SYNTHETIC STUDY OF INDOLIZIDINE ALKALOIDS WITH STRUCTURAL DIVERSITY: INDOLIZIDINE 167B, INDOLIZIDINE 209D, TABERTINGINE, TASHIROMINE AND SPIROINDOLIZIDINE-OXINDOLE

By
MR. Kittisak THAMMAPICHAI

A Thesis Submitted in Partial Fulfillment of the Requirements
for Master of Science (CHEMISTRY)
Department of CHEMISTRY
Graduate School, Silpakorn University
Academic Year 2020

การศึกษาการสังเคราะห์อินโดลิซิดีนอัลคาลอยด์ที่มีความหลากหลายทางโครงสร้าง Indolizidine 167B และ Indolizidine 209D Tabertinggine Tashiromine และ Spiroindolizidine-oxindole

โดย

นายกิตติศักดิ์ ธรรมาภิชัย

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรวิทยาศาสตรมหาบัณฑิต

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Title	Synthetic Study of Indolizidine Alkaloids with Structural Diversity: Indolizidine 167B, Indolizidine 209D, Tabertingine, Tashiromine and Spiroindolizidine-Oxindole
By	Kittisak THAMMAPICHAI
Field of Study	(CHEMISTRY)
Advisor	Assistant Professor Punlop Kuntiyong , Ph.D.

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MR. KITTISAK THAMMAPICHAI : SYNTHETIC STUDY OF INDOLIZIDINE ALKALOIDS WITH STRUCTURAL DIVERSITY: INDOLIZIDINE 167B, INDOLIZIDINE 209D, TABERTINGINE, TASHIROMINE AND SPIROINDOLIZIDINE-OXINDOLE THESIS ADVISOR : ASSISTANT PROFESSOR PUNLOP KUNTIYONG, Ph.D.

Indolizidine alkaloids are an important class of secondary metabolites with a variety of reported biological activities and structural diversity. For examples indolizidine 167B and indolizidine 209D have been reported to be non-competitive blockers for muscle type and ganglionic nicotinic receptors. Herein we present a synthetic approach toward 5-aryl and 5-alkylindolizidine frameworks using kinetic resolution of racemic secondary alcohol with a chiral succinimide derivative. The racemic secondary alcohols were obtained from reaction of allylmagnesium bromide and anisaldehyde or heptanal. *S*-dibenzylaminosuccinimide another starting material was synthesized from L-asparagine. *S*-dibenzylaminosuccinimide reacted with racemic secondary alcohols using Mitsunobu conditions to give the *N*-alkylsuccinimide and recovered unreacted alcohol. The *N*-alkylated product was obtained in highly diastereoselective fashion and this compound and the recovered unreacted secondary alcohol were found to be optically active. This result showed that kinetic resolution of the racemic secondary alcohol occurred during the Mitsunobu reaction. However, the desired product was obtained in low yield.

Tabertinggine, another indolizidine alkaloids which have a various biological activities was also study. Tabertinggine isolated from *Tabernaemontana Apocyanaceae* which are found in America, Africa and Asia. Herein we reported the synthetic of Tabertinggine and Tabertinggine anolog which have a aryl-analog instead of indole ring that provided a less compicated in synthetic route to study a reaction that could be provided for Tabertinggine synthesis. We used *N*-acyliminium ion cyclization as a key step to construct the tricyclic indolizidine core and tetracyclic indolizidine core for Tabertinggine analog and Tabertinggine respectively. *N*-dibenzylamino group in indolizidine core was removed using Cope elimination to provide a cyclic enamide that was removed a conjugate double bond by using Cordes reduction method. Alkylation with alkynyl halide provided ene-yne product as a key intermediate. An ene-yne metathesis was used as a key reaction to construct a bridged aza-bicyclo[3.2.1]octene which was an important part of Tabertinggine. Finally, desulfurnation followed by oxidative cleavage provided Tabertinggine.

This study has resulted in a synthesis of 5-arylindolizidine, 8-hydroxymethylindolizidine, benzoindolizidine, indoloindolizidine and spiroindolizidine-oxindole systems. In the synthetic study of Tabertinggine, an *in situ* benzoindolizidine ene-yne intermediate underwent unexpected cyclization to give the 2-azabicyclo[3.2.1]nonane found in Tabertingine.

ACKNOWLEDGEMENTS

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Additionally, I would like to take this opportunity to thank all the people who have supported me during my education. I would like to thank Department of Chemistry, Faculty of Science, Silpakorn University for supporting my education and laboratory equipment and I would like to express my appreciation to the all staff for their help as well.

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Finally, I would like to thank my beloved family and Kitsana Jancharoen for their love and supports throughout the period of studying in Master's degree.

Kittisak THAMMAPICHAI

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CHAPTER 1
INTRODUCTION

Background and Signification of the Research Problem

Alkaloids[1-3] are a type of compound from natural product which can be isolated from a large variety of organisms including animal sources, plants, bacteria and fungi. Alkaloids have been used for a wide range of pharmacology for example antimalarial (quinine), analgesic (morphine) and antiaddiction (Tabertinggine). 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. Exemplified classifications are shown in figure 1.

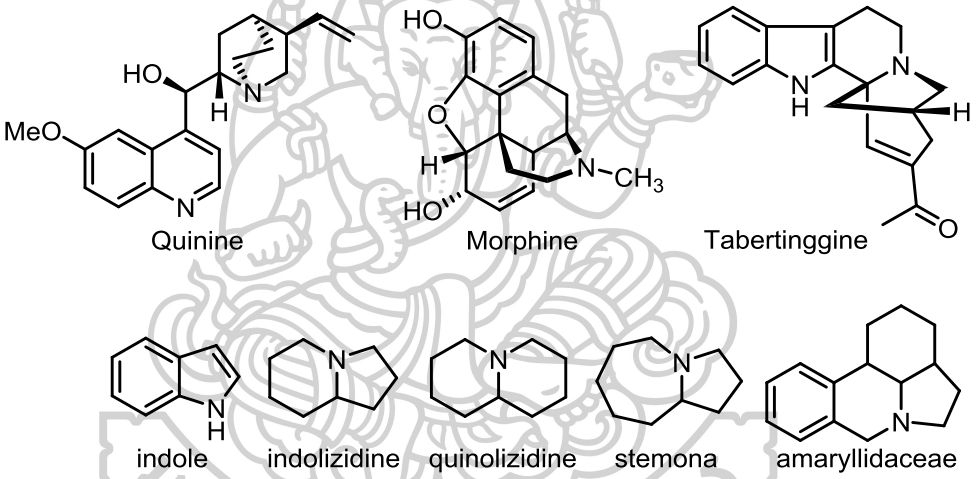
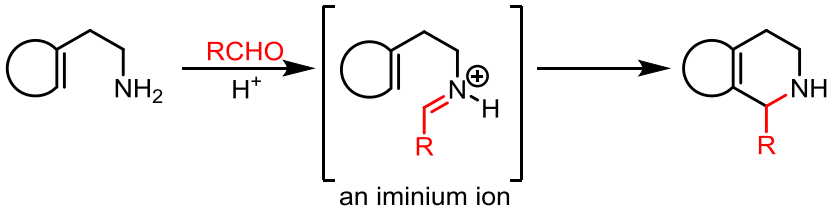


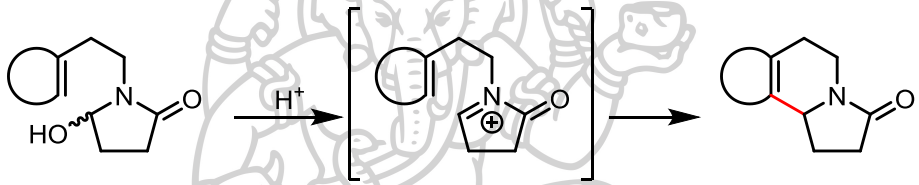
Figure 1 Examples of alkaloids and exemplified classifications

Due to their biological activities and variety of structural complexity, synthetic chemists have been intrigued and numerous synthetic studies and total syntheses of biologically active alkaloids and their analogues have been reported. Our research group has been interested in synthetic studies of quinolizidine and indolizidine alkaloids. Benzoquinolizidine can also be classified as tetrahydroisoquinoline derivative. One of the most common reactions for synthesis of tetrahydroisoquinoline is Pictet-Spengler reaction. It is a cyclization of an *in situ* iminium ion formed between an amine carrying an aromatic ring and an aldehyde that is usually catalyzed by an acid (scheme 1).



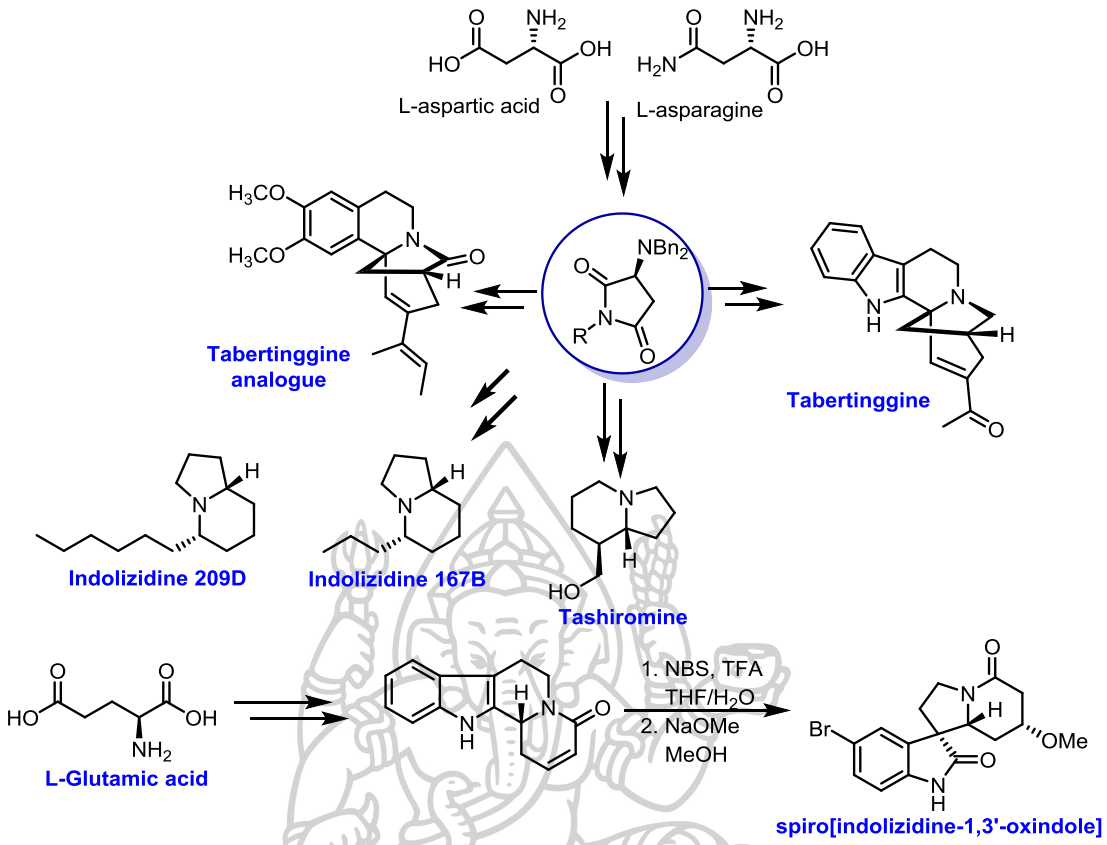
Scheme 1 Pictet-Spengler reaction

N-acyliminium ion cyclization[4-8] is a variation of Pictet-Spengler reaction which has been employed in organic synthesis. *N*-acyliminium ions are very reactive intermediates and can act as highly electron-deficient electrophiles toward weak nucleophiles. It is an especially useful method for intramolecular cyclization. Besides aromatic ring, alkene can also act as nucleophile in this reaction. When aldehyde and acyl moiety are in the same molecule this reaction can deliver poly cyclic systems such as benzoquinolizidine and benzoindolizidine (scheme 2).



Scheme 2 *N*-acyliminium ion cyclization

In this research, we will discuss synthetic studies of a variety of indolizidine alkaloids with different level of structural complexities. The key reaction of the syntheses is *N*-acyliminium ion cyclization using L-aspartic acid, L-asparagine or L-glutamic acid as the starting material. The targets include tabertinggine, indolizidines 167B and 209D, tashiromine and spiro[indolizidine-oxindole] (scheme 3). Indolizidine167B, Indolizidine 209D are simple non-aromatic indolizidine alkaloids with C5 substituent. Tabertinggine is a bridged indoloindolizidine alkaloid fused with indole ring. We also investigate a synthetic route toward its benzene analog. In our research plan for tabertinggine and its analog ene-yne metathesis[9] is another key reaction. Tashiromine is another simple non-aromatic indolizidine alkaloid with C8 substituent. Finally, spiro[indolizidine-oxindole] is envisioned to be synthesized from indoloquinolizidinone via oxidative rearrangement.



Scheme 3 Target molecule of this research

Objectives of Research

1. To study a synthetic methodology of tabertinggine

2. To study a synthetic methodology of tabertinggine analog

3. To study and develop the *N*-acyliminium ion cyclization and the ene-yne metathesis

4. To study a synthetic methodology of indolizidine 167B

5. To study a synthetic methodology of indolizidine 209D

6. To study and develop the Mitsunobu reaction and Tsuji-Trost allylation

7. To study a synthetic methodology of Tashiromine

8. To study a synthetic methodology of Spiroindolizidine-oxindole

CHAPTER 2
LITERATURE REVIEW

Tabertinggine

Tabertinggine is one of the members of indolizidine alkaloids. It was first isolated by Kam and co-workers in 2013 from plants in the genus *Tabernaemontana (Apocynaceae)*[10] which are found in America, Africa and Asia. Moreover, tabertinggine show a wild range of pharmacological effects such as antiaddiction, antifungal or antilipase, antiHIV-1, anticholinesterasic and leishmanicide activities. The structure consists of five linked rings containing two stereogenic centers on indolizidine core and fused with indole ring and bridged aza-bicyclo[3.2.1]octene.

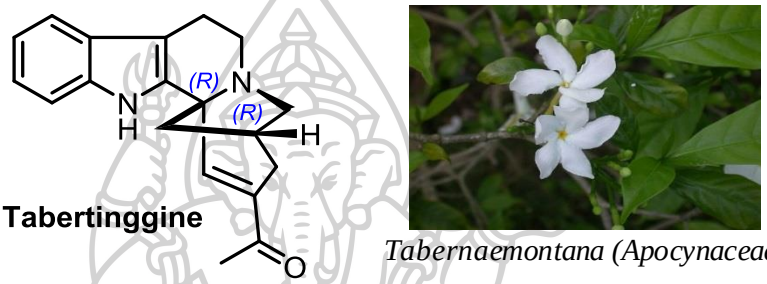
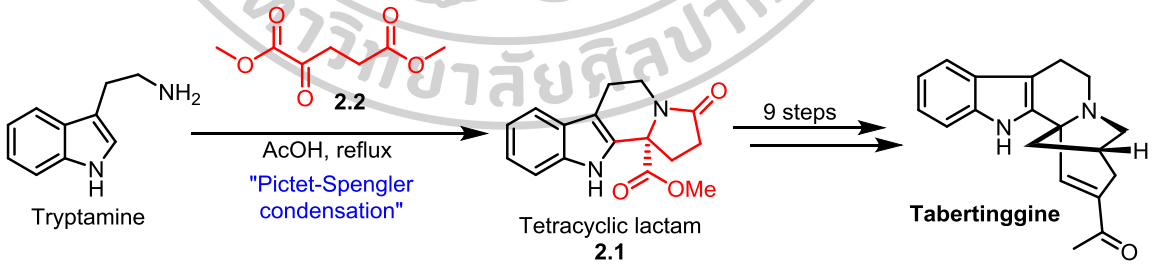


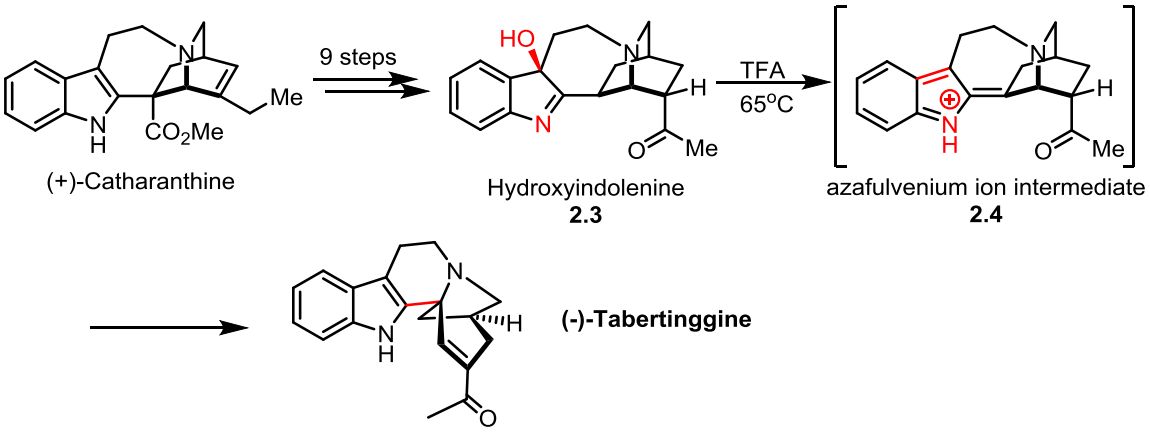
Figure 2 Structurre of tabertinggine and *Tabernaemontana (Apocynaceae)*

She[11] group was reported a total synthesis of tabertinggine. In 2016, they reported a total synthesis of tabertinggine. A key step for this synthesis was a one-pot Pictet-Spengler condensation between tryptamine and keto-diester **2.2** to provide tetracyclic lactam **2.1**. After that tetracyclic lactam **2.1** was converted to tabertinggine in 9 steps (scheme 4).



Scheme 4 Synthesis of tabertinggine by She and coworkers

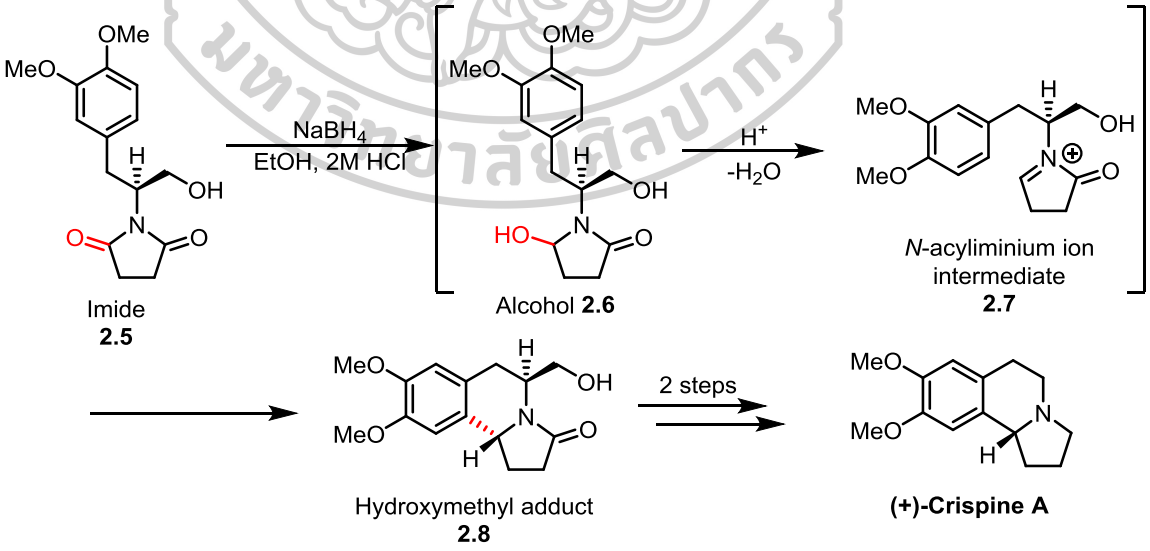
In 2019, Han[12] and coworkers reported the first semi-synthesis of (-)-tabertinggine. The synthesis was completed in 10 steps and starting from (+)-catharanthine. A key step for this synthesis was a rearrangement of hydroxyindolenine **2.3** through the azafulvenium ion intermediate **2.4** under acid condition in the last step to give (-)-tabertinggine (scheme 5).



Scheme 5 Synthesis of (-)-tabertinggine by Han and coworkers

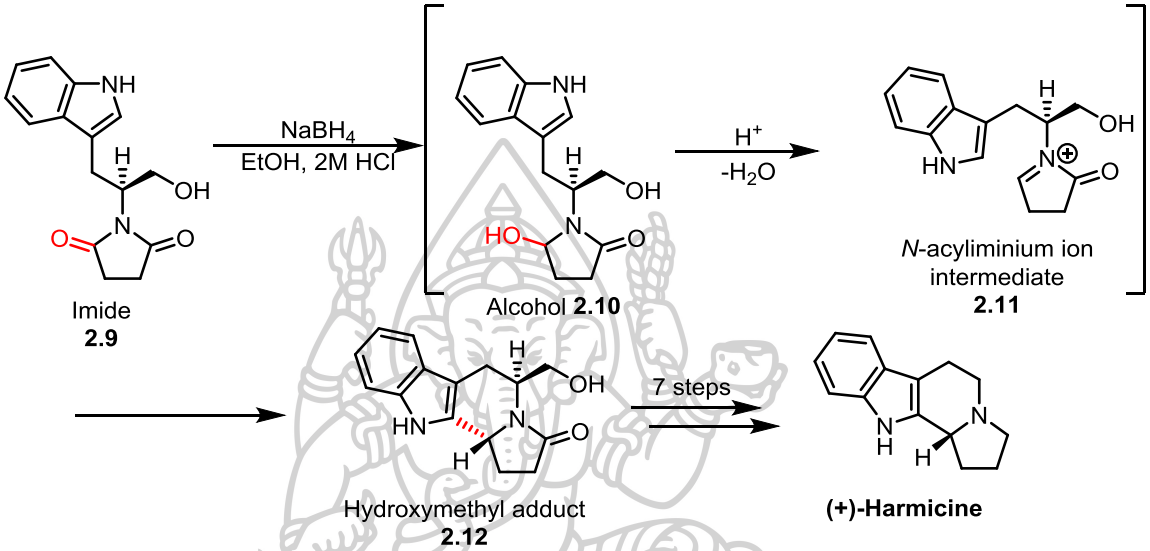
***N*-acyliminium ion cyclization**

N-acyliminium ion cyclization is useful in a few of the syntheses that we have seen before. Additional selected syntheses of the natural and non-natural analogues of alkaloids via *N*-acyliminium ion cyclization will be discussed. Asymmetric synthesis of the anti-tumor alkaloid (+)-crispine A via highly diastereoselective *N*-acyliminium ion cyclization was reported by Allin[13] and coworkers in 2007. The synthesis started with reduction of imide **2.5** using $NaBH_4$ and subsequent acid-catalysed *N*-acyliminium ion cyclization to give hydroxymethyl adduct **2.8** in good yield. A new stereocenter was controlled by the hydroxymethyl group with high stereoselectivity. Finally, hydroxymethyl group and carbonyl group was removed in 2 steps to afford (+)-crispine A in moderate yield with 95%ee (scheme 6).



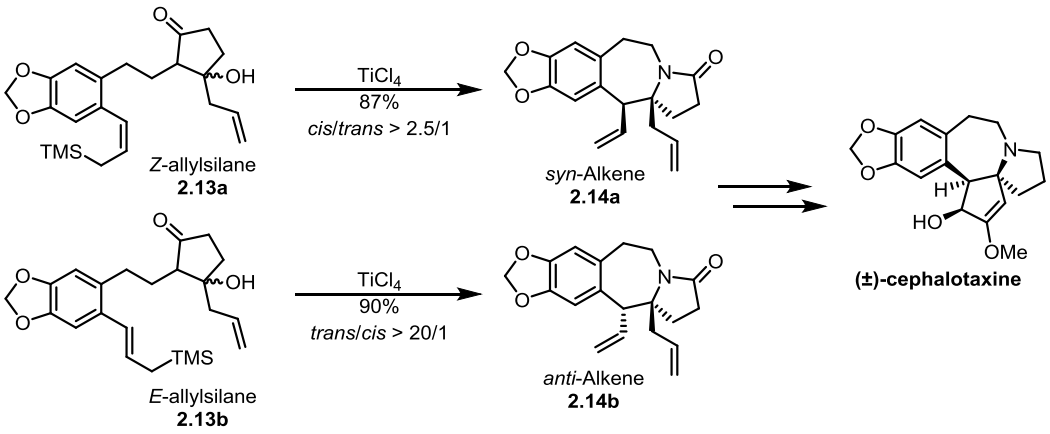
Scheme 6 Synthesis of (+)-crispine A by Allin and coworkers

In the same year, they reported asymmetric synthesis of (+)-harmicine[14] via a highly diastereoselective *N*-acyliminium ion cyclization reaction. The synthesis started with reduction of imide **2.9** using $NaBH_4$ and subsequent acid-catalysed *N*-acyliminium ion cyclization to give hydroxymethyl adduct **2.12** in good yield. A new stereocenter was controlled by the hydroxymethyl group with high stereoselectivity like a synthesis of (+)-crispine A. Then, it was removed in 7 steps to furnish (+)-harmicine (scheme 7).



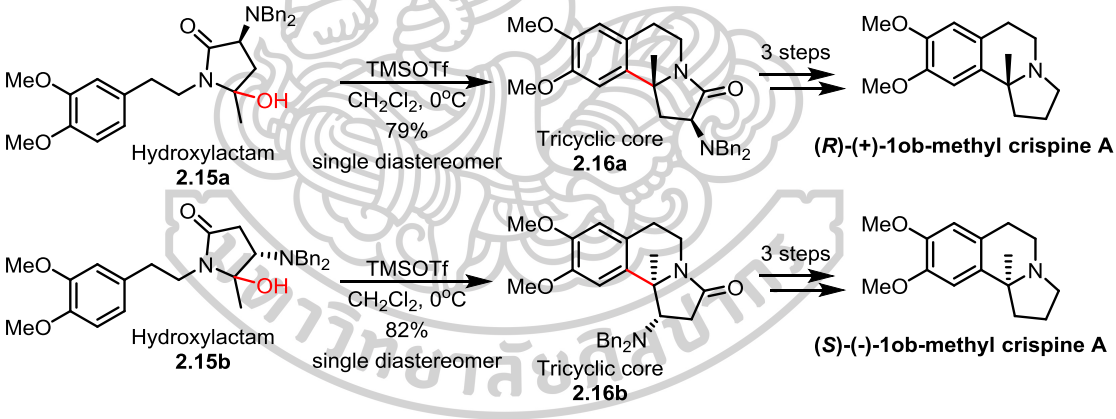
Scheme 7 Synthesis of (+)-harmicine by Allin and coworkers

As mention before, alkene can act as nucleophile in order to generated a new C-C bond via *N*-acyliminium ion cyclization and stereoselectivity dependence on the stereoelectronic effect of the isomer of alkene. An interesting example is a formal synthesis of (±)-cephalotaxine which was reported by Hong[15] and coworkers in 2015. Both isomers of alkene were treated with $TiCl_4$. *Z*-allylsilane **2.13a** gave *syn*-alkene **2.14a** with lower stereoselectivity than the product from *E*-allylsilane **2.13b** which gave anti-alkene **2.14b**. Then, both diastereomers arising from the cyclization were merged into the formal synthesis of (±)-cephalotaxine (scheme 8).



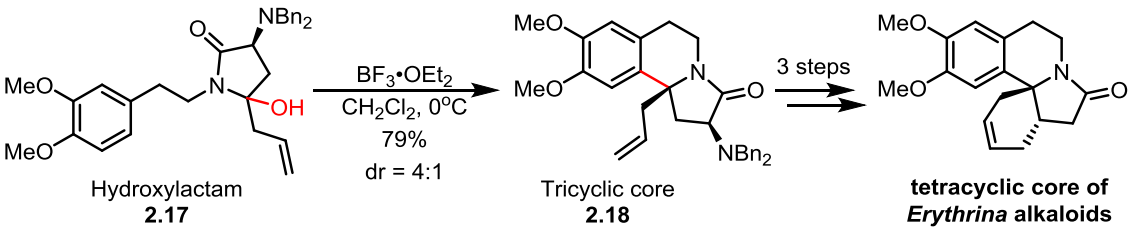
Scheme 8 Formal synthesis of (±)-cephalotaxine by Hong and coworkers

The synthesis of crispine A analogues was reported by Kuntiyong[16] and coworkers. Hydroxylactam **2.15a** and **2.15b** derived from L-aspartic acid in 4 steps was treated with TMSOTf to generated *N*-acyliminium ion which cyclized to provide tricyclic core **2.16a** and **2.16b** respectively. A new stereocenters of both tricyclic core were controlled by the *N*,*N*-dibenzylamino group which was removed using Cope-elimination in the next step followed by reduction and hydrogenation to give (*R*)-(+)-10b-methyl crispine A and (*S*)-(-)-10b-methyl crispine A as shown below (scheme 9).



Scheme 9 Synthesis of crispine A analogues by Kuntiyong and coworkers

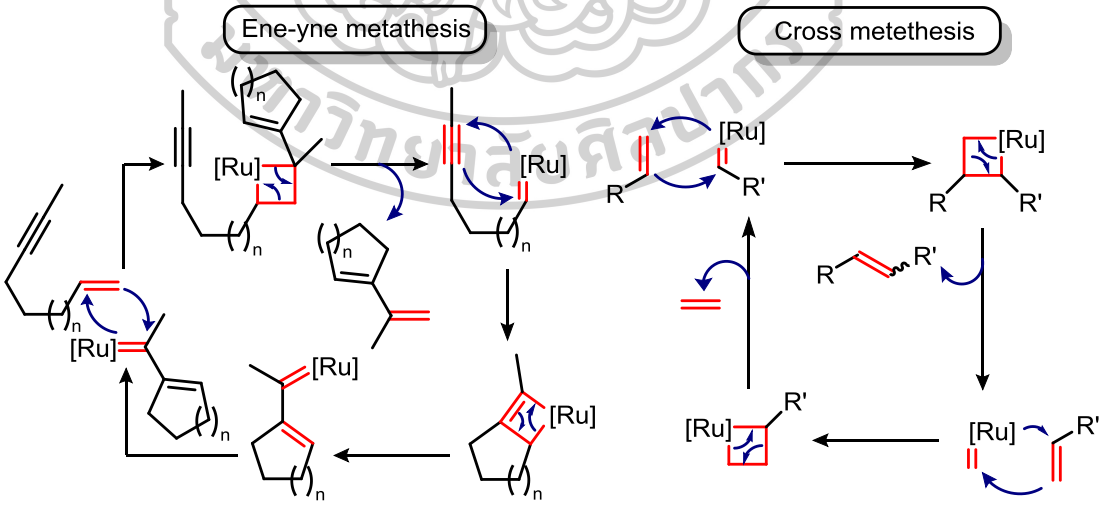
Moreover, they also reported the synthesis of tetracyclic core of *Erythrina* alkaloids. *N*-acyliminium ion cyclization of hydroxylactam **2.17** using $BF_3 \cdot OEt_2$ gave tricyclic core **2.18** in good yield with dr = 4:1. Finally, it was converted to tetracyclic core of *Erythrina* alkaloids in 3 steps via Cope elimination, Michael addition and ring closing metathesis (scheme 10).



Scheme 10 Synthesis of tetracyclic core of Erythrina alkaloids by Kuntiyong and coworkers

Ene-yne metathesis

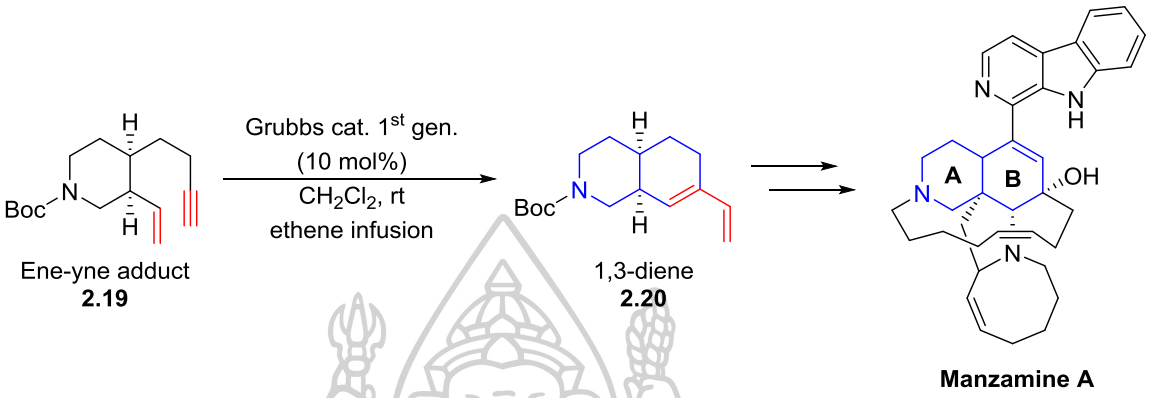
Ene-yne metathesis is a ruthenium-catalyzed bond reorganization reaction between alkynes and alkenes to produce 1,3-dienes. First, Alkene reacted with ruthenium catalyst to give a ruthenium carbene complex, then ruthenium carbene complex undergo with 2+2 cycloaddition process followed by cycloreversion of corresponding cyclobutene to give ruthenium conjugate carbene complex. Another alkene was attacked by ruthenium conjugate carbene complex to give cyclobutane and followed by cycloreversion to give 1,3-diene product and ruthenium carbene complex can undergo to the next catalytic cycle. As mention previously, cross metathesis was also a catalyzed ruthenium carbenoids to produce cross coupling product via metallacyclobutane intermediate It has been used in both intramolecular and intermolecular applications. Ene-yne metathesis bears a mechanistic kinship to alkene metathesis. The ene-yne bond reorganization is atom economical and is driven by the enthalpic stability of the conjugated 1,3-diene produced. However, stereoselectivity is often low in intermolecular cases but can be controlled in intramolecular cases.



Scheme 11 Mechanism of ene-yne meathesis

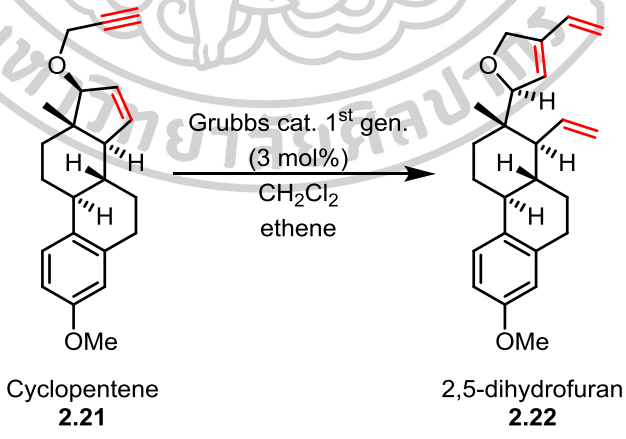
For example, in 2001 a concise enantioselective synthesis of AB-ring system of the manzamine alkaloids was reported by Clark[17] and coworkers. This synthesis

was prepared from (-)-quinine in 6 steps to give ene-yne adduct **2.19**. Intramolecular ene-yne metathesis using Grubbs 1st generation catalyst under ethylene infusion provided 1,3-diene **2.20** which was transform to AB-ring of manzamine A in 3 steps (scheme 12).



Scheme 12 Synthesis of AB-ring of manzamine A by Clark and coworkers

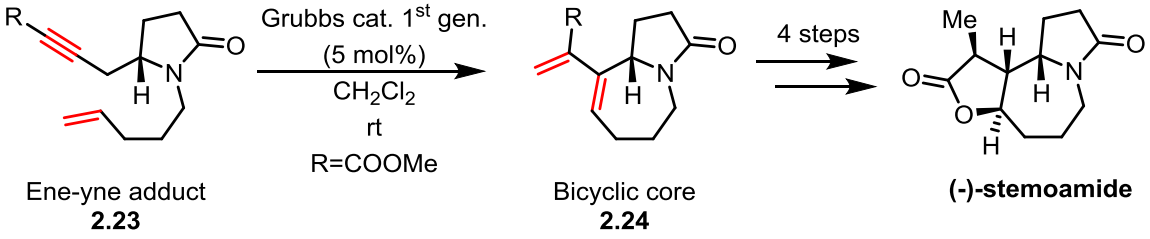
Moreover, ene-yne metathesis not only a ring closing metathesis process it also provides a ring opening metathesis process too. In 2002, Blechert[18] and coworkers reported a study of a rearrangement of steroid using ene-yne metathesis. The first procedure is a ring opening metathesis of cyclopentane **2.21** by treated with Grubbs 1st generation catalyst followed by ene-yne metathesis in order to generated new 2,5-dihydrofuran ring **2.22** (scheme 13).



Scheme 13 Rearrangement study of steroids by Blechert and coworkers

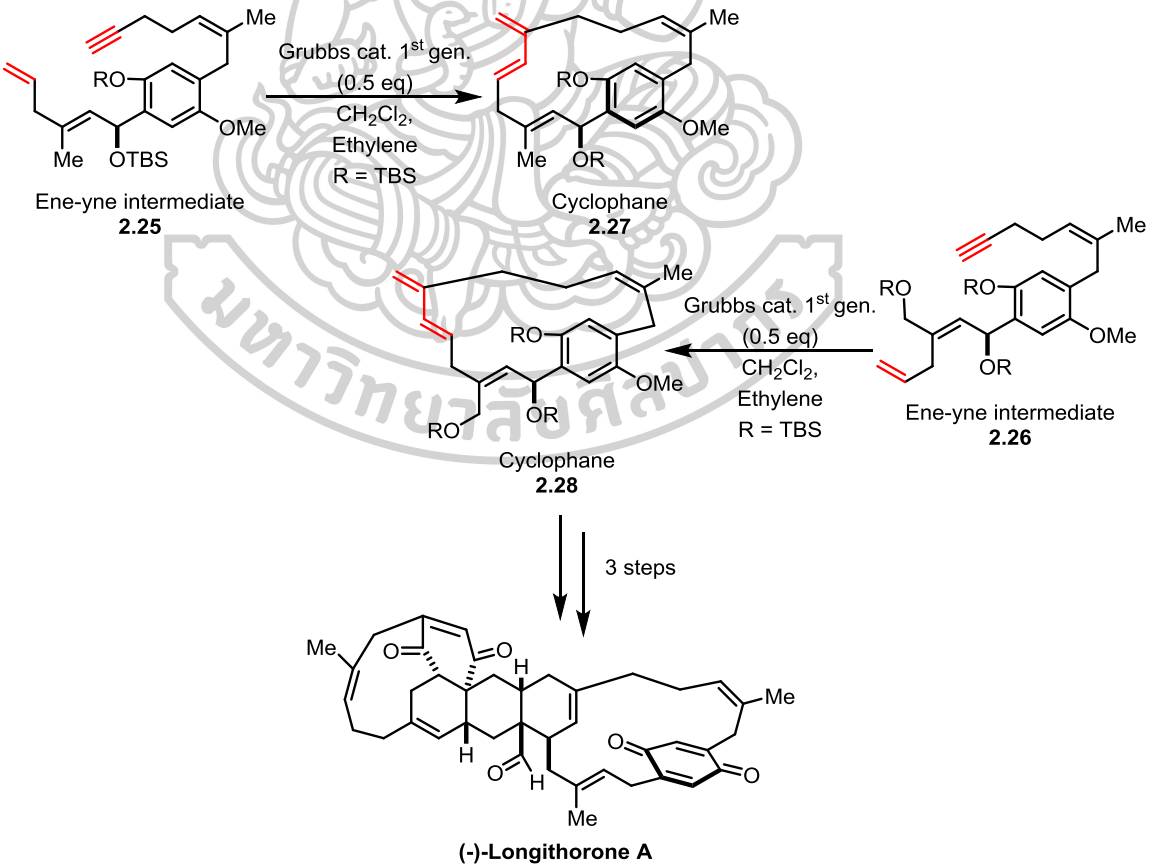
The first total synthesis of (-)-stemoamide which was reported by Mori[19] and coworkers in 1996 was also achieved using ring-closing ene-yne metathesis as a key reaction in the formation of a bicyclic core of *stemona* alkaloids. The starting ene-yne adduct **2.23** was prepared from (-)-pyroglutamic acid in 6 steps. Ene-yne

metathesis of adduct **2.23** by using Grubb 1st generation catalyst gave bicyclic core **2.24**. they converted bicyclic core **2.24** to (-)-stemoamide in 4 steps (scheme 14).



Scheme 14 Synthesis of (-)-stemoamide by Mori and coworkers

In 2002, Shair[20] and coworkers reported biomimetic synthesis of (-)-longithorone A which was a macrocyclic natural product. They used ene-yne metathesis as a key reaction to generated a two cyclophane compounds (**2.27** and **2.28**) which were connected to each other to provide cyclohexene intermediate by using an intermolecular Diels-Alder reaction. Finally, they converted cyclohexene intermediate to (-)-longithorone A in 2 steps in good yield (scheme 15).



Scheme 15 Synthesis of (-)-longithorone A by Shair and coworkers

Indolizidine 167B & Indolizidine 209D

Indolizidine 167B is an indolizidine alkaloids containing 2 stereocenters with propyl side chain. Indolizidine 167B was isolated from skin of "poison dart frog" *Dendrobates auratus*[21], caught on Isla de Colón, Panama. It was also obtained from *Phyllobates terribilis*[22] which was caught on the Pacific coast of Colombia.

Indolizidine 209D is an indolizidine alkaloids containing 2 stereocenters like indolizidine 167B but it different at alkyl side chain which was a *n*-hexyl group. Indolizidine 209D was isolated from "Harlequin poison dart frog" *Oophaga histrionica[23],* which was found on the El Chocó region of western Colombia.

Both of indolizidine alkaloids had a wild range of neurological activities. They were found to be noncompetitive blockers of the neuromuscular transmission receptor and nicotinic acetylcholine receptors, which were allowed these compounds to be promising drug candidates for epilepsy, schizophrenia, Parkinson disease and Alzheimer disease.

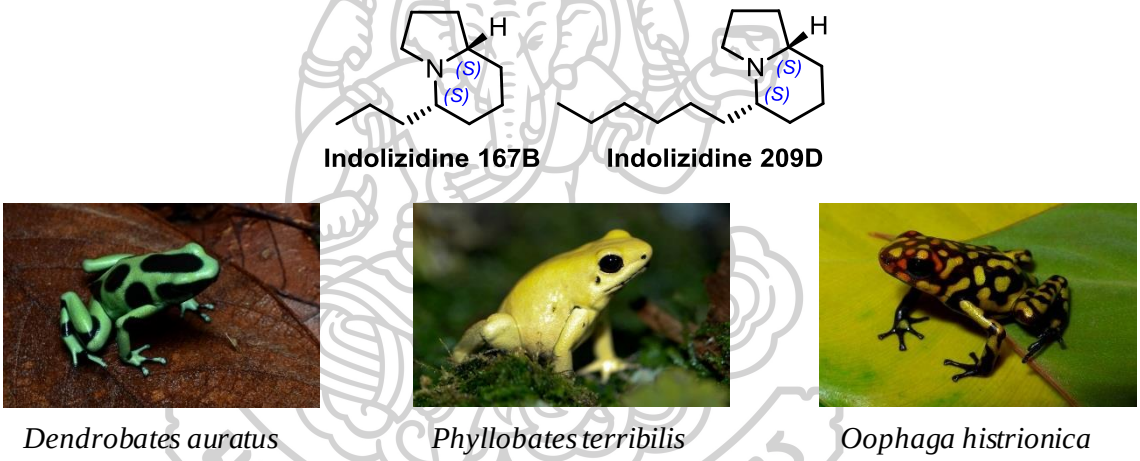
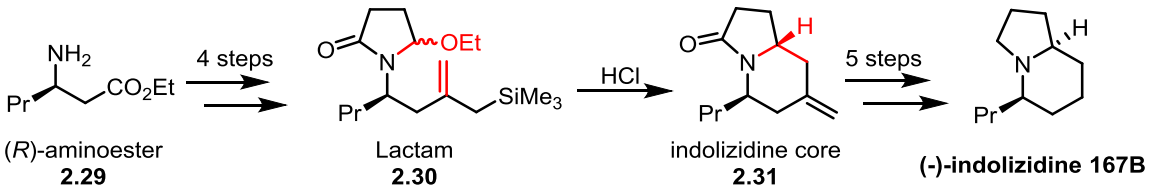


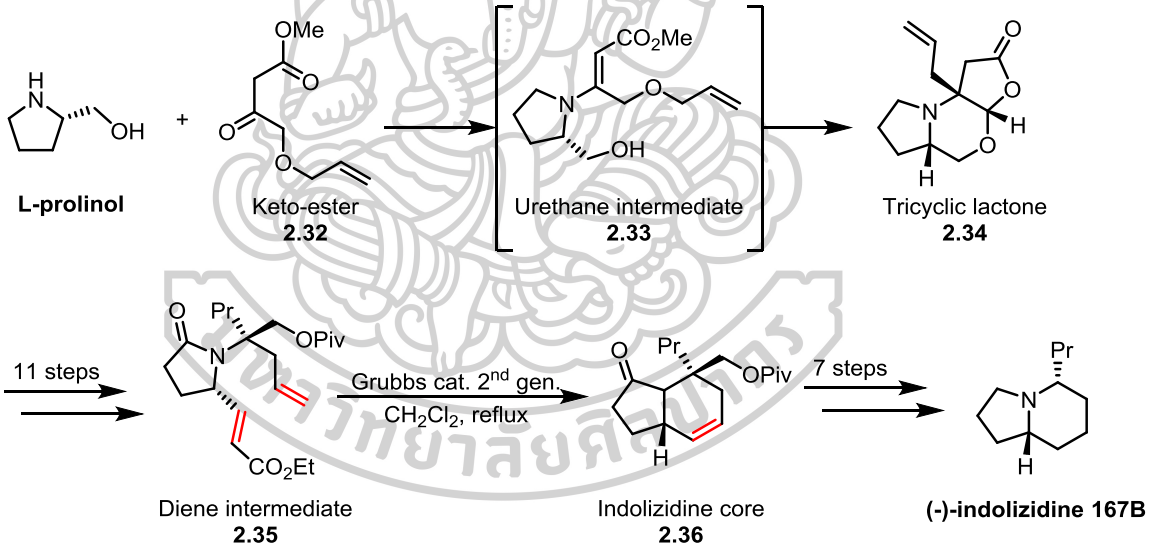
Figure 3 Structure of indolizidine 167B indolizidine 209D and poison dart frog

Remuson[24] and coworkers reported enantioselective synthesis of (-)-indolizidine 167B by using *N*-acyliminium ion cyclization as a key reaction to construct indolizidine core. This synthesis started with (*R*)-aminoester **2.29** converted to lactam **2.30** in 4 steps. Then, *N*-acyliminium ion cyclization of lactam **2.30** provided indolizidine core **2.31**. A new stereocenter of indolizidine core **2.31** was controlled by chiral propyl group. An indolizidine core **2.31** was converted to (-)-indolizidine 167B in 5 steps (scheme 16).



Scheme 16 Synthesis of (-)-indolizidine 167B by Remuson and coworkers

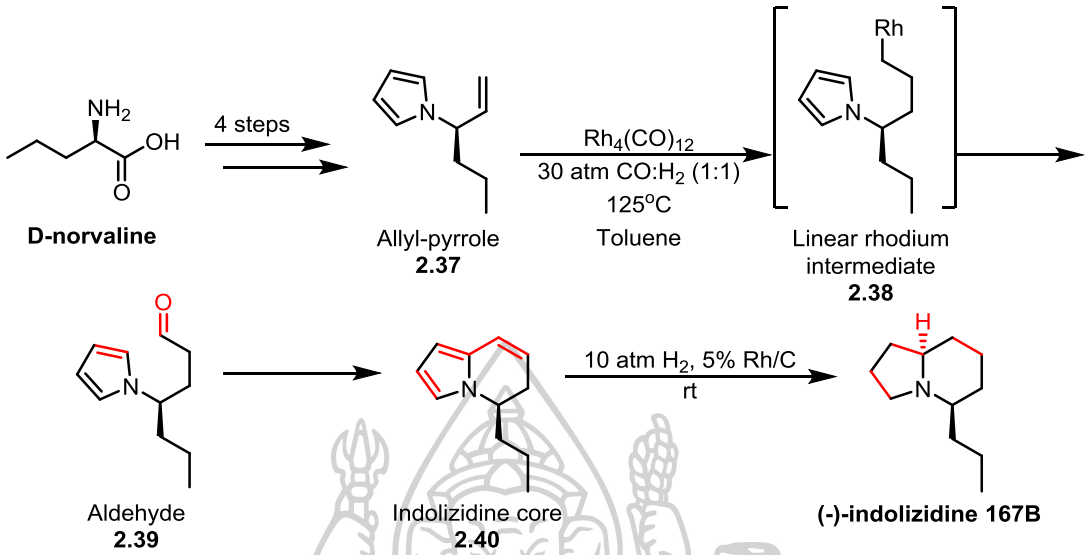
In 2015, Li[25] and coworkers reported a total synthesis of (-)-indolizidine 167B by using tricyclic lactone as a chiral starting material. An indolizidine core was constructed by using ring-closing metathesis as a key step. Tricyclic lactone **2.34**, a chiral starting material was obtained from the [3,3]-sigmatropic rearrangement of urethane intermediate **2.33**, which was condensed by L-prolinol and keto-ester **2.32**. Tricyclic lactone **2.34** was converted to diene intermediate **2.35** in 11 steps synthesis and ring-closing metathesis of the corresponding diene intermediate **2.35** provided indolizidine core **2.36**. (-)-indolizidine 167B synthesis was accomplished in 7 steps from indolizidine core **2.36** (scheme 17).



Scheme 17 Synthesis of (-)-indolizidine 167B by Li and coworkers

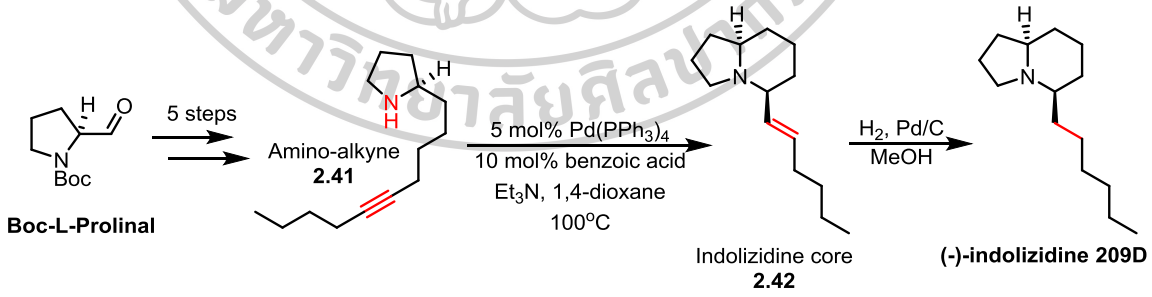
Settambolo[26] and coworkers reported a 3 steps synthesis of (-)-indolizidine 167B in 2008. A chiral starting material allyl-pyrrole **2.37** was prepared from D-norvaline in 4 steps. They used domino hydroformylation cyclization reactions as a key reaction to give (-)-indolizidine 167B. The rhodium-catalyzed hydroformylation of olefins is an important industrial tool for the production aldehydes. Metal insertion of rhodium to olefin under 30 atm of $CO:H_2$ 1:1 provided linear rhodium intermediate **2.38** which was oxidized under hydroformylation process to give aldehyde **2.39**. Subsequent cyclization of aldehyde **2.39** provided indolizidine core **2.40** which was

converted to (-)-indolizidine 167B by using hydrogenation in high pressure with rhodium catalyst with high ee (scheme 18).



Scheme 18 Synthesis of (-)-indolizidine 167B by Settambolo and coworkers

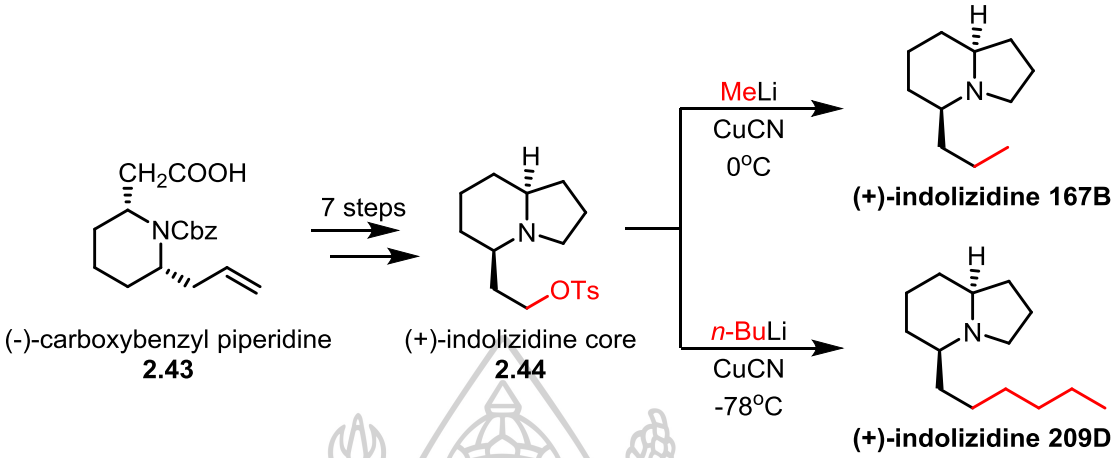
In 2005, Yamamoto[27] and coworkers reported a synthesis of (-)-indolizidine 209D by using intramolecular hydroamination of alkynes as a key reaction in order to generated indolizidine core. This synthesis started with the commercially available aldehyde which was converted to amino alkyne **2.41** in 5 steps. Intramolecular hydroamination of alkyne with palladium catalyst gave indolizidine core **2.42**. Hydrogenation of the corresponding indolizidine core **2.42** provided (-)-indolizidine 209D (scheme 19).



Scheme 19 Synthesis of (-)-indolizidine 209D by Yamamoto and coworkers

The latest work was reported in 2017, Chiou[28] and coworkers reported a synthesis of (+)-indolizidine 167B and (+)-indolizidine 209D from an (+)-indolizidine core **2.44** as a key intermediate. This synthesis started with (-)-carboxybenzyl piperidine **2.43** converted to (+)-indolizidine core **2.44** in 7 steps. Nucleophilic

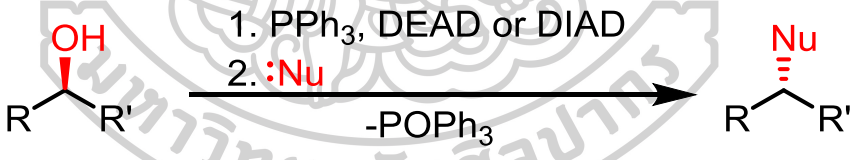
substitution with different nucleophile such as MeLi and *n*-BuLi provided (+)-indolizidine 167B and (+)-indolizidine 209D respectively (scheme 20).



Scheme 20 Synthesis of (+)-indolizidine 167B and (+)-indolizidine 209D by Chiou and coworkers

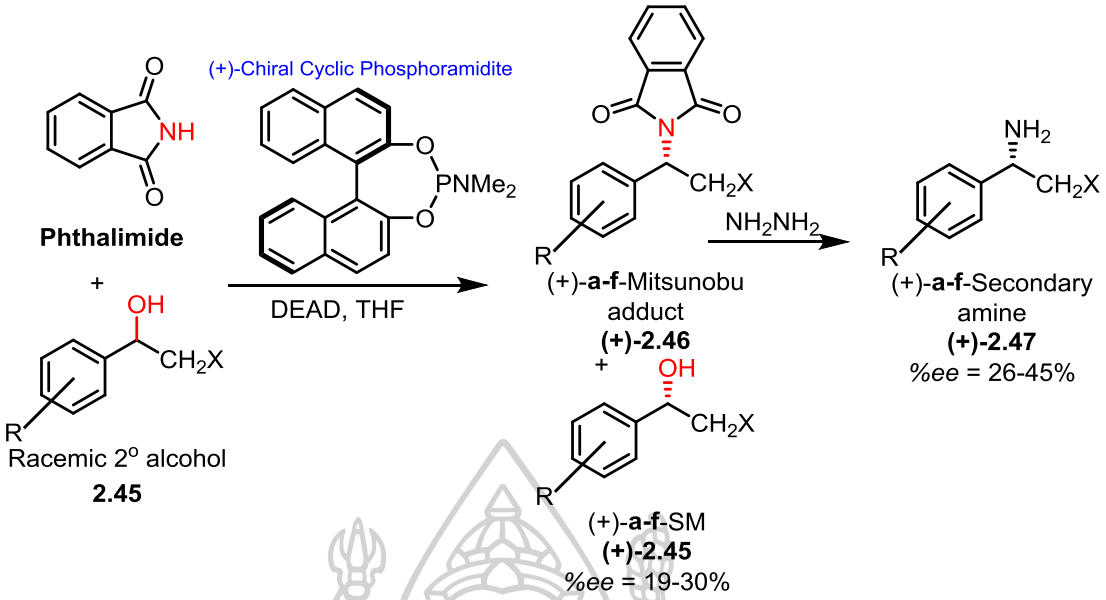
Mitsunobu reaction

Mitsunobu reaction is an inter- and intramolecular nucleophilic displacement of alcohols with inversion using dialkyl azodicarboxylate and triphenylphosphine and mildly acidic nucleophiles. In this research we used Mitsunobu reaction for synthesized an indolizidine 167B and indolizidine 209D which are containing an indolizidine core structure and alkyl side chain (scheme 21).



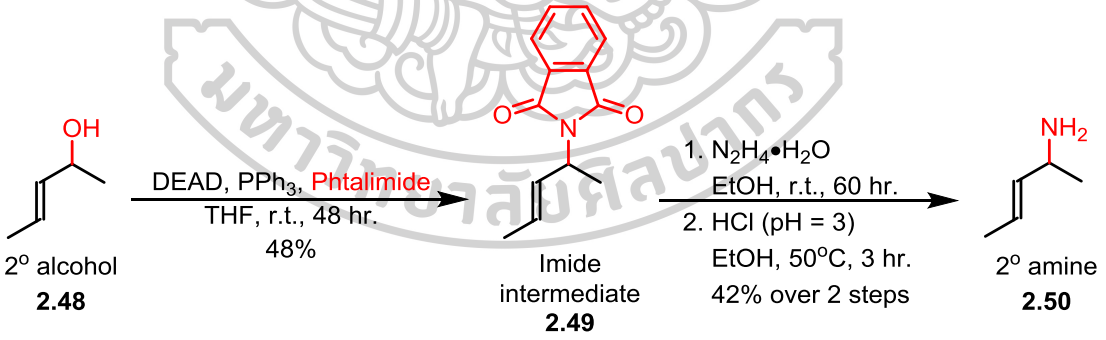
Scheme 21 Mitsunobu reaction

Examples of Mitsunobu reaction in synthesis are shown in the following schemes. Tang[29] and coworkers reported a Mitsunobu reaction by using phtalimide and racemic secondary alcohol which provided a desired product under kinetic resolution process in order to generated a chiral amine. This synthesis started with phtalimide reacted with racemic secondary alcohol **2.45** under mitsunobu conditions by using chiral cyclic phosphoramidite instead of triphenylphosphine. This reaction gave (+)-Mitsunobu adduct **(+)-2.46** and unreacted secondary alcohol **(+)-2.45**. Hydrolysis (+)-Mitsunobu adduct **(+)-2.46** with hydrazine hydrate provided (+)-secondary amine **(+)-2.47** as a product (scheme 22).



