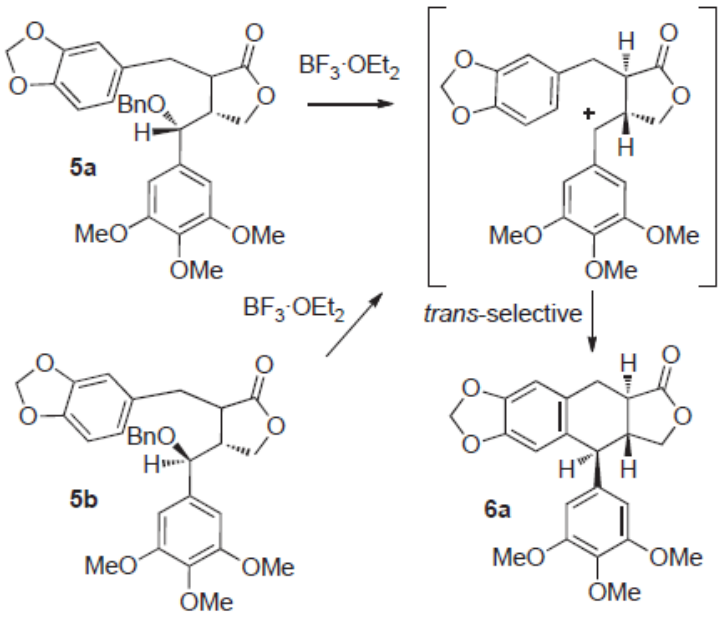


Scheme 1.10 Speculated mechanisms for the ring-opening cyclizations of cyclopropylcarbinol

Therefore, we investigated the reaction mechanism and found that the Lewis acid-mediated ring-opening cyclization of cyclopropylcarbinol and the simple cyclization of 7-benzyloxydibenzyl lignan lactone give *trans* isomers (Scheme 1.11, 12). Based on these results, the mechanism of these cyclizations was tested via the S_N1 pathway via the *trans*-selective Friedel-Crafts reaction, which was confirmed to be the S_N1 pathway; the S_N1 pathway was found to be the most likely route to the *trans* isomer.



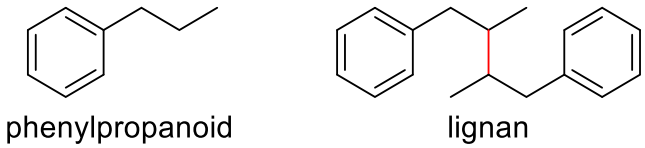
Scheme 1.11 Ring-opening cyclizations of cyclopropylcarbinol.



Scheme 1.12 Mechanisms for the cyclizations of benzyloxy dibenzyl lignan lactones.

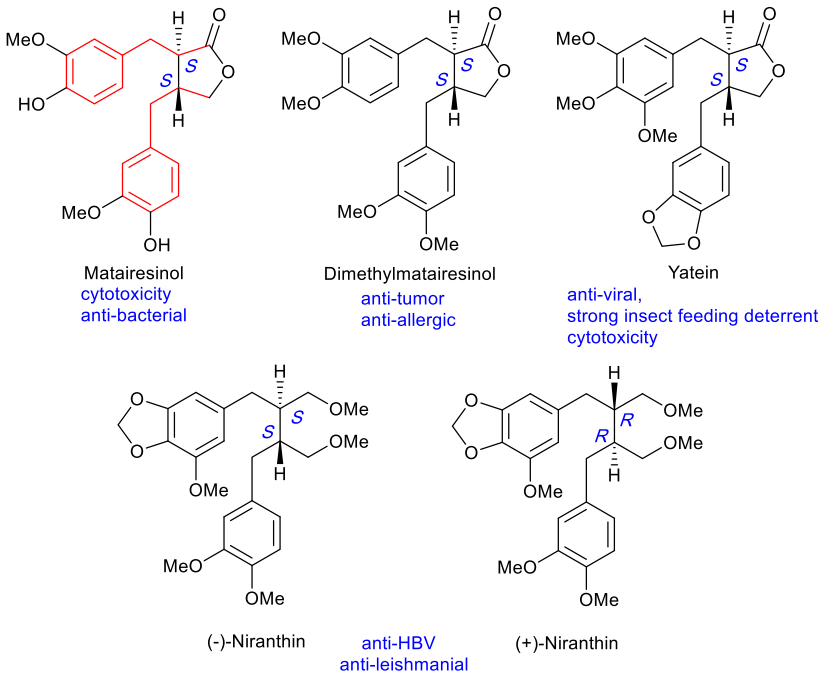
1.4 Lignans

Lignans are compounds with two C_6C_3 units found in various plants and have a structure in which two phenylpropanoid units are joined at the β-position of the propane chain (Scheme 1.13), and have diverse biological activities [22].



Scheme 1.13 Carbon frameworks of phenylpropanoid and lignan

Lignans, which are widely distributed in plants, have attracted attention because of their varied bioactivities[24-28]. For example, matairesinol[25], dimethylmatairesinol[26], yatein[27], and niranthin[28] are found in nature and exhibit *e.g.*, cytotoxicity[25b,d,26b,27b], anti-bacterial[25c], anti-allergic[26c], anti-viral[27d,28b,e], antileishmanial[28d], and strong insect-feeding-deterrent activity[27c] (Scheme 1.17).



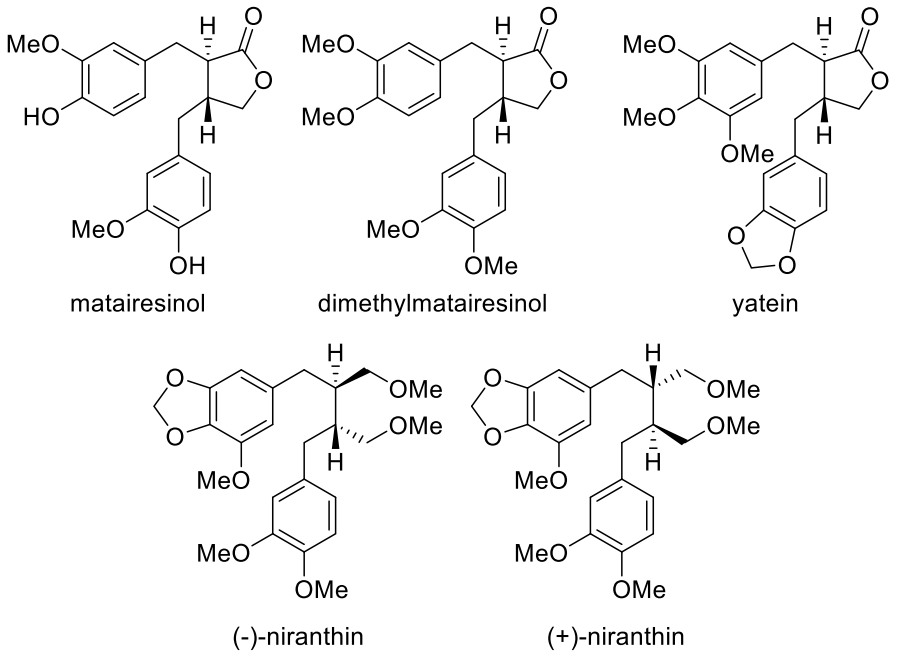
Scheme 1.14 Stractures of various lignans

1.5 Outline of study

1.5.1 Exploration of a key reaction for the asymmetric total synthesis of bioactive lignans : matairesinol, dimethylmatairesinol, yatein, (-)- and (+)-niranthin (Catalytic hydrogenolysis of enantioenriched Donor-Acceptor cyclopropanes)

Lignans are known to have a variety of bioactivity. Although niranthin exhibits anti-viral activity toward the hepatitis B virus (HBV), 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, I aimed to synthesize five bioactive lignans, including (-)-niranthin and (+)-niranthin (Scheme 1.15). However, the 1,5-addition reaction (Scheme 1.3) and the oxy-homo-Michael reaction (Scheme 1.5) developed in our laboratory give products with an alkyl or hydroxy group substituted at the 7-position. The ring-opening cyclization (Scheme 1.9) also gives a product with a cyclic structure. In view of the above, it is necessary to develop a new reaction to synthesize lignans with no substitution at the 7-position.

Therefore, I investigated the development of a novel reaction to synthesize bioactive lignans .



Scheme 1.15 Target lignans

1.5.2 Asymmetric total synthesis of several bioactive lignans using donor–acceptor cyclopropanes and bioassay of (-)- and (+)-niranthin against HBV and IFV

Using the Pd-catalyzed reductive ring-opening of activated cyclopropanes, I achieved the asymmetric total synthesis of five bioactive lignans, matairesinol, dimethylmatairesinol, yatein, (-)-niranthin, and (+)-niranthin. (Scheme 1.15)

1.5.3 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 (Fig 1.3).

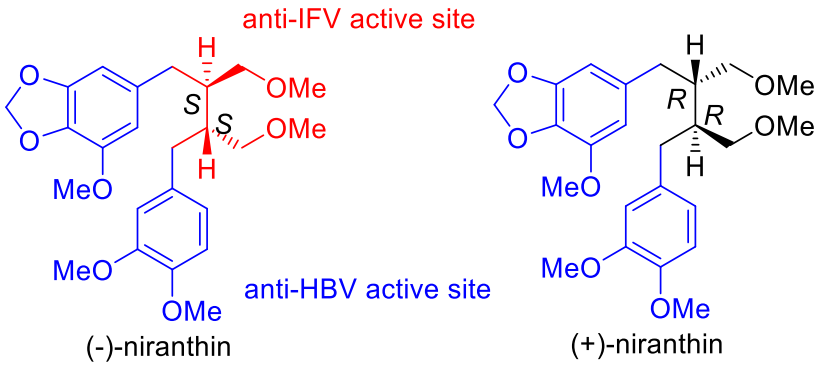


Figure 1.3 A speculation for the bioactive site of niranthin against HBV and IFV.

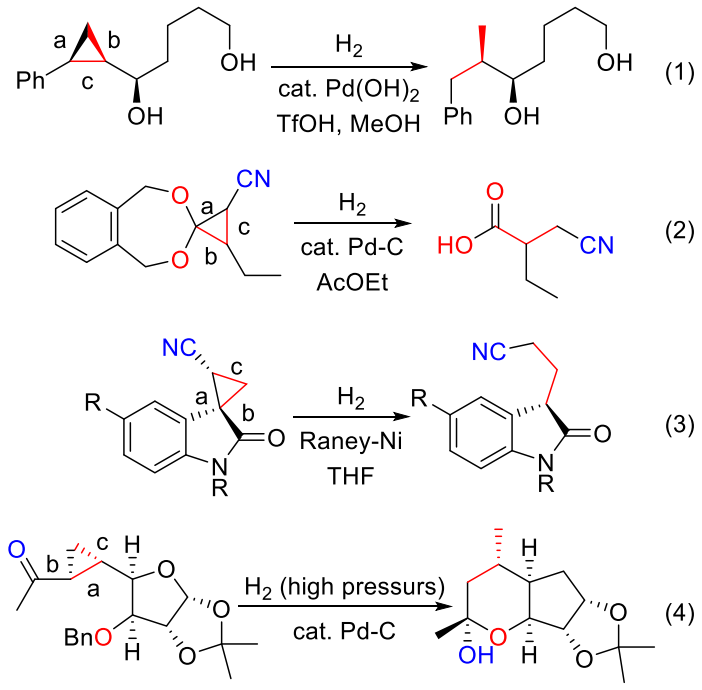
Chapter 2

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

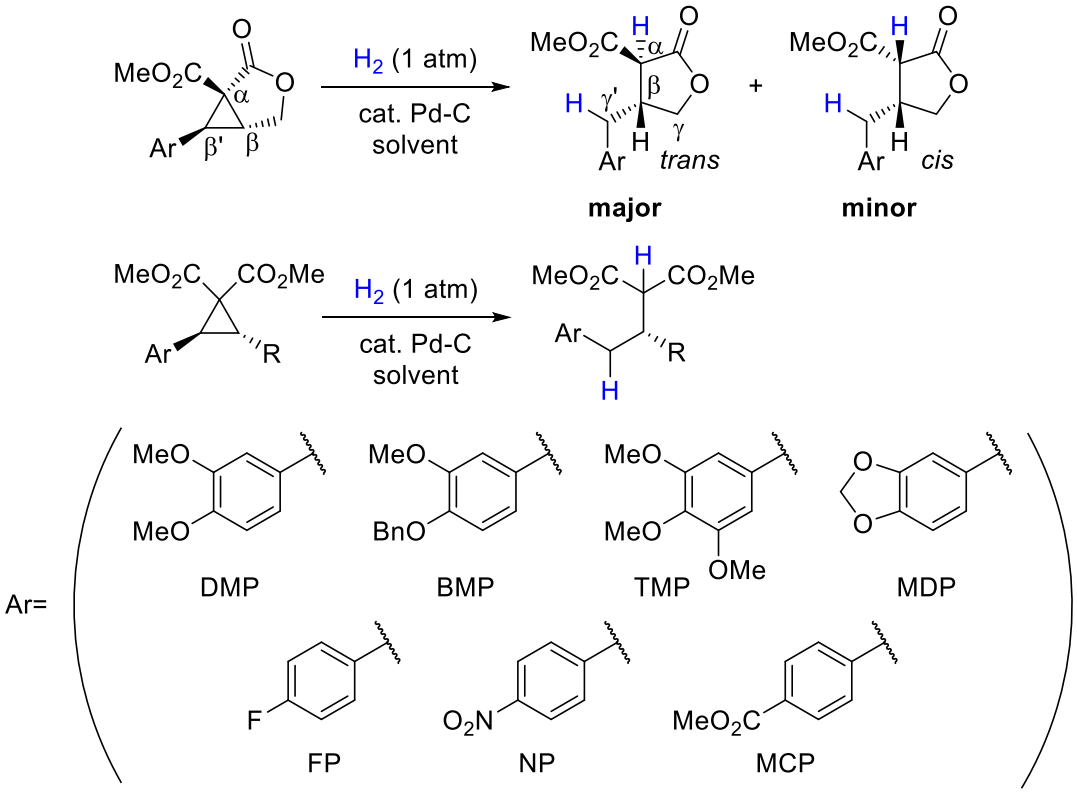
Chapter 2 Catalytic hydrogenolysis of enantioenriched donor-acceptor cyclopropanes using H_2 and Palladium on charcoal

2.1 Introduction

Although the hydrogenolysis of several types of cyclopropanes using H_2 (1 atm) in combination with heterogeneous Pd or Ni catalysts has been studied[29], the background information on the hydrogenolysis of cyclopropanes in the scientific literature is not sufficient to establish comprehensive guidelines for the regioselectivity of the bond cleavage (Scheme 2.1) For example, phenyl-substituted acceptorless cyclopropanes are cleaved at bond a [Equation(1)]. In the case of D–A cyclopropanes such as aryl-cyanocyclopropanes, the ring-opening of the cyclopropanes occurs at bond a, i.e., the bond between the donor and the acceptor group [Equations (2) and (3)]. However, bond a between the donor and acceptor group was not cleaved during the hydrogenolysis of alkyl- and acetyl-substituted D–A cyclopropanes [Equation (4)]. To the best of our knowledge, the hydrogenolysis of representative D–A cyclopropanes of the type 2-arylcyclopropane-1,1-dicarboxylic diester has not yet been reported. In this paper, we report the hydrogenolysis of D–A cyclopropanes, including enantioenriched bicyclic lactones and arylcyclopropanedicarboxylic diesters, using H_2 (1 atm) and a catalytic amount of palladium on charcoal (Pd/C; Scheme 2.2)



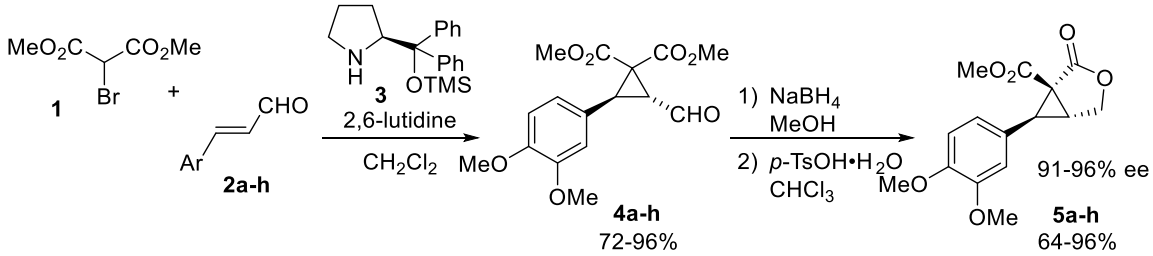
Scheme 2.1 Examples of the hydrogenolysis of cyclopropanes that contain donor and/or acceptor groups.



Scheme 2.2 Hydrogenolysis of D-A cyclopropane

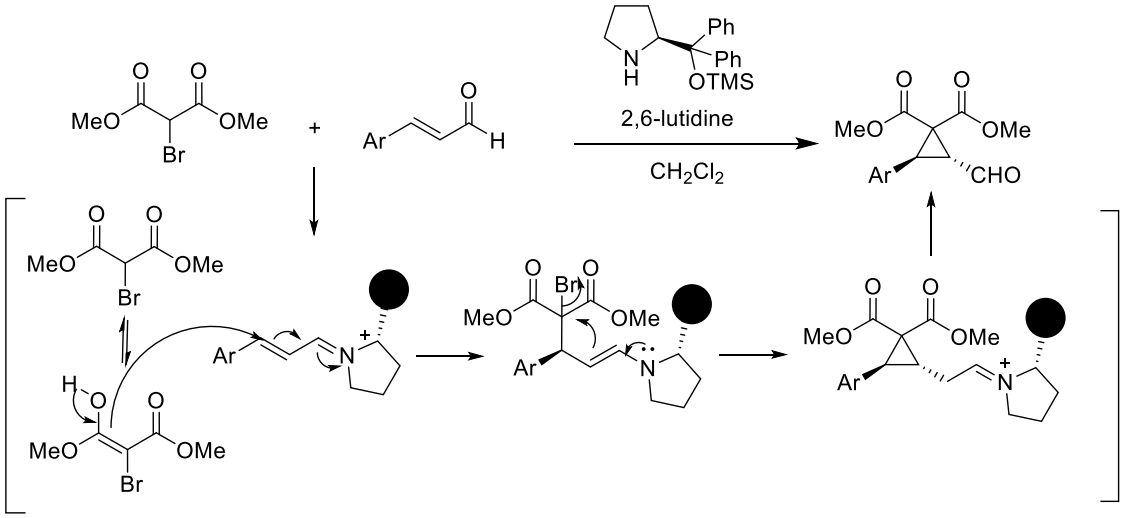
2.2 Synthesis of bicyclolactone and arylcyclopropanediesters

First, asymmetric cyclopropanation of dimethyl α-bromomalonate **1** and cinnamaldehyde derivatives **2a-h** was carried out using L-proline-derived Hayashi-Jørgensen catalyst **3**. The cyclopropanes **4a-h** were reduced with sodium borohydride and intramolecular lactonization with *p*-toluenesulfonic acid monohydrate to form bicyclolactones **5a-h** in two steps (Scheme 2.3).



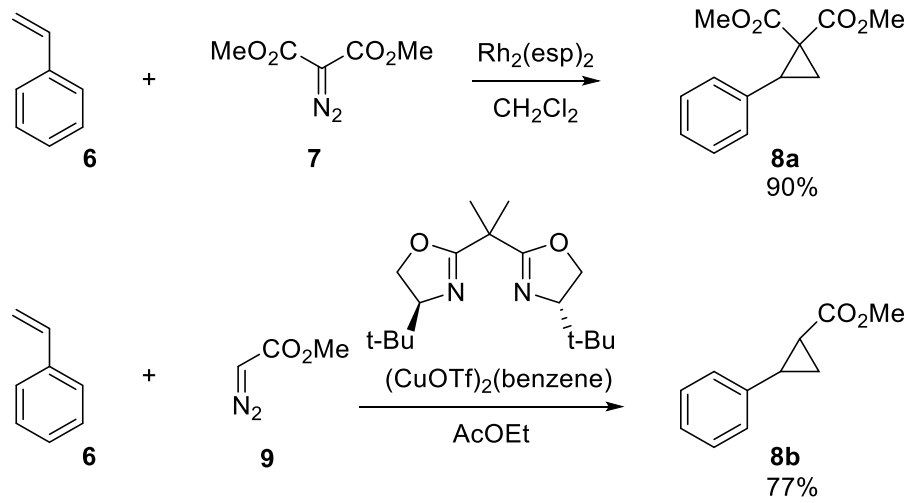
Scheme 2.3 Synthesis of bicyclolactones

The reaction mechanism of asymmetric cyclopropanation is shown below. (Scheme 2.4)



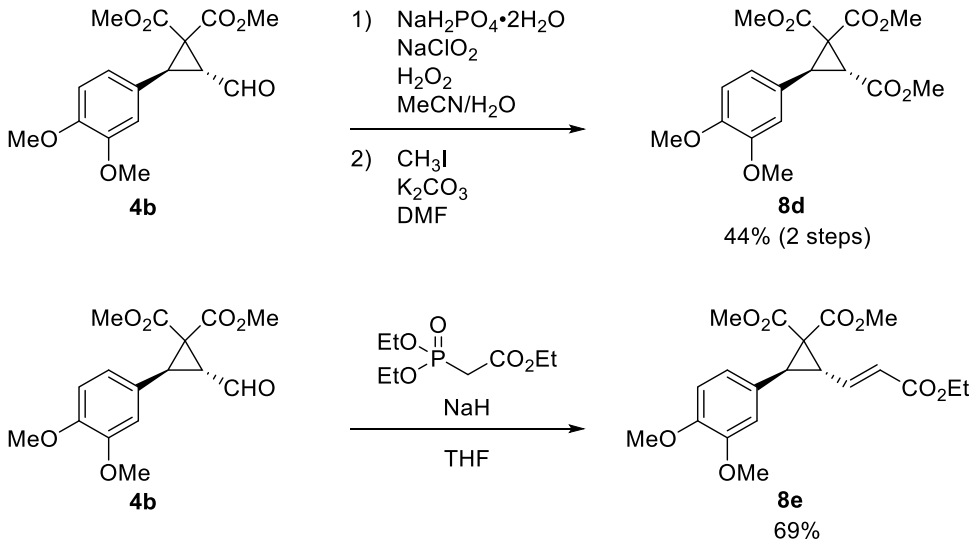
Scheme 2.4 Reaction mechanism of asymmetric cyclopropanation

The reaction of styrene **6** with dimethyl-α-diazomalonate **7** in the presence of Rh catalyst[30] gave arylcyclopropanediesters **8a**. The reaction of styrene **6** with diazoacetate **9** in the presence of Cu catalyst[31] afforded arylcyclopropane monoesters **8b** (Scheme 2.5).



Scheme 2.5 Synthesis of arylcyclopropane diesters and arylcyclopropane monoesters

Cyclopropane triester **8d** was synthesized from aldehyde **4b** by Pinnick oxidation followed by methylation. Alkenylcyclopropanediester **8e** was synthesized by Horner-Wadsworth-Emmons reaction to aldehyde **4b** (Scheme 2.6).



Scheme 2.6 Synthesis of cyclopropane triester and alkenylcyclopropanediester

2.3 Investigation of hydrolysis of bicyclolactone

First, hydrogenolysis was performed on bicyclolactone under an H_2 atmosphere (1 atm). The reaction of bicyclolactone **5a** in the presence of Pd-C catalyst in THF solvent at room temperature resulted in reductive ring-opening to afford trans-α,β-disubstituted lactone **10a** as the main product in 61% yield (Table 2.1, entry 1). A similar reaction using AcOEt as solvent gave **10a** in good yield, and the yield was improved by reducing the reaction temperature to 0°C (entry 2, 3). The same reaction was performed with MeOH as the solvent, and the yield was improved (entry 4). In order to examine the reaction conditions under mild conditions for various aryl groups, the reaction conditions were set to 0°C in AcOEt solvent. Hydrogenolysis to bicyclolactone **5b-d** with electron-donating aryl groups gave the corresponding ring opening compound **10b-d** in high yield (entry 5-7). The steric structures of **5c** and **5d** were determined from ^{1}H-NMR spectral data in the literature to indicate that the trans isomer is the main product[32](Fig 2.1). The other products were also assigned to the trans isomer as the main product by analogy with the ^{1}H-NMR spectral data. The reaction of bicyclolactone **5e** with benzyloxymethoxyphenyl (BMP) at 0°C for 1h resulted in a high yield of **10** (entry 8). The reaction at 23h at room temperature gave the **10e'** in high yield, in which ring-opening and debenzylation occurred (entry 9). Hydrogenolysis to bicyclolactone **5f-h** with electron-withdrawing aryl groups also gave the corresponding ring opening compound **10f-h** in high yield (entry 10-12). Bicyclolactone **5h** with nitrophenyl (NP) also gave lactone **10h'** in high yield, in which the nitro group was reduced along with the ring opening by changing the reaction conditions to rt in MeOH solvent (entry 13).

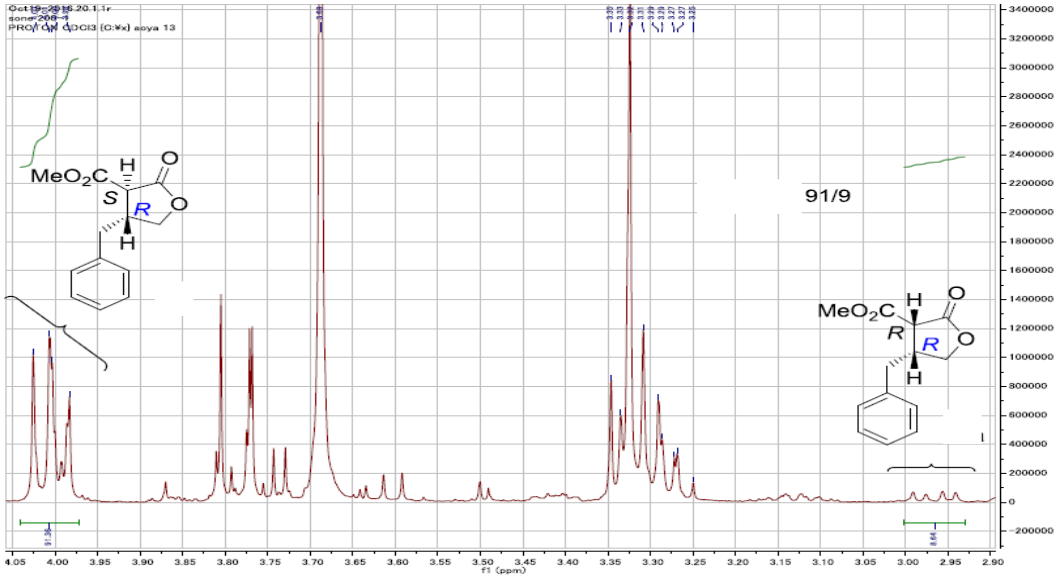
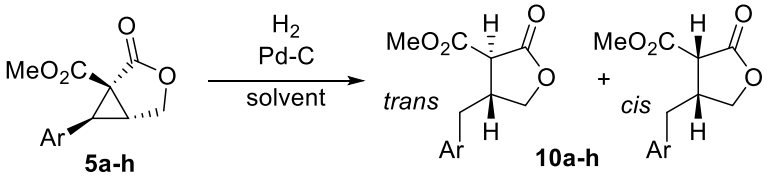


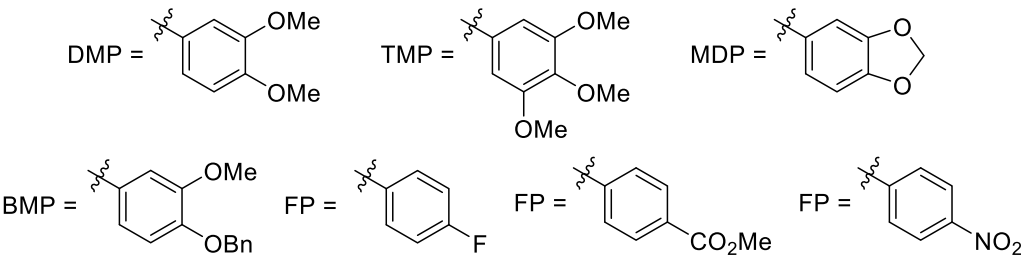
Fig 2.1 ^{1}H NMR spectra after hydrogenolysis of D-A cyclopropane **5a**

Table 2.1 Hydrogenolysis of bicyclolactones



entry	**5**	Ar	solvent	Temp. (°C)	**10**	yield %	dr *trans*/*cis*
1	**5a**	Ph	THF	rt	**10a**	61	91/9
2			AcOEt	rt	**10a**	65	91/9
3				0	**10a**	78	91/9
4			MeOH	rt	**10a**	78	91/9
5	**5b**	DMP	AcOEt	0	**10b**	93	91/9
6	**5c**	TMP	AcOEt	0	**10c**	87	93/7
7	**5d**	MDP	AcOEt	0	**10d**	94	92/8
8	**5e**	BMP	AcOEt	0	**10e**	90	95/5
9			AcOEt	rt[a]	**10e'**	80	95/5
10	**5f**	FP	AcOEt	0	**10f**	96	92/8
11	**5g**	MCP	AcOEt	0	**10g**	97	95/5
12	**5h**	NP	AcOEt	0	**10h**	75	92/8
13			MeOH	rt[b]	**10h'**	92	92/8

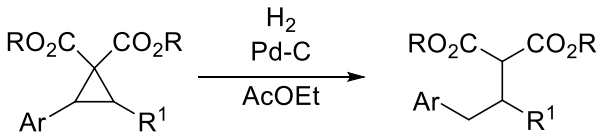
[a] t = 23 h. [b] t = 18 h



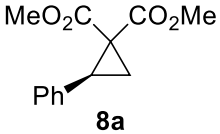
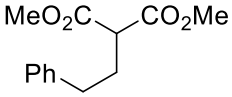
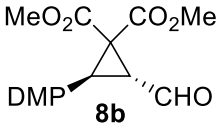
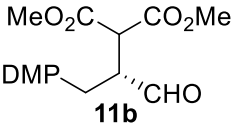
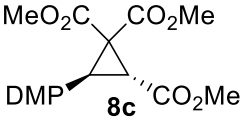
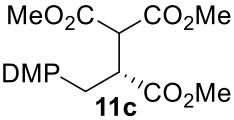
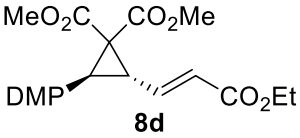
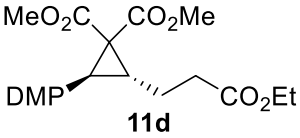
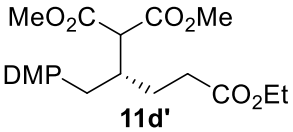
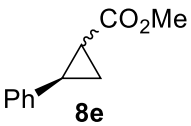
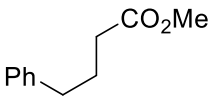
2.4 Investigation of hydrogenolysis of arylcyclopropanediesters

Hydrogenolysis of cyclopropanes **8a-e** was next examined (Table 2.2). When cyclopropanediester **8a** was reacted at 0 °C for 30 min, ring-opening compound **16a** was obtained in high yield (entry 1). On the other hand, when cyclopropanemonoester **8e** was reacted under similar conditions, the yield of ring-opening compound **11e** decreased and the starting material **8e** was recovered (entry 2). However, by extending the reaction time to 1.5 h, the yield of **11e** was improved (entry 3). Next, cyclopropanes **8b** and **8c** having electron-withdrawing groups such as formyl and ester groups at the β-position were reacted under the same conditions, but no ring cleavage occurred and the starting materials **8b** and **8c** were recovered (entries 4-6). The reactivity of the substrate to hydrogenation was reduced when the β-position is an electron-withdrawing group. In a similar reaction to electron-withdrawing alkenylcyclopropane **8d**, no ring cleavage occurred in 30 min, and olefin-reduced **11d** was obtained in low yield and the starting material **8d** was recovered (entry 8). However, by increasing the reaction time to 18h, ring-opening and olefin-reduced **11d'** were obtained (entry 9).

