SYNTHESIS OF LYCORINE

By
MISS Wichita KHEAKWANWONG

A Thesis Submitted in Partial Fulfillment of the Requirements
for Master of Science (CHEMISTRY)
Department of CHEMISTRY
Silpakorn University
Academic Year 2022

การสังเคราะห์ไลโครีน

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Title	Synthesis of Lycorine
By	MISS Wichita KHEAKWANWONG
Field of Study	(CHEMISTRY)
Advisor	Assistant Professor Punlop Kuntiyong, Ph.D.

Faculty of Science, Silpakorn University in Partial Fulfillment of the Requirements for the Master of Science

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MISS Wichita KHEAKWANWONG : Synthesis of Lycorine Thesis advisor : Assistant Professor Punlop Kuntiyong, Ph.D.

Alkaloids are a type of natural products which can be isolated from many kinds of creature such as plants, animals, fungi, and bacteria. These kinds of natural products possess interesting biological activities for instance anticancer, antiflamatory, and antimalarial. Because of the useful properties, scientists including the synthetic chemists intensely pay attention to alkaloids. They have attempt to synthesize natural and unnatural analogues of alkaloids. One of the most commom reaction for synthesis alkaloids is the *N*-acyliminium ion cyclization.

This thesis reports a synthetic study of alkaloids. The alkaloid is lycorine which is found in the Amaryllidaceae family as *Clivia miniata* and *Daffodil bulb*. The structure is a pentacyclic benzoindolizidine structure containing four stereo centers. The heck reaction and *N*-acyliminium ion cyclization were applied as the crucial reactions for the synthetic route. The synthetic strategy of lycorine was designed in two synthetic routes. First, the construction of the tricyclic core from *N*-acyliminium ion cyclization. However, this result was observed without the hydroxylactam peak of the carbon NMR spectrum at 76.5 ppm. And second, the synthesis involved Suzuki reaction followed by metathesis for generated tricyclic core from *N*-acyliminium ion cyclization but metathesis did not give the desired product. Now, an alternative route devised and it involves witting olefination and metathesis for generating a C-C bond linkage.

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Finally, I would like to thank my beloved family including my parents and my friends for all their support throughout the period of studying in Master's degree.

MISS Wichita KHEAKWANWONG

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CHAPTER 1

INTRODUCTION

Alkaloids[1] are a major family of Natural Products with diverse structural architectures and intriguing biological activities. Many plants containing alkaloids have been used as herbal medicines since prehistoric time in all parts of the world. Modern medicines also employ small molecule alkaloids as drugs for various diseases. The structural complexity and medicinal benefits make alkaloids compelling targets for synthetic chemists. Alkaloids can be divided in numerous subgroups. The criteria for categorizing alkaloids include the origins of the compound as well as the common core structures. Our research group studies substrate controlled asymmetric synthesis of quinolizidine alkaloids with 1-azabicyclo[4.4.0]decane system, indolizidine alkaloids with 1-azabicyclo[4.3.0]nonane system, and other related alkaloids. We have reported synthesis of Schulzeine B and C, Crispine A analogs as well as synthesis of core structures of *Erythrina* alkaloids, hyperkinetic movement disorder drug Tetrabenazine, and neuroprotective Rhynchophylline shown in Figure 1.

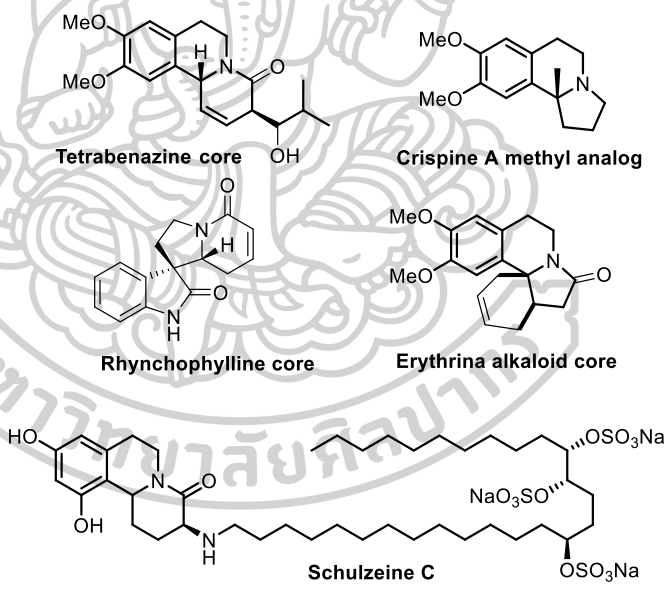
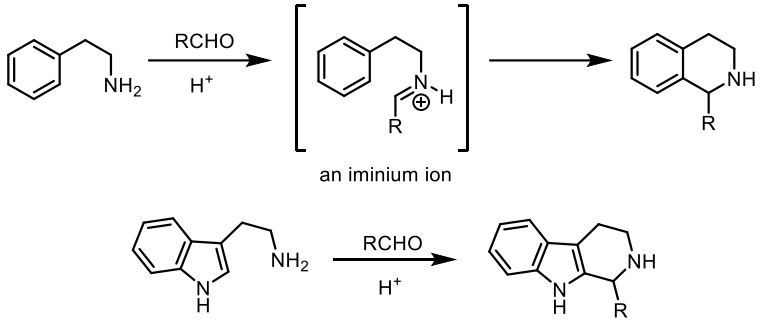


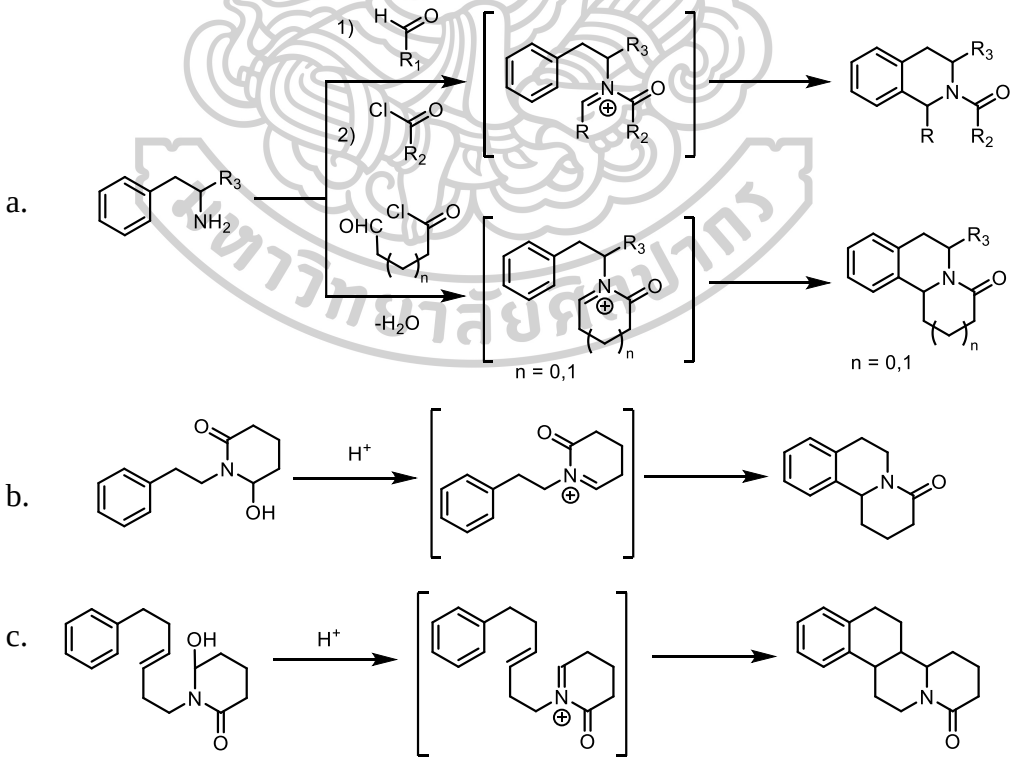
Figure 1 Examples of indolizidine and quinolizidine alkaloids

Benzoquinolizidine[2] and benzoindolizidine structural moieties found in the targets in Figure 1 can also be categorized as tetrahydroisoquinoline derivatives. The reaction which is well-known for synthesis of tetrahydroquinoline alkaloids is the Pictet-Spengler reaction. It is a cyclization between an arylethylamine and an aldehyde that is usually catalyzed by acid. An intermediate of Pictet-Spengler reaction is an iminium ion. Originally, the reaction employed formaldehyde and phenethylamine to give the tetrahydroisoquinoline skeleton. The analogous reaction of tryptamine results in tetrahydro-β-carboline system (Scheme 1).



Scheme 1 Pictet-Spengler reaction

N-acyliminium ion cyclization[2] is a more reactive variant of Pictet-Spengler reaction which is very useful in alkaloid synthesis. *N*-acyliminium ions can be formed from acylation of imine or cyclization of amido-aldehyde in acidic conditions are very reactive intermediates and can act as high electron-deficient electrophiles toward weak nucleophiles. Besides the aromatic ring, alkene can also act as nucleophile in the reaction The reactions are especially useful method for intramolecular cyclization. Tandem *N*-acyliminium ion cyclizations where the initial cyclization intermediate can be trapped by nearby second nucleophile can lead to polycyclic framework in a single operation (Scheme 2).



Scheme 2 *N*-acyliminium ion cyclizations

Currently we are exploring the application of chiral succinimide and glutarimide synthesized from cheap and readily available chiral pool starting materials, namely, L-aspartic acid, L-asparagine or L-glutamic acid and L-glutamine as chiral building block for alkaloid synthesis. The selected targets are shown in figure 2 such as quinolizidine alkaloids (Protoemetinol and Lupinine), Indolizidine alkaloids (FR901483, Tabertinggine, Lycorine, and Tashiromine, and a related *Amaryllidaceae* alkaloid, Plicamine . We envision that N-acyliminium ion cyclization and other reactions of the chiral cyclic imide intermediates would lead to asymmetric total synthesis of these biologically active alkaloids.

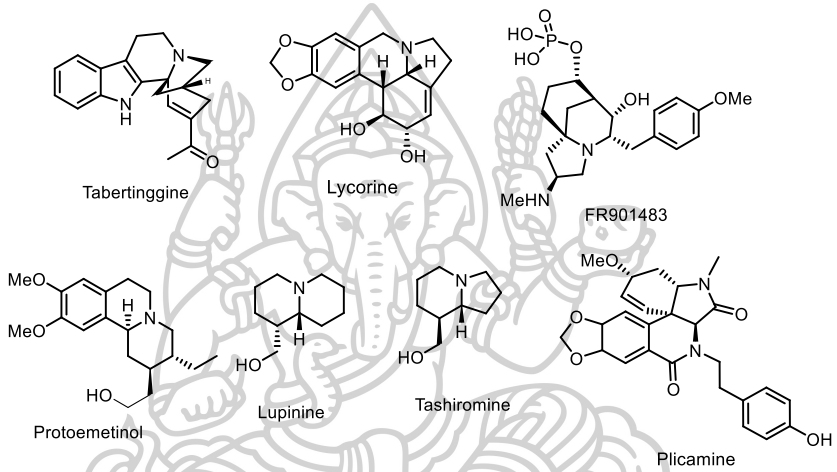


Figure 2 Example of quinolizidine, indolizidine and related alkaloids

Crispine A and *Erythrina* alkaloids whose structures are shown in Figure 1 are benzo[g]indolizidine alkaloids. In this research, we will discuss synthetic studies of lycorine which has the benzene ring fused to a different side of indolizidine. Its structure consists of a pentacyclic system with benzo[f]indolizidine ABD core fused with a dioxolane and a cyclohexene-diol (C ring) containing four stereocenters.

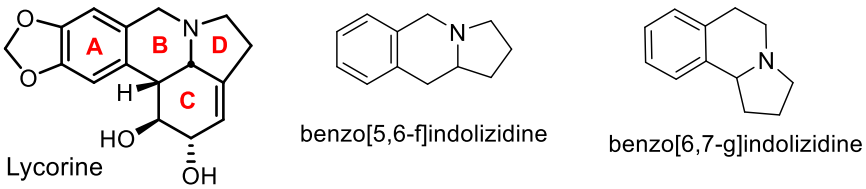
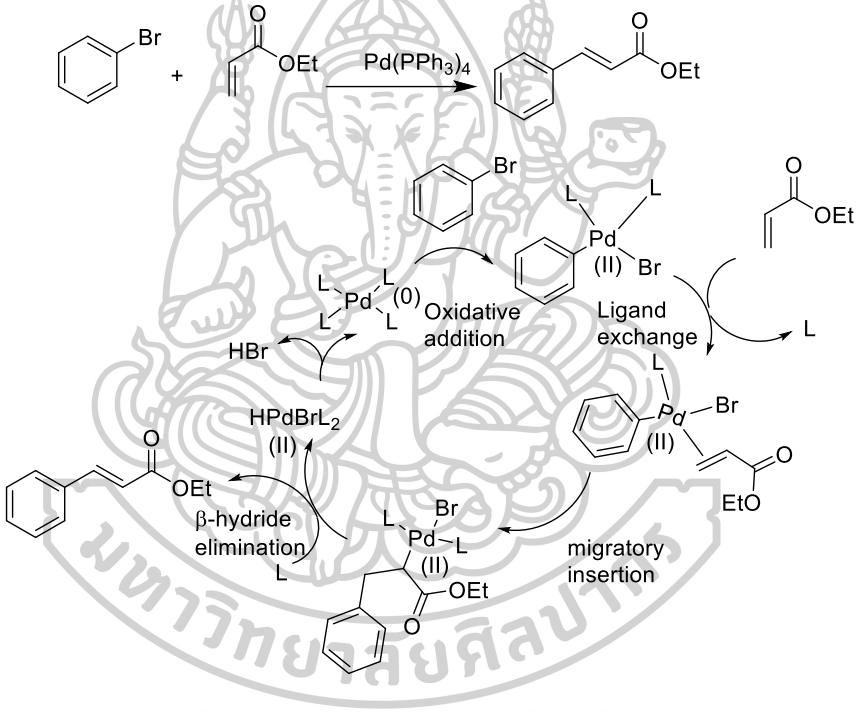


Figure 3 Lycorine structure

Our synthesis plan has evolved during the course of our study. However, the main strategy utilizes chiral succinimide intermediate prepared from *L*-asparagine to form the D ring. This moiety is combined with bromopiperonyl which represents the A ring and the resulting intermediate would be the precursor for closure of the B ring with various methods. Among the methods that we have attempted for

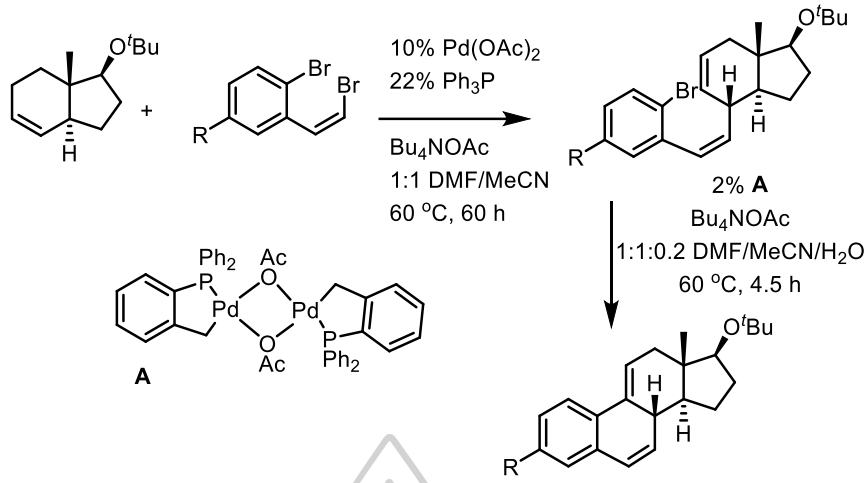
construction of the B ring are *N*-acyliminium ion cyclization and Wittig reaction. During the preparation *N*-acyliminium ion cyclization precursor multiple reactions have been employed such as the Heck reaction, Suzuki reaction, Wittig olefination and
aza-Sakurai reaction.

Heck reaction is the chemical reaction of an unsaturated halide with an alkene in the presence of a base and palladium catalyst to give a substituted alkene. Heck reaction is important in organic synthesis since it is an especially useful method for formation of a C-C bond. The intermolecular Heck reaction begins with oxidative addition of Pd (0) to the aryl halide to form aryl-Pd (II) intermediate that adds into the C=C bond to give alkyl-palladium complex that undergoes β-hydride elimination to give the arylated alkene product.



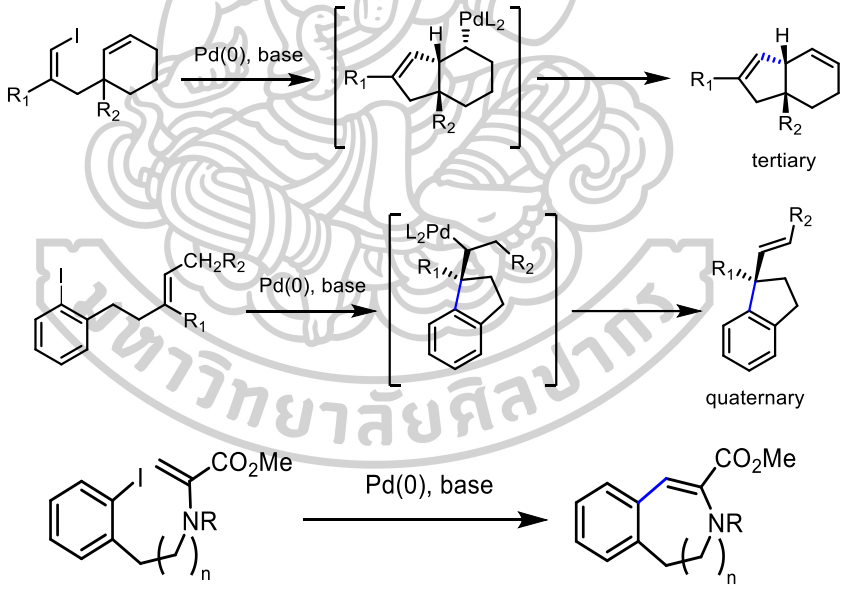
Scheme 3 Heck reaction and mechanism

Besides being powerful coupling reaction in an intermolecular fashion, Heck reaction is a useful method for intramolecular cyclization. For example, in a synthesis of a steroid by Tietz[3] in 1998 (Scheme 4), *Z*-2-bromostyrene underwent oxidative addition with a palladium (0) catalyst formed in situ from palladium (II) acetate and triphenyl phosphine and reacted with hydroindene in an intermolecular Heck reaction to form *Z*-styrene-indene intermediate. Subsequently, aryl-bromide underwent oxidative addition with dimeric trans-bis(acetato)bis[o-(diphenylphosphino)benzyl]dipalladium(II) (A) resulting in an intramolecular Heck reaction to form the B ring of the steroid estrone.



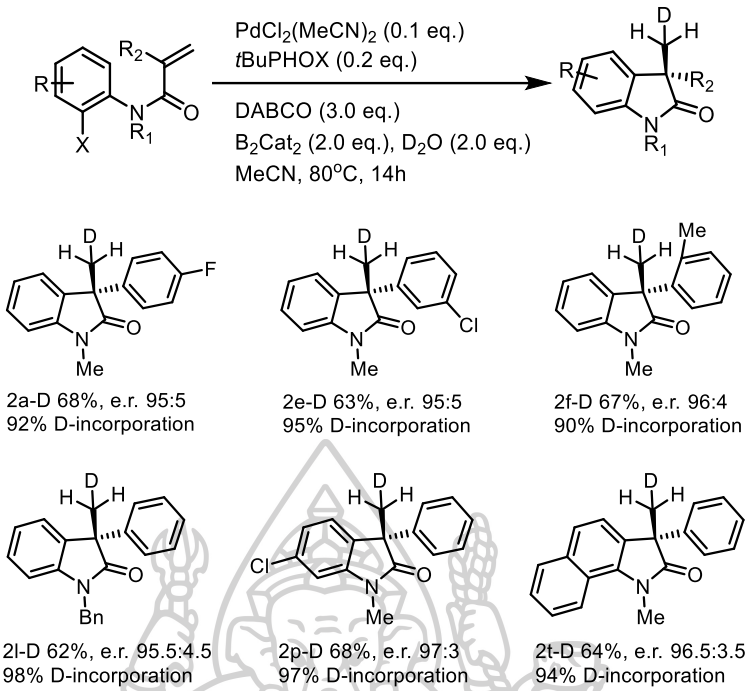
Scheme 4 Example of Heck reaction by Tietz

Asymmetric Heck reactions can also construct tertiary or quaternary stereocenters. In the instance of establishing a quaternary center adjacent to the palladium-carbon bond, β-hydride elimination is not possible. Thus, quaternary stereocenters can be formed in a conformationally restricted system (Scheme 5).



Scheme 5 Asymmetric Heck reaction

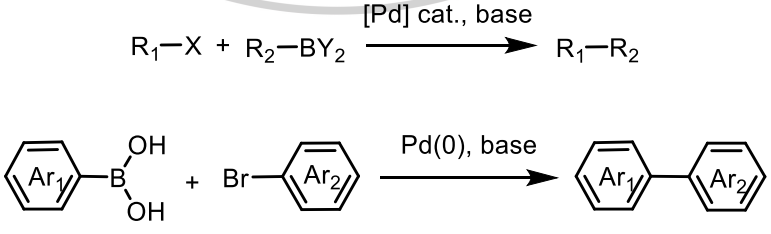
In 2017, Kong and a co-worker[4] developed the first Pd-catalyzed asymmetric reductive Heck reaction using diboron-H_2O as a hydride donor. C3-quaternary stereocenter, a series of enantioenriched oxindoles were obtained in excellent yield with high enantioselectivity (Scheme 6). In this example, initial addition of the aryl-palladium to the alkene led to alkyl-palladium intermediate with quaternary center that cannot undergo β-hydride elimination. The organopalladium intermediate undergoes hydride reduction to give the methyl substituent instead.

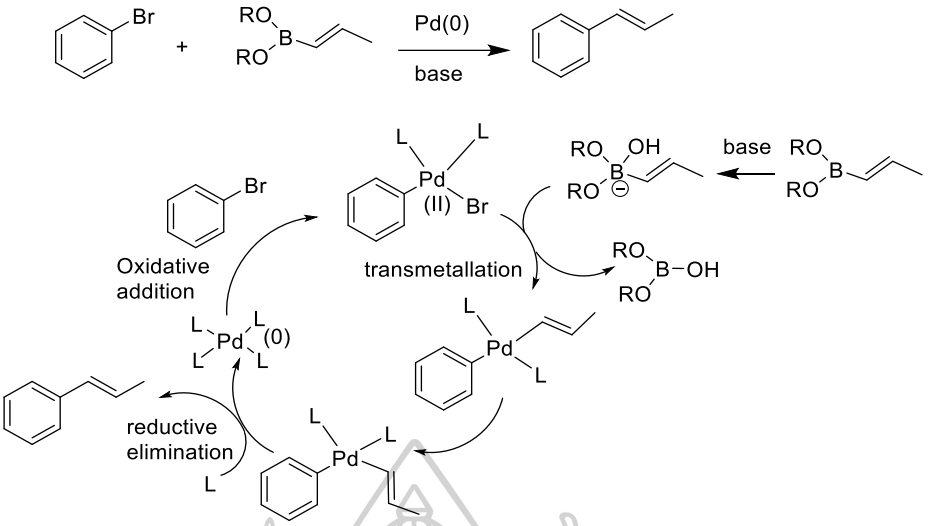


Scheme 6 Enantioselective synthesis of D-labeled oxindoles by Kong and a co-worker

The role of water as hydride donor could be verified when D_2O was used. In this way, the CH_2D substituted oxindoles were synthesized using D_2O as a D-donor and a high level of D incorporation.

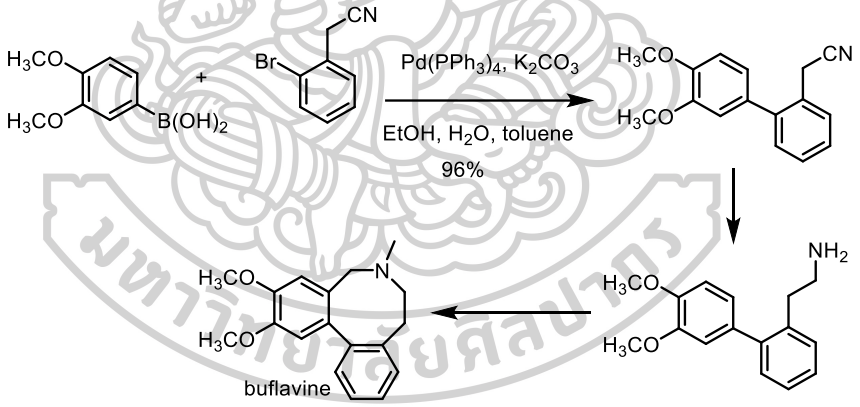
Suzuki reaction is a reaction that a C-C bond is formed by coupling an organoboron species and a halide using a palladium-catalyst and a base. The base produces a trialkyl borate species which is more nucleophilic and more reactive towards the palladium complex present in the transmetalation step. Suzuki reaction is widely used to synthesize polyolefin, styrenes, and substituted biphenyl.





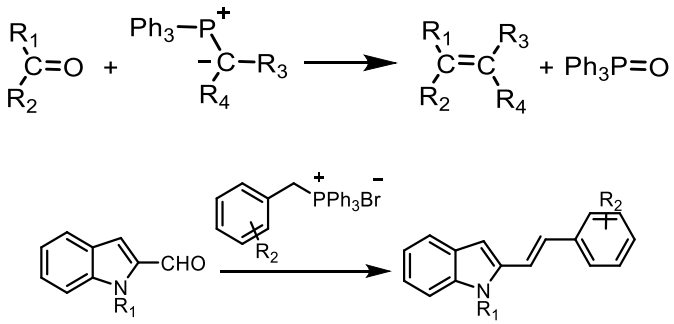
Scheme 7 Suzuki reactions and mechanism

For example, in synthesis of buflavine by Somsak Ruchirawat[5], 3,4-dimethoxyphenylboronic acid reacted with (2-bromophenyl)acetonitrile in the presence of tetrakistriphenylphosphinne palladium as catalyst and potassium carbonate as base to give biaryl product in 96% yield.



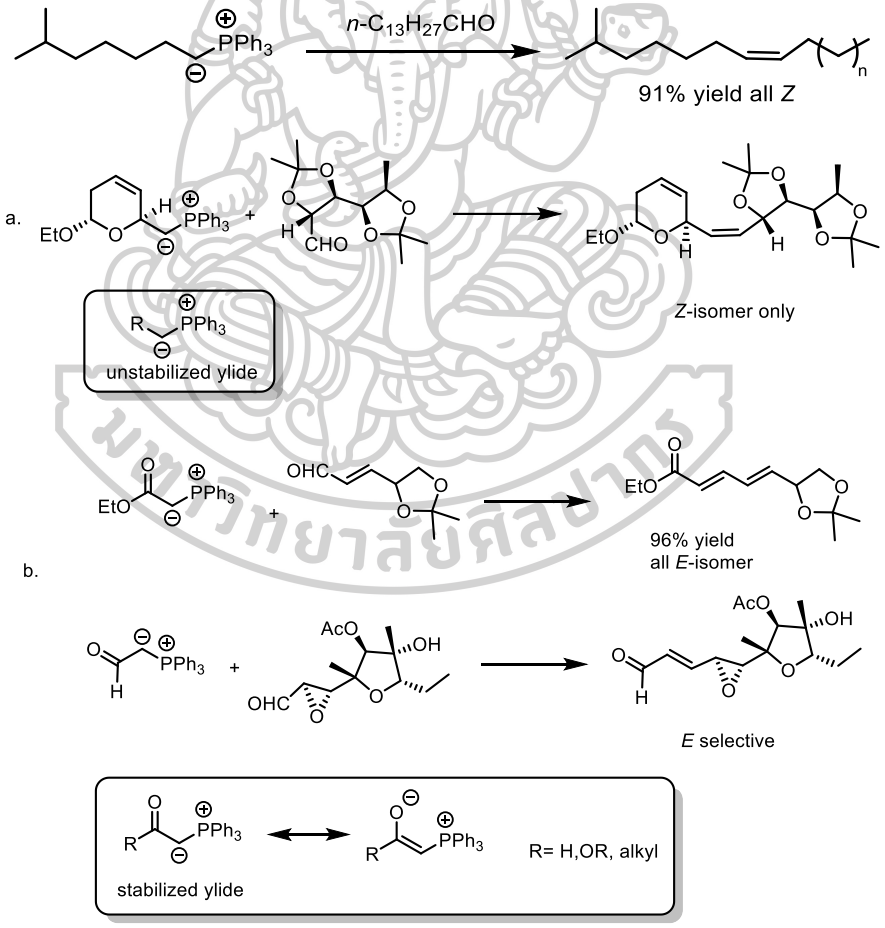
Scheme 8 An example of Suzuki reaction

Wittig reaction is olefination of a ketone or an aldehyde with triaryl (or alkyl) phosphonium ylide known as Wittig reagent. This reaction is most commonly used to convert ketones and aldehydes to alkenes from methylene group using methylenetriphenylphosphorane ($PH_3P{=}CH_2$) to other more highly substituted alkenes.



Scheme 9 Wittig reaction

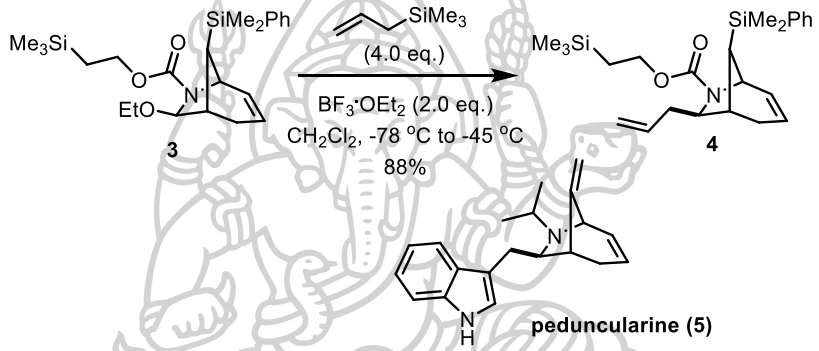
Wittig reaction can give *E/Z* selectivity depending on the type of phosphonium ylide used for the reaction. Non-stabilized phosphonium ylides with alkyl substituent give *Z*-alkene selectively, whereas stabilized phosphonium ylides with substituent that can stabilized carbanion give *E*-alkene selectively.



