（様式５）(Style5)

学位論文全文に代わる要約
Extended Summary in Lieu of Dissertation

氏名：　Hazna Sartiva
Name

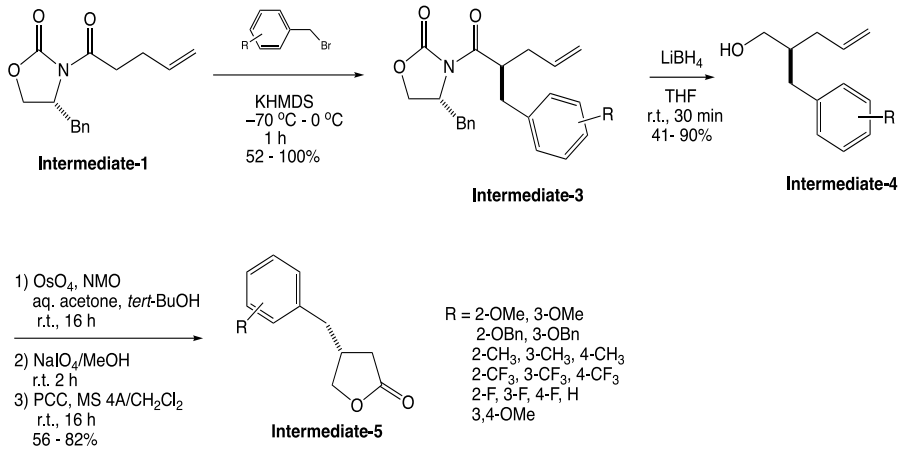
学位論文題目：
Title of Dissertation

Biological activities of benzylidene-γ-butyrolactone lignan and 3-(1-arylprop-2-yl)coumarin lignan
(ベンジリデン-γ-ブチロラクトン型リグナンと3-(1-アリールプロピ-2-イル)クマリン型リグナンの生物活性)

