SYNTHETIC STUDIES OF GRANDISINE A AND STEMOAMIDE

By
MR. Nantachai INPRUNG

A Thesis Submitted in Partial Fulfillment of the Requirements
for Master of Science (ORGANIC CHEMISTRY)
Department of CHEMISTRY
Graduate School, Silpakorn University
Academic Year 2017

การศึกษาการสังเคราะห์แกรนดิซีนเอ และสเตโมเอไมด์

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Title	Synthetic Studies of Grandisine A and Stemoamide
By	Nantachai INPRUNG
Field of Study	(ORGANIC CHEMISTRY)
Advisor	Punlop Kuntiyong

Graduate School Silpakorn University in Partial Fulfillment of the Requirements for the Master of Science

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

This thesis reports a synthetic study of two alkaloids. The first alkaloid is grandisine which possesses a human δ-opioid receptor affinity (IC_{50} = 2.7 μM). The structure consists of four linked rings containing bis-dihydropyran and indolizidine core. Other alkaloid is stemoamide which is found in the *Stemonaceae* family have been used in folk medicine in East Asia for thousands of years. The synthetic route employs the necessary reactions for instance imide formation, regioselective reduction, cross metathesis and *N*-acyliminium ion cyclization. The synthesis of grandisine A was not successful to form an intermediate for cyclization. In addition, The synthetic strategy of stemoamide was designed in three synthetic routes. First, a construction of tricyclic core from tandem *N*-acyliminium ion cyclization but it did not provide a desired target. However, this result was useful for other molecules and it led to the synthesis of two related alkaloids. Second, the synthesis involved the construction of pyrrole-azepine core of stemoamide via *N*-acyliminium ion cyclization. Lastly, we employed the cross metathesis reaction between tethered succinimide and component of lactone ring.

According to the failure of tandem *N*-acyliminium ion cyclization, a beneficial result could be adaptable for the synthetic approach of tashiromine and lupinine via *N*-acyliminium ion cyclization. Thus, it gave important skeletons of the alkaloids which could potentially be converted to natural anlogues in a few step.

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Nantachai INPRUNG

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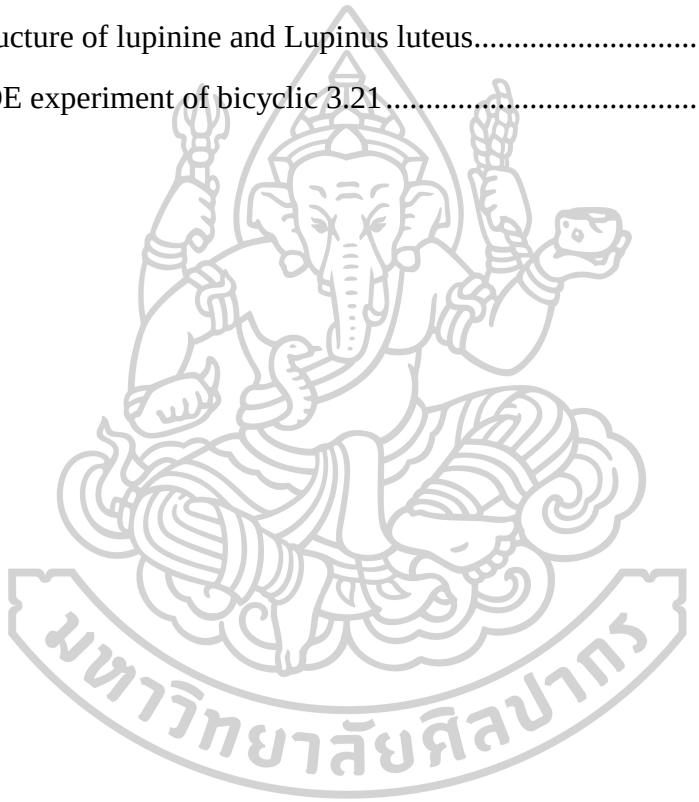

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CHAPTER 1

INTRODUCTION

Background and Signification of the Research Problem

Alkaloids [1] are a type of compound from natural sources which can be isolated from a large variety of organisms including animals, plants, bacteria and fungi. Alkaloids have been used for a wide range of pharmacology for example antimalarial (quinine), analgesic (morphine) and antibacterial (chelerythrine). The elementary alkaloids contain carbon, hydrogen and nitrogen and may consist of other elements such as oxygen, sulphur, chlorine, bromine and phosphorus. Alkaloids can be classified using various criteria for instance it can be based on the ring structure containing the nitrogen, their pharmacological action and their taxonomy [2]. Exemplified classifications are shown in figure 1.

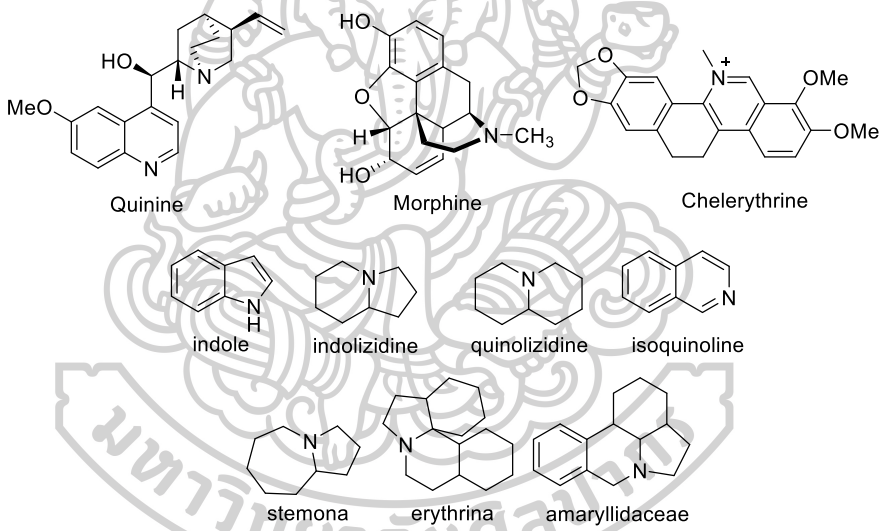
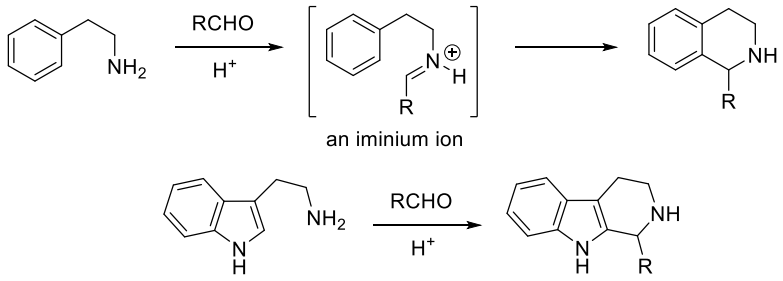


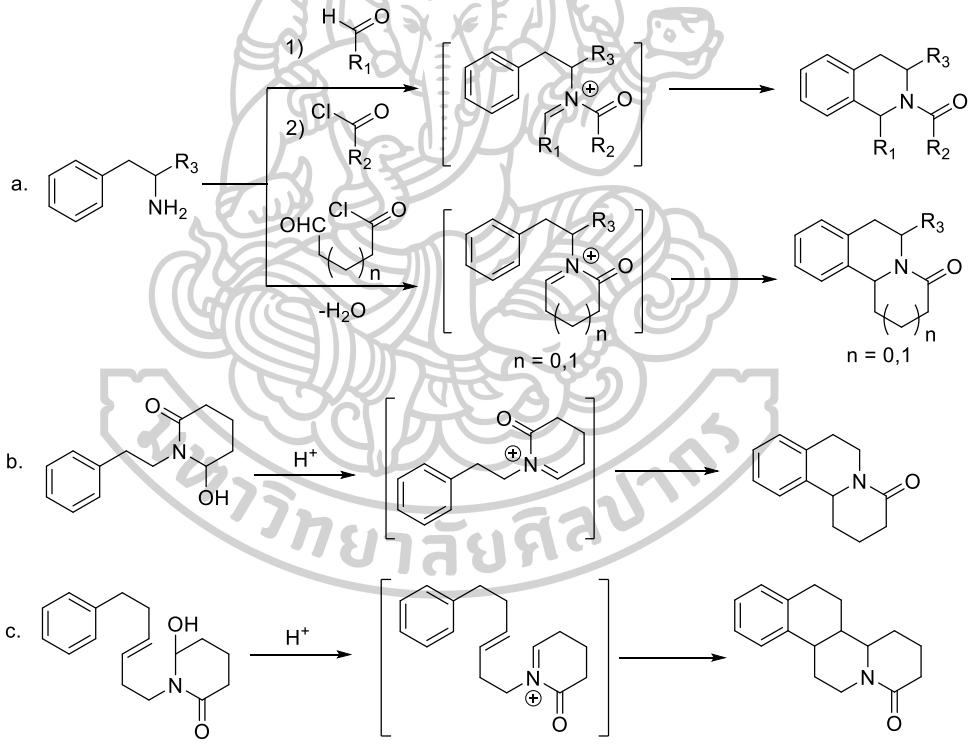
Figure 1 Examples of alkaloids and exemplified classifications

We have seen that alkaloids are important for medicine and pharmacology. Thus, the synthetic chemists have synthesized biologically active alkaloids and their analogues. A reaction which is well-known for synthesis of tetrahydroquinoline, a class of alkaloids, is Pictet-Spengler reaction. It is a cyclization between an amine carrying an aromatic ring and an aldehyde that is usually catalysed by acid. An intermediate of Pictet-Spengler reaction is an iminium ion. Originally, the reaction employed formaldehyde and phenylamine to give the tetrahydroisoquinoline skeleton (scheme 1).



Scheme 1 Pictet-Spengler reaction

N-acyliminium ion cyclization [3-7] and tandem *N*-acyliminium ion cyclization are other forms of Pictet-Spengler reaction which are important in organic synthesis. *N*-acyliminium ions are very reactive intermediates and can act as high electron-deficient carbocations toward weak nucleophiles which is an especially useful method in form an intramolecular cyclization. Besides aromatic ring, alkene can also act as nucleophile in this reaction (scheme 2).



Scheme 2 *N*-acyliminium ion cyclization

In this research, we will discuss synthetic studies of two members of pyrrolidine containing alkaloids which are grandisine A, a tricyclic indolizidine alkaloids and stemoamide, a stemona alkaloid and related alkaloids via *N*-acyliminium ion cyclization or tandem *N*-acyliminium ion cyclization as a key step.

Objectives of Research

1. To study a synthetic methodology of grandisine A.
2. To study a synthetic methodology of stemoamide.
3. To study a synthetic methodology of related alkaloids.
4. To develop the *N*-acyliminium ion cyclization and tandem *N*-acyliminium ion cyclization.

CHAPTER 2

LITERATURE REVIEW

Grandisine A

Grandisine A is one of the members of indolizidine alkaloids [8-10]. It was first isolated by Carroll and co-workers [11] in 2005 from the leaves of the Australian rainforest tree *Elaeocarpus grandis* (Blue Quandong). Moreover, grandisine A possesses a human δ-opioid receptor affinity (IC_{50} = 2.7 μM). The structure consists of four linked rings containing bis-dihydropyran and indolizidine core. There are five stereogenic centers.

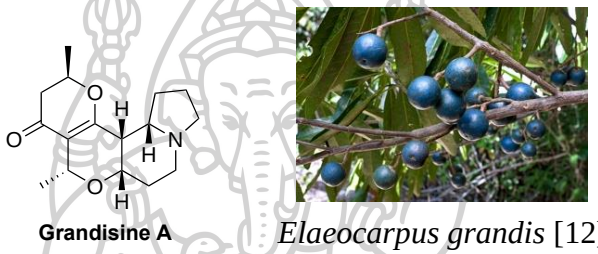
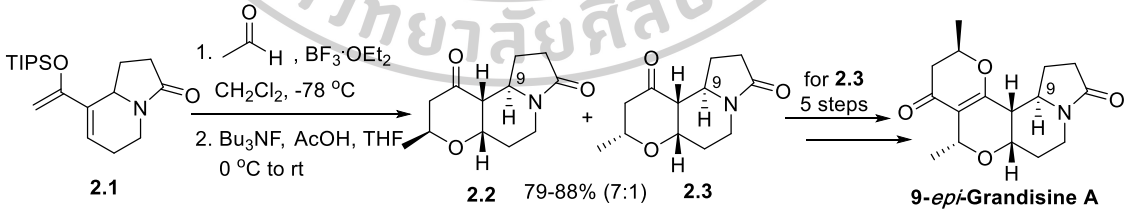


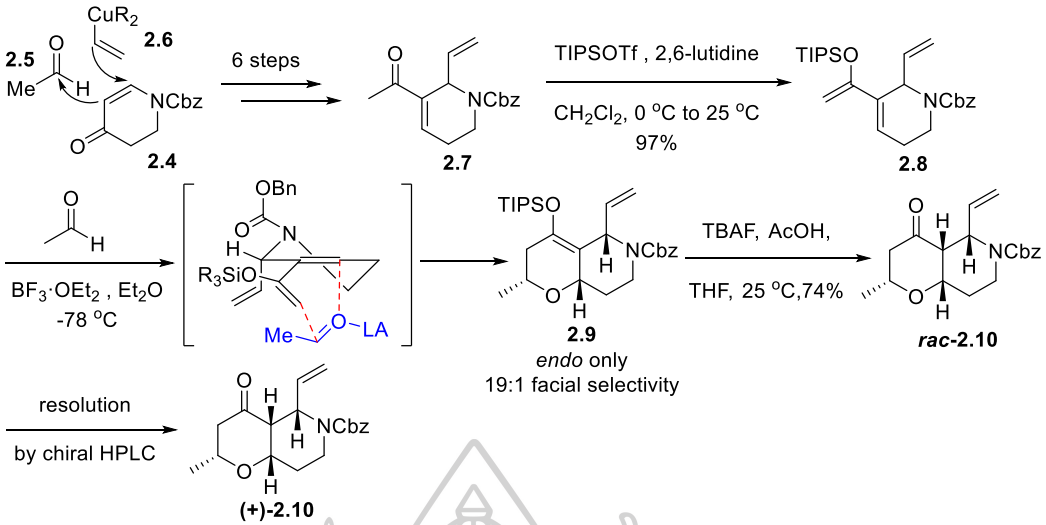
Figure 2 Structure of grandisine A and *Elaeocarpus grandis*

Maloney and Danishefsky was the only one group that has reported a total synthesis of grandisine A. In 2007, they reported a total synthesis of 9-*epi*-grandisine A [13]. A key step for the synthesis was a cycloaddition between diene **2.1** and acetaldehyde in the presence of $BF_3{\cdot}OEt_2$ followed by cleavage of TIPS group to give tricyclic **2.2** and **2.3**. After that, the tricyclic **2.3** was converted to 9-*epi*-grandisine A in 5 steps (scheme 3).



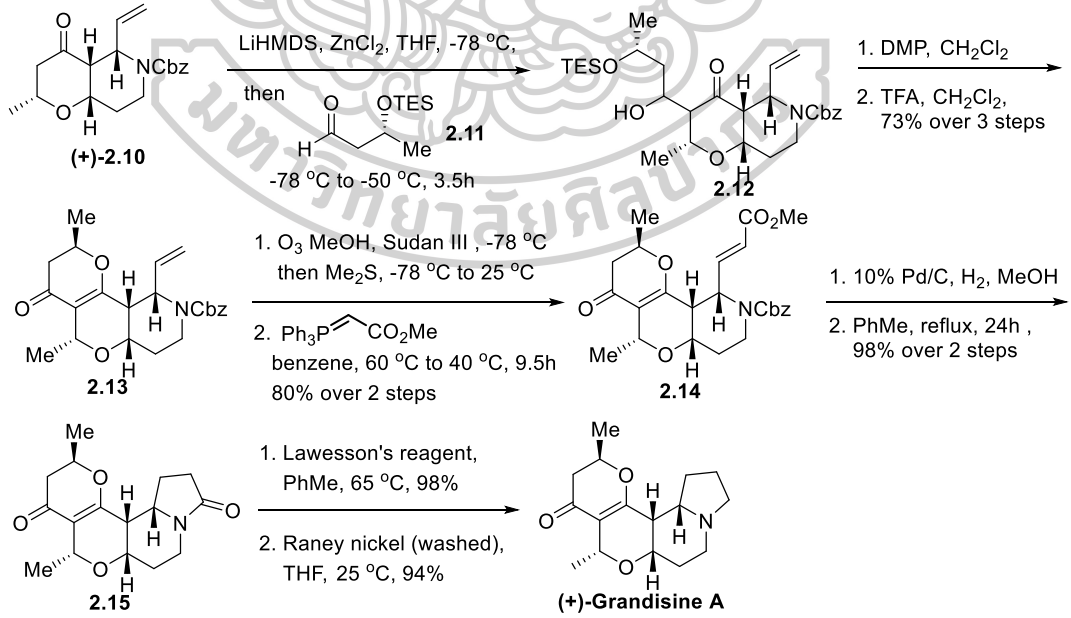
Scheme 3 Synthesis of 9-*epi*-grandisine A by Maloney and Danishefsky

In the same year, they reported the first total synthesis of (+)-grandisine A [14]. The synthesis was completed in 18 steps and started from dihydropyridone **2.4**. The key step of the synthesis was a Lewis acid catalyzed diene-aldehyde cyclocondensation to construct dihydropyran **2.9**. Diene **2.8** was reacted with acetaldehyde in a cycloaddition in the presence of $BF_3{\cdot}OEt_2$ which provided *endo* adduct of bicyclic **2.9**. After that, bicyclic *rac*-**2.10** was resoluted by a chiral HPLC to give an enantiomer of bicyclic (+)-**2.10** (scheme 4).



Scheme 4 Key step for synthesis of (+)-grandisine A by Maloney and Danishefsky

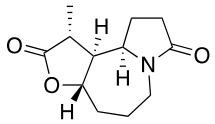
To complete the synthesis, (+)-bicyclic **2.10** was transformed to (+)-grandisine A in 9 steps. Adol reaction of (+)-bicyclic **2.10** with aldehyde **2.11** followed by oxidation and deprotection gave tricyclic **2.13**. Installation of allyl ester was succeeded by ozonolysis and Wittig reaction to give unsaturated ester **2.14**. To construct a tetracyclic core **2.15**, hydrogenation and removal of Cbz group of unsaturated ester **2.14** gave a desired tetracyclic **2.15**. Reduction of lactam was accomplished by Lawesson's reagent followed by Ranel nickel to give (+)-grandisine A (scheme 5).



Scheme 5 Completed synthesis of (+)-grandisine A by Maloney and Danishefsky

Stemoamide

Stemoamide is a member of *Stemona* alkaloids [15] which was isolated from the roots of *Stemona tuberosa* Lour by Xu and co-workers [16] in 1992. It possesses a wide variety of interesting activities ranging from usage as Chinese traditional medicine, herbicide, and insecticide. Stemoamide contains a tricyclic core azepine γ-lactone and four stereogenic centers.

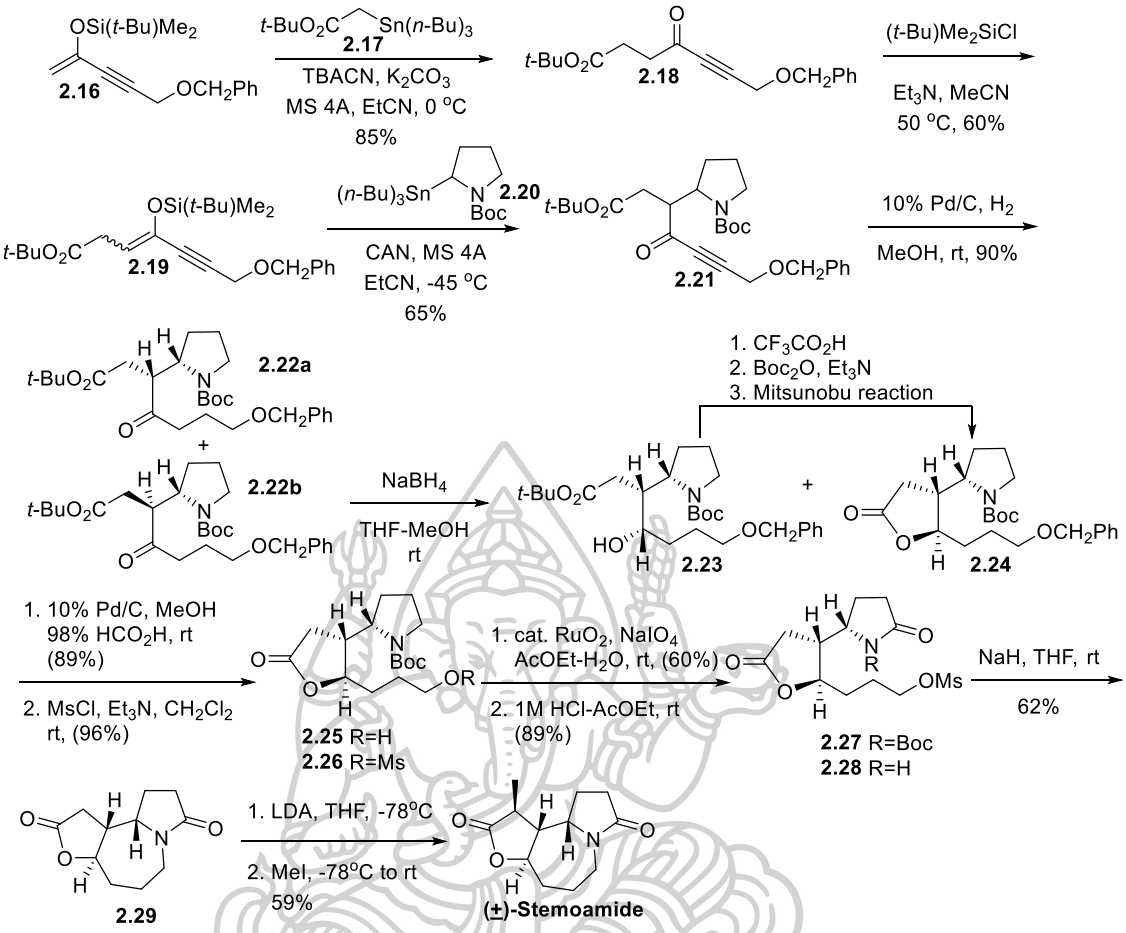


Stemoamide

Stemona tuberosa [17]

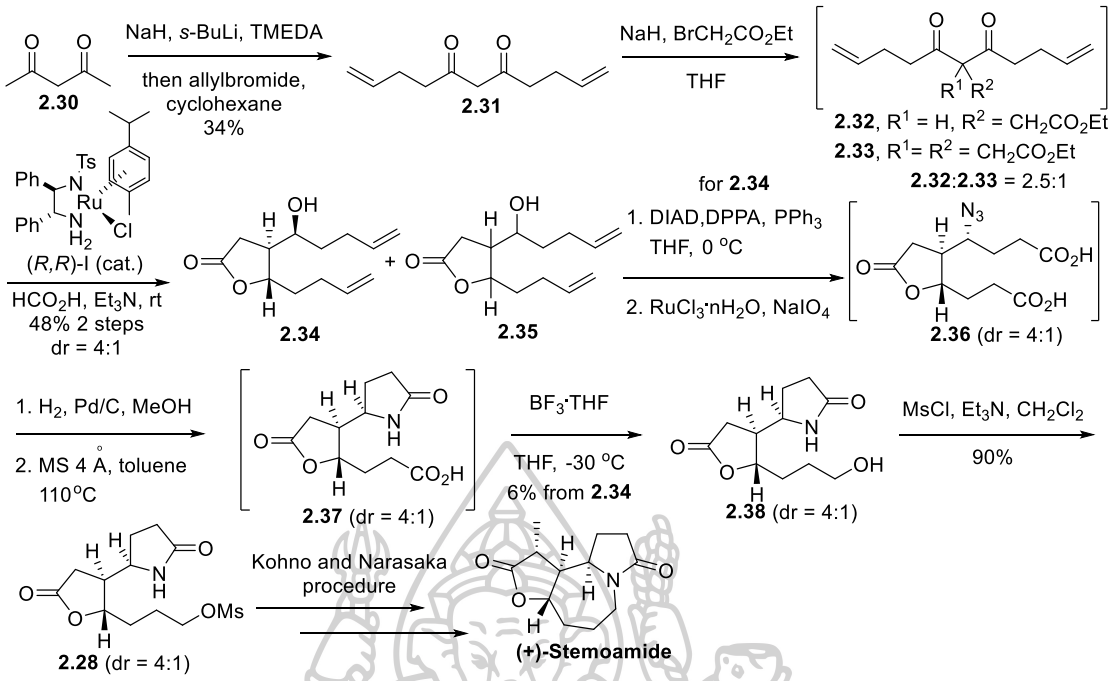
Figure 3 Structure of stemoamide and *Stemona tuberosa*

The synthetic chemists have reported a synthesis of stemoamide in both racemic and enantioselective routes [18]. Herein, the selected syntheses of stemoamide will be exemplified. In 1996, Kohno and Narasaka [19] reported a racemic synthesis of stemoamide. The synthesis started from the oxidative radical addition reaction of the silyl enol ether **2.16** and stannous **2.17** with TBACN in the presence of K_2CO_3 to give an acetylenic keto ester **2.18**. The adduct **2.18** was converted to a silyl enol ether **2.19** with (*t*-Bu)Me_2SiCl and Et_3N. Then, Oxidation of the stannyl pyrrolidine **2.20** with CAN in the presence of the silyl enol ether **2.19** provided compound **2.21**. Hydrogenation of alkyne **2.21** gave two diastereomers of **2.22a** and **2.22b**. The compound **2.22b** was reduced by $NaBH_4$ to give alcohol **2.23** and lactone **2.24** and alcohol **2.23** could be converted to lactone **2.24** in 3 steps. Cleavage of the benzyl group and subsequent mesylation afforded compound **2.26**. RuO_4 oxidation and deprotection of Boc group furnished lactam **2.28**. To construct a tricyclic core, lactam **2.28** was treated with NaH to give tricyclic **2.29** which was converted to (±)-stemoamide by methylation (scheme 6).



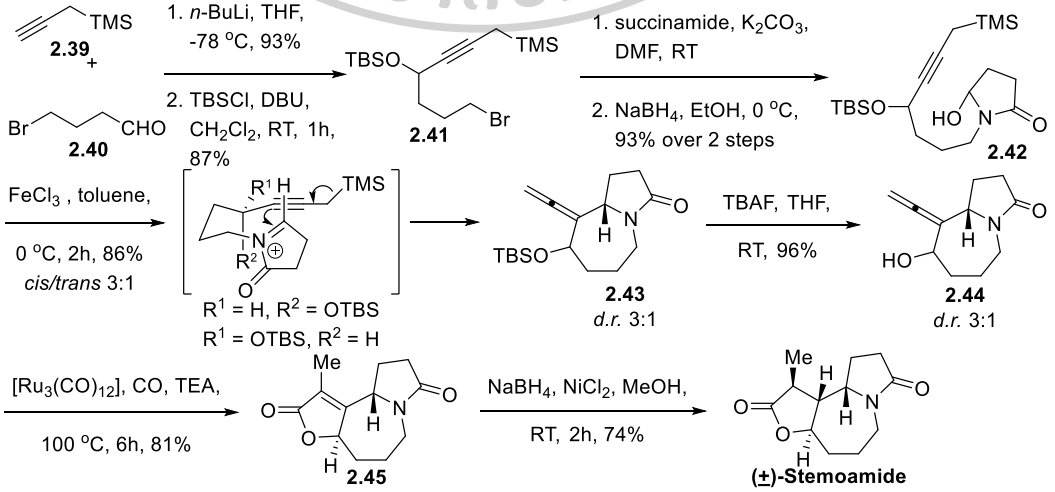
Scheme 6 Total synthesis of (±)-stemoamide by Kohno and Narasaka

In 2006, Bogliotti and co-workers [20] reported a formal synthesis of (+)-stemoamide. The diketoester **2.33** was synthesized from bis-allylation of acetylacetone **2.30** to give compound **2.31**. The treatment of diketone **2.31** with NaH and bromoacetate provided an inseperable mixture of monoalkylated compound **2.32** and dialkylated compound **2.33**. Desymetrization of diketone **2.33** by Noyori's catalyst (*R*,*R*)-I under hydrogen transfer condition gave a desired lactone **2.34** and an undesired lactone **2.35**. To construct the lactam ring, hydroxy lactone **2.34** was converted to corresponding azide under Mitsunobu reaction followed by ruthenium-catalyzed periodate oxidative cleavage to give azide **2.36**. Then, hydrogenolysis of azide **2.36** and subsequent cyclization furnished lactam **2.37**. At the end, the carboxylic acid was reduced selectively to the alcohol **2.38** with borane in THF followed by mesylation to give compound **2.28**. Since the racemic form of mesylate **2.28** had been previously converted to (±)-stemoamide by Kohno and Narasaka [19], this approach constitutes a formal synthesis of (+)-stemoamide (scheme 7).



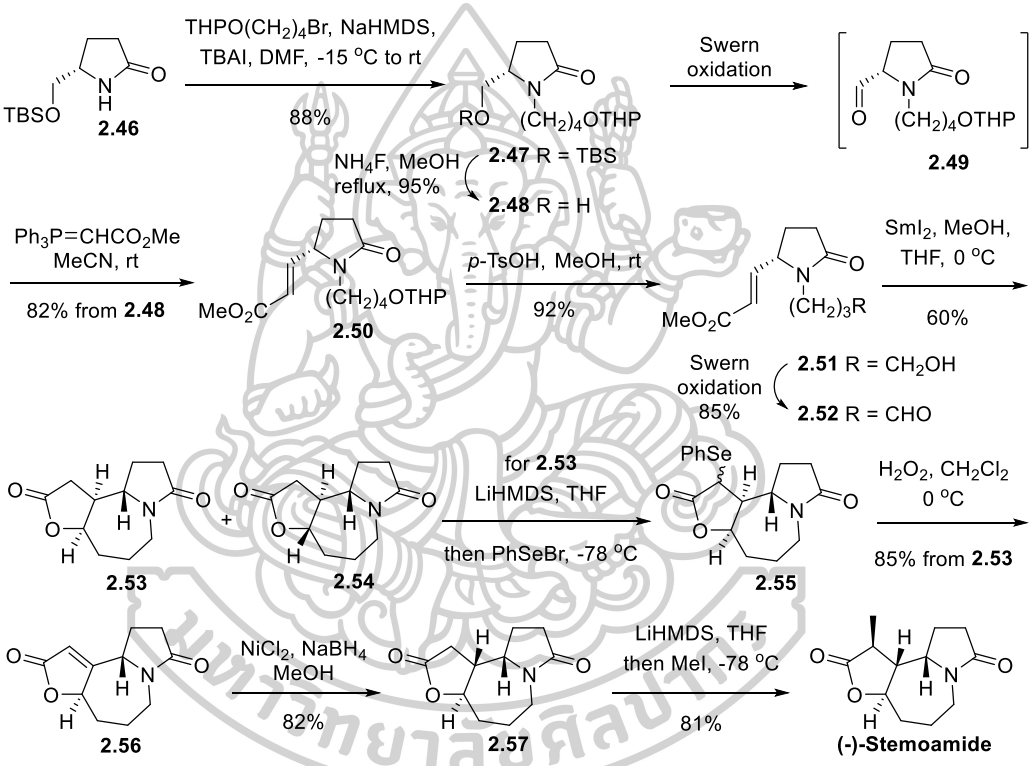
Scheme 7 Formal synthesis of (+)-stemoamide

In 2011, the most recent racemic synthesis was introduced by Wang and co-workers [21]. The synthesis started from alkynylayion of propargyl trimethylsilane **2.39** and aldehyde **2.40** to give bromide **2.41**. Then, *N*-alkylation followed by reduction furnished hydroxylactam **2.42**. The pyrole-azepine ketene core **2.43** of stemoamide was constructed by *N*-acyliminium ion cyclization in the presence of $FeCl_3$. The subsequent removal of TBS provided alcohol **2.44**. The conversion of bicyclic **2.44** into tricyclic **2.45** was succeeded by ruthenium-catalyzed CO-insertion reaction. Finally, a nickel-catalyzed reduction accomplished (±)-stemoamide. The synthesis was completed in 8 steps, 37% overall yield from commercially available propargylsilane **2.39** (scheme 8).



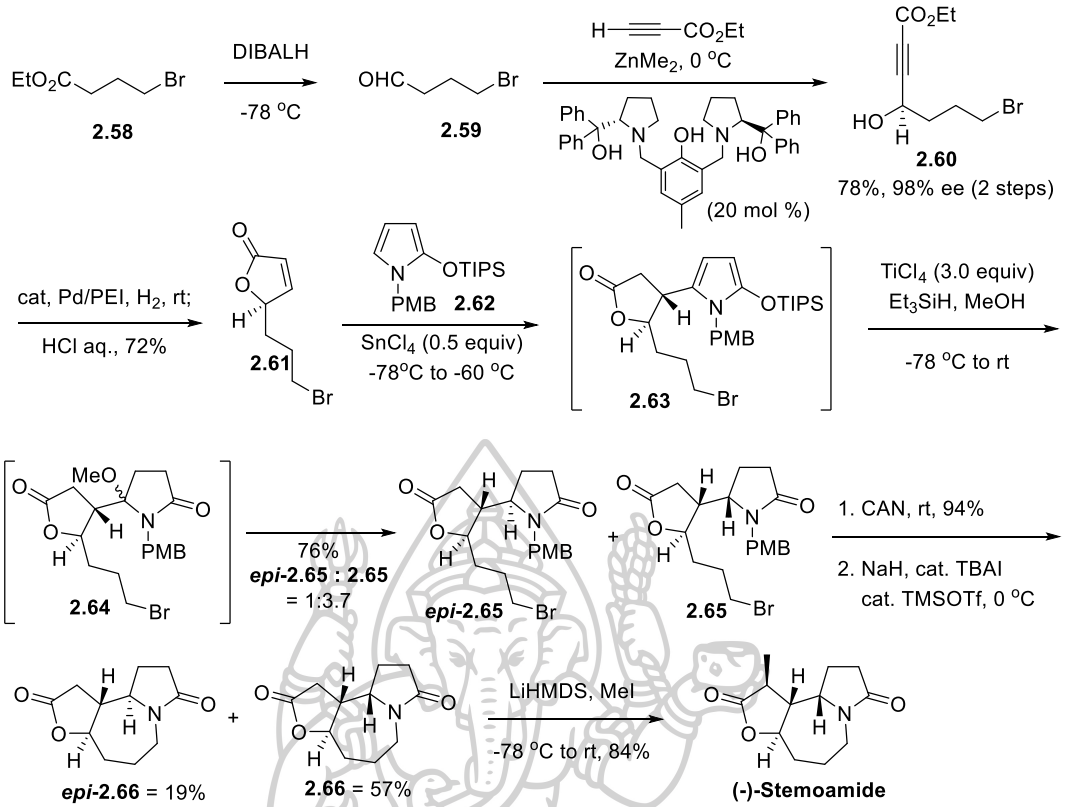
Scheme 8 Synthesis of (±)-stemoamide by Wang and co-workers

In the same year, Honda and co-workers [22] reported a diastereoselective synthesis of (-)-stemoamide. The synthesis started with *N*-alkylation of lactam **2.46** followed by removal of TBS group to give alcohol **2.48**. Then, Swern oxidation and subsequent Wittig reaction provided unsaturated ester **2.50**. The treatment of *p*-TsOH afforded alcohol **2.51** which was oxidized to a corresponding aldehyde **2.52**. An intramolecular samarium diiodide-promoted 7-*exo-trig* cyclization of a ketyl radical generated from the corresponding aldehyde gave an inseparable diastereoisomeric mixture of coupling products **2.53** and **2.54**. For tricyclic **2.53**, it was treated with phenylselenyl bromide in the presence of LiHMDS to give selenide **2.55** which was converted to lactone **2.56** by H_2O_2. Reduction by $NiCl_2$ and $NaBH_4$ followed by a stereoselective methylation furnished (-)-stemoamide (scheme 9).



Scheme 9 Synthesis of (-)-stemoamide by Honda and co-workers

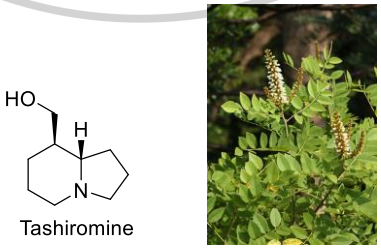
The recent enantioselective synthesis of (-)-stemoamide reported by Yoritate and co-workers [23] in 2017 was achieved in 8 steps. It started from DIBALH reduction of commercially available ethyl 4-bromobutyrate **2.58** followed by an enantioselective alkynylation to afford alcohol **2.60**. Hydrogenation of alcohol **2.60** by Sajiki's catalyst (Pd/PEI) resulted in the methyl *Z*-enolate which was immediately transformed to lactone **2.61** by acidic workup. The coupling reaction of *N*-PMB-2-siloxypyrrole **2.62** and lactone **2.61** by Michael addition followed by subsequent one-pot reduction provided an inseparable mixture of *epi*-**2.65** and **2.65**. After clevage of PMB group, the construction of tricyclic core of *epi*-**2.65** and **2.65** with NaH in the presence of TBAI and TMSOTf gave a separable mixture of **2.66** and *epi*-**2.66**. Finally, the stereoselective methylation of tricyclic **2.66** furnished (-)-stemoamide (scheme 10).



Scheme 10 Synthesis of (-)-stemoamide by Yoritate and co-workers

Tashiromine

Tashiromine is a naturally occurring indolizidine alkaloid which was first isolated from an Asian deciduous shrub *Maackia tashiroi* by Ohmiya and co-workers [24]. Tashiromine is one of the structurally simple indolizidine alkaloids. The structure consists of indolizidine core substituted by hydroxymethyl group and contains two stereocenters.

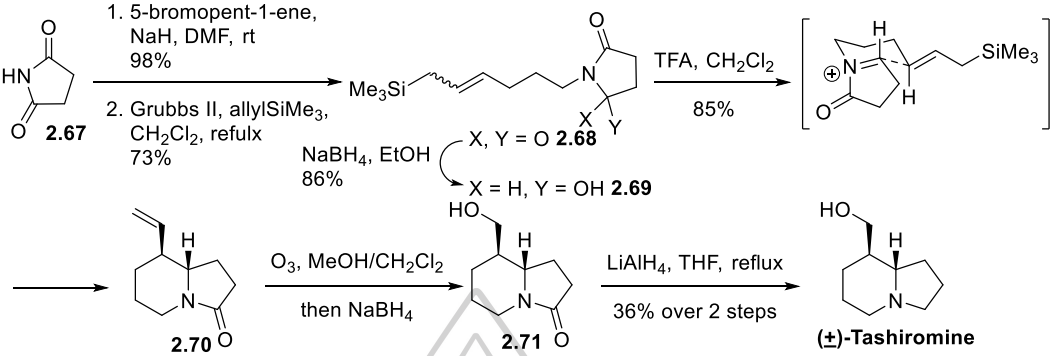


Maackia tashiroi [25]

Figure 4 Structure of tashiromine and *Maackia tashiroi*

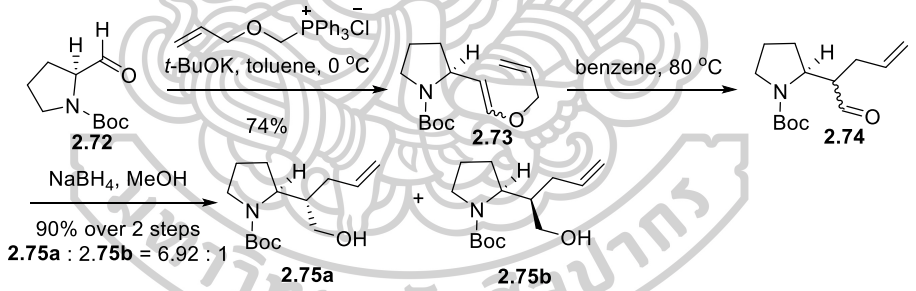
Due to a simple structure, tashiromine has been popular for synthetic chemists. In 2008, Marsden and McElhinney [26] reported a racemic synthesis of tashiromine. The synthesis started from *N*-alkylation of succinimide **2.67** followed by cross metathesis to give imide **2.68**. Then, it was transformed to hydroxylactam **2.69**, a precursor of *N*-acyliminium ion cyclization with $NaBH_4$ reduction. A treatment of

hydroxylactam **2.69** with TFA gave bicyclic **2.70**. After that, oxidative cleavage and subsequent reduction afforded alcohol **2.71** which was converted to tashiromine by $LiAlH_4$ reduction (scheme 11).



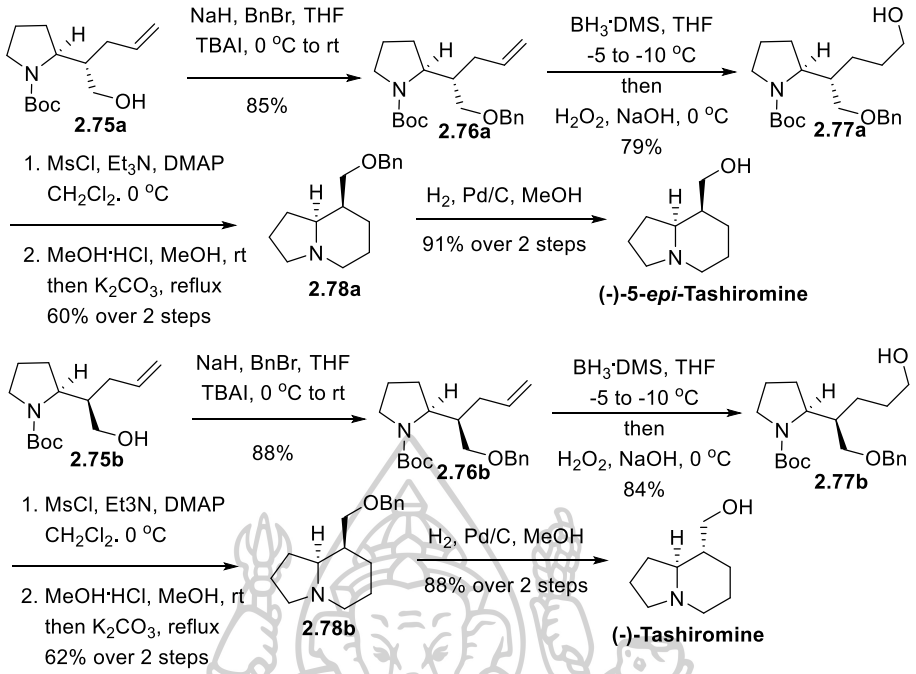
Scheme 11 Synthesis of tashiromine by Marsden and McElhinney

The other example of a synthetic route of tashiromine features a highly enantioselective synthesis. In 2011, Gavhane and co-workers[27] reported asymmetric synthesis of (-)-5-*epi*-tashiromine and (-)-tashiromine. The synthesis started from Wittig olefination of *L*-prolinal derived from *L*-proline to give allyl vinyl ether **2.73** which was subjected to a Claisen rearrangement in refluxing benzene to give corresponding aldehyde **2.74**. Then, the treatment of aldehyde **2.74** with $NaBH_4$ furnished alcohol **2.75a** and **2.75b** (scheme 12).



Scheme 12 Synthesis of alcohol **2.75a** and **2.75b**

After obtaining alcohol **2.75a** and **2.75b**, they were converted to (-)-5-*epi*-tashiromine and (-)-tashiromine respectively in separated route using the same approach. The construction of piperidine ring started from protection of alcohol **2.75a** and **2.75b** followed by hydroboration/oxidation to give desired alcohols **2.77a** and **2.77b**. Then, Alcohols **2.77a** and **2.77b** upon mesylation, Boc-deprotection and cyclization afforded indolizidines **2.78a** and **2.78b**. Finally, bicyclic **2.78a** and **2.78b** was converted to (-)-5-*epi*-tashiromine and (-)-tashiromine by hydrogenation (scheme 13).



Scheme 13 Completed synthesis of (-)-5-*epi*-tashiromine and (-)-tashiromine

Lupinine

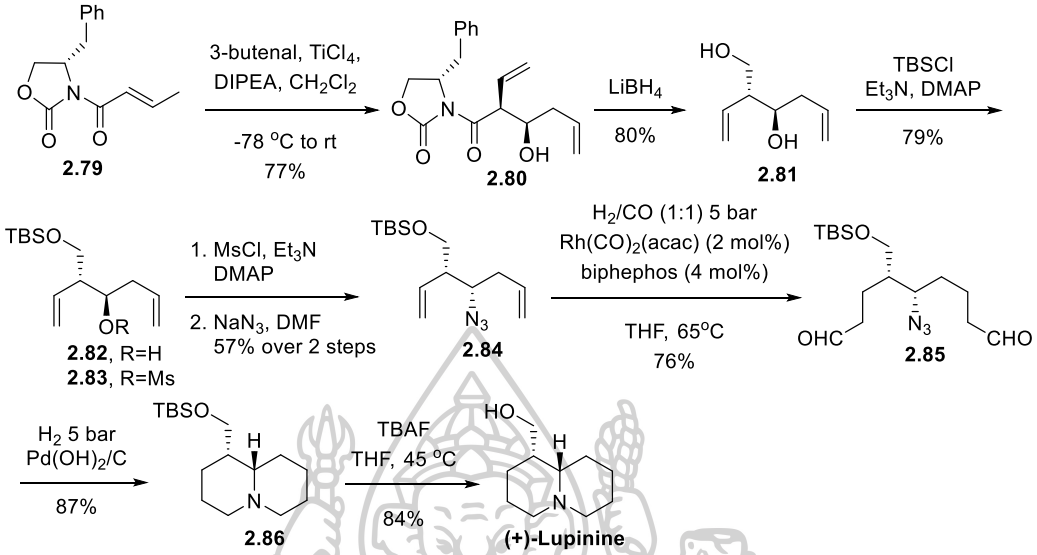
Lupinine is a member of quinolizidine alkaloids [8-10], first isolated from seeds of *Lupinus luteus* by Ohmiya and Otomasu in 1975 [28]. A structure of lupinine consists of core skeleton of quinolizidine, a linked bipiperidine, substituted by hydroxymethyl group. It contains two stereogenic centers at ring junction and substituent group.

