# SYNTHESIS OF NON-AROMATICS INDOLIZIDINE ALKALOIDS

By
MISS Sineenart ATTANONCHAI

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

# การสังเคราะห์นอนอะโรมาติก อินโดลิซิดีน อัลคาลอยด์


โดย

นางสาวสินีนาฏ อรรถนนท์ชัย

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| By | MISS Sineenart ATTANONCHAI |
| Field of Study | (CHEMISTRY) |
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MISS SINEENART ATTANONCHAI : SYNTHESIS OF NON-AROMATICS INDOLIZIDINE ALKALOIDS THESIS ADVISOR : ASSISTANT PROFESSOR PUNLOP KUNTIYONG, Ph.D.

Indolizidine alkaloids are chemical constituents which can isolated from a variety of terrestrial and marine plants and animals.Indolizidine alkaloids possess 1-azabicyclo [4.3.0] nonane system as the core structure.This alkaloids have been used for a wide range of pharmacology with a various biological activities. It was isolated from plant in families *Asclepiadaceae, Convolvulaceae* (morning glory), *Orchidaceae* (orchid), *Fabaceae* (or Leguminosae) and *Pandanaceae*. In this research, we will discuss synthetic studies of two members of non-aromatic indolizidine containing alkaloids which are tashiromine, a 5-hydroxymethylindolizidine alkaloid and indolizidine 167B via N-acyliminium ion cyclization as a key step.

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MISS Sineenart ATTANONCHAI

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# CHAPTER 1

# INTRODUCTION

## Background and Signification of the Research Problem

Indolizidine alkaloids are chemical constituents which can be isolated from a variety of terrestrial and marine plants and animals. Indolizidine alkaloids possess 1-azabicyclo [4.3.0] nonane system as the core structure. This alkaloid has been used for a wide range of pharmacology with a various biological activity. They have been isolated from plants in families *Asclepiadaceae*, *Convolvulaceae* (morning glory), *Orchidaceae* (orchid), *Fabaceae* (or Leguminosae) and *Pandanaceae*. The structures of indolizidine alkaloids encompass wide variety of architechture[1]. Exemplified molecules are shown in figure 1.

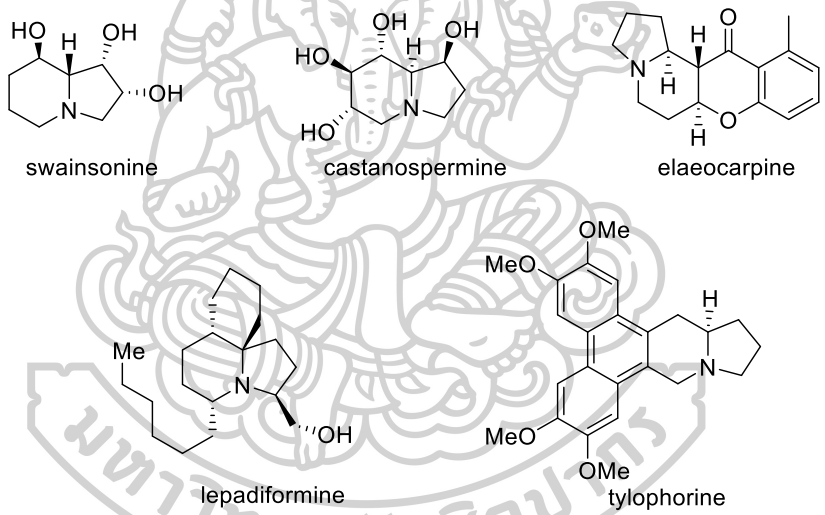
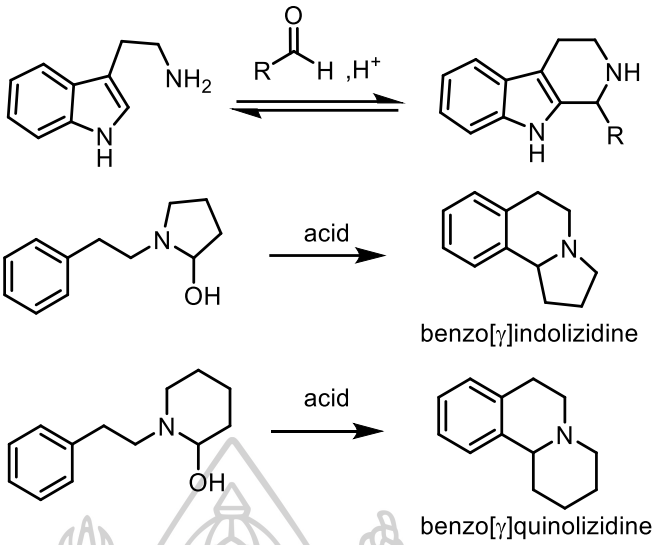


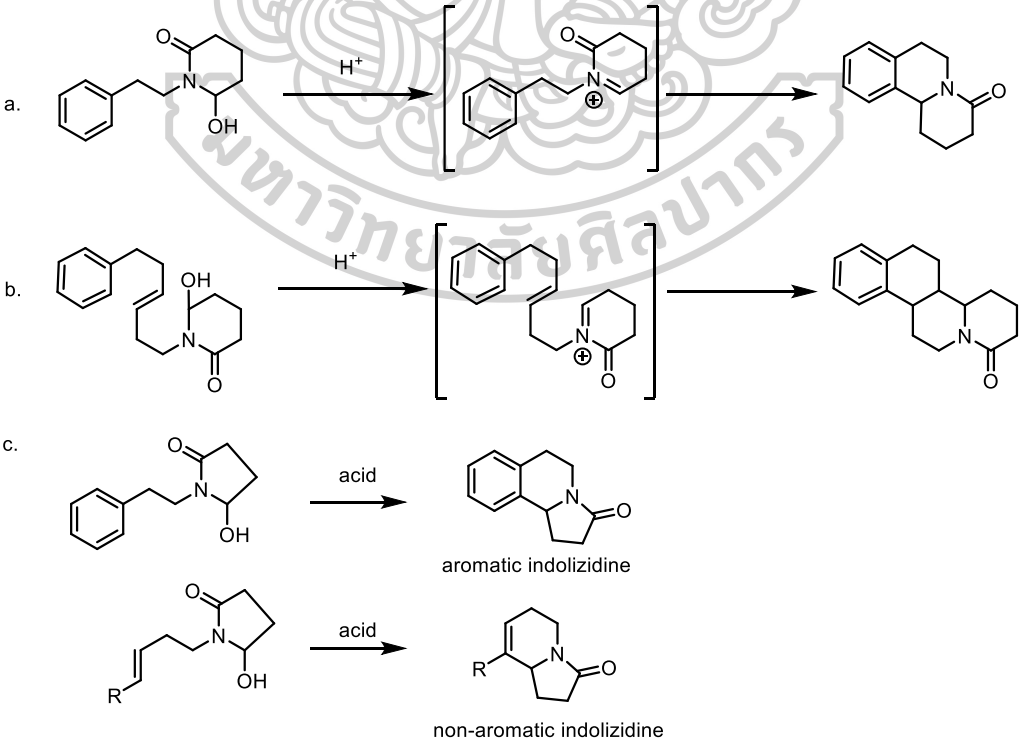

**Figure 1** Examples molecules of indolizidine alkaloids

In the synthesis of alkaloid compounds, cyclization step is a widely used process exemplified by some very well-known reactions such as Mannich or Pictet-Spengler reactions. The Pigtet-Spengler reaction is a chemical reaction in which a β-arylethylamine undergoes condensation with an aldehyde or ketone followed by ring closure via an iminium ion intermediate. This reaction is most frequently acid catalyzed. When the arylethyl-iminium ion precursor is part of a ring such as γ-hydroxylactam or δ-hydroxylactam the reaction can give tricyclic benzoindolizidine or benzoquinolizidine alkaloid products respectively.




**Scheme 1** Pictet-Spengler reaction

The other form of Pictet-Spengler reaction is *N*-acyliminium ion cyclization[2]. *N*-acyliminium ion is more reactive than *N*-iminium ion so that it can react with less reactive nucleophile such as alkene. Tandem *N*-acyliminium ion cyclization involving multiple π-system can lead to polycyclic alkaloids. It is a useful strategy to affect intramolecular cyclization with aromatic ring and alkene as nucleophiles to form aromatic and non-aromatic alkaloids, respectively.




**Scheme 2** *N*-acyliminium ion cyclization

We are interested in application of diastereoselective N-acyliminium ion cyclization to synthesis of various quinolizidine and indolizidine alkaloids. Some examples are shown in Figure 2. Aromatic quinolizidine alkaloids are represented by schulzeines. and protoemetinol. Aromatic indolizidine alkaloids such as tabertinggine, lycorine, intrigacine-oxa-aglycone are shown. Non-aromatic quinolizidine alkaloids include epiquinamide, and lupinine. Non-aromatic indolizidine alkaloids are slaframine, tashiromine, grandisine and FR901483. Related pyrroloazepine, stemoamide can also be synthesized using the same strategy. Tandem *N*-acyliminium ion cyclization can potentially create the tetrahydrofuran or tetrahydropyran fused system observed in grandisine, intrigarcine, stemoamide.

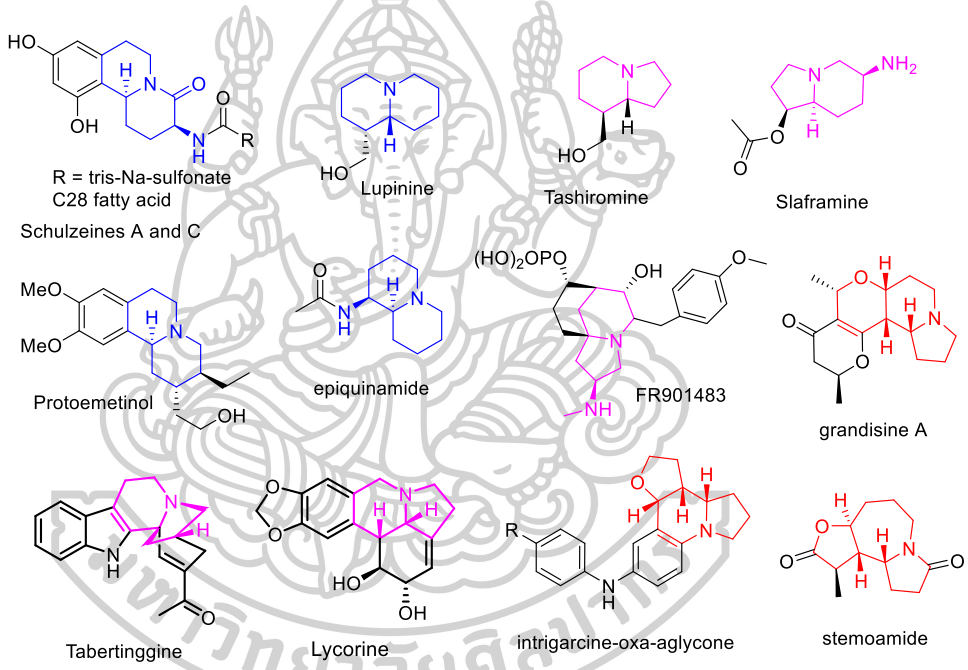



**Figure 2** Examples of quinolizidine and indolizidine alkaloids of interest

In this thesis, we will discuss asymmetric synthetic studies of two members of non-aromatic indolizidine containing alkaloids which are tashiromine, a 5-hydroxymethylindolizidine alkaloid and indolizidine 167B via *N*-acyliminium ion cyclization as the key step. The key chiral *N*-alkenylsuccinimide bearing dibenzylamino group could be synthesized from cheap and readily available chiral pool starting material, L-asparagine. Tandem *N*-acyliminium ion cyclization to form tetrahydrofuran-fused indolizidine system was also investigated.

# CHAPTER 2

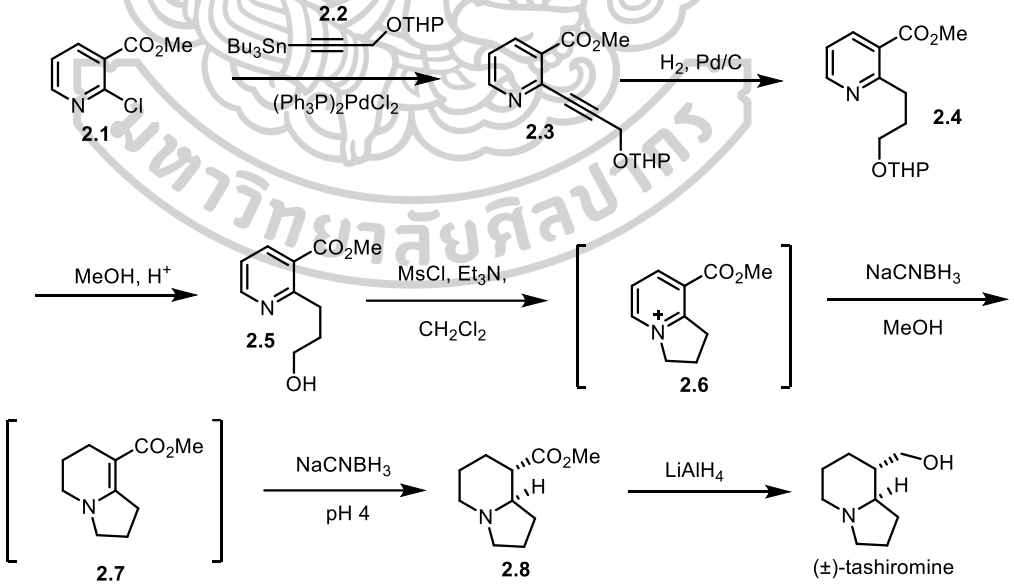
# LITERATURE REVIEW

## Tashiromine

Tashiromine is a naturally occurring alkaloid as one of the structurally simpler indolizidine alkaloids which was first isolated from an Asian deciduous shrub *Maackia tashiroi*[3]. It has attracted considerable interest from both synthetic and medicinal chemists. The structure consists of indolizidine core substituted by hydroxymethyl group and contains two stereocenters.


**Figure 3** Structure of Tashiromine and *Maackia tashiroi* [4]

## Previous syntheses of Tashiromine

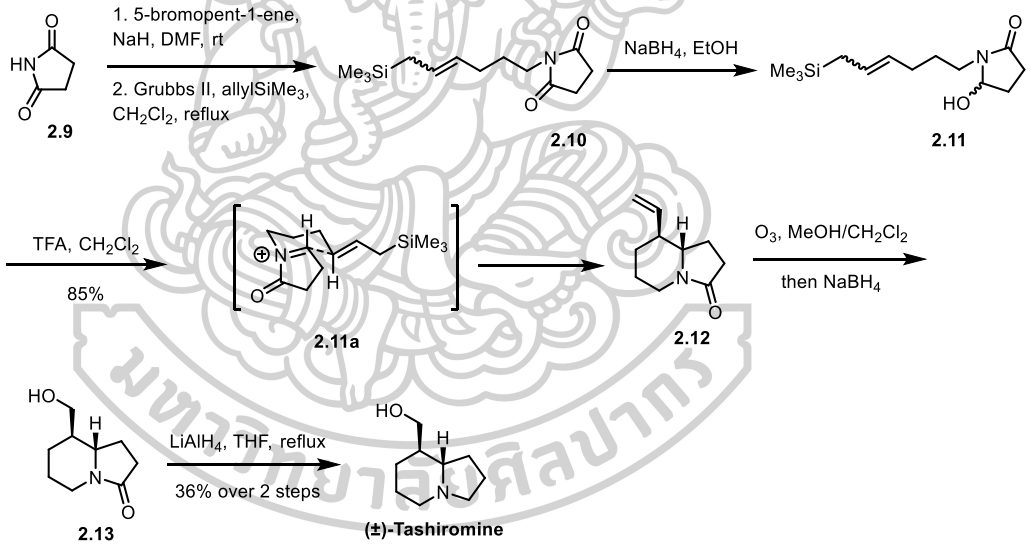



**Scheme 3** Synthesis of (±)-tashiromine by Bates and co-workers

Bates and co-workers reported a synthesis of (±)-tashiromine in 2001[5]. They started with methyl 2-chloronicotinate **2.1** which was coupled with tri-*n*-butyltin

derivative of the THP ether of propargyl (prop-2-ynyl) alcohol **2.2** under typical Stille conditions to give alkyne **2.3**. Reduction of the alkyne **2.3** to the corresponding protected propanol **2.4** and deprotection of the alcohol group with methanol to give alcohol **2.5**. Treatment of the alcohol **2.5** with mesyl chloride and a base to promote the pyridinium salt **2.6**. and reduction with sodium cyanoborohydride, first under near-neutral conditions and then with addition of methanolic HCl (Bromocresol Green indicator) in titration style to maintain a pH of about 4 to give carbamate compound **2.7**. Then, the product of the acidic reduction is the saturated indolizidine ester **2.8** as a single diastereomer in 66% yield from alcohol **2.5**. Finally, Reduction of ester group with litium aluminium hydride provided (±)-tashiromine (scheme 3).