Table 2.2 Hydrogenolysis of arylcyclopropanediesters



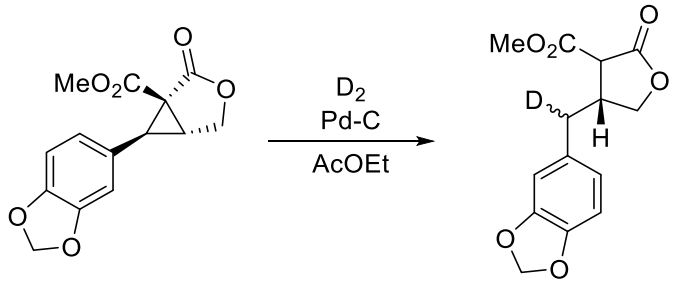
8 **11**

entry	**8**	Time. (h)	Temp. (°C)	**11**	yield %
1	 **8a**	0.5	0	 **11a**	95
2	 **8b**	3	0	 **11b**	0
3		3	0		0[a]
4	 **8c**	3	0	 **11c**	0
5	 **8d**	0.5	0	 **11d**	33
6		18	r.t.	 **11d'**	85
7	 **8e**	0.5	0	 **11e**	13
8		1.5	0		90

[a] $Pd(OH)_2$-C was used instead of Pd-C.

2.5 Labeling of bicyclolactone with deuterium under the hydrogenolytic reaction conditions

Using deuterium instead of hydrogen, I performed the hydrogenolysis of bicyclolactones. Hydrogenolysis of bicyclolactone **5d** in the presence of Pd-C catalyst in AcOEt solvent under D_2 gave deuterated ring opening product **15i** in 85% yield (Scheme 2.7). However, deuteration occurred only at the benzyl position, and no deuterated product at the α-position of ester group was obtained. The hydrogen at the α-position in product **15i** could come from the carbon in Pd-C or H_2O in the solvent. The same reaction in CD_3OD also gave the same product. The mechanism of this reaction is still not clearly understood and mechanistic studies are ongoing.



5d **15i** 85%

Scheme 2.7 Hydrogenolysis of bicyclolactone under deuterium atmosphere

Chapter 3

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

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

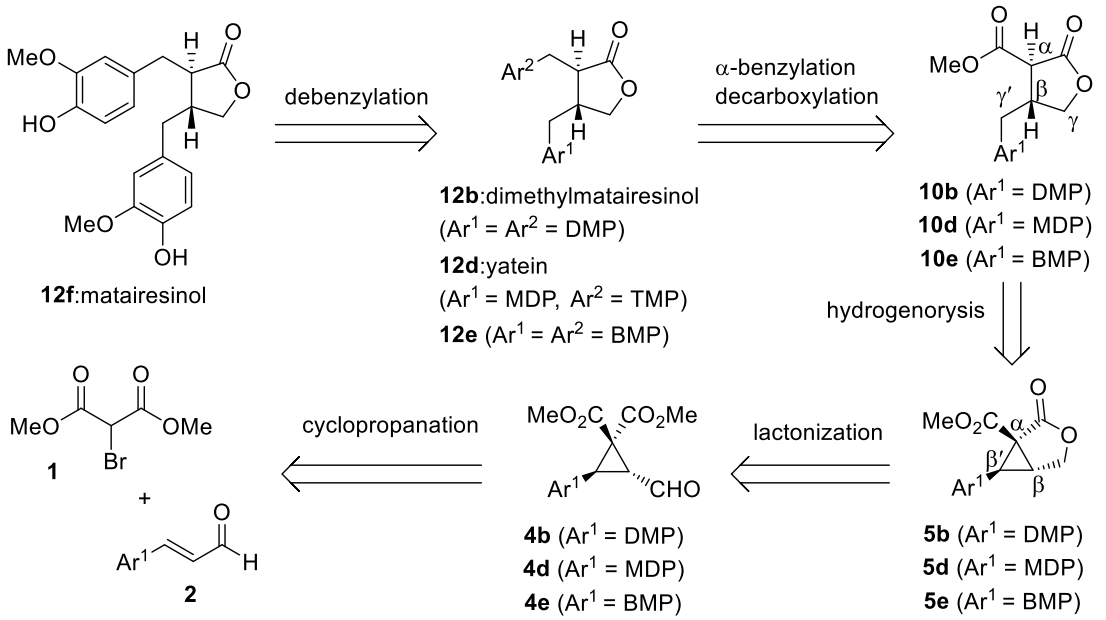
3.1 Introduction

Matairesinol is a compound isolated from *Linum Usitatissimum* and has anti-bacterial and cytotoxic effects[25]. Dimethylmatairesinol is a compound isolated from *Taiwania cryptomerioides*, and has anti-allergic and cytotoxic effects[26]. Yatein is a compound isolated from the plant *Cupressaceae*, and has antiviral activity and strong insect feeding inhibition[27]. Furthermore, niranthin is found in *Phyllanthus urinaria L* and has been reported to possess anti-hepatitis B virus activity and anti-leishmanial activity[28]. In this study, we attempted the asymmetric total synthesis of the lignan natural products matylesinol, dimethylmatairesinol, yatein, (-)- and (+)-niranthin using the hydrogenolysis of bicyclolactone as the key reaction.

3.2 Retrosynthetic analysis

3.2.1 Matairesinol, dimethylmatairesinol and yatein

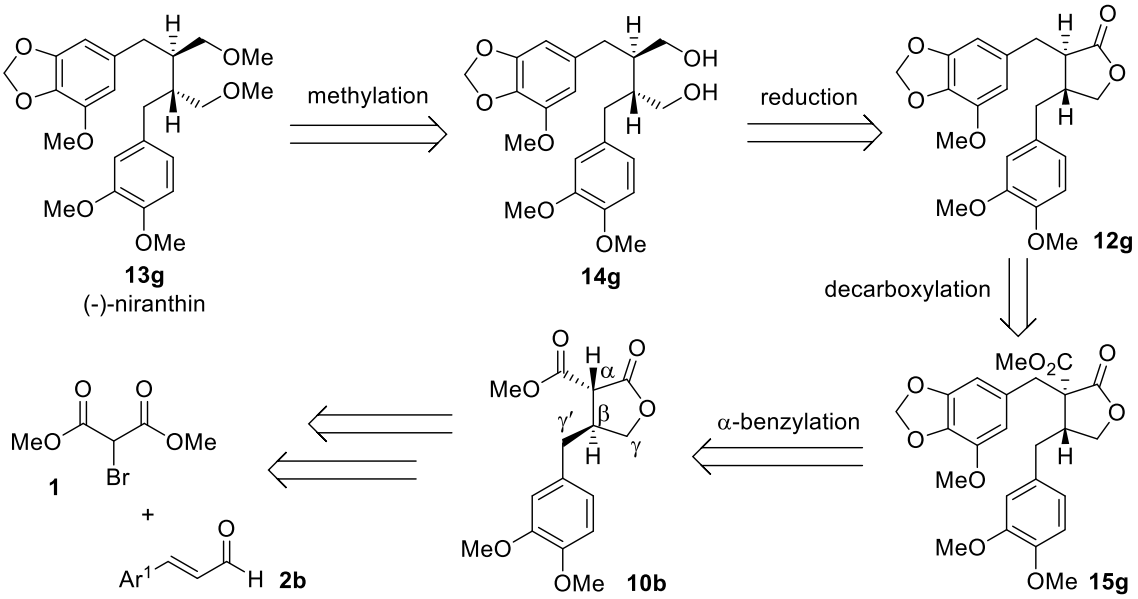
Matairesinol (**12f)** is obtained from **12e** by debenzylation. Dimethylmatairesinol (**12b)**, yatein (**12d)** and **12e** are obtained from **10** by decarboxylation and α-benzylation of the lactone. **10** is obtained from bicyclolactone **5** by hydrogenolysis. **5** can be derived from cyclopropanaldehyde **4** by intramolecular lactonization and reduction of the aldehyde. **4** is obtained by Hayashi-Jørgensen-catalyzed asymmetric cyclopropanation of α,β-unsaturated aldehyde **2** and dimethyl α-bromomalonate (**1)** (Scheme 3.1).



Scheme 3.1 Retrosynthetic analysis of Matairesinol, dimethylmatairesinol and yatein

3.2.2 (-)- and (+)-niranthin

I considered that (-)-niranthin **13g** could be derived from lignanlactone **12g** by methylation of the diol and reduction of the lactone. **12g** can be synthesized by decarboxylation of compound **15g**, and **15g** can be synthesized by α-benzylation of the lactone in **10b** (Scheme 3.2). We considered that (+)-niranthin **13d** could be synthesized by the same procedure using a catalyst derived from D-proline during asymmetric cyclopropanation.

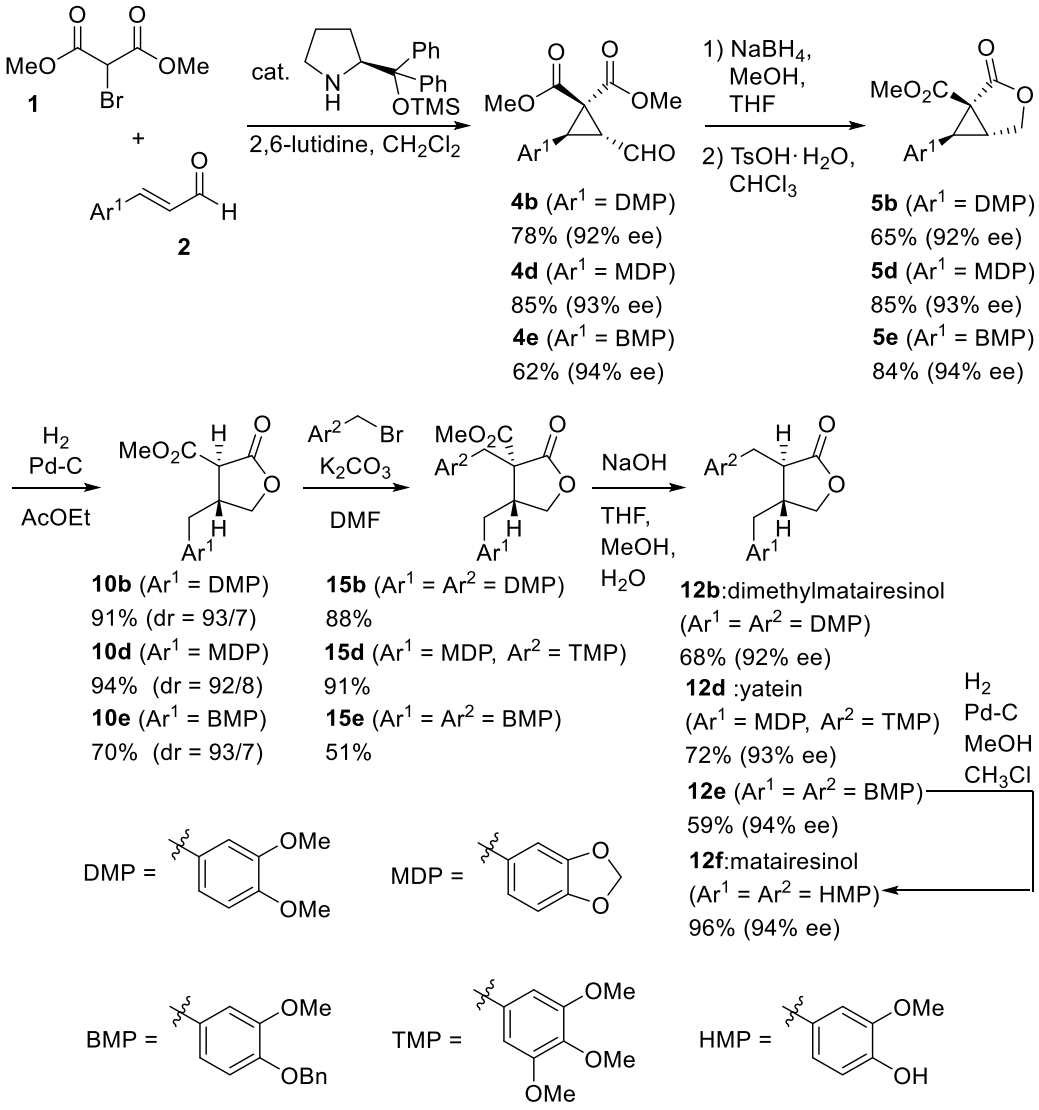


Scheme 3.2 Retrosynthetic analysis of (-)-niranthin

3.3 Synthetic route

3.3.1 Matairesinol, dimethylmatairesinol and yatein

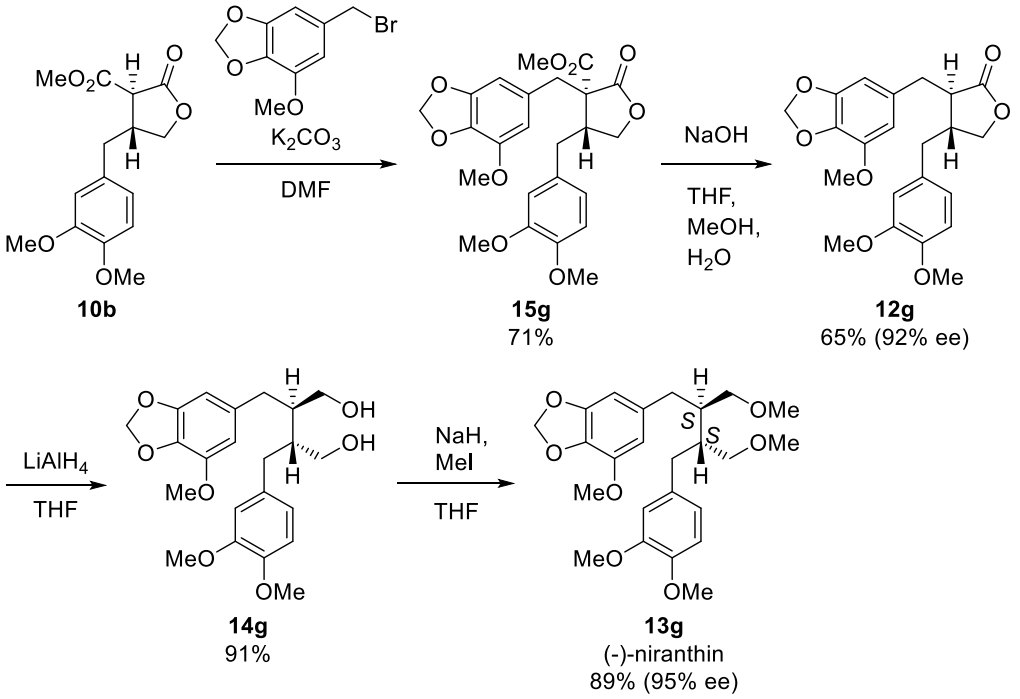
Asymmetric cyclopropanation of dimethyl monobromomalonate (**1**) and cinnamaldehyde derivatives **2** with L-proline-derived Hayashi-Jørgensen catalyst afforded cyclopropane **4**. The cyclopropane **4** was reduced with sodium borohydride, and bicyclolactone **5** was synthesized by lactonization using *p*-toluenesulfonic acid monohydrate. Next, ring-opening product **10** was obtained by hydrogenolysis of the bicyclolactone **5**. Subsequently, **12e**, dimethylmatiresinol **12b**, and yatein **12d** were synthesized by α-benzylation of **10** and decarboxylation via hydrolysis under basic conditions. Furthermore, matairesinol (**12f**) was synthesized by debenzylation of **12e** (Scheme 3.3).



Scheme 3.3 Synthesis of matairesinol, dimethylmatairesinol and yatein

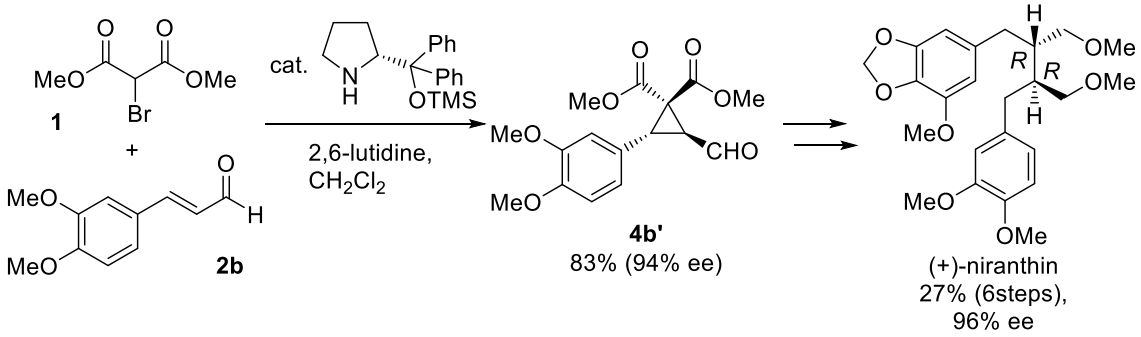
3.3.2 (-)- and (+)-niranthin

(-)-Niranthin **13g** was synthesized by the following method. Lignan lactone **15g** was synthesized byα-benzylation of the ring-opening product **10b**. Further decarboxylation via hydrolysis under basic conditions gave **12g** of the compound. Subsequently, compound **14g** was synthesized by LAH reduction followed by methylation to give (-)-niranthin **13g** (Scheme 3.4).



Scheme 3.4 Synthesis of (-)-niranthin

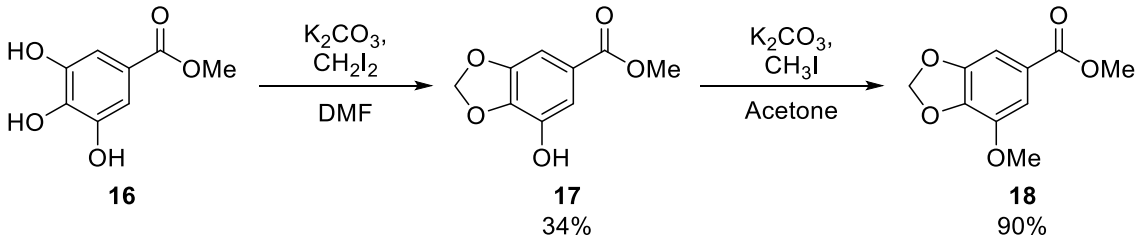
(+)-niranthin was synthesized by the same synthetic route, changing the catalyst used for asymmetric cyclopropanation to one derived from D-proline (Scheme 3.5). There was no significant difference in yield, enantiomer ratio, or diastereomeric ratio.



Scheme 3.5 Synthesis of (+)-niranthin

The trisubstituted benzylbromide used for α-benzylation was derived from methyl gallate (**16**). Initially we investigated a synthetic route in which two of the three hydroxy groups were converted to methylenedioxy groups, and then the remaining hydroxy groups

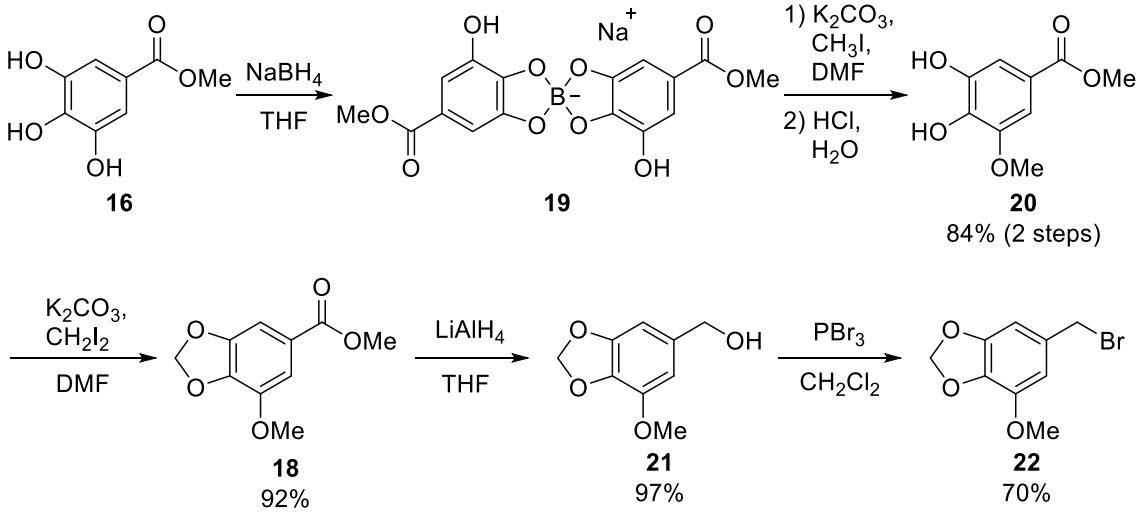
were converted to methoxy groups (Scheme 3.6). The conditions for the synthesis of compound **17** were investigated, but the yield was low at 34%[33]. The amounts of diiodomethane and base were increased and the reaction time was extended. However, the reaction became complicated and it became difficult to isolate only the target product. When the base was reduced to 1.25 equivalents, starting material **16** and compound **18** were obtained. In addition, the starting material **16** and compound **18** were difficult to dissolve in extraction solvents (ethyl acetate, diethyl ether, chloroform, etc.), making extraction and purification difficult.



Scheme 3.6 Synthesis of **18**

To solve this problem, we decided to change the order of conversion of hydroxy groups. However, selective monomethylation is not possible. Therefore, protection using boron was considered. It is known that compounds with two or more hydroxy groups, such as methyl gallate, react with sodium borohydride to form spiroborates[34].

Compound **19** was obtained by adding sodium borohydride to methyl gallate **16**, followed by selective methylation with iodomethane to give compound **20** in two-step yield of 84%. The remaining hydroxy groups were converted to a methylenedioxy group using diiodomethane to afford compound **18** in 92% yield. Further, LAH reduction of the ester and bromination of the hydroxy group with phosphorus tribromide afforded 3-methoxy-4,5-methylenedioxybenzylbromide **22** in 70% yield (Scheme 3.7).



Scheme 3.7 Improved synthetic route for trisubstituted benzyl bromides

Chapter 4

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

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

4.1　introduction

Niranthin is found in Phyllanthus urinaria L and has been reported to possess anti-hepatitis B virus activity[28]. However, the correlation between the asymmetric environment and the activity has not been clarified. In this study, I performed asymmetric total synthesis of (-)- and (+)-niranthin using the hydrolysis of bicyclolactone as the key reaction. And With the help of Dr. Noriko Shimazaki of the National Institute of Infectious Diseases, I investigated the activity of the synthesized (-)- and (+)-niranthin against hepatitis B virus and influenza virus.

4.2　Results of activity test against HBV

The studies with HBV-infected HepG2-hNTCP-C4 cells and HBV-replicating Hep38.7-tet cells showed a concentration-dependent decrease in the amount of HBs antigen and no cytotoxicity with niranthin. The 50% inhibitory concentration (IC50) in HBV-infected cells was 14.3 ± 0.994 μM for (-)-niransin and 9.11 ± 0.998 μM for (+)-niransin (Figure 4.1). The IC50 in HBV replicating cells was 16.2 ± 0.992 μM for (-)-niransin and 24.2 ± 0.993 μM for (+)-niransin (Figure 4.2). These results indicate that (-)- and (+)-niransin showed anti-HBV activity, with no significant difference in anti-HBV activity.