Scheme 10 *Z*-selective and *E*-selective Wittig reactions

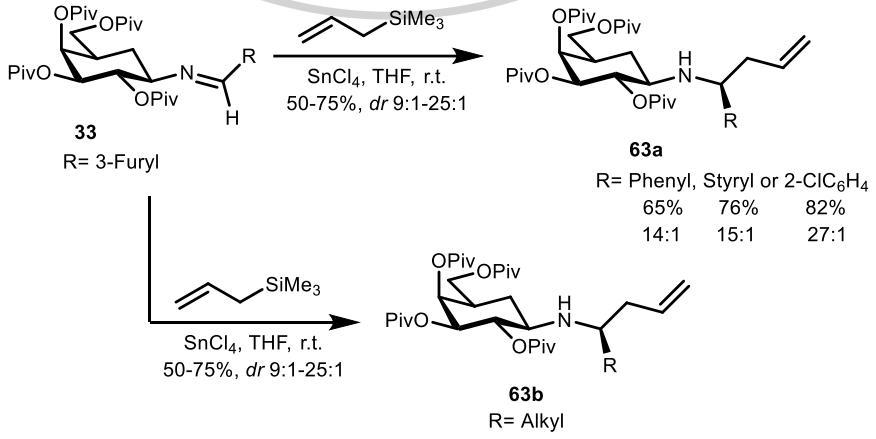
Aza-Sakurai reaction is one of an important reactions in organic synthesis. It is an especially useful method for formation of a C-C bond between an allylsilane as nucleophile and an iminium ion as electrophile. The transformation can be either intermolecular or intramolecular reaction that began with strong Lewis acid activation (titanium tetrachloride, boron trifluoride, tin tetrachloride, and $AlCl(Et)_2$ being essential for complete reaction between electrophilic carbon of iminium ion and allyltrimethylsilane.

For example, Woerpel and Roberson[6] reported stereoselective total synthesis of peduncularine in 2002, using an intermolecular aza-Sakurai allylation of *N,O*-acetal **3** with allyltrimethylsilane. The reaction was mediated by $BF_3{\cdot}OEt_2$ as a Lewis acid at low temperature and gave the desired allylated product **4** as a single stereoisomer in excellent yield (Scheme 11)



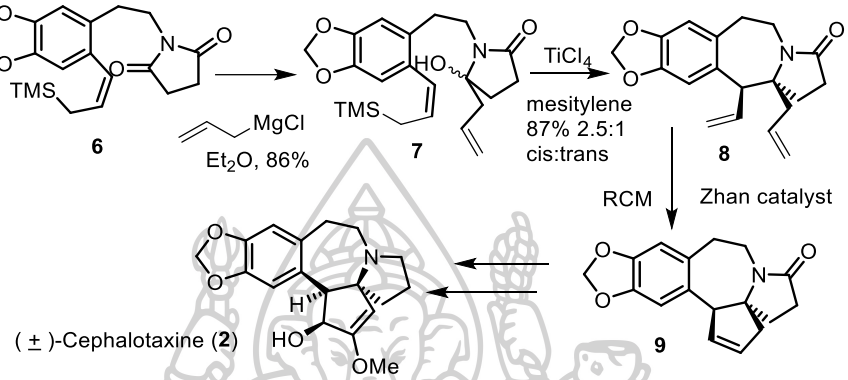
Scheme 11 Intermolecular aza-Sakurai in synthesis of peduncularine reported by Woerpel and Roberson

In 2013, synthesis of homoallylamines which is an intermediate for preparation of carbohydrate-derived auxiliaries was reported by Kunz[7]. Aza-Sakurai reaction of the *N*-galactosyl imine **33** in the presence of tin(IV)chloride with allylsilanes yielded homoalkylamines **63** (Scheme 12).



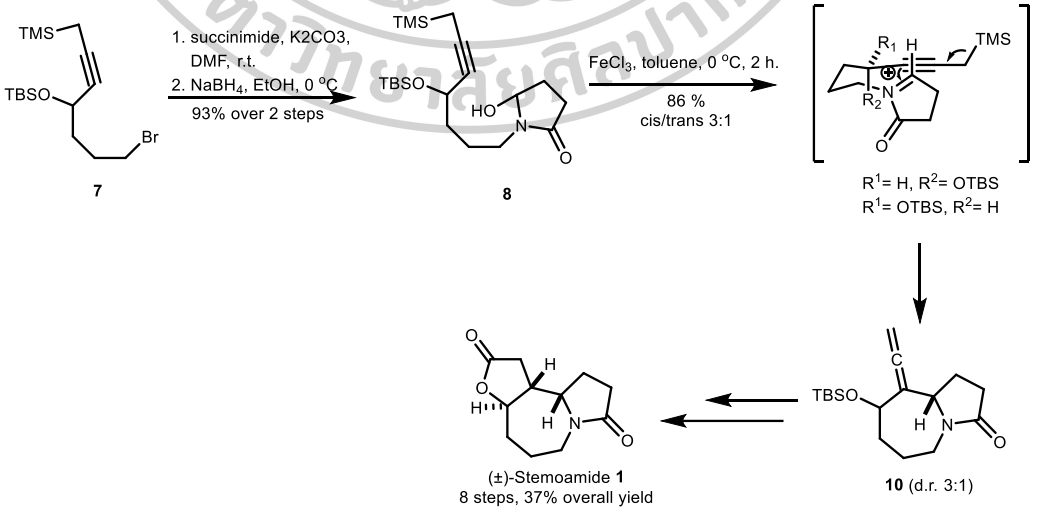
Scheme 12 Syntheses of homoallylamines reported by Kunz

Moreover, intramolecular aza-Sakurai reaction can form polycyclic framework of alkaloids with high selectivity. For example, this reaction was used in a synthesis of racemic cephalotaxine by Liu and coworkers[8] in 2015 (Scheme 13). The precursor *N*-arylethylsuccinimide **6** reacted with allylmagnesium chloride to give hydroxylactam intermediate **7**. Treatment of this *Z*-TMS-allyl-hydroxylactam precursor with titanium tetrachloride in mesitylene at -45 °C gave a 2.5:1 mixture of *cis:trans* tricyclic core **8** of cephalotaxine (**2**) in good yield.



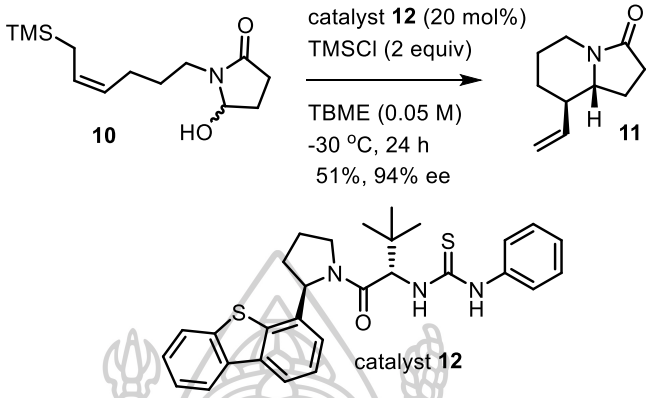
Scheme 13 Intramolecular aza-Sakurai reaction in cephalotaxine synthesis reported by Liu

Wang and co-worker[9] reported a bioinspired and concise synthesis of (±)-Stemoamide (Scheme 14). The propargylsilane-hydroxylactam **8** could be prepared from the corresponding bromide **7** and succinimide via N-alkylation and subsequent reduction using $NaBH_4$. This precursor was subjected to a $FeCl_3$-promoted cyclization in toluene at 0 °C to give 3:1 mixture of *cis:trans* bicyclic core **10** of stemoamide (**1**).



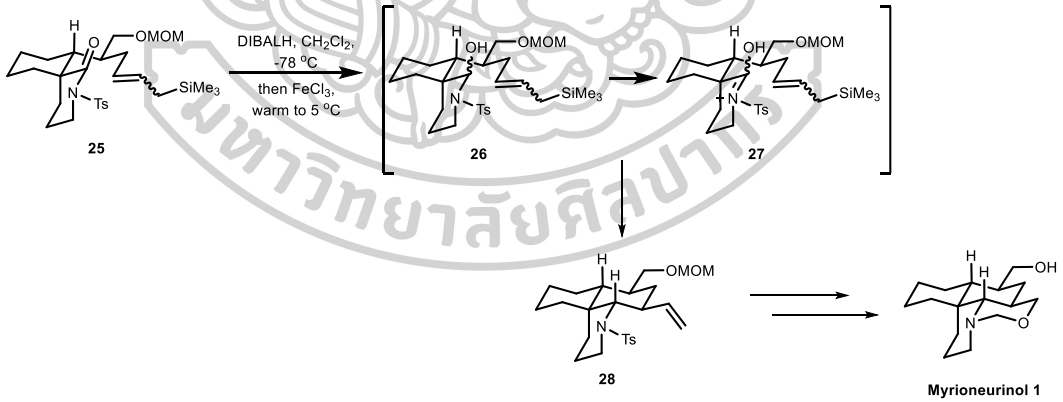
Scheme 14 Bioinspired and concise synthesis of (±)-Stemoamide reported by Wang

Enantioselective aza-Sakurai reaction using chiral catalyst has been developed by Park[10] (Scheme 15). *N*-(6-Trimethylsilyl-4-hexen-1-yl)-γ-hydroxylactam **10** reacted with TMSCl in the presence of chiral thiourea catalyst **12** yielded 8-vinylindolizidinone **11** in moderate yield with high enantiomeric excess.



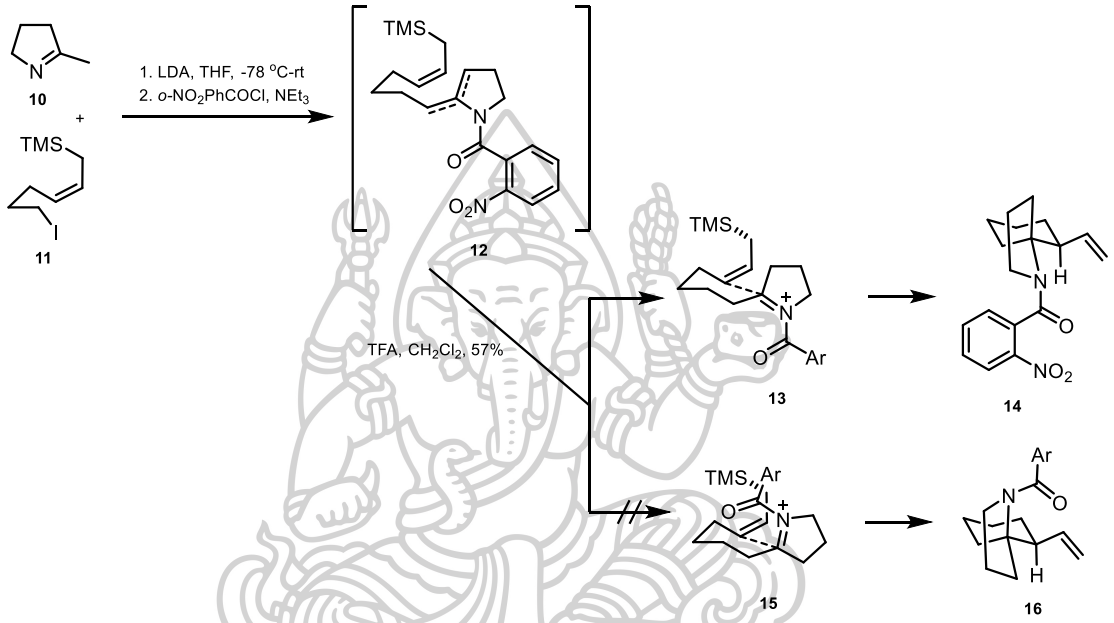
Scheme 15 Enantioselective intramolecular aza-Sakurai reaction in synthesis of 8-vinylindolizidine by Park.

Nocket and co-worker[11] reported a total synthesis of the tetracyclic antimalarial alkaloid (±)-Myrioneurinol (Scheme 16). The precursor *N*-tosyl lactam **25** reacted with DIBAL-H to give allylsilane-hydroxylactam intermediate **26**. Subsequent addition of ferric chloride and slow warming to approximately 5 °C gave spirotricyclic core **28** of myrioneurinol as a single stereoisomer in good yield.



Scheme 16 The total synthesis of the Tetracyclic Antimalarial Alkaloid (±)-Myrioneurinol reported by Nocket.

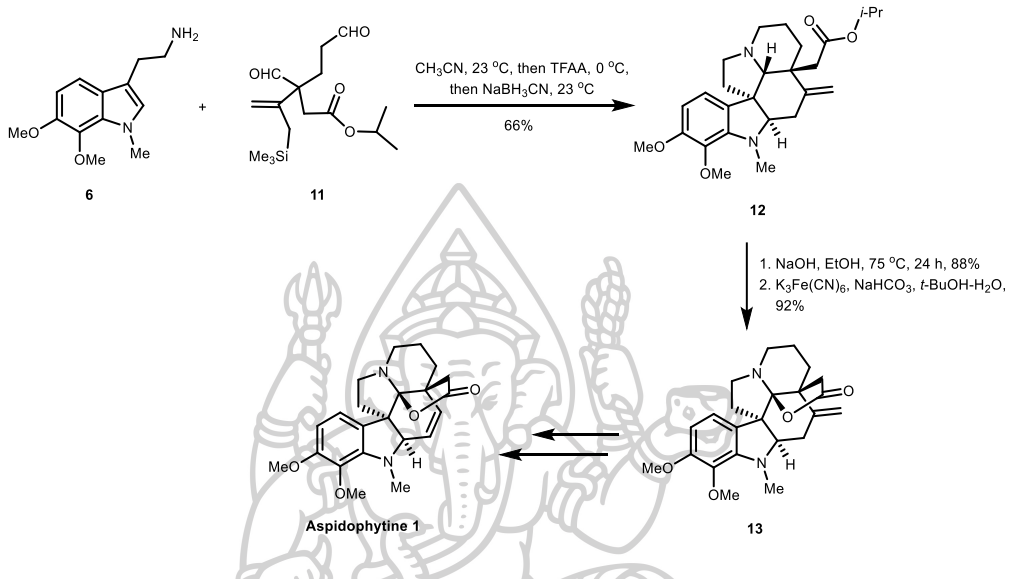
A total synthesis of the marine tunicate alkaloid lepadiformine was reported by Sun[12] (Scheme 17) using aza-Sakurai reaction for producing spiro[cyclohexane-pyrrolidine] **14** which is an intermediate for lepadiformine (Scheme 3). Starting with combination of 2-methyl-1-pyrroline **10**, which was first lithiated and reacted with *Z*-[7-iodohex-2-enyl]trimethylsilane **11** via alkylation. Subsequent *N*-acylation with *o*-nitrobenzoyl chloride gave a mixture of regioisomeric enamide **12** which was treated with trifluoroacetic acid to generate spirocyclic **14** as a single stereoisomer in 57% overall yield based upon **10**.



Scheme 17 A new total synthesis of the marine Tunicate alkaloid Lepadiformine by Sun.

They proposed that spirocyclic **14** was formed via *N*-acyliminium ion in conformation **13** while conformer **15** was probably destabilized relative to **13** due to a steric interaction between the *N*-*o*-nitrobenzoyl group and the allylsilane.

Enantioselective total synthesis of aspidophytine was reported by He[13] (Scheme 18). The heart of the synthesis of aspidophytine **1** was a cascade reaction initiated by condensation of dialdehyde-allylsilane **11** with tryptamine **6**. The resulting dihydropyridinium ion underwent intramolecular aza-Sakurai cyclization to form the pentacyclic framework of aspidophytine in a single step after treatment with TFAA and subsequently, $NaBH_3CN$ in acetonitrile.



Scheme 18 Enantioselective total synthesis of aspidophytine reported by He

In this study, Heck reaction was used to synthesize *β*-arylacrylate intermediate which would be converted to the *N*-acyliminium ion cyclization precursor in the first synthetic route. In the second synthetic plan. Suzuki reaction/Olefin metathesis sequence was used as an alternative approach to install the aryl-allylsilane which would be suitable for an aza-Sakurai reaction to form the B ring instead of *N*-acyliminium ion cyclization. In the third approach, Wittig reaction installed the methylene group to 6-bromopiperonal and subsequent Olefin metathesis with trimethylallylsilane could also deliver the aryl-allylsilane for the aza-Sakurai reaction to form the B ring.

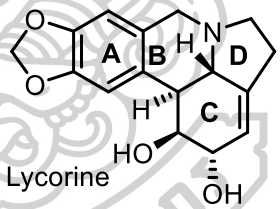
Objectives of Research

1. To develop a synthetic methodology for lycorine
2. To develop the *N*-acyliminium ion cyclization and other equivalent reaction such as aza-Sakurai reaction to synthesize benzo[f]indolizidine system

CHAPTER 2
LITERATURE REVIEW

In this research, we would like to present the synthetic study of lycorine containing a benzo[5,6-f]indolizidine tricyclic system. Lycorine is one of the members of Amaryllidaceae alkaloid. It was first isolated by Gerrand and was called narcissia in 1877 from the plant is Narcissus pseudonarcissus[14]. The alkaloid was later named lycorine in 1897 by Morishima. Most reported Amaryllidaceae[14] species contain lycorine including *Leucojum aestivum, Crinum macowanii, Brunsvigia, Ammocharis coranica, Hippeastrum equestre, Hymenocallis littoralis, Leucojum aestivum,* flowers of *Clivia nobillis,* and *Lycoris radiate*. Lycorine[14] is a colorless crystal with a melting point of 260-262 ^{o}C and is insoluble in ether and alcohol solutions. In addition, the biological activity of lycorine includes inhibition of the termination of protein synthesis, anti-poliovirus in infected HeLa cells, bactericidal effects in several bacterial strains, inhibition of DNA topoisomerase-I activity which is important for the growth of cells in parasites, inhibition of NF-κB signaling that is one of the inflammatory effects, and anti-tumor effect with an IC50 value not exceeding 7.5 μM. The structure consists of five linked rings containing a benzo[5,6-f]indolizidine core fused with an dioxolane and a cyclohexne diol with four stereogenic centers.

Narcissus pseudonarcissus[15]

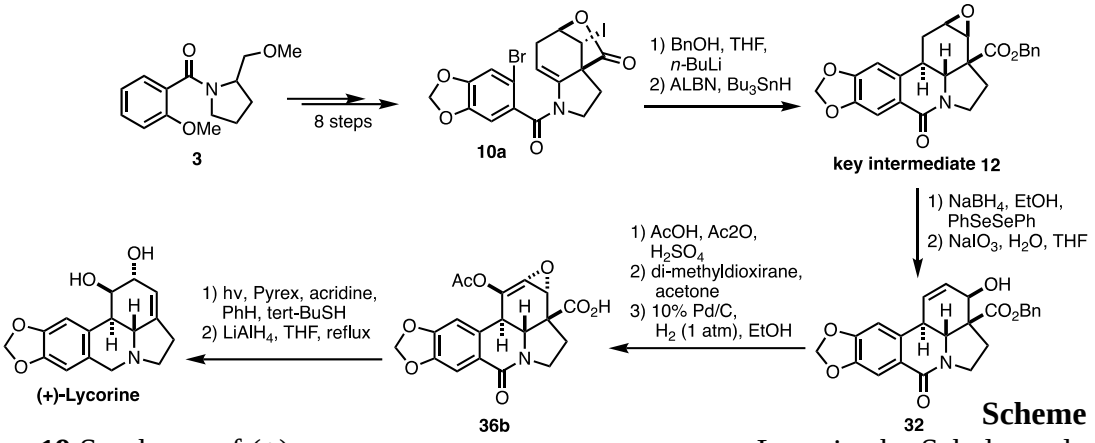


Lycorine

Figure 4 Structure of lycorine and Narcissus pseudonarcissus

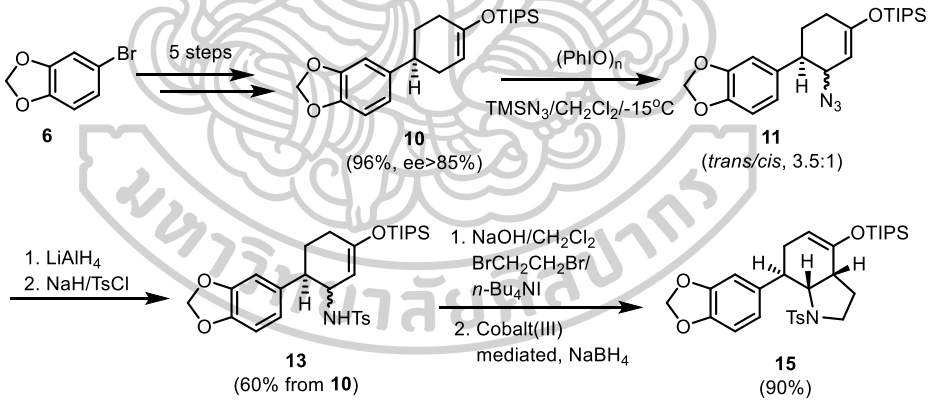
Previous Synthesis Studies of Lycorine and Lycoranes

In 1996, Schults and a co-worker[16] reported the first asymmetric total synthesis of (+)-lycorine. A key step for the synthesis was the completely regio- and stereoselective intramolecular radical cyclization reaction of aryl bromide and enamine to give key ABCD core intermediate **12** which was converted to (+)-lycorine in 7 steps (Scheme 11).



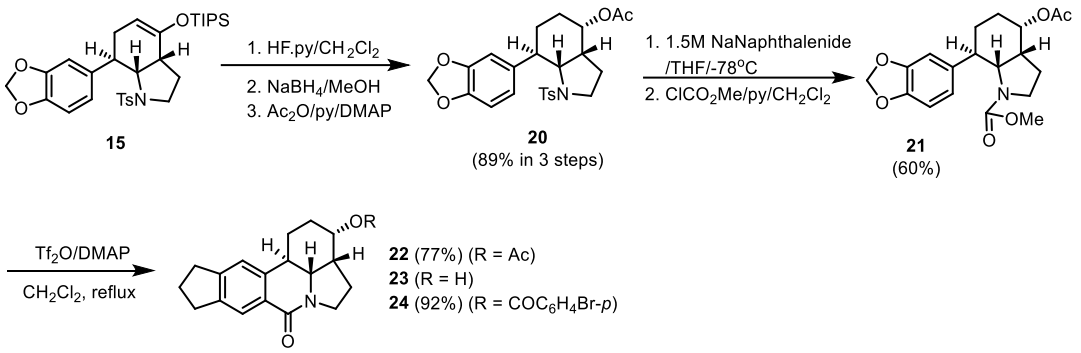
Scheme 19 Syntheses of (+)-Lycorine by Schultz and a co-worker

In 1999, Magnus and a co-worker[17] reported the synthesis of lycorane core structure in an enantiomerically enriched form. The synthesis was completed in 16 steps to give the lycorane core structure and started from benzodioxole **6**. The key reaction of the synthesis was a β-azidonation reaction to construct the mixture *cis*- and *trans*- of compound **11** by reacting bicyclic **10** with $(PhIO)_n/TMSN_3$ in CH_2Cl_2. Reduction of the azide and treated with NaH/TsCl gave sulfonamide **13** which underwent cobalt (III)-mediated radical cyclization and dehydrogenation in the presence of $NaBH_4$/MeOH in excellent yield (Scheme 12).



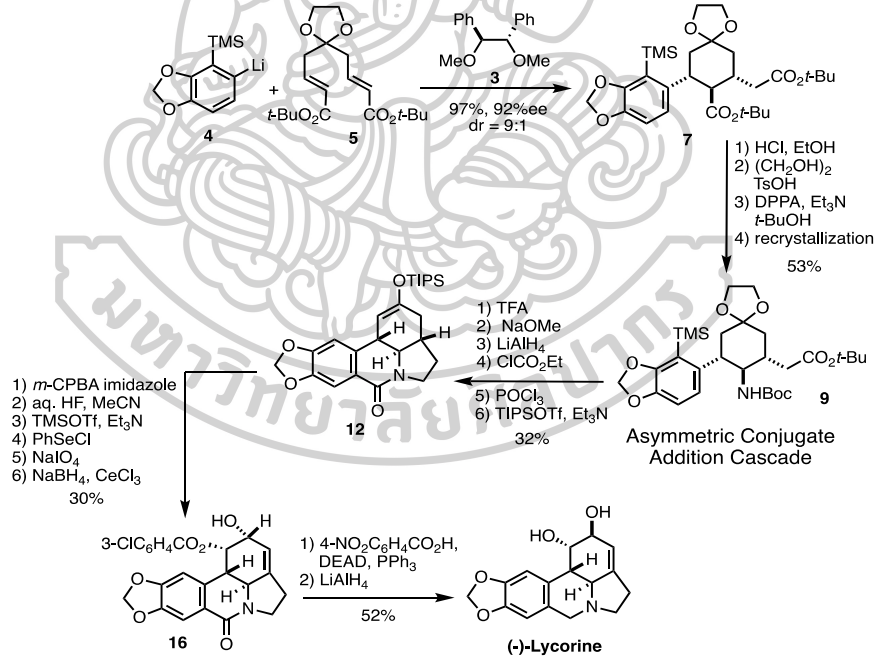
Scheme 20 Key step for synthesis of the lycorane core structure by Magnus and a co-worker

To complete the synthesis, the researcher reductively removed the sulfonamide from **15** followed by Pictet-Spengler cyclization to give the lycorane core structure. But the cyclization step gave low yield and undesired byproduct was also obtained. So, they removed the triisopropylsilyl group from **15** followed by acetylation to afford indolyl acetate **20**. Reductive removal of the sulfonamide group and acylation with methyl chloroformate gave the carbamate **21**. Next, Bischler-Napieralski reaction to give **22**, which was hydrolyzed to alcohol **23** followed by conversion to p-bromobenzoate **24** (Scheme 13).



Scheme 21 Completed synthesis of the lycorane core structure by Magnus and a co-worker

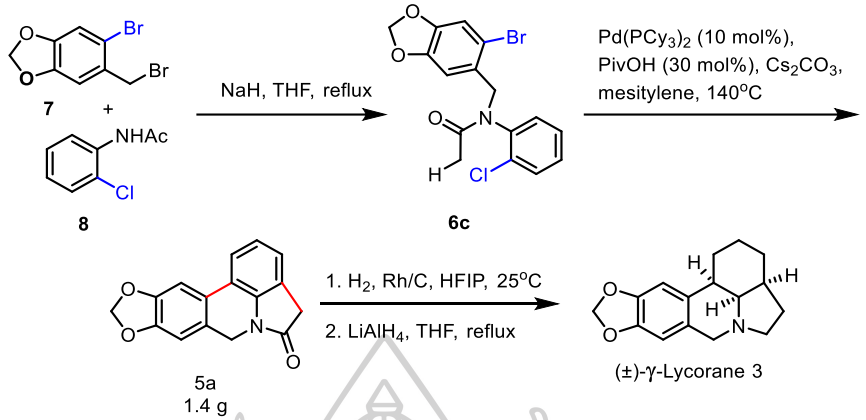
In 2009, Yamada and a co-worker[18] reported that synthesis of (-)-lycorine was completed using a chiral ligand-controlled asymmetric cascade conjugate addition methodology that formed of two C-C bonds and generated three stereogenic centers in one pot to afford chiral cyclohexane derivative **7**. The core structure of lycorine could be synthesized from Curtius rearrangement and a Bischler-Napieralski reaction (Scheme 14).



Scheme 22 Total Syntheses of (-)-Lycorine by Yamada and a co-worker

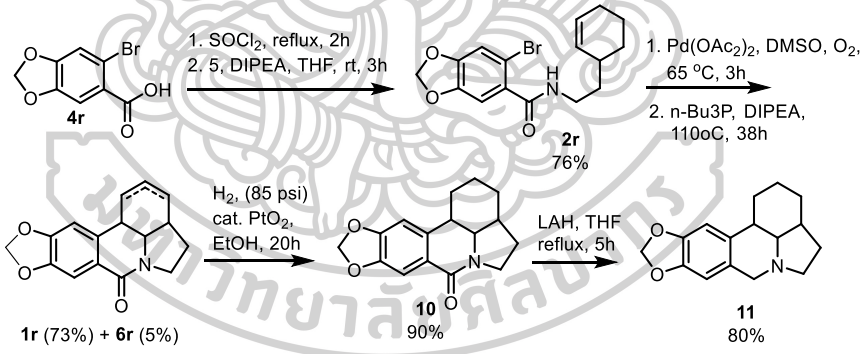
In 2018, Rocaboy and a co-worker[19] reported the synthesis of lycorine alkaloids in four steps. Palladium(0)-catalyzed double C-X/C-H arylation was the key step. Starting with commercially available precursors **7** and **8** were combined using NaH in THF to give the C-H arylation precursor 6C. Compound 6C was converted to pyrrolophenanthridinone **5a** via C-H arylation and selective hydrogenation of

5a followed by reduction of the carbonyl group gave the desired product, (±)-*γ*-Lycorane **3** (Scheme 15).