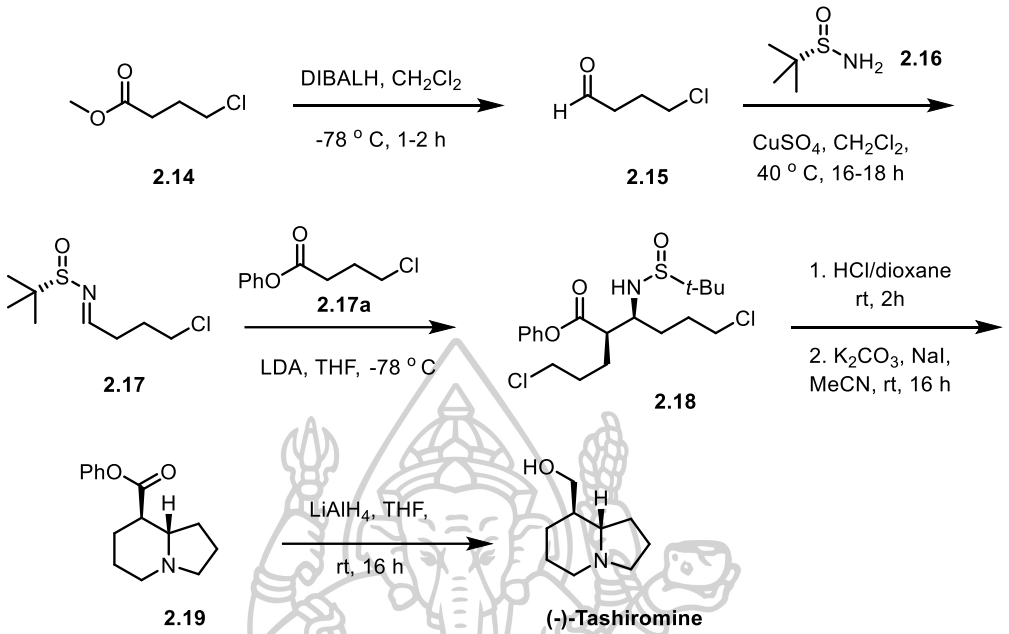
In 2008, Marsden and McElhinney reported a racemic synthesis of tashiromine[6].This synthesis used the allyltrimethylsilane cross-metathesis approach for construction of the key cyclization precursor compound **2.11** in 3 steps from commercial starting materials. The cyclization step was acid-induced cyclization to give the desired bicyclic indolizidine skeleton (scheme 4).




**Scheme 4** Racemic synthesis of (±)-Tashiromine by Marsden and McElhinney

The synthesis started from *N*-alkylation of succinimide **2.9** with 5-bromo-1-pentene in near quantitative yield to give metathesis precursor followed by cross metathesis carried out using allyltrimethylsilane and 5 mol% of Grubbs' second-generation catalyst in refluxing dichloromethane. The resulting imide **2.10** was transformed to hydroxylactam compound **2.11**, a precursor of *N*-acyliminium ion cyclization with sodium borohydride reduction. Treatment of the hydroxylactam with TFA gave bicyclic compound **2.12**. Nucleophilic addition of the allylsilane to the *N*-acyliminium ion proceeded via a chair-like transition state. After that, oxidative cleavage and subsequent reduction afforded alcohol **2.13** which was converted to tashiromine by $LiAlH_4$ reduction. Simple functional group interconversions allowed

the completion of the total synthesis of racemic tashiromine in six steps (19% overall yield).

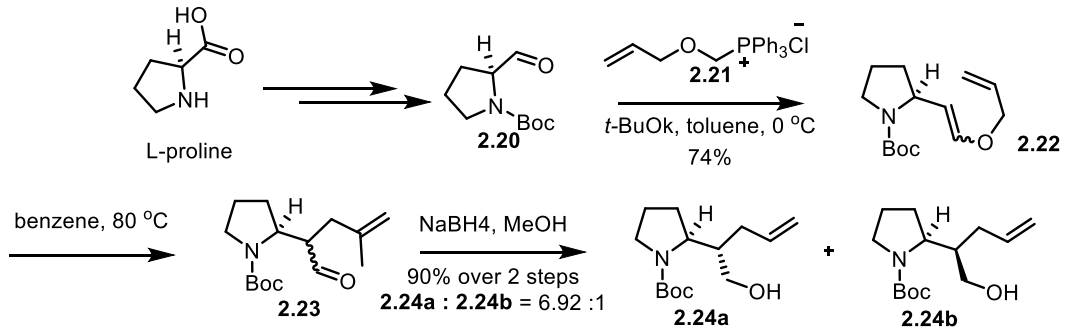



**Scheme 5** Synthesis of (-)-Tashiromine by Cutter and co-workers

In 2011 Cutter and co-workers reported a synthesis of (-)-Tashiromine[7]. The key step of this research is imino-aldol reactions of *tert*-butanesulfinyl imine to set up the configurations of two stereocenters. The reaction of chloroalkyl chains with enolate and imine and *N*-deprotection of the imino-aldol product would result in direct double cyclization to construct the required indolizidine system (scheme 5).

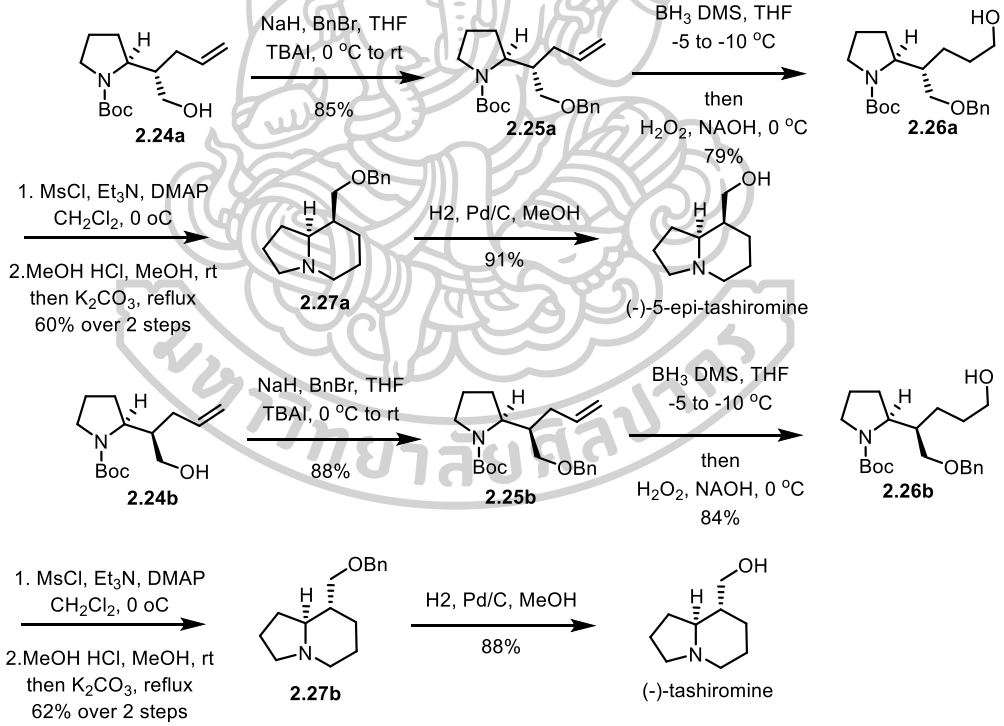
Chloroalkyl ester **2.14** was converted to (*S*)-*tert*-butanesulfinyl imine **2.17** in two steps using chiral sulfonamide **2.16** as a chiral auxiliary**.** The asymmetric imino-aldol reaction between (*S*)-*tert*-butanesulfinyl imine **2.17** and phenyl ester compound **2.17a** afforded to dichlorosulfonamide **2.18** with high yield. Deprotection of the *N*-sulfinyl protecting group using HCl in dioxane afforded the primary amine, followed by the key double cyclization under basic conditions to give the bicyclic compound **2.19**. Ester reduction using $LiAlH_4$ gave (-)-Tashiromine in 6 steps.

In 2015, Gavhane and co-workers reported asymmetric synthesis of (-)-5-epi-tashiromine and (-)-tashiromine[8]. which features a highly enantioselective approach (scheme 6).




**Scheme 6** Synthesis of (-)-5-epi-tashiromine and (-)-tashiromine by Gavhane and co-workers

They started from Wittig reaction of aldehyde **2.20** with allyloxymethylene-triphenylphosphonium chloride **2.21** to give allyl vinyl ether **2.22** in 74% yield as a mixture of *E*- and *Z*-isomers. The mixture was then subjected to a Claisen rearrangement in refluxing benzene to give diastereomeric mixture of 4-pentenal **2.23**. Then, treatment of aldehyde **2.23** with $NaBH_4$ furnished alcohol **2.24a** and **2.24b**.

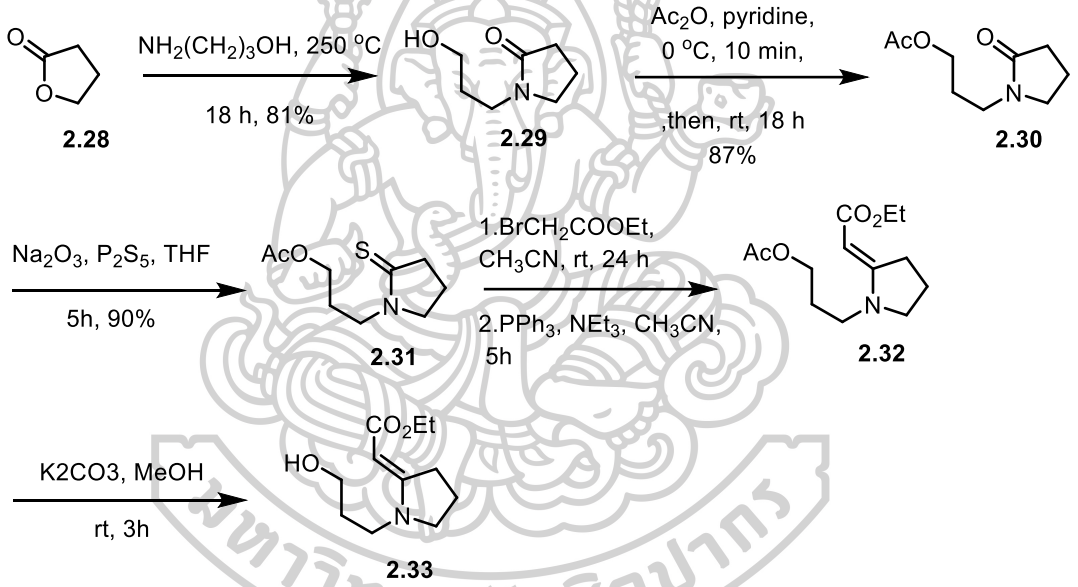



**Scheme 7** Synthesis of (-)-5-epi-tashiromine and (-)-tashiromine by Gavhane and co-workers

After obtaining alcohol **2.24a** and **2.24b**, they were converted to (-)-5-epi-tashiromine and (-)-tashiromine, respectively in separated routes using the same approach. They started from protection of hydroxy group of alcohols **2.24a** and **2.24b**

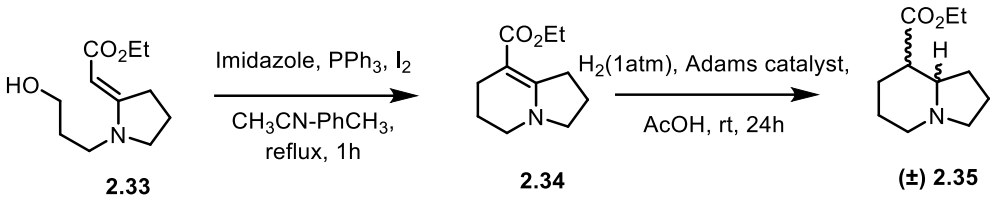
with benzyl bromide to give benzyl ethers **2.25a** and **2.25b.** This was followed by hydroboration/oxidation to give alcohols **2.26a** and **2.26b.** Mesylation, Boc-deprotection and cyclization then afforded bicyclic compounds **2.27a** and **2.27b.** Hydrogenation of bicyclic compounds **2.27a** and **2.27b** finally gave (-)-5-epi-tashiromine and (-)-tashiromine, respectively (scheme 7).

In 2016, Riley and co-workers reported a synthesis of (±)-tashiromine and (±)-epitashiromine[9] via enaminone intermediates. 3-amino-1-propanol was condensed with γ-butyrolactone **2.28** in a sealed Carius tube at 250 °C, affording alcohol **2.29** in 81% yield. The hydroxy group was protected with acetate group to give acetate **2.30**. This was followed by thionation with phosphorus pentasulfide to afford thiolactam **2.31**. Eschenmoser reaction of thiolactam **2.31** with α-halocarbonyl afforded enaminones **2.32**. Deacetylation with potassium carbonate in methanol afforded the corresponding alcohol **2.33** in good yield (scheme 8).



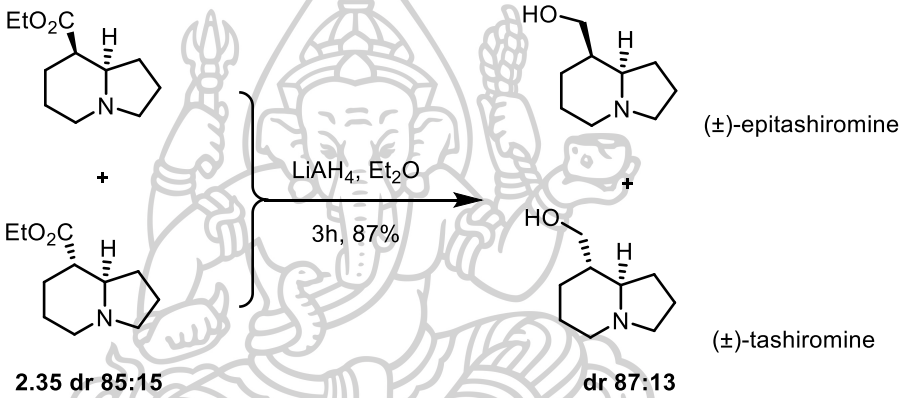

**Scheme 8** Synthesis of (±)-tashiromine and (±)-epitashiromine by Riley and co-workers

The key step was alkylating cyclization of the liberated alcohol **2.33** to produce the indolizidine core of bicyclic compound **2.34**. The cyclization was achieved by deprotection of enaminone with imidazole and triphenylphosphine in acetonitrile followed by iodine under refluxing conditions afforded to the bicyclic product **2.34**. The hydrogenation of the bicyclic iminium system gave a racemic mixture of diastereomers **2.35** (scheme 9).




**Scheme 9** Synthesis of (±)-tashiromine and (±)-epitashiromine by Riley and co-workers

Finally, reduction of the ester group of diastereomers **2.35** with lithium aluminium hydride in diethyl ether gave (±)-tashiromine and (±)-epitashiromine in an overall yield of 87% and in a 13:87 ratio (scheme 10).




**Scheme 10** Synthesis of (±)-tashiromine and (±)-epitashiromine by Riley and co-workers

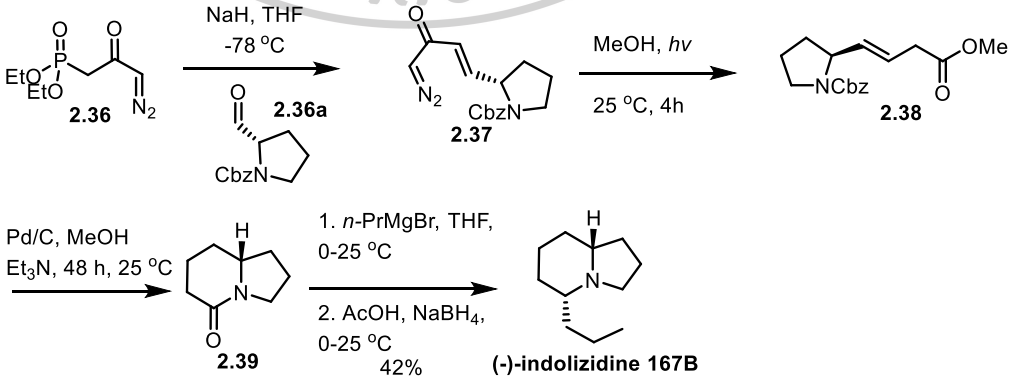
**Indolizidine 167B**

Indolizidine 167B was isolated from the skin secretions of certain neotropical amphibians. The bioactivities of this molecule are blockers of ganglionic and muscular nicotinic receptor channels. The structure of Indolizidine 167B is shown in figure 4 as an indolizidine system with a propyl group at C5 and the absolute configurations of 8a*S* and 5*S*.