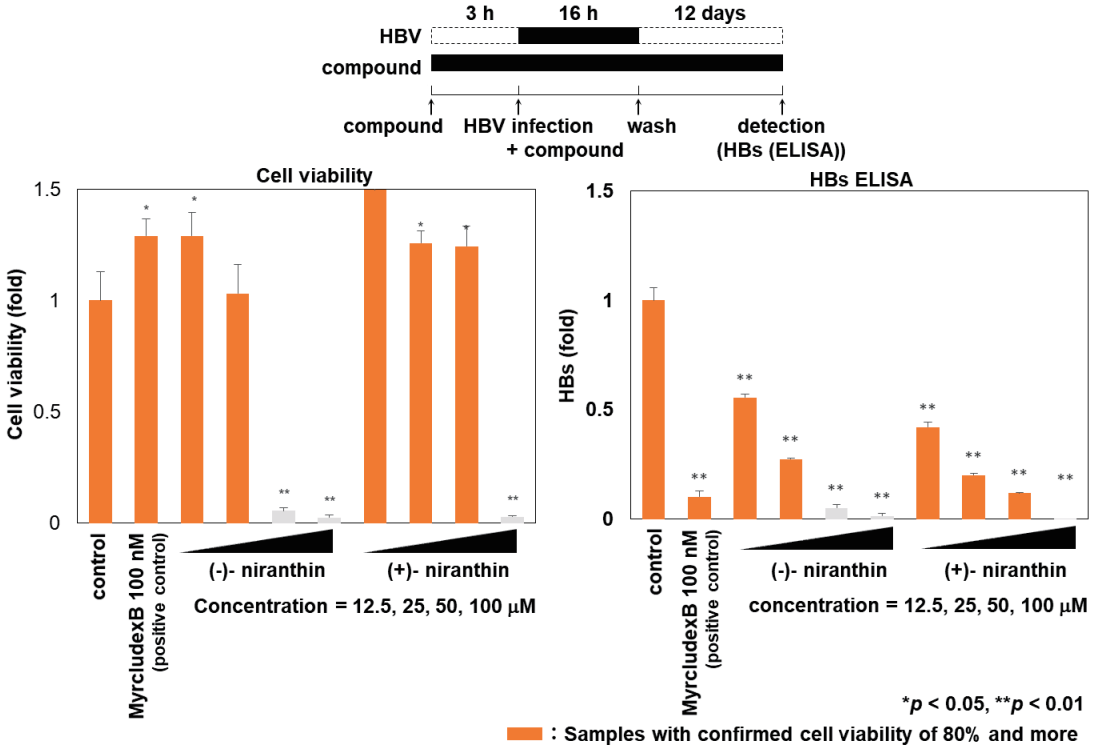


Figure 4.1　HBV-infection assay using (-)- and (+)-niranthin

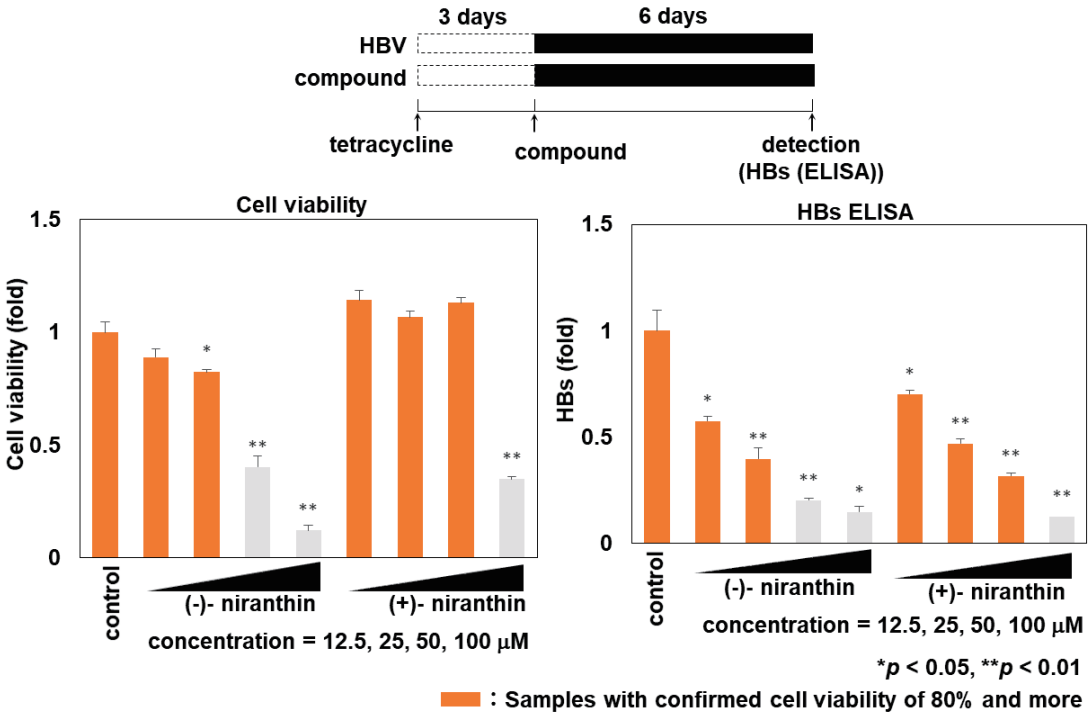


Figure 4.2 HBV-replication assay using (-)- and (+)-niranthin

4.3 Results of activity test against IFV

The study of (-)- and (+)-niranthin against IFV in MDCK cells show that the cytotoxicity of (-)-niranthin appears above 400 μM. And (-)-niranthin inhibits IFV infection in a concentration-dependent manner in the region below 400 μM, showing anti-IFV activity at 200-400 μM (Figure 4.3). However, (+)-niranthin shows no anti-IFV activity and, like (-)-niranthin, becomes cytotoxic above 400 μM. In summary, the anti-IFV activity of (-)- and (+)-niranthin is clearly different.

These results suggest that the enantiomeric site of (-)-niranthin gives it stronger anti-IFV activity than (+)-niranthin. It can then be inferred that the anti-HBV active site of niransin is part of the molecular structure, such as aromatics, away from the chiral center, while the anti-IFV active site is located closer to the chiral center.

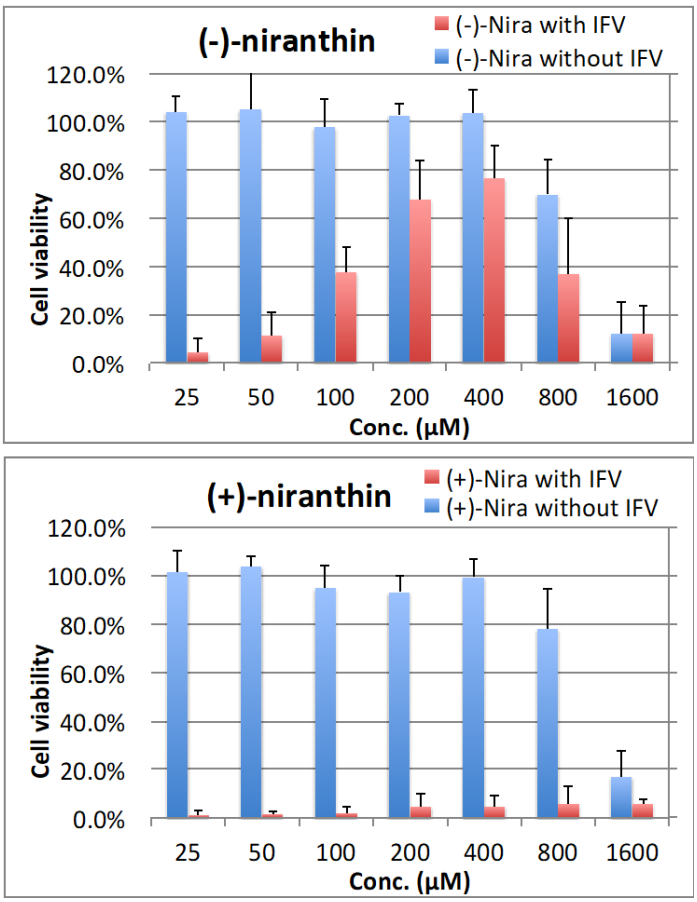


Figure 4.3 Growth-inhibition assay of IFV using (-)- and (+)-niranthin

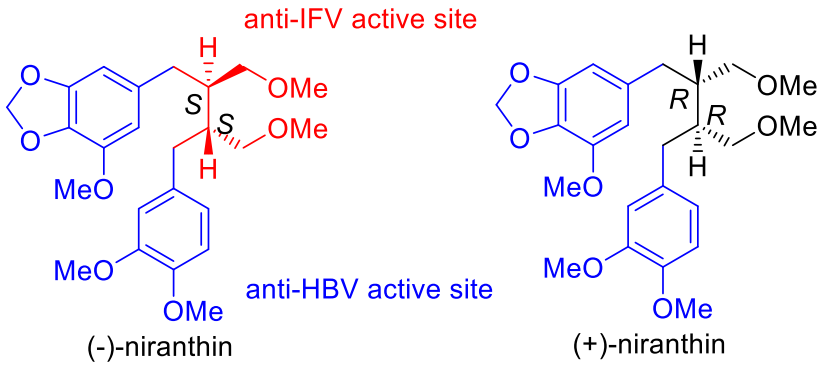


Figure 4.4 A speculation for the bioactive site of niranthin against HBV and IFV

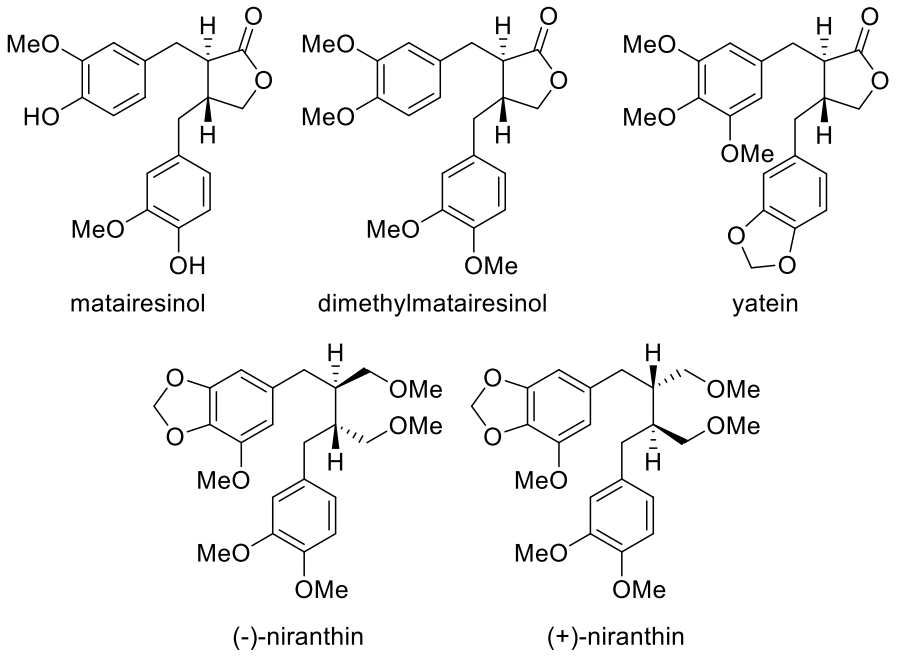
Chapter 5

Summary

Chapter 5 Summary

Lignans are known to have a variety of bioactivity. Although niranthin exhibits anti-viral activity toward the hepatitis B virus (HBV), 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, I aimed to synthesize five bioactive lignans, including (-)-niranthin and (+)-niranthin (Scheme 1.15). However, the 1,5-addition reaction (Scheme 1.3) and the oxy-homo-Michael reaction (Scheme 1.5) developed in our laboratory give products with an alkyl or hydroxy group substituted at the 7-position. The ring-opening cyclization (Scheme 1.9) also gives a product with a cyclic structure. In view of the above, it is necessary to develop a new reaction to synthesize lignans with no substitution at the 7-position.

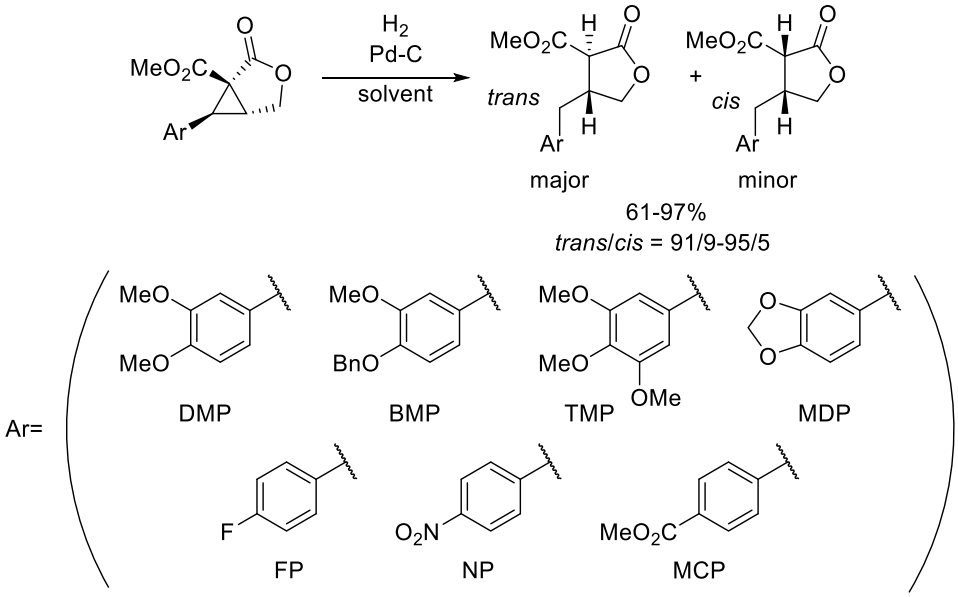
Therefore, I investigated the development of a novel reaction to synthesize bioactive lignans .



Scheme 1.15 Target lignans

5.1 Exploration of a key reaction for the asymmetric total synthesis of bioactive lignans

Pd-C catalyzed hydrogenolysis to bicyclolactone under reaction conditions of 0°C in AcOEt solvent was highly trans-selective, yielding ring opening compound in high yield. Bicyclolactones with benzyloxymethoxyphenyl also gave high yields of ring openings in which ring opening and debenzylation occurred when the reaction temperature was set to rt. Furthermore, bicyclolactones with nitrophenyl gave lactones in which the nitro group was reduced along with ring opening in high yield by changing the reaction conditions to rt in MeOH solvent.

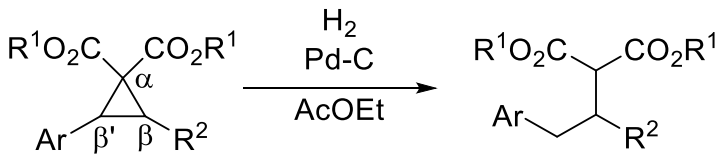


Scheme 5.1 Hydrogenolysis of bicyclolactone

In the hydrogenolysis of cyclopropane diesters and cyclopropane monoesters, ring opening compound were obtained in high yields when the reaction conditions were 0°C in AcOEt solvent.

However, in the case of the hydrogenolysis of cyclopropane having electron-withdrawing groups such as formyl and ester groups at the β-position, ring cleavage did not occur and the raw material was recovered. Hydrogenolysis may be inactivated when the β-position is an electron-withdrawing group. The reaction using the same conditions to electron-withdrawing alkenylcyclopropanes did not result in ring cleavage, and cyclopropanes in which only the olefin was reduced were obtained in low yield.

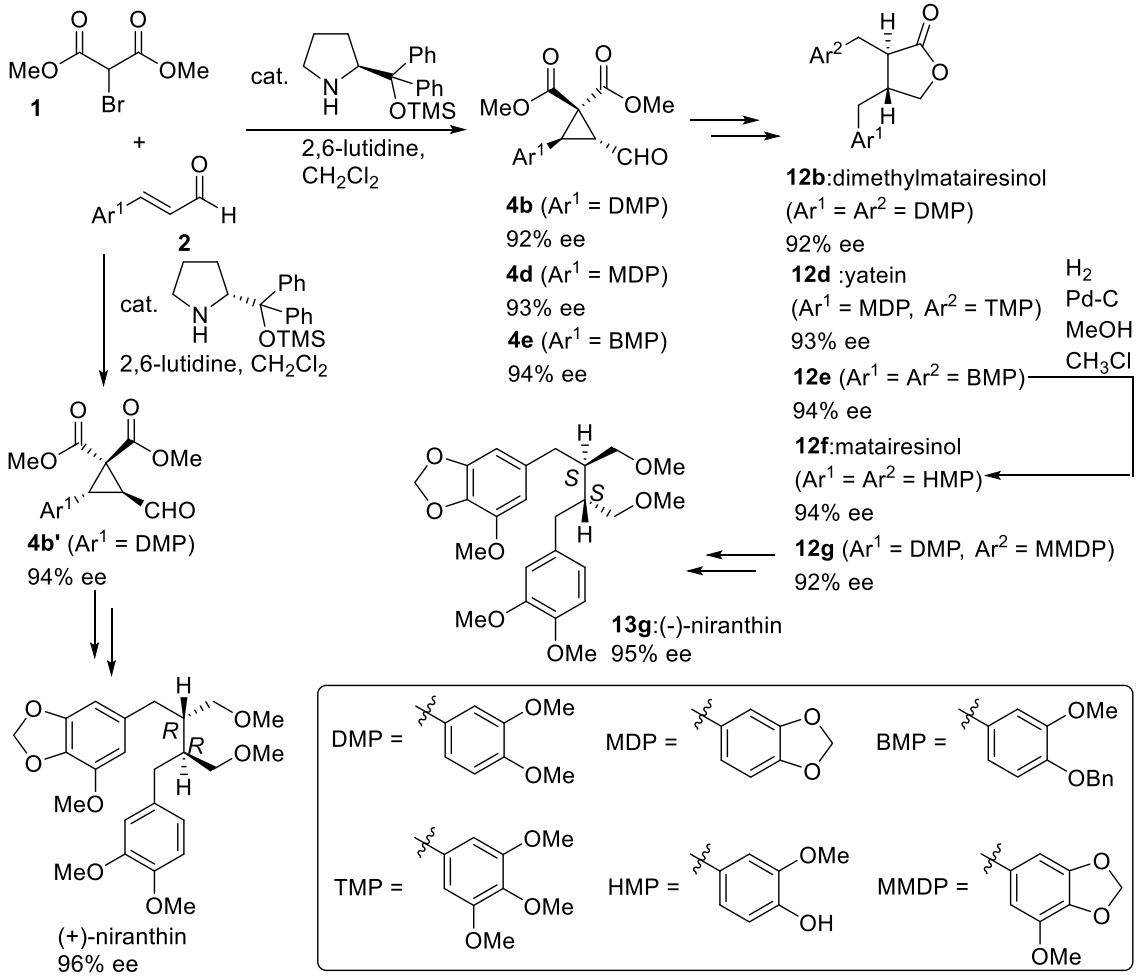
However, by increasing the reaction time, ring cleavage and reduced olefin were obtained.



Scheme 5.2 Hydrogenolysis of arylcyclopropanediesters

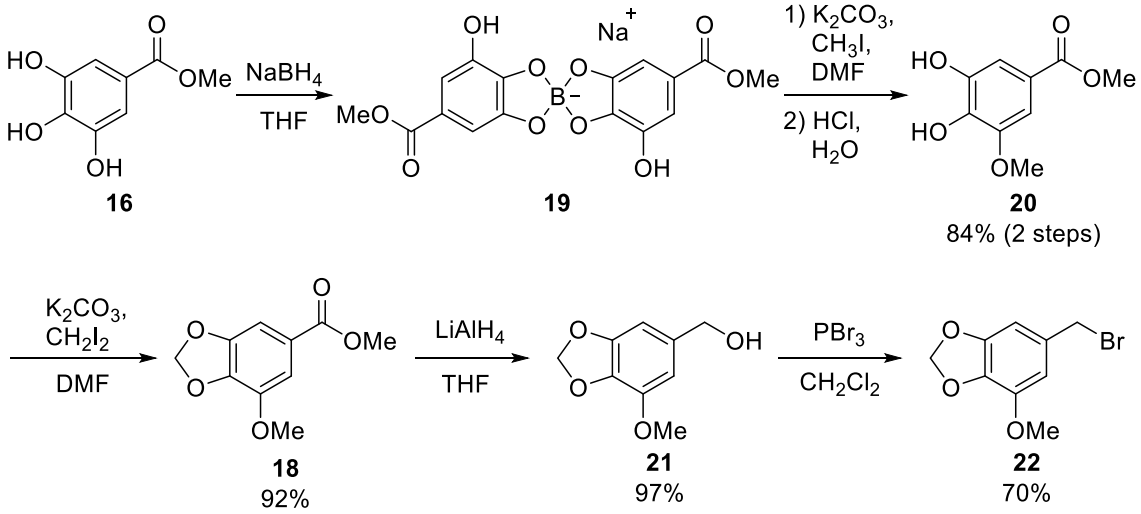
5.2 Asymmetric total synthesis of five bioactive lignans

Five lignans reported to possess various biological activities were synthesized asymmetrically via a synthetic pathway in which the key reaction is the hydrolysis of bicyclolactone (Scheme 5.1). For (+)-niranthin, the catalyst used in the asymmetric cyclopropanation was changed to one derived from D-proline, and the total synthesis was carried out by the same synthetic route.



Scheme 5.3 Synthetic route of bioactive lignans

In the synthesis of trisubstituted benzyl bromides for α-benzylation, there was a problem in the derivation of methyl gallate **21** to compound **23**. However, a simple and high yield synthesis was achieved by changing the order of conversion of substituents and via dimerization with sodium borohydride (Scheme 5.4).

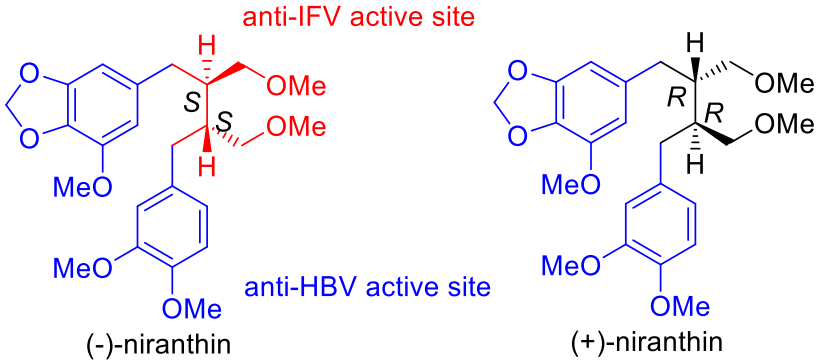


Scheme 5.4 Synthesis of trisubstituted benzylbromide

5.3 Bioactivity of (-)- 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 showed that (-)- and (+)-niranthin showed anti-HBV activity, with no significant difference in anti-HBV activity. It was also found that (-)-niranthin showed anti-IFV activity at 200-400 μM, while (+)-niranthin showed no anti-IFV activity.

My findings suggest that the enantiomeric site (red part) in niranthin endows (-)-niranthin with more potent anti-IFV activity than (+)-niranthin. We 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 (blue part). In contrast, anti-IFV active site of niranthin might be closer to the chiral centers (Scheme 5.5).



Scheme 5.5 A speculation for the bioactive site of niranthin against HBV and IFV.

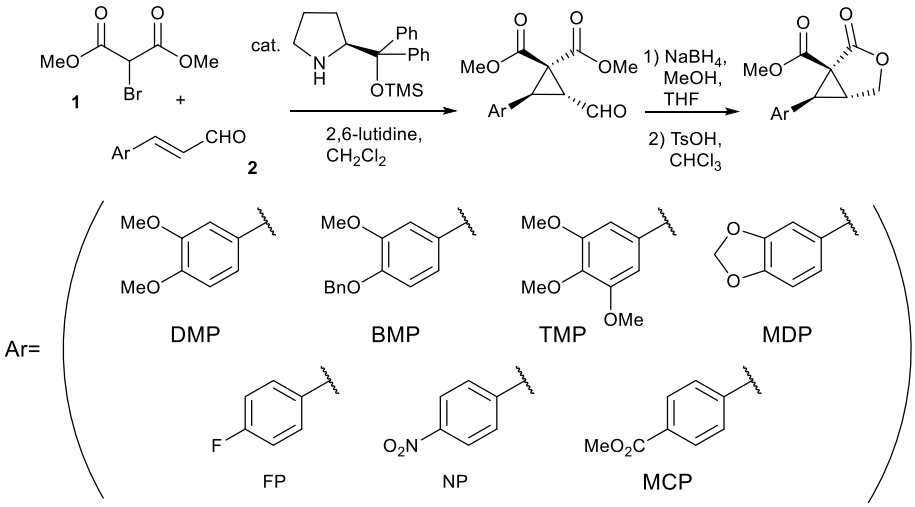
Experimental methods

1 General methods and materials

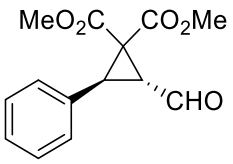
All reactions were carried out in oven-dried glassware under an argon atmosphere. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Column chromatography was performed with Kanto chemical CO., INC., silica gel 60 N (spherical, neutral, 40-50 μm). TLC analysis was performed on 0.25 mm Silica gel Merck 60 F_{254} plates. FT-IR spectra were recorded on a SHIMADZU IRTracer-100 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER AVANCE NEO NanoBay (400 MHz for ^{1}H NMR, 101 M Hz for ^{13}C NMR) instrument. Chemical shifts (δ ppm) in $CDCl_3$ were reported downfield from TMS (= 0) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to $CDCl_3$ (77.16 ppm) as an internal reference. Mass spectra were obtained by APCI. HPLC analysis was performed on a JASCO GULLIVER SERIES.

2 Experimental procedures and characterization data for compounds

Asymmetric synthesis of enantioenriched bicyclic lactones



Dimethyl (2R,3S)-2-formyl-3-phenylcyclopropane-1,1-dicarboxylate (4a)

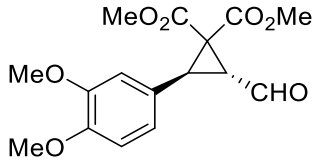


A solution of catalyst **3** (928 mg, 2.9 mmol) in CH_2Cl_2 (5.8 ml) was added to a solution of aldehyde **2a** (2.5 g, 19 mmol) in CH_2Cl_2 (19 ml) at 0°C under an Ar atmosphere, additionally, a solution of dimethyl a-bromomalonate **1** (3.7 ml, 23 mmol) in CH_2Cl_2 (9.3 ml) and 2,6-lutidine (2.3 ml, 8.3 mmol)

was added to the reaction mixture at the same temperature, followed by being stirred at 0°C for 92 h. Then, the reaction was quenched with 1M-HCl aqueous solution (20 mL). Water (10 ml) was added to the mixture, which was extracted with $CHCl_3$ (20 mL x 4). The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 3/1) to give the product **4a** (4.8 g, 96% yield).

4a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.39 (dd, *J* = 4.5, 7.6 Hz, 1H), 3.47 (s, 3H), 3.83 (d, *J* = 7.6 Hz, 1H), 3.83 (s, 3H), 7.22-7.31 (m, 5H), 9.50 (d, *J* = 4.5 Hz, 1H).

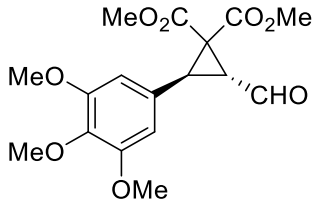
Dimethyl (2R,3S)-2-formyl-3-(3,4-dimethoxyphenyl)cyclopropane-1,1-dicarboxylate (4b)



Following the procedure for the preparation of **4a**, the reaction using (E)-3-(3,4-dimethoxyphenyl)-propen-1-al instead of (E)-3-phenylpropen-1-al gave the product **4b**(73% yield).

4b: colorless liquid; $[\alpha]^{21}_D$ = -35.9 (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.35 (dd, *J* = 4.6, 7.5 Hz, 1H), 3.51 (s, 3H), 3.79 (d, *J* = 7.5 Hz, 1H), 3.83 (s, 3H), 3.86 (s, 3H), 3.89 (s, 3H), 6.73-6.79 (m, 3H), 9.48 (d, *J* = 4.6 Hz, 1H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 35.9, 39.0, 45.0, 53.4, 53.7, 56.2, 56.3, 111.3, 111.9, 121.0, 124.8, 149.3, 165.5, 167.0, 196.5; IR (NaCl, neat) 3474, 2955, 1738, 1715, 1591, 1520, 1454, 1435, 1146, 1026, 816 cm^{-1} ; HRMS (APCI) calcd for $C_{16}H_{18}O_7$ $(M+H)^+$ 321.0969 , found 321.0960.

Dimethyl (2R,3S)-2-formyl-3-(3,4,5-trimethoxyphenyl)cyclopropane-1,1-dicarboxylate (4c)

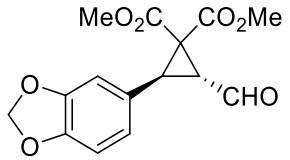


Following the procedure for the preparation of **4a**, the reaction using (E)-3-(3,4,5-trimethoxyphenyl)-propen-1-al instead of (E)-3-phenylpropen-1-al gave the product **4c**(96% yield).

4c: yellow solid; mp 118.5-120.5˚C; $[\alpha]^{25}_D$ = -33.3 (*c* 1.01, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.35 (dd, *J* = 7.5, 4.5 Hz, 1H), 3.55 (s, 3H), 3.78 (d, *J* = 7.5 Hz, 1H), 3.82 (s, 3H), 3.84 (s, 9H), 6.44 (s, 2H), 9.48 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 36.2, 39.1, 45.0, 53.4, 53.8, 56.6, 61.2, 105.9, 128.1, 138.2, 153.6, 165.5, 166.9, 196.3; IR (KBr, neat) 2967, 2943,

2862, 1757, 1734, 1707, 1589, 1132 cm^{-1}.

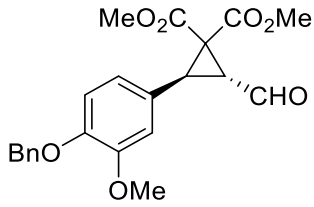
Dimethyl (2R,3S)-2-formyl-3-(3,4-methylenedioxyphenyl)cyclopropane-1,1-dicarboxylate (4d)



Following the procedure for the preparation of **4a**, the reaction using (E)-3-(3,4-methylenedioxyphenyl)-propen-1-al instead of (E)-3-phenylpropen-1-al gave the product **4d**(85% yield).