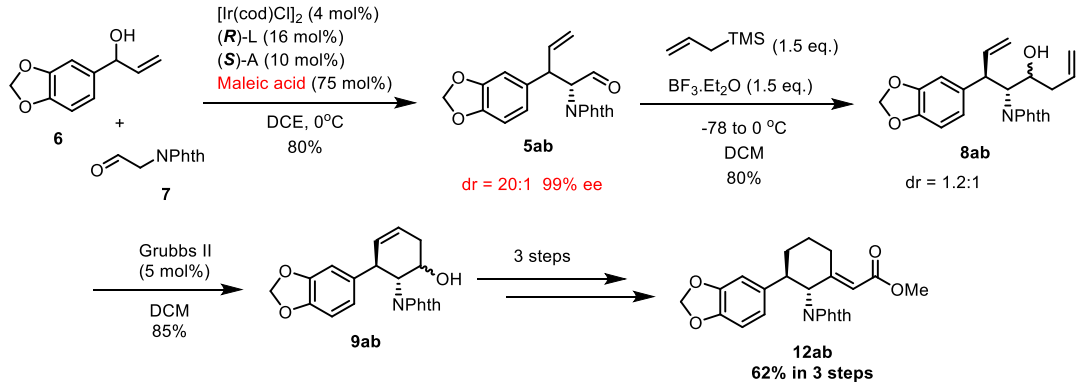
Scheme 23 synthesis of (±)-*γ*-Lycorane **3** by Rocaboy and a co-worker

In 2020, Tang and a co-worker[20] synthesized racemic *γ*-lycorane **11** which was *cis/cis* fused aza-tetracyclic structure. Its involved a one-pot reaction between a palladium(II)-catalyzed aerobic aza-Wacker reaction, followed by a palladium(0)-catalyzed Heck reaction to afford compound 1r and 6r which converted to lycorane **11** in 2 steps via hydrogenation and reduction of the lactam carbonyl (Scheme 16)

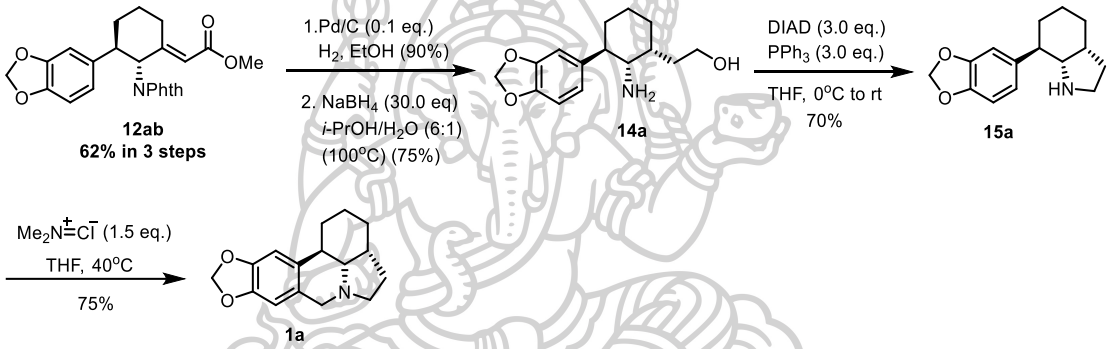


Scheme 24 One-pot reaction; aza-Wacker reaction and Heck reaction of Tang and a co-worker

In 2022, Zhang and a co-worker[21] reported the first collectively asymmetric total synthesis of (+)-*α*-, (+)-*β*-, (+)-*γ*-, and (-)-*δ*-Lycoranes. The key reaction of this synthesis as an asymmetric, stereodivergent Ir/amine dual catalytic α-allylation of 2-phthalimidoactadehyde. benzylic alcohol **6** was combined with 2-phthalimido-acetaldehyde **7** using proline-derived amine (*S*)-A, Carreira ligand (*R*)-L, and maleic acid to give aldehyde 5ab. Sakurai reaction and ring closing metathesis gave the A-C ring fragment **9** which was converted to carbomethoxymethylene-cyclohexene intermediated **12** which was the common intermediate for total synthesis of (+)-*α*-Lycorane (**1a**) and (+)-*β*-Lycorane (**1b**) (Scheme 17).

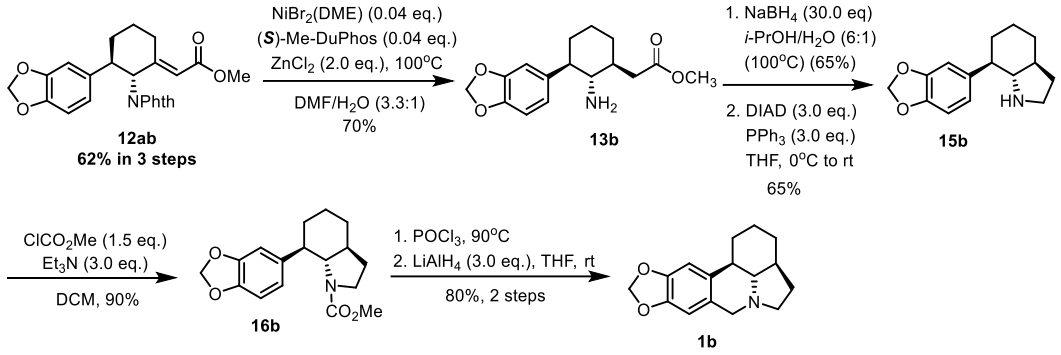


Scheme 25 Synthesis of intermediated 12 of total synthesis of (+)-α-Lycorane (**1a**) and (+)-β-Lycorane (**1b**) by Zhang and a co-worker



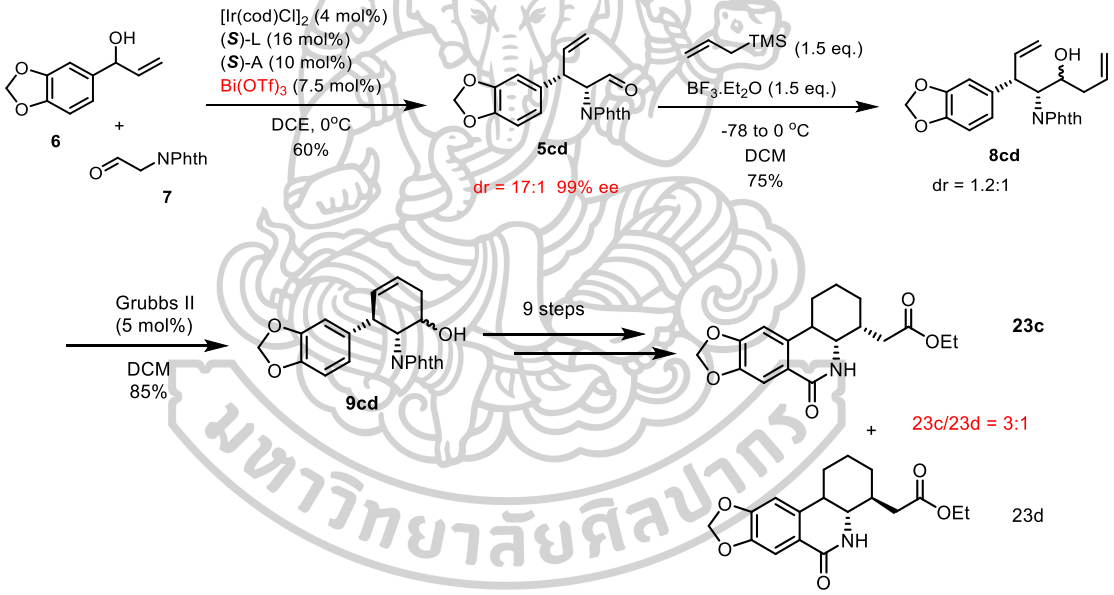
Scheme 26 Synthesis of (+)-α-Lycorane (**1a**) by Zhang and a co-worker

Intermidiate **12ab** was converted to amino alcohol 14a with a high stereoselectivity from hydrogenation using palladium(0) in charcoal. This was followed by intramolecular nucleophilic Mitsunobu reaction to give indoline **15a**. To complete the synthesis, (+)-α-Lycorane (**1a**) could be synthesized from indoline **15a** via Pictet Spengler reaction in 75% yield (Scheme 18). An epimer of (+)-α-Lycorane (**1a**), (+)-β-Lycorane (**1b**) could be generated using nickel-catalyzed asymmetric transfer hydrogenation of intermediated **12** to give **13b** in 70%. and reduction of methyl ester followed by intramolecular Mitsunobu reaction to afford **15b** which was converted to carbamate **16b**. This was converted to **1b** via an oxo-lycorane intermediate by reaction with $POCl_3$ and reduction with lithium aluminum hydride in 80% in two steps (Scheme 19).



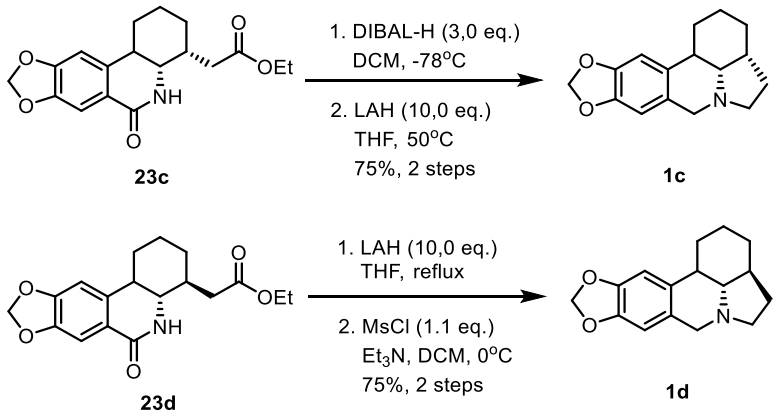
Scheme 27 Synthesis of (+)-*β*-Lycorane (**1b**) by Zhang and a co-worker

Next, Synthesis of (+)-*γ*-, and (-)-*δ*-Lycorane, also used the same precursor as previous synthesis. However, the step of the combination was different. In this synthesis they used Carreira ligand (*S*)-A, (*S*)-L, and $Bi(OTf)_3$ instead, and after **11** steps this route gave a mixture of precursors **23c** and **23d** (Scheme 20).



Scheme 28 Synthesis of precursor **23c** and **23d** by Zhang and a co-worker

(+)-*γ*-Lycorane (**1c**) and (-)-*δ*-Lycorane (**1d**) were completed in 2 steps. Compound **23c** underwent intramolecular reductive amination via methyl ester reduction to aldehyde, imine formation/reduction with DIBALH. LAH reduction of the lactam carbonyl gave (+)-*γ*-Lycorane (**1c**), 75% in two steps. (-)-*δ*-Lycorane (**1d**) could be synthesized from minor compound **23d** via reduction using LAH followed by mesylate formation and intramolecular displacement by the isoquinoline N to close the D ring and gave (-)-*δ*-Lycorane (**1d**) 65% in two steps (Scheme 21).

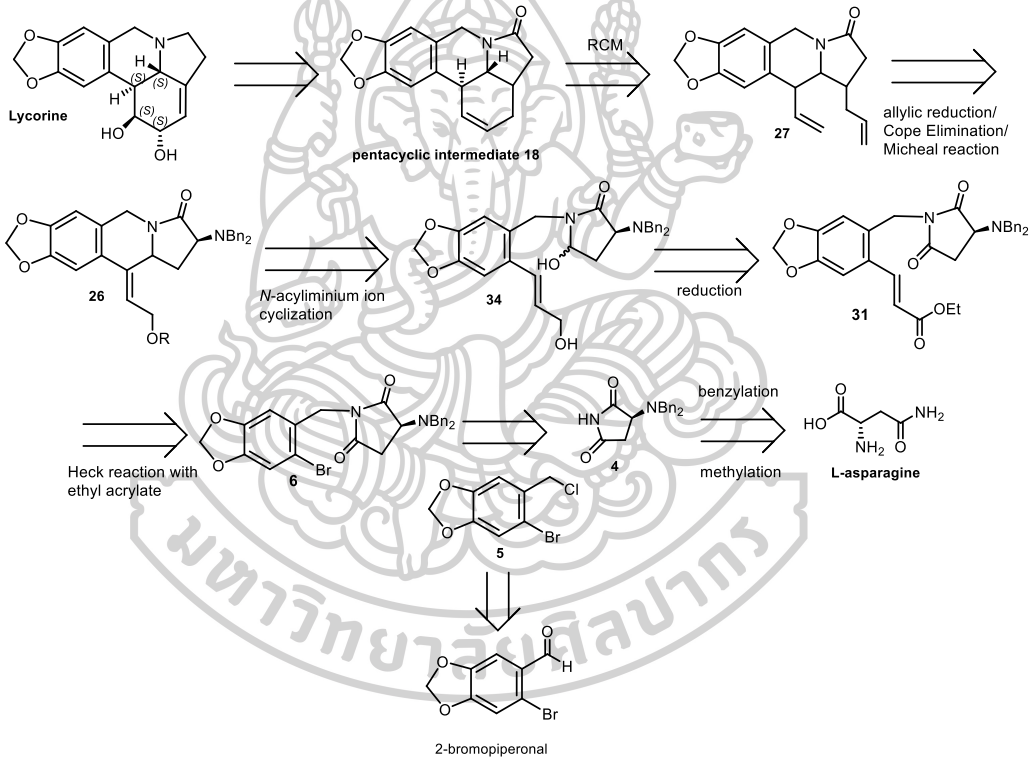


Scheme 29 Synthesis of (+)-γ-Lycorane (**1c**) and (-)-δ-Lycorane (**1d**) by Zhang and a co-worker

CHAPTER 3
SYNTHESIS STUDY

We have been studying the synthesis of Lycorine in many synthetic routes. In this research, I will discuss Heck reaction which is the key reaction for our approach toward lycorine. Starting with L-asparagine derivative as a chiral starting material with a stereogenic center bearing a dibenzylamino group that can be used for controls of regioselectivity and stereoselectivity of the reactions in the synthetic route. Our synthesis plan for lycorine utilizes chiral dibenzylamino succinimide intermediate which could be prepared from L-asparagine in a few steps sequence.

Retrosynthetic analysis I of lycorine



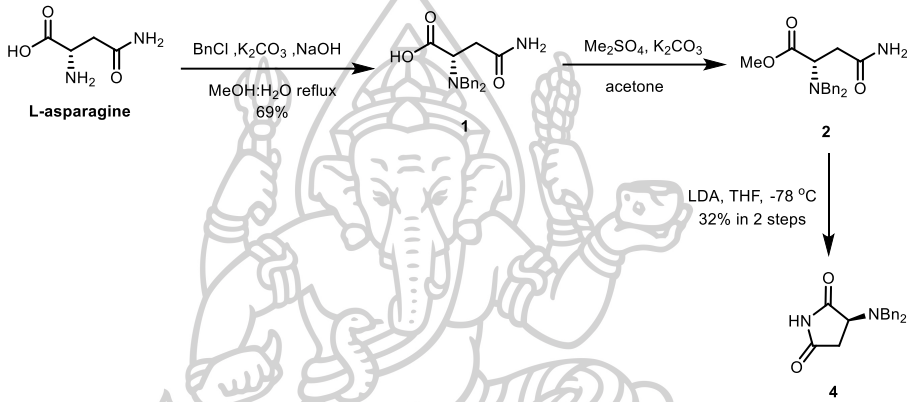
Scheme 30 Retrosynthetic analysis I of lycorine

Scheme 22 illustrates our first retrosynthetic analysis of lycorine. Pentacyclic intermediate **18** is the advanced intermediate of Lycorine which could be prepared from diene **27** via RCM. The ABD core-diene **27** could be prepared from allylic reduction with transposition of the C=C bond, Cope elimination and Michael addition of dibenzylamino lactam **26**. The B ring of lycorine is envisioned to be derived from reduction and *N*-acyliminium ion cyclization of 3-*N*,*N*-dibenzyl-*N*-(ethoxyacryloarylmethyl)succinimide **31** which could be made from intermolecular Heck reaction between *N*-aryl-methyl succinimide **6** and ethyl acrylate. *N*-aryl-

methylsuccinimide **6** could be synthesized from 3-dibenzylaminosuccinimide **4** and 2-bromoarylmethyl chloride **5** via N-alkylation and 2-bromoarylmethyl chloride **5** could be made from 2-bromopiperonal in 2 steps.

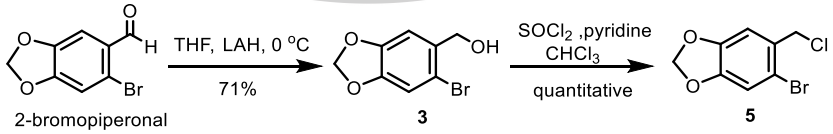
Synthetic study I of lycorine

The synthesis study of lycorine started from the benzylation of commercially available L-asparagine in basic condition with benzyl chloride, NaOH, and K_2CO_3 in MeOH and H_2O to give *N,N*-dibenzyl-L-asparagine **1** in 69% yield. Methylation of *N,N*-dibenzyl- L-asparagine **1** in Me_2SO_4 and K_2CO_3 in acetone gave methyl ester **2** followed by imide formation using LDA in THF to deliver desired succinimide **4** in 32% yield in 2 steps (Scheme 23).



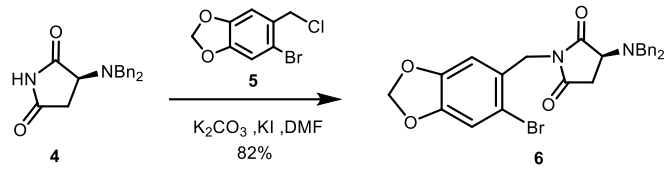
Scheme 31 Synthesis of 3-dibenzylaminosuccinimide **4** from L-asparagine

According to the retrosynthetic analysis, *N*-arylmethylsuccinimide **6** could be derived from *N*-alkylation of succinimide **4** and 2-bromoarylmethyl chloride **5**. 2-Bromoarylmethyl chloride **5** could be synthesized from 2-bromopiperonal by reduction with $LiAlH_4$ to give 2 -bromopiperonol **3** in 71% yield. The alcohol was reacted with $SOCl_2$ and pyridine in $CHCl_3$ to affect chlorination and yielded the desired product **5** in excellent yield (Scheme 24).



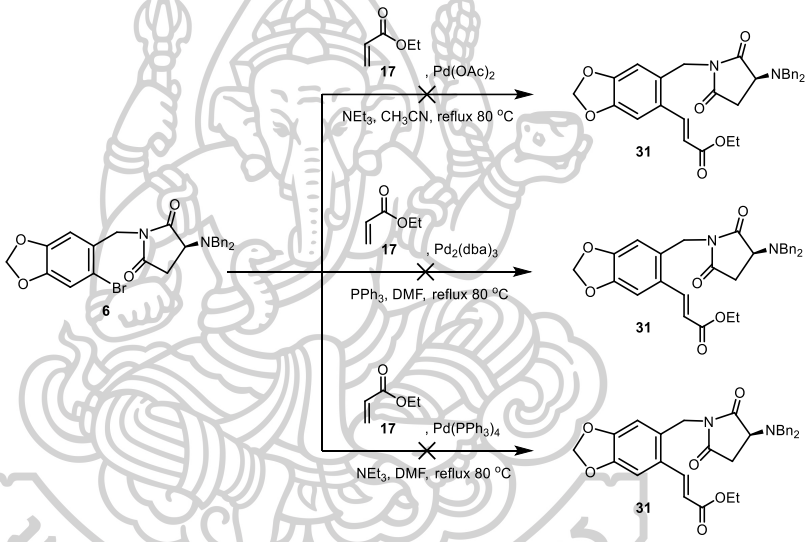
Scheme 32 Synthesis of 2-bromoarylmethyl chloride **5** from 2-bromopiperonal

After obtaining precursors **4** and **5**, we synthesized *N*-arylmethylsuccinimide **6** by *N*-alkylation using K_2CO_3 and KI in DMF to give 82% yield (Scheme 25). N-arylmethyl-succinimide **6** is a key intermediate of this lycorine synthesis plan.



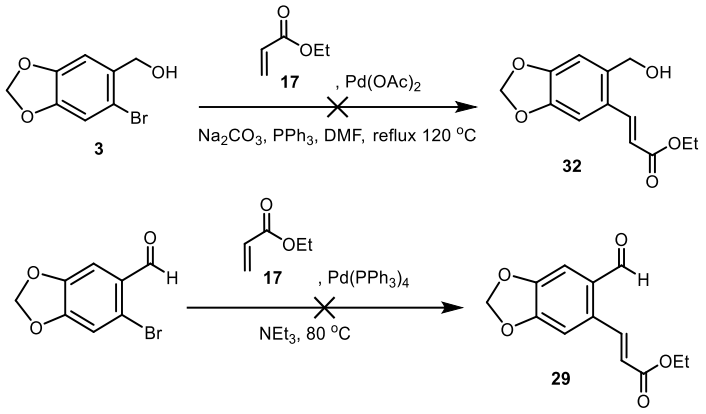
Scheme 33 Synthesis of *N*-arylmethylsuccinimide **6**

From retrosynthetic analysis, we investigated intermolecular Heck reaction of *N*-bromoarylmethylsuccinimide **6** with ethyl acrylate **17**. A variety of reaction conditions were investigated. Different palladium catalysts such as $Pd(OAc)_2$, $Pd_2(dba)_3$ and $Pd(PPh_3)_4$ were trialed, however we failed to obtain the desired product (Scheme 26). We think *N*-bromoarylmethylsuccinimide **6** has too much steric hindrance. we then tried to change the substrate.



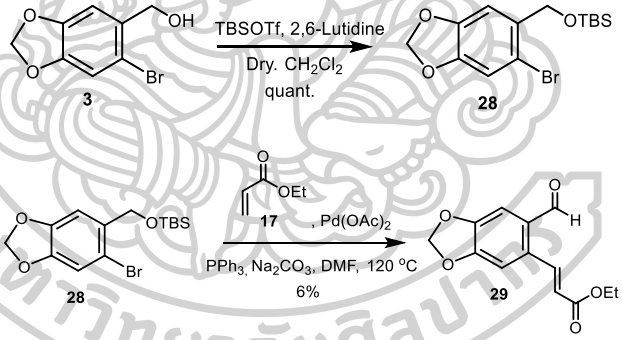
Scheme 34 A variety of reaction conditions of heck reaction

Next, we investigated Heck reaction of 2-bromopiperonal and 2-bromopiperonol **3** with ethyl acrylate. However, both of them did not yield the desired product **31** (Scheme 27). 2-Bromopiperonal reacted with ethyl acrylate in the presence of $Pd(PPh_3)_4$ and triethylamine did not give the coupling product. In case of 2-bromopiperonol **3**, we found that the benzylic hydroxyl group was oxidized to 2-bromopiperonal in the presence of $Pd(OAc)_2$, Na_2CO_3, PPh_3 in DMF and Heck reaction did not proceed.



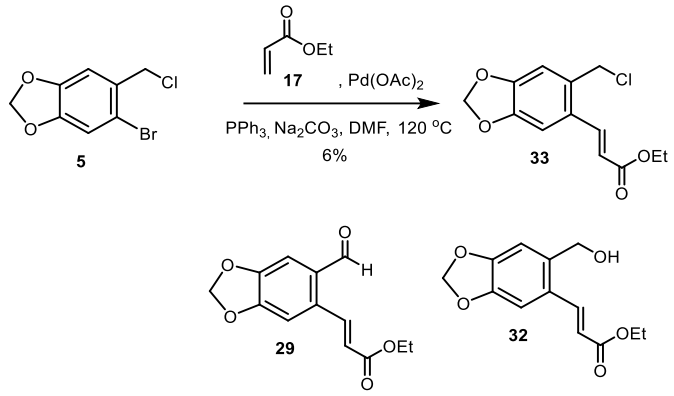
Scheme 35 Heck reaction of 2-bromopiperonal and 2-bromopiperonol **3** with ethyl acrylate

To prevent benzylic oxidation, we protected the alcohol as a TBS-silyl ether with TBSOTf to give silyl ether **28** in quantitative yield (Scheme 10). Then silyl ether **28** reacted with ethyl acrylate **17** in the presence of $Pd(OAc)_2$, Na_2CO_3, PPh_3 in DMF via Heck reaction to give ethyl aryl acrylate **29** in 6% yield with concomitant desilylation of silyl group and subsequent oxidation to the aldehyde was also observed (Scheme 28).



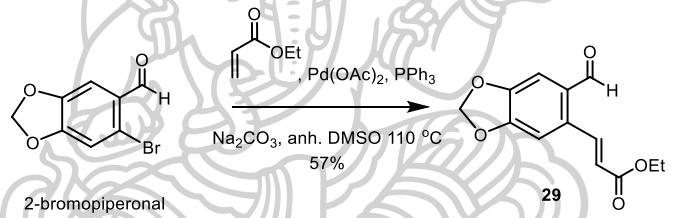
Scheme 36 Heck reaction of silyl ether **28** and ethyl acrylate

The result suggested that the benzylic alcohol and its silyl ether were not compatible with the reaction condition and prone to oxidation. Once oxidation of the alcohol to aldehyde occurred Heck reaction did not proceed in the selected conditions. We then attempted Heck reaction of 2-bromoarylmethyl chloride **5** with ethyl acrylate using $Pd(OAc)_2$, Na_2CO_3, PPh_3 in refluxing DMF. The expected product **33** was obtained in 6% yield. We also found that hydrolysis of benzylic chloride to give compound **32** as well as subsequent oxidation to the corresponding aldehyde **29** were also observed (scheme 29).



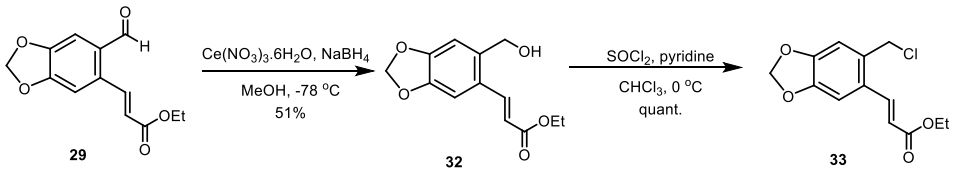
Scheme 37 Heck reaction of 2-bromoarylmethyl chloride **5**

All the results suggested that benzylic oxidation was difficult to prevent. Therefore we explored for a reaction condition for Heck coupling that would be compatible with the aldehyde. Gratifyingly, 2-bromopiperonal reacted with ethyl acrylate using $Pd(OAc)_2$, Na_2CO_3, and PPh_3 in DMSO as solvent afforded the desired product **29** in 57% yield (Scheme 30).



Scheme 38 Synthesis of 2-(ethyl arylacrylate)piperonal **29**

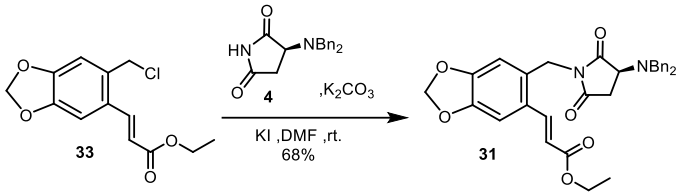
Then, 2-(arylacrylate)piperonal was converted to chloride **33** with reduction. We were cautious to find a selective condition that would affect the reduction of the aldehyde without hydride addition to the acrylate moiety in a 1,4-addition mode. This was achieved using a Luche-type reduction with $Ce(NO_3)_3.H_2O$ and $NaBH_4$ in MeOH to give ethyl 2-(arylacrylate) piperonol **32** in 51% yield. This was followed by chlorination with thionyl chloride and pyridine in $CHCl_3$ to give 2-(ethyl arylacrylate)piperonyl chloride **33** (Scheme 31).



Scheme 39 Synthesis of 2-(ethyl arylacrylate)piperonyl chloride **33**

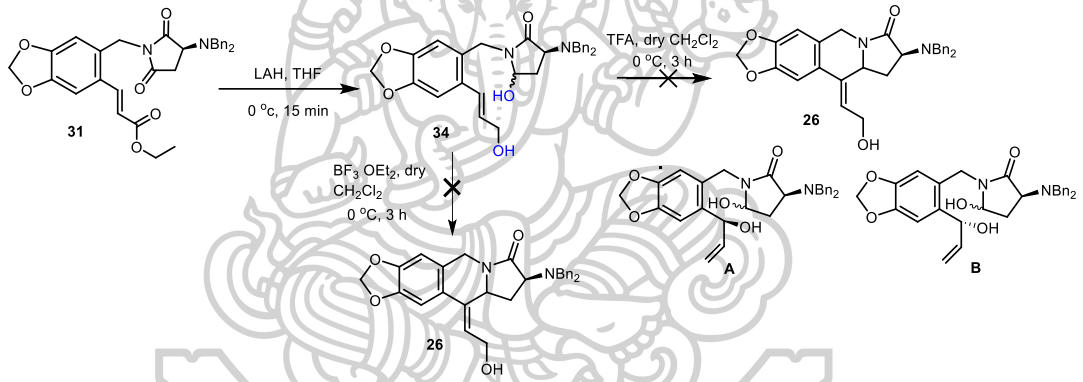
After obtaining precursors succinimide **4** and 2-(ethyl arylacrylate)piperonyl chloride **33**, we then synthesized the key intermediate **31**. 3-*N*,*N*-dibenzyl-N-(ethoxyacryloarylmethyl)-succinimide **31** could be prepared from *N*-alkylation of

succinimide **4** with benzylic chloride **33** to give the desired product in 68% yield (Scheme 32)



Scheme 40 Synthesis of 3-N,N-dibenzyl-N-(ethoxyacryloarylmethyl)succinimide **31**

The next task is to prepare the precursor for the key *N*-acyliminium ion cyclization to form the ABD core of lycorine. This was achieved by reduction of the imide and the ethyl ester concomitantly using $LiAlH_4$ in dry THF to give hydroxylactam **34**. With the key precursor in hand, we attempted the *N*-acyliminium ion cyclization of hydroxylactam **34** using 3 acid catalysts; TMSOTf, trifluoroacetic acid (TFA) and BF_3-OEt_2 in dry CH_2Cl_2.



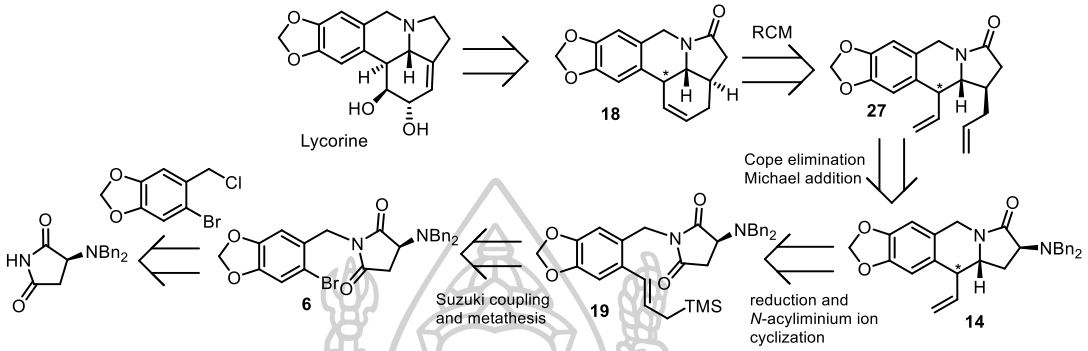
Scheme 41 Synthesis of ABD core structure **26**

Unfortunately, none of the conditions has delivered the desired cyclized product. TMSOTf gave a complex mixture of crude product which could not be identified. In the case of TFA, isomerization of the primary allylic alcohol to two diastereomers of benzylic alcohols without participation of the hydroxylactam in the reaction (scheme 33).