Scheme 22 Synthesis of chiral amine by Tang and coworkers

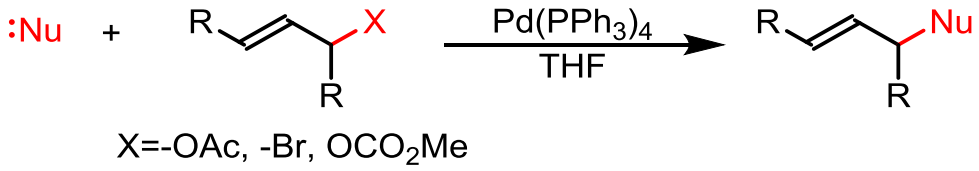
In 1995, Brunker[30] and coworkers reported a racemic amine synthesis in order to study a photooxygenation of allylic amine. This study began with a synthesis of starting material, secondary amine. Mitsunobu reaction of secondary alcohol 2.48 under mild condition gave imide intermediate 2.49. Subsequent hydrolysis using hydrazine hydrate under acidic condition provided secondary amine as a product (scheme 23).



Scheme 23 Secondary amine synthesis by Brunker and coworkers

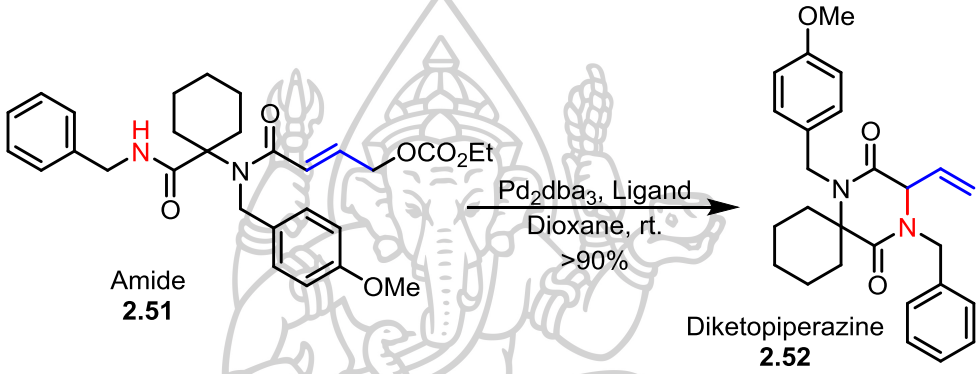
Tsuji-Trost allylation

Tsuji-Trost allylation was used in an indolizidine 167B and indolizidine 209D synthesis. Tsuji-Trost allylation is a palladium-catalyzed allylation of nucleophile with allylic compound such as allyl acetates or allyl halides.



Scheme 24 Tsuji-Trost allylation

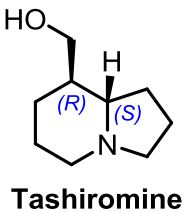
In 2019, Ruijter[31] and coworkers reported a synthesis of diketopiperazines by using Tsuji-Trost allylation as a key reaction. They converted amide 2.51 to diketopiperazine 2.52 in one step under Tsuji-Trost condition (scheme 25).



Scheme 25 Synthesis of diketopiperazine by Ruijter and coworkers

Tashiromine

Tashiromine is a naturally occurring indolizidine alkaloid which was first isolated from an Asian deciduous shrub *Maackia tashiroi*[32] by Ohmiya and co-workers. Tashiromine is one of the structurally simple indolizidine alkaloids. The structure consists of indolizidine core substituted by hydroxymethyl group and contains two stereocenters.

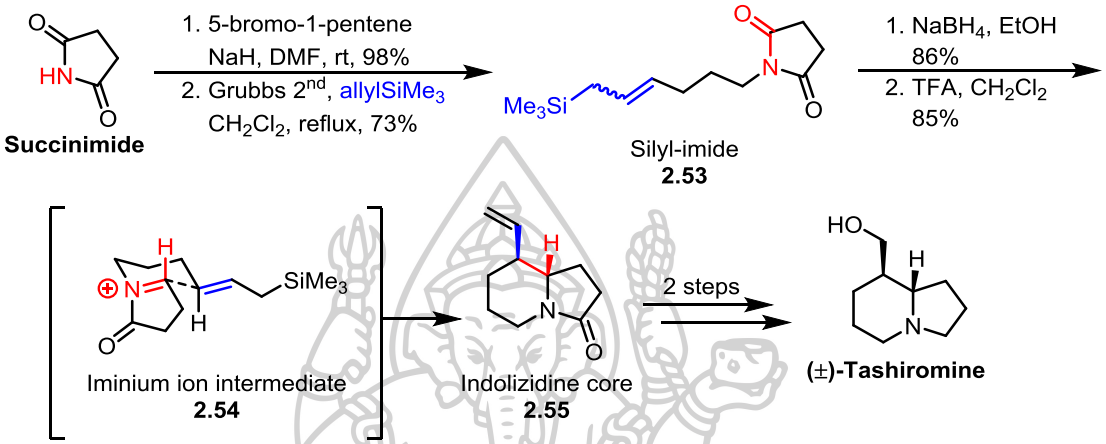


Tashiromine

Maackia tashiroi

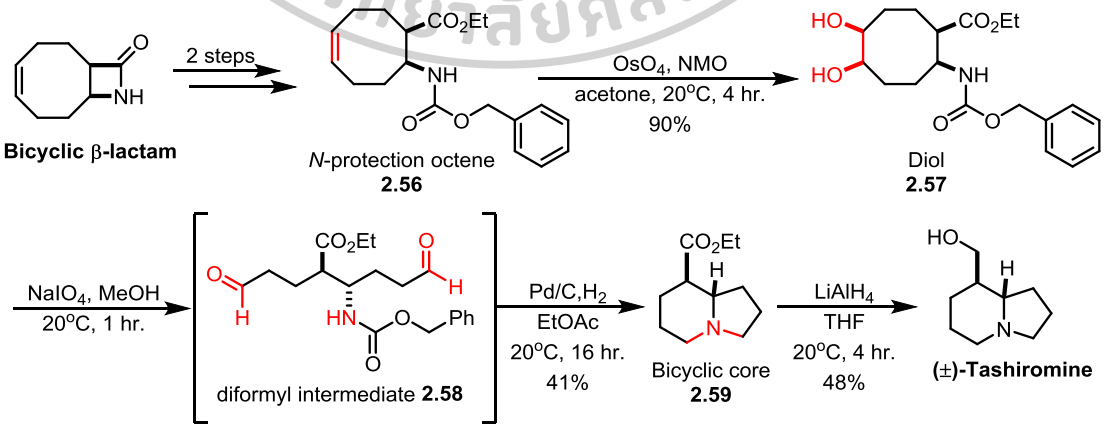
Figure 4 Structure of tashiromine and Maackia tashiroi

Due to a simple indolizidine alkaloids structure, tashiromine has been popular for synthetic chemists. In 2008, Marsden[33] and coworkers reported a racemic synthesis of tashiromine. This work used succinimide as a starting material. *N*-alkylation of succinimide followed by cross metathesis by using Grubb's catalyst provided silyl-imide **2.53**. Reduction of carbonyl gave hydroxylactam followed by subsequent *N*-acyliminium ion cyclization with TFA gave indolizidine core **2.55**. Indolizidine core **2.55** was converted to *rac*-tashiromine in 2 steps (scheme 26).



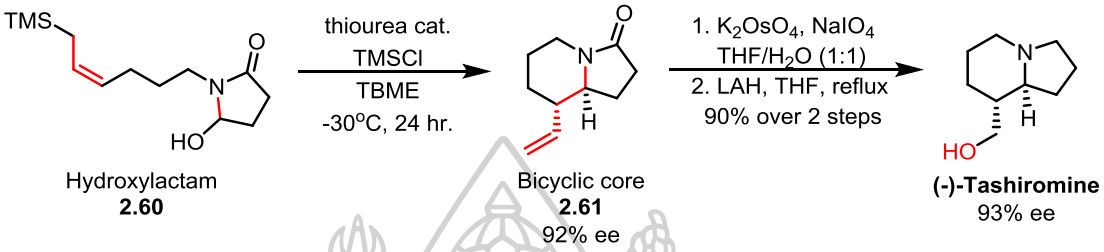
Scheme 26 Synthesis of (±)-tashiromine by Marsden and coworkers

In 2015, Fulop[34] and coworkers also reported a racemic synthesis of tashiromine. This synthesis started from N-protection octene **2.56** which was derived from bicyclic β-lactam in 2 steps. Dihydroxylation with osmium tetroxide provided diol **2.57**. Oxidative ring-opening using $NaIO_4$ gave unstable diformyl intermediate **2.58** followed by double cyclization-reduction process gave bicyclic core **2.59**. Finally, reduction in simple condition using lithiumaluminium hydride furnished tashiromine (scheme 27).



Scheme 27 Synthesis of (±)-tashiromine by Fulop and coworkers

The other example of a synthesis route of tashiromine features a highly enantioselective synthesis. In 2016, Jacobsen[35] and coworkers reported an enantioselective aza-sukurai cyclization using thourea catalyst to produce indolizidine and quinolizidine core. This work started from aza-sakurai cyclization of hydroxylactam **2.60** to give bicyclic core **2.61** in highly enantiomeric excess. Lamieux-Johnson oxidation of bicyclic core **2.61** followed by global reduction gave (-)-tashiromine in 90% yield over 2 steps (scheme 28).



Hydroxylactam **2.60**

Bicyclic core **2.61** 92% ee

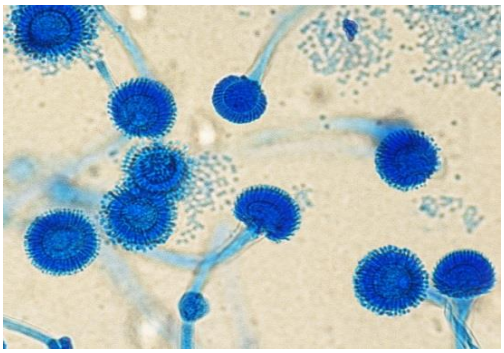
(-)-Tashiromine 93% ee

Scheme 28 Synthesis of (-)-tashiromine by Jacobsen and coworkers

Spiroindolizidine-Oxindole

Spirooxindole is an important class of natural alkaloids with a diversity of structural variations and intriguing biological activities. Some of these alkaloids are found in native plants of Thailand which have been used for medicinal purposes, such as rhynchophylline and mitraphylline from *Uncaria* plants and *Mitragyna speciosa*[36, 37] 'Kratom'. These alkaloids have been found to be non-competitive NMDA antagonists and calcium channel blockers affecting the cardiovascular and central nervous systems. Spirooxindole-pyrrolidines have also been under investigation for antiproliferation and cytotoxic activity, therefore they are potential chemotherapeutic agents for cancers. For example, spirotryprostatin B is a spiropyrrolo-oxindole with 2,5-diketopiperazine moiety found in *Aspergillus fumigatus*[38] fungus. It exhibits cytotoxicity via antimitotic property. Other non-natural spiroindolizidine-oxindoles have also been reported to have interesting biological activities.

Mitragyna speciosa



Aspergillus fumigatus

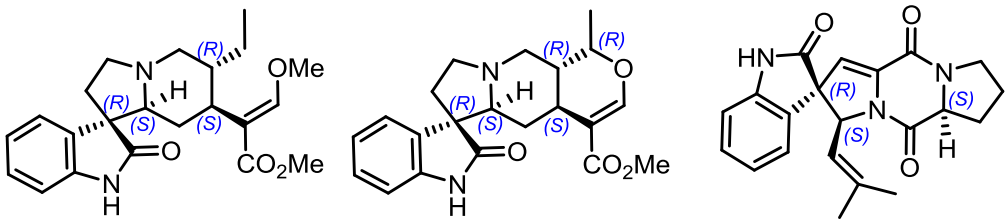
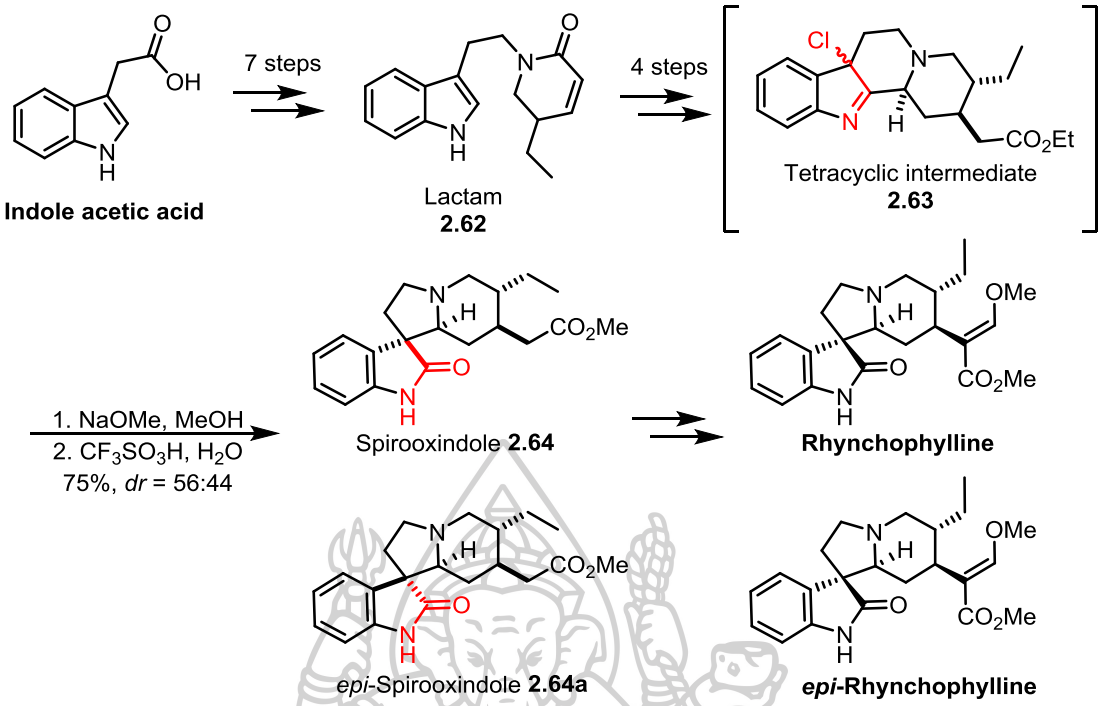
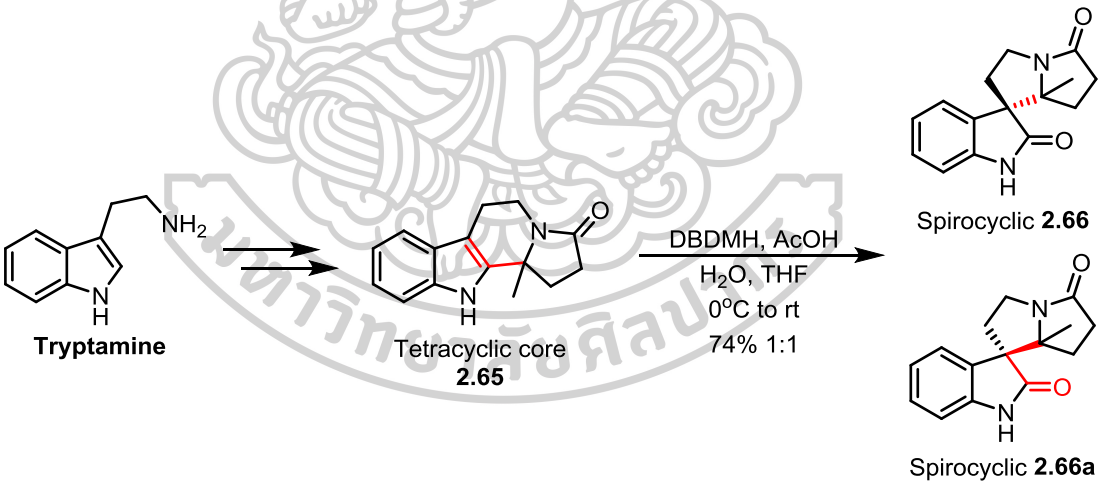


Figure 5 Structure of Spirooxindole alkaloids, *Mitragyna speciose* and *Aspergillus fumigatus*

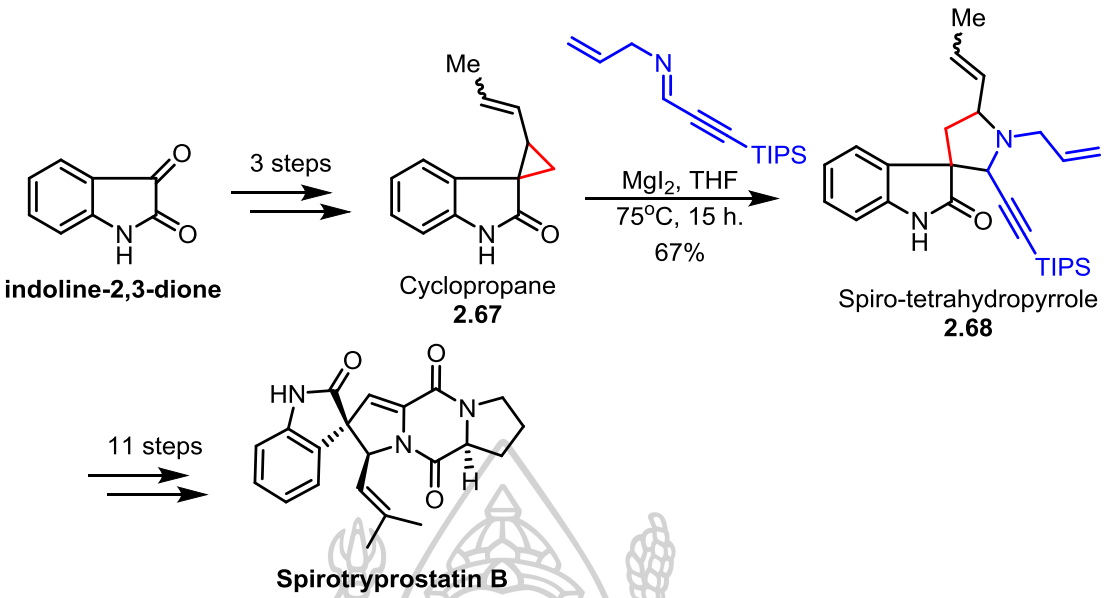
Synthesis of spiro[indolizidine-1,3'-oxindole] can be achieved biosynthetically by oxidative rearrangement of indolo[2,3-a]quinolizidine. Several syntheses of spiroindolizidine-oxindole have been reported both as racemic and enantioselective routes. Some of the reported syntheses are based on the biomimetic approach. For examples Martin's[39] synthesis of rhynchophylline in 2006 (scheme 28) and Sen's[40] synthesis of non-natural spiro-heterocyclic scaffolds in 2015 (scheme 29). However, in these reported works the spiroindolizidine-oxindole systems were obtained in racemic form. Alternative approaches were also reported such as Carreira's[41] construction of spiropyrrolo-oxindole framework via MgI_2-mediated ring-expansion reaction of a spiro[cyclopropane-1,3'-oxindole] with an aldimine. The resolution of the racemic spiropyrrolo-oxindole product was carried out for the completion of a total synthesis of (-)-spirotryprostatin B (scheme 30). Most recently in 2017, Perez and Amat[42] reported an enantioselective synthesis of spiro[indolizidine-1,3'-oxindoles] via a three steps procedure consisting of a stereoselective cyclocondensation reaction between (S)-tryptophanol and a δ-oxoester, bromination and stereoselective spirocyclization (scheme 31).



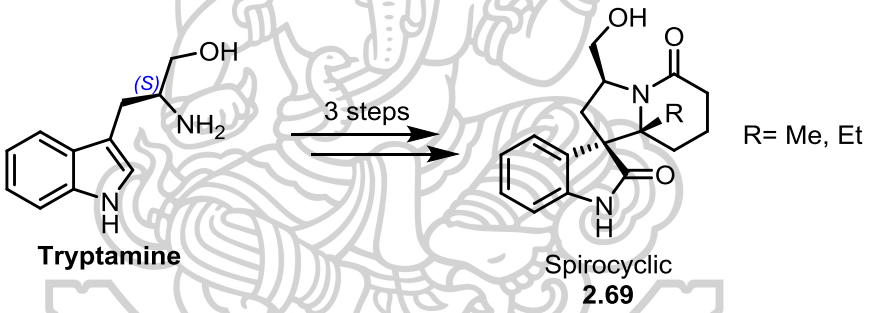
Scheme 29 Synthesis of Rhynchophylline by Martin and coworkers



Scheme 30 Synthesis of Spirocyclic scaffolds by Sen and coworkers



Scheme 31 Synthesis of Spirotryprostatin B by Carreira and coworkers

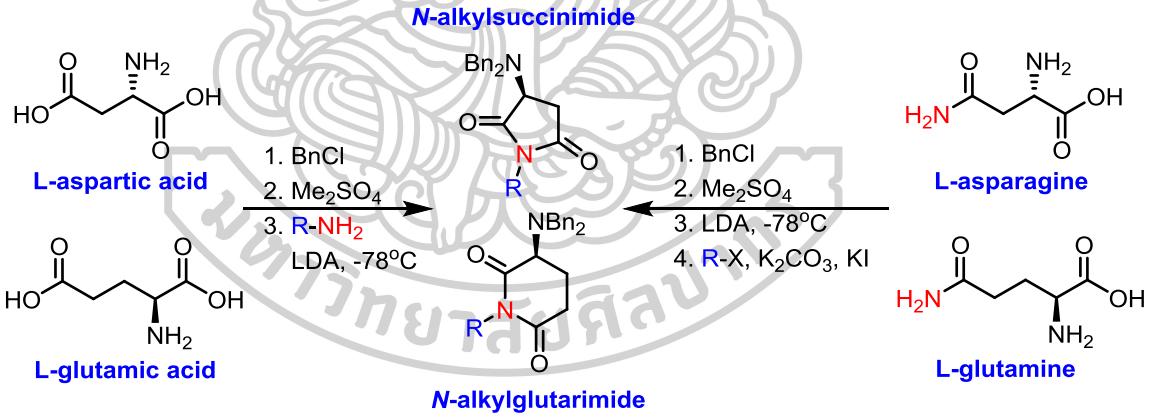


Scheme 32 Enantioselective synthesis of spirooxindole by Perez and coworkers

CHAPTER 3
SYNTHETIC STUDY

A synthesis study of natural product alkaloids in this laboratory used a commercially available starting materials such as L-aspartic acid, L-glutamic acid, L-asparagine and L-glutamine. All synthetic studies began with a benzylation, *O*-methylation and imide formation to generated a chiral *N*,*N*-dibenzylaminosuccinimide and *N*,*N*-dibenzylaminoglutarimide which was a key intermediate that can converted to core structure of indolizidine alkaloids and quinolizidine alkaloids respectively[43].

A key intermediate was synthesized by a commercially available amino acid as mention before and alkyl-primary amine or alkyl-halide. If we had a commercial alkyl-primary amine which had low cost and easy to contain, we used L-aspartate and L-glutamate which were prepared from L-aspartic acid and L-glutamic acid respectively, to generated chiral *N*-alkylsuccinimide and chiral *N*-alkylglutarimide with N-atom of imide originated from primary amine. In contrast, if we had alkyl-halide which had cheaper than alkyl-primary amine. We generated chiral succinimide and chiral glutarimide first from L-asparaginate and L-glutaminate respectively via intramolecular imide formation which was contained N-atom on amide group of chiral staring materials followed by *N*-alkylation reaction under basic condition to provide chiral *N*-alkylsuccinimide and chiral *N*-alkylglutarimide (scheme 33).

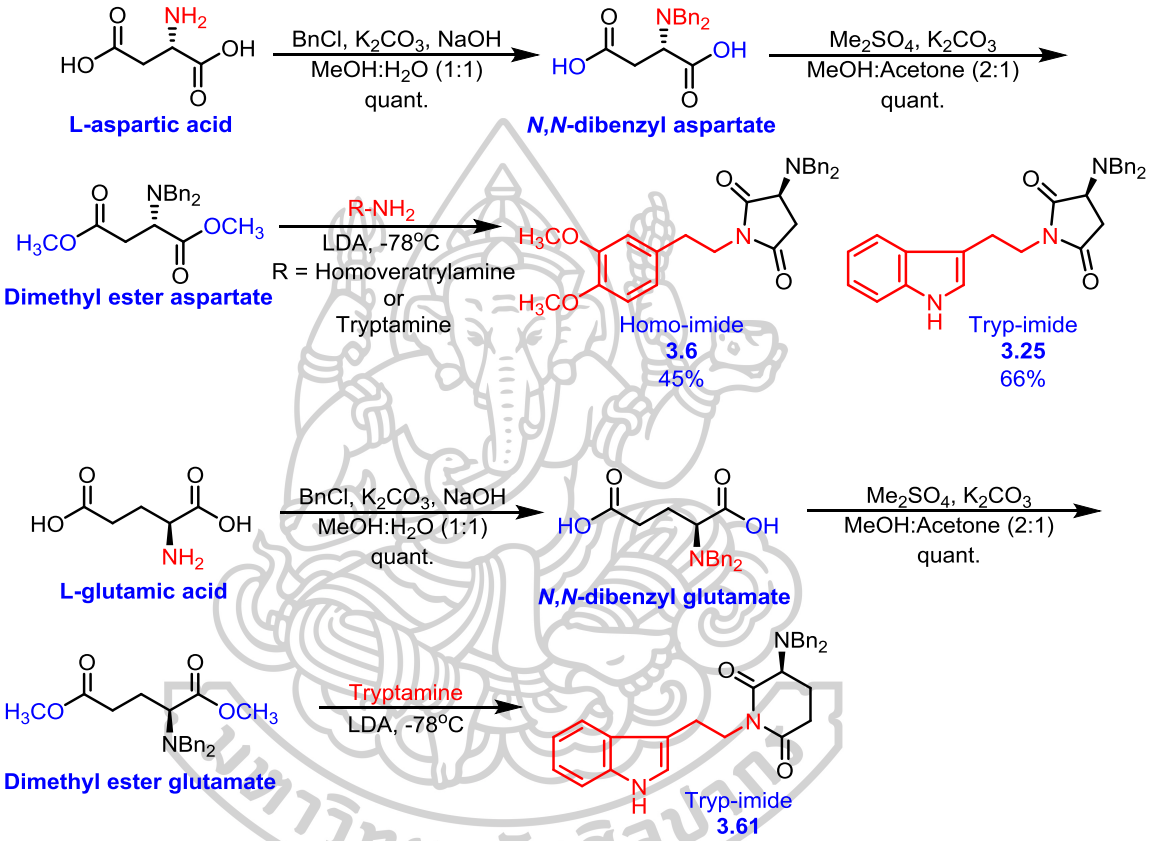


Scheme 33 Synthesis of chiral *N*-alkylsuccinimide and chiral *N*-alkylglutarimide

This synthesis methodology is useful that we have seen above, in this research used this method to synthesized a chiral *N*-alkylsuccinimide as a chiral substrate with R-group is aryl-ethyl group and indole-ethyl group. Benzylation of L-aspartic acid with benzyl chloride under basic condition provided *N*,*N*-dibenzyl aspartate as a white solid in quantitative yield after adding 1M HCl to controlled a pH of solution between 1.6-2.0. Benzylation reaction was required for uv-detection to followed a reaction in late step. *O*-methylation of *N*,*N*-dibenzyl aspartate with dimethylsulfate gave dimethyl

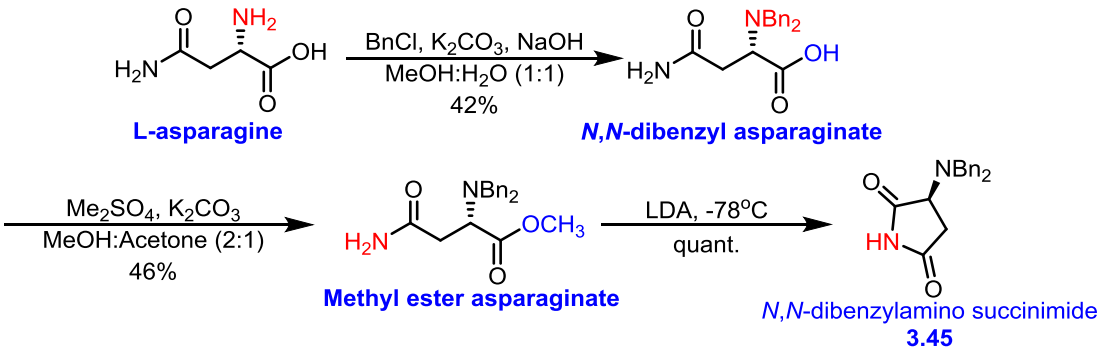
ester aspartate as yellowish oil in quantitative yield. Imide formation of the corresponding dimethyl ester aspartate with homoveratrylamine and tryptamine to furnish a homo-imide **3.6** and tryp-imide **3.25** as a chiral substrate.

In addition, tryp-imide **3.61** was prepared in the same procedure starting with *N*,*N*-dibenzyl glutamate. L-glutamic acid was converted to tryp-imide **3.61** in 3 steps, benzylation with benzyl chloride, methylation with dimethylsulfate followed by imide formation in basic condition with tryptamine (scheme 34).



Scheme 34 Synthesis of chiral substrate **3.6, 3.25** and **3.61**

N,*N*-dibenzylamino succinimide **5.7** another chiral substrate was also prepared. L-asparagine was converted to *N*,*N*-dibenzyl asparaginate via benzylation with benzyl chloride under basic condition. O-methylation of *N*,*N*-dibenzyl asparaginate with dimethyl sulfate gave methyl ester asparaginate followed by subsequent imide formation using LDA provided *N*,*N*-dibenzylamino succinimide **5.7** in quantitative yield (scheme 35).

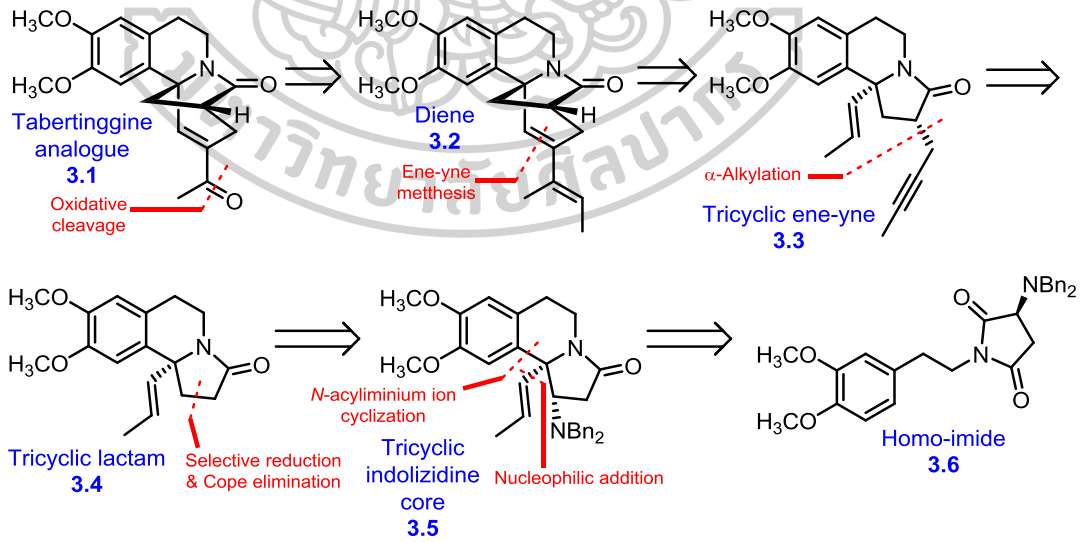


Scheme 35 Synthesis of *N*,*N*-dibenzylaminosucinimide **3.45**

Part A: Synthetic studies of tabertinggine analogue

Retrosynthetic analysis

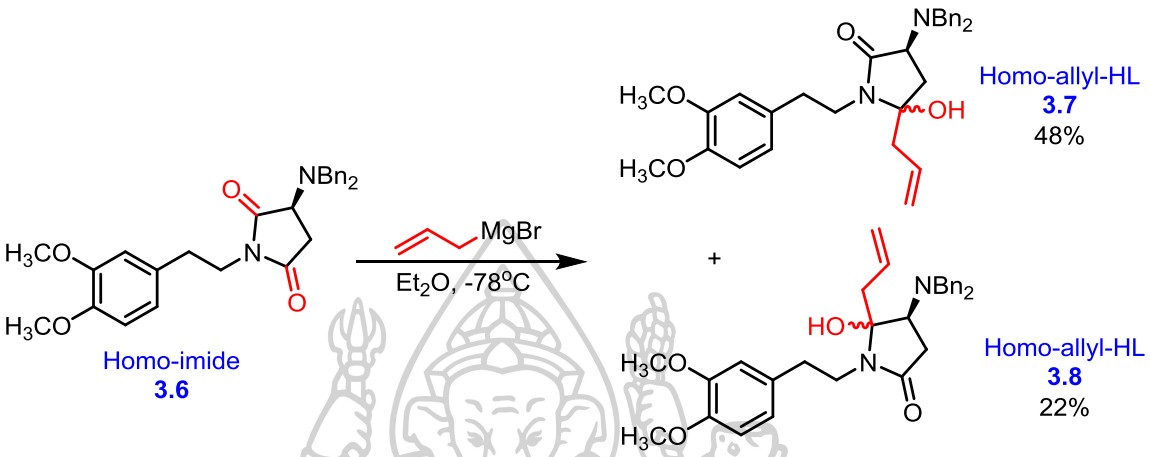
The synthesis of tabertinggine analogue **3.1** was envisioned that it would be derived from diene intermediate **3.2** from oxidative cleavage. Diene intermediate **3.2** could be prepared from tricyclic ene-yne **3.3** via ene-yne metathesis. Tricyclic ene-yne **3.3** could be traced back to tricyclic lactam **3.4** via α-alkylation with 1-bromo-2-butyne. Lactam **3.4** could be prepared from tricyclic indolizidine core **3.5** by using Cope elimination and Cordes reduction method. Tricyclic indolizidine core **3.5** could be prepared from homo-imide **3.6** via nucleophilic addition using Grignard reagent and *N*-acyliminium ion cyclization (scheme 36).



Scheme 36 Retrosynthetic analysis of tabertinggine analogue **3.1**

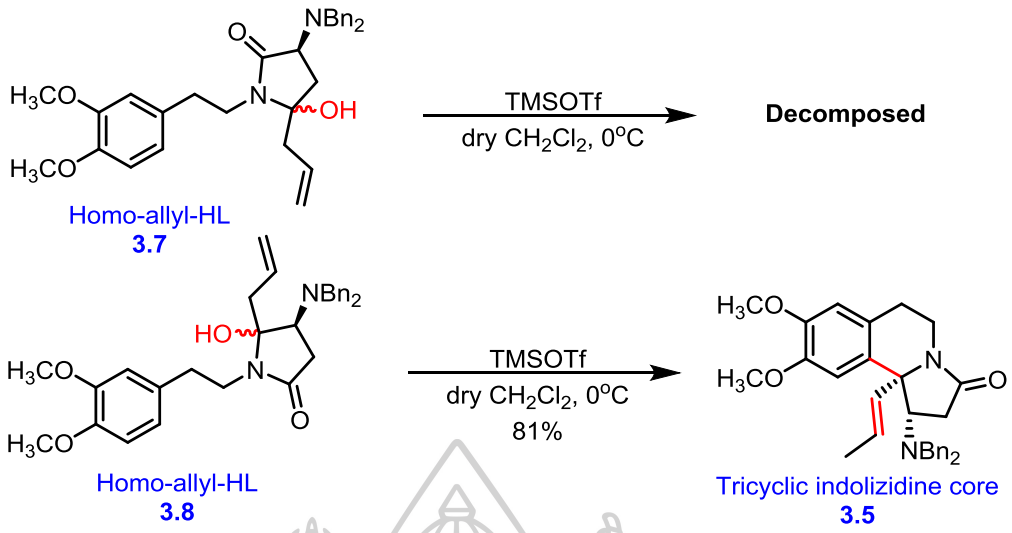
Synthetic study of tabertinggine analogue

The synthetic study of tabertinggine analogue started with nucleophilic addition of homo-imide **3.6** with allylmagnesium bromide gave homo-allyl-hydroxylactam **3.7** and homo-allyl-hydroxylactam **3.8** with regioisomeric ratio 3.5:1 as a product with unreacted starting material in good yield (scheme 37).

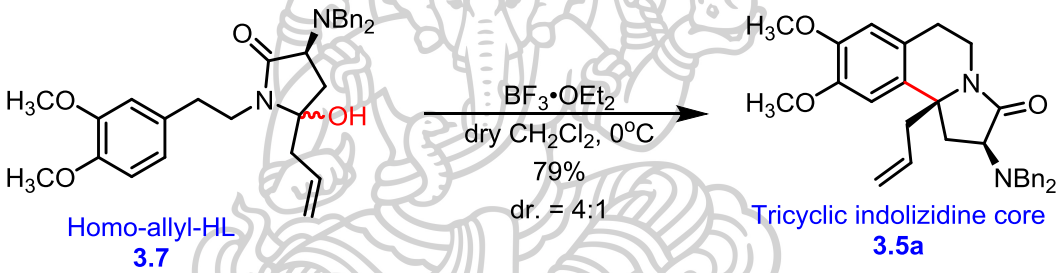


Scheme 37 Synthesis of homo-allyl-hydroxylactam **3.7** and **3.8**

To generated a tricyclic indolizidine core **3.5**, we treated homo-allyl-hydroxylactam **3.8** with TMSOTf to give tricyclic indolizidine core **3.5** with concomitant isomerization of C=C double bond. Unfortunately, homo-allyl-hydroxylactam **3.7** was decomposed when treated with TMSOTf (scheme 38). So, we used BF_3•OEt_2, another lewis acid instread of TMSOTf reacted with homo-allyl-hydroxylactam **3.7** in order to generated an iminium ion followed by cyclization. A reaction was accomplished by using BF_3•OEt_2 to give tricyclic indolizidine core **3.5a** with no isomerization of alkene with diastereomeric ratio 4:1 (scheme 39).

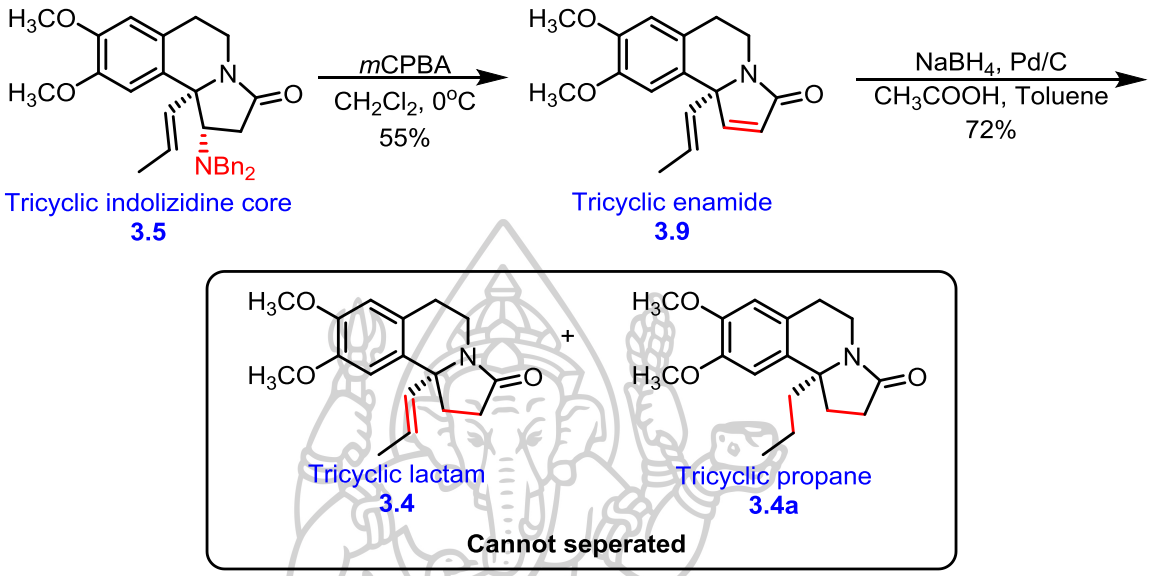


Scheme 38 Syntheis of tricyclic indolizidine core **3.5**



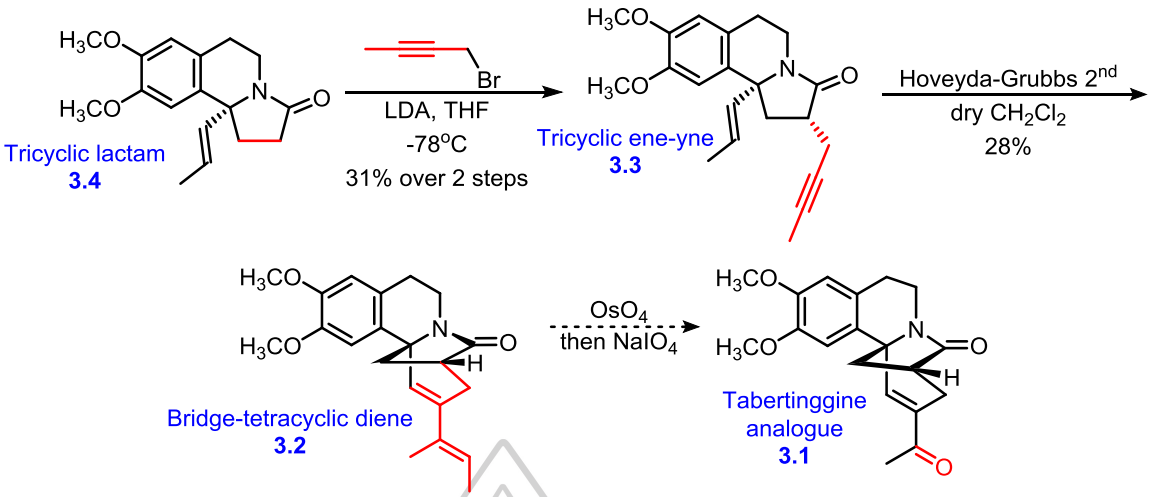
Scheme 39 Synthesis of tricyclic indolizidine core **3.5a**

We converted tricyclic indolizidine core **3.5** to tricyclic enamide **3.9** via Cope elimination in order to removed *N*,*N*-dibenzylamino group followed by Cordes[44] reduction method which resulted in selective conjugate reduction to provide tricyclic lactam **3.4** with tricyclic propane **3.4a** as a by-product that cannot to separate from each other (scheme 40).



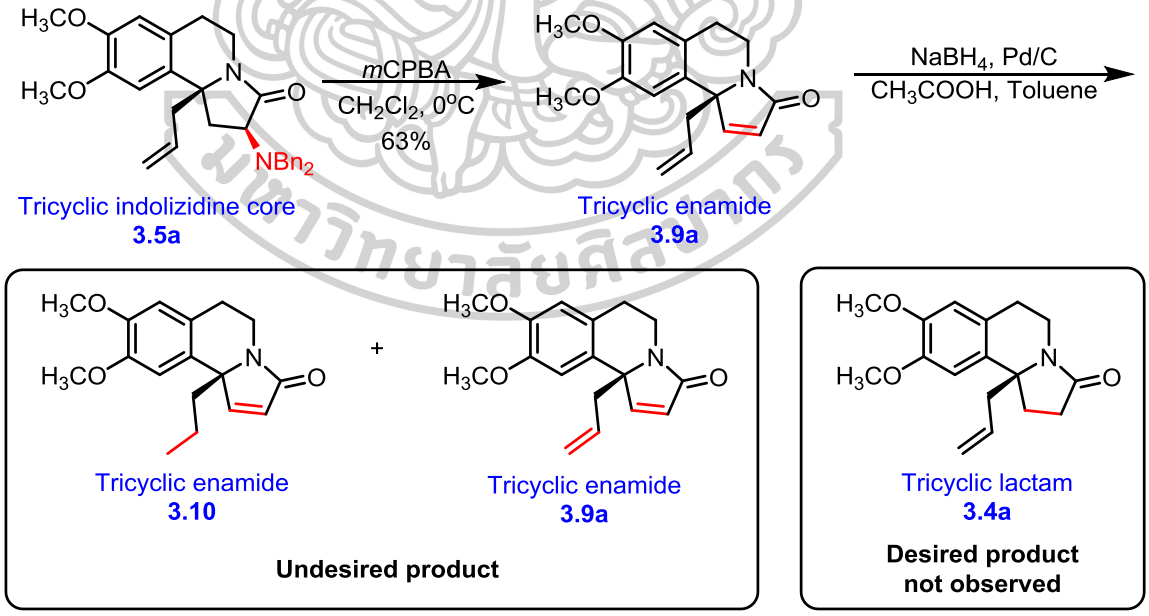
Scheme 40 Synthesis of tricyclic lactam **3.4**

Alkylation of tricyclic lactam **3.4** provided tricyclic ene-yne **3.3** which was a key ene-yne intermediate. An ene-yne metathesis of tricyclic ene-yne **3.3** using Hoveyda-Grubbs' 2nd generation gave a bridge-tetracyclic diene **3.2** in low yield. Optimization of this synthesis route an application of this method for a total synthesis of tabertinggine are underway. Therefore, to complete the synthesis of tabertinggine analogue, the synthesis plan was envisioned that a dihydroxylation followed by an oxidative cleavage of bridge-tetracyclic diene **3.2** will provide tabertinggine analogue **3.1** (scheme 41).



Scheme 41 Synthesis of bridge-tetracyclic diene **3.2** & plan for tabertinggine analogue **3.1**

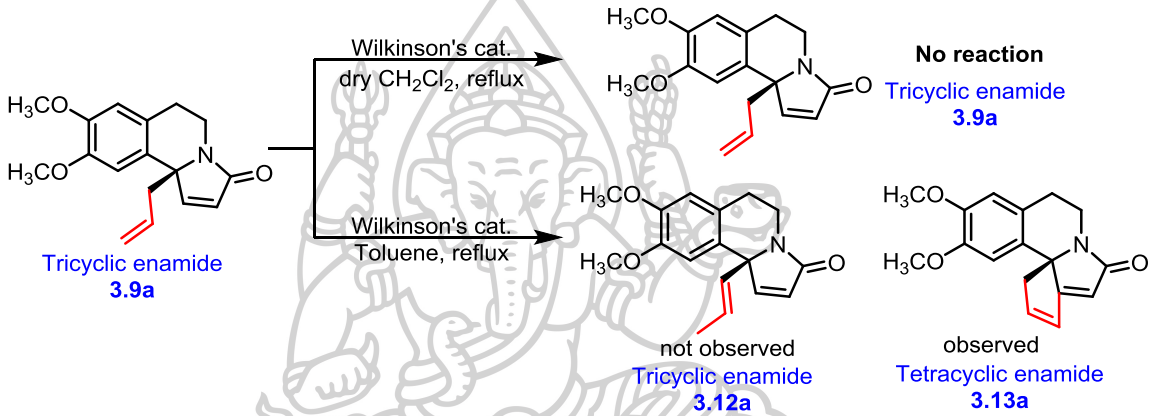
On the other hand, tricyclic indolizidine core **3.5a** was converted to tricyclic enamide **3.9a** via Cope elimination. We used Cordes reduction method[44] as a tricyclic lactam **3.4** synthesis. Unfortunately, Cordes reduction of tricyclic enamide **3.9a** was resulted an undesired product with recovery tricyclic enamide **3.9a** and desired product not observed in this reaction (scheme 42).



Scheme 42 Synthesis of tricyclic lactam **3.4a**

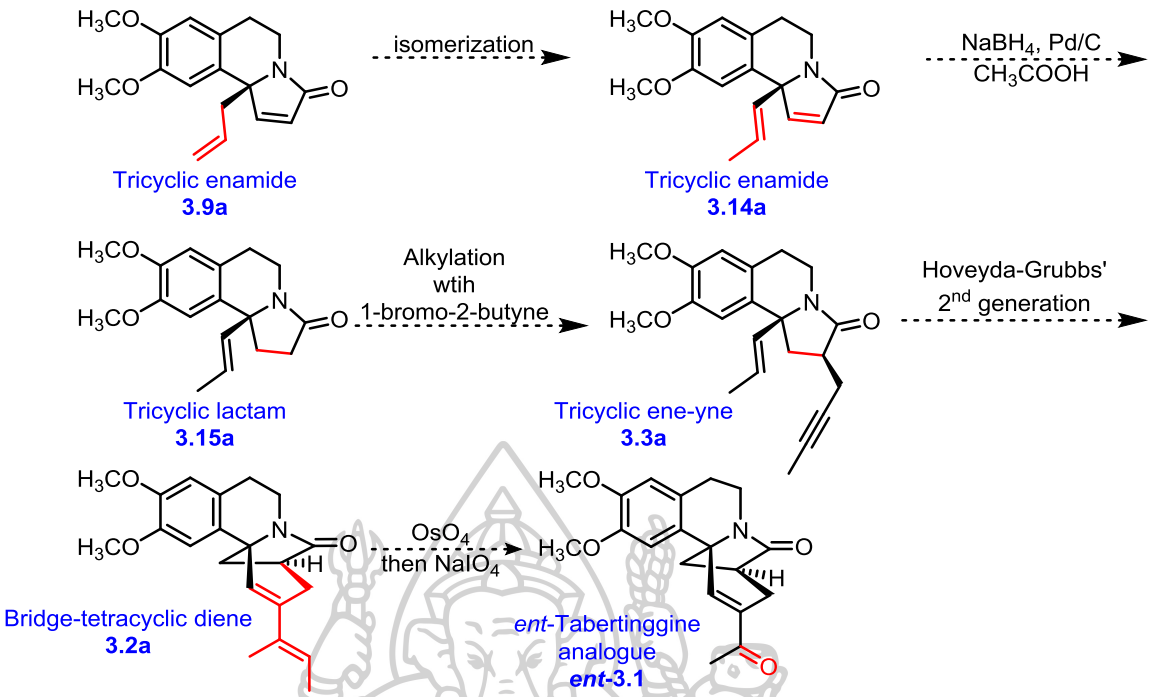
This resulted show a selective conjugate reduction was reduced a conjugate double bond prior to internal alkene. In contrast, this reaction was reduced terminal

alkene which was a more reactive alkene first followed by conjugate double bond. So, we tried to isomerization a terminal alkene to internal alkene before used a selective conjugate reduction reaction. We treated tricyclic enamide **3.9a** with Wilkinson's catalyst in order to isomerization of alkene via reductive elimination process of catalytic cycle. First, we optimization reaction in dry CH_2Cl_2 and stirred overnight, the result was shown a recovery starting materials with no concomitant isomerization product. So, we changed a solvent to toluene in order to increase a reaction temperature. A desired product **3.12a** was not observed but we observe a tetracyclic enamide **3.13a** in moderate yield, we rationalize that the insertion of Wilkinson's catalyst at terminal alkene was reacted with conjugate double bond seem like a 1,4-addition to provide tetracyclic enamide **3.13a** (scheme 43).



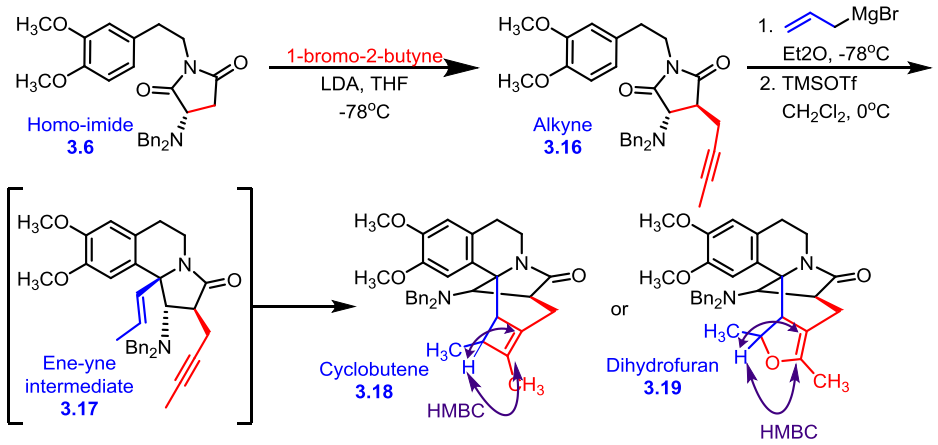
Scheme 43 Synthesis of tricyclic enamide **3.12a**

Based on results of isomerization of terminal alkenes in our studies, we planned to Base on results of isomerization of terminal alkenes in our studies, we planned to optimization a 2 steps reaction that provided isomerization product, an addition of halide to alkene followed by elimination reaction. Therefore, to complete the synthesis of *ent*-tabertinggine analogue, the synthetic plan was envisioned that we used the same synthesis route as tabertinggine analogue synthesis (scheme 44).



Scheme 44 Synthesis plan for *ent*-tabertinggine **ent-3.1**

Due to the difficulty encountered in the previous route involving selective reduction, lactam α-alkylation and subsequent ene-yne metathesis, an alternative route was devised. In this route imide **3.6** was treated with strong base and 1-bromo-2-butyne to give the alkylated product **3.16**. This compound underwent Grignard addition with allylmagnesiumbromide to give the corresponding hydroxylactam which was treated with TMSOTf. The hydroxylactam underwent *N*-acyliminium ion cyclization as well as isomerization of the double bond. We expected to obtain the ene-yne intermediate **3.17**. However, from the analysis of ^{1}H, ^{13}C and 2D NMR, we concluded that the ene-yne cyclized product was obtained. The true nature of the product requires the HRMS data to be fully realized but we suspect it to be either cyclobutene derivative **3.18** or dihydrofuran **3.19** (scheme 45).

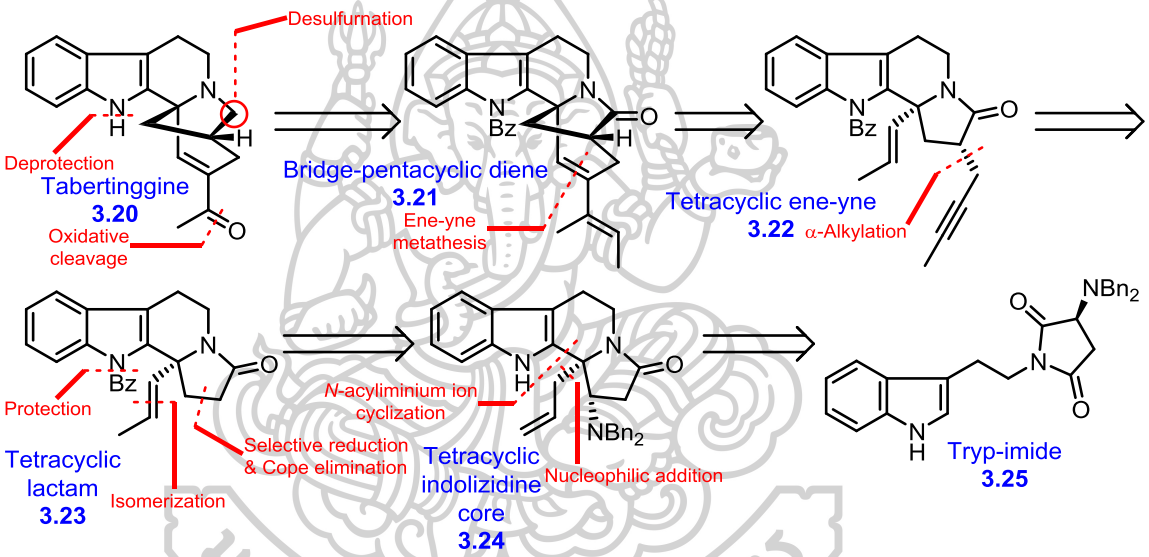


Scheme 45 An alternative route that led to unexpected Ene-Yne cyclization

Part B: Synthetic studies of tabertinggine

Retrosynthetic analysis

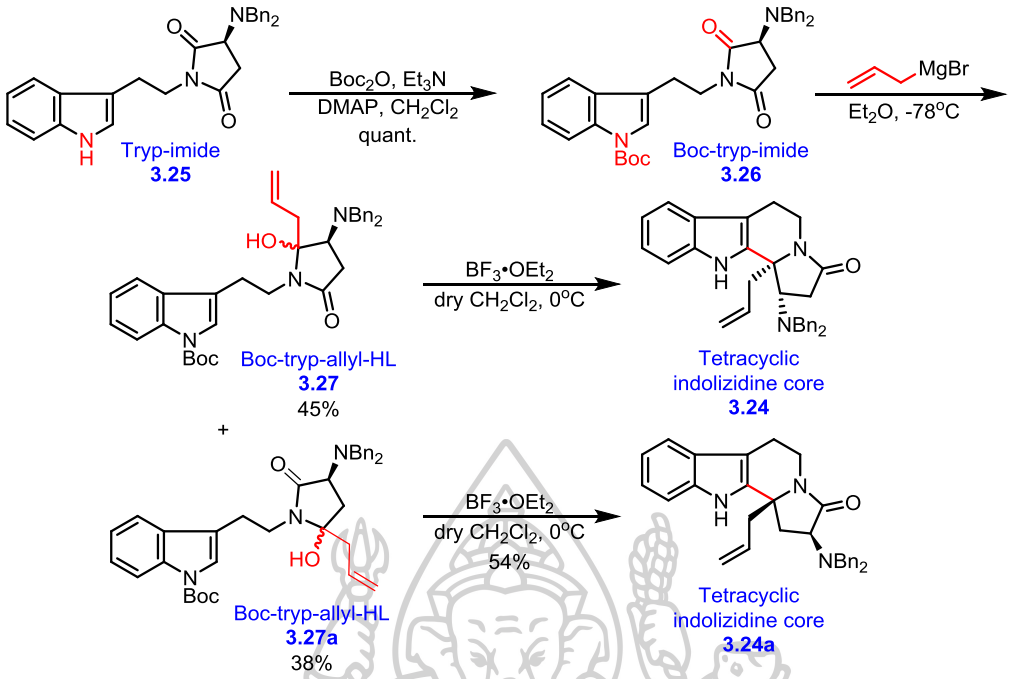
The synthesis of tabertinggine **3.20** was envisioned that it would be derived from bridge-pentacyclic diene **3.21** via desulfurnation, oxidative cleavage and deprotection. Bridge-pentacyclic diene **3.21** could be prepared from tetracyclic ene-yne intermediate **3.22** by using ene-yne metathesis. Compound **3.22** could be traced back to tetracyclic lactam **3.23** via α-alkylation with 1-bromo-2-butyne. Tetracyclic lactam **3.23** could be prepared from tetracyclic indolizidine core **3.24** via benzoyl-protection, isomerization and selective conjugate reduction. Compound **3.24** could be prepared from tryptamine-imide **3.25** via nucleophilic addition using Grignard reagent followed by *N*-acyliminium ion cyclization (scheme 46).