4d: colorless crystal ; mp = 100-101 °C ; $[\alpha]^{24}_{D}$ = -56.0 (*c* 1.00, chloroform, λ = 589 nm) ; ^{1}H NMR(400 MHz,$CDCl_3$) δ 3.31 (dd, *J* = 4.5, 7.5 1H), 3.55 (s, 3H), 3.74 (d, *J* = 7.5 1H), 3.82 (s, 3H), 5.92 (s, 2H), 6.75-6.68 (m, 3H), 9.47 (d, *J* = 4.5 1H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 35.9, 39.0, 45.0, 53.4, 53.7, 101.7, 108.6, 109.2, 122.3 126.2, 147.9, 148.2, 165.4, 166.4, 196.3 ; IR (KBr,neat) 3468, 3419, 3018, 2956, 2870, 1739, 1703, 1502, 1442, 1294, 1242, 1217, 1033 ; HRMS (APCI) calcd for $C_{15}H_{14}O_7$ $(M-H)^-$ 305.0656 , found 305.0654.

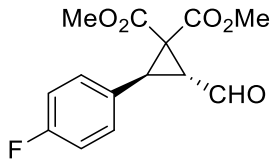
Dimethyl (2R,3S)-2-formyl-3-(4-benzyloxy-3-methoxyphenyl)cyclopropane-1,1-dicarboxylate (4e)



Following the procedure for the preparation of **4a**, the reaction using (E)-3-(4-benzyloxy-3-methoxyphenyl)-propen-1-al instead of (E)-3-phenylpropen-1-al gave the product **4e**(68% yield).

4e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.33 (dd, *J* = 1.2, 7.5 Hz, 1H), 3.48 (s, 3H), 3.77 (d, *J* = 7.6, 1H), 3.83(s, 3H), 3.87(s, 3H), 5.12 (s, 2H), 6.69 (dd, *J* = 2.0, 7.8 Hz, 1H), 6.76 (d, *J* = 2.0 Hz, 1H), 6.80 (d, *J* = 8.3 Hz, 1H), 7.29-7.42 (m, 1H, 5H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 35.9, 39.0, 45.0, 53.4, 53.7, 56.5, 71.4, 112.5, 114.2, 121.0, 125.4, 127.7, 128.3, 128.9, 137.3, 148.4, 150.0, 165.5, 167.0, 196.5 ; IR (KBr, neat) 2961, 2876, 1736, 1705, 1591, 1520, 1439, 1300, 1250, 1207, 1148, 1034, 739 cm^{-1} ; HRMS (APCI) calcd for $C_{22}H_{22}O_7$ $(M+H)^+$ 397.1282 , found 397.1277.

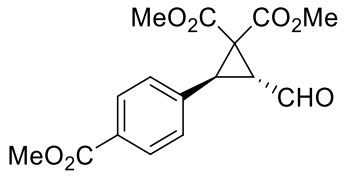
Dimethyl (2R,3S)-2-formyl-3-(4-fluorophenyl)cyclopropane-1,1-dicarboxylate (4f)



Following the procedure for the preparation of **4a**, the reaction using (E)-3-(4-fluorophenyl)-propen-1-al instead of (E)-3-phenylpropen-1-al gave the product **4f**(70% yield).

4f: ^{1}H NMR (400 MHz,$CDCl_3$) δ 3.36 (dd, *J* = 4.4, 7.6 1H), 3.50 (s, 3H), 3.78 (d, *J* = 7.6 1H), 3.83 (s, 3H), 6.98-7.02 (m, 2H), 7.20-7.23 (m, 2H), 9.50 (d, *J* = 4.4 1H).

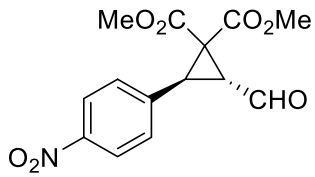
Dimethyl (2R,3S)-2-formyl-3-(4-methoxycarbonylphenyl)cyclopropane-1,1-dicarboxylate (4g)



Following the procedure for the preparation of **4a**, the reaction using (E)-3-(4-methoxycarbonylphenyl)-propen-1-al instead of (E)-3-phenylpropen-1-al gave the product **4g**(72% yield).

4g: ^{1}H NMR (400 MHz,$CDCl_3$) δ 3.44 (dd, *J* = 4.2, 7.6 1H), 3.48 (s, 3H), 3.84 (d, *J* = 7.6 Hz, 1H), 3.91 (s, 3H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.98 (d, *J* = 8.4 Hz, 2H), 9.54 (d, *J* = 4.2 Hz, 1H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 35.8, 38.5, 45.1, 52.6, 53.5, 53.9, 129.0, 130.1, 137.8, 165.3, 166.6, 166.9, 195.9 ; IR (KBr, neat) 2957, 1736, 1719, 1612, 1437, 1283, 1109, 702 cm^{-1} ; HRMS (APCI) calcd for $C_{16}H_{16}O_7$ $(M+H)^+$ 321.0969 , found 321.0976.

Dimethyl (2R,3S)-2-formyl-3-(4-nitrophenyl)cyclopropane-1,1-dicarboxylate (4h)

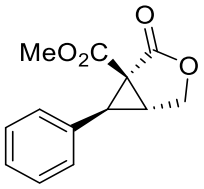


Following the procedure for the preparation of **4a**, the reaction using (E)-3-(4-nitrophenyl)-propen-1-al instead of (E)-3-phenylpropen-1-al gave the product **4h**.

4h: $[\alpha]^{20}_D$ = -38.5 (*c* 1.00, chloroform, λ = 589 nm) ; ^{1}H NMR (400 MHz,$CDCl_3$) δ 3.47 (dd, *J* = 3.8,

7.6 Hz, 1H), 3.53 (s, 3H), 3.85 (s, 3H), 3.85-3.87 (m, 1H), 7.41-7.46 (m, 2H), 8.16-8.21 (m, 2H), 9.59 (d, *J* = 4.0 Hz, 1H) .

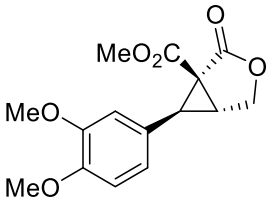
(1*S*,5*R*,6*S*)-1-Methoxycarbonyl-6-phenyl-3-oxabicyclo[3,1,0]hexan-2-one (5a)



$NaBH_4$ (334 mg, 8.9 mmol) was added to a solution of cyclopropane **4a** (4.8 g, 18 mmol) in MeOH (25 mL) at 0°C under an Ar atmosphere, followed by being stirred at rt for 30 minutes. Then, the reaction was quenched with sat. NH_4Cl aqueous solution. Water was added to the mixture, which was extracted with AcOEt (ca. 15 mL x 5). The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was resolved in $CHCl_3$ (36 mL), then *p*-TsOH･H_2O (293 mg, 1.3 mmol) was added to the solution, followed by being stirred at 45°C for 1 h. Then, the reaction was quenched with sat. $NaHCO_3$ aqueous solution. Water was added to the mixture, which was extracted with $CHCl_3$ (ca. 15 mL x 3). The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 2/1) to give the product **5a** (3.2 g, 77% yield, 95% ee).

5a: colorless solid; $[\alpha]^{24}_D$ = -53.0 (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz,$CDCl_3$) δ 2.92 (d, *J* = 5.7 Hz, 1H), 3.29-3.31 (m, 1H), 3.52 (s, 3H), 4.37 (d, *J* = 9.5 Hz, 1H), 4.50 (dd, *J* = 9.5, 4.9 Hz, 1H), 7.23-7.26 (m, 2H), 7.29-7.35 (m, 3H); 95% ee [Daicel CHIRALPAK IC (25cm) at 25°C, flow rate 1.0 ml/min, solvent: hexane / ethanol = 2/1, t_R(racemic) = 9.87 min and 12.09 min, t_R(**1a)** = 12.11 min for major and 9.79 min for minor].

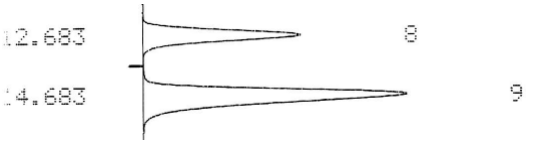
(1*S*,5*R*,6*S*)-1-Methoxycarbonyl-6-(3,4-dimethoxyphenyl)-3-oxabicyclo[3,1,0]hexan-2-one (5b)



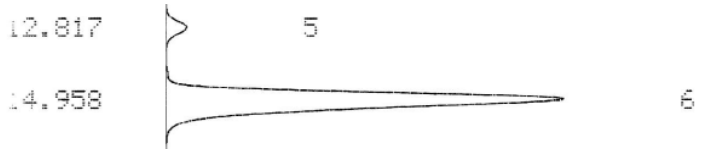
Following the procedure for the preparation of **5a**, the reaction using **4b** instead of **4a** gave the product **5b** (64% yield, 92% ee).

5b: colorless crystal; $[\alpha]^{24}_D$ = -30.5 (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ

2.90 (d, *J* = 5.6 Hz, 1H), 3.26 (m, 1H), 3.56 (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 4.37 (d, *J* = 9.3 Hz, 1H), 4.50 (dd, *J* = 9.3, 4.9 Hz, 1H), 6.79-6.83 (m, 2H), 6.77 (s, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 28.3, 38.2, 38.3, 53.1, 56.2, 56.4, 67.7, 111.2, 112.3, 121.3, 124.4, 149.2, 149.4, 164.51, 170.5. HPLC analysis: 92% ee [Daicel CHIRALPAK IG (15 cm) at 25°C, flow rate 0.8 ml/min, solvent: hexane / 2-propanol = 2/1, t_R(racemic) = 12.68 min and 14.68 min, t_R(**5b)** = 12.82 min for minor and 14.96 min for major].



Racemic-**5b**: HPLC analysis using chiral column.

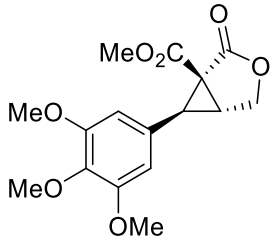


Enantioenriched **5b** (92% ee) : HPLC analysis using chiral column.

5	12.817	58282	2215	3.7148
6	14.958	1462803	44656	93.2376

Based on this enantiomeric ratio (93.24/3.71), 92% ee was estimated.

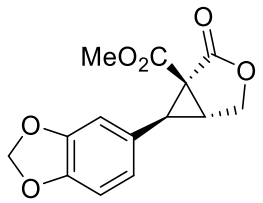
(1*S*,5*R*,6*S*)-1-Methoxycarbonyl-6-(3,4,5-trimethoxyphenyl)-3-oxabicyclo[3,1,0]hexan-2-one (5c)



Following the procedure for the preparation of **5a**, the reaction using **4c** instead of **4a** gave the product **5c** (86% yield, 95% ee).

5c: colorless crystal ; mp = 126-128.5 °C ; $[\alpha]^{24}_D$ = -18.9 (*c* 1.04, chloroform, λ = 589 nm) ;^{1}H NMR (400 MHz, $CDCl_3$) δ 2.87 (d, *J* = 5.5 Hz, 1H), 3.22-3.27 (m, 1H), 3.60 (s, 3H), 3.83 (s, 3H), 3.84 (s, 6H), 4.37 (d, *J* = 9.4 Hz, 1H), 4.50 (dd, *J* = 9.4, 4.8 Hz, 1H), 6.46 (s, 2H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 28.4, 38.2, 38.3, 53.2, 56.6, 61.3, 67.7, 106.2, 127.8, 138.3, 153.5, 164.4, 170.4; HRMS (APCI) calcd for $C_{16}H_{18}O_7$ (M-OMe)+ 291.0863 , found 291.0864; IR (KBr, neat) 3001, 2955, 2835, 1784, 1742, 1591, 1126, 1069 cm^{-1}; HPLC analysis: 95% ee [Daicel CHIRALPAK IC (25cm) at 25°C, flow rate 1.0 ml/min, solvent: hexane / ethanol = 1/1, t_R(racemic) = 11.43 min and 13.07 min, t_R(**1d)** = 11.48 min for minor and 13.07 min for major].

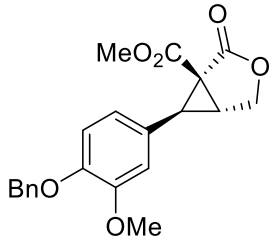
(1*S*,5*R*,6*S*)-1-Methoxycarbonyl-6-(3,4-methylenedioxyphenyl)-3-oxabicyclo[3,1,0]hexan-2-one (5d)



Following the procedure for the preparation of **5a**, the reaction using **4d** instead of **4a** gave the product **5d** (77% yield, 94% ee).

5d: colorless crystal ; mp =161.5-162 °C ; $[\alpha]^{24}_{D}$ = -48.4 (*c* 1.00, chloroform, λ = 589 nm) ; ^{1}H NMR (400 MHz,$CDCl_3$) δ 2.86 (d, *J* = 8.7 1H), 3.21 (m, 1H), 3.63 (s, 3H), 4.34 (d, *J* = 9.6 1H), 5.96 (s, 2H), 6.71-6.77 (m, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 28.4, 38.0, 38.1, 53.1, 67.6, 101.7, 108.6, 109.4, 122.8 125.7, 147.9, 148.2, 164.5, 170.3 ; IR (KBr,neat) 3527, 3431, 2960, 2922, 1774, 1722, 1504, 1446, 1371, 1342, 1261, 1240, 1199, 1099, 1058, 1033, 927, 802 cm^{-1} ; HRMS (APCI) calcd for $C_{14}H_{12}O_6$ $(M\text{-}OMe)^+$ 245.0444 , found 245.0443 ; HPLC analysis: 94% ee [Daicel CHIRALPAK IC (25cm) at 25°C, flow rate 1.0 ml/min, solvent: hexane / ethanol = 2/1, t_R(racemic) = 13.52 min and 18.47 min, t_R(**1c)** = 13.25 min for minor and 18.00 min for major].

(1*S*,5*R*,6*S*)-1-Methoxycarbonyl-6-(4-benzyloxy-3-methoxyphenyl)-3-oxabicyclo[3,1,0]hexan-2-one (5e)

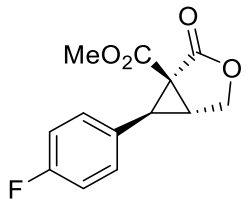


Following the procedure for the preparation of **5a**, the reaction using **4e** instead of **4a** gave the product **5e** (70% yield, 94% ee).

5e: colorless crystal; mp 148-151°C; $[\alpha]^{26}_{D}$ = -27.1 (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.87 (d, *J* = 5.6 Hz, 1H), 3.24 (t, *J* = 5.0 Hz, 1H), 3.54 (s, 3H), 3.87 (s, 3H), 4.34 (d, *J* = 9.3, 1H), 4.48 (dd, *J* = 4.8, 9.3Hz, 1H), 5.13 (s, 3H), 6.71 (dd, *J* = 2.0, 8.2Hz, 1H), 6.79 (d, *J* = 2.0, 1H), 6.82 (d, *J* = 8.3, 1H), 7.27-7.43 (m, 10H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.7, 28.2, 38.3, 53.1, 56.5, 67.7, 71.3, 112.8, 114.0, 121.2, 125.0, 127.7, 128.3, 129.0, 137.2, 148.5, 149.9, 164.5, 170.5; IR (KBr, neat) 2953, 1784, 1721, 1520, 1439, 1256, 1142, 1103, 1072, 1016 cm^{-1} ; HRMS (APCI) calcd

for $C_{21}H_{20}O_6$ $(M+H)^+$ 369.1333 , found 369.1333 ; HPLC analysis: 94% ee [Daicel CHIRALPAK IC (25cm) at 25°C, flow rate 0.5 ml/min, solvent: hexane / ethanol = 1/1, tR(racemic) = 21.4 min and 28.7 min, tR(**1e)** = 21.5 min for minor and 28.8 min for major].

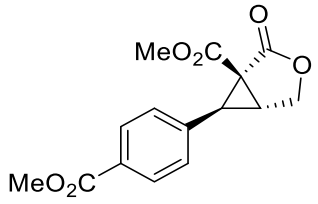
(1*S*,5*R*,6*S*)-1-Methoxycarbonyl-6-(4-fluorophenyl)-3-oxabicyclo[3,1,0]hexan-2-one (5f)



Following the procedure for the preparation of **5a**, the reaction using **4f** instead of **4a** gave the product **5f** (77% yield, 91% ee).

5f: colorless solid ; mp = 129.5- 131 °C ; $[\alpha]^{24}_D$ = -51.2 (*c* 1.00, chloroform, λ = 589 nm) ^{1}H NMR (400 MHz,$CDCl_3$) δ 2.89 (d, *J* = 5.6 Hz, 1H), 3.25-3.27 (m, 1H), 3.56 (s, 3H), 4.37 (d, *J* = 9.3 Hz, 1H), 4.50 (dd, *J* = 9.3, 5.0 Hz, 1H), 6.99-7.05 (m, 2H), 7.21-7.25 (m, 2H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 28.4, 37.3, 38.0, 53.1, 67.6, 115.8 (d, $J_{C\text{-}F}$ = 22.2 Hz), 127.9 (d, $J_{C\text{-}F}$ = 3.5 Hz), 130.8 (d, $J_{C\text{-}F}$ = 21.6 Hz), 162.8 (d, $J_{C\text{-}F}$ = 21.6 Hz), 170.3; IR (KBr,neat) 3093, 3007, 2981, 2960, 1774, 1724, 1517, 1444, 1371, 1267, 1157, 1107, 1068, 1010, 800 cm^{-1} ; HRMS (APCI) calcd for $C_{14}H_{12}O_6$ $(M\text{-}OMe)^+$ 245.0444 , found 245.0443 ; HPLC analysis: 91% ee [Daicel CHIRALPAK IC (25cm) at 25°C, flow rate 1.0 ml/min, solvent: hexane /ethanol = 2/1, t_R(racemic) = 7.54 min and 9.46 min, t_R(**1b)** = 9.69 min for major and 7.69 min for minor]

(1*S*,5*R*,6*S*)-1-Methoxycarbonyl-6-(4-methoxycarbonylphenyl)-3-oxabicyclo[3,1,0]hexan-2-one (5g)

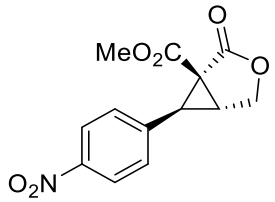


Following the procedure for the preparation of **5a**, the reaction using **4g** instead of **4a** gave the product **5g** (72% yield, 98% ee).

5g: colorless crystal; mp 147-150°C; $[\alpha]^{24}_D$ = -38.7 (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.93 (d, *J* = 5.6, 1H), 3.33 (t, *J* = 5.0 Hz, 1H), 3.54 (s, 3H), 3.91 (s, 3H), 4.39 (d, *J* = 9.5 Hz, 1H), 4.53 (dd, *J* = 4.8, 9.5 Hz, 1H), 7.32 (d, *J* = 7.9 Hz, 2H), 8.00 (d, *J* = 8.4 Hz, 2H) ; ^{13}C

NMR (101 MHz, $CDCl_3$) δ 28.3, 37.4, 38.3, 52.6, 53.2, 67.6, 129.1, 130.1, 130.4, 137.3, 164.2, 166.9, 170.0 ; IR (KBr, neat) 2978, 1776, 1726, 1447, 1369, 1285, 1103, 1065, 746 cm^{-1} ; HRMS (APCI) calcd for $C_{15}H_{14}O_6$ $(M+H)^+$ 291.0863 , found 291.0859 ; 98% ee [Daicel CHIRALPAK IG (25cm) at 25°C, flow rate 1.0 ml/min, solvent: hexane / CH2Cl2 = 1/1, tR(**1g)** = 10.6 min for minor and 15.4 min for major].

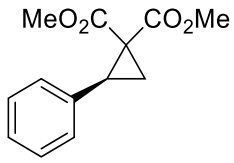
(1*S*,5*R*,6*S*)-1-Methoxycarbonyl-6-(4-nitrophenyl)-3-oxabicyclo[3,1,0]hexan-2-one (5h)



Following the procedure for the preparation of **5a**, the reaction using **4h** instead of **4a** gave the product **5h** (64% yield, 94% ee).

5h: colorless crystal; mp 147-150°C; $[\alpha]^{25}_D$ = -50.8 (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.95 (d, *J* = 5.4 Hz, 1H), 3.33 (t, *J* = 5.0 Hz, 1H), 3.59 (s, 3H), 4.41 (d, *J* = 9.7 Hz, 1H), 4.55 (dd, *J* = 4.8, 9.6 Hz, 1H), 7.41-7.46 (m, 2H), 8.18-8.23 (m, 2H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 28.8, 36.7, 38.2, 53.3, 67.5, 124.0, 130.2, 139.7, 148.0, 164.2, 169.7; IR (KBr, neat) 2982, 1775, 1724, 1516, 1352, 1069, 854 cm^{-1}, HRMS (APCI) calcd for $C_{13}H_{11}NO_6$ $(M+H)^+$ 278.0659 , found 278.0658.

Dimethyl (2*S*)-2-phenylcyclopropane-1,1-dicarboxylate (8a)

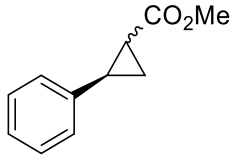


A CH_2Cl_2-solution (2.3 ml) of dimethyl-1,1-diazomalonate (472 mg, 3.0 mmol) was added dropwise to a mixture of styrene (240 mg, 2.3 mmol) and $Rh_2(esp)_2$ (2mg, 2.3 mmol) in CH_2Cl_2 (2.3 ml) at 0 °C while taking a time of 3h, followed by being stirred at the room temperature for 1h. Then, sat. thiourea aqueous solution (10 ml) was added to the reaction mixtur, which was extracted with CHCl (ca. 10ml x 3). The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by column chromatography (SiO2, hexane/AcOEt = 9/1) to give the product 8**a** (488 mg, 90% yield).

8a: colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75 (dd, *J* = 5.2, 9.3 Hz, 1H), 2.20 (dd, *J* = 5.2,

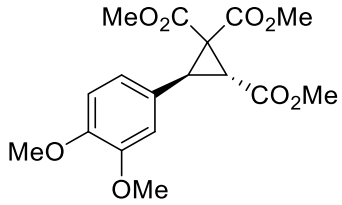
8.0 Hz, 1H), 3.23 (t, *J* = 8.7 Hz, 1H), 3.36 (s, 3H), 3.79 (s, 3H), 7.16-7.31 (m, 5H)

Methyl (2*R*)-2- phenylcyclopropane-1-carboxylate 8b



Ester **8b** was prepared following the reported method using $Cu(acac)_2$ instead of chiral ligand-Cu(OTf).
trans-**8b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.2 Hz, 1H), 1.30-1.34 (m, 0.3H), 1.57-1.62 (m, 0.3H), 1.87-1.93 (m, 0.3H), 2.48-2.56 (m, 0.3H), 4.17 (q, *J* = 7.2 Hz, 0.67H).
cis-**8b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, *J* = 7.1 Hz, 3H), 1.29-1.36 (m, 1H), 1.67-1.75 (m, 1H), 2.08 (ddd, *J* = 5.6, 7.3, 9.3 Hz, 1H), 2.58 (dt, *J* = 8.4, 16.6 Hz, 1H), 3.87 (q, *J* = 7.1 Hz, 2H).

Torimethyl (2*S*,3*R*)-2-(3,4-dimethoxyphenyl)-cyclopropane-1,1,3- tricarboxylate (8d)

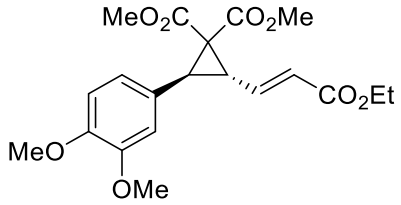


NaH_2PO_4−H_2O (48 mg, 0.31mmol) and 35%-H_2O_2 (0.12ml, 1.24mmol) was added to a solution of **4b** (preparation of **4b** was already described above.) (200 mg, 0.62 mmol) in acetonitrile (0.62 ml) at 0°C. Then, $NaClO_2$ (84 mg, 0.93mmol) aqueous solution (1.24 ml) was added to the mixture at 0 °C, and followed by being stirred for room temperature for 30 min. Then, sat. $Na_2S_2O_3$ solution (10 ml) was added to the reaction mixtur, which was extracted with $CHCl_3$ (ca. 10ml x 3). The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was dissolved in DMF (1ml). Then, the solution was added to a mixture of K_2CO_3 (86 mg, 0.62 mmol) and CH3I (39 #L, 0.62 mmol) in DMF (0.5 ml) at 0°C, and followed by being stirred at room temperature for 30 minutes. Water (20 ml) was added to the reaction mixture, which was extracted with ether (ca. 10ml x 3). The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 3/2) to give the product **8d** (97 mg, 44% yield).

8d: colorless liquid ; $[\alpha]^{21}_D$ = -39.2 (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.22 (d, *J* = 7.5, Hz, 1H), 3.52 (s, 3H), 2.59 (d, *J* = 7.5 Hz, 1H), 3.75 (s, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 3.85 (s, 3H), 6.75-6.80 (m, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 166.9, 166.1, 149.1, 149.0, 125.6, 121.1, 112.0, 111.2, 56.3, 56.2, 53.5, 53.3, 53.0, 44.6, 36.2, 31.6 ; IR (NaCl, neat) 3638, 3553,

3460, 3003, 2955, 2839, 1755, 1738, 1732, 1591, 1592, 1454, 1435, 1115, 1026, 914, 733 cm^{-1}, HRMS (APCI) calcd for $C_{17}H_{20}O_8$ $(M+H)^+$ 353.1231 , found 353.1224.

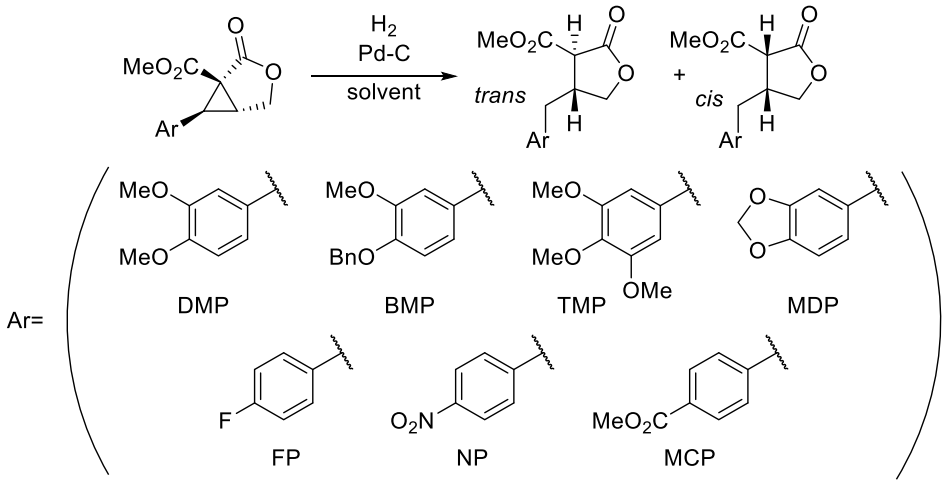
Dimethyl (2S,3R)-2-(3,4-dimethoxyphenyl)-3-((E)-3-ethoxy-3-oxoprop-1-en-1-yl)cyclopropane-1,1-dicarboxylate (8e)



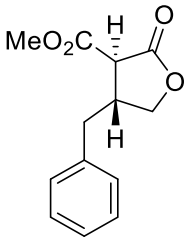
A 5M-THF-solution of triethyl phosphonoacetate (0.20 ml, 1.0 mmol) was added dropwise to a suspension of NaH (40 mg, 1.0 mmol) in THF (0.77 ml) at 0 °C, followed by being stirred at the same temperature for 30 minutes. Then, a solution of **4b** (250 mg, 0.78 mmol) in THF (1.6 ml) was added to the reaction mixtur, followed by being stirred at the room temperature for 30 minutes. Water was added to the reaction mixture, which was extracted with AcOEt (ca. 10mL, x 5). The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 3/2) to give the product **8e** (209mg, 69%).

8e: colorless liquid ; $[\alpha]^{21}_D$ = 9.2 (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7.1 Hz, 3H), 3.20 (dd, *J* = 7.8, 9.4 Hz, 1H), 3.45 (d, *J* = 7.8 Hz, 1H), 3.49 (s, 3H), 3.81 (s, 3H), 3.85 (s, 3H), 3.85 (s, 3H), 4.20 (q, *J* = 7.1 Hz, 2H), 6.20 (dd, *J* = 0.3, 15.6 Hz, 1H), 6.65-6.80 (m, 4H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 166.7, 166.1, 149.2, 149.0, 142.6, 126.3, 125.2, 120.8, 112.0, 111.3, 60.9, 56.3, 56.2, 53.5, 53.1, 45.1, 37.4, 33.2, 14.6 ; IR (NaCl, neat) 2955, 1732, 1715, 1651, 1520, 1435, 1180, 1142, 1028, 916, 733 cm^{-1}, HRMS (APCI) calcd for $C_{20}H_{24}O_8$ $(M+H)^+$ 393.1544 , found 393.1553.