Retrosynthetic analysis II of lycorine

From the results of attempted *N*-acyliminium ion cyclization, we assumed that the 3-arylallyl alcohol in precursor **34** was not a sufficient nucleophile for our purpose. Therefore, an alternative route was devised. We envision that the B ring can be formed using allylsilane as the nucleophile to react intramolecularly with the *N*-acyliminium ion derived from the hydroxylactam in aza-Sakurai type reaction. The retrosynthetic analysis II for lycorine is shown in scheme 34. The ABD core diene **27** is the common intermediate used in retrosynthetic analysis I. It is envisioned

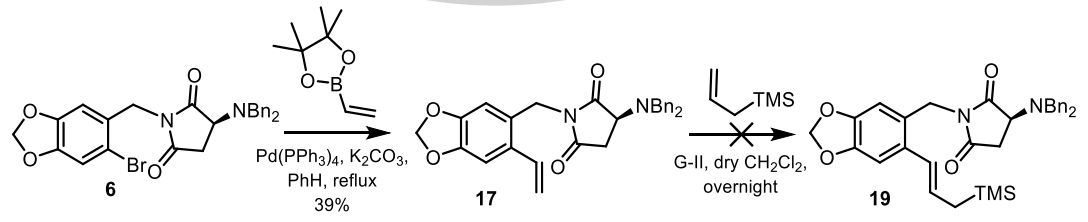
to be derived from Cope elimination and 1,4-addition with allyl-metal nucleophile of vinyl-ABD core **14**. This intermediate, in turn, would be derived from reduction and *N*-acyliminium ion cyclization with the allylsilane in compound **19**. This compound is envisioned to be derived from Suzuki coupling reaction of *N*-bromoarylmethylsuccinimide **6** with vinyl boronic acid and subsequent metathesis with TMSallylsialne.



Scheme 42 Retrosynthetic analysis II

Synthetic study II of lycorine

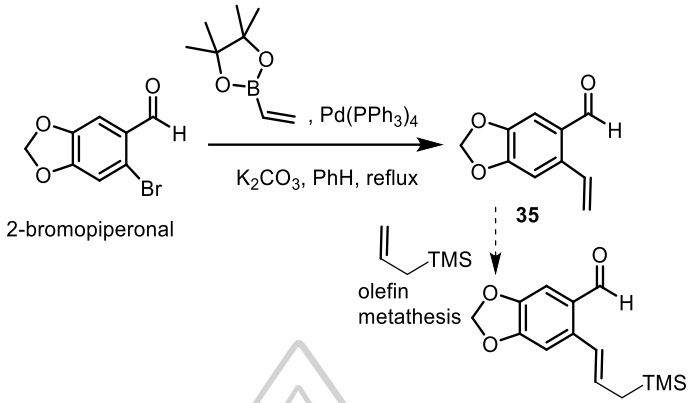
As previously described, the *N*-bromoarylmethylsuccinimide **6** was synthesized from succinimide **4** which reacted with 2-bromoarylmethyl chloride **5** via *N*-alkylation**.** According retrosynthetic analysis we would like to generate allylsilane **19**. In the first step, *N*-bromoarylmethylsuccinimide **6** reacted with vinyl boronic acid pinacol ester via Suzuki coupling using $Pd(PPh_3)_4$ as the catalyst and K_2CO_3 as base in benzene to afford the desired vinylarene **17** in 39% yield. Unfortunately, subsequent olefin metathesis with allyltrimethylsilane in the presence of either Grubbs' 2nd generation catalyst or Hoveyda-Grubbs' 2nd generation catalyst did not give a desired product. This was similar to the failure to perform Heck reaction with *N*-bromoarylmethylsuccinimide **6**. We assumed that there was too much steric hindrance around the reaction center (Scheme 35).



Scheme 43 Synthesis of allylsilane **19**

After that we try to change a substrate of Suzuki coupling reaction to 2-bromopiperonal. The conditions of the reaction will be similar to the previous synthesis. That gave desired product in low yield and the material was not enough for attempting olefin metathesis with allyltrimethylsilane in the next step (Scheme 36).

The result of Suzuki reaction was unreliable and depends strongly on the quality of the vinyl boronic acid pinacol ester used each time.



Scheme 44 Synthesis of vinylpiperonal **35**

From the difficulty in forming the allylsilane for intramolecular *N*-acyliminium ion cyclization to form the ABD core which we expected that it is resulted from steric hindrance around the reaction center, we turned our attention to an intermolecular version of the reaction. In this regard, reaction of arylallylsilane with the chiral hydroxylactam in the aza-Sakurai version can couple the A and D ring by forming C12b and C3a bond prior to forming C7 and C8a bond.

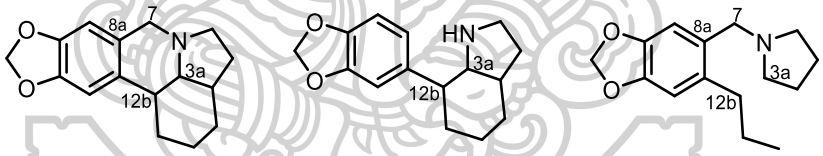
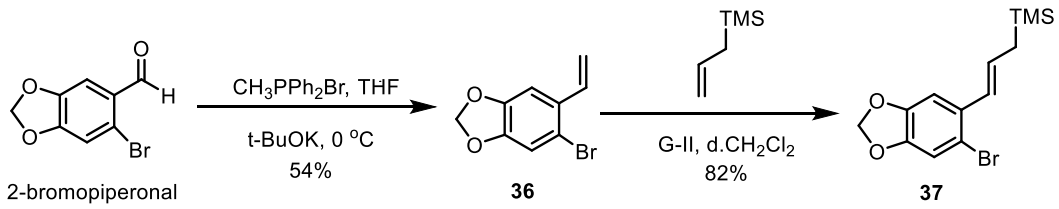


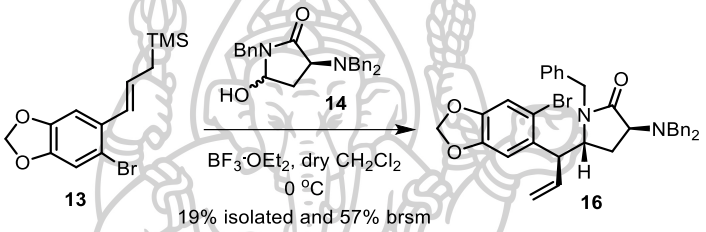
Figure 5 Forming of A and D ring of Lycorine core structure

We started to synthesize arylallylsilane with Wittig olefination of 2-bromopiperonal using methyl phosphoniumbromide, *t*-BuOK in THF to give 2-bromoallyl **36** in 54% yield. Subsequent reaction with allyltrimethylsilane via metathesis using Grubbs' 2nd generation catalyst in dry CH_2Cl_2 afforded the desired product **37** in 82% yield (Scheme 37).



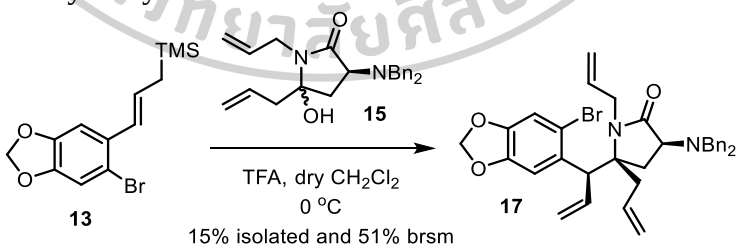
Scheme 45 Synthesis of 2-bromoallyl **36** and 2-bromoarylallylsilane **37**

After obtaining 6-bromoarylallylsilane **37** and the hydroxylactams, we investigated the aza-Sakurai reactions. First, 6-bromoaryl-allylsilane **37** reacted with *N*-Bn-hydroxy-lactam **38** in the presence of $BF_3{\cdot}OEt_3$ (0.06 mL) and dry CH_2Cl_2 as the solvent to give the coupled product **39** in 57% brsm (Scheme 46). The product was obtained as a single diastereomer (d.r.>20:1, ^1H NMR detection limit). The dibenzylamino group exerted the stereocontrol of the reaction. The configuration of the product was assigned according to the approach of the allylsilane from the opposite side of the dibenzylamino on the lactam ring. The assignment of the configuration of compound **39** was based on NOESY experiments in which correlations between olefinic protons at 5.8 and 5.1 ppm with the methine proton CH-N at 4.1 ppm on newly generated adjacent stereogenic centers were observed, indicating that the vinyl group and the methine proton are *cis*. This C-C bond formation corresponds to the C4a-C10b linkage in lycorine synthesis.



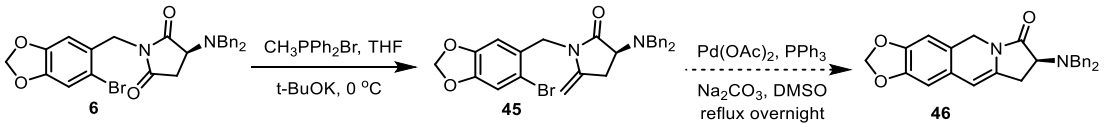
Scheme 46 Synthesis of 2-N-Bn-(6-bromopiperonyl)- pyrrolidine **39**

Secondly, 6-bromoarylallylsilane **37** reacted with *N*-allyl-γ-allylhydroxylactam **41** in the presence of TFA (0.04 mL) as mediator in dry CH_2Cl_2 to give the coupled product **42** in 51% brsm (Scheme 47). The assignment of the configuration of compound **42** was based on the same analogy as that of compound **39**. The lower yield of this reaction could be attributed to the difficulty in forming the quaternary center with intermolecular reaction. The C-C bond formation corresponds to the C4-C5 linkage in cephalotaxine synthesis. In both reactions, the unreacted allylsilane **37** and hydroxylactam **38** or **41** were recovered.



Scheme 47 Synthesis of 2-*N*-allyl-(6-bromopiperonyl) pyrrolidine **42**

Meanwhile, we try the Wittig olefination of *N*-arylmethylsuccinimide **6** with methylphosphoniumbromide, *t*-BuOK in THF to give *N*-vinylsuccinimide **45** and then we expect to generate the B ring using intramolecular Heck reaction as shown in Scheme 39.



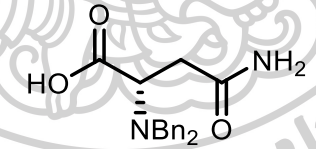
Scheme 47 Wittig olefination of *N*-arylmethylsuccinimide **6**

CHAPTER 4
EXPERIMENTAL PROCEDURE

General

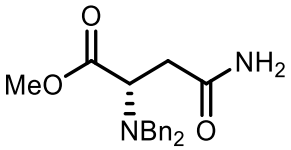
Starting materials and reagents were obtained from commercial sources and were used without further purification. Solvents were dried by distillation from the appropriate drying reagents immediately prior to use. Tetrahydrofuran was distilled from sodium and benzophenone under argon. Toluene and dichloromethane were distilled from calcium hydride under argon. Moisture and air-sensitive reactions were carried out under an atmosphere of argon. Reaction flasks and glassware were oven-dried at 105 ^{o}C overnight. Unless otherwise stated, concentration was performed under reduced pressure. Analytical thin-layer chromatography (TLC) was conducted using Fluka precoated TLC plates (0.2 mm layer thickness of silica gel 60 F-254). Compounds were visualized by ultraviolet light and/or by heating the plate after dipping in a 1% solution of vanillin in 0.1 M sulfuric acid in EtOH. Flash chromatography was carried out using Scientific Absorbents Inc. silica gel (40 mm particle size). Optical rotations were measured with a Krüss digital polarimeter P3000 series at ambient temperature using a 1 dm cell with 1 mL capacity which a value was reported in grams per 100 mL. Infrared (IR) spectra were recorded on a Perkin Elmer spectrum 100 FT-IR spectrometer. Proton and carbon nuclear magnetic resonance (NMR) spectra were obtained using a Bruker Avance-300 spectrometer.

1. Synthesis of *N*, *N*-dibenzyl-L-asparagine **1**



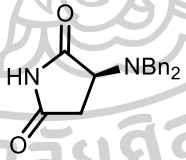
L-Asparagine (5.16 g, 0.039 mol) benzyl chloride (18 mL, 0.156 mol), NaOH (3.92 g, 0.098 mol), and K_2CO_3 (13.5 g, 0.098 mol) dissolved in MeOH : H_2O ratio 1:1 (100 mL) reflux 24 hours. When finished, added 1 M HCl (100 mL) followed by extracted by CH_2Cl_2 (3 ×150 mL) and removed water from organic phase using anh. Na_2SO_4Next concentrated under reduced pressure. Purified by plate chromatography (silica gel, EtOAc pure) to give yellow oil product (8.35 g, 69%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.13 (m, 10H), 6.00 (br s, 1H), 5.37 (br s, 2H), 5.30 (s, 2H), 4.08 (d, *J* = 13.4 Hz, 2H), 4.03-3.87 (m, 3H), 3.00 (dd, *J* = 16.3, 6.4 Hz, 1H), 2.72 (dd, *J* = 16.3, 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 172.3, 135.4, 129.6, 128.9, 128.3, 59.8, 54.8, 33.4; $[a]_D^{25}$-48.8 (*c* 1.7, CHCl3); ν_{max} (film) 3192, 3064, 2924, 2852, 1669, 1495, 1456, 1365, 1285, 1182 cm^{-1}; ESI-HRMS calculated for $C_{18}H_{20}N_2NaO_3$ $[M+Na]^+$ 335.1368.

2. Synthesis of methyl dibenzyl-L-asparaginate **2**



To a solution of dibenzyl-L-asparagine **1** (4.06 g, 12.3 mmol) in acetone (50 mL) was added K_2CO_3 (2.55 g, 18.43 mmol) and Me_2SO_4 (1.75 mL, 18.4 mmol) and the mixture was stirred at room temperature overnight. The mixture was filtered to remove K_2CO_3 and to the solution was added dropwise sat. aq. NH_4Cl (30 mL). Then the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with 5% NaOH (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 2:1 hexane/EtOAc) to give methyl dibenzyl-L-asparaginate (3.2) (1.97 g, 59%) as a colorless oil. R_f (2:1 hexane/EtOAc) 0.08; ^{1}H NMR (300 MHz, CDCl3) δ 7.42-7.17 (m, 10H), 6.16 (brs, 1H), 5.49 (brs, 1H), 3.93-3.82 (m, 3H), 3.80 (s, 3H), 3.57 (d, J = 13.6 Hz, 2H), 2.68 (dd, J = 15.0, 6.0 Hz, 1H), 2.61 (dd, J = 15.0, 6.0 Hz, 1H); ^{13}C NMR (75 MHz, CDCl3) δ 173.4, 172.4, 139.0 (2C), 129.0 (4C), 128.5 (4C), 127.3 (2C), 58.3, 54.9 (2C), 51.6, 35.6; $[\alpha]^{D}_{25}$ -103.8 (c 1.6, $CHCl_3$); ν_{max} (film) 3349, 3355, 3196, 2951, 2844, 1730, 1672, 1495, 1453, 1366, 1173 cm^{-1}; ESI-HRMS calculated for $C_{19}H_{22}N_2NaO_3$ $[M+Na]^+$ 349.1523, found 349.1520.

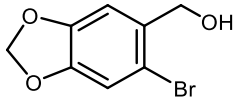
3. Synthesis of succinimide **4**



To a solution of *N*, *N*-dibenzyl-L-asparagine **1** (1.25 g, 3.83 mmol) in dry THF (10 mL) under argon atmosphere at -78 °C was added LDA (4.82 mL of 1.59 M solution, 7.67 mmol) and the mixture was stirred for 2 hours at -78 °C. To this mixture was added dropwise sat. aq. NH_4Cl (20 mL) and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 4 : 1 hexane/EtOAc) to give chiral succinimide 3.3 (2.50 g, 32%) as a white crystal. R_f (2:1 hexane/EtOAc) 0.38; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.21 (br s, 1H); 7.40 - 7.20 (m, 10H), 3.94 (dd, *J*= 8.7, 5.7 Hz,1H), 3.82 (d, *J*= 13.5 Hz,2H, 3.62 (d, *J*= 15 Hz, 2H), 2.78 (dd *J*= 18, 9 Hz, 1H), 2.60 (dd *J*= 16.5, 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.56 -C, 176.19 -C, 138.22 -C, 128.77 -CH, 128.48 -CH, 127.93 -CH, 58.98 -CH, 54.71 -CH_2, 31.84 -

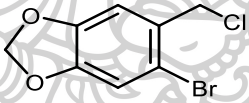
CH_2; ν_{max} (film) 3234, 2923, 2849, 1782, 1705, 1494, 1454, 1338, 1191, 1165 cm^{-1}; ESI-HRMS calculated for $C_{18}H_{18}N_2O_2$ $[M+H]^+$ 317.1260, found 317.1260.

4. Synthesis of 2-bromopiperanol **3**



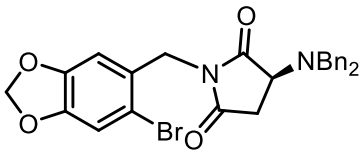
To a solution of 2-bromopiperonal (3.00 g, 13.1 mmol) in dry THF (10 mL) under argon atmosphere at 0 °C was added $LiAlH_4$ (0.99 g, 26.2 mmol) and the mixture was stirred for 30 minutes at 0 °C. To this mixture was added dropwise sat. aq. $NaHCO_3$ (5 mL). Then the mixture was extracted with EtOAc (3×15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 4:1 hexane/EtOAc) to give 2-bromopiperonol **3** (2.15 g, 71%) as a brown crystal. R_f (2:1 hexane/EtOAc) 0.53; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.97 (s, 1H), 6.95 (s, 1H), 5.97 (s, 2H), 4.62 (s, 2H), 2.30 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.72 -C, 147.49 -C, 133.06 -C, 133.06 -CH, 112.64 -C, 109.06 -CH, 101.77 -CH_2, 64.88 -CH_2.

5. Synthesis of 2-bromoarylmethyl chloride **5**



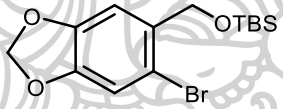
To a solution of 2-bromopiperanol **3** (2.15 g, 9.31 mmol) in $CHCl_3$ (10 mL) under argon atmosphere was added pyridine (0.70 mL, 8.75 mmol) and the mixture was stirred at 0 °C. Then, it was added $SOCl_2$ (0.74 mL, 10.2 mmol) and stirred overnight. The reaction was quenched with adding 5 M HCl (10 mL). The mixture was washed with water (2×20 mL) and 10% Na_2CO_3 (100 mL). Then the organic layer was extracted with water (2×20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The product was obtained without purification to give 2-bromoarylmethyl chloride **5** (2.08 g, 76%). R_f (4:1 hexane/EtOAc) 0.83; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (s, 1H), 6.91 (s, 1H), 5.97 (s, 2H), 4.61 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.50 -C, 147.43 -C, 129.54 -C, 1145.01 -CH, 112.95 -C, 110.22 -CH, 102.08 -CH_2, 46.49 -CH_2.

6. Synthesis of *N*-arylmethylsuccinimide **6**



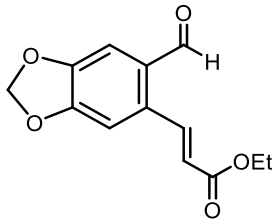
To a solution of succinimide **4** (1.20 g, 4.09 mmol) in DMF (15 mL) under argon atmosphere was added KI (0.082 g, 0.49 mmol), K_2CO_3 (2.66 g 8.18 mmol), and 2-Bromoarylmethyl chloride **5** (1.23 g, 4.91 mmol) and the mixture was stirred for 3 hours. When finished, to this mixture was base filtered and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with water (5 × 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product was obtained without purification (silica gel, hexane : EtOAc 4:1) as a yellow oil (1.58 g, 68%). R_f (4:1 hexane/EtOAc) 0.52; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.20 (m, 10H), 6.97 (s, 1H), 6.67 (s, 1H), 5.92 (s, 2H), 4.68 (s, 2H), 4.00 - 3.95 (m, 1H), 3.97 (dd, *J*= 9, 6 Hz, 1H), 3.84 (d, *J*= 12 Hz, 1H), 3.67 (d, *J*= 12 Hz, 1H), 2.81 (dd *J*= 18, 9 Hz, 1H), 2.69 (dd *J*= 18, 6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.93, 174.79, 148.01, 147.56, 138.23, 77.58, 77.14, 76.72, 57.52, 54.76, 42.39, 32.38.

7. Synthesis of protected alcohol **28**



To a solution of 2-bromopiperanol **3** (0.2467 g, 1.07 mmol) in dry CH_2Cl_2 (10 mL) under argon atmosphere was added 2,6-Lutidine (0.27 mL 2.35 mmol) followed by TBSOTf (0.54 mL 2.35 mmol) the mixture was stirred at room temperature. To this mixture was added dropwise sat. aq. $NaHCO_3$ and extracted by CH_2Cl_2 (3×30 mL) the combined organic layers were dried over anhydrous Na_2 SO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, hexane : EtOAc 4:1) to give protected alcohol **28** (483.6 mg, quant.) as a brown oil. R_f (4:1 hexane/EtOAc) 0.92; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (s, 1H), 6.83 (s, 1H), 5.83 (s, 2H), 4.51 (s, 2H), 0.74 (s, 9H), -0.11 (s, 6H).

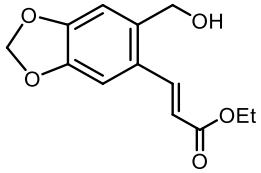
8. Synthesis of aryl acrylate piperonal **29**



Method 1; To a solution ethyl acrylate (0.054 mL, 0.51 mmol) in dimethylformamide (5 mL) under argon atmosphere was added Na_2CO_3 (0.11 g, 1.01 mmol), $Pd(OAc)_2$ (0.011 g, 0.051 mmol), and PPh_3 (0.03 g, 0.10 mmol) was stirred at room temperature. And then was added protected alcohol **28** (0.1581 g, 0.506 mmol) and the mixture was refluxed for 24 hours. When finished, the mixture was filtered by celite and extracted with H_2O (5×70 mL) and EtOAc (2×70 mL) the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, hexane : EtOAc 4:1) to give product **29** (7.3 mg, 6%) as a white powder.

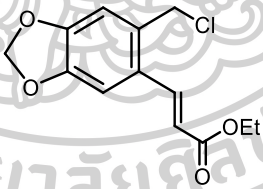
Method 2; To a solution ethyl acrylate (208.1 mL, 1.95 mmol) was added Na_2CO_3 (414.0 mg, 3.91 mmol), $Pd(OAc)_2$ (5 mol%), and PPh_3 (51.0 mg, 0.20 mmol) in DMSO (6 mL) under argon atmosphere. The mixture was slightly stirred. And then took 2-bromopiperonal was dissolved in DMSO mixed in the previous mixture. and the mixture was refluxed overnight at 110 ^oC. The mixture was filtered with celite, extracted by H_2O (6x30 mL), the combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure The crude product was purified by column chromatography (silica gel, hexane : EtOAc 4:1) to desired product **29** (22.2 mg, 46%). R_f (4:1 hexane/EtOAc) 0.45; ^1H NMR (300 MHz, $CDCl_3$) δ 10.27 (s, 1H), 8.43 (d, *J*= 18 Hz, 1H), 7.26 (s, 1H), 7.06 (s, 1H), 6.32 (d, *J*= 12 Hz,1H), 6.10 (s, 2H), 4.30 (q, *J*= 7 Hz, 2H), 1.34 (t, *J*= 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.8 -CH, 165.3 -C, 151.7 -C, 148.5 -C, 138.5 -CH, 132.9 -C, 128.6 -C, 121.4 -CH, 108.1 -CH, 105.8 -CH, 101.5 $-CH_2$, 59.9 $-CH_2$, 32.38 $-CH_3$; ν_{max} (film) 1712, 1670, 1633, 1504, 1483, 1379, 1263, 1197 cm^{-1}.

9. Synthesis of aryl acrylate piperonol **32**



To solution **29** (177.2 mg, 0.71 mmol) dissolved MeOH (5 mL) at -78 ^{o}C under argon atmosphere was added $Ce(NO_3)_3.6H_2O$ (465.0 mg, 0.11 mmol) in the previous solution and stirred 5 minutes. Followed by added $NaBH_4$ (40 mg, 0.11 mmol) and keep stirring 1 hours. When finished took the mixture added sat. NH_4Cl, stirred and removed MeOH by concentrated under reduced pressure. Next extract with Et_2O (3x20 mL) followed by brine solution (20 mL). the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure The crude product was purified by column chromatography (silica gel, hexane : EtOAc 4:1) to give product **32 (**35.9 mg, 51%) as a white powder. R_f (2:1 hexane/EtOAc) 0.48; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, *J*= 15.7 Hz, 1H), 7.06 (s, 1H), 6.92 (s, 1H), 6.23 (d, *J*= 15.7 Hz, 1H), 5.99 (s, 2H), 4.74 (s, 2H), 4.25 (q, *J*= 7.1 Hz, 2H), 1.33 (t, *J*= 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0 -C, 149.1 -C, 147.0 -C, 140.4 -CH, 135.4 -C, 126.2 -C, 117.2 -CH, 108.8 -CH, 105.58 -CH, 101.4 -CH_2, 61.8 -CH_2, 60.3 -CH_2, 14.0 -CH_3; ν_{max} (film) 3450, 2924, 1708, 1632, 1505, 1481, 1379, 1265, 1180 cm^{-1}.

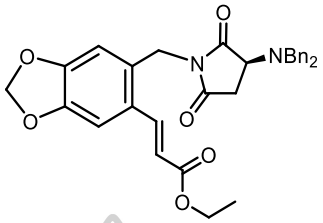
10. Synthesis of arylacrylte chloride **33**



To a solution of **32** (35.9 mg, 0.14 mmol) in $CHCl_3$ (3 mL) under argon atmosphere was added pyridine (0.011 mL, 0.14 mmol) and the mixture was stirred at 0 ^{o}C. Then, it was added $SOCl_2$ (0.012 mL, 0.17 mmol) and stirred overnight. The reaction was quenched with adding 5 M HCl (10 mL). The mixture was washed with water (2×20 mL) and 10% Na_2CO_3 (100 mL). Then the organic layer was extracted with water (2×20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The product was obtained without purification to give **33** in quantitative yield. R_f (4:1 hexane/EtOAc) 0.57; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J*= 15.7 Hz, 1H), 6.96 (s, 1H), 6.74 (s, 1H), 6.19 (d, *J*= 15.7 Hz, 1H), 5.91 (s, 2H), 4.54 (s, 2H), 4.18 (q, *J*= 7.1 Hz, 2H), 1.25 (t, *J*= 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7 -C, 148.3 -C, 147.5 -C, 138.8 -CH, 130.05 -C, 126.8 -C, 118.1 -CH, 109.3 -CH, 105.3 -CH, 100.9 -CH_2, 59.5 -CH_2 ,

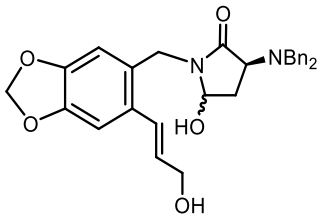
42.3 -CH_2 , 13.4 -CH_3; ν_{max} (film) 2908, 1706, 1633, 1506, 1485, 1366, 1296, 1179, 1038 cm^{-1}.

11. Synthesis of *N*,*N*-dibenzyl ethyl arylacrylo succinimide **31**



To a solution of succinimide **4** (98.1 mg, 0.33 mmol) in DMF (5 mL) under argon atmosphere was added KI (0.5 mg, 0.03 mmol), K_2CO_3 (182.0 mg, 0.56 mmol), and **33** (89.7 mg, 0.33 mmol) and the mixture was stirred for 3 h. When finished, to this mixture was base filtered and the mixture was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with water (5 ×2 0 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The product was obtained without purification (silica gel, hexane : EtOAc 4:1) as a yellow oil (118.9 mg, 68%). R_f (4:1 hexane/EtOAc) 0.27; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, *J*= 15.6 Hz, 1H), 7.45-7.22 (m, 10H), 7.00 (s, 1H), 6.87 (s, 1H), 6.21 (d, *J*= 15.6 Hz, 1H), 5.96 (s, 2H), 4.75 (d, *J*= 14.7 Hz, 1H), 4.67 (d, *J*= 14.7 Hz, 1H), 4.26 (q, *J*= 7.1 Hz, 2H), 3.94 (dd, *J*= 9.0, 5.3 Hz, 1H), 3.82 (d, *J*= 13.6 Hz, 1H), 3.64 (d, *J*= 13.4 Hz, 1H), 2.80 (dd *J*= 18.9, 9.3 Hz, 1H), 2.63 (dd *J*= 18.6, 5.4 Hz, 1H), 1.34 (t, *J*= 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3 -C, 172.3 -C, 164.5 -C, 147.1 -C, 145.8 -C, 138.8 -C, 127.3 -CH, 126.6 -CH, 126.2 -CH, 125.2 -CH, 116.7 -CH, 107.9 -CH, 103.6 -CH, 99.4 -CH_2, 58.2 -CH, 55.0 -CH_2, 52.4 -CH_2, 37.0 -CH_2, 30.1 -CH_2, 12.0 -CH_3. $[\alpha]_{25}^{D}$ -33; ν_{max} (film) 2927, 1702, 1633, 1505, 1486, 1454, 1380, 1336, 1289, 1257, 1178 cm^{-1}.

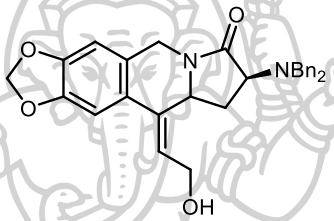
12. Synthesis of diol **34**



To a solution Imide-acrylate (41.5 mg, 0.078 mmol) in THF (8 mL) under argon atmosphere. At 0 ^oC and was added $LiAlH_4$ (6.0 mg, 0.16 mmol). The mixture was stirred for around 15 minutes. When finished, To this mixture was added dropwise sat. aq. $NaHCO_3$ until the gas bubble was gone. Followed by extracted with EtOAc (3x20 mL). The combined organic layers were dried over anhydrous Na_2SO_4

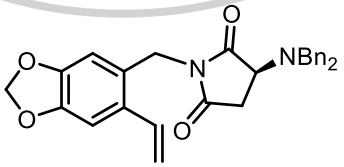
and concentrated under reduced pressure. Purified by plate chromatography (silica plate, hexane : EtOAc 1:1). To give diol product **34** (7.3 mg, 19%) as a yellow color. R_f (1:1 hexane/EtOAc) 0.51; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.20 (m, 10H), 6.89 (d, *J*= 16.5 Hz, 1H), 6.85 (s, 1H), 6.78 (s, 1H), 6.00-5.91 (m, 3H), 4.93 (d, *J*= 14.8 Hz, 1H), 4.69 (dd, *J*= 6.7, 4.9 Hz, 1H), 4.20-4.15 (m, 2H), 4.11 (d, *J*= 14.6 Hz, 1H), 3.91 (d, *J*= 13.4 Hz, 1H), 3.91 3.68 (d, *J*= 13.7 Hz, 1H), 3.46 (dd, *J*= 9.3, 8.2 Hz, 1H), 2.40 (ddd, *J*= 13.9, 9.3, 7.0 Hz, 1H), 1.72 (ddd, *J*= 12.9, 8.1, 4.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6 -C, 145.6 -C, 45.2 -C, 137.4 -C, 128.8, 127.8 -CH, 126.7 -CH, 125.8 -CH, 125.2 -C, 125.0 -CH, 108.7 -CH, 104.2 -CH, 99.1 -CH_2, 76.5 -CH, 60.8 -CH, 56.9 -CH_2, 52.6 -CH_2, 38.7 -CH_2, 29.9 -CH_2. $[\alpha]_{25}^{D}$ +60; ν_{max} (film) 3352, 2908, 1667, 1485, 1449, 1371, 1258, 1242, 1157 cm^{-1}.