学位論文要約：
Dissertation Summary

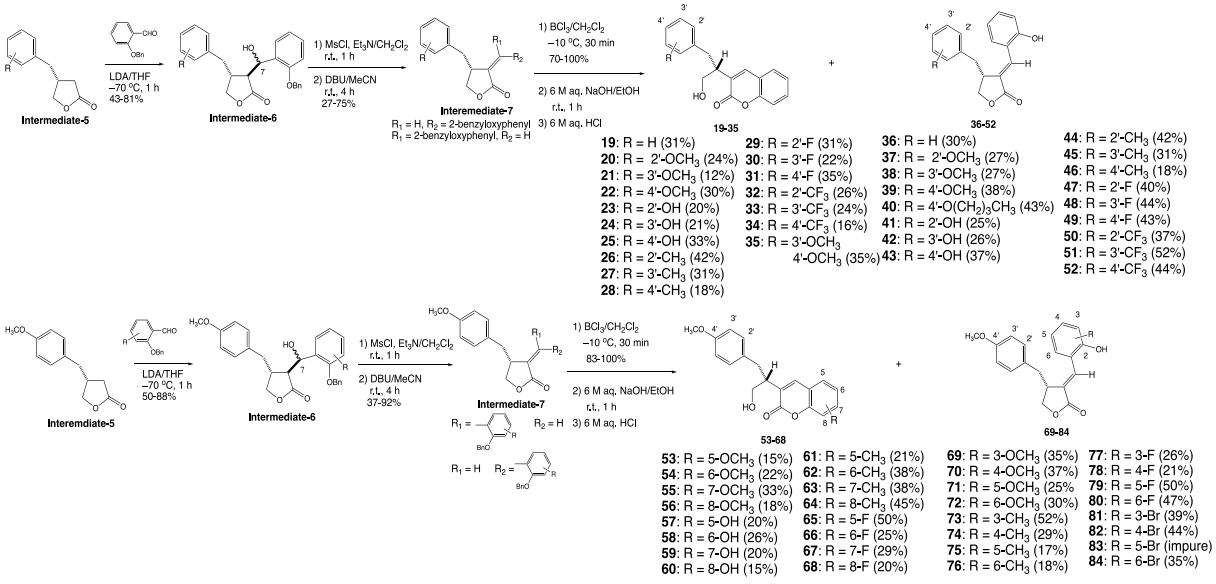
Lignan is a large group of natural products biosynthesized or isolated from many plants,[1–4] some of them are lariciresinol,[5,6] verrucosin,[7,8] butyrolactone,[9,10] sesamin,[11,12] phenprocoumon,[13] dihidroguaiaretic acid,[14,15] savinin,[16–18] phellinsin[19]. The isolation, pharmaceutical, synthetic, and chemical research of coumarino-lignans [20–30]and phenylalkylcoumarin-lignan related compounds[31–44] have been reported. However, its function in agrochemicals has not been known. This research should consider the further metabolism or isomerization of usual lignans and clarify the plant growth regulatory activity of coumarin bearing a lignan structure, which is an isomer of usual butyrolactone lignan, and anti-phytotoxic fungal *β*-benzyl-*α*-benzylidene-*γ*-butyrolactone with the 9,9′-lactone lignan structure. This research focuses on synthesizing *γ*-butyrolactone and coumarin lignan and its biological activities on plant and fungal strains. The *E*-form of *β*-benzyl-*α*-2-hydroxybenzylidene-*γ*-butyrolactone could be produced by radical isomerization from *Z*-*β*-benzyl-*α*-2-hydroxybenzylidene-*γ*-butyrolactone[45] even by metabolism in life body. *Z*-Benzylidene could be converted from 3-(7'-aryl-9'-hydroxyprop-8'-yl)coumarin through the *trans*-lactonization. Therefore, this research was conducted with the following three main objectives: (1) to synthesize the derivatives of coumarin and benzylidene type lignan; (2) to determine the effect of each subtituent in the coumarin ring on the plant growth inhibitory activity; and (3) to identify the effects of substituents on the anti-phytotoxic fungal *β*-benzyl-*α*-2-hydroxybenzylidene-*γ*-butyrolactone with 9,9'-lactone lignan structure.

A synthesis method of this research is started by synthesizing lactone. Lactones were synthesized by stereoselective benzylation of **Intermediate-1** followed by reductive gave primary hydroxy group **Intermediate 4**. The oxidative cleavage of alkene followed by pyridinium chlorochromate oxidation of the resulting hemiacetal gave lactone product **Intermediate 5**.

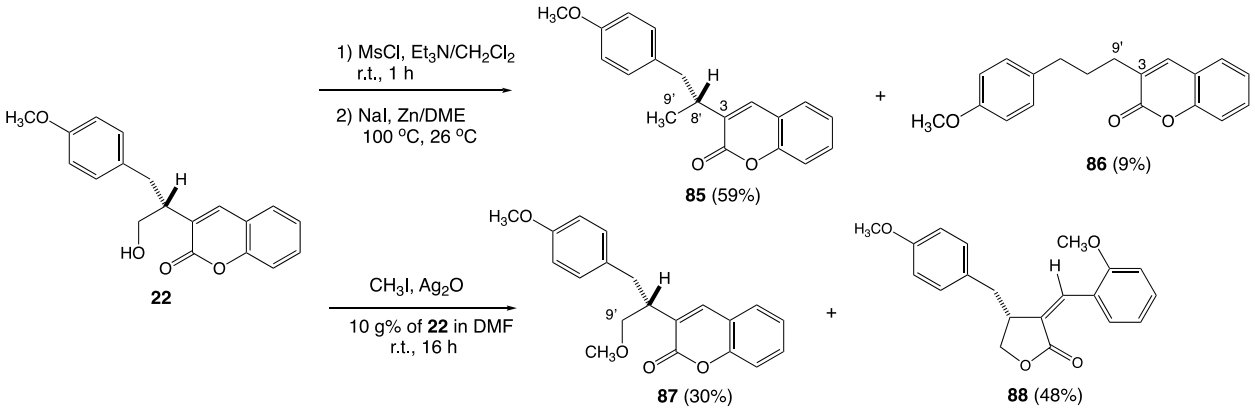


Scheme 1. Preparation of intermediate 5 (2)