Lupinus luteus [29]

Figure 5 Structure of lupinine and *Lupinus luteus*

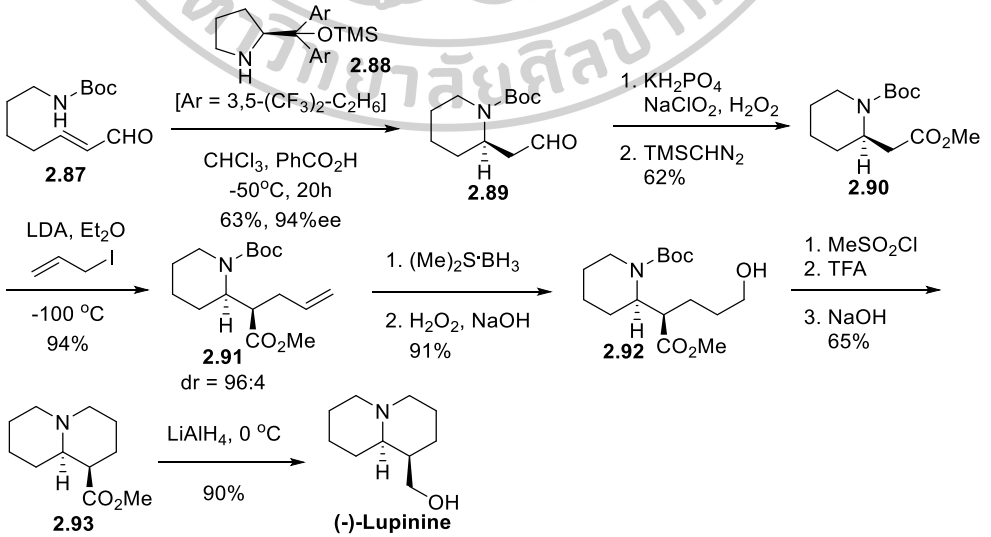
Owing to an incomplex structure, chemists chose lupinine as a target molecule for synthesis to feature different quinolizidine formations. In 2009, a short synthesis of (+)-lupinine was reported by Airiau and co-workers [30]. The synthesis started from Evans adol reaction between oxazolidinone **2.79** and 3-butenal to give alcohol **2.80** as a single diastereomer. Then, the chiral auxiliary was removed by $LiBH_4$ to provide diol **2.81**. The primary alcohol was protected as a TBS ether while the secondary alcohol was converted to azide **2.84**. After that, hydroformylation catalyzed by Rh catalyst gave corresponding aldehyde **2.85** and subsequent azide

reduction/reductive amination provided bicyclic **2.86**. In the end, the treatment of quinolizidine core **2.86** with TBAF afforded (+)-lupinine in 8 steps (from **2.79**) with an overall yield of 15% (scheme 14).



Scheme 14 Synthesis of (+)-lupinine by Airiau and co-workers

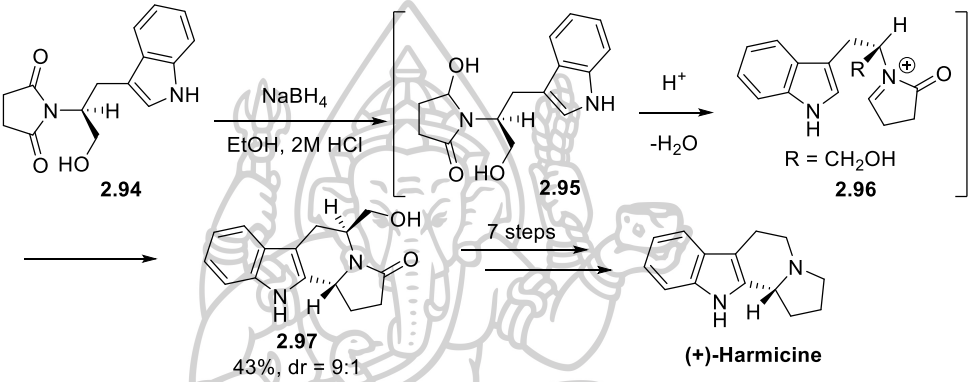
In 2011, an enantioselective synthesis of (-)-lupinine was reported by Fustero and co-workers [31]. The synthetic approach started form highly diastereoselective aza-Michael addition of unsaturated aldehyde **2.87** which was treated with Jørgensen diarylprolinol **2.88** to give piperidine **2.89**. Then, aldehyde **2.89** was converted to methyl ester **2.90** in 2 steps via oxidation followed by treatment with $TMSCHN_2$. Allylation of ester **2.90** with allyliodide provided compound **2.91** which was transformed to alcohol **2.92** by hydroboration/oxidation. Then, alcohol **2.92** upon mesylation, Boc-deprotection and cyclization gave quinolizidine **2.93**. Finally, $LiAlH_4$ reduction of quinolizidine **2.93** afforded (-)-lupinine (scheme 15).



Scheme 15 Synthesis of (+)-lupinine by Fustero and co-workers

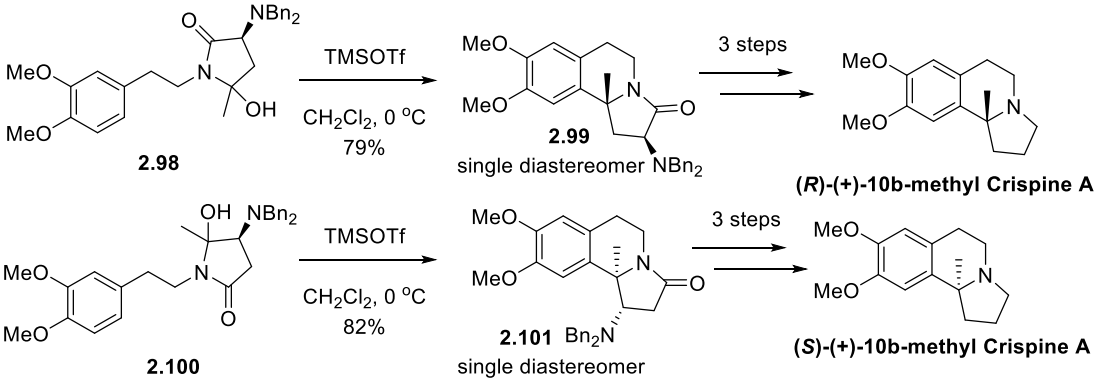
N-acyliminium ion cyclization

N-acyliminium ion cyclization is useful in a few of the syntheses that we have seen above. Additional selected syntheses of natural and non-natural analogues of alkaloids via *N*-acyliminium ion cyclization will be discussed. Asymmetric approach for the synthesis of (+)-harmicine via a highly diastereoselective *N*-acyliminium ion cyclization was reported by Allin and co-workers [32]. The synthesis started with $NaBH_4$ reduction of imide **2.94** and subsequent acid-catalysed *N*-acyliminium ion cyclization to give tetracyclic core **2.97** in 43% (dr = 9:1). A new stereocenter was controlled by the hydroxymethyl auxiliary group with high stereoselectivity. Then, it was removed in 7 steps to afford (+)-harmicine (scheme 16).



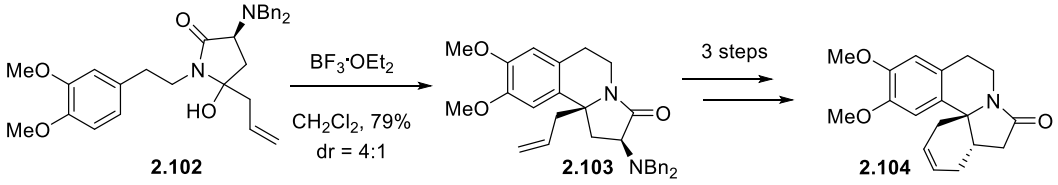
Scheme 16 Synthesis of (+)-harmicine

The synthesis of analogues of crispine A was reported by Kuntiyong and co-workers [33]. Hydroxylactam **2.98** derived from L-aspartic acid was treated with TMSOTf to generate *N*-acyliminium ion which cyclized to give tricyclic **2.99** as a single diastereomer. It was transformed to (*R*)-(+)-10b-methyl crispine A in 3 steps. In the same way, hydroxylactam **2.100** was converted to tricyclic **2.101** via *N*-acyliminium ion and it was transformed to (*S*)-(-)-10b-methyl crispine A. The new stereocenters of tricyclic **2.99** and **2.101** were controlled by the dibenzylamino group (NBn_2) (scheme 17).



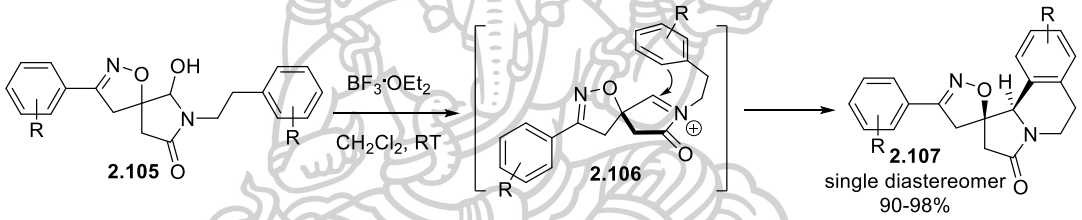
Scheme 17 Synthesis of analogues of crispine A

Moreover, they also reported the synthesis of tetracyclic core of *Erythrina* alkaloids. *N*-acyliminium ion cyclization of hydroxylactam **2.102** using $BF_3{\cdot}OEt_2$ provided tricyclic **2.103** with dr = 4:1. Finally, it was converted to core of *Erythrina* alkaloids **2.104** in 3 steps (scheme 18).



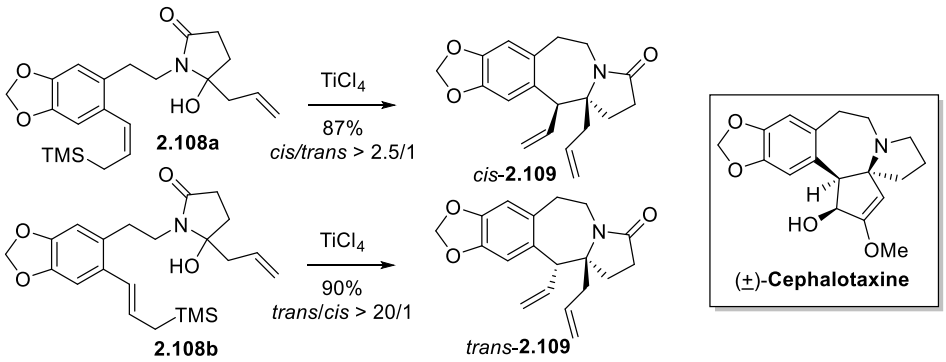
Scheme 18 Synthesis of core of *Erythrina* alkaloids

The synthesis of substituted spiro[isoxazolopyrroloisoquinolines] via diastereoselective *N*-acyliminium ion cyclization was reported by Ledovskaya and co-workers [34]. The reaction occurs by direct attack on the *N*-acyliminium ion intermediate **2.106** by the π-aromatic system linked to the nitrogen atom of the pyrrolidinone ring from the less hindered isoxazole side to produce the spiro[isoxazolopyrroloisoquinolines] **2.107** (scheme 19).



Scheme 19 Diastereoselectivity in *N*-acyliminium ion cyclization

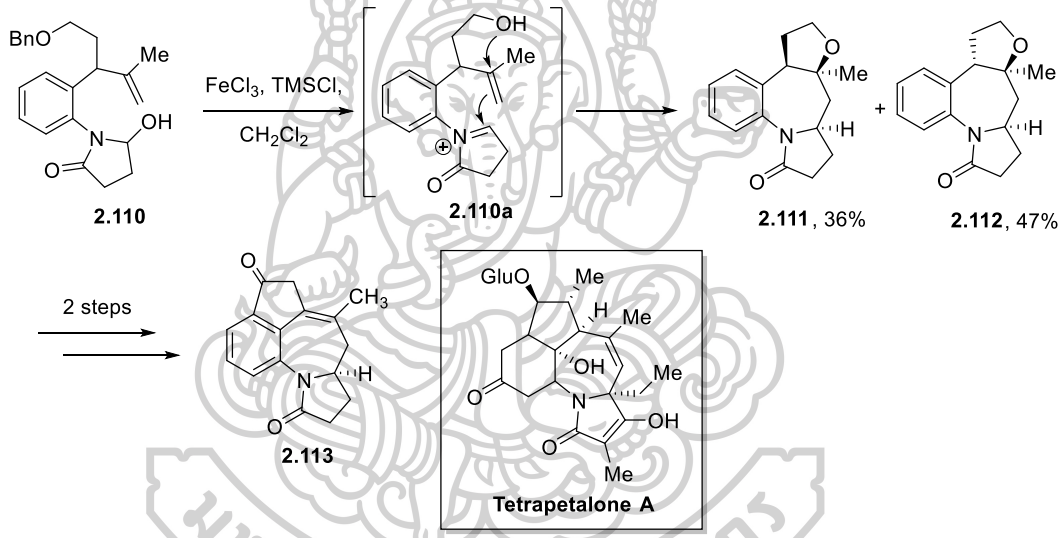
When the nucleophile is an internal alkene the stereochemical outcome in the *N*-acyliminium ion cyclization was dependent on the stereoelectronic effect of the *Z*- or *E*-isomer. An interesting example is shown below. The formal synthesis of (±)-cephalotaxine was reported by Liu and co-workers [35]. *Z*- and *E*-allylsilane was treated with $TiCl_4$. *Z*-allylsilane **2.108a** gave *cis*-**2.109** (cis/trans > 2.5/1) with lower stereoselectivity than the product from *E*-allylsilanec **2.108b** which gave *trans*-**2.109** (trans/cis > 20/1). Then, two diastereomers arising from the cyclization were merged into the formal synthesis of (±)-cephalotaxine (scheme 20).



Scheme 20 Formal synthesis of (±)-cephalotaxine

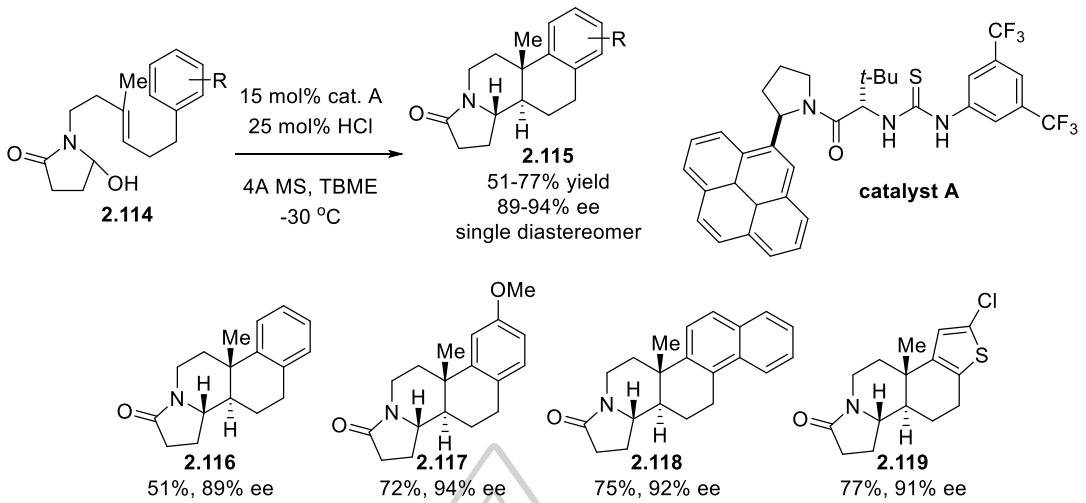
Tandem *N*-acyliminium ion cyclization

Alkene and alkyne can also serve as π-nucleophile in intramolecular *N*-acyliminium ion cyclization. Additionally, when the carbocationic intermediate can be trapped intramolecularly by a second nucleophile, i.e. a heteroatom, the process becomes a tandem cyclization in which two rings are formed in one step. An interesting example is shown below. The synthesis of a tetracyclic core of tetrapetalone A via tadem *N*-acyliminium ion cyclization was reported by Li and co-workers [36] in 2009. A conversion of hydroxylactam **2.110** catalysed by $FeCl_3$ afforded intermediate **2.110a**. An alcohol of *N*-acyliminium ion **2.110a** attacked to alkene which in turn attacked the *N*-acyliminium ion resulting in tandem cyclization accomplishing two diastereomers of tetracyclic **2.111** and **2.112**. Finally, tetracyclic **2.112** was transformed to tetracyclic **2.113** which was a core of tetrapetalone A (scheme 21).



Scheme 21 Synthesis of a tetracyclic core of tetrapetalone A

The other example of tandem *N*-acyliminium ion cyclization was reported in 2010. Knowles and co-workers [37] reported asymmetric synthesis of indolizidine containing tetracyclic system via the enantioselective cationic polycyclization. The hydroxylactam **2.114** was treated with 15 mol% of catalyst thiourea A, 25 mol% of HCl in TBME containing 4 Å molecular sieves at -30 °C resulting in the ploycyclic **2.116-2.119** (51-77% yield and 89-94% ee) with high enantioselectivity. Stabilizing cation-π interactions play a principal role in asymmetric induction (scheme 22).



Scheme 22 Tandem *N*-acyliminium ion cyclization in polycyclic cyclization

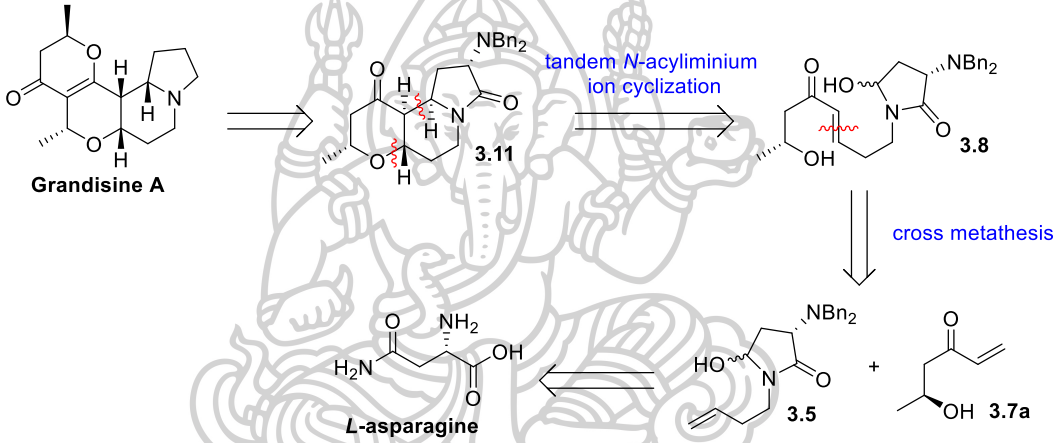
CHAPTER 3

SYNTHETIC STUDY

Part A: Synthetic studies of grandisine A

Retrosynthetic analysis

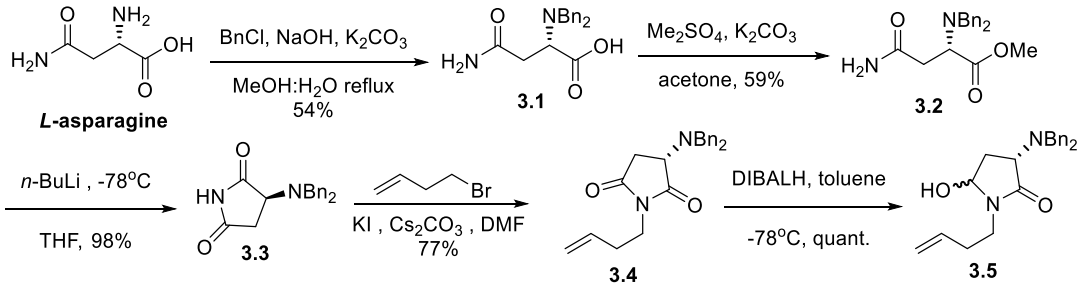
The synthesis of grandsine A was envisioned that it would be derived from tricyclic **3.11** from dihydropyranone formation. The tricyclic **3.11** could be derived from hydroxylactam **3.8** via tandem *N*-acyliminium ion cyclization. The hydroxylactam **3.8** wolud be synthesized from cross metathesis of unsaturated ketone **3.7** and hydroxylactam **3.5** which would be derived from *L*-asparagine (scheme 23).



Scheme 23 Retrosynthetic analysis of grandisine A

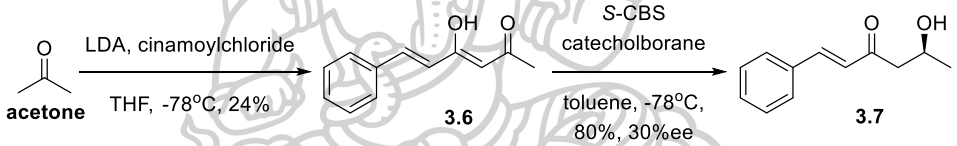
Synthetic study of grandisine A

The synthetic study of grandisine A started form benzylation of commercially available *L*-asparagine in basic condition using bezylchloride, NaOH and K_2CO_3 in MeOH and H_2O to give *N*,*N*-diBn-*L*-asparagine **3.1** in 54% . The methylation of benzylated asparagine **3.1** in the presence of Me_2SO_4 and K_2CO_3 in acetone provided methylester **3.2** in 59% yield. This was transformed to chiral succinamide **3.3** with *n*-BuLi in THF in excellent yield. Then, the conversion of imide **3.3** via *N*-alkylation with 4-bromo-1-butene afforded desired product **3.4** in 77% yield. Finally, the steric effect of dibenzylamino group played an important role in the regioselective reduction by DIBALH in toluene to give hydroxylactam **3.5** in quantitative yield (scheme 24).



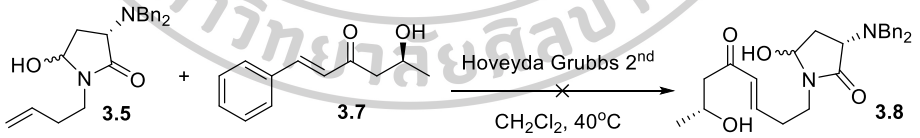
Scheme 24 Synthesis of hydroxylactam **3.5**

According to the retrosynthetic analysis, an alkene **3.8** would be derived from the cross metathesis of unsaturated ketone **3.7a** and hydroxylactam **3.5**. Herein, styrene **3.7** was used as the unsaturated ketone **3.7a** due to the availability of the starting material and the benzene ring can provide a chromophore for UV detection of the product. The synthesis of styrene **3.7** started from acylation between acetone and cinnamoylchloride to provide corresponding enol **3.6**. After that, the Corey-Bakshi-Shibata reduction of enol **3.6** catalysed by *S*-CBS in the presence of catecholborane afforded alcohol **3.7** (scheme 25).



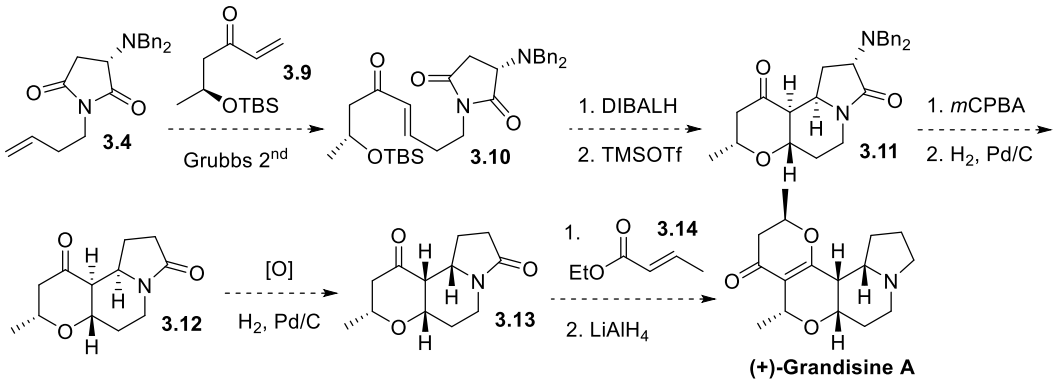
Scheme 25 Synthesis of alcohol **3.7**

After obtaining precursor **3.5** and **3.7**, however, the cross metathesis between hydroxylactam **3.5** and styrene **3.7** catalysed by Hoveyda-Grubbs 2nd generation catalyst in CH_2Cl_2 did not yield the desired product **3.8** (scheme 26).



Scheme 26 Synthesis of alkene **3.8**

Based on results of cross metathesis between terminal alkenes in our other studies which provided cross coupled products in good yield, we rationalize that the alkene derived from cinnamoyl chloride was not suitable and did not give the product. Therefore, to complete the synthesis of grandisine A, the synthetic plan was envisioned that imide **3.10** would be synthesized from cross metathesis of imide **3.4** and unsaturated ketone **3.9** catalysed by Grubbs 2nd generation to construct imide **3.10**. Then, it would be converted to tricyclic core **3.11** with DIBALH reduction and tandem *N*-acyliminium ion cyclization. After that, amino dibenzyl group would be removed by Cope elimination. Finally, the remaining steps would involve construction of the tetracyclic core to complete the synthesis of grandisine A (scheme 27).



Scheme 27 Synthetic plan for grandisine A (I)

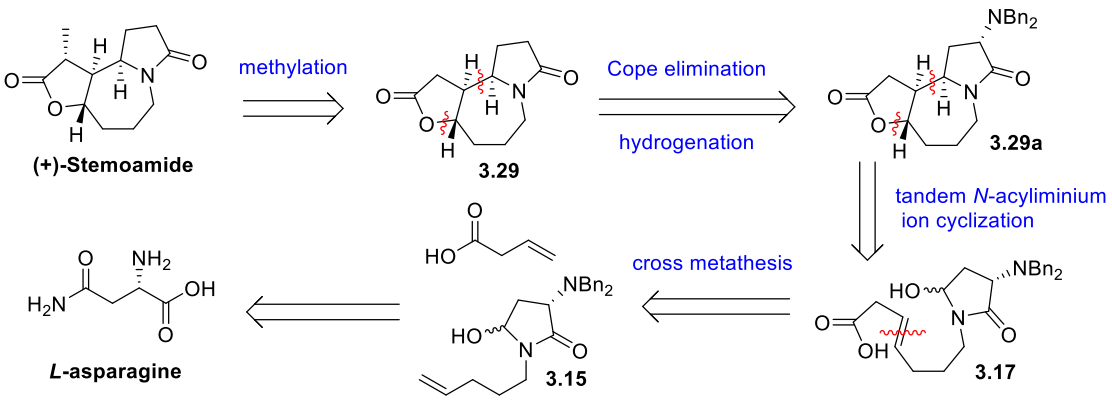
We will revisit the synthetic study of grandisine A after some interesting finding in the synthetic study of stemoamide.

Part B: Synthetic studies of stemoamide

The synthetic studies of stemoamide were divided into 3 routes. First, the synthetic methodology (route I and III) was envisioned that stemoamide would be derived via tandem *N*-acyliminium ion cyclization. Another route would rely on *N*-acyliminium ion cyclization.

Retrosynthetic analysis (I)

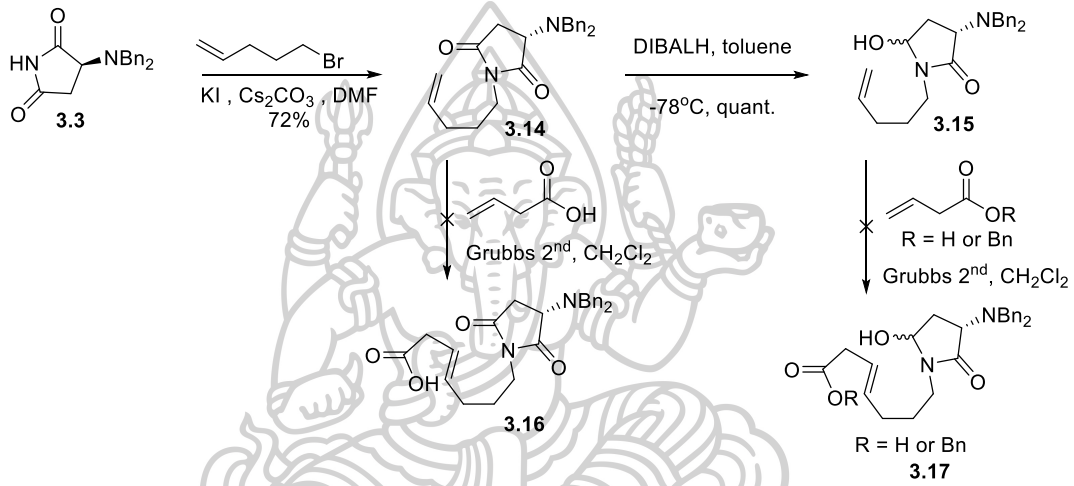
The initial retrosynthetic analysis was envisioned that stemoamide would be derived from lactone **3.29** via diastereoselective methylation. The lactone **3.29** would be synthesized form tricyclic **3.29a** with Cope elimination and subsequent hydrogenation. The tricyclic core of stemoamide could be obtained from precursor **3.17** through diastereoselective tandem *N*-acyliminium ion cyclization in which the stereochemistry would be controlled by the chiral substrate. The precursor **3.17** would be a cross metathesis product of butenoic acid and hydroxylactam **3.15** which could be prepared form *L*-asparagine (scheme 28).



Scheme 28 Retrosynthetic analysis of stemoamide (I)

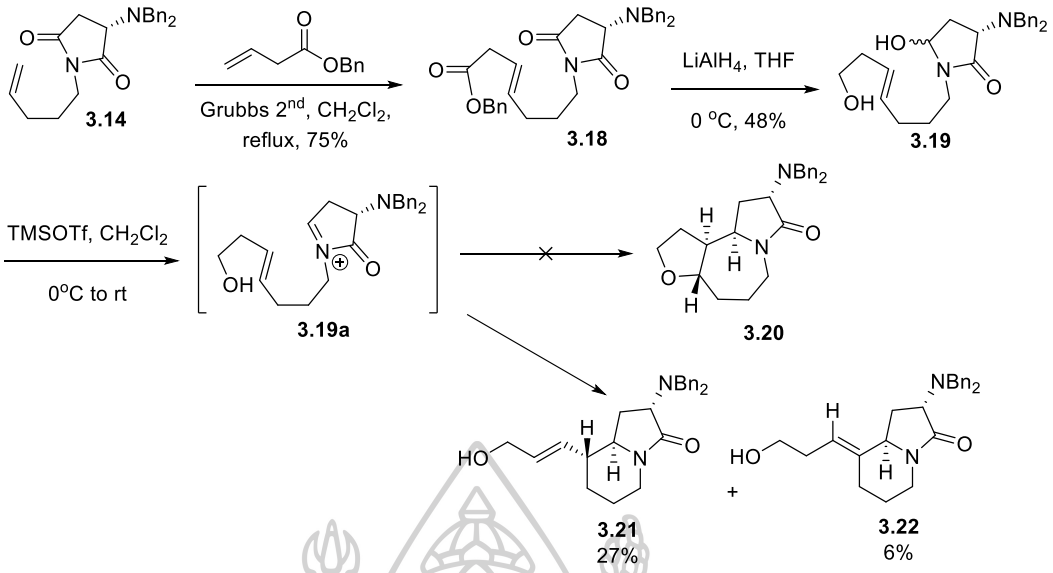
Synthetic study of stemoamide (I)

The synthetic study of stemoamide began with *N*-alkylation of chiral succinimide **3.3**, which derived from *L*-asparagine (scheme 22), with 5-bromopent-1-ene, Cs_2CO_3 and KI in DMF to give imide **3.14** in high yield. The regioselective reduction with DIBALH in toluene gave hydroxylactam **3.15** in quantitative yield. The attempt of cross metathesis between imide **3.14** and butenoic acid did not give the desired product **3.16**. Additionally, cross metathesis between hydroxylactam **3.15** and butenoic acid or benzyl but-3-enoate did not yield the desired product **3.17**. So, it was assumed that the functional groups of hydroxylactam and carboxylic acid were not suitable for the cross metathesis reaction (scheme 29).



Scheme 29 Synthetic approach for stemoamide (I)

However, an attempt to succeed the cross metathesis would go on. The cross metathesis between imide **3.14** and benzyl but-3-enoate catalysed by Grubbs 2nd generation refluxing in CH_2Cl_2 provided imide **3.18** in high yield. The treatment of imide **3.18** with $LiAlH_4$ in THF provided hydroxylactam **3.19**. Then, it was treated with TMSOTf in CH_2Cl_2 to give an intermediate *N*-acyliminium ion **3.19a**. The results of tandem *N*-acyliminium ion cyclization failed to construct a tricyclic core of stemoamide **3.20**. On the other hand, *N*-acyliminium ion cyclization employing *6-endo-trig* mode of Baldwin's rule [38, 39] gave bicyclic **3.21** and **3.22** instead of tricyclic **3.20** which would be resulted from *7-endo-trig* mode (scheme 30).



Scheme 30 The construction a tricyclic core of stemoamide

However, this result led to a new synthetic approach of stemoamide and the syntheses of two related alkaloids (tashiromine and lupinine) which will be discussed in part C and D.

An absolute configuration of new stereocenters from *N*-acyliminium ion cyclization was investigated by NOE experiment (figure 6). The proton (C) at the ring junction showed correlations with an alkene proton (A) and a benzylic proton (B). Therefore we assigned that proton C had *cis* relative configuration with proton B. Moreover, proton C also had *cis* relative configuration with the propenol substituent group.

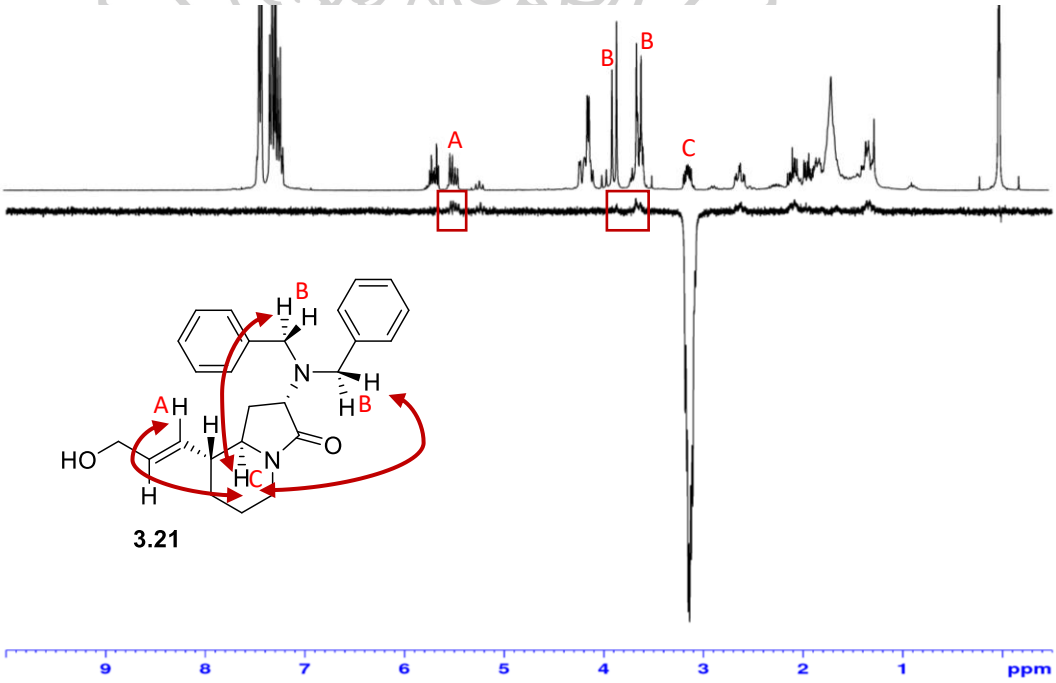
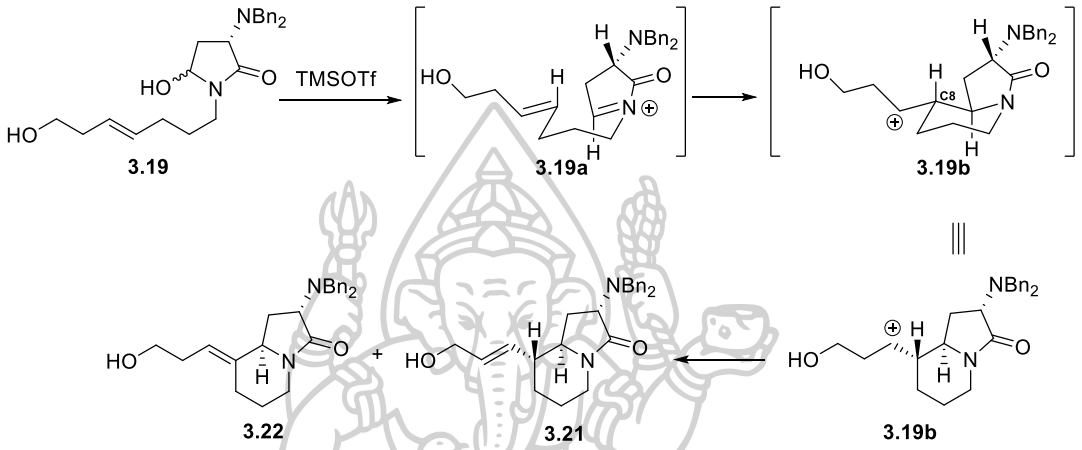


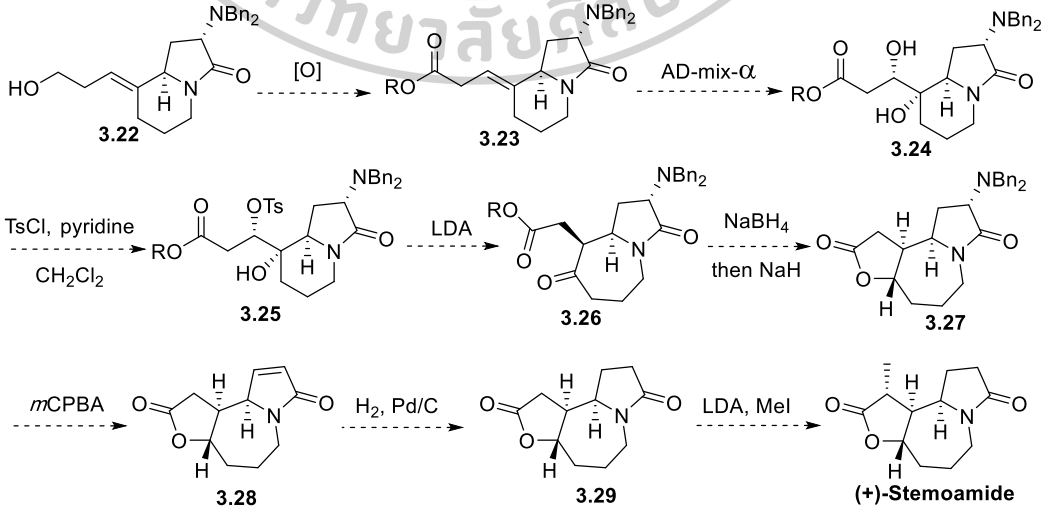
Figure 6 NOE experiment of bicyclic **3.21**

From the result of NOE experiment, a transition state for *N*-acyliminium ion cyclization of bicyclic **3.21** and **3.22** was proposed in scheme 31. After hydroxylactam **3.19** was treated with TMSOTf, intermediate **3.19a** was generated and arranged in chair-like conformation. After that, π-electron from alkene attacked to *N*-acyliminium ion from opposite side of the dibenzylamino group forming chair conformation of cationic intermediate **3.19b** with the protons at ring junction and at C8 arranged in axial positions. Finally, the elimination of proton of intermediate **3.19b** provided bicyclic **3.21** and **3.22** (scheme 31).



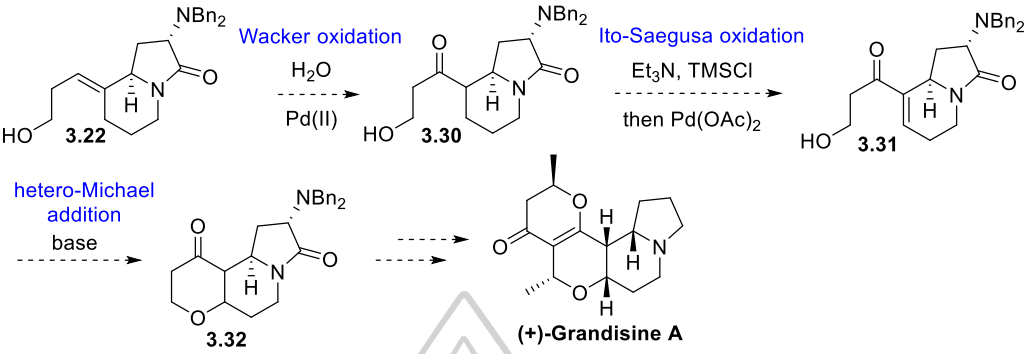
Scheme 31 Proposed transition state for *N*-acyliminium ion cyclization

The synthetic strategy for completion of a synthesis of stemoamide is show in scheme 32. The plan would involve ring expansion from six-membered ring **3.22** to seven-membered ring **3.26** in 4 steps. Then, a construction of tricyclic core would employ $NaBH_4$ reduction and subsequent lactone formation. The treatment of *m*CPBA would remove dibenzylamino group and hydrogenation to give lactam **3.29**. In the final step, methylation would provide stemoamide.



Scheme 32 Synthetic plan for stemoamide (I)

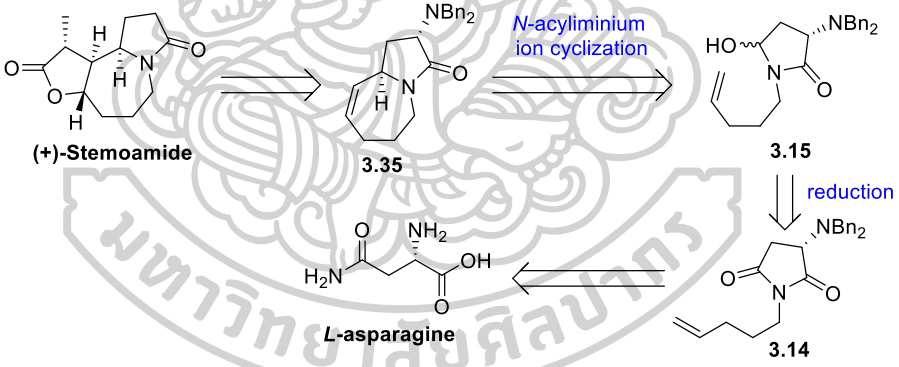
We also envision that compound **3.22** can be used to synthesize a tricyclic core of grandisine A by conversion to unsaturated ketone in 2 steps involving Wacker oxidations. Then, intramolecular hetero-Michael addition should give the tricyclic core of grandisine A (scheme 33).



Scheme 33 Synthetic plan for grandisine A (II)

Retrosynthetic analysis (II)

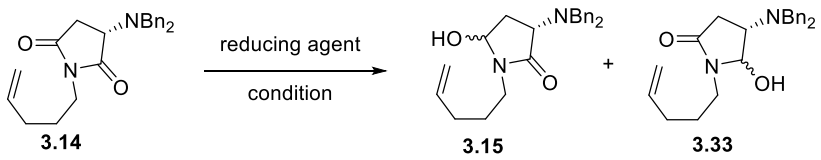
The second synthetic route of stemoamide employed lactonization of bicyclic **3.35**. The pyrrole-azepine core **3.35** could be synthesized from hydroxylactam **3.15** via *N*-acyliminium ion cyclization. The hydroxylactam **3.15** would be prepared from previous route which has been explained (scheme 34).



Scheme 34 Retrosynthetic analysis of stemoamide (II)

Synthesis of Stemoamide (II)

As previously described, imide **3.14** was synthesized from *L*-asparagine. In this approach, one of the most necessary steps is a regioselective reduction. Previously, imide **3.14** was reduced with DIBALH to give hydroxylactam **3.15**. However, reduction of another carbonyl group of imide **3.14** will give regioisomer **3.33**. We envision that it could lead to another enantiomer of stemoamide. The results of reduction of *N*- alkenylsuccinimide **3.14** by various reducing agents and conditions are shown in scheme 35. For reduction by DIBALH and $LiAlH_4$, hydroxylactam **3.15** was obtained exclusively (entries 1-2). Attempts to accomplish another regioisomer of hydroxylactam were succeeded by reduction with $NaBH_4$ (entry 3) which provided hydroxylactam **3.15** and hydroxylactam **3.33** in 22% and 10% yields, respectively.