Scheme 46 Retrosynthetic analysis of tabertinggine **3.20**

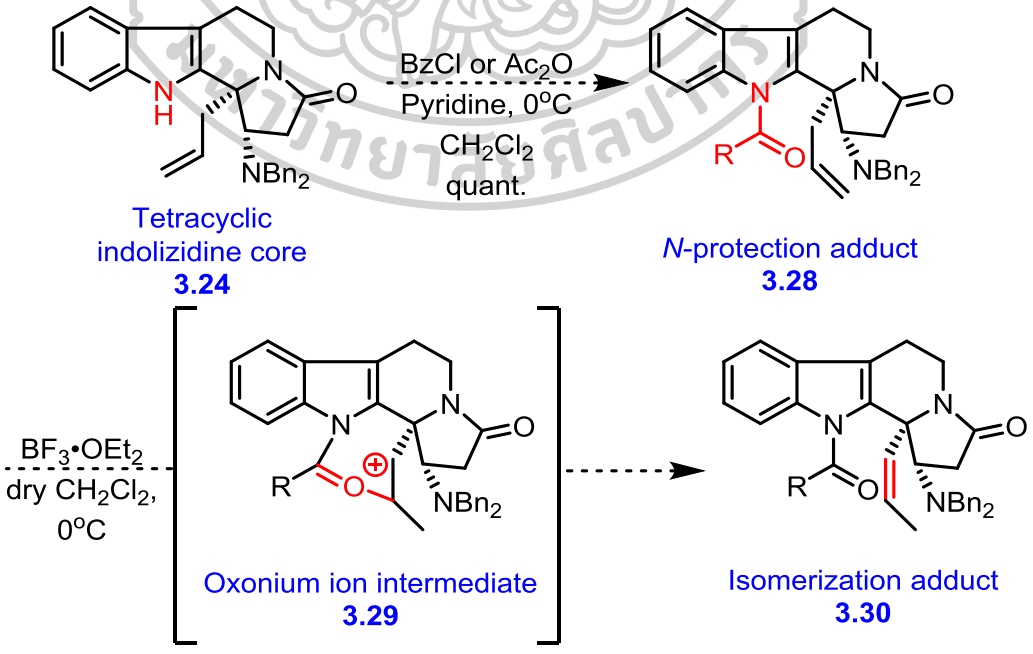
Synthetic study of tabertinggine

The synthesis study of tabertinggine started with protection of N-atom in tryp-imide **3.25** using Boc_2O in basic condition provided Boc-tryp-imide **3.26** in quantitative yield. Nucleophilic addition using Grignard reagent gave hydroxylactam **3.27** and **3.27a** with regioisomeric ratio 1.5:1. Subsequent *N*-acyliminium ion cyclization of hydroxylactam **3.27** using $BF_3{\bullet}OEt_2$ provided tetracyclic indolizidine core **3.24** (scheme 47).



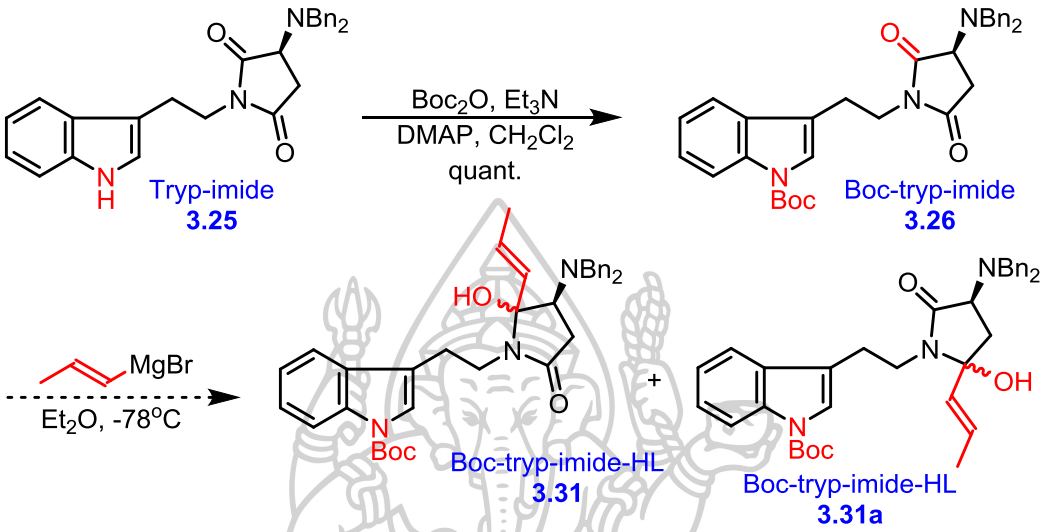
Scheme 47 Synthesis of tetracyclic indolzidine core **3.24** & **3.24a**

We planned to protection of indole ring in tetracyclic indolizidine core **3.24** using benzoyl chloride or acetic anhydride under basic condition gave *N*-protection adduct **3.28**. We expect an isomerization of alkene could undergo in acidic condition due to a stabilization of oxonium ion with conjugate system to give isomerization adduct **3.30**. Unfortunately, we cannot observe protection adduct **3.28** (scheme 48).



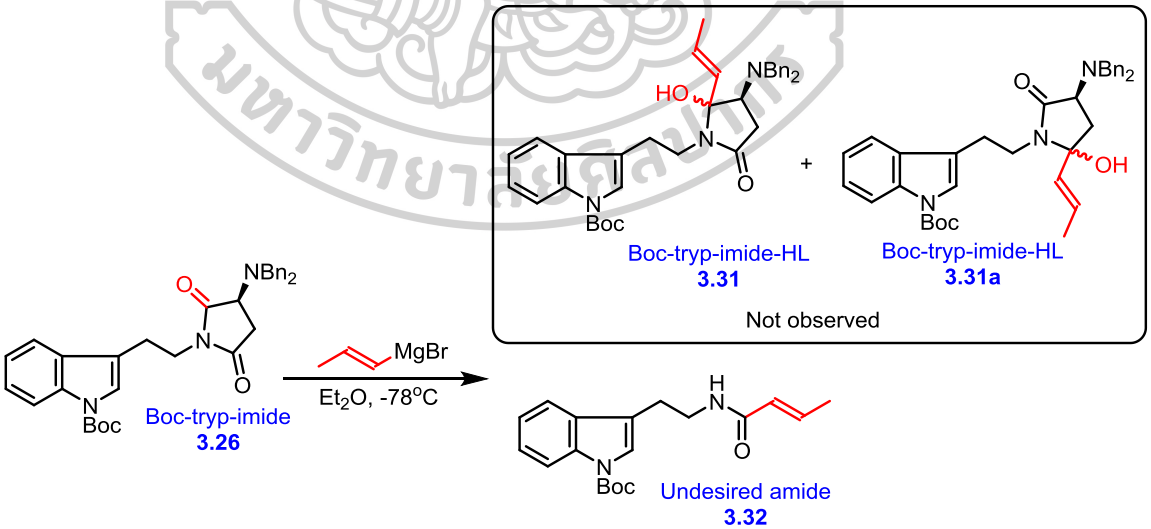
Scheme 48 Synthesis plan for isomerization adduct **3.30**

Based on results of unsuccessfully protection and isomerization. We planned to change a Grignard's reagent to 1-propenylmagnesiumbromide instead of allylmagnesiumbromide in order to generated a desired C=C double bond product (scheme 49).



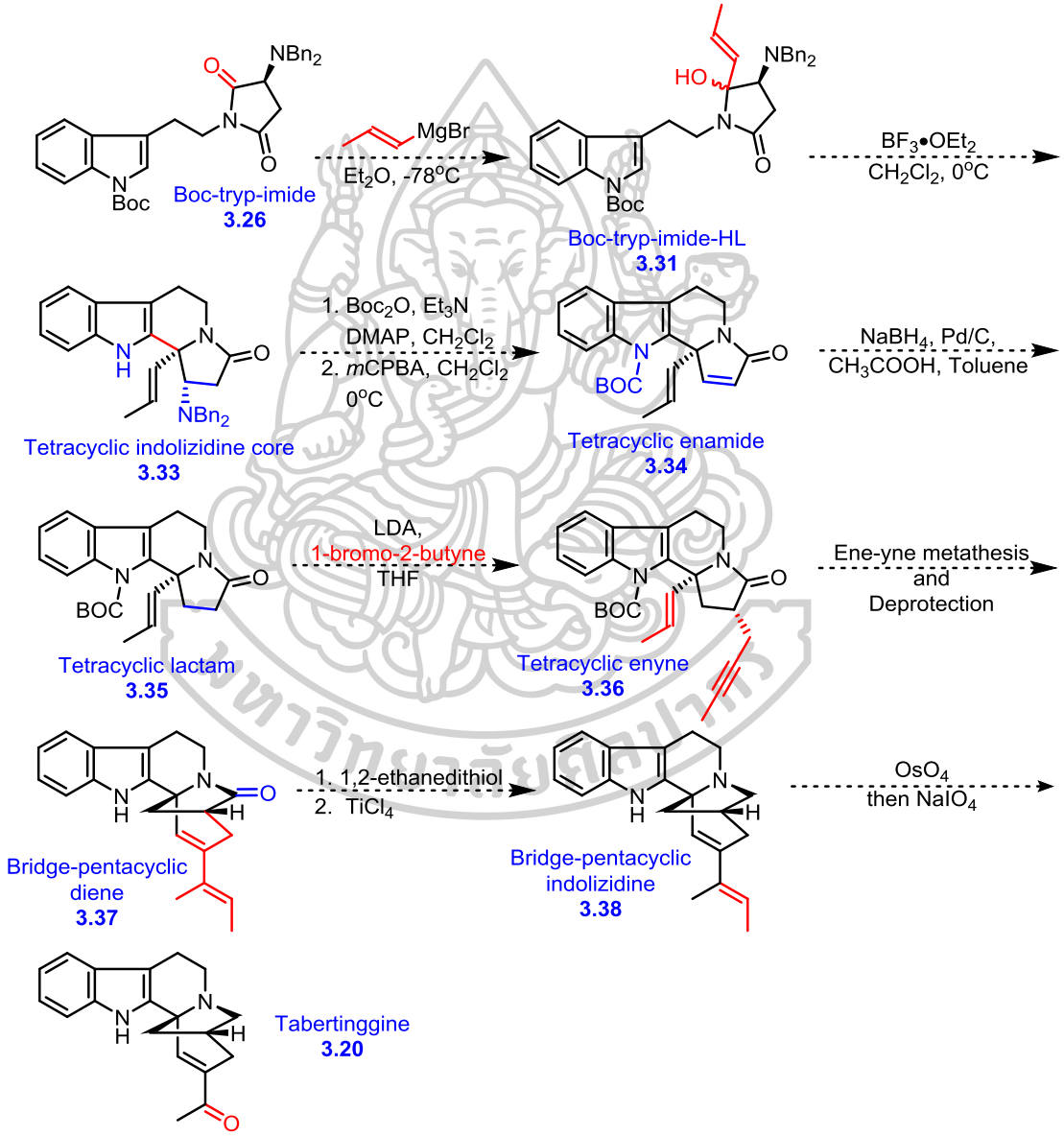
Scheme 49 Synthesis plan for Boc-tryp-imide-HL **3.31** & **3.31a**

Nucleophilic addition using 1-propenylmagnesiumbromide provided undesired amide **3.32**. We cannot observe a desired product (scheme 50).



Scheme 50 Synthesis of undesired amide **3.32**

We planned to optimized reaction condition that will provide boc-tryp-imide-HL **3.31** followed by subsequent *N*-acyliminium ion cyclization to give tetracyclic indolizidine core **3.33**. Reprotection indole ring using boc-anhydride followed by cope elimination will furnish tetracyclic enamide **3.34** which can be converted to tetracyclic lactam **3.35** by using selective reduction. Alkylation under basic condition will give tetracyclic enyne **3.36**. Ene-yne metathesis will give bridge-pentacyclic diene **3.37**. Protection carbonyl group with 1,2-ethanedithiol follow by desulfurnation reaction will provide bridge—pentacyclic indolizidine **3.38**. Finally, dihydroxylation follow by oxidative cleavage will provide tabertinggine **3.20** (scheme 51).

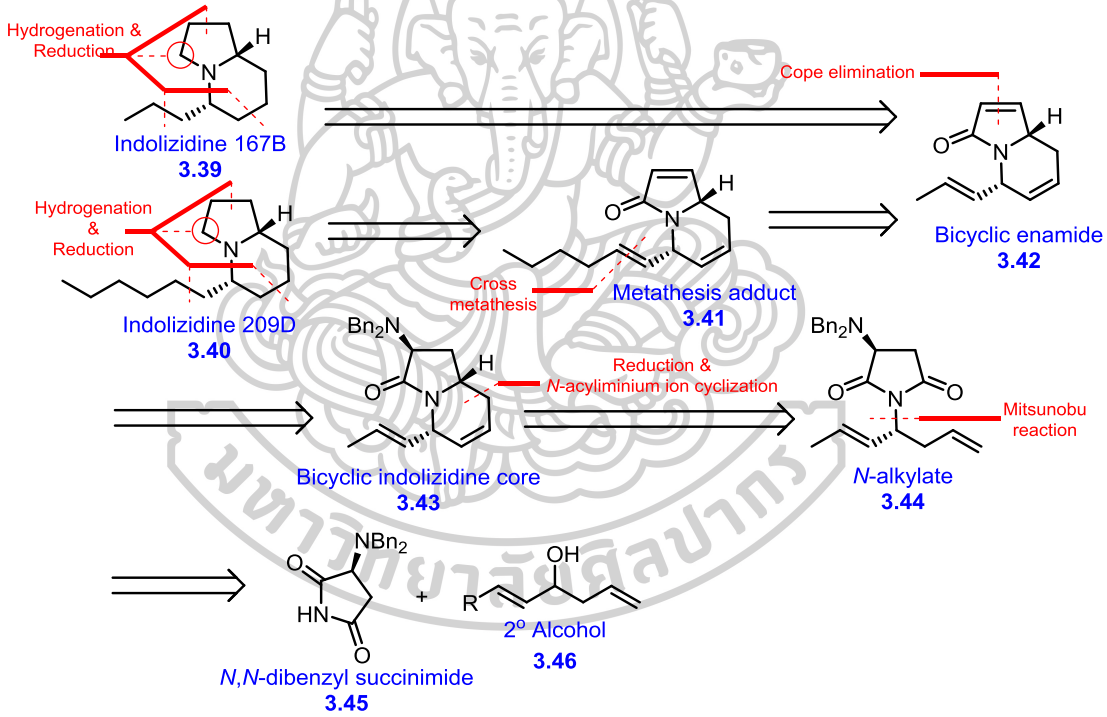


Scheme 51 Synthesis plan for tabertinggine **3.20**

Part C: Synthetic studies of indolizidine 167B & indolizidine 209D

Retrosynthetic analysis

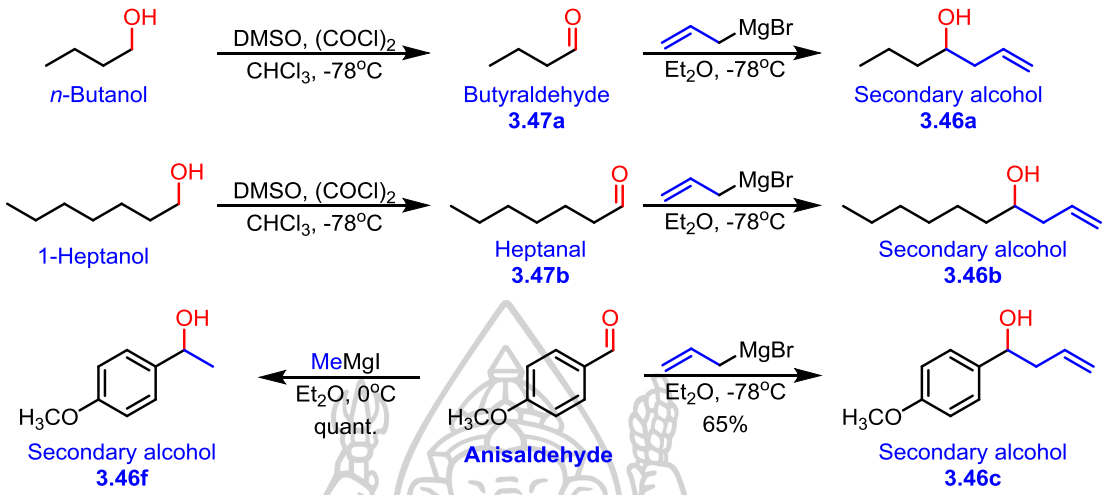
The synthesis of indolizidine 167B **3.39** and indolizidine 209D **3.40** was envisioned that it would be derived from the same bicyclic enamide intermediate **3.42** via hydrogenation and reduction for indolizidine 167B **3.39** and hydrogenation, reduction and cross metathesis for indolizidine 209D **3.40**. Bicyclic enamide **3.42** could be prepared from bicyclic indolizidine core **3.43** via cope elimination. Bicyclic indolizidine core **3.43** could be traced back to *N*-alkylate **3.44** via regioselective reduction and *N*-acyliminium ion cyclization. *N*-alkylate **3.44** could be prepared from *N*,*N*-dibenzylsuccinimide **3.45** and secondary alcohol **3.46** (scheme 52).



Scheme 52 Retrosynthetic analysis of indolizidine 167B **3.39** & indolizidine 209D **3.40**

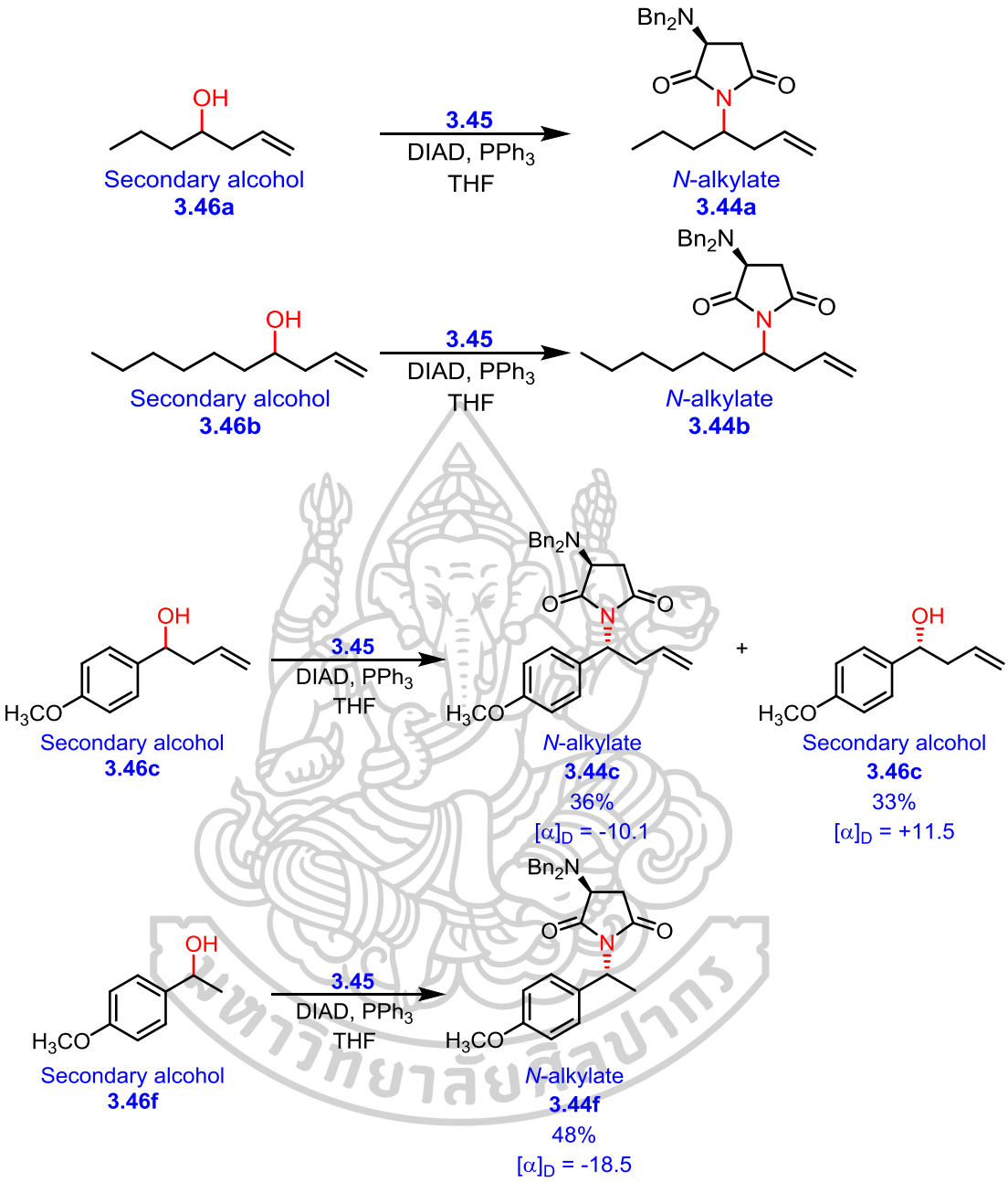
First, we prepared secondary alcohol **3.46** by using swern oxidation of primary alcohol such as *n*-butanol and 1-heptanol to give aldehyde **3.47a** and **3.47b** respectively, subsequent nucleophilic addition using allylmagnesiumbromide provided secondary alcohol **3.46a** and **3.46b** in low yield with an impurity which cannot be purified.

In the other hand, we decided to prepare another secondary alcohol, secondary alcohol **3.46c** and **3.46f** from anisaldehyde with allylmagnesiumbromide and methylmagnesiumiodide respectively (scheme 53).



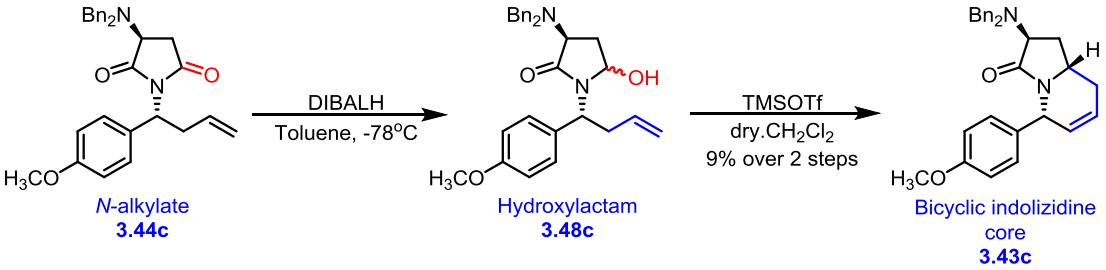
Scheme 53 Synthesis of secondary alcohol **3.46**

Mitsunobu reaction between *N*,*N*-dibenzylamino succinimide **3.45** and secondary alcohol **3.46** provided *N*-alkylate product **3.44a** and **3.44b** respectively, Unfortunately this reaction gave a desired product in low yield because a position of secondary alcohol **5.10** are aliphatic alcohol which was an unreactive species. We optimized Mitsunobu reaction by using another starting aldehyde such as anisaldehyde which was resulted a secondary alcohol at the benzylic position in secondary alcohol **3.46c** and **3.46f**. Mitsunobu reaction of secondary alcohol **3.46c** with *N*,*N*-dibenzylamino succinimide **3.45** provided *N*-alkylate **3.44c** as a single diastereoisomer with unreacted secondary alcohol. The product and the recovered unreacted alcohol were optically active, therefore the reaction proceeded with kinetic resolution of the racemic secondary alcohol. The configuration is tentatively assigned. In the same route, secondary alcohol **3.46f** was converted to *N*-alkylate **3.44f** successfully with optically active. So, we summarized a reactivity of secondary alcohol position. The most reactive secondary alcohol is on benzylic position (scheme 54).



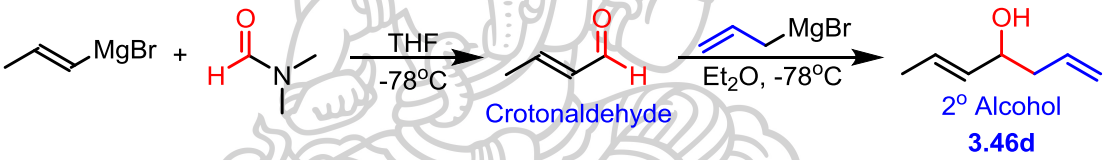
Scheme 54 Synthesis of *N*-alkylate **3.44**

We decided to converted *N*-alkylate **3.44c** to hydroxylactam **3.48c** followed by subsequent *N*-acyliminium ion cyclization reaction in order to investigated a method to installed an indolizidine core **3.43c** for synthesis of indolizidine 167B and indolizidine 209D. However, a diasteromer mixture of bicyclic indolizidine core **3.43c** was obtained in low yield with recovery hydroxylactam **3.48c** (scheme 55).



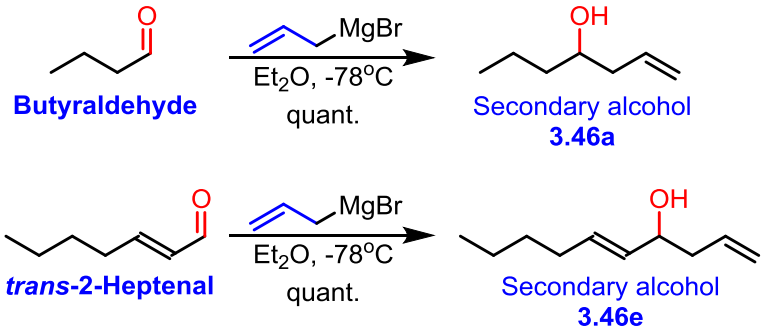
Scheme 55 Synthesis of bicyclic indolizidine core **3.43c**

As mention before, reactivity of aliphatic alcohol is less than either of allylic alcohol and benzylic alcohol. So, we turned an aliphatic alcohol to allylic alcohol by using Grignard reagent and dimethylformamide (DMF). We prepared secondary alcohol by using nucleophilic addition between 1-propenylmagnesiumbromide and DMF provided crotonaldehyde followed by nucleophilic addition using allylmagnesiumbromide to give secondary alcohol **3.46d**. Regrettably, this synthesis method gave a product with low yield and mixed with a highly level of impurity which cannot be further purified (scheme 56).



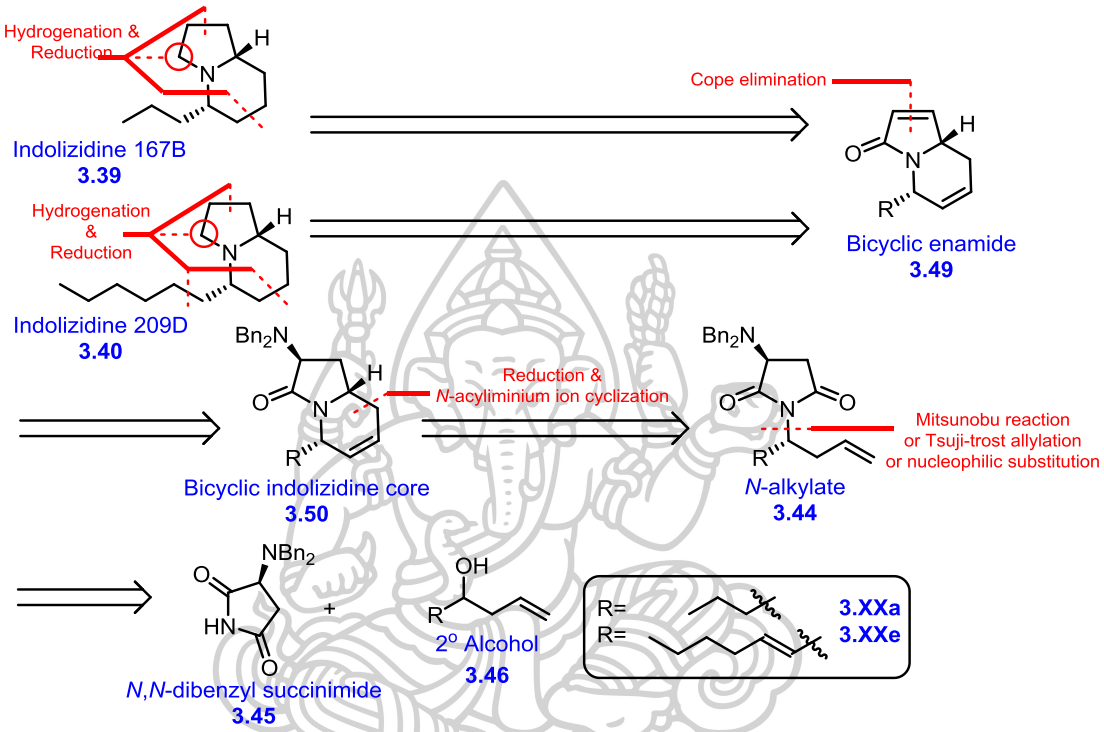
Scheme 56 Synthesis of secondary alcohol **3.46**

Based on results of an aldehyde synthesis which provided a product in low yield and cannot be further purified. Luckily, we found an old reagent from chemical store. Butyraldehyde and *trans*-2-heptenal are available. Butyraldehyde was converted to secondary alcohol **3.46a** in quantitative yield with no impurity, *trans*-2-heptenal another starting material was converted to secondary alcohol **3.46e** in good yield with hydroxy group established on allylic position which was desired product (scheme 57).



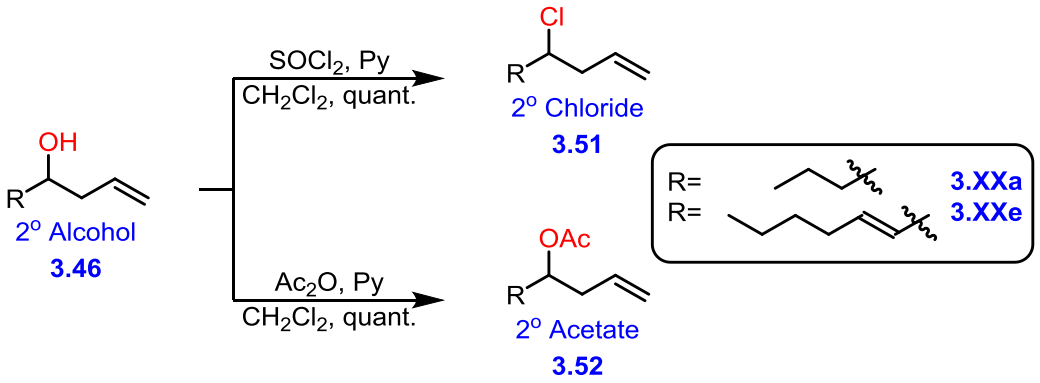
Scheme 57 Synthesis of Secondary alcohol **3.46a** & **3.46e**

As mention before, we obtained secondary alcohol **3.46a** and **3.46e** in quantitative yield. So, we changed a retrosynthetic analysis. Cross metathesis between hexene and bicyclic enamide **3.49** for indolizidine 209D was excepted due to an available side chain from starting material. We optimized a reaction to generated a new C-N bond in *N*-alkylate **3.44** by using Mitunobu reaction, Tsuji-trost allylation or nucleophilic substitution under basic condition (scheme 58).



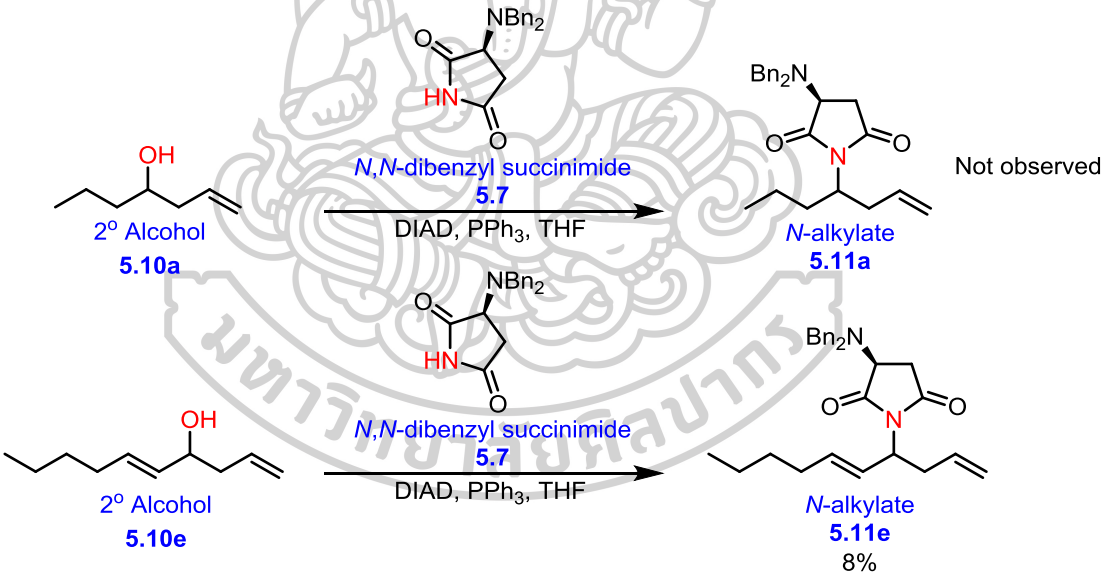
Scheme 58 Retrosynthetic analysis for indolizidine 167B **3.39** & indolizidine 209D **3.40**

Secondary chloride **3.51a**, **3.51e** and secondary acetate **3.52a**, **3.52e** another starting materials were also prepared. Secondary alcohol **3.46a**, **3.46e** was converted to secondary chloride **3.51a**, **3.51e** by using thionylchloride under basic condition. Secondary acetate **3.52a**, **3.52e** was also prepared by using acetic anhydride instead of thionylchloride under basic condition in excellent yield (scheme 59).



Scheme 59 Synthesis of Secondary chloride **3.51** and Secondary acetate **3.52**

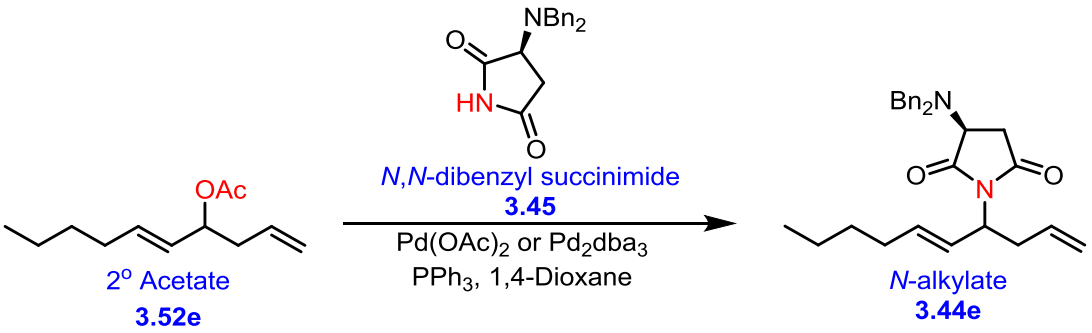
First, secondary alcohol **5.10a**, **5.10e** was converted to *N*-alkylate **5.11a**, **5.11e** by using Mitsunobu reaction between secondary alcohol and *N*,*N*-dibenzyl succinimide **5.7**. This reaction not provided *N*-alkylate **5.11a** because of a reactivity of secondary alcohol. However, *N*-alkylate product **5.11e** was observed in low yield (scheme 60).



Scheme 60 Synthesis of *N*-alkylate **5.11a** and **5.11e** via Mitsunobu reaction

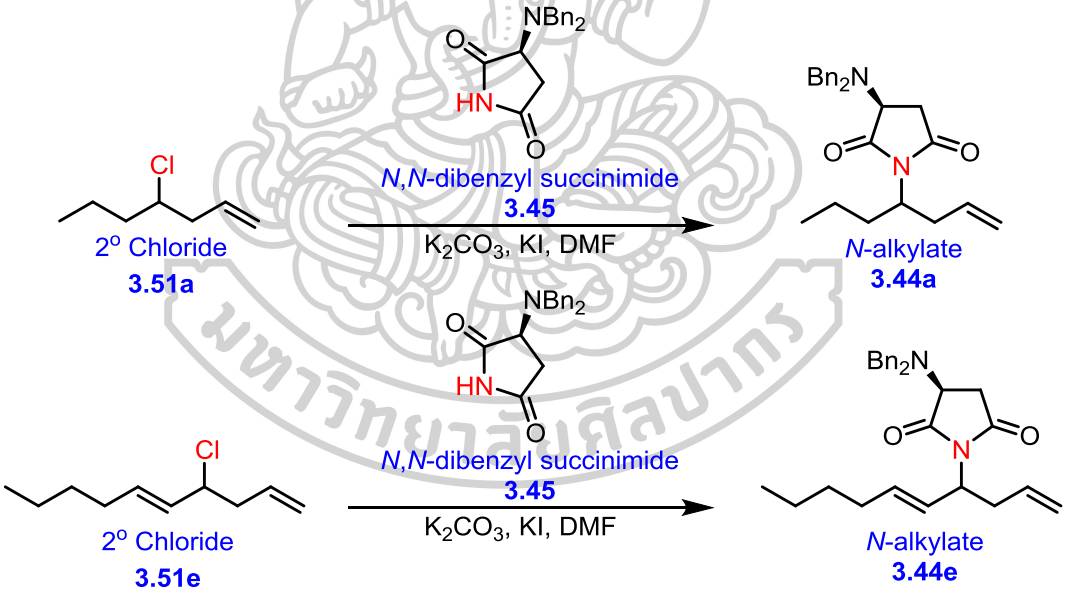
Because of *N*-alkylate product **3.44e** was obtained in low yield. So, we turned Mitsunobu reaction to Tsuji-Trost reaction in order to generated a new C-N bond. *N*,*N*-dibenzyl succinimide **3.45** was acted as nucleophile attack at the allylic acetate which was a good leaving group position. Secondary acetate **3.52e** was reacted with *N*,*N*-dibenzyl succinimide **3.45** by using palladium catalyst such as $Pd(OAc)_2$ or Pd_2dba_3 to give *N*-alkylate **3.44e**. We optimized reaction condition in different temperature. The result shown that a product was achieved in high temperature by

using data from crude ^{1}H-NMR. Unfortunately, crude product cannot be separated by using silica gel (scheme 61).



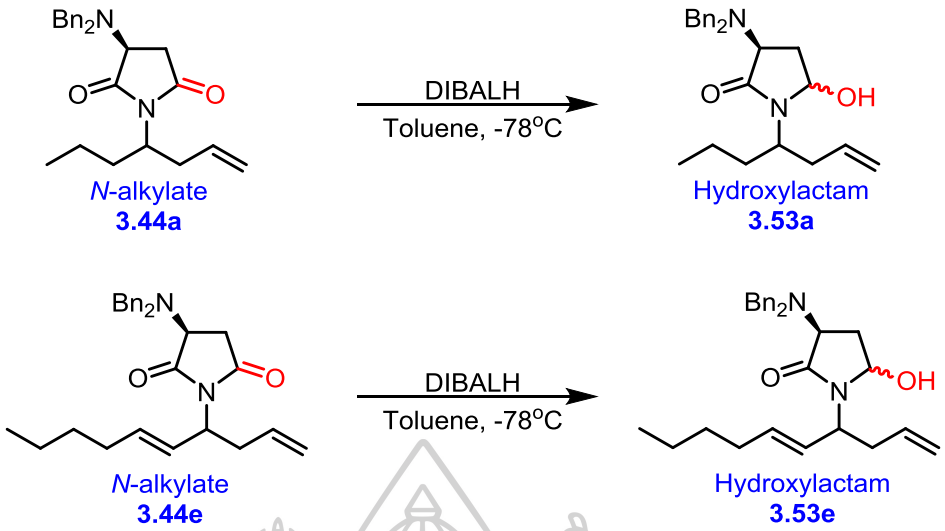
Scheme 61 Synthesis of *N*-alkylate **3.44e** via Tsuji-Trost reaction

The last method to connect a new C-N bond is a nucleophilic substitution under basic condition. We used secondary chloride **3.51** as a starting material to produce *N*-alkylate **3.44**. As mention before, we decided to use crude product to synthesis next step (scheme 62).



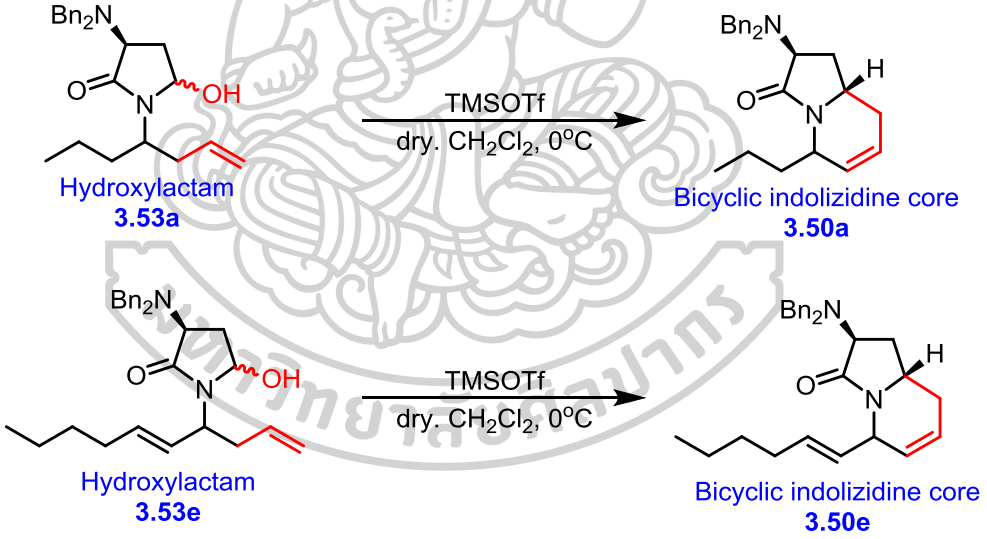
Scheme 62 Synthesis of *N*-alkylate **3.44** via nucleophilic substitution

Regioselective reduction of *N*-alkylate **3.44** with diisobutylaluminium hydride gave hydroxylactam **3.53** (scheme 63).



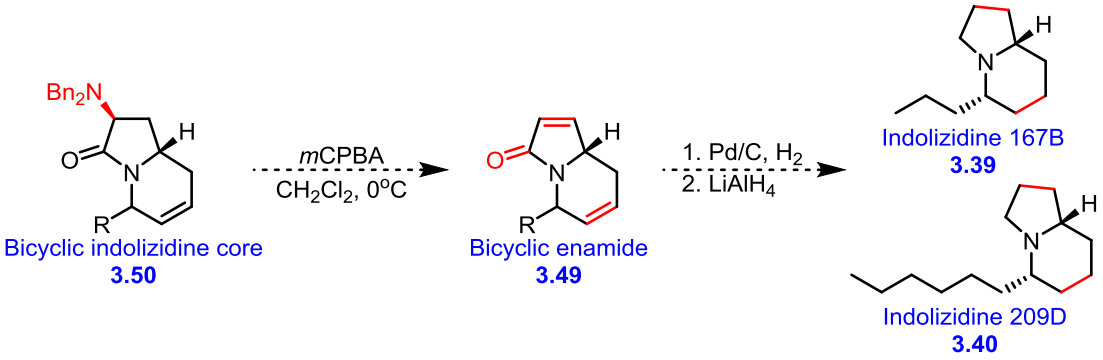
Scheme 63 Synthesis of hydroxylactam **3.53**

N-acyliminium ion cyclization of the corresponding hydroxylactam **3.53** provided bicyclic indolizidine core **3.50** (scheme 64).



Scheme 64 Synthesis of bicyclic indolizidine core **3.50**

We plan to optimized the *N*-acyliminium ion cyclization to give bicyclic indolizidine core **5.12** in better yield. Then indolizidine167B **5.1** and indolizidine 209D **5.2** will give in 3 steps via cope elimination, hydrogenation and reduction (scheme 65).

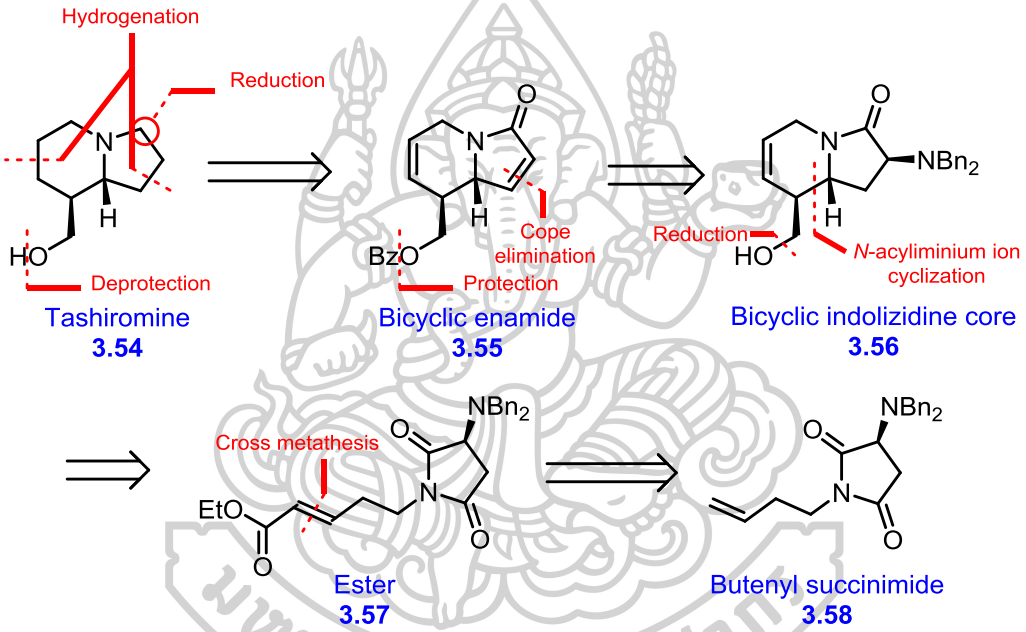


Scheme 65 Synthesis plan for indolizidine 167B **3.39** & indolizidine 209D **3.40**

Part D: Synthetic studies of tashiromine

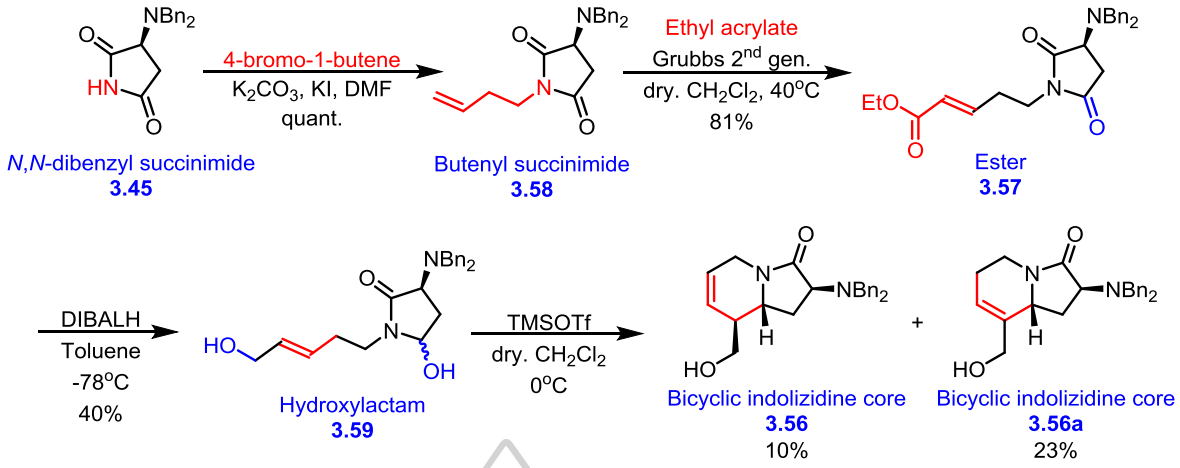
Retrosynthetic analysis

The synthesis of tashiromine **3.54** was envisioned that it would be derived from the bicyclic enamide **3.55** via hydrogenation, reduction and hydrogenation. Bicyclic enamide **3.55** could be prepared from bicyclic indolizidine core **3.56** by using cope elimination and benzoate protection. Bicyclic indolizidine core **3.56** could be prepared from ester **3.57** via reduction followed by subsequent *N*-acyliminium ion cyclization as a key step to provide indolizidine core. Ester **3.57** could be traced back to butenyl succinimide **3.58** which was prepared from *N*,*N*-dibenzylamino succinimide 3.45 as abovementioned (scheme 66).



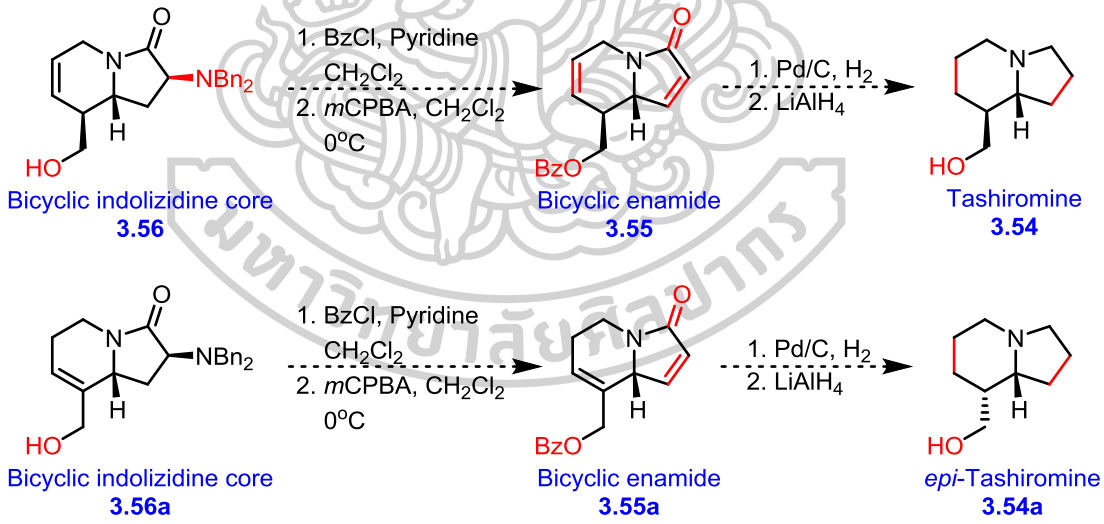
Scheme 66 Retrosynthetic analysis for tashiromine **3.54**

This synthesis started with *N*-alkylation of *N*,*N*-dibenzyl succinimide **3.45** with 4-bromo-1-butene. Cross metathesis using Grubb's catalyst 2nd generation gave ester **3.57**. Reduction of ester **3.57** followed by subsequent *N*-acyliminium ion cyclization provided bicyclic indolizidine core **3.56** & **3.56a** which was a key intermediate to converted to tashiromine **3.54** and *epi*-tasiromine **3.54a** (scheme 67).



Scheme 67 Synthesis of bicyclic indolizidine core **3.56** & **3.56a**

We plan to protection a mixture of bicyclic indolizidine core **3.56** and **3.56a** with benzoyl chloride in order to separate from each other. Cope elimination of benzoate ester intermediate provided bicyclic enamide **3.55** and **3.55a**. Finally, hydrogenation and reduction will give tashiromine **3.54** and *epi*-tashiromine **3.54a** as a product (scheme 68).



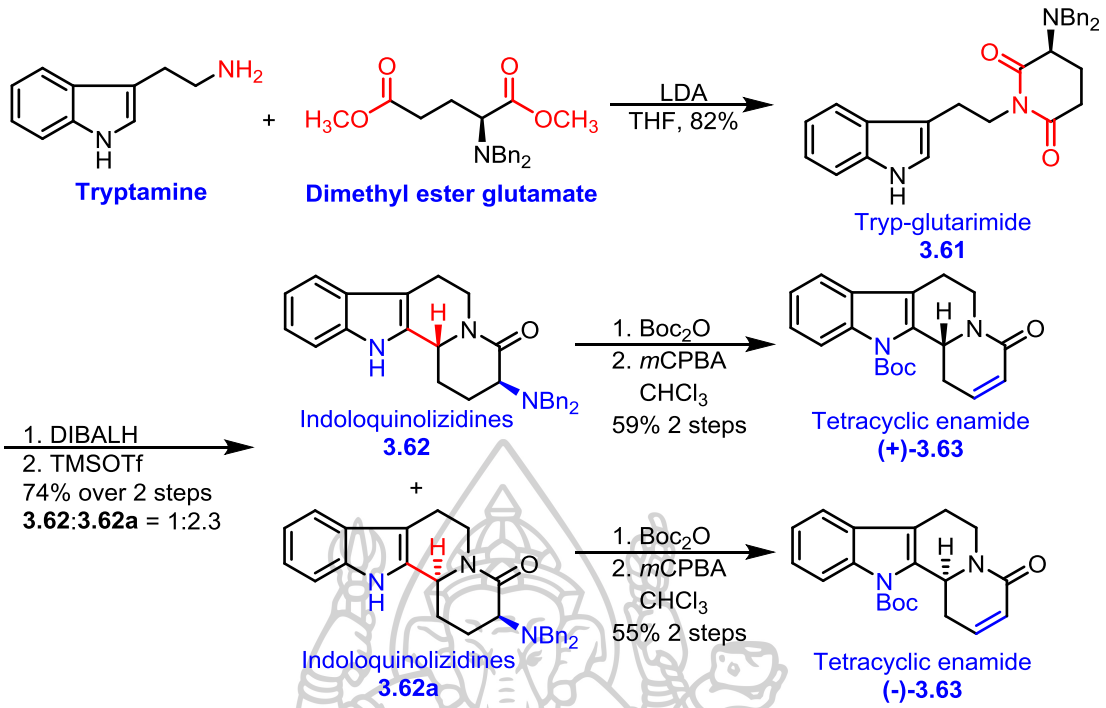
Scheme 68 Synthesis plan for tashiromine **3.54** & *epi*-tashiromine **3.54a**

Part E: Synthesis of Spiro[indolizidine-1,3'-oxindole]

At this stage of our synthetic study, we have made a few indolizidine alkaloids such as 5-arylindolizidine, 8-hydroxymethylindolizidine, benzoindolizidine and indoloindolizidine systems. To explore the scope of this methodology we became interested in synthetic study of another group of related indolizidine alkaloids which derived biosynthetically from Corynanthe indole alkaloids, namely, spiroindolizidine-oxindole alkaloids. The result of this study led to a novel method for enantio- and diastereodivergent synthesis of spiro[indolizidine-1,3'-oxindole] and the details of this study are discussed in the next section.

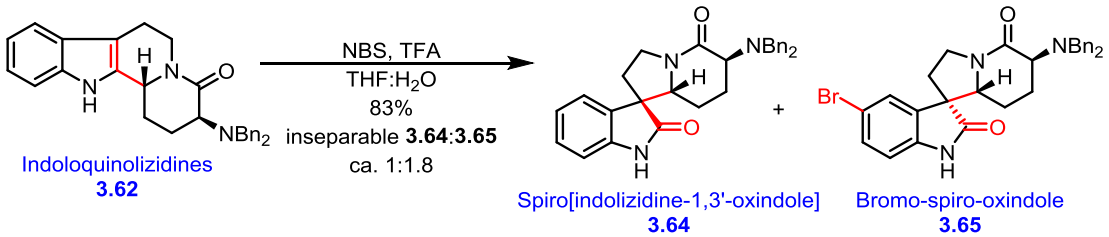
We have previously reported a synthesis of benzoquinolizidine, and benzoindolizidine systems from L-glutamic acid and L-aspartic acids[16, 43], respectively. The synthesis was based on diastereoselective cyclization of chiral *N*-acyliminium ion and was applied for synthesis of natural α-glucosidase inhibitors schulzeines B and C as well as analogs of cytotoxic crispine A and a spiro-tetracyclic core of *Erythrina* alkaloids.

In our previous study, chiral *N*-indolylethylglutarimide **3.61** was obtained from tryptamine and 1-benzyl *N*,*N*-dibenzyl glutamate via amide formation and subsequent cyclization. In this work, an improved route was established where glutarimide **3.61** was formed directly from condensation of tryptamine and dimethyl ester *N*,*N*-dibenzylglutamate, prepared in two steps from L-glutamic acid, in the presence of LDA with THF as the solvent. Subsequent steps proceeded according to our reported route in which the glutarimide **3.61** was selectively reduced at the less hindered carbonyl. *N*-acyliminium ion cyclization occurred upon treatment of the hydroxylactam with TMSOTf to give two diastereomeric indoloquinolizidines 3.**62** and **3.62a** which were separable by column chromatography (dr = 1:2.3). The two diastereomers were converted to a pair of enantiomers via Cope elimination of the dibenzylamino group following the protection of the indole nitrogen as a Boc carbamate (scheme 69).