The aldol condensation of this lactone with 2-benzyloxybenzladehyde using lithium diisopropylamide gave aldol product **Intermediate-6** as a mixture of *β-R*/*β-S*. On the other hand, the use of potassium bis(trimethysilyl)amide as a base gave predominantly a *β-S* isomer. After conversion to styryl lactone **Intermediate-7** as a *E*/*Z* mixture, debenzylation using BCl_3 and re-lactonization by treatment with aqueous NaOH followed by diluted aq. HCl gave mixture of *E*-2-hydroxybenzylidene butyrolactone derivative and coumarin-lignan structure. The syntheses of 4-methoxy derivatives were started from the aldol condensations of (*R*)-3-(4-methoxybenzyl)-4-butanolide with benzylated salicylaldehyde derivatives bearing different substituents to give the final product of this scheme 2.

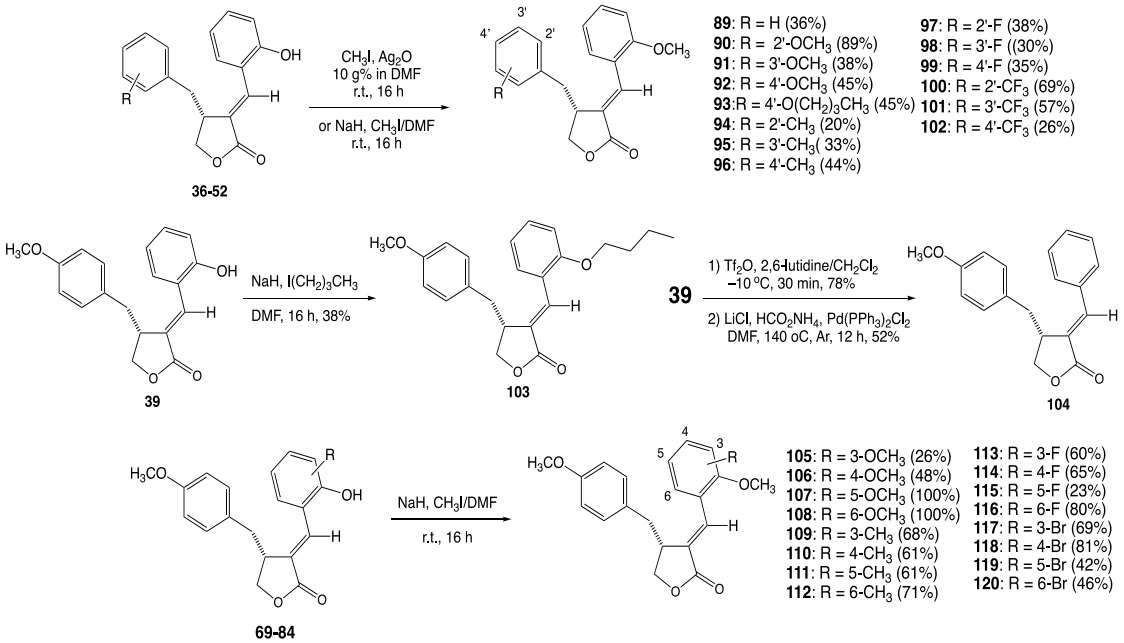


Scheme 2. Syntheses of coumarin derivatives and *E*-2-hydroxbenzylidene butyrolactones



Scheme 3. Syntheses of 9'-derivatives of 3-(7'-aryl-9'-hydroxyprop-8'-yl)coumarin-lignan

In this Scheme 3, the primary hydroxy group of **22** was removed by the conversion to mesylate, followed by treatment with NaI and Zn to give dehydroxy derivative **85** (59%) (Scheme 4). In this reaction condition, the rearrangement product **86**, in which the 3-position of coumarin is bound to the 9'-position of the phenylpropyl[46] group, was obtained (9%). The primary hydroxy group of **22** was also converted to methyl ether **87** (30%) by treatment with Ag_2O and CH_3I in DMF along with *Z*-styryl lactone **88** (48%) bearing 2-methoxyphenyl group. The other derivatives were synthesized according to this synthetic method with modification.