13. Synthesis of ABD core **26**



To a solution hydroxylactam (55.0 mg, 0.11 mmol) dissolved in dry CH_2Cl_2 (5 mL) under argon atmosphere and was added $BF_3.OEt_2$ (0.01 mL) at 0^{o}C. And stirred around 3 hours. When completed. The mixture was added sat. $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purified by column chromatography. To give ABD core **26** (4.6 mg, 65%).

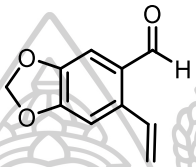
14. Synthesis of vinylsuccinimide **17**



To a solution *N*-arylmethylsuccinimide **6** (140.8 mg, 0.28 mmol), vinyl boronic pinacol ester (0.05 mL, 0.28 mmol), $Pd(PPh_3)_4$ (3 mol%), and K_2CO_3 (181.0 mg, 1.11 mmol) in benzene (5 mL) under argon atmosphere. The mixture was refluxed overnight at 110^{o}C. The mixture was filtered with celite, extracted by H_2O (6x20 mL), the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure The crude product was purified by column chromatography (silica gel, hexane : EtOAc 4:1) to desired product **17** (49.7 mg, 39%) as a yellow oil. R_f (4:1 hexane/EtOAc) 0.57; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.18 (m, 10H), 6.92 (s, 1H), 6.86 (s, 1H), 6.53 (dd, *J*= 8.3, 6.7 Hz, 1H), 5.89 (s,

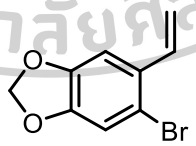
2H), 5.47 (d, *J*= 17.3 Hz. 1H), 5.24 (d, *J*= 11.3 Hz. 1H), 4.66 (d, *J*= 11.4 Hz, 1H), 4.58 (d, *J*= 14.2 Hz, 1H), 3.89 (dd, *J*= 14.0, 5.2 Hz, 1H), 3.78 (d, *J*= 9.6 Hz, 2H), 3.60 (d, *J*= 12.9 Hz, 2H), 2.80-2.52 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0 -C, 174.9 -CH, 147.8 -C, 147.3 -C, 138.2 -C, 137.3 -CH, 128.8 -CH, 128.5 -CH, 127.5 -C, 127.4 -CH, 115.3 -CH, 110.2 -CH, 105.7 -CH, 101.2 -CH_2, 57.4 -CH, 54.7 -CH_2, 39.4 -CH_2, 32.2 -CH_2. $[\alpha]_{25}^{D}$ -34; ν_{max} (film) 2917, 1775, 1699, 1503, 1483, 1454, 1392, 1368, 1336, 1248, 1146 cm^{-1}.

15. Synthesis of vinylpiperonal **35**



To a solution 2-bromopiperonal (150.3 mg, 0.65 mmol), vinyl boronic pinacol ester (0.11 mL, 0.65 mmol), $Pd(PPh_3)_4$ (3 mol%), and K_2CO_3 (360.0 mg, 2.62 mmol) in benzene (7 mL) under argon atmosphere. The mixture was refluxed overnight at 110^{o}C. The mixture was filtered with celite, extracted by H_2O (6x30 mL), the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure The crude product was purified by column chromatography (silica gel, hexane : EtOAc 10:1) to desired product **35** (1.3 mg, 1%) as a brown color. R_f (10:1 hexane/EtOAc) 0.50; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.21 (s, 1H), 7.41 (dd, *J*= 16.8, 10.8 Hz, 1H), 7.31 (s, 1H), 6.98 (s, 1H), 6.06 (s, 1H), 5.62 (d, *J*= 17.0 Hz, 1H), 5.48 (d, *J*= 10.9 Hz, 1H).

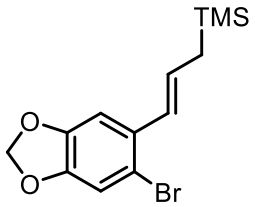
16. Synthesis of vinylbromide **36**



To a solution methylphosphoniumbromide (2.38 g, 6.66 mmol) in THF (5 mL) under argon atmosphere and was added t-BuOK (749.0 mg, 6.66 mmol) at 0^{o}C. Then added 2-bromopiperonal (509.0 mg, 2.22 mmol) dissolved in THF (15.0 mL). The mixture was stirred overnight. The reaction was quenched with adding sat. aq. NH_4Cl (10 mL) and extracted by CH_2Cl_2 (3x20 mL), the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure The crude product was purified by column chromatography (silica gel, hexane) to desired product **36** (274.4 mg, 54%) as a colorless oil. R_f (hexane) 0.48; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02-6.96 (m, 3H), 5.94 (s, 2H), 5.53 (d, *J*= 17.2 Hz. 1H), 5.23 (d, *J*= 10.9

Hz. 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.1 -C, 147.8 -C, 135.5 -CH, 131.0 -C, 114.9 -CH, 114.7 -CH_2, 113.2 -CH, 112.6 -C, 101.8 -CH_2

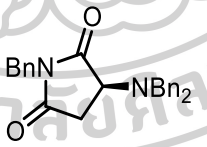
17. Synthesis of allylsilane **37**



To a solution vinylbromide **36** (274.4 mg, 1.21 mmol) in dry CH_2Cl_2 (10 mL) under argon atmosphere and was added allyltrimethylsilane (1.54 mL, 9.67 mmol) followed by Grubb's 2nd generation catalyst (8 mol%). The mixture was refluxed over 2 nights. When finished, took a magnetic bar out of the mixture and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, hexane) to desired product **37** (314.0 mg, 82%) as a colorless oil. R_f (hexane) 0.46; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (s, 1H), 6.83 (s, 1H), 6.40 (d, *J*= 15.3 Hz, 1H), 5.95 (dt, *J*= 16.5, 8.4 Hz, 1H), 5.83 (s, 2H), 1.62 (d, *J*= 8.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.3 -C, 148.6 -C, 133.6 -CH, 131.2 -C, 129.0 -CH, 115.1 -CH, 114.2 -CH, 107.7 -C, 103.5 -CH_2, 25.7 -CH_2, 0.1 -CH_3.

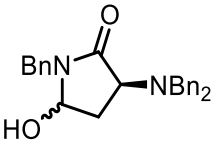
18. Synthesis of *N*-Benzylsuccinimide

(Substrate of *N*-benzylhydroxylactam **38**)



To a solution of chiral succinimide **4** (319.3 mg, 1.86 mmol) in DMF (10 mL) under argon atmosphere at room temperature was added K_2CO_3 (179.7 mg, 1.30 mmol), KI (21.6 mg, 0.13 mmol) and BnCl (0.15 mL, 1.30 mmol) and the mixture was stirred for overnight. The mixture was filtered to remove K_2CO_3. To this mixture was added water (20 mL) and the mixture was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with water (5×20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product was obtainedwithout purification to give N-benzyl imide (367.1 mg, 51%) as a yellow crystal. R_f (4:1 hexane/EtOAc) 0.65; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.15 (m, 15H), 4.50 (d, J= 4.3 Hz, 2H), 3.90 (dd, J= 9.0, 5.3 Hz, 1H), 3.75 (d, J= 16.5 Hz, 2H), 3.55 (d, J= 13.5 Hz, 2H), 2.80 (dd, J=18.7, 9.1 Hz, 1H); 2.65 (dd, J=18.7, 5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 173.6, 159.5, 137.0 (2C), 134.5, 127.6 (3C), 127.0 (3C), 126.4, 126.2 (2C), 56.2, 53.4 (2C), 40.9, 31.0, 28.4.

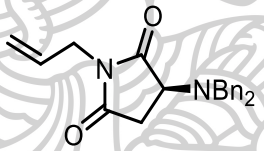
19. Synthesis of *N*-benzylhydroxylactam **38**



To a solution of *N*-Benzylsuccinimide (201.5 mg 0.52 mmol) in dry CH_2Cl_2 (6 mL) under argon atmosphere at -78°C and was added DIBAL-H (1.32 mL, 1.57 mmol). The mixture was stirred around 15 minutes. The reaction was quenched with adding sat. aq. $NaHCO_3$ (10 mL) and extracted by EtOAc (3x20 mL), the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The product was obtained without purification to desired product **38** (183.1 mg, 90%) as a brown color. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.05 (m, 15H), 4.85-4.72 (m, 2H), 4.12 (d, *J*= 14.6 Hz, 1H), 3.92 (d, *J*= 13.7 Hz, 2H), 3.73 (d, *J*= 8.7 Hz, 2H), 3.57-3.48 (m, 1H), 2.43-2.28 (m, 1H), 1.81-1.68 (m, 1H).

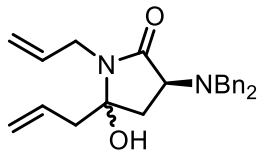
20. Synthesis of *N*-allylsuccinimide

(Substrate of *N*-allylhydroxylactamsuccinimide **41**



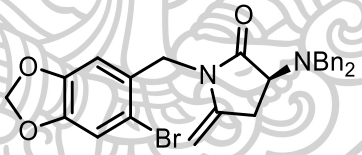
To a solution of chiral succinimide **4** (203.7 mg, 0.69 mmol) in DMF (5 mL) under argon atmosphere at room temperature was added K_2CO_3 (114.4 mg, 0.83 mmol), KI (14.0 mg, 0.008 mmol) and allyl bromide (0.07 mL, 0.81 mmol) and the mixture was stirred for overnight. The mixture was filtered to remove K_2CO_3. To this mixture was added water (20 mL) and the mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with water (5×10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The product was obtained without purification to give N-allylsuccinimide (220.4 mg, 95%) as a colorless oil. R_f (4:1 hexane/EtOAc) 0.68; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.15 (m, 10H), 5.75 (dddd, J= 16.2, 9.9, 6.0, 6.0 Hz, 1H), 4.85 (d, J= 7.1 Hz, 2H), 3.92 (dd, J= 9, 5.6 Hz, 1H), 3.82 (d, J= 13.6 Hz, 2H), 3.63 (d, J= 13.3 Hz, 2H), 2.75 (dd, J= 18.8, 5.6 Hz, 1H), 2.61 (dd, J= 18.5, 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 174.6, 138.2 (2C), 130.7, 129.6 (4C), 129.1 (4C), 127.4 (2C), 118.5, 57.4, 54.6 (2C), 40.6, 32.1; $[\alpha]_{25}^{D}$ -8.3.

21. Synthesis of *N*-allylhydroxylactamsuccinimide **41**



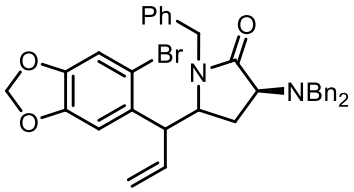
To a solution of magnesium (171.0 mg, 7.02 mmol) in ether (4 mL) under argon atmosphere and was refluxed without heater. Then added allylbromide (0.31 mL, 3.52 mmol). The mixture was observed to bubble gas. At -78ºC The mixture was added *N*-allylsuccinimide (171.0 mg, 7.02 mmol). The mixture was stirred for 3 hours. When finished, The reaction was filtered magnesium under reduced pressure. Then added sat. aq. NH_4Cl (10 mL) and the mixture was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product was obtained without purification to give *N*-allylhydroxylactamsuccinimide **41** (229.2 mg, 87%) as a yellow color. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.11 (m, 10H); 5.75 (dddd, J= 16.2, 9.9, 6.0, 6.0 Hz, 1H), 5.55 (dddd, *J*= 17.2, 10.0, 7.0, 7.0 Hz, 1H), 5.28-4.98 (m, 4H); 4.10-3.31 (m, 7H), 2.62-2.11 (m, 2H), 1.93 (dd, *J*= 13.6, 8.0 Hz, 1H), 0.86 (dd, *J*= 14.1, 6.3 Hz, 1H).

22. Synthesis of *N*-vinylsuccinimide **45**



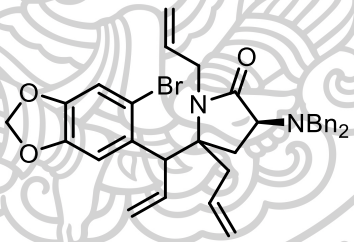
To a solution methylphosphoniumbromide (531.4 mg, 1.49 mmol) in THF (5 mL) under argon atmosphere and was added t-BuOK (215.0 mg, 1.91 mmol) at 0ºC. Then added *N*-arylmethylsuccinimide **6** (215.5 mg, 0.43 mmol) dissolved in THF (15.0 mL). The mixture was stirred overnight. The reaction was quenched with adding sat. aq. NH_4Cl (10 mL) and extracted by CH_2Cl_2 (3x20 mL), the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by plate chromatography (silica gel, hexane : EtOAc 4:1) to desired product **45** (95.2 mg, 44%) as a yellow oil. R_f (4:1 hexane/EtOAc) 0.49; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.28 (m, 10H), 6.99 (d, *J*= 4.3 Hz, 1H), 6.69 (d, *J*= 6.0 Hz, 1H), 5.96 (s, 2H); 5.04 (s, 1H), 4.92 (s, 1H); 4.69 (s, 2H), 3.98 (dd, *J*= 9.0, 6.0 Hz, 1H), 3.85 (d, *J*= 13.2 Hz, 2H), 3.68 (d, *J*= 13.5 Hz, 2H), 2.84 (dd, *J*= 18.6, 9.0 Hz, 1H), 2.68 (dd, *J*= 18.6, 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9 -C, 152.2 -C, 149.3 -C, 146.8 -C, 137.8, 127.3, 128.2 -CH, 128.1 -CH, 127.2 -CH, 112.0 -CH, 108.6 -C, 107.8 -C, 101.1 -CH_2, 89.3 -CH_2, 69.0 -CH, 56.5, 54.1, 31.7.

23 Synthesis of compound **39**



To a solution allylsilane **37** (117.0 mg, 0.37 mmol) and *N*-benzylhydroxylactam **38** (95.8 mg, 0.25 mmol) were dissolved in dry CH_2Cl_2 (5 mL) under argon atmosphere. And at 0 ^oC added BF_3-OEt_2 (0.06 mL, 0.50 mmol). The mixture was stirred overnight. The reaction was quenched with adding sat. aq. $NaHCO_3$ (10 mL) and extracted by CH_2Cl_2 (3x20 mL), the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by plate chromatography (silica gel, hexane : EtOAc 4:1) to desired product **39** (28.0 mg, 19%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61-7.10 (m, 15H), 6.91 (s, 1H), 6.61 (s, 1H), 5.96 (s, 2H), 5.74 (ddd, *J*= 18.0, 12.0, 9.0 Hz, 1H), 5.28-4.95 (m, 4H), 4.06 (dd, *J*= 9.0, 3.0 Hz, 1H), 3.95 (d, *J*= 12.0 Hz, 2H), 3.76--3.67 (m, 1H), 3.63 (d, *J*= 12.0 Hz, 2H), 2.22-1.99 (m, 1H), 1.93-1.72 (m, 3H).

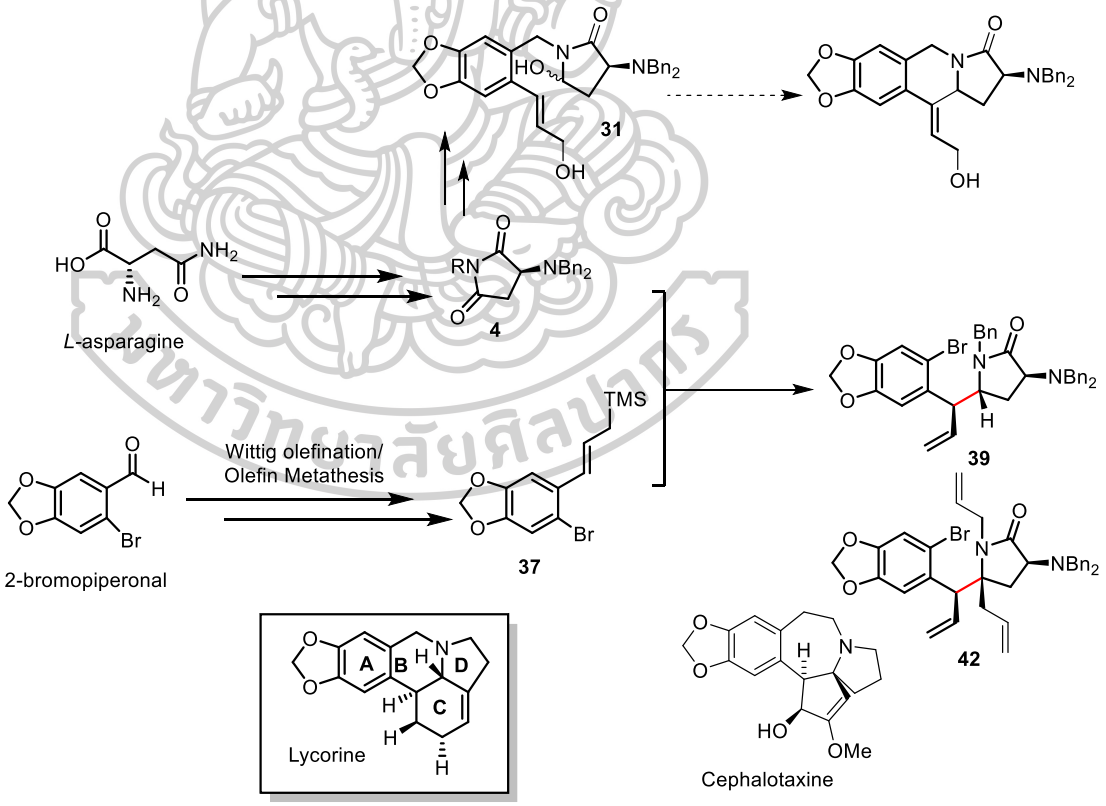
24. Synthesis of compound **42**



To a solution allylsilane **37** (72.6 mg, 0.23 mmol) and *N*-allyl-g-allyl-hydroxylactam **41** (58.2 mg, 0.15 mmol) were dissolved in dry CH_2Cl_2 (5 mL) under argon atmosphere. And at 0 ^oC added TFA (0.04 mL, 0.31 mmol). The mixture was stirred overnight. The reaction was quenched with adding sat. aq. $NaHCO_3$ (10 mL) and extracted by CH_2Cl_2 (3x20 mL), the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by plate chromatography (silica gel, hexane : EtOAc 4:1) to desired product **39** (28.0 mg, 19%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.22 (m, 10H), 6.97 (s, 1H), 6.84 (s, 1H), 6.10-5.70 (m, 3H), 5.99 (s, 2H), 5.28 (d, *J*= 15.0 Hz, 2H), 4.97 (d, *J*= 12.0 Hz, 2H), 4.85 (d, *J*= 18.0 Hz, 2H), 4.08-3.45 (m, 7H), 2.88-2.58 (m, 3H).

CHAPTER 5
CONCLUSION

In summary, the synthetic studies of lycorine have been discussed. This research illustrates that the chiral succinimide **4** synthesized from *L*-asparagine can be useful in synthetic approach of indolizidine alkaloids. Heck reaction and *N*-acyliminium ion cyclization were applied as the crucial reactions for the synthetic route. Heck reaction and subsequent reduction generated intermediated **31** for constructing tricyclic ABD core structure of lycorine but *N*-acyliminium ion cyclization has not been successful. At present, we are attempting to form C3a-C12b bond linkage intermolecularly prior to closing the B ring using Wittig olefination, olefin metathesis which gave bromoarylallylsilane **37**. We have synthesized 2-(6-bromopiperonyl) pyrrolidines **39** and **42** by forming the key C-C linkage using aza-Sakurai reaction between 6-bromoallylsilane **37** with the corresponding hydroxylactams. The products were obtained in high diastereoselectivity. We are working on improving the efficiency of the synthetic routes and the key reaction. The obtained aza-Sakurai products are our potential precursors for completion of lycorine and cephalotaxine synthesis.



Scheme 48 Conclusion of finding from this research

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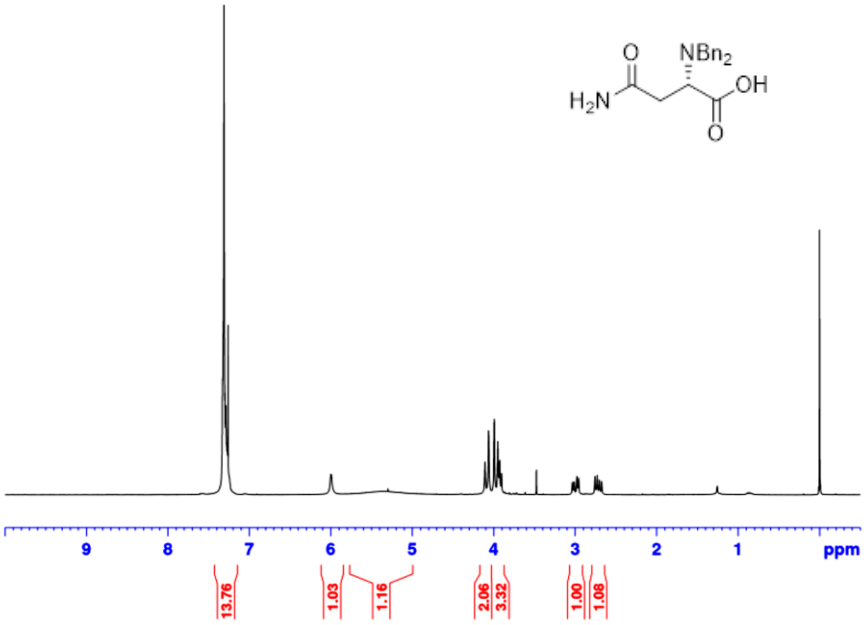
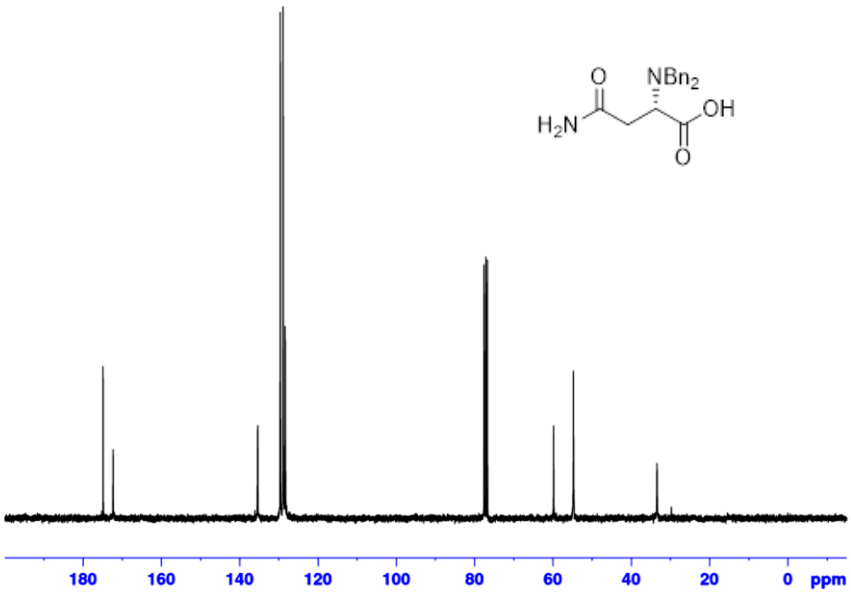
APPENDIX



^{1}H NMR of *N*,*N*-dibenzyl asparagine **1**



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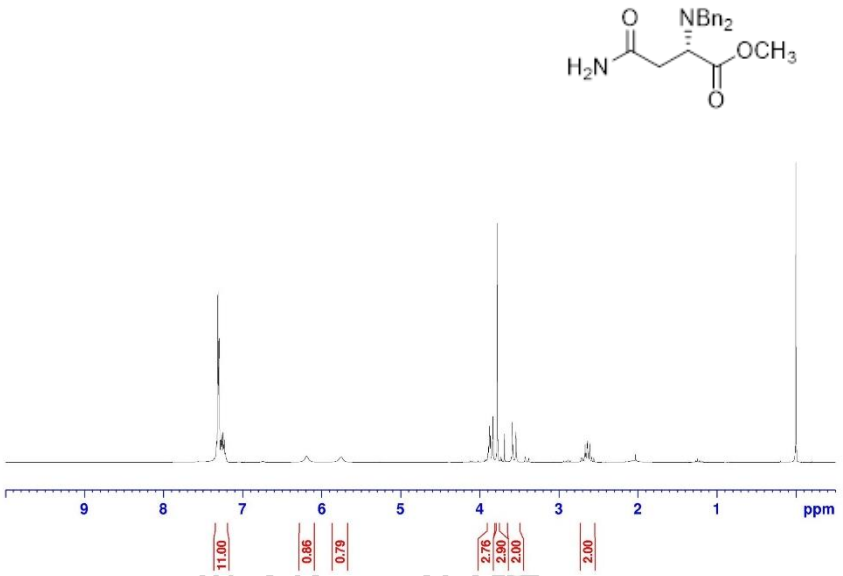
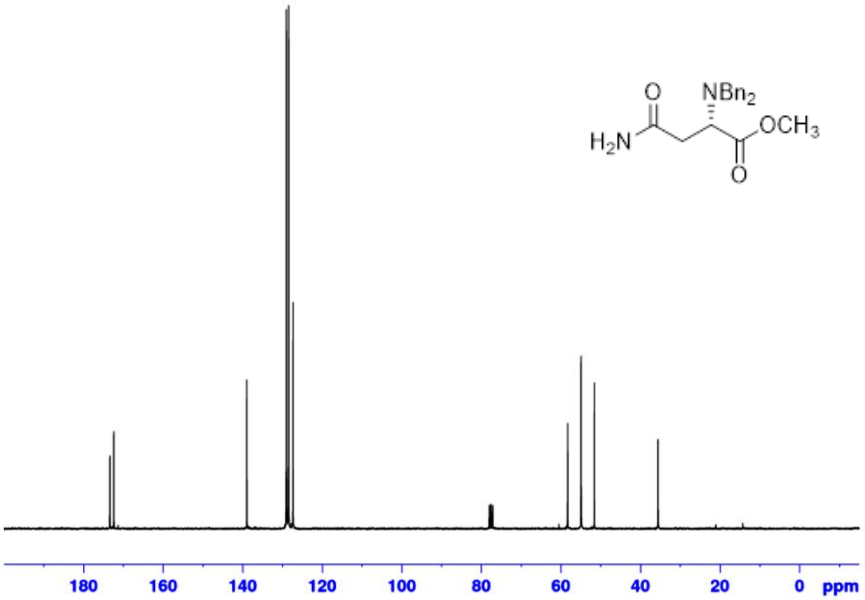


^{1}H NMR of methyl ester asparagine **2**



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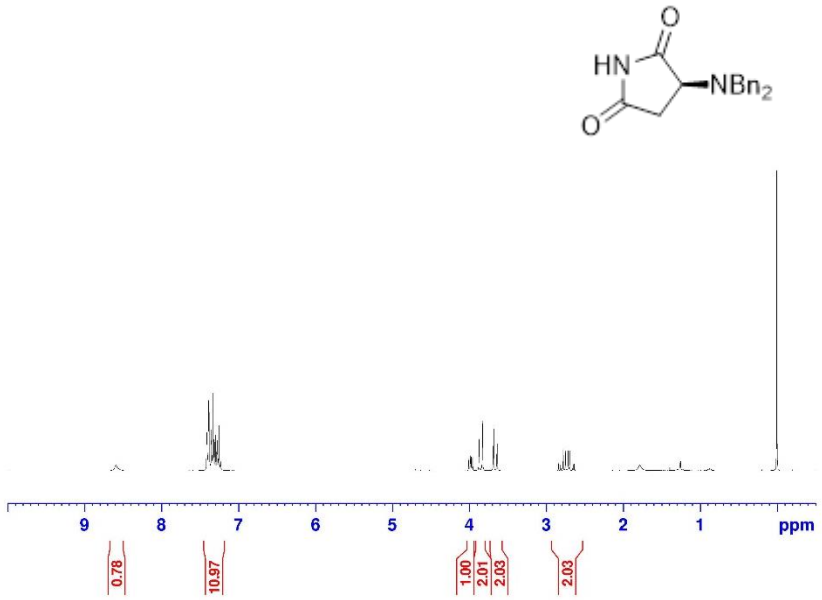
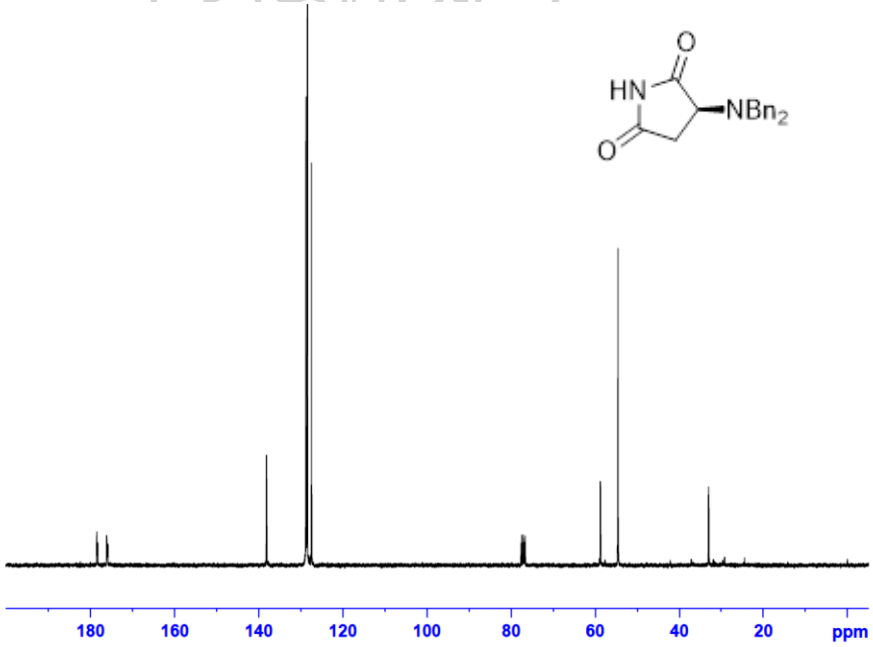