**Figure 4** Structure of Indolizidine 167B and a Dendrobatid frog [10]

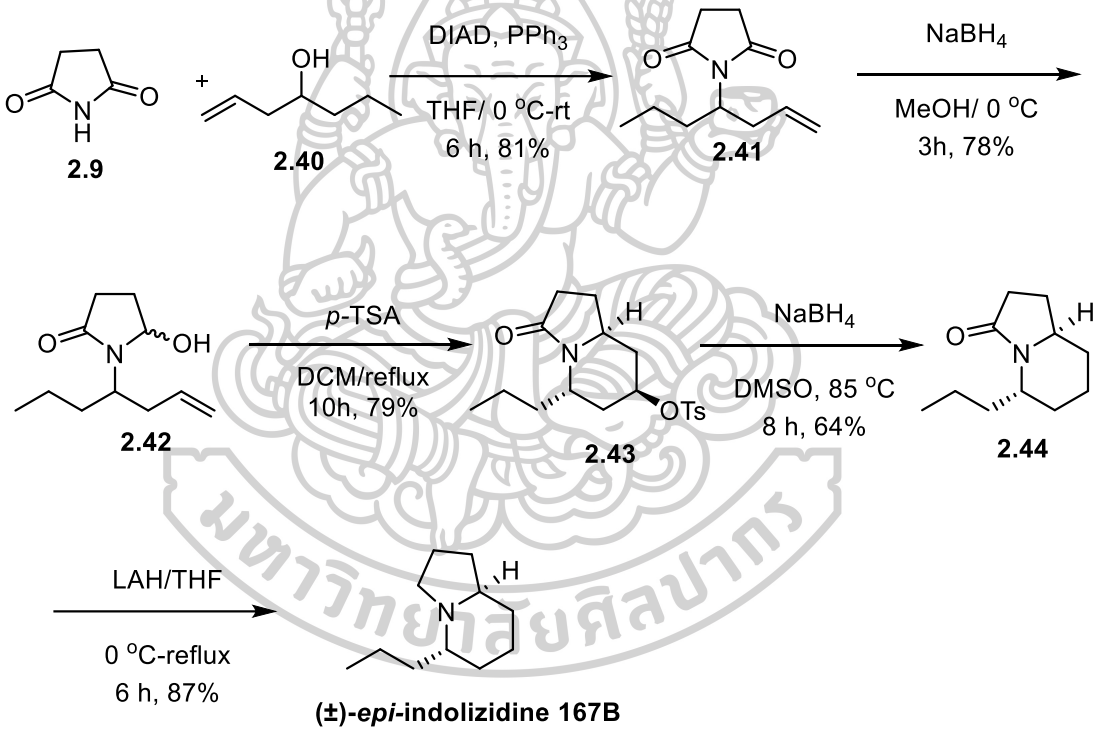
**Previous syntheses of Indolizidine 167B**

In 2012, a total synthesis of (-)-indolizidine 167B via an unusual Wolff rearrangement from an α,β-unsaturated diazoketone was reported by Pinho and co-workers[11]. The α,β-unsaturated diazoketone **2.37** was prepared from 3-diazo-2-oxopropylphosphonate **2.36** and aldehyde **2.36a** to give the product as a single *E* isomer. Then, Wolff rearrangement of α,β-unsaturated diazoketone **2.37** provided ester **2.38** in high yield. Deprotection followed by reduction of the double bond and cyclization gave bicyclic compound **2.39** in a single pot. Bicyclic compound **2.39** was then reacted with propylmagnesium bromide and AcOH/$NaBH_4$ to give (-)-indolizidine 167B in a 42% yield (scheme 11).




**Scheme 11** Synthesis of (-)-indolizidine 167B by Pinho and co-worker

In 2014, Saikia and co-workers reported the (±)-epi-indolizidine 167B[12]. in this research demonstrated the role of p-TSA in *endo-trig* cyclization for the synthesis. First, Mitsunobu reaction between homoallyl alcohol **2.40** and commercially available succinimide **2.9** gave homoallyl imide **2.41**. Then, reduction of carbonyl group using $NaBH_4$ gave hydroxylactam **2.42**. This compound was reacted with *p*-TSA via aza-Prins cyclization reaction. In the presence of p-TSA the cyclization proceeded via the corresponding *N*-acyliminium ion intermediate with the propyl substituent in axial position via 6-*endo*-trig cyclization. The tosyl nucleophile attacked the carbocation intermediate in an equatorial position to give tosylated azabicyclic compound **2.43** with *syn*-relative configuration. This was followed by reduction using $NaBH_4$ in DMSO to remove the tosylate and gave the lactam compound **2.44**. At the end, the carbonyl group was reduced with $LiAlH_4$ to give (±)-*epi*-indolizidine 167B (scheme 12).

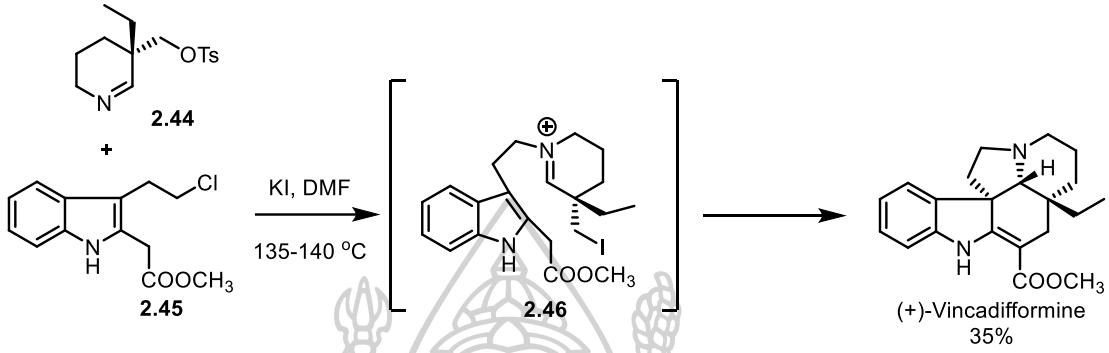



**Scheme 12** Synthesis of (±)-epi-indolizidine by Saikia and co-workers

### *N*-Acyliminum Ion Cyclization

*N*-acyliminium ion cyclizations are widely applied in the syntheses of alkaloids. They can be frequently found in synthesis natural and non-natural analogues of alkaloids in which they usually represent the key step. We have seen examples of synthesis of tashiromine and Indolizidine 167B using N-acyliminium ion cyclization. Another interesting example is discussed below. The synthesis of (+)-Vincadifformine via a highly diastereoselective was reported by Pandey and co-workers in 2011[13]. The coupling of imine **2.44** and indole fragment **2.45** via the iminium ion triggered

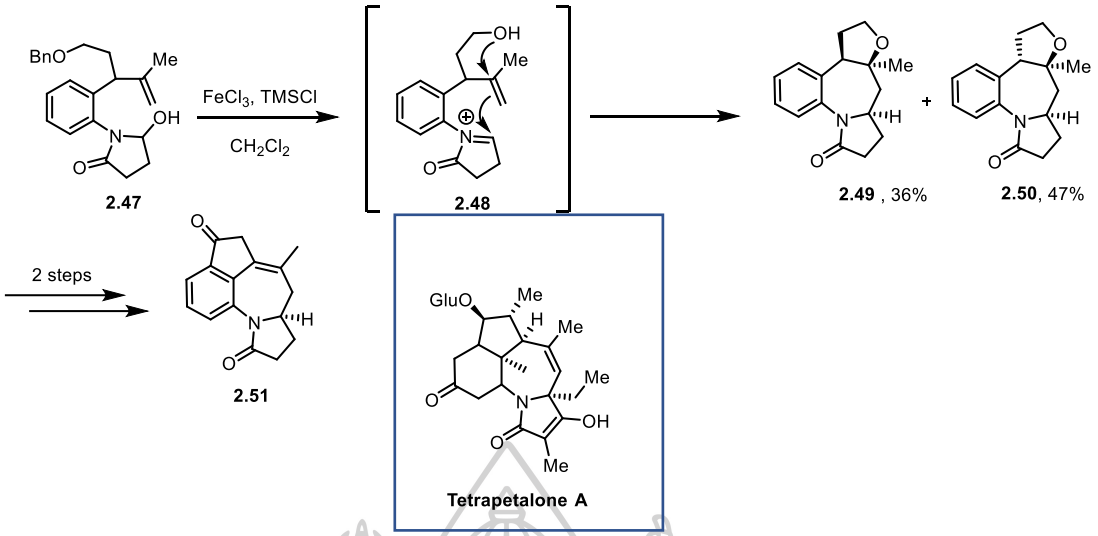
cascade cyclization by iminium ion intermediate **2.46** which was formed by N-alkylation of the imine to give (+)-Vincadifformine in 35% yield. The strategy allows simultaneous construction of two new rings, three new sigma bonds, and two new stereocenters in one pot with complete stereochemical control (scheme 13).




**Scheme 13** Synthesis of (+)-Vincadifformine by Pandey and co-workers

**Tandem *N*-acyliminium ion cyclization**

Alkene and alkyne can be π-nucleophile in intramolecular *N*-acyliminium ion cyclization. Furthermore, when the carbocationic intermediate can be trapped intramolecularly by a second nucleophile such as heteroatom, the process becomes a tandem cyclization to construct two rings in one step. In 2009 Li and co-worker [14]reported the synthesis of a tetracyclic core of tetrapetalone A via tadem *N*-acyliminium ion cyclization. Hydroxylactam **2.47** was converted to tetracyclic compounds **2.49** and **2.50.** The alcohol of *N*-acyliminium ion **2.48** attacked to alkene which in turn attacked the *N*-acyliminium ion resulting in tandem cyclization transformed to two diastereomers. Tetracyclic compound **2.50** was converted to tetracyclic core **2.51** of tetrapetalone A (scheme 14).




**Scheme 14** Synthesis of a tetracyclic core of tetrapetalone A

# CHAPTER 3

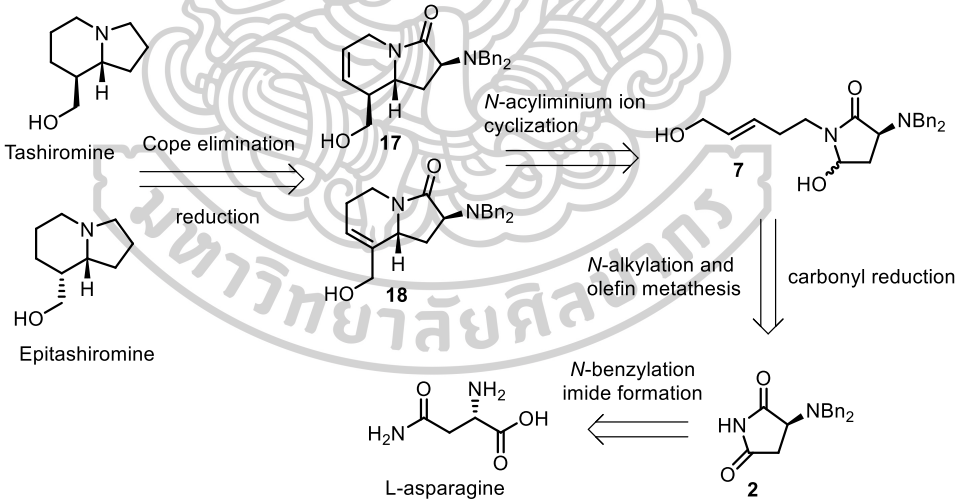
# SYNTHETIC STUDY

## Synthetic Studies of Tashiromine

Our synthetic strategy uses cheap and readily available chiral pool starting material (L-amino acid) to construct a chiral succinimide intermediate which represents the pyrrolidine ring in indolizidine alkaloids. The cyclization would proceed via a chiral *N*-acyliminium ion intermediate that cyclizes with alkene as nucleophile that would give non-aromatic indolizidinone product with high diastereoselectivity.

## Retrosynthetic analysis (I)

Tashiromine and *epi*-tashiromine would be derived from bicyclic indolizidinones **17** and **18** via Cope-elimination, hydrogenation and reduction sequence. The bicyclic compounds **17** and **18** would be synthesized from 3-dibenzylamino-*N*-(penten-5-ol-1-yl)-γ-hydroxylactam **7** via *N*-acyliminium ion cyclization. The stereocenter bearing the dibenzylamino group would give the stereocontrol of the cyclization. Hydroxylactam **7** could be derived from 3-*N*, *N*-dibenzylaminosuccinimide **2** via *N*-alkylation, olefin metathesis and carbonyl reduction. The chiral succinimide (scheme 15)

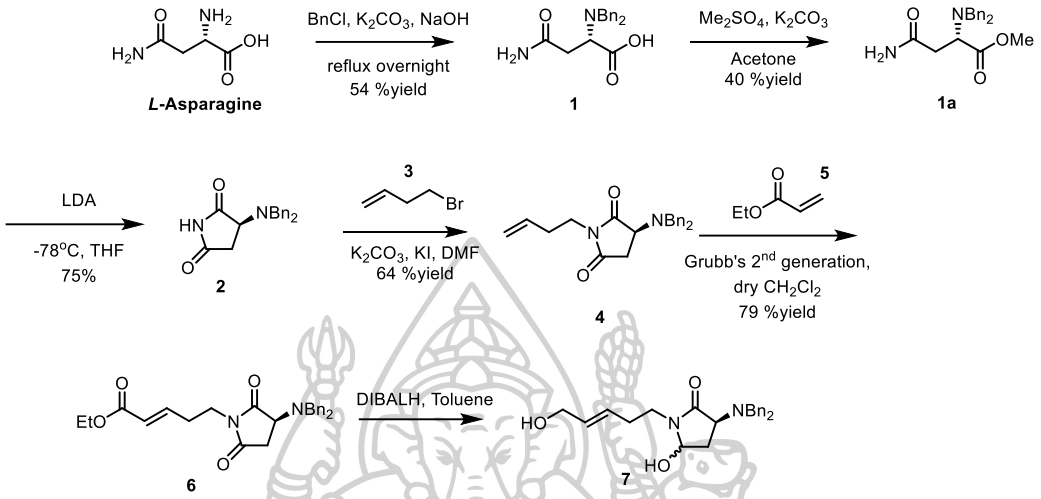



**Scheme 15** Retrosynthetic analysis of Tashiromine (I)

## Synthetic route

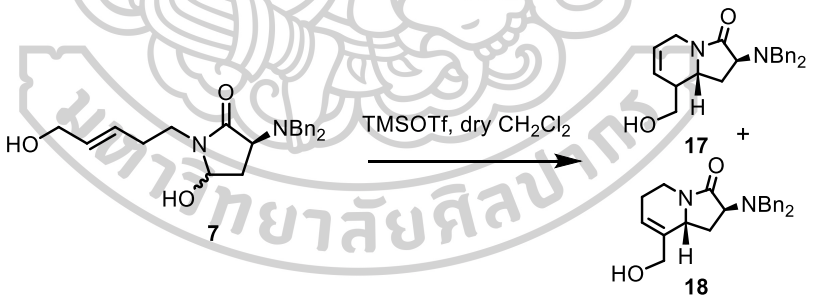
The synthetic study of tashiromine started from benzylation of commercially available L-asparagine in basic condition and imide formation to give *N*, *N*-dibenzylaminosuccinimide **2** Then, conversion of *N*, *N*-dibenzylaminosuccinimide **2** via *N*-alkylation with 4-bromo-1-butene afforded *N*-butenyl-3-dibenzylamino succinimide **4**. This compound was reacted with ethyl acrylate via olefin metathesis

using Grubb's catalyst 2[nd]generation to give *N*-(ethyl pentanoate) succinimide **6** in 79% yield. Finally, reduction of both the ester and succinimide carbonyl in compound **6** by DIBALH gave *N*-(pentenol)-γ-hydroxylactam **7** (scheme 16)



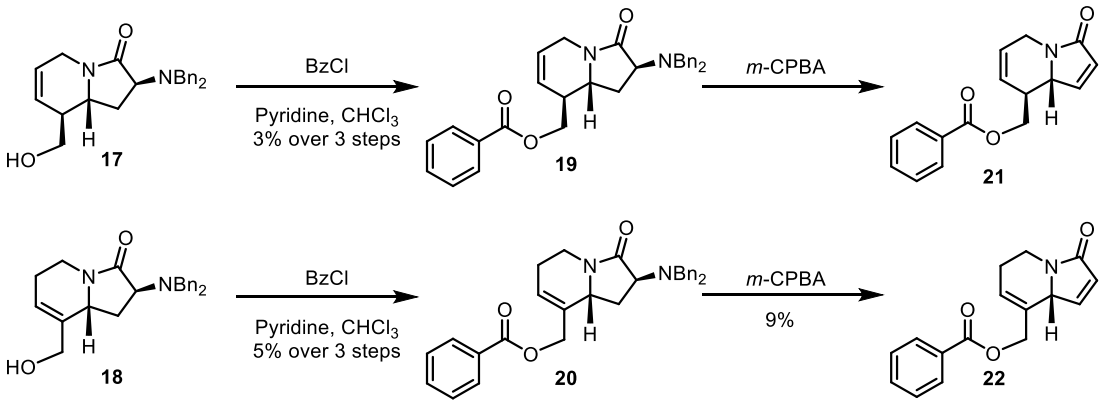

**Scheme 16** Synthesis of N-(pentenol)-γ-hydroxylactam **7**

The *N*-acyliminium ion cyclization of hydroxylactam compound **7** was mediated by treatment with trimethylsilyltrifluoromethane sulfonate (TMSOTf) to give a mixture of bicyclic indolizidinones **17** and **18** (scheme 17).