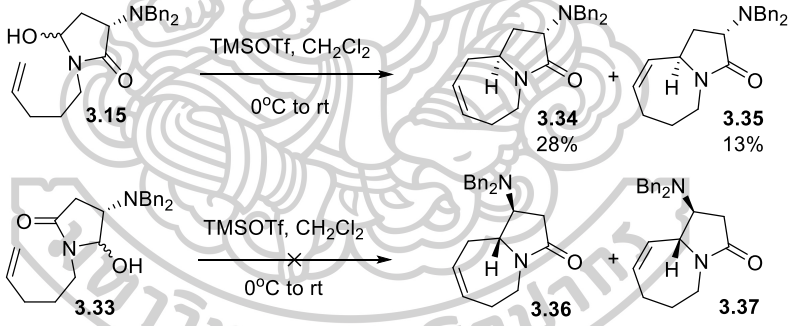


3.14 3.15 3.33

Entry	Reducing agent	Solvent	Temperature (ºC)	Yield of 3.15/3.33 (%)
1	DIBALH	toluene	-78	95/0
2	$LiAlH_4$	THF	0	88/0
3	$NaBH_4$	EtOH	0	22/10

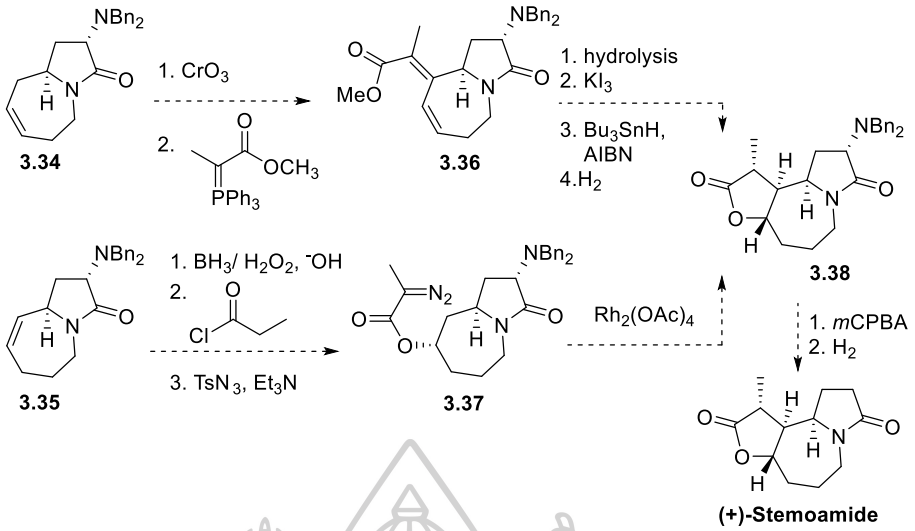
Scheme 35 Reduction of imide **3.14**

To construct pyrrole-azepine core of stemoamide, hydroxylactam **3.15** was treated with TMSOTf to give the corresponding regioisomeric pyrrole-azepines **3.34** and **3.35** (2.2 : 1), each of which is a single diastereomer employing *7-endo-trig* cyclization. The new sterogenic center was investigated by NOE experiment of pyrrole-azepine **3.34** which showed correlation between the ring junction proton (3.57 ppm) and the benzylic proton (3.92 ppm). Attempts of cyclization of hydroxylactam **3.33** with TMSOTf and $BF_3{\cdot}OEt_2$ did not yield the desired bicyclic product presumably due to steric hindrance of the dibenzylamino group (scheme 36).



Scheme 36 *N*-acyliminium ion cyclization of hydroxylactam **3.15** and **3.33**

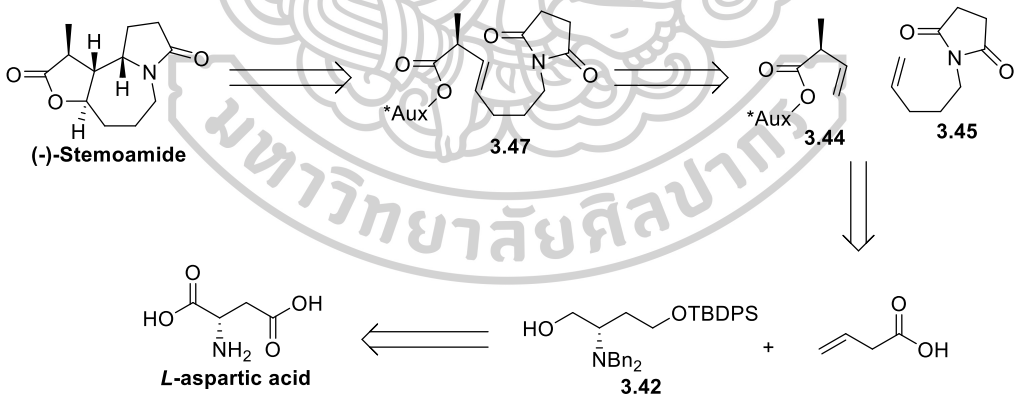
The plan for completion of a synthesis of (+)-stemoamide is shown in scheme 37. Both pyrrole-azepines **3.34** and **3.35** would be converted to tricyclic core **3.38** in two separate routes toward the key intermediate **3.38** involving allylic oxidation, Wittig reaction and iodolactonization for **3.34** and hydroboration/oxidation, esterification, diazo formation and carbene C-H insertion for **3.35**. Then Cope elimination followed by hydrogenation would provide (+)-stemoamide.



Scheme 37 The plan for completion of a synthesis of (+)-stemoamide

Retrosynthetic analysis (III)

The third strategy for synthesis of stemoamide was envisioned that stereocenters would be controlled by chiral auxiliary in the step of cyclization. Stemoamide would be synthesized from compound **3.47** via tandem *N*-acyliminium ion cyclization. Imide **3.47** could be derived from cross metathesis of chiral ester **3.44** and imide **3.45**. The ester **3.44** would be synthesize from butenoic acid and chiral auxiliary **3.42** derived from *L*-aspartic acid (scheme 38).

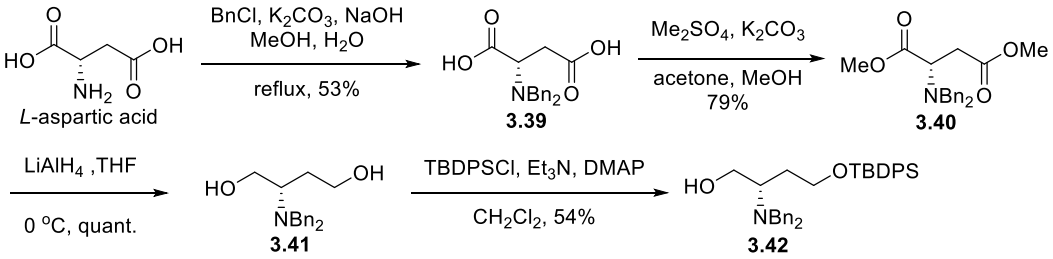


Scheme 38 Retrosynthetic analysis of stemoamide (III)

Synthesis of Stemoamide (III)

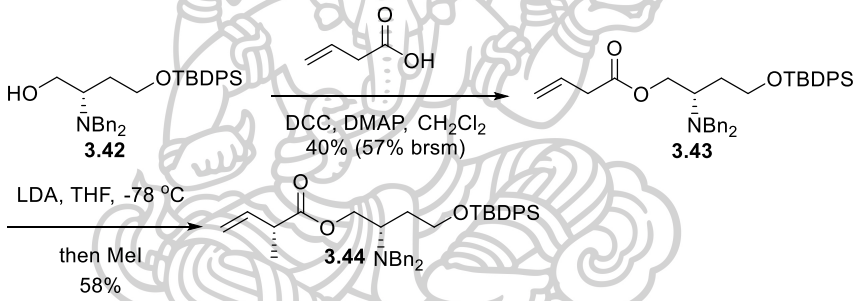
The synthesis of chiral auxiliary **3.42** started from benzylation of *L*-aspartic acid to provide *N, N*-dibenzyl-*L*-aspartic acid **3.39** in 53% yield. Then, the conversion of acid **3.39** via methylation with dimethyl sulfate in the presence of K_2CO_3 to dimethyl ester furnished dimethyl ester **3.40** which was a substrate for reduction with $LiAlH_4$ in THF to afford diol **3.41** in excellent yield. For the first attempt, the acid **3.39** could be reduced directly by $LiAlH_4$ but it gave a low yield from low solubility

of the acid **3.39** in THF. After obtaining diol **3.41**, it was protected with TBDPS group to provide the chiral auxiliary **3.42** (scheme 39).



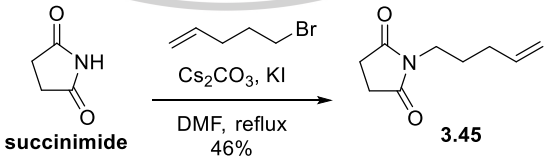
Scheme 39 Synthesis of chiral auxiliary **3.42**

Then, esterification of chiral auxiliary **3.42** and butenoic acid using DCC and DMAP in catalytic amount provided corresponding ester **3.43**. For α-methylation, ester **3.43** was treated with LDA in THF to generate enolate anion and installed methyl group with MeI resulting in the desired ester **3.44** as a single diastereomer. A new stereocenter was controlled by amino dibenzyl group (scheme 40).



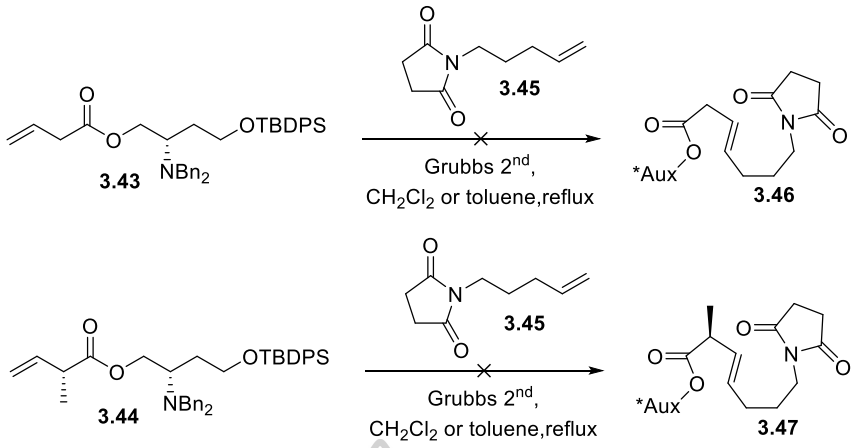
Scheme 40 Asymmetric alkylation

The synthesis of tethered succinimide was achieved by *N*-alkylation of succinimide and 5-bromopent-1-ene in the presence of Cs_2CO_3 and KI in catalytic amount to give tethered succinimide **3.45** (scheme 41).



Scheme 41 Synthesis of tethered succinimide **3.45**

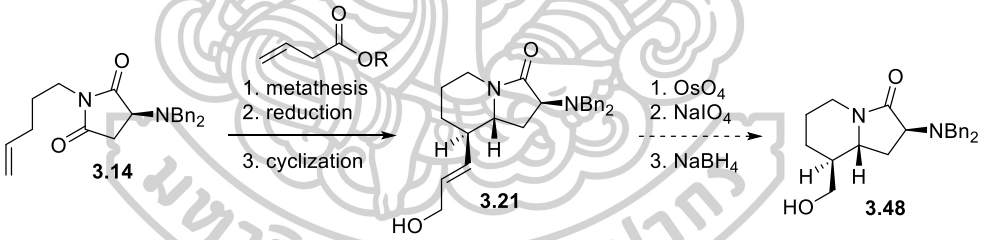
After deriving both intermediates the cross metathesis reaction was attempted. However, ester **3.43** failed to react with imide **3.45** the the presence of Grubbbs catalyst 2nd generation in CH_2Cl_2 or toluene. In addition, the reaction of ester **3.44** did not succeed as well. So, this route for synthesis of stemoamide was not continued (scheme 42).



Scheme 42 Cross metathesis between chiral ester and tethered succinimide

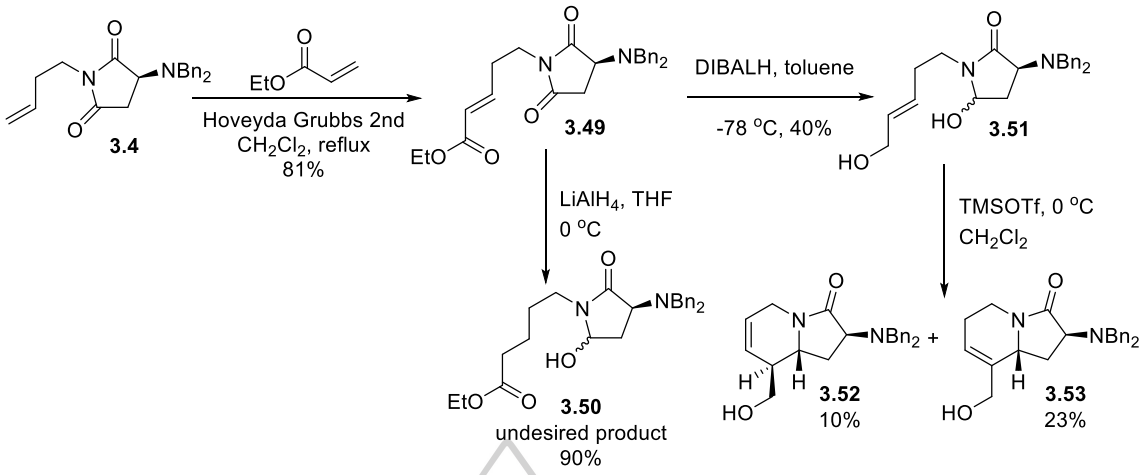
Part C: Synthetic studies of Tashiromine

We envision that the result from synthetic study of stemoamide (scheme 30) can be useful for a synthesis of tashiromine. Indolizidine **3.21** would undergo oxidative cleavage and reduction to give alcohol **3.48**. The remaining steps involving Cope elimination, hydrogenation and lactam reduction should give tashitromine. However, to circumvent unnecessary oxidative cleavage steps, a new route was designed.



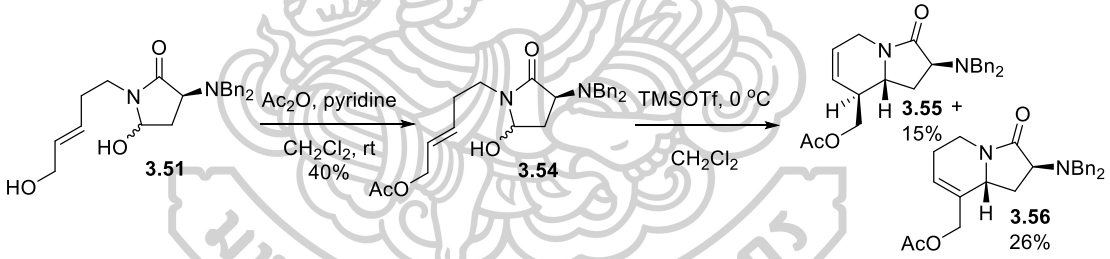
Scheme 43 Synthesis of bicyclic core **3.48**

The synthesis of indolizidine alkaloid core started from cross metathesis between tethered imide **3.4** and ethyl acrylate catalysed by Hoveyda Grubbs 2nd catalyst to give unsaturated ester **3.49**. Then, the first approach, ester **3.49** was reduced with $LiAlH_4$ resulting in attacking of hydride to unsaturated ester and carbonyl of imide to give hydroxylactam **3.50** which was an undesired product. Another way of reduction was succeeded with DIBALH which provided hydroxylactam **3.51**. Finally, it was treated with TMSOTf via *N*-acyliminium ion cyclization to afford bicyclic **3.52** and **3.53** (scheme 44).



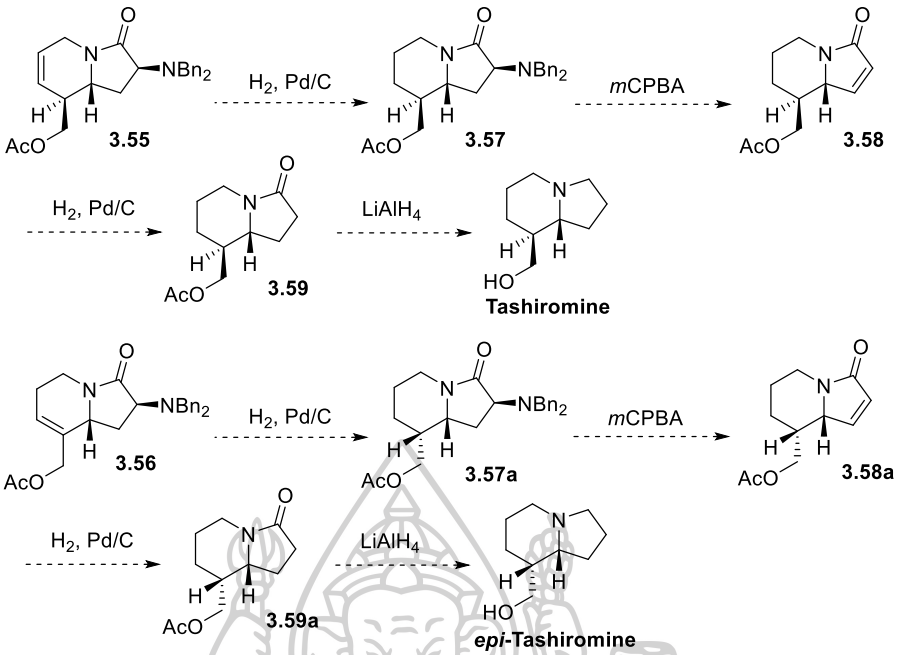
Scheme 44 Synthesis of bicyclic core of tashiromine (I)

Due to a low yield of cyclization and a difficulty to detect polar products, it was assumed that primary alcohol of hydroxylactam **3.52** interfered with *N*-acyliminium ion cyclization. So, the primary alcohol was protected with acetate group using Ac_2O and pyridine in catalytic amount to afford protected alcohol **3.54**. The conversion upon *N*-acyliminium ion cyclization with TMSOTf resulted in bicyclic **3.55** and **3.56** (scheme 45).



Scheme 45 Synthesis of bicyclic core of tashiromine (II)

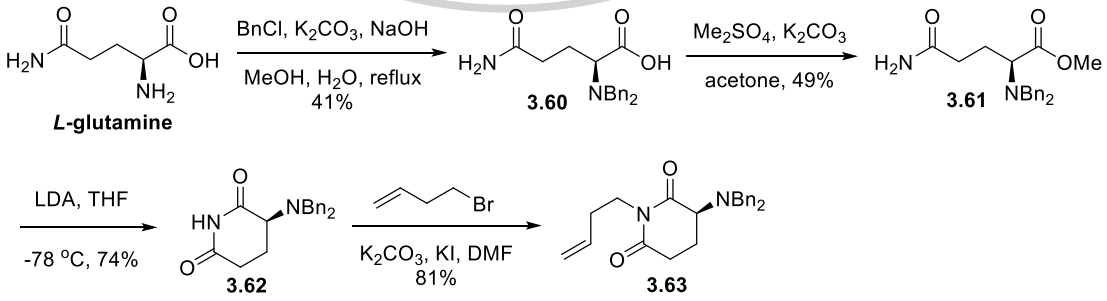
To complete the synthesis of tashiromine, we envision that bicyclic **3.55** and **3.56** would be converted to bicyclic **3.57** and **3.57a** respectively via hydrogenation in separated route. In the case of bicyclic **3.56**, we expect that proton would be added in convex face to give bicyclic **3.57a** which has opposite configuration at C8 position to bicyclic **3.57**. The remaining steps involve removal of other functional groups via Cope elimination, hydrogenation and reduction to afford tashiromine and *epi*-tashiromine, respectively. (scheme 46).



Scheme 46 Synthesis plan for tashiromine and *epi*-tashiromine

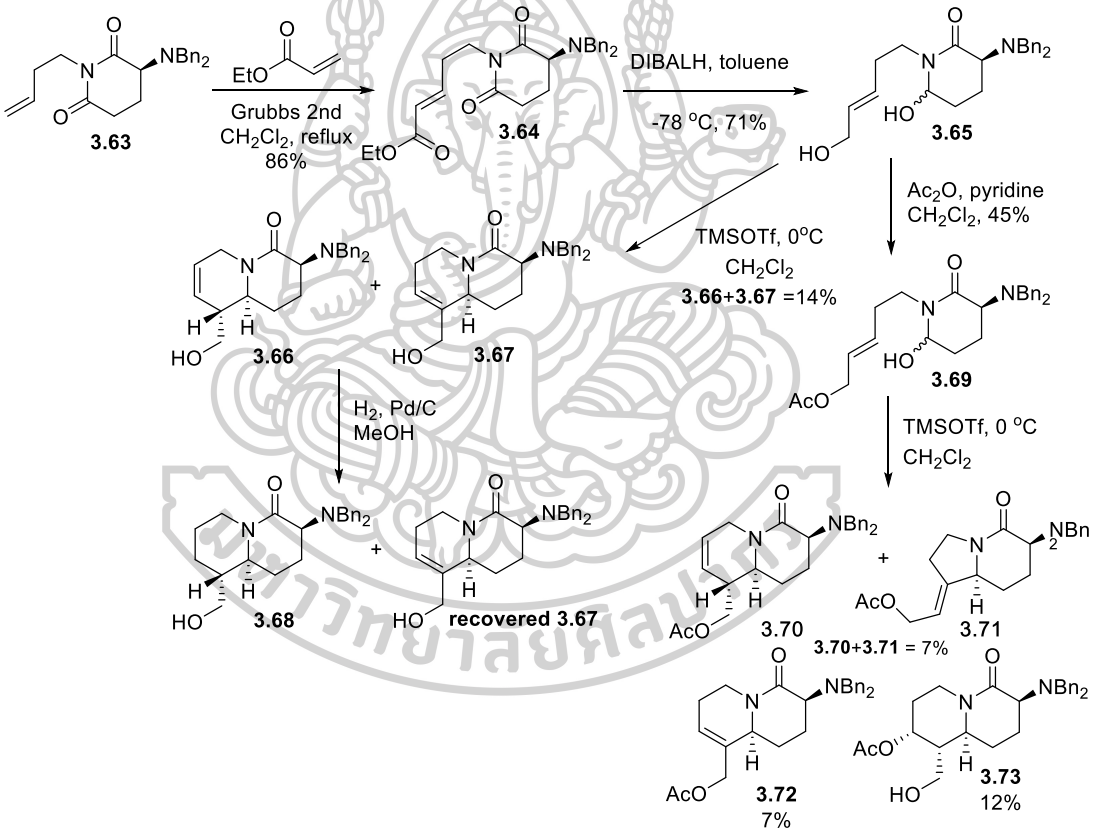
Part D: Synthetic studies of Lupinine

Lupinine is a quinolizidine alkaloid and a homolog of tashiromine. Thus, the synthetic methodology can be similar. The starting material was changed from *L*-asparagine into *L*-glutamine in order to extend bicyclic ring. The synthesis of lupinine started with construction of piperidine ring from *L*-glutamine. Benzylation of *L*-glutamine in basic condition gave *N,N*-dibenzyl *L*-glutamine **3.60** which was converted to methyl ester **3.61** with Me_2SO_4 and K_2CO_3 in acetone. Then, imide formation of methyl ester **3.61** in the presence of LDA in THF afforded corresponding chiral glutarimide **3.62**. The treatment of chiral glutarimide **3.62** with 4-bromo-1-butene, K_2CO_3 and KI via *N*-alkylation resulted in tethered imide **3.63** (scheme 47).



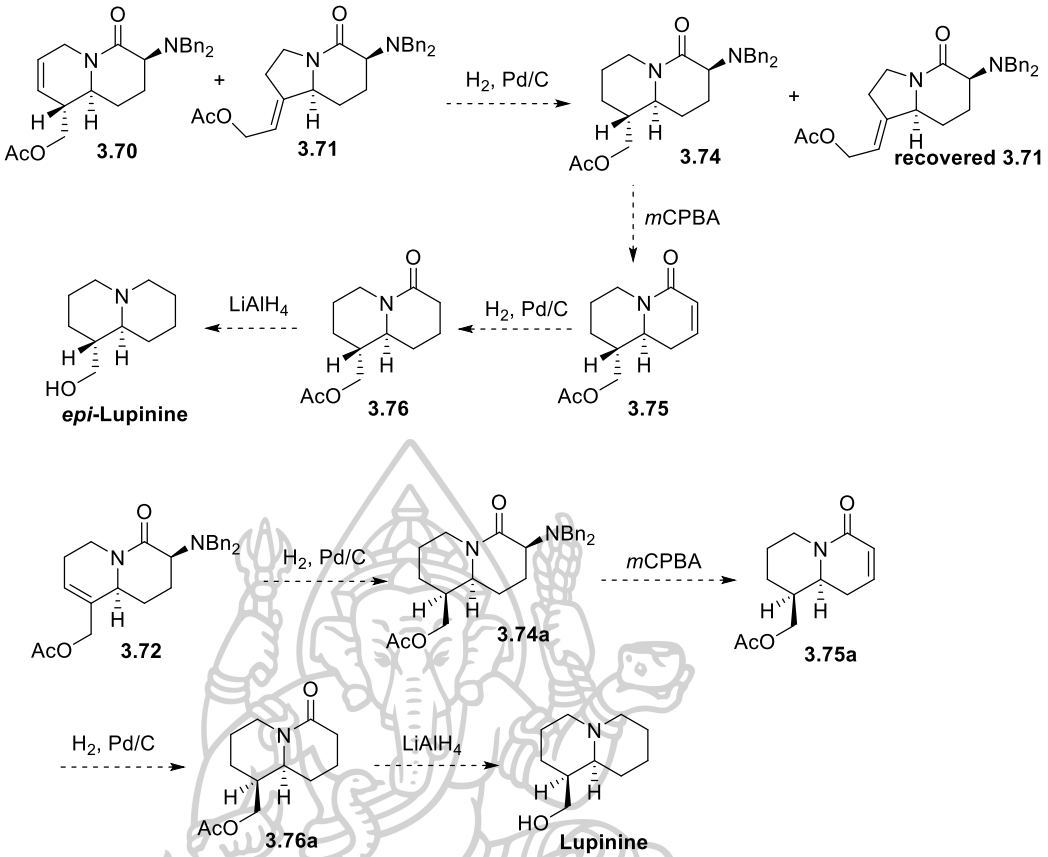
Scheme 47 Synthesis of tethered imide **3.63**

In the same way as in synthetic study of tashiromine, the synthetic methodology of lupinine would involve *N*-acyliminium ion cyclization to give a bicyclic core. Cross metathesis between imide **3.63** and ethyl acrylate catalysed by Grubbs 2nd catalyst gave unsaturated ester **3.64**. After that, it was treated with DIBALH in toluene to provide hydroxylactam **3.65**. Firstly. Hydroxylactam **3.65** was treated with TMSOTf to give a mixture of bicyclic **3.66** and **3.67** which was inseparable. Then, hydrogenation of the mixture of bicyclic **3.66** and **3.67** gave bicyclic **3.68** and recovered bicyclic **3.69**. However, this approach gave a low yield and a trouble for detecting a product. To avoid this problem, another route employed protection of the primary alcohol of hydroxylactam **3.65** via acetylation. Then, *N*-acyliminium ion cyclization of protected alcohol **3.69** gave a mixture of bicyclic **3.70** and **3.71**, which was inseparable, bicyclic **3.72** and unexpected alcohol **3.73** (scheme 48).



Scheme 48 Synthesis of bicyclic core of lupinine

The plan for completion of the synthesis of lupinine is shown in scheme 49. The bicyclic **3.70** and **3.72** would be converted to desired bicyclic **3.74** and **3.74a** respectively in separated route via hydrogenation. Then, the unnecessary functional groups would be removed via Cope elimination, hydrogenation and reduction to afford *epi*-lupinine and lupinine, respectively.



Scheme 49 Synthesis plan for lupinine

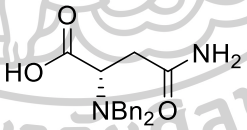
CHAPTER 4

EXPERIMENTAL PROCEDURE

General

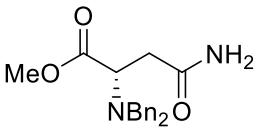
Starting materials and reagents were obtained from commercial sources and were used without further purification. Solvents were dried by distillation from the appropriate drying reagents immediately prior to use. Tetrahydrofuran was distilled from sodium and benzophenone under argon. Toluene and dichloromethane 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 0.9998 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.

Synthesis of dibenzyl-*L*-asparagine (3.1)



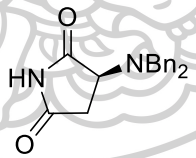
To a solution of *L*-asparagine (5.00 g, 33.3 mmol) in MeOH and H_2O (1:1, 100 mL) was added NaOH (3.33 g, 83.3 mmol), K_2CO_3 (11.5 g, 83.8 mmol) and BnCl (15.46 mL, 133 mmol). The mixture was heated to reflux at 95 ^{o}C overnight and acidified with 1M HCl. Then the mixture was extracted with CH_2Cl_2 (3 × 100 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, 10:1 CH_2Cl_2/MeOH) to give dibenzyl-*L*-asparagine (**3.1**) (6.00 g, 54%) as a pale-yellow oil. R_f (9:1 CH_2Cl_2/MeOH) 0.36; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.13 (m, 10H), 6.00 (brs, 1H), 5.37 (brs, 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 (2C), 129.6 (4C), 128.9 (4C), 128.3 (2C), 59.8, 54.8 (2C), 33.4; $[\alpha]_{25}^{D}$ -48.8 (c 1.7, $CHCl_3$); ν_{max} (film) 3192, 3064, 2924, 2852, 1669, 1495, 1456, 1365, 1285, 1182 cm^{-1}; ESI-HRMS calculated for $C_{18}H_{20}N_2NaO_3$ $[M+Na]^+$ 335.1366, found 335.1368.

Synthesis of methyl dibenzyl-*L*-asparaginate (3.2)



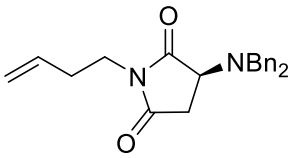
To a solution of dibenzyl-*L*-asparagine (**3.1**) (4.06 g, 12.3 mmol) in acetone (50 mL) was added K_2CO_3 (2.55 g, 18.43 mmol) and Me_2SO_4 (1.75 mL, 18.4 mmol) and the mixture was stirred at room temperature overnight. The mixture was filtered to remove K_2CO_3 and to the solution was added dropwise 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, $CDCl_3$) 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, $CDCl_3$) 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; $[\alpha]_{25}^{D}$ -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.

Synthesis of (*S*)-3-(dibenzylamino)pyrrolidine-2,5-dione (3.3)



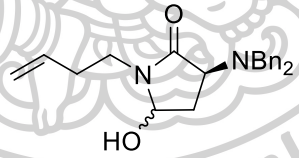
To a solution of methyl dibenzyl-*L*-asparaginate (**3.2**) (1.25 g, 3.83 mmol) in dry THF (10 mL) under argon atmosphere at -78 °C was added LDA (4.82 mL of 1.59 M solution, 7.67 mmol) and the mixture was stirred for 2 hours at -78 °C. To this mixture was added dropwise sat. aq. NH_4Cl (20 mL) and the 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** (1.10 g, 98%) as a white crystal. R_f (2:1 hexane/EtOAc) 0.38; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.31 (brs, 1H), 7.43-7.14 (m, 10H), 3.91 (dd, *J* = 9.0, 6.0 Hz, 1H), 3.81 (d, *J* = 13.5 Hz, 2H), 3.61 (d, *J* = 13.5 Hz, 2H), 2.61 (dd, *J* = 18.0, 6.0 Hz, 1H), 2.71 (dd, *J* = 18.0, 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.7, 178.6, 176.3, 176.2, 138.3 (2C), 128.9 (4C), 128.6 (4C), 127.6 (2C), 58.8, 54.7 (2C), 33.1; $[\alpha]_{25}^{D}$ -25.4 (c 1.6, $CHCl_3$); 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.

Synthesis of (*S*)-1-(but-3-en-1-yl)-3-(dibenzylamino)pyrrolidine-2,5-dione (3.4)



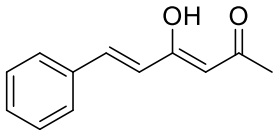
To a solution of chiral succinimide **3.3** (57.0 mg, 0.194 mmol) in DMF (5 mL) under argon atmosphere at room temperature was added Cs_2CO_3 (136.9 g, 0.388 mmol), KI (3.2 mg, 0.019 mmol) and 4-bromo-1-butene (0.024 mL, 0.23 mmol) and the mixture was stirred for 2 hours. To this mixture was added water (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 tethered imide **3.4** (52.3 mg, 77%) as a green oil. R_f (4:1 hexane/EtOAc) 0.63; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.08 (m, 10H), 5.71 (ddt, *J* = 17.1, 10.2, 7.0 Hz, 1H), 5.11-4.90 (m, 2H), 3.87 (dd, *J* = 8.9, 5.4 Hz, 1H), 3.80 (d, *J* = 13.5 Hz, 2H), 3.67-3.52 (m, 4H), 2.70 (dd, *J* = 18.5, 9.0 Hz, 1H), 2.57 (dd, *J* = 18.5, 5.4 Hz, 1H), 2.33 (q, *J* = 7.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 175.2, 138.3 (2C), 134.5, 128.7 (4C), 128.5 (4C), 127.4 (2C), 117.58, 57.2, 54.6, 37.7, 32.1 (2C); $[\alpha]_{25}^{D}$ -45.5 (*c* 0.6, $CHCl_3$); ν_{max} (film) 3084, 3029, 2939, 2847, 1774, 1702, 1398m 1360, 1195, 1130cm^{-1}; ESI-HRMS calculated for $C_{22}H_{24}N_2NaO_2$ $[M+Na]^+$ 371.1730, found 371.1725.

Synthesis of (3*S*)-1-(but-3-en-1-yl)-3-(dibenzylamino)-5-hydroxypyrrolidin-2-one (3.5)



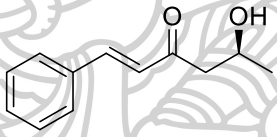
To a solution of tethered imide **3.4** (72.8 mg, 0.209 mmol) in toluene (5 mL) was added DIBALH (0.42 mL of 1 M solution, 0.42 mmol) at -78 °C. The mixture was stirred for 2 hours. To this mixture was added dropwise MeOH (1 mL) and sat. aq. $NaHCO_3$ (10 mL). Then the mixture was extracted with EtOAc (3 × 20 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 give hydroxylactam **3.5** (74.0 mg, quantitative yield) as an orange oil; R_f (4:1 hexane/EtOAc) 0.23; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65-7.10 (m, 10H), 5.79 (ddt, *J* = 17.0, 10.1, 6.8 Hz, 1H), 5.13-5.23-4.94 (m, 3H), 3.95 (d, *J* = 13.7 Hz, 2H), 3.75 (d, *J* = 13.7 Hz, 2H), 3.66-3.47 (m, 2H), 3.47-3.25 (m, 1H), 2.55 (ddd, *J* = 14.0, 9.5, 6.8 Hz, 1H), 2.41-2.28 (m, 2H), 1.78 (ddd, *J* = 14.0, 7.6, 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 172.9, 139.4, 135.5, 128.9, 128.3, 127.1, 117.0, 80.4, 59.0, 54.9, 39.4, 33.4, 32.1.

Synthesis of (3*Z*,5*E*)-4-hydroxy-6-phenylhexa-3,5-dien-2-one (3.6)



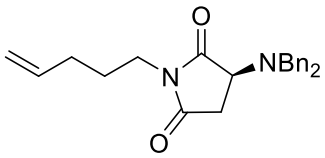
To a solution of acetone (0.50 mL, 6.81 mmol) in dry THF (5 mL) under argon atmosphere at -78 ^{o}C was added LDA (5.14 mL of 1.59 M solution, 8.17 mmol) and the mixture was stirred at -78 ^{o}C for 30 minutes. Then cinnamoyl chloride (1.36 g, 8.17 mmol) was added in to the reaction flask for 2 hours at -78 ^{o}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 enol **3.6** (305.4 mg, 24%) as a yellow crystal; R_f (4:1 hexane/EtOAc) 0.65; ^{1}H NMR (300 MHz, $CDCl_3$) 15.37 (brs, 1H), 7.62 (d, *J* = 16.0 Hz, 1H), 7.58-7.50 (m, 2H), 7.48-7.35 (m, 3H), 6.49 (d, *J* = 15.8 Hz, 1H), 5.68 (s, 1H), 2.19 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 176.9, 139.8, 135.1, 129.9, 128.9 (2C), 127.9 (2C), 122.7, 101.2, 27.1.

Synthesis of (*S*,*E*)-5-hydroxy-1-phenylhex-1-en-3-one (3.7)



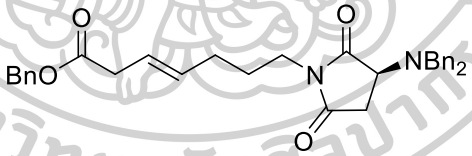
To a solution of **enol 3.6** (102.9 mg, 0.547 mmol) in drytoluene under argon atmosphere at -78 ^{o}C was added *S*-CBS (0.27 mL of 1 M solution in toluene, 0.27 mmol) and the mixture was stirred for 30 minutes. Then, it was added catechol borane (0.12 mL, 1.1 mmol) and stirred at -78 ^{o}C for 2 hours. The reaction was quenched with adding ether (3 mL) and 1 M NaOH (3 mL) and stirring at room temperature for 1 hour until it was turn to be a brown solution. The mixture was extracted with 1 M NaOH (5 × 5 mL) and washed with water and brine. 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, 2:1 hexane/EtOAc) to give alcohol **3.7** (80 mg, 77%) as a yellow crystal; R_f (4:1 hexane/EtOAc) 0.23; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65-7.51 (m, 3H), 7.51-7.34 (m, 3H), 6.74 (d, *J* = 16.2 Hz, 1H), 4.35 (dtt, *J* = 11.7, 6.2, 3.1 Hz, 1H), 2.91 (dd, *J* = 17.4, 3.1 Hz, 1H), 2.78 (dd, *J* = 17.4, 8.7 Hz, 1H), 1.28 (d, *J* = 6.3 Hz, 4H).

Synthesis of (*S*)-3-(dibenzylamino)-1-(pent-4-en-1-yl)pyrrolidine-2,5-dione (3.14)



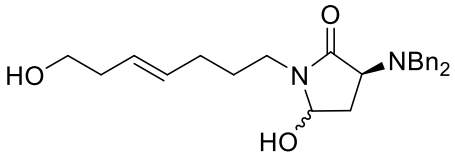
To a solution of chiral succinimide **3.3** (877.1 mg, 2.98 mmol) in DMF (5 mL) under argon atmosphere at room temperature was added Cs_2CO_3 (1.16 g, 3.58 mmol), KI (59.4 mg, 0.358 mmol) and 5-bromo-1-pentene (0.42 mL, 3.58 mmol) and the mixture was stirred for 2 hours. To this mixture was added water (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 obtained without purification to give tethered imide **3.14** (994 mg, quantitative yield) as a green oil. R_f (4:1 hexane/EtOAc) 0.55; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49-7.17 (m, 10H), 5.78 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.08-4.94 (m, 2H), 3.91 (dd, *J*=9.0, 5.3 Hz, 1H), 3.82 (d, *J*= 13.4 Hz, 2H), 3.63 (d, *J* = 13.4 Hz, 2H), 3.50 (t, *J* = 7.4, 2H), 2.75 (dd, *J* = 18.6, 9.0 Hz, 1H), 2.60 (dd, *J* = 18.5, 5.3 Hz, 1H), 2.10-2.00 (m, 2H), 1.65 (p, *J* = 7.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 175.2, 138.2 (2C), 137.2, 128.8 (4C), 128.5 (4C), 127.5 (2C), 115.4, 57.3, 54.6 (2C), 38.1, 32.2, 31.0, 26.9; $[\alpha]_{25}^{D}$ -25.6 (*c* 1.6, $CHCl_3$); ν_{max} (film) 2925, 2841, 1775, 1701, 1494, 1455 cm^{-1}.

Synthesis of benzyl (*S*,*E*)-7-(3-(dibenzylamino)-2,5-dioxopyrrolidin-1-yl)hept-3-enoate (3.18)



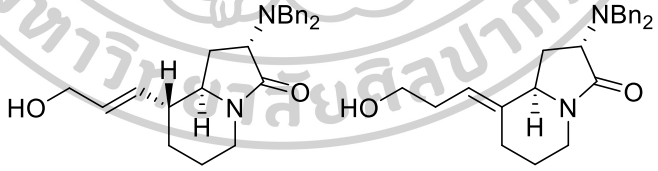
To a solution of tethered imide **3.14** (235.3 mg, 0.649 mmol) in dry CH_2Cl_2 (10 mL) under argon atmosphere at room temperature was added benzyl but-3-enoate (571.0 mg, 0.3246 mmol) and Grubbs catalyst 2nd generation (5.5 mg, 6.49 μmol). Then the mixture was heated to reflux at 40 ^{o}C overnight. To this mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 4:1 hexane/EtOAc) to give benzyl ester **3.18** (247.5 mg, 75%) as a yellow oil. R_f (4:1 hexane/EtOAc) 0.33; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.14 (m, 15H), 5.69-5.43 (m, 2H), 5.11 (s, 1H), 3.91 (dd, *J* = 9.0, 5.3 Hz,, 1H), 3.82 (d, *J* = 13.4 Hz, 2H), 3.63 (d, *J* = 13.4 Hz, 2H), 3.48 (t, *J* = 7.4 Hz, 2H), 3.13-3.03 (m, 2H), 2.76 (dd, *J* = 18.5, 9.0 Hz, 1H), 2.60 (dd, *J* = 18.5, 5.3 Hz, 1H) 2.10-1.99 (m, 2H), 1.70-1.54 (m, 2H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 175.2, 171.7, 138.2 (2C), 133.0, 128.8 (4C), 128.5 (3C), 128.5 (4C), 128.2 (3C), 127.5 (2C), 122.7, 66.4, 57.3, 54.6 (2C), 38.1, 37.9, 32.1, 29.8, 27.1; $[\alpha]_{25}^{D}$ -17.7 (*c* 1.0, $CHCl_3$).

Synthesis of (3*S*)-3-(dibenzylamino)-5-hydroxy-1-((*E*)-7-hydroxyhept-4-en-1-yl)pyrrolidin-2-one (3.19)



To a solution of benzyl ester **3.18** (247.5 mg, 0.4848 mmol) in dry THF (5 mL) under argon atmosphere at 0 °C was added $LiAlH_4$ (55.3 mg, 1.45 mmol) and the mixture was stirred for 2 hours at 0 °C. To this mixture was added dropwise sat. aq. $NaHCO_3$ (5 mL). Then the mixture was extracted with EtOAc (3 × 10 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, 2:1 hexane/EtOAc) to give hydroxylactam **3.19** (95.3 mg, 48%) as an orange oil. R_f (2:1 hexane/EtOAc) 0.30; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58-7.03 (m, 10H), 5.49-5.25 (m, 2H), 4.96 (dd, *J* = 6.7, 4.8 Hz, 1H), 3.85 (d, *J* = 13.8 Hz, 2H), 3.64 (d, *J* = 13.8 Hz, 2H), 3.56 (t, *J* = 6.1 Hz, 2H), 3.53-3.45 (m, 1H), 3.44-3.31 (m, 1H), 3.15 (ddd, *J* = 13.8, 7.2, 6.6 Hz, 1H), 2.42 (ddd, *J* = 14.0, 9.3, 6.7 Hz, 1H), 2.17 (q, *J* = 6.2 Hz, 2H), 1.94 (q, *J* = 6.7 Hz, 2H), 1.79 (ddd, *J* = 13.4, 8.1, 4.8 Hz, 1H), 1.67-1.48 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 139.4 (2C), 131.9, 128.7 (4C), 128.2 (4C), 127.6, 127.0 (2C), 79.5, 61.8, 58.8, 54.5 (2C), 38.7, 35.8, 31.9, 29.7, 26.7.

Synthesis of (2*S*,8a*R*)-2-(dibenzylamino)-8-((*E*)-3-hydroxyprop-1-en-1-yl)hexahydroindolizin-3(2*H*)-one (3.21) and (2*S*,8a*R*,*E*)-2-(dibenzylamino)-8-(3-hydroxypropylidene)hexahydroindolizin-3(2*H*)-one (3.22)



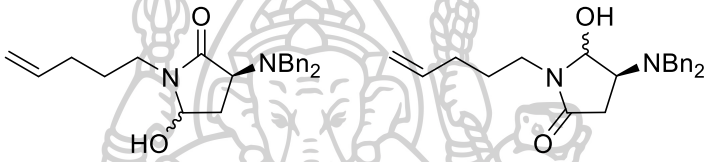
To a solution of hydroxylactam **3.19** (95.3 mg, 0.234 mmol) in dry CH_2Cl_2 (5 mL) under argon atmosphere at 0 °C was added TMSOTf (0.13 mL, 0.70 mmol) and the mixture was stirred for 2 hours at 0 °C to room temperature. To this mixture was added dropwise sat. aq. $NaHCO_3$ (5 mL) and the mixture was extracted with CH_2Cl_2 (3 × 10 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, 1:1 hexane/EtOAc) to give bicyclic **3.21** (24.5 mg, 27%) and bicyclic **3.22** (5.3 mg, 6 %) as pale-yellow oils.