Scheme 69 Synthesis of indoloquinolizidines **(+)-3.63** and **(-)-3.63**

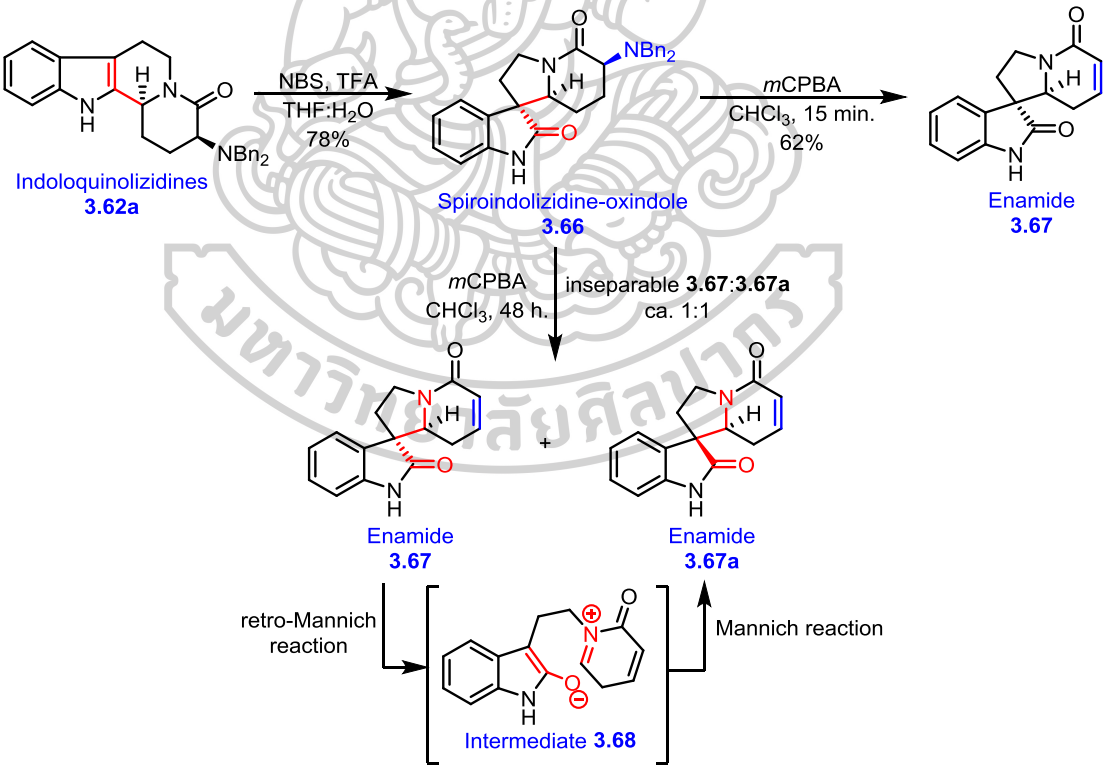
The dibenzylamino group was used for stereocontrol and was subsequently removed in a single step via Cope elimination to give enamide functionality that is suitable for further steps in the synthesis such as installation of substituents on the piperidine ring via Michael addition and α-alkylation. Several syntheses of *Corynanthe* and related spirocyclic alkaloids used tryptophan as the chiral starting material and the carboxyl or hydroxymethylene group has to be removed at later stage of the synthesis. This requires multi-step manipulations such as oxidation/ decarboxylation or deoxygenation. We first investigated oxidative rearrangement of diastereomeric tetracyclic indoloquinolizidinones **3.62** and **3.62a**. Previously reported spirocyclic formations via this method starting from indoloquinoizidinone with substituents on the lactam ring gave products with low diastereoselectivity. Treatment of **3.62** with *N*-bromosuccinimide in aqueous THF in the presence of catalytic amount of trifluoroacetic acid gave a mixture of spiro[indolizidine-1,3'-oxindole] **3.64** and brominated spirooxindole **3.65** (scheme 70).



Scheme 70 Oxidative rearrangement of tetracyclic indoloquinolizidine **3.62**

The mixture was not separable by chromatography and the existence of the brominated product was determined by high resolution mass spectrometry. The HRMS analysis found the exact mass of 452.2324 $[M+H]^+$ and 532.1412 $[M+H]^+$ for compounds **3.64** and **3.65**, respectively. The mixture was reacted with *m*CPBA to give the corresponding unsaturated lactams. Unfortunately, the products were also inseparable. However, the different patterns of the aromatic protons of the Cope elimination products of **3.64** and **3.65** became clearly visible.

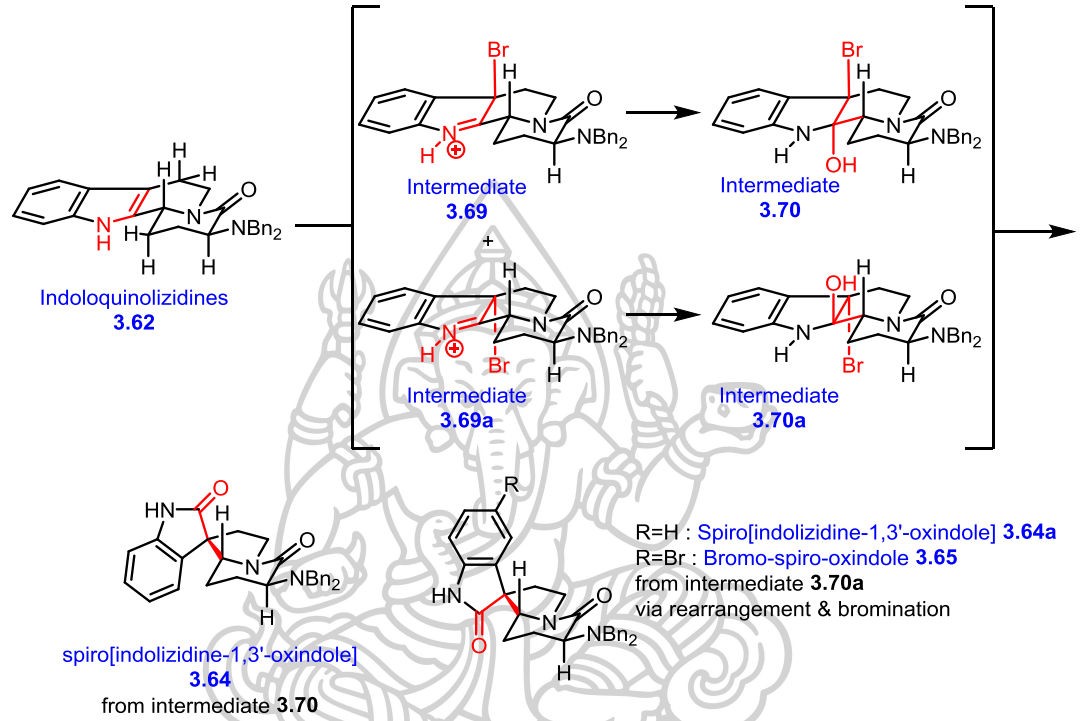
Next, we investigated the oxidative ring contraction of indoloquinolizidinone **3.62a** using the same condition. Gratifyingly, the product spiroindolizidine-oxindole **3.66** was obtained as a single diastereomer. The relative configurations of the spiro[indolizidine-1,3'-oxindole] products were determined by NOESY experiments. Interestingly, no brominated product was observed. Cope elimination of the dibenzylamino group upon treatment with *m*CPBA in chloroform was accomplished in 15 minutes giving the corresponding enamide **3.67**. Prolonged reaction time resulted in epimerization of the spiroindolizidine-oxindole core to give inseparable mixture of diastereomeric spiroindolizidine-oxindole enamide **3.67** and **3.67a** (ca. 1:1 mixture after 48 hours). Epimerization of spirooxindole has been reported to occur via retro-Mannich/Mannich process in acidic conditions (scheme 71).



Scheme 71 Oxidative rearrangement of tetracyclic indoloquinolizidine **3.62a**

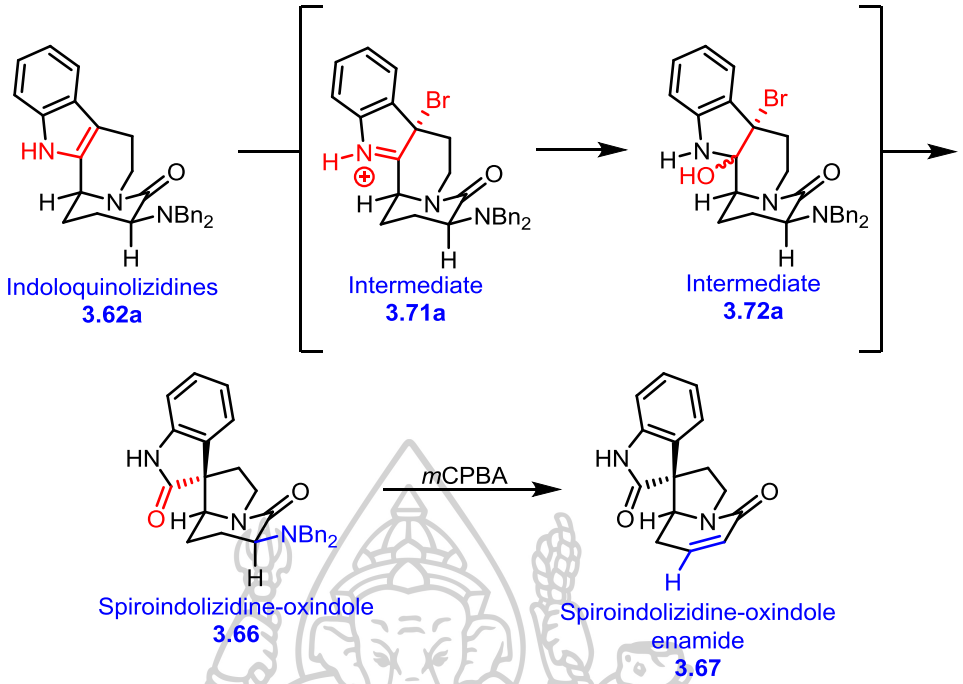
We rationalize the stereochemical outcomes of the reactions by considering the conformation of the starting materials. The syn-diastereomer **3.62** has a molecular

structure that is rather flat and there is little steric bias between the two diastereotopic faces of the molecule. The initial bromination of the indole ring from either face of the molecule leads to different diastereomers. Furthermore, C5 of the resulting oxindole **3.64a** is more accessible for electrophilic aromatic bromination and gave the brominated product **3.65** while C5 of spirooxindole **3.64** is hindered in the concave face of the indolizidine moiety (Scheme 72).



Scheme 72 Stereochemistry of oxidative rearrangement of **3.62**

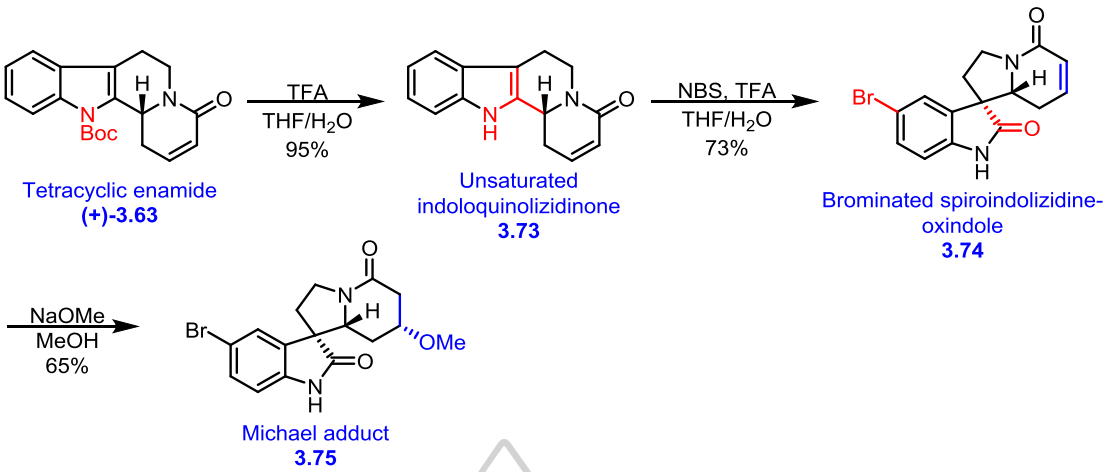
On the other hand, the oxidative ring contraction of diastereomer **3.62a** gave a single product as a single diastereomer. This is explicable by the molecular shape of the molecule which appears to be arched as shown in scheme 71. The initial bromination step occurred only on the convex side of the molecule leading to a single diastereomer of spiroindolizidine-oxindole **3.66**. Electrophilic aromatic bromination was not observed due to the steric hindrance of the indolizidine moiety (Scheme 73).



Scheme 73 Stereochemistry of oxidative rearrangement of **3.62a**

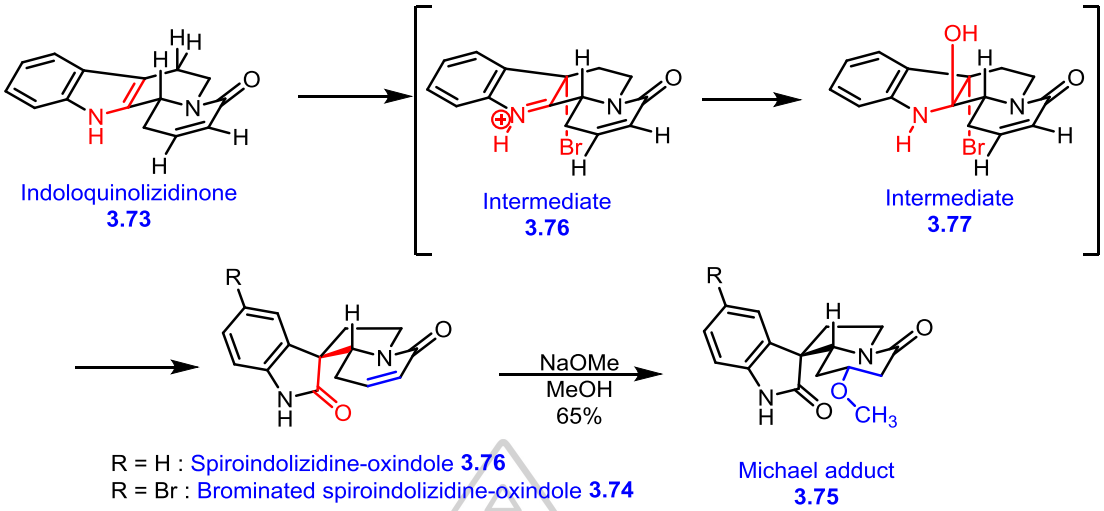
This result is very satisfactory considering that it has been reported that oxidative rearrangement of indoloquinolizidine with substituents on the quinolizidine moiety gave spiroindolizidine-oxindole product with low diastereoselectivities. In addition, we envision that conversion of dibenzylamino-lactam to unsaturated lactam would be more synthetically useful for introduction of other substituents in the form of nucleophiles for Michael and hetero-Michael reactions.

The low diastereoselectivity of oxidative rearrangement of indoloquinolizidine **3.62** and the inseparable nature of the product mixture made it a less attractive starting material. Next, we endeavored in oxidative rearrangement of unsubstituted indoloquinolizidinone enamide **(+)-3.63**. Treatment of this compound with NBS in aqueous THF and catalytic TFA did not yield any desired product. Removal of the Boc protecting group was required and gave the unsaturated indoloquinolizidinone **3.73**. To our pleasant surprise, oxidative rearrangement of this compound gave brominated spiroindolizidine-oxindole **3.74** as a single product and single diastereomer (scheme 74).



Scheme 74 Oxidative rearrangement of indoloquinolizidinone **3.73**

Conformation analysis of tetracyclic enamide **3.73** reveals that the molecule is also flat like indoloquinolizidine **3.62**. However additional steric bias arises from the C1 allylic β-proton of the unsaturated lactam. Bromination of the indole ring occurred from the bottom and subsequent addition of water and rearrangement gave spiroindolizidine-oxindole as a single diastereomer. Electrophilic aromatic bromination then occurred at the accessible C5 to give the brominated product **3.74** (scheme 75). The unsaturated lactam functionality is suitable for installation of substituents at the β-carbon via nucleophilic conjugate addition and potentially at the α-carbon via either tandem α-alkylation of the resulting enolate or subsequent C-alkylation of the lactam. To demonstrate this strategy, unsaturated spirolactam **3.74** was treated with sodium methoxide in methanol to install methyl ether substituent on C2. Gratifyingly, the product **3.75** was obtained as a single diastereomer. The new stereogenic center has the *R*-configuration due to methoxide attack from the *re*-face of the enamide while the *si*-face was blocked by the oxindole ring.



Scheme 75 Stereochemistry of oxidative rearrangement of **3.73** and subsequent conjugate addition

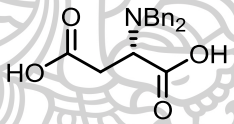
Spiroindolizidine-oxindoles **3.66** and **3.74** were synthesized diastereoselectively in enantiomerically pure form. The spiroindolizidine-oxindole **3.66** has the amino substituent that can be converted to other amine base functionality and potentially can be utilized for synthesis of *N*-substituted analog of spiroindolizidine-oxindole. Elimination of this group by Cope elimination led to unsaturated spirolactam **3.67**. Oxidative ring contraction of tetracyclic enamide **3.73** gave a single diastereomer of brominated spirooxindole **3.74** which has opposite absolute configurations to spirooxindole **3.67a**. The enantiomer **(-)-3.63** would give ***ent*-3.74** making this procedure enantiodivergent from the same starting material, L-glutamic acid. The functionalities of spiroindolizidine-oxindole **3.74**, namely, aryl bromide, enamide and oxindole NH, provide points for further functionalization and synthesis of analogs for biological activity screening.

CHAPTER 4
EXPERIMENTAL PROCEDURE

General

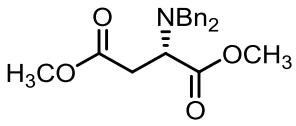
Starting materials and reagents were obtained from commercial sources and were used without further purification. Solvents were dried by distillation from the appropriate drying reagents immediately prior to use. Tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone under argon gas. Toluene and dichloromethane were distilled from calcium hydride under argon gas. Moisture and air-sensitive reactions were carried out under an atmosphere of argon gas. Reaction flasks and glassware were ovendried 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-aspatate



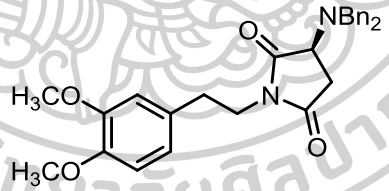
To a solution of L-aspatate (2.00 g, 15.0 mmol) in MeOH and H_2O (1:1, 40 mL) was added NaOH (1.50 g, 37.6 mmol), K_2CO_3 (5.19 g, 37.6 mmol) and BnCl (6.92 ml, 60.1 mmol). The mixture was heated to reflux at 115 ^{o}C overnight and acidified with 1M HCl (pH = 1.6-2.0). Then the reaction was filtrate to give dibenzyl-L-aspatate **3.3** (4.69 g, quant.) as a white solid; ^{1}H 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;
νmax (film) 1751, 1599, 1229, 1170, 1081, 987, 888 cm^{-1}.

Synthesis of dimethyl dibenzyl-L-aspatate



To a solution of dibenzyl-L-aspatate (4.83 g, 15.4 mmol) in Acetone and MeOH (2:1, 150 ml) was added K_2CO_3 (3.20 g, 23.2 mmol) and Me_2SO_4 (3.23 ml, 34.0 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 dimethyl dibenzyl-L-aspatate (5.26 g, quant.) as a yellowish 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; νmax (film) 3029, 2951, 2844, 1733, 1495, 1454, 1436, 1295, 1205, 1166 cm^{-1}.

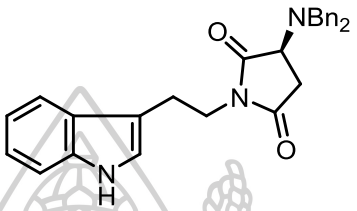
Synthesis of *(S)*-3-(dibenzylamino)-1-(3,4-dimethoxyphenethy)pyrrolidine-2,5-dione (Homo-imide **3.6**)



To a solution of homoveratrylamine (0.11 ml, 0.67 mmol) in dry THF (6 mL) under argon atmosphere at -78 °C was added LDA (0.85 mL of 2.0M solution, 1.69 mmol) and the mixture was stirred for 15 minutes. Then added dimethyl dibenzyl-L-aspatate (0.19 g, 0.56 mmol) to the reaction and the mixture was stirred at room temperature for 3 hours. To this mixture was added dropwise sat. aq. NH_4Cl (10 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 homo imide **3.6** (0.11 g, 45%) as a yellow oil R_f (4:1 hexane/EtOAc) 0.30; ^{1}H NMR (300 MHz,$CDCl_3$) δ 7.35 (dd, *J* = 8.5, 1.9 Hz, 5H), 7.36 – 7.22 (m, 4H), 7.27 – 7.17 (m, 1H), 6.84 – 6.61 (m, 3H), 3.85 (d, *J* = 6.2 Hz, 1H), 3.84 (s, 3H), 3.86 – 3.65 (m, 3H), 3.69 (s, 3H), 3.61 (d, *J* = 13.5 Hz, 2H), 3.45

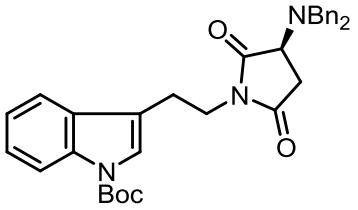
(d, *J* = 13.5 Hz, 2H), 2.98 – 2.79 (m, 2H), 2.68 (dd, *J* = 18.5, 9.0 Hz, 1H), 2.50 (dd, *J* = 18.5, 5.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.15, 176.99, 175.18, 175.06, 138.24, 129.82, 128.78, 128.52, 128.45, 128.37, 127.46, 127.43, 127.37, 120.99, 111.88, 110.96, 57.26, 55.84, 55.64, 54.40, 52.38, 39.36, 32.83, 32.00.

Synthesis of *(S)*-1-(2-(1H-indol-3-yl)ethyl)-3-(dibenzylamino)pyrrolidine-2,5-dione (Tryp-imide **3.25**)



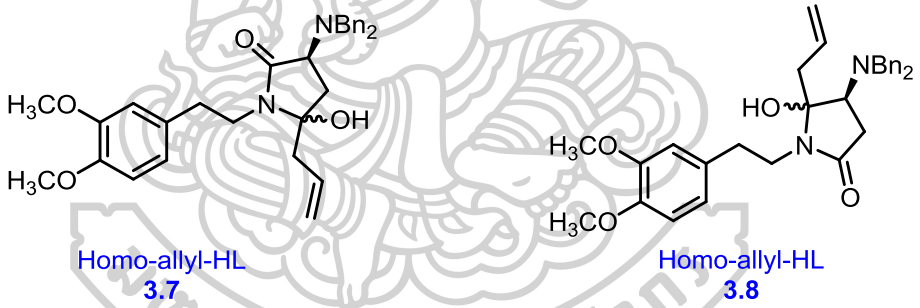
To a solution of tryptamine (0.11 g, 0.69 mmol) in dry THF (6 mL) under argon atmosphere at -78 ^{o}C was added LDA (0.86 mL of 2.0M solution, 1.72 mmol) and the mixture was stirred for 15 minutes. Then added dimethyl dibenzyl-L-aspatate (0.20 g, 0.57 mmol) to the reaction and the mixture was stirred at room temperature for 3 hours. To this mixture was added dropwise sat. aq. NH_4Cl (10 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 tryp-imide **3.25** (0.15 g, 66%) as a green oil R_f (4:1 hexane/EtOAc) 0.20; ^{1}H NMR (300 MHz,$CDCl_3$) δ 8.28 – 8.21 (m, 1H), 7.66 – 7.57 (m, 1H), 7.34 – 7.20 (m, 7H), 7.25 – 7.18 (m, 1H), 7.23 – 7.14 (m, 1H), 7.18 – 7.07 (m, 1H), 7.11 – 6.98 (m, 2H), 6.91 (d, *J* = 2.3 Hz, 1H), 3.90 – 3.66 (m, 5H), 3.54 (d, *J* = 13.5 Hz, 2H), 3.35 (d, *J* = 13.5 Hz, 2H), 3.07 (dt, *J* = 12.2, 6.2 Hz, 1H), 3.04 – 2.92 (m, 1H), 2.54 (dd, *J* = 18.4, 8.8 Hz, 1H), 2.42 (dd, *J* = 18.4, 5.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.19, 175.32, 140.05, 138.30, 136.07, 128.73, 128.37, 128.15, 127.39, 127.34, 126.96, 122.34, 121.93, 119.37, 118.52, 111.58, 111.23, 60.38, 57.41, 54.30, 53.03, 39.15, 31.69, 23.11, 20.98, 14.16.

Synthesis of tert-butyl*(S)*-3-(2-(3-(dibenzylamino)-2,5-dioxopyrrolidin-1-yl)ethyl)-1H-indole-1-carboxylate (Boc-tryp imide **3.26**)



To a solution of tryp-imide **3.25** (0.26 g, 0.58 mmol) in CH_2Cl_2 (6 mL) was added Et_3N (0.41 mL, 2.93 mmol), DMAP (0.01 g, 0.07 mmol) and Boc_2O (0.67 mL, 2.93 mmol). The mixture was stirred at room temperature overnight. To this mixture was added H_2O (50 mL) and the mixture was extracted with CH_2Cl_2 (3 x 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 Boc-tryp-imide **3.26** (354.9 mg, 91%) as a light green oil R_f (4:1 hexane/EtOAc) 0.36; ^{1}H NMR (300 MHz,$CDCl_3$) δ 8.08 (d, *J* = 8.4 Hz, 1H), 7.66 – 7.57 (m, 1H), 7.45 (s, 1H), 7.40 – 7.17 (m, 10H), 3.99 – 3.59 (m, 5H), 3.59 – 3.44 (m, 2H), 3.14 – 2.86 (m, 2H), 2.81 – 2.49 (m, 2H), 1.63 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.12, 175.17, 138.19, 129.43, 128.80, 128.46, 127.45, 124.50, 123.49, 122.59, 118.87, 116.52, 115.30, 83.51, 71.89, 59.22, 57.37, 54.69, 54.46, 54.32, 38.30, 32.09, 28.16, 23.20.

Synthesis of (3S)-5-allyl-3-(dibenzylamino)-1-(3,4-dimethoxyphenethyl)-5-hydroxypyrrolidin-2-one (Homo-allyl-HL **3.7**) **and (4S)-5-allyl-4-(dibenzylamino)-1-(3,4-dimethoxyphenethyl)-5-hydroxypyrrolidin-2-one** (Homo-allyl-HL **3.8**)



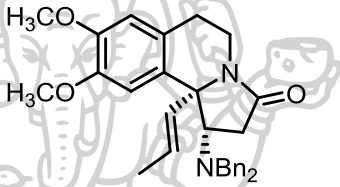
To a solution of homo-imide **3.6** (840 mg, 1.840 mmol) in Et_2O (20 mL) was added freshly prepared AllylMgBr (Allyl bromide 0.48 mL, 5.52 mmol, Mg 402 mg, 16.56 mmol) at -78 ^{o}C and the mixture was stirred for 3 h. To this mixture was added dropwise sat. aq. NH_4Cl (30 mL) and the mixture was extracted with CH_2Cl_2 (3 x 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 a homo-allyl-HL **3.7** (445 mg, 48%) and homo-allyl-HL **3.8** (203 mg, 22%) as a yellowish oil R_f (2:1 hexane/EtOAc) 0.40, 020 for **3.7** and **3.8** reespectively;

Homo-allyl-HL **3.7**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.32 (m, 4H), 7.32 – 7.14 (m, 6H), 6.78 – 6.64 (m, 3H), 5.51 (ddt, *J* = 17.2, 9.7, 7.1 Hz, 1H), 5.08 – 4.94 (m, 2H), 3.88 (d, *J* = 13.8 Hz, 2H), 3.87 – 3.73 (m, 6H), 3.66 (s, 1H), 3.62 (s, 1H), 3.53 (q, *J* = 9.3 Hz, 2H), 3.27 (ddd, *J* = 13.4, 9.9, 6.1 Hz, 1H), 2.89 (dddd, *J* = 34.5, 13.1,

9.9, 5.8 Hz, 2H), 2.40 (ddd, *J* = 13.7, 8.3, 5.6 Hz, 2H), 2.22 (dd, *J* = 14.0, 7.2 Hz, 1H), 1.87 (dd, *J* = 13.7, 8.4 Hz, 1H).

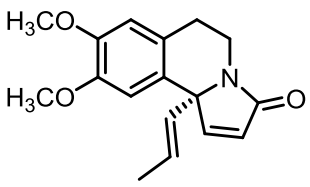
Homo-allyl-HL **3.8**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.19 (m, 10H), 6.83 – 6.73 (m, 2H), 6.65 (d, *J* = 8.0 Hz, 1H), 6.26 (s, 1H), 5.22 (ddt, *J* = 18.8, 9.2, 7.2 Hz, 1H), 4.85 – 4.73 (m, 2H), 3.84 (s, 3H), 3.82 – 3.69 (m, 5H), 3.75 – 3.62 (m, 1H), 3.52 – 3.43 (m, 1H), 3.40 (s, 1H), 3.38 – 3.23 (m, 2H), 3.04 – 2.85 (m, 2H), 2.62 (dd, *J* = 18.0, 1.3 Hz, 1H), 2.51 – 2.14 (m, 3H).

Synthesis of (1S,10bR)-1-(dibenzylamino)-8,9-dimethoxy-10b-((E)-prop-1-en-1-yl)-1,5,6,10b tetrahydropyrrolo[2,1-a]isoquinolin-3(2H)-one (Tricyclic indolizidine core **3.5**)



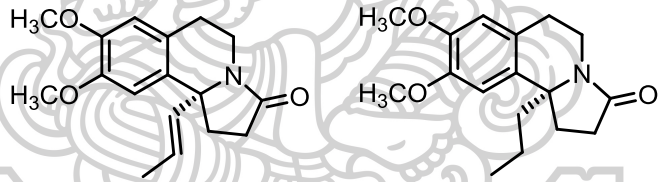
To a solution of homo-allyl-HL **3.8** (100 mg, 0.201 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added TMSOTf (0.11 mL, 0.603 mmol) via syringe. The mixture was stirred at this temperature for 3 h CH_2Cl_2 (10.0 mL) and sat. aq. $NaHCO_3$ (10 mL) were added and phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 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 provide tricyclic indolizidine core **3.5** (56 mg, 58%) as yellowish oils R_f (2:1 hexane/EtOAc) 0.23; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.21 (m, 8H), 6.55 (s, 1H), 5.86 (dq, *J* = 15.5, 1.5 Hz, 1H), 5.36 (dq, *J* = 15.5, 6.5 Hz, 1H), 4.33 – 4.21 (m, 1H), 4.00 (d, *J* = 14.2 Hz, 2H), 3.88 – 3.74 (m, 7H), 3.58 (d, *J* = 14.2 Hz, 2H), 3.09 – 2.81 (m, 2H), 2.64 – 2.47 (m, 2H), 2.05 (dd, *J* = 16.4, 8.0 Hz, 1H), 1.62 (dd, *J* = 6.5, 1.6 Hz, 3H).

Synthesis of (S,E)-8,9-dimethoxy-10b-(prop-1-en-1-yl)-6,10b-dihydropyrrolo[2,1-a]isoquinolin-3(5H)-one (Tricyclic enamide **3.9**)



To a solution of tricyclic indolizidine core **3.5** (56 mg, 0.117 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added m-CPBA (58 mg, 0.234 mmol) and the mixture was stirred for 24 h. To this mixture was added sat. aq. Na_2CO_3 (10 mL) and the mixture was stirred for 15 min. The phases were separated and the organic layer was 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 tricyclic enamide **3.9** (14 mg, 41%) as a colorless oil; R_f (1:1 hexane/EtOAc) 0.25; ^{1}H NMR (300 MHz,$CDCl_3$) δ 7.33 (d, J = 5.7 Hz, 1H), 6.68 (s, 1H), 6.65 (s, 1H), 6.14 (d, J = 5.8 Hz, 1H), 5.50-5.40 (m, 2H), 4.33 (ddd, J = 13.2, 6.7, 1.2 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.21 (ddd, J = 13.1, 11.5, 4.8 Hz, 1H), 2.95 (ddd, J =16.4, 11.3, 6.5 Hz, 1H), 2.67 (ddd, J = 16.0, 4.7, 1.5 Hz, 1H), 1.70 (d, J = 4.8 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 170.1, 151.5, 148.4, 147.4, 131.1, 129.1, 126.5, 126.4, 125.3, 112.0, 110.4, 69.4, 56.2, 55.9, 34.6, 29.0, 17.7; ; $[\alpha]_{25}^{D}$ 76.4 (c 0.6, CHCl3); ν_{max} (film) 2938, 1686, 1516, 1265, 735 cm^{-1}; ESI-HRMS calculated for $C_{17}H_{20}NO_3$ $[M+H]^+$ 286.1438, found 286.1431.

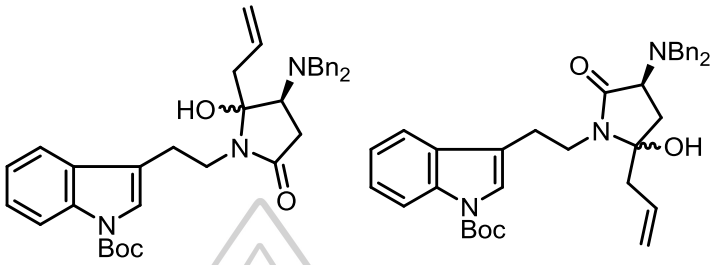
Synthesis of (*R*,*E*)-8,9-dimethoxy-10b-(prop-1-en-1-yl)-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3(2*H*)-one (Tricyclic lactam **3.4** & Tricyclic propane **3.4a**)



Tricyclic lactam **3.4** Tricyclic propane **3.4a**

To solution of tricyclic enamide **3.9** (22 mg, 0.076 mmol) in Toluene (1 mL) was added Palladium on carbon (0.01 g, 25 mol%), CH_3COOH (0.01 mL, 0.15 mmol) and $NaBH_4$ (11 mg, 0.306 mmol). The mixture was stirred at room temperature for 30 minutes and acidified with 1M HCl then sat. aq. $NaHCO_3$ (5 mL) were added and phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 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 flash chromatography (silica gel, 2:1 hexane/EtOAc) to provide a mixture of tricyclic lactam **3.4** and tricyclic propane **3.4a**(16 mg, 72%) as colorless oils R_f (1:1 hexane/EtOAc) 0.33; ^{1}H NMR (300 MHz,$CDCl_3$) δ 6.61 – 6.53 (m, 2H), 4.25 (dddd, *J* = 34.4, 12.6, 6.5, 1.8 Hz, 1H), 3.87 (dd, *J* = 6.6, 1.5 Hz, 5H), 3.17 – 2.80 (m, 2H), 2.73 – 2.60 (m, 1H), 2.66 – 2.51 (m, 1H), 2.51 – 2.32 (m, 2H), 2.22 – 2.03 (m, 1H), 1.81 (ddd, *J* = 9.3, 6.0, 2.4 Hz, 1H), 1.67 (dd, *J* = 6.5, 1.6 Hz, 1H), 1.48 – 1.18 (m, 1H), 0.91 (t, *J* = 7.3 Hz, 1H).

Synthesis of tert-butyl 3-(2-((3S)-2-allyl-3-(dibenzylamino)-2-hydroxy-5-oxopyrrolidin-1-yl)ethyl)-1H-indole-1-carboxylate (Boc-tryp-allyl HL **3.27**) **and tert-butyl 3-(2-((4S)-2-allyl-4-(dibenzylamino)-2-hydroxy-5-oxopyrrolidin-1-yl)ethyl)-1H-indole-1-carboxylate** (Boc-tryp-allyl-HL **3.27a**)



Boc-tryp-allyl-HL **3.27** Boc-tryp-allyl-HL **3.27a**

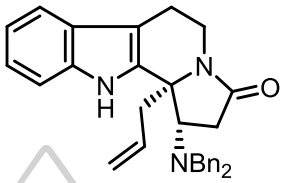
To a solution of Boc-typ imide **3.26** (287 mg, 0.536 mmol) in Et_2O (6 mL) was added freshly prepared AllylMgBr (Allyl bromide 0.14 mL, 1.61 mmol, Mg 117 mg, 4.82 mmol) at -78 ^oC and the mixture was stirred for 3 h. To this mixture was added dropwise sat. aq. NH_4Cl (30 mL) and the mixture was extracted with CH_2Cl_2 (3 x 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 a Boc-tryp-allyl HL **3.27** (118 mg, 38%) and Boc-tryp-allyl-HL **3.27a** (116 mg, 45%) as a yellowish oil R_f (2:1 hexane/EtOAc) 0.33, 013 for **3.27** and **3.27a** reespectively;

Boc-tryp-allyl HL **3.27**; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, *J* = 2.2 Hz, 1H), 7.72 – 7.63 (m, 1H), 7.45 – 7.17 (m, 11H), 7.22 – 7.07 (m, 1H), 7.13 – 6.99 (m, 1H), 6.94 – 6.87 (m, 1H), 5.51 (ddt, *J* = 17.3, 10.2, 7.2 Hz, 1H), 5.07 – 4.93 (m, 2H), 3.85 (dd, *J* = 31.2, 13.4 Hz, 2H), 3.68 (s, 1H), 3.69 – 3.51 (m, 2H), 3.54 – 3.27 (m, 2H), 3.16 – 2.97 (m, 2H), 2.39 (ddd, *J* = 13.7, 8.2, 5.6 Hz, 2H), 2.23 (dd, *J* = 13.7, 6.5 Hz, 1H), 1.86 (dd, *J* = 13.7, 8.2 Hz, 1H), 1.26 (s, 9H). ^{13}C (75 MHz, $CDCl_3$) δ 173.30, 139.42, 136.18, 131.47, 128.93, 128.83, 128.73, 128.26, 127.26, 127.03, 122.26, 121.93, 120.05, 119.33, 118.95, 113.04, 111.25, 88.55, 59.07, 54.77, 43.05, 40.14, 36.95, 29.68, 28.18, 24.96.

Boc-tryp-allyl-HL **3.27a**; ^1H NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.74 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.35 (s, 1H), 7.38 – 7.30 (m, 1H), 7.33 – 7.13 (m, 12H), 7.11 (ddd, *J* = 6.6, 4.3, 1.6 Hz, 2H), 6.97 (d, *J* = 2.2 Hz, 1H), 5.32 – 5.12 (m, 1H), 4.83 – 4.70 (m, 2H), 3.85 (s, 1H), 3.81 (s, 1H), 3.79 – 3.67 (m, 1H), 3.53 – 3.28 (m, 5H), 3.22 – 3.05 (m, 2H), 2.64 (d, *J* = 17.9 Hz, 1H), 2.43 (dd, *J* = 18.0, 8.3 Hz, 1H), 2.25 (t, *J* = 6.8 Hz, 2H), 1.26 (s, 9H). ^{13}C (75 MHz, $CDCl_3$) δ 172.17, 137.35, 136.25, 131.56, 128.93,

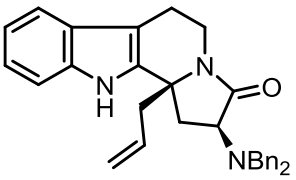
128.70, 127.69, 127.37, 122.06, 121.82, 119.22, 119.03, 113.04, 111.14, 89.76, 57.88, 54.77, 42.83, 40.36, 29.73, 29.67, 25.13.

Synthesis of (1S,11bS)-1-(dibenzylamino)-11b-((E)-prop-1-en-1-yl)-1,2,5,6,11,11b-hexahydro-3H-indolizino[8,7-b]indol-3-one (Tetracyclic indolizidine core **3.24**)



To a solution of Boc-tryp-allyl HL **3.27** (104 mg, 0.179 mmol) in CH_2Cl_2 (5 mL) at 0°C was added BF_3•OEt_2 (0.14 mL, 0.537 mmol) via syringe. The mixture was stirred at this temperature for 3 h CH_2Cl_2 (10.0 mL) and sat. aq. $NaHCO_3$ (10 mL) were added and phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 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 provide Tetracyclic indolizidine core **3.24** (40 mg, 48%) as yellowish oils R_f (2:1 hexane/EtOAc) 0.73; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.33 (m, 5H), 7.37 – 7.09 (m, 9H), 7.15 – 7.02 (m, 1H), 5.82 (ddt, *J* = 17.3, 9.9, 7.3 Hz, 1H), 5.25 – 5.05 (m, 2H), 4.58 – 4.36 (m, 1H), 4.04 – 3.89 (m, 2H), 3.74 (d, *J* = 13.8 Hz, 2H), 3.66 – 3.46 (m, 1H), 3.25 (td, *J* = 12.8, 12.3, 5.1 Hz, 1H), 3.03 – 2.78 (m, 1H), 2.65 (dd, *J* = 15.1, 6.0 Hz, 2H), 2.57 – 2.38 (m, 1H), 2.37 – 2.23 (m, 1H). ^{13}C (75 MHz, $CDCl_3$) δ 175.40, 139.48, 128.69, 128.63, 128.36, 128.29, 128.21, 127.01, 126.94, 126.76, 122.30, 120.57, 119.83, 118.40, 111.01, 108.11, 54.85, 45.59, 36.00, 31.79, 31.74, 31.58, 20.27.

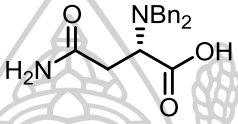
Synthesis of (2S,11bR)-11b-allyl-2-(dibenzylamino)-1,2,5,6,11,11b-hexahydro-3H-indolizino[8,7-b]indol-3-one (Tetracyclic indolizidine core **3.24a**)



To a solution of Boc-tryp-allyl HL **3.27a** (98.2 mg, 0.205 mmol) in CH_2Cl_2 (5 mL) at 0°C was added BF_3•OEt_2 (0.16 mL, 0.615 mmol) via syringe. The mixture was stirred at this temperature for 3 h CH_2Cl_2 (10.0 mL) and sat. aq. $NaHCO_3$ (10 mL) were added and phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 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 provide Tetracyclic indolizidine core **3.24a** (28 mg, 29%) as yellowish oils R_f (2:1 hexane/EtOAc) 0.35;

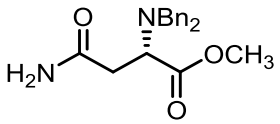
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.46 – 7.22 (m, 5H), 7.18 – 7.03 (m, 3H), 5.49 (ddt, *J* = 17.1, 9.5, 4.6 Hz, 1H), 5.04 (dt, *J* = 17.1, 1.9 Hz, 1H), 4.92 (dt, *J* = 10.1, 1.8 Hz, 1H), 4.54 – 4.41 (m, 1H), 4.00 (d, *J* = 13.8 Hz, 2H), 3.75 (dd, *J* = 11.5, 8.3 Hz, 1H), 3.54 (d, *J* = 13.8 Hz, 2H), 3.23 (dt, *J* = 14.0, 8.6 Hz, 1H), 3.14 (ddd, *J* = 14.2, 4.5, 2.2 Hz, 1H), 2.88 – 2.79 (m, 1H), 2.79 – 2.66 (m, 3H), 2.44 (dd, *J* = 16.2, 8.4 Hz, 1H).^{13}C (75 MHz, $CDCl_3$) δ 171.51, 138.33, 136.14, 135.55, 133.78, 129.19, 128.90, 128.79, 127.84, 126.74, 126.49, 121.73, 119.53, 118.55, 118.28, 111.53, 107.44, 77.46, 77.24, 77.04, 76.62, 65.30, 65.17, 56.82, 39.99, 36.02, 30.21, 20.63, 0.34.

Synthesis of dibenzyl-L-asparaginate



To a solution of L-aspagine (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, 83.3 mmol) and BnCl (15.46 ml, 133 mmol). The mixture was heated to reflux at 115 °C overnight and acidified with 1M HCl. Then the mixture was extracted with CH_2Cl_2 (3 x 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-asparaginate (6.00 g, 54%) as a pale-yellow oil R_f (2:1 hexane/EtOAc) 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, CDCl3) 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.

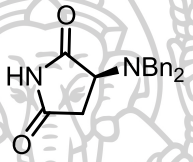
Synthesis of methyl ester dibenzyl-L-asparaginate



To a solution of dibenzyl-L-asparaginate (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

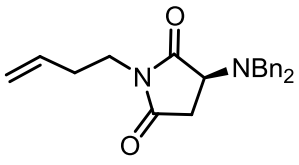
concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 2:1 hexane/EtOAc) to give methyl ester dibenzyl-L-asparaginate (1.97 g, 59%) as a colorless oil. R_f (2:1 hexane/EtOAc) 0.08; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.17 (m, 10H), 6.16 (brs, 1H), 5.49 (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, 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 (c1.6, $CHCl_3$); 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 (*N*,*N*-dibenzylamino-succinimide **3.45**)



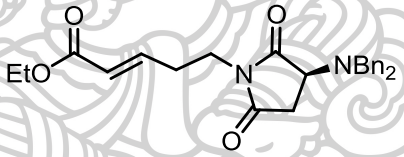
To a solution of methyl ester dibenzyl-L-asparaginate (1.25 g, 3.83 mmol) in dry THF (10 mL) under argon atmosphere at -78 °C was added LDA (4.82 mL of 1.59M solution, 7.67 mmol) and the mixture was stirred for 2 hours at -78 °C. To this mixture was added dropwise sat. aq. NH_4Cl (20 mL) and the mixture 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 *N*,*N*-dibenzylamino-succinimide **3.45** (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); 13C NMR (75 MHz, CDCl3) 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 (Butenyl succinimide **3.58**)



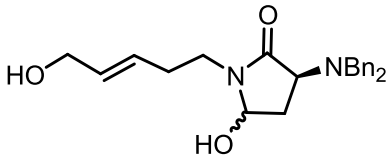
To a solution of *N*,*N*-dibenzylamino-succinimide **3.45** (57.0 mg, 0.194 mmol) in DMF (5 mL) under argon atmosphere at room temperature was added K_2CO_3 (0.05 g, 0.388 mmol), KI (3.2 mg, 0.019 mmol) and 4-bromo-1-butene (0.024 mL, 0.23 mmol) and the mixture was stirred for 2 hours. To this mixture 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 Butenyl succinimide **3.58** (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); 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, $CHCl_3$); 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 ethyl (*S*,*E*)-5-(3-(dibenzylamino)-2,5-dioxopyrrolidin-1-yl)pent-2-enoate (Ester **3.57**)



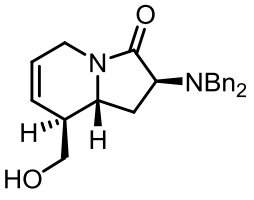
To a solution of Butenyl succinimide **3.58** (335.1 mg, 0.9616 mmol) in dry CH_2Cl_2 (10 mL) under argon atmosphere at room temperature was added ethylacrylate (0.51 mL, 4.8081 mmol) and Hoveyda-Grubbs catalyst^{TM} 2nd generation (6.0 mg, 9.616 µmol). Then the mixture was heated to reflux at 40 ^{o}C 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 Ester **3.57** (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, 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; $[\alpha]_{25}^{D}$ -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 (Hydroxylactam **3.59**)

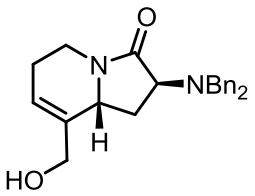


To a solution of Ester **3.57** (447.6 mg, 1.0643 mmol) in toluene (10 mL) under argon atmosphere at -78 °C was added DIBALH (3.19 mL of 1 M solution, 3.1930 mmol) and the mixture was stirred for 2 hours at -78 °C. To this mixture was added dropwise MeOH (3 mL) and sat. aq. $NaHCO_3$ (20 mL). Then the 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 **3.59** (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, 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; $[\alpha]_{25}^{D}$+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)-1,5,8,8atetrahydroindolizin-3(2*H*)-one (Bicyclic indolizidine core **3.56**) **and (2*S*)-2-(dibenzylamino)-8(hydroxymethyl)1,5,6,8atetrahydroindolizin-3(2*H*)-one** (Bicyclic indolizidine core **3.56a**)



Bicyclic indolizidine core
3.56



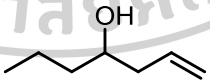
Bicyclic indolizidine core
3.56a

To a solution of hydroxylactam **3.59** (24.0 mg, 0.0631 mmol) in dry CH_2Cl_2 (3 mL) under argon atmosphere at 0°C was added TMSOTf (34 µL, 0.189 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 preparative thin layer chromatography (silica gel, 1:2 hexane/EtOAc) to give bicyclic indolizidine core **3.56** (2.3 mg, 10%) and bicyclic **3.56a** (5.3 mg, 23 %) as yellow oils.

(2*S*)-2-(dibenzylamino)-8-(hydroxymethyl)-1,5,8,8a-tetrahydroindolizin-3(2*H*)-one (3.56); 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, CDCl3) 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.

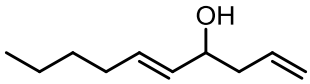
(2*S*)-2-(dibenzylamino)-8-(hydroxymethyl)-1,5,6,8a-tetrahydroindolizin-3(2*H*)-one (3.56a); R_f (1:2 hexane/EtOAc) 0.31; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.12 (m, 10H), 5.74 (d, *J* = 5.6 Hz, 1H), 4.26 (dd, *J* = 13.0, 6.3 Hz, 1H), 4.09 (d, *J* =12.0 Hz, 2H), 3.86 (d, *J* = 13.5 Hz, 2H), 3.68 (d, *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 hept-1-en-4-ol (2° alcohol **3.46a**)



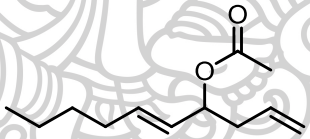
To a solution of butyraldehyde (0.4 mL, 4.44 mmol) in Et_2O (20 mL) was added freshly prepared AllylMgBr (Allyl bromide 1.15 mL, 13.3 mmol, Mg 0.97 g, 40.0 mmol) at 0°C and the mixture was stirred for 3 h. To this mixture was added dropwise sat. aq. NH_4Cl (20 mL) and the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was not purified and give 2° alcohol **3.46a** (0.82 g, quant.) as a yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.02 – 5.56 (m, 1H), 5.20 – 4.77 (m, 2H), 3.94 – 3.56 (m, 1H), 2.39 – 2.07 (m, 2H), 1.73 – 1.25 (m, 4H), 1.06 – 0.80 (m, 3H).

Synthesis of (*E*)-deca-1,5-dien-4-ol (2° alcohol **3.46e**)



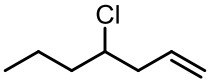
To a solution of trans-2-Heptenal (0.3 mL, 2.27 mmol) in Et_2O (15 mL) was added freshly prepared AllylMgBr (Allyl bromide 0.59 mL, 6.81 mmol, Mg 0.50 g, 20.4 mmol) at -78 °C and the mixture was stirred for 3 h. To this mixture was added dropwise sat. aq. NH_4Cl (20 mL) and the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was not purified and give 2° alcohol **3.46e** (0.45 g, quant.) as a yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92 – 5.54 (m, 2H), 5.48 (ddt, *J* = 15.4, 6.8, 1.4 Hz, 1H), 5.19 – 5.05 (m, 2H),4.16-4.07 (q, 1H), 2.38 – 2.19 (m, 2H), 2.04 (q, *J* = 6.7 Hz, 2H), 1.47 – 1.23 (m, 4H), 0.90 (m, 3H).

Synthesis of *(E)*-deca-1,5-dien-4-yl acetate (2° acetate **3.52e**)



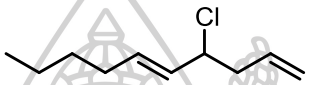
To a solution of 2° alcohol **3.46e** (0.85 g, 5.54 mmol) in CH_2Cl_2 (20 mL) was added pyridine (0.54 mL, 6.65 mmol) at 0°C and then added Ac_2O (0.63 mL, 6.65 mmol). The mixture was stirred at room temperature overnight. To this mixture was added water (20 mL) and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was not purified and give 2° acetate **3.52e** (0.71 g, 65%) as a brown oil; ^{1}H NMR (300 MHz,$CDCl_3$) δ 5.85 – 5.59 (m, 2H), 5.32 – 5.01 (m, 2H), 5.09 (s, 1H), 4.17-4.07 (q, 1H), 2.44 – 2.19 (m, 2H), 2.06 (s, 3H), 2.12 – 1.96 (m, 2H), 1.44 – 1.20 (m, 4H), 0.97 – 0.83 (m, 3H).

Synthesis of 4-chlorohept-1-ene (2° chloride **3.51a**)



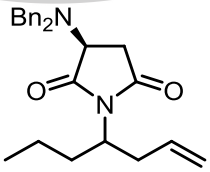
To a solution of 2º alcohol **3.46a** (0.32 g, 2.80 mmol) in CH_2Cl_2 (30 mL) was added pyridine (0.23 mL, 2.80 mmol) at 0ºC and then added $SOCl_2$ (0.20 mL, 2.80 mmol). The mixture was stirred at room temperature overnight. To this mixture was acidified with 5M HCl and the mixture was extracted with CH_2Cl_2 (3 × 10 mL), H_2O (3 × 10 mL) and and sat. aq. Na_2CO_3 (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was not purified and give 2º chloride **3.51a** (0.16 g, 44%) as a brown oil.

Synthesis of *(E)*-4-chlorodeca-1,5-diene (2º chloride **3.51e**)



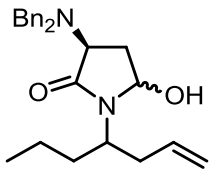
To a solution of 2º alcohol **3.46e** (0.80 g, 5.20 mmol) in CH_2Cl_2 (40 mL) was added pyridine (0.42 mL, 5.20 mmol) at 0ºC and then added $SOCl_2$ (0.38 mL, 5.20 mmol). The mixture was stirred at room temperature overnight. To this mixture was acidified with 5M HCl and the mixture was extracted with CH_2Cl_2 (3 × 10 mL), H_2O (3 × 10 mL) and and sat. aq. Na_2CO_3 (10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was not purified and give 2º chloride **3.51e** (0.63 g, 71%) as a brown oil; ^{1}H NMR (300 MHz,$CDCl_3$) δ 5.91 – 5.63 (m, 2H), 5.63 – 5.46 (m, 1H), 5.19 – 4.99 (m, 2H), 4.37 (dq, *J* = 8.4, 6.5 Hz, 1H), 2.80 (td, *J* = 6.3, 1.5 Hz, 1H), 2.56 (tt, *J* = 6.8, 1.3 Hz, 1H), 2.11 – 1.98 (m, 1H), 1.88 – 1.70 (m, 1H), 1.49 – 1.29 (m, 4H), 0.91 (dt, *J* = 7.3, 3.3 Hz, 3H).

Synthesis of (3S)-3-(dibenzylamino)-1-(hept-1-en-4-yl)pyrrolidine-2,5-dione (*N*-alkylate **3.44a**)



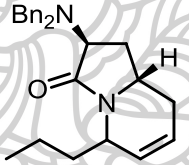
To a solution of 2º chloride **3.51a** (45 mg, 0.34 mmol) in DMF (5 mL) under argon atmosphere at room temperature was added K_2CO_3 (57 mg, 0.41 mmol), KI (6.8 mg, 0.041 mmol) and *N*,*N*-dibenzylamino-succinimide **3.45** (0.10 g, 0.34 mmol) and the mixture was stirred for 2 hours. To this mixture 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 *N*-alkylate **3.44a** (0.11 g, 81%) as a brown oil.

Synthesis of (3S)-3-(dibenzylamino)-1-(hept-1-en-4-yl)-5-hydroxypyrrolidin-2-one (Hydroxylactam **3.53a**)



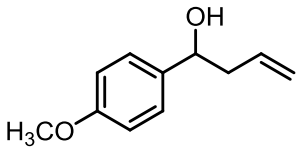
To a solution of *N*-alkylate **3.44a** (36 mg, 0.09 mmol) in toluene (10 mL) under argon atmosphere at -78 °C was added DIBALH (0.23 mL of 1.2 M solution, 0.27 mmol) and the mixture was stirred for 2 hours at -78 °C. To this mixture was added dropwise MeOH (3 mL) and sat. aq. $NaHCO_3$ (20 mL). Then 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 **3.53a** (39 mg, quant.) as a brown oil. R_f (2:1 hexane/EtOAc) 0.03.

Synthesis of (2S,8aS)-2-(dibenzylamino)-5-propyl-1,5,8,8a-tetrahydroindolizin-3(2H)-one (Bicyclic indolizidine core **3.50a**)



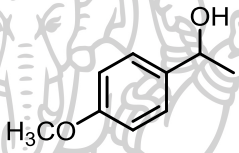
To a solution of hydroxylactam **3.53a** (38.5 mg, 0.097 mmol) in dry CH_2Cl_2 (3 mL) under argon atmosphere at 0°C was added TMSOTf (50 µL, 0.29 mmol) and the mixture was stirred for 2 hours at 0°C to room temperature. To this mixture was added dropwise sat. aq. $NaHCO_3$ (5 mL) and the mixture was 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 preparative thin layer chromatography (silica gel, 2:1 hexane/EtOAc) to give bicyclic indolizidine core **3.50a** (2.3 mg, 10%) as a yellowish oil.

Synthesis of 1-(4-methoxyphenyl)but-3-en-1-ol (Secondary alcohol **3.46c**)



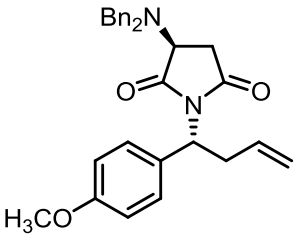
To a solution of freshly prepared AllylMgBr (Allyl bromide 1.53 mL, 17.6 mmol, Mg 1.29 g, 52.9 mmol) in Et_2O (10 mL) at -78 °C was added anisaldehyde (0.54 mL, 4.41 mmol) and the mixture was stirred for 3 h. To this mixture was added dropwise sat. aq. NH_4Cl (10 mL) and the mixture was extracted with CH_2Cl_2 (2 x 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 secondary alcohol **3.46c** (511 mg, 65%) as a colorless oil R_f (4:1 hexane/EtOAc) 0.53; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 8.9, 2.4 Hz, 2H), 6.93 – 6.84 (m, 2H), 5.80 (ddt, *J* = 17.2, 10.1, 7.1 Hz, 1H), 5.16 (dq, *J* = 10.3, 1.3 Hz, 1H), 5.17 – 5.08 (m, 1H), 4.69 (td, *J* = 6.5, 3.0 Hz, 1H), 3.81 (s, 3H), 2.56 – 2.44 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.05, 134.62, 127.09, 118.26, 113.81, 77.45, 77.03, 76.61, 72.99, 55.29, 43.76.

Synthesis of 1-(4-methoxyphenyl)ethan-1-ol (Secondary alcohol **3.46f**)



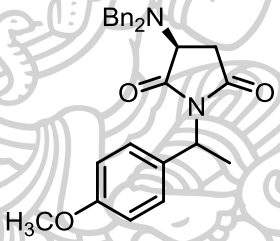
To a solution of freshly prepared MethylMgBr (Methyliodide 1.10 mL, 17.6 mmol, Mg 1.29 g, 52.9 mmol) in Et_2O (10 mL) at 0 °C was added anisaldehyde (0.54 mL, 4.41 mmol) and the mixture was stirred for 3 h. To this mixture was added dropwise sat. aq. NH_4Cl (10 mL) and the mixture was extracted with CH_2Cl_2 (2 x 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 secondary alcohol **3.46f** (0.7414 g, quant.) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.6 Hz, 3H), 6.79 (d, *J* = 8.7 Hz, 3H), 4.71 (q, *J* = 6.4 Hz, 2H), 3.70 (s, 6H), 1.37 (d, *J* = 6.5 Hz, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.66, 138.46, 126.81, 113.72, 113.68, 69.37, 54.95, 25.17.