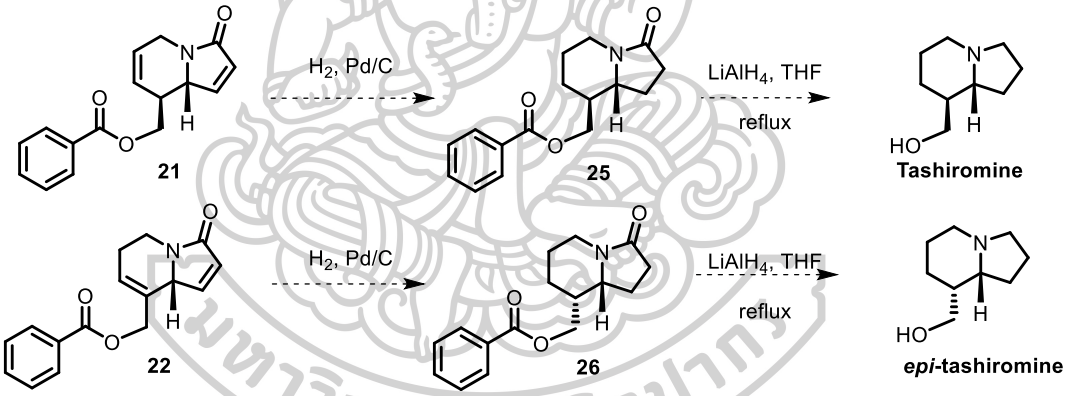

**Scheme 17** Synthesis of bicyclic indolizidinones **17** and **18**

The hydroxy group was converted to benzoate ester. The benzoyl group was installed to serve as a chromophore for detection of the product on the uv-active TLC plate in the next steps in the synthetic route after removal of the dibenzylamino group using *m*-CPBA via Cope elimination and to prevent epoxidation of alkene in the same step which may be caused by hydrogen bonding of hydroxyl group and m-CPBA. The protection of bicyclic indolizidinones **17** and **18** with benzoyl chloride gave benzoate esters **19** and **20**. Cope elimination of the dibenzylamino group of benzoate esters using *m*-CPBA gave enamides **21** and **22** (scheme 18).




**Scheme 18** Synthesis of enamide **21** and **22**

To complete the synthesis of tashiromine, we envision that enamide compound **21** and **22** would be converted to saturated indolizidinones **25** and **26,** respectively via hydrogenation in separated route. The final step is removing the carbonyl group via reduction with LAH to afford tashiromine and *epi*-tashiromine, respectively (scheme 19).

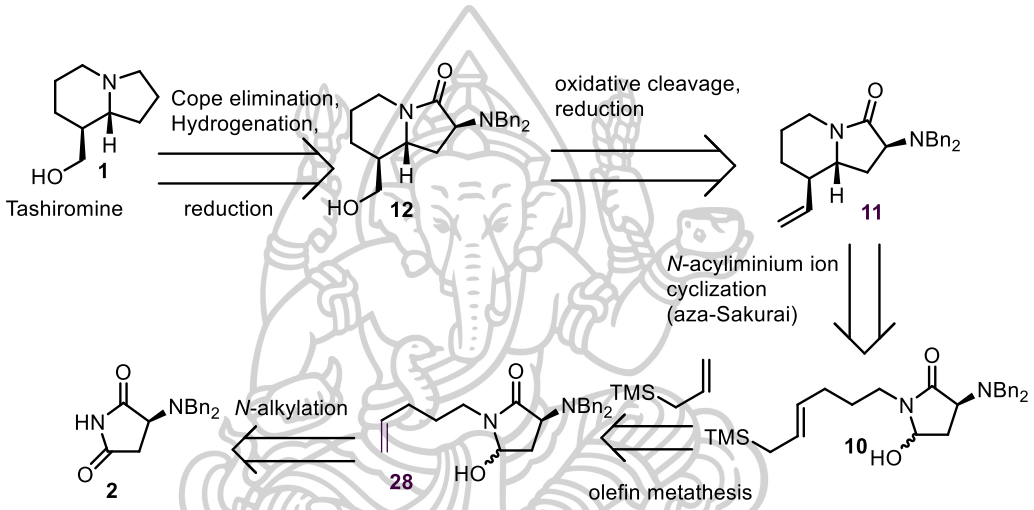



**Scheme 19** Synthesis plan of tashiromine and *epi*-tashiromine

The result of *N*-acyliminum ion cyclization of *N*-(pentenol)-g-hydroxylactam in the first synthetic route was not satisfactory giving low yield and mixture of 2 regioisomeric products. In addition, reduction of the succinimide and ethyl acrylate in the same step gave low yield. To circumvent this problem, we turn our attention to a more active nucleophile in the form of allylsilane which would react with the *N*-acyliminium ion in an aza-Sakurai fashion. Thus, a new retrosynthetic analysis was devised as shown below.

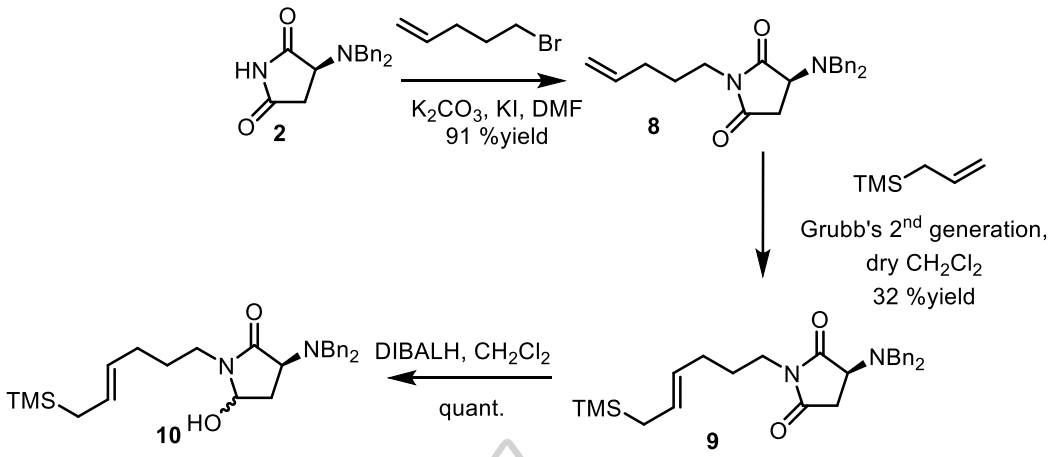
**Retrosynthetic analysis II**

The second synthetic route of tashiromine is shown in scheme 3.6. Tashiromine is envisioned to be derived from the advanced intermediate **12** by Cope elimination, hydrogenation and reduction. This compound, in turn, would be derived from oxidative cleavage and subsequent reduction of the vinyl group in 9-vinylindolizidinone **11**. The vinylindolizidine core could be synthesized from hydroxylactam compound via *N*-acyliminium ion cyclization with allylsilane or aza-Sakurai reaction. The hydroxylactam tethered with the 6-trimethylsilylhexenyl group could be synthesized by *N*-alkylation and olefin metathesis with trimethylallylsilane of 3-dibenzylaminosuccinimide. The chiral succinimide was synthesized from L-asparagine as previously discussed.



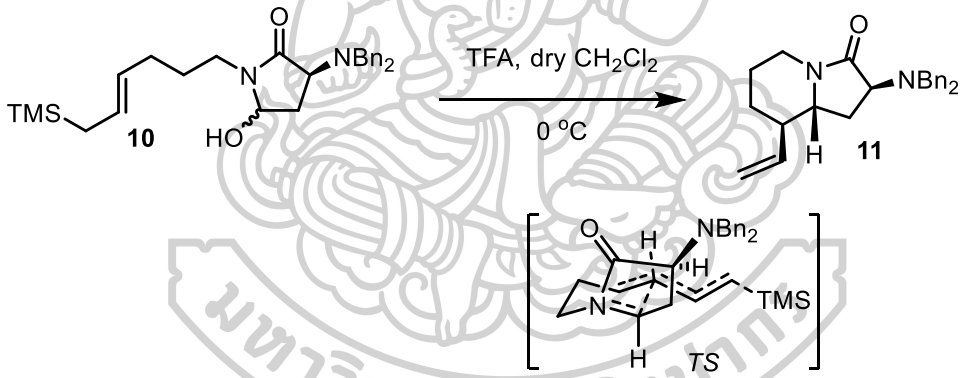

**Scheme 20** Retrosynthetic analysis of tashiromine (II)

*N*, *N*-dibenzylaminosuccinimide **2** was converted to *N*-pentenyl-3-dibenzylaminosuccinimide **8** by *N*-alkylation under basic condition using pentenyl bromide in 91 %. *N*-pentenyl-3-dibenzylaminosuccinimide **8** and allyltrimethylsilane were coupled to give *N*-(6-(trimethylsilyl) hex-4-en-1-yl)-3-dibenzylaminosuccinimide compound **9** by olefin metathesis using Grubb's catalyst 2$^{nd}$ generation. *N*-[6-(trimethylsilyl) hex-4-en-1-yl]-3-dibenzylaminosuccinimide **9**. Reduction of this compound was converted to hydroxylactam **10** by DIBALH reduction (scheme 21).



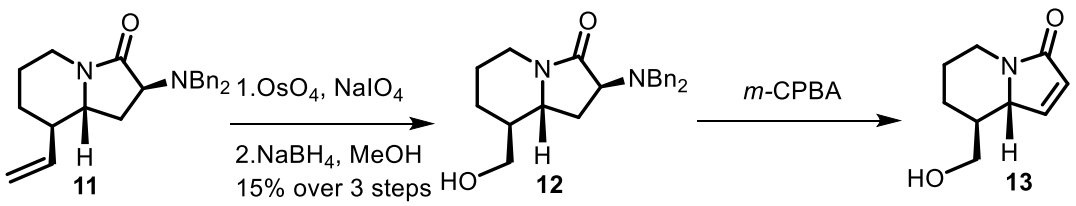

**Scheme 21** Synthesis of hydroxylactam **10**

The hydroxylactam **10** was converted to vinyl indolizidines compound **11** via *N*-acyliminium ion cyclization using TFA. The dibenzylamino group is used for stereocontrol where the cyclization occurs from the opposite face to the dibenzylamino group *via* a 6-membered chair transition state (scheme 22).



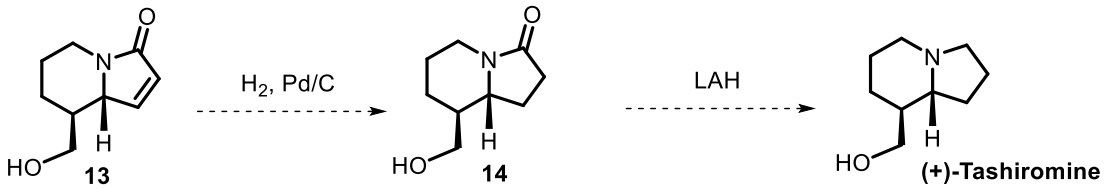

**Scheme 22** Synthesis of vinyl indolizidine compound **11**

The vinyl Indolizidine compound **11** was converted to enamide compound **13** *via* oxidative cleavage using $OsO_4$, $NaBH_4$ reduction and Cope–elimination using *m*-CPBA. This intermediate has the spectral data matched the reported data of previous synthesis confirming the relative configuration of the synthetic compound to be in accordance with (+)-tashiromine (scheme 23).




**Scheme 23** Synthesis of enamide compound **13**

The remaining steps for completion of total synthesis of tashiromine are hydrogenation of the C=C and reduction of the amide carbonyl to give (+)-tashiromine from enamide compound **13** (scheme 24).



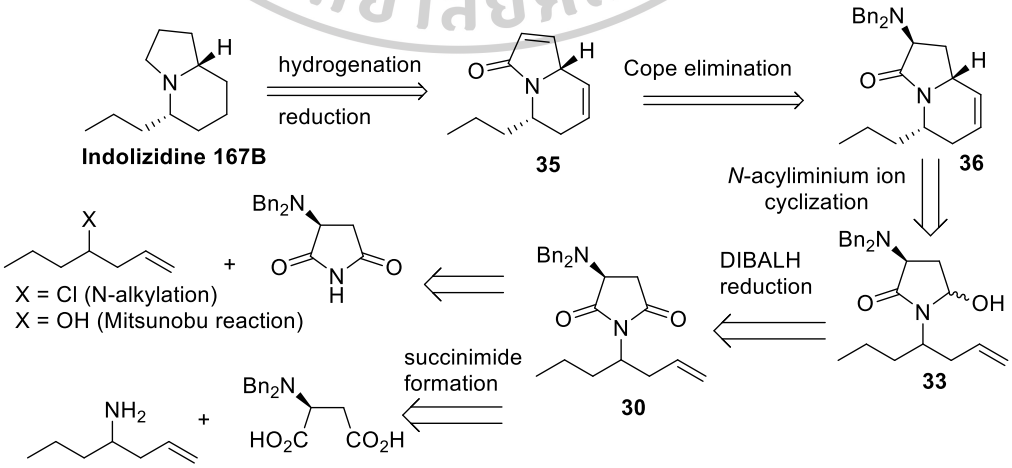

**Scheme 24** Synthesis plan of (+)-tashiromine

**Synthetic Studies of Indolizidine 167B**

Tashiromine is a non-aromatic 9-hydroxymethylindolizidine whereas indolizidine 167B is a non-aromatic 5-substituted indolizidine alkaloid. Synthesis of indolizidine 167B using the same methodology with *N*-acyliminium ion cyclization will require synthesis of chiral succinimide with *N*-alkyl group having *N*-secondary carbon bond. The synthesis of the key succinimide can be approached either from *N*-alkylation of succinimide **2** with secondary alkyl halide or secondary alcohol using Mitsunobu condition or succinimide formation of amine with the amino group on the secondary carbon of an alkyl chain.