Hydrogenolysis of bicyclolactones



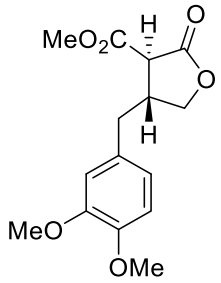
(α*S*, β*R*)-β-phenylmethyl-γ-butyrolactone (10a)



Pd-C (12 mg, 5 mol %) was added to a solution of ester **5a** (50 mg, 0.22 mmol) in AcOEt (1.1 ml) at 0°C, followed by being stirred at the same temperature for 1h under hydrogen atmosphere (balloon). After a filtration, the filtrate solution was concentrated. The obtained crude oil was purified by column chromatography (SiO2, hexane/AcOEt = 2/1) to give a **10a** (39 mg, 78% yield, dr = 91/9).

10a: colorless liquid; $[\alpha]^{26}_{D}$ = 34.4 (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.79-2.89 (m, 2H), 3.35-3.25 (m, 2H), 3.69 (s, 3H), 4.01 (dd, *J* = 8.0, 9.1 Hz, 1H), 4.43 (dd, *J* = 7.0, 9.1 Hz, 1H), 7.14-7.34 (m, 5H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 38.2, 42.0, 52.2, 53.4, 71.8, 127.5, 129.2, 129.3, 137.3, 168.1, 172.1 ; IR (NaCl, neat) 2953, 1778, 1738, 1437, 1250, 1207, 1146, 1018, 702 cm^{-1}, HRMS (APCI) calcd for $C_{13}H_{14}O_4$ $(M+H)^+$ 233.0808 , found 233.0805 ; HPLC analysis: 95% ee [Daicel CHIRALPAK IC (25cm) at 25°C, flow rate 1.0 ml/min, solvent: hexane / ethanol = 2/1, tR(racemic) = 10.2 min and 13.7 min, tR(**10a)** = 9.6 min for major and 12.9 min for minor]. Selected data for **10'a** (minor product): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63 (dd, J = 9.7, 13.9 Hz, 0.1H), 2.97 (dd, J = 6.1, 13.9 Hz, 0.1H), 3.07-3.20 (m, 0.1H), 3.61 (d, J = 8.7 Hz, 0.1H), 3.81 (s, 0.3H), 4.22-4.29 (m, 0.2).

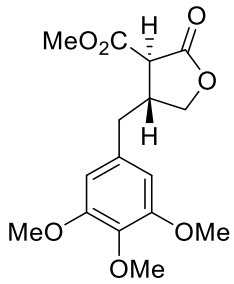
(α*S*, β*R*)- β-(3,4-dimethoxyphenyl)methyl-γ-butyrolactone (10b)



Following the procedure for the preparation of **10a**, the reaction using **5b** instead of **5a** gave the product **10b** (93% yield, dr = 93/7).

10b: colorless solid; mp 83-86°C; $[\alpha]^{24}_{D}$ = -30.5 (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.72-2.84 (m, 2H), 3.22-3.36 (m, 2H), 3.71 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 4.01 (dd, *J* = 7.7, 9.0 Hz, 1H), 4.43 (dd, *J* = 7.2, 9.0 Hz, 1H), 6.66 (d, *J* = 1.9 Hz, 1H), 6.69 (dd, *J* = 1.9, 8.1 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 37.8, 42.1, 52.2, 53.4, 56.3, 56.3, 71.8, 111.9, 112.3, 121.3, 129.8, 148.5, 149.6, 168.2, 172.1 ; IR (KBr, neat) 2968, 1775, 1736, 1591, 1520, 1456, 1285, 1252, 1161, 1020, 813, 660 cm^{-1}, HRMS (APCI) calcd for $C_{15}H_{18}O_6$ $(M+H)^+$ 293.1020 , found 293.1035 ; HPLC analysis: 95% ee [Daicel CHIRALPAK IC (25cm) at 25°C, flow rate 0.8 ml/min, solvent: hexane / ethanol = 2/1, tR(**10b)** = 23.6 min for major and 31.7 min for minor]. Selected data for **10'b** (minor product): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.57 (dd, J = 9.7, 13.9 Hz, 0.08H), 2.91 (dd, J = 6.2, 13.9 Hz, 0.08H), 3.05-3.16 (m, 0.08H), 3.61 (d, J = 8.7 Hz, 0.08H), 3.81 (s, 0.24H), 4.21-4.30 (m, 0.16H).

(α*R*, β*S*)- β-(3,4,5-trimethoxyphenyl)methyl-γ-butyrolactone (10c)

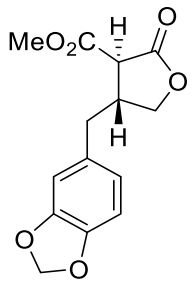


Following the procedure for the preparation of **10a**, the reaction using **5c** instead of **5a** gave the product **10c** (87% yield, dr = 93/7).

10c: colorless solid; mp 91-94°C; $[\alpha]^{21}_{D}$ = 20.2 (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.73-2.82 (m, 2H), 3.24-3.38 (m, 2H), 3.72 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 3.85 (s, 3H), 4.02 (dd, *J* = 7.7, 9.0 Hz, 1H), 4.46 (dd, *J* = 7.1, 9.0 Hz, 1H), 6.36 (s, 2H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 38.5, 41.9, 52.3, 53.4, 56.6, 61.2, 71.8, 106.2, 133.0, 137.4, 153.9, 168.2, 172.0 ; IR (KBr,

neat) 2965, 1776, 1744, 1722, 1591, 1506, 1462, 1327, 1246, 1140, 1024, 829, 685 cm^{-1}, HRMS (APCI) calcd for $C_{16}H_{20}O_7$ $(M+H)^+$ 323.1125 , found 323.1126 ; HPLC analysis: 95% ee [Daicel CHIRALPAK IC (25cm) at 25°C, flow rate 0.8 ml/min, solvent: hexane / ethanol = 2/1, tR(racemic) = 25.4 min and 29.4 min, tR(**10c)** = 26.8 min for major and 31.7 min for minor]. Selected data for **10'c** (minor product): ^1H NMR (400 MHz, $CDCl_3$) δ 2.56 (dd, J = 9.7, 13.9 Hz, 0.08H), 2.91 (dd, J = 6.0, 13.9 Hz, 0.08H), 3.05-3.16 (m, 0.08H), 3.62 (d, J = 8.7 Hz, 0.08H), 4.23-4.32 (m, 0.16H).

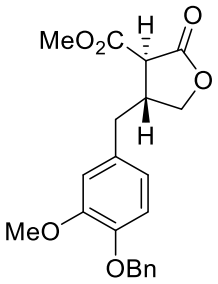
(α*R*, β*S*)- β-(3,4-methylenedioxyphenyl)methyl-γ-butyrolactone (10d)



Following the procedure for the preparation of **10a**, the reaction using **5d** instead of **5a** gave the product **10d** (94% yield, dr = 92/8).

10d: colorless liquid; $[\alpha]^{21}_D$ = 8.5 (*c* 1.00, chloroform, λ = 589 nm); ^1H NMR (400 MHz, $CDCl_3$) δ 2.68-2.82 (m, 2H), 3.23 (m, 1H), 3.32 (d, *J* = 8.7 Hz, 1H), 3.74 (s, 3H), 3.99 (dd, *J* = 9.0, 7.7 Hz, 1H), 4.42 (dd, *J* = 9.0, 7.2 Hz, 1H), 5.95 (s, 2H), 6.60 (dd, *J* = 7.9, 1.7 Hz, 1H), 6.64 (d, *J* = 1.7 Hz, 1H), 6.75 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 37.9, 42.1, 52.1, 71.8, 101.5, 108.9, 109.4, 122.3, 131.0, 147.1, 148.4, 168.1, 172.0 ; IR (NaCl, neat) 2955, 2909, 1778, 1738, 1504, 1491, 1445, 1242, 1148, 1038, 1018, 928, 812 cm^{-1}, HRMS (APCI) calcd for $C_{14}H_{14}O_6$ $(M+H)^+$ 277.0707 , found 277.0715 ; HPLC analysis: 93% ee [Daicel CHIRALPAK IC (25cm) at 25°C, flow rate 0.8 ml/min, solvent: hexane / ethanol = 2/1, tR(**10d)** = 14.4 min for minor and 19.9 min for major]. Selected data for **10'd** (minor product): ^1H NMR (400 MHz, $CDCl_3$) δ 2.55 (dd, 9.8, 14.0 Hz, 0.09H), 2.88 (dd, J = 6.2, 14.0 Hz, 0.09H), 3.00-3.12, (m, 0.09H), 3.59 (d, J = 8.7 Hz, 0.09H), 3.81 (s, 0.27H), 4.20-4.30 (m, 0.18H).

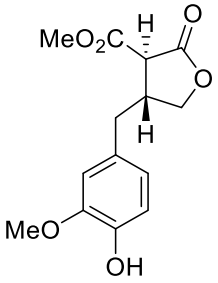
(α*R*, β*S*)- β-(4-benzyloxy-3-methoxyphenyl)methyl-γ-butyrolactone (10e)



Following the procedure for the preparation of **10a**, the reaction using **5e** instead of **5a** gave the product **10e** (90% yield, dr = 93/7).

10e: colorless solid; mp 73-76°C; $[\alpha]^{26}_{D}$ = 17.9 (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.71-2.80 (m, 2H), 3.20-3.34 (m, 2H), 3.67 (s, 3H), 3.88 (s, 3H), 3.99 (dd, *J* = 9.0, 7.7 Hz, 1H), 4.42 (dd, *J* = 9.1, 7.2 Hz, 1H), 5.13 (s, 2H), 6.61 (dd, *J* = 2.0, 8.1 Hz, 1H), 6.67 (d, *J* = 2.0 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 7.28-7.44 (m, 5H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 37.8, 42.1, 52.2, 53.4, 56.5, 71.5, 71.8, 112.9, 114.7, 121.3, 127.7, 128.3, 129.0, 130.4, 137.5, 147.6, 150.3, 168.2, 172.1 ; IR (KBr, neat) 2951, 1773, 1759, 1736, 1514, 1265, 1231, 1163, 1001, 746, 696 cm^{-1}, HRMS (APCI) calcd for $C_{21}H_{22}O_6$ $(M+H)^+$ 369.1333 , found 369.1341 . Selected data for **10'e** (minor product): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.55 (dd, J = 9.8, 14.0, 0.07H), 2.89 (dd, J = 6.2, 14.0 Hz, 0.07H), 3.03-3.15 (m, 0.07H), 3.60 (d, J = 8.7 Hz, 0.07H), 4.20-4.30 (m, 0.14H).

(α*R*, β*S*)- β-(4-hydroxy-3-methoxyphenyl)methyl-γ-butyrolactone (10ee)

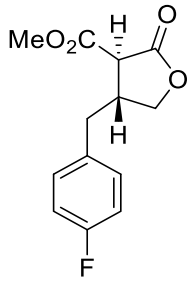


Following the procedure for the preparation of **10a**, the reaction using **5e** instead of **5a** gave the product **10ee** (80% yield, dr = 91/9).

10ee: colorless solid; mp 112-115°C; $[\alpha]^{26}_{D}$ = 18.4 (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70-2.82 (m, 2H), 3.20-3.35 (m, 2H), 3.71 (s, 3H), 3.89 (s, 3H), 4.00 (dd, *J* = 7.7, 9.0 Hz, 1H), 4.43 (dd, *J* = 7.2, 9.0 Hz, 1H), 5.53 (s, 1H), 6.62-6.66 (m, 2H), 6.85 (d, *J* = 8.7 Hz, 1H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 37.9, 42.2, 52.2, 53.4, 56.4, 71.8, 111.6, 115.0, 122.0, 129.1, 145.1, 147.1, 168.2, 172.1 ; IR (KBr, neat) 3350, 2938, 1763, 1728, 1605, 1514, 1435, 1315, 1273, 1242, 1217, 1152, 1016, 829, 829, 665 cm^{-1}, HRMS (APCI) calcd for $C_{14}H_{16}O_6$ $(M+H)^+$ 279.0863 , found 279.0874 . Selected data for **10'ee** (minor product): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.55 (dd, J = 9.8, 14.0, 0.1H), 2.89 (dd, J = 6.2, 14.0 Hz, 0.1H), 3.05-3.18 (m, 0.1H), 3.60 (d, J = 8.7 Hz, 0.1H), 4.20-

4.32 (m, 0.2H).

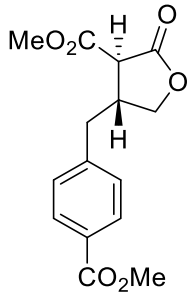
(α*R*, β*S*)- β-(4-fluorophenyl)methyl-γ-butyrolactone (10f)



Following the procedure for the preparation of **10a**, the reaction using **5f** instead of **5a** gave the product **10f** (96% yield, dr = 92/8).

10f: colorless solid; mp 87-90°C; $[\alpha]^{26}_{D}$ = 32.6 (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.81 (d, *J* = 7.3 Hz, 2H), 3.21-3.35 (m, 2H), 3.68 (s, 3H), 3.99 (dd, *J* = 8.0, 8.9 Hz, 1H), 4.43 (dd, *J* = 7.2, 9.0 Hz, 1H), 6.97-7.04 (m, 2H), 7.10-7.16 (m, 2H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 37.4, 42.1, 52.2, 53.4, 71.7, 116.1 (d, JC-F = 21.4 Hz), 130.7 (d, JC-F = 8.1 Hz), 133.1 (d, JC-F = 3.2 Hz), 162.3 (d, JC-F = 245.9 Hz), 168.0, 171.9 ; IR (KBr, neat) 2957, 1771, 1740, 1510, 1441, 1260, 1225, 1167, 1070, 1030, 1018, 841, 694 cm^{-1}, HRMS (APCI) calcd for $C_{13}H_{13}FO_4$ $(M+H)^+$ 251.0714 , found 251.0720 . Selected data for **10'f** (minor product): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63 (dd, J = 9.5, 14.0 Hz, 0.08H), 2.93 (dd, J = 6.4, 14.0 Hz, 0.08H), 3.05-3.17 (m 0.08H), 3.60 (d, J = 8.7 Hz, 0.08), 3.82 (s, 0.24H), 4.19-4.30 (m, 0.16H).

(α*R*, β*S*)- β-(4-methoxycarbonylphenyl)methyl-γ-butyrolactone (10g)

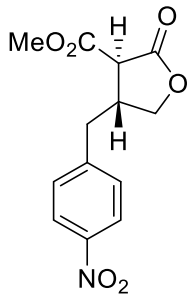


Following the procedure for the preparation of **10a**, the reaction using **5g** instead of **5a** gave the product **10g** (97% yield, dr = 95/5).

10g: colorless solid; mp 98-101°C; $[\alpha]^{21}_{D}$ = 18.8 (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.84-2.95 (m, 2H), 3.27-3.38 (m, 2H), 3.69 (s, 3H), 3.92 (s, 3H), 3.97-4.03 (m, 1H), 4.41-4.46 (m, 1H), 7.24 (d, *J* = 8.2 Hz, 2H), 8.00 (d, *J* = 8.2 Hz, 2H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ

171.8, 167.9, 142.8, 130.5, 129.5, 129.2, 71.7, 53.4, 52.5, 52.2, 41.7, 38.1 ; IR (KBr, neat) 2959, 1771, 1759, 1738, 1715, 1437, 1302, 1281, 1150, 1111, 1024, 772, 712 cm^{-1}, HRMS (APCI) calcd for $C_{15}H_{16}O_6$ $(M+H)^+$ 293.1020, found 293.1016 . Selected data for **2'g** (minor product): ^1H NMR (400 MHz, $CDCl_3$) δ 2.72 (dd, J = 9.3, 13.8 Hz, 0.06H), 3.02 (dd, J = 6.3, 13.8 Hz, 0.06H), 3.11-3.20 (m 0.06H), 3.60 (d, J = 8.7 Hz, 0.06H), 3.80 (s, 0.18H), 4.21-4.32 (m, 0.12H).

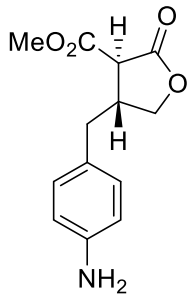
(α*R*, β*S*)- β-(4-nitrophenyl)methyl-γ-butyrolactone (10h)



Following the procedure for the preparation of **10a**, the reaction using **5h** instead of **5a** gave the product **10h** (75% yield, dr = 92/8).

10h: colorless solid; mp 78-81°C; $[\alpha]^{21}_D$ = 1.6 (*c* 1.00, chloroform, λ = 589 nm); ^1H NMR (400 MHz, $CDCl_3$) δ 2.90-3.02 (m, 2H), 3.29-3.40 (m, 2H), 3.71 (s, 3H), 3.97-4.04 (m, 1H), 4.43-4.49 (m, 1H), 7.33-7.38 (m, 2H), 8.18-8.23 (m, 2H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 167.8, 147.6, 145.1, 130.1, 124.5, 71.5, 53.6, 52.1, 41.5, 38.0 ; IR (KBr, neat) 2957, 1763, 1736, 1603, 1518, 1437, 1346, 1281, 1261, 1202, 1153, 1067, 1018, 1009, 856 cm^{-1}, HRMS (APCI) calcd for $C_{13}H_{13}NO_6$ $(M+H)^+$ 280.0816 , found 280.0819 . Selected data for **10'h** (minor product): ^1H NMR (400 MHz, $CDCl_3$) δ 2.82-2.89 (m 0.09H), 3.04-3.18 (m, 0.09H), 3.19-3.26 (m, 0.09H), 3.61 (d, J = 8.4, 0.09H), 3.48 (s, 0.27H), 4.24-4.36 (m, 0.18H).

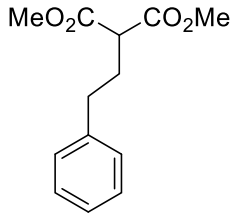
(α*R*, β*S*)- β-(4-aminophenyl)methyl-γ-butyrolactone (15hh)



Following the procedure for the preparation of **10a**, the reaction using **5h** instead of **5a** gave the product **10hh** (75% yield, dr = 92/8).

10hh: colorless liquid; $[\alpha]^{21}_{D}$ = 23.0 (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.65-2.78 (m, 2H), 3.16-3.28 (m, 1H), 3.31 (d, *J* = 8.8 Hz, 1H), 3.72 (s, 3H), 3.99 (dd, *J* = 7.8, 9.0 Hz, 1H), 4.41 (dd, *J* = 7.3, 9.0 Hz, 1H), 6.60-6.65 (m, 2H), 6.90-6.95 (m, 2H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 168.3, 145.8, 130.1, 126.9, 115.8, 71.9, 53.4, 52.2, 42.3, 37.2 ; IR (NaCl, neat) 3455, 3374, 3001, 2953, 2913, 1776, 1736, 1626, 1518, 1437, 1281, 1252, 1180, 1150, 1016, 912, 829, 733 cm^{-1}, HRMS (APCI) calcd for $C_{13}H_{15}NO_4$ $(M+H)^+$ 250.1074 , found 250.1062 . Selected data for **10'hh** (minor product): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (dd, J = 9.8, 14.0 Hz, 0.09H), 2.83 (dd, 6.0, 14.0 Hz, 0.09H), 2.99-3.11 (m, 0.09H), 3.78 (s, 0.27H), 4.18-4.28 (m, 0.18H).

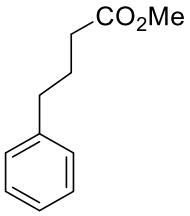
dimethyl 2-phenethylmalonate (11a)



Following the procedure for the preparation of **10a**, the reaction using **8a** instead of **5a** gave the product **11a** (95% yield).

11a: colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20-2.27 (m, 2H), 2.65 (t, *J* = 7.7 Hz, 2H), 3.38 (t, *J* = 7.5 Hz, 1H), 3.74 (s, 6H), 7.61-7.32 (m, 5H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 140.9, 128.9, 126.6, 52.9, 51.3, 33.7, 30.8; IR (NaCl, neat) 2953, 1755, 1738, 1497, 1435, 1227, 1202, 1150, 1040, 700 cm^{-1}; HRMS (APCI) calcd for $C_{13}H_{16}O_4$ $(M+H)^+$ 237.1121 , found 237.1118 .

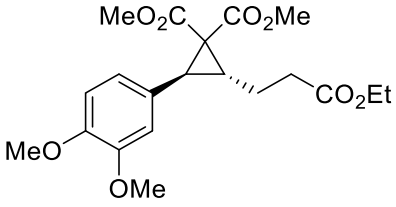
methyl 4-phenylbutanoate (11b)



Following the procedure for the preparation of **10a**, the reaction using **8b** instead of **5a** gave the product **11b** (90% yield).

11b: colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.1 Hz, 3H), 1.91-2.01 (m, 2H), 2.32 (t, *J* = 7.5 Hz, 2H), 2.65 (t, *J* = 7.5 Hz, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 7.15-7.31 (m, 5H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 141.9, 128.9, 128.8, 126.4, 60.7, 35.6, 34.2, 27.0, 14.7 ; IR (NaCl, neat) 2980, 2936, 1732, 1497, 1454, 1373, 1202, 1179, 1032, 746, 700 cm^{-1}; HRMS (APCI) calcd for $C_{12}H_{16}O_2$ $(M+H)^+$ 193.1223 , found 193.1216.

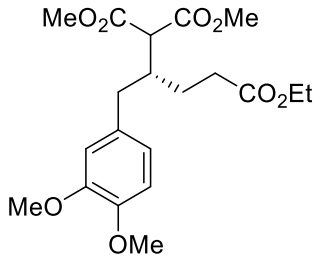
dimethyl (2S,3R)-2-(3,4-dimethoxyphenyl)-3-(3-ethoxy-3-oxopropyl)cyclopropane-1,1-dicarboxylate (11e)



Following the procedure for the preparation of **10a**, the reaction using **8e** instead of **5a** gave the product **11e** (33% yield).

11e: colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.1 Hz, 3H), 1.80-1.94 (m, 2H), 2.44-2.56 (m, 3H), 3.07 (d, *J* = 8.1 Hz, 1H), 3.43 (s, 3H), 3.81 (s, 3H), 3.84 (s, 3H), 3.85 (s, 3H), 4.13 (q, *J* = 7.1 Hz, 2H), 6.70-6.79 (m, 3H).

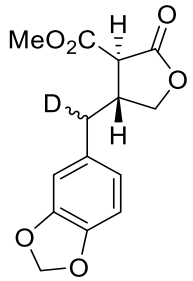
4-ethyl 1,1-dimethyl (R)-2-(3,4-dimethoxybenzyl)butane-1,1,4-tricarboxylate (11e')



Following the procedure for the preparation of **10a**, the reaction using 8e instead of **5a** gave the product **11e'** (85% yield).

11e': colorless liquid; $[\alpha]^{21}_{D}$ = -9.6 (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.1 Hz, 3H), 1.70-1.84 (m, 2H), 2.28-2.36 (m, 2H), 2.40-2.48 (m, 1H), 2.57-2.71 (m, 2H), 3.45 (d, *J* = 5.9 Hz, 1H), 3.72 (s, 3H), 3.75 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 4.10 (q, *J* = 7.1 Hz, 2H), 6.69-6.81 (m, 3H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 169.6, 169.4, 148.0, 132.3, 121.6, 112.8, 111.6, 60.8, 56.3, 56.2, 54.2, 52.8, 52.8, 40.4, 37.7, 32.4, 26.8, 14.6; IR (NaCl, neat) 2953, 1732, 1591, 1518, 1464, 1437, 1261, 1240, 1194, 1157, 1028, 733 cm^{-1}; HRMS (APCI) calcd for $C_{20}H_{28}O_8$ $(M-H)^-$ 395.1700 , found 395.1714.

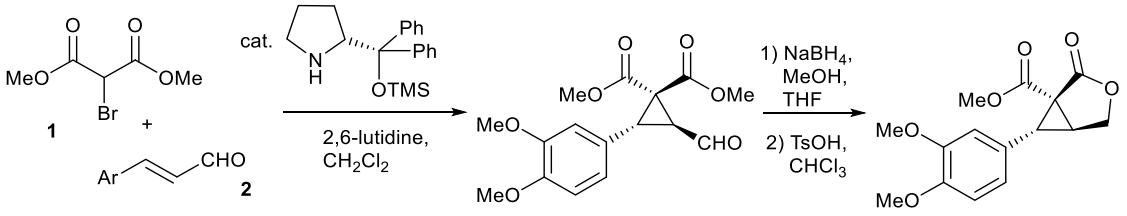
Deuterated compound (10i)



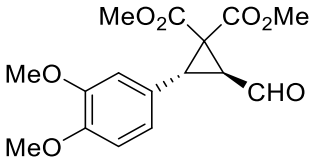
Following the procedure for the preparation of **10d**, the reaction using D_2 instead of H_2 gave the product **10i** (85% yield, dr = 93/7)を得た。

10i: colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.76 (d, *J* = 6.9 Hz, 1H), 3.17-3.27 (m, 1H), 3.32 (d, *J* = 8.8), 3.74 (s, 3H), 3.99 (dd, *J* = 7.8, 9.0 Hz, 1H), 4.42 (dd, *J* = 7.4, 9.0 Hz, 1H), 5.95 (s, 2H), 6.60 (dd, *J* = 1.7, 7.9 Hz, 1H), 6.64 (d, *J* = 1.7, 1H), 6.75 (d, *J* = 7.9 Hz, 1H); (APCI) calcd for $C_{14}H_{13}DO_6$ $(M+H)^+$ 280.0926, found 280.0914. Selected data for **10'i** (minor product): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.86 (d, J = 6.2 Hz, 0.09H), 3.00-3.10, (m, 0.09H), 3.59 (d, J = 8.8 Hz, 0.09H), 3.81 (s, 0.27H), 4.20-4.30 (m, 0.18H).

(1*R*,5*S*,6*R*)-1-Methoxycarbonyl-6-(3,4-dimethoxyphenyl)-3-oxabicyclo[3,1,0]hexan-2-one (4b')



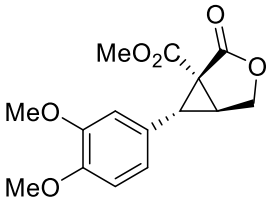
Dimethyl (2*S*,3*R*)-2-formyl-3-(3,4-dimethoxyphenyl)cyclopropane-1,1-dicarboxylate (4b')



Following the procedure for the preparation of **4b**, the reaction using (R)-(Diphenyltrimethylsiloxymethyl)-pyrrolidine instead of (S)-(Diphenyltrimethylsiloxymethyl)-pyrrolidine gave the product **4b'** (3.480 g, 83%).

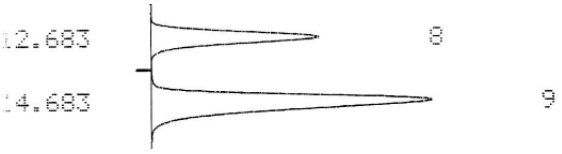
4b': colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (d, *J* = 4.6 Hz, 1H), 6.79 – 6.76 (m, 2H), 6.74 (d, *J* = 1.4 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.79 (d, *J* = 7.5 Hz, 1H), 3.51 (s, 3H), 3.35 (dd, *J* = 7.5, 4.6 Hz, 1H).

(1*R*,5*S*,6*R*)-1-Methoxycarbonyl-6-(3,4-dimethoxyphenyl)-3-oxabicyclo[3,1,0]hexan-2-one (5b')

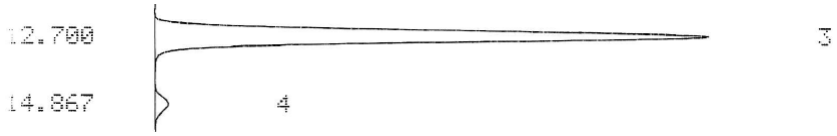


Following the procedure for the preparation of **5b**, the reaction using **4b'** instead of **4b** gave the product **5b'** (2.23 g, 71% (2 steps), 94% ee).

5b'; colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 – 6.75 (m, 3H), 4.50 (dd, *J* = 9.3, 4.8 Hz, 1H), 4.37 (d, *J* = 9.2 Hz, 1H), 3.87 (s, 3H), 3.87 (s, 3H), 3.57 (s, 3H), 3.26 (t, *J* = 5.0 Hz, 1H), 2.90 (d, *J* = 5.6 Hz, 1H).; HPLC analysis: 94% ee [Daicel CHIRALPAK IG (15 cm) at 25°C, flow rate 0.8 ml/min, solvent: hexane / 2-propanol = 2/1, t_R(racemic) = 12.68 min and 14.68 min, t_R(**5b'**) = 12.70 min for major and 14.87 min for minor]. The ee value of **5b'** (94% ee) was actually observed by HPLC analysis.



Racemic-**5b'**: HPLC analysis using chiral column.