Synthesis of *(S)*-3-(dibenzylamino)-1-(*(R)*-1-(4-methoxyphenyl)but-3-en-1yl)pyrrolidine-2,5-dione (*N*-alkylate **3.44c**)



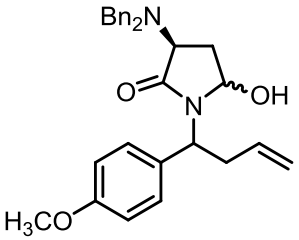
To a solution of Secondary alcohol **3.46c** (0.60 g, 3.39 mmol) in THF (10 mL) was added succinimide **3.45** (0.99 g, 3.39 mmol), PPh_3 (0.89 g, 3.39 mmol) and DIAD (0.67 mL, 3.39 mmol). The mixture was heated to reflux at 120 °C overnight. To this mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 2:1 hexane/EtOAc) to give *N*-alkylate **3.44c** (63 mg, 36%) as a yellowish oil R_f (4:1 hexane/EtOAc) 0.33; ^{1}H NMR (300 MHz,$CDCl_3$) δ 7.45 – 7.20 (m, 12H), 6.87 – 6.78 (m, 2H), 5.81 – 5.60 (m, 1H), 5.28 (ddd, *J* = 11.0, 9.4, 5.7 Hz, 1H), 5.19 – 5.06 (m, 1H), 5.01 (ddd, *J* = 10.4, 1.8, 0.8 Hz, 1H), 3.91 – 3.68 (m, 2H), 3.76 (s, 4H), 3.56 (d, *J* = 13.6 Hz, 2H), 3.42 – 3.22 (m, 1H), 2.89 – 2.74 (m, 1H), 2.68 (dt, *J* = 18.4, 9.2 Hz, 1H), 2.51 (ddd, *J* = 18.5, 7.0, 5.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.43, 175.20, 159.25, 138.39, 134.59, 134.51, 130.74, 130.56, 129.47, 129.43, 128.71, 128.46, 127.40, 118.27, 118.18, 113.77, 56.85, 55.22, 54.58, 54.50, 54.24, 54.17, 34.57, 34.53, 32.29, 31.98, 31.93. $[\alpha]_{25}^{D}$-10.1 (c1.6, $CHCl_3$)

Synthesis of *(3S)*-3-(dibenzylamino)-1-(1-(4-methoxyphenyl)ethyl)pyrrolidine-2,5-dione (*N*-alkylate **3.44f**)



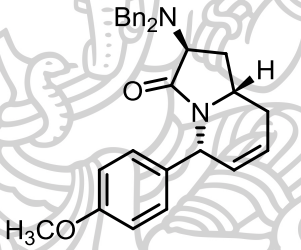
To a solution of Secondary alcohol **3.46f** (0.26 g, 1.73 mmol) in THF (6 mL) was added succinimide **3.45** (0.51 g, 1.73 mmol), PPh_3 (0.45 g, 1.73 mmol) and DIAD (0.34 mL, 1.73 mmol). The mixture was heated to reflux at 120 °C overnight. To this mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 2:1 hexane/EtOAc) to give *N*-alkylate **5.11f** (354 mg, 48%) as a colorless oil R_f (4:1 hexane/EtOAc) 0.36; ^{1}H NMR (300 MHz,$CDCl_3$) δ 7.42 – 7.18 (m, 12H), 6.87 – 6.78 (m, 2H), 5.39 (dd, *J* = 7.5, 6.1 Hz, 1H), 3.91 – 3.72 (m, 5H), 3.71 (d, *J* = 13.5 Hz, 1H), 3.57 (dd, *J* = 13.5, 6.3 Hz, 2H), 2.69 (ddd, *J* = 18.5, 9.1, 3.2 Hz, 1H), 2.52 (ddd, *J* = 18.5, 5.2, 3.1 Hz, 1H) 1.78 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.28, 177.20, 175.08, 175.03, 159.10, 138.32, 131.86, 131.59, 130.35, 128.89, 128.84, 128.77, 128.47, 127.43, 113.68, 77.46, 77.04, 76.62, 56.93, 56.78, 55.22, 54.67, 54.52, 54.48, 49.77, 49.65, 32.45, 32.23, 16.84, 16.69. $[\alpha]_{25}^{D}$-18.5 (c1.6, $CHCl_3$)

Synthesis of *(3S)*-3-(dibenzylamino)-5-hydroxy-1-(1-(4-methoxyphenyl)but-3-en-1-yl)pyrrolidin-2-one (hydroxylactam **3.48c**)



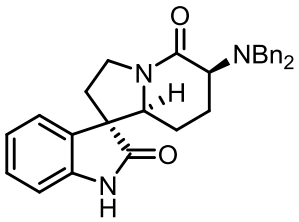
To a solution of *N*-alkylate **3.44c** (0.30 g, 0.65 mmol) in dry toluene (5 mL) at -78 °C was added DIBALH (1.63 mL, 1.63 mmol) and the mixture was stirred for 1 h. To this mixture was added dropwise sat. aq. $NaHCO_3$ (10 mL) and the mixture was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product was obtained without purification to give hydroxylactam **3.48a** (0.30 g, 82%) as a yellowish oil

Synthesis of *(2S)*-2-(dibenzylamino)-5-(4-methoxyphenyl)-1,5,8,8a-tetrahydroindolizin-3*(2H)*-one (Bicyclic indolizidine core **3.43c**)



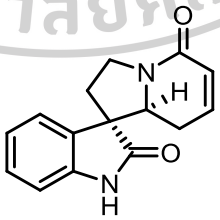
To a solution of hydroxylactam **3.48c** (0.22 g, 0.48 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C was added TMSOTf (0.22 mL, 1.21 mmol) and the mixture was stirred for 3 h. To this mixture was added dropwise sat. aq. $NaHCO_3$ (10 mL) and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic 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 indolizidine core **3.43c** (15 mg, 9%) as a white oil R_f (2:1 hexane/EtOAc) 0.70; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.22 (m, 6H), 7.27 – 7.15 (m, 1H), 6.82 (ddd, *J* = 11.2, 8.7, 6.5 Hz, 1H), 6.01 – 5.71 (m, 1H), 5.70 – 5.48 (m, 1H), 4.04 – 3.84 (m, 1H), 3.88 – 3.68 (m, 3H), 3.71 – 3.48 (m, 2H). 2.76 - 2.48 m, 1H), 2.46 - 2.35 (m, 1H), 2.32 - 2.25 (m, 1H), 2.25 - 2.19 (m, 1H), 2.17 - 1.98 (m, 1H), 1.97 - 1.76 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.15, 139.81, 139.70, 132.52, 129.44, 129.17, 128.85, 128.75, 128.69, 128.43, 128.31, 128.23, 127.79, 126.91, 126.70, 126.48, 125.61, 124.27, 113.82, 77.45, 77.03, 76.60, 59.77, 58.78, 55.26, 54.79, 54.60, 54.48, 52.33, 51.72, 47.89, 47.37, 47.17, 46.38, 33.65, 32.45, 29.78, 29.71, 28.99, 27.53.

Synthesis of Spiro[6-dibenzylaminoindolizidine-1,3'-oxindole] 3.66



To a solution of dibenzylamino-indoloquinolizidinone **3.62a** (452 mg, 1.04 mmol) in THF (10 mL) and H_2O (10 mL) was added NBS (407 mg, 2.20 mmol) in one portion. To this mixture was added TFA (10 mL) and the mixture was stirred for 16 h. Saturated aqueous solution of $NaHCO_3$ (10 mL) and EtOAc (10 mL) were added and the phases were separated. The aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried (anh. Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 1:2 hexane/EtOAc) to give the spiroindolizidine-oxindole **3.66** as colorless oil (366 mg, 78%); R_f (1:2 hexane/EtOAc) 0.29; ^1H (300 MHz, $CDCl_3$) 9.00 (s, 1H), 7.42 (d, *J* = 7.2 Hz, 4H) 7.34-7.16 (m, 7H), 7.08-6.93 (m, 3H), 4.13-4.01 (m, 1H), 4.08 (d, *J* = 13.9 Hz, 2H), 3.91-3.78 (m, 2H), 3.68 (d, *J* = 14.0 Hz, 2H), 3.37 (t, *J* = 6.8 Hz, 1H), 2.48 (dd, *J* = 12.6, 10.3 Hz, 1H), 2.06 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 1.88-1.74 (m, 2H), 1.55 (dd, *J* = 13.6, 5.8 Hz, 1H), 1.19 (dd, *J* = 13.6, 8.1 Hz, 1H); ^{13}C (75 MHz, $CDCl_3$) 177.9, 171.0 140.4, 140.2 (2C), 129.8, 128.7, 128.6 (4C), 128.2 (4C), 126.8 (2C), 124.0, 122.9, 110.4, 63.3, 57.5, 56.0, 55.3, 44.0, 33.3, 29.6, 25.1, 22.2; $[\alpha]_{25}^{D}$ +45.5 (c 1.1, CH_2Cl_2); ν_{max} (film) 3202, 2946, 2890, 1723, 1618, 1471, 1333, 1315, 818 cm^{-1}; ESI-HRMS calculated for $C_{29}H_{30}N_3O_2$ $[M+H]^+$ 452.2332, found 452.2324.

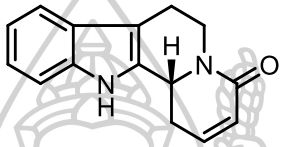
Synthesis of Spiro[indolizidine-1,3'-oxindole] 3.67



To a solution of benzoindolizidine **3.66** (301 mg, 0.66 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added *m*CPBA (70%w/w, 197 mg, 0.80 mmol) and the mixture was stirred for 15 minutes. To this mixture was added sat. aq. Na_2CO_3 (10 mL) and the mixture was stirred for 15 min. The phases were separated and the organic layer was dried (anhyd. 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 enamide **(+)-3.67** (106 mg, 62%) as a colorless oil; R_f (1:2 hexane/EtOAc) 0.20; ^1H (300 MHz, $CDCl_3$) 8.06 (brs, 1H), 7.30 (td, *J* =7.7, 1.1 Hz, 1H), 7.14 (d, *J* = 7.0 Hz,

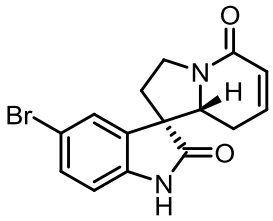
1H), 7.10 (t, *J* = 7.7 Hz, 1H), 6.97 (d, *J* = 7.7 Hz, 1H), 6.45 (ddd, *J* = 9.8, 6.2, 2.0 Hz, 1H), 5.95 (dd, *J* = 9.8, 2.9 Hz, 1H), 4.28 (dd, *J* = 13.9, 5.7 Hz, 1H) 4.05 (dd, *J* = 11.2, 10.5 Hz, 1H), 3.99 (ddd, *J* = 10.7, 7.6, 7.6 Hz, 1H), 2.53 (dt, *J* = 12.7, 10.5 Hz, 1H), 2.12 (ddd, *J* = 12.5, 7.4, 1.3 Hz, 1H, 2.04 (dt, *J* = 17.5, 6.0 Hz, 1H), 1.84 (dddd, *J* = 17.1, 14.2, 2.7, 2.7 Hz, 1H); ^{13}C (75 MHz, $CDCl_3$); 177.2, 163.9, 139.9, 138.3, 129.9, 128.8, 125.1, 124.6, 123.2, 110.2, 62.4, 57.3, 43.6, 33.7, 25.3; $[\alpha]_{25}^{D}$ +20.5 (c 1.0, $CHCl_3$); ν_{max} (film) 3204, 2926, 1720, 1655, 1471, 1336, 1228, 1155, 822, 795 cm^{-1}; ESI-HRMS calculated for $C_{15}H_{15}N_2O_2$ $[M+H]^+$ 255.1134, found 255.1126.

Synthesis of Indoloquinolizidine-enamide 3.73



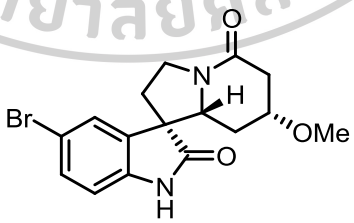
To a solution of *N*-Boc-indoloquinolizidine-enamide **(+)-3.63** (260 mg, 0.77 mmol) in THF (10 mL) at 0°C was added TFA (0.12 mL, 1. 54 mmol) and the mixture was stirred for 3 h. To this mixture was added sat. aq. $NaHCO_3$ (10 mL). The phases were separated and the organic layer was dried (anhyd Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 1:2 hexane/EtOAc) to give indoloquinolizidine-enamide **(+)-3.73** (174 mg, 95%) as a colorless oil; R_f (1:2 hexane/EtOAc) 0.50; ^{1}H (300 MHz, $CDCl_3$); 7.91 (brs, 1H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.36 (d, *J* = 7.5 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 6.67 (ddd, *J* = 9.8, 6.4, 2.4 Hz, 1H), 6.10 (dd, *J* = 9.8, 3.0 Hz, 1H), 5.03 (ddd, *J* = 12.8, 4.6, 3.1 Hz, 1H), 4.89 (dd, *J* = 13.6, 4.7 Hz, 1H), 2.98-2.82 (m, 4H), 2.46 (dddd, *J* = 16.6, 14.0, 2.6, 2.6 Hz, 1H); ^{13}C (75 MHz, $CDCl_3$); 163.5, 136.7, 135.0, 130.9, 126.9, 125.6, 121.1, 118.1, 116.8, 109.8, 108.0, 50.0, 37.3, 29.7, 19.4; $[\alpha]_{25}^{D}$ +50.0 (c 1.3, $CHCl_3$); ν_{max} (film) 3261, 2847, 1656, 1599, 1325, 1303, 1138, 1056, 816 cm^{-1}; ESI-HRMS calculated for $C_{15}H_{14}N_2NaO$ $[M+Na]^+$ 261.0998, found 261.0996.

Synthesis of Spiro[indolizidine-1,3'-bromooxindole] 3.74



To a solution of indoloquinolizidinone **3.73** (160 mg, 0.67 mmol) in THF (8 mL) and H_2O (8 mL) was added NBS (263 mg, 1.48 mmol) in one portion. To this mixture was added TFA (6 mL) and the mixture was stirred for 16 h. Saturated aqueous solution of $NaHCO_3$ (10 mL) and EtOAc (10 mL) were added and the phases were separated. The aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried (anh. Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 1:2 hexane/EtOAc) to give the spiroindolizidine-bromooxindole **3.74** as a colorless oil (163 mg, 73%); R_f (1:2 hexane/EtOAc) 0.20; ^1H (300 MHz, $CDCl_3$) 8.81 (brs, 1H), 7.43 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.27 (d, *J* = 1.9 Hz, 1H), 6.89 (d, *J* = 8.3 Hz, 1H), 6.46 (ddd, *J* = 9.8, 6.1, 2.0 Hz, 1H), 5.99 (dd, *J* = 9.8, 2.5 Hz, 1H), 4.26 (dd, *J* = 14.0, 5.6 Hz, 1H), 4.07 (t, *J* = 10.8 Hz, 1H), 3.92-3.80 (m, 1H), 2.53 (dt, *J* = 12.7, 10.3 Hz, 1H), 2.13 (ddd, *J* = 12.9, 7.8, 1.6 Hz, 1H), 2.06 (dt, *J* = 17.4, 5.7 Hz, 1H), 1.88 (dddd, *J* = 17.4, 14.2, 2.7, 2.7 Hz, 1H) ; ^{13}C (75 MHz, $CDCl_3$) 174.8, 161.8, 137.0, 139.3, 136.1, 129.7, 129.6, 125.2, 122.9, 113.6, 109.6, 60.2, 55.4, 41.2, 31.4, 23.1; $[\alpha]_{25}^{D}$ +35.1 (c 1.1, CH_2Cl_2); ν_{max} (film) 3195, 3018, 2920, 2891, 1725, 1656, 1596, 1473, 1336, 1205, 1165, 823, 800 cm^{-1}; ESI-HRMS calculated for $C_{15}H_{13}BrN_2NaO_2$ $[M+Na]^+$ 355.0058, found 355.0053.

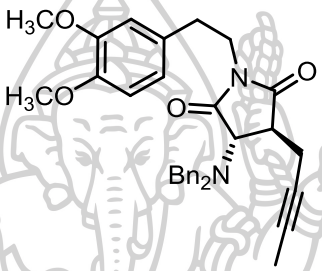
Synthesis of Spiro[7-methoxyindolizidine-1,3'-bromooxindole] 3.75



To a solution of NaOMe in MeOH (26 mg of Na, 1.14 mmol, in 5 mL of MeOH) was added a solution of benzoindolizidine **3.74** (127 mg, 0.38 mmol) in MeOH (3 mL) at 0 °C and the mixture was stirred for 3 h. To this mixture were added sat. 1N HCl (8 mL) and CH_2Cl_2 (12 mL). The phases were separated and the organic layer was dried (anhyd 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 spiro[7-methoxyindolizidine-1,3'-bromooxindole] **3.75** (90 mg, 65%) as a colorless oil; R_f (1:2 hexane/EtOAc) 0.38; ^1H (300 MHz, $CDCl_3$); 8.32

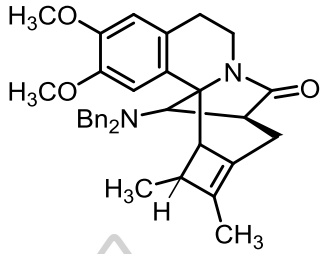
(brs, 1H), 7.41 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.05 (d, *J* =1.7 Hz, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 4.21 (dd, *J* = 11.5, 3.6 Hz, 1H), 4.06-3.78 (m, 2H), 3.76-3.68 (m, 1H), 3.29 (s, 3H), 2.75-2.20 (m, 3H), 2.09 (ddd, *J* = 12.9, 8.7, 2.0 Hz, 1H), 1.89 (ddd, *J* = 13.7, 6.1, 3.6 Hz, 1H), 1.00 (td, *J* = 13.7, 2.0 Hz, 1H); ^{13}C (75 MHz, $CDCl_3$); 175.2, 166.1, 137.5, 130.5, 130.1, 125.2, 114.3, 110.2, 58.5, 55.5, 54.6, 42.3, 34.6, 31.5, 28.1, 25.8; $[\alpha]_{25}^{D}$ -45.5 (c 0.4, $CHCl_3$); ν_{max} (film) 3455, 2970, 2920, 2850, 1737, 1725, 1615, 1365, 1228, 1217, 1205, 1262, 764, 749 cm^{-1}; ESI-HRMS calculated for $C_{16}H_{18}BrN_2O_3$ $[M+H]^+$ 365.0501, found 365.0495.

Synthesis of (3S,4S)-3-(but-2-yn-1-yl)-4-(dibenzylamino)-1-(3,4-dimethoxyphenethyl)pyrrolidine-2,5-dione (Alkyne **3.16**)



To a solution of Homo-imide (0.32 g, 0.71 mmol) in dry THF (7 mL) under argon atmosphere at -78 ºC was added LDA (0.36 mL of 2.0M solution, 0.71 mmol) and the mixture was stirred for 30 minutes. Then added butynyl bromide (0.03 mL, 0.36 mmol) to the reaction and the mixture was stirred at room temperature for 3 hours. To this mixture was added dropwise sat. aq. NH_4Cl (10 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 alkyne **3.16** (112 mg, 73%) as a yellow oil R_f (4:1 hexane/EtOAc) 0.30; ^{1}H NMR (300 MHz,$CDCl_3$) 7.46 – 7.15 (m, 9H), 6.92 (s, 0H), 6.81 – 6.62 (m, 2H), 3.87 (s, 3H), 3.83 – 3.79 (m, 1H), 3.77 (d, *J* = 3.4 Hz, 1H), 3.73 (d, *J* = 6.6 Hz, 2H), 3.71 (s, 2H), 3.55 (s, 1H), 2.95 – 2.79 (m, 1H), 2.72 – 2.54 (m, 2H), 2.48 – 2.25 (m, 1H), 1.60 – 1.42 (m, 3H). ^{13}C (75 MHz, $CDCl_3$) 176.37, 176.07, 148.92, 148.45, 148.42, 147.78, 138.56, 129.94, 128.99, 128.83, 128.79, 128.53, 128.38, 127.59, 127.35, 126.95, 120.97, 111.89, 110.90, 78.86, 78.79, 73.34, 61.44, 61.31, 55.86, 55.66, 55.26, 55.22, 43.49, 39.33, 32.90, 18.02.

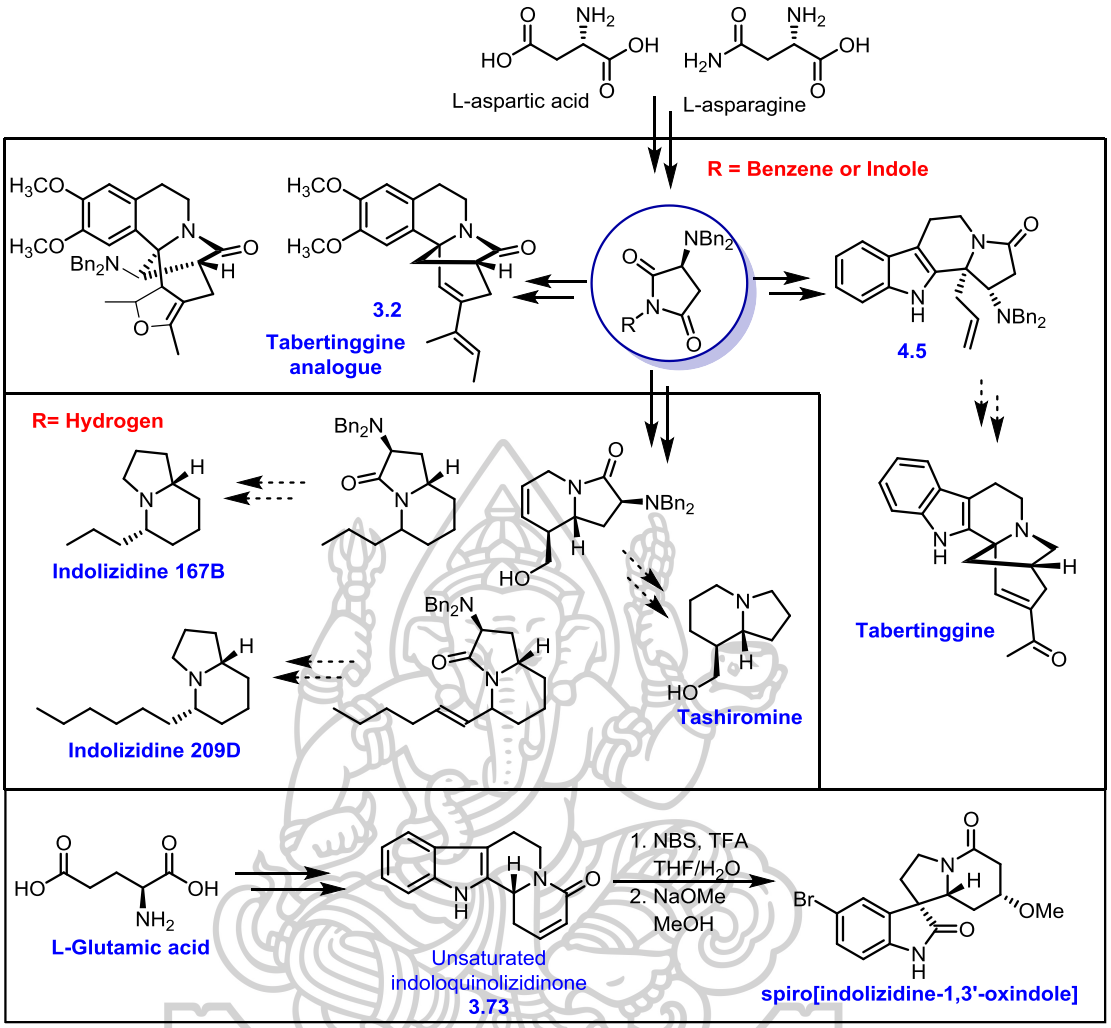
Synthesis of (4S)-13-(dibenzylamino)-10,11-dimethoxy-1,2-dimethyl-1,3,4,7,8,12c-hexahydro-5H-4,12b-methanocyclobuta[3,4]azepino[2,1-a]isoquinolin-5-one (Cyclobutene **3.18**)



To a solution of Hydroxylactam intermediate which was synthesized from nucleophilic addition with allylmagnesiumbromide without purification from Alkyne **3.16** (109 mg, 0.197 mmol) in CH_2Cl_2 (2 mL) at 0°C was added TMSOTf (0.11 mL, 0.591 mmol) via syringe. The mixture was stirred at this temperature for 3 h CH_2Cl_2 (10.0 mL) and sat. aq. $NaHCO_3$ (10 mL) were added and phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 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 provide cyclobutene **3.18** (24 mg, 30% 2 steps) as yellowish oils ^{1}H NMR (300 MHz,$CDCl_3$) 7.44 – 7.35 (m, 4H), 7.35 – 7.12 (m, 5H), 6.63 (s, 1H), 6.54 (s, 1H), 4.29 (ddd, *J* = 13.2, 7.4, 2.8 Hz, 1H), 3.85 (s, 1H), 3.95 – 3.75 (m, 7H), 3.73 (s, 1H), 3.50 – 3.37 (m, 3H), 3.30 – 3.14 (m, 1H), 3.09 – 2.89 (m, 2H), 2.82 – 2.60 (m, 2H), 2.50 (dq, *J* = 12.5, 6.8 Hz, 1H), 2.23 – 2.01 (m, 4H), 1.88 (t, *J* = 13.1 Hz, 1H), 1.54 (dd, *J* = 13.3, 11.8 Hz, 1H), 1.36 – 1.19 (m, 1H), 0.99 (d, *J* = 6.8 Hz, 3H). ^{13}C (75 MHz, $CDCl_3$) 170.96, 147.94, 147.55, 140.24, 139.53, 134.24, 133.26, 128.91, 128.73, 128.20, 126.96, 125.03, 120.61, 116.37, 111.98, 107.91, 77.47, 77.04, 76.62, 66.58, 60.63, 55.93, 55.80, 54.43, 42.97, 42.92, 34.69, 29.26, 28.88, 27.33, 19.54, 16.62, 14.21.

CHAPTER 5
CONCLUSION

In summary, the synthetic studies of tabertinggine analogue, tabertinggine, indolizidine 167B, Indolizidine 209D and tashiromine have been discussed. This research shows that the useful succinimide intermediate which was derived from L-aspartic acid or L-asparagine can be a good option in synthetic approach of natural products especially alkaloids which containing pyrrolidine ring such as tabertinggine, indolizidine and tashiromine. Glutarimide which was derived from L-glutamic acid and L-glutamine can be also useful in synthesis of natural product such as lupinine, a quinolizidine homolog of tashiromine. The key step of the synthesis, *N*-acyliminium ion cyclization was achieved to construct an indolizidine core of tabertinggine and its analog. Ene-yne metathesis, another key step to construct a bridge-azabicyclo[3.2.1]octene was also successful. While Tsuji-Trost allylation gave product in low yield. In addition, the versatility of this methodology led to a synthesis of related indolizidine alkaloid, namely, spiroindolizidine-oxindole alkaloids from oxidative rearrangement of indoloquinolizidinone precursor synthesized from L-glutamic acid.



Scheme 76 Conclusion for this research

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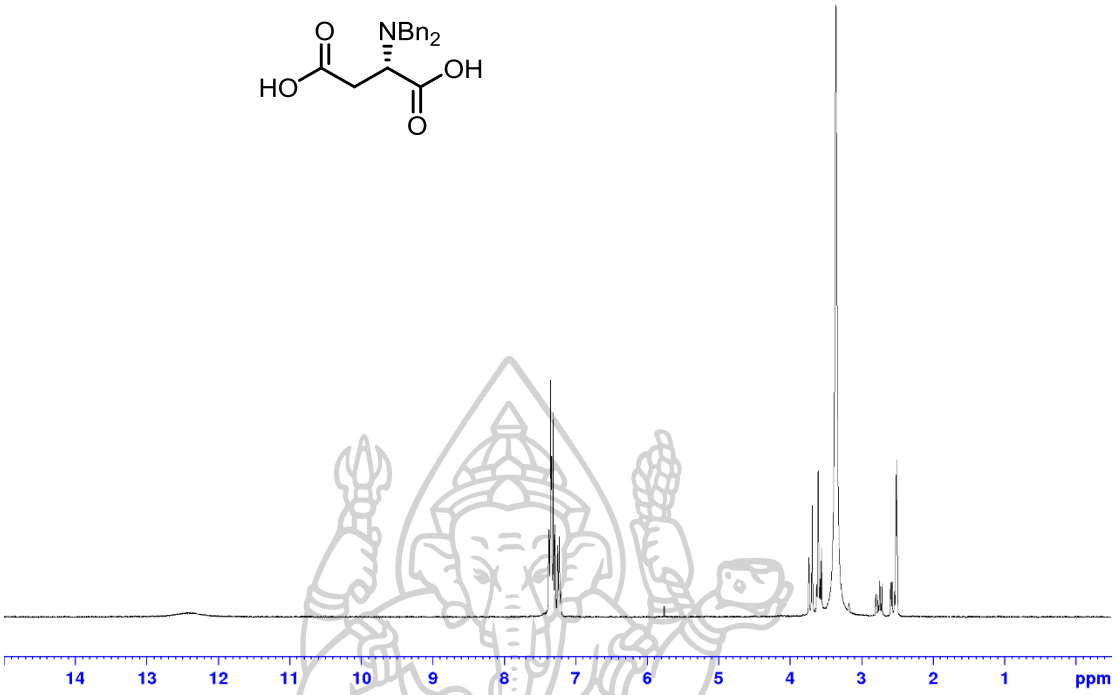
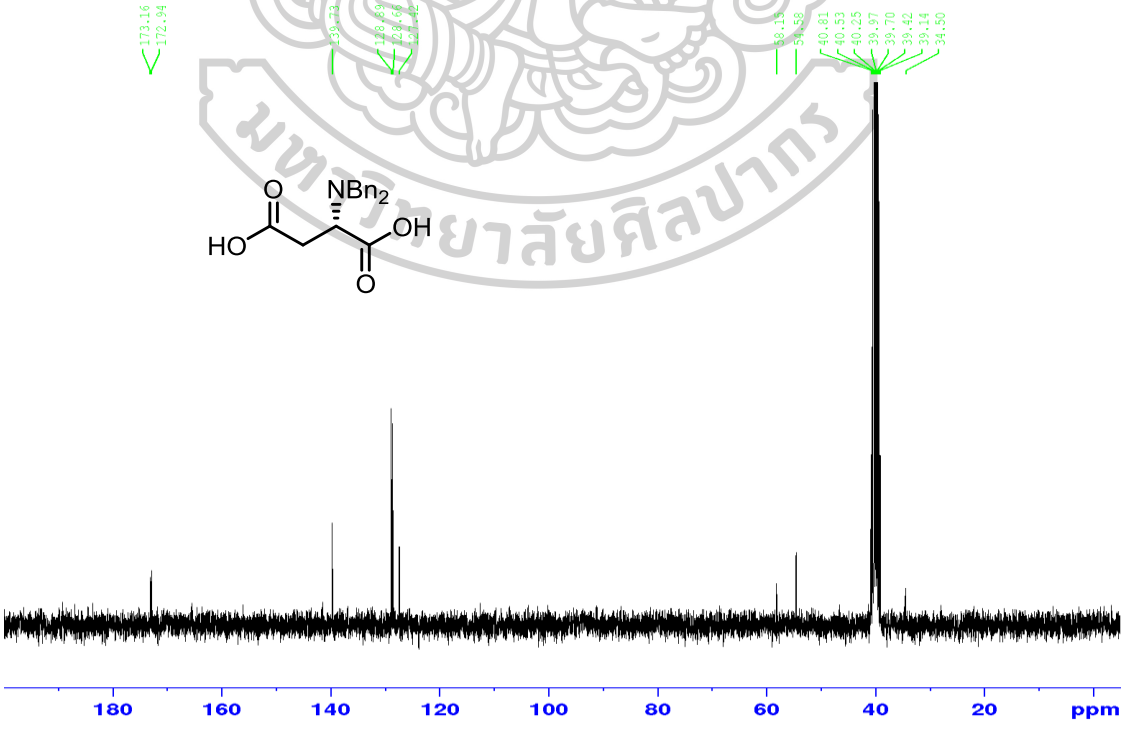
APPENDIX



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



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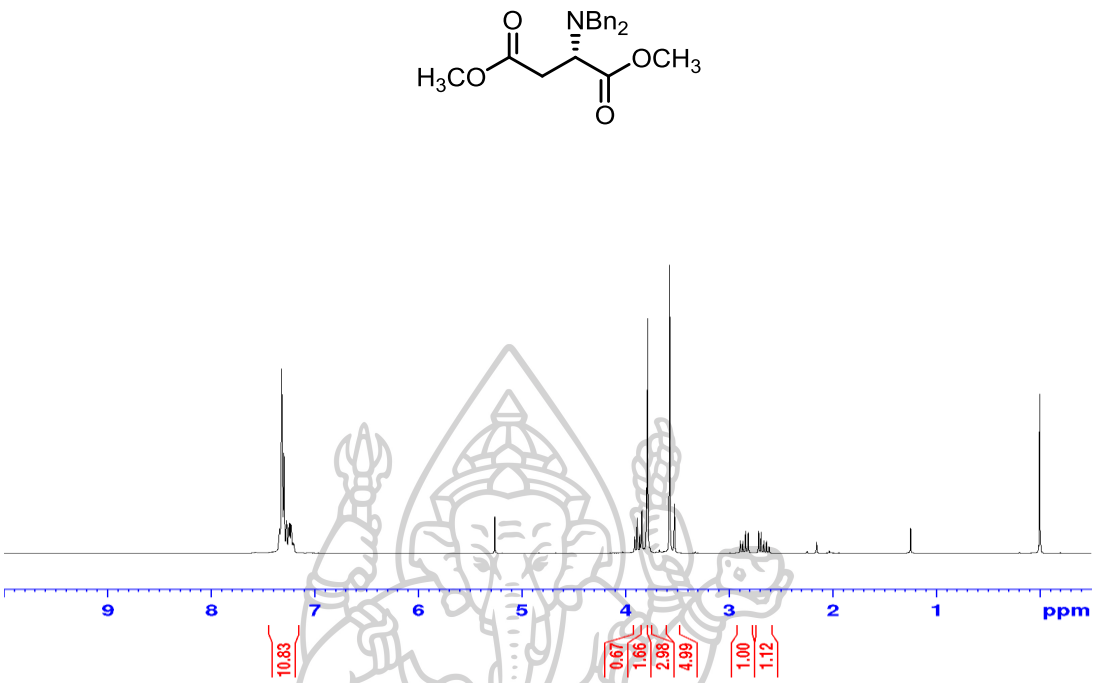

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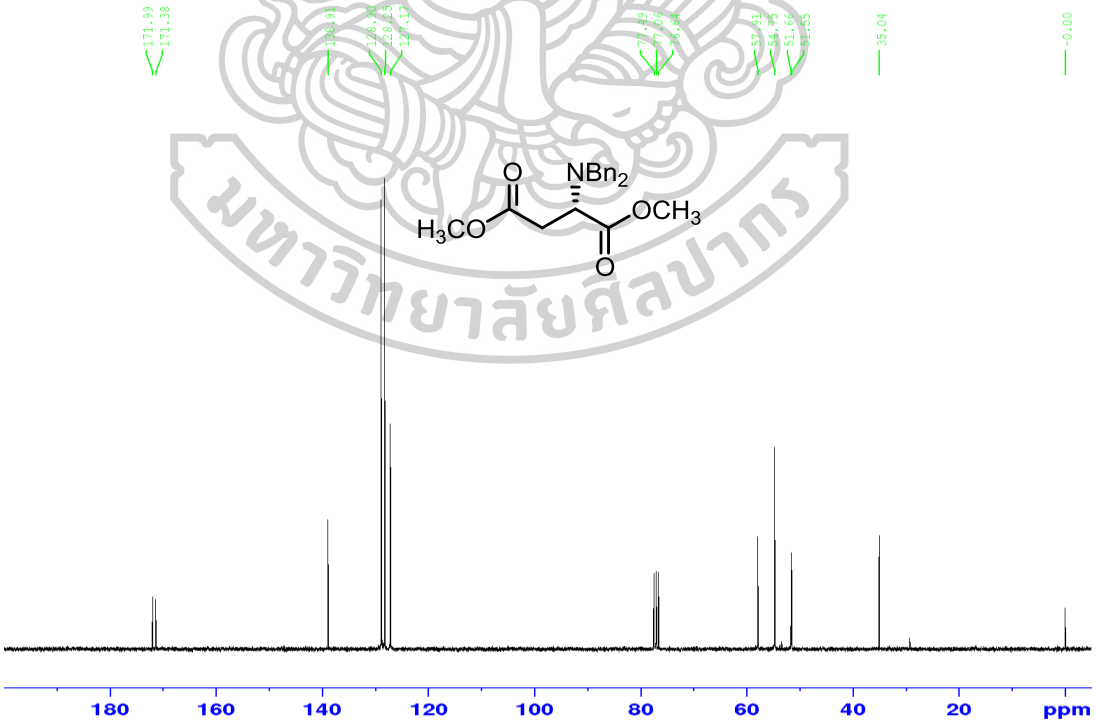

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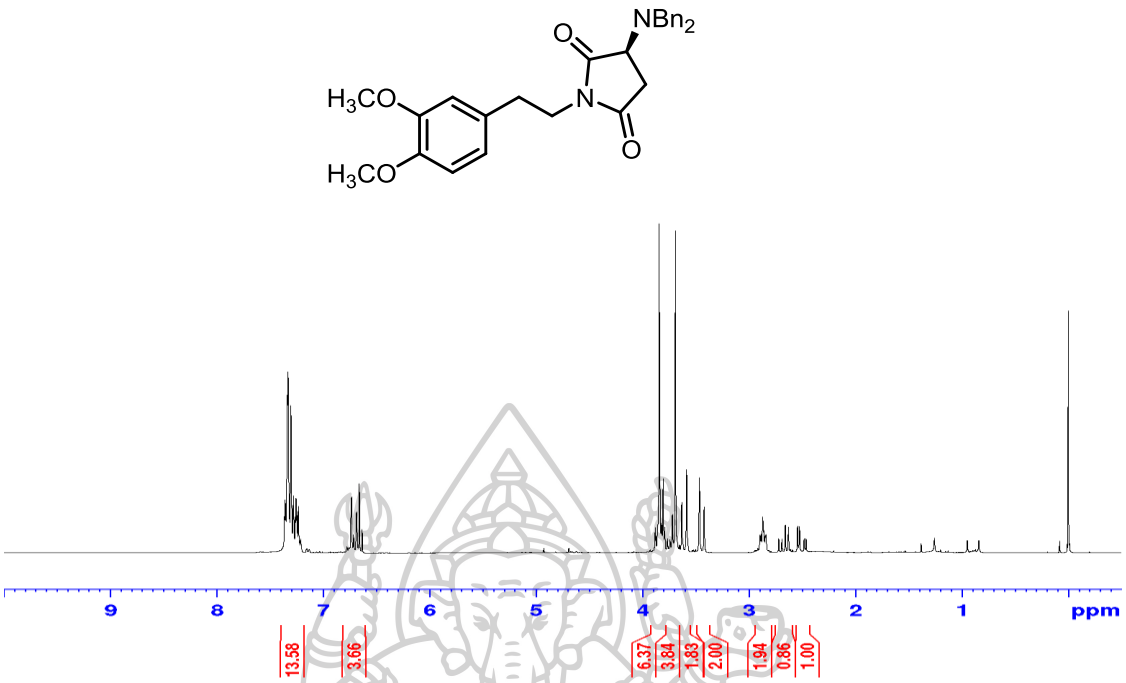
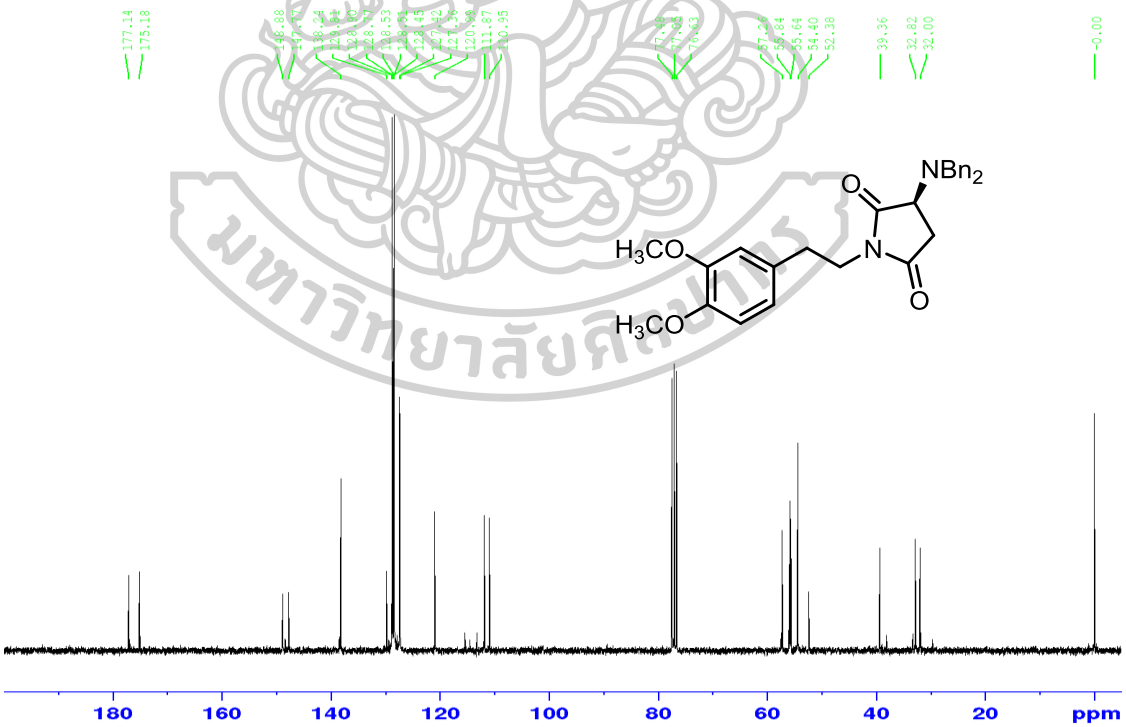


^{1}H NMR of Homo-imide **3.6**



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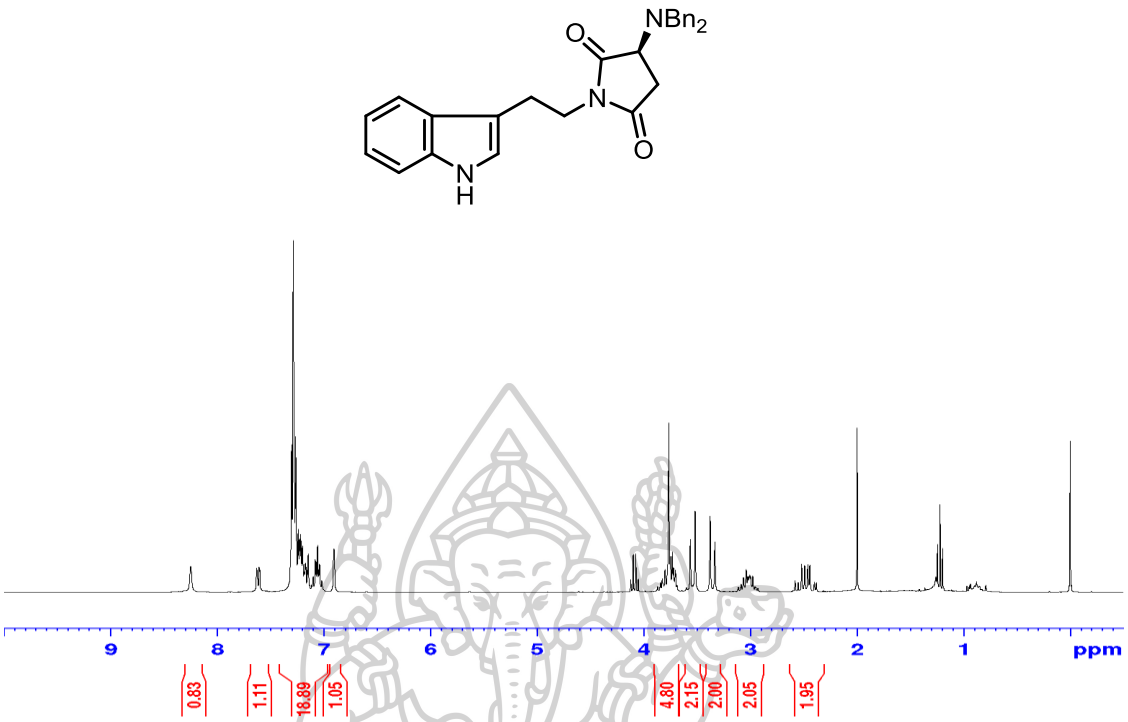

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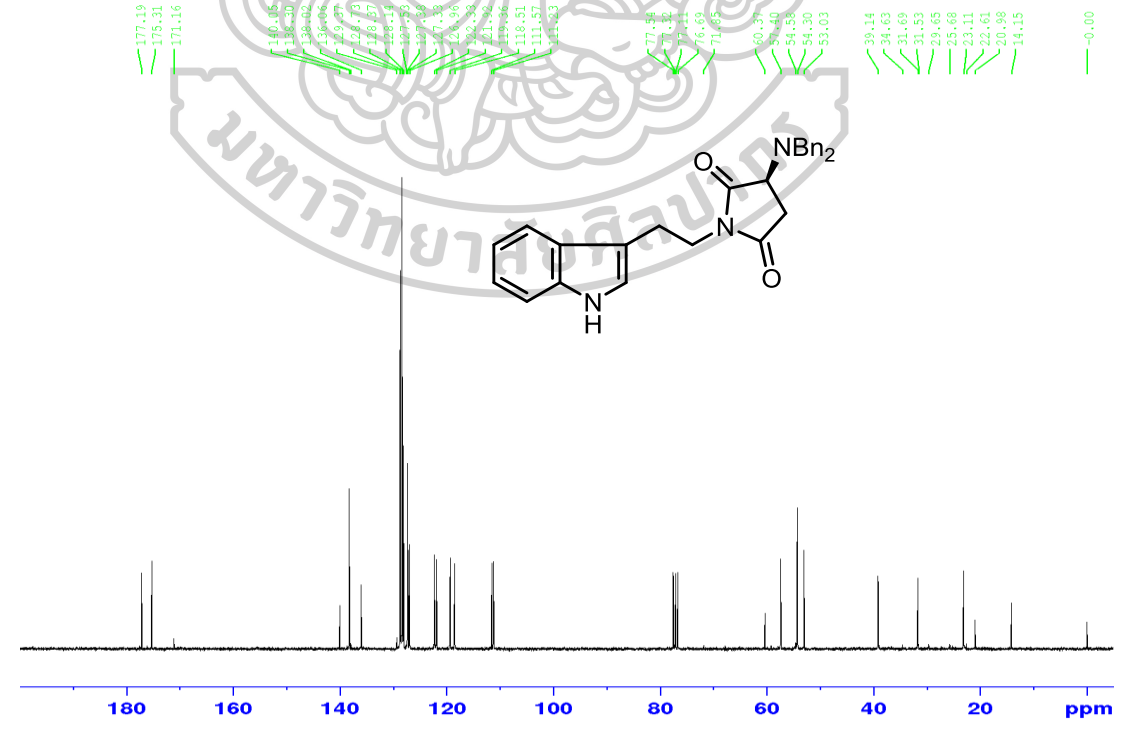

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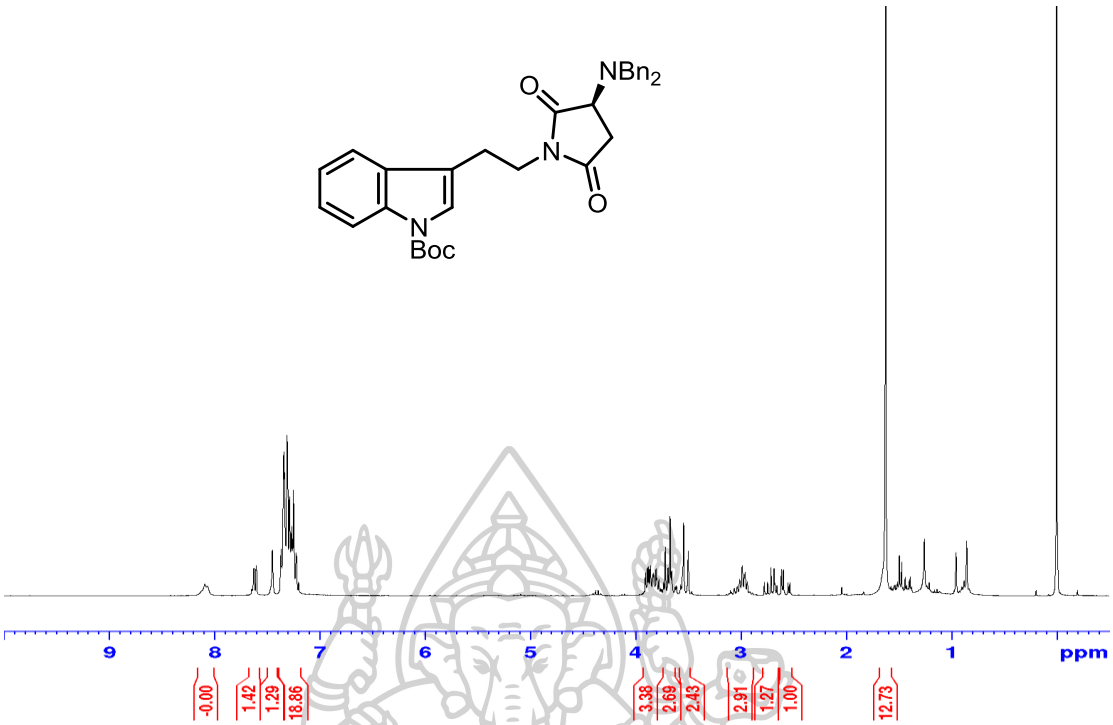

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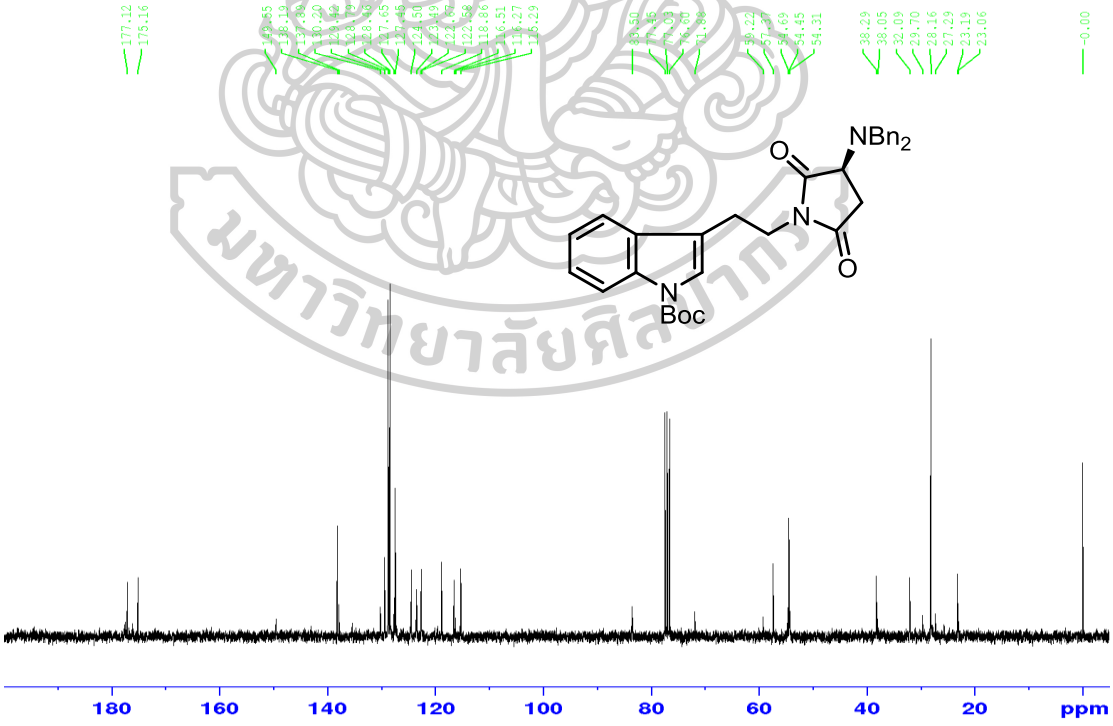

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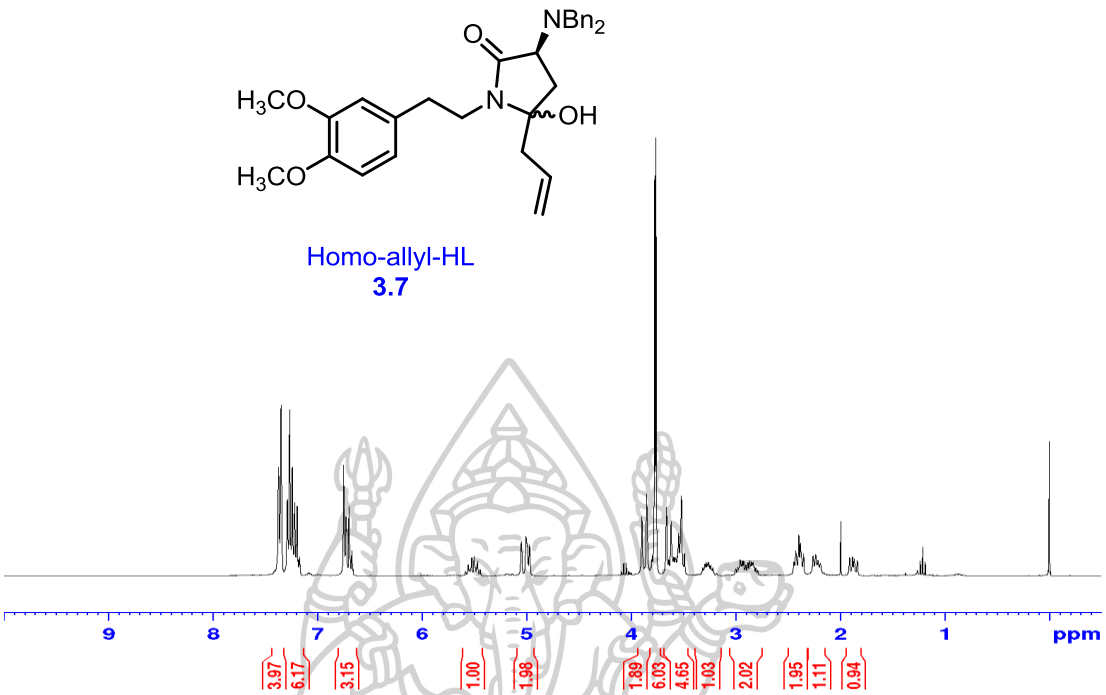
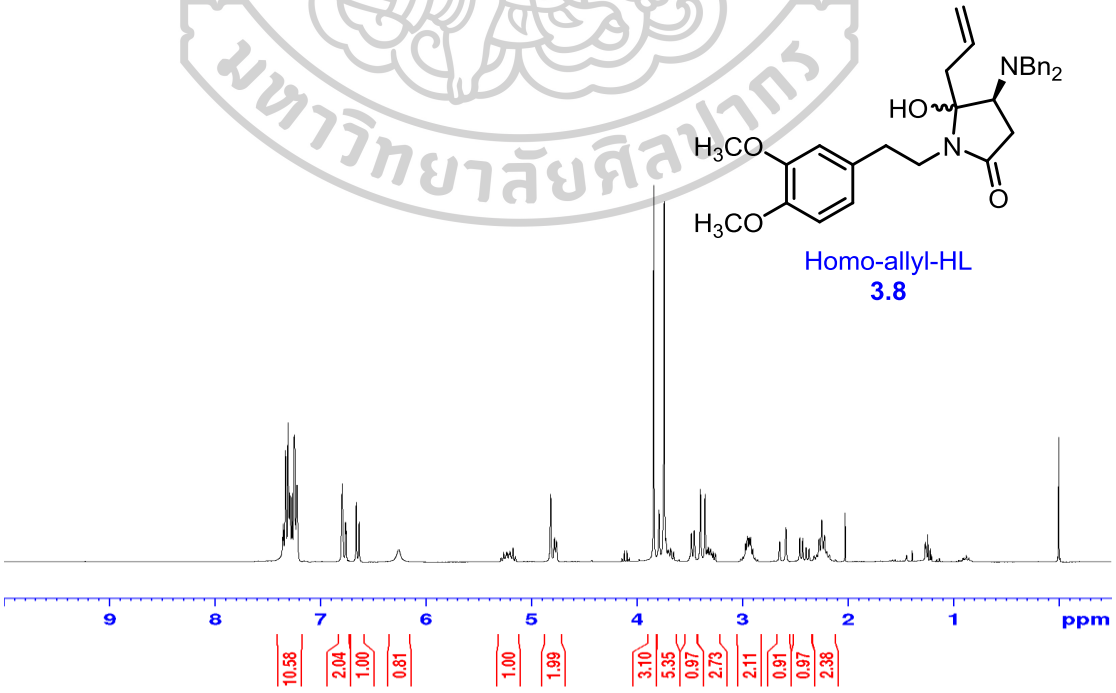
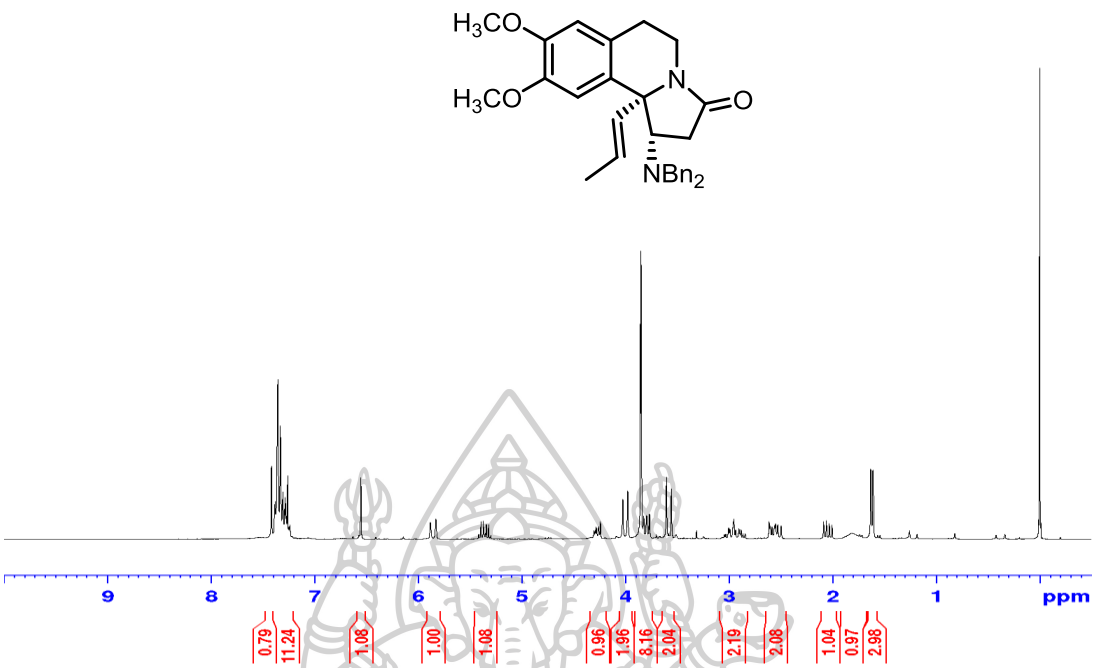