^{1}H NMR of succinimide **4**



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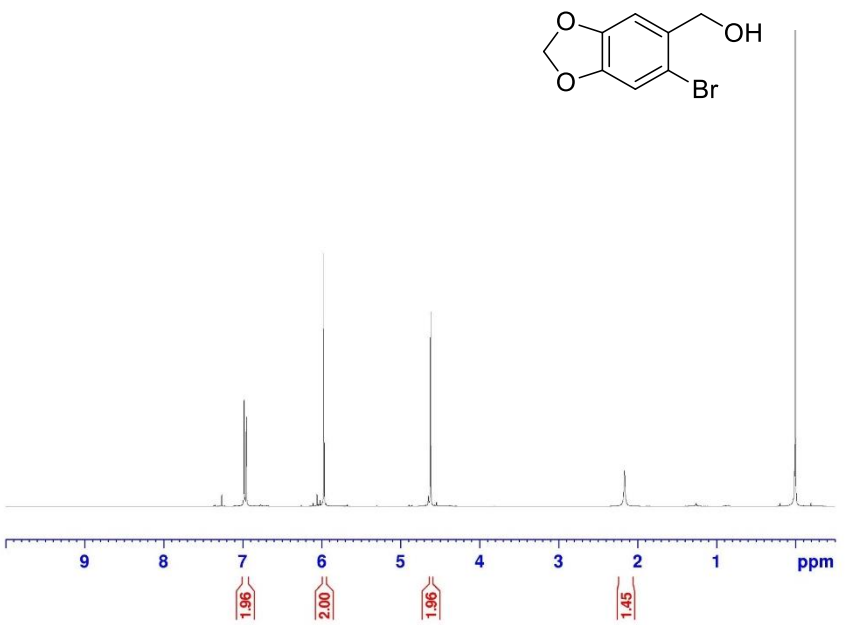

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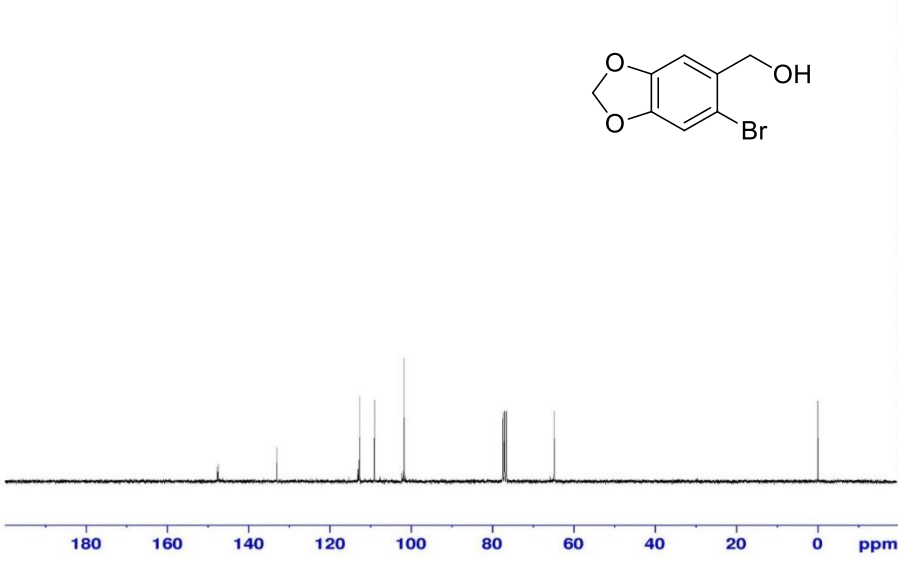

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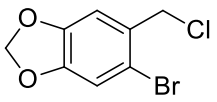
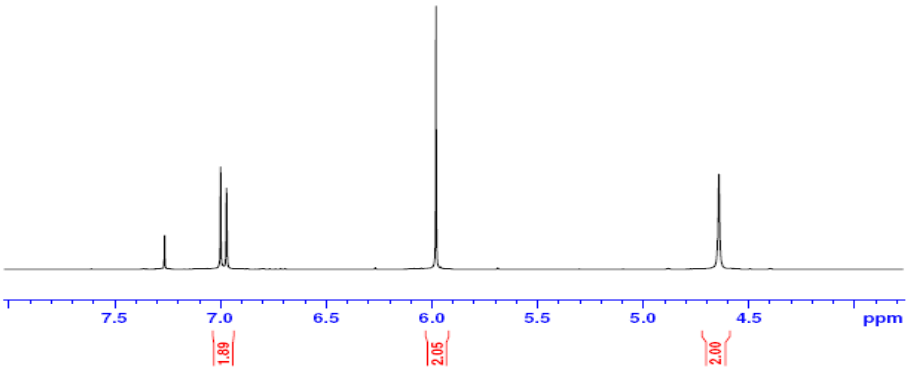
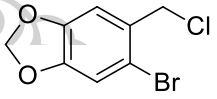
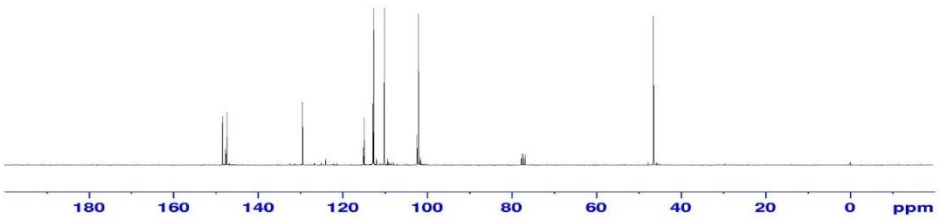




^{1}H NMR of 2-Bromoarylmethyl chloride **5**





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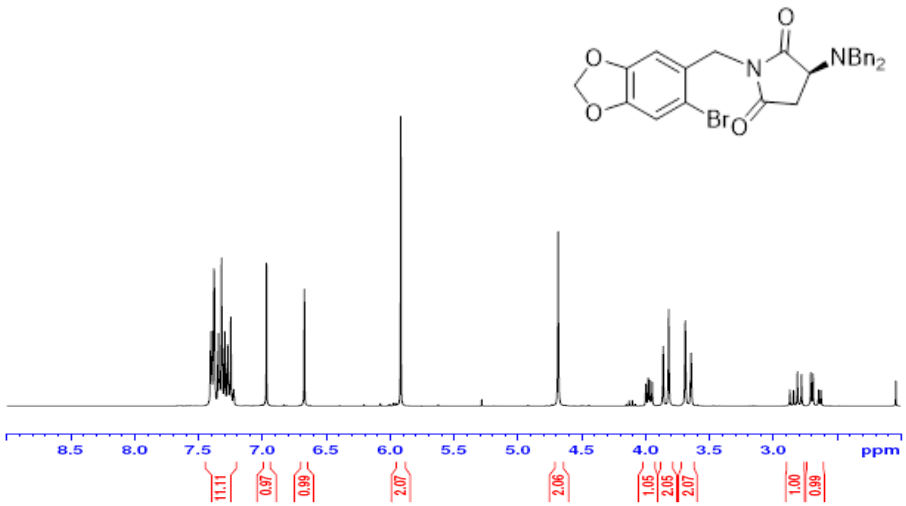
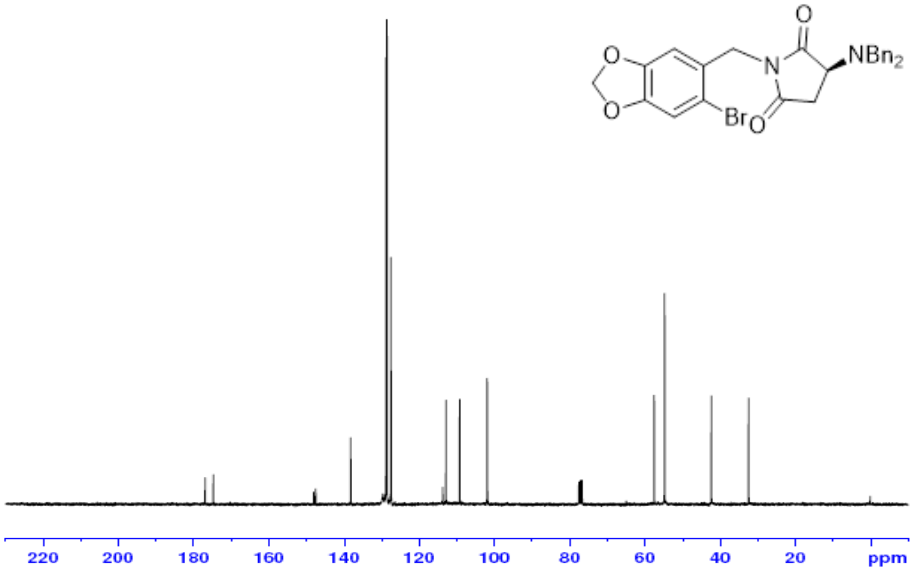


^{1}H NMR of *N*-arylmethylsuccinimide **6**



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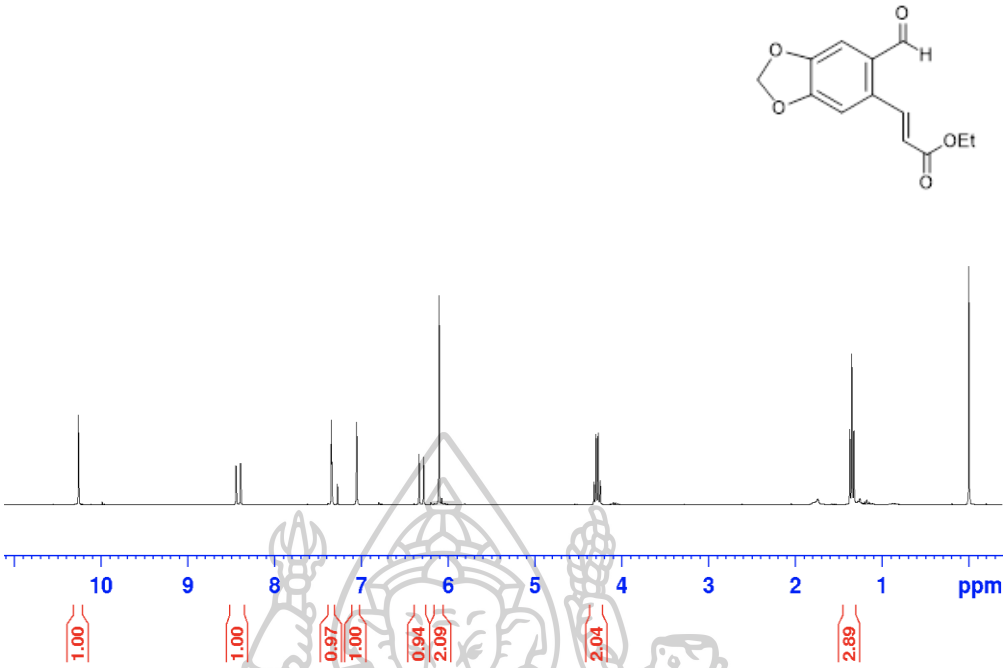

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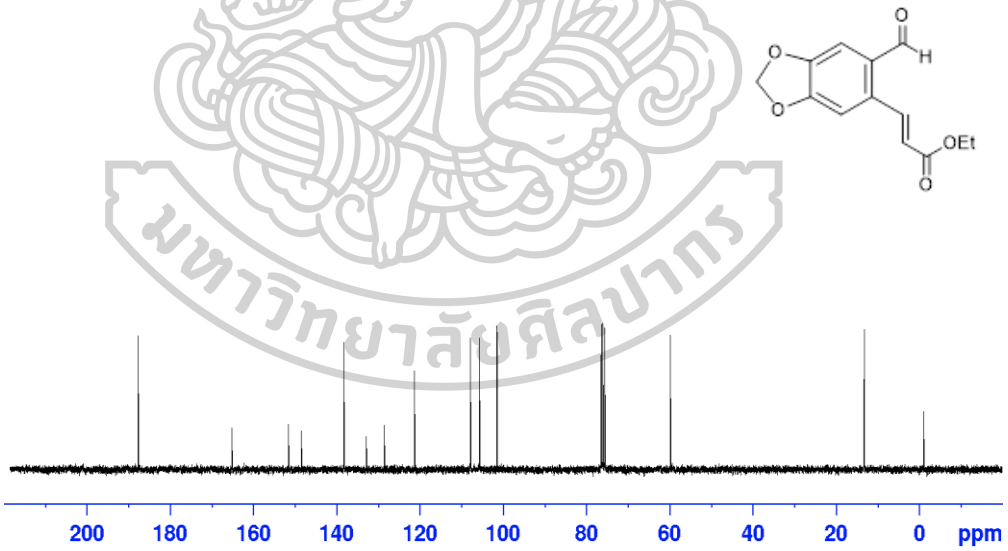

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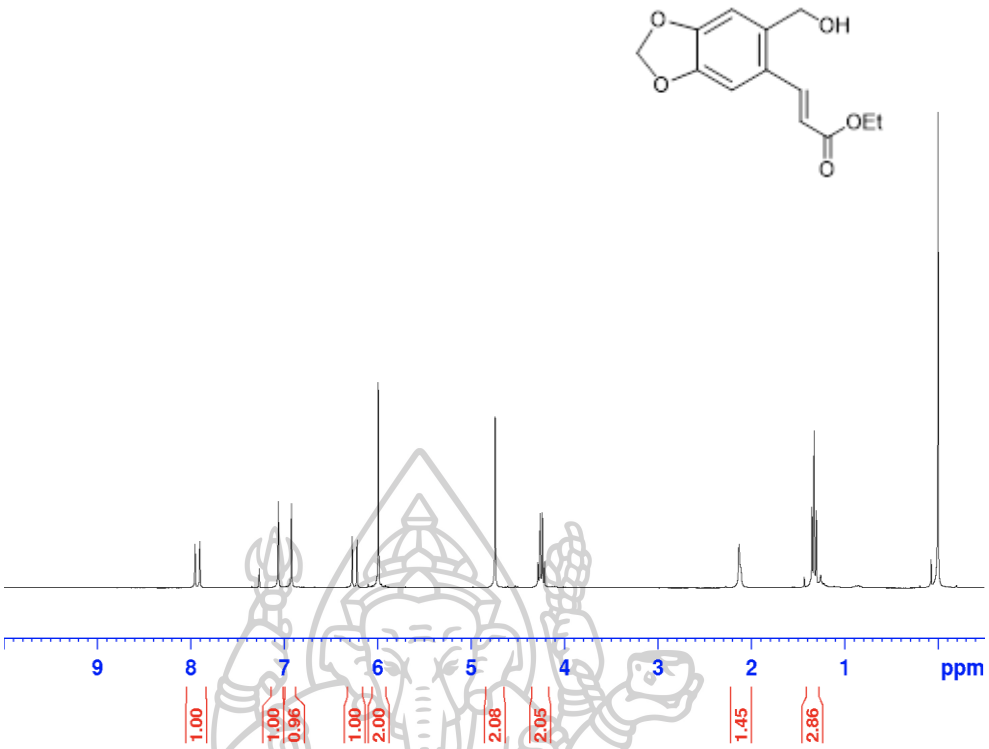
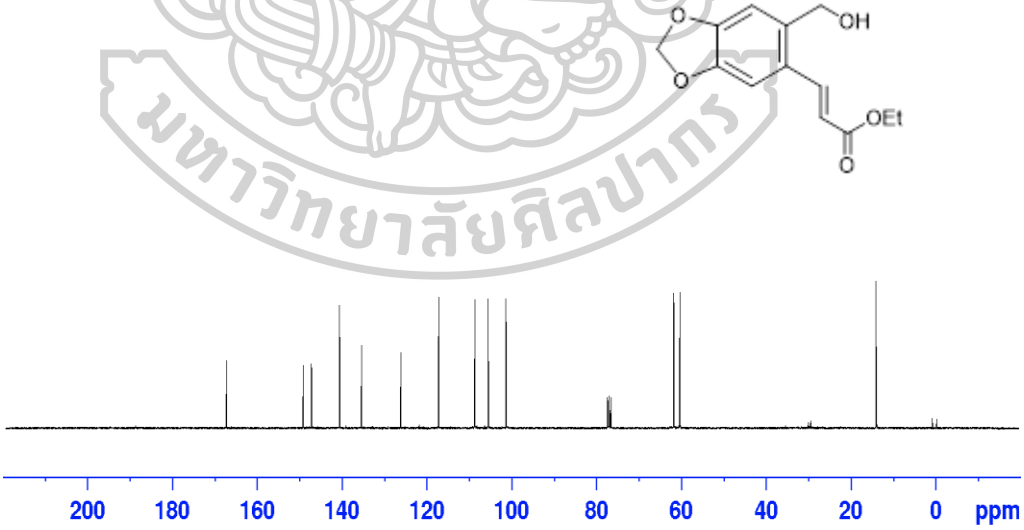


^{1}H NMR of aryl acrylate piperonol **32**



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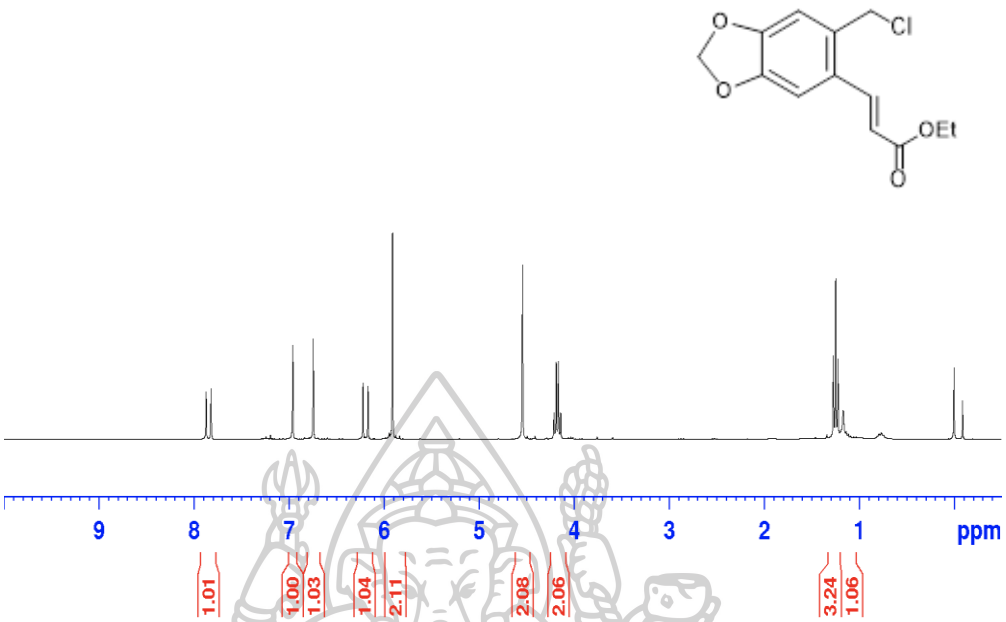
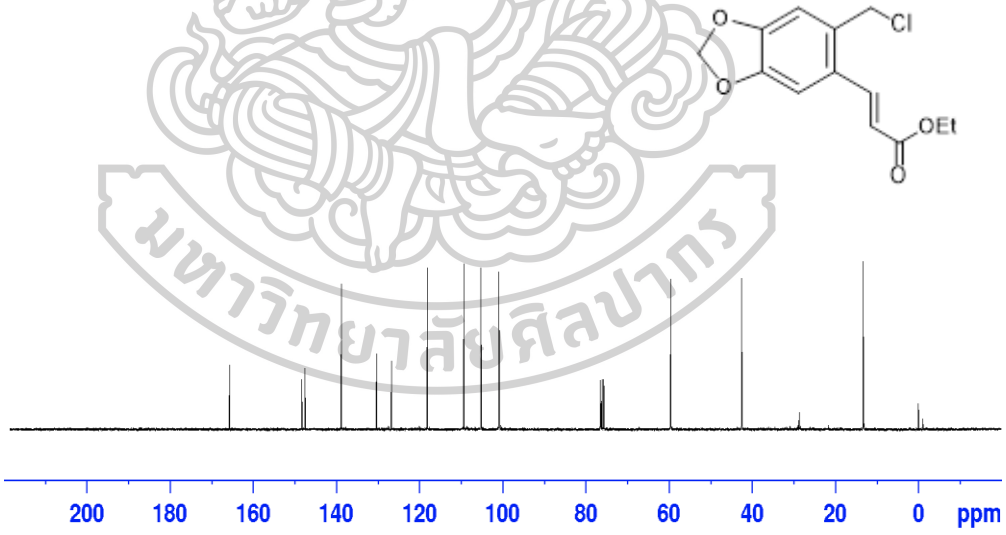


^{1}H NMR of arylacrylate chloride **33**



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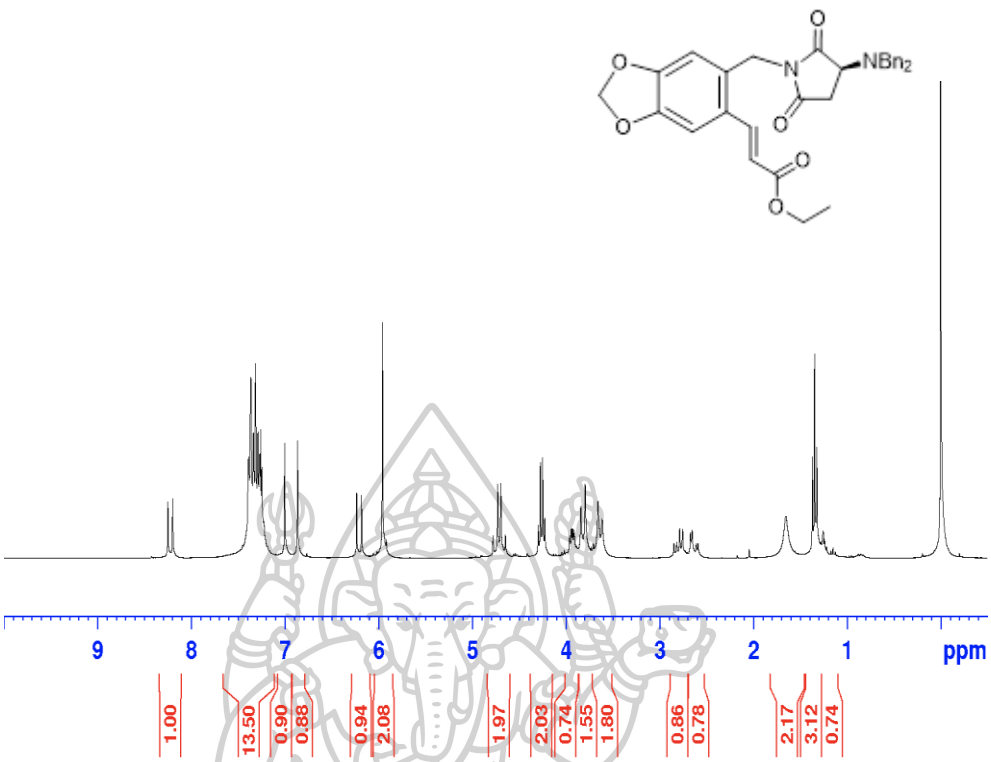
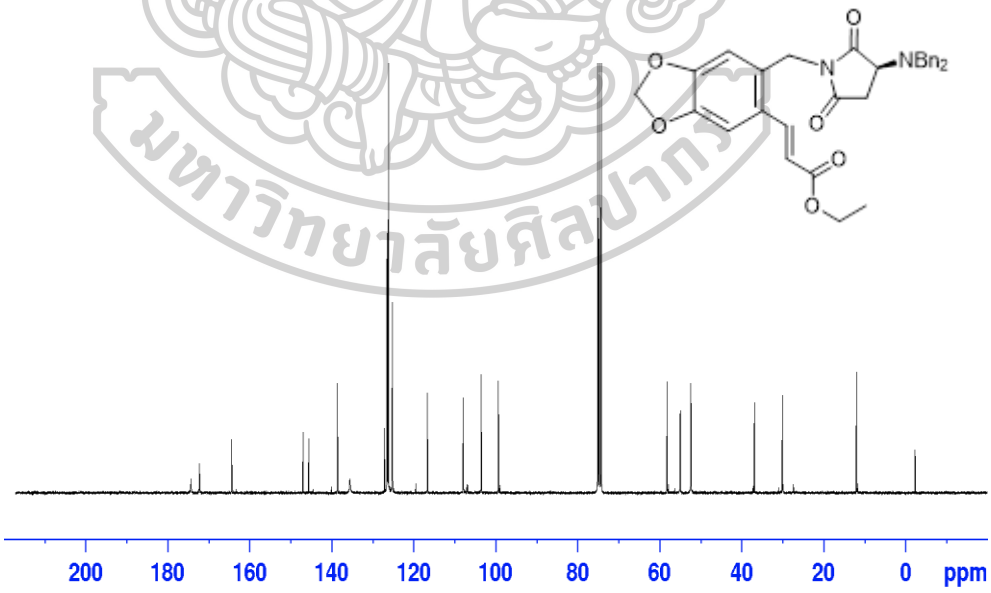


^{1}H NMR of *N*,*N*-dibenzyl ethyl arylacrylo succinimide **31**



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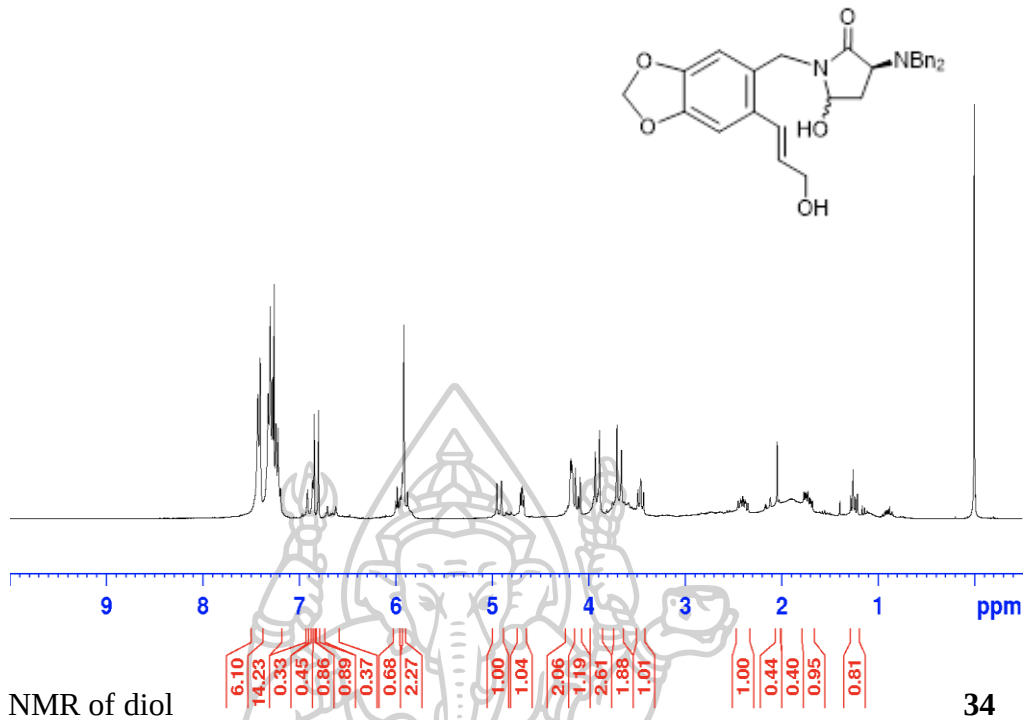
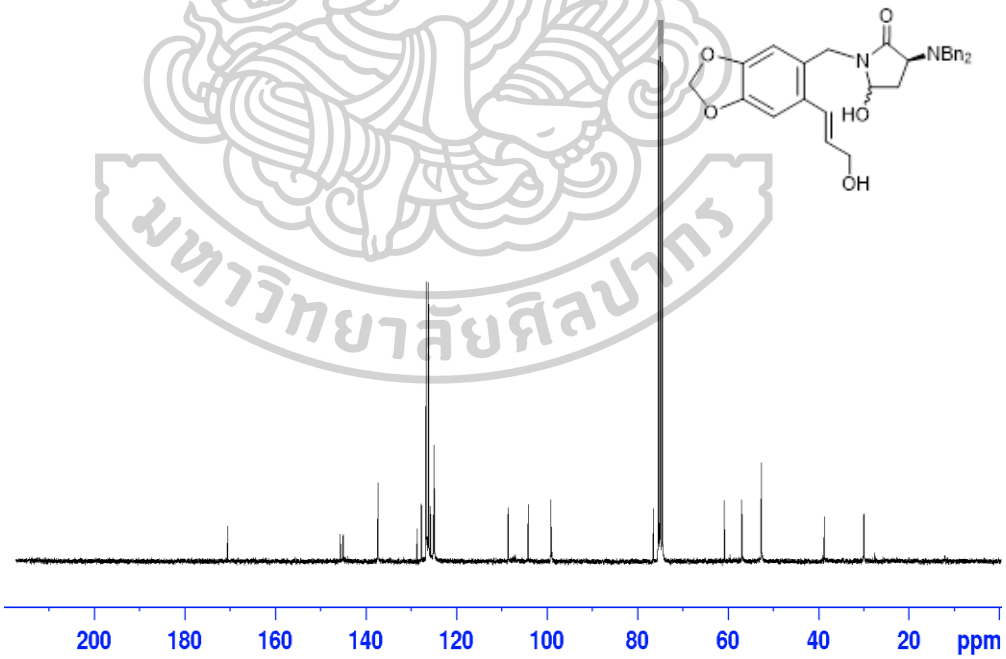