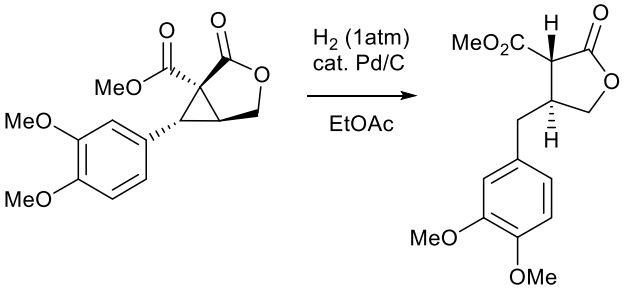


Enantioenriched **5b'** (94% ee) : HPLC analysis using chiral column.

3	12.700	1742152	67506	95.5683
4	14.867	51500	1583	2.8251

Based on this enantiomeric ratio (95.57/2.83), the ee value was estimated as 94% ee.

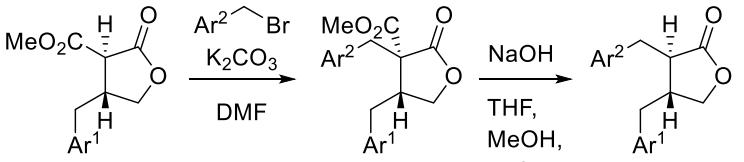
(α*R*, β*S*)- β-(3,4-dimethoxyphenyl)methyl-γ-butyrolactone (10b')



Following the procedure for the preparation of **10a**, the reaction using 5b' instead of **5a** gave the product **10b'** (97% yield, dr = 91/9).

10b'; colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (d, *J* = 8.1 Hz, 1H), 6.69 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.65 (d, *J* = 1.9 Hz, 1H), 4.43 (dd, *J* = 9.0, 7.1 Hz, 1H), 4.01 (dd, *J* = 8.9, 7.6 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.72 (s, 3H), 3.36 – 3.22 (m, 2H), 2.84 – 2.72 (m, 2H).

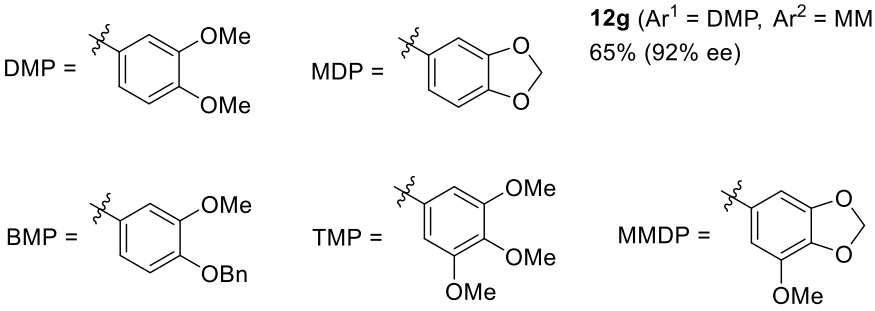
α-benzylation of lactones and decarboxylation of lactones to afford trans-lactones



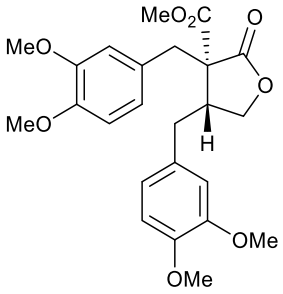
10b (Ar^1 = DMP)
91% (dr = 93/7)
10d (Ar^1 = MDP)
94% (dr = 92/8)
10e (Ar^1 = BMP)
70% (dr = 93/7)

15b (Ar^1 = Ar^2 = DMP)
88%
15d (Ar^1 = MDP, Ar^2 = TMP)
91%
15e (Ar^1 = Ar^2 = BMP)
51%
15g (Ar^1 = DMP, Ar^2 = MMDP)
71%

12b:dimethylmatairesinol
(Ar^1 = Ar^2 = DMP)
68% (92% ee)
12d :yatein
(Ar^1 = MDP, Ar^2 = TMP)
72% (93% ee)
12e (Ar^1 = Ar^2 = BMP)
59% (94% ee)
12g (Ar^1 = DMP, Ar^2 = MMDP)
65% (92% ee)



(α*R*, β*R*)-α-Methoxycarbonyl-α-(3,4-dimethoxyphenyl)methyl–β-(3',4'-dimethoxyphenyl) methyl-γ-butyrolactone (15b)

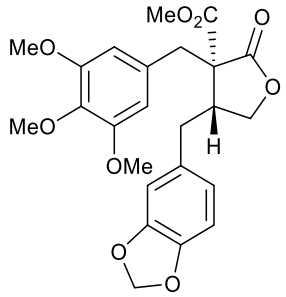


A DMF (1.0 ml) solution of **10b** (0.500 g, 1.7 mmol) was added to a suspension of K_2CO_3 (0.704 g, 5.1 mmol) in DMF (1.0 ml) at 0 °C. Then, a DMF solution (1.5 ml) of 4-benzyloxy-3-methoxybenzylbromide (0.589 g, 2.6 mmol) was added to the reaction solution at 0 °C, followed by being stirred at room temperature for 5.5h. 1M-HCl aqueous solution was added to the reaction mixture, which was extracted with AcOEt. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 5/3) to give the product **15b (**0.665g, 88% yield).

15b: colorless oil ; $[\alpha]^{27}_D$ = -17.9 (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (dd, *J* = 8.2, 2.9 Hz, 2H), 6.69 (d, *J* = 1.9 Hz, 1H), 6.66 – 6.58 (m, 2H), 6.53 (d, *J* = 1.9 Hz, 1H), 4.07 – 3.98 (m, 2H), 3.90 (s, 3H), 3.85 (d, *J* = 1.4 Hz, 9H), 3.82 (s, 3H), 3.44 (d, *J* = 14.4 Hz, 1H),

3.18 (d, J = 14.4 Hz, 1H), 2.83 (dd, J = 13.7, 5.1 Hz, 1H), 2.70 (dtd, J = 15.2, 10.0, 5.1 Hz, 1H), 2.32 (dd, J = 13.7, 9.9 Hz, 1H).; ^{13}C NMR (101 MHz,$CDCl_3$) δ175.4, 169.4, 149.1, 149.0, 148.3, 148.0, 130.0, 127.7, 122.9, 120.4, 113.5, 111.6, 111.4, 111.0, 70.8, 59.0, 55.9, 55.9, 55.8, 55.8, 53.0, 42.6, 36.0, 33.9; IR (KBr , neat) 3003, 2959, 2938, 2837, 1775, 1736, 1591, 1518, 1466, 1420, 1265, 1238, 1159, 1144, 1084, 1028, 864, 814, 766 cm^{-1}; HRMS (APCI) calcd for $C_{24}H_{28}O_8$ $(M)^+$ 444.1779, found 444.1728.

(α*R*, β*R*)-α-Methoxycarbonyl-α-(3,4,5-trimethoxyphenyl)methyl–β-(3',4'-methylenedioxyphenyl) methyl-γ-butyrolactone (15d)

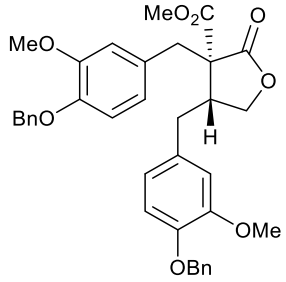


Following the procedure for the preparation of **15b**, the reaction using **10d** instead of **10b** gave **15d** (91% yield).

15d : colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (dd, J = 10.0, 13.7 Hz, 1H), 2.66-2.77 (m, 1H), 2.81 (dd, J = 4.9, 13.7 Hz, 1H), 3.13 (d, J = 14.3 Hz, 1H), 3.43 (d, J = 14.3 Hz, 1H), 3.82 (s, 3H), 3.83 (s, 3H), 3.89 (s, 3H), 3.99-4.10 (m, 2H), 5.91-5.94 (m, 2H), 6.53 (s, 2H), 6.48-6.55 (m, 2H), 6.71 (d, J = 7.8 Hz, 1H) ; ^{13}C NMR (101 MHz, $CDCl_3$) δ 34.5, 37.0, 42.8, 53.4, 56.5, 59.4, 61.2, 71.2, 101.5, 108.0, 108.9, 109.1, 121.7, 131.2, 131.5, 137.6, 147.0, 148.4, 153.7, 169.6, 175.6.

(α*R*, β*R*)-α-Methoxycarbonyl-α-(4-benzyloxy-3-methoxyphenyl)methyl–β-(4'-benzyloy-3'-

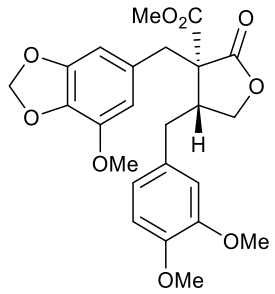
methoxyphenyl) methyl-γ-butyrolactone (15e)



Following the procedure for the preparation of **15b**, the reaction using **10e** instead of **10b** gave **15e** (51% yield).

15b: colorless amorphous solid; $[\alpha]^{27}_D$ = -7.5 (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 53.3 Hz, 10H), 6.77 (d, *J* = 1.7 Hz, 1H), 6.75 (d, *J* = 1.8 Hz, 1H), 6.70 (d, *J* = 2.0 Hz, 1H), 6.55 – 6.48 (m, 3H), 5.12 (s, 2H), 5.10 (s, 2H), 4.00 (d, *J* = 9.4 Hz, 2H), 3.88 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 3.41 (d, *J* = 14.3 Hz, 1H), 3.14 (d, *J* = 14.4 Hz, 1H), 2.79 (dd, *J* = 13.8, 5.2 Hz, 1H), 2.72 – 2.61 (m, 1H), 2.29 (dd, *J* = 13.8, 9.7 Hz, 1H); ^{13}C NMR (101 MHz,$CDCl_3$) δ175.4, 169.4, 149.8, 149.7, 147.5, 147.1, 137.1, 137.1, 130.6, 128.6, 128.6, 128.3, 127. 9, 127.3, 127.2, 122.9, 120.4, 114.3, 114.1, 113.9, 112.3, 71.1, 71.1, 70.8, 59.1, 56.0, 56.0, 53.0, 42.5, 36.0, 33.9; IR (KBr , neat) 3032, 3005, 2936, 2872, 1778, 1740, 1607, 1589, 1520, 1465, 1420, 1381, 1260, 1144, 1084, 1032, 856, 810, 768, 739, 698 cm^{-1}; HRMS (APCI) calcd for $C_{36}H_{36}O_8$ $(M)^+$ 596.2405 found 596.2361.

(α*R*, β*R*)-α-methoxycarbonyl-α-(5-methoxy-3,4-methylenedioxyphenyl)methyl–β-(3,4-dimethoxyphenyl)methyl-γ-butyrolactone (15g)

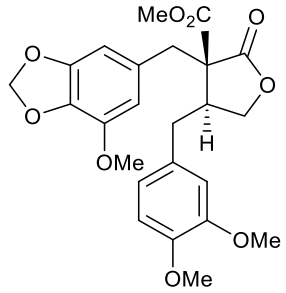


Following the procedure for the preparation of **15b**, the reaction using 5-Methoxy-3,4-methylenedioxybenzylbromide instead of **3,4-**dimethoxybenzylbromide gave **15g** (71% yield).

15g: yellow oil; $[\alpha]^{27}_D$ = -25.1 (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (d, *J* = 8.1 Hz, 1H), 6.60 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.57 (d, *J* = 2.0 Hz, 1H), 6.31 (dd, *J* = 13.3, 1.4 Hz, 2H), 5.93 (dd, *J* = 4.1, 1.4 Hz, 2H), 4.04 (d, *J* = 9.4 Hz, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.40 (d, *J* = 14.4 Hz, 1H), 3.14 (d, *J* = 14.4 Hz, 1H), 2.82 (dd, *J* = 13.6, 5.0 Hz, 1H), 2.71

(qd, *J* = 9.5, 5.0 Hz, 1H), 2.32 (dd, *J* = 13.6, 9.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ175.3, 169.3, 149.3, 149.1, 148.1, 143.7, 134.6, 130.1, 129.6, 120.5, 111.6, 111.5, 110.1, 104.7, 101.6, 70.9, 59.1, 56.7, 56.0, 55.8, 53.1, 42.7, 36.4, 34.0; IR (KBr , neat) 3001, 2955, 2909, 2839, 1772, 1741, 1635, 1516, 1456, 1437, 1263, 1238, 1138, 1094, 1030, 926, 814, 765, 731 cm^{-1};HRMS (APCI) calcd for $C_{24}H_{26}O_9$ $(M)^+$ 458.1571, found 458.1529.

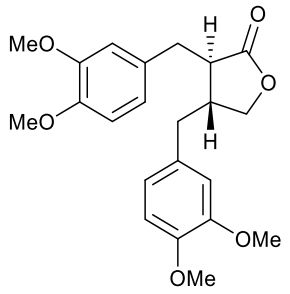
(α*S*, β*S*)-α-methoxycarbonyl-α-(5-methoxy-3,4-methylenedioxyphenyl)methyl–β-(3,4-dimethoxyphenyl)methyl-γ-butyrolactone (15g')



Following the procedure for the preparation of **15b**, the reaction using **10b'** instead of **10b** gave **15g'** (76% yield).

15g': yellow oil; $[\alpha]^{26}_D$ = 24.5 (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (d, *J* = 8.1 Hz, 1H), 6.64 – 6.54 (m, 2H), 6.31 (dd, *J* = 13.1, 1.0 Hz, 2H), 5.93 (dd, *J* = 4.0, 1.2 Hz, 2H), 4.04 (d, *J* = 9.3 Hz, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.40 (d, *J* = 14.4 Hz, 1H), 3.14 (d, *J* = 14.4 Hz, 1H), 2.82 (dd, *J* = 13.6, 5.0 Hz, 1H), 2.71 (qd, *J* = 9.5, 5.0 Hz, 1H), 2.32 (dd, *J* = 13.6, 9.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 169.3, 149.3, 149.1, 148.1, 143.7, 134.6, 130.0, 129.6, 120.5, 111.6, 111.5, 110.0, 104.7, 101.6, 70.9, 59.1, 56.7, 56.0, 55.8, 53.1, 42.7, 36.4, 34.0.

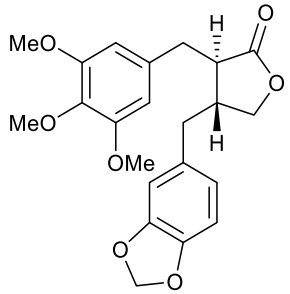
Dimethylmatairesinol (12b)



A 3M-NaOH aqueous solution (0.36 ml, 1.1 mmol) was added to a THF (8.0 ml) and MeOH (1.3 ml) solution of **15b** (0.098 g, 0.22 mmol), followed by being stirred for 3h at 65°C. After cooling to 0°C, 1M-HCl aqueous solution was added to the reaction mixture, which was extracted with AcOEt. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 2/1) to give dimethylmatairesinol **12b** (59 mg, 68% yield).

Dimethylmatairesinol: colorless oil; $[\alpha]^{27}_D$ = -23.9 (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (t, *J* = 7.8 Hz, 2H), 6.70 – 6.64 (m, 2H), 6.55 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.49 (d, *J* = 2.0 Hz, 1H), 4.13 (dd, *J* = 9.2, 7.0 Hz, 1H), 3.90 – 3.87 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H), 3.02 – 2.87 (m, 2H), 2.71 – 2.43 (m, 4H); ^{13}C NMR (101 MHz,$CDCl_3$) δ 178.7, 149.1, 149.0, 148.0, 147.9, 130.5, 130.2, 121.4, 120.6, 112.4, 111.8, 111.3, 111.1, 71.3, 55.9, 55.9, 55.8, 46.6, 41.1, 38.2, 34.5.

Yatein (12d)

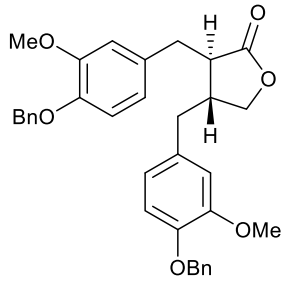


Following the procedure for the preparation of **12b**, the reaction using **15d** instead of **15b** gave yatein **12d** (72% yield).

yatein: colorless liquid; $[\alpha]^{21}_D$ = -24.7 (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43-2.66 (m, 4H), 2.85-2.97 (m, 2H), 3.83 (s, 3H), 3.83 (s, 6H), 3.85-3.91 (m, 1H), 4.18 (dd, *J* = 7.2, 9.1 Hz, 1H), 5.92-5.95 (m, 2H), 6.36 (s, 2H), 6.45-6.49 (m, 2H), 6.70 (d, *J* = 7.5 Hz, 1H) ; ^{13}C NMR (101 MHz,$CDCl_3$) δ 178.9, 153.7, 148.3, 146.8, 137.3, 133.8, 132.0, 121.9, 109.2, 108.7, 106.7, 101.5, 71.6, 61.3, 56.5, 46.9, 41.4, 38.7, 35.7; IR (NaCl, neat) 2938, 1778, 1771, 1591, 1504, 1489,

1456, 1346, 1128, 1038, 1011, 926, 733 cm^{-1}; HRMS (APCI) calcd for $C_{22}H_{24}O_7$ $(M+H)^+$ 401.1595 , found 401.1593.

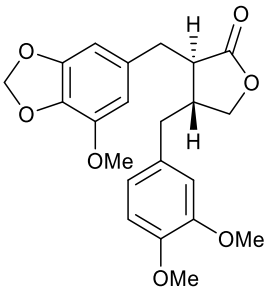
(α*R*, β*R*)-α-(4-Benzyloxy-3-methoxyphenyl)methyl–β-(4'-benzyloxy-3'-methoxyphenyl)methyl-γ-butyrolactone (12e)



Following the procedure for the preparation of **12b**, the reaction using **15e** instead of **15b** gave **12e** (59% yield).

12e: colorless oil; $[\alpha]^{27}_D$ = -11.3 (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.5 Hz, 4H), 7.37 – 7.28 (m, 6H), 6.76 (t, *J* = 8.1 Hz, 2H), 6.70 (d, *J* = 1.9 Hz, 1H), 6.57 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.49 (d, *J* = 1.9 Hz, 1H), 6.45 (dd, *J* = 8.1, 1.9 Hz, 1H), 5.12 (s, 4H), 4.11 (dd, *J* = 9.2, 1.9 Hz, 1H), 3.85 (dd, *J* = 6.9, 5.1 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 2.92 (qd, *J* = 14.1, 6.0 Hz, 2H), 2.57 (dt, *J* = 11.6, 6.8 Hz, 2H), 2.52 – 2.43 (m, 2H); ^{13}C NMR (101 MHz,$CDCl_3$) δ178.7, 149.8, 149.8, 147.1, 147.0, 137.2, 137.1, 131.1, 130.9, 128.6, 128.6, 127.9, 127.9, 127.3, 127.3, 121.4, 120.6, 114.3, 114.1, 112.9, 112.5, 71.3, 71.1, 56.0, 46.5, 41.1, 38.2, 34.6; IR (KBr , neat) 3032, 3005, 2934, 2857, 1767, 1604, 1589, 1514, 1454, 1420, 1381, 1263, 1231, 1140, 1016, 854, 806, 737, 696 cm^{-1}; HRMS (APCI) calcd for $C_{34}H_{34}O_6$ $(M)^+$ 538.2350, found 538.2309.

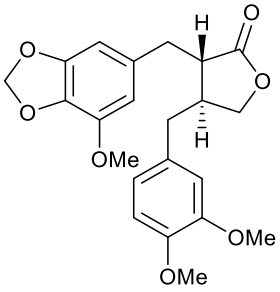
(α*R*, β*R*)-α-(5-methoxy-3,4-methylenedioxyphenyl)methyl–β-(3,4-dimethoxyphenyl)methyl-γ-butyrolactone (12g)



Following the procedure for the preparation of **12b**, the reaction using **15g** instead of **15b** gave **12g** (65% yield).

12g: colorless oil; $[\alpha]^{27}_{D}$ = -26.5 (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (d, *J* = 8.1 Hz, 1H), 6.57 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.50 (d, *J* = 2.0 Hz, 1H), 6.32 (d, *J* = 1.4 Hz, 1H), 6.30 (d, *J* = 1.4 Hz, 1H), 5.94 (dd, *J* = 2.8, 1.5 Hz, 2H), 4.16 (dd, *J* = 9.1, 7.0 Hz, 1H), 3.90 (d, *J* = 7.6 Hz, 1H), 3.86 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 2.94 (dd, *J* = 14.0, 5.1 Hz, 1H), 2.86 (dd, *J* = 14.0, 6.6 Hz, 1H), 2.67 – 2.45 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.6, 149.2, 149.1, 148.0, 143.7, 134.1, 132.2, 130.5, 120.7, 111.8, 111.4, 108.7, 103.3, 101.5, 71.4, 56.7, 56.0, 55.9, 46.6, 41.3, 38.3, 35.1; IR (KBr , neat) 3001, 2938, 2907, 2837, 1769, 1634, 1516, 1452, 1433, 1263, 1238, 1198, 1157, 1138, 1092, 1026, 924, 810, 766, 733 cm^{-1}; HRMS (APCI) calcd for $C_{22}H_{24}O_7$ $(M)^+$ 400.1517, found 400.1476.

(α*S*, β*S*)-α-(5-methoxy-3,4-methylenedioxyphenyl)methyl–β-(3,4-dimethoxyphenyl)methyl-γ-butyrolactone (12g')

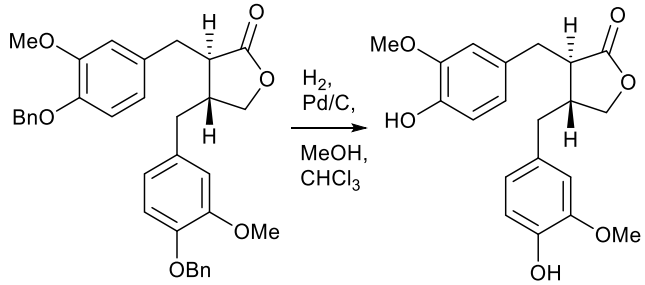


Following the procedure for the preparation of **12b**, the reaction using **15g'** instead of **15b** gave **12g'** (76% yield).

12g': colorless oil; $[\alpha]^{26}_{D}$ = 22.5 (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (d, *J* = 8.1 Hz, 1H), 6.57 (dd, *J* = 8.1, 1.9 Hz, 1H), 6.51 (d, *J* = 1.9 Hz, 1H), 6.31 (d, *J* = 6.7 Hz, 2H), 5.93 (d, *J* = 1.4 Hz, 2H), 4.16 (dd, *J* = 9.1, 7.0 Hz, 1H), 3.89 (d, *J* = 7.5 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 2.89 (ddd, *J* = 20.7, 14.0, 5.8 Hz, 2H), 2.66 – 2.45 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.5, 149.1, 149.0, 147.9, 143.6, 134.0, 132.1, 130.5, 120.6, 111.7, 111.3, 108.7, 103.3,

101.4, 71.3, 56.6, 55.9, 55.8, 46.5, 41.2, 38.2, 35.0.

Deprotection of benzyl ethers to afford matairesinol

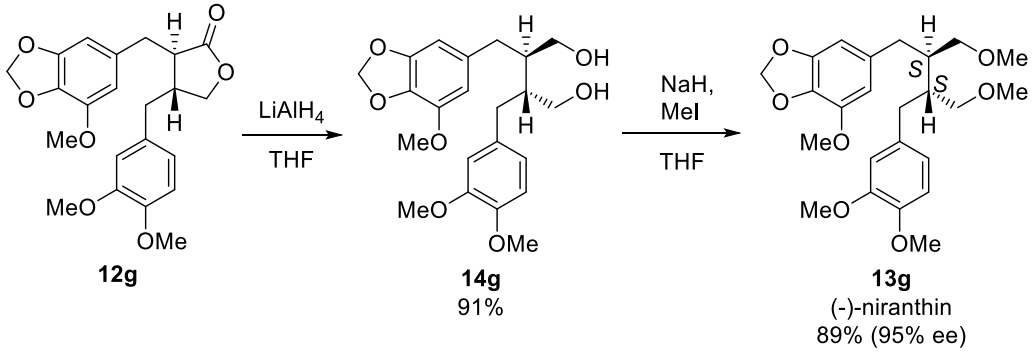


12e **12f**:matairesinol
96% (94% ee)

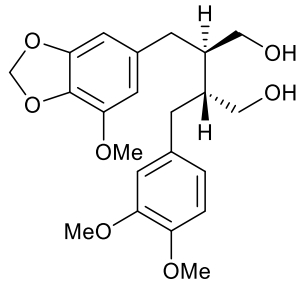
Pd-C (0.010 g, 10 mol %) was added to a solution of **7a** (0.030 g, 0.093 mmol) in MeOH (1.9 ml) and $CHCl_3$ (0.19 ml) at room temperature, followed by being stirred at the same temperature for 7h under hydrogen atmosphere (balloon). After a filtration, the filtrate solution was concentrated. The obtained crude oil was purified by column chromatography (SiO_2, Hexane/AcOEt = 1/1) to give matairesinol (0.032 g, 96%, 94% ee).

Matairesinol: colorless amorphous solid ; $[\alpha]^{27}_D$ = -37.2 (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (t, *J* = 7.9 Hz, 2H), 6.62 – 6.58 (m, 2H), 6.51 (dd, *J* = 8.0, 1.9 Hz, 1H), 6.41 (d, *J* = 1.9 Hz, 1H), 5.51 (s, 1H), 5.49 (s, 1H), 4.15 (dd, *J* = 8.9, 7.1 Hz, 1H), 3.91 – 3.86 (m, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 2.92 (qd, *J* = 14.1, 6.0 Hz, 2H), 2.65 – 2.43 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.9, 146.7, 146.6, 144.5, 144.4, 129.8, 129.6, 122.1, 121.3, 114.4, 114.1, 111.5, 111.0, 71.4, 55.9, 55.8, 46.6, 41.0, 38.3, 34.6.

Alternative synthesis of (-)-niranthin



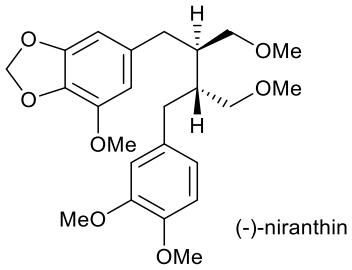
(2*S*,3*S*)-2-(5”-methoxy-3”,4”-methylenedioxyphenyl)methyl-3-(3’,4’-dimethoxyphenyl)methyl butane-1,4-diol (14g)



A THF (5.0 ml) solution of **7c** (0.494 g, 1.2 mmol) was added to a suspention of $LiAlH_4$ (0.094 g, 2.5 mmol) in THF (7.0 ml) at 0 °C under an Ar atmosphere, followed by being stirred at same temperature for 3h. Subsequently, sat. potassium tartrate aqueous solution was added to the reaction mixture, which was extracted with AcOEt. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 1/1) to give the product **8** (0.455 g, 91% yield).

14g: colorless solid; mp 119-121°C; $[\alpha]^{27}_D$ = -29.5 (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (d, *J* = 8.1 Hz, 1H), 6.71 – 6.62 (m, 2H), 6.32 (dd, *J* = 13.7, 1.1 Hz, 2H), 5.91 (s, 2H), 3.84 (s, 6H), 3.83 (s, 3H), 3.82 – 3.77 (m, 4H), 3.53 (d, *J* = 3.9 Hz, 1H), 3.50 (d, *J* = 3.9 Hz, 1H), 2.75 (ddd, *J* = 13.4, 10.8, 8.5 Hz, 2H), 2.64 (td, *J* = 13.1, 6.4 Hz, 2H), 1.86 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.9, 148.8, 147.4, 143.5, 135.3, 133.4, 133.2, 121.1, 112.2, 111.2, 108.3, 103.1, 101.3, 60.4, 60.3, 56.7, 56.0, 55.9, 44.1, 44.0, 36.4, 35.9; IR (KBr , neat) 3211, 2936, 2835, 1634, 1514, 1460, 1433, 1327, 1236, 1196, 1094, 1036, 966, 924, 854, 808 cm^{-1}; HRMS (APCI) calcd for $C_{22}H_{28}O_7$ $(M)^+$ 404.1830, found 404.1790.