(2*S*,8a*R*)-2-(dibenzylamino)-8-((*E*)-3-hydroxyprop-1-en-1-yl)hexahydro-indolizin-3(2*H*)-one (3.21); R_f (1:1 hexane/EtOAc) 0.25; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-7.18 (m, 10H), 5.67 (dt, *J* = 15.4, 5.2 Hz, 1H), 5.74 (dd, *J* = 15.5, 7.8

Hz, 1H), 4.24-4.10 (m, 3H), 4.13 (d, *J* = 5.3 Hz, 2H), 3.86 (d, *J* = 13.7 Hz, 2H), 3.67-3.56 (m, 4H), 3.18-3.08 (m, 1H), 2.60 (td, *J* = 12.6, 3.8 Hz, 1H), 2.14-2.00 (m, 1H), 1.93 (dd, *J* = 10.3, 4.6 Hz, 1H), 1.87-1.78 (m, 2H), 1.77-1.59 (m, 1H), 1.40-1.23 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 139.6 (2C), 132.0, 131.0, 128.8 (4C), 128.2 (4C), 126.9 (2C), 63.3, 58.9, 58.5, 54.6 (2C), 47.6, 39.6, 30.7, 27.6, 24.3.

(2*S*,8a*R*,*E*)-2-(dibenzylamino)-8-(3-hydroxypropylidene)hexahydro-indolizin-3(2*H*)-one (3.22); R_f (1:1 hexane/EtOAc) 0.19; ^{1}H NMR (300 MHz, $CDCl_3$) δ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 139.6 (2C), 128.8 (4C), 128.2 (4C), 127.0 (2C), 62.2, 59.0, 58.3, 54.8 (2C), 40.1, 30.4, 26.9, 25.5, 25.2.

Synthesis of (3*S*)-3-(dibenzylamino)-5-hydroxy-1-(pent-4-en-1-yl)pyrrolidin-2-one (3.15) and (4*S*)-4-(dibenzylamino)-5-hydroxy-1-(pent-4-en-1-yl)pyrrolidin-2-one (3.33)



Method 1; To a solution of tethered imide **3.14** (334.0 mg, 0.92 mmol) in toluene (5 mL) under argon atmosphere at -78 °C was added DIBALH (1.84 mL of 1 M solution, 1.84 mmol) and the mixture was stirred for 2 hours at -78 °C. To this mixture was added dropwise MeOH (1 mL) and sat. aq. $NaHCO_3$ (10 mL). Then the mixture was extracted with EtOAc (3 × 20 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 give hydroxylactam **3.15** (320 mg, 95%) as an orange oil.

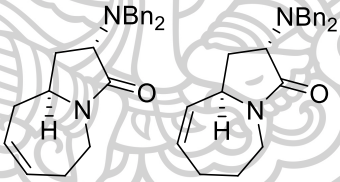
Method 2; To a solution of tethered imide **3.14** (52.8 mg, 0.146 mmol) in dry THF (5 mL) under argon atmosphere at 0 °C was added $LiAlH_4$ (11.1 mg, 0.292 mmol) and the mixture was stirred for 2 hours at 0 °C. To this mixture was added dropwise sat. aq. $NaHCO_3$ (5 mL). Then the mixture was extracted with EtOAc (3 × 10 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 give hydroxylactam **3.15** (46.8 mg, 88%) as an orange oil.

Method 3; To a solution of tethered imide **3.14** (201 mg, 0.555 mmol) in EtOH (5 mL) under argon atmosphere at 0 °C was added $NaBH_4$ (42 mg, 1.109 mmol) and the mixture was stirred for 2 hours at 0 °C. To this mixture was added dropwise sat. aq. $NaHCO_3$ (10 mL). Then the mixture was extracted with EtOAc (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, 2:1 hexane/EtOAc) to give hydroxylactam **3.15** (45.1 mg, 22%) and hydroxylactam **3.33** (20.7 mg, 10%) as colorless oils.

(3*S*)-3-(dibenzylamino)-5-hydroxy-1-(pent-4-en-1-yl)pyrrolidin-2-one (3.15); R_f (2:1 hexane/EtOAc) 0.43; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.13 (m, 10H), 5.78 (ddt, *J* = 16.9, 10.3, 6.6 Hz, 1H), 5.11-4.98 (m, 3H), 3.90 (d, *J* = 13.7 Hz, 2H), 3.71 (d, *J* = 13.7 Hz, 2H), 3.52 (dd, *J* = 9.5, 7.5 Hz, 1H), 3.43 (ddd, *J* = 13.7, 8.8, 6.8 Hz, 1H), 3.18 (ddd, *J* = 13.9, 8.7, 5.7 Hz, 1H), 2.50 (ddd, *J* = 14.1, 9.5, 6.8 Hz, 1H), 2.03 (q, *J* = 7.2, Hz, 2H), 1.74 (ddd, *J* = 14.1, 7.5, 4.4 Hz, 1H), 1.71-1.49 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 139.5, 137.7, 128.8, 128.5, 127.0, 115.1, 79.8, 58.9, 54.7, 39.5, 32.6, 31.2, 26.7; $[\alpha]_{25}^{D}$ -4.8 (c 1.8, $CHCl_3$); ν_{max} (film) 3334, 2925, 2851, 1667, 1490, 1455 cm^{-1}.

(4*S*)-4-(dibenzylamino)-5-hydroxy-1-(pent-4-en-1-yl)pyrrolidin-2-one (3.33); R_f (2:1 hexane/EtOAc) 0.26; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.22 (m, 10H), 5.80 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.13-4.82 (m, 3H), 3.76 (d, *J* = 14.0 Hz, 2H), 3.68 (d, *J* = 14.0 Hz, 2H), 3.51-3.24 (m, 3H), 2.50 (dd, *J* = 16.5, 8.2 Hz, 1H), 2.40 (dd, *J* = 16.5, 8.0 Hz, 1H), 2.10-1.97 (m, 2H), 1.75-1.51 (m, 2H); ^{13}C NMR (75 MHz, CDCl3) δ 173.1, 138.7, 137.6, 128.6, 128.4, 127.3, 115.3, 85.5, 61.7, 54.5, 39.5, 31.8, 31.2, 28.8; $[\alpha]_{25}^{D}$ +44.6 (c 0.3, $CHCl_3$); ν_{max}(film) 3370, 2925, 2851, 1673, 1493, 1455 cm^{-1}.

Synthesis of (2S,9aR)-2-(dibenzylamino)-1,2,5,6,9,9a-hexahydro-3H-pyrrolo[1,2-a]azepin-3-one (3.34) and (2S,9aS)-2- (dibenzylamino)-1,2,5,6,7,9a-hexahydro3H-pyrrolo[1,2-a]azepin-3-one (3.35)



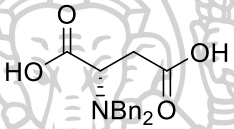
To a solution of hydroxylactam **3.15** (45.1 mg, 0.124 mmol) in dry CH_2Cl_2 (5 mL) under argon atmosphere at 0 ^{o}C was added TMSOTf (0.067 mL, 0.372 mmol) and the mixture was stirred for 2 hours at 0 ^{o}C to room temperature. To this mixture was added dropwise sat. aq. $NaHCO_3$ (5 mL) and the mixture was extracted with CH_2Cl_2 (3 × 10 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 bicyclic **3.34** (12.1 mg, 28%) and bicyclic **3.35** (5.7 mg, 13 %) as pale-yellow oils.

(2S,9aR)-2-(dibenzylamino)-1,2,5,6,9,9a-hexahydro-3H-pyrrolo[1,2-a]azepin-3-one (3.34); R_f (2:1 hexane/EtOAc) 0.35; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49- 7.11 (m, 10H), 5.87 (dddd, *J* = 11.7, 7.1, 5.1, 2.3 Hz, 1H), 5.72 (dddd, *J* = 11.2, 7.4, 3.9, 1.7 Hz, 1H), 4.07 (ddd, *J* = 13.4, 5.7, 3.4 Hz, 1H), 3.92 (d, *J* = 13.8 Hz, 2H), 3.74 (dd, *J* = 9.4, 8.0 Hz, 1H), 3.65 (d, *J* = 13.8 Hz, 2H), 3.57 (tt, *J* = 8.7, 3.0 Hz, 1H), 2.84 (ddd, *J* = 13.1, 9.5, 3.2 Hz, 1H), 2.28-2.08 (m, 6H), 1.77 (ddd, *J* = 13.6, 9.4, 3.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 139.8 (2C), 131.7, 128.7 (4C), 128.4, 128.2 (4C), 126.9 (2C), 58.8, 56.0, 54.6 (2C), 41.6, 37.5, 30.0, 28.1; $[\alpha]_{25}^{D}$ -21.2

(c 1.0, $CHCl_3$); ν_{max}(film) 3468, 2922, 2851, 1681, 1493, 1453, 1432, 1367, 1340, 1127 cm^{-1}.

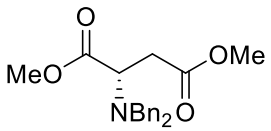
(2S,9aS)-2-(dibenzylamino)-1,2,5,6,7,9a-hexahydro-3H-pyrrolo[1,2-a]azepin-3-one (3.35). R_f (2:1 hexane/EtOAc) 0.30; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50- 7.09 (m, 10H), 5.67 (dtd, *J* = 11.0, 5.4, 2.6Hz, 1H), 5.41 (dq, *J* = 11.1, 1.7 Hz, 1H), 4.26 (dq, *J* = 9.0, 2.2 Hz, 1H), 4.14 (ddd, *J* = 14.0, 8.9, 5.4 Hz, 1H), 3.96 (d, *J* = 13.9 Hz, 2H), 3.76-3.61 (m, 3H), 2.99 (dt, *J* = 13.6, 5.1 Hz, 1H), 2.31-2.12 (m, 4H), 1.94 (ddd, *J* = 12.7, 8.4, 1.9 Hz, 1H), 1.88-1.76 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 139.9 (2C), 132.7, 132.4, 128.7 (4C), 128.2 (4C), 126.9 (2C), 59.0, 54.9, 54.6 (2C), 43.0, 30.9, 27.4, 26.2; $[\alpha]_{25}^{D}$ -38.5 (c 0.4, $CHCl_3$); ν_{max} (film) 3436, 2922, 2851, 1682, 1494, 1454, 1346, 1145, 1075, 982 cm^{-1}.

Synthesis of *N,N*-dibenzyl-*L*-aspartic acid (3.39)



To a solution of *L*-aspartic acid (5.00 g, 0.038 mol) in MeOH and H_2O (1:1, 100 mL) was added NaOH (3.93 g, 0.09 mol), K_2CO_3 (13.57 g, 0.09 mmol) and BnCl (18.41 mL, 0.16 mmol). The mixture was heated to reflux at 95 ^oC overnight and acidified with 1M HCl (excess). Then the mixture was extracted with CH_2Cl_2 (100 mL). The aqueous phase was heated until precipitation of a white solid to give *N,N*-dibenzyl-*L*-aspartic acid (**3.39**) (6.31 g, 53%) as a white cristal. ^1H NMR (300 MHz, DMSO-d_6) δ 12.40 (brs, 2H), 7.40-7.19 (m, 10H), 3.72 (d, *J* = 14.0 Hz, 2H), 3.64-3.54 (m, 3H), 2.76 (dd, *J* = 16.0, 9.1 Hz, 1H), 2.55 (dd, *J* = 16.0, 5.7 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.2, 172.9, 139.7 (2C), 128.9 (4C), 128.7 (4C), 127.4 (2C), 58.2, 54.58 (2C), 34.5; ν_{max} (film) 1751, 1599, 1229, 1170, 1081, 987, 888 cm^{-1}.

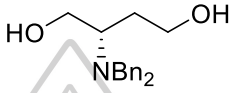
Synthesis of dimethyl *N,N*-dibenzyl-*L*-aspartate (3.40)



To a solution of *N,N*-dibenzyl-*L*-aspartic acid (**3.39**) (4.20 g, 0.0134 mol) in acetone (40 mL) and MeOH (20 mL) was added K_2CO_3 (4.64 g, 0.0336 mol) and Me_2SO_4 (3.20 mL, 0.0336 mol). 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 (50 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, 4:1 hexane/EtOAc) to give

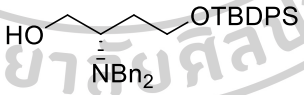
dimethyl *N*,*N*-dibenzyl-*L*-aspartate (**3.40**) (3.62 g, 79%) as a colorless oil. R_f (2:1 hexane/EtOAc) 0.75; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.19 (m, 10), 3.89 (t, *J* = 7.6 Hz, 1H), 3.81 (d, *J* = 13.7 Hz, 2H), 3.78 (s, 3H), 3.57 (s, 3H), 3.55 (d, *J* = 13.8 Hz, 2H), 2.85 (dd, *J* = 15.6, 7.8 Hz,1H), 2.67 (dd, *J* = 15.6, 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 171.4, 138.9 (2C), 128.9 (4C), 128.3 (4C), 127.2 (2C), 57.9, 54.8 (2C), 51.7, 51.6, 35.0; ν_{max} (film) 3029, 2951, 2844, 1733, 1495, 1454, 1436, 1295, 1205, 1166 cm^{-1}.

Synthesis of (*S*)-2-(dibenzylamino)butane-1,4-diol (3.41)



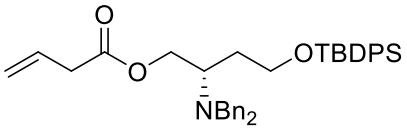
To a solution of dimethyl *N*,*N*-dibenzyl-*L*-aspartate (**3.40**) (3.79 g, 0.0111 mol) in dry THF (20 mL) under argon atmosphere at 0 °C was added $LiAlH_4$ (1.27 g, 0.0334 mol) and the mixture was stirred for 2 hours at 0 °C. To this mixture was added dropwise sat. aq. $NaHCO_3$ (30 mL). Then the mixture was extracted with EtOAc (3 × 50 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 give diol **3.41** (3.18 g, quantitative yield) as a yellow oil. R_f (2:1 hexane/EtOAc) 0.23; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65-7.20 (m, 10H), 3.77 (d, *J* = 13.2 Hz, 2H), 3.73-3.62 (m, 4H), 3.61 (d, *J* = 13.4 Hz, 2H), 3.02-2.93 (m, 1H), 2.03 (ddt, *J* = 13.6, 7.6, 5.8 Hz, 1H), 1.51 (ddt, *J* = 13.6, 7.7, 5.6 Hz, 1H); ν_{max} (film) 3369, 2936, 2877, 1956,1878, 1811, 1494, 1453, 1073, 1029 cm^{-1}.

Synthesis of (*S*)-4-((*tert*-butyldiphenylsilyl)oxy)-2-(dibenzylamino)butan-1-ol (3.42)



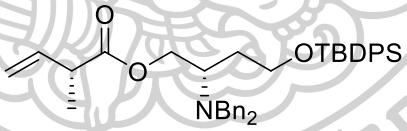
To a solution of diol **3.41** (672.3 mg, 2.359 mmol) in dry CH_2Cl_2 under argon atmosphere at room temperature was a Et_3N (0.33 mL, 2.359 mmol), DMAP (34.6 mg, 0.283 mmol) and TBDPSCl (0.61 mL, 2.359 mmol) and the mixture was stirred at room temperature overnight. To this mixture was quenched with $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 50 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, 15:1 hexane/EtOAc) to give alcohol **3.42** (667.2 mg, 54 %) as a colourless oil. R_f (15:1 hexane/EtOAc) 0.40; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68-7.58 (m, 5H), 7.48-7.34 (m, 5H), 7.32-7.17 (m, 10H), 3.77 (d, J = 13.3 Hz, 2H), 3.70-3.57 (m, 2H), 3.52-3.40 (m, 2H), 3.36 (d, J = 13.3 Hz, 2H), 3.18 (brs, 1H), 2.09-1.96 (m, 1H), 1.45 (ddt, J = 15.3, 9.6, 6.0 Hz, 1H), 1.04 (s, 1H); ν_{max} (film) 3446, 2931,2857, 1958, 1889, 1823, 1472, 1454, 1428, 1112 cm^{-1}.

Synthesis of (*S*)-4-((*tert*-butyldiphenylsilyl)oxy)-2-(dibenzylamino)butyl but-3-enoate (3.43)



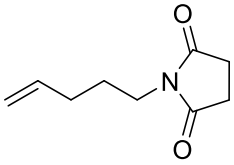
To a solution of alcohol **3.42** (370.3 mg, 0.7070 mmol) in CH_2Cl_2 (10 mL) was added DCC (219.0 g, 1,060 mmol), DMAP (10.0 mg, 0.0848 mmol) and butanoic acid (91.2 g, 1.060 mmol) and the mixture was stirred at room temperature for overnight. Then the solution was filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, xx CH_2Cl_2/MeOH) to give ester **3.43** (168.4 g, 40 %) as a colourless oil and revovered alcohol 3.40 (106.7 mg). R_f (10:1 hexane/EtOAc) 0.55; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65-7.57 (m, 5H), 7.46-7.30 (m, 5H), 7.29-7.13 (m, 10H), 5.92 (ddt, *J* = 17.7, 9.8, 6.9 Hz, 1H), 5.22-5.11 (m, 2H), 4.24 (dd, *J* = 11.5, 6.7 Hz, 1H), 4.10 (dd, *J* = 11.4, 4.8 Hz, 1H), 3.79-3.53 (m, 7H), 3.08 (d, *J* = 6.9 Hz, 2H), 1.90 (dt, *J* = 13.8, 6.9 Hz, 1H), 1.63 (dt, *J* = 13.8, 6.9 Hz, 1H), 0.99 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 139.9 (2C), 135.5 (4C), 133.8, 133.7, 130.2, 129.6 (2C), 128.7 (4C), 128.1 (4C), 127.6 (4C), 126.8 (2C), 118.6 (2C), 64.3, 61.9, 54.0 (2C), 53.2, 39.3, 31.3, 26.8 (3C), 19.1.

Synthesis of (*S*)-4-((*tert*-butyldiphenylsilyl)oxy)-2-(dibenzylamino)butyl (*R*)-2-methylbut-3-enoate (3.44)



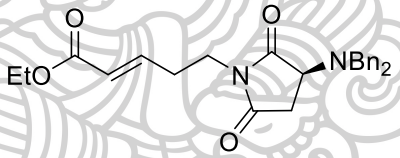
To a solution of ester **3.43** (149.6 mg, 0.2528 mmol) in dry THF (5 mL) at -78 ^{o}C was added LDA (0.13 mL of 2 M solution, 0.2528 mmol) and the mixture was stirred at -78 ^{o}C for 30 minutes. Then it was added MeI (0.0157 mL, 0.2528 mmol) at -78 ^{o}C for 2 hours. To this mixture was added dropwise 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, 10:1 hexane/EtOAc) to give ester **3.44** (89.3 mg, 58%) as a colourless oil. R_f (10:1 hexane/EtOAc) 0.58; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64-7.57 (m, 5H), 7.44-7.31 (m, 5H), 7.29-7.16 (m, 10H), 5.92 (dddd, *J* = 17.5, 10.4, 7.5, 3.0 Hz, 1H), 5.21-5.05 (m, 2H), 4.21 (ddd, *J* = 11.6, 6.6, 1.3 Hz, 1H), 4.11 (ddd, *J* = 11.6, 4.7, 1.5 Hz, 1H), 3.78-3.53 (m, 6H), 3.22-3.02 (m, 2H), 1,99-1.85 (m, 1H), 1.69-1.54 (m, 1H), 1.28 (dd, *J* = 7.1, 3.2 Hz, 3H), 0.98 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 140.0 (2C), 137.1, 135.6 (4C), 133.9, 129.6 (2C), 128.7 (4C), 128.2 (4C), 127.6 (4C), 126.8 (2C), 116.0 (2C), 64.4, 61.9, 54.1 (2C), 53.3, 43.9, 31.3, 26.9, 19.1, 16.7.

Synthesis of 1-(pent-4-en-1-yl)pyrrolidine-2,5-dione (3.45)



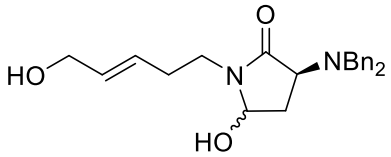
To a solution of succinimide (0.61 g, 6.20 mmol) in DMF (10 mL) under argon atmosphere at room temperature was added Cs_2CO_3 (2.42 g, 7.44 mmol), KI (0.12 mg, 0.744 mmol) and 5-bromo-1-pentene (0.88 mL, 7.44 mmol) and the mixture was heated to reflux overnight. To this mixture was added water (20 mL) and it 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 to give tethered imide **3.45** (0.47 g, 46%) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80 (ddt, *J* = 16.7, 10.2, 6,6, 1H), 5.12-4.92 (m, 2H), 3.52 (t, *J* = 7.4 Hz, 2H), 2.70 (s, 4H), 2.07 (q, *J* = 7.5 Hz, 2H), 1.68 (p, *J* = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2 (2C), 137.3, 115.3, 38.5, 31.0, 28.2 (2C), 26.7.

Synthesis of ethyl (*S*,*E*)-5-(3-(dibenzylamino)-2,5-dioxopyrrolidin-1-yl)pent-2-enoate (3.49)



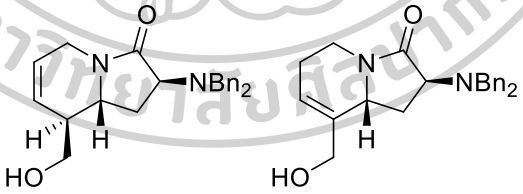
To a solution of tethered imide **3.4** (335.1 mg, 0.9616 mmol) in dry CH_2Cl_2 (10 mL) under argon atmosphere at room temperature was added ethylacrylate (0.51 mL, 4.8081 mmol) and Hoveyda-Grubbs catalyst^{TM} 2nd generation (6.0 mg, 9.616 μmol). Then the mixture was heated to reflux at 40 ^{o}C overnight. To this mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 4:1 hexane/EtOAc) to give unsaturated ester **3.49** (327.4 mg, 81%) as a yellow oil. R_f (2:1 hexane/EtOAc) 0.50; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55-7.12 (m, 10H), 6.82 (dt, *J* = 15.7, 7.1 Hz, 1H), 5.82 (dt, *J* = 15.6, 1.5 Hz, 1H), 4.05 (q, *J* = 7.2 Hz, 2H), 3.88 (dd, *J* = 8.9, 5.3 Hz, 1H), 3.77 (d, *J* = 13.5 Hz, 2H), 3.70-3.51 (m, 4H), 2.71 (dd, *J* = 18.6, 8.9 Hz, 1H), 2.58 (dd, *J* = 18.6, 5.4 Hz, 1H), 2.47 (q, *J* = 7.0 Hz, 2H), 1.18 (t, *J* = 7.1 Hz, 3H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 174.9, 165.6, 143.9, 138.2 (2C), 128.8 (4C), 128.4 (4C), 127.4 (2C), 123.9, 60.3, 57.3, 54.5 (2C), 36.8, 32.0, 30.3, 14.1; $[\alpha]_{25}^{D}$ -26.3 (*c* 0.8, $CHCl_3$); ν_{max} (film) 3029, 2939, 2847, 1776, 1705, 1657, 1398, 1367, 1326, 1195 cm^{-1}; ESI-HRMS calculated for $C_{26}H_{30}N_2O_4$ $[M+Na]^+$ 443.1941, found 443.1935.

Synthesis of (3*S*)-3-(dibenzylamino)-5-hydroxy-1-((*E*)-5-hydroxypent-3-en-1-yl)pyrrolidin-2-one (3.51)



To a solution of unsaturated ester **3.49** (447.6 mg, 1.0643 mmol) in toluene (10 mL) under argon atmosphere at -78 ºC was added DIBALH (3.19 mL of 1 M solution, 3.1930 mmol) and the mixture was stirred for 2 hours at -78 ºC. To this mixture was added dropwise MeOH (3 mL) and sat. aq. $NaHCO_3$ (20 mL). Then the mixture was extracted with EtOAc (3 × 20 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 give hydroxylactam **3.51** (163.1 mg, 40%) as an orange oil. R_f (1:2 hexane/EtOAc) 0.28; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.15 (m, 10H), 5.60-5.53 (m, 2H), 4.95 (t, *J* = 5.8 Hz, 1H), 3.94 (s, 2H), 3.86 (d, *J* = 13.7 Hz, 2H), 3.64 (d, *J* = 13.7 Hz, 2H), 3.57-3.35 (m, 2H), 3.32-3.19 (m, 1H), 2.45 (ddd, *J* = 13.5, 9.4, 6.5 Hz, 1H), 2.34-2.19 (m, 2H), 1.77 (ddd, *J* = 13.4, 8.2, 4.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 139.5, (2C), 131.2, 129.1, 128.8 (4C), 128.3 (4C), 127.1 (2C), 79.9, 62.9, 59.0, 54.6 (2C), 39.6, 32.2, 30.7; $[\alpha]_{25}^{D}$ +33.3 (*c* 0.5, $CHCl_3$); ν_{max} (film) 3335, 2919, 2850, 1668, 1494, 1455, 1371, 1076, 1028, 973 cm^{-1}; ESI-HRMS calculated for $C_{23}H_{28}N_2NaO_3$ $[M+Na]^+$ 403.1992, found 403.1987.

Synthesis of (2*S*)-2-(dibenzylamino)-8-(hydroxymethyl)-1,5,8,8a-tetrahydroindolizin-3(2*H*)-one (3.52) and (2*S*)-2-(dibenzylamino)-8-(hydroxymethyl)-1,5,6,8a-tetrahydroindolizin-3(2*H*)-one (3.53)



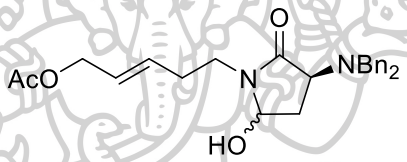
To a solution of hydroxylactam **3.51** (24.0 mg, 0.0631 mmol) in dry CH_2Cl_2 (3 mL) under argon atmosphere at 0 ºC was added TMSOTf (34 μL, 0.189 mmol) and the mixture was stirred for 2 hours at 0 ºC to room temperature. To this mixture was added dropwise sat. aq. $NaHCO_3$ (5 mL) and the mixture was extracted with CH_2Cl_2 (3 × 10 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, 1:2 hexane/EtOAc) to give bicyclic **3.52** (2.3 mg, 10%) and bicyclic **3.53** (5.3 mg, 23 %) as yellow oils.

(2*S*)-2-(dibenzylamino)-8-(hydroxymethyl)-1,5,8,8a-tetrahydroindolizin-3(2*H*)-one (3.52); R_f (1:2 hexane/EtOAc) 0.40; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.10 (m, 10H), 5.86-5.79 (m, 1H), 5.65 (ddd, *J* = 10.3, 4.1, 1.9 Hz, 1H), 4.35 (ddd, *J* =

18.8, 5.5, 2.9 Hz, 1H), 3.92 (d, *J* = 13.7 Hz, 2H), 3.72-3.58 (m, 7H), 3.67-3.52 (m, 1H), 3.51-3.45 (m, 1H), 2.29 (ddd, *J* = 14.1, 8.6, 7.1 Hz, 1H), 2.06 (ddd, *J* = 13.8, 9.9, 3.6 Hz, 1H)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 139.6 (2C), 128.79 (4C), 128.26 (4C), 127.0 (2C), 126.2, 125.6, 63.6, 58.6, 54.6 (2C), 52.9, 44.2, 39.6, 28.1.

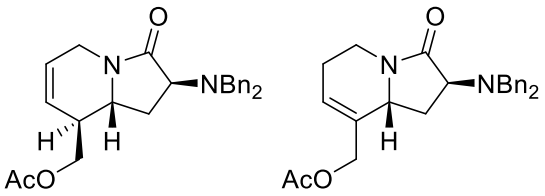
(2*S*)-2-(dibenzylamino)-8-(hydroxymethyl)-1,5,6,8a-tetrahydroindolizin-3(2*H*)-one (3.53); R_f (1:2 hexane/EtOAc) 0.31; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.12 (m, 10H), 5.74 (d, *J* = 5.6 Hz, 1H), 4.26 (dd, *J* = 13.0, 6.3 Hz, 1H), 4.09 (d, *J* = 12.0 Hz, 2H), 3.86 (d, *J* = 13.5 Hz, 2H), 3.68 (d, *J* = 13.5 Hz, 2H), 3.61 (dd, *J* = 10.3, 3.3 Hz, 1H), 2.80 (ddd, *J* = 13.0, 11.2, 5.0 Hz, 1H), 2.30 (ddd, *J* = 13.9, 8.2, 3.3 Hz, 1H), 2.23-2.12 (m, 1H), 2.11-2.01 (m, 1H), 1.94 (ddd, *J* = 13.9, 10.3, 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 139.8 (2C), 138.4, 128.9 (4C), 128.3 (4C), 127.0 (2C), 122.1, 63.8, 59.9, 54.9 (2C), 54.2, 36.2, 28.4, 24.3.

Synthesis of (*E*)-5-((3*S*)-3-(dibenzylamino)-5-hydroxy-2-oxopyrrolidin-1-yl)pent-2-en-1-yl acetate (3.54)



To a solution of hydroxylactam **3.51** (279.2 mg, 0.7347 mmol) in dry CH_2Cl_2 at room temperature (10 mL) was added pyridine (5.9 μL, 0.07347 mmol) and Ac_2O (0.10 mL, 1.1021 mmol). The mixture was stirred at room temperature for overnight. To this solution was added sat. $NaHCO_3$ and it was extracted with CH_2Cl_2 (3 × 10 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, 1:1 hexane/EtOAc) to give hydroxylactam **3.54** (123.7 mg, 40%) as pale-yellow oil. R_f (1:2 hexane/EtOAc) 0.75; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.09 (m, 10H), 5.75-5.63 (m, 1H), 5.62-5.46 (m, 1H), 4.90 (dd, *J* = 6.7, 4.9 Hz, 1H), 4.48 (d, *J* = 5.5 Hz, 2H), 3.94-3.79 (m, 2H), 3.62-3.46 (m, 3H), 3.44-3.31 (m, 1H), 3.30-3.15 (m, 1H), 2.51 (ddd, *J* = 13.9, 9.4, 6.7 Hz, 1H), 2.40-2.18 (m, 2H), 1.90 (s, 3H), 1.74 (ddd, *J* = 13.7, 8.2, 4.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 171.0, 139.3 (2C), 132.4, 128.8 (4C), 128.3 (4C), 127.1 (2C), 126.5, 81.0, 64.9, 57.8, 54.5 (2C), 39.6, 32.3, 30.6, 20.8; ν_{max} (film) 3330, 2931, 2852, 1736, 1676, 1494, 1454, 1367, 1233.

Synthesis of ((2*S*)-2-(dibenzylamino)-3-oxo-1,2,3,5,8,8a-hexahydroindolizin-8-yl)methyl acetate (3.55) and ((2*S*)-2-(dibenzylamino)-3-oxo-1,2,3,5,6,8a-hexahydroindolizin-8-yl)methyl acetate (3.56)

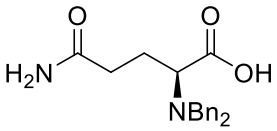


To a solution of hydroxy;actam **3.54** (50.5 mg, 0.1143 mmol) in dry CH_2Cl_2 (3 mL) under argon atmosphere at 0 ºC was added TMSOTf (0.04 mL, 0.343 mmol) and the mixture was stirred for 2 hours at 0 ºC to room temperature. To this mixture was added dropwise sat. aq. $NaHCO_3$ (5 mL) and the mixture was extracted with CH_2Cl_2 (3 × 10 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, 2:1 hexane/EtOAc) to give bicyclic **3.55** (6.8 mg, 15%) and **3.56** (12.2 mg, 26 %) as pale-yellow oils.

((2*S*)-2-(dibenzylamino)-3-oxo-1,2,3,5,8,8a-hexahydroindolizin-8-yl)methyl acetate (3.55); R_f (2:1 hexane/EtOAc) 0.33; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.16 (m, 10H), 5.79 (ddd, *J* = 10.3, 5.9, 2.7 Hz, 1H), 5.60 (dd, *J* = 10.3, 2.2 Hz, 1H), 4.35 (ddd, *J* = 18.7, 5.7, 2.7 Hz, 1H), 4.10 (dd, *J* = 11.3, 5.6 Hz, 1H), 4.01 (dd, *J* = 11.2, 5.6 Hz, 1H), 3.90 (d, *J* = 13.7 Hz, 2H), 3.74-3.60 (m ,3H), 3.51 (ddd, *J* = 18.7, 4.7, 2.2 Hz, 1H), 3.37 (td, *J* = 9.1, 3.6 Hz, 1H), 2.33-2.14 (m, 2H), 2.11-1.98 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 139.4, 128.8, 128.3, 127.1, 125.6, 125.1, 64.5, 58.6, 54.7, 53.4, 41.5, 39.6, 27.9, 20.9.

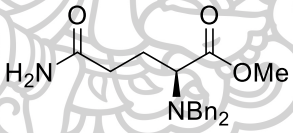
((2*S*)-2-(dibenzylamino)-3-oxo-1,2,3,5,6,8a-hexahydroindolizin-8-yl)methyl acetate (3.56); R_f (2:1 hexane/EtOAc) 0.26; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.14 (m, 10H), 5.81 (d, *J* = 5.5 Hz, 1H), 4.57 (d, *J* = 12.7 Hz, 1H), 4.41 (d, *J* = 12.6 Hz, 1H), 4.26 (dd, *J* = 13.0, 6.4 Hz, 1H), 4.21-4.11 (m, 1H), 3.86 (d, *J* = 13.5 Hz, 2H), 3.68 (d, *J* = 13.6 Hz, 2H), 3.61 (dd, *J* = 10.3, 3.4 Hz, 1H), 2.80 (ddd, *J* = 13.0, 11.1, 5.0 Hz, 1H), 2.26 (dd, *J* = 8.3, 3.5 Hz, 1H), 2.22 (dd, *J* = 8.3, 3.5 Hz, 1H), 2.08-2.03 (m, 4H), 1.93 (ddd, *J* = 14.0, 10.3, 7.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 139.3, 133.9, 128.9, 128.3, 127.1, 125.9, 125.1, 64.72, 59.8, 55.0, 54.3, 36.1, 28.4, 24.4, 20.9.

Synthesis of dibenzyl-*L*-glutamine (3.60)



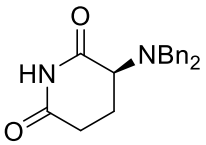
To a solution of *L*-glutamine (5.00 g, 34.2 mmol) in MeOH and H_2O (1:1, 100 mL) was added NaOH (3.42 g, 85.5 mmol), K_2CO_3 (11.8 g, 85,5 mmol) and BnCl (15.8 mL, 137 mmol). The mixture was heated to reflux at 95 ^oC overnight and acidified with 1M HCl. Then the mixture was extracted with CH_2Cl_2 (3 × 100 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, 20:1 CH_2Cl_2/MeOH) to give dibenzyl-*L*-glutamine (**3.60**) (4.58 g, 41%) as a pale-yellow oil. R_f (10:1 CH_2Cl_2/MeOH) 0.50; ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (brs, 1H), 7.38-7.18 (m, 10H), 6.98 (d, *J* = 4.4 Hz, 1H), 6.70 (d, *J* = 4.4 Hz, 1H), 3.73 (d, *J* = 13.6 Hz, 2H), 3.61 (d, *J* = 13.6 Hz, 2H), 3.21 (dd, *J* = 16.8, 7.0 Hz, 1H), 2.43 (dt, *J* = 16.8, 7.4 Hz, 1H), 2.19-1.99 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 177.5, 138.8 (2C), 128.78 (4C), 128.7 (4C), 127.5 (2C), 60.6, 54.3 (2C), 32.2, 20.1; $[\alpha]_{25}^{D}$ +6.45 (*c* 0.8, $CHCl_3$); ν_{max} (film) 3454, 3199, 3086, 3029, 2929, 2848, 2604, 1707, 1495, 1454 cm^{-1} ; ESI-HRMS calculated for $C_{19}H_{22}N_2O_3$ $[M+Na]^+$ 349.1523, found 349.1520.

Synthesis of methyl dibenzyl-*L*-glutaminate (3.61)



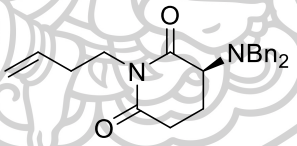
To a solution of dibenzyl-*L*-glutamine (**3.60**) (1.72 g, 5.27 mmol) in acetone (25 mL) was added K_2CO_3 (1.09 g, 7.91 mmol) and Me_2SO_4 (0.76 mL, 7.91 mmol) and the mixture was stirred at room temperature overnight. The mixture was filtered to remove K_2CO_3 and to the solution was added dropwise sat. aq. NH_4Cl. Then the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with 5% NaOH (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 1:1 hexane/EtOAc) to give methyl dibenzyl-*L*-glutaminate (**3.61**) (889.3 g, 49%) as a colorless oil. R_f (1:1 hexane/EtOAc) 0.45; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.15 (m, 10H), 6.54 (brs, 1H), 5.94 (brs, 1H), 3.73 (d, *J* = 13.6 Hz, 2H), 3.64 (s, 3H), 3.61 (d, *J* = 14.7 Hz, 5H), 3.14 (dd, *J* = 7.4, 5.9 Hz, 1H), 2.66 (dt, *J* = 16.5, 7.2 Hz, 1H), 2.38 (dt, *J* = 16.5, 7.5 Hz, 1H), 2.22 – 1.98 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1, 173.9, 139.0 (2C), 128.8 (4C), 128.6 (4C), 127.4 (2C), 60.7, 54.3 (2C), 51.6, 32.0, 20.4; $[\alpha]_{25}^{D}$ +12.0 (*c* 0.8, $CHCl_3$); ν_{max} (film) 3457, 3344, 3196, 3029, 2951, 2843, 1735, 1683, 1495, 1454 cm^{-1}; ESI-HRMS calculated for $C_{20}H_{24}N_2O_3$ $[M+Na]^+$ 363.1679, found 363.1676.

Synthesis of (*S*)-3-(dibenzylamino)piperidine-2,6-dione (3.62)



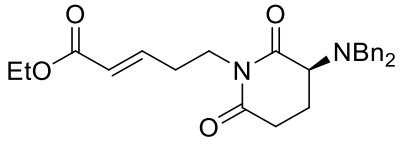
To a solution of methyl dibenzyl-*L*-glutaminate (**3.61**) (500.0 mg, 2.13 mmol) in dry THF (10 mL) under argon atmosphere at -78 ºC was added LDA (2.13 mL of 1.6 M solution, 4.26 mmol) and the mixture was stirred for 2 hours at -78 ºC. To this mixture was added dropwise sat. aq. NH_4Cl (30 mL) and the mixture was extracted with CH_2Cl_2 (3 × 30 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 glutarimide **3.62** (328.0 g, 74%) as a green oil. R_f (2:1 hexane/EtOAc) 0.38; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (brs, 1H), 7.57-7.04 (m, 10H), 4.03 (d, *J* = 13.9 Hz, 2H), 3.77 (d, *J* = 13.9 Hz, 2H), 3.52 (dd, *J* = 11.3, 6.5 Hz, 2H), 2.71 (dt, *J* = 17.4, 3.6 Hz, 1H), 2.43 (ddd, *J* = 17.5, 11.5, 7.2 Hz, 1H), 2.21-2.02 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 172.5, 139.4 (2C), 128.5 (4C), 128.4 (4C), 127.2 (2C), 58.6, 55.0 (2C), 31.6, 23.1; $[\alpha]_{25}^{D}$ +28.3 (*c* 0.9, $CHCl_3$); ν_{max} (film) 3196, 3086, 3029, 2885, 2853, 1719, 1701, 1453, 1365, 1191 cm^{-1}; ESI-HRMS calculated for $C_{19}H_{20}N_2NaO_2$ $[M+Na]^+$ 331.1417, found 331.1410.

Synthesis of (*S*)-1-(but-3-en-1-yl)-3-(dibenzylamino)piperidine-2,6-dione (3.63)



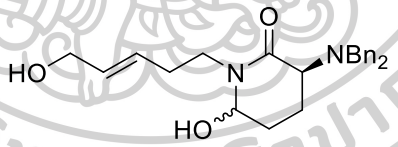
To a solution of chiral glutarimide **3.62** (437.4 mg, 1.4201 mmol) in DMF (10 mL) under argon atmosphere at room temperature was added K_2CO_3 (235.5 g, 1.7042 mmol), KI (28.3 mg, 0.1704 mmol) and 4-bromo-1-butene (0.17 mL, 1.7042 mmol) and the mixture was stirred for 2 hours. To this mixture was added 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 obtained without purification to give tethered glutarimide **3.63** (416.4 mg, 81%) as a blue oil. R_f (2:1 hexane/EtOAc) 0.75; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.11 (m, 11H), 5.75 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.07-4.91 (m, 2H), 4.01 (d, *J* = 14.0 Hz, 2H), 3.81 (t, *J* = 7.1 Hz, 2H), 3.73 (d, *J* = 14.0 Hz, 2H), 3.45 (dd, *J* = 11.1, 6.6 Hz, 1H), 2.71 (dt, *J* = 17.2, 3.5 Hz, 1H), 2.48-2.19 (m, 3H), 2.12-1.91 (m, 2H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 171.7, 139.6, (2C), 135.14, 128.5 (4C), 128.3 (4C), 127.1 (2C), 116.8, 59.3, 55.0 (2C), 38.7, 32.5, 32.2, 22.5; $[\alpha]_{25}^{D}$ +60.9 (*c* 0.1, $CHCl_3$); ν_{max} (film) 3028, 2961, 2926, 2852, 1726, 1675, 1347, 1320, 1185, 1125 cm^{-1}; ESI-HRMS calculated for $C_{23}H_{27}N_2O_2$ $[M+H]^+$ 363.2067, found 363.2058.

Synthesis of ethyl (*S*,*E*)-5-(3-(dibenzylamino)-2,6-dioxopiperidin-1-yl)pent-2-enoate (3.64)



To a solution of tethered glutarimide **3.63** (270.4 mg, 0.7470 mmol) in dry CH_2Cl_2 (10 mL) under argon atmosphere at room temperature was added ethylacrylate (0.40 mL, 3.7299 mmol) and Grubbs catalyst^{TM} 2nd generation (6.33 mg, 7.460 μmol). Then the mixture was heated to reflux at 40 ^{o}C overnight. To this mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 4:1 hexane/EtOAc) to give unsaturated ester **3.64** (280.1 mg, 86%) as a blue oil. R_f (2:1 hexane/EtOAc) 0.58; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.15 (m, 10H), 6.88 (dt, *J* = 15.6, 7.3 Hz, 1H), 5.82 (dt, *J* = 15.6, 1.5 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 4.00 (d, *J* = 14.0 Hz, 2H), 3.95-3.82 (m, 2H), 3.72 (d, *J* = 13.9 Hz, 2H), 3.52-3.41 (m, 2H), 3.52-3.41 (m, 1H), 2.77 (dt, *J* = 17.2, 3.6 Hz, 1H), 2.53 (m, 3H), 1.21 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 171.7, 166.1, 144.88, 139.5, 128.6, 128.4, 127.2, 123.3, 60.3, 59.3, 55.0, 38.0, 32.2, 30.9, 22.54, 14.17; $[\alpha]_{25}^{D}$ -40.8 (*c* 0.2, $CHCl_3$); ν_{max} (film) 2963, 2900, 2851, 1720, 1677, 1366, 1346, 1322, 1189, 1150 cm^{-1}; ESI-HRMS calculated for $C_{26}H_{30}N_2NaO_4$ $[M+Na]^+$ 457.2098, found 457.2102.

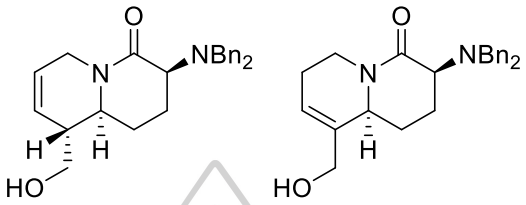
Synthesis of (3*S*)-3-(dibenzylamino)-6-hydroxy-1-((*E*)-5-hydroxypent-3-en-1-yl)piperidin-2-one (3.65)



To a solution of unsaturated ester **3.64** (181.8 mg, 0.4184 mmol) in toluene (10 mL) under argon atmosphere at -78 ^{o}C was added DIBALH (1.26 mL of 1 M solution, 1.26 mmol) and the mixture was stirred for 1 hours at -78 ^{o}C. To this mixture was added dropwise MeOH (3 mL) and sat. aq. $NaHCO_3$ (20 mL). Then the mixture was extracted with EtOAc (3 × 20 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 give hydroxylactam **3.65** (117.2 mg, 71%) as an orange oil. R_f (1:2 hexane/EtOAc) 0.34; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.15 (m, 10H), 5.70-5.59 (m, 2H), 4.80 (dd, *J* = 8.6, 4.8 Hz, 1H), 4.05-3.92 (m, 4H), 3.67 (d, *J* = 14.3 Hz, 2H), 3.52-3.37 (m, 1H), 3.34-3.23 (m, 2H), 2.40-2.28 (m, 2H), 2.27-2.15 (m, 1H), 1.98-1.82 (m, 1H), 1.81-1.65 (m, 1H), 1.61-1.45 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 140.4 (2C), 131.0, 129.8, 128.6 (4C), 128.2 (4C), 126.9 (2C), 80.3, 63.2, 58.2, 55.4 (2C), 42.3, 31.5, 31.0, 23.2; $[\alpha]_{25}^{D}$ -27.2 (*c* 0.4,

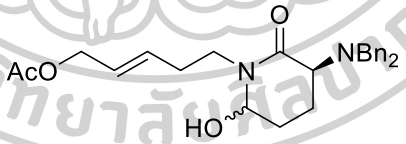
$CHCl_3$); ν_{max} (film) 3369, 2931, 2665, 2360, 1627, 1494, 1454, 1365, 1326, 1202cm^{-1}; ESI-HRMS calculated for $C_{24}H_{30}N_2NaO_3$ $[M+Na]^+$ 417.2149, found 417.2147.