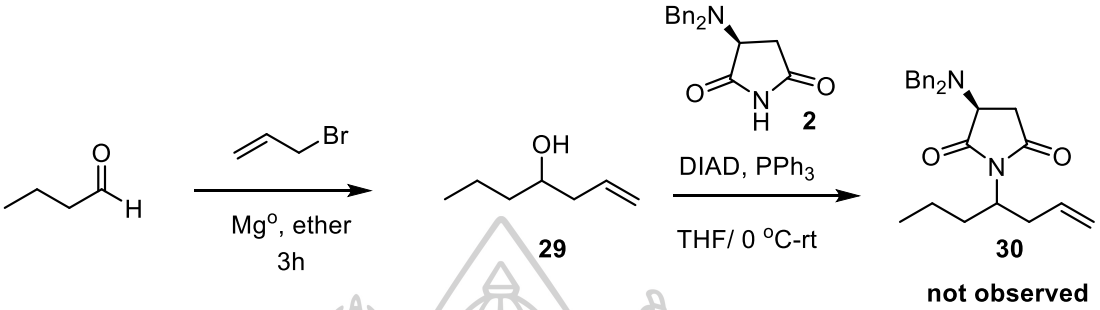
**Retrosynthetic analysis (I)**

Indolizodine 167B would be prepared from bicyclic dihydroindolizinone **35** via hydrogenation and carbonyl reduction. The bicyclic compound **35** would be derived from Cope elimination of dibenzylaminoindolizidinone **36** which would be the product of the key *N*-acyliminium ion cyclization of N-(1-hepten-4-yl)-g-hydroxylactam **33**. The key intermediate would be the product of hydride reduction of the corresponding succinimide 30 whose synthesis could be conceived by two different routes as mentioned earlier (scheme 25).



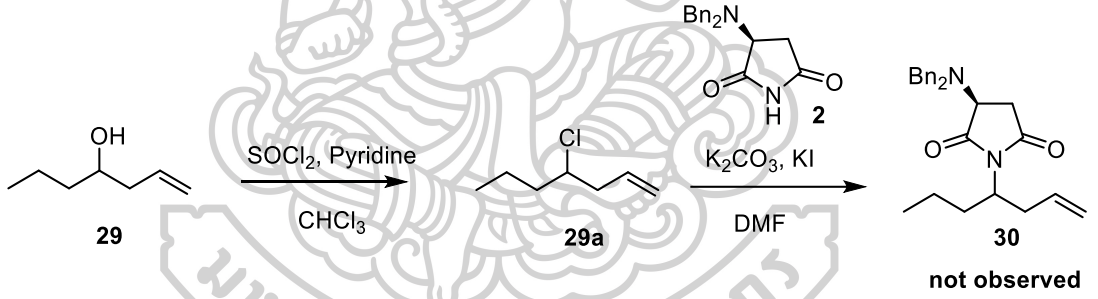

**Scheme 25** Retrosynthetic analysis of indolizidine 167B

Synthetic study of indolizidine 167B began with synthesis of homoallylic alcohol 1-hepten-4-ol by Grignard reaction between butyraldehyde and allylmagnesium bromide to give homoallyl alcohol **29**. Then, homoallyl alcohol compound **29** was reacted with *N, N*-dibenzylaminosuccinimide compound **2** via Mitsunobu reaction. Unfortunately, the homoallyl chiral imide compound **30** is not observed (scheme 26).




**Scheme 26** Synthesis of homoallyl chiral imide compound **30**

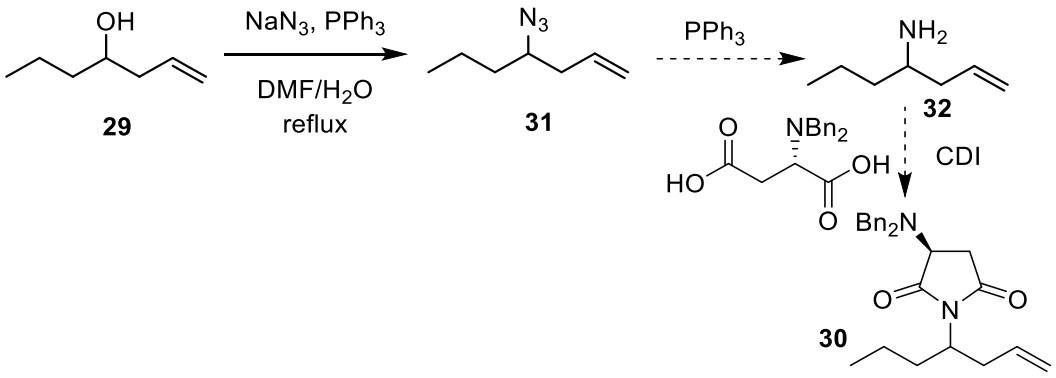
The second synthetic attempt of the homoallyl chiral imide **30** employed chlorination of homoallyl alcohol compound **29** using $SOCl_2$ to give homoallyl chloride **31**. However, subsequent *N*-Alkylation with *N, N*-dibenzyl-aminosuccinimide compound **2** also did not yield the desired homoallyl chiral imide **30** (scheme 27).




**Scheme 27** synthesis of homoallyl chiral imide compound **30**

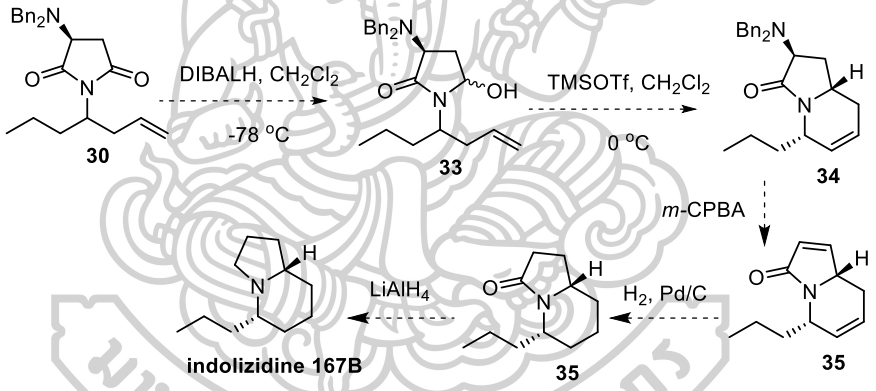
We suspect that the dibenzylaminosuccinimide behave in a different way than the simple succinimide which is known to react with secondary alcohol or secondary alkyl halide to give the *N*-alkylated succinimide product. This may be resulted from the bulky dibenzylamino group that prevents the nucleophilic substitution.

Therefore, an alternative route employing succinimide formation with hept-1-en-4-amine **32** synthesized from homoallyl alcohol via azidination and reduction will be attempted (scheme 28).




**Scheme 28** Synthesis plan for *N*-(1-hepten-4-yl) succinimide **30**

The remaining steps are DIBALH reduction followed by the pivotal *N*-acyliminium ion cyclization to establish the indolizidinone system diastereoselectively controlled by the dibenzylamino group, Cope-elimination, hydrogenation and carbonyl reduction to give Indolizodine 167B (scheme 29).




**Scheme 29** Synthesis plan of indolizidine 167B

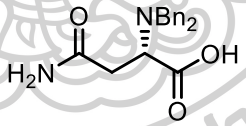
# CHAPTER 4

## EXPERIMENTAL PROCEDURE

### General

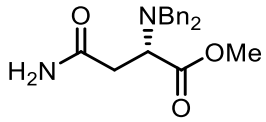
Starting materials and reagents were obtained from commercial sources and were used without further purification. Solvents were dried by distillation from the appropriate drying reagents immediately prior to use. Tetrahydrofuran was distilled from sodium and benzophenone under argon. Toluene and dichloromethane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

### Synthesis of dibenzyl-L-asparagine (1)



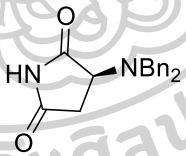

To a solution of L-asparagine (5.00 g, 33.3 mmol) in MeOH and $H_2O$ (1:1, 100 mL) was added NaOH (3.33 g, 83.3 mmol), $K_2CO_3$ (11.5 g, 83.8 mmol) and BnCl (15.46 mL, 133 mmol). The mixture was heated to reflux at 95 $^{o}$C overnight and acidified with 1M HCl. Then the mixture was extracted with $CH_2Cl_2$ (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,2:1 Hexane/EtOAc) to give dibenzyl-L-asparagine compound **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, $CDCl_3$) $\delta$ 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, $CHCl_3$); $\nu_{max}$ (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 (1a)**



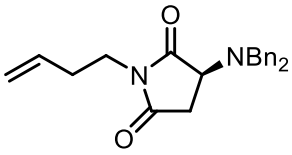
To a solution of dibenzyl-L-asparagine **1** (4.06 g, 12.3 mmol) in acetone (50 mL) was added $K_2CO_3$ (2.55 g, 18.43 mmol) and $Me_2SO_4$ (1.75 mL, 18.4 mmol) and the mixture was stirred at room temperature overnight. The mixture was filtered to remove $K_2CO_3$ and to the solution was added dropwise sat. aq. $NH_4Cl$ (30 mL). Then the mixture was extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic layers were washed with 5% NaOH (100 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 2:1 hexane/EtOAc) to give methyl dibenzyl-L asparaginate **1a** (1.97 g, 59%) as a colorless oil. $R_f$ (2:1 hexane/EtOAc) 0.08; 1H 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); 13C NMR (75 MHz, CDCl3) δ 173.4, 172.4, 139.0 (2C), 129.0 (4C), 128.5 (4C), 127.3 (2C), 58.3, 54.9 (2C), 51.6, 35.6. $[\alpha]_{25}^{D}$-103.8 (c 1.6, $CHCl_3$); $\nu_{max}$ (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 (2)**



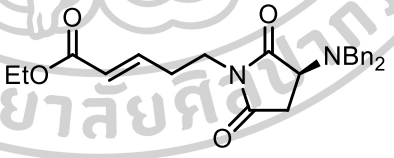
To a solution of methyl dibenzyl-L-asparaginate (1.58 g, 4.80 mmol) in dry THF (10 mL) under argon atmosphere at -78 $^oC$ was added LDA (7.27 mL, 14.5 mmol) and the mixture was stirred for 3 hours at -78 $^oC$. To this mixture was added dropwise sat. aq. $NH_4Cl$ (20 mL) and the mixture was extracted 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 **2** (1.06 g, 75%) as a white crystal. $R_f$ (2:1 hexane/EtOAc) 0.38; $^1H$ NMR (300 MHz, $CDCl_3$ ) δ 7.37 – 7.16 (m, 10H) ; 3.86 (dd, J= 8.4,6.0 Hz,1H) ; 3.77 (d, J= 13.5 Hz, 2H) ; 3.58 (d, J= 13.5 Hz, 2H) ; 2.67 (dd, J= 18.6,8.4 Hz, 1H) ; 2.59 (dd, J= 18.0, 5.7 Hz,1H) $^{13}C$ NMR (75 MHz, $CDCl_3$) δ178.7, 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, $CHCl_3$); $\nu_{max}$ (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 (4)**




To a solution of chiral succinimide **2** (890.0 mg, 3.03 mmol) in DMF (10 mL) under argon atmosphere at room temperature was added $K_2CO_3$ (503.1 g, 3.64 mmol), KI (60.4 mg, 0.364 mmol) and 4-bromo-1-butene (0.37 mL, 3.64 mmol) and the mixture was stirred for overnight. The mixture was filtered to remove $K_2CO_3$ and the mixture was extracted with CH2Cl2 (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 butenyl succinimide **4** (68.1mg, 64%) as a yellow oil. $R_f$ (4:1 hexane/EtOAc) 0.63; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.36 – 7.16 (m, 10H) ; 5.68 (dddd, J= 17.1, 10.1, 6.9, 6.9 Hz,1H) ; 5.02-4.95 (m, 2H) ; 3.81-3.74 (m,3H) ; 3.56-3.49 (m,4H) ; 2.64-2.55(dd, J= 18.6,8.7 Hz,1H) ; 2.54-2.46(dd, J= 18.6, 5.7 Hz,1H) ; 2.33-2.26(q, J= 20Hz,2H); 13C NMR (75 MHz, CDCl3) 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, $CHCl_3$); $\nu_{max}$ (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.

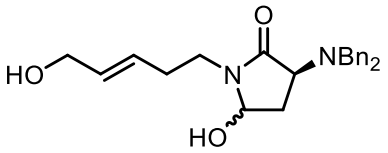
**Synthesis of ethyl (*S, E*)-5-(3-(dibenzylamino)-2,5-dioxopyrrolidin-1-yl) pent-2-enoate 6**




To a solution of butenyl succinimide **4** (680.8 mg, 1.95 mmol) in dry $CH_2Cl_2$ (10 mL) under argon atmosphere at room temperature was added ethyl acrylate (1.04 mL, 9.77 mmol) and Grubbs catalyst 2$^{nd}$ generation (16.6 mg, 0.00195mol). 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 **6** (647.5 mg, 79%) as a yellow oil. $R_f$ (4:1 hexane/EtOAc) 0.50; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.24 (m, 10H) ; 6.82 (dt, J= 15.6,7.2 Hz,1H) ; 5.82 (dt, J= 15.9, 1.2 Hz,1H) ; 4.07 (q, J= 7.2 Hz, 2H) ; 3.91 (dd, J= 9.0, 5.4 Hz, 1H) ; 3.79 (d, J= 13.5 Hz,2H) ; 3.71-3.59 (m, 4H) ; 2.72 (dd, J= 13.5, 9 Hz,1H) ; 2.60 (dd, J= 18.6, 5.4 Hz,1H) ; 2.49(q, J= 7.5 Hz, 2H) ; 1.19 (t, J= 7.2 Hz, 3H) ; 13C NMR (75 MHz, CDCl3) 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. $[\alpha]_{25}^{D}$ (*c* 0.8,

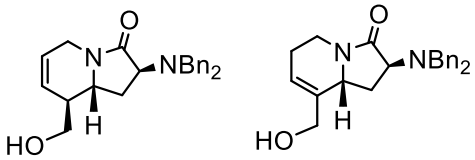
$CHCl_3$); $\nu_{max}$ (film) 3029, 2939, 2847, 1776, 1705, 1657, 1398, 1367, 1326, 1195 $cm^{-1}$; ESI-HRMS calculated for $C_{26}H_{30}N_2O_4$ $[M+Na]^+$ 443.1941, found 443.1935.

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



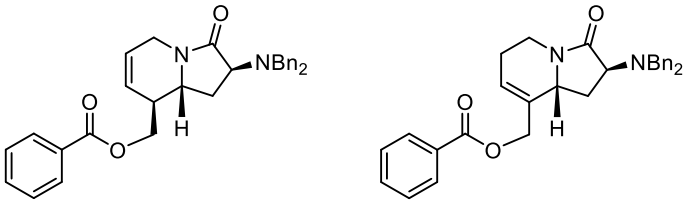

To a solution of unsaturated ester succinimide **6** (647.5 mg, 1.54 mmol) in dry Toluene (5 mL) under argon atmosphere at -78 $^oC$ was added DIBALH (4.62 mL, 1.54 mmol) and the mixture was stirred for 2 hours. To this mixture was added dropwise sat. $NaHCO_3$. Then the mixture was extracted with EtOAc (3 × 30 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 **7** (583.6 mg) as an orange oil. The crude product was carried on to the next step without purification. 1H 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); 13C NMR (75 MHz, CDCl3) 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; $\nu_{max}$ (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 (2S)-2-(dibenzylamino)-8-(hydroxymethyl)-1,5,8,8atetrahydroindolizin-3(2H)-one (17) and (2S)-2-(dibenzylamino)-8-(hydroxymethyl)-1,5,6,8a-tetrahydroindolizin-3(2H)-one (18)**



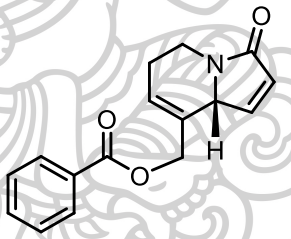

To a solution of hydroxylactam **7** (420.7 mg, 1.11mmol) in dry $CH_2Cl_2$ (10 mL) under argon atmosphere at 0 $^oC$ was added TMSOTf (0.6 mL, 3.32 mmol) and the mixture was stirred for 3 hours at 0 $^oC$ to room temperature. To this mixture was added dropwise sat. aq. $NaHCO_3$ and the mixture was 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 product was obtained without purification to give bicyclic **17** and **18** as yellow oils. The crude product was carried on to the next step without purification.