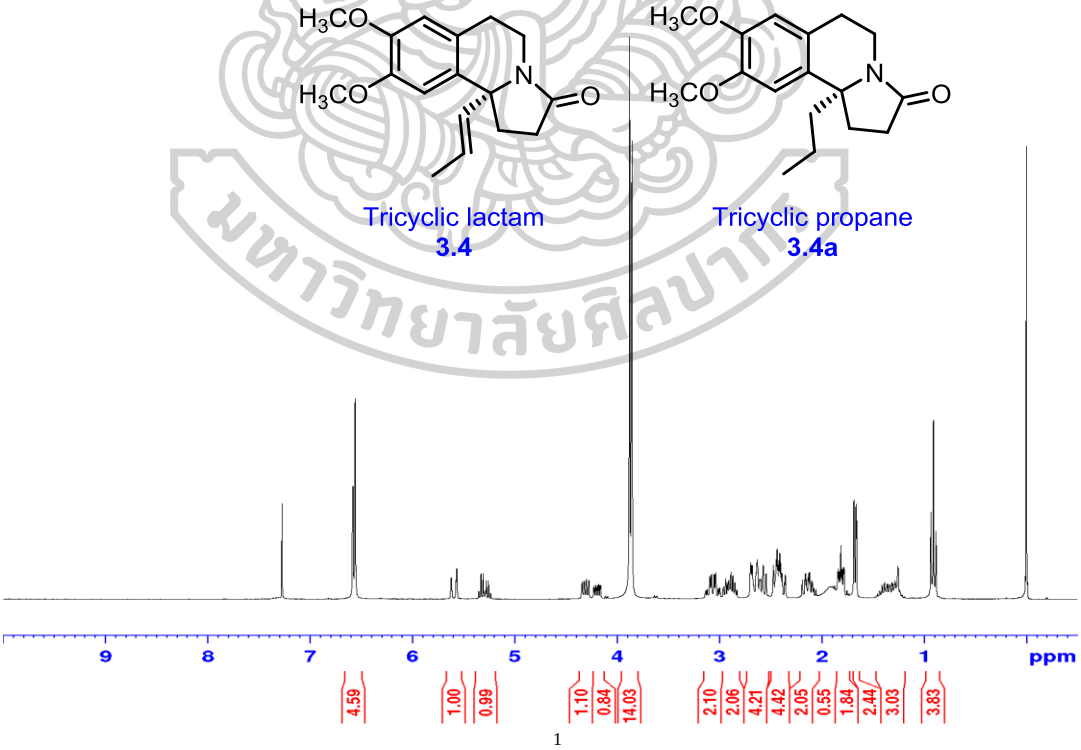
^{1}H NMR of Homo-allyl-HL **3.7**



^{1}H NMR of Homo-allyl-HL **3.8**



^{1}H NMR of Tricyclic indolizidine core **3.5**



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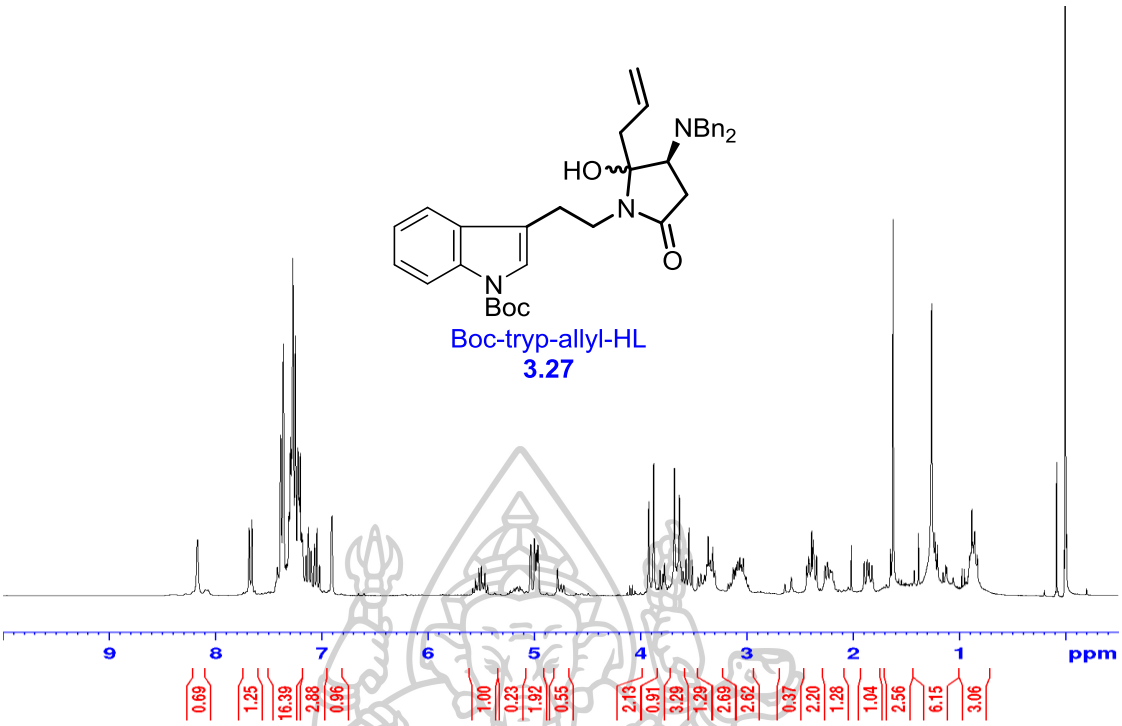
H NMR of Tricyclic lactam **3.4** & Tricyclic propane **3.4a**



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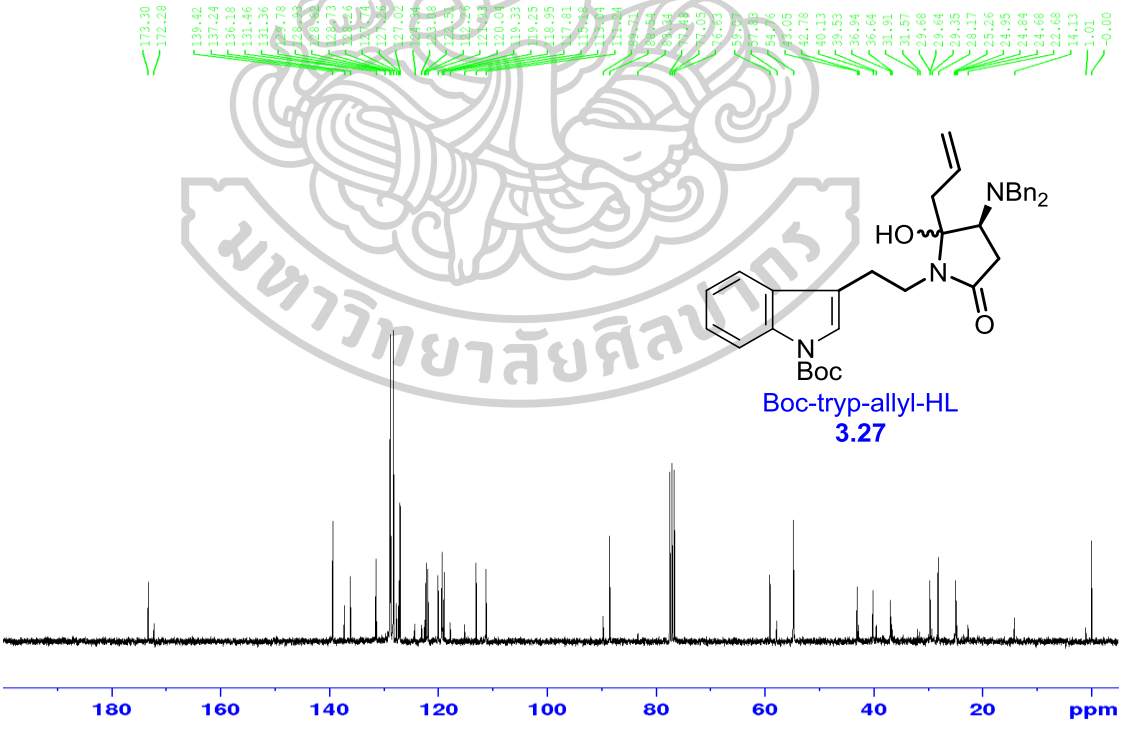

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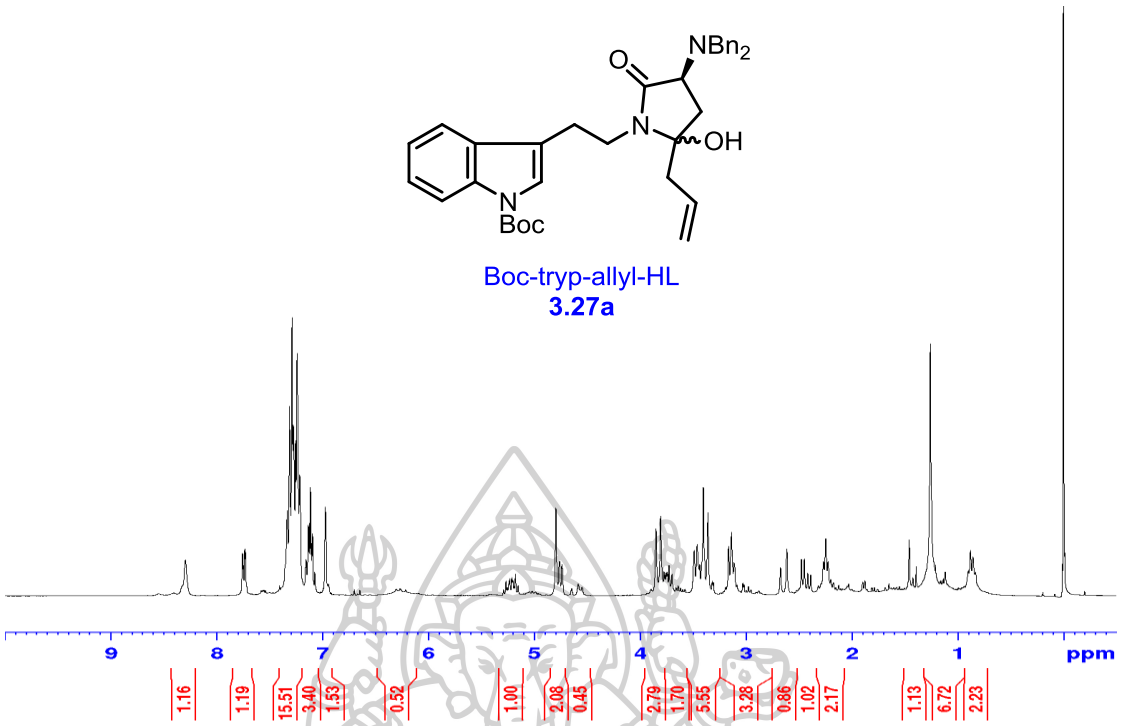

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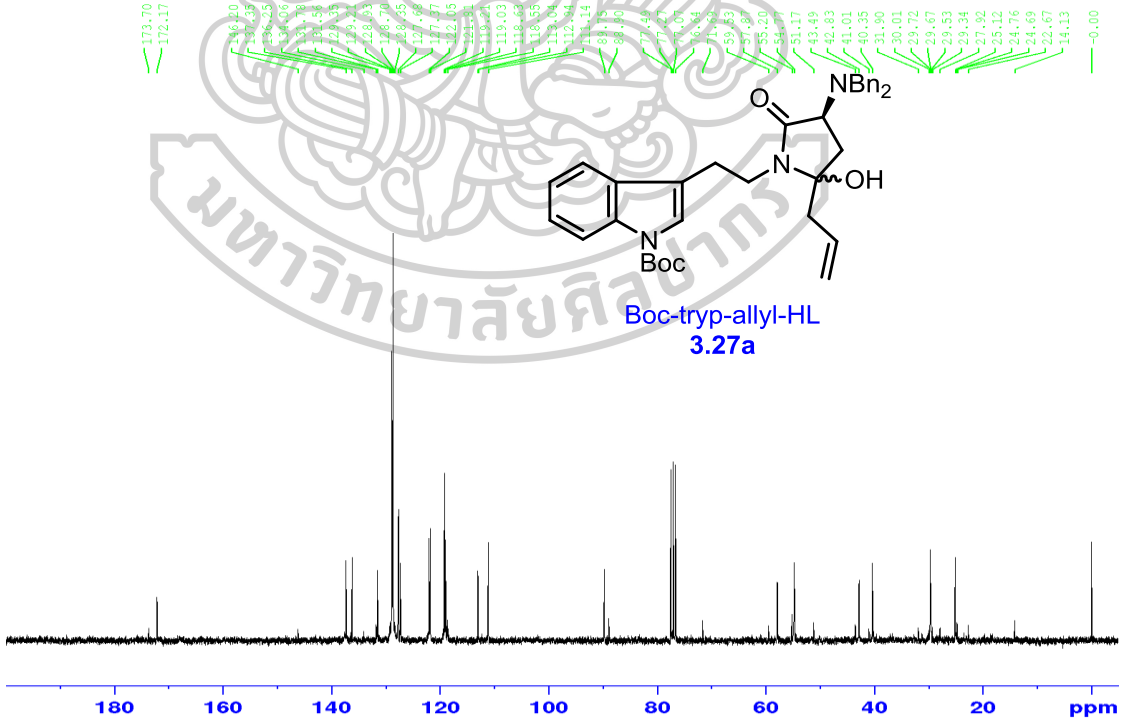
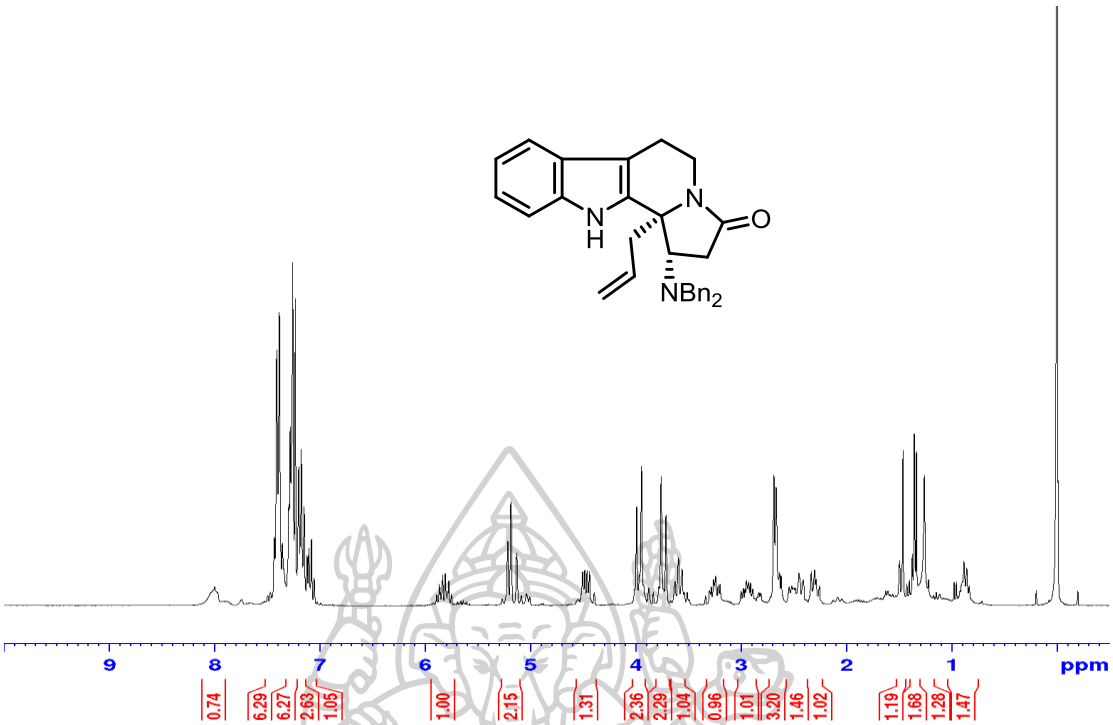
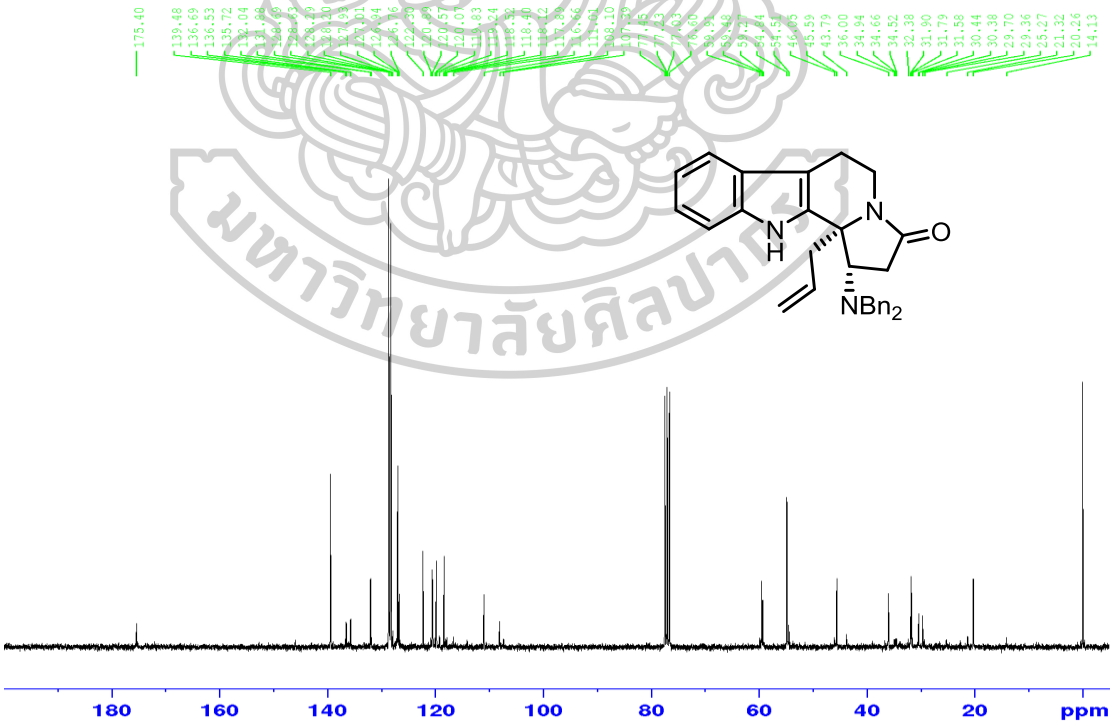


^{13}C NMR of Boc-tryp-allyl HL **3.27a**



^{1}H NMR of Tetracyclic indolizidine core **3.24**



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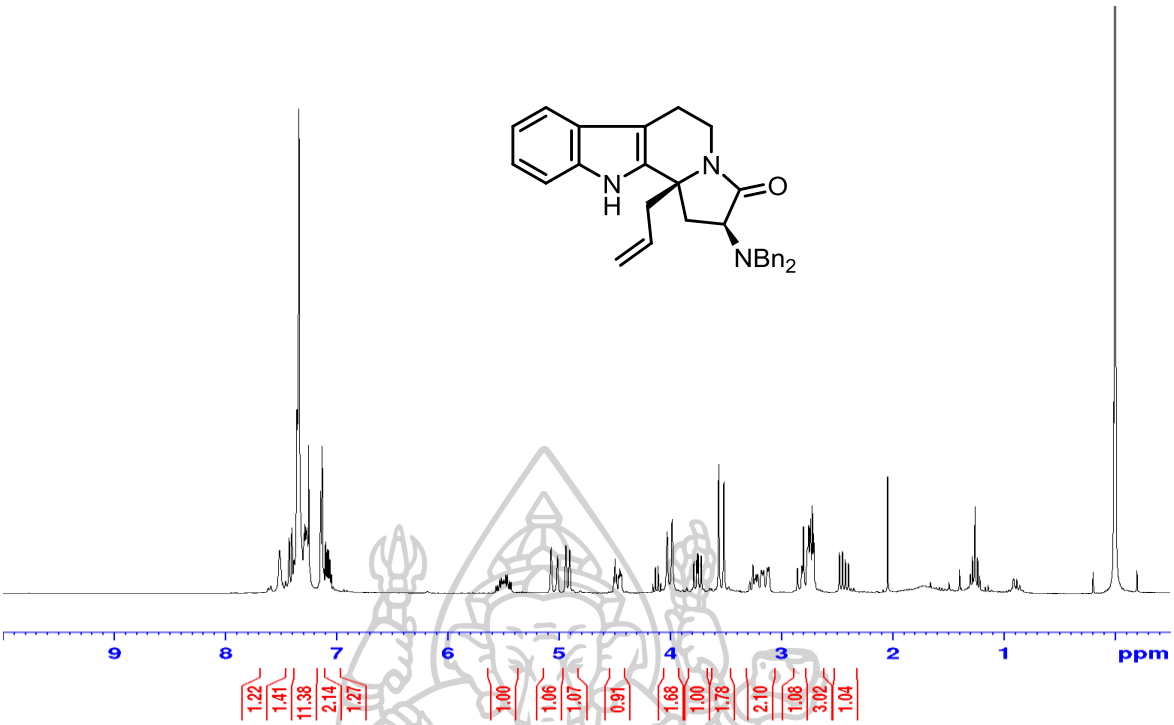

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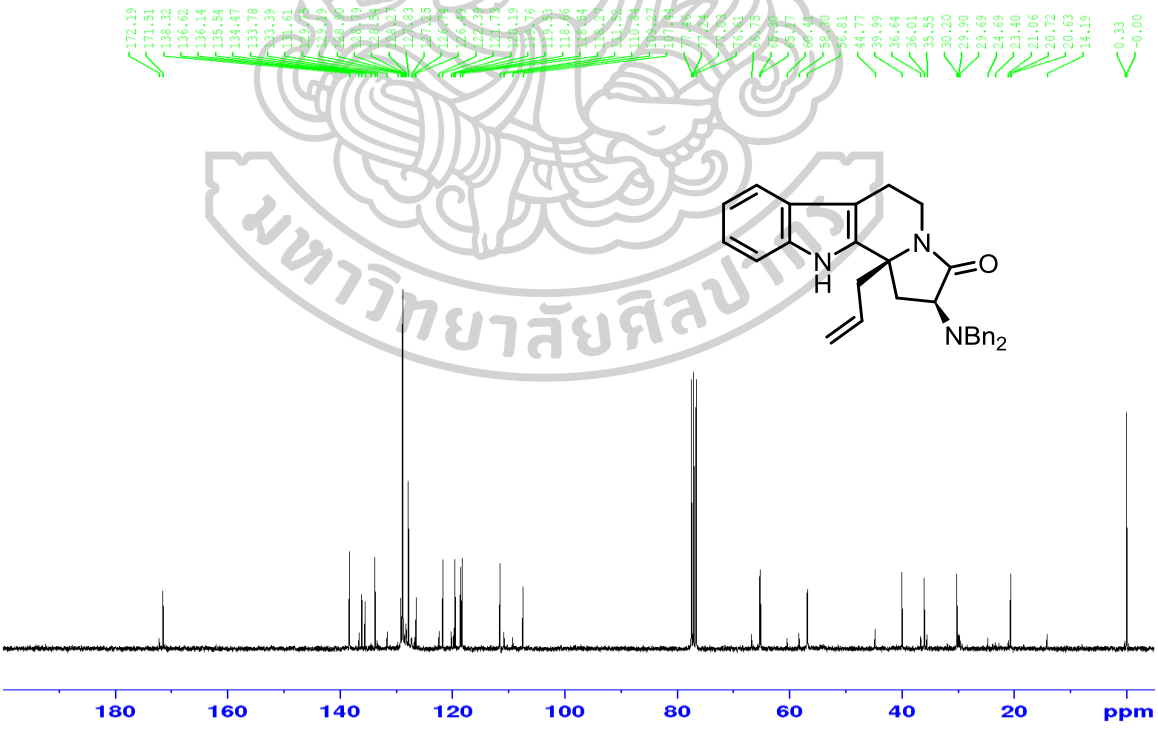
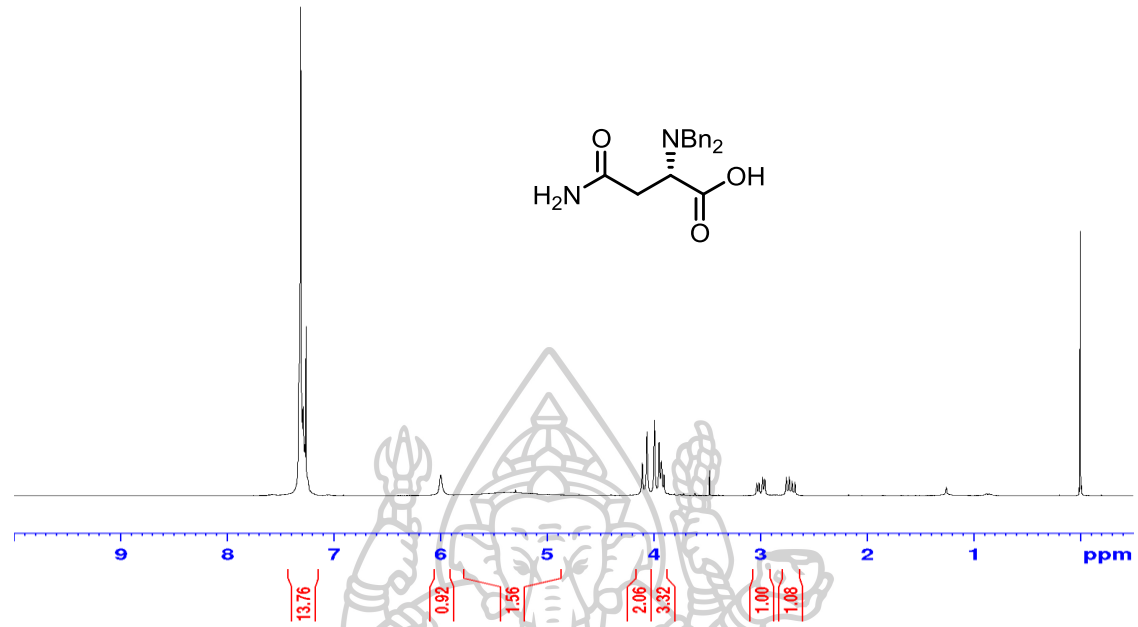
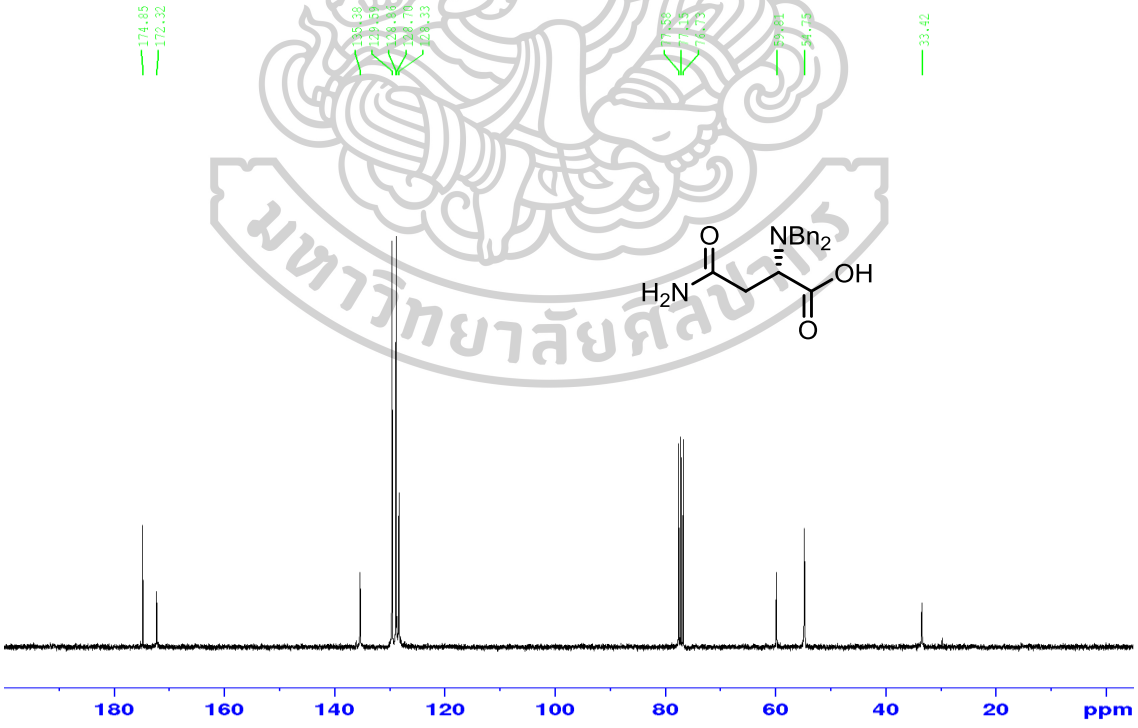


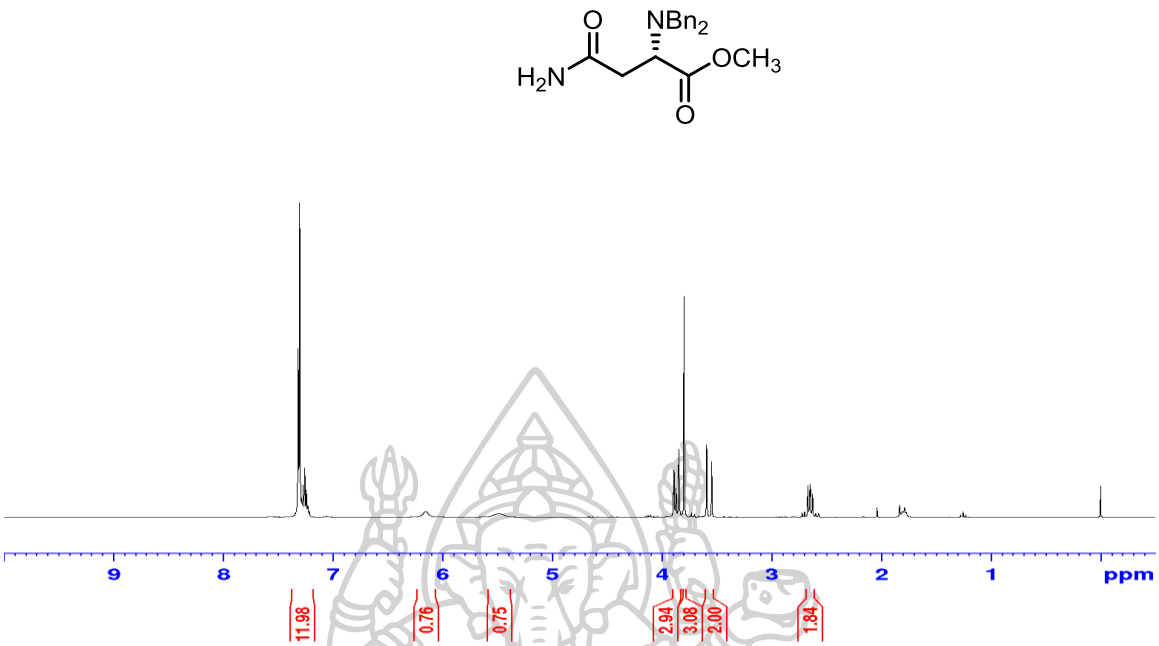
^{13}C NMR of Tetracyclic indolizidine core **3.24a**



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



^{13}C NMR of *N*,*N*-dibenzyl-L-asparaginate



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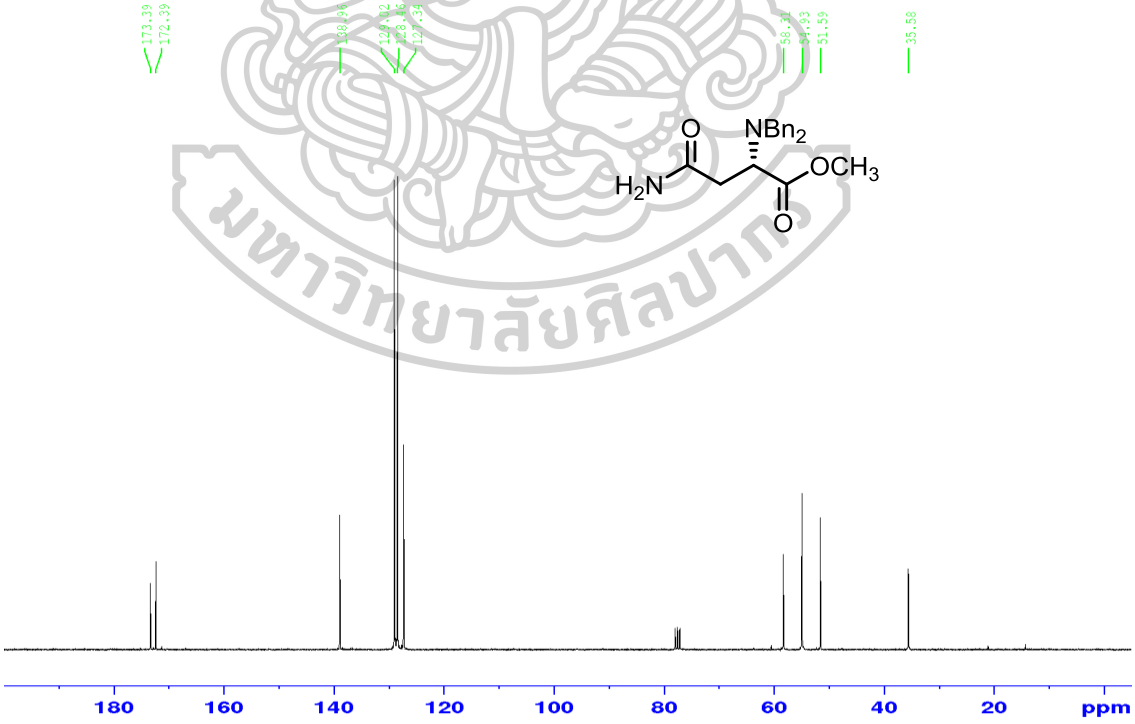
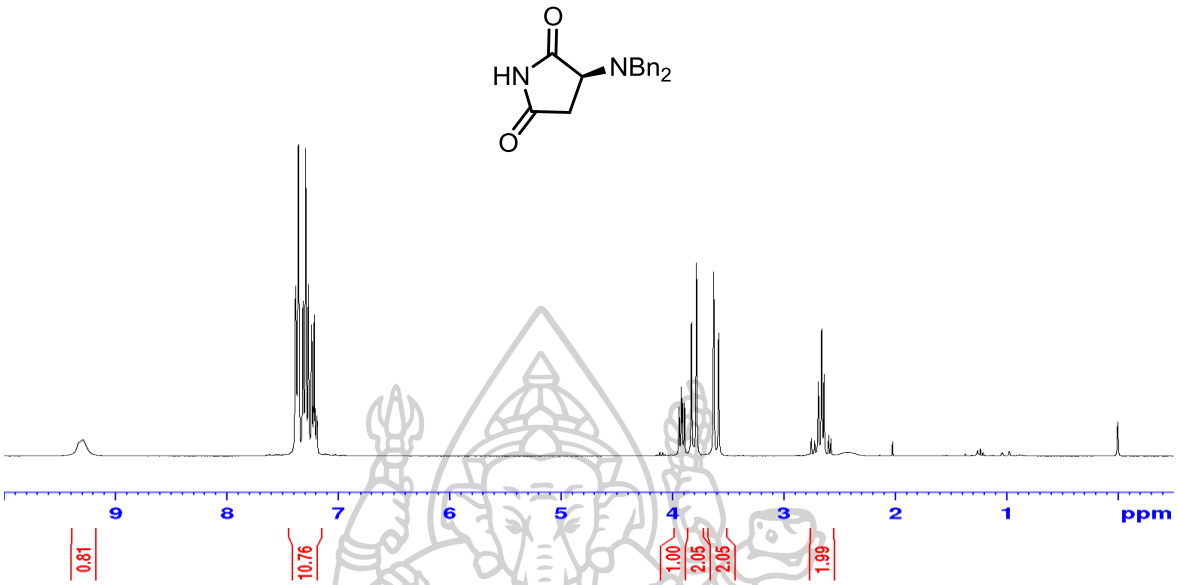
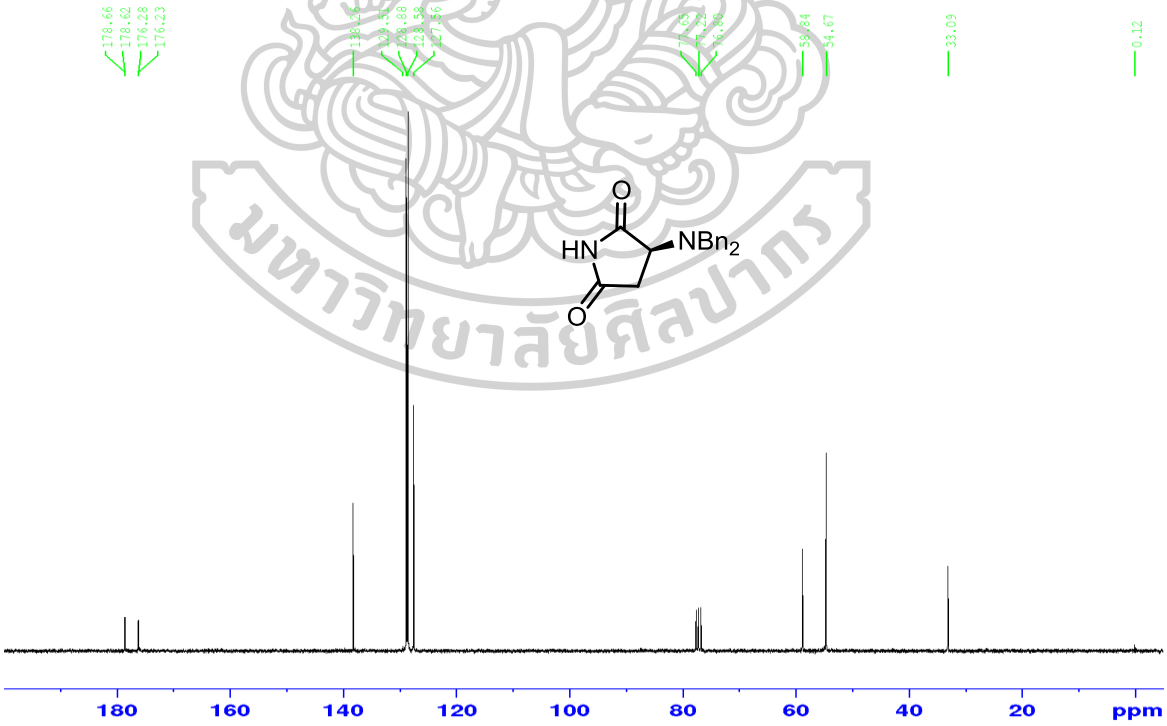


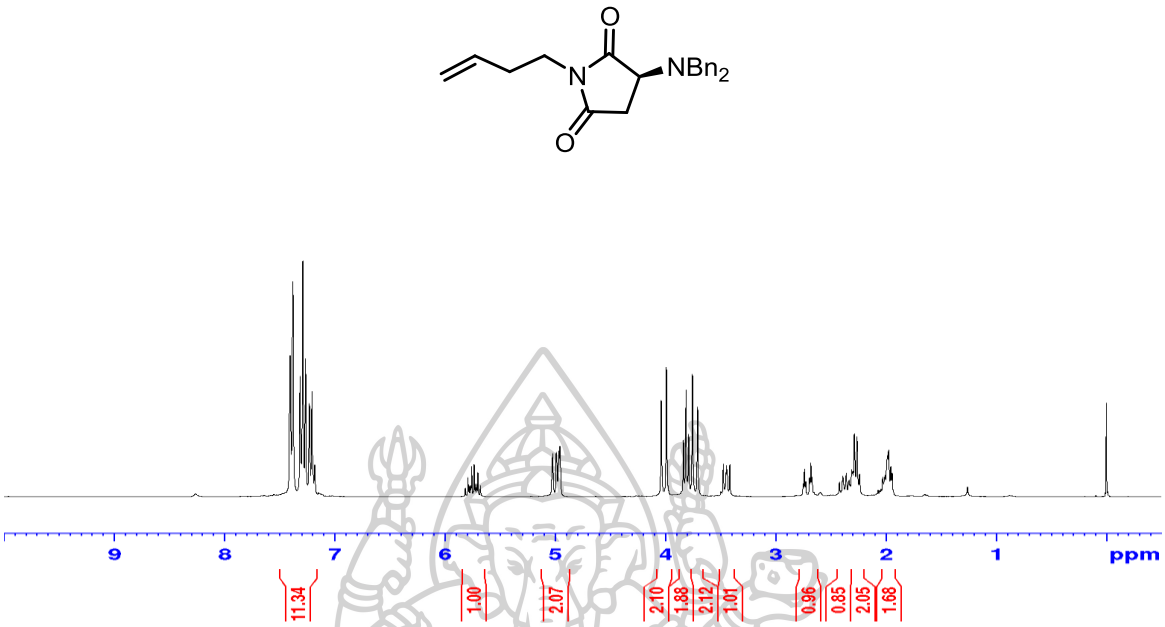
^{13}C NMR of methyl ester dibenzyl-L-asparaginate



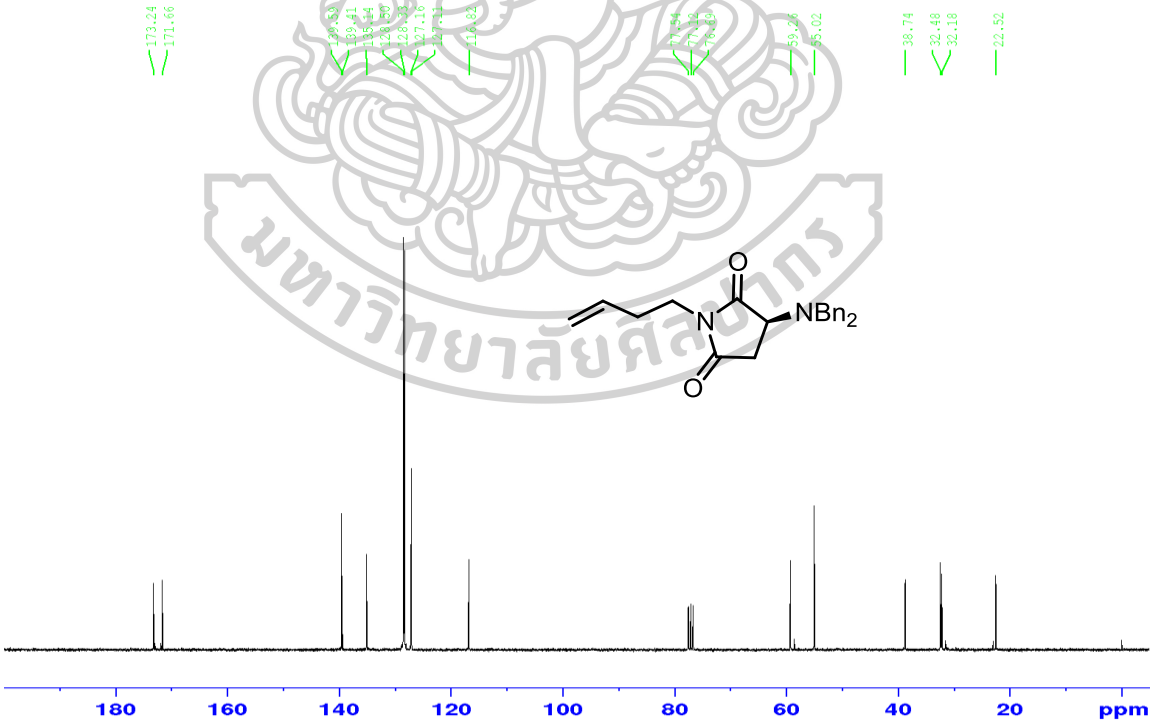
^{1}H NMR of *N*,*N*-dibenzylamino-succinimide **3.45**



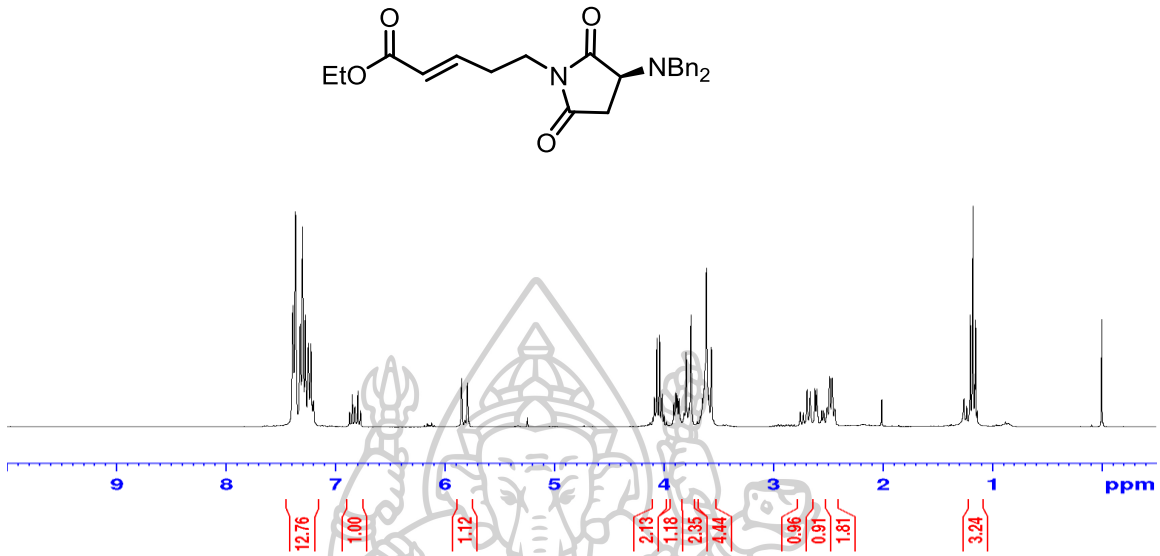
^{13}C NMR of *N*,*N*-dibenzylamino-succinimide **3.45**



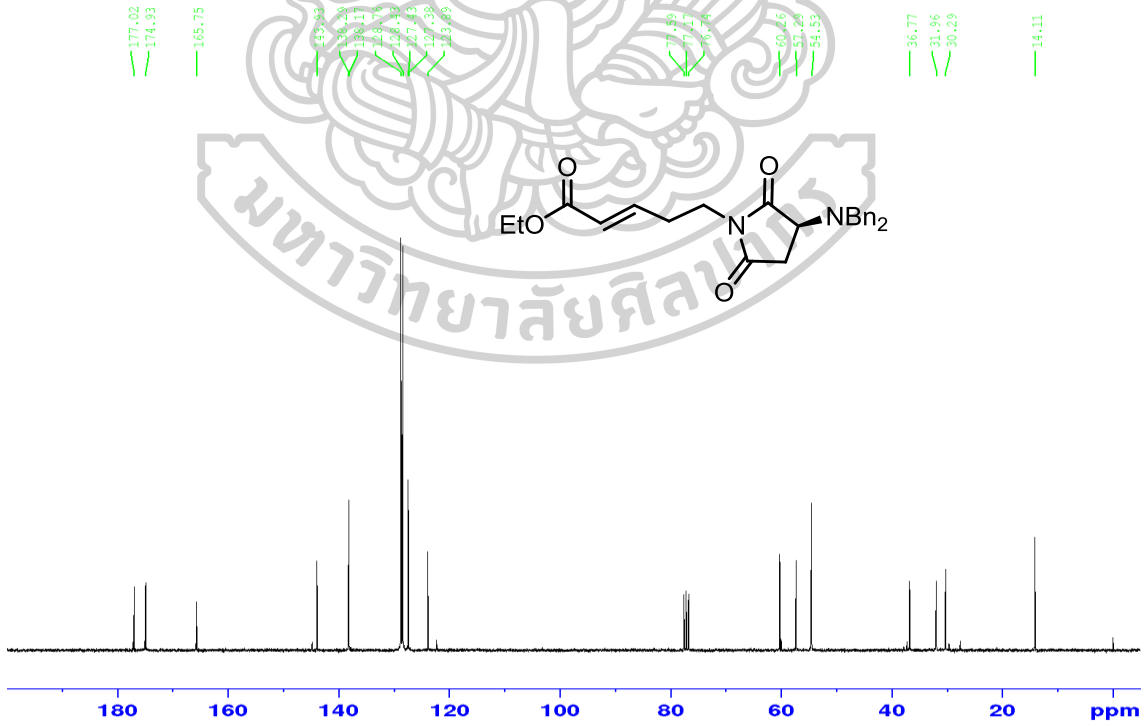
^{1}H NMR of Butenyl succinimide **3.58**



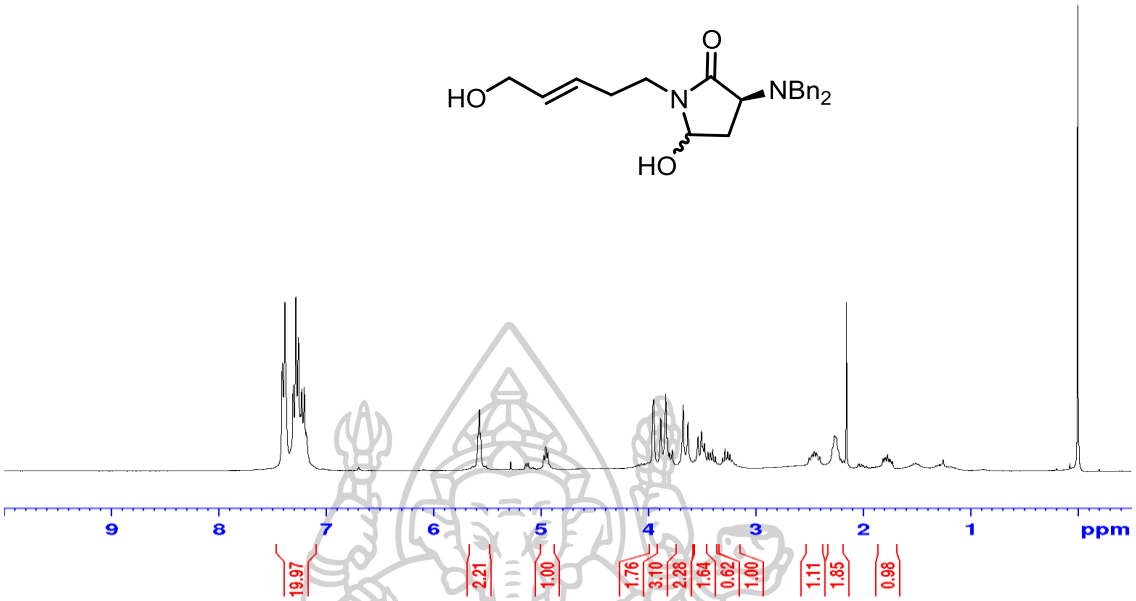
^{13}C NMR of Butenyl succinimide **3.58**



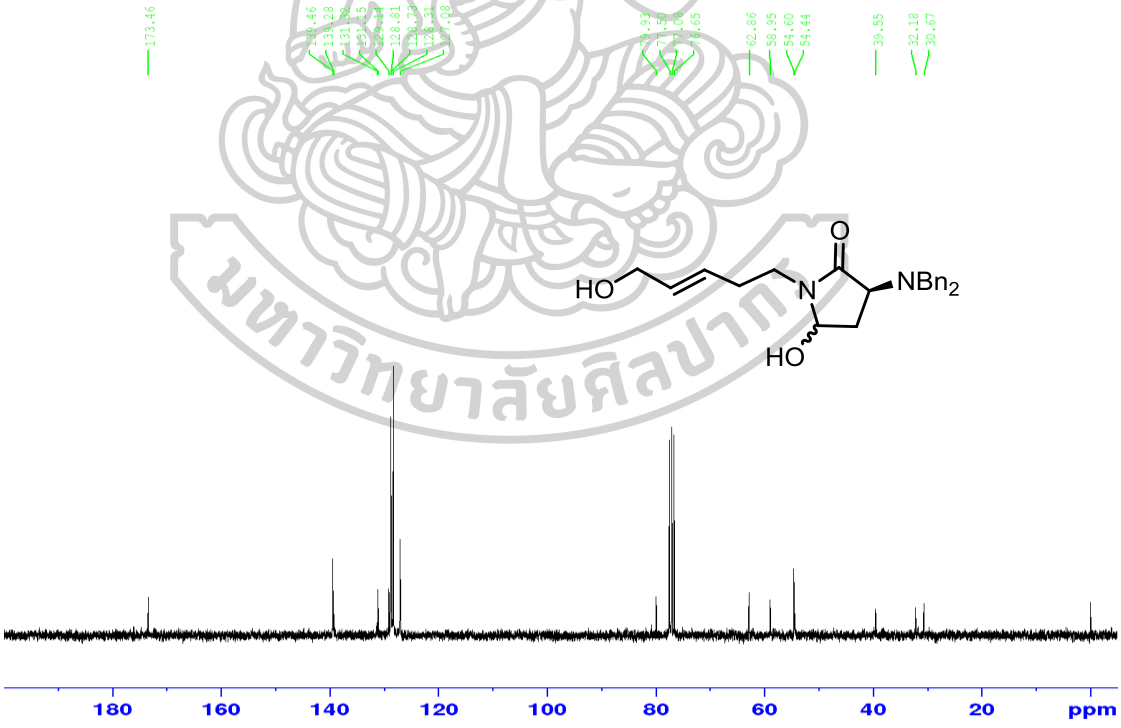
^{1}H NMR of Ester **3.57**



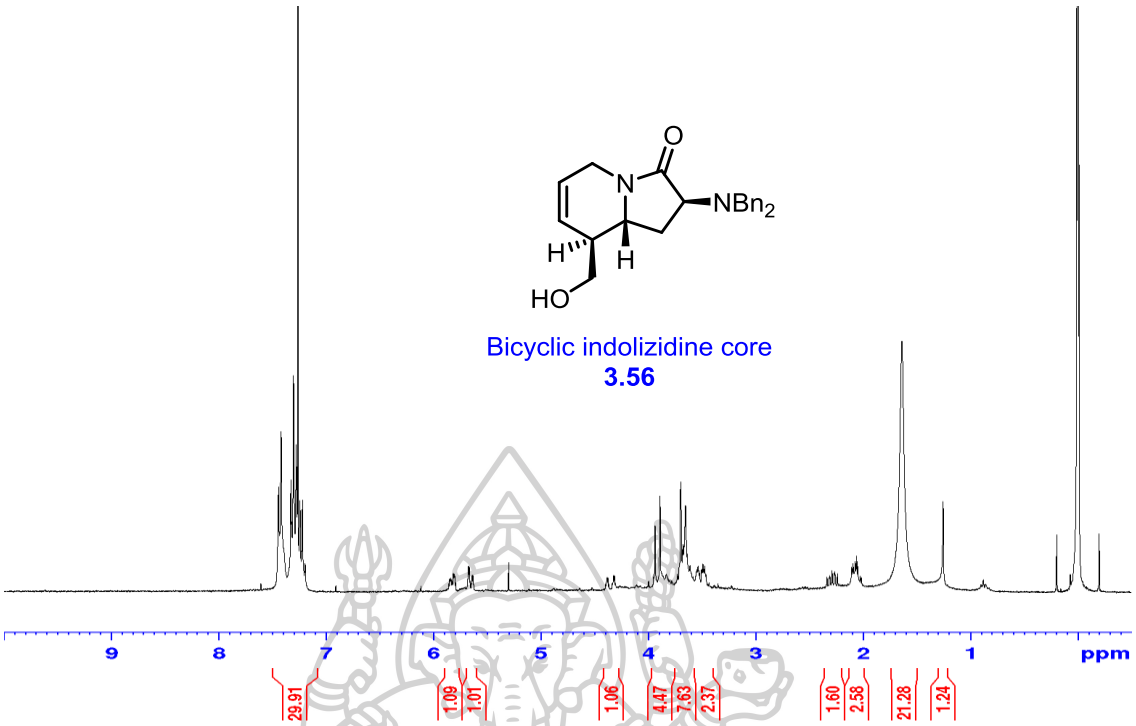
^{13}C NMR of Ester **3.57**



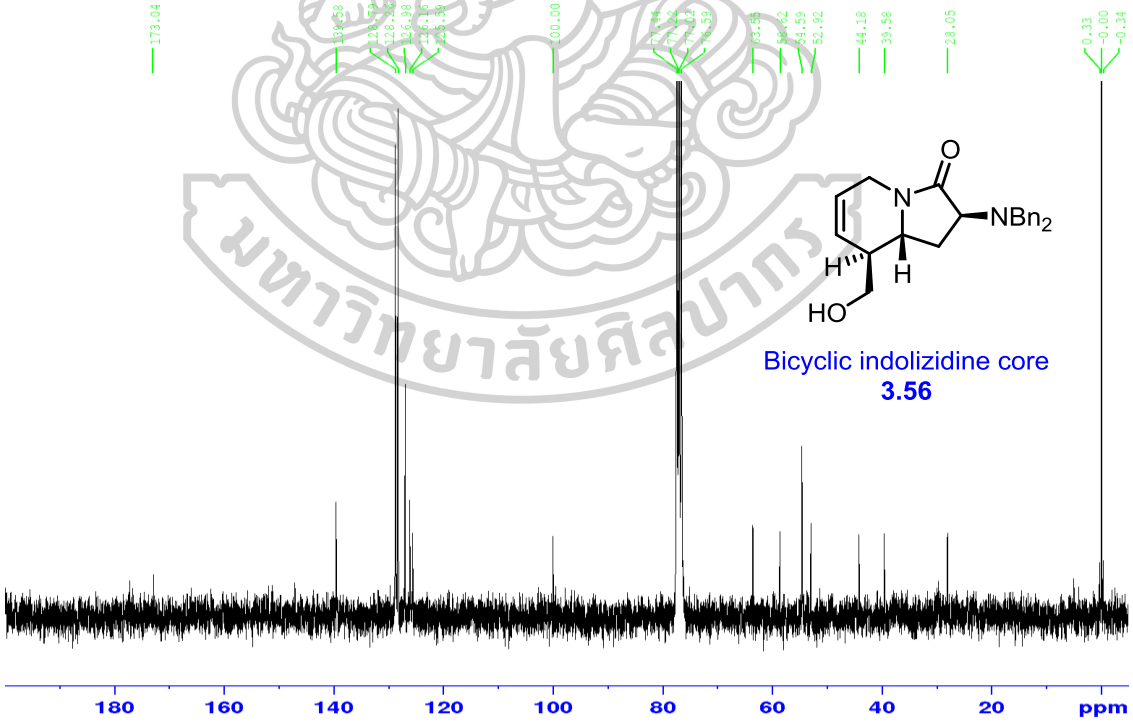
^{1}H NMR of Hydroxylactam **3.59**



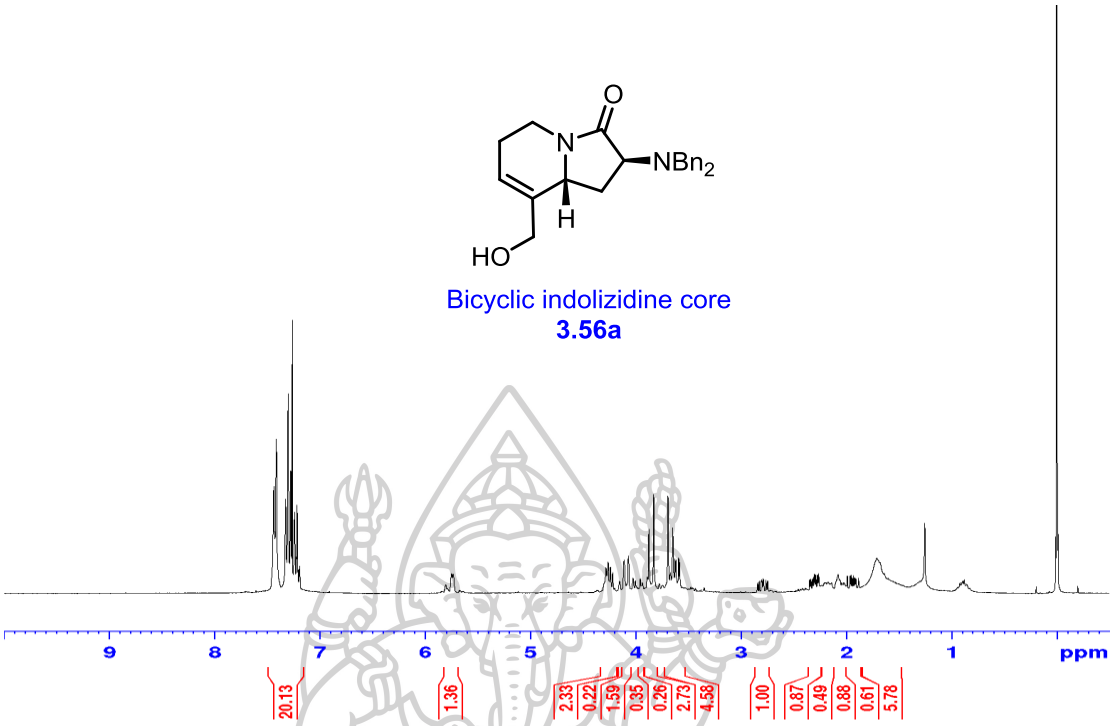
^{13}C NMR of Hydroxylactam **3.59**



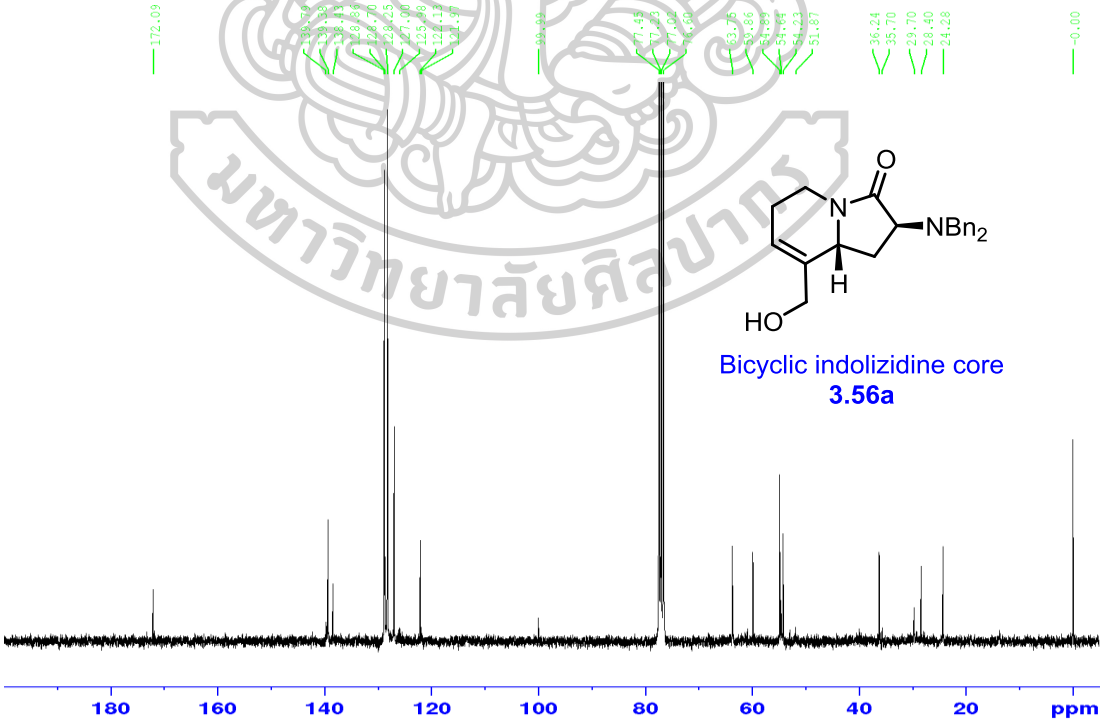
^{1}H NMR of Bicyclic indolizidine core **3.56**