Synthesis of (3*S*)-3-(dibenzylamino)-9-(hydroxymethyl)-1,2,3,6,9,9a-hexahydro-4*H*-quinolizin-4-one (3.66) and (3*S*)-3-(dibenzylamino)-9-(hydroxymethyl)-1,2,3,6,7,9a-hexahydro-4*H*-quinolizin-4-one (3.67)



To a solution of hydroxylactam **3.65** (195.9 mg, 0.5003 mmol) in dry CH_2Cl_2 (5 mL) under argon atmosphere at 0 ^oC was added TMSOTf (0.19 mL, 1.50 mmol) and the mixture was stirred for 3 hours at 0 ^oC to room temperature. To this mixture was added dropwise sat. aq. $NaHCO_3$ (5 mL) and the mixture was extracted with CH_2Cl_2 (3 × 10 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, 1:1 hexane/EtOAc) to give a mixture of bicyclic **3.66** and bicyclic **3.67** (25.3 mg, 14%) as yellow oils; R_f (1:2 hexane/EtOAc) 0.55; ν_{max} (film) 3406, 3028, 2925, 2854, 1623, 1494, 1454, 1361, 1073, 1028; ESI-HRMS calculated for $C_{24}H_{29}N_2O_2$ $[M+H]^+$ 377.2223, found 377.2216.

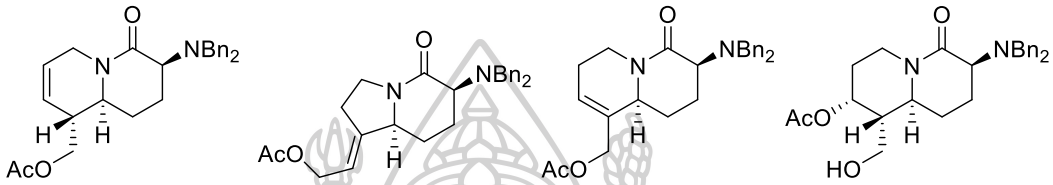
Synthesis of (*E*)-5-((3*S*)-3-(dibenzylamino)-6-hydroxy-2-oxopiperidin-1-yl)pent-2-en-1-yl acetate (3.69)



To a solution of hydroxylactam **3.67** (240.6 mg, 0.6145 mmol) in dry CH_2Cl_2 at room temperature (10 mL) was added pyridine (5.0 μL, 0.06145 mmol) and Ac_2O (0.09 mL, 0.9217 mmol). The mixture was stirred at room temperature for overnight. To this solution was added sat. $NaHCO_3$ and it was extracted with CH_2Cl_2 (3 × 10 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, xx hexane/EtOAc) to give hydroxylactam **3.69** (120.0 mg, 45%) as pale-yellow oils; R_f (1:2 hexane/EtOAc) 0.73; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49-7.17 (m, 10H), 5.75 (dt, *J* = 15.4, 7.0 Hz, 1H), 5.58 (dt, *J* = 15.4, 6.1 Hz, 1H), 4.81 (brs, 1H), 4.47 (d, *J* = 6.2 Hz, 2H), 3.98 (d, *J* = 14.1, 2H), 3.78 (d, *J* = 14.0 Hz, 2H), 3.61-3.36 (m, 2H), 3.26 (dd, *J* = 11.4, 6.0 Hz, 1H), 2.52-2.29 (m, 2H), 2.27-2.10 (m, 1H), 1.92 (s, 3H), 1.82-1.68 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 171.1, 140.2 (2C), 132.9, 128.7 (4C), 128.2 (4C), 126.9 (2C), 126.3, 80.3, 65.1, 59.0, 55.4

(2C), 45.8, 31.2, 29.6, 21.5, 20.9; $[\alpha]_{25}^{D}$ -11.5 (*c* 0.5, $CHCl_3$); ν_{max} (film) 3393, 2926, 2854, 1738, 1625, 1493, 1454, 1366, 1324, 1233 cm^{-1}.

Synthesis of ((3*S*)-3-(dibenzylamino)-4-oxo-1,3,4,6,9,9a-hexahydro-2*H*-quinolizin-9-yl)methyl acetate (3.70) , 2-((6S,E)-6-(dibenzylamino)-5-oxohexahydroindolizin-1(5H)-ylidene)ethyl acetate (3.71), ((3*S*)-3-(dibenzylamino)-4-oxo-1,3,4,6,7,9a-hexahydro-2*H*-quinolizin-9-yl)methyl acetate (3.72) and (7*S*)-7-(dibenzylamino)-1-(hydroxymethyl)-6-oxooctahydro-2*H*-quinolizin-2-yl acetate (3.73)



To a solution of hydroxylactam **3.69** (22.3 mg, 0.0514 mmol) in dry CH_2Cl_2 (5 mL) under argon atmosphere at 0 °C was added TMSOTf (0.019 mL, 0.154 mmol) and the mixture was stirred for 2 hours at 0 °C to room temperature. To this mixture was added dropwise sat. aq. $NaHCO_3$ (5 mL) and the mixture was extracted with CH_2Cl_2 (3 × 5 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, 2:1 hexane/EtOAc) to give a mixture of bicyclic **3.70** and **3.71** (1.5 mg, 7 %) which was inseparable, bicyclic **3.72** (1.6 mg, 7 %) and bicyclic **3.73** (2.5 mg, 12 %)as pale-yellow oils.

((3*S*)-3-(dibenzylamino)-4-oxo-1,3,4,6,9,9a-hexahydro-2*H*-quinolizin-9-yl)methyl acetate (3.70) and 2-((6S,E)-6-(dibenzylamino)-5-oxohexahydro indolizin-1(5H)-ylidene)ethyl acetate (3.71); R_f (2:1 hexane/EtOAc) 0.50.

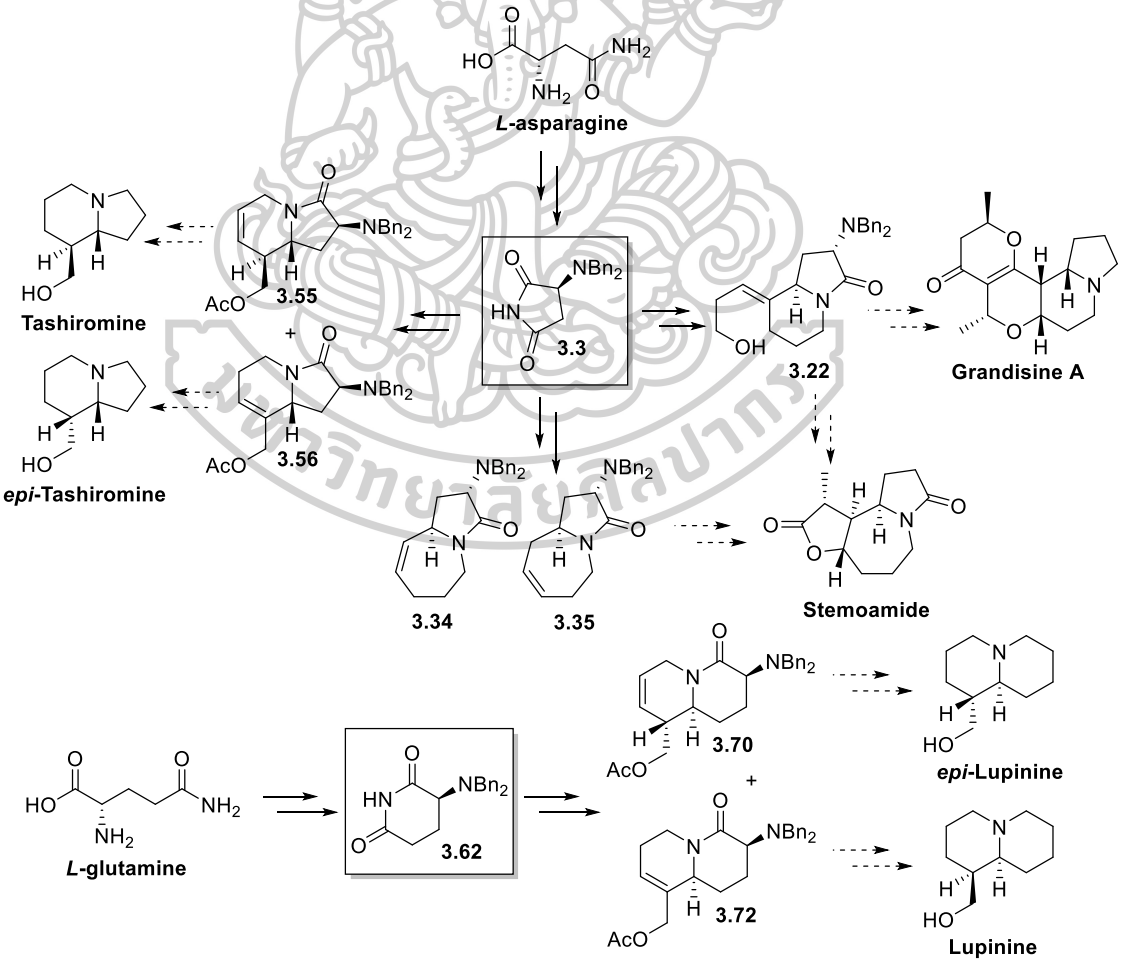
((3*S*)-3-(dibenzylamino)-4-oxo-1,3,4,6,7,9a-hexahydro-2*H*-quinolizin-9-yl)methyl acetate (3.72); R_f (2:1 hexane/EtOAc) 0.43; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.16 (m, 10H), 5.99 (d, *J* = 5.9 Hz, 1H), 4.70 (dd, *J* = 12.8, 5.5 Hz, 1H), 4.57 (d, *J* = 12.6 Hz, 1H), 4.42 (d, *J* = 12.6 Hz, 1H), 4.06 (d, *J* = 14.2 Hz, 2H), 4.02-3.95 (m, 1H), 3.74 (d, *J* = 14.2 Hz, 2H), 3.36 (t, *J* = 7.8 Hz, 1H), 2.66 (td, *J* = 12.2, 4.3 Hz, 1H), 2.37-2.22 (m, 1H), 2.15-2.08 (m, 1H), 2.05 (s, 3H), 1.94-1.74 (m, 2H).

(7*S*)-7-(dibenzylamino)-1-(hydroxymethyl)-6-oxooctahydro-2*H*-quinolizin-2-yl acetate (3.73); ; R_f (2:1 hexane/EtOAc) 0.08; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49-7.13 (m, 10H), 4.58 (dd, *J* = 13.5, 4.4 Hz, 1H), 4.21 (dd, *J* = 11.4, 8.3 Hz, 1H), 4.16-4.09 (m, 1H), 4.08-3.99 (m, 3H), 3.73 (d, *J* = 14.0 Hz, 2H), 3.68-3.60 (m, 1H), 3.30 (dd, *J* = 10.3, 5.8 Hz, 1H), 2.88 (td, *J* = 13.0, 2.7 Hz, 1H), 2.07 (s, 3H), 1.94-1.73 (m, 5H), 1.70-1.53 (m, 2H).

CHAPTER 5

CONCLUSION

In summary, the synthetic studies of grandisine A, stemoamide, tashiromine and lupinine have been discussed. This research shows that the chiral succinimide **3.3** synthesized form *L*-asparagine can be useful in synthetic approach of natural products containing pyrrolidine ring such as indolizidine and stemona alkaloids. In the same way, a synthetic methodology involving chiral succinimide **3.3** can be applied for the synthesis involving the chiral gutarimide **3.62** derived from *L*-glutamine. It led to the synthesis of piperidine containing compound, such as quinolizidine alkaloids. The key step of the synthesis, *N*-acyliminium ion cyclization, succeeded in constructing pyrrol-azepine core of stemoamide and tethered quinolizidine for grandisine A. In addition, the same approach was applied for syntheses of bicyclic core of tashitromine and lupinine. The remaining steps involve removal of unnecessary functional groups to complete the natural products.



Scheme 50 Conclusion of finding from this research

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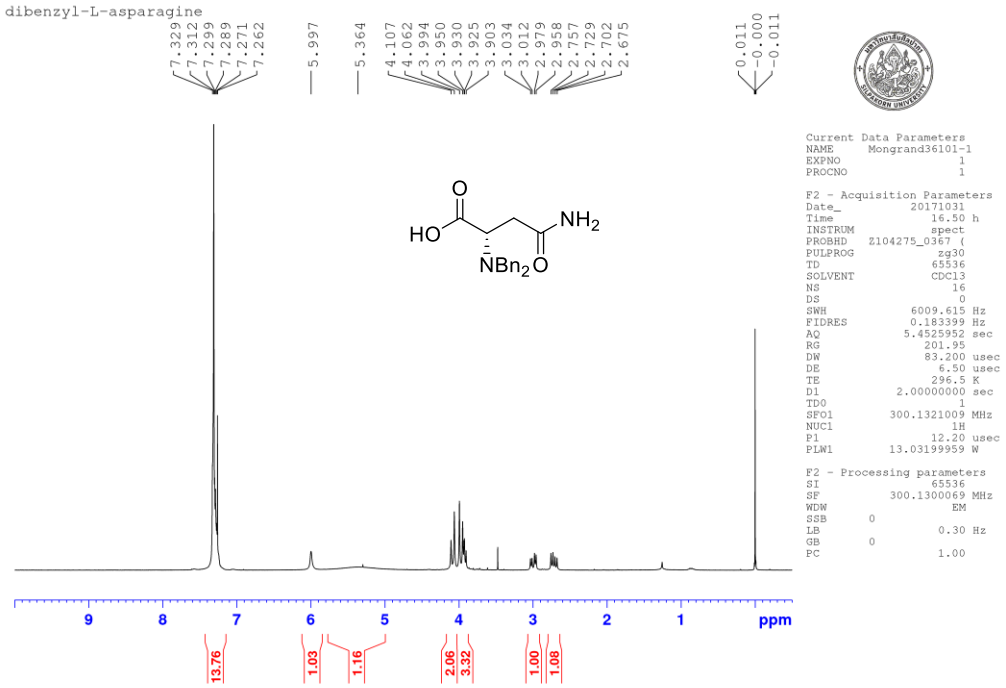
APPENDIX



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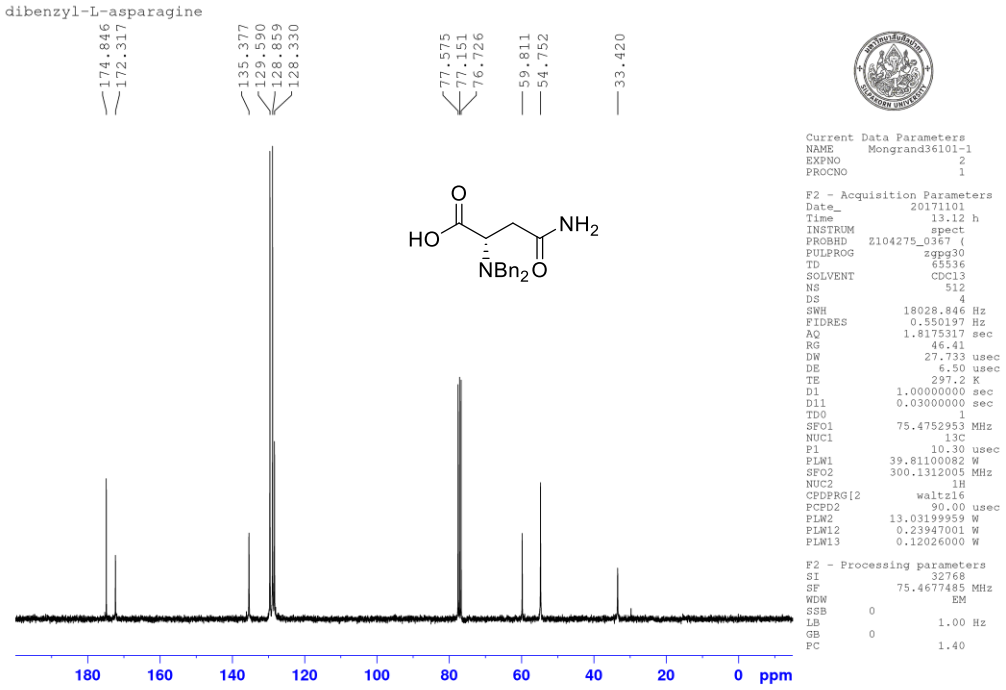

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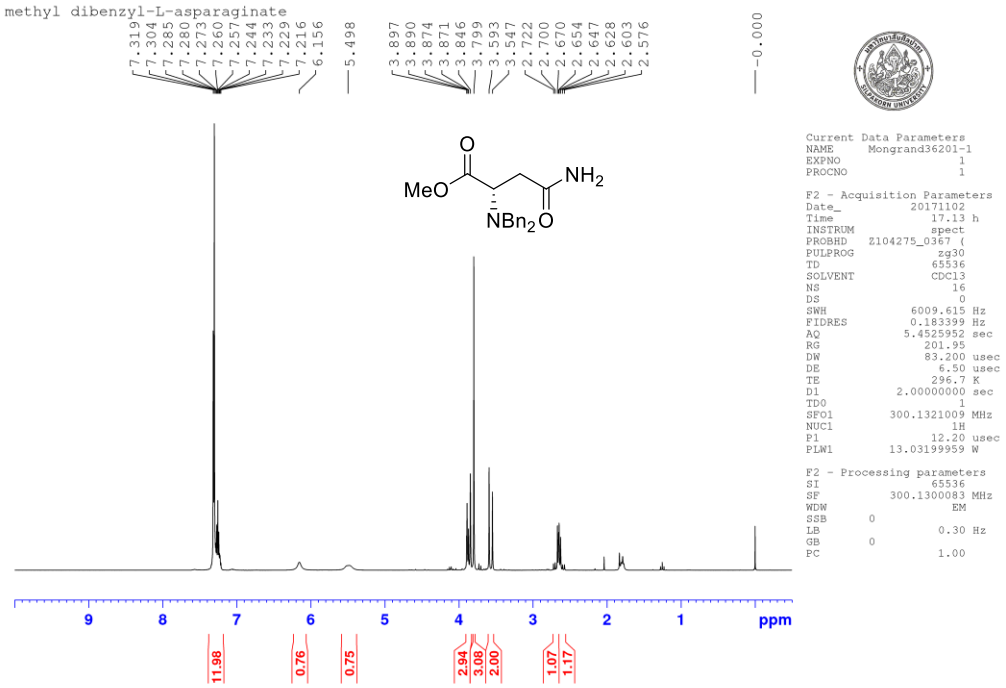

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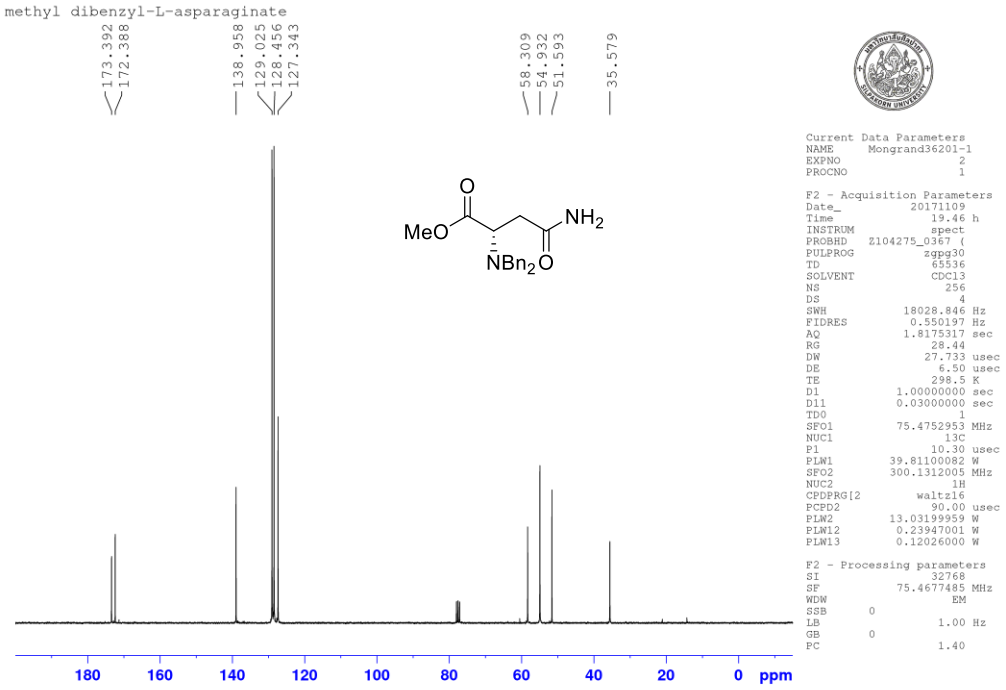

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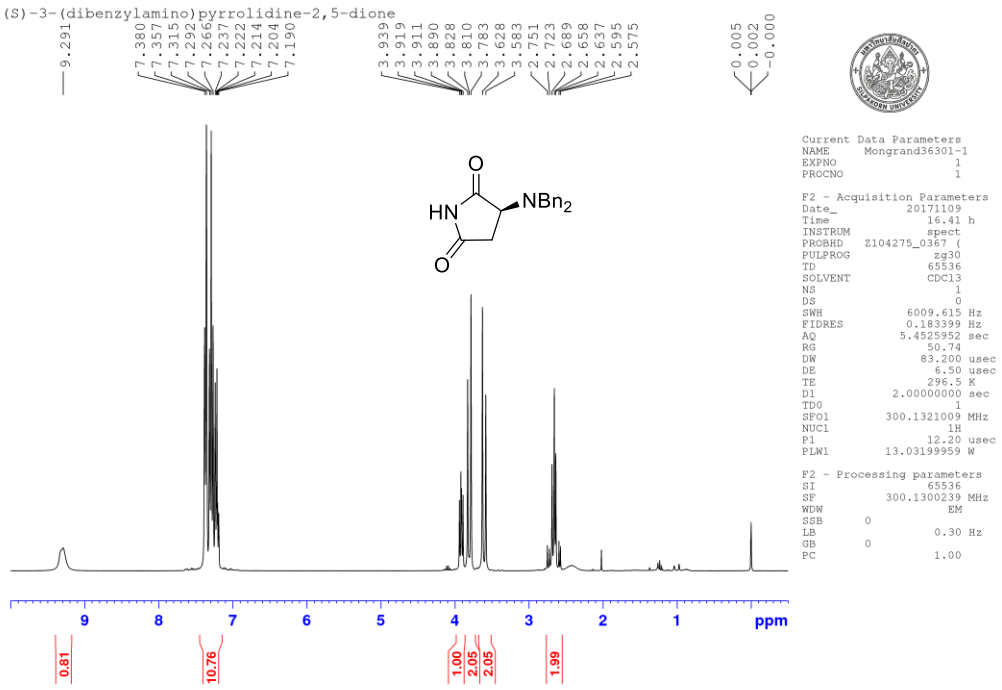

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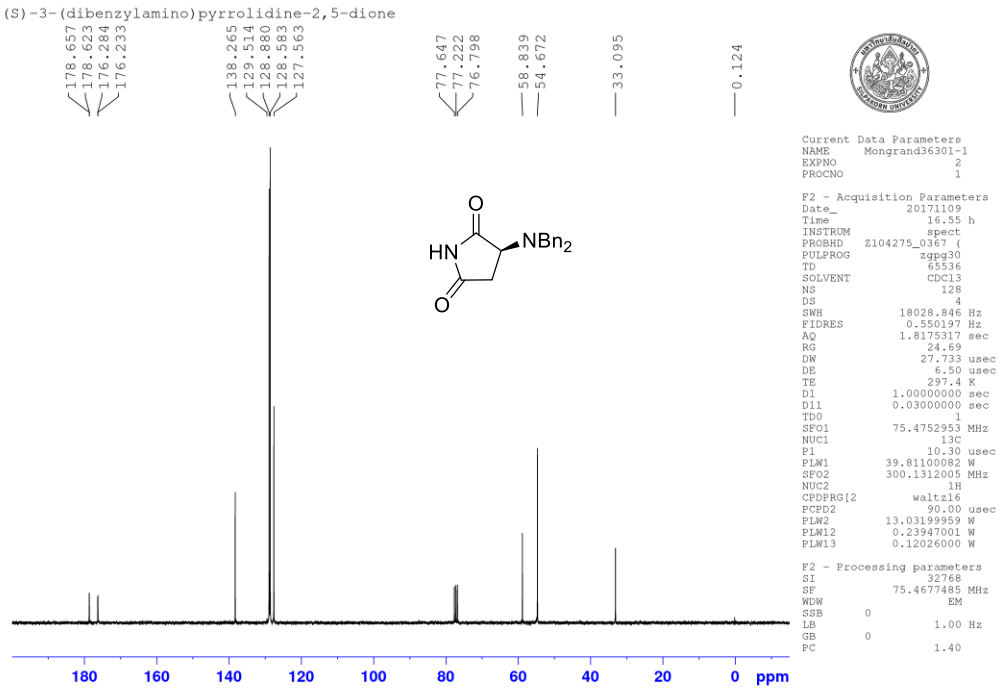

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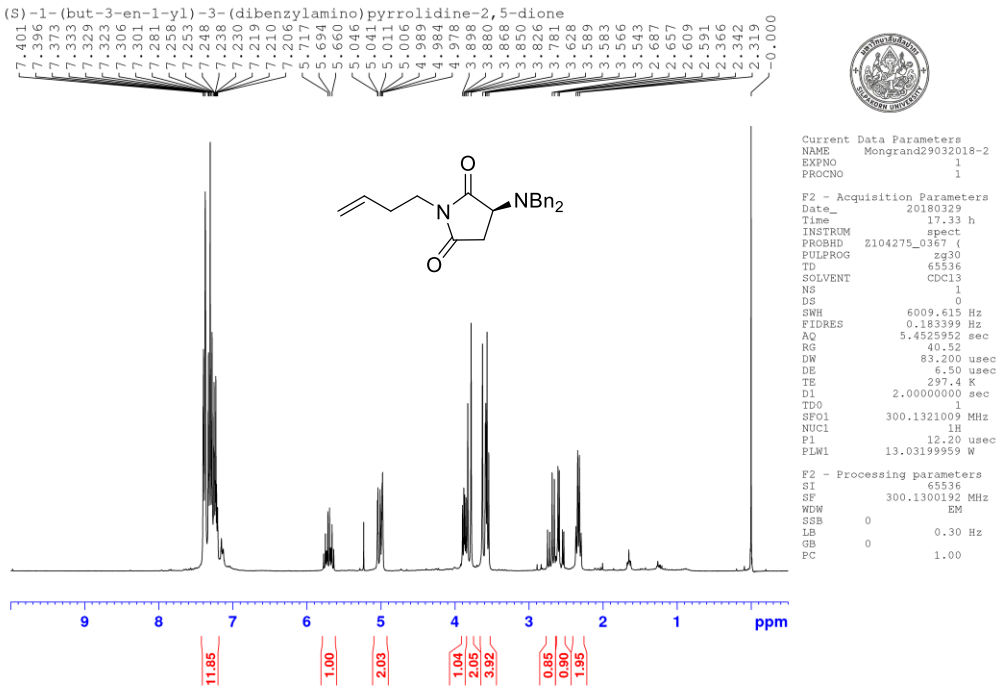

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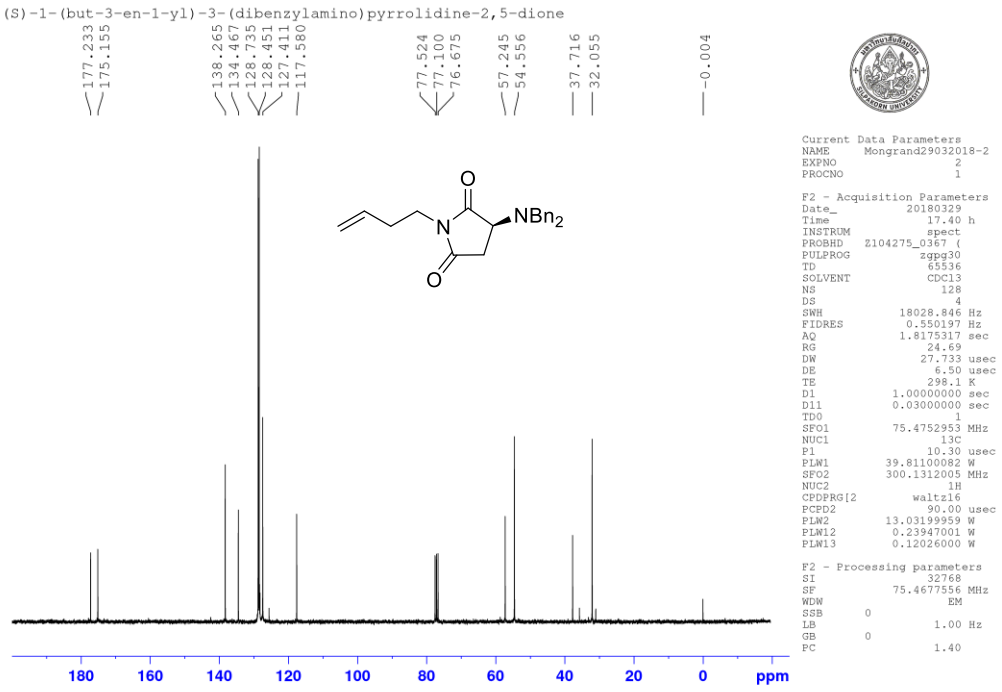

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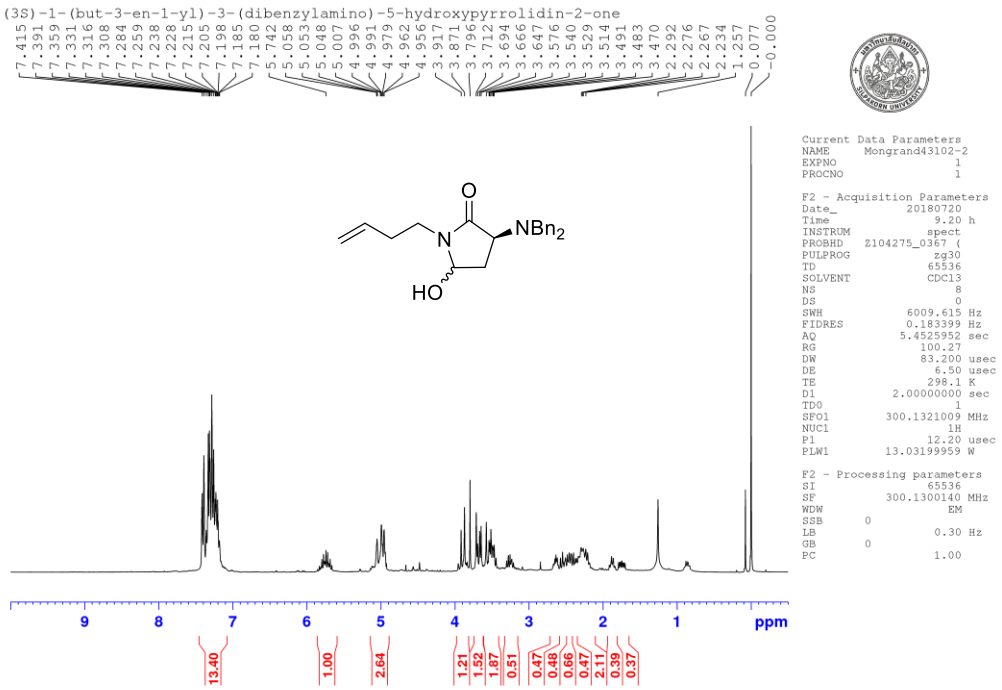

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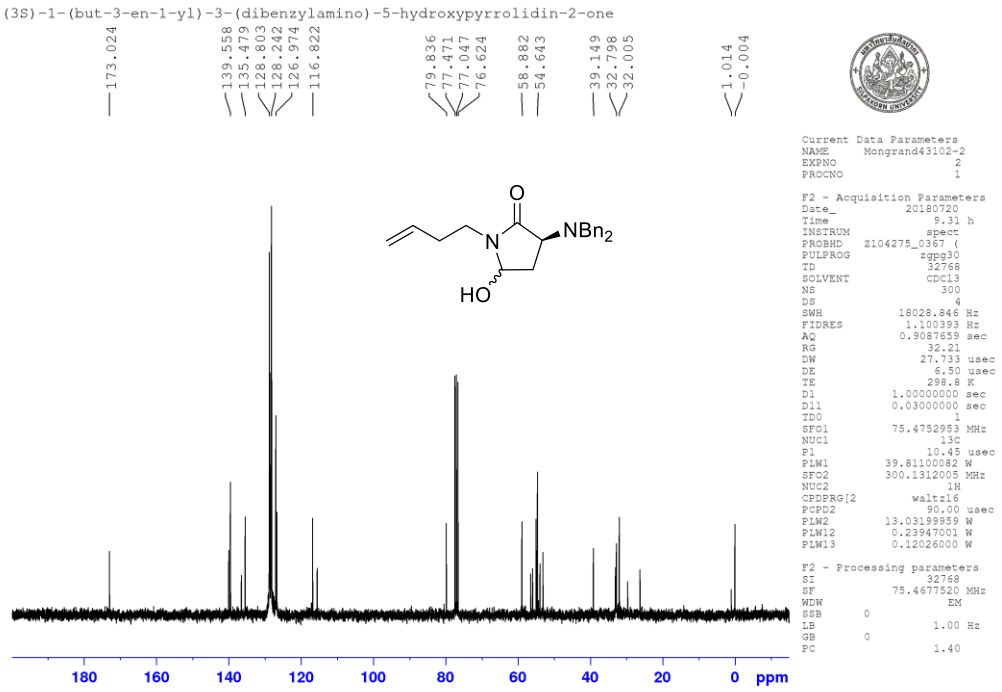

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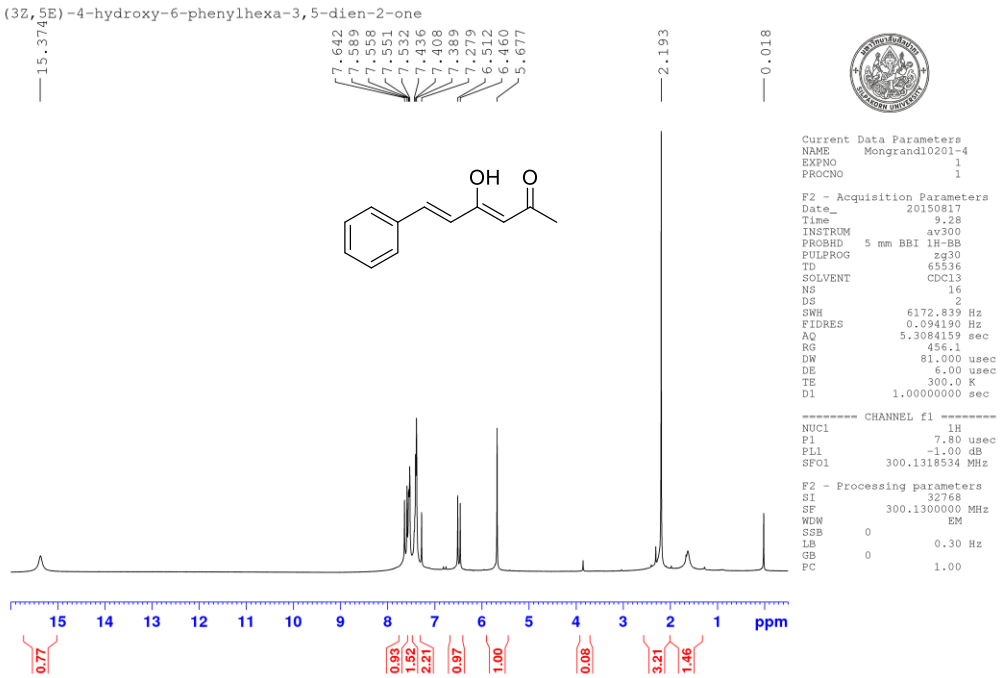

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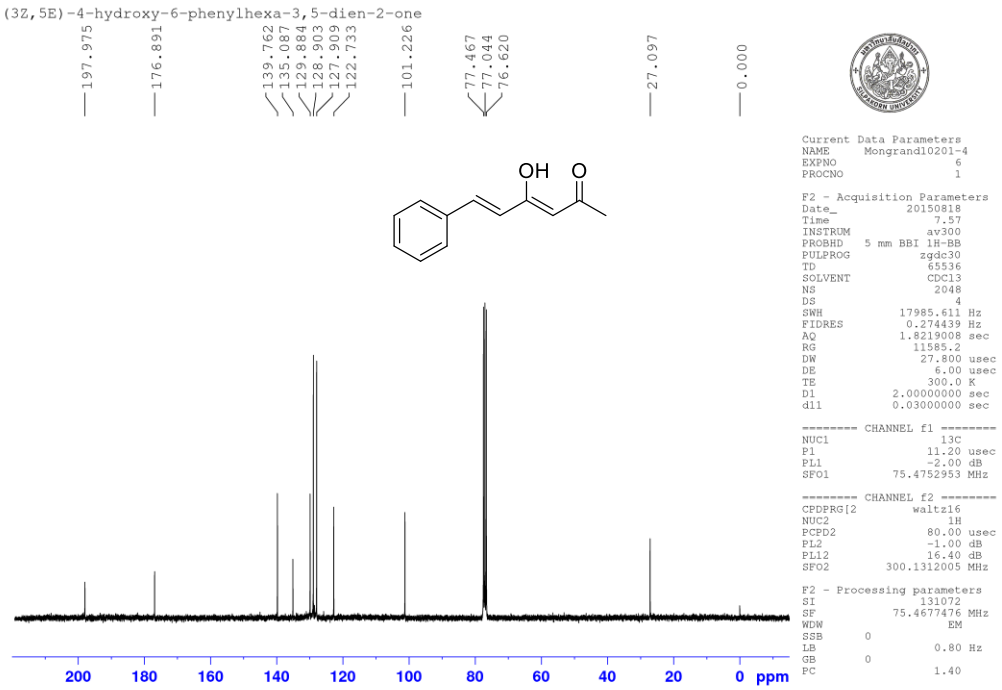

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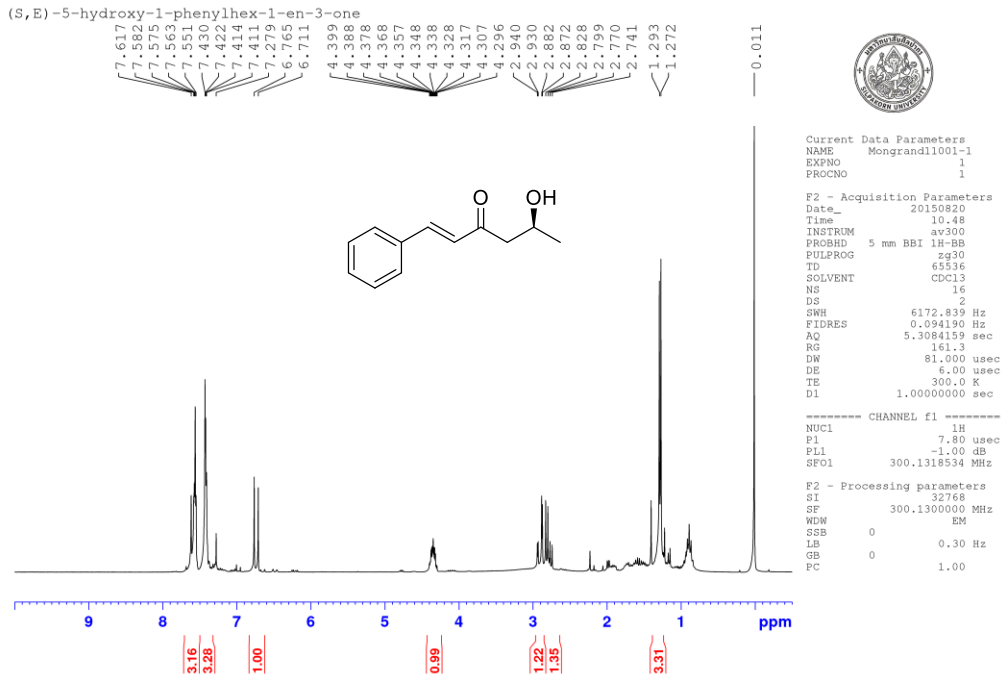

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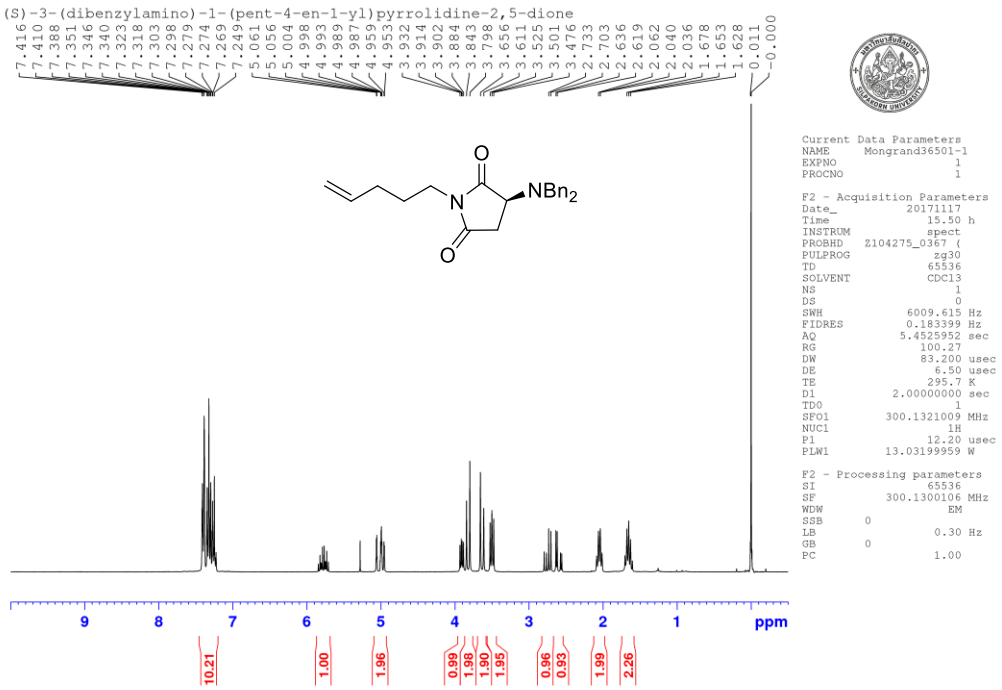

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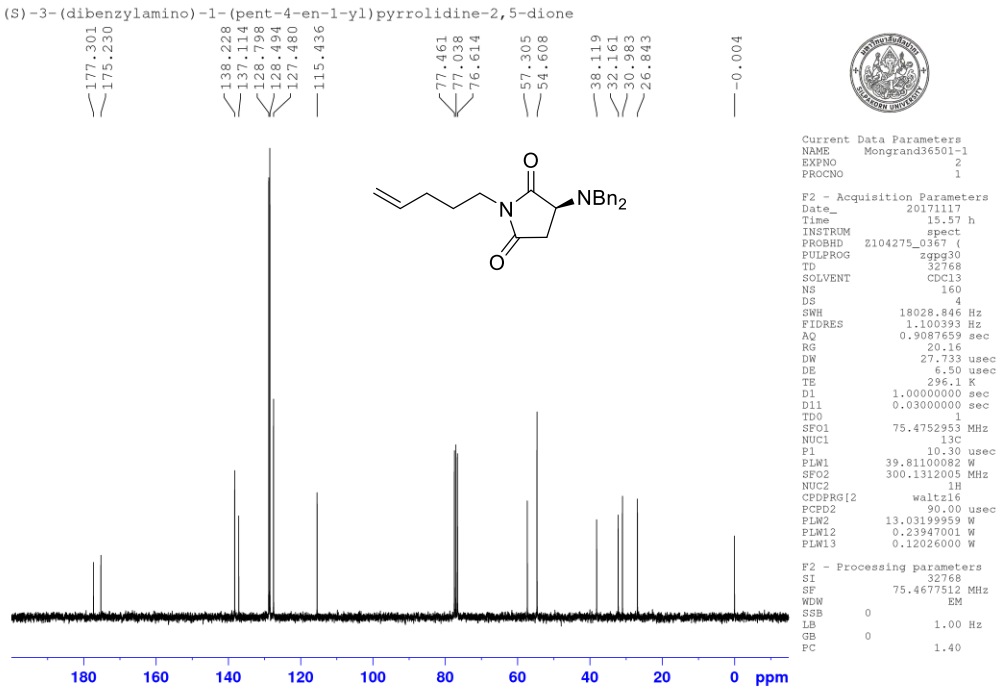