**Synthesis of benzoate ester 19 and 20**



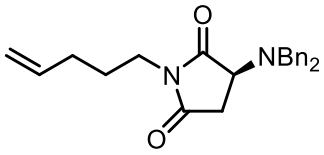
To a solution of bicyclic **17** and **18** (1.11mmol) in dry $CH_2Cl_2$ (11 mL) under argon atmosphere was added pyridine (0.27 mL, 3.32 mmol) and benzoyl chloride (0.0385 mmol). the mixture was stirred for 24 hours at to room temperature. To this mixture was added dropwise sat. $NaHCO_3$ and the mixture 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 product was obtained without purification to give product benzoate ester **19** and **18** as dark yellow oils. (benzoate ester **19,** 0.0249 g, 3.46% over 3 steps and benzoate ester **20,** 0.0352g, 4.89% over 3 steps)

**Synthesis of enamide 22**



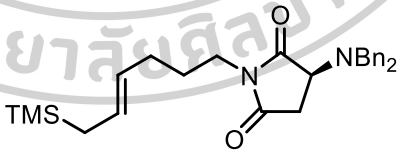
To a solution of benzoate ester **20** (35.2 mg, 0.0754 mmol) in dry $CH_2Cl_2$ (10 mL) under argon atmosphere was added *m*-CPBA (23 mg, 70% w/w, 0.091 mmol) and the mixture was stirred for 30 minutes. To this mixture was added dropwise sat. aq. $NaCO_3$(20 mL) and the mixture was extracted with $CH_2Cl_2$ (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, 2:1 hexane/EtOAc) to give enamide **22** as a yellow oil. (1.8 mg, 8.8%) $^1$H NMR (300 MHz, $CDCl_3$) δ 8.34-6.85 (m, 7H), 6.29(d, J= 6.0 Hz, 1H), 5.26(d, J= 12.3 Hz, 1H), 5.07(d, J= 12.5 Hz, 1H), 4.63-4.57 ( m, 1H), 3.84(dt, J= 21.5, 8.7 Hz, 1H), 3.59(dt, J= 13.9, 3.8Hz, 1H), 2.16-1.95 (m, 2H)

**Synthesis of (S)-3-(dibenzylamino)-1-(pent-4-en-1-yl) pyrrolidine-2,5-dione (8)**




To a solution of chiral succinimide **2** (263.6 mg, 0.897 mmol) in DMF (5 mL) under argon atmosphere at room temperature was added $K_2CO_3$ (149.0 mg, 1.08 mmol), KI (17.1 mg, 0.108mmol) and 5-bromo-1-pentene (0.13 mL, 1.08 mmol) and the mixture was stirred for overnight. 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 pentenyl succinimide **8** (364.5 mg, 91%) as a yellow oil. Rf (4:1 hexane/EtOAc) 0.55; 1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.21 (m, 10H), 5.78 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H), 5.05-4.95 (m, 2H), 3.89 (dd, J=9.0, 5.3 Hz, 1H), 3.81 (d, J= 13.4 Hz, 2H), 3.62 (d, J = 13.4 Hz, 2H), 3.48 (t, J = 7.4, 2H), 2.71 (dd, J = 18.0, 9.0 Hz, 1H), 2.57 (dd, J = 18.5, 5.4 Hz, 1H), 2.04 (q, J= 7.1, 2H), 1.65 (p, J = 7.6 Hz, 2H); 13C 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, $CHCl_3$); $\nu_{max}$ (film) 2925, 2841, 1775, 1701, 1494, 1455 $cm^{-1}$.

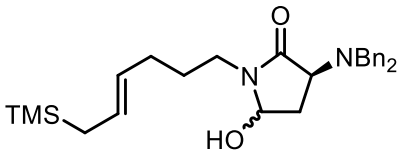
**Synthesis of (*S*, *E*)-3-(dibenzylamino)-1-(6-(trimethylsilyl) hex-4-en-1-yl) pyrrolidine-2,5-dione 9**




To a solution of pentenyl succinimide **8** (610.0 mg, 1.69 mmol) in dry $CH_2Cl_2$ (10 mL) under argon atmosphere at room temperature was added allyl TMS (1.34 mL, 8.43 mmol) and Grubbs catalyst 2nd generation (14.0 mg, 0.017 mmol). Then the mixture was heated to reflux at 40 °C overnight. To this mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 6:1 hexane/EtOAc) to give allyl TMS succinimide compound **9** as a yellow oil. (246.5 mg, 32%) $^1$H NMR (300 MHz, CDCl3) $\delta$ 7.41-7.26(m, 10H), 5.49-5.36(m, 1H), 5.32-5.10(m,1H), 3.93(dd, J = 5.3 Hz, 1H), 3.85(d, J =13.4 Hz, 2H), 3.66(d, J =13.4 Hz, 2H), 3.56-3.48(m, 2H), 2.78(dd, J =18.5, 4.6 Hz, 1H), 2.62(dd, J =18.5, 5.3 Hz,1H), 2.03-1.98(m, 2H), 1.67-1.58(m, 2H), 1.48-1.37(m, 2H), 0.055-(-0.046)(m,9H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 179.3, 177.3, 140.3(2C), 130.8(4C), 130.5(4C), 129.4(2C),

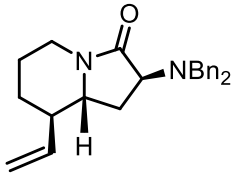
127.6, 127.1, 59.3, 56.6(2C), 40.1, 34.2, 32.1, 29.9, 24.6, 1.9(3C); $\nu_{max}$ (film) 2950, 1775, 1698, 1494, 1454 $cm^{-1}$.

**Synthesis of (3*S*)-3-(dibenzylamino)-5-hydroxy-1-((E)-6-(trimethylsilyl) hex-4-en-1-yl) pyrrolidin-2-one 10**




To a solution of allyl TMS succinimide (135.1 mg, 0.301 mmol) in dry $CH_2Cl_2$ (5 mL) under argon atmosphere at -78 $^oC$ was added DIBALH (0.75 mL, 0.903 mmol) and the mixture was stirred for 2 hours. To this mixture was added dropwise sat. $NaHCO_3$. Then the mixture was extracted with EtOAc (3 × 30 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 **10** (126.5 mg) $^1H$ NMR (300 MHz, CDCl3) δ 7.55-7.21(m, 10H), 5.48-5.33(m, 1H), 5.30-5.12(m, 1H), 5.03-4.98(m,1H), 3.93(d, J =13.8 Hz, 1H), 3.72(d, 13.8 Hz, 1H), 3.58-3.51(m, 1H), 3.50-3.41(m, 1H), 3.30-3.14(m, 1H), 2.50(ddd, 14.2, 9.5, 7.0 Hz, 1H), 2.12-1.95(m, 2H), 1.83-1.77(m, 1H), 1.74-1.55(m, 1H), 1.50-1.34(m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 174.9, 141.4, 131.1(4C), 130.8(4C), 129.4(2C), 128.4, 128.1, 81.9, 60.9, 56.7, 42.0, 34.7, 32.4, 29.5, 24.7, 1.9(3C); $\nu_{max}$ (film) 3329, 3028, 2954, 2802, 1661, 1492, 1453 $cm^{-1}$.

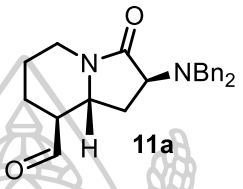
**Synthesis of (2S,8R,8aR)-2-(dibenzylamino)-8-vinylhexahydroindolizin-3(2H)-one 11**




To a solution of hydroxylactam **10** (60.7 mg, 0.135 mmol) in dry $CH_2Cl_2$ (5 mL) under argon atmosphere at 0 $^oC$ was added TFA (0.04 mL, 0.0539 mmol) and the mixture was stirred for 3 hours at 0 $^oC$. To this mixture was added dropwise sat. $NaHCO_3$. Then 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. to give vinyl indolizidine **11**. $^{1}$H NMR (300 MHz, CDCl3) δ 7.65-7.10(m, 10H), 5.80-5.62(m, 1H), 5.14-4.96(m, 2H), 4.15(dd, J =13, 4.3 Hz, 1H), 3.85(d, 13.6 Hz, 2H), 3.65-3.51(m, 5H), 3.12(dt, 1H), 2.61(dt, 1H), 2.10-1.97(m, 1H), 1.95-1.87(m, 1H), 1.85-1.42(m, 3H), 1.39-1.23(m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 172.2, 139.8, 139.6, 138.6, 128.9(4C), 128.8(4C), 126.9(2C), 116.2, 58.8(2C), 54.9(2C), 48.9, 39.9, 30.5, 27.4, 24.3; ); $\nu_{max}$ (film) 3339, 3028, 2934, 2341, 1682, 1494, 1453 cm$^{-1}$.

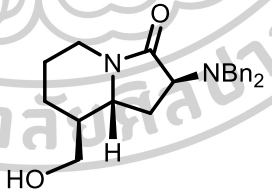
**Synthesis of aldehyde 11a**




**11a**

To a solution of vinyl indolizidine (160.4 mg, 0.445 mmol) in dioxane/water 3:1 (4 mL) at room temperature was added 2,6-lutidine (0.10 mL, 0.890 mmol), $OsO_4$ (0.0005, 0.0089 mmol) and $NaIO_4$ (380.7 mg, 1.78 mmol) the mixture was stirred for 1 hours. To this mixture was added dropwise of water. Then 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. to give aldehyde **11a**. The crude product was carried on to the next step without purification.

**Synthesis of (2S,8S,8aR)-2-(dibenzylamino)-8- (hydroxymethyl) -hexahydroindolizin-3(2H)-one 12**

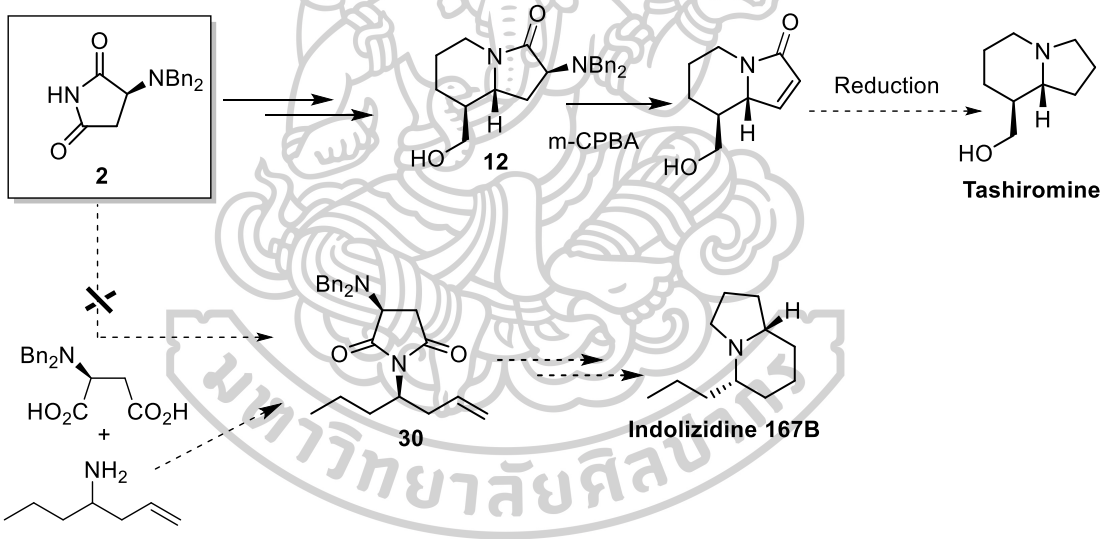



To a solution of aldehyde **11a** (98.7 mg, 0.272 mmol) in ethanol (5 mL) at 0 $^{o}$C was added $NaBH_4$ (21.1 mg, 0.545 mmol) the mixture was stirred for 30 minutes. To this mixture was added dropwise of $NH_4Cl$. Then the mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 1:2 hexane/EtOAc) to give alcohol compound **12** as a yellow oil. (15.6 mg, 15% over 3 steps) $^{1}$H NMR (300 MHz, $CDCl_3$) δ 7.55-7.14(m, 10H), 4.17(dd, J =13.1, 3.9 Hz, 1H), 3.85(d, J =13.6 Hz, 2H), 3.71-3.53(m, 5H), 3.23(dt, 12.9, 5.2 Hz, 1H), 2.57(dt, J= 12.3, 3.51 Hz, 1H), 2.19(ddd, 14.0, 8.4, 2.1 Hz, 1H), 2.04-1.87(m, 1H), 1.44-1.13(m, 4H) ; $^{13}$C NMR (75 MHz, $CDCl_3$) δ 172.1, 139.4, 128.8(4C), 128.7(4C), 126.9(2C), 64.3, 59.9, 58.7, 55.3(2C), 45.6, 39.7, 28.8, 28.0, 24.2; $\nu_{max}$ (film) 3397, 2927, 1661, 1493, 1454 cm$^{-1}$.

# CHAPTER 5

# CONCLUSION

In summary, the synthetic studies of tashiromine have been discussed. The chiral succinimide **2** synthesized form *L*-asparagine was the key intermediate of tashiromine synthesis. The key step of the synthesis, *N*-acyliminium ion cyclization with hydroxyalkene and allylsilane as nucleophile. We succeeded in constructing indolizidine core for syntheses of bicyclic core **12** of tashiromine. This intermediate has the spectral data that matched the reported data of previous synthesis confirming the relative configuration of the synthetic compound to be in accordance with (+)-tashiromine. The remaining steps involve removal of unnecessary functional groups to complete the natural product. Synthetic study of indolizidine 167B has not made progress due to difficulty in synthesis of chiral succinimide with *N*-secondary carbon substituent.




**Scheme 30** Conclusions of finding from this research

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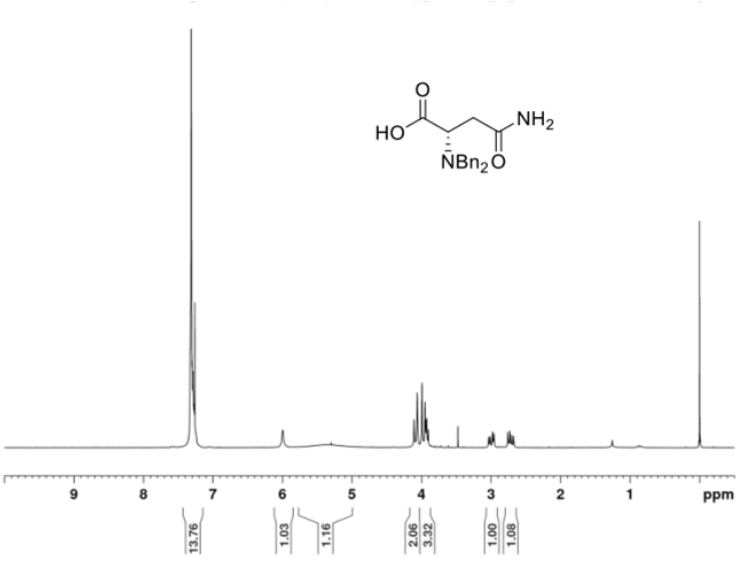
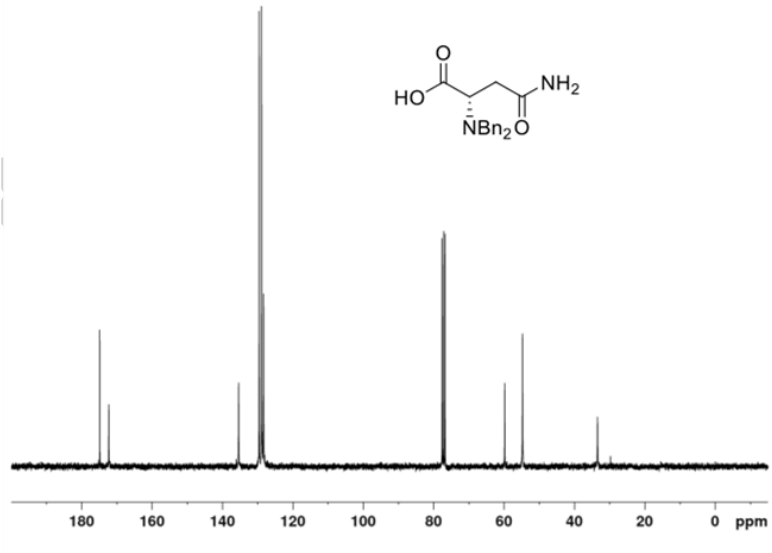
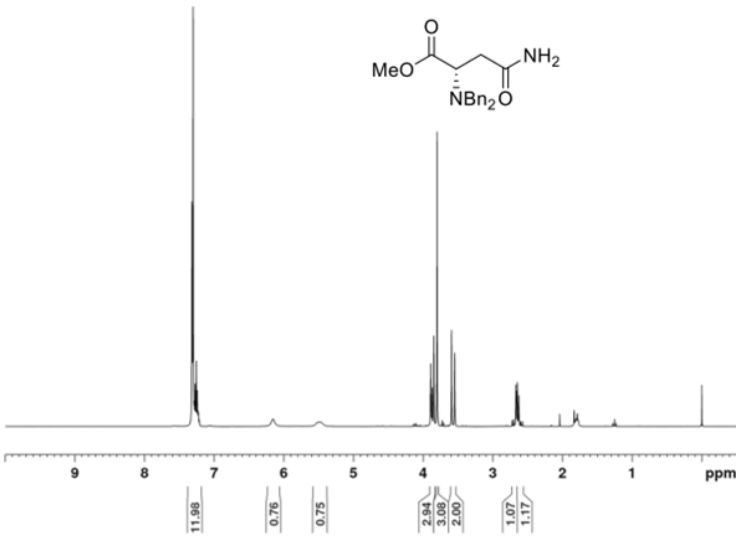
# APPENDIX