Scheme 4. Syntheses of *E*-benzylidene butyrolactone derivatives

The *E*-2-methoxybenzylidene **92** and *ent*-**92** were prepared by methylation using CH_3I and Ag_2O from phenol **40** and *ent*-**40**, respectively. The chemical shift of *E*-benzylidene olefinic proton of **92** was resonated at lower field (7.98 ppm) than *Z*-benzylidene olefinic proton of **88** (7.45 ppm).[10,18] The

NOE between synthesized *E*-benzylidene olefinic proton and benzylic proton was not observed. The *E*-2-butoxybenzylidene **103** was prepared from **40**. The 2-dehydroxybenzylidene **104** was prepared by conversion of phenolic benzylidene **40** to trifluoromethanesulfonate, followed by treatment with $Pd(PPh_3)_2Cl_2$, LiCl, and HCO_2NH_4. The enantiomeric compounds up to compound number **142** are synthesized using the same procedure as these schemes with a different starting material.

The plant growth regulation activities of our synthesized compounds were evaluated using Italian ryegrass and Lettuce seedling. A sheet of filter paper (diameter = 90 mm) was put in a 90 mm Petri dish and wetted with 500 μL of test sample solution dissolved in acetone. After the filter paper had dried, 3 mL of water was poured into the dish to adjust the final concentration from 1000 to 200 μM. Thirty seeds of each plant were placed on the filter paper, and the Petri dishes were sealed with parafilm. The Petri dishes were then incubated in the dark at 20°C. The lengths of roots and shoots were measured after 5 days for Italian ryegrass seedlings by using an ordinary ruler. The shoot and root lengths of the control were 2 and 3 cm for Italian ryegrass seedlings, respectively. Experiments were performed in triplicate for each sample at 1000 to 100 μM. The data are presented as percentage differences from the control, respectively.

The plant growth inhibitory activity of 3-(7'-aryl-9'-hydroxyprop-8'-yl)coumarin, which is a structural isomer of a popular butyrolactone type lignan biosynthesized by plants, was shown for the first time. The *R*-configuration in the 7'-aryl-9'-hydroxyprop-8'-yl moiety was more effective than *S*-configuration. Especially, the stereospecificity was observed in the growth inhibitory test against lettuce shoots and roots. The derivatives bearing *R*-configuration was stereoselectively synthesized in this research. It was shown that the hydroxy group at the 9'-postion was important for the activity. Among the aryl derivatives, the most effective derivatives against ryegrass roots were 3'-methoxy, 4'-methoxy, and 4'-trifluoromethyl derivatives **21**, **22**, **34** (IC_{50} = 0.22-0.26 mM). The activities against ryegrass shoots were not observed. On the other hand, 2'-methoxy derivative **20** was most potent against lettuce shoots (IC_{50} = 0.34 mM) and 4'-methoxy derivative **22** was most effective against lettuce roots (IC_{50} = 0.36 mM).

Derivatives of a lignan-type coumarin bearing a phenylpropanoid unit at the 3-position **22-68** were synthesized to clarify the effect of each substituent in the coumarin ring on the plant growth inhibitory activity. No remarkable growth inhibitory activity against the shoots of either lettuce or Italian ryegrass seedlings was observed. For lettuce roots, the growth inhibitory activity of the 8-OCH_3

derivative **56** was 1.6-times higher than the compound without substituents **22**. The activities of the other derivatives were lower against lettuce roots. For Italian ryegrass roots, the 5-CH_3 derivative **61** had the highest activity among the 5-substituted derivatives, suggesting that a hydrophobic group at the 5-position is advantageous. No activity was found for the 6-substituted derivatives. Of the 7-substituted derivatives, only the 7-OCH_3 derivative **55** was potent, displaying the same level of activity as the compound without substituents **22**. As for the 8-position, the hydrophobic electron donating group was suggested, thus the 8-OCH_3, 8-CH_3 derivatives **56**, **64** were more effective. This is the first report on the effect of substituents at each position from the 5-position to the 8-position on a coumarin ring with phenylpropanoid unit.