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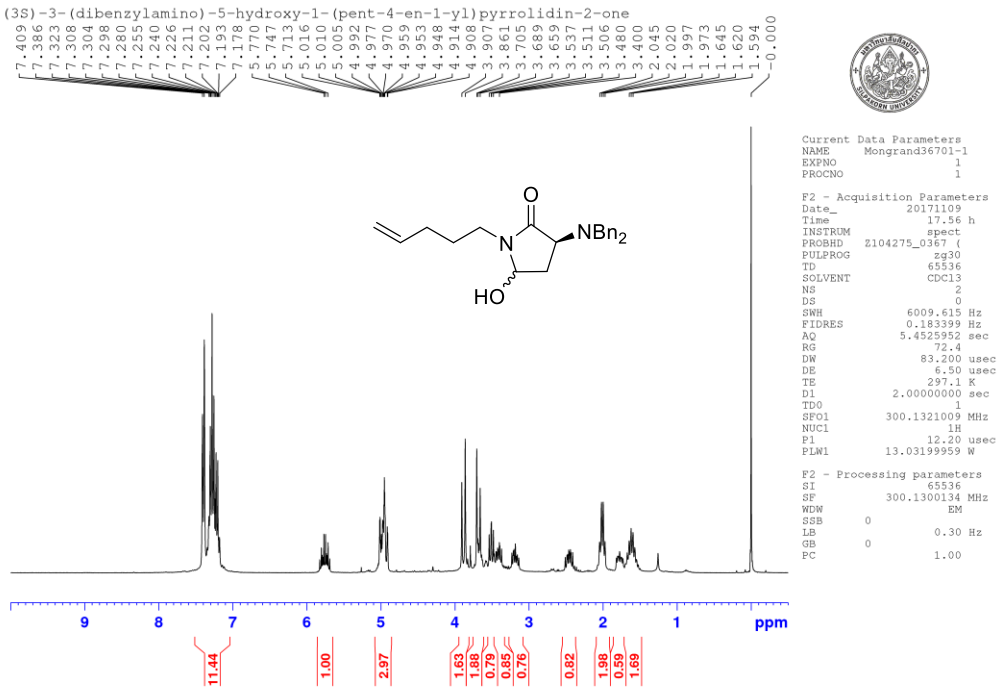

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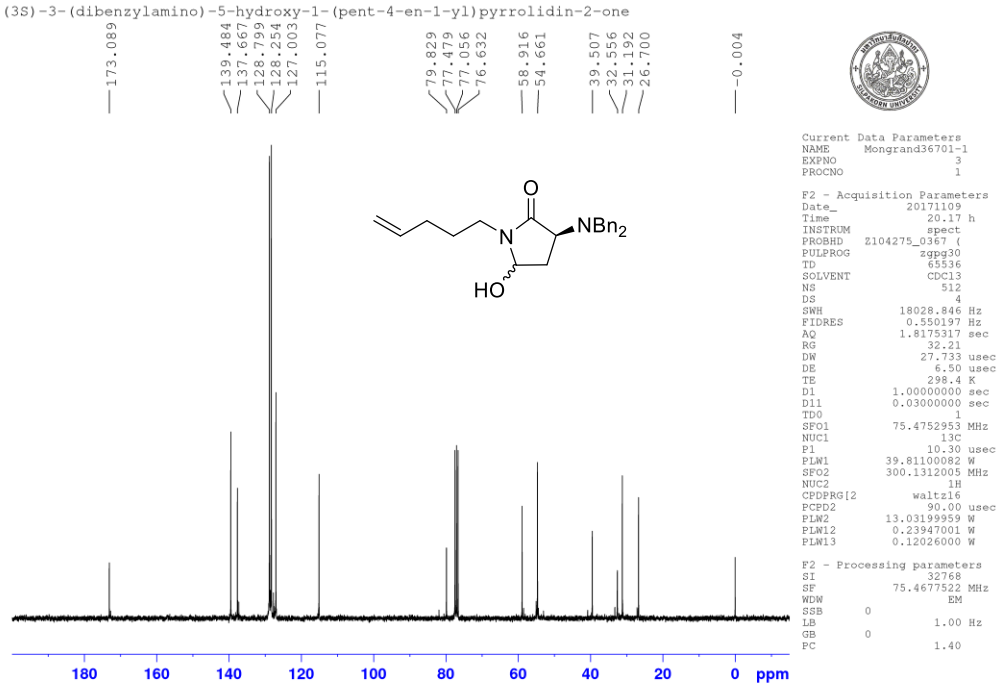

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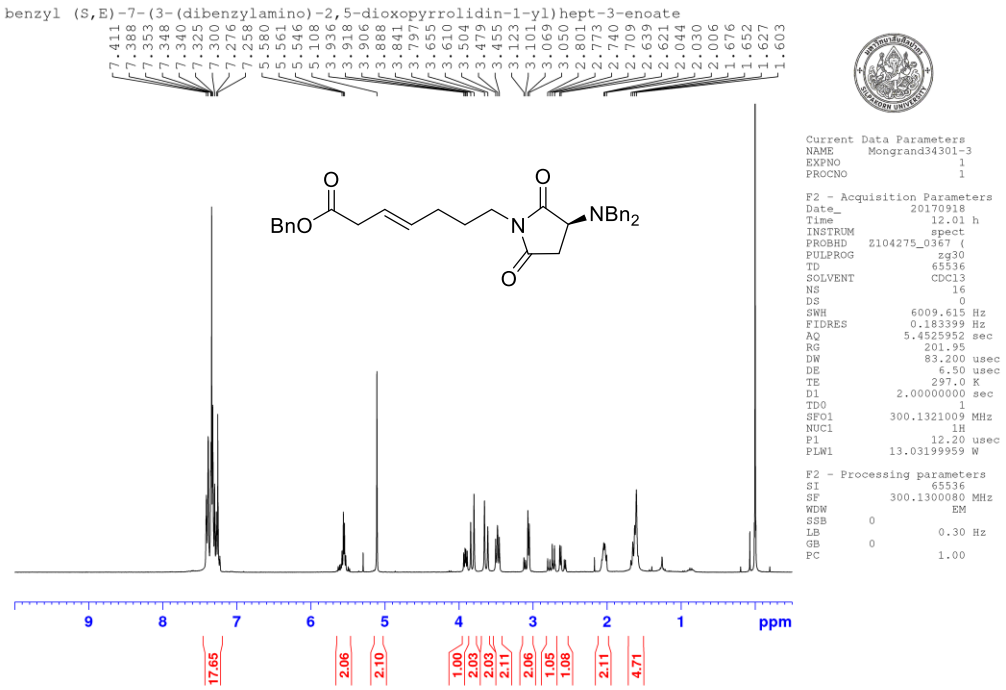

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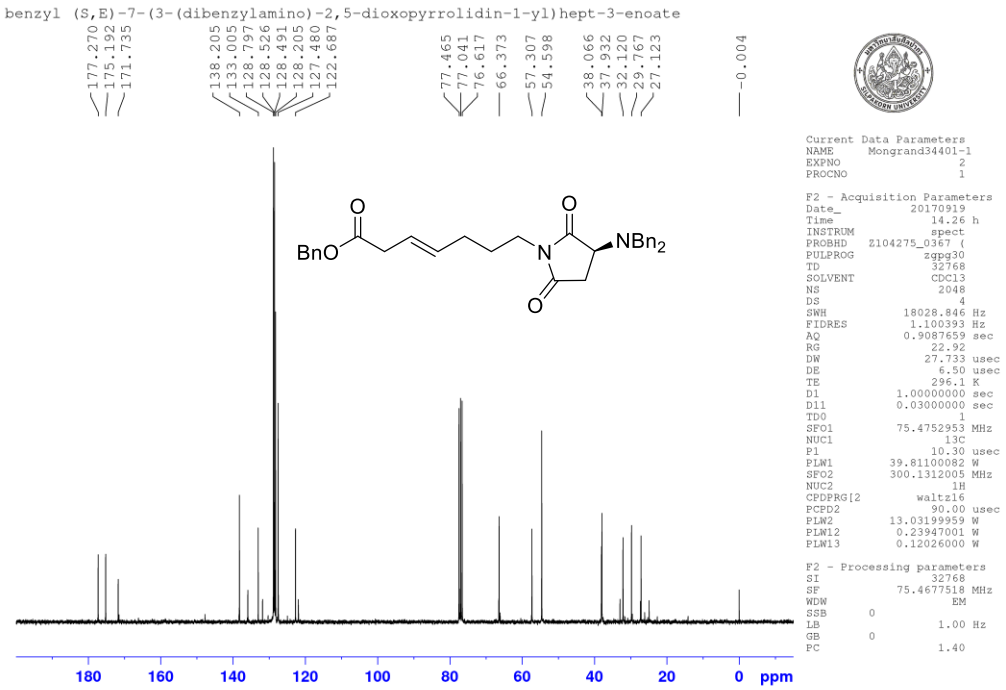

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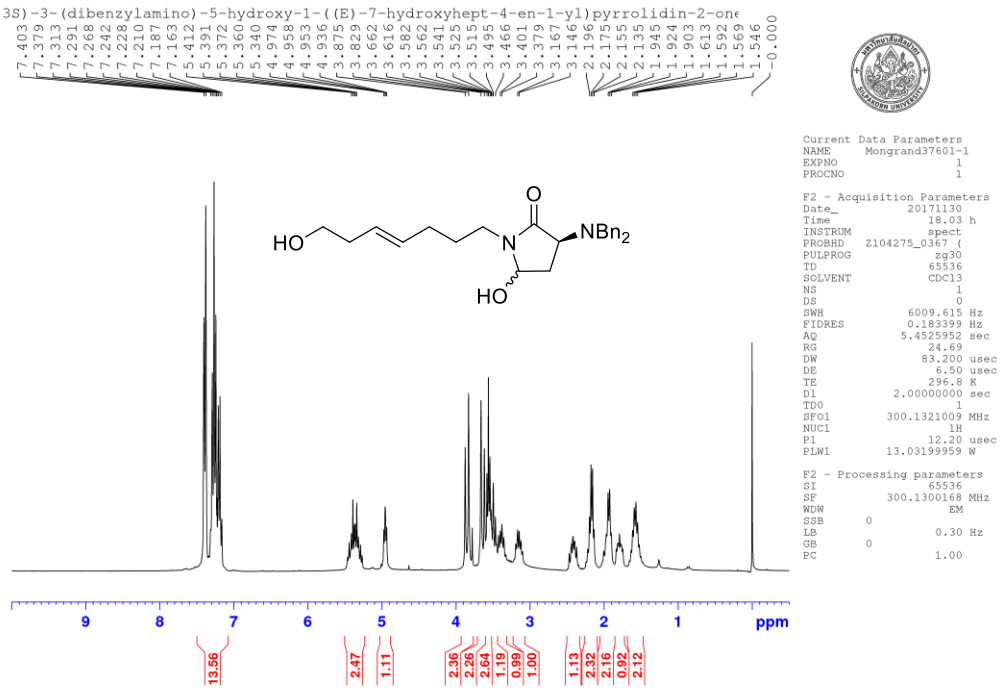

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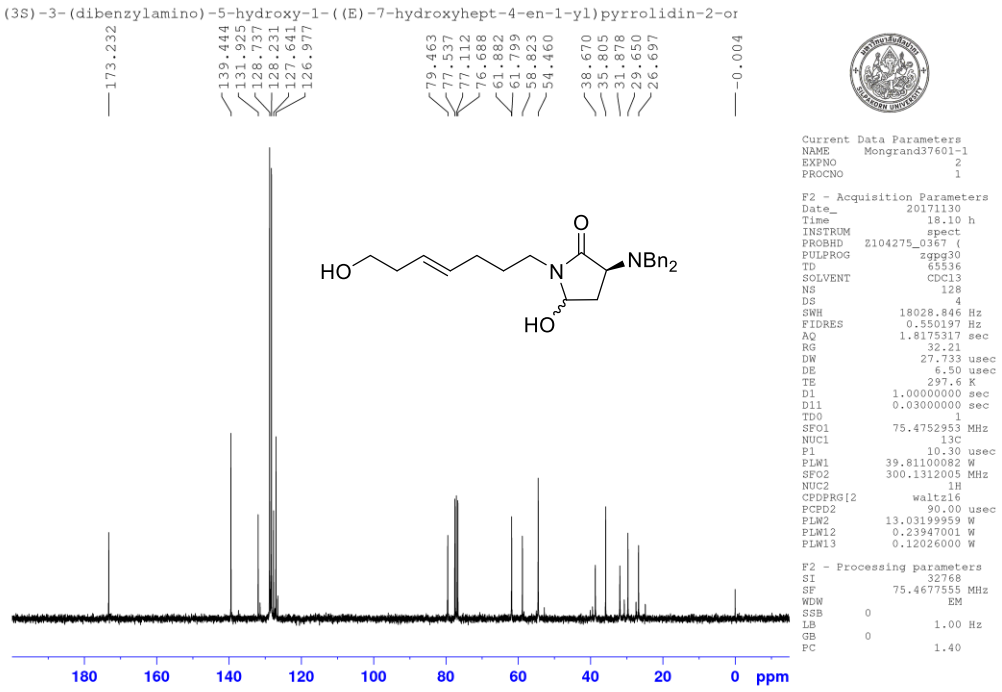

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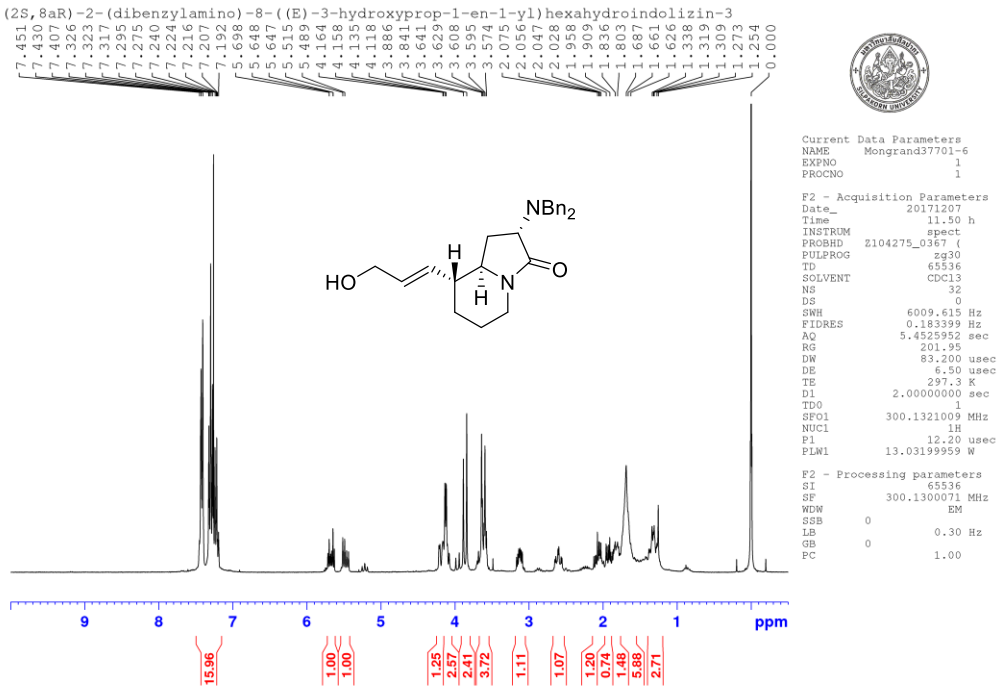

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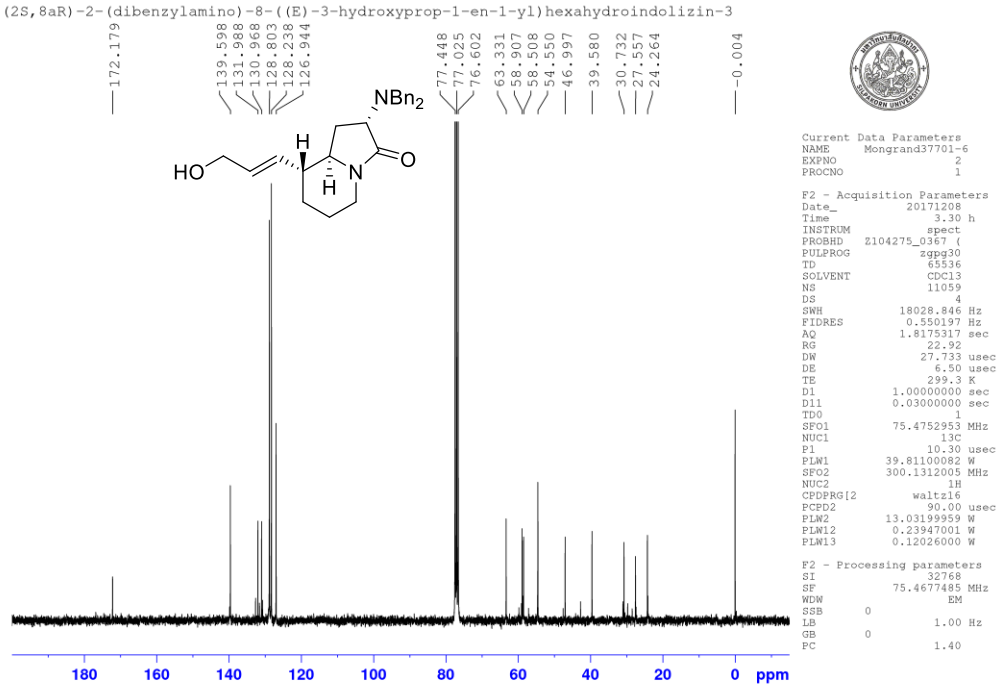

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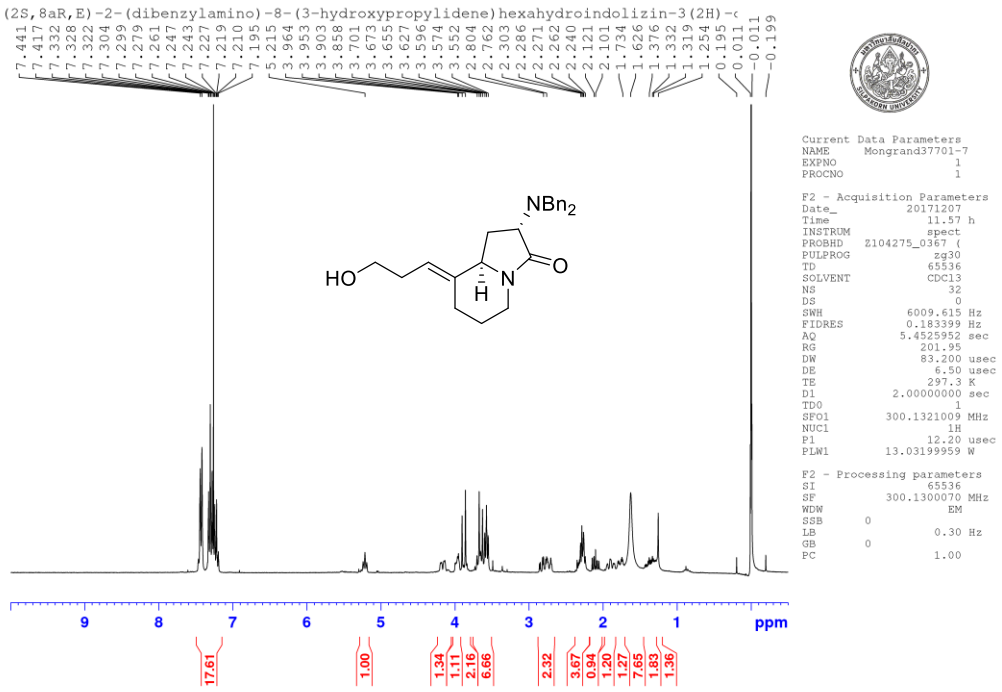

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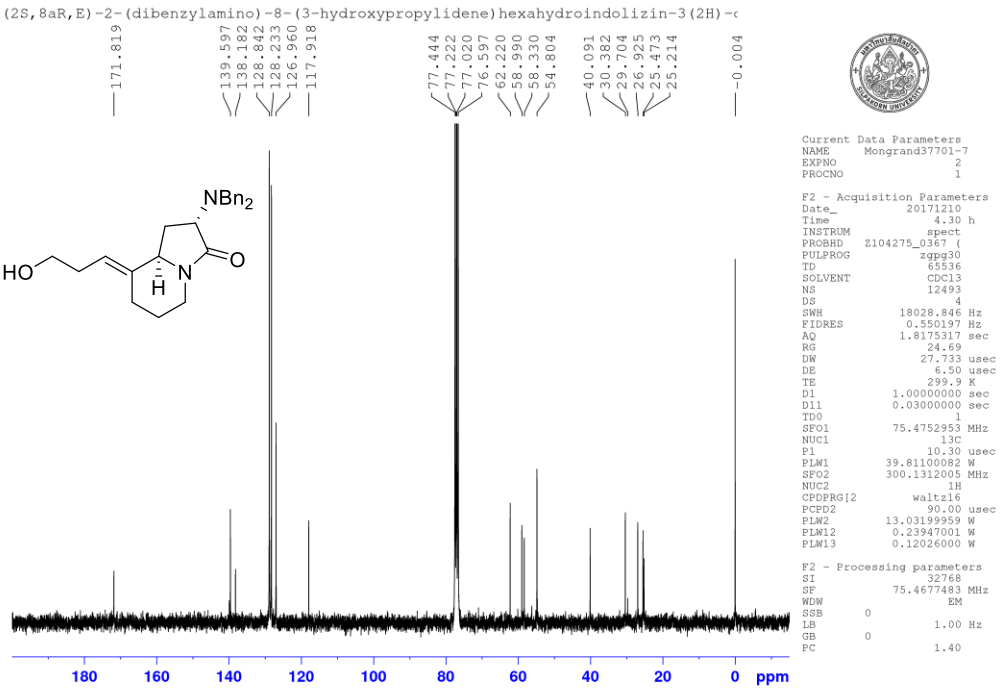

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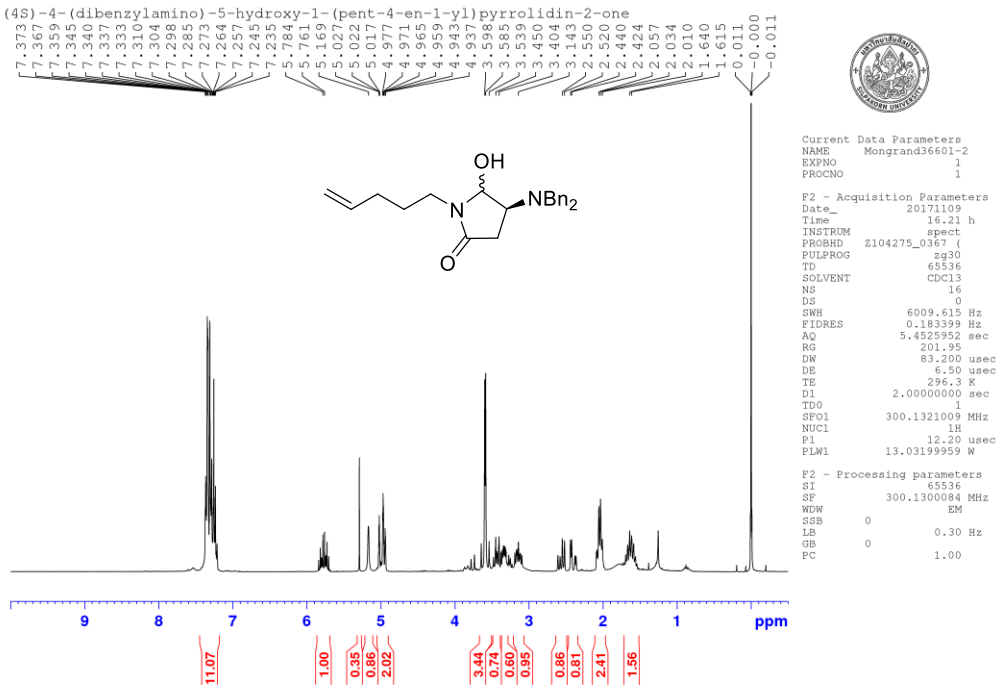

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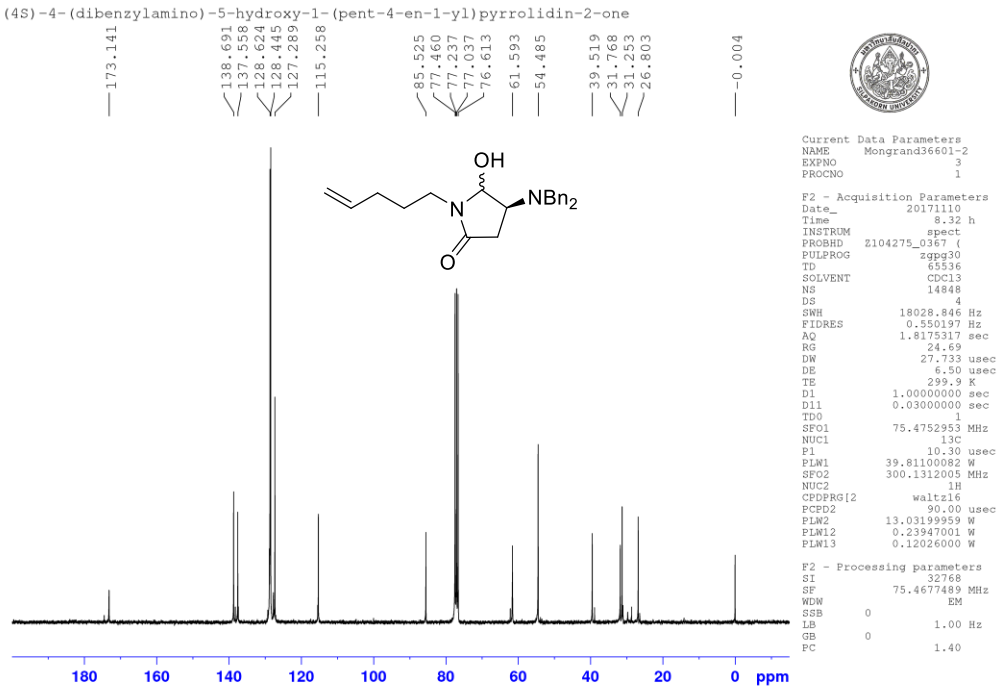

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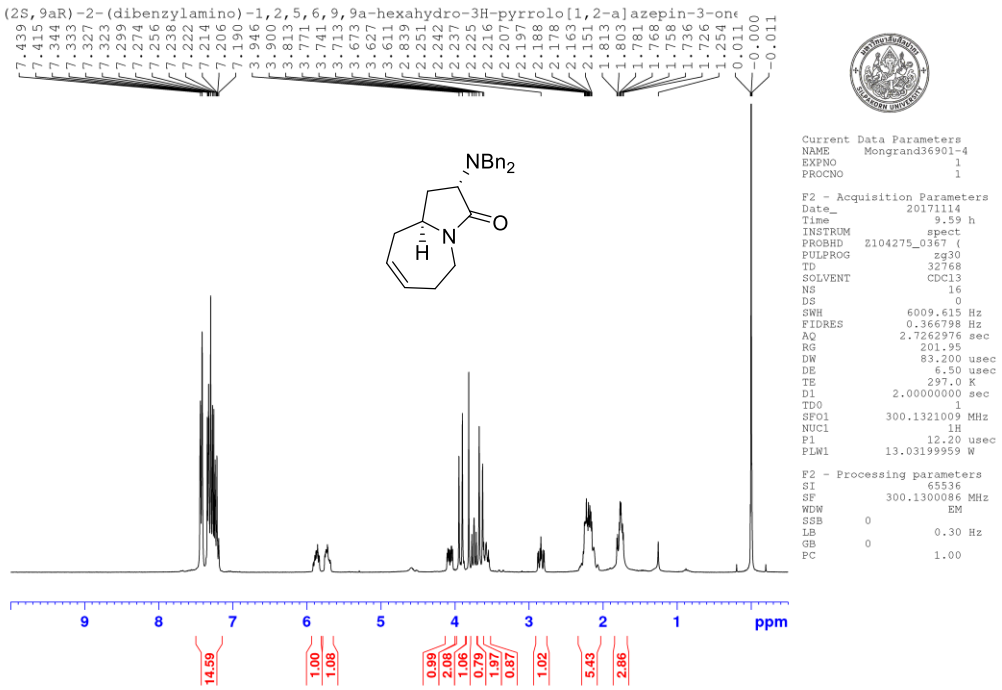
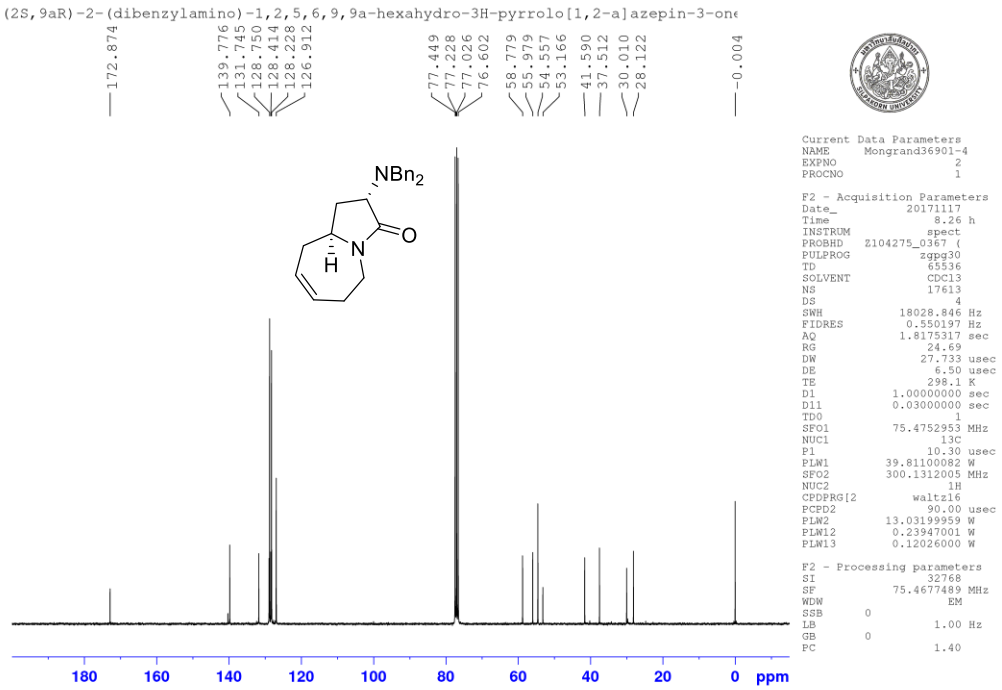
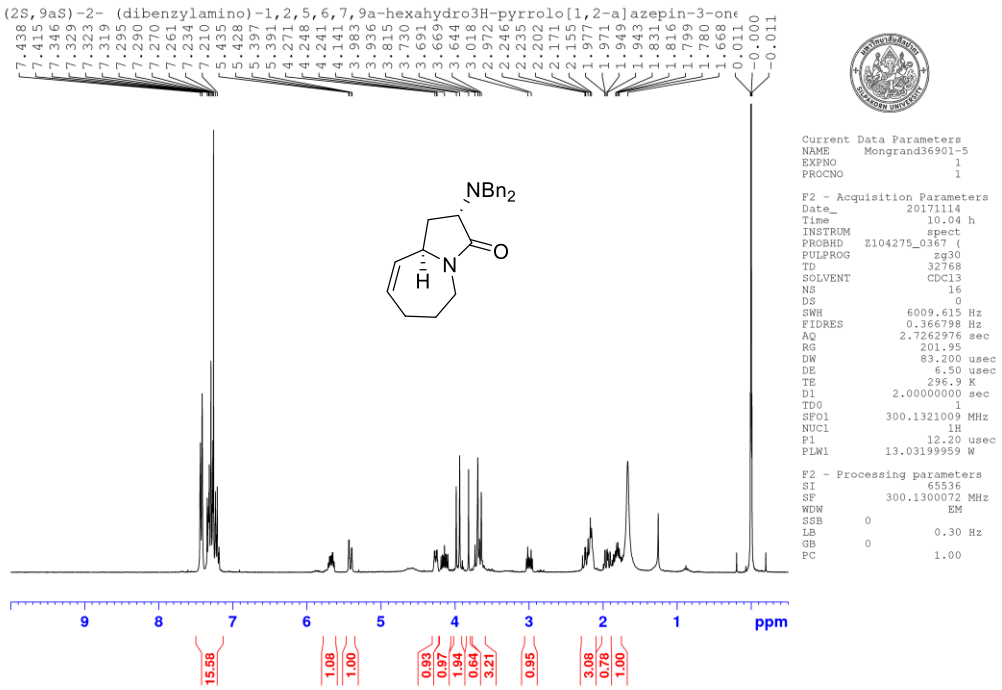


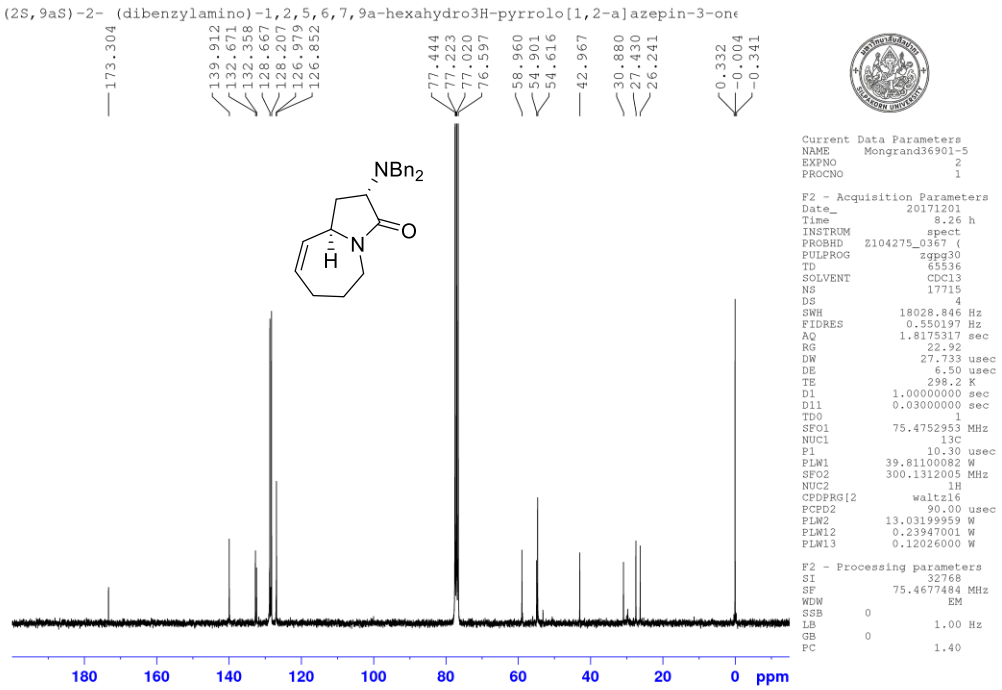
^{1}H NMR of compound **3.34**



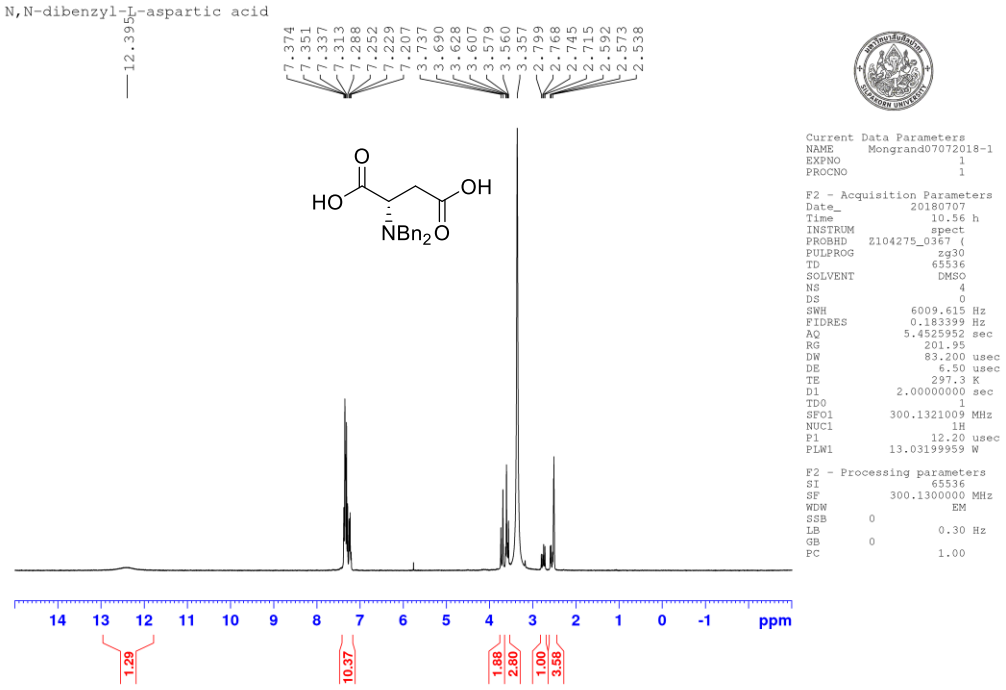
^{13}C NMR of compound **3.34**



^{1}H NMR of compound **3.35**



^{13}C NMR of compound **3.35**



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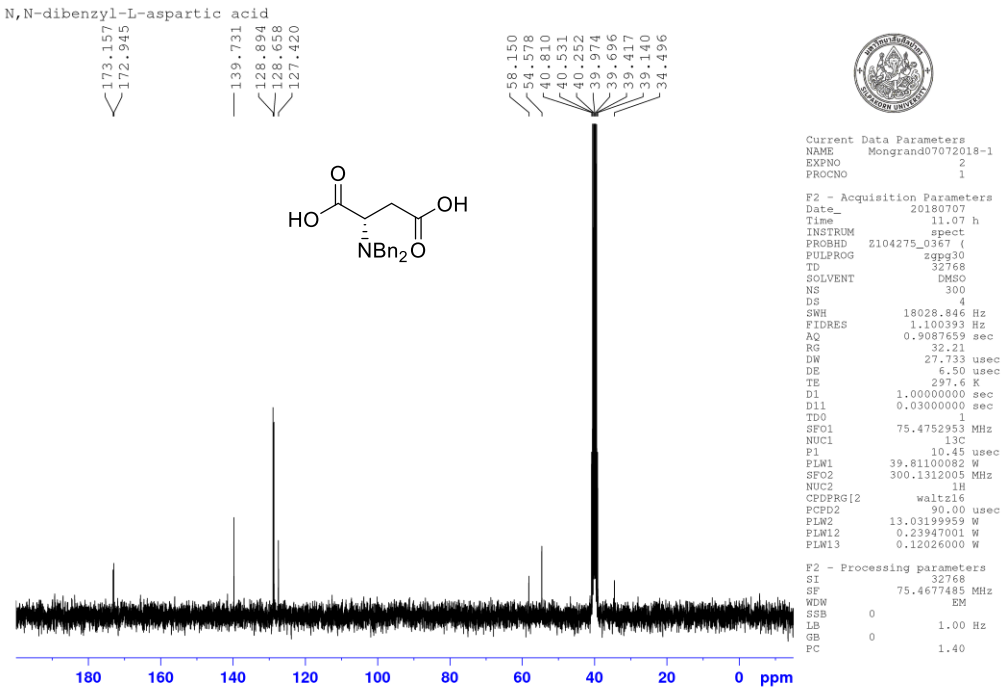
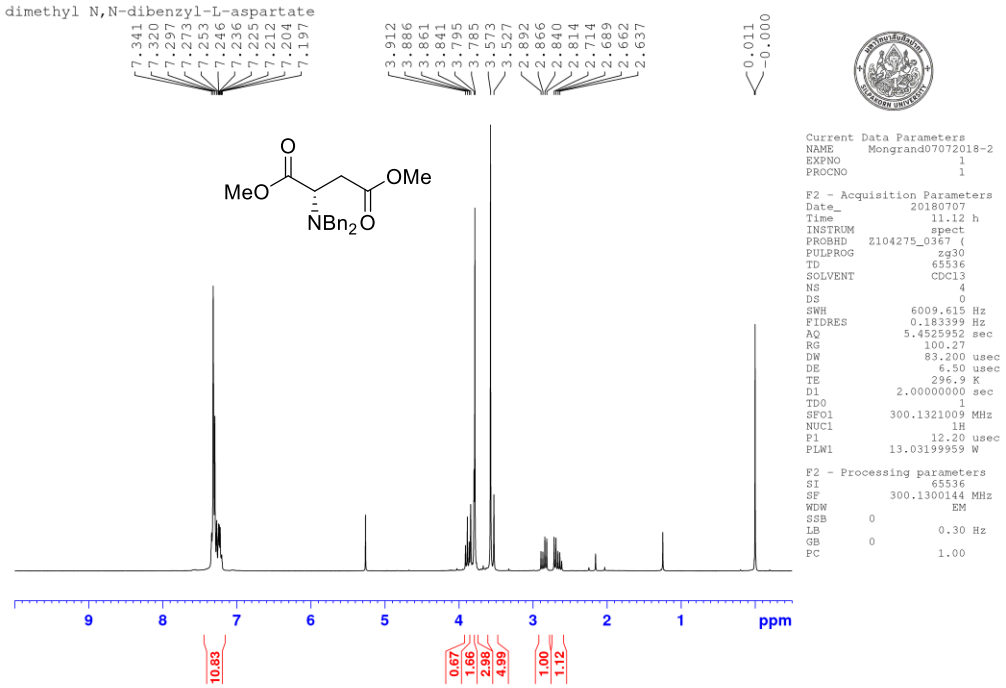
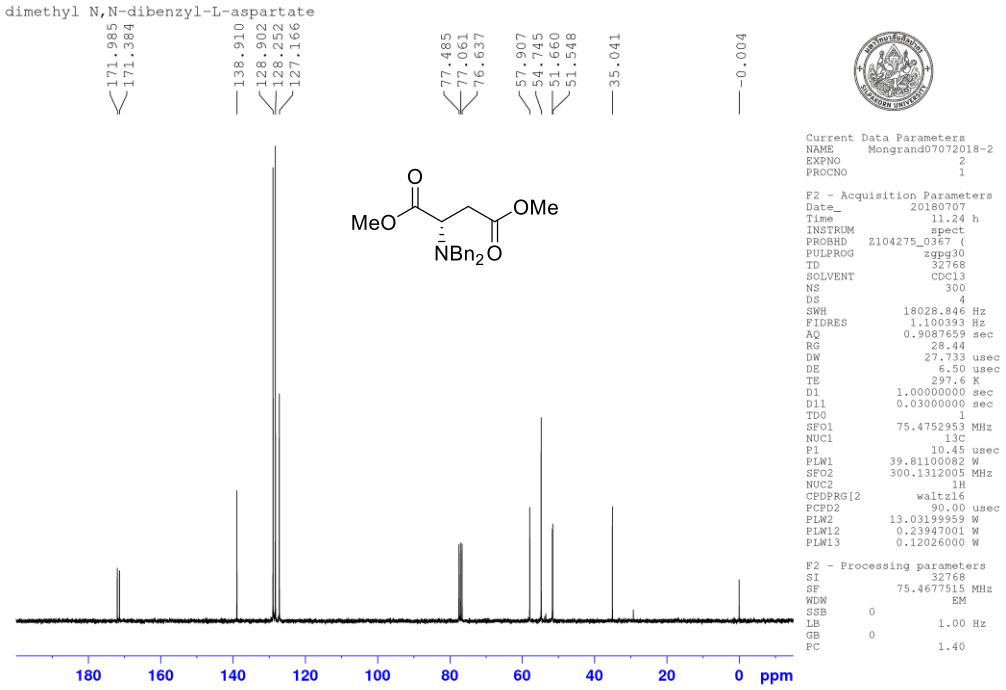