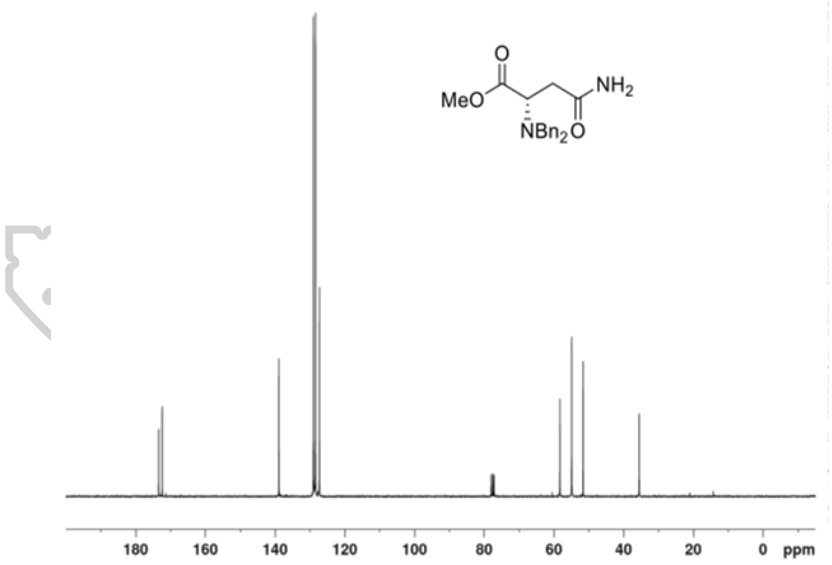

**$^{1}$H NMR of compound 1**



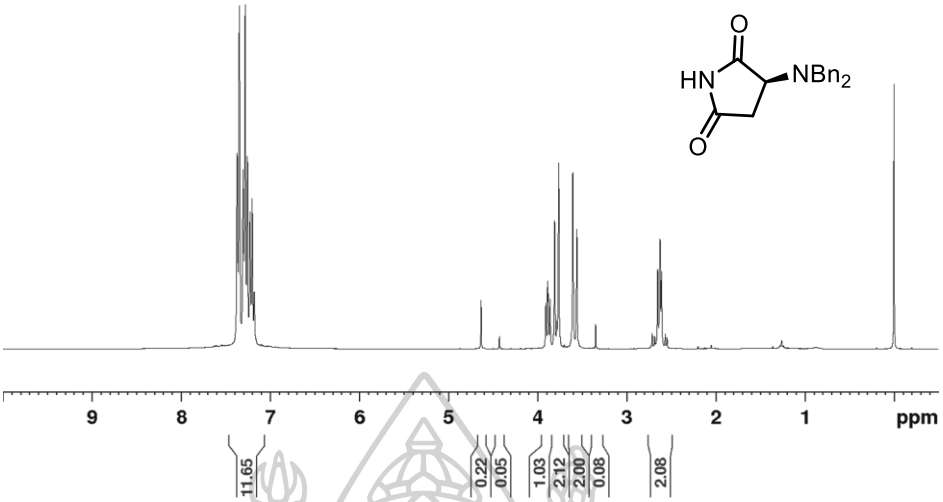

**$^{13}$C NMR of compound 1**



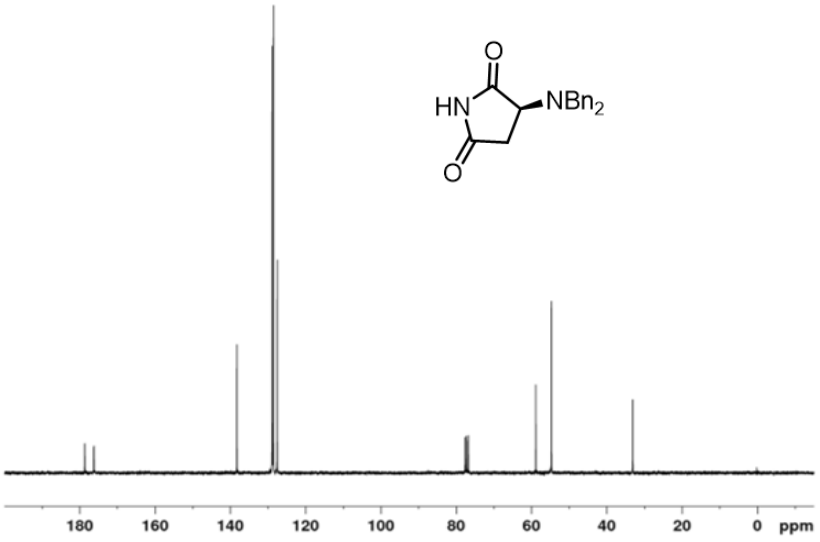

**$^{1}$H NMR of compound 1a**



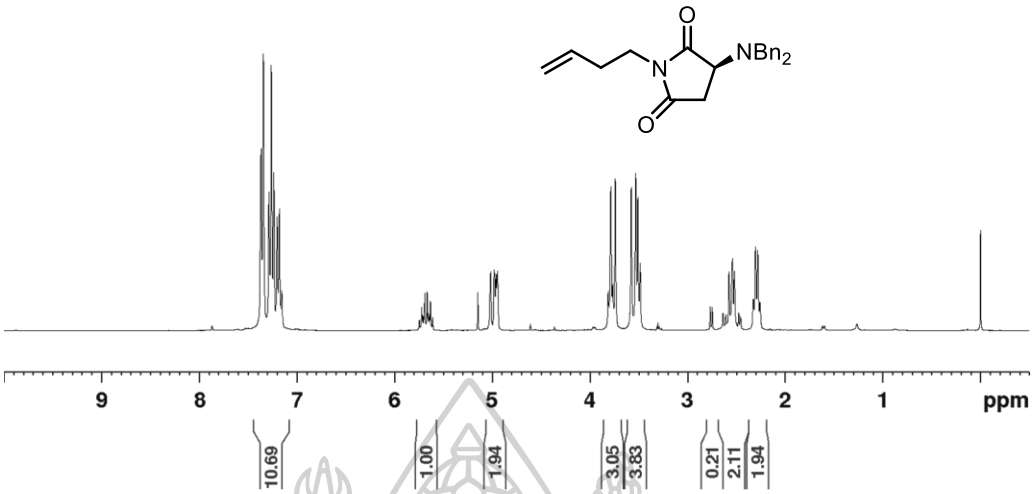

**$^{13}$C NMR of compound 1a**



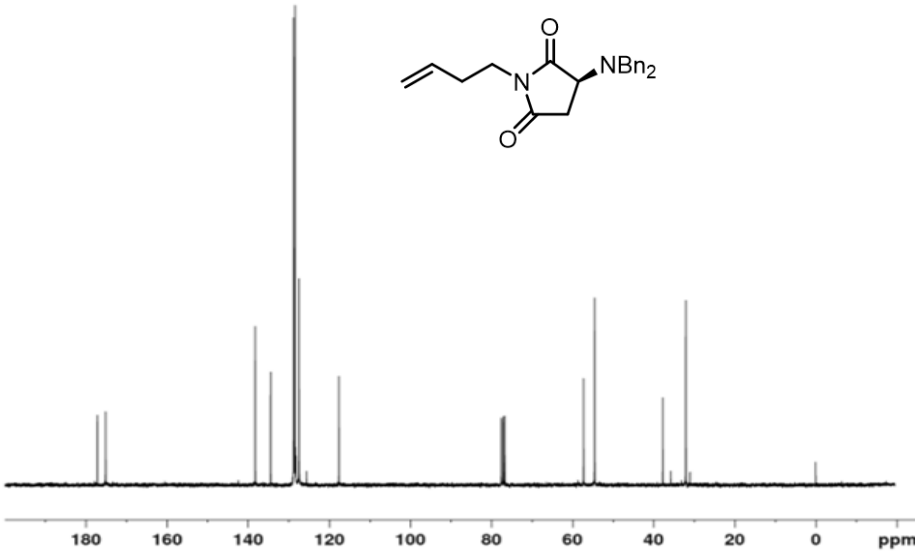

**$^{1}$H NMR of compound 2**




**$^{13}$C NMR of compound 2**

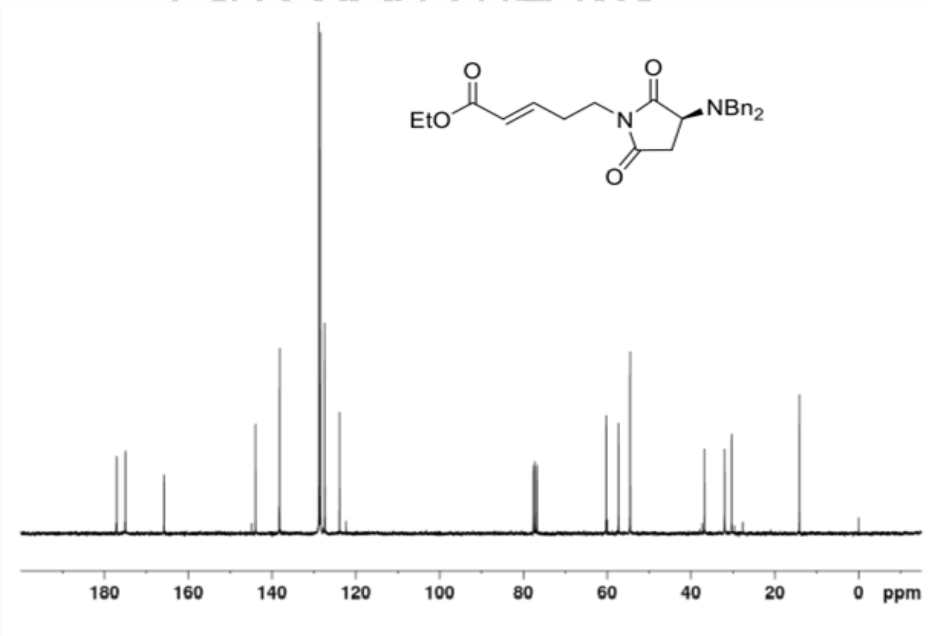



**$^{1}$H NMR of compound 4**

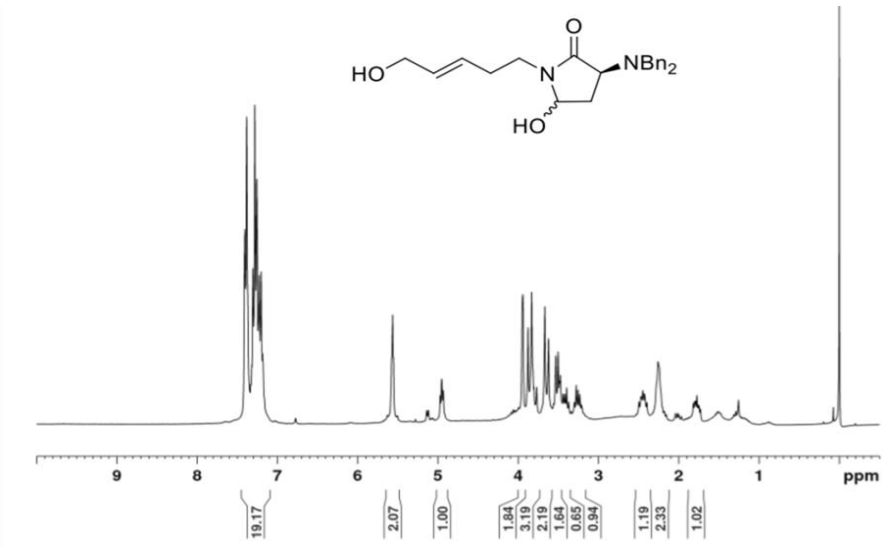



**$^{13}$C NMR of compound 4**

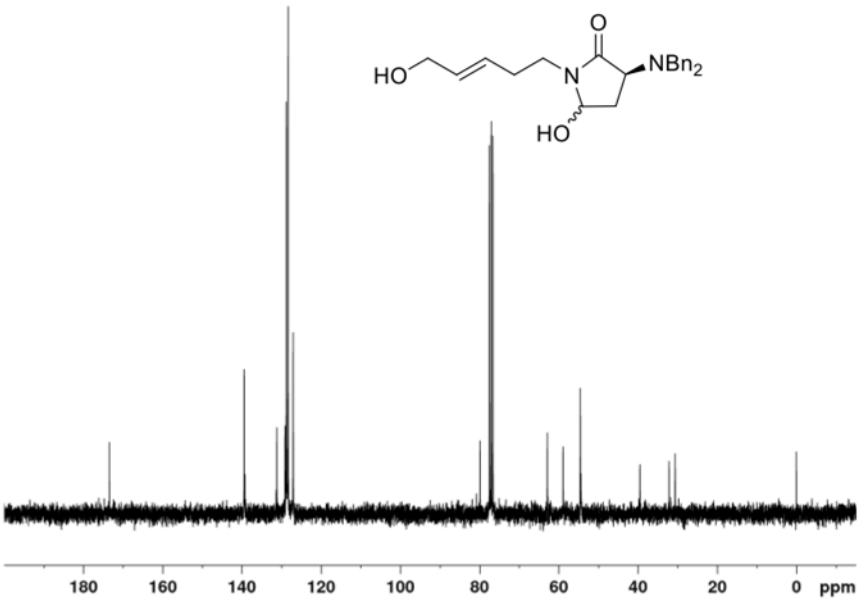

**$^{1}$H NMR of compound 6**



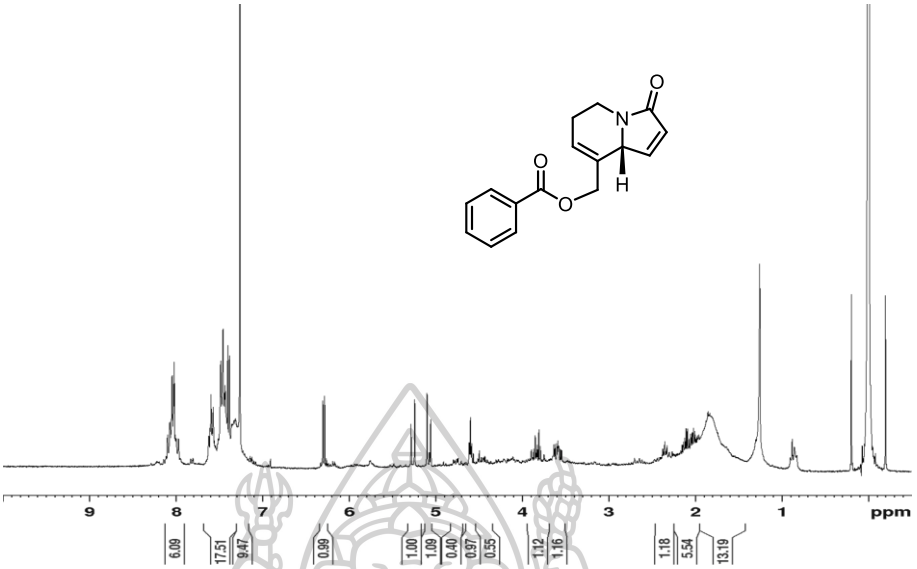

**$^{13}$C NMR of compound 6**



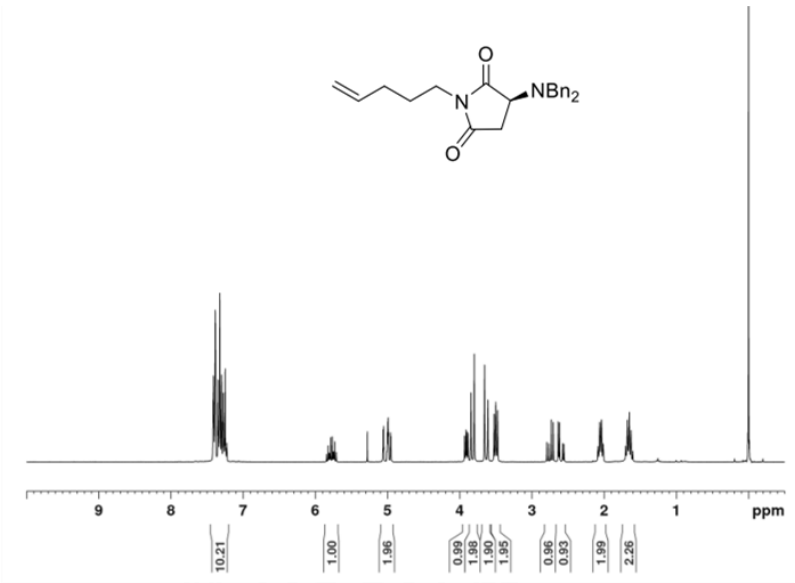

**$^{1}$H NMR of compound 7**



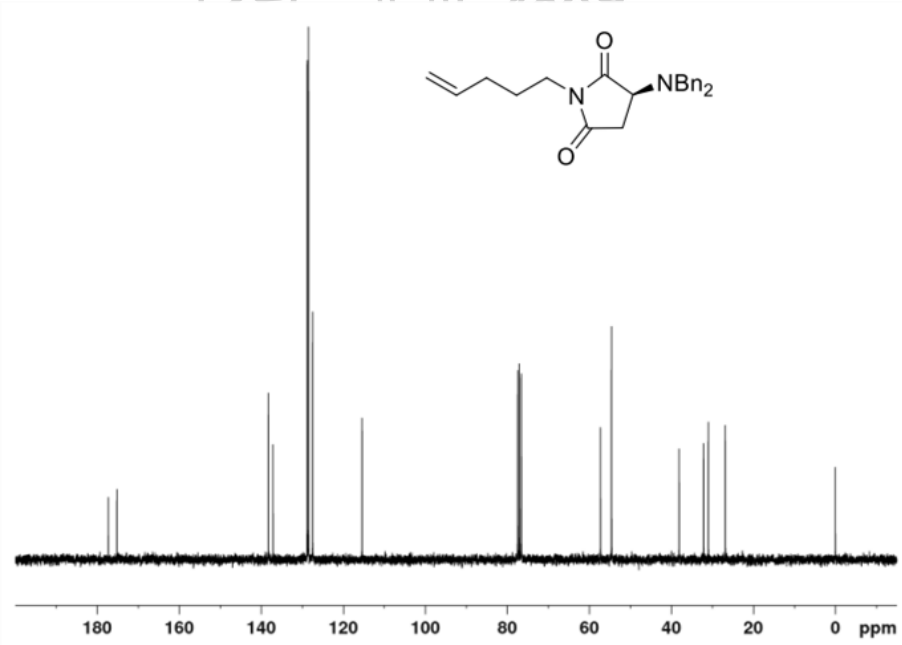