(-)-niranthin 13g

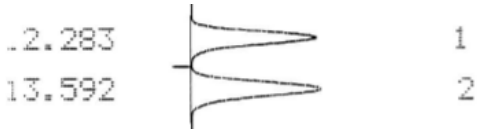


(-)-niranthin

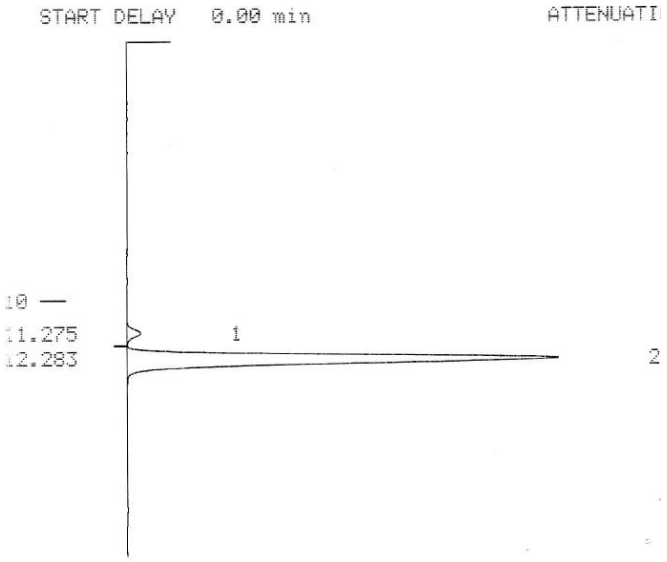
A THF (5.5 ml) solution of **8** (0.350 g, 0.87 mmol) was added to a suspension of sodium hydride (0.086 g, 2.2 mmol) in THF (3.3 ml) at 0°C under an Ar atmosphere, followed by being stirred at same temperature for 30min. Then, iodomethane (0.14 ml, 2.2 mmol) was added to the reaction mixture, followed by being stirred at room temperature for 24h. Subsequently, water was added to the reaction mixture and extracted with AcOEt. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 3/1) to give (-)-niranthin (0.333 g, 89%, 95% ee).

(-)-niranthin: colorless solid; mp 63-65°C; $[\alpha]^{27}_D$ = -9.8 (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (d, *J* = 8.1 Hz, 1H), 6.65 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.63 (d, *J* = 1.8 Hz, 1H), 6.30 (d, *J* = 1.2 Hz, 1H), 6.26 (d, *J* = 1.0 Hz, 1H), 5.93 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.35 – 3.30 (m, 2H), 3.30 (s, 6H), 3.29 – 3.25 (m, 2H), 2.70 – 2.56 (m, 4H), 2.08 – 1.97 (m, 2H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.8, 148.7, 147.2, 143.4, 135.8, 133.6, 133.3, 121.2, 112.2, 111.1, 108.2, 103.3, 101.3, 72.7, 72.6, 58.8, 56.5, 56.0, 55.8, 41.0, 40.8, 35.5, 35.0.;

HPLC analysis: 95% ee [Daicel CHIRALPAK IG (15 cm) at 25°C, flow rate 0.8 ml/min, solvent: hexane / 2-propanol = 9/1, t_R(racemic) = 12.28 min and 13.59 min, t_R((-)-niranthin) = 11.28 min for minor and 12.28 min for major].



Racemic-niranthin: HPLC analysis using chiral column.



Enantioenriched (-)-niranthin (95% ee) : HPLC analysis using chiral column.

-- % CALCULATION RESULT --

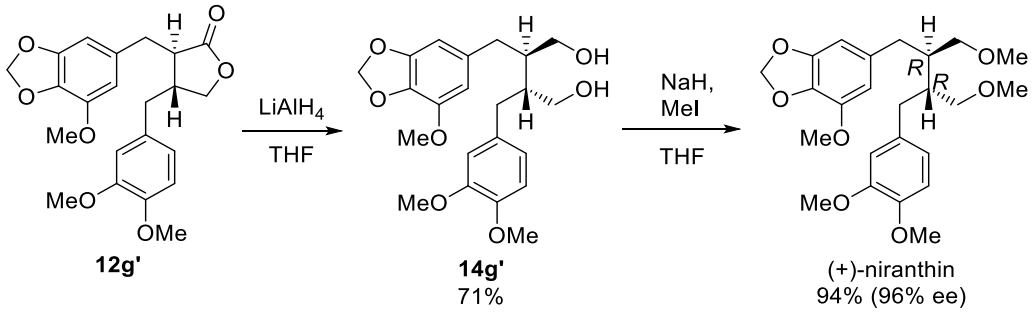
ACE R

WINDOW = 0 % SCALE FACTOR = 1.0000 PEAK AREA

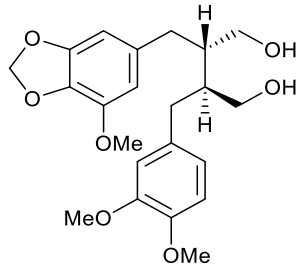
PEAK#	RT(min)	AREA	HEIGHT	MK	AREA%
1	11.275	39949	1970	V	2.6343
2	12.283	1476541	63349	V	97.3657
	TOTAL	1516490	65319		100.0000

Based on this enantiomeric ratio (97.37/2.63), the ee value was estimated as 95% ee.

Alternative synthesis of (+)-niranthin



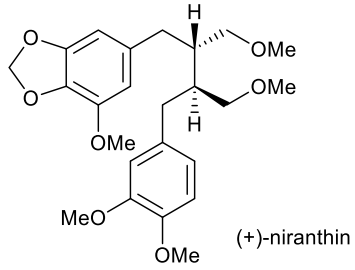
(2*R*,3*R*)-2-(5"-methoxy-3",4"-methylenedioxyphenyl)methyl-3-(3',4'-dimethoxyphenyl)methyl butane-1,4-diol (14g')



Following the procedure for the preparation of **14g**, the reaction using **12g'** instead of **12g** gave **14g'** (71% yield).

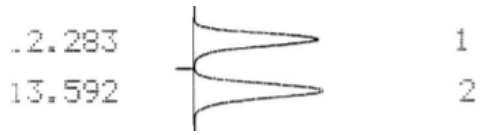
14g': colorless solid; mp 119-121°C; $[\alpha]^{27}_{D}$ = 30.2 (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (d, *J* = 8.1 Hz, 1H), 6.69 (dd, *J* = 8.1, 1.9 Hz, 1H), 6.66 (d, *J* = 1.8 Hz, 1H), 6.34 (d, *J* = 1.3 Hz, 1H), 6.30 (d, *J* = 1.2 Hz, 1H), 5.93 (s, 2H), 3.86 (s, 6H), 3.84 (s, 3H), 3.84 – 3.79 (m, 2H), 3.57 (d, *J* = 4.3 Hz, 1H), 3.54 (d, *J* = 4.4 Hz, 1H), 2.82 – 2.60 (m, 6H), 1.88 (s, 2H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.9, 148.8, 147.4, 143.5, 135.3, 133.4, 133.2, 121.1, 112.2, 111.2, 108.4, 103.1, 101.3, 60.5, 60.3, 56.7, 56.0, 55.9, 44.1, 44.0, 36.4, 35.9.

(+)-niranthine

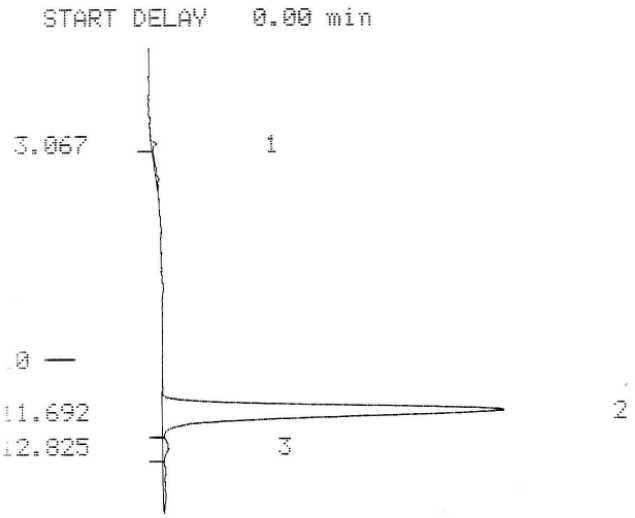


Following the procedure for the preparation of (-)-niranthin, the reaction using **14g'** instead of **14g** gave (+)-niranthin (0.286 g, 94%, 96% ee).

(+)-niranthin: colorless solid; mp 63-65°C; $[\alpha]^{27}_D$ = 10.5 (*c* 1.00, chloroform, λ = 589 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (d, *J* = 8.1 Hz, 1H), 6.68 – 6.60 (m, 2H), 6.30 (s, 1H), 6.26 (s, 1H), 5.93 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.35 – 3.30 (m, 2H), 3.30 (s, 6H), 3.28 – 3.25 (m, 2H), 2.70 – 2.56 (m, 4H), 2.07 – 1.97 (m, 2H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.8, 148.7, 147.2, 143.4, 135.8, 133.6, 133.3, 121.2, 112.2, 111.1, 108.2, 103.3, 101.2, 72.7, 72.6, 58.8, 58.8, 56.5, 56.0, 55.8, 41.0, 40.8, 35.5, 35.0; HPLC analysis: 92% ee [Daicel CHIRALPAK IG (15 cm) at 25°C, flow rate 0.8 ml/min, solvent: hexane / 2-propanol = 9/1, t_R(racemic) = 12.28 min and 13.59 min, t_R((+)-niranthin) = 11.69 min for major and 12.83 min for minor].



Racemic-niranthin: HPLC analysis using chiral column.



Enantioenriched (+)-niranthin (96% ee) : HPLC analysis using chiral column.

-- % CALCULATION RESULT --

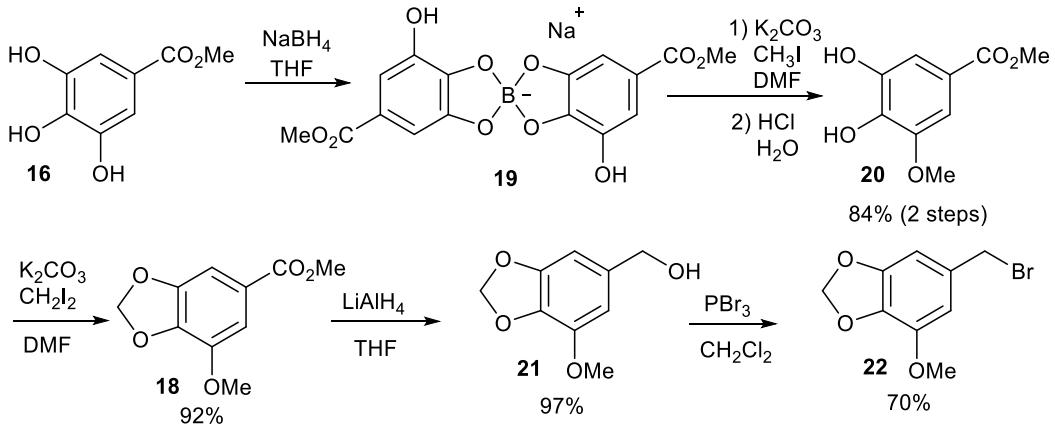
ACE R

WINDOW = 0 % SCALE FACTOR = 1.0000 PEAK AREA

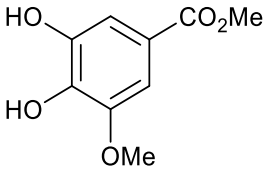
PEAK#	RT(min)	AREA	HEIGHT	MK	AREA%
1	3.067	1185	149	V	0.4482
2	11.692	258540	10389	V	97.7879
3	12.825	4663	177	V	1.7639
	TOTAL	264389	10715		100.0000

Based on this enantiomeric ratio (97.79/1.76), the ee value was estimated as 96% ee.

Preparation of 3,4-Methylenedioxy-5-methoxybenzylbromide.



Methyl 3-methoxy-4,5-dihydroxybenzoate (20)

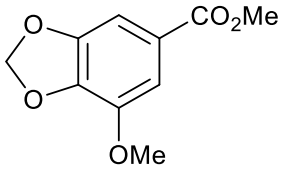


$NaBH_4$ (0.113 g, 2.99 mmol) was added to a THF (16.0 ml) solution of Methyl Gallate (1.000 g, 5.43 mmol) at room temperature under an Ar atmosphere, followed by being stirred at same temperature for 18h, and then the reaction mixture was concentrated.

The obtained crude oil was resolved in DMF (10.0 mL), then K_2CO_3 (1.504 g, 10.88 mmol) and iodomethane (0.68 ml, 10.88 mmol) was added to the solution at 0°C under an Ar atmosphere, followed by being stirred 70°C for 14h. 1M-HCl aqueous solution was added to the reaction mixture, which was extracted with Et_2O. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 2/1) to give the product **20** (0.909 g, 84%).

20; colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 1.8 Hz, 1H), 7.20 (d, *J* = 1.8 Hz, 1H), 6.07 (s, 1H), 5.83 (s, 1H), 3.90 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (101 MHz, CDCl3) δ 167.3, 146.7, 143.6, 137.2, 121.7, 111.2, 105.0, 56.5, 52.3.

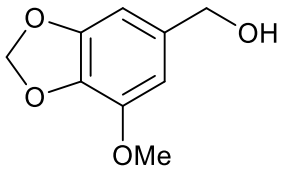
Methyl 5-methoxy-3,4-methylenedioxybenzoate (18)



A DMF solution (5.0 ml) of **20** (0.909 g, 4.57 mmol) was added to a suspension of K_2CO_3 (1.902 g, 13.76 mmol) in DMF (10.0 ml), followed by being stirred at 0°C. Then, diiodomethane (0.44 ml, 5.50 mmol) was added to the reaction mixture at 0°C under an Ar atmosphere, followed by being stirred at 70°C for 2h. Then, 1M-HCl aqueous solution was added to the reaction mixture and extracted with AcOEt. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 4/1) to give the product **18** (0.885 g, 92%).

18: colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 1.4 Hz, 1H), 7.21 (d, *J* = 1.4 Hz, 1H), 6.05 (s, 2H) ,3.94 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 148.8, 143.4, 139.6, 124.5, 110.1, 104.0, 102.4, 56.7, 52.3; IR (KBr,neat): 2960, 2837, 2799, 1707.

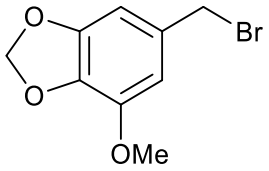
(5-Methoxy-3,4-methylenedioxyphenyl)methanol (21)



A THF solution (3.0 ml) of **18** (0.443 g, 2.11 mmol) was added to a suspension of $LiAlH_4$ (1.953 g, 14.13 mmol) in THF (20.0 ml) at 0°C under an Ar atmosphere, followed by being stirred at same temperature for 30min. Then, saturated Potassium tartrate aqueous solution and saturated NH_4Cl aqueous solution were added to the reaction mixture and extracted with AcOEt. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 4/1) to give the product **21** (0.343 g, 97%).

21: colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (s, 1H), 6.54 (s, 1H), 5.95 (s, 2H), 4.56 (d, *J* = 2.2 Hz, 2H), 3.89 (s, 3H), 1.96 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0, 143.8, 135.7, 134.7, 106.5, 101.6, 101.4, 65.4, 56.6; IR (KBr,neat): 3235, 2964, 2907, 2841.

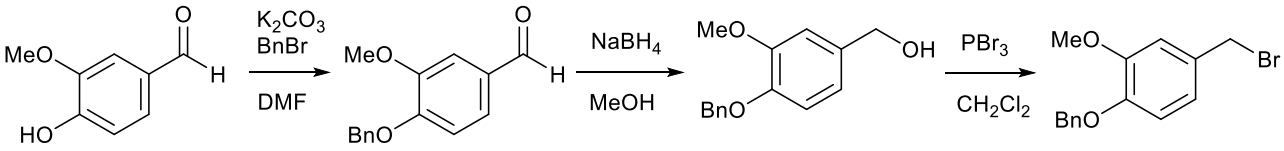
5-Methoxy-3,4-methylenedioxybenzylbromide (22)



PBr_3 (1.05 ml, 11.08 mmol) was added to a solution of **21** (1.553 g, 9.24 mmol) in CH_2Cl_2 (14.0 ml) at 0°C under an Ar atmosphere, followed by being stirred at same temperature for 1h. Then, saturated $NaHCO_3$ aqueous solution was added to the reaction mixture and extracted with AcOEt. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by recrystallization (hexane/AcOEt) to give the product **22** (1.602 g, 70%).

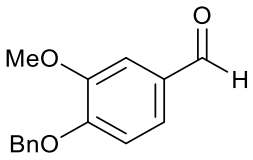
22: brown solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58 (d, J = 1.5 Hz, 1H), 6.57 (d, J = 1.5 Hz, 1H), 5.97 (s, 2H), 4.44 (s, 2H), 3.90 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.1, 143.6, 135.6, 132.1, 108.9, 103.5, 101.9, 56.7, 34.4.; IR (KBr,neat): 3078, 2970, 2843, 2792, 1707.

Preparation of 4-Benzyloxy-3-methoxybenzylbromide.



23 | **24** 95% | **25** 94% | **26** 47%

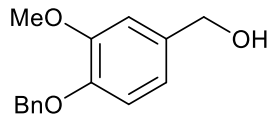
4-(Benzyloxy)-3-methoxybenzaldehyde (24)



K_2CO_3 (2.4 g, 17.4 mmol) was added to a solution of **23** (2.2 g, 14.5 mmol) in DMF (14 ml) at 0°C under an Ar atmosphere. Then, benzyl bromide (2.1ml, 17.4 mmol) was added to the reaction mixture at the same temperature, followed by being stirred at room temperature for 5h. Then, water was added to the reaction mixture and extracted with AcOEt. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 5/1) to give the product **24** (3.316 g, 95%).

24: white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (s, 1H), 7.44 (dd, J = 7.1, 1.6 Hz, 3H), 7.39 (ddd, J = 7.5, 3.8, 2.4 Hz, 3H), 7.35 – 7.30 (m, 1H), 6.99 (d, J = 8.2 Hz, 1H), 5.25 (s, 2H), 3.95 (s, 3H).

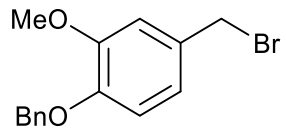
(4-Benzyloxy-3-methoxyphenyl)methanol (25)



$NaBH_4$ (0.185 g, 4.9 mmol) was added to a solution of **24** (3.316 g, 13.7 mmol) in MeOH (56 ml) at 0°C, followed by being stirred at same temperature for 30min. Then, 1M-HCl aqueous solution was added to the reaction mixture, which was extracted with Et_2O. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by column chromatography (SiO_2, hexane/AcOEt = 3/1) to give the product **25** (3.156 g, 94%).

25: white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.2 Hz, 2H), 7.37 (dd, *J* = 11.3, 4.2 Hz, 2H), 7.30 (d, *J* = 7.1 Hz, 1H), 6.96 (d, *J* = 1.5 Hz, 1H), 6.83 (dt, *J* = 8.2, 4.9 Hz, 2H), 5.16 (s, 2H), 4.62 (d, *J* = 5.0 Hz, 2H), 3.91 (s, 3H).

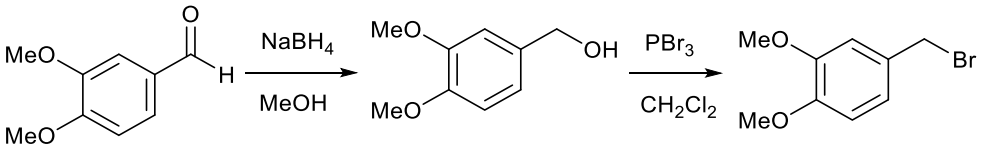
4-Benzyloxy-3-methoxybenzylbromide (26)



Following the procedure for the preparation of **22**, the reaction using **25** instead of **21** gave **26** (47% yield).

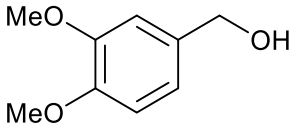
26: white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.40 (m, 2H), 7.39 – 7.33 (m, 2H), 7.33 – 7.27 (m, 1H), 6.93 (d, *J* = 2.0 Hz, 1H), 6.88 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 5.15 (s, 2H), 4.48 (s, 2H), 3.90 (s, 3H).

Preparation of 3,4-Dimethoxybenzylbromide.



27 **28** 75% **29** 99%

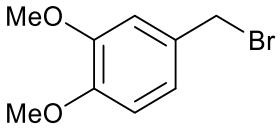
(3,4-Dimethoxyphenyl)methanol (28)



Following the procedure for the preparation of **25**, the reaction using **27** instead of **24** gave **28** (75% yield).

28: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 – 6.90 (m, 2H), 6.81 (d, J = 8.2 Hz, 1H), 4.51 (s, 2H), 3.90 (s, 3H), 3.88 (s, 3H).

3,4-Dimethoxybenzylbromide (29)



Following the procedure for the preparation of **22**, the reaction using **28** instead of **21** gave **29** (99% yield).

29: white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 – 6.89 (m, 2H), 6.81 (d, J = 8.2 Hz, 1H), 4.50 (s, 2H), 3.90 (s, 3H), 3.88 (s, 3H).

3 Bioassay

3.1. Bioassay of (-)-niranthin and (+)-niranthin against HBV

Cell culture

HepG2-hNTCP-C4, a highly HBV-susceptible cell line,[n] and Hep38.7-Tet cells, which replicate HBV upon depletion of tetracycline in the medium,[o] were cultured with DMEM/F12- plus GlutaMAX supplemented with 10% FBS, 10 mM HEPES, 100 unit/ml penicillin, 100 µg/ml streptomycin, 5 µg/ml insulin in the presence of G418 at 400 µg/ml (HepG2-hNTCP-C4 cells) or 500 µg/ml (Hep38.7-Tet cells).

[n] M. Iwamoto, K. Watashi, S. Tsukuda, H. H. Aly, M. Fukasawa, A. Fujimoto, R. Suzuki, H. Aizaki, T. Ito, O. Koiwai, H. Kusuhara, T. Wakita, *Biochem Biophys Res Commun.* **2014**, *443*, 808; [o] N. Ogura, K. Watashi, T. Noguchi, T. Wakita, *Biochem Biophys Res Commun.* **2014**, *452*, 315.

Reagents

The peptide consisting of aa 2-48 of the HBV preS1 region modified with myristoylation at the amino terminus, generally known as MyrcludexB, was synthesized by Scrum.

HBV preparation and infection

HBV genotype D was prepared from the culture supernatant of Hep38.7-Tet cells as previously described. In the infection assay, an HBV susceptible cell line, HepG2-hNTCP-C4 cells, was incubated with the above HBV at 12,000 GEq/cell in the presence of 4% PEG8000 for 16 h. After washing out of free virus, the cells were cultured for an additional 12 days to detect HBs antigen.[p]

[p] K. Watashi, A. Sluder, T. Daito, S. Matsunaga, A. Ryo, S. Nagamori, M. Iwamoto, S. Nakajima, S. Tsukuda, K. Borroto-Esoda, M. Sugiyama, Y. Tanaka, Y. Kanai, H. Kusuhara, M. Mizokami, T. Wakita, *Hepatology.* **2014**, *59*, 1726.

HBs production in an HBV-replicating cells

Hep38.7-Tet cells incubated in the absence of tetracycline to induce HBV replication were treated with compounds for 6 days and the supernatant were recovered to detect HBs antigen.[p]

HBs ELISA

HBs antigens were quantified by enzyme-linked immunosorbent assay (ELISA). ELISA plates were prepared by treating with anti -HBs antibody at dilution of 1:5000 overnight at 4°C and coating with 0.2% BSA and 0.02 % NaN_3. The culture supernatant of the HBV-infected HepG2-hNTCP-C4 or Hep38.7-Tet cells was incubated on the in-house ELISA plate that was subjected to the ELISA assay as described previously, using horseradish peroxidase-labeled goat anti-HBs antibody. The absorbance of the plates was measured for three wells on each concentration using microplate reader xMark^{TM} (Bio-RAD Laboratories.Inc.).[q]

[q] K. Watashi, G. Liang, M. Iwamoto, H. Marusawa, N. Uchida, T. Daito, K. Kitamura, M. Muramatsu, H. Ohashi, T. Kiyohara, *Journal of Biological Chemistry.* **2013**, *288*, 31715.

MTT assay

Cell viability was detected by 3-(4,5-dimethylethimal-2yl)-2, 5-diphenyltetrazolium bromide (MTT) assay as described previously.[r]

[r] T. Passioura, K. Watashi, K. Fukano, S. Shimura, W. Saso, R. Morishita, Y. Ogasawara, Y. Tanaka, M. Mizokami, C. Sureau, H. Suga, T. Wakita, *Cell Chem Biol.* **2018**, *25*, 906.

Statistical analysis

The HBs antigens and the cell viability were analyzed statistically for significant differences between the control and each concentration of (-)-niranthin or (+)-nirantin.

Results

Table 1. HBV infection assay

		Cell viability (fold)	HBs (fold)	error range Cell viability	raw data HBs
Control		1 ± 0.128	1 ± 0.058	0.128014322	0.057741802
MyrcludexB (positive control)		1.289 ± 0.077	0.102 ± 0.027	0.077103826	0.026507319
(−)-niranthin	12.5 μM	1.290 ± 0.106	0.556 ± 0.014	0.106058160	0.013882803
	25 μM	1.031 ± 0.132	0.275 ± 0.005	0.132328820	0.005369726
	50 μM	0.056 ± 0.013	0.050 ± 0.017	0.013149778	0.016573514
	100 μM	0.025 ± 0.013	0.014 ± 0.012	0.013225606	0.012132804
(+)-niranthin	12.5 μM	1.497 ± 0.134	0.421 ± 0.023	0.133708638	0.022815099
	25 μM	1.258 ± 0.053	0.200 ± 0.007	0.053316664	0.007493353
	50 μM	1.243 ± 0.091	0.119 ± 0.001	0.090638476	0.001231900
	100 μM	0.028 ± 0.004	0.001 ± 0.001	0.003559026	0.001231900

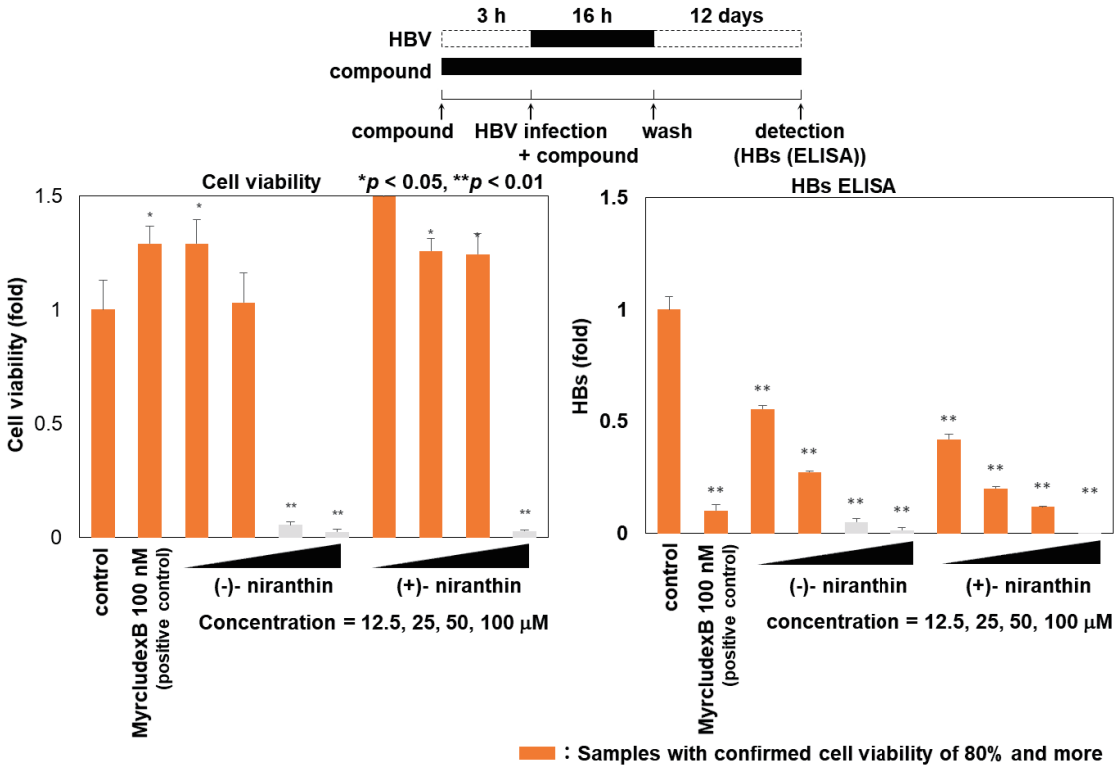
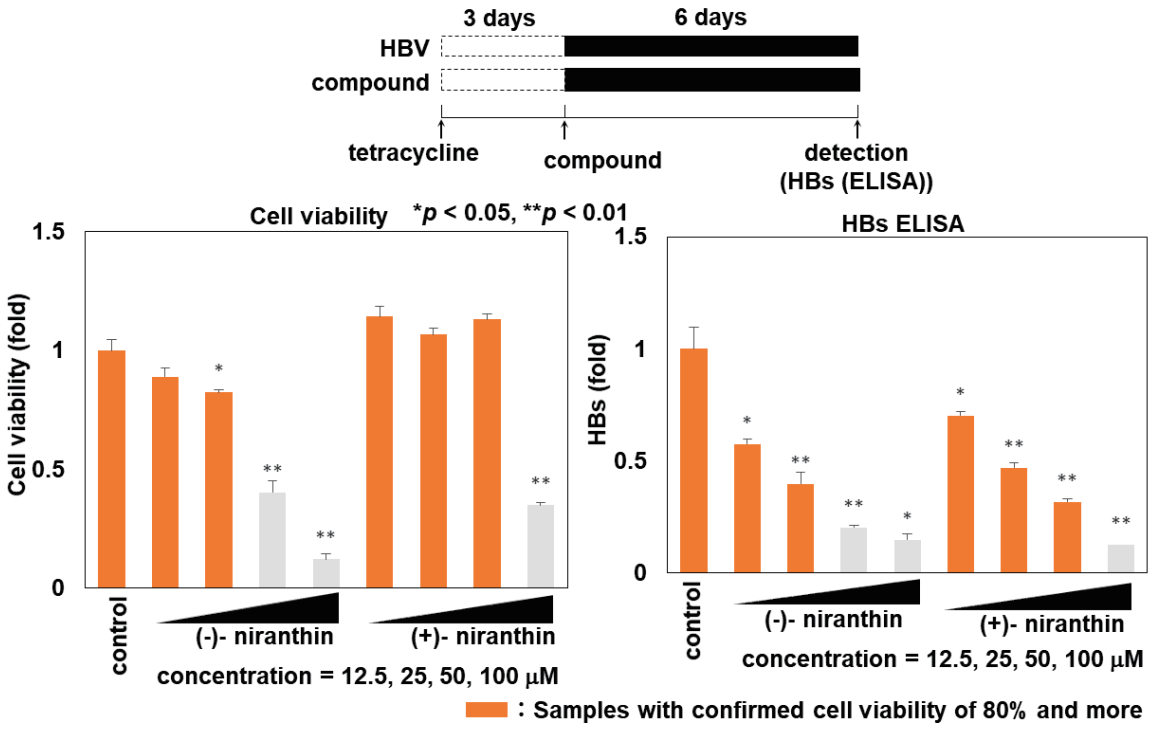


Table 2. HBV replication assay

		Cell viability (fold)	HBs (fold)
Control		1 ± 0.046	1 ± 0.094
(−)−niranthin	12.5 μM	0.889 ± 0.038	0.575 ± 0.021
	25 μM	0.824 ± 0.009	0.396 ± 0.053
	50 μM	0.402 ± 0.049	0.201 ± 0.010
	100 μM	0.120 ± 0.024	0.147 ± 0.027
(+)−niranthin	12.5 μM	1.142 ± 0.044	0.700 ± 0.018
	25 μM	1.066 ± 0.029	0.469 ± 0.020
	50 μM	1.132 ± 0.022	0.317 ± 0.014
	100 μM	0.349 ± 0.011	0.126 ± 0.092

error range raw data

Cell viability	HBs
0.045559485	0.094111131
0.037897889	0.020683882
0.009486833	0.053158696
0.049118903	0.009631418
0.024308778	0.027368529
0.044184273	0.018492741
0.029263174	0.020414374
0.022181073	0.013872675
0.010996211	0.009190047



3.2. Bioassay of (-)-niranthin and (+)-niranthin against IFV

Growth Inhibition assay

Inhibition of IFV growth was assayed as described in a previous study[s] with modification. Briefly, Madin–Darby canine kidney (MDCK) cells were cultured in Minimum Essential Medium (MEM) supplemented with 10% fetal bovine serum in 5% CO_2 incubator at 37°C. A confluent monolayer of MDCK cells was prepared in each well of a 96-well plate. Various concentrations (25–1600 μM) of (-)-niranthin or (+)-niranthin were mixed with 100 tissue culture infectious dose 50% ($TCID_{50}$) of H1N1 influenza A virus (A/Puerto Rico/8/34 (PR8)) in the presence of trypsin or without in MEM supplemented with 0.2% bovine serum albumin and incubated at for 30 min. MDCK cells were washed with PBS(-) and the viral mixture was added to the cells. Treated cells were then incubated for four days at 34°C under 5% CO_2. After incubation, the medium was removed and cells were fixed with a 10% formaldehyde solution.