^{1}H NMR of diol **34**



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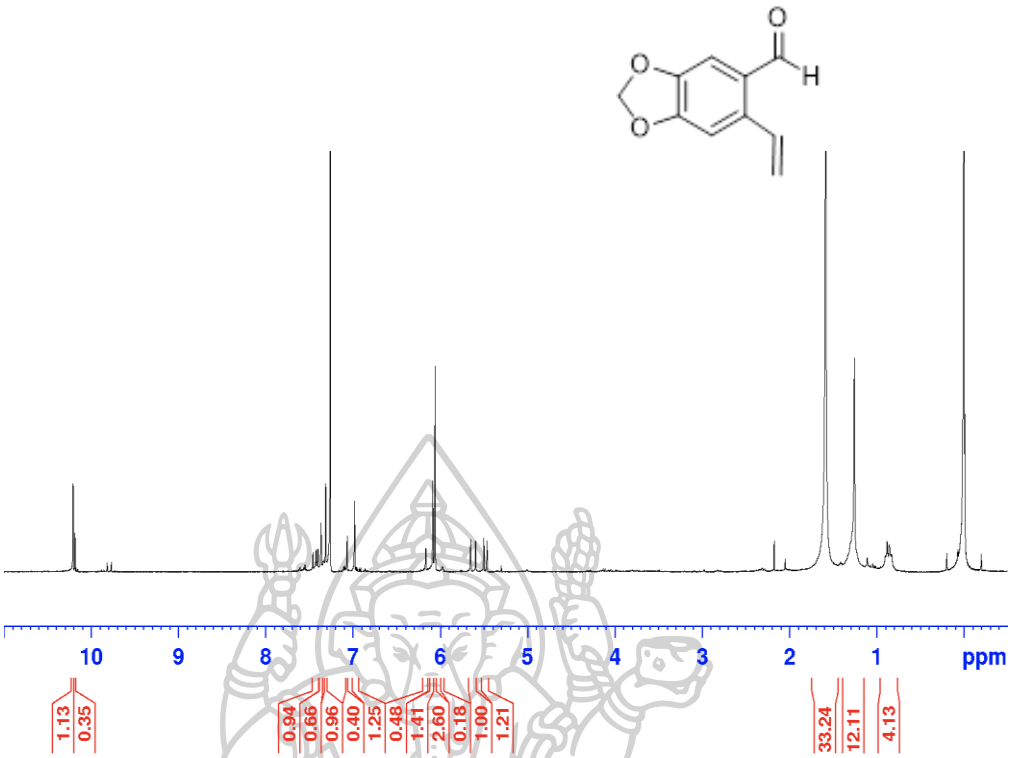

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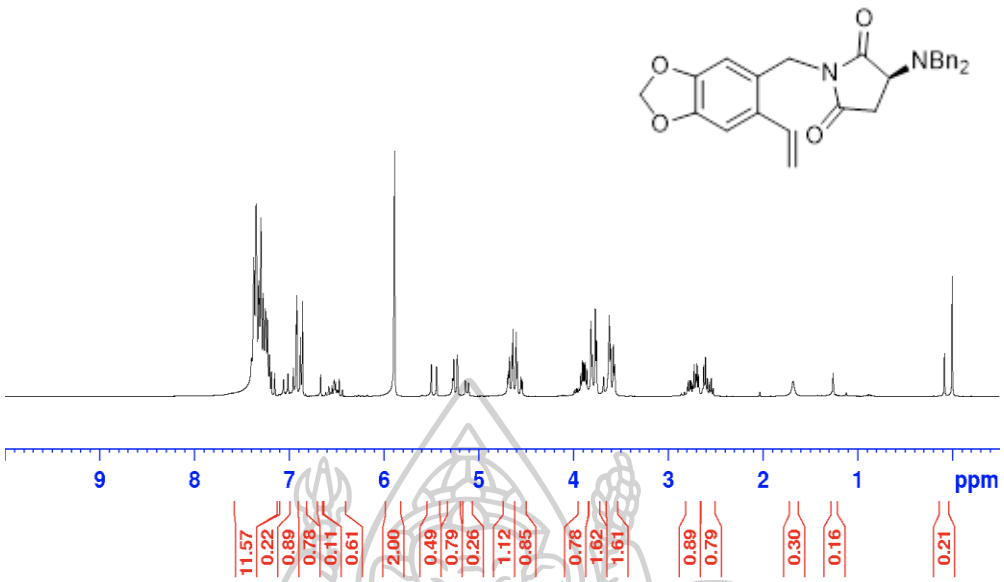
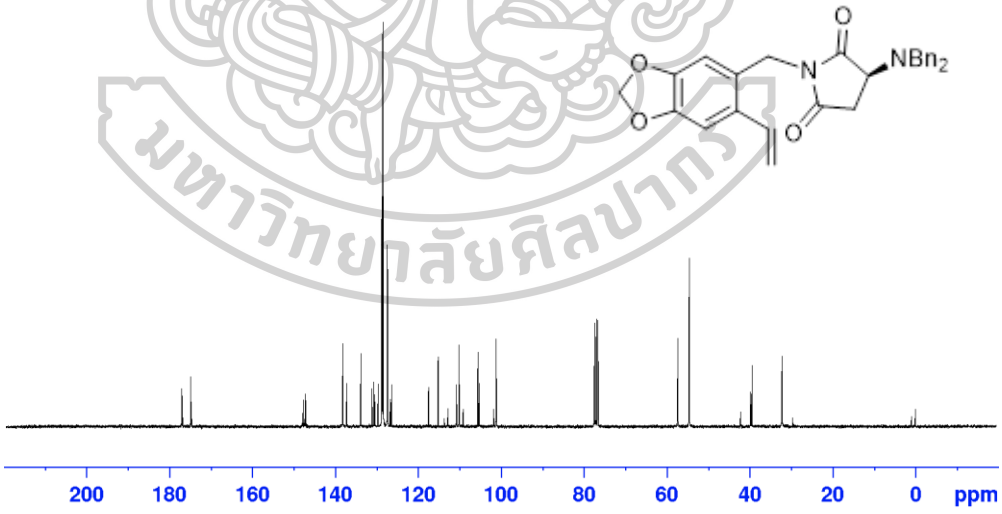


^{1}H NMR of vinylsuccinimide **17**



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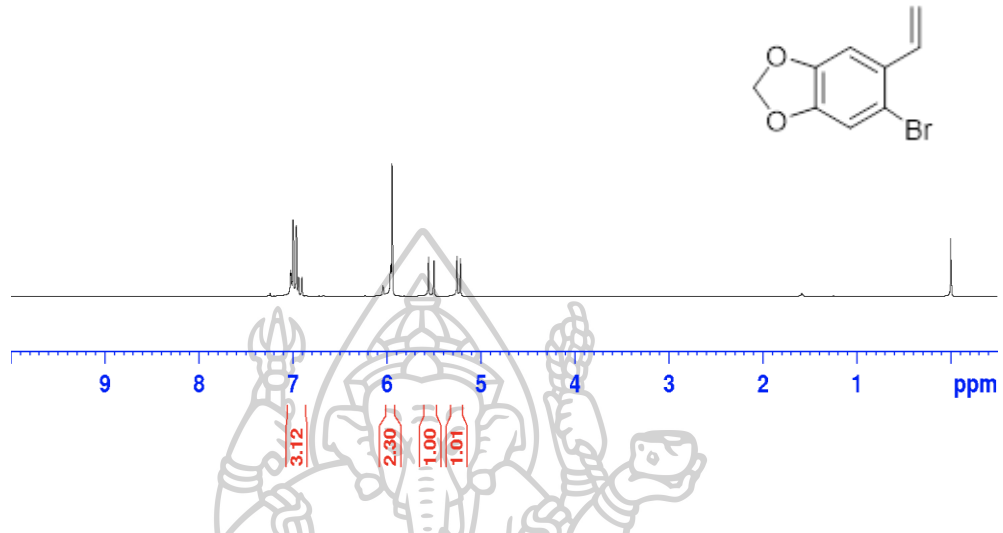
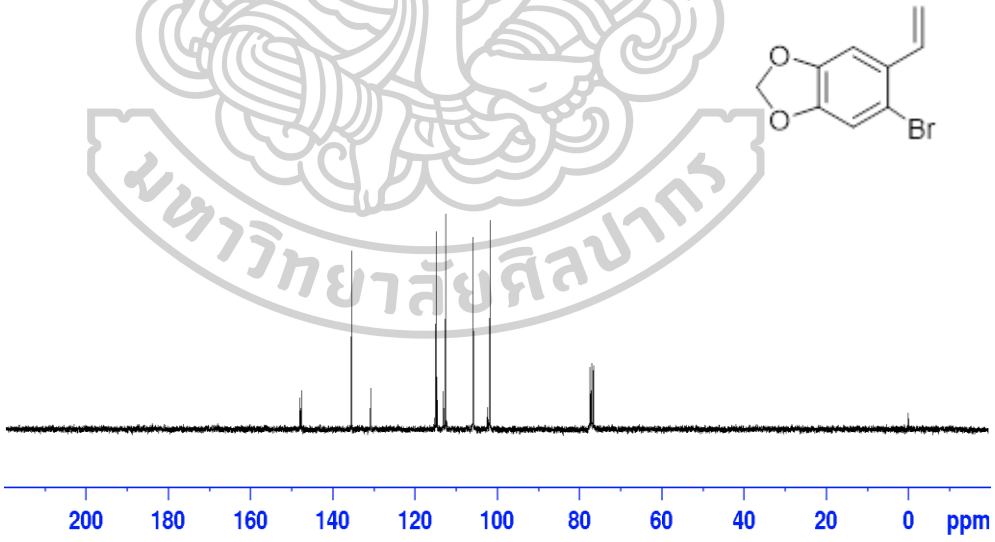


^{1}H NMR of vinylbromide **36**



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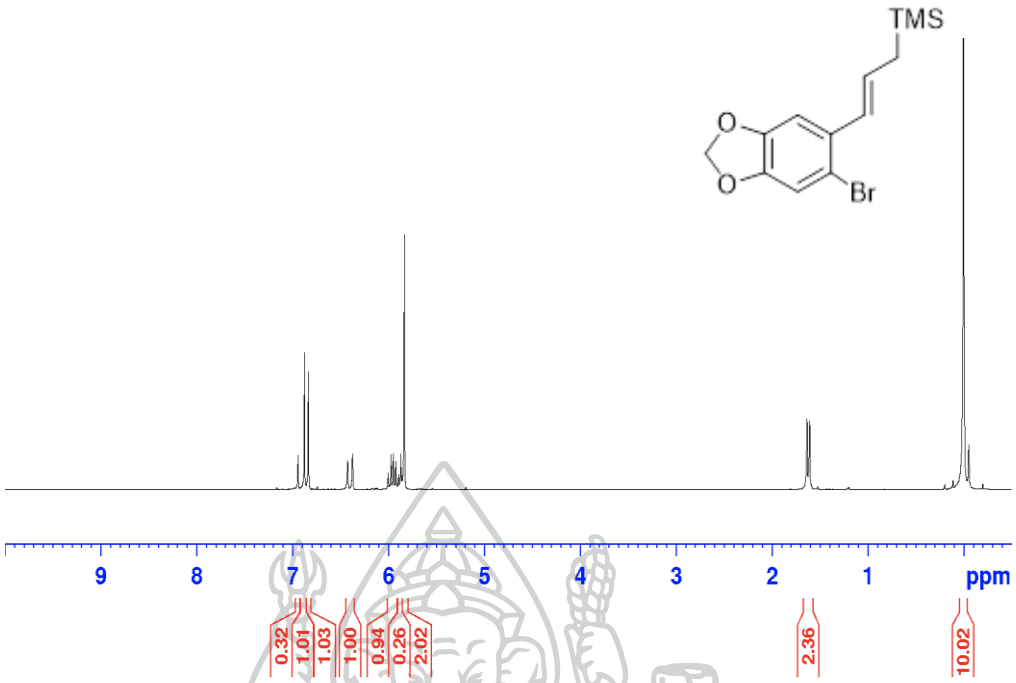

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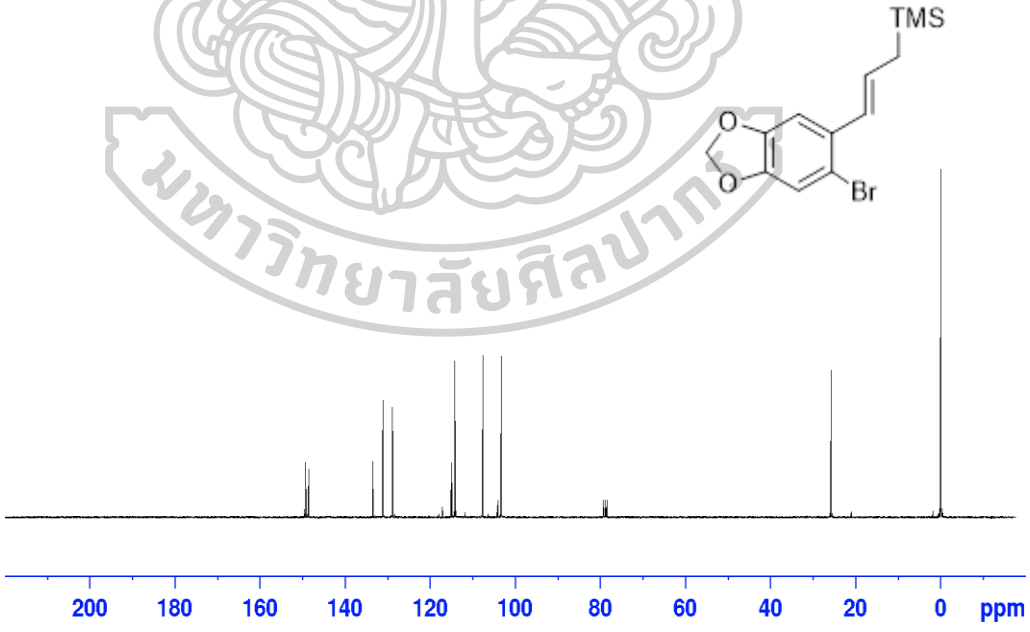
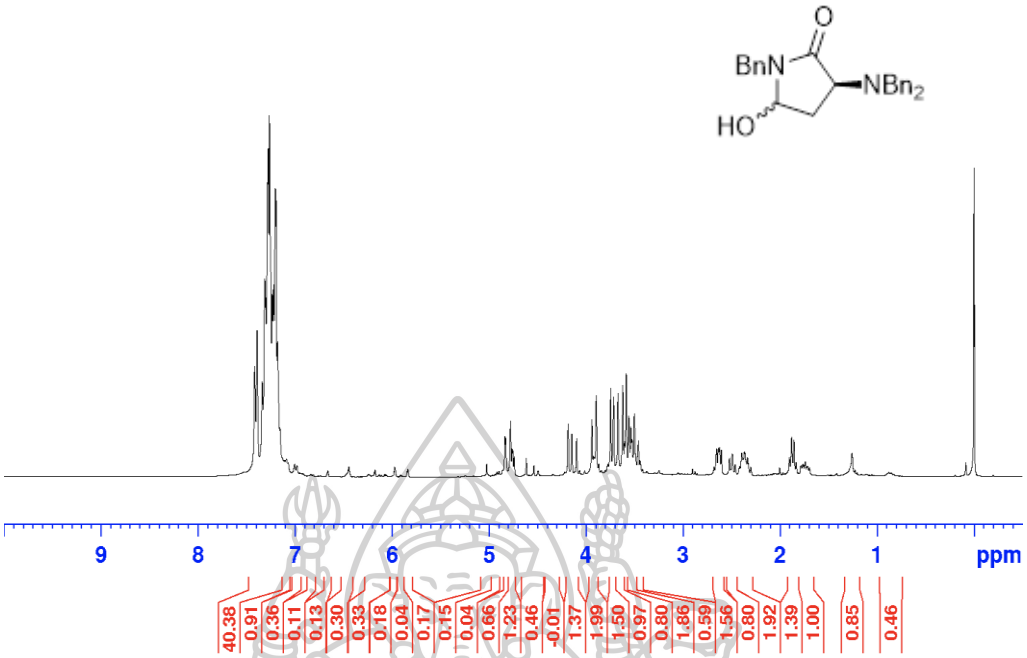
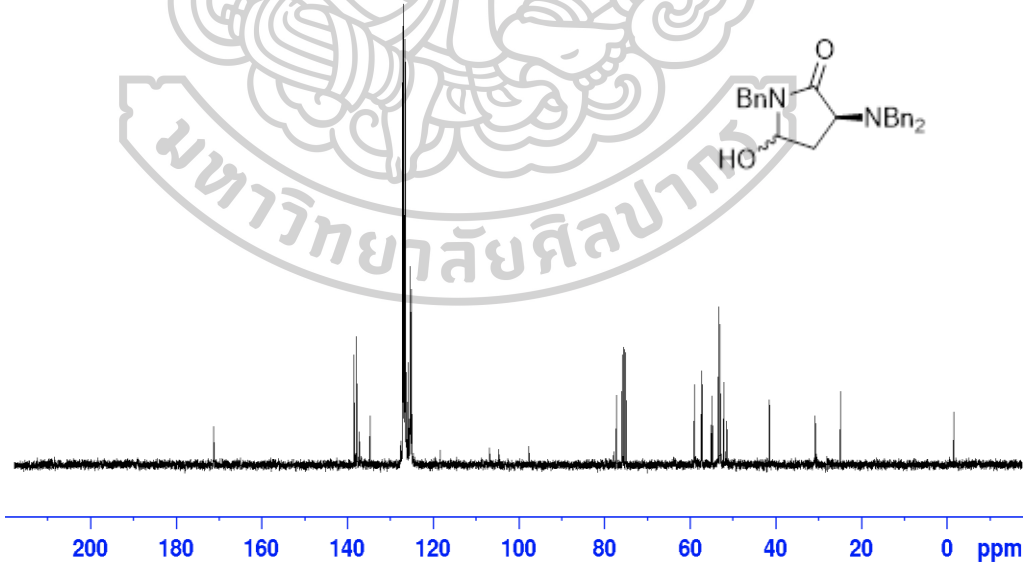


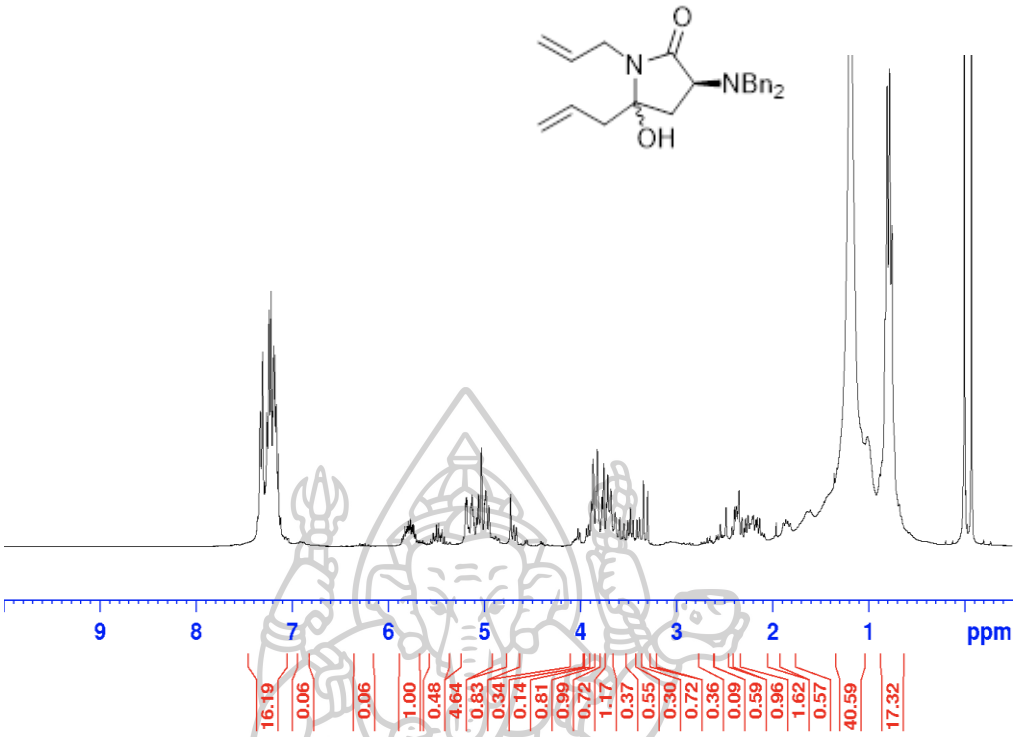
^{13}C NMR of allylsilane **37**



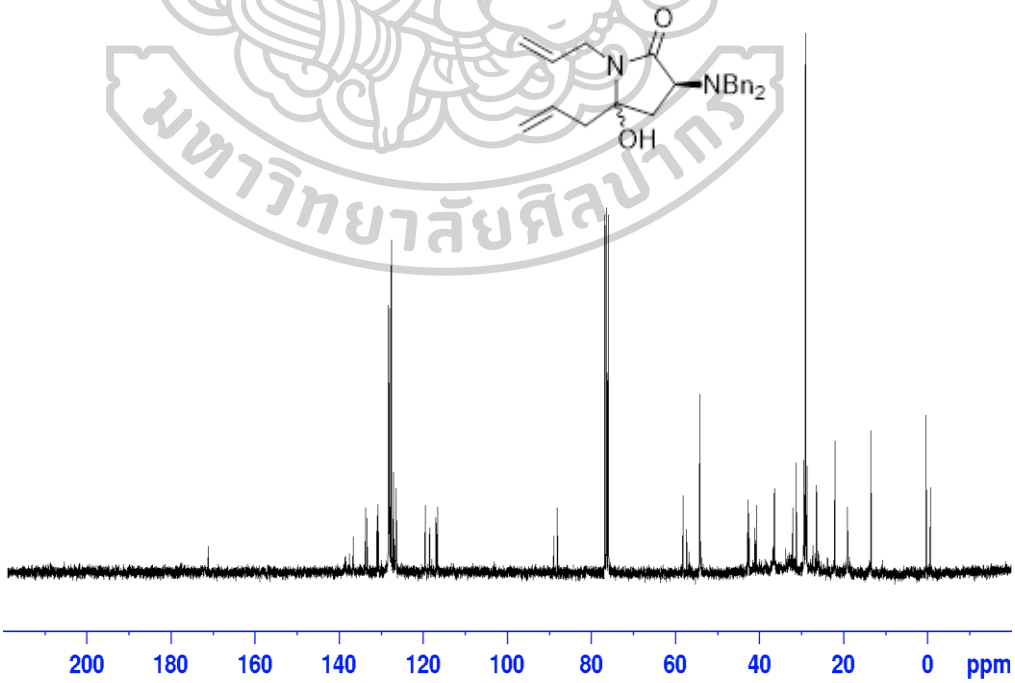
^{1}H NMR of *N*-benzylhydroxylactam **38**



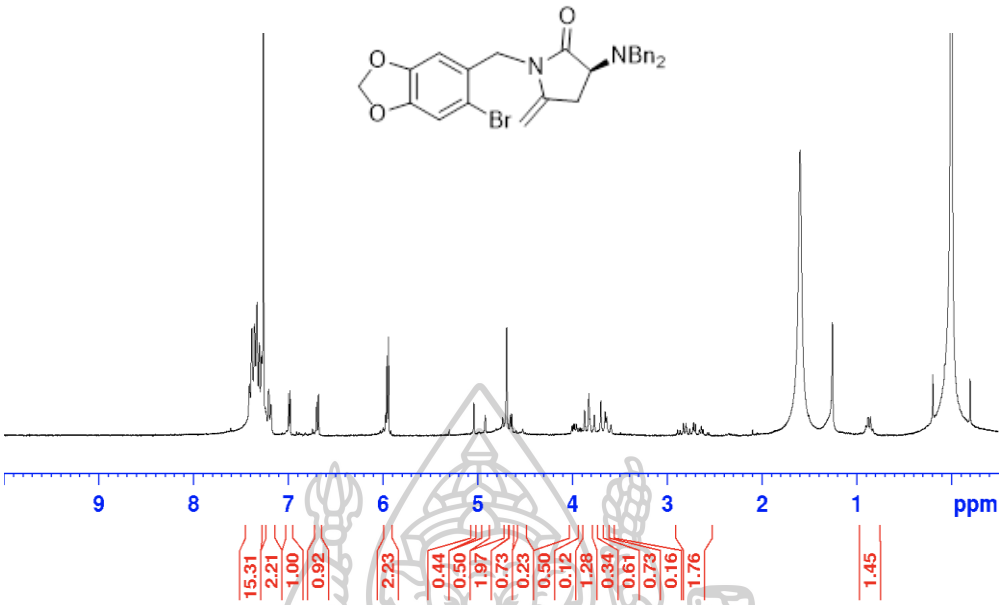
^{13}C NMR of *N*-benzylhydroxylactam **38**



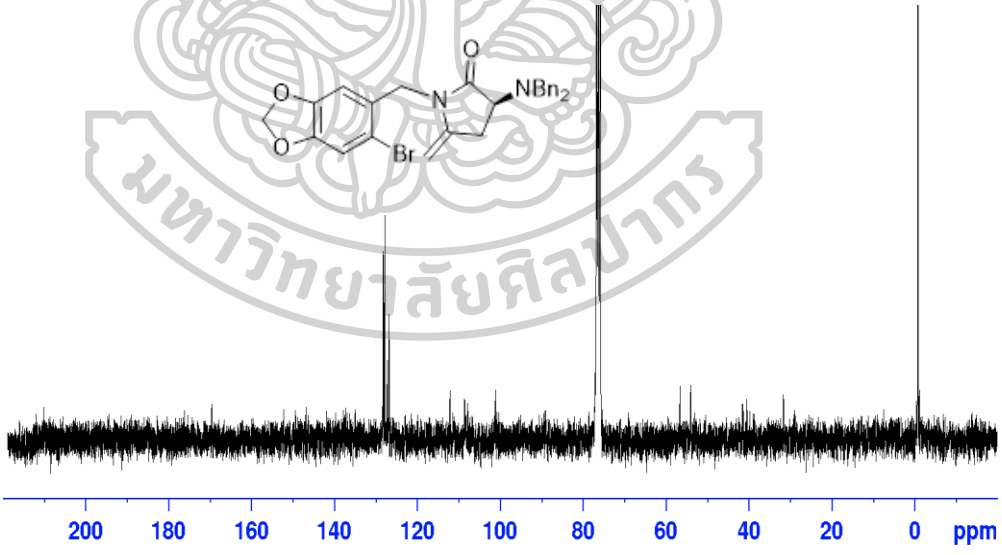
^{1}H NMR of *N*-allylhydroxylactamsuccinimide **41**



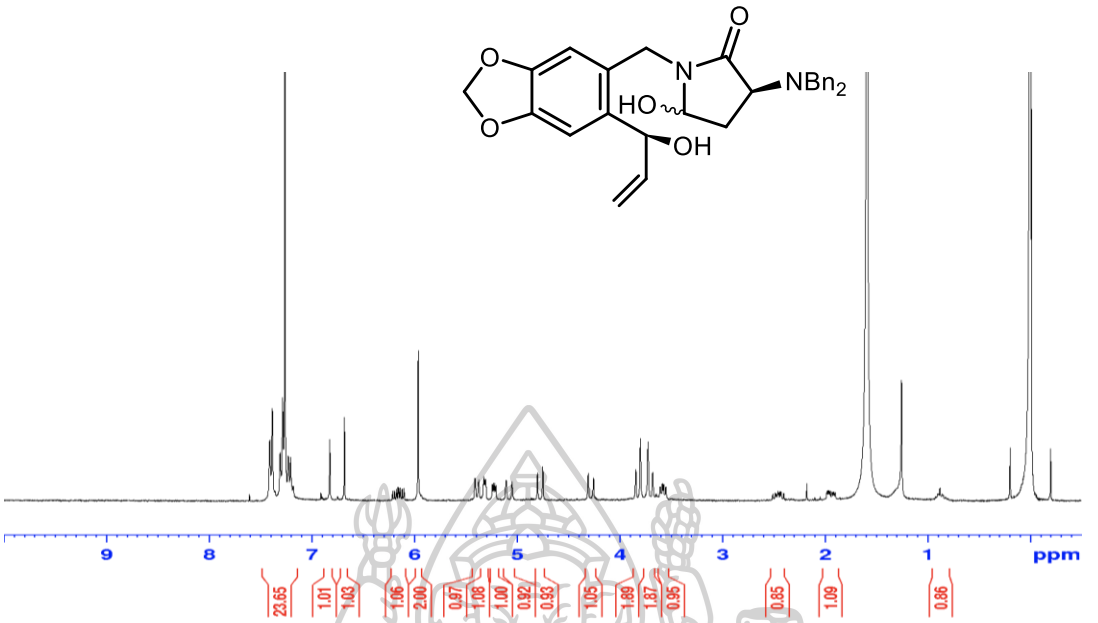
^{13}C NMR of *N*-allylhydroxylactamsuccinimide **41**



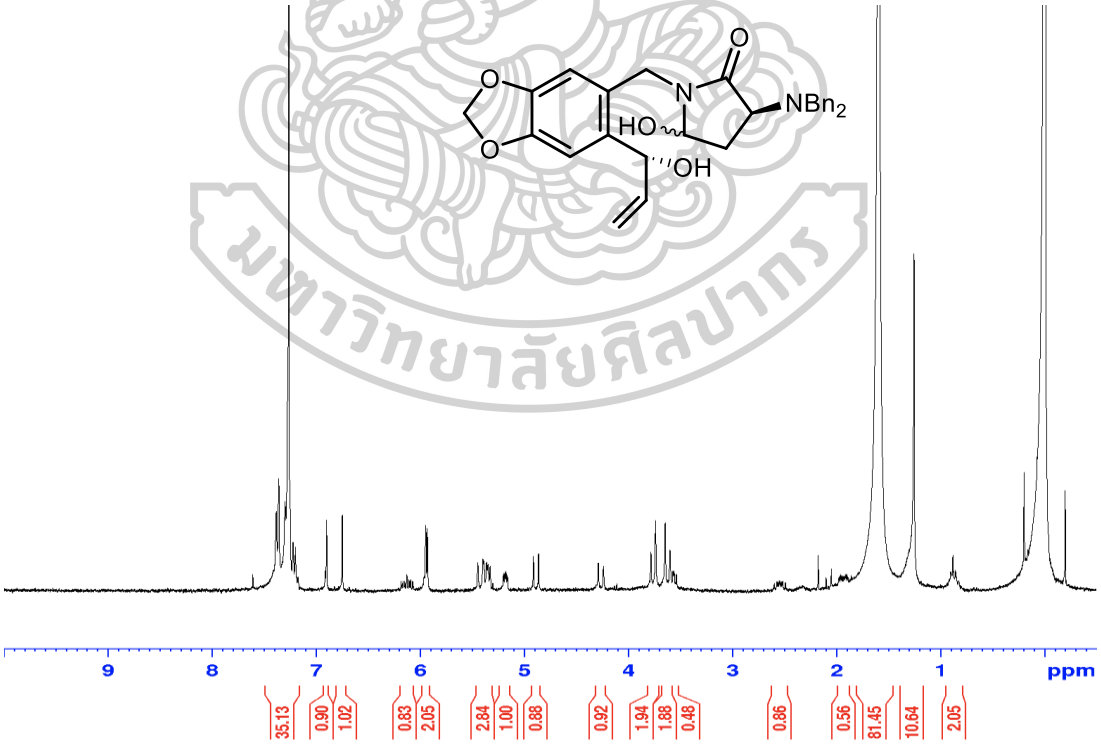
^{1}H NMR of *N*-vinylsuccinimide **45**