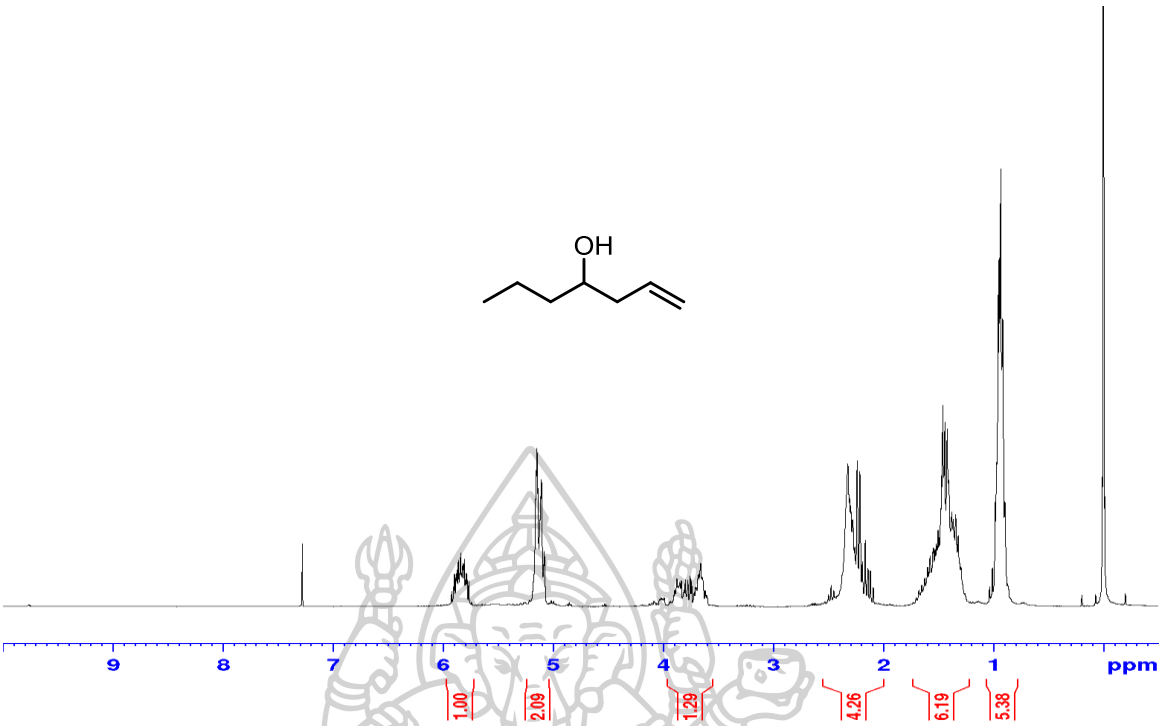
^{13}C NMR of Bicyclic indolizidine core **3.56**



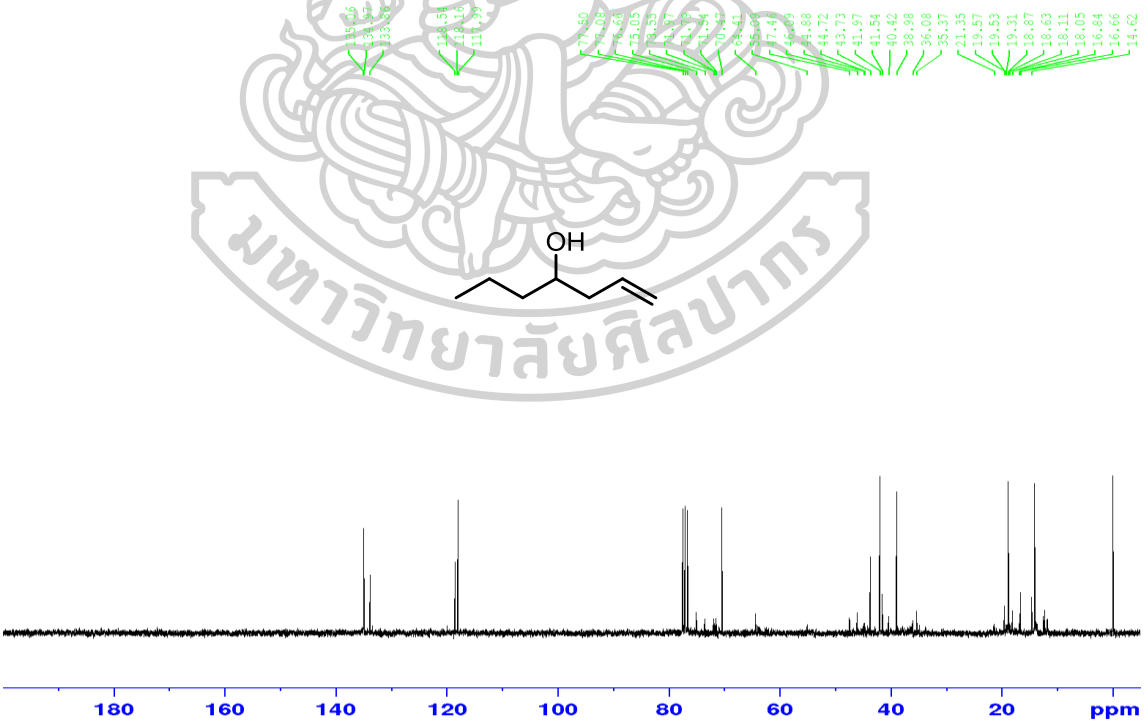
^{1}H NMR of Bicyclic indolizidine core **3.56a**



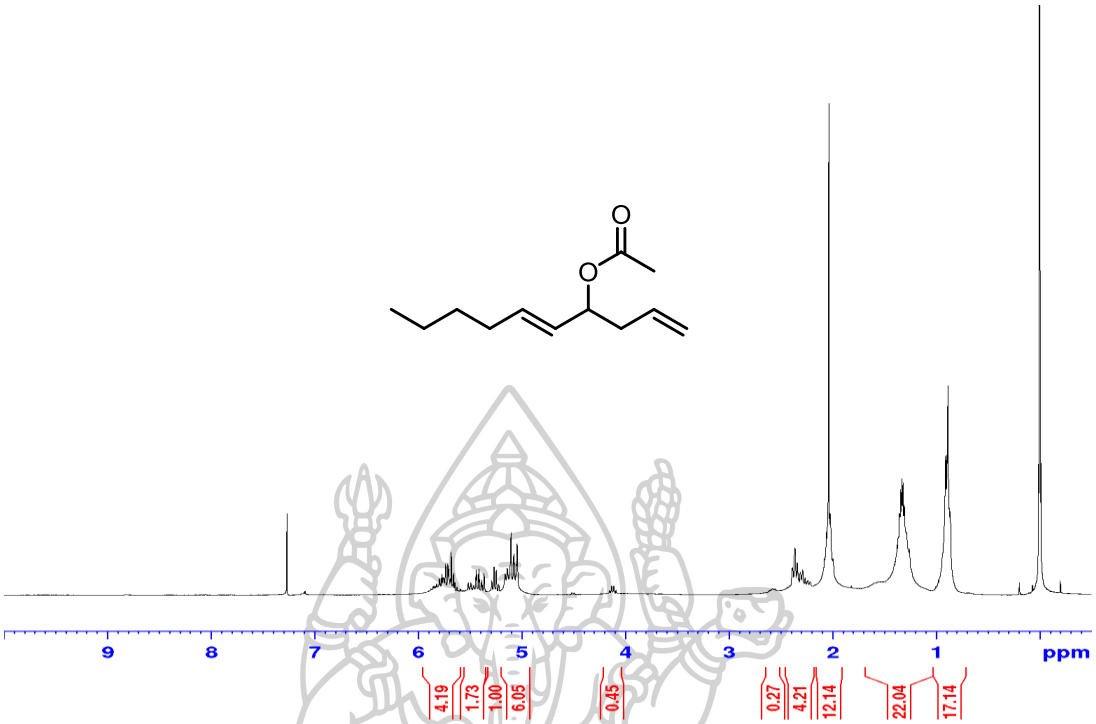
^{13}C NMR of Bicyclic indolizidine core **3.56a**



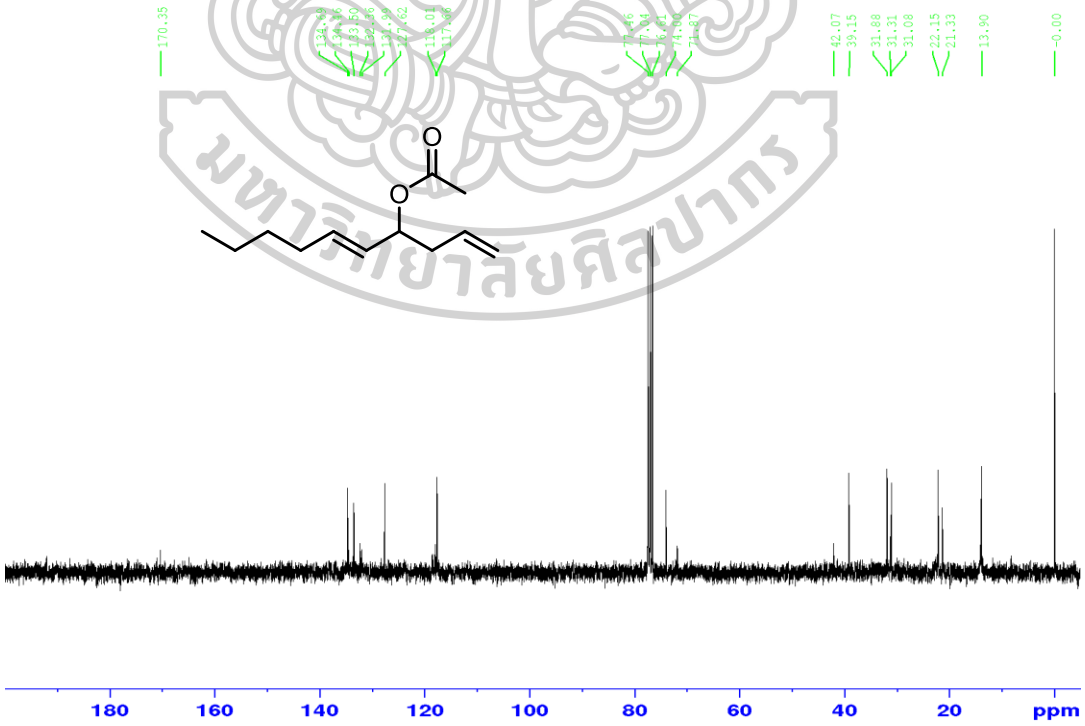
^{1}H NMR of 2^{o} alcohol **3.44a**



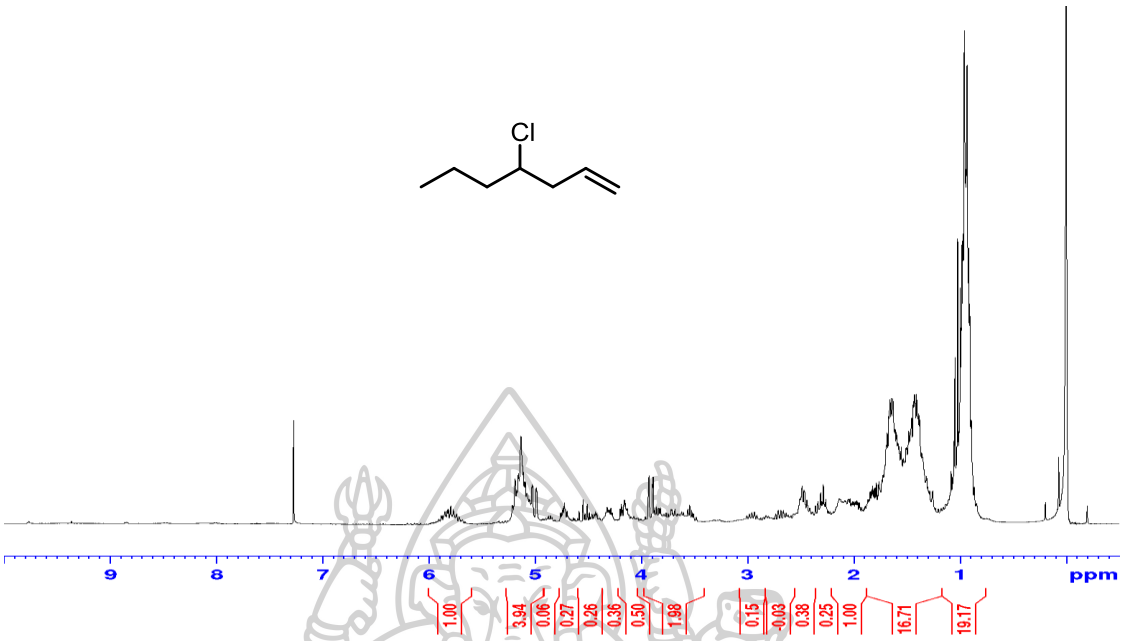
^{13}C NMR of 2^{o} alcohol **3.44a**



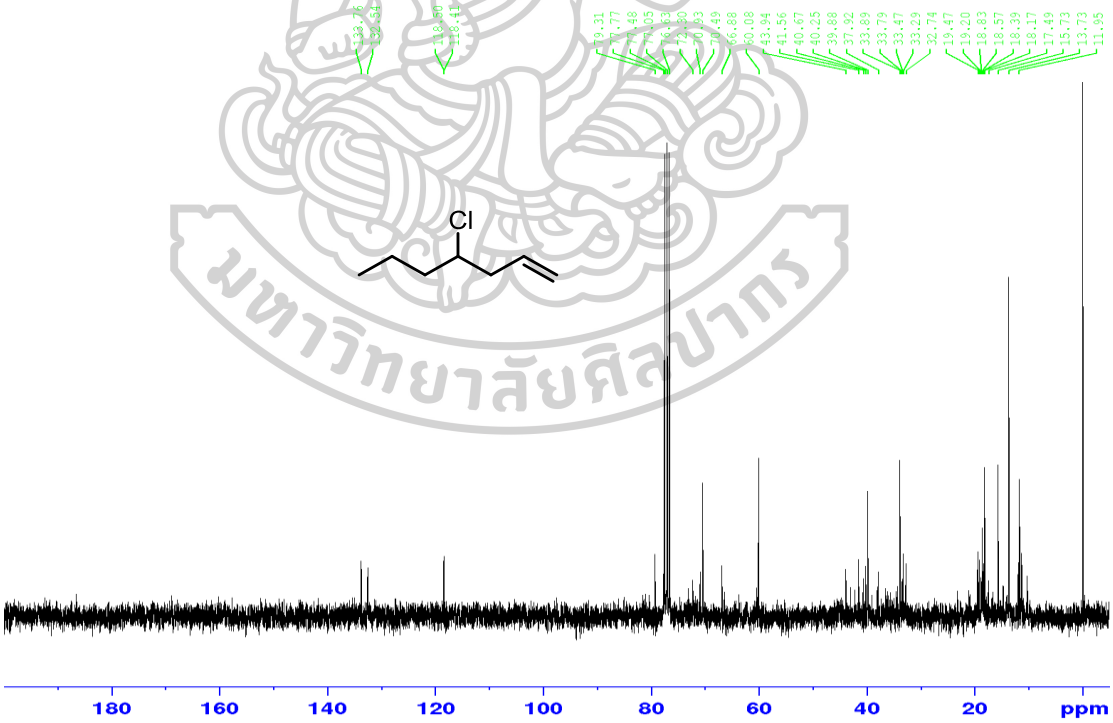
^{1}H NMR of 2^{o} acetate **3.52e**



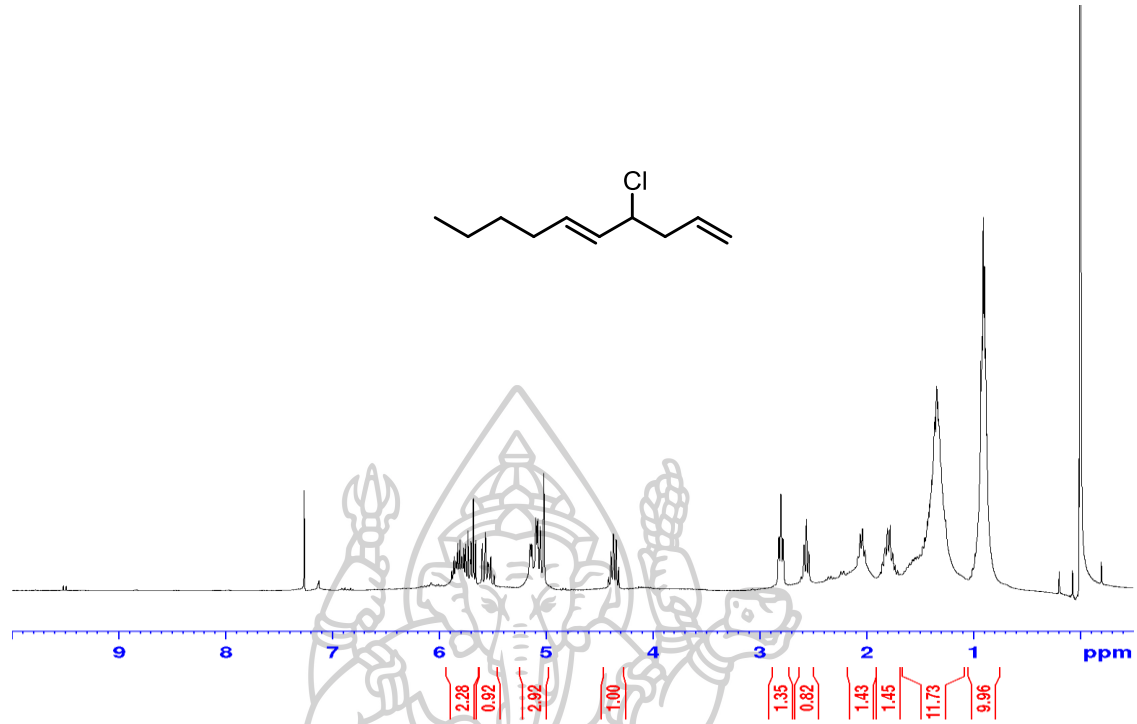
^{13}C NMR of 2^{o} acetate **3.52e**



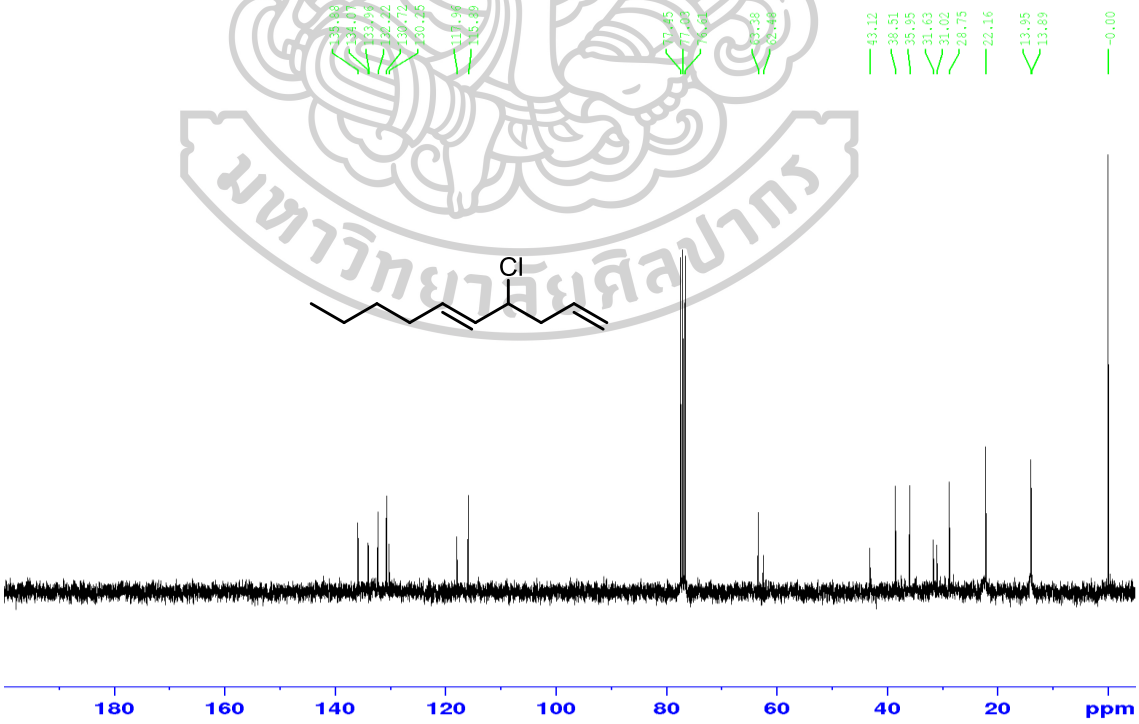
^{1}H NMR of 2^{o} chloride **3.51a**



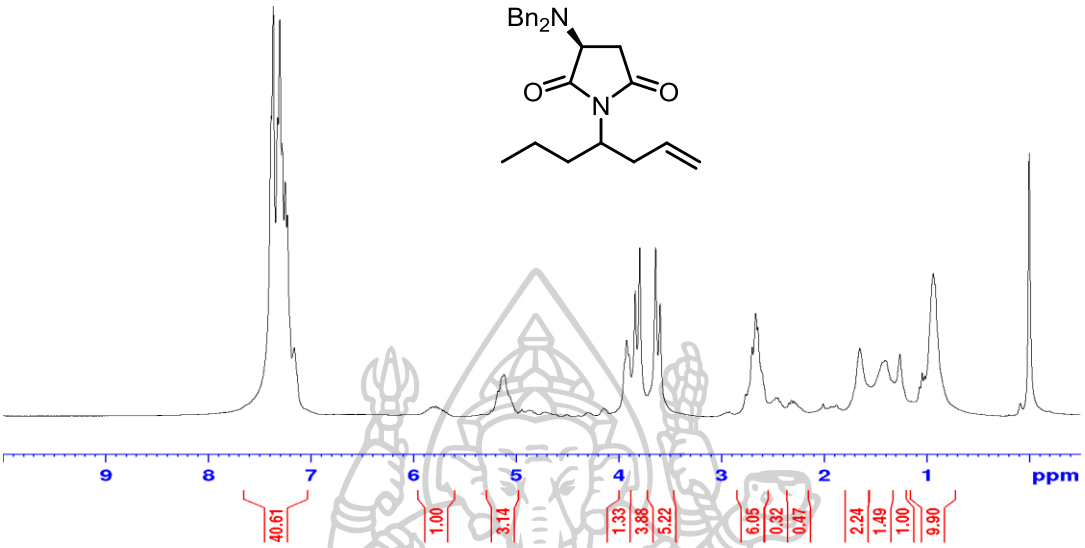
^{13}C NMR of 2^{o} chloride **3.51a**



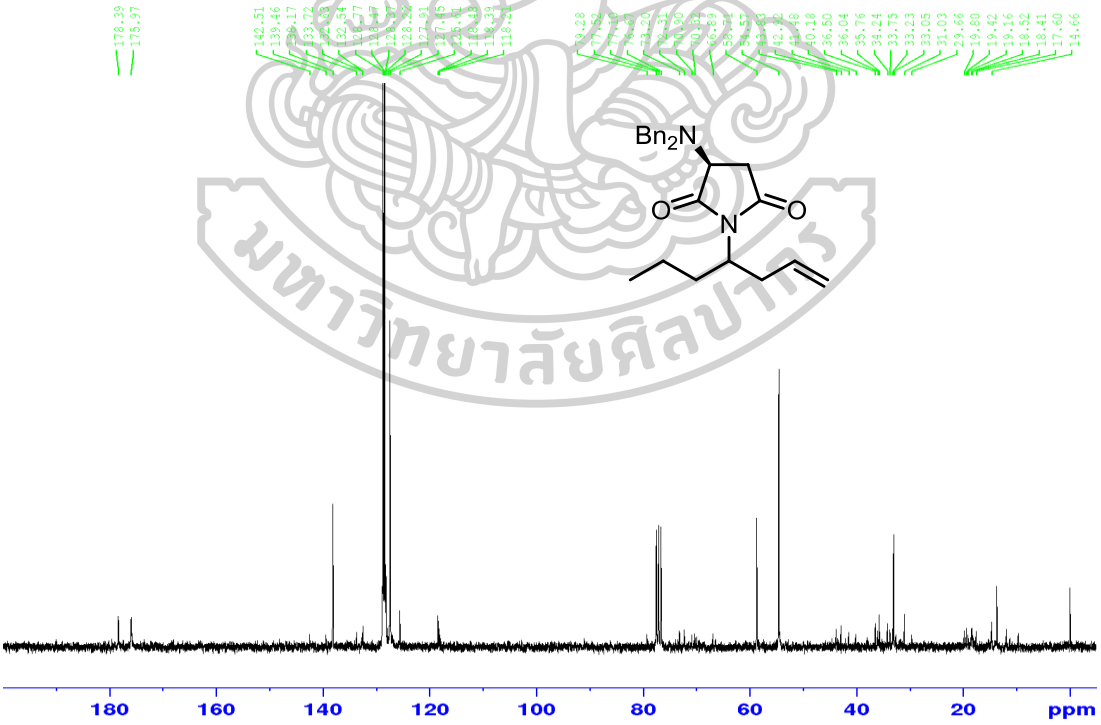
^{1}H NMR of 2^{o} chloride **3.51e**



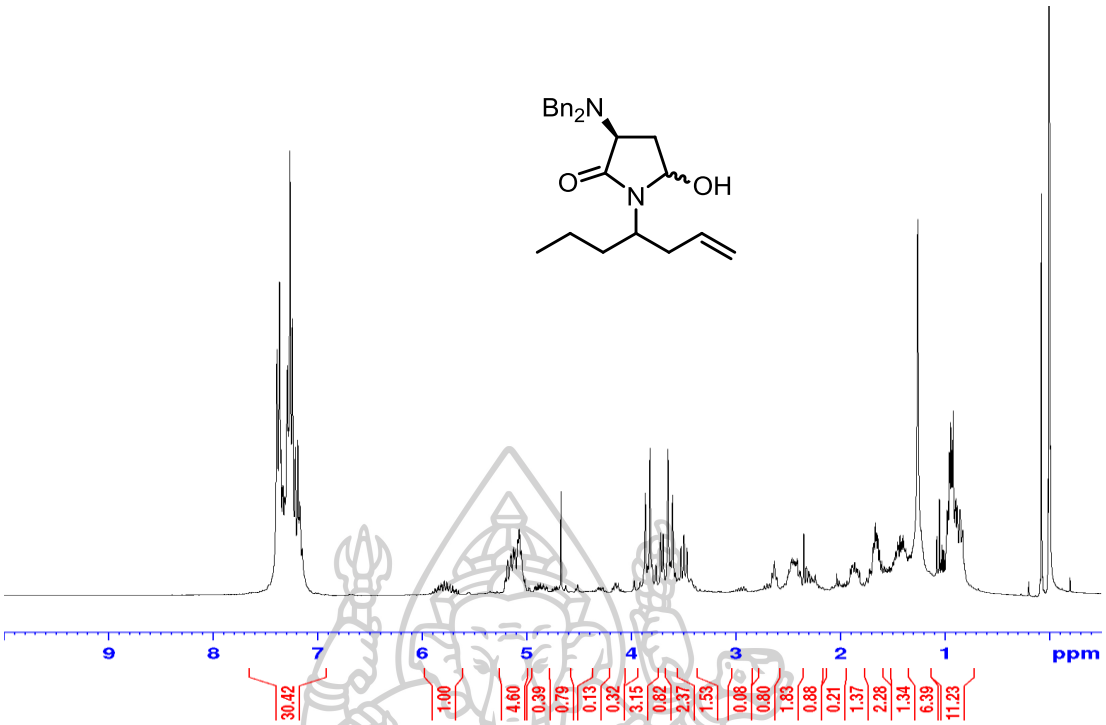
^{13}C NMR of 2^{o} chloride **3.51e**



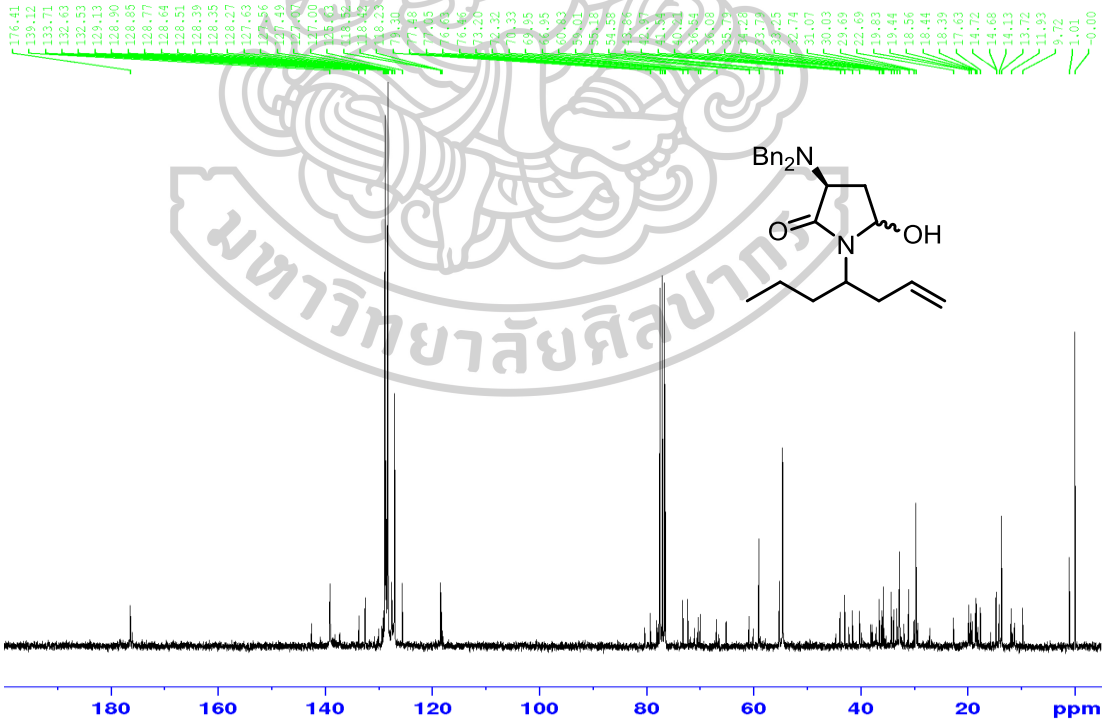
^{1}H NMR of *N*-alkylate **3.44a**



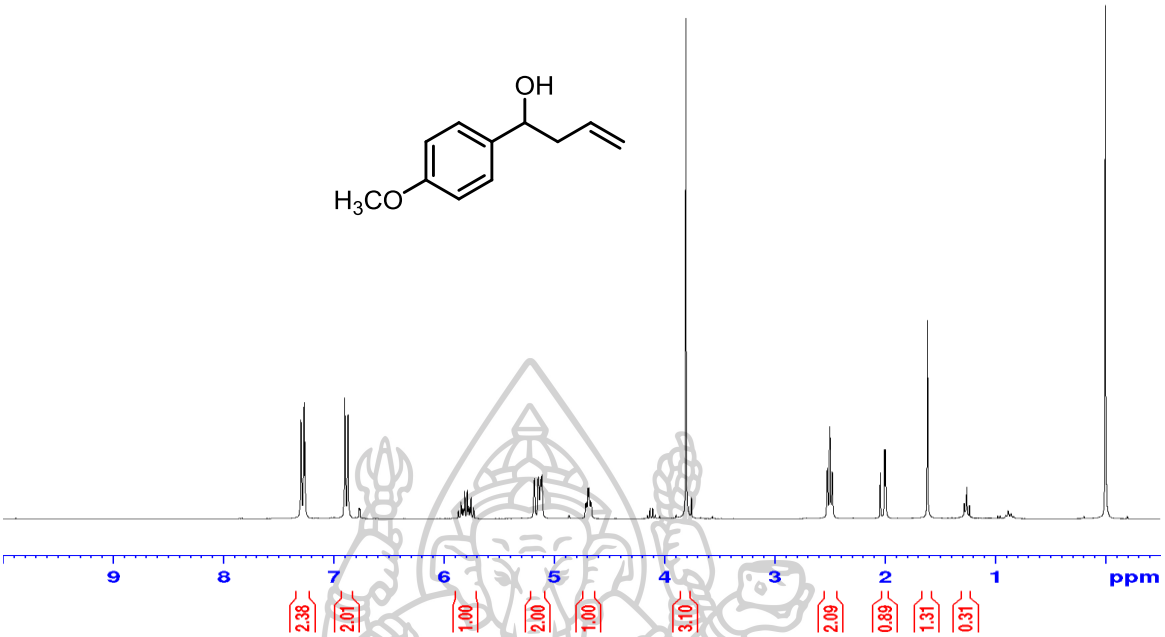
^{13}C NMR of *N*-alkylate **3.44a**



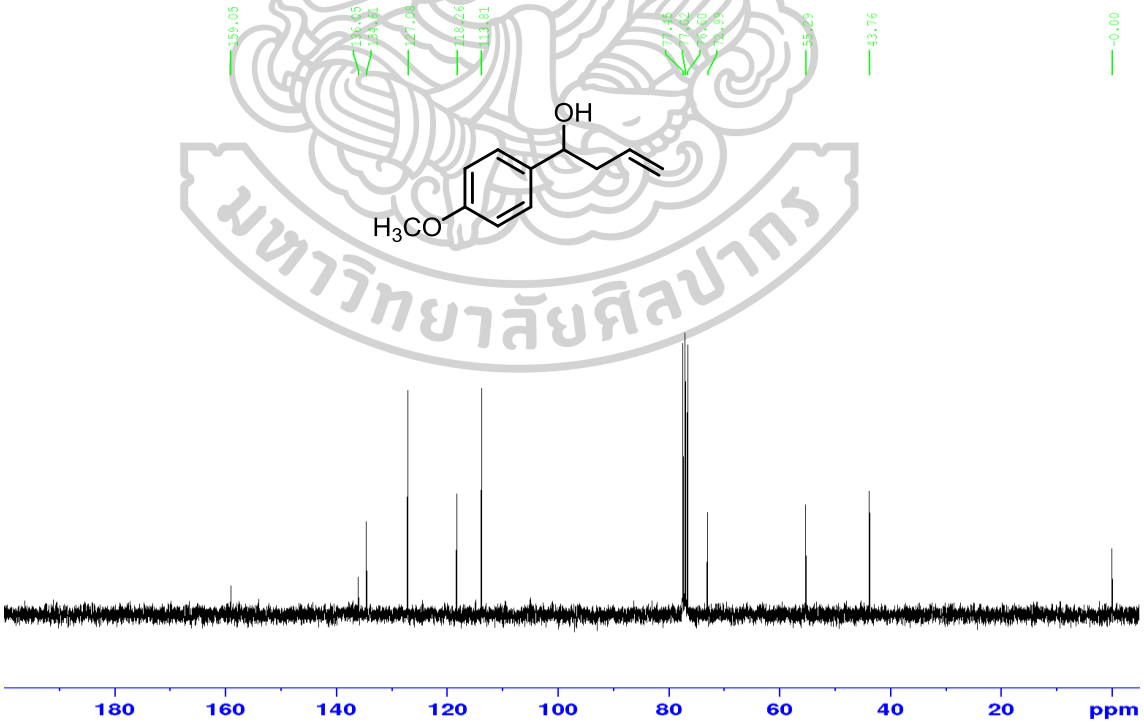
^{1}H NMR of Hydroxylactam **3.53a**



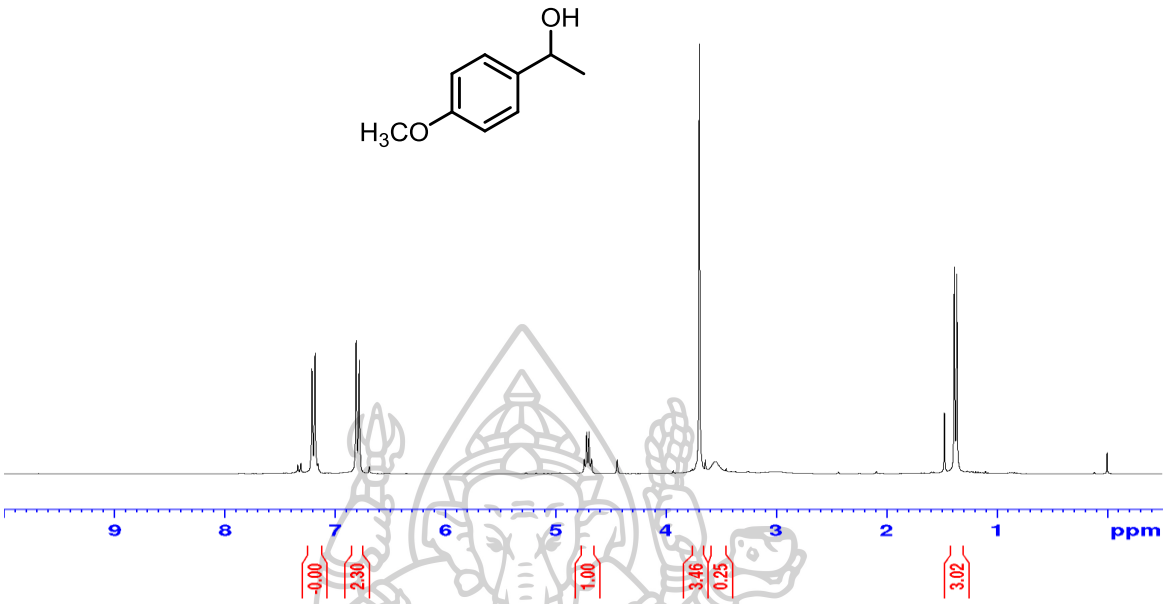
^{13}C NMR of Hydroxylactam **3.53a**



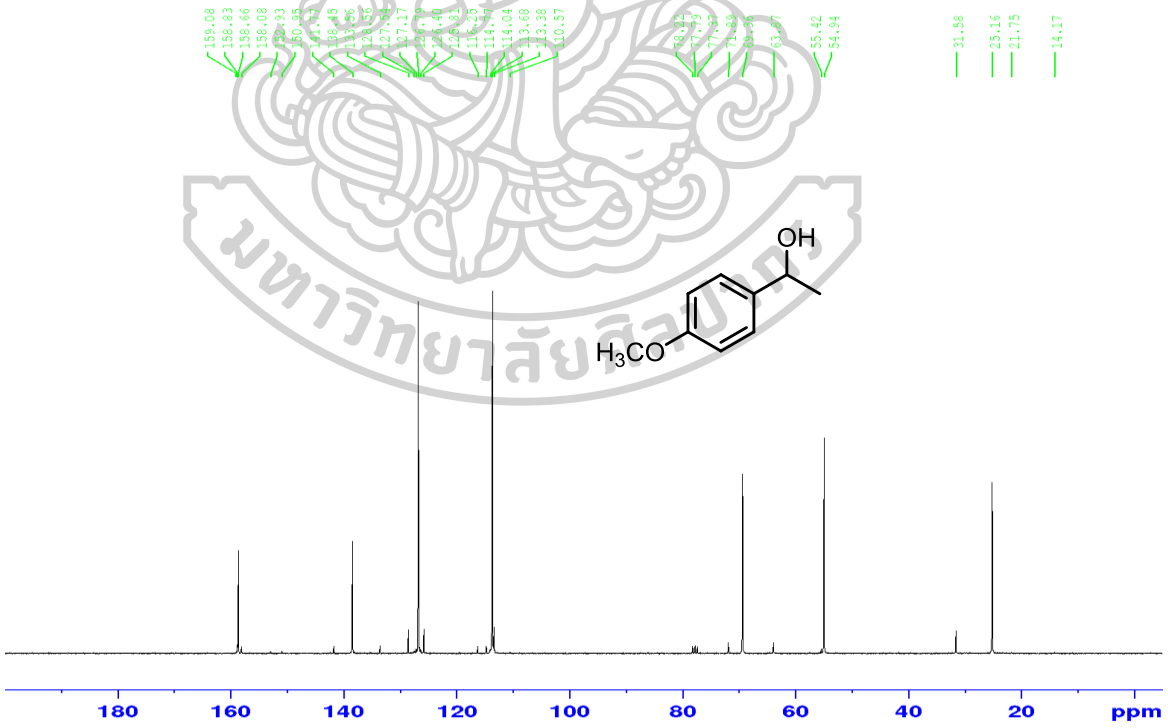
^{1}H NMR of Secondary alcohol **3.46c**



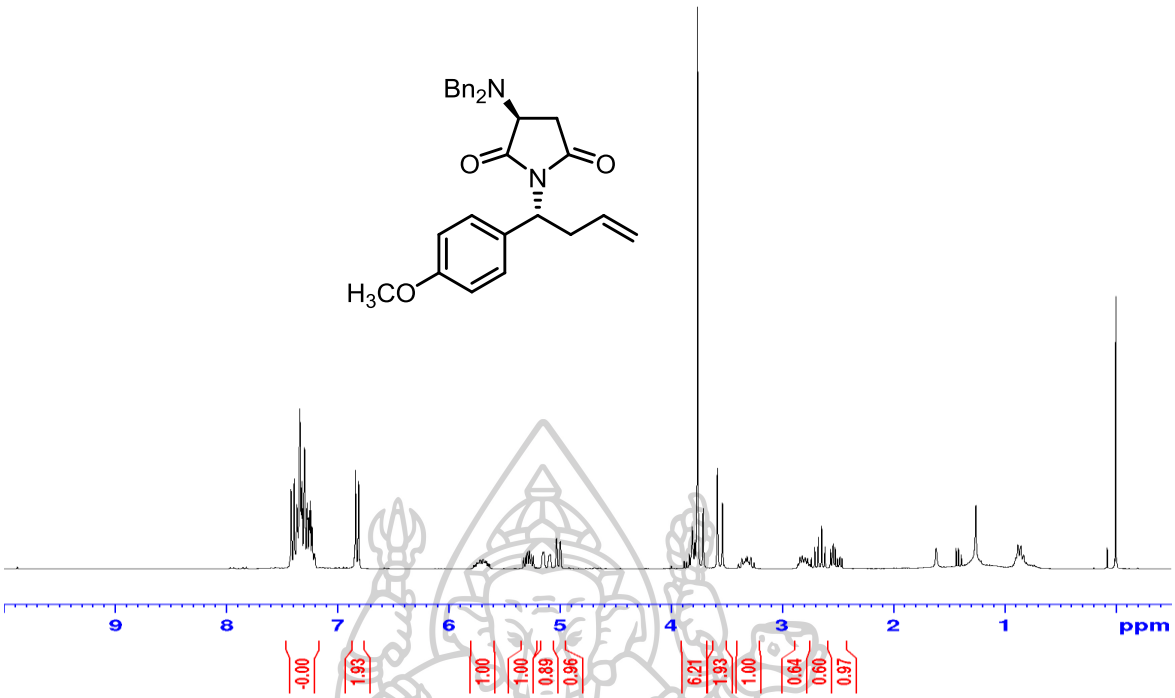
^{13}C NMR of Secondary alcohol **3.46c**



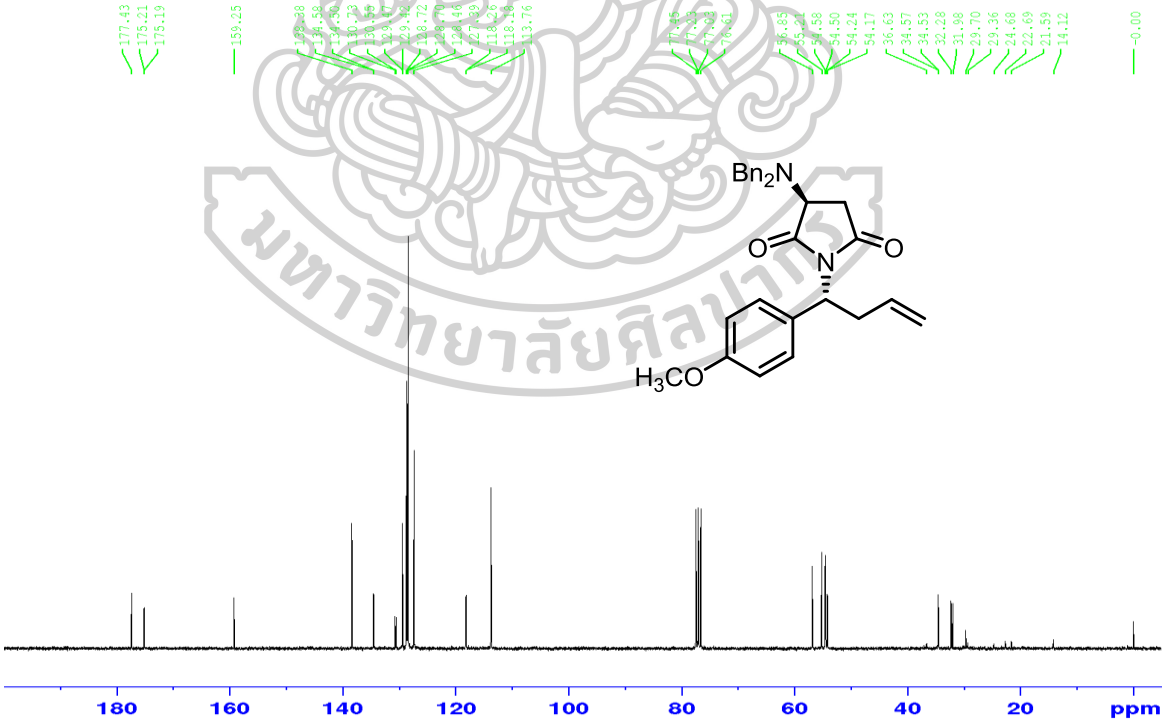
^{1}H NMR of Secondary alcohol **3.46f**



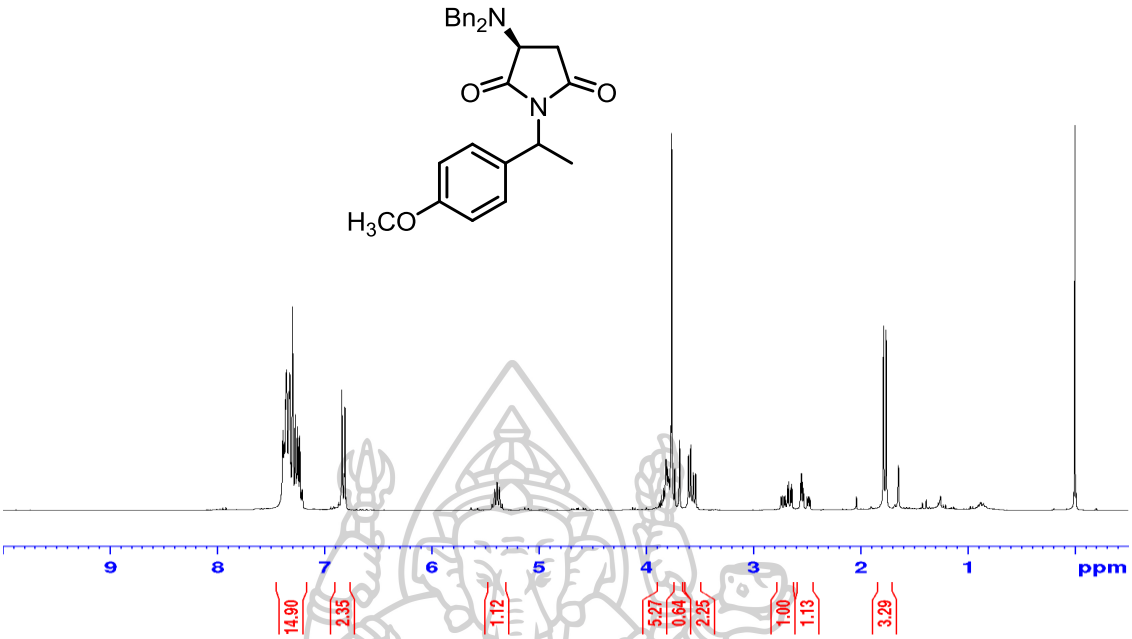
^{13}C NMR of Secondary alcohol **3.46f**