Viable cells were stained with 0.1% crystal violet in isopropyl alcohol and the OD_{585} was measured. Cell viability was calculated based on a calibration of the OD_{585} values observed in mock-infected and virus only wells as 100% and 0%, respectively. The tests were repeated five times independently.

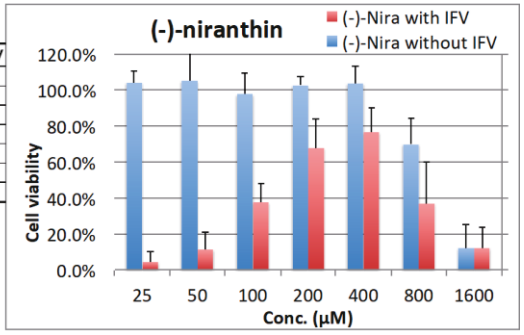
[s] Y. Iwai, H. Takahashi, D. Hatakeyama, K. Motoshima, M. Ishikawa, K. Sugita, Y Hashimoto, Y.

Harada, S. Itamura, T. Odagiri, M. Tashiro, Y. Sei, K. Yamaguchi, T. Kuzuhara, *Bioorg Med Chem.* **2010**, *18*, 5379.

Results

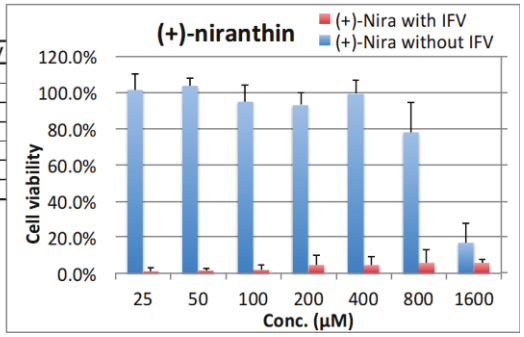
◎(−)-niranthin

	Average (n=5)	S.D.	Average (n=5)	S.D.
final Conc.(μM)	(−)-Nira with IFV	(−)-Nira with IFV	(−)-Nira without IFV	(−)-Nira without IFV
1600	12.0%	0.112	12.2%	0.133
800	36.7%	0.233	69.7%	0.145
400	76.4%	0.138	103.5%	0.093
200	67.7%	0.160	102.6%	0.052
100	37.5%	0.103	97.6%	0.120
50	11.3%	0.096	105.1%	0.159
25	4.3%	0.061	104.1%	0.066
12.5	6.8%	0.098		



◎(+)-niranthin

	Average (n=5)	S.D.	Average (n=5)	S.D.
final Conc.(μM)	(+)-Nira with IFV	(+)-Nira with IFV	(+)-Nira without IFV	(+)-Nira without IFV
1600	5.8%	0.018	16.8%	0.110
800	5.8%	0.069	77.8%	0.163
400	4.8%	0.046	99.1%	0.073
200	4.8%	0.050	92.9%	0.070
100	2.0%	0.024	94.6%	0.094
50	1.6%	0.013	103.7%	0.038
25	1.0%	0.024	101.2%	0.091
12.5	3.2%	0.009		



Reference

1) Maitland Jones. Jr, Steven A. Fleming, ジョーンズ有機化学 (上), 第 5 版, 2000 年, 東京化学同人.

2) (a) C.A. Coulson, W.E. Moffitt, *J. Chem. Phys.,* **1947**, *15*, 151.; (b) C.A. Coulson, W.E. Moffitt, *Phil. Mag*, **1949**, *40*, 1.

3) (a) A.D. Walsh, *Nature,* **1947**, *165*, 712.; (b) A.D. Walsh, *Trans. Faraday Soc*., **1949**, *45* 179.

4) O. G. Kulinkovich, Cyclopropanes in Organic Synthesis, Wiley, **2015**.

5) a) A. Brandi, S. Cicchi, F. M. Cordero, A. Goti, *Chem. Rev*. **2003**, *103*, 1213; b) M. Rubin, M. Rubina, V. Gevorgyan, *Chem. Rev*. **2007**, *107,* 3117; c) C. A. Carson, M. A. Kerr, *Chem. Soc. Rev*. **2009**, *38*, 3051; d) S. J. Gharpire, L. N. Nanda, *Tetrahedron Lett*. **2017**, *58*, 711. i) W. A. Donaldson, *Tetrahedron,* **2001**, *57,* 8589; e) D. Y.-K. Chen, R. H. Pouwer, J.-A. Richard, *Chem. Soc. Rev*. **2012**, *41*, 4631.

6) Kang, Q.-K.; Wang, L.; Liu, Q.-J.; Tang, Y. *J. Am. Chem. Soc.* **2015***, 46*, 14594.

7) a) J. Zhang, S. Xing, J. Ren, S. Jiang, Z. Wang, *Org. Lett*. **2015**, *17*, 218; b) Y. Xia, X. Liu, H. Zheng, L. Lin, X. Fen, *Angew. Chem. Int. Ed*. **2015**, *54*, 227; *Angew. Chem*. **2015**, *127*, 229; c) K. S. Halskov, F. Kniep, V. H. Lauridsen, E. H. Iversen, B. S. Donslund, K. A. Jørgensen*, J. Am. Chem. Soc.* **2015**, *137,* 1685; d) Q.-Q. Cheng, Y. Qian, P. Y. Zavalij, M. P. Doyle, *Org. Lett*. **2015**, *17*, 3568; e) K. L. Ivanov, E. V. Villemson, E. M. Budynina, O. A. Ivanova, I. V. Trushkov, M. Y. Melnikov, *Chem. Eur. J*. **2015**, *21*, 4975; f) A. Ghosh, A. K. Pandey, P. Barjee, *J. Org. Chem.* **2015**, *80*, 7235; g) R. A. Novikov, A. V. Tarasova, V. A. Korolev, E. V. Shulishov, V. P. Timifeev, Y. V. Tomilov, *J. Org. Chem*. **2015,** *80*, 8225; h) Y. ivano, L. Lin, F. Chang, X. Fu, X. Liu, X. Feng, *Angew. Chem. Int. Ed*. **2015**, *54*, 13748; *Angew. Chem*. **2015**, *127*, 13952; i) L. K. B. Garve, M. Pawliczek, P. G. Jones, D. B. Werz, *Chem. Eur. J.* **2016**, *22*, 521; j) L. K. B. Garve, M. Petzold, P. G. Jones, D. B. Werz, *Org. Lett.* **2016**, *18*, 564; k) E. Sanchez-Diez, D. L. Vesga, E. Reyes, U. Uria, L. Carrillo, J. L. Vicario, *Org. Lett*. **2016**, *18*, 1270; l) J. E. C. Tejeda, B. K. Landschoot, xiaM. A. Kerr, *Org. Lett*. **2016**, *18*, 2142; m) E. M. zhangnina, K. L. Ivanov, A. O. Chagarovskiy V. B. Rybakov, I. V. Trushkov, M. Y. Melnikov, *Chem. Eur. J*. **2016**, *22*, 3692; n) V. Ortega, A. G. Csákÿ, *J. Org. Chem*. **2016**, *81*, 3917; o) R. K. Varshnaya, P. Banerjee, *Eur. J. Org. Chem*. **2016**, 4059; p) A. Ghosh, S. Mandal, P. K. Chattaraj, P. Banerjee, *Org. Lett*. **2016**, *18*, 4940; q) J.-Q. Han, H.-H. Zhang, P.-F. Xu, Y.-C. Luo, *Org. Lett.* **2016**, *18*, 5212; r) S. Das, C. G. Daniliuc, A. Studer, *Org. Lett*. **2016**, *18*, 5576; s) J. Sabbatani, N. Maulide, *Angew. Chem. Int. Ed*. **2016**, *55*, 6780; *Angew. Chem*. **2016**, *128*, 6892; t) T. Kaicharla, T. Roy, M. Thangaraj, R. G. Gonnade, A. T. Biju, *Angew. Chem. Int. Ed*. **2016**, *55*, 10061; *Angew. Chem*. **2016**, *128*, 10215; u) J.-A. Xiao, J. Li, P.-J. Xia, Z.-F. Zhou, Z.-X. Deng, H.-Y. Xiang, X.-Q. Chen, H. Yang, *J. Org. Chem.* **2016**, *81*, 11185; v) R. A. Novikov, A. V. Tarasova, D. A. Denisov, D. D. Borisov, V. A. Korolev, V. P.

Timofeev, Y. V. Tomilov*, J. Org. Chem*. **2017**, *82*, 2724; w) K. Mondal, S. C. Pan*, Eur. J. Org. Chem.* **2017**, 537.

8) (a) 西井良典(**1998**). Synthetic Study on *gem*-Dihalo- and Halocyclopropanes: Its Cationic, Radical, Anionic Approaches, 関西学院大学院理学部博士論文; (b) 西井良典, *有機合成化学協会誌*, **2015**, *73*, 701.;(c) 西井良典, *有機合成化学協会誌*, **2018**, *76*, 992.

9) (a) E. Yoshida, K. Nishida, K. Toriyabe, R. Taguchi, J. Motoyoshiya, Y. Nishii, *Chem. Lett*., **2010**, *39*, 194; (b) D. Sakuma, J. Ito, R. Sakai, R. Taguchi, Y. Nishii, *Chem. Lett*., **2014**, *43*, 610; (c) J. Ito, D. Sakuma, Y. Nishii, *Chem. Lett.*, **2015**, *44*, 297; (d) D. Sakuma, Y. Yamada, K. Sasazawa, Y. Nishii, *Chem. Lett*., **2015**, *44*, 818; (e) S. Takada, K. Iwata, T. Yubune, Y. Nishii, *Tetrahedron Lett*., **2016**, *57*, 2422; (f) S. Takada, T. Saito, K. Iwata, Y. Nishii, *Asian J. Org. Chem*., **2016**, *5,* 1225; (g) K. Sasazawa, S. Takada, T. Yubune, N. Takaki, R. Ota, Y. Nishii, *Chem. Lett.*, **2017**, *46*, 524; (h) S. Takada, N. Takaki, K. Yamada, Y. Nishii, *Org. Biomol. Chem*., **2017**, *15*, 2443; (i) Y. Kimura, Y. Sone, T. Saito, T. Mochizuki, Y. Nishii, *Asian J. Org. Chem.*, **2017**, *6*, 977.

10) H. Xie, L. Zu, and W. Wang, *J. Am. Chem. Soc*., **2007**, *129*, 10886.

11) (a) M. Marigo, T. C. Wabnitz, D. Fielenbach and K. A. Jørgensen, *Angew. Chem., Int. Ed*., **2005**, *44,* 794; (b) Y. Hayashi, H. Gotoh, T. Hayashi and M. Shoji, *Angew. Chem., Int. Ed*., **2005**, *44*, 4212; (c) J. Franz´en, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard and K. A. Jørgensen, *J. Am. Chem. Soc*., **2005**, *127*, 18296; (d) G. J. Reyes-Rodriguez, N. M. Rezayee, A. Vidal-Albalat and K. A. Jørgensen, *Chem. Rev*., **2019**, *119,* 4221.

12) a) F. López, A. J. Minnaard, B. L. Feringa, *Acc. Chem. Res*. **2007**, *40*, 179; b) A. Alexakis, J. E. Bäckvall, N. Krause, O. Pámies, M. Diéguez, *Chem. Rev*. **2008**, *108*, 2796; c) S. R. Harutyuyan, T. den Hartog, K. Geurts, A. J. Minnaard, B. L. Feringa, *Chem. Rev*. **2008**, *108*, 2796; d) T. E. Schmid, S. Drissi-Amraoui, C. Crévisy, O. Baslé, M. Mauduit, Beilstein *J. Org. Chem.* **2015**, *11*, 2418.

13) a) C. Mioskowski, S. Manna, J. R. Falck, *Tetrahedron Lett*. **1983,** *24*, 5521; b) E. W. Thomas, J. R. Szmuszkovicz, *J. Org. Chem*. **1990**, *55*, 6054; c) J. W. Herndon, M. D. Reid, *J. Am. Chem. Soc*. **1994**, *116*, 383.

14) T. Ok, A. Jeon, J. Lee, J. H. Lim, C. S. Hong, H.-S. Lee, *J. Org. Chem*. **2007,** *72*, 7390.

15) a) Lifchits, O.; Alberico, D.; Zakharian, J.; Charette, A. B. *J. Org. Chem*. **2008**, *73*, 6838; b) Leduc, A. B.; Lebold, T. P.; Kerr, M. A. *J. Org. Chem*. **2009**, *74*, 8414; c) Lebold, T. P.; Leduc, A. B.; Kerr, M. A. *Org. Lett*. **2009**, *11*, 3770.

16) Newhouse, T. R.; Kaib, P. S. J.; Gross, A. W.; Corey, E. *J. Org. Lett.* **2013**, *15*, 1591.

17) Yankee, E. W.; Cram, D. J. *J. Am. Chem. Soc*. **1970**, *92*, 6331.

18) a) Pohlhus, P. D.; Johnson, J. S. *J. Am. Chem. Soc*. **2005**, *127*, 16014; b) Sapeta, K.; Kerr, M. A. *J. Org. Chem*. **2007**, *72*, 8597; c) Karadeolian, A.; Kerr, M. A. *J. Org. Chem*. **2007**, *72*, 10251; d) Pohlhus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc*. **2008**, *130*,

8642; e) Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc*. **2009**, *131*, 3122; f) Campbell, M. J.; Johnson, J. S.; Parsons, A. T.; Pohlhus, P. D.; Sanders, S. D. *J. Org. Chem*. **2010**, *75*, 6317; g) Benfatti, F.; de Nantenul, F.; Waser, *J. Chem. Eur. J*. **2012**, *18,* 4844.

19) a) Lifchits, O.; Charette, A. B. *Org. Lett*. **2008**, *10*, 2809; b) Parsons, A. T.; Smith, A. G.; Neel, A. J.; Johnson, J. S. *J. Am. Chem. Soc*. **2010**, *132,* 9688; c) Emmett, M. R.; Kerr, M. A. *Org. Lett*. **2011**, *13*, 4180; d) Zhou, Y.-Y.; Wang, L.-J.; Li, J.; Sun, X.-L.; Tang, Y. *J. Am. Chem. Soc*. **2012**, *134*, 9066; e) Wales, S. M.; Walker, M. M.; Johnson, J. S. *Org. Lett*. **2013**, *15,* 2558.

20) a) H.-U. Reissig, R. Zimmer, *Chem. Rev*. **2003**, *103*, 1151; b) C. A. Carson, M. A. Kerr, *Chem. Soc. Rev*. **2009**, *38*, 3051.

21) a) M. A. Cavitt, L. H. Phun, S. France, *Chem. Soc. Rev*. **2014**, *43*, 804; b) T. F. Schneider, J. Kaschel, D. B. Werz, *Angew. Chem., Int. Ed.* **2014**, *53*, 5504; c) M. C. Martin, R. Shenje, S. France, *Isr. J. Chem*. **2016**, *56*, 499.

22) a) R. S. Ward, *Nat. Prod. Rep.*, **1999**, *16*, 75; b) M. Saleem, H. J. Kim, M. S. Ali and Y. S. Lee, *Nat. Prod. Rep.*, **2005**, *22*, 696; c) J.-Y. Pan, S.-L. Chen, M.-H. Yang, J. Wu, J. Shinkkonen and K. Zou, *Nat. Prod. Rep*., **2009**, *26*, 1251; d) R. G. Reynolds, H. Q. A. Nguyen, J. C. T. Reddel and R. J. Thomson, *Nat. Prod. Rep*., **2022**, DOI: 10.1039/ D1NP00057H.

23) a) A. Brandi, S. Cicchi, F. M. Cordero, A. Goti, *Chem. Rev.* **2003**, *103*, 1213; b) M. Rubin, M. Rubina, V. Gevorgyan, *Chem. Rev.* **2007**, *107*, 3117; c) C. A. Carson, M. A. Kerr, *Chem. Soc. Rev*. **2009**, *38*, 3051; d) S. J. Gharpire, L. N. Nanda, *Tetrahedron Lett*. **2017**, *58*, 711. i) W. A. Donaldson, *Tetrahedron* **2001**, *57*, 8589; e) D. Y.-K. Chen, R. H. Pouwer, J.-A. Richard, *Chem. Soc. Rev*. **2012**, *41*, 4631.

24) a) R. S. Ward, *Nat. Prod. Rep*. **1999**, *16*, 75; b) M. Saleem, H. J. Kim, M. S. Ali, Y. S. Lee, *Nat. Prod. Rep*. **2005**, *22*, 696; c) J-Y.Pan, S-L. Chen, M-H. Yang, J. Wu, J. Shinkkonen, K. Zou, *Nat. Prod. Rep*. **2009**, *26*, 1251; d) R. G. Reynolds, H. Q. A. Nguyen, J. C. T. Reddel, R. J. Thomson, *Nat. Prod. Rep*. **2022**, DOI: 10.1039/D1NP00057H and other recent references cited therein.

25) a) T. H. Esterfield, J. Bee, *J. Chem. Soc., Trans.* **1910**, *97,* 1028; b) T. Hirano, M. Gotoh, K. Oka, *Life Sci*. **1994**, *55,* 1061; c) Y. Kumarasamy, L. Nahar, P. J. Cox, L. N. Dinan, C. A. Ferguson, D. A. Finnie, M. Jaspars.,S. D. Sarker, *Pharm Biol.* **2003**, *41*, 203; d) S. Su, X. Cheng, M. Wink, *J. Pharm. Pharmacol.* **2015**, *67*, 1316; for a reference of synthesis of matairesinol, see: e) P. C. Eklund, F. J. Sundell, A. I. Smeds, R. E. Sjöholm, *Org. Biomol. Chem*. **2004**, *2*, 2229.

26) a) D. Takaoka, N. Takamatsu, Y. Saheki, K. Kono, C. Nakaoka, M. Hiroi, *Nippon Kagaku Kaishi* **1975**, *12*, 2192; b) S.-T. Chang, D. S.-Y. Wang, C.-L. Wu, S.-G. Shiah, Y.-H. Kuo, C.-J. Chang, *Phytochemistry* **2000**, *55*, 227; c) H. Tanabe, R. Fukutomi, K. Yasui, A. Kaneko, S. Imai, T. Nakayama, M. Isemura, *J. Health Sci.* **2011**, *57*, 184; for a recent reference of synthesis of dimatairesinol, see: d) S. Yamauchi, A. Nishimoto, H. Nishiwaki, K. Nishi, T. Sugahara, *Bioorg. Med. Chem. Lett*. **2020**, *30*, 127191.

27) a) P. B. McDoniel, J. R. Cole, *J. Pharm. Sci*. **1972**, *61*, 1992; b) M. Novelo, J. G. Cruz, L. Hernández, R. Pereda-Miranda, H. Chai, W. Mar, J. M. Pezzuto, *J. Nat. Prod*. **1993**, *56*, 1728. c) J. Harmatha, J. Nawrot, *Entomologia Experimentalis et Applicata*. **2002**, *104*, 51; d) Y.-C. Kuo, Y.-H. Kuo, Y.-L. Lin, W.-J. Tsai. *Antivir. Res.* **2006**, *70*, 112.

28) For the reference regarding the isolation of natural (-)-niranthin, see: a) A. S. R. Anjaneyulu, K. J. Rao, L. R. Row, C. Subrahmanyam, *Tetrahedron* **1973**, *29*, 1291; for references regarding bioassays using isolated natural (-)-niranthin, see: b) R.-L. Huang, Y.-L. Huang, J.-C. Ou, C.-C. Chen, F.-L. Hsu, C. Chang, *Phytother. Res*. **2003**, *17,* 449; c) C. A. L. Kassuya, A. Silvestre, O. Menezes-de-Lima, D. M. Marotta, V. L. G. Rehder, J. B. Calixto, *Eur. J. Pharmacol*. **2006**, *546*, 182 (anti-inflammatory); d) S. Chowdhury, T. Mukherjee, R. Mukhopadhyay, B. Mukherjee, S. Sengupta, S. Chattopadhyay, P. Jaisankar, S. Roy, H. K. Majumder, *EMBO Mol Med*. **2012**, *4*, 1126; e) S. Liu, W. Wei, K. Shi, X. Cao, M. Zhou, Z. Liu, *J. Ethnopharmacol*. **2014**, *155*, 1061; for a reference regarding the total synthesis of (±)-niranthin, see: G. E. Schneiders, R. Stevenson, *Org. Prep. Proced. Int*. **1982**, *14* ,1.

29) Examples for hydrogenolysis of cyclopropanes using H_2 gas with Pd or Ni catalyst, see: a) Gröger, C.; Musso, H.; Roßnagel, I. *Chem. Ber*. **1980**, *113*, 3621. b) Danishevsky, S.; Singh, R. K. J. Am. Chem. Soc. **1975**, *97*, 3239. c) Careira, E. M.; Ledford, B. E. *J. Braz. Chem. Soc*. **1998**, *9*. 405. d) Royer, F.; Felpin, F-X.; Doris, E. *J. Org. Chem*. **2001**, *66*, 6487. e) Mohapatra, D. K.; Chaudhuri, S. R.; Schoo, G.; Gurjar, K. *Tetrahedron, Asymmetry*, **2006**, *17*, 2609. f) González-Juárez, D. E.; García-Vázquez, J. B.; Zúñga-García, V.; Trujillo-Serrato, J. J.; Suárez-Casttillo, O. R.; Joseph-Nathan, P.; Morales-Ríos, M. S. *Tetrahedron*, **2012**, *68*, 7187.

30) F. G-Bobes, M. D. B. Fenster, S. Kiau, L. Kolla, S. Kolotuchin, M. Soumeillanta, *Adv. Synth. Catal.* **2008**, *350*, 813.

31) M. Itagaki, Y. Yamamoto, *Tetrahedron Letters,* **2006,** *47*, 523.

32) a) K. Yamada, T. Konishi, M. Nakano, S. Fujii, R. Cadou, Y. Yamamoto, K. Tomioka *J. Org. Chem.*, **2012**, *77*, 5775; b) L. Ferrie, D. Bouyssi, G. Balme, *Org. Lett.*, **2005**, *7*, 3143.

33) a) C. Song, P. Zhao, Z. Hu, S. Shi, Y. Cui, J. Chang, *Bioorg. Med. Chem. Lett*., **2010**, *20*, 2297; b) S. Takaoka, N. Takaoka, Y. Minoshima, J.-M. Huang, M. Kubo, K. Harada, H. Hioki, Y. Fukuyama, *Tetrahedron*, **2009***, 65*, 8354.

34) a) K. Cormier, R. D. Curry, M. P. Betsch, J. A. Goguen, C. M. Vogels, A. Decken, S. Turcotte, S. A. Westcott, *J. Heterocycl. Chem*., **2016**, *53*, 1807; (b) G. R. Pettit, S. B. Singh, *Can. J. Chem*., **1987**, *65*, 2390.

Acknowledgement

本研究を進めるにあたり、御指導・御鞭撻を賜りました西井良典教授、藤本哲也准教授、本吉谷教授に厚く御礼申し上げます。NMR 測定を含む様々な面で本研究を御支援して下さいました吉岡佐知子技官、MS 測定の依頼を快くお受けいただいた木村睦教授、共同研究だけでなく短期留学時にもご助力いただいた森正悟教授、実験に必要な環境を整えて下さった佐々木弘子事務員、本間みね子事務員、論文の執筆やデータを測定し提供してくださった国立感染症研究所 嶋崎典子博士、渡士幸一博士、大嶋美月博士、リーディングプログラムを履修してから多大なサポートをしてくださった三浦幹彦先生、池田朋子さん、に深く御礼申し上げます。

研究内容は異なるものの 9 年間勉強･研究を共にしてくれた齊藤泰千さんをはじめとし、研究の流れや考え方を教えていただきました笹澤和也さん、曽根祥智さん、高田誠二郎さん、木村友海さん、土谷晃弘さん、望月武人さん、湯舟俊英さん、また共に学び共に苦労した高木直也さん、菅原拓人さん、原田卓哉さん、山田慧さん、柄澤大地さん、小髙いずみさん、佐藤あかりさん、柴田和輝さん、清水祐花さん、髙木諒平さん、荒木優介さん、庄田愛子さん、その他お世話になった先輩・後輩に心より感謝申し上げます。

また、9 年間の大学生活において御指導を賜りました諸先生方、共に大学生活を送った友人を始めとするお世話になった方々へ感謝申し上げます。

最後に、学士・修士・博士課程の 9 年もの長きにわたる学生生活を見守り、最大級の支援をして頂いた家族に心より感謝申し上げます。

令和 4 年度