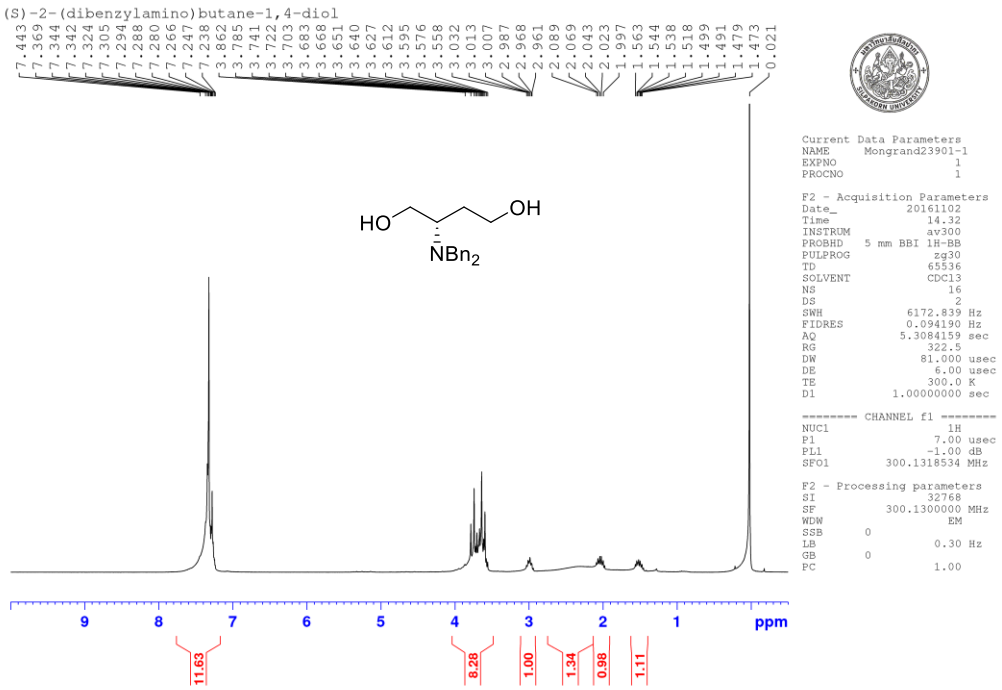
^{13}C NMR of compound **3.39**



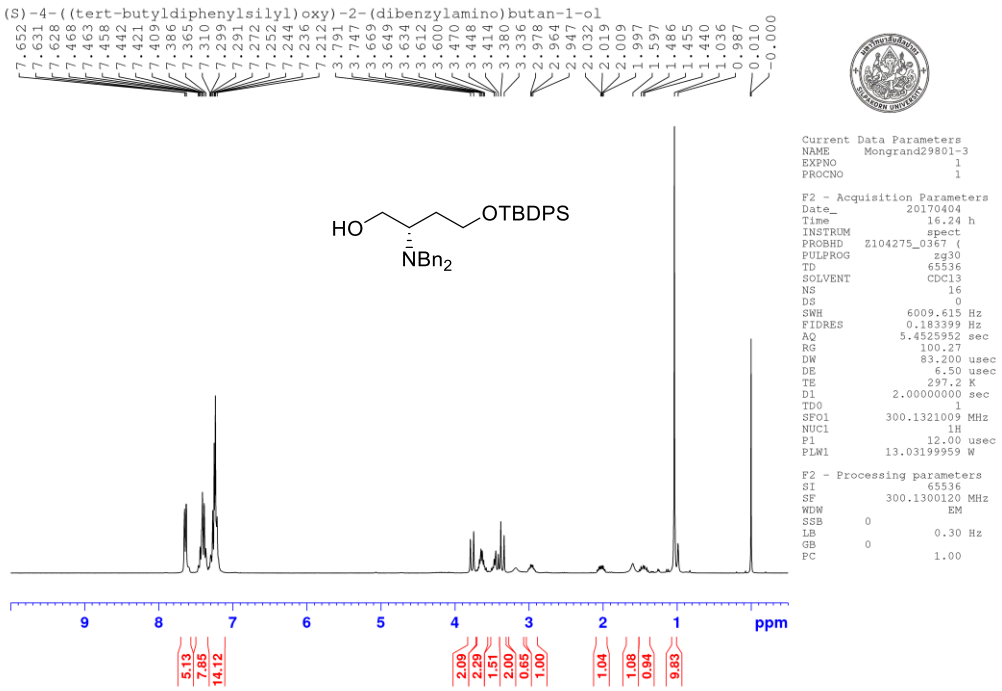
^{1}H NMR of compound **3.40**



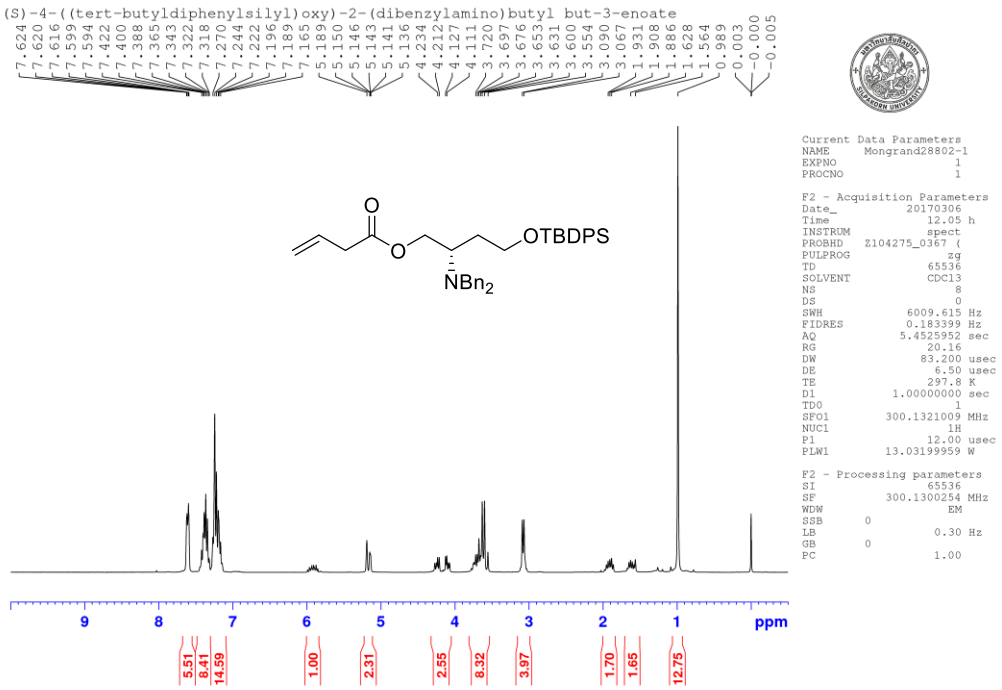
^{13}C NMR of compound **3.40**



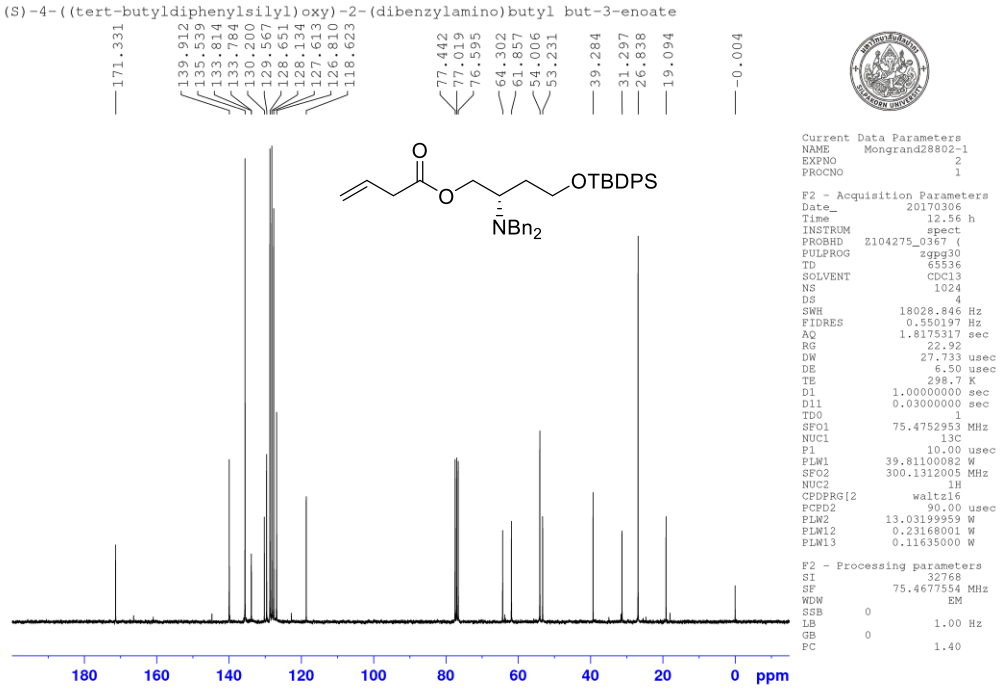
^{1}H NMR of compound **3.41**



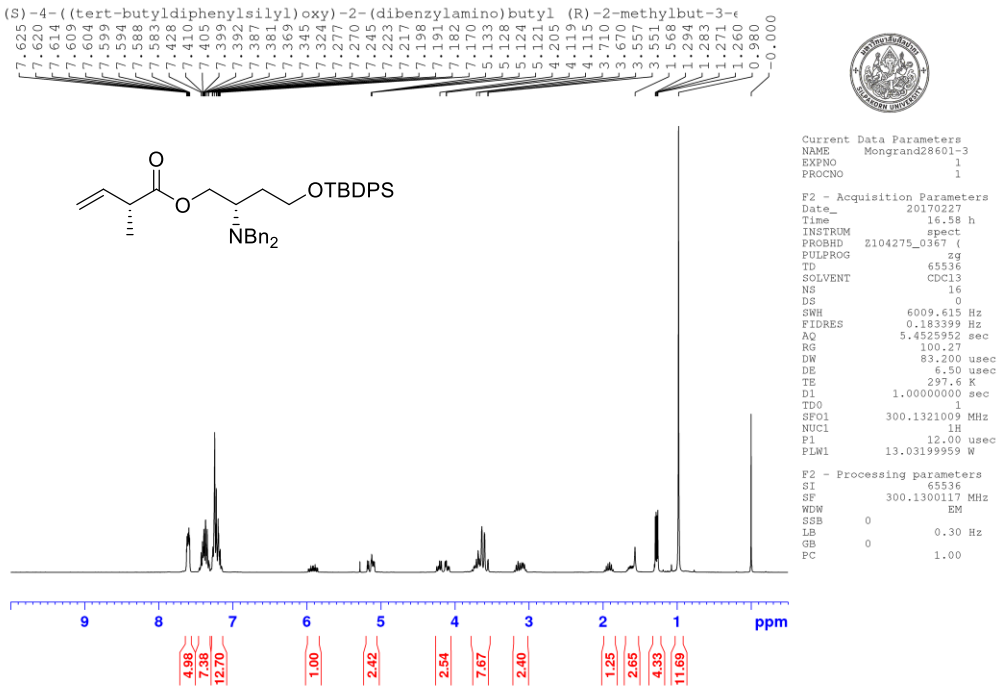
^{1}H NMR of compound **3.42**



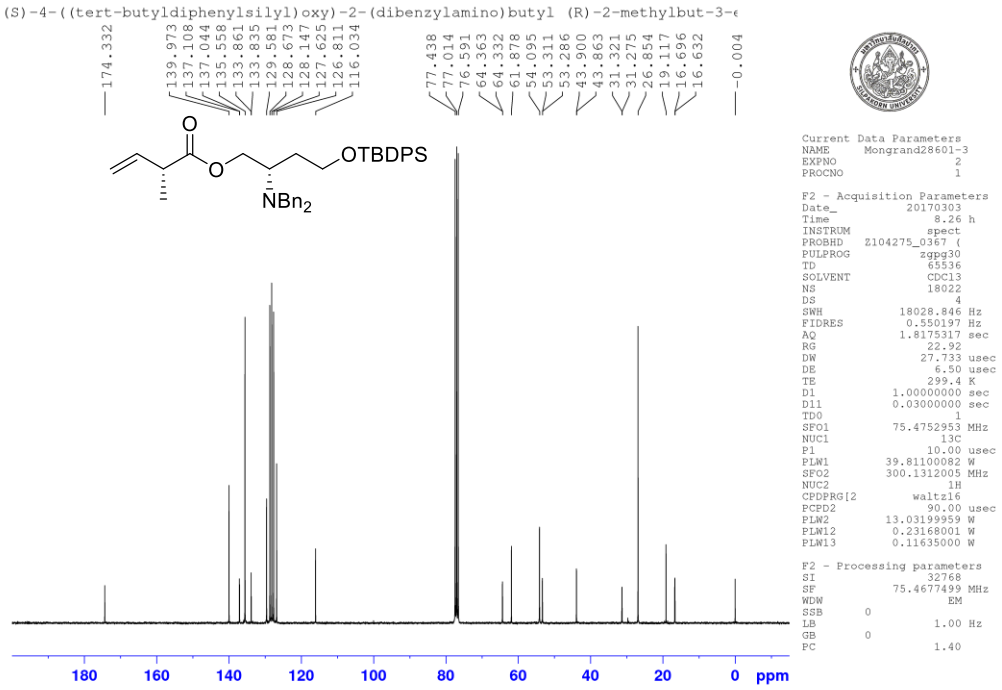
^{1}H NMR of compound **3.43**



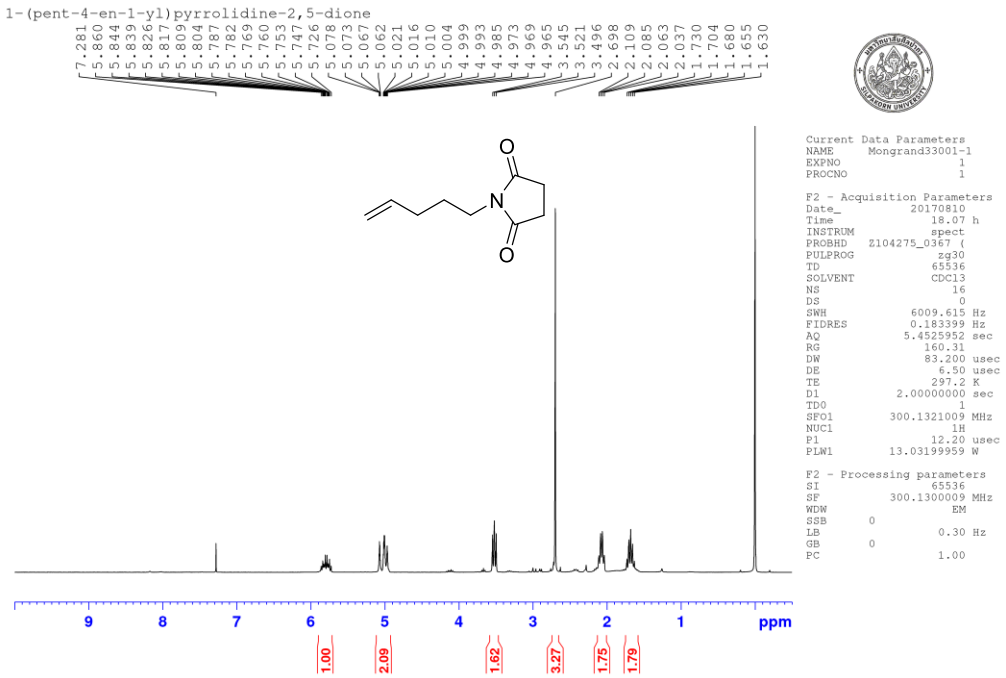
^{13}C NMR of compound **3.43**



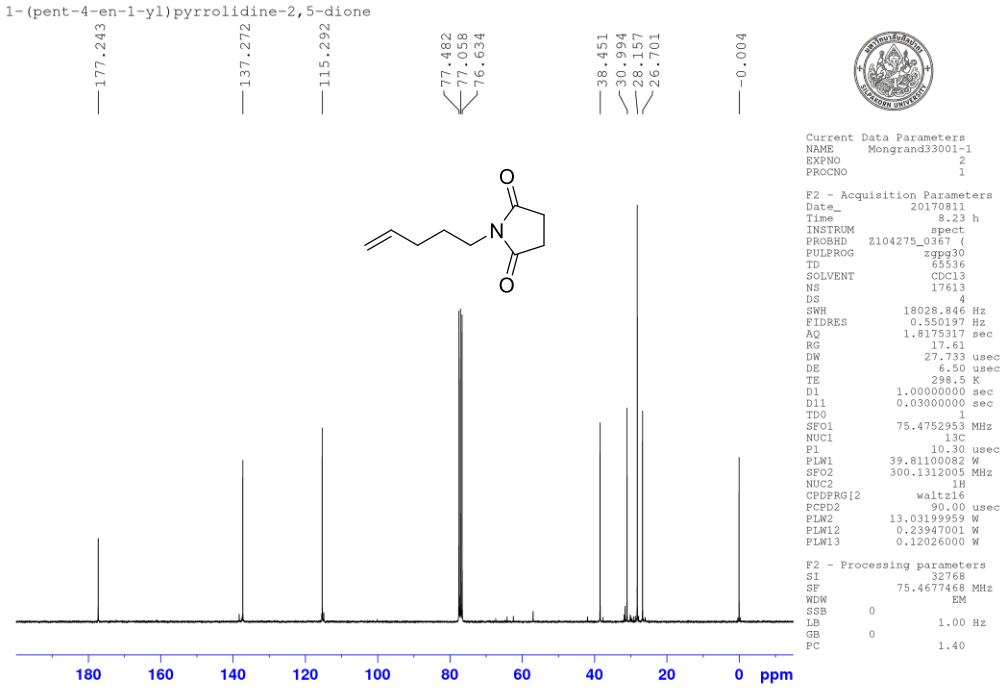
^{1}H NMR of compound **3.44**



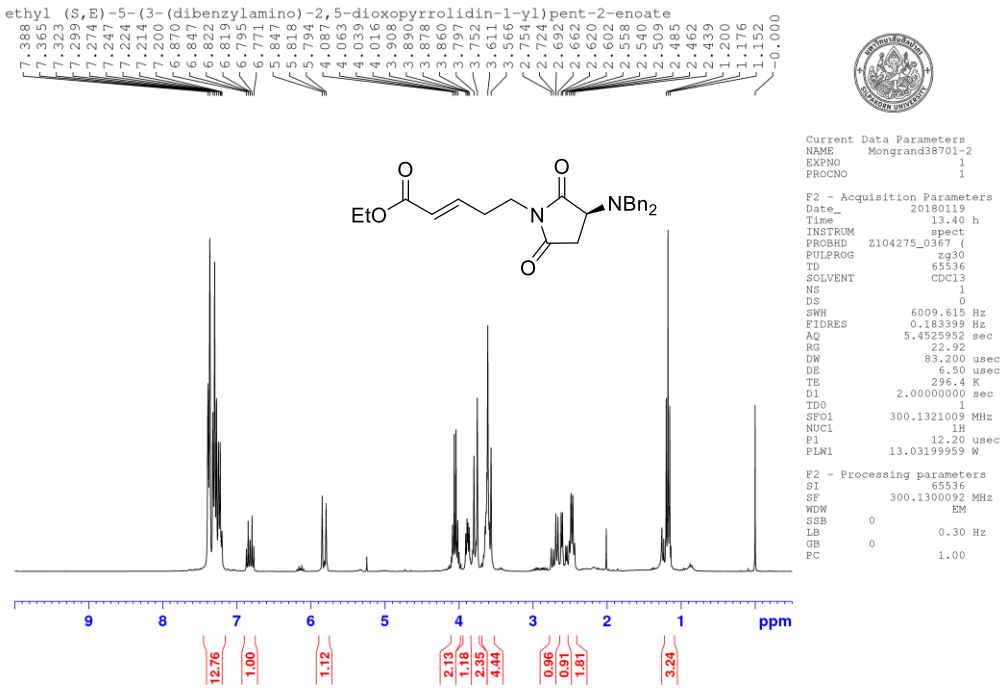
^{13}C NMR of compound **3.44**



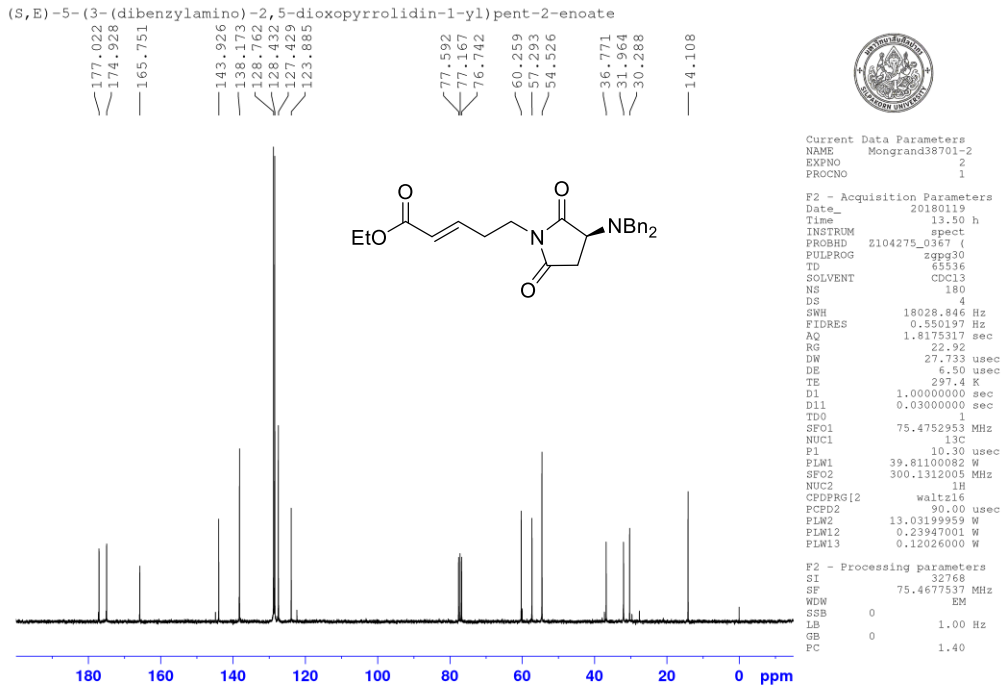
^{1}H NMR of compound **3.45**



^{13}C NMR of compound **3.45**



^{1}H NMR of compound **3.49**



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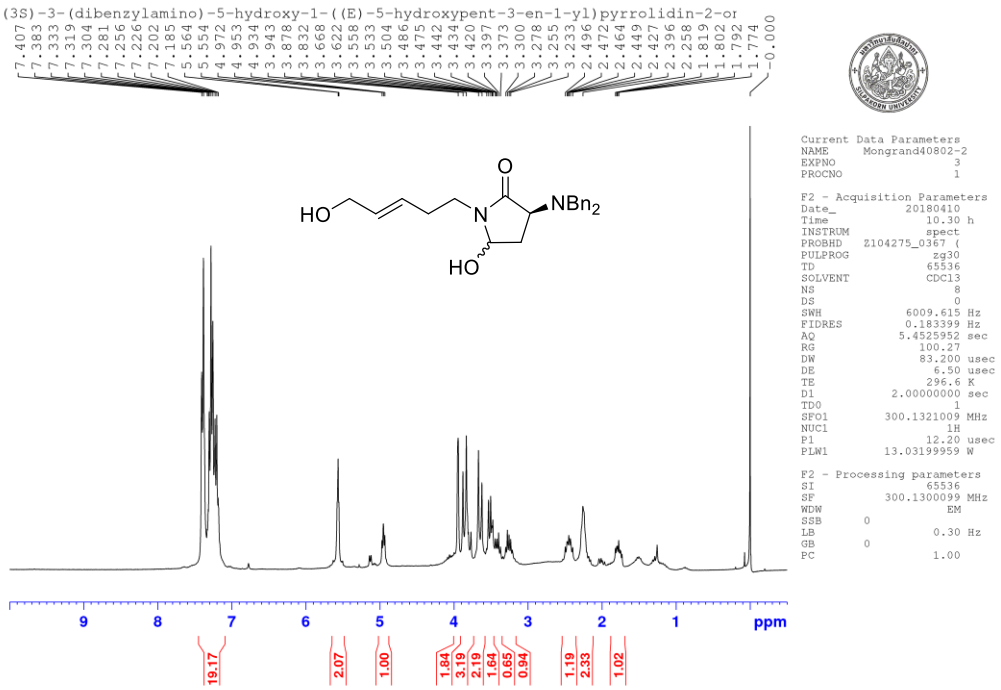

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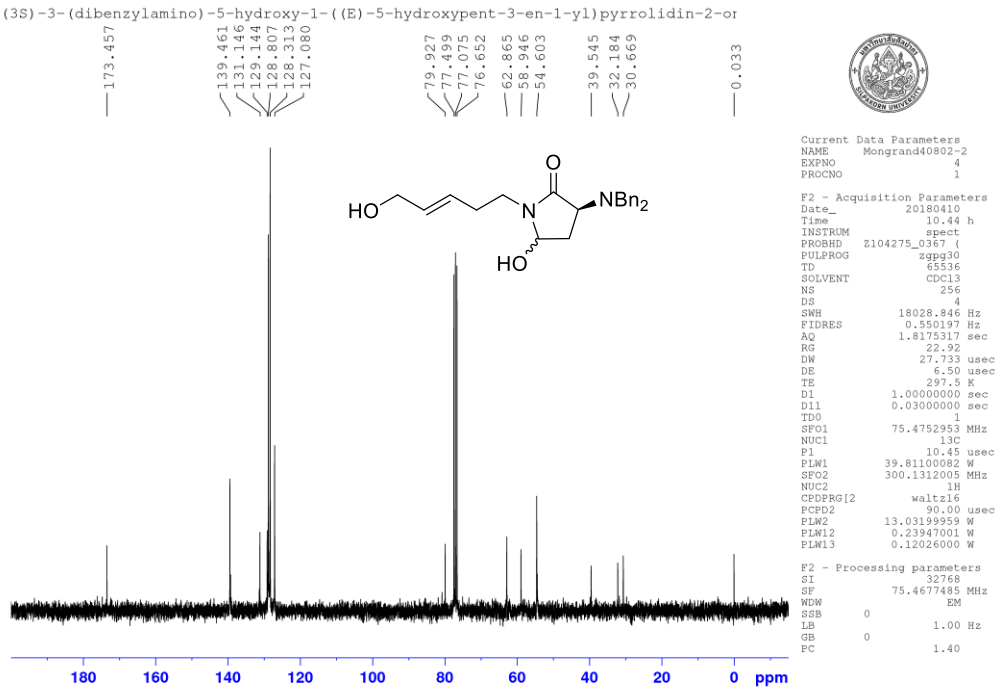

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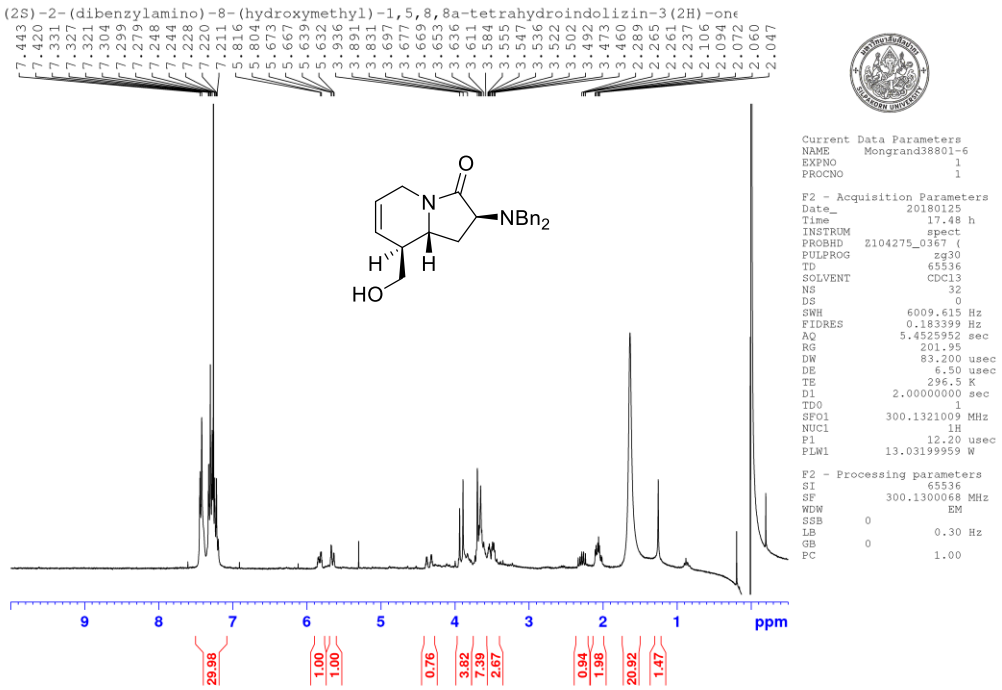

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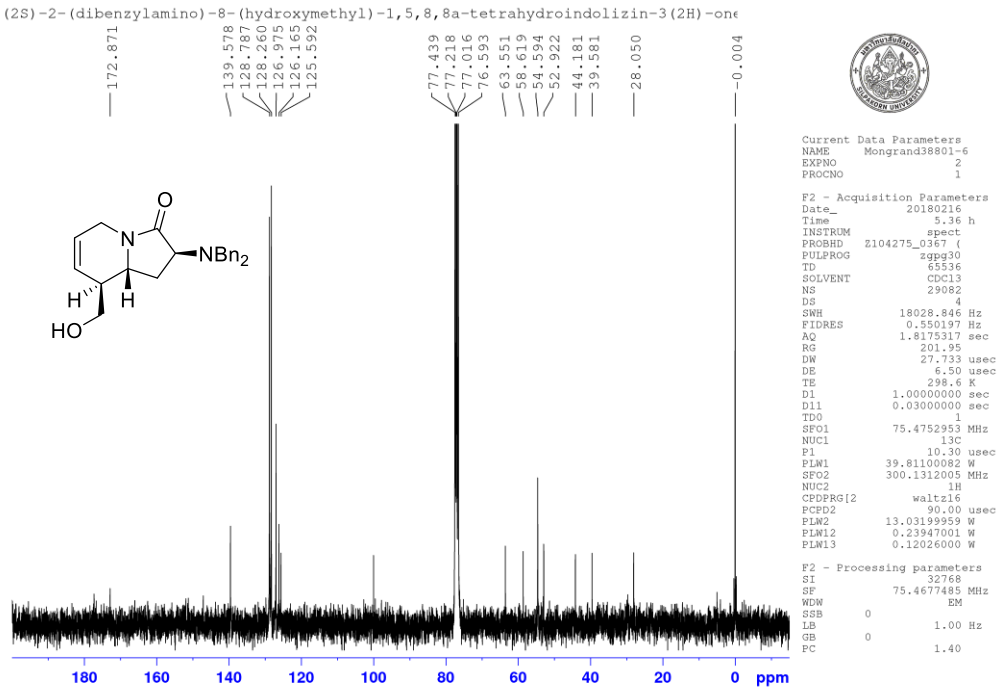

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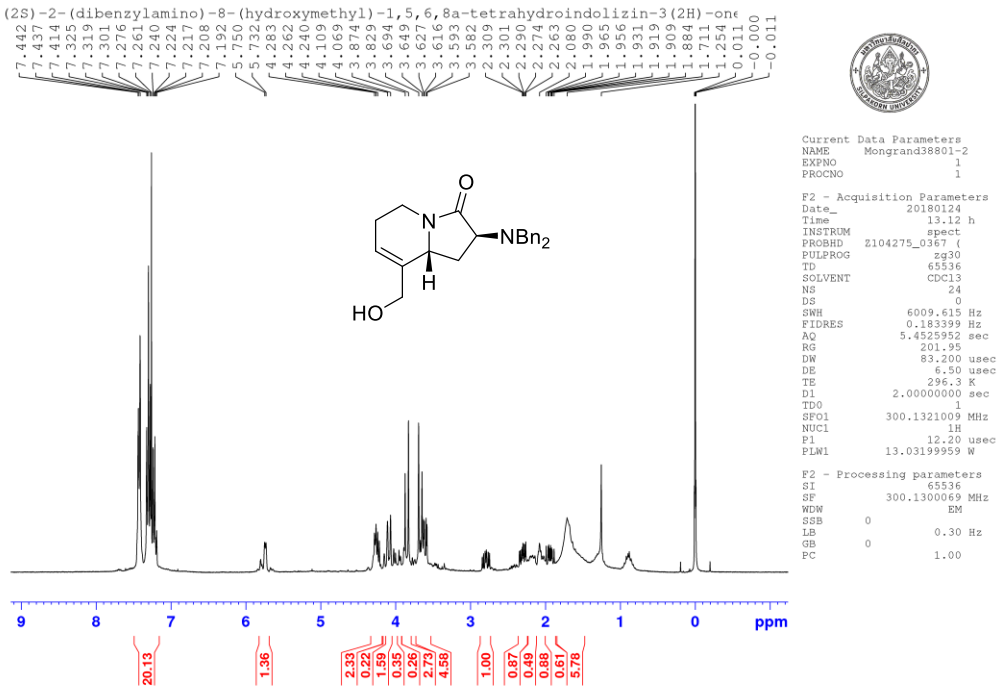
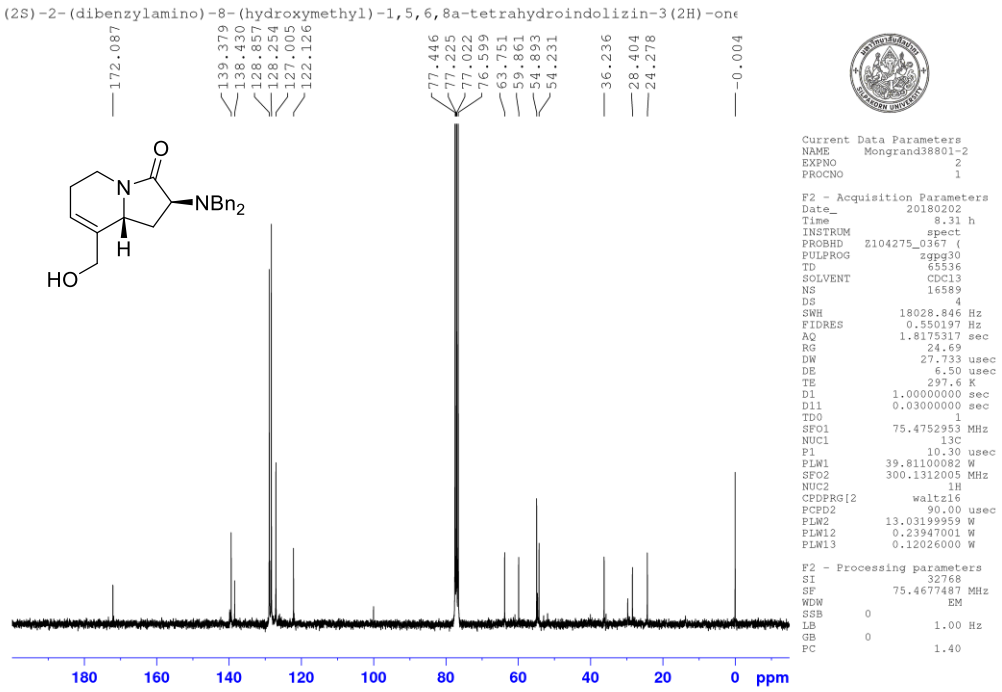


^{1}H NMR of compound **3.53**



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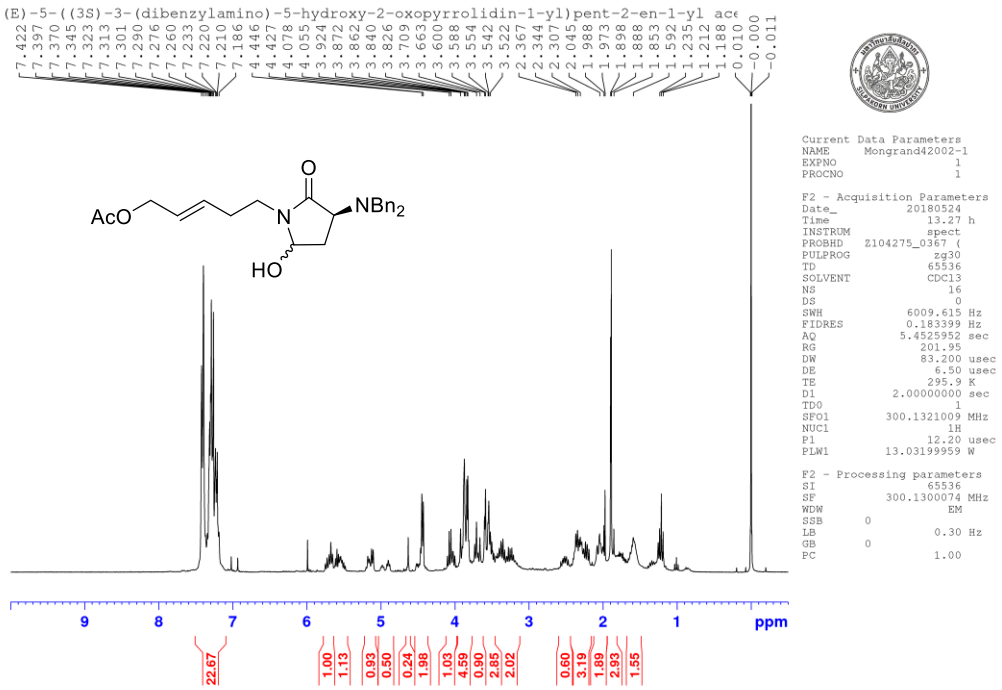
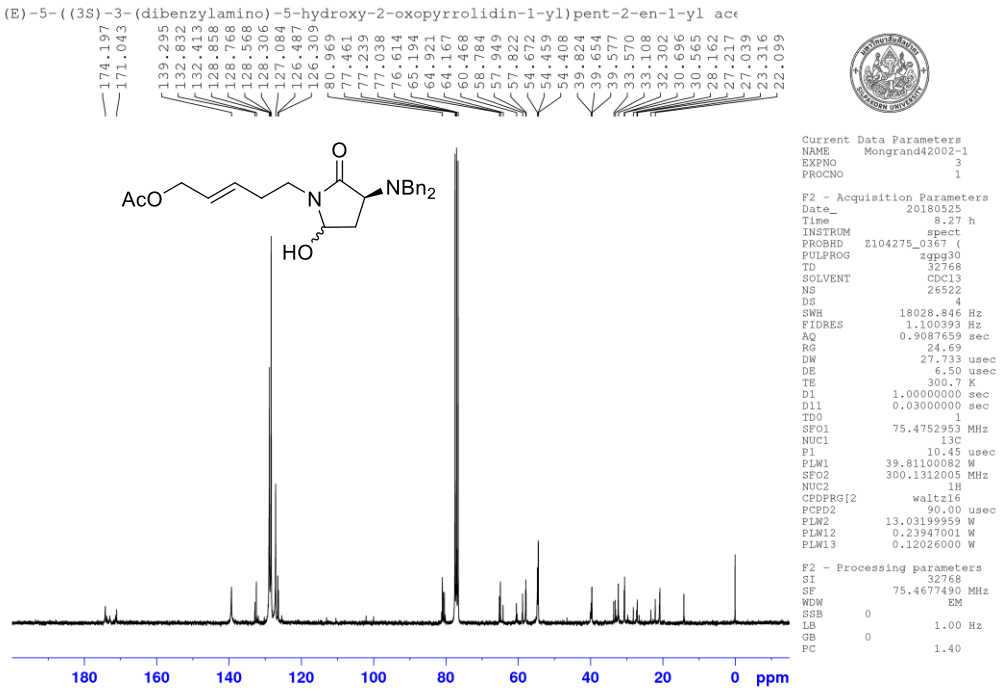
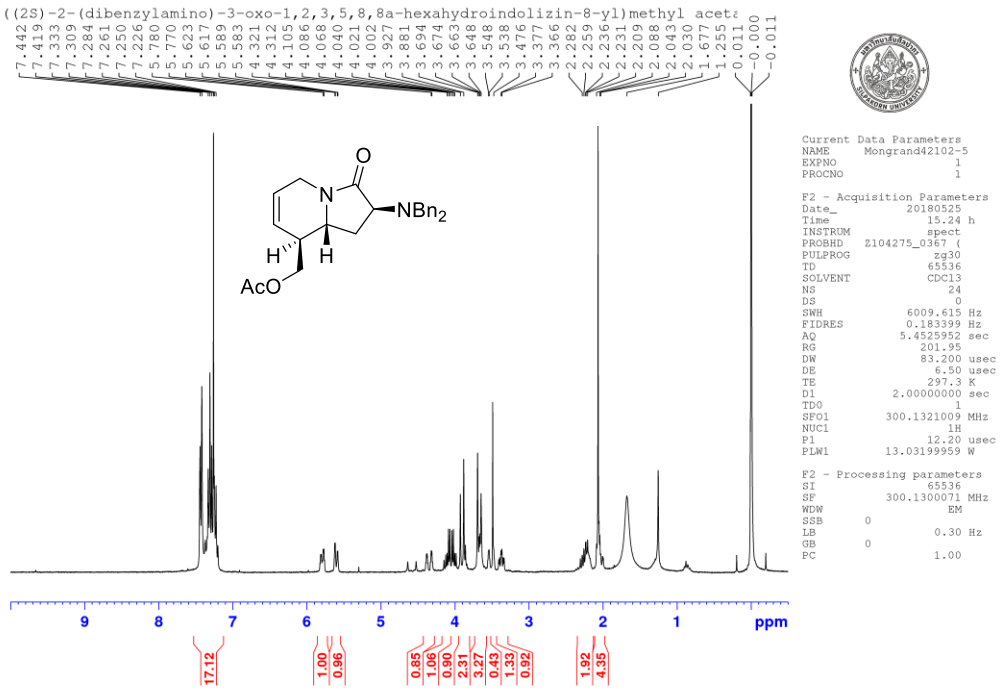


^{1}H NMR of compound **3.54**



^{13}C NMR of compound **3.54**



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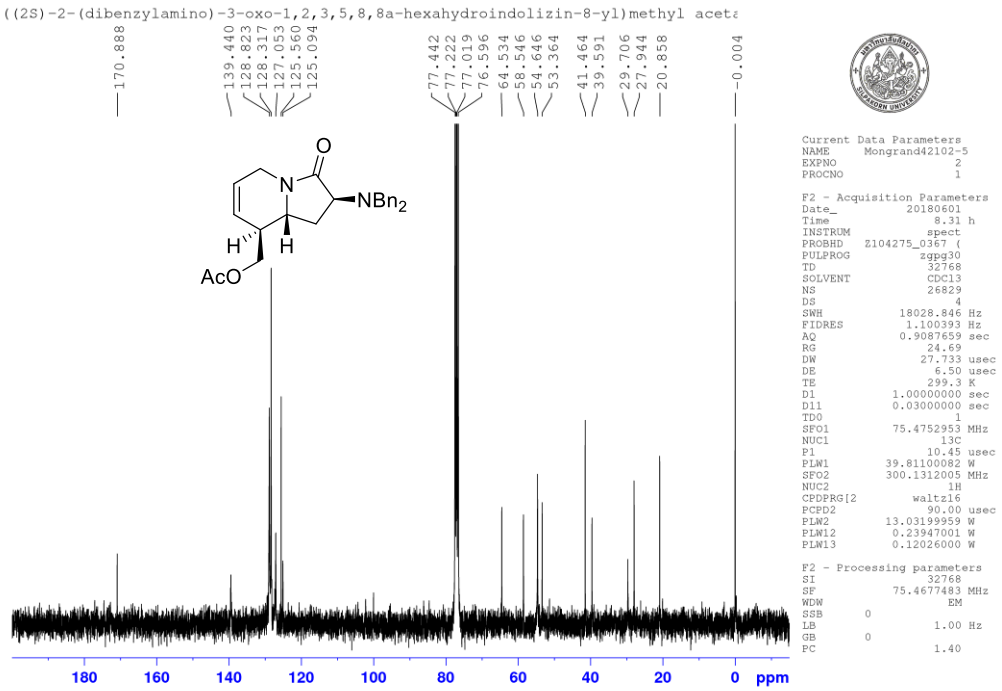