**$^{13}$C NMR of compound 7**



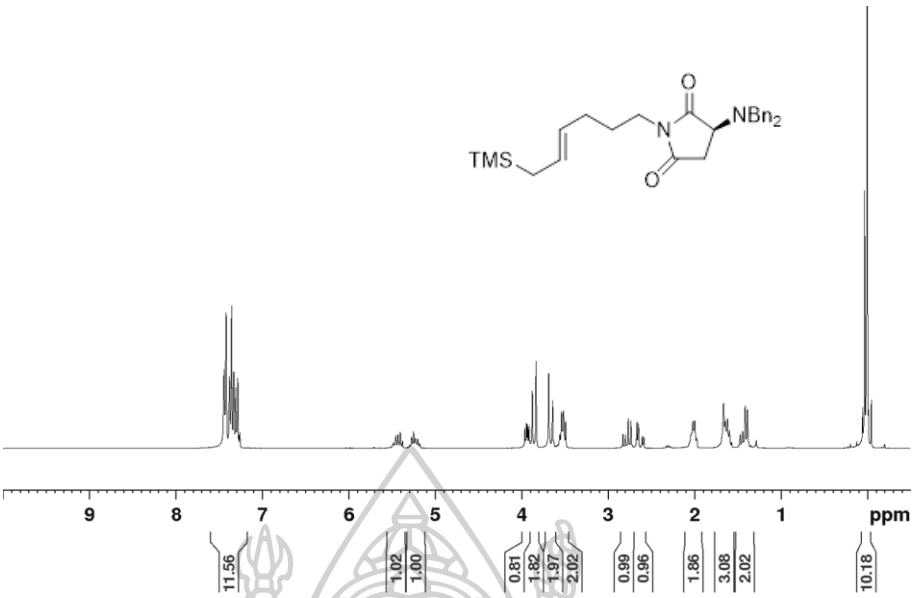

**$^{1}$H NMR of compound 22**



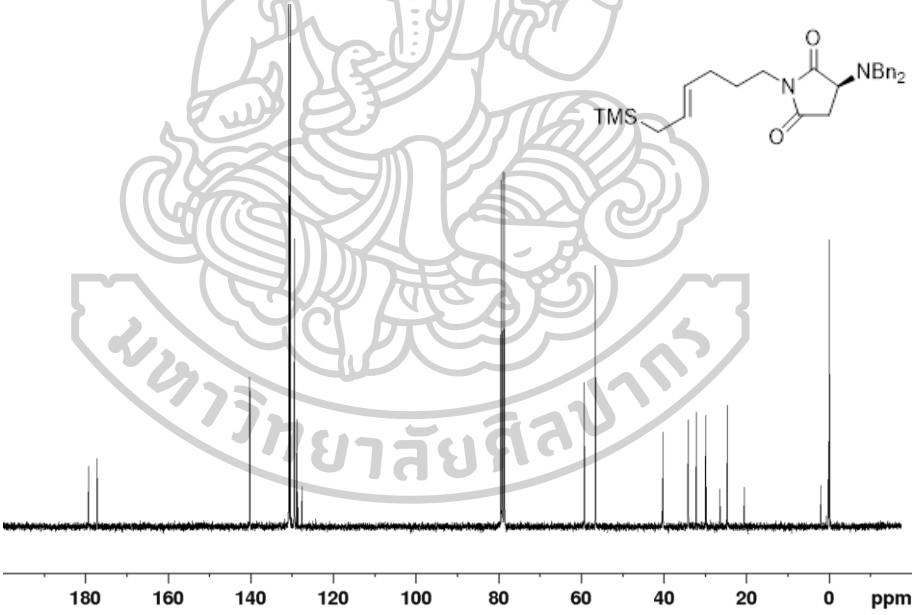

**$^{1}$H NMR of compound 8**



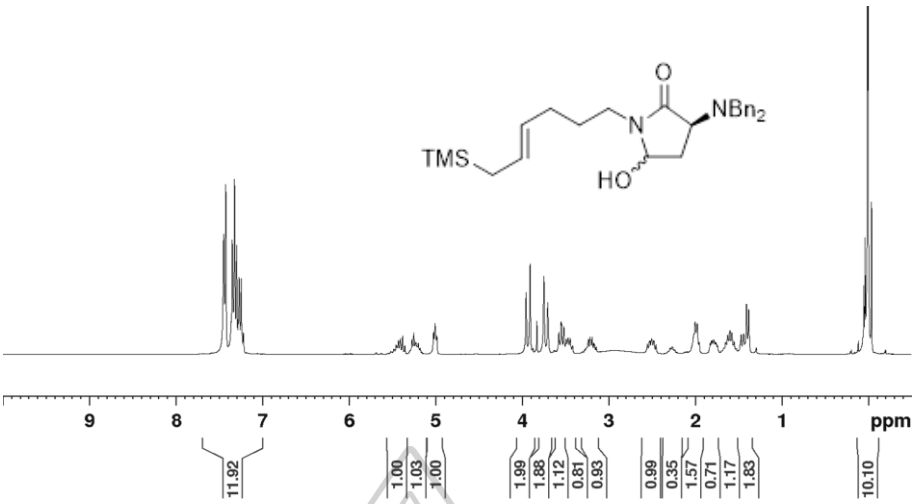

**$^{13}$C NMR of compound 8**



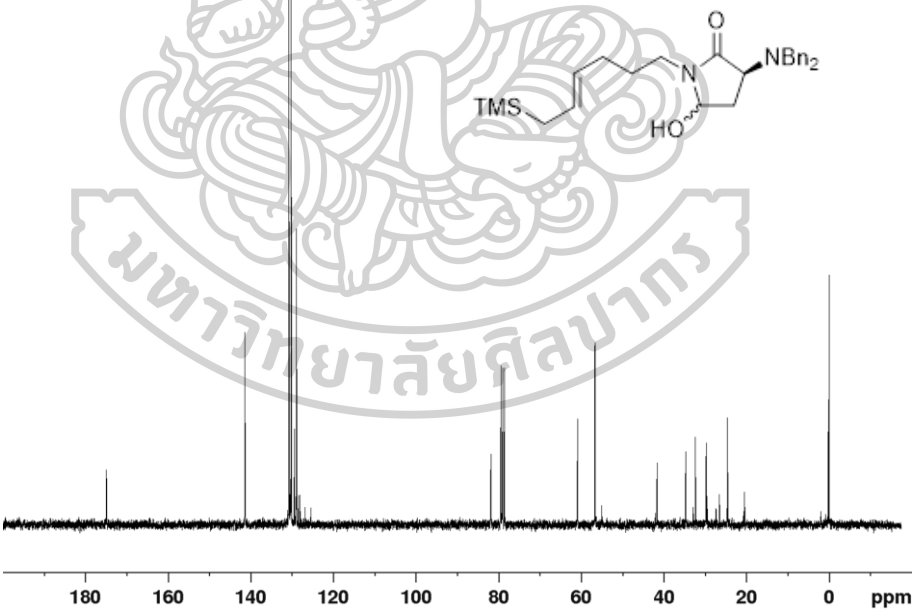

**$^{1}$H NMR of compound 9**



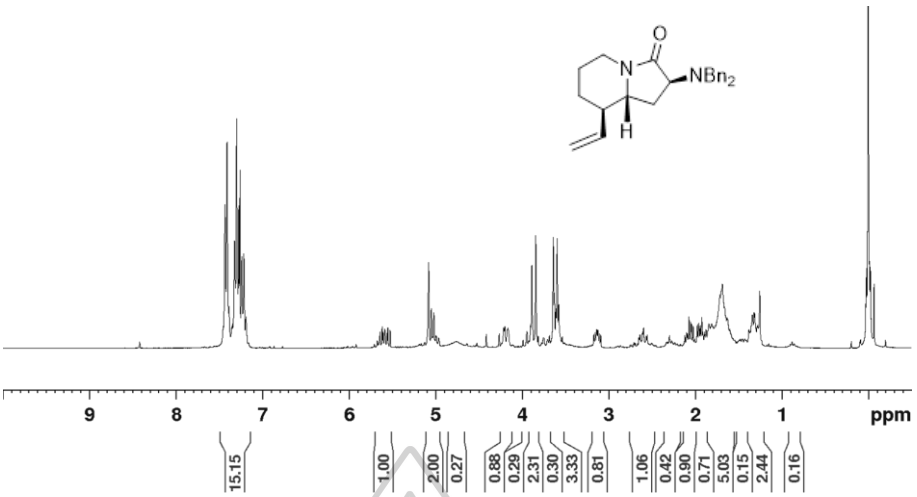

**$^{13}$C NMR of compound 9**



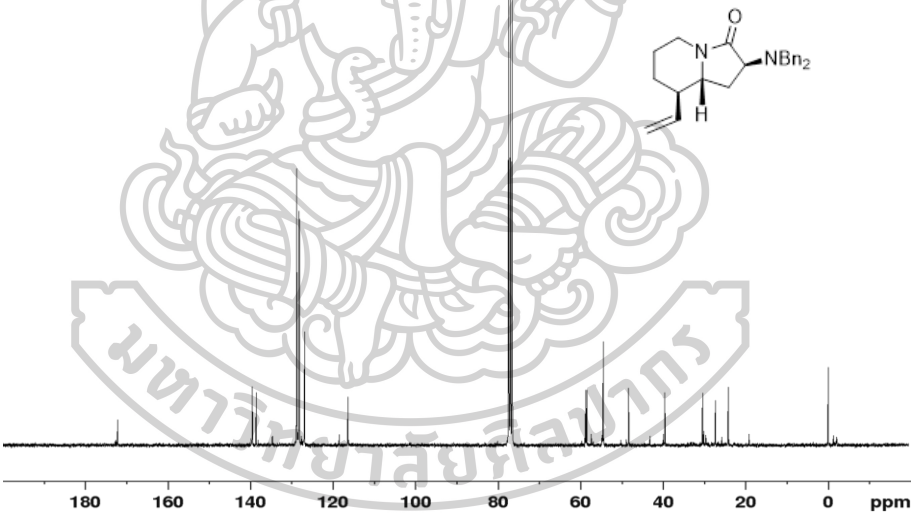

**$^{1}$H NMR of compound 10**



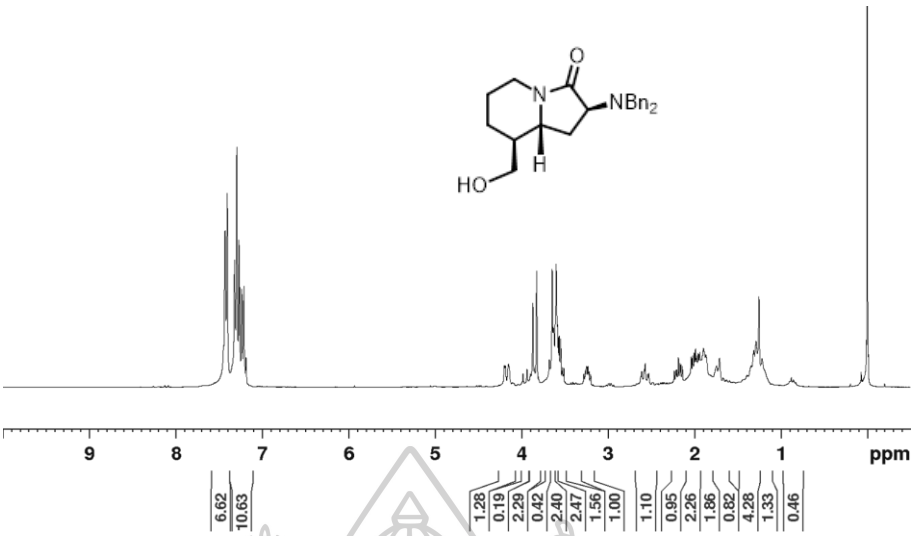

**$^{13}$C NMR of compound 10**



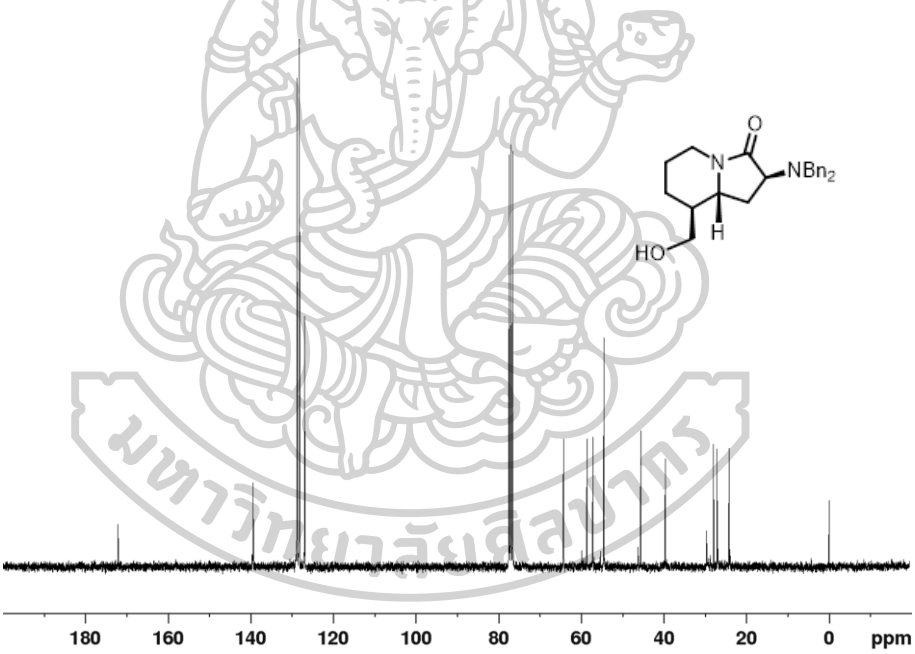

**$^{1}$H NMR of compound 11**




**$^{13}$C NMR of compound 11**




**$^{1}$H NMR of compound 12**




**$^{13}$C NMR of compound 12**

# VITA

| | |
|---|---|
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