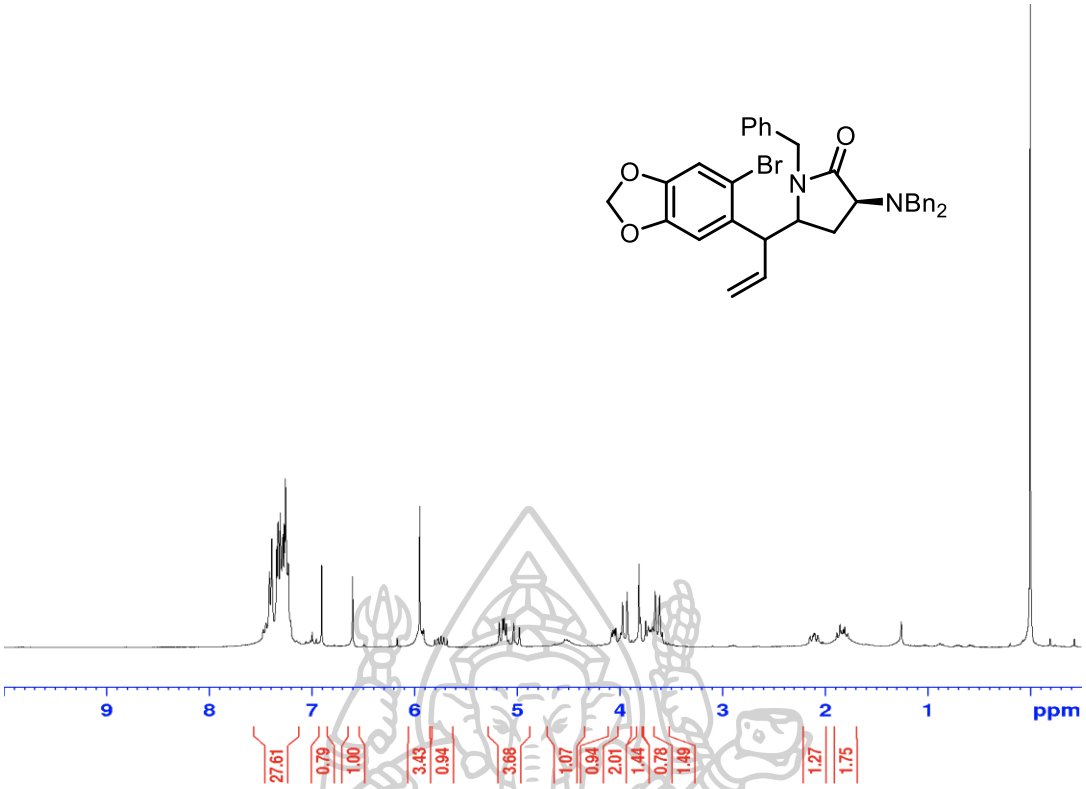
^{13}C NMR of *N*-vinylsuccinimide **45**



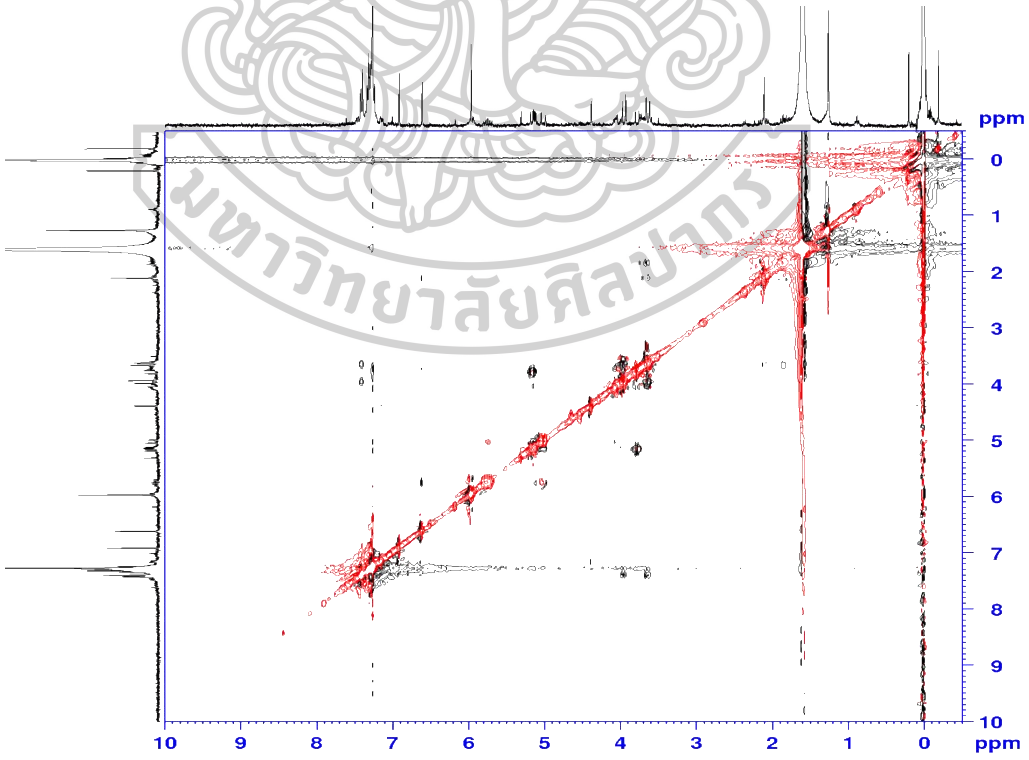
^{1}H NMR of compound **A**



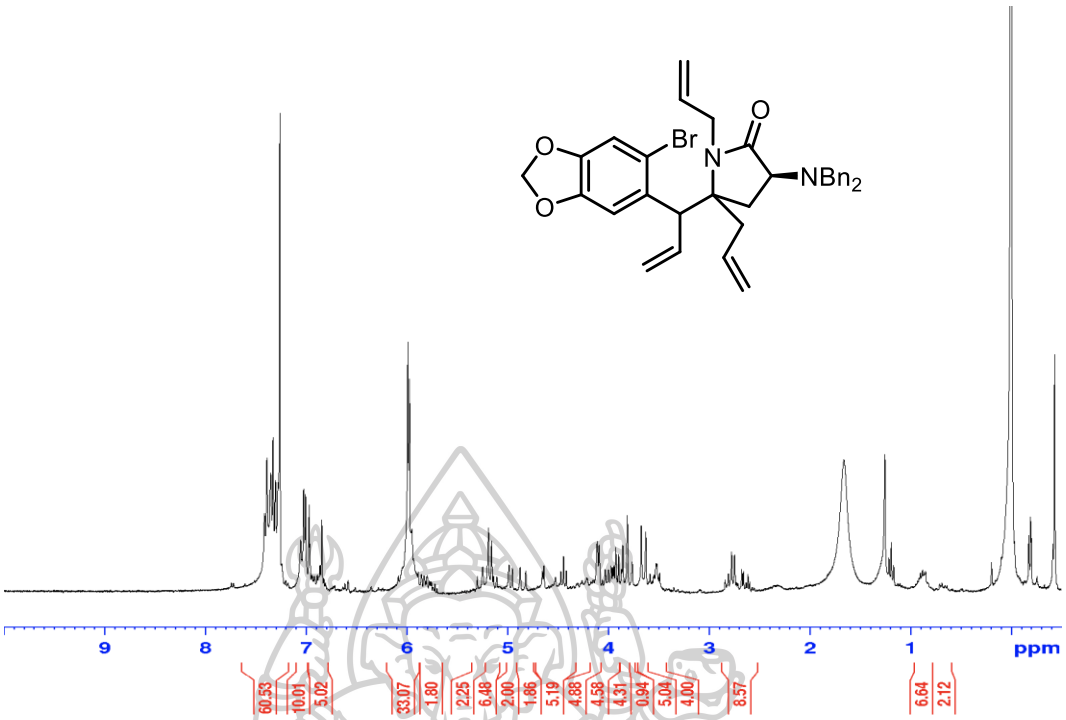
^{1}H NMR of compound **B**



^{1}H NMR of compound **39**



NOESY of compound **39**



^{1}H NMR of compound **42**

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Synthesis of 2-(6-bromopiperonyl) pyrrolidine via diastereoselective aza-Sakurai reaction

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Abstract:

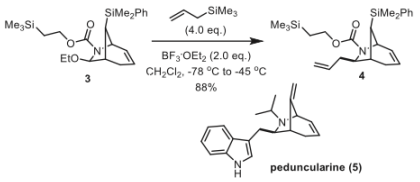
2-(Piperonyl)pyrrolidine is a common structural motif found in several natural products such as lycorine-type and *Cephalotaxus* alkaloids. Herein we describe a diastereoselective synthesis of 2-(6-bromopiperonyl)pyrrolidine via aza-Sakurai reaction using L-asparagine as a chiral starting material. We envision that this structural motif could be a synthetic scaffold for total synthesis of lycorine-type and *Cephalotaxus* alkaloids. 1-(Bromoaryl)allyltrimethylsilane was synthesized in 2 steps from 6-bromopiperonal using Wittig reaction and olefin metathesis with allyltrimethylsilane. The chiral γ-hydroxy-γ-lactams precursor were synthesized from L-asparagine in 3-4 steps, involving *N*-benzylation, succinimide formation, *N*-alkylation and nucleophilic addition to the succinimide carbonyl. Reaction of the (arylallyl)trimethylsilane with the hydroxylactams gave the acid-mediated aza-Sakurai reaction products moderate yields. The products were obtained in high diastereoselectivity (d.r. > 20:1). The dibenzylamino group exerts the stereocontrol and the addition occurred from the face of the *N*-acyliminium ion opposite to the dibenzylamino group. The *N*-substituent (R) and substituent on the γ-carbon (R') were selected for further steps in synthetic studies of lycorine and cephalotaxine.

1. Introduction

Several biologically active alkaloid natural products contain a 2-(6-bromopiperonyl)pyrrolidine structural motif in the compound such as lycorine-type and *Cephalotaxus* alkaloids. Lycorine (**1**) is an *Amaryllidaceous* alkaloid possessing a tetracyclic indolizidine structure with several biological activities including antivirus, anti-parasite, anti-inflammatory, and anti-tumor effects.[1] Homoharringtonine (HHT), a *Cephalotaxus* alkaloid, is the ester of cephalotaxine (**2**) with antileukemic property by inhibiting protein synthesis at the level of the ribosome machinery (Figure 1).[2] Our research goal is to synthesize 2-(6-bromopiperonyl)pyrrolidine which can be used as the key intermediate for synthesizing these alkaloid natural products. In this work, we discuss construction of C-C bond linkage of 2-(6-bromopiperonyl)-pyrrolidine via aza-Sakurai reaction in various conditions.

Figure 1. 2-(6-bromopiperonyl)pyrrolidine present in Lycorine (**1**) and cephalotaxine (**2**).

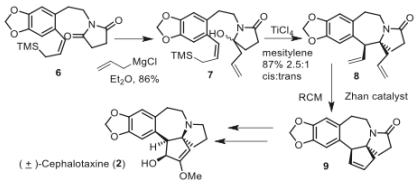
Aza-Sakurai reaction is an important reaction in organic synthesis. It is an especially useful method for formation of a C-C bond between an allylsilane nucleophile and an iminium ion electrophile. The transformation can be either intermolecular or intramolecular reaction that began with Lewis acid activation of the electrophilic carbon in the presence of allyltrimethylsilane.[3] For example, Hiemstra and Speckamp reported stereoselective total synthesis of peduncularine (**5**) in 1989, using an intermolecular aza-Sakurai allylation of *N,O*-acetal **3** with allyltrimethylsilane. The reaction was mediated by $BF_3{\cdot}OEt_2$ as a Lewis acid at low temperature and gave the desired allylated product **4** as a single stereoisomer in excellent yield (Scheme 1).[4]



Scheme 1 Intermolecular aza-Sakurai in synthesis of peduncularine reported by Hiemstra and Speckamp.

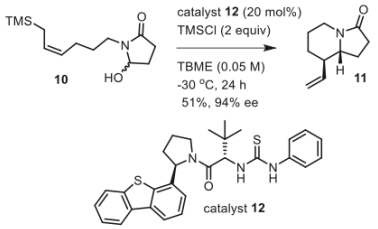
Moreover, intramolecular aza-sakurai reaction can form polycyclic framework of alkaloids with high selectivity. For example, synthesis of racemic cephalotaxine by Hong and coworkers in 2015 (Scheme 2).[5] The precursor *N*-arylethylsuccinimide **6** reacted with

allylmagnesium chloride to give hydroxylactam intermediate **7**. Treatment of this *Z*-TMSallyl-hydroxylactam precursor with titanium tetrachloride in mesitylene at -45 °C gave a 2.5:1 mixture of *cis:trans* tricyclic core **8** of cephalotaxine (**2**) in good yield.



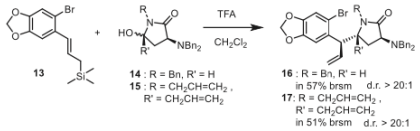
Scheme 2 Intramolecular aza-Sakurai reaction in cephalotaxine synthesis reported by Hong.

Enantioselective aza-Sakurai reaction using chiral catalyst has been developed by Jacobsen (Scheme 3).[6] *N*-(6-Trimethylsilyl-4-hexen-1-yl)-γ-hydroxylactam **10** reacted with TMSCl in the presence of chiral thiourea catalyst **12** yielded 8-vinylindolizidinone **11** in moderate yield with high enantiomeric excess.



Scheme 3 Enantioselective intramolecular aza-Sakurai reaction in synthesis of 8-vinylindolizidine by Jacobsen.

We have been interested in asymmetric synthesis of biologically active alkaloids using cheap and readily available chiral starting materials. Herein we describe a diastereoselective synthesis of 2-(6-bromopiperonyl)pyrrolidines **16** and **17** via aza-Sakurai reaction of 3-(bromoaryl)allylsilane **13** and hydroxylactam **14** and **15** using L-asparagine as the chiral starting material (Scheme 4). We envision that this structural motif could be a synthetic scaffold for total synthesis of lycorine-type and *Cephalotaxus* alkaloids.



Scheme 4 Synthesis of 2-(6-bromopiperonyl) pyrrolidine via diastereoselective aza-Sakurai reaction.

2. Materials and Methods

2.1 Materials

Starting materials and reagents were obtained from commercial sources and were used without further purification. Solvents were dried by distillation from the appropriate drying reagents immediately prior to use. Toluene was distilled from calcium hydride under argon. Tetrahydrofuran was distilled from sodium and benzophenone under argon. Moisture and air-sensitive reactions were carried out under an atmosphere of argon. Reaction flasks and glassware were oven dried at 105 °C overnight. Unless otherwise stated, concentration was performed under reduced pressure. Analytical thin-layer chromatography (TLC) was conducted using Fluka precoated TLC plates (0.2 mm layer thickness of silica gel 60 F-254). Compounds were visualized by ultraviolet light and/or by heating the plate after dipping in a 1% solution of vanillin in 0.1 M sulfuric acid in EtOH. Flash column chromatography was carried out using Scientific Absorbents Inc. silica gel (40 mm particle size).

2.2 Spectroscopic measurement

Optical rotations were measured with a Krüss digital polarimeter P3000 series at ambient temperature using a 1 dm cell with 1 mL capacity which a value was reported in grams per 100 mL. Infrared (IR) spectra were recorded on a Perkin Elmer spectrum 100 FT-IR spectrometer. Proton and carbon nuclear magnetic resonance (NMR) spectra were obtained using a Bruker Avance-300 spectrometer.

2.3 Synthesis of compounds

2.3.1 Synthesis of 5-bromo-6-vinylbenzo-[*d*][1,3]dioxole (20)

To a solution methylphosphoniumbromide (2.38 g, 6.66 mmol) in THF (5 mL) under argon atmosphere and was added *t*-BuOK (749 mg, 6.66 mmol) at 0 °C. To this mixture was added a solution of 2-bromopiperonal (509 mg, 2.22 mmol) in THF (15 mL). The mixture was stirred overnight at room temperature. The reaction was quenched with sat. aq. NH_4Cl (10 mL) and

extracted by CH_2Cl_2 (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure The crude product was purified by column chromatography (silica gel, hexanes) to give the desired product **20** (274 mg, 54%) as a colorless oil: R_f (hexanes) 0.79; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02-6.96 (m, 3H), 5.94 (s, 2H), 5.53 (d, J = 17.2 Hz. 1H), 5.23 (d, J = 10.9 Hz. 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.1, 147.8, 135.5, 131.0, 114.9, 114.7, 113.2, 112.6, 101.8. This material was used immediately for the next step.

2.3.2 Synthesis of (*E*)-(3-(6-bromobenzo[*d*]-[1,3]dioxol-5-yl)allyl)trimethylsilane (13)

To a solution 6-bromostyrene-dioxolone **20** (274 mg, 1.21 mmol) in dry CH_2Cl_2 (10 mL) under argon atmosphere was added allyltrimethylsilane (1.54 mL, 9.67 mmol) followed by Grubb's 2nd generation catalyst (5 mg, 5 mol%). The mixture was heated at reflux for 24 hours. The mixture was then concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, hexanes) to give the desired bromoarylallylsilane **13** (314 mg, 82%) as a colorless oil.: R_f (hexanes) 0.81; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (s, 1H), 6.83 (s, 1H), 6.40 (d, J = 15.3 Hz, 1H), 5.95 (dt, J = 15.5, 8.4 Hz, 1H), 5.83 (s, 2H), 1.62 (d, J = 8.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.3, 148.6, 133.6, 131.2, 129.0, 115.1, 114.2, 107.7, 103.5, 25.7, 0.1; IR (film) ν_{max} 2923, 2853, 1545, 1474, 1379, 1230, 1112 cm^{-1}; ESI-HRMS calculated for $C_{13}H_{18}BrO_2Si^+$ $[M+H]^+$ 313.0254, found 313.0256.

2.3.3 Synthesis of 3-dibenzylamino-*N*-benzyl-γ-hydroxylactam (14)

To a solution of *N*-Benzylsuccinimide (201 mg 0.52 mmol) in dry CH_2Cl_2 (6 mL) under argon atmosphere at -78 °C and was added DIBALH (1.32 mL, 1.57 mmol). The mixture was stirred around 15 minutes. The reaction was quenched with adding sat. aq. $NaHCO_3$ (10 mL) and extracted by EtOAc (3×20 mL), the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The product **14** was obtained without purification (183 mg, 90%) as a brown oil and used directly in the subsequent step.: R_f (4:1 hexanes/EtOAc) 0.32; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.05 (m, 15H), 4.85-4.72 (m, 2H), 4.12 (d, J = 14.6 Hz, 1H), 3.92 (d, J = 13.7 Hz, 2H), 3.73 (d, J = 13.7 Hz, 2H), 3.57-3.48 (m, 1H), 2.43-2.28 (m, 1H), 1.81-1.68 (m, 1H), 1.30 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 139.9 (2C), 138.9, 128.7 (4C), 128.4 (2C), 128.2 (4C), 127.5 (2C), 126.9 (2C), 126.6, 79.2, 60.9, 59.2, 59.0, 43.2, 26.5; IR (film) ν_{max} 3335, 2919, 2850, 1668, 1494, 1455, 1371, 1076, 1028, 973 cm^{-1}; This material was used immediately for the next step.

2.3.4 Synthesis of 2-*N*-Bn-(6-bromopiperonyl)-pyrrolidine (16)

6-Bromoarylallylsilane **13** (117 mg, 0.37 mmol) and *N*-benzylhydroxylactam **14** (96 mg, 0.25 mmol) were dissolved in dry CH_2Cl_2 (5 mL) under argon atmosphere. To this solution at 0 °C was added BF_3•OEt_2 (0.06 mL, 0.50 mmol). The mixture was stirred overnight at room temperature. The reaction was quenched with sat. aq. $NaHCO_3$ (10 mL) and extracted by CH_2Cl_2 (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by preparative thin layer chromatography (silica gel, hexanes : EtOAc 4:1) to give the desired product **16** (28.0 mg, 19% isolated, 57% based on recovered starting material (brsm) as a yellow oil: R_f (4:1 hexanes/EtOAc) 0.54; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61-7.10 (m, 15H), 6.91 (s, 1H), 6.61 (s, 1H), 5.96 (s, 2H), 5.74 (ddd, J = 18.0, 12.0, 9.0 Hz, 1H), 5.28-5.10 (m, 3H), 5.01 (d, J = 18 Hz, 1H), 4.06 (dd, J = 9.0, 3.0 Hz, 1H), 3.95 (d, J = 13.0 Hz, 2H), 3.76-3.67 (m, 1H), 3.63 (d, J = 13.0 Hz, 2H), 2.22-1.99 (m, 1H), 1.93-1.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 143.2,139.7 (2C), 139.5, 135.0, 134.5, 128.8 (4C), 128.6 (2C), 128.4 (4C), 128.2 (2C), 127.0 (2C), 126.9, 120.1, 116.4, 113.0, 109.5, 107.8, 100.5, 58.5, 56.4, 54.5 (2C), 50.2, 44.5, 27.0; $[\alpha]_D^{25}$ +20.5 (*c* 2.0, CH_2Cl_2); IR (film) ν_{max} 2922, 2851, 1681, 1493, 1453, 1432, 1367, 1340, 1127 cm^{-1}; ESI-HRMS calculated for $C_{35}H_{34}BrN_2O_3^+$ $[M+H]^+$ 609.1747, found 609.1746.

2.3.5 Synthesis of 3-dibenzylamino-*N*-allyl-γ-allyl-γ-hydroxylactam (15)

To a suspension of magnesium (242 mg, 10.6 mmol) in ether (4 mL) under argon atmosphere was added allylbromide (0.31 mL, 3.52 mmol). The exothermic generation of allylmagnesium bromide was observed after 5 minutes. The mixture was allowed to stir for 30 minutes and cooled to -78 °C. To this mixture was added *N*-allylsuccinimide (391 mg, 1.17 mmol). The mixture was stirred for 3 hours. The reaction mixture was filtered to remove magnesium under reduced pressure. Then sat. aq. NH_4Cl (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were

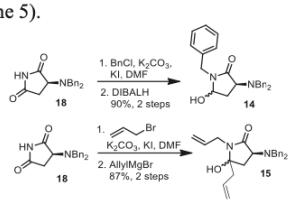
dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product *N*-allyl-γ-allyl-γ-hydroxylactam **15** was obtained without purification (383 mg, 87%) as a yellow color and used directly in the subsequent step.: R_f (4:1 hexanes/EtOAc) 0.30; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.11 (m, 10H); 5.75 (ddt, J = 16.2, 9.9, 6.0 Hz, 1H), 5.55 (ddt, J = 17.2, 10.0, 7.0 Hz, 1H), 5.28-4.98 (m, 4H), 3.92 (d, J = 13.0 Hz, 2H), 3.90-3.61 (m, 3H), 3.60 (t, J = 8.0 Hz, 1H), 3.37 (d, J = 12.0 Hz, 1H), 2.62-2.11 (m, 3H), 1.93 (dd, J = 13.6, 8.0 Hz, 1H), 1.29 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 137.9 (2C), 134.9, 134.5, 129.4 (4C), 129.2 (4C), 127.5 (2C), 119.6, 117.7, 89.0, 58.9, 58.1, 54.8, 43.2, 41.3, 29.5; IR (film) ν_{max} 3334, 2925, 2851, 1667, 1490, 1455 cm^{-1}. This material was used immediately for the next step.

2.2.6 Synthesis of 2-*N*-allyl-(6-bromopiperonyl) -pyrrolidine (17)

Bromoarylallylsilane **13** (73 mg, 0.23 mmol) and *N*-allyl-γ-allylhydroxylactam **15** (58 mg, 0.15 mmol) were dissolved in dry CH_2Cl_2 (5 mL) under argon atmosphere. To this solution was added TFA (0.04 mL, 0.31 mmol) at 0 °C. The mixture was stirred overnight at room temperature. The reaction was quenched with sat. aq. $NaHCO_3$ (10 mL) and extracted by CH_2Cl_2 (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by preparative thin layer chromatography (silica gel, hexanes:EtOAc 4:1) to give the desired product **17** (14 mg, 15% isolated, 51% brsm) as a colorless oil: R_f (4:1 hexanes/EtOAc) 0.62; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.22 (m, 10H), 6.97 (s, 1H), 6.84 (s, 1H), 6.10-5.90 (m, 4H), 5.84 5.74 (ddd, J = 18.0, 12.0, 9.0 Hz, 1H), 5.40-5.10 (m, 4H), 5.00 (d, J = 12.0 Hz, 1H), 4.85 (d, J = 18.0 Hz, 1H), 4.14 (d, J = 8.0 Hz, 2H), 3.97 (dd, J = 10.0, 7.2 Hz, 1H), 3.83 (d, J = 13.7 Hz, 2H), 3.70 (d, J = 13.7 Hz, 2H), 2.88-2.58 (m, 3H), 0.92-0.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 176.0, 147.1 (2C), 146.9, 137.3, 131.2, 129.8, 127.9 (2C), 127.8 (4C), 127.6 (4C), 126.6 (2C), 117.8, 117.3, 114.6, 111.7, 111.6, 106.9, 106.3, 100.9, 66.1, 59.8, 56.6, 49.4, 39.8, 31.4, 28.8; $[\alpha]_D^{25}$ +40.5 (*c* 1.4, CH_2Cl_2); IR (film) ν_{max} 2922, 2851, 1682, 1494, 1454, 1346, 1145, 1075, 982 cm^{-1}; ESI-HRMS calculated for $C_{34}H_{36}BrN_2O_3^+$ $[M+H]^+$ 599.1904, found 599.1905.

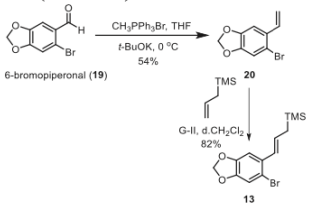
3. Results & Discussion

Hydroxylactam precursors **14** and **15** for aza-Sakurai reaction were synthesized in 2 steps from known 3*S*-dibenzylaminosuccinimide **18**.[7] *N*-Bn-hydroxylactam **14** was synthesized via *N*-alkylation of succinimide **18** using BnCl and K_2CO_3 and KI in DMF to give the corresponding *N*-benzylsuccinimide. Subsequent DIBALH reduction then gave the hydroxylactam **14** in 90% yield over 2 steps. In a similar fashion, *N*-allyl-γ-allylhydroxylactam **15** was constructed from *N*-alkylation using allyl bromide and K_2CO_3 and KI in DMF to give the corresponding *N*-allylsuccinimide. Subsequent reaction with allylmagnesium bromide then gave *N*-allyl-γ-allylhydroxylactam **15** in 87% yield over 2 steps (Scheme 5).



Scheme 5 Synthesis of *N*-alkyl-hydroxylactams **14** and **15**.

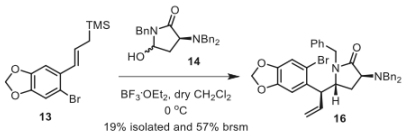
The key arylallylsilane **13** was synthesized in 2 steps from commercially available 6-bromopiperonal. Wittig olefination of 6-bromopiperonal using methyltriphenyl-phosphonium bromide and *t*-BuOK in THF at 0 °C gave bromostyrene **20** in 54% yield. Subsequent reaction with allyltrimethylsilane via metathesis using Grubb's 2nd generation catalyst in dry CH_2Cl_2 afforded the desired bromoarylallylsilane **13** in 82% yield (Scheme 6).[8]



Scheme 6 Synthesis of 6-bromoarylallylsilane **13**.

After obtaining 6-bromoarylallylsilane **13** and the hydroxylactams, we investigated the aza-Sakurai reactions. First, 6-bromoaryl-allylsilane **13** reacted with *N*-Bn-hydroxy-

lactam **14** in the presence of $BF_3{\cdot}OEt_3$ (0.06 mL) and dry CH_2Cl_2 as the solvent to give the coupled product **16** in 57% brsm (Scheme 7). The product was obtained as a single diastereomer (d.r.>20:1, ^1H NMR detection limit). The dibenzylamino group exerted the stereocontrol of the reaction.[9] The configuration of the product was assigned according to the approach of the allylsilane from the opposite side of the dibenzylamino on the lactam ring. The assignment of the configuration of compound **16** was based on NOESY experiments in which correlations between olefinic protons at 5.8 and 5.1 ppm with the methine proton CH-N at 4.1 ppm on newly generated adjacent stereogenic centers were observed, indicating that the vinyl group and the methine proton are *cis*. This C-C bond formation corresponds to the C4a-C10b linkage in lycorine synthesis.

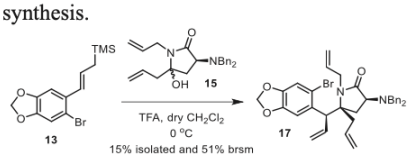


Scheme 7 Synthesis of 2-*N*-Bn-(6-bromopiperonyl)-pyrrolidine **16**.

Secondly, 6-bromoarylallylsilane **13** reacted with *N*-allyl-γ-allylhydroxylactam **15** in the presence of TFA (0.04 mL) as mediator in dry CH_2Cl_2 to give the coupled product **17** in 51% brsm (Scheme 8). The assignment of the configuration of compound **17** was based on the same analogy as that of compound **16**. The lower yield of this reaction could be attributed to the difficulty in forming the quaternary center with intermolecular reaction. The C-C bond formation corresponds to the C4-C5 linkage in cephalotaxine synthesis. In both reactions, the unreacted allylsilane **13** and hydroxylactam **14** or **15** were recovered.

4. Conclusion

In conclusion, we have synthesized 2-(6-bromopiperonyl) pyrrolidines **16** and **17** by forming the key C-C linkage using aza-Sakurai reaction between 6-bromoallylsilane **13** with the corresponding hydroxylactams **14** or **15** The products were obtained in high diastereoselectivity. We are working on improving the efficiency of the synthetic routes and the key reaction. The obtained aza-Sakurai products are our potential precursors for completion of lycorine and cephalotaxine synthesis.



Scheme 8 Synthesis of 2-*N*-allyl-(6-bromopiperonyl) pyrrolidine **17**.

Acknowledgements

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