The antifungal assay of our synthesized compounds was evaluated using *A. alternata*[15,47–54] Japanese pear pathotype and *C. lagenarium*[55]. Thirty microliters of dimethyl sulfoxide solution containing each test compound was added to 3 mL of PDA at 50°C, followed by rapid mixing, and the resultant mixture was poured into a Petri dish (diameter 50 mm) to prepare the PDA agar plate containing the test compound. Dimethyl sulfoxide without any test compound served as the negative control. After inoculating each strain on the center of the PDA agar plate and incubation at 28°C for 3 days for *A. alternata* and *A. citri* and for 5 days for *C. lagenarium*, respectively, the diameter of the mycelial colony was measured with a caliper. All assays were performed in triplicate.

The previous research showed that butane-type[15,56] lignan and tetrasubstituted tetrahydrofuran[57,58] lignan with the phenolic group have significantly different activity against *Alternaria alternata*. *Alternaria alternata* is a pathogenic fungus[47–54,59] caused black spots and other diseases on many plant variants including Japanese pear, tomato, and rice. The recent experiment introduced a new type of lignan without any hydroxy group for *Alternaria alternata Japanese pear pathotype* and *Colletotrichum lagenarium*[55] antifungal tests.

The regiospecific and enantiospecific antifungal activities of α-benzylidene-β-benzyl-γ-butyrolactone were found out, 3*R*-*E*-β-benzyl-α-benzylidene compound **92** showing higher activity than *Z*-form and *S*-configuration. The importance of 2-OCH_3 group and the double bond of benzylidene structure for the increased activity was confirmed by the syntheses of the compounds without benzylidene structure or 2-OCH_3 group. The more effective compounds were searched by syntheses and biological assay of the novel derivatives bearing different substituents on the two aromatic rings. The more effective antifungal derivatives were (2-OCH_3, 4'-CH_3)-derivative **96**, (2-OCH_3, 4'-CF_3)-derivative

102, (2-OCH_3, 6-CH_3, 4'-OCH_3)-derivative **112**, (2-OCH_3, 6-F, 4'-OCH_3)-derivative **116**, and (2-OCH_3, 6-Br, 4'-OCH_3)-derivative **120**, whose EC_{50} values were 0.1-0.3 mM against *A. alternata* Japanese pear pathotype. It was assumed that some size of the hydrophobic group at 4'-position on the benzylic aromatic ring and hydrophobic group at 6-position on the benzylidene aromatic ring would accelerate the activity. The remarkable activities were not found against *C. lagenarium*, only 3-CH_3 derivative **109** showed weak activity against *C. lagenarium* (EC_{50} = 240 mM). Some effective derivatives **102**, **112**, **116**, and **120** were subjected to the tests against other *Alternaria* species. Although the remarkable activities were not observed, (2-OCH_3, 4'-CF_3)-derivative **102** and (2-OCH_3, 6-CH_3, 4'-OCH_3)-derivative **112** showed EC_{50} values of 150 mM and 145 mM, respectively, against *Alternaria citri*. The species-specific antifungal effects against *A. alternata* Japanese pear pathotype were clarified.

This research developed outstanding antifungal lignans of β-benzyl-α-benzylidene-γ-butyrolactones without a phenolic group that was more potent than previously synthesized tetrahydrofuran type lignan with phenolic and electron withdrawing groups.[57] The more selective toxicity against *A. alternata* was also observed in benzylidene compound. This is a first report on the antifungal benzylidene with lignano-9,9'-lactone structure biosynthesized by some plants.[1]

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