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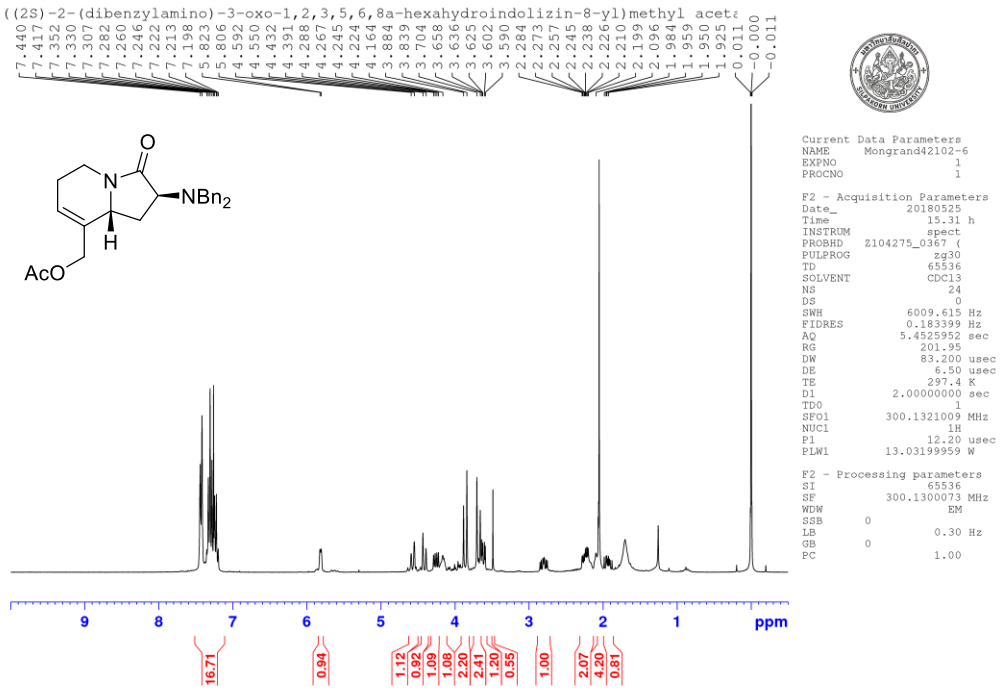
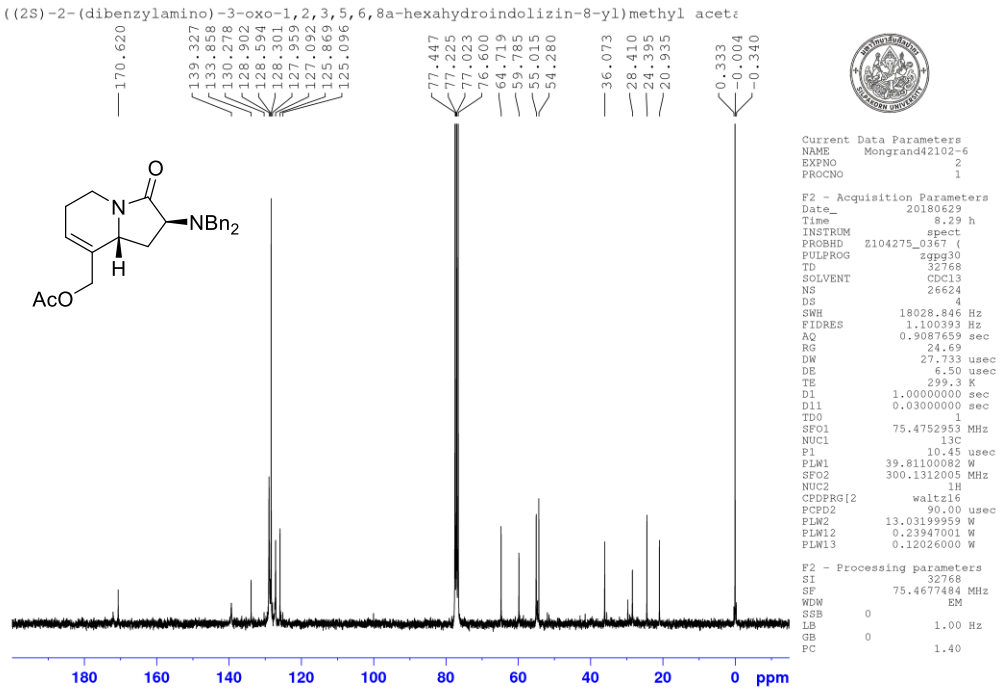
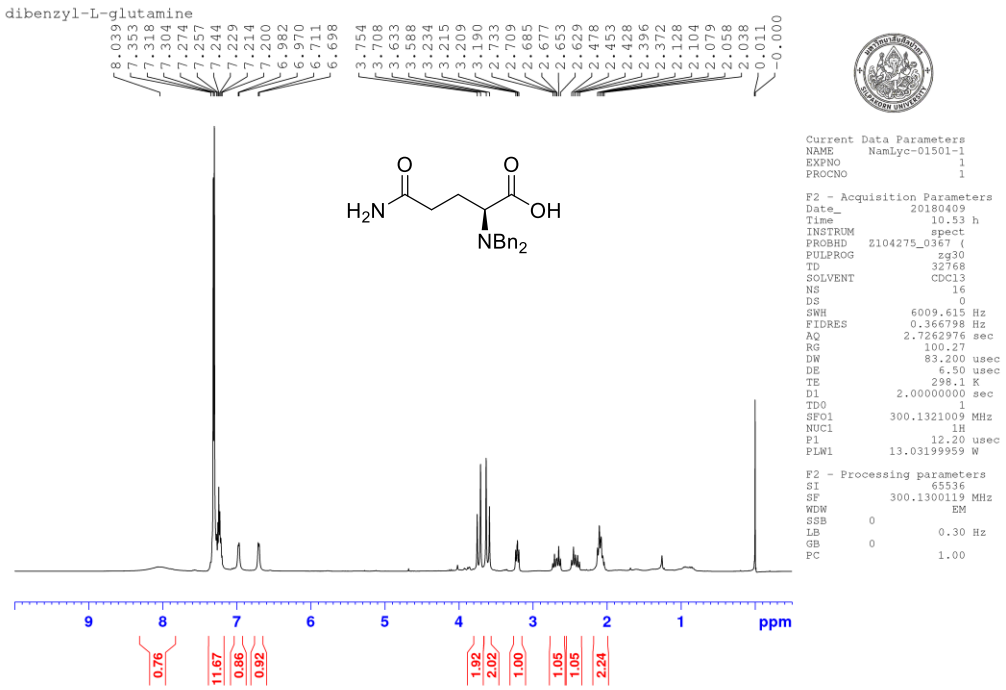


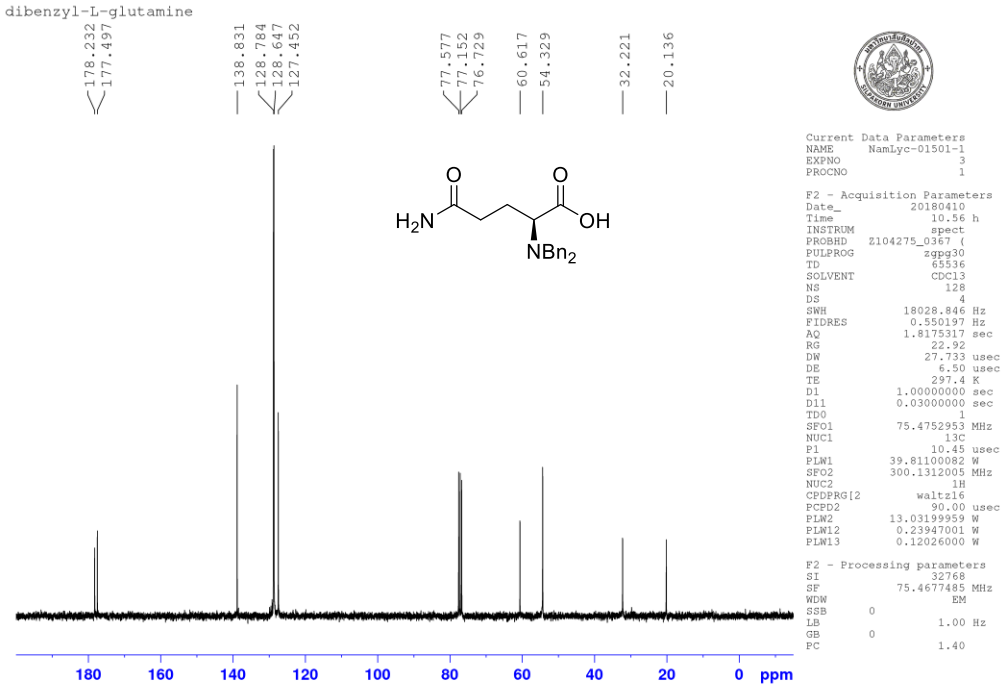
^{1}H NMR of compound **3.56**



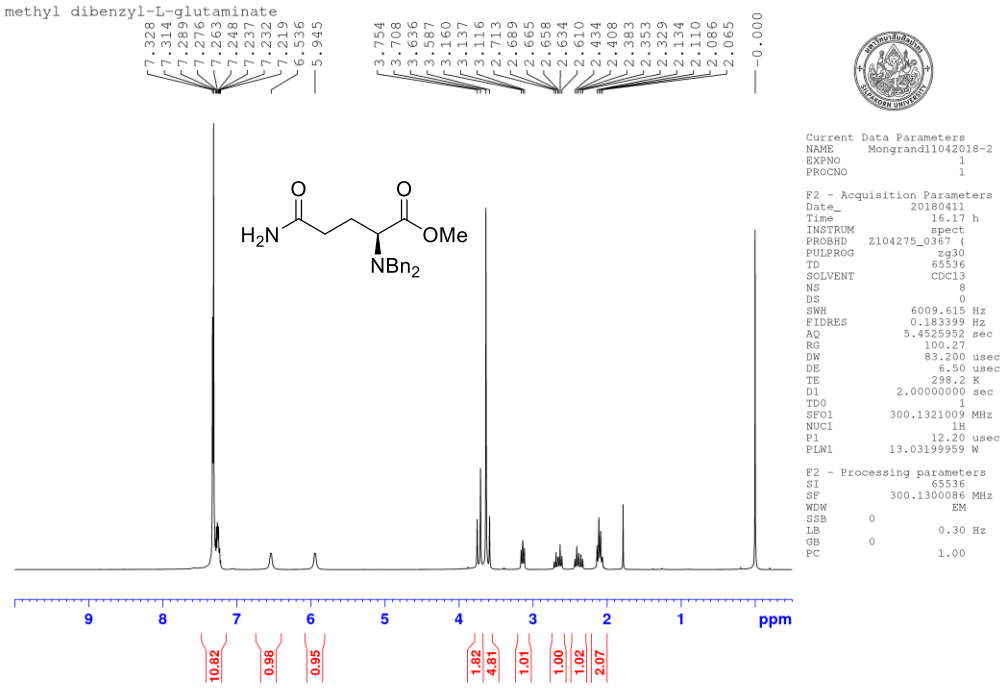
^{13}C NMR of compound **3.56**



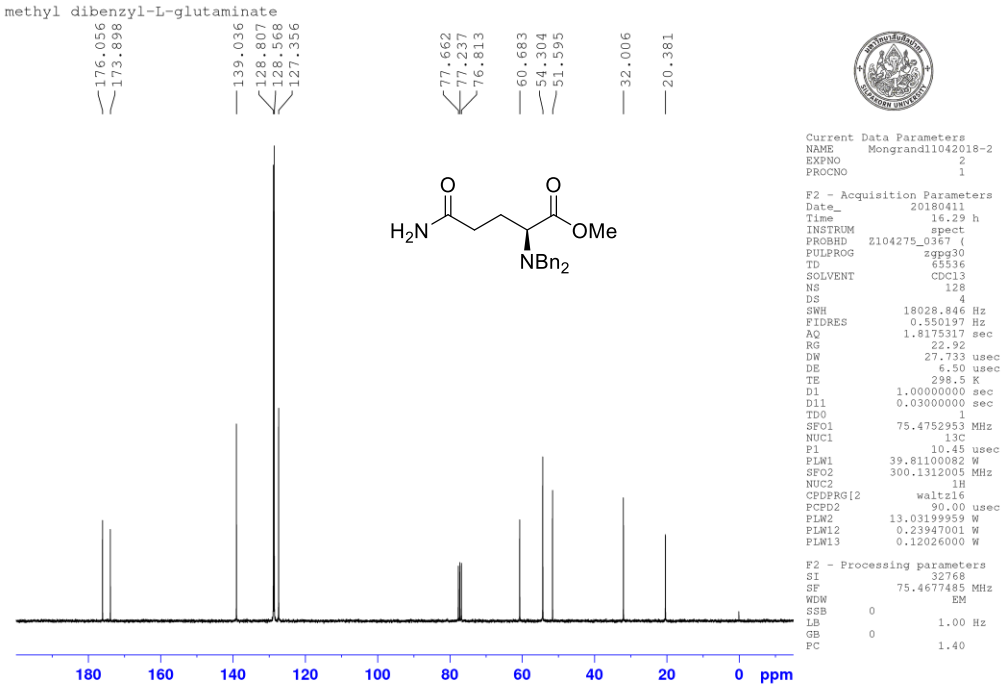
^{1}H NMR of compound **3.60**



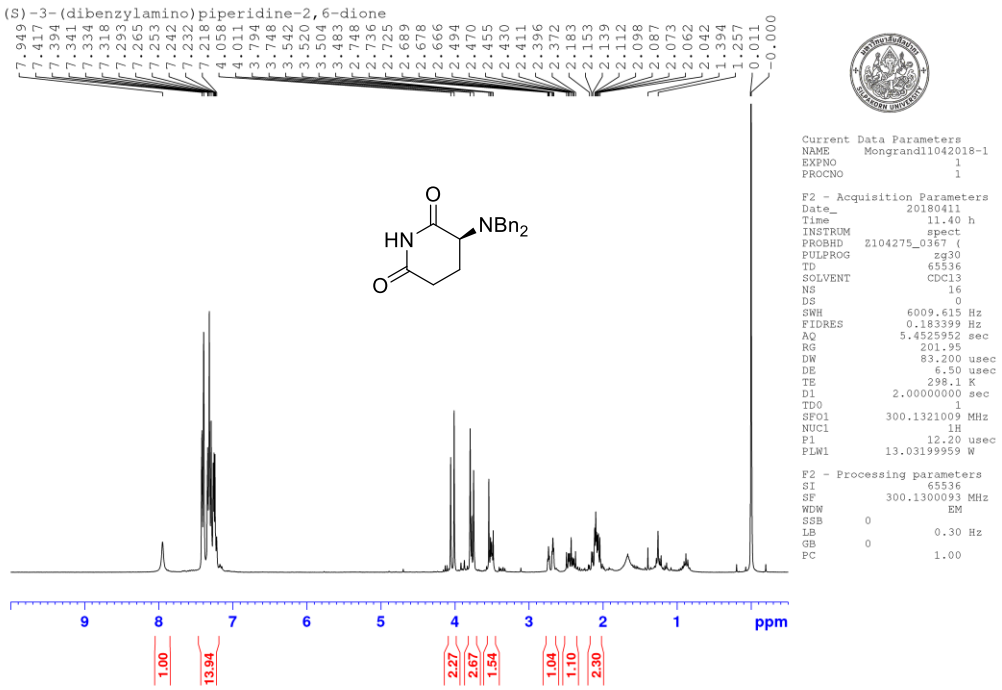
^{13}C NMR of compound **3.60**



^{1}H NMR of compound **3.61**



^{13}C NMR of compound **3.61**



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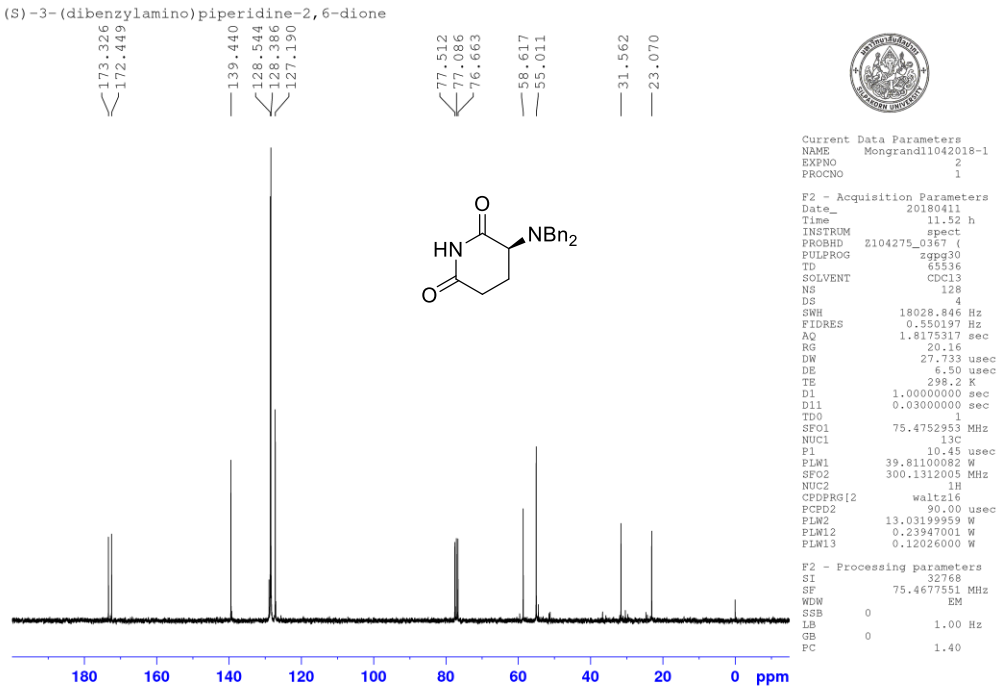
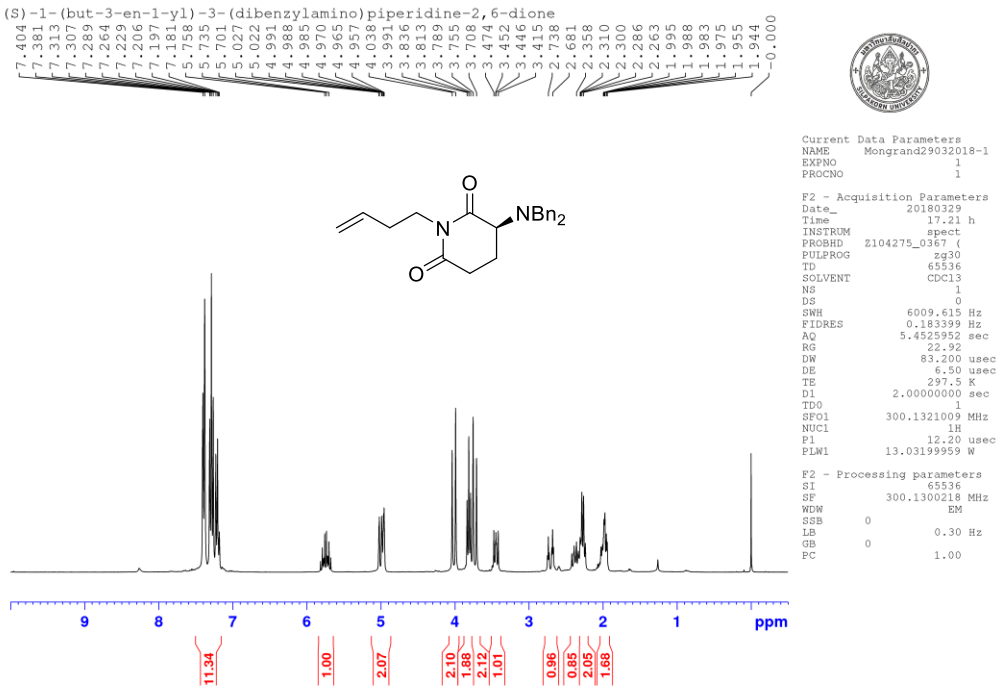
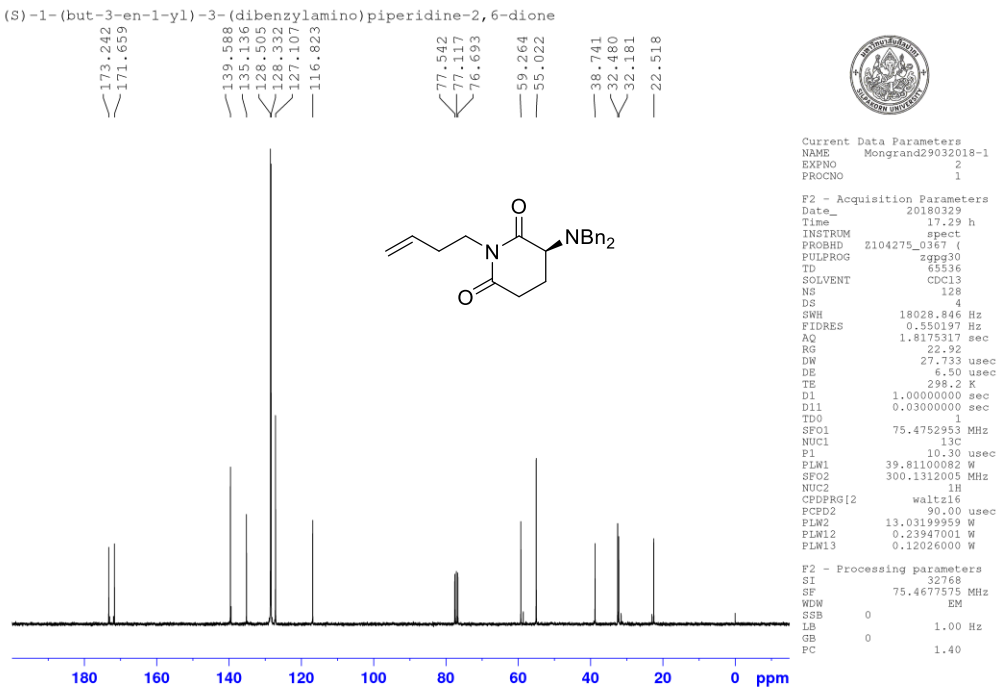


^{13}C NMR of compound **3.62**



^{1}H NMR of compound **3.63**



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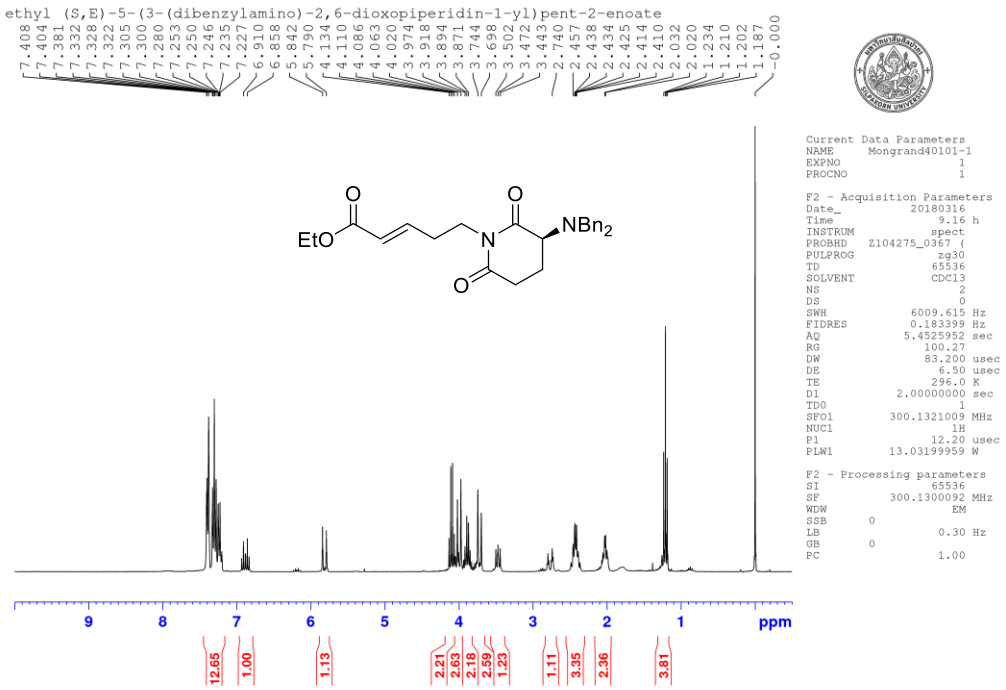
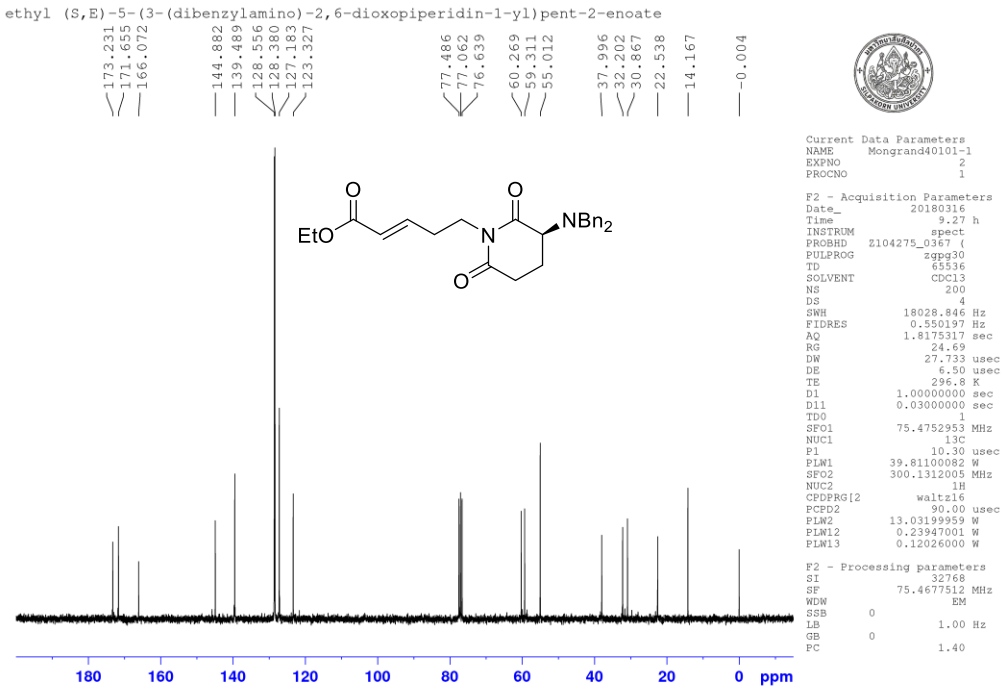


^{1}H NMR of compound **3.64**



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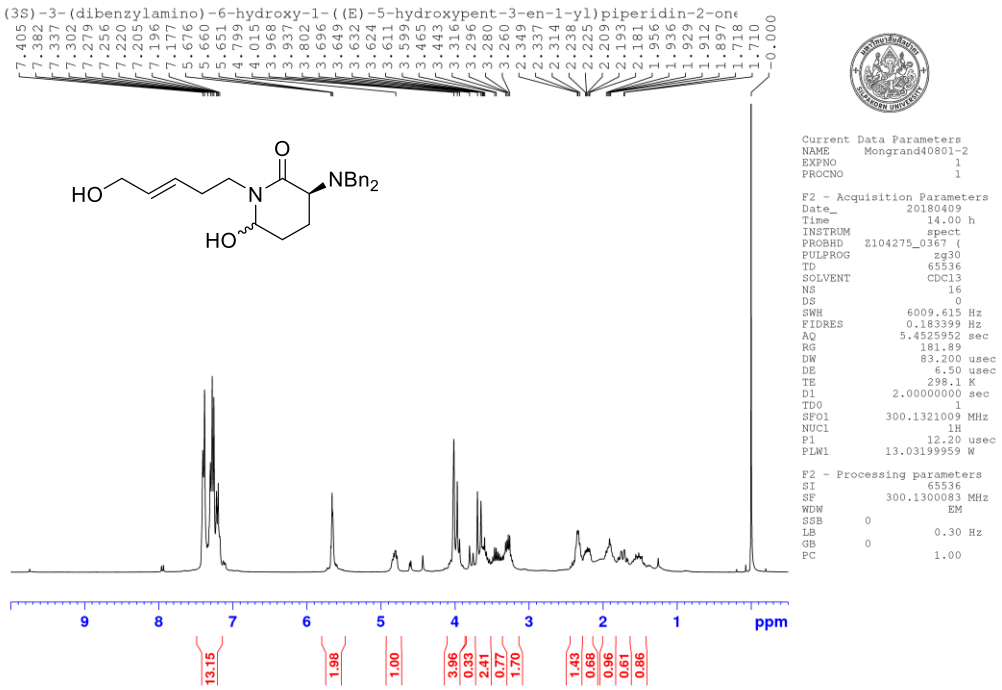
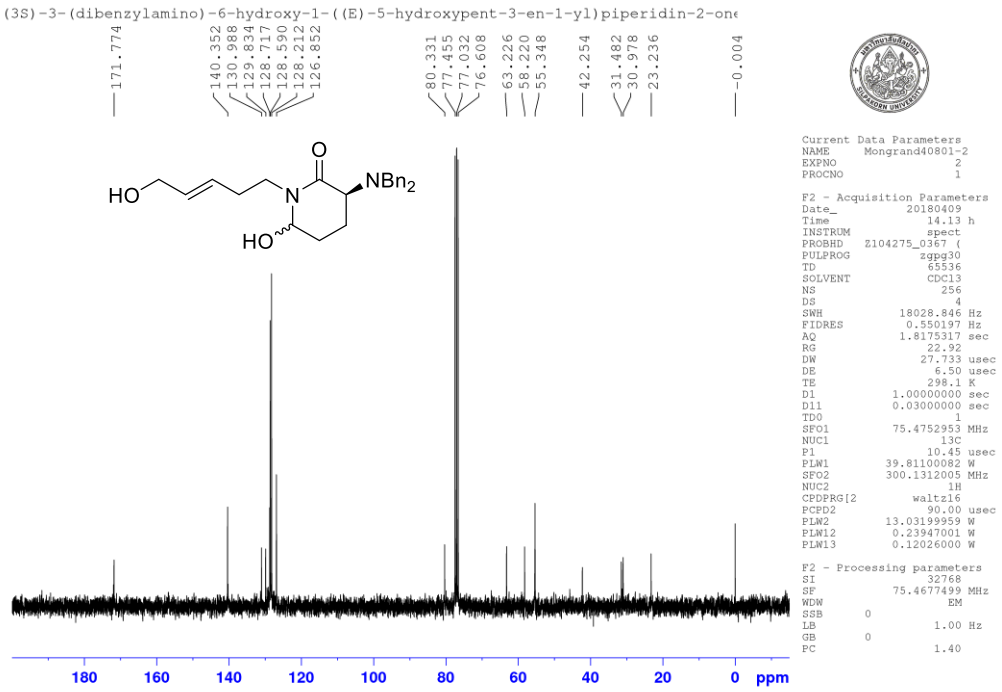
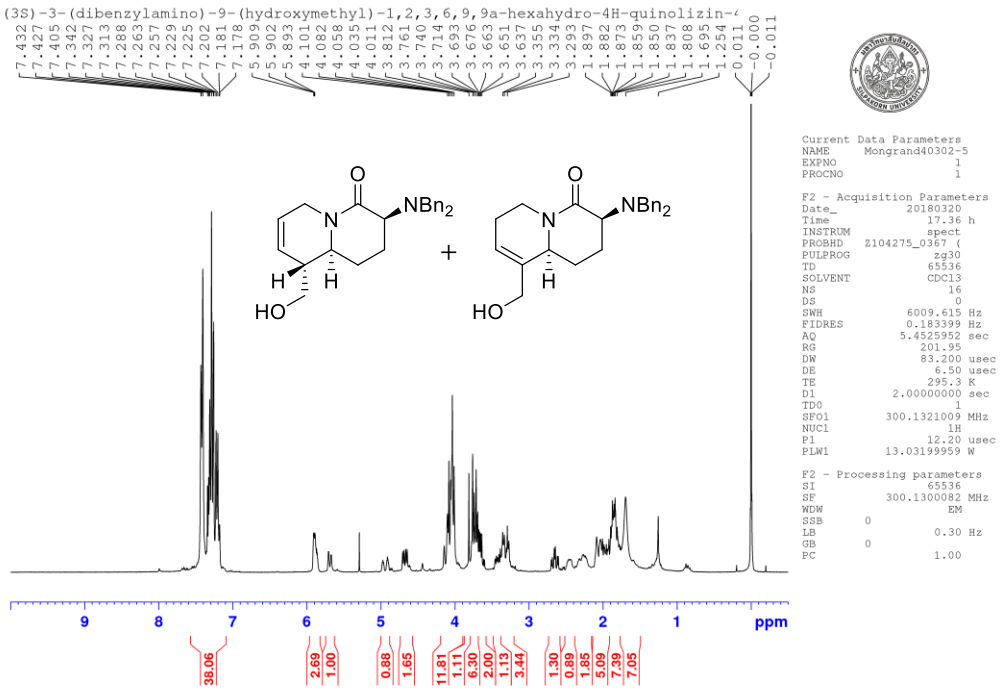


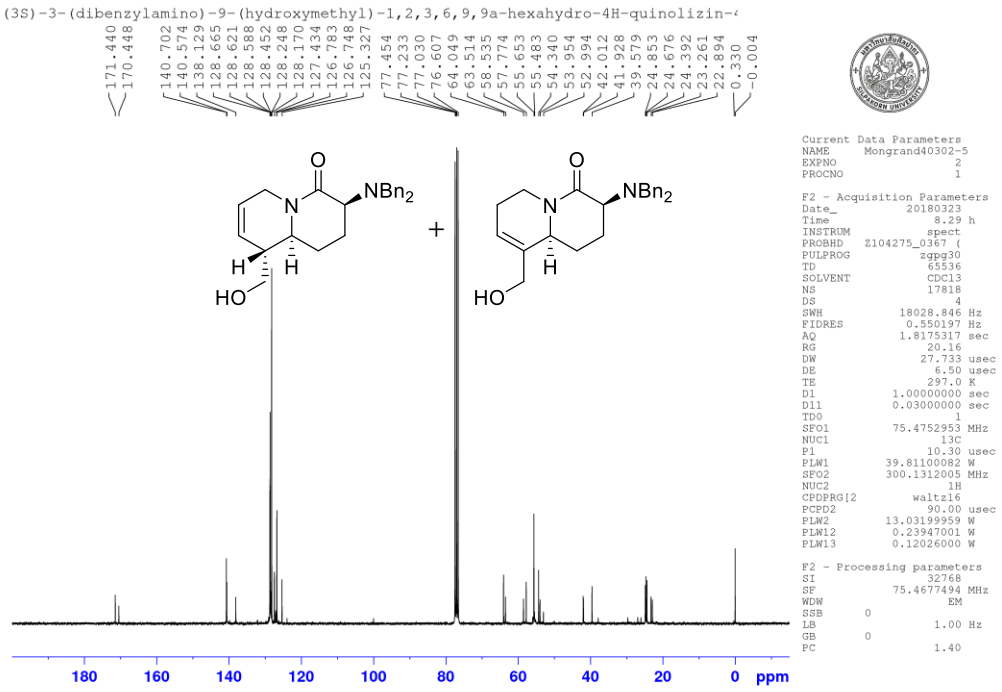
^{1}H NMR of compound **3.65**



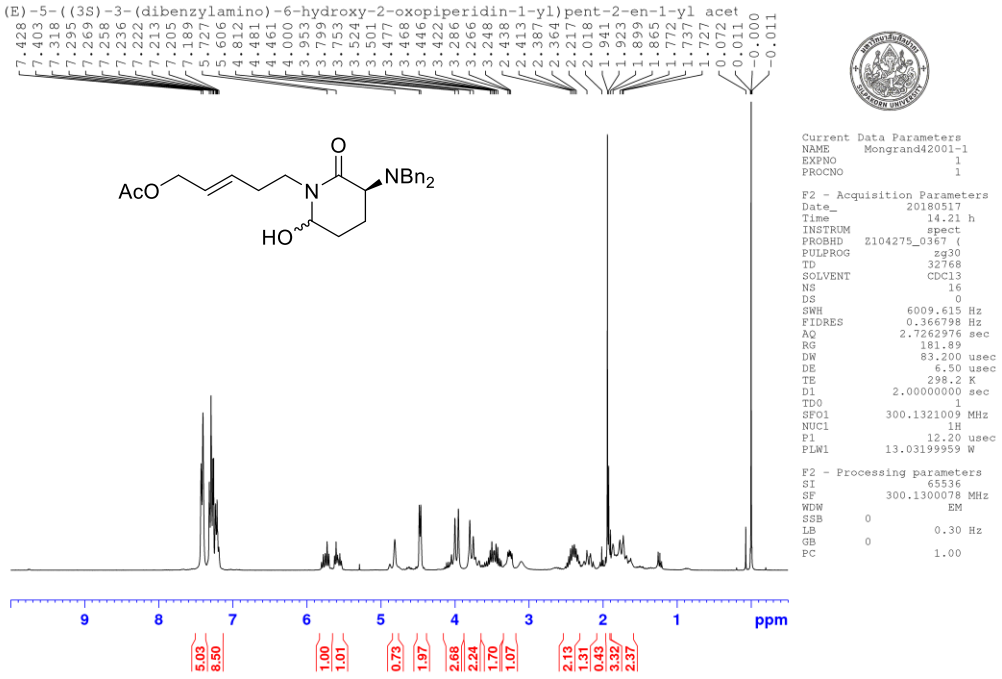
^{13}C NMR of compound **3.65**



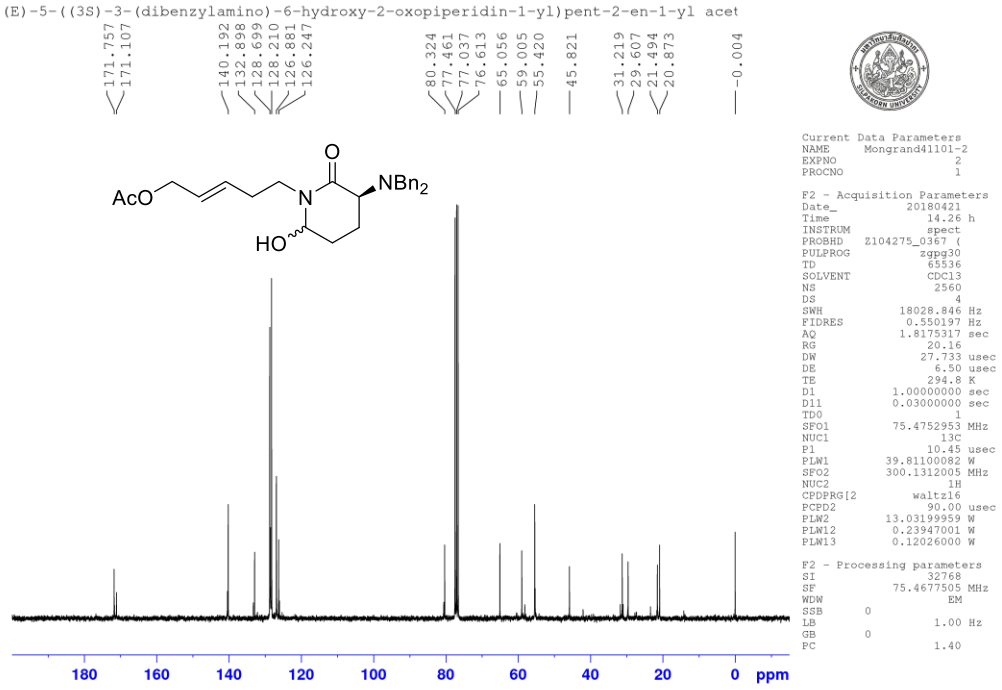
^{1}H NMR of compound **3.66** and **3.67**



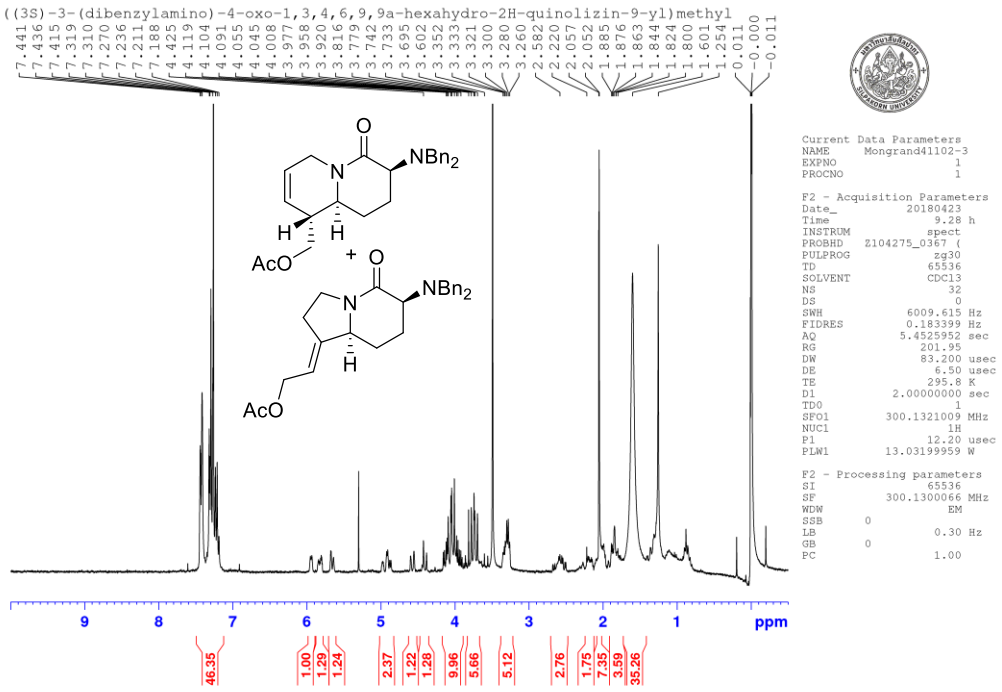
^{13}C NMR of compound **3.66** and **3.67**



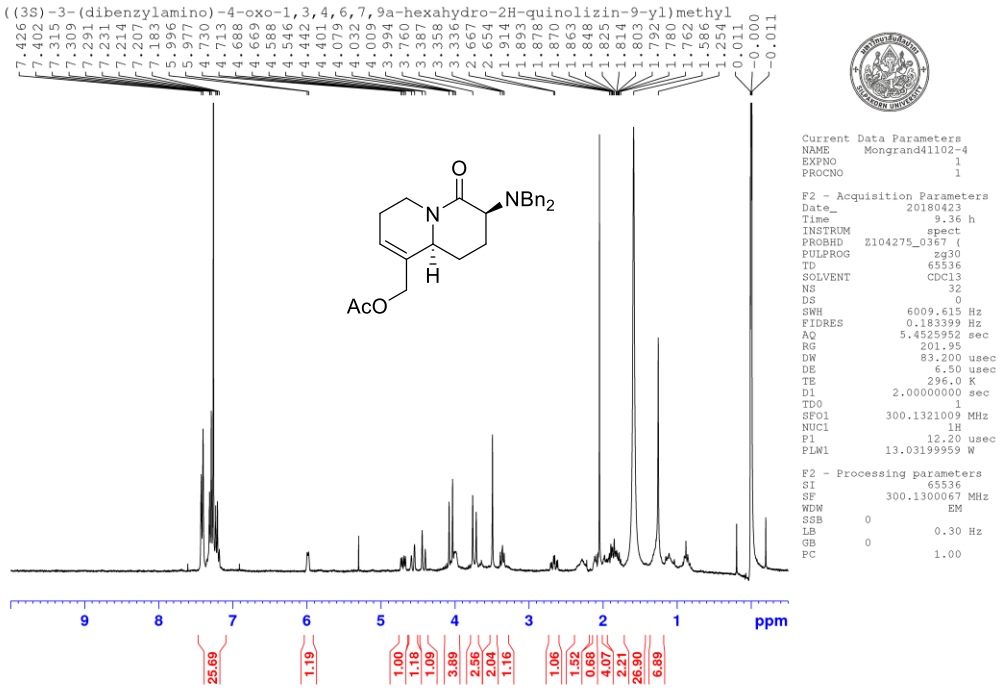
^{1}H NMR of compound **3.69**



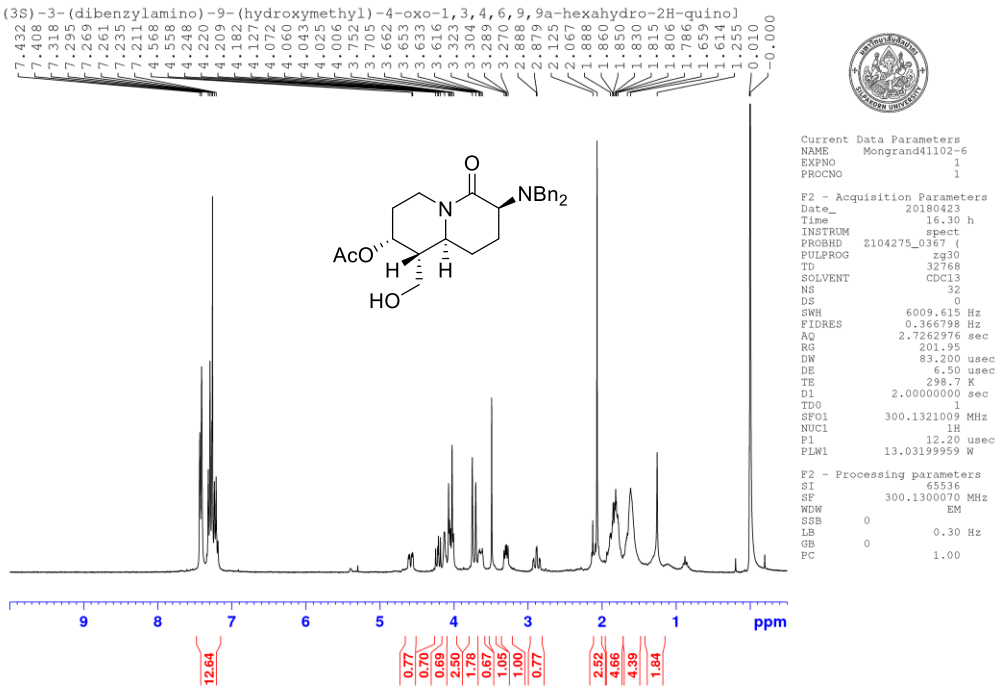
^{13}C NMR of compound **3.69**



^{1}H NMR of compound **3.70** and **3.71**



^{1}H NMR of compound **3.72**



^{1}H NMR of compound **3.73**

VITA

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PUBLICATION	1. Inprung, N.; Taosiriwong, S. and Kuntiyong, P. (2018). Synthesis of pyrrole – azepine core of stemoamide. Proceedings of Pure and Applied Chemistry International Conference 2018, Thailand, 7-9 February 2018. pp. OR76-OR81. 2. Kuntiyong, P.; Bunrod, P.; Namborisut, D.; Inprung, N.; Sathongjin, J.; Sae-guay, C.; Thongteerapab, S.; Khemthong, P. "Synthesis of a tetracyclic core of Erythrina alkaloids and analogs of crispine A", Tetrahedron 2017, 73 (30), 4426–4432.
AWARD RECEIVED	Best oral presentation in organic and medicinal chemistry session in Pure and Applied Chemistry International Conference 2018 (PACCON 2018), Hat -Yai, Songkhla, Thailand