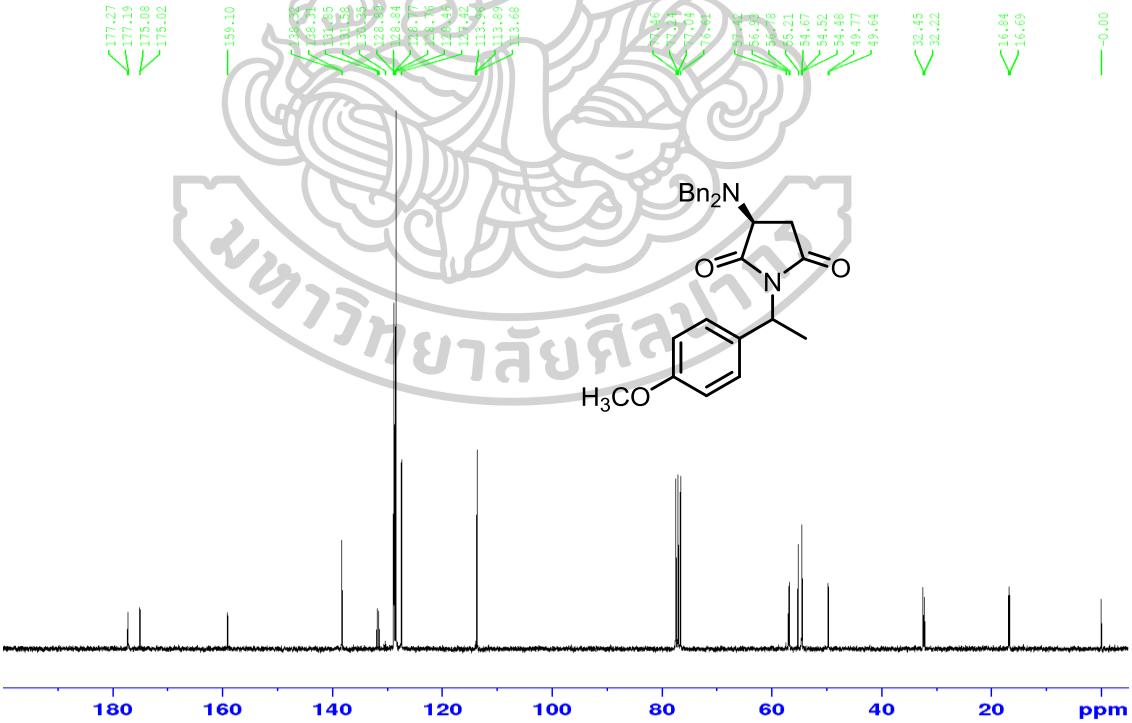
^{1}H NMR of *N*-alkylate **3.44c**



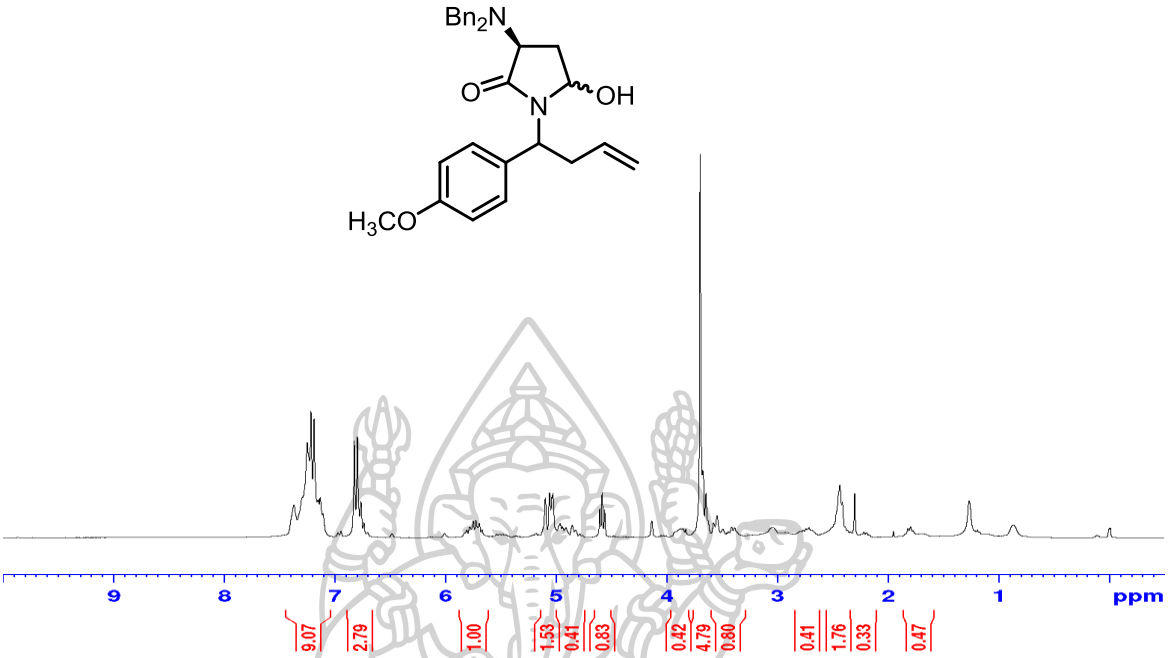
^{13}C NMR of *N*-alkylate **3.44c**



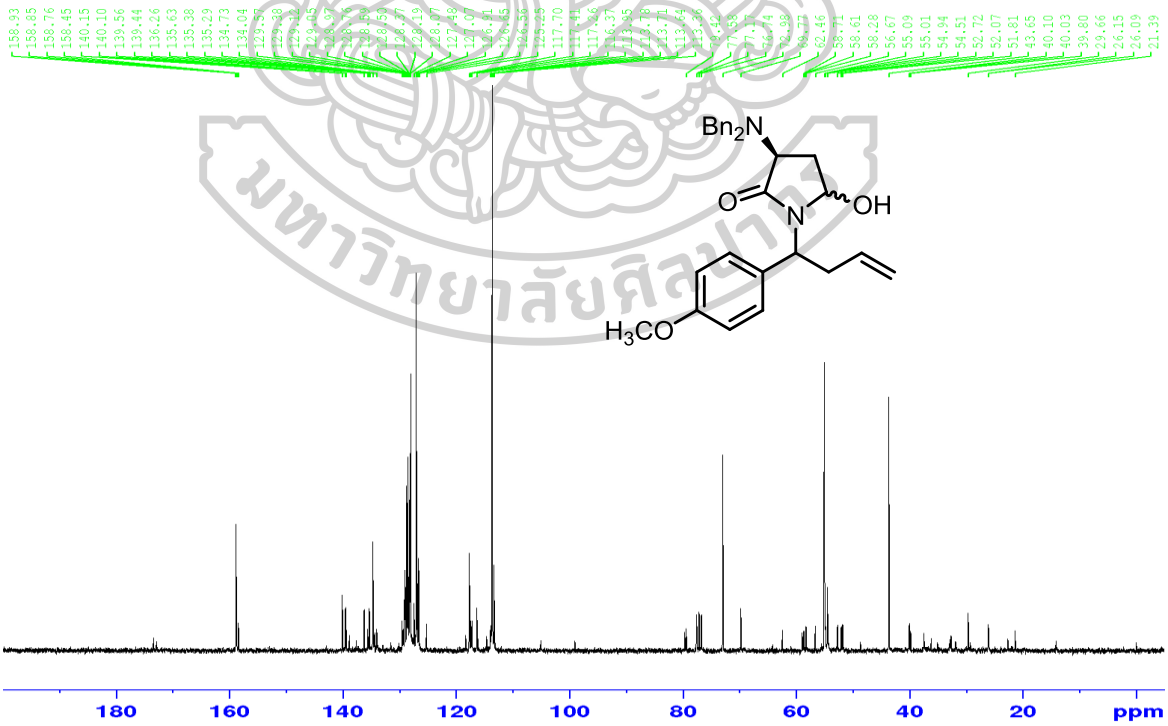
^{1}H NMR of *N*-alkylate **3.44f**



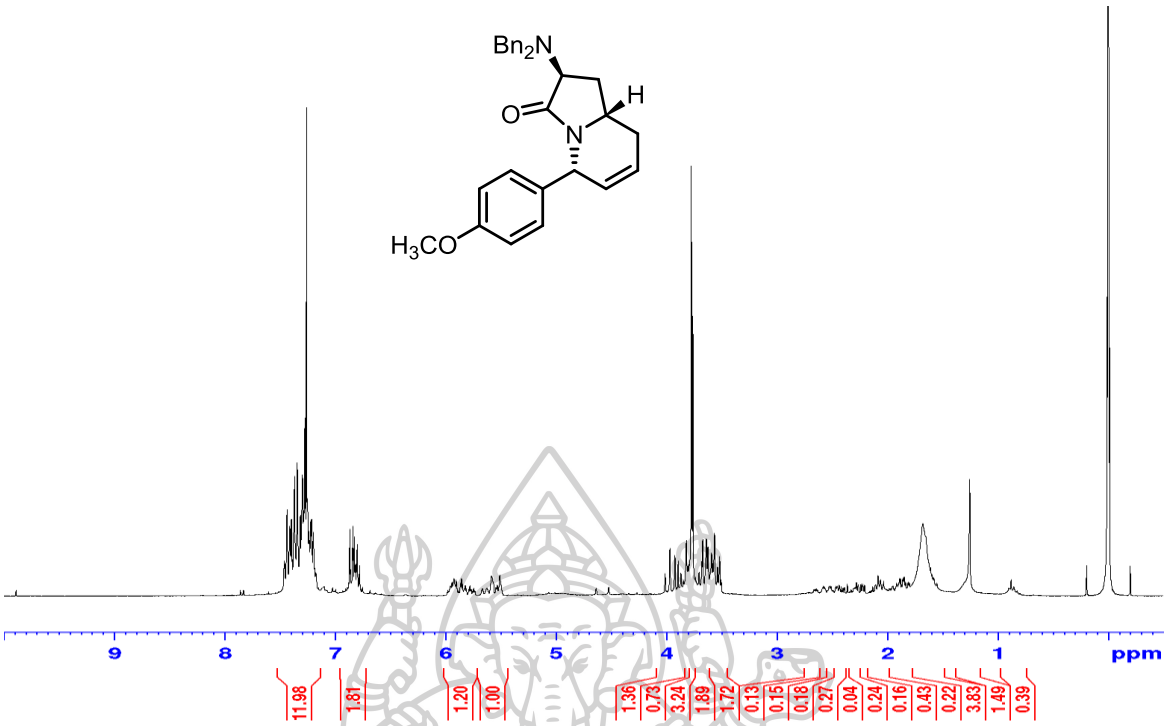
^{13}C NMR of *N*-alkylate **3.44f**



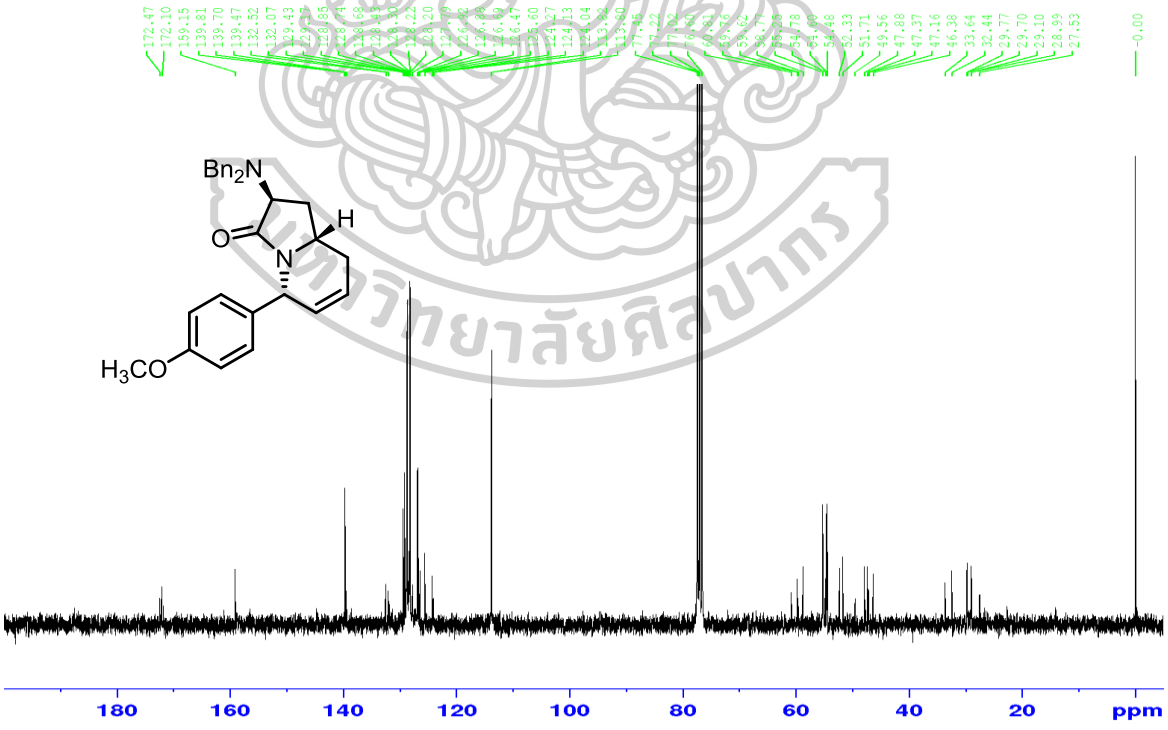
^{1}H NMR of Hydroxylactam **3.48c**



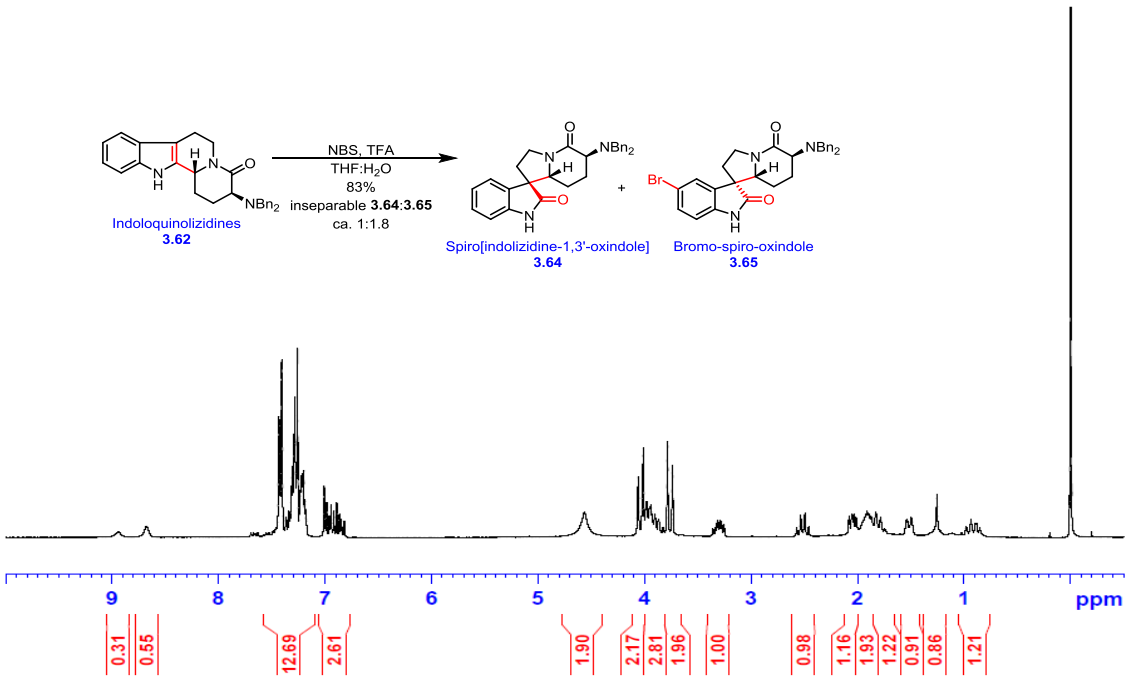
^{13}C NMR of Hydroxylactam **3.48c**



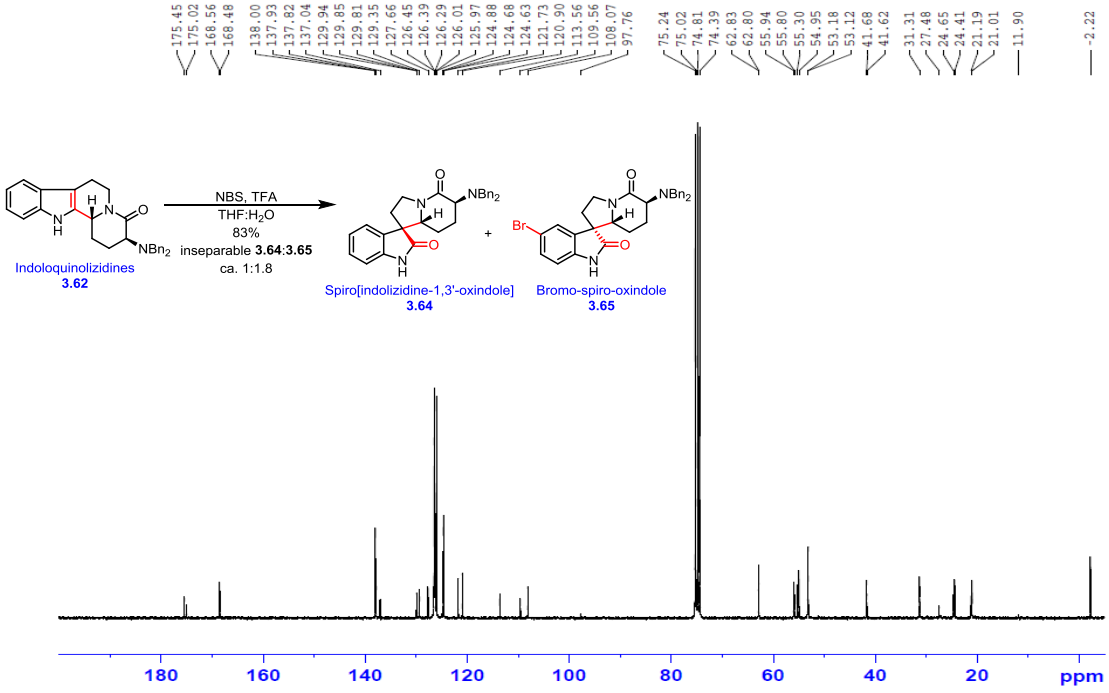
^{1}H NMR of bicyclic indolizidine core **3.43c**



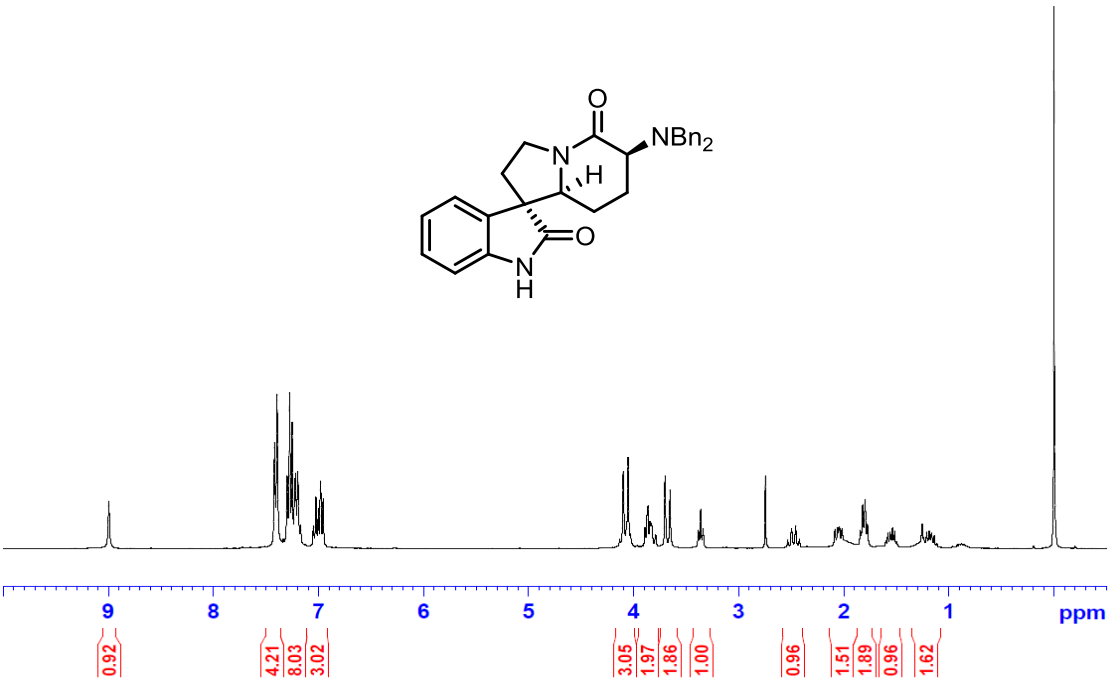
^{13}C NMR of bicyclic indolizidine core **3.43c**



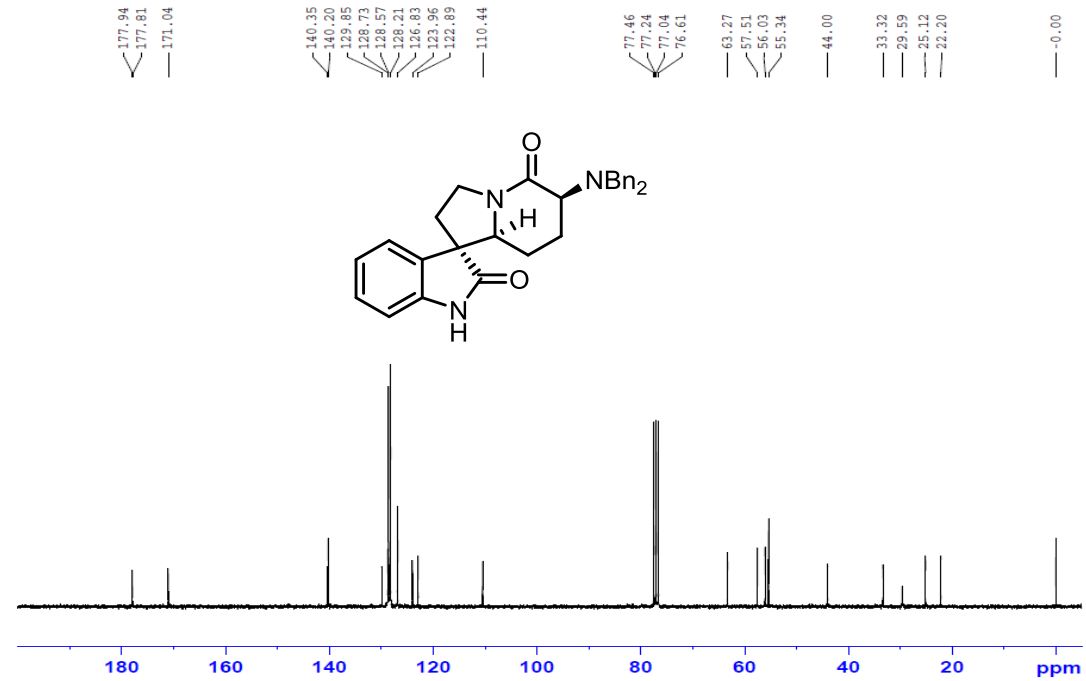
^{1}H NMR of spiro[indolizidine-1,3'-oxindole] **3.64**



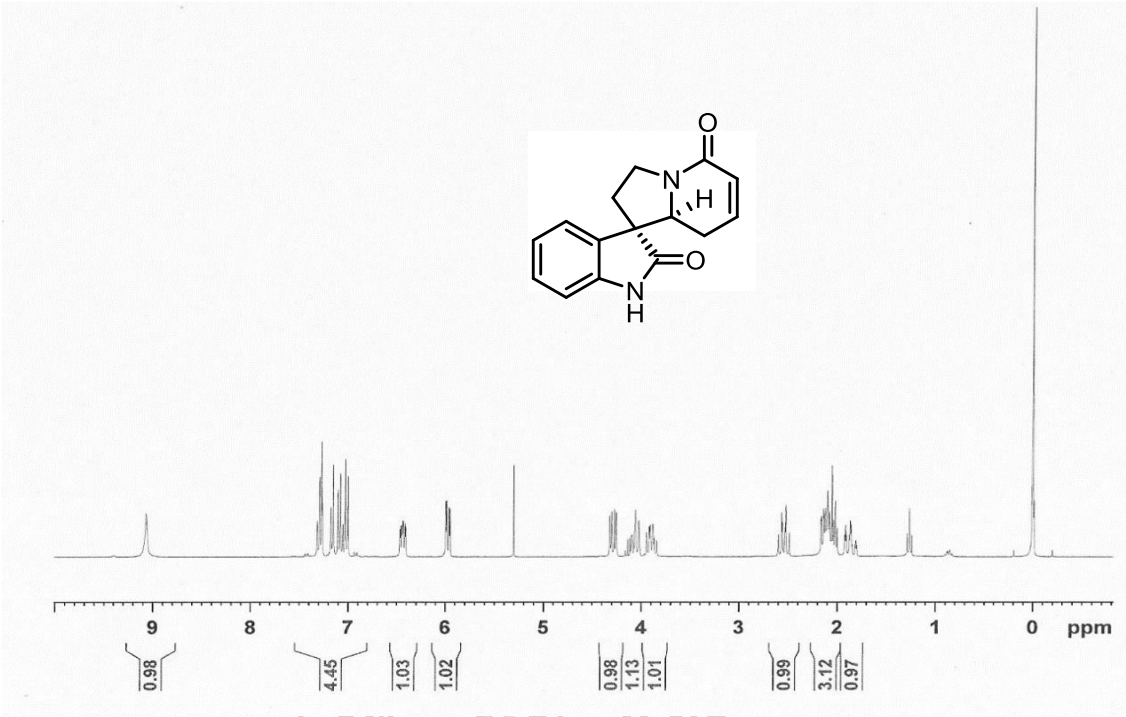
^{13}C NMR of spiro[indolizidine-1,3'-oxindole] **3.64**



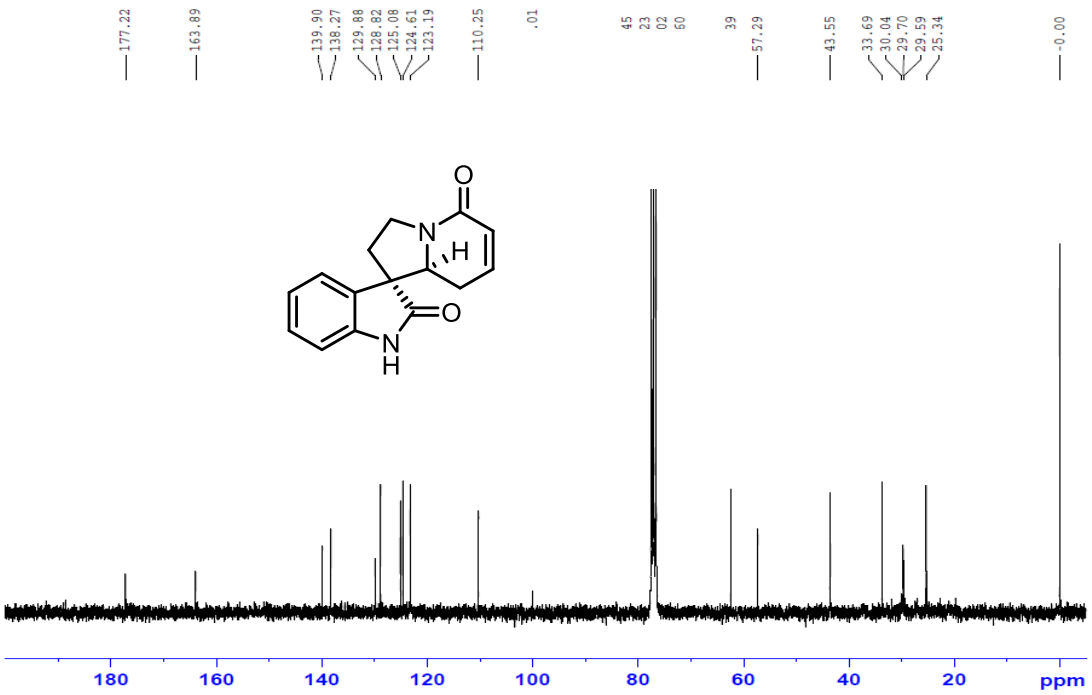
^{1}H NMR of Spiroindolizidine-oxindole **3.66**



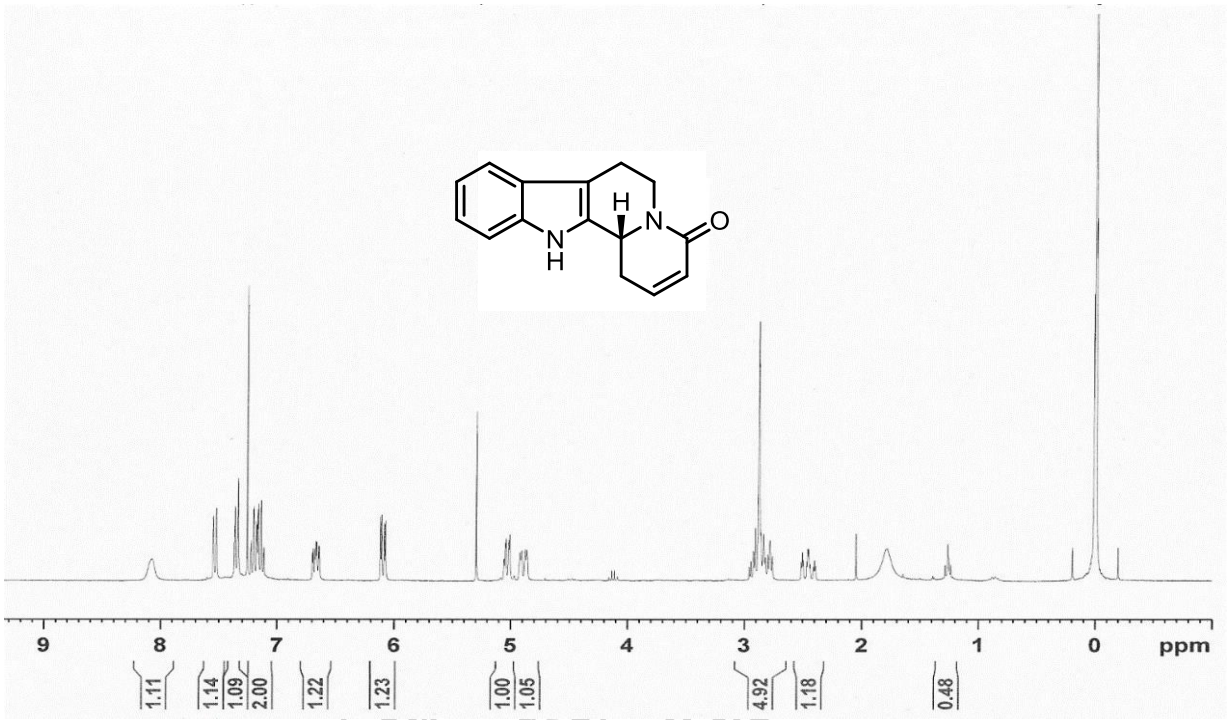
^{13}C NMR of Spiroindolizidine-oxindole **3.66**



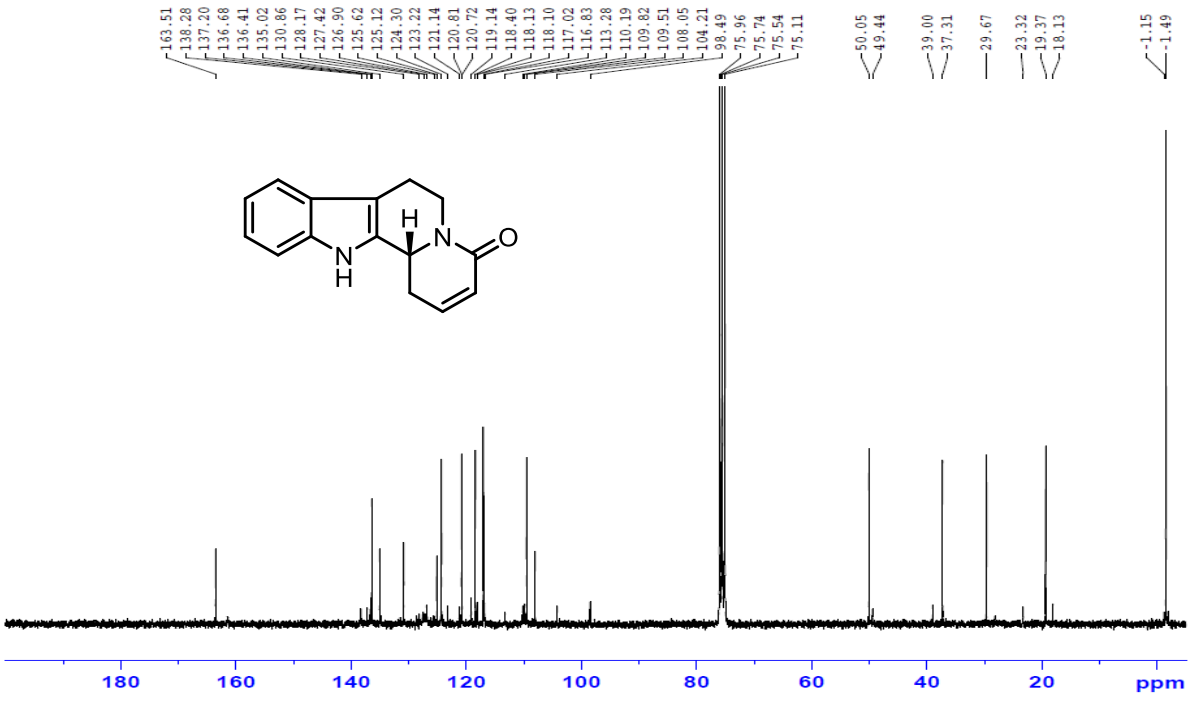
^{1}H NMR of Enamide **3.67**



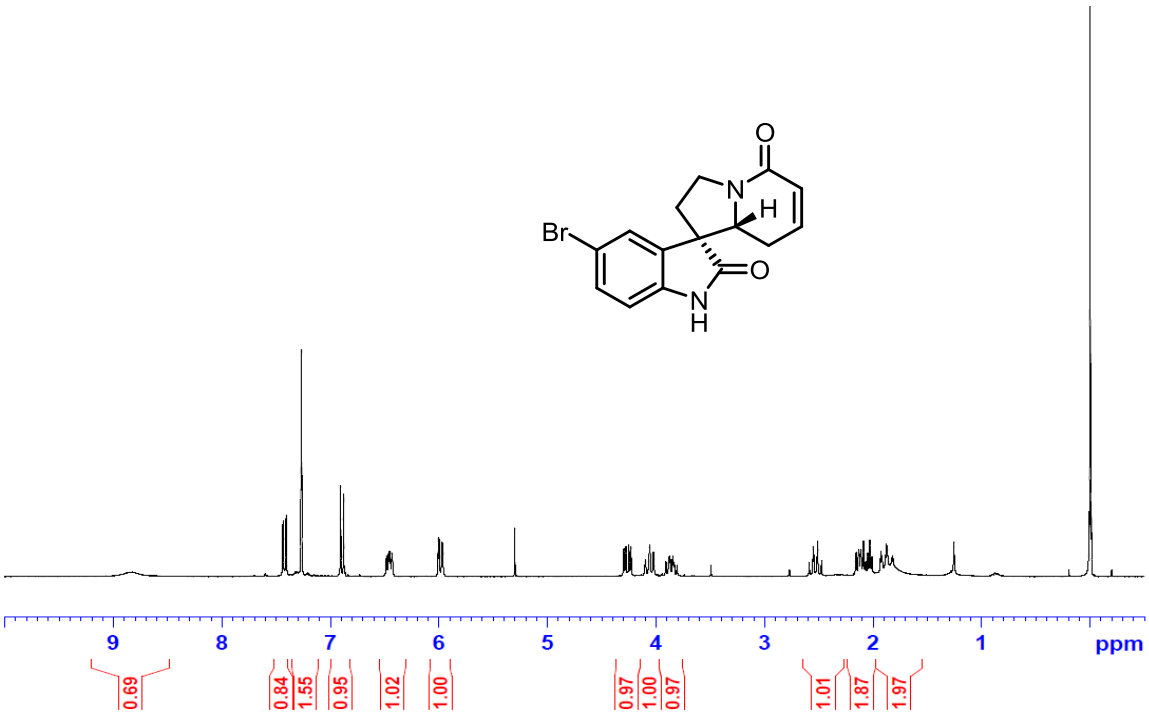
^{13}C NMR of Enamide **3.67**



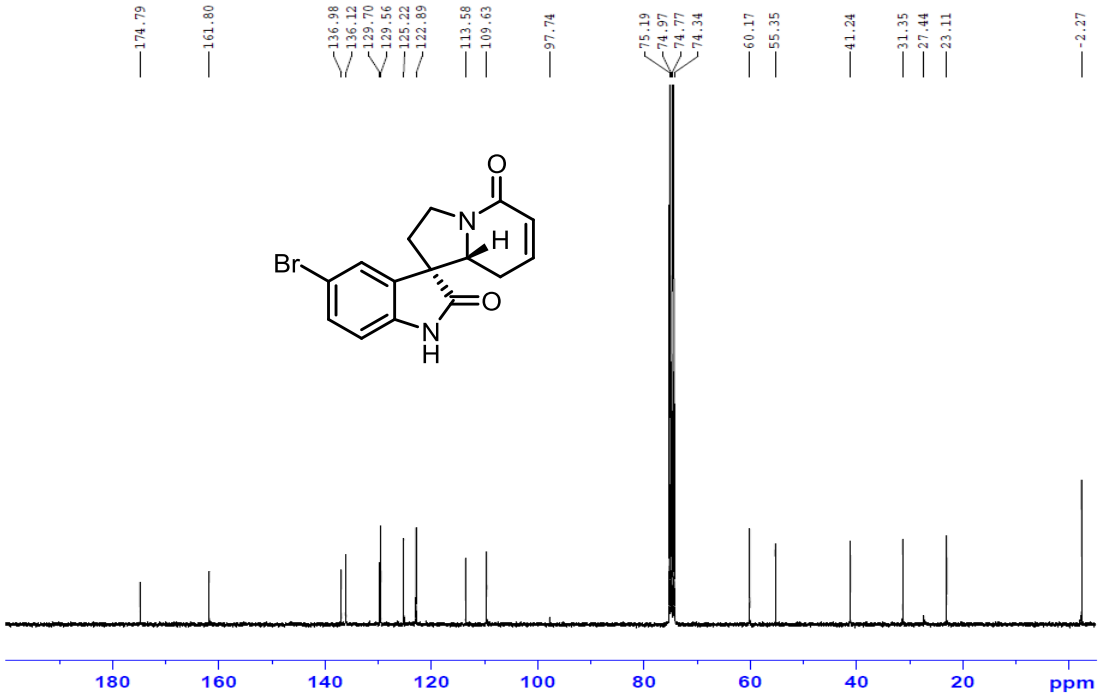
^{1}H NMR of indoloquinolizidinone **3.73**



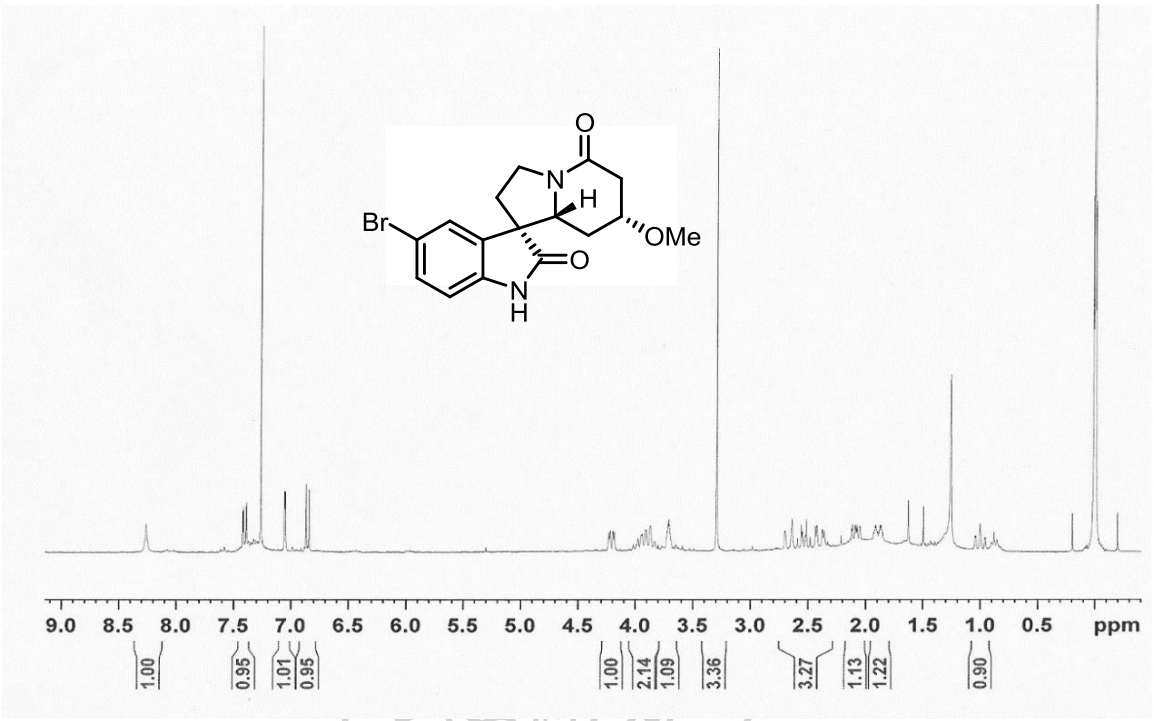
^{13}C NMR of indoloquinolizidinone **3.73**



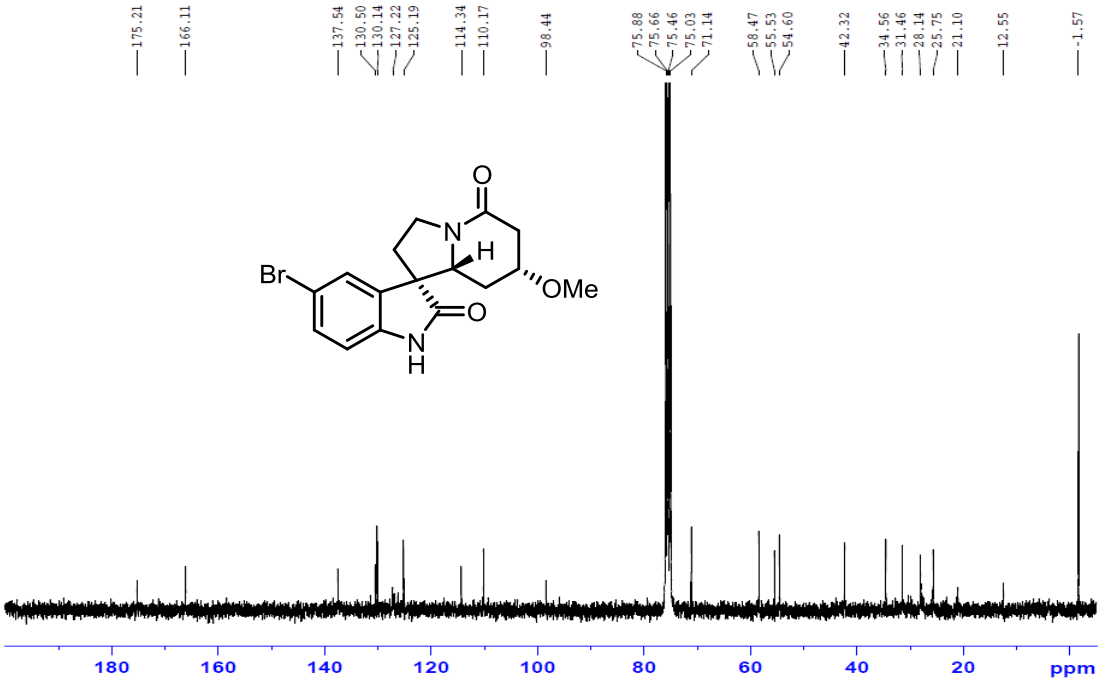
^{1}H NMR of Spiro[indolizidine-1,3'-bromooxindole] **3.74**



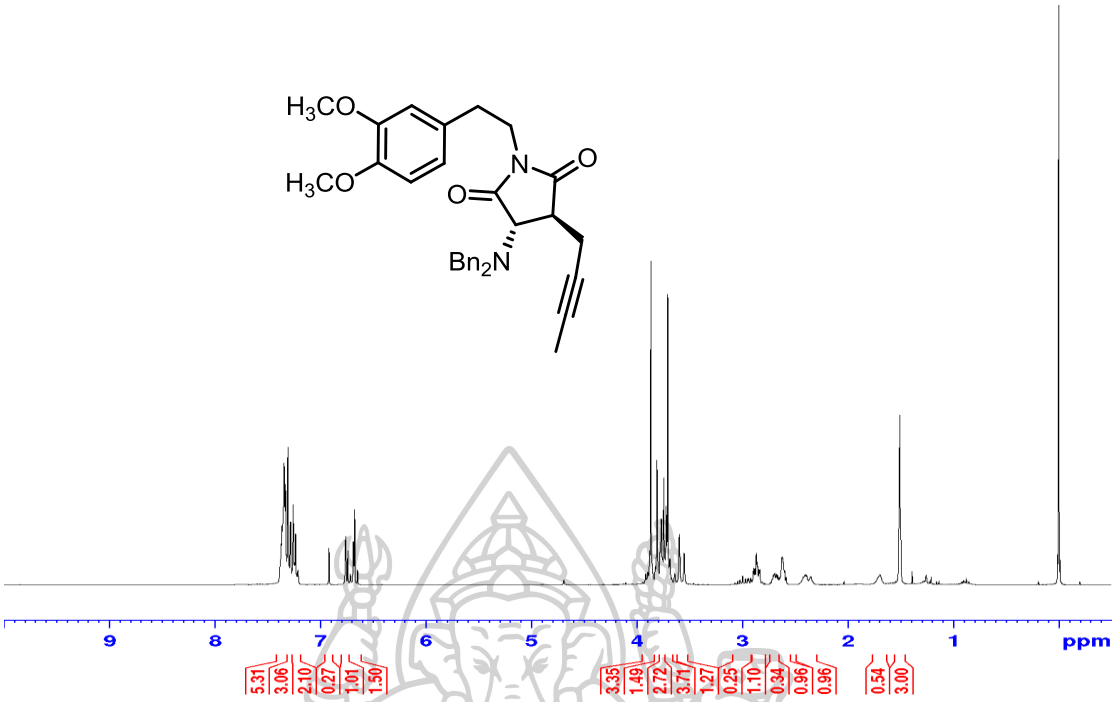
^{13}C NMR of Spiro[indolizidine-1,3'-bromooxindole] **3.74**



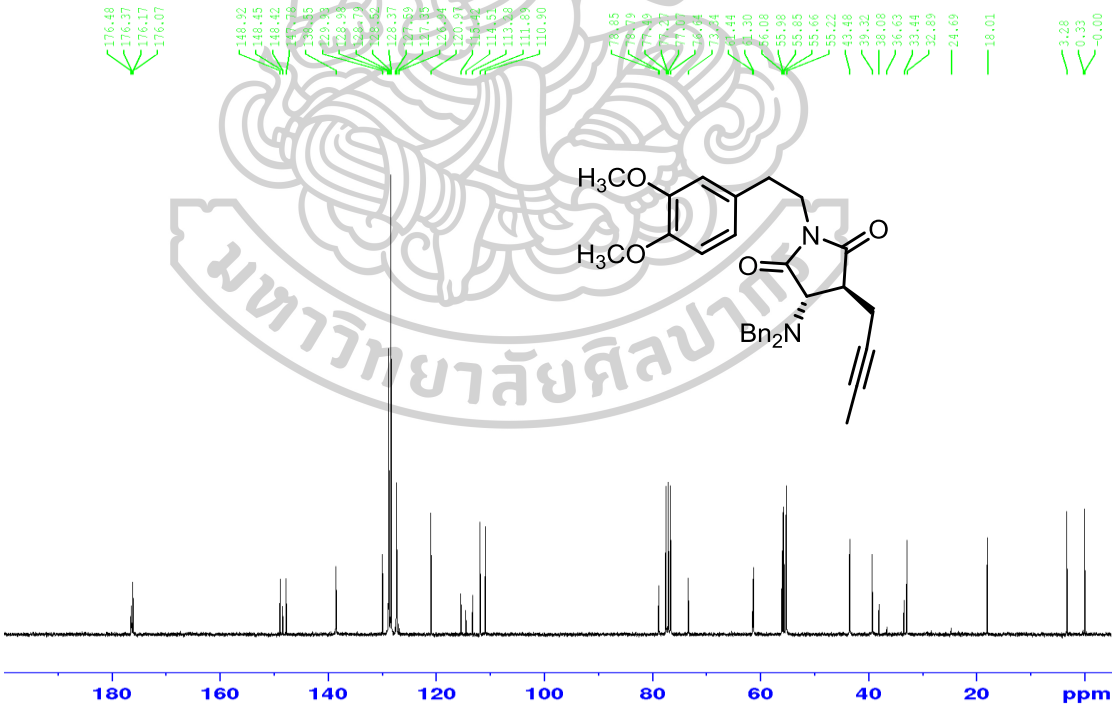
^{1}H NMR of Spiro[7-methoxyindolizidine-1,3'-bromooxindole] **3.75**



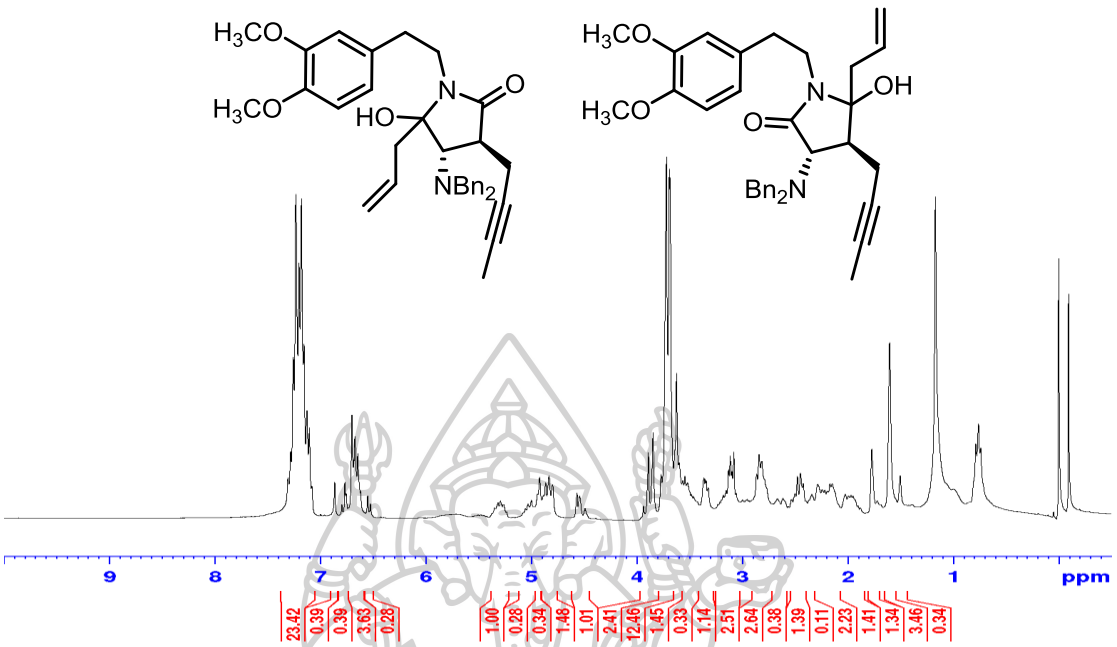
^{13}C NMR of Spiro[7-methoxyindolizidine-1,3'-bromooxindole] **3.75**



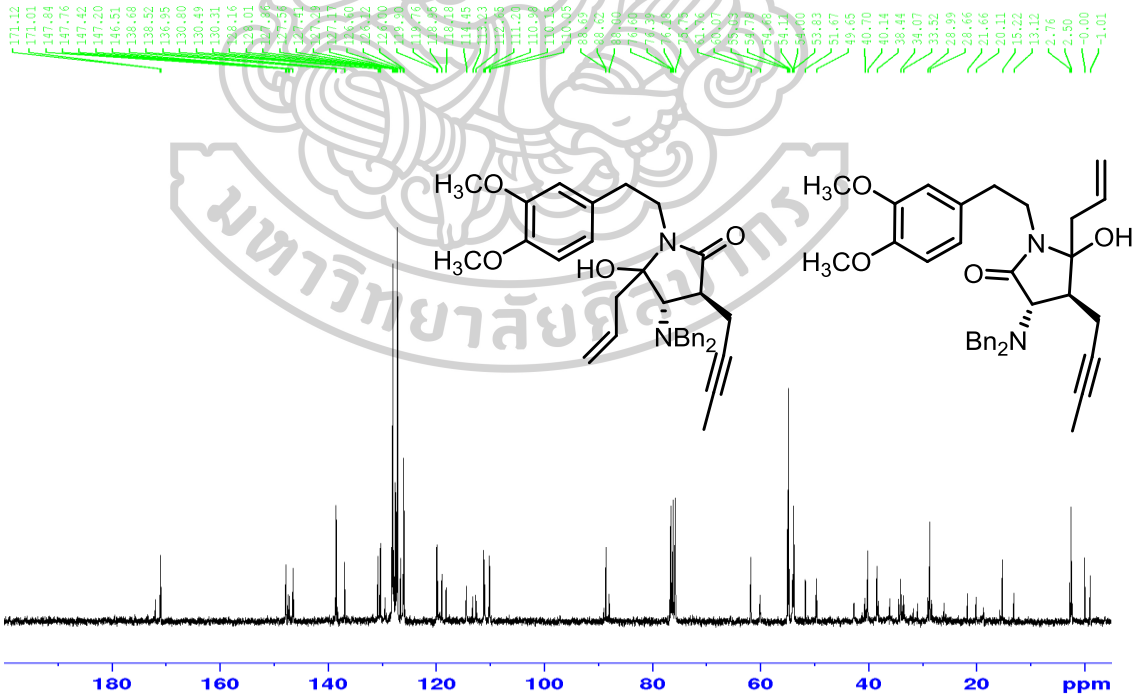
^{1}H NMR of Alkyne **3.16**



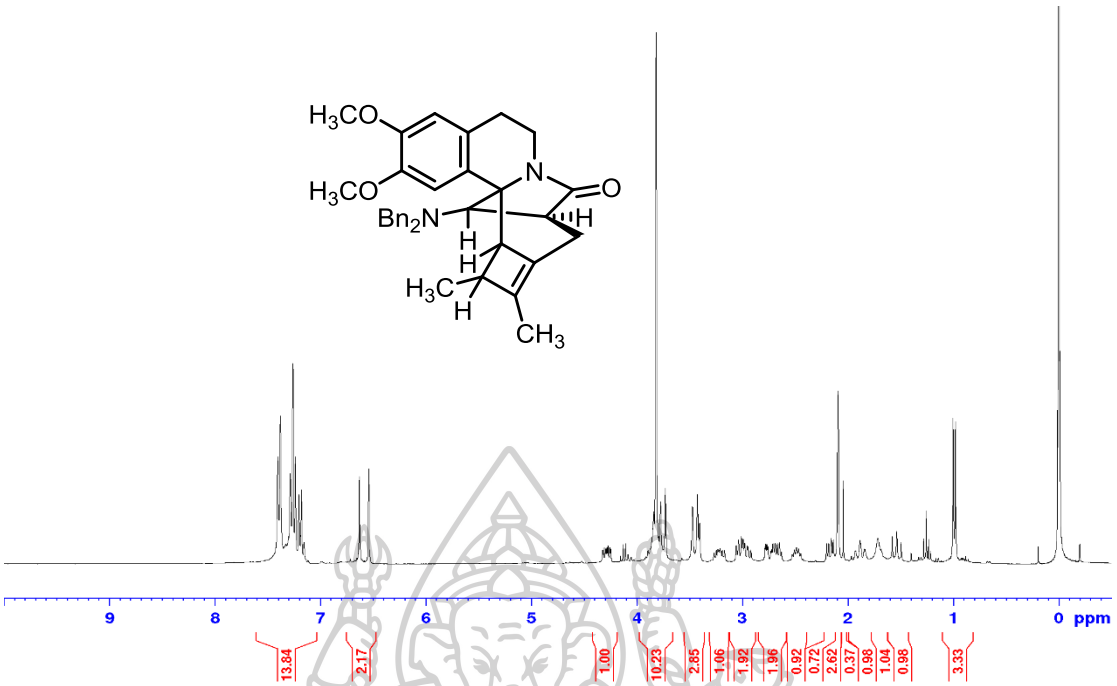
^{13}C NMR of Alkyne **3.16**



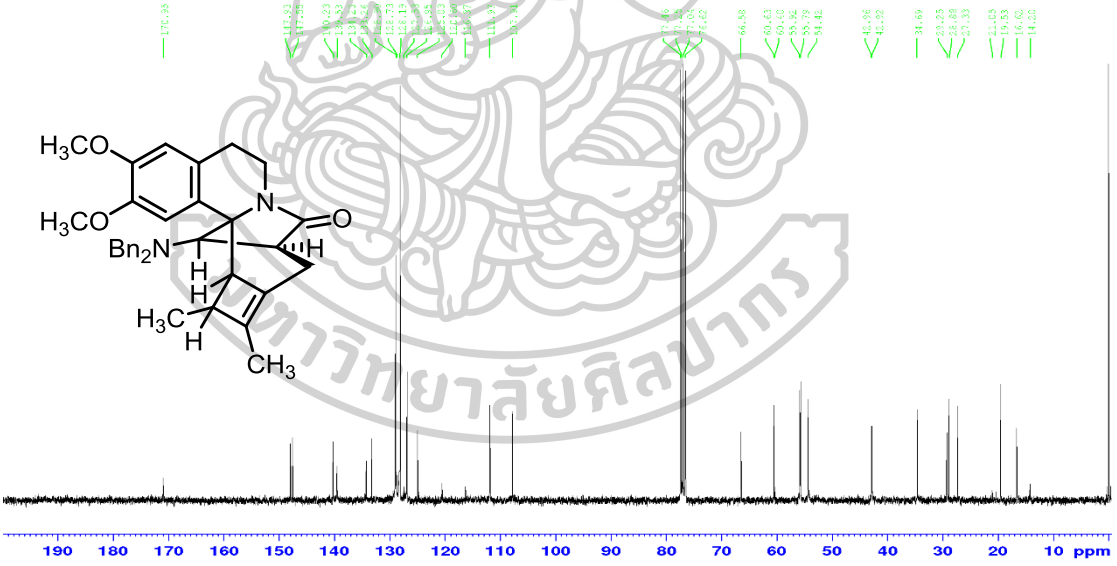
^{1}H NMR of Hydroxylactam intermediate



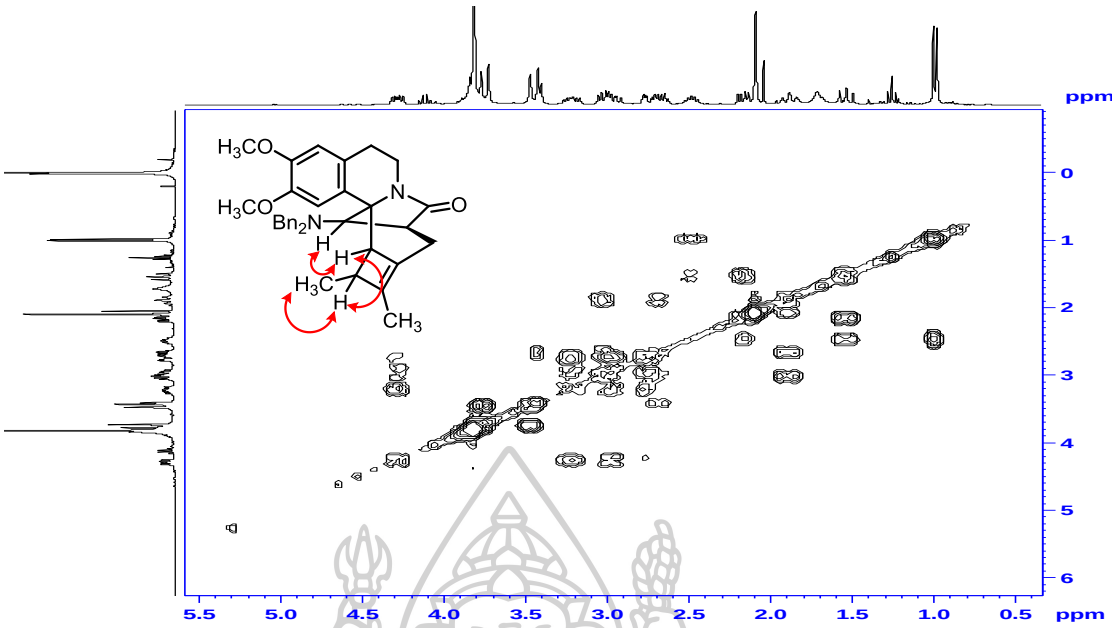
^{13}C NMR of Hydroxylactam intermediate



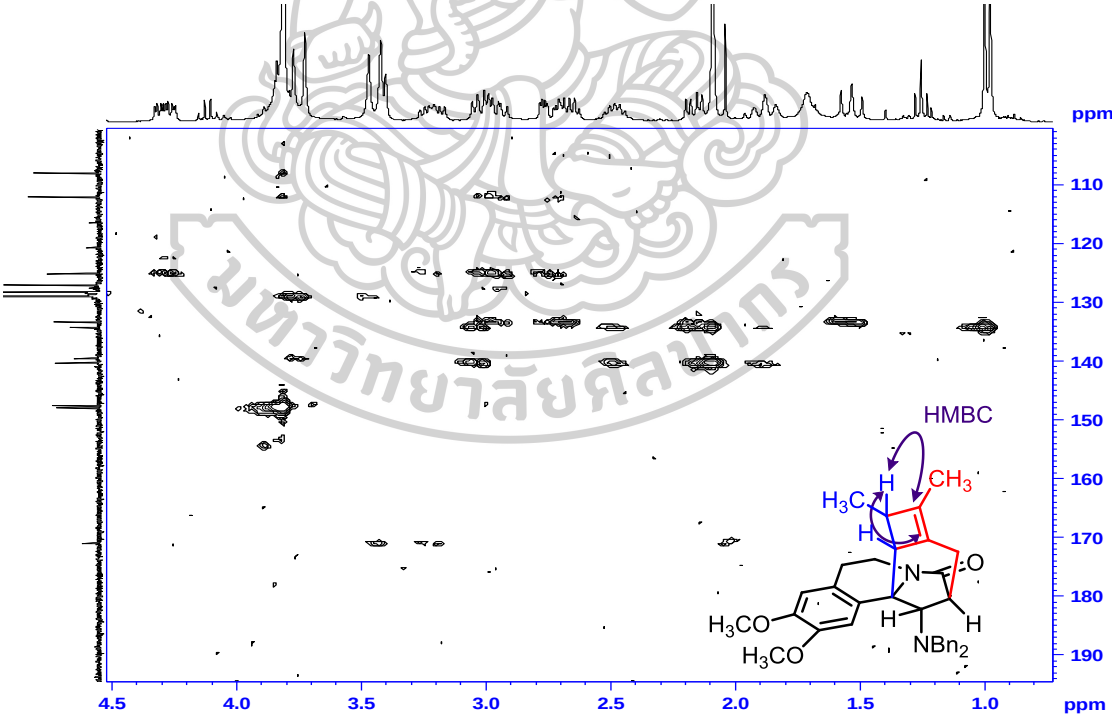
^{1}H NMR of Cyclobutene **3.18**



^{13}C NMR of Cyclobutene **3.18**



2D-COSY NMR of Cyclobutene **3.18**



2D-HMBC NMR of Cyclobutene **3.18**

VITA

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AWARD RECEIVED	1. Outstanding student poster award in organic synthesis and medicinal chemistry session in Pure and Applied Chemistry International Conference 2019 (PACCON 2019), BITEC, Bangkok, Thailand 2. Outstanding poster presentation award winners in organic and medicinal chemistry session in Pure and Applied Chemistry International Conference 2020 (PACCON 2020), Muangthong Thani, Nonthaburi